Supporting Information for:

Expedient Access to α,β-Difunctionalized Azepenes using Alpha-Halo Eneformamides: Application to the Synthesis of 2-Benzazepanes

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Contents:

2. Experimental Section

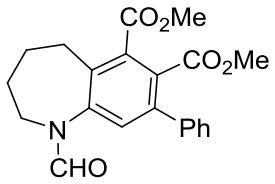
All experiments involving air and moisture sensitive reagents such as palladium precatalysts were carried out under an inert atmosphere of argon or nitrogen and using freshly distilled solvents. Anhydrous 1,4-dioxane was used as purchased. Dichloromethane was distilled from $MgSO_4$. Aryl iodides, boronic acids, terminal alkynes, and simple dienophiles were obtained from commercial sources. 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. ^1H, ^{13}C, DEPT-135, and 2D-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).

General Procedure A: Synthesis of 2-benzazepanes

A 5 mL tube was flame-dried, evacuated and flushed with nitrogen. A solution of the desired dienophile (0.10 M in dioxane) was added to a solution of the diene[1] (0.10 M in dioxane) under nitrogen. The mixture was heated to the desired temperature whiles being stirred. Upon completion (TLC and GC-MS or LC-MS monitoring), the mixture was cooled to room temperature and SeO_2 (3 equiv) was added. The heterogeneous mixture was heated to 130 ^oC for 30 min to give the crude benzazepane (s).

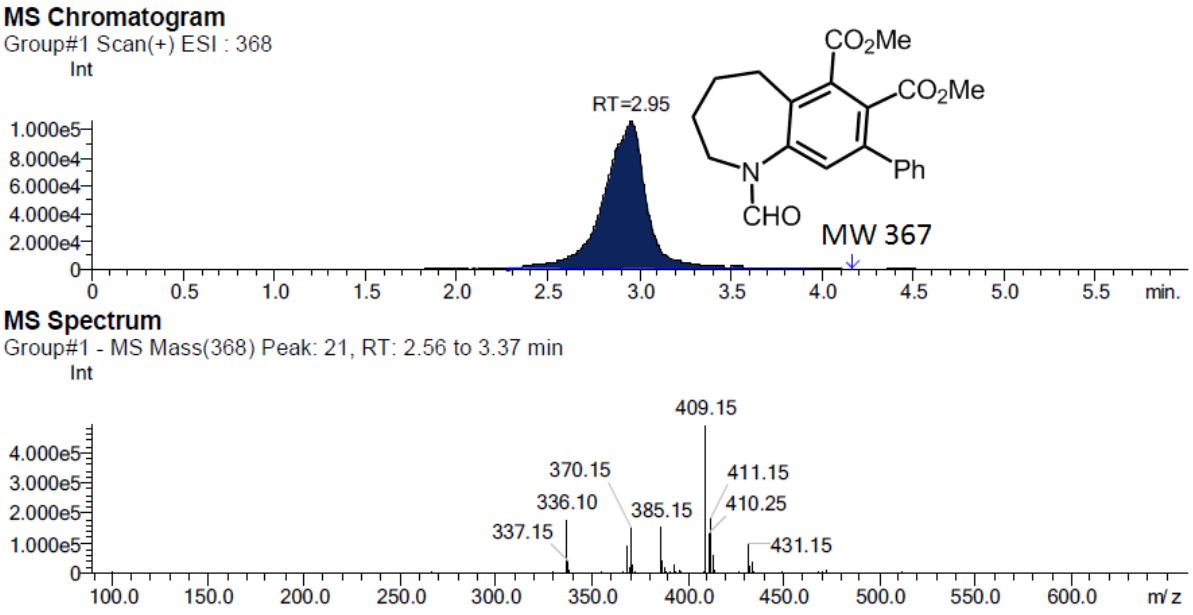
General Procedure B: C-3 arylation of α-halo eneformamides[2]

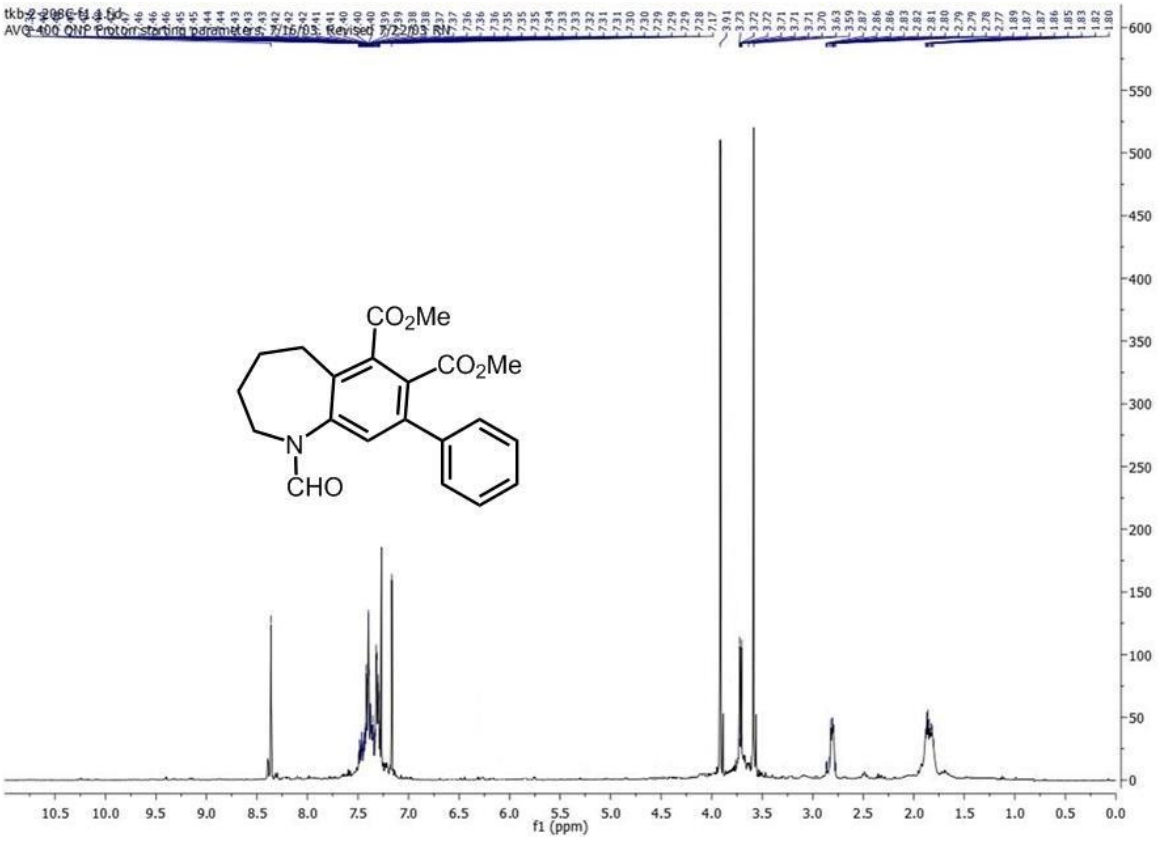
To a vial was added the eneformamide (0.5 mmol), aryl iodide (1.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (12 mg, 10 mol %), Bu_4NCl (70 mg, 0.25 mmol, 0.5 equiv), $NaHCO_3$ (47 mg, 0.55 mmol, 1.1 equiv), and AgCl (86 mg, 0.6 mmol, 1.2 equiv) were mixed in DMSO/dioxane (5 mL/1 mL). The reaction vessel was then capped and stirred at 80 °C for the indicated length of time prior to cooling to room temperature. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the crude product.



17a

Prepared from **7a** (227.3 mg, 1.0 mmol), dimethyl maleate (0.51 mL, 4 mmol, 4 equiv), and SeO_2 (3 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 ^{o}C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 235 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H), 7.49 to 7.17 (5H), 3.91 (1H), 3.73 to 3.70 (2H), 3.63 (1H), 2.87 to 2.77 (2H), 1.89 to 1.80 (4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.24, 168.06, 161.67, 143.31, 140.67, 138.78, 136.45, 134.24, 128.87, 128.51, 128.11, 128.01, 52.88, 52.44, 44.85, 29.98, 27.28, 24.97. HRMS calc for $C_{21}H_{21}NO_5$ 367.1420, found 367.1426.

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CO2Me
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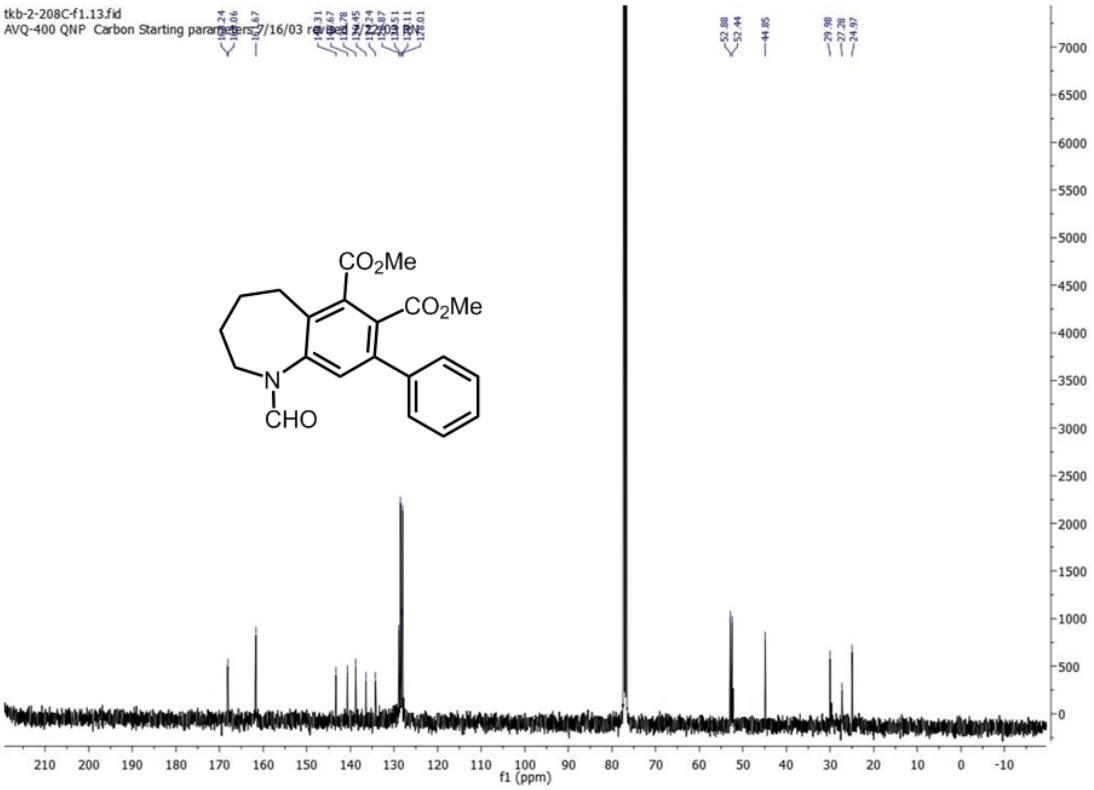
CHO
f1 (ppm)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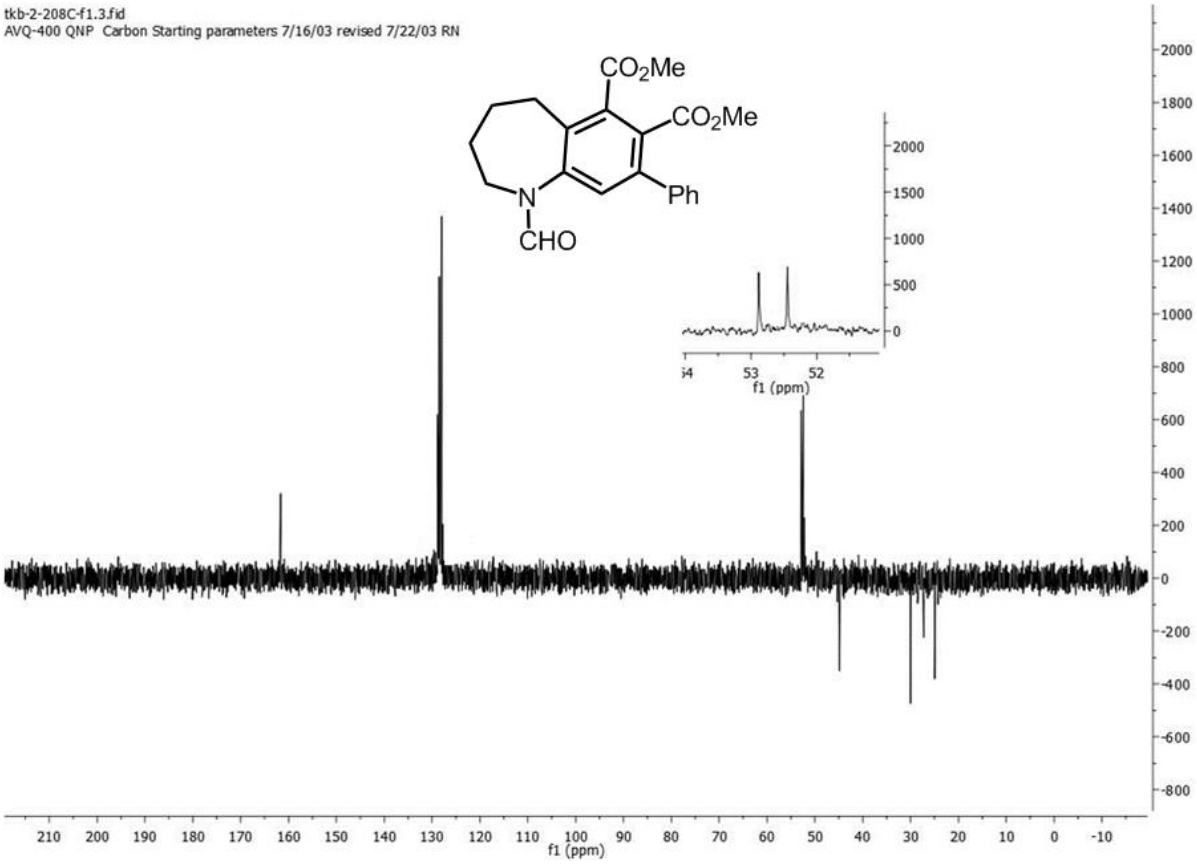
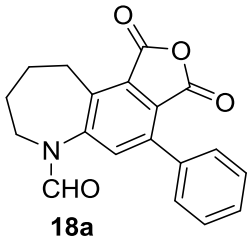
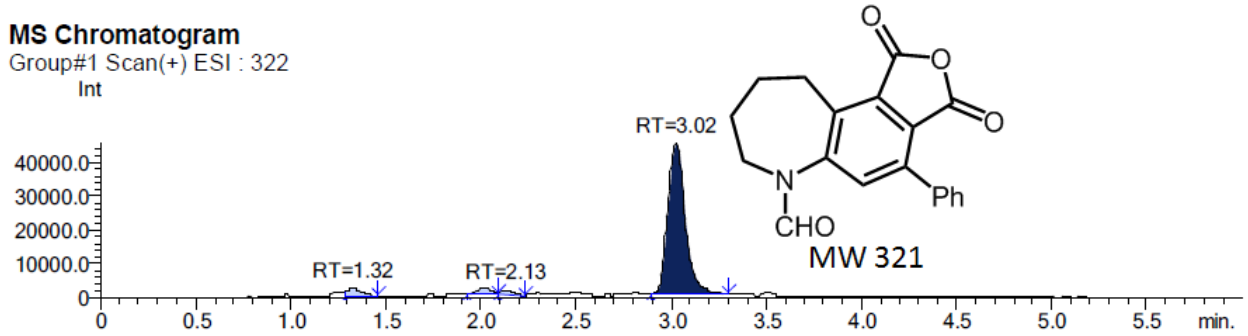




18a

Prepared from **7a** (227.3 mg, 1.0 mmol), maleic anhydride (392 mg, 4 mmol, 4 equiv), and selenium dioxide using **General Procedure A.** Temp = 100 ^{o}C, Time = 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 241 mg, 75%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.99 (1H), 7.28 to 7.15 (5H), 6.45 (1H), 3.36 to 3.33 (2H), 2.97 to 2.86 (2H), 1.43 to 1.17 (4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.50, 161.38, 160.85, 149.17, 142.46, 140.33, 134.10, 133.98, 133.55, 129.71, 129.17, 128.62, 125.47, 45.07, 27.78, 26.59, 24.53. HRMS calc for $C_{19}H_{15}NO_4$ 321.1001, found 321.0997.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RT=3.02
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2.0
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5.0
5.5
min.
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O
O
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CHO
Ph
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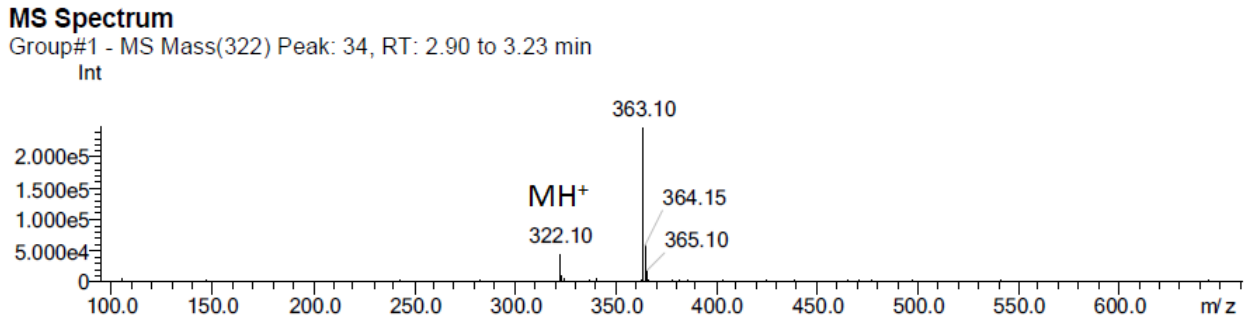
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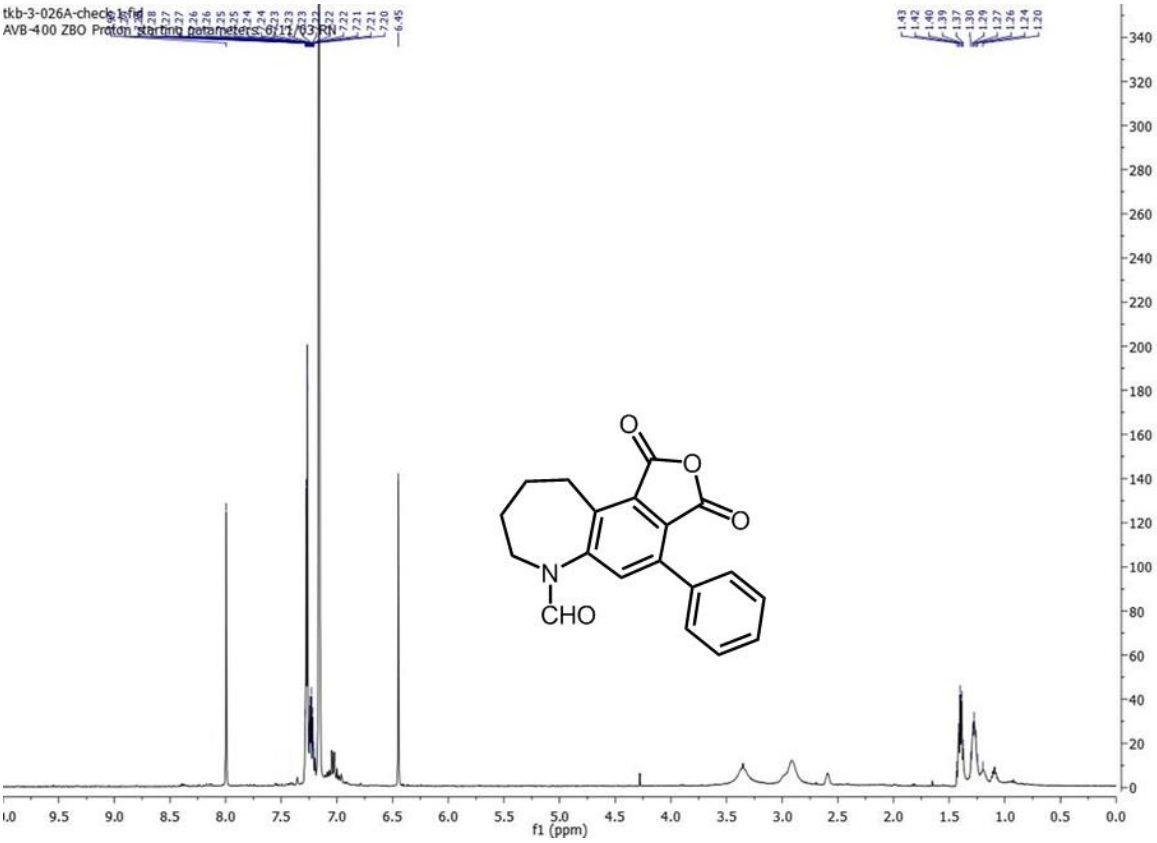
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
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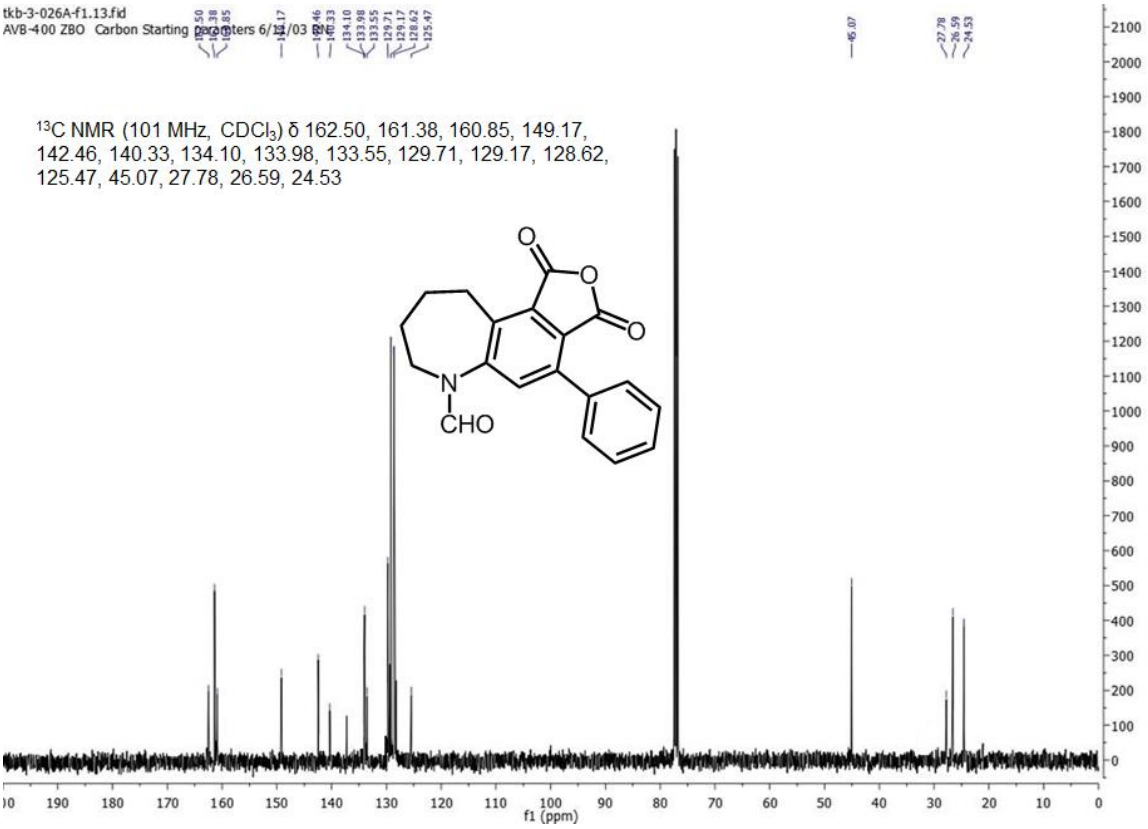
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^{13}C NMR (101 MHz, $CDCl_3$) δ 162.50, 161.38, 160.85, 149.17, 142.46, 140.33, 134.10, 133.98, 133.55, 129.71, 129.17, 128.62, 125.47, 45.07, 27.78, 26.59, 24.53
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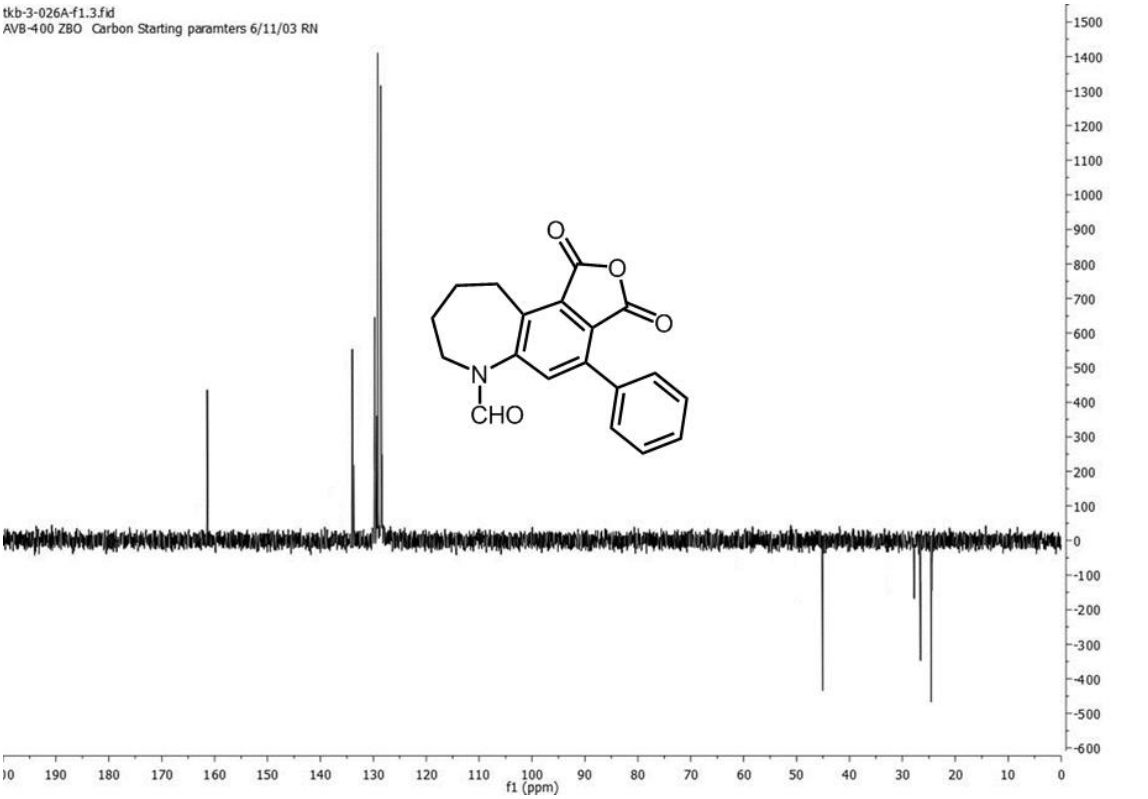
f1 (ppm)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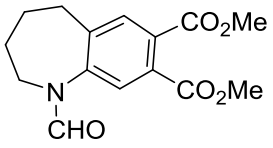
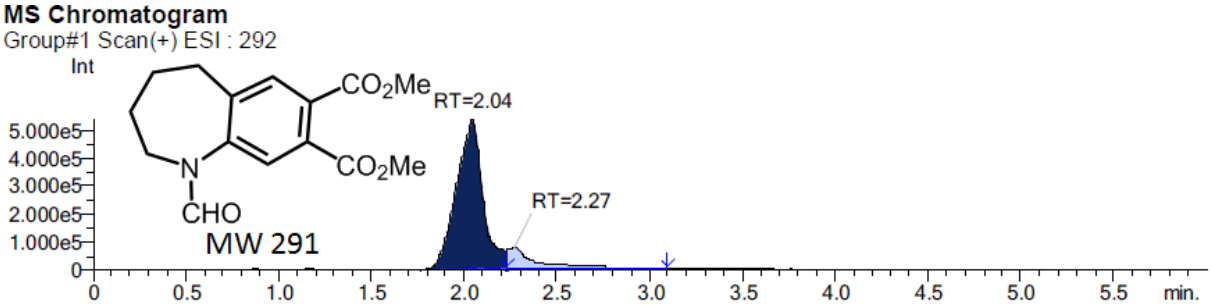
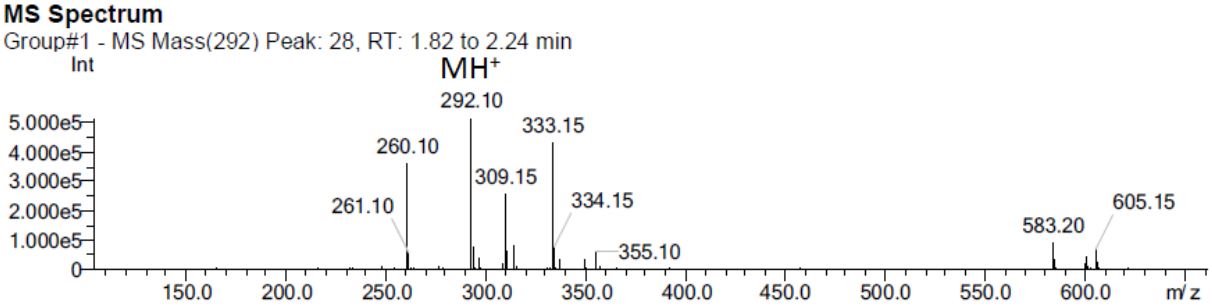
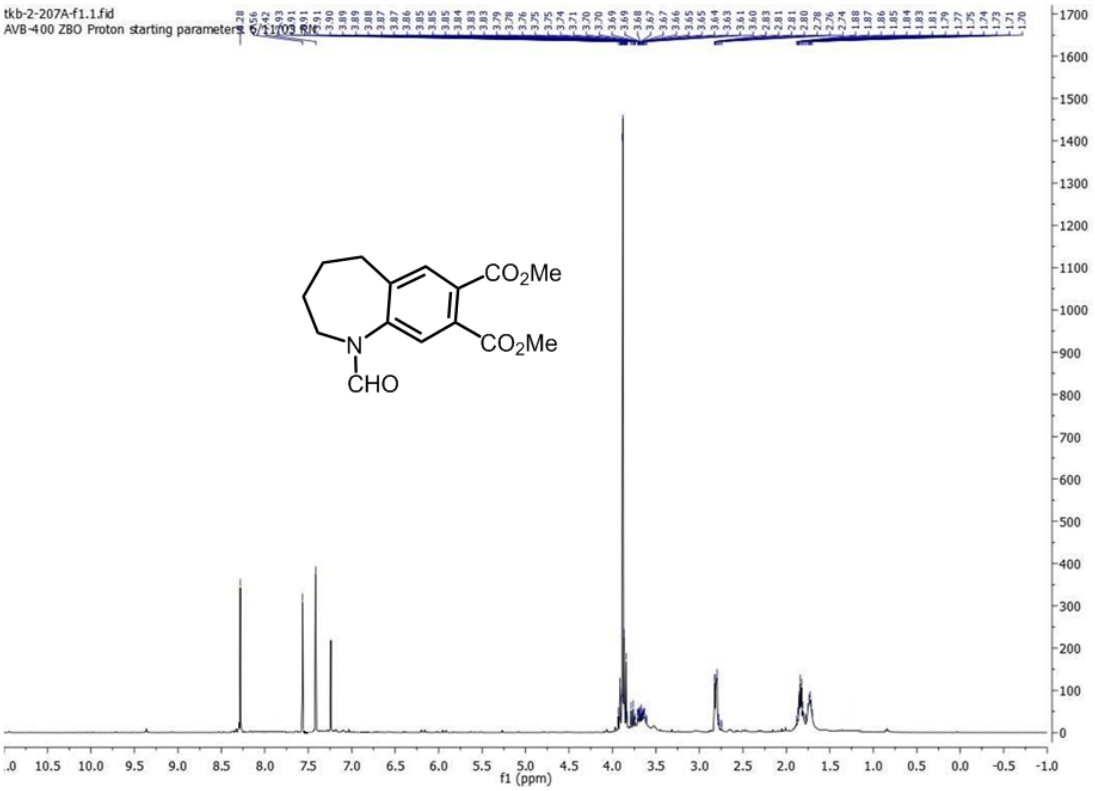


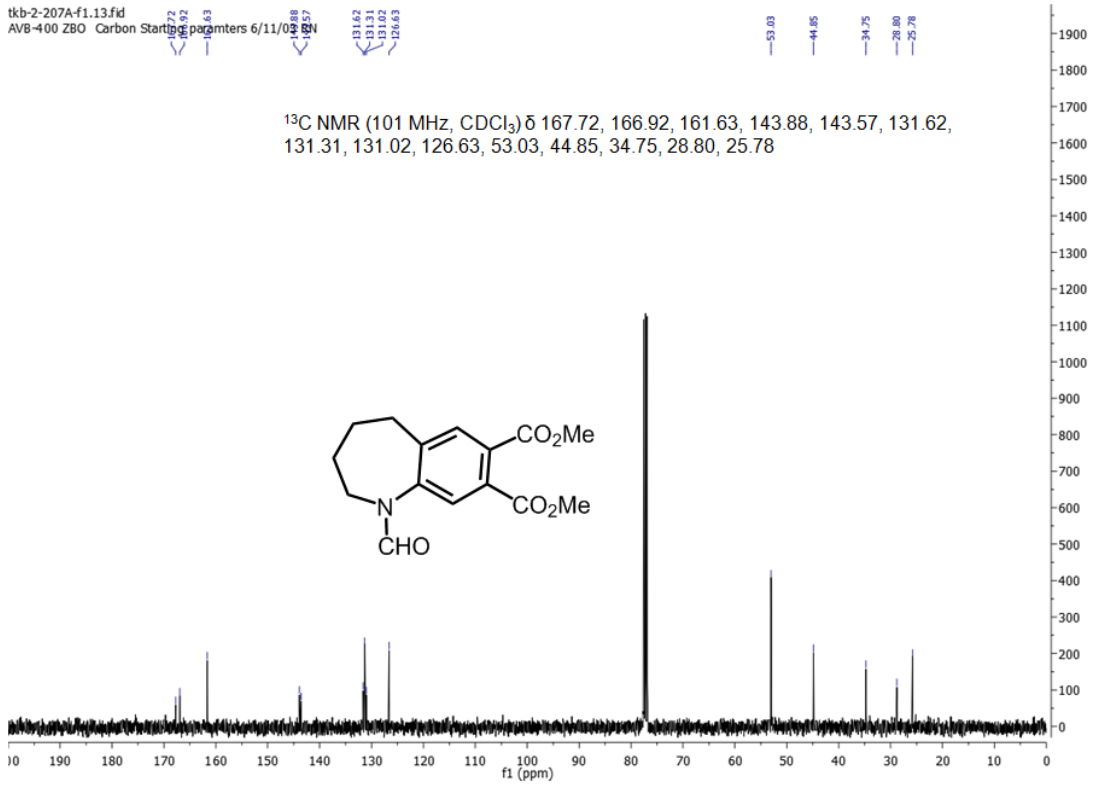
19a

Prepared from **7b** (209.2 mg, 1.0 mmol), and methyl acrylate (0.554 mL, 6 mmol, 6 equiv) and selenium dioxide (3 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 ^{o}C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 195 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H), 7.55 (1H), 7.45 (1H), 3.89 to 3.64 (8H), 2.88 to 2.84 (2H), 1.88 to 1.55 (4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.72, 166.92, 161.63, 143.88, 143.57, 131.62, 131.31, 131.02, 126.63, 53.03, 44.85, 34.75, 28.80, 25.78. HRMS calc for $C_{15}H_{17}NO_5$ 291.1107, found 291.1103.

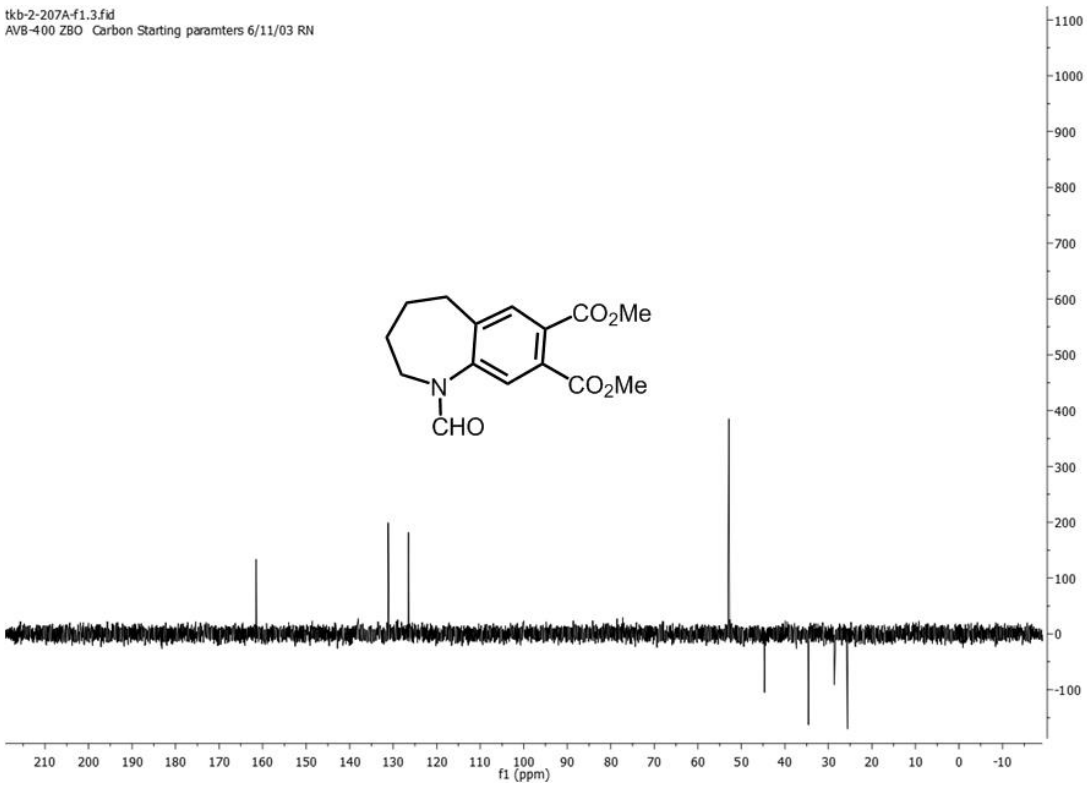


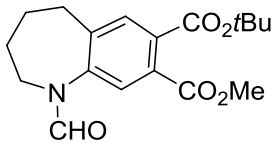






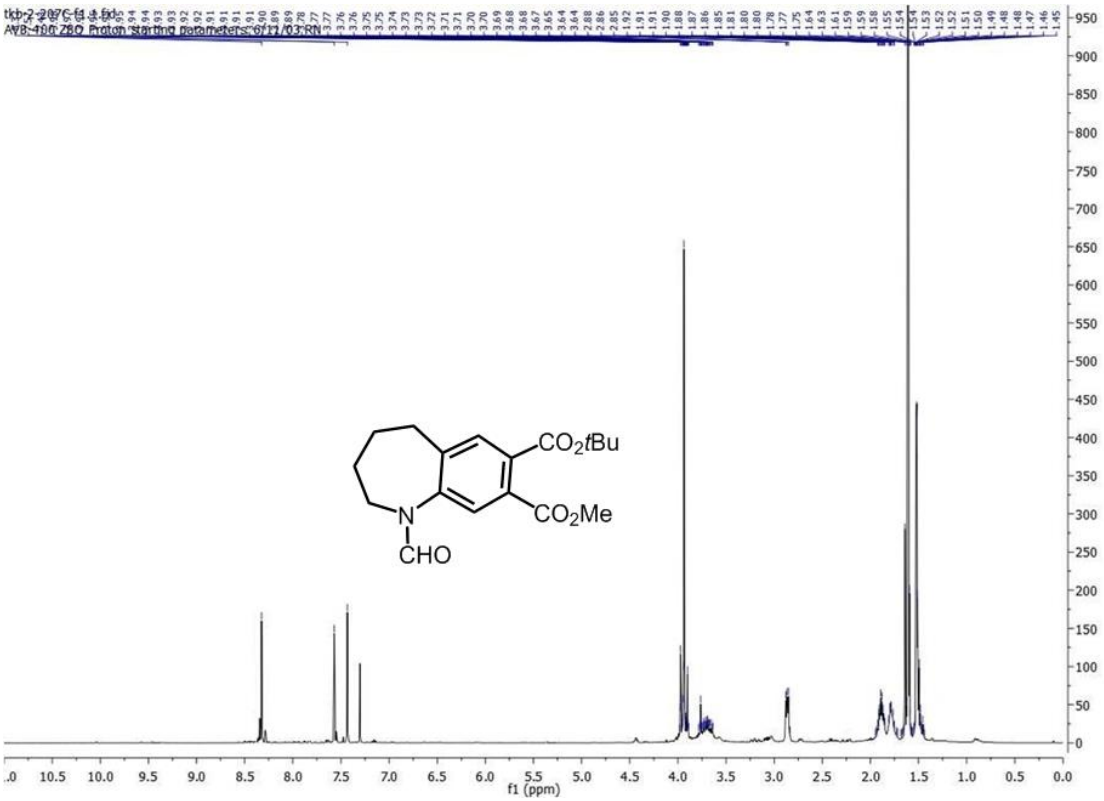
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.72, 166.92, 161.63, 143.88, 143.57, 131.62, 131.31, 131.02, 126.63, 53.03, 44.85, 34.75, 28.80, 25.78

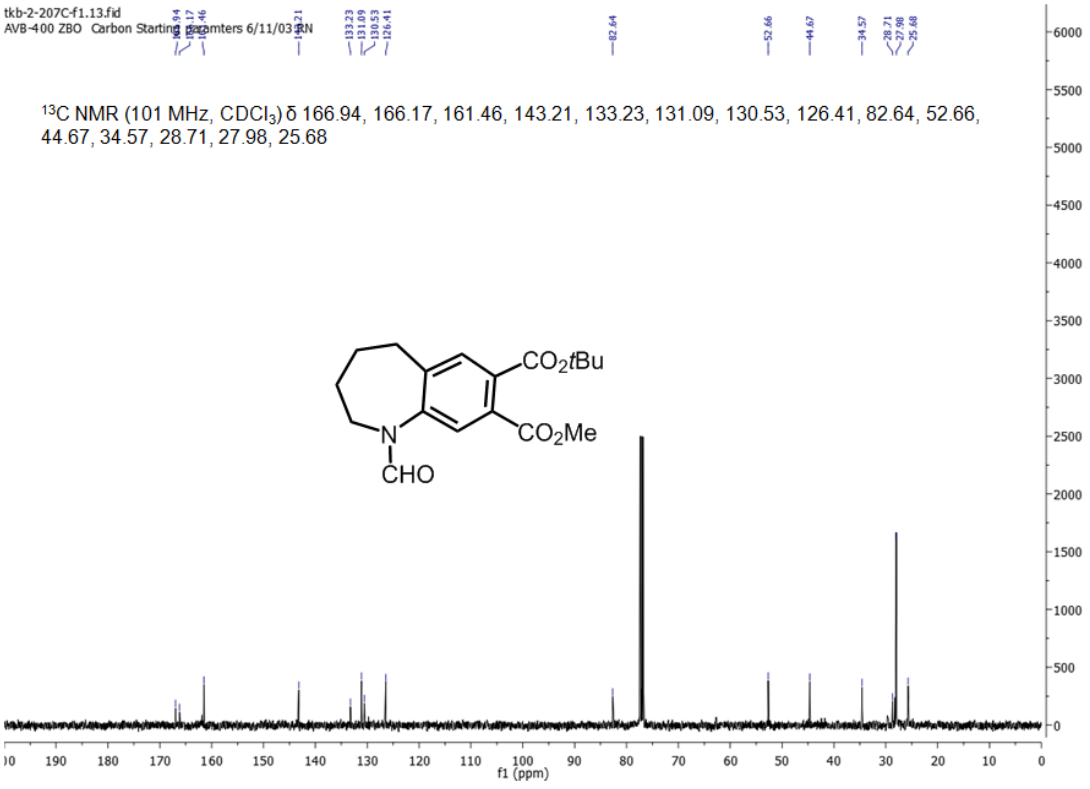




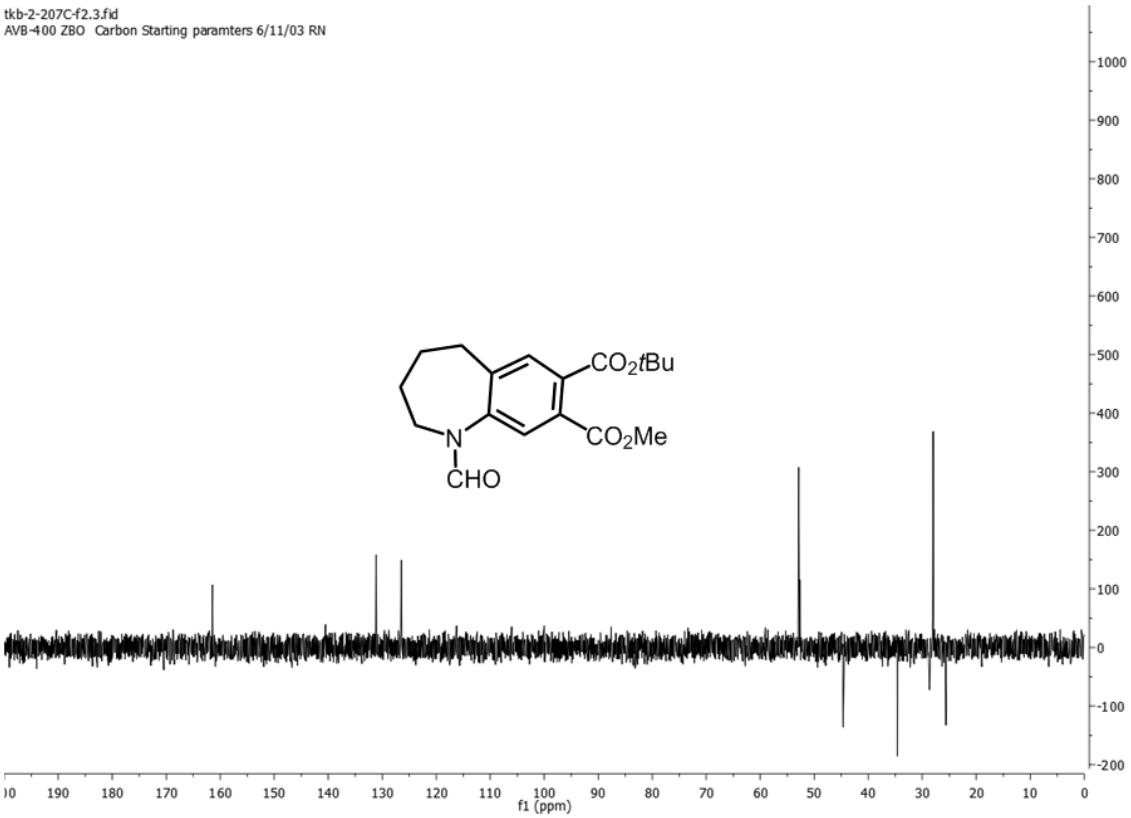
20a

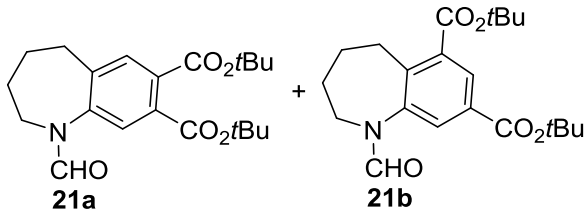
Prepared from **7b** (209.2 mg, 1.0 mmol), *tert*-butyl acrylate (0.29 mL, 2 mmol, 2 equiv), and selenium dioxide (3 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 ^{o}C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 70:30). Yield = 243 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H), 7.57 (1H), 7.43 (1H), 3.98 to 3.64 (5H), 2.88 to 2.84 (2H), 1.95 to 1.44 (13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.94, 166.17, 161.46, 143.21, 133.23, 131.09, 130.53, 126.41, 82.64, 52.66, 44.67, 34.57, 28.71, 27.98, 25.68. . HRMS calc for $C_{18}H_{23}NO_5$ 333.1576, found 333.1572.





^{13}C NMR (101 MHz, $CDCl_3$) δ 166.94, 166.17, 161.46, 143.21, 133.23, 131.09, 130.53, 126.41, 82.64, 52.66, 44.67, 34.57, 28.71, 27.98, 25.68

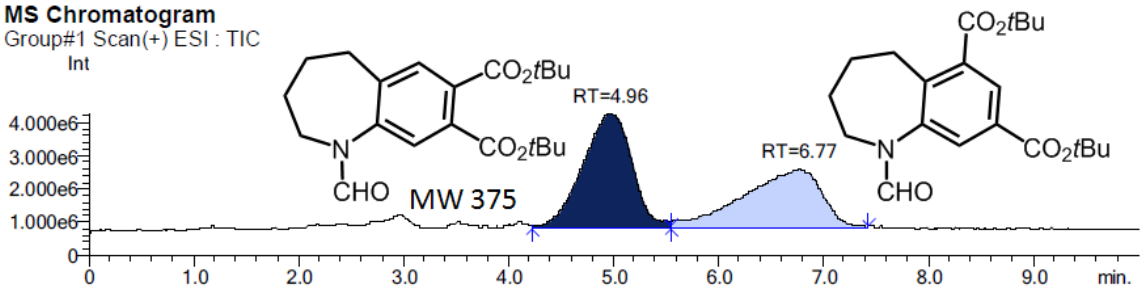


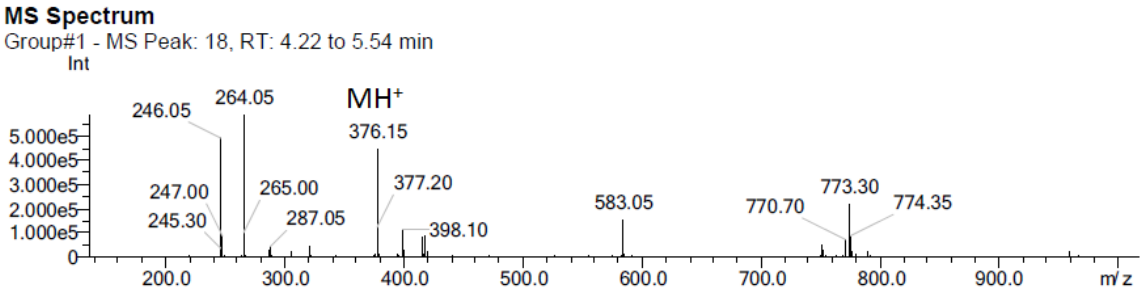


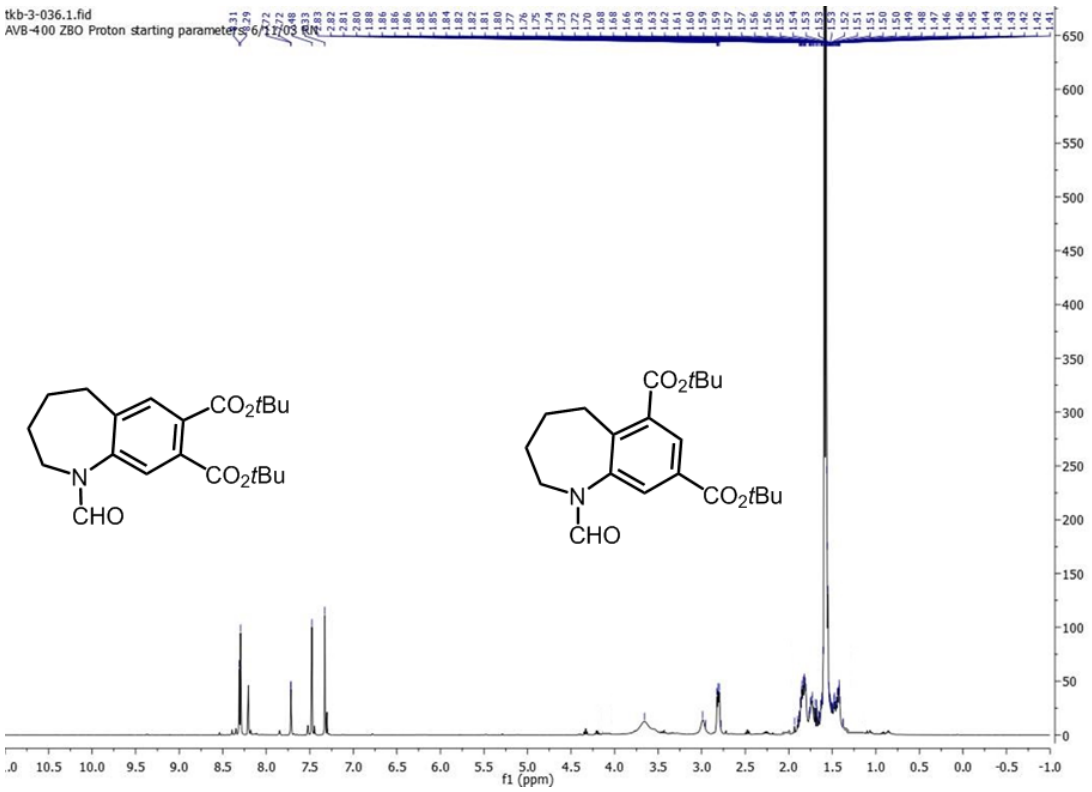
21a **21b**

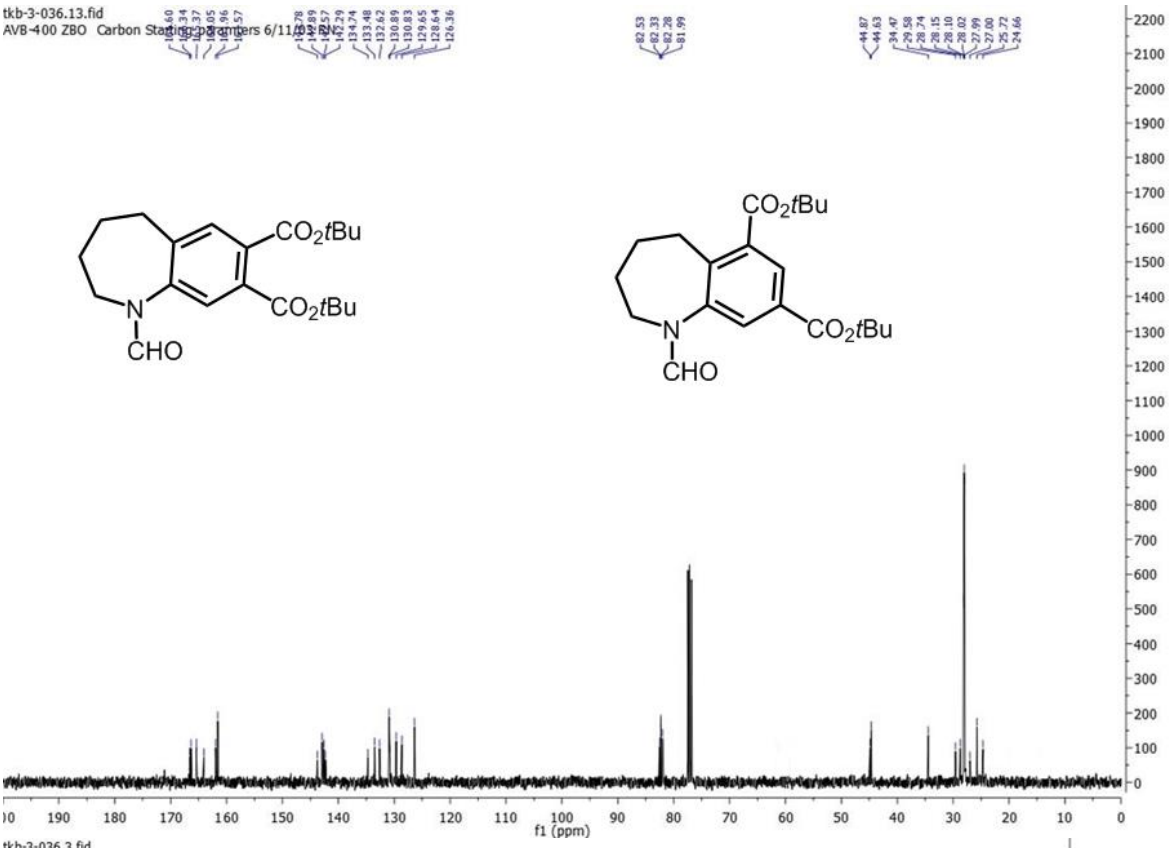
Prepared from **7c** (251.3 mg, 1.0 mmol) and *tert*-butyl acrylate (0.29 mL, 2 mmol, 2 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 ^{o}C. Purification: Flash chromatography on silica (pretreated with 1% Et3N) eluting with hexane/EtOAc (90:10 to 80:20). Yield = 289 mg, 77%. 1H NMR (400 MHz, $CDCl_3$) δ 8.31, 8.29, 7.72, 7.72, 7.48, 7.33, 3.66, 2.99, 2.96, 2.83, 2.82, 2.81, 2.80, 2.78, 1.93, 1.90, 1.89, 1.88, 1.88, 1.86, 1.86, 1.86, 1.85, 1.85, 1.84, 1.82, 1.82, 1.81, 1.80, 1.77, 1.76, 1.75, 1.74, 1.73, 1.72, 1.70, 1.68, 1.68, 1.66, 1.66, 1.65, 1.64, 1.63, 1.63, 1.62, 1.61, 1.60, 1.59, 1.59, 1.57, 1.57, 1.56, 1.56, 1.55, 1.54, 1.53, 1.53, 1.53, 1.52, 1.51, 1.51, 1.50, 1.50, 1.49, 1.48, 1.47, 1.46, 1.46, 1.45, 1.44, 1.43, 1.43, 1.42, 1.42, 1.41, 1.38, 1.37. 13C NMR (101 MHz, CDCl3) δ 166.60, 166.34, 165.37, 164.05, 161.96, 161.57, 143.78, 142.89, 142.57, 142.29, 134.74, 133.48, 132.62, 130.89, 130.83, 129.65, 128.64, 126.35, 82.53, 82.33,

82.28, 81.99, 44.87, 44.63, 34.47, 29.58, 28.74, 28.15, 28.10, 28.02, 27.99, 27.00, 25.72, 24.66. HRMS calc for C21H29NO5 375.2046, found 375.2040.





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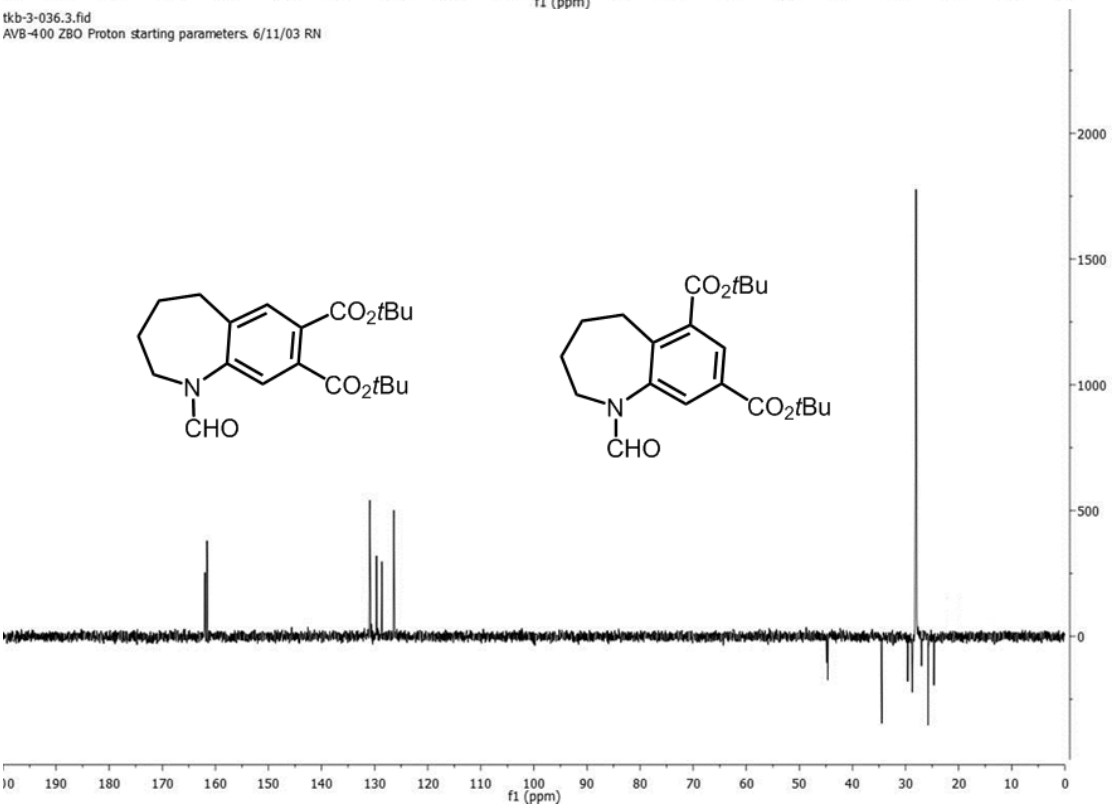
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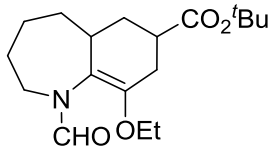
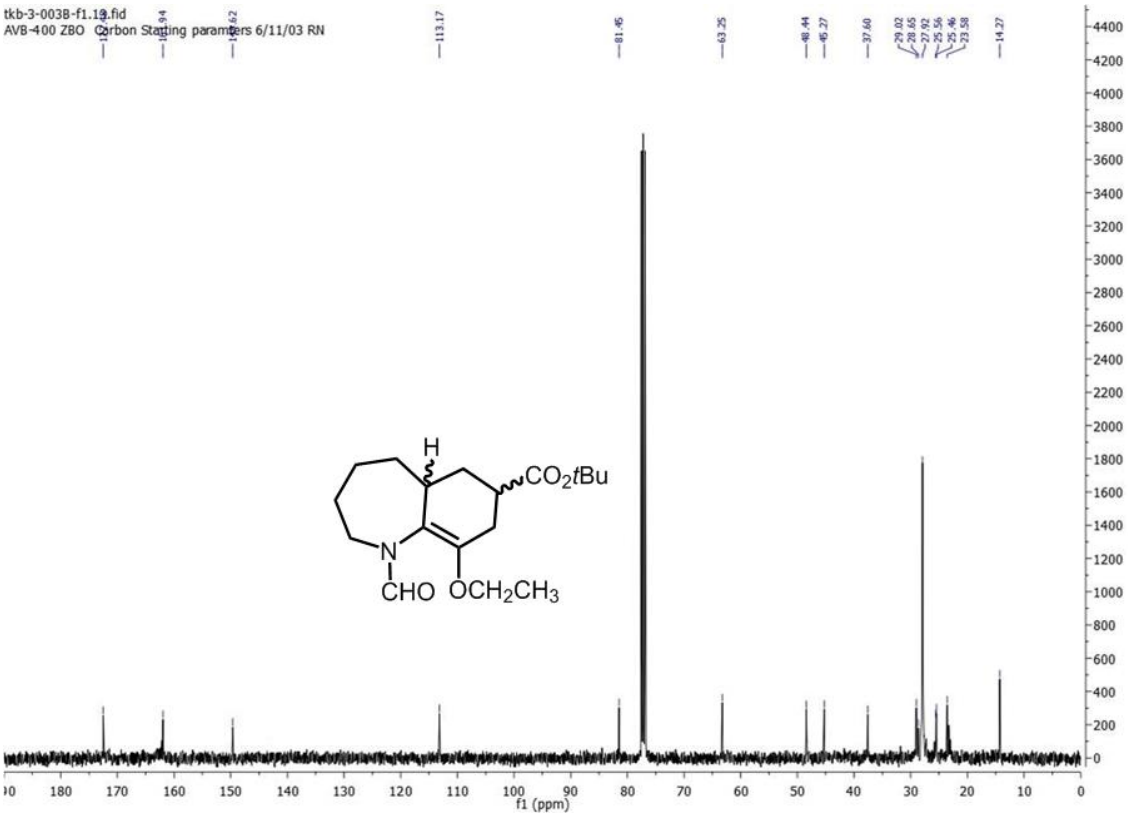
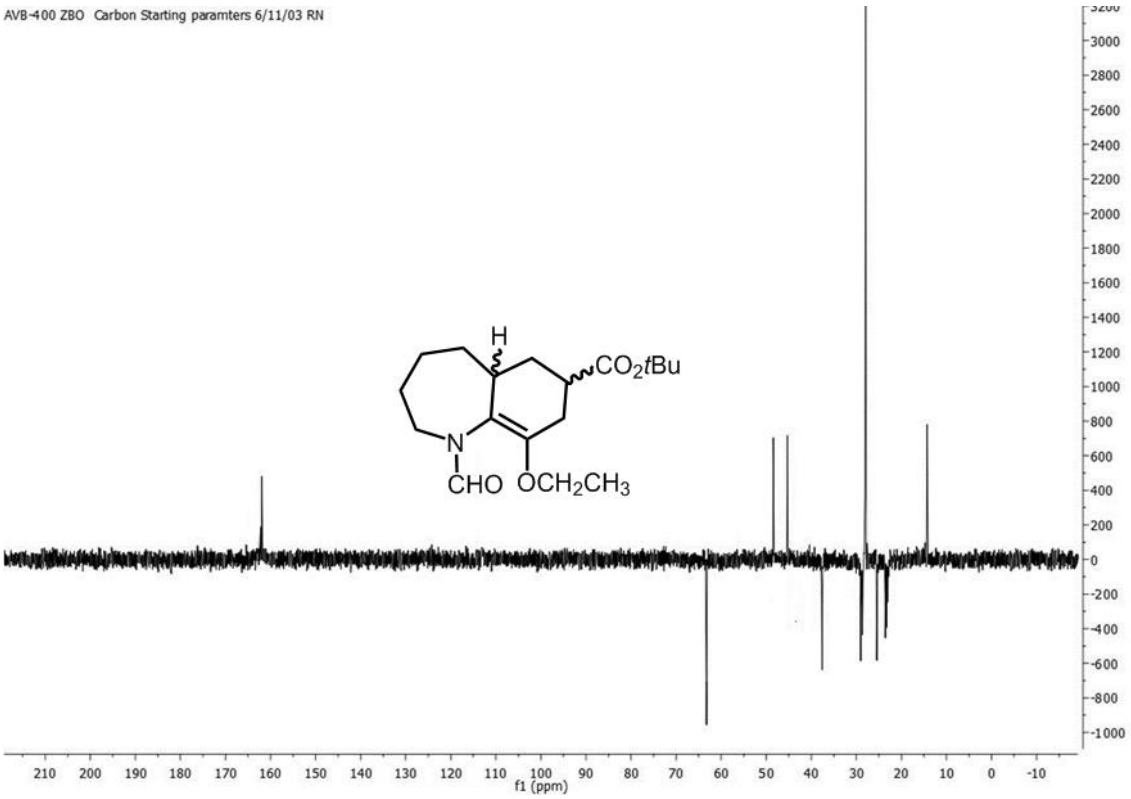


22a

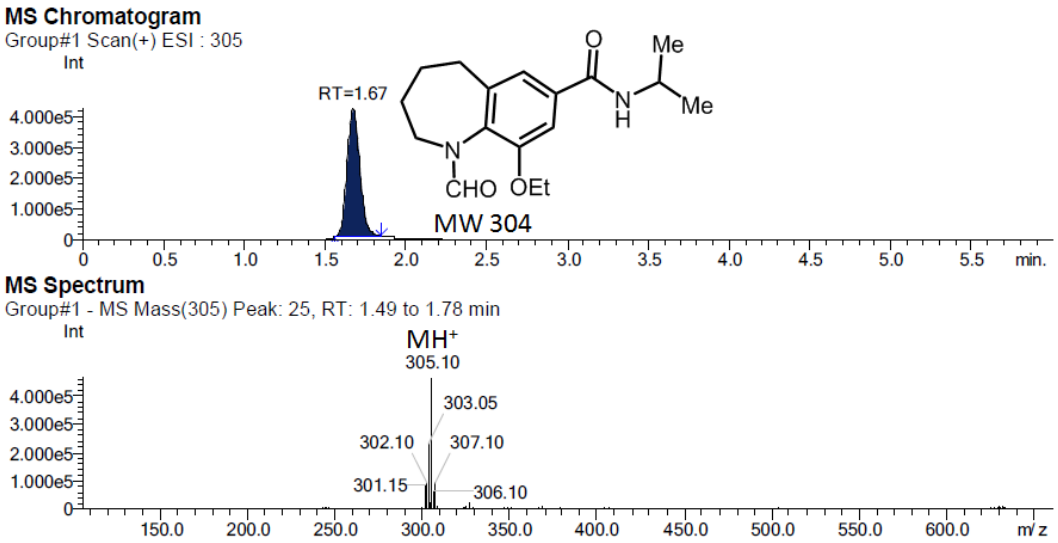
Prepared from **9** (195.3 mg, 1.0 mmol) and *tert*-butyl acrylate (0.29 mL, 2 mmol, 2 equiv) using **General Procedure A.** Time = 2 h, T = 100 ^{o}C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (60:40 to 10:90). Yield = 259 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H), 4.17 to 4.12 (2H), 3.83 to 3.71 (2H), 3.59 to 3.23 (3H), 3.08 to 2.34, 1.93 to 1.37. ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.48, 161.94, 149.62, 113.17, 81.46, 63.25, 48.44, 45.27, 37.60, 29.01, 28.65, 27.92, 25.56, 25.46, 23.58, 23.27, 14.27.

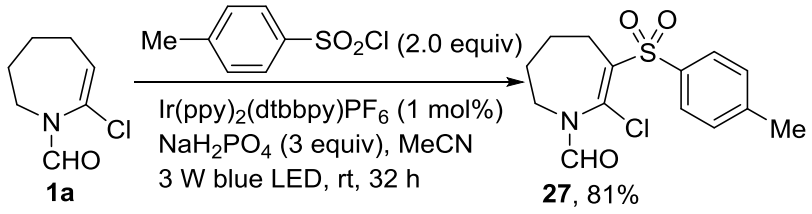




23a

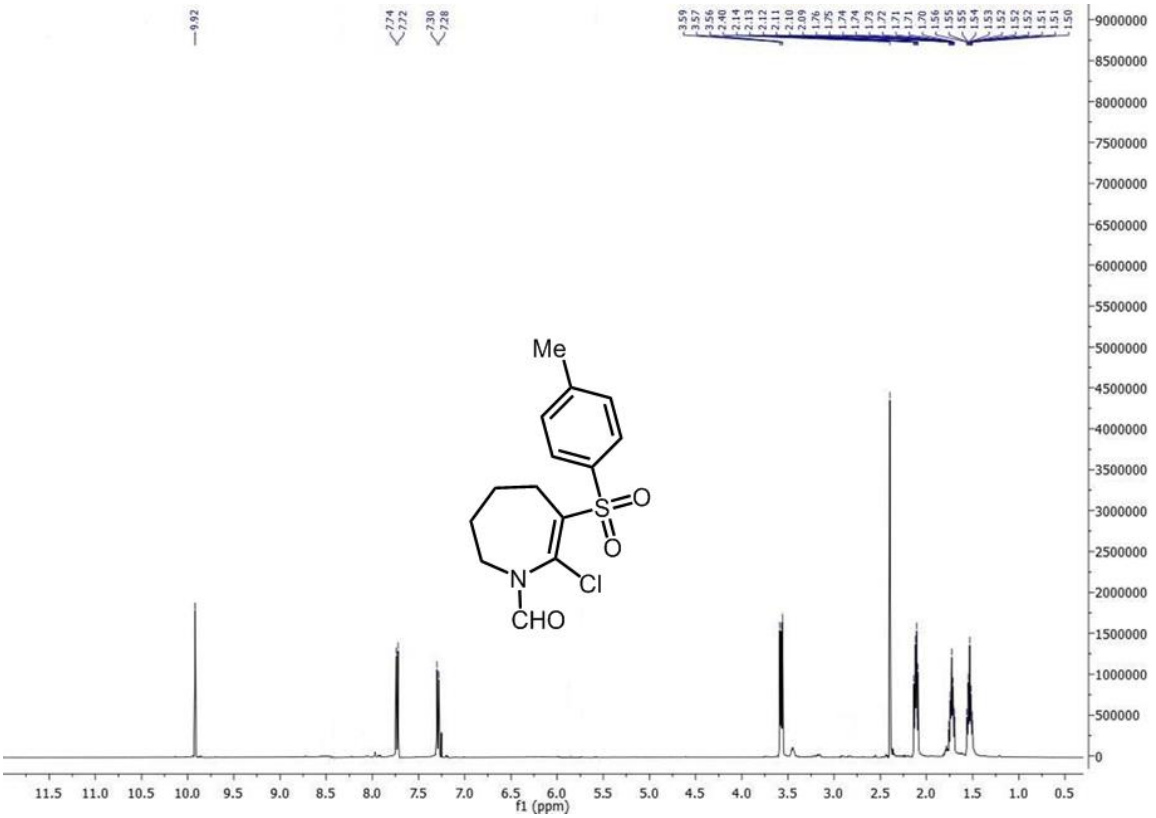
Obtained in trace amounts from **9** (19.5 mg, 0.10 mmol), *N*-isopropyl acrylamide (22.6 mg, 0.20 mmol, 2 equiv), selenium dioxide (3 equiv) using **General Procedure A.** Time = 2 h.

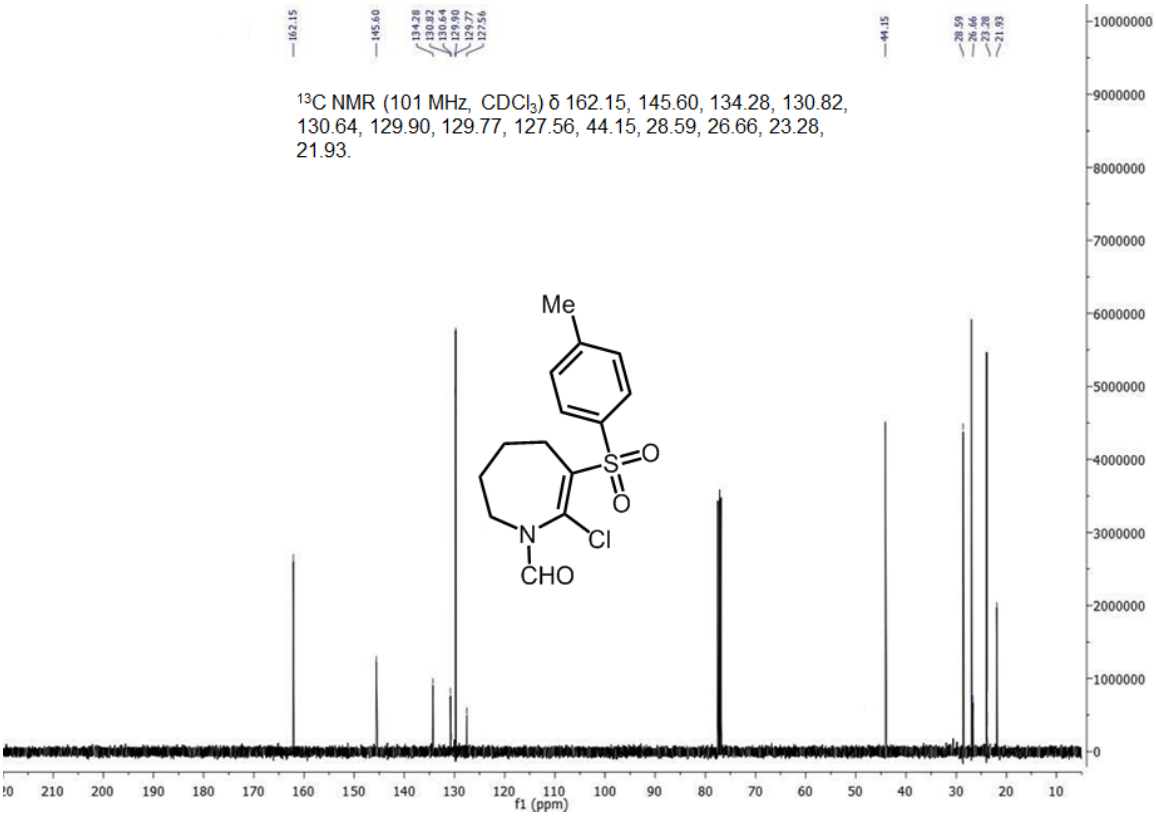




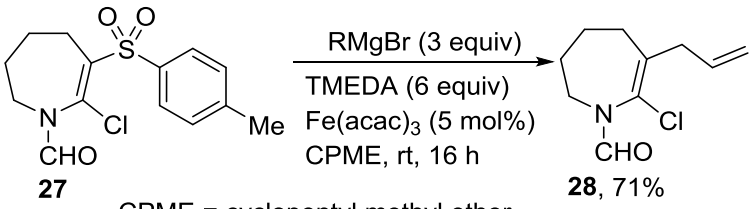
*β-Sulfonation of α-chloro eneformamide **1a**[3]*

To a 100 mL flask was equipped with a rubber septum and magnetic stir bar was added α-chloro eneformamide **1a** (800 mg, 5.0 mmol, 1.0 equiv), *p*-toluenesulfonyl chloride (1.91 g, 10 mmol, 2.0 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%), Na_2HPO_4 (15.0 mmol, 3 equiv). The flask was evacuated and backfilled with argon for several times. CH_3CN (50 mL, 0.1 M) was added via syringe under argon. The mixture was then irradiated by a 3 W blue LED strip at a distance of 5 cm. After the reaction was complete (as judged by GC-MS and TLC monitoring, ~32 h), the mixture was poured into a separatory funnel containing H_2O (50 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (hexane/EtOAc, 60:40) on silica gel to afford 1.27 g of the desired product as an amorphous solid in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H), 7.73 (2H), 7.28 (2H), 3.59 to 3.56 (2H), 2.40 (3H), 2.14 to 2.09 (2H), 1.76 to 1.70 (2H), 1.56 to 1.50 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.6, 134.3, 130.8, 130.6, 129.9, 129.8, 127.6, 44.1, 28.6, 26.7, 23.3, 21.9. HRMS calc for $C_{14}H_{16}ClNO_3S$ 313.0539, found 313.0551.





^{13}C NMR (101 MHz, $CDCl_3$) δ 162.15, 145.60, 134.28, 130.82, 130.64, 129.90, 129.77, 127.56, 44.15, 28.59, 26.66, 23.28, 21.93.

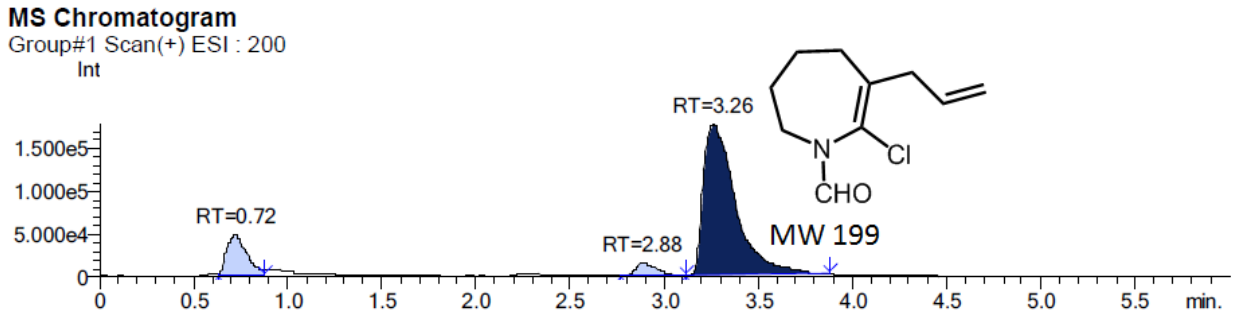


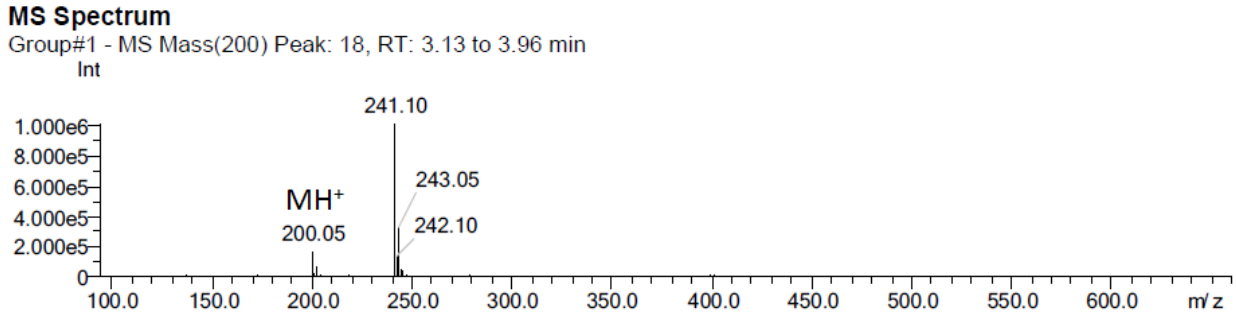
27 **28**, 71%

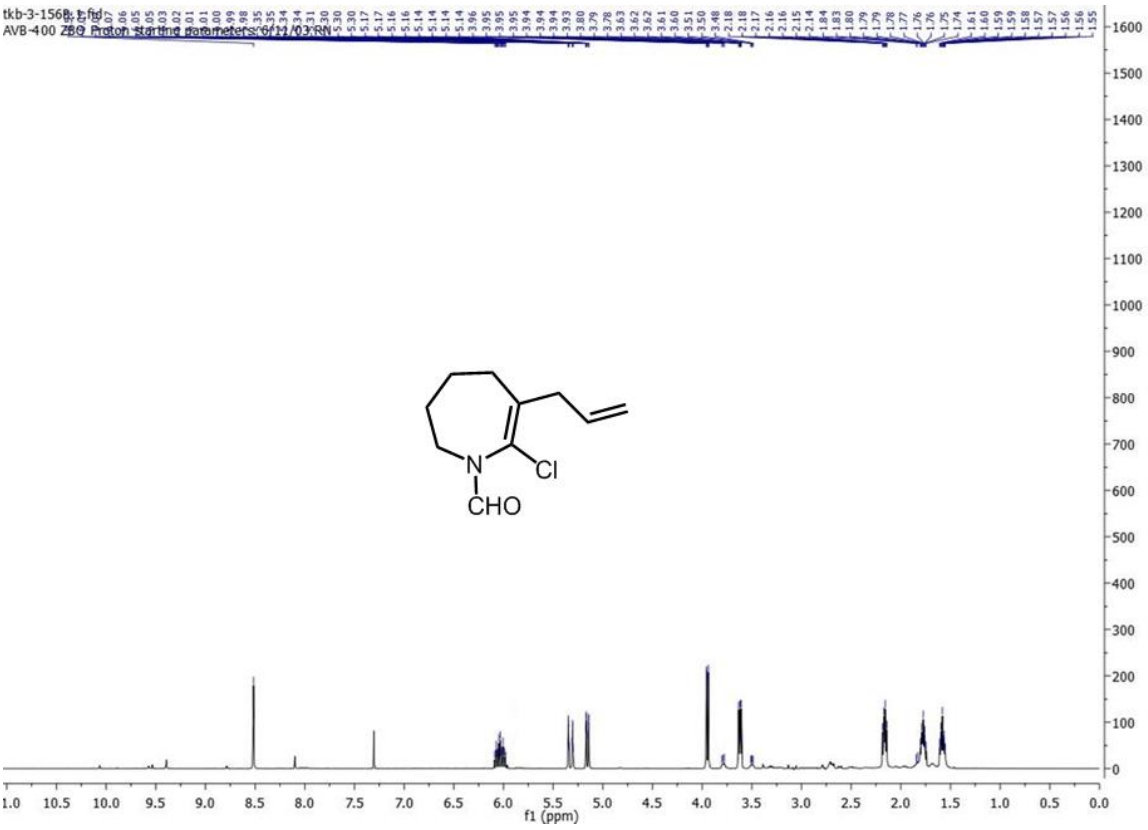
CPME = cyclopentyl methyl ether

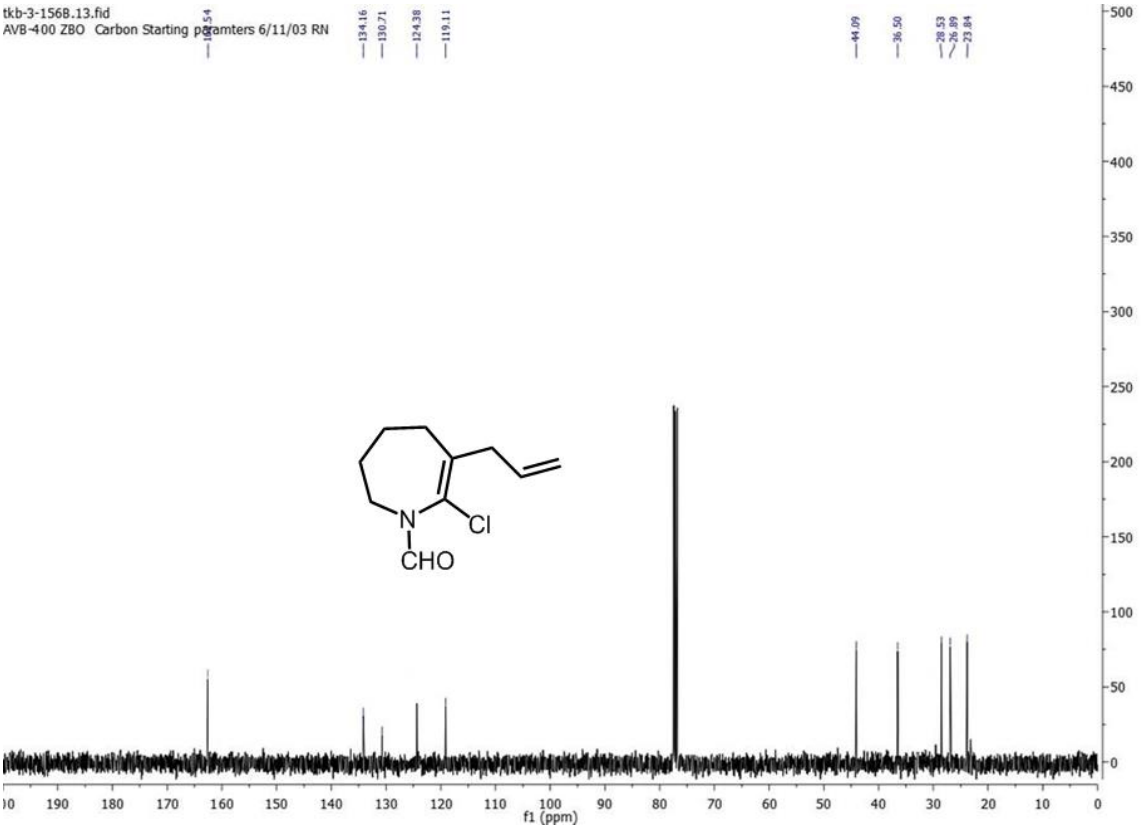
To an oven-dried, septum-capped two-necked flask equipped with a stir bar were added freshly distilled TMEDA (0.90 mL, 6.00 mmol, 6.0 equiv), allylmagnesium bromide (1.0 M in THF, 3.00 mL, 3.00 mmol, 3.0 equiv) diluted with anhydrous cyclopentyl methyl ether (CPME, 3.0 mL) via syringe under an argon atmosphere. One of the septa was opened and $Fe(acac)_3$ (20 mg, 0.050 mmol, 5 mol%) was rapidly introduced and the suspension was diluted with CPME (5.0 mL) was added. After several minutes (~5 min), vinyl sulfone **27** (313 mg, 1.00 mmol, 1.0 equiv) in CPME (5.0 mL) was added. The suspension was sonicated until a clear solution was obtained (~10 min, longer time required for less suluble Grignard reagents). After 5 h at rt (TLC and GC-MS monitoring), the mixture was quenched by slow addition of *sat* NH_4Cl. It was then filtered through a pad of Celite under vacuum and the remaining residue was rinsed with EtOAc. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4 (30 min), filtered, and concentrated in under reduced pressure to give the crude product.

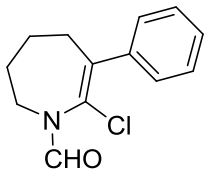
Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 70:30). Yield = 141 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H), 6.09 to 5.98 (1H), 5.31 (1H), 5.16 (1H), 3.95 (2H), 3.63 to 3.60 (2H), 2.18 to 2.14 (2H), 1.84, to 1.74 (2H), 1.61 to 1.55 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 134.2, 130.7, 124.4, 119.1, 44.1, 36.5, 28.5, 26.9, 23.8. HRMS calc for $C_{10}H_{14}ClNO$ 199.0607, found 199.0610.


MS Chromatogram
Group#1 Scan(+) ESI : 200
Int
1.500e5
1.000e5
5.000e4
0
RT=0.72
RT=2.88
RT=3.26
N
Cl
CHO
MW 199
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
min.


MS Spectrum
Group#1 - MS Mass(200) Peak: 18, RT: 3.13 to 3.96 min
Int
1.000e6
8.000e5
6.000e5
4.000e5
2.000e5
0
241.10
243.05
242.10
MH+
200.05
100.0
150.0
200.0
250.0
300.0
350.0
400.0
450.0
500.0
550.0
600.0
m/z

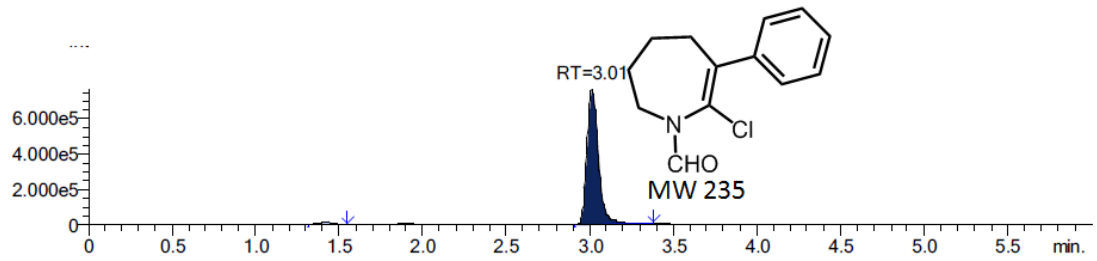

N
Cl
CHO
f1 (ppm)





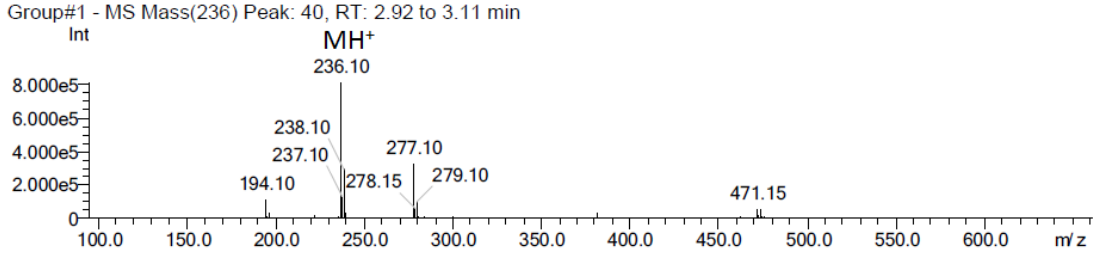
29

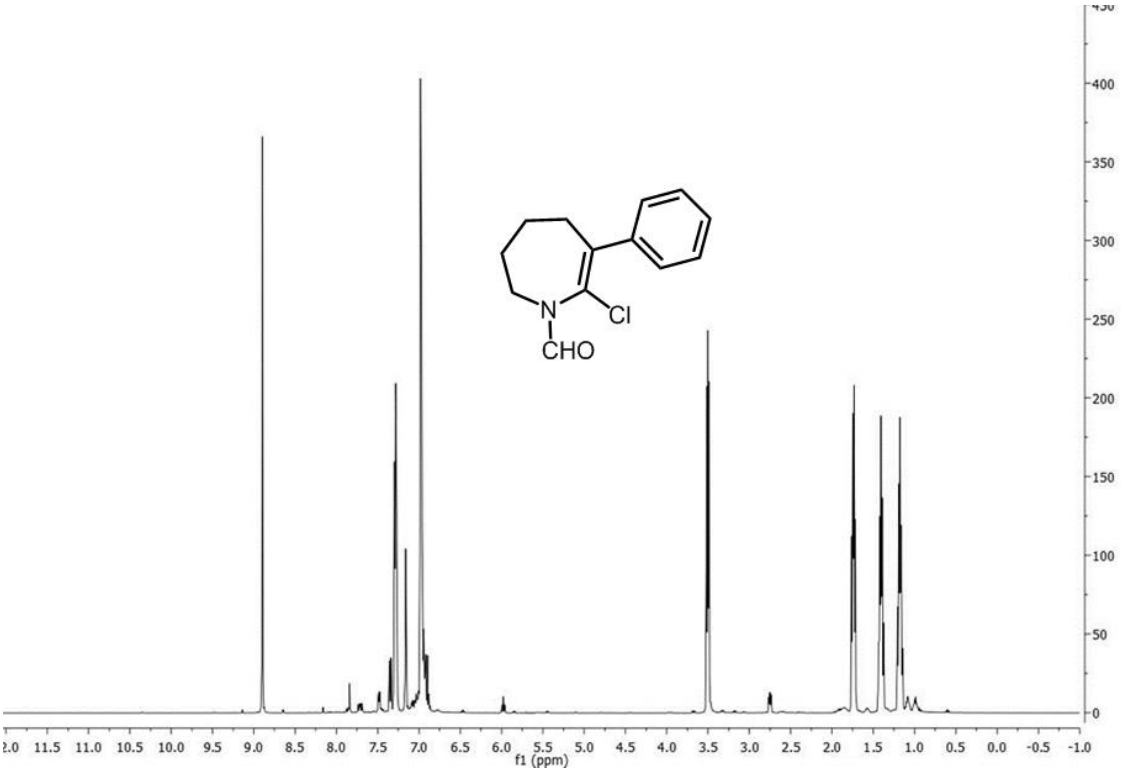
Prepared from vinyl sulfone **27** (1 mmol) in the same way as was **28**; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 207 mg, 88%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.90 (1H), 7.30 to 6.96 (5H), 3.52 to 3.49 (2H), 1.76 to 1.72 (2H), 1.44 to 1.38 (2H), 1.21 to 1.15 (2H), 1.10 to 1.07 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.89, 133.09, 132.11, 130.09, 129.70, 126.27, 123.04, 44.39, 28.44, 27.94, 24.59. HRMS calc for $C_{13}H_{14}ClNO$ 235.0764, found 235.0760.

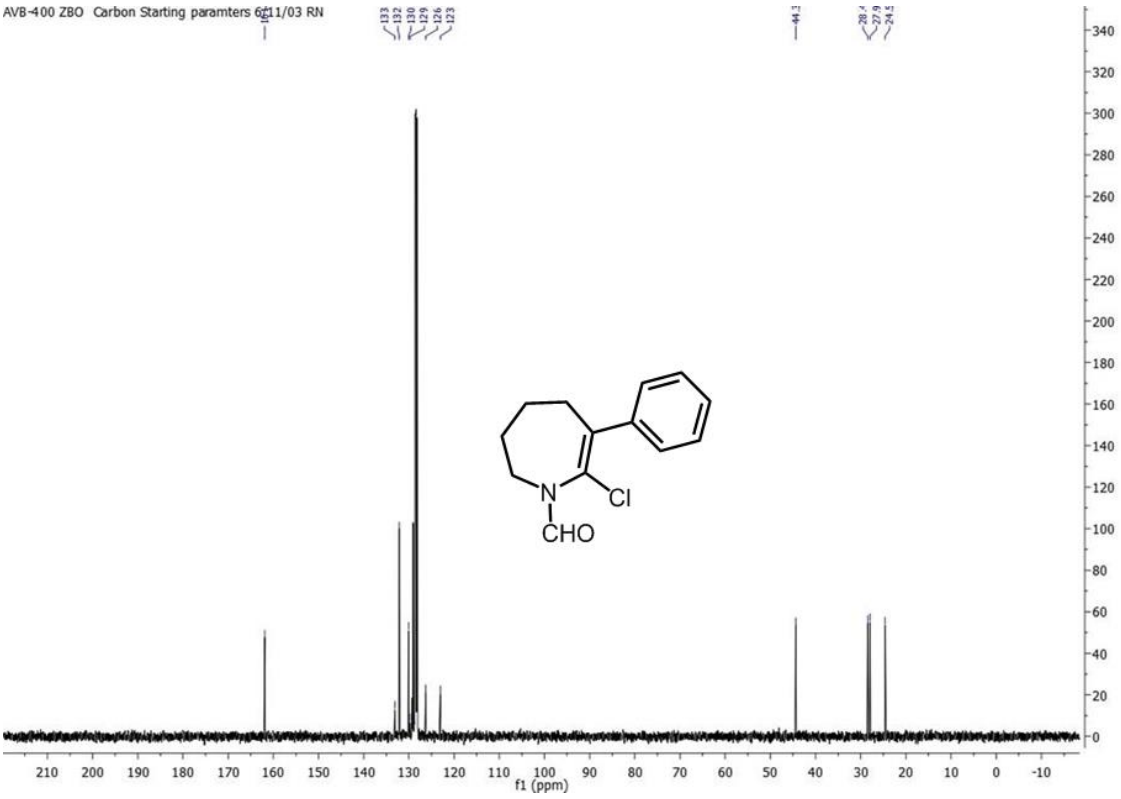


MS Spectrum

Group#1 - MS Mass(236) Peak: 40, RT: 2.92 to 3.11 min

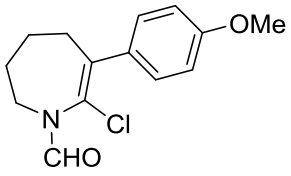






29

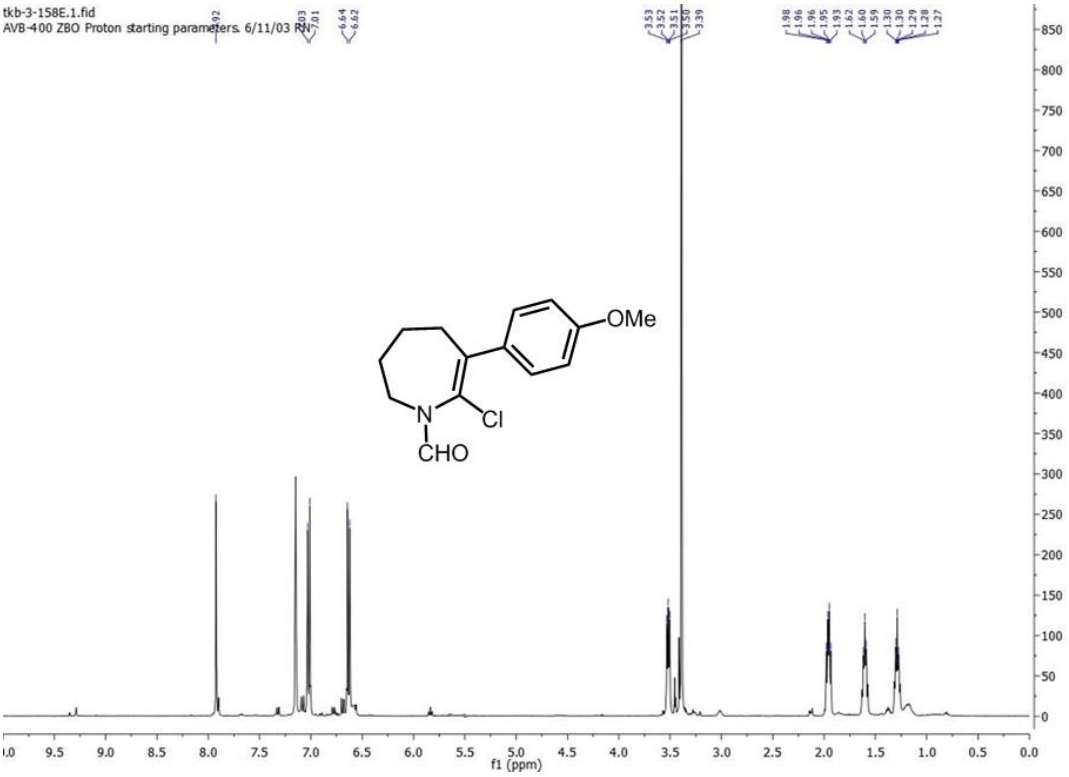
Prepared from **1a** (80 mg, 0.5 mmol) and iodobenzene (204 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 85.8 mg, 73%.

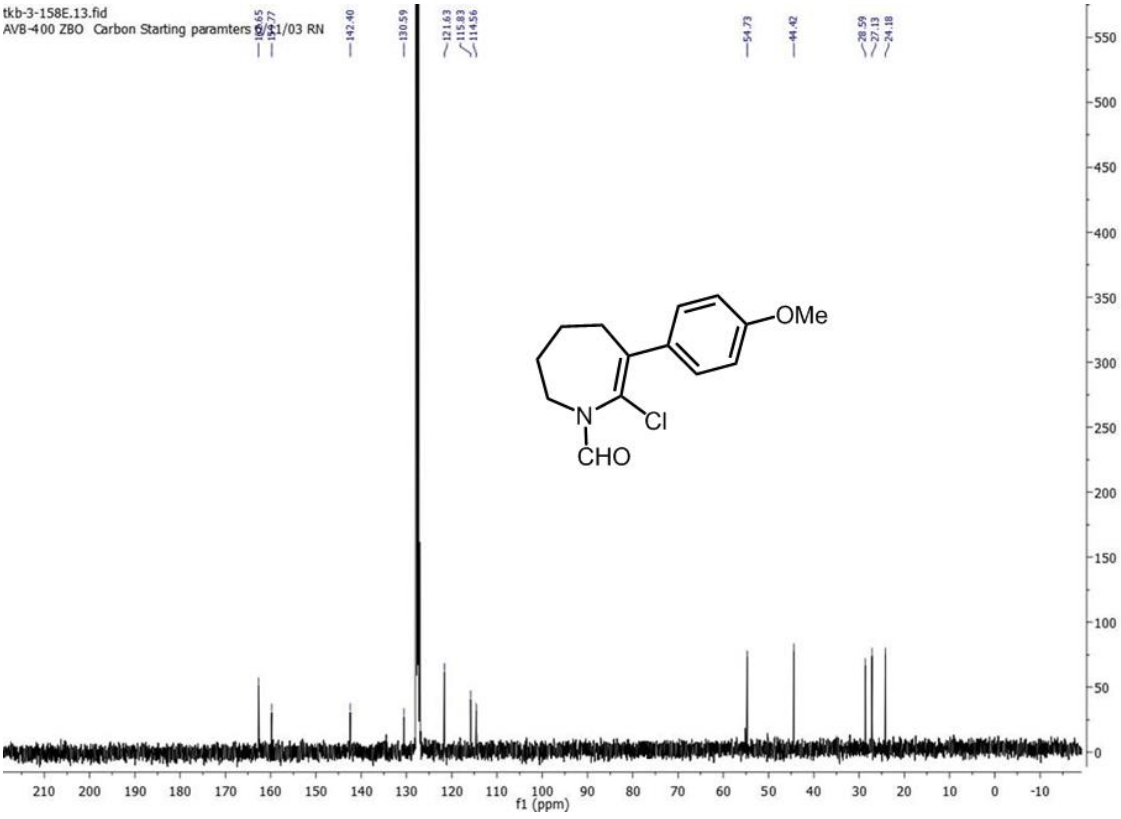


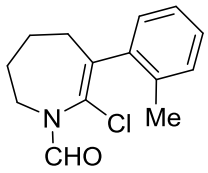
30

Prepared from **1a** (80 mg, 0.5 mmol) and 4-iodoanisole (234 mg, 2 equiv) using **General Procedure B.** Time = 16 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 20:80). Yield = 114 mg, 86%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.92 (1H), 7.03 (2H), 6.63 (2H), 3.53 to 3.50 (2H), 3.39 (3H), 1.98 to 1.93 (2H), 1.62 to 1.59 (2H), 1.31 to 1.28 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 162.65, 159.77, 142.40, 130.59,

121.63, 115.83, 114.56, 54.73, 44.42, 28.59, 27.13, 24.18. HRMS calc for $C_{14}H_{16}ClNO_2$ 265.0870, found 265.0874.

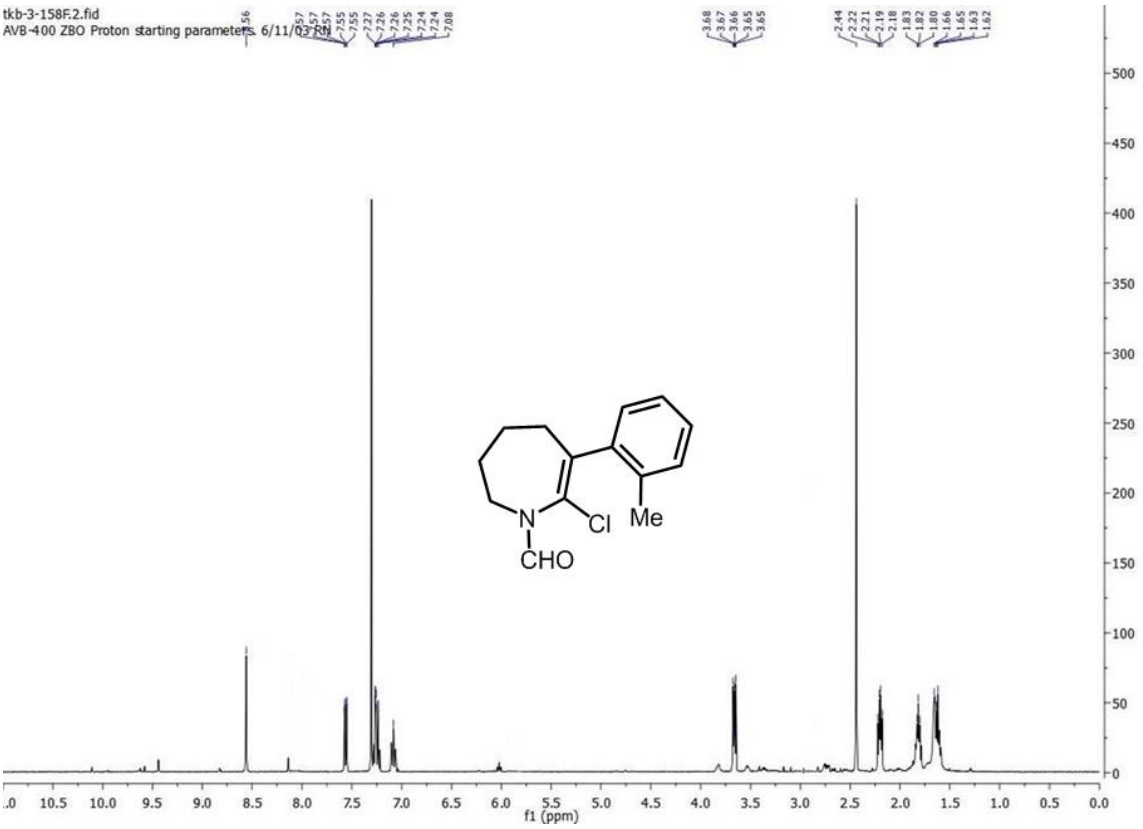


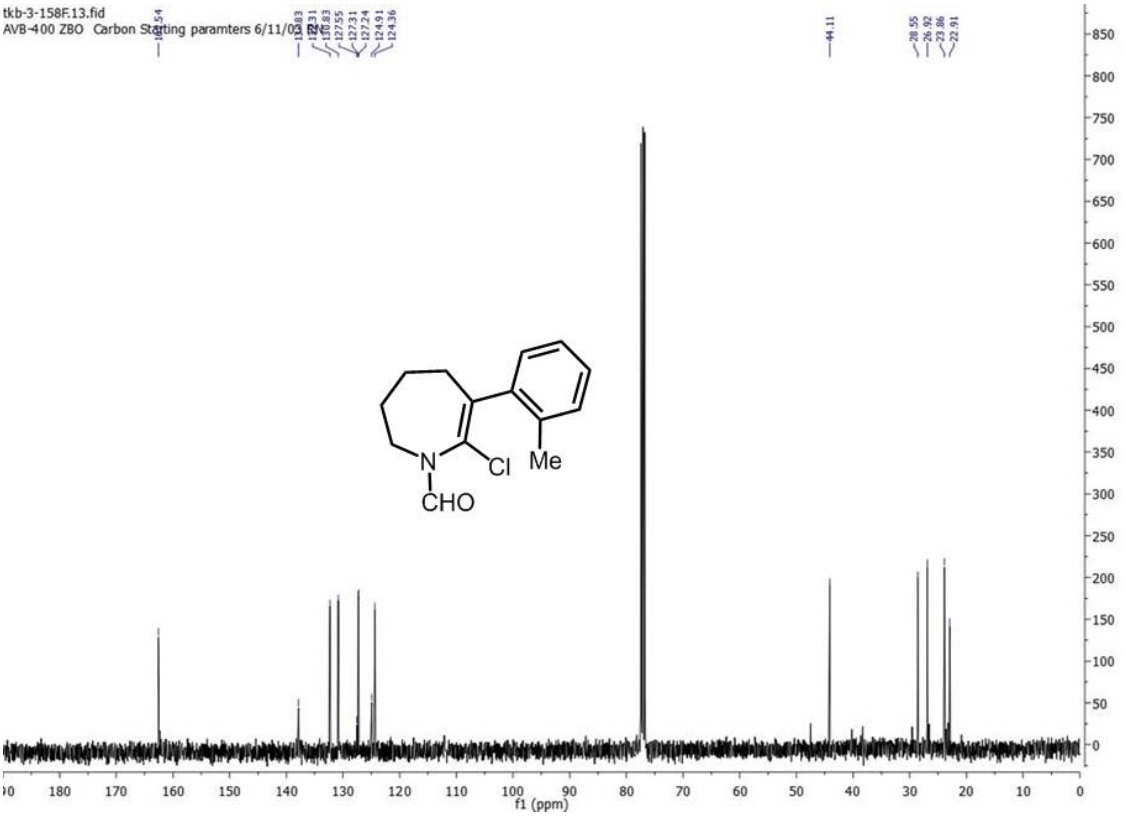


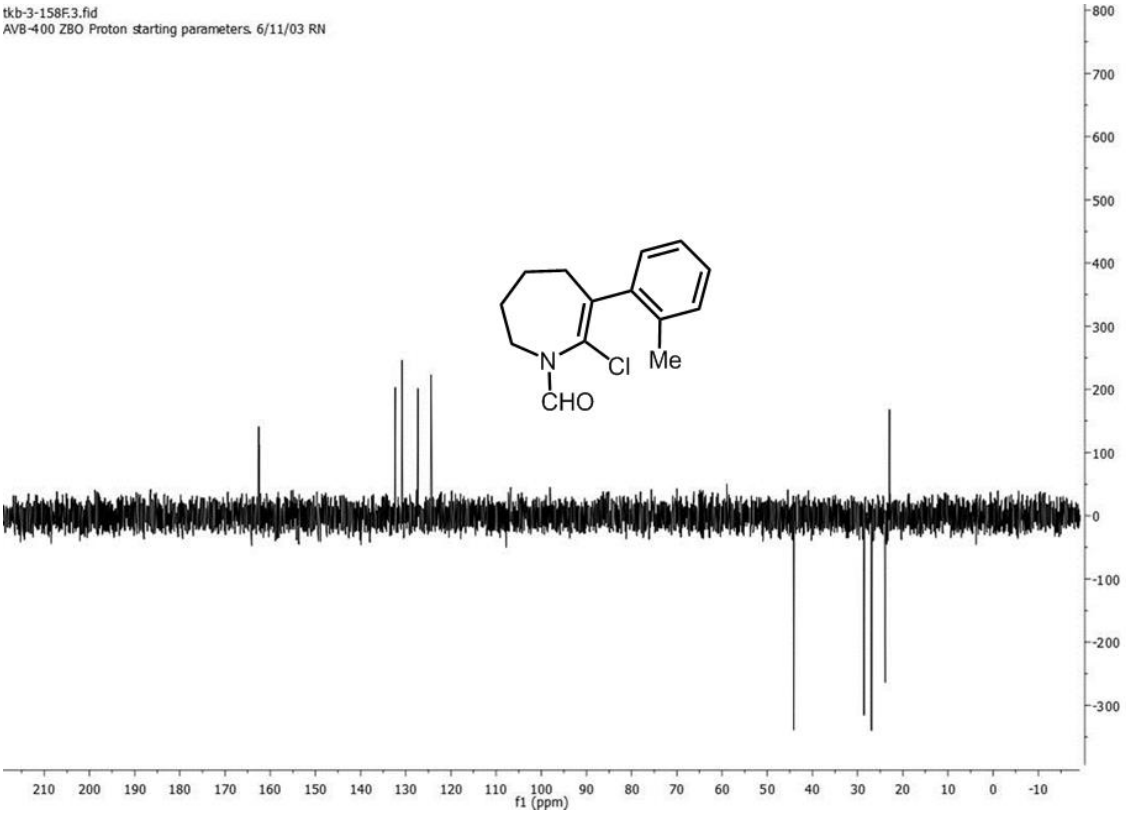


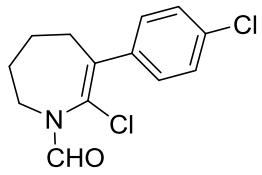
31

Prepared from **1a** (80 mg, 0.5 mmol) and iodotoluene (218 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 76 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H), 7.57 (1H), 7.27 to 7.24 (2H), 7.08 (1H), 3.68 to 3.65 (2H), 2.44 (3H), 2.22 to 2.18 (2H), 1.83 to 1.80 (2H), 1.66 to 1.62 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.54, 137.83, 132.31, 130.83, 127.55, 127.31, 127.24, 124.91, 124.36, 44.11, 28.55, 26.92, 23.86, 22.91. HRMS calc for $C_{14}H_{16}ClNO$ 249.0920, found 249.0912.



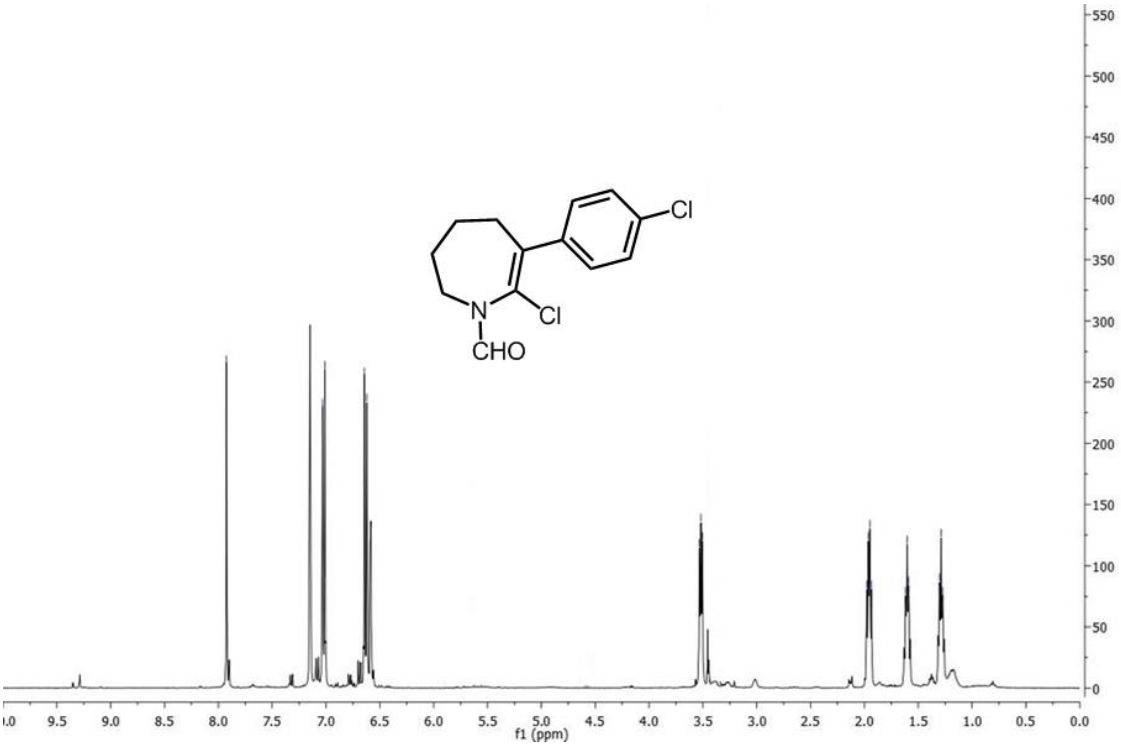

tkb-3-158F.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
44.11
28.55
26.92
23.86
22.91
N
Cl
Me
CHO
f1 (ppm)

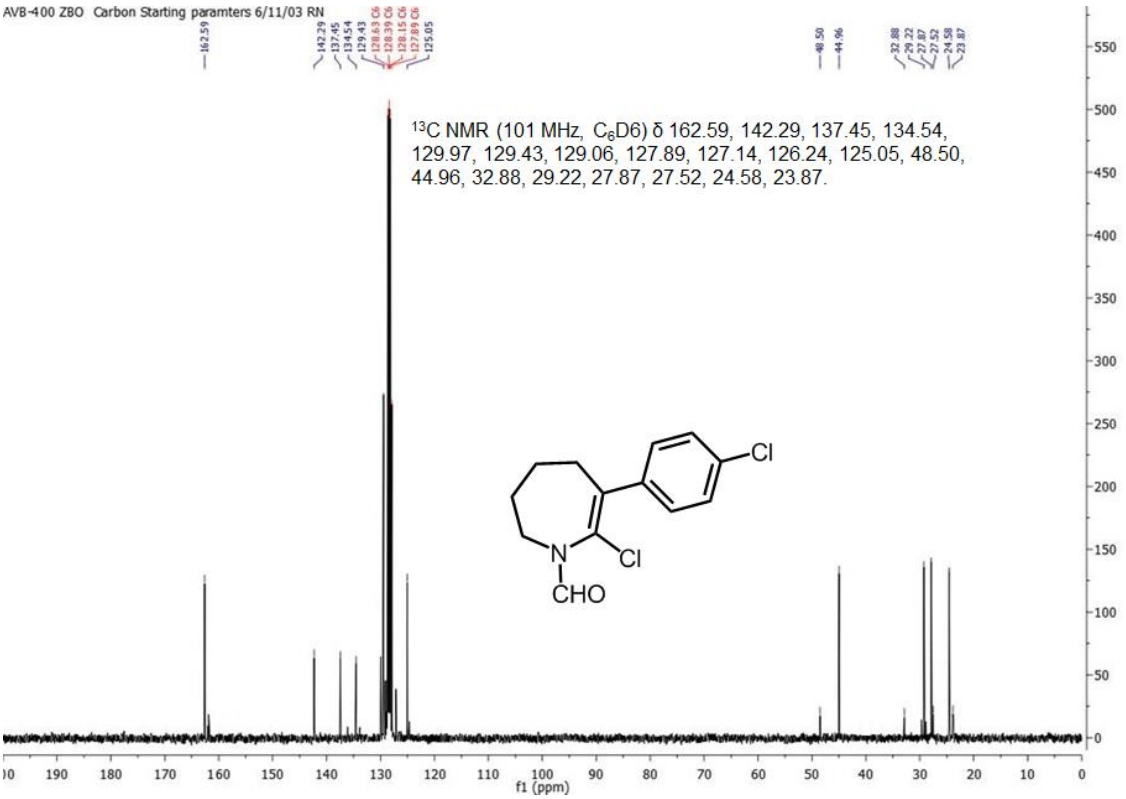

tkb-3-158F.3.fid
AVB-400 ZBO Proton starting parameters 6/11/03 RN
N
Cl
Me
CHO
f1 (ppm)

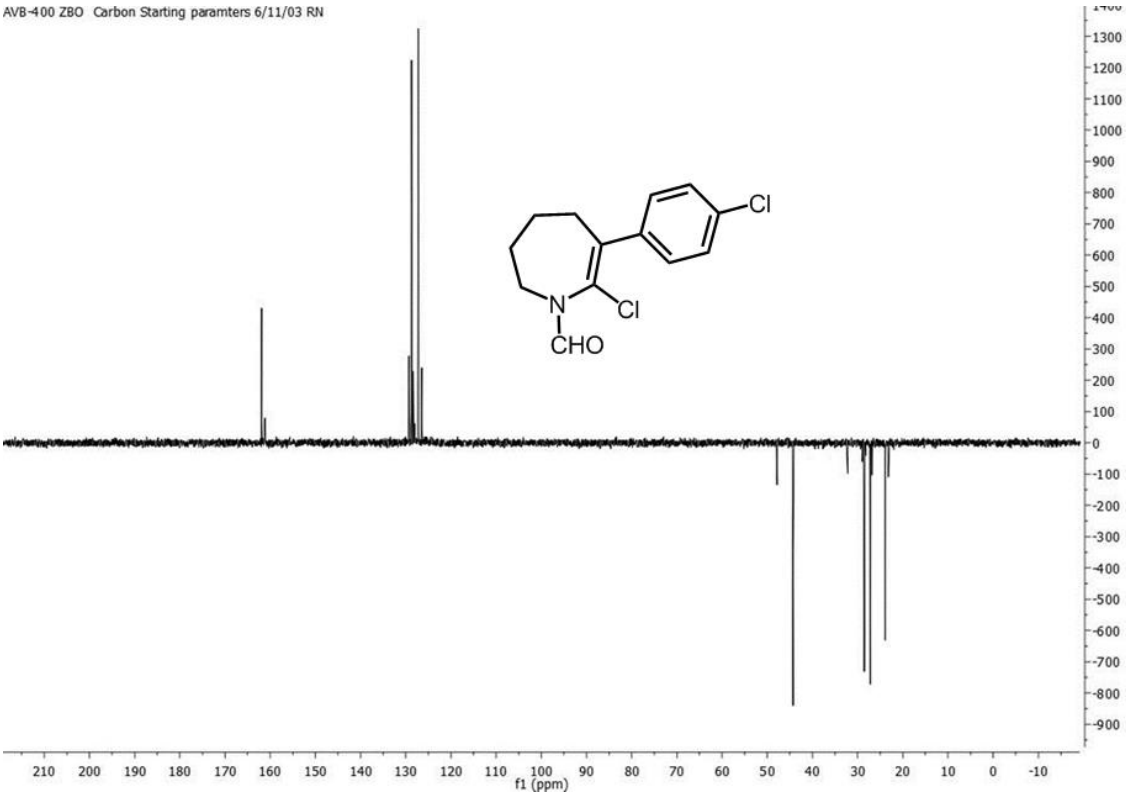


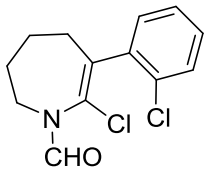
32

Prepared from **1a** (80 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (238 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 88.8 mg, 66%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 7.92 (1H), 7.02 (2H) 6.63 (2H), 3.52 (2H), 1.98 to 1.93 (2H), 1.62 to 1.59 (2H), 1.30 to 1.26 (2H). ^{13}C NMR (101 MHz, C_6D6) δ 162.59, 142.29, 137.45, 134.54, 129.97, 129.43, 129.06, 127.89, 127.14, 126.24, 125.05, 48.50, 44.96, 32.88, 29.22, 27.87, 27.52, 24.58, 23.87. HRMS calc for $C_{13}H_{13}Cl_2NO$ 269.0374, found 269.0366.



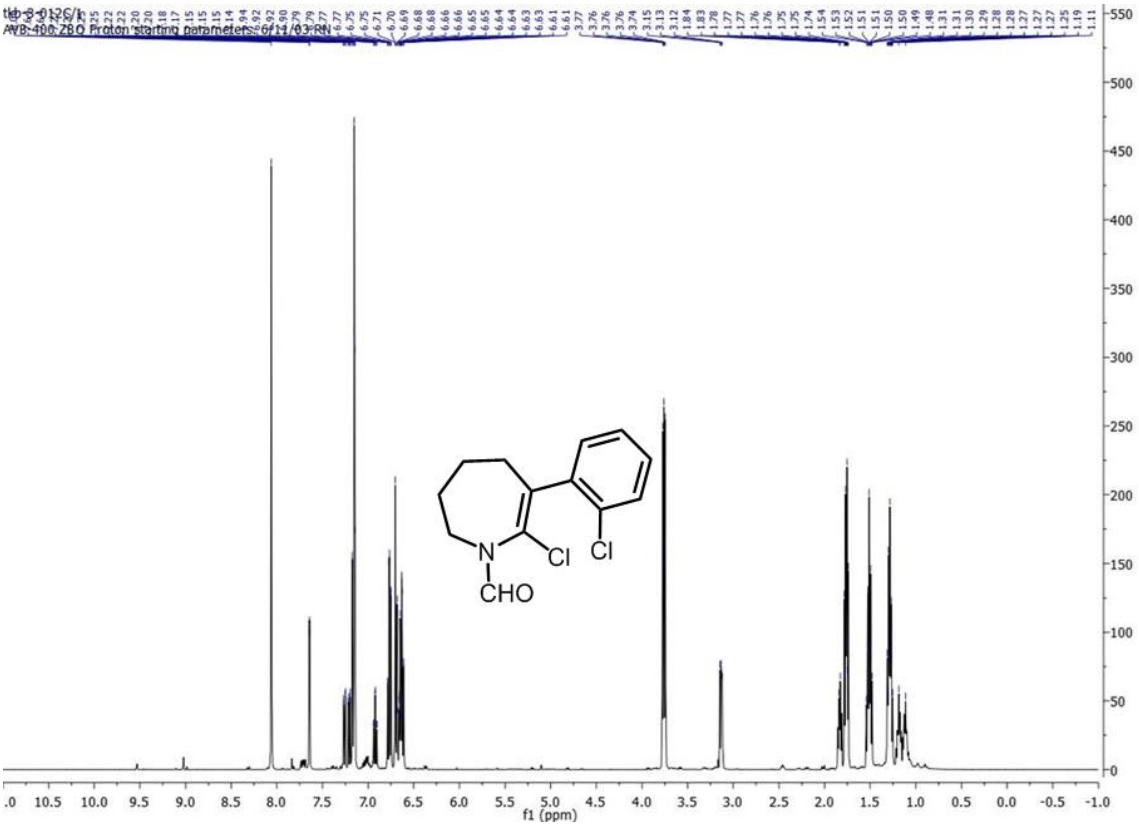

AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
^{13}C NMR (101 MHz, C_6D6) δ 162.59, 142.29, 137.45, 134.54, 129.97, 129.43, 129.06, 127.89, 127.14, 126.24, 125.05, 48.50, 44.96, 32.88, 29.22, 27.87, 27.52, 24.58, 23.87.
Cl
Cl
N
CHO
f1 (ppm)

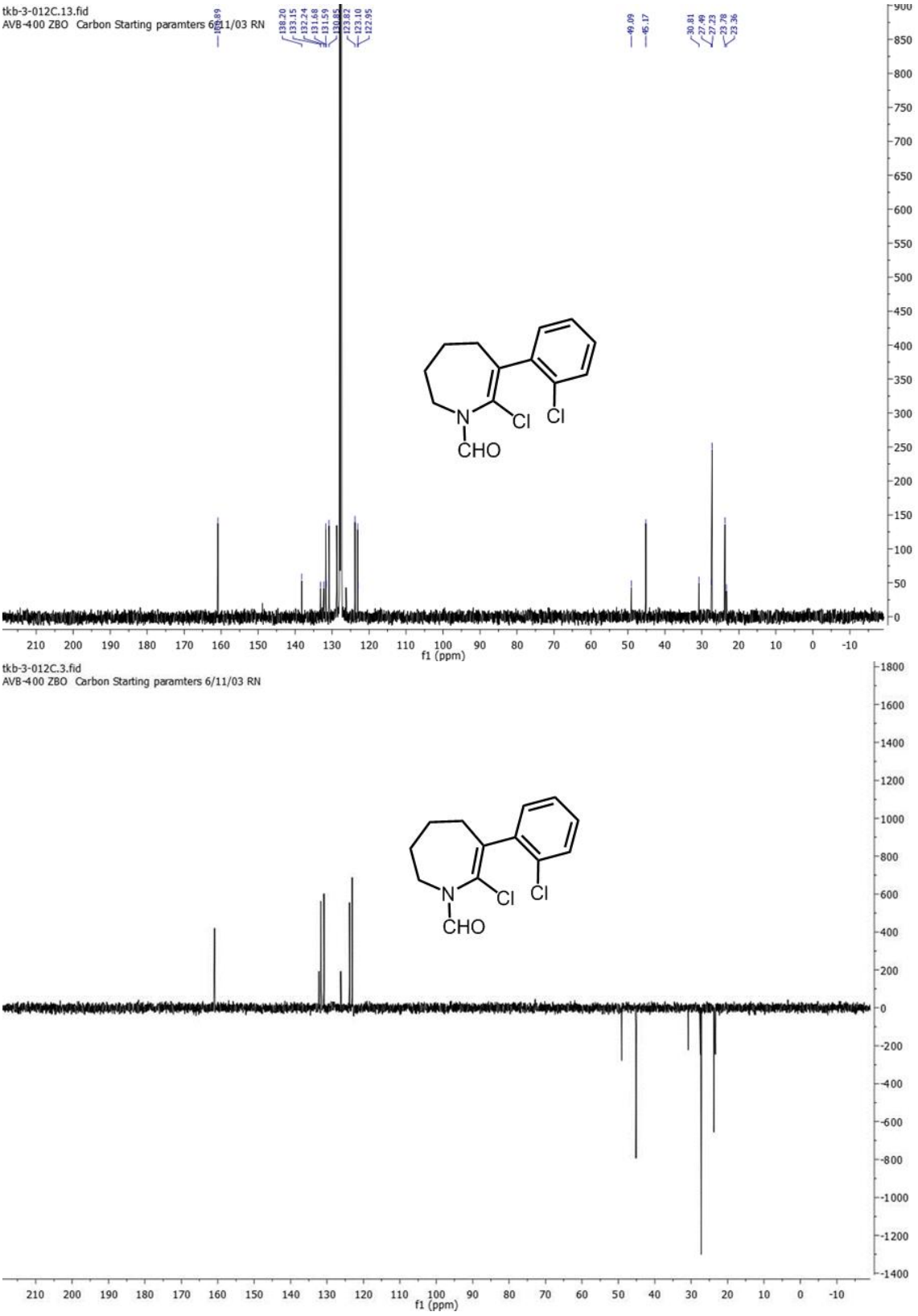

AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
Cl
Cl
N
CHO
f1 (ppm)

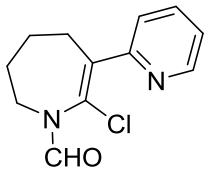


33

Prepared from **1a** (80 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (238 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 64.6 mg, 48%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 8.06 (1H), 7.64 (1H, minor), 7.27 to 6.61 (8H, both), 3.77 to 3.74 (2H), 3.15 to 3.12 (2H, minor), 1.86 to 1.81 to 1.74 (4H, both), 1.53 to 1.48 (2H), 1.31 to 1.19 (6H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.89, 138.20, 133.15, 132.24, 131.68, 131.59, 130.85, 123.82, 123.10, 122.95, 49.09, 45.17, 30.81, 27.49, 27.23, 23.78, 23.36. HRMS calc for $C_{13}H_{13}Cl_2NO$ 269.0374, found 269.0366.

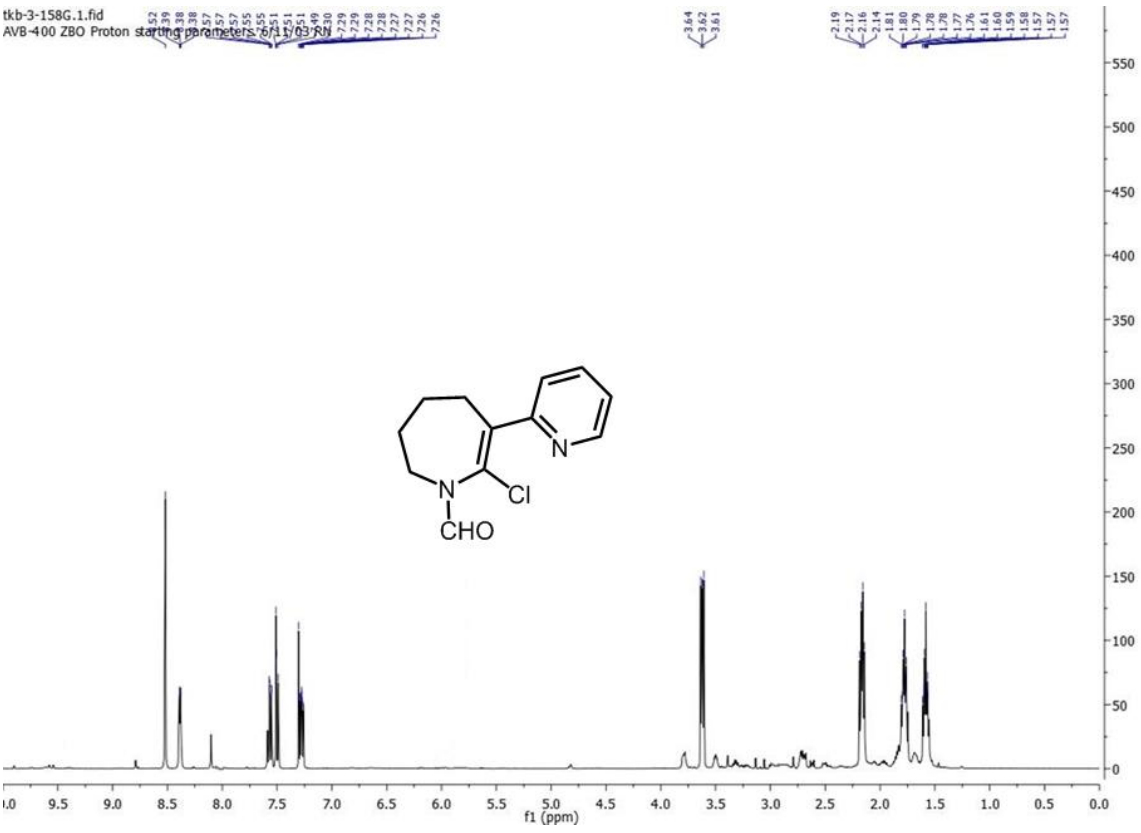


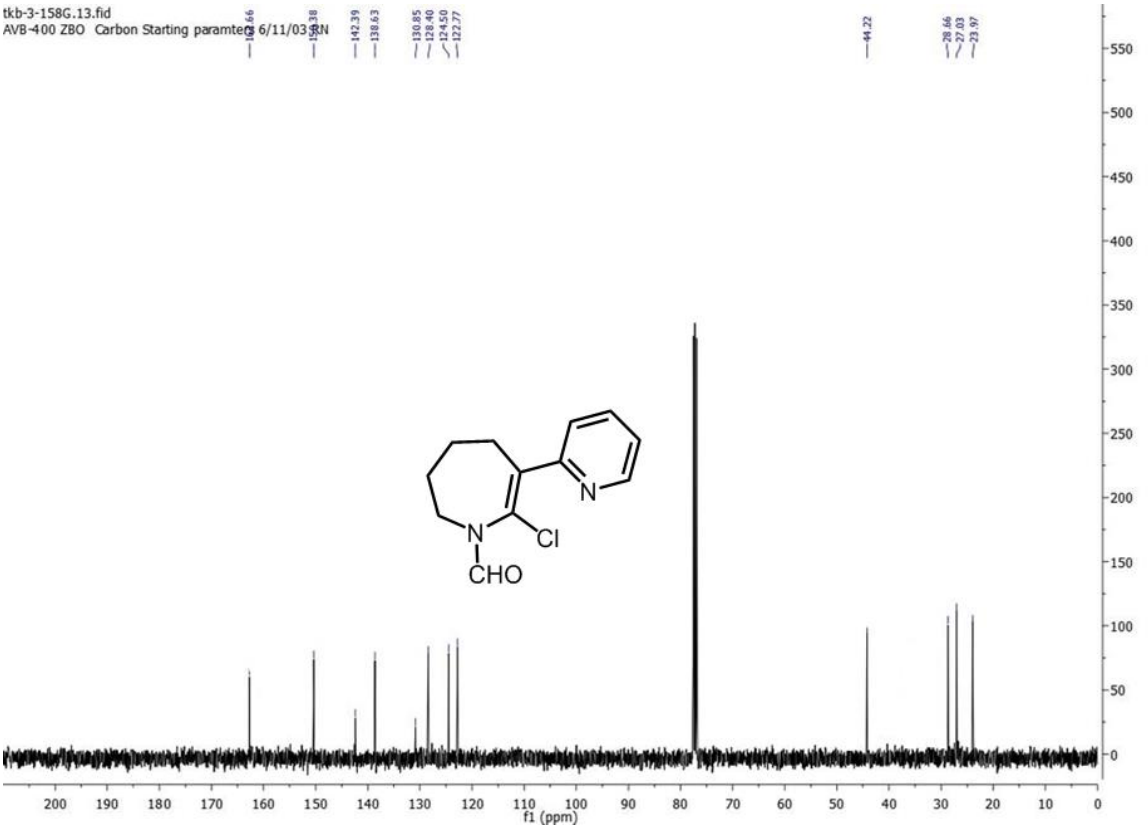

tkb-3-012C.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
159.89
138.20
133.15
132.24
131.68
131.59
130.85
123.82
123.10
122.95
49.09
45.17
30.81
27.49
27.23
23.78
23.36
N
CHO
Cl
Cl
f1 (ppm)
tkb-3-012C.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
N
CHO
Cl
Cl
f1 (ppm)

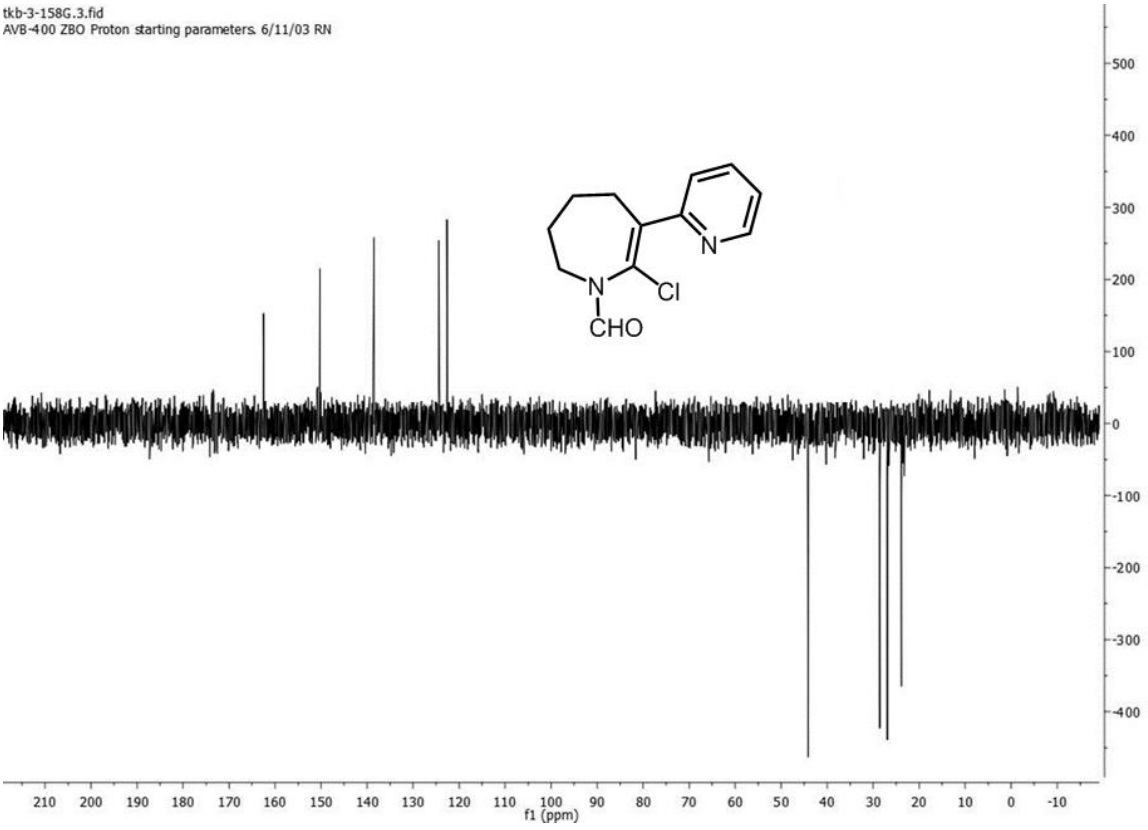


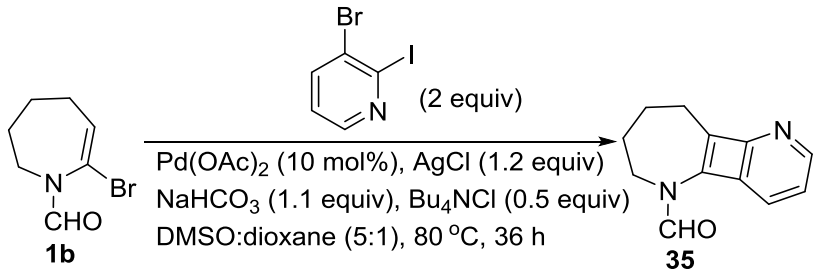
34

Prepared from **1a** (80 mg, 0.5 mmol) and 2-iodopyridine (205 mg, 2 equiv) using **General Procedure B.** Time = 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 10:90). Yield = 35.4 mg, 30%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H), 8.37 (1H), 7.57 to 7.49 (2H), 7.28 (1H), 3.62 (2H), 2.19 to 2.14 (2H), 1.81 to 1.76 (2H), 1.61 to 1.56 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.66, 150.38, 142.39, 138.63, 130.85, 128.40, 124.50, 122.77, 44.22, 28.66, 27.03, 23.97. HRMS calc for $C_{12}H_{13}ClN_2O$ 236.0716, found 236.0712.

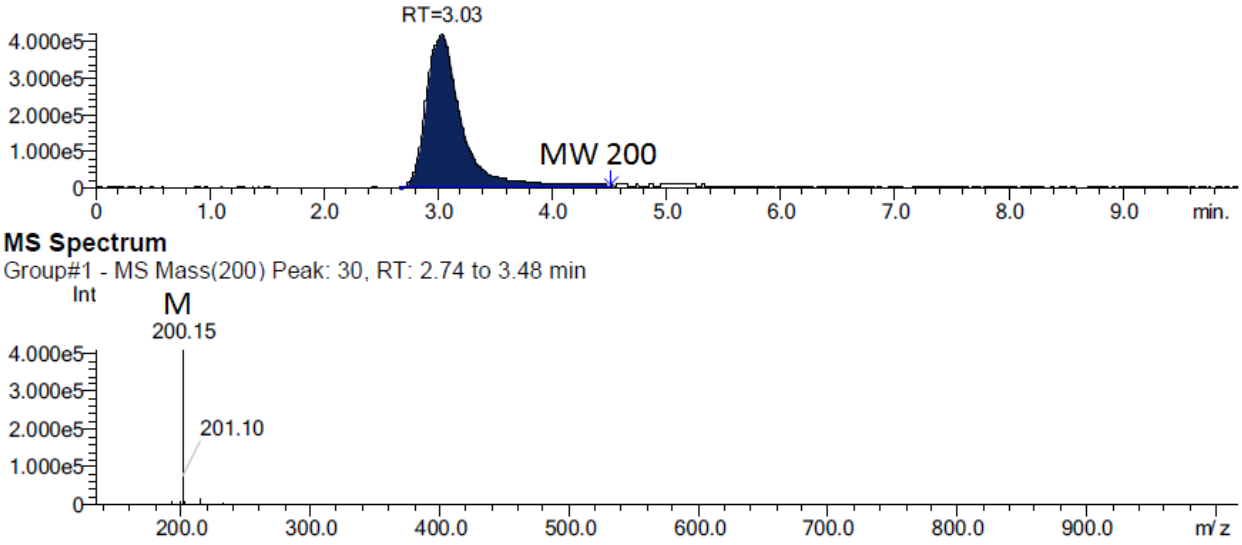


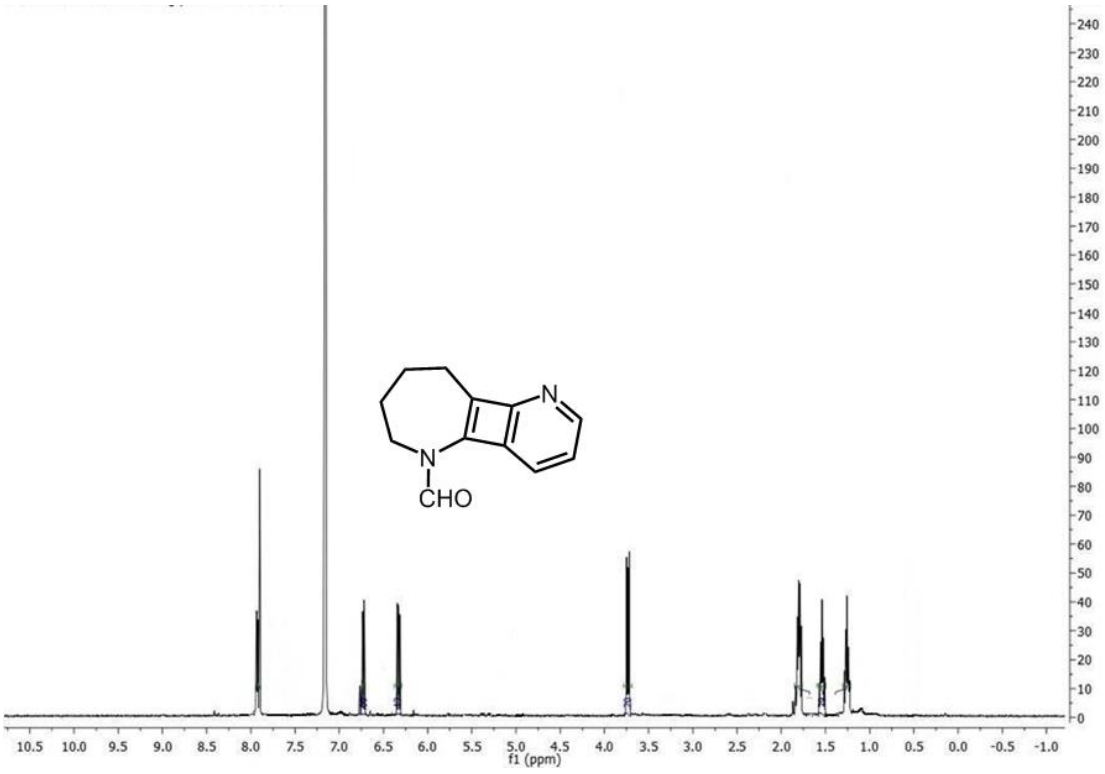

tkb-3-158G.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
162.66
150.38
142.39
138.63
130.85
128.40
124.50
122.77
44.22
28.66
27.03
23.97
N
N
Cl
CHO
f1 (ppm)

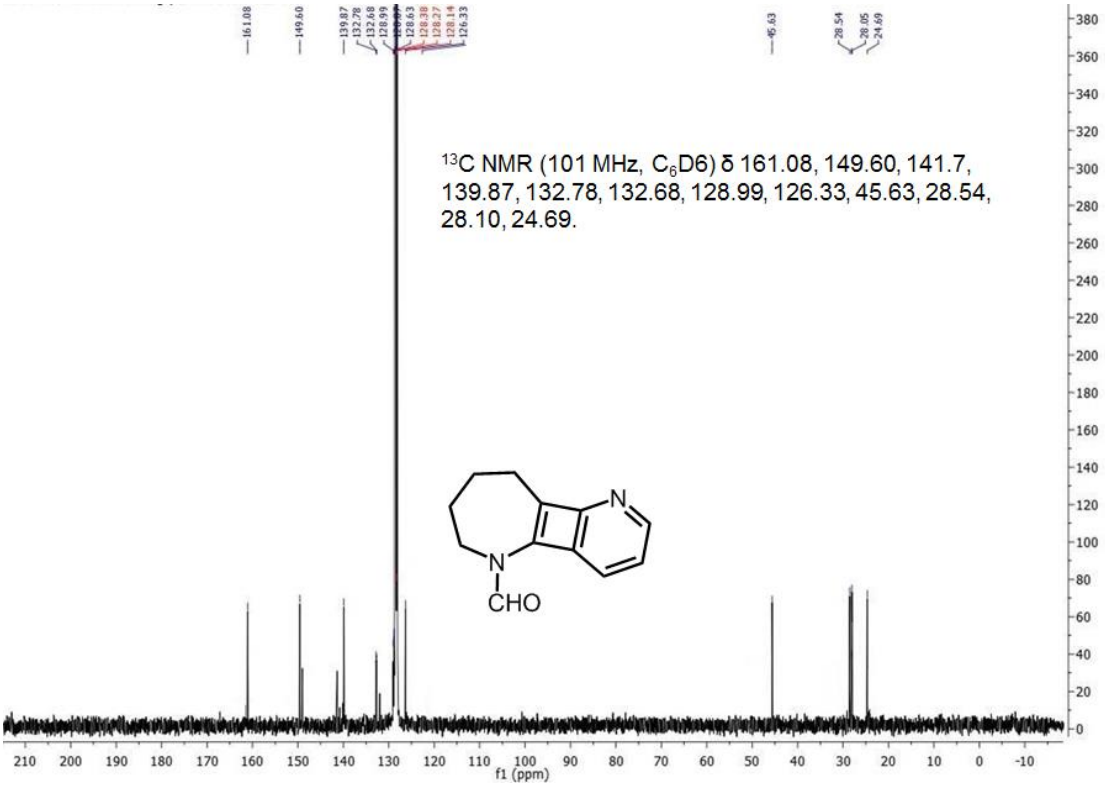

tkb-3-158G.3.fid
AVB-400 ZBO Proton starting parameters 6/11/03 RN
N
N
Cl
CHO
f1 (ppm)

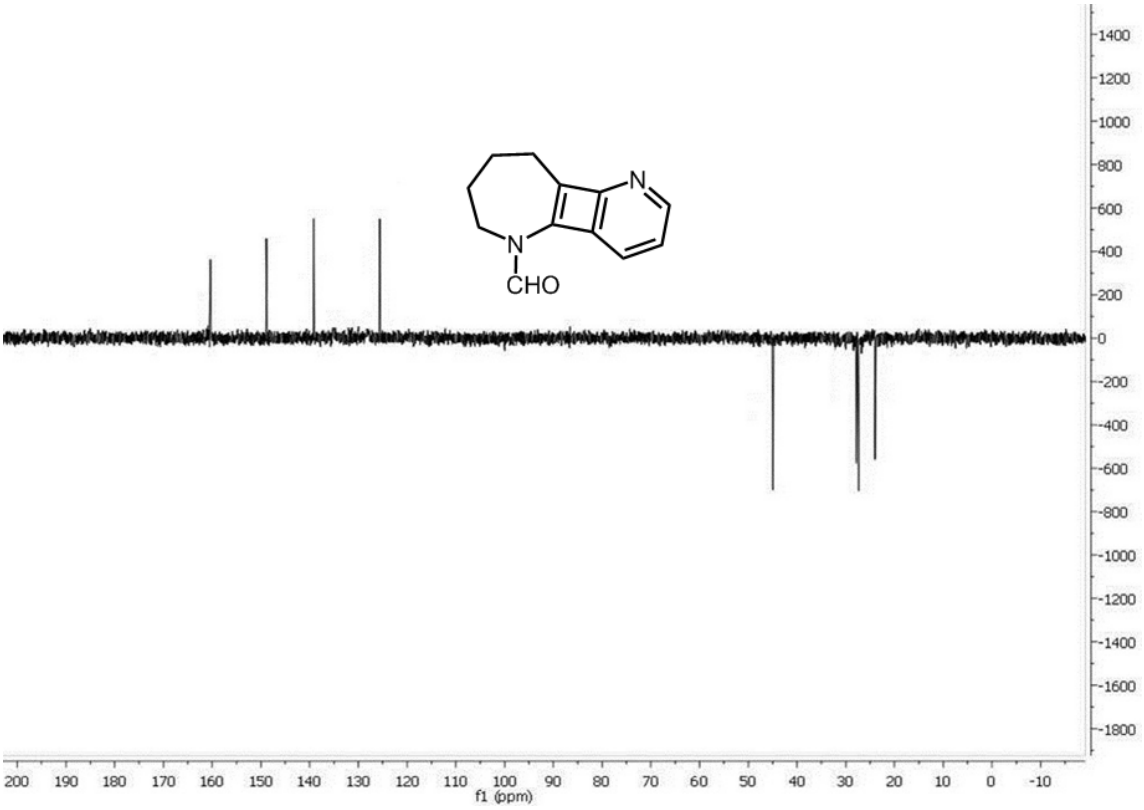


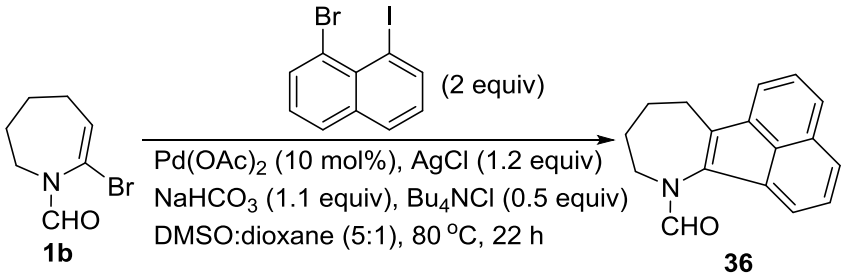
Prepared from **1b** (102 mg, 0.5 mmol) and 3-bromo-2-iodopyridine (284 mg, 2 equiv) using **General Procedure B.** Time = 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 10:90). Yield = 36 mg, 36%.^{1}H NMR (400 MHz, C_6D_6) δ 7.94 to 7.90 (2H), 6.73 (1H), 6.33 (2H), 3.73 (2H), 1.85 to 1.79 (2H), 1.57 to 1.51 (2H), 1.29 to 1.23 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.08, 149.60, 141.7, 139.87, 132.78, 132.68, 128.99, 126.33, 45.63, 28.54, 28.10, 24.69. HRMS calc for $C_{12}H_{12}N_2O$ 200.0950, found 200.0954.



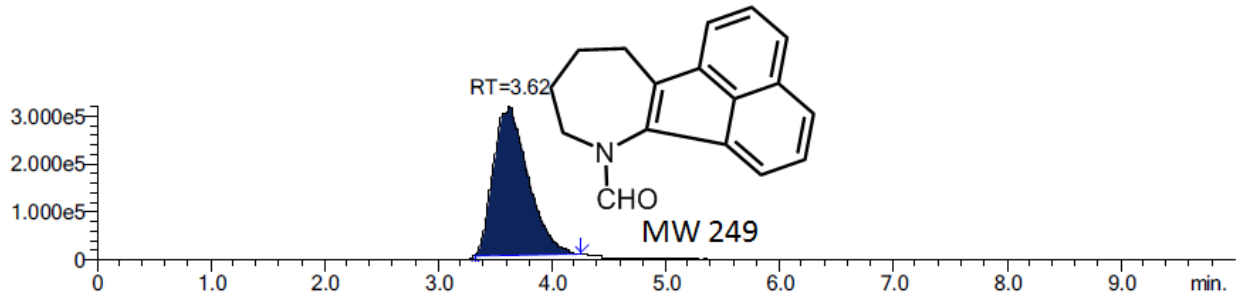

N
N
CHO
f1 (ppm)


^{13}C NMR (101 MHz, C_6D6) δ 161.08, 149.60, 141.7, 139.87, 132.78, 132.68, 128.99, 126.33, 45.63, 28.54, 28.10, 24.69.
N
N
CHO
f1 (ppm)



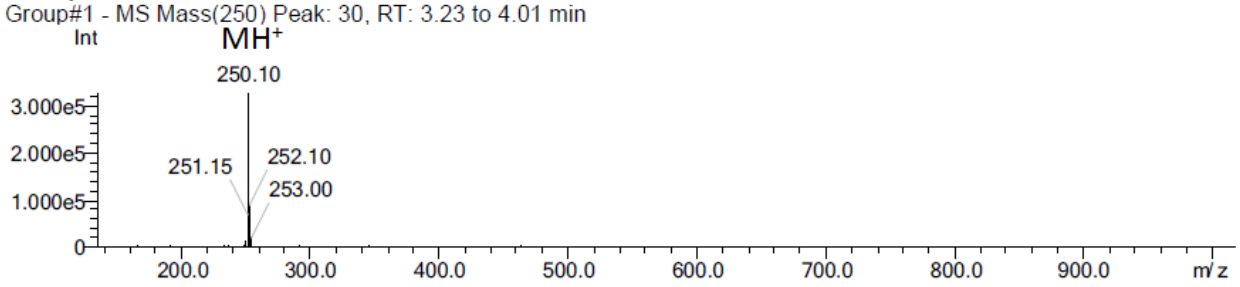


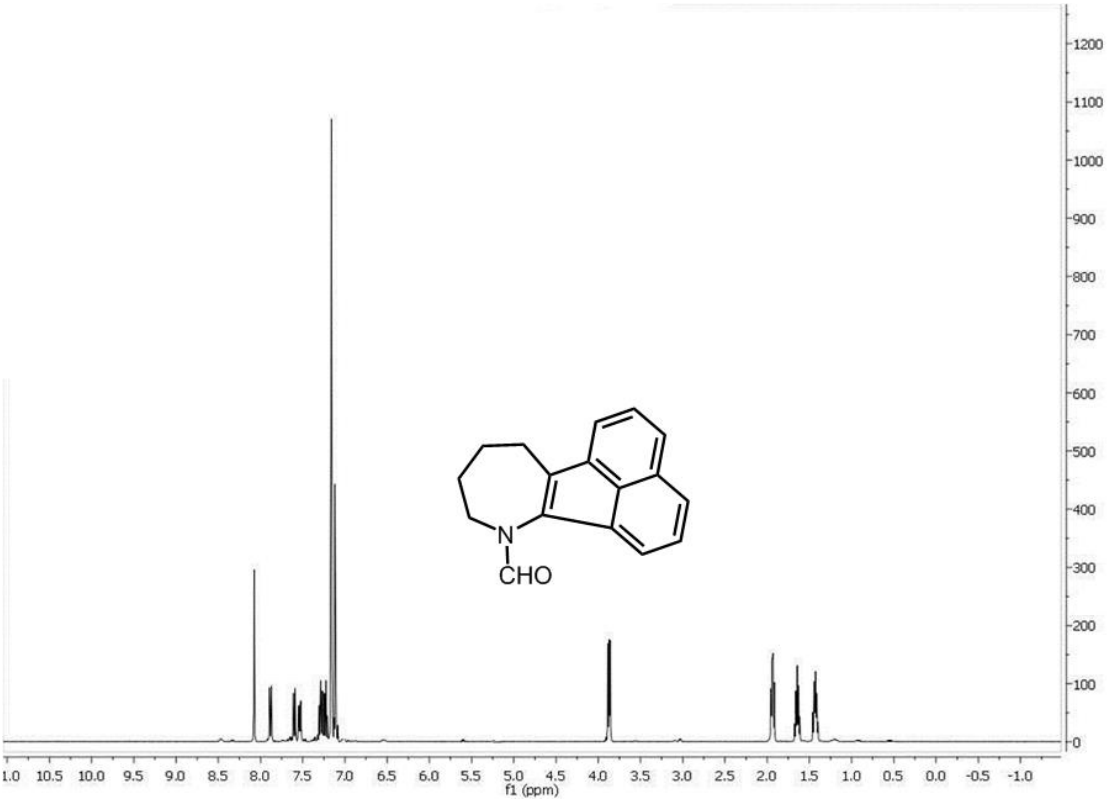
Prepared from **1b** (102 mg, 0.5 mmol) and 1-bromo-8-iodonaphthalene (333 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 85.9 mg, 69%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.07 (1H), 7.89 (1H), 7.61 to 7.51 (2H), 7.31 to 7.09 (3H), 3.87 (2H), 1.97 to 1.91 (2H), 1.66 to 1.62 (2H), 1.46 to 1.40 (2H). ^{13}C NMR (101 MHz, C_6D6) δ 161.68, 141.37, 136.50, 134.05, 131.24, 129.00, 128.64, 126.62, 125.95, 125.17, 124.90, 122.24, 44.83, 27.43, 27.11, 24.25. HRMS calc for $C_{17}H_{15}NO$ 249.1154, found 249.1148.

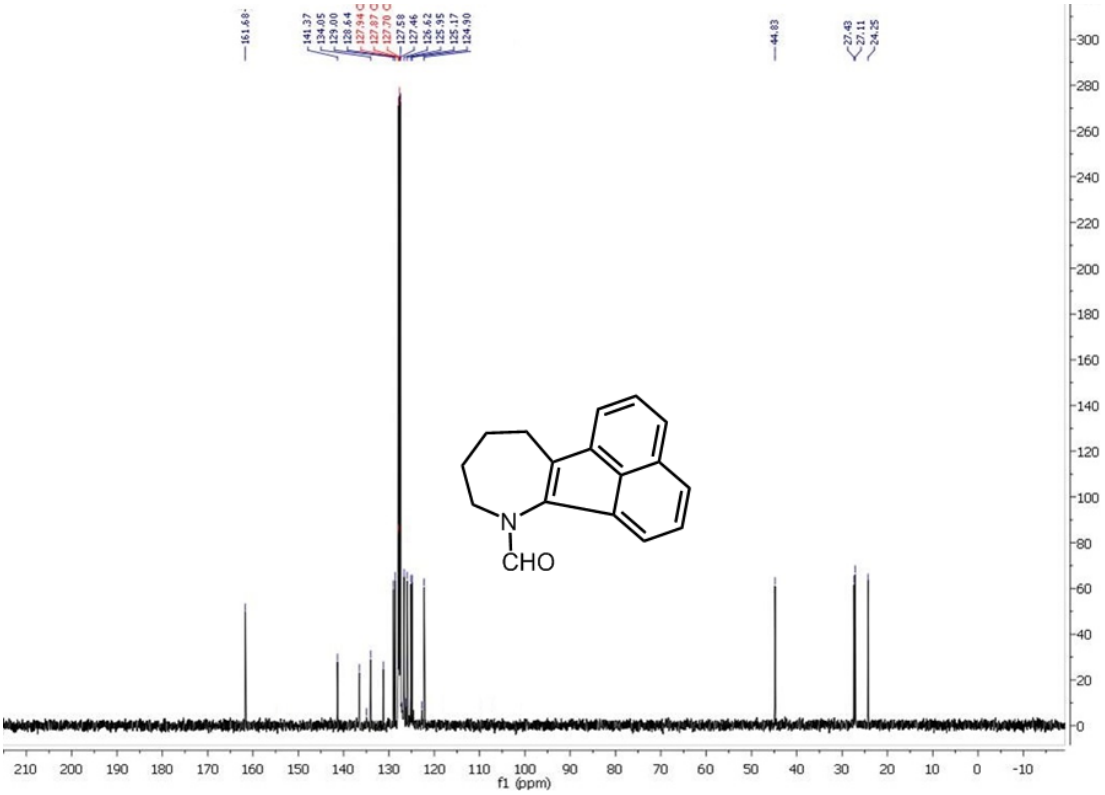


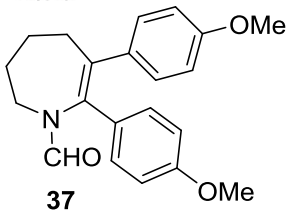
MS Spectrum

Group#1 - MS Mass(250) Peak: 30, RT: 3.23 to 4.01 min





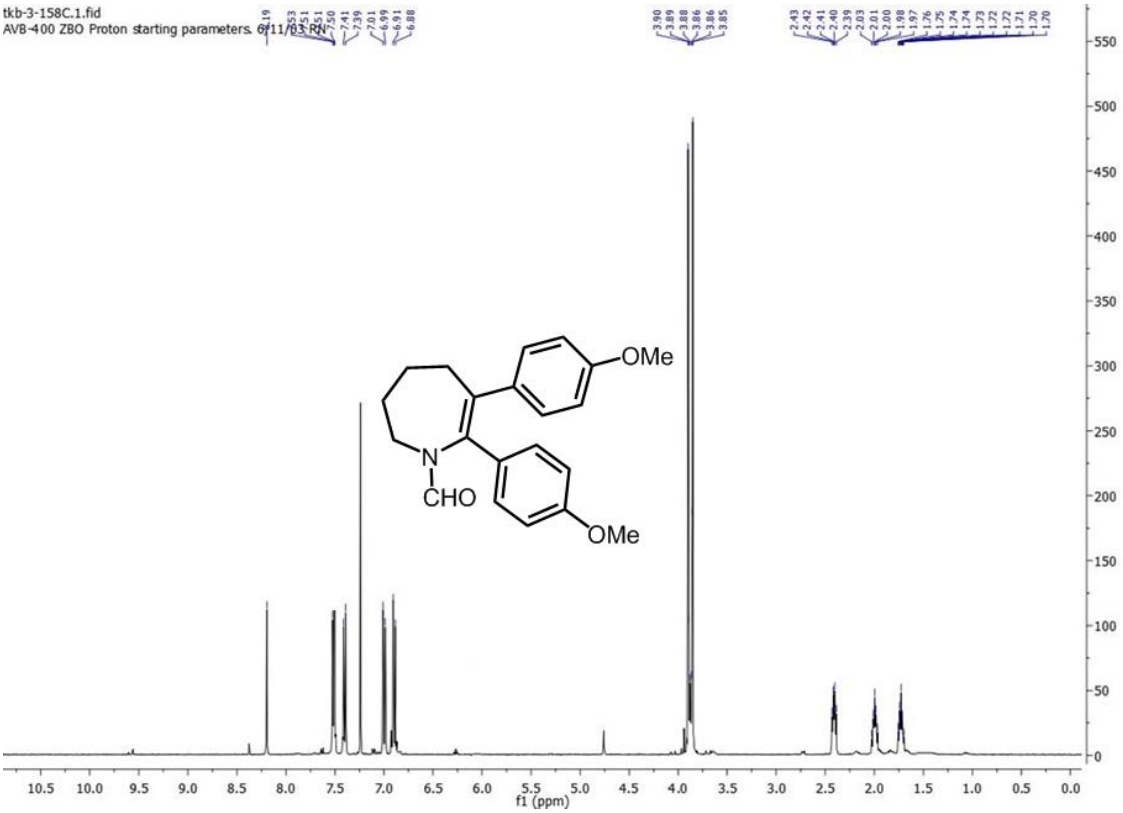


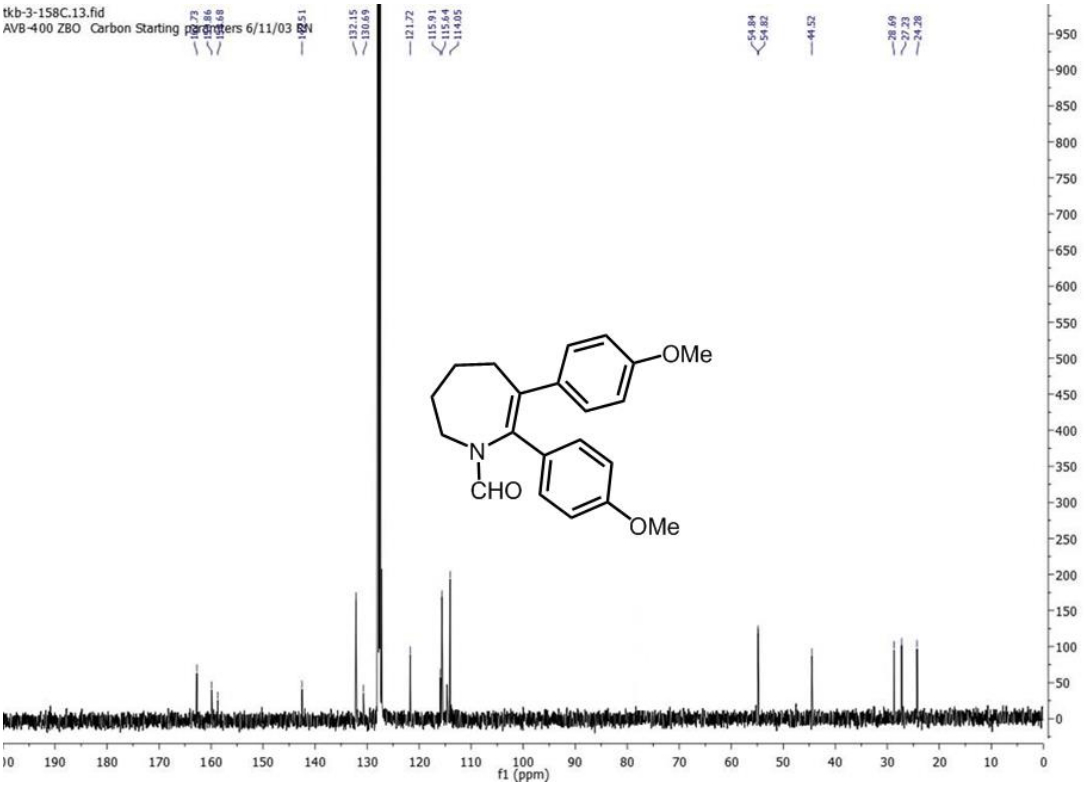


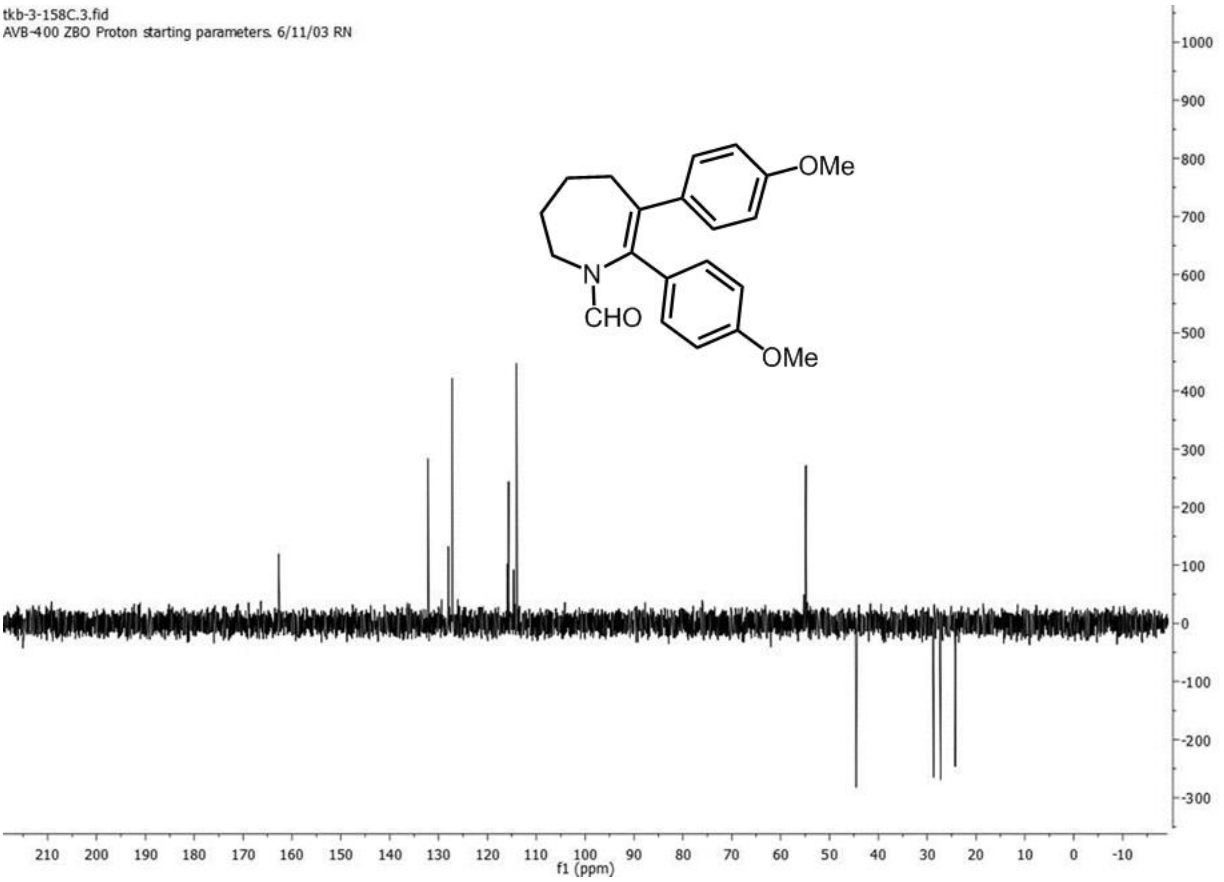
37

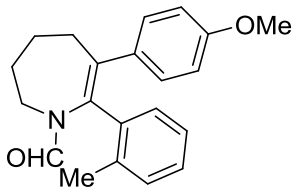
To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added **30** (26.6 mg, 0.1 mmol, 1.0 equiv) in DMF (1 mL) under an argon or nitrogen atmosphere. 4-methoxyphenyl boronic acid (23 mg, 0.15 mmol, 1.5 equiv) was added followed by addition of Et_3N (0.12 mL, 0.5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (3.5 mg, 5 mol%) was added rapidly. The mixture was then heated to 60 ^oC and stirred for 4 h (TLC and LC-MS monitoring). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~5 mL and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 20:80). Yield = 25.6 mg, 76%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H), 7.52 (2H), 7.39 (2H), 6.99 (2H), 6.88 (2H), 3.90 to 3.85 (8H), 2.43 to 2.39 (2H), 2.03 to 1.97 (2H), 1.76 to 1.70 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.73, 159.86, 158.68, 142.51, 132.15, 130.69, 121.72, 115.91,

115.64, 114.05, 54.84, 54.82, 44.52, 28.69, 27.23, 24.28. HRMS calc for $C_{21}H_{23}NO_3$ 337.1678, found 337.1684.



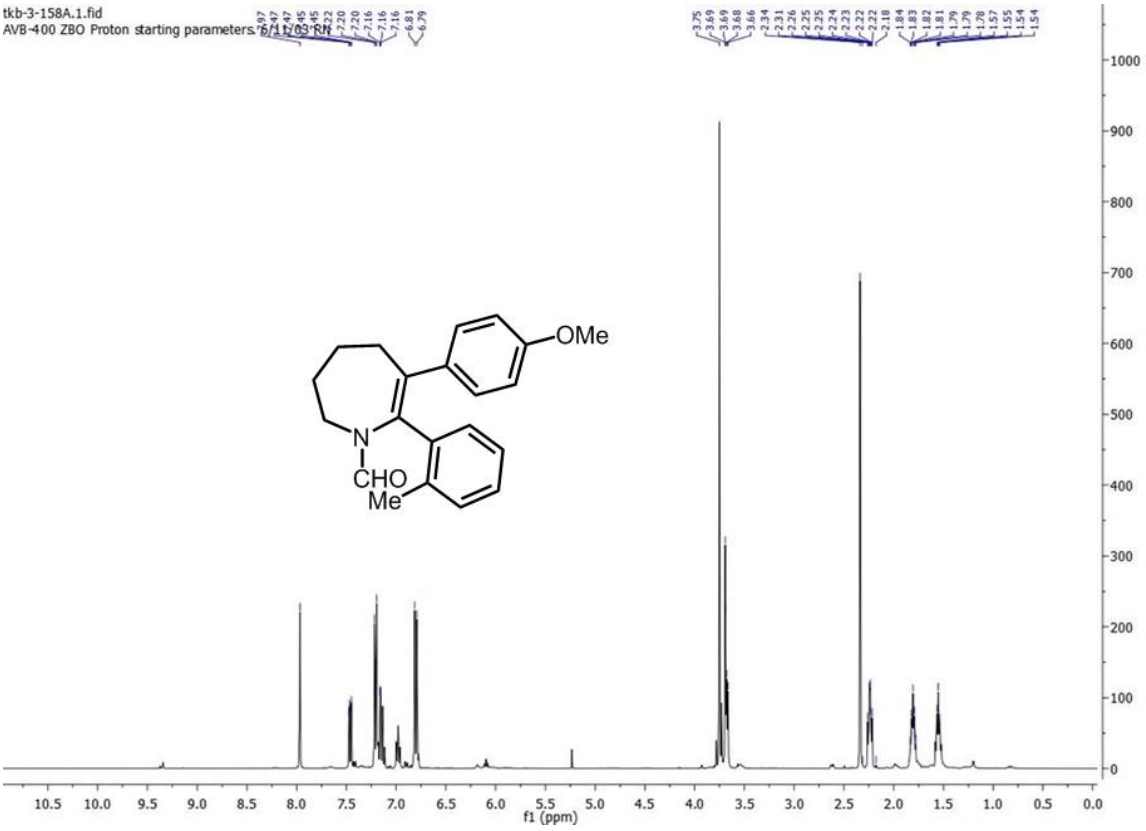






38

Prepared in the same way as **37** using *o*-toluylboronic acid (20.4 mg). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 18.3 mg, 57%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.97 (1H), 7.46 (1H), 7.22 to 7.16 (4H), 6.81 (1H), 6.79 (2H), 3.69 to 3.66 (5H), 2.34 (3H), 2.26 to 2.18 (2H), 1.84 to 1.78 (2H), 1.57 to 1.54 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 163.12, 159.73, 142.36, 137.77, 132.24, 130.75, 130.59, 127.16, 124.85, 115.95, 114.64, 114.05, 55.29, 44.74, 28.69, 27.32, 24.34, 22.85. HRMS calc for $C_{21}H_{23}NO_2$ 321.1729, found 321.1723.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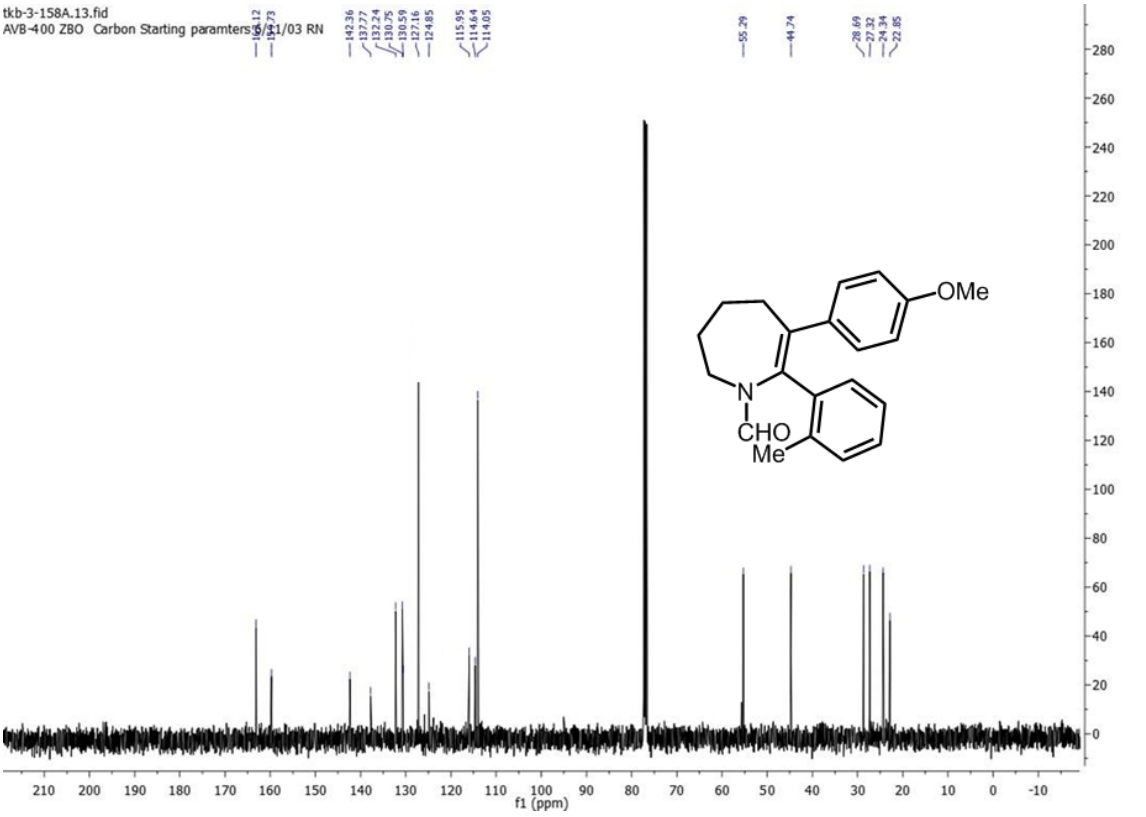
OMe
N
CHO
Me
f1 (ppm)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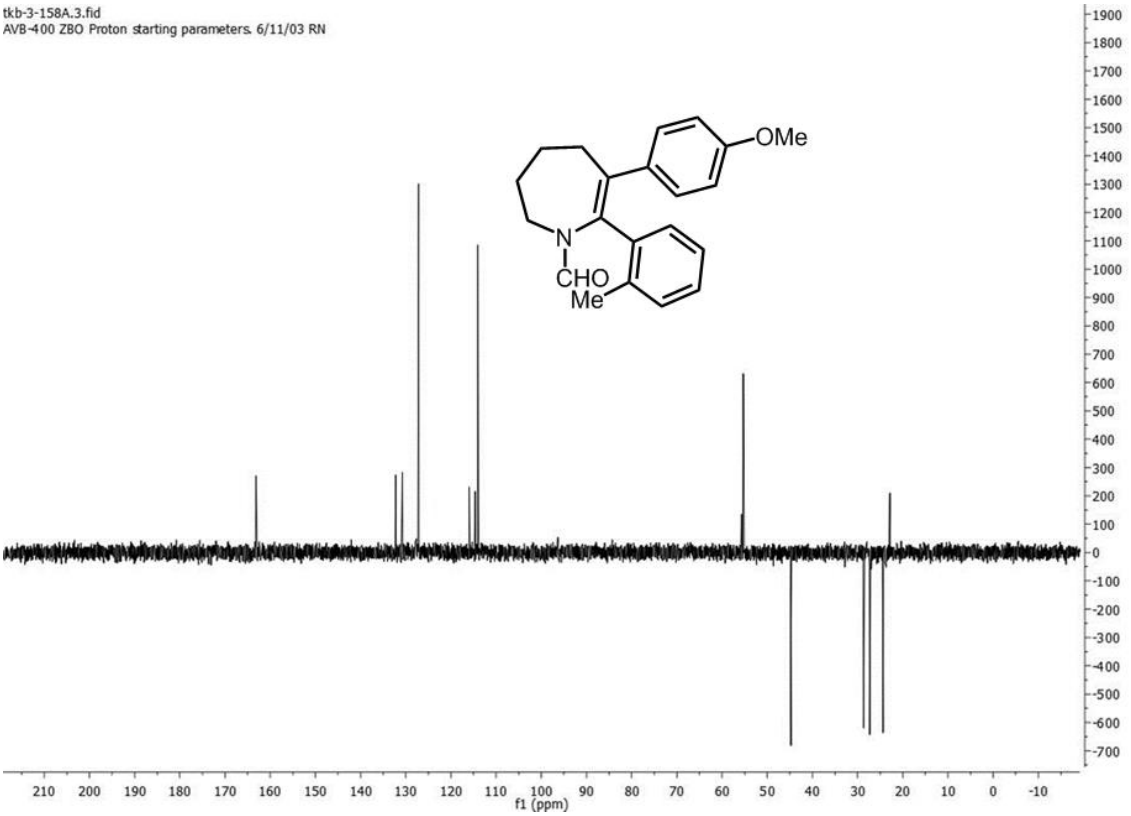
OMe
N
CHO
Me
f1 (ppm)

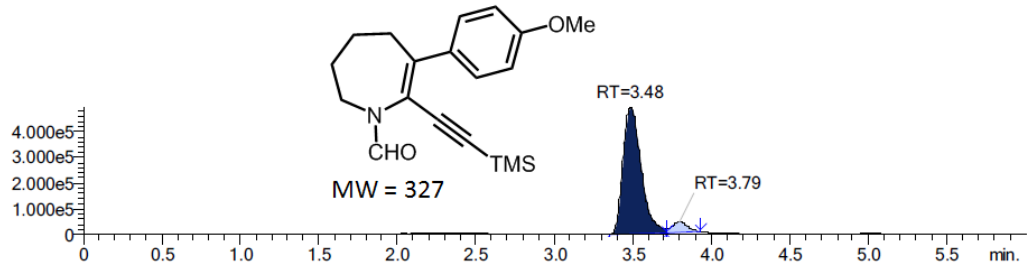


39

To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added **30** (26.6 mg, 0.1 mmol, 1.0 equiv) in DMF (1 mL) under an argon or nitrogen atmosphere. TMS acetylene (0.043 mL, 0.30 mmol, 3 equiv) was added followed by addition of Et_3N (0.12 mL, 0.5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (3.5 mg, 5 mol%) and CuI (0.5 mg, 1 mol%) were added rapidly and concurrently. The mixture was then heated to 60 ^oC and stirred for 1 h (TLC and LC-MS monitoring). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~5 mL and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 53 mg, 81%. ^1H NMR (400 MHz, C_6D_6) δ 8.93 (1H), 7.17 (2H), 6.38 (2H), 3.42 (2H), 3.10 (3H), 1.63 to 1.59 (2H), 1.35 to 1.29 (2H), 1.11 to 1.05 (2H), 0.10 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.04, 158.74, 132.15, 129.71, 125.68, 115.65, 112.70,

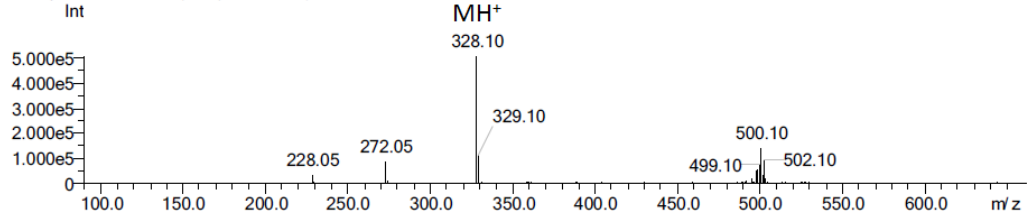
101.79, 94.61, 54.46, 43.61, 27.61, 27.07, 23.78, -0.68. HRMS calc for $C_{19}H_{25}NO_2Si$ 327.1655, found 327.1649.

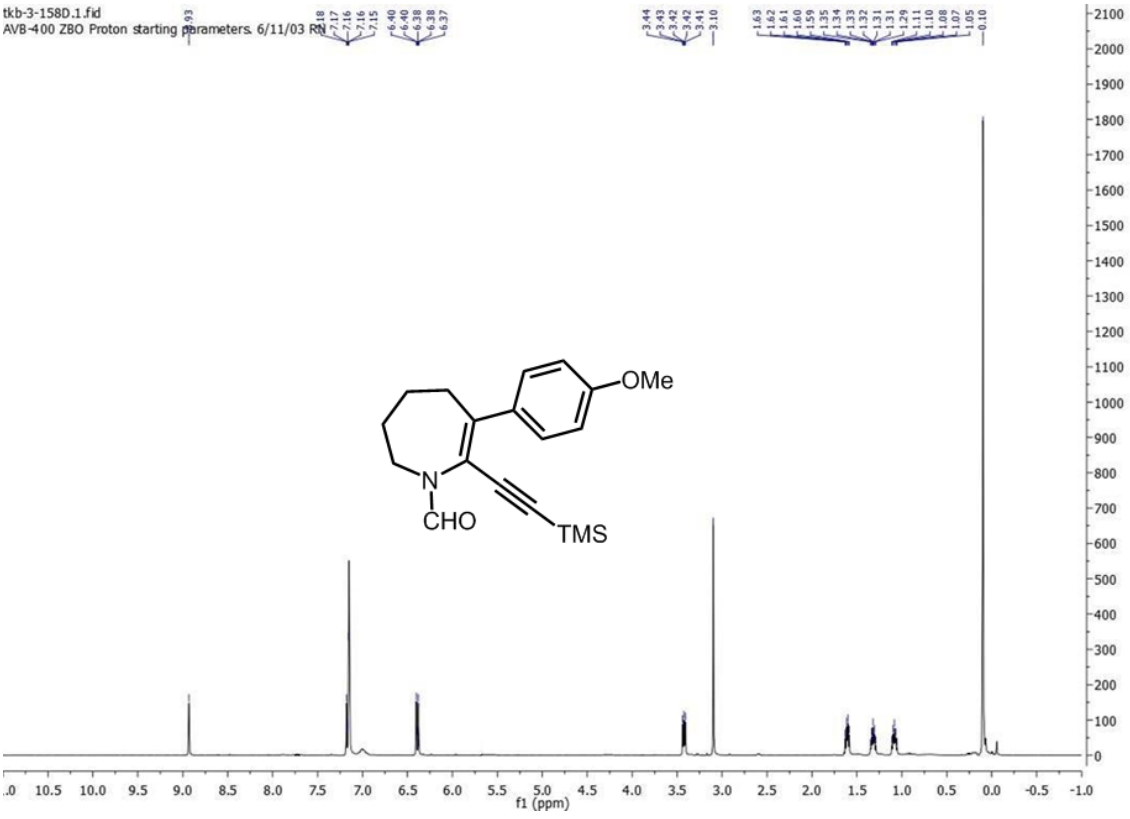
Experiment: tbeng_20140511_08
Experiment Description:
Sample: tbeng_20140511_08_001
Sample Description:
Data File Name: C:\LabSolutions\Data\Project1\tbeng\tbeng_20140511_08_001.lcd
Sample Location: Plate Number: 1 - Position: 52
Run By: tbeng
Run Started: Sunday, May 11, 2014 10:26:05 PM
Run Finished: Sunday, May 11, 2014 10:33:50 PM
Method: 30_95_6mrun1mLminLowMW(125-625m/z)

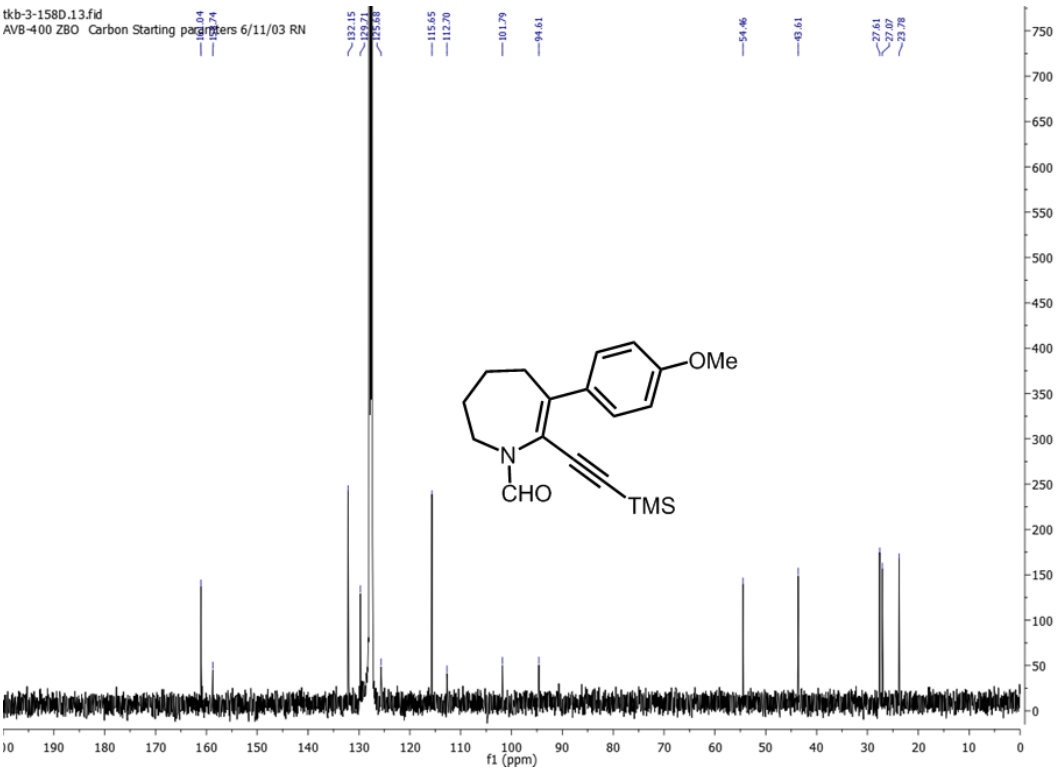


MS Spectrum

Group#1 - MS Mass(328) Peak: 34, RT: 3.35 to 3.72 min






tkb-3-158D.13.fid
AVB-400 ZBO Carbon Starting parameters 6/11/03 RN
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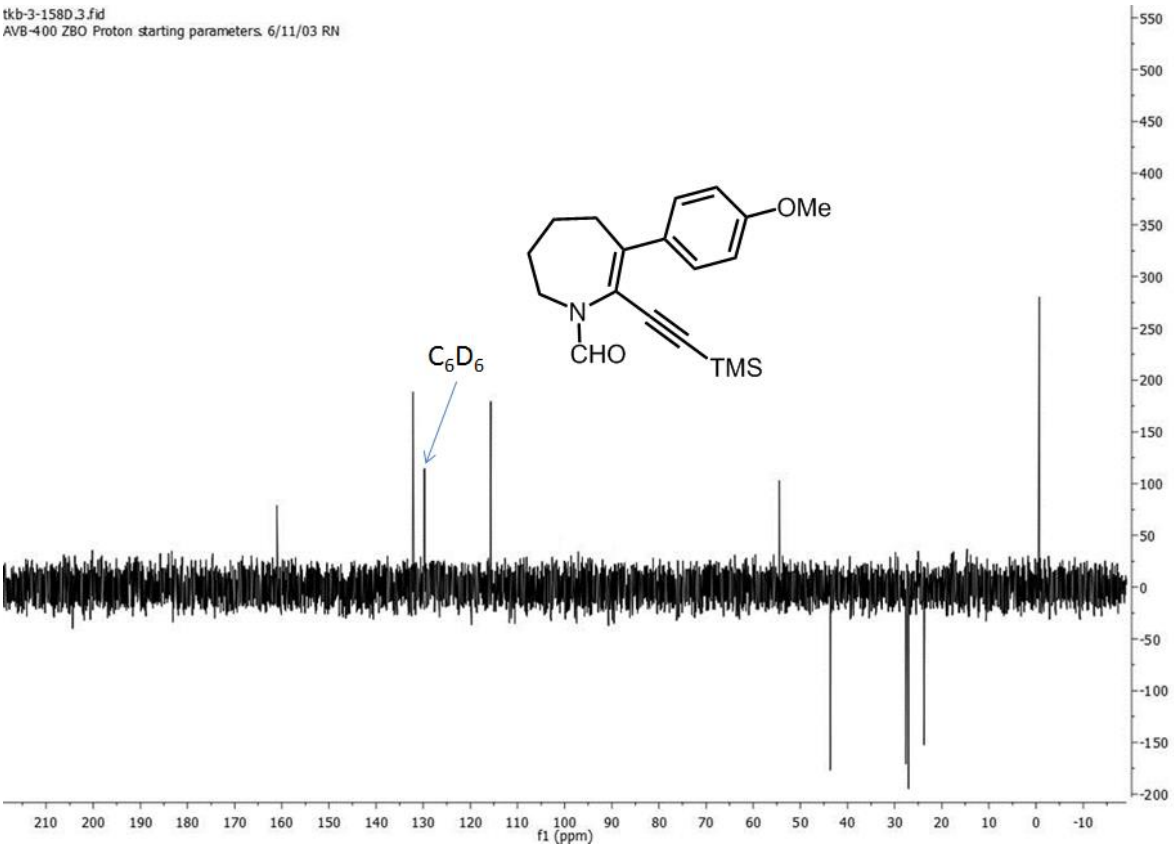
129.71
125.68
115.65
112.70
101.79
94.61
54.46
43.61
27.61
27.07
23.78
OMe
N
CHO
TMS
f1 (ppm)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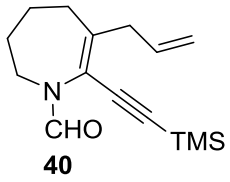
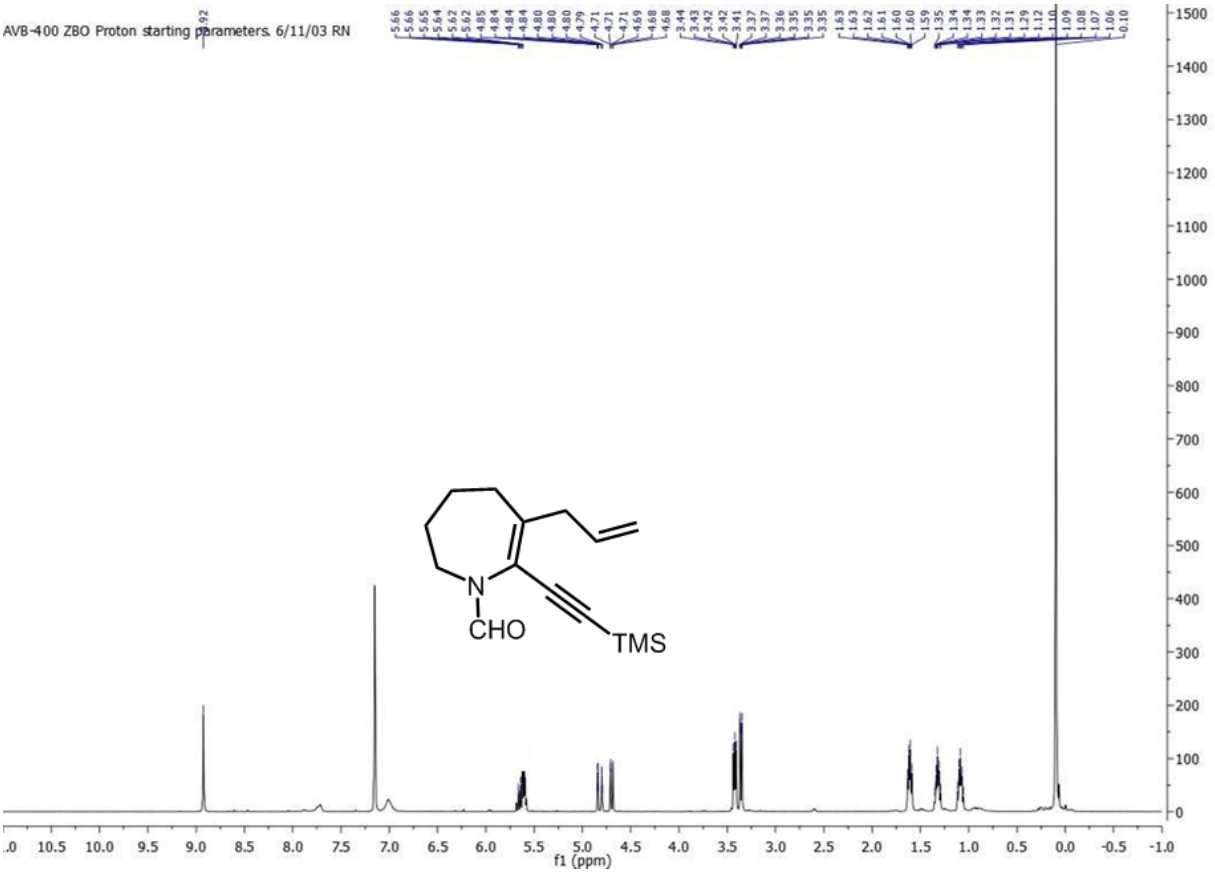
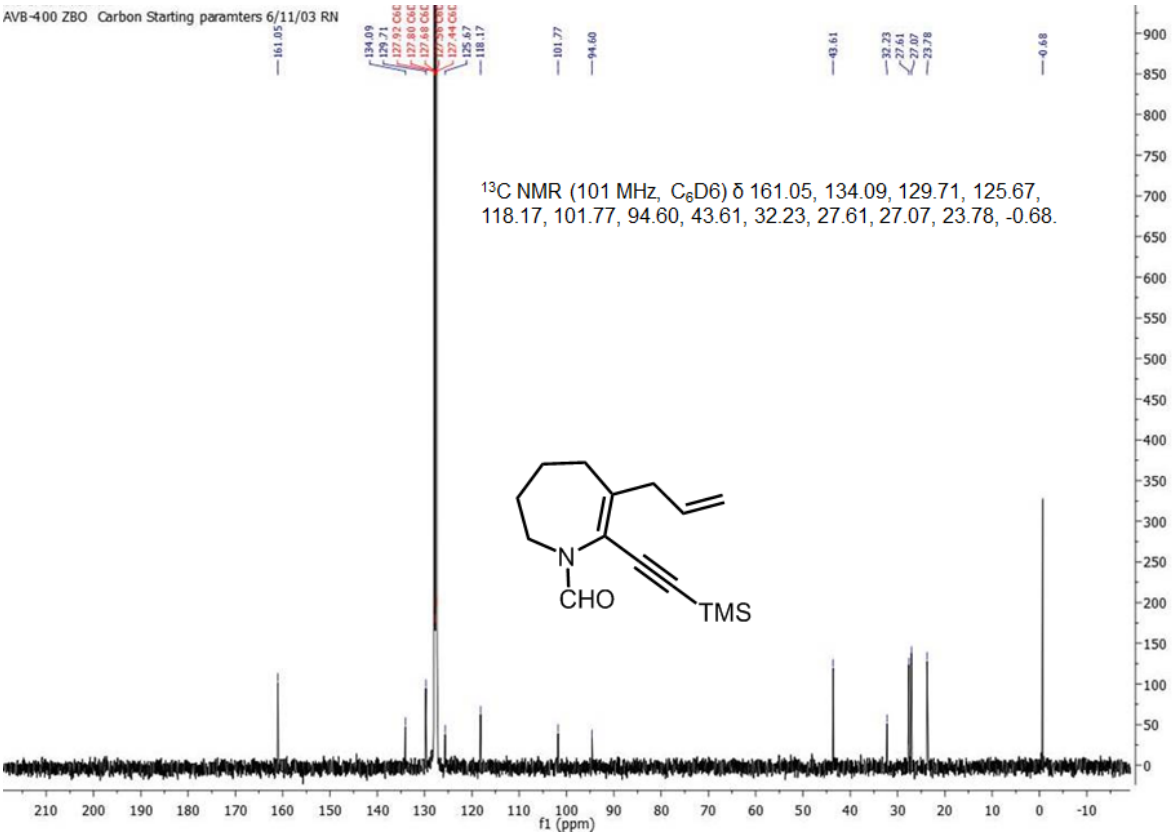
N
CHO
TMS
C6D6
f1 (ppm)



40

Prepared from **28** (0.1 mmol) in the same way as was **39** from **30**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 53 mg, 86%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.92 (1H), 5.65 (1H), 4.85 to 4.68 (2H), 3.44 to 3.35 (4H), 1.63, to 1.59 (2H), 1.35 to 1.29 (2H), 1.12 to 1.06 (2H), 0.10 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.05, 134.09, 129.71, 125.67, 118.17, 101.77, 94.60, 43.61, 32.23, 27.61, 27.07, 23.78, -0.68.





References

(1) Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R. *Org. Lett.* **2014**, *16*, 916.
(2) Yu, Y.-Y.; Bi, L.; Georg, G. I. *J. Org. Chem.* **2013**, *78*, 6163.
(3) Beng, T. K.; Bassler, D. P. *Tetrahedron Lett.* **2014**, *55*, 6662.