Supporting Information

Asymmetric δ-Lactam Synthesis with a Monomeric Streptavidin Artificial Metalloenzyme

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1. General methods

Flash column chromatography was performed on SiliCycle Inc.® silica gel 60 (230-400 mesh). Thin Layer chromatography was performed on SiliCycle Inc.® 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm) or $KMnO_4$ staining.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 300, 400 or 500 MHz spectrometers at ambient temperature. ^{1}H-NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform ($CDCl_3$) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets) and coupling constant (*J* in Hz unit). ^{13}C-NMR is reported as the following: chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm.

Low-resolution mass spectra (LSMS) were obtained on ACQUITY Waters UPLC/mass spectrometer equipped with electrospray ionization.

Infrared spectra (IR) were recored on a Perkin Elmer Paragon 1000 FT-IR spectrometer.

2. Preparation of starting materials

2-substituted acrylic acids for **2b** and **2d** were prepared according to the procedure.[i]

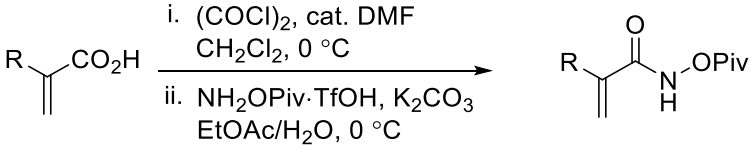
2-ethoxy acrylic acid for **2c** was prepared according the procedure.[ii]

2-aryl acrylic acid for **2e** was prepared according to the procedure.[iii]

Partial esterification of itaconic acid for **2f** was prepared according to the literature procedure.[iv]

All alkenes in this study were purchased from commercial sources and used without further purification.

N-(pivaloyloxy) α-substituted acrylamides

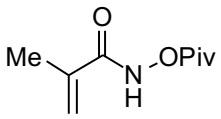


i. To a solution of 2-substituted acrylic acid (1 equiv) in dry CH_2Cl_2 (0.17 M) at 0°C (ice bath) under N_2 was added dropwise oxalyl chloride (1.1 equiv) and a few drops of DMF. The reaction was then stirred at 0 °C to room temperature (typically 2-3 h). The volatiles were removed under reduced pressure to give a crude acid chloride.

ii. To the solution of $NH_2OPiv·TfOH$ (1.1 equiv), K_2CO_3 (2.0 equiv) and EtOAc/H_2O (2/1 by v/v, 0.1M) at 0 °C (ice bath), the crude acid chloride was added dropwise (while a small amount of EtOAc can be used as a solvent). The mixture was stirred at the same temperature for 0.75 - 1 h (prolonged reaction time led to the decomposition of the N-pivaloyloxy acrylamide). Upon the completion (monitored by TLC), saturated $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (×3), washed with brine, dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a crude N-(pivaloyloxy)

α-substituted acrylamide, which was purified by a flash column chromatography (5% to 25% EtOAc/hexane).[v]

N-(Pivaloyloxy)methacrylamide (2a)



2a

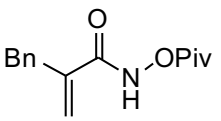
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, NH), 5.84 (s, 1H), 5.50 – 5.47 (m, 1H), 1.99 (t, *J* = 1.3 Hz, 3H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.90, 167.26, 136.91, 121.97, 38.39, 26.98, 18.29

IR (neat, cm^{-1}) 3225, 2977, 1782, 1671, 1629, 1481, 1055, 1033, 1015.

LRMS (ESI) m/z calcd for $C_9H_{15}NO_3$ $[M+H]^+$: 186.1, found: 186.2.

2-Benzyl-N-(pivaloyloxy)acrylamide (2b)



2b

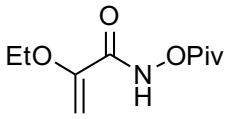
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, NH), 7.35 (t, *J* = 7.4 Hz, 2H), 7.26 (m, 2H), 5.96 (s, 1H), 5.39 (t, *J* = 1.3 Hz, 1H), 3.69 (s, 2H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.73, 166.93, 141.07, 137.47, 129.00, 128.75, 126.82, 122.52, 38.39, 38.10, 26.99.

IR (neat, cm^{-1}) 3217, 2981, 1780, 1668, 1080.

LRMS (ESI) m/z calcd for $C_{15}H_{19}NO_3$ $[M+H]^+$: 262.1, found: 262.2.

2-Ethoxy-N-(pivaloyloxy)acrylamide (2c)



2c

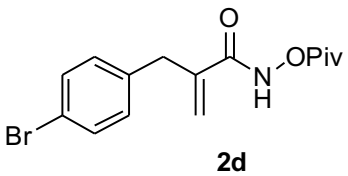
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 5.36 (s, 59H), 4.49 (s, 1H), 3.84 (q, *J* = 6.8 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 5H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.18, 160.01, 151.78, 91.76, 64.25, 38.35, 26.95, 14.18.

IR (neat, cm^{-1}) 3245, 2979, 2937, 1782, 1693, 1628, 1479, 1300, 1059, 1081.

LRMS (ESI) m/z calcd for $C_{10}H_{17}NO_4$ $[M+H]^+$: 216.1, found: 216.2.

2-(4-Bromobenzyl)-N-(pivaloyloxy)acrylamide (2d)



2d

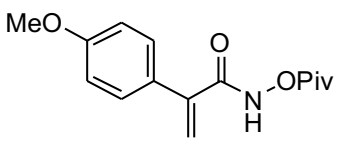
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, NH), 7.45 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 5.91 (s, 1H), 5.39 (t, *J* = 1.4 Hz, 1H), 3.63 (s, 2H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.77, 166.75, 140.84, 136.60, 131.78, 130.74, 122.28, 120.69, 38.39, 37.57, 26.98.

IR (neat, cm^{-1}) 3221, 29675, 1779, 1668, 1624, 1487, 1073, 1032, 1012.

LRMS (ESI) m/z calcd for $C_{15}H_{18}BrNO_3$ $[M+H]^+$: 340.1, 342.1, found: 340.0, 342.0.

2-(4-methoxyphenyl)-N-(pivaloyloxy)acrylamide (2e)



2e

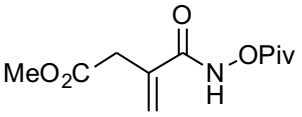
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, NH), 7.38 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.97 (s, 1H), 5.66 (s, 1H), 3.79 (s, 3H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.60, 166.48, 160.04, 141.04, 129.00, 127.96, 121.19, 114.11, 55.29, 38.34, 26.99.

IR (neat, cm^{-1}) 3229, 2973, 1780, 1670, 1608, 1513, 1252, 1181, 1076, 1033, 837.

LRMS (ESI) m/z calcd for $C_{15}H_{19}NO_4$ $[M+H]^+$, $[M+Na]^+$: 278.1, found: 278.1.

Methyl 3-((pivaloyloxy)carbamoyl)but-3-enoate (2f)



2f

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, NH), 6.07 (s, 1H), 5.63 (s, 1H), 3.74 (s, 3H), 3.42 (s, 2H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.49, 171.40, 166.39, 134.56, 125.32, 52.48, 38.39, 37.77, 27.02.

IR (neat, cm^{-1}) 2972, 1741, 1055, 1033, 1013.

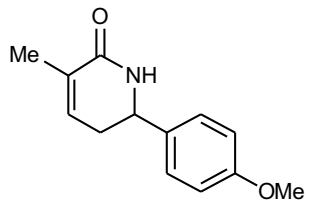
LRMS (ESI) m/z calcd for $C_{11}H_{17}NO_5$ $[M+H]^+$, $[M+Na]^+$: 244.1, found: 244.1, 266.1.

3. General procedures for dihydropyridone synthesis (racemic)

Substituted *N*-(pivaloyloxy) acrylamide (0.1 mmol, 1 eq), $[Cp^*RhCl_2]_2$ (0.0025 mmol, 2.5 mol%), CsOAc (0.025 mmol, 0.25 equiv) and alkene (0.11 mmol, 1.1 equiv) were added to a dram vial charged with a stir bar. Trifluoroethanol (TFE) (0.33 mL, 0.3 M) was added and the mixture was stirred at room temperature until the starting material was consumed (monitoring by TLC). The reaction was quenched with saturated $NaHCO_3$ and extracted 3 times with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and solvent was evaporated to obtain crude product. The crude product was purified by column chromatography using gradient 10% to 50% EtOAc/hexane containing 1% Et_3N as an eluent to obtain the product.

4. Product characterizations (racemic)

6-(4-Methoxyphenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4aa)



4aa

Off-white solid (17.8 mg, 82% yield)

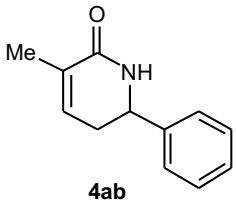
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.34 (ddd, *J* = 5.0, 3.7, 1.7 Hz, 1H), 5.56 (s, 1H), 4.64 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.80 (s, 3H), 2.45 (ddd, *J* = 8.1, 4.0, 1.8 Hz, 2H), 1.92 (d, *J* = 1.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.75, 159.48, 134.45, 133.32, 130.86, 127.62, 114.22, 55.71, 55.33, 33.47, 16.61.

IR (neat, cm^{-1}) 3204, 2923, 1673, 1627, 1512, 1244, 1176, 1033, 826.

LRMS (ESI) m/z calcd for $C_{13}H_{15}NO_2$ $[M+H]^+$: 218.1, found: 218.2.

3-Methyl-6-phenyl-5,6-dihydropyridin-2(1*H*)-one (4ab)



4ab

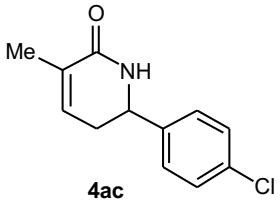
Off-white solid (13.1 mg, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 6.34 (m, 1H), 5.66 (s, NH), 4.70 (dd, *J* = 10.5, 6.7 Hz, 1H), 2.50 (m, 2H), 1.93 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.73, 141.35, 134.27, 130.92, 128.90, 128.23, 126.39, 56.21, 33.37, 16.61. IR (neat, cm^{-1}) 3214, 3063, 2923, 2886, 1676, 1633, 699.

LRMS (ESI) m/z calcd for $C_{12}H_{13}NO$ $[M+H]^+$: 188.1, found: 188.2.

6-(4-Chlorophenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4ac).



4ac

Light-orange solid (28.1 mg, 63%).

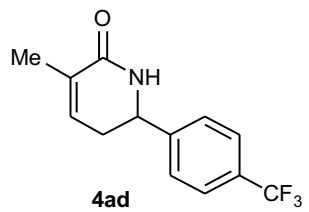
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.33 (ddd, *J* = 5.2, 3.2, 1.6 Hz, 1H), 5.65 (s, 1H), 4.68 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.71 – 2.28 (m, 3H), 2.16 – 1.67 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.61, 139.83, 134.05, 134.00, 130.99, 129.06, 127.73, 55.53, 33.23, 16.53.

IR (neat, cm^{-1}) 3194, 3062, 2976, 2950, 2920, 2807, 1675, 1631, 1578, 1494, 1495, 1421, 1408, 1374, 1345, 1286, 1246, 1179.

HRMS (ASAP) m/z calcd for $C_{12}H_{13}ClNO$ $[M+H]^+$: 222.0686, found: 222.0687.

3-Methyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4ad)



4ad

Off-white solid (18.1 mg, 71% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 6.32 (dt, *J* = 3.5, 1.7 Hz, 1H), 5.87 (s, 1H), 4.78 (dd, *J* = 10.9, 5.8 Hz, 1H), 2.70 – 2.36 (m, 2H), 1.91 (d, *J* = 1.9 Hz, 3H).

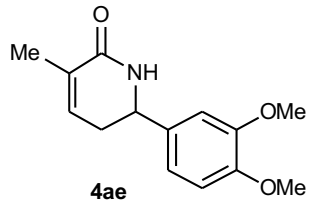
^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.65, 145.42, 133.81, 131.12, 130.61, 130.35, 126.75, 125.93, 125.90, 125.87, 125.84, 124.98, 55.63, 33.08, 16.56.

^{19}F NMR ($CDCl_3$, 282 MHz) δ -61.78.

IR (neat, cm^{-1}) 3194, 2924, 1673, 1630, 1324, 1109, 1068, 906, 730.

LRMS (ESI) m/z calcd for $C_{13}H_{12}F_3NO$ $[M+H]^+$: 256.1, found: 256.1.

6-(3,4-Dimethoxyphenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4ae).



4ae

Reaction run on a 0.200 mmol scale.

Light-orange solid (32.5 mg, 66%).

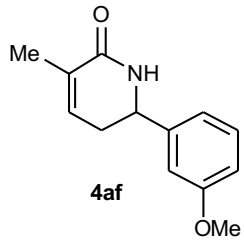
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 – 6.62 (m, 3H), 6.35 (tt, *J* = 3.6, 1.9 Hz, 1H), 5.62 (s, 1H), 4.63 (dd, *J* = 10.2, 7.5 Hz, 1H), 3.87 (d, *J* = 3.1 Hz, 6H), 2.59 – 2.25 (m, 2H), 1.92 (d, *J* = 2.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.75, 149.22, 148.87, 134.45, 133.73, 130.78, 118.71, 111.13, 109.18, 56.04, 55.91, 55.89, 33.53, 16.55.

IR (neat, cm^{-1}) 3249, 3223, 3066, 3001, 2935, 2833, 1673, 1629, 1516, 1458, 1421, 1261, 1253.

HRMS (ASAP) m/z calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1287, found: 248.1284.

6-(3-Methoxyphenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4af).



4af

Reaction run on a 0.200 mmol scale.

Light-orange solid (32.8 mg, 75%).

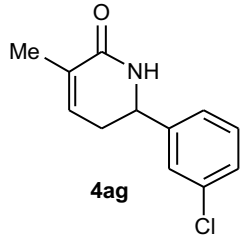
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.71 (m, 3H), 6.35 (ddd, *J* = 5.2, 3.5, 1.6 Hz, 1H), 5.63 (s, 1H), 4.67 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.81 (s, 3H), 2.74 – 2.35 (m, 2H), 1.92 (q, *J* = 1.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.66, 159.96, 142.93, 134.30, 130.86, 129.95, 118.59, 113.58, 111.95, 56.18, 55.26, 33.32, 16.56.

IR (neat, cm^{-1}) 3209, 3052, 2946, 2920, 2840, 1677, 1633, 1600, 1487, 1454, 1429.

HRMS (ASAP) m/z calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1181, found: 218.1180.

6-(3-Chlorophenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4ag).



4ag

Reaction run on a 0.200 mmol scale.

Orange solid (26.8 mg, 61%).

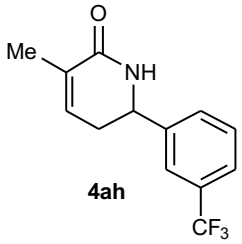
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H), 7.22 (ddd, *J* = 6.0, 3.2, 1.8 Hz, 1H), 6.32 (ddd, *J* = 5.1, 3.2, 1.6 Hz, 1H), 5.74 (s, 1H), 4.67 (dd, *J* = 11.1, 5.8 Hz, 1H), 2.91 – 2.27 (m, 2H), 2.16 (s, 0H), 2.06 – 1.69 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.54, 143.44, 134.74, 133.88, 131.01, 130.16, 128.34, 126.63, 124.48, 55.59, 33.09, 16.52.

IR (neat, cm^{-1}) 3256, 3216, 3070, 2953, 2920, 2880, 2844, 1677, 1629, 1600, 1575, 1454, 1425.

HRMS (ASAP) m/z calcd for $C_{12}H_{13}ClNO$ $[M+H]^+$: 222.0686, found: 222.0680.

3-Methyl-6-(3-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4ah).



4ah

Reaction run on a 0.200 mmol scale.

Light-orange solid (24.7 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.53 (m, 3H), 7.50 (t, *J* = 7.7 Hz, 1H), 6.34 (ddd, *J* = 5.1, 3.2, 1.6 Hz, 1H), 5.84 (s, 1H), 4.78 (dd, *J* = 11.2, 5.7 Hz, 1H), 2.76 – 2.37 (m, 2H), 2.00 – 1.80 (m, 2H).

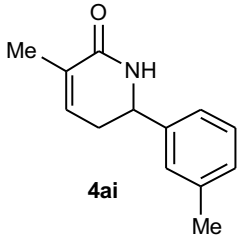
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.64, 142.43, 133.85, 131.30 (q, *J* = 32.4 Hz), 131.11, 129.72, 129.44, 125.07 (q, *J* = 3.8 Hz), 123.83 (q, *J* = 270.5 Hz), 123.25 (q, *J* = 3.8 Hz), 55.75, 33.18, 16.51.

^{19}F NMR (470 MHz, $CDCl_3$) δ -61.79.

IR (neat, cm^{-1}) 3216, 3070, 2979, 2953, 2924, 2888, 1677, 1633, 1451, 1429, 1326.

HRMS (ASAP) m/z calcd for $C_{13}H_{13}F_3NO$ $[M+H]^+$: 256.0949, found: 256.0945.

3-Methyl-6-(m-tolyl)-5,6-dihydropyridin-2(1H)-one (4ai).



4ai

Reaction run on a 0.200 mmol scale.

Light-brown oil (25.6 mg, 64%).

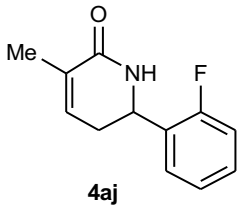
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 1H), 7.19 – 7.09 (m, 3H), 6.33 (ddd, *J* = 5.3, 3.6, 1.7 Hz, 1H), 5.64 (s, 1H), 4.65 (dd, *J* = 9.8, 7.6 Hz, 1H), 2.47 (ddt, *J* = 7.8, 3.7, 2.1 Hz, 2H), 2.35 (s, 3H), 1.92 (d, *J* = 1.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.65, 141.27, 138.59, 134.26, 130.82, 128.88, 128.72, 127.01, 123.37, 56.10, 33.32, 21.37, 16.54.

IR (neat, cm^{-1}) 3212, 3052, 3030, 2950, 2920, 2884, 1673, 1629, 1491, 1454, 1429.

HRMS (ASAP) m/z calcd for $C_{13}H_{16}NO$ $[M+H]^+$: 202.1232, found: 202.1230.

6-(2-Fluorophenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4aj).



4aj

Reaction run on a 0.200 mmol scale.

Off-white solid (13.3 mg, 32%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (td, *J* = 7.6, 1.8 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.20 – 7.12 (m, 1H), 7.05 (ddd, *J* = 10.6, 8.2, 1.2 Hz, 1H), 6.31 (tt, *J* = 3.6, 1.7 Hz, 1H), 5.79 (s, 1H), 5.06 (ddd, *J* = 10.0, 5.9, 1.6 Hz, 1H), 2.91 – 2.19 (m, 2H), 1.91 (d, *J* = 1.9 Hz, 3H).

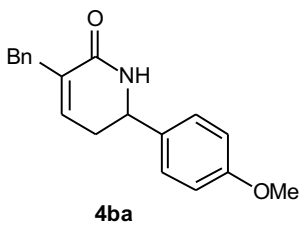
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.84, 159.95 (d, J_{C-F} = 246.9 Hz), 134.04, 130.86, 129.52 (d, J_{C-F} = 8.2 Hz), 128.44 (d, J_{C-F} = 12.8 Hz), 127.39 (d, J_{C-F} = 3.7 Hz), 124.52 (d, J_{C-F} = 3.6 Hz), 115.69 (d, J_{C-F} = 21.7 Hz), 48.95 (d, J_{C-F} = 3.6 Hz), 31.25, 16.56.

^{19}F NMR (470 MHz, $CDCl_3$) δ -118.24.

IR (neat, cm^{-1}) 3260, 3194, 3143, 3063, 2957, 2924, 2891, 1677, 1629, 1585, 1483, 1451, 1429.

HRMS (ASAP) m/z calcd for $C_{12}H_{13}FNO$ $[M+H]^+$: 206.0981, found: 206.0982.

3-Benzyl-6-(4-methoxyphenyl)-5,6-dihydropyridin-2(1*H*)-one (4ba)



4ba

Off-white solid (26.0 mg, 89% yield).

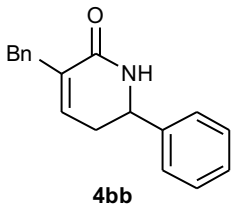
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.15 (m, 4H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.14 (ddd, *J* = 4.6, 3.0, 1.7 Hz, 1H), 5.68 (s, 1H), 4.62 (t, *J* = 8.6 Hz, 1H), 3.80 (s, 3H), 3.66 (t, *J* = 2.1 Hz, 2H), 2.46 (ddt, *J* = 9.5, 4.0, 1.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.02, 159.50, 139.33, 135.16, 134.95, 133.18, 129.34, 128.41, 127.67, 126.19, 114.22, 55.38, 55.34, 36.05, 33.50.

IR (neat, cm^{-1}) 3207, 3060, 3027, 2932, 2836, 1672, 1629, 1512, 1247, 1032, 826, 700.

LRMS (ESI) m/z calcd for $C_{19}H_{19}NO_2$ $[M+H]^+$, $[M+Na]^+$: 294.1, 316.1, found: 294.1, 316.1.

3-Benzyl-6-phenyl-5,6-dihydropyridin-2(1H)-one (4bb)



4bb

Off-white solid (22.2 mg, 85% yield).

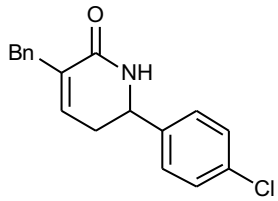
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 8H), 7.28 – 7.19 (m, 4H), 6.14 (td, *J* = 3.6, 1.8 Hz, 1H), 5.68 (s, 1H), 4.90 – 4.26 (m, 1H), 3.67 (s, 1H), 2.69 – 2.35 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.96, 141.20, 139.29, 135.01, 134.99, 129.35, 128.91, 128.42, 128.27, 126.45, 126.21, 55.91, 36.06, 33.41.

IR (neat, cm^{-1}) 3206, 3061, 3027, 2917, 1673, 1630, 1494, 1453, 1424, 1290, 698.

LRMS (ESI) m/z calcd for $C_{18}H_{17}NO$ $[M+H]^+$: 265.1, found: 265.1.

3-Benzyl-6-(4-chlorophenyl)-5,6-dihydropyridin-2(1*H*)-one (4bc)



4bc

Off-white solid (21.2 mg, 71% yield).

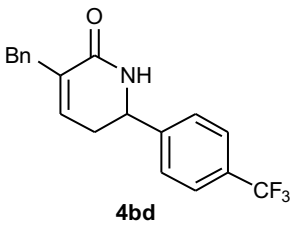
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.28 (m, 4H), 7.24-7.19 (m, 5H), 6.10 (m, 1H), 5.88 (s, NH), 4.65 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.62 (s, 2H), 2.53-2.49 (m, 1H), 2.44-2.38 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.94, 139.74, 139.17, 135.12, 134.68, 133.98, 129.31, 129.04, 128.43, 127.82, 126.25, 55.15, 36.06, 33.25.

IR (neat, cm^{-1}) 3207, 3061, 3028, 2921, 1674, 1631, 1492, 1092, 1014, 822, 699.

LRMS (ESI) m/z calcd for $C_{18}H_{16}ClNO$ $[M+H]^+$: 298.1, found: 298.1.

3-Benzyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one (4bd)



4bd

Off-white solid (15.3 mg, 46% yield).

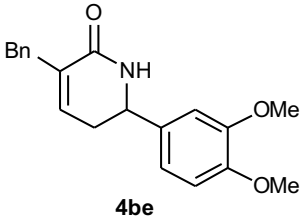
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.32 (m, 2H), 7.25 (m, 3H), 6.16 (m, 1H), 5.93 (s, NH), 4.78 (dd, *J* = 10.7, 5.7 Hz, 1H), 3.68 (s, 2H), 2.84-2.56 (m, 1H), 2.55-2.38 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.87, 145.23, 139.07, 135.23, 134.49, 130.49, 129.28, 128.44, 126.79, 126.29, 125.88, 55.30, 36.07, 33.12.

IR (neat, cm^{-1}) 3212, 3064, 2922, 1675, 1630, 1324, 1164, 1121, 1068, 826, 700.

LRMS (ESI) m/z calcd for $C_{19}H_{16}F_3NO$ $[M+H]^+$: 332.1, found: 332.1.

3-Benzyl-6-(3,4-dimethoxyphenyl)-5,6-dihydropyridin-2(1H)-one (4be).



4be

Reaction run on a 0.200 mmol scale.

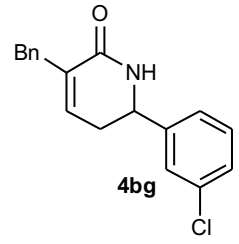
Light-orange oil (49.1 mg, 76%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 7.27 – 7.18 (m, 3H), 6.88 – 6.79 (m, 3H), 6.16 (td, *J* = 3.8, 2.2 Hz, 1H), 5.65 (s, 1H), 4.62 (dd, *J* = 9.5, 7.9 Hz, 1H), 3.86 (d, *J* = 11.6 Hz, 6H), 3.65 (s, 1H), 2.48 (ddt, *J* = 7.8, 4.0, 1.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.95, 149.23, 148.89, 139.25, 135.18, 134.86, 133.62, 129.25, 128.37, 126.16, 118.75, 111.15, 109.20, 55.92, 55.87, 55.71, 36.01, 33.53.

IR (neat, cm^{-1}) 3092, 3070, 3033, 1961, 1819, 1677, 1629, 1516, 1476, 1454, 1418, 1264, 1235, 1137, 1031, 670.

HRMS (ESI) m/z calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1600, found: 324.1608.

3-Benzyl-6-(3-chlorophenyl)-5,6-dihydropyridin-2(1*H*)-one (4bg)



4bg

Off-white solid (17.4 mg, 58% yield).

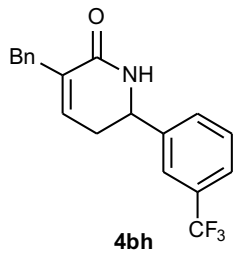
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 7.23-7.18 (m, 4H), 6.13 (m, 1H), 5.82 (s, NH), 4.67 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.55 (s, 2H), 2.58-2.53 (m, 1H), 2.49-2.43 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.84, 143.33, 139.13, 135.11, 134.78, 134.64, 130.20, 129.29, 128.45, 128.41, 126.69, 126.25, 124.57, 55.29, 36.04, 33.16.

IR (neat, cm^{-1}) 3204, 2897, 1674, 1630, 1422, 696.

LRMS (ESI) m/z calcd for $C_{18}H_{16}ClNO$ $[M+H]^+$: 298.1, found: 298.1.

3-Benzyl-6-(3-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one (4bh)



4bh

Off-white solid (14.5 mg, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.61 (d, *J* = 10.0 Hz, 1H), 7.54-7.48 (m, 2H), 7.36-7.31 (m, 2H), 7.26-7.23 (m, 3H), 6.17 (m, 1H), 5.90 (s, NH), 4.79 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.69 (s, 2H), 2.64-2.59 (m, 1H), 2.54-2.47 (m, 1H).

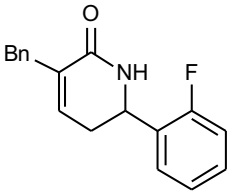
^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.90, 142.31, 139.07, 135.20, 134.58, 131.46, 131.20, 130.94, 129.80, 129.46, 129.28, 128.46, 126.28, 125.11, 123.27, 55.43, 36.02, 33.21.

^{19}F NMR ($CDCl_3$, 282 MHz) δ -61.82.

IR (neat, cm^{-1}) 2939, 1676, 1631, 1328, 700.

LRMS (ESI) m/z calcd for $C_{19}H_{16}F_3NO$ $[M+H]^+$: 332.1, found: 332.1.

3-Benzyl-6-(3-fluorophenyl)-5,6-dihydropyridin-2(1*H*)-one (4bj)



4bj

Yellow oil (19.9 mg, 71% yield).

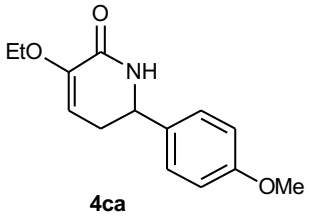
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (m, 3H), 7.23-7.20 (m, 3H), 7.09 (d, *J* = 7.8, Hz, 1H), 7.06-6.97 (m, 2H), 6.13 (m, 1H), 5.80 (s, NH), 4.68 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.65 (s, 2H), 2.58-2.52 (m, 1H), 2.49-2.42 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.85, 163.94, 161.98, 143.87, 143.82, 139.14, 135.09, 134.68, 130.54, 130.48, 129.31, 128.44, 126.25, 122.04, 122.01, 115.25, 115.08, 113.58, 113.40, 55.33, 36.04, 33.18.

IR (neat, cm^{-1}) 3208, 3062, 3028, 2920, 1674, 1631, 784, 699.

LRMS (ESI) m/z calcd for $C_{18}H_{16}FNO$ $[M+H]^+$: 282.1, found: 282.1.

3-Ethoxy-6-(4-methoxyphenyl)-5,6-dihydropyridin-2(1H)-one (4ca)



4ca

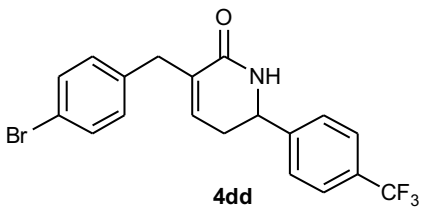
Off-white solid (12.6 mg, 51% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.70 (s, 1H), 5.41 (s, 1H), 4.66 (dd, *J* = 11.8, 5.5 Hz, 1H), 3.88 – 3.83 (m, 2H), 3.83 (s, 3H), 2.69 – 2.44 (m, 2H), 1.44 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 163.49, 159.54, 146.86, 132.82, 127.60, 114.24, 104.68, 63.56, 55.55, 55.33, 32.00, 14.34.

IR (neat, cm^{-1}) 3227, 1680, 1633, 1513, 1247, 1177, 912.

LRMS (ESI) m/z calcd for $C_{14}H_{17}NO_3$ $[M+H]^+$: 248.1, found: 248.2, 270.1.

3-(4-Bromobenzyl)-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4dd)



4dd

Off-white solid (24.2 mg, 59% yield)

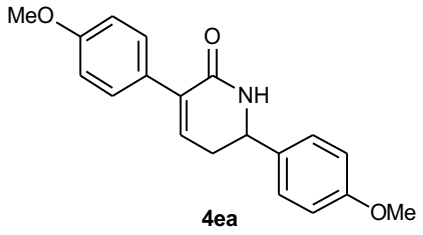
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.43 (dd, *J* = 10.2, 8.1 Hz, 4H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.20 (ddt, *J* = 5.0, 3.2, 1.5 Hz, 1H), 6.04 (s, NH), 4.77 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.61 (d, *J* = 2.1 Hz, 2H), 2.77 – 2.58 (m, 1H), 2.50 (dddt, *J* = 17.8, 10.7, 3.6, 2.1 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 166.66, 145.08, 138.16, 134.78, 134.73, 131.49, 130.97, 130.67, 130.41, 126.78, 125.94, 125.91, 125.88, 125.85, 124.96, 122.79, 120.16, 55.25, 35.64, 33.08.

^{19}F NMR ($CDCl_3$, 282 MHz) δ -61.76.

IR (neat, cm^{-1}) 4210, 2923, 1674, 1629, 1323, 1162, 1120, 1067.

LRMS (ESI) m/z calcd for $C_{19}H_{15}BrF_3NO$ $[M+H]^+$: 410.0, found: 410.1.

3,6-Bis(4-methoxyphenyl)-5,6-dihydropyridin-2(1H)-one (4ea)



4ea

Off-white solid (16.4 mg, 53% yield)

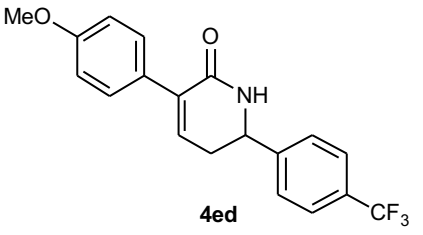
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.91 (t, *J* = 8.8 Hz, 3H), 6.64 (t, *J* = 4.5 Hz, 1H), 5.77 (s, 1H), 4.75 (t, *J* = 8.6 Hz, 1H), 3.82 (d, *J* = 1.2 Hz, 6H), 2.65 (dd, *J* = 8.8, 4.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.34, 159.57, 159.33, 135.50, 135.01, 133.04, 129.74, 128.83, 127.72, 114.30, 113.53, 55.36, 55.31, 33.80.

IR (neat, cm^{-1}) 3184, 1665, 1610, 1510, 1300, 1247, 1181, 1033, 825.

LRMS (ESI) m/z calcd for $C_{19}H_{19}NO_3$ $[M+H]^+$: 310.1, found: 310.1, 332.1.

3-(4-Methoxyphenyl)-6-(4-(trifluoromethyl)phenyl-5,6-dihydropyridin-2(1H)-one (4ed)



4ed

Off-white solid (5.6 mg, 16% yield)

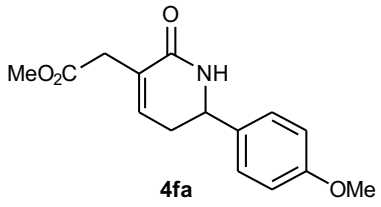
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.65 (dd, *J* = 5.5, 3.4 Hz, 1H), 5.97 (s, NH), 4.97 – 4.82 (m, 1H), 3.84 (s, 3H), 2.81 (dtd, *J* = 17.6, 5.6, 1.1 Hz, 1H), 2.68 (ddd, *J* = 17.6, 10.7, 3.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 166.26, 159.47, 145.11, 135.19, 134.77, 129.73, 128.45, 126.83, 126.00, 125.97, 125.94, 113.58, 55.36, 55.32, 33.47, 29.71.

^{19}F NMR ($CDCl_3$, 282 MHz) δ -61.77.

IR (neat, cm^{-1}) 3195, 3060, 2922, 1667, 1609, 1511, 1324, 1118, 827.

LRMS (ESI) m/z calcd for $C_{19}H_{16}F_3NO_2$ $[M+H]^+$: 348.1, found: 348.2.

Methyl 2-(6-(4-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridin-3-yl)acetate (4fa)



4fa

Off-white solid (20.4 mg, 74% yield)

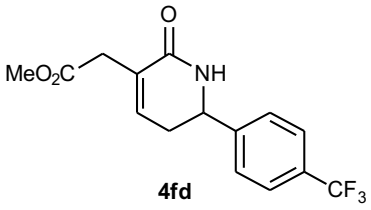
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.52 – 6.46 (m, 1H), 5.64 (s, 1H), 4.71 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.34 (ddd, *J* = 66.8, 16.5, 1.4 Hz, 2H), 2.62 – 2.49 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.76, 166.20, 159.56, 137.58, 132.99, 128.65, 127.70, 114.26, 55.37, 55.34, 52.02, 35.62, 33.44.

IR (neat, cm^{-1}) 3210, 2961, 2837, 1734, 1677, 1513, 1246, 1159, 1029, 830.

LRMS (ESI) m/z calcd for $C_{15}H_{17}NO_4$ $[M+H]^+$: 276.1, found: 276.1, 298.1.

Methyl 2-(2-oxo-6-(4-(trifluoromethyl)phenyl)-1,2,5,6-tetrahydropyridin-3-yl)acetate (4fd)



4fd

Off-white solid (23.2 mg, 74% yield)

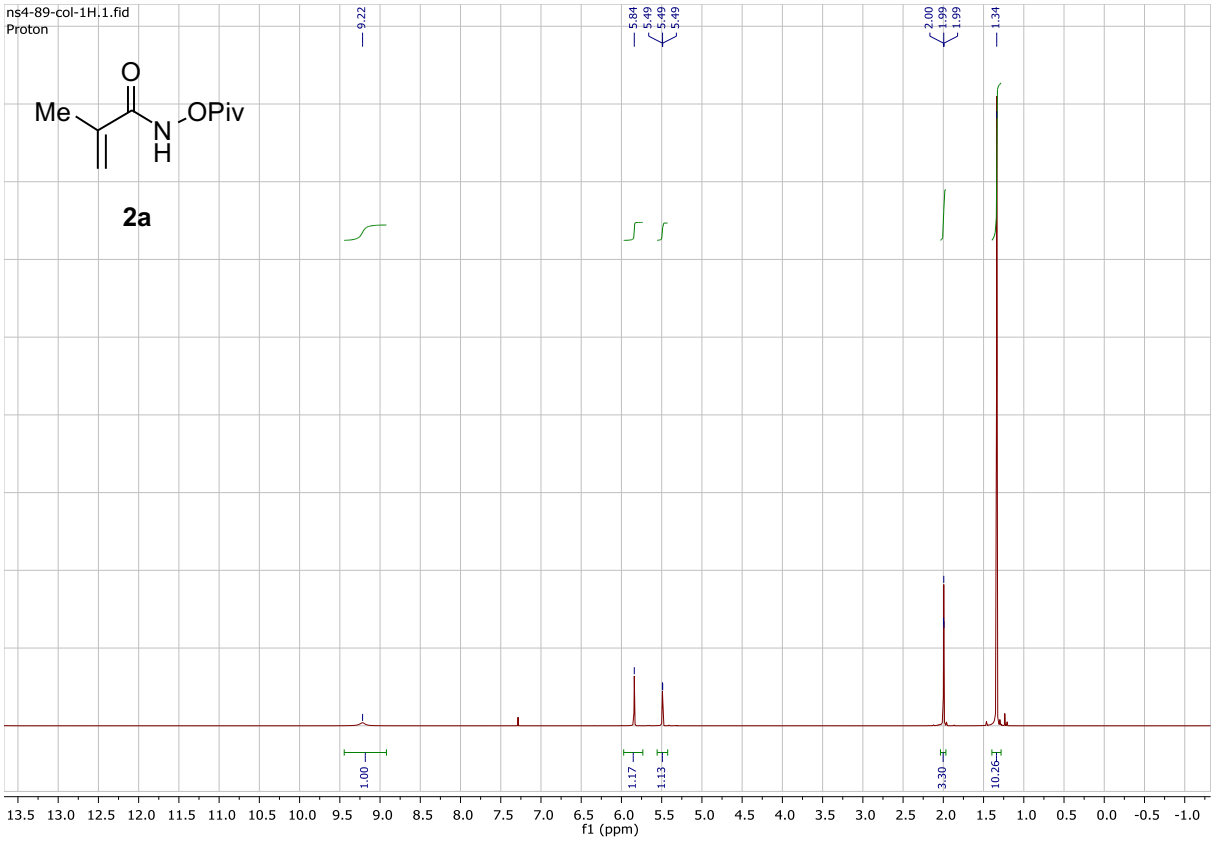
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 6.48 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.14 (s, NH), 4.87 (ddd, *J* = 10.5, 5.8, 1.6 Hz, 1H), 3.71 (s, 3H), 3.38 – 3.29 (m, 2H), 2.73 (dt, *J* = 17.7, 5.6 Hz, 1H), 2.61 – 2.46 (m, 1H). **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 171.60, 166.14, 145.14, 136.85, 130.63, 130.37, 128.93, 126.86, 125.92, 125.89, 125.86, 125.84, 124.99, 122.82, 55.16, 52.01, 35.59, 32.98, 29.70.

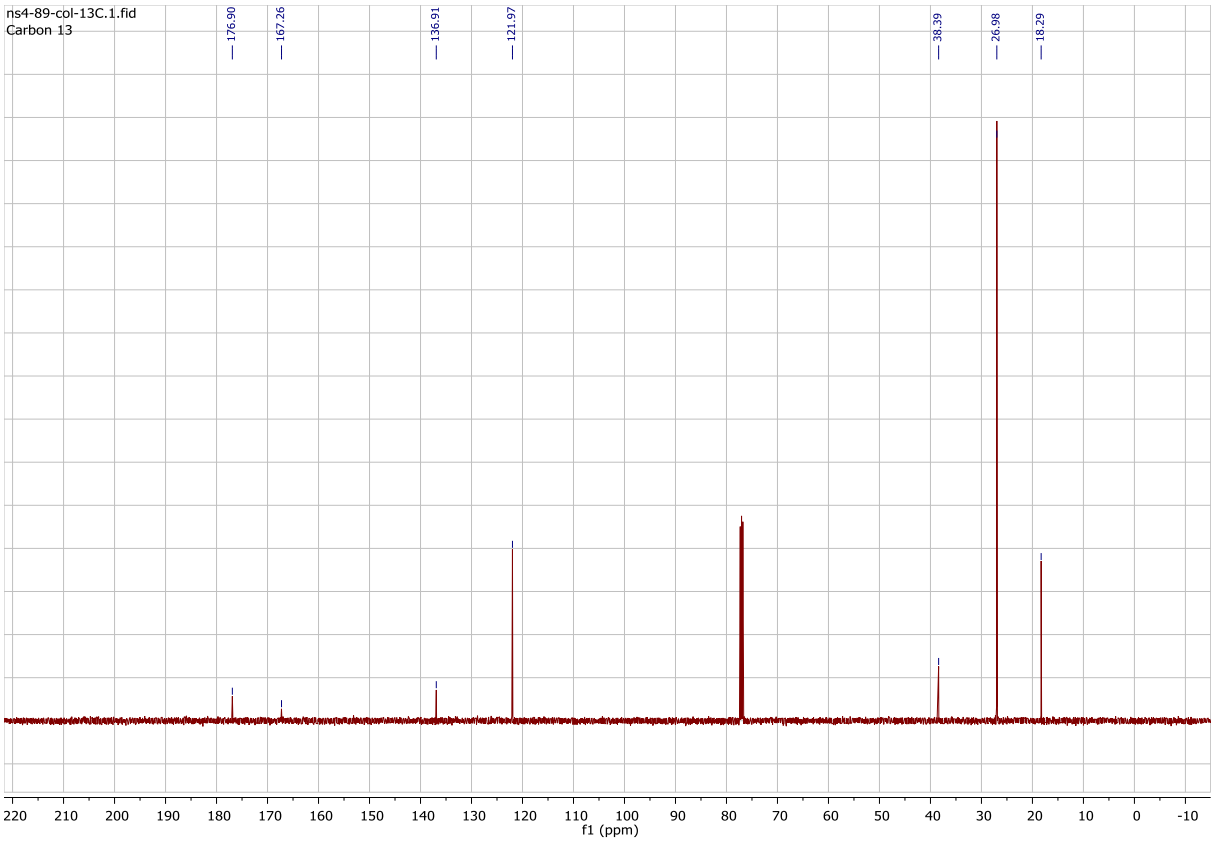
^{19}F NMR ($CDCl_3$, 282 MHz) δ -61.77.

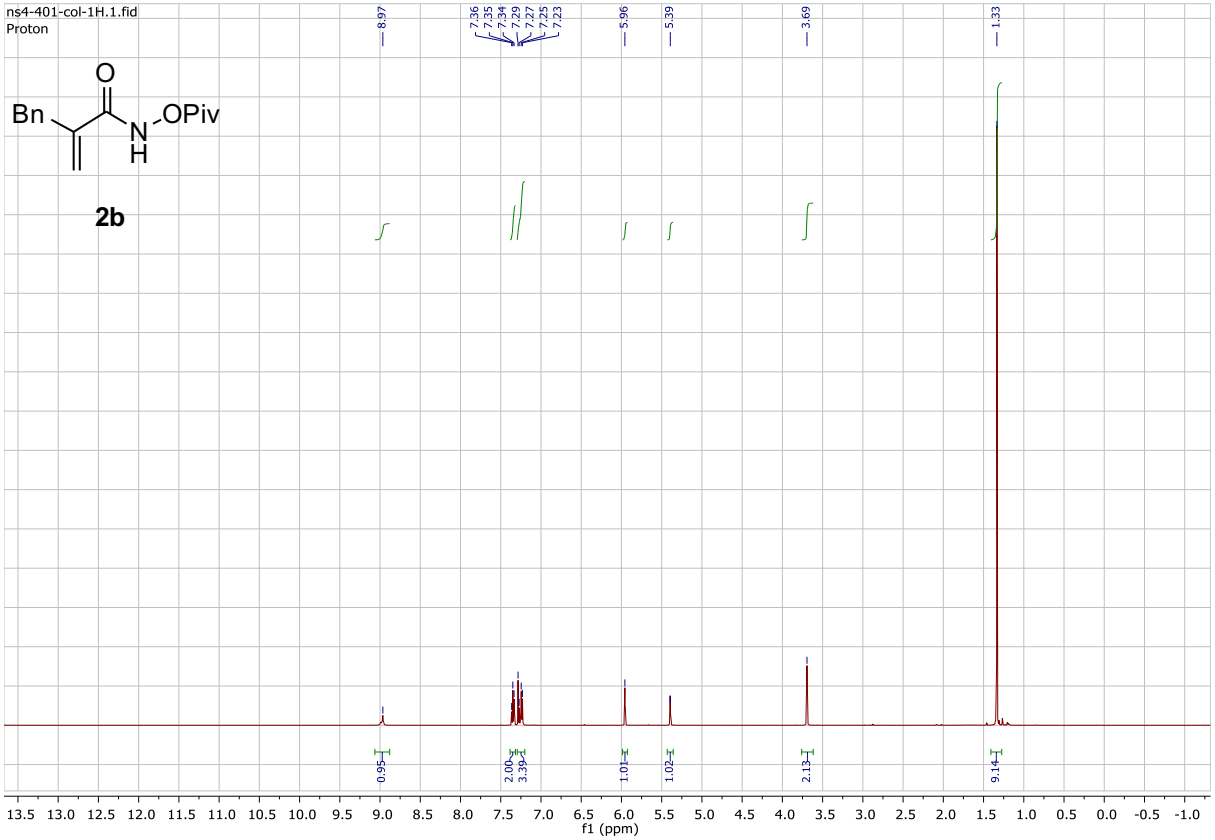
IR (neat, cm^{-1}) 3203, 1722, 1685, 1639, 1330, 1154, 1114, 1070.

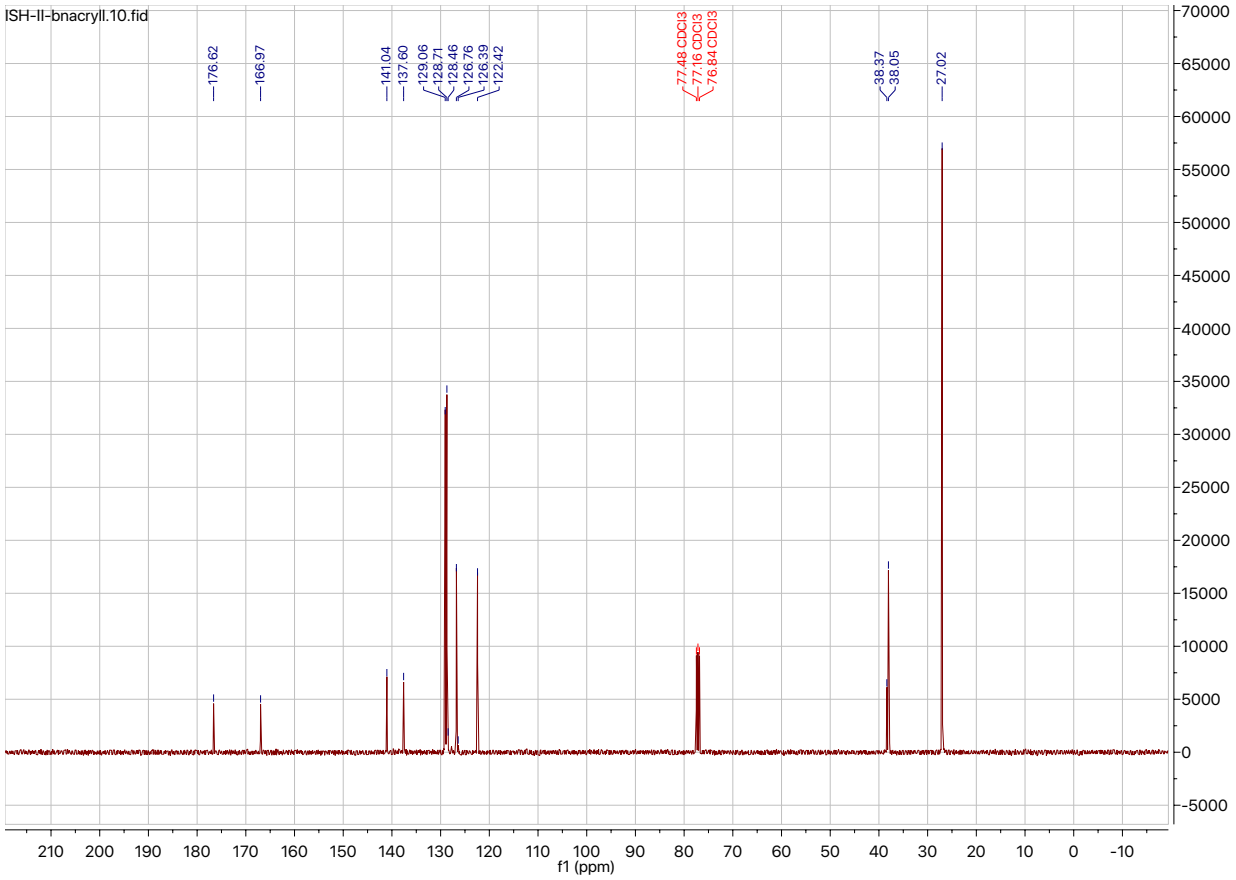
LRMS (ESI) m/z calcd for $C_{15}H_{14}F_3NO_3$ $[M+H]^+$: 314.1, found: 314.1, 336.0.

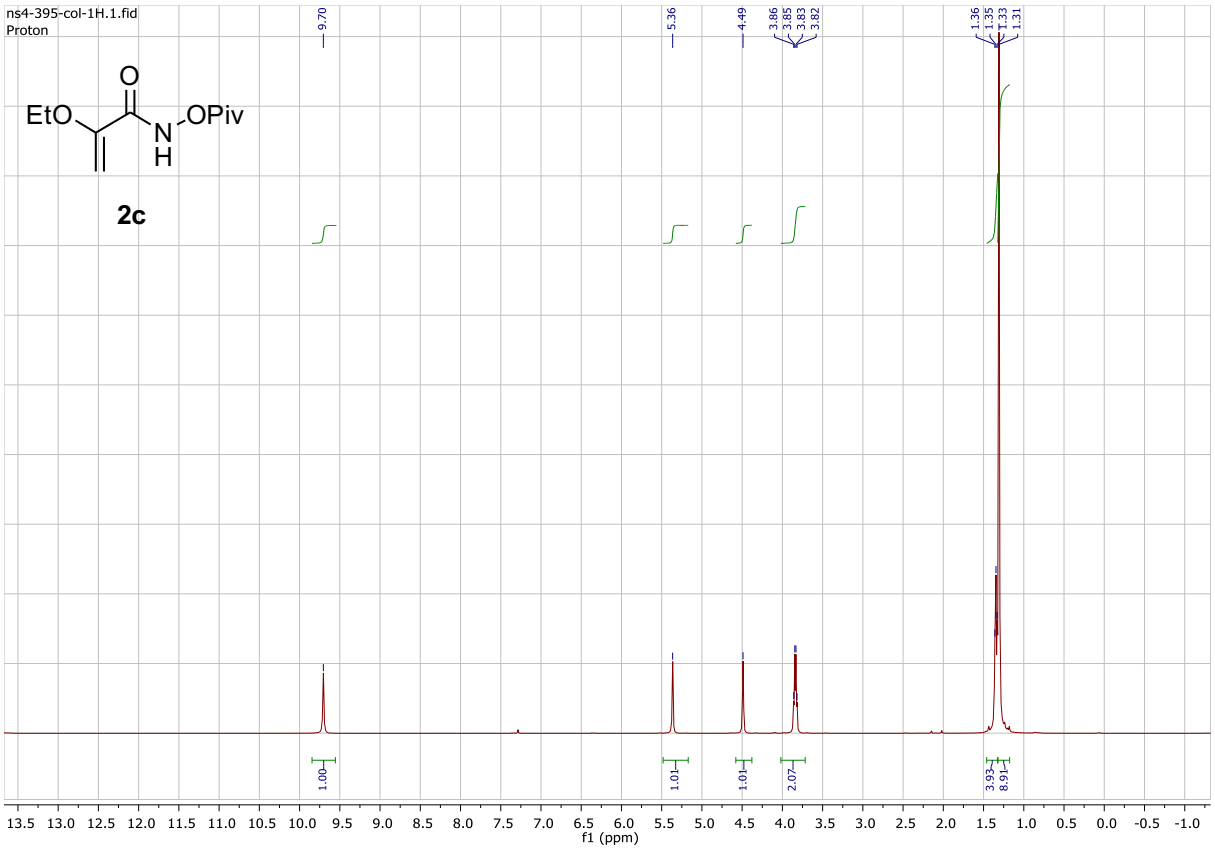
5. Copies of NMR spectra

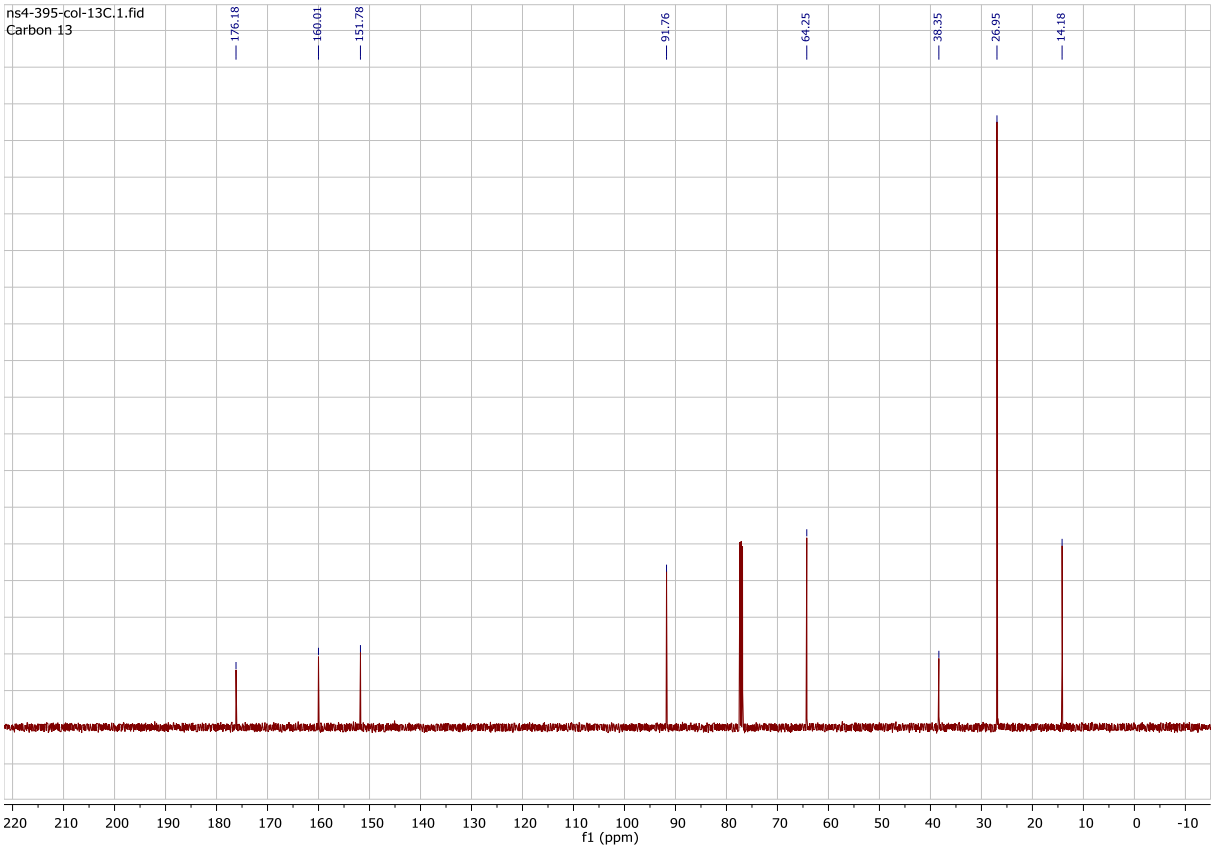


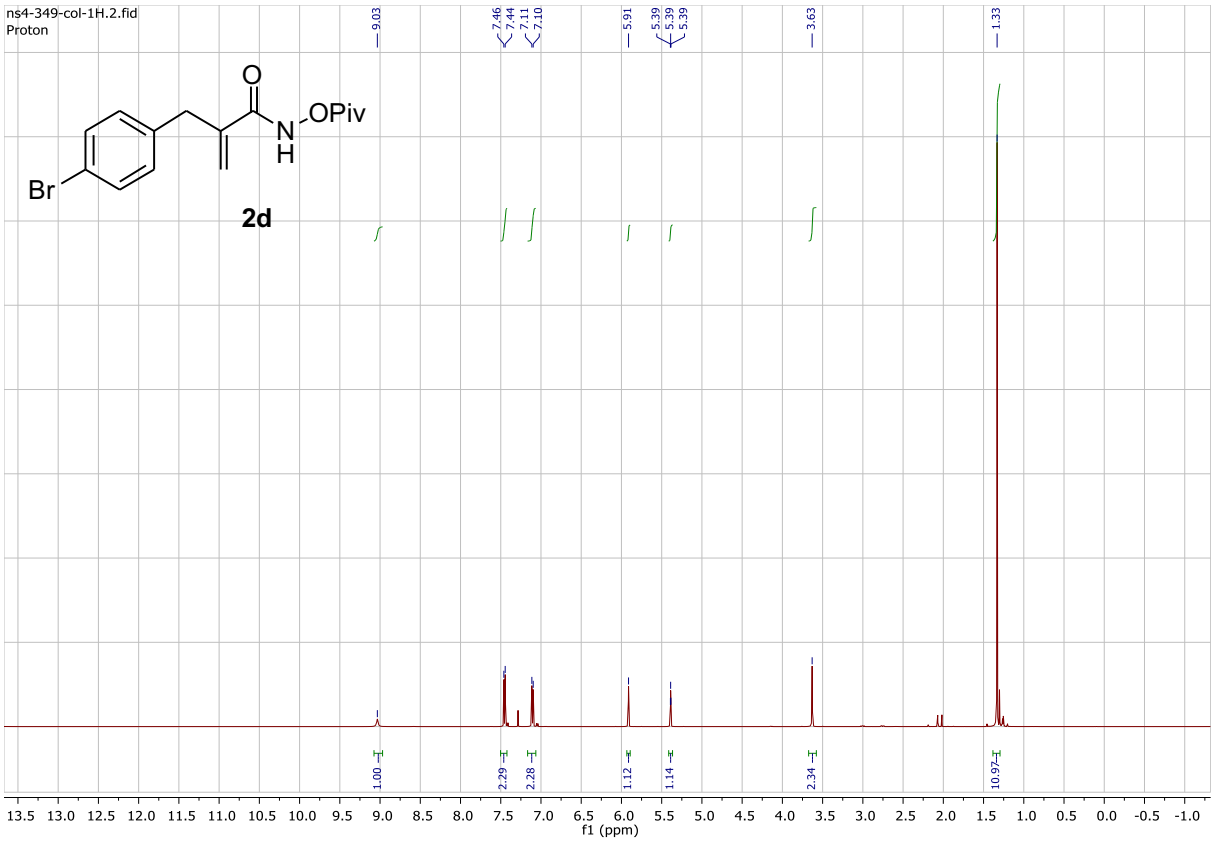

ns4-89-col-13C.1.fid
Carbon 13
176.90
167.26
136.91
121.97
38.39
26.98
18.29
f1 (ppm)

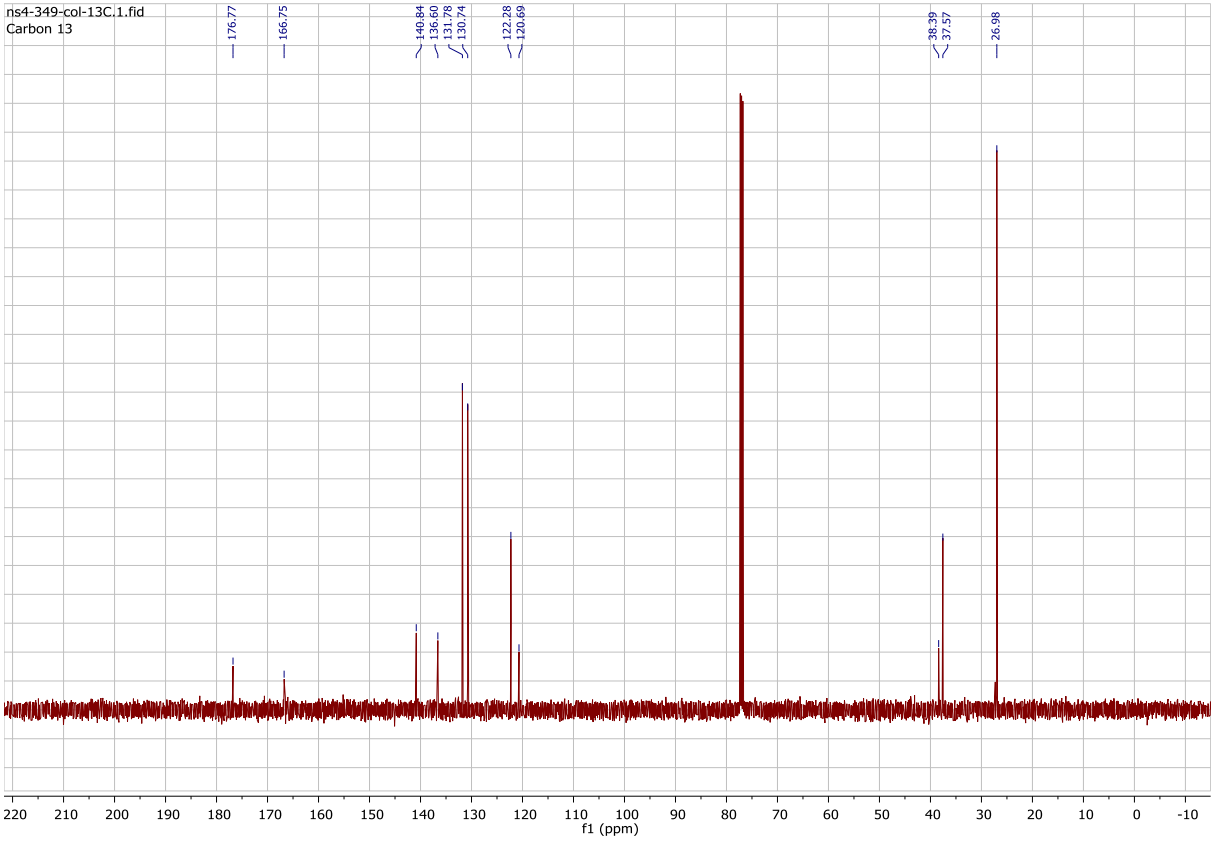

ns4-401-col-1H.1.fid
Proton
8.97
7.36
7.35
7.34
7.29
7.27
7.25
7.23
5.96
5.39
3.69
1.33
Bn
O
N
H
OPiv
2b
0.95
2.00
3.39
1.01
1.02
2.13
9.14
f1 (ppm)

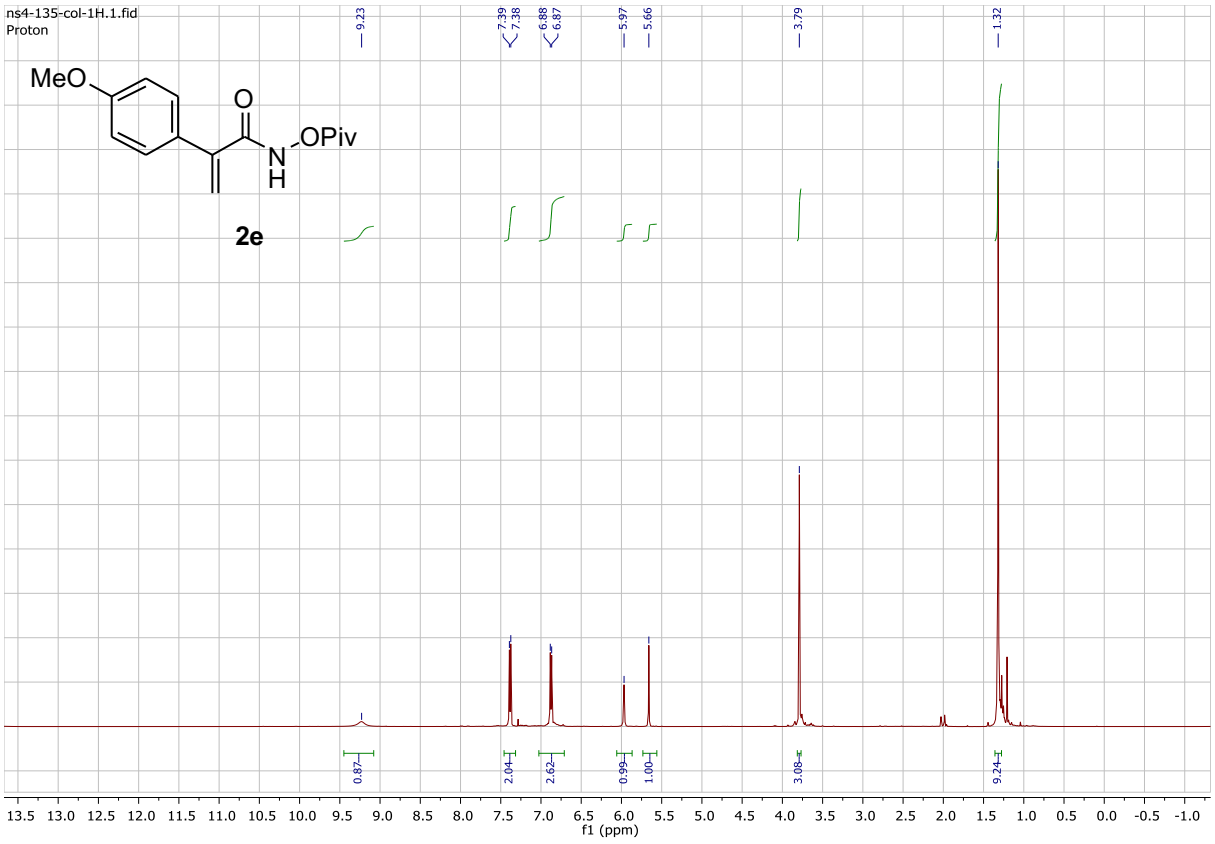

ISH-II-bnacryll.10.fid
176.62
166.97
141.04
137.60
129.06
128.71
128.46
126.76
126.39
122.42
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
38.37
38.05
27.02
f1 (ppm)

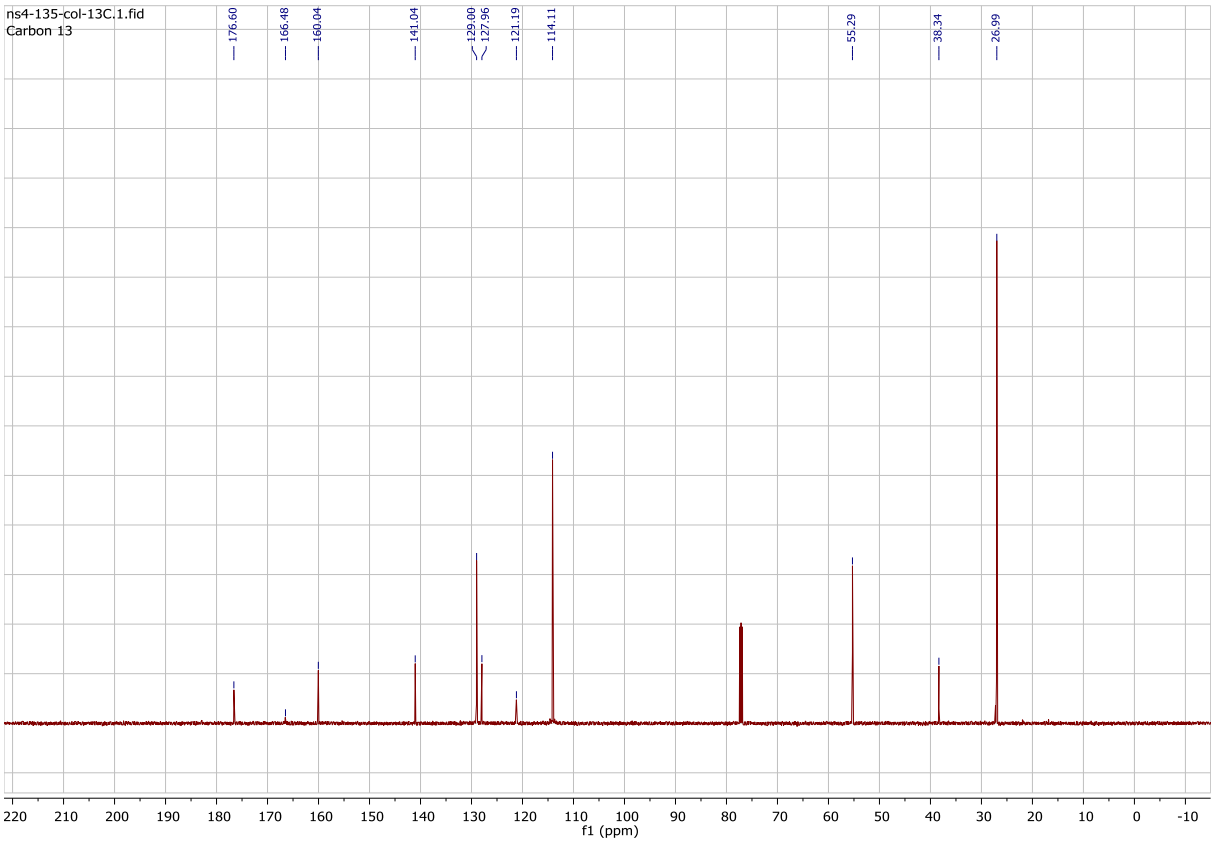

ns4-395-col-1H.1.fid
Proton
EtO
O
N
H
OPiv
2c
9.70
5.36
4.49
3.86
3.85
3.83
3.82
1.36
1.35
1.33
1.31
1.00
1.01
1.01
2.07
3.93
8.91
f1 (ppm)

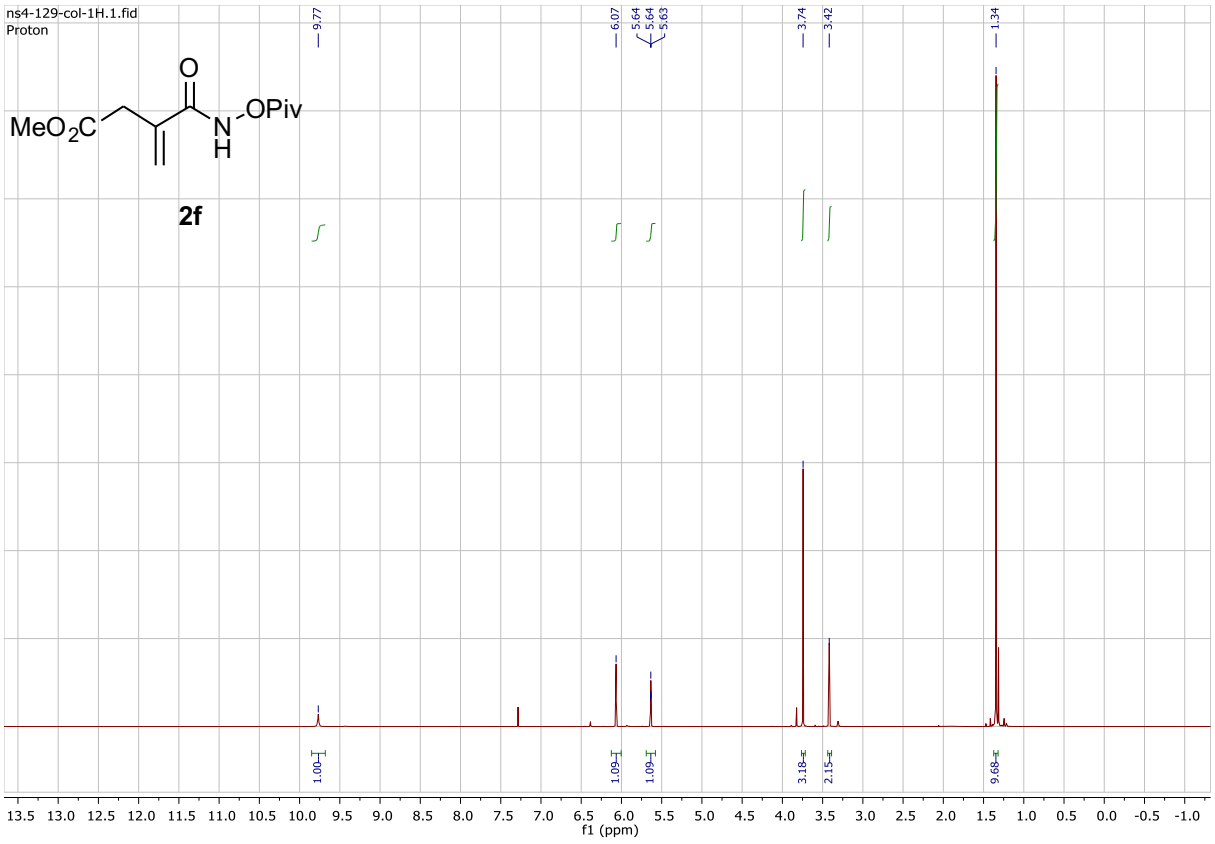

ns4-395-col-13C.1.fid
Carbon 13
176.18
160.01
151.78
91.76
64.25
38.35
26.95
14.18
f1 (ppm)

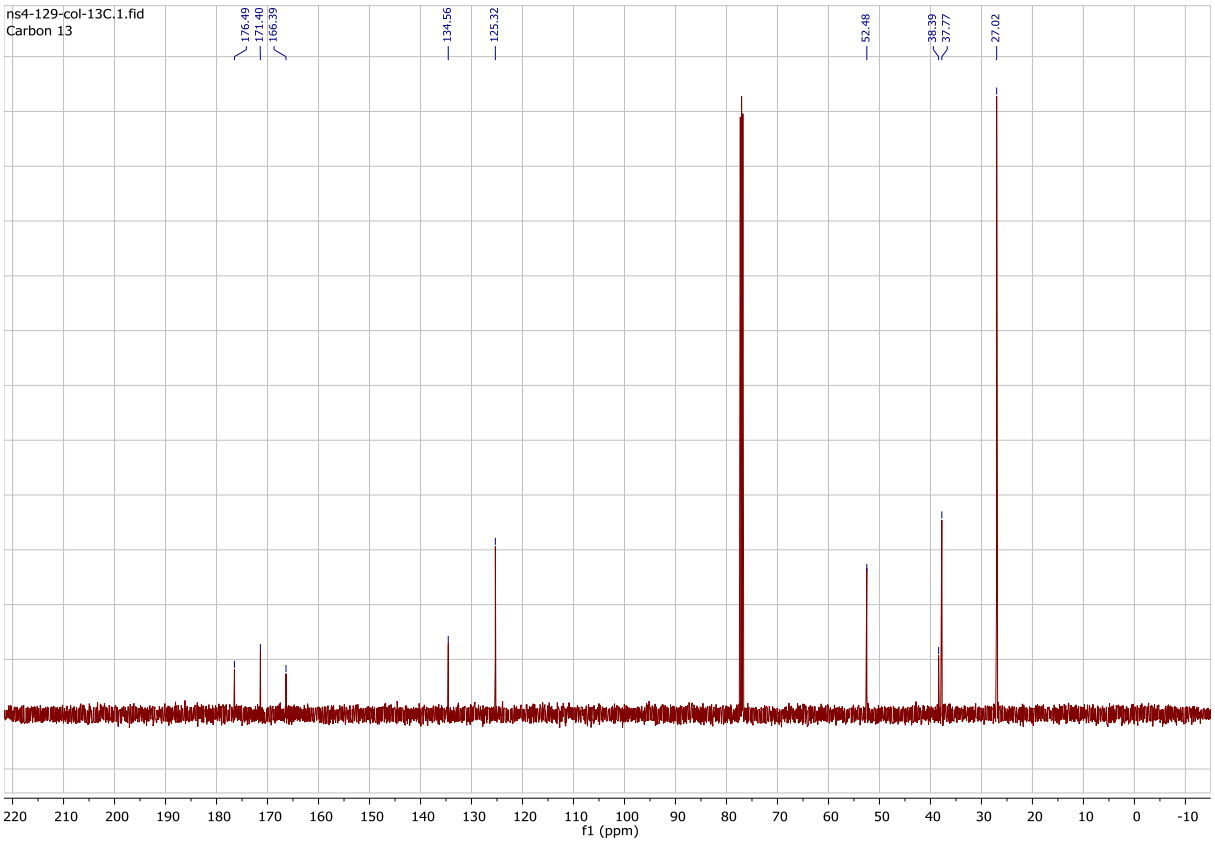

ns4-349-col-1H.2.fid
Proton
9.03
7.46
7.44
7.11
7.10
5.91
5.39
5.39
5.39
3.63
1.33
O
N
H
OPiv
Br
2d
1.00
2.29
2.28
1.12
1.14
2.34
10.97
f1 (ppm)

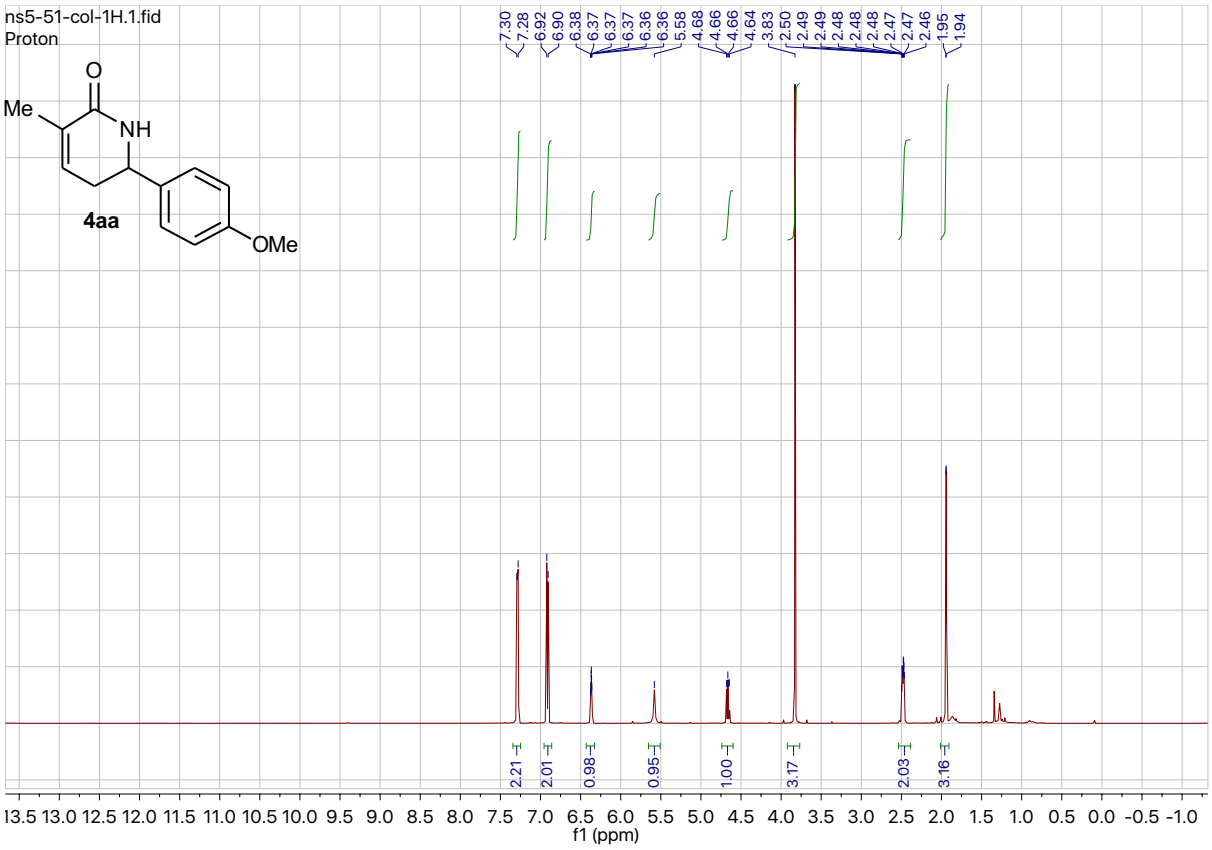

ns4-349-col-13C.1.fid
Carbon 13
176.77
166.75
140.84
136.60
131.78
130.74
122.28
120.69
38.39
37.57
26.98
f1 (ppm)

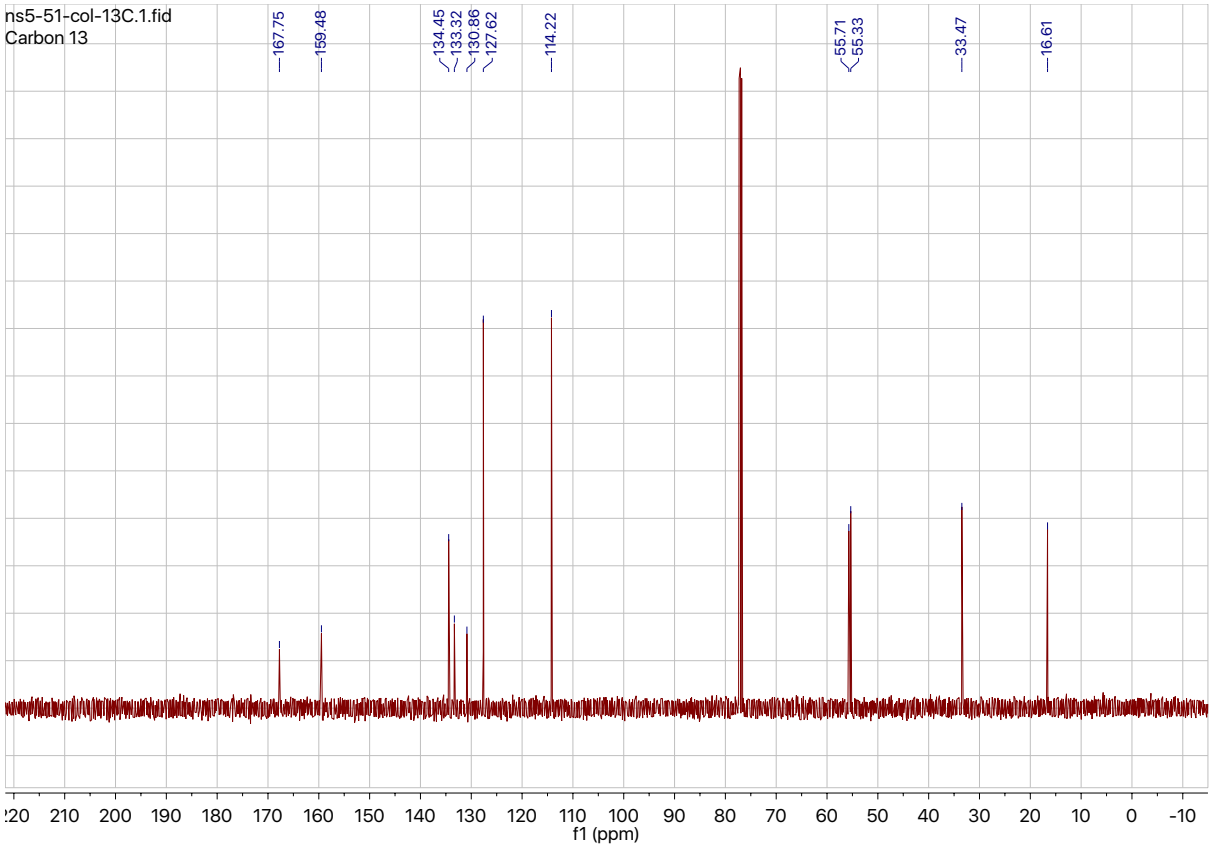

ns4-135-col-1H.1.fid
Proton
MeO
O
N
H
OPiv
2e
9.23
7.39
7.38
6.88
6.87
5.97
5.66
3.79
1.32
0.87
2.04
2.62
0.99
1.00
3.08
9.24
f1 (ppm)

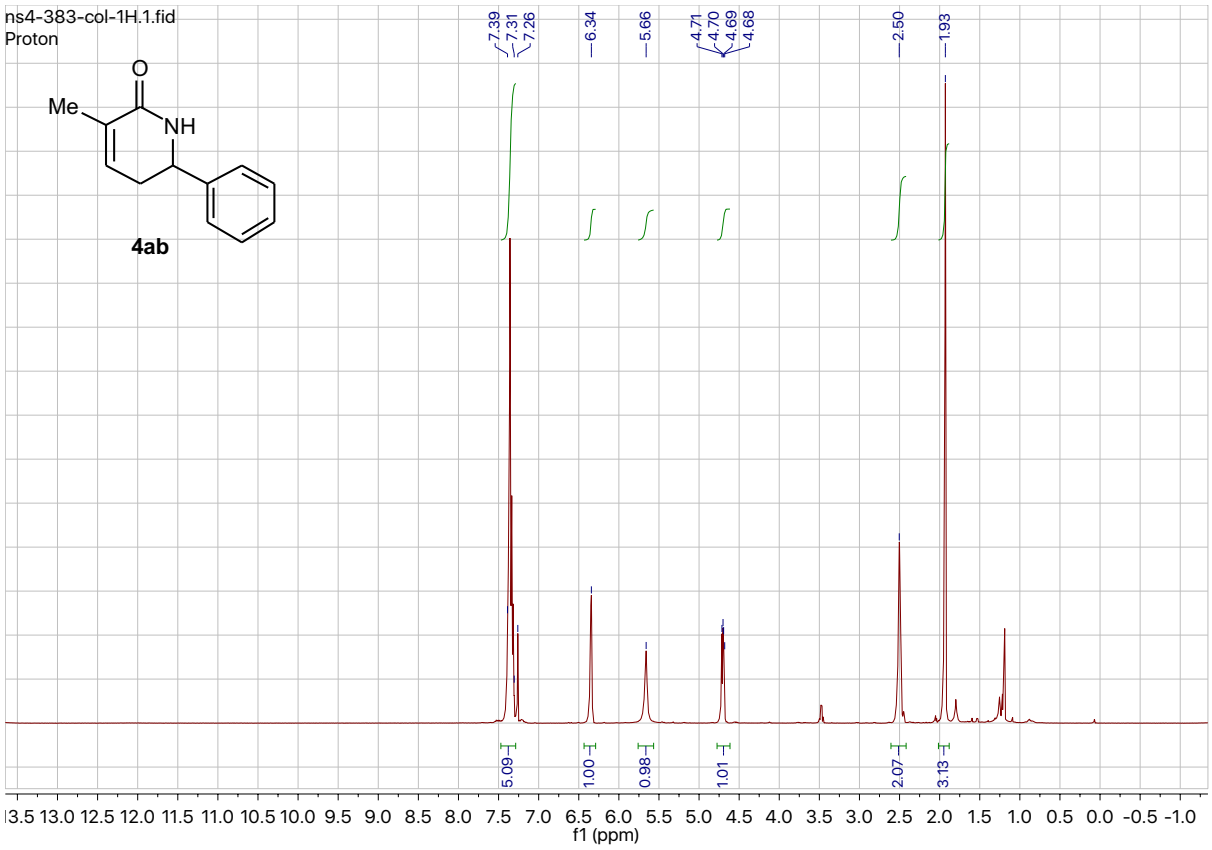

ns4-135-col-13C.1.fid
Carbon 13
176.60
166.48
160.04
141.04
129.00
127.96
121.19
114.11
55.29
38.34
26.99
f1 (ppm)

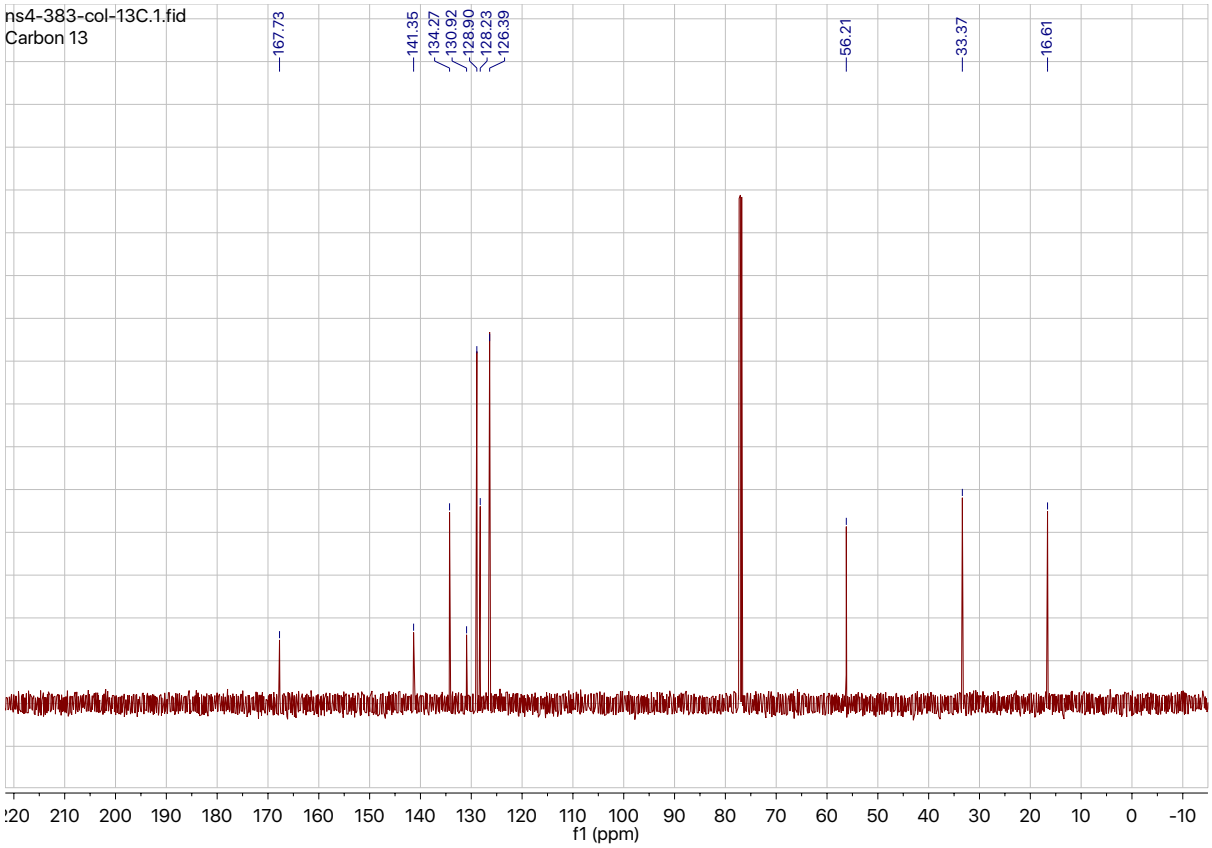

ns4-129-col-1H.1.fid
Proton
MeO2C
O
N
H
OPiv
2f
9.77
6.07
5.64
5.64
5.63
3.74
3.42
1.34
1.00
1.09
1.09
3.18
2.15
9.68
f1 (ppm)

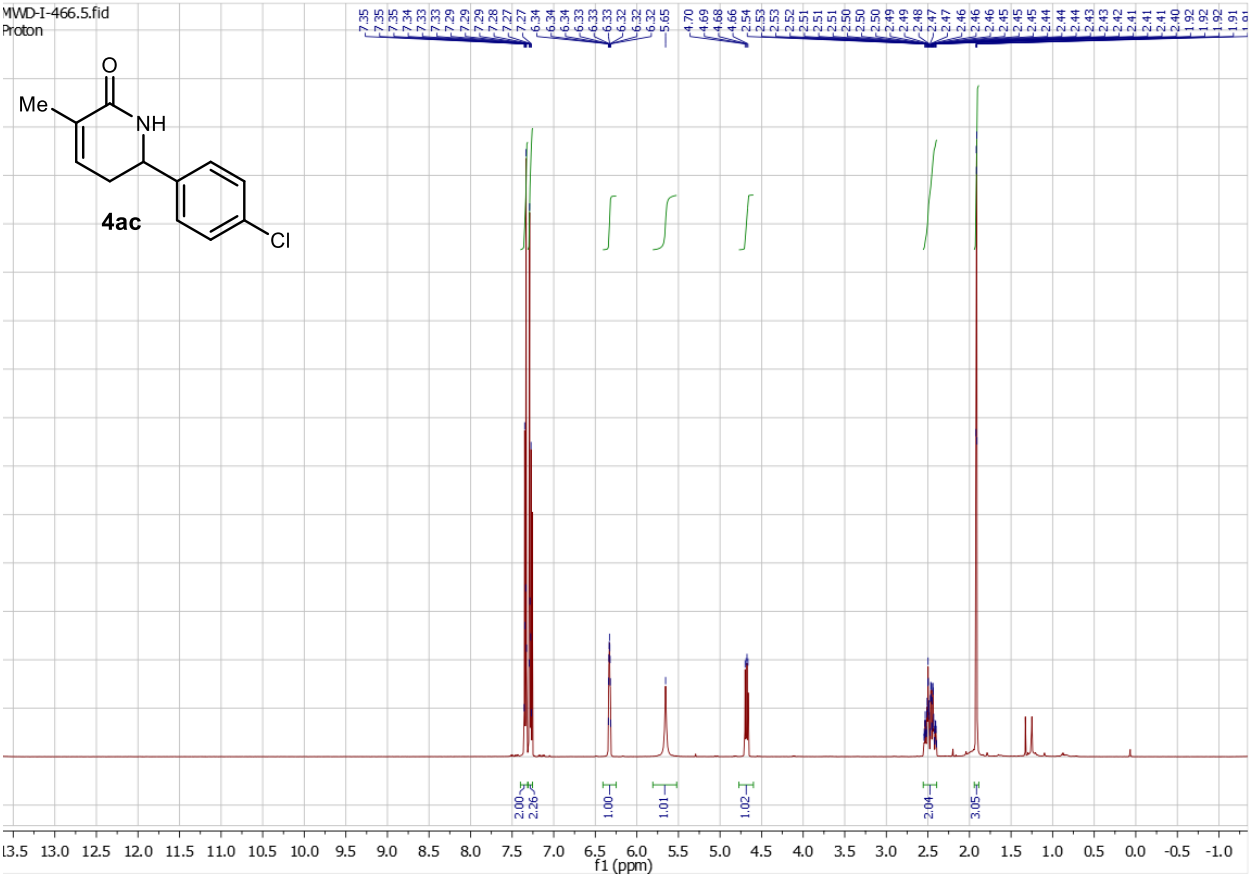

ns4-129-col-13C.1.fid
Carbon 13
176.49
171.40
166.39
134.56
125.32
52.48
38.39
37.77
27.02
f1 (ppm)

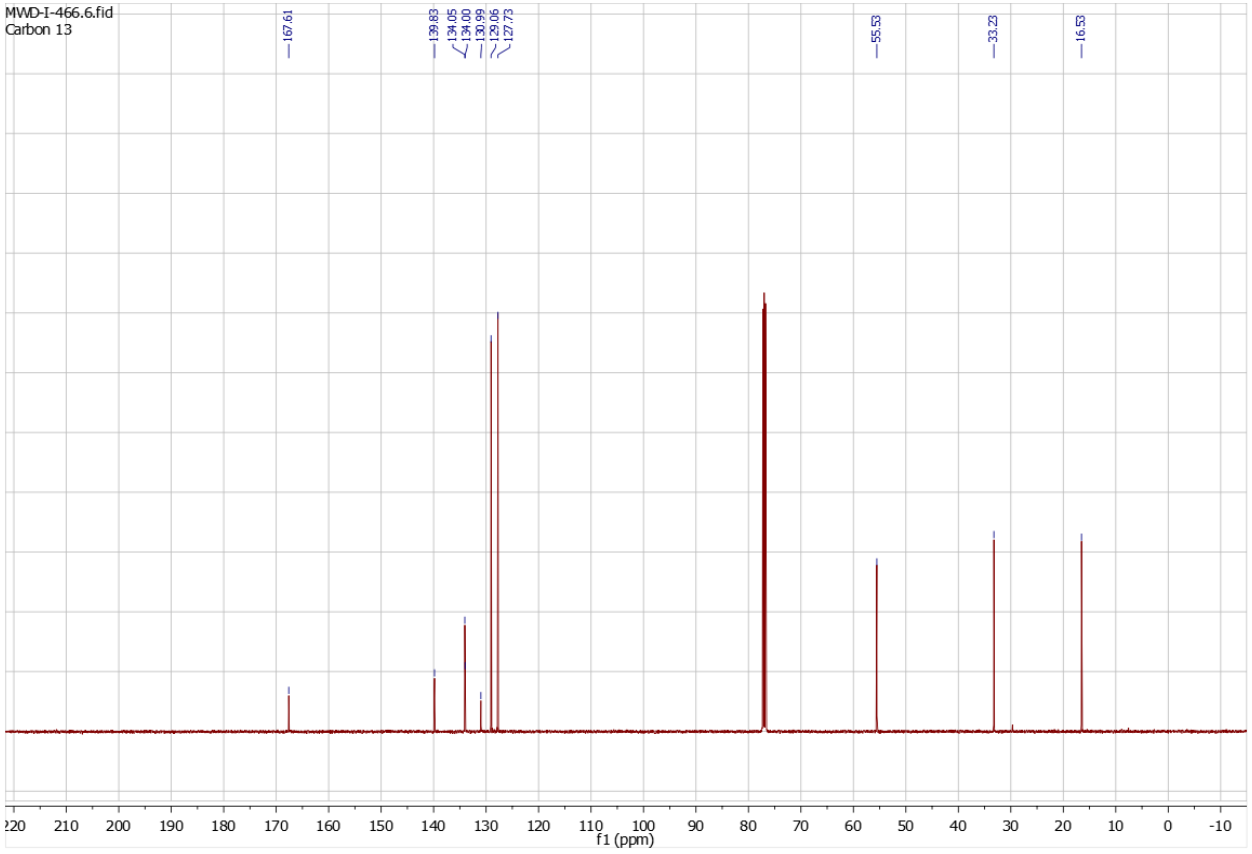

ns5-51-col-1H.1.fid
Proton
Me
O
NH
OMe
4aa
7.30
7.28
6.92
6.90
6.38
6.37
6.37
6.37
6.36
6.36
5.58
4.68
4.66
4.66
4.64
3.83
2.50
2.49
2.49
2.48
2.48
2.48
2.47
2.47
2.46
1.95
1.94
2.21
2.01
0.98
0.95
1.00
3.17
2.03
3.16
f1 (ppm)

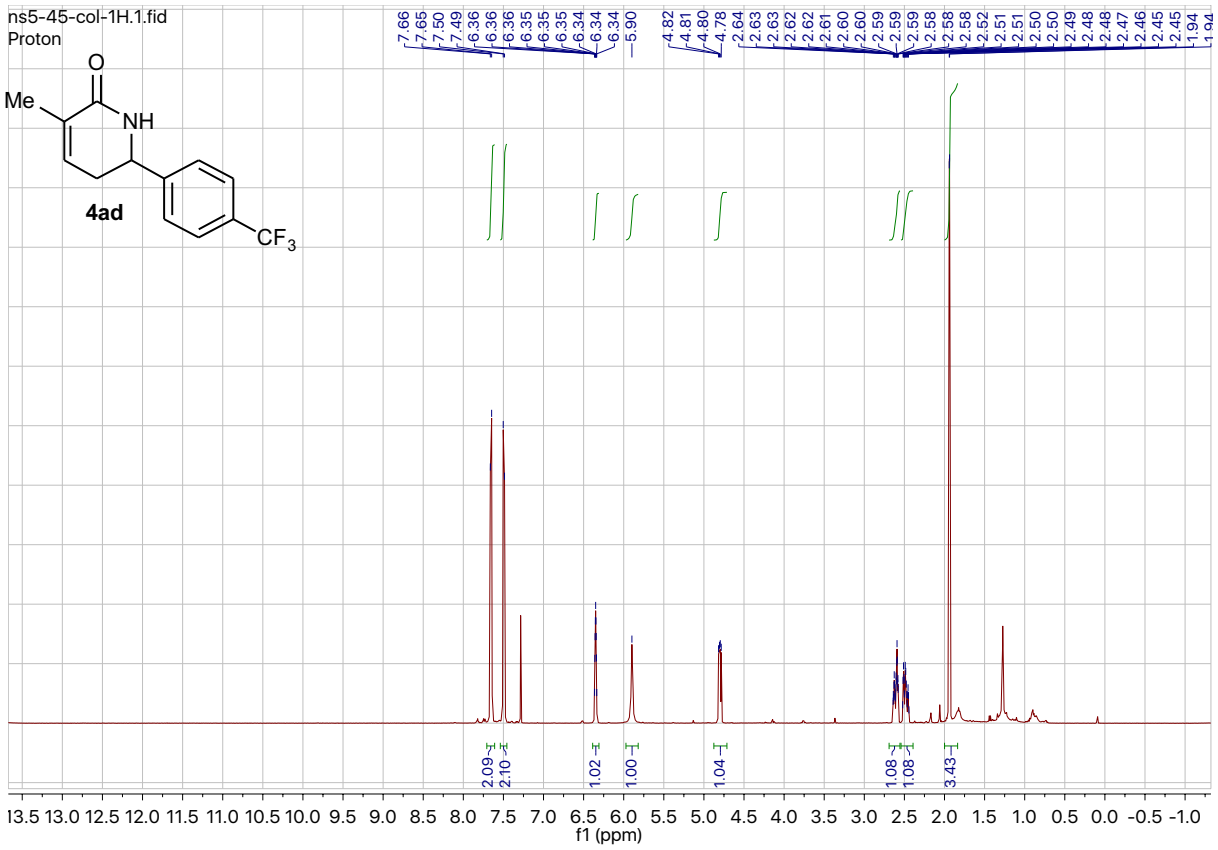

ns5-51-col-13C.1.fid
Carbon 13
167.75
159.48
134.45
133.32
130.86
127.62
114.22
55.71
55.33
33.47
16.61
f1 (ppm)

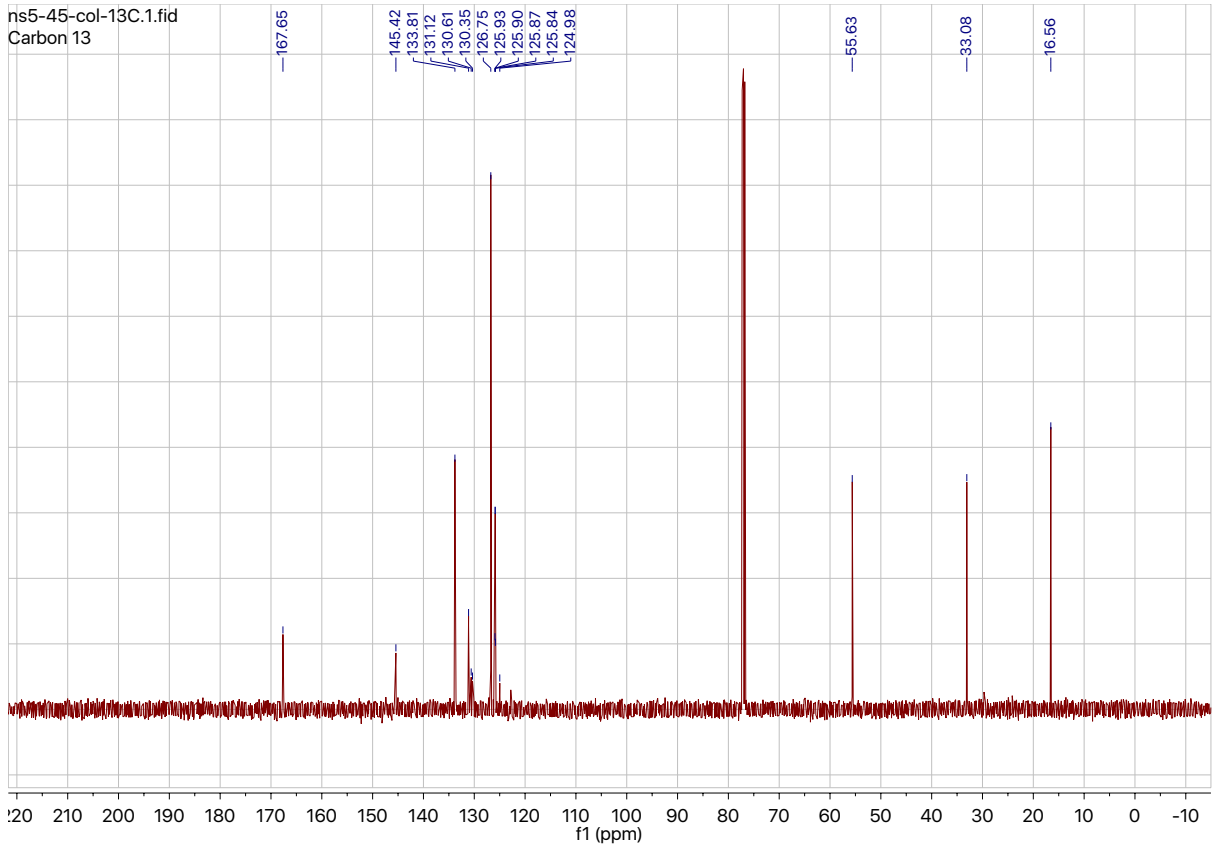

ns4-383-col-1H.1.fid
Proton
Me
O
NH
4ab
7.39
7.31
7.26
6.34
5.66
4.71
4.70
4.69
4.68
2.50
1.93
5.09
1.00
0.98
1.01
2.07
3.13
f1 (ppm)

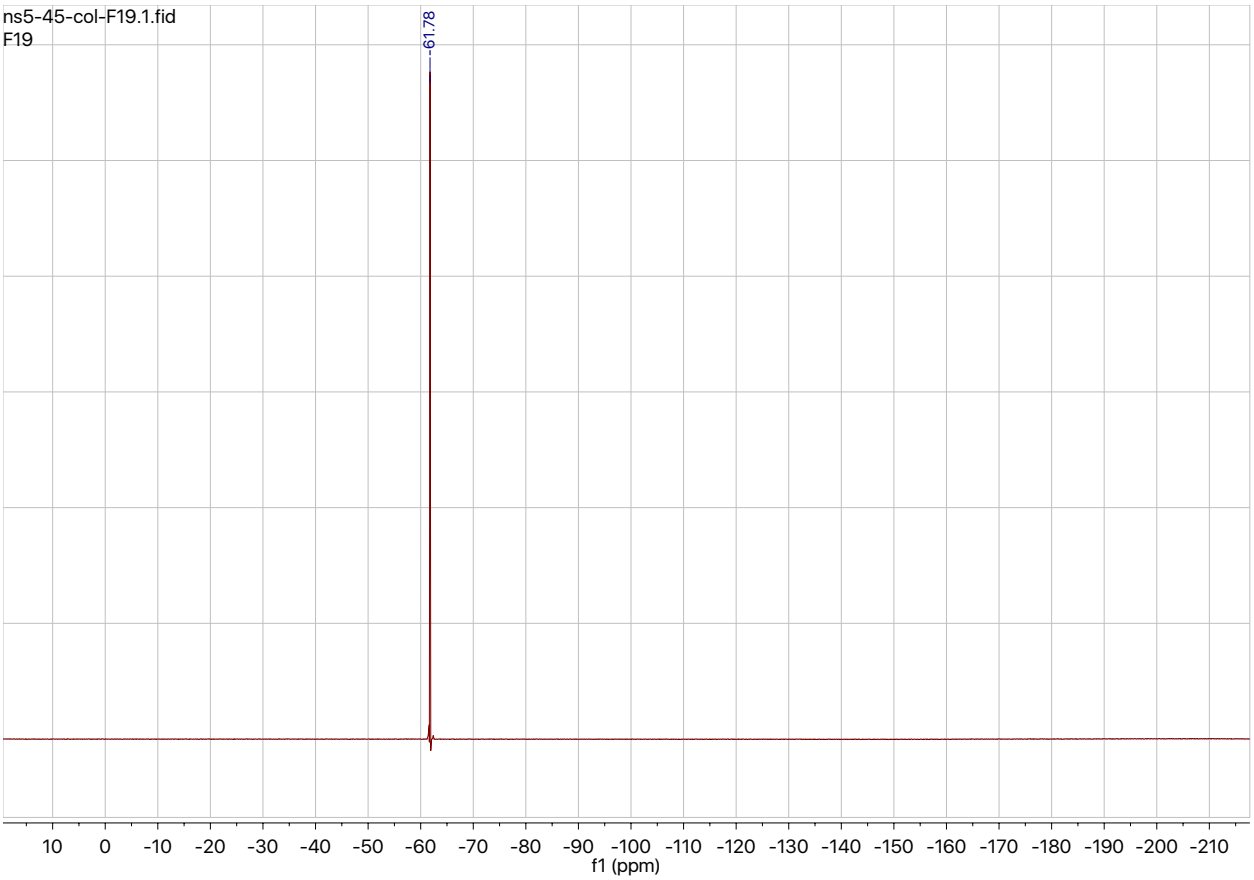

ns4-383-col-13C.1.fid
Carbon 13
167.73
141.35
134.27
130.92
128.90
128.23
126.39
56.21
33.37
16.61
f1 (ppm)

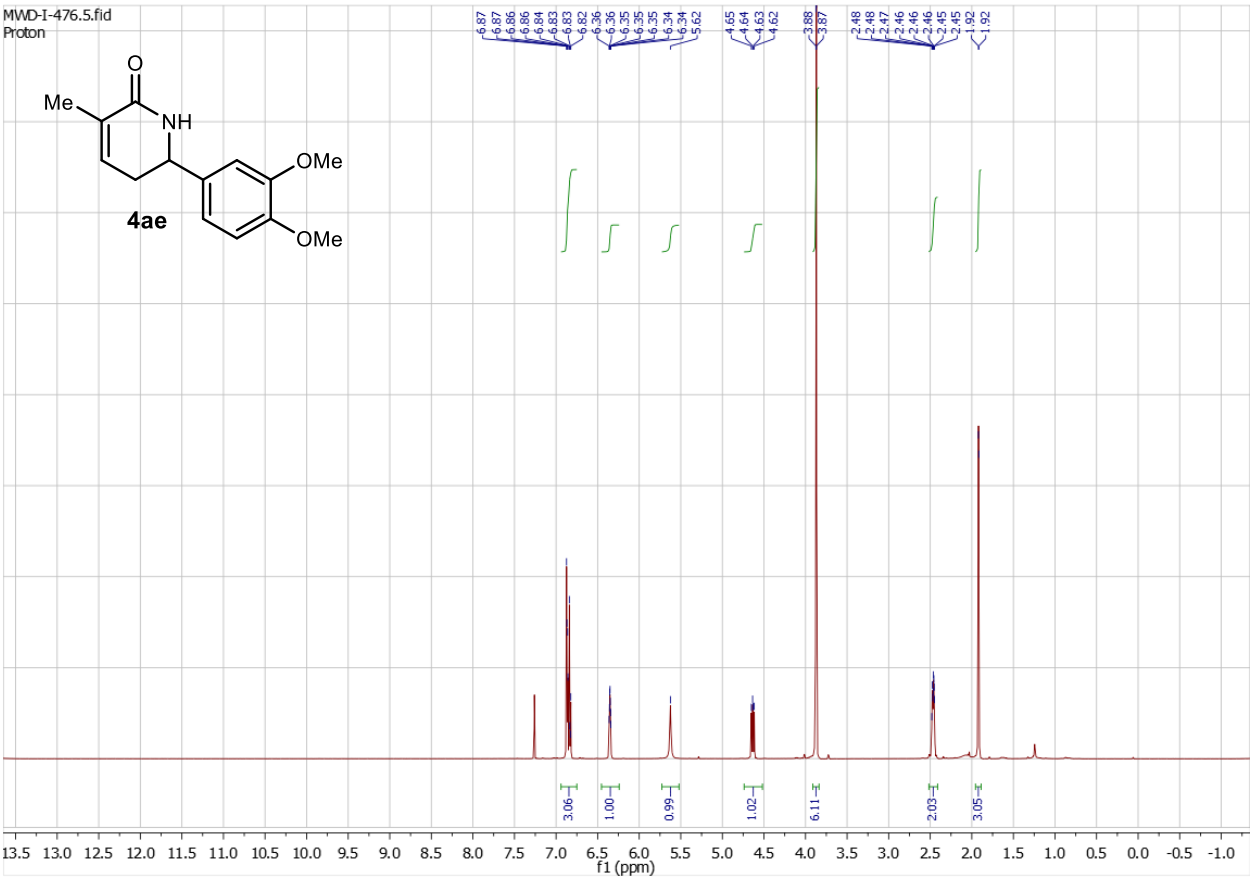

MWD-I-466.5.fid
Proton
Me
NH
O
Cl
4ac
f1 (ppm)

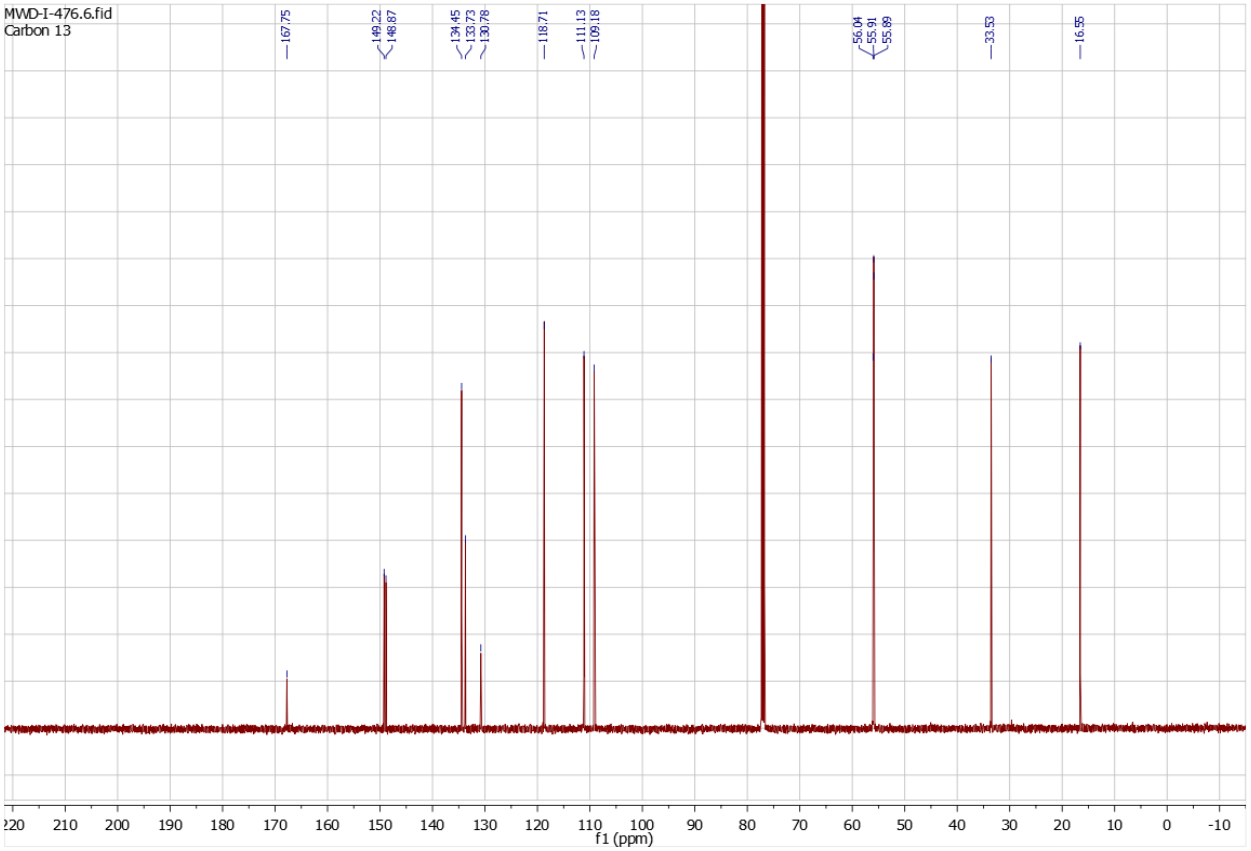

MWD-I-466.6.fid
Carbon 13
167.61
139.83
134.05
134.00
130.99
129.06
127.73
55.53
33.23
16.53
f1 (ppm)

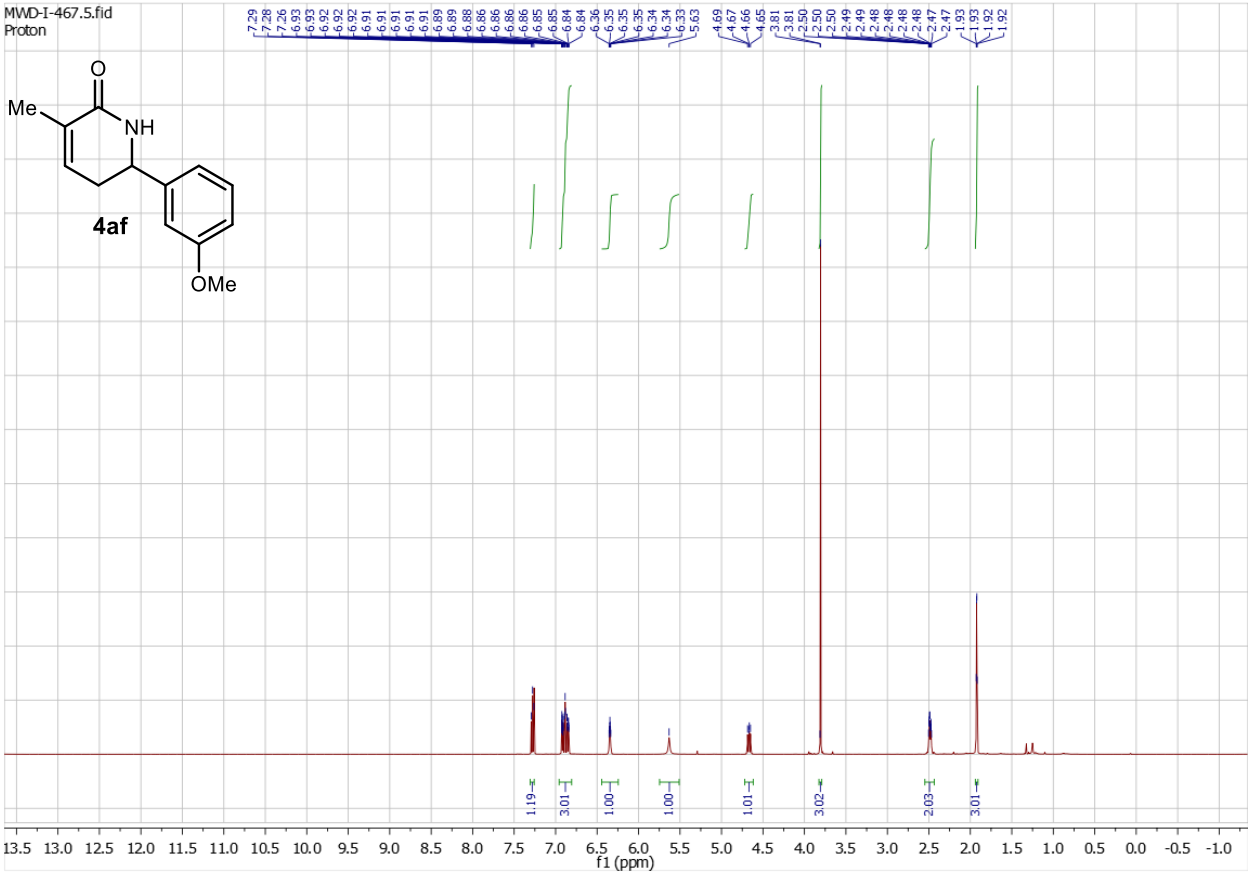

ns5-45-col-1H.1.fid
Proton
Me
NH
O
4ad
CF3
f1 (ppm)

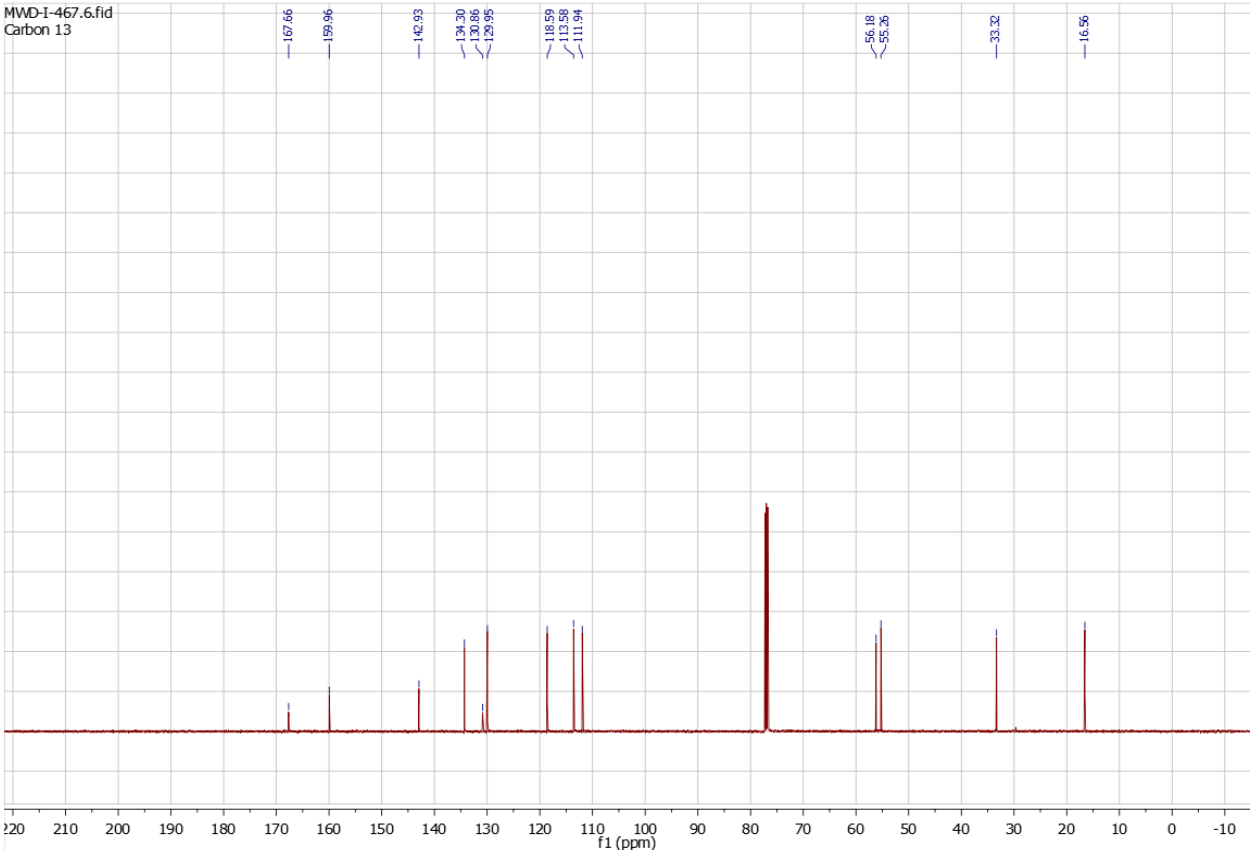

ns5-45-col-13C.1.fid
Carbon 13
f1 (ppm)

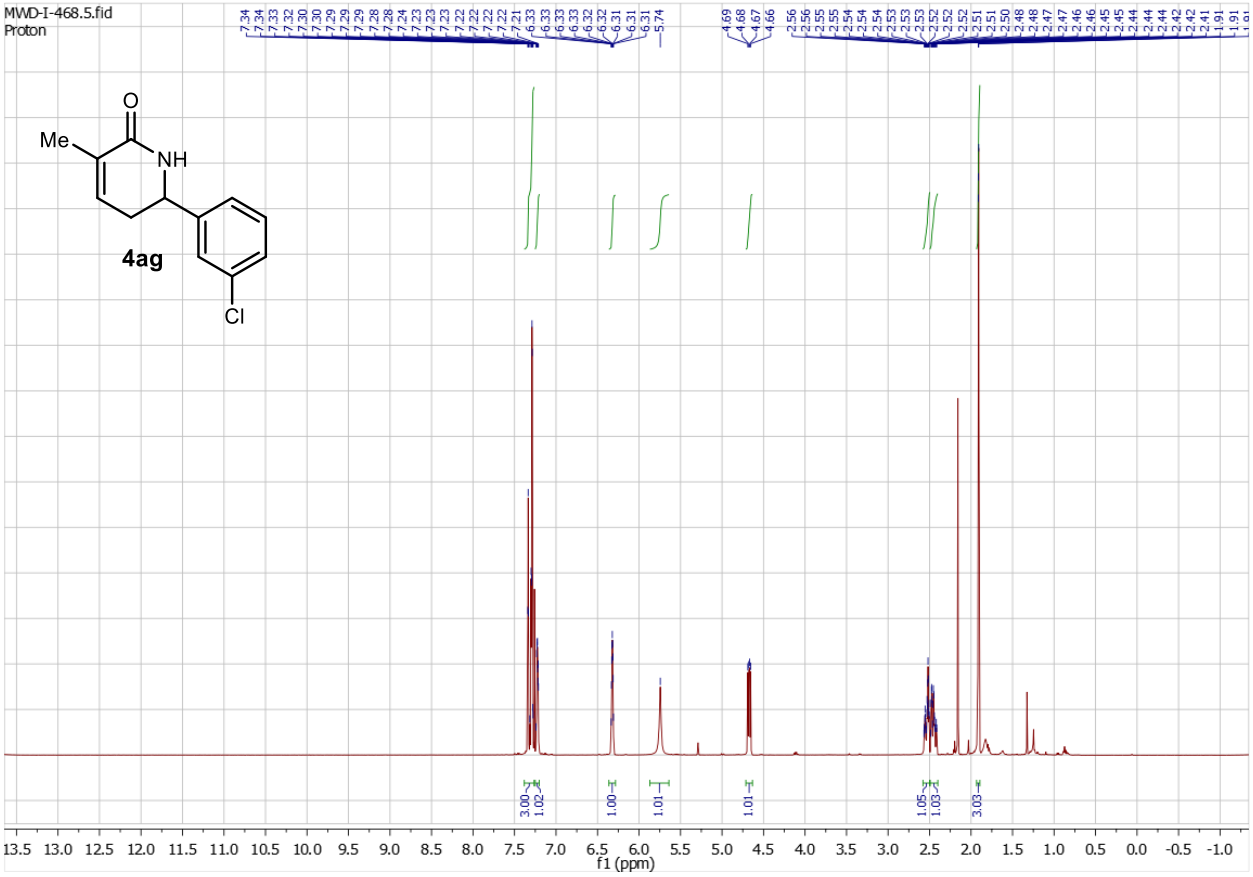

ns5-45-col-F19.1.fid
F19
-61.78
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

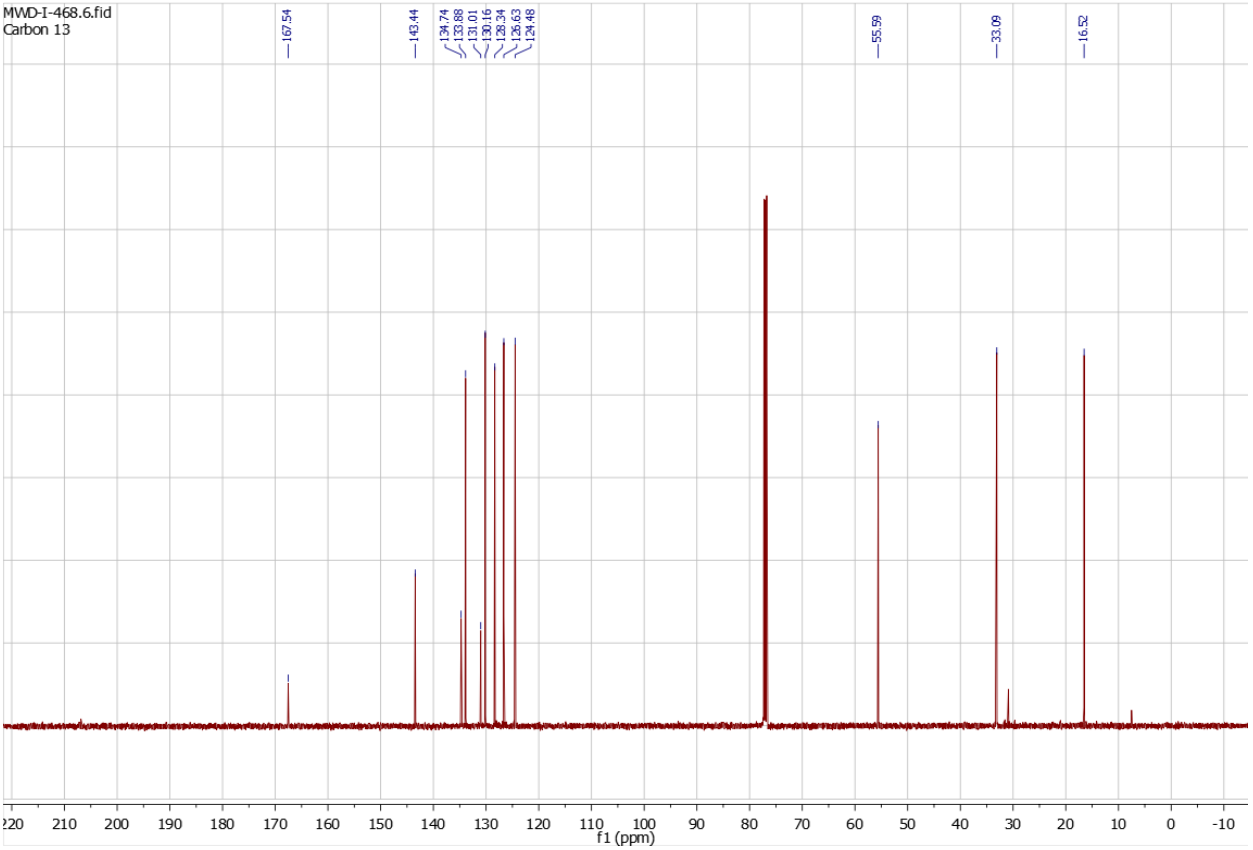

MWD-I-476.5.fid
Proton
Me
NH
OMe
OMe
4ae
6.87
6.87
6.86
6.86
6.84
6.83
6.83
6.82
5.36
5.35
5.35
5.35
5.34
5.34
5.62
4.65
4.64
4.63
4.62
3.88
3.87
2.48
2.48
2.47
2.46
2.46
2.46
2.45
2.45
1.92
1.92
3.06
1.00
0.99
1.02
6.11
2.03
3.05
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

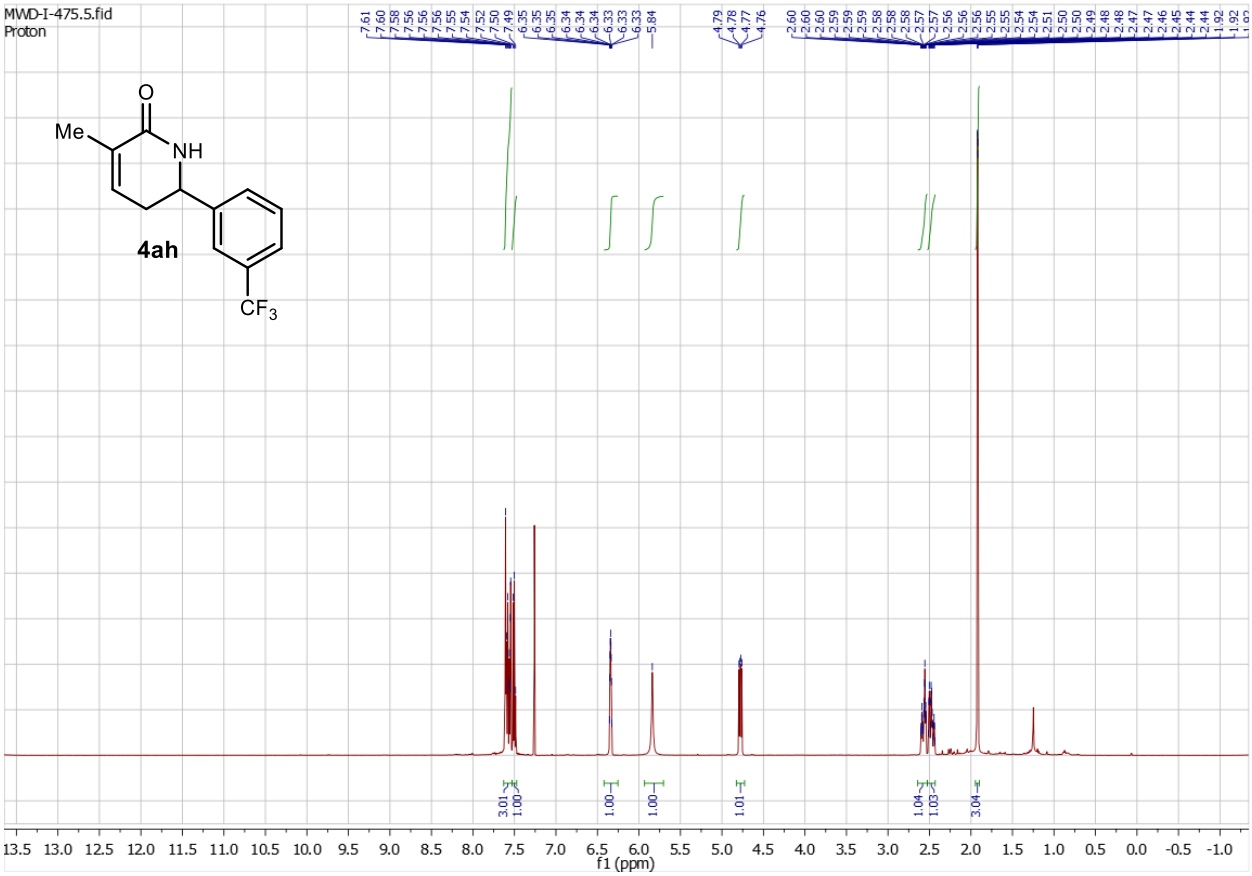

MWD-I-476.6.fid
Carbon 13
167.75
149.22
148.87
134.45
133.73
130.78
118.71
111.13
109.18
56.04
55.91
55.89
33.53
16.55
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

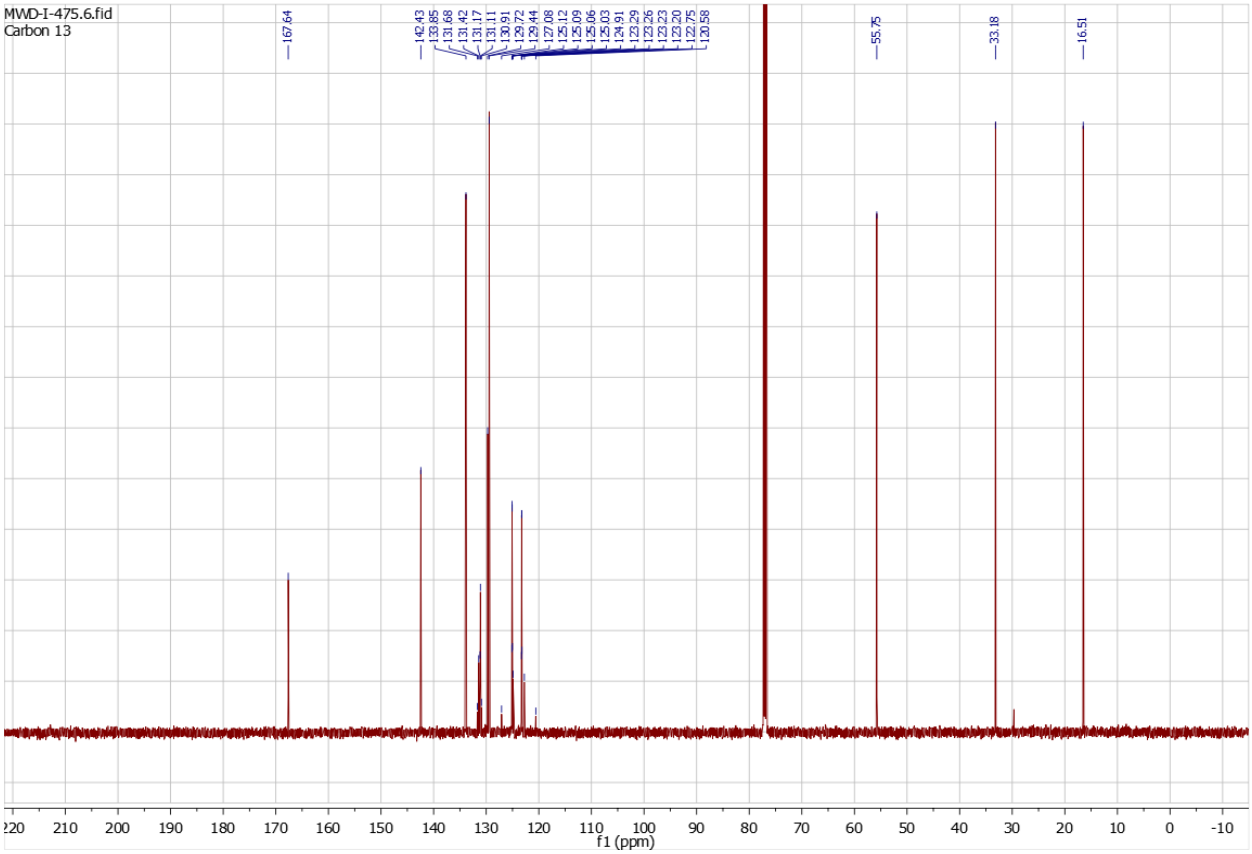

MWD-I-467.5.fid
Proton
Me
NH
O
4af
OMe
f1 (ppm)

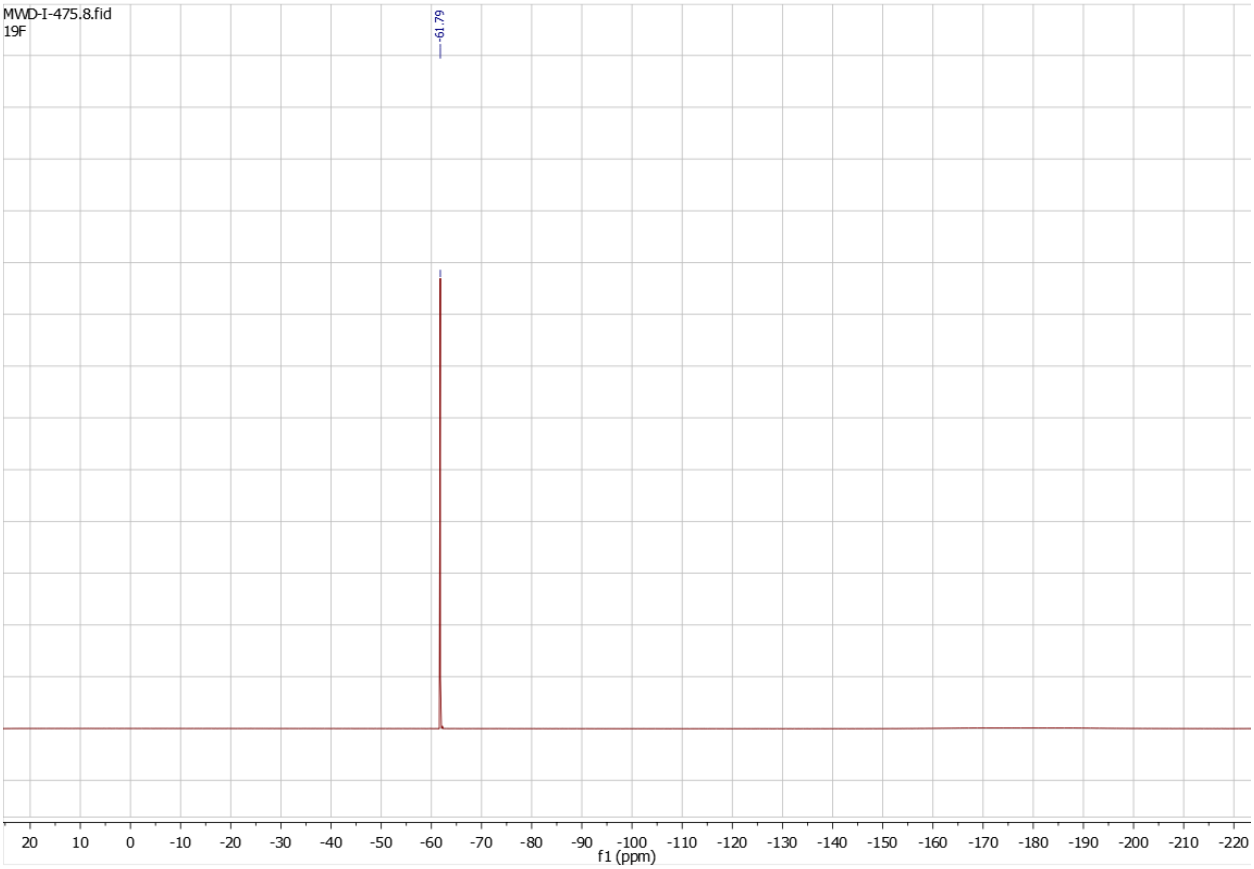

MWD-I-467.6.fid
Carbon 13
f1 (ppm)

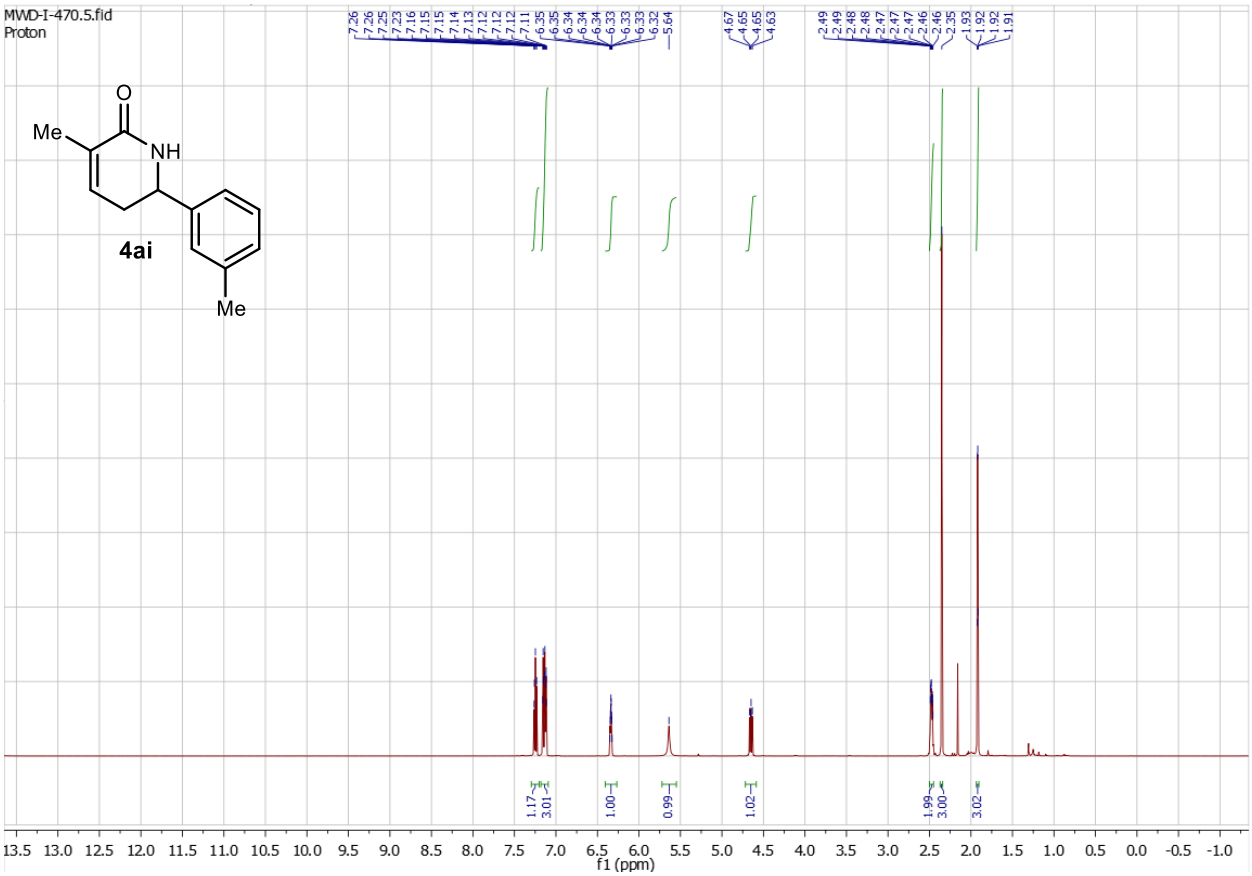

MWD-I-468.5.fid
Proton
Me
NH
O
Cl
4ag
f1 (ppm)

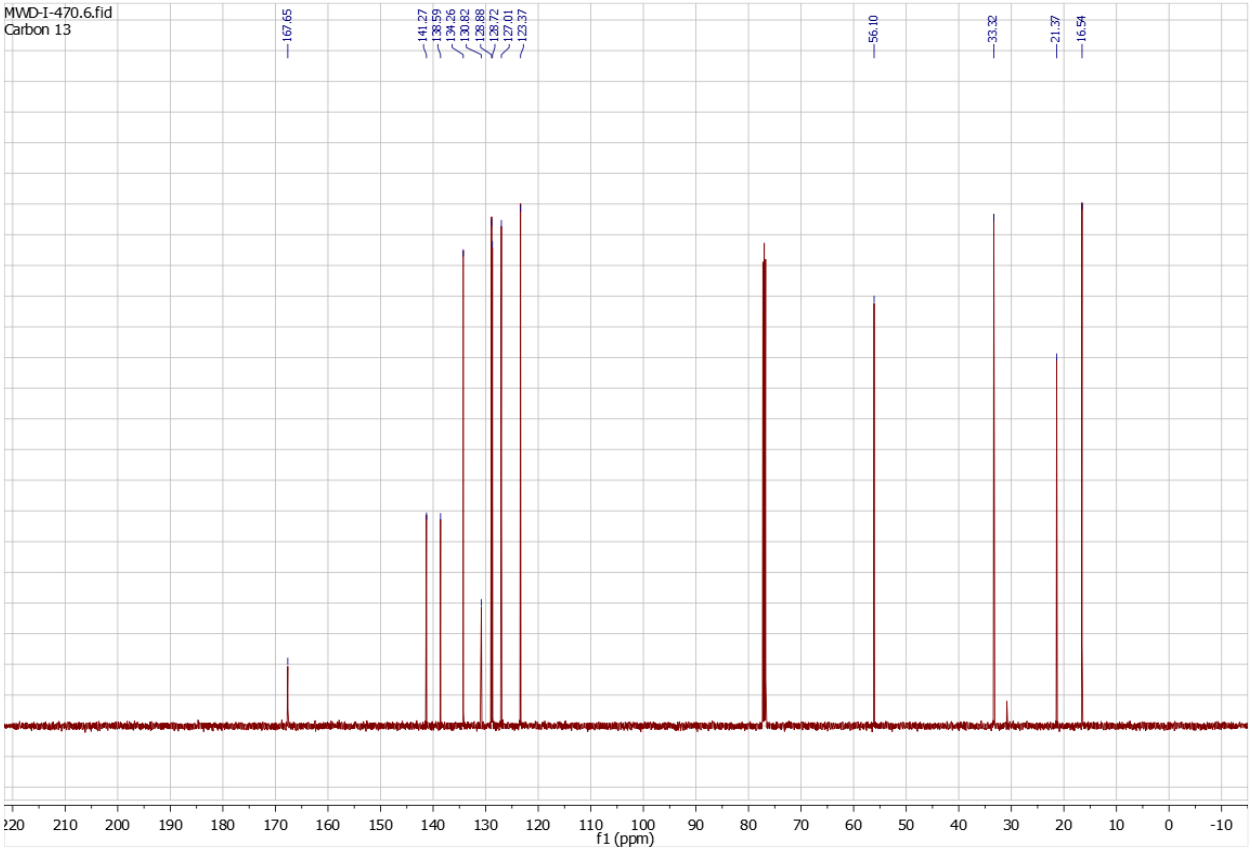

MWD-I-468.6.fid
Carbon 13
167.54
143.44
134.74
133.88
131.01
130.16
128.34
126.63
124.48
55.59
33.09
16.52
f1 (ppm)

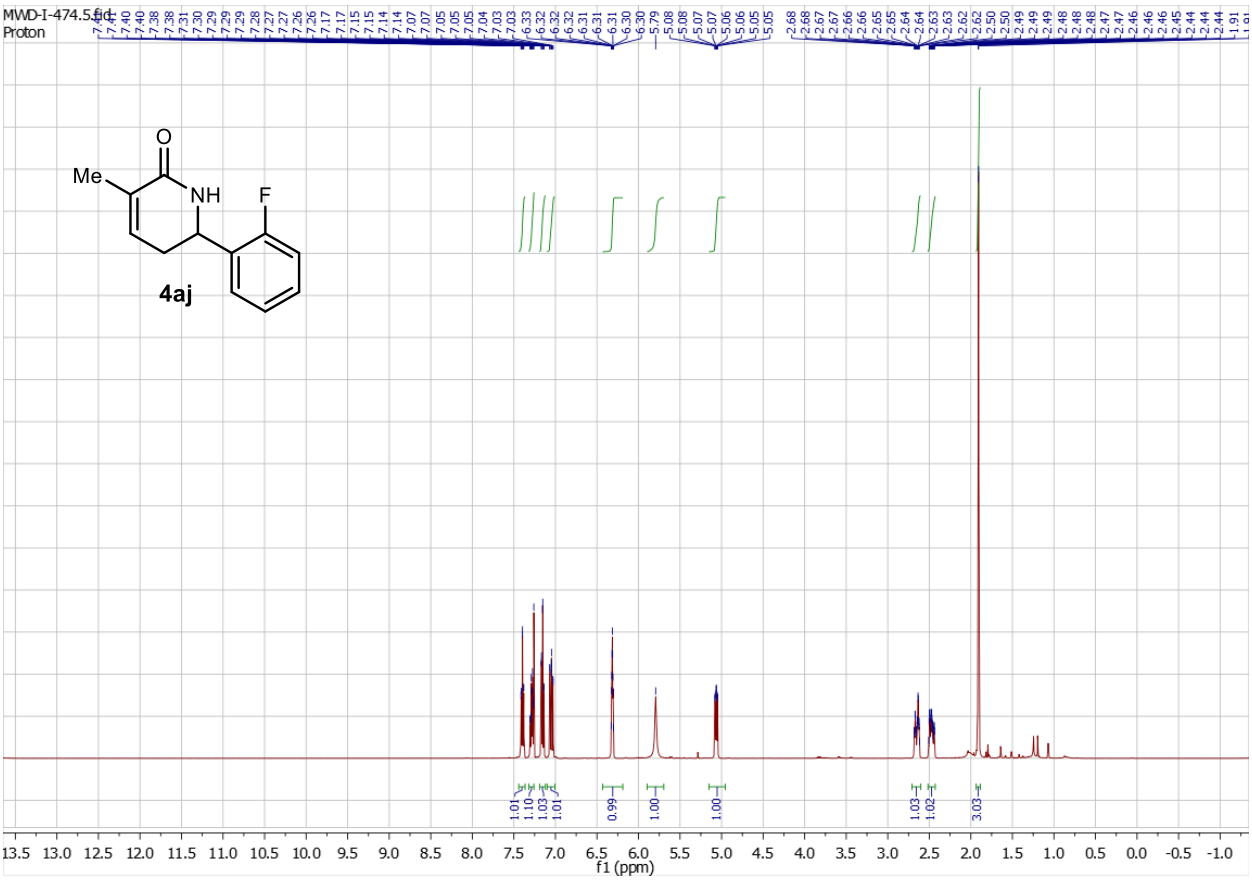

MWD-I-475.5.fid
Proton
Me
NH
O
4ah
CF3
f1 (ppm)


MWD-I-475.6.fid
Carbon 13
f1 (ppm)


MWD-I-475.8.fid
19F
-61.79
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


MWD-I-470.5.fid
Proton
O
Me
NH
4ai
Me
f1 (ppm)


MWD-I-470.6.fid
Carbon 13
167.65
141.27
138.59
134.26
130.82
128.88
128.72
127.01
123.37
56.10
33.32
21.37
16.54
f1 (ppm)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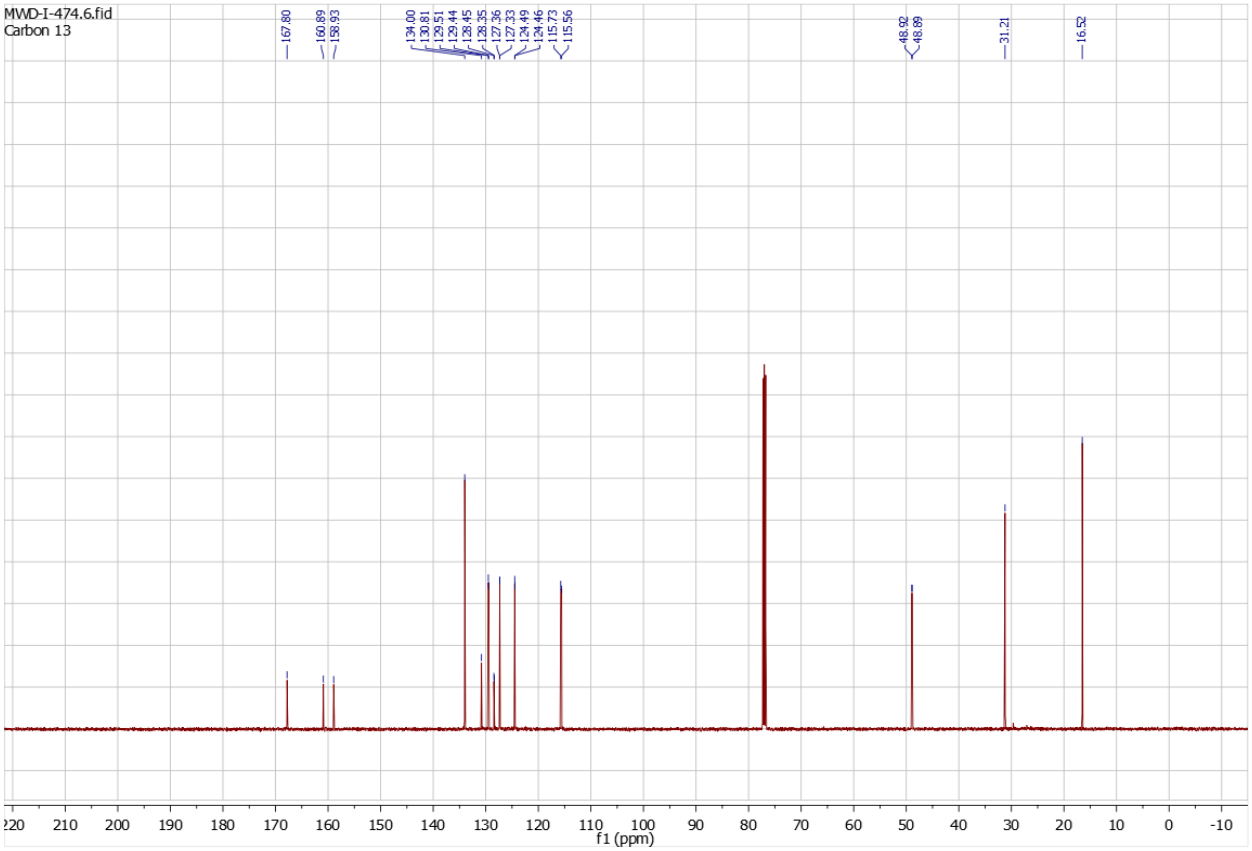
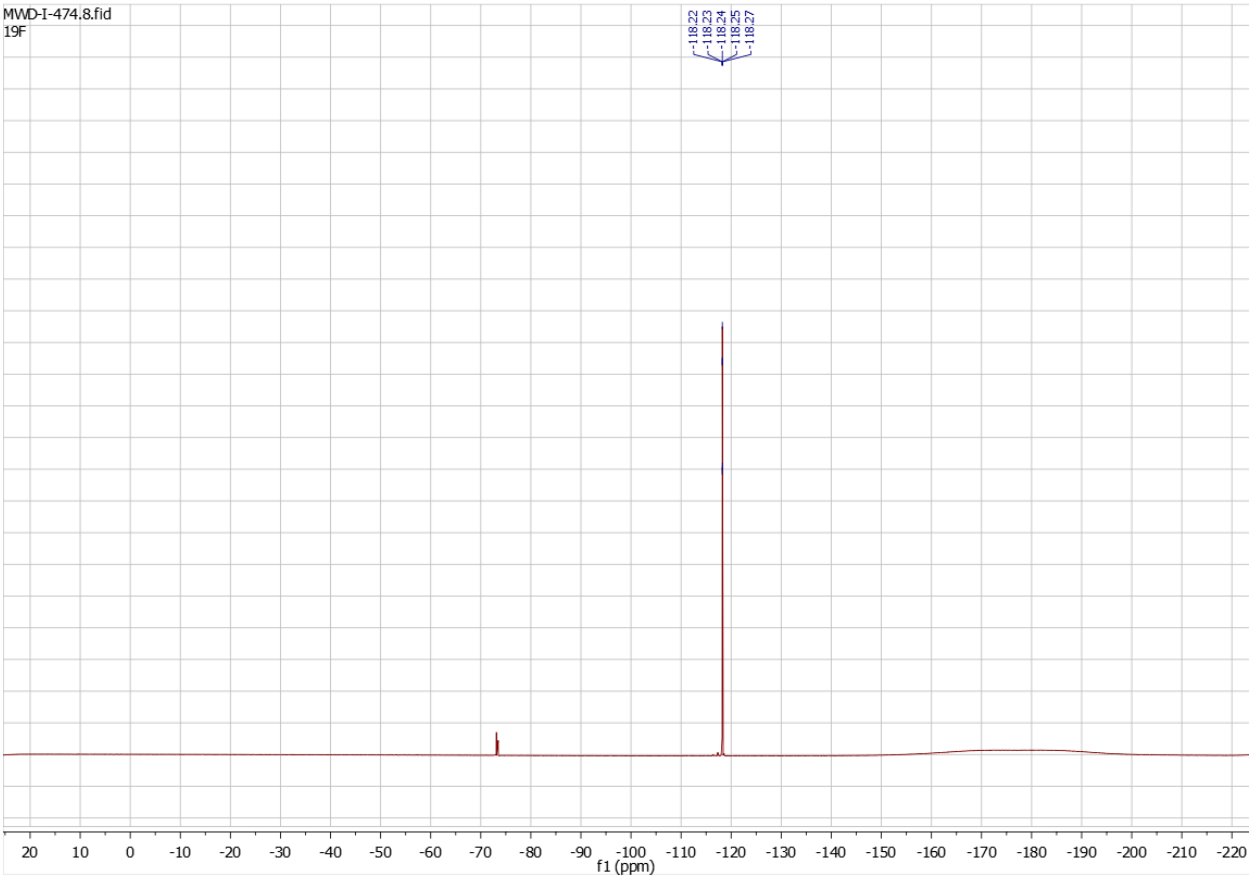
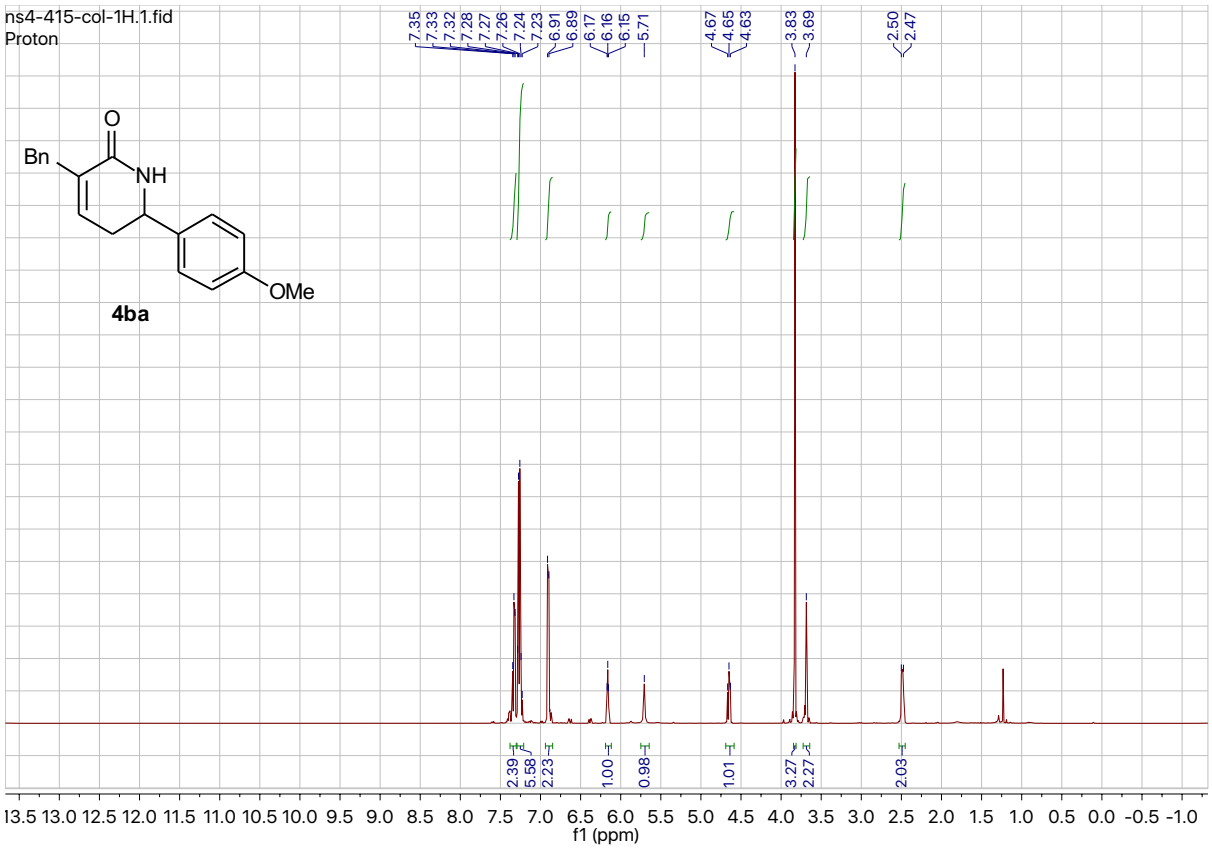
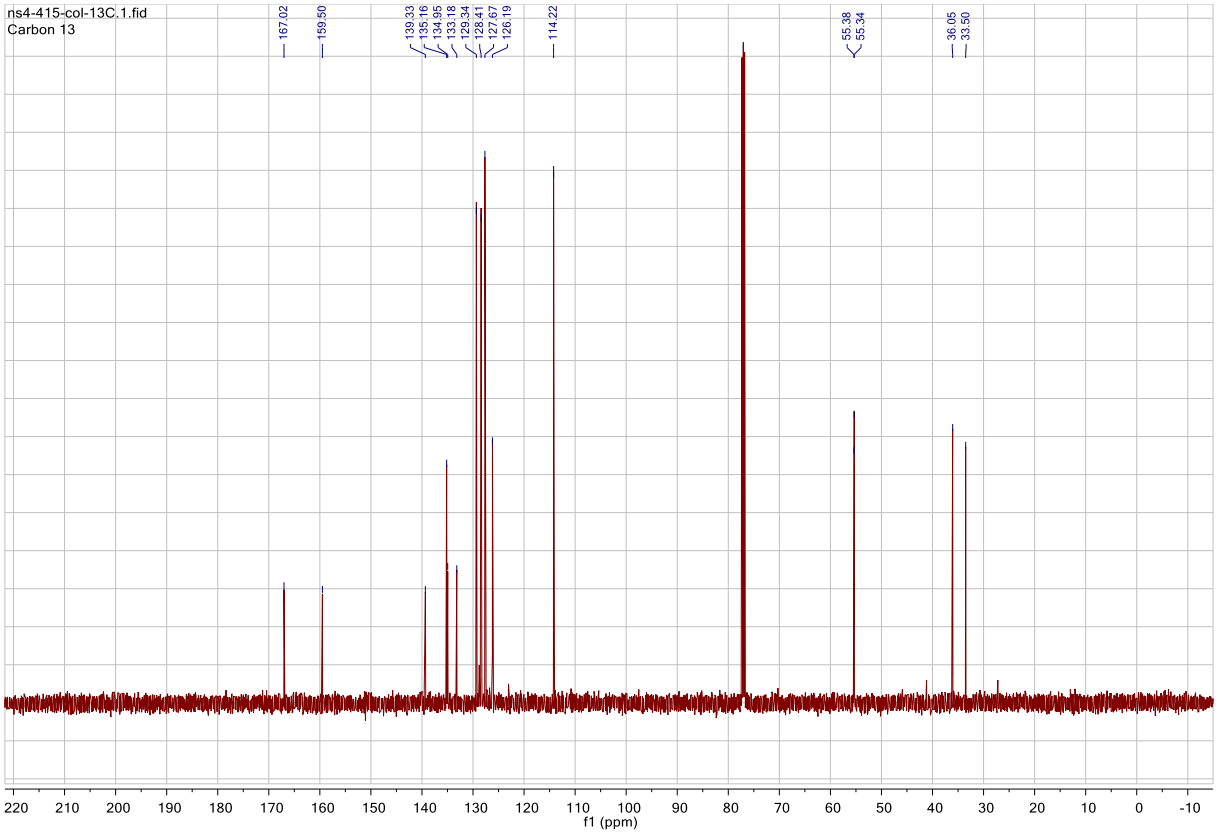
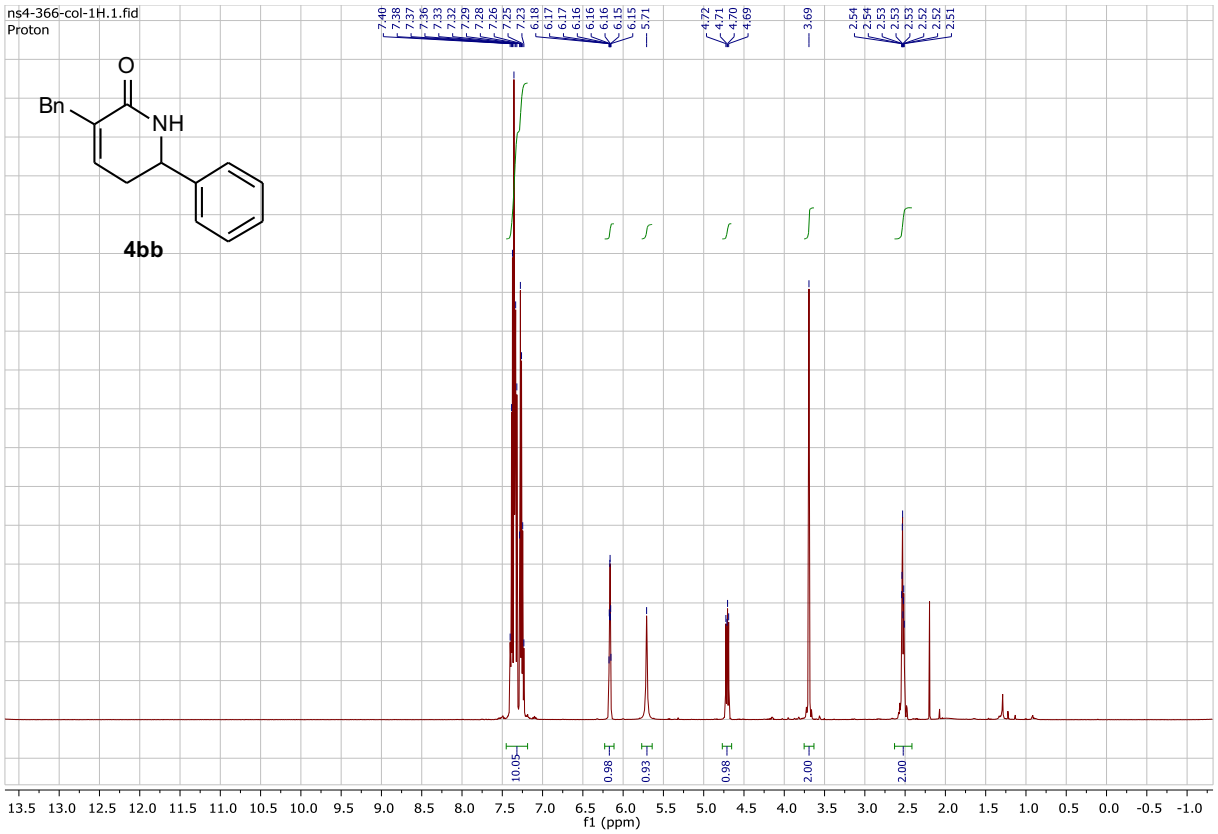
Proton
O
Me
NH
F
4aj
f1 (ppm)

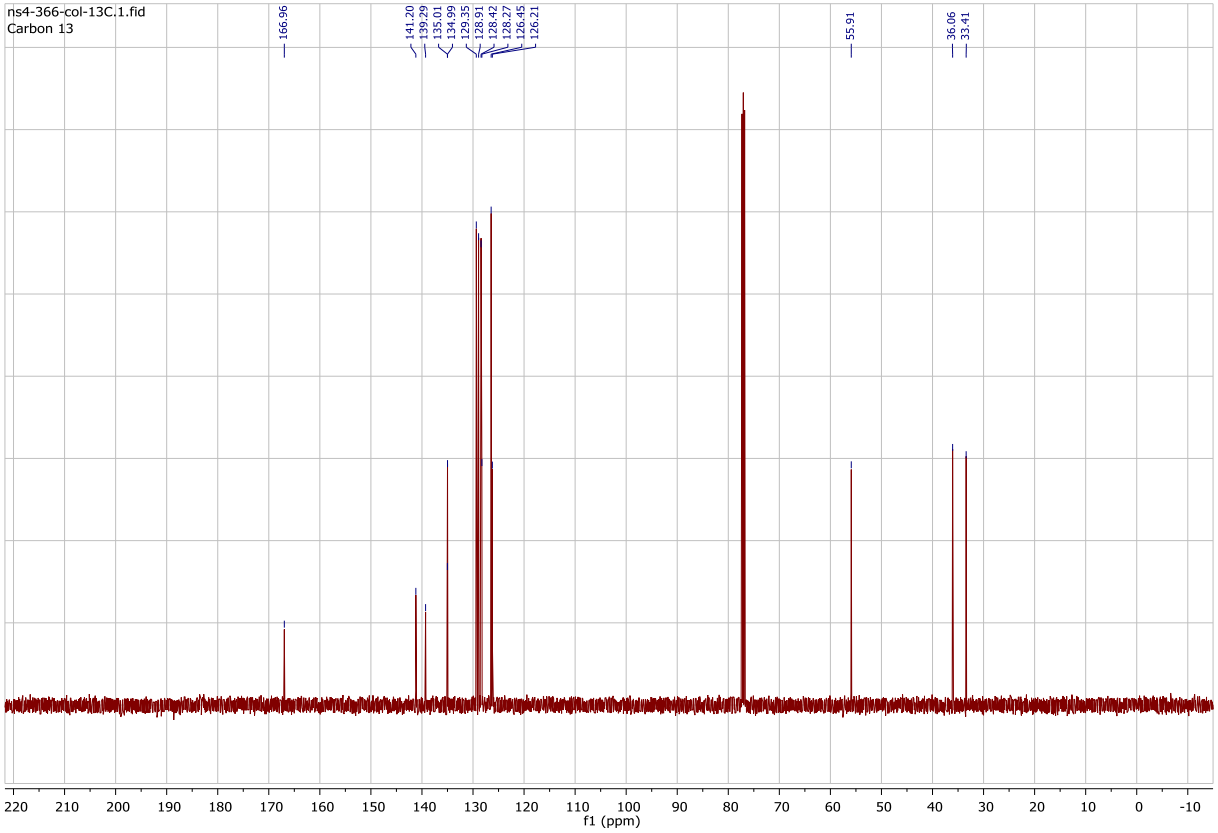

MWD-I-474.6.fid
Carbon 13
f1 (ppm)

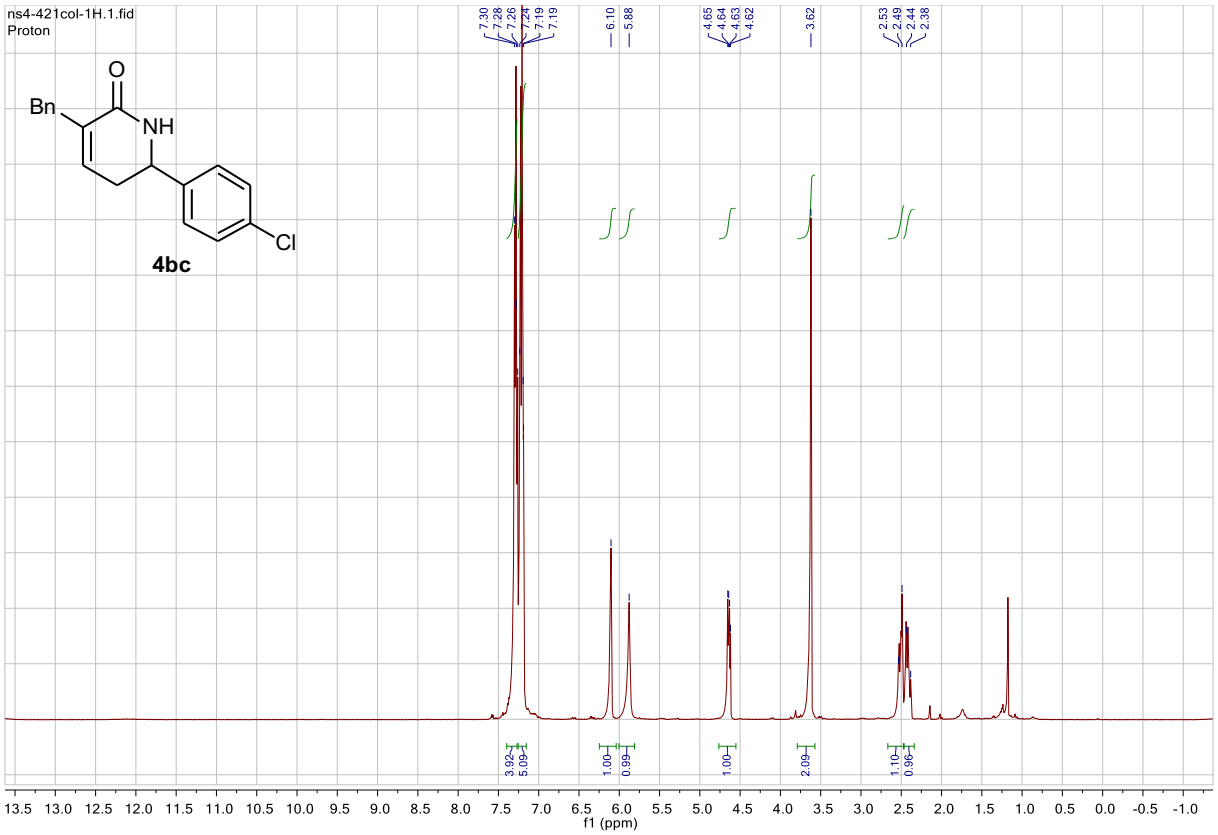

MWD-I-474.8.fid
19F
-118.22
-118.23
-118.24
-118.25
-118.27
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

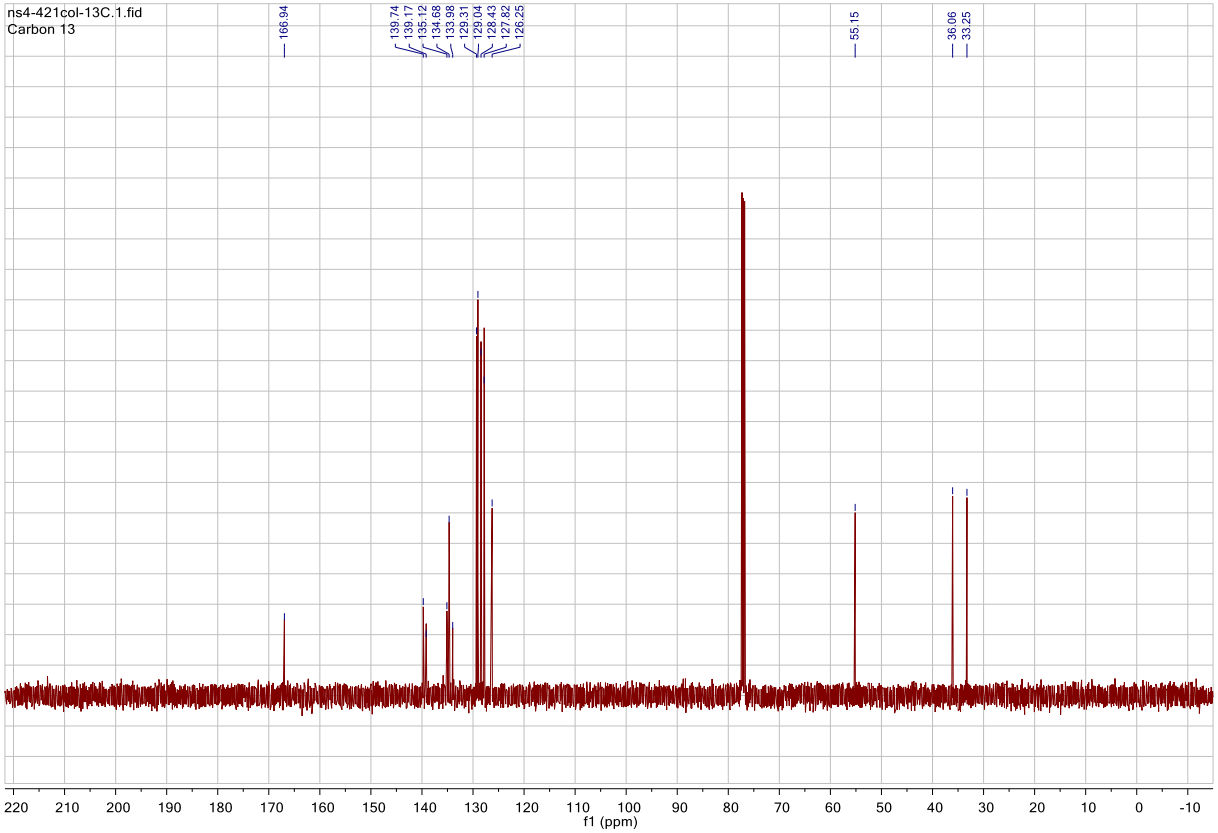

ns4-415-col-1H.1.fid
Proton
7.35
7.33
7.32
7.28
7.27
7.26
7.24
7.23
6.91
6.89
6.17
6.16
6.15
5.71
4.67
4.65
4.63
3.83
3.69
2.50
2.47
O
Bn
NH
OMe
4ba
2.39
5.58
2.23
1.00
0.98
1.01
3.27
2.27
2.03
f1 (ppm)

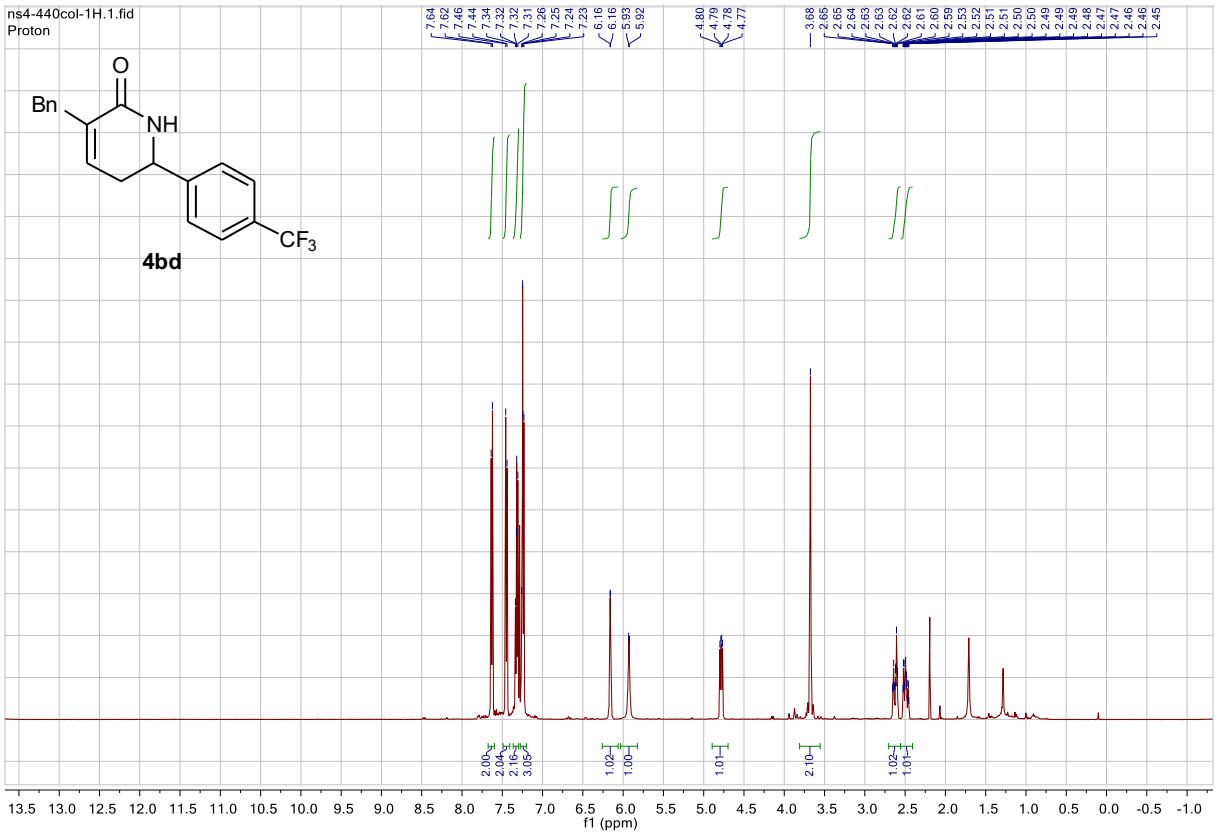

ns4-415-col-13C.1.fid
Carbon 13
167.02
159.50
139.33
135.16
134.95
133.18
129.34
128.41
127.67
126.19
114.22
55.38
55.34
36.05
33.50
f1 (ppm)

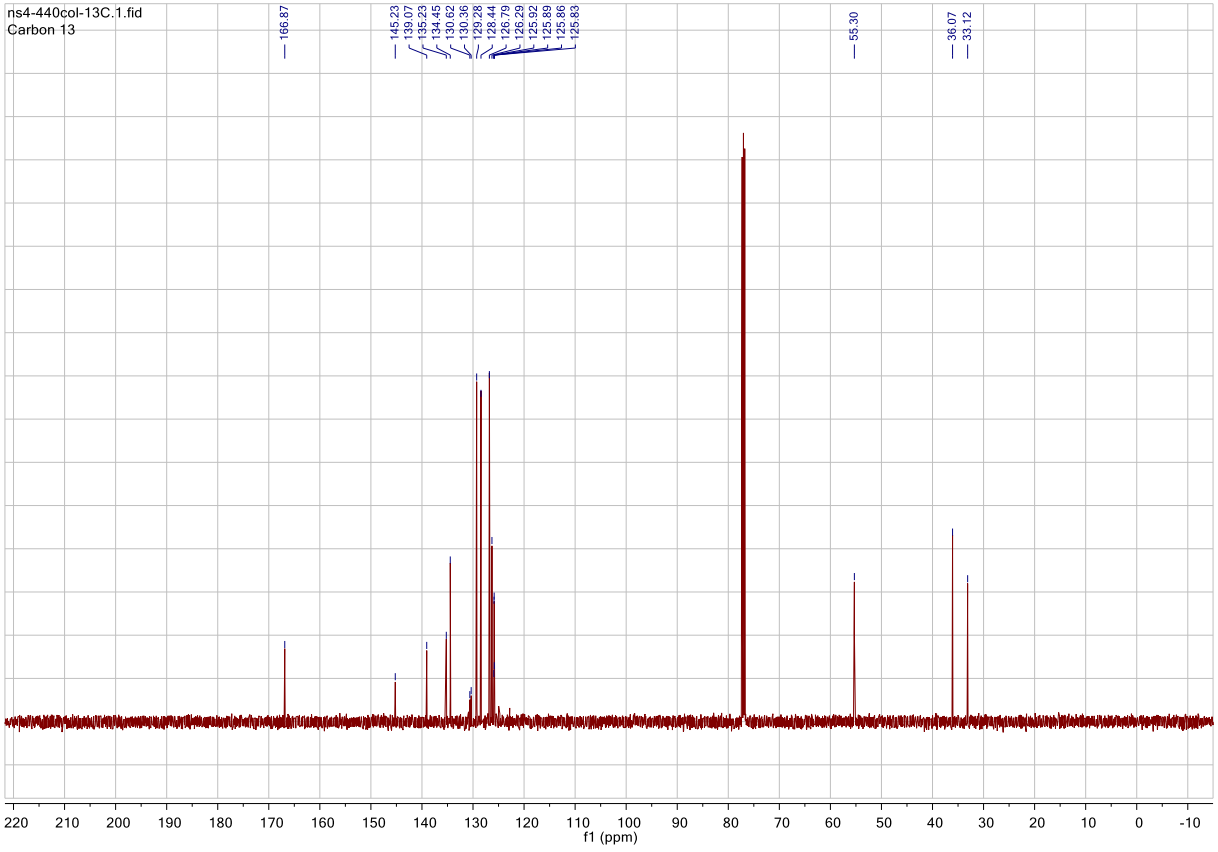

ns4-366-col-1H.1.fid
Proton
Bn
O
NH
4bb
7.40
7.38
7.37
7.36
7.33
7.32
7.29
7.28
7.26
7.25
7.23
6.18
6.17
6.17
6.16
6.16
6.16
6.15
6.15
5.71
4.72
4.71
4.70
4.69
3.69
2.54
2.54
2.53
2.53
2.53
2.52
2.52
2.51
10.05
0.98
0.93
0.98
2.00
2.00
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

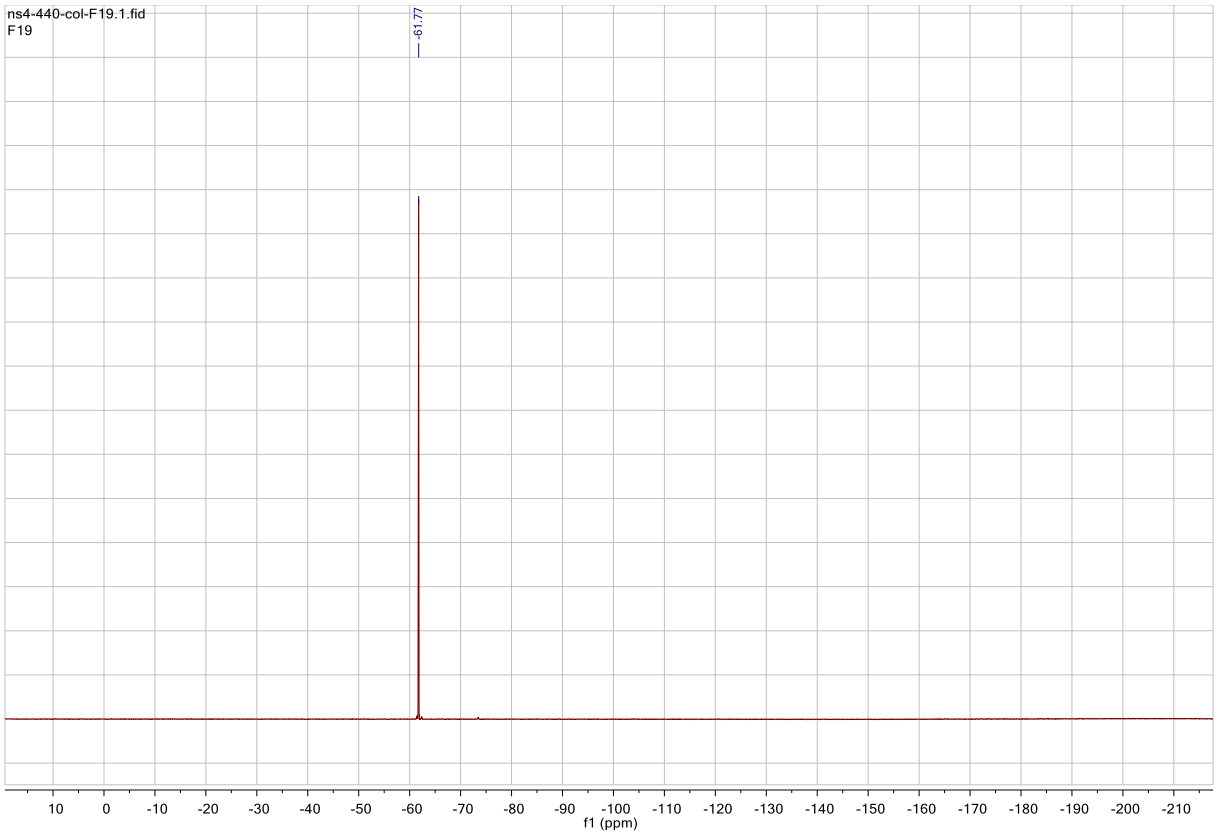

ns4-366-col-13C.1.fid
Carbon 13
166.96
141.20
139.29
135.01
134.99
129.35
128.91
128.42
128.27
126.45
126.21
55.91
36.06
33.41
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

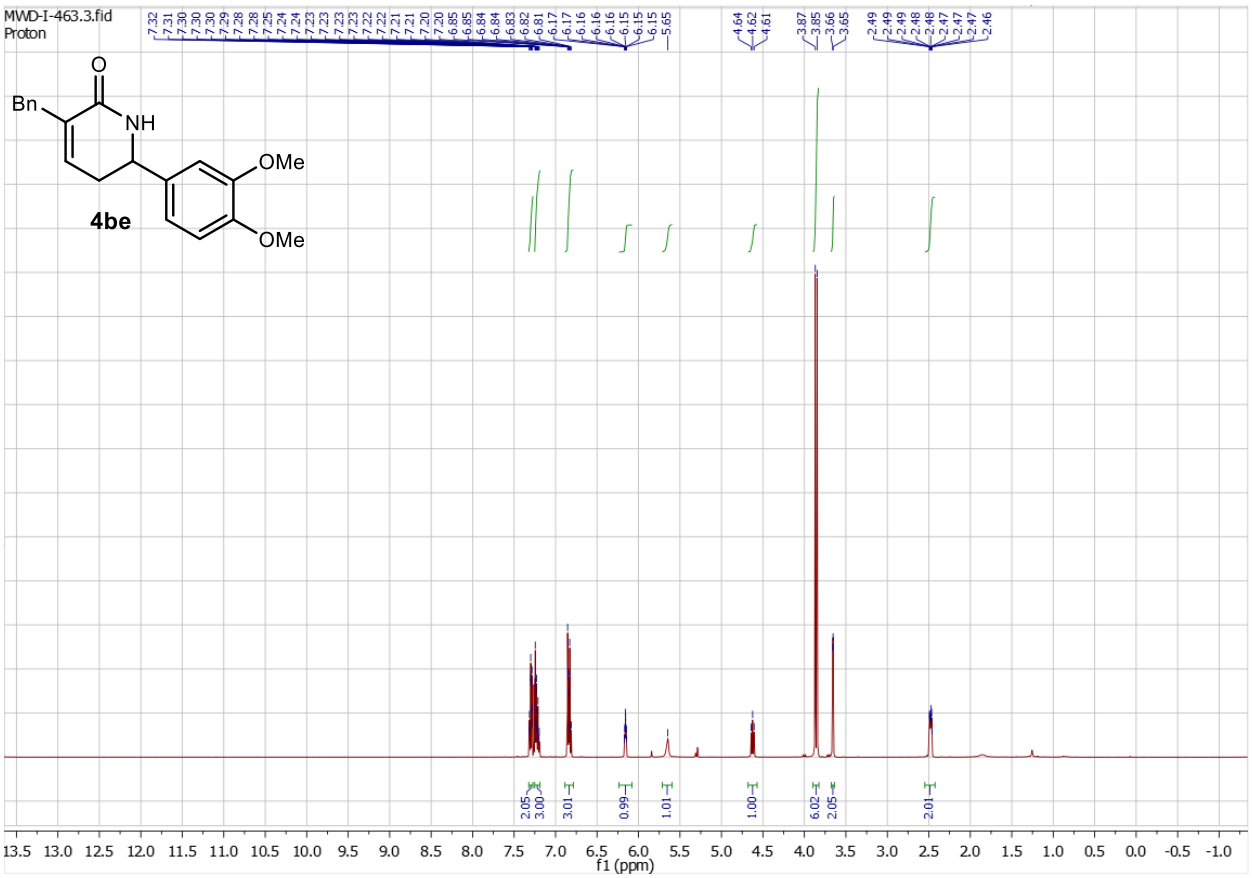

ns4-421col-1H.1.fid
Proton
Bn
O
NH
Cl
4bc
7.30
7.28
7.26
7.24
7.19
7.19
6.10
5.88
4.65
4.64
4.63
4.62
3.62
2.53
2.49
2.44
2.38
3.92
5.09
1.00
0.99
1.00
2.09
1.10
0.96
f1 (ppm)

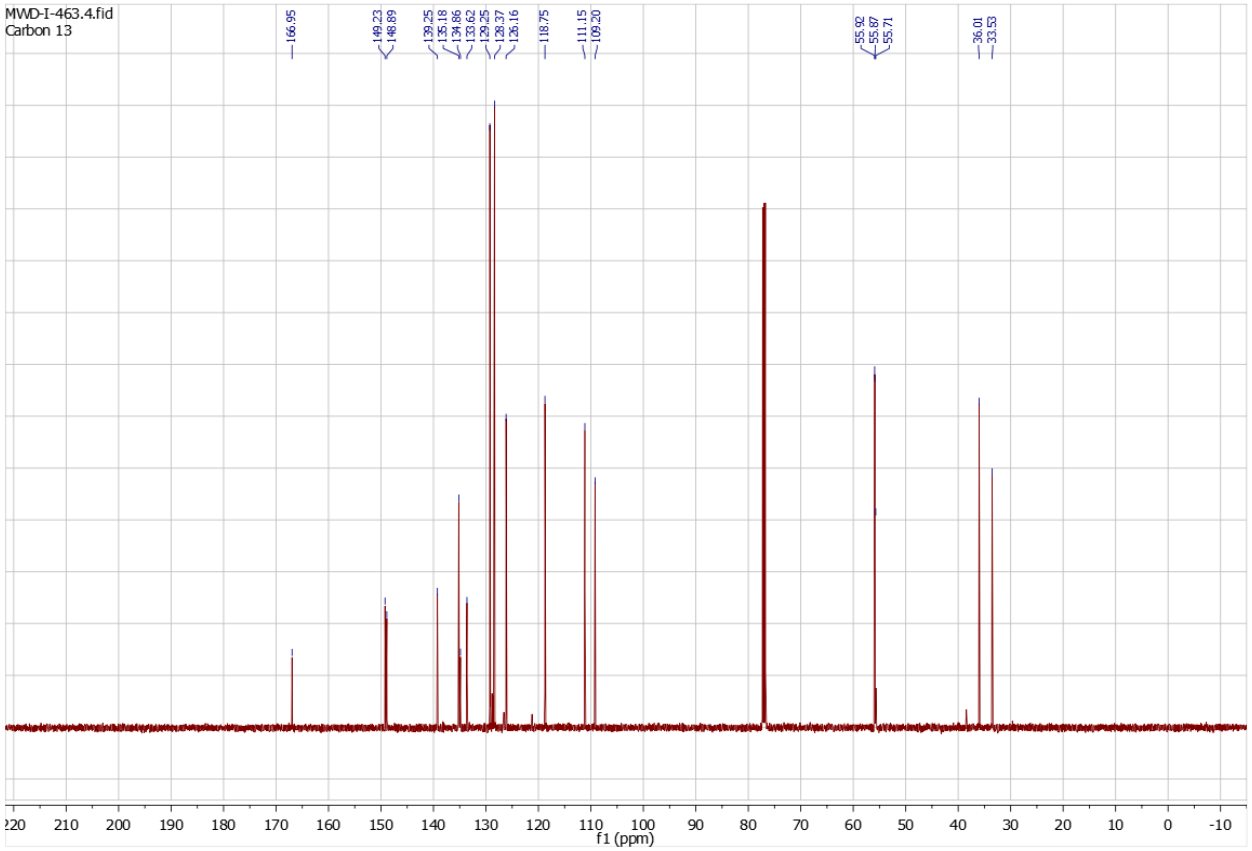

ns4-421col-13C.1.fid
Carbon 13
166.94
139.74
139.17
135.12
134.68
133.98
129.31
129.04
128.43
127.82
126.25
55.15
36.06
33.25
f1 (ppm)

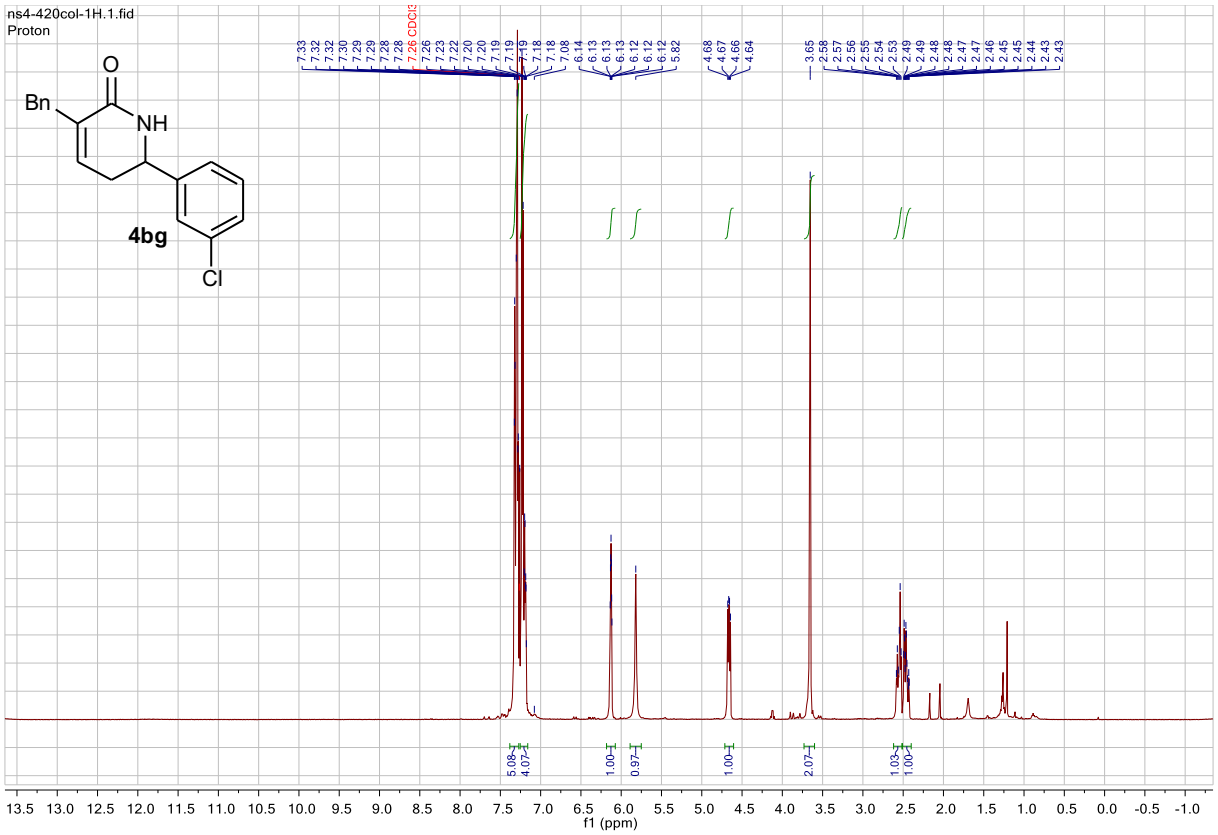

ns4-440col-1H.1.fid
Proton
Bn
NH
O
CF3
4bd
f1 (ppm)

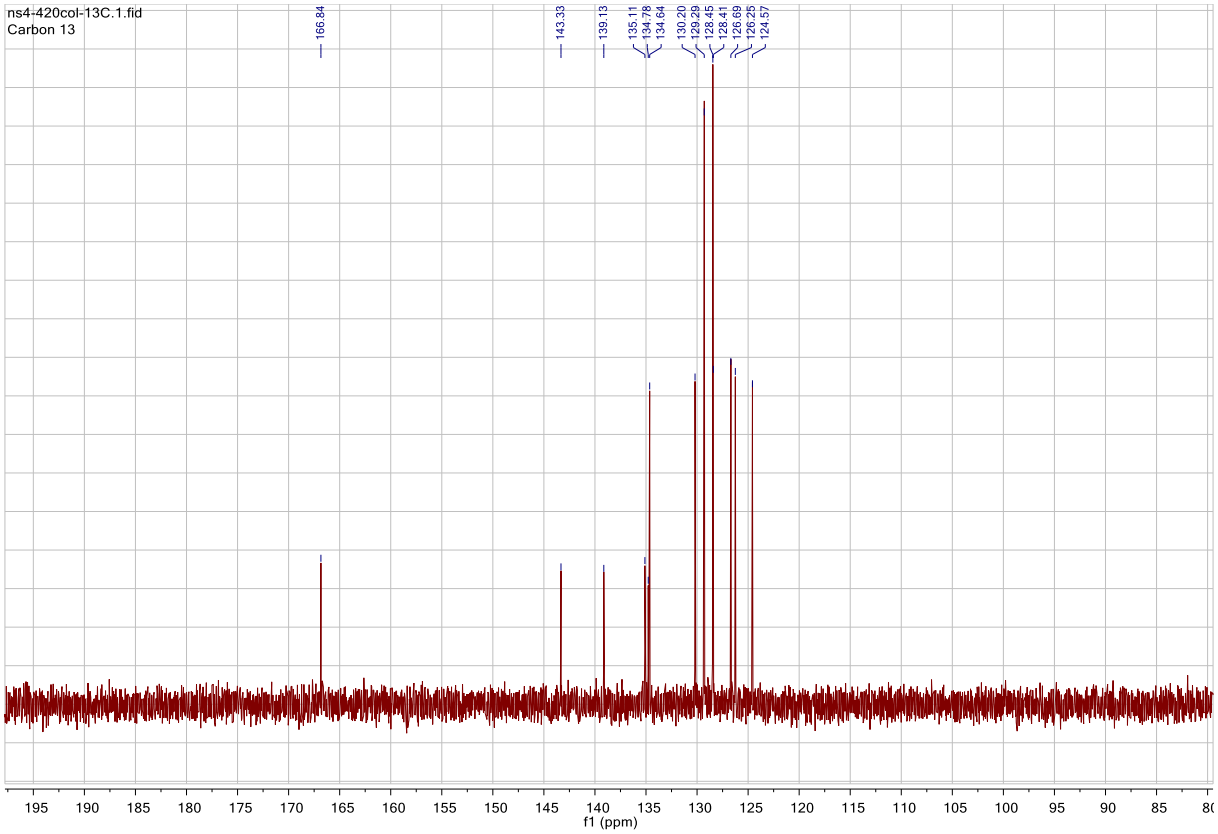

ns4-440col-13C.1.fid
Carbon 13
f1 (ppm)

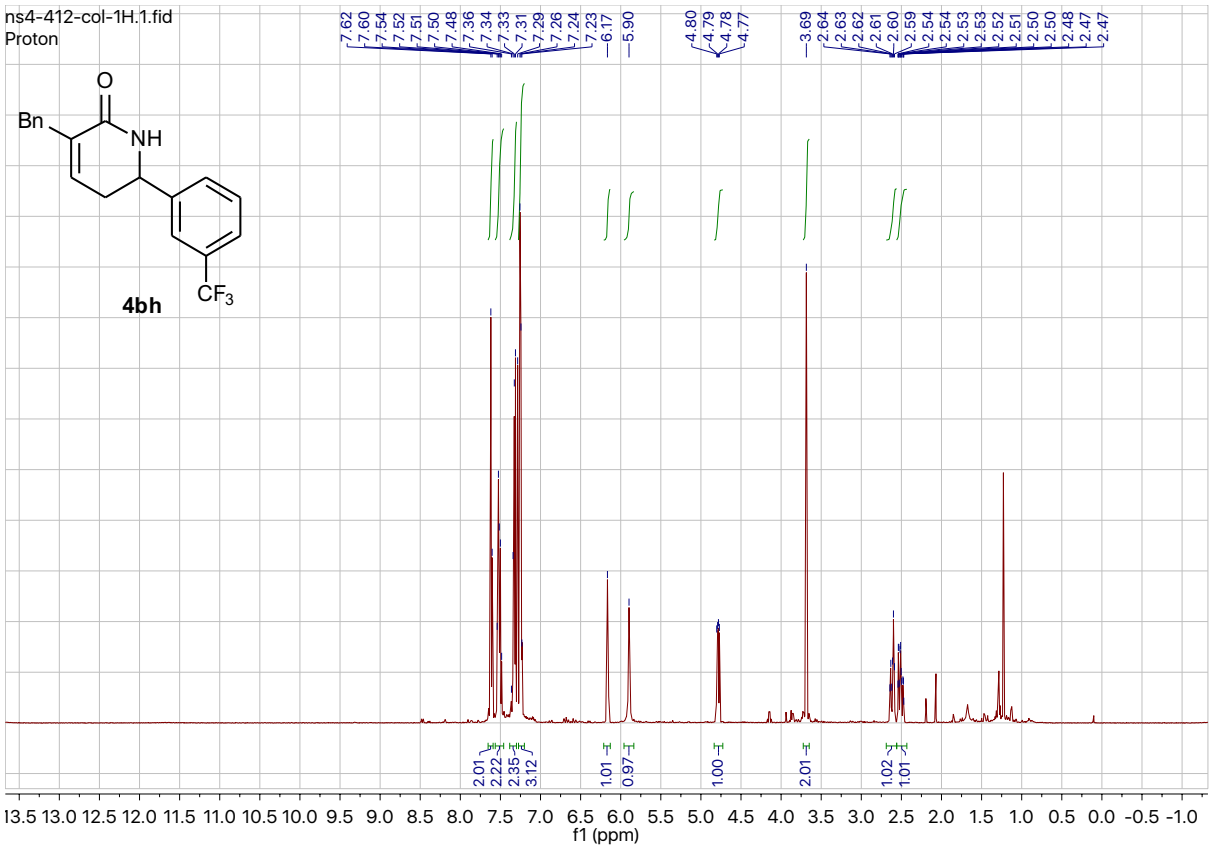

ns4-440-col-F19.1.fid
F19
-61.77
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

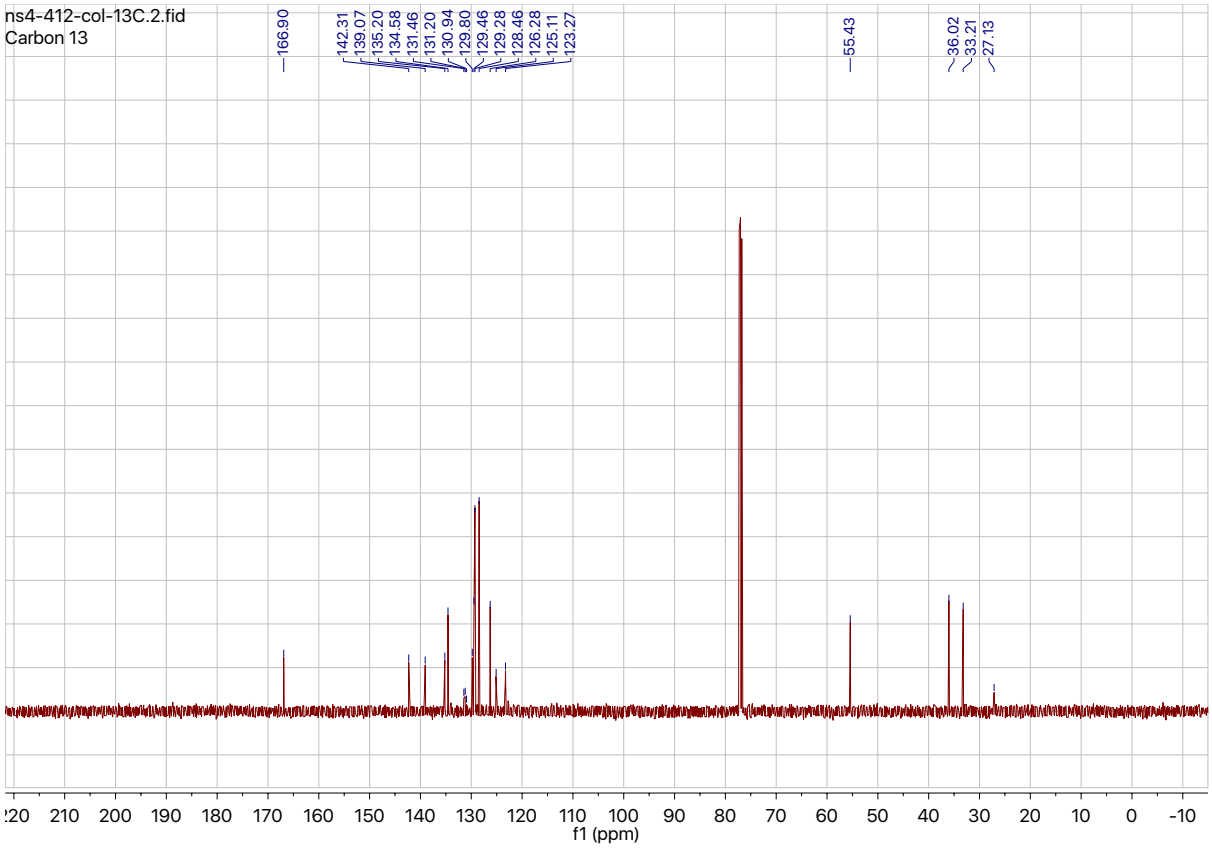

MWD-I-463.3.fid
Proton
Bn
NH
O
OMe
OMe
4be
f1 (ppm)

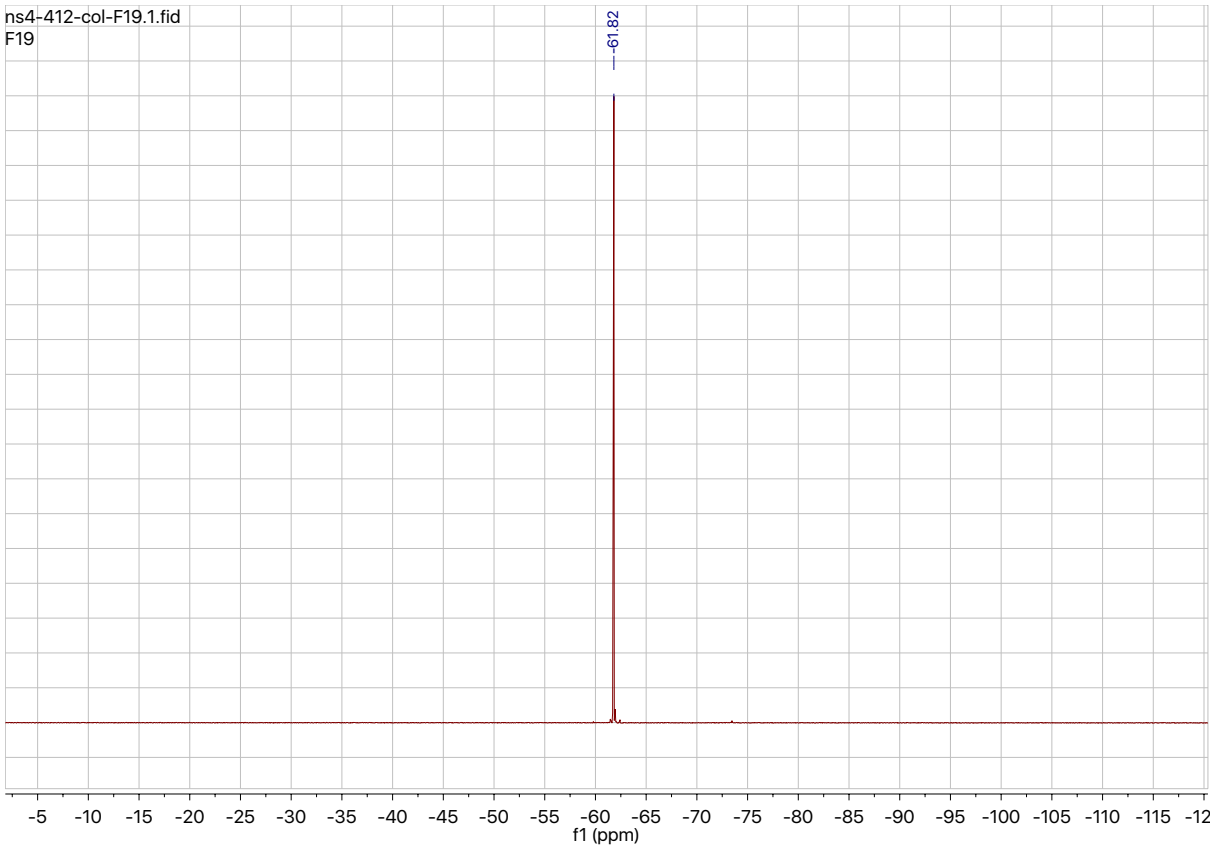

MWD-I-463.4.fid
Carbon 13
f1 (ppm)

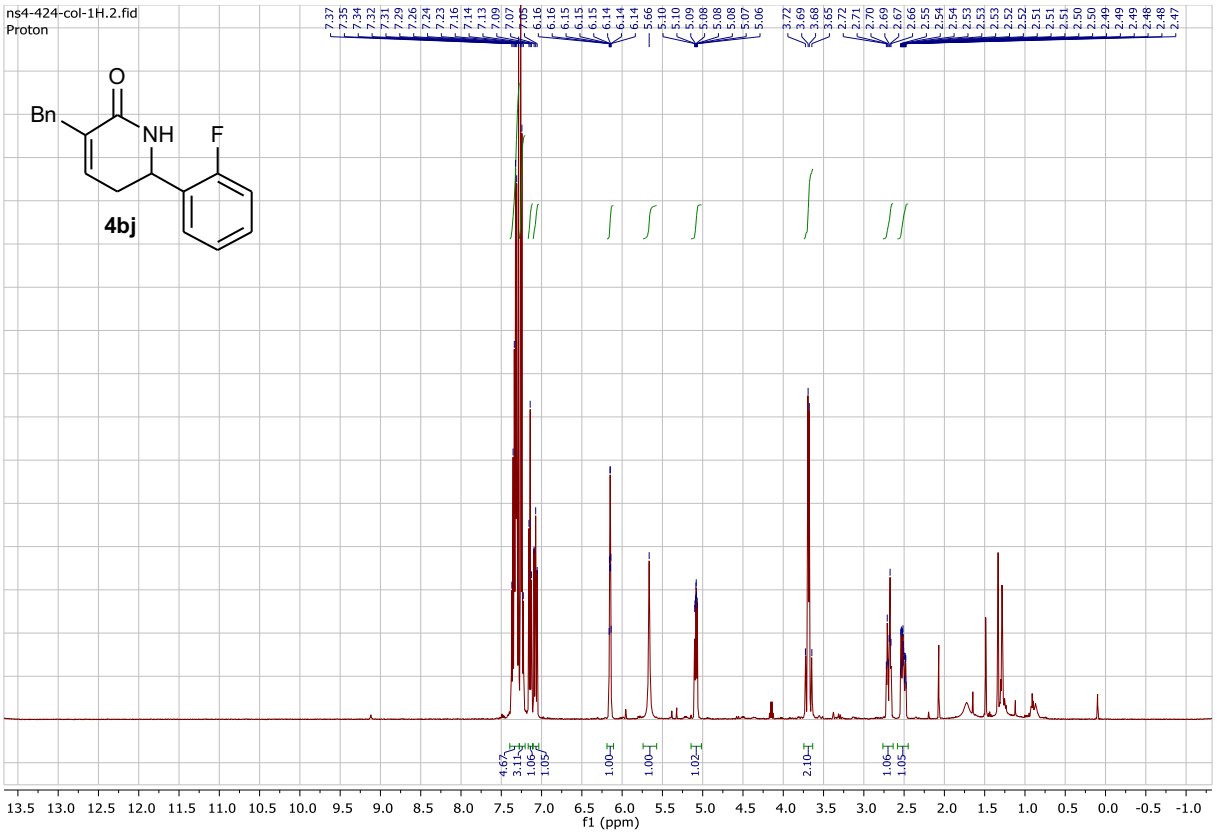

ns4-420col-1H.1.fid
Proton
Bn
NH
O
4bg
Cl
f1 (ppm)

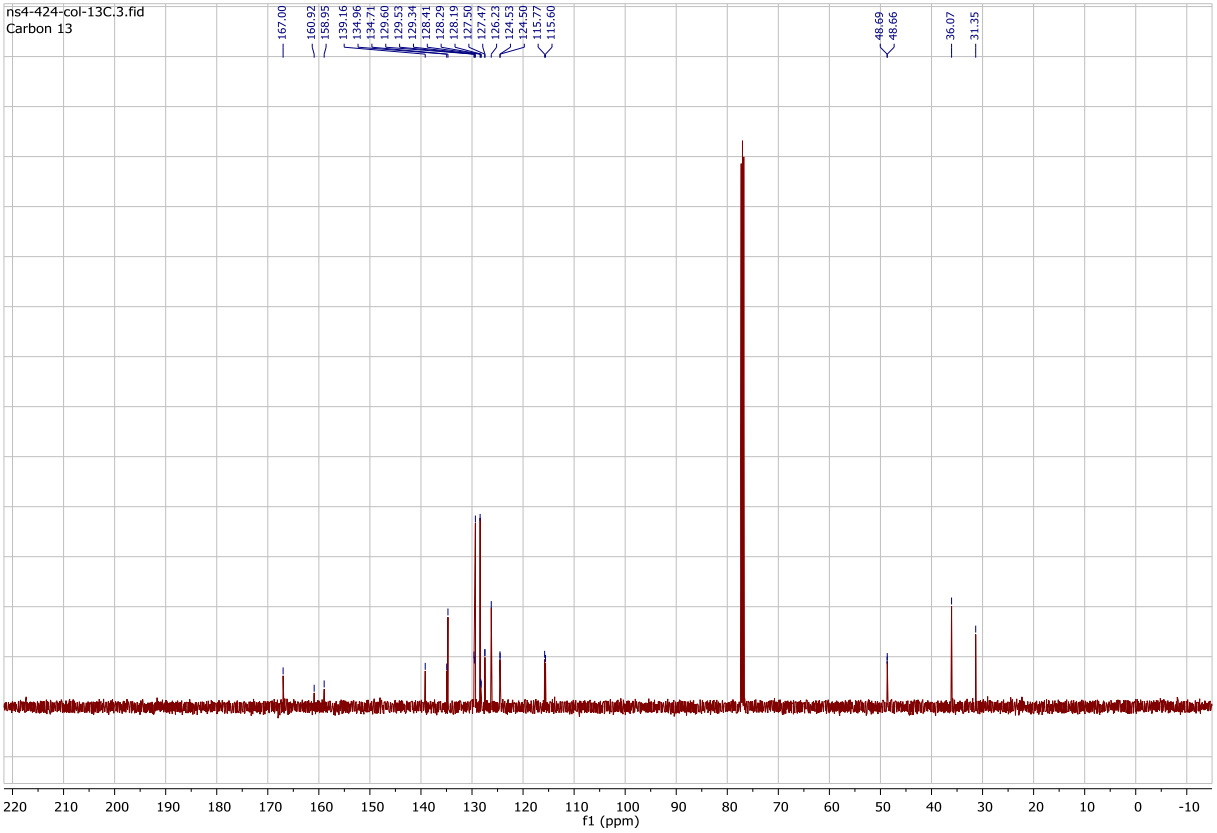

ns4-420col-13C.1.fid
Carbon 13
f1 (ppm)

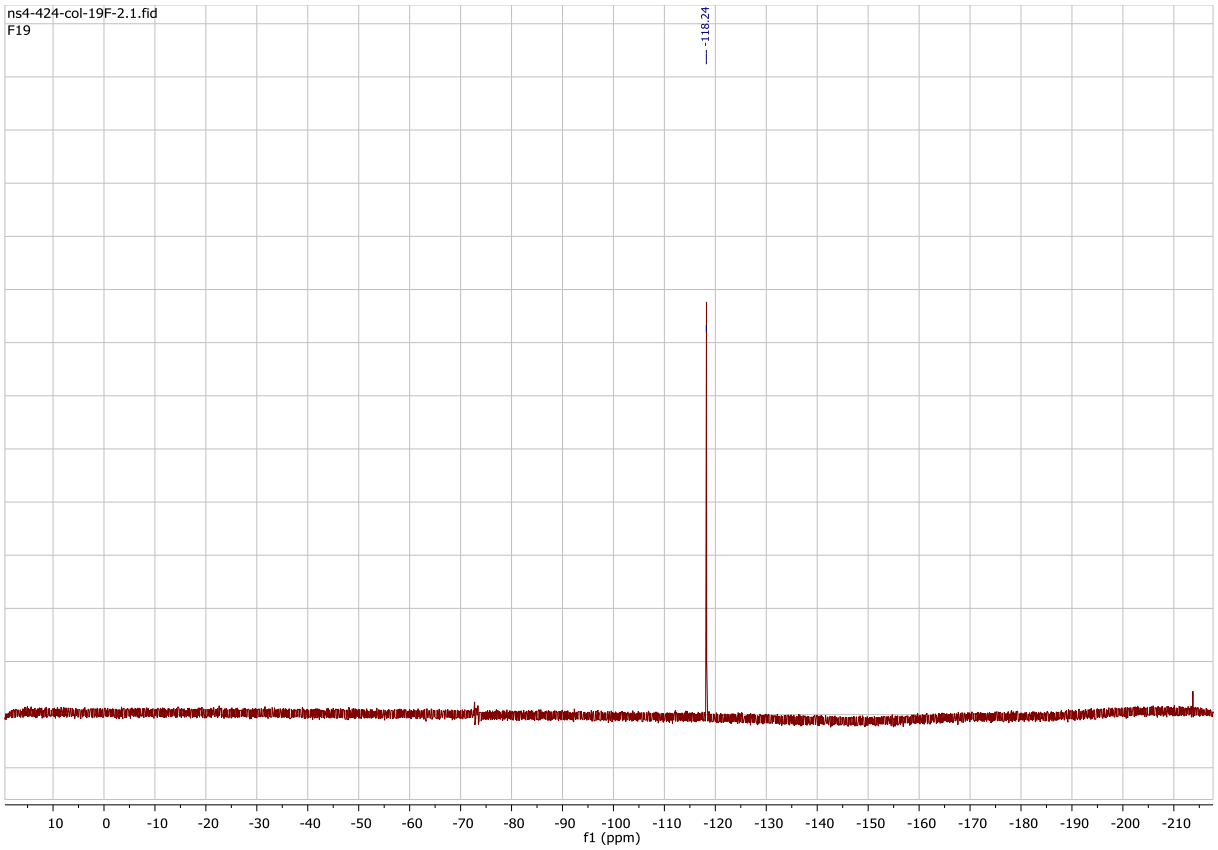

ns4-412-col-1H.1.fid
Proton
Bn
NH
O
CF3
4bh
f1 (ppm)

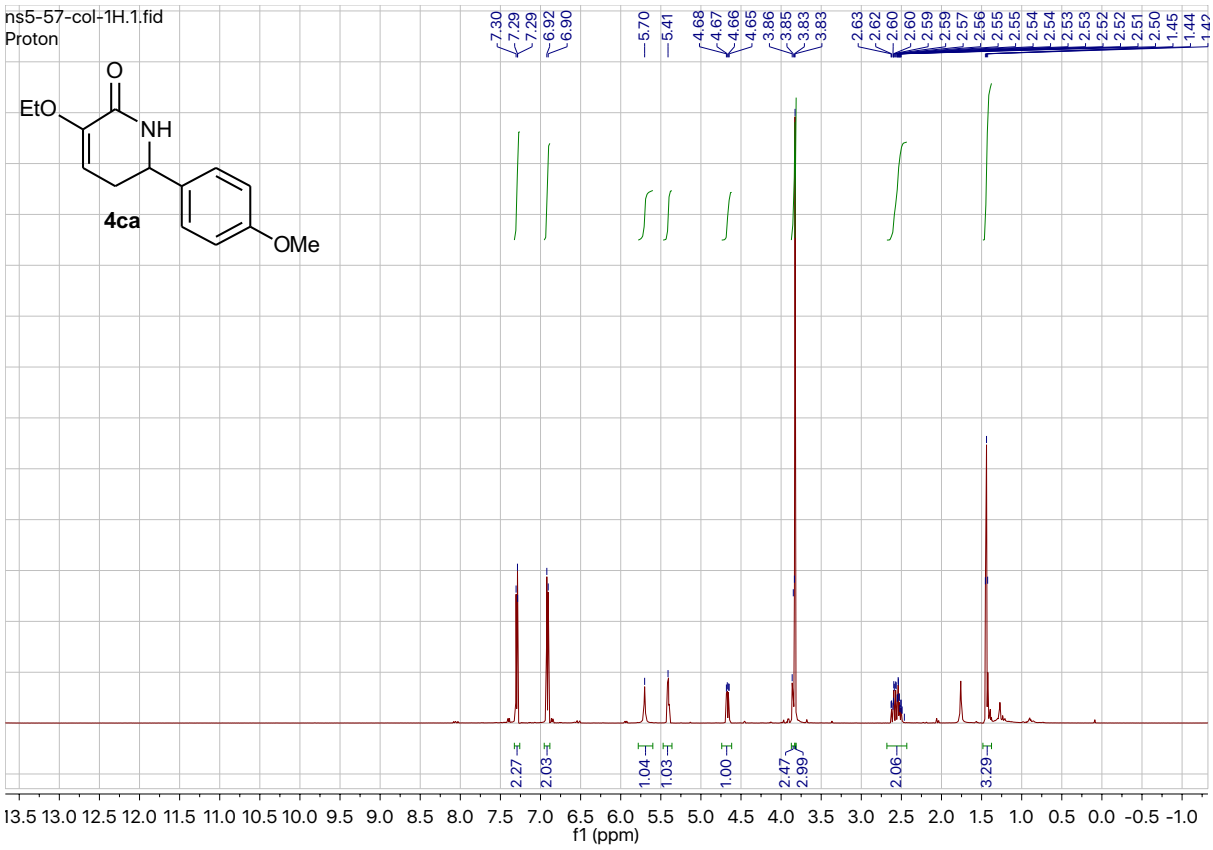

ns4-412-col-13C.2.fid
Carbon 13
f1 (ppm)

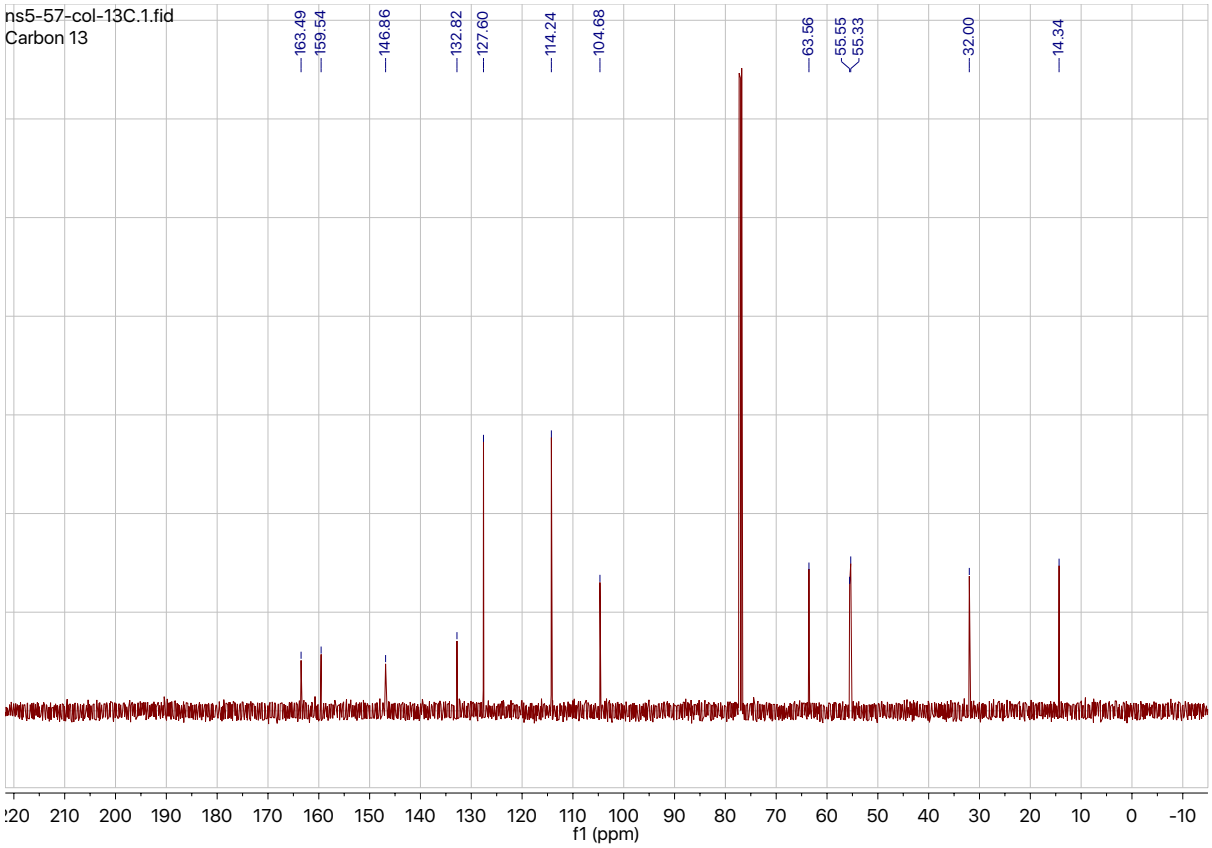

ns4-412-col-F19.1.fid
F19
-61.82
-5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -12
f1 (ppm)

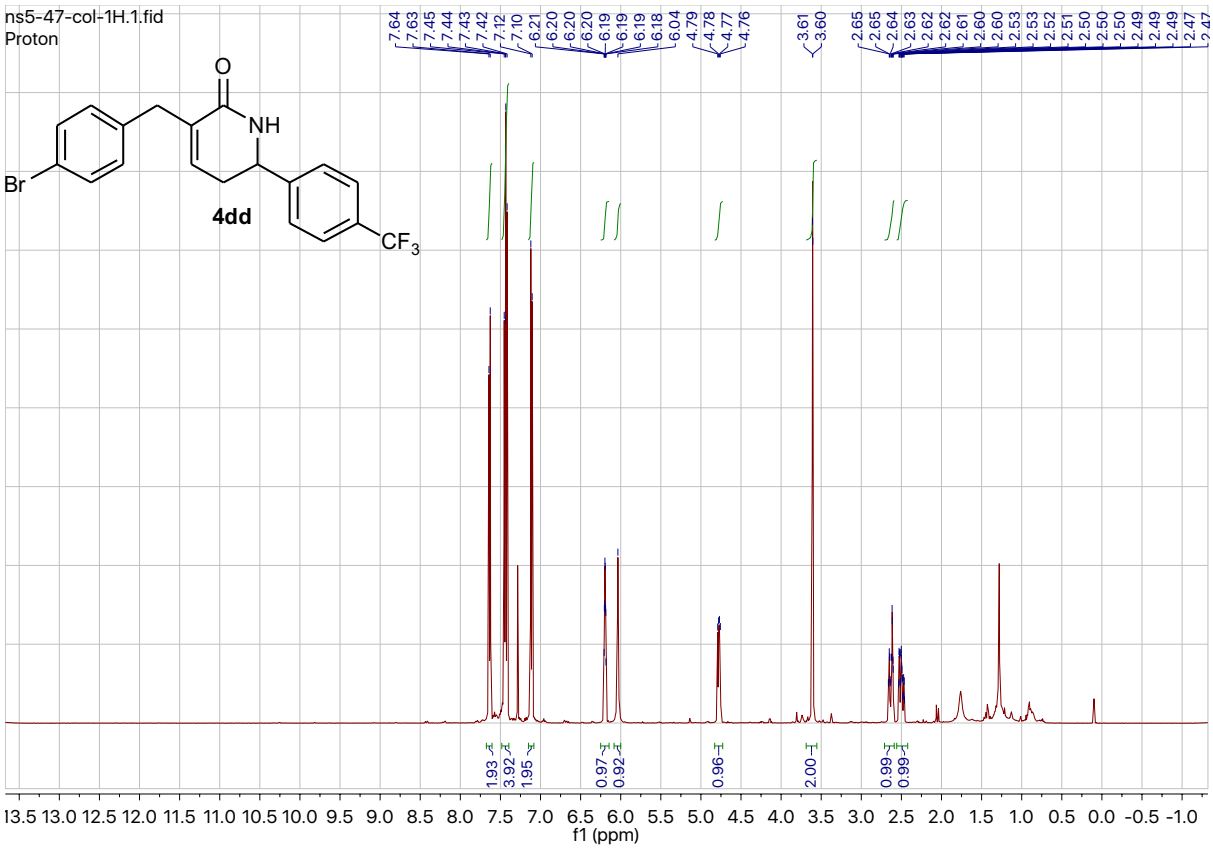

ns4-424-col-1H.2.fid
Proton
O
Bn
NH
F
4bj
f1 (ppm)

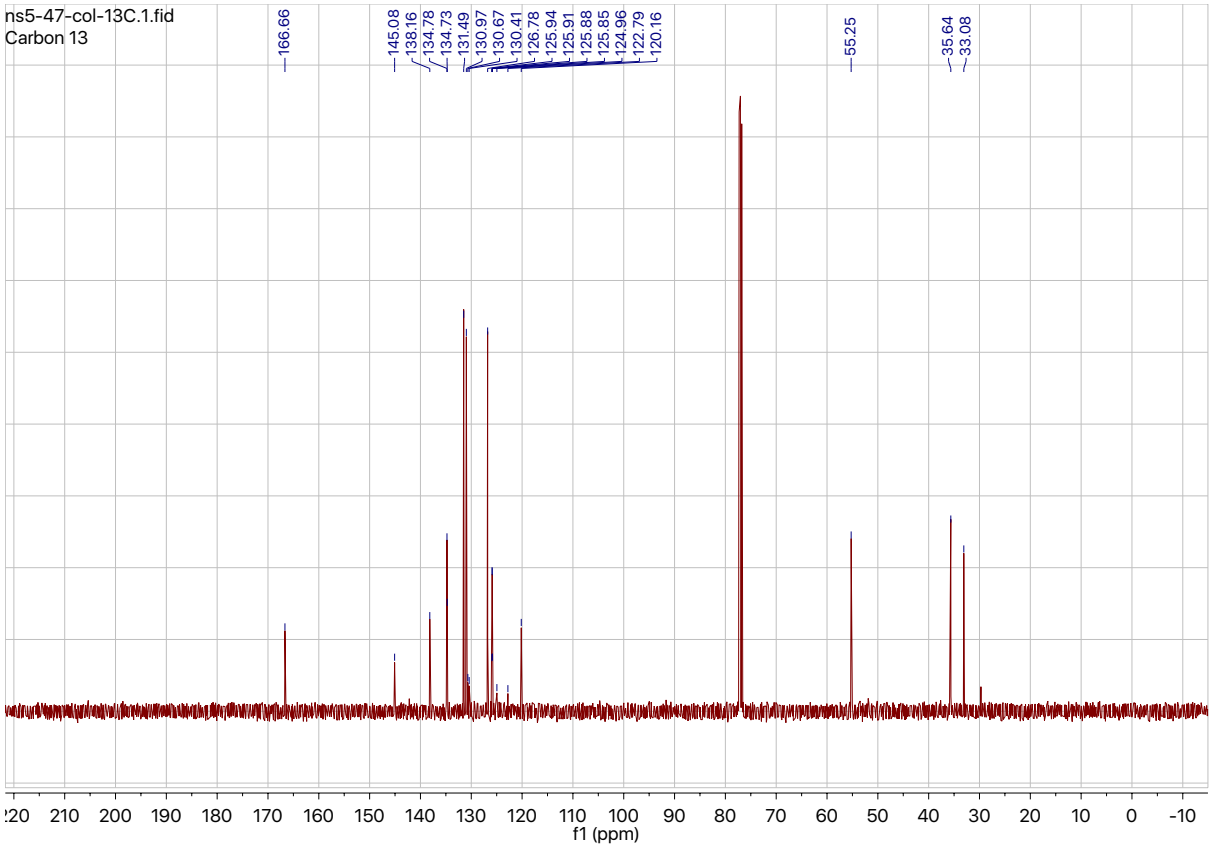

ns4-424-col-13C.3.fid
Carbon 13
f1 (ppm)

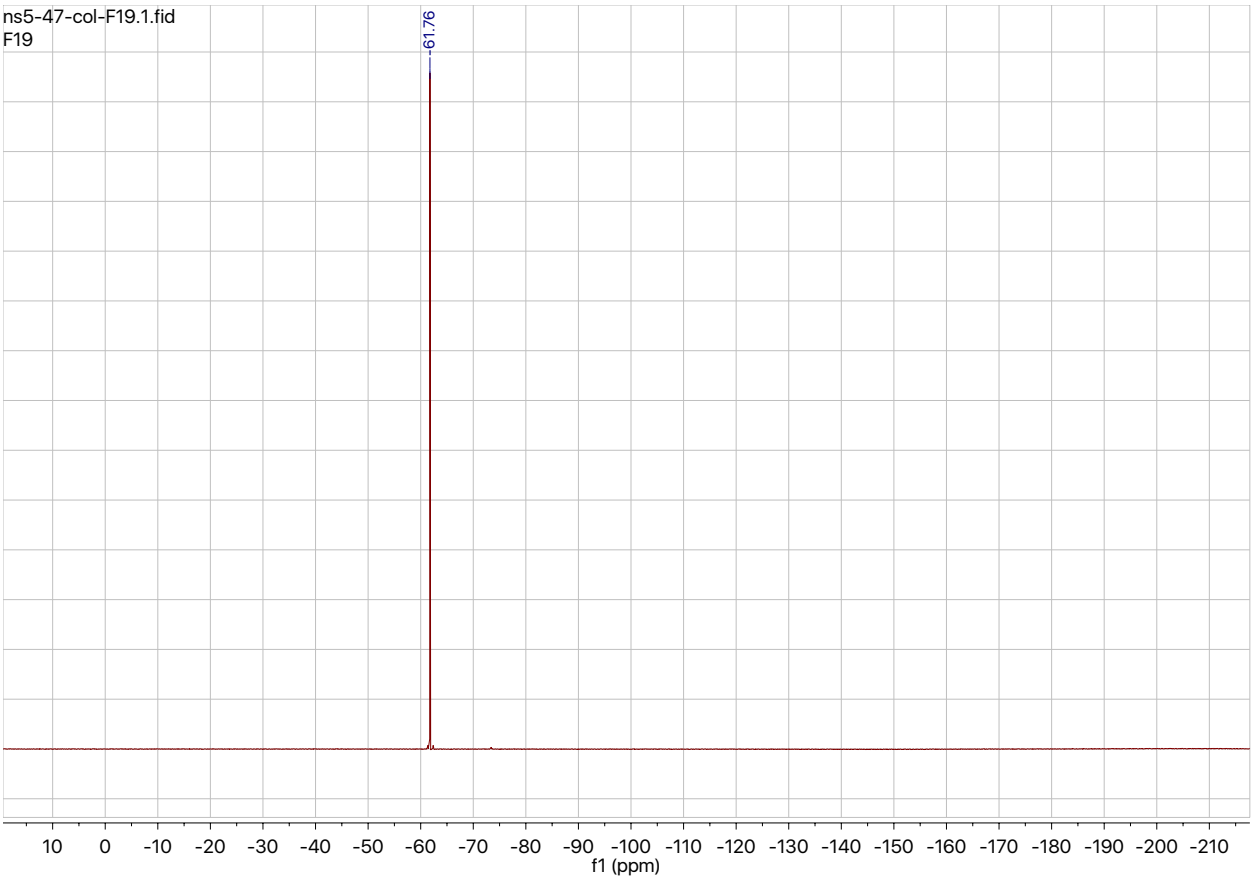

ns4-424-col-19F-2.1.fid
F19
-118.24
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

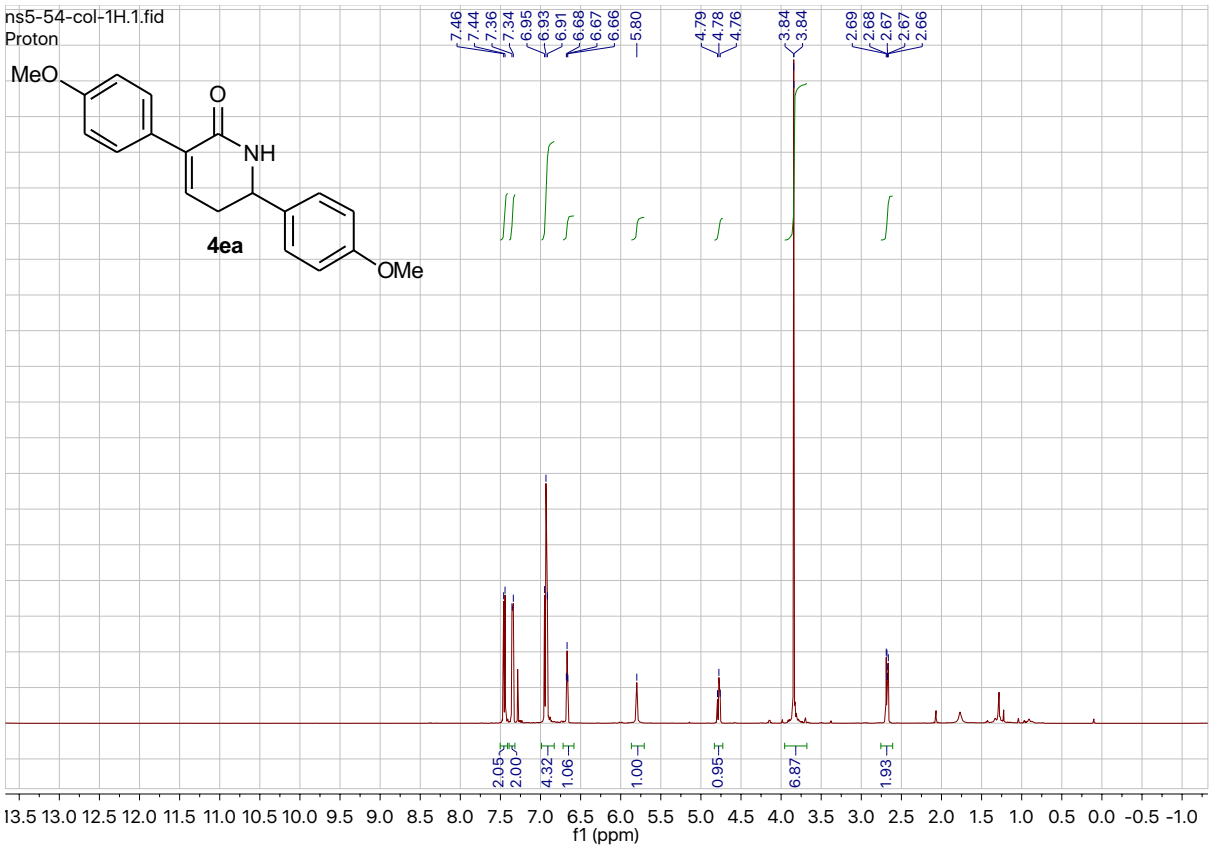

ns5-57-col-1H.1.fid
Proton
O
EtO
NH
4ca
OMe
7.30
7.29
7.29
6.92
6.90
5.70
5.41
4.68
4.67
4.66
4.65
3.86
3.85
3.83
3.83
2.63
2.62
2.60
2.60
2.59
2.59
2.57
2.56
2.55
2.55
2.54
2.54
2.53
2.53
2.52
2.52
2.51
2.50
1.45
1.44
2.27
2.03
1.04
1.03
1.00
2.47
2.99
2.06
3.29
f1 (ppm)

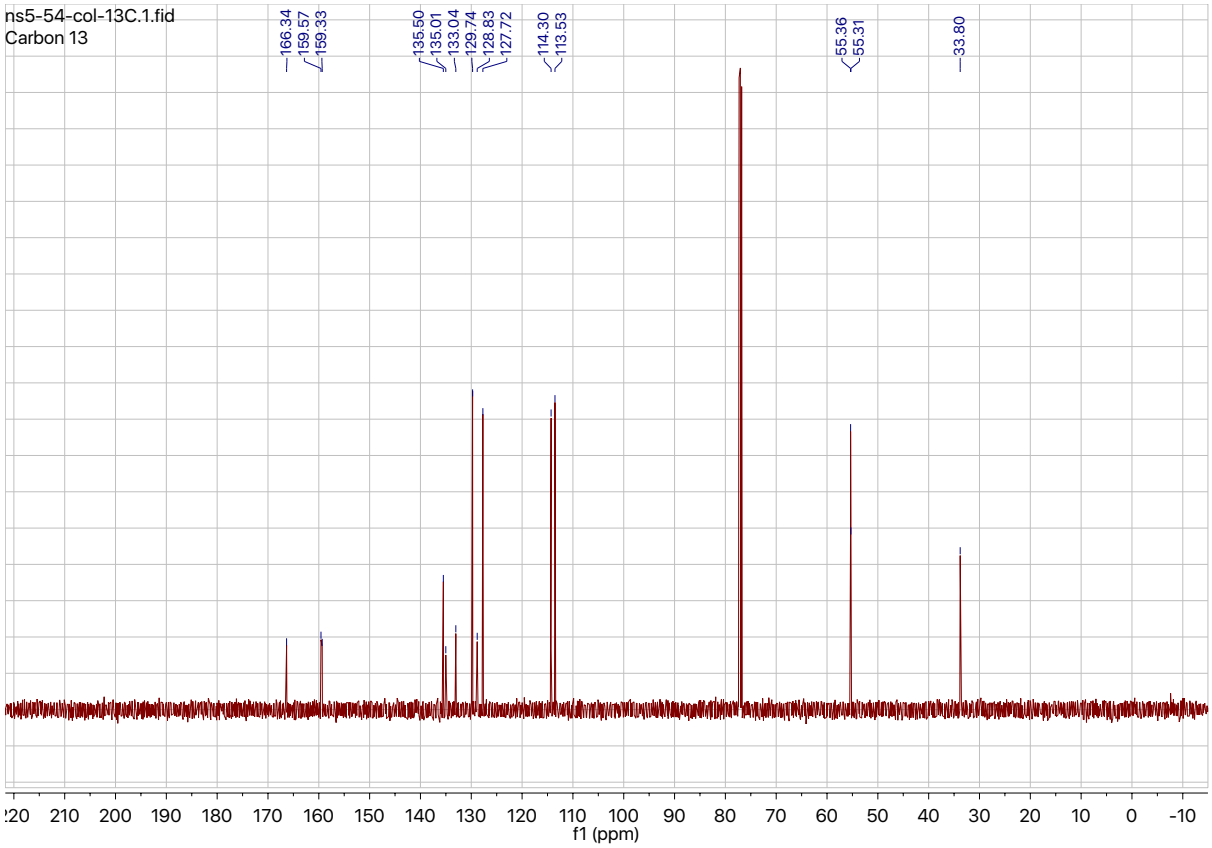

ns5-57-col-13C.1.fid
Carbon 13
163.49
159.54
146.86
132.82
127.60
114.24
104.68
63.56
55.55
55.33
32.00
14.34
f1 (ppm)

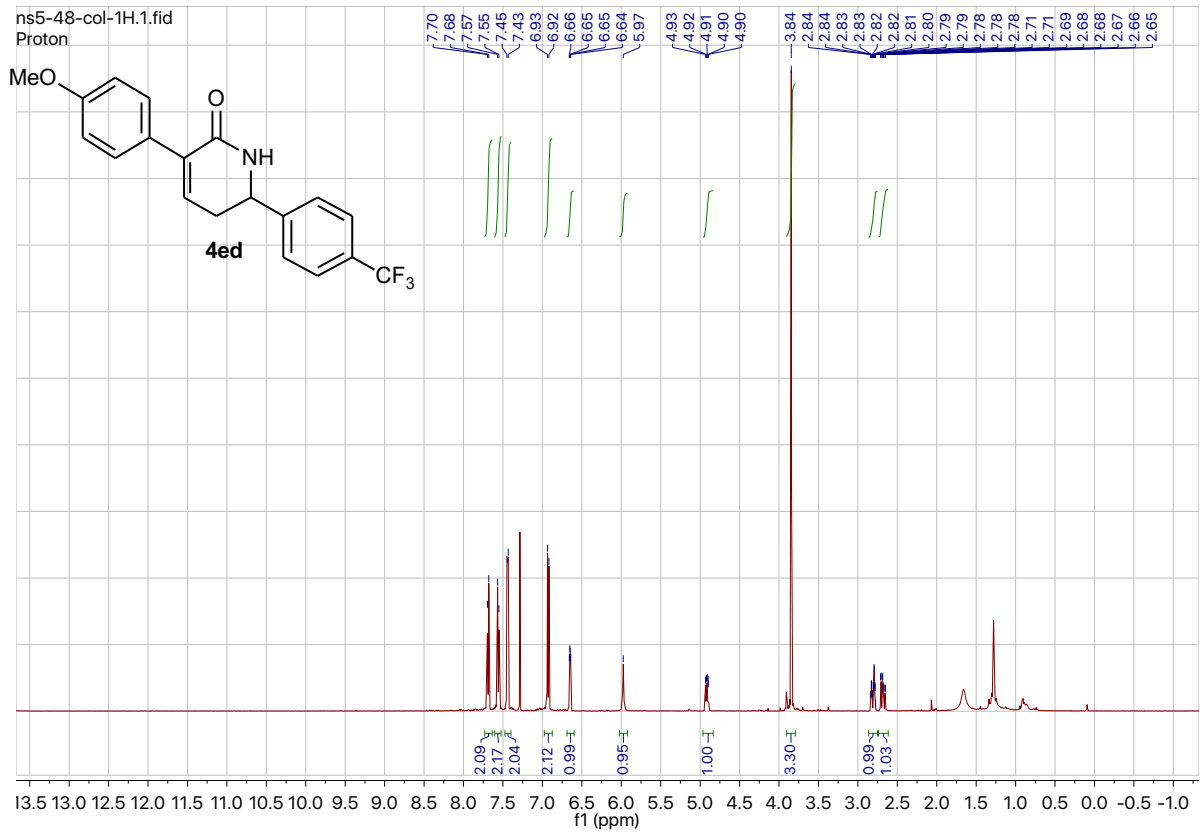

ns5-47-col-1H.1.fid
Proton
O
NH
Br
4dd
CF3
f1 (ppm)

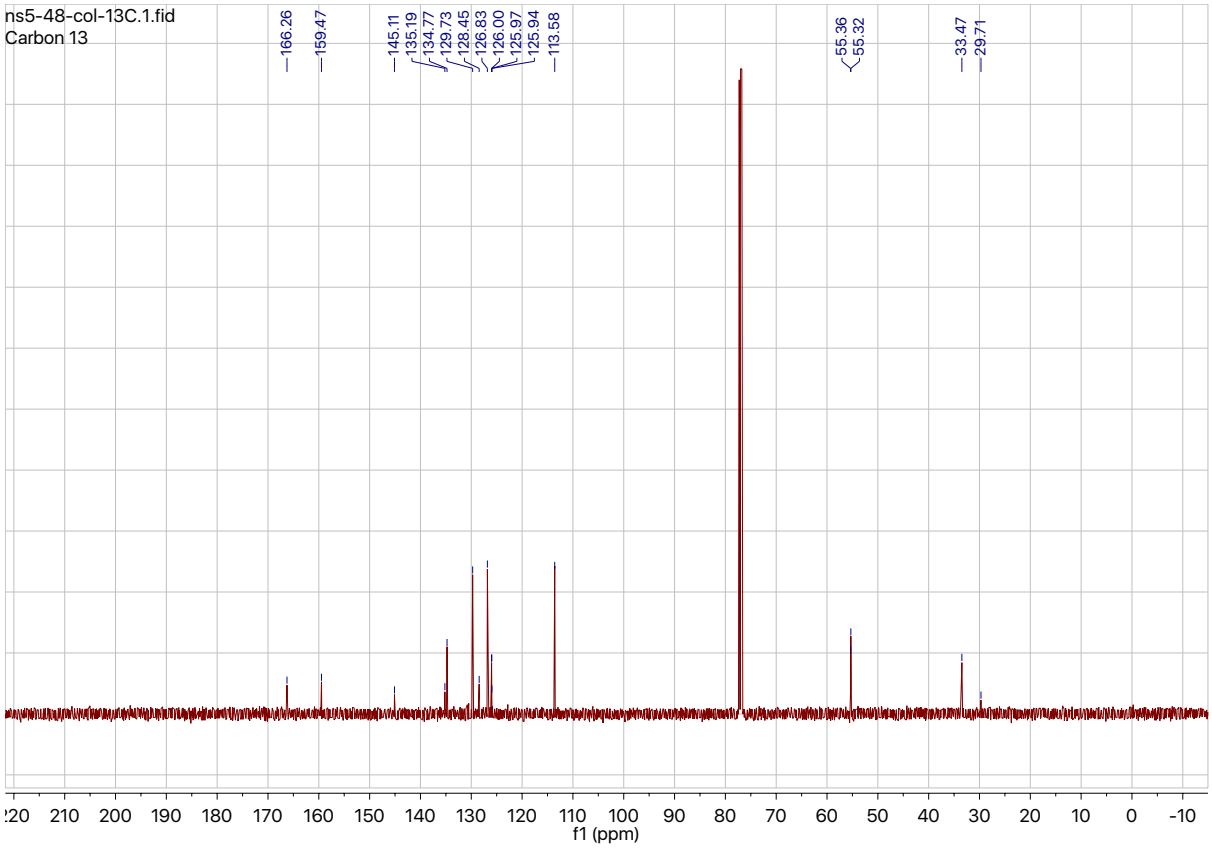

ns5-47-col-13C.1.fid
Carbon 13
f1 (ppm)

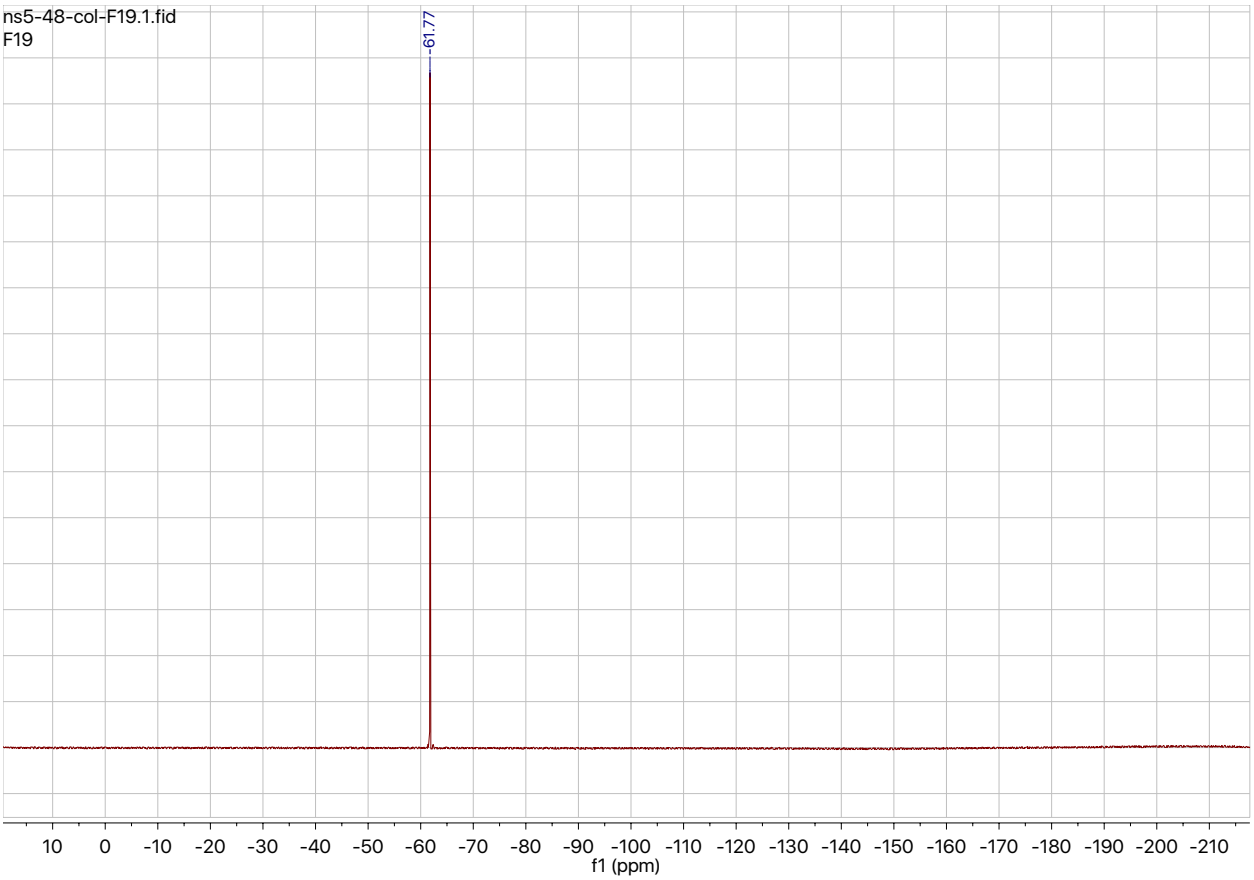

ns5-47-col-F19.1.fid
F19
-61.76
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

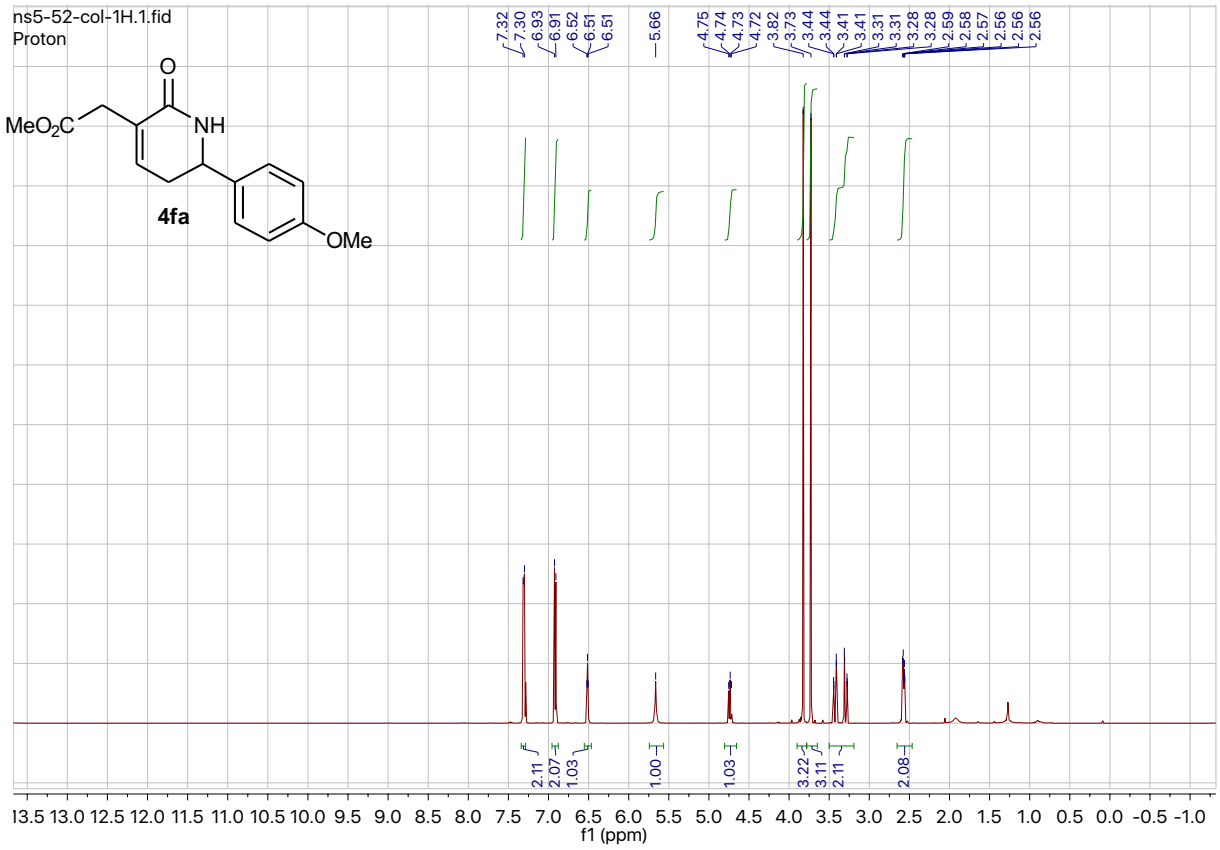

ns5-54-col-1H.1.fid
Proton
MeO
O
NH
4ea
OMe
7.46
7.44
7.36
7.34
6.95
6.93
6.91
6.68
6.67
6.66
5.80
4.79
4.78
4.76
3.84
3.84
2.69
2.68
2.67
2.67
2.66
2.05
2.00
4.32
1.06
1.00
0.95
6.87
1.93
f1 (ppm)


ns5-54-col-13C.1.fid
Carbon 13
166.34
159.57
159.33
135.50
135.01
133.04
129.74
128.83
127.72
114.30
113.53
55.36
55.31
33.80
f1 (ppm)


ns5-48-col-1H.1.fid
Proton
MeO
O
NH
4ed
CF3
f1 (ppm)


ns5-48-col-13C.1.fid
Carbon 13
f1 (ppm)


ns5-48-col-F19.1.fid
F19
-61.77
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


ns5-52-col-1H.1.fid
Proton
MeO2C
O
NH
OMe
4fa
7.32
7.30
6.93
6.91
6.52
6.51
6.51
5.66
4.75
4.74
4.73
4.72
3.82
3.73
3.44
3.44
3.41
3.41
3.31
3.31
3.28
3.28
2.59
2.58
2.57
2.56
2.56
2.56
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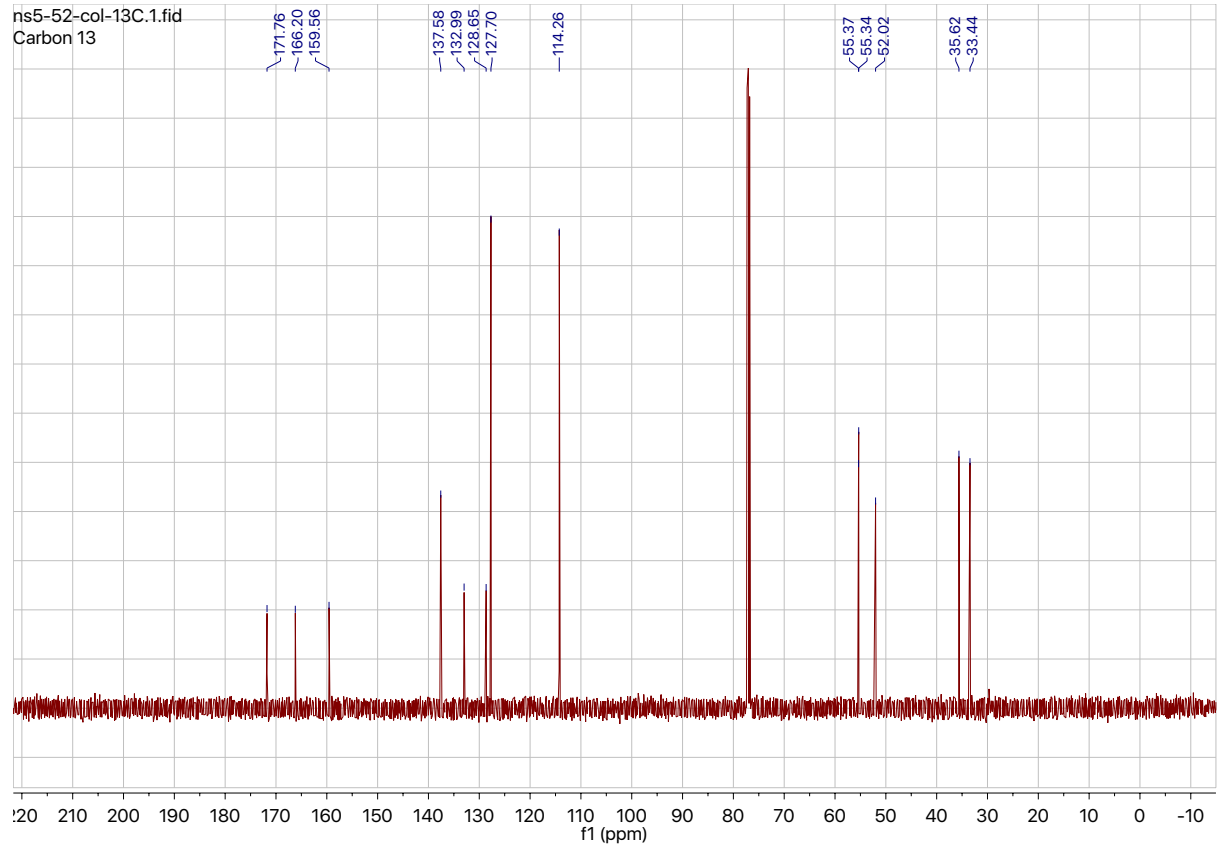
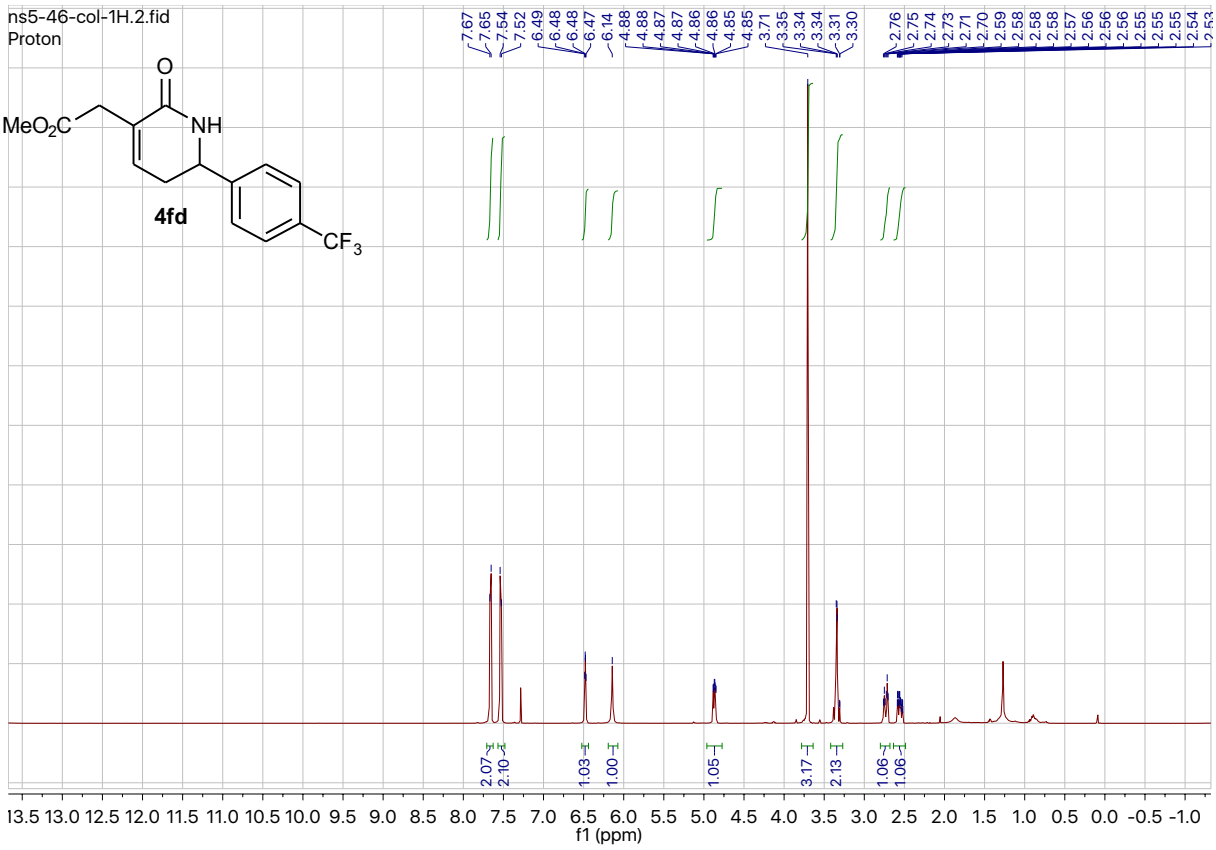
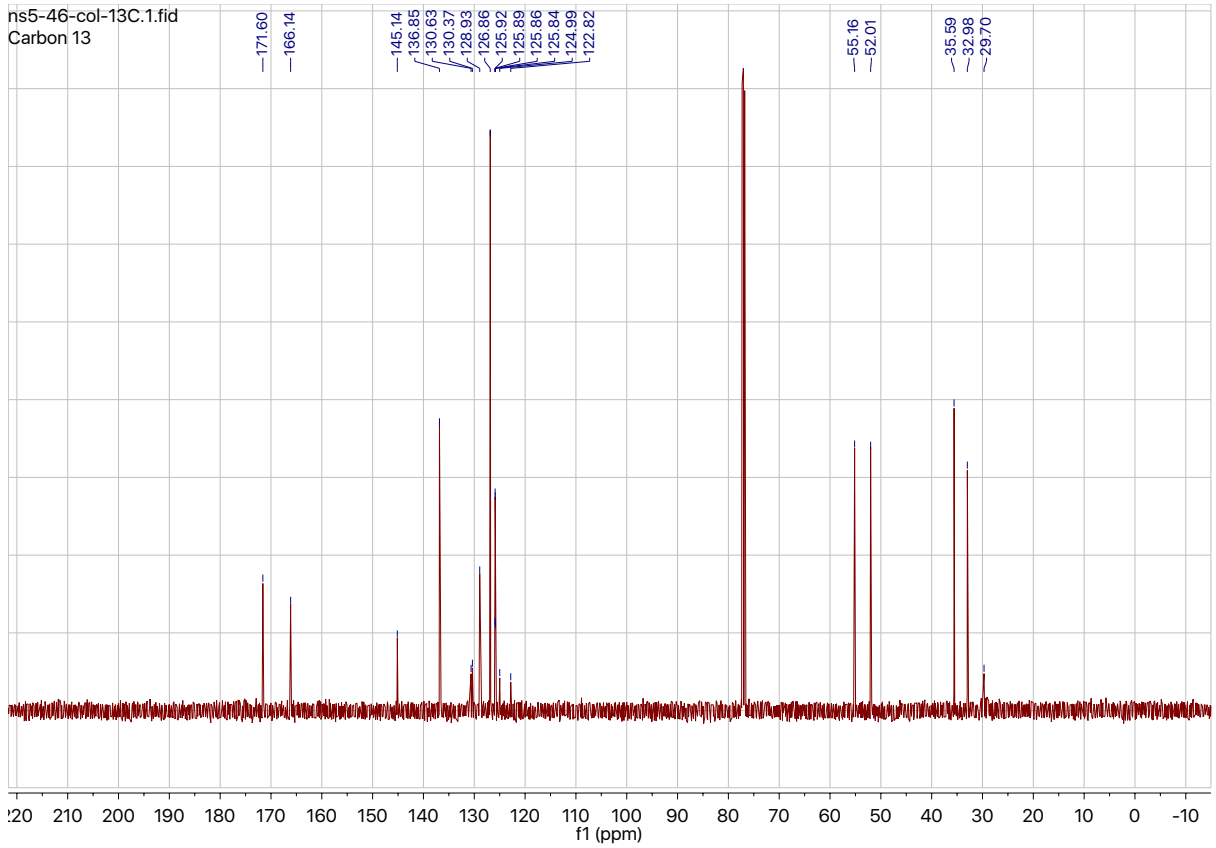
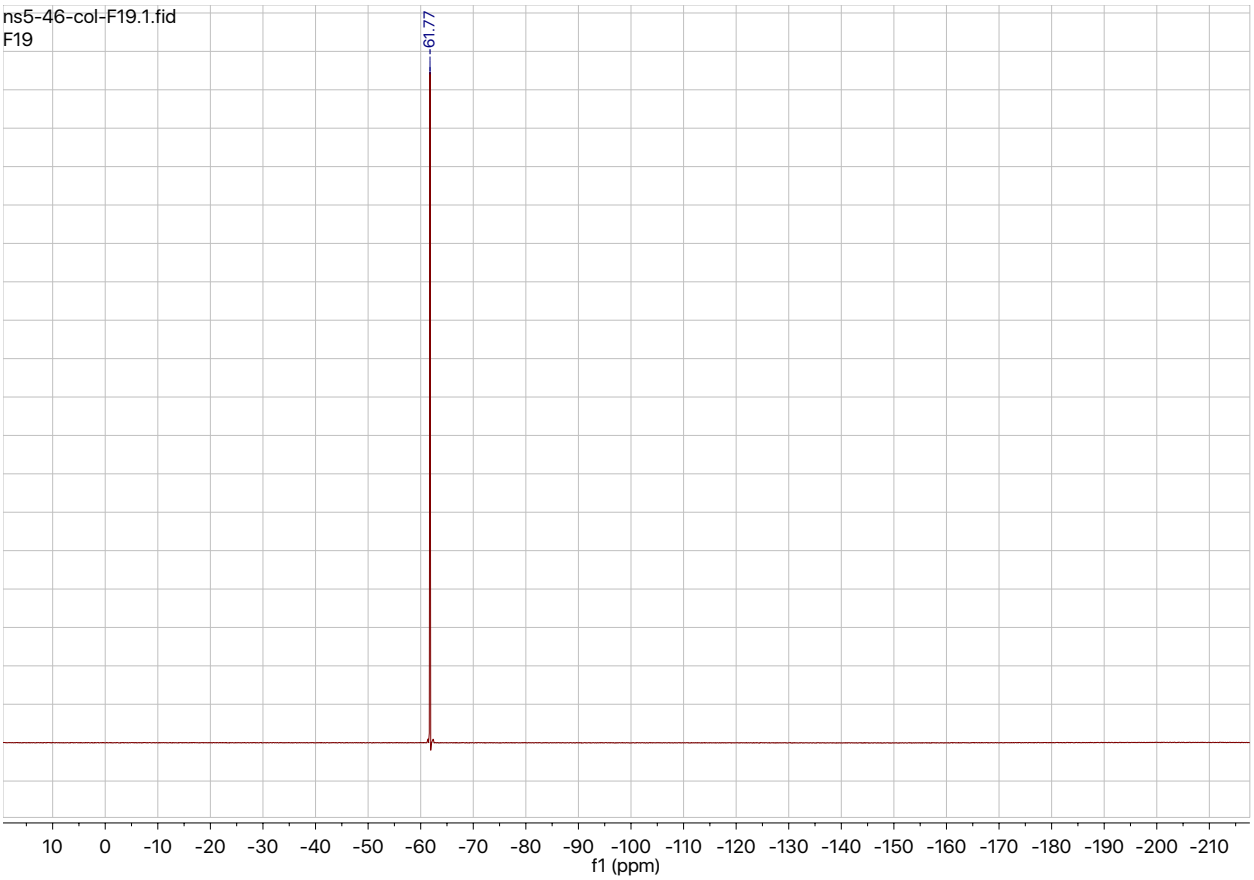
2.07
1.03
1.00
1.03
3.22
3.11
2.11
2.08
f1 (ppm)


ns5-52-col-13C.1.fid
Carbon 13
171.76
166.20
159.56
137.58
132.99
128.65
127.70
114.26
55.37
55.34
52.02
35.62
33.44
f1 (ppm)


ns5-46-col-1H.2.fid
Proton
MeO2C
O
NH
CF3
4fd
f1 (ppm)


ns5-46-col-13C.1.fid
Carbon 13
f1 (ppm)


ns5-46-col-F19.1.fid
F19
-61.77
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

6. General procedures for asymmetric dihydropyridone synthesis

General procedure A for asymmetric dihydropyridone synthesis

To a 750 μL clear glass shell vial (8 x 30mm) equipped with a parylene coated stir bar (1.67 x 2.01 x 4.80mm) was added a solution of the acrylamide in MeOH (3.0 μL, 1.0 M, 0.0030 mmol). The alkene (0.0015 mmol) was added followed by 125 μL of acetate buffer (100 mM NaOAc, 100 mM NaCl, pH 7.4). 75 μL of the monomeric streptavidin wild-type metalloenzyme (600 μM, 3 mol%, 0.000045 mmol) in salt water (100 mM NaCl, pH 7.4) was added to the vial achieving the desired reaction mixture (225 μM enzyme, 62.5 mM NaOAc, 100 mM NaCl, pH 7.4). The vial was placed in a 24-well high-throughput experimentation block and the reaction mixture was allowed to stir at 200 rpm at 25 °C. After 72 h the reaction is diluted with ethyl acetate and filtered through a Celite plug into a 20 mL scintillation vial. The reaction vial was washed twice more with ethyl acetate and filtered through the Celite plug into the scintillation vial. The Celite plug was washed an additional three times with ethyl acetate, collecting the filtrate into the scintillation vial. The contents of the scintillation vial were carefully removed via concentration under vacuum. The crude residue of the scintillation vial was dissolved in 600 μL of MeOD. A trimethyl(phenyl)silane internal standard (0.258 μL, 0.0015 mmol) was added to the solution, and mixed thoroughly. The sample was then analyzed by NMR (400 MHz or 500 MHz, MeOD, minimum of 400 scans), and the yield was determined relative to the trimethyl(phenyl)silane internal standard. Enantioselectivity was determined by chiral HPLC.[vi]

General procedure B for asymmetric dihydropyridone synthesis

To a 750 μL clear glass shell vial (8 x 30mm) equipped with a parylene coated stir bar (1.67 x 2.01 x 4.80mm) was added a solution of the acrylamide in MeOH (1.5 μL, 1.0 M, 0.0015 mmol). The alkene (0.0030 mmol) was added followed by 25 μL of acetate buffer (100 mM NaOAc, 100 mM NaCl, pH 7.4). 75 μL of the monomeric streptavidin wild-type metalloenzyme (600 μM, 3 mol%, 0.000045 mmol) in salt water (100 mM NaCl, pH 7.4) was added to the vial achieving the desired reaction mixture (450 μM enzyme, 25 mM NaOAc, 100 mM NaCl, pH 7.4). The vial was placed in a 24-well high-throughput experimentation block and the reaction mixture was allowed to stir at 200 rpm at 25 °C. After 48 h the reaction is diluted with either diethyl ether or ethyl acetate and filtered through a Celite plug into a 20 mL scintillation vial. The reaction vial was washed twice more with diethyl ether or ethyl acetate and filtered through a Celite plug into the scintillation vial. The Celite plug was washed an additional three times with diethyl ether or ethyl acetate, collecting the filtrate into the scintillation vial. The contents of the scintillation vial were carefully removed via concentration under vacuum. Yield was determined either by Chiral HPLC Analysis or NMR Analysis. Enantioselectivity was determined by chiral HPLC.[vi]

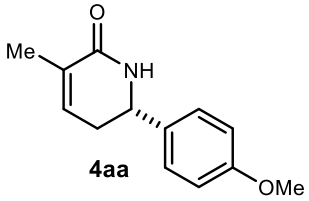
Chiral HPLC Analysis - The crude residue of the scintillation vial was rediluted with 120 µL of HPLC grade isopropanol and 300 µL of HPLC grade hexanes. 1.5 µL of a 1,3,5-trimethoxybenzene solution (1.0 M in MeOH) was added to the scintillation vial. The contents of the scintillation vial were thoroughly mixed via pipette to ensure uniformity of the solution. 180 µL of the uniform solution were incorporated into at 200 µL vial insert, and the sample was submitted for analysis. Yield was determined by chiral HPLC relative to a 1,3,5-trimethoxybenzene internal standard. Enantioselectivity was also determined by chiral HPLC.

NMR Analysis - The crude residue of the scintillation vial was dissolved in 600 µL of MeOD. A trimethyl(phenyl)silane internal standard (0.258 µL, 0.0015 mmol) was added to the solution, and mixed thoroughly. The sample was then analyzed by NMR (400 MHz or 500 MHz, MeOD, minimum of 400 scans), and the yield was determined relative to the trimethyl(phenyl)silane internal standard. Enantioselectivity was determined by chiral HPLC.

7. Analytical data for enantioenriched dihydropyridones (NMR/HPLC)

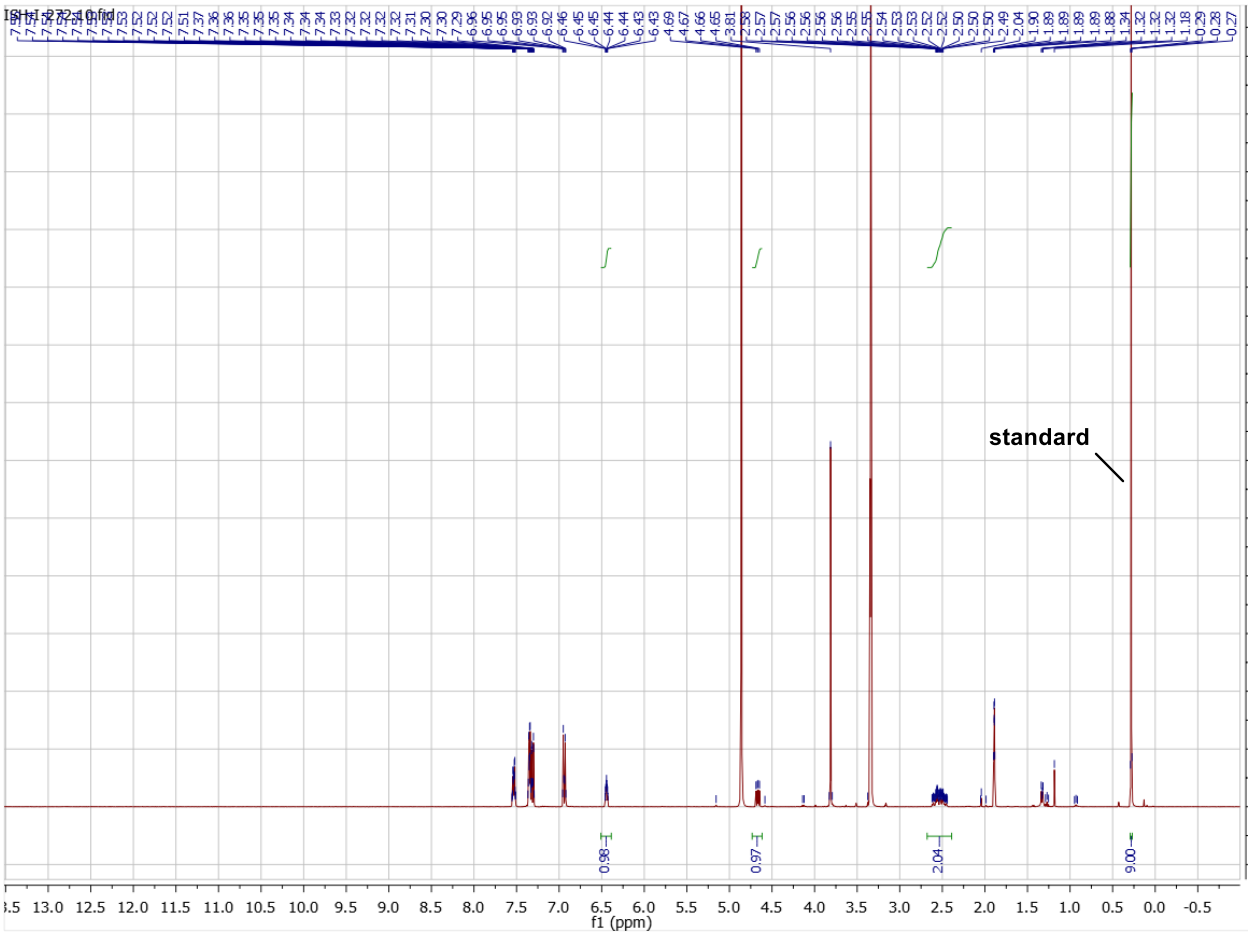
6-(4-Methoxyphenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4aa).

Product synthesized according to general procedure A. Product yield was determined to be 99% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 91% ee by chiral HPLC analysis. (Chiralpak IE, 20% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, minor) = 30.8 min, $t_r(e_2$, major) = 34.1 min).[vii]

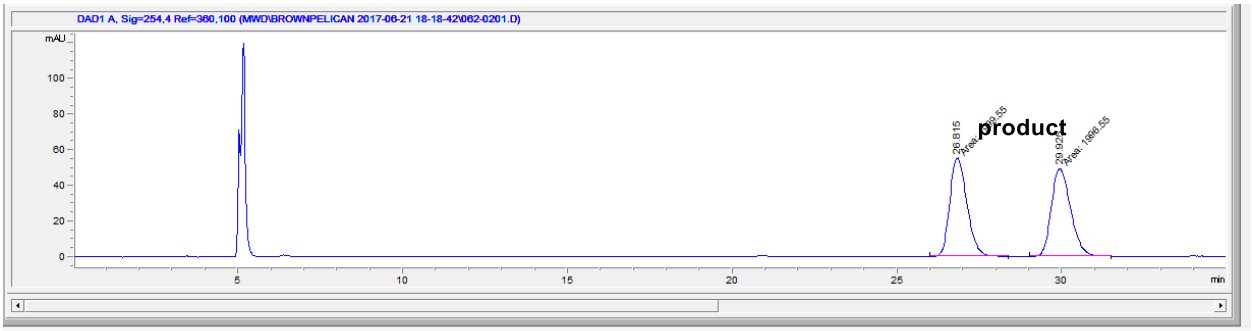


4aa

NMR Yield Data

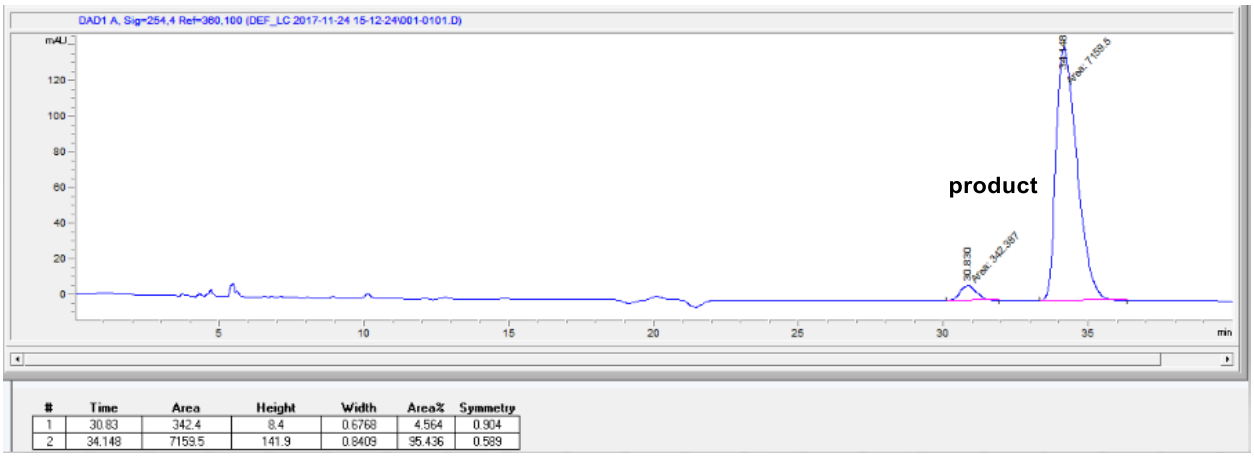


HPLC Racemic Assay (Full)



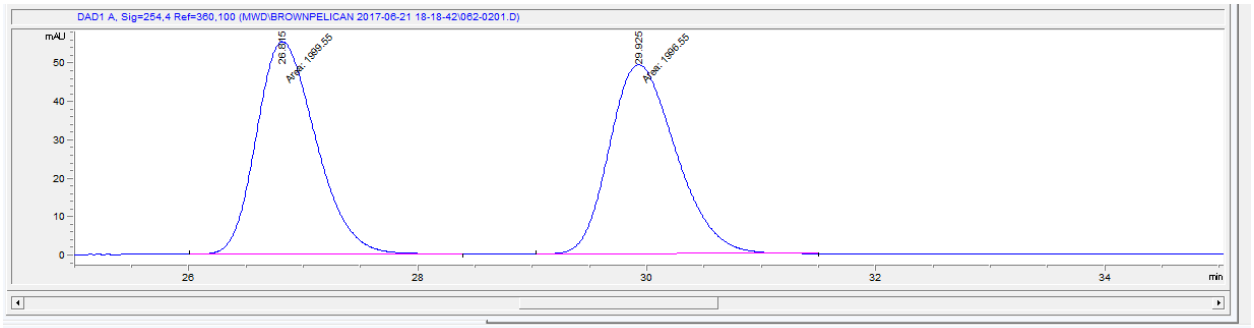
#	Time	Area	Height	Width	Area%	Symmetry
1	26.815	1999.6	55.4	0.6017	50.038	0.75
2	29.925	1996.6	49.3	0.6751	49.962	0.758

HPLC Enantioselective Assay (Full)



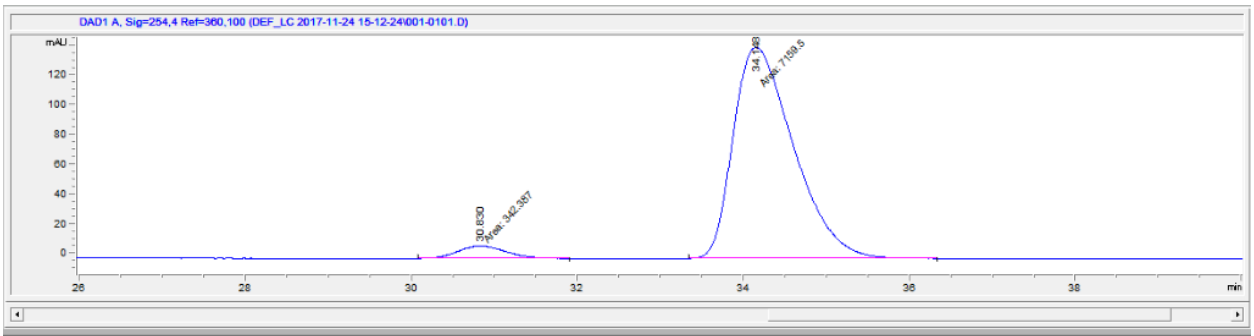
#	Time	Area	Height	Width	Area%	Symmetry
1	30.83	342.4	8.4	0.6768	4.564	0.904
2	34.148	7159.5	141.9	0.8409	95.436	0.589

HPLC Racemic Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	26.815	1999.6	55.4	0.6017	50.038	0.75
2	29.925	1996.6	49.3	0.6751	49.962	0.758

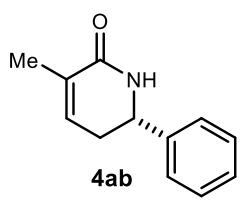
HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	30.83	342.4	8.4	0.6768	4.564	0.904
2	34.148	7159.5	141.9	0.8409	95.436	0.589

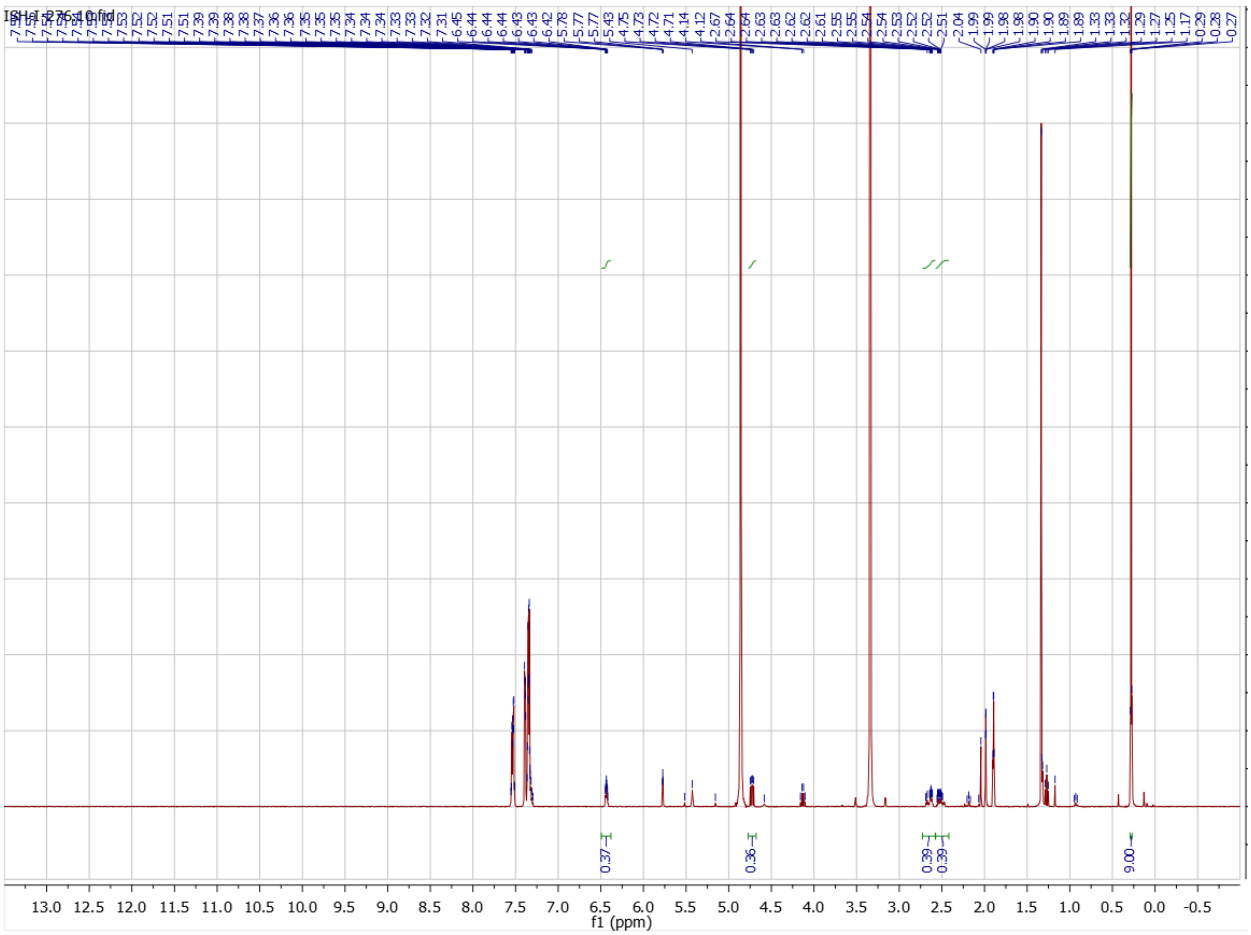
3-Methyl-6-phenyl-5,6-dihydropyridin-2(1*H*)-one (4ab).

Product synthesized according to general procedure A. Product yield was determined to be 39% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 63% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 12.3 min, t_r(e_2, major) = 13.7 min).

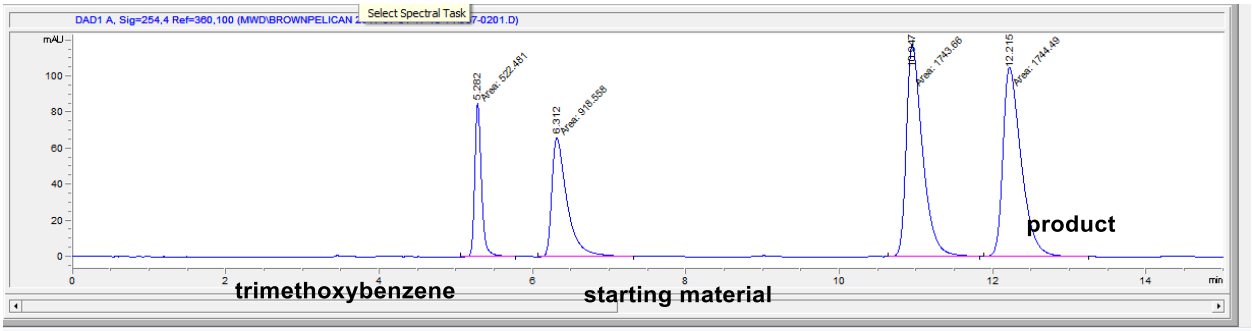


4ab

NMR Yield Data

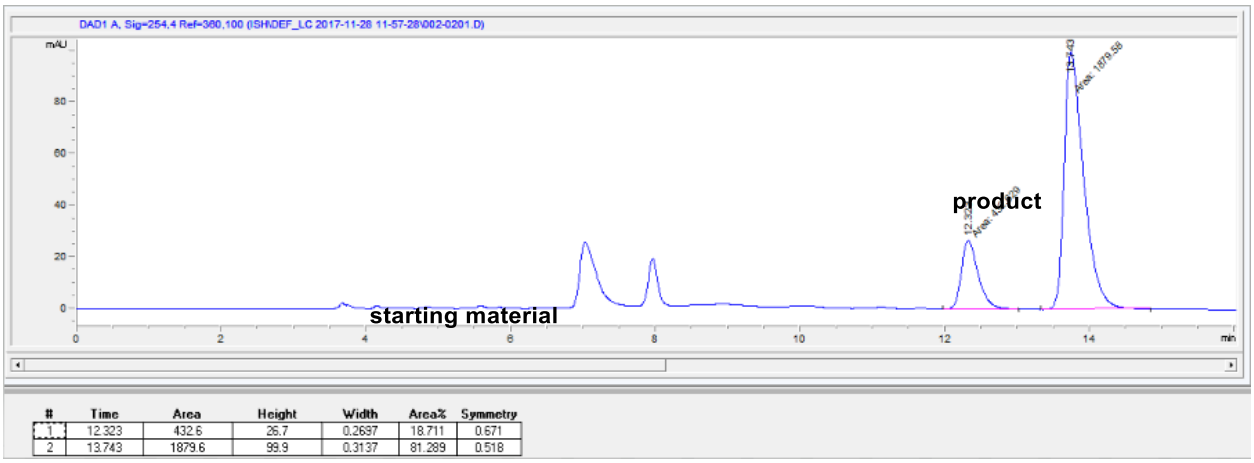


HPLC Racemic Assay (Full)



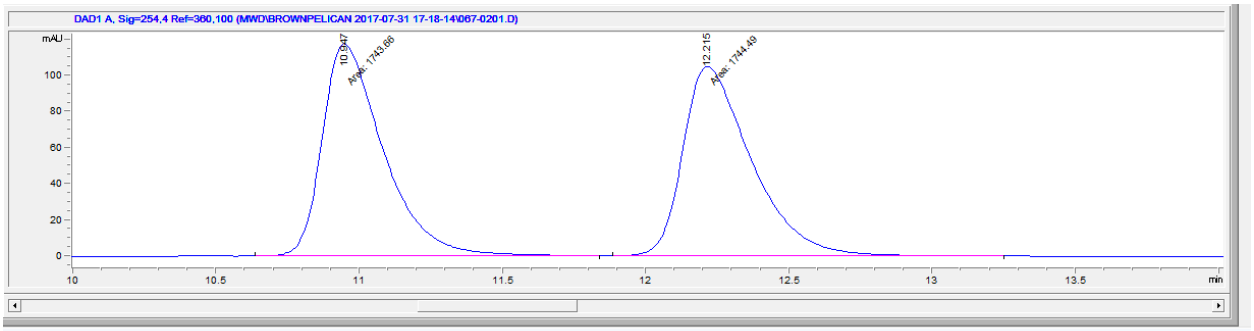
#	Time	Area	Height	Width	Area%	Symmetry
1	5.282	522.5	85.1	0.1023	10.600	0.742
2	6.312	918.6	65.9	0.2322	18.635	0.469
3	10.947	1743.7	117.7	0.247	35.374	0.556
4	12.215	1744.5	105	0.277	35.391	0.546

HPLC Enantioselective Assay (Full)



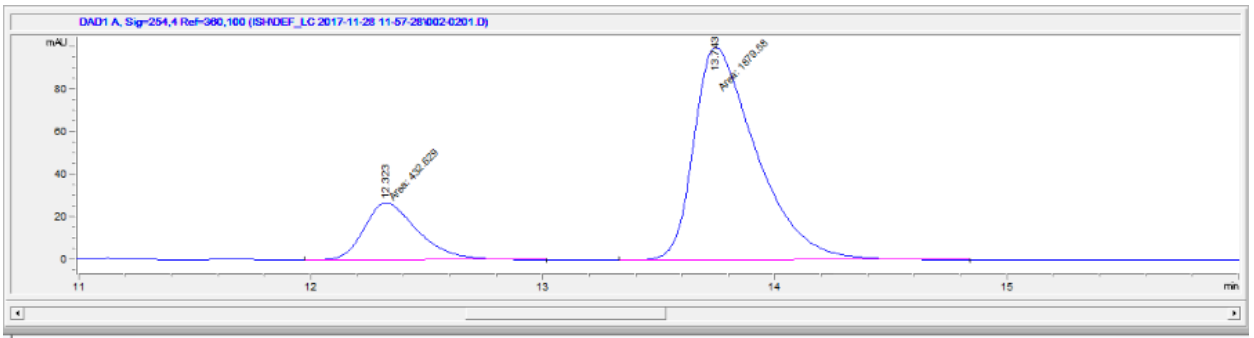
#	Time	Area	Height	Width	Area%	Symmetry
1	12.323	432.6	26.7	0.2697	18.711	0.671
2	13.743	1879.6	99.9	0.3137	81.289	0.518

HPLC Racemic Assay (Product)



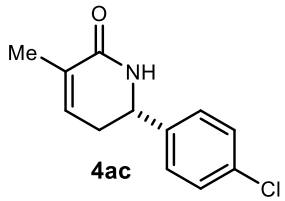
#	Time	Area	Height	Width	Area%	Symmetry
1	10.947	1743.7	117.7	0.247	49.988	0.556
2	12.215	1744.5	105	0.277	50.012	0.546

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	12.323	432.6	26.7	0.2697	18.711	0.671
2	13.743	1879.6	99.9	0.3137	81.289	0.518

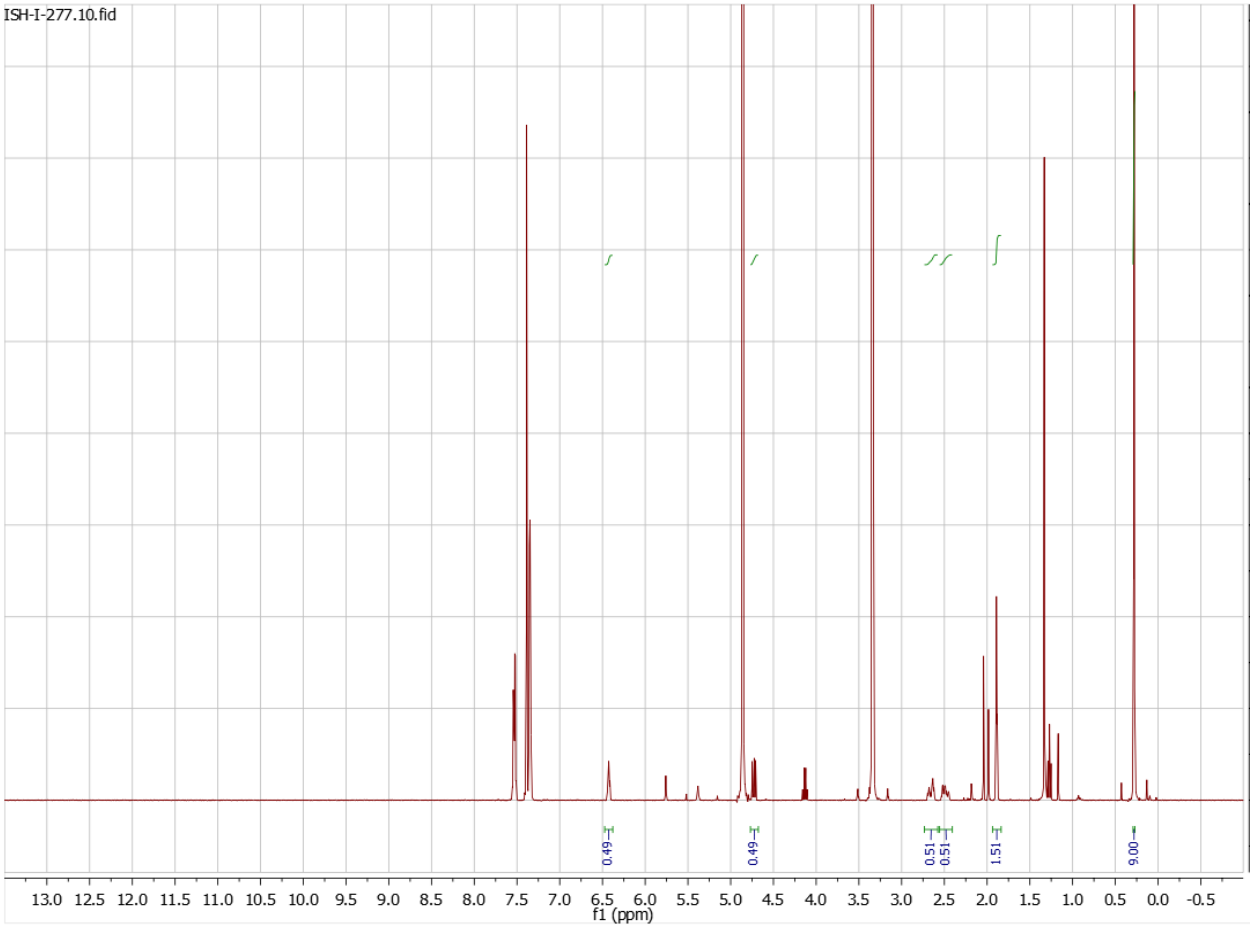
6-(4-Chlorophenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4ac).



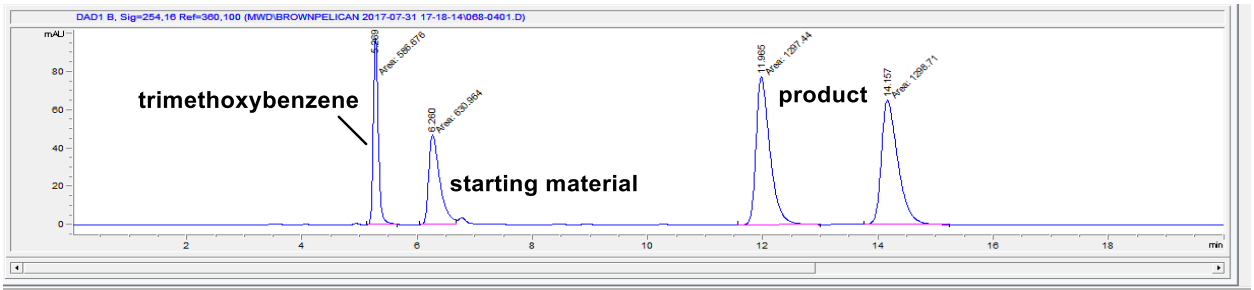
4ac

Product synthesized according to general procedure A. Product yield was determined to be 51% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 91% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 13.4 min, t_r(e_2, major) = 15.7 min).

NMR Yield Data

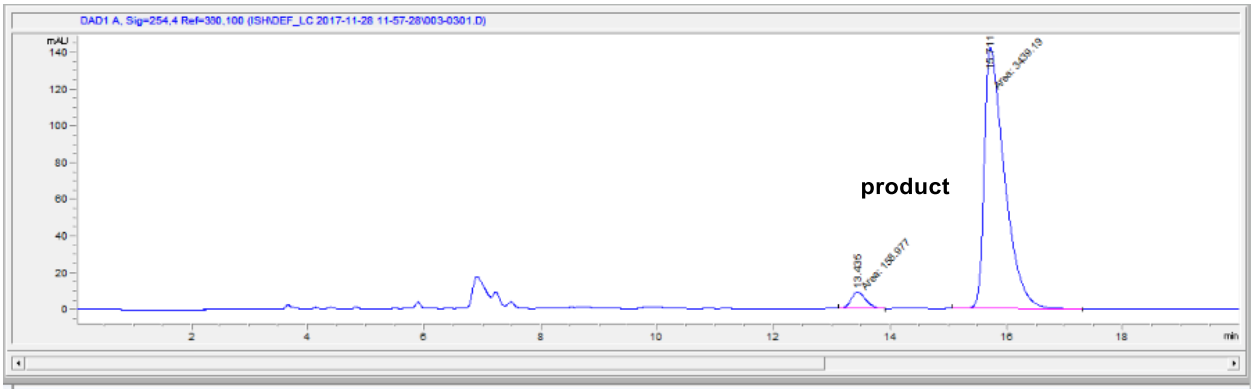


HPLC Racemic Assay (Full)



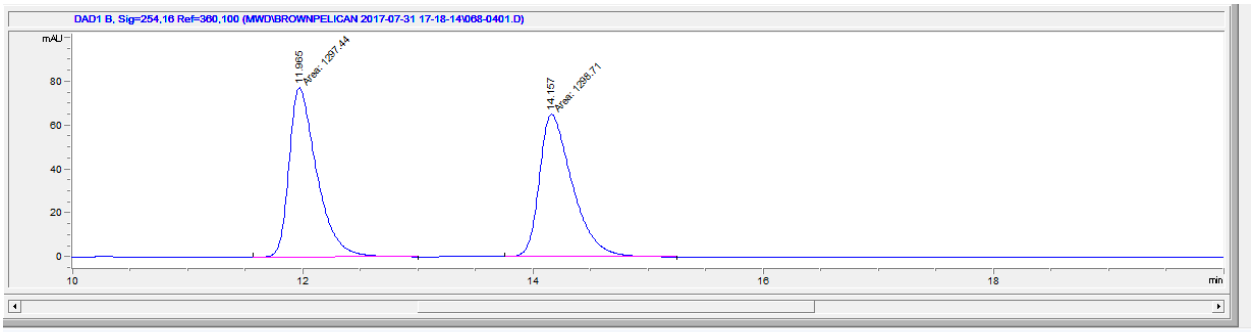
#	Time	Area	Height	Width	Area%	Symmetry
1	5.269	586.7	97.5	0.1003	15.383	0.768
2	6.26	631	46.9	0.2243	16.544	0.513
3	11.965	1297.4	77.2	0.2799	34.020	0.57
4	14.157	1298.7	65.1	0.3327	34.053	0.567

HPLC Enantioselective Assay (Full)



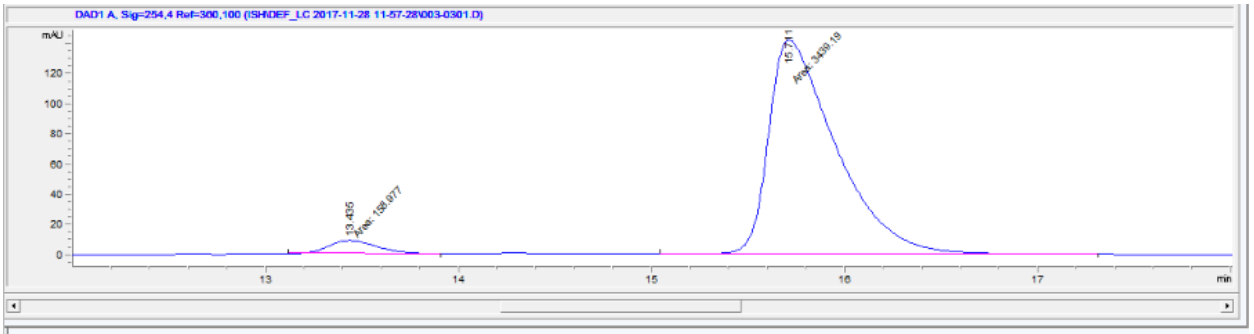
#	Time	Area	Height	Width	Area%	Symmetry
1	13.435	159	8.9	0.2971	4.418	0.763
2	15.711	3439.2	141.8	0.4042	95.582	0.427

HPLC Racemic Assay (Product)



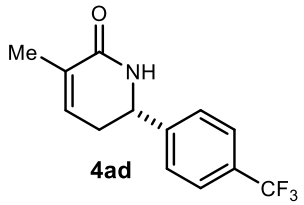
#	Time	Area	Height	Width	Area%	Symmetry
1	11.965	1297.4	77.2	0.2799	49.976	0.57
2	14.157	1298.7	65.1	0.3327	50.024	0.567

HPLC Enantioselective Assay (Product)



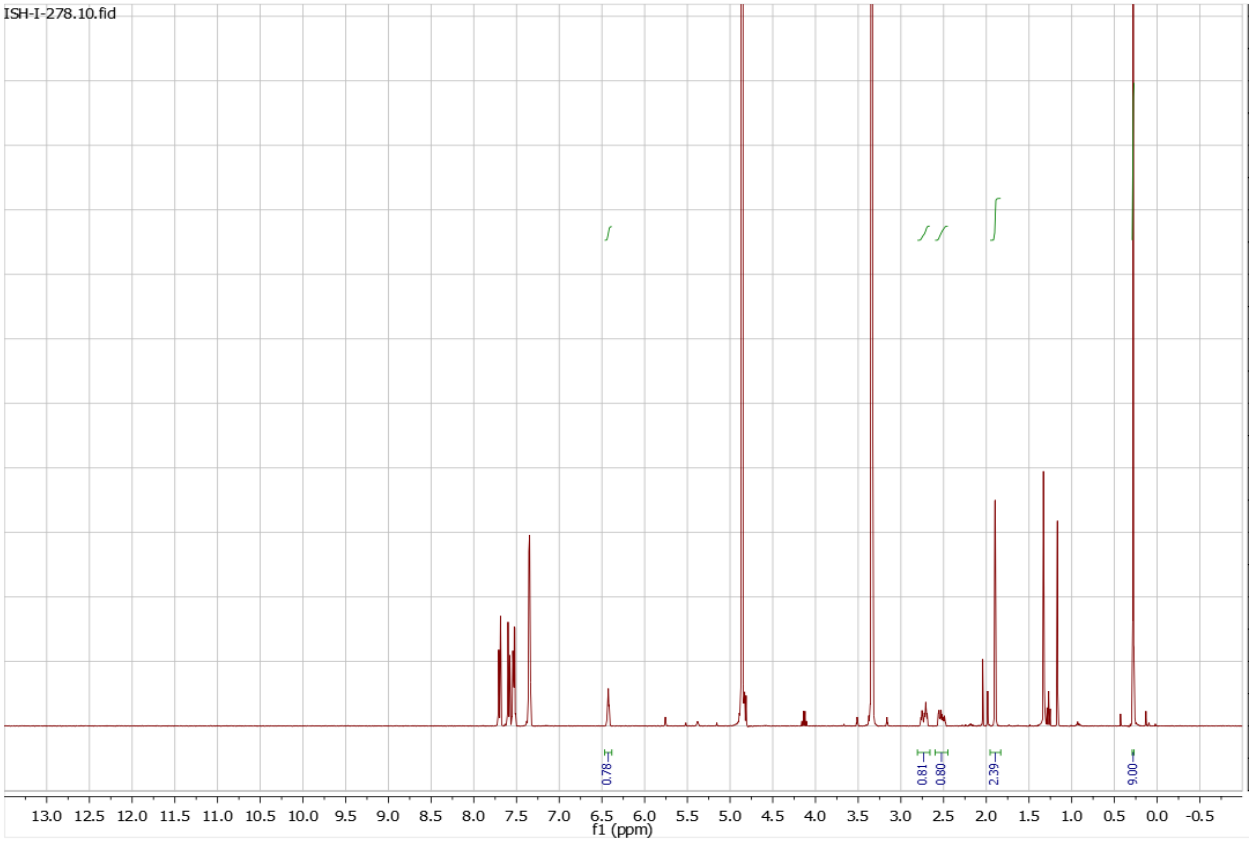
#	Time	Area	Height	Width	Area%	Symmetry
1	13.435	159	8.9	0.2971	4.418	0.763
2	15.711	3439.2	141.8	0.4042	95.582	0.427

3-Methyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4ad).

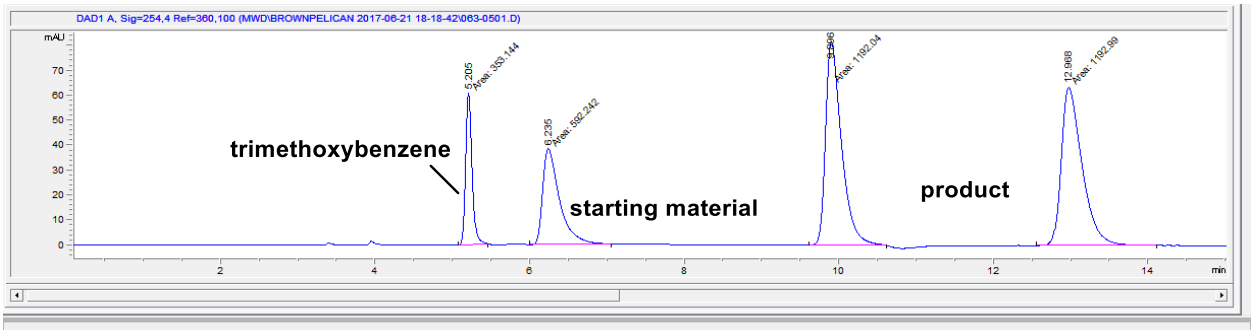


Product synthesized according to general procedure A. Product yield was determined to be 81% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 96% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, minor) = 11.0 min, $t_r(e_2$, major) = 14.1 min).

NMR Yield Data

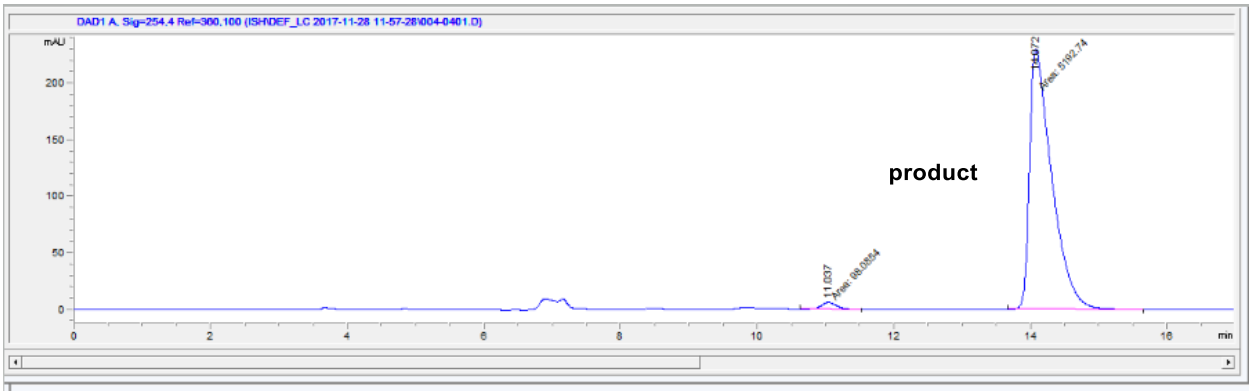


HPLC Racemic Assay (Full)



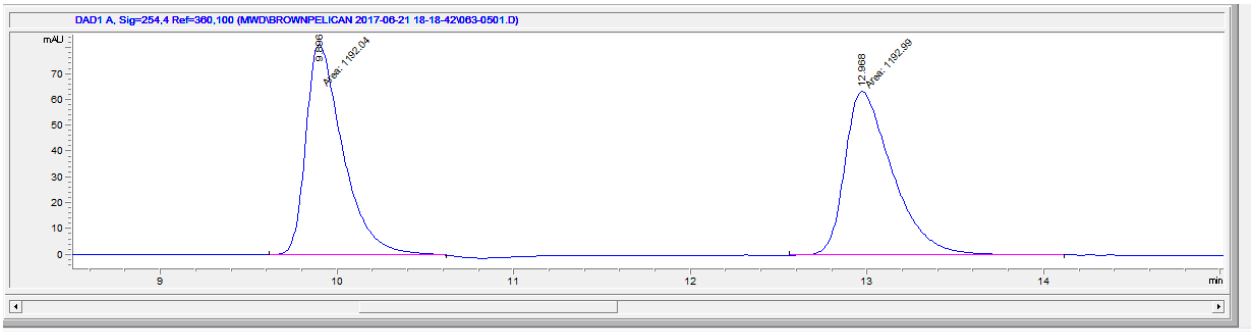
#	Time	Area	Height	Width	Area%	Symmetry
1	5.205	353.1	61.2	0.0961	10.604	0.791
2	6.235	592.2	38.5	0.2566	17.783	0.481
3	9.896	1192	81.4	0.2439	35.792	0.544
4	12.968	1193	63.5	0.3133	35.821	0.542

HPLC Enantioselective Assay (Full)



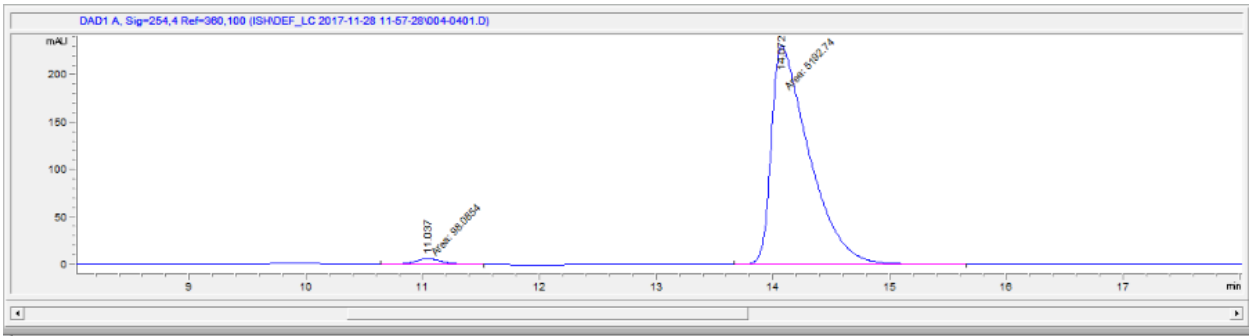
#	Time	Area	Height	Width	Area%	Symmetry
1	11.037	98.1	6.2	0.2653	1.854	0.826
2	14.072	5192.7	229.9	0.3765	98.146	0.375

HPLC Racemic Assay (Product)



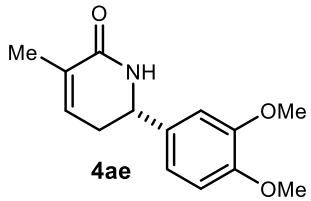
#	Time	Area	Height	Width	Area%	Symmetry
1	9.896	1192	81.4	0.2439	49.980	0.544
2	12.968	1193	63.5	0.3133	50.020	0.542

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	11.037	98.1	6.2	0.2653	1.854	0.826
2	14.072	5192.7	229.9	0.3765	98.146	0.375

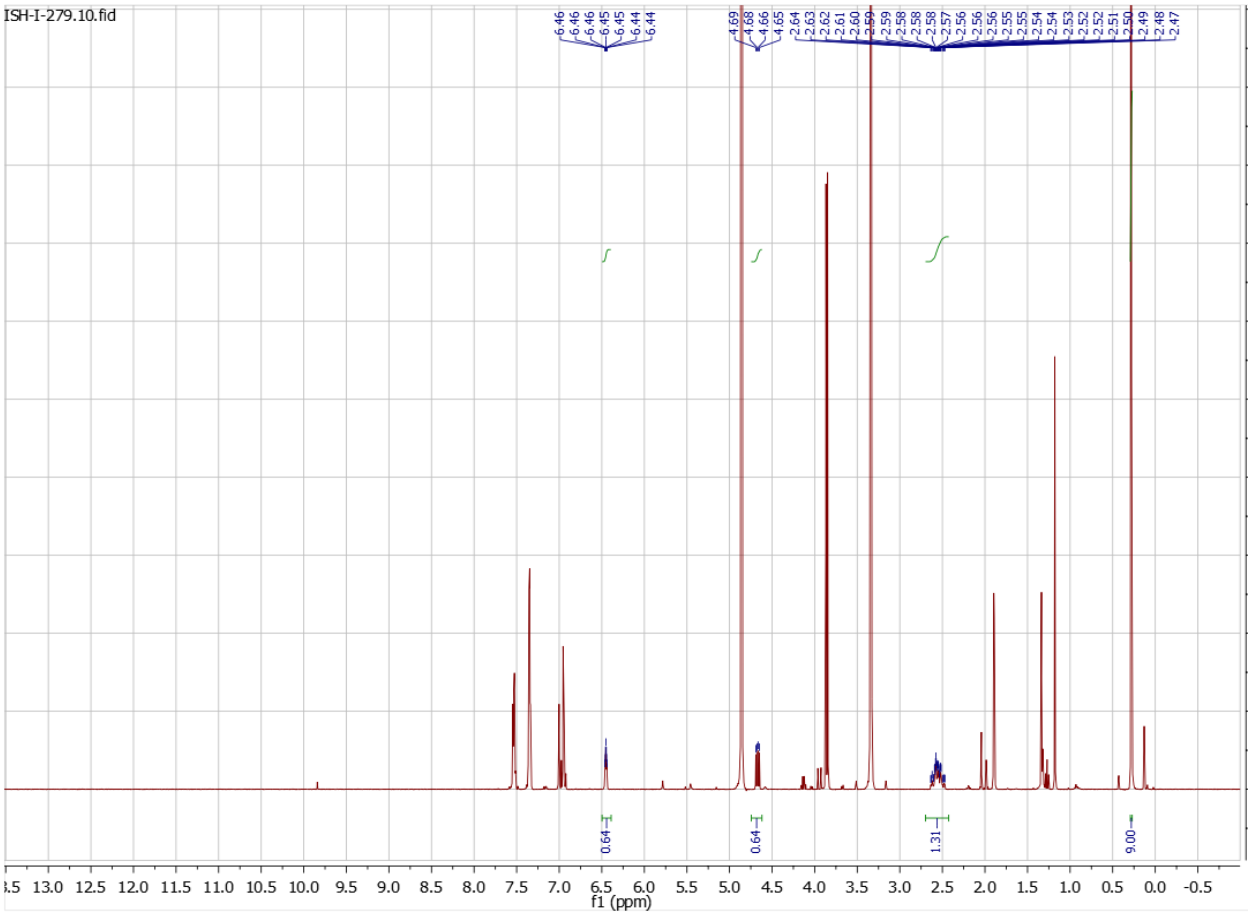
6-(3,4-Dimethoxyphenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4ae).



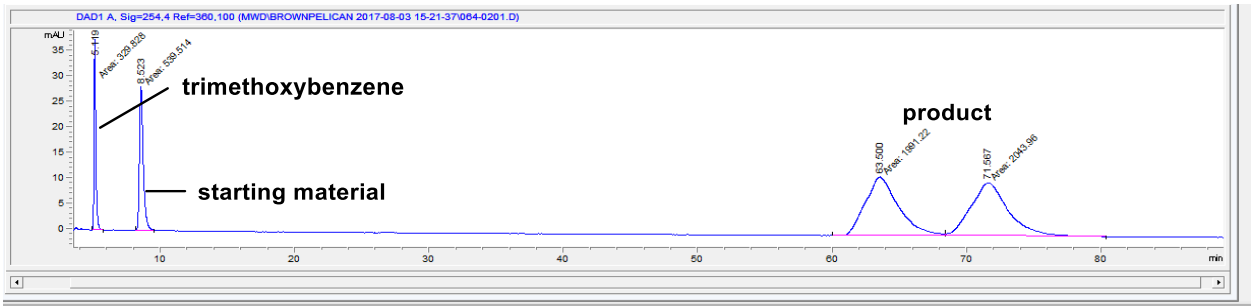
4ae

Product synthesized according to general procedure A. Product yield was determined to be 65% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 92% ee by chiral HPLC analysis. (Chiralpak IA, 5% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, major) = 79.9 min, $t_r(e_2$, minor) = 93.9 min).

NMR Yield Data

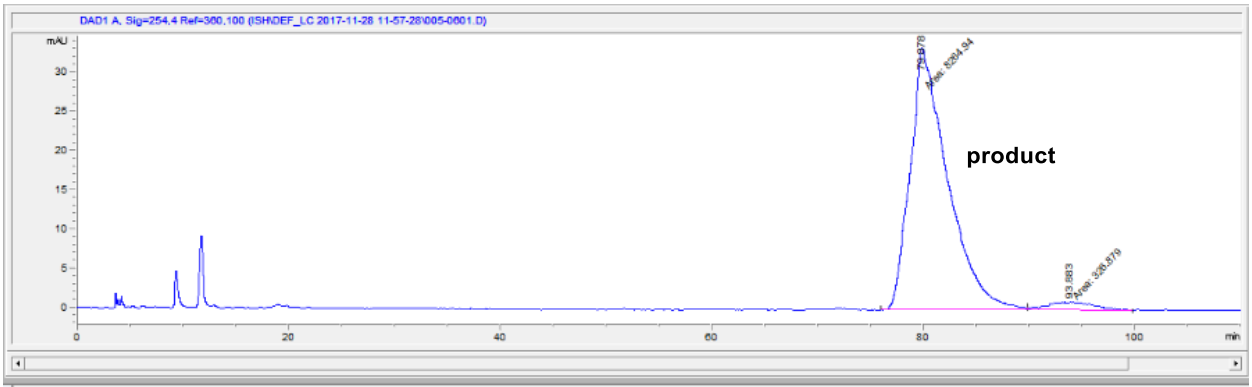


HPLC Racemic Assay (Full)



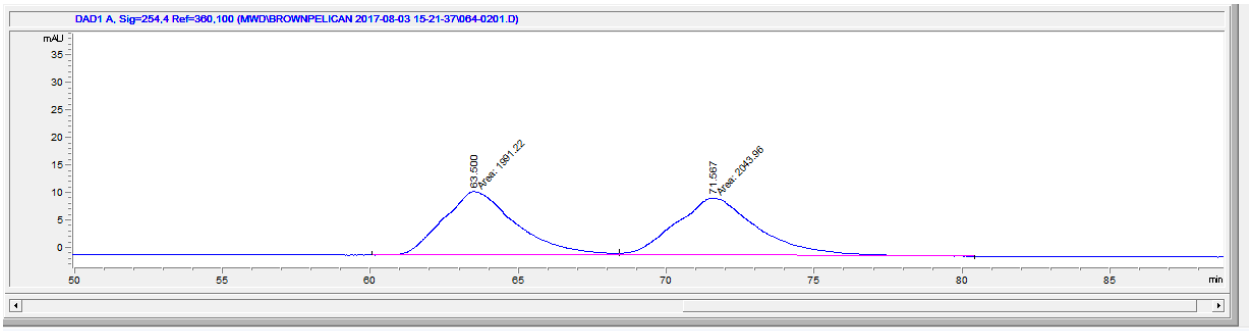
#	Time	Area	Height	Width	Area%	Symmetry
1	5.119	329.8	37.4	0.1471	6.725	0.683
2	8.523	539.5	28.2	0.3187	11.000	0.649
3	63.5	1991.2	11.6	2.8686	40.600	0
4	71.567	2044	10.4	3.2682	41.675	0.807

HPLC Enantioselective Assay (Full)



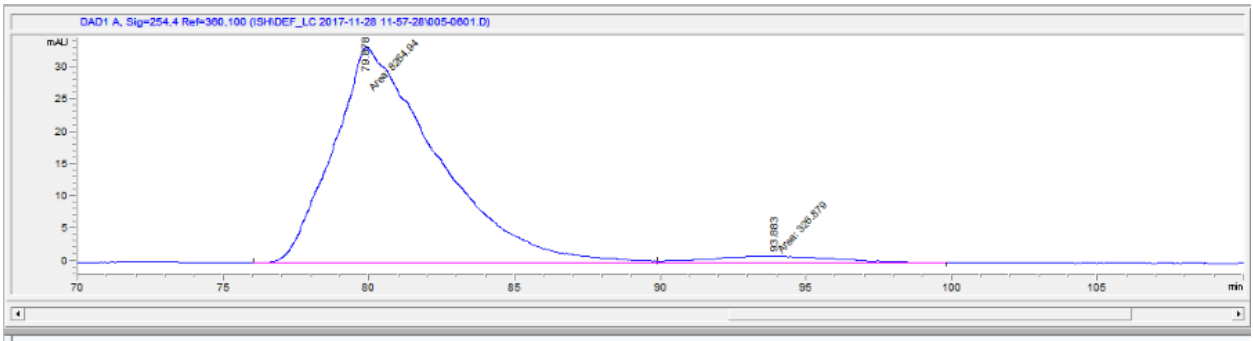
#	Time	Area	Height	Width	Area%	Symmetry
1	79.878	8264.9	33.4	4.1247	96.195	0
2	93.883	326.9	1	5.2199	3.805	0.968

HPLC Racemic Assay (Product)



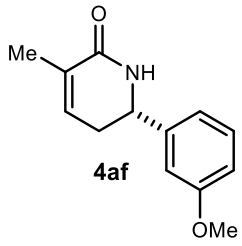
#	Time	Area	Height	Width	Area%	Symmetry
1	63.5	1991.2	11.6	2.8686	49.346	0
2	71.567	2044	10.4	3.2682	50.654	0.807

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	79.878	8264.9	33.4	4.1247	96.195	0
2	93.883	326.9	1	5.2199	3.805	0.968

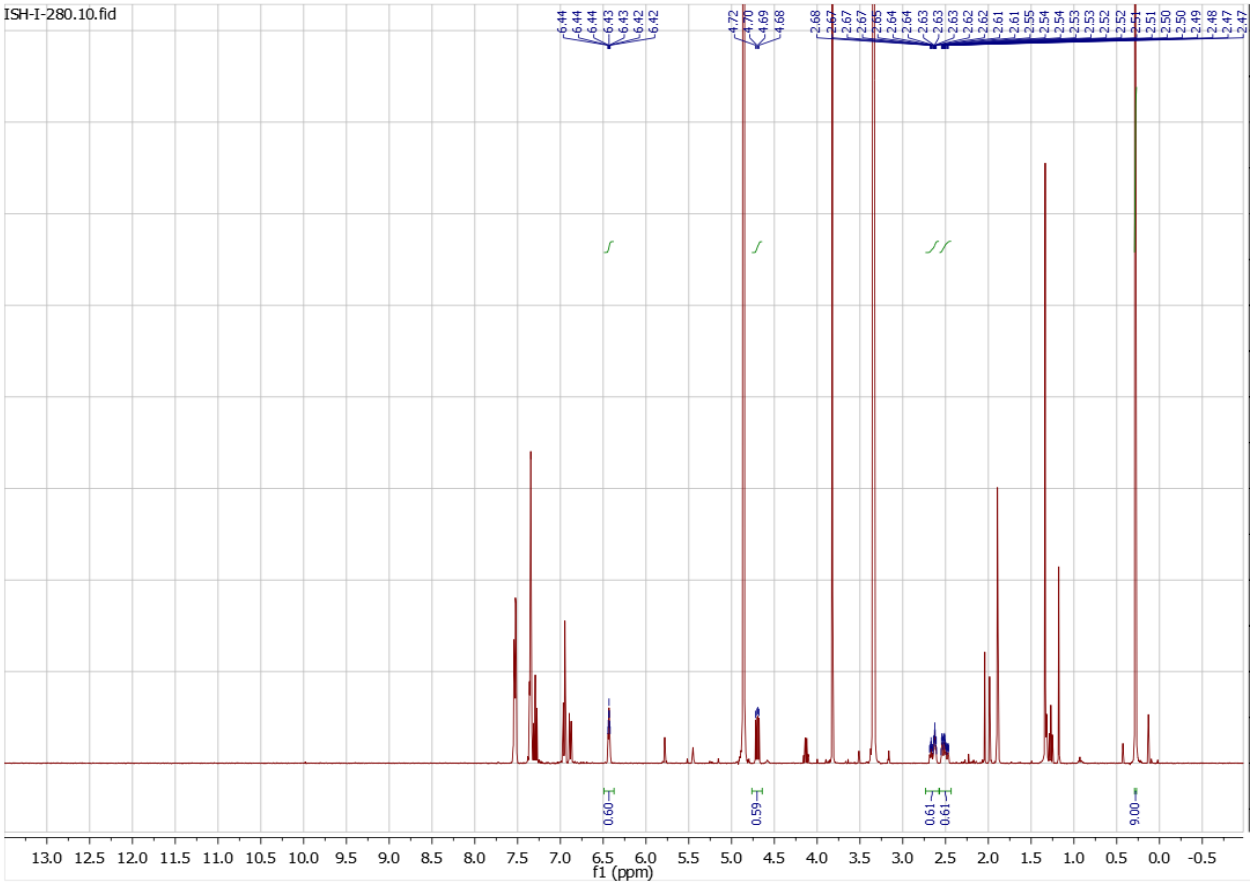
6-(3-Methoxyphenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4af).



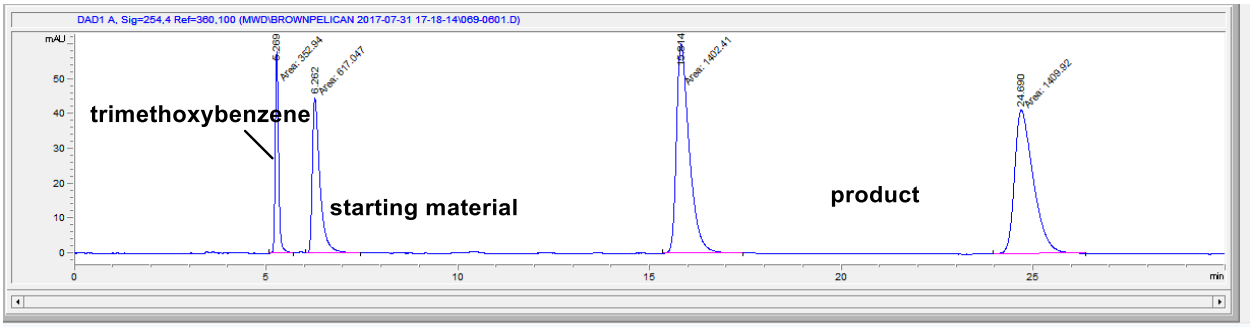
4af

Product synthesized according to general procedure A. Product yield was determined to be 61% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 77% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, minor) = 17.7 min, $t_r(e_2$, major) = 27.6 min).

NMR Yield Data

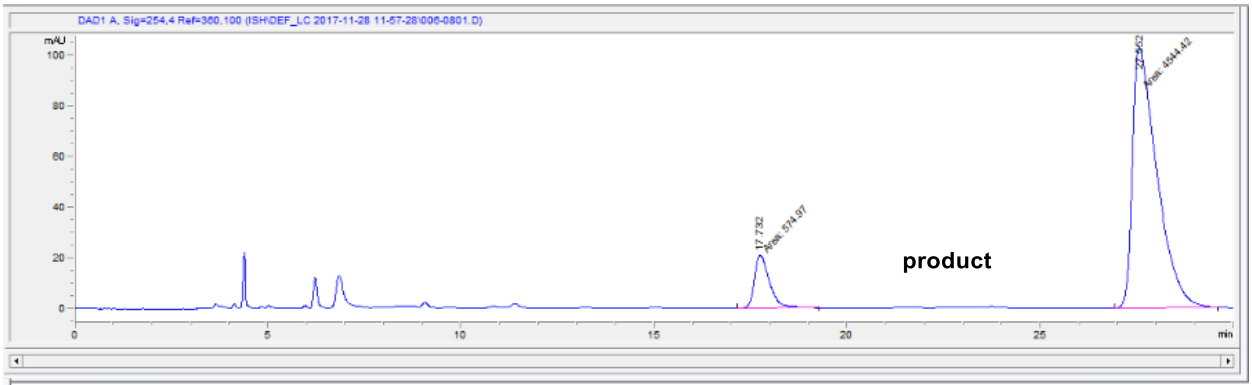


HPLC Racemic Assay (Full)



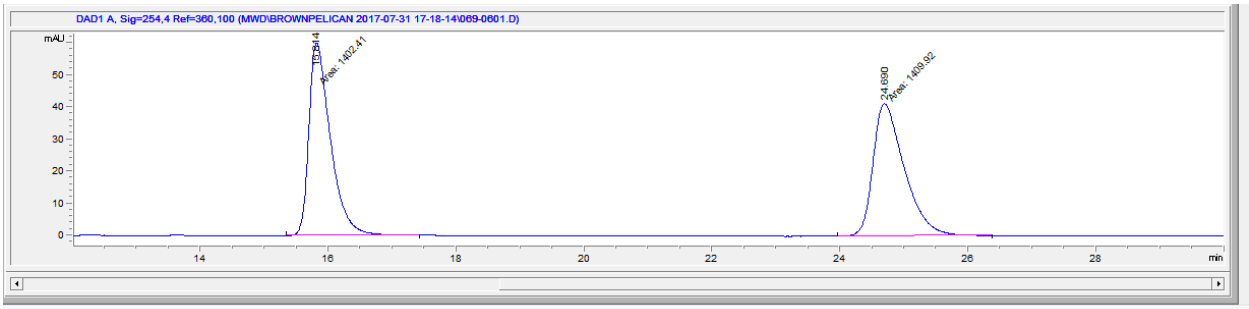
#	Time	Area	Height	Width	Area%	Symmetry
1	5.269	352.9	58	0.1014	9.331	0.765
2	6.262	617	44.5	0.2309	16.314	0.482
3	15.814	1402.4	60.1	0.3892	37.078	0.533
4	24.69	1409.9	41.2	0.5699	37.277	0.55

HPLC Enantioselective Assay (Full)



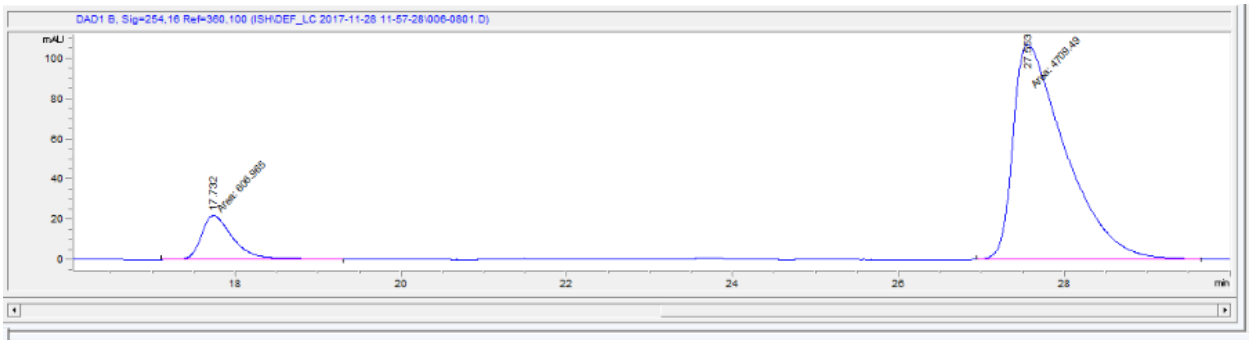
#	Time	Area	Height	Width	Area%	Symmetry
1	17.732	575	21.1	0.4532	11.231	0.579
2	27.552	4544.4	103.1	0.7346	88.769	0.373

HPLC Racemic Assay (Product)



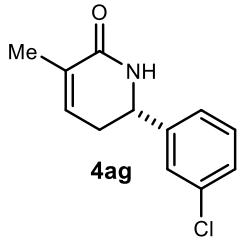
#	Time	Area	Height	Width	Area%	Symmetry
1	15.814	1402.4	60.1	0.3892	49.867	0.533
2	24.69	1409.9	41.2	0.5699	50.133	0.55

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	17.732	607	22	0.4595	11.417	0.578
2	27.553	4709.5	106.9	0.7345	88.583	0.374

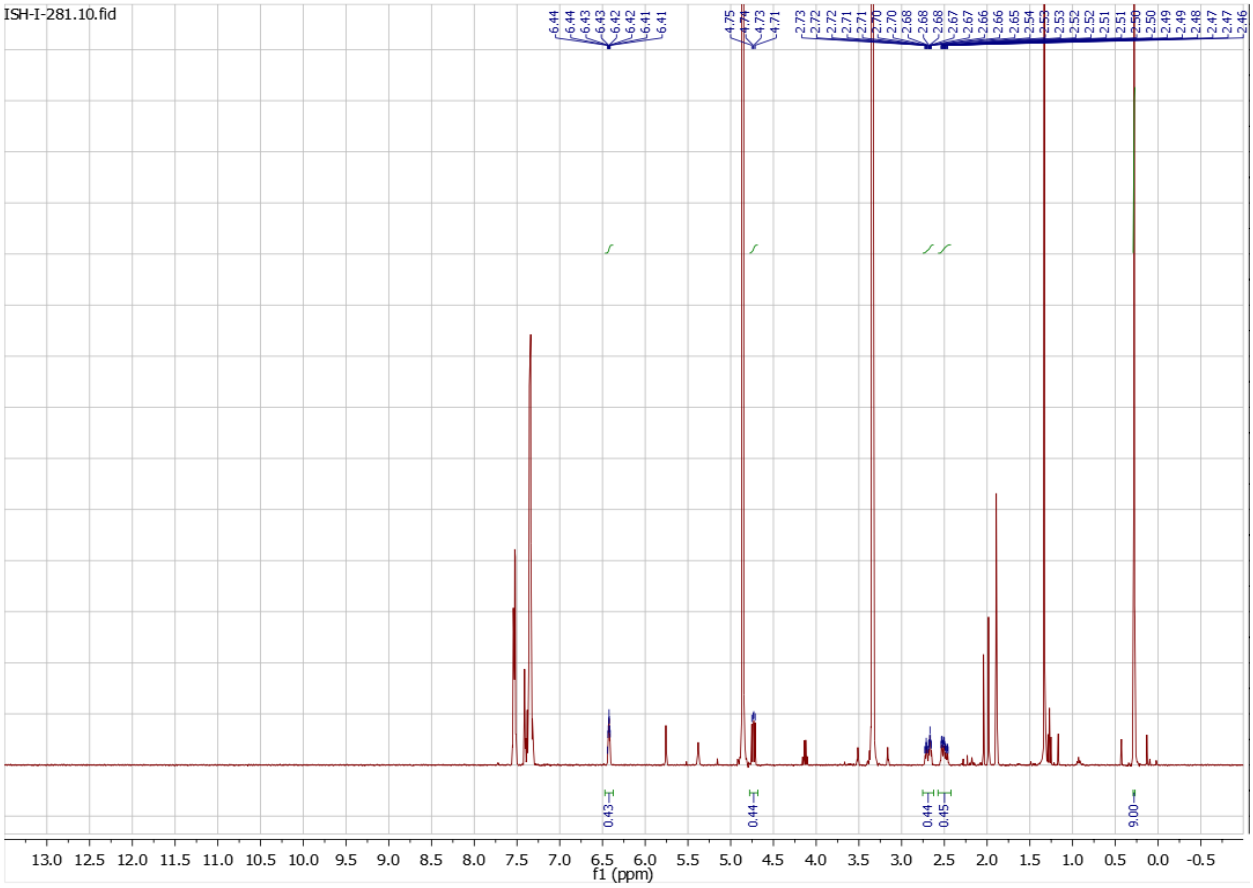
6-(3-Chlorophenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4ag).



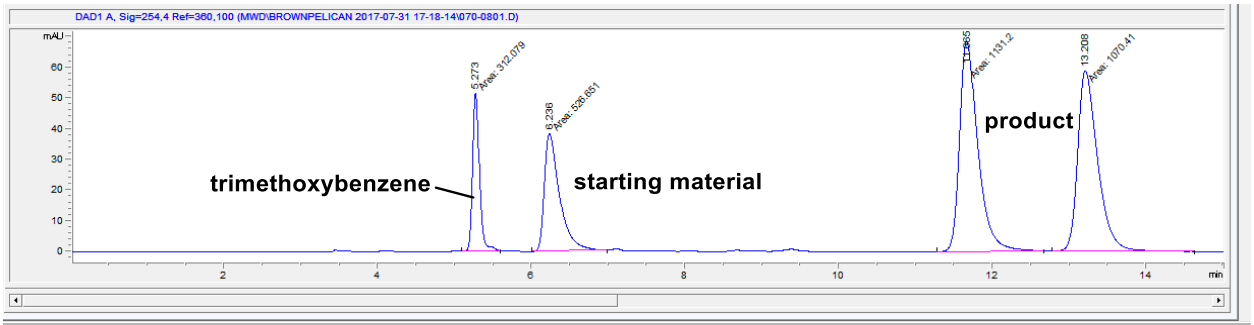
4ag

Product synthesized according to general procedure A. Product yield was determined to be 45% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 88% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 12.6 min, t_r(e_2, major) = 14.1 min).

NMR Yield Data

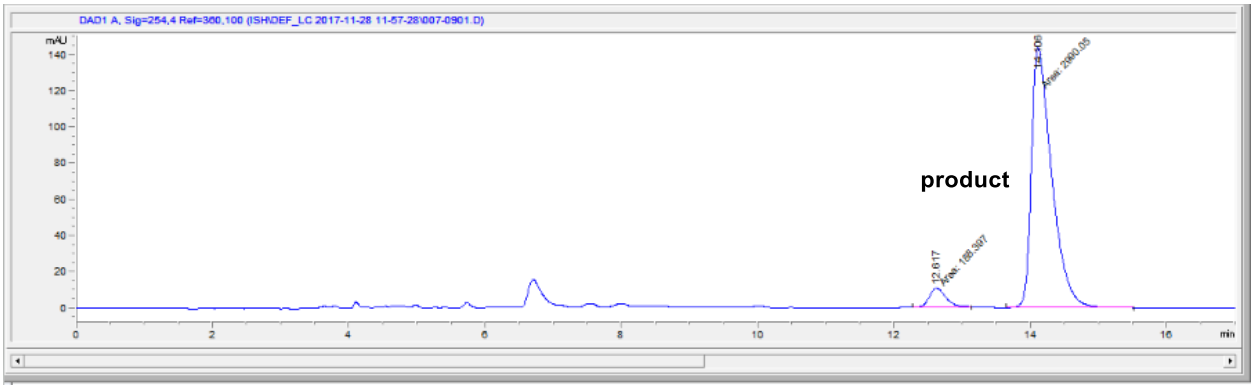


HPLC Racemic Assay (Full)



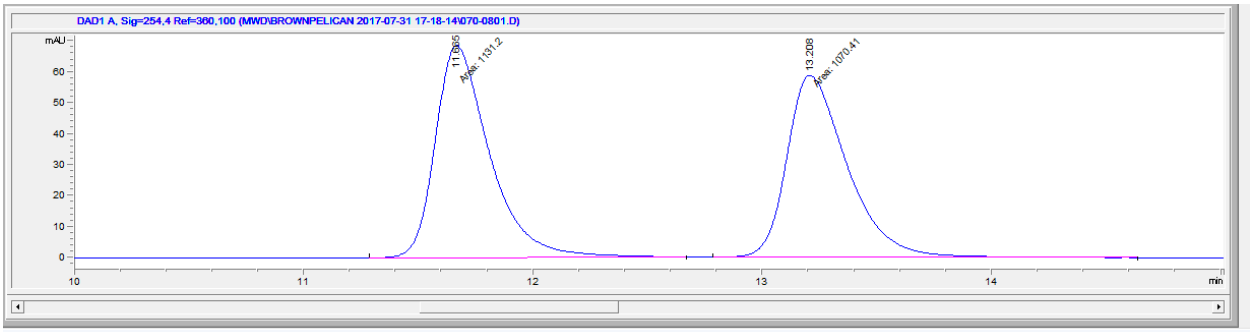
#	Time	Area	Height	Width	Area%	Symmetry
1	5.273	312.1	51.5	0.1009	10.265	0.774
2	6.236	526.7	38.3	0.2294	17.322	0.501
3	11.665	1131.2	68.5	0.2752	37.206	0.611
4	13.208	1070.4	58.7	0.3037	35.207	0.605

HPLC Enantioselective Assay (Full)



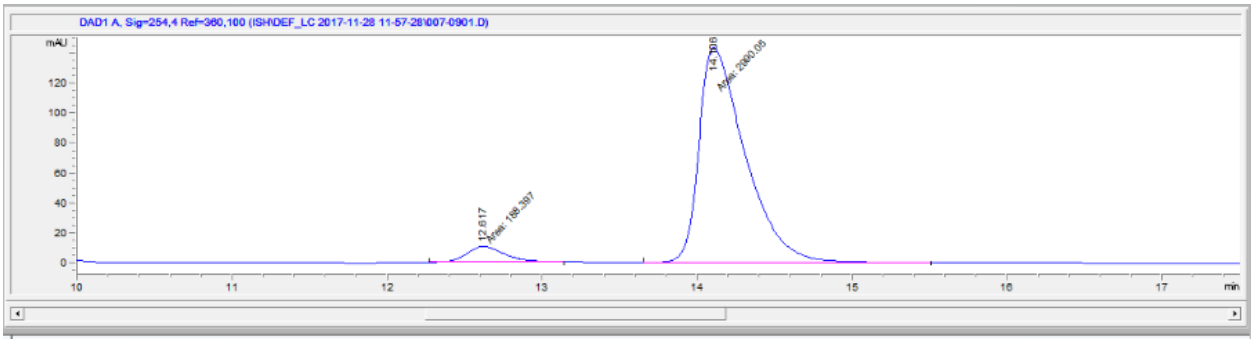
#	Time	Area	Height	Width	Area%	Symmetry
1	12.617	188.4	10.7	0.2935	5.927	0.742
2	14.106	2990	143.8	0.3466	94.073	0.471

HPLC Racemic Assay (Product)



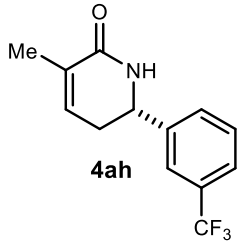
#	Time	Area	Height	Width	Area%	Symmetry
1	11.665	1131.2	68.5	0.2752	51.381	0.611
2	13.208	1070.4	58.7	0.3037	48.619	0.605

HPLC Enantioselective Assay (Product)



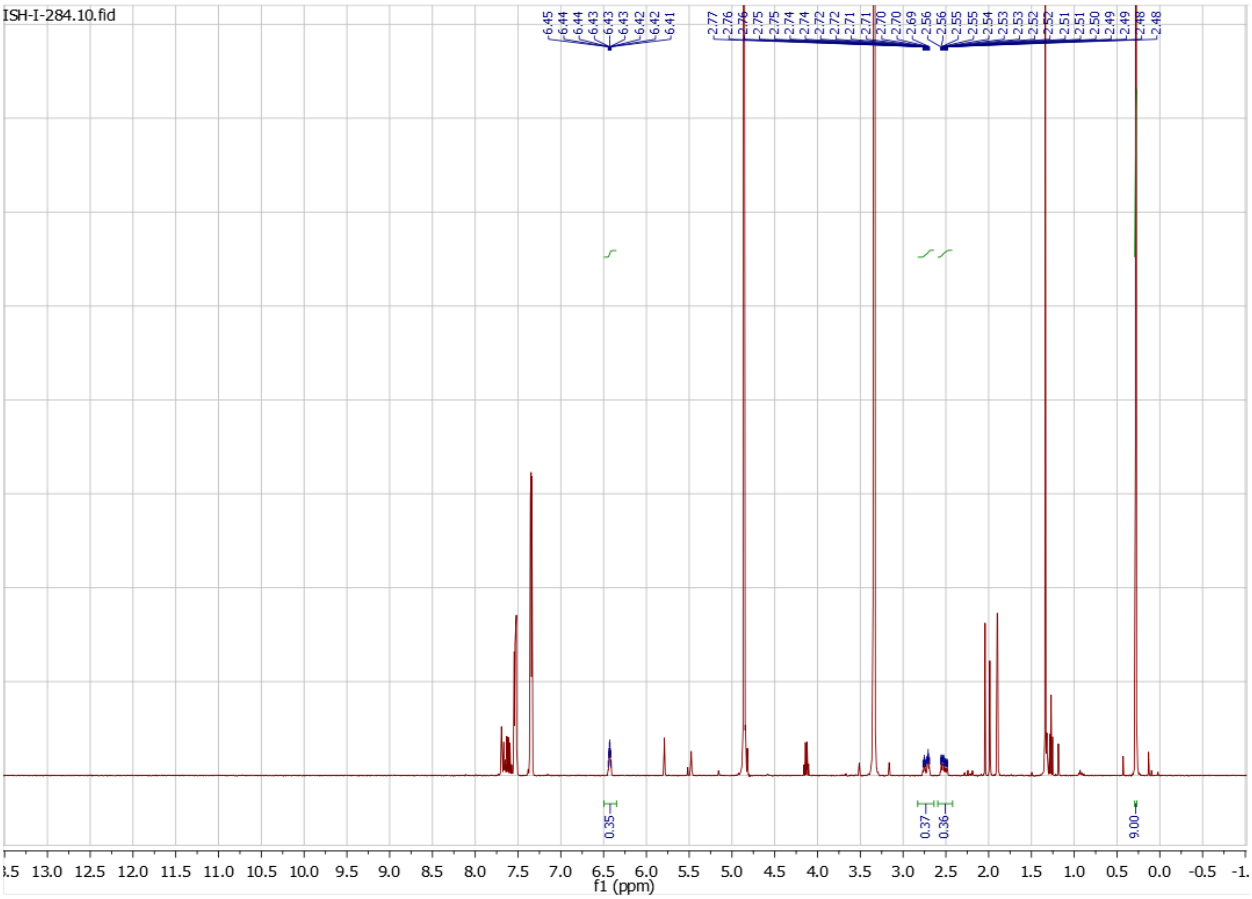
#	Time	Area	Height	Width	Area%	Symmetry
1	12.617	188.4	10.7	0.2935	5.927	0.742
2	14.106	2990	143.8	0.3466	94.073	0.471

3-Methyl-6-(3-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4ah).

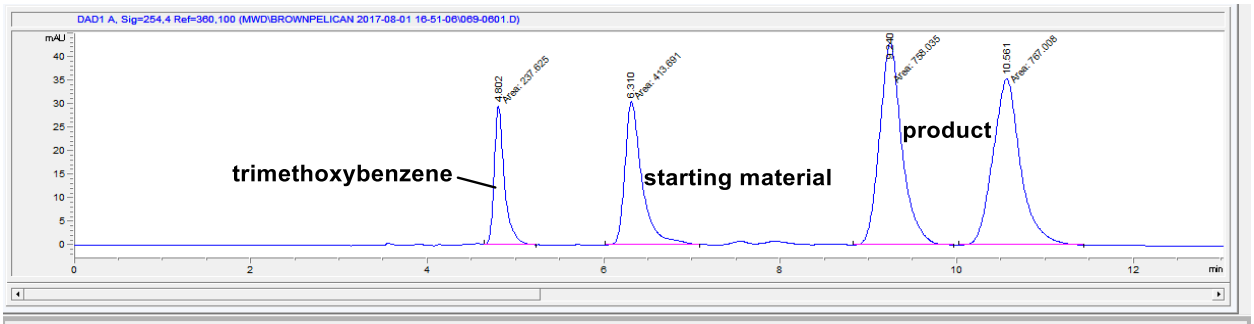


Product synthesized according to general procedure A. Product yield was determined to be 37% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 85% ee by chiral HPLC analysis. (Chiralpak IA, 7% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, major) = 9.9 min, t_r(e_2, minor) = 11.5 min).

NMR Yield Data

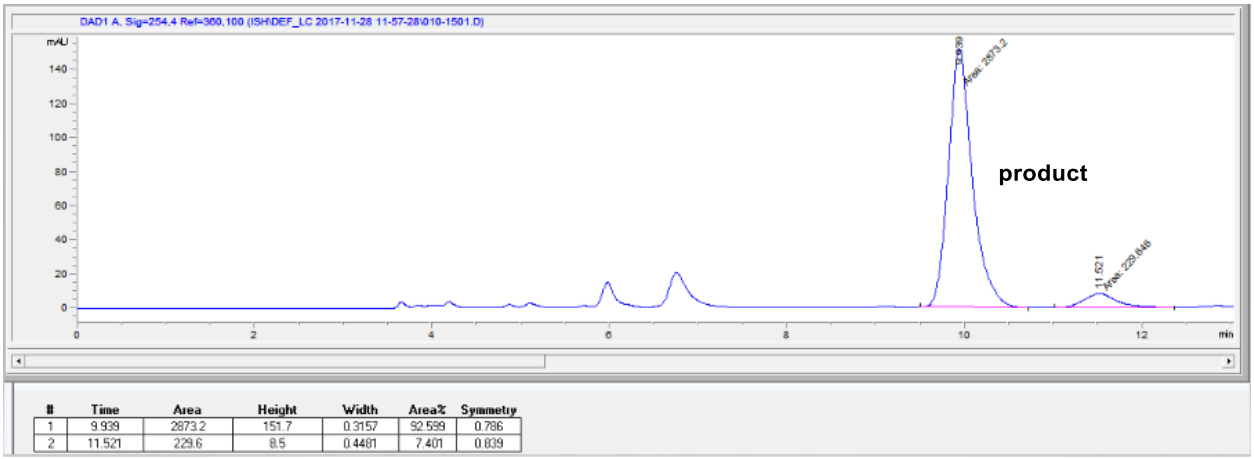


HPLC Racemic Assay (Full)



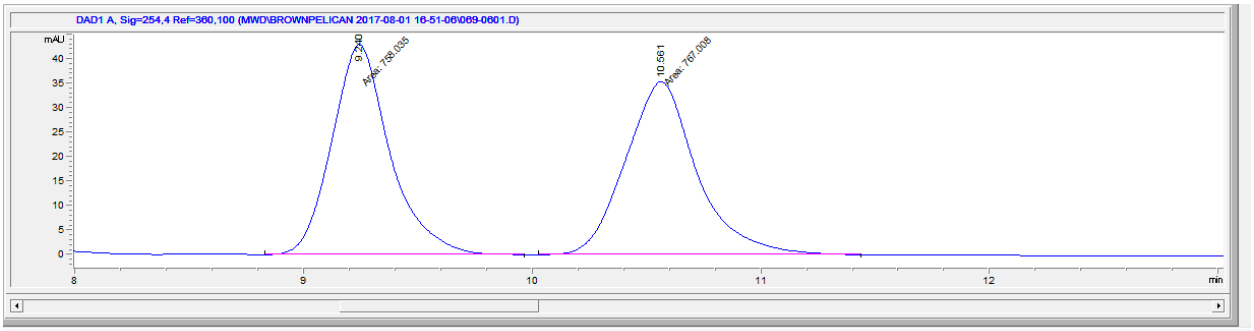
#	Time	Area	Height	Width	Area%	Symmetry
1	4.802	237.6	29.5	0.1342	10.918	0.666
2	6.31	413.7	30.5	0.2264	19.008	0.593
3	9.24	758	42.9	0.2944	34.830	0.859
4	10.561	767	35.3	0.362	35.243	0.944

HPLC Enantioselective Assay (Full)



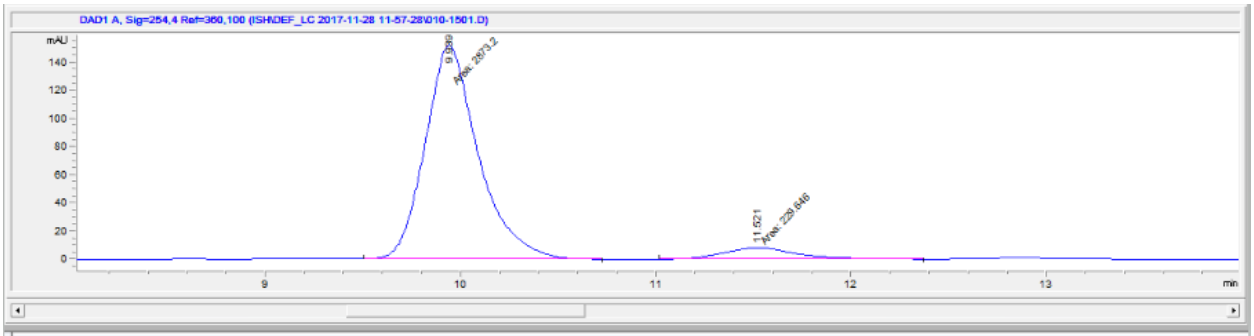
#	Time	Area	Height	Width	Area%	Symmetry
1	9.939	2873.2	151.7	0.3157	92.599	0.786
2	11.521	229.6	8.5	0.4481	7.401	0.839

HPLC Racemic Assay (Product)



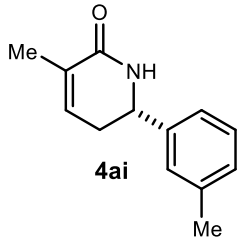
#	Time	Area	Height	Width	Area%	Symmetry
1	9.24	758	42.9	0.2944	49.706	0.859
2	10.561	767	35.3	0.362	50.294	0.944

HPLC Enantioselective Assay (Product)



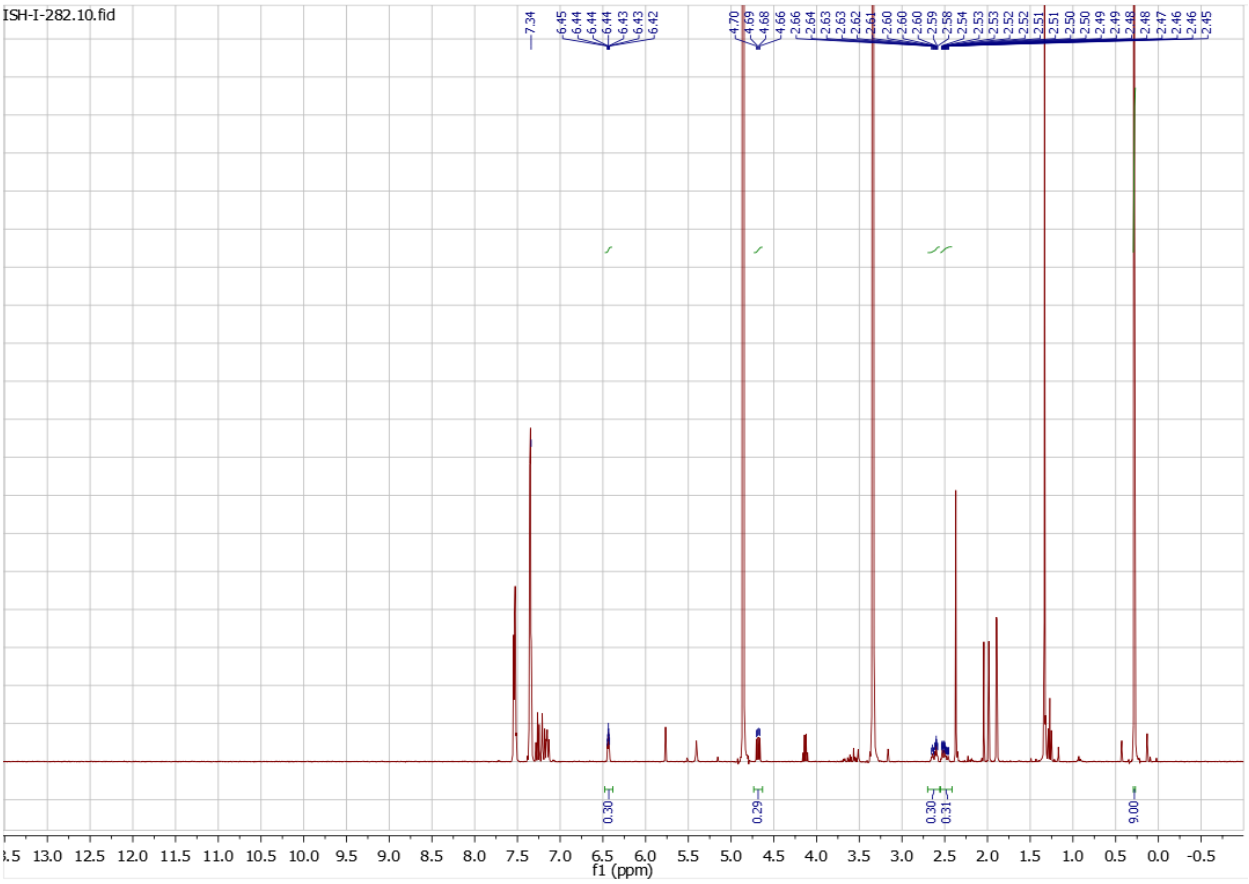
#	Time	Area	Height	Width	Area%	Symmetry
1	9.939	2873.2	151.7	0.3157	92.599	0.786
2	11.521	229.6	8.5	0.4481	7.401	0.839

3-Methyl-6-(m-tolyl)-5,6-dihydropyridin-2(1H)-one (4ai).

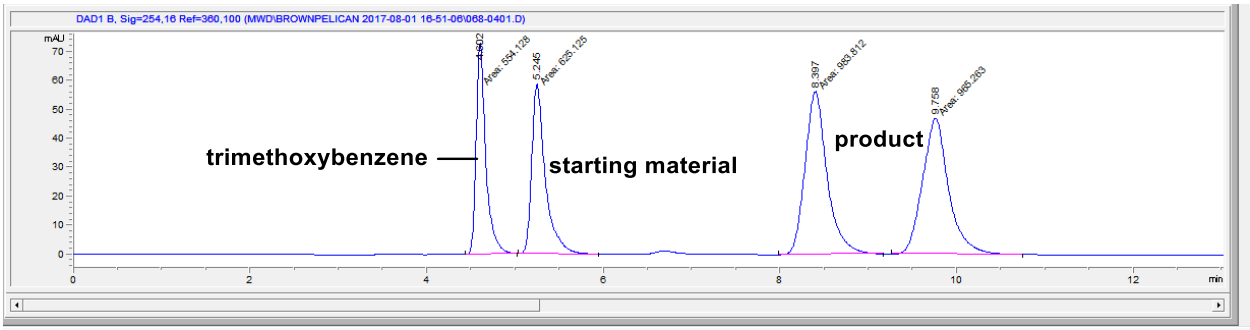


Product synthesized according to general procedure A. Product yield was determined to be 31% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 82% ee by chiral HPLC analysis. (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, major) = 8.9 min, t_r(e_2, minor) = 10.5 min).

NMR Yield Data

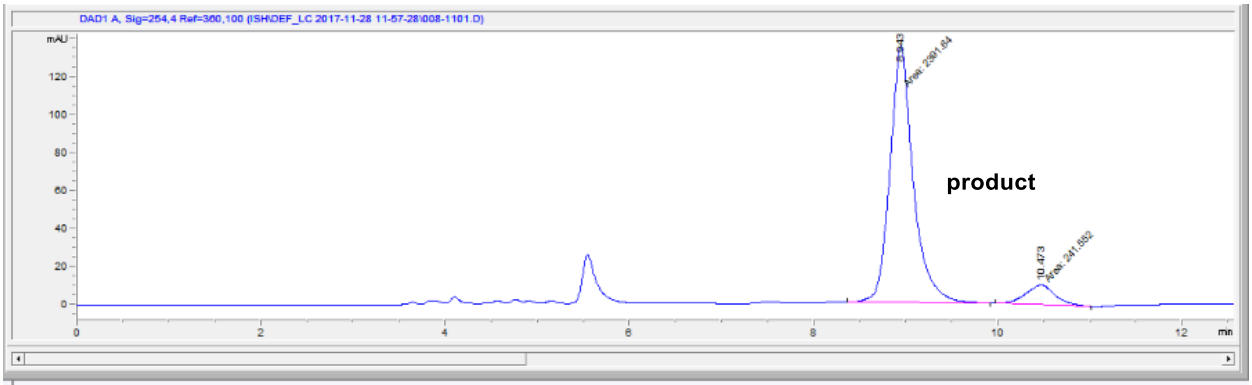


HPLC Racemic Assay (Full)



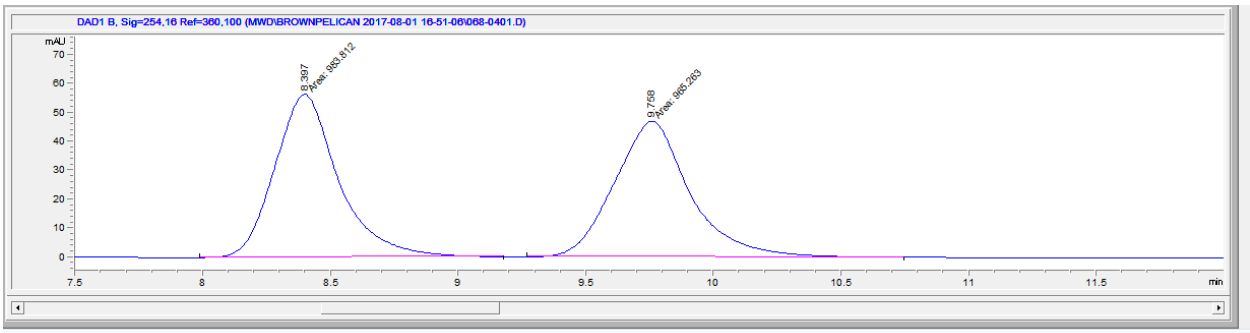
#	Time	Area	Height	Width	Area%	Symmetry
1	4.602	554.1	72.9	0.1267	17.713	0.663
2	5.245	625.1	58.7	0.1775	19.983	0.586
3	8.397	983.8	56.3	0.2911	31.448	0.834
4	9.758	965.3	46.9	0.3429	30.856	0.937

HPLC Enantioselective Assay (Full)



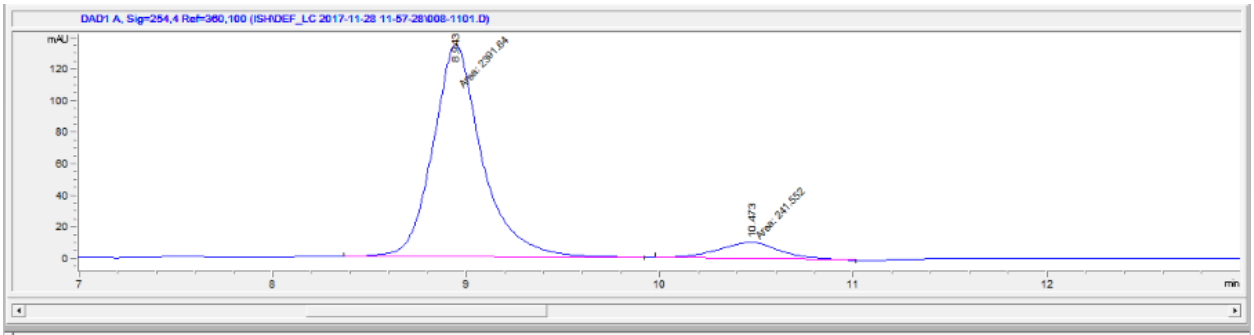
#	Time	Area	Height	Width	Area%	Symmetry
1	8.943	2391.6	135	0.2953	90.827	0.834
2	10.473	241.6	10.5	0.3817	9.173	1.035

HPLC Racemic Assay (Product)



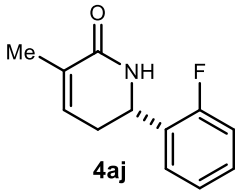
#	Time	Area	Height	Width	Area%	Symmetry
1	8.397	983.8	56.3	0.2911	50.476	0.834
2	9.758	965.3	46.9	0.3429	49.524	0.937

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	8.943	2391.6	135	0.2953	90.827	0.834
2	10.473	241.6	10.5	0.3817	9.173	1.035

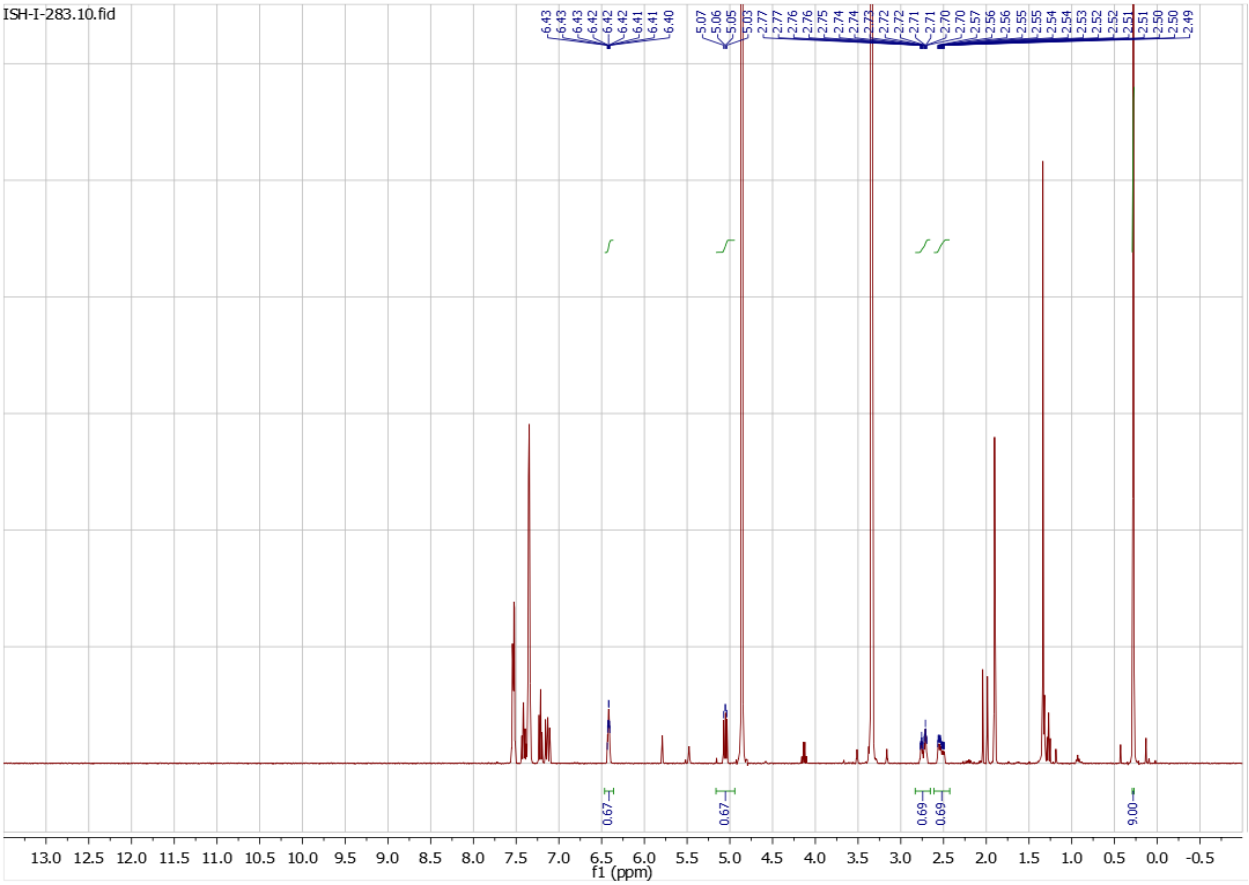
6-(2-Fluorophenyl)-3-methyl-5,6-dihydropyridin-2(1H)-one (4aj).



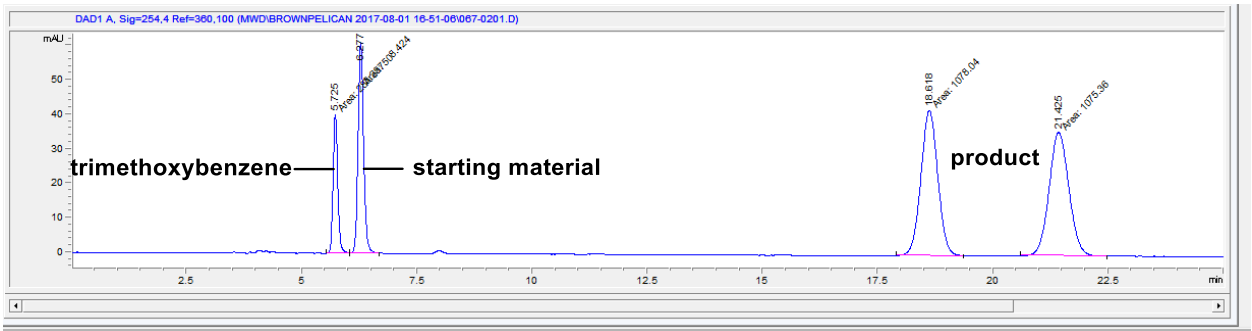
4aj

Product synthesized according to general procedure A. Product yield was determined to be 69% by ^{1}H NMR analysis (400 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 57% ee by chiral HPLC analysis. (Chiralpak IC, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 19.8 min, t_r(e_2, major) = 22.9 min).

NMR Yield Data

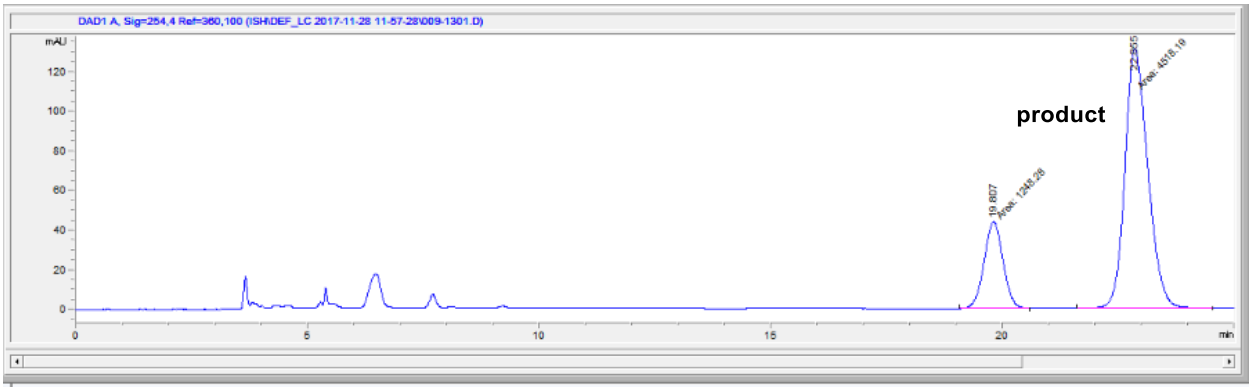


HPLC Racemic Assay (Full)



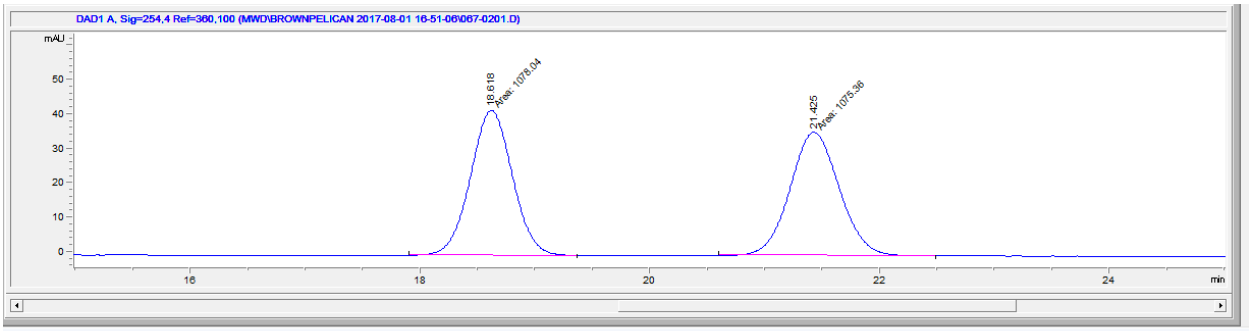
#	Time	Area	Height	Width	Area%	Symmetry
1	5.725	283.2	40.3	0.1172	9.617	0.871
2	6.277	508.4	60.8	0.1394	17.264	0.875
3	18.618	1078	42.1	0.4265	36.605	0.97
4	21.425	1075.4	35.8	0.5	36.514	0.909

HPLC Enantioselective Assay (Full)



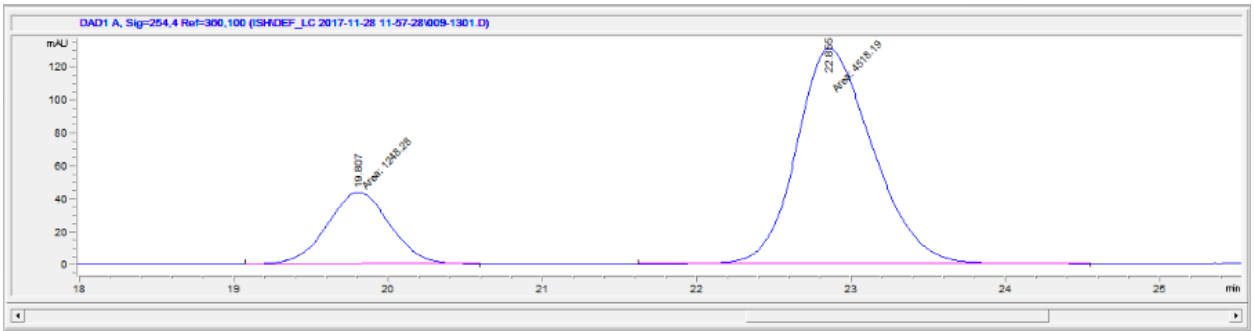
#	Time	Area	Height	Width	Area%	Symmetry
1	19.807	1248.3	43.7	0.4756	21.647	0.977
2	22.855	4518.2	130.9	0.5752	78.353	0.741

HPLC Racemic Assay (Product)



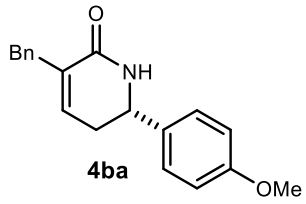
#	Time	Area	Height	Width	Area%	Symmetry
1	18.618	1078	42.1	0.4265	50.062	0.97
2	21.425	1075.4	35.8	0.5	49.938	0.909

HPLC Enantioselective Assay (Product)



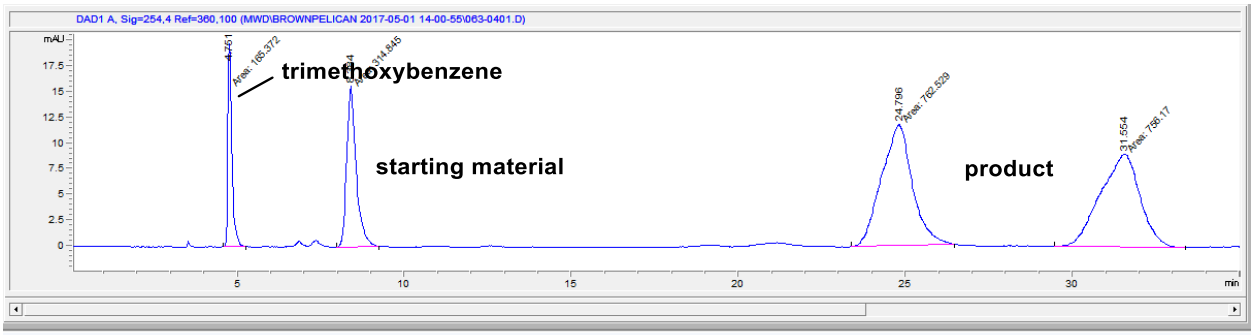
#	Time	Area	Height	Width	Area%	Symmetry
1	19.807	1248.3	43.7	0.4756	21.647	0.977
2	22.855	4518.2	130.9	0.5752	78.353	0.741

3-Benzyl-6-(4-methoxyphenyl)-5,6-dihydropyridin-2(1*H*)-one (4ba).



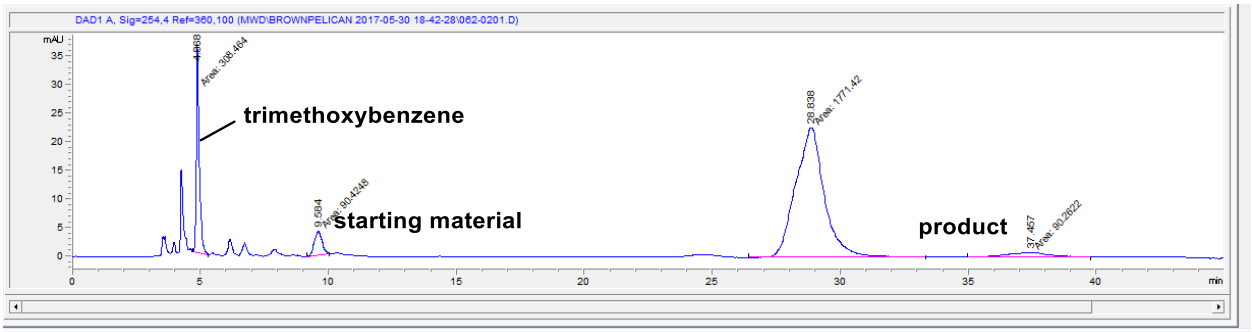
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 65% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 90% ee by chiral HPLC analysis. (Chiralpak IA, 7% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, major) = 28.8 min, t_r(e_2, minor) = 37.5 min).

Full HPLC Racemic Assay



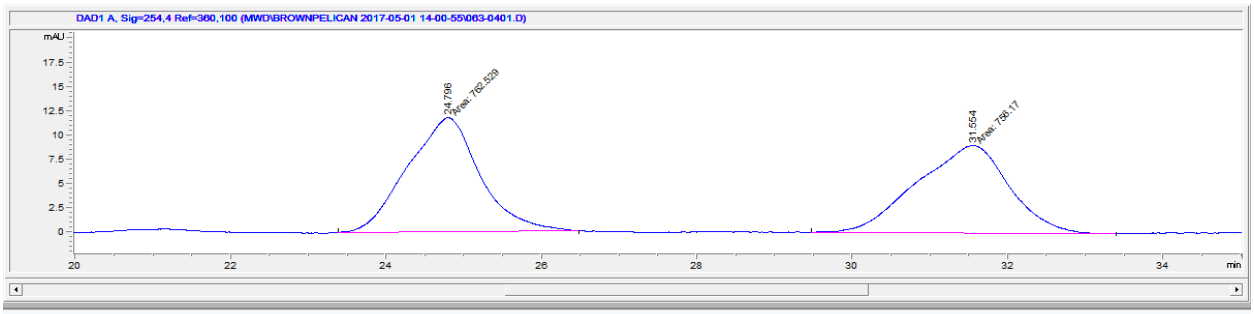
#	Time	Area	Height	Width	Area%	Symmetry
1	4.751	165.4	19.9	0.1384	8.273	0.655
2	8.384	314.8	15.7	0.3344	15.751	0.729
3	24.796	762.5	11.8	1.0766	38.147	1.223
4	31.554	756.2	9.1	1.388	37.829	1.495

Full HPLC Enantioselective Assay (for yield)



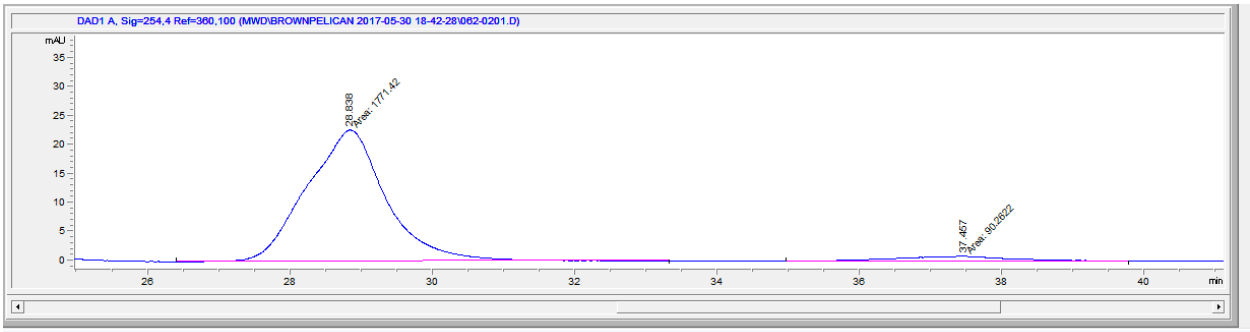
#	Time	Area	Height	Width	Area%	Symmetry
1	4.868	308.5	36.5	0.1409	13.645	0.675
2	9.584	90.4	4.3	0.3535	4.000	1
3	28.838	1771.4	22.7	1.3003	78.362	1.112
4	37.457	90.3	8.1E-1	1.8562	3.993	1.349

HPLC Racemic Assay (Product)



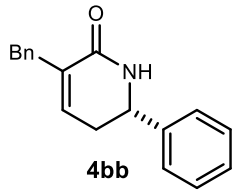
#	Time	Area	Height	Width	Area%	Symmetry
1	24.796	762.5	11.8	1.0766	50.209	1.223
2	31.554	756.2	9.1	1.388	49.791	1.495

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	28.838	1771.4	22.7	1.3003	95.152	1.112
2	37.457	90.3	8.1E-1	1.8562	4.848	1.349

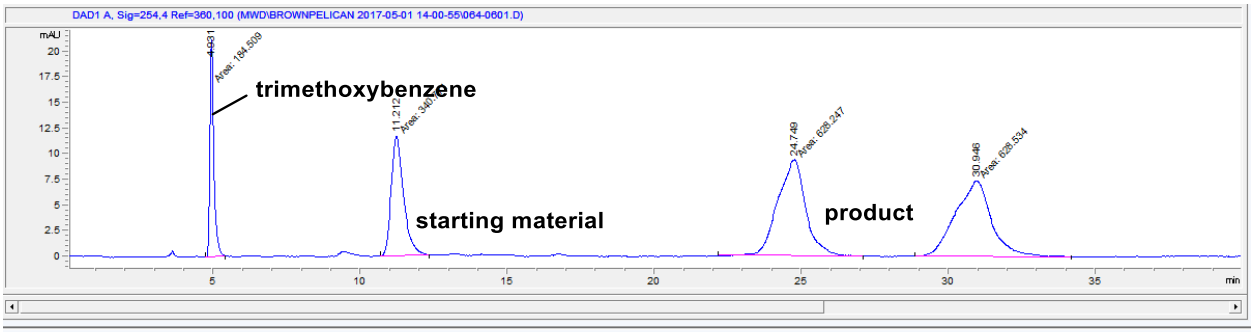
3-Benzyl-6-phenyl-5,6-dihydropyridin-2(1H)-one (4bb).



4bb

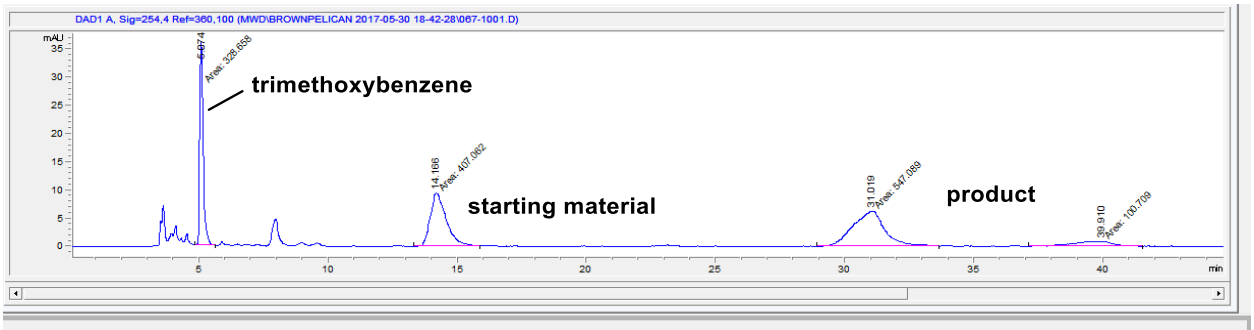
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 29% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 69% ee by chiral HPLC analysis. (Chiralpak IA, 5% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, major) = 31.0 min, $t_r(e_2$, minor) = 39.9 min).

Full HPLC Racemic Assay



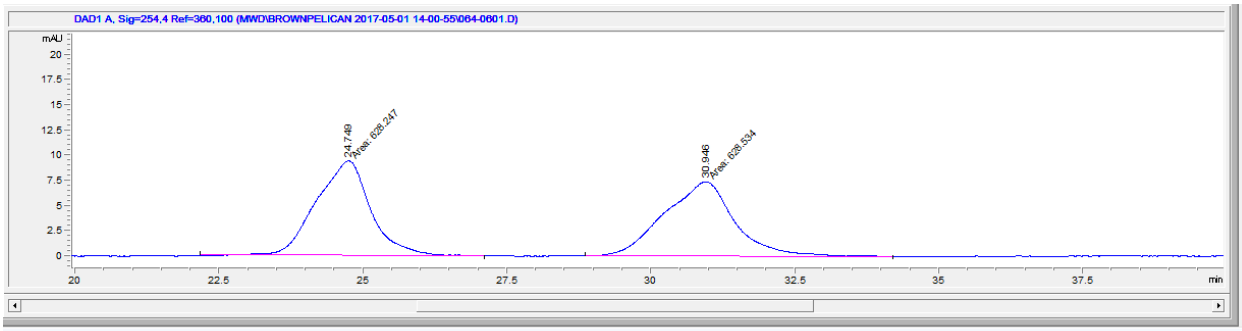
#	Time	Area	Height	Width	Area%	Symmetry
1	4.931	184.5	21.2	0.1453	10.354	0.68
2	11.212	340.8	11.7	0.4871	19.122	0.707
3	24.749	628.2	9.4	1.1125	35.254	1.398
4	30.946	628.5	7.4	1.4218	35.270	1.327

Full HPLC Enantioselective Assay (for yield)



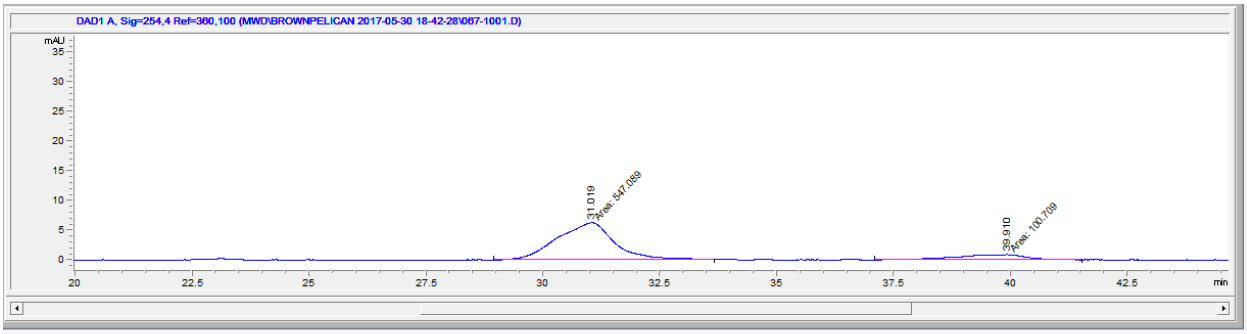
#	Time	Area	Height	Width	Area%	Symmetry
1	5.074	328.7	35.9	0.1525	23.755	0.701
2	14.166	407.1	9.4	0.7208	29.422	0.577
3	31.019	547.1	6.3	1.4524	39.543	1.295
4	39.91	100.7	9.1E-1	1.8403	7.279	2.294

HPLC Racemic Assay (Product)



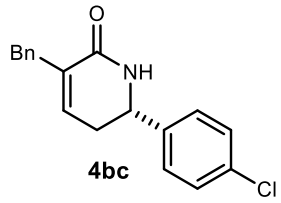
#	Time	Area	Height	Width	Area%	Symmetry
1	24.749	628.2	9.4	1.1125	49.989	1.398
2	30.946	628.5	7.4	1.4218	50.011	1.327

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	31.019	547.1	6.3	1.4524	84.454	1.295
2	39.91	100.7	9.1E-1	1.8403	15.546	2.294

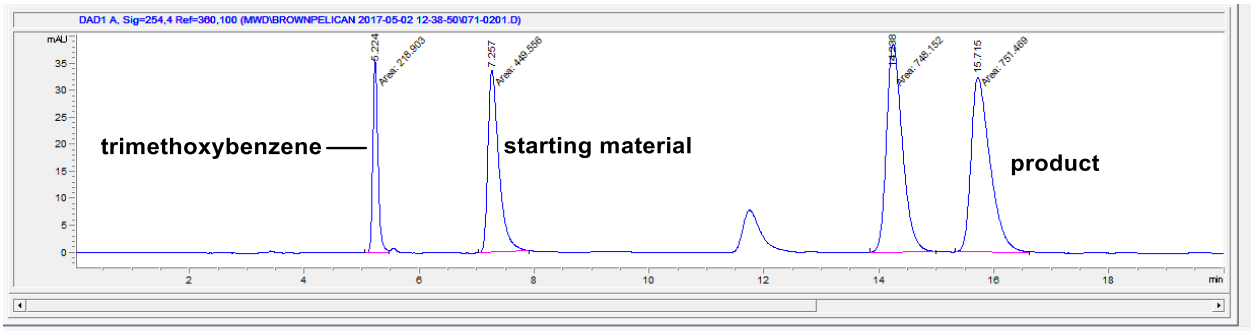
3-Benzyl-6-(4-chlorophenyl)-5,6-dihydropyridin-2(1*H*)-one (4bc).



4bc

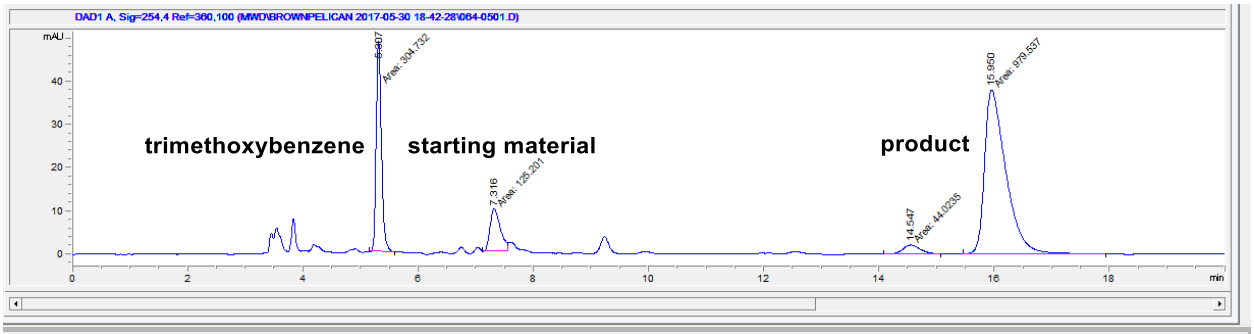
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 49% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 91% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, minor) = 14.5 min, $t_r(e_2$, major) = 16.0 min).

Full HPLC Racemic Assay



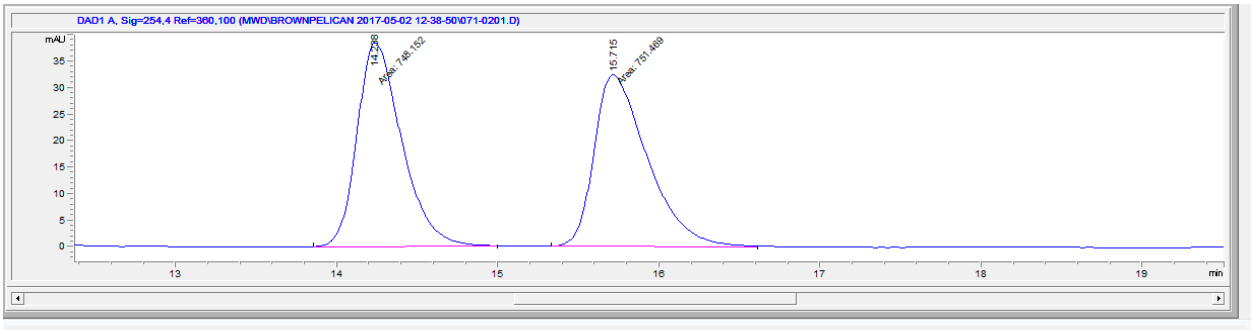
#	Time	Area	Height	Width	Area%	Symmetry
1	5.224	218.9	36	0.1014	10.097	0.775
2	7.257	449.6	33.7	0.2224	20.735	0.545
3	14.238	748.2	38.5	0.3235	34.508	0.671
4	15.715	751.5	32.4	0.3863	34.661	0.542

Full HPLC Enantioselective Assay (for yield)



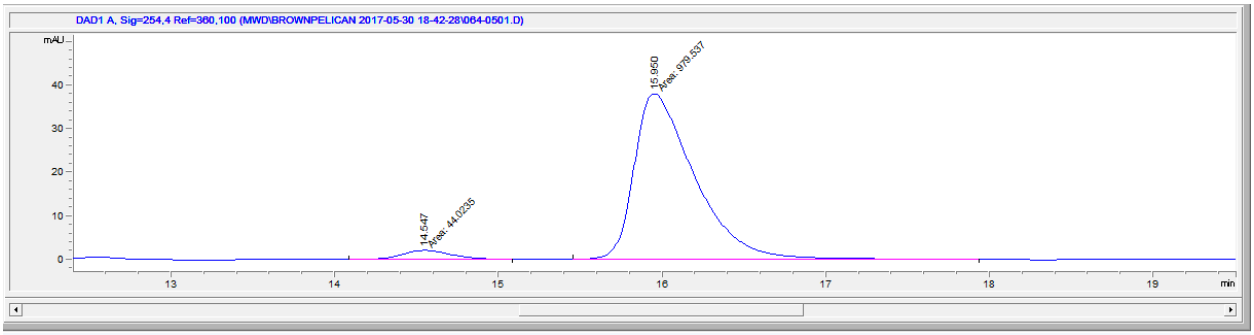
#	Time	Area	Height	Width	Area%	Symmetry
1	5.307	304.7	48.7	0.1042	20.965	0.765
2	7.316	125.2	9.8	0.2121	8.614	0.64
3	14.547	44	2.1	0.3498	3.029	0.849
4	15.95	979.5	38	0.4292	67.392	0.483

HPLC Racemic Assay (Product)



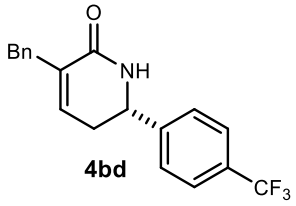
#	Time	Area	Height	Width	Area%	Symmetry
1	14.238	748.2	38.5	0.3235	49.889	0.671
2	15.715	751.5	32.4	0.3863	50.111	0.542

HPLC Enantioselective Assay (Product)



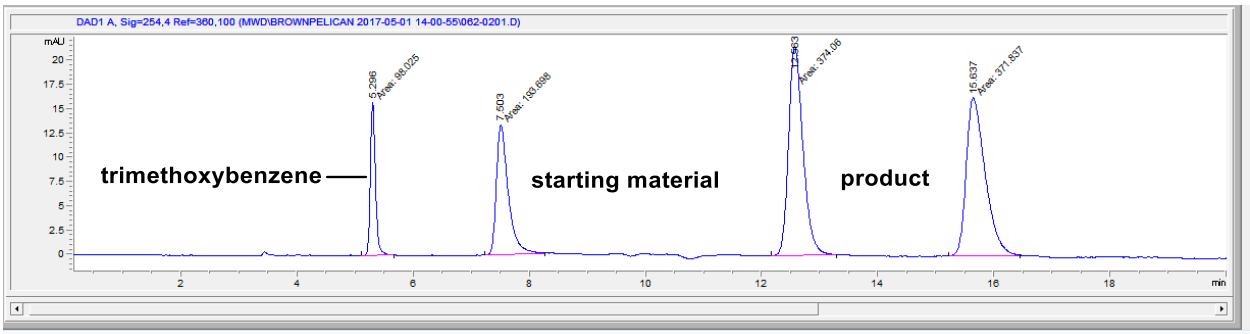
#	Time	Area	Height	Width	Area%	Symmetry
1	14.547	44	2.1	0.3498	4.301	0.849
2	15.95	979.5	38	0.4292	95.699	0.483

3-Benzyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one (4bd).



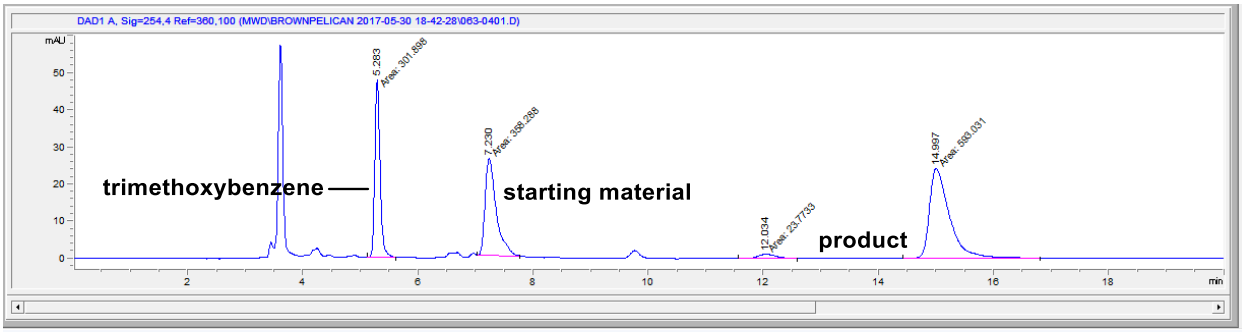
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 27% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 92% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, minor) = 12.0 min, $t_r(e_2$, major) = 15.0 min).

Full HPLC Racemic Assay



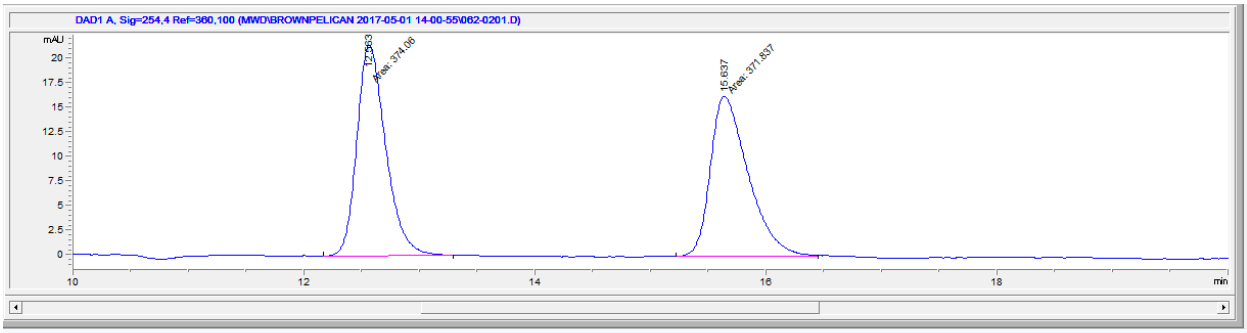
#	Time	Area	Height	Width	Area%	Symmetry
1	5.296	98	15.8	0.1031	9.447	0.786
2	7.503	193.7	13.4	0.2403	18.668	0.566
3	12.563	374.1	21.5	0.2897	36.050	0.72
4	15.637	371.8	16.3	0.3804	35.836	0.567

Full HPLC Enantioselective Assay (for yield)



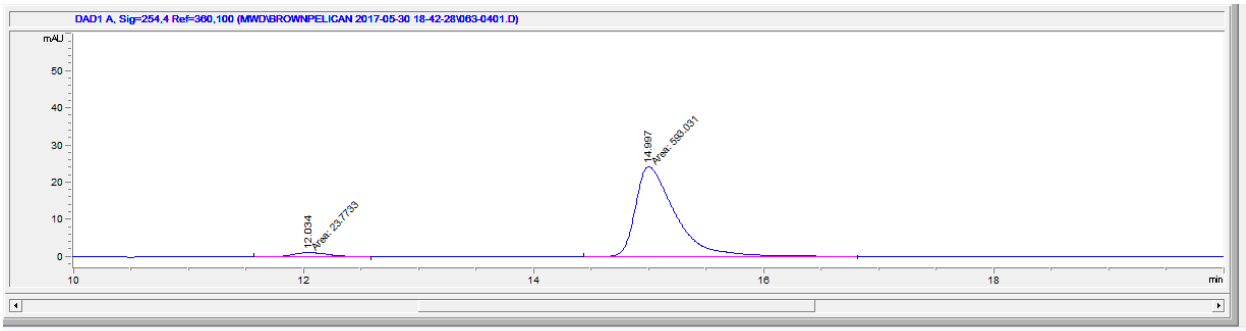
#	Time	Area	Height	Width	Area%	Symmetry
1	5.283	301.9	48	0.1047	23.641	0.757
2	7.23	358.3	26.4	0.2265	28.057	0.546
3	12.034	23.8	1.1	0.3569	1.862	0.738
4	14.997	593	24.3	0.4072	46.440	0.476

HPLC Racemic Assay (Product)



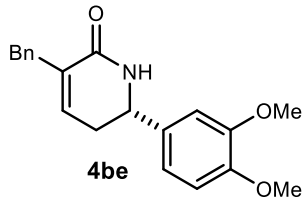
#	Time	Area	Height	Width	Area%	Symmetry
1	12.563	374.1	21.5	0.2897	50.149	0.72
2	15.637	371.8	16.3	0.3804	49.851	0.567

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	12.034	23.8	1.1	0.3569	3.854	0.738
2	14.997	593	24.3	0.4072	96.146	0.476

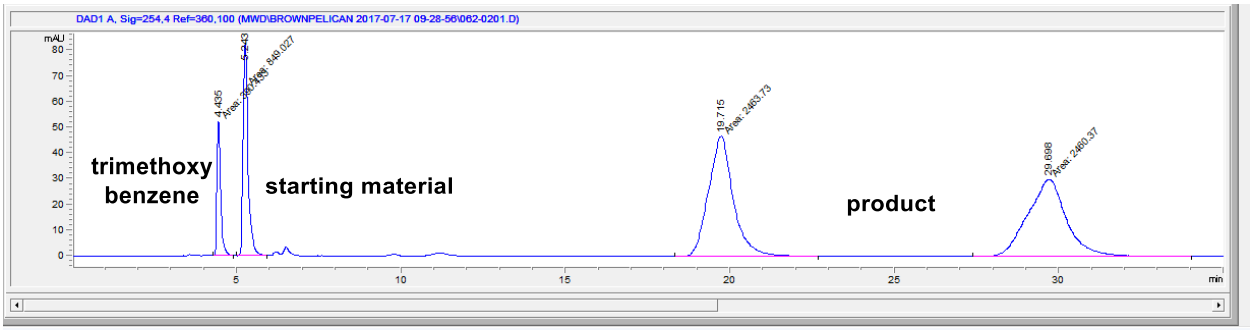
3-Benzyl-6-(3,4-dimethoxyphenyl)-5,6-dihydropyridin-2(1H)-one (4be).



4be

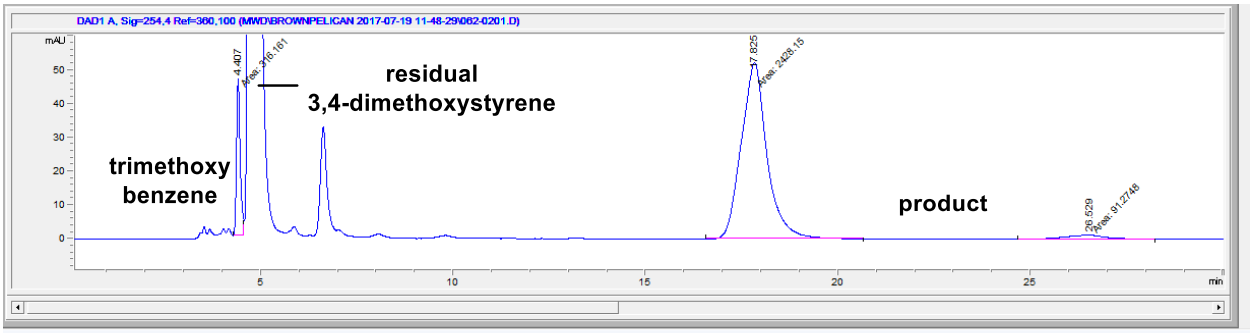
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 62% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 93% ee by chiral HPLC analysis. (Chiralpak IA, 15% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, major) = 17.8 min, $t_r(e_2$, minor) = 26.5 min).

Full HPLC Racemic Assay



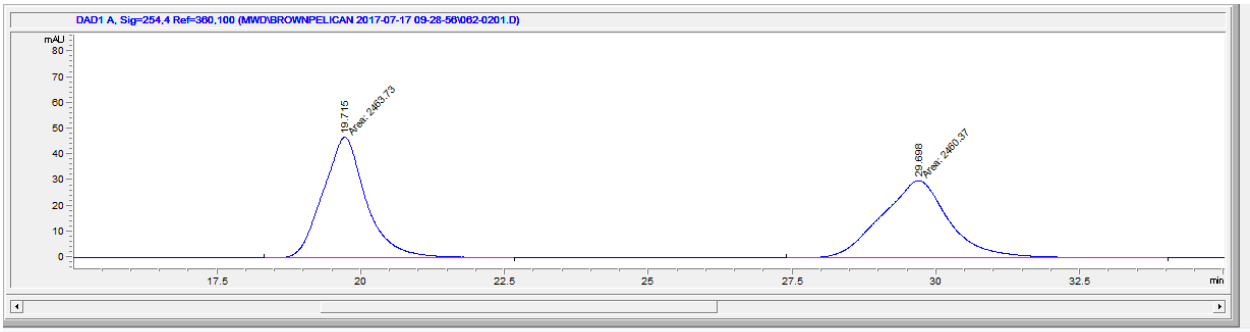
#	Time	Area	Height	Width	Area%	Symmetry
1	4.435	390.4	52	0.1251	6.335	0.72
2	5.243	849	82.6	0.1714	13.775	0.651
3	19.715	2463.7	46.8	0.8768	39.973	0.955
4	29.698	2460.4	30.1	1.364	39.918	1.163

Full HPLC Enantioselective Assay (for yield)



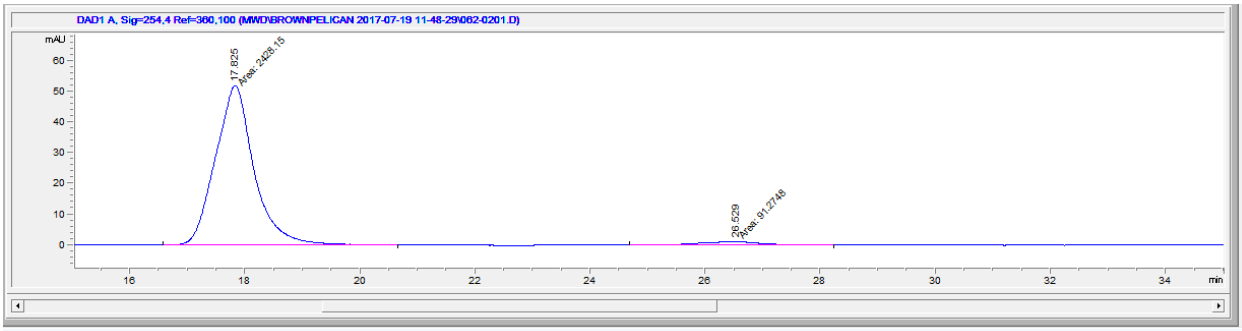
#	Time	Area	Height	Width	Area%	Symmetry
1	4.407	316.2	46.3	0.1138	11.150	0.707
2	17.825	2428.2	52.1	0.7765	85.631	0.981
3	26.529	91.3	1.2	1.2468	3.219	1.394

HPLC Racemic Assay (Product)



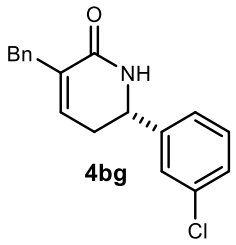
#	Time	Area	Height	Width	Area%	Symmetry
1	19.715	2463.7	46.8	0.8768	50.034	0.955
2	29.698	2460.4	30.1	1.364	49.966	1.163

HPLC Enantioselective Assay (Product)



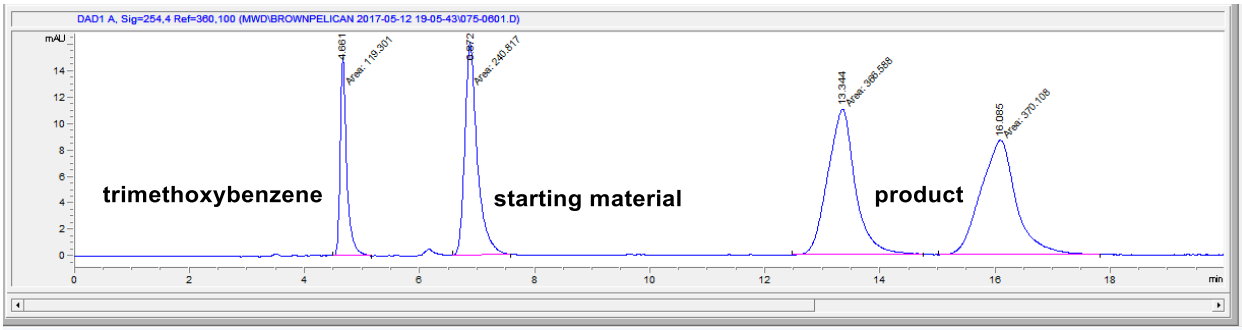
#	Time	Area	Height	Width	Area%	Symmetry
1	17.825	2428.2	52.1	0.7765	96.377	0.981
2	26.529	91.3	1.2	1.2468	3.623	1.394

3-Benzyl-6-(3-chlorophenyl)-5,6-dihydropyridin-2(1*H*)-one (4bg).



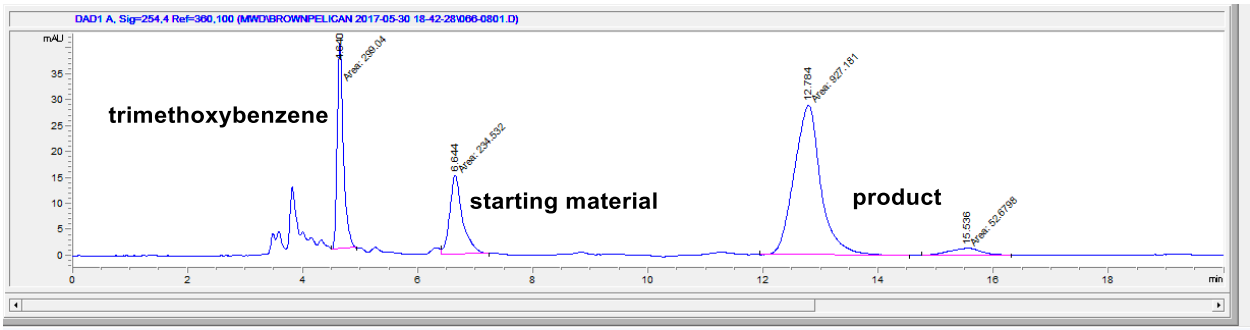
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 52% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 89% ee by chiral HPLC analysis. (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, major) = 12.8 min, t_r(e_2, minor) = 15.5 min).

Full HPLC Racemic Assay



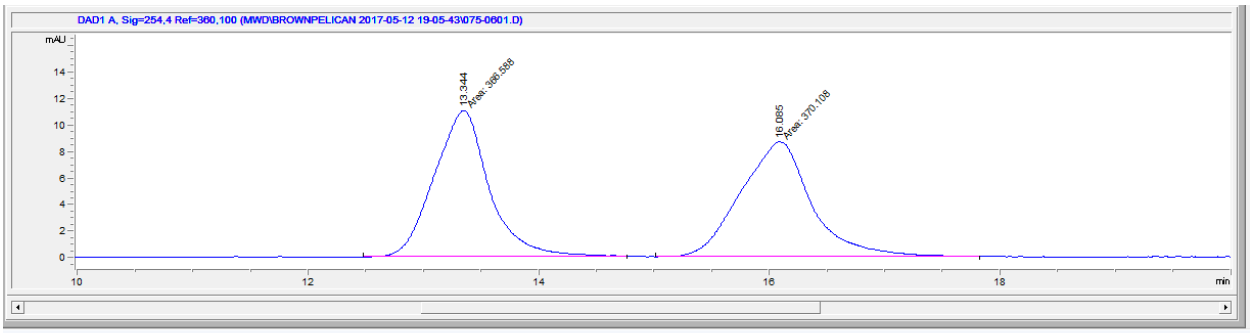
#	Time	Area	Height	Width	Area%	Symmetry
1	4.661	119.3	15	0.1323	10.877	0.652
2	6.872	240.8	16	0.2513	21.956	0.691
3	13.344	366.6	11	0.5551	33.423	1.085
4	16.085	370.1	8.6	0.7141	33.744	1.144

Full HPLC Enantioselective Assay (for yield)



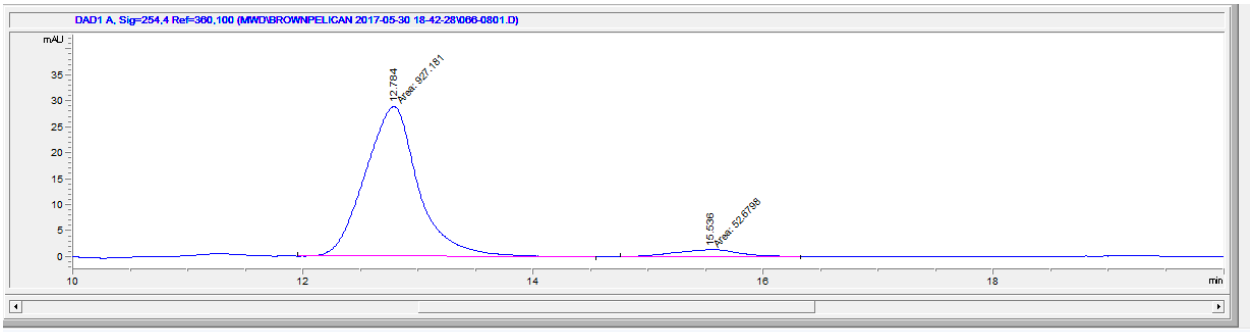
#	Time	Area	Height	Width	Area%	Symmetry
1	4.64	299	39.6	0.1257	19.759	0.696
2	6.644	234.5	15.2	0.2569	15.497	0.708
3	12.784	927.2	28.9	0.5354	61.263	1.111
4	15.536	52.7	1.4	0.6474	3.481	1.192

HPLC Racemic Assay (Product)



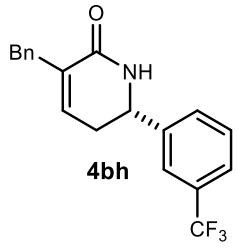
#	Time	Area	Height	Width	Area%	Symmetry
1	13.344	366.6	11	0.5551	49.761	1.085
2	16.085	370.1	8.6	0.7141	50.239	1.144

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	12.784	927.2	28.9	0.5354	94.624	1.111
2	15.536	52.7	1.4	0.6474	5.376	1.192

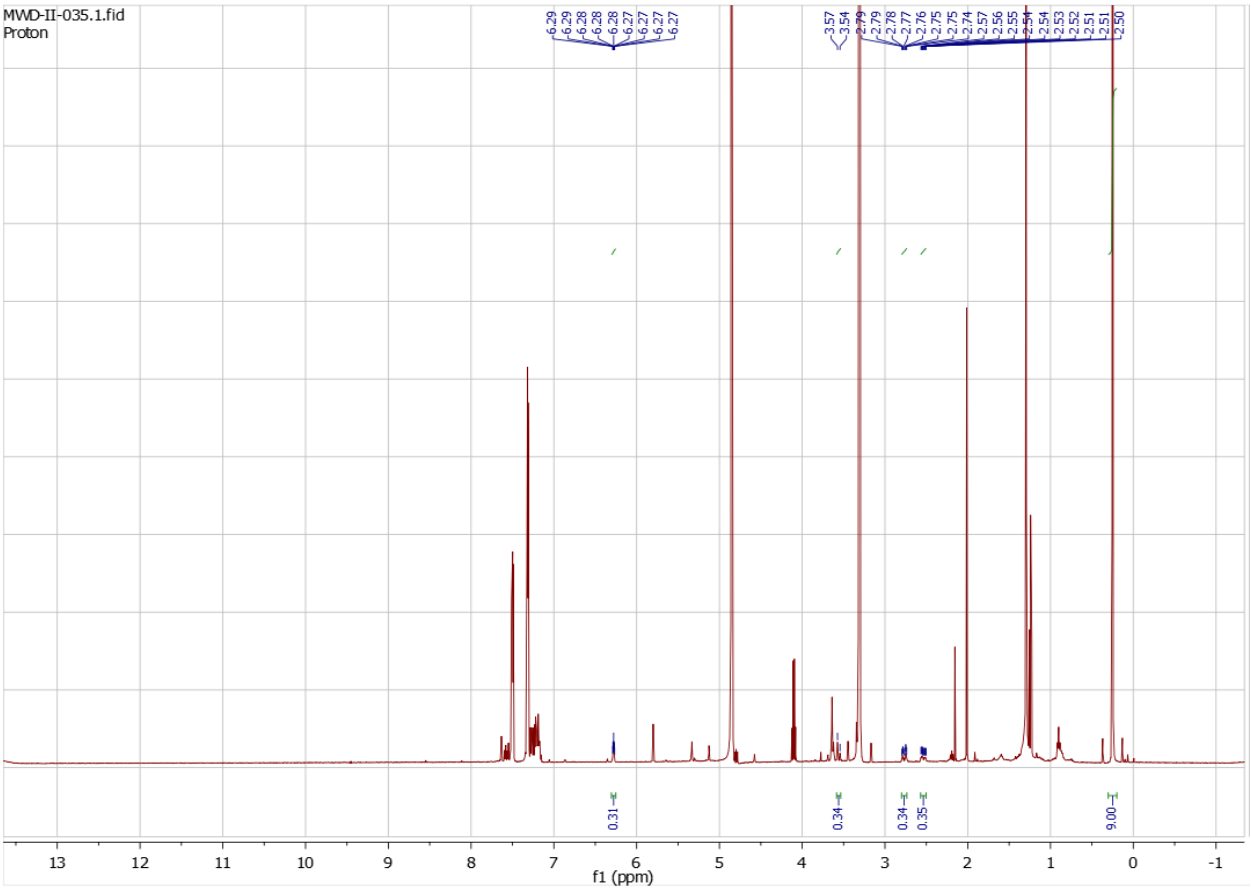
3-Benzyl-6-(3-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one (4bh).



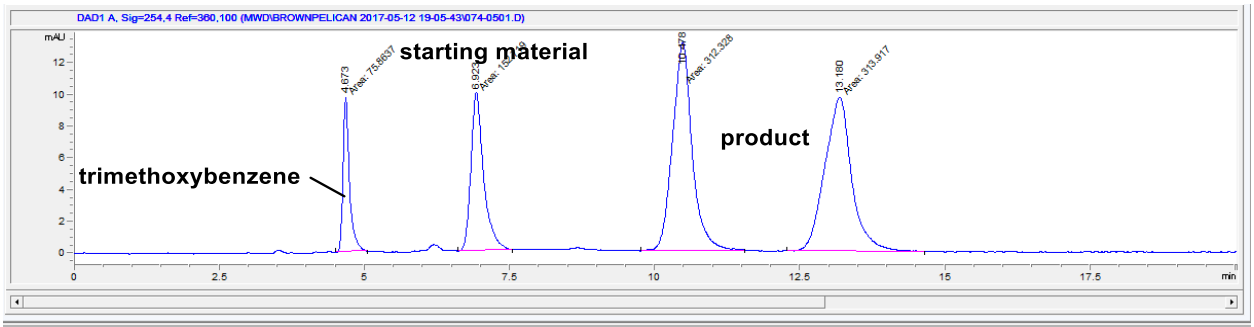
4bh

Product synthesized according to general procedure B, and extracted with ethyl acetate. Product yield was determined to be 32% by ^{1}H NMR analysis (500 MHz, MeOD) relative to a trimethyl(phenyl)silane internal standard. The product was determined to be 86% ee by chiral HPLC analysis. (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(e_1$, major) = 10.8 min, $t_r(e_2$, minor) = 13.1 min).

NMR Yield Data

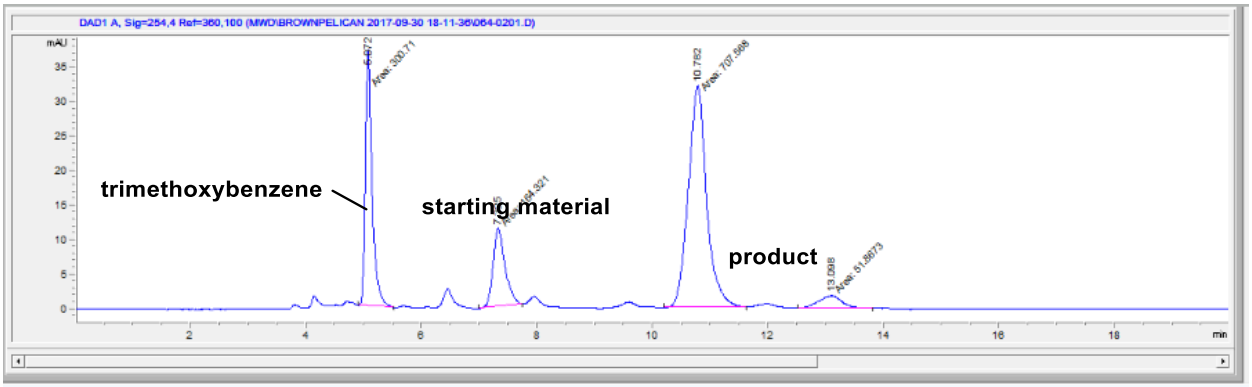


Full HPLC Racemic Assay



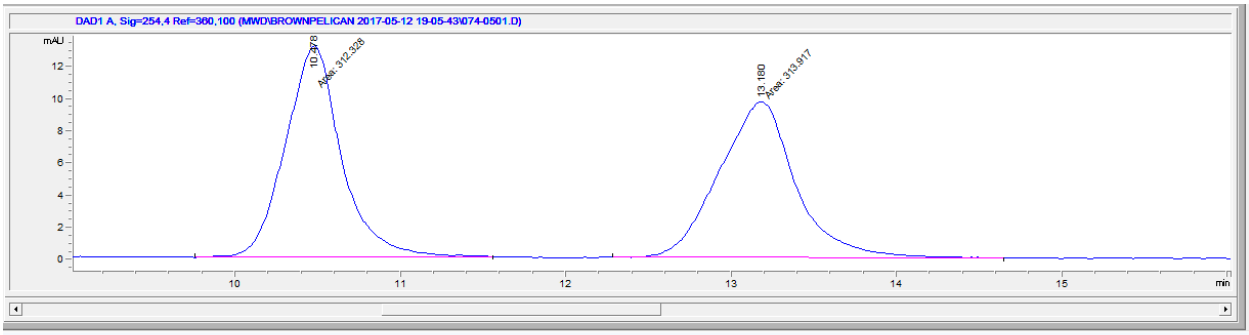
#	Time	Area	Height	Width	Area%	Symmetry
1	4.673	75.9	9.8	0.1296	8.875	0.672
2	6.923	152.7	10	0.2553	17.865	0.704
3	10.478	312.3	13.2	0.3957	36.537	1.012
4	13.18	313.9	9.7	0.5393	36.723	1.138

Full HPLC Enantioselective Assay



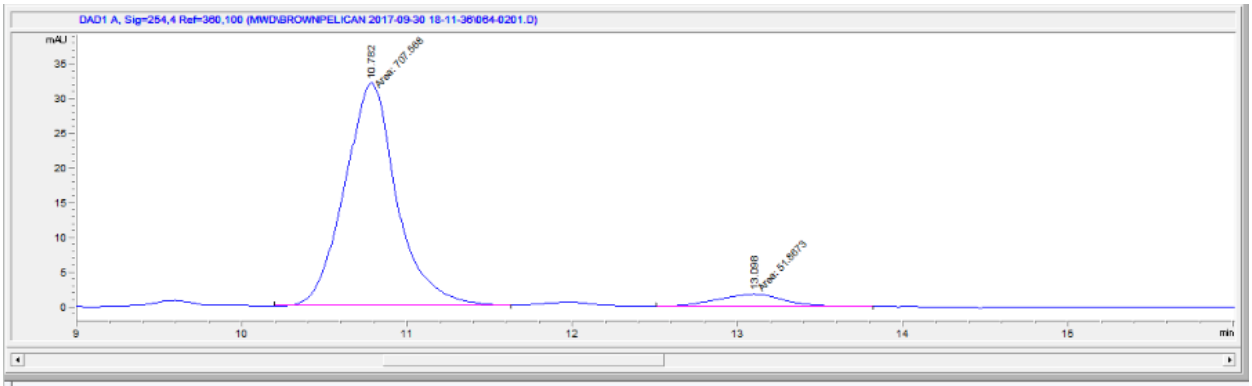
#	Time	Area	Height	Width	Area%	Symmetry
1	5.072	300.7	37.1	0.1351	24.558	0.654
2	7.325	164.3	11.3	0.2415	13.420	0.72
3	10.782	707.6	32.1	0.3671	57.786	1.025
4	13.098	51.9	1.8	0.4736	4.236	1.223

HPLC Racemic Assay (Product)



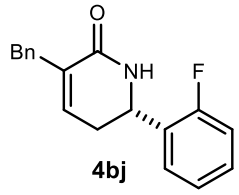
#	Time	Area	Height	Width	Area%	Symmetry
1	10.478	312.3	13.2	0.3957	49.873	1.012
2	13.18	313.9	9.7	0.5393	50.127	1.138

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	10.782	707.6	32.1	0.3671	93.170	1.025
2	13.098	51.9	1.8	0.4736	6.830	1.223

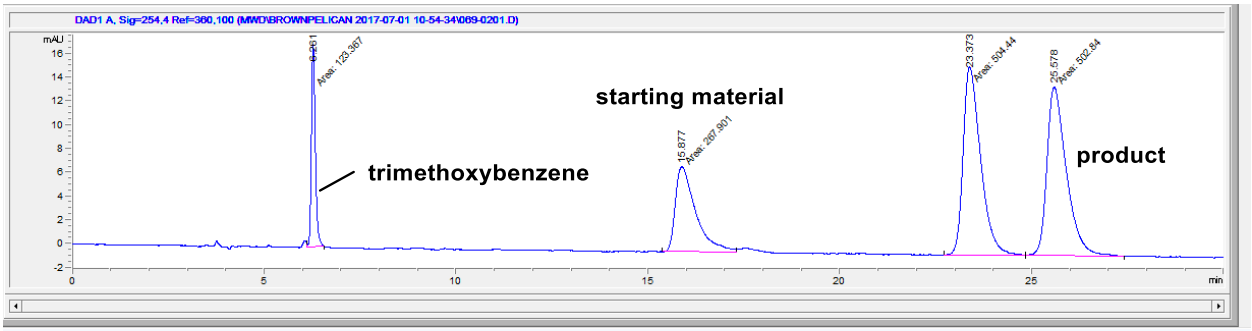
3-Benzyl-6-(3-fluorophenyl)-5,6-dihydropyridin-2(1*H*)-one (4bj).



4bj

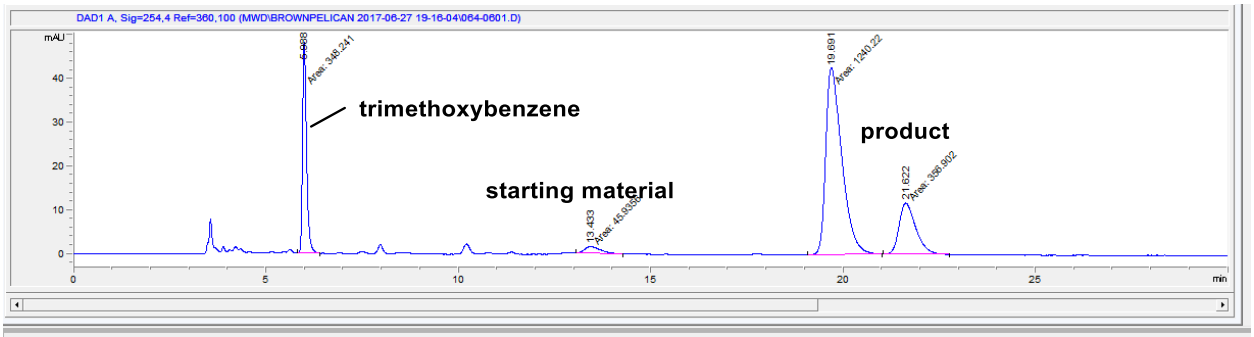
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 55% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 55% ee by chiral HPLC analysis. (Chiralpak IB, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, major) = 19.7 min, t_r(e_2, minor) = 21.6 min).

Full HPLC Racemic Assay



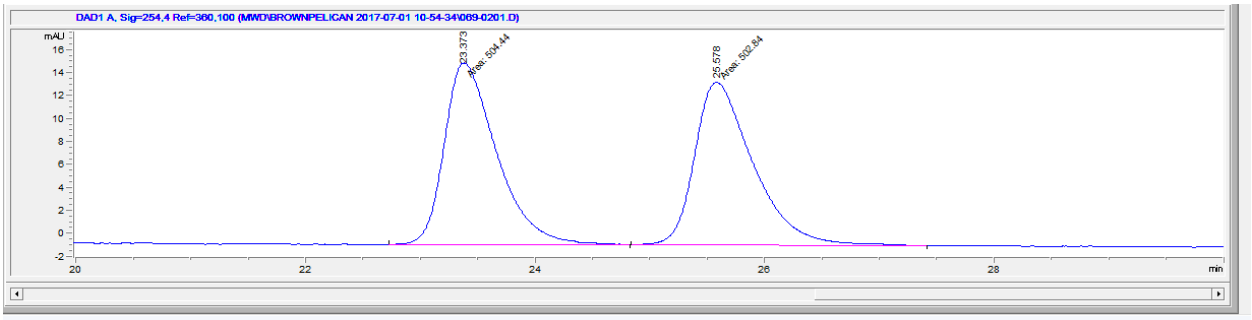
#	Time	Area	Height	Width	Area%	Symmetry
1	6.261	123.4	17.1	0.1204	8.821	0.742
2	15.877	267.9	7.2	0.6219	19.156	0.459
3	23.373	504.4	15.8	0.5309	36.069	0.58
4	25.578	502.8	14.2	0.5909	35.954	0.583

Full HPLC Enantioselective Assay (for yield)



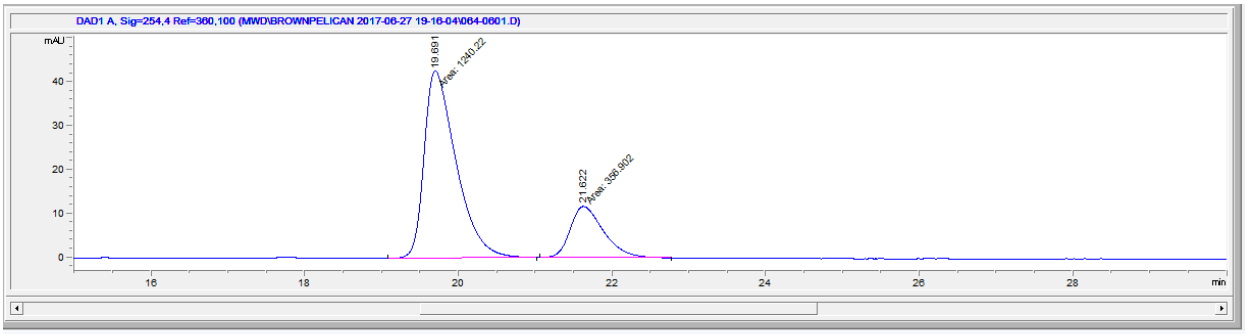
#	Time	Area	Height	Width	Area%	Symmetry
1	5.988	348.2	48.1	0.1206	17.488	0.679
2	13.433	45.9	1.6	0.4931	2.307	0.563
3	19.691	1240.2	42.7	0.4843	62.282	0.524
4	21.622	356.9	11.7	0.5087	17.923	0.637

HPLC Racemic Assay (Product)



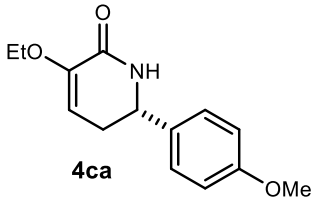
#	Time	Area	Height	Width	Area%	Symmetry
1	23.373	504.4	15.8	0.5309	50.079	0.58
2	25.578	502.8	14.2	0.5909	49.921	0.583

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	19.691	1240.2	42.7	0.4843	77.654	0.524
2	21.622	356.9	11.7	0.5087	22.346	0.637

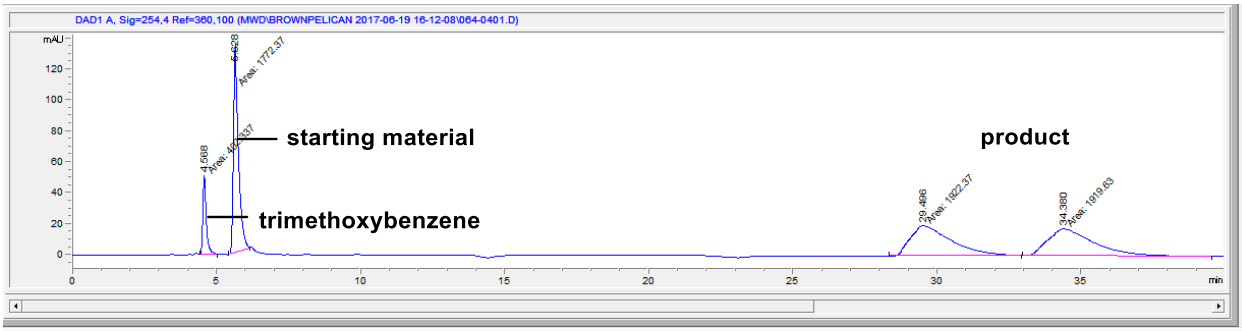
3-Ethoxy-6-(4-methoxyphenyl)-5,6-dihydropyridin-2(1H)-one (4ca).



4ca

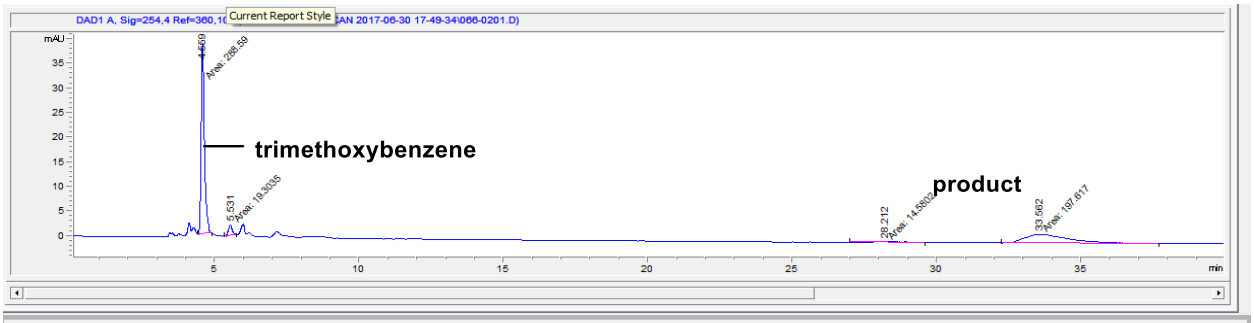
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 8% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 87% ee by chiral HPLC analysis. (Chiralpak IA, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 28.2 min, t_r(e_2, major) = 33.6 min).

Full HPLC Racemic Assay



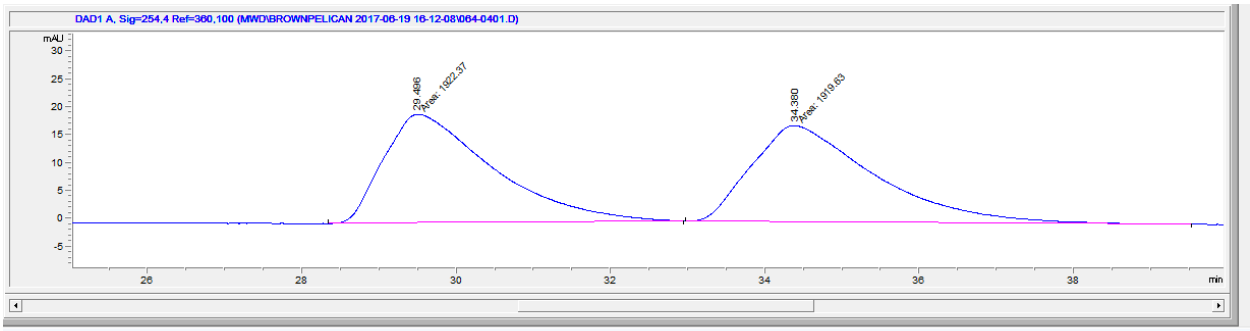
#	Time	Area	Height	Width	Area%	Symmetry
1	4.568	402.3	50.9	0.1317	6.687	0.647
2	5.628	1772.4	134.7	0.2192	29.457	0.54
3	29.496	1922.4	19.5	1.6454	31.951	0.446
4	34.38	1919.6	17.3	1.851	31.905	0.52

Full HPLC Enantioselective Assay (for yield)



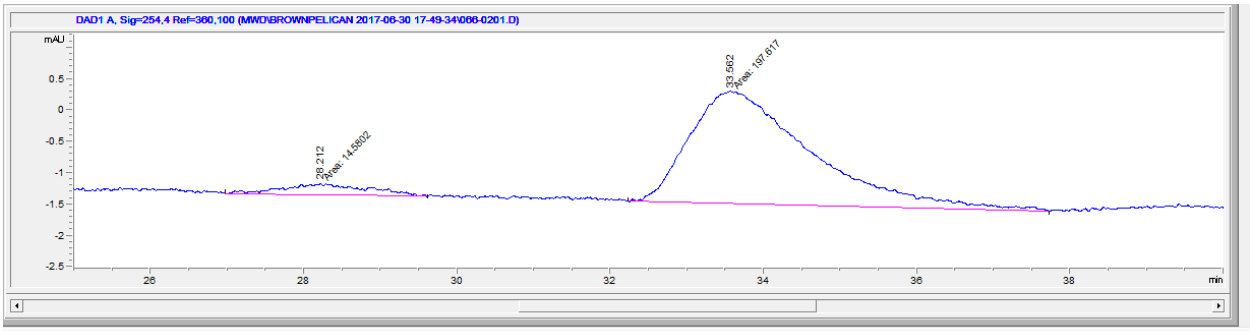
#	Time	Area	Height	Width	Area%	Symmetry
1	4.559	288.6	38.7	0.1243	55.488	0.685
2	5.531	19.3	2.2	0.1483	3.712	0.958
3	28.212	14.6	1.8E-1	1.3143	2.803	0.769
4	33.562	197.6	1.8	1.8366	37.997	0.499

HPLC Racemic Assay (Product)



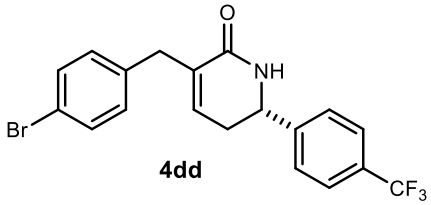
#	Time	Area	Height	Width	Area%	Symmetry
1	29.496	1922.4	19.5	1.6454	50.036	0.446
2	34.38	1919.6	17.3	1.851	49.964	0.52

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	28.212	14.6	1.8E-1	1.3143	6.871	0.769
2	33.562	197.6	1.8	1.8366	93.129	0.499

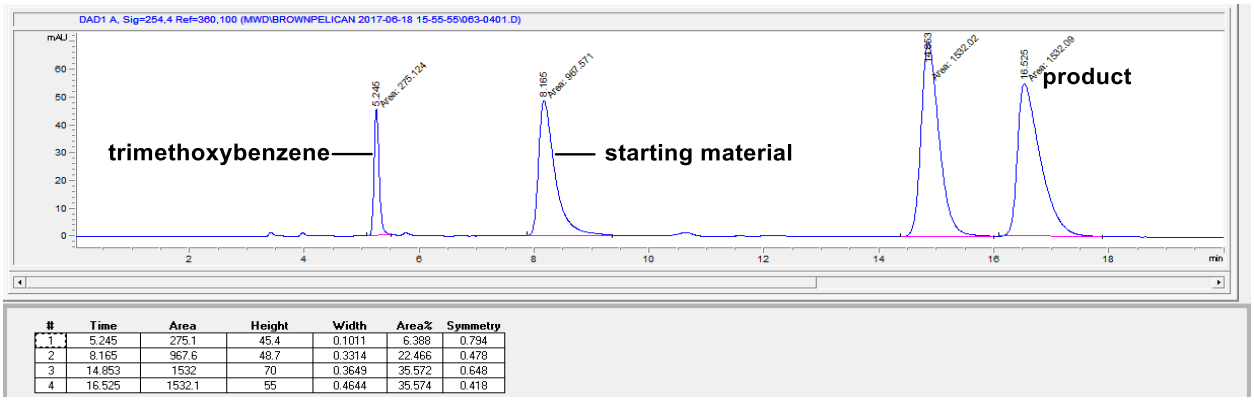
3-(4-Bromobenzyl)-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4dd).



4dd

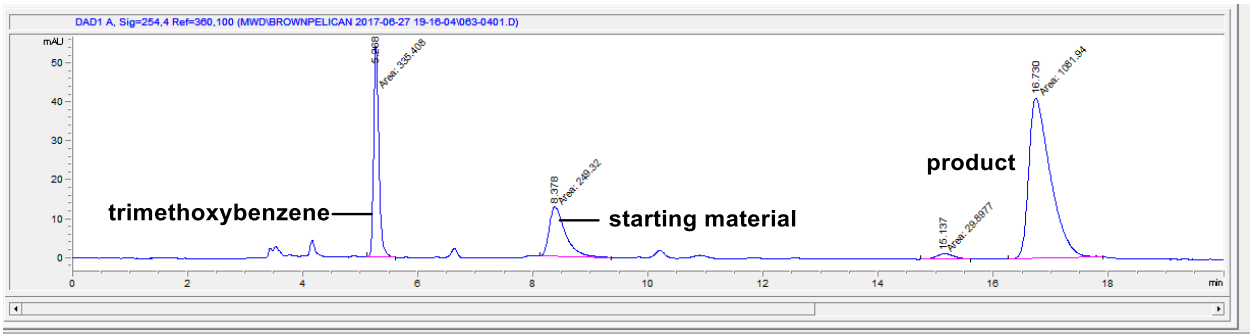
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 30% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 95% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 15.1 min, t_r(e_2, major) = 16.7 min).

Full HPLC Racemic Assay



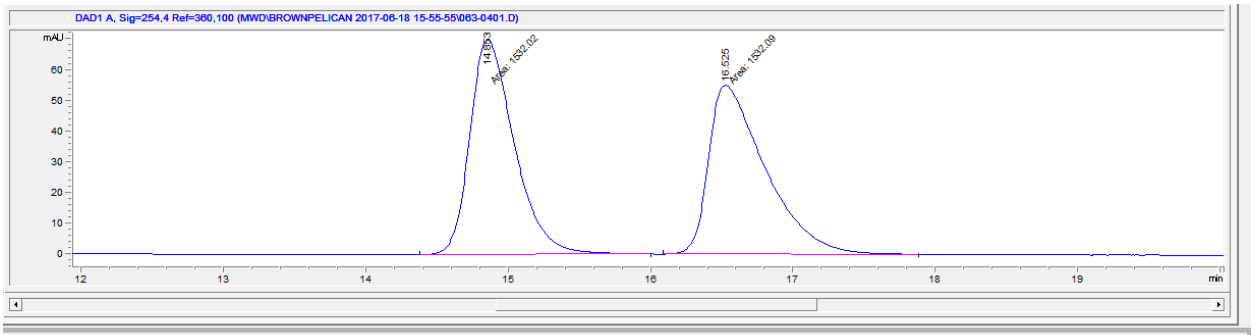
#	Time	Area	Height	Width	Area%	Symmetry
1	5.245	275.1	45.4	0.1011	6.388	0.794
2	8.165	967.6	48.7	0.3314	22.466	0.478
3	14.853	1532	70	0.3649	35.572	0.648
4	16.525	1532.1	55	0.4644	35.574	0.418

Full HPLC Enantioselective Assay (for yield)



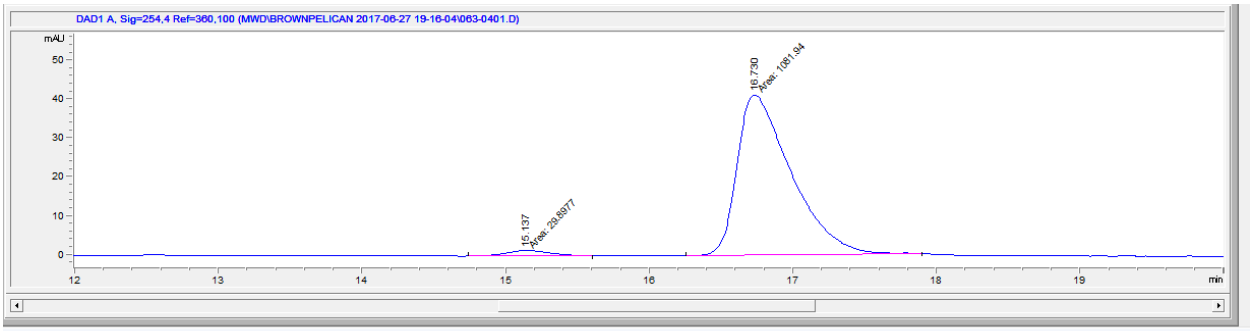
#	Time	Area	Height	Width	Area%	Symmetry
1	5.268	335.4	54.1	0.1034	19.770	0.751
2	8.378	249.3	12.7	0.3263	14.696	0.522
3	15.137	29.9	1.4	0.3579	1.762	0.772
4	16.73	1081.9	41.2	0.4377	63.772	0.464

HPLC Racemic Assay (Product)



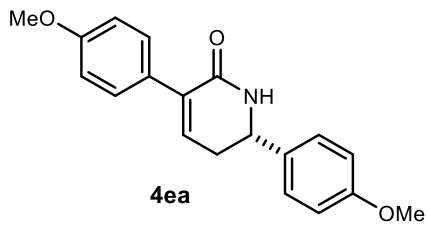
#	Time	Area	Height	Width	Area%	Symmetry
1	14.853	1532	70	0.3649	49.999	0.648
2	16.525	1532.1	55	0.4644	50.001	0.418

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	15.137	29.9	1.4	0.3579	2.689	0.772
2	16.73	1081.9	41.2	0.4377	97.311	0.464

3,6-Bis(4-methoxyphenyl)-5,6-dihydropyridin-2(1H)-one (4ea).

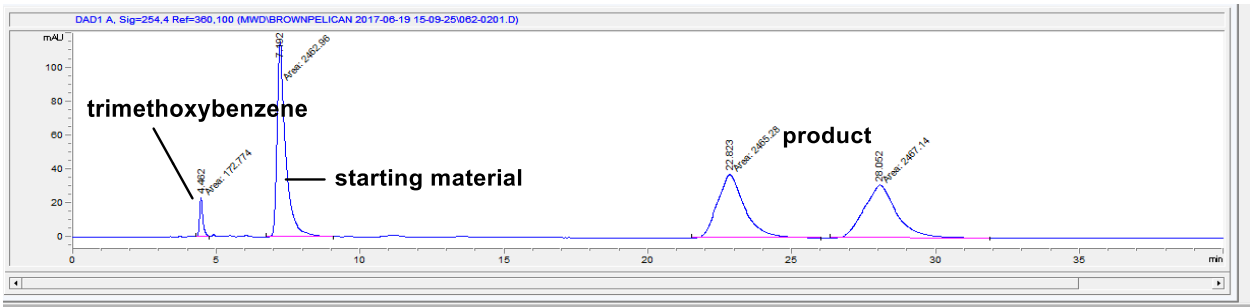


4ea

Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 29% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 53% ee by

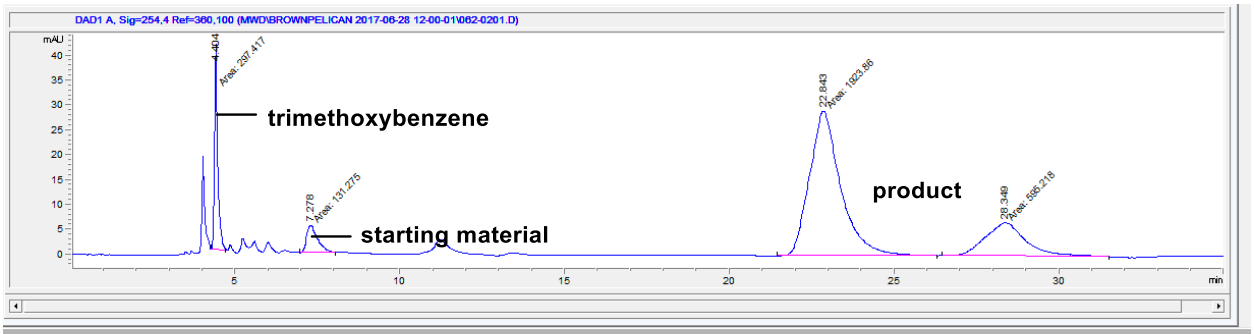
chiral HPLC analysis. (Chiralpak IA, 15% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, major) = 22.8 min, t_r(e_2, minor) = 28.3 min).

Full HPLC Racemic Assay



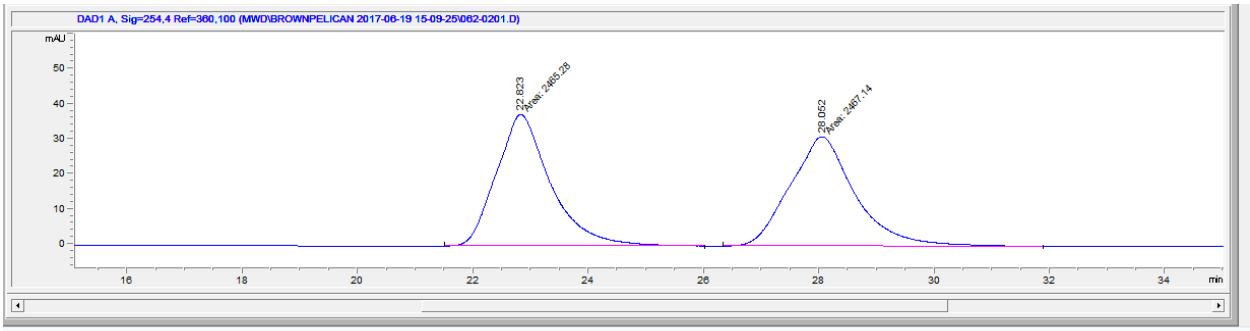
#	Time	Area	Height	Width	Area%	Symmetry
1	4.462	172.8	23.1	0.1248	2.283	0.712
2	7.192	2463	114.8	0.3577	32.544	0.489
3	22.823	2465.3	37.6	1.0934	32.574	0.778
4	28.052	2467.1	31.3	1.3143	32.599	0.921

Full HPLC Enantioselective Assay (for yield)



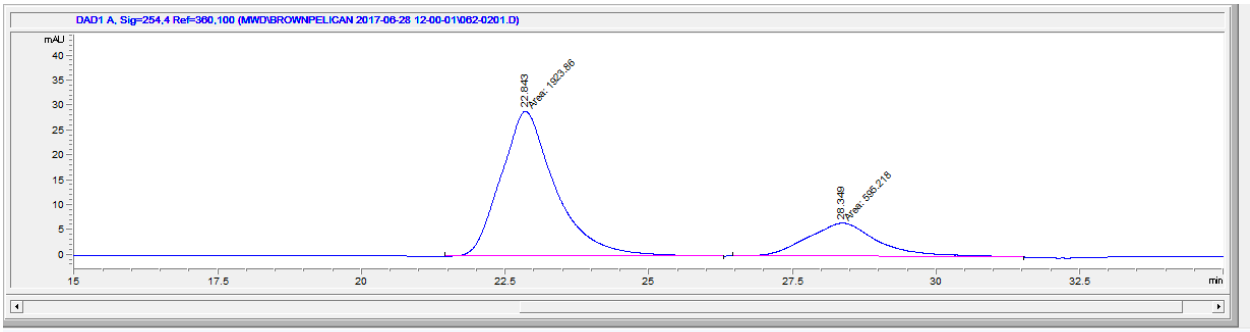
#	Time	Area	Height	Width	Area%	Symmetry
1	4.404	297.4	41.4	0.1197	10.090	0.665
2	7.278	131.3	5.6	0.3932	4.453	0.516
3	22.843	1923.9	29.1	1.1015	65.265	0.764
4	28.349	595.2	6.7	1.4706	20.192	0.879

HPLC Racemic Assay (Product)



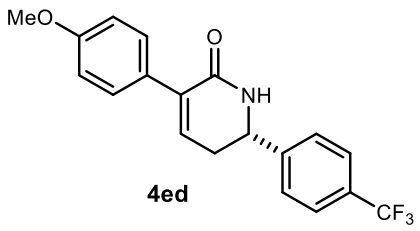
#	Time	Area	Height	Width	Area%	Symmetry
1	22.823	2465.3	37.6	1.0934	49.981	0.778
2	28.052	2467.1	31.3	1.3143	50.019	0.921

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	22.843	1923.9	29.1	1.1015	76.372	0.764
2	28.349	595.2	6.7	1.4706	23.628	0.879

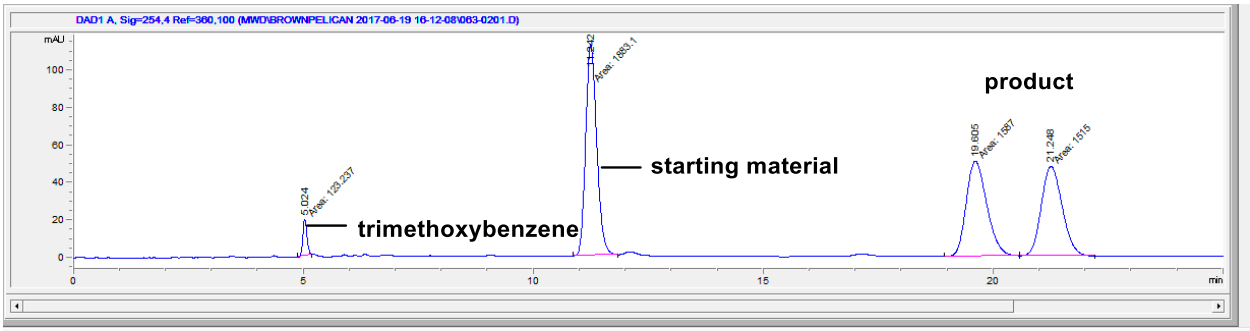
3-(4-Methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (4ed).



4ed

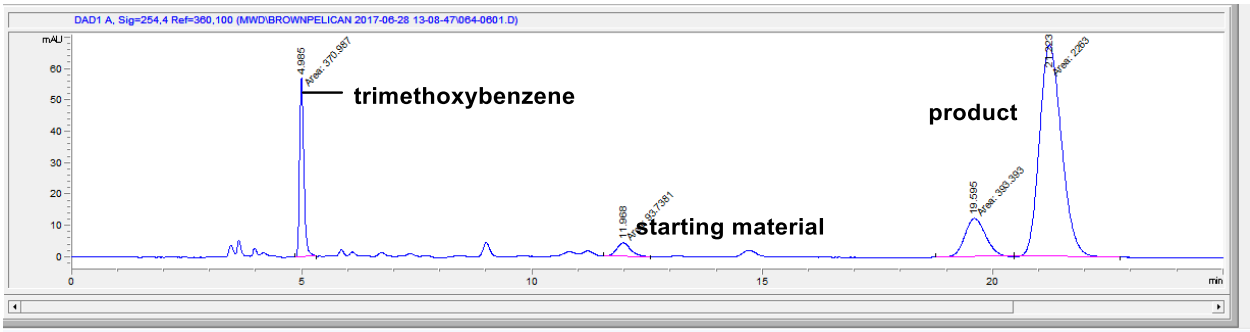
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 29% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 70% ee by chiral HPLC analysis. (Chiralpak IE, 20% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 19.6 min, t_r(e_2, major) = 21.2 min).

Full HPLC Racemic Assay



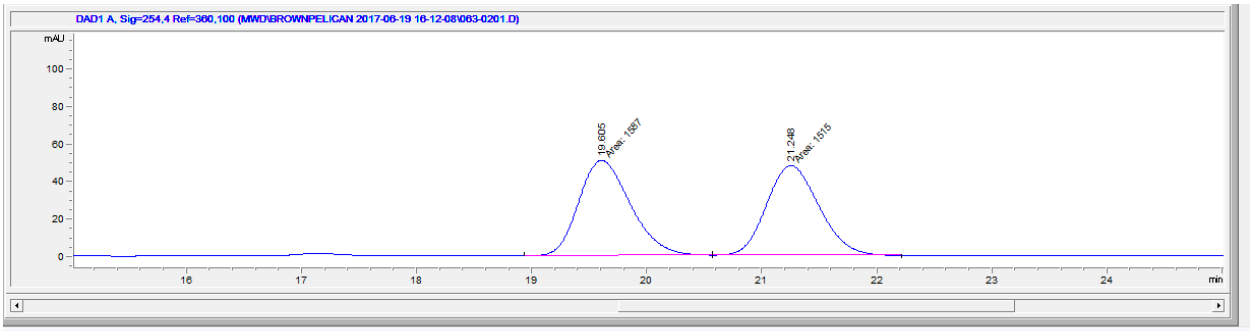
#	Time	Area	Height	Width	Area%	Symmetry
1	5.024	123.2	19.6	0.1049	2.412	0.828
2	11.242	1883.1	112.5	0.2789	36.863	0.812
3	19.605	1587	50.8	0.5205	31.067	0.768
4	21.248	1515	47.9	0.5274	29.657	0.827

Full HPLC Enantioselective Assay (for yield)



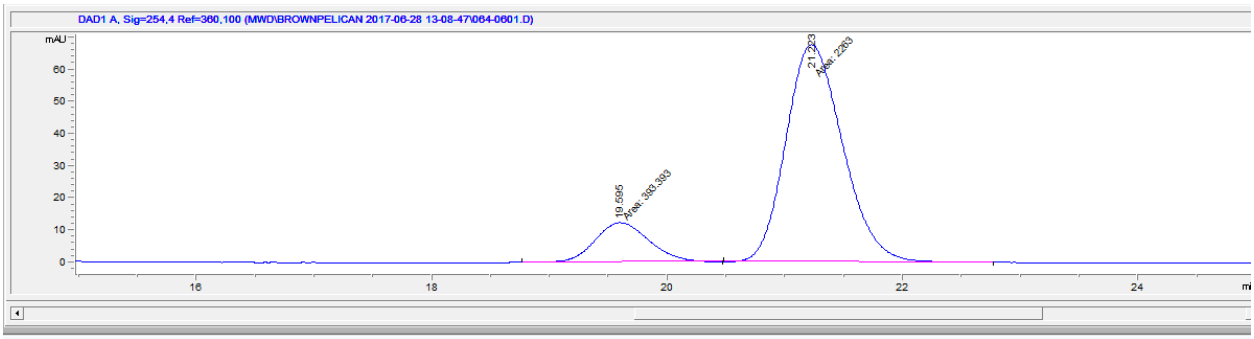
#	Time	Area	Height	Width	Area%	Symmetry
1	4.985	371	56.9	0.1086	11.886	0.738
2	11.968	93.7	4.4	0.3576	3.003	0.811
3	19.595	393.4	12.3	0.5332	12.604	0.83
4	21.223	2263	67.6	0.558	72.506	0.799

HPLC Racemic Assay (Product)



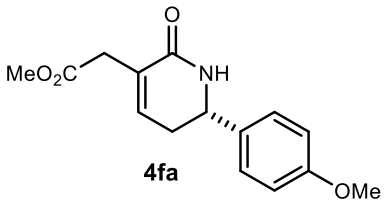
#	Time	Area	Height	Width	Area%	Symmetry
1	19.605	1587	50.8	0.5205	51.160	0.768
2	21.248	1515	47.9	0.5274	48.840	0.827

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	19.595	393.4	12.3	0.5332	14.809	0.83
2	21.223	2263	67.6	0.558	85.191	0.799

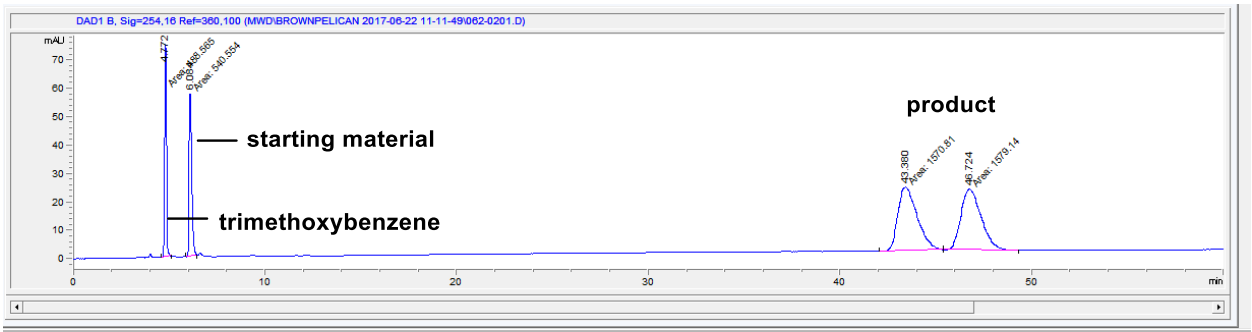
Methyl 2-(6-(4-methoxyphenyl)-2-oxo-1,2,5,6-tetrahydropyridin-3-yl)acetate (4fa).



4fa

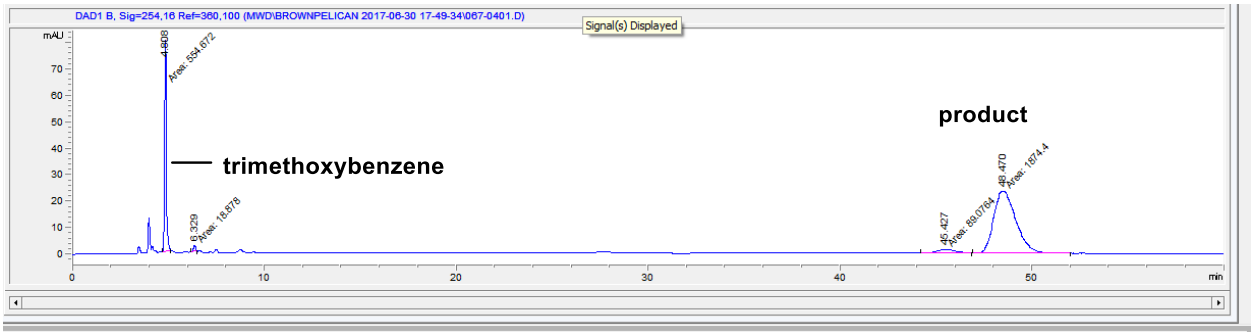
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 54% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 91% ee by chiral HPLC analysis. (Chiralpak IE, 30% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 45.4 min, t_r(e_2, major) = 48.5 min).

Full HPLC Racemic Assay



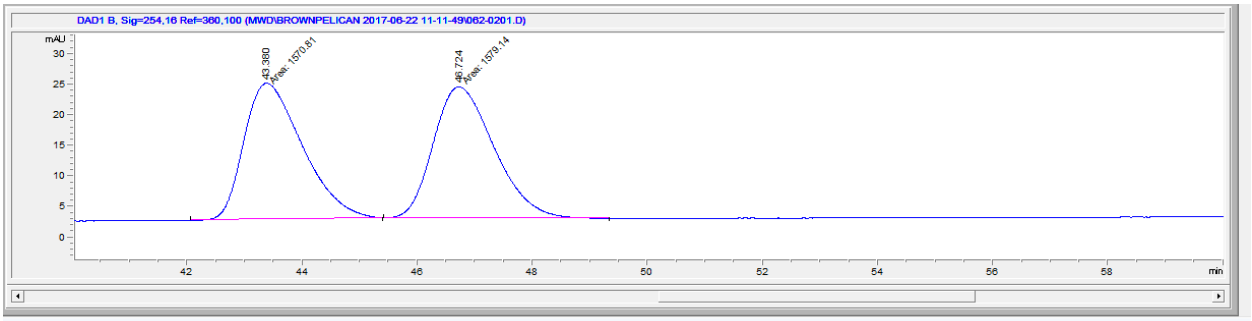
#	Time	Area	Height	Width	Area%	Symmetry
1	4.772	488.6	74.5	0.1092	11.691	0.773
2	6.084	540.6	57.2	0.1575	12.935	0.787
3	43.38	1570.8	22.3	1.1735	37.588	0.618
4	46.724	1579.1	21.5	1.2246	37.787	0.714

Full HPLC Enantioselective Assay (for yield)



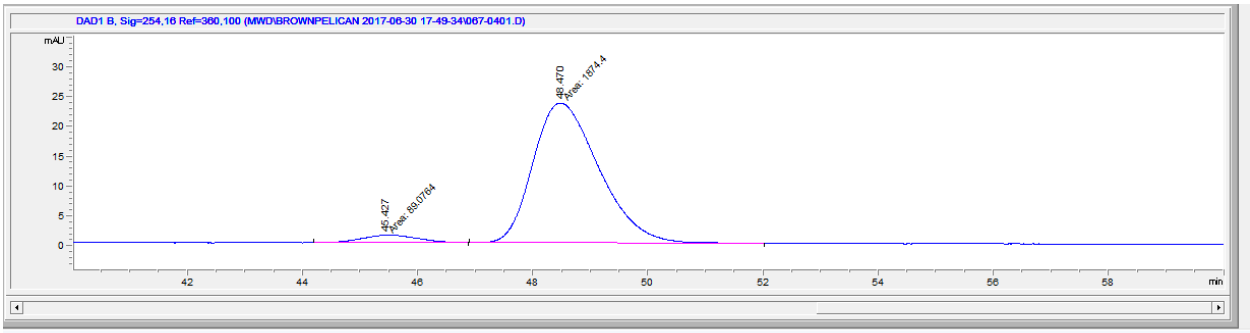
#	Time	Area	Height	Width	Area%	Symmetry
1	4.808	554.7	80	0.1156	21.863	0.68
2	6.329	18.9	2.5	0.1269	0.744	0.878
3	45.427	89.1	1.3	1.1669	3.511	0.714
4	48.47	1874.4	23.5	1.3296	73.882	0.687

HPLC Racemic Assay (Product)



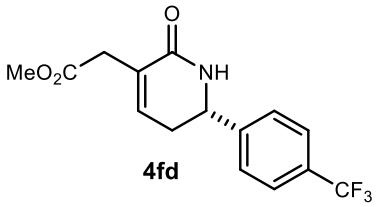
#	Time	Area	Height	Width	Area%	Symmetry
1	43.38	1570.8	22.3	1.1735	49.868	0.618
2	46.724	1579.1	21.5	1.2246	50.132	0.714

HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	45.427	89.1	1.3	1.1669	4.537	0.714
2	48.47	1874.4	23.5	1.3296	95.463	0.687

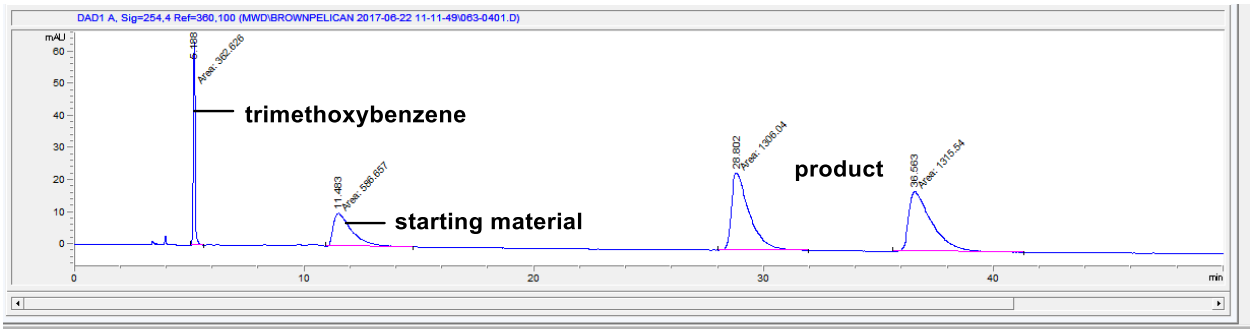
Methyl 2-(2-oxo-6-(4-(trifluoromethyl)phenyl)-1,2,5,6-tetrahydropyridin-3-yl)acetate (4fd).



4fd

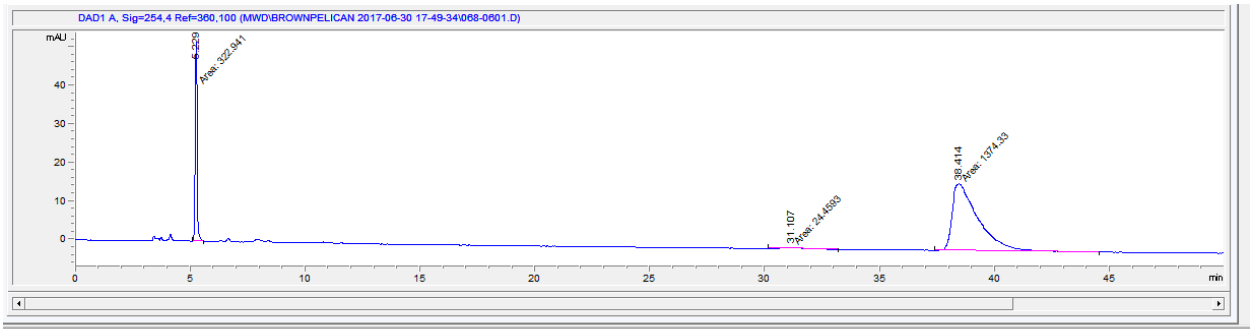
Product synthesized according to general procedure B, and extracted with diethyl ether. Product yield was determined to be 60% by chiral HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. The product was determined to be 97% ee by chiral HPLC analysis. (Chiralpak IB, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(e_1, minor) = 31.1 min, t_r(e_2, major) = 38.4 min).

Full HPLC Racemic Assay



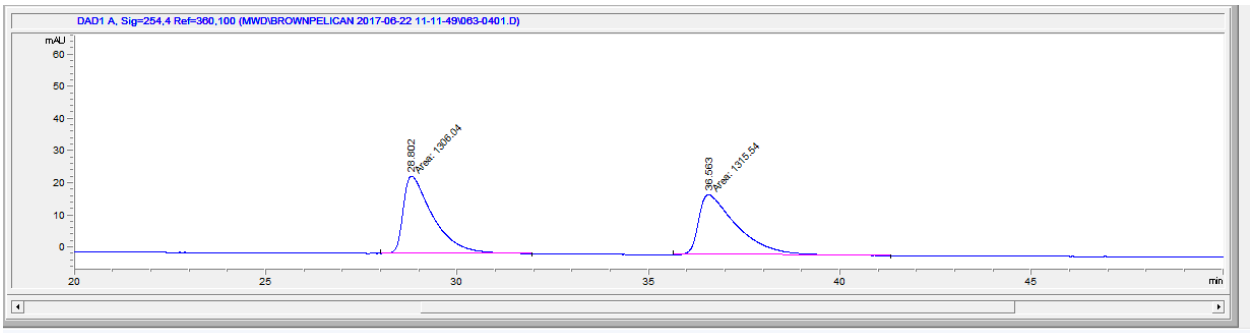
#	Time	Area	Height	Width	Area%	Symmetry
1	5.188	362.6	63.2	0.0956	10.155	0.771
2	11.483	586.7	10.3	0.947	16.429	0.362
3	28.802	1306	24.1	0.9036	36.575	0.382
4	36.563	1315.5	18.7	1.1716	36.841	0.346

Full HPLC Enantioselective Assay (for yield)



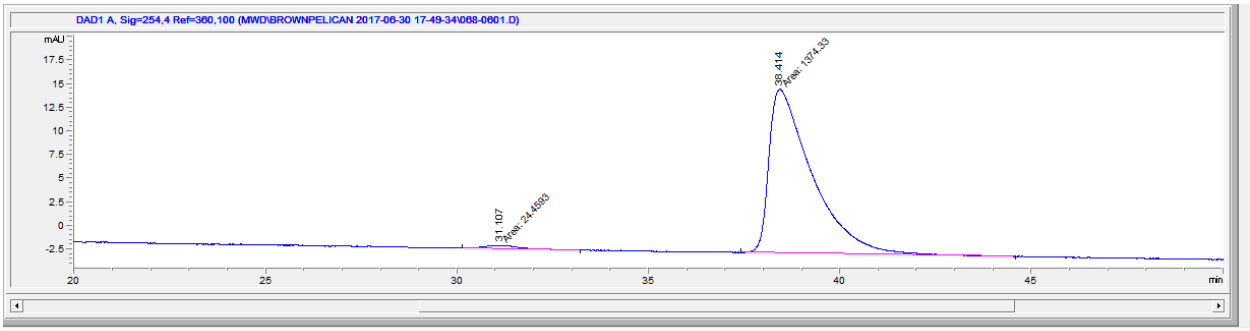
#	Time	Area	Height	Width	Area%	Symmetry
1	5.229	322.9	51.8	0.1039	18.757	0.743
2	31.107	24.5	3.7E-1	1.0889	1.421	0.677
3	38.414	1374.3	17.4	1.3189	79.823	0.314

HPLC Racemic Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	28.802	1306	24.1	0.9036	49.819	0.382
2	36.563	1315.5	18.7	1.1716	50.181	0.346

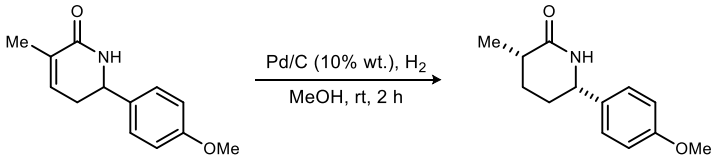
HPLC Enantioselective Assay (Product)



#	Time	Area	Height	Width	Area%	Symmetry
1	31.107	24.5	3.7E-1	1.0889	1.749	0.677
2	38.414	1374.3	17.4	1.3189	98.251	0.314

8. Product derivatization to piperidines (procedure, characterization, and spectra)

Derivatization of enantioenriched substrate



(3*S*,6*S*)-6-(4-Methoxyphenyl)-3-methylpiperidin-2-one (5aa). A round bottom flask equipped with a stir bar was flame dried under vacuum and purged with N_2. Upon cooling, Pd/C (3.26 mg, 10% by weight) was quickly added, and the flask was evacuated and refilled with N_2 (3x). The piperidone (32.6 mg, 150 µmol) was added to the flask as a solution in MeOH (1.75 mL, 0.1 M), and it was ensured that all Pd/C was properly suspended. The flask was then evacuated once more before being refilled with H_2 (balloon), and the resulting mixture was allowed to stir for 4 h at rt before TLC analysis. The resulting solution was filtered through a Celite plug and washed with EtOAc. The solvent was removed *in vacuo* to afford the desired lactam as a white solid (32.6 mg, 99% yield, 10:1 dr). When this reaction was conducted on enantioenriched **4aa**, **5aa** was generated in 99% yield, 91% ee and 10**:**1 dr by chiral HPLC analysis; (Chiralpak AD-H, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(*anti*, major/minor) = 36.43 min, t_r(*syn*, major/minor) = 38.39 min, t_r(*anti*, minor/major) = 43.05 min, t_r(*syn*, minor/major) = 45.60 min.

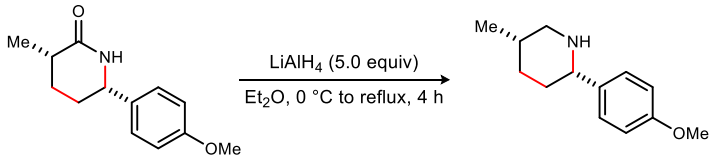
^{1}H NMR (*for major diastereomer only*, 400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.74 (br s, 1H), 4.53 (ddd, J = 7.2, 4.8, 1.6 Hz, 1H), 3.80 (s, 3H), 2.51 (ddq, J = 7.2, 6.0, 6.0 Hz, 1H), 2.07-1.99 (m, 1H), 1.94-1.72 (m, 2H), 1.64-1.55 (m, 1H), 1.32 (d, J = 7.2 Hz, 3H).

^{13}C NMR (*for major diastereomer only*, 500 MHz, $CDCl_3$) δ 175.89, 159.14, 134.72, 127.17, 114.08, 56.78, 55.31, 35.36, 29.30, 26,19, 18.02.

IR (neat, cm^{-1}) 3281, 3192, 3064, 2957, 2932, 2872, 2838, 1643, 1613, 1587, 1515, 1468, 1404, 1361, 1336, 1302, 1281, 1247, 1175.

HRMS (ASAP) m/z calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338, found: 220.1342.

(2*S*,5*S*)-2-(4-Methoxyphenyl)-5-methylpiperidine (5ab).



To an oven-dried flask equipped with a stir bar was added $LiAlH_4$ (28.2 mg, 743 µmol) and dry Et_2O (15.0 mL, 0.01 M). The suspension was chilled to 0 °C before the addition of the piperidone (32.9 mg, 148.5 µmol). The solution was refluxed overnight and then chilled back to 0 °C. A 10% sodium hydroxide solution (10 mL/0.1 mol) was added dropwise to the chilled solution and the resulting mixture stirred for another hour at rt. The phases were then separated, and the aqueous layer was extracted with ethyl acetate (3x). The

combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash column chromatography of the residue (SiO_2, 1-2-5-10-20% methanol in dichloromethane) afforded the desired product as a clear viscous oil (24.7 mg, 81% yield, 6:1 dr). The product was determined to be 92% ee and 6:1 dr by chiral HPLC analysis, derivatized as its corresponding NBoc amide; (Chiralpak IE, 5% ^{i}PrOH/hexanes, 1 mL/min, t_r(*syn*, major/minor) = 17.1 min, t_r(*anti*, major/minor) = 18.7 min, t_r(*anti*, minor/major) = 19.4 min, t_r(*syn*, minor/major) = 22.1 min.[viii]

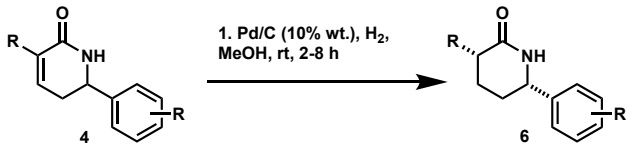
^{1}H NMR (*for major diastereomer only*, 500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.05 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.72 (s, 3H), 2.94 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.67 (dd, *J* = 12.5, 6.5 Hz, 1H), 2.30-2.20 (m, 1H), 2.17-2.02 (m, 2H), 1.80-1.71 (m, 1H), 1.56-1.47 (m, 1H), 1.06 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (*for both diastereomers*, 500 MHz, $CDCl_3$) δ 159.92, 159.55, 129.58, 129.36, 128.57, 127.15, 114.16, 114.07, 60.27, 56.81, 55.16, 55.10, 51.44, 47.43, 32.19, 30.05, 29.67, 28.09, 27.96, 26.80, 24.86, 18.69, 17.86.

IR (neat, cm^{-1}) 3404, 2933, 2759, 2701, 2528, 1612, 1585, 1514, 1448, 1301, 1256, 1181.

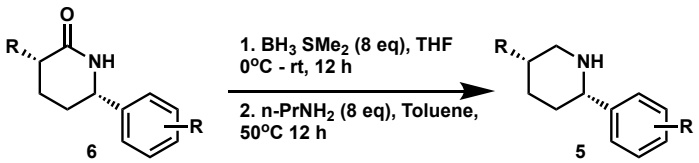
HRMS (ASAP) m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1545, found: 206.1555.

<u>*Derivatization of racemic substrate*</u>



4 6

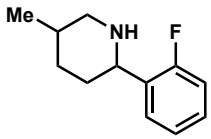
General procedure is the same as that mentioned above for enantioenriched substrate.



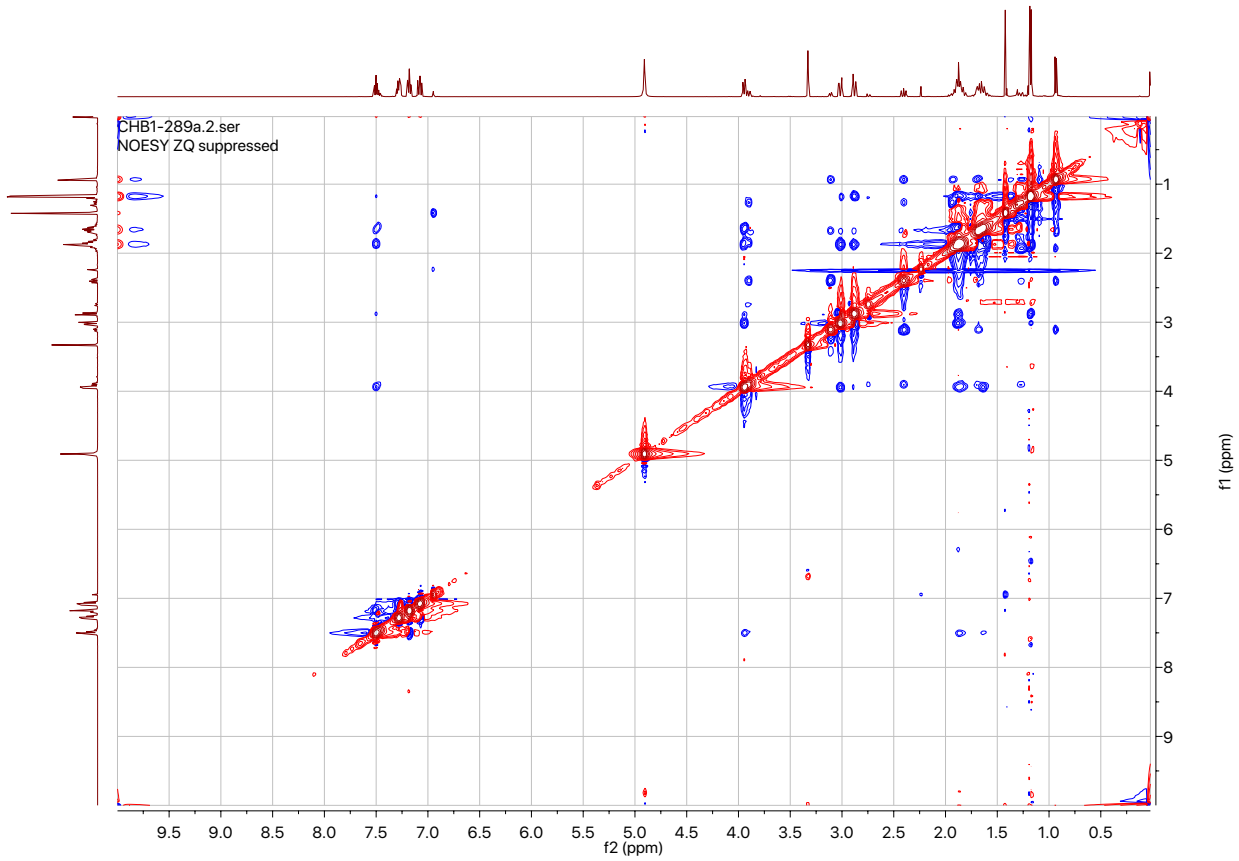
6 5

General procedure is the same as that mentioned above for enantioenriched substrate.

The stereochemical relationship between the two chiral centers was determined via 2D NOESY for the following substrate:

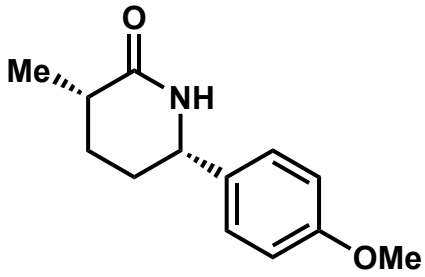


5aj



Spectral data for product derivatization

6-(4-methoxyphenyl)-3-methylpiperidin-2-one (6aa)



6aa

White solid (29.7 mg, 99% yield, 13:1 dr)

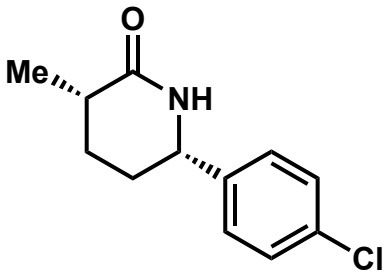
^{1}H NMR (*major diastereomer only,* 400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.06 (s, 1H), 4.52 (td, *J* = 5.9, 4.8, 1.8 Hz, 1H), 3.79 (s, 3H), 2.58 – 2.34 (m, 1H), 2.02 (m, 1H), 1.93 – 1.69 (m, 2H), 1.64 – 1.45 (m, 1H), 1.30 (d, *J* = 7.3 Hz, 2H).

^{13}C NMR (*major diastereomer only,* 101 MHz, $CDCl_3$) δ 176.29, 159.24, 134.82, 127.28, 114.19, 56.78, 55.42, 35.43, 29.38, 26.23, 18.08.

IR (neat, cm^{-1}) 3205.53, 2932.35, 1655.51, 1512.00, 1464.39, 1406.17, 1336.1, 1247.67, 1176.76, 1112.27, 1031.88, 833.93, 570.23

HRMS (ASAP+) m/z calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1181 , found: 218.1175

6-(4-chlorophenyl)-3-methylpiperidin-2-one (6ac)



6ac

Light-orange solid (55.9 mg, 99% yield, 19:1 dr)

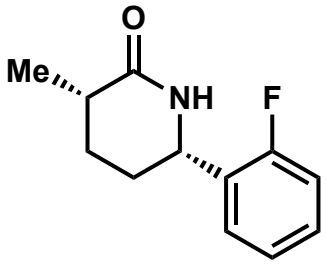
^{1}H NMR (*major diastereomer only,* 400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.19 – 6.11 (s, 1H), 4.60 (ddd, *J* = 2.6 Hz, 1H), 3.78 (s, 3H), 2.89 (dd, *J* = 16.1, 4.6 Hz, 1H), 2.80 (m, 1H), 2.55 (dd, *J* = 16.1, 8.2 Hz, 1H), 1.91 – 1.72 (m, 1H).

^{13}C NMR (*both diastereomers,* 101 MHz, $CDCl_3$) δ 172.68, 159.16, 134.69, 127.34, 114.11, 55.39, 51.79, 37.84, 30.00, 22.73.

IR (neat, cm^{-1}) 2950, 1735, 1657, 1512, 1465, 1342, 1248, 1176, 1032, 836.

HRMS (ASAP+) m/z calcd for $C_{12}H_{14}ClNO$ $[M_{deschloro}+H]^+$: 190.1232, found: 190.1229

6-(2-fluorophenyl)-3-methylpiperidin-2-one (6aj)



6aj

Off-white solid (28.7 mg, 95% yield, 4:1 dr)

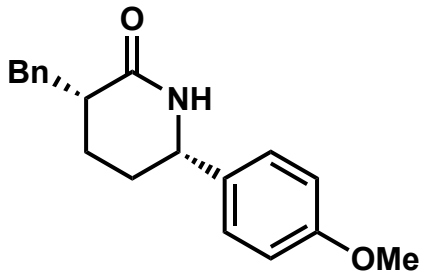
^{1}H NMR (*major diastereomer only,* 400 MHz, $CDCl_3$) δ 7.33 (td, *J* = 7.6, 1.8 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.00 (td, *J* = 10.7, 8.1, 1.2 Hz, 1H), 6.08 (s, 1H), 4.86 (dd, *J* = 9.8, 4.7 Hz, 1H), 2.55 – 2.31 (m, 1H), 2.19 – 2.02 (m, 2H), 1.93 – 1.79 (m, 1H), 1.60 – 1.39 (m, 1H), 1.26 (d, *J* = 7.2 Hz, 2H).

^{13}C NMR (*major diastereomer only* , 101 MHz, $CDCl_3$) δ 176.34, 161.05, 158.60, 129.28 (d, *J* = 8.3 Hz), 127.59 (d, *J* = 4.1 Hz), 124.36 (d, *J* = 3.6 Hz), 115.72 (d, *J* = 21.3 Hz), 50.81 (d, *J* = 3.0 Hz), 35.87, 25.93, 17.73.

IR (neat, cm^{-1}) 2935, 1656, 1485, 758

HRMS (ASAP+) m/z calcd for $C_{12}H_{14}FNO$ $[M+H]^+$: 208.1138, found: 208.1134

3-benzyl-6-(4-methoxyphenyl)piperidin-2-one (6ba)



6ba

Light-orange solid (28.7 mg, 99% yield, 10:1 dr)

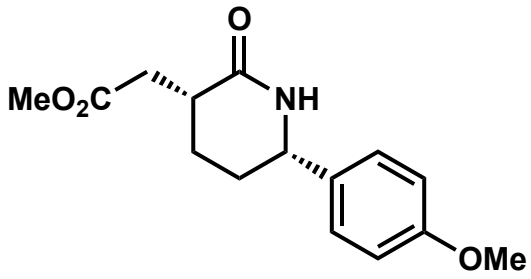
^{1}H NMR (*major diastereomer only,* 400 MHz, $CDCl_3$)

^{13}C NMR (*both diastereomers,* 101 MHz, $CDCl_3$) δ 174.44, 159.17, 139.57, 134.66, 129.61, 128.5, 127.28, 126.41, 114.12, 56.54, 5v5.42, 42.43, 37.66, 29.49, 21.9

IR (neat, cm^{-1}) 3203.3, 3025.67, 2932.12, 1651.96, 1511.14, 1246.61, 1176.07, 1032.58, 833.89, 1752.84, 702.11

HRMS (ASAP+) m/z calcd for $C_{19}H_{21}NO_2$ $[M+H]^+$: 296.1650, found: 296.1654

methyl 2-(6-(4-methoxyphenyl)-2-oxopiperidin-3-yl)acetate (6fa)



6fa

Off-white solid (4.4 mg, 93% yield, 19:1 dr)

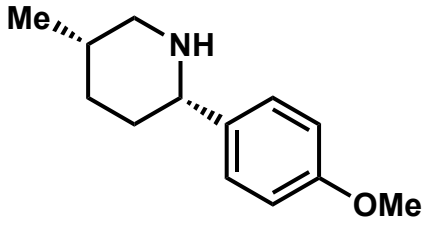
^{1}H NMR (*major diastereomer only,* 500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.17 (s, 1H), 4.60 (dd, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 2.95 – 2.86 (m, 1H), 2.84 – 2.76 (m, 1H), 2.55 (dd, *J* = 16.2, 8.3 Hz, 1H), 2.19 – 2.06 (m, 1H), 1.88 – 1.75 (m, 2H), 1.70 – 1.56 (m, 1H).

^{13}C NMR (*major diastereomer only,* 126 MHz, $CDCl_3$) δ 173.62, 172.68, 159.12, 134.70, 127.33, 114.08, 55.85, 55.38, 51.79, 37.84, 35.99, 30.00, 22.70.

IR (neat, cm^{-1}) 2952, 1734, 1661, 1511, 1248, 1175, 1034

HRMS (ASAP+) m/z calcd for $C_{15}H_{19}NO_4$ $[M+H]^+$: 278.1392, found: 278.1385.

2-(4-methoxyphenyl)-5-methylpiperidine (5aa)



5aa

Pale-yellow oil (20.7 mg, 76% yield, 8:1 dr)

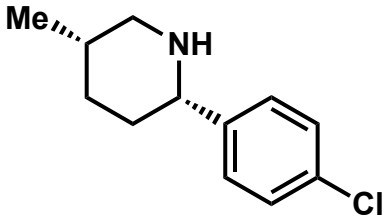
^{1}H NMR (*major diastereomer only,* 400 MHz, $CDCl_3$) δ 7.36 – 7.28 (d, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 3.65 – 3.53 (d, 1H), 2.99 (dd, *J* = 11.8, 3.4 Hz, 1H), 2.91 – 2.80 (d, 1H), 1.89 – 1.81 (m, 1H), 1.78 – 1.72 (m, 2H), 1.59 (dd, *J* = 9.8, 1.3 Hz, 2H), 1.14 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (*major diastereomer only,* 101 MHz, $CDCl_3$) δ 158.60, 137.68, 113.79, 61.05, 55.38, 52.46, 30.84, 29.63, 27.87, 17.34.

IR (neat, cm^{-1}) 2926.74, 2853.9, 1675.4, 1629.8, 1512.3, 1458.7, 1249.6, 1169.8, 1033, 831.47, 785.85, 732.63, 702.22

HRMS (ASAP+) m/z calcd for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1545, found: 206.1541

2-(4-chlorophenyl)-5-methylpiperidine (5ac)



5ac

Clear oil (119.0 mg, 87% yield, 5:1 dr)

^{1}H NMR (*major diastereomer only,* 400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 4H), 3.60 (dt, *J* = 7.0, 2.5 Hz, 1H), 2.98 (dd, *J* = 11.8, 3.4 Hz, 1H), 2.85 (ddd, *J* = 11.8, 3.0, 1.5 Hz, 1H), 1.85 (ddd, *J* =

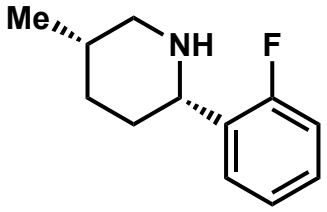
6.7, 4.6, 3.0 Hz, 1H), 1.74 (ddt, *J* = 10.5, 5.9, 2.5 Hz, 2H), 1.63 – 1.55 (m, 2H), 1.15 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (*major diastereomer only,* 101 MHz, $CDCl_3$) δ 144.07, 132.36, 128.41, 128.07, 60.99, 52.29, 30.68, 29.80, 27.77, 17.21.

IR (neat, cm^{-1}) 2926.74, 2849.87, 2764.63, 1490.43, 1443.67, 1378.61, 1328.54, 1189.01, 1013.35, 813.46, 764.66, 637.65, 531.18, 462.27

HRMS (ASAP+) m/z calcd for $C_{12}H_{17}ClN$ $[M+H]^+$: 210.1049, found: 210.1053.

2-(2-fluorophenyl)-5-methylpiperidine (5aj)



5aj

Clear oil (25.5 mg, 61% yield, 3:1 dr)

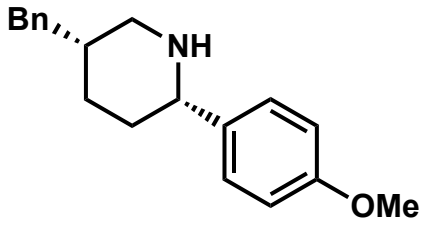
^{1}H NMR (*major diastereomer only,* 500 MHz, MeOD) δ 7.51 (d, *J* = 1.8 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.20 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.09 (ddd, *J* = 11.0, 8.2, 1.2 Hz, 1H), 3.96 (dd, *J* = 10.3, 3.1 Hz, 1H), 3.03 (dd, *J* = 12.8, 3.4 Hz, 1H), 2.89 (dt, *J* = 12.7, 2.2 Hz, 1H), 2.03 – 1.79 (m, 3H), 1.79 – 1.53 (m, 2H), 1.19 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (*major diastereomer only,* 101 MHz, MeOD) δ 160.53, 129.76, 129.13, 125.46, 116.40, 56.31 (d, *J* = 2.7 Hz), 52.84, 35.00, 31.51, 28.46, 17.26.

IR (neat, cm^{-1}) 3372.04, 2925.85, 1584.57, 1489.75, 1451.12, 1829.88, 1331.99, 1281.46, 1225.98, 1121.42, 1116.23, 1089, 1009.78, 754.9, 536.59

HRMS (ASAP+) m/z calcd for $C_{12}H_{17}FN$ $[M+H]^+$: 194.1345, found: 194.1342.

5-benzyl-2-(4-methoxyphenyl)piperidine (5ba)



5ba

Clear oil (84.7 mg, 86% yield, 6:1 dr)

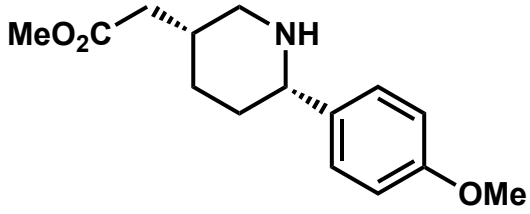
^{1}H NMR (*major diastereomer only,* 500 MHz, MeOD) δ 7.38 – 7.33 (d, 2H), 7.31 – 7.23 (m, 3H), 7.21 – 7.15 (m, 2H), 6.92 (d, *J* = 8.7 2H), 3.78 (s, 3H), 3.63 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.47 (ddd, *J* = 22.5, 11.6, 2.6 Hz, 1H), 2.92 (d, *J* = 3.4 Hz, 1H), 2.84 (dd, *J* = 7.8, 4.0 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.79 – 1.57 (m, 5H).

^{13}C NMR (*major diastereomer only,* 101 MHz, $CDCl_3$) δ 158.60, 141.98, 138.00, 129.27, 127.76, 125.73, 113.77, 61.32, 55.33, 50.40, 37.24, 35.42, 30.27, 28.56.

IR (neat, cm^{-1}) 3024.13, 2926.04, 2849.2, 1609.84, 1511.02, 1442.07, 1301.85, 1244.73, 1174.11, 1106.58, 1036.14, 829.06, 771.16, 700.17, 651.50, 542.82

HRMS (ASAP+) m/z calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1854 .

methyl 2-(6-(4-methoxyphenyl)piperidin-3-yl)acetate (5fa)



5fa

Clear oil (22.0 mg, 78% yield, 5:1 dr)

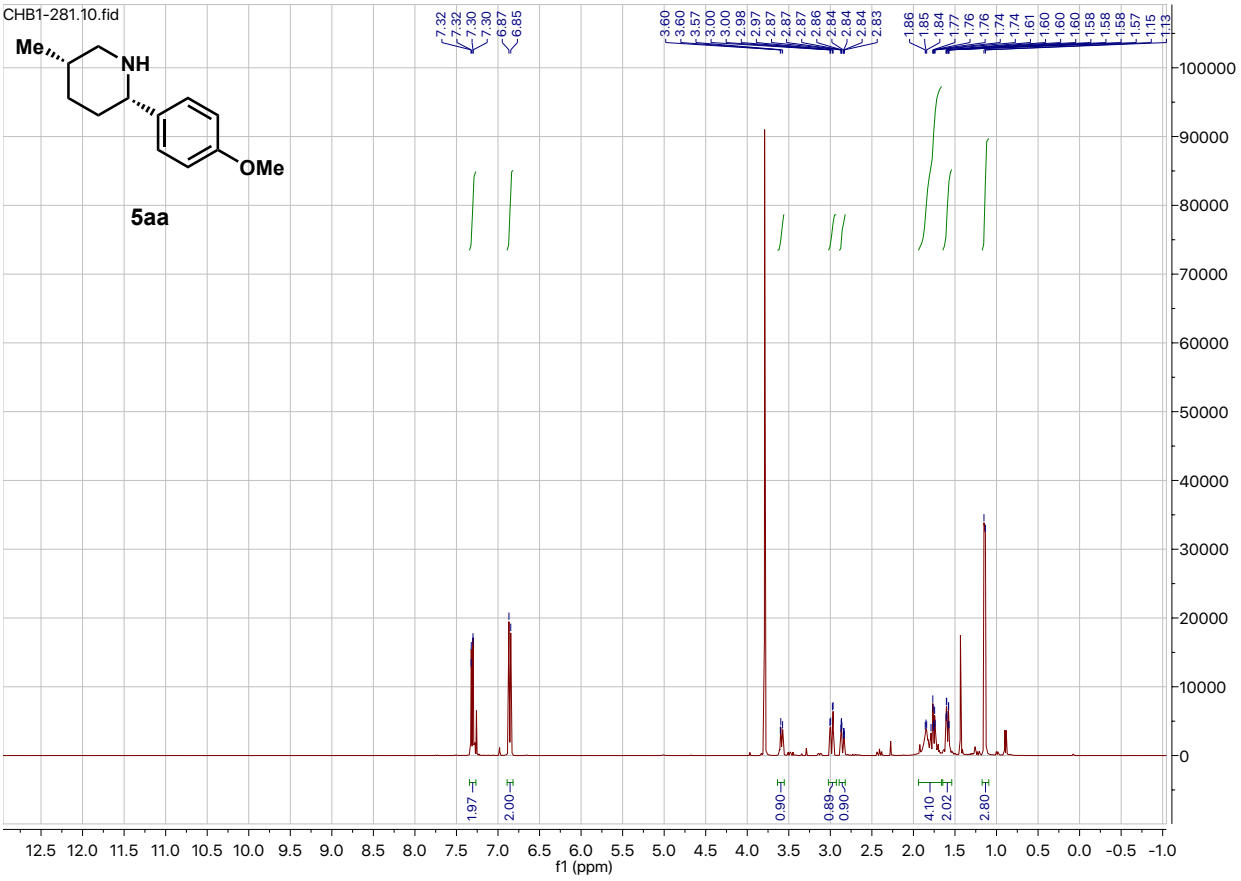
^{1}H NMR (*major diastereomer only,* 400 MHz, MeOD) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 2.99 (d, *J* = 3.5 Hz, 2H), 2.70 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.60 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.34 – 2.12 (m, 2H), 1.88 – 1.58 (m, 5H).

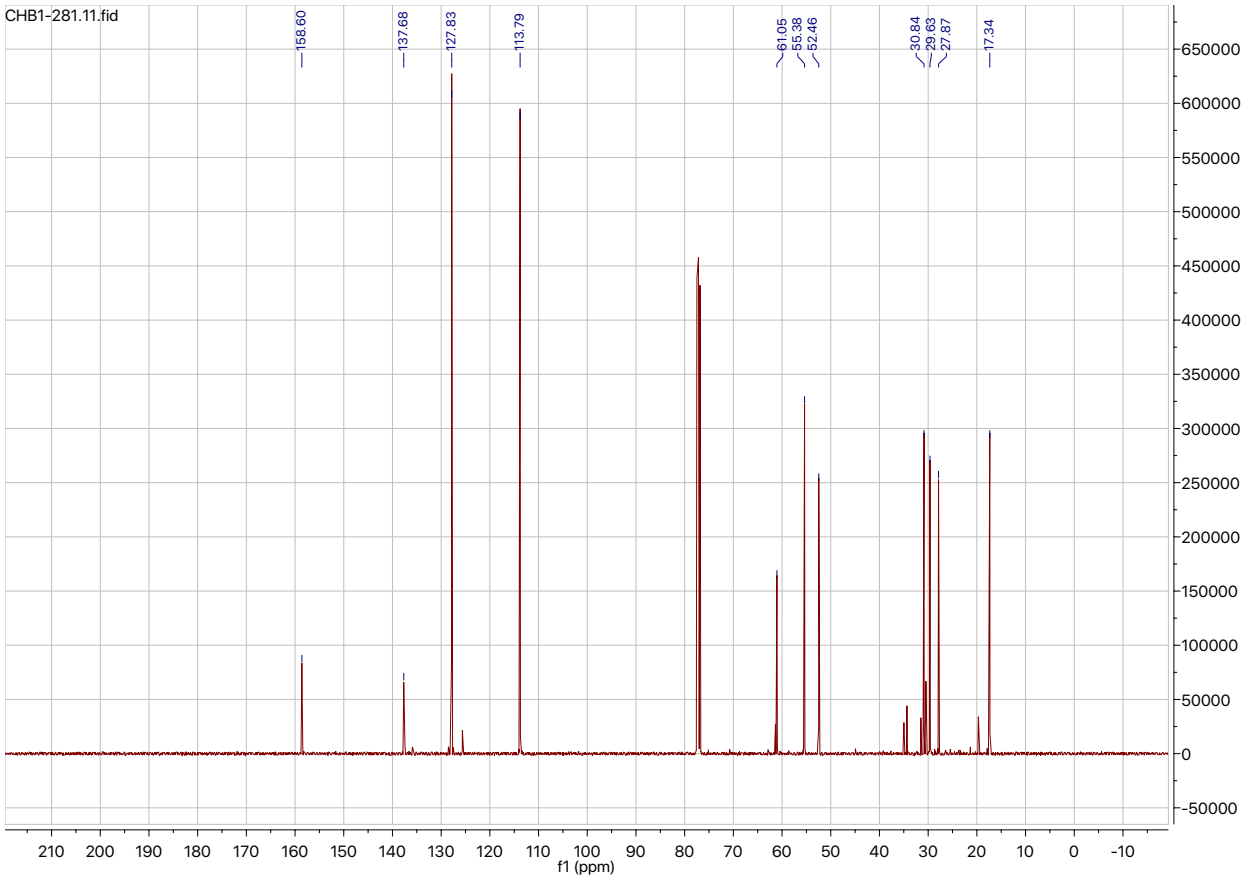
^{13}C NMR (*major diastereomer only,* 101 MHz, MeOD)

IR (neat, cm^{-1}) 2928.05, 2834.93, 1732.16, 1610.65, 1532.35, 1511.06, 1437.37, 1276.57, 1169.39, 1035.44, 890.71, 829.59, 772.23, 644.48, 503.09

HRMS (ASAP+) m/z calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1600, found: 264.1591.

Copies of NMR spectra

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113.79
61.05
55.38
52.46
30.84
29.63
27.87
17.34
650000
600000
550000
500000
450000
400000
350000
300000
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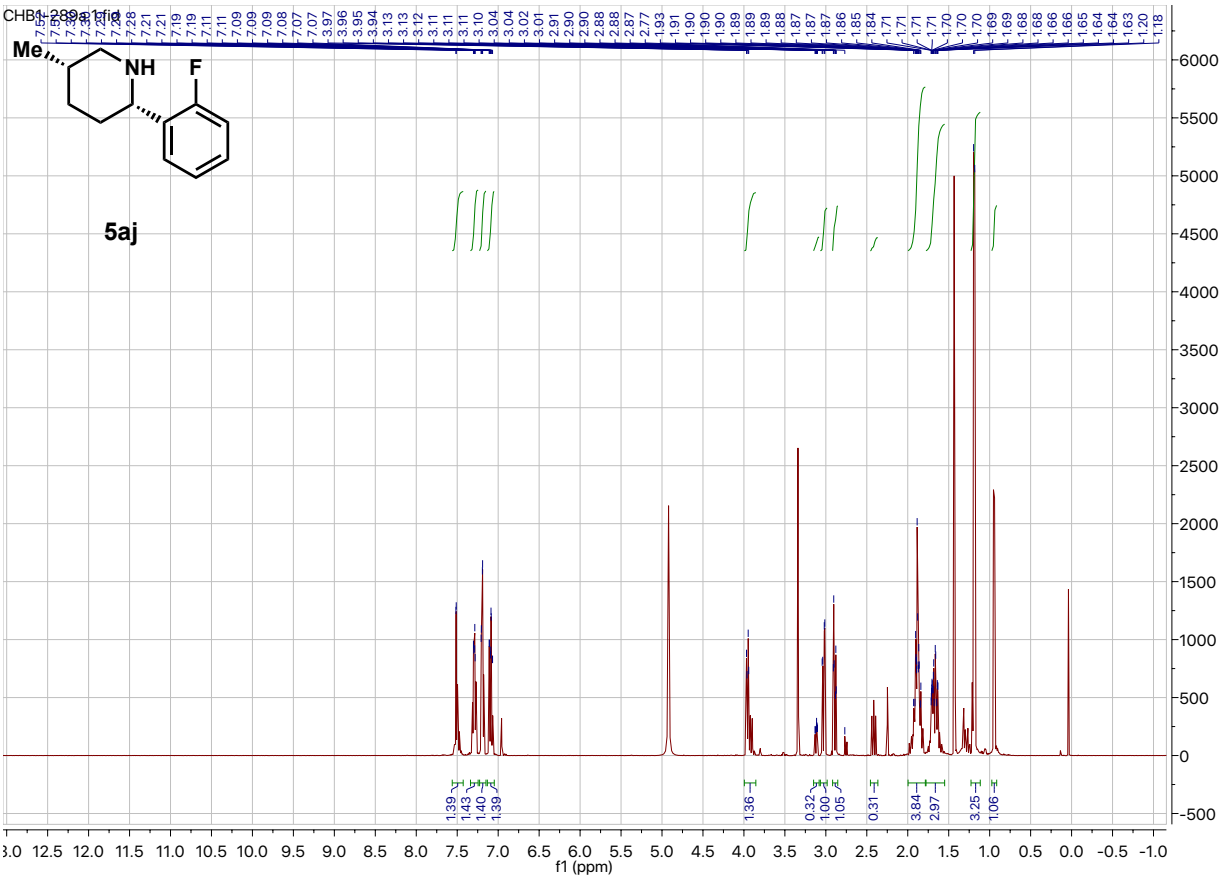
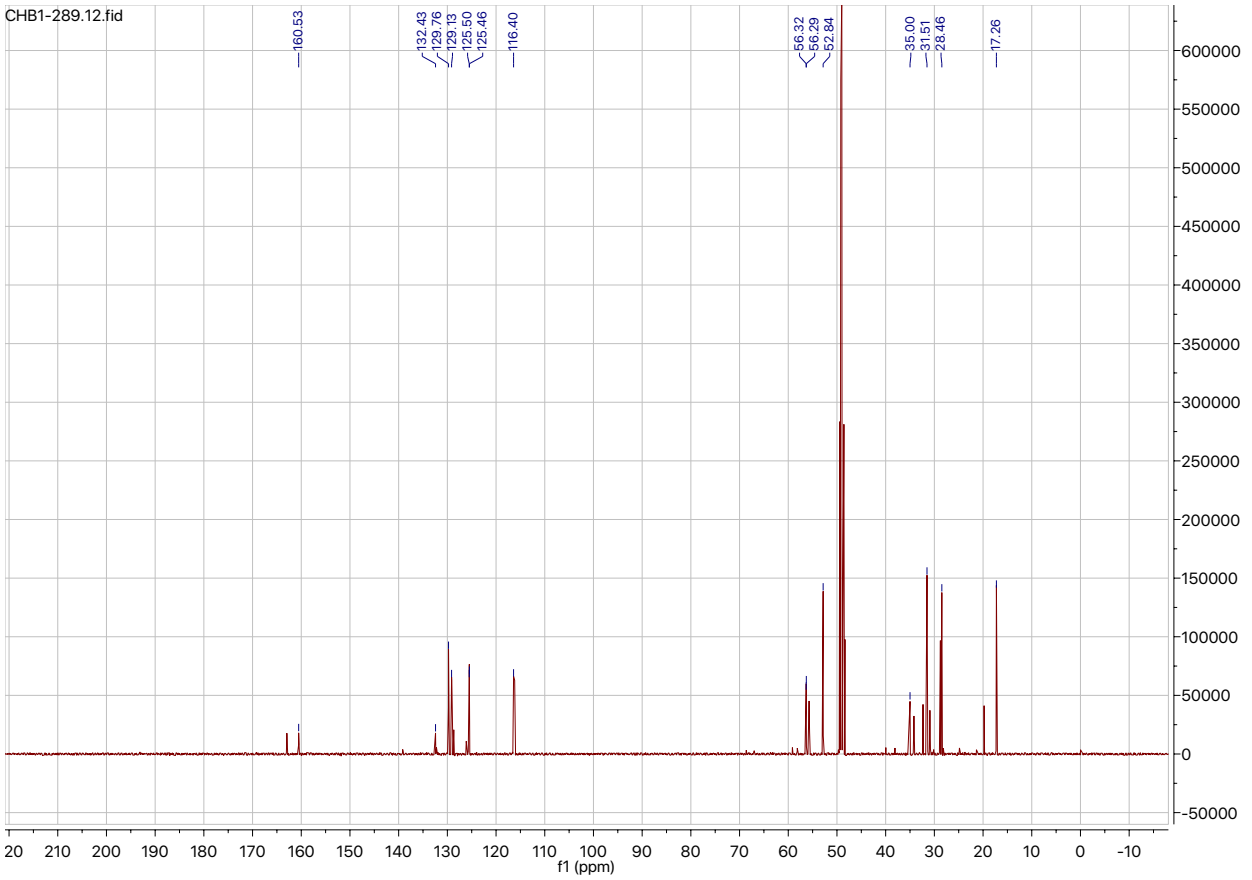
200000
150000
100000
50000
0
-50000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CHB1-289a.1.fid
Me
NH
F
5aj
f1 (ppm)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17.26
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500000
450000
400000
350000
300000
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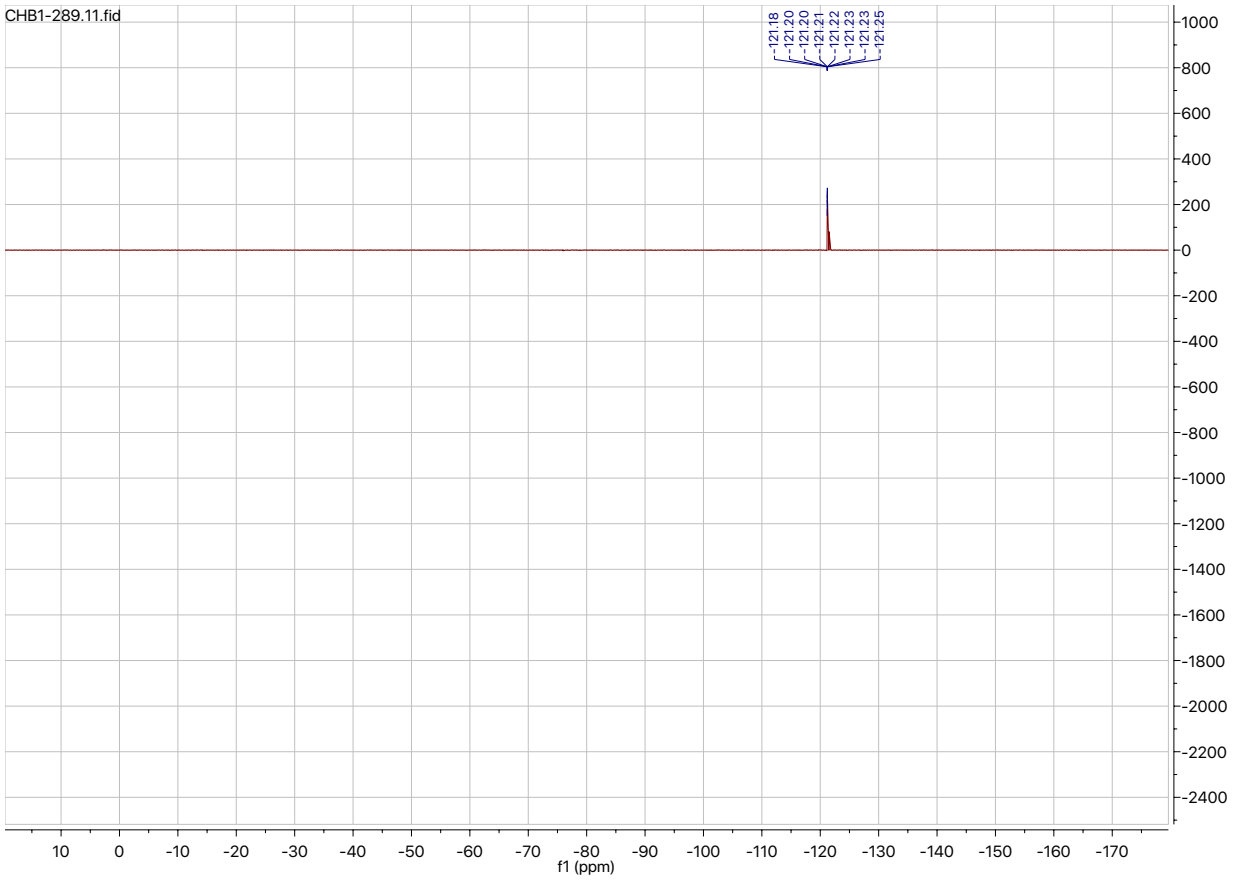
f1 (ppm)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-2400
10
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-10
-20
-30
-40
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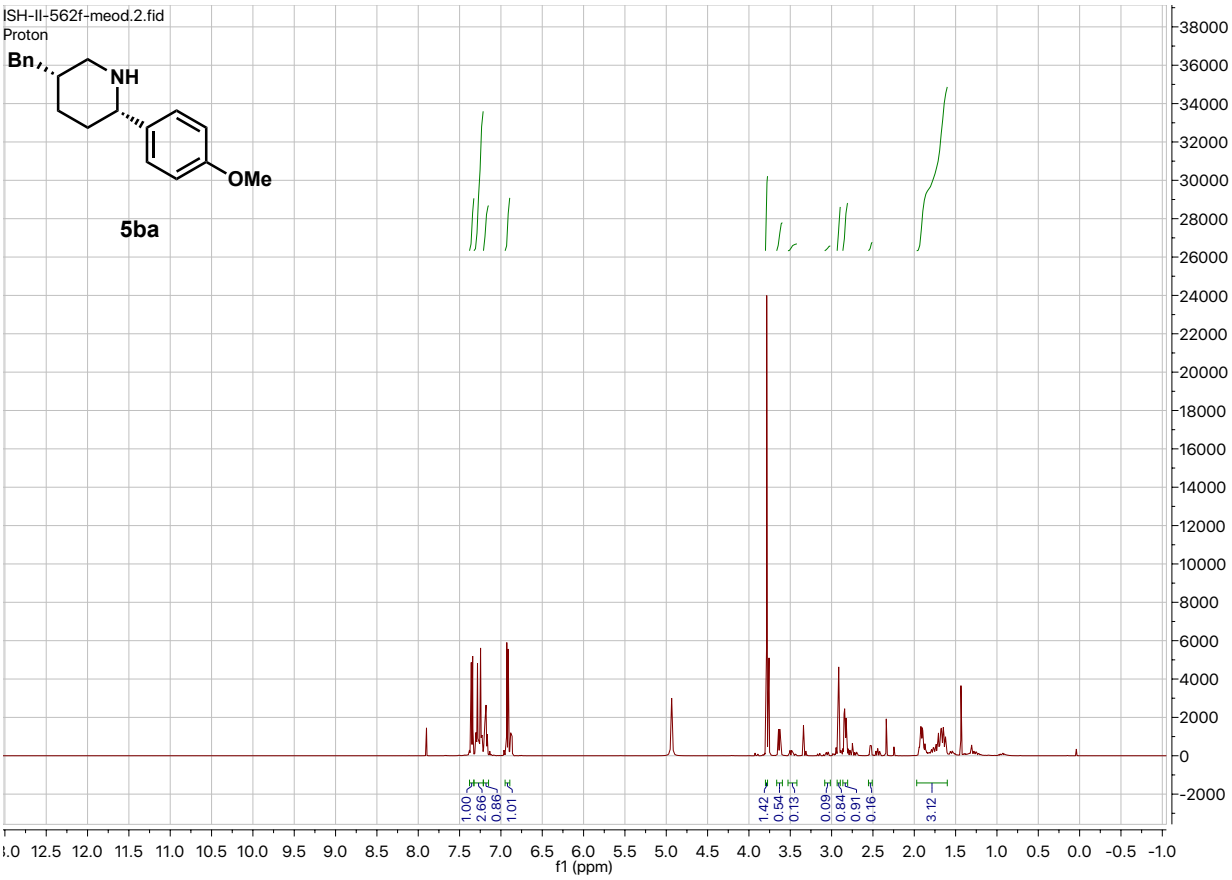
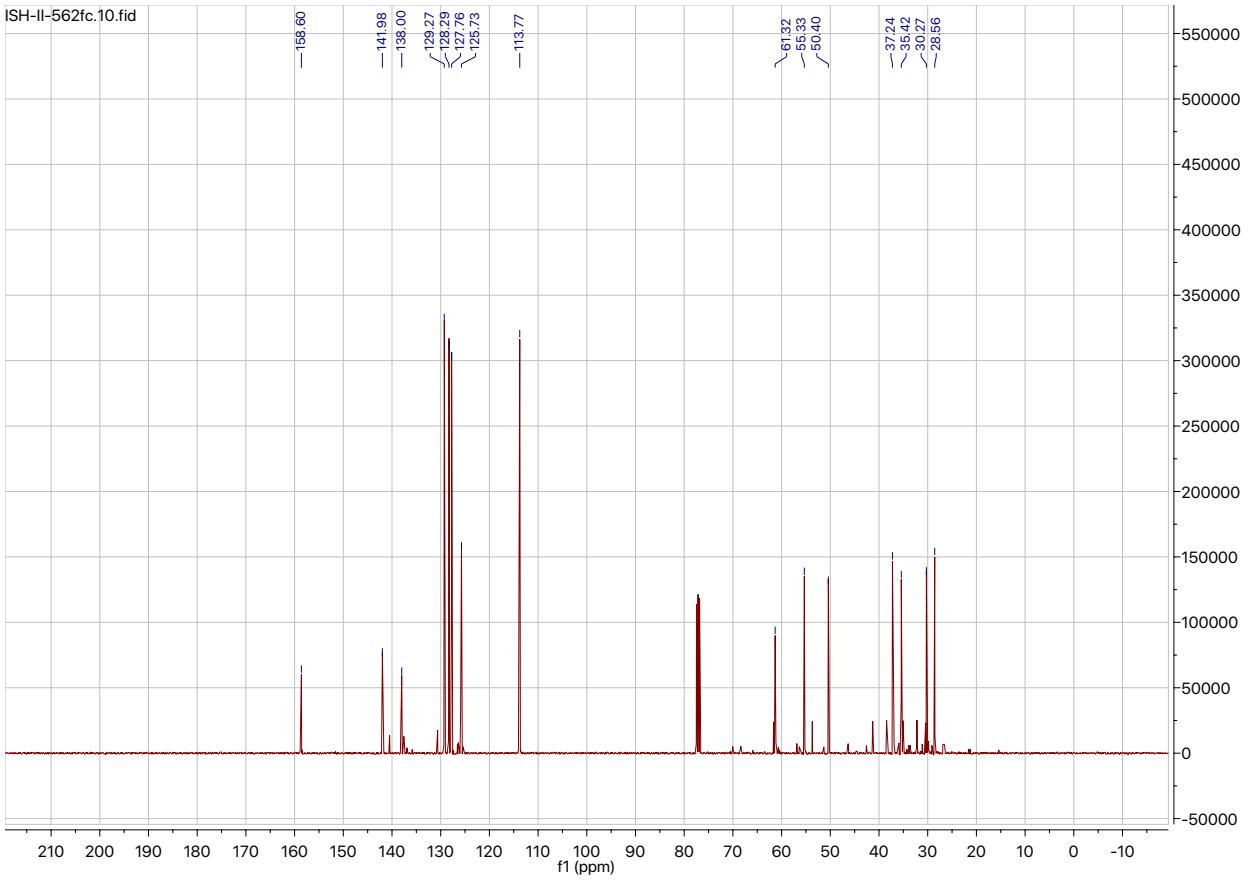
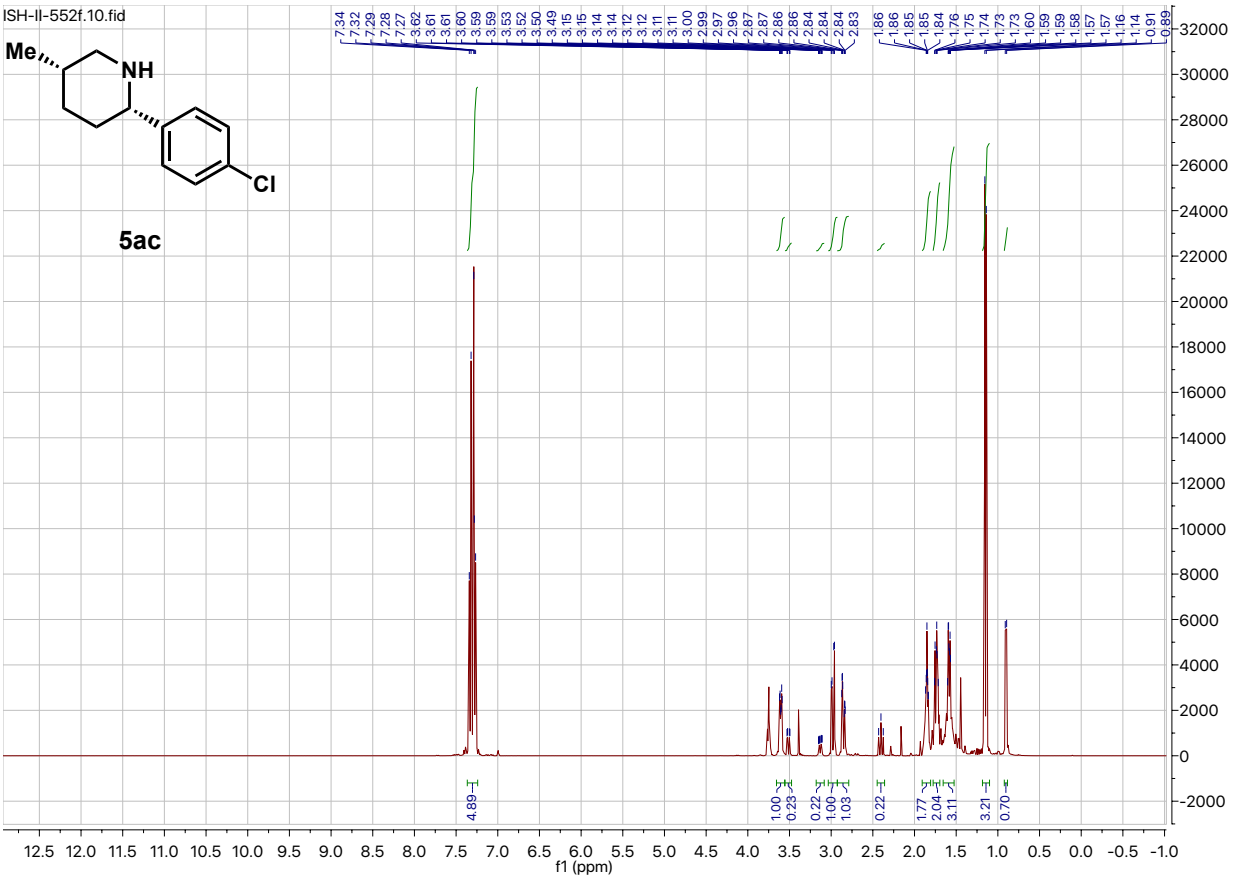
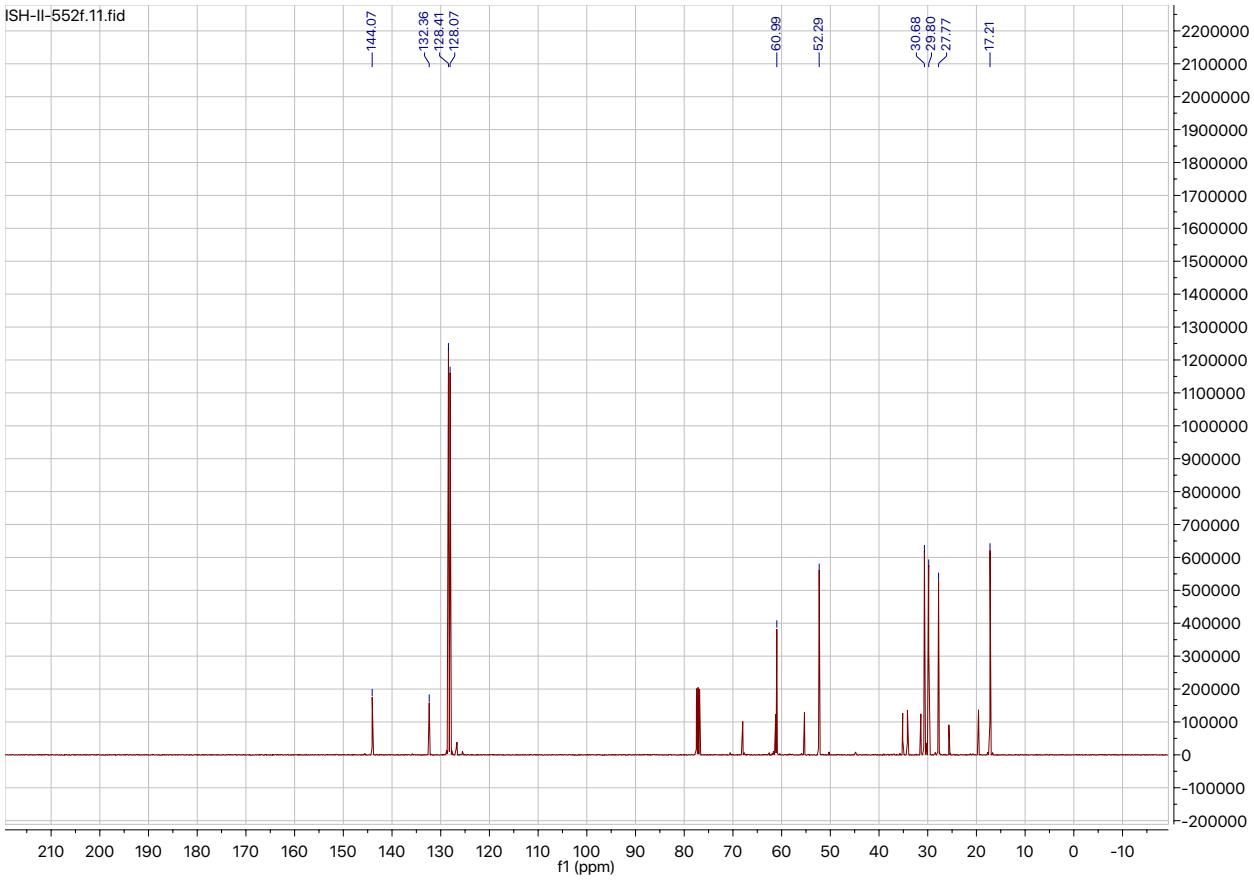
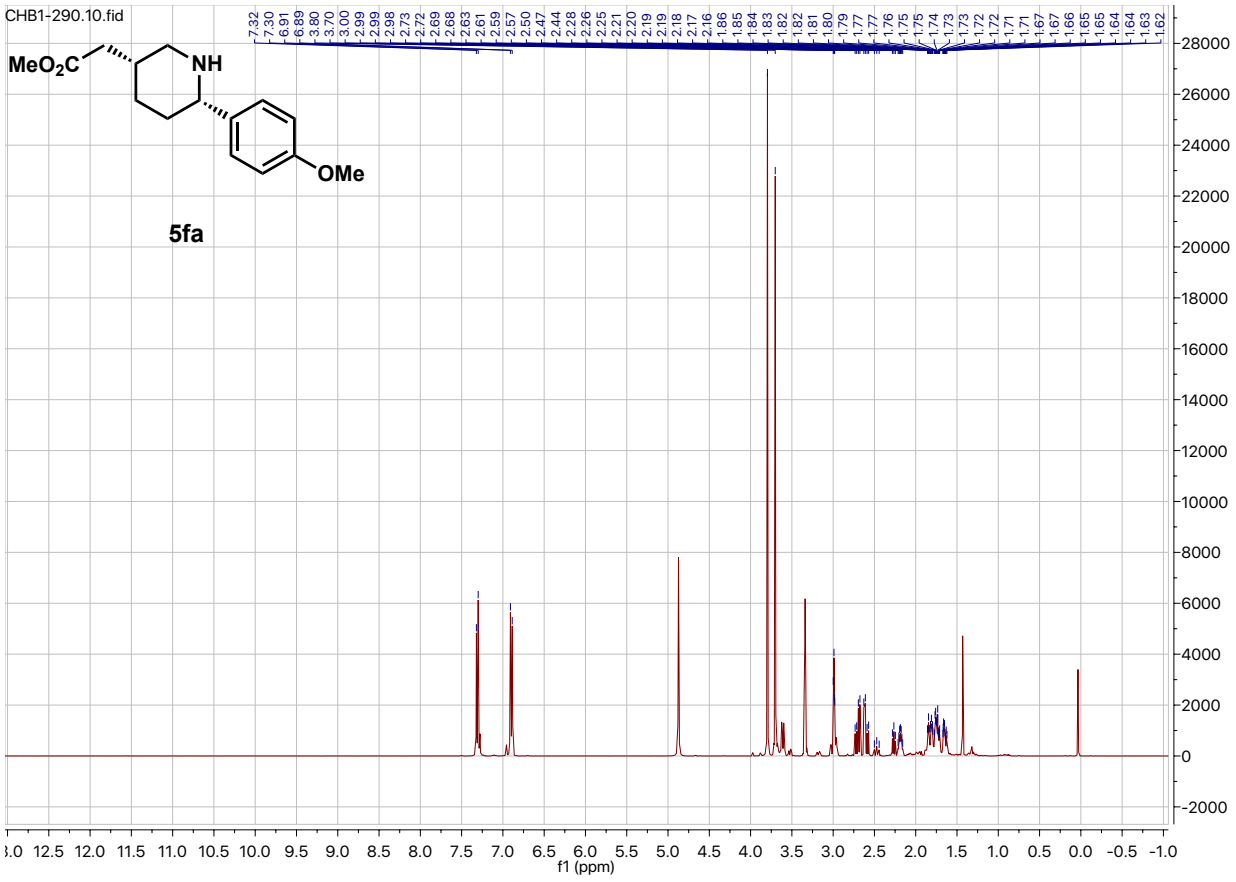
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)

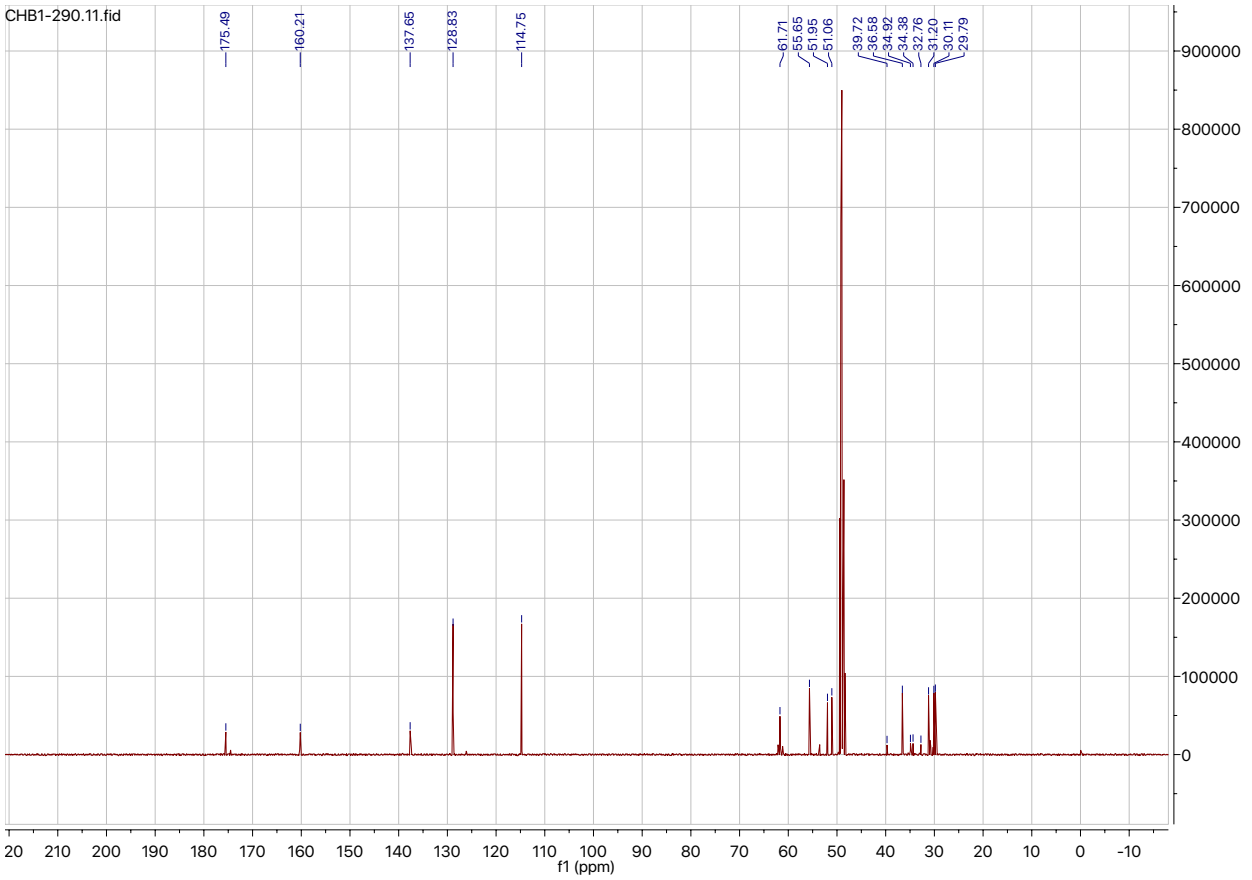

ISH-II-562f-meod.2.fid
Proton
Bn
NH
OMe
5ba
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
1.00
2.66
0.86
1.01
1.42
0.54
0.13
0.09
0.84
0.91
0.16
3.12
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

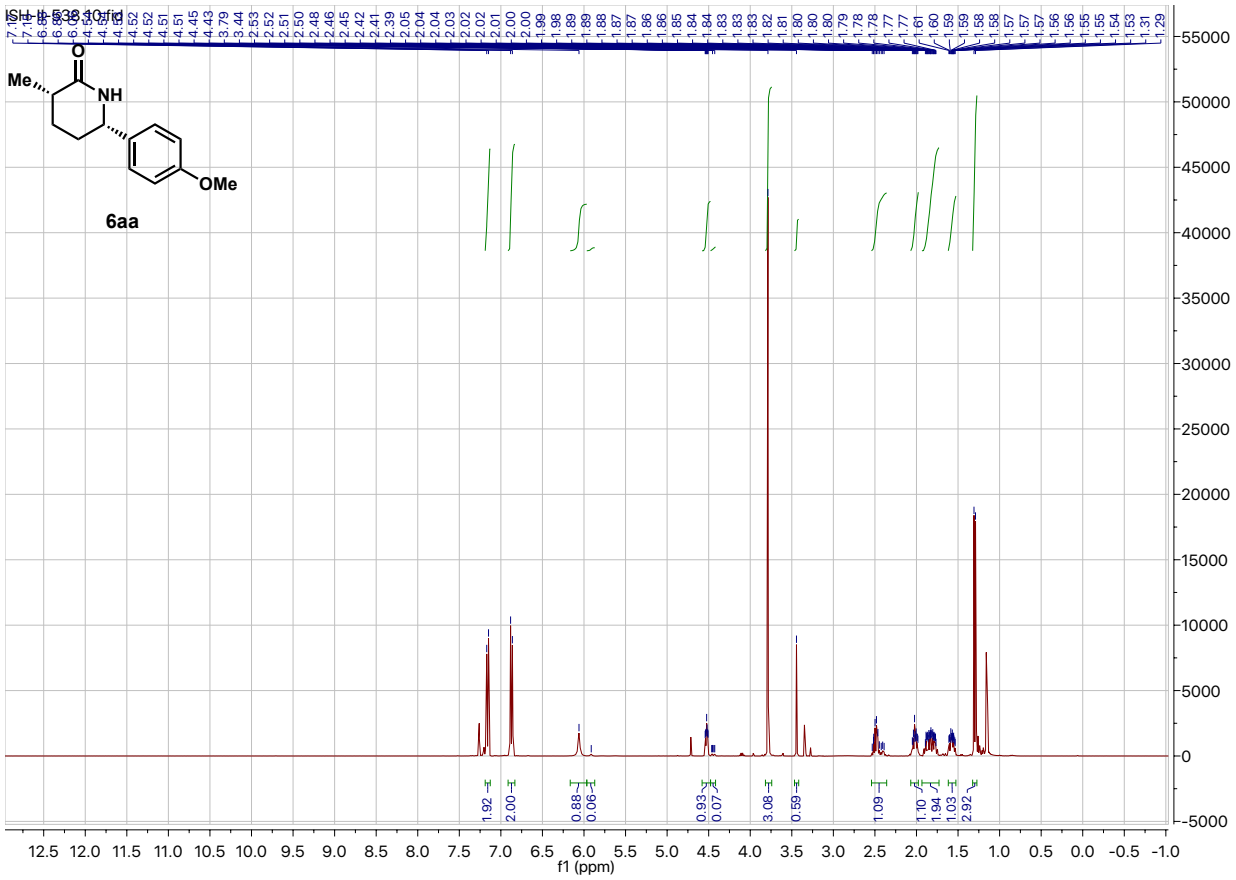

ISH-II-562fc.10.fid
158.60
141.98
138.00
129.27
128.29
127.76
125.73
113.77
61.32
55.33
50.40
37.24
35.42
30.27
28.56
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

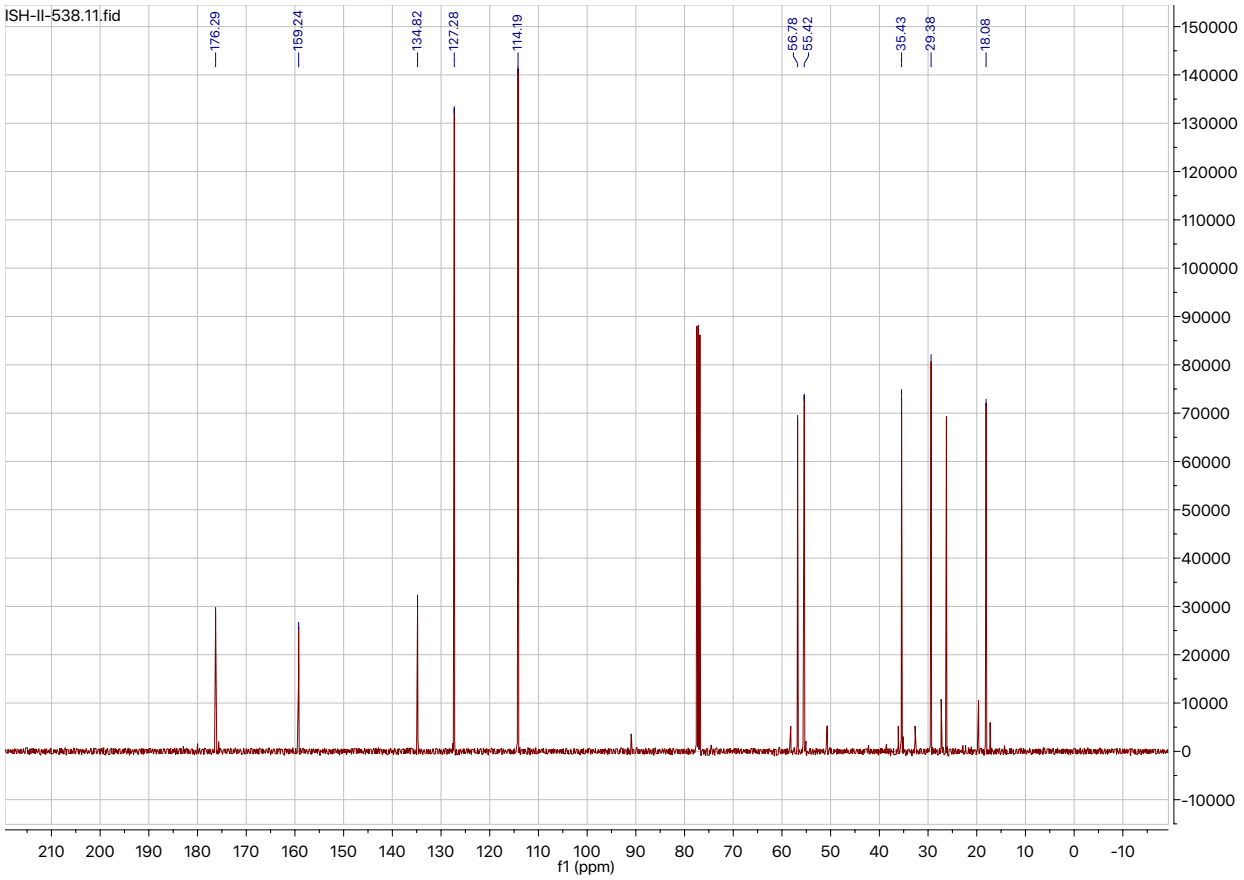

ISH-II-552f.10.fid
Me
NH
Cl
5ac
f1 (ppm)

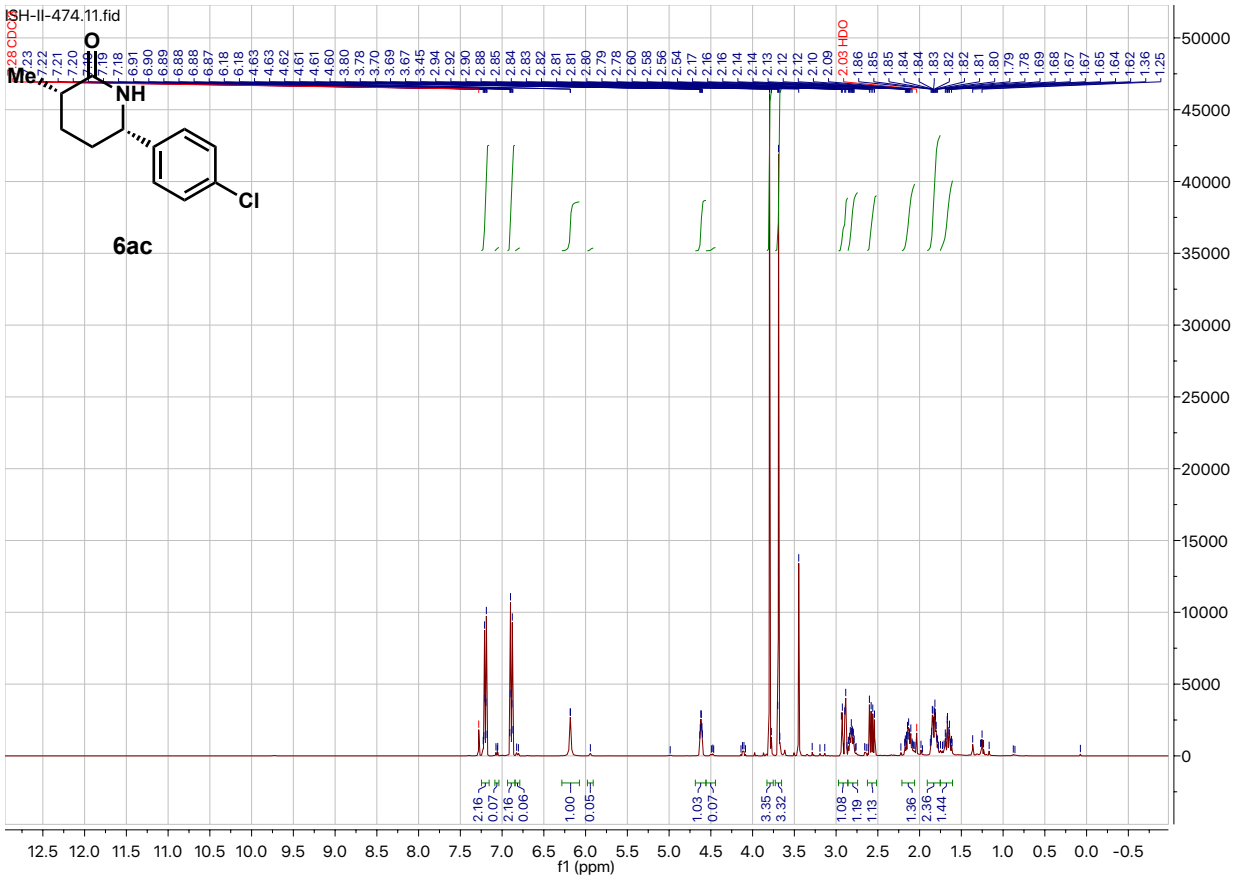

ISH-II-552f.11.fid
144.07
132.36
128.41
128.07
60.99
52.29
30.68
29.80
27.77
17.21
f1 (ppm)

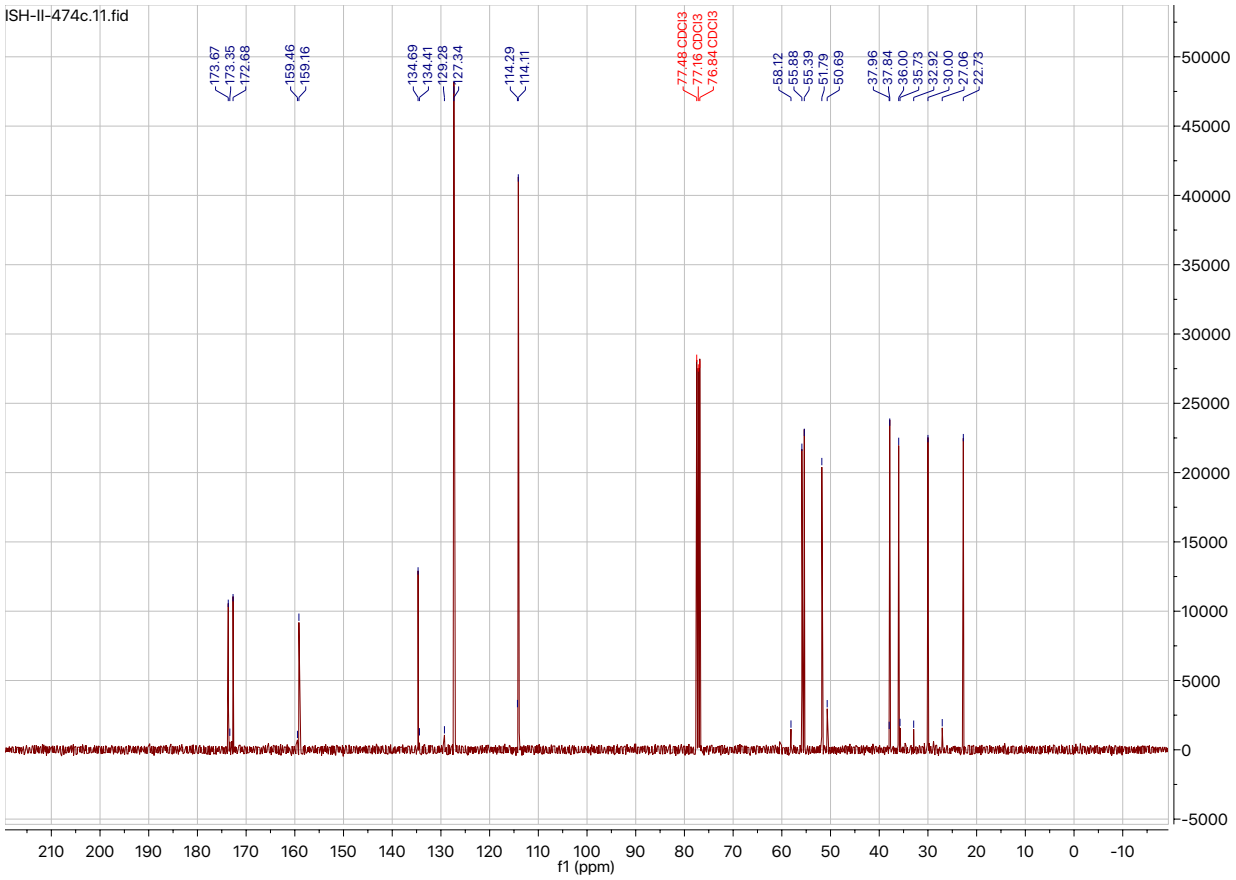

CHB1-290.10.fid
MeO2C
NH
OMe
5fa
f1 (ppm)

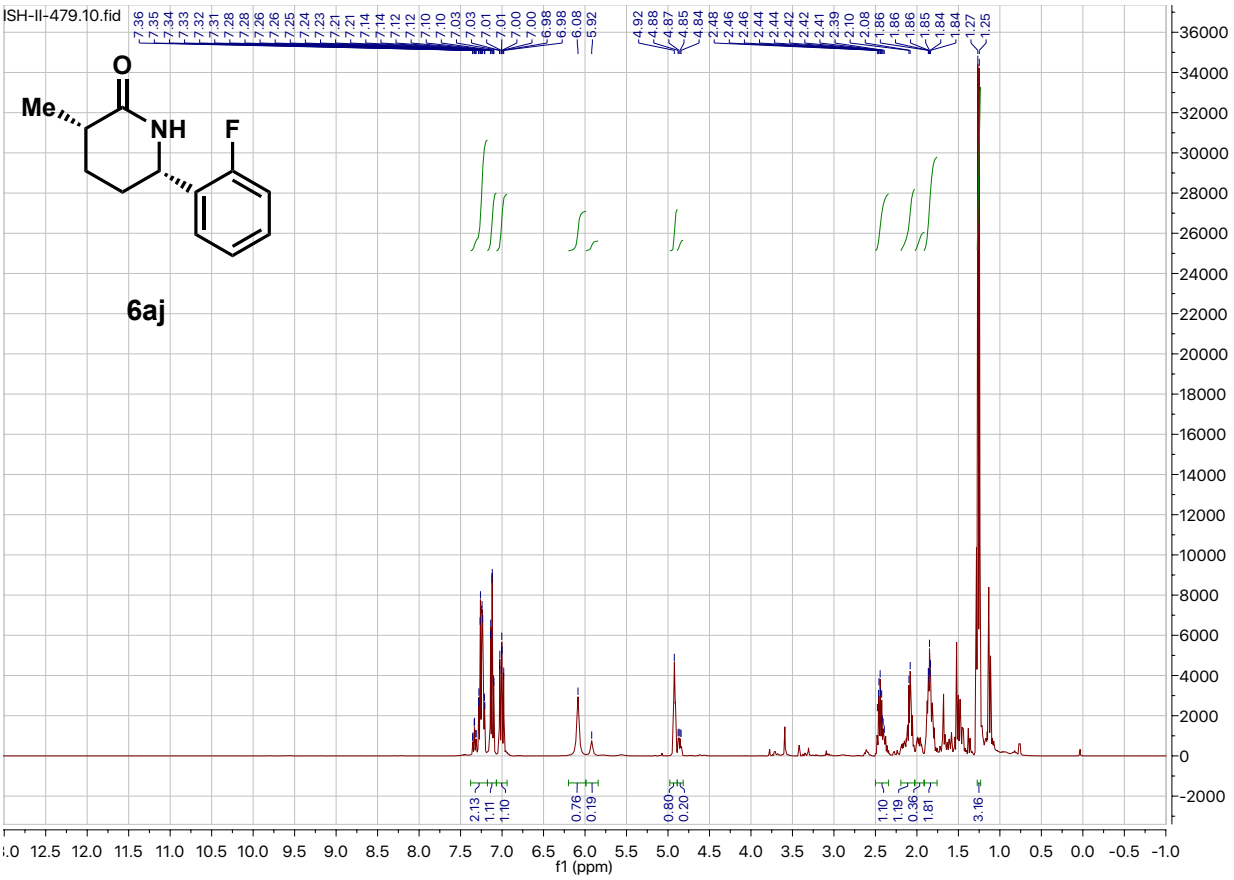

CHB1-290.11.fid
175.49
160.21
137.65
128.83
114.75
61.71
55.65
51.95
51.06
39.72
36.58
34.92
34.38
32.76
31.20
30.11
29.79
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

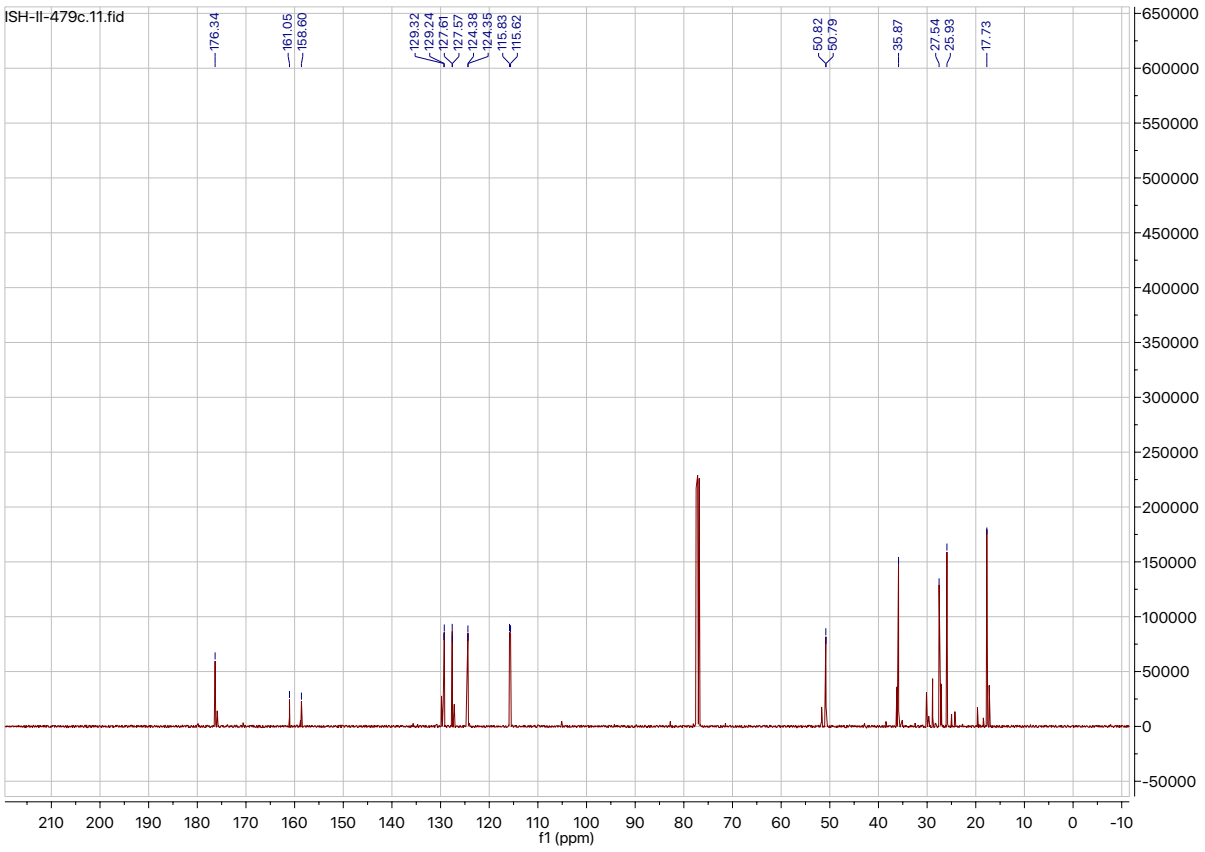

Me
O
NH
OMe
6aa
f1 (ppm)

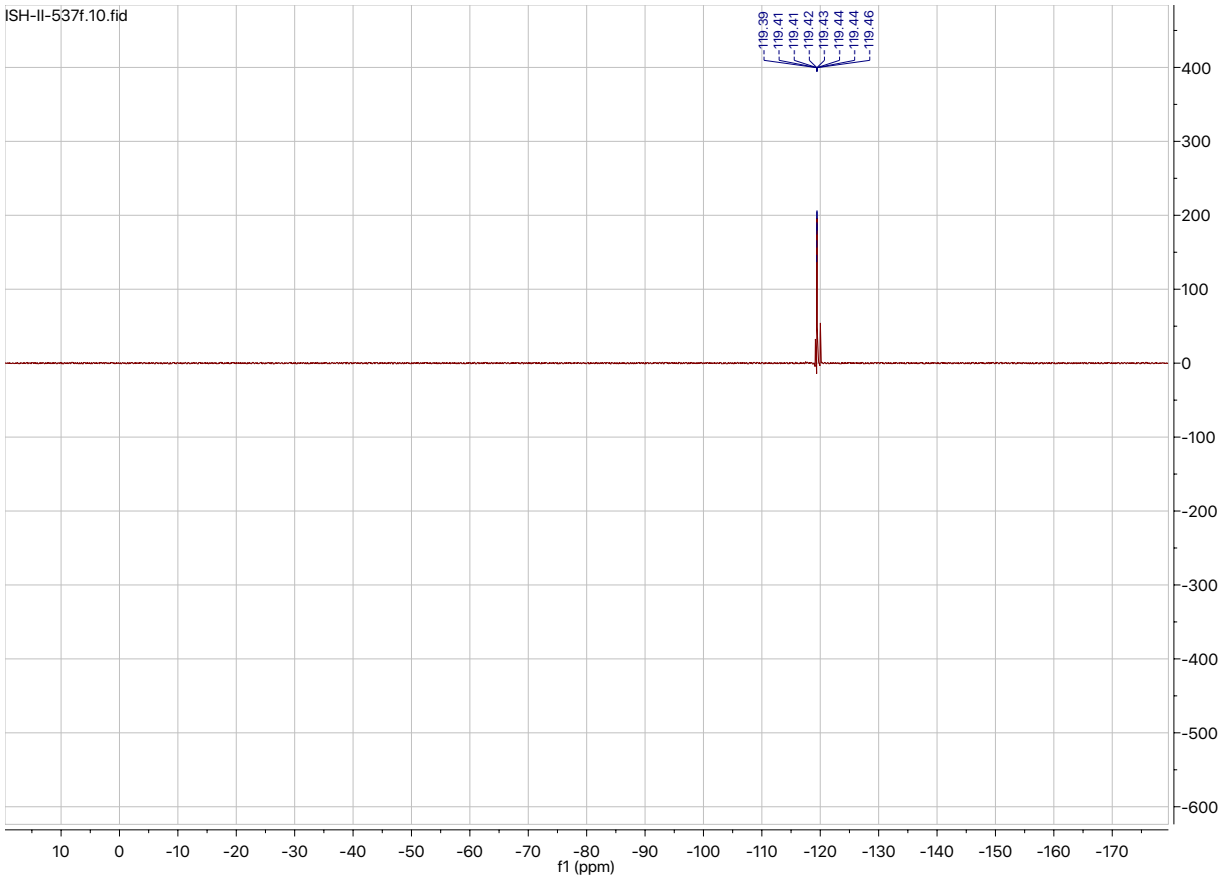

ISH-II-538.11.fid
176.29
159.24
134.82
127.28
114.19
56.78
55.42
35.43
29.38
18.08
f1 (ppm)

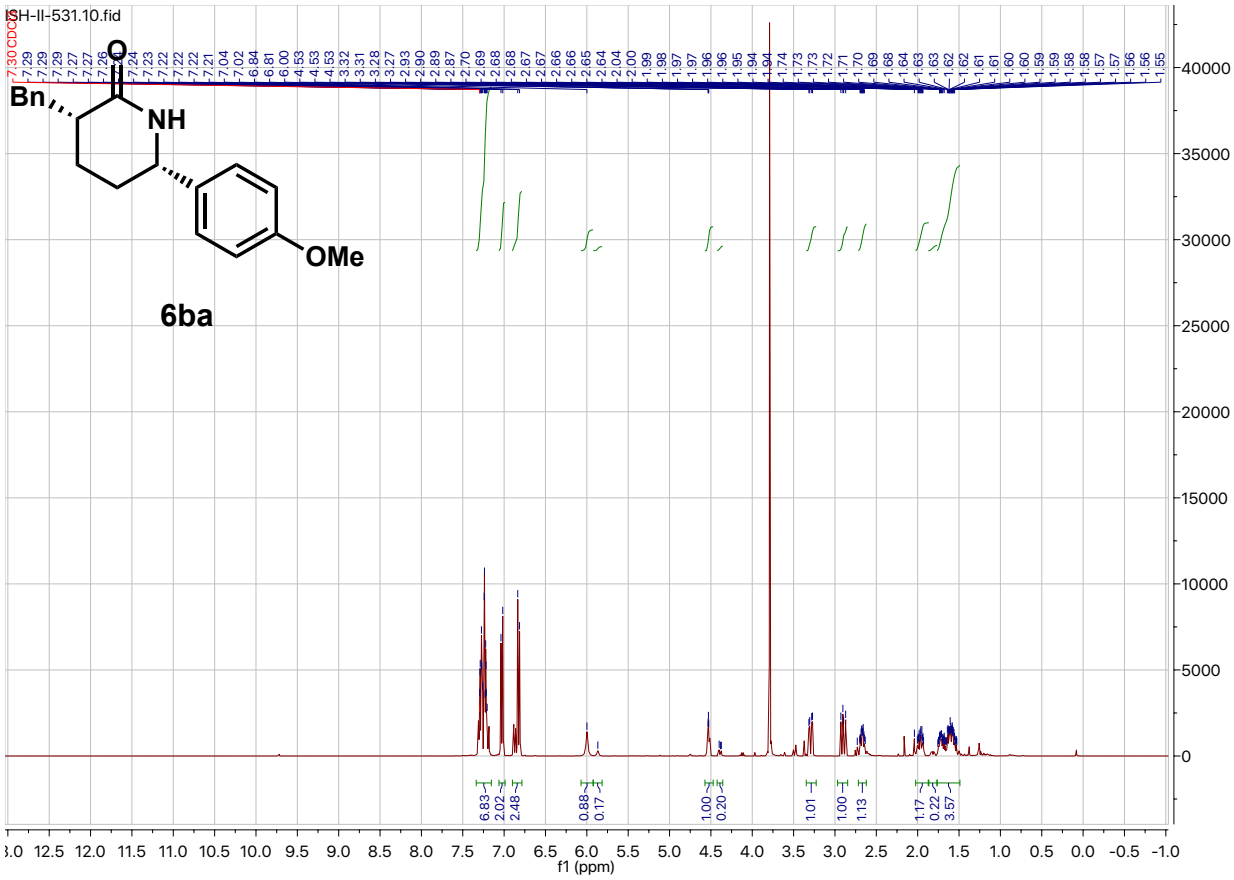

ISH-II-474.11.fid
O
Me
NH
Cl
6ac
f1 (ppm)

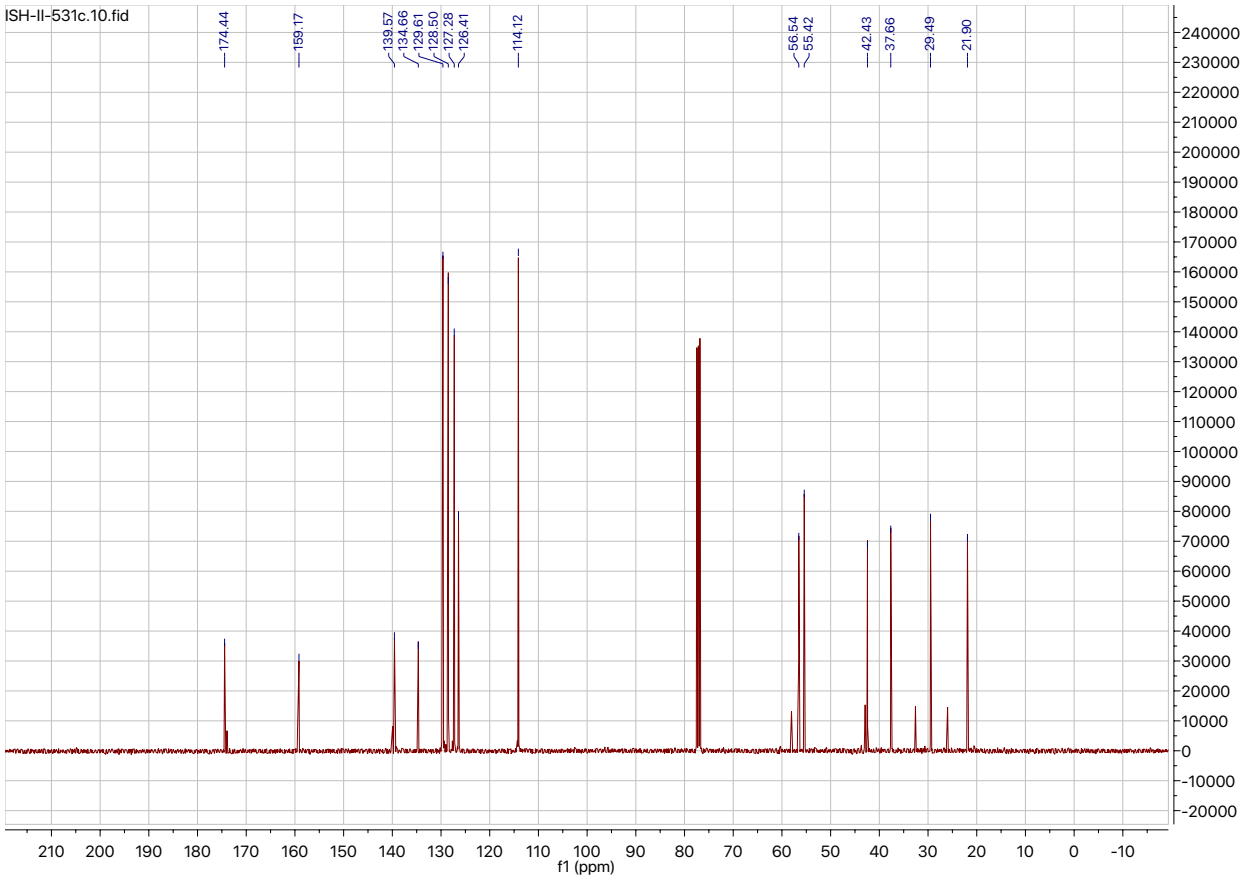

ISH-II-474c.11.fid
173.67
173.35
172.68
159.46
159.16
134.69
134.41
129.28
127.34
114.29
114.11
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
58.12
55.88
55.39
51.79
50.69
37.96
37.84
36.00
35.73
32.92
30.00
27.06
22.73
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

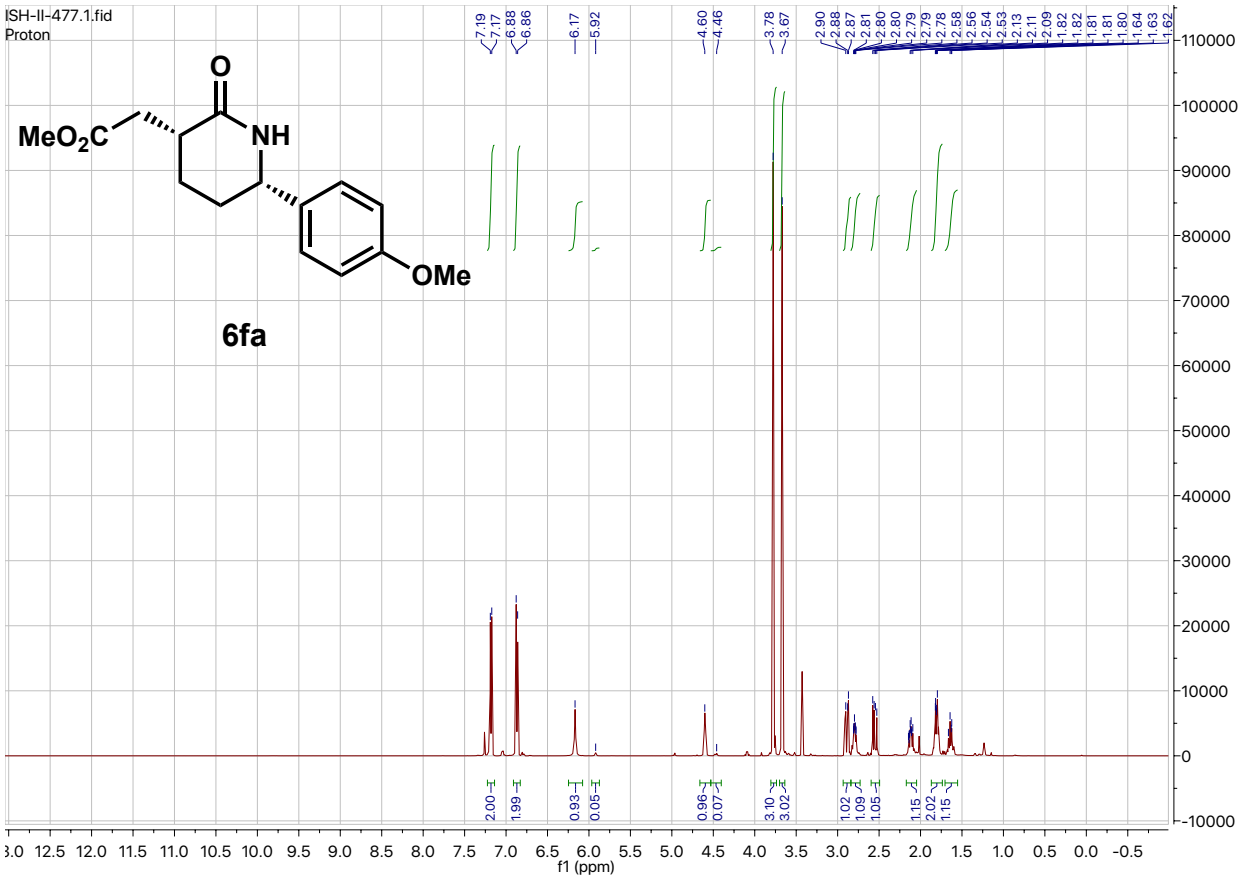

ISH-II-479.10.fid
O
Me
NH
F
6aj
f1 (ppm)

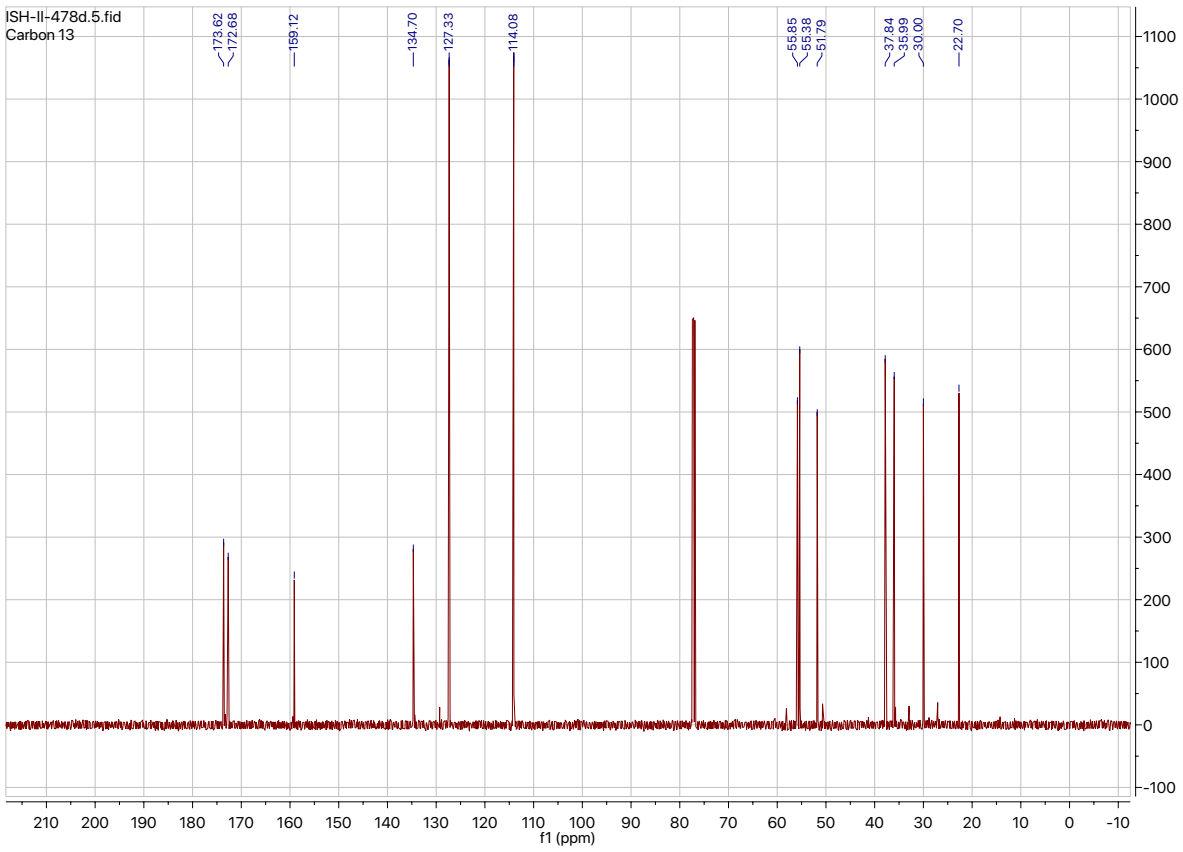

ISH-II-479c.11.fid
176.34
161.05
158.60
129.32
129.24
127.61
127.57
124.38
124.35
115.83
115.62
50.82
50.79
35.87
27.54
25.93
17.73
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

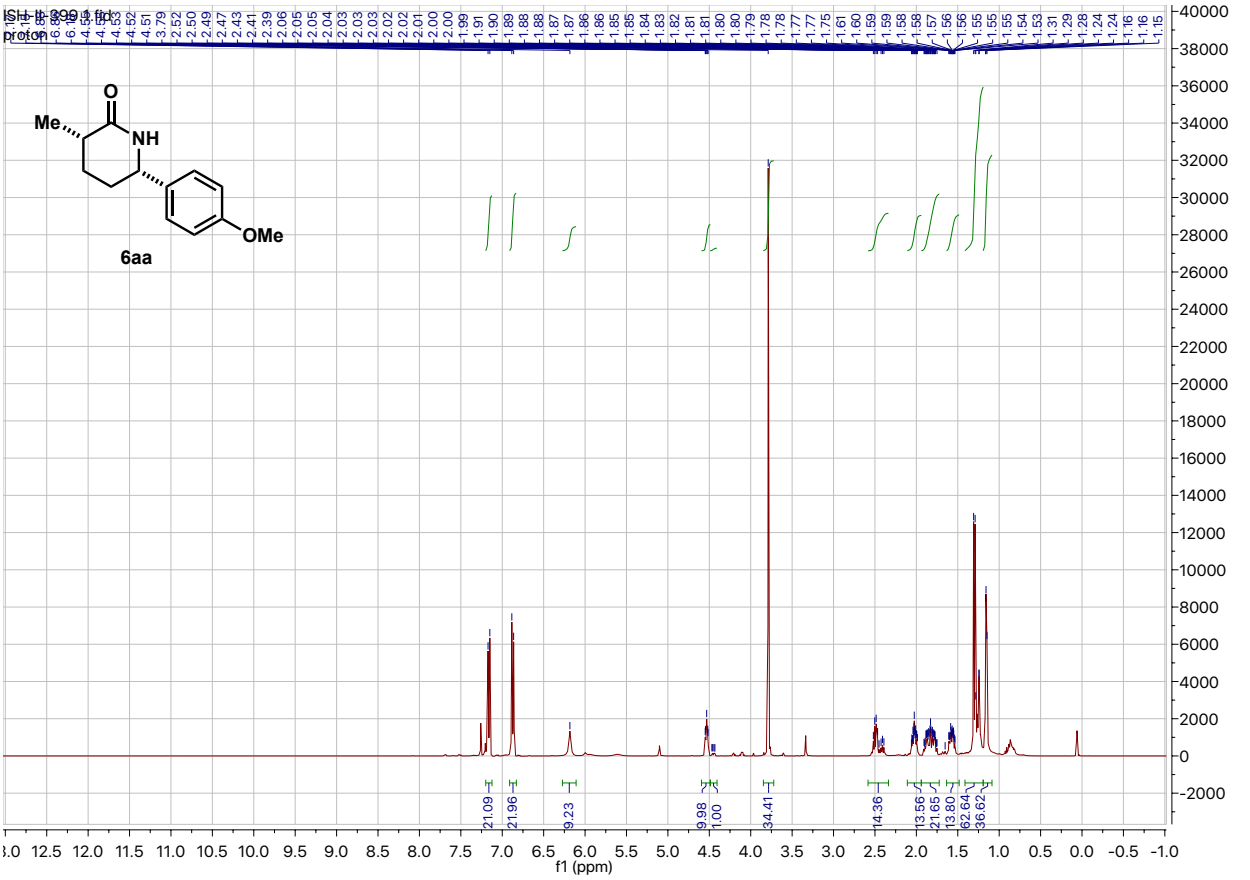

ISH-II-537f.10.fid
-119.39
-119.41
-119.41
-119.42
-119.43
-119.44
-119.44
-119.46
400
300
200
100
0
-100
-200
-300
-400
-500
-600
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)

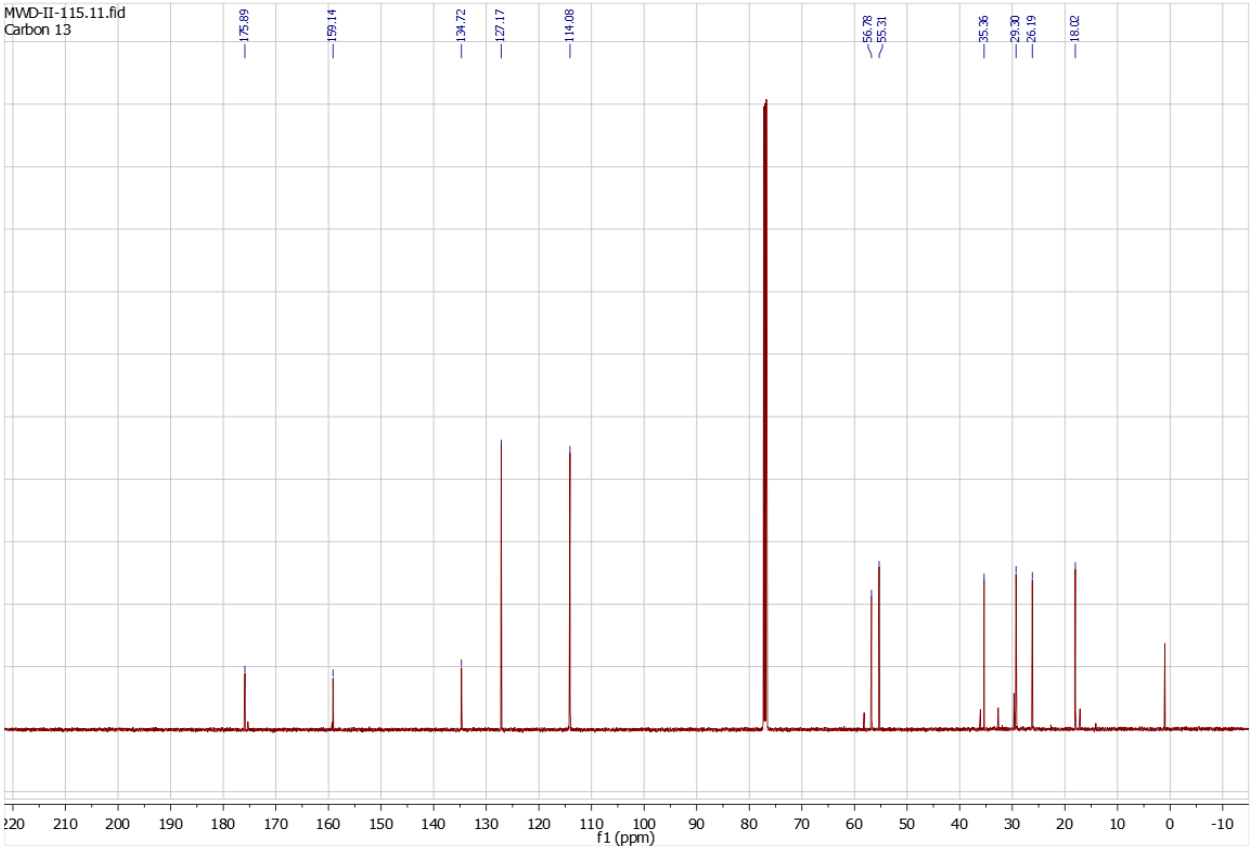

ISH-II-531.10.fid
Bn
NH
O
OMe
6ba
f1 (ppm)

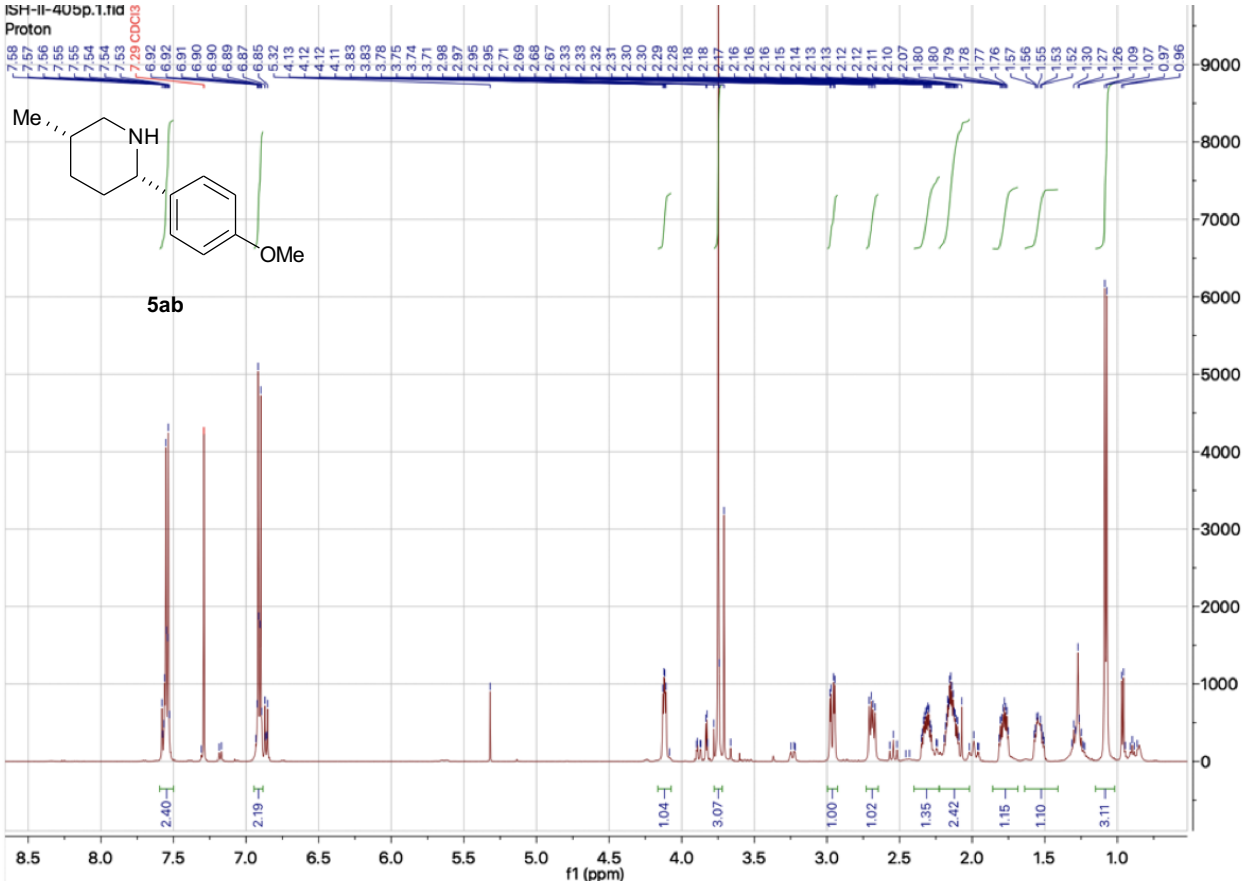

ISH-II-531c.10.fid
174.44
159.17
139.57
134.66
129.61
128.50
127.28
126.41
114.12
56.54
55.42
42.43
37.66
29.49
21.90
f1 (ppm)

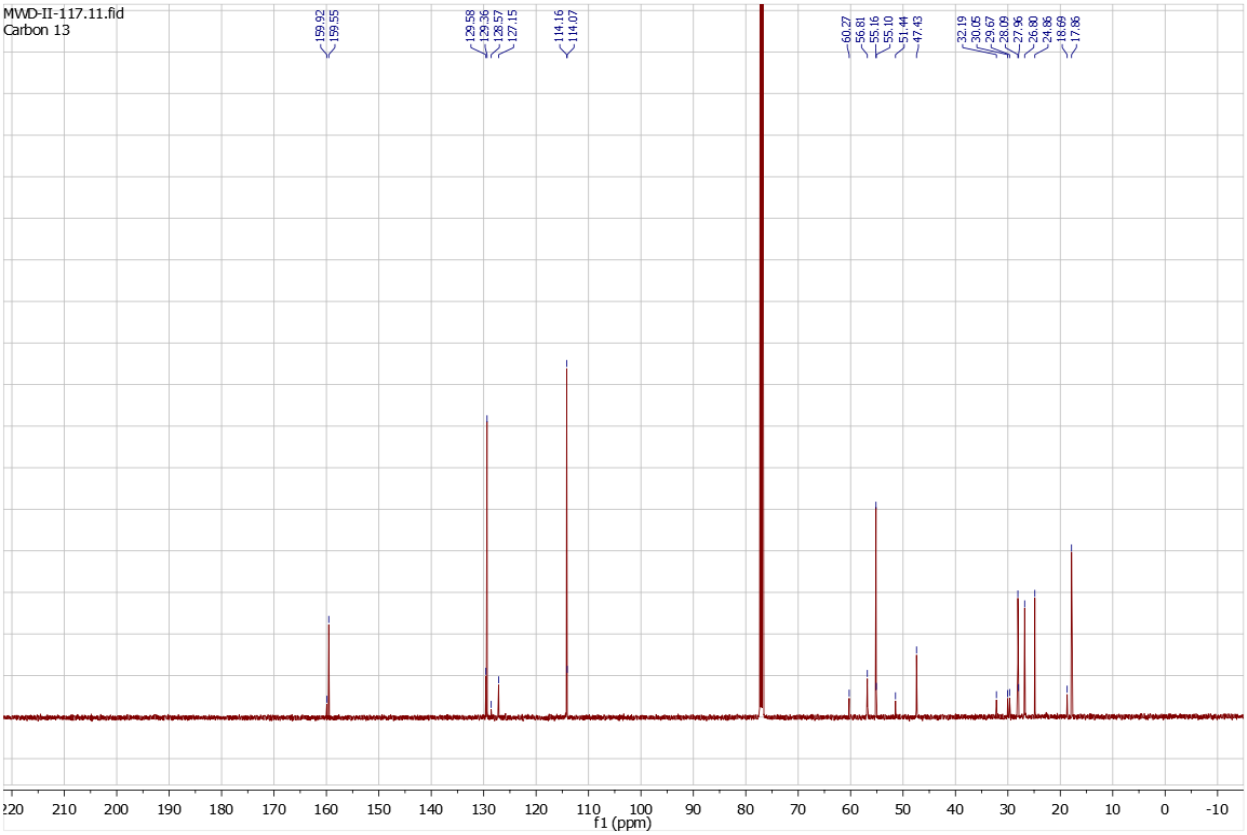

ISH-II-477.1.fid
Proton
O
MeO2C
NH
OMe
6fa
f1 (ppm)


ISH-II-478d.5.fid
Carbon 13
173.62
172.68
159.12
134.70
127.33
114.08
55.85
55.38
51.79
37.84
35.99
30.00
22.70
f1 (ppm)

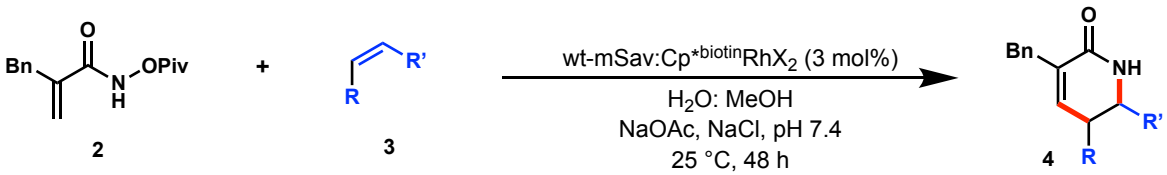

proton
O
Me
NH
OMe
6aa
f1 (ppm)

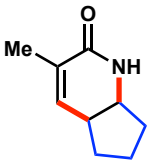

MWD-II-115.11.fid
Carbon 13
175.89
159.14
134.72
127.17
114.08
56.78
55.31
35.36
29.30
26.19
18.02
f1 (ppm)


ISH-II-405p.1.fid
Proton
Me
NH
OMe
5ab
f1 (ppm)

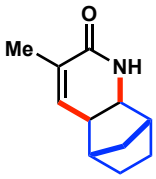


9. Coupling with unactivated alkenes

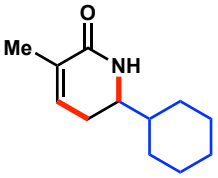




4ga: 26% conversion
trace % product
0 % ee



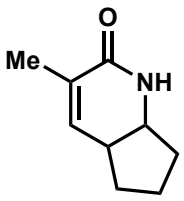
4gb: 94% conversion
49 % product
8 % ee



4gc: 38% conversion
7 % product
0% ee

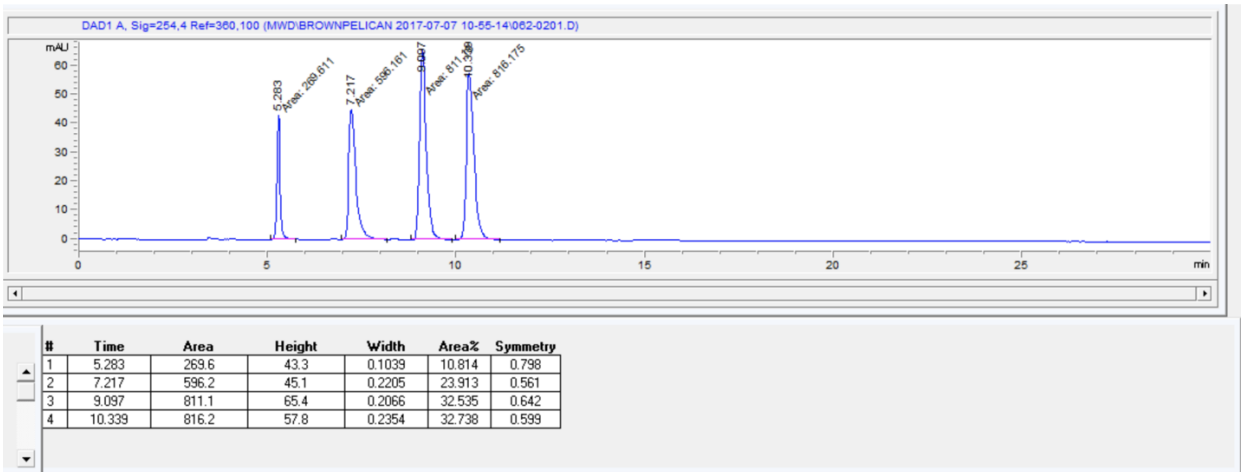
[a]Reaction conditions: **2a** (3.0 μmol), **3** (1.5 μmol), catalyst, in 200 μL of acetate buffer. [b]Yields determined by HPLC analysis relative to a 1,3,5-trimethoxybenzene internal standard. Enantiomeric excess determined by HPLC analysis.

HPLC traces



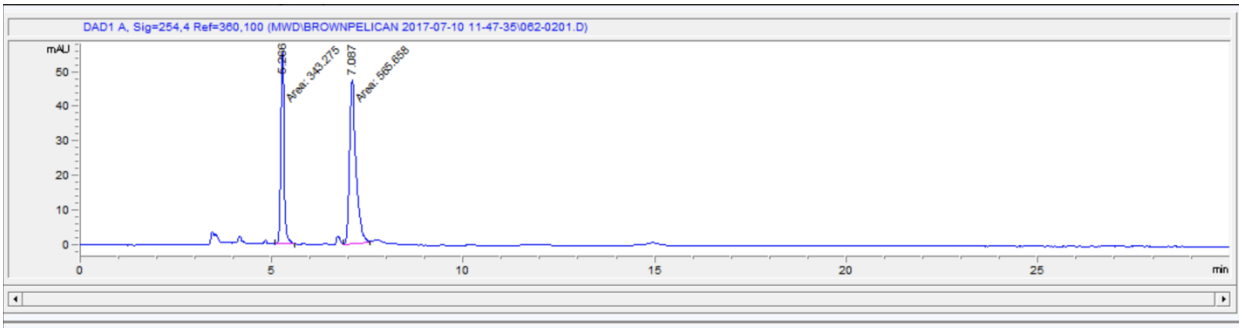
4ga

Starting material:1,3,5-trimethoxybenzene:Cyclopentene

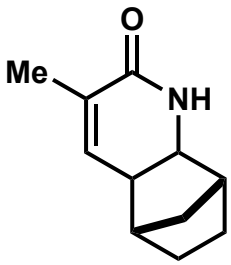


#	Time	Area	Height	Width	Area%	Symmetry
1	5.283	269.6	43.3	0.1039	10.814	0.798
2	7.217	596.2	45.1	0.2205	23.913	0.561
3	9.097	811.1	65.4	0.2066	32.535	0.642
4	10.339	816.2	57.8	0.2354	32.738	0.599

Reaction mixture with internal standard

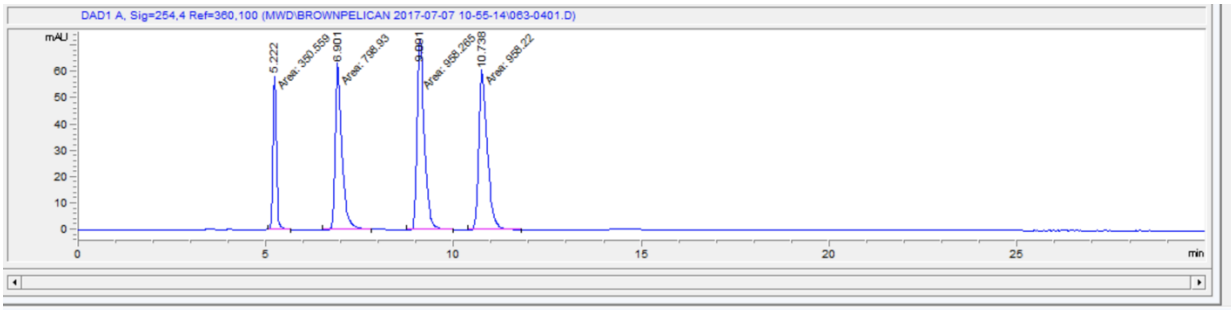


#	Time	Area	Height	Width	Area%	Symmetry
1	5.266	343.3	55.5	0.1031	37.767	0.765
2	7.087	565.7	47.6	0.1981	62.233	0.596



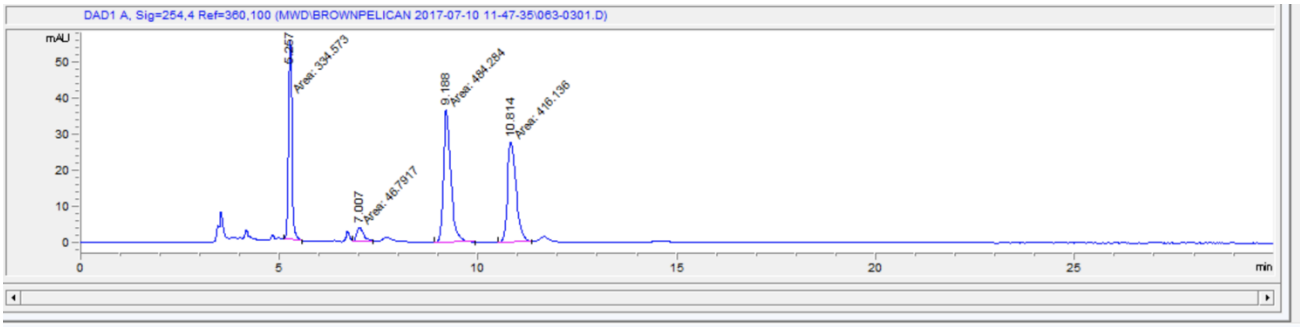
4gb

Starting material:1,3,5-trimethoxybenzene:Norbornene

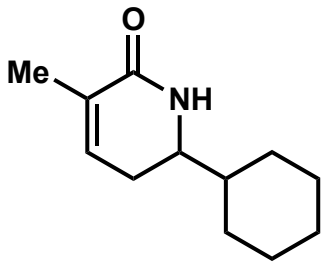


#	Time	Area	Height	Width	Area%	Symmetry
1	5.222	350.6	58.1	0.1005	11.434	0.77
2	6.901	798.9	63.3	0.2102	26.058	0.557
3	9.091	958.3	72	0.2219	31.255	0.58
4	10.738	958.2	60.9	0.2623	31.253	0.555

Reaction mixture with internal standard

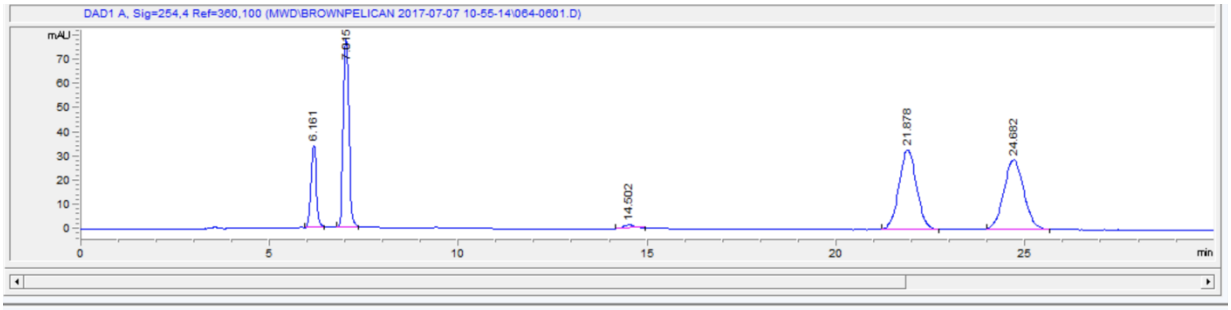


#	Time	Area	Height	Width	Area%	Symmetry
1	5.257	334.6	55.1	0.1012	26.102	0.769
2	7.007	46.8	3.8	0.2039	3.651	0.602
3	9.188	484.3	36.7	0.2197	37.782	0.638
4	10.814	416.1	27.7	0.2506	32.465	0.671

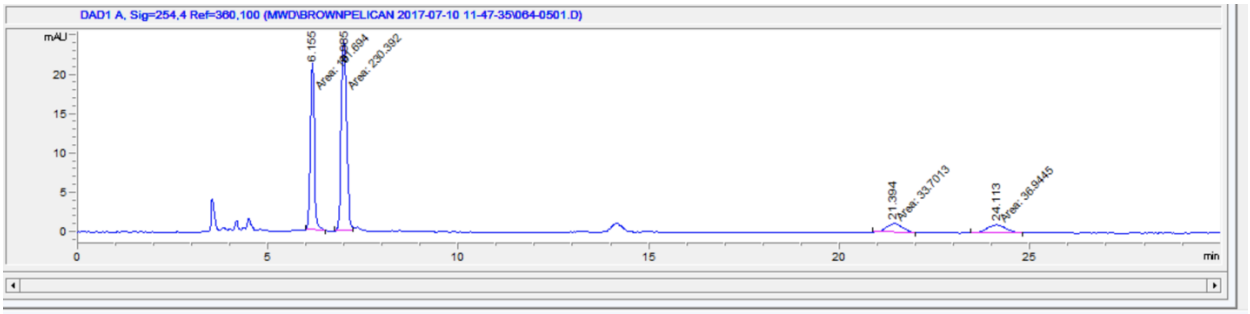


4gc

Starting material:1,3,5-trimethoxybenzene:Vinylcyclohexane



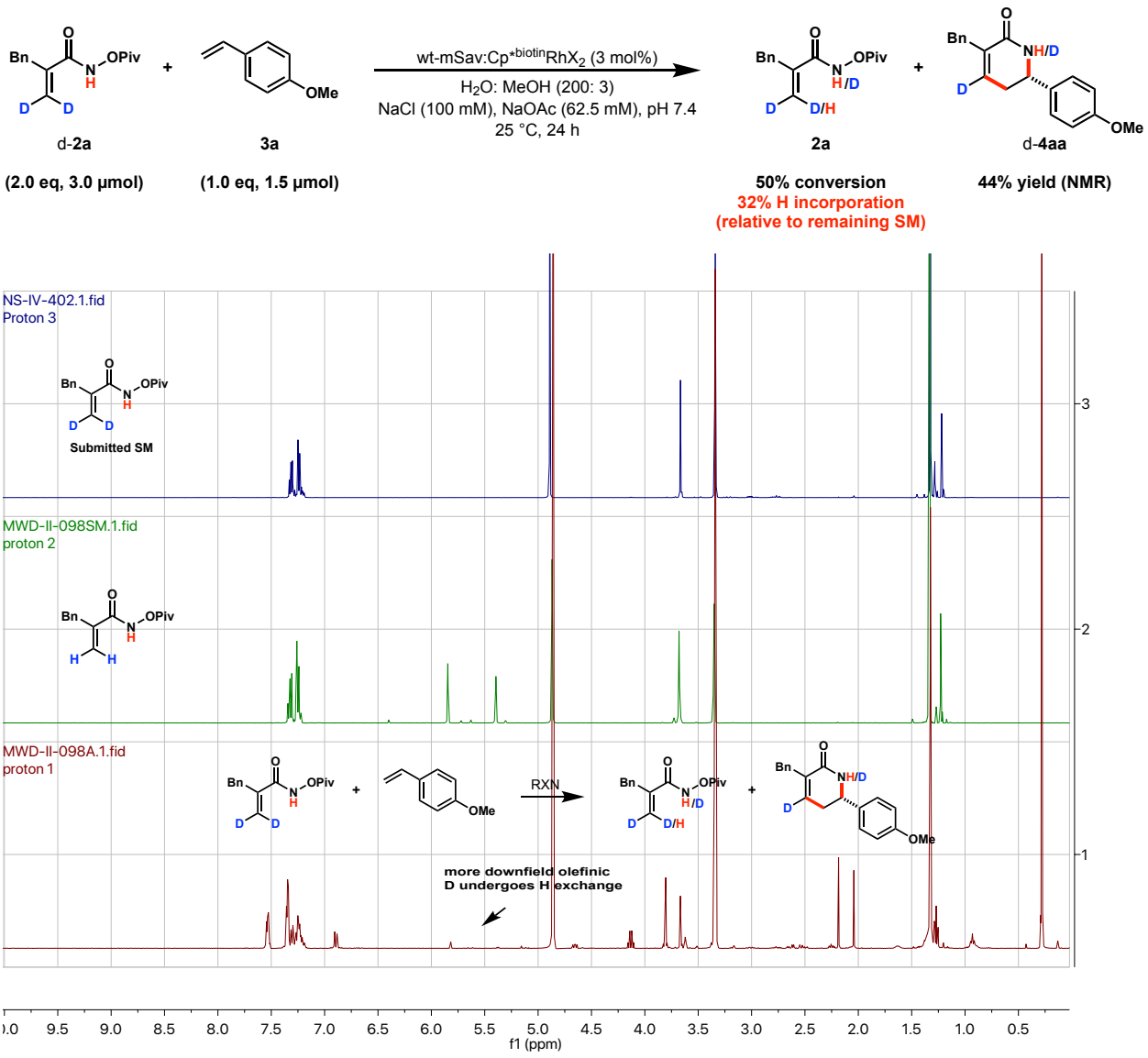
#	Time	Area	Height	Width	Area%	Symmetry
1	6.161	332.7	34	0.1522	10.185	0.935
2	7.015	781.7	77.9	0.155	23.934	0.871
3	14.502	30	1.4	0.2864	0.920	0.992
4	21.878	1062.7	32.9	0.4991	32.538	0.941
5	24.682	1058.9	28.8	0.5556	32.423	0.934

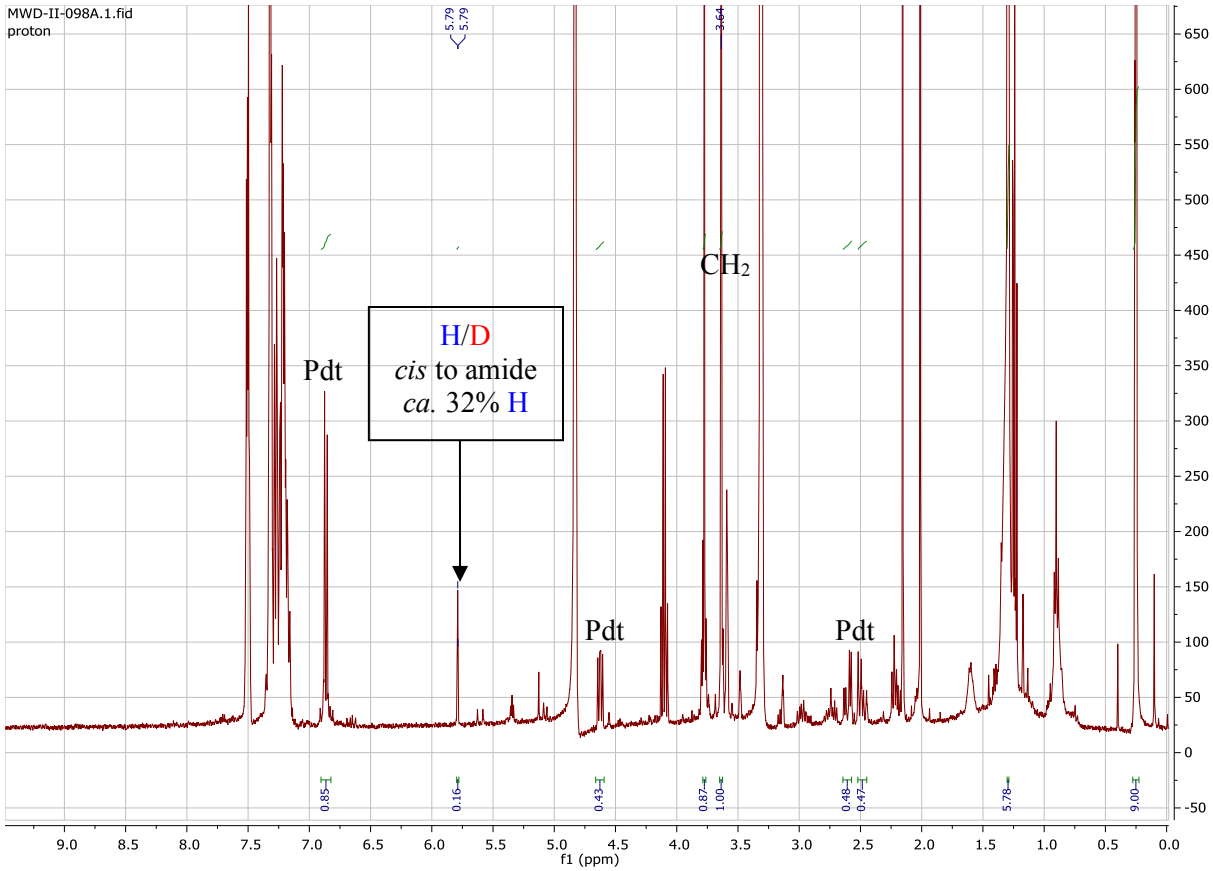


#	Time	Area	Height	Width	Area%	Symmetry
1	6.155	151.7	21.2	0.1192	33.506	0.868
2	6.985	230.4	24.2	0.1584	50.889	0.909
3	21.394	33.7	1.1	0.5054	7.444	0.796
4	24.113	36.9	1	0.5909	8.160	1.127

10. Control experiments and mechanistic studies

An experiment was conducted in which deuterated acrylamide d-**2a** was coupled with 4-methoxystyrene (**3a**) under enzymatic/aqueous conditions. After a 24 h reaction time (ca. 50% conversion), 32% proton incorporation into d-**2a** at the C-H bond *cis* to the amide was observed. This result suggest that the C-H activation step is reversible. Additionally, this result suggests that the charge effect from the mSav protein scaffold is not due to concerted metalation deprotonation (CMD) acceleration.


wt-mSav:Cp*biotinRhX2 (3 mol%)
H2O: MeOH (200: 3)
NaCl (100 mM), NaOAc (62.5 mM), pH 7.4
25 °C, 24 h
d-2a
3a
2a
d-4aa
(2.0 eq, 3.0 µmol)
(1.0 eq, 1.5 µmol)
50% conversion
32% H incorporation
(relative to remaining SM)
44% yield (NMR)
NS-IV-402.1.fid
Proton 3
Submitted SM
MWD-II-098SM.1.fid
proton 2
MWD-II-098A.1.fid
proton 1
RXN
more downfield olefinic
D undergoes H exchange
f1 (ppm)


MWD-II-098A.1.fid
proton
5.79
5.79
3.64
CH2
H/D
cis to amide
ca. 32% H
Pdt
Pdt
Pdt
0.85
0.16
0.43
0.87
1.00
0.48
0.47
5.78
9.00
f1 (ppm)

11. Preparation of artificial metalloenzyme

Protein production and purification:

MBP-mSav was expressed from plasmid pET-MBP-mSav purchased from addgene (plasmid #52319). Plasmid was transformed into BL21 (DE3) *E.coli* for protein production. An overnight culture was grown in LB containing kanamycin at 37 °C shaking at 200 RPM and used to inoculate 1 L (x8) of LB containing kanamycin at 37 °C shaking at 200 RPM for 3.5 hrs to an OD_{600} of 0.6-0.9. Culture was then induced with IPTG (final concentration of 1 mM) and brought to 20 °C shaking at 200 RPM overnight. Cells were harvested by centrifugation (5000 RPM for 10 min at 4 °C) and resuspended in acetate glycerol lysis buffer (10 mL, 25 mM sodium acetate, 100 mM sodium chloride, 10% glycerol, 0.2% Triton-X-100, pH 7.4) with a protease inhibitor tablet (1/2 tablet, Roche cOmplete ULTRA Tables, Mini, EDTA free, EASYpack). Cell suspension was subject to one freeze-thaw cycle at -20 °C followed by sonication (6 min cycle, 50% amplitude, over ice). Cell lysate was cleared by centrifugation (9500 RPM for 20 min at 4 °C) and the supernatant was incubated with Ni-NTA agarose resin (2 mL) rotating overnight at 4 °C. The resin was collected by centrifugation (4750 RPM for 10 min at 4 °C) and washed with acetate wash buffer (50 mL, 25 mM sodium acetate, 100 mM sodium chloride, 50 mM imidazole, pH 7.4). Protein was then eluted with acetate elution buffer (12 mL, 25 mM sodium acetate, 100 mM sodium chloride, 400 mM imidazole, pH 7.4) and dialyzed in acetate buffer (2 L, 25 mM sodium acetate, 100 mM sodium chloride, pH 7.4) overnight. Purified protein was then observed by SDS-PAGE.

Protein cleavage and re-purification:

Purified MBP-mSav was then subjected to a TEV protease cleavage. TEV protease was expressed from plasmid pRK793 purchased from addgene (plasmid #8827). An overnight culture was grown in LB containing chloramphenicol and carbenicillin at 37 °C shaking at 200 RPM and used to inoculate 1 L (x2) of LB containing chloramphenicol and carbenicillin at 37 °C shaking at 200 RPM for 3 hrs to an OD_{600} of ~0.5. Culture was then induced with IPTG (final concentration of 1 mM) and brought to 30 °C shaking at 200 RPM overnight. Cells were harvested by centrifugation (5000 RPM for 10 min at 4 °C) and resuspended in acetate glycerol lysis buffer (10 mL, 25 mM sodium acetate, 100 mM sodium chloride, 10% glycerol, 0.2% Triton-X-100, pH 7.4) with a protease inhibitor tablet (1/2 tablet, Roche cOmplete ULTRA Tables, Mini, EDTA free, EASYpack). Cell suspension was subject to one freeze-thaw cycle at -20 °C followed by sonication (2 min cycle, 50% amplitude, over ice). Cell lysate was cleared by centrifugation (9500 RPM for 20 min at 4 °C) and the supernatant was incubated with Ni-NTA agarose

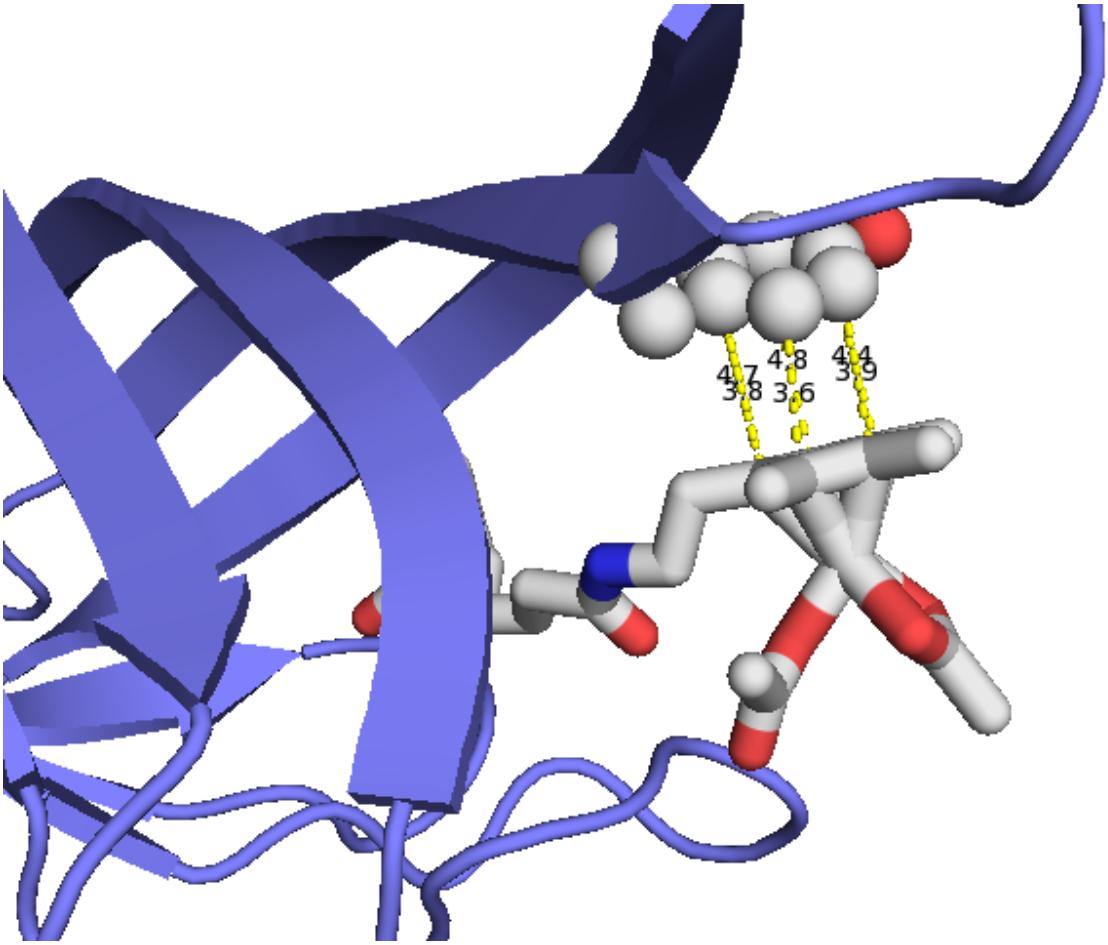
resin (1 mL) rotating for 30 min at 4 °C. The resin was collected by centrifugation (4750 RPM for 10 min at 4 °C) and washed with acetate wash buffer (50 mL, 25 mM sodium acetate, 100 mM sodium chloride, 50 mM imidazole, pH 7.4). Protein was then eluted with acetate elution buffer (12 mL, 25 mM sodium acetate, 100 mM sodium chloride, 400 mM imidazole, pH 7.4) and dialyzed in acetate buffer (2 L, 25 mM sodium acetate, 100 mM sodium chloride, pH 7.4) overnight. Purified protein was then observed by SDS-PAGE.

Purified TEV protease was then added to purified MBP-mSav (100 mg protein to 1 mg protease) and rotated for 48 hrs at 4 °C. Ni-NTA resin was then added to cleavage mixture and rotated for ~12 hrs at 4 °C. Supernatant was separated from the resin. Cleaved and re-purified protein was observed by SDS-PAGE.

Metalloenzyme preparation:

The metalloenzyme was prepared by incubating purified mSav with Cp*biotinRh (30uM protein:60uM biotin) in acetate buffer at RT rotating overnight. Mixtures were then centrifuged to eliminate any precipitation (14000 RPM, 10 min) and transferred to a 10 kDa MWCO ultracentrifugal filter unit for several washes with acetate buffer. Protein solution will now have a yellowish tint due to binding of Rh.

12. Measurement of π-π stacking interaction between Cp* and Y112



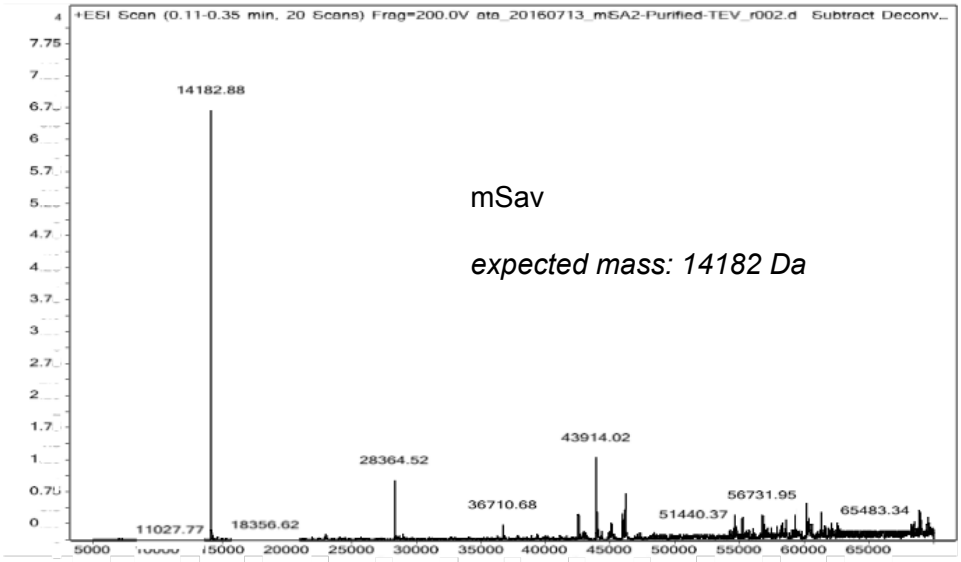
Average distance = 4.2 Å

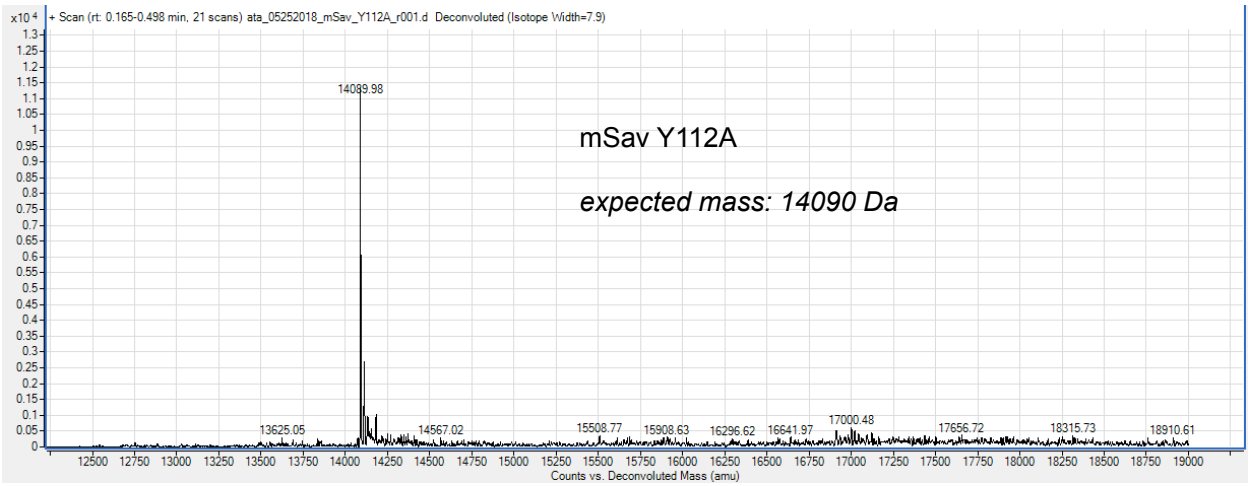
13. Protein sequences

mSav –
GAEAGITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRVE
WNNSTENCHSRTEWRGQYQGGAEARINTQWNLTYEGGSGPATEQGQDTFTKVKPSAASGSDY
KDDDDK

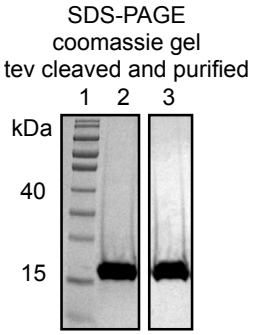
mSav Y112A –
GAEAGITGTWYNQHGSTFTVTAGADGNLTGQYENRAQGTGCQNSPYTLTGRYNGTKLEWRVE
WNNSTENCHSRTEWRGQYQGGAEARINTQWNLTAEGGSGPATEQGQDTFTKVKPSAASGSDY
KDDDDK

14. Protein mass spectrometry analysis (TOFMS)



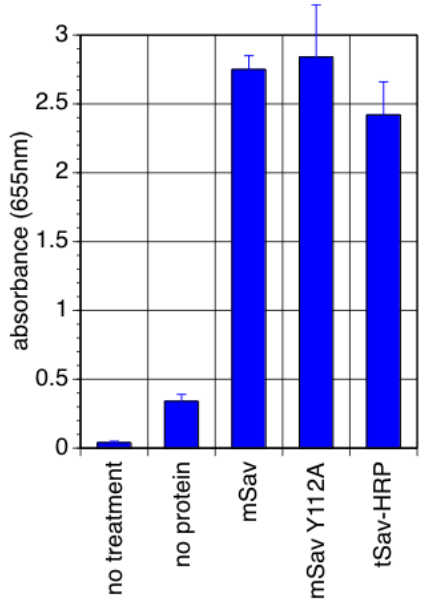


15. Protein gel



1. Ladder
2. mSav
3. mSav Y112A

16. Biotin binding ELISA



Biotin plate ELISA to test biotin binding efficiency. mSav and mSav Y112A contain a flag tag and protein binding to biotin plate was observed using an anti-flag-HRP.

17. Protein data bank

mSav – 4JNJ

tSav – 3RY1

References

[1] Lai, Y; Sun, L; Sit, M. K.; Wang, Y.; Dai, W.-M. *Tetrahedron* **2016**, *72*, 664-673
[2] Gloegaard, C.; Berg, T. C. US Patent Application Publication 2008/0242889 A1
[3] Felpin, F. X.; Miqueu, K.; Sotiropoulos, J. M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191 – 5204
[4] Gowda, R. R.; Chen, E. Y.-X. *Org. Chem. Front.* **2014**, *1*, 230

[i] Lai, Y; Sun, L; Sit, M. K.; Wang, Y.; Dai, W.-M. *Tetrahedron* **2016**, *72*, 664-673

[ii] Gloegaard, C.; Berg, T. C. US Patent Application Publication 2008/0242889 A1

[iii] Felpin, F. X.; Miqueu, K.; Sotiropoulos, J. M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191 – 5204

[iv] Gowda, R. R.; Chen, E. Y.-X. *Org. Chem. Front.* **2014**, *1*, 230

[v] The protected hydroxylamine triflic acid salt ($NH_2OPiv{\cdot}TfOH$) can be synthesized in gram quantities via a simple two step synthetic sequence from commercially available starting material. Commercially available acid chlorides or carboxylic acids (converted to their corresponding acid chlorides *in situ*) are treated with $NH_2OPiv{\cdot}TfOH$ to afford the desired library of acrylamides in very efficient reaction times (0.75 - 4 h).

[vi] All C-H functionalization reactions between acrylamide and styrene coupling partners were repeated independently and in duplicate. HPLC and NMR yields were nearly identical (typically within 5% of each run), and enantioselection was completely identical in duplicate runs. Each data point was the average to two runs, with the exception of the methyl acrylamide and 4-methoxystyrene, which was the average of three runs.

[vii] The absolute configuration of the δ-lactam products was determined to be the (*S*)-enantiomer. This was assigned by direct analogy of the configurations previously reported by Cramer and colleagues (Science **2012**, *338*, 504-506). Cramer furnished the (*R*)-enantiomer of the reported isoquinolinone products as described in the manuscript and HPLC traces in the supporting information. In our work, we repeated one of Cramer's C-H functionalization reactions (benzhydroxamide and 4-methoxystyrene) with our monomeric streptavidin (mSav) metalloenzymes. Upon using the same HPLC assay and chiral column that Cramer reports, we observed a complete reversal in product enantiosense when utilizing our mSav metalloenzymes, hence the (*S*)-enantiomer by analogy. Interestingly, when the same reaction is repeated with the tetrameric streptavidin (tSav) metalloenzyme, the (*R*)-enantiosense is retained in correlation with Cramer's HPLC data. The reversal in enantiosense between mSav and tSav is once again observed when using acrylamide and styrene coupling partners. Based on this evidence, we reported by analogy, that the tSav metalloenzyme give the (*R*)-enantiomer of our δ-lactam product, whereas the mSav metalloenzyme give the (*S*)-enantiomer. The inherent assumption is that benzamide and acrylamide binds identically in the mSav pocket but given that they both proceed in similar enantioselectivities and since the enantioselectivities related to the prochiral element (styrene) which is identical in both transformations, we believe this is justified.

[viii] For HPLC analysis only, a Boc protecting group was installed on the free amine of the piperidine to account for polarity on the chiral column. The retention times reported are associated with the Boc-protected piperidine.