Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of illudalic acid and analogous LAR phosphatase inhibitors

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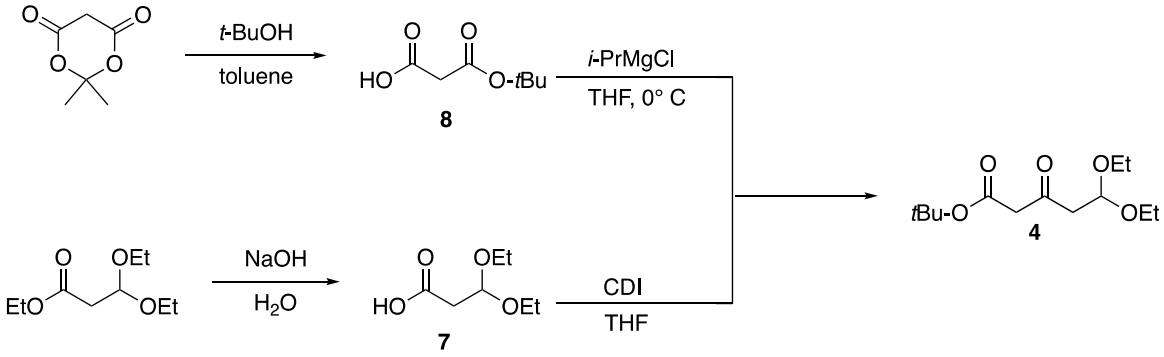
Experimental

Chemistry. All the chemicals were used as received unless otherwise stated. Diethyl ether (Et_2O), tetrahydrofuran (THF) and methylene chloride (DCM) were dried over a column of molecular sieves under argon. All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. Crude products were purified in Biotage Isolera One Flash Purification System using Biotage prepacked cartridges (50 µm irregular silica). Yields refer to isolated material considered to be ≥ 95% pure following silica gel chromatography. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL 400 MHz spectrometer using $CDCl_3$ and DMSO-d_6 as the deuterated solvent (≥99.8 atom % D, contains 0.03% (v/v) TMS). The chemical shifts (δ) were reported in parts per million (ppm) relative to the internal standard TMS. High-resolution mass spectral (HRMS) data were obtained on a UHR-TOF maXis 4G instrument (Bruker Daltonics, Bremen, Germany) using electrospray ionization (ESI).

Preparation of *tert*-butyl 5,5-diethoxy-3-oxopentanoate (4)



3,3-diethoxypropanoic acid (7) A mixture of ethyl 3,3-diethoxypropanoate (10.0 g, 52.6 mmol, 1.0 equiv.), NaOH (7.15 g, 158 mmol, 3.0 equiv.) and water (1.0 M) was stirred at 70°C for 3 hrs. After the reaction, the mixture was cooled in an ice bath, carefully acidified with concentrated HCl and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a colorless liquid which was used in the next step without purification (7.91 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 6H), 2.72 (d, 2H), 3.58 (dq, 2H), 3.69 (dq, 2H), 4.97 (t, 1H), 11.22 ppm (br s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 15.19, 39.75, 62.09, 99.31, 175.83.

3-(*tert*-butoxy)-3-oxopropanoic acid (8) To a solution of Meldrum's acid (10.58 g, 73.4 mmol, 1.0 equiv.) in toluene (1.25 M) was added *tert*-butanol (6.53 mL, 88.1 mmol, 1.2 equiv.). The solution was refluxed for 3 h, before being concentrated *in vacuo*. The viscous clear liquid was taken on to the next step without further purification (11.5 g, 71.8 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 3.36 (s, 2H), 11.41 ppm (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 27.93, 42.08, 83.00,166.32,172.24.

tert-butyl 5,5-diethoxy-3-oxopentanoate (4)

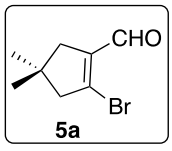
Mixture A. 1,1'-Carbonyldiimidazole (8.15 g, 50.3 mmol, 1.1 eq) was added in 3 portions to a solution of the acetal **7** (7.41 g, 45.7 mmol, 1.0 equiv.) and THF (0.2 M). The resulting mixture was stirred for 1 hr at room temperature.

Mixture B. To solution of the ester **8** (10.98 g, 68.5 mmol, 1.5 eq) in THF (0.5 M) at 0°C, isopropylmagnesium chloride (73.1 mL, 3.2 equiv., 2.0 M in THF) was added dropwise using a syringe pump, set at a rate of 5 mL/min. The solution was continued to stir for an additional hour at room temperature.

Using a canula, Mixture B was transferred to Mixture A. The creamy mixture was stirred at room temperature for 12-15 hrs. After the reaction, the mixture was quenched with saturated NH_4Cl, stirred for an additional 15 mins and extracted with ethyl acetate. The organic layer was washed brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by automatic flash column chromatography on silica gel (gradient elution from 2% to 20% EtOAc–hexanes) to afford **4** as a light yellow, viscous liquid (72% yield, 93:7 mixture of keto and enol tautomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, 6H), 1.47 (s, 9H), 2.85 (d, 2H), 3.41 (s, 2H), 3.54 (dq, 2H), 3.67 (dq, 2H), 4.89 ppm (t, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 15.26, 28.00, 47.61, 51.62, 62.51, 81.93, 99.77, 166.30, 200.63. HRMS (ESI, *m/z*) for $C_{13}H_{24}O_5$ $[M - H]^-$: calcd, 259.1551; found, 259.1553.

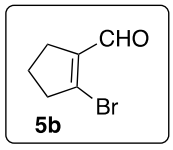
General Procedure for the Vilsmeier-Haack Formylation

Phosphorus tribromide (PBr_3, 2.2 equiv.) was added dropwise to a solution of DMF (3.0 equiv.) in DCM (1.0 M) previously cooled at 0°C. After 90 mins of stirring, the ketone (1.0 equiv.) was added neat. The white slurry was then warmed to ambient temperature and stirred for 60 hrs. After the reaction, the orange mixture was poured on crushed ice, neutralized with solid $NaHCO_3$ and extracted with DCM. The combined organic extracts were dried over $NaSO_4$, concentrated under reduced pressure and purified by automatic flash column chromatography on silica gel (step gradient: 3% then 5% EtOAc–hexanes).



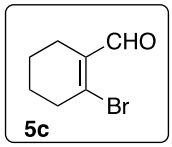
5a

Obtained as colorless, volatile liquid (1.7 g, 63% isolated yield of **5a**, plus estimated 30% isomeric by-product, not shown). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 6H), 2.32 (t, 2H), 2.70 (t, 2H), 9.86 ppm (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 29.51, 37.68, 43.98, 56.95, 139.16, 139.65, 189.58.

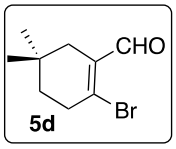


5b

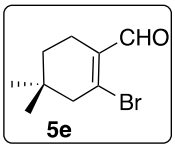
Obtained as colorless, volatile liquid (5.722 g, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (quint, 2H), 2.54 (tt, 2H), 2.91 (tt, 2H), 9.90 ppm (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.43, 29.32, 42.61, 140.04, 141.57, 189.30



Obtained as colorless liquid (4.524 g, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65-1.73 (m, 2H), 1.74-1.81 (m, 2H), 2.28 (tt, 2H), 2.75 (tt, 2H), 10.02 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.19, 24.37, 25.10, 38.92, 135.36, 143.67, 193.75.



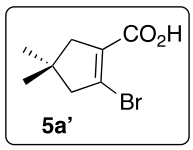
Obtained as colorless liquid (3.795 g, 52% yield, 76% brsm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 6H), 1.52 (t, 2H), 2.08 (m, 2H), 2.76 (tt, 2H), 10.03 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 27.68, 28.52, 28.53, 36.81, 38.34, 134.04, 142.72, 193.93.



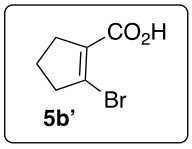
Obtained as colorless liquid (2.935 g, 43% isolated yield of **5e**, 61% brsm, plus 1.554 g of isomer **5d**, 23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 6H), 1.47 (t, 2H), 2.31 (tt, 2H), 2.54 (t, 2H), 10.04 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 22.75, 27.89, 32.33, 33.90, 52.43, 134.03, 142.81, 193.75.

General Procedure for the Pinnick Oxidation

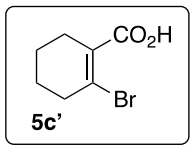
A mixture containing the bromo-enal (**5a-5e**, 1.0 equiv), monopotassium phosphate (0.16 equiv.), acetonitrile (1.0 M) and 30% H_2O_2 (1.05 equiv.) was cooled to 0°C and stirred for 15 mins. Sodium chlorite (1.5 equiv., 1.3 M in water) was then added and the mixture was stirred at ambient temperature for 5 hrs with formation of a precipitate (except for **5d'**). The heterogenous mixture was acidified with 3M HCl. The solids were filtered, washed with cold water and air dried. For **5d'**, The resulting yellow solution was extracted with ethyl acetate and concentrated *in vacuo*. The products were then used in the next step without further purification.



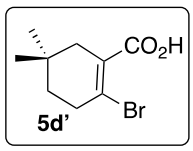
Obtained as white crystalline solid (666 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 6H), 2.48 (s, 2H), 2.66 ppm (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 29.40, 37.32, 47.55, 57.83, 130.31, 133.98, 169.16. HRMS (ESI, m/z) for $C_8H_{12}BrO_2$ $[M + H]^+$: calcd, 220.0049; found, 220.0048.



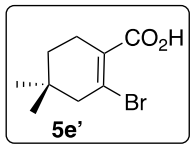
Obtained as white powdery solid (715 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (quint, 2H), 2.68 (tt, 2H), 2.86 ppm (tt, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.67, 32.96, 43.65, 131.47, 135.79, 169.19.



Obtained as white crystalline solid (4.117 g, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (m, 4H), 2.43 (m, 2H), 2.64 ppm (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.46, 23.99, 28.76, 38.13, 129.51, 129.79, 172.72.



Obtained as white crystalline solid (850 mg, 81% yield). $_{1}$H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 6H), 1.48 (t, 2H), 2.22 (s, 2H), 2.65 ppm (tt, 2H). $_{13}C\{_{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 27.68, 28.71, 36.10, 36.57, 42.13, 128.38, 128.76, 172.54. HRMS (ESI, m/z) for $C_9H_{14}BrO_2$ $[M + H]^+$: calcd, 233.0172; found, 233.0169.



Obtained as white crystalline solid (1.154 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 6H), 1.48 (t, 2H), 2.42-2.50 ppm (m, 4H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 26.50, 27.77, 31.77, 34.15, 51.73, 128.04, 129.24, 172.58. HRMS (ESI, m/z) for $C_9H_{14}BrO_2$ $[M + H]^+$: calcd, 234.0205; found, 234.0203.

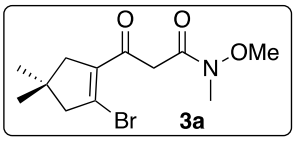
General Procedure for the Synthesis of the Beta-Ketoamide

Mixture A: 1,1'-Carbonyldiimidazole (1.1 equiv.) was added in 3 portions to a solution of the carboxylic acid (1.0 equiv.) and THF (0.2 M). The resulting mixture was stirred for 1 hour at room temperature.

Mixture B: To solution of LHMDS (3.2 equiv., 1.0 M in THF) and THF (0.5 M) at - 78°C, *N*-methoxy-*N*-methylacetamide (3.2 eq) was added dropwise using a syringe pump. The mixture was stirred for 1 hr at the same temperature.

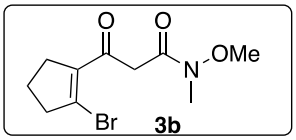
Mixture A was transferred slowly to Mixture B using a cannula. The creamy mixture was warmed to ambient temperature and stirred for 12-15 hrs. After the reaction, the mixture was quenched

with saturated NH_4Cl, stirred for an additional 15 mins and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by automatic flash column chromatography on silica gel (gradient elution from 5% to 40% EtOAc–hexanes).



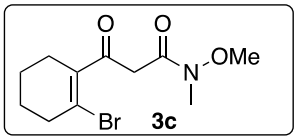
3a

Obtained as light orange crystalline solid (476 mg, 91% yield, 1:1 mixture of keto and enol tautomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 6H), 1.15 (s, 6H), 2.44 (t, 2H), 2.50 (t, 2H), 2.64 (t, 2H), 2.71 (t, 2H), 3.23 (s, 6H), 3.69 (s, 3H), 3.73 (s, 3H), 4.04 (s, 2H), 5.93 (s, 1H), 13.81 ppm (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl3): δ 29.29, 29.53, 31.94 (br), 32.15 (br), 36.77, 36.86, 47.03, 47.82, 47.88, 57.69, 58.24, 61.44, 61.61, 88.16, 122.69, 129.56, 133.27, 138.98, 167.68, 168.65, 172.50, 191.69. HRMS (ESI, m/z) for $C_{12}H_{19}BrNO_3$ $[M + H]^+$: calcd, 305.0576; found, 305.0571.



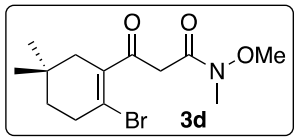
3b

Obtained as light pink crystalline solid (1.250 g, 90% yield, 1:1 mixture of keto and enol tautomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (sextet, 4H), 2.64 (tt, 2H), 2.70 (tt, 2H), 2.83 (tt, 2H), 2.91 (tt, 2H), 3.23 (s, 6H), 3.69 (s, 3H), 3.73 (s, 3H), 4.05 (s, 2H), 5.96 (s, 1H), 13.81 ppm (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.26, 21.55, 31.96 (br), 32.16 (br), 33.28, 33.42, 43.43, 44.22, 47.09, 61.46, 61.62, 88.29, 124.54, 131.41, 134.48, 140.05, 167.70, 168.69, 172.50, 191.70. HRMS (ESI, m/z) for $C_{10}H_{15}BrNO_3$ $[M + H]^+$: calcd, 277.0263; found, 277.0260.



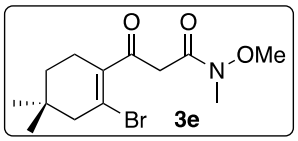
3c

Obtained as light yellow solid (1.253 g, 81% yield, 1:1 mixture of keto and enol tautomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66-1.78 (m, 8H), 2.32-2.40 (m, 4H), 2.54- 2.62 (m, 4H), 3.22 (s, 3H), 3.23 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 3.98 (s, 2H), 5.64 (s, 1H), 13.78 ppm (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.38, 21.77, 24.14, 24.30, 29.02, 29.76, 31.80 (br), 32.12 (br), 36.73, 37.01, 47.01, 61.54, 61.84, 89.23, 122.37, 123.00, 133.45, 138.91, 167.95, 172.33, 173.35, 199.27. HRMS (ESI, m/z) for $C_{11}H_{17}BrNO_3$ $[M + H]^+$: calcd, 291.0420; found, 291.0415.



3d

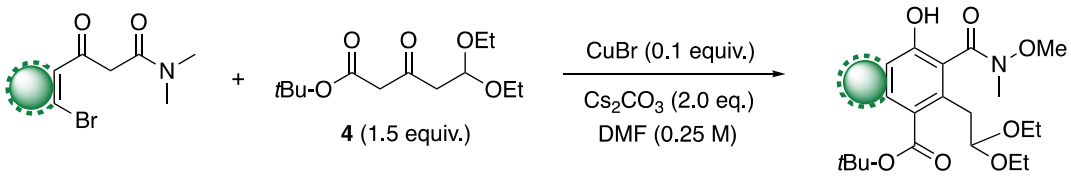
Obtained as light orange crystalline solid (1.120 g, 79% yield, 3:2 mixture of keto and enol tautomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 12H), 1.49 (t, 4H), 2.15 (m, 4H), 2.58 (m, 4H), 3.22 (s, 3H), 3.23 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.98 (s, 2H), 5.63 (s, 1H), 13.77 ppm (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl3): δ 27.60, 27.72, 28.66, 28.88, 31.83 (br), 32.14 (br), 34.74, 34.97, 36.77, 36.87, 42.36, 43.17, 46.97, 61.53, 61.85, 89.26, 121.17, 121.77, 132.35, 137.94, 167.94, 172.34, 173.40, 199.21. HRMS (ESI, m/z) for $C_{13}H_{21}BrNO_3$ $[M + H]^+$: calcd, 318.0699; found, 318.0690.

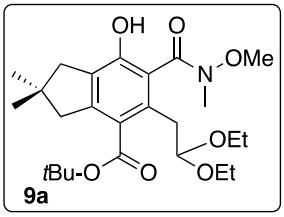


Obtained as light orange crystalline solid (1.126 g, 80% yield, 3:2 mixture of keto and enol tautomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 12H), 1.46 (m, 4H), 2.38 (m, 8H), 3.21 (s, 3H), 3.23 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 3.98 (s, 2H), 5.65 (s, 1H), 13.80 ppm (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 26.86, 27.35, 27.70, 27.81, 31.77 (br), 31.81, 31.91, 32.06 (br), 34.03, 34.37, 47.06, 50.28, 50.55, 61.45, 61.76, 89.20, 121.41, 121.87, 132.02, 137.49, 167.84, 172.26, 173.14, 198.93. HRMS (ESI, m/z) for $C_{13}H_{21}BrNO_3$ [M + H]$^+$: calcd, 319.0733; found, 319.0731.

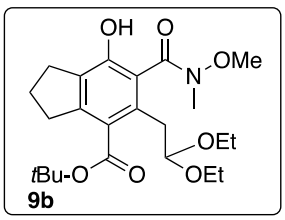
General Procedure for the Cu-Catalyzed Benzannulation Reaction

A mixture of the ketoamide (**3a**-**3e)** (1.0 equiv.), Cs_2CO_3 (2.0 equiv.) and DMF (0.25 M) was stirred at ambient temperature for 5 mins. 3-(*tert*-butoxy)-3-oxopropanoic acid (**4**) was added (1.5 equiv.) to the suspension followed by copper(I) bromide (0.1 equiv.) after 15 mins. The green mixture was heated to 60°C and stirred for 24 hrs. The mixture was then cooled to room temperature, diluted with distilled water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by automatic flash column chromatography on silica gel (gradient elution from 10% to 80% EtOAc–hexanes).

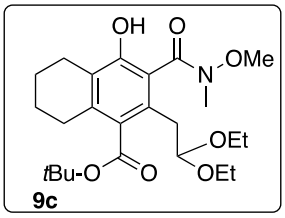




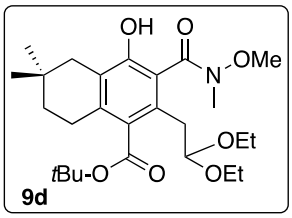
Obtained as light orange solid (390 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06-1.17 (m, 12H), 1.58 (s, 9H), 2.66 (s, 2H), 2.82 (q, 2H), 3.00-3.22 (m, 2H), 3.28 (s, 3H), 3.32-3.48 (m, 2H), 3.50-3.68 (m, 5H), 4.55 (t, 1H), 7.23 ppm (br s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 15.32, 15.39, 28.37, 29.06, 29.09, 35.73, 39.71, 43.55, 48.80, 61.16 (br), 62.00 (br), 62.68, 81.31, 103.86, 121.76, 124.92, 128.87, 133.39, 146.51, 151.05, 168.02. HRMS (ESI, m/z) for $C_{25}H_{38}NO_7$ [M - H]$^-$: calcd, 464.2654; found, 464.2655.



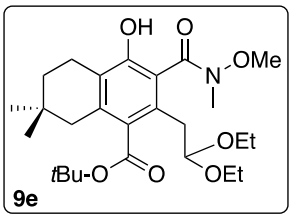
Obtained as light-yellow solid (1.330 g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, 3H), 1.14 (t, 3H), 1.58 (s, 9H), 1.94-2.09 (m, 2H), 2.78 (t, 2H), 2.96 (sextet, 2H), 3.04-3.23 (m, 2H), 3.27 (br s, 3H), 3.32-3.52 (m, 2H), 3.52-3.61 (m, 2H), 3.65 (br s, 3H), 4.56 (t, 1H), 7.54 ppm (br s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 15.33, 15.42, 24.54, 28.36, 29.00, 33.94, 35.70, 61.25 (br), 61.84 (br), 62.62, 81.33, 103.76, 121.87, 124.69, 130.06, 133.25, 147.10, 150.76, 168.06. HRMS (ESI, m/z) for $C_{23}H_{34}NO_7$ [M - H]$^-$: calcd, 436.2341; found, 436.2343.



Obtained as light yellow crystalline solid (1.339 g, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, 3H), 1.15 (t, 3H), 1.59 (s, 9H), 1.74 (m, 4H), 2.59 (m, 2H), 2.69 (m, 2H), 2.89-3.12 (m, 2H), 3.28 (s, 3H), 3.33-3.67 (m, 7H), 4.58 (t, 1H), 7.84 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.25, 15.34, 20.80, 22.01, 22.46, 23.12, 27.27, 28.17, 36.43, 61.33 (br), 61.58, 62.72 (br), 81.86, 103.61, 118.85, 124.29, 129.19, 129.26, 136.71, 152.53, 169.18. HRMS (ESI, m/z) for $C_{24}H_{36}NO_7$ $[M - H]^-$: calcd, 450.2497; found, 450.2502.



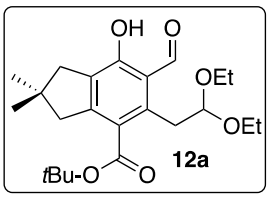
Obtained as light yellow solid (1.178 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 6H), 1.10 (t, 3H), 1.15 (t, 3H), 1.53 (t, 2H), 1.60 (s, 9H), 2.44 (m, 2H), 2.74 (t, 2H), 2.89-3.10 (m, 2H), 3.29 (s, 3H), 3.33-3.64 (m, 7H), 4.57 (t, 1H), 7.74 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.24, 15.34, 24.32, 27.99, 28.17, 28.34, 28.43, 35.07, 36.68, 36.76, 61.37 (br), 61.84, 62.87 (br), 81.95, 103.75, 118.35, 123.43, 128.98, 129.23, 135.61, 153.03, 169.29. HRMS (ESI, m/z) for $C_{26}H_{40}NO_7$ $[M - H]^-$: calcd, 478.2810; found, 478.2815.



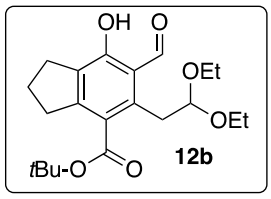
Obtained as light yellow solid (382 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 6H), 1.10 (t, 3H), 1.14 (t, 3H), 1.55 (t, 2H), 1.59 (s, 9H), 2.46 (s, 2H), 2.67 (t, 2H), 2.90-3.12 (m, 2H), 3.30 (s, 3H), 3.33-3.64 (m, 7H), 4.56 (t, 1H), 7.64 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.29, 15.38, 20.80, 28.08, 28.15, 28.22, 28.90, 34.53, 36.71, 41.05, 61.48 (br), 61.94, 62.88 (br), 81.94, 103.79, 118.21, 122.71, 129.52, 129.60, 136.36, 152.77, 169.25. HRMS (ESI, m/z) for $C_{26}H_{40}NO_7$ $[M - H]^-$: calcd, 478.2810; found, 478.2812.

General Procedure for the Partial Reduction of the Weinreb Amide

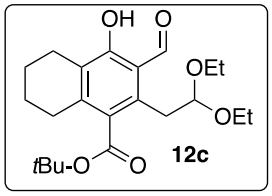
To a solution of the Weinreb amide (**9a**-**9e**) (1.0 equiv.) in THF (0.1 M) cooled to 0°C, lithium aluminum hydride (1.0 equiv., 1.0 M in THF) was added dropwise. The mixture was stirred for 1 hr at 0°C. While the mixture is still cold, ethyl acetate was added slowly followed by 1M HCl. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by automatic flash column chromatography on silica gel (gradient elution from 5% to 40% EtOAc–hexanes).



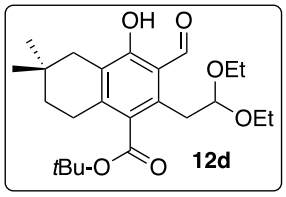
Obtained as white crystalline solid (43 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 6H), 1.17 (s, 6H), 1.60 (s, 9H), 2.72 (s, 2H), 2.82 (s, 2H), 3.32 (d, 2H), 3.41 (dq, 2H), 3.69 (dq, 2H), 4.06 (t, 1H), 10.35 (s, 1H), 12.54 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.32, 28.34, 29.14, 33.44, 39.64, 43.18, 49.08, 63.60, 82.19, 104.00, 117.78, 124.72, 130.15, 138.41, 152.07, 160.51, 167.66, 197.61. HRMS (ESI, m/z) for $C_{23}H_{33}O_6$ $[M - H]^-$: calcd, 405.2283; found, 405.2286.



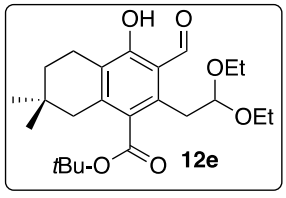
Obtained as white crystalline solid (310 mg, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 6H), 1.60 (s, 9H), 2.11 (quint, 2H), 2.91 (t, 2H), 3.03 (t, 2H), 3.32 (d, 2H), 3.41 (dq, 2H), 3.70 (dq, 2H), 4.66 (t, 1H), 10.36 (s, 1H), 12.58 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.31, 24.31, 28.32, 28.68, 33.49, 34.39, 63.59, 82.18, 104.01, 117.72, 124.48, 131.04, 138.32, 152.77, 160.31, 167.74, 197.61. HRMS (ESI, m/z) for $C_{21}H_{31}O_6$ $[M + H]^+$: calcd, 379.2115; found, 379.2111.



Obtained as white crystalline solid (120 mg, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, 6H), 1.61 (s, 9H), 1.78 (m, 4H), 2.69 (m, 4H), 3.15 (d, 2H), 3.39 (dq, 2H), 3.69 (dq, 2H), 4.61 (t, 1H), 10.31 (s, 1H), 12.74 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.32, 21.73, 22.26, 22.45, 27.82, 28.21, 33.92, 63.58, 82.60, 103.92, 115.77, 125.57, 128.86, 133.42, 142.82, 161.64, 168.94, 197.25. HRMS (ESI, m/z) for $C_{22}H_{33}O_6$ $[M + H]^+$: calcd, 393.2272; found, 393.2457.



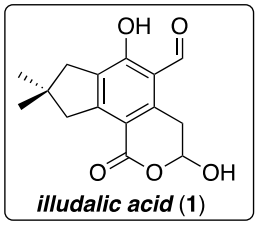
Obtained as white crystalline solid (160 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.13 (t, 6H), 1.56 (t, 2H), 1.62 (s, 9H), 2.46 (s, 2H), 2.75 (t, 2H), 3.16 (d, 2H), 3.39 (dq, 2H), 3.69 (dq, 2H), 4.62 (t, 1H), 10.32 (s, 1H), 12.77 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.32, 25.05, 28.23, 28.26, 28.29, 33.96, 34.86, 35.95, 63.57, 82.64, 103.89, 115.88, 124.93, 128.66, 133.38, 141.68, 161.91, 168.97, 197.25. HRMS (ESI, m/z) for $C_{24}H_{37}O_6$ $[M + H]^+$: calcd, 421.2585; found, 421.2575.



Obtained as white crystalline solid (100 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 6H), 1.13 (t, 6H), 1.57 (t, 2H), 1.61 (s, 9H), 2.47 (s, 2H), 2.70 (t, 2H), 3.16 (d, 2H), 3.39 (dq, 2H), 3.69 (dq, 2H), 4.61 (t, 1H), 10.32 (s, 1H), 12.75 ppm (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.31, 20.12, 28.12, 28.23, 28.96, 33.95, 34.29, 41.60, 63.58, 82.56, 103.89, 115.80, 124.28, 129.10, 133.67, 142.27, 161.52, 168.89, 197.29. HRMS (ESI, m/z) for $C_{24}H_{35}O_6$ $[M - H]^-$: calcd, 419.2439; found, 419.2444.

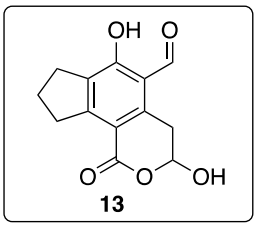
General Procedure for the Lactonization to form illudalic acid (IA1) and analogues

To a solution of the aldehyde (**12a**-**12e**) in acetone (0.04 M) stirred at room temperature was added 6M HCl (150 equiv.), and the solution was allowed to stir for 5 hours (can also let go overnight). The clear, light-yellow solution would slowly become cloudy and ultimately a dense precipitate would form signifying the end of the reaction. The solid was isolated via vacuum filtration, washed with water, cold ether, and dried. The filter cake was removed by washing it through the filter into a evaporation flask with acetone, the pure product was recovered *in vacuo*.



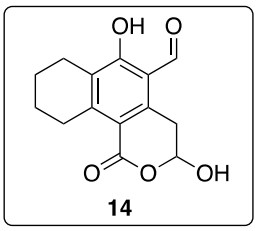
***illudalic acid* (1)**

Obtained as white powdery solid (24 mg, 81% yield) (mp 201-203 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.12 (s, 3H), 1.13 (s, 3H), 2.64 (s, 2H), 3.09 (s, 2H), 3.38 (dd, 1H), 3.55 (dd, 1H), 5.74 (dt, 1H), 7.71 (d, 1H), 10.32 (s, 1H), 12.02 ppm (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 28.74, 30.45, 39.06, 42.49, 49.83, 94.48, 114.01, 116.71, 130.00, 142.14, 155.86, 161.48, 162.72, 195.31.



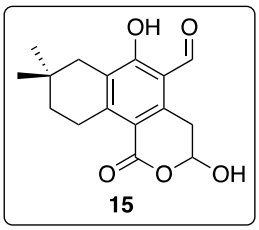
13

Obtained as white powdery solid (82 mg, 80% yield) (mp 206-209 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.05 (pentet, 2H), 2.81 (t, 2H), 3.24 (t, 2H), 3.38 (dd, 1H), 3.54 (dd, 1H), 5.71- 5.77 (m, 1H), 7.70 (d,1H), 10.32 (s, 1H), 12.08 ppm (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 23.76, 28.03, 30.44, 35.18, 94.46, 113.80, 116.59, 131.03, 142.16, 156.83, 161.31, 162.70, 195.36. HRMS (ESI, m/z) for $C_{13}H_{13}O_5$ $[M + H]^+$: calcd, 249.0757; found, 249.0755.



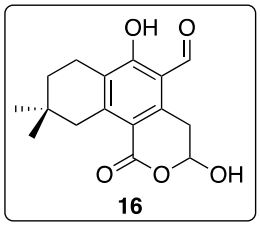
14

Obtained as white powdery solid (43 mg, 69% yield) (mp 177-179 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.61-1.75 (m, 4H), 2.54-2.67 (m, 2H), 3.04-3.12 (m, 2H), 3.31 (dd, 1H), 3.57 (dd, 1H), 5.66 (dt, 1H), 7.67 (d, 1H), 10.27 (s, 1H), 12.77 ppm (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 20.81, 21.93, 22.38, 29.49, 30.46, 93.97, 114.11, 116.03, 125.45, 140.93, 149.80, 162.34, 163.08, 196.48. HRMS (ESI, m/z) for $C_{14}H_{13}O_5$ $[M - H]^-$: calcd, 261.0768; found, 261.0771.



15

Obtained as white powdery solid (31 mg, 73% yield) (mp 196-197 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.92 (s, 3H), 0.93 (s, 3H), 1.40-1.50 (m, 2H), 2.36 (q, 2H), 3.10 (qt, 2H), 3.29 (dd, 1H), 3.55 (dd, 1H), 5.64 (dt, 1H), 7.65 (d,1H), 10.24 (s, 1H), 12.77 ppm (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ 26.70, 27.17, 27.57, 27.94, 30.42, 34.42, 35.93, 93.94, 114.28, 115.75, 124.76, 141.08, 148.54, 162.42, 163.32, 196.522. HRMS (ESI, m/z) for $C_{16}H_{19}O_5$ $[M + H]^+$: calcd, 291.1227; found, 291.1221.

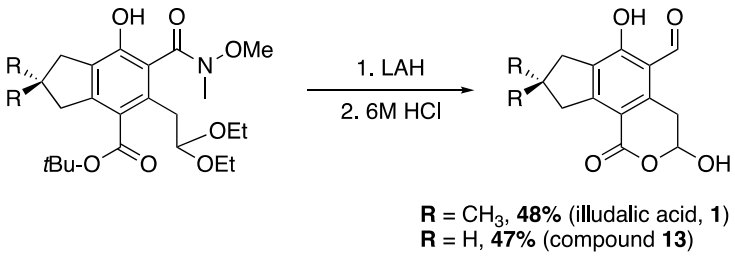


16

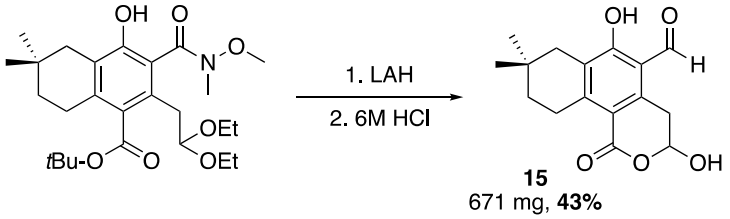
Obtained as white powdery solid (39 mg, 85% yield (mp 185-187 °C). 1H NMR (600 MHz, DMSO-d_6): δ 0.90 (s, 3H), 0.94 (s, 3H), 1.51 (t, 2H), 2.56-2.68 (m, 2H), 2.88 (q, 2H), 3.29 (dd, 1H), 3.59 (dd, 1H), 5.66 (dt, 1H), 7.67 (d, 1H), 10.27 (s, 1H), 12.77 ppm (s, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6): δ 19.96, 27.38, 28.23, 28.34, 30.52, 33.05, 42.80, 93.96, 114.10, 116.20, 124.20, 141.19, 148.82, 162.35, 162.96, 196.46. HRMS (ESI, m/z) for $C_{16}H_{17}O_5$ $[M - H]^-$: calcd, 289.1081; found, 289.1084.

General Procedure for the One-Pot Reduction-Lactonization

To a mixture of the Weinreb amide (**9a**, **9b or 9d**) (1.0 equiv.) in THF (0.1 M) cooled at 0°C, lithium aluminum hydride (1.0 equiv., 1.0 M in THF) was added dropwise. The mixture was stirred for 1 hour at 0°C. While the mixture is still cold, 6M HCl (150 equiv.) was added dropwise. The mixture was warmed to ambient temperature and stirred for 2 hrs. After the reaction, the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The crude product was purified by automatic flash column chromatography on silica gel (gradient elution from 20% to 100% EtOAc–hexanes).



R = CH_3, **48%** (illudalic acid, **1**)
R = H, **47%** (compound **13**)



15
671 mg, **43%**

Enzyme Inhibition Assays

The catalytic domains of enzymes (PTPRD 97 nM, LAR 42 nM, PTPRS 1.8 nM, CD45 50 nM, SHP2 50 nM, PTP1B 50 nM) were incubated with DTT (10 mM) in pH 7.5 buffer (50 mM HEPES, 100 mM NaCl, 1 mM EDTA, 0.02% tween) for 30 min on ice. The activity assays were performed in black U bottom 96-well plates with a total volume of 50 µL (35 µL buffer, 5 µL inhibitor in DMSO, and 5 µL PTPRD 9.7 nM, LAR 4.2 nM, PTPRS 180 pM, CD45 5 nM, SHP2 5 nM, PTP1B 5 nM). The DMSO concentration was held constant at 10% in each assay. After incubating the enzyme with inhibitor for 30 min at 37°C, the activity assay was initiated by the addition of 5 µL of an aqueous 300 µM DiFMUP solution for a final concentration of 30 µM DiFMUP. Enzyme catalyzed DiFMUP hydrolysis at 37°C was measured over 30 min, with fluorescence readings (λ_{ex} = 350 nm and λ_{em}= 455) taken every 30 s. Each concentration of inhibitor was investigated in triplicate and the results averaged to determine the initial rate of DiFMUP hydrolysis. Percent inhibition was calculated using a DMSO control.

Time-Dependent Inhibition Assays

The time-dependence of illudalog-mediated LAR inhibition was measured using a similar assay protocol as that outlined above, with the exception that the inhibitor was incubated with enzyme for varying lengths of time before DiFMUP was added and hydrolysis monitored by fluorescence. The k_{obs} values were calculated from plots of enzyme activity vs time using Kaleidagraph curve fitting software and the following equation from Liu *et al*. (*JACS* 2008; reference 26 in the main text):

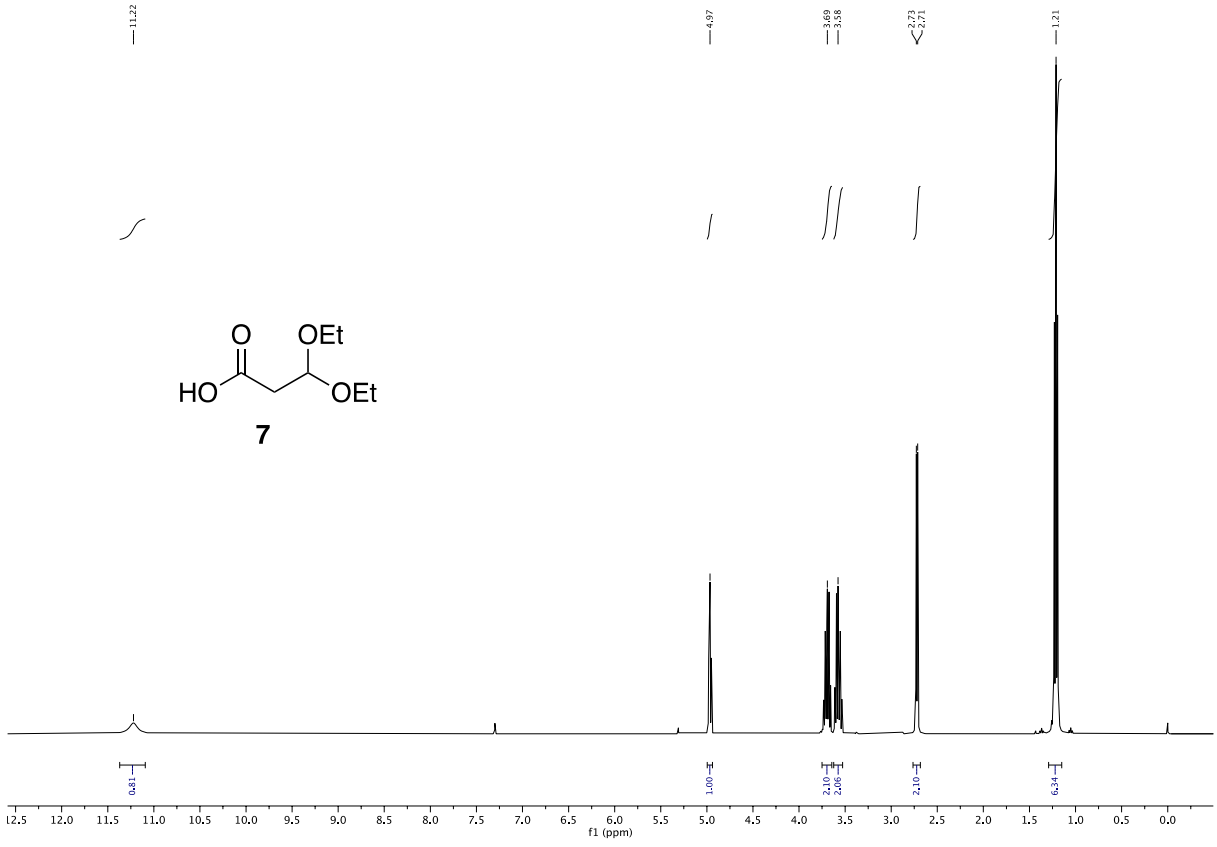
$$\frac{\mathrm{A}_t}{\mathrm{A}_0} = \frac{\mathrm{A}_\infty}{\mathrm{A}_0} - \left(\frac{\mathrm{A}_0 - \mathrm{A}_\infty}{\mathrm{A}_0} \right) \exp\left(-k_{obs} \bullet t\right)$$

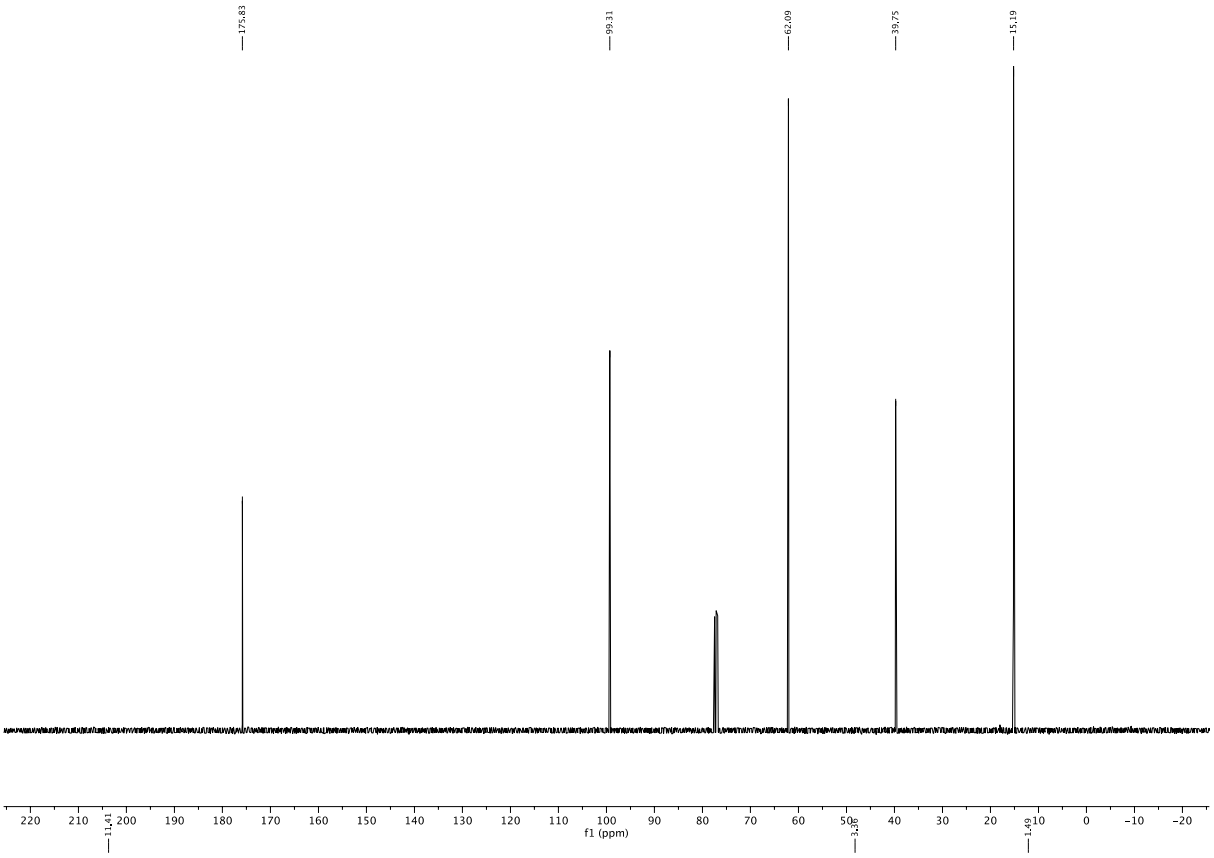
The k_{inact} and K_I values were calculated by fitting the curve obtained from plotting k_{obs} vs inhibitor concentration to the following equation (Liu *et al*; reference 26) using Kaleidagraph software.

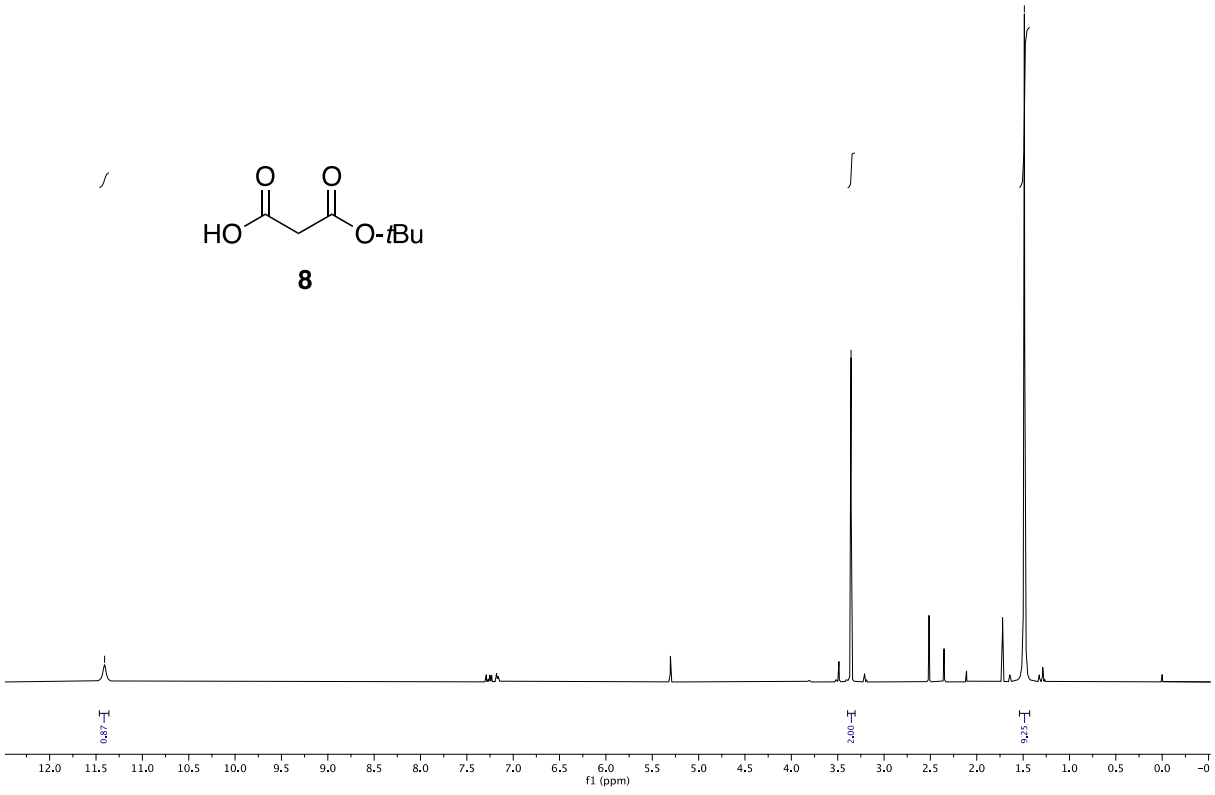
$$k_{obs} = \frac{k_{inact}\left[I\right]}{K_I + \left[I\right]}$$

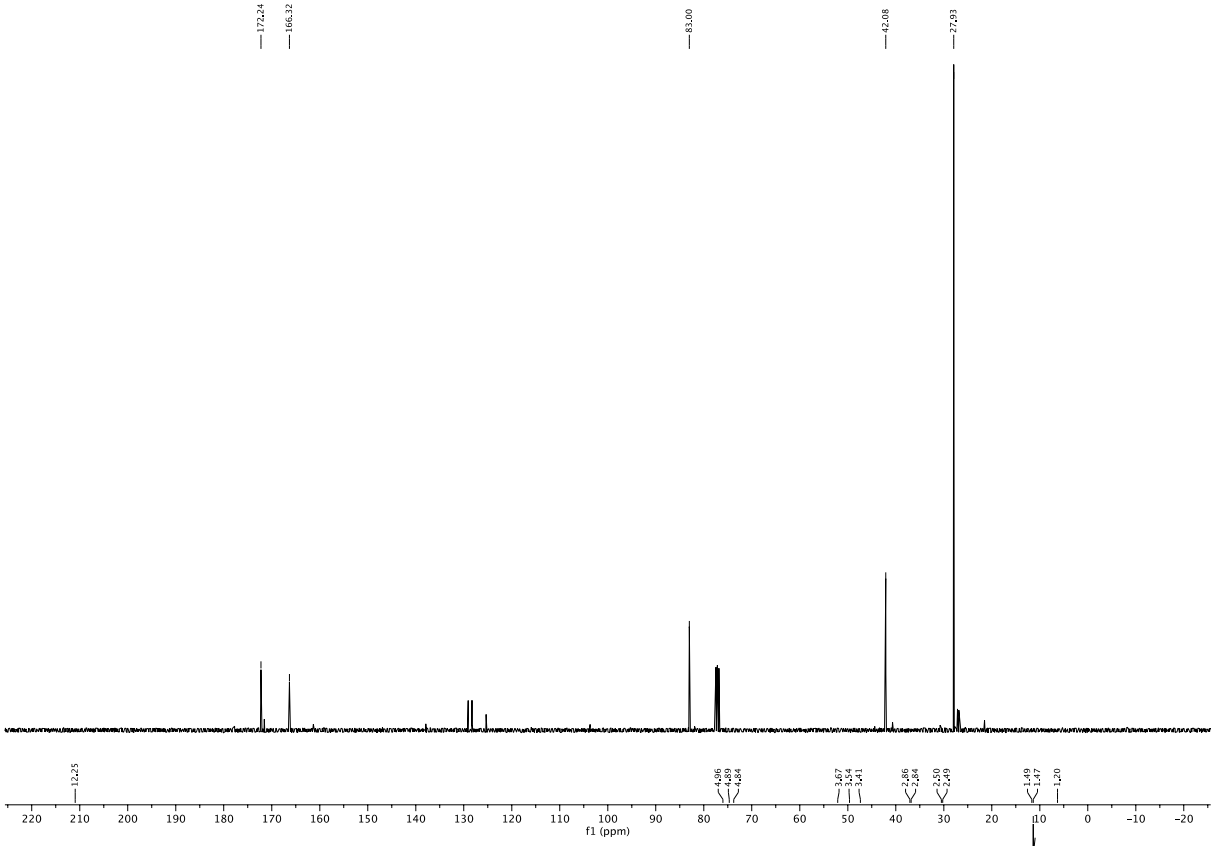
Determination of pK_a values

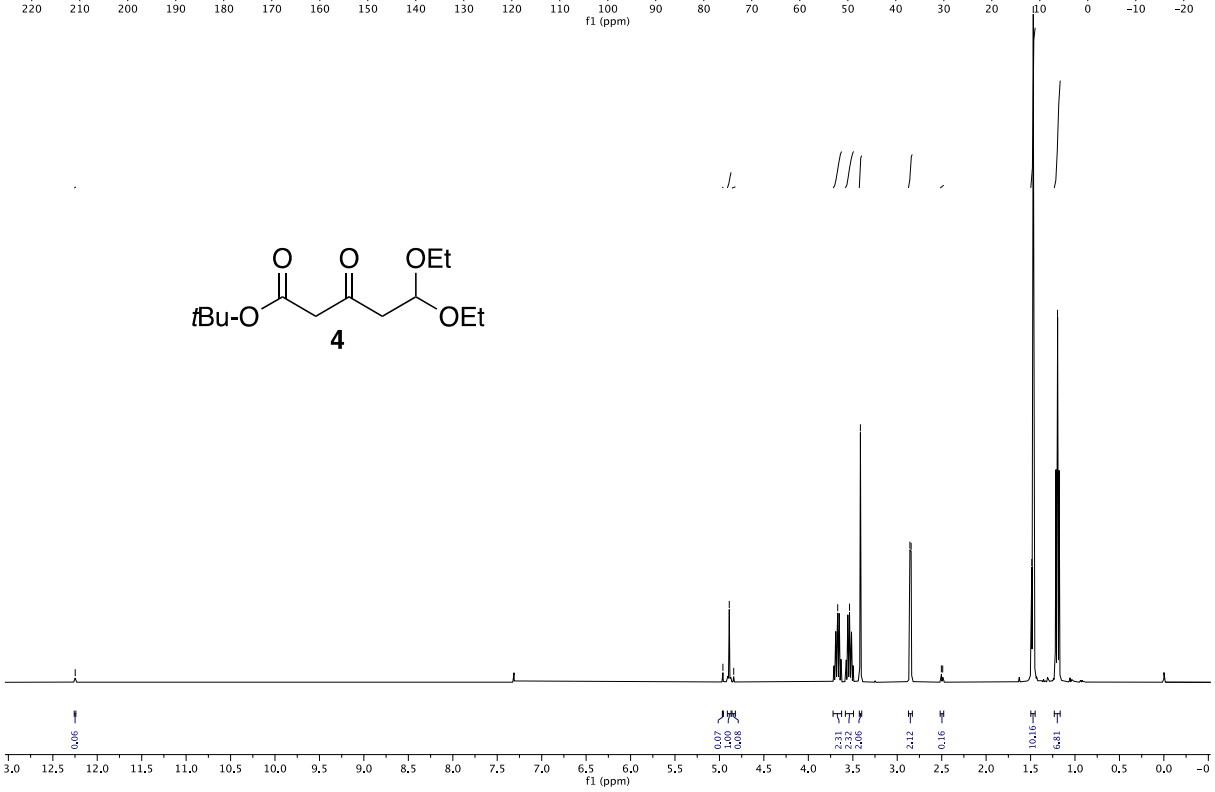
A nominally 1 M solution of NaOH in deionized water was standardized using oven-dried KHP (actual concentration of NaOH = 0.93 M). Solutions of inhibitor (10 mM) in DMSO were prepared and then diluted to 1 mM using deionized water. The solution was actively stirred throughout the titration. The standardized NaOH solution was slowly titrated into the sample, as volume of NaOH added and resulting pH were recorded. The pK_a values of the compound were defined as the pH at half the inflection point of the curve.

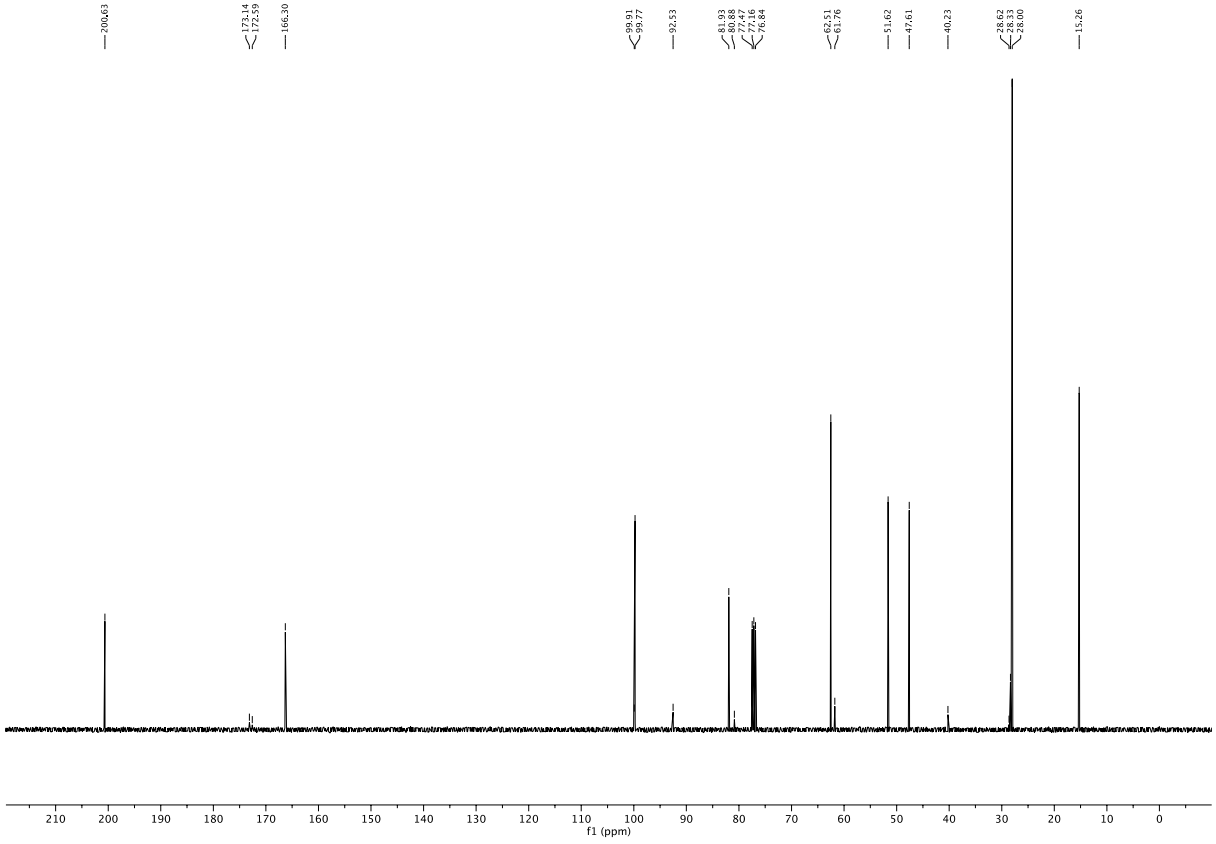

11.22
4.97
3.69
3.58
2.73
2.71
1.21
O
OEt
HO
OEt
7
0.81
1.00
2.10
2.06
2.10
6.34
f1 (ppm)

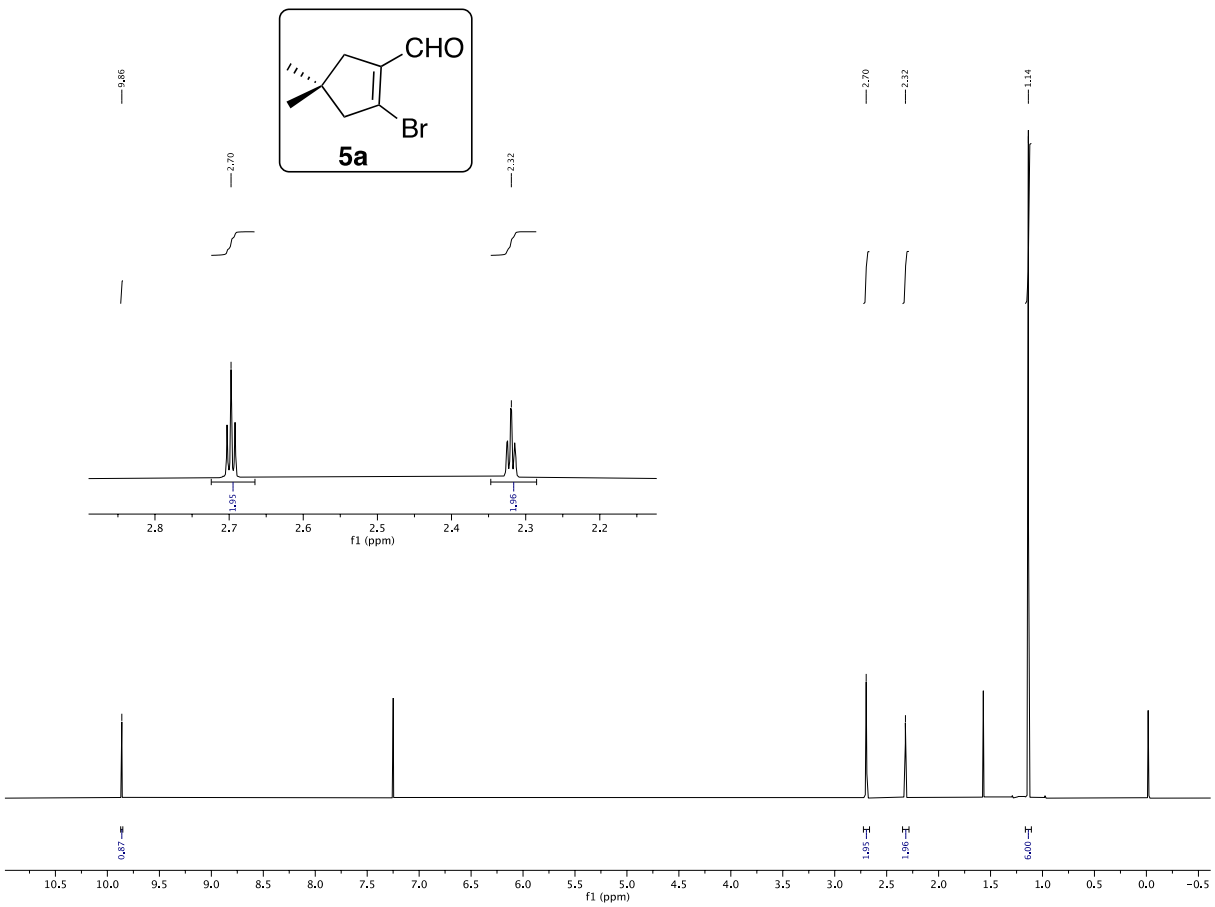

175.83
99.31
62.09
39.75
15.19
f1 (ppm)

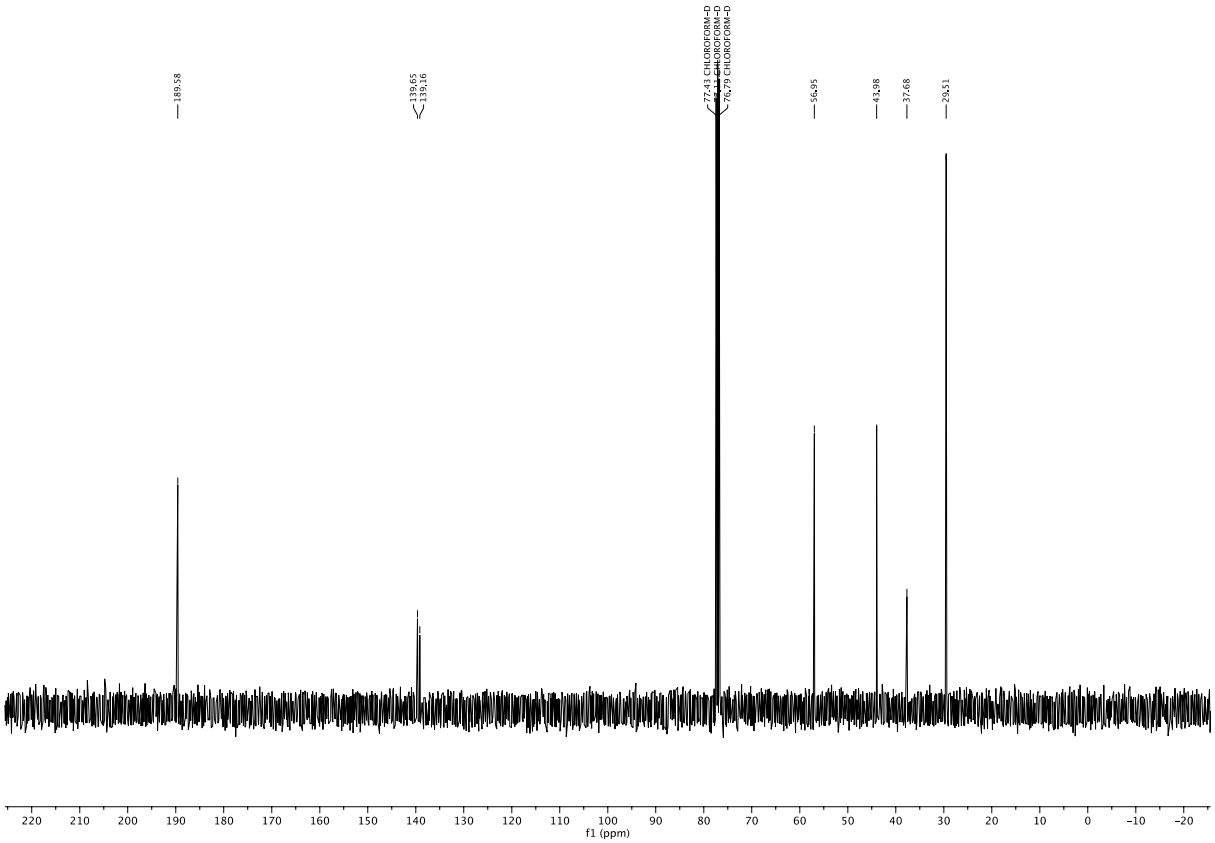

HO
O
O
O-tBu
8
0.87
2.00
9.25
f1 (ppm)

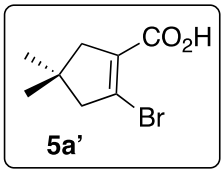

172.24
166.32
83.00
42.08
27.93
12.25
4.06
4.03
4.01
3.67
3.54
3.41
2.86
2.84
2.50
2.49
1.49
1.47
1.20
f1 (ppm)


O
O
OEt
tBu-O
OEt
4
0.06
0.07
1.00
0.08
2.31
2.32
2.06
2.12
0.16
10.16
6.81
f1 (ppm)


200.63
173.14
172.59
166.30
99.91
99.77
92.53
81.93
80.88
77.47
77.16
76.84
62.51
61.76
51.62
47.61
40.23
28.62
28.33
28.00
15.26
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

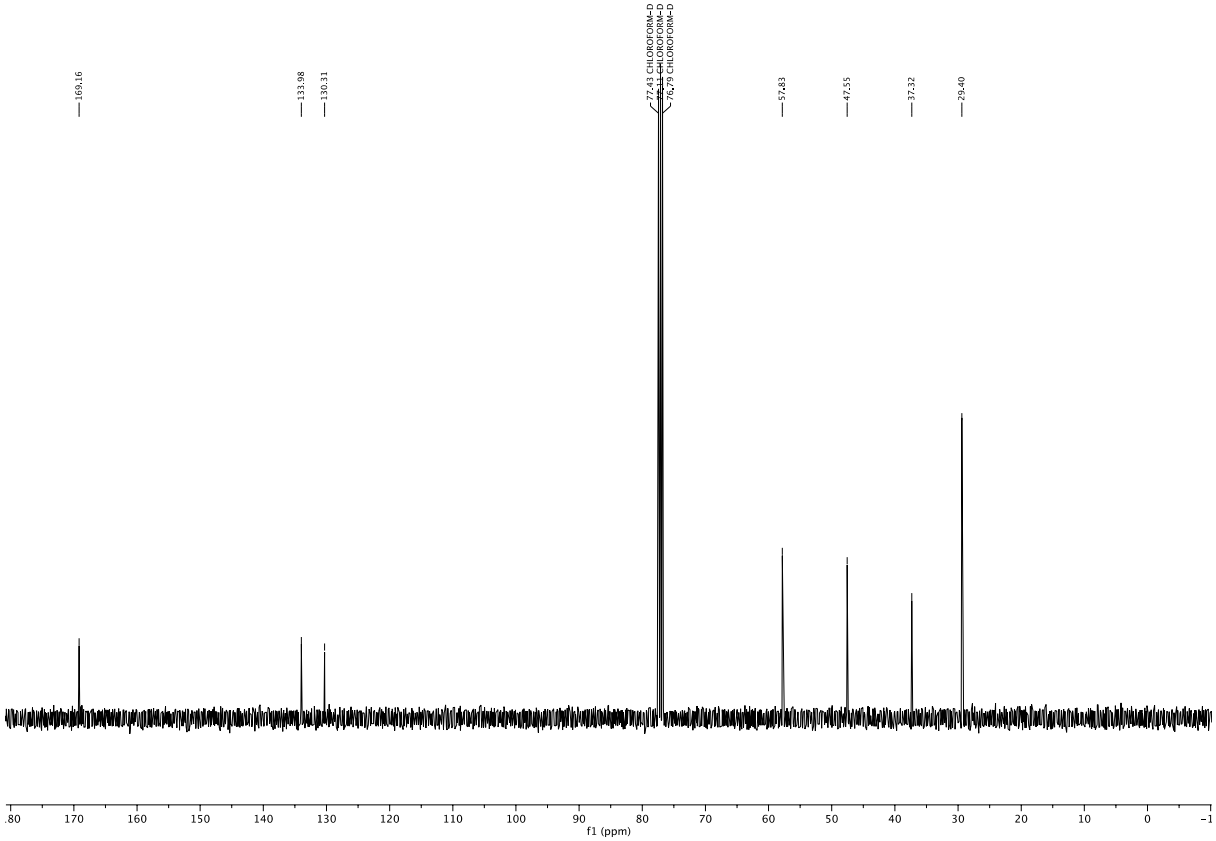

CHO
Br
5a
9,86
2,70
2,32
1,14
1,95
1,96
f1 (ppm)
0,87
6,00

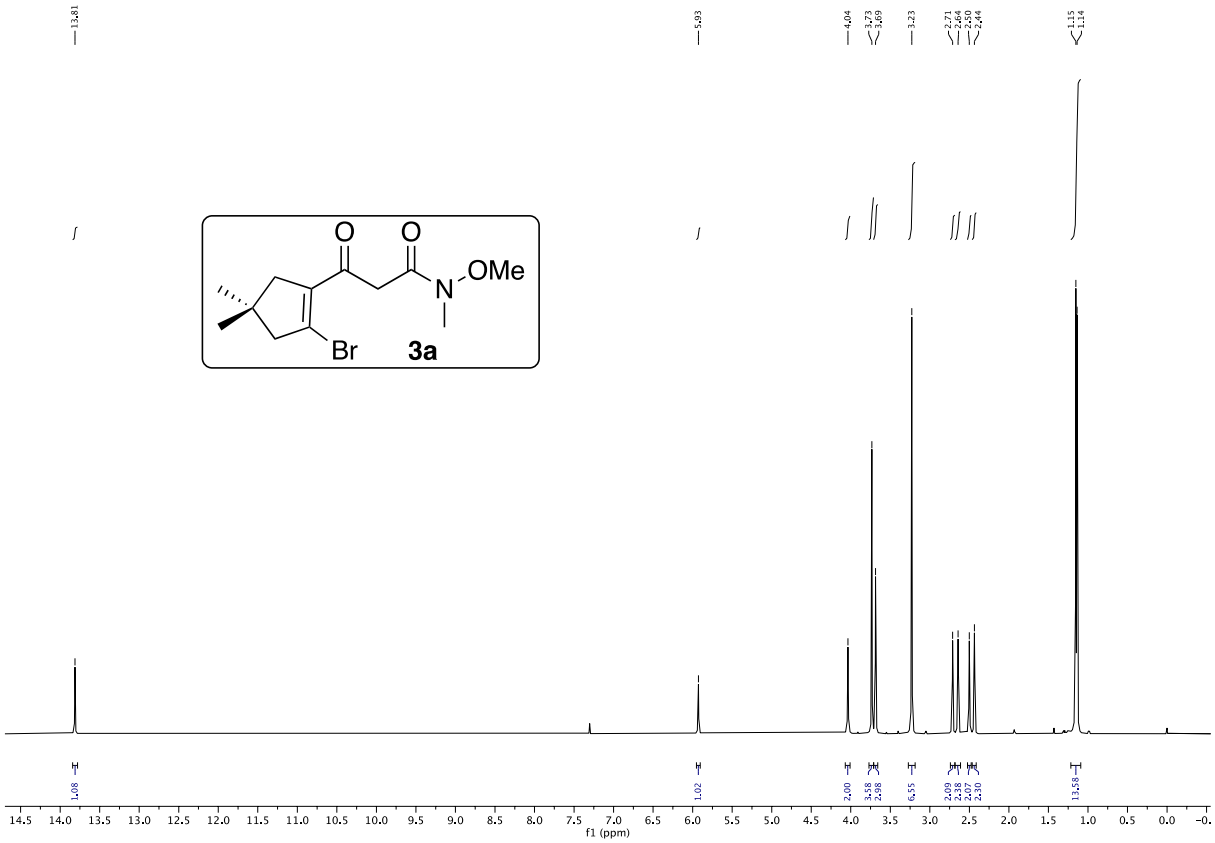

189,58
139,65
139,16
77,43 CHLOROFORM-D
77,11 CHLOROFORM-D
76,79 CHLOROFORM-D
56,95
43,98
37,68
29,51
f1 (ppm)

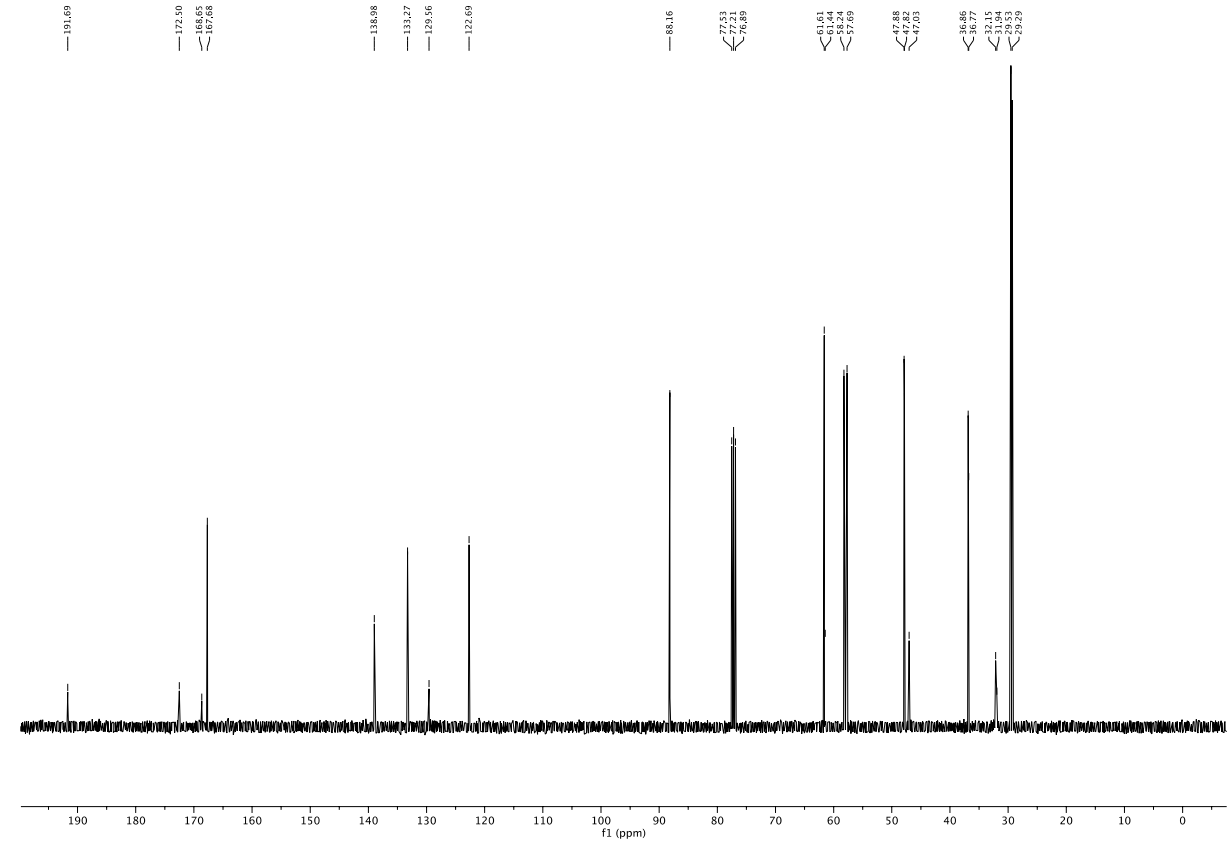

CO2H
Br

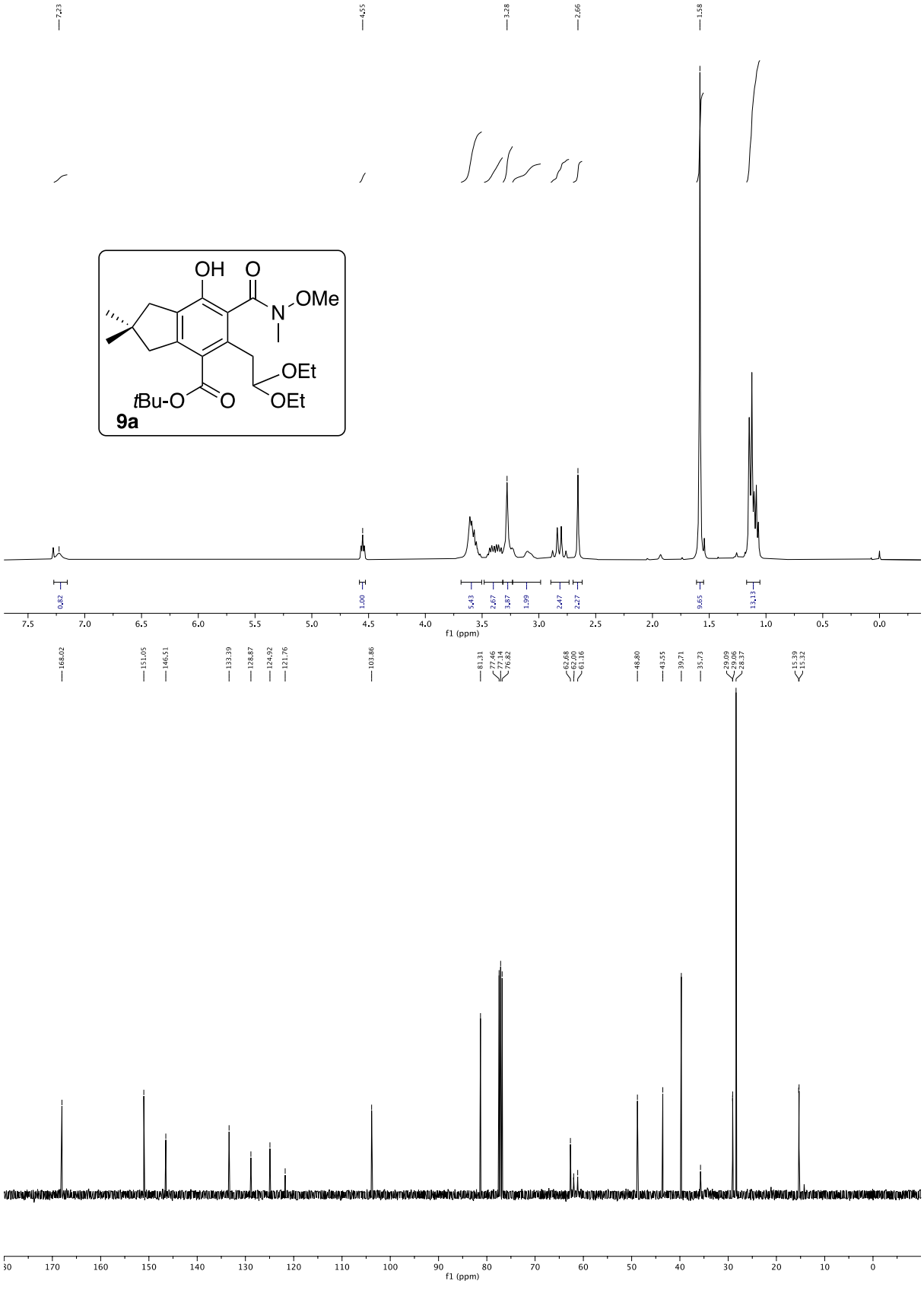
5a'

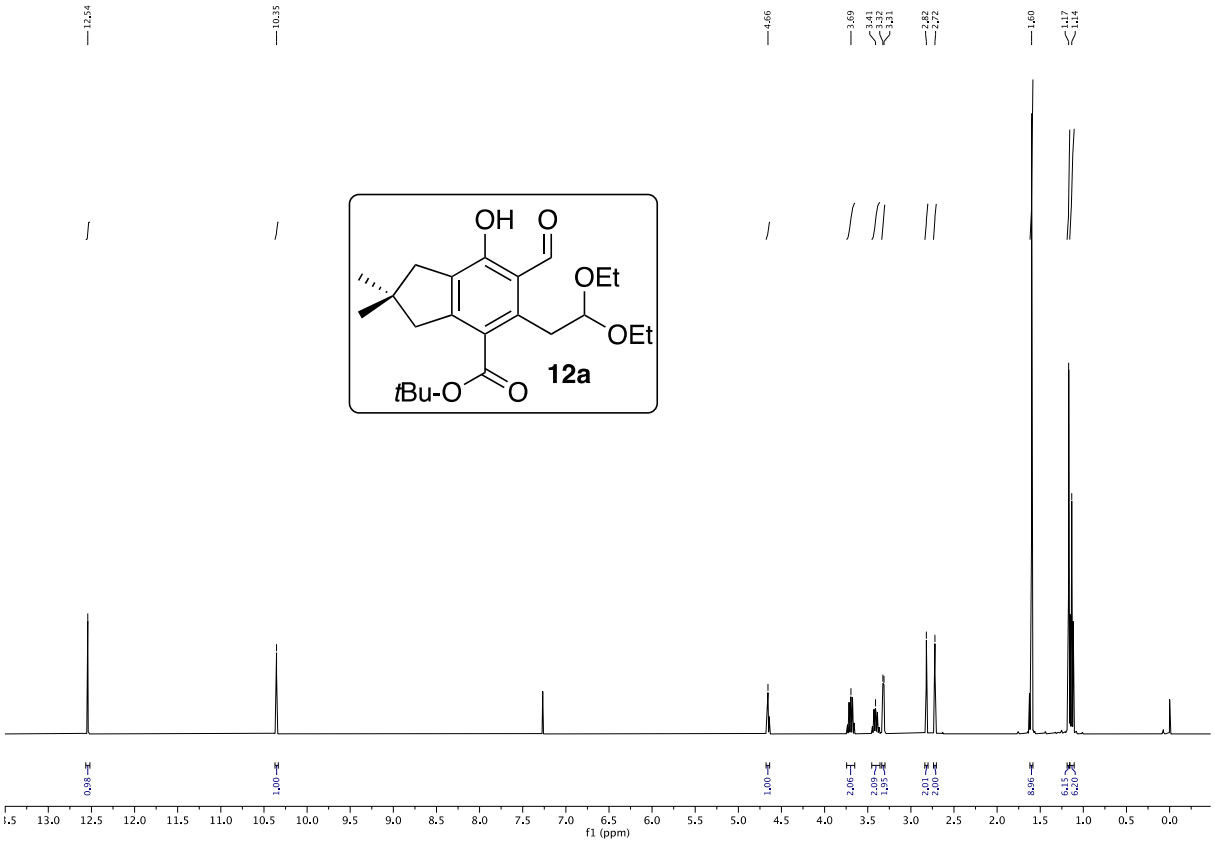
2.66
2.48
1.15
1.97
1.98
6.00
f1 (ppm)

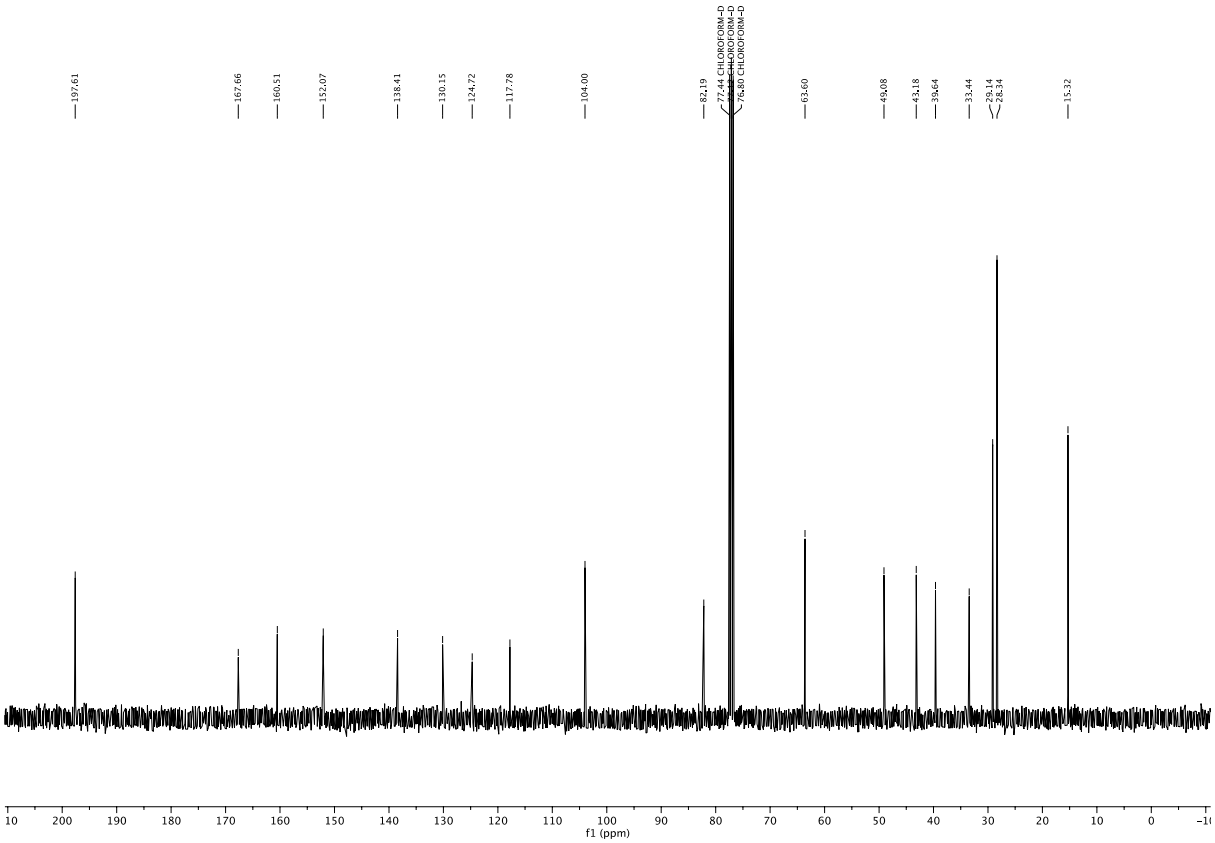

169.16
133.98
130.31
77.43 CHLOROFORM-D
77.11 CHLOROFORM-D
76.79 CHLOROFORM-D
57.83
47.55
37.32
29.40
f1 (ppm)

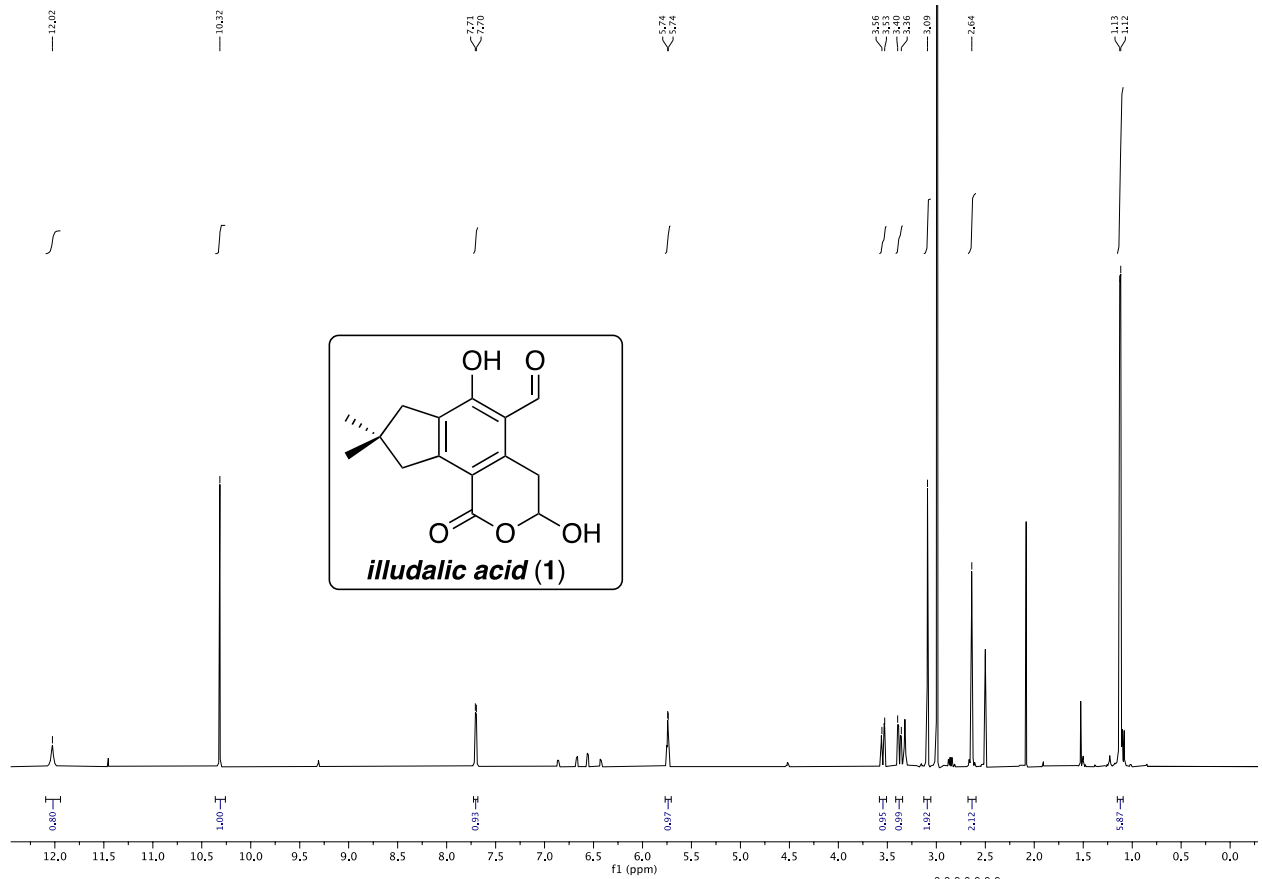

13.81
5.93
4.04
3.73
3.69
3.23
2.71
2.64
2.50
2.44
1.15
1.14
O
O
N
OMe
Br
3a
1.08
1.02
2.00
3.58
2.98
6.55
2.09
2.38
2.27
2.30
13.58
f1 (ppm)

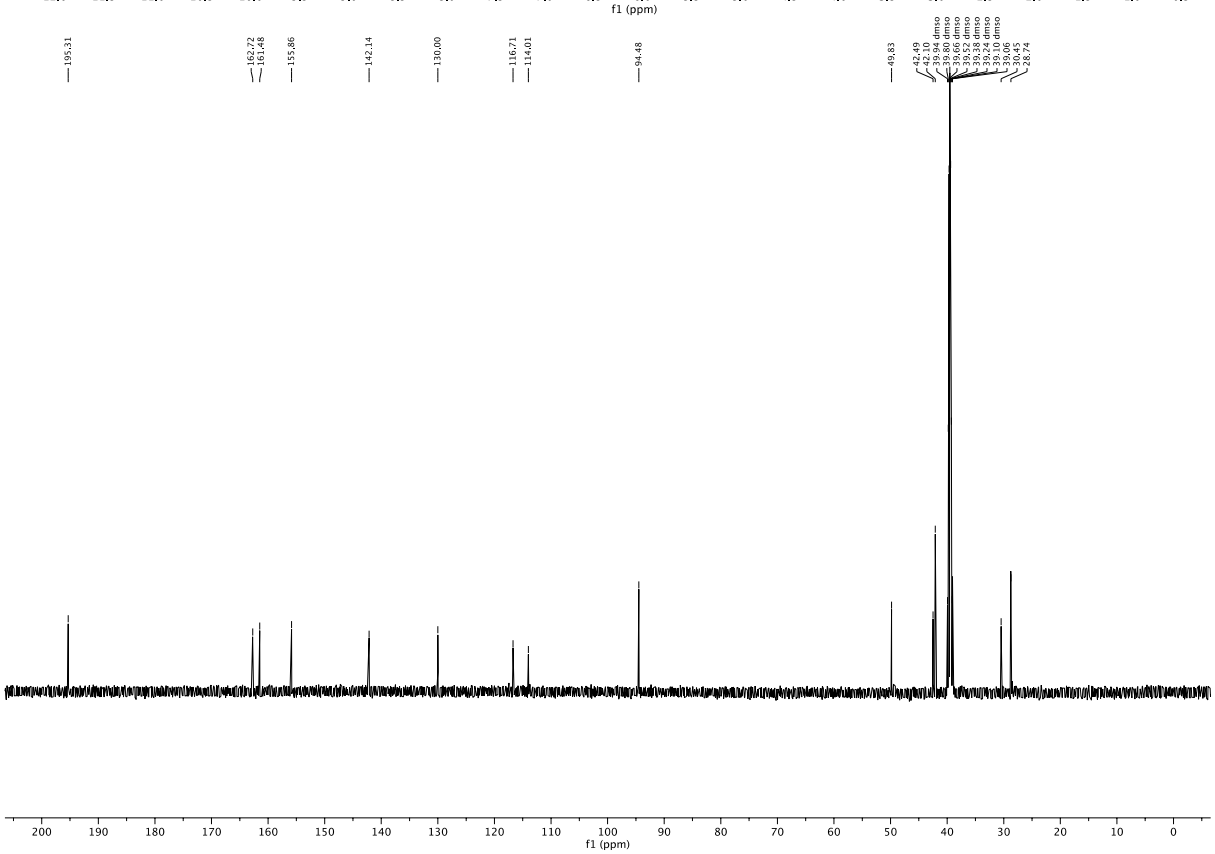

191.69
172.50
168.65
167.88
138.98
133.27
129.56
122.69
88.16
77.53
77.21
76.89
61.61
61.44
58.74
57.69
47.88
47.82
47.03
36.86
36.77
32.15
31.94
30.53
29.29
f1 (ppm)

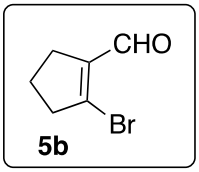

7.23
4.55
3.28
2.66
1.58
OH
O
N
OMe
OEt
OEt
tBu-O
O
9a
0.82
1.00
5.43
2.67
3.87
1.99
2.47
2.27
9.65
13.13
f1 (ppm)
168.02
151.05
146.51
133.39
128.87
124.92
121.76
103.86
81.31
77.46
77.14
76.82
62.68
62.00
61.16
48.80
43.55
39.71
35.73
29.09
29.06
28.37
15.39
15.32
f1 (ppm)


12.54
10.35
4.66
3.69
3.41
3.32
3.31
2.82
2.72
1.60
1.17
1.14
OH
O
OEt
OEt
tBu-O
O
12a
0.98
1.00
1.00
2.06
2.09
1.97
2.01
2.00
8.96
6.15
6.20
f1 (ppm)

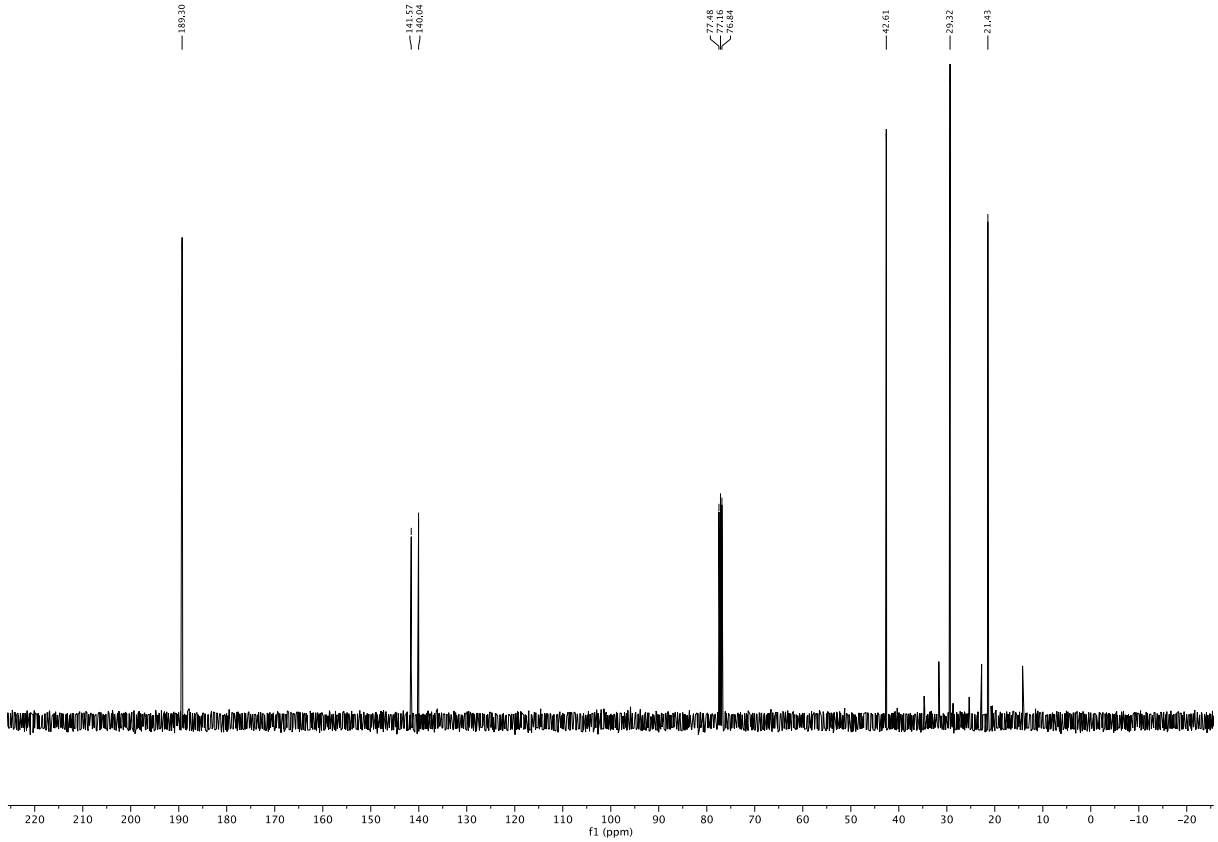

197.61
167.66
160.51
152.07
138.41
130.15
124.72
117.78
104.00
82.19
77.44 CHLOROFORM-D
77.00 CHLOROFORM-D
76.80 CHLOROFORM-D
63.60
49.08
43.18
39.64
33.44
29.14
28.34
15.32
f1 (ppm)

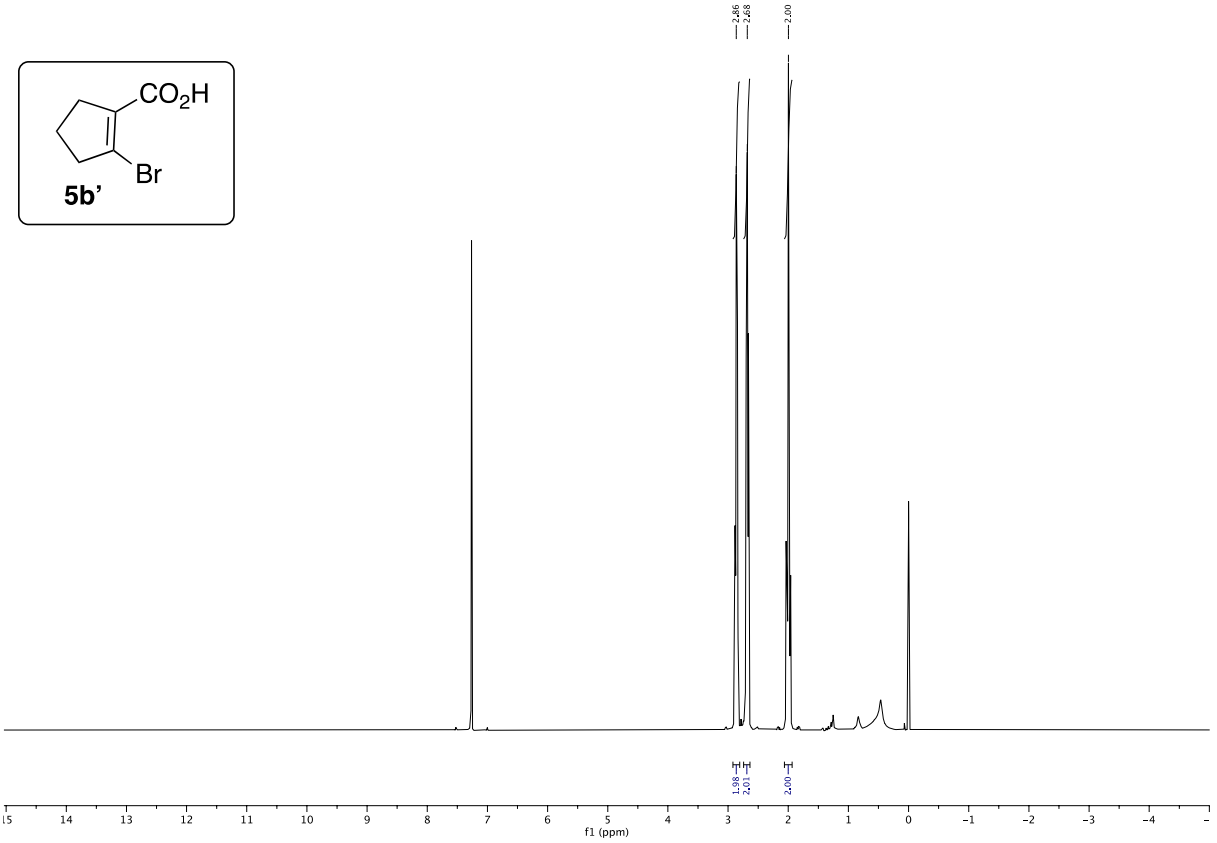

12.02
10.32
7.71
7.70
5.74
5.74
3.56
3.53
3.40
3.36
3.09
2.64
1.13
1.12
OH
O
O
O
OH
illudalic acid (1)
0.80
1.00
0.93
0.97
0.95
0.99
1.92
2.12
5.87
f1 (ppm)

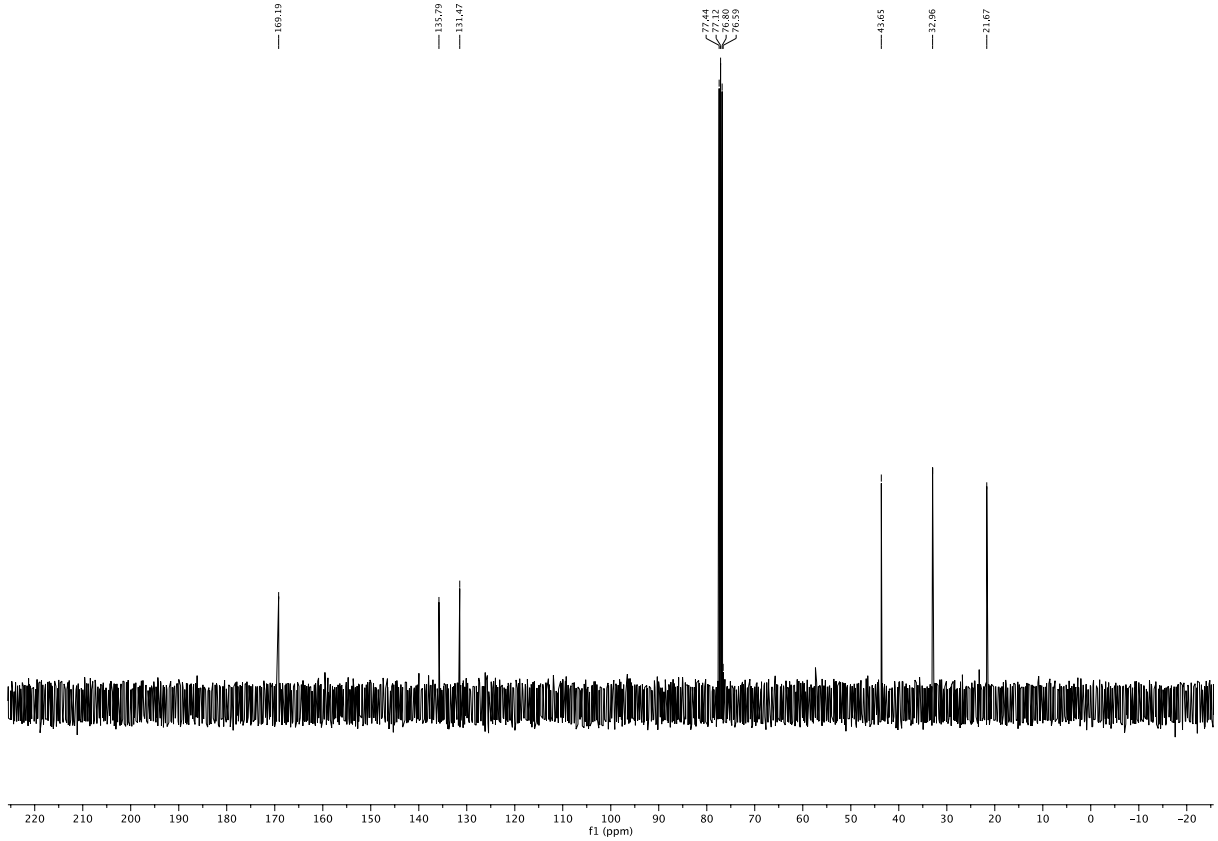

195.31
162.72
161.48
155.86
142.14
130.00
116.71
114.01
94.48
49.83
42.49
42.28
39.94 dmso
39.80 dmso
39.66 dmso
39.52 dmso
39.38 dmso
39.24 dmso
39.10 dmso
33.06
30.45
28.74
f1 (ppm)

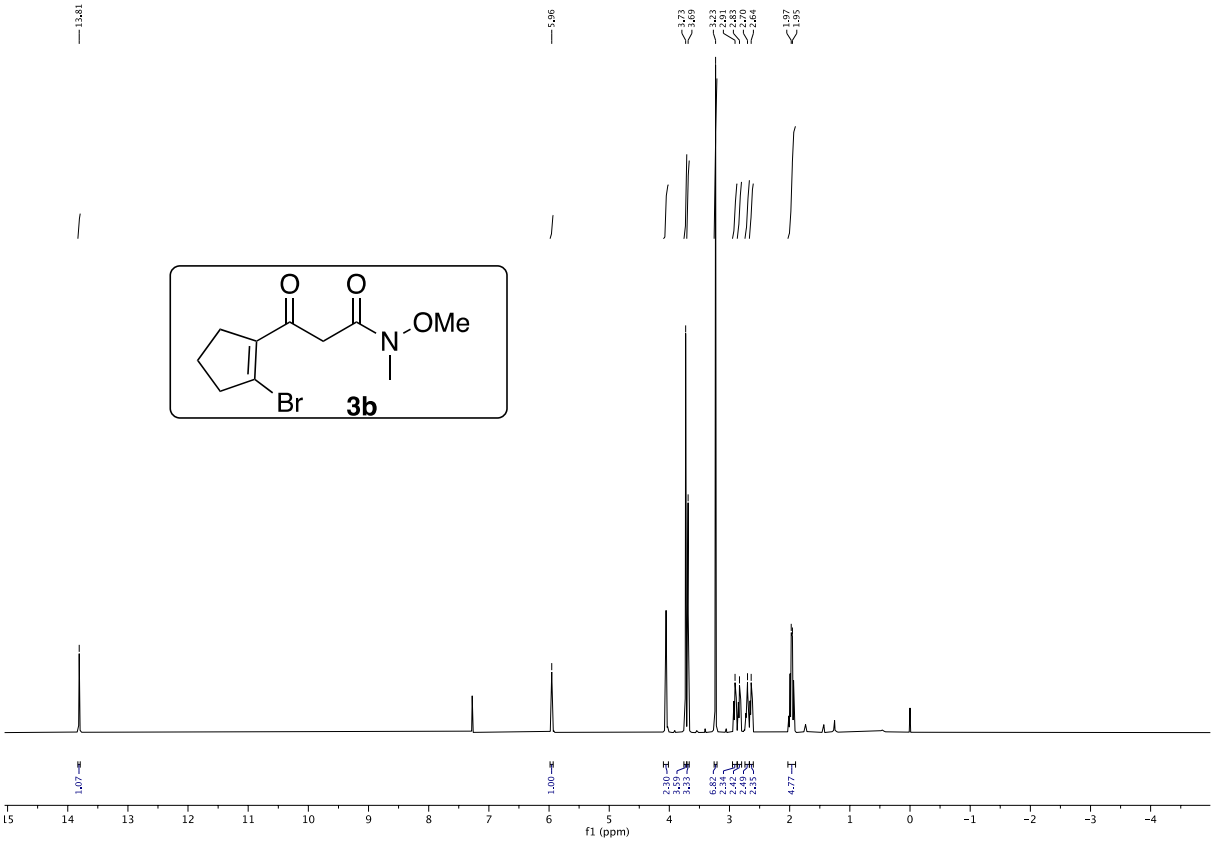

CHO
Br
5b

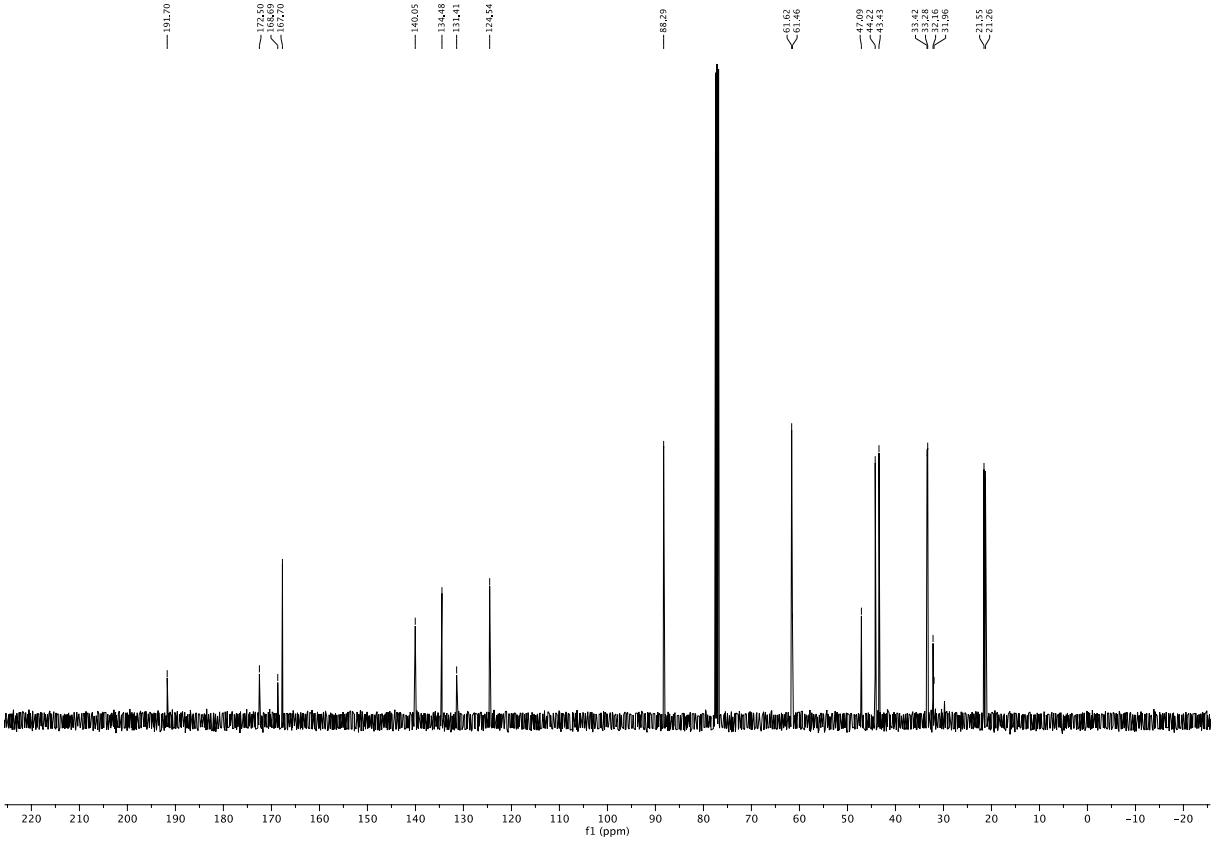
9.90
2.94
2.93
2.91
2.56
2.55
2.55
2.54
2.03
0.72
1.89
1.92
2.00
f1 (ppm)

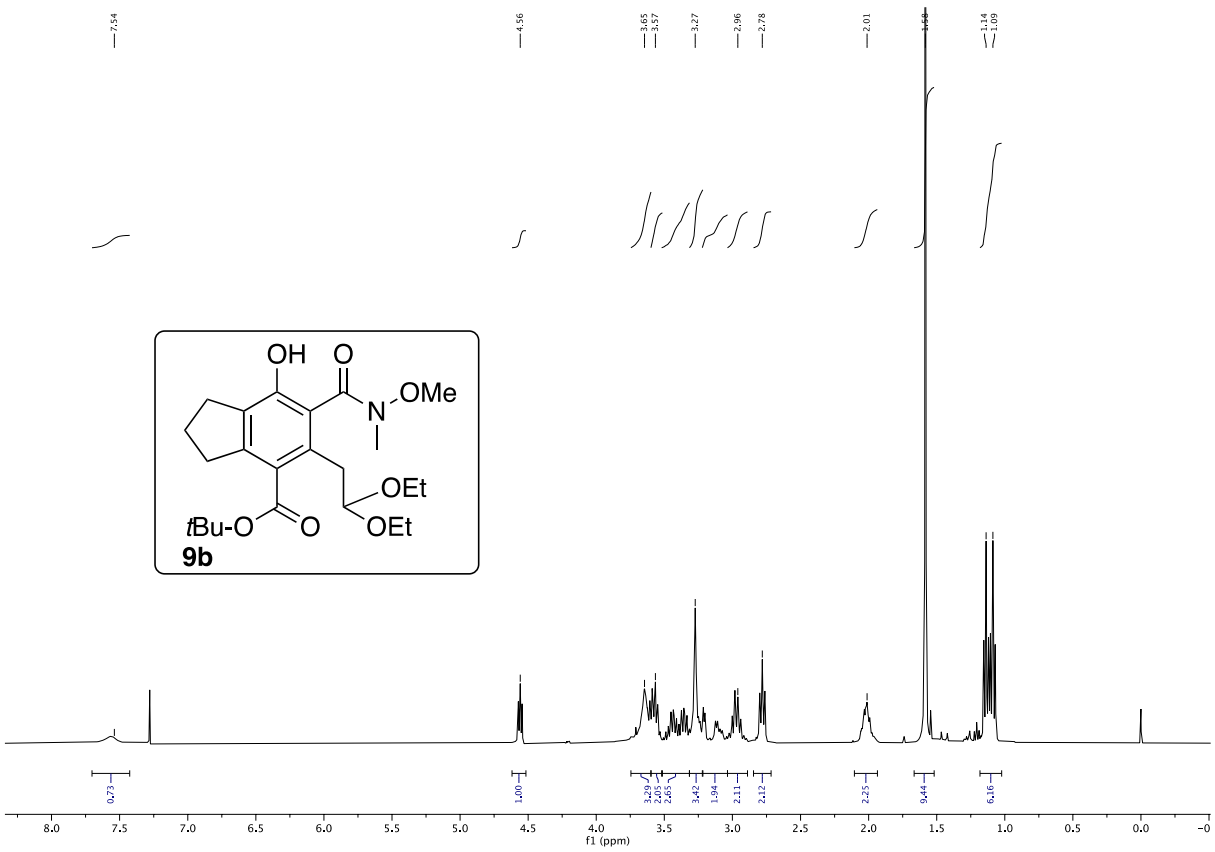

189.30
141.57
140.04
77.48
77.16
76.84
42.61
29.32
21.43
f1 (ppm)

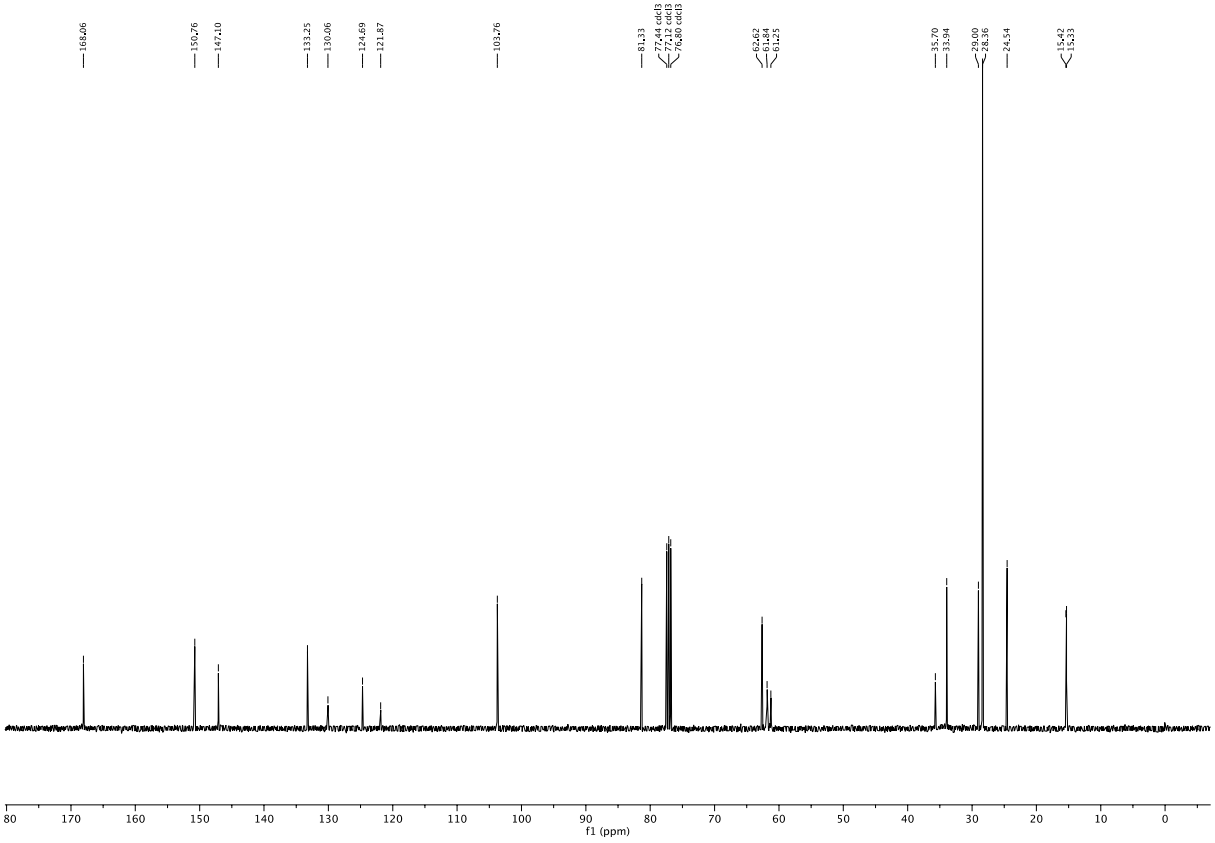

CO2H
Br
5b'
2.86
2.68
2.00
1.88
2.01
2.00
f1 (ppm)

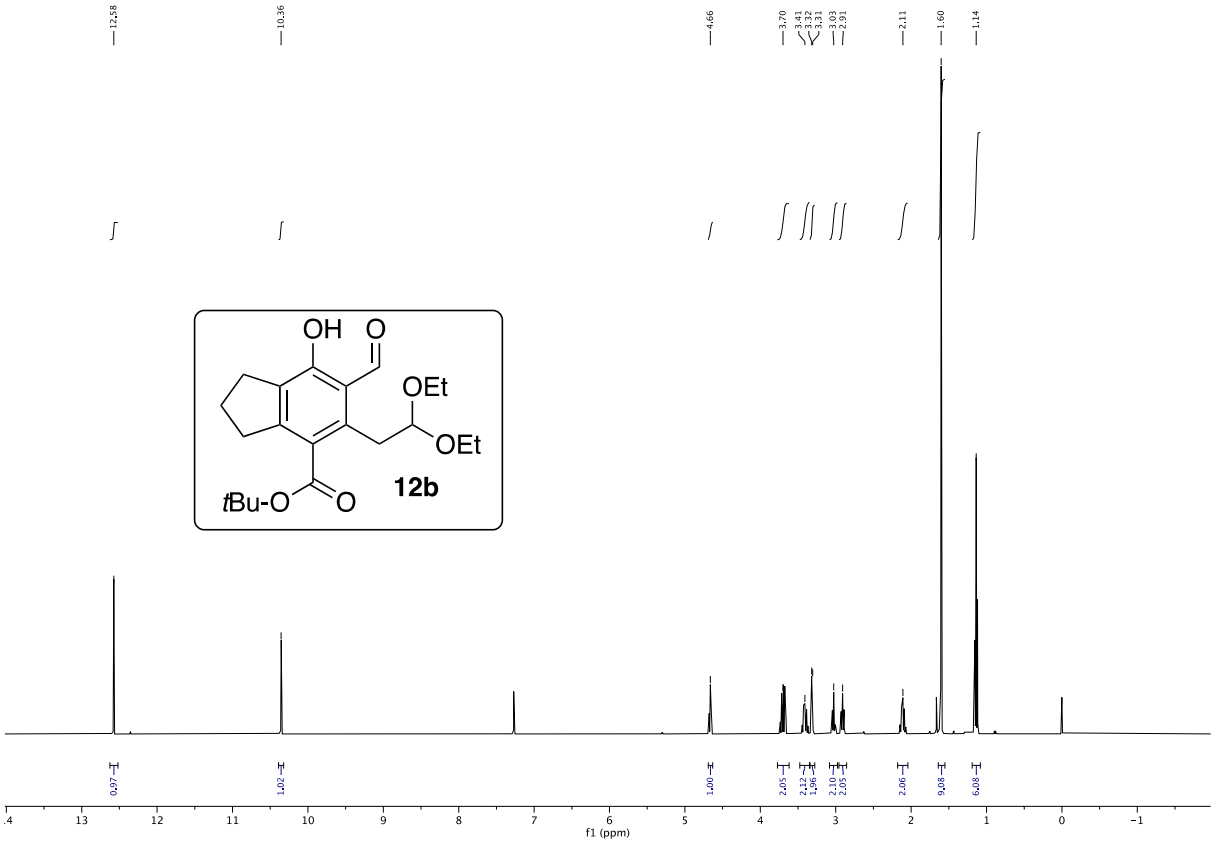

169.19
135.79
131.47
77.44
77.12
76.80
76.59
43.65
32.96
21.67
f1 (ppm)


13.81
5.96
3.73
3.69
3.23
2.91
2.83
2.70
2.64
1.97
1.95
O
O
N
OMe
Br
3b
1.07
1.00
2.30
3.59
3.33
6.82
2.34
2.42
2.40
2.38
4.77
f1 (ppm)


191.70
172.50
168.69
167.70
140.05
134.48
131.41
124.54
88.29
61.62
61.46
47.09
44.72
43.43
33.42
33.38
32.16
31.96
21.55
21.26
f1 (ppm)


7.54
4.56
3.65
3.57
3.27
2.96
2.78
2.01
1.14
1.09
OH
O
N
OMe
OEt
OEt
tBu-O
O
9b
0.73
1.00
3.20
3.03
2.65
3.42
1.94
2.11
2.12
2.25
9.44
6.16
f1 (ppm)


168.06
150.76
147.10
133.25
130.96
124.69
121.87
103.76
81.33
77.44 cdcl3
77.12 cdcl3
76.80 cdcl3
62.62
61.84
61.25
35.70
33.94
29.00
28.36
24.54
15.42
15.33
f1 (ppm)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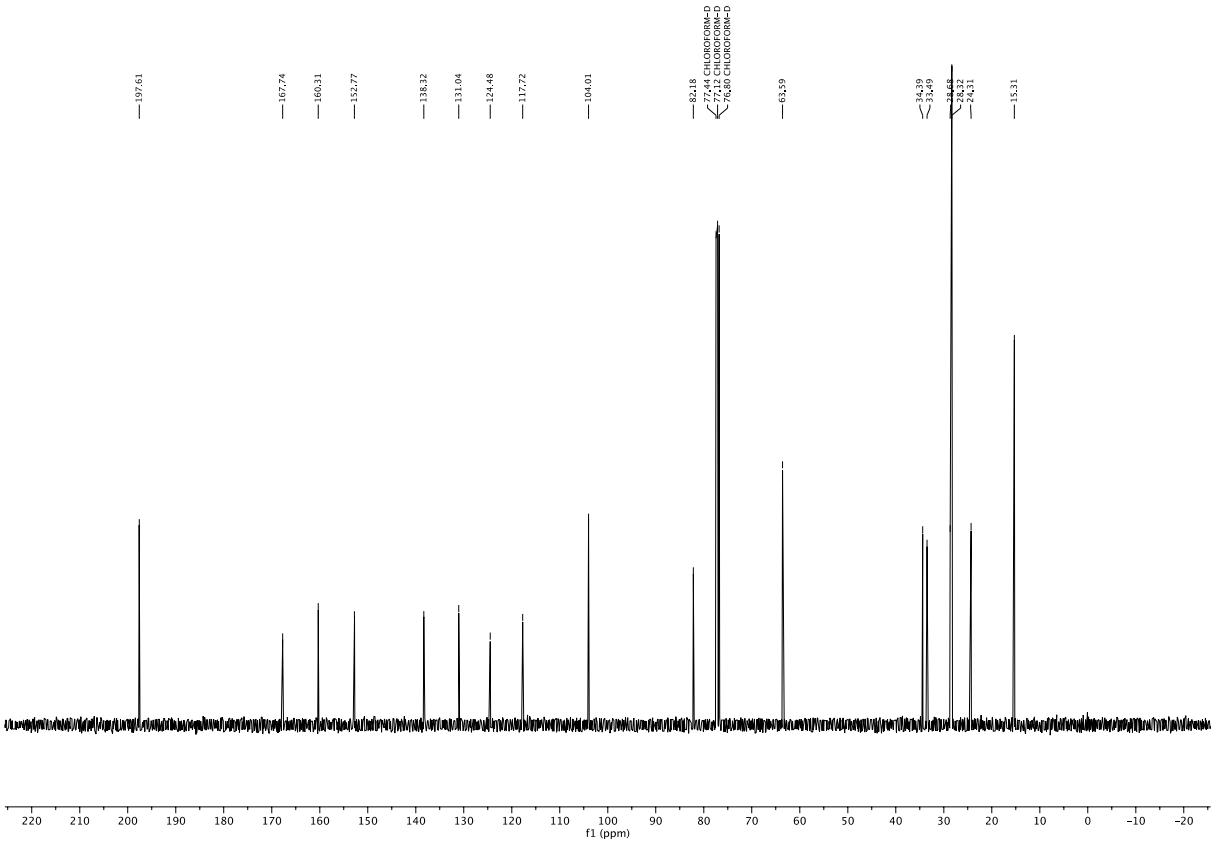
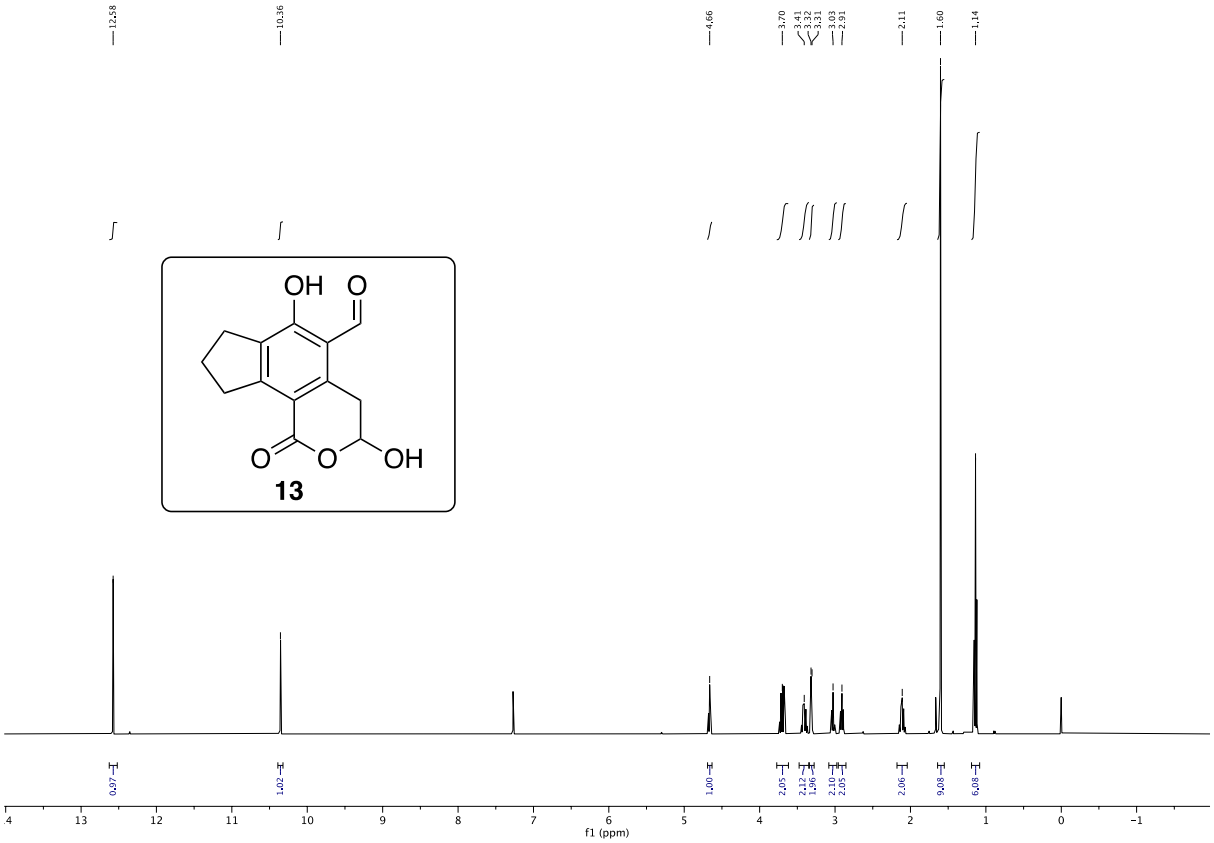
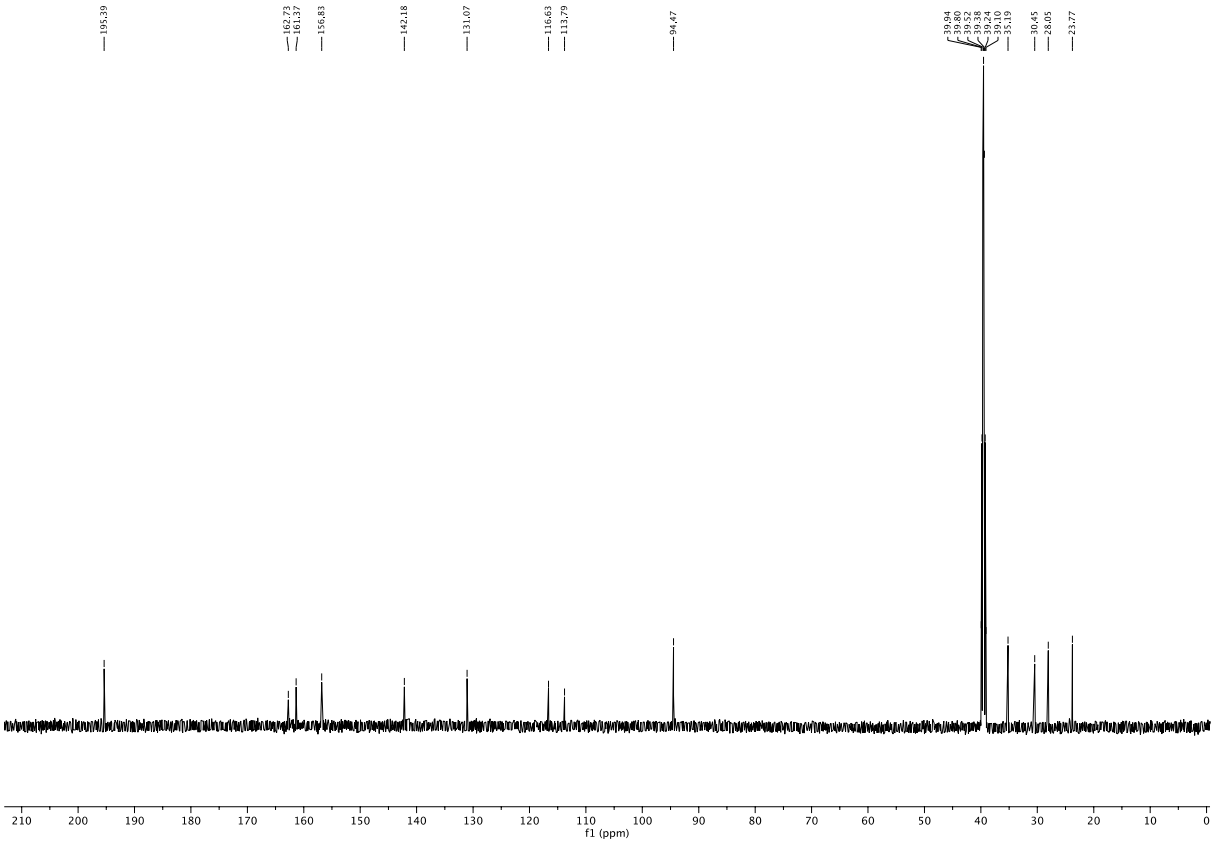
10.36
4.66
3.70
3.41
3.32
3.31
3.03
2.91
2.11
1.60
1.14
OH
O
OEt
OEt
tBu-O
O
12b
0.97
1.02
1.00
2.05
2.12
1.98
2.10
2.05
2.06
9.08
6.08
f1 (ppm)


197.61
167.74
160.31
152.77
138.32
131.04
124.48
117.72
104.01
82.18
77.44 CHLOROFORM-D
77.13 CHLOROFORM-D
76.80 CHLOROFORM-D
63.59
34.39
33.49
28.68
28.32
24.31
15.31
f1 (ppm)


12.58
10.36
4.66
3.70
3.41
3.32
3.31
3.03
2.93
2.11
1.60
1.14
OH
O
O
O
OH
13
0.97
1.02
1.00
2.05
2.12
1.96
2.10
2.05
2.06
9.08
6.08
f1 (ppm)


195.39
162.73
161.37
156.83
142.18
131.07
116.63
113.79
94.47
39.94
39.80
39.52
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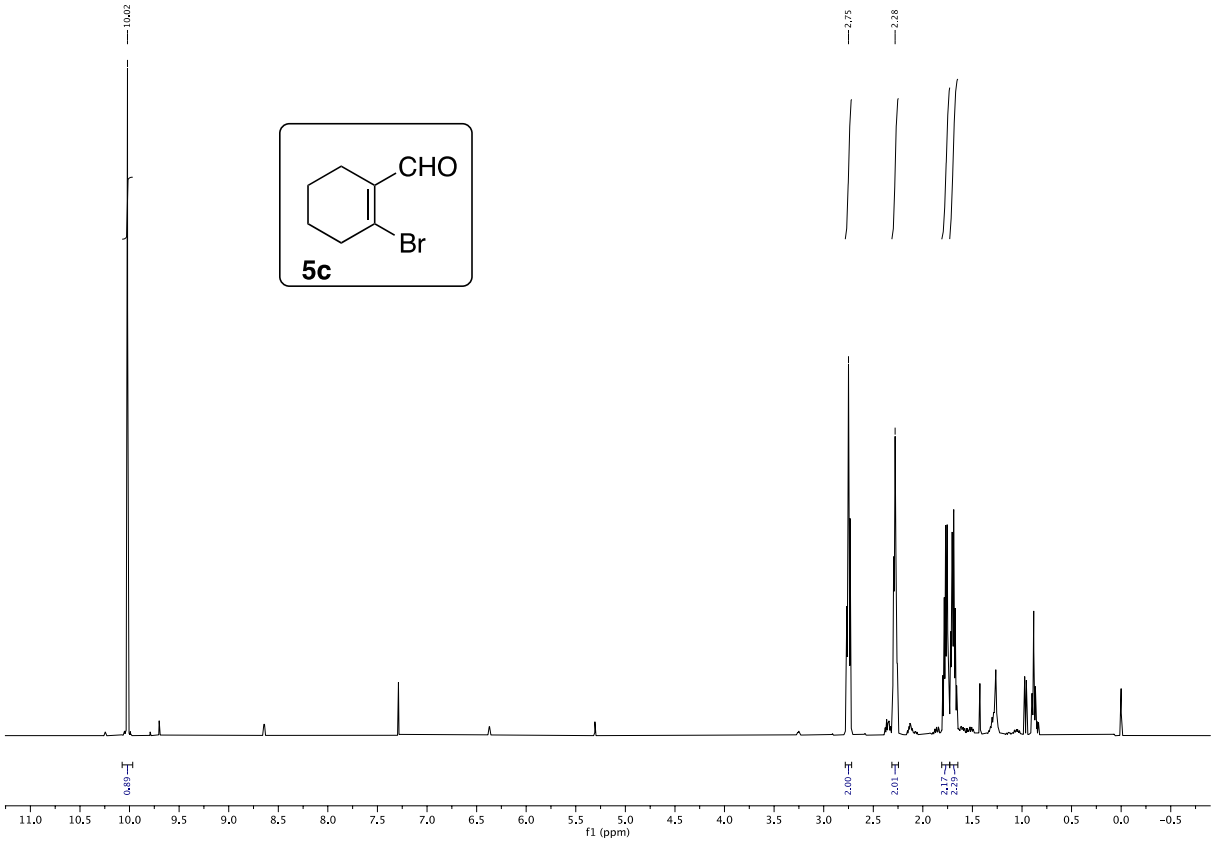
35.19
30.45
28.05
23.77
f1 (ppm)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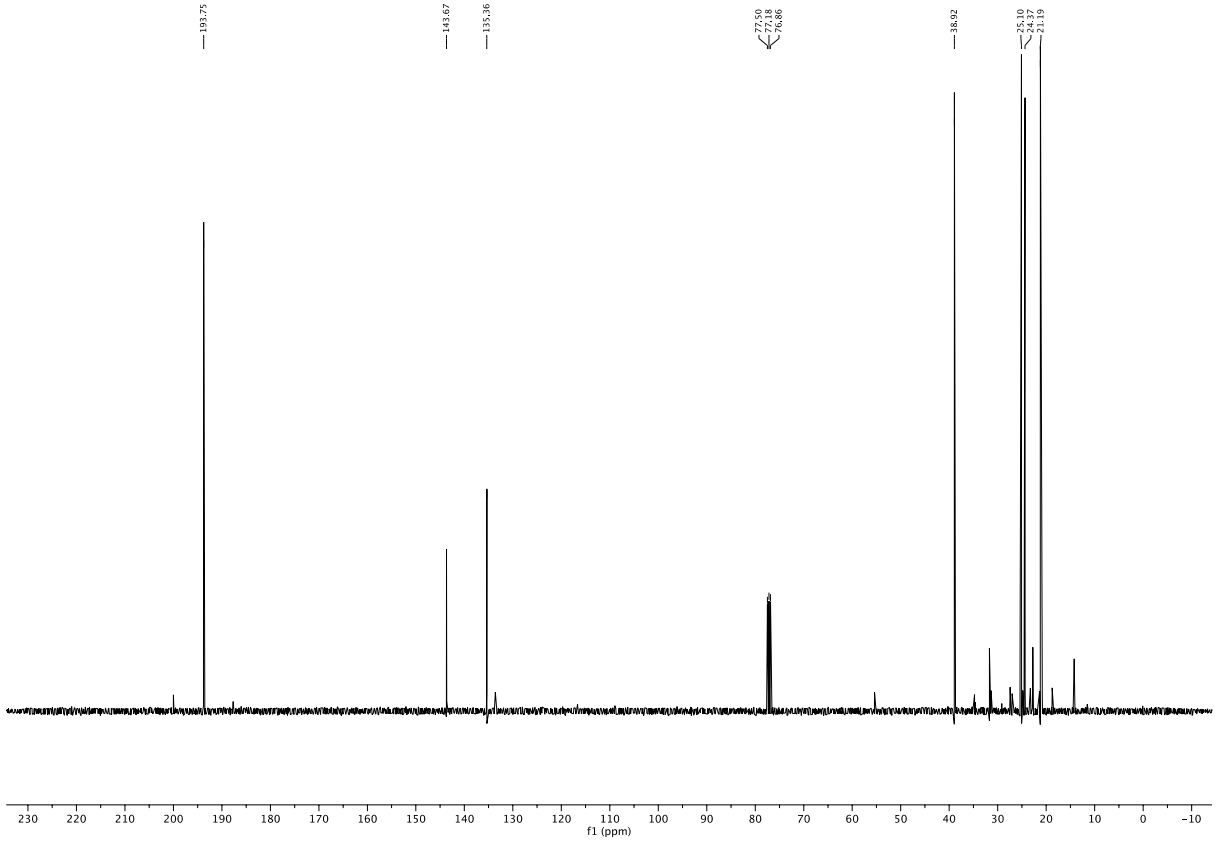
2.75
2.28
CHO
Br
5c
0.89
2.00
2.01
2.17
2.29
f1 (ppm)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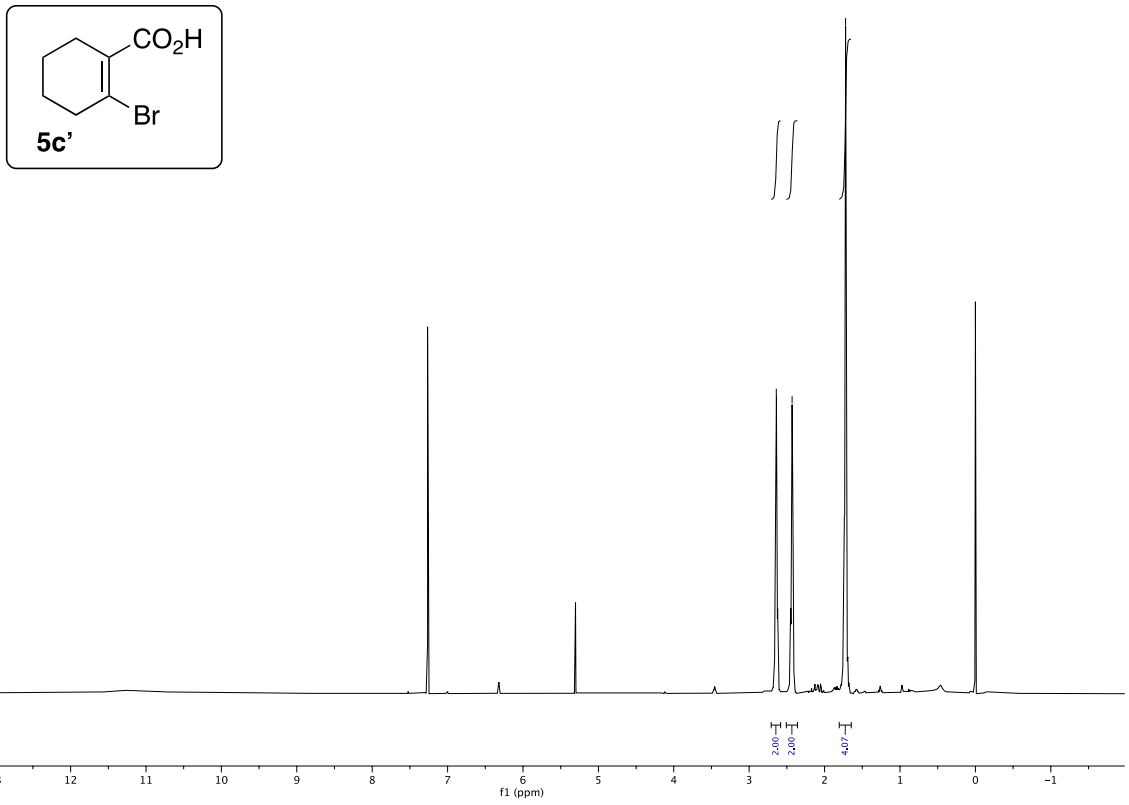
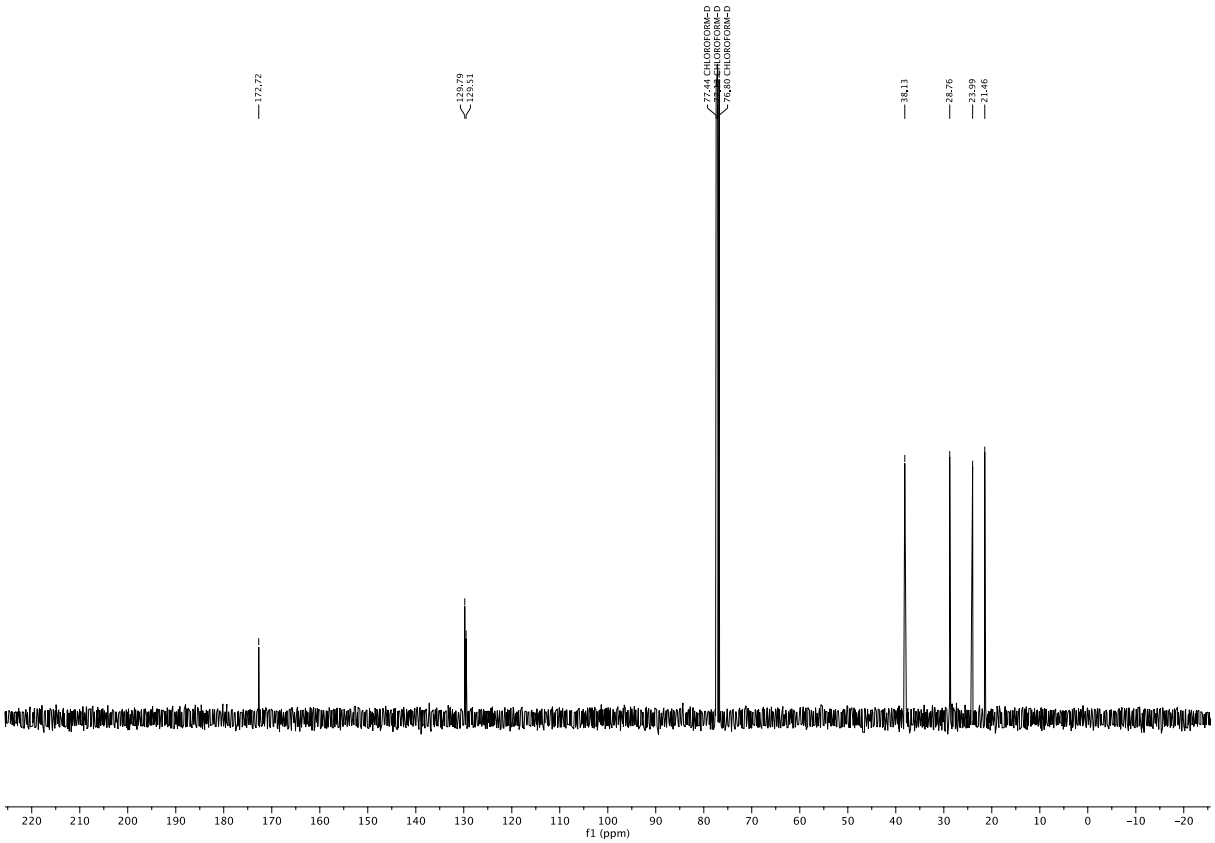
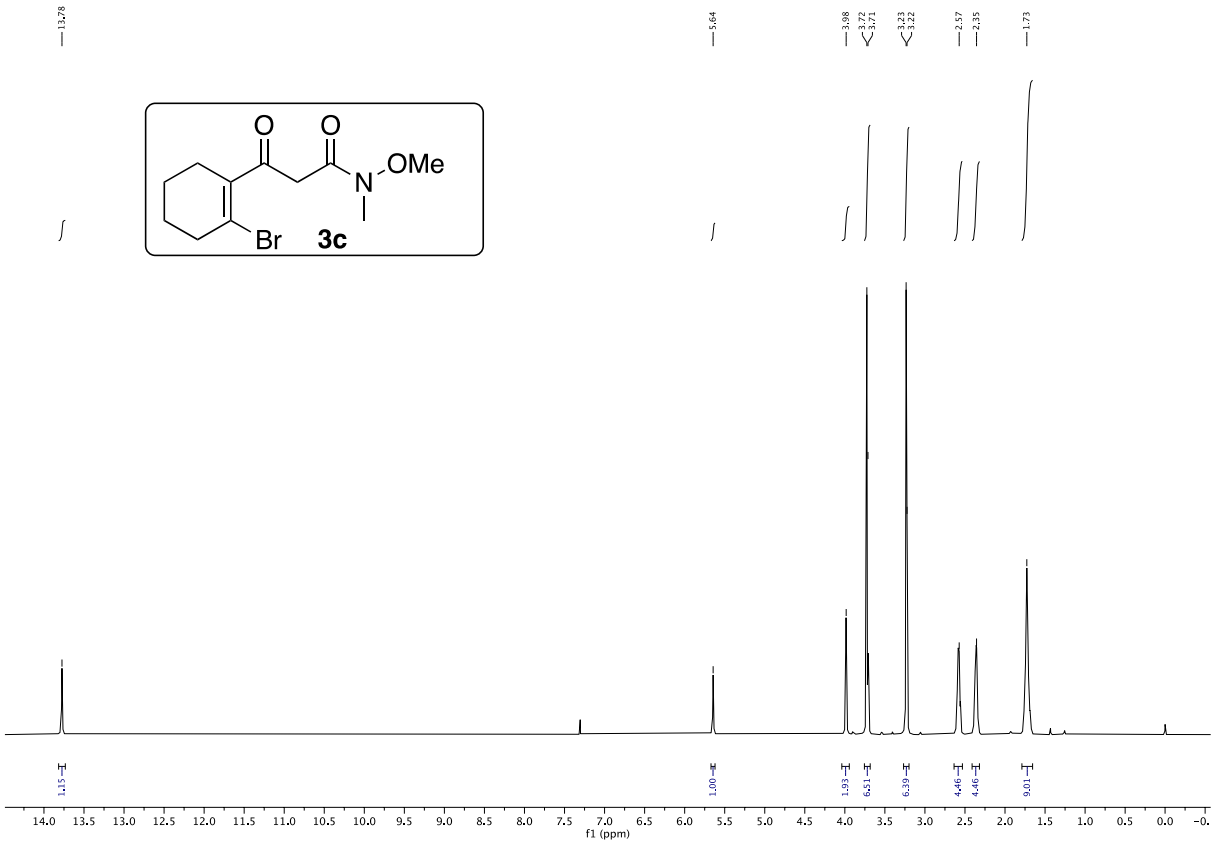
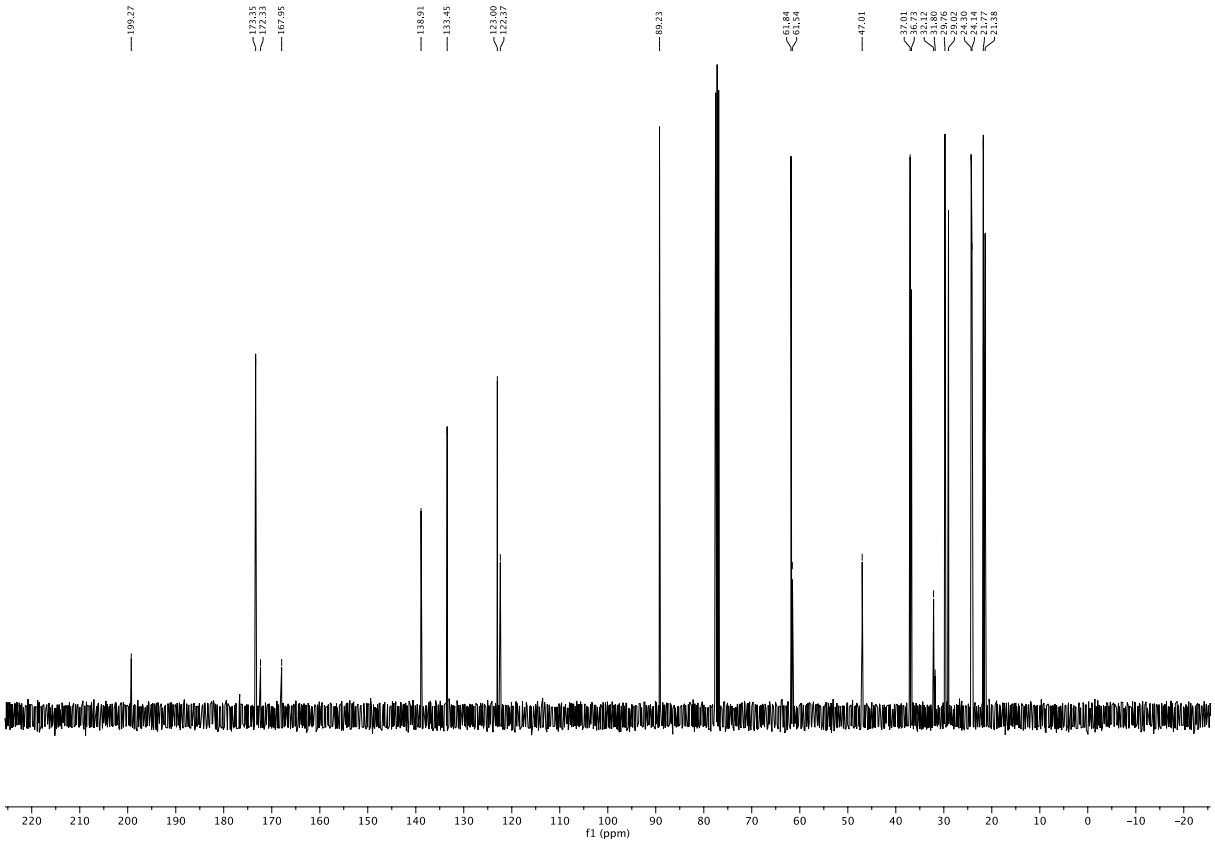
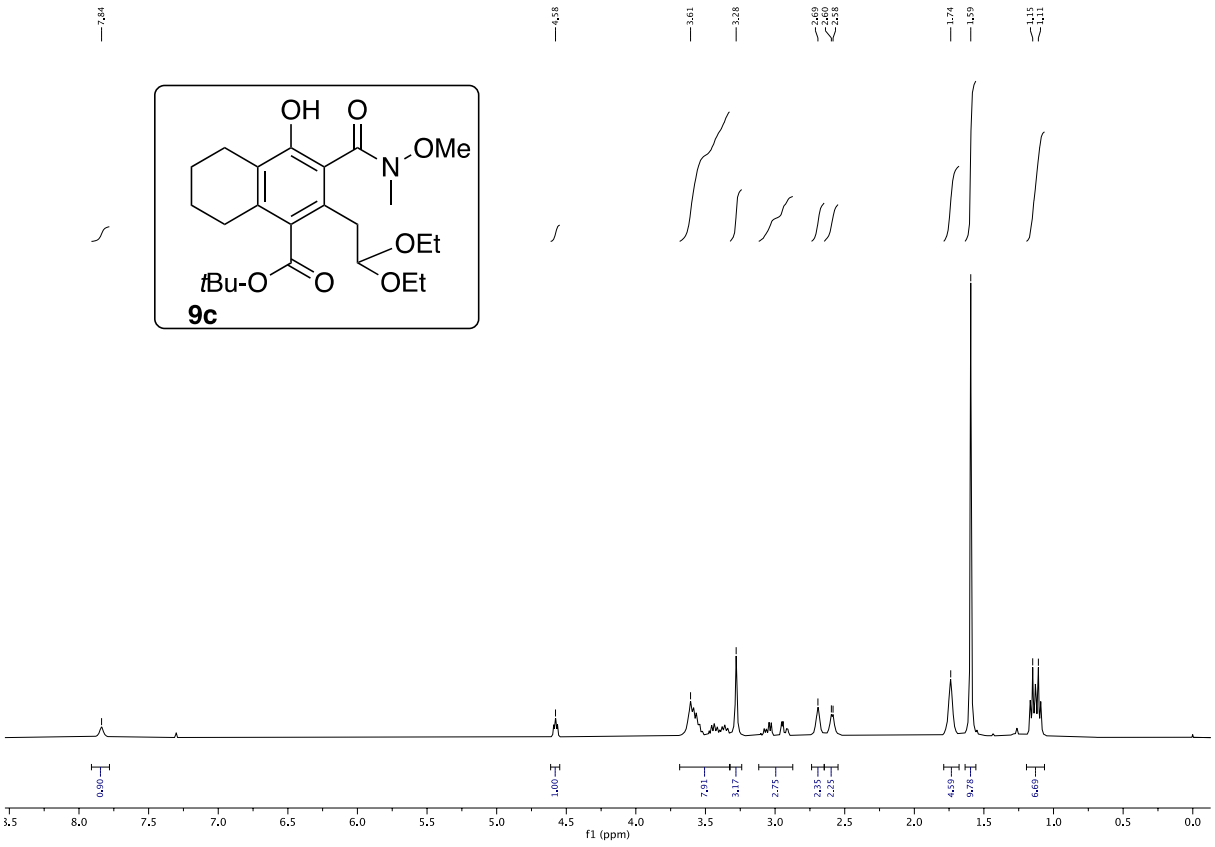
143.67
135.36
77.50
77.18
76.86
38.92
25.10
24.37
21.19
f1 (ppm)

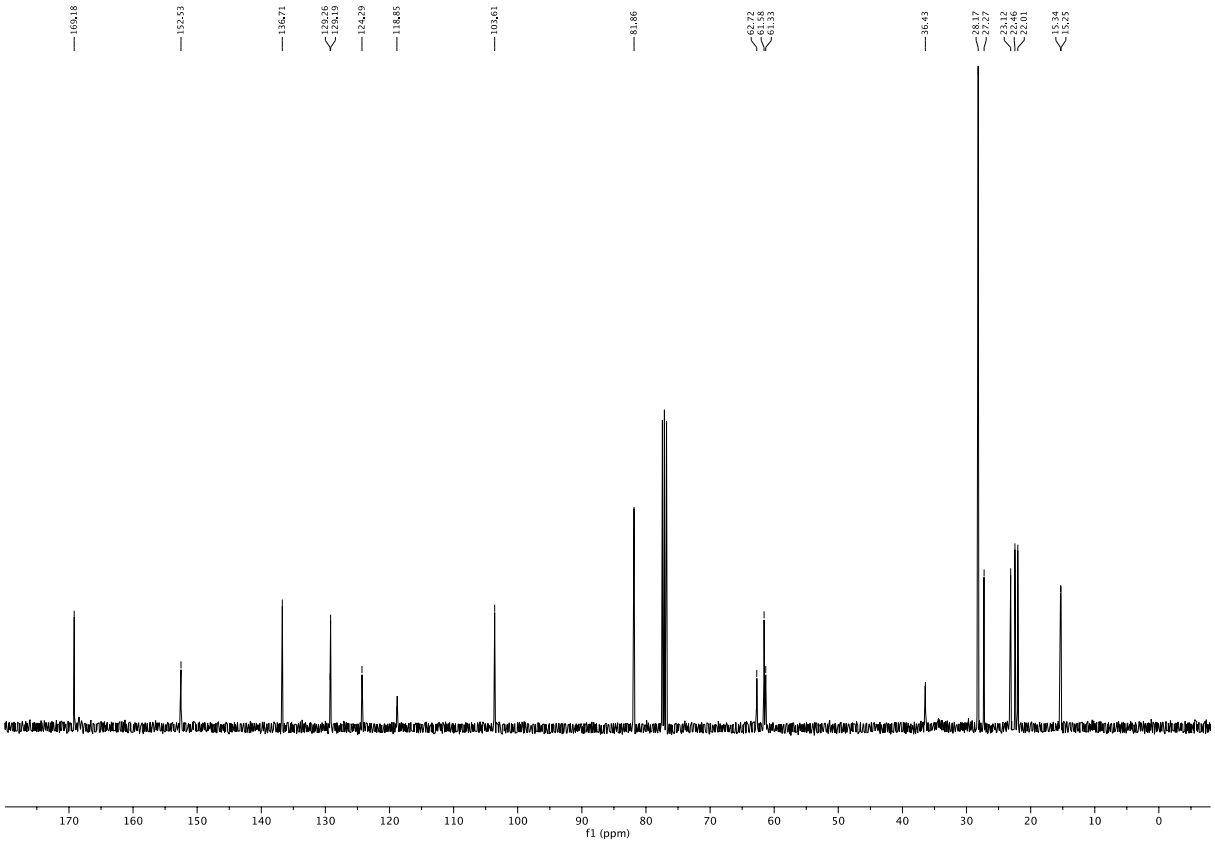

CO2H
Br
5c'
2.64
2.43
1.72
2.00
2.00
4.07
f1 (ppm)

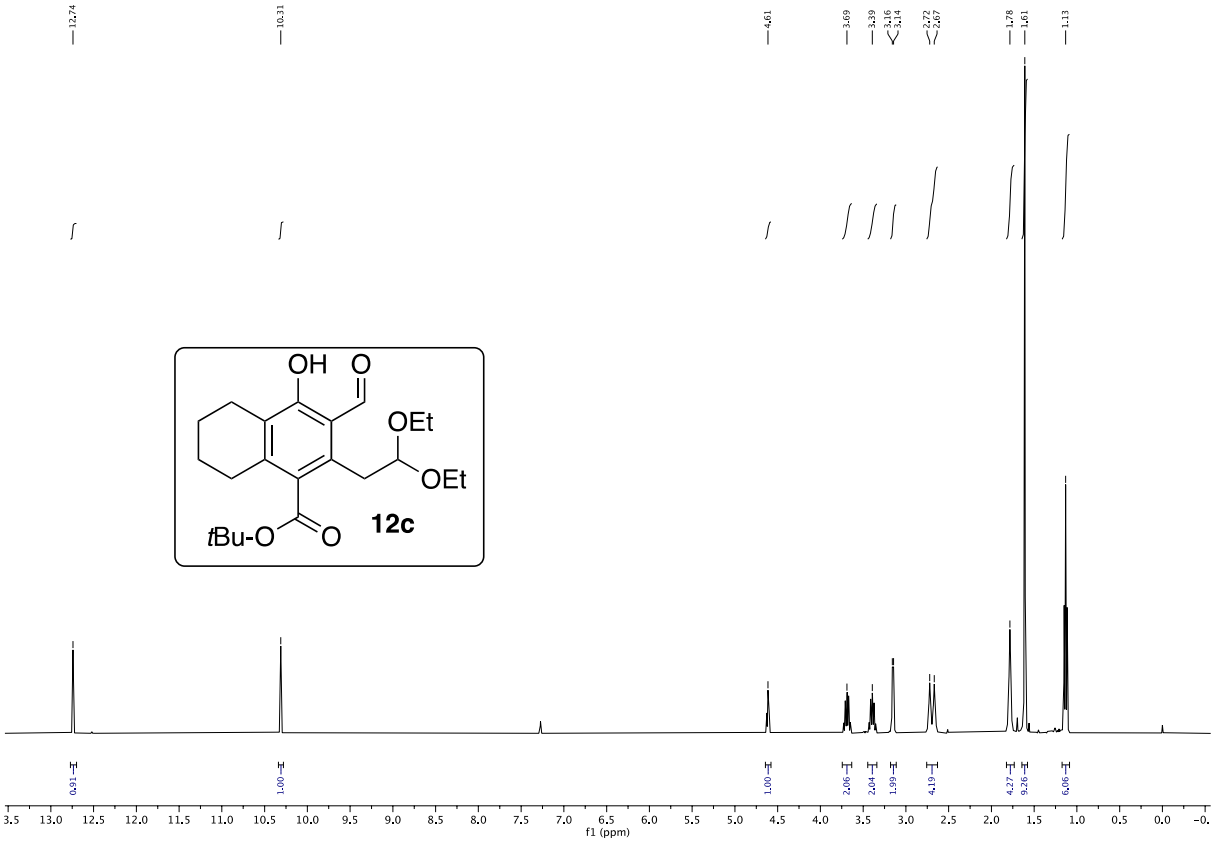

172.72
129.79
129.51
77.44 CHLOROFORM-D
77.12 CHLOROFORM-D
76.80 CHLOROFORM-D
38.13
28.76
23.99
21.46
f1 (ppm)


13.78
5.64
3.98
3.72
3.71
3.23
3.22
2.57
2.35
1.73
O
O
N
OMe
Br
3c
1.15
1.00
1.93
6.51
6.39
4.46
4.46
9.01
f1 (ppm)


199.27
173.35
172.33
167.95
138.91
133.45
122.00
122.37
89.23
61.84
61.54
47.01
37.01
36.73
32.12
31.80
29.76
29.03
24.30
24.14
21.77
21.38
f1 (ppm)


7.84
4.58
3.61
3.28
2.69
2.60
2.58
1.74
1.59
1.15
1.11
OH
O
N
OMe
OEt
OEt
tBu-O
O
9c
0.90
1.00
7.91
3.17
2.75
2.35
2.25
4.59
9.78
6.69
f1 (ppm)


169.18
152.53
136.71
130.26
128.19
124.29
118.85
103.61
81.86
62.72
61.58
61.33
36.43
28.17
27.27
23.12
22.46
22.01
15.34
15.25
f1 (ppm)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4.61
3.69
3.39
3.16
3.14
2.72
2.67
1.78
1.61
1.13
OH
O
OEt
OEt
tBu-O
O
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1.00
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2.04
1.99
4.19
4.27
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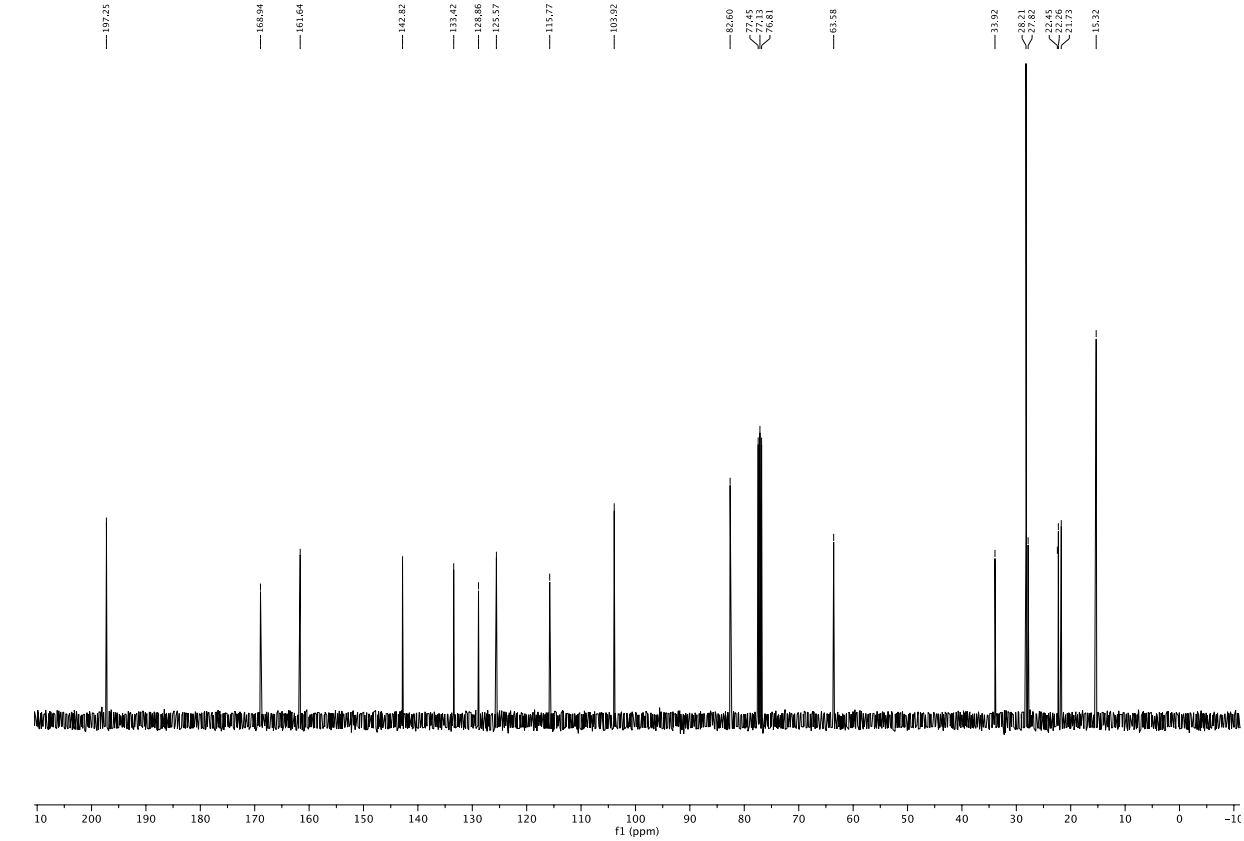
6.06
f1 (ppm)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161.64
142.82
133.42
128.86
125.57
115.77
103.92
82.60
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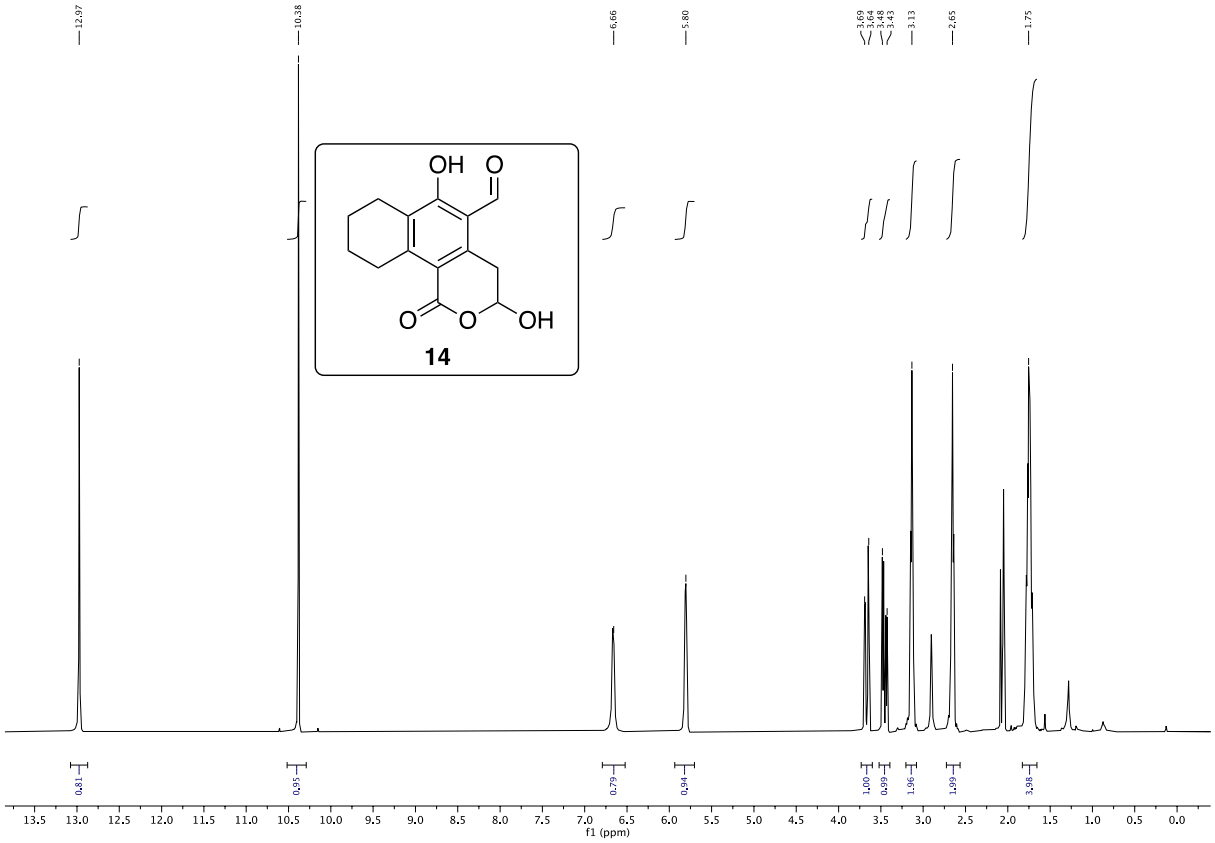
63.58
33.92
28.21
27.82
22.45
22.26
21.73
15.32
f1 (ppm)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3.64
3.48
3.43
3.13
2.65
1.75
OH
O
O
O
OH
14
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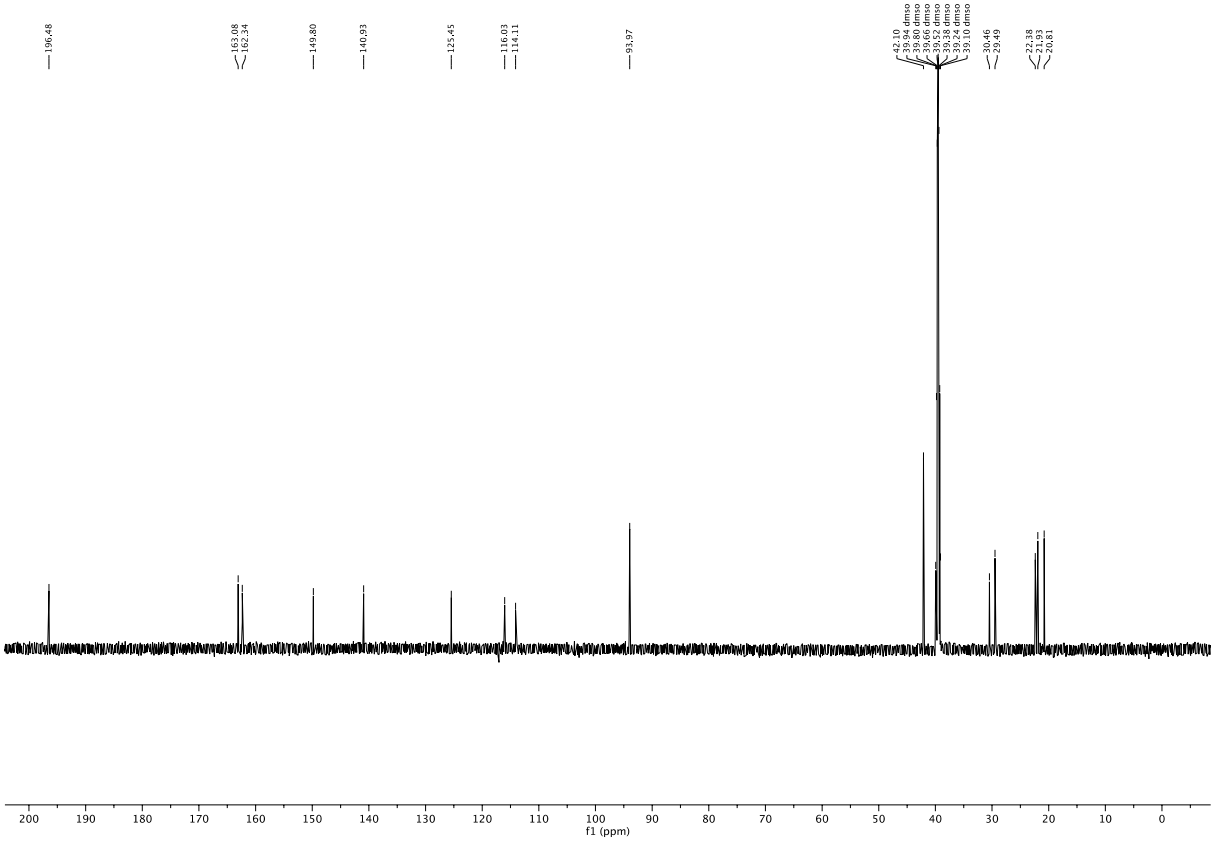
0.95
0.79
0.94
1.00
0.99
1.96
1.99
3.98
f1 (ppm)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149.80
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114.11
93.97
42.10
39.94 dmso
39.80 dmso
39.66 dmso
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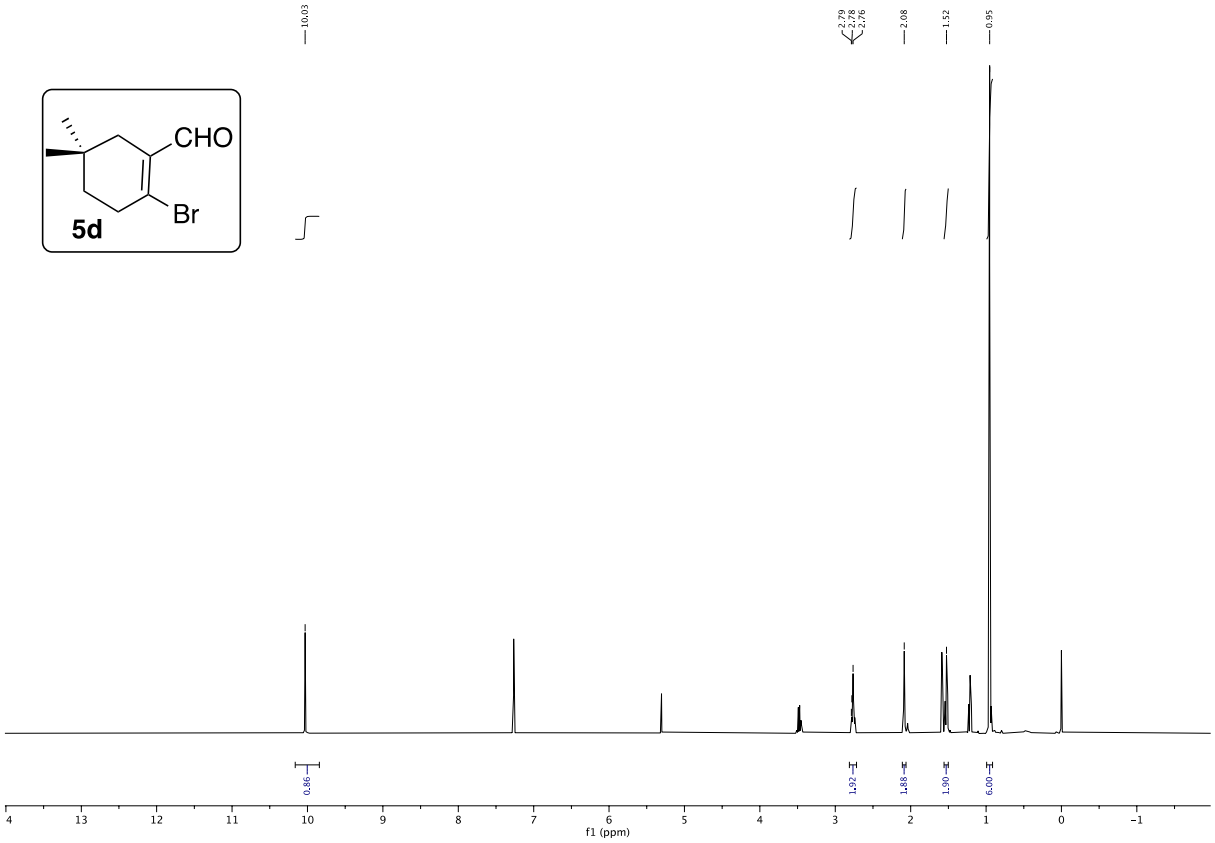
39.24 dmso
39.10 dmso
30.46
29.49
22.38
21.83
20.81
f1 (ppm)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CHO
Br
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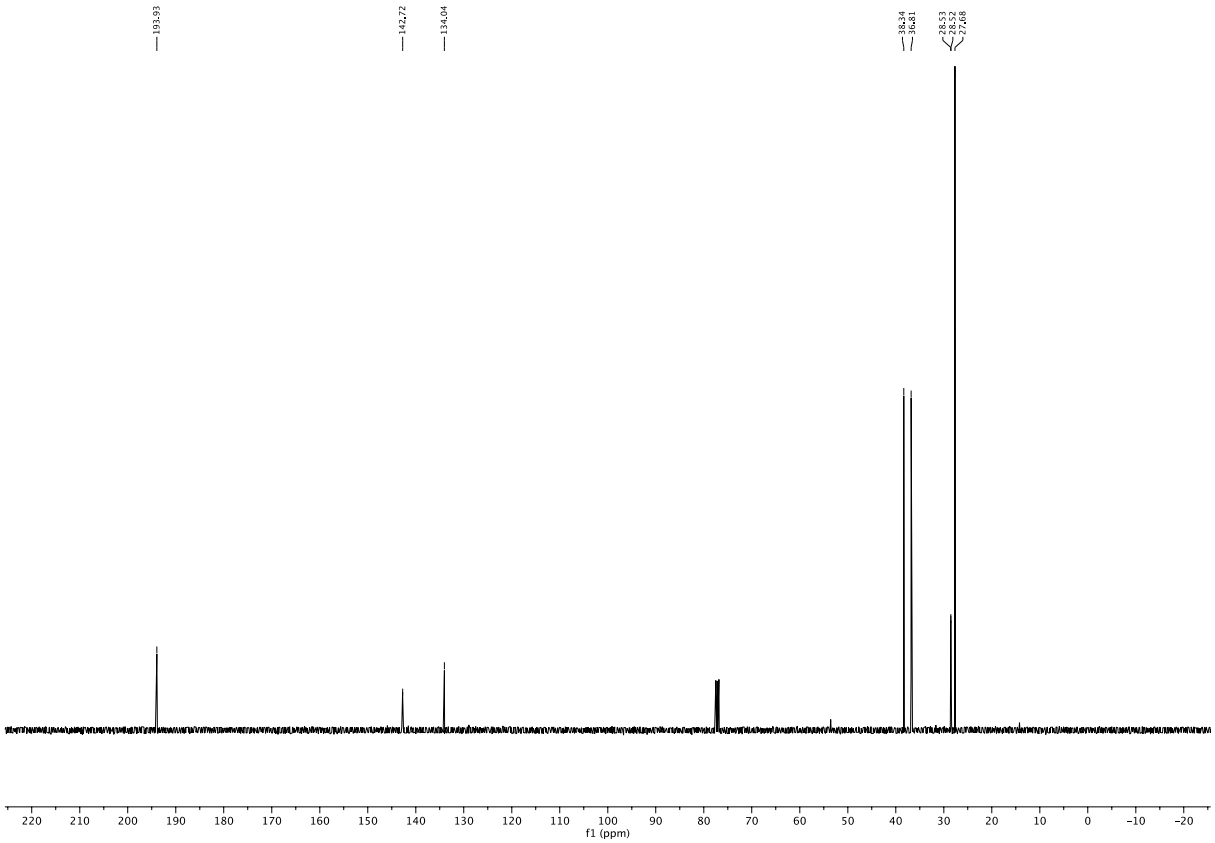
6.00
f1 (ppm)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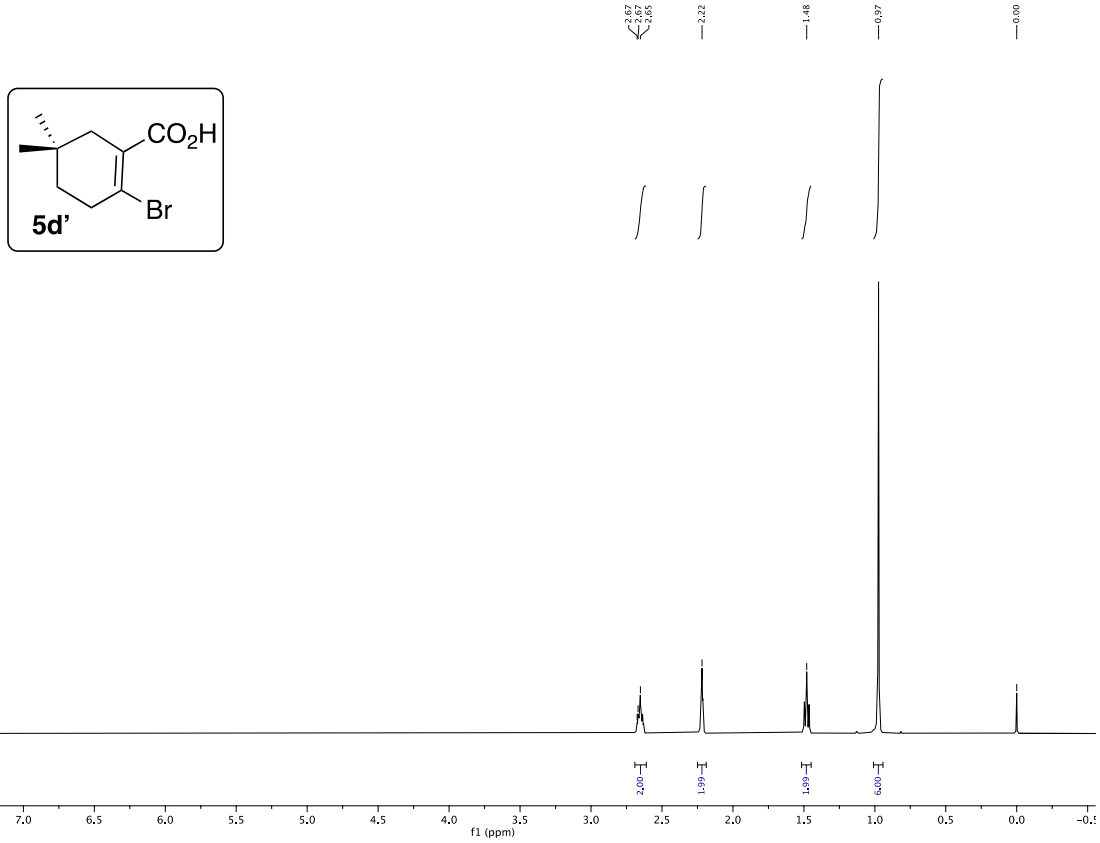
f1 (ppm)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0.00
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Br
5d'
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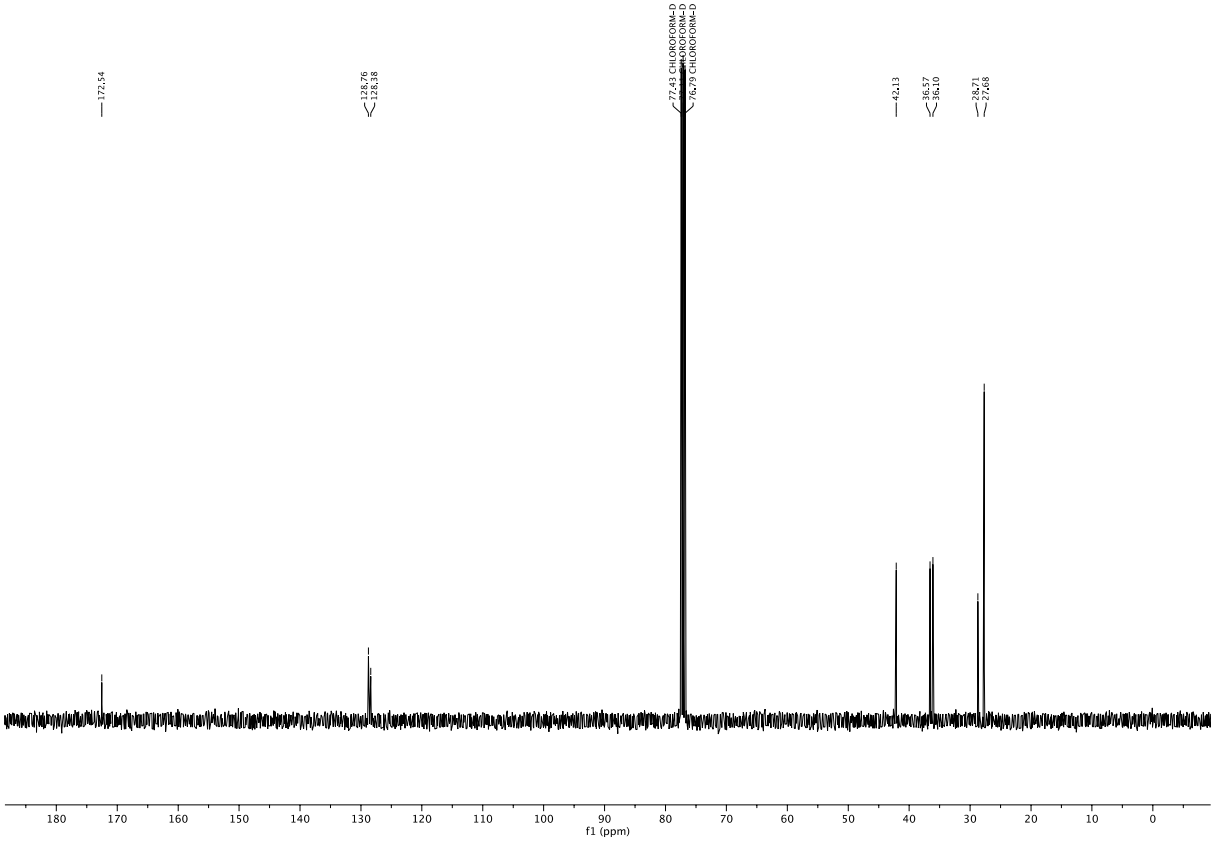
1.99
1.99
6.00
f1 (ppm)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128.38
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76.79 CHLOROFORM-D
42.13
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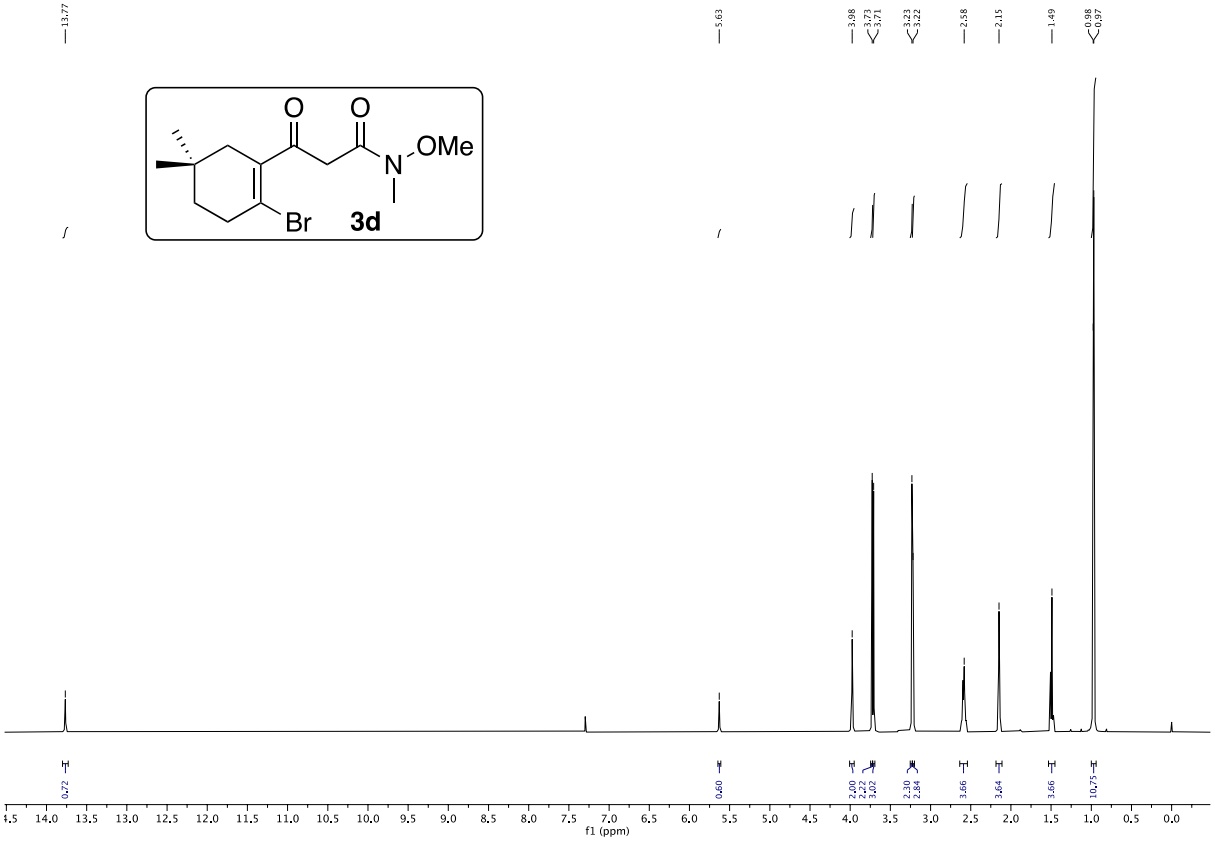
36.10
28.71
27.68
f1 (ppm)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3.23
3.22
2.58
2.15
1.49
0.98
0.97
O
O
N
OMe
Br
3d
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0.60
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2.22
3.02
2.30
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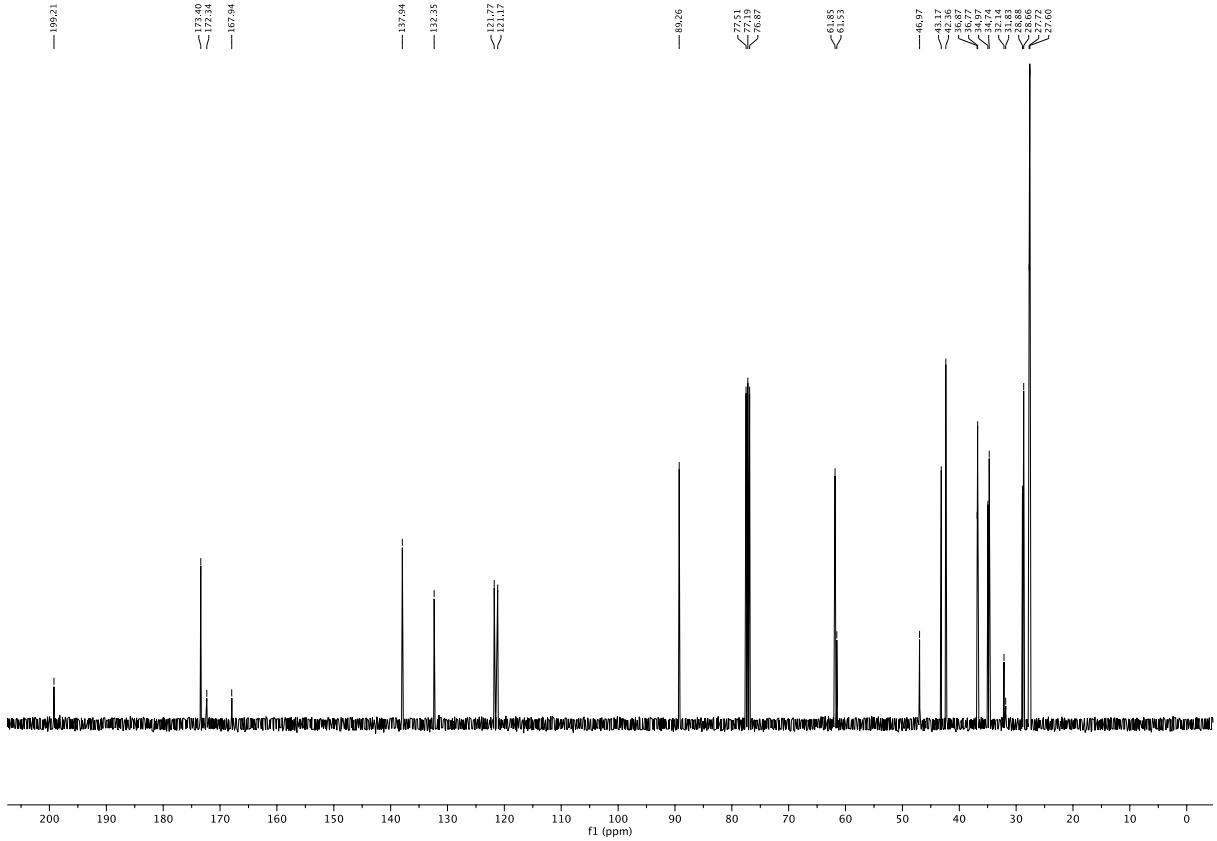
3.64
3.66
10.75
f1 (ppm)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167.94
137.94
132.35
121.77
121.17
89.26
77.51
77.19
76.87
61.85
61.53
46.97
43.17
42.36
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36.77
34.97
34.74
32.14
31.88
28.88
28.66
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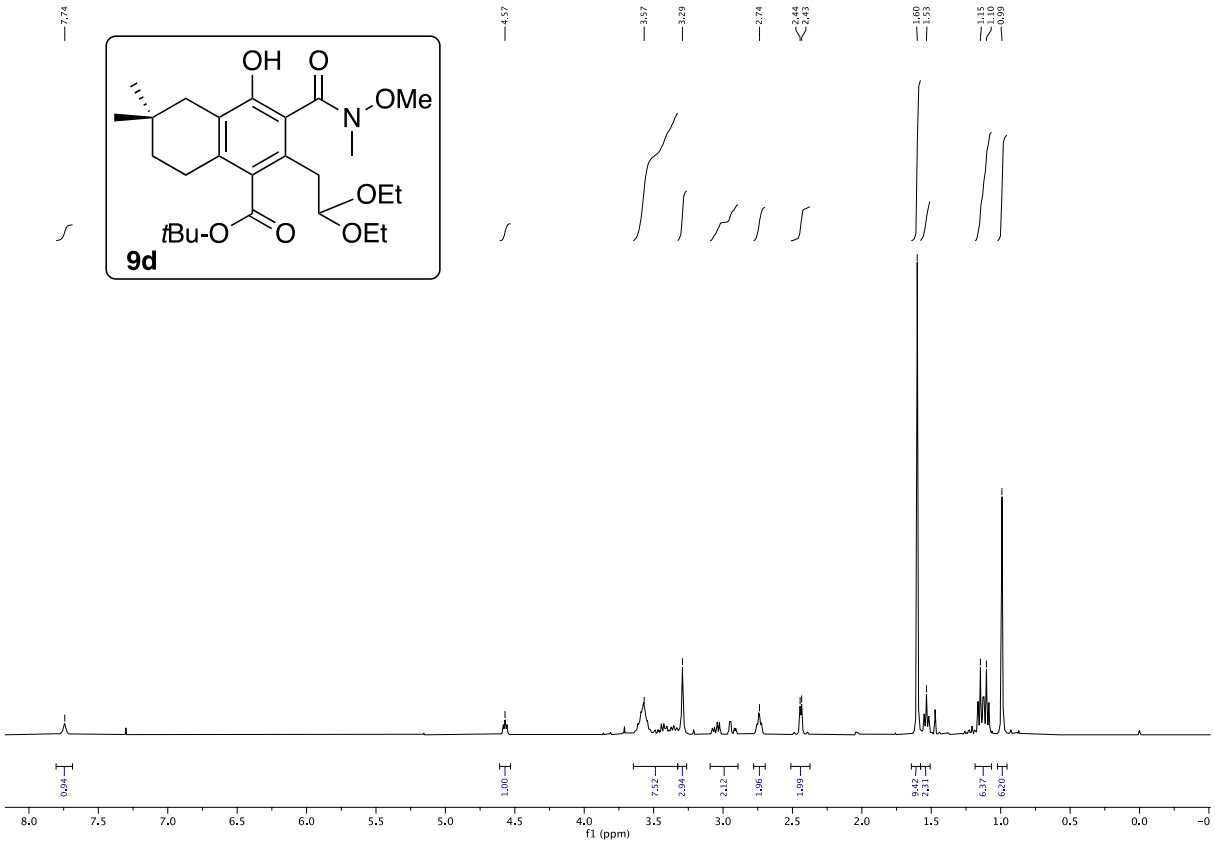
27.60
f1 (ppm)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1.60
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1.15
1.10
0.99
OH
O
N
OMe
OEt
OEt
tBu-O
O
9d
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2.94
2.12
1.06
1.09
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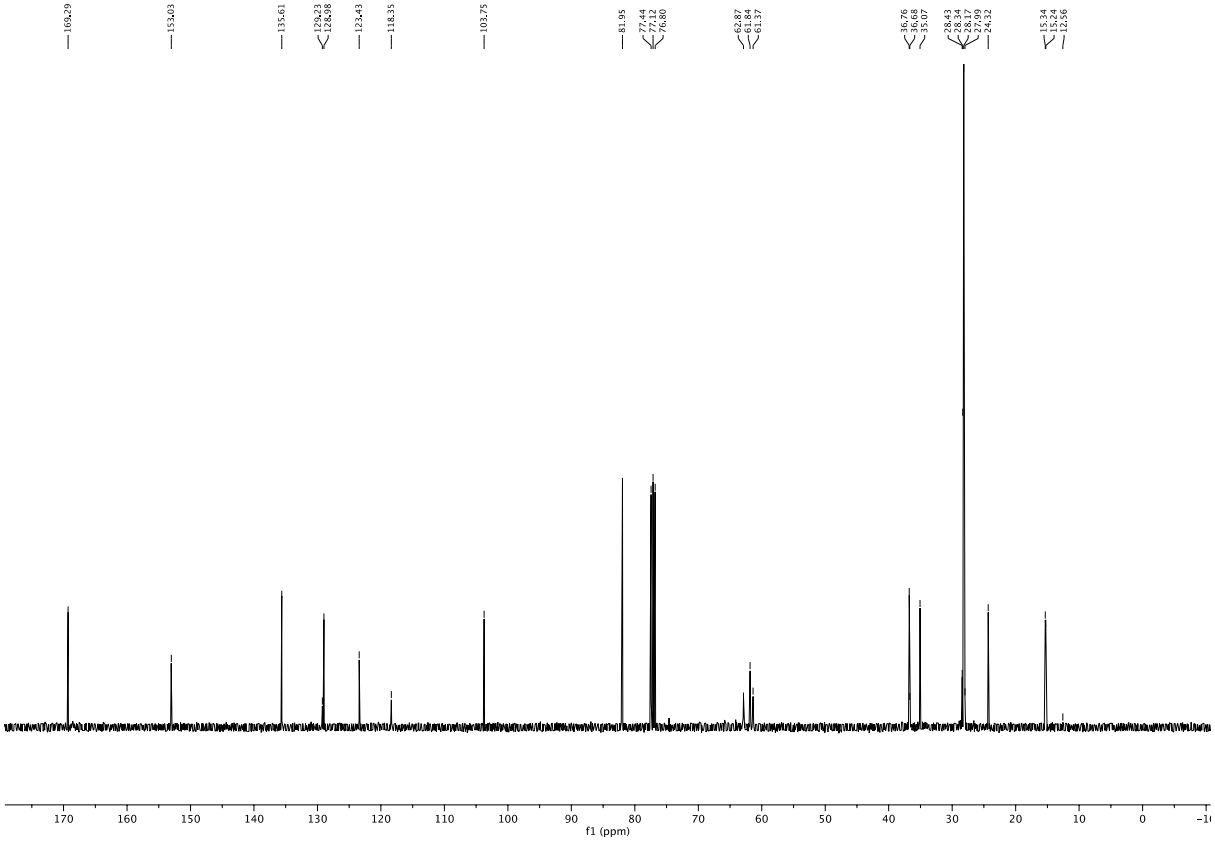
6.20
f1 (ppm)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61.84
61.37
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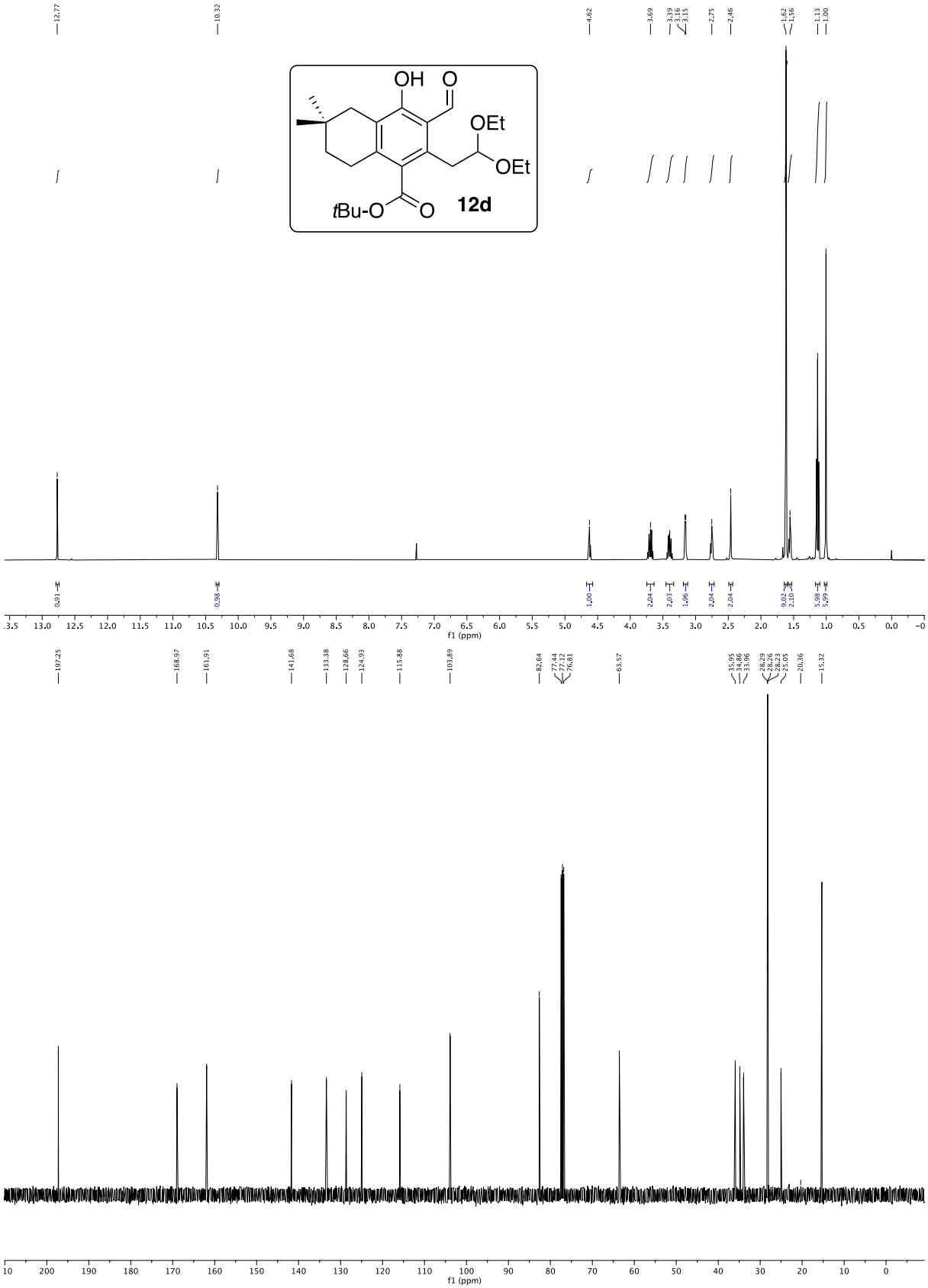
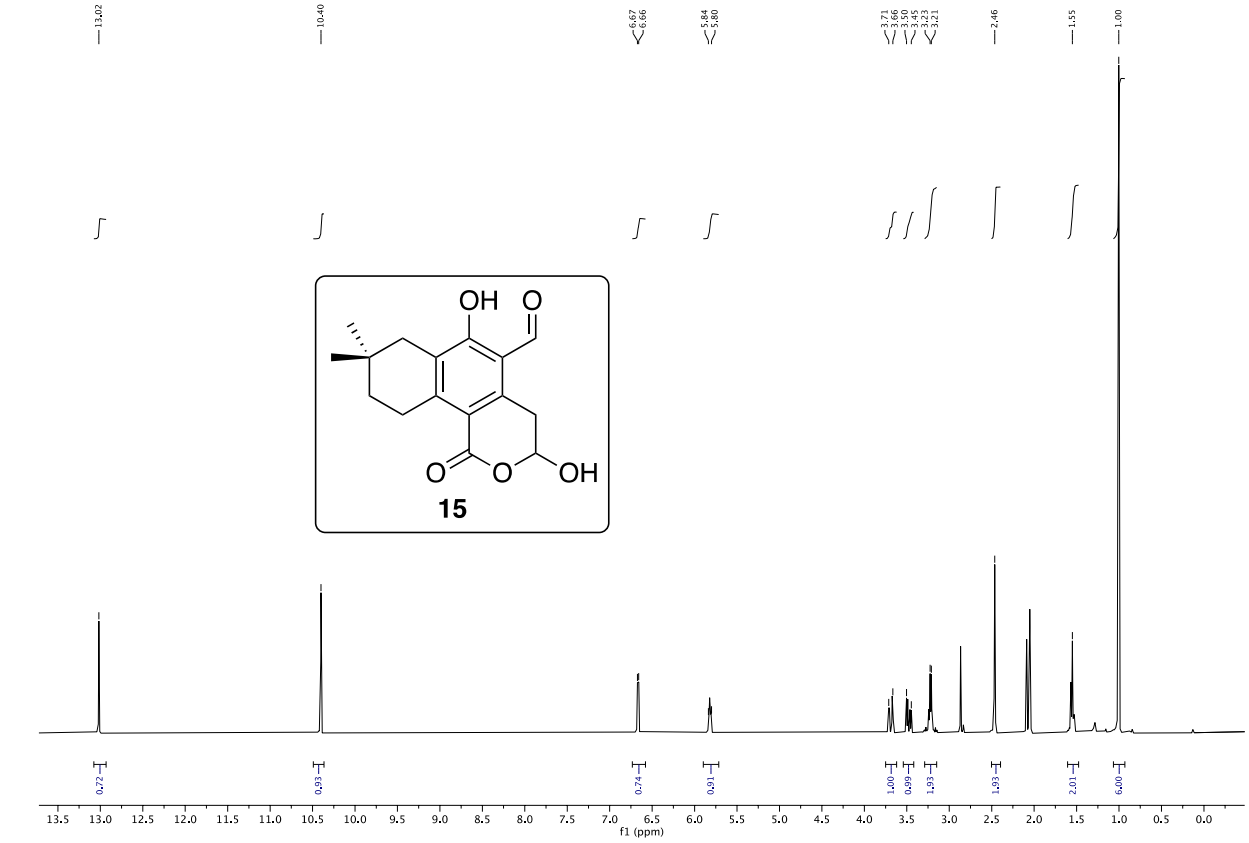
15.34
15.24
12.56
f1 (ppm)


OH
O
OEt
OEt
tBu-O
O
12d
f1 (ppm)
f1 (ppm)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5.80
3.71
3.66
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3.45
3.23
3.21
2.46
1.55
1.00
OH
O
O
O
OH
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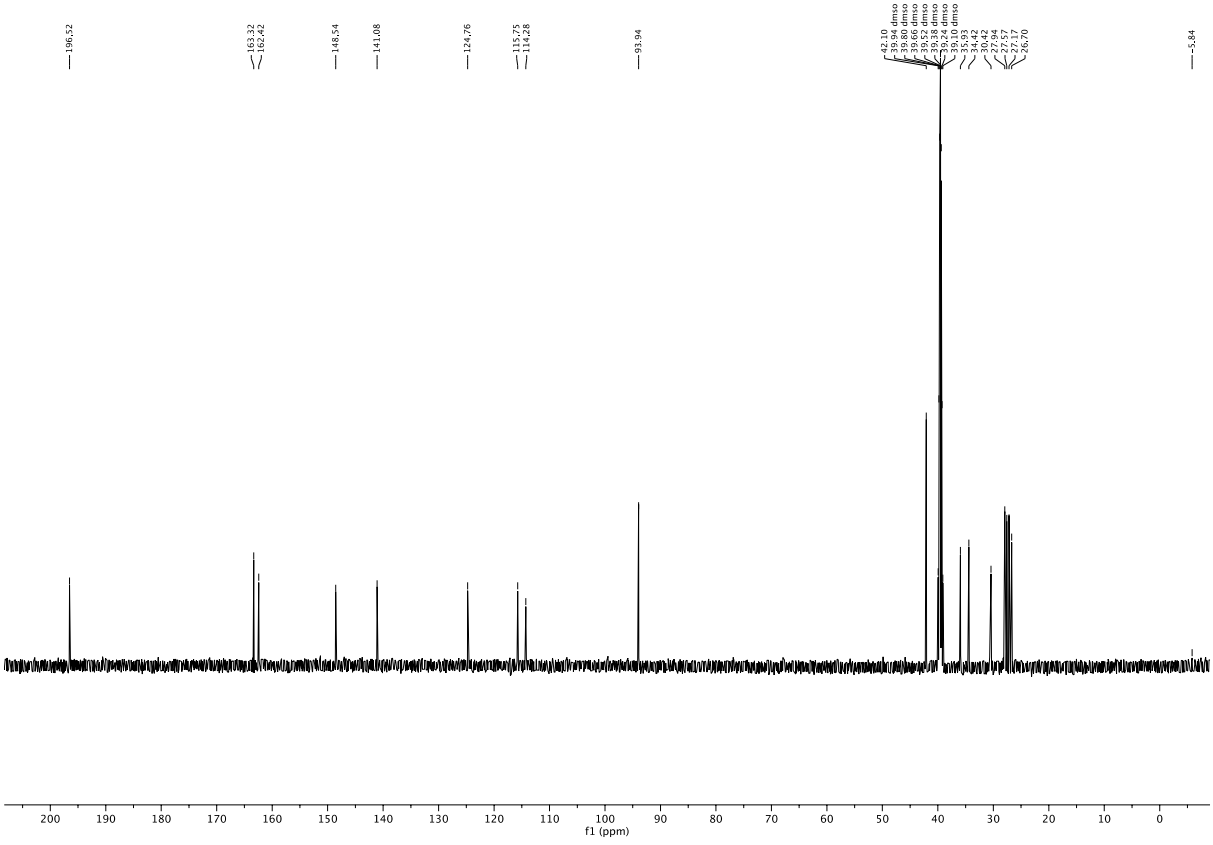
0.74
0.91
1.00
0.99
1.93
1.93
2.01
6.00
f1 (ppm)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141.08
124.76
115.75
114.28
93.94
42.10
39.94 dmso
39.80 dmso
39.66 dmso
39.52 dmso
39.38 dmso
39.24 dmso
39.10 dmso
35.93
30.42
27.94
27.57
27.17
26.70
5.84
f1 (ppm)


10.04
2.54
2.31
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0.98
CHO
Br
5e
0.88
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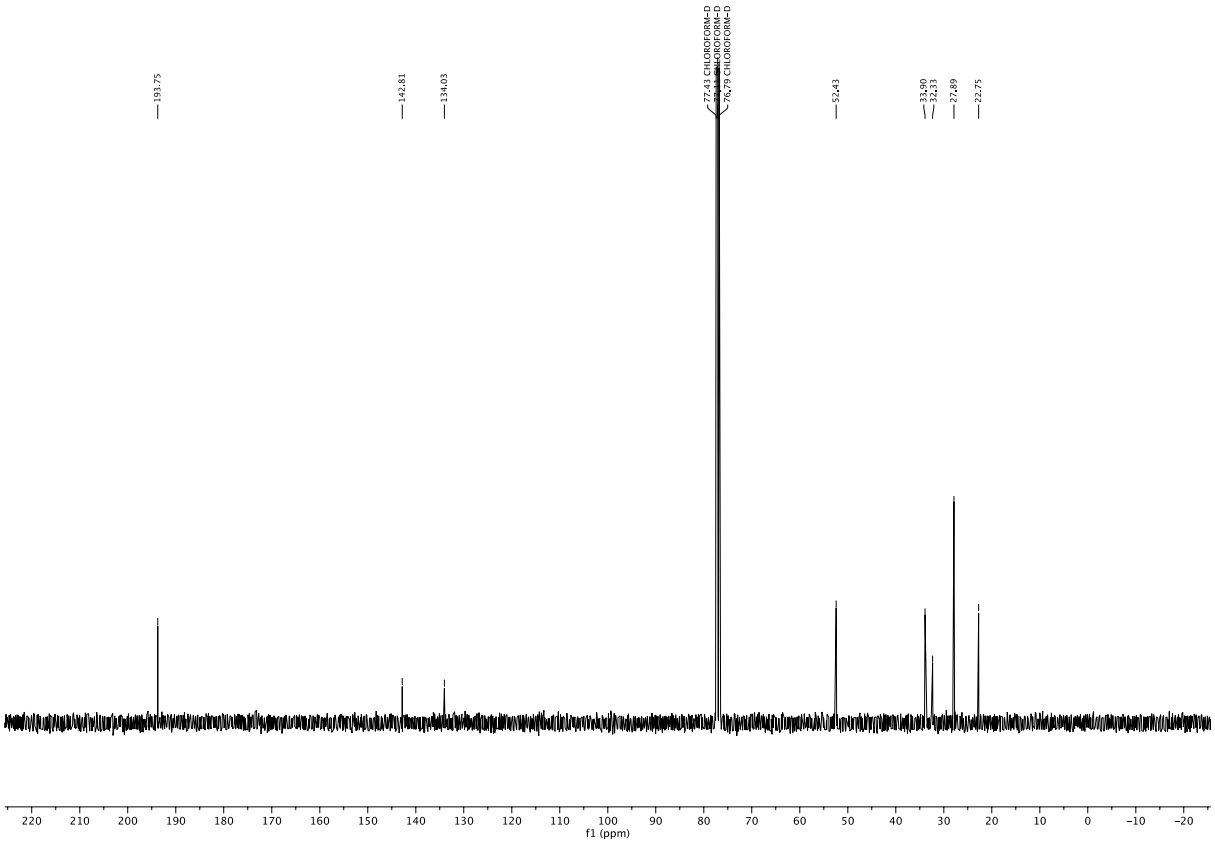
2.00
1.99
6.00
f1 (ppm)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134.03
77.43 CHLOROFORM-D
77.00 CHLOROFORM-D
76.79 CHLOROFORM-D
52.43
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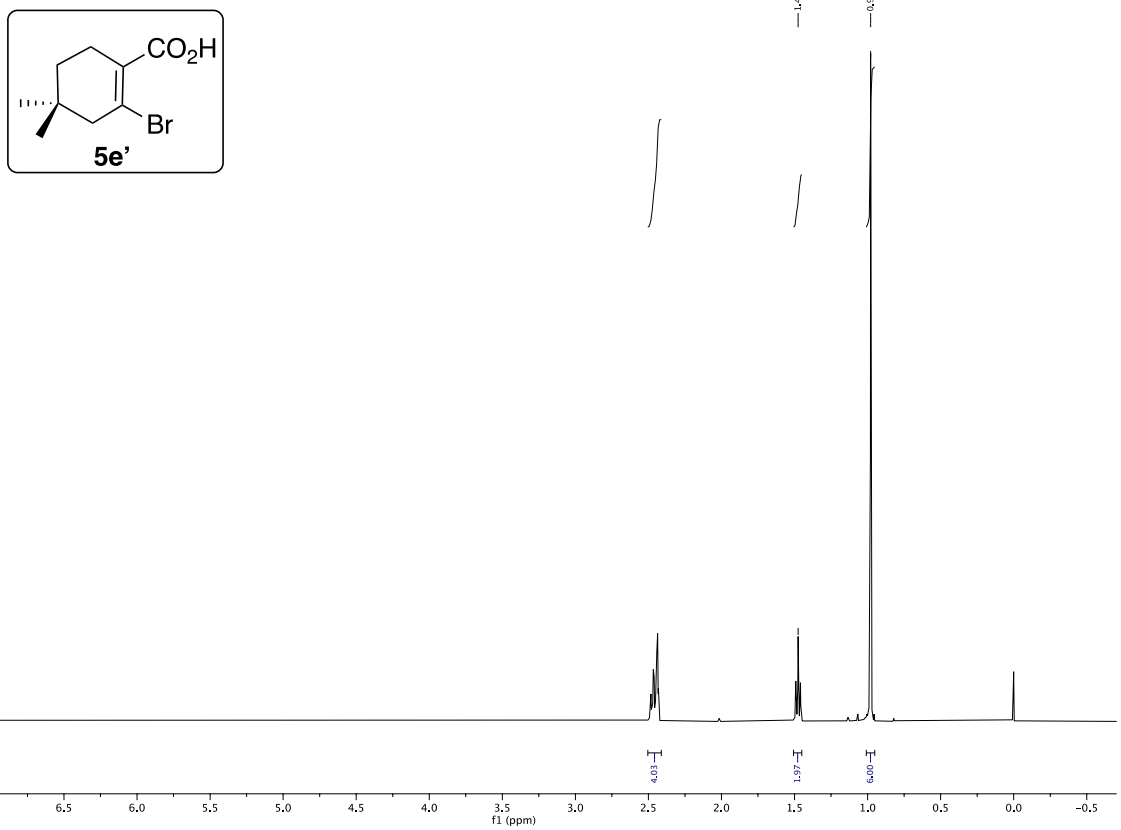
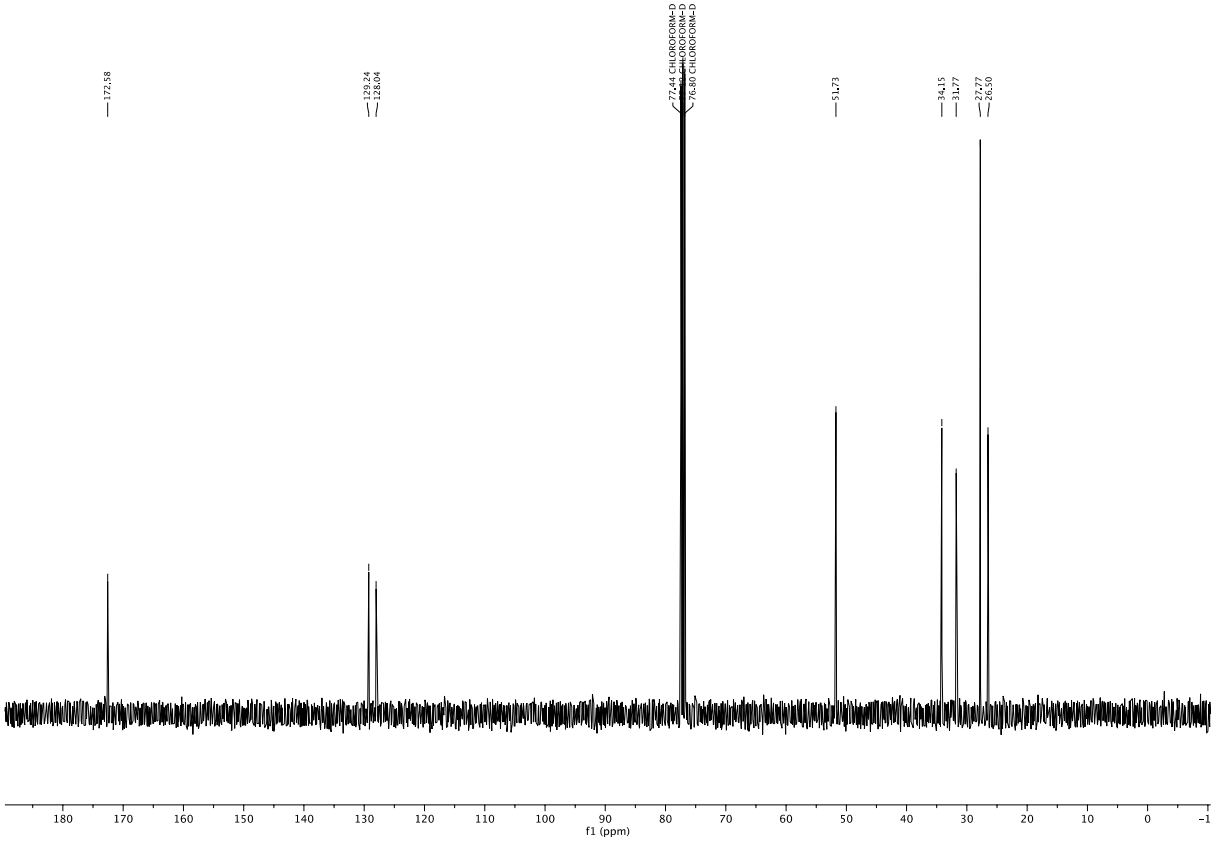
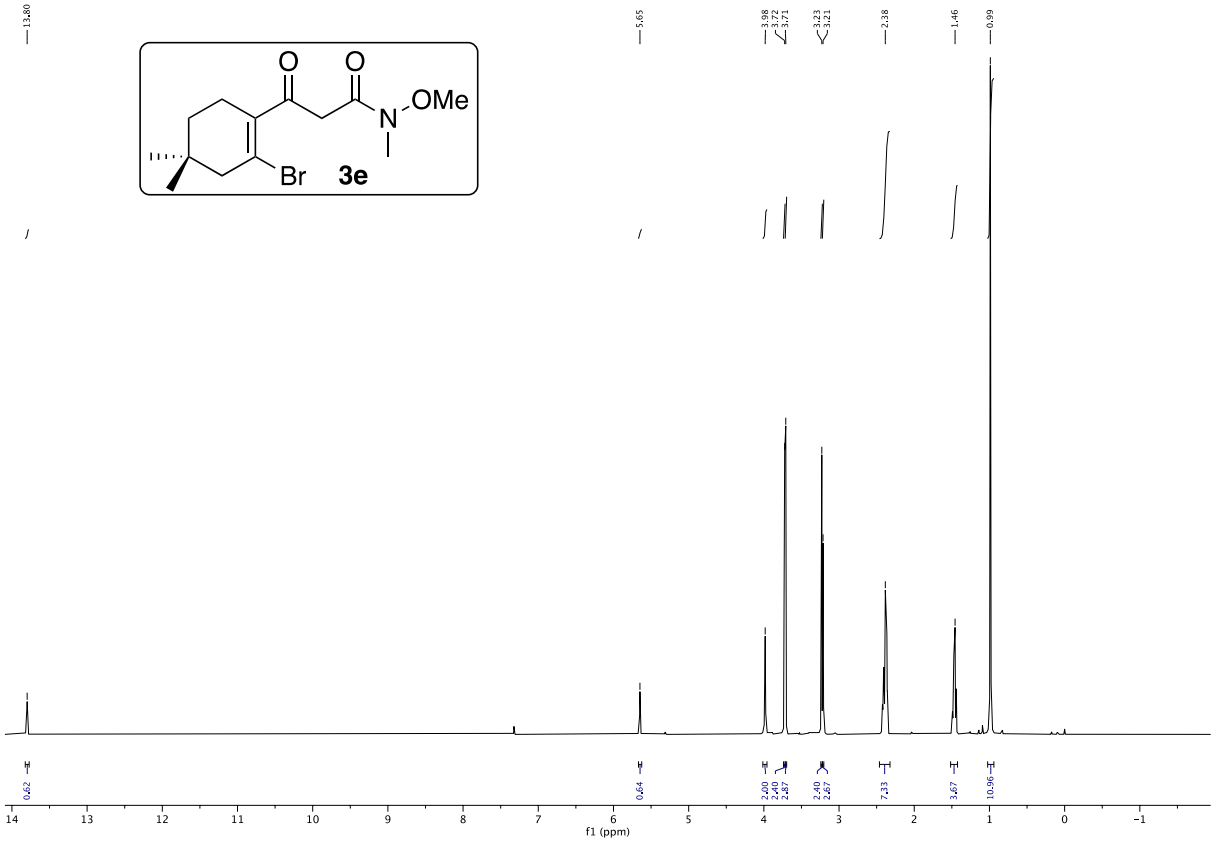
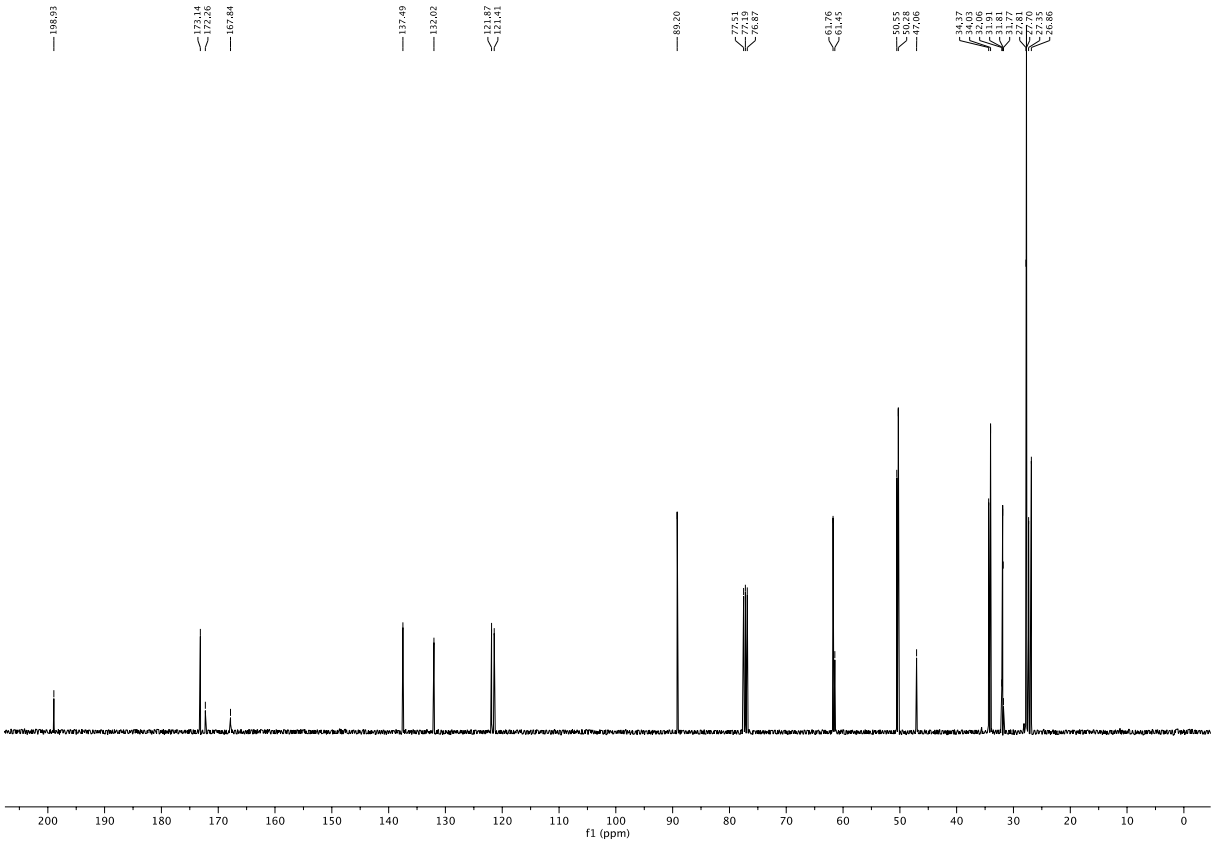
32.33
27.89
22.75
f1 (ppm)


CO2H
Br
5e'
1.48
0.98
4.03
1.97
6.00
f1 (ppm)


172.58
129.24
128.04
77.44 CHLOROFORM-D
77.23 CHLOROFORM-D
76.80 CHLOROFORM-D
51.73
34.15
31.77
27.77
26.50
f1 (ppm)


13.80
5.65
3.98
3.72
3.71
3.23
3.21
2.38
1.46
0.99
O
O
N
OMe
Br
3e
0.62
0.64
2.00
2.40
2.87
2.40
2.87
7.33
3.67
10.96
f1 (ppm)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173.14
172.26
167.84
137.49
132.02
121.87
121.41
89.20
77.51
77.19
76.87
61.76
61.45
50.55
50.28
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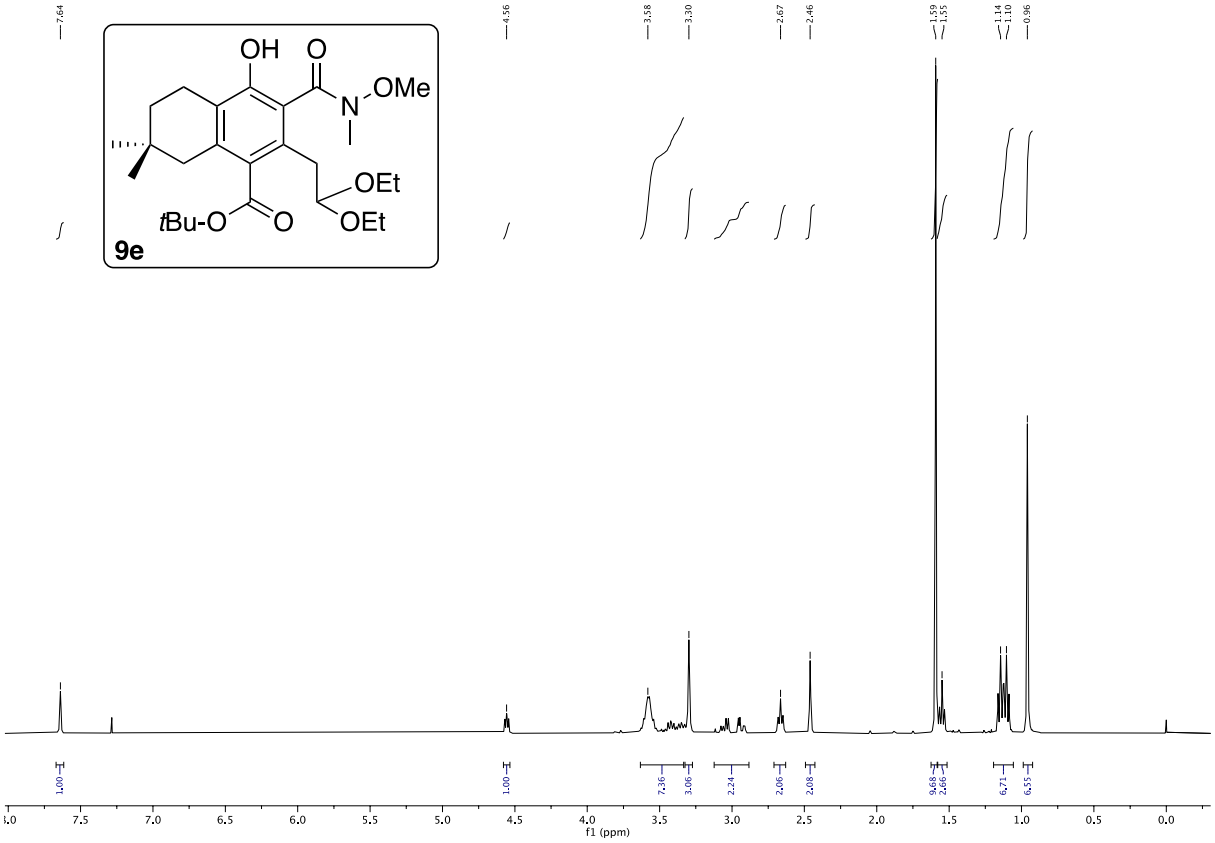
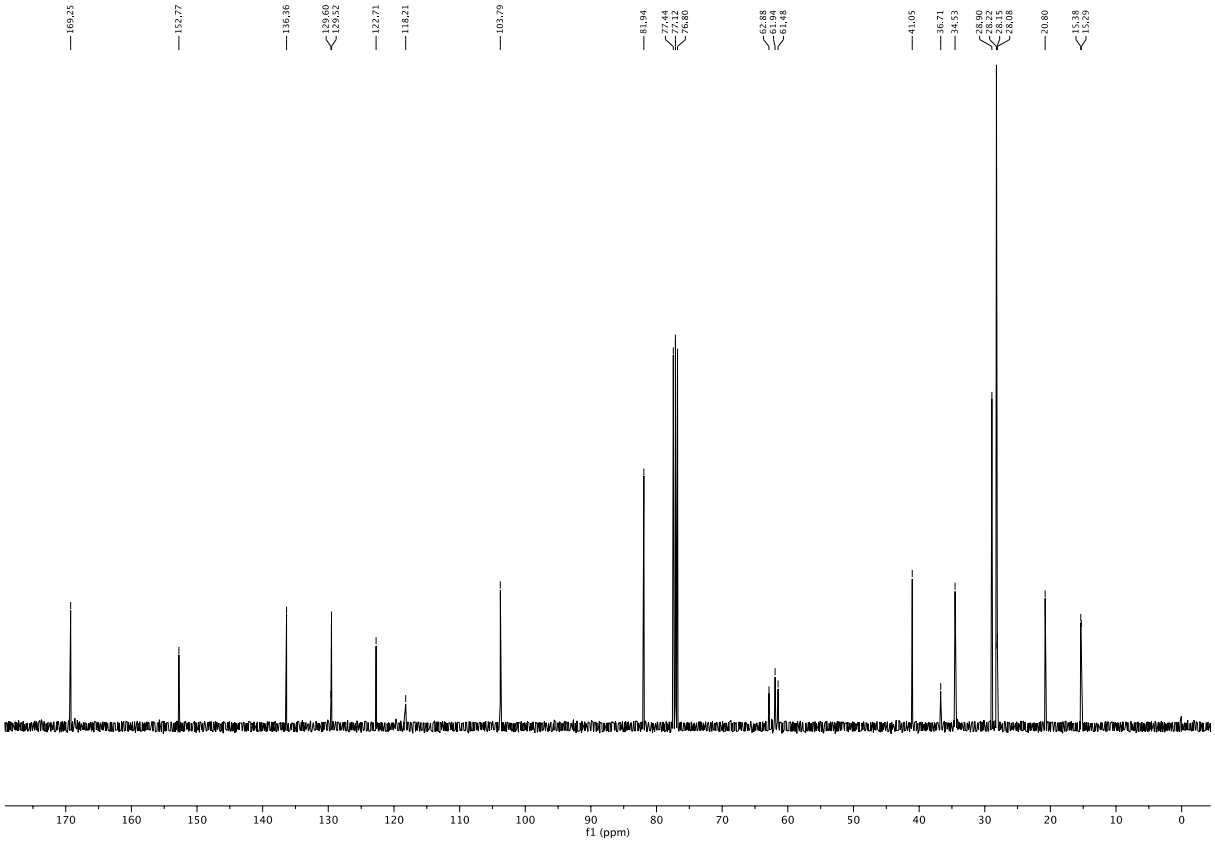

OH
O
N
OMe
OEt
OEt
tBu-O
O
9e
f1 (ppm)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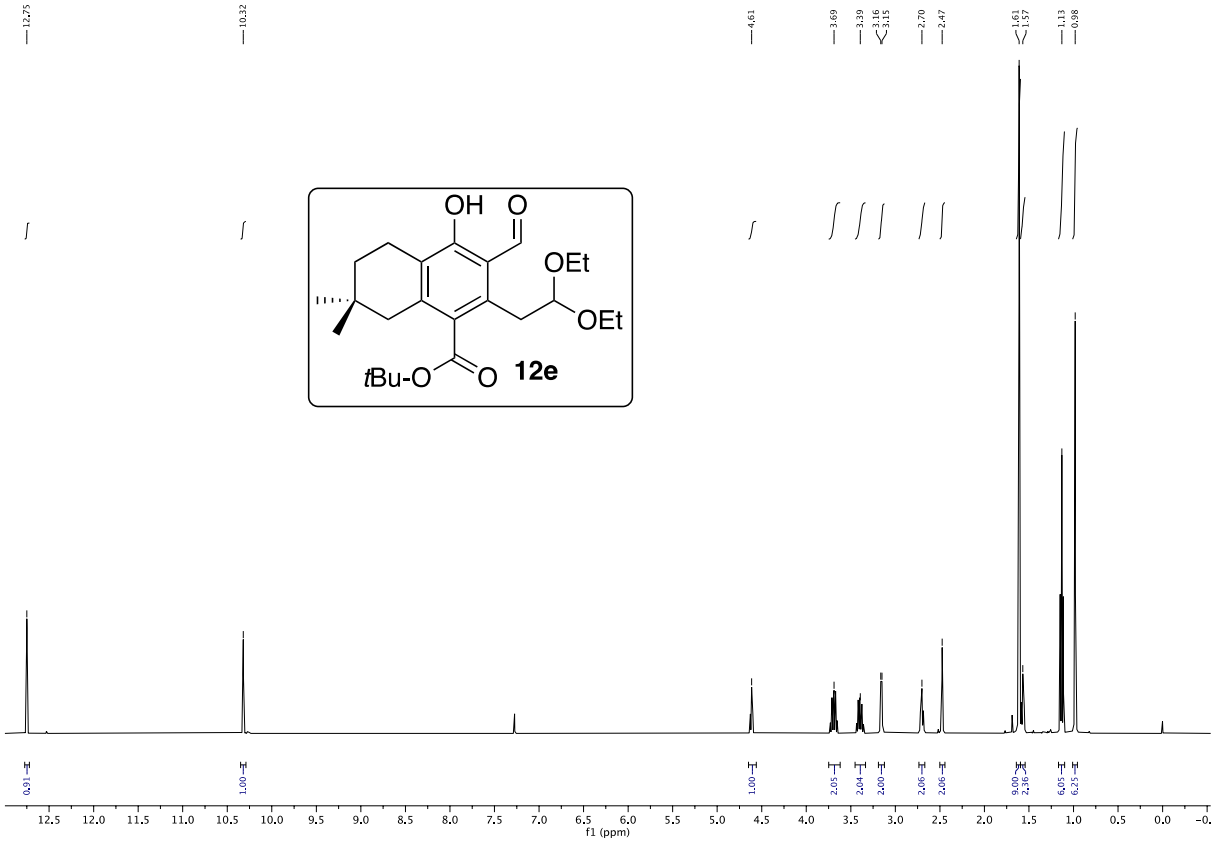
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1.61
1.57
1.13
0.98
OH
O
OEt
OEt
tBu-O
O
12e
0.91
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2.06
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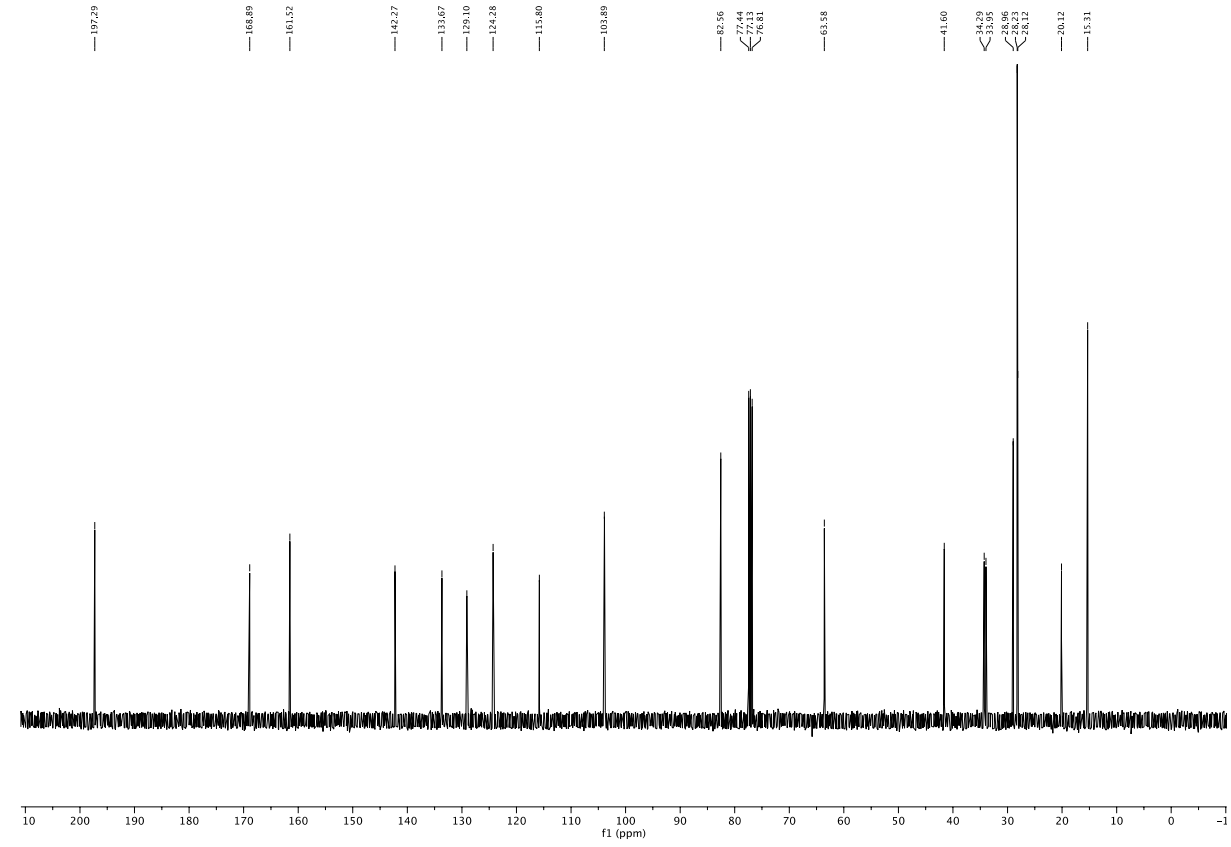
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82.56
77.44
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28.23
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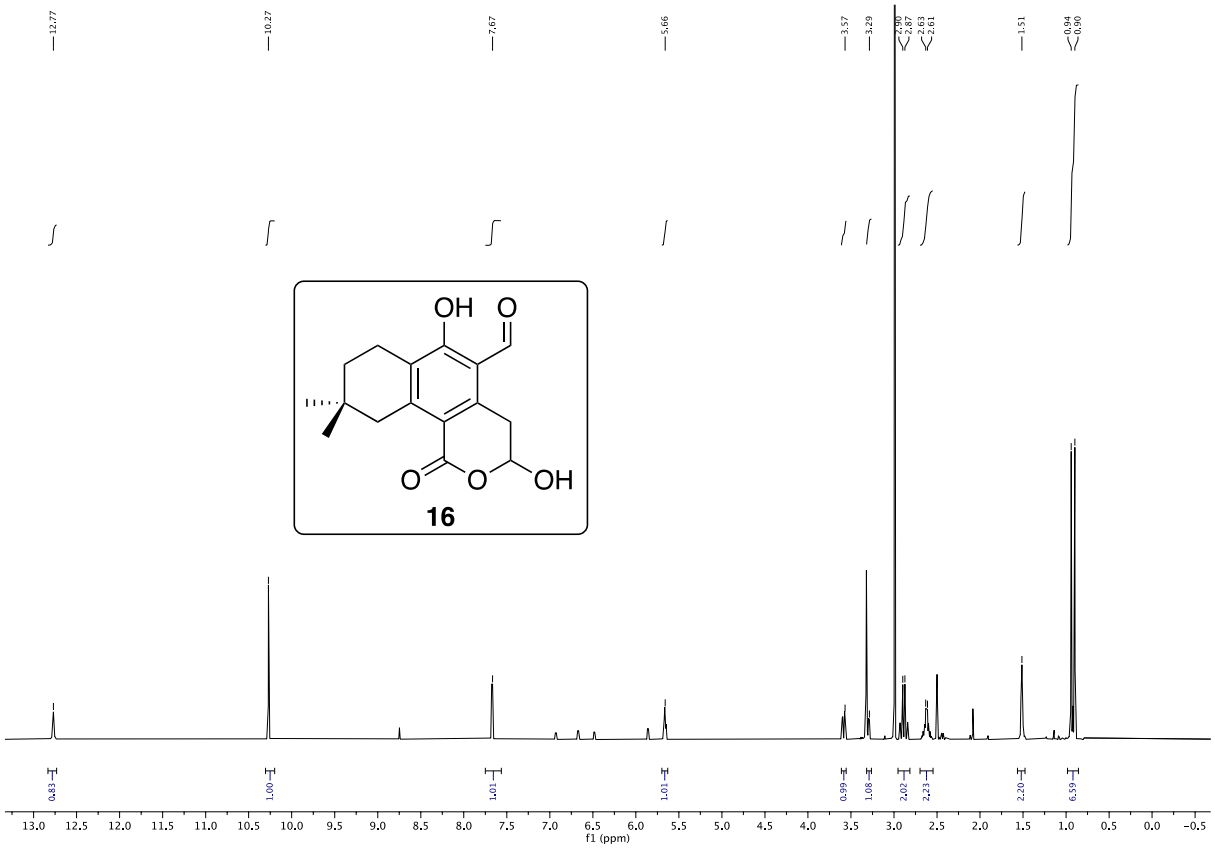
20.12
15.31
f1 (ppm)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2.87
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2.61
1.51
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O
O
O
OH
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1.08
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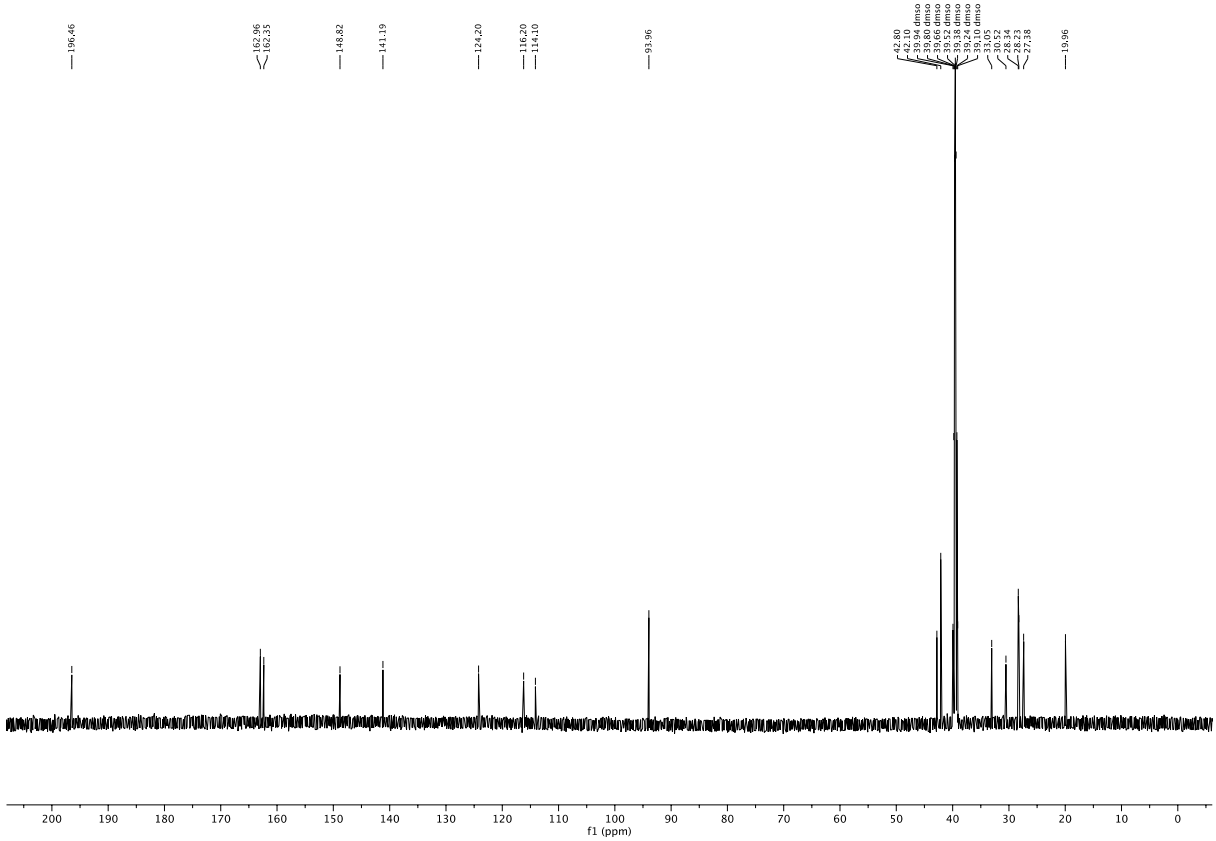
2.23
2.20
6.59
f1 (ppm)


196.46
162.96
162.35
148.82
141.19
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114.10
93.96
42.80
42.10
39.94 dmso
39.80 dmso
39.66 dmso
39.52 dmso
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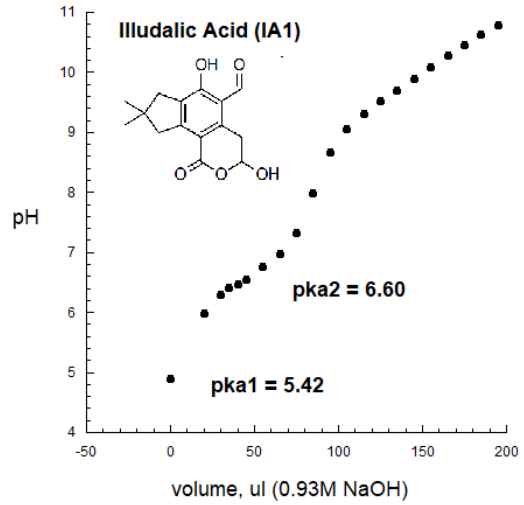
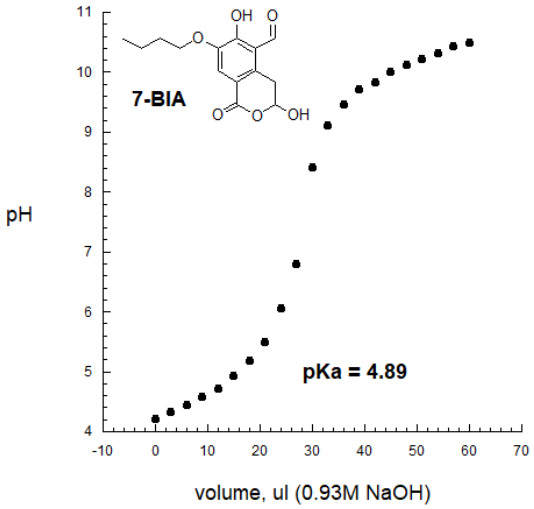
39.10 dmso
33.05
30.52
28.54
28.23
27.38
19.96
f1 (ppm)



Titration of Illudalic Acid (IA1): pKa1 = 5.42, pka2 = 6.60

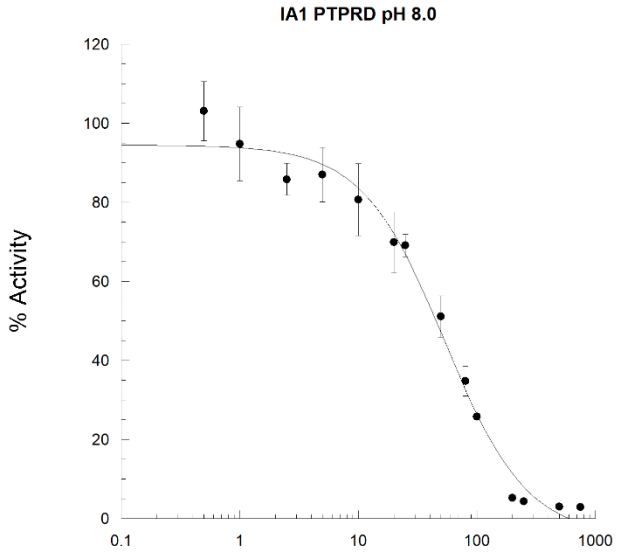


Titration of 7-BIA: pKa = 4.89

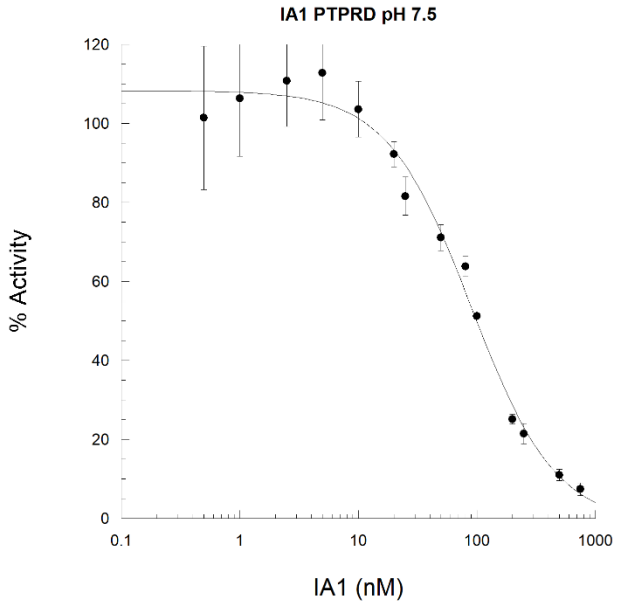
IC_{50} Values

Enzyme	Inhibitor	pH	IC_{50} (nM)
PTPRD	1 (IA1)	8	53.5 ± 7.3
PTPRD	1 (IA1)	7.5	90.0 ± 14.2
PTPRD	1 (IA1)	7	427.7 ± 82.0
PTPRD	1 (IA1)	6.5	2,924.3 ± 854.2
PTPRS	1 (IA1)	7.5	38.1 ± 1.9
LAR	1 (IA1)	7.5	52.1 ± 10
PTPRD	13 (IA1-8H2)	7.5	111.6 ± 9.7
PTPRS	13 (IA1-8H2)	7.5	63.2 ± 5.1
PTPRD	7-BIA	7.5	2,086 ± 162.8
PTPRD	15 (IA2-8Me2)	7.5	44.7 ± 2.4
LAR	15 (IA2-8Me2)	7.5	32.4 ± 5.3
PTPRS	15 (IA2-8Me2)	7.5	20.3 ± 1.1

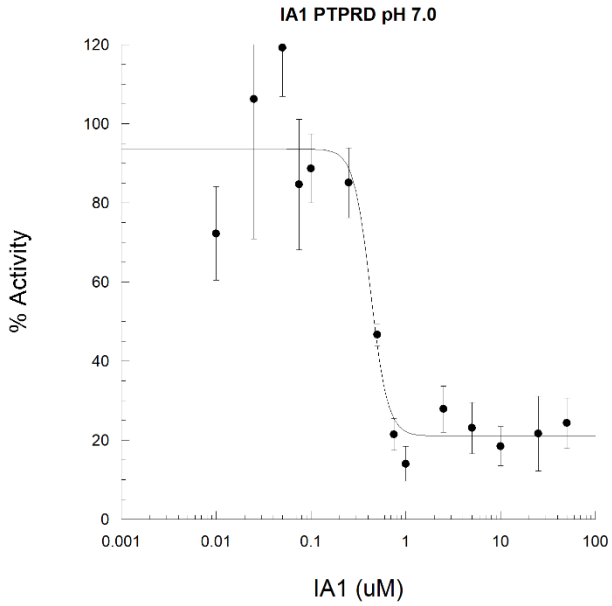
Table of IC_{50} values: These values were obtained using the inhibition assays protocol and fitted using Kaleidagraph software. The pH 6.5 buffer was done in 50 mM bis-tris.



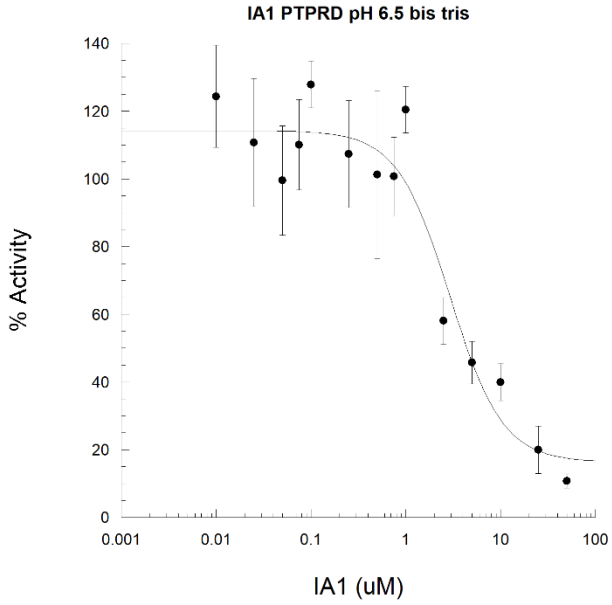
IC_{50} Curve: Illudalic Acid, pH 8.0, PTPRD



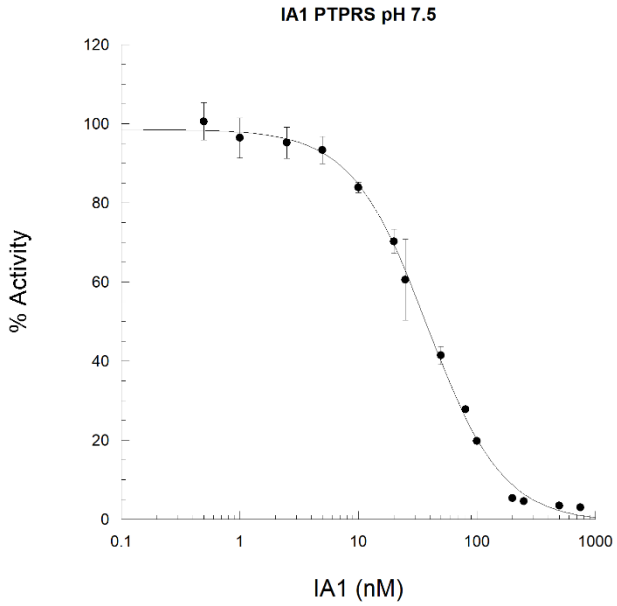
IC_{50} Curve: Illudalic Acid, pH 7.5, PTPRD



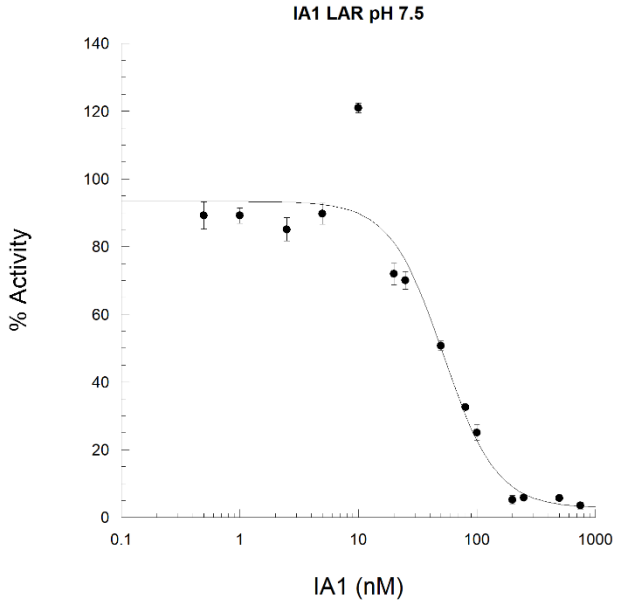
IC_{50} Curve: Illudalic Acid, pH 7.0, PTPRD



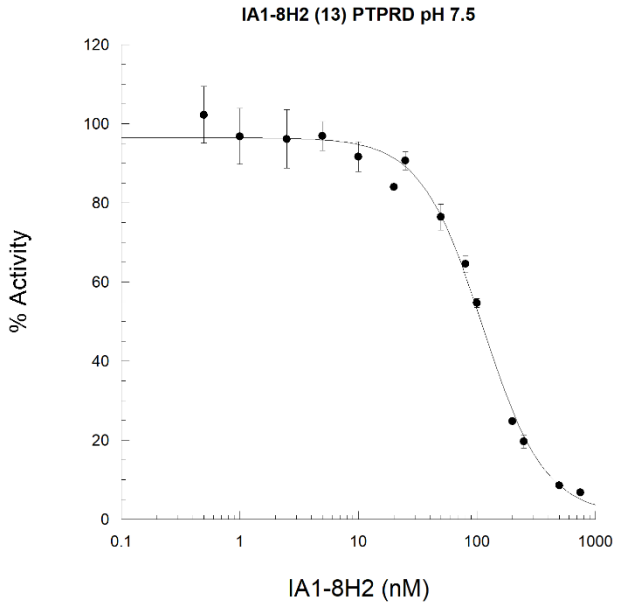
IC_{50} Curve: Illudalic Acid, pH 6.5, PTPRD



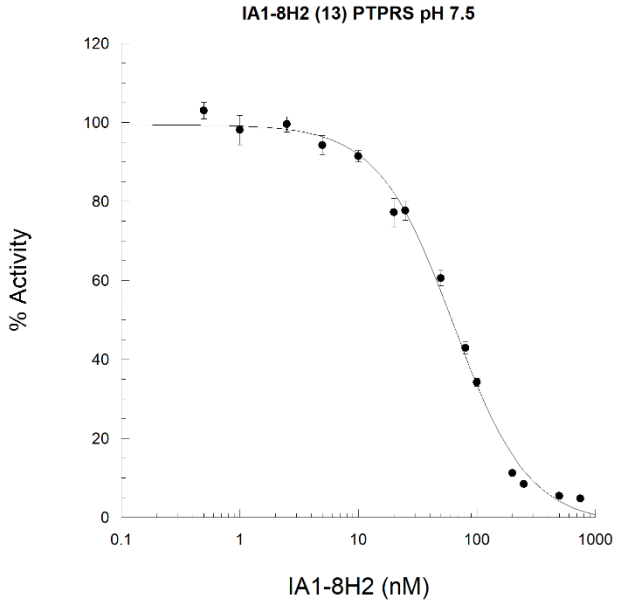
IC_{50} Curve: Illudalic Acid, pH 7.5, PTPRS



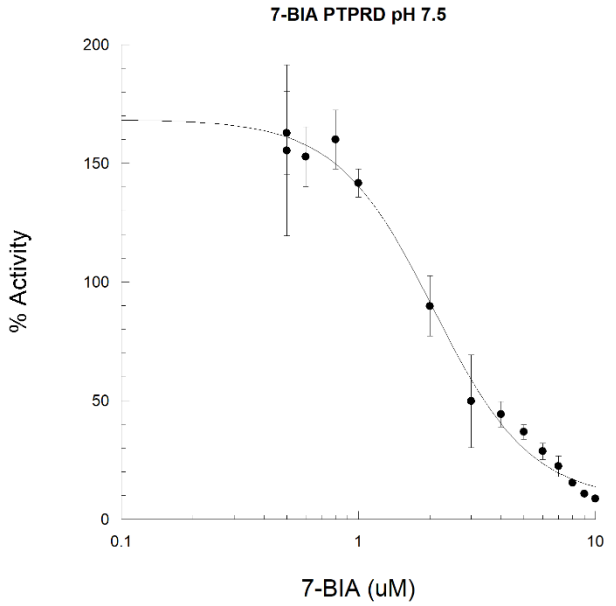
IC_{50} Curve: Illudalic Acid, pH 7.5, LAR



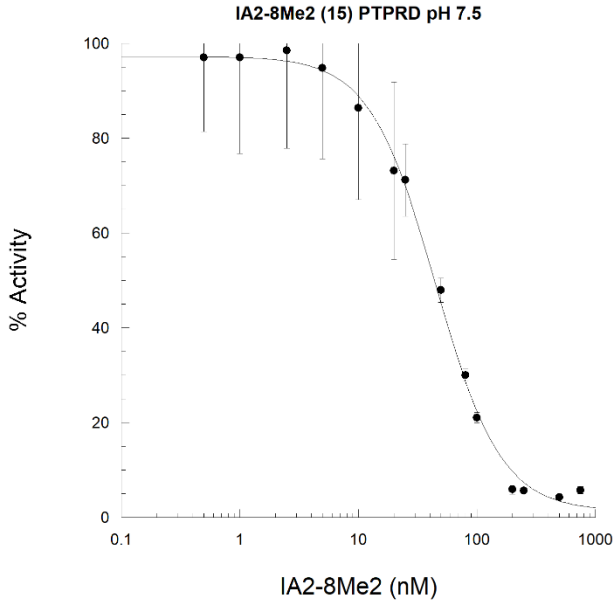
IC_{50} Curve: IA1-8H2 (13), pH 7.5, PTPRD



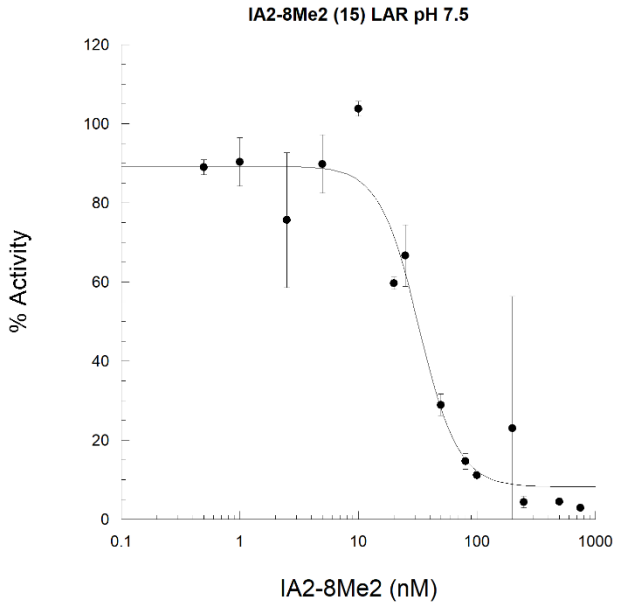
IC_{50} Curve: IA1-8H2 (13), pH 7.5, PTPRS



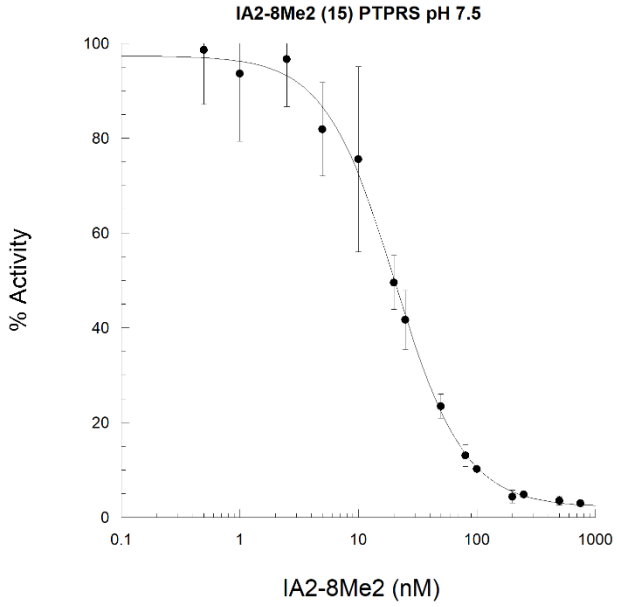
IC_{50} Curve: 7-BIA, pH 7.5, PTPRD



IC_{50} Curve: IA2-8Me2 (15), pH 7.5, PTPRD



IC_{50} Curve: IA2-8Me2 (15), pH 7.5, LAR



IC_{50} Curve: IA2-8Me2 (15), pH 7.5, PTPRS