Supporting Information

A metal-free method for facile synthesis of indanones *via* intramolecular hydroacylation of 2-vinylbenzaldehydes

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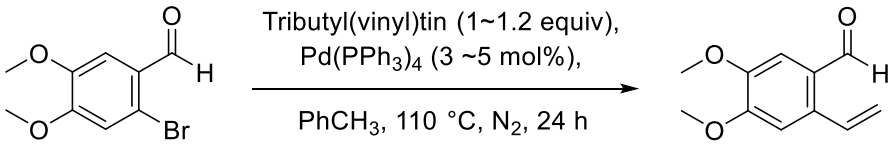
I. General Experimental Information

4,5-dimethoxy-2-vinylbenzaldehyde (**1a**) derivatives are commercially available and synthesized by reference. Metal-free-catalyzed reactions at 100 ℃ and in the air atmosphere. TLC was performed on silica gel GF_{254} plates (Qingdao Marine Chemical Co., Ltd., China) and was visualized with UV lamp (254 nm). Flash column chromatography was performed on silica gel (200−400 mesh). ^{1}H NMR spectra were recorded on 400 MHz NMR spectrometer (Bruker). ^{13}C NMR spectra were recorded on 100 MHz NMR spectrometer. The ^{1}H and ^{13}C chemical shifts are referenced to signals at δ 0.00 (TMS). ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet) and m (multiplet). HRMS were performed using EI mode analyzer. All new products were identified through NMR and HRMS.

II. General Experimental Procedures for the Reaction

General Procedure for the Synthesis of 4,5-Dimethoxy-2-vinylbenzaldehyde (1a) Derivatives.

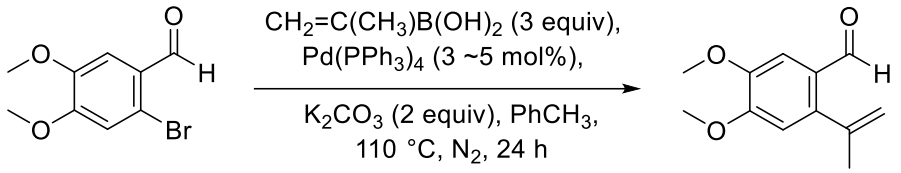


1a

4,5-Dimethoxy-2-vinylbenzaldehyde (**1a**) derivatives are commercially available, and obtained by references.[1]

A 25 mL round bottom flask, 2-bromo-4,5-dimethoxybenzaldehyde (2 mmol), $Pd(PPh_3)_4$ (3 mol %), tributylvinyltin (2 mmol) in anhydrous $PhCH_3$ (3 mL) was added and stirred at 110 ℃ for about 24 h under a nitrogen atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature, filtered with diatomite, washed filter cake with ethyl acetate, then collected filtrate and removal of the solvent under vacuum, and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:20) to provide the corresponding product **1a** (92%).

General Procedure for the Synthesis of 4,5-Dimethoxy-2-(prop-1-en-2-yl)benzaldehyde (1k).



1k

4,5-Dimethoxy-2-(prop-1-en-2-yl)benzaldehyde (**1k**) derivatives are commercially available, and obtained by references.[2]

A 25 mL round bottom flask, 2-bromo-4,5-dimethoxybenzaldehyde (2 mmol), Isopropenylboronic acid (6 mmol), $Pd(PPh_3)_4$ (3 mol %) in anhydrous $PhCH_3$ (3 mL) was added and stirred at 110 ℃ for about 24 h under a nitrogen atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature, filtered with diatomite, washed filter cake with ethyl acetate, then collected filtrate and removal of the solvent under vacuum, and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:20) to provide the corresponding product **1k** (81%).

4,5-Dimethoxy-2-(prop-1-en-2-yl)benzaldehyde (**1k**). Brown liquid, 334 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (d, J = 1.3 Hz, ^{1}H), 7.44 (d, J = 0.9 Hz, 1H), 6.76 (s, 1H), 5.42 (d, J = 1.3 Hz, 1H), 4.93 (s, 1H), 3.95 (dd, J = 11.3, 1.1 Hz, 7H), 2.17 (d, J = 0.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 153.5, 148.4, 143.3, 141.1, 126.6, 119.0, 110.2, 108.6, 56.1, 56.1, 25.4. HRMS (EI-DFS) *m/z* calcd for $C_{12}H_{14}O_3$ $[M]^+$ 206.0943, found 206.0934.

4,5-dimethoxy-2-(pent-1-en-1-yl)benzaldehyde (**1m**). Brown liquid, 267 mg, 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.36 (s, 1H), 7.05 (d, J = 15.6 Hz, 1H), 6.90 (s, 1H), 6.08 (dt, J = 15.5, 6.9 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 2.27 (dd, J = 7.4, 1.2 Hz, 2H), 1.54 (dt, J = 14.6, 7.3 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 153.8, 148.4, 136.9, 136.7, 126.1, 124.8, 109.8, 109.2, 56.1, 56.1, 35.4, 22.4, 13.8. HRMS (EI-DFS) *m/z* calcd for $C_{14}H_{18}O_3$ $[M]^+$ 234.1256, found 234.1249.

2-(2-cyclopropylvinyl)-4,5-dimethoxybenzaldehyde (**1o**). Brown liquid, 297 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.33 (s, 1H), 7.17 (d, J = 15.5 Hz, 1H), 6.86 (s, 1H), 5.58 (dd, J = 15.5, 9.1 Hz, 1H), 3.96 (s, 3H), 3.92 (d, J = 2.5 Hz, 4H),

1.72~1.60 (m, 1H), 0.94~0.84 (m, 2H), 0.61~0.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 153.7, 148.2, 140.4, 136.6, 125.6, 122.0, 110.0, 108.6, 56.0, 56.0, 15.1, 7.6. HRMS (EI-DFS) *m/z* calcd for $C_{14}H_{18}O_3$ $[M]^+$ 232.1099, found 232.1101.

The synthesis of 2-(2-(1-benzylpiperidin-4-yl)vinyl)-4,5-dimethoxybenzaldehyde (**1t**).

A 25 mL round bottom flask, 2-bromo-4,5-dimethoxybenzaldehyde (2 mmol), 4-allyl-1-benzylpiperidine (2 mmol), $Pd(OAc)_2$ (5 mol %), tri-*o*-tolylphosphane (10 mol %) in triethylamine (5 mL) was added and stirred at 125 ℃ for about 12 h under a nitrogen atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature, water was added and extracted with ethyl acetate (10 mLx2), the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:4) to provide the corresponding product **1t** (44%).

2-(2-(1-benzylpiperidin-4-yl)vinyl)-4,5-dimethoxybenzaldehyde (**1t**). Brown liquid, 333 mg, 44%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.33 (d, J = 5.2 Hz, 5H), 7.31~7.28 (m, 1H), 7.03 (d, J = 15.6 Hz, 1H), 6.86 (s, 1H), 6.04~5.96 (m, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.71 (s, 2H), 3.09 (d, J = 11.1 Hz, 2H), 2.23 (dd, J = 10.5, 4.7 Hz, 2H), 2.15 (t, J = 10.7 Hz, 2H), 1.75 (d, J = 9.6 Hz, 2H), 1.49 (d, J = 4.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 153.8, 148.5, 136.5, 135.2, 134.1, 130.1, 128.4, 127.8, 126.5, 126.1, 110.1, 109.2, 62.1, 56.1, 56.0, 52.8, 39.9, 35.5, 30.9. HRMS (EI-DFS) *m/z* calcd for $C_{24}H_{29}NO_3$ $[M]^+$ 379.2147, found 379.2151.

General Procedure for the Synthesis of 5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one (2a).

A 25 mL round bottom flask, 4,5-dimethoxy-2-vinylbenzaldehyde (**1a**) (58 mg, 0.3 mmol), L-proline (7 mg, 20 mol %) in glacial acetic acid (3 mL) was added and stirred at 120 ℃ for about 24 h under an air atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature and removal of the solvent under vacuum, the resulting mixture was extracted with ethyl acetate (10 mLx2), the combined organic layers were washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, concentrated under reduced pressure, and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:6) to provide the corresponding product **2a** (52 mg, 90%).

5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one **(2a)**. Brown solid, 52 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.90 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.10~2.98 (m, 2H), 2.71~2.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 155.4, 150.4, 149.4, 129.9, 107.5, 104.1, 56.1, 56.1, 36.5, 25.6. HRMS (EI-DFS) *m/z* calcd for $C_{11}H_{12}O_3$ $[M]^+$ 192.0786, found 192.0779.

6-Hydroxy-5-methoxy-2,3-dihydro-1*H*-inden-1-one **(2b)**. Brown liquid, 44 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.88 (s, 1H), 5.73 (s, 1H), 3.99 (s, 3H), 3.07~3.01 (m, 2H), 2.68~2.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 152.8, 149.3, 145.7, 130.6, 107.9, 107.1, 56.2, 36.5, 25.6. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_8O_3$ $[M]^+$ 176.0473, found 176.0469.

6,7-Dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one **(2c)**. Brown solid, 43 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.83 (s, 1H), 6.07 (s, 2H), 3.05~3.00 (m, 2H), 2.71~2.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 154.2, 152.7, 148.3, 131.7, 105.7, 102.3, 102.2, 36.7, 25.8. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_8O_3$ $[M]^+$ 176.0473, found 176.0470.

2,3-Dihydro-1*H*-cyclopenta[*a*]naphthalen-1-one **(2d)**. Brown solid, 47 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.79 (dd, J = 26.7, 8.5 Hz, 2H), 7.71~7.61 (m, 2H), 3.51~3.36 (m, 2H), 2.86 (dd, J = 8.1, 2.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 156.5, 136.6, 134.5, 130.6, 129.2, 128.9, 128.5, 127.1, 124.4, 119.5, 36.2, 24.4. HRMS (EI-DFS) *m/z* calcd for $C_{13}H_{10}O$ $[M]^+$ 182.0732, found 182.0725.

6-Methoxy-2,3-dihydro-1*H*-inden-1-one **(2e)**. Brown solid, 42 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.0, 2.0 Hz, 1H), 7.19 (dd, J = 7.3, 2.3 Hz, 2H), 3.84 (s, 3H), 3.12~3.02 (m, 2H), 2.77~2.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 159.4, 148.0, 138.2, 127.4, 124.1, 104.9, 55.6, 37.0, 25.1. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0681, found 162.0668.

6-Hydroxy-2,3-dihydro-1*H*-inden-1-one **(2f)**. Brown liquid, 36 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.2, 2.5 Hz, 1H), 6.47 (s, 1H), 3.09~3.03 (m, 2H), 2.72 (dd, J = 6.5, 4.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 155.8, 147.9, 138.2, 127.6, 123.6, 108.7, 37.1, 25.2. HRMS (EI-DFS) *m/z* calcd for $C_9H_8O_2$ $[M]^+$ 148.0524, found 148.0518.

5-Methyl-2,3-dihydro-1*H*-inden-1-one **(2g)**. Brown solid, 33 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.18 (d, J = 8.1 Hz, 1H),

3.09 (s, 2H), 2.71~2.64 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 155.8, 151.2, 146.0, 128.6, 127.0, 123.6, 36.4, 25.7, 22.1. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_{10}O$ $[M]^+$ 146.0732, found 146.0726.

5-Hydroxy-2,3-dihydro-1*H*-inden-1-one **(2h)**. Brown liquid, 37 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 1H), 7.23 (s, 1H), 7.17 (dd, J = 7.8, 2.1 Hz, 1H), 3.10~3.03 (m, 2H), 2.75~2.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 155.7, 147.7, 138.2, 127.6, 123.6, 108.7, 37.1, 25.2. HRMS (EI-DFS) *m/z* calcd for $C_9H_8O_2$ $[M]^+$ 148.0524, found 148.0522.

4-Methyl-2,3-dihydro-1*H*-inden-1-one **(2i)**. Brown solid, 27 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 3.08~3.00 (m, 2H), 2.74~2.67 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 154.2, 136.9, 135.9, 135.1, 127.5, 121.1, 36.2, 24.9, 17.8. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_{10}O$ $[M]^+$ 146.0732, found 146.0726.

2,3-Dihydro-1*H*-inden-1-one **(2j)**. Brown solid, 18 mg, 45%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 1H), 7.62~7.56 (m, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.40~7.35 (m, 1H), 3.17~3.13 (m, 2H), 2.72~2.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 155.2, 137.1, 134.6, 127.3, 126.7, 123.7, 36.2, 25.8. HRMS (EI-DFS) *m/z* calcd for C_9H_8O $[M]^+$ 132.0575, found 132.0570.

5,6-Dimethoxy-3-methyl-2,3-dihydro-1*H*-inden-1-one **(2k)**. Brown solid, 34 mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.89 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.35 (d, J = 6.3 Hz, 1H), 2.93 (dd, J = 18.8, 7.3 Hz, 1H), 2.26 (d, J = 18.8 Hz, 1H), 1.27 (d, J = 12.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 155.6, 155.3, 149.5, 106.1, 104.0, 56.2, 56.1, 45.5, 32.6, 21.5. HRMS (EI-DFS) *m/z* calcd for $C_{12}H_{14}O_3$ $[M]^+$ 206.0943, found 206.0939.

5,6-Dimethoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one **(2l)**. Brown solid, 52 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 6.5 Hz, 2H), 7.27~7.21 (m, 2H), 7.12 (d, J = 6.0 Hz, 2H), 6.64 (s, 1H), 4.51~4.45 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.21 (dd, J = 19.0, 7.5 Hz, 1H), 2.63 (dd, J = 19.0, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 155.8, 153.1, 149.9, 143.9, 129.9, 128.9, 127.6, 127.0, 107.5, 103.7, 56.2, 56.1, 47.2, 44.2. HRMS (EI-DFS) *m/z* calcd for $C_{17}H_{16}O_3$ $[M]^+$ 268.1099, found 268.1097.

5,6-Dimethoxy-2-propyl-2,3-dihydro-1*H*-inden-1-one **(2m)**. Brown solid, 53 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.86 (s, 1H), 3.95 (s, 3H), 3.90 (s,

3H), 3.22 (dd, *J* = 16.8, 7.4 Hz, 1H), 2.71 (dd, *J* = 16.9, 3.2 Hz, 1H), 2.68~2.58 (m, 1H), 1.91 (t, *J* = 9.8 Hz, 1H), 1.49~1.38 (m, 3H), 0.95 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 207.9, 155.4, 149.4, 149.0, 129.6, 107.4, 104.3, 56.2, 56.1, 47.6, 33.9, 32.6, 20.7, 14.1. HRMS (EI-DFS) *m/z* calcd for $C_{14}H_{18}O_3$ $[M]^+$ 234.1256, found 234.1250.

2-Butyl-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one **(2n)**. Brown solid, 53 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.15 (s, 1H), 6.85 (s, 1H), 3.94 (d, *J* = 0.8 Hz, 3H), 3.88 (d, *J* = 0.8 Hz, 3H), 3.20 (dd, *J* = 16.9, 7.4 Hz, 1H), 2.70 (dd, *J* = 16.9, 3.2 Hz, 1H), 2.62 (dt, *J* = 12.1, 3.9 Hz, 1H), 1.97~1.87 (m, 1H), 1.41~1.30 (m, 5H), 0.89 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 207.9, 155.4, 149.4, 149.1, 129.6, 107.4, 104.3, 56.2, 56.1, 47.7, 32.6, 31.4, 29.6, 22.8, 14.0. HRMS (EI-DFS) *m/z* calcd for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412, found 248.1405.

2-Cyclopropyl-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one **(2o)**. Brown solid, 56 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.17 (s, 1H), 6.85 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.16 (dd, *J* = 17.1, 7.6 Hz, 1H), 2.71 (dd, *J* = 17.1, 3.2 Hz, 1H), 2.30 (td, *J* = 7.8, 3.3 Hz, 1H), 1.03~0.93 (m, 1H), 0.65~0.56 (m, 1H), 0.54~0.38 (m, 2H), 0.23 (dt, *J* = 14.1, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 206.5, 155.1, 149.0, 148.5, 129.1, 107.0, 104.1, 55.8, 55.7, 50.0, 31.5, 12.6, 2.9, 1.1. HRMS (EI-DFS) *m/z* calcd for $C_{14}H_{16}O_3$ $[M]^+$ 232.1099, found 232.1092.

4-Hydroxy-2-methyl-2,3-dihydro-1*H*-inden-1-one **(2r)**. Brown solid, 20 mg, 42%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.37 (d, *J* = 7.5 Hz, 1H), 7.30~7.25 (m, 1H), 7.03 (dd, *J* = 7.8, 0.7 Hz, 1H), 3.35 (dd, *J* = 17.0, 7.8 Hz, 1H), 2.79~2.71 (m, 1H), 2.64 (dd, *J* = 17.0, 3.7 Hz, 1H), 1.34 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 209.6, 153.3, 139.7, 138.2, 129.0, 120.2, 116.3, 42.0, 31.1, 16.4. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0681, found 162.0667.

5-Hydroxy-3,4-dihydronaphthalen-1(2*H*)-one **(2s)**. Brown solid, 19 mg, 40%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.71~7.62 (m, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.98 (dd, *J* = 7.9, 1.1 Hz, 1H), 2.90 (t, *J* = 6.2 Hz, 2H), 2.69~2.61 (m, 2H), 2.15 (dt, *J* = 12.8, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 198.5, 153.0, 134.0, 131.0, 126.8, 119.6, 119.5, 38.8, 22.7, 22.5. HRMS (EI-DFS) *m/z* calcd for $C_{10}H_{10}O_2$ $[M]^+$ 162.0681, found 162.0671.

Donepezil **(2t)**. White solid, 87 mg, 77%. ^{1}H NMR (500 MHz, CDCl*3*) *δ* 7.36~7.30 (m, 4H), 7.26~7.22 (m, 1H), 7.16 (s, 1H), 6.85 (s, 1H), 3.95 (s, 3H), 3.90 (s,

3H), 3.51 (s, 2H), 3.23 (dd, J = 17.5, 8.1 Hz, 1H), 2.90 (t, J = 9.9 Hz, 2H), 2.75~2.66 (m, 2H), 1.98 (tdd, J = 11.6, 5.6, 2.6 Hz, 2H), 1.94~1.88 (m, 1H), 1.77~1.70 (m, 1H), 1.69~1.63 (m, 1H), 1.55~1.45 (m, 1H), 1.35 (dddd, J = 15.8, 13.5, 11.1, 4.7 Hz, 3H). 13C NMR (125 MHz, $CDCl_3$) δ 207.8, 155.5, 149.5, 148.7, 138.4, 129.3, 129.2, 128.1, 126.9, 107.4, 104.4, 63.4, 56.2, 56.1, 53.8, 45.5, 38.7, 34.4, 33.4, 33.0, 31.8. HRMS (EI-DFS) *m/z* calcd for $C_{24}H_{29}NO_3$ $[M]^+$ 379.2147, found 379.2141.

General Procedure for the Synthesis of Deuterium Containing Compound (D1-2a).

A 25 mL round bottom flask, 4,5-dimethoxy-2-vinylbenzaldehyde (**1a**) (58 mg, 0.3 mmol), L-proline (7 mg, 20 mol %) in CD_3CO_2D (3 mL) was added and stirred at 120 ℃ for about 24 h under an air atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature and removal of the solvent under vacuum, the resulting mixture was extracted with ethyl acetate (10 mLx2), the combined organic layers were washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, concentrated under reduced pressure. and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:6) to provide the corresponding product **D1-2a** (51 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.86 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.01 (s, 2H), 2.62 (s, 1H).

General Procedure for the Synthesis of Deuterium Containing Compound (D-1j and D-1a).

A 25 mL dry round bottom three-necked flask, 1-bromo-2-vinylbenzene (182 mg, 2 mmol), dry THF (8 mL) and n-BuLi (1.6 M, 2.5 mL, 4 mmol) added slowly through a syringe, stirred at -78 ℃ for about 0.5 h under a nitrogen atmosphere, then DMF-*d*7 (0.6 mL, 8 mmol) added slowly with syringe stirred at -78 ℃ for about 0.5 h. Added NH_4Cl saturated solution (4 mL), the resulting mixture was extracted with ethyl acetate (10 mLx3), the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure. and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:20) to provide the corresponding product **D-1j** (228 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88~7.80 (m, 1H), 7.60~7.49 (m, 3H), 7.47~7.40 (m, 1H), 5.70 (d, *J* = 17.4 Hz, 1H), 5.52 (d, *J* = 11.0 Hz, 1H).

For **D-1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 17.3, 11.0 Hz, 1H), 7.35 (s, 1H), 6.96 (s, 1H), 5.63 (d, J = 17.3 Hz, 1H), 5.48 (d, J = 11.0 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H).

General Procedure for the Synthesis of Deuterium Containing Compound (D-2j and D2-2a).

A 25 mL round bottom flask, **D-1j** (26 mg, 0.2 mmol), L-proline (5 mg, 20 mol %) in glacial acetic acid (3 mL) was added and stirred at 120 ℃ for about 24 h under an air atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature and removal of the solvent under vacuum, the resulting mixture was extracted with ethyl acetate (10 mLx2), the combined organic layers were washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, concentrated under reduced pressure. and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:6) to provide the corresponding product **D-2j** (10 mg, 39%).

^{1}H NMR (400 MHz, DMSO) δ 7.70~7.65 (m, 1H), 7.64~7.58 (m, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.28~7.20 (m, 1H), 3.16~3.06 (m, 2H), 2.66~2.60 (m, 2H).

For **D2-2a**: 32 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.88 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.07~3.00 (m, 2H), 2.71~2.62 (m, 2H).

General Procedure for the Synthesis of Intermediate C-2g.

A 25 mL round bottom flask, **1g** (44 mg, 0.3 mmol), tetrahydroisoquinoline (80 mg, 0.6 mmol) in glacial acetic acid (3 mL) was added and stirred at 100 ℃ for about 12 h under an air atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature and removal of the solvent under vacuum, the resulting mixture was extracted with ethyl acetate (10 mLx2), the combined organic layers were washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, concentrated under reduced pressure. and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:10) to provide the corresponding product **C-2g** (5 mg, 5%).

Brown liquid, 5 mg, 5%.^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, J = 7.9 Hz, 1H), 7.29~7.18 (m, 2H), 7.13~7.06 (m, 3H), 7.04~6.98 (m, 1H), 6.26 (dd, J = 7.1, 4.0 Hz,

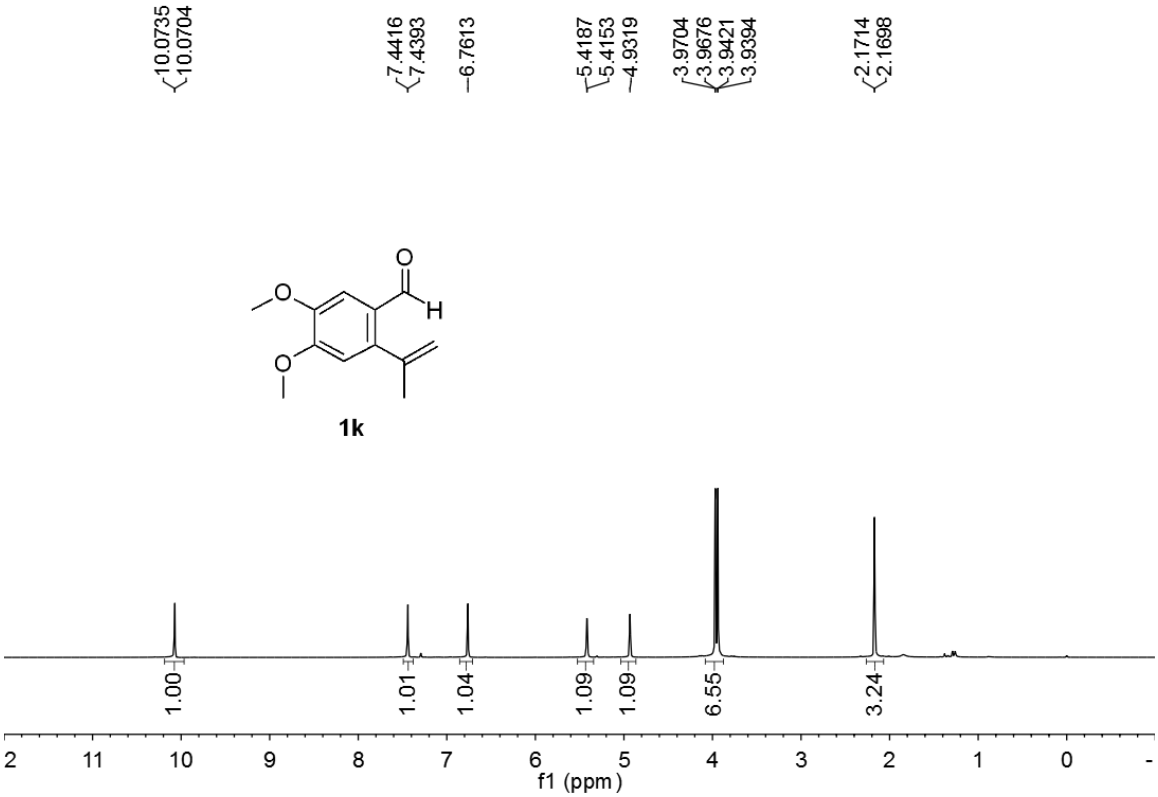
1H), 4.78 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.75 (dd, *J* = 65.1, 14.8 Hz, 2H), 2.90 (t, *J* = 5.7 Hz, 2H), 2.84~2.72 (m, 2H), 2.66 (ddd, *J* = 14.6, 7.1, 4.7 Hz, 1H), 2.36 (s, 3H), 2.20 (ddd, *J* = 14.7, 7.8, 4.0 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.6, 142.1, 138.9, 138.6, 133.8, 133.7, 129.9, 128.3, 126.3, 126.2, 125.8, 125.5, 125.2, 76.7, 67.4, 51.3, 45.9, 32.5, 28.5, 20.0, 19.8. HRMS (EI-DFS) *m/z* calcd for $C_{21}H_{23}NO_2$ $[M]^+$ 321.1729, found 321.1721.

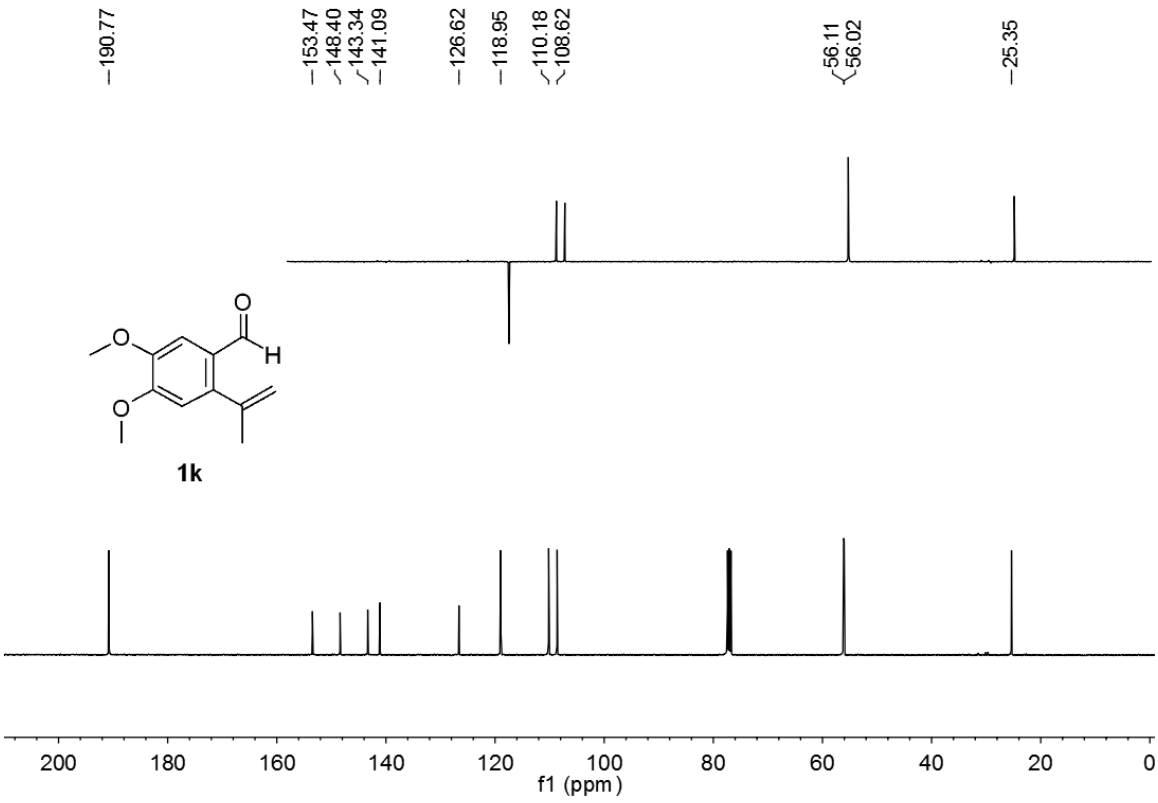
III. References

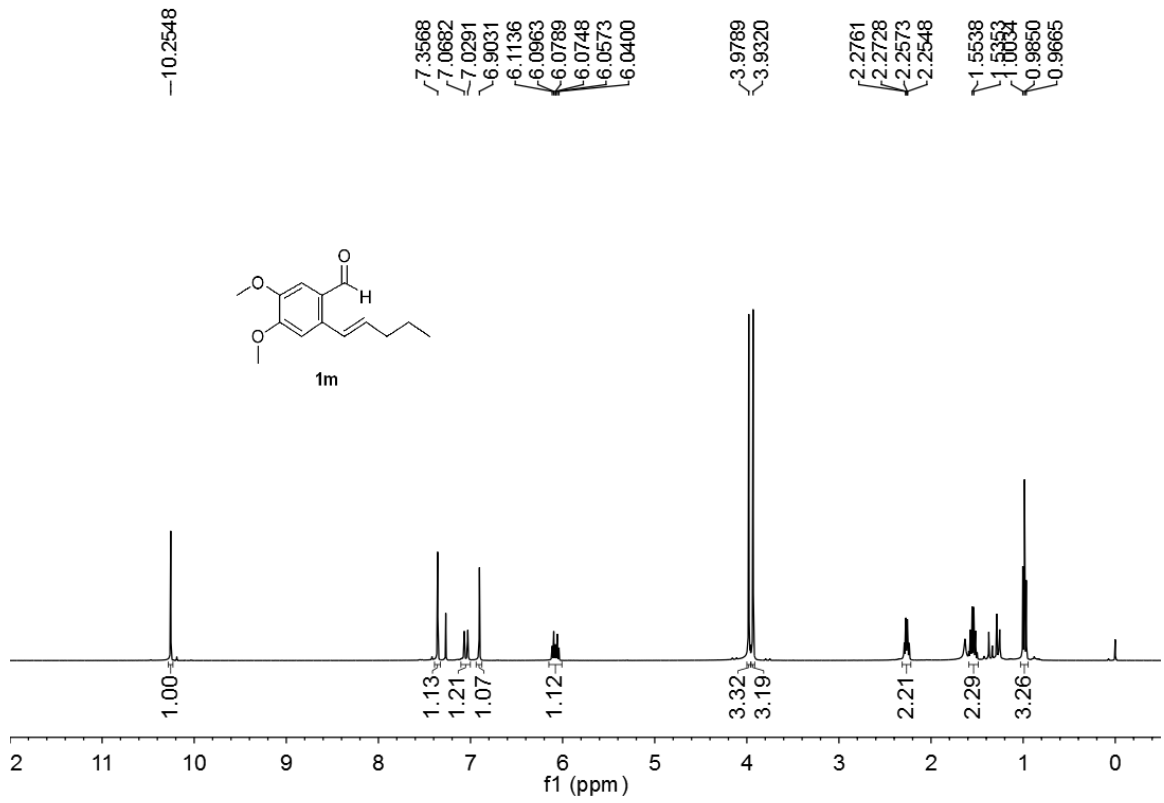
[1] N. R. Vautravers, D. D. Regent, B. Breit, *Chem. Commun.*, 2011, **47**, 6635.

[2] E. Peyroux, F. Berthiol, H. Doucet, M. Santelli, *Eur. J. Org. Chem.*, 2004, **2004**, 1075.

IV. ^{1}H NMR and ^{13}C NMR Spectra



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2.2548
1.5538
1.5353
1.0034
0.9850
0.9665
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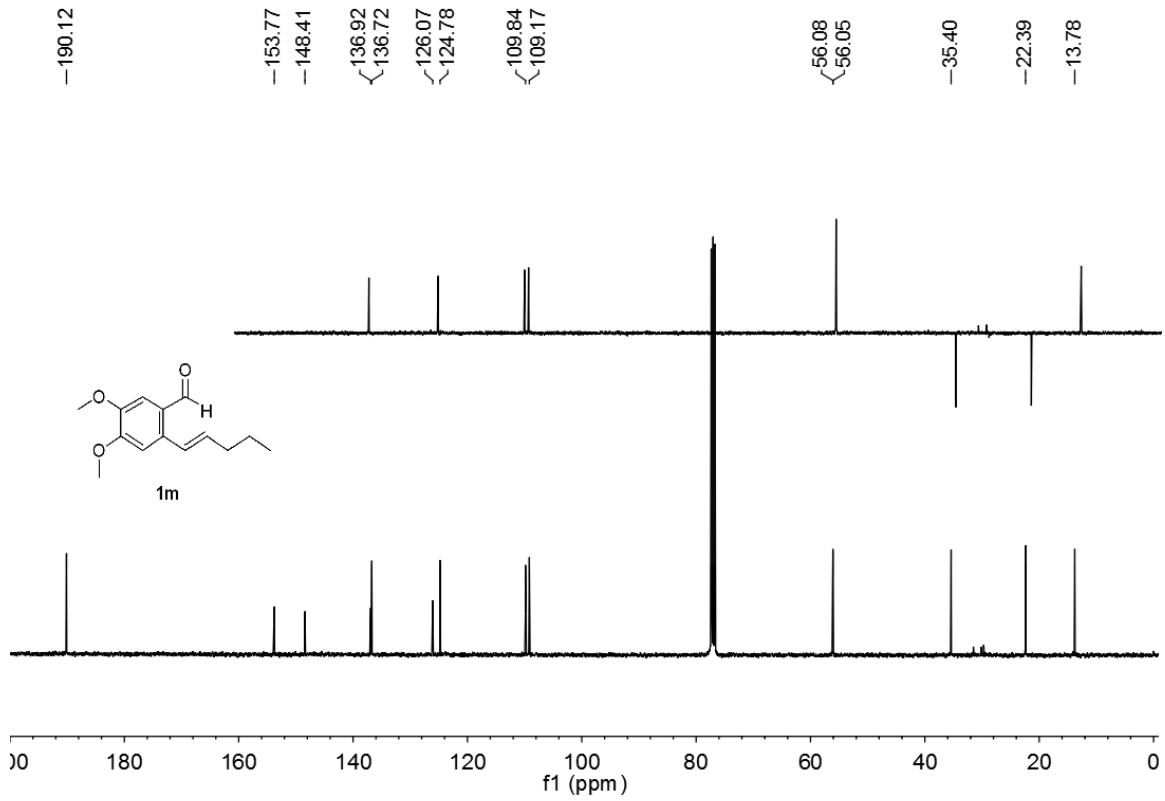
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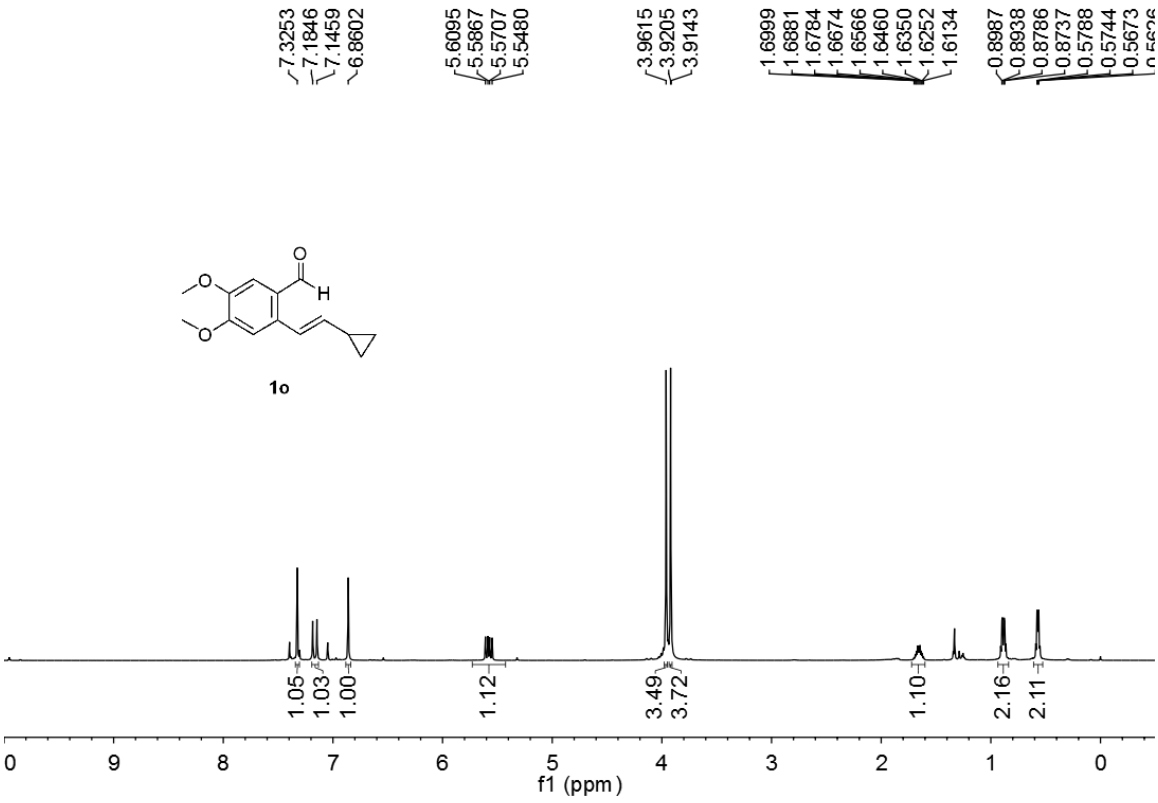
1m
f1 (ppm)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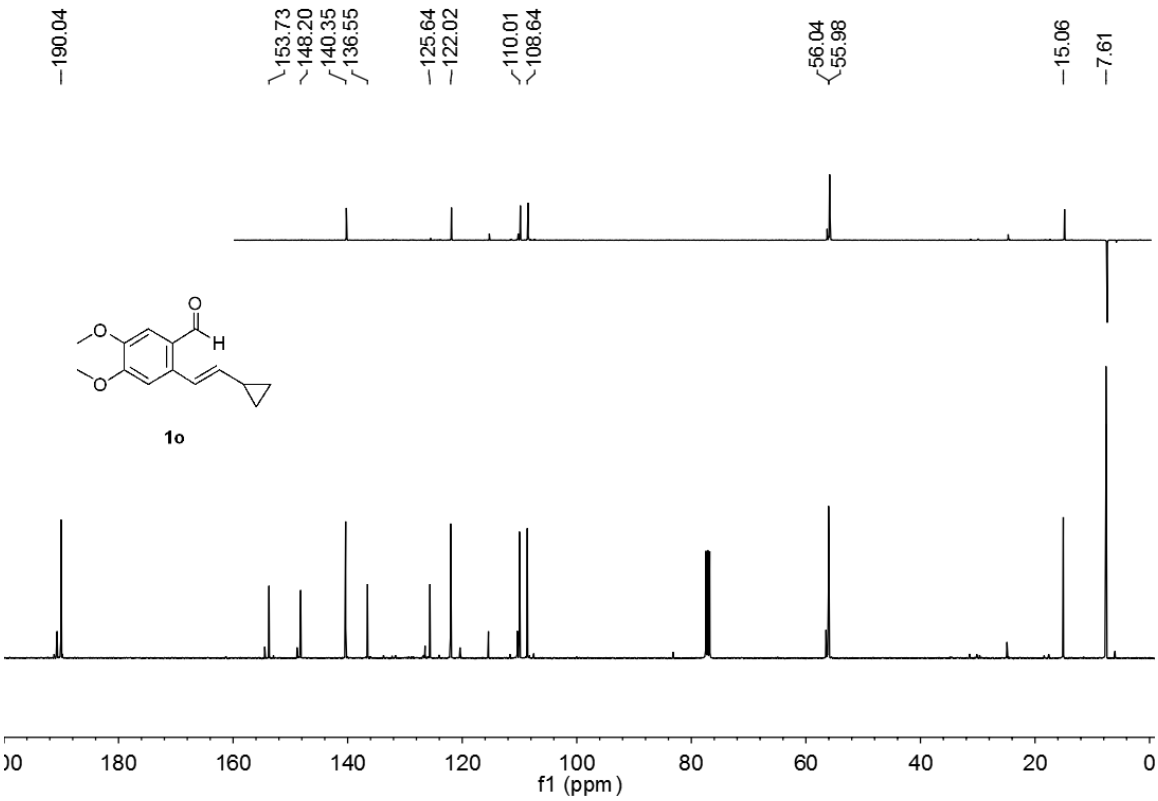
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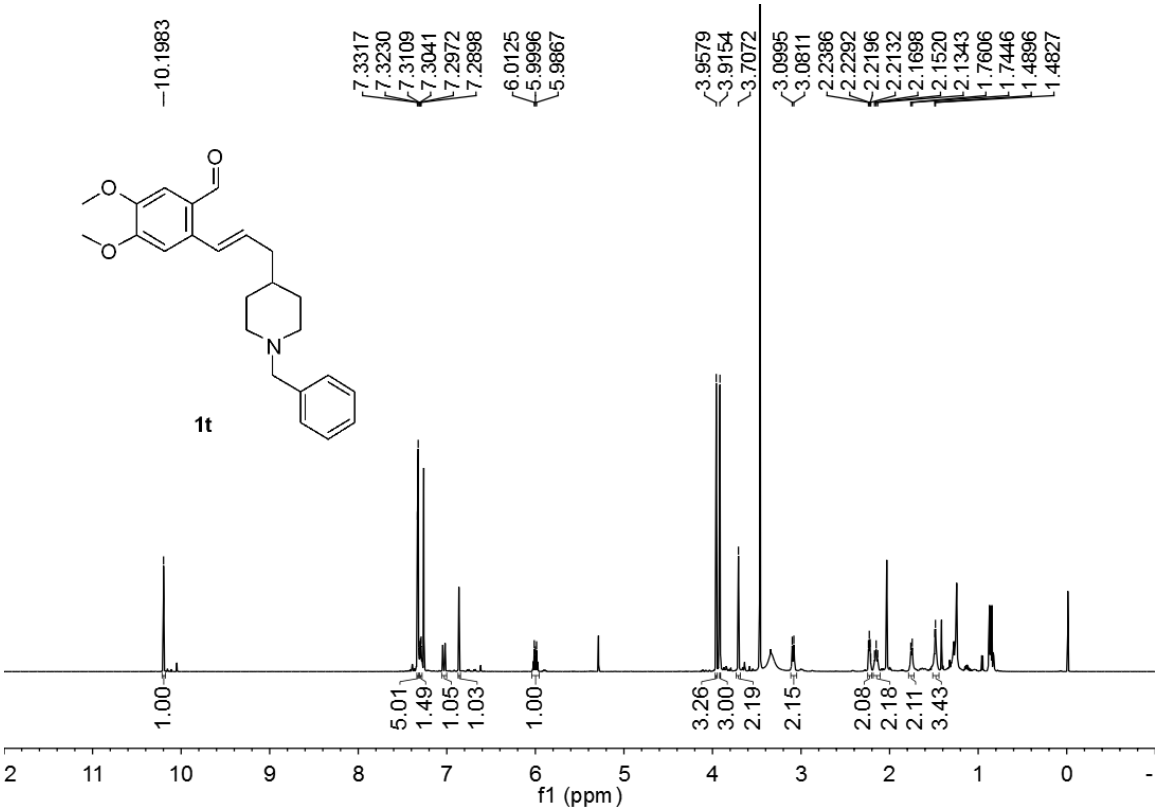
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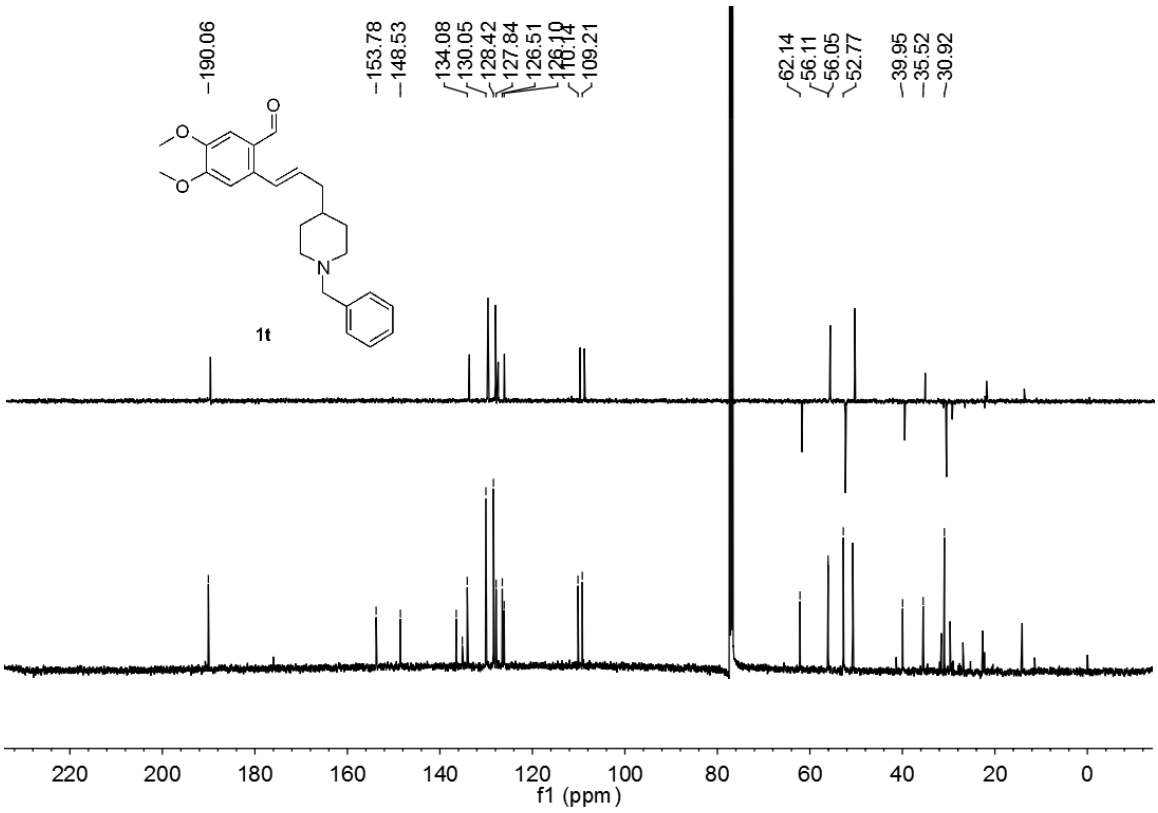
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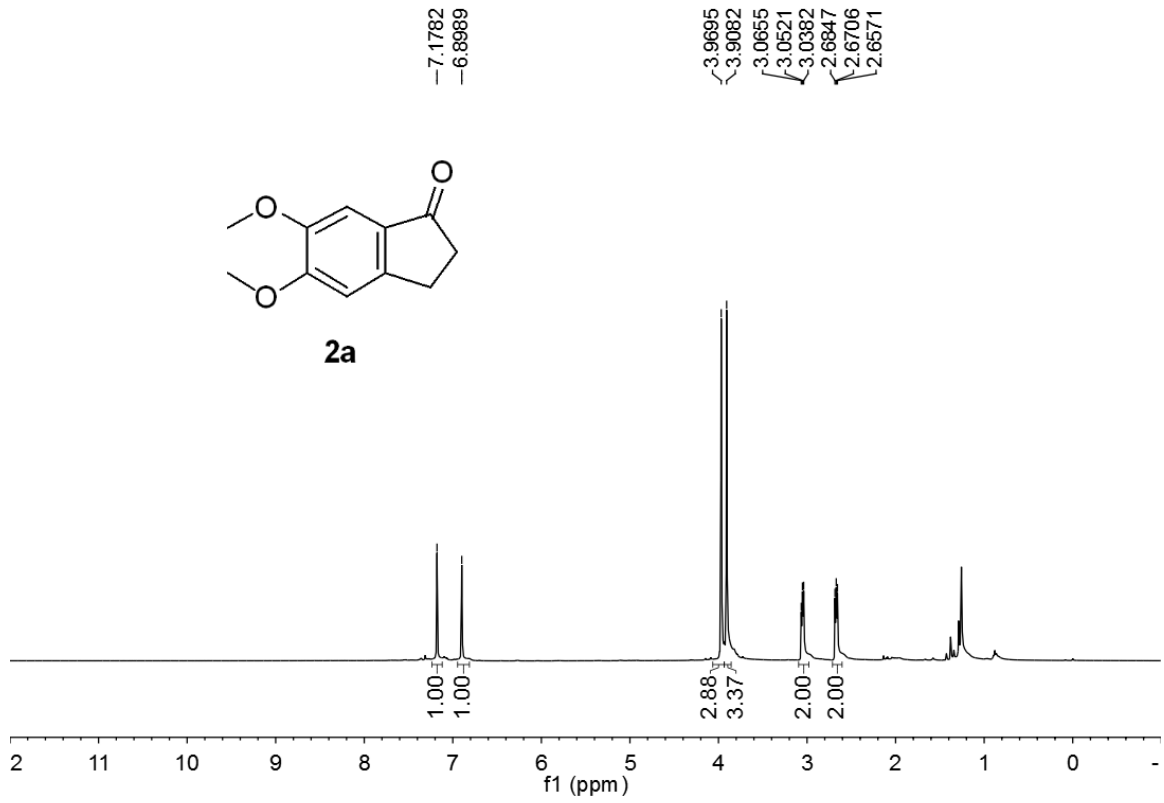
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3.37
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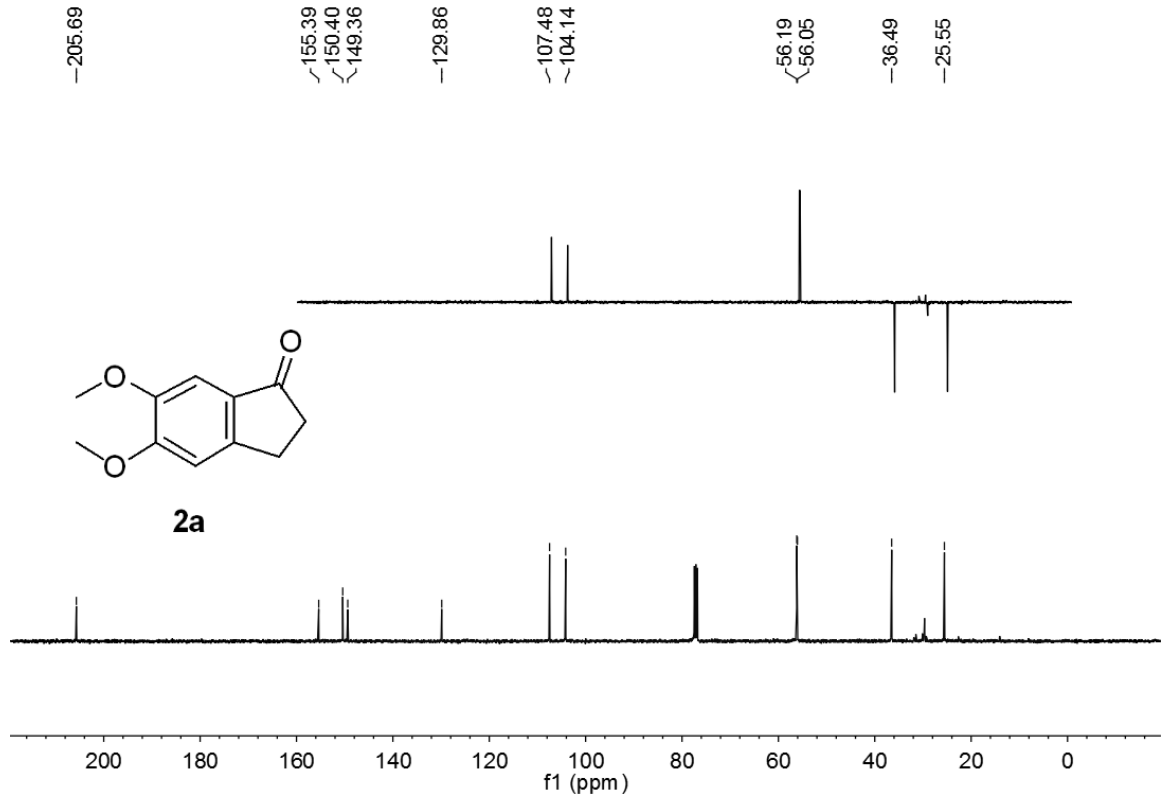
f1 (ppm)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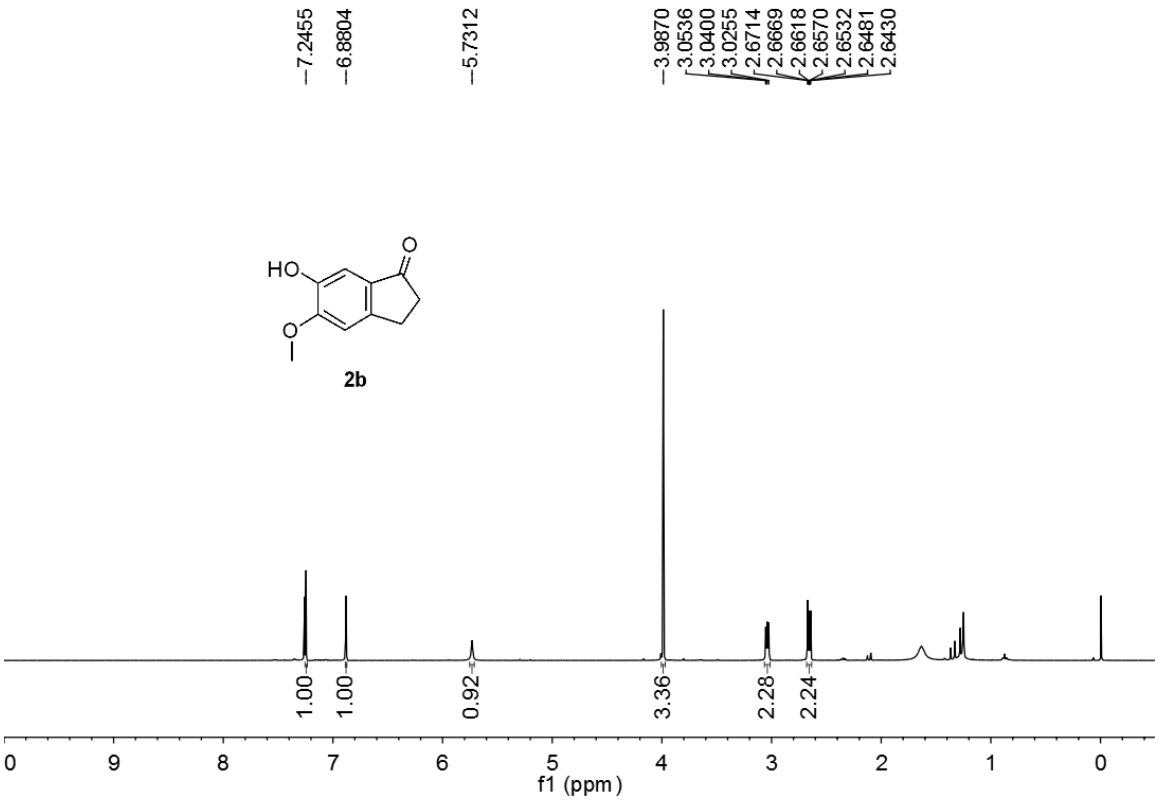
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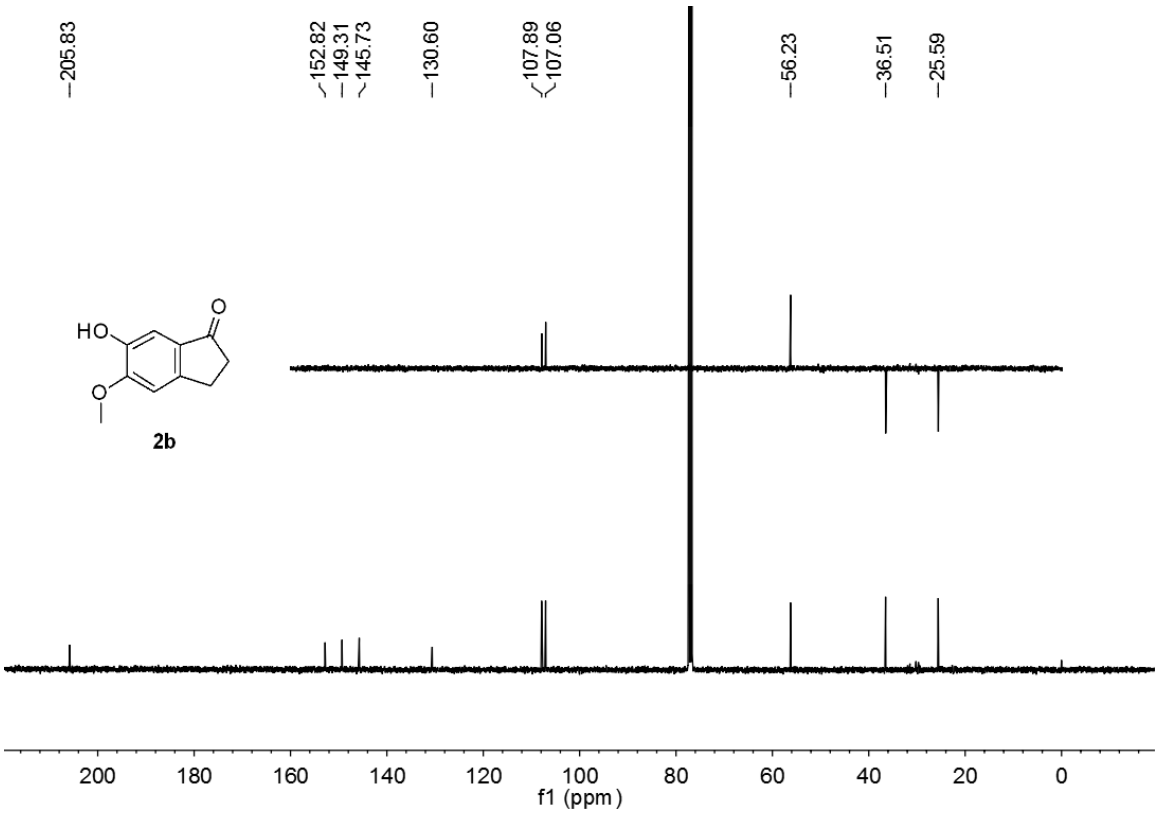
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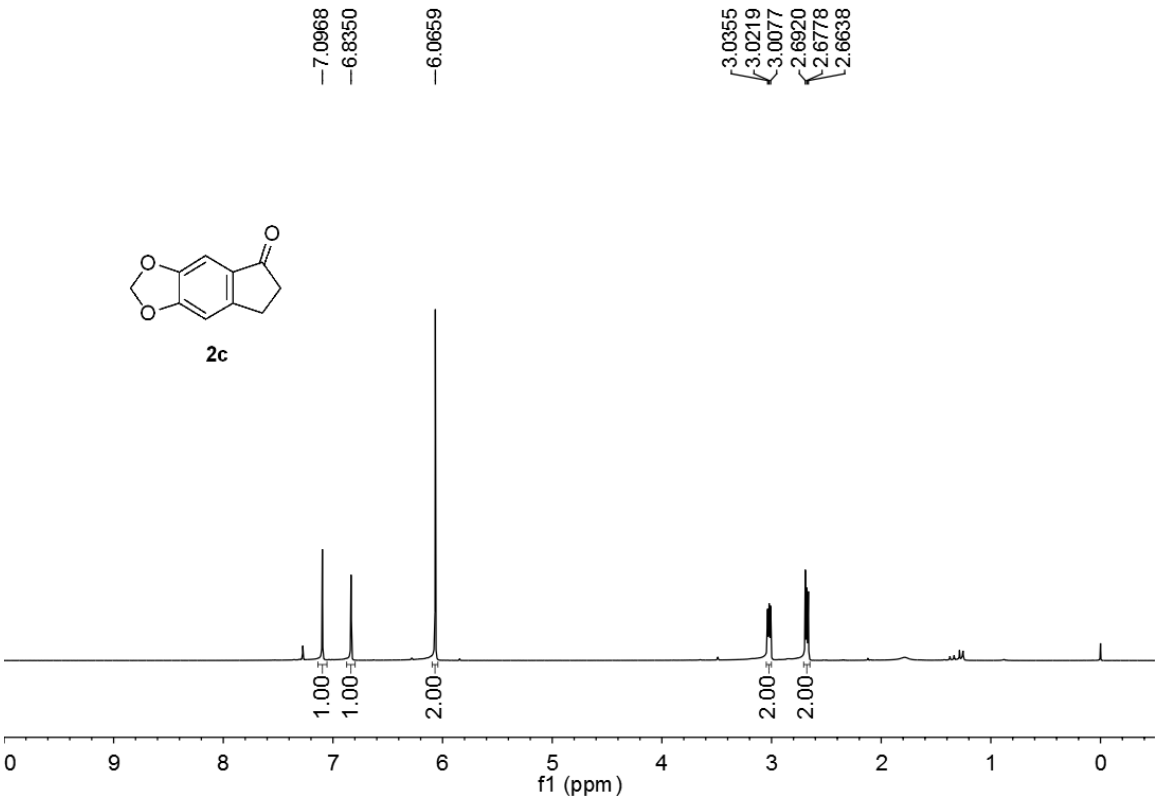
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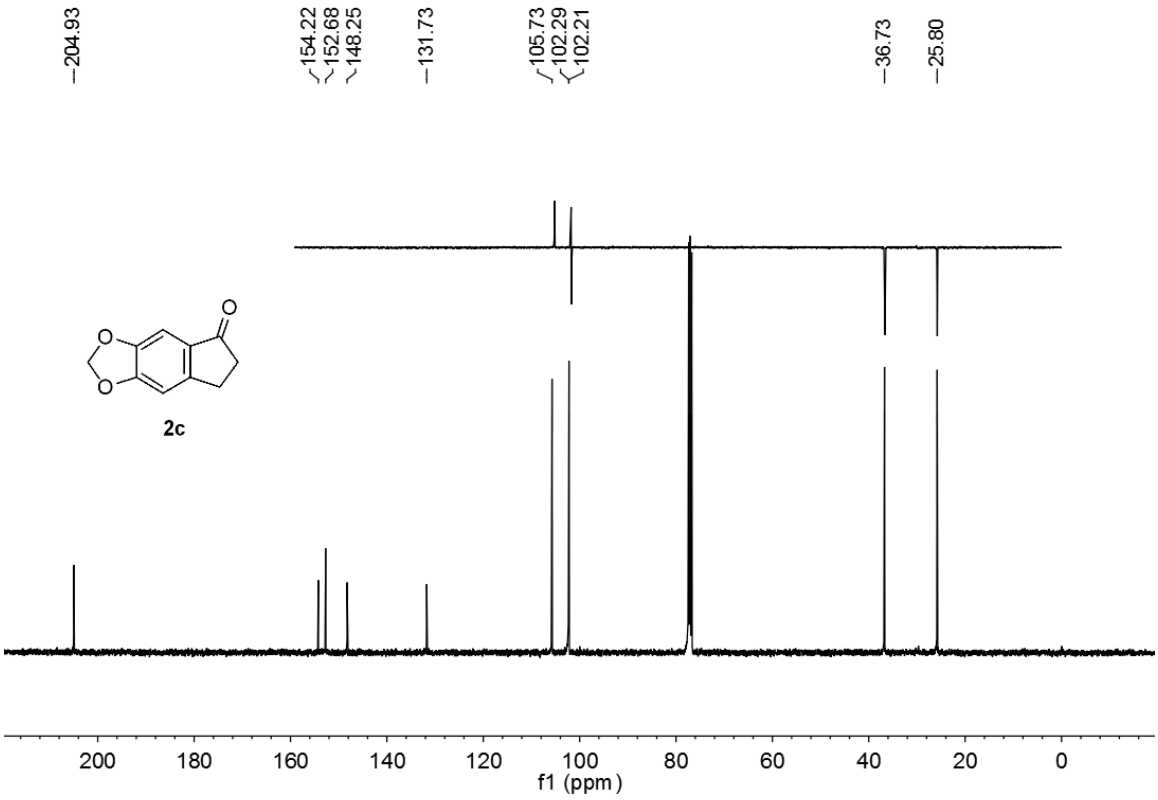
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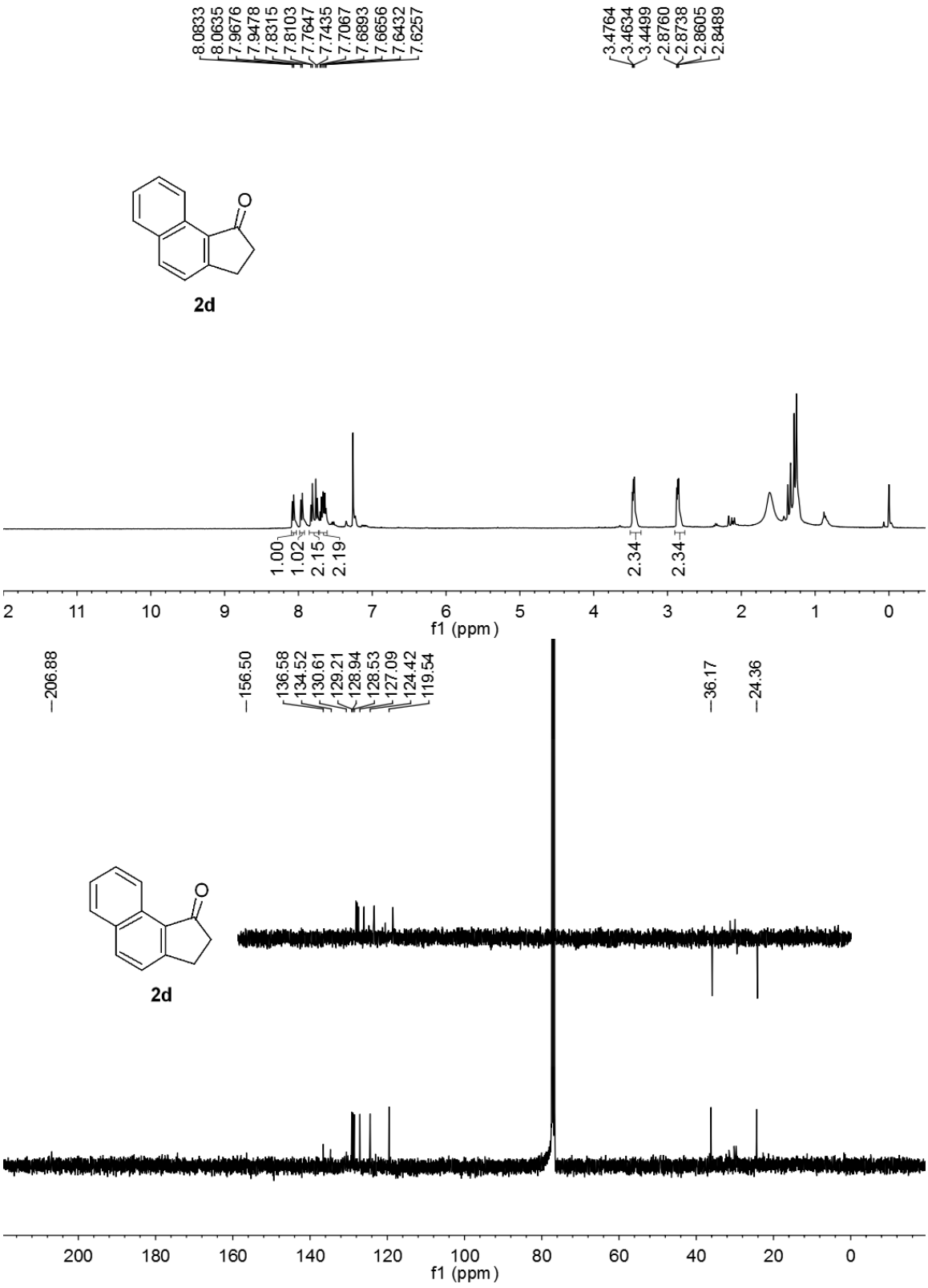
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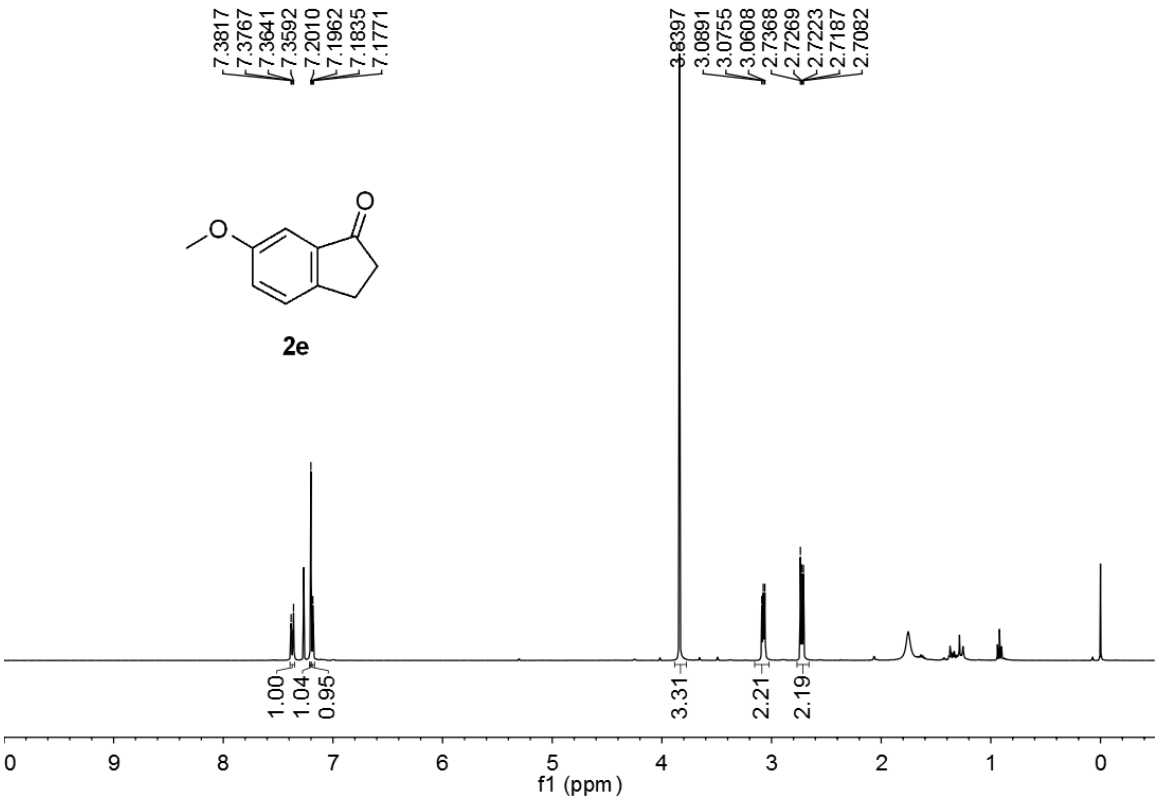
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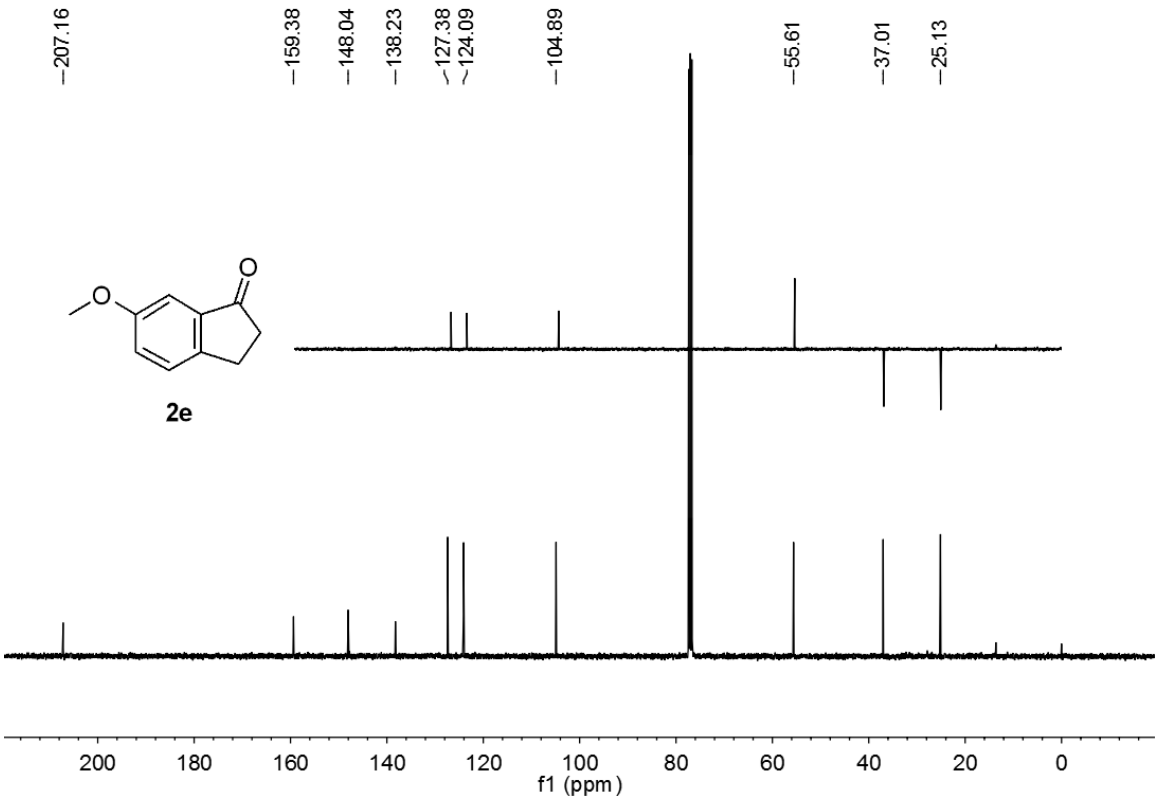
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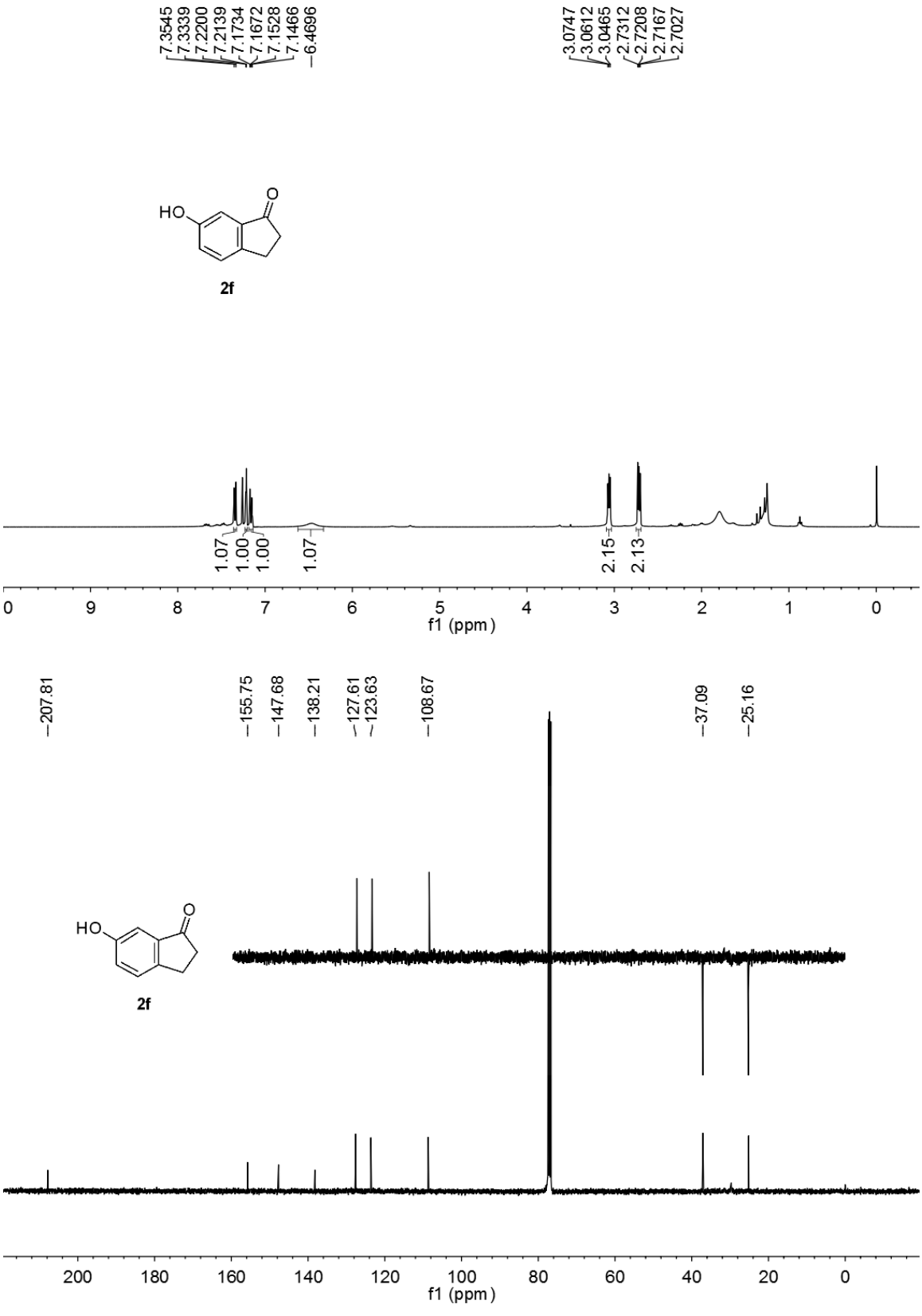
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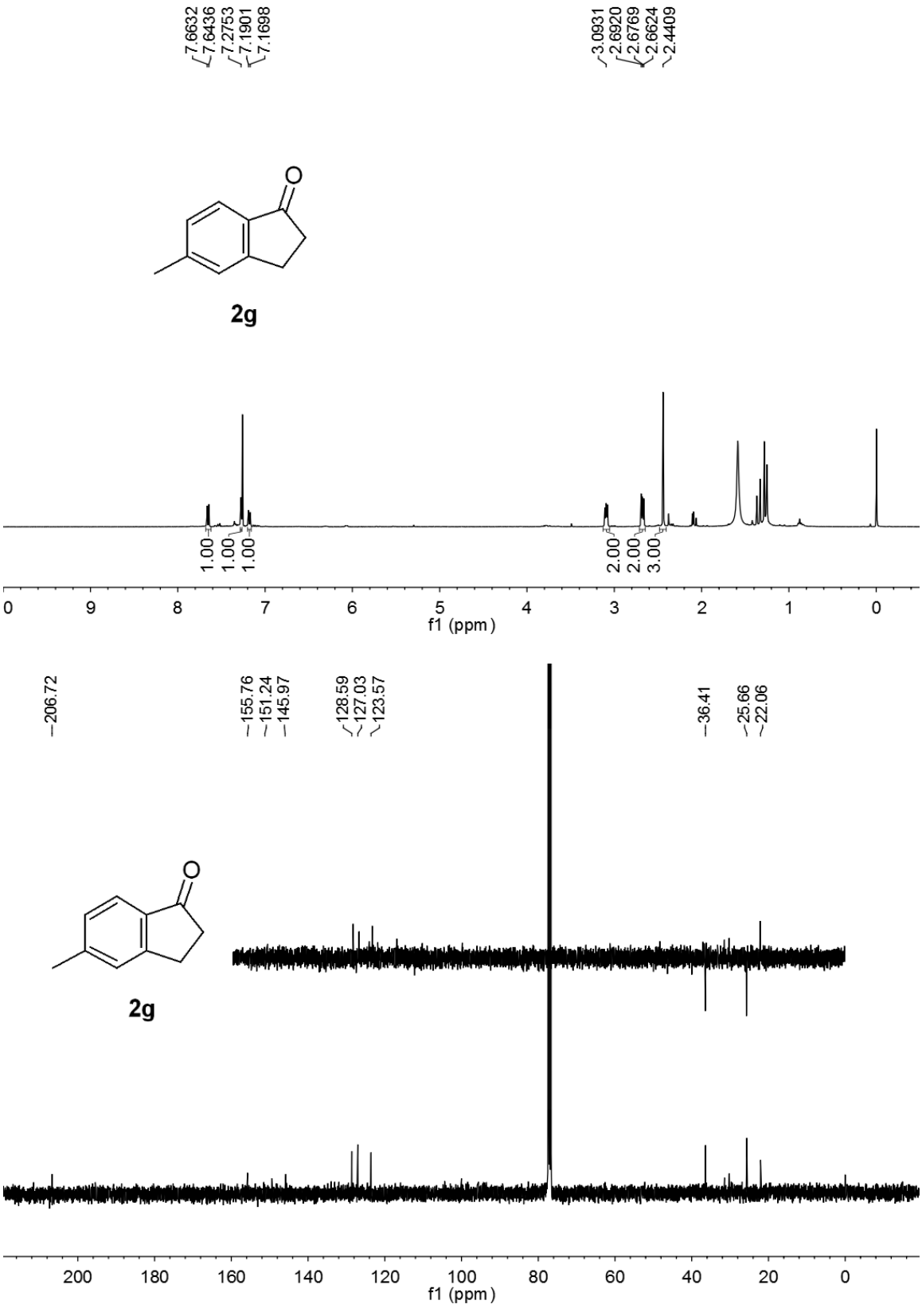
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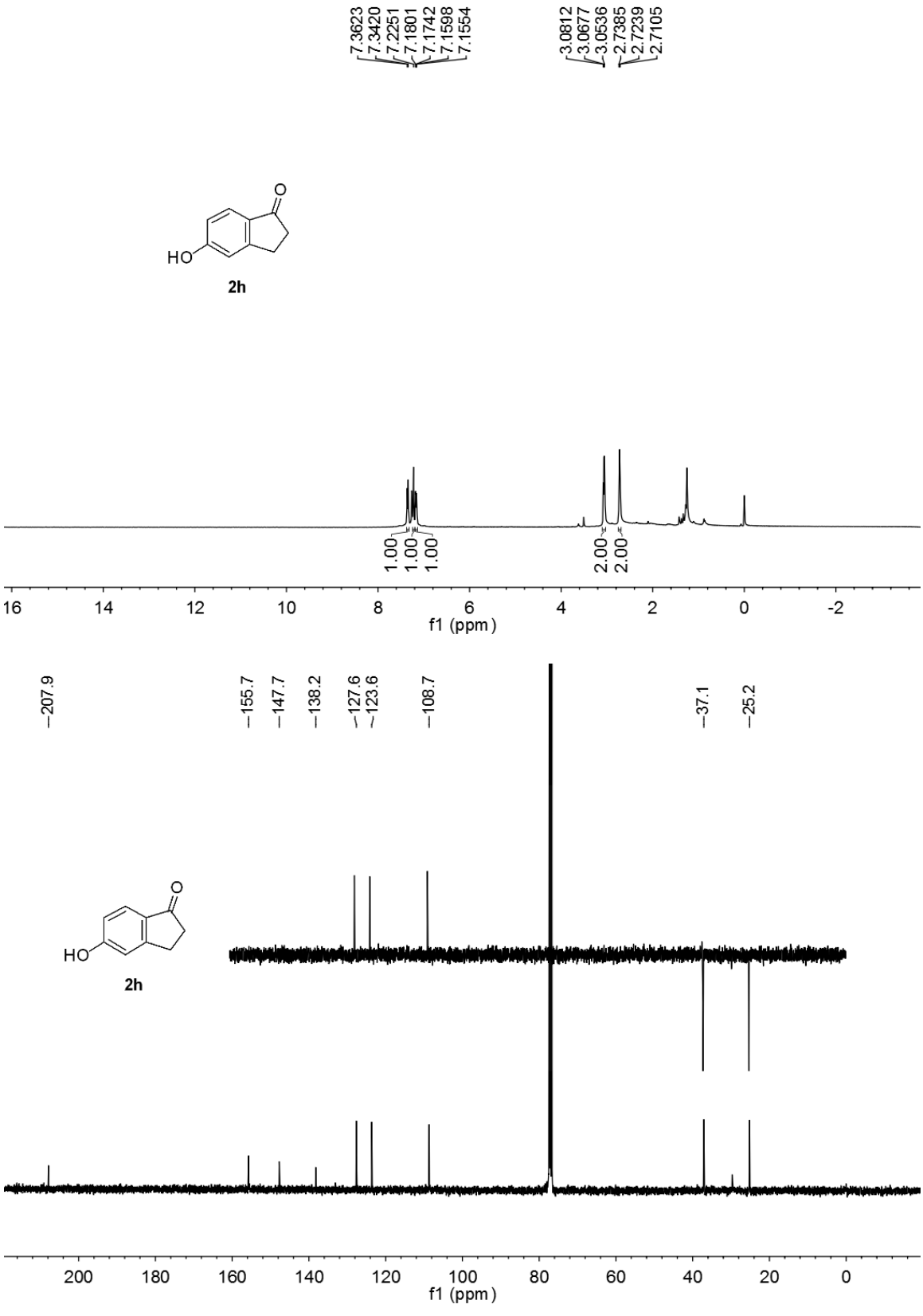
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12
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8
6
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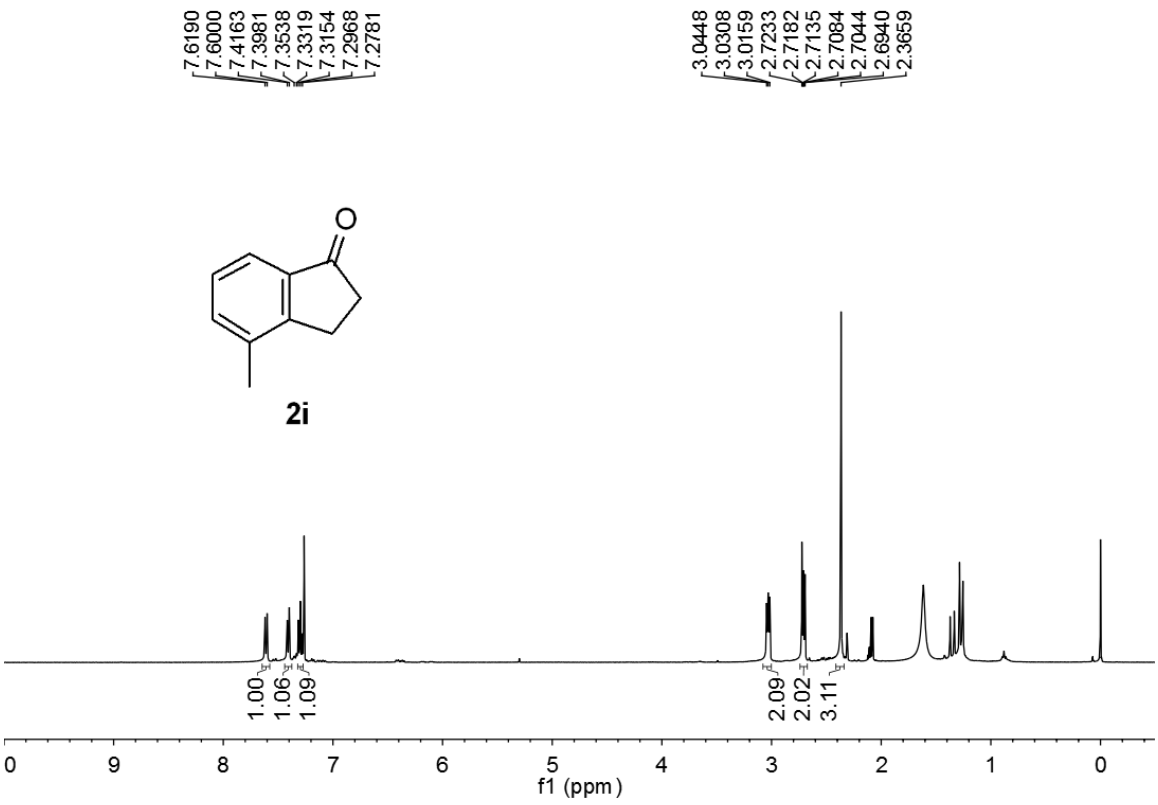
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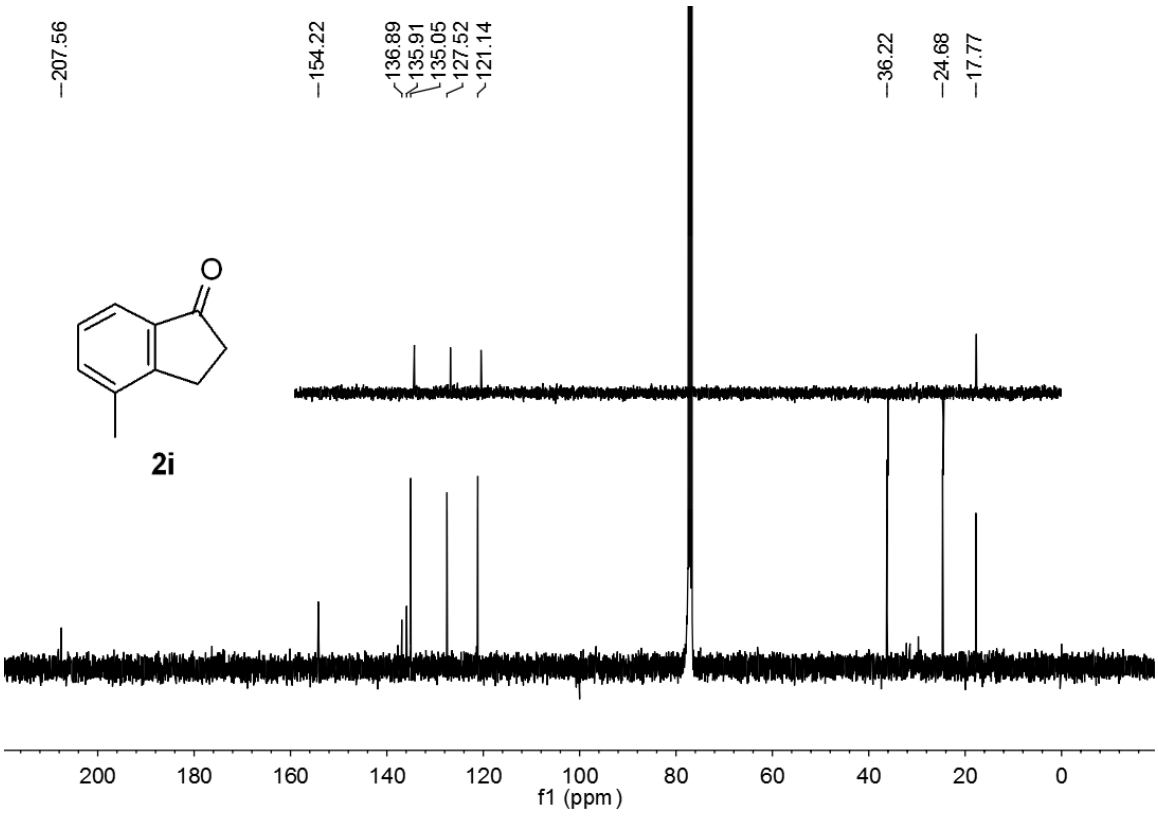
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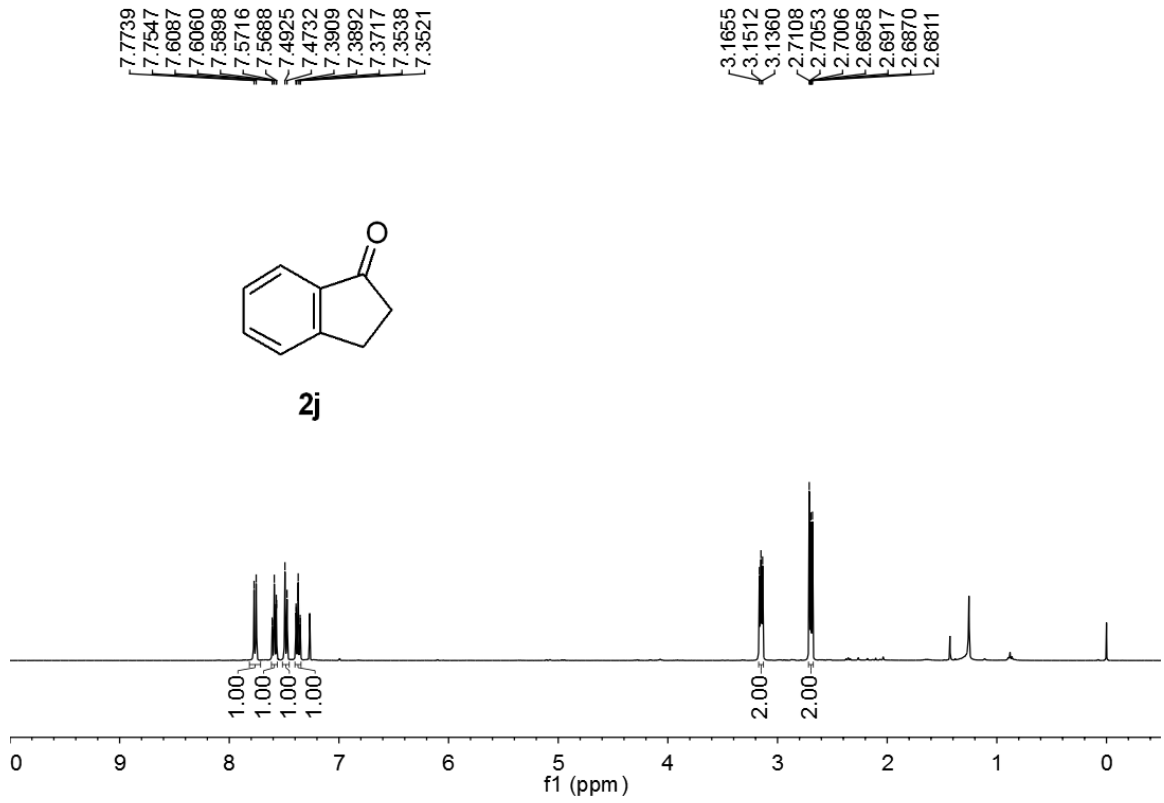
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5
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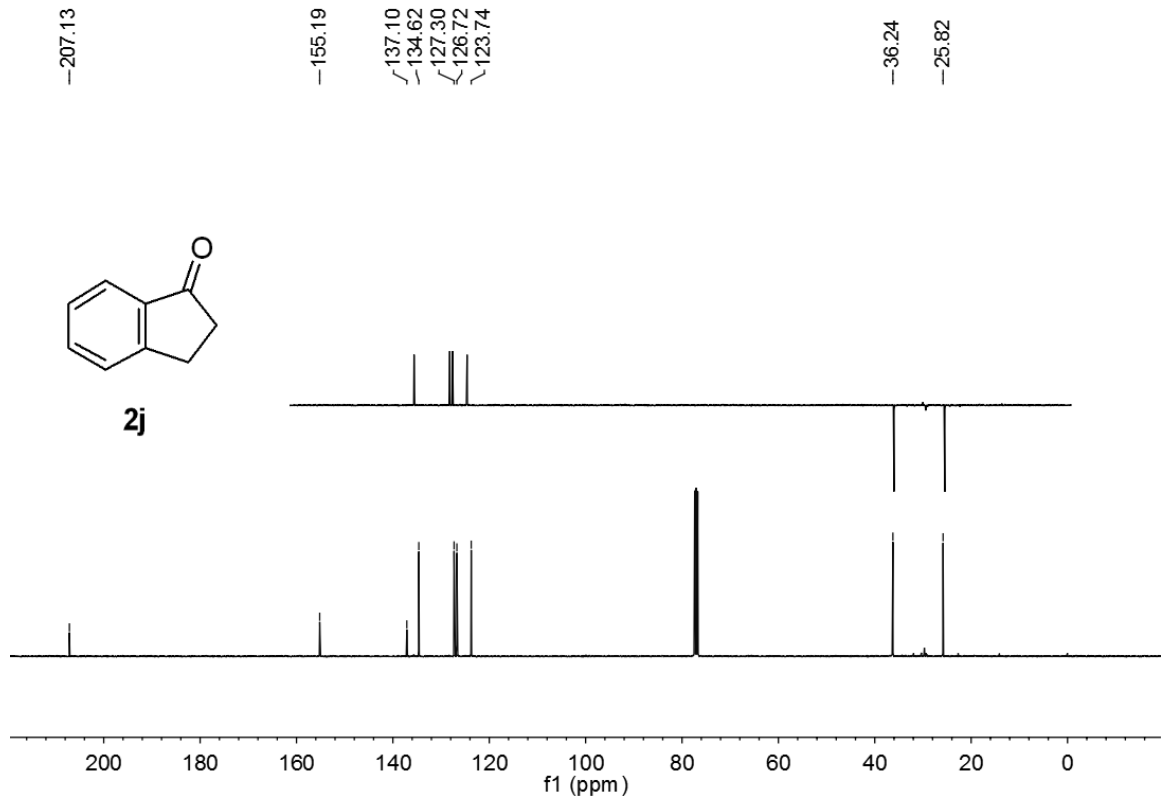
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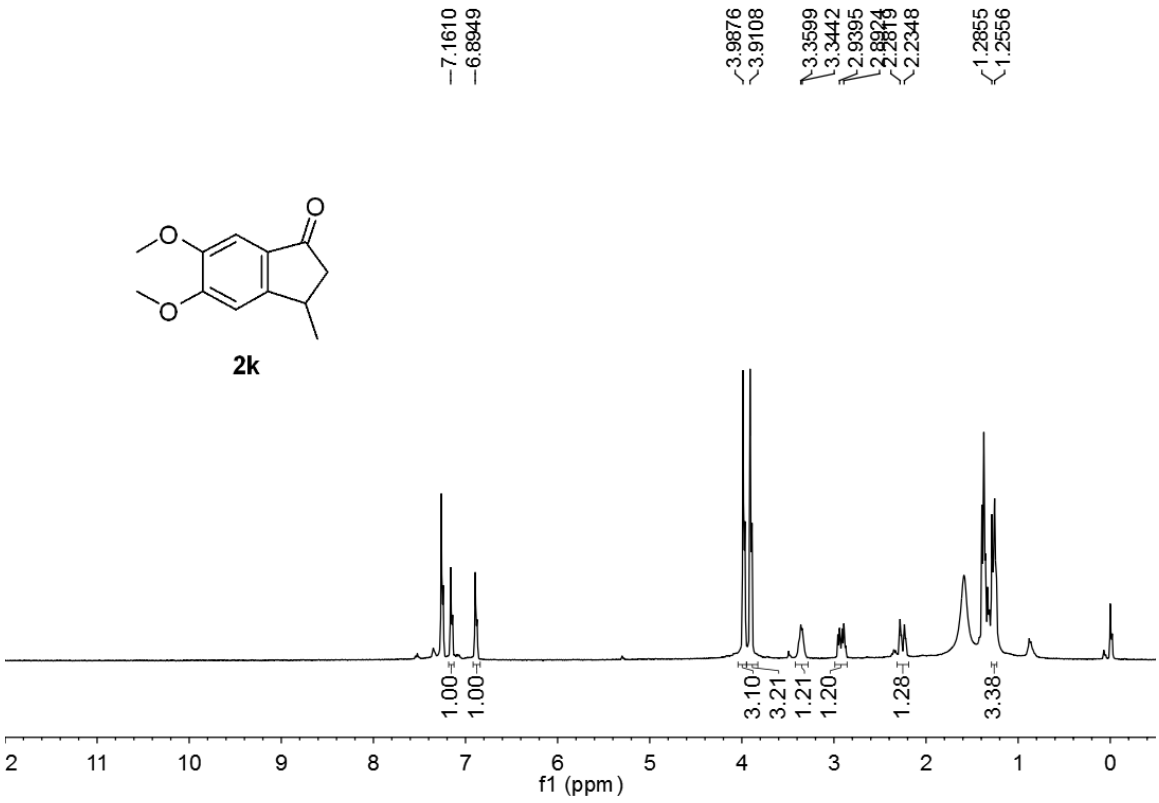
120
100
80
60
40
20
0
f1 (ppm)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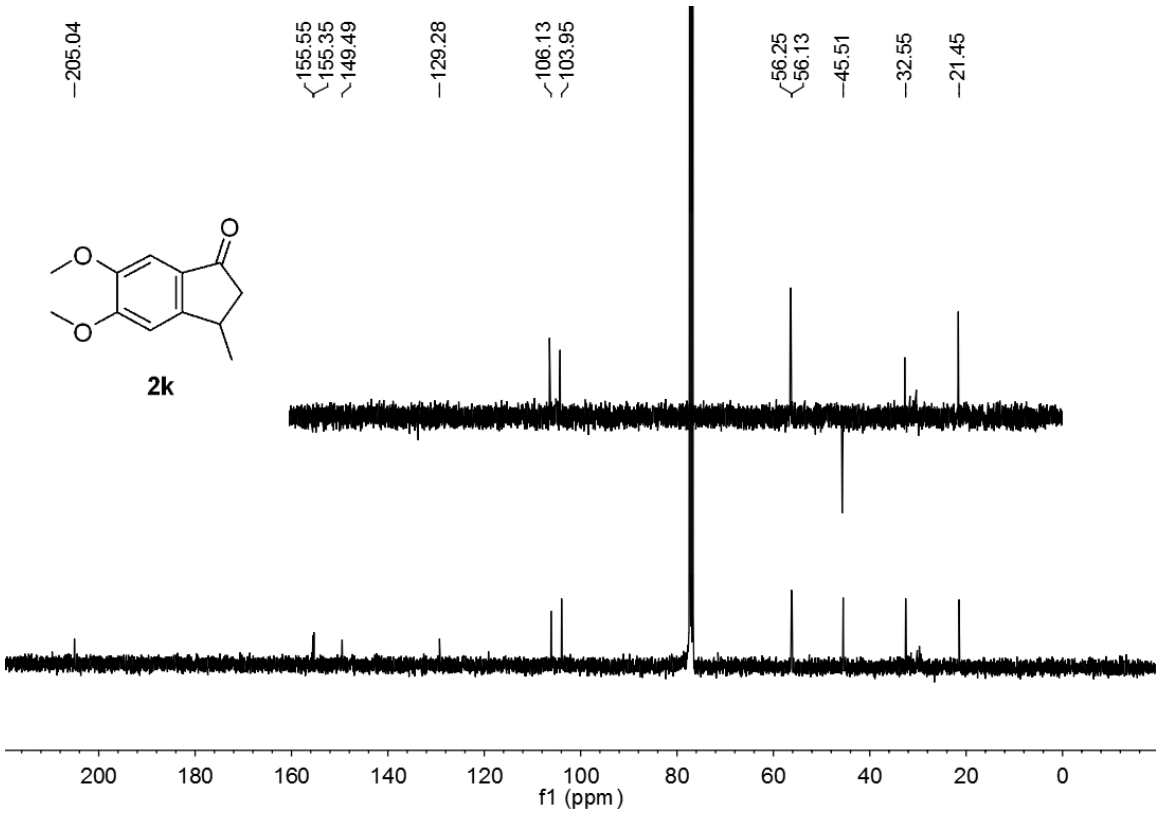
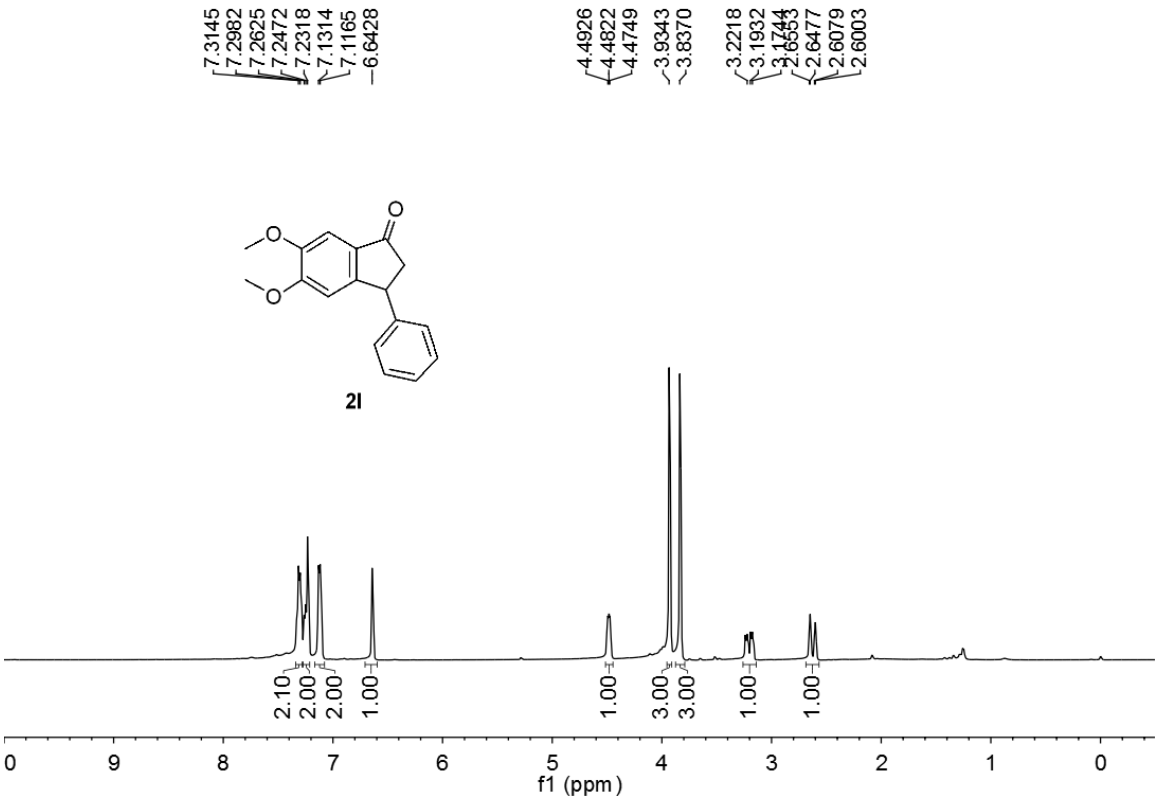
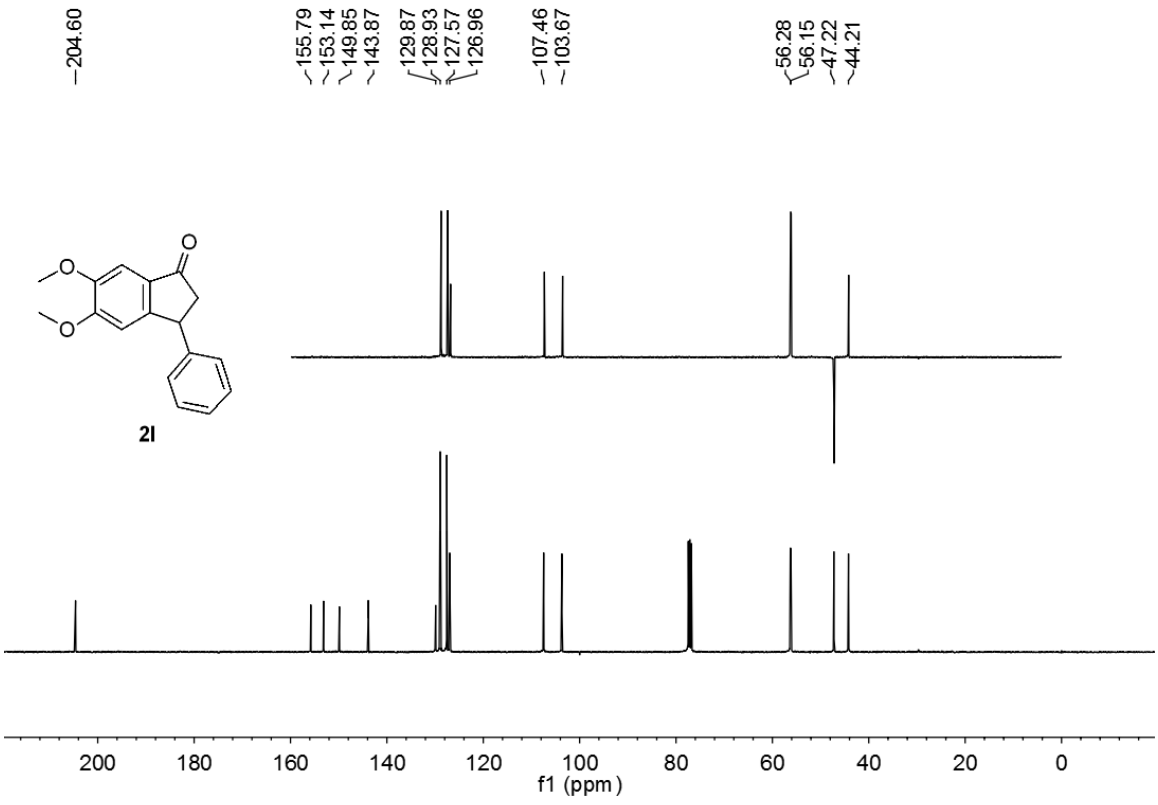
6.8949
3.9876
3.9108
3.3599
3.3442
2.9395
2.2348
1.2855
1.2556
1.00
1.00
3.10
3.21
1.21
1.20
1.28
3.38
f1 (ppm)

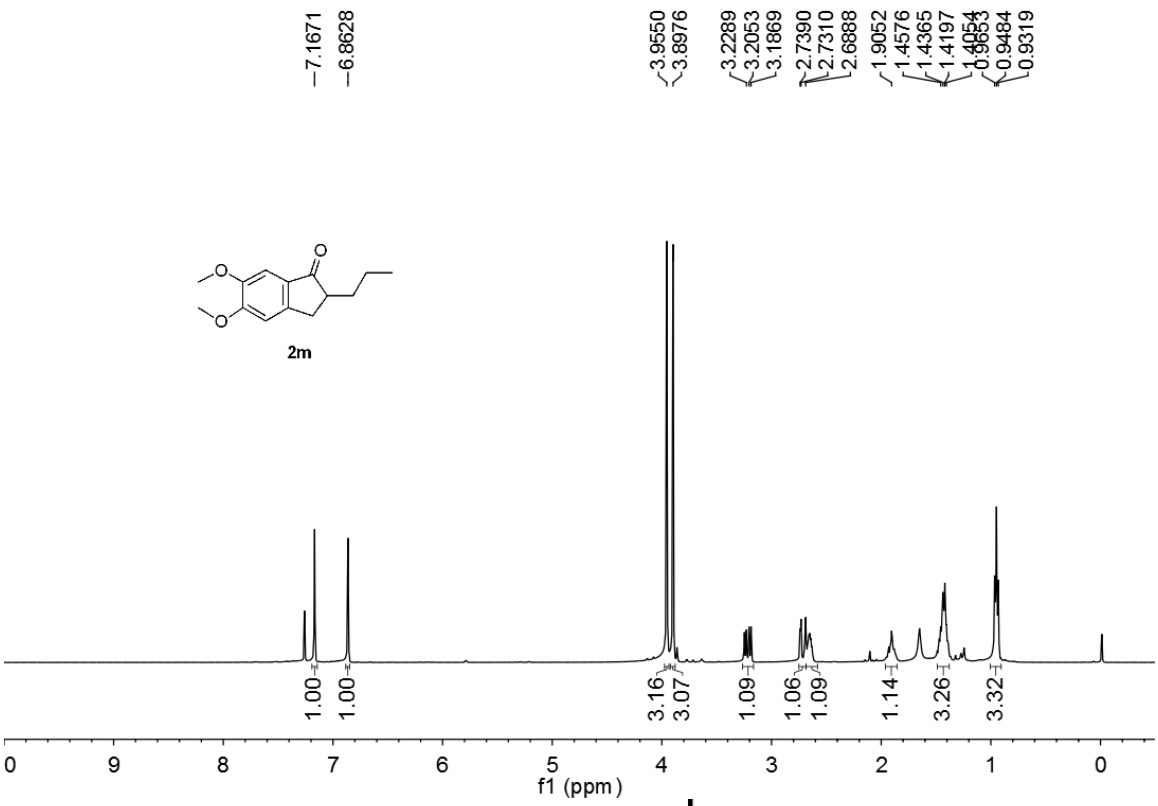
2k


205.04
155.55
155.35
149.49
129.28
106.13
103.95
56.25
56.13
45.51
32.55
21.45
f1 (ppm)

2k


7.3145
7.2982
7.2625
7.2472
7.2318
7.1314
7.1165
6.6428
4.4926
4.4822
4.4749
3.9343
3.8370
3.2218
3.1932
2.6553
2.6477
2.6079
2.6003
2l
2.10
2.00
2.00
1.00
1.00
3.00
3.00
1.00
1.00
f1 (ppm)


204.60
155.79
153.14
149.85
143.87
129.87
128.93
127.57
126.96
107.46
103.67
56.28
56.15
47.22
44.21
2l
f1 (ppm)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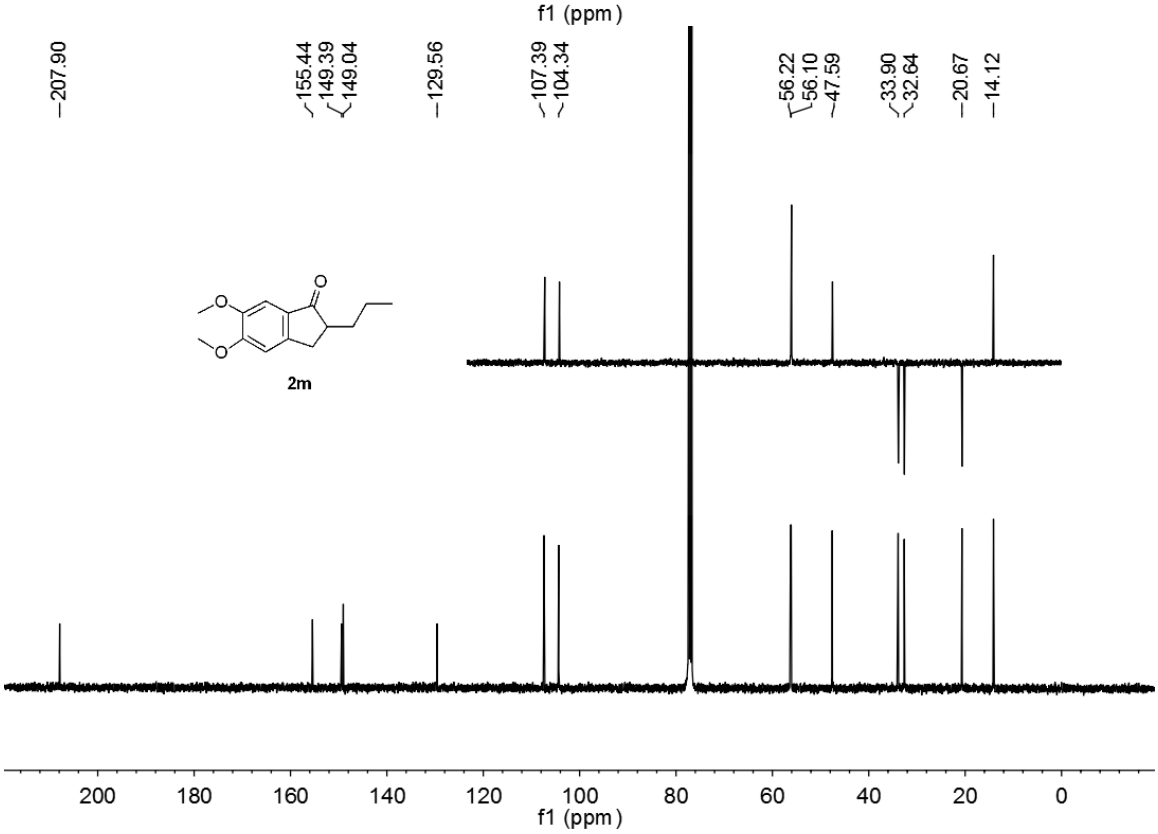
6.8628
3.9550
3.8976
3.2289
3.2053
3.1869
2.7390
2.7310
2.6888
1.9052
1.4576
1.4365
1.4197
0.9653
0.9484
0.9319
2m
1.00
1.00
3.16
3.07
1.09
1.06
1.09
1.14
3.26
3.32
f1 (ppm)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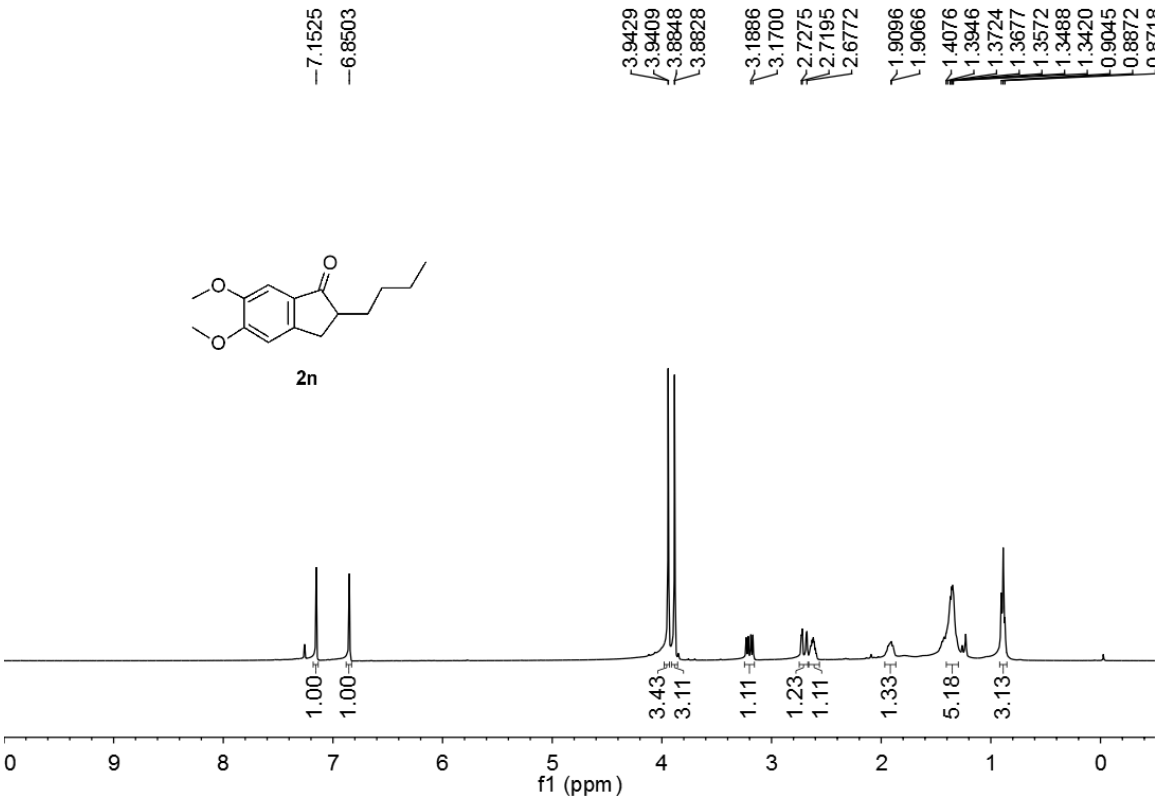
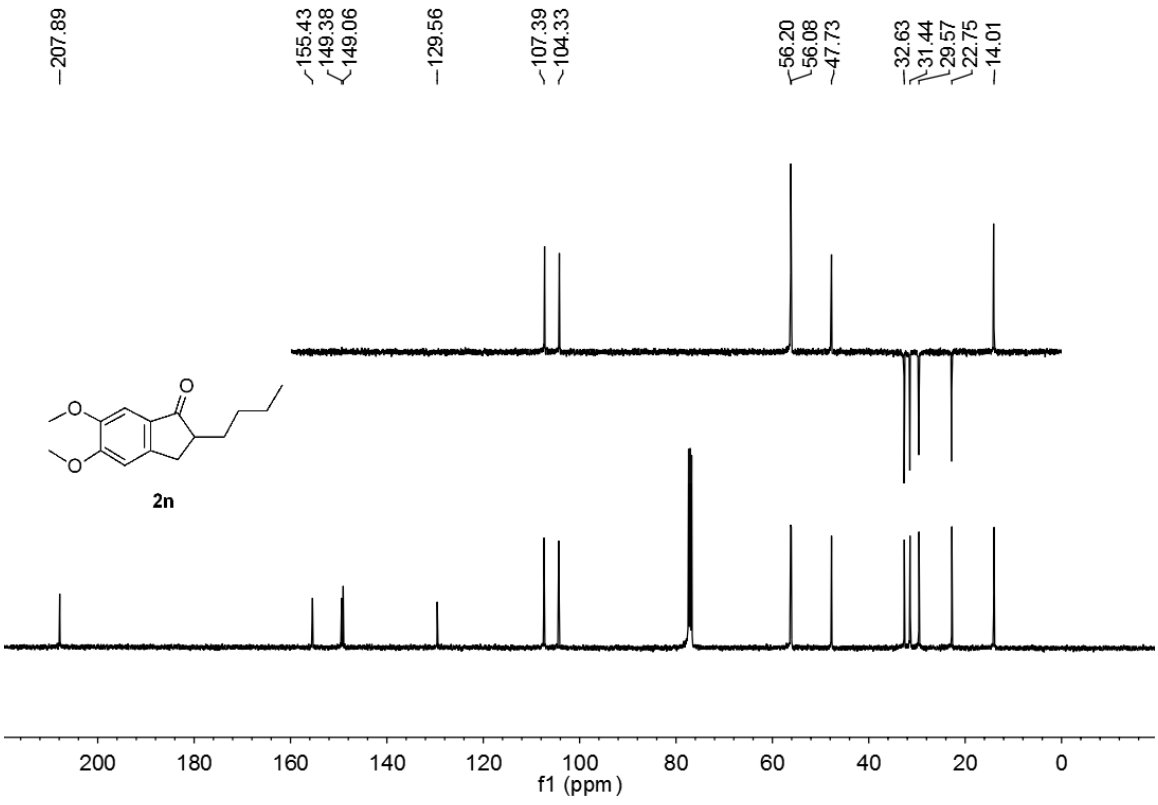
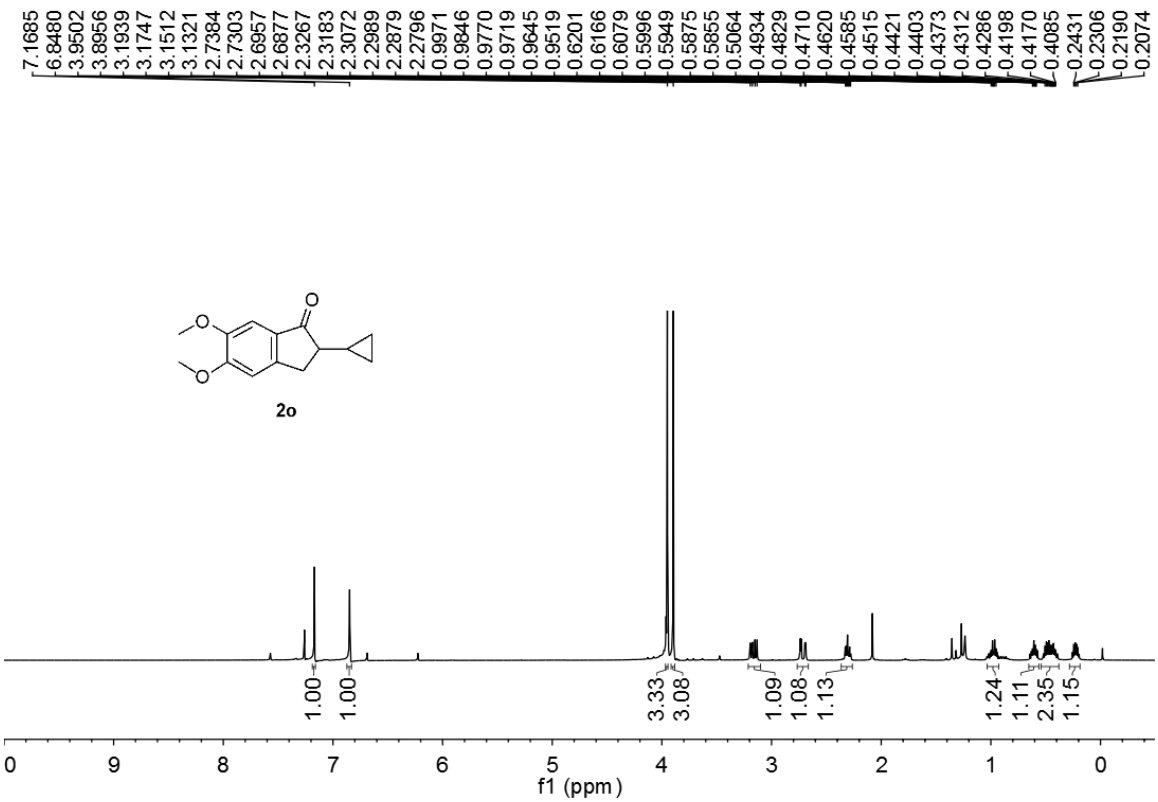
155.44
149.39
149.04
129.56
107.39
104.34
56.22
56.10
47.59
33.90
32.64
20.67
14.12
2m
f1 (ppm)


7.1525
6.8503
3.9429
3.9409
3.8848
3.8828
3.1886
3.1700
2.7275
2.7195
2.6772
1.9096
1.9066
1.4076
1.3946
1.3724
1.3677
1.3572
1.3488
1.3420
0.9045
0.8872
2n
1.00
1.00
3.43
3.11
1.11
1.23
1.11
1.33
5.18
3.13
f1 (ppm)


207.89
155.43
149.38
149.06
129.56
107.39
104.33
56.20
56.08
47.73
32.63
31.44
29.57
22.75
14.01
2n
f1 (ppm)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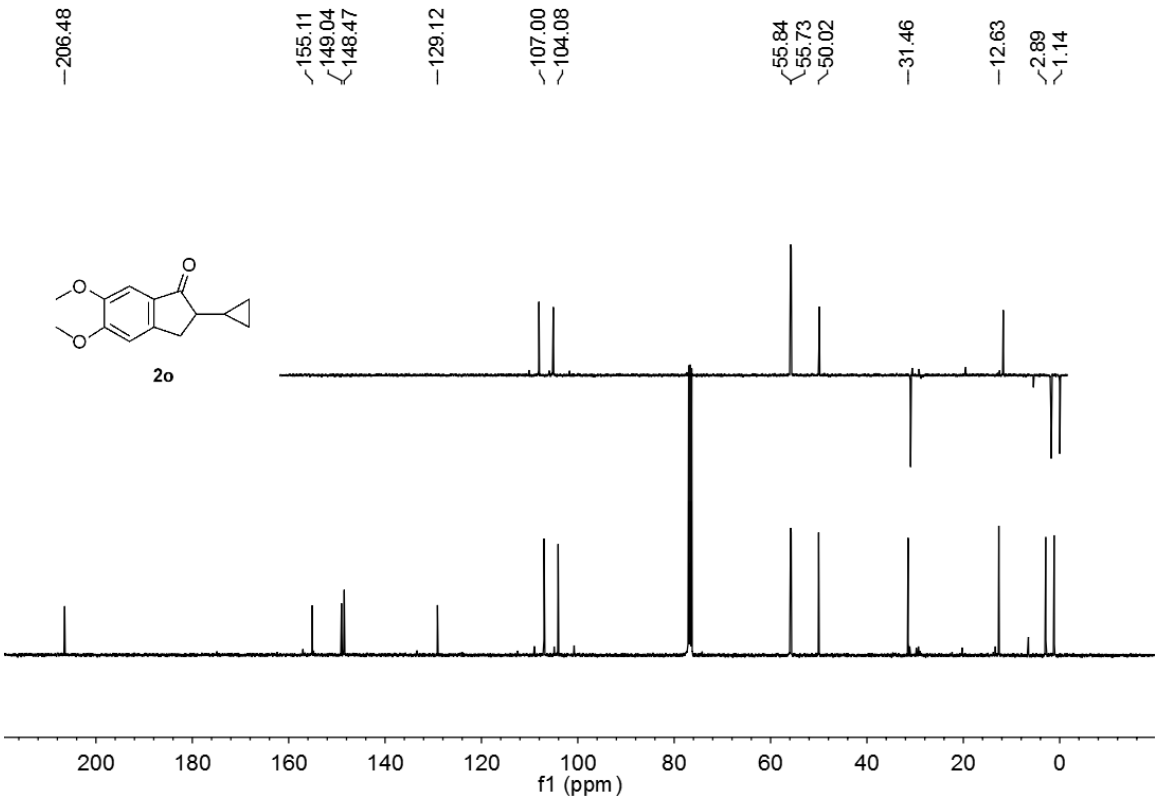
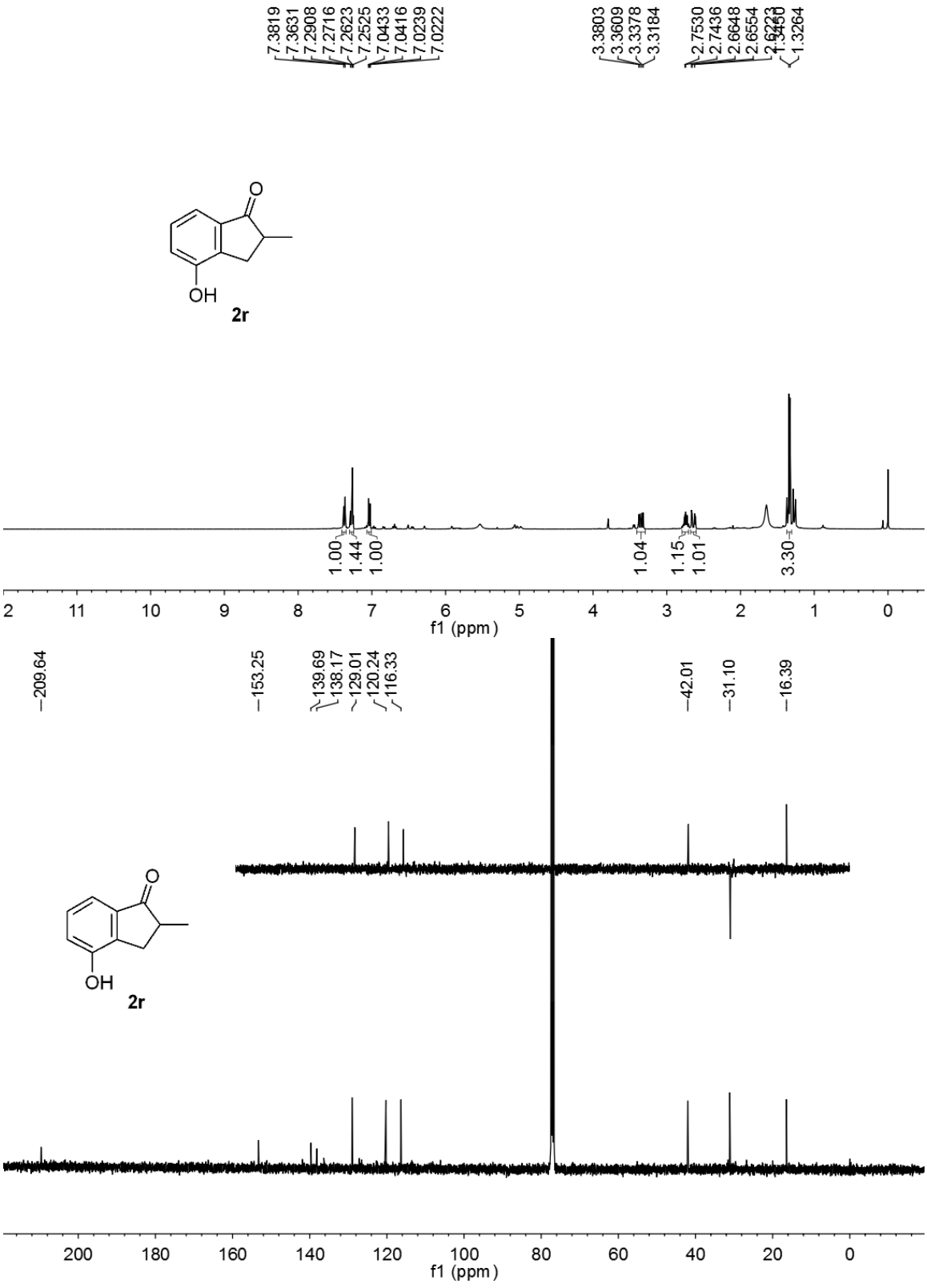
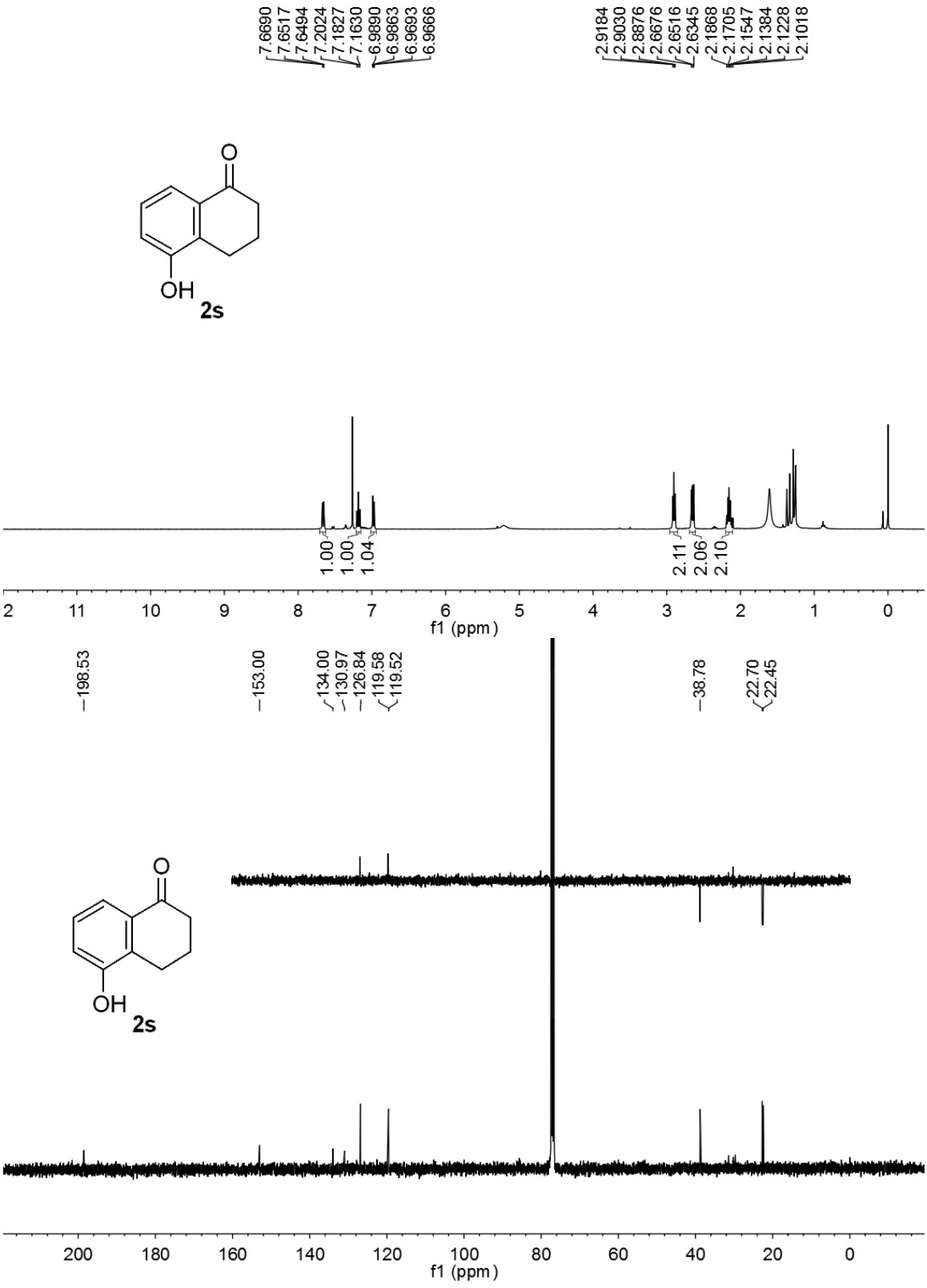
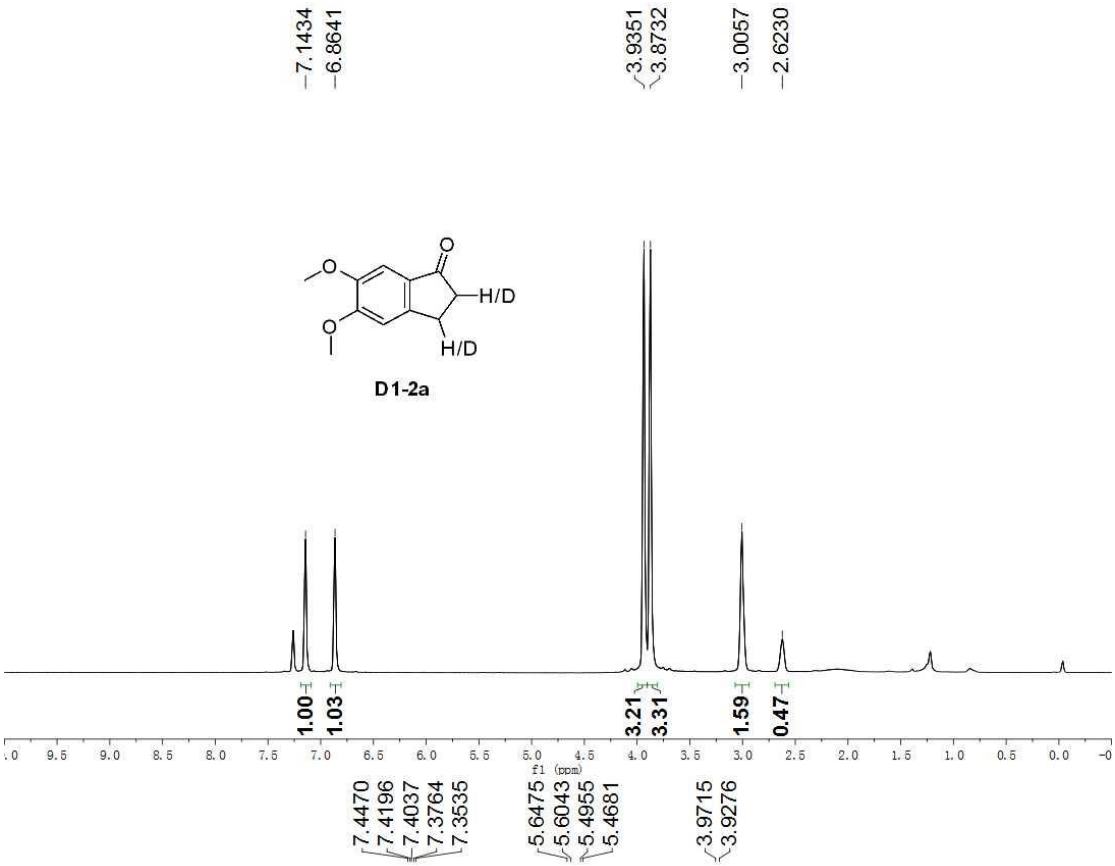
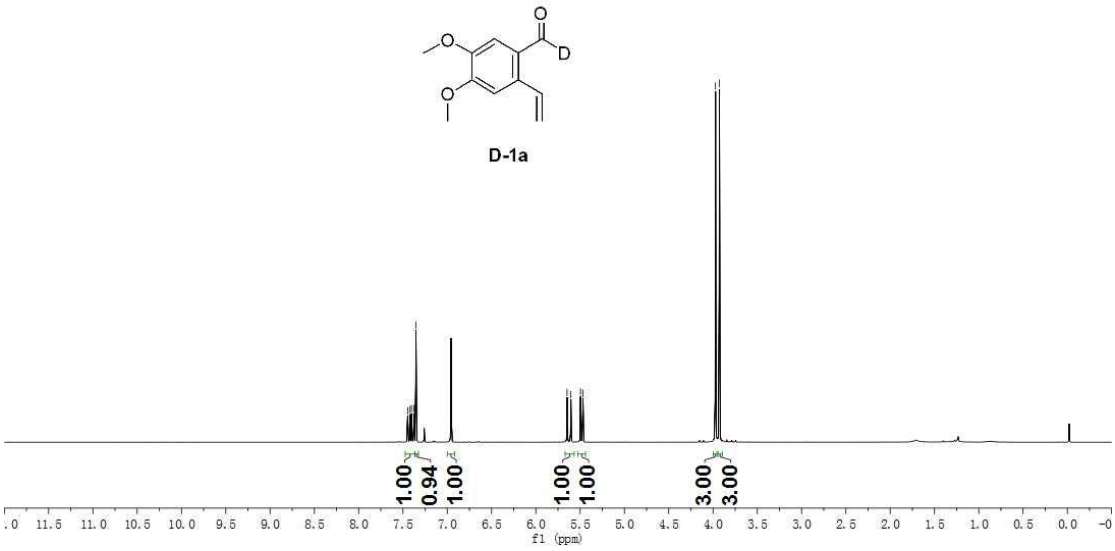
6.8480
3.9502
3.8956
3.1939
3.1747
3.1512
3.1321
2.7384
2.7303
2.6957
2.6877
2.3267
2.3183
2.3072
2.2989
2.2879
2.2796
0.9971
0.9846
0.9770
0.9719
0.9645
0.9519
0.6201
0.6166
0.6079
0.5996
0.5949
0.5875
0.5855
0.5064
0.4934
0.4829
0.4710
0.4620
0.4585
0.4515
0.4421
0.4403
0.4373
0.4312
0.4286
0.4198
0.4170
0.4085
0.2431
0.2306
0.2190
0.2074
2o
1.00
1.00
3.33
3.08
1.09
1.08
1.13
1.24
1.11
2.35
1.15
0
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

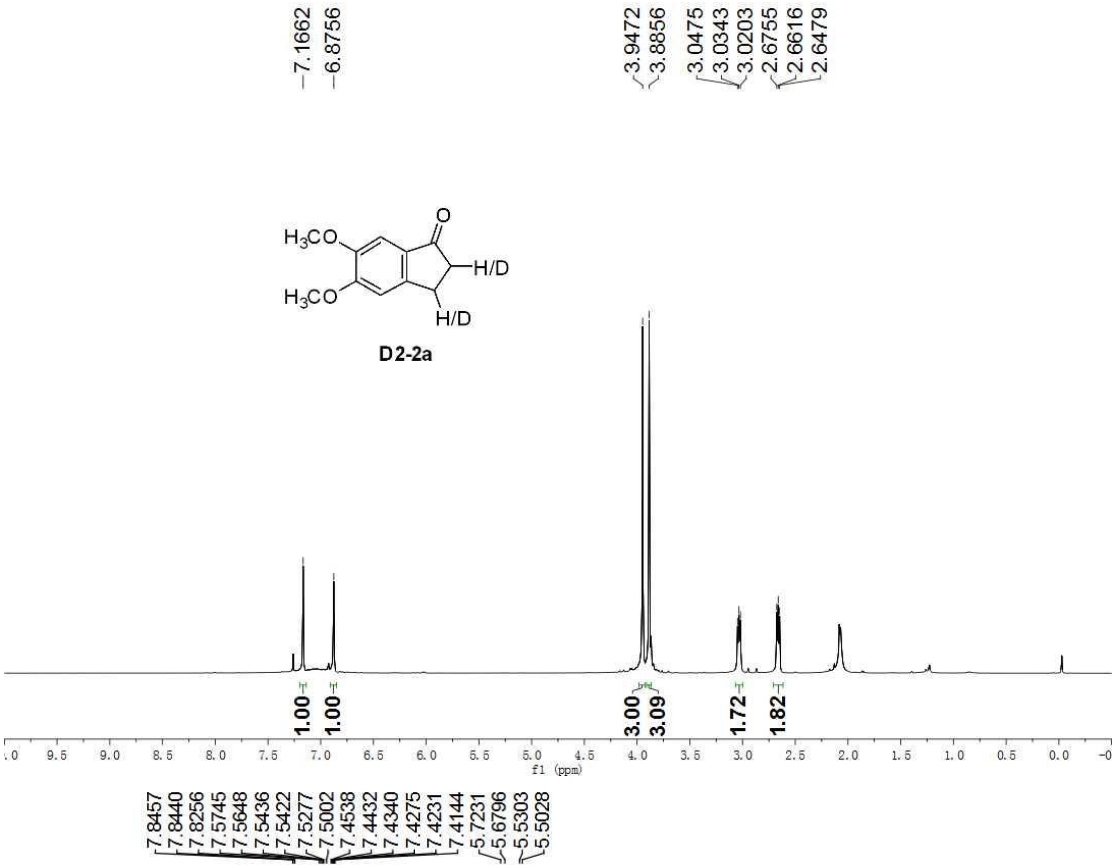

206.48
155.11
149.04
148.47
129.12
107.00
104.08
55.84
55.73
50.02
31.46
12.63
2.89
1.14
2o
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


7.3819
7.3631
7.2908
7.2716
7.2623
7.2525
7.0433
7.0416
7.0239
7.0222
3.3803
3.3609
3.3378
3.3184
2.7530
2.7436
2.6648
2.6554
1.3450
1.3264
O
OH
2r
1.00
1.44
1.00
1.04
1.15
1.01
3.30
f1 (ppm)
209.64
153.25
139.69
138.17
129.01
120.24
116.33
42.01
31.10
16.39
O
OH
2r
f1 (ppm)


7.6690
7.6517
7.6494
7.2024
7.1827
7.1630
6.9890
6.9863
6.9693
6.9666
2.9184
2.9030
2.8876
2.6676
2.6516
2.6345
2.1868
2.1705
2.1547
2.1384
2.1228
2.1018
O
OH
2s
1.00
1.00
1.04
2.11
2.06
2.10
f1 (ppm)
198.53
153.00
134.00
130.97
126.84
119.58
119.52
38.78
22.70
22.45
O
OH
2s
f1 (ppm)

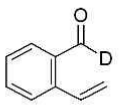

7.1434
6.8641
3.9351
3.8732
3.0057
2.6230
O
O
O
H/D
H/D
D1-2a
1.00
1.03
3.21
3.31
1.59
0.47
f1 (ppm)
7.4470
7.4196
7.4037
7.3764
7.3535
5.6475
5.6043
5.4955
5.4681
3.9715
3.9276


O
O
O
D
D-1a
1.00
0.94
1.00
1.00
1.00
3.00
3.00
f1 (ppm)

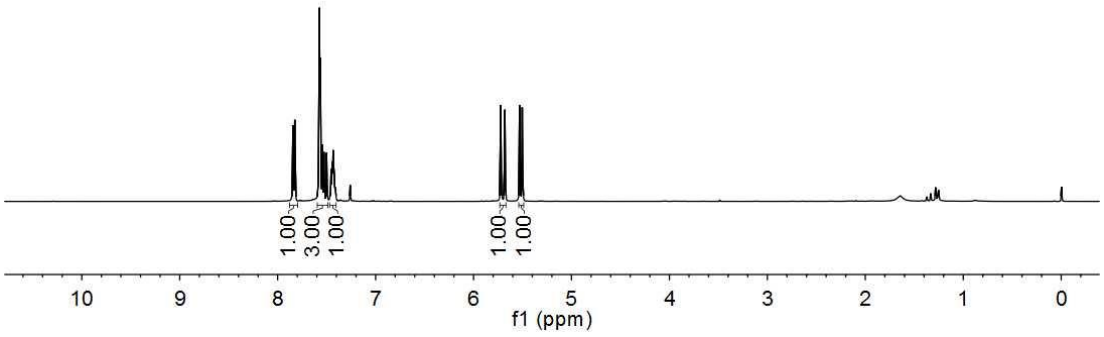

7.1662
6.8756
3.9472
3.8856
3.0475
3.0343
3.0203
2.6755
2.6616
2.6479
O
H3CO
H3CO
H/D
H/D
1.00
1.00
3.00
3.09
1.72
1.82
f1 (ppm)

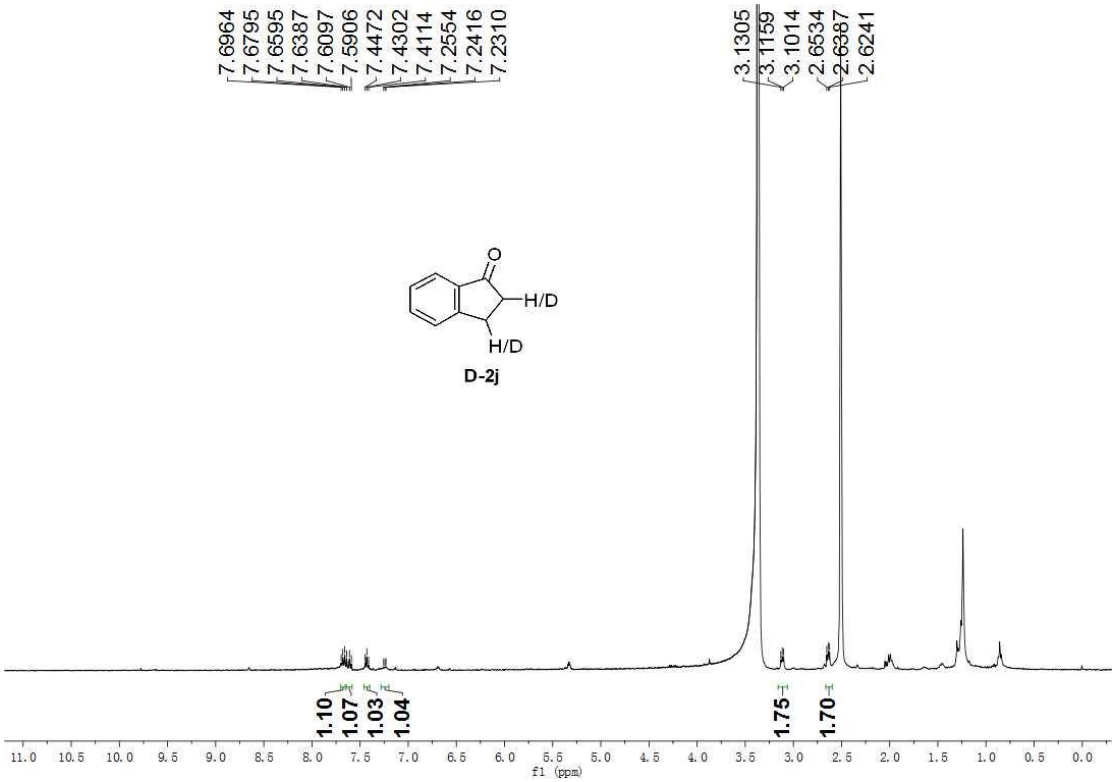
D2-2a

7.8457
7.8440
7.8256
7.5745
7.5648
7.5436
7.5422
7.5277
7.5002
7.4538
7.4432
7.4340
7.4275
7.4231
7.4144
5.7231
5.6796
5.5303
5.5028


O
D

D-1j


1.00
3.00
1.00
1.00
1.00
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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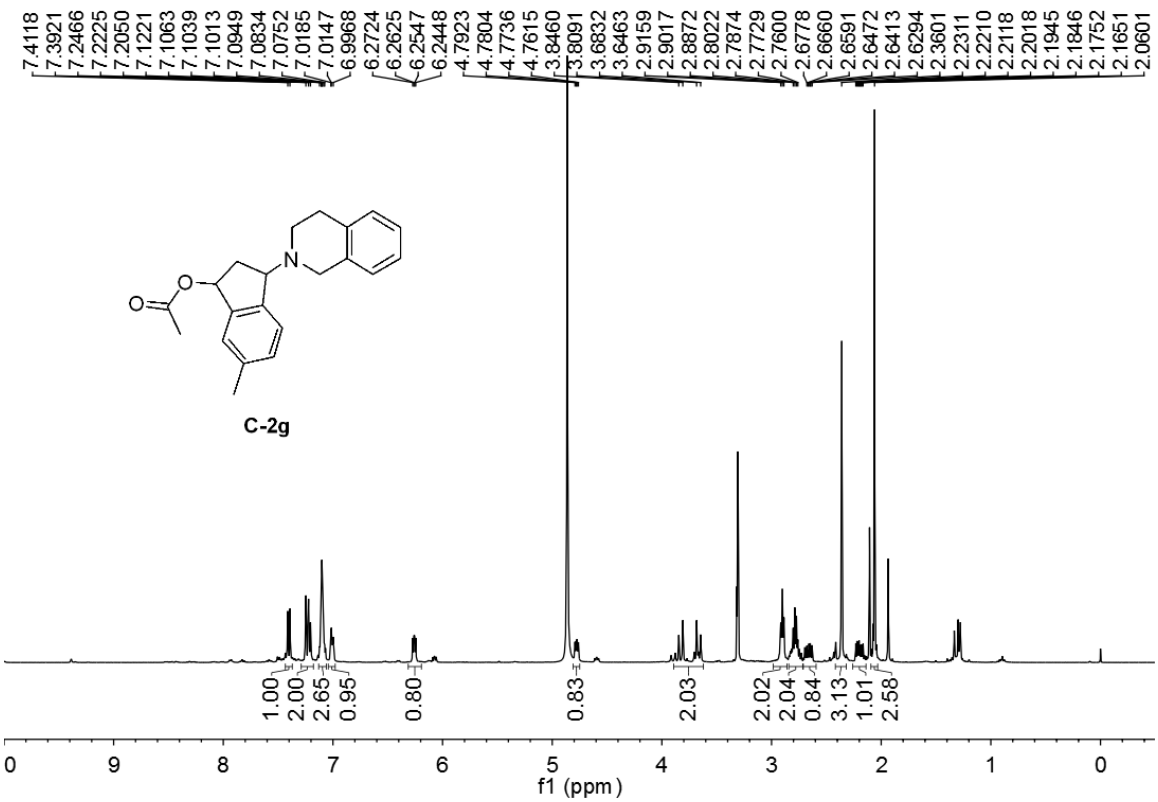
7.6795
7.6595
7.6387
7.6097
7.5906
7.4472
7.4302
7.4114
7.2554
7.2416
7.2310
3.1305
3.1159
3.1014
2.6534
2.6387
2.6241
O
H/D
H/D
D-2j
1.10
1.07
1.03
1.04
1.75
1.70
f1 (ppm)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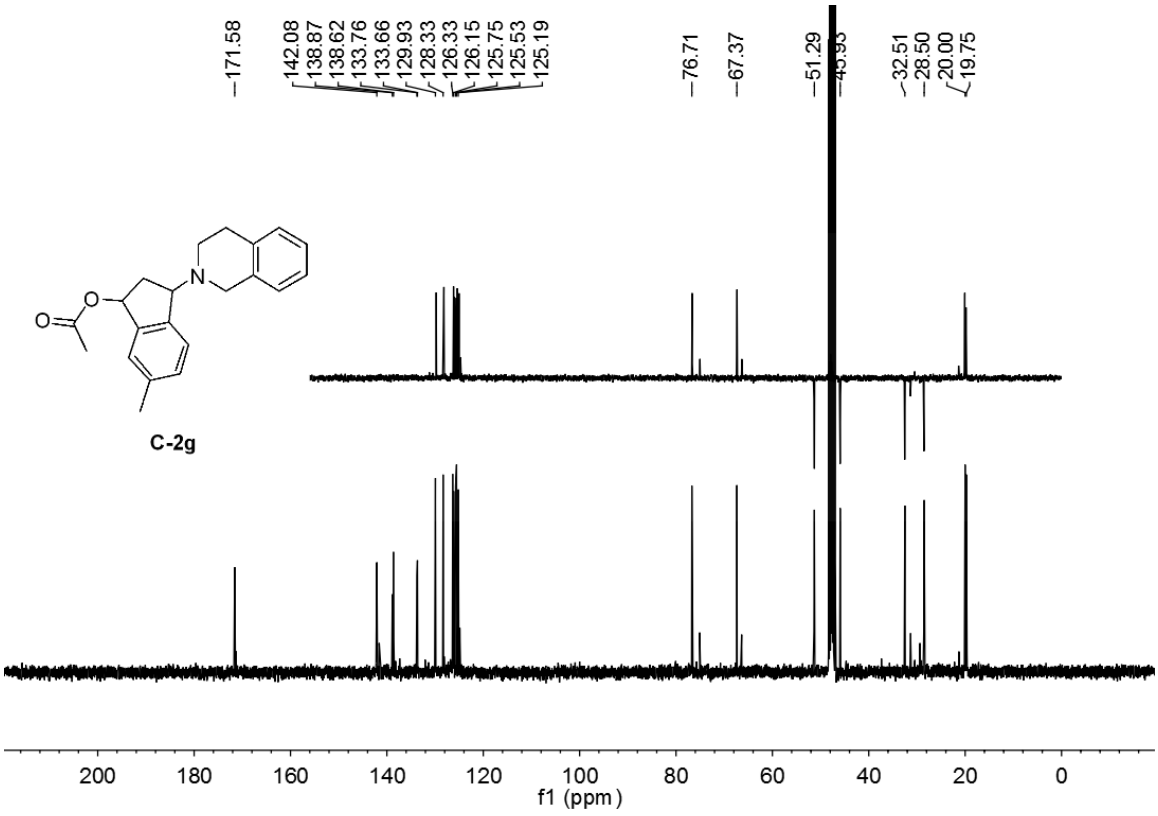
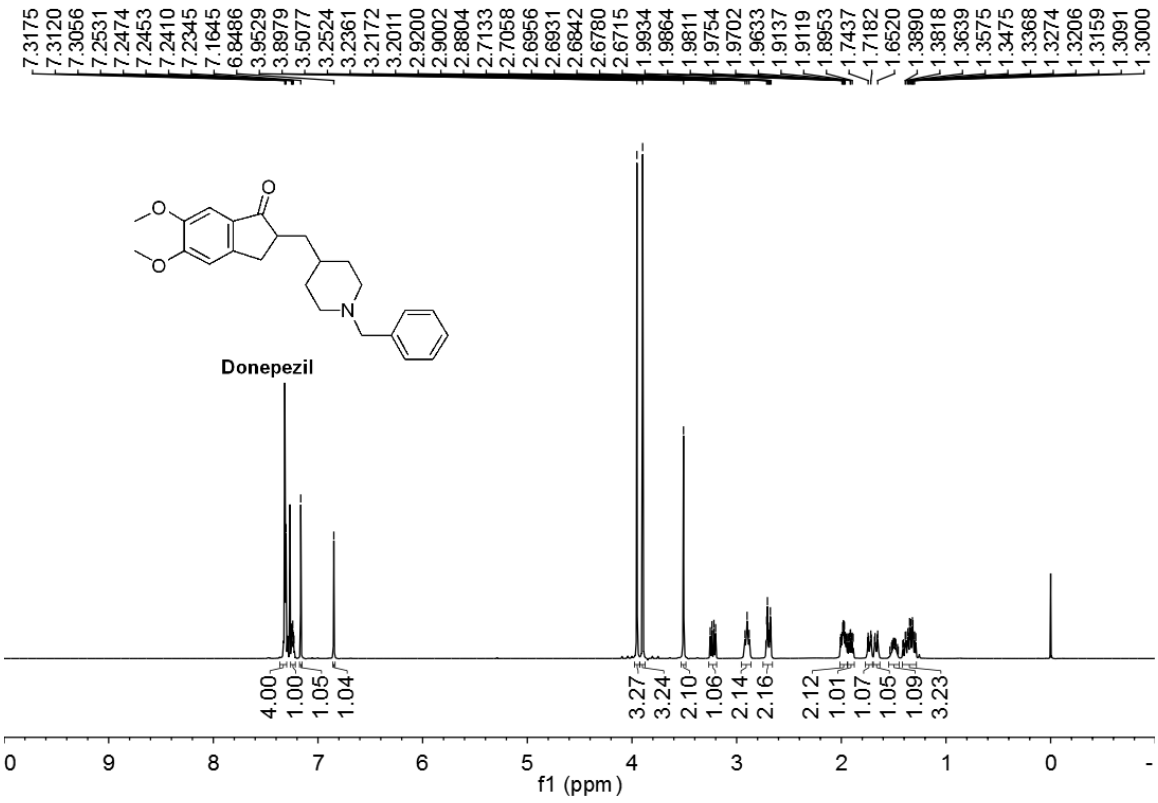
7.3921
7.2466
7.2225
7.2050
7.1221
7.1063
7.1039
7.1013
7.0949
7.0834
7.0752
7.0185
7.0147
6.9968
6.2724
6.2625
6.2547
6.2448
4.7923
4.7804
4.7736
4.7615
3.8460
3.8091
3.6832
3.6463
2.9159
2.9017
2.8872
2.8022
2.7874
2.7729
2.7600
2.6778
2.6660
2.6591
2.6472
2.6413
2.6294
2.3601
2.2311
2.2210
2.2118
2.2018
2.1945
2.1846
2.1752
2.1651
2.0601
O
O
N
C-2g
1.00
2.00
2.65
0.95
0.80
0.83
2.03
2.02
2.04
0.84
3.13
1.01
2.58
f1 (ppm)


171.58
142.08
138.87
138.62
133.76
133.66
129.93
128.33
126.33
126.15
125.75
125.53
125.19
76.71
67.37
51.29
45.93
32.51
28.50
20.00
19.75
O
O
N
C-2g
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)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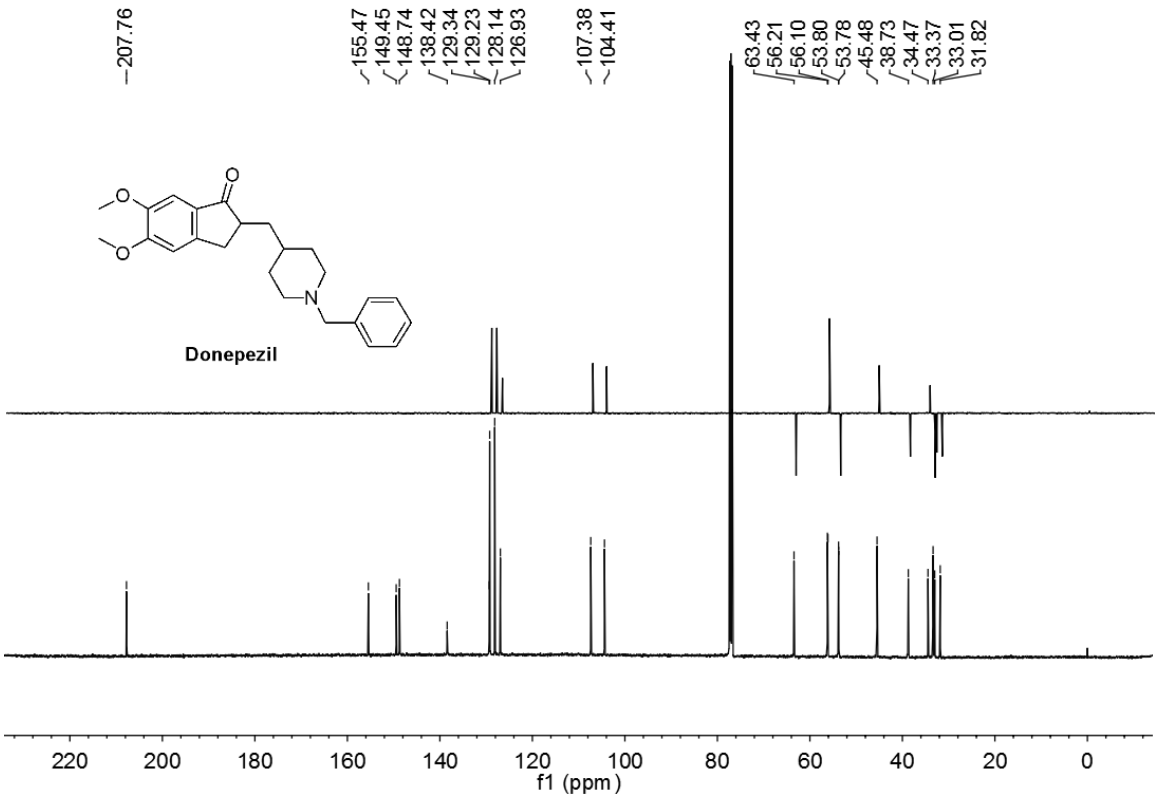
7.3056
7.2531
7.2474
7.2453
7.2410
7.2345
7.1645
6.8486
3.9529
3.8979
3.5077
3.2524
3.2361
3.2172
3.2011
2.9200
2.9002
2.8804
2.7133
2.7058
2.6956
2.6931
2.6842
2.6780
2.6715
1.9934
1.9864
1.9811
1.9754
1.9702
1.9633
1.9137
1.9119
1.8953
1.7437
1.7182
1.6520
1.3890
1.3818
1.3639
1.3575
1.3475
1.3368
1.3274
1.3206
1.3159
1.3091
1.3000
Donepezil
4.00
1.00
1.05
1.04
3.27
3.24
2.10
1.06
2.14
2.16
2.12
1.01
1.07
1.05
1.09
3.23
f1 (ppm)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148.74
138.42
129.34
129.23
128.14
126.93
107.38
104.41
63.43
56.21
56.10
53.80
53.78
45.48
38.73
34.47
33.37
33.01
31.82
Donepezil
f1 (ppm)