Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals

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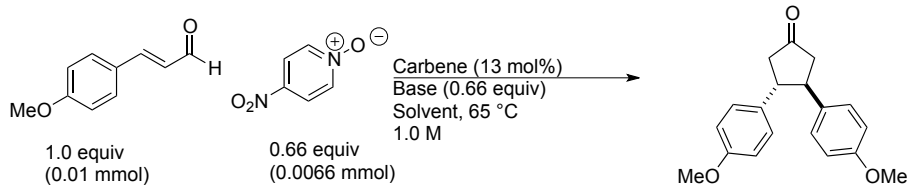
Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Trifluorotoluene was purchased from Aldrich in a Sure-Seal container and stored in a glove box. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Tetrahydrofuran was degassed with argon and passed through one column of neutral alumina. Sodium acetate was purchased from Aldrich. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light or KMnO4 stain followed by heating.

^{1}H NMR spectra were recorded on Varian 400 MHz spectrometers at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm) or acetone-D_6 (2.03 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR were recorded on Varian 400 MHz spectrometers (at 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.36 ppm) or acetone-D_6 (205.87, 30.6 ppm). The ^{13}C NMR show an anomaly at 194.8 ppm (in $CDCl_3$) that is an artifact of the instrument. Mass spectra were recorded on an Agilent 6130 Quadrupole LC/MS. Aldehydes were either purchased from Aldrich or prepared via known literature procedures. Nitroarenes were purchased from Aldrich.

High-Throughput Experimentation Optimization

-Screen of Solvents vs. Bases

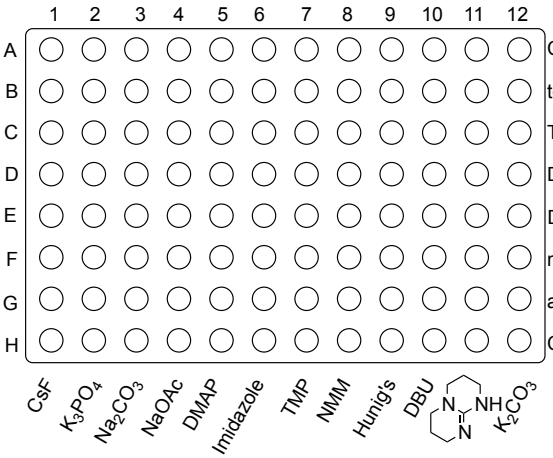


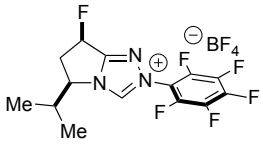
Bases x 12

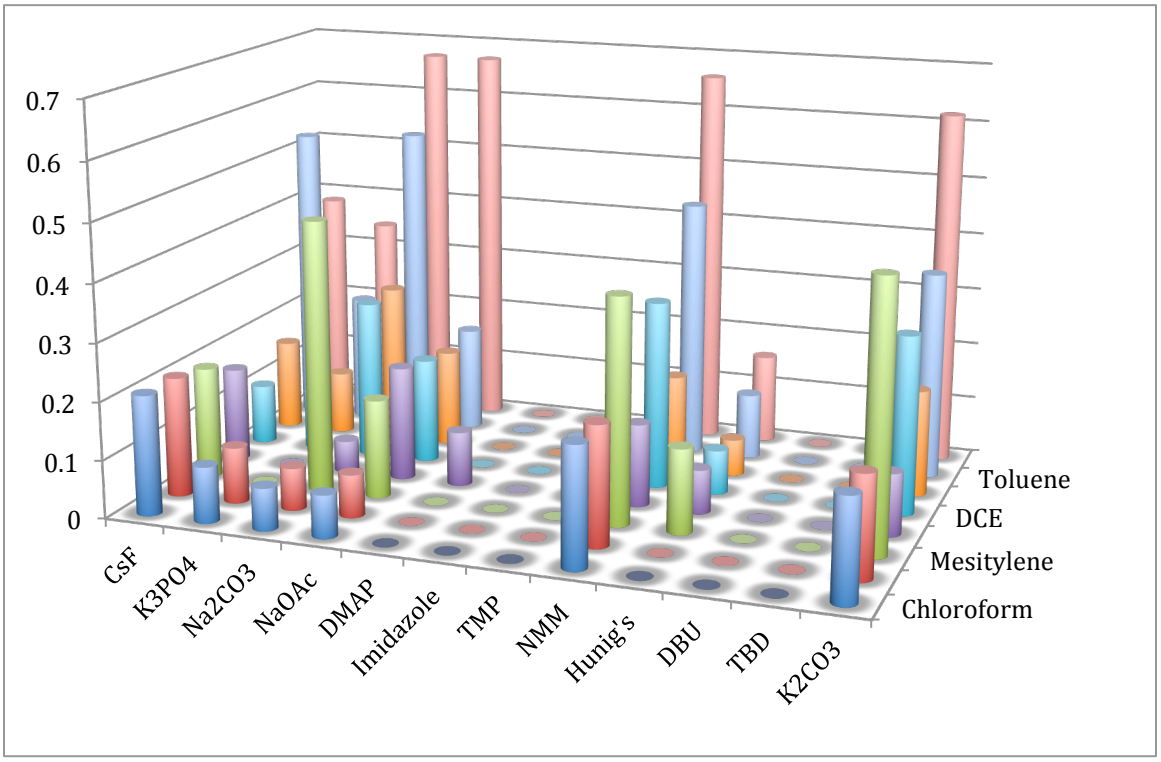
CsF	TMP
K_3PO_4	NMM
Na_2CO_3	Hunig's
NaOAc	DBU
DMAP	1,5,7-TRIAZABICYCLO[4.4.0]DEC-5-ENE
Imidazole	K_2CO_3

Solvent x 8

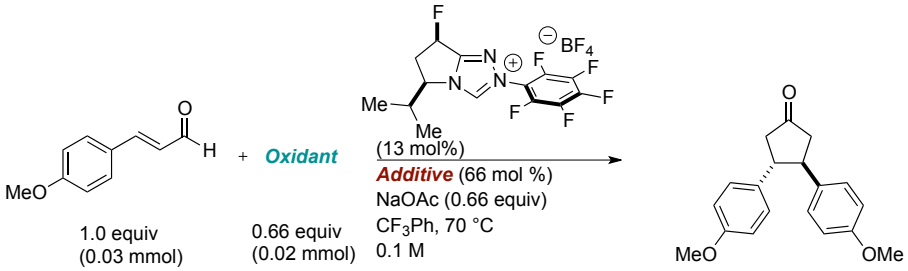
CF_3-toluene	Dioxane
toluene	xylene
THF	acetonitrile
DCE	Cl-Benzene



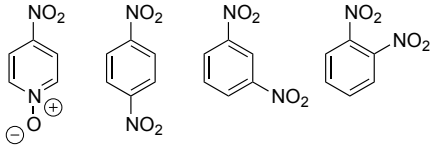




-Screen of Lewis Acids vs. Oxidants



Oxidant x 4



Additive x 6

1 $Sc(OTf)_3$

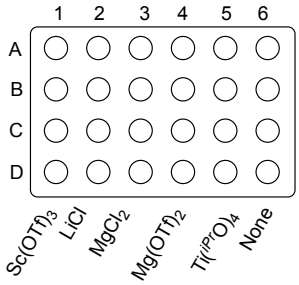
2 LiCl

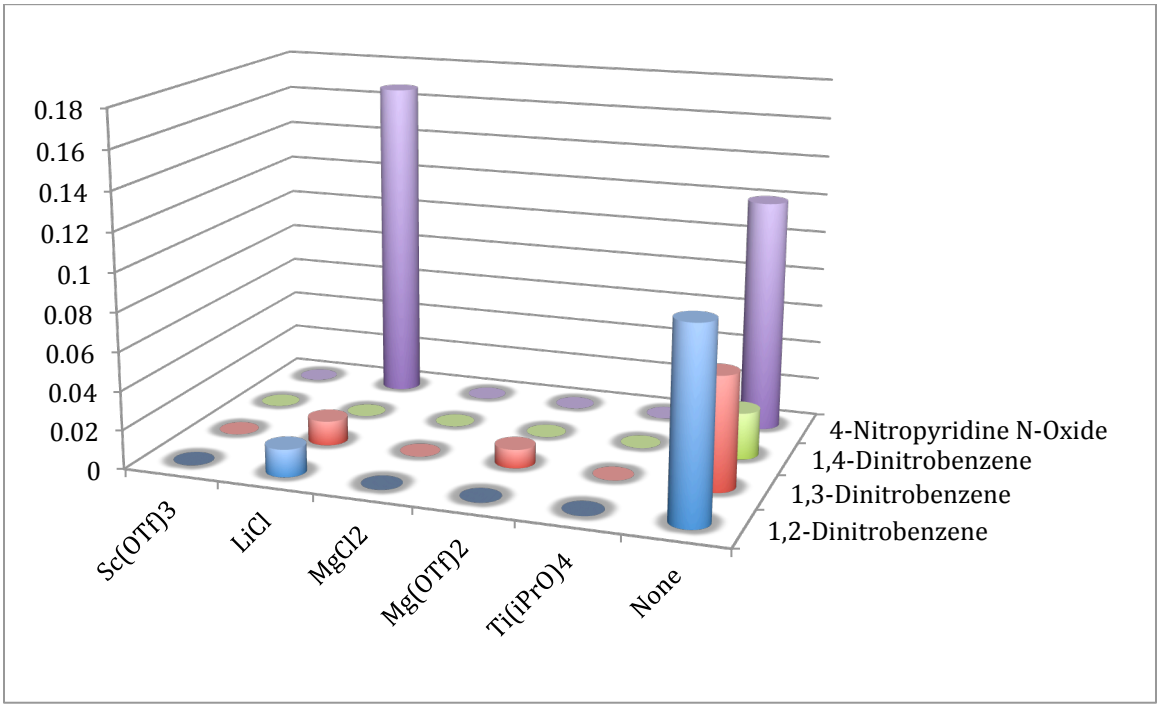
3 $MgCl_2$

4 $Mg(OTf)_2$

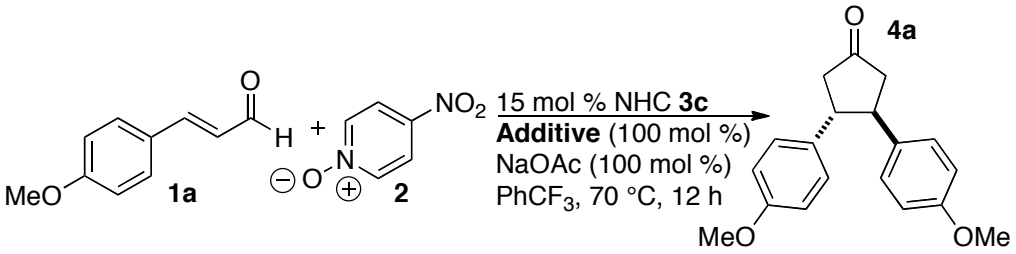
5 $Ti(^{iPr}O)_4$

6 None





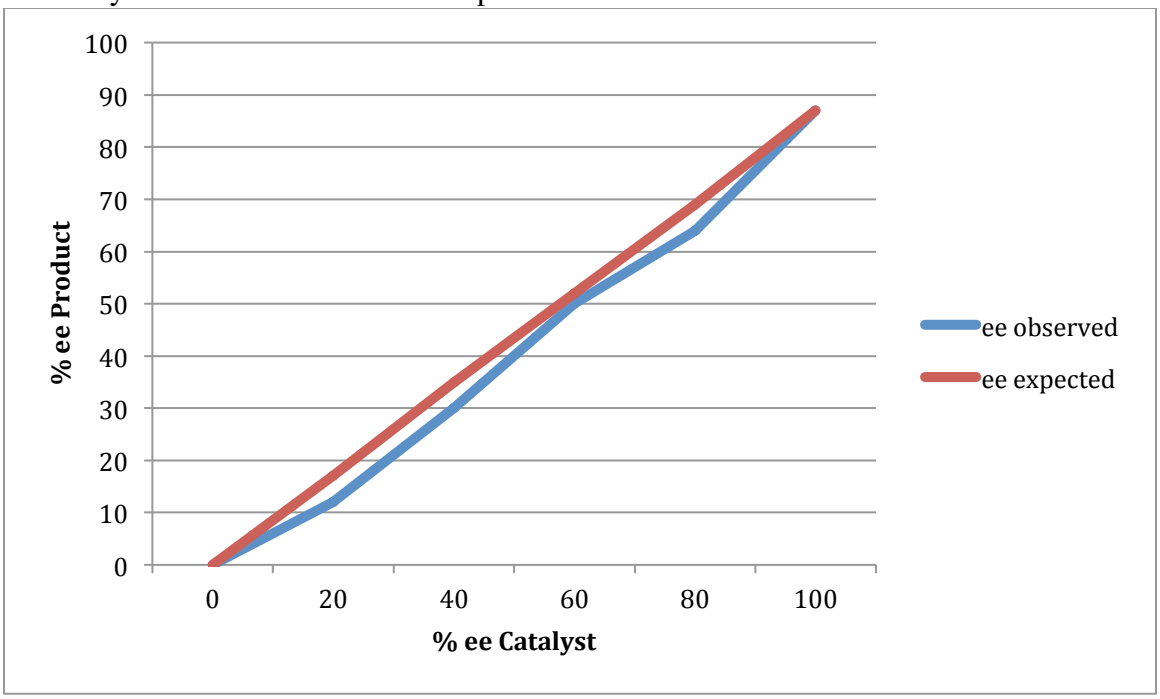
-Screen of Lithium Salts



Entry	Additive	YIeld (%)	ee (%)
1	-	64	84
2	LiBr	56	84
3	LiI	68	82
4	LiF	70	84
5	Li_2CO_3	47	84
6	$LiClO_4$	57	83
7	$LiBF_4$	76	84
8	**LiCl**	**79**	**84**
9	NaCl	55	84

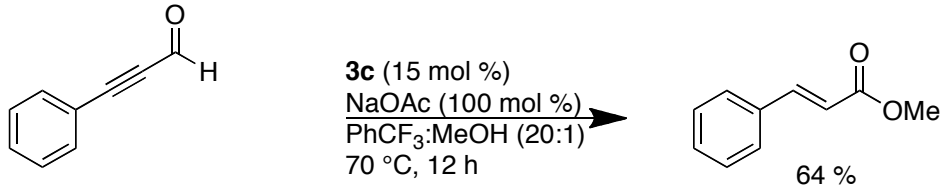
Mechanistic Probes
– Non-Linear Effects

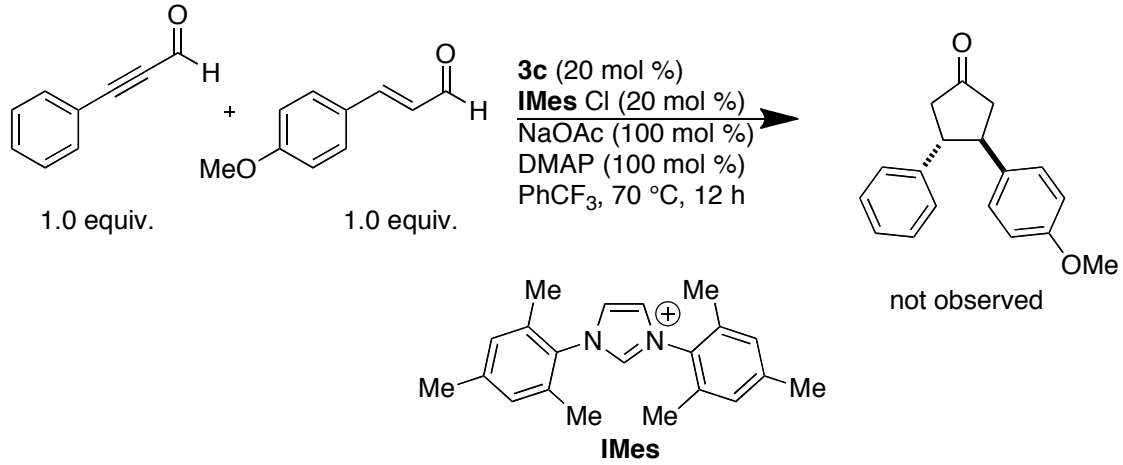
In an attempt to further elucidate the mechanism, we looked for the presence of non-linear effects. We propose two equivalents of NHC catalyst are required for the transformation; thus a non-linear effect might be observed. Unfortunately, we did not observe the expected non-linear effect. A possible explanation for this is that two stereocenters are set during the bond-forming event. Thus, when opposite antipodes of catalyst are involved in the bond-forming event, a different diastereomeric transition state may be encountered, potentially leading to enrichment of the meso adduct at the expense of ee increase or decrease. The meso intermediate may then lead to other products. In Kise's electrochemical reductive coupling of cinnamates, he observes that the meso adduct does not close to the cyclopentanone.[1] In our investigation into non-linear effects, we always saw >20:1 dr of the *trans* product.



– Probing the Intervention of an Acyl Azolium

Catalyst **3c** is competent at inducing formation of an acyl azolium from an ynal substrate as shown below. A referee has suggested the use of two catalysts to probe crossover between an ynal and electron-rich enal. That experiment does not lead to cyclopentanone product (shown below).





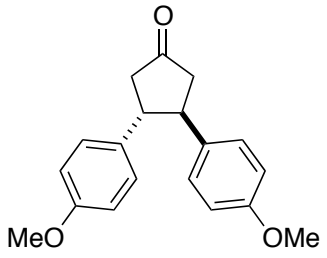
General Procedure for the Enal Dimerization to Form Cyclopentanones

To a flame dried screw cap vial charged with a stirbar was added triazolium salt **3c** (17 mg, 0.04 mmol), 4-methoxycinnamaldehyde **1a** (49 mg, 0.3 mmol), 4-nitropyridine N-oxide **2** (28 mg, 0.2 mmol), NaOAc (16 mg, 0.2 mmol), and LiCl (8 mg, 0.2 mmol). This vial was then transferred to a glove box containing an argon atmosphere. 1.0 mL of dry trifluorotoluene ($PhCF_3$) was then added and the cap tightly screwed on, removed from the glove box, and wrapped in parafilm tape. The reaction was then heated to 70 °C and stirred for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified via silica gel chromatography (7:3 hexanes:ether) to yield 35 mg (80 %) (3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone **4a** as an off-white solid in 84 % ee as a single diastereomer.

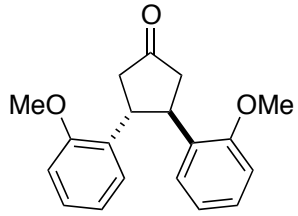
General Procedure for the Cross Annulation to Form Cyclopentanones

To a flame dried screw cap vial charged with a stirbar was added triazolium salt **3c** (17 mg, 0.04 mmol), cinnamaldehyde **1c** (26 mg, 0.2 mmol), 4-methoxycinnamaldehyde **1a** (131 mg, 0.8 mmol), 4-nitropyridine N-oxide **2** (112 mg, 0.8 mmol), NaOAc (66 mg, 0.8 mmol), and LiCl (34 mg, 0.8 mmol). This vial was then transferred to a glove box containing an argon atmosphere. 3.0 mL of dry trifluorotoluene ($PhCF_3$) was then added and the cap tightly screwed on, removed from the glove box, and wrapped in parafilm tape. The reaction was then heated to 70 °C and stirred for 12 hours. After 12 hours the reaction was concentrated via rotary evaporation and then purified via silica gel chromatography (8:2 hexanes:ether) to yield 35 mg (65 %) (3*R*,4*R*)-3-(4-methoxyphenyl)-4-phenylcyclopentanone **5a** as an off-white solid in 83 % ee as a single diastereomer.

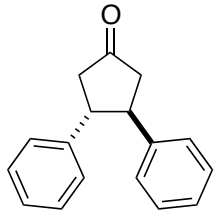
Product Characterization



(3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone (**4a**): Off-White Amorphous Solid. 79 % yield, 84 % ee, >20:1 dr., Rf: 0.25 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -67.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC Analysis**: Chiralpak IB column 80:20 hexanes/*iso*propanol, 1.0 mL/min, Major: 10.6 min, minor: 10.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.04-7.01 (m, 4H), 6.80-6.76 (m, 4H), 3.76 (s, 6H), 3.42-3.33 (m, 2H), 2.85-2.79 (m, 2H), 2.56-2.49 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 216.1, 158.3, 132.9, 128.1, 113.9, 55.2, 49.6, 47.3. Spectra matched that of the previously reported compound.[1]

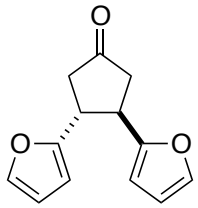


(3*R*,4*R*)-3,4-bis(2-methoxyphenyl)cyclopentanone (**4b**): Off-White Amorphous Solid. 71 % yield, 91 % ee, >20:1 dr., Rf: 0.31 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -60.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 98:2 hexanes/*iso*propanol, 1.0 mL/min, Major: 12.8 min, minor: 13.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.16-7.12 (m, 4H), 6.85-6.81 (m, 4H), 4.04-3.97 (m, 2H), 3.78 (s, 5H), 2.93-2.86 (m, 2H), 2.48-2.40 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 218.0, 157.5, 130.2, 127.52, 127.46, 120.6, 110.5, 55.2, 46.1, 41.5. Spectra matched that of the previously reported compound.[1]

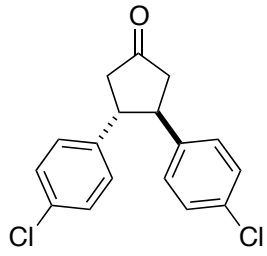


(3*R*,4*R*)-3,4-diphenylcyclopentanone (**4c**): Off-White Amorphous Solid. 74 % yield, 84 % ee, >20:1 dr., Rf: 0.42 (8:2 hexanes:ether); $[\alpha]_D^{21}$ = -64.1 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Reverse phase Chiralpak IB column 95:5 H-$_2$O/acetonitrile, 1.0 mL/min, Major: 21.2 min, minor: 20.8 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.34-7.01 (m, 10H), 3.54-3.45 (m, 2H), 2.90-2.84 (m, 2H), 2.67-2.51 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.8, 140.8, 128.5, 127.2, 126.8, 50.2, 47.2. Spectra matched that of the previously reported compound.[1]

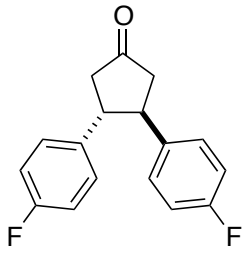
[1] Kise, N.; Iitaka, S.; Iwasaki, K.; Ueda, N. *J. Org. Chem.* **2002**, *67*, 8305.



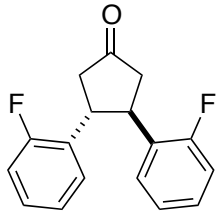
(3*R*,4*R*)-3,4-di(furan-2-yl)cyclopentanone (**4d**): Pale Yellow Oil. 66 % yield, 65 % ee, >20:1 dr., Rf: 0.53 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -24.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 95:5 hexanes/*iso*propanol, 1.0 mL/min, Major: 7.6 min, minor: 7.0 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.34 (dd, *J* = 1.9, 0.8 Hz, 2H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 2H), 6.05 (d, *J* = 3.2 Hz, 2H), 3.72-3.64 (m, 2H), 2.80-2.73 (m, 2H), 2.62-2.54 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.0, 154.5, 141.7, 110.2, 105.9, 43.3, 40.8. Spectra matched that of the previously reported compound.[1]



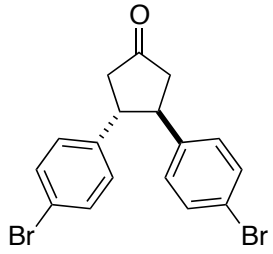
(3*R*,4*R*)-3,4-bis(4-chlorophenyl)cyclopentanone (**4e**): Off-White Amorphous Solid. 63 % yield, 84 % ee, >20:1 dr., Rf: 0.13 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -77.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 80:20 hexanes/*iso*propanol, 1.0 mL/min, Major: 10.1 min, minor: 9.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.22 (d, *J* = 8.2 Hz, 4H), 7.02 (d, *J* = 8.3 Hz, 4H), 3.44-3.35 (m, 2H), 2.88-2.82 (m, 2H), 2.57-2.50 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.4, 138.8, 132.8, 128.8, 128.5, 49.8, 46.9. **IR** (ATR neat): 2910, 1745, 1492, 1412, 1192, 1142, 1091, 1013, 826. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 305.0, found 304.9



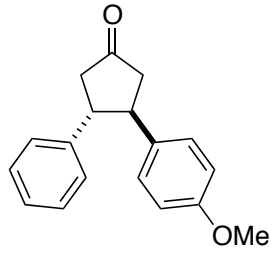
(3*R*,4*R*)-3,4-bis(4-fluorophenyl)cyclopentanone (**4f**): Pale Yellow Oil. 65 % yield, 85 % ee, >20:1 dr., Rf: 0.20 (7:3 hex:ether); $[\alpha]_D^{21}$ = -41.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralcel OC column 97:3 30 hexanes/*iso*propanol, 1.0 mL/min, Major: 13.0 min, minor: 11.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.07-7.03 (m, 4H), 6.96-6.91 (m, 4H), 3.44-3.35 (m, 2H), 2.88-2.82 (m, 2H), 2.59-2.50 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.9, 161.89 (d, J_{CF} = 245.45 Hz), 136.11 (d, J_{CF} =3.48 Hz), 128.57 (d, J_{CF} = 7.74 Hz), 115.46 (d, J_{CF} = 21.33 Hz), 49.9, 47.1. Spectra matched that of the previously reported compound.[1]



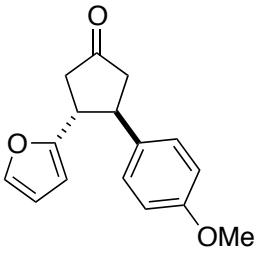
(3*R*,4*R*)-3,4-bis(2-fluorophenyl)cyclopentanone (**4g**): Pale Yellow Oil. 54 % yield, 62 % ee, >20:1 dr., Rf: 0.44 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -72.6 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis:** Chiralpak IB column 97:3 hexanes/*iso*propanol, 1.0 mL/min, Major: 14.2 min, minor: 15.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.24-7.14 (m, 4H), 7.04 (td, *J* = 7.5, 1.3 Hz, 2H), 6.97 (ddd, *J* = 10.8, 8.2, 1.2 Hz, 2H), 3.98-3.89 (m, 2H), 2.93-2.86 (m, 2H), 2.60-2.52 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.1, 161.1 (d, J_{CF} = 245.51 Hz), 128.5 (d, J_{CF} = 8.52 Hz), 128.2 (d, J_{CF} = 4.71 Hz), 127.5 (d, J_{CF} = 13.58 Hz), 124.3 (d, J_{CF} = 3.71 Hz), 115.7 (d, J_{CF} = 22.35 Hz), 45.9, 41.6. **IR** (ATR neat): 3066, 2962, 1745, 1616, 1585, 1492, 1456, 1404, 1368, 1230, 1189, 1143, 756. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd. 295.1, found 295.1



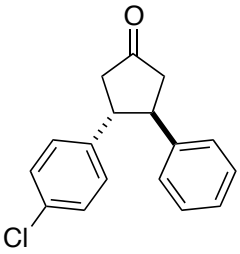
(3*R*,4*R*)-3,4-bis(4-bromophenyl)cyclopentanone (**4h**): White Solid 60 % yield, 84 % ee, >20:1 dr., Rf: 0.21 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -78.9 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 22.1 min, minor: 20.4 min. **^{1}** (400 MHz; $CDCl_3$): δ 7.37 (d, *J* = 8.5 Hz, 4H), 6.97 (d, *J* = 8.5 Hz, 4H), 3.42-3.34 (m, 2H), 2.88-2.81 (m, 2H), 2.58-2.47 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.4, 139.3, 131.8, 128.9, 120.8, 49.8, 46.9. **IR** (ATR neat): 2917, 1743, 1489, 1402, 1188, 1139, 1073, 1009, 822. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 395.0, found 394.9



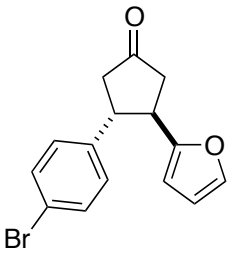
(3*R*,4*R*)-3-(4-methoxyphenyl)-4-phenylcyclopentanone (**4ac**): Off-White Amorphous Solid. 65 % yield, 85 % ee, >20:1 dr., Rf: 0.53 (7:3 hexanes:ether): $[\alpha]_D^{21}$ = -62.3 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Reverse phase Chiralpak IB column 95:5 H_2O:acetonitrile, 1.0 mL/min, Major: 21.1 min, minor: 20.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.26-7.16 (m, 3H), 7.13-7.11 (m, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 3.48-3.39 (m, 2H), 2.89-2.81 (m, 2H), 2.61-2.50 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.9, 158.4, 140.9, 132.8, 128.5, 128.1, 127.2, 126.8, 113.9, 55.2, 50.4, 49.4, 47.31, 47.23. **IR** (ATR neat): 2959, 2936, 1742, 1603, 1513, 1249, 1178, 1129, 1034. **LRMS** (ESI + APCI) *m/z* [M+H] calcd.267.1, found 267.1



(3*R*,4*R*)-3-(furan-2-yl)-4-(4-methoxyphenyl)cyclopentanone (**4ad**): Pale yellow oil. 59 % yield, 80 % ee, >20:1 dr., Rf: 0.15 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -76.4 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 99:5 hexanes/*iso*propanol, 1.0 mL/min, Major: 12.0 min, minor: 11.4 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.31 (t, *J* = 0.9 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.23 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.92 (d, *J* = 3.2 Hz, 1H), 3.78 (s, 3H), 3.58-3.45 (m, 2H), 2.83-2.76 (m, 2H), 2.66-2.59 (m, 1H), 2.53-2.46 (m, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.5, 158.5, 154.4, 141.4, 133.0, 128.0, 114.0, 110.1, 106.0, 55.2, 46.8, 46.5, 44.4, 43.6. **IR** (ATR neat): 2931, 2837, 1744, 1612, 1514, 1463, 1303, 1248, 1179, 1149, 1033, 830. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd 279.1, found 279.0

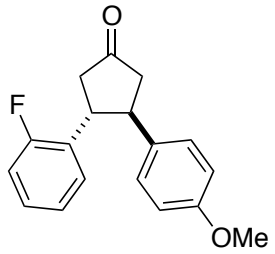


(3*R*,4*R*)-3-(4-chlorophenyl)-4-phenylcyclopentanone (**4ce**): Pale Yellow Oil. 61 % yield, 86 % ee, >20:1 dr.; Rf: 0.28 (7:3 hexanes:ether); $[\alpha]_D^{21}$ = -41.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IA column 97:3 hexanes/*iso*propanol, 1.0 mL/min, Major: 13.0 min, minor: 11.6 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.25-7.15 (m, 7H), 7.09-7.07 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 3.48-3.36 (m, 2H), 2.88-2.80 (m, 2H), 2.60-2.47 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.2, 140.4, 139.2, 132.6, 128.69, 128.64, 128.52, 127.16, 127.05, 50.3, 49.7, 47.16, 47.01. **IR** (ATR neat): 3029, 2914, 1744, 1492, 1402, 1190, 1136, 1091, 1013, 765, 699. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 271.1, found 271.1

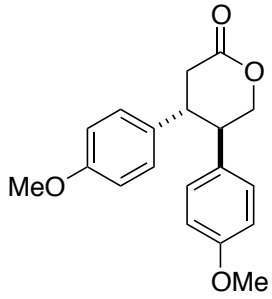


(3*R*,4*R*)-3-(4-bromophenyl)-4-(furan-2-yl)cyclopentanone (**4dh**):Pale Pink Amorphous Solid. 56 % yield, 75 % ee, >20:1 dr., Rf: 0.36 (1:1 hexanes:ether); $[\alpha]_D^{21}$ = -82.2 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 10.7 min, minor: 10.2 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.31 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.92 (d, *J* = 3.2 Hz, 1H), 3.59-3.45 (m, 2H), 2.84-2.77 (m, 2H), 2.65 (ddd, *J* = 18.6, 10.8, 1.5 Hz, 1H), 2.49 (ddd, *J* = 18.6, 11.3, 1.6 Hz, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.6, 153.7, 141.7, 139.9, 131.7, 128.8, 120.8,

110.2, 106.3, 47.2, 46.1, 44.3, 43.4. **IR** (ATR neat): 2920, 2745, 1489, 1402, 1191, 1148, 1073, 1010, 823,737. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 305.0, found 305.0

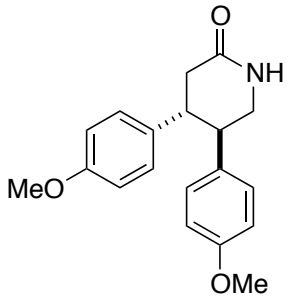


(3*R*,4*R*)-3-(2-fluorophenyl)-4-(4-methoxyphenyl)cyclopentanone (**4ag**): Off-White Amorphous Solid. 60 % yield, 82 % ee, >20:1 dr., Rf: 0.41 (7:3 hexanes:ether): $[\alpha]_D^{21}$ = -56.1 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralcel OB-H column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 32.5 min, minor: 46.7 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.17 (tdd, *J* = 10.1, 5.3, 2.5 Hz, 2H), 7.10-6.94 (m, 4H), 6.78 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 3.71 (dt, *J* = 11.3, 5.6 Hz, 1H), 3.60 (ddd, *J* = 16.7, 11.1, 5.4 Hz, 1H), 2.84 (dt, *J* = 18.1, 9.0 Hz, 2H), 2.60-2.48 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 215.7, 159.9, 158.4, 132.6, 130.3, 128.45, 128.41, 128.35, 128.26, 127.97, 127.82, 124.28, 124.24, 115.8, 115.5, 114.5, 113.9, 55.2, 47.37, 47.19, 45.90, 45.88, 43.7. **IR** (ATR neat): 2926, 1743, 1672, 1602, 1513, 1492, 1456, 1305, 1248, 1228, 1179, 1136, 1033, 829, 758. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd. 307.1, found 307.1



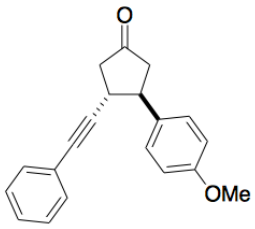
(4*R*,5*R*)-4,5-bis(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-one (**8**): To a flame dried vial charged with a magnetic stirbar was added (3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone **4a** (47 mg, 0.16 mmol) and 1.0 mL dichloromethane and cooled to 0 °C in an ice water bath. Then mCPBA (102 mg, 0.416 mmol) and trifluoroacetic acid (12 μL, 0.16 mmol) were added and the vial was sealed with a cap. The reaction was then allowed to warm to room temperature over the course of an hour and then stirred for an additional hour at room temperature. Upon completion, the reaction was diluted with an additional 3 mL of dichloromethane and quenched with 3 mL saturated sodium bicarbonate. The organic layer was then separated in a separatory funnel and the sodium bicarbonate was extracted with an additional 3 mL dichloromethane. The organic layers were then combined and washed 2x with 6 mL brine, dried over sodium sulfate and concentrated via rotary evaporation. The crude residue was then purified via column chromatography (3:1 ether:hexanes) to yield 44 mg (89 %) (4*R*,5*R*)-4,5-bis(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-one as a colorless oil in 84 % ee, and as a single diastereomer. Rf: 0.35 (3:1 ether:hexanes). $[\alpha]_D^{21}$ = -48.5 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 70:30 hexanes/*iso*propanol, 1.0 mL/min, Major: 18.0 min, minor: 16.9 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.03-6.97 (m, 4H), 6.77-6.74 (m, 4H), 4.46 (dd, *J* = 11.5, 5.0 Hz, 1H), 4.36 (dd, *J* = 11.5, 10.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.35 (td, *J* = 10.2, 6.4 Hz, 1H), 3.22 (td, *J* = 10.4, 5.0

Hz, 1H), 3.01 (dd, *J* = 17.7, 6.4 Hz, 1H), 2.74 (dd, *J* = 17.7, 9.8 Hz, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 170.9, 158.7, 158.4, 133.8, 130.0, 128.8, 128.1, 114.14, 114.10, 73.2, 55.2, 46.1, 43.4, 37.9. **IR** (ATR neat): 2956, 2933, 2909, 2836, 1734, 1611, 1513, 1464, 1248, 1179, 1032, 830. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 313.1, found 313.2

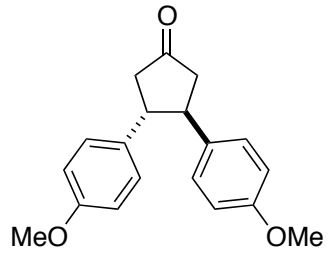


(4*R*,5*R*)-4,5-bis(4-methoxyphenyl)piperidin-2-one (**9**):
To a flame dried vial charged with a magnetic stir bar was added (3*R*,4*R*)-3,4-bis(4-methoxyphenyl)cyclopentanone **4a** (65 mg, 0.22 mmol), hydroxylamine hydrochloride (23 mg, 0.33 mmol), NaOAc (36 mg, 0.44 mmol), and 5 mL MeOH. The cap was screwed on and the reaction was allowed to stir at room temperature for 6 hours at room temperature. After 6 hours, the mixture was concentrated via rotary evaporation and the crude residue was dissolved in 10 mL $CHCl_3$. The resulting solution was washed with H_2O and brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude oxime was used in the next step without further purification. The crude oxime from the previous step was then dissolved in 10 mL dichloromethane and added *p*-bromobenzenesulfonyl chloride (84 mg, 0.33 mmol), Et_3N (51 μL, 0.37 mmol), and a catalytic amound of DMAP. The reaction was stirred at room temperature for 1 hour then concentrated via rotary evaporation. The residue was then dissolved in 5 mL AcOH and stirred at room temperature for 1 hour. After 1 hour, the reaction was quenched with saturated, aqueous $NaHCO_3$. The mixture was extracted 2x with dichloromethane and the organic layers were combined and washed with brine. The solution was then dried with sodium sulfate and concentrated via rotary evaporation. The residue was purified via column chromatography (1:1 hexanes:EtOAc to 100 EtOAc) to yield 51 mg (75 %, over two-steps) (4*R*,5*R*)-4,5-bis(4-methoxyphenyl)piperidin-2-one as an off-white amorphous solid in 84 % ee and as a single diastereomer. Rf: 0.22 (100 % ethyl acetate); $[\alpha]_D^{21}$ = -92.8 (c = 0.010 g/ml, CH_2Cl_2); **HPLC analysis**: Chiralpak IB column 90:10 hexanes/*iso*propanol, 1.0 mL/min, Major: 56.4 min, minor: 63.9 min. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.01-6.95 (m, 4H), 6.70 (d, *J* = 8.0 Hz, 4H), 6.57 (bs, 1H), 3.70 (s, 6H), 3.52-3.42 (m, 2H), 3.30-3.24 (m, 1H), 3.20-3.14 (m, 1H), 2.77-2.71 (m, 1H), 2.63-2.55 (m, 1H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 158.2, 158.0, 134.2, 132.0, 128.8, 128.2, 113.85, 113.82, 55.1, 48.8, 45.2, 43.8, 39.96, 39.94. **IR** (ATR neat): 3217, 2953, 2932, 2909, 2835, 1663, 1611, 1512, 1246, 1178, 1033, 828. **LRMS** (ESI + APCI) *m/z* [M+H] calcd. 312.2, found 312.2[2]

[2] White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871.



trans-3-(4-methoxyphenyl)-4-(phenylethynyl)cyclopentan-1-one (**S1**) Prepared according to the standard procedure for the synthesis of unsymmetrical cyclopentanones using catalyst **3a**. 48 % yield, >20:1 dr., Rf = 0.27 (6:4 hexanes:ether), **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.36-7.26 (m, 7H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.50-3.42 (m, 1H), 3.19 (td, *J* = 10.5, 7.6 Hz, 1H), 2.89-2.74 (m, 2H), 2.57-2.43 (m, 2H). **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 214.8, 158.8, 132.4, 131.6, 128.20, 128.07, 128.01, 114.1, 89.6, 83.1, 55.3, 48.2, 45.6, 45.3, 36.5. **IR** (ATR neat): 2915, 1746, 1514, 1490, 1442, 1249, 1180, 1033, 757. **LRMS** (ESI + APCI) *m/z* [M+Na] calcd. 313.1, found 313.2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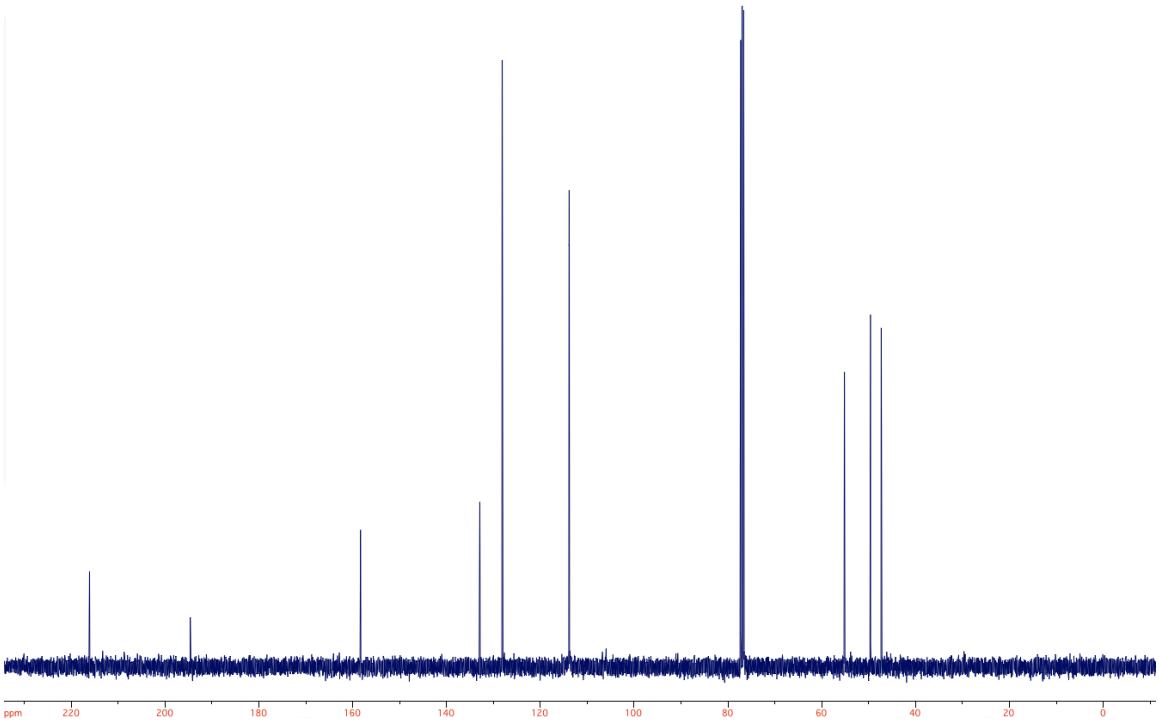
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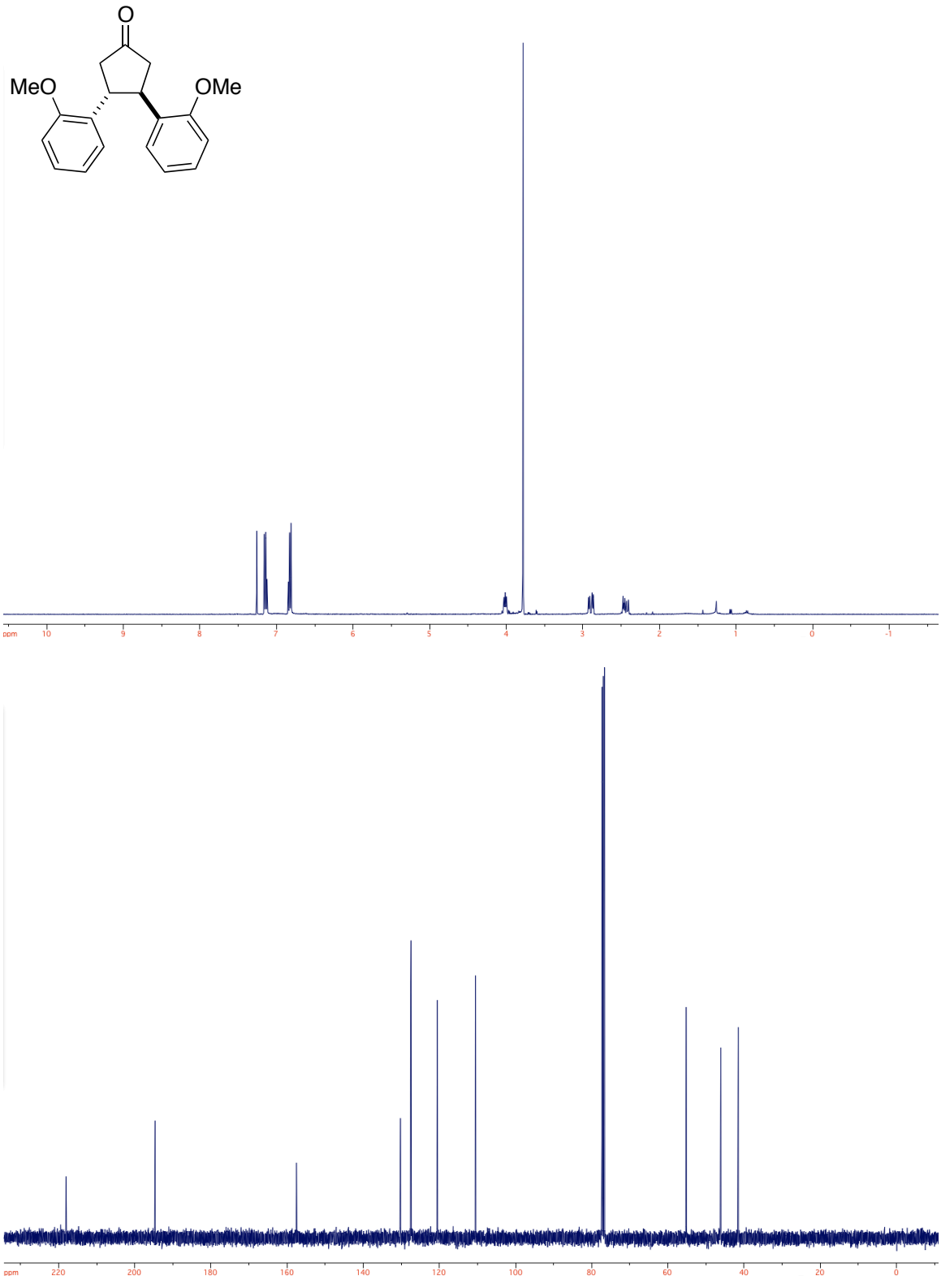
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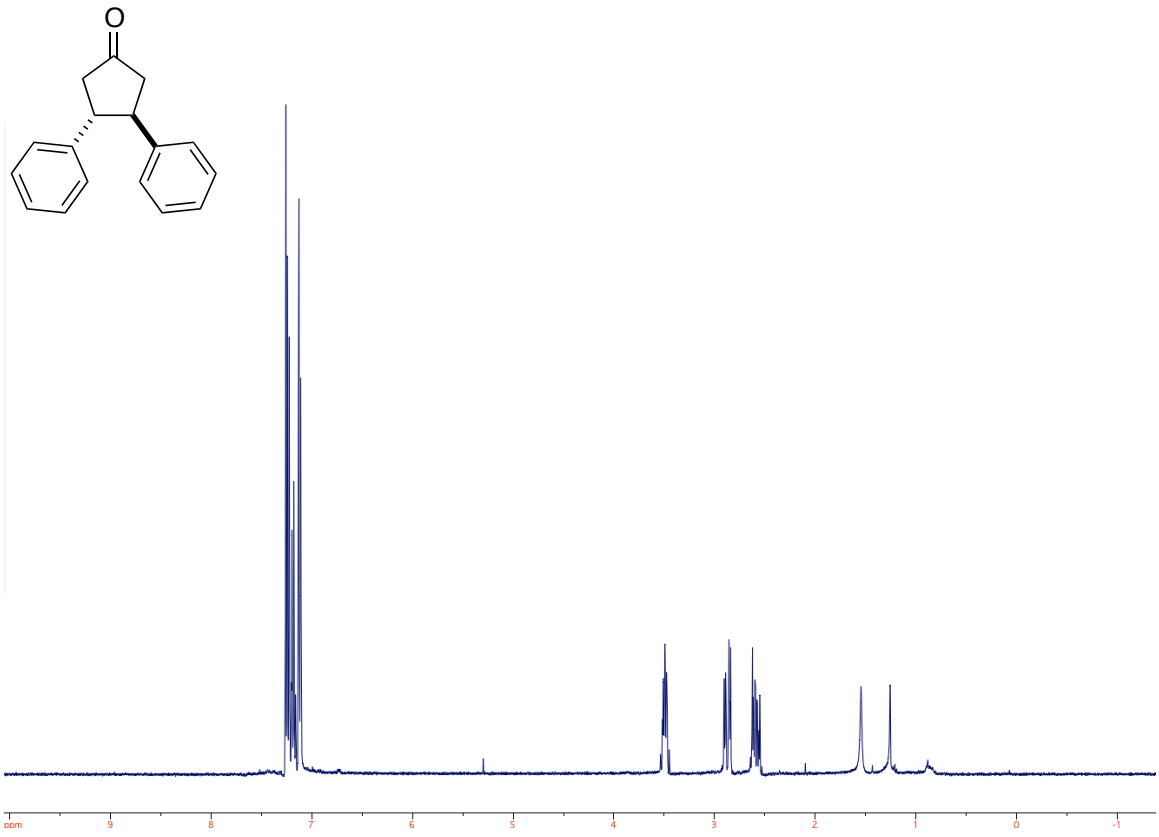
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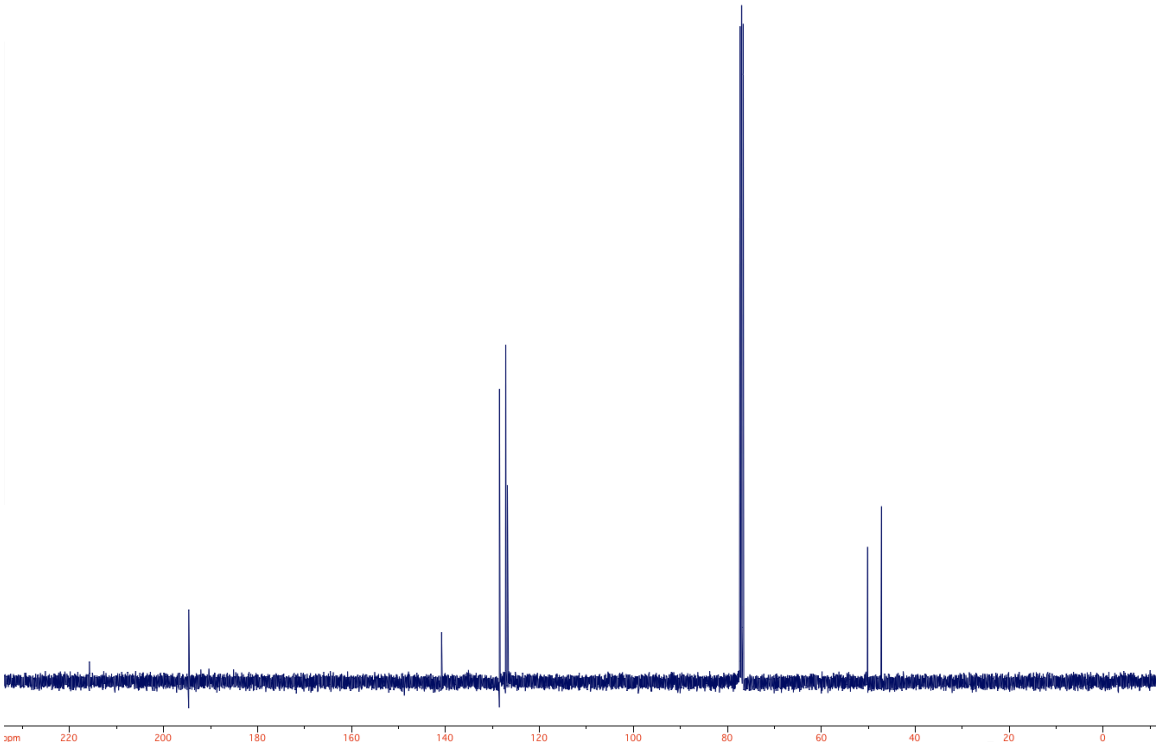
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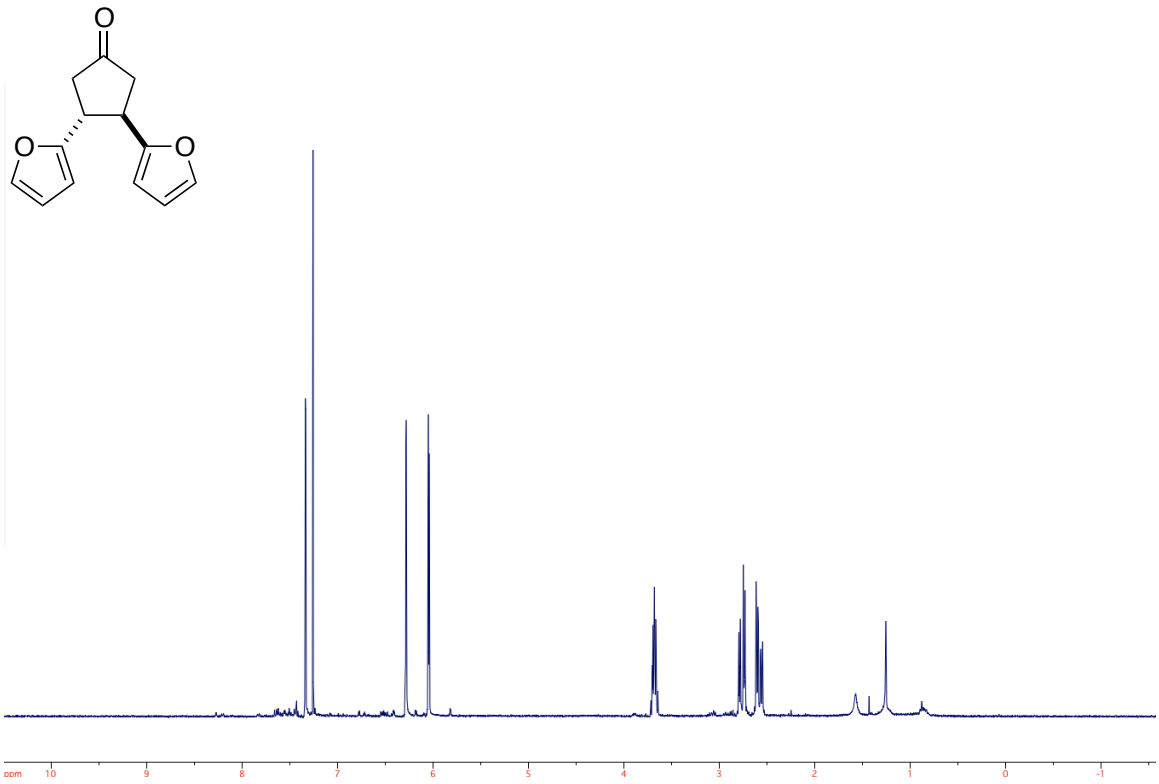
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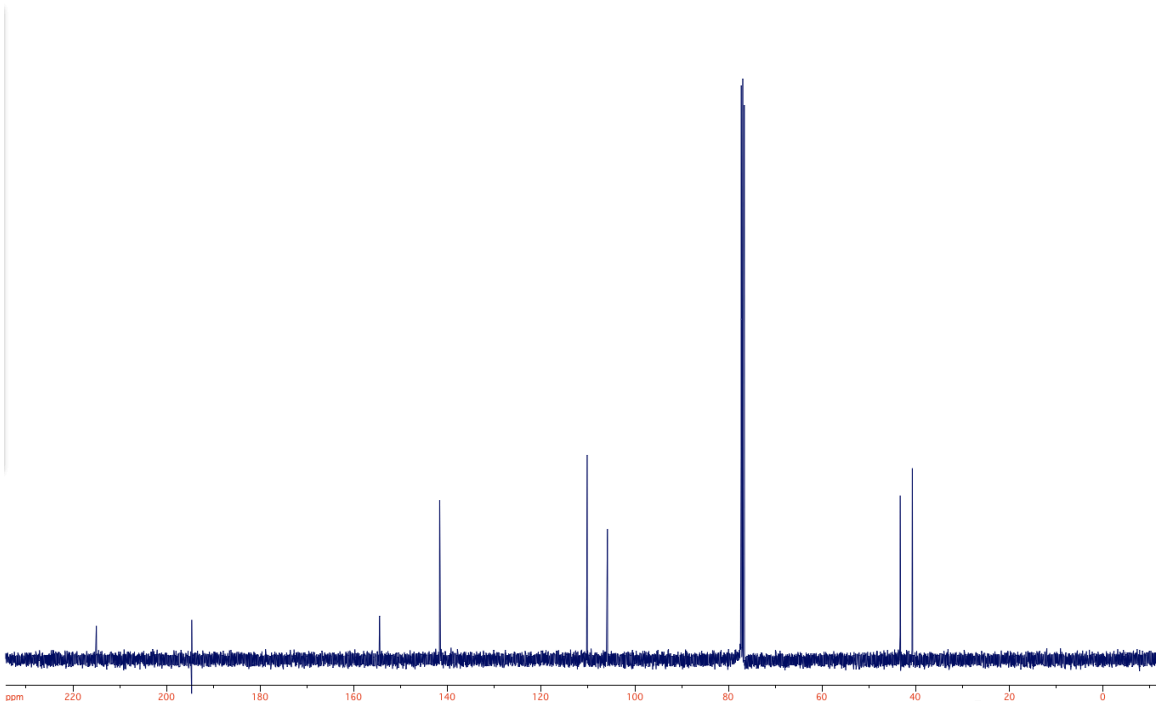
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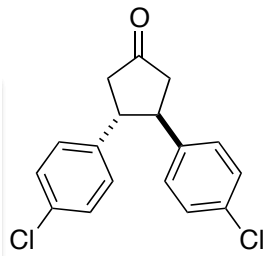
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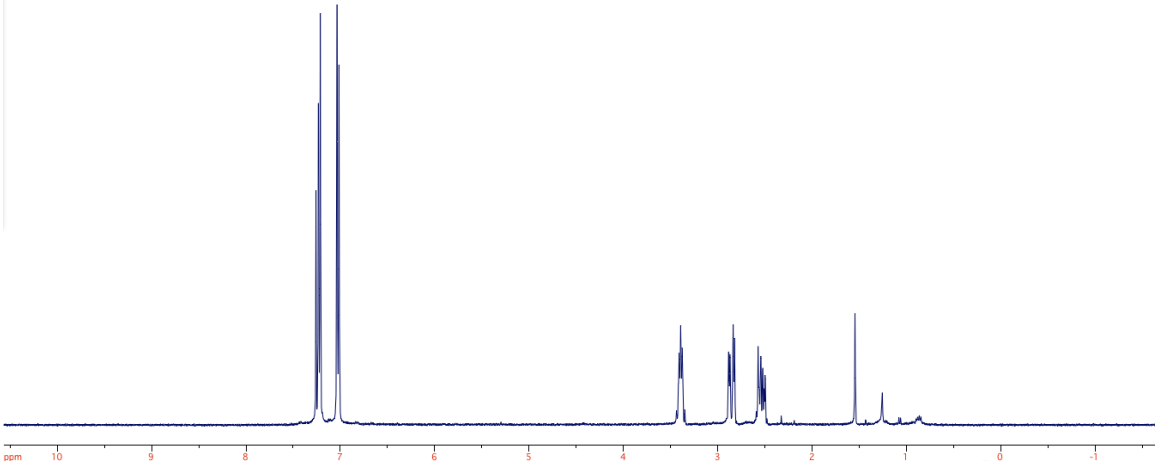
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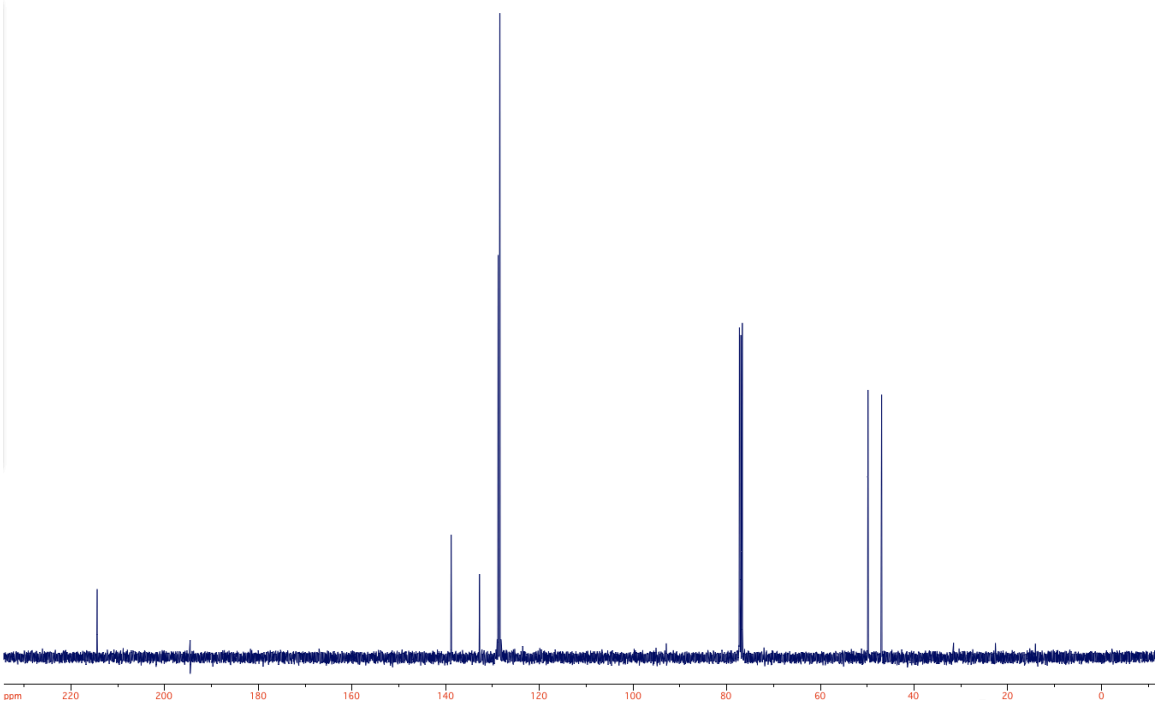
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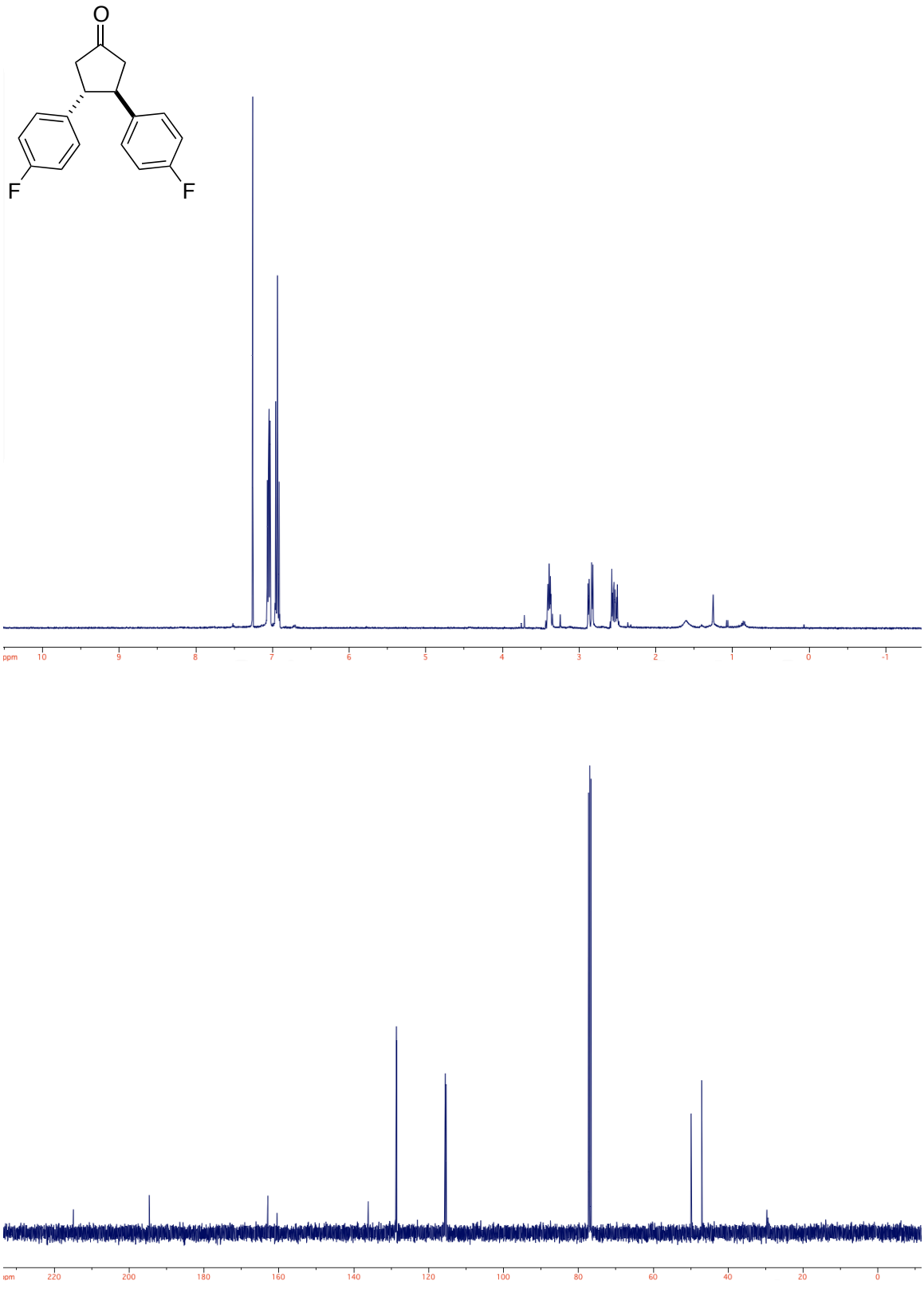
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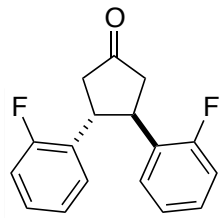
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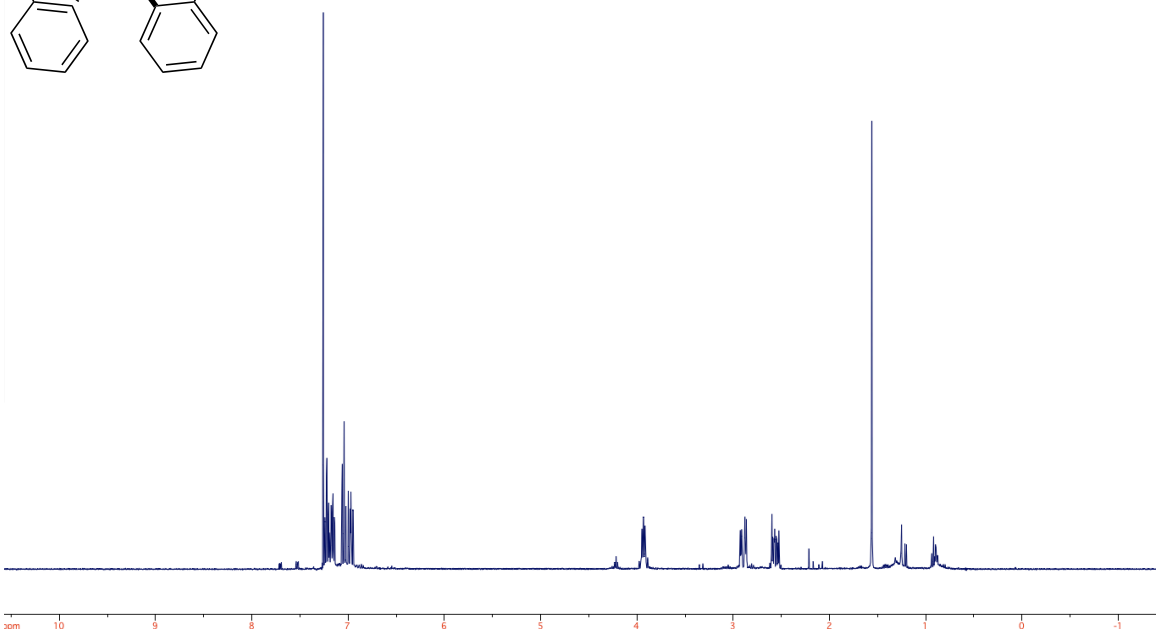
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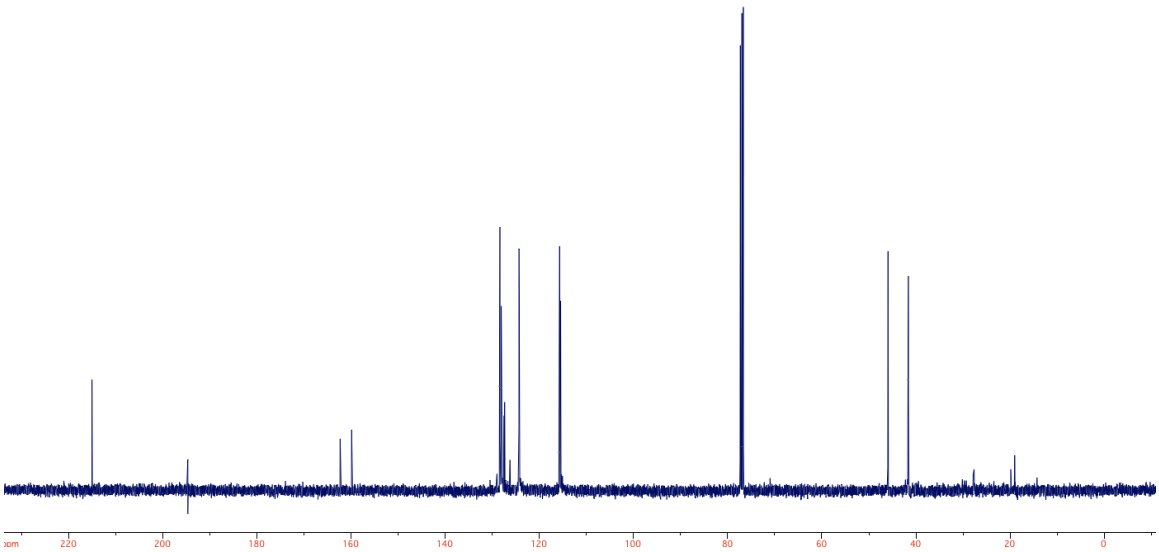
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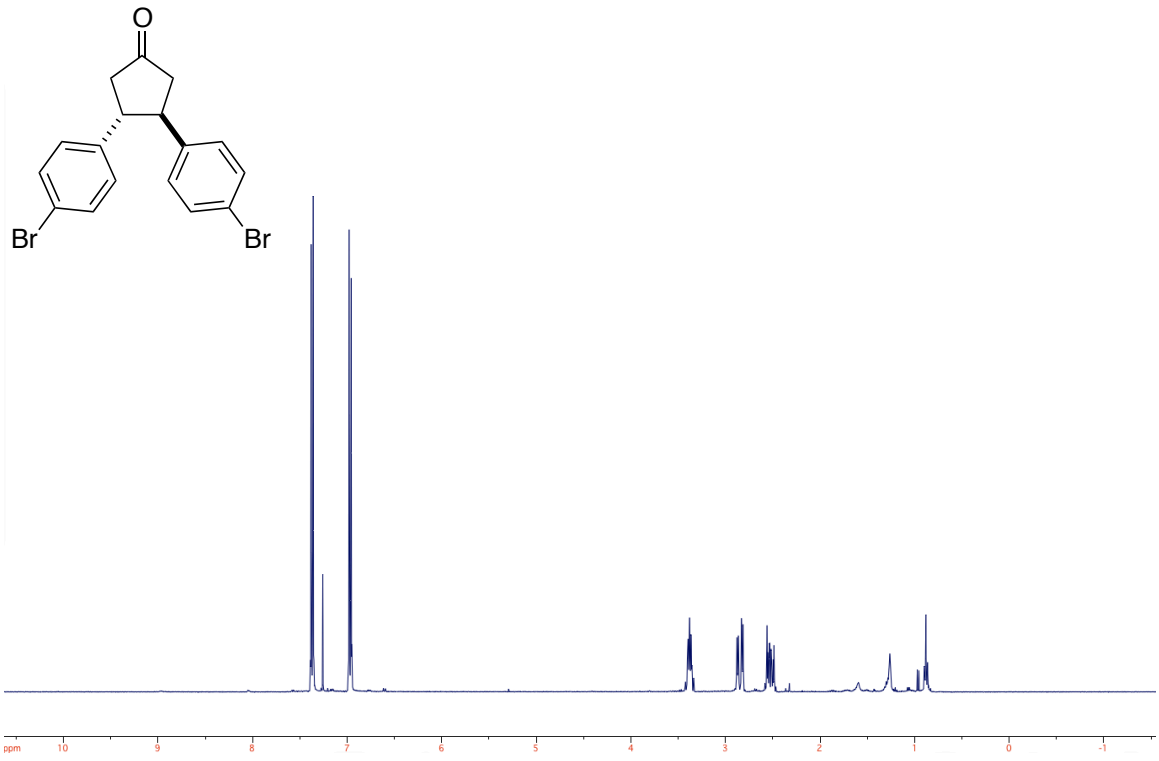
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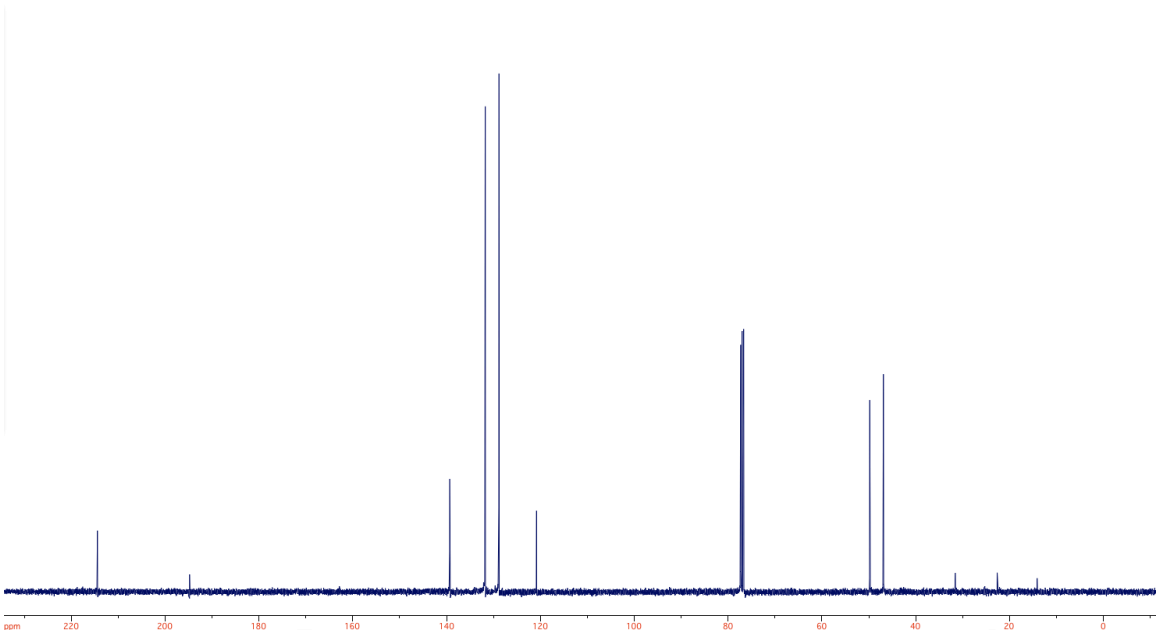
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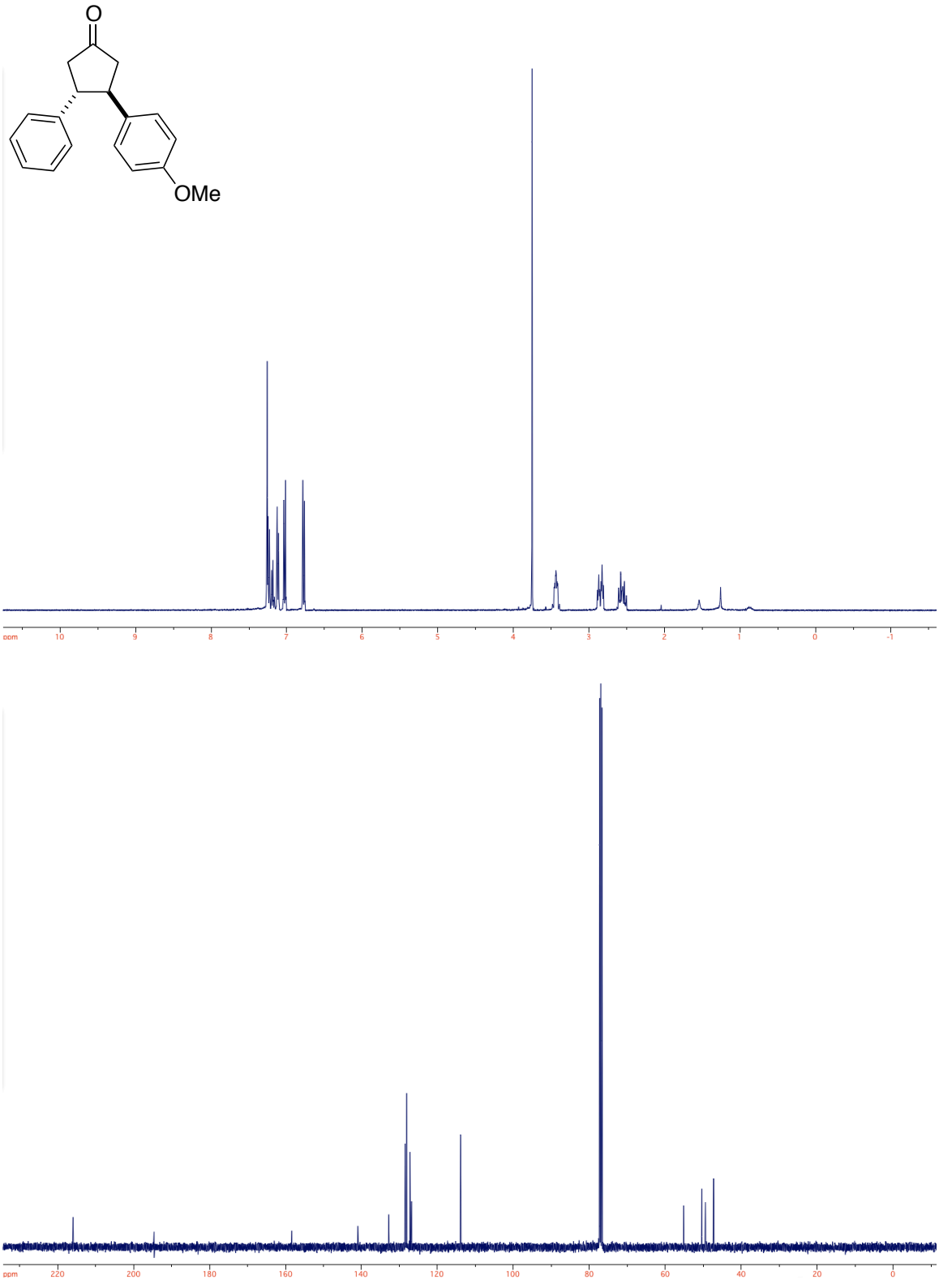
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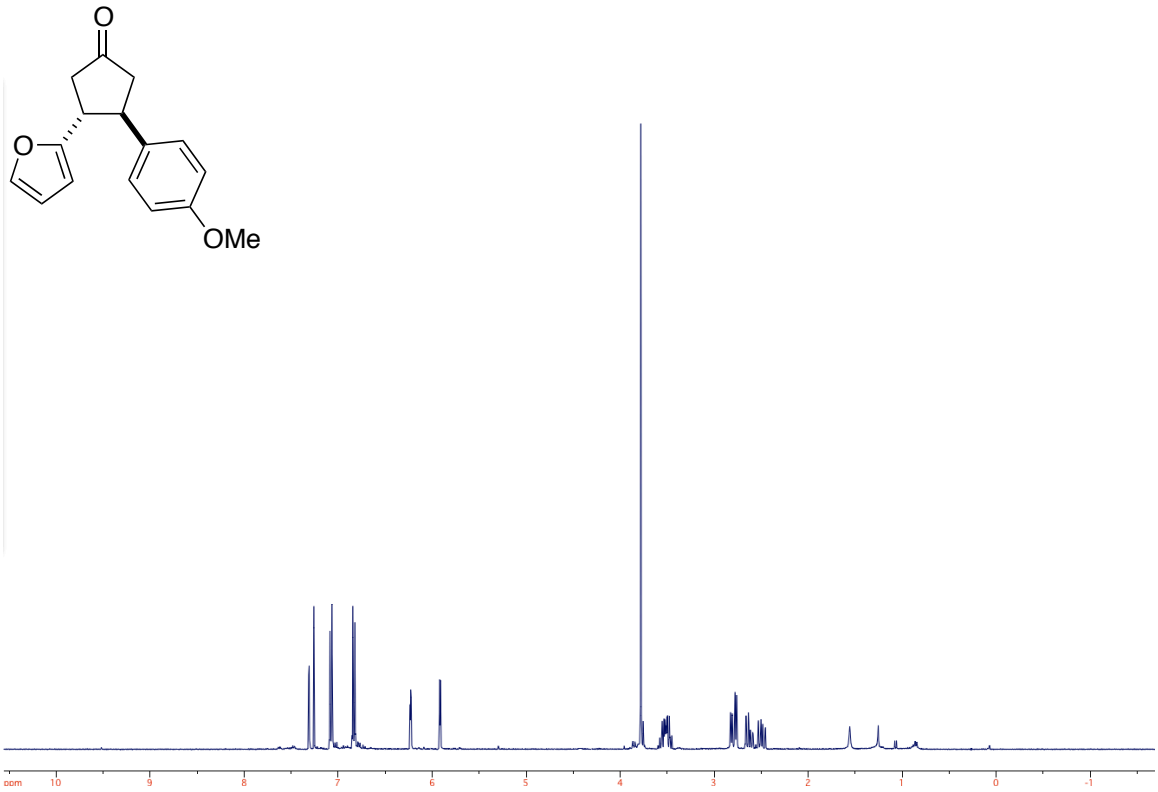
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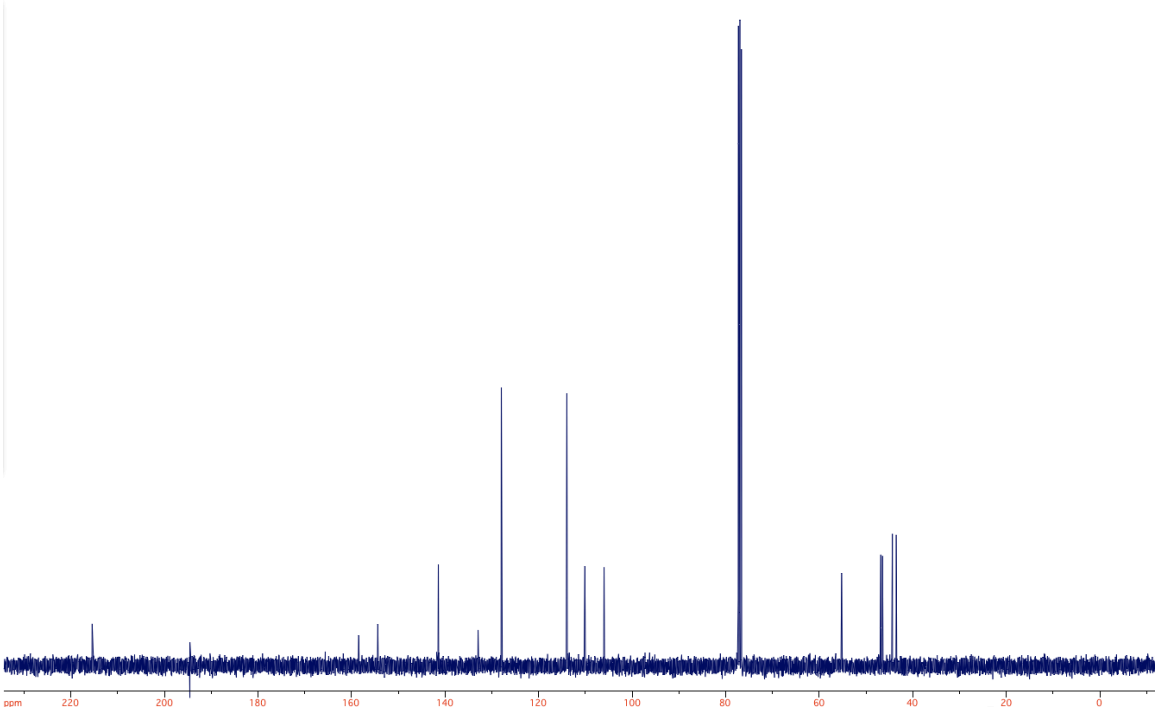
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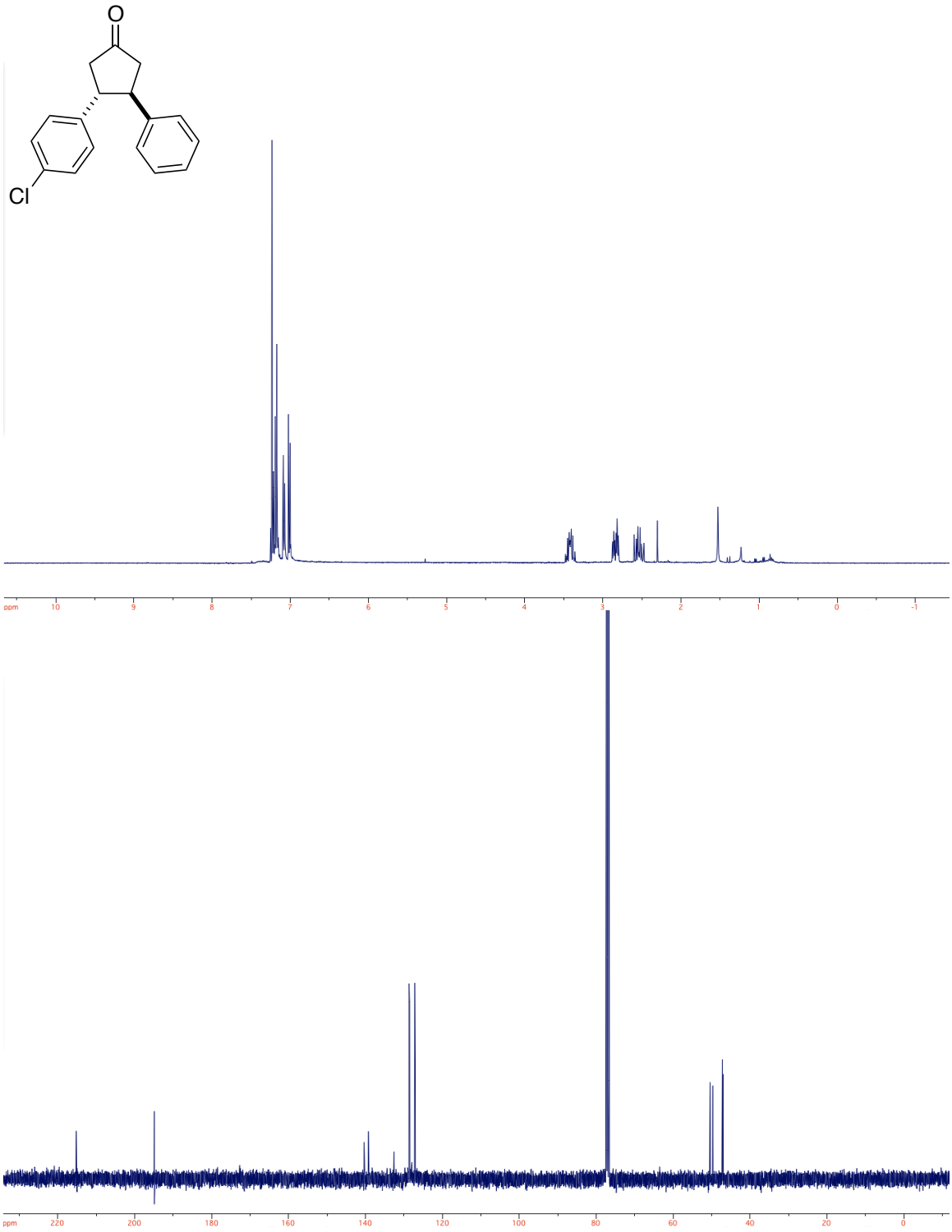
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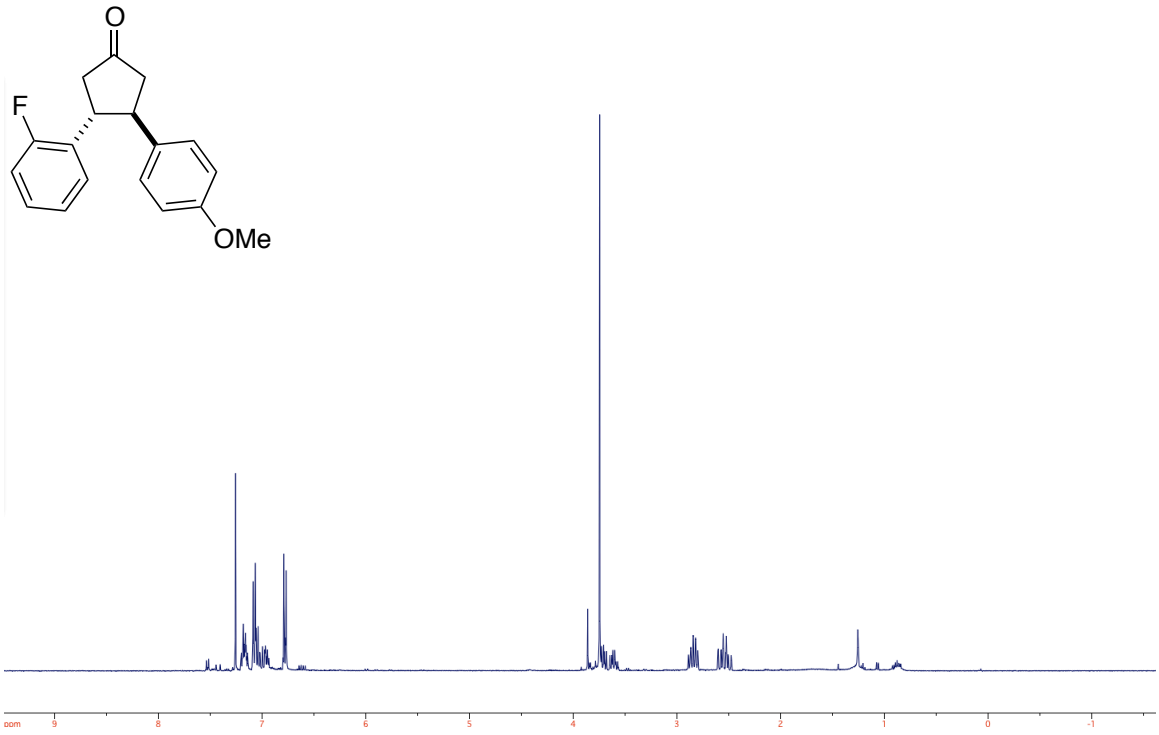
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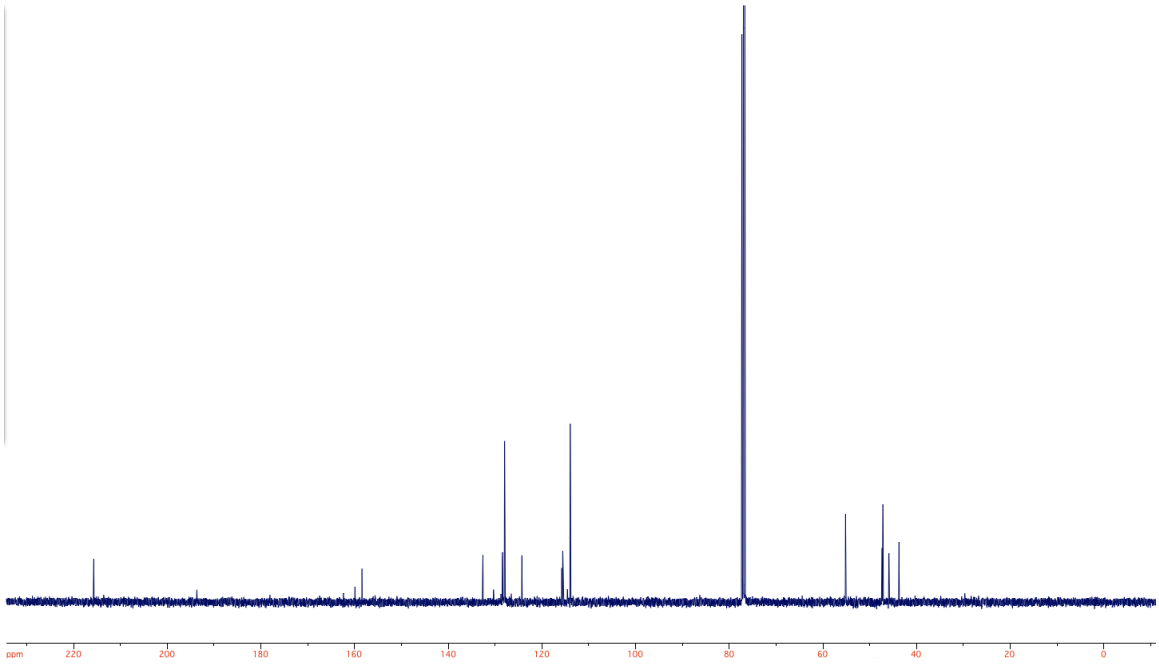
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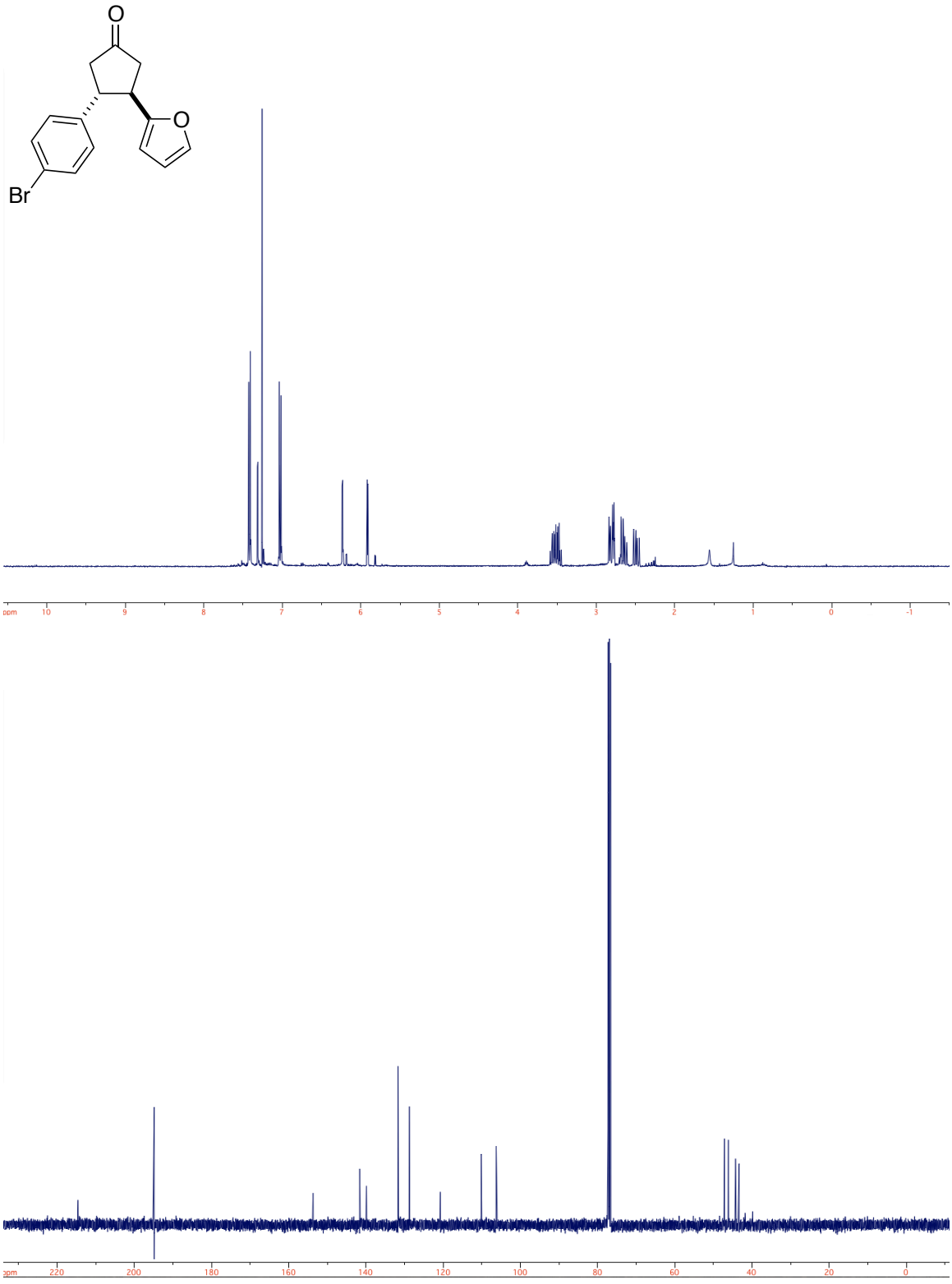
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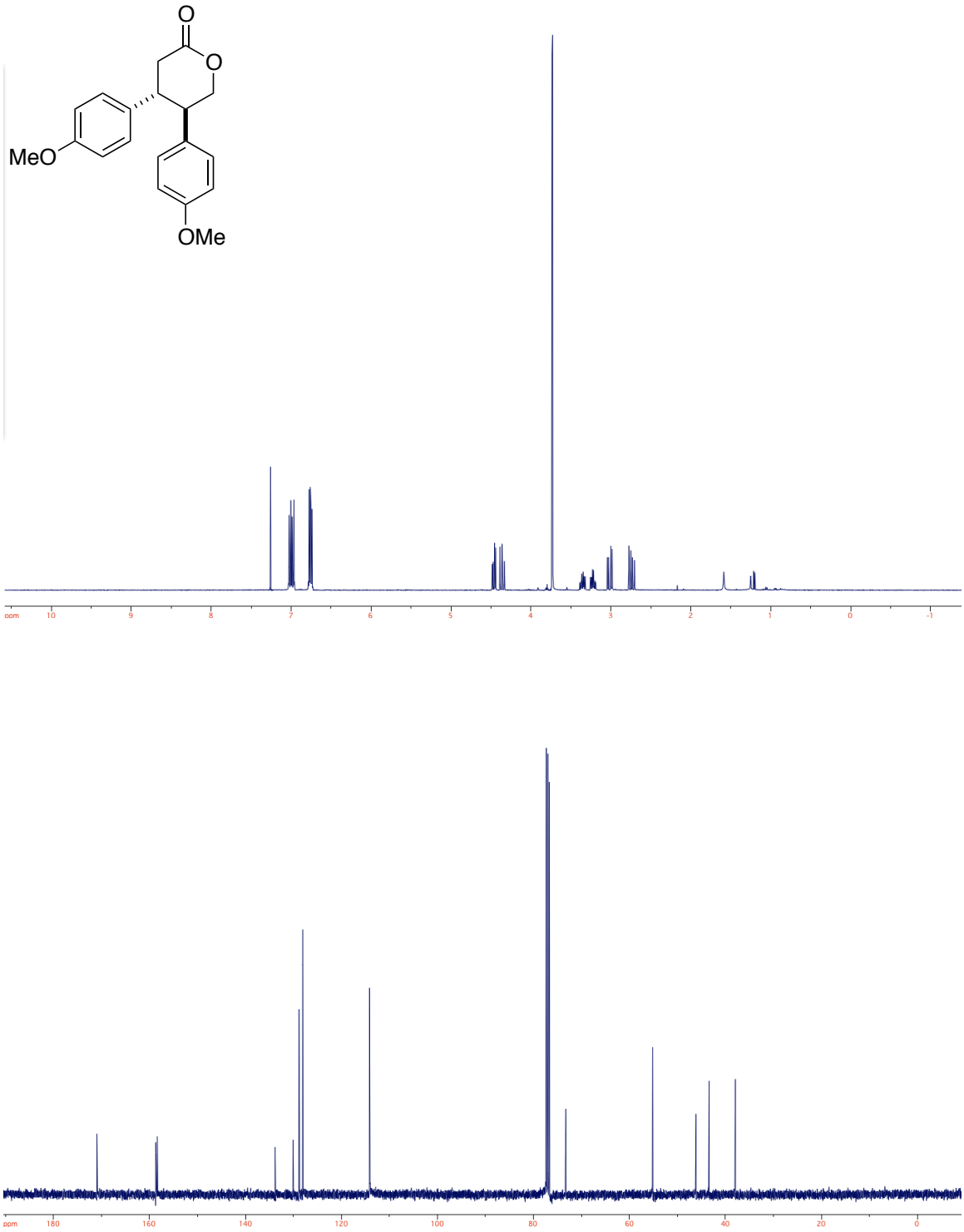
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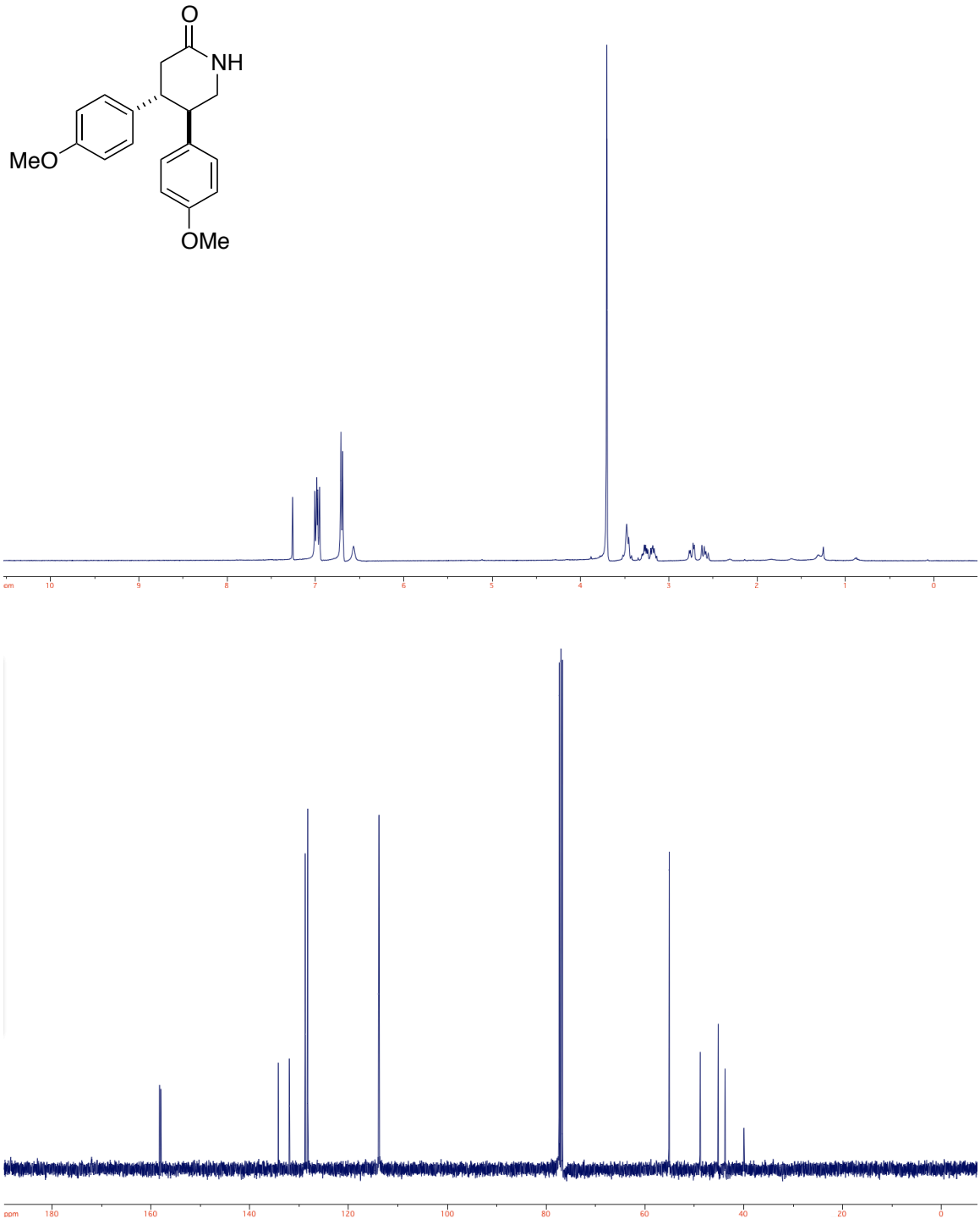
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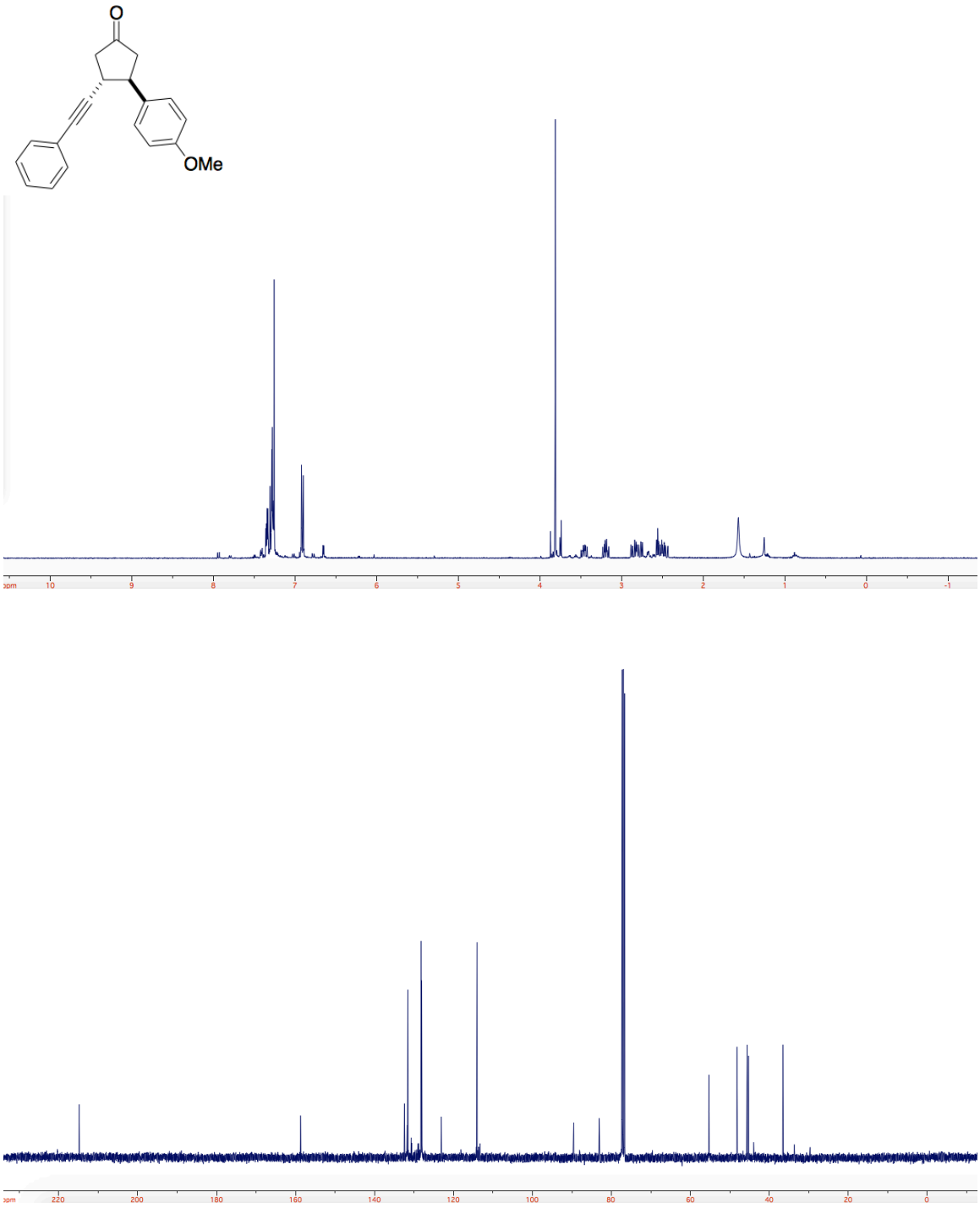
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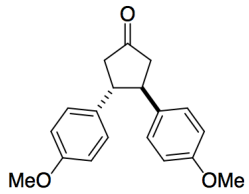
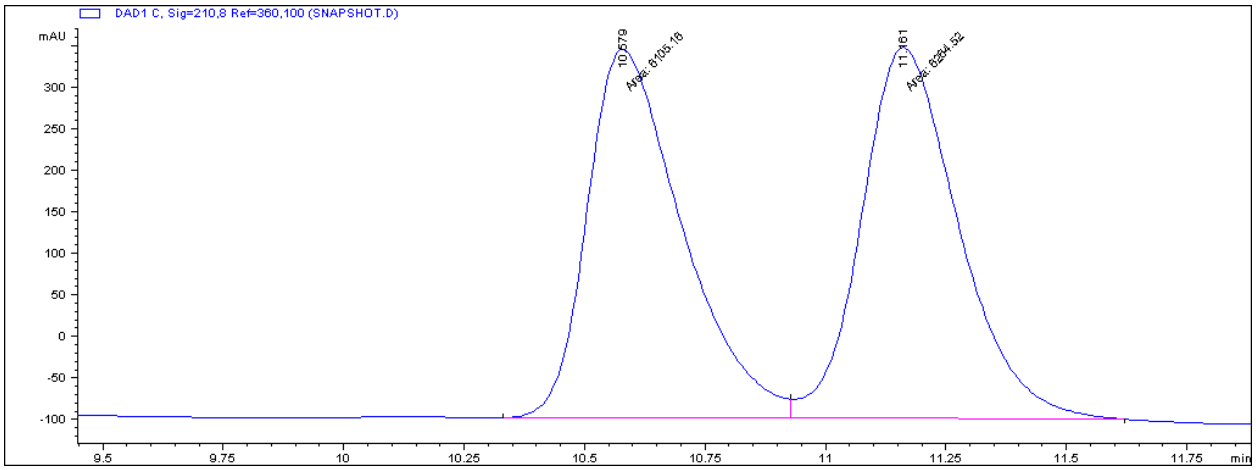
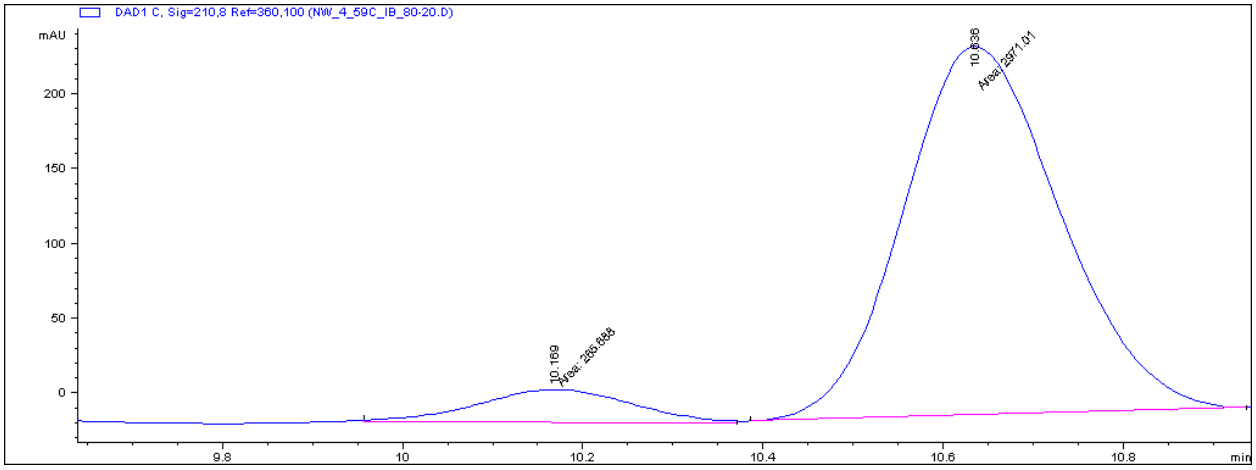


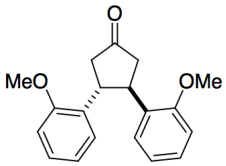


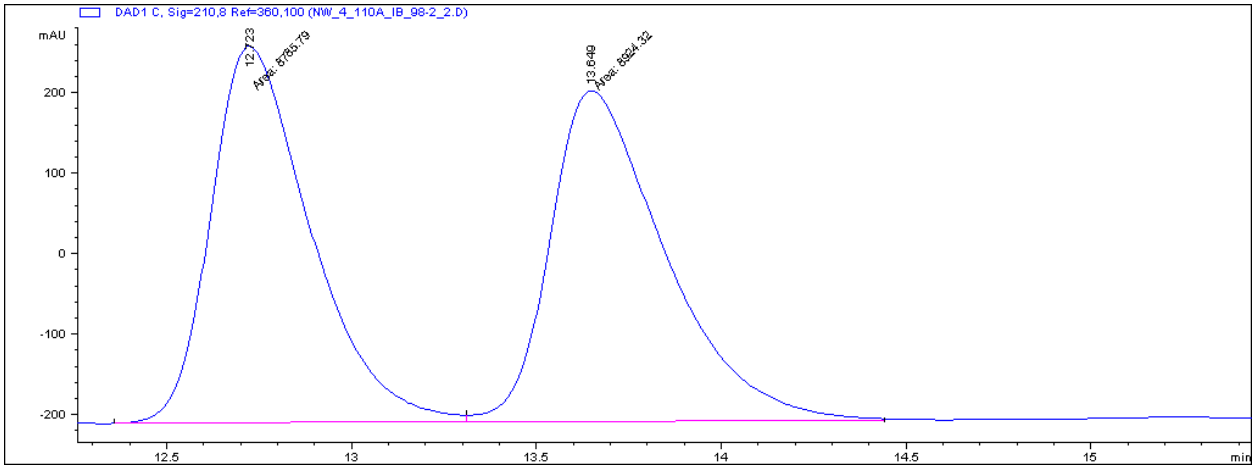
#	Time	Area	Height	Width	Area%	Symmetry
1	10.579	6105.2	447.2	0.2275	49.356	0.537
2	11.161	6264.5	448.9	0.2326	50.644	0.727



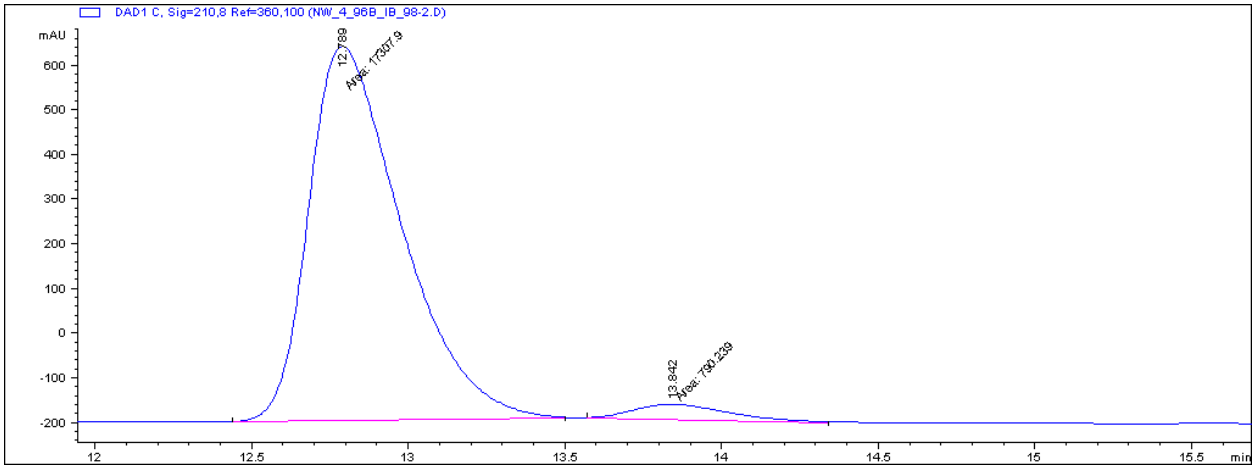
	Time	Area	Height	Width	Area%	Symmetry

#	Time	Area	Height	Width	Area%	Symmetry
1	10.169	265.7	22.2	0.1997	8.209	1.073
2	10.636	2971	247.9	0.1997	91.791	0.742

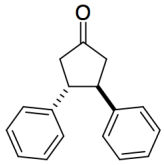


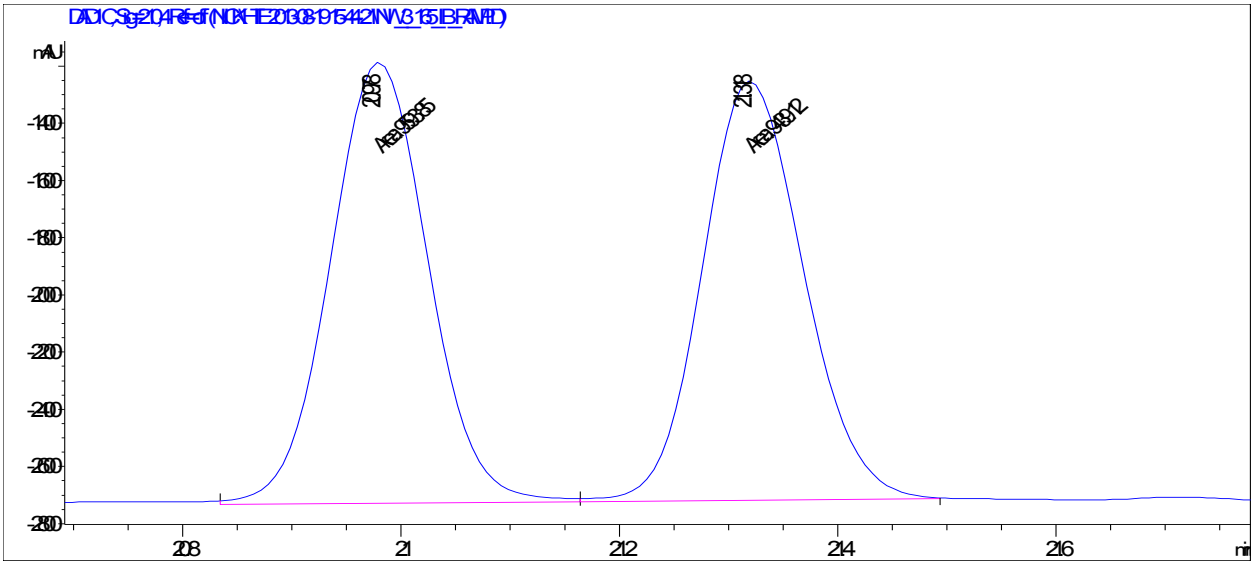


#	Time	Area	Height	Width	Area%	Symmetry
1	12.723	8785.8	468.2	0.3127	49.609	0.683
2	13.649	8924.3	412.4	0.3606	50.391	0.511

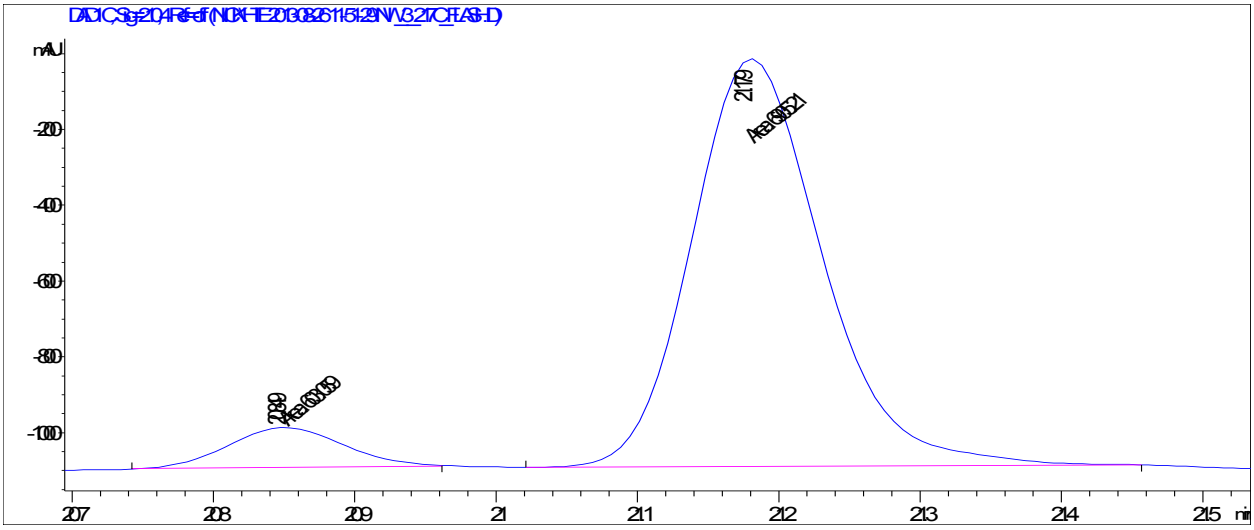


#	Time	Area	Height	Width	Area%	Symmetry
1	12.789	17307.9	839.6	0.3436	95.634	0.563
2	13.842	790.2	35.2	0.3737	4.366	0.612

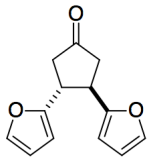


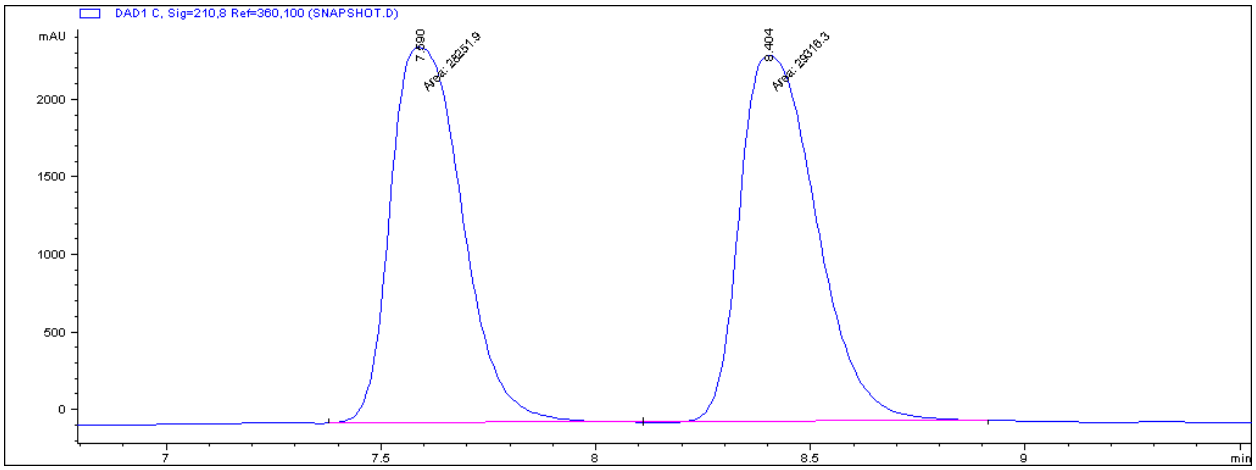


#	Time	Area	Height	Width	Area%	Symmetry
1	20.978	9593.9	1542.9	0.1036	50.406	0.952
2	21.318	9439.1	1466.8	0.1073	49.594	0.861

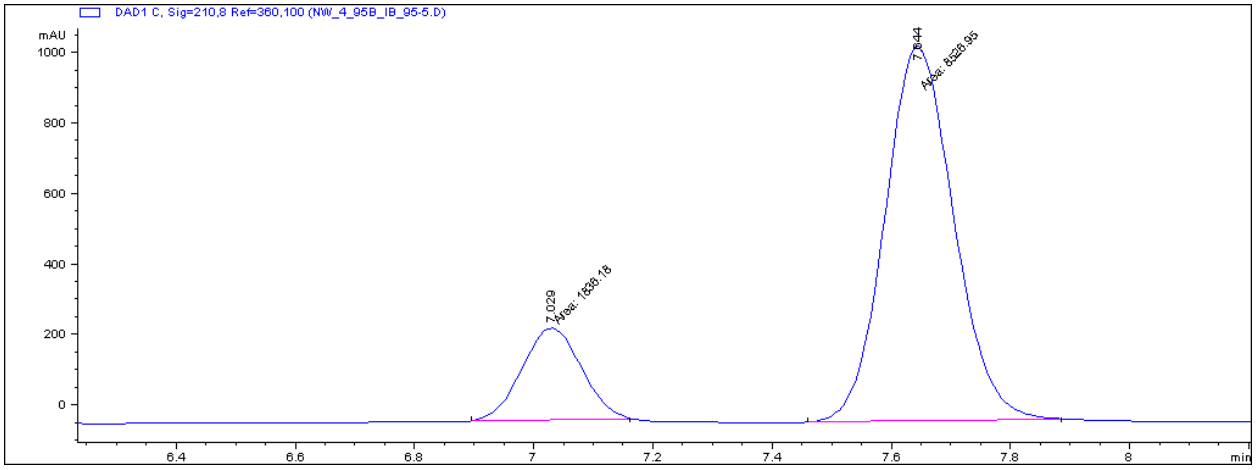


#	Time	Area	Height	Width	Area%	Symmetry
1	20.849	603.1	105.9	0.0949	8.032	0.939
2	21.179	6905.2	1076.5	0.1069	91.968	0.82

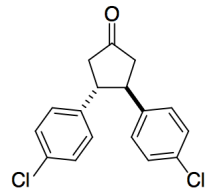


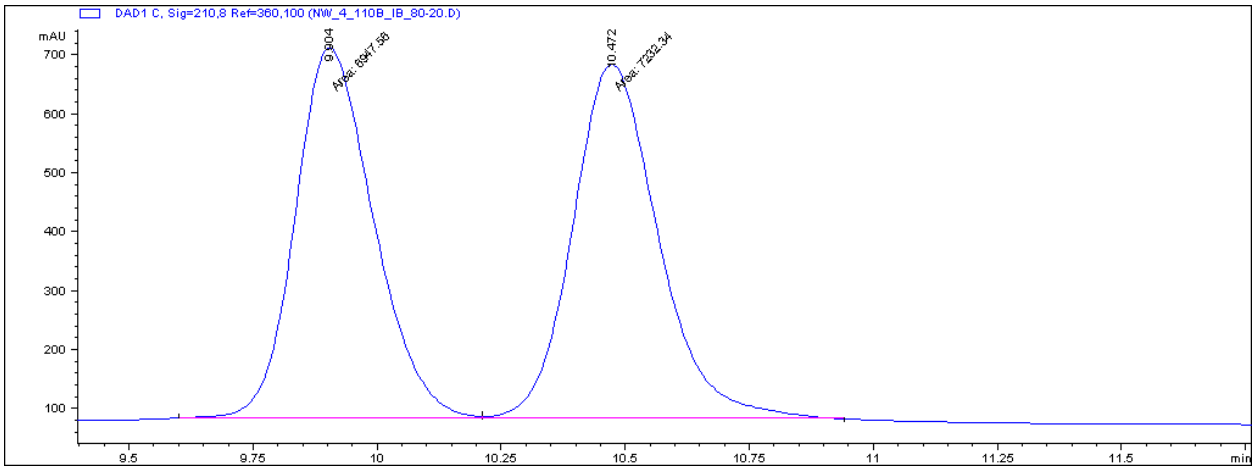


#	Time	Area	Height	Width	Area%	Symmetry
1	7.59	28251.9	2427.9	0.1939	49.076	0.71
2	8.404	29316.3	2380.4	0.2053	50.924	0.521

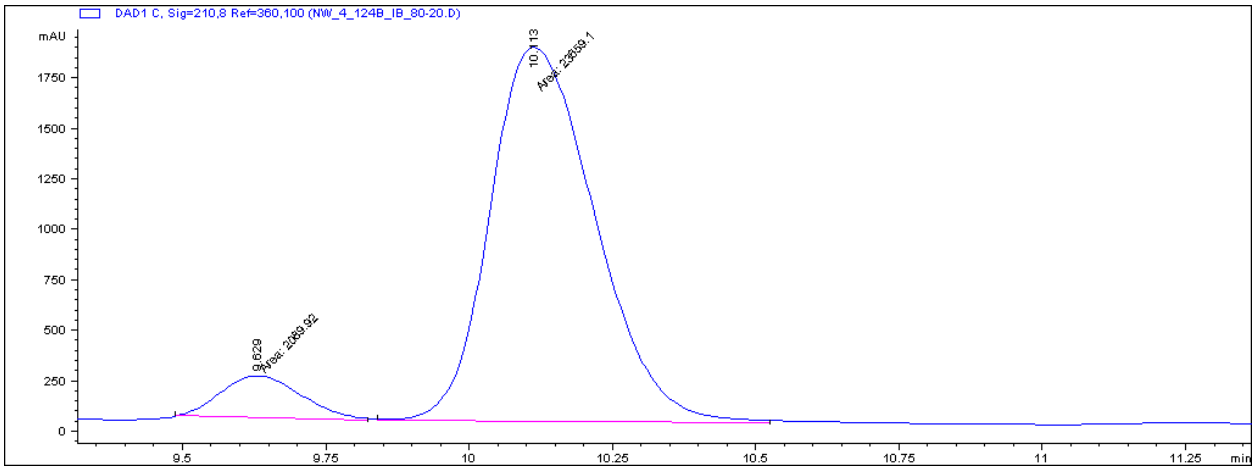


#	Time	Area	Height	Width	Area%	Symmetry
1	7.029	1836.2	265.5	0.1152	17.718	1.005
2	7.644	8527	1069.9	0.1328	82.282	1.054

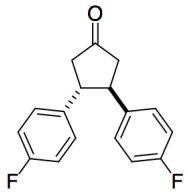


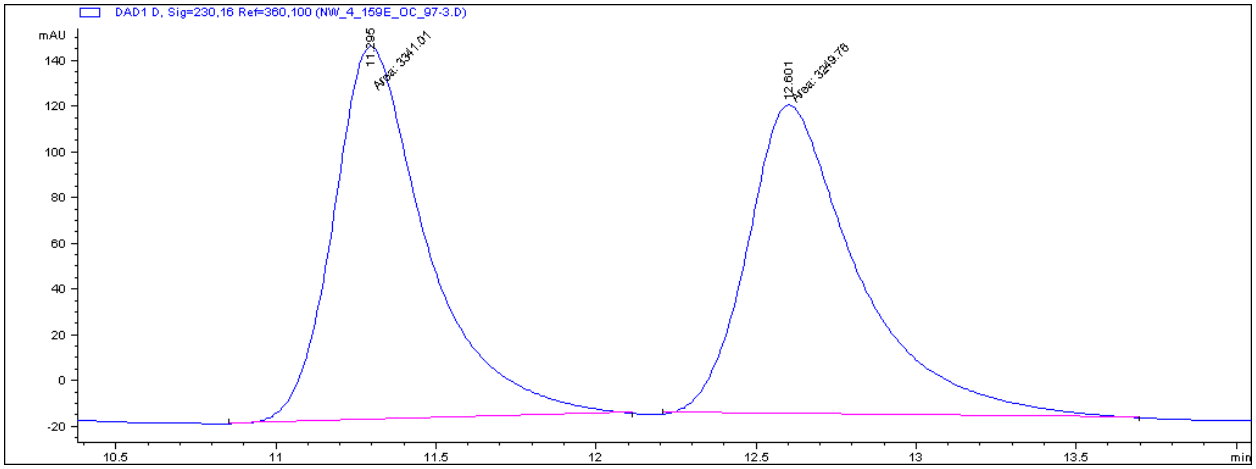


#	Time	Area	Height	Width	Area%	Symmetry
1	9.904	6947.6	634.3	0.1826	48.996	0.695
2	10.472	7232.3	603.6	0.1997	51.004	0.971

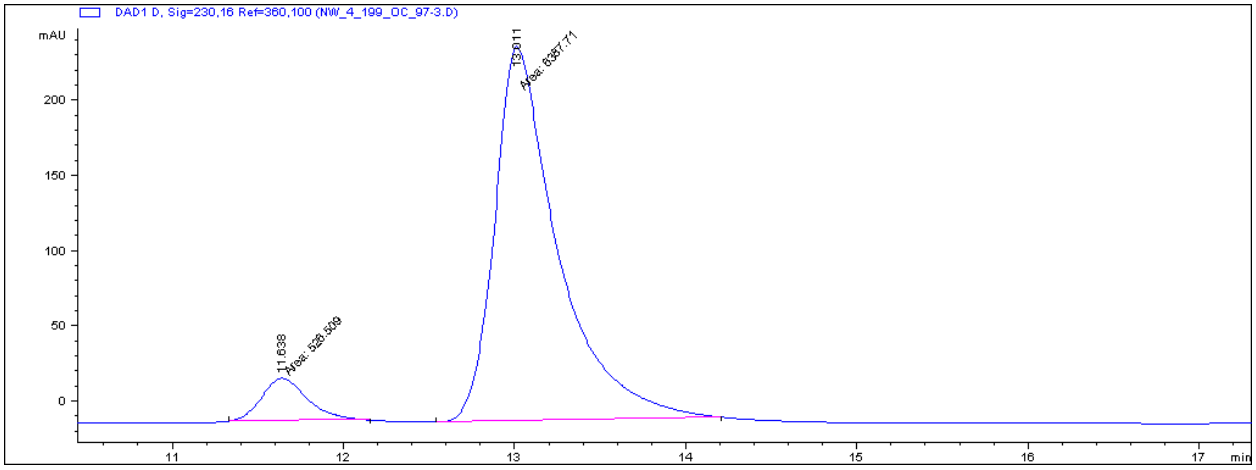


#	Time	Area	Height	Width	Area%	Symmetry
1	9.629	2089.9	211.2	0.165	8.117	0.704
2	10.113	23659.1	1861.2	0.2119	91.883	0.693

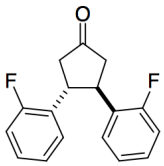


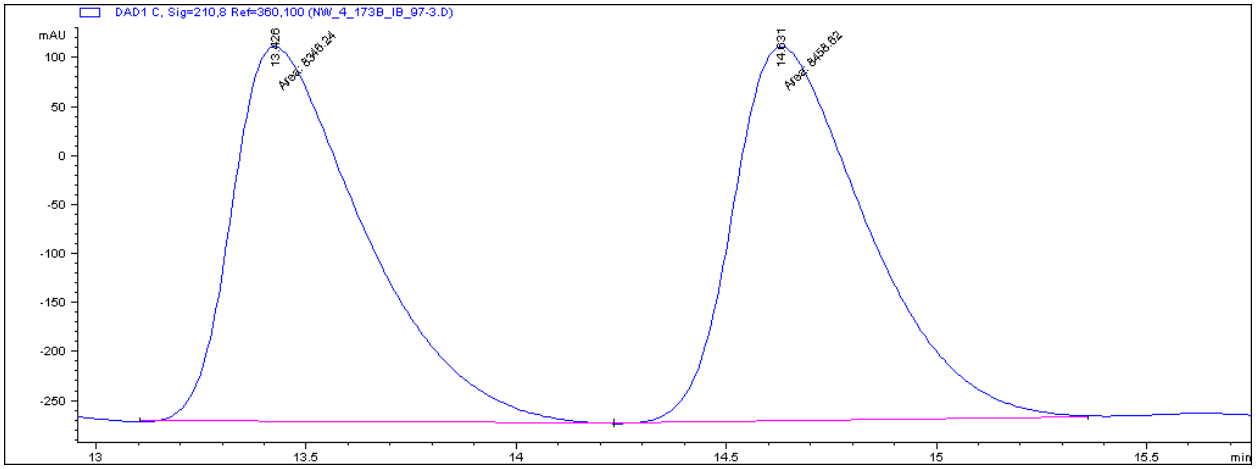


#	Time	Area	Height	Width	Area%	Symmetry
1	11.295	3341	163.5	0.3406	50.692	0.642
2	12.601	3249.8	135.3	0.4003	49.308	0.583

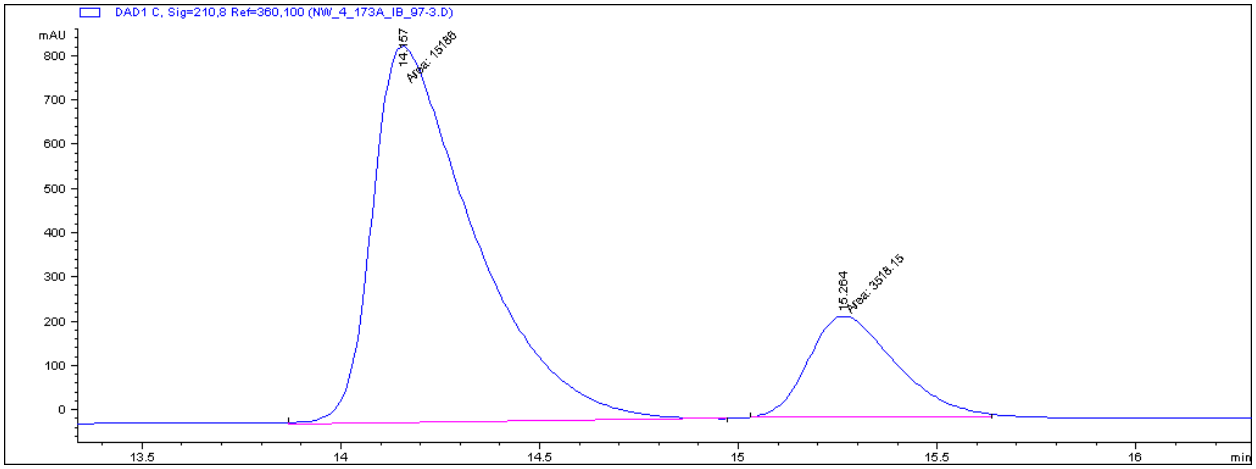


#	Time	Area	Height	Width	Area%	Symmetry
1	11.638	526.5	28.3	0.3103	7.615	0.799
2	13.011	6387.7	248.6	0.4282	92.385	0.53

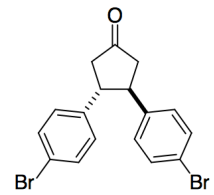


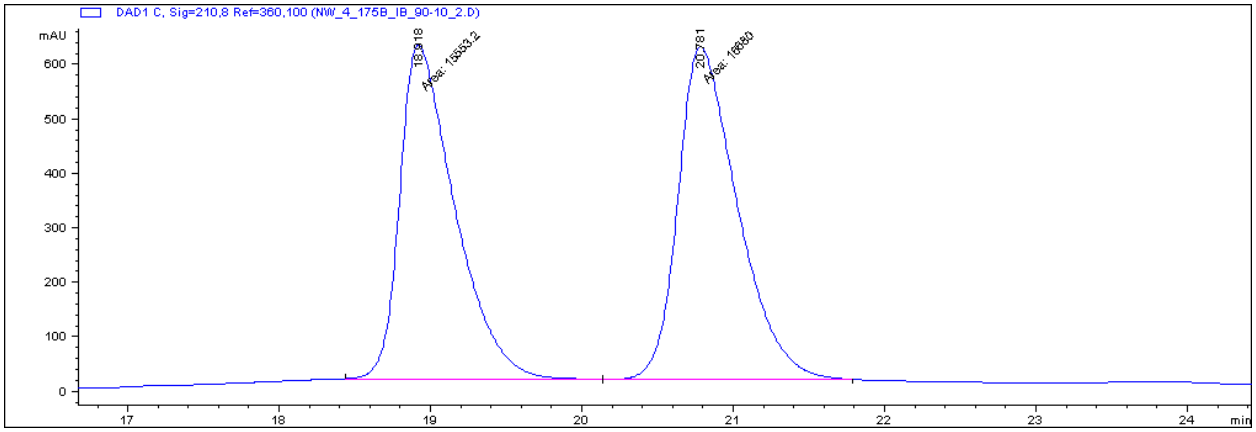


#	Time	Area	Height	Width	Area%	Symmetry
1	13.426	8346.2	383.5	0.3627	49.666	0.497
2	14.631	8458.6	382.8	0.3683	50.334	0.592

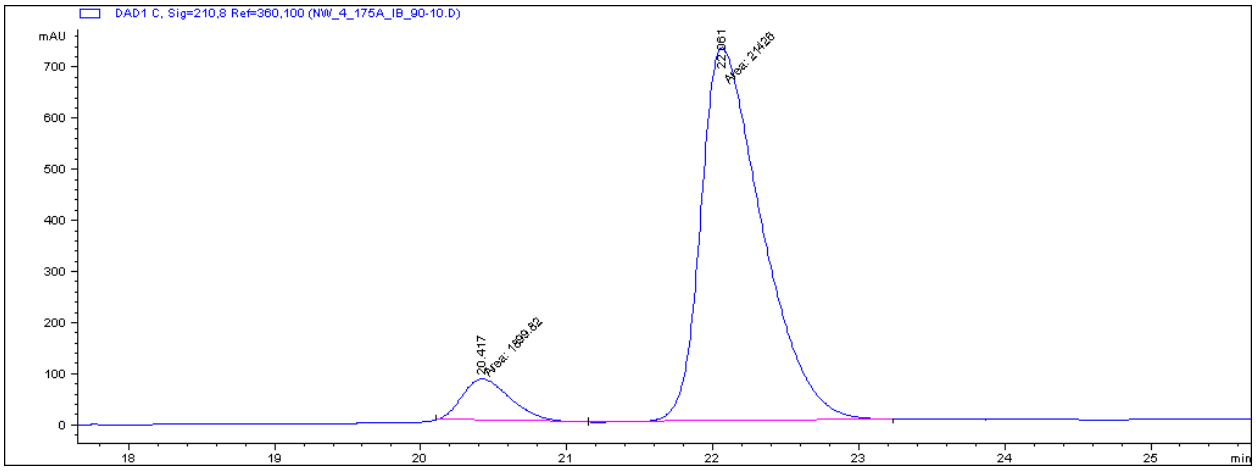


#	Time	Area	Height	Width	Area%	Symmetry
1	14.157	15186	851.5	0.2972	81.191	0.469
2	15.264	3518.2	229.3	0.2557	18.809	0.714

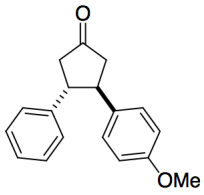


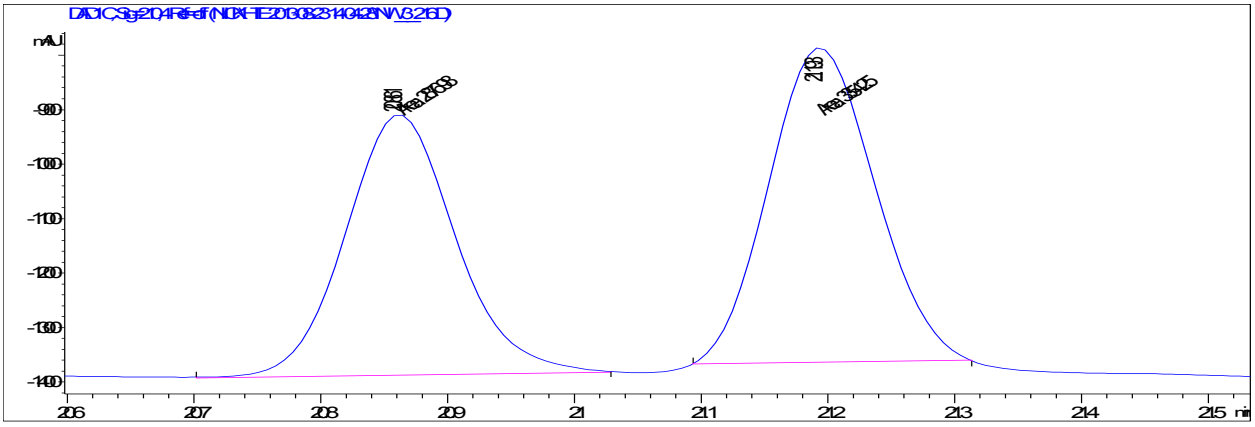


#	Time	Area	Height	Width	Area%	Symmetry
1	18.918	15553.2	614.1	0.4221	48.252	0.534
2	20.781	16680	610.6	0.4553	51.748	0.641

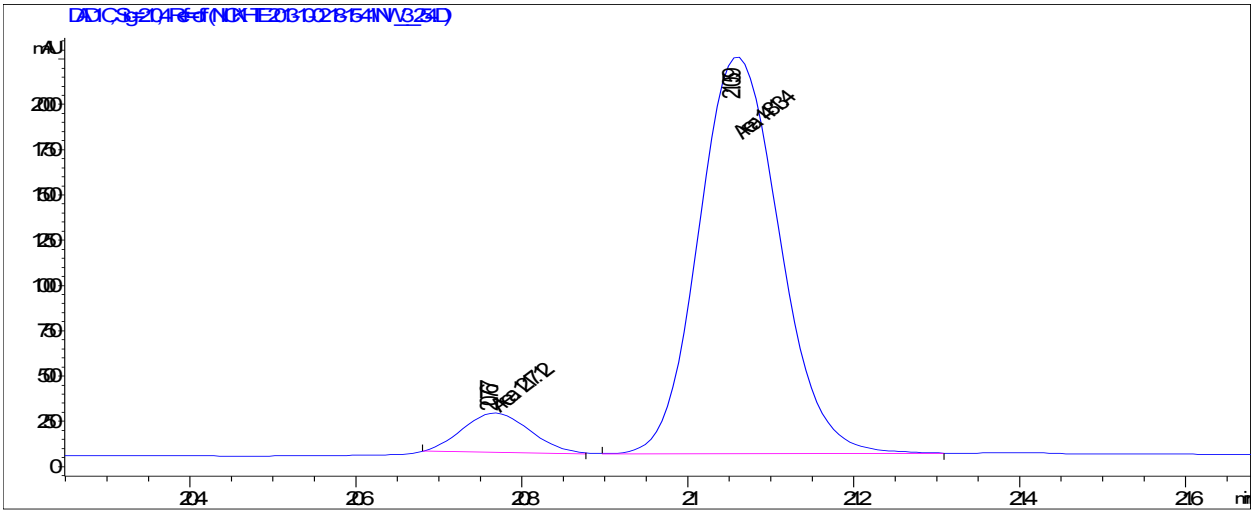


#	Time	Area	Height	Width	Area%	Symmetry
1	20.417	1899.8	81.5	0.3883	8.145	0.698
2	22.061	21426	732	0.4878	91.855	0.526

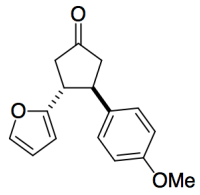


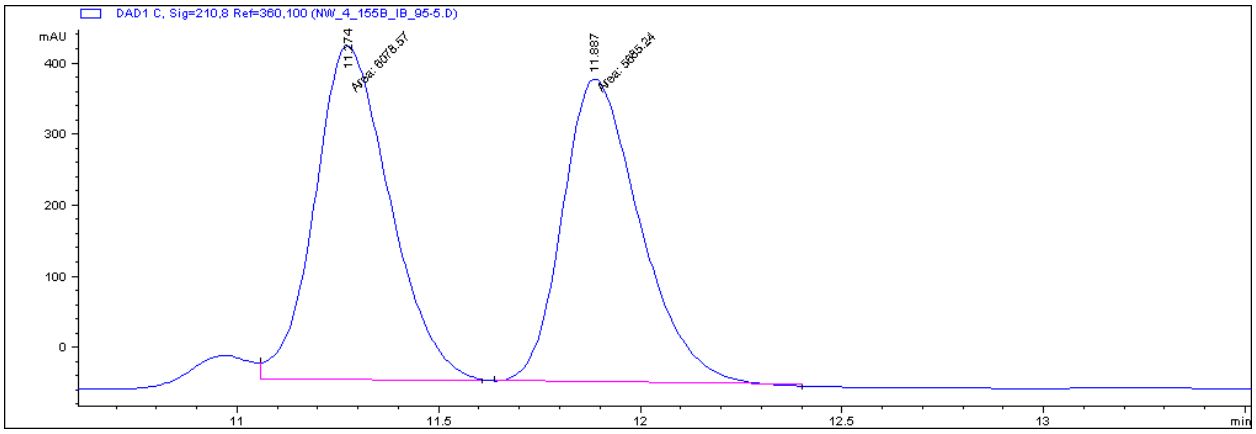


#	Time	Area	Height	Width	Area%	Symmetry
1	20.861	2877	478.9	0.1001	46.170	0.925
2	21.193	3354.3	578.1	0.0967	53.830	0.897

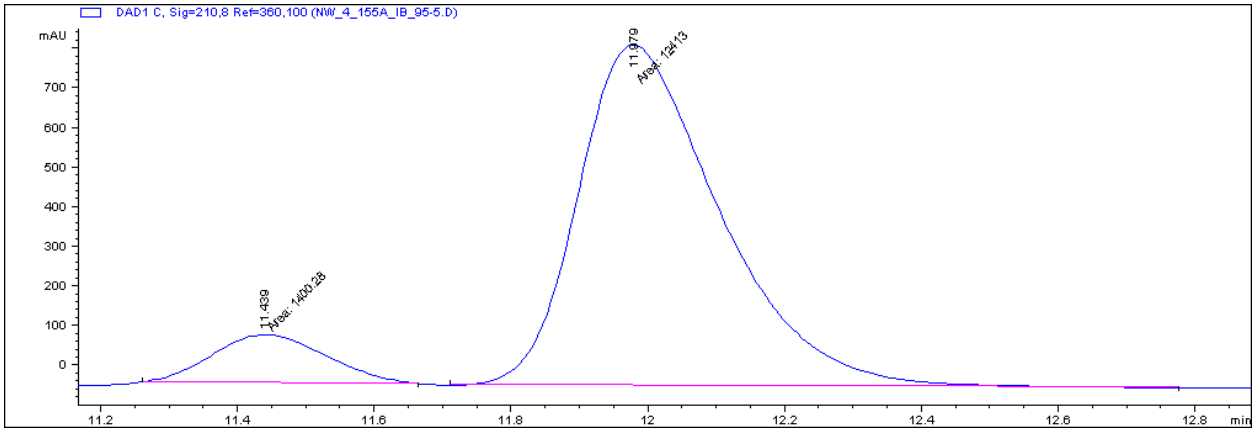


#	Time	Area	Height	Width	Area%	Symmetry
1	20.767	1217.1	216.7	0.0936	7.593	0.889
2	21.059	14813.4	2192.2	0.1126	92.407	0.874

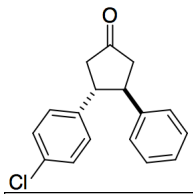


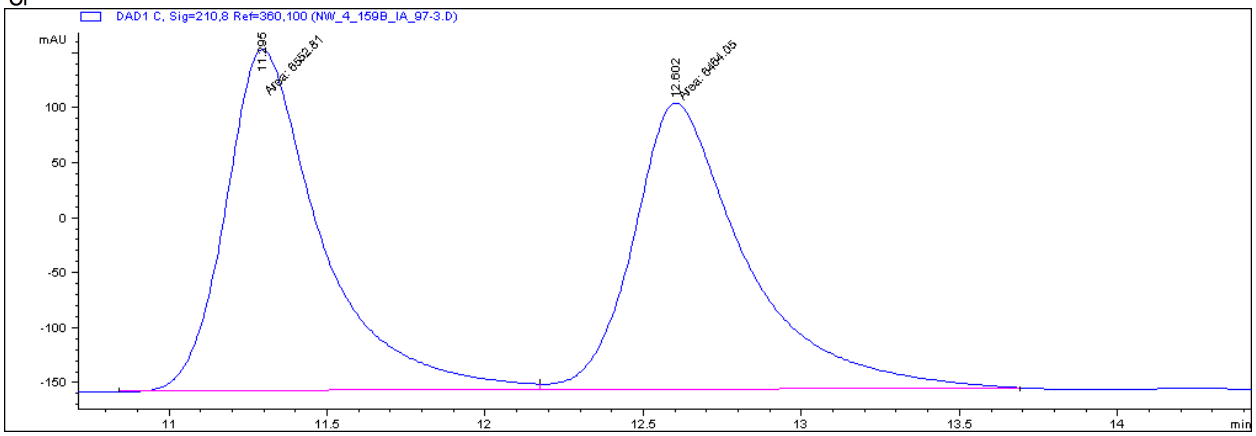


#	Time	Area	Height	Width	Area%	Symmetry
1	11.274	6078.6	471.6	0.2148	51.672	0.803
2	11.887	5685.2	428.2	0.2213	48.328	0.664

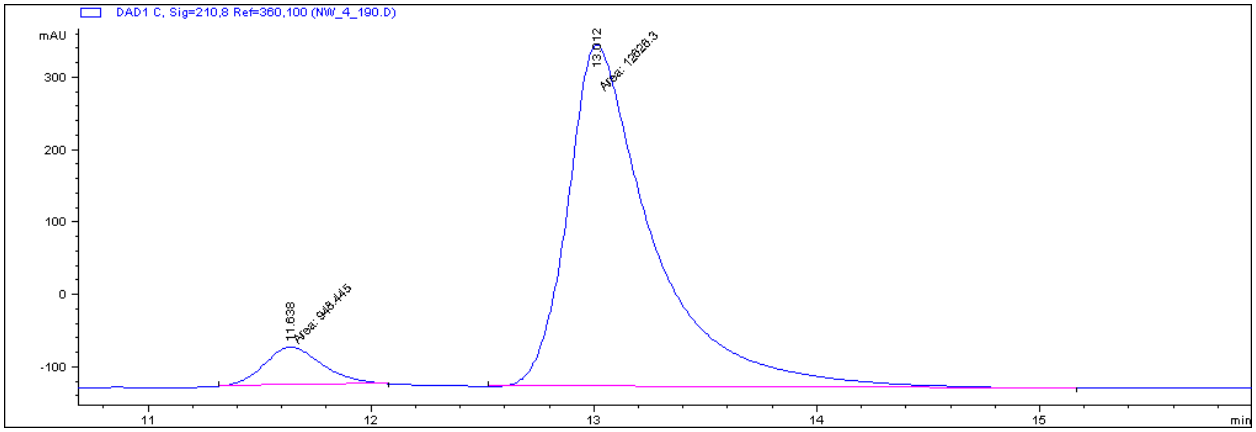


#	Time	Area	Height	Width	Area%	Symmetry
1	11.439	1400.3	121.5	0.1921	10.137	1.025
2	11.979	12413	863.5	0.2396	89.863	0.628

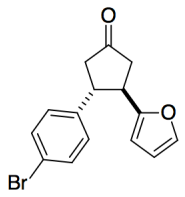


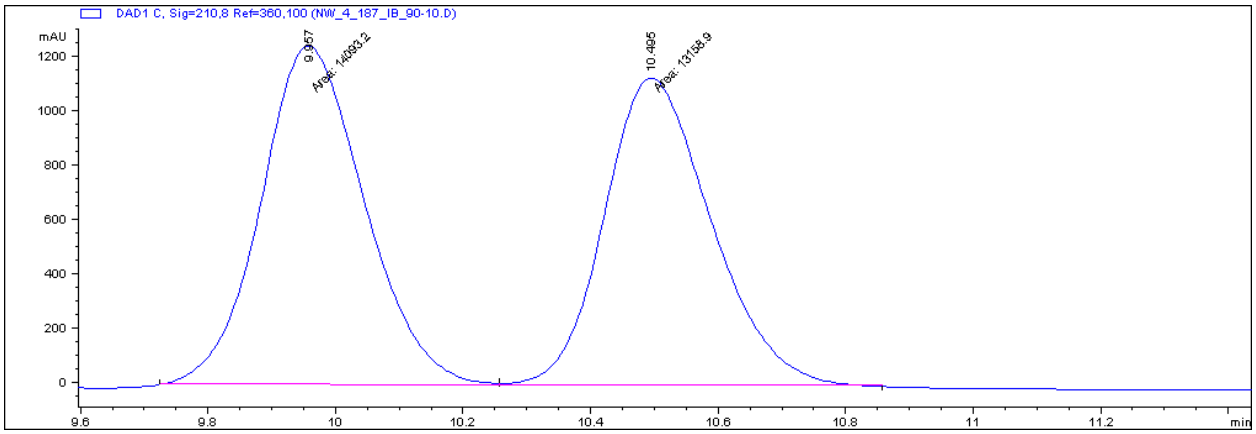


#	Time	Area	Height	Width	Area%	Symmetry
1	11.295	6552.8	311.2	0.3509	50.341	0.646
2	12.602	6464	260.5	0.4136	49.659	0.621

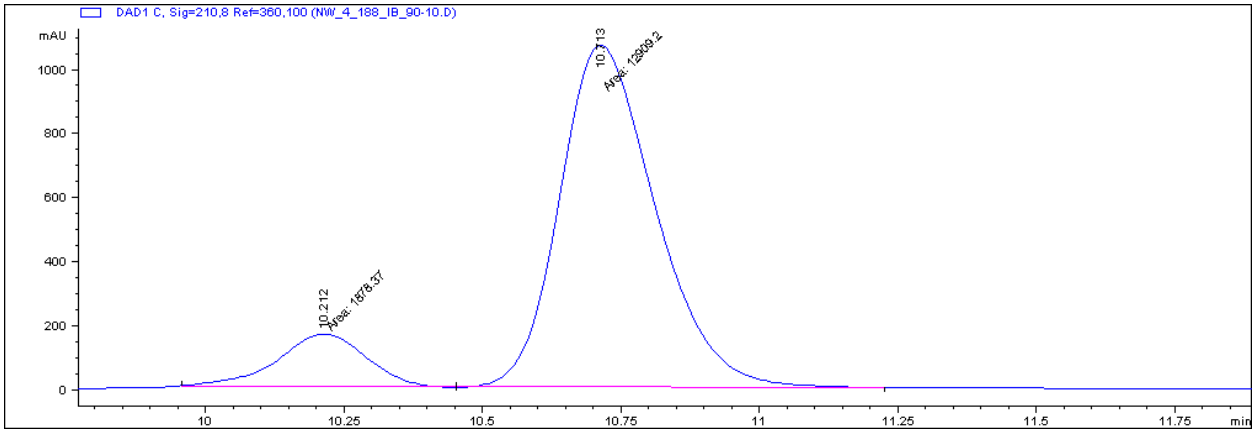


#	Time	Area	Height	Width	Area%	Symmetry
1	11.638	948.4	52.8	0.2996	6.987	0.858
2	13.012	12626.3	473.1	0.4448	93.013	0.502

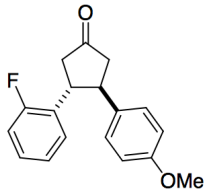


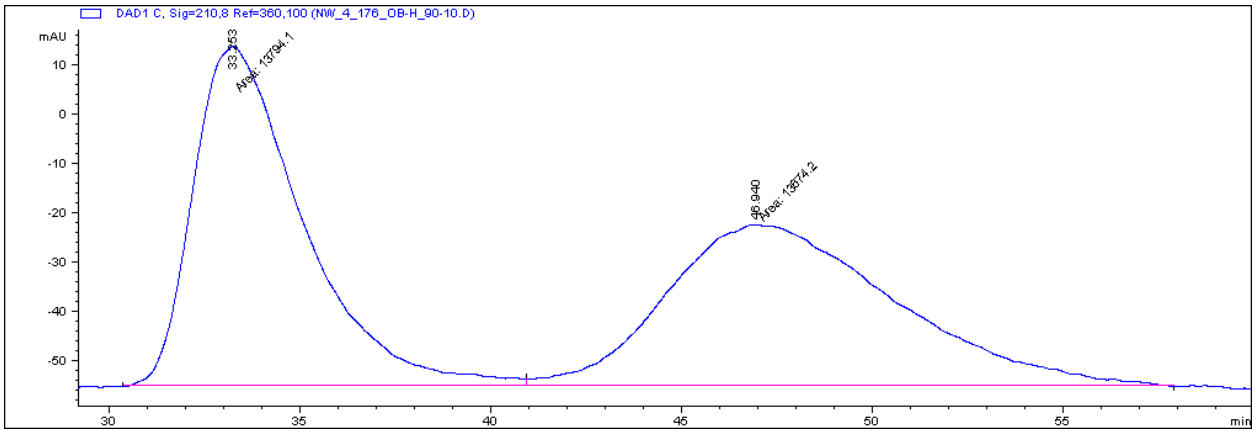


#	Time	Area	Height	Width	Area%	Symmetry
1	9.957	14093.2	1252.6	0.1875	51.714	0.981
2	10.495	13158.9	1137.1	0.1929	48.286	0.842

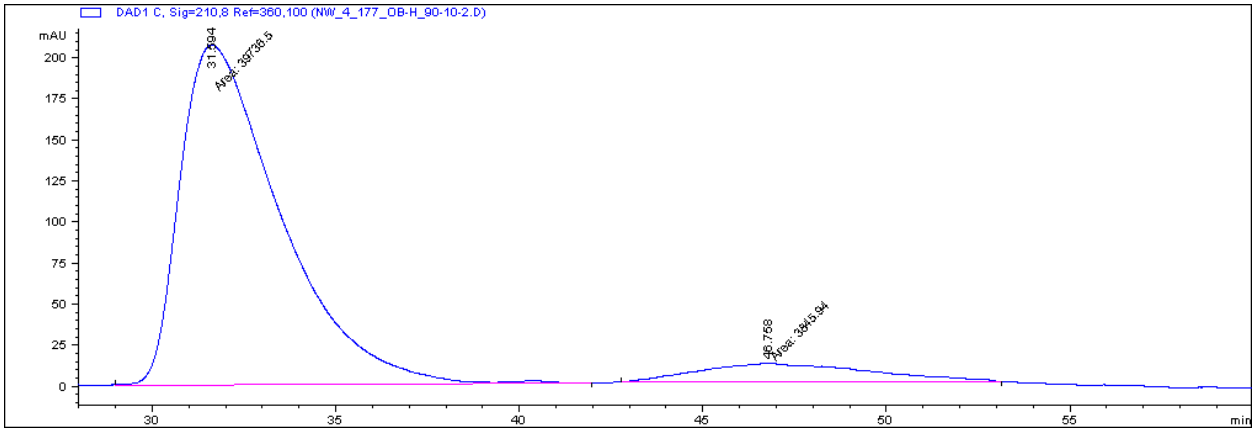


#	Time	Area	Height	Width	Area%	Symmetry
1	10.212	1878.4	166.8	0.1876	12.702	0.935
2	10.713	12909.2	1075.3	0.2001	87.298	0.701

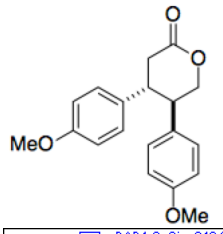


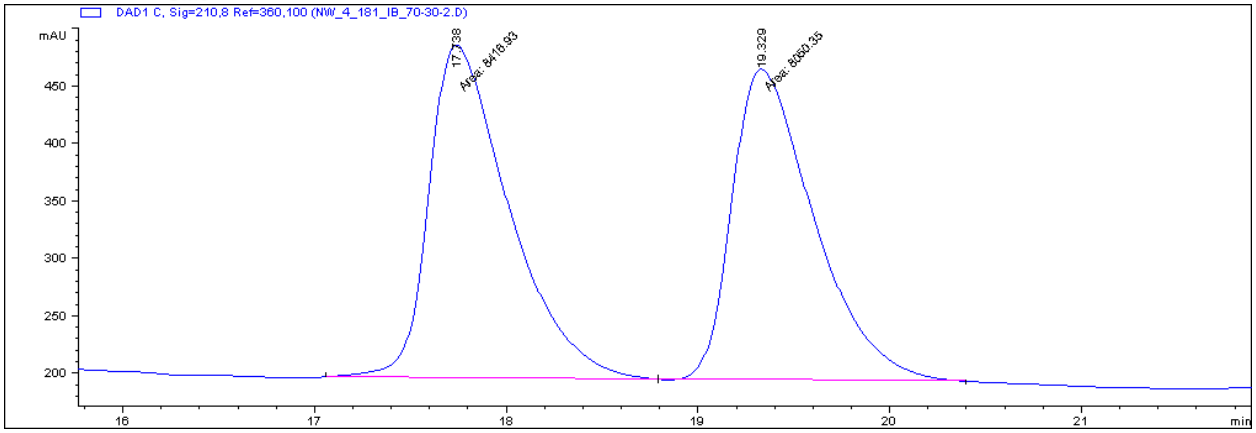


#	Time	Area	Height	Width	Area%	Symmetry
1	33.253	13794.1	69.1	3.3265	50.218	0.566
2	46.94	13674.2	32.8	6.9497	49.782	0.641

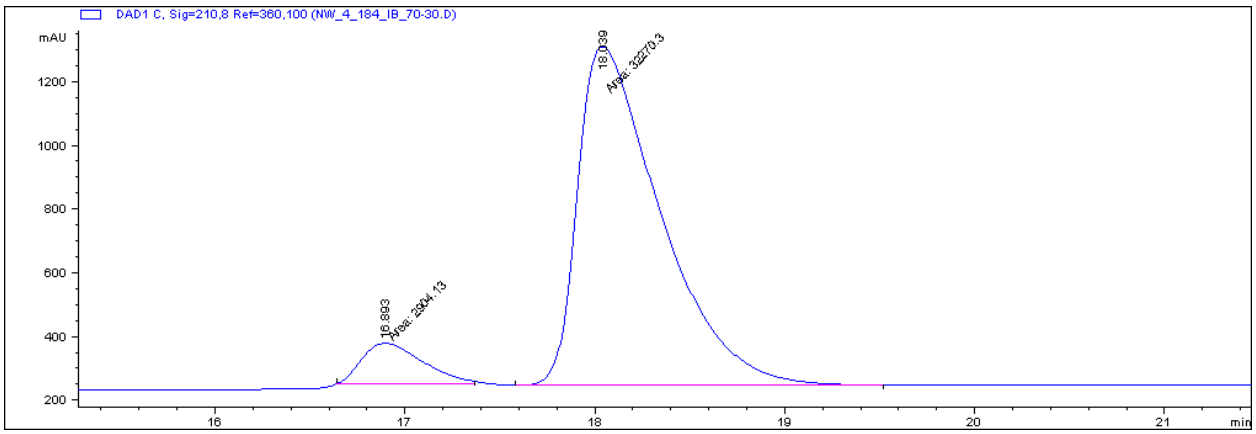


#	Time	Area	Height	Width	Area%	Symmetry
1	31.594	39736.5	207.6	3.19	91.175	0.44
2	46.758	3845.9	11.5	5.5913	8.825	0.655

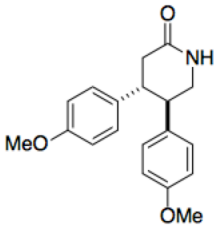


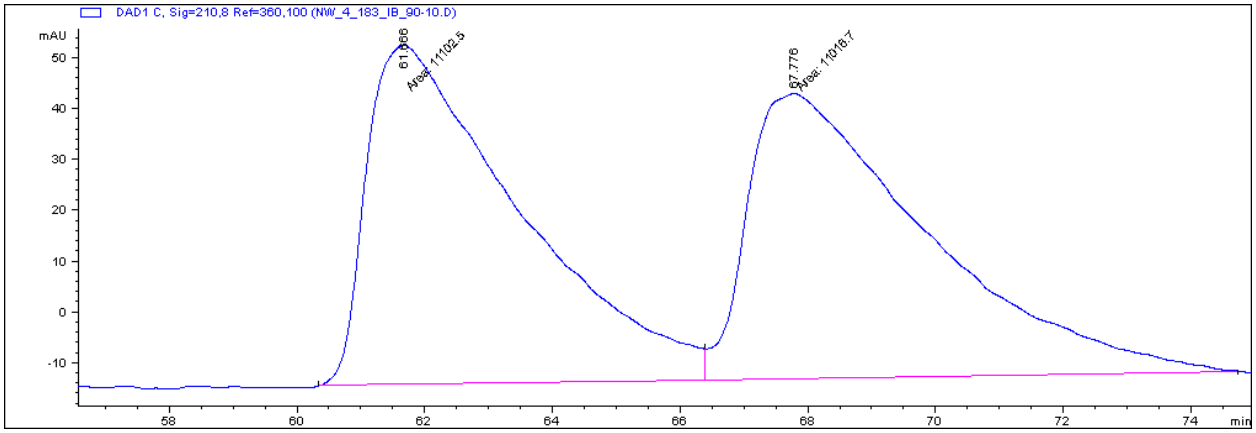


#	Time	Area	Height	Width	Area%	Symmetry
1	17.739	8607.9	291.6	0.4921	51.244	0.516
2	19.329	8189.9	272.1	0.5016	48.756	0.572

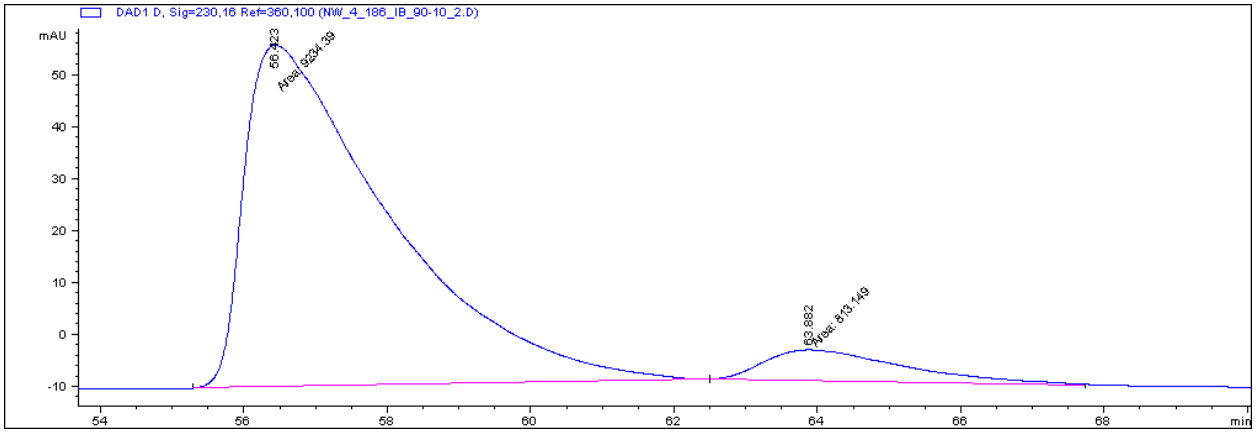


#	Time	Area	Height	Width	Area%	Symmetry
1	16.893	2904.1	128.7	0.3761	8.256	0.551
2	18.039	32270.3	1063	0.506	91.744	0.433





#	Time	Area	Height	Width	Area%	Symmetry
1	61.666	11102.5		66.9	2.7672	50.194	0.312
2	67.776	11016.7		56.2	3.2662	49.806	0.336



#	Time	Area	Height	Width	Area%	Symmetry
1	56.423	9234.4	65.7	2.3411	91.907	0.261
2	63.882	813.1	6	2.2702	8.093	0.442