Supporting Information for:

Direct access to functionalized benzotropinones, azepanes, and piperidines by reductive cross-coupling of α-bromo enones with α-bromo enamides

Timothy K. Beng, Kayla Sincavage, Ann Wens V. Silaire, Amir Alwali, Daniel P. Bassler, Laura E. Spence, and Oliver Beale*

Department of Chemistry, Susquehanna University, Selinsgrove, PA 17870, USA
beng@susqu.edu

Contents:

1. Experimental Section

All experiments involving air and moisture-sensitive reagents such as cobalt precatalysts and phosphine ligands were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. All electrophiles such as aryl and vinyl bromides were newly purchased and used without further purification. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by $KMnO_4$ staining. Unless otherwise indicated, ^1H, ^{13}C, DEPT-135, COSY 45, and HMQC NMR spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

Compounds **5**[1] and **6**[2] were prepared using known methods.

Compounds **7** to **9** were prepared using a procedure analogous to that employed by Georg for iodoenones.[3]

General Procedure A: Reductive Cross-Coupling[4]: To a solution of $CoBr_2$ (22 mg, 0.10 mmol, 10 mol%), PPh_3 (26.2 mg, 0.10 mmol, 10 mol%), and manganese powder (275 mg, 5 mmol, 5 equiv) in acetonitrile (5 mL) was added the aryl bromide (2 mmol, 2 equiv) at room temperature. A solution of the bromo eneformamide (1 mmol, 1 equiv) in acetonitrile (5 mL) was added slowly. After completion (as judged by TLC and GC-MS), the reaction mixture was treated with a mild acid such as 10% H_3PO_4 (aq) and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired coupling product as an oil. Purification was carried out by flash chromatography on silica (pretreated with 1% Et_3N).

General Procedure B: Removal of Boc group

To the *N*-Boc-compound (1.0 equiv) dissolved in freshly distilled CH_2Cl_2, was added CF_3CO_2H (3 equiv) under argon at 0 °C. The resulting solution was stirred for 3 h at this temperature and concentrated in vacuo to obtain the imine.

General Procedure C: *N*-acyl iminium reduction[5]

To a stirred solution of the crude enecarbamate or eneformamide (~0.1 mmol) in CH_2Cl_2 (2 mL) were added $NaBH_3CN$ (33 mg, 0.5 mmol, 5 equiv) at –40 °C (or at rt in the case of eneformamides) followed by TFA (0.08 mL, 1.0 mmol, 10 equiv). The resulting suspension was stirred for 5 h at this temperature (TLC and LCMS monitoring). The reaction was quenched with *satd*. $NaHCO_3$ (aq), diluted with CH_2Cl_2 (5 mL) and the organic layer was separated. The

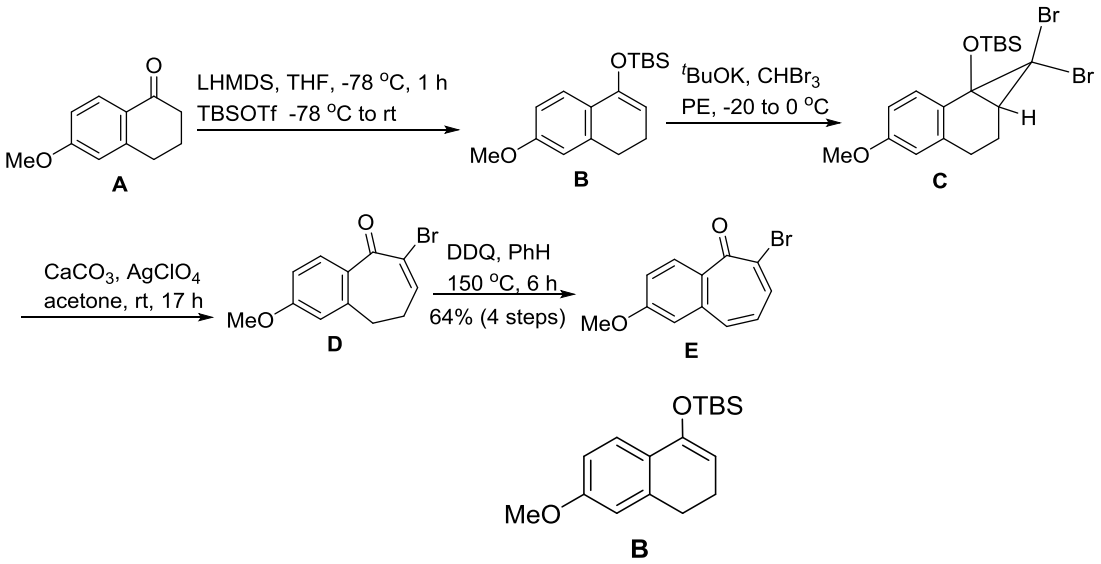
aqueous layer was extracted with CH_2Cl_2. The combined organic layers dried over Na_2SO_4 (30 min), filtered, and concentrated under reduced pressure to give the crude product.

General Procedure D: Catalytic hydrogenation

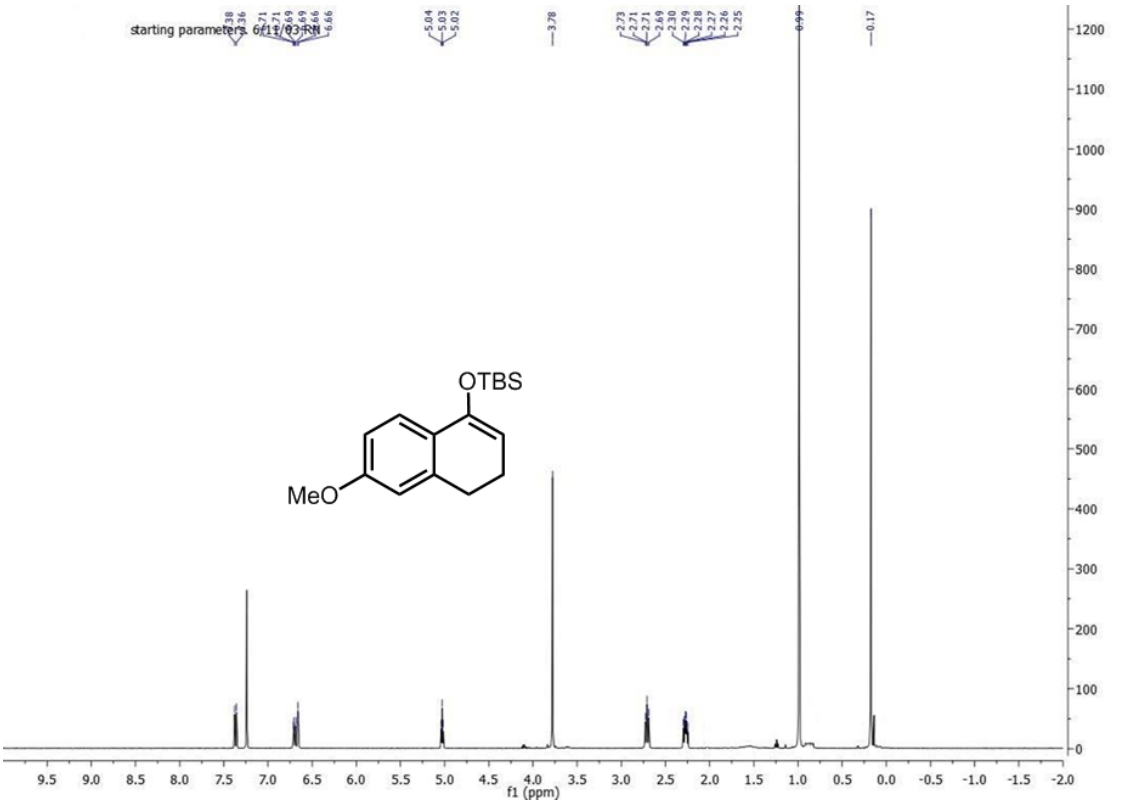
EtOAc was added to a flask containing 10% Pd/C at room temperature. The flask was degassed and placed under an inert atmosphere of nitrogen. A solution of the enamide in EtOAc was added. After complete addition, the nitrogen line was cut off and then replaced with a balloon of hydrogen. After complete consumption of the enamide (based on LC-MS and TLC monitoring), the mixture was filtered through a plug of Celite and concentrated under reduced pressure.

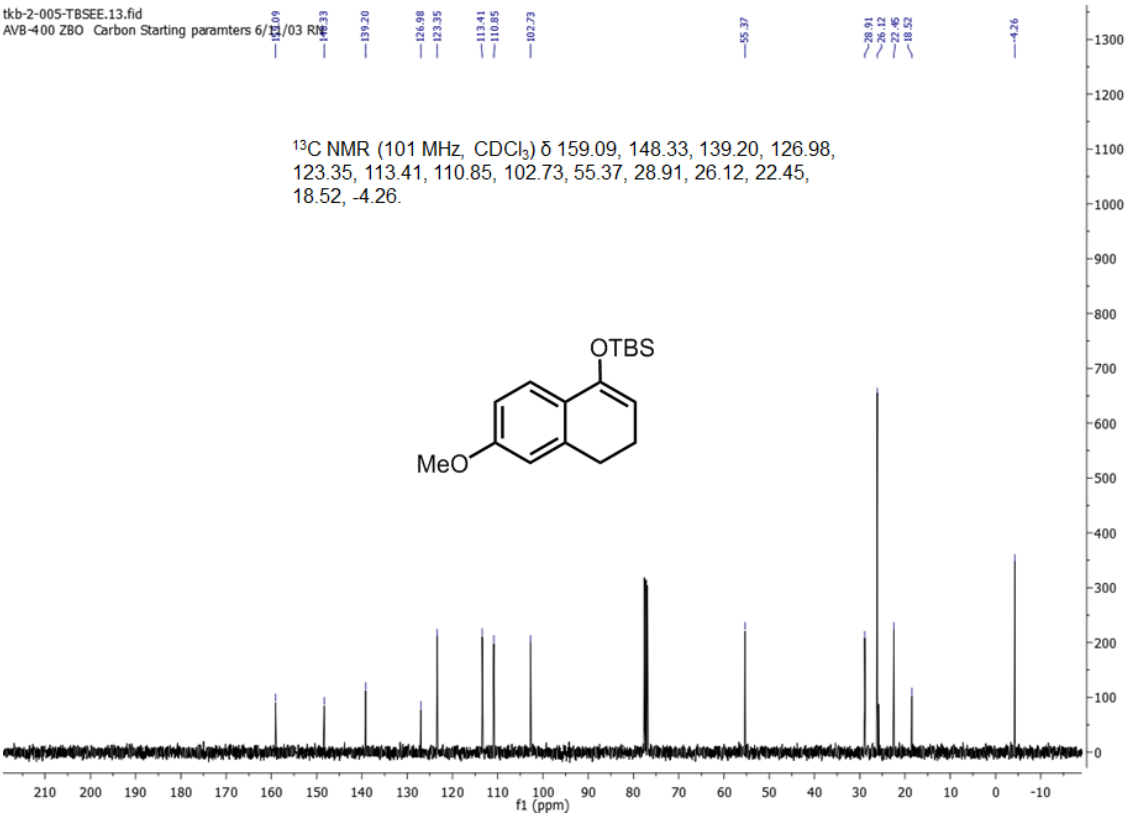
Note: Compounds **1** and **3** were synthesized (from the corresponding tetralones) in the same way as compound **2,** whose synthesis is outlined below:

The conversion from **B** to **D** follows a closely related sequence pioneered by Yang and coworkers.[6]

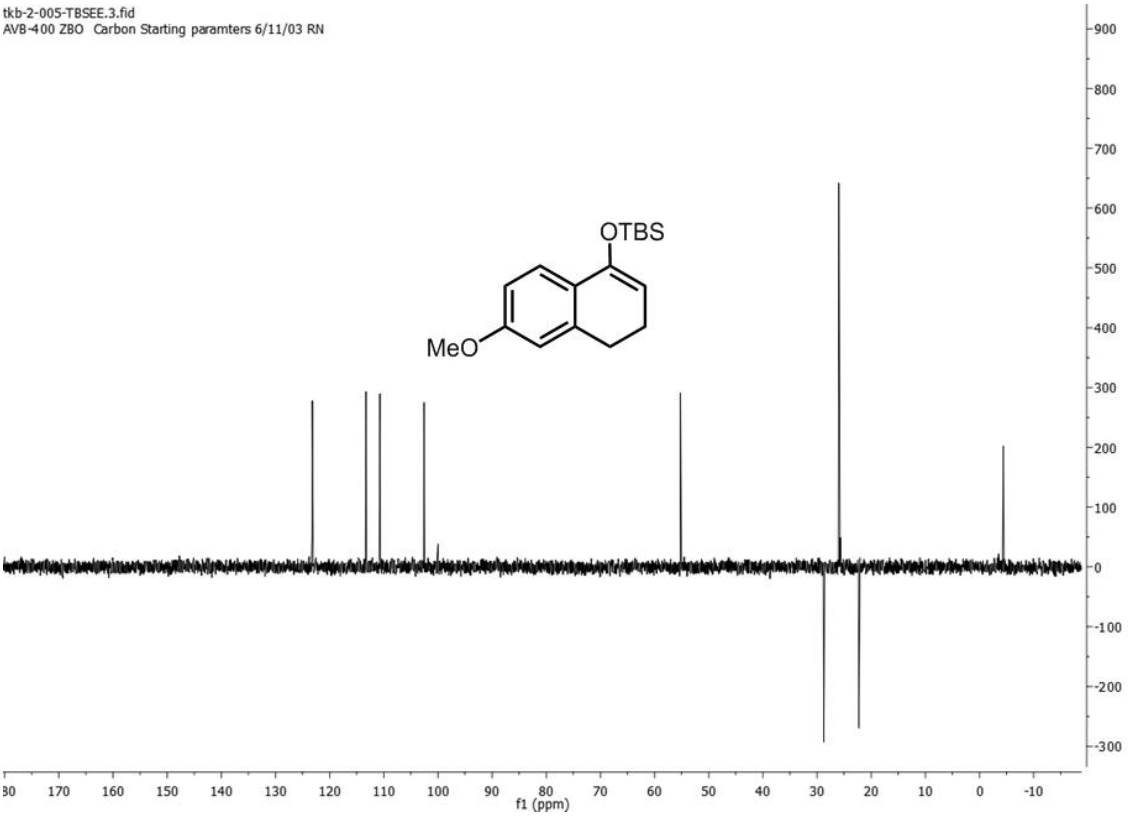


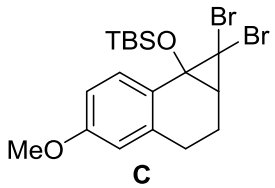
A solution of LHMDS (20 mL, 20 mmol, 1.0 M in THF) was added dropwise to a solution of tetralone **A** (20 mmol) in THF (100 mL) and the mixture was stirred for 30 min. TBSOTf (22 mmol, 1.2 equiv) was added slowly at −78 °C and the stirring was continued for 2 h. The mixture was quenched with saturated $NaHCO_3$(aq) and warmed to room temperature. Standard extractive workup with EtOAc and brine washes afforded silyl enol ether **B** in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, d), 6.71 to 6.66 (2H, overlapping doublet & singlet), 5.03 (1H, t), 3.78 (3H, s), 2.73 to 2.69 (2H, m), 2.30, to 2.25 (2H, m), 0.99 (9H, s), 0.17 (6H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.09, 148.33, 139.20, 126.98, 123.35, 113.41, 110.85, 102.73, 55.37, 28.91, 26.12, 22.45, 18.52, -4.26.





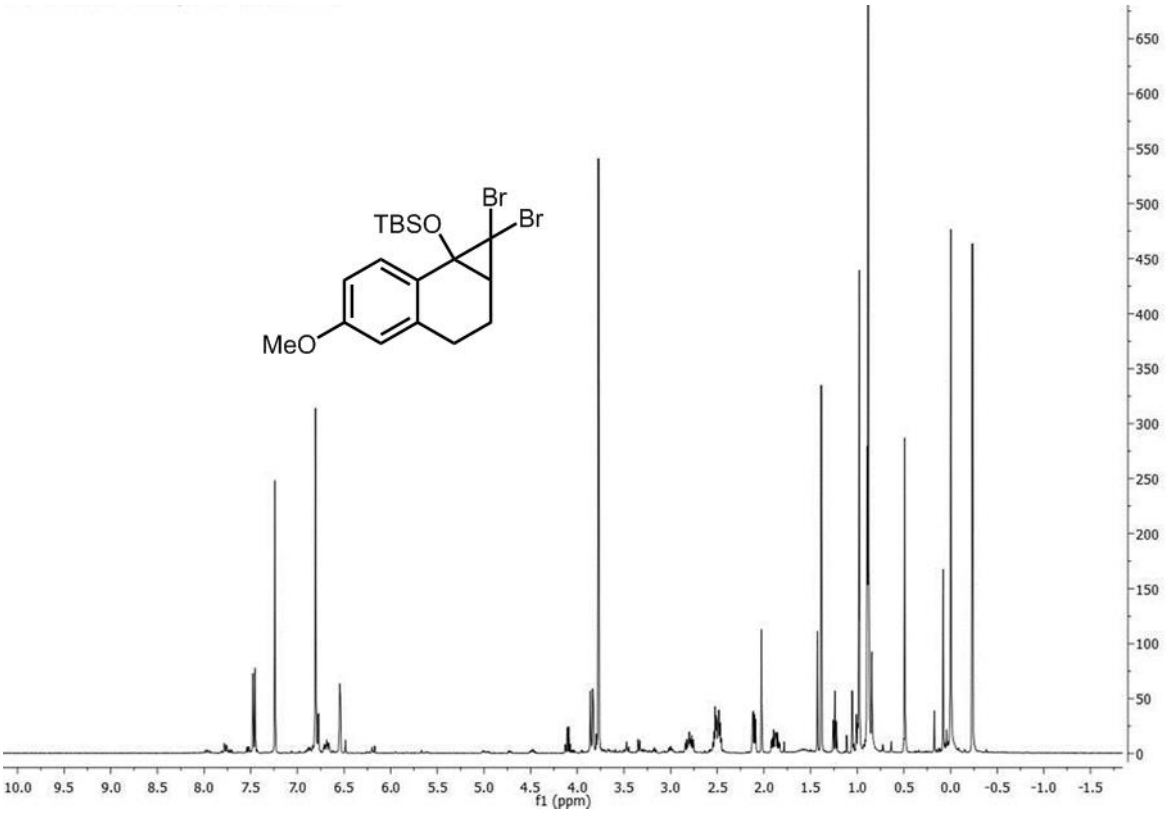
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.09, 148.33, 139.20, 126.98, 123.35, 113.41, 110.85, 102.73, 55.37, 28.91, 26.12, 22.45, 18.52, -4.26.

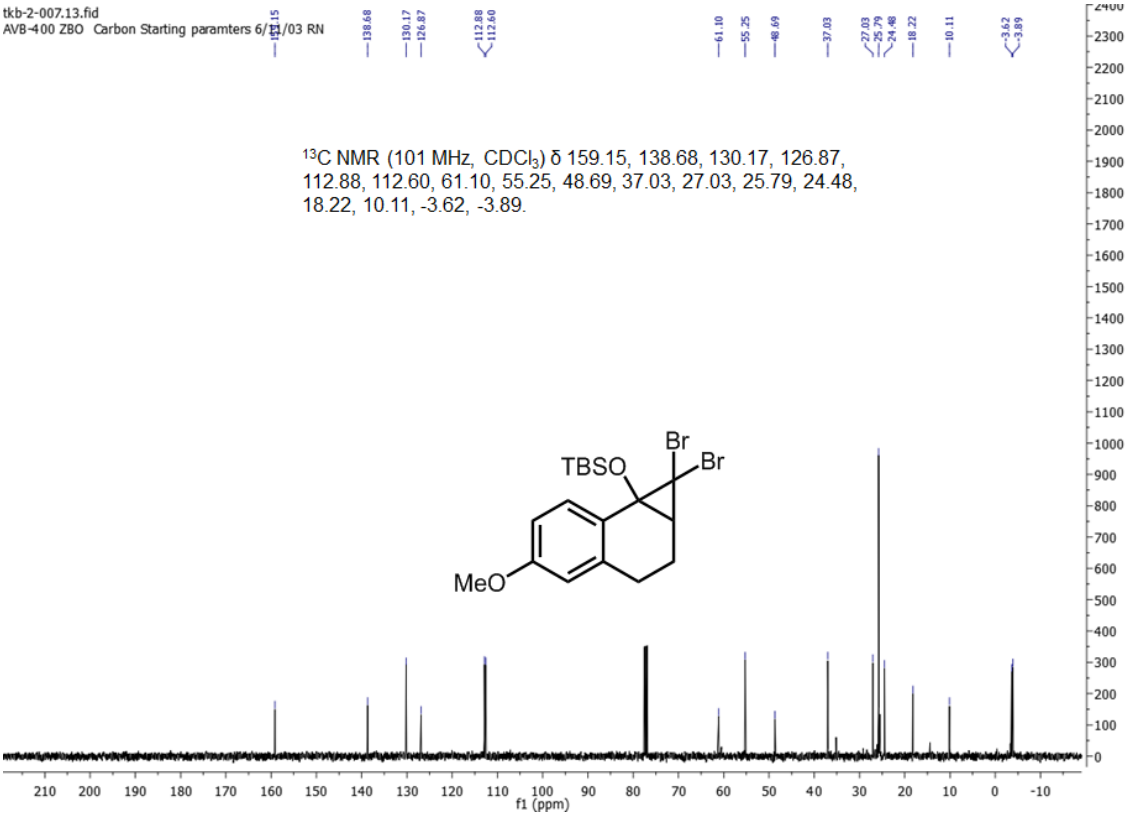




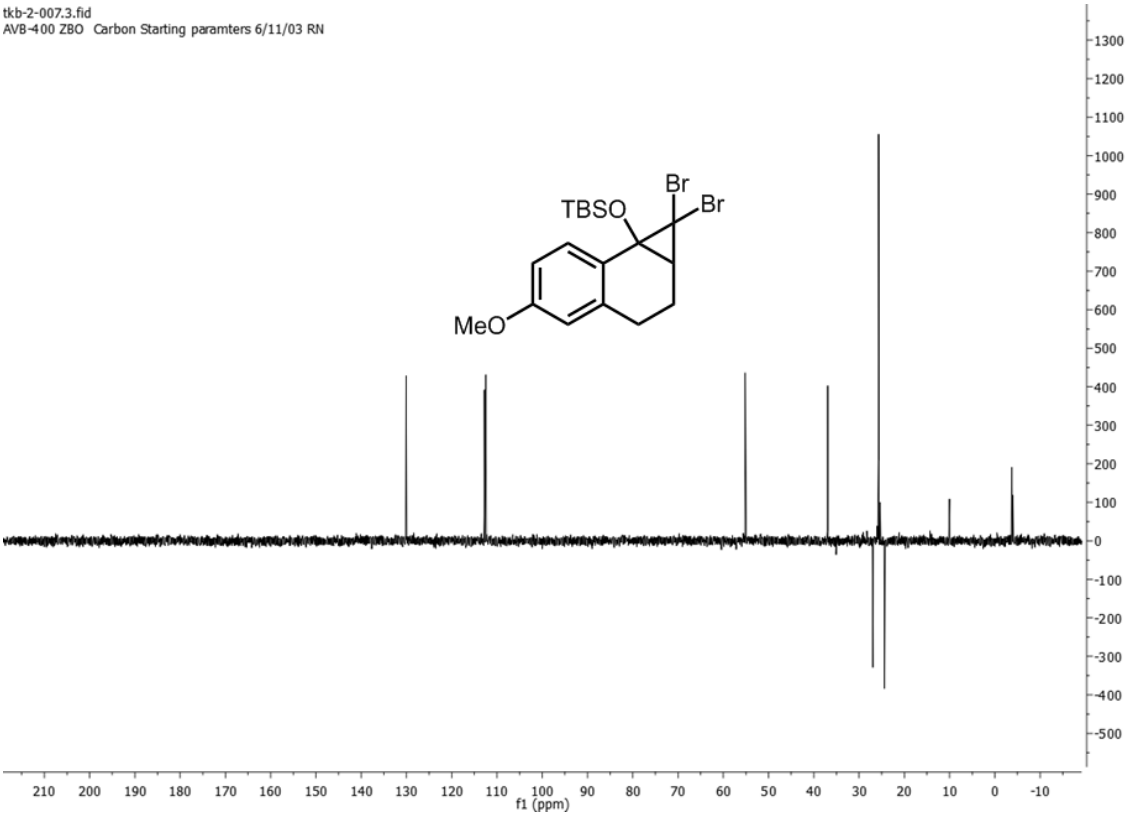
C

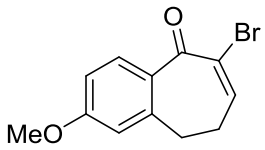
A suspension of potassium *tert*-butoxide (3 equiv) in petroleum ether (10 mL) was cooled to −20 ^{o}C and bromoform (3 equiv), diluted with petroleum ether (2 mL), was added followed by silyl enol ether **B** (2 mmol, 1 equiv). The mixture was warmed slowly to 0 ^{o}C. After complete consumption of **B** (LC-MS monitoring), the mixture was filtered through silica/Celite (1:1) and the filtrate was concentrated and used in the next step. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.15, 138.68, 130.17, 126.87, 112.88, 112.60, 61.10, 55.25, 48.69, 37.03, 27.03, 25.79, 24.48, 18.22, 10.11, -3.62, -3.89.





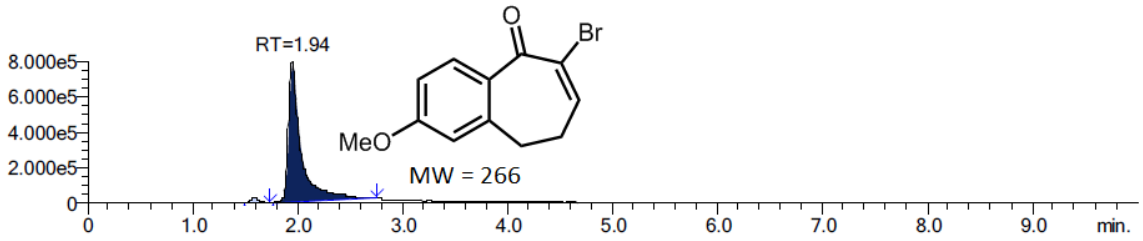
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.15, 138.68, 130.17, 126.87, 112.88, 112.60, 61.10, 55.25, 48.69, 37.03, 27.03, 25.79, 24.48, 18.22, 10.11, -3.62, -3.89.





4

Crude dibromo cyclopropane **C** was dissolved in reagent grade acetone (10 mL) and $AgClO_4 \cdot H_2O$ (2 equiv) and $CaCO_3$ (4 equiv) were added. After stirring for 17 h at room temperature, filtration through Celite and evaporation of the solvent provided bromo enone **4**. ^{1}H NMR (400 MHz, C_6D_6) δ 7.91 (1H, d), 6.83 (1H, t), 6.42 to 6.39 (1H, d), 6.33 (1H, s), 3.17 (3H, s), 2.21 to 2.18 (2H, m), 1.63 to 1.59 (2H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 186.01, 163.42, 147.77, 141.95, 133.99, 131.82, 114.85, 112.33, 55.34, 34.07, 31.28.



MS Spectrum

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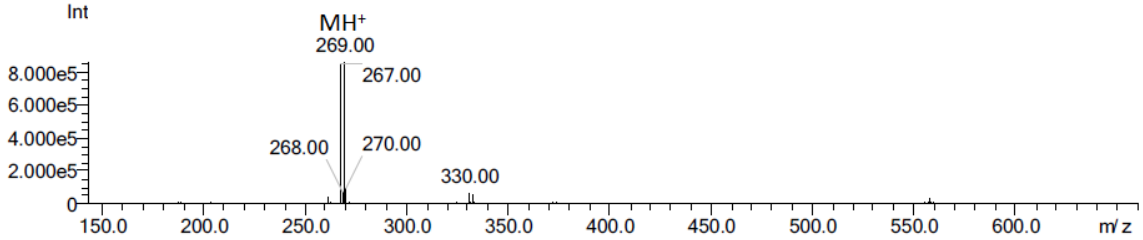

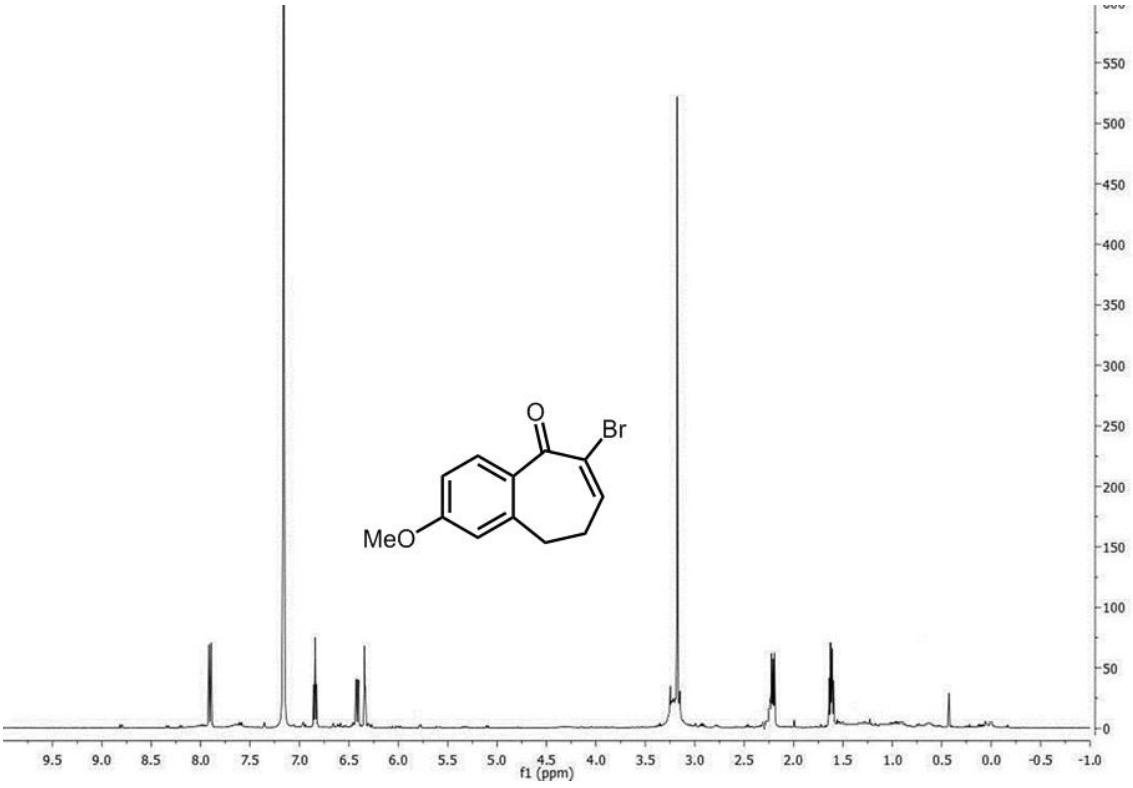

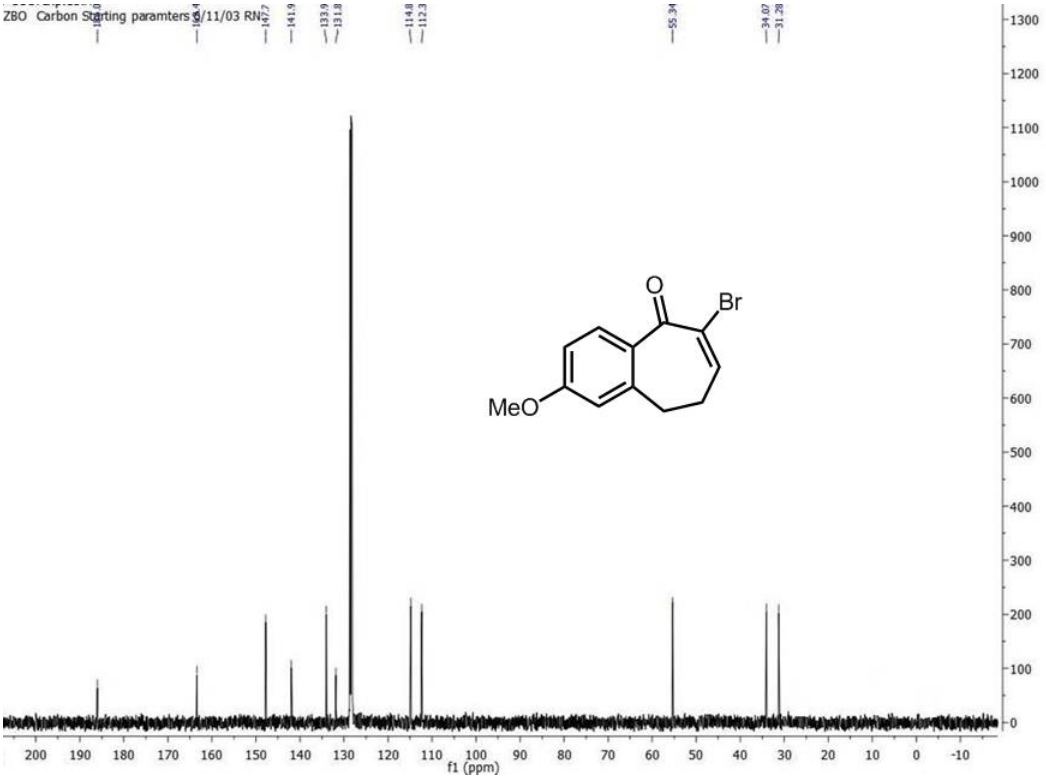
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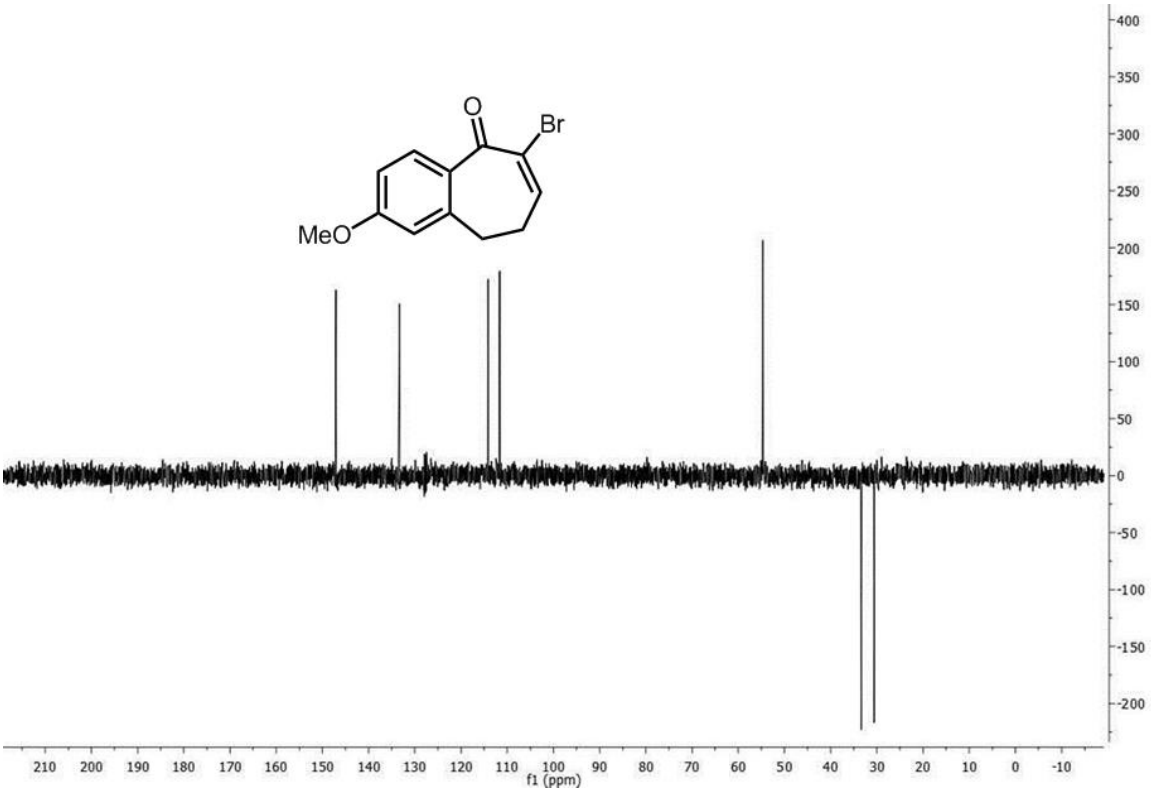
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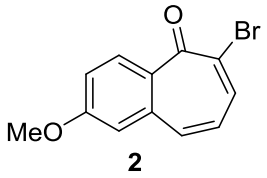
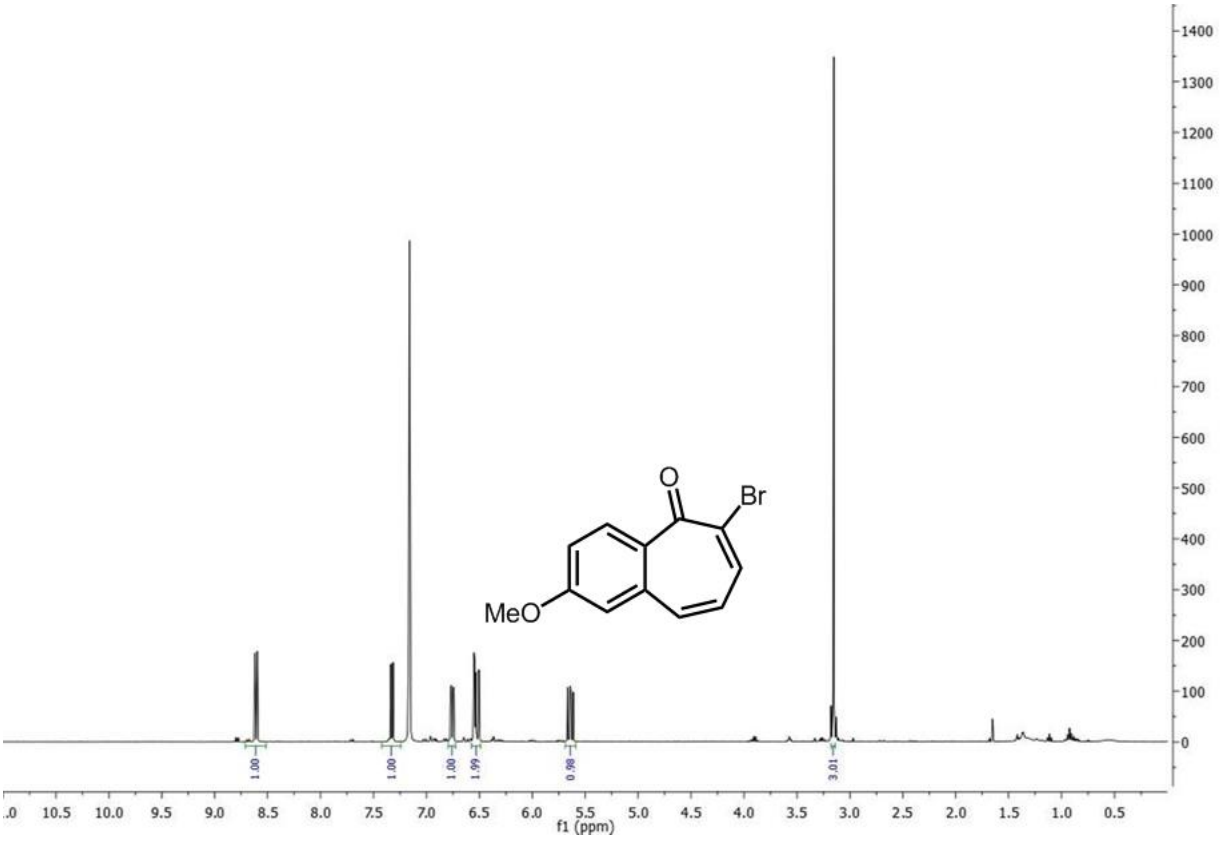
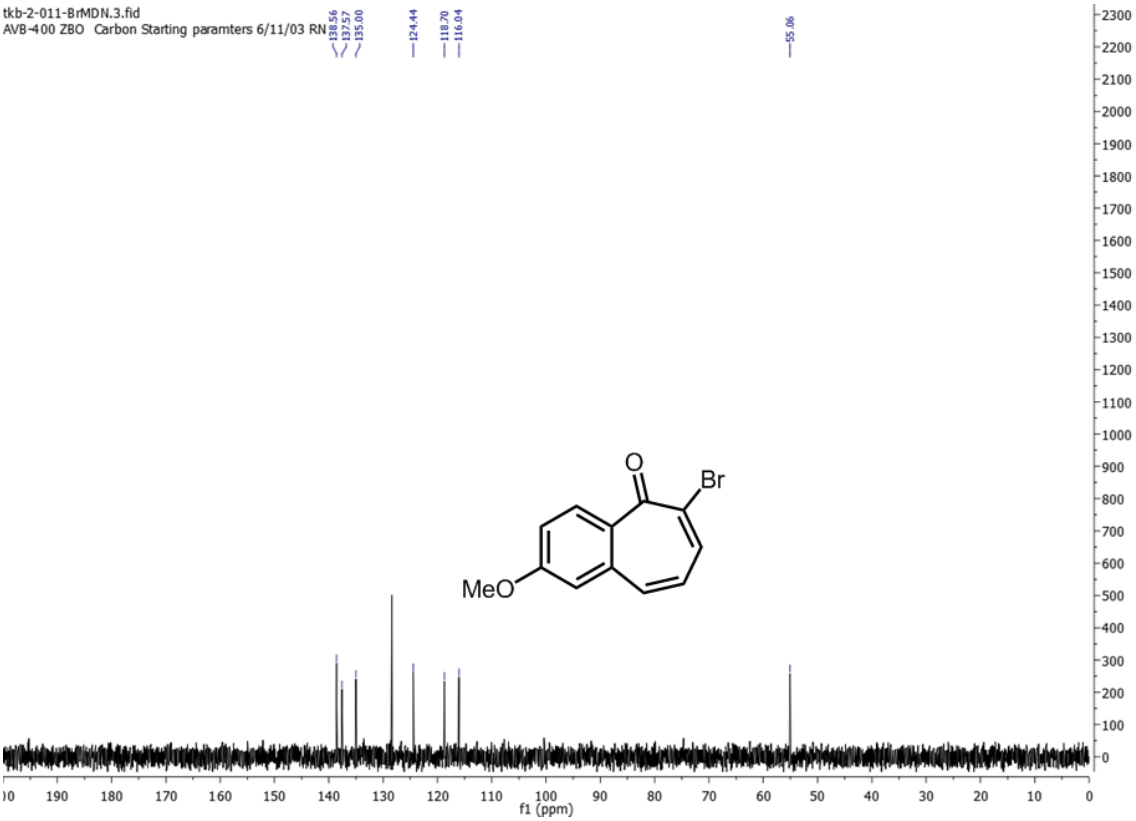
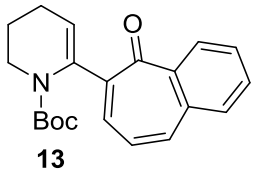


2

To a solution of enone **4** (1 mmol) in benzene (5 mL) was added a fresh sample of DDQ (1 equiv) and the suspension was stirred at 150 ^{o}C, under microwave irradiation for 6 h (LC-MS monitoring). It was filtered through basic alumina and solid residue was washed several times with EtOAc. The combined filtrate was concentrated and purified by flash chromatography on silica eluting with Hexane/EtOAc (50:50 to 20:80) to afford **2** as a yellowish oil is 64% overall yield (from tetralone **A**). ^{1}H NMR (400 MHz, C_6D_6) δ 8.62 (1H, d), 7.32 (1H, d), 6.77 to 6.74 (1H, d), 6.55 to 6.50 (2H, overlapping doublet and singlet), 5.67 to 5.61 (1H, dd), 3.15 (3H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 186.1, 162.3, 140.5, 138.1, 137.1, 136.8, 134.6, 129.6, 124.0, 118.3, 115.6, 54.6. HRMS calc for $C_{12}H_9BrO_2$ 263.9786, found 263.9994.

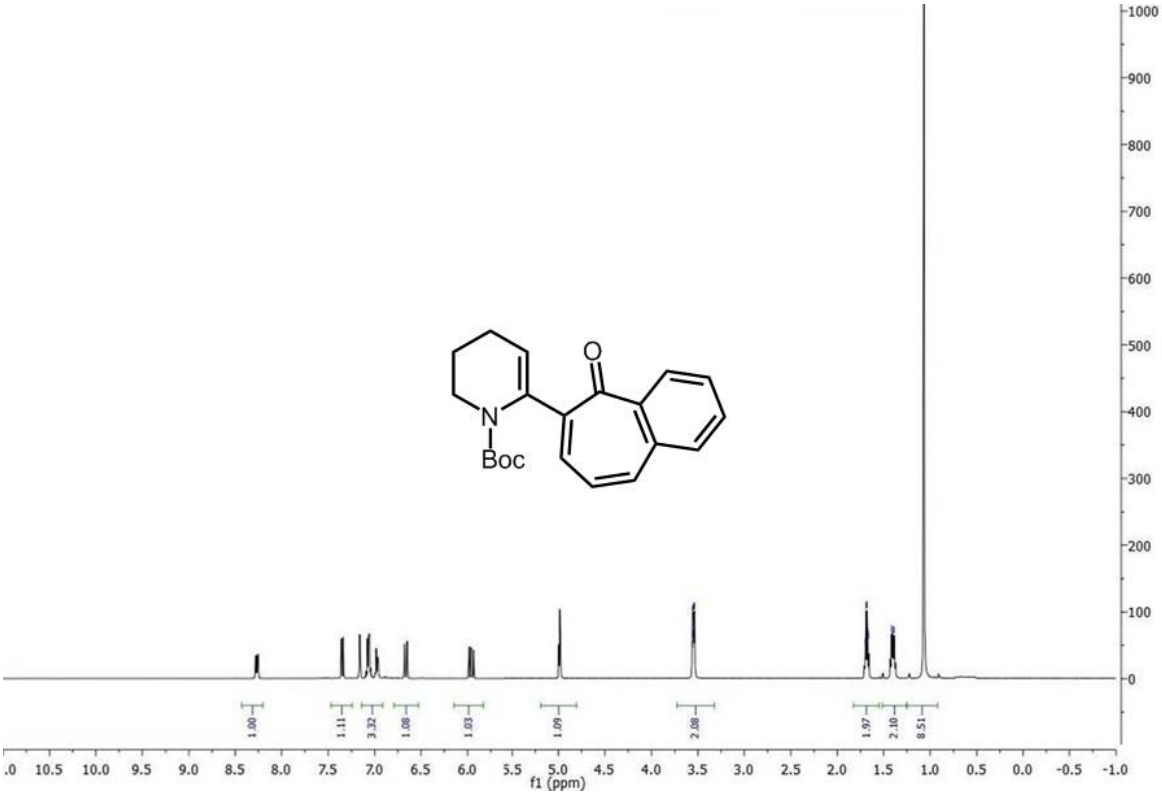






13

Prepared from **10** (260 mg, 1.0 mmol) and bromo enone **1** (280 mg, 1.2 mmol, 1.2 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 270 mg, 79%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.29 (1H, d), 7.36 (1H, d), 7.06 to 6.90 (3H, m), 6.60 (1H, d), 5.91 to 5.86 (1H, dd), 5.13 (1H, t), 3.56 to 3.53 (2H, t), 1.70 to 1.66 (2H, t), 1.42 to 1.39 (2H, m), 1.07 (9H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 187.7, 157.8, 141.7, 140.8, 137.3, 136.0, 134.6, 132.4, 131.9, 131.1, 130.4, 124.9, 52.4, 79.8, 44.0, 27.4, 23.3, 23.1. HRMS calc for $C_{21}H_{23}NO_3$ 337.1678, found 337.1682.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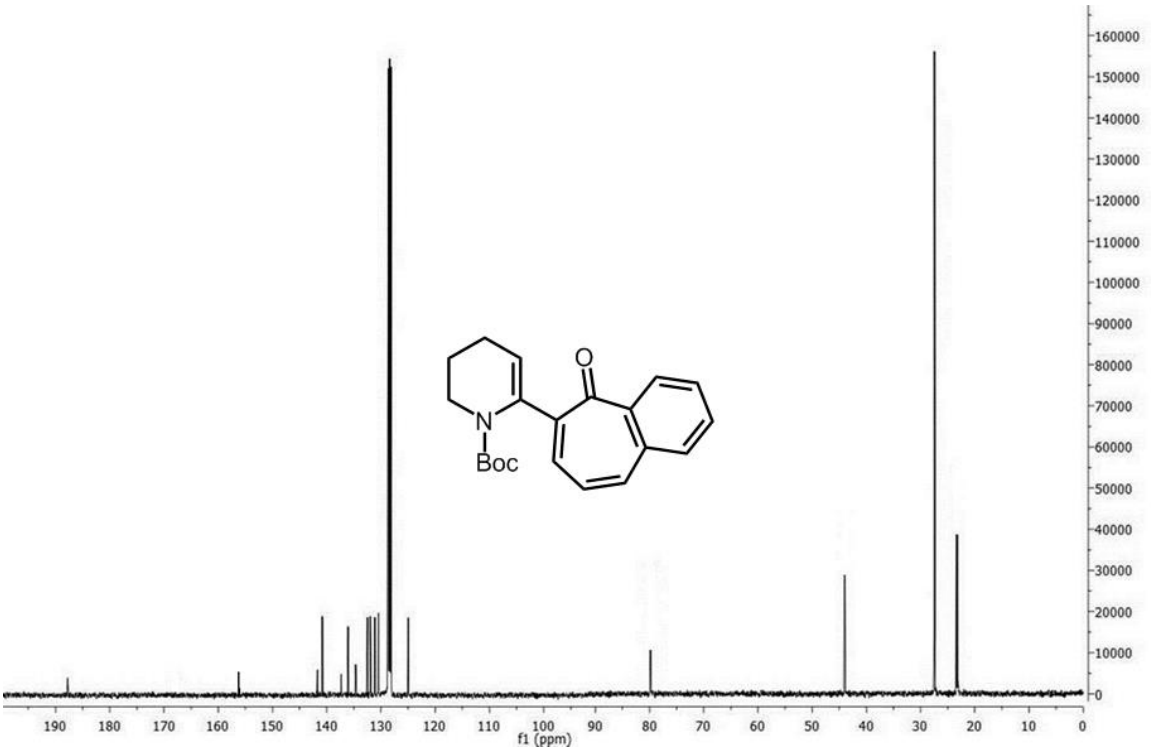
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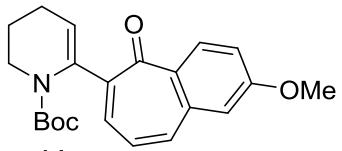
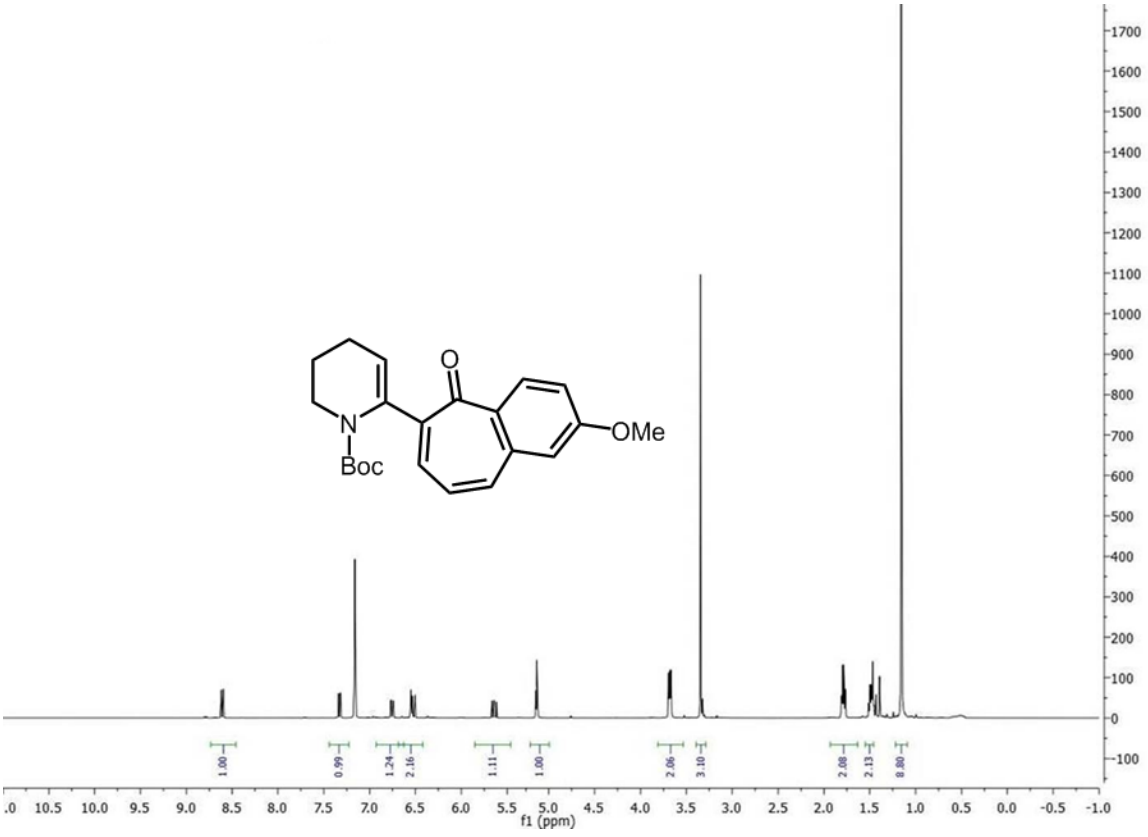
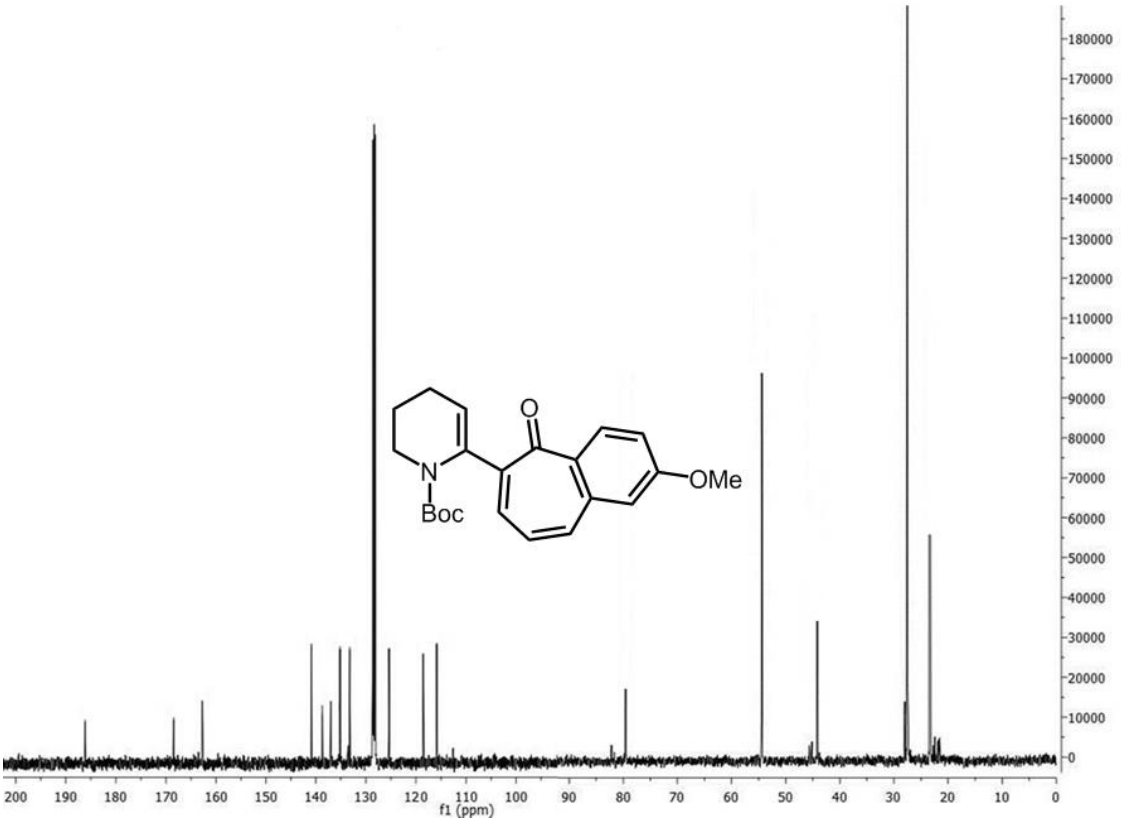
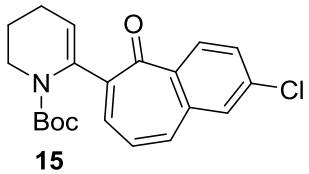


14

Prepared from **10** (260 mg, 1.0 mmol) and bromo enone **2** (317 mg, 1.2 mmol, 1.2 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 20:80). Yield = 319 mg, 87%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.62 (1H, d), 7.33 (1H, d), , 6.75 (1H, d), 6.66 to 6.50 (2H, overlapping singlet and doublet), 5.67 to 5.61 (1H, dd), 5.14 to 5.12 (1H, t), 3.69 to 3.67 (2H, t), 3.35 (3H, s), 1.81 to 1.77 (2H, t), 1.51 to 1.43 (2H, m), 1.16 (9H, s). ^{13}C NMR (101 MHz, C_6D6) δ 186.17, 168.45, 162.72, 140.91, 138.72, 137.03, 135.33, 135.17, 133.23, 125.41, 118.54, 115.87, 79.53, 54.42, 44.20, 27.51, 23.43, 23.41. HRMS calc for $C_{22}H_{25}NO_4$ 367.1684, found 367.1688.

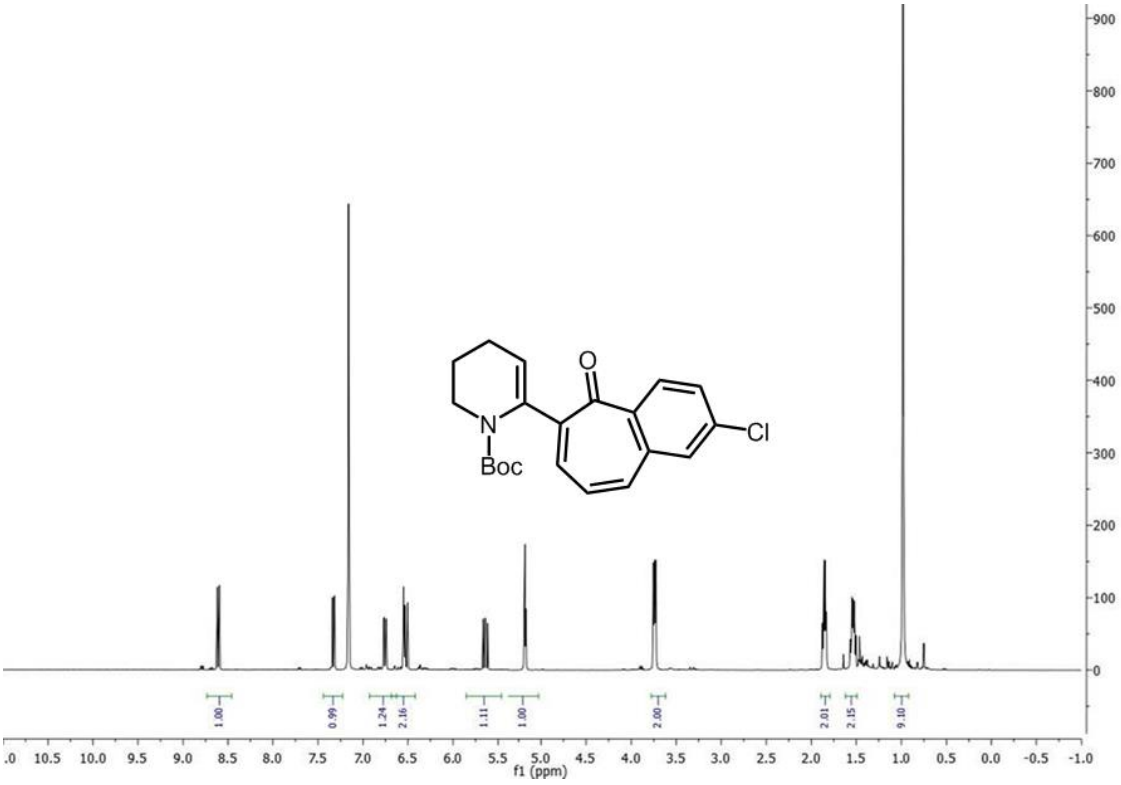






15

Prepared from **10** (65 mg, 0.25 mmol) and bromo enone **3** (80 mg, 0.30 mmol, 1.2 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 67 mg, 72%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.61 (1H, d), 7.32 (1H, d), 6.75 (1H, d), 6.55 to 6.50 (2H, two overlapping signals), 5.67 to 5.61 (1H, dd), 5.19 to 5.17 (1H, t), 3.75 to 3.73 (2H, t), 1.88 to 1.83 (2H, t), 1.57 to 1.47 (2H, m), 0.98 (9H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 186.17, 162.72, 140.91, 138.72, 137.03, 135.33, 135.17, 133.23, 125.41, 118.54, 115.87, 79.80, 44.01, 27.43, 23.38, 23.17. HRMS calc for $C_{21}H_{22}NO_3Cl$ 371.1288, found 371.1281.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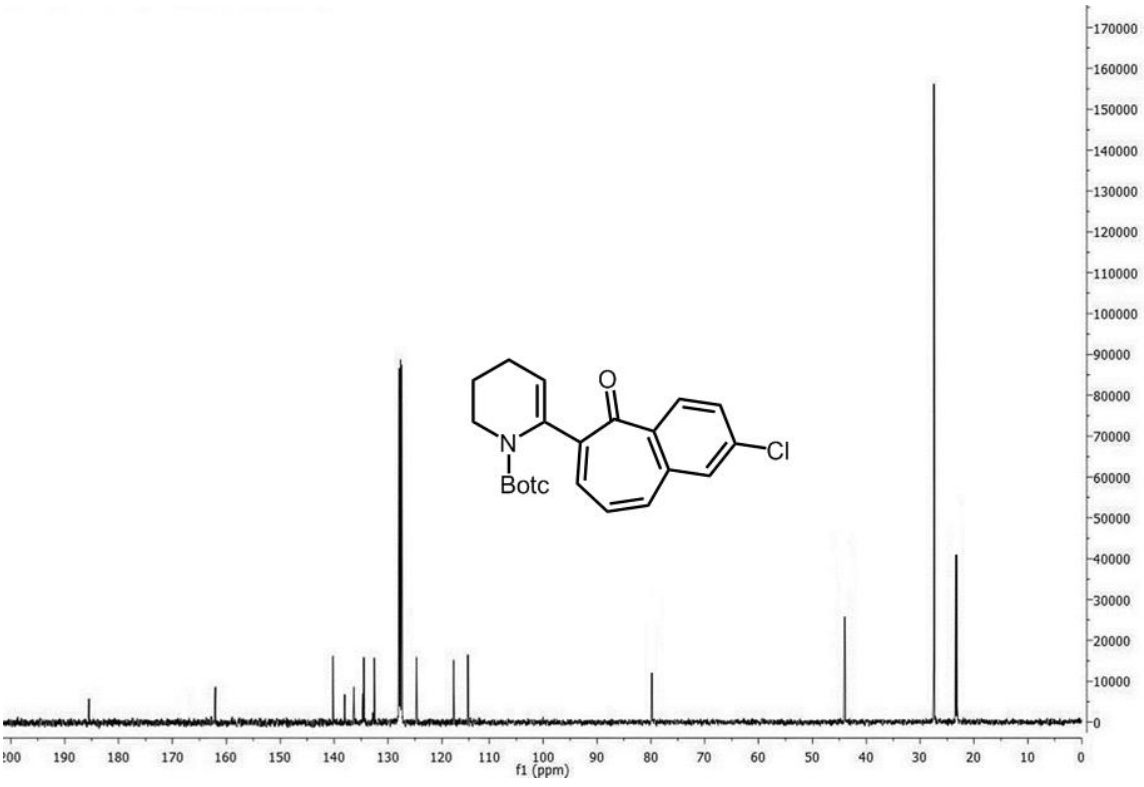
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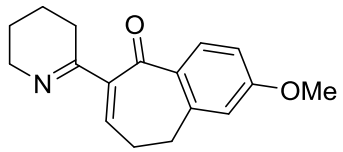
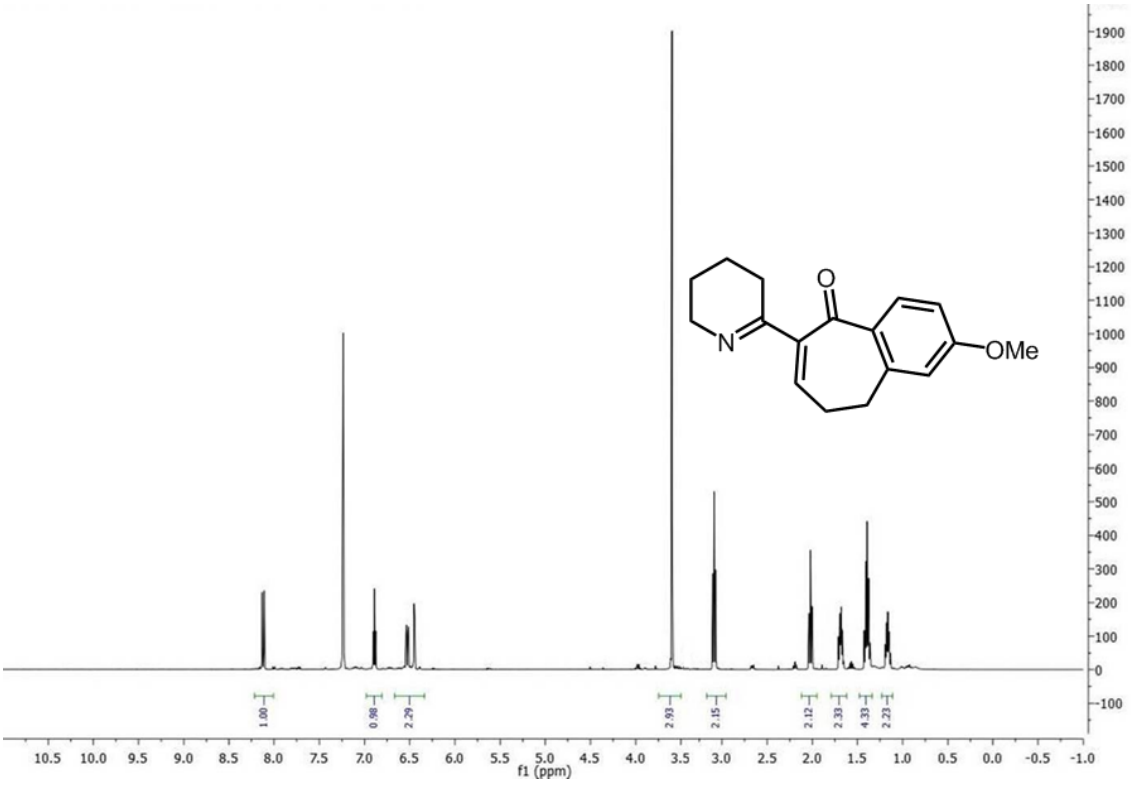
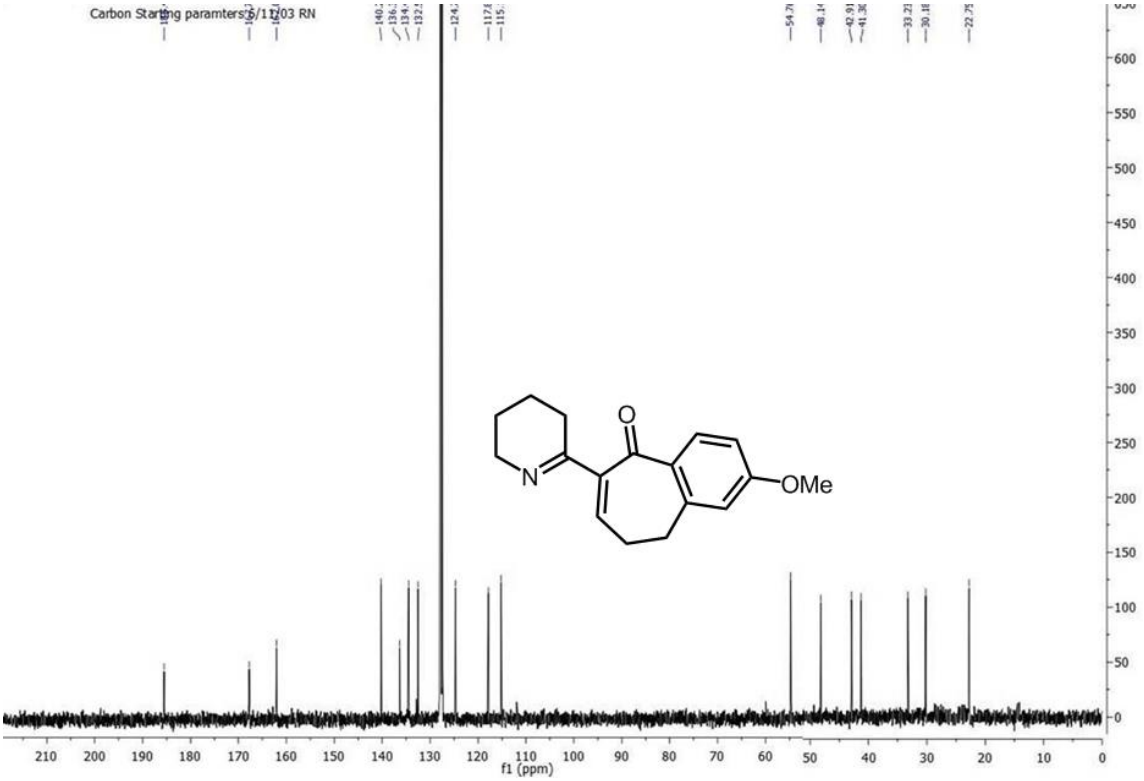
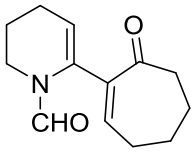


16

Prepared from **10** (260 mg, 1.0 mmol) and bromo enone **4** (319 mg, 1.2 mmol, 1.2 equiv), using General Procedures A and B. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (40:60 to 100:0). Yield = 196 mg, 73%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.11 (1H, d), 6.89 (1H, t), 6.54 (1H, d), 6.45 (1H, s), 3.60 (3H, s), 3.10 to 3.07 (2H, t), 2.04 to 2.00 (2H, t), 1.71 to 1.67 (2H, m), 1.42 to 1.36 (4H, m), 1.19 to 1.15 (2H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 185.49, 167.76, 162.03, 140.22, 136.34, 134.48, 132.54, 124.72, 117.86, 115.18, 54.76, 51.76, 48.14, 42.91, 41.30, 33.23, 30.18, 22.75. HRMS calc for $C_{17}H_{19}NO_2$ 269.1416, found 269.1422.



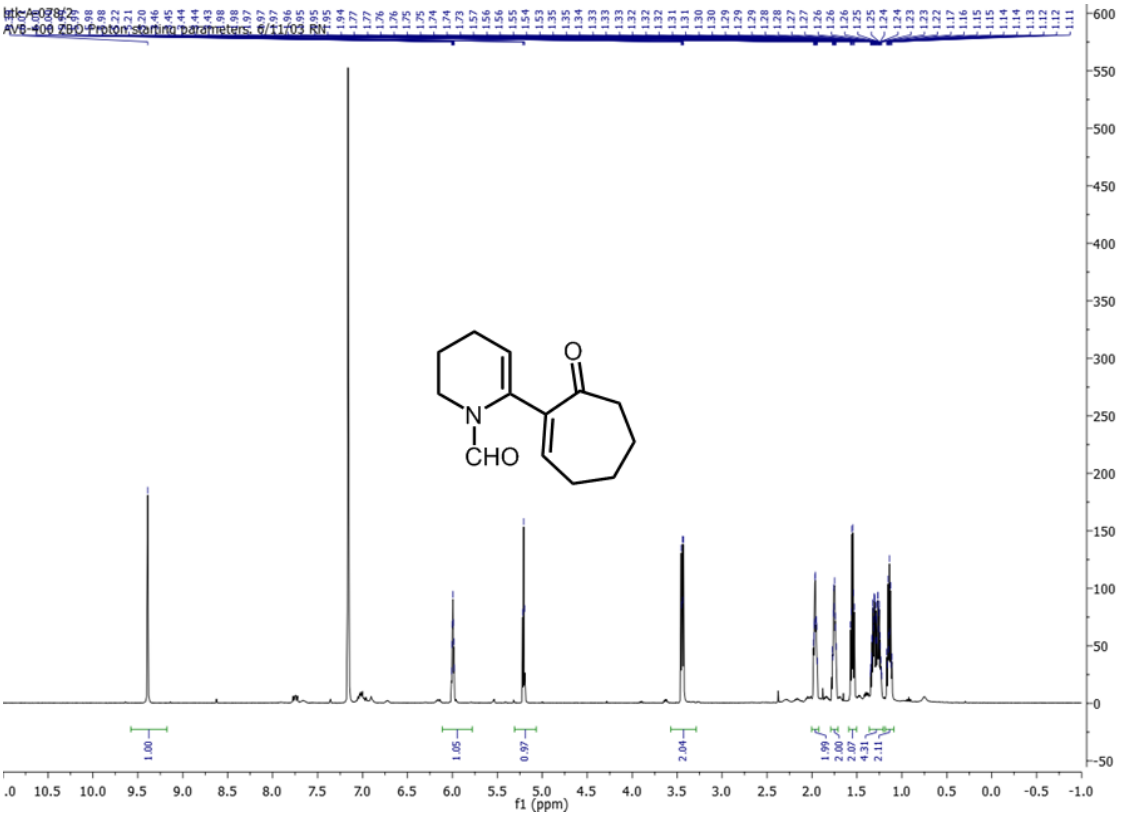




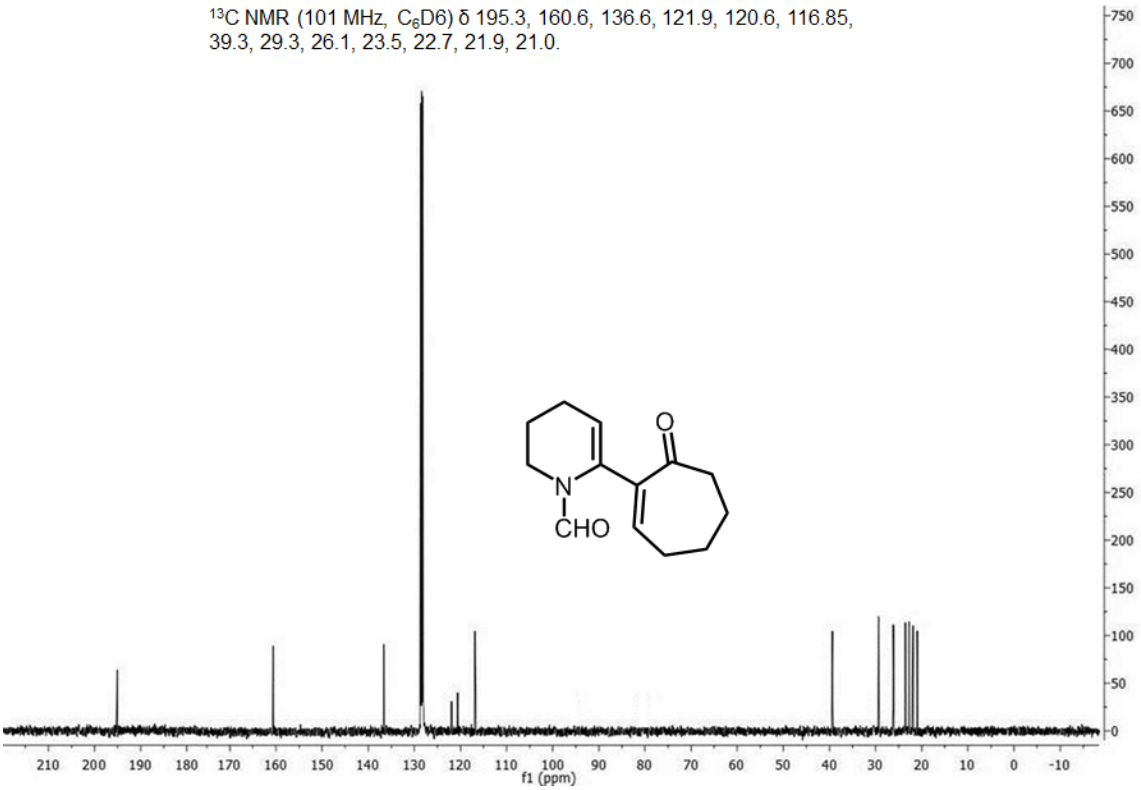
17

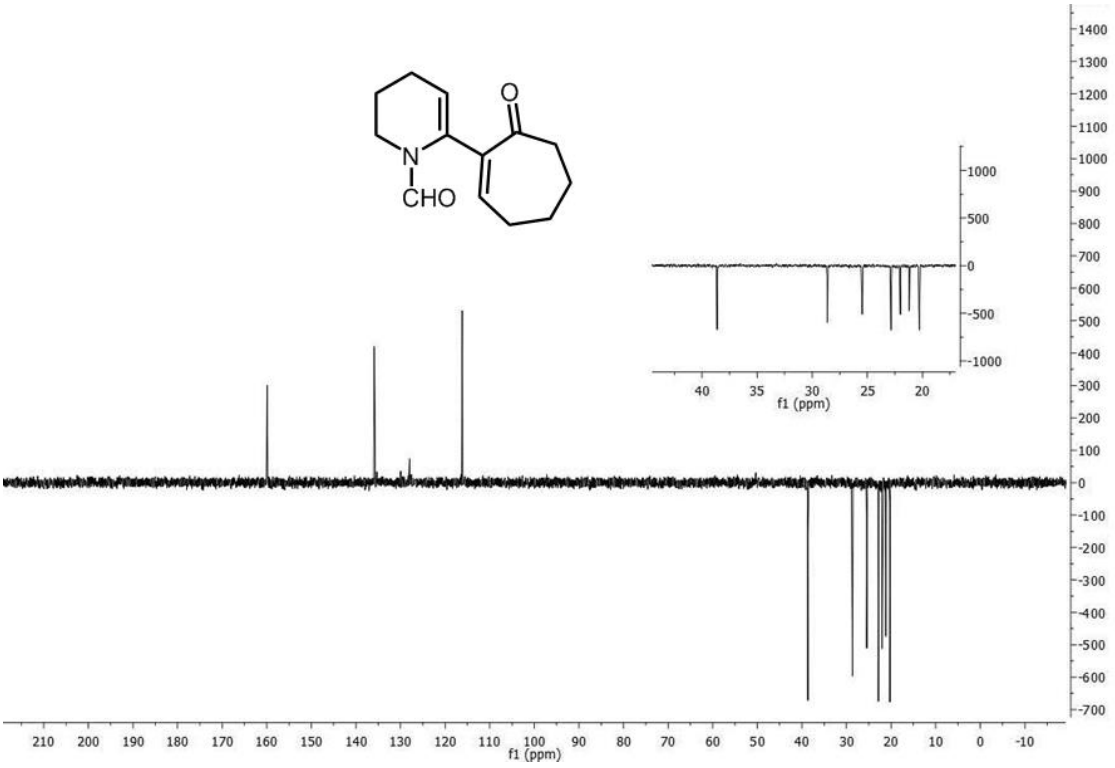
Prepared from **11** (189 mg, 1.0 mmol) and bromo enone **5** (376 mg, 2.0 mmol, 2.0 equiv), using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 90 mg, 41%. ^{1}H NMR (400 MHz, C_6D_6) δ 9.39 (1H, s), 6.01 to 5.98 (1H, t), 5.22 to 5.20 (1H, t), 3.46 to 3.43 (2H, m), 1.98 to 1.94 (2H, m), 1.77 to 1.73 (2H, m), 1.57 to 1.53 (2H, m), 1.35 to 1.22 (4H, m), 1.17 to 1.11 (2H, m). ^{13}C NMR (101 MHz, C_6D6) δ 195.3, 160.6, 136.6, 121.9, 120.6, 116.85, 39.3, 29.3, 26.1, 23.5, 22.7, 21.9, 21.0. HRMS calc for $C_{13}H_{17}NO_2$ 219.1259, found 219.1265.

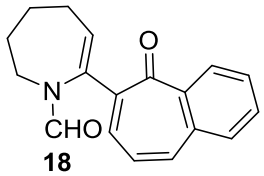
Note: The yield of **17** improves to 57% when **5** is added slowly over the course of an hour.



^{13}C NMR (101 MHz, C_6D6) δ 195.3, 160.6, 136.6, 121.9, 120.6, 116.85, 39.3, 29.3, 26.1, 23.5, 22.7, 21.9, 21.0.

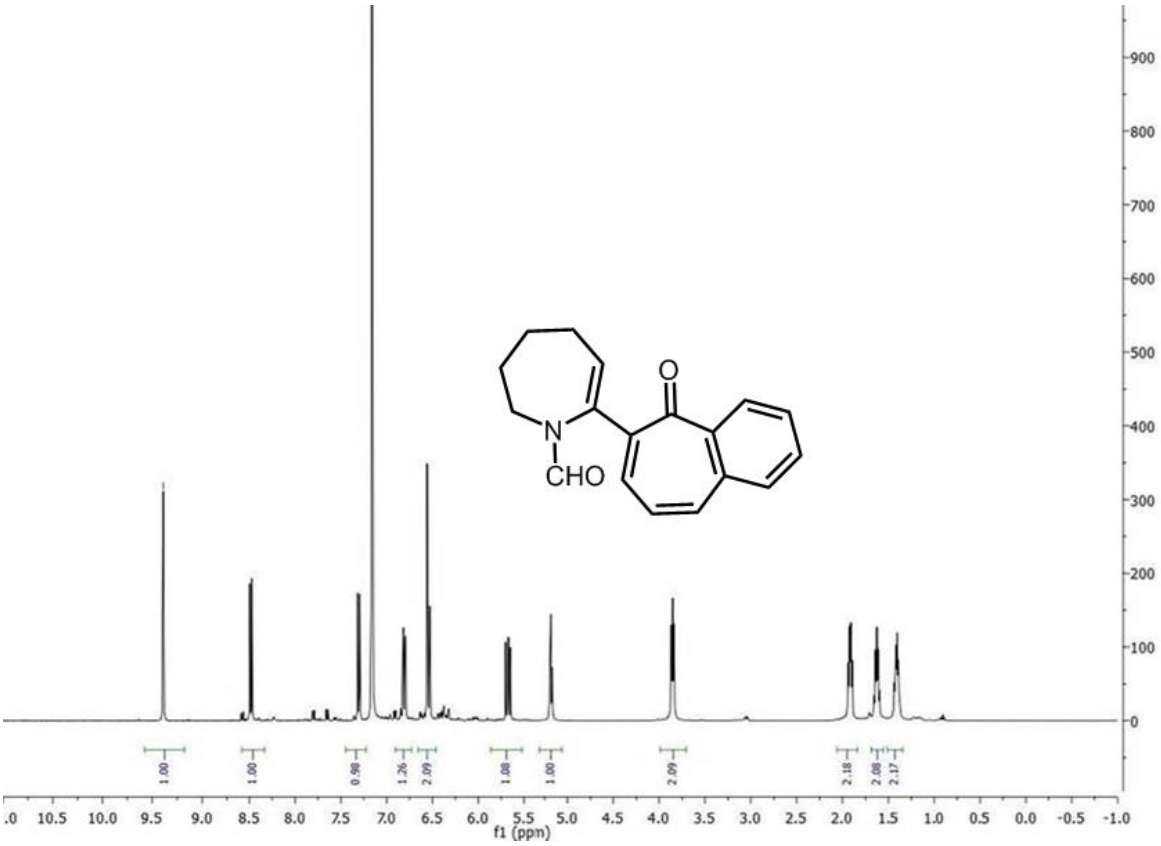


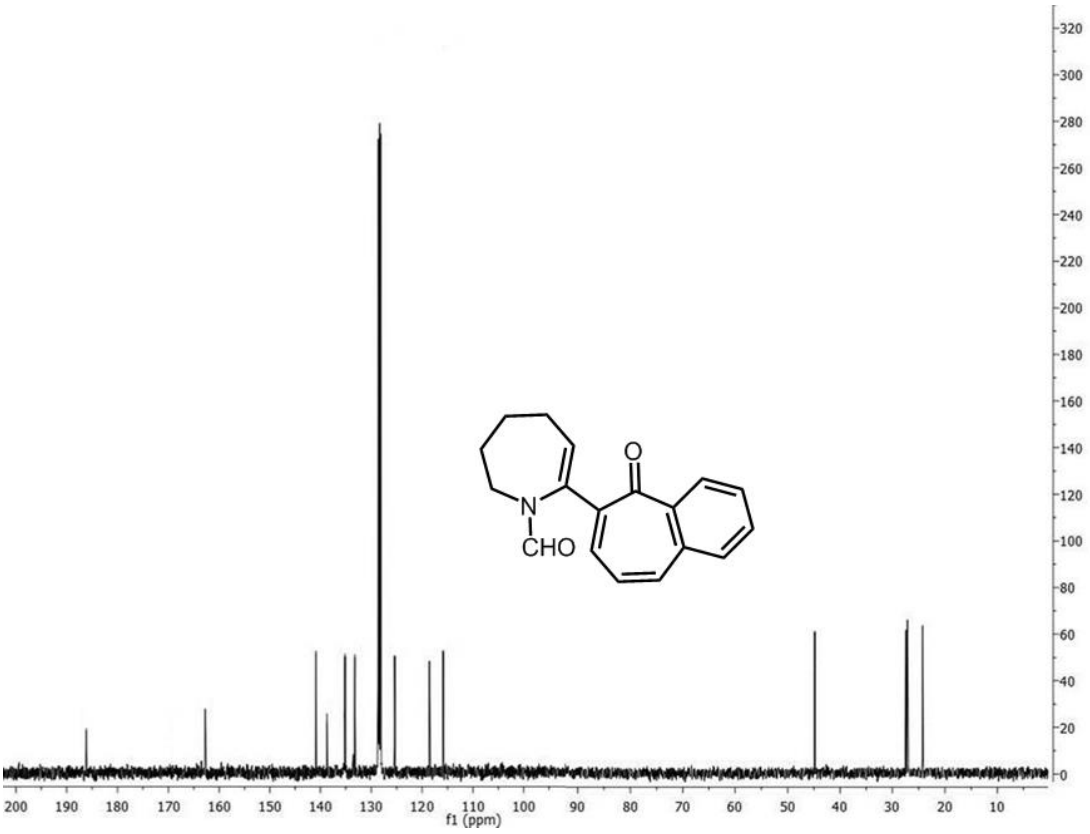


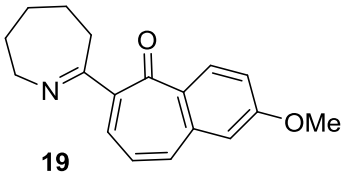


18

Prepared from **12** (51 mg, 0.25 mmol) and bromo enone **1** (62.5 mg, 1.2 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 53 mg, 75%. ^{1}H NMR (400 MHz, C_6D_6) 9.37 (1H, s), 8.27 (1H, d), 7.29 (1H, d), 6.81 (1H, d), 6.58 to, 6.51 (1H, overlapping singlet and doublet), 5.73 to 5.70 (1H, dd), 5.20 to 5.17 (1H, t), 3.87 to 3.84 (2H, t), 1.94 to 1.89 (2H, m), 1.66 to 1.60 (2H, m), 1.43 to 1.37 (2H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 187.79, 163.2, 141.71, 140.80, 137.32, 136.05, 124.98, 118.46, 116.12, 44.83, 27.43, 27.11, 24.25. HRMS calc for $C_{18}H_{17}NO_2$ 279.1259, found 279.1266.

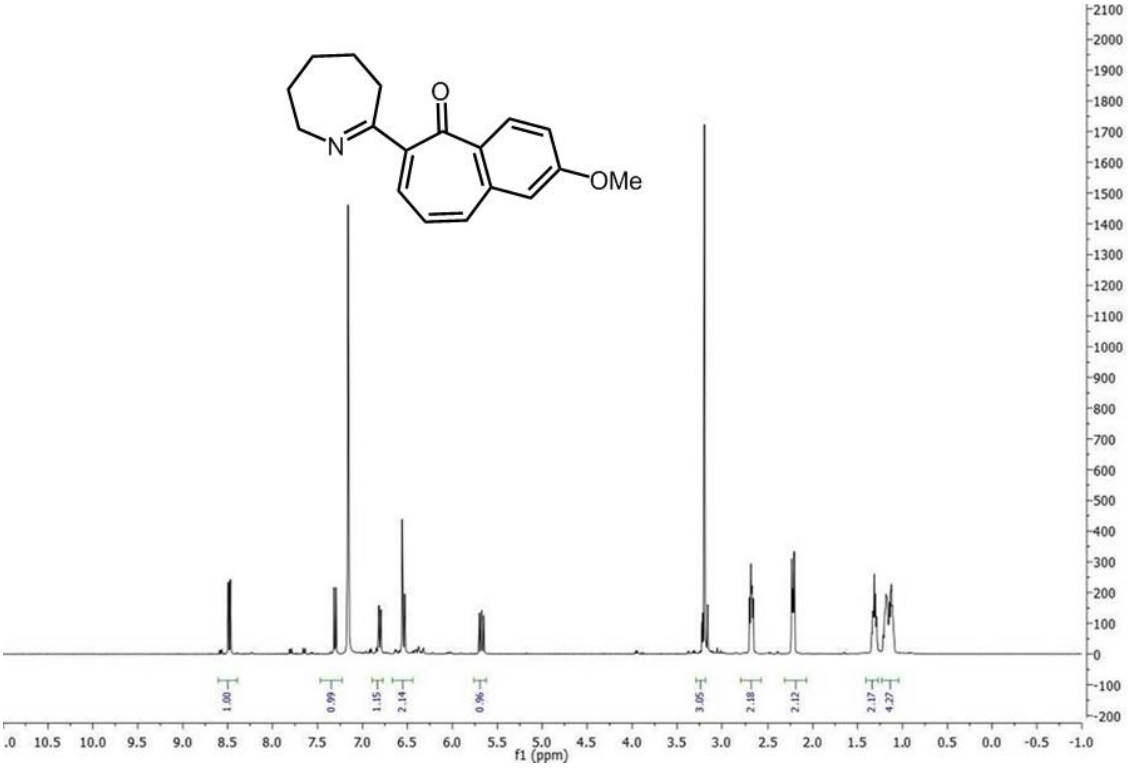

O
N
CHO
1.00
1.00
0.98
1.26
2.09
1.08
1.00
2.09
2.18
2.08
2.17
f1 (ppm)

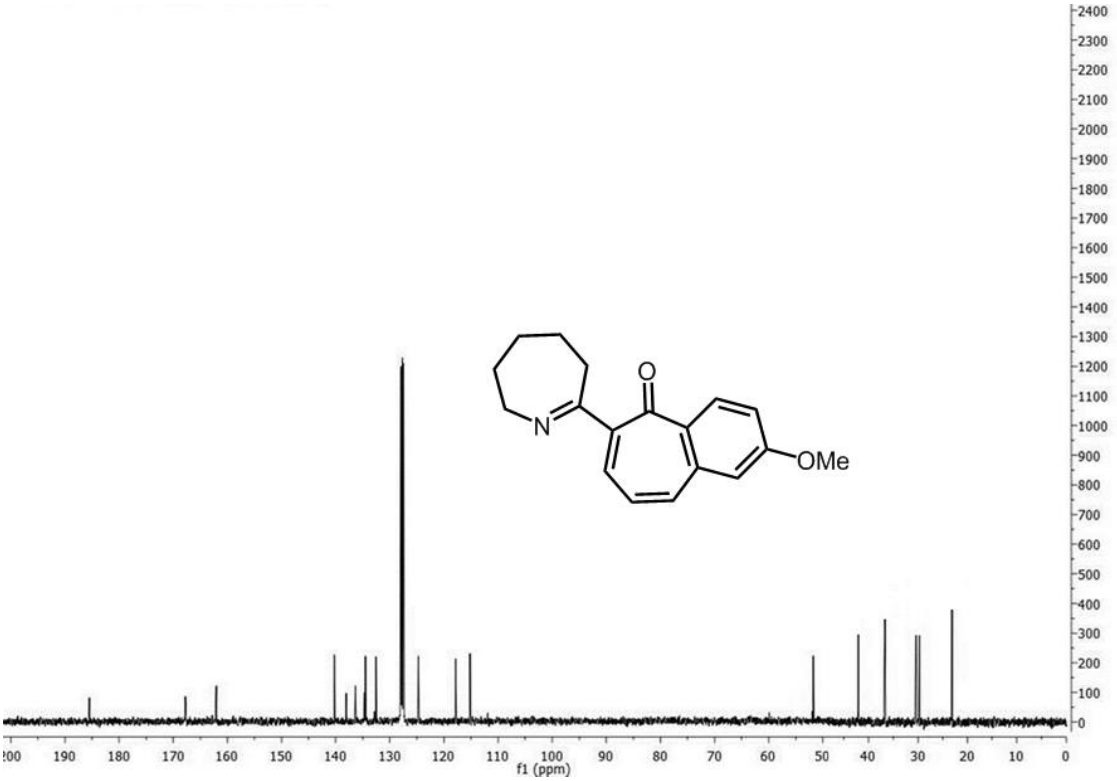

O
N
CHO
f1 (ppm)

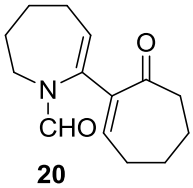


19

Prepared from **12** (260 mg, 1.0 mmol) and bromo enone **2** (319 mg, 1.2 mmol, 1.2 equiv), using General Procedures A and B. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 100:0). Yield = 242 mg, 86%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.48 (1H, d), 7.30 (1H, d), 6.79 (1H, d), 6.56 to 6.53 (2H, overlapping singlet and doublet), 5.70 to 5.65 (1H, dd), 3.20 (3H, s), 2.70 to 2.67 (2H, t), 2.23 to 2.21 (2H, m), 1.34 to 1.10 (6H, m). ^{13}C NMR (101 MHz, C_6D_6) 186.17, 168.45, 162.72, 140.91, 138.72, 137.03, 135.33, 135.17, 133.23, 125.41, 118.54, 115.87, 52.2, 42.09, 36.73, 30.34, 29.70, 23.14. HRMS calc for $C_{18}H_{19}NO_2$ 281.1416, found 281.1423.

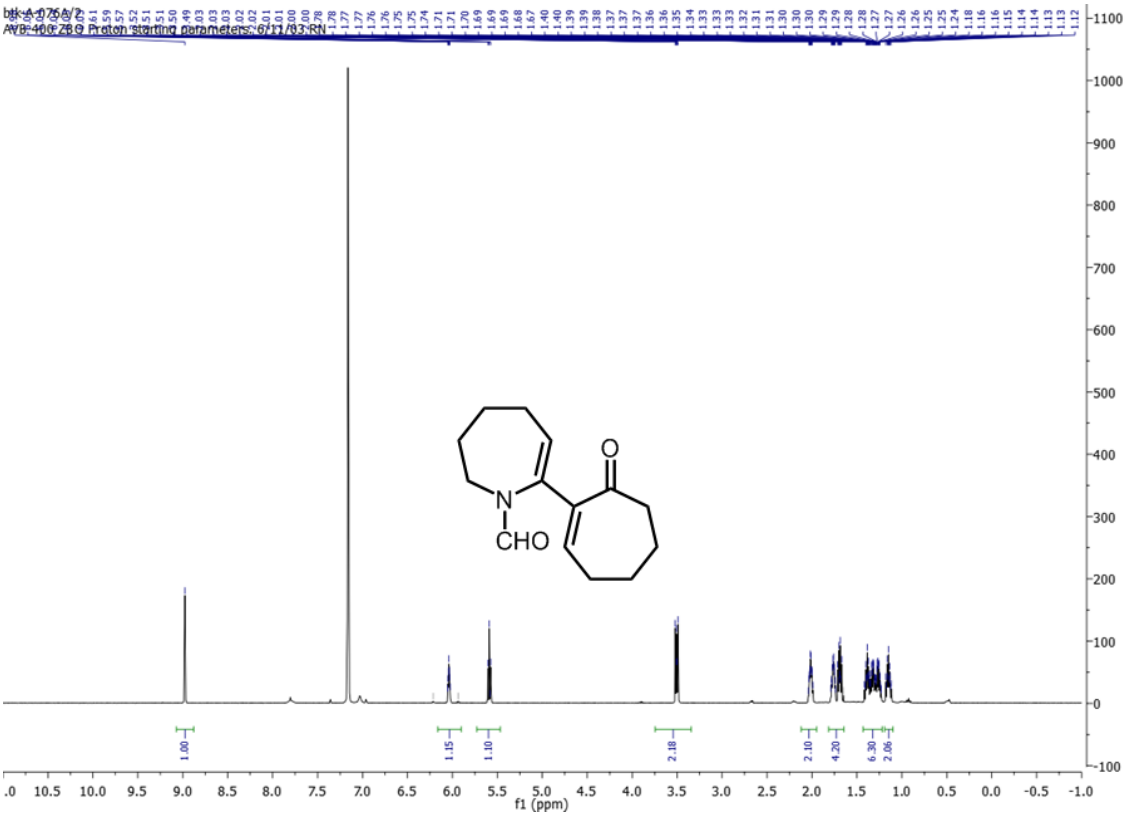


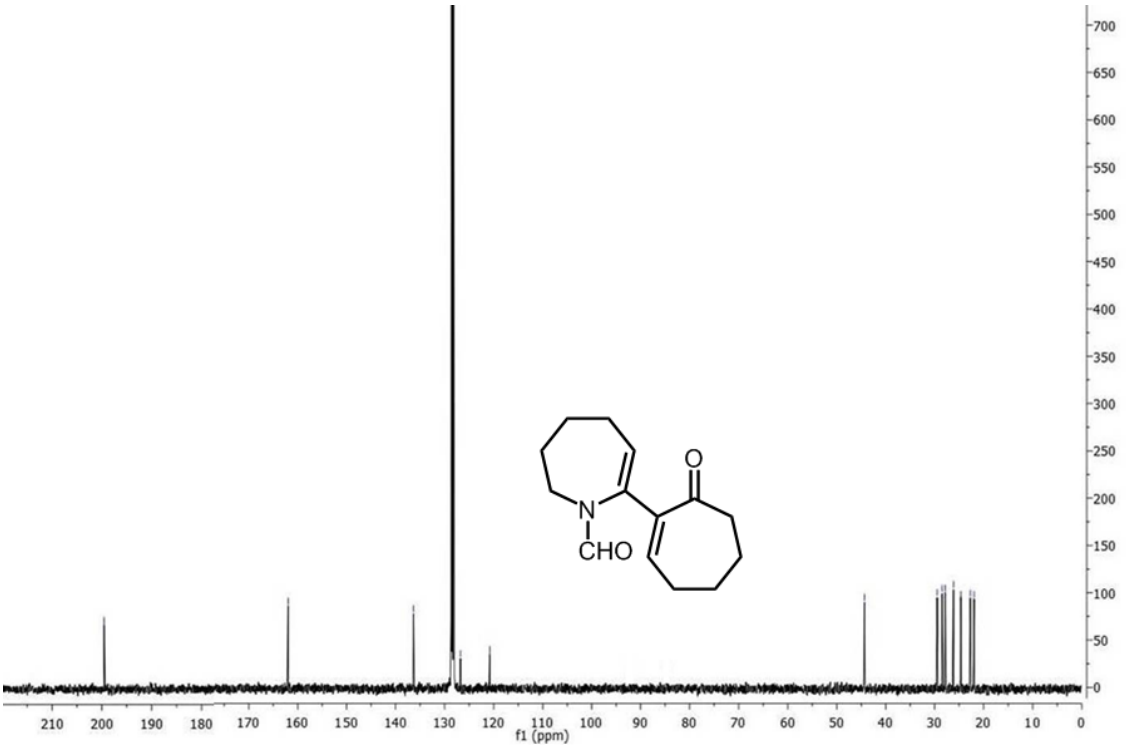


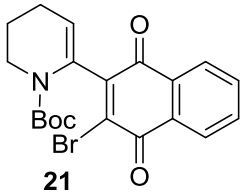


20

Prepared from **12** (203 mg, 1.0 mmol) and bromo enone **5** (376 mg, 2.0 mmol, 2.0 equiv), using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 110 mg, 47%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.98 (1H, s), 6.05 to 6.02 (1H, t) 5.61 to 5.57 (1H, t), 3.52 to 3.49 (2H, m), 2.04 to 1.99 (2H, m), 1.79 to 1.65 (4H, m), 1.42 to 1.12 (8H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 199.5, 161.95, 136.36, 128.52, 126.76, 120.81, 44.35, 29.49, 28.46, 27.84, 26.18, 24.69, 22.75, 21.94. HRMS calc for $C_{13}H_{17}NO_2$ 233.1416, found 233.1423.

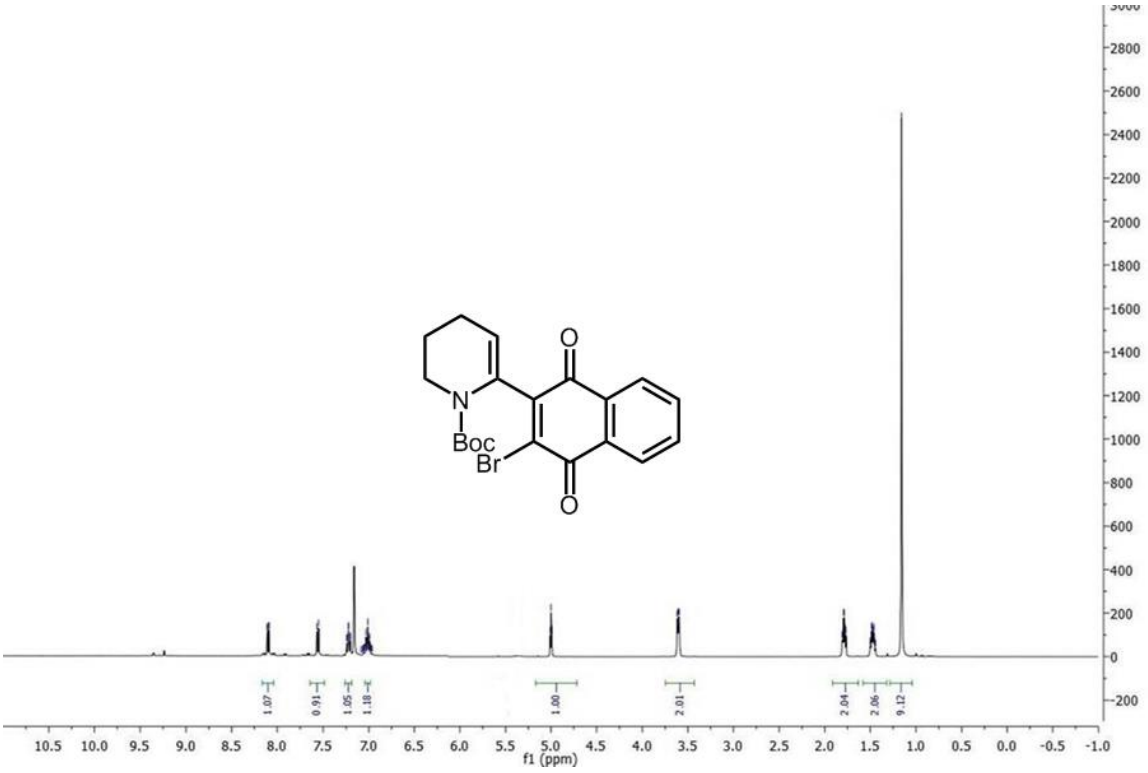

O
N
CHO
1.00
1.15
1.10
2.18
2.10
4.20
6.30
2.06
f1 (ppm)

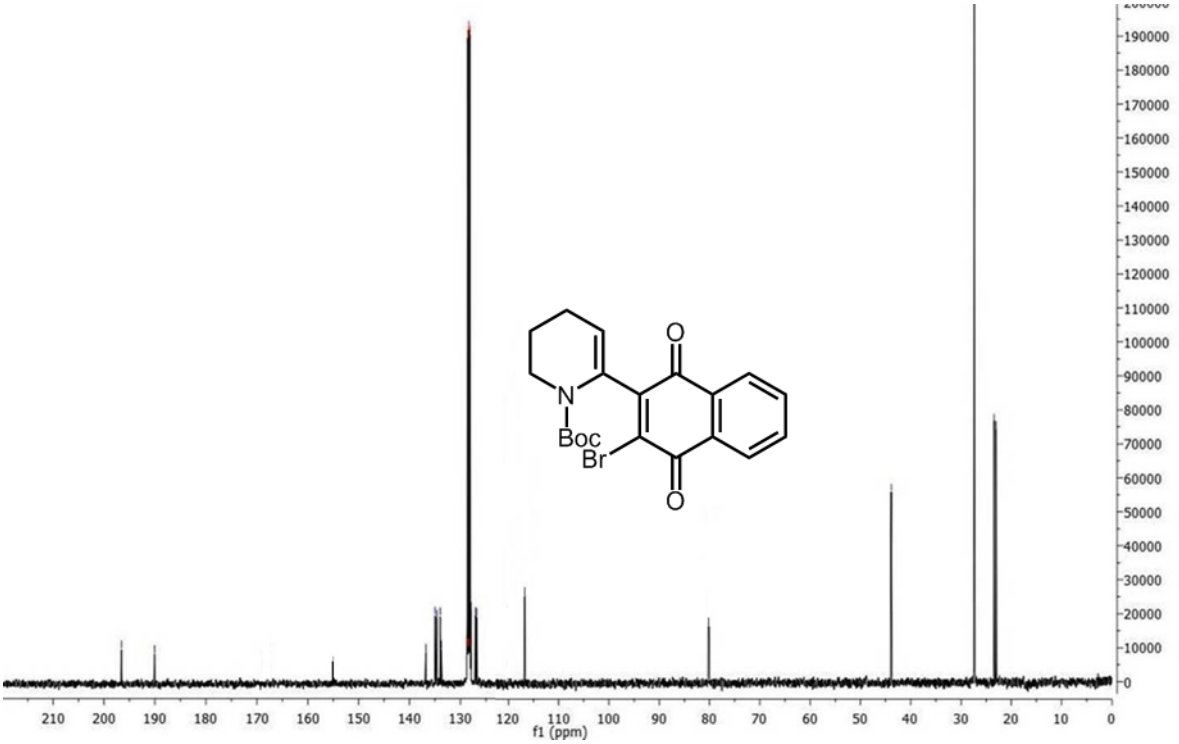

O
N
CHO
f1 (ppm)

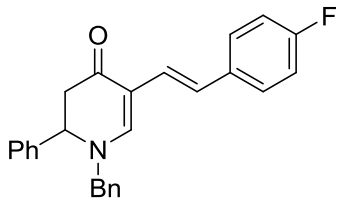


21

Prepared from **10** (65 mg, 0.25 mmol) and dibromo quinone **6** (94 mg, 0.30 mmol, 1.2 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 70:30). Yield = 67 mg, 37%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.11 (1H, d), 7.56 (2H, d), 7.24 (1H, t), 7.09 to 6.96 (1H, t), 5.01 to 4.99 (1H, t), 3.62 to 3.59 (2H, t), 1.81 to 1.77 (2H, t), 1.50 to 1.44 (2H, m), 1.16 (9H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 196.61, 190.06, 155.01, 136.80, 134.99, 134.66, 133.99, 133.76, 128.62, 127.95, 127.10, 126.78, 116.78, 80.19, 43.87, 27.38, 23.39, 23.01. HRMS calc for $C_{20}H_{20}BrNO_4$ 417.0576, found 417.0604.

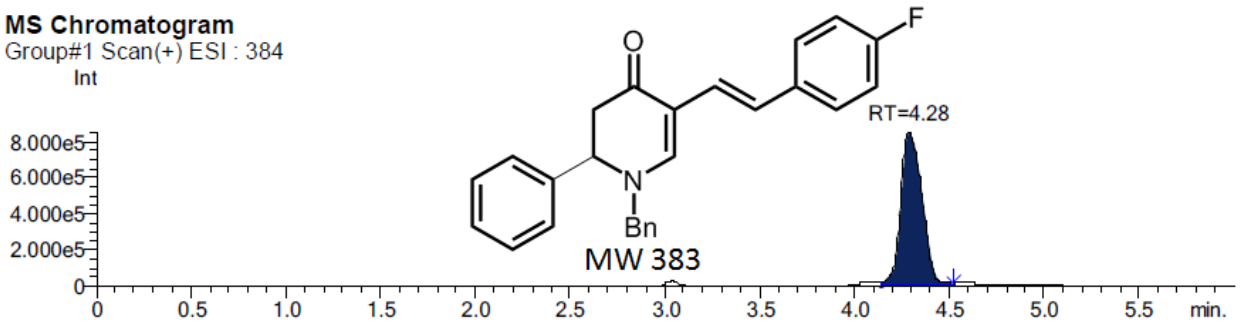


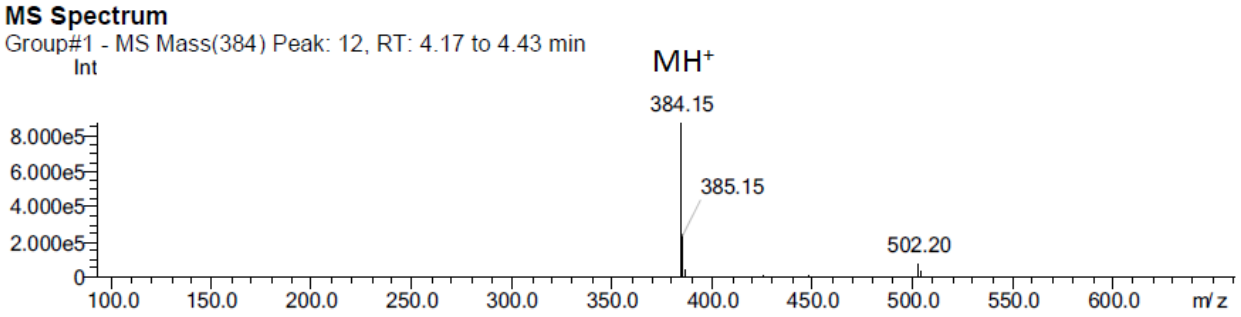


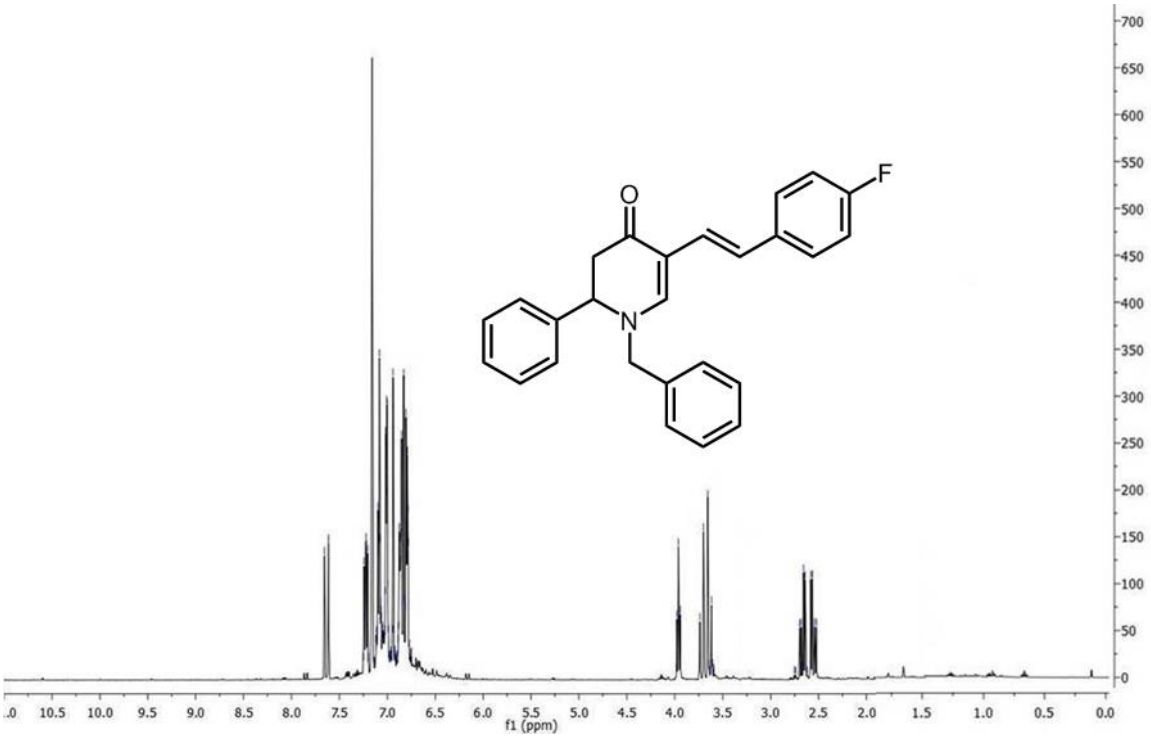


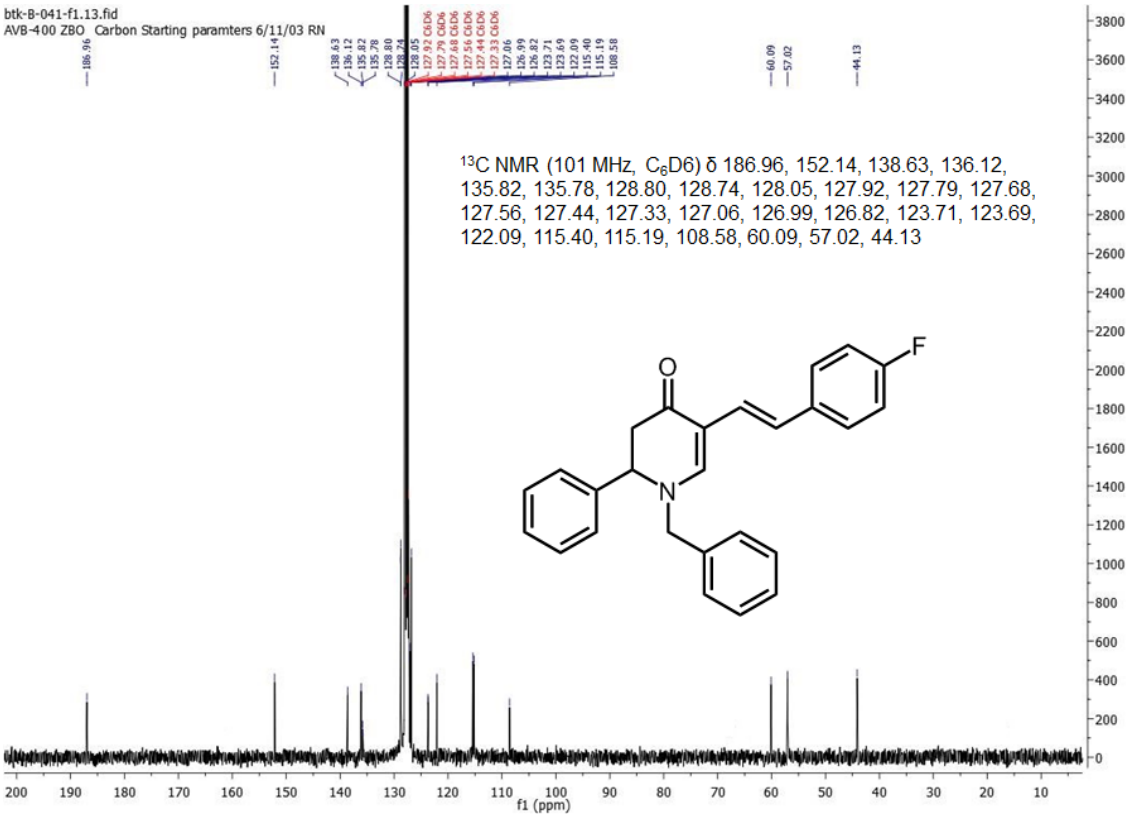
22

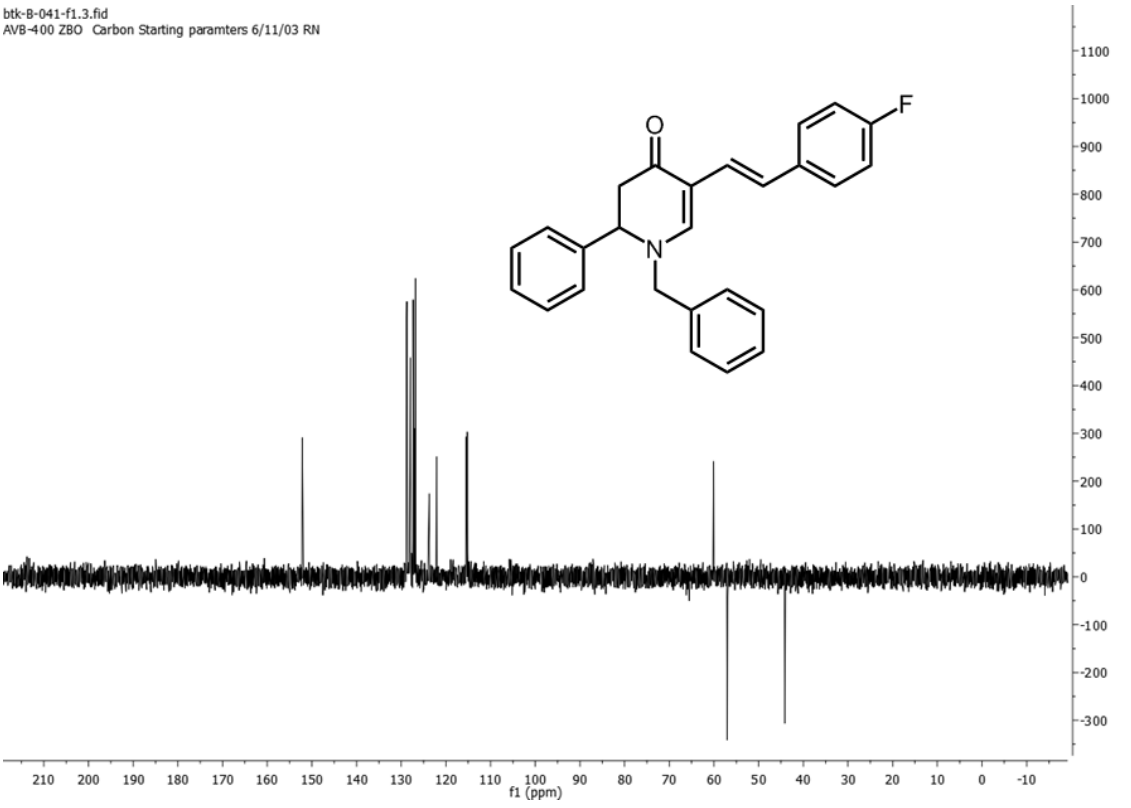
Prepared from *p*-fluoro-β-bromostyrene (400 mg, 2 mmol, 2 equiv) and bromo enaminone **7** (341 mg, 1.0 mmol, 1.0 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 50:50). Yield = 295 mg, 77%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.66 (1H, d), 7.25 to 6.75 (15H, m), 3.98 to 3.94 (1H, t), 3.74 to 3.61 (2H, m), 2.75 to 2.52 (2H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 186.96, 152.14, 138.63, 136.12, 135.82, 135.78, 128.80, 128.74, 128.05, 127.92, 127.79, 127.68, 127.56, 127.44, 127.33, 127.06, 126.99, 126.82, 123.71, 123.69, 122.09, 115.40, 115.19, 108.58, 60.09, 57.02, 44.13. HRMS calc for $C_{26}H_{22}FNO$ 383.1685, found 383.1694.

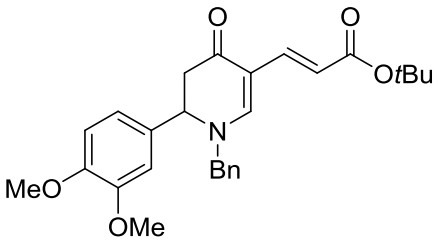

MS Chromatogram
Group#1 Scan(+) ESI : 384
Int
8.000e5
6.000e5
4.000e5
2.000e5
0
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
min.
RT=4.28
O
F
N
Bn
MW 383


MS Spectrum
Group#1 - MS Mass(384) Peak: 12, RT: 4.17 to 4.43 min
Int
8.000e5
6.000e5
4.000e5
2.000e5
0
MH+
384.15
385.15
502.20
100.0
150.0
200.0
250.0
300.0
350.0
400.0
450.0
500.0
550.0
600.0
m/z


O
F
N
f1 (ppm)

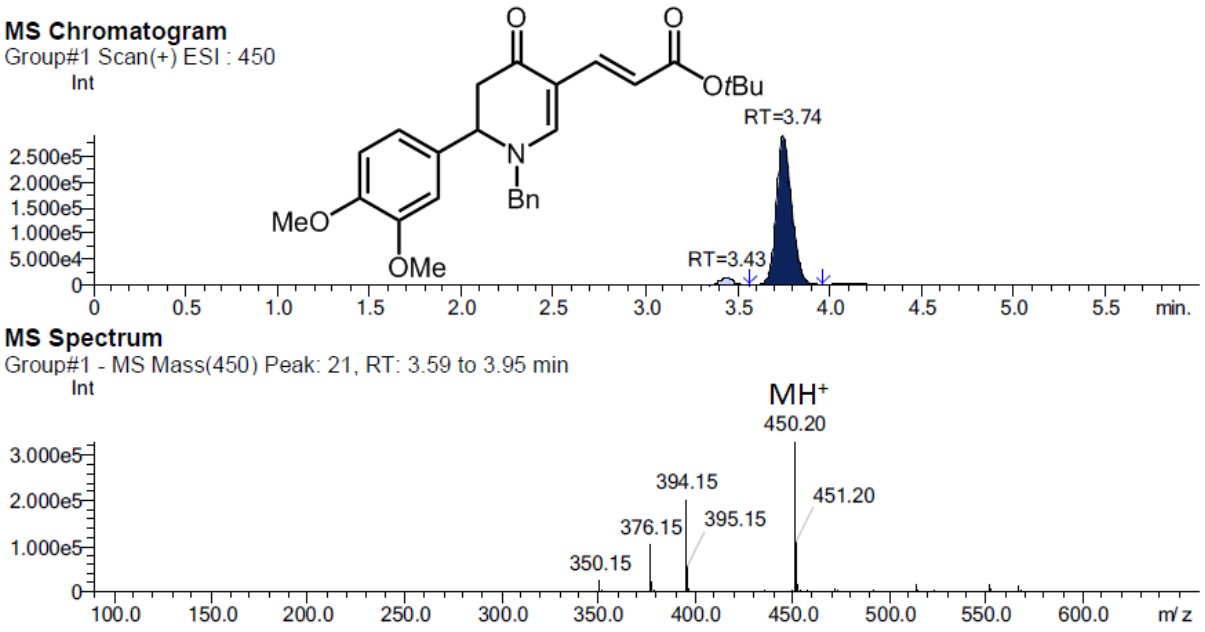

btk-B-041-f1.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
186.96
152.14
138.63
136.12
135.82
135.78
128.80
128.74
128.05
127.92 C6D6
127.79 C6D6
127.68 C6D6
127.56 C6D6
127.44 C6D6
127.33 C6D6
127.06
126.99
126.82
123.71
123.69
122.09
115.40
115.19
108.58
60.09
57.02
44.13
13C NMR (101 MHz, C6D6) δ 186.96, 152.14, 138.63, 136.12, 135.82, 135.78, 128.80, 128.74, 128.05, 127.92, 127.79, 127.68, 127.56, 127.44, 127.33, 127.06, 126.99, 126.82, 123.71, 123.69, 122.09, 115.40, 115.19, 108.58, 60.09, 57.02, 44.13
O
N
F
f1 (ppm)

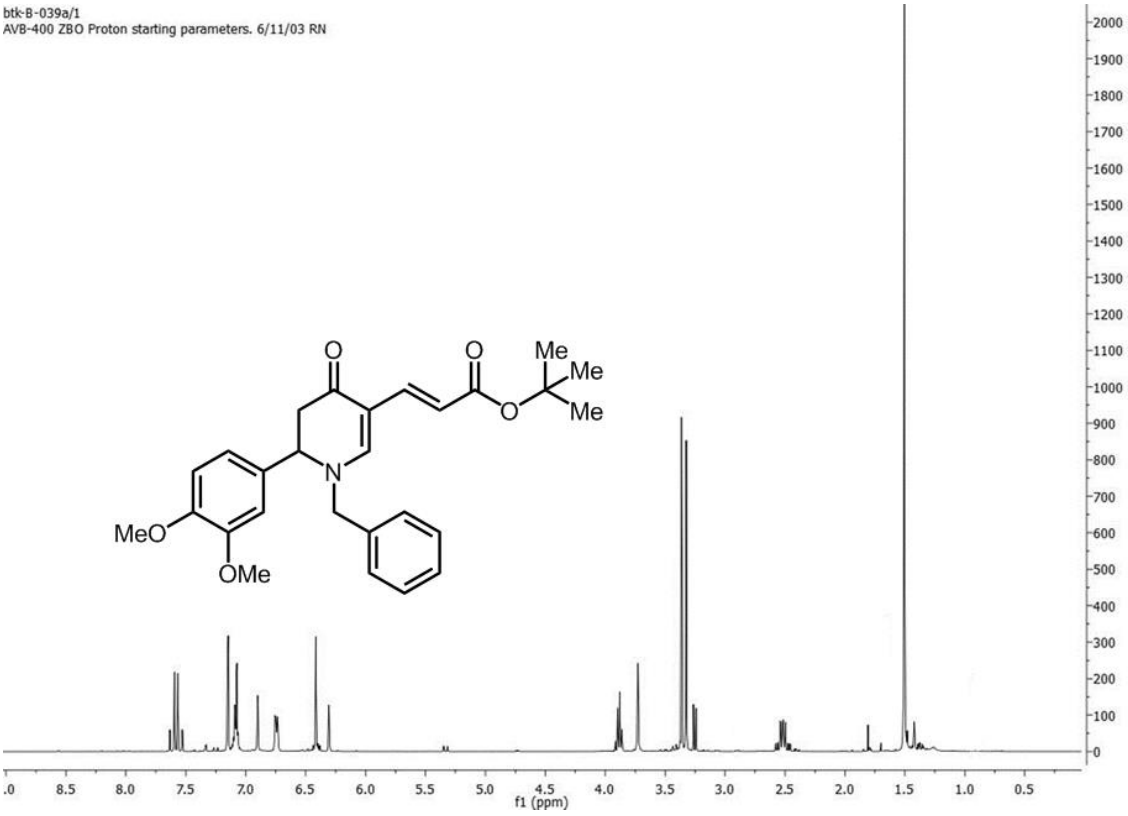

btk-B-041-f1.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
O
N
F
f1 (ppm)

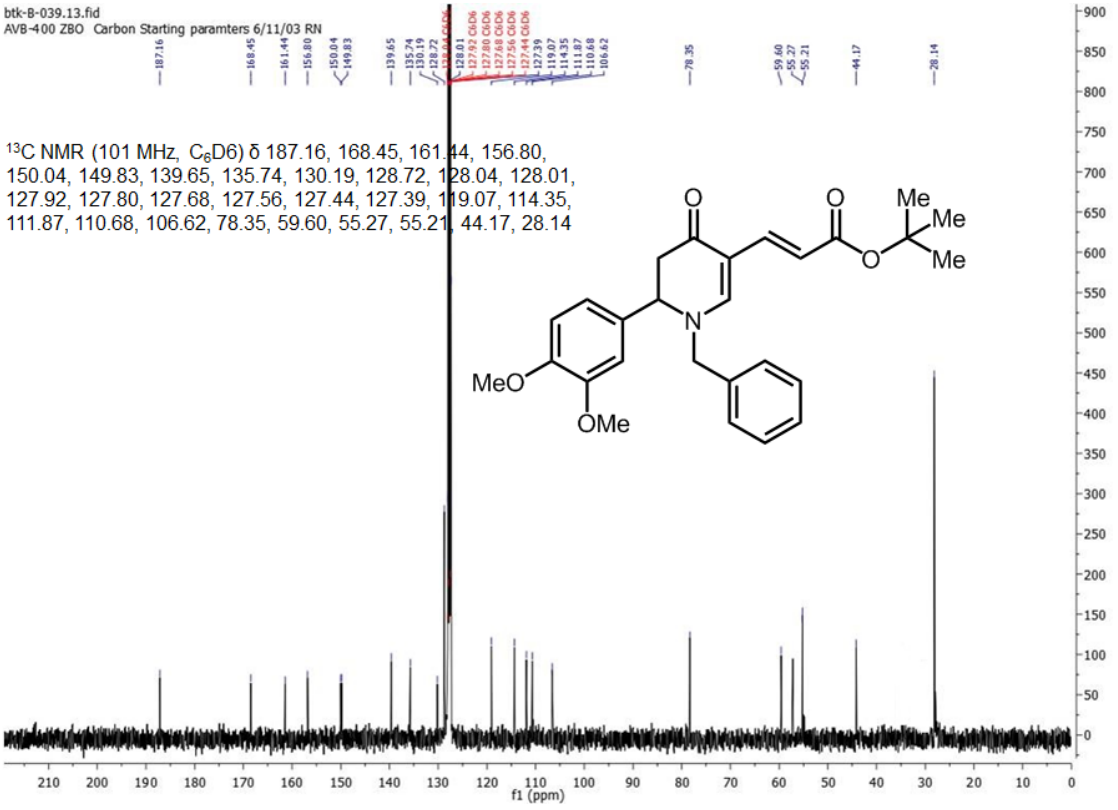


23

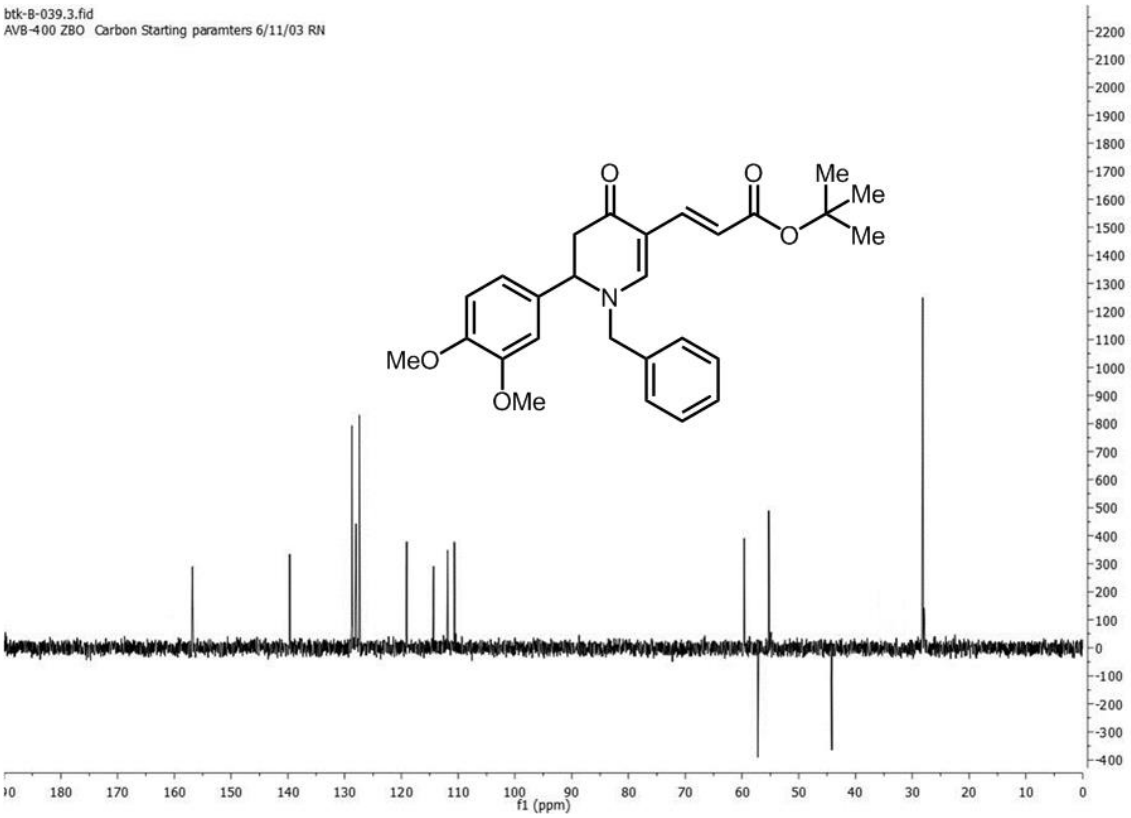
Prepared from β-bromo-*tert*-butylacrylate (206 mg, 1 mmol, 2 equiv) and bromo enaminone **8** (201 mg, 0.5 mmol, 1.0 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 20:80). Yield = 156 mg, 69%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.63 (2H, m), 7.10 to 7.07 (5H, m), 6.90 (1H, s), 6.76 to 6.73 (1H, d), 6.41 (2H, unresolved signals), 3.91 to 3.86 (1H, t), 3.73 (1H, s), 3.41 (3H, s), 3.38 (3H, s), 3.24 (1H, d), 2.53 to 2.46 (2H, m), 1.50 (9H), s. ^{13}C NMR (101 MHz, C_6D_6) δ 187.1, 168.4, 161.4, 156.8, 150.0, 149.8, 139.6, 135.7, 130.1, 128.7, 128.0, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 119.0, 114.3, 111.8, 110.6, 106.6, 78.3, 59.6, 55.2, 55.2, 44.1, 28.1. HRMS calc for $C_{27}H_{31}NO_5$ 449.2202, found 449.2610.

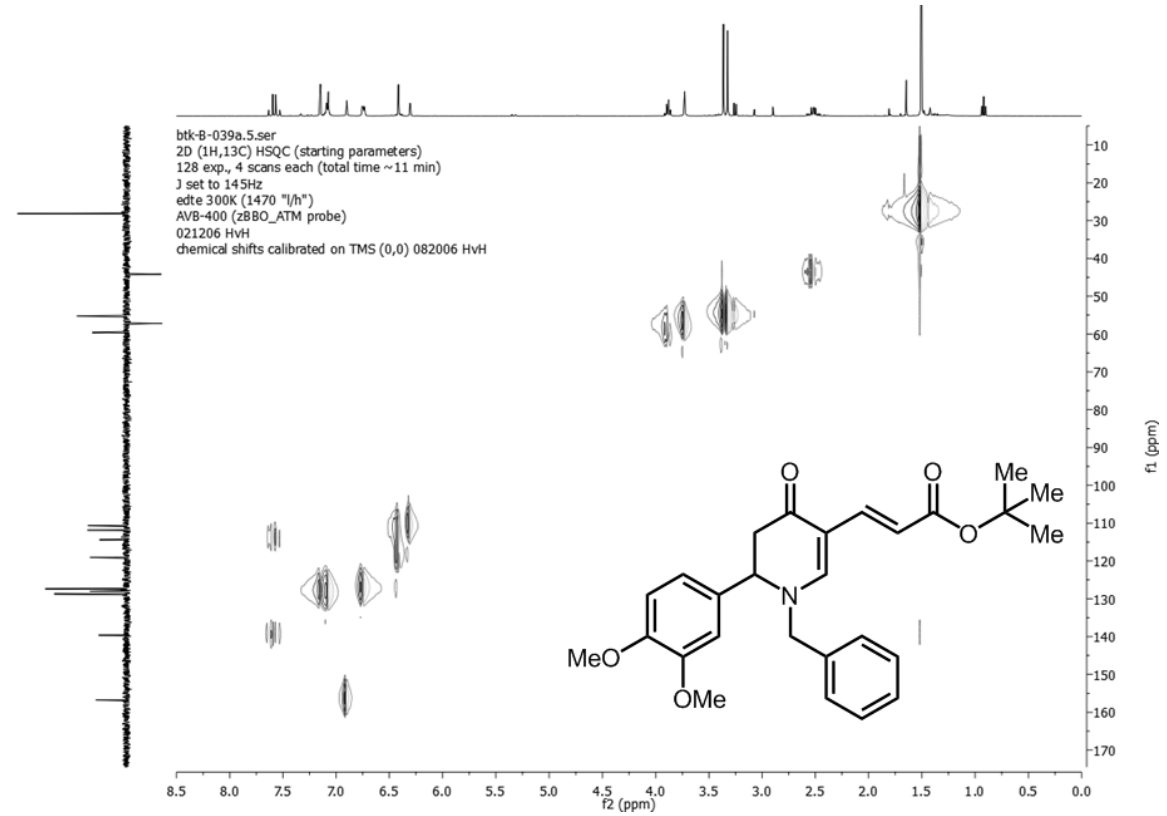


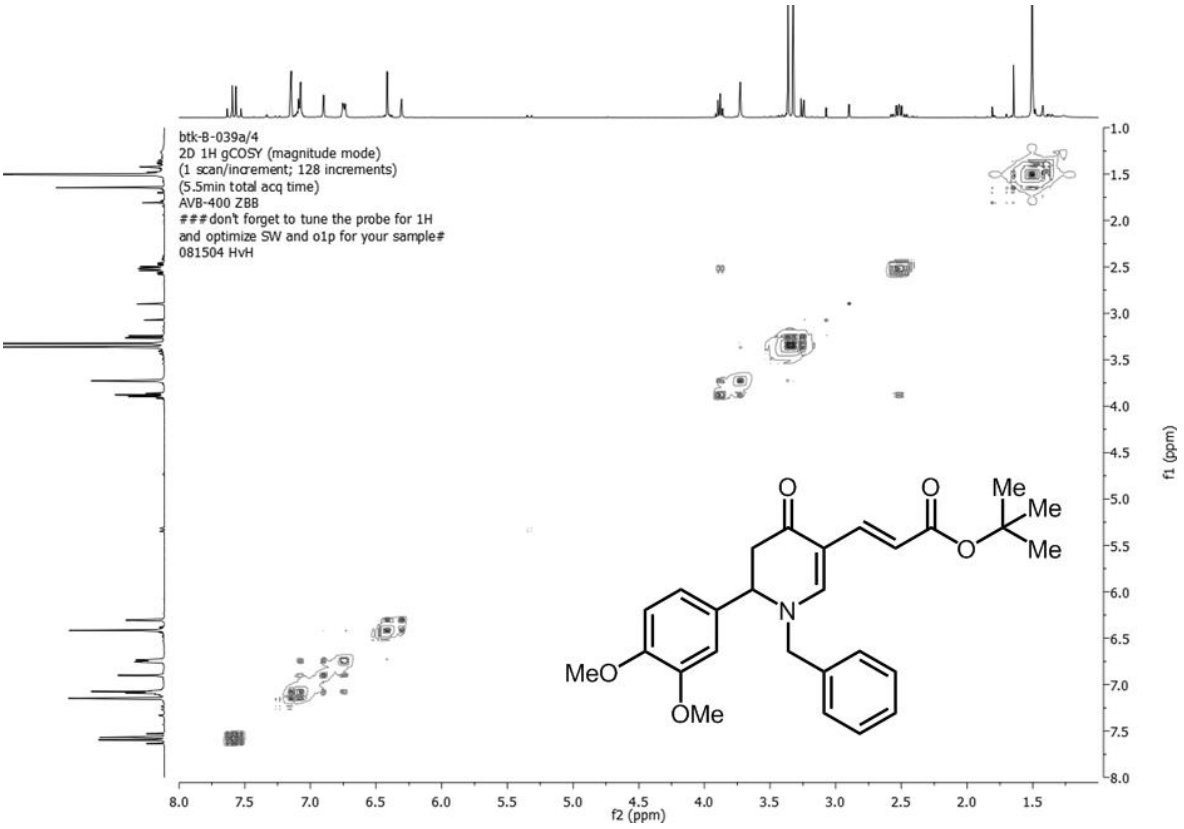


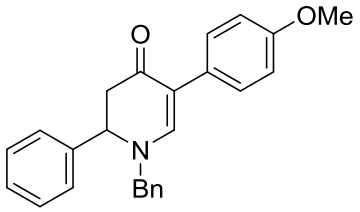


^{13}C NMR (101 MHz, C_6D6) δ 187.16, 168.45, 161.44, 156.80, 150.04, 149.83, 139.65, 135.74, 130.19, 128.72, 128.04, 128.01, 127.92, 127.80, 127.68, 127.56, 127.44, 127.39, 119.07, 114.35, 111.87, 110.68, 106.62, 78.35, 59.60, 55.27, 55.21, 44.17, 28.14


btk-B-039.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
O
O
Me
Me
Me
O
N
MeO
OMe
f1 (ppm)

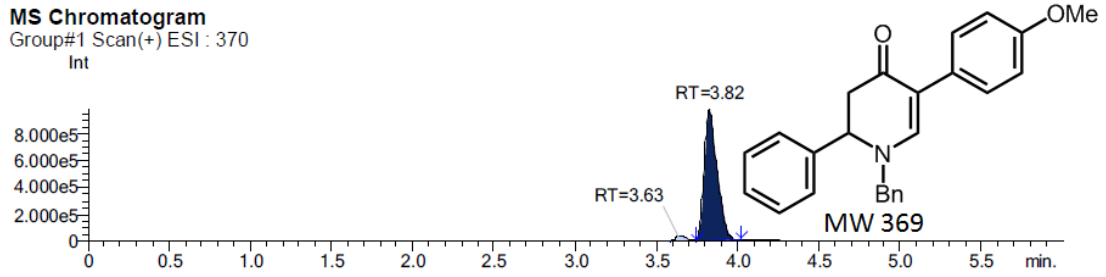

btk-B-039a.5.ser
2D (1H,13C) HSQC (starting parameters)
128 exp., 4 scans each (total time ~11 min)
J set to 145Hz
edte 300K (1470 "l/h")
AVB-400 (zBBO_ATM probe)
021206 HvH
chemical shifts calibrated on TMS (0,0) 082006 HvH
O
O
Me
Me
Me
O
N
MeO
OMe
f2 (ppm)
f1 (ppm)





24

Prepared from bromobenzene (2 mmol, 2 equiv) and bromo enaminone **7** (341 mg, 1.0 mmol, 1.0 equiv), using General Procedure A. T = 23 ^{o}C, time = 48 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 50:50). Yield = 229 mg, 62%. Spectroscopic data as reported.[7] ^{1}H NMR (400 MHz, C_6D_6) δ 7.73 (1H, d), 7.44 (2H, d), 7.10 to 6.64 (12H, m), 4.07 to 4.04 (1H, dd), 3.91 (2H, m), 3.89 (3H, s), 2.91 (1H, dd), 2.82 (1H, dd). ^{13}C NMR (101 MHz, C_6D_6) δ 186.59, 158.98, 158.13, 151.44, 139.09, 136.53, 133.63, 128.91, 128.74, 128.62, 128.06, 127.92, 127.80, 127.76, 127.68, 127.56, 127.44, 127.00, 114.23, 113.64, 60.61, 56.78, 56.44, 54.52, 44.63. HRMS calc for $C_{25}H_{23}NO_2$ 369.1729, found 369.1733.


MS Chromatogram
Group#1 Scan(+) ESI : 370
Int
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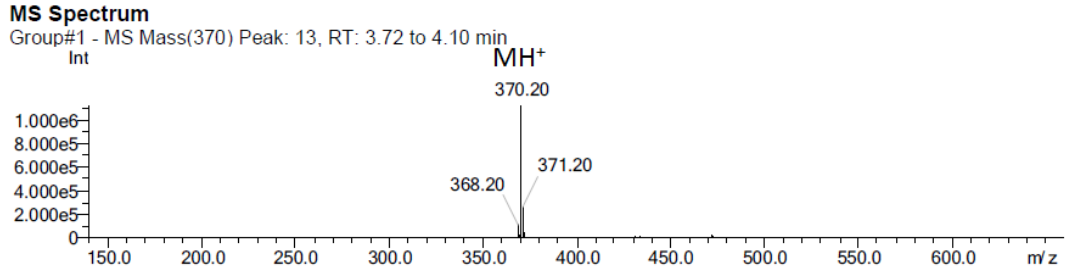
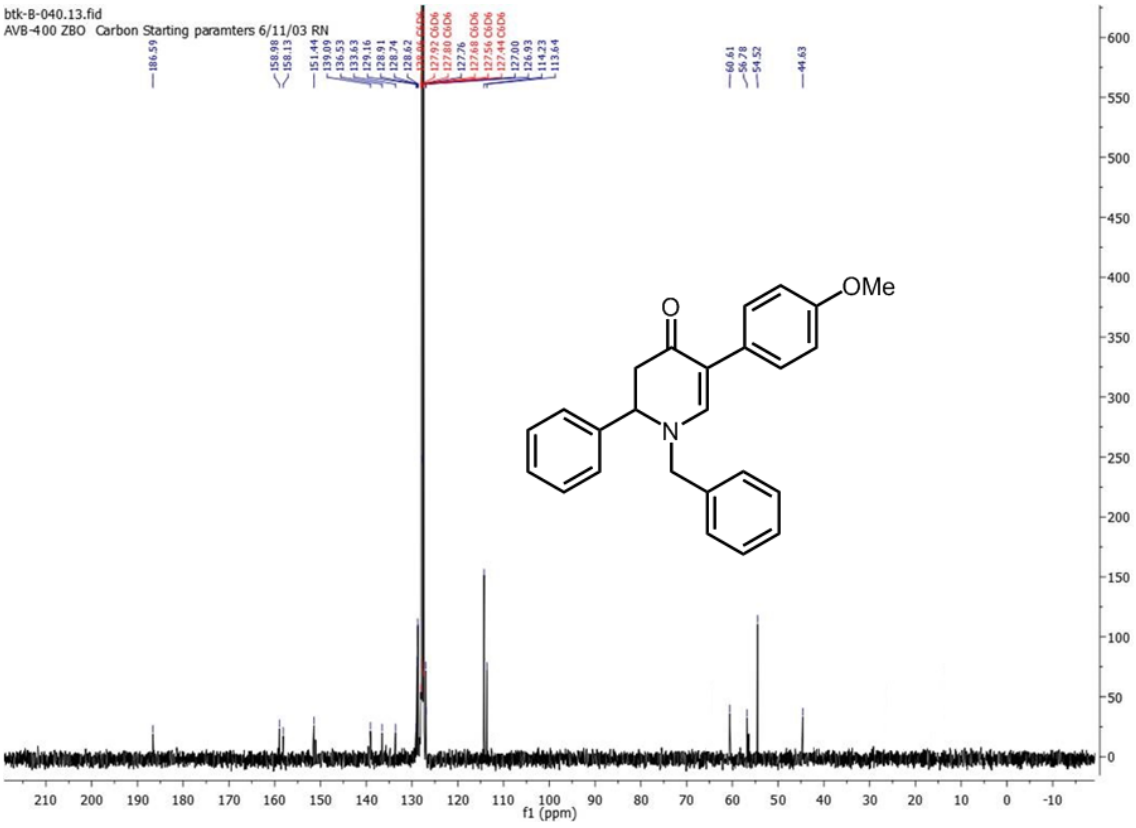
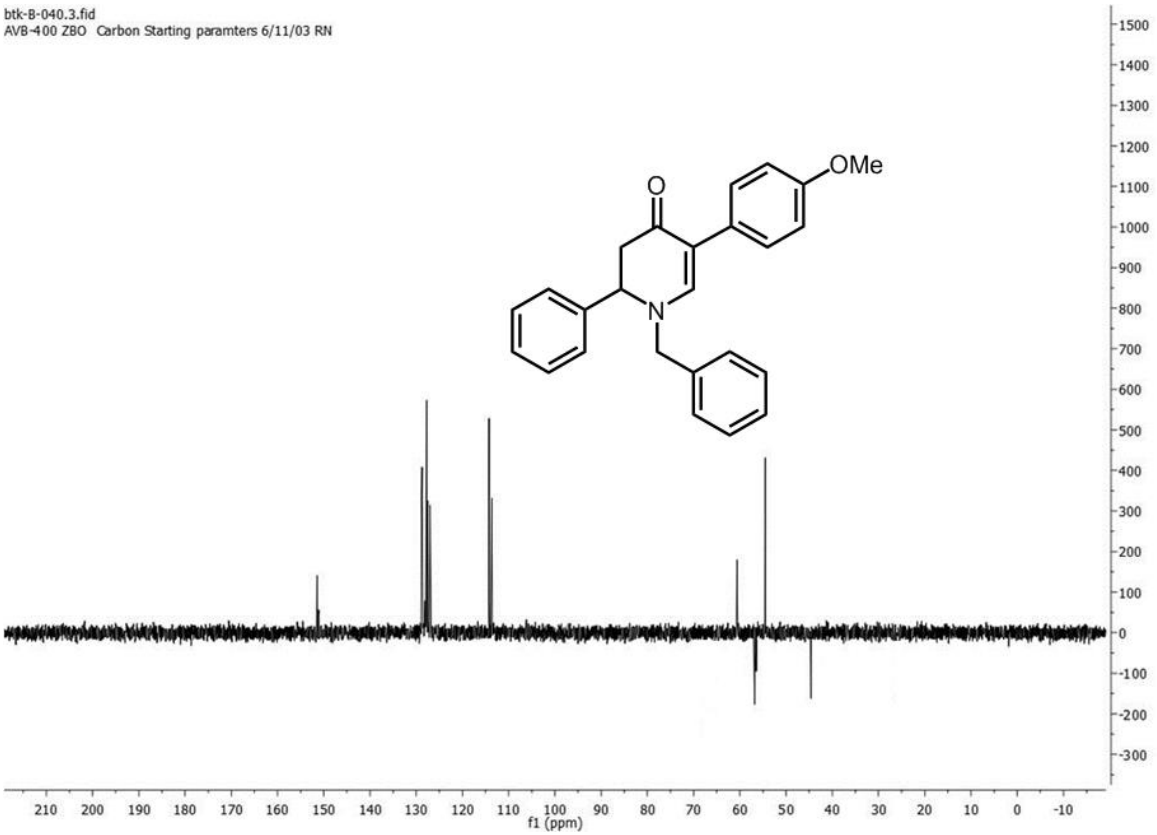
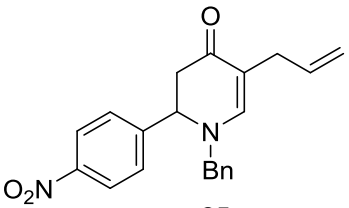
6.000e5
4.000e5
2.000e5
0
RT=3.82
RT=3.63
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 min.
OMe
O
N
Bn
MW 369


MS Spectrum
Group#1 - MS Mass(370) Peak: 13, RT: 3.72 to 4.10 min
Int
MH+
370.20
371.20
368.20
1.000e6
8.000e5
6.000e5
4.000e5
2.000e5
0
150.0 200.0 250.0 300.0 350.0 400.0 450.0 500.0 550.0 600.0 m/z

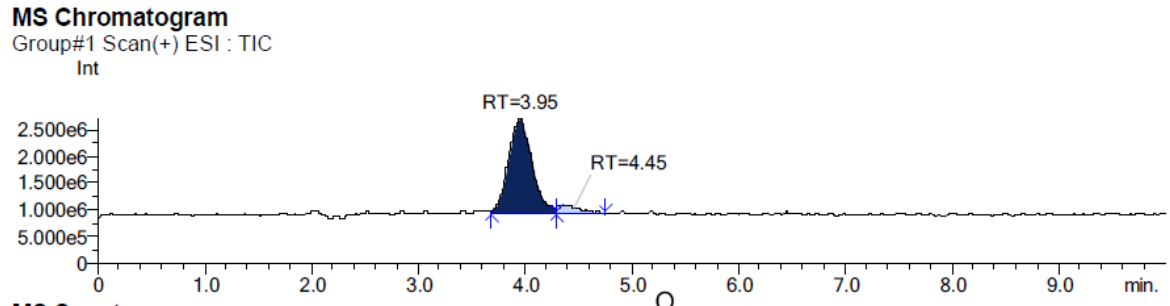

btk-B-040.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
OMe
O
N
f1 (ppm)





25

Prepared from allyl bromide (480 mg, 4 mmol, 4 equiv) and bromo enaminone **9** (386 mg, 1.0 mmol, 1.0 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 100:0). Yield = 223 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (2H, d), 7.45 to 7.14 (8H, m), 5.96 to 5.84 (1H, m), 5.13 to 5.05 (2H, m), 4.61 to 4.58 (1H, t), 4.47 (1H, d) 4.12 (1H, d), 3.00 to 2.89 (3H, m), 2.70 to 2.64 (1H, dd). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.1, 152.7, 147.8, 146.3, 137.1, 135.6, 129.2, 128.6, 128.1, 127.7, 124.4, 109.2, 60.1, 57.9, 43.4, 30.9. HRMS calc for $C_{21}H_{20}N_2O_3$ 348.1474, found 348.1479.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1.500e6
1.000e6
5.000e5
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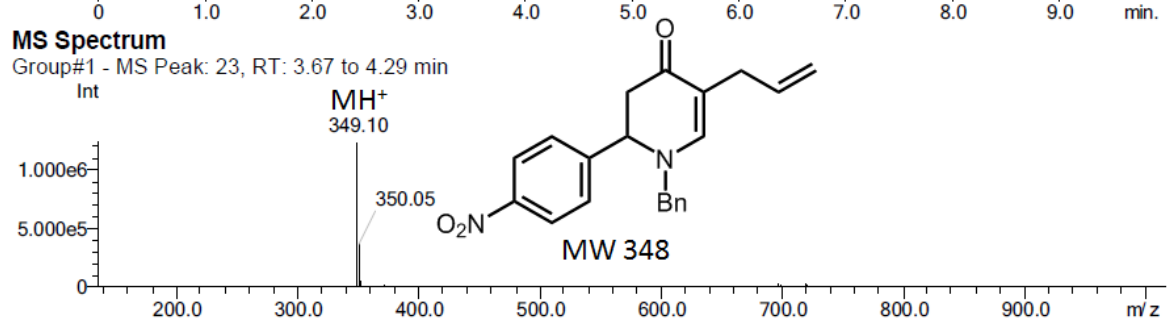
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
min.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Group#1 - MS Peak: 23, RT: 3.67 to 4.29 min
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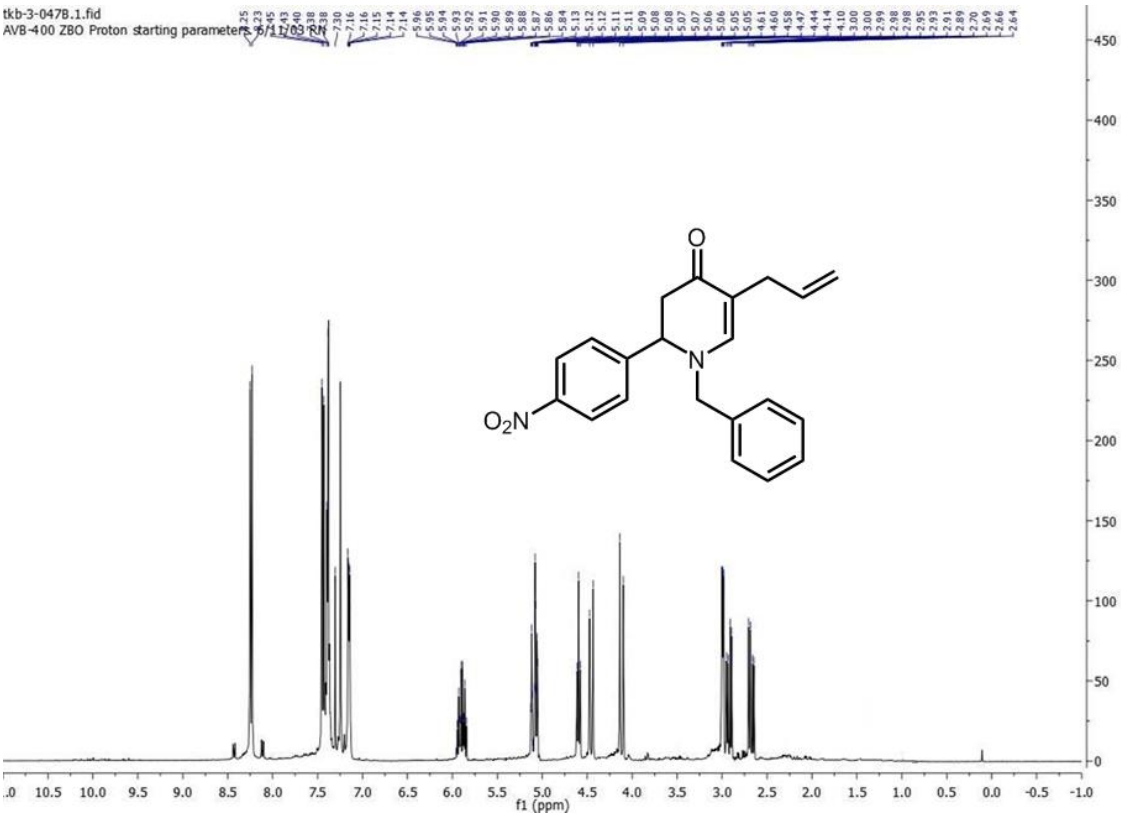
350.05
1.000e6
5.000e5
0
200.0
300.0
400.0
500.0
600.0
700.0
800.0
900.0
m/z
O
N
Bn
O2N
MW 348


tkb-3-0478.1.fid
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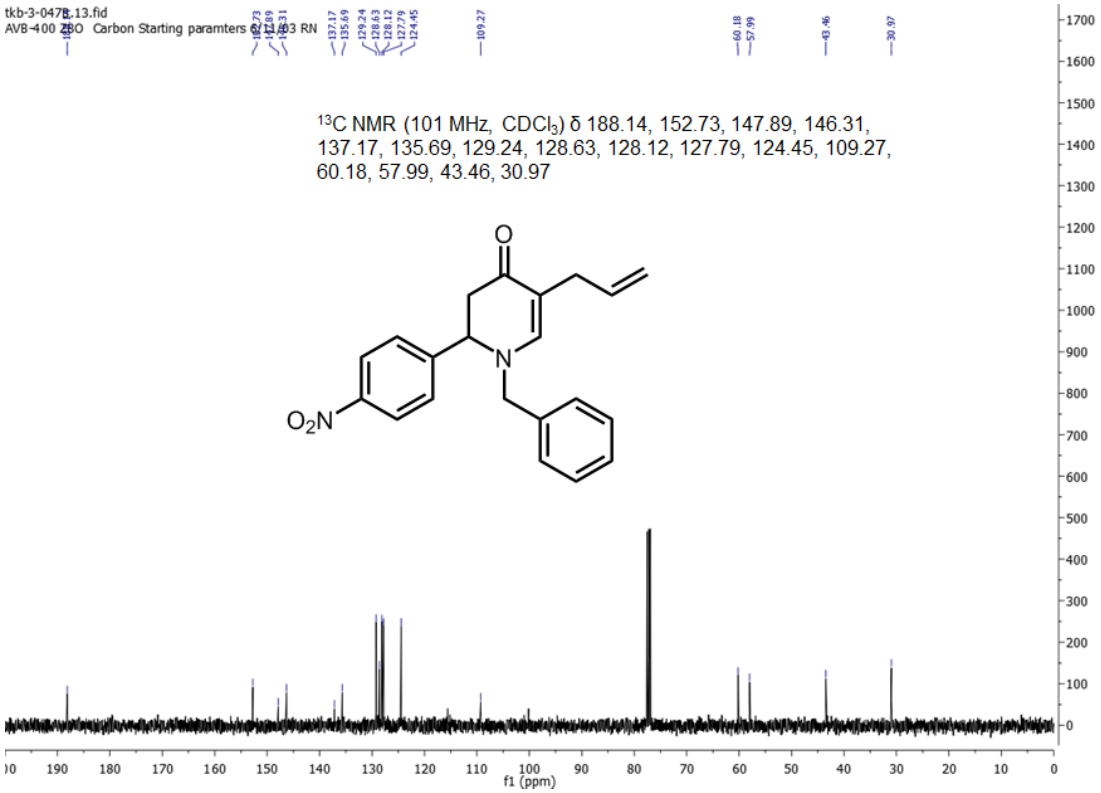
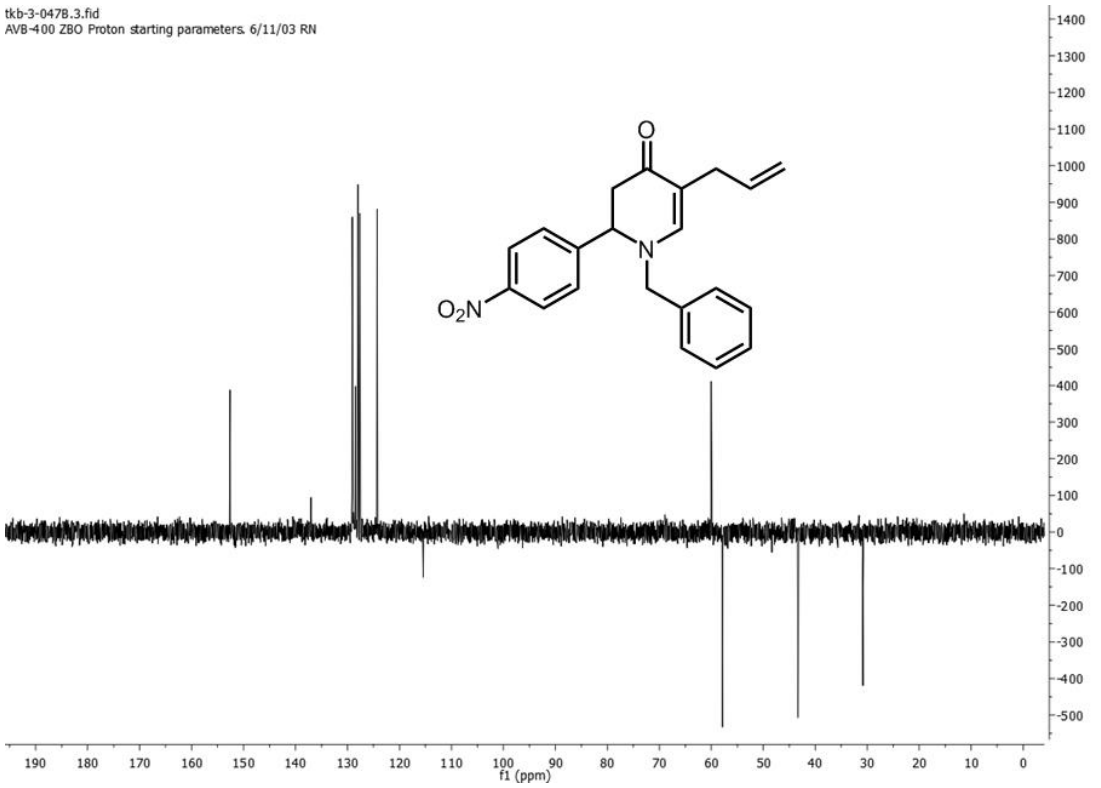
O
N
O2N
450
400
350
300
250
200
150
100
50
0
f1 (ppm)


tkb-3-047B.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
188.14
152.73
147.89
146.31
137.17
135.69
129.24
128.63
128.12
127.79
124.45
109.27
60.18
57.99
43.46
30.97
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.14, 152.73, 147.89, 146.31, 137.17, 135.69, 129.24, 128.63, 128.12, 127.79, 124.45, 109.27, 60.18, 57.99, 43.46, 30.97
O
N
O_2N
f1 (ppm)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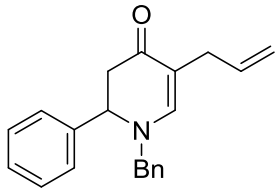
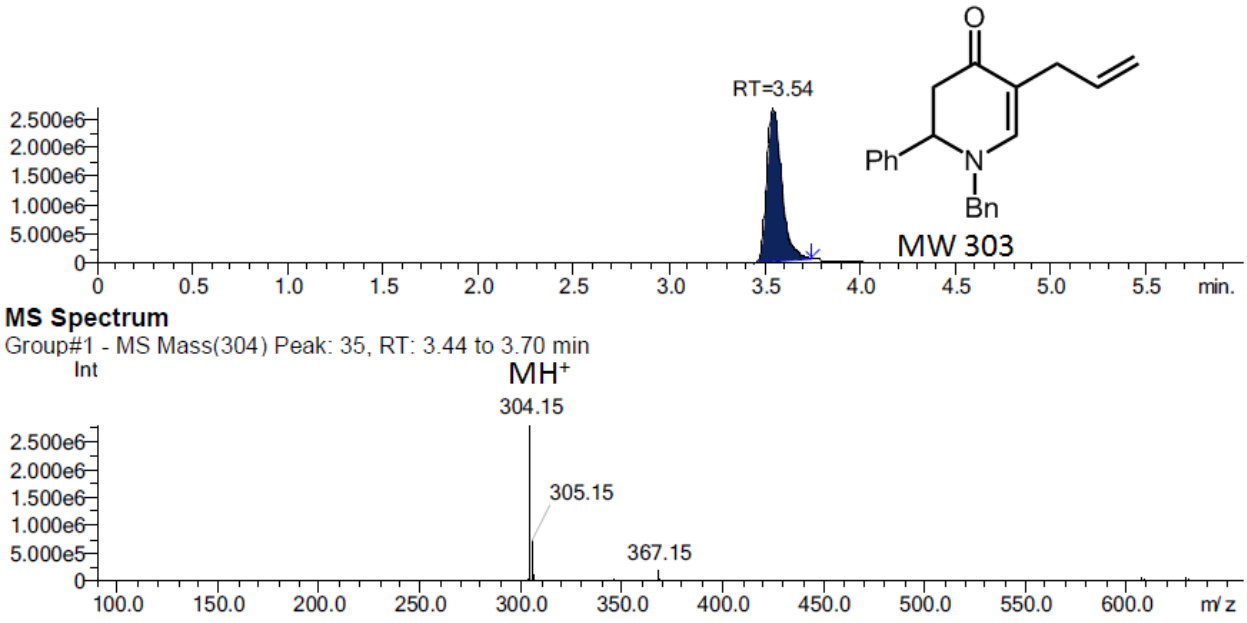
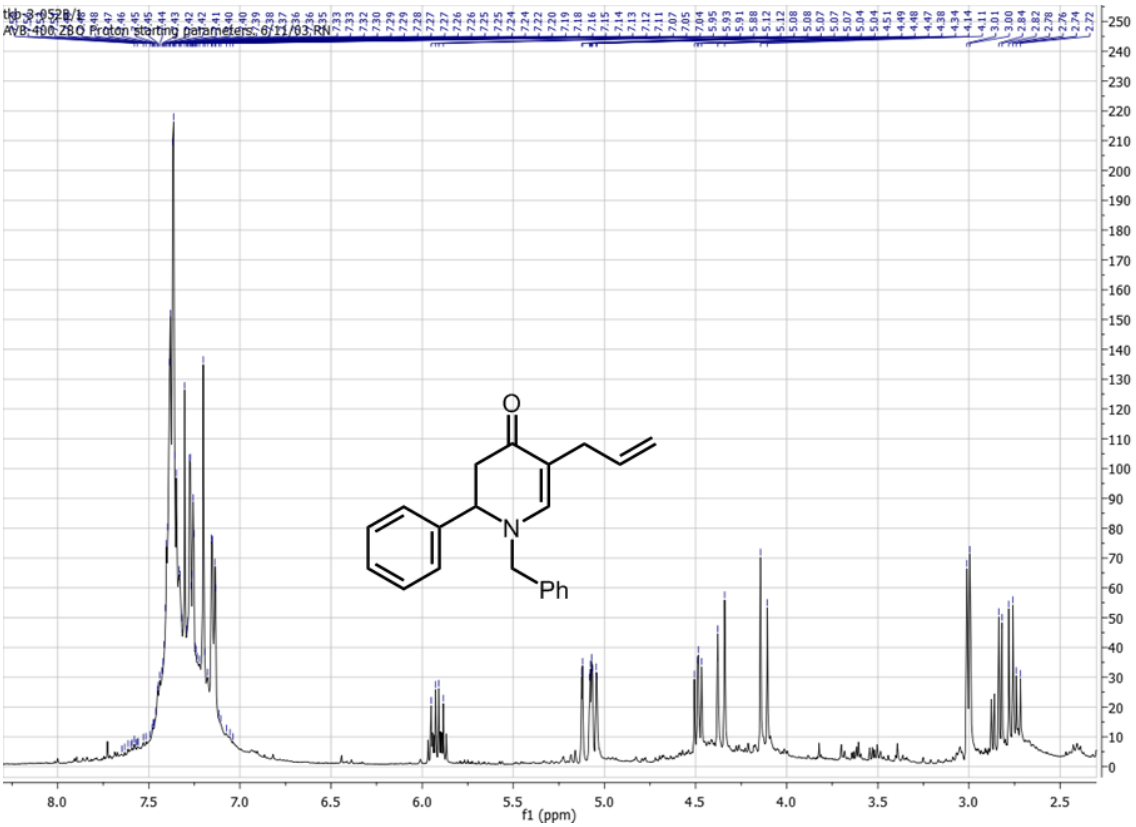
AVB-400 ZBO Proton starting parameters 6/11/03 RN
O
N
O_2N
f1 (ppm)

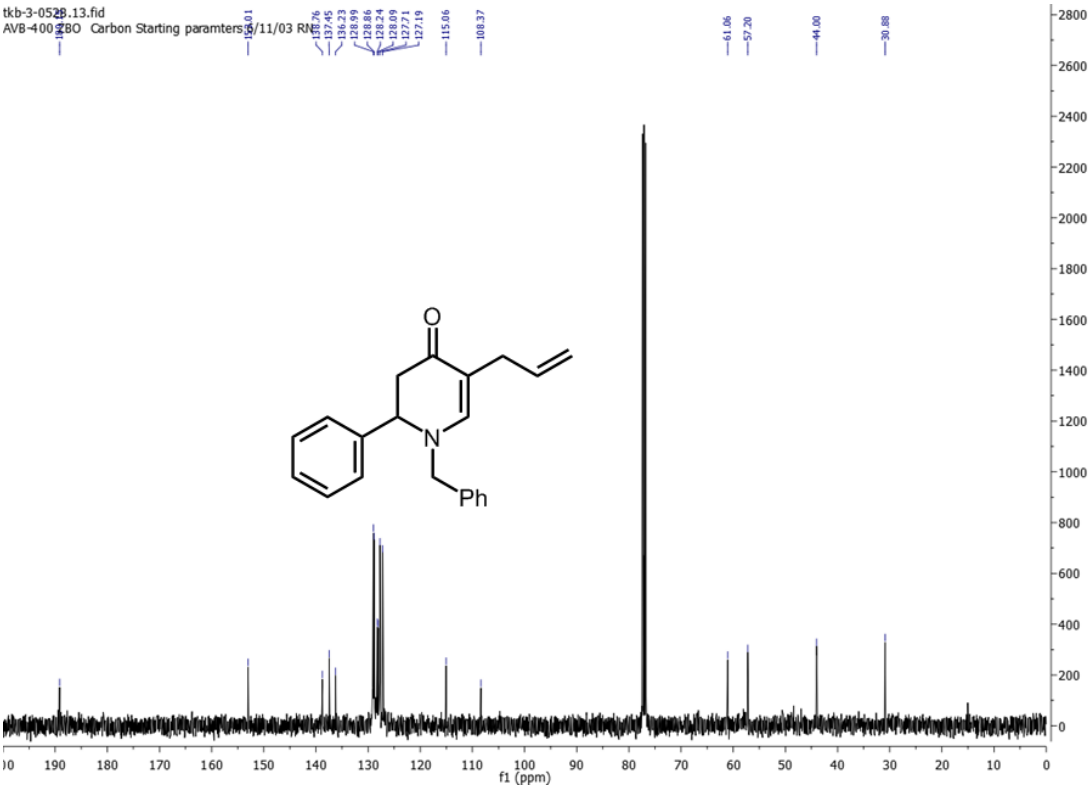


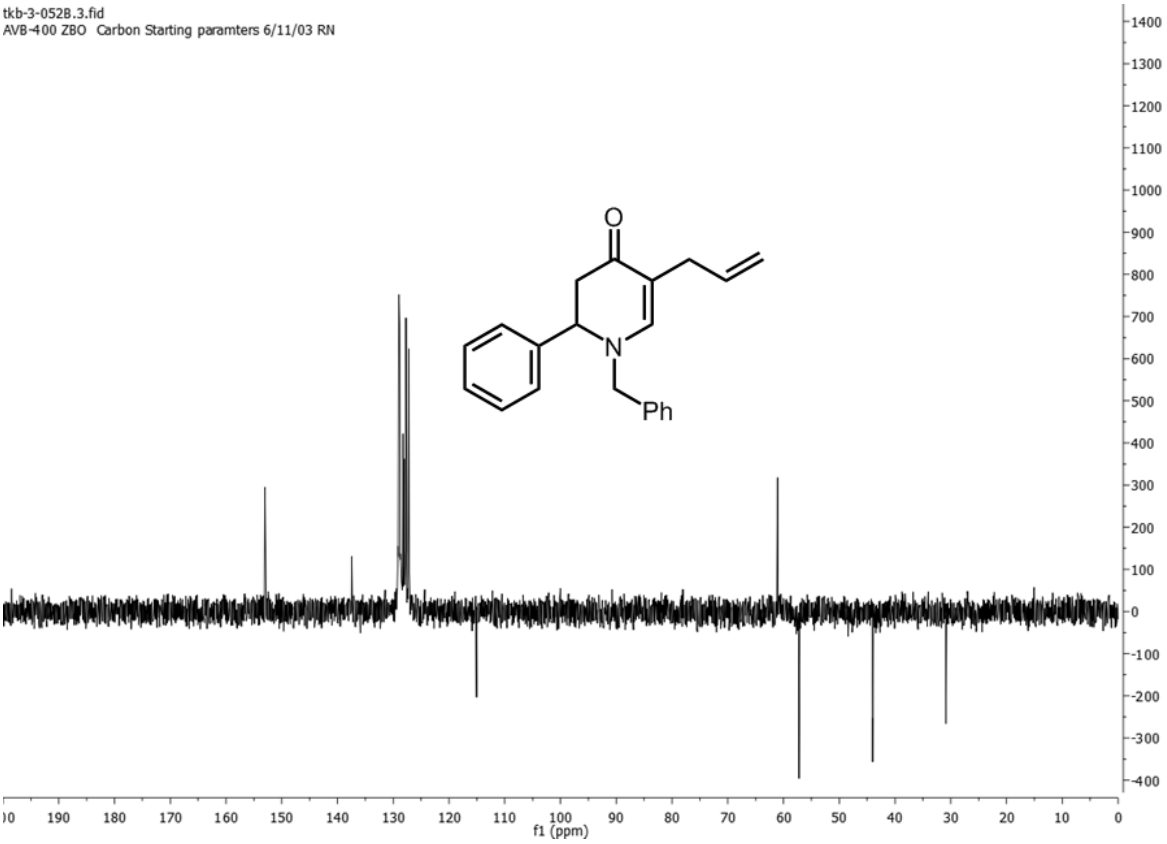
25

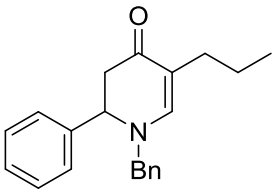
Prepared from allyl bromide (480 mg, 4 mmol, 4 equiv) and bromo enaminone **7** (341 mg, 1.0 mmol, 1.0 equiv), using General Procedure A. T = 23 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 50:50). Yield = 223 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 to 7.04 (11H, m), 5.95 to 5.88 (1H, m), 5.12 to 5.04 (2H, m), 4.51 to 4.47 (1H, t), 4.38 (1H, d), 4.14 (1H, d), 3.01 to 2.82 (2H, m), 2.78 to 2.72 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.15, 153.01, 138.76, 137.45, 136.23, 128.99, 128.86, 128.24, 128.09, 127.71, 127.19, 115.06, 108.37, 61.06, 57.20, 44.00, 30.88. HRMS calc for $C_{21}H_{21}NO$ 303.1623, found 303.1628.




AVB-400 ZBO Proton starting parameters 6/11/03 RN
O
N
Ph
f1 (ppm)

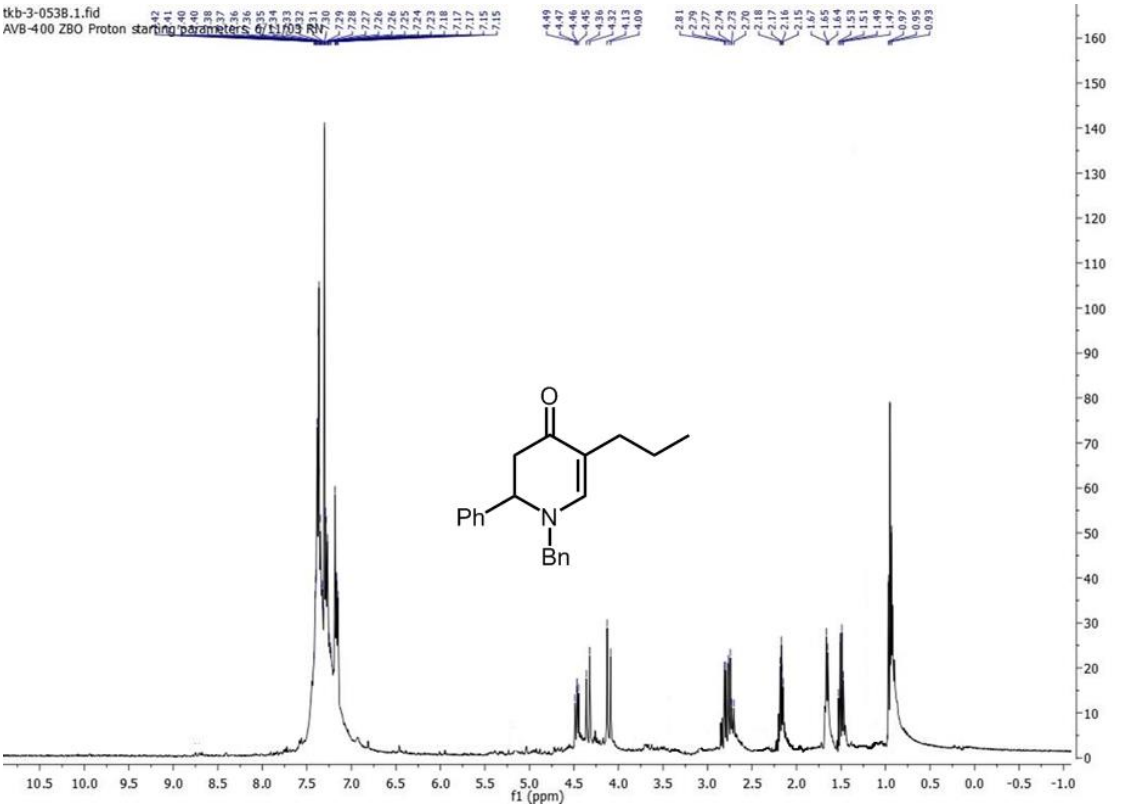

tkb-3-052B.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
O
N
Ph
f1 (ppm)

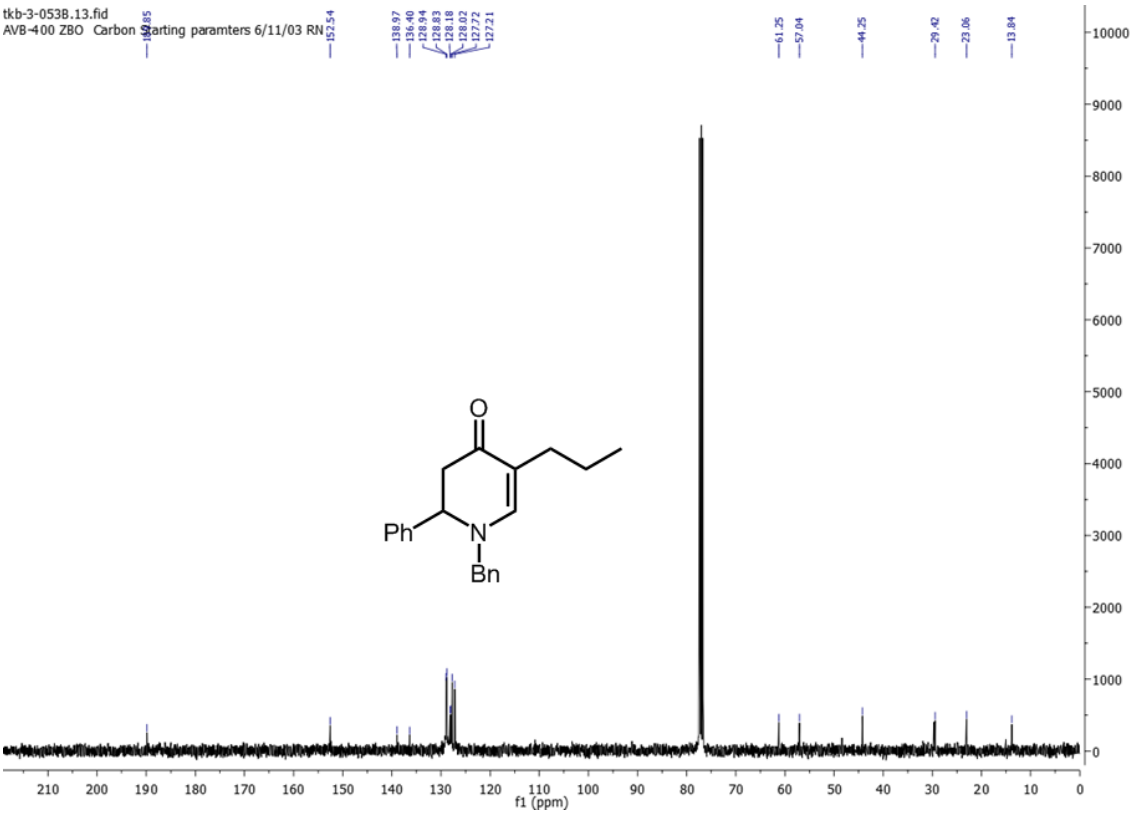




27

Prepared from **26** (60.3 mg, 0.20 mmol), and 10% Pd/C (30 mg), using **General Procedure D**, temp = 24 ^{o}C, time = 3 h. No purification required. Yield = 60 mg, 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 to 7.15 (11H, m), 4.49 to 4.43 (1H, t), 4.34 (1H, d), 4.11 (1H, d), 2.85 to 2.70 (2H, m), 2.22 to 2.06 (1H, m), 1.68 to1.63 (1H, m), 1.53 to 1.45 (2H, m), 0.97 to 0.87 (3H, t). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.85, 152.54, 138.97, 136.40, 128.94, 128.83, 128.18, 128.02, 127.72, 127.21, 61.25, 57.04, 44.25, 29.42, 23.06, 13.84. HRMS calc for $C_{21}H_{23}NO$ 305.1780, found 305.1784.


tkb-3-053B.1.fid
AVB-400 ZBO Proton starting paramters 6/11/03 RN
O
Ph
N
Bn
f1 (ppm)


tkb-3-053B.13.fid
AVB-400 ZBO Carbon starting paramters 6/11/03 RN
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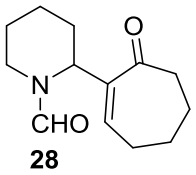
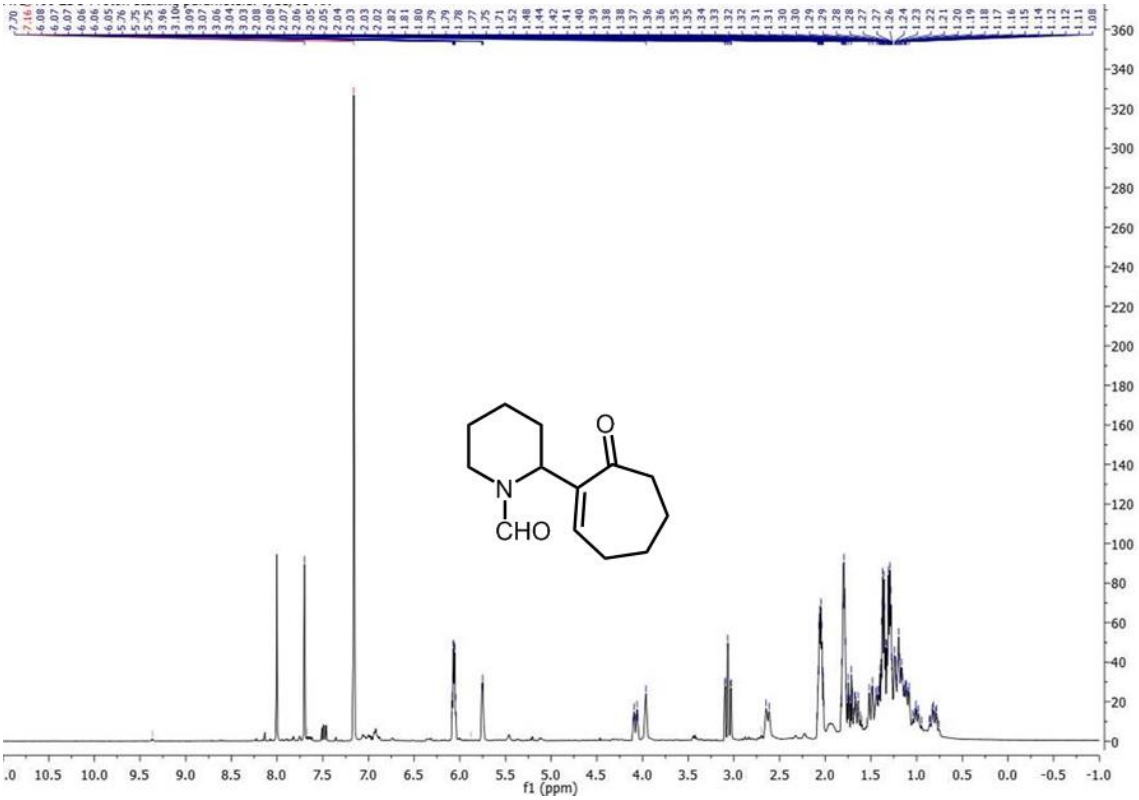
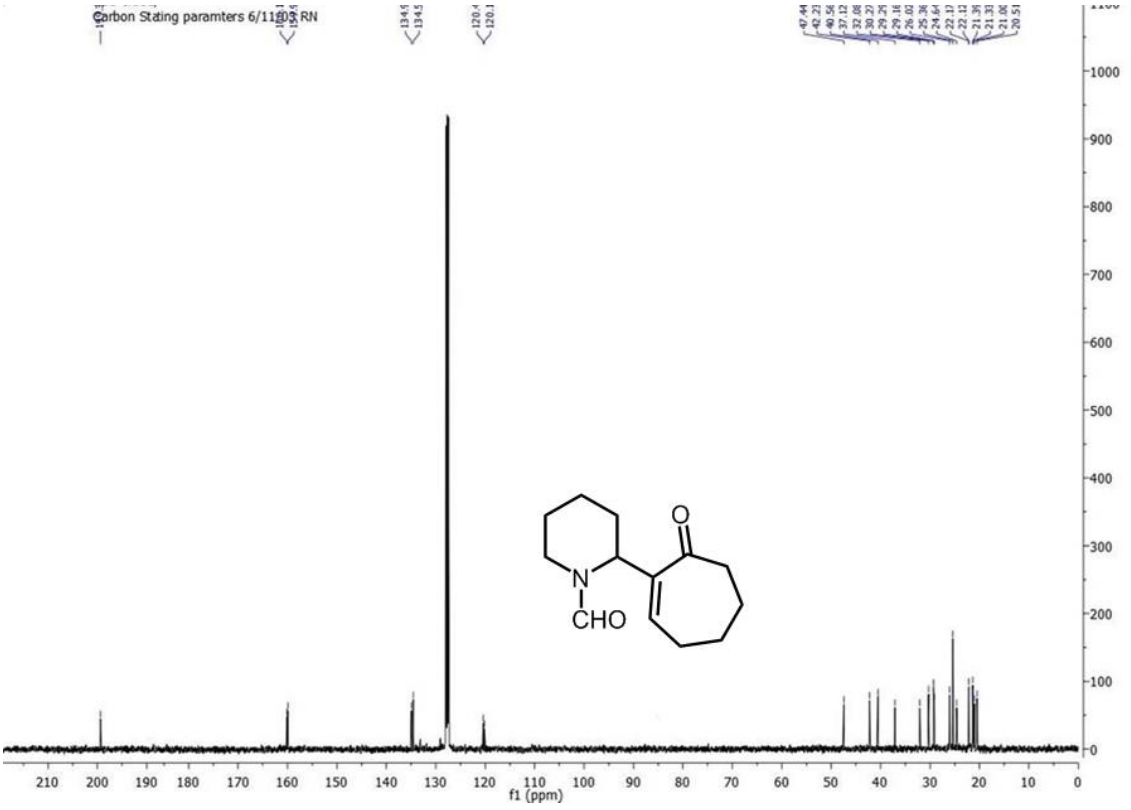
138.97
136.40
128.94
128.83
128.18
128.02
127.72
127.21
61.25
57.04
44.25
29.42
23.06
13.84
O
Ph
N
Bn
f1 (ppm)

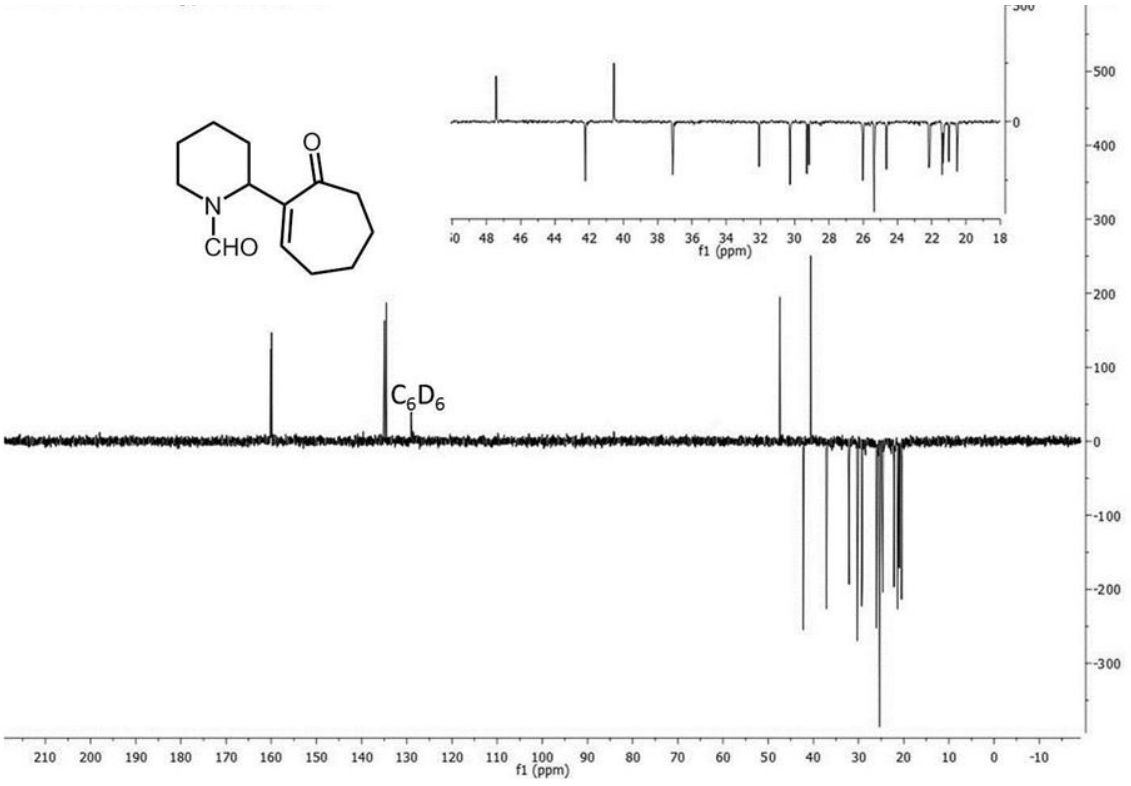


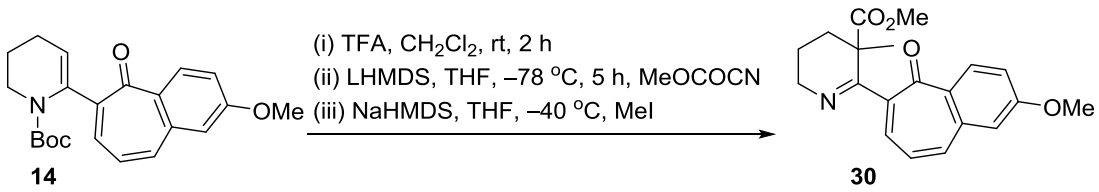
28

Prepared from **17** (55 mg, 0.25 mmol) using **General Procedure C**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 70:30). Yield = 38 mg, 77%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 8.00 and 7.23 (1H, s), 6.09 to 6.04 (1H, t) 5.76 (1H, broad singlet), 4.10 to 3.96 (2H, m), 3.10 to 3.03 (2H, t), 2.70 to 2.61 (1H, dd), 2.09 to 0.75 (12H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 198.1, 160.15, 159.94, 134.93, 134.54, 120.42, 120.15, 47.44, 42.23, 40.56, 37.12, 32.08, 30.27, 29.29, 29.16, 26.02, 25.36, 24.64, 22.17, 22.12, 21.39, 21.33, 21.00, 20.51. HRMS calc for $C_{13}H_{19}NO_2$ 221.1416, found 221.1466.




Carbon Stding paramters 6/11/09 RN
O
N
CHO
f1 (ppm)

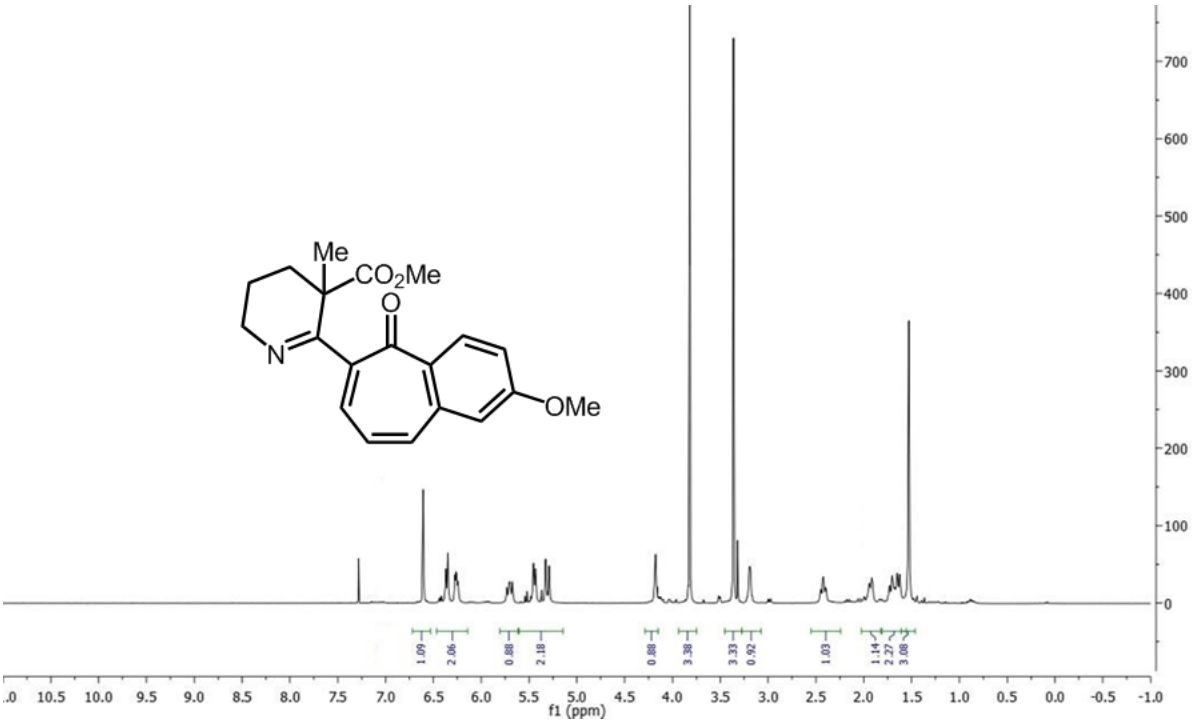

O
N
CHO
C6D6
f1 (ppm)

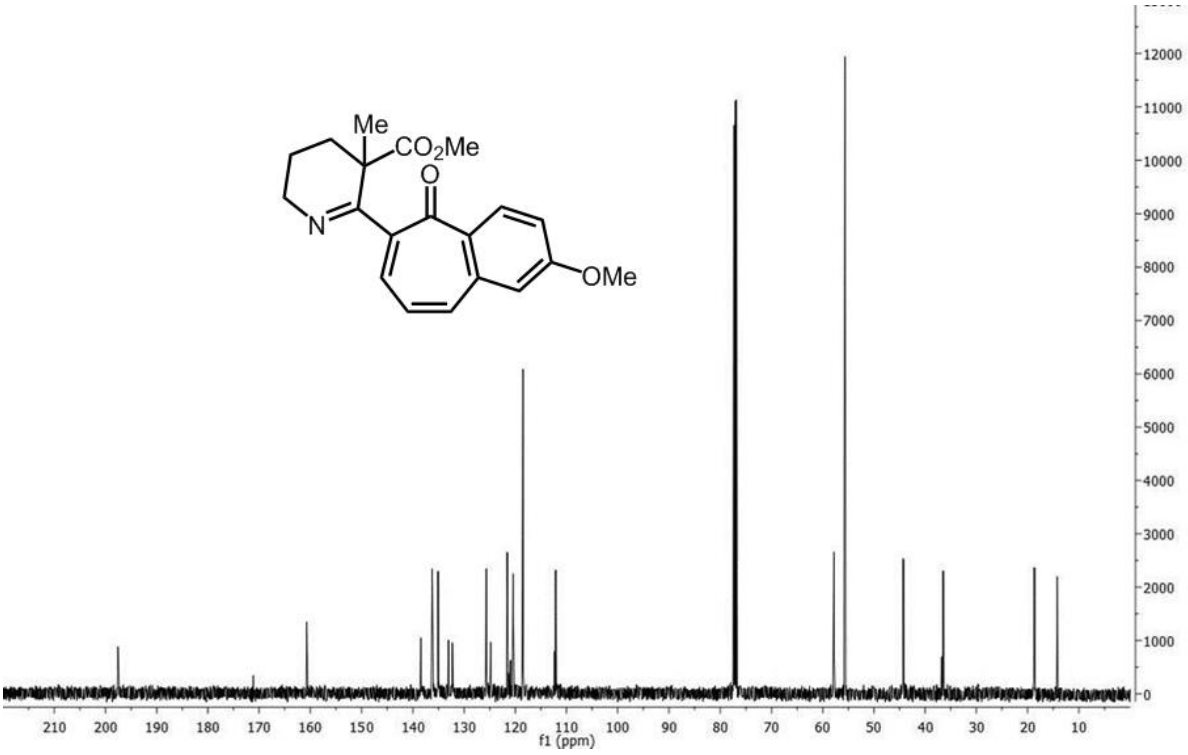


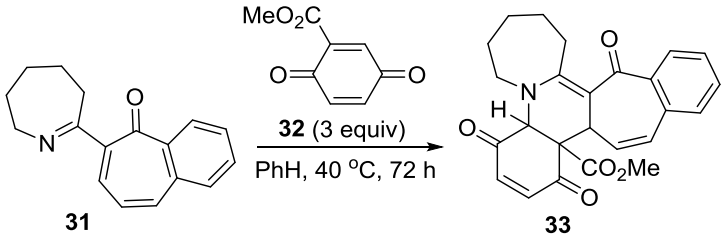
Enecarbamate **14** (0.5 mmol) was deprotected using General Procedure B.

A solution of LHMDS (1 mL, 1 mmol, 1.0 M in THF, 2 equiv) was added dropwise to a solution of deprotected **14** in THF (5 mL) and the mixture was stirred for 5 h at −78 °C (LCMS-monitoring). A precooled solution of Mander's reagent (methyl cyanoformate, 2.4 equiv) in THF (2 mL) was added slowly. Stirring was continued for 2 h prior to warming slowly to room temperature overnight. After quenching with saturated $NaHCO_3$ (aq), extractive workup with EtOAc followed by brine washes afforded the α-imino ester, which was used without further purification.

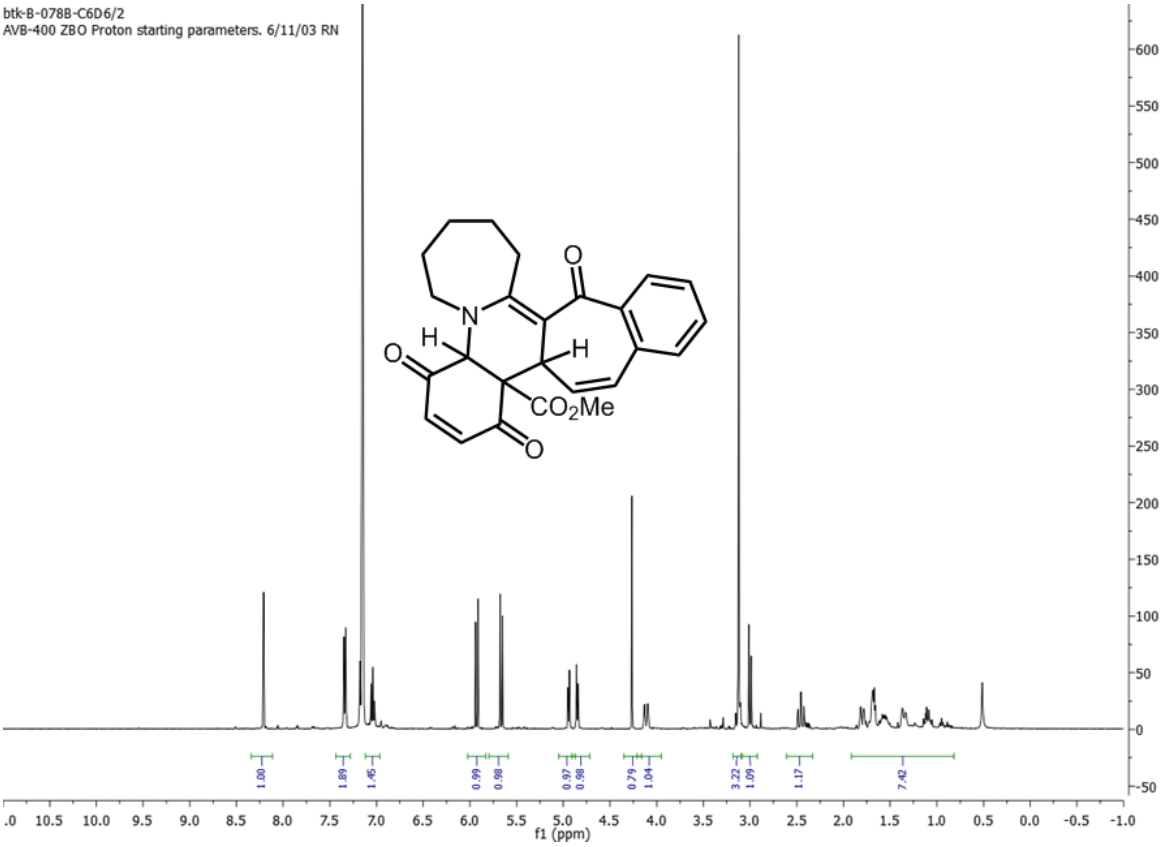
Methylation: A solution of NaHMDS (1 mL, 1 mmol, 1.0 M in THF, 2 equiv) was added dropwise to a solution of the imino ester in THF (5 mL) and the mixture was stirred for 10 min at −78 °C then for 1 h at −40 °C (LCMS-monitoring). After cooling to −78 °C, methyl iodide (3 equiv) was added slowly. The mixture was allowed to warm slowly to room temperature overnight. After quenching with saturated NH_4Cl (aq), extractive workup with EtOAc followed by brine washes afforded the desired crude 2,2-disubstituted imine. Purification by flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (20:80) afforded the pure product in 59% yield from **14**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, s), 6.44 to 6.24 (2H, m), 5.73 to 5.29 (3H, m), 4.18 to 4.10 (1H, unresolved triplet), 3.84 (3H, s), 3.39 (3H, s), 3.22 to 3.17 (1H, unresolved), 2.45 to 2.39 (1H, t), 2.00 to 1.91 (1H, m), 1.73 to 1.44 (5H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 171.1, 160.7, 160.6, 138.4, 138.4, 136.2, 135.0, 125.6, 124.8, 121.5, 120.9, 120.4, 118.6, 118.5, 112.3, 112.1, 57.8, 55.6, 44.2, 36.8, 36.4, 18.6, 14.2. HRMS calc for $C_{20}H_{21}NO_4$ 339.1471, found 339.1488.

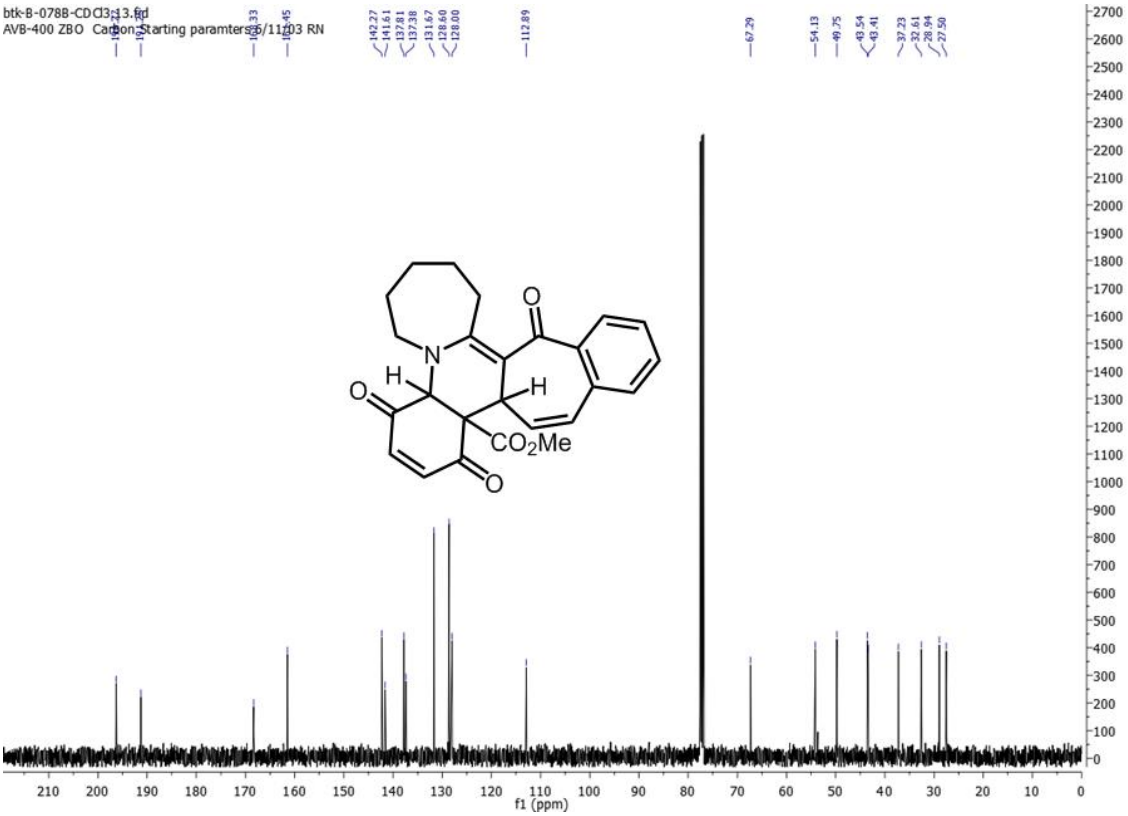

Me
CO2Me
O
N
OMe
f1 (ppm)


Me
CO2Me
O
N
OMe
f1 (ppm)



A 5 mL tube was flame-dried, evacuated and flushed with nitrogen. A solution of dienophile **32** (1.0 mL, 0.1 M in benzene) was added to a solution of imino diene **31** (1.0 mL, 0.1 M in benzene) under nitrogen. The mixture was heated to 40 ^{o}C for 72 h. The solvent was removed *in vacuo* to obtain the crude product as an oil. Purification by flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (70:30 to 10:90) afforded the pure product in 56% yield. ^{1}H NMR (400 MHz, C_6D_6) δ 8.21 (1H, d), 7.35 to 7.33 (2H, d), 7.06 (1H, t), 5.91 (1H, d), 5.68 (1H, d), 4.95 (1H, d), 4.86 (1H, d) 4.26 (1H, s), 4.13 (1H, d), 3.12 (3H, s), 3.01 (1H, d), 2.48 to 2.42 (1H, t), 1.82 to 0.95 (7H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 191.2, 168.3, 161.4, 142.2, 141.6, 137.8, 137.3, 131.6, 128.6, 128.0, 112.8, 67.2, 54.1, 49.7, 43.5, 43.4, 37.2, 32.6, 28.9, 27.5. HRMS calc for $C_{25}H_{23}NO_5$ 417.1576, found 417.1582.





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