Rapid Construction of (-)-Paroxetine and (-)-Femoxetine via *N*-Heterocyclic Carbene Catalyzed Homoenolate Addition to Nitroalkenes

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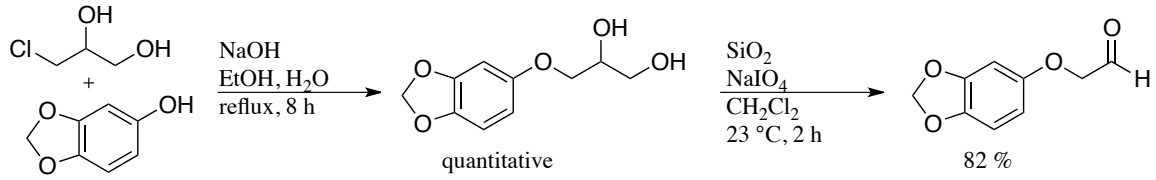
Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dichloromethane was degassed with argon and passed through two col- umns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Ethanol was purchased from Fisher Scientific and dried with activated 3Å molecular sieves. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light or KMnO4 stain followed by heating.

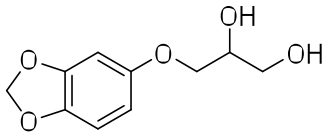
^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm) or acetone-D_6 (2.03 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR were recorded on a Varian 400 MHz spectrometer (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.36 ppm) or acetone-D_6 (205.87, 30.6 ppm). Mass spectra were obtained on an Agilent Technologies 6130 Quadrupole Mass Spec (LRMS). Infrared spectra were collected on a Bruker Tensor 27 FT-IR spectrometer or a Nicolet SX-60 FT-IR spectrometer.

Aldehydes were either purchased from Aldrich or prepared via literature procedures.

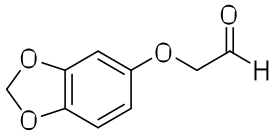
Synthesis of Aldehyde 2



Aldehyde **2** is commercially available from Aurora Building Blocks. Catalogue number: A00.552.03. However, we chose to synthesize it via the above route.

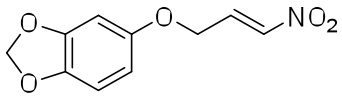


3-(benzo[d][1,3]dioxol-5-yloxy)propane-1,2-diol (S1): Prepared according to a literature procedure.[i] A 100 mL round bottom flask was charged with sesamol (6.906 g, 50.0 mmol) and dissolved in 30 mL EtOH. To this solution was added a solution of NaOH (2.50 g, 62.5 mmol, 1.2 eq.) in 10 mL H_2O and the mixture was heated to reflux for 10 min. After this time, a solution of 3-chloro-1,2-propane diol (5.0 mL, 6.6 g, 60.0 mmol, 1.25 eq.) in 5 mL EtOH was added and the resulting mixture was allowed to reflux overnight (~8 hr) until TLC indicated complete reaction. After this time, solution was allowed to cool to rt and volatiles were removed *in vacuo*. The resulting residue was diluted with EtOAc (50 mL) and H_2O (50 mL), and the layers separated. The aqueous layer was extracted with EtOAc (6 x25 mL) and the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale orange off-white solid (10.9 g) which was used in the next step without further purification. Rf= 0.12 in (3:2 Hexanes:EtOAc); quant., **1H-NMR** (400 MHz; $(CD_3)_2CO$): δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 2.8 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.91 (s, 2H), 4.11 – 3.87 (m, 4H), 3.72 – 3.59 (m, 3H) **13C NMR** (101 MHz; $(CD_3)_2CO$): δ 154.7, 148.3, 141.6, 107.7, 105.7, 101.1, 97.8, 70.5, 70.4, 63.2; **LRMS** (ESI) *m/z* calcd 212.1, found 212.0; **IR** (neat) 3320, 2933, 2894, 1487, 1194, 1038, 928 cm^{-1}

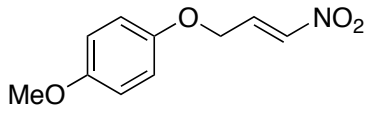


2-(benzo[d][1,3]dioxol-5-yloxy)acetaldehyde (2): Prepared according to a literature procedure.i To a vigorously stirred solution of silica gel (50 g) in 350 mL CH_2Cl_2 was added a solution of 6.952 g $NaIO_4$ (32.5 mmol) in 50 mL H_2O, followed by a solution of 5.305 g 3-(benzo[d][1,3]dioxol-5-yloxy)propane-1,2-diol (25.0 mmol) in 50 mL CH_2Cl_2. The resulting mixture was allowed to stir at rt open to the air for 2 hr until TLC completed complete reaction. After this time, the reaction mixture was filtered over a bed of silica gel and the silica gel was rinsed with ~1 L of CH_2Cl_2. The Solvent was then removed *in vacuo* to give 3.63 g (20.5 mmol) 2-(benzo[d][1,3]dioxol-5-yloxy)acetaldehyde as an analytically pure white solid. Rf= 0.42 in (3:2 Hexanes:EtOAc); 82 % yield, **1H-NMR** (400 MHz; $(CD_3)_2CO$): δ 9.75 (s, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.94 (s, 2H), 4.67

(s, 2H) **13C NMR** (101 MHz; $(CD_3)_2CO$): δ 198.4, 153.6, 148.5, 142.3, 107.8, 105.9, 101.3, 97.9, 73.5.; **LRMS** (ESI) *m/z* calcd 180.0, found 180.0; **IR** (neat) 2900, 2832, 1738, 1503, 1488, 1187, 1037 cm^{-1}

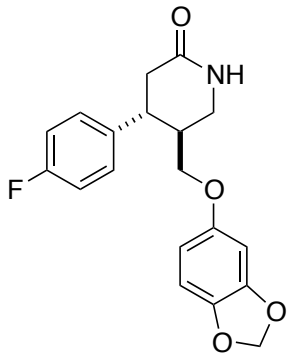


(E)-5-((3-nitroallyl)oxy)benzo[d][1,3]dioxole (3): To an oven-dried round bottom flask was added 3.42 g 2-(benzo[d][1,3]dioxol-5-yloxy)acetaldehyde (19.0 mmol), 1.5 mL nitromethane (28.0 mmol), and 1:1 THF/*t*-BuOH (25 mL). This solution was then cooled to 0 °C and 426 mg potassium tert-butoxide (3.8 mmol) was added in one portion. The reaction was allowed to stir at 0 °C for 15 min then warmed to room temperature and stirred for another 2 h until TLC indicated complete reaction. After completion, saturated aqueous NH_4Cl solution (50 mL) was added to quench the reaction and then the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. After drying the crude residue under vacuum (4 mm) for 0.5 h, CH_2Cl_2 (50 mL) was added and the solution was cooled to 0 °C. Trifluoroacetic anhydride (3.0 mL, 10.9 mmol) was then added followed by the slow dropwise addition of 5.6 mL Et_3N (40 mmol). After stirring for ~15 min at 0 °C the reaction was diluted with H_2O (30 mL) and CH_2Cl_2 (50 mL) and the layers separated. The organic layer was then washed with sat. aq. NH_4Cl (2 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give brown-yellow solid, which was then purified by column chromatography (3:1 hexanes:ethyl acetate) to give 2.893 g (13.0 mmol) of (E)-5-((3-nitroallyl)oxy)benzo[d][1,3]dioxole as a bright yellow solid. Rf= 0.4 in (3:1 Hexanes:EtOAc); 68 % yield, **1H-NMR** (400 MHz; $(CD_3)_2CO$): δ 7.47 (dt, *J* = 13.6, 3.6 Hz, 1H), 7.39 (dt, *J* = 13.6, 2.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.95 (s, 2H), 4.11 (dd, *J* = 3.6, 2.0 Hz, 2H), **13C NMR** (101 MHz; $(CD_3)_2CO$): δ 153.3, 148.5, 142.4, 139.7, 137.9, 107.8, 106.0, 101.4, 101.4, 98.0, 64.6; **LRMS** (ESI) *m/z* calcd 223.1, found 223.0; **IR** (neat) 3439, 3124, 1635, 1435, 933, 733 cm^{-1}

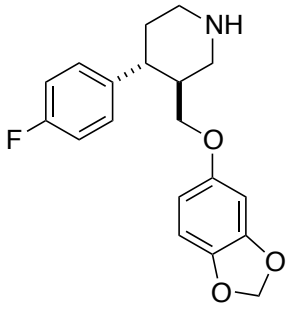


(*E*)-1-methoxy-4-((3-nitroallyl)oxy)benzene (8):In a dry round bottom flask, 1.69 g (10.17 mmol) of 2-(4-methoxyphenoxy)acetaldehyde (prepared according to reference 1) was dissolved in 40 mL of a 1:1 solution of THF/tBuOH. 0.82 ml (15.25 mmol, 1.5 equiv.) of Nitromethane was added, and the reaction was cooled to 0 °C in an ice water bath. Potassium t-Butoxide (228 mg, 2.03 mmol, 0.2 equiv) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with a saturated NH4Cl solution and extracted with EtOAc (3 x 20 ml). The organic layers were combined and washed with a brine solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. The crude oil was then dissolved in CH_2Cl_2 (30 ml) and cooled to 0 °C. Trifluoroacetic anhydride (1.41ml, 10.17 mmol, 1 equiv) was added to the reaction, followed by slow addition of Et_3N (2.83 ml, 20.39 mmol, 2 equiv). The reaction was stirred at 0 °C for 2 hours, then quenched with water. The organic layer was washed with saturated NH_4Cl. The organic extract

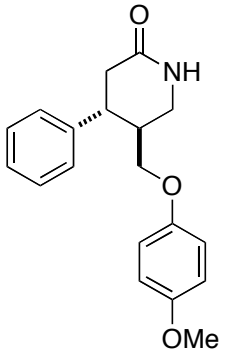
was dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by silica gel column chromatography, eluting with 0 to 20% EtOAc/Hexanes. Isolated 424 mg (20% yield) of an orange solid. **1H-NMR** (400 MHz; $CDCl_3$): δ 7.39-7.28 (m, 2H), 6.85 (s, 4H), 4.73 (dd, *J* = 3.3, 1.9 Hz, 2H), 3.77 (s, 3H). **13-C NMR** (101 MHz; $CDCl_3$): δ 154.7, 151.5, 140.2, 136.9, 115.7, 114.8, 64.5, 55.7; LR**MS**: m/z [M-1] calcd 209.1, found 208.1; **IR**: 3123, 3052, 2907, 2836, 1788, 1659, 1526, 1505, 1440, 1359, 1226, 1033, 936, 824, 732 cm^{-1}



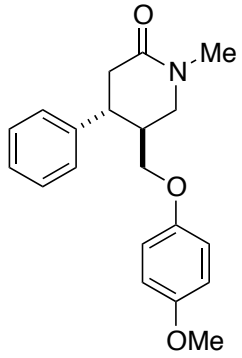
(4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-2-one (5): To a 100 mL flame dried round bottom flask containing a magnetic stirbar was added nitroalkene **3** (2.01 g, 9 mmol, 1.0 equiv), NHC **1b** (377 mg, 0.9 mmol, 10 mol%), sodium acetate (370 mg, 4.5 mmol, 0.5 equiv), 4-fluorocinnamaldehyde (2.03 g, 13.5 mmol, 1.5 equiv), followed by 30 mL ethanol. The flask was then fitted with a rubber septum and stirred under an atmosphere of argon for 12 hours at 23 °C. After 12 hours, the septum was removed and zinc dust (5.85 g, 90 mmol, 10 equiv) was added followed by 30 ml of acetic acid. The flask was then fitted with a reflux condenser and heating mantle. The reaction was then refluxed for four hours. After four hours, the heat source was removed and the reaction was allowed to cool. Upon cooling, the reaction was filtered through celite and rinsed with 30 mL EtOAc. The filtrate was then diluted with an additional 20 mL EtOAc and quenched with 60 mL saturated $NaHCO_3$. The organic layer was then separated, washed with brine (1 x 60 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was then purified by column chromatography (5 % MeOH in CH_2Cl_2) to yield 1.8 g (4*R*,5*S*)-5-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-2-one, 58 %, 10:1 dr, and 82 % ee as an off-white solid. **Rf**: 0.51 (10:1:0.1 Dicholoromethane:Methanol:NH_4OH); **HPLC Analysis**: Chiralpak IA column, 80:20 hexanes/*iso*-propanol, 1.0 mL/min. Major: 12.27 min, minor 16.74 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.16 (dt, *J* = 6.8, 3.5 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.90 (bs, 1H), 5.88 (s, 2H), 3.69-3.59 (m, 2H), 3.52 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.46-3.40 (m, 1H), 3.08 (td, *J* = 11.2, 5.6 Hz, 1H), 2.71-2.51 (m, 2H), 2.44-2.35 (m, 1H).; **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 171.5, 161.8 (d, J=245.5 Hz, C), 153.8, 148.2, 141.9, 137.1 (d, J=3.2 Hz, C), 128.6 (d, J=7.9 Hz, CH), 115.9, 107.9 (d, J=21.3 Hz, CH), 105.5, 101.2, 97.9, 68.3, 44.5, 40.2, 39.3, 38.7.; **IR**: (ATR neat) 3214, 2923, 1664, 1507, 1485, 1362, 1226, 1184, 1135, 1101, 1034, 927, 842, 759 cm^{-1}; **LRMS**: (ESI + APCI) *m/z* [M+H] calcd 344.1, found 344.1; **Optical Rotation**: $[\alpha]_D^{21}$ = - 72.2



(-)-Paroxetine (6): To a flame dried 250 mL round bottom flask containing a stirbar was added 1.22 g lactam **5** (3.55 mmol, 1.0 equiv) and 120 mL dry THF. This flask was fitted with a rubber septum connected to an argon line and cooled to 0 °C in an ice bath. At 0 °C, 228 mg $LiAlH_4$ (6 mmol, 1.5 equiv) was added portionwise over the course of five minutes. The reaction was allowed to stir at 0 °C for 1 hour and then the ice bath was removed and the flask was fitted with a reflux condenser and the reaction was refluxed for four hours. After four hours the heat source was removed and the flask was cooled to 0 °C in an ice bath and carefully quenched with 100 mL saturated Rochelle's salt and stirred until complete separation was observed, approximately 1 hour. The solution was then transferred to a separatory funnel and extracted 3 x 70 mL CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was removed via rotary evaporation. The crude oil was purified by column chromatography (100 % EtOAc to 10:1:01 CH_2Cl_2:MeOH:NH_4OH) to yield 1.0 g paroxetine as a colorless oil. **Rf**: 0.34 (10:1:0.1 Dicholoromethane:Methanol:NH_4OH); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.17 (dd, *J* = 8.6, 5.3 Hz, 2H), 6.96 (t, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.86 (bs, 2H), 5.52 (s, 1H), 3.58-3.54 (m, 2H), 3.46-3.39 (m, 2H), 2.94-2.84 (m, 2H), 2.73 (td, *J* = 11.8, 3.8 Hz, 1H), 2.35 (dddd, *J* = 13.8, 10.7, 6.6, 3.7 Hz, 1H), 2.05 (qd, *J* = 13.0, 3.9 Hz, 1H), 1.90 (dd, *J* = 13.7, 3.0 Hz, 1H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 161.8 (J=245.9 Hz, C), 153.7, 148.2, 142.0, 137.1 (J=3.1 Hz, C), 128.9 (J=7.8 Hz, CH), 115.8 (J=21.3 Hz, CH), 107.8, 105.5, 101.2, 97.9, 67.4, 46.7, 44.4, 41.6, 39.3, 29.9; **IR**: (ATR neat) 3394, 2925, 1609, 1510, 1482, 1464, 1226, 1187, 1136, 1097, 1038, 930, 831 cm^{-1}; **LRMS**: (ESI + APCI) *m/z* [M+H] calcd 330.2, found 330.2

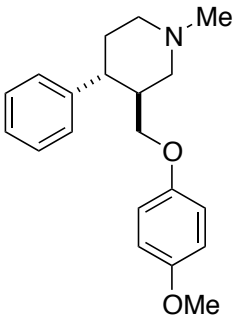


(4*S*,5*R*)-5-((4-methoxyphenoxy)methyl)-4-phenylpiperidin-2-one (10): To a screw cap vial containing a magnetic stirbar was added 42 mg nitroalkene **8** (0.2 mmol, 1.0 equiv), 40 mg cinnamaldehyde (0.3 mmol, 1.5 equiv), 8 mg NHC **1b** (0.02 mmol, 10 mol%), 8 mg NaOAc (0.1 mmol, 50 mol%), and 0.6 mL ethanol. The vial was flushed with argon and the screwcap replaced and stirred at 23 °C for 12 hours. After 12 hours, the screw cap was removed and 130 mg zinc dust (2.0 mmol, 10 equiv) was added, followed by 0.6 mL AcOH. The screw cap was replaced and the reaction was refluxed for four hours. After four hours, the heat source was removed and the reaction was allowed to cool. Upon cooling, the reaction was filtered through celite and rinsed with 10 mL EtOAc. The filtrate was then diluted with an additional 5 mL EtOAc and quenched with 20 mL saturated $NaHCO_3$. The organic layer was then separated, washed with brine (1 x 20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was then purified by column chromatography (5 % MeOH in CH_2Cl_2) to yield 33 mg (4*S*,5*R*)-5-((4-methoxyphenoxy)methyl)-4-phenylpiperidin-2-one 53 %, 7:1 dr, and 82 % ee as an off-white solid. **Rf**: 0.34 (95:5 Dicholromethane:Methanol); **HPLC**: Chiralpak IA column, 85:15 hexanes/*iso*-propanol, 1.0 mL/min. Major: 21.84 min, minor: 23.68 min; **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.32 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 3.6 Hz, 1H), 7.20-7.18 (m, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.65 (d, *J* = 9.1 Hz, 2H), 6.56 (bs, 1H), 3.72 (s, 3H), 3.71-3.63 (m, 2H), 3.54 (dd, *J* = 9.3, 7.7 Hz, 1H), 3.42 (dd, *J* = 21.5, 11.0 Hz, 1H), 3.06 (td, *J* = 11.0, 5.7 Hz, 1H), 2.63 (qd, *J* = 19.4, 8.5 Hz, 2H), 2.48-2.39 (m, 1H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 171.9, 154.0, 152.5, 141.5, 129.0, 127.23, 127.17, 115.3, 114.6, 68.3, 55.7, 44.7, 41.0, 39.1, 38.6; **IR**: (ATR neat) 3250, 2931, 1675, 1508, 1242, 1035, 832, 705 cm^{-1}; **MS**: (ESI + APCI) *m/z* [M+H] calcd 312.2, found 312.1; **Optical Rotation**: $[\alpha]_D^{21}$ = - 26.4

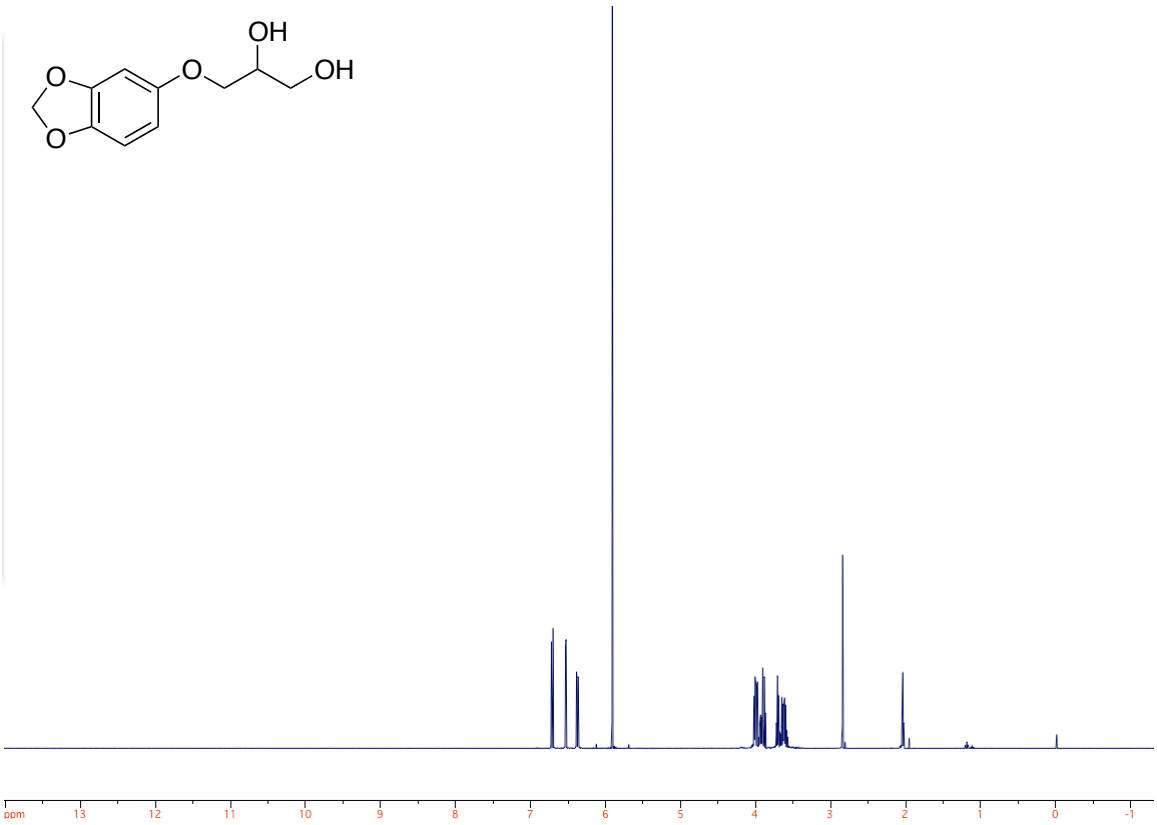


(4*R*,5*S*)-5-((4-methoxyphenoxy)methyl)-1-methyl-4-phenylpiperidin-2-one (S2): (4*R*,5*S*)-5-((4-methoxyphenoxy)methyl)-4-phenylpiperidin-2-one (34 mg, 0.11mmol) was dissolved in dry THF (2 ml) in a round bottom flask and

cooled to 0 °C. NaH (6 mg, 0.16 mmol, 1.5 equiv., 60% dispersion in mineral oil) was added to the reaction, followed by 10 μL of MeI (0.16 mmol, 1.5 equiv). The reaction was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The organic fractions were collected, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography, eluting with 0 to 10%MeOH/DCM. Isolated 20 mg of a pale orange oil (55% yield). **1H-NMR** (400 MHz; $CDCl_3$): δ 7.30 (d, *J* = 7.6 Hz, 3H), 7.25 (s, 2H), 7.19-7.17 (m, 2H), 6.75 (d, *J* = 9.1 Hz, 3H), 6.68-6.65 (m, 2H), 3.72 (s, 3H), 3.72-3.67 (m, 4H), 3.60-3.52 (m, 3H), 3.44 (dd, *J* = 12.3, 10.4 Hz, 1H), 3.05-3.03 (m, 1H), 3.02 (s, 3H), 2.66 (dd, *J* = 27.0, 8.6 Hz, 2H). **13-C NMR** (101 MHz; $CDCl_3$): δ 169.2, 154.0, 152.5, 141.3, 128.9, 127.19, 127.13, 115.3, 114.6, 55.7, 52.5, 41.4, 39.7, 39.4, 34.5; **MS**: m/z=326.21 (M+); **IR**: 3060, 3028, 2923, 1643, 1506, 1465, 1420, 1355, 1229, 1144, 1035, 825, 745, 702; $[\mathbf{a}]_D^{23}$ = -17°



Femoxetine (11): 16 mg (0.05 mmol) of (4*R*,5*S*)-5-((4-methoxyphenoxy)methyl)-1-methyl-4-phenylpiperidin-2-one was dissolved in THF (2 ml) and 4 mg of $LiAlH_4$ (0.1 mmol, 2 equiv) was added carefully. The reaction was stirred at room temperature overnight. The reaction was cooled to 0 °C and $Na_2SO_4x10H_2O$ was added carefully (approx. 200 mg). The slurry was stirred for 2 hours at room temperature. The mixture was filtered through a plug of celite, washing with EtOAc. The filtrate was concentrated and then purified by silica gel column chromatography, eluting with 0.5%NH_4OH/10%MeOH/DCM. Isolated 13mg as a pale yellow oil (87% yield). ^{1}H NMR, ^{13}C NMR and mass match previously reported synthesis[ii].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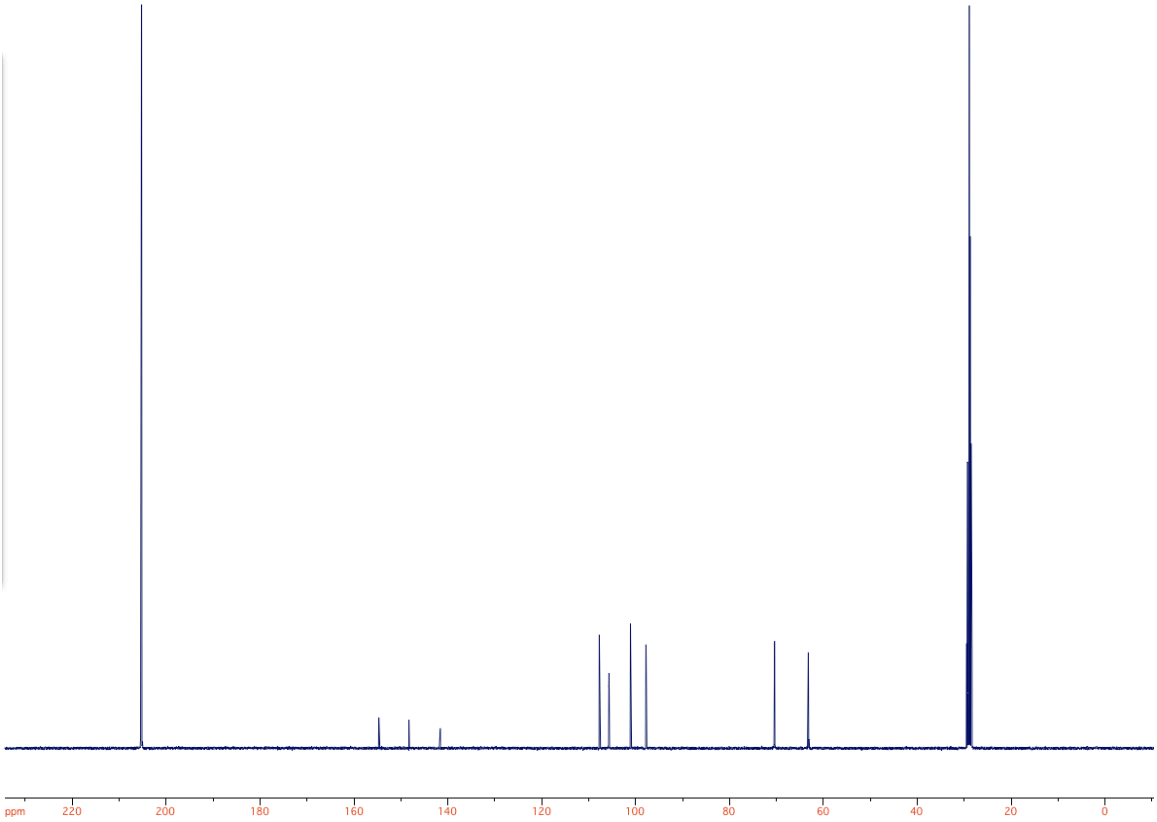
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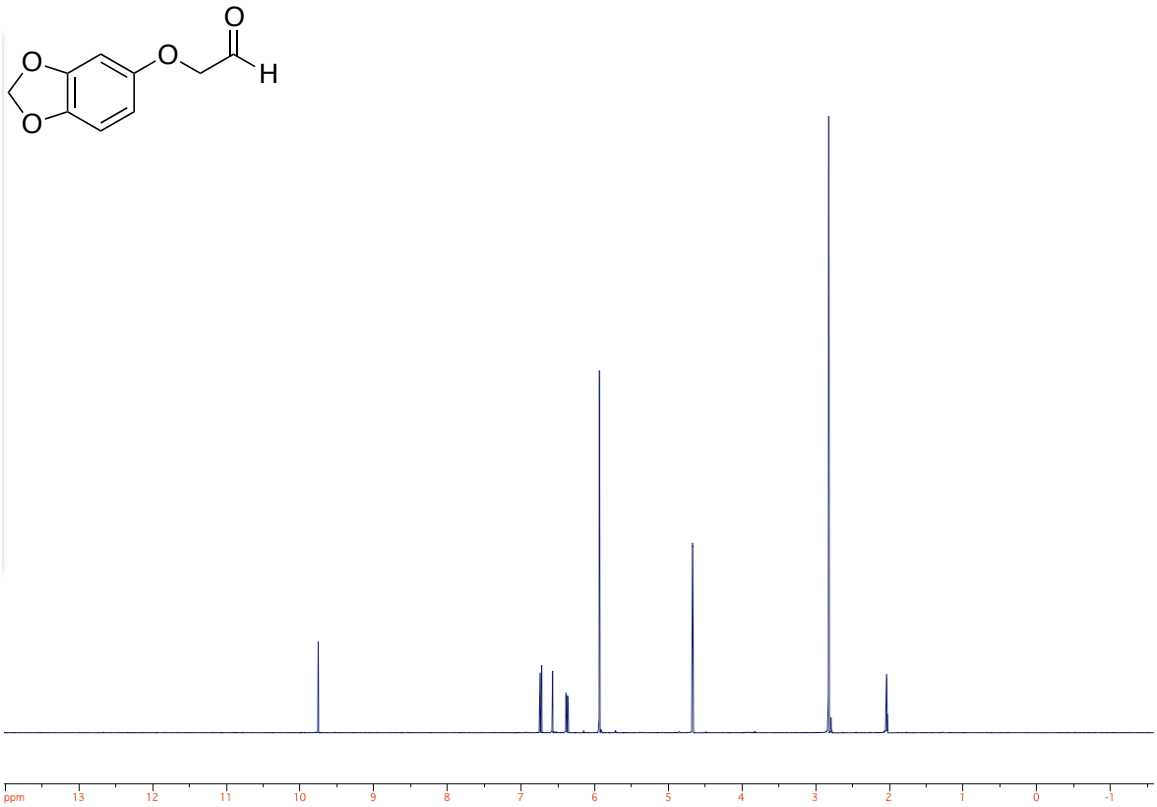
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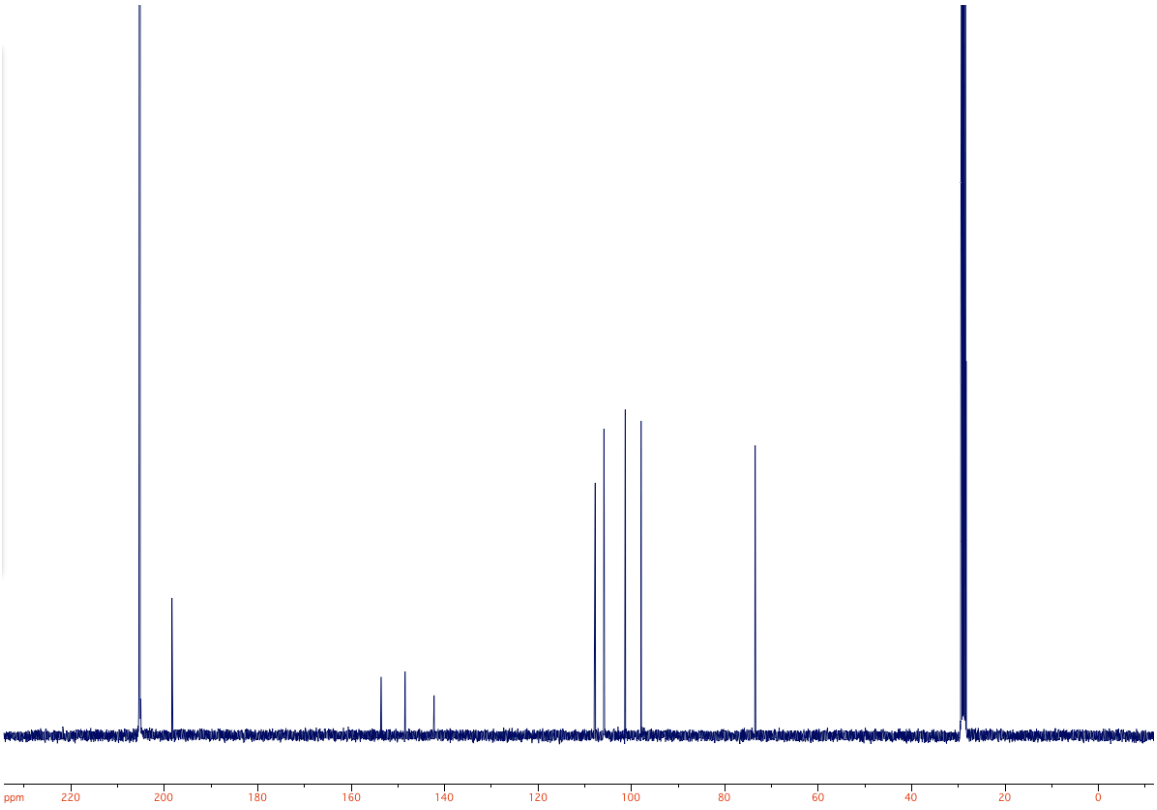
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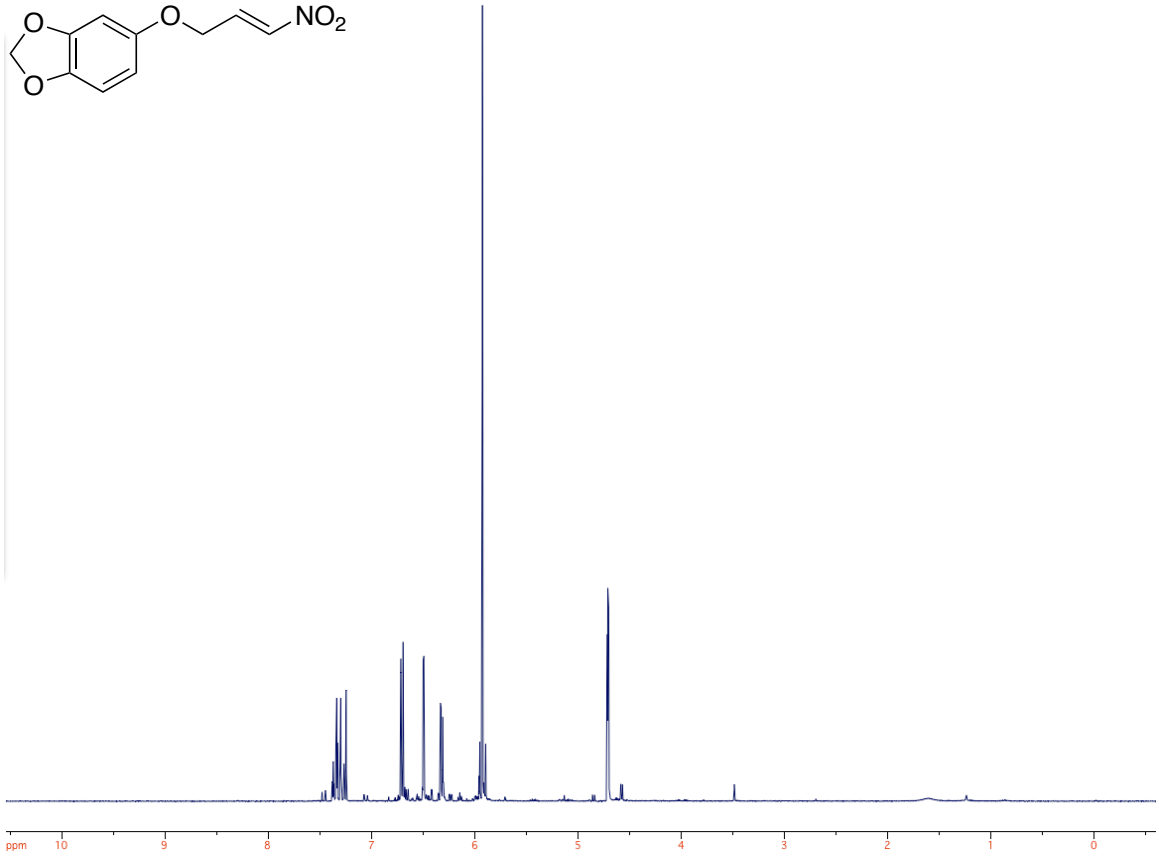
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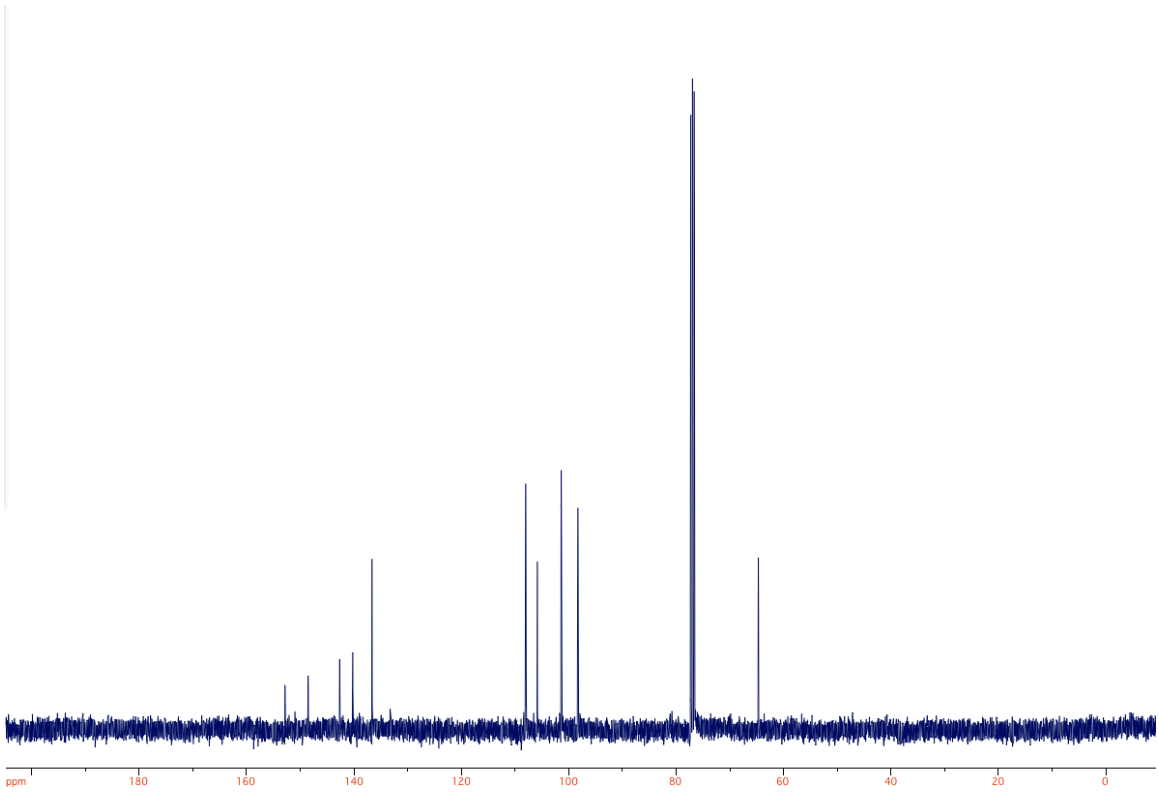
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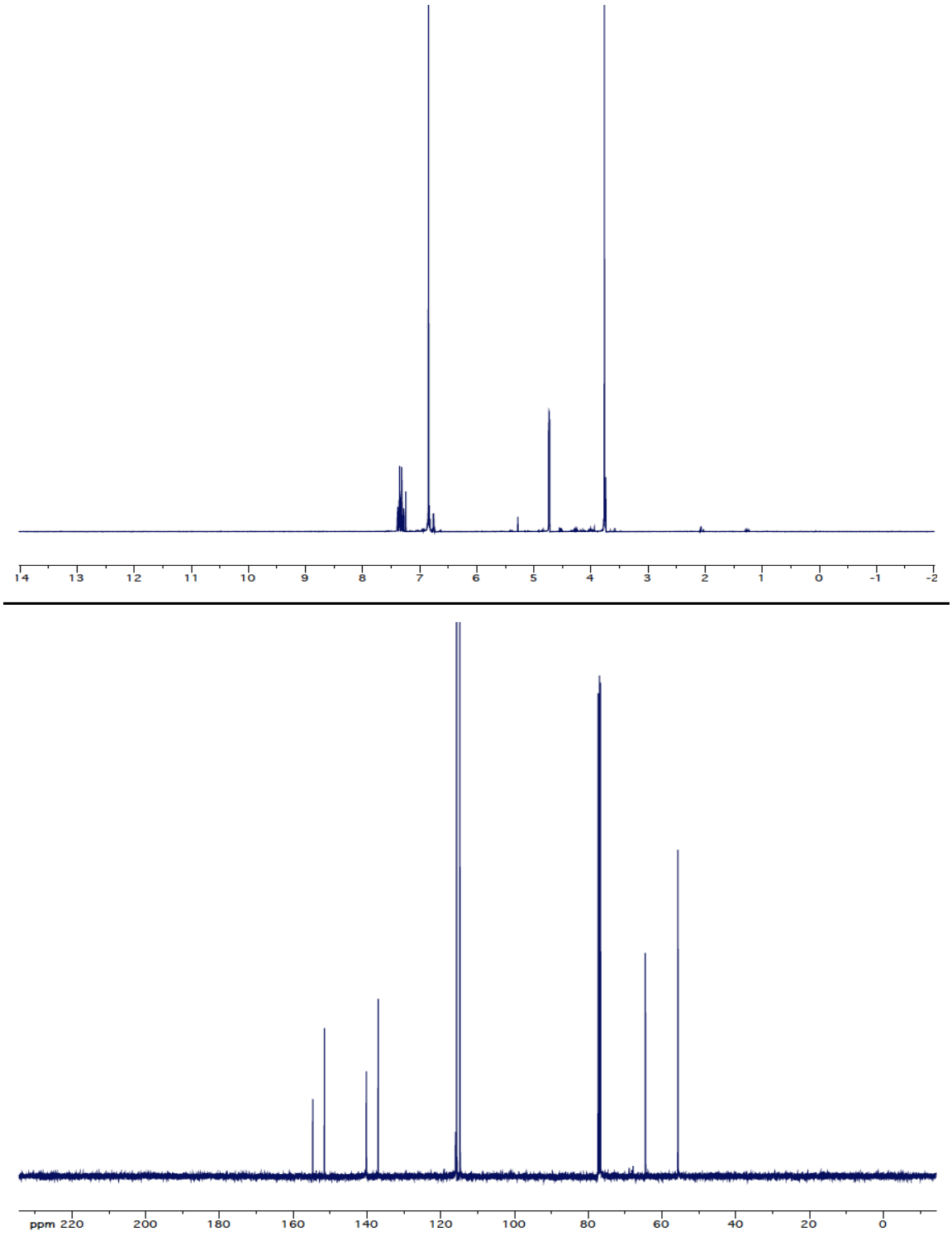
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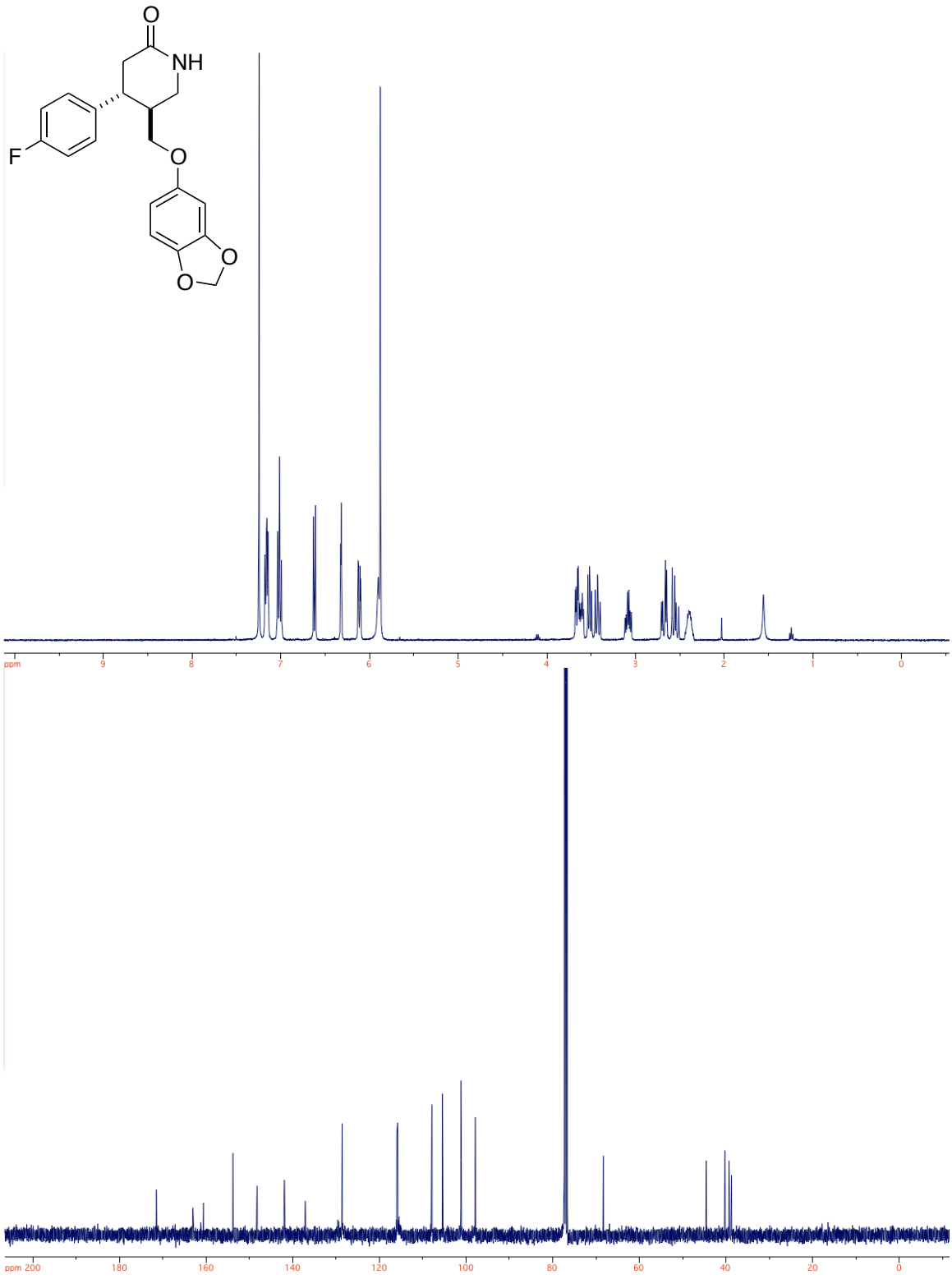
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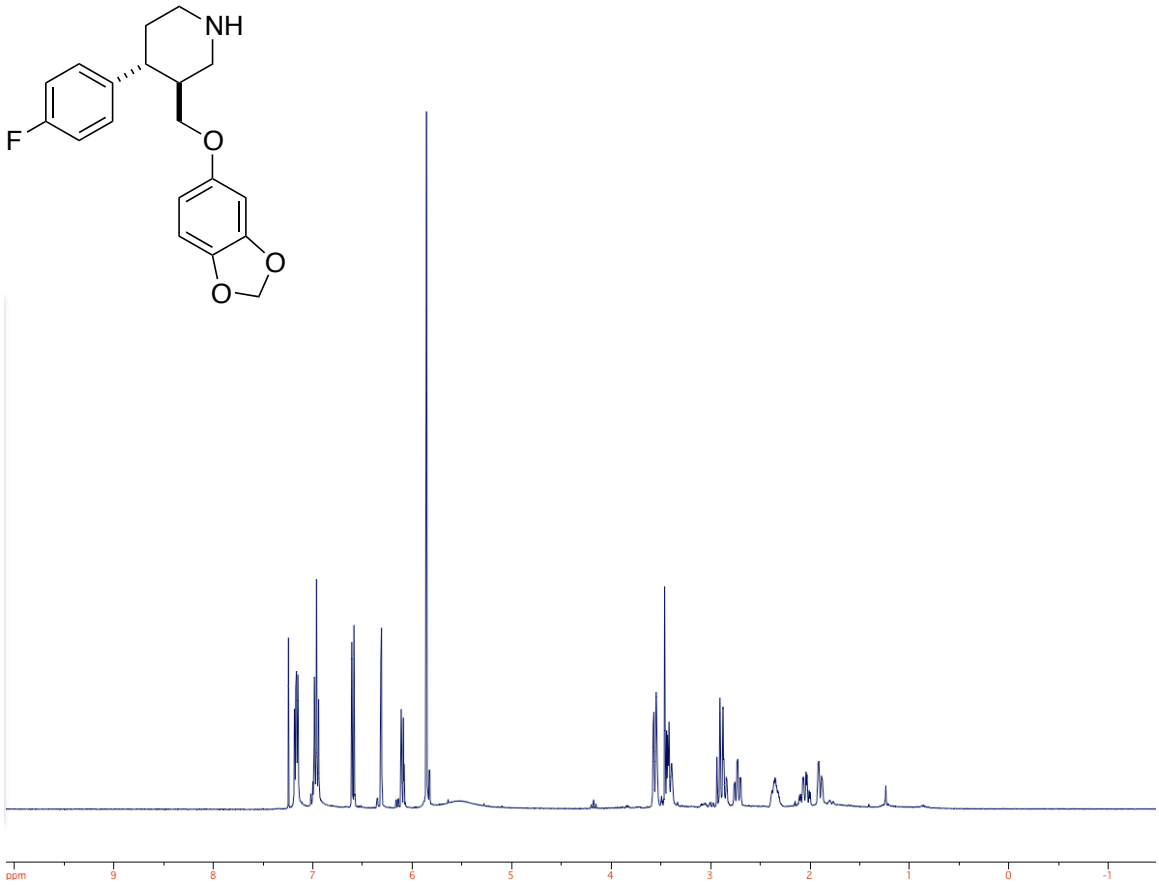
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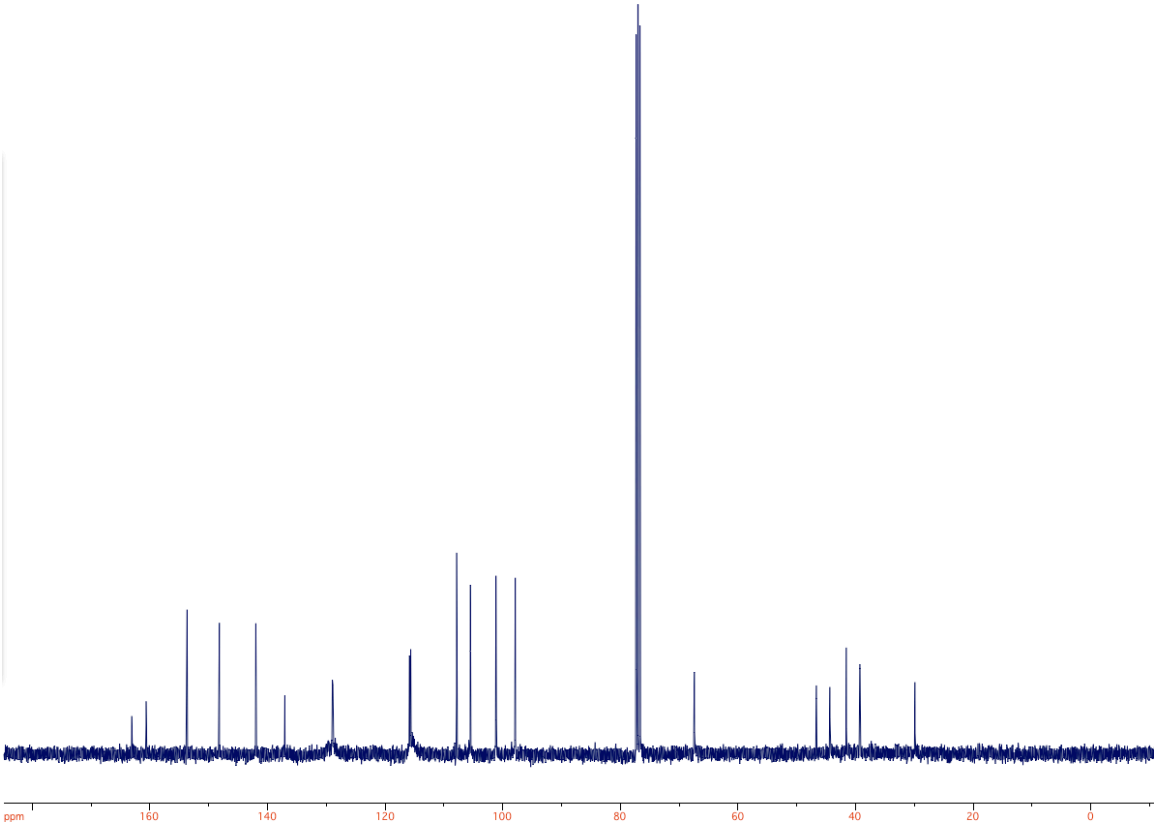
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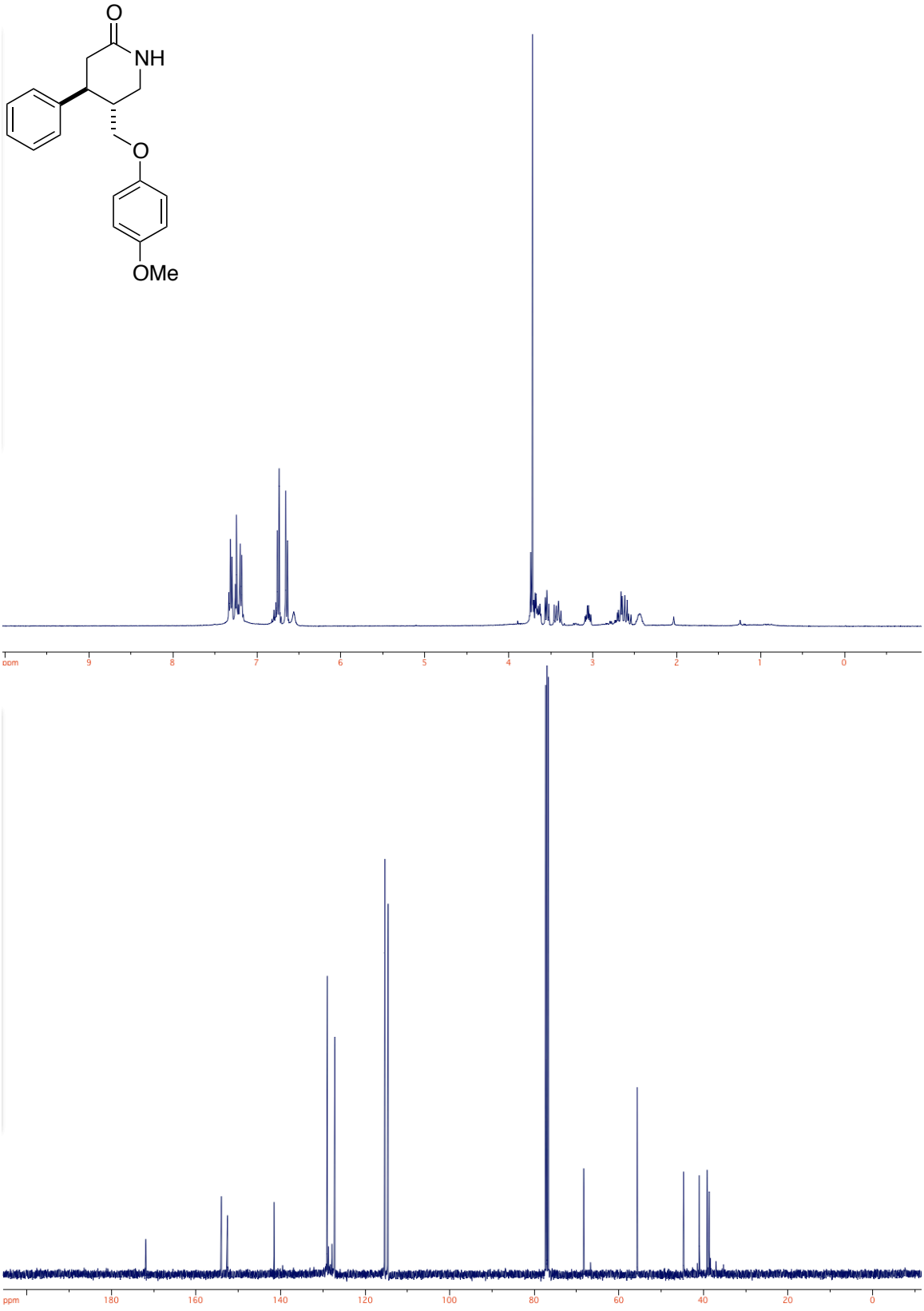
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ppm
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4
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2
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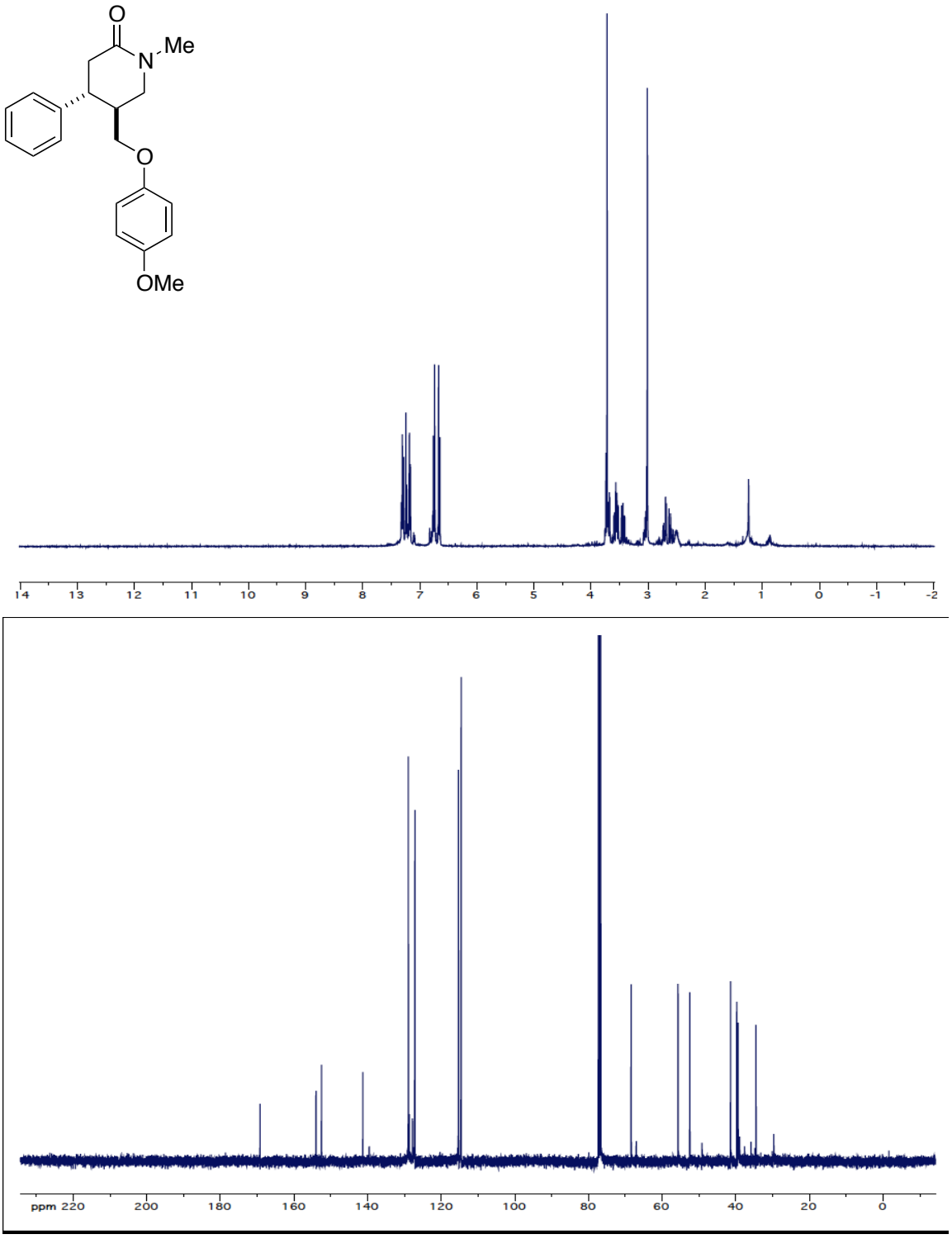
O
N
Me
O
OMe
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
ppm 220 200 180 160 140 120 100 80 60 40 20 0

References:

[i] N, Guimond.; M. J. MacDonald; V. Lemieux; A. M. Beauchemin. *J. Am. Chem. Soc.* **2012**, *134*, 16571-16577.
[ii] M. Amat, J. Bosch, J. Hidalgo, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque *J. Org. Chem*. **2000**, *65*, 3074-3084.