Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Formal Ring-Opening/Cross-Coupling Reactions of 2-Pyrones: Iron-Catalyzed Entry into Stereodefined Dienyl Carboxylates**

*Chang-Liang Sun and Alois Fürstner**

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Supporting Crystallographic Information

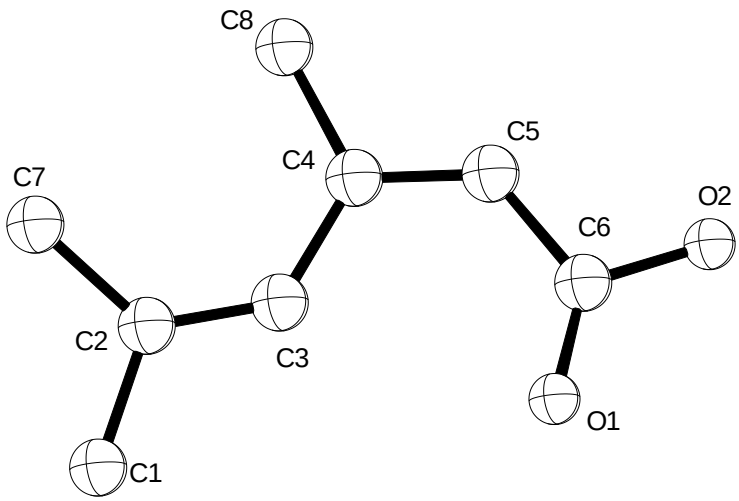


Figure S-1. Structure of compound **5a** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level, hydrogen atoms are omitted for clarity.

X-ray Crystal Structure Analysis of Compound 5a. $C_8H_{12}O_2$, M_r = 140.18 g · mol^{-1}, colorless plate, crystal size 0.33 x 0.09 x 0.04 mm, monoclinic, space group $P2_1/c$, a = 7.3045(4) Å, b = 7.2696(4) Å, c = 15.0537(9) Å, β = 94.071(3)°, V = 797.35(8) Å^3, T = 100 K, Z = 4, D_{calc} = 1.168 g·cm^3, λ = 1.54178 Å, μ(Cu-K_α) = 0.670 mm^{-1}, Empirical absorption correction (T_{min} = 0.84, T_{max} = 0.98), Bruker AXS Proteum X8 diffractometer, 5.89 < θ < 65.08°, 17835 measured reflections, 1359 independent reflections, 1069 reflections with $I > 2\sigma(I)$, Structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.052 [$I > 2\sigma(I)$], wR_2 = 0.132, 96 parameters, extinction coefficient = 0.010(2), H atoms riding, S = 1.039, residual electron density 0.3 / -0.2 e Å^{-3}.

CCDC-953753 contains the supplementary crystallographic data for this paper. This information can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Determination of the Stereostructure by NMR

According to a previous study,[1] the four possible isomers of 3,5-dimethyl-2,4-alkadienoic acids show the following characteristic signals in their ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$):

(2*Z*, 4*E*): Me^{b} : ≈ 2.03 ppm; H^{b}: ≈ 6.46 ppm
(2*Z*, 4*Z*): Me^{b} : ≈ 2.03 ppm; H^{b}: ≈ 6.40 ppm
(2*E*, 4*E*): Me^{b} : ≈ 2.25 ppm; H^{b}: ≈ 5.72 ppm
(2*E*, 4*Z*): Me^{b} : ≈ 2.25 ppm; H^{b}: ≈ 5.73 ppm

(2*Z*, 4*E*): Me^{b} : ≈ 18.5 ppm; Me^{a} : ≈ 25.5 ppm
(2*Z*, 4*Z*): Me^{b} : ≈ 25.5 ppm; Me^{a} : ≈ 23.7 ppm
(2*E*, 4*E*): Me^{b} : ≈ 19.6 ppm; Me^{a} : ≈ 18.3 ppm
(2*E*, 4*Z*): Me^{b} : ≈ 23.8 ppm; Me^{a} : ≈ 19.6 ppm

This pattern allows the two isomers **5a** and **6a** of 3,5-dimethyl-2,4-hexadienoic acid formed by the pyrone ring opening/cross coupling under different experimental conditions to be unambiguously assigned (Figure S-2); in addition, the configuration of the 2*Z*-isomer was corroborated by X-ray diffraction (see above). Based on this evidence, all other products were assigned analogously; a representative example (**5e**) is shown in Figure S-3.

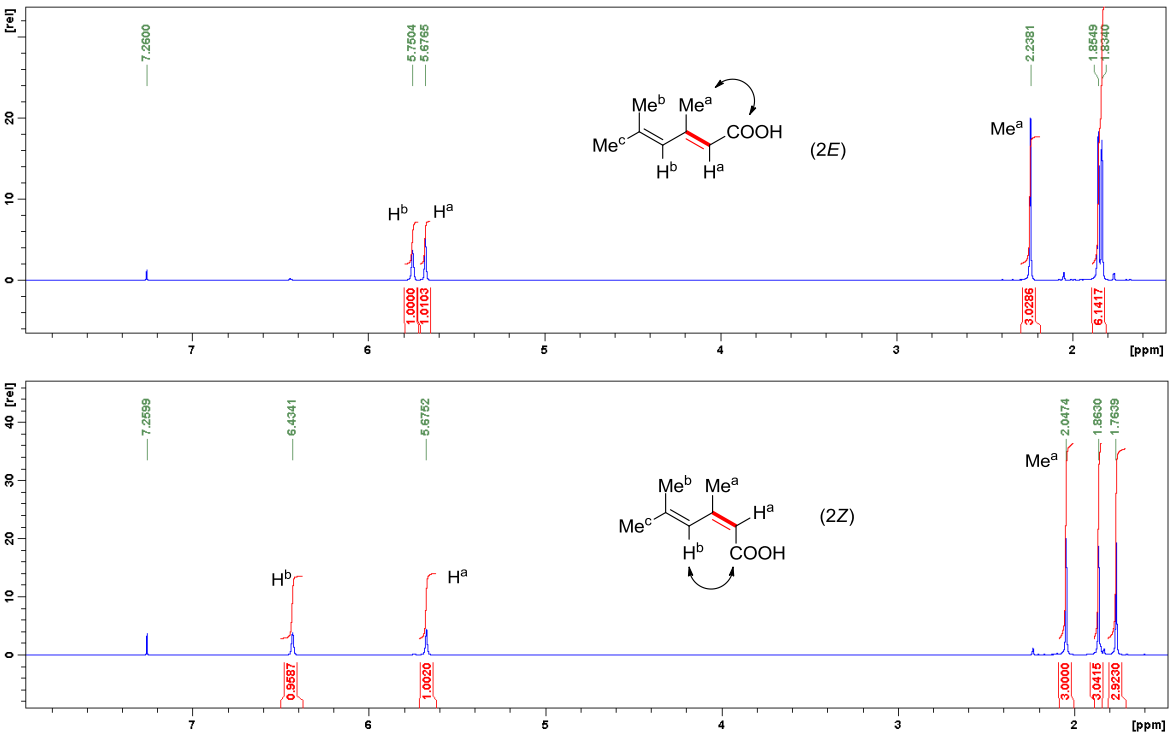


Figure S-2. Comparison of the ^{1}H NMR spectra ($CDCl_3$) of **6a** (top) and **5a** (bottom) shows the characteristic shift differences of the two geometric isomers

[1] K. Koseki, Y. Takahashi, K. Shimazaki, T. Ebata, T. Chuman, K. Mori, *Biosci. Biotechnol. Biochem*. **1992**, *56*, 1728–1731.

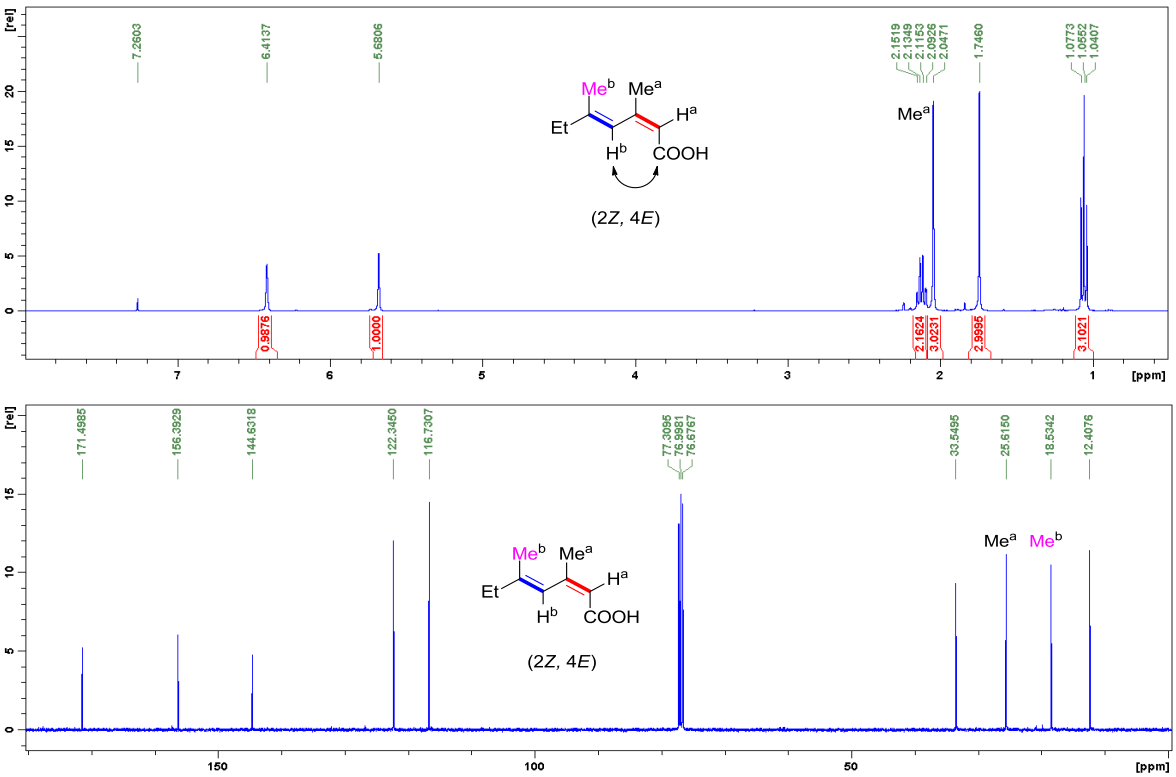


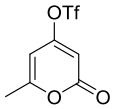
Figure S-3. The configuration of compound **5e** was assigned based on the characteristic shift pattern in its ^{1}H (top) and ^{13}C NMR (bottom) spectra.

General. All reactions were carried out in flame-dried glassware under Argon. All solvents were purified by distillation over the drying agents indicated and were transferred under Argon: THF (Mg-anthracene), diethyl ether (Mg-anthracene), dichloromethane (CaH_2), acetonitrile (CaH_2), triethylamine (CaH_2), hexane (Na/K), toluene (Na/K). HOAc and MeOH were used as received. Flash chromatography: Merck silica gel 60 (230-400 mesh). IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200, MS (CI): Finnigan MAT 95, MS (ESI) ESQ 3000; accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). NMR: Spectra were recorded on a Bruker DPX 300, AV 400 or AV 500 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references ($CDCl_3$: δ_H = 7.24 ppm, δ_C = 77.0 ppm) and the chemical shifts converted to the TMS scale. Unless stated otherwise, all commercially available compounds (Acros, Sigma-Aldrich, Fluka, Alfa Aesar, Lancaster, Strem) were used as received.

Substrates

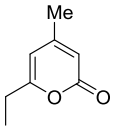
2-Pyrone, 4,6-dimethyl-2-pyrone, 6-pentyl-2-pyrone, coumarin, and 4*H*-chromen-4-one were purchased and used as received; compounds **4i**,[2] **4k**,[3] **4j**,[4] **4l**,[5] and **13**[6] were prepared according to the literature.

Compound 1. The solution of triflic anhydride (4.23 g, 15 mmol) in CH_2Cl_2 (5 mL) was slowly added at



−20°C to a stirred solution of 4-hydroxy-6-methyl-2-pyrone (1.43 g, 11 mmol) and triethylamine (1.52 g, 15 mmol) in CH_2Cl_2 (15 mL). Once the addition was complete, the cooling bath was removed and stirring continued overnight at ambient temperature. For work up, the mixture was washed with HCl aq (1 M) and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 8:1) to give the title compound as a pale yellow oil (2.35 g, 83%). The spectral and analytical data were identical to those reported in the literature.[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 6.05 (s, 1H), 6.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 99.6, 102.4, 118.4 (q, $J_{C,F}$ = 318.8 Hz) (113.6, 116.8, 120.0, 123.2), 160.9, 161.5, 165.5. MS (EI): *m/z* (%) 258 (100), 229 (51), 165 (7), 123 (20), 113 (27), 97 (100), 69 (98).

Representative Procedure for the Preparation of 6-Alkyl-2-pyrone Derivatives. 6-Ethyl-4-methyl-2*H*-pyran-2-one (4e).[8,9] A mixture of ethyl 3-methyl-2-butenoate (0.64 g, 5 mmol) and



propanoyl chloride (0.55 g, 6 mmol) in CH_2Cl_2 (5 mL) was added to a stirred and cooled suspension of $AlCl_3$ (1.60 g, 12 mmol) and CH_2Cl_2 (15 mL) at a rate as to maintain gentle reflux. Once the addition was complete, the mixture was stirred under reflux for 3 h before it was cooled and carefully decomposed by slowly pouring it into excess ice-water. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layer were dried over $MgSO_4$ and evaporated. The residue was added to a mixture of conc. H_2SO_4 (10 mL) and HOAc (20 mL) and the resulting solution stirred at 40 °C until TLC control indicated complete conversion. The mixture was carefully poured into crushed ice and the resulting phase was neutralized with sat. aq. Na_2CO_3. Extraction of the aqueous layer with EtOAc (3 x 30 mL), drying of the combined organic phases over Na_2SO_4 and evaporation of the solvent gave a residue that was purified by flash chromatography (hexane/EtOAc, 4:1) to give the title compound as a yellow liquid (529 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.6 Hz, 3H), 2.12 (s, 3H), 2.49 (q, *J* = 7.4 Hz, 2H), 5.83 (s, 1H), 5.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 21.4, 26.8, 104.8, 110.6, 156.2, 163.3, 166.0. IR (film, cm^{-1}): 2981, 1769, 1731, 1712, 1698, 1643, 1561, 1437, 1408, 1377, 1225, 1133,

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2 A. D. Wadsworth, J. Sperry, M. A. Brimble, *Synthesis* **2010**, *15*, 2604–2608.

3 K. C. Majumdar, P. K. Basu, P. P. Mukhopadhyay, S. Sarkar, S. K. Ghosh, P. Biswas, *Tetrahedron* **2003**, *59*, 2151–2157.

4 D. A. Burr, X. B. Chen, J. C. Vederas, *Org. Lett*. **2007**, *9*, 161–164.

5 K. C. Majumdar, P. Debnath, A. K. Pal, S. K. Chattopadhyay, A. Biswas, *Can. J. Chem*. **2007**, *85*, 445–452.

6 L. Liu, J. Hu, X.-C. Wang, M.-J. Zhong, X.-Y. Liu, S.-D. Yang, Y.-M. Liang, *Tetrahedron* **2012**, *68*, 5391–5395.

7 J.-T. Pierson, A. Dumètre, S. Hutter, F. Delmas, M. Laget, J.-P. Finet, N. Azas, S. Combes, *Eur. J. Med. Chem*. **2010**, *45*, 864–869.

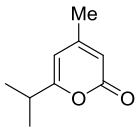
8 G. Lohaus, W. Friedrich, J. P. Jeschke, *Chem. Ber.* **1967**, *100*, 658–677.

9 A. O. Pittet, E. M. Klaiber, *J. Agric. Food Chem.* **1975**, *23*, 1189–1195.

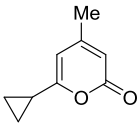
1063, 1030, 995, 913, 891, 861, 830. MS (EI): *m/z* (%) 138 (52), 110 (62), 109 (100), 95 (85), 67 (8), 53 (81), 39 (9).

The following compounds were prepared analogously:

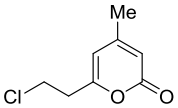
Compound 4d.[8,9] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.9 Hz, 6H), 2.11(s, 3H), 2.65-2.72 (m, 1H), 5.81 (s, 1H), 5.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 21.5, 32.5, 103.4, 110.6, 156.2, 163.2, 169.5. IR (film, cm^{-1}): 3082, 2973, 2936, 2877, 1769, 1724, 1698, 1642, 1561, 1442, 1409, 1378, 1366, 1311, 1226, 1123, 1081, 1068, 1026, 974, 942, 881, 835. MS (EI): *m/z* (%) 152 (22), 124 (18), 109 (100), 53 (28), 27 (5).



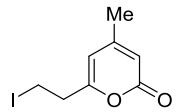
Compound 4f. Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91-0.95 (m, 2H), 1.04-1.08 (m, 2H), 1.68-1.75 (m, 1H), 2.09 (s, 3H), 5.86 (s, 1H), 5.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 14.0, 21.3, 104.4, 109.4, 156.5, 163.0, 165.5. IR (film, cm^{-1}): 3082, 3014, 1713, 1638, 1549, 1442, 1415, 1378, 1227, 1189, 1161, 1062, 1028, 952, 864, 850, 811. MS (EI): *m/z* (%) 150 (65), 122 (100), 109 (40), 93 (25), 79 (61), 69 (10), 53 (55), 39 (21), 27 (14). HRMS (EI): *m/z*: calcd for $C_9H_{10}O_2$ [*M*]: 150.06794, found: 150.06808.



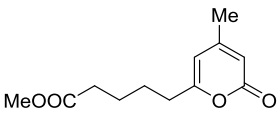
Compound 4g.[8,9] Pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.89 (t, *J* = 6.5 Hz, 2H), 3.79 (t, *J* = 6.5 Hz, 2H), 5.95 (s, 1H), 6.01 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 36.7, 40.4, 107.8, 111.7, 155.8, 159.6, 162.6. IR (film, cm^{-1}): 2967, 1843, 1768, 1724, 1698, 1647, 1562, 1441, 1406, 1379, 1294, 1226, 1132, 1032, 980, 929, 891, 853, 831. MS (EI): *m/z* (%) 174 (8), 172 (24), 146 (10), 144 (31), 109 (53), 95 (100), 79 (6), 53 (51), 27 (14). HRMS (EI): *m/z*: calcd for $C_8H_9O_2Cl$ [*M*]: 172.02895, found: 172.02911.



Compound 4h.[10] A mixture containing compound **4g** (172.5 mg, 1 mmol) and NaI (300 mg, 2 mmol) in anhydrous acetone was refluxed for 20 h. Evaporation of the solvent followed by flash chromatography (hexane/EtOAc, 4:1) furnished the title compound as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 3.01 (t, *J* = 7.0 Hz, 2H), 3.39 (t, *J* = 7.0 Hz, 2H), 5.91 (s, 1H), 6.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.6, 21.5, 37.5, 107.2, 111.7, 155.8, 161.2, 162.6. IR (film, cm^{-1}): 3416, 3074, 3040, 2982, 2957, 2915, 2854, 2287, 1717, 1641, 1616, 1561, 1471, 1438, 1425, 1399, 1373, 1328, 1293, 1243, 1226, 1171, 1154, 1144, 1118, 1024, 969, 948, 916, 876, 853, 844, 737. MS (EI): *m/z* (%) 264 (29), 236 (8), 136 (7), 109 (100), 95 (9), 79 (13), 53 (41). HRMS (EI): *m/z*: calcd for $C_8H_9O_2I$ [*M*]: 263.96450, found: 263.96473.

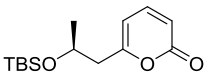


Compound 4r.[8,9] Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64-1.72 (m, 4H), 2.11 (s, 3H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 3.67 (s, 3H), 5.84 (s, 1H), 5.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 24.2, 26.2, 33.3, 33.6, 51.6, 105.9, 110.8, 156.1, 163.2, 164.1, 173.7. IR (film, cm^{-1}): 2953, 2869, 1729, 1644, 1561, 1437, 1408, 1377, 1199, 1174, 1078, 1029, 857. MS (EI): *m/z* (%) 224 (13), 192 (21), 164 (7), 149 (9), 137 (100), 109 (40), 95 (13), 53 (30). HRMS (ESI^{+}): *m/z*: calcd for $C_{12}H_{16}O_4Na$ [$M+Na^{+}$]: 247.09362, found: 247.09408.

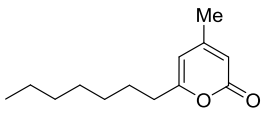


[10] L. Castedo, J. E. Borges, C. F. Marcos, G. Tojo, *Synth. Commun*. **1995**, *25*, 1717–1727.

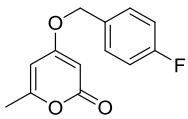
Compound 7.[11] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.10 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.20 (d, J = 5.9 Hz, 3H), 2.51-2.59 (m, 2H), 4.18-4.26 (m, 1H), 6.01 (d, J = 6.6 Hz, 1H), 6.16 (d, J = 9.2 Hz, 1H), 7.24 (dd, J = 6.4 Hz, J = 9.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2, –4.7, 17.9, 24.0, 25.7, 44.2, 66.2, 104.8, 113.4, 143.5, 162.8, 163.9. IR (film, cm^{-1}): 2956, 2930, 2893, 2857, 1732, 1636, 1559, 1472, 1463, 1378, 1362, 1255, 1217, 1128, 1091, 995, 939, 893, 836, 807, 776, 721, 661. MS (EI): m/z (%) 268 (0.1), 211 (100), 167 (32), 159 (5), 139 (32), 111 (17), 95 (4), 73 (21), 59 (4), 39 (6). HRMS (ESI$^+$): m/z: calcd for $C_{14}H_{24}O_3SiNa$ [$M+Na^+$]: 291.13841, found: 291.13869.



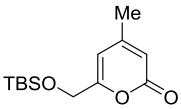
Compound 10.[8,9] Pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.9 Hz, 3H), 1.26-1.32 (m, 8H), 1.59-1.67 (m, 2H), 2.10 (s, 3H), 2.43 (t, J = 7.6 Hz, 2H), 5.82 (s, 1H), 5.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.4, 22.5, 26.8, 28.8, 28.9, 31.6, 33.6, 105.6, 110.5, 156.1, 163.3, 165.0. IR (film, cm^{-1}): 2954, 2927, 2856, 1724, 1644, 1561, 1465, 1441, 1406, 1377, 1224, 1148, 1132, 1105, 1024, 961, 833, 816, 724, 681. MS (EI): m/z (%) 208 (32), 180 (12), 163 (8), 151 (6), 137 (36), 124 (37), 109 (100), 95 (64), 82 (35), 67 (14), 53 (73), 41 (26). HRMS (EI): m/z: calcd for $C_{13}H_{20}O_2$ [M]: 208.14615, found: 208.14633.



Compound 4m.[5] 4-Fluorobenzyl bromide (1.13 g, 6 mmol) and K_2CO_3 (1.03 g, 7.5 mmol) were added to a solution of 4-hydroxy-6-methyl-2-pyrone (0.63 g, 5 mmol) in anhydrous DMF and the resulting mixture was stirred for 3 h under Ar. For work up, the mixture was diluted with aq. sat. NH_4Cl (30 mL), the aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic phases were dried over $MgSO_4$ and evaporated, and the resiude purified by flash chromatography (hexane/EtOAc, 3:1) to give the title compound as a white solid (585 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 4.97 (s, 2H), 5.48 (s, 1H), 5.82 (s, 1H), 7.07-7.11 (m, 2H), 7.33-7.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 69.9, 88.5, 100.4, 115.7+115.9 (d, J_{F-C} = 22.1 Hz), 129.7+129.8 (d, J_{F-C} = 8.0 Hz), 130.22+130.25 (d, J_{F-C} = 3.0 Hz), 161.7+164.1 (d, J_{F-C} = 246.2 Hz), 162.3, 164.8, 170.1. IR (film, cm^{-1}): 1742, 1727, 1651, 1605, 1571, 1515, 1458, 1379, 1322, 1259, 1226, 1188, 1161, 1148, 1040, 1015, 953, 867, 825, 816. MS (EI): m/z (%) 234 (4), 150 (3), 109 (100), 83 (9), 43 (4). HRMS (ESI$^+$): m/z: calcd for $C_{13}H_{11}FO_3Na$ [$M+Na^+$]: 257.05846, found: 257.05844.



Compound 4q. A solution of TBSCl (83 mg, 0.55 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of 6-hydroxymethyl-4-methyl-2*H*-pyran-2-one (70 mg, 0.5 mmol)[12] and imidazole (37.4 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was stirred for 2 h. A standard extractive work up followed by flash chromatography (hexanes/EtOAc, 4:1) gave the title compound as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 6H), 0.94 (s, 9H), 2.16 (s, 3H), 4.42 (s, 2H), 5.97 (s, 1H), 6.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5, 18.3, 21.7, 25.8, 61.3, 103.9, 111.5, 156.2, 162.3, 163.3. IR (film, cm^{-1}): 2954, 2929, 2857, 2886, 1732, 1651, 1568, 1472, 1409, 1387, 1368, 1299, 1254, 1227, 1151, 1119, 1007, 954, 830, 779. MS (EI): m/z (%) 239 (2), 197(100), 169 (51), 153 (4), 141 (5), 125 (11), 109 (4),



[11] a) T.-Y. Yuen, M. A. Brimble, *Org. Lett*. **2012**, *14*, 5154–5157; b) Y.-G. Suh, J.-K. Jung, S.-Y. Seo, K.-H. Min, D.-Y. Shin, Y.-S. Lee, S.-H. Kim, H.-J. Park, *J. Org. Chem.* **2002,** *67,* 4127–4137; c) L. Anastasia, C. Xu, E. Negishi, *Tetrahedron Lett*. **2002**, *43*, 5673–5676.

[12] C. Bhakta, *J. Indian Chem. Soc*. **1985**, *62*, 380–382.

95 (59), 75 (42), 53 (9), 41 (8). HRMS (ESI$^+$): *m/z*: calcd for $C_{13}H_{22}O_3SiNa$ [*M+Na*$^+$]: 277.12314, found: 277.12304.

Iron Catalyzed Cross Coupling of 4-Triflyloxy-2-pyrones

Representative Procedure: Preparation of 4-Isopropyl-6-methyl-2*H*-pyran-2-one (2c). A solution of isopropylmagnesium bromide (2 M in THF, 1.25 mmol, 0.63 mL) was quickly added via syringe at –78 °C to a vigorously stirred solution of $Fe(acac)_3$ (8.8 mg, 0.025 mmol,) and 4-trifloxy-6-methyl-2-pyrone (129.0 mg, 0.5 mmol) in THF (5.0 mL) and NMP (0.5 mL). Stirring was continued at this temperature for 20 min before the reaction was quenched with sat. aq. NH_4Cl. The pH value of the aqueous phase was adjusted to 2~3 by addition of HCl (1 M) before it was extracted with EtOAc (5 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give the title compound as a colorless oil (59.7 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 7.0 Hz, 6H), 2.20 (s, 3H), 2.53-2.63 (m, 1H), 5.87 (s, 1H), 5.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 21.2, 33.5, 104.1, 107.5, 161.4, 163.7, 165.8. IR (film, cm^{-1}): 2967, 2932, 2876, 1721, 1644, 1560, 1467, 1449, 1385, 1366, 1341, 1291, 1224, 1181, 1147, 1126, 1105, 1072, 1026, 979, 941, 871, 850, 829, 687. MS (EI): *m/z* (%) 152 (34), 124 (35), 109 (100), 81 (15), 65 (5), 53 (7), 43 (42), 39 (11). HRMS (EI): *m/z*: calcd for $C_9H_{12}O_2$ [*M*]: 152.08379, found: 152.08373.

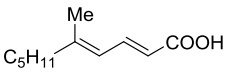
The following compounds were prepared analogously:

Compound 2b. The reaction was performed in Et_2O; pale yellow solid (74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3H), 1.25-1.32 (m, 20H), 1.50-1.60 (m, 4H), 2.22 (s, 3H), 2.32 (t, *J* = 7.6 Hz, 2H), 5.84 (s, 1H), 5.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.8, 22.7, 25.7, 28.1, 29.1, 29.3, 29.3, 29.5, 29.6, 29.6, 29.7, 31.9, 32.8, 35.2, 105.6, 109.6, 160.5, 161.3, 163.5. IR (film, cm^{-1}): 2922, 2853, 1732, 1645, 1562, 1465, 1377, 1228, 1028, 848, 721. MS (EI): *m/z* (%) 306 (8), 263 (6), 249 (6), 235 (4), 193 (9), 179 (4), 165 (3), 151 (8), 137 (99), 124 (100), 109 (18), 96 (70), 81 (12), 67 (10), 55 (12), 43 (43). HRMS (ESI$^+$): *m/z*: calcd for $C_{20}H_{34}O_2Na$ [*M+Na*$^+$]: 329.24505, found: 329.24510.

Compound 2d. Colorless oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 6H), 1.78-1.88 (m, 1H), 2.18 (s, 3H), 2.18 (d, *J* = 6.9 Hz, 2H), 5.81 (s, 1H), 5.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 22.2, 27.8, 44.5, 105.7, 110.4, 159.4, 161.2, 163.2. IR (film, cm^{-1}): 3382, 2961, 2874, 1732, 1646, 1467, 1370, 1217, 1167, 942, 819. MS (EI): *m/z* (%) 166 (38), 151 (14), 138 (7), 124 (31), 109 (8), 96 (100), 81 (7), 67 (14), 53 (9), 43 (75), 27 (9). HRMS (EI): *m/z*: calcd for $C_{10}H_{14}O_2$ [*M*]: 166.09921, found: 166.09938.

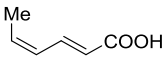
Compound 2e. Pale yellow oil (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77-1.84 (m, 2H), 2.12 (s, 3H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 5.76 (s, 1H), 5.86 (s, 1H), 7.07-7.13 (m, 3H), 7.18-7.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 29.5, 34.4, 35.0, 105.4, 109.6, 126.0, 128.3, 128.4, 141.0, 160.0, 161.4, 163.3. MS (EI): *m/z* (%) 228 (28), 124 (100), 104 (9), 96 (70), 91 (20), 77 (7), 65 (8), 43 (24). HRMS (ESI$^+$): *m/z*: calcd for $C_{15}H_{16}O_2Na$ [*M+Na*$^+$]: 251.10449, found: 251.10425.

Iron Catalyzed Ring Opening/Cross Coupling

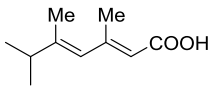


Representative Procedure for the Iron-Catalyzed Ring-Opening/Cross Coupling of 2-Pyrones to afford (*2E,4E*)-Configured Diene Carboxylic Acids. Preparation of (2*E*,4*E*)-5-Methyldeca-2,4-dienoic Acid (6c). A solution of MeMgBr (3 M in Et_2O, 0.75 mmol, 0.25 mL) was quickly added via syringe to a rapidly stirred solution of $Fe(acac)_3$ (4.4 mg, 5 mol%, 0.0125 mmol) and 6-pentyl-2-pyrone **4c** (41.5 mg, 0.25 mmol) in diethylether (5.0 mL) and toluene (5.0 mL) at –30 °C. The mixture was allowed to reach ambient temperature while stirring for 40 min. The reaction was quenched with aq. sat. NH_4Cl and the pH of the aqueous layer adjusted to 2~3 upon addition of HCl (1 M). The aqueous layer was extracted with EtOAc (5 x 20 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give the title compound in the form of colorless crystals (41.9 mg, 92%) (2*E*,4*E*) : (2*Z*,4*E*) > 10 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.24-1.35 (m, 4H), 1.43-1.50 (m, 2H), 1.90 (s, 3H), 2.14 (t, *J* = 7.5 Hz, 2H), 5.78 (d, *J* = 15.1 Hz, 1H), 6.03 (d, *J* = 11.6 Hz, 1H), 7.68 (dd, *J* = 11.8, 15.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 17.4, 22.5, 27.3, 31.5, 40.3, 117.7, 123.0, 143.4, 152.1, 172.9. IR (film, cm^{-1}): ~3600-2300 (br), 2935, 2857, 1683, 1623, 1608, 1416, 1309, 1282, 1237, 1171, 977, 939, 884, 693. MS (EI): *m/z* (%) 182 (9), 167 (7), 137 (14), 125 (6), 122 (6), 111 (100), 97 (36), 93 (21), 81 (37), 79 (25), 77 (14), 67 (18), 55 (34), 41 (30), 29 (14). HRMS (EI): *m/z*: calcd for $C_{11}H_{18}O_2$ [*M*]: 182.13054, found: 182.13068.

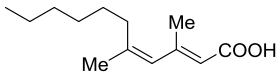
The following compounds were prepared analogously:



Compound 6b. White solid (88%, (2*E*,4*Z*) : (2*Z*,4*Z*) = 8 : 1); the NMR spectra are in full accord with those reported in the literature;[13] IR (film, cm^{-1}): ~3600-2300 (br), 1686, 1628, 1606, 1417, 1373, 1277, 1201, 1138, 994, 948, 871, 687. MS (EI): *m/z* (%) 112 (59), 97 (100), 67 (58), 65 (21), 55 (17), 43 (18), 41 (57), 39 (58). HRMS (EI): *m/z*: calcd for $C_6H_8O_2$ [*M*]: 112.05233, found: 112.05243.



Compound 6d. The reaction was performed in THF at 0°C → RT; colorless oil (82%, (2*Z,4E*):(2*E,4E*) = 1:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.9 Hz, 6H), 1.80 (s, 3H), 2.24 (s, 3H), 2.27-2.37 (m, 1H), 5.69 (s, 1H), 5.76 (s, 1H), ~10.0-13.5 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 20.1, 21.2, 37.9, 116.9, 125.9, 148.6, 157.6, 172.6. IR (film, cm^{-1}): ~3600-2400 (br), 2981, 2935, 1690, 1638, 1561, 1439, 1378, 1292, 1255, 1202, 1157, 1032, 991, 946, 886, 849, 730, 683. MS (EI): *m/z* (%) 168 (0.48), 125 (100), 111 (7), 107 (14), 97 (8), 91 (11), 79 (11), 67 (8), 55 (6), 41 (9). HRMS (EI): *m/z*: calcd for $C_{10}H_{16}O_2$ [*M*]: 168.11491, found: 168.11503.



Compound 6e. The reaction with hexylmagnesium bromide was performed at –30°C for 60 min; the product was isolated as a colorless oil in 84% ((2*E,4Z*):other isomers > 10 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3H), 1.24-1.33 (m, 6H), 1.39-1.45 (m, 2H), 1.80 (s, 3H), 2.18-2.21 (m, 2H), 2.23 (s, 3H), 5.68 (s, 1H), 5.74 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.8, 22.6, 24.4, 28.2, 29.3, 31.6, 33.1, 115.9, 128.5, 143.4, 157.2, 171.1. IR (film, cm^{-1}): 2927, 2857, 1686, 1620, 1597, 1467, 1418, 1376, 1291, 1251, 1178, 1146, 933, 890, 725. MS (EI): *m/z* (%) 210 (1), 195 (4), 125 (100), 109 (8), 97 (15), 81 (10), 67 (10), 55 (8), 43 (12). HRMS (ESI$^+$): *m/z*: calcd for $C_{13}H_{22}O_2Na$ [*M+Na*$^+$]: 233.15115, found: 233.15120.

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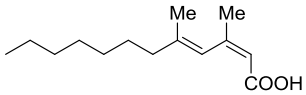
[13] I. K. Cigić, J. Plavec, S. S. Možina, L. Zupančič-Kralj, *J. Chromatogr. A* **2001**, *905*, 359–366.

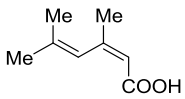
Compound 6f. The reaction with $Ph(CH_2)_3MgBr$ was performed at –30°C for 60 min; the product was isolated as a colorless oil in 82% ((2*E*,4*Z*):other isomers > 10 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73-1.80 (m, 2H), 1.81 (s, 3H), 2.21 (s, 3H), 2.27 (t, *J* = 7.8 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 5.67 (s, 1H), 5.77 (s, 1H), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 24.3, 30.1, 32.8, 35.8, 116.4, 125.8, 128.3, 128.4, 128.9, 142.0, 142.6, 157.0, 171.9. IR (film, cm^{-1}): 3027, 2933, 1682, 1618, 1496, 1453, 1375, 1291, 1253, 1181, 891, 749, 699. MS (EI): *m*/*z* (%) 244 (0.3), 229 (52), 140 (29), 125 (9), 104 (100), 96 (49), 91 (44), 81 (26), 77 (12), 65 (11), 53 (7), 43 (52). HRMS (CI): *m*/*z*: calcd for $C_{16}H_{21}O_2$ [$M+H^+$]: 245.15395, found: 245.15415.



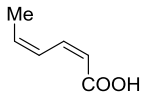
Representative Procedure for the Iron-Catalyzed Ring-Opening/Cross Coupling of 2-Pyrones to afford (*2Z,4E*)-Configured Diene Carboxylic Acids. Preparation of (*Z*)-3,5-Dimethyldodeca-2,4-dienoic Acid (11). A solution of MeMgBr (3 M in Et_2O, 2.5 mL, 7.5 mmol) was quickly added via syringe to a rapidly stirred solution of $Fe(acac)_3$ (44.5 mg, 0.125 mmol) and pyrone **10** (520 mg, 2.5 mmol) in diethylether (25 mL) and toluene (25 mL) at –30 °C. Stirring was continued for 20 min at this temperature before the reaction was quenched with aq. sat. NH_4Cl and the pH of the aqueous layer adjusted to 2~3 upon addition of HCl (1 M). The aqueous layer was extracted with EtOAc (5 x 20 mL), the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give the title compound in the form of a pale yellow liquid (460.5 mg, 83%), (2*Z*,4*E*) : others > 20 : 1, ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.4 Hz, 3H), 1.26-1.33 (m, 8H), 1.42-1.49 (m, 2H), 1.73 (s, 3H), 2.04 (s, 3H), 2.10 (t, *J* = 7.5 Hz, 2H), 5.68 (s, 1H), 6.40 (s, 1H), ~9.5-13.5 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 18.6, 22.7, 25.7, 27.8, 29.2, 31.8, 40.9, 116.7, 123.4, 143.5, 156.2, 171.0. IR (film, cm^{-1}): ~3600-2400 (br), 2926, 2855, 1685, 1625, 1592, 1440, 1377, 1289, 1251, 1201, 1161, 1028, 934, 853, 722, 707. MS (EI): *m*/*z* (%) 224 (4), 209 (9), 179 (6), 125 (100), 111 (6), 107 (14), 95 (11), 93 (12), 79 (12), 67 (7), 55 (9), 41 (16). HRMS (EI): *m*/*z*: calcd for $C_{14}H_{24}O_2$ [*M*]: 224.17744, found: 224.17763.

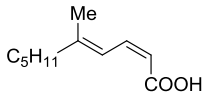
The following compounds were prepared analogously:

Compound 5a. Colorless crystals (96%, (2*Z*:2*E* > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 3H), 1.86 (s, 3H), 2.05 (s, 3H), 5.69 (s, 1H), 6.44 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 25.6, 27.3, 116.6, 123.7, 140.0, 156.0, 171.0. IR (film, cm^{-1}): ~3600-2400 (br), 2981, 2935, 1690, 1638, 1561, 1439, 1378, 1292, 1255, 1202, 1157, 1032, 991, 946, 886, 849, 730, 683. MS (EI): *m*/*z* (%) 140 (4), 125 (100), 112 (4), 97 (53), 96 (9), 82 (8), 81 (23), 79 (22), 69 (8), 67 (6), 55 (7), 53 (8), 43 (37), 41 (15), 39 (11). HRMS (EI): *m*/*z*: calcd for $C_8H_{12}O_2$ [*M*]: 140.08372, found: 140.08373.



Compound 5b. The reaction was performed at –60°C for 40 min; white solid (86%, (2*Z*,4*E*) : (2*Z*,4*Z*) = 1 : 7); the NMR spectra are in full accord with those reported in the literature;[13] IR (film, cm^{-1}): ~3600-2300 (br), 1679, 1635, 1600, 1433, 1247, 1224, 1000, 961, 839, 780. MS (EI): *m*/*z* (%) 112 (59), 97 (100), 67 (58), 65 (21), 55 (17), 43 (18), 41 (57), 39 (58). HRMS (EI): *m*/*z*: calcd for $C_6H_8O_2$ [*M*]: 112.05233, found: 112.05243.

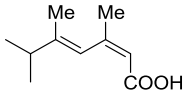




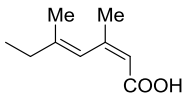
Compound 5c. The reaction was performed at –60°C for 40 min; white solid, (94%, (2*E*,4*E*) : (2*Z*,4*E*) < 1 : 10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 3H), 1.25-1.35 (m, 4H), 1.44-1.52 (m, 2H), 1.86 (s, 3H), 2.18 (t, *J* = 6.3 Hz, 2H), 5.58

(d, J = 11.5 Hz, 1H), 6.99 (t, J = 11.4 Hz, 1H), 7.17 (d, J = 11.8, 1H), ~10.0-13.5 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 16.7, 22.5, 27.5, 31.6, 40.7, 113.9, 121.5, 142.9, 152.4, 172.1. IR (film, cm^{-1}): ~3600-2300 (br), 2929, 2858, 1682, 1623, 1591, 1440, 1289, 1228, 930, 892, 825, 726. MS (EI): *m/z* (%) 182 (9), 167 (7), 137 (14), 125 (6), 122 (6), 111 (100), 97 (36), 93 (21), 81 (37), 79 (25), 77 (14), 67 (18), 55 (34), 41 (30), 29 (14). HRMS (EI): *m/z*: calcd for $C_{11}H_{18}O_2$ [*M*]: 182.13054, found: 182.13068.

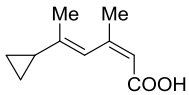
Compound 5d. Colorless crystals (92%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (d, J = 6.9 Hz, 6H), 1.68 (s, 3H), 2.02 (s, 3H), 2.29-2.39 (m, 1H), 5.69 (s, 1H), 6.34 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 21.1, 25.7, 37.6, 116.9, 121.6, 147.7, 156.8, 171.6. IR (film, cm^{-1}): ~3600-2400 (br), 2963, 2874, 1683, 1621, 1439, 1377, 1288, 1252, 1203, 1156, 1084, 1028, 940, 851, 704. MS (EI): *m/z* (%) 168 (0.35), 153 (2), 125 (100), 111 (4), 107 (8), 97 (11), 91 (5), 79 (7), 67 (6), 55 (6), 43 (18). HRMS (EI): *m/z*: calcd for $C_{10}H_{16}O_2$ [*M*]: 168.11520, found: 168.11503.



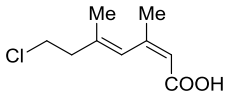
Compound 5e. Colorless crystals (93%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, J = 7.6 Hz, 3H), 1.75 (s, 3H), 2.05 (s, 3H), 2.13 (q, J = 7.6 Hz, 2H), 5.69 (s, 1H), 6.42 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 18.5, 25.6, 33.5, 116.7, 122.3, 144.6, 156.4, 171.5. IR (film, cm^{-1}): ~3600-2500 (br), 2969, 2938, 2879, 1682, 1624, 1591, 1439, 1377, 1290, 1249, 1199, 1178, 1156, 1031, 998, 937, 887, 849, 705. MS (EI): *m/z* (%) 154 (1.29), 139 (10), 125 (100), 109 (9), 97 (16), 93 (11), 79 (10), 67 (11), 55 (11), 43 (24), 41 (16), 39 (13). HRMS (EI): *m/z*: calcd for $C_9H_{14}O_2$ [*M*]: 154.09946, found: 154.09938.



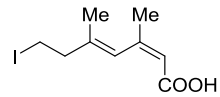
Compound 5f. Colorless crystals (90%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56-0.60 (m, 2H), 0.65-0.69 (m, 2H), 1.47-1.54 (m, 1H), 1.63 (s, 3H), 2.05 (s, 3H), 5.65 (s, 1H), 6.53 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.6, 16.2, 20.2, 25.7, 116.5, 121.8, 144.3, 155.9, 171.5. IR (film, cm^{-1}): ~3600-2400 (br), 3085, 2978, 1683, 1613, 1439, 1381, 1256, 1150, 1022, 950, 929, 848, 814, 704, 681. MS (ESI$^+$): *m/z* 167 [*M+H*], 333 [*2*M+H*], 355 [*2*M+Na*]. HRMS (EI): *m/z*: calcd for $C_{10}H_{14}O_2$ [*M*]: 166.09923, found: 166.09938.



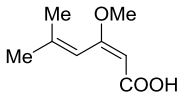
Compound 5g. White solid (90%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (s, 3H), 2.04 (m, 3H), 2.56 (t, J = 7.3 Hz, 2H), 3.63 (t, J = 7.3 Hz, 2H), 5.73 (s, 1H), 6.38 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 25.4, 42.6, 43.1, 117.6, 126.3, 137.3, 155.5, 171.3. IR (film, cm^{-1}): ~3500-2300 (br), 2911, 2762, 2585, 1679, 1641, 1595, 1431, 1384, 1277, 1248, 1193, 926, 863, 843, 738, 714. MS (EI): *m/z* (%) 188 (0.06), 173 (7), 125 (100), 109 (9), 97 (30), 91 (7), 79 (10), 67 (10), 53 (9), 43 (33). HRMS (EI): *m/z*: calcd for $C_9H_{13}O_2Cl$ [*M*]: 188.06058, found: 188.06041.



Compound 5h. White solid (68%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (s, 3H), 2.05 (m, 3H), 2.68 (t, J = 7.6 Hz, 2H), 3.27 (t, J = 7.6 Hz, 2H), 5.74 (s, 1H), 6.37 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.35, 17.9, 25.4, 44.3, 117.5, 125.9, 139.7, 155.6, 171.0. IR (film, cm^{-1}): ~3700-2400 (br), 2964, 1682, 1621, 1435, 1378, 1290, 1250, 1170, 1026, 943, 887, 725. MS (ESI$^+$): *m/z* 281 [*M+H*]. HRMS (ESI$^+$): *m/z*: calcd for $C_9H_{13}IO_2Na$ [*M+Na*$^+$]: 302.98559, found: 302.98524.

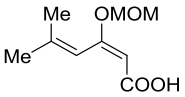


Compound 5i. White solid (72%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 3H), 1.93 (s, 3H), 3.71 (s, 3H), 5.01 (s, 1H), 6.74 (s, 1H), ~9.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 27.9, 55.3, 90.2, 118.1, 146.2, 171.1, 172.1. IR (film, cm^{-1}): ~3400-2400 (br), 2923, 2852, 1731, 1681, 1639, 1566, 1440, 1377, 1298, 1202,

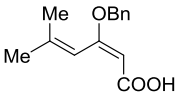


1169, 1129, 1078, 1040, 928, 794, 721. MS (EI): *m/z* (%) 156 (2), 141 (19), 112 (82), 97 (100), 79 (81), 67 (90), 53 (18), 44 (12). HRMS (CI): *m/z*: calcd for $C_8H_{13}O_3$ [$M+H^+$]: 157.08635, found: 157.08647.

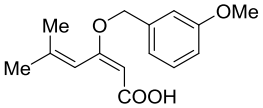
Compound 5j. White solid (80%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 1.96 (s, 3H), 3.48 (s, 3H), 5.09 (s, 2H), 5.20 (s, 1H), 6.74 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 28.0, 56.9, 93.5, 94.1, 117.9, 146.4, 168.2, 172.6. IR (film, cm^{-1}): ~3500-2300 (br), 2938, 1676, 1633, 1568, 1416, 1374, 1288, 1217, 1199, 1147, 1017, 982, 922, 829, 720. MS (EI): *m/z* (%) 186 (2), 171 (3), 154 (3), 141 (4), 124 (5), 109 (3), 95 (6), 83 (21), 55 (13), 45 (100). HRMS (EI): *m/z*: calcd for $C_9H_{14}O_4$ [*M*]: 186.08903, found: 186.08921.



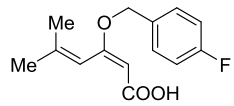
Compound 5k. White solid (88%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 6H), 4.93 (s, 2H), 5.15 (s, 1H), 6.79 (s, 1H), 7.33-7.39 (m, 5H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 28.0, 70.5, 91.4, 118.2, 127.8, 128.3, 128.6, 135.4, 146.4, 170.1, 172.4. IR (film, cm^{-1}): 3032, 2915, 1728, 1650, 1566, 1453, 1375, 1248, 1138, 1093, 1015, 892, 808, 733, 695. MS (EI): *m/z* (%) 188 (0.31), 145 (2), 131 (2), 91 (100), 83 (51), 65 (12), 55 (2), 39 (3). HRMS (ESI$^+$): *m/z*: calcd for $C_{14}H_{16}O_3Na$ [$M+Na^+$]: 255.09909, found: 255.09917.



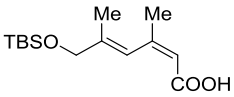
Compound 5l. White solid (85%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 3H), 1.94 (s, 3H), 3.82 (s, 3H), 4.90 (s, 2H), 5.14 (s, 1H), 6.79 (s, 1H), 6.87-6.89 (m, 1H), 6.93-6.96 (m, 2H), 7.28-7.31 (m, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 28.0, 55.2, 70.4, 91.5, 113.2, 113.8, 118.2, 119.9, 129.7, 136.9, 146.4, 159.8, 170.0, 172.4. IR (film, cm^{-1}): 3424, 2938, 1703, 1626, 1603, 1587, 1564, 1490, 1464, 1388, 1361, 1266, 1234, 1179, 1155, 1112, 1040, 1020, 873, 818, 785, 738, 694. MS (EI): *m/z* (%) 262 (0.35), 218 (2), 162 (17), 135 (4), 121 (100), 91 (17), 83 (27), 78 (9), 77 (7), 65 (5), 51 (2), 41 (3), 39 (4). HRMS (EI): *m/z*: calcd for $C_{15}H_{18}O_4Na$ [$M+Na^+$]: 285.10966, found: 285.10973.

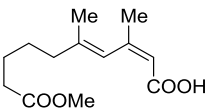


Compound 5m. White solid (86%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 1.91 (s, 3H), 4.88 (s, 2H), 5.13 (s, 1H), 6.77 (s, 1H), 7.05-7.09 (m, 2H), 7.34-7.37 (m, 2H), ~9.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 28.0, 69.8, 91.4, 115.5+115.7 (d, J_{F-C} = 21.1 Hz), 118.1, 129.7+129.8 (d, J_{F-C} = 8.5 Hz), 131.15+131.18 (d, J_{F-C} = 3.0 Hz), 146.5, 161.5+163.9 (d, J_{F-C} = 245.4 Hz), 169.9, 172.2. IR (film, cm^{-1}): 3358, 2931, 1888, 1693, 1604, 1562, 1509, 1454, 1417, 1365, 1220, 1156, 1096, 1012, 821, 760, 704, 666. MS (EI): *m/z* (%) 250 (2), 150 (2), 109 (100), 83 (13), 69 (2), 57 (2), 39 (4). HRMS (ESI$^+$): *m/z*: calcd for $C_{14}H_{15}O_3FNa$ [$M+Na^+$]: 273.08969, found: 273.08974.



Compound 5n. Colorless oil (78%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H), 0.92 (s, 9H), 1.71 (s, 3H), 2.07 (s, 3H), 4.10 (s, 2H), 5.71 (s, 1H), 6.76 (s, 1H), ~10.5-13.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.4, 15.6, 18.4, 25.5, 25.9, 68.2, 117.4, 122.0, 141.1, 155.6, 171.3. IR (film, cm^{-1}): ~3500-2500 (br), 2929, 2856, 1684, 1632, 1594, 1443, 1250, 1200, 1112, 1079, 938, 833, 774, 707, 671. MS (EI): *m/z* (%) 240 (10), 213 (7), 195 (4), 171 (28), 169 (20), 127 (7), 125 (16), 115 (5), 97 (6), 89 (21), 75 (100), 73 (44), 59 (8), 43 (12). HRMS (ESI$^+$): *m/z*: calcd for $C_{14}H_{26}O_3SiNa$ [$M+Na^+$]: 293.15424, found: 293.15434.

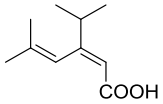




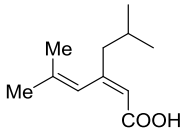
Compound 5o. Colorless oil (72%, (2*Z,4E*):(2*E,4E*) > 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (m, 2H), 1.65 (m, 2H), 1.72 (s, 3H), 2.03 (s, 3H), 2.12 (t, *J* = 7.2 Hz, 2H), 3.27 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 5.69 (s, 1H), 6.37 (s, 1H). ^{13}C NMR (100

MHz, $CDCl_3$): δ = 18.4, 24.3, 25.6, 27.1, 33.9, 40.2, 51.5, 116.9, 123.9, 142.2, 155.9, 170.4, 174.2. IR (film, cm^{-1}): ~3600-2500 (br), 2938, 1735, 1682, 1624, 1589, 1435, 1375, 1251, 1200, 1144, 1083, 1021, 927, 852, 706. MS (EI): *m/z* (%) 209 (0.84), 196 (3), 181 (3), 163 (2), 149 (5), 125 (100), 107 (25), 97 (19), 81 (10), 67 (12), 55 (9). HRMS (ESI^+): *m/z*: calcd for $C_{13}H_{20}O_4Na$ [$M+Na^+$]: 263.12525, found: 263.12538.

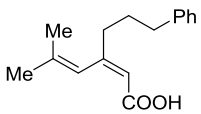
Compound 5p. Colorless oil (68%, (2*Z,4E*):(2*E,4E*) > 20:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.8 Hz, 6H), 1.60 (s, 3H), 1.84 (s, 3H), 2.39-2.49 (m, 1H), 5.76 (s, 1H), 5.84 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 21.2, 25.9, 37.1, 114.6, 121.1, 138.9, 164.9, 171.0. IR (film, cm^{-1}): ~3600-2400 (br), 2967, 2933, 2875, 1697, 1625, 1465, 1415, 1384, 1291, 1238, 1183, 1023, 943, 871, 667. MS (EI): *m/z* (%) 168 (0.48), 153 (100), 125 (19), 111 (41), 97 (12), 83 (16), 67 (17), 55 (14), 43 (87). HRMS (EI): *m/z*: calcd for $C_{10}H_{16}O_2$ [*M*]: 168.11496, found: 168.11503.



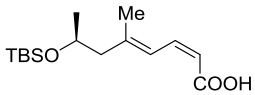
Compound 5q. Pale yellow oil (84%, (2*Z,4E*):(2*E,4E*) > 20:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 6H), 1.66 (s, 3H), 1.72-1.81 (m, 1H), 1.83 (s, 3H), 2.11 (d, *J* = 7.2 Hz, 2H), 5.69 (s, 1H), 5.97 (s, 1H), ~9.0-12.0 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 22.4, 26.4, 27.1, 48.9, 117.2, 122.7, 138.7, 159.1, 171.3. IR (film, cm^{-1}): ~3600-2400 (br), 2957, 2931, 2870, 1689, 1618, 1465, 1415, 1368, 1291, 1246, 1194, 1164, 979, 884, 822, 712. MS (EI): *m/z* (%) 182 (2), 167 (100), 139 (9), 125 (25), 111 (23), 96 (12), 81 (19), 67 (8), 55 (10), 43 (69), 27 (7). HRMS (EI): *m/z*: calcd for $C_{11}H_{18}O_2$ [*M*]: 182.13051, found: 182.13068.



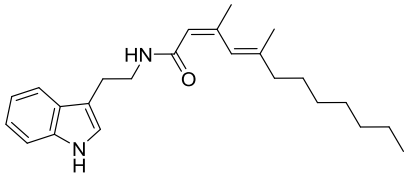
Compound 5r. Pale yellow oil (73%, (2*Z,4E*):(2*E,4E*) > 20:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 3H), 1.67-1.74 (m, 2H), 1.76 (s, 3H), 2.20 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 5.66 (s, 1H), 5.94 (s, 1H), 7.07-7.13 (m, 3H), 7.17-7.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 26.4, 29.8, 35.4, 38.6, 116.5, 122.5, 125.9, 128.3, 128.4, 138.9, 141.7, 159.6, 171.1. IR (film, cm^{-1}): ~3600-2500 (br), 3027, 2934, 2860, 1688, 1622, 1496, 1453, 1416, 1378, 1292, 1245, 1195, 1079, 1030, 873, 748, 699. MS (EI): *m/z* (%) 244 (0.29), 229 (52), 140 (29), 125 (9), 104 (100), 96 (49), 91 (44), 81 (26), 77 (12), 65 (11), 53 (7), 43 (52). HRMS (CI): *m/z*: calcd for $C_{16}H_{21}O_2$ [$M+H^+$]: 245.15395, found: 245.15415.



Compound 8. The reaction was performed at –60°C for 40 min; colorless oil (80%, (2*Z,4E*):(2*E,4E*) > 10:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.89 (s, 3H), 2.23-2.37 (m, 2H), 3.97-4.05 (m, 1H), 5.60 (d, *J* = 11.4 Hz, 3H), 6.97 (t, *J* = 11.7 Hz, 1H), 7.18 (d, *J* = 11.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9, –4.5, 17.8, 18.0, 23.9, 25.8, 50.7, 67.7, 114.3, 124.0, 142.3, 148.8, 171.7. IR (film, cm^{-1}): 3420, 2931, 2858, 1705, 1378, 1256, 1175, 1132, 993, 835, 777, 669. MS (EI): *m/z* (%) 240 (5), 227 (17), 209 (15), 183 (34), 159 (62), 135 (9), 119 (17), 115 (26), 107 (17), 103 (21), 91 (11), 75 (100), 73 (90), 59 (13), 41 (9). HRMS (ESI^+): *m/z*: calcd for $C_{15}H_{28}O_3SiNa$ [$M+Na^+$]: 307.16998, found: 307.16999.

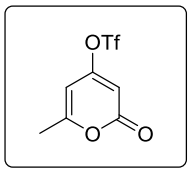


Granulatamide B. Triethylamine (45.5 mg, 0.45 mmol), 1-hydroxybenzotriazole (44.6 mg, 0.33 mmol) and EDC·HCl (86.3 mg, 0.45 mmol) were added to a solution of tryptamine (52.8 mg, 0.33 mmol) and acid **11** (67.2 mg, 0.30 mmol) in DMF (0.3 mL) and CH_2Cl_2 (5 mL). The mixture was stirred overnight before the solvent was evaporated. The residue was treated with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed successively with aq. citric acid solution (5%, 3



x 20 mL), sat. aq. $NaHCO_3$ (3 x 30 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexane/EtOAc, 4:1) to give the title compound as colorless oil (90.0 mg, 82%). The spectral data are in agreement with those reported in the literature.[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.17-1.32 (m, 10H), 1.56 (s, 3H), 1.83 (t, *J* = 7.3 Hz, 2H), 1.86 (s, 3H), 2.96 (t, *J* = 6.9 Hz, 2H), 3.64 (q, *J* = 6.6 Hz, 2H), 5.68 (s, 1H), 5.86 (s, 1H), 6.21 (br, 1H), 6.99 (s, 1H), 7.08-7.12 (m, 1H), 7.17-7.20 (m, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 8.48 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 17.7, 22.6, 25.3, 25.4, 27.8, 29.1, 29.3, 31.8, 39.5, 39.5, 111.2, 112.9, 118.6, 119.2, 121.9, 122.0, 122.3, 122.8, 127.3, 136.4, 142.3, 145.8, 166.8. IR (film, cm^{-1}): 3403, 3278, 3056, 2925, 2853, 1643, 1598, 1522, 1456, 1435, 1375, 1339, 1260, 1229, 1097, 1031, 1010, 923, 841, 804, 737. MS (EI): *m*/*z* (%) 366 (13), 267 (29), 224 (13), 143 (100), 130 (25), 124 (6), 95 (5), 77 (5), 55 (5), 43 (5). HRMS (ESI^+): *m*/*z*: calcd for $C_{24}H_{34}N_2ONa$ [$M+Na^+$]: 389.25598, found: 389.25633.

[14] F. Reyes, R. Martín, R. Fernández, *J. Nat. Prod.* **2006,** *69,* 668–670.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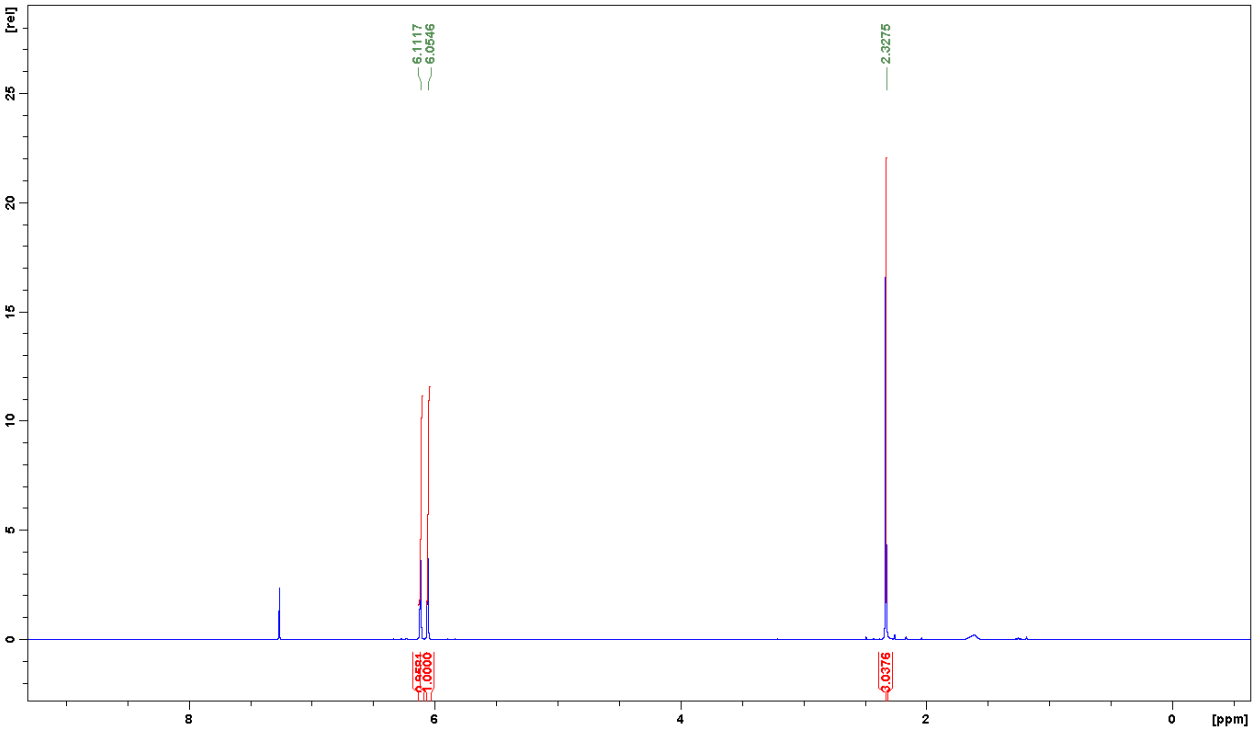
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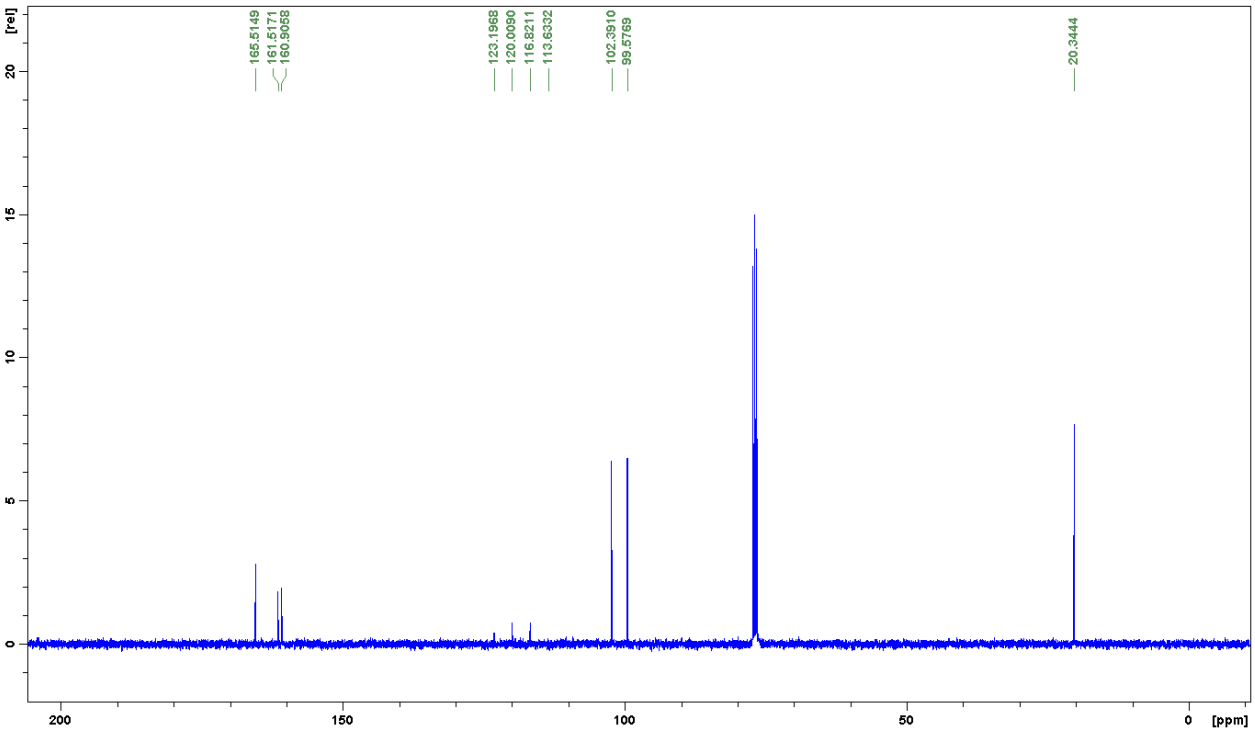
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20.3444
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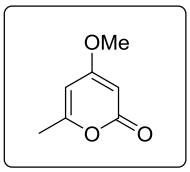
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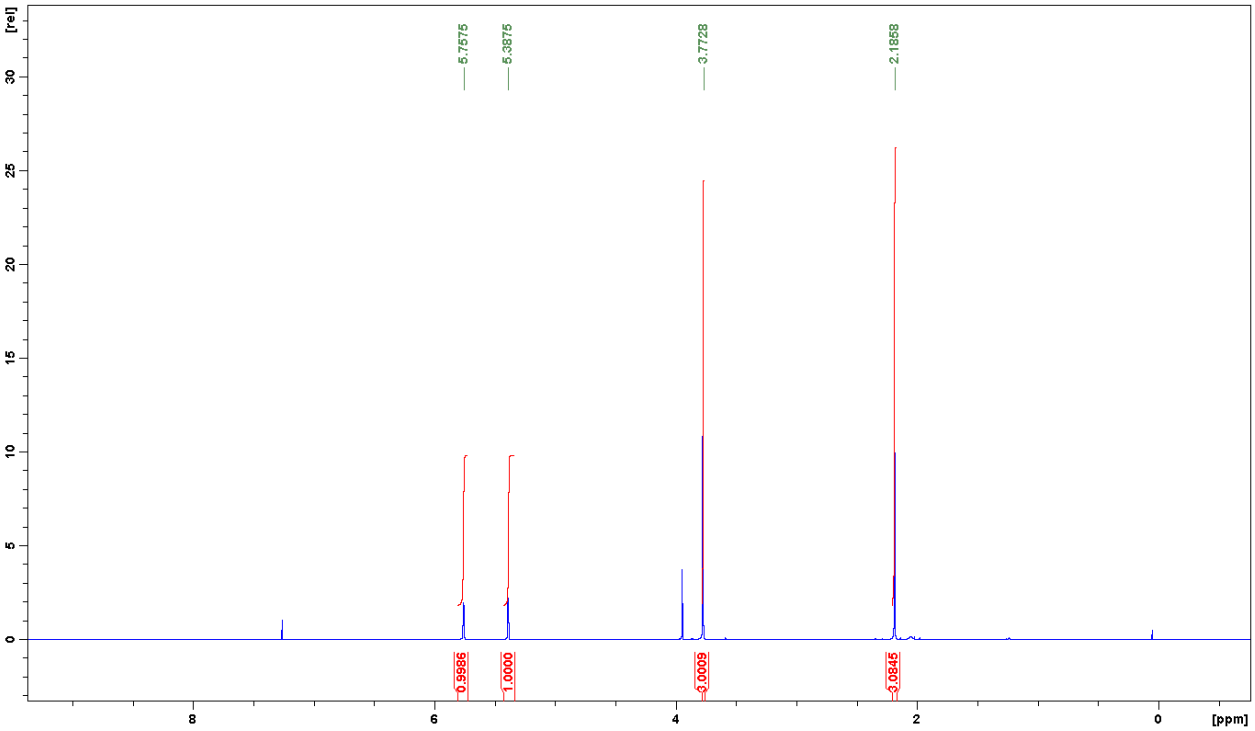
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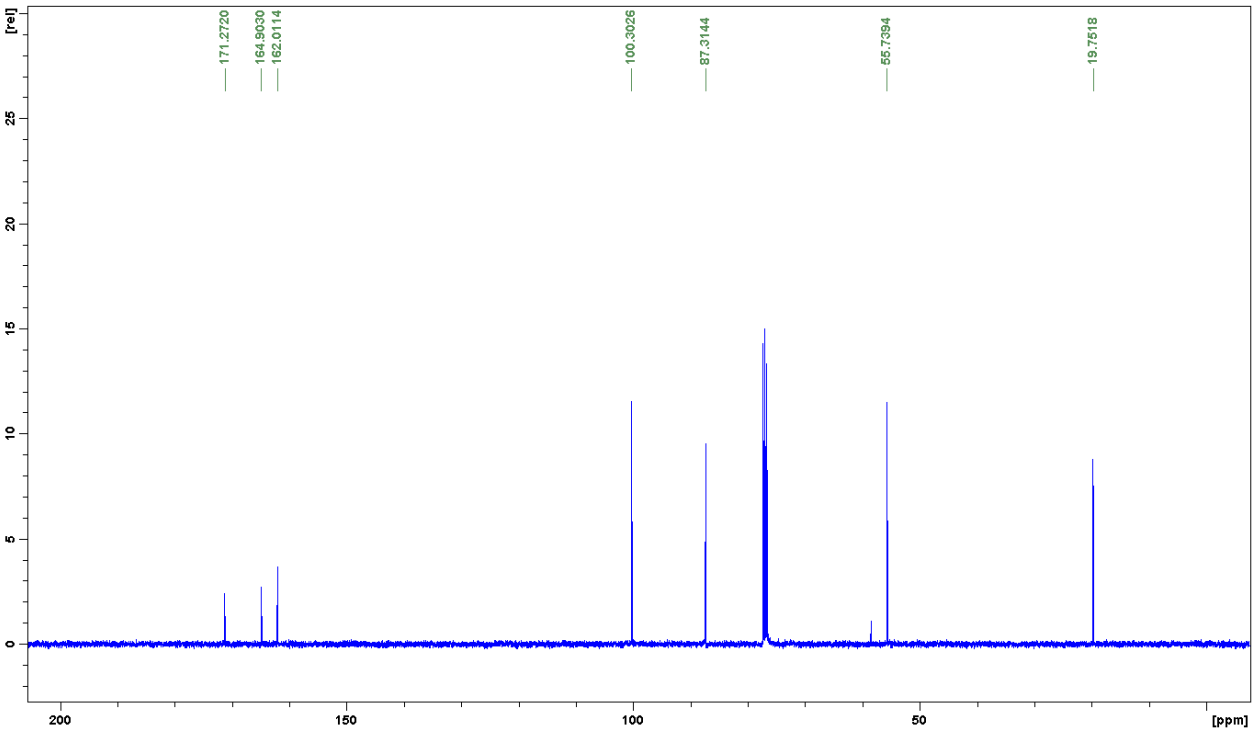
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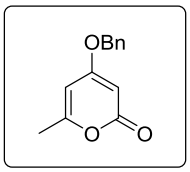
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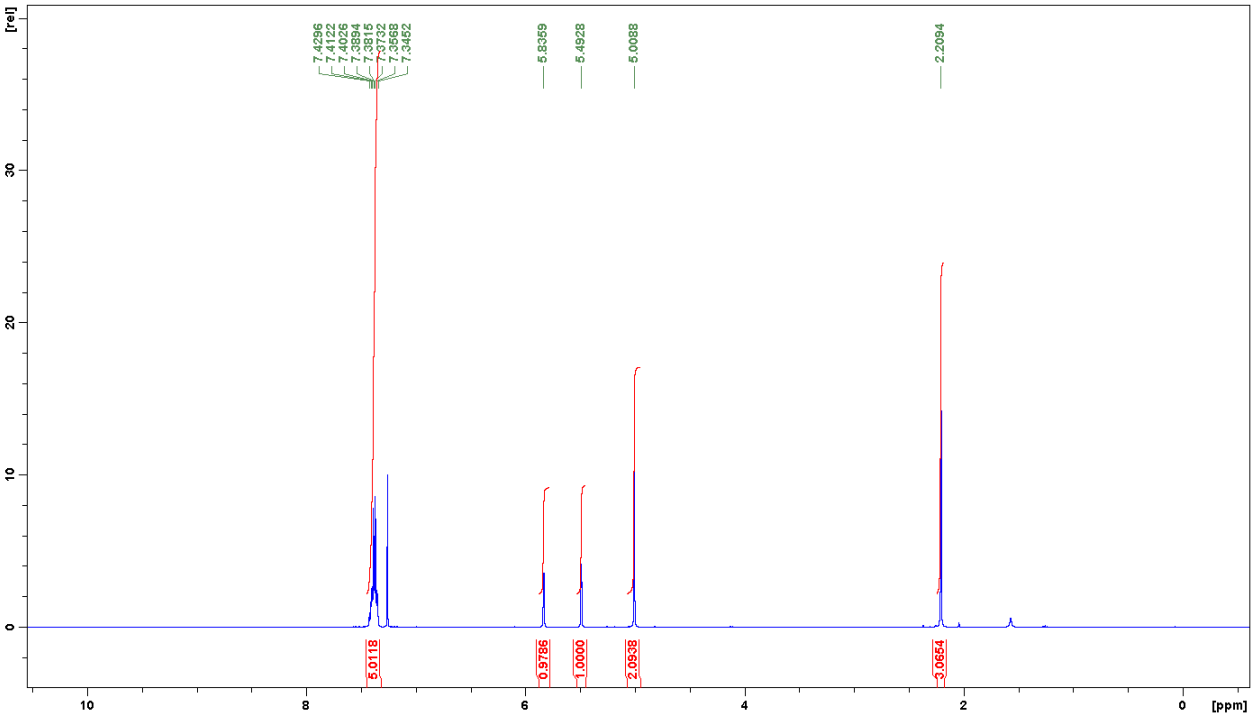
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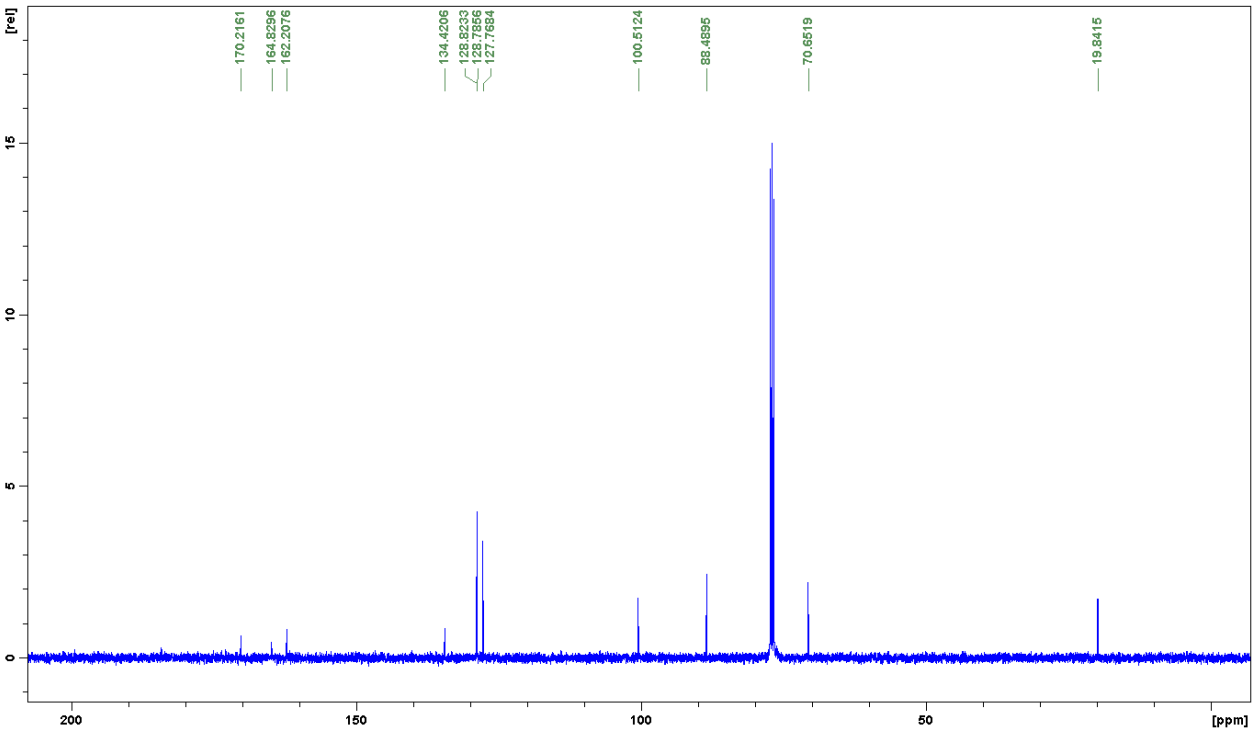
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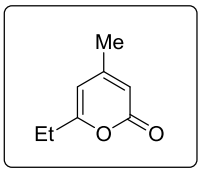
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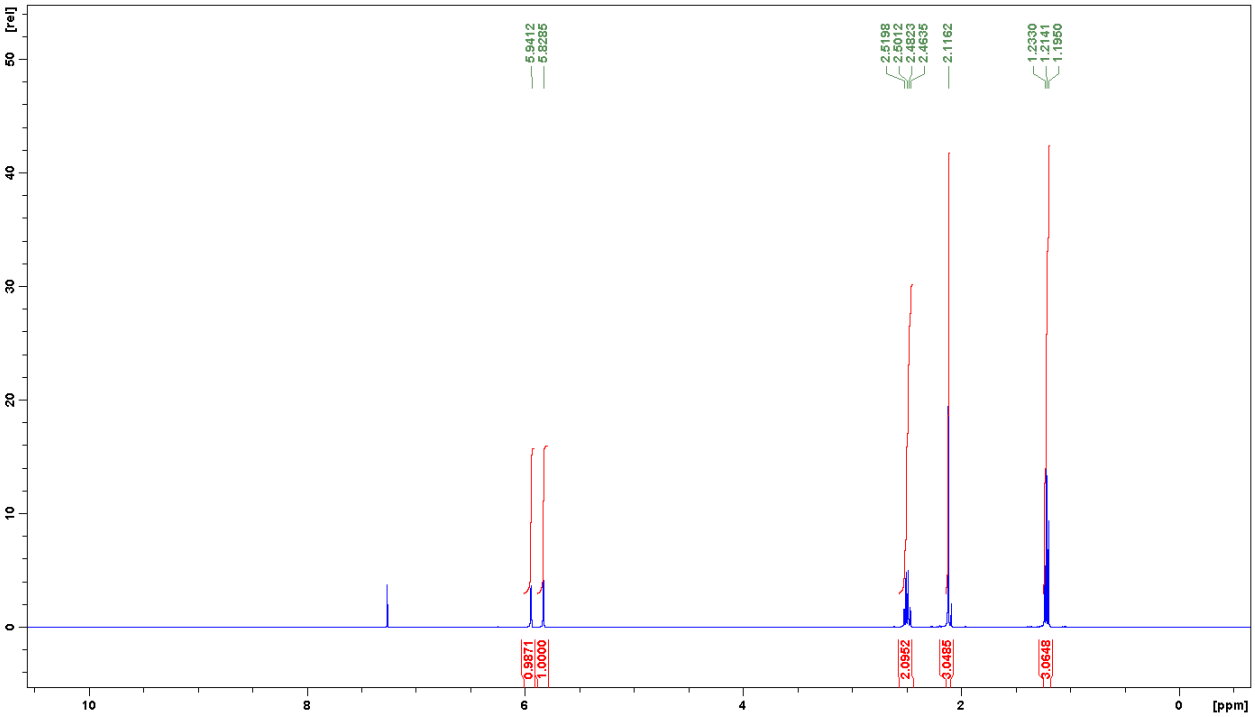
O
O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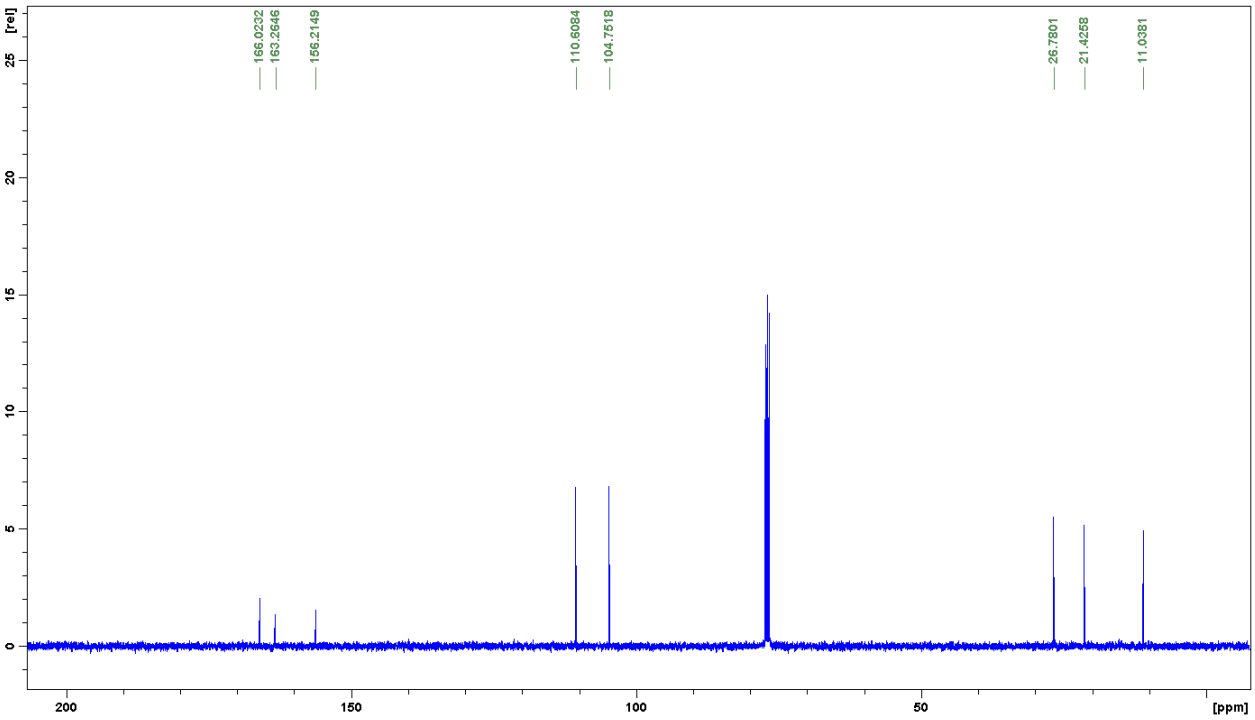
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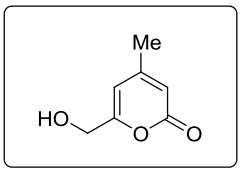
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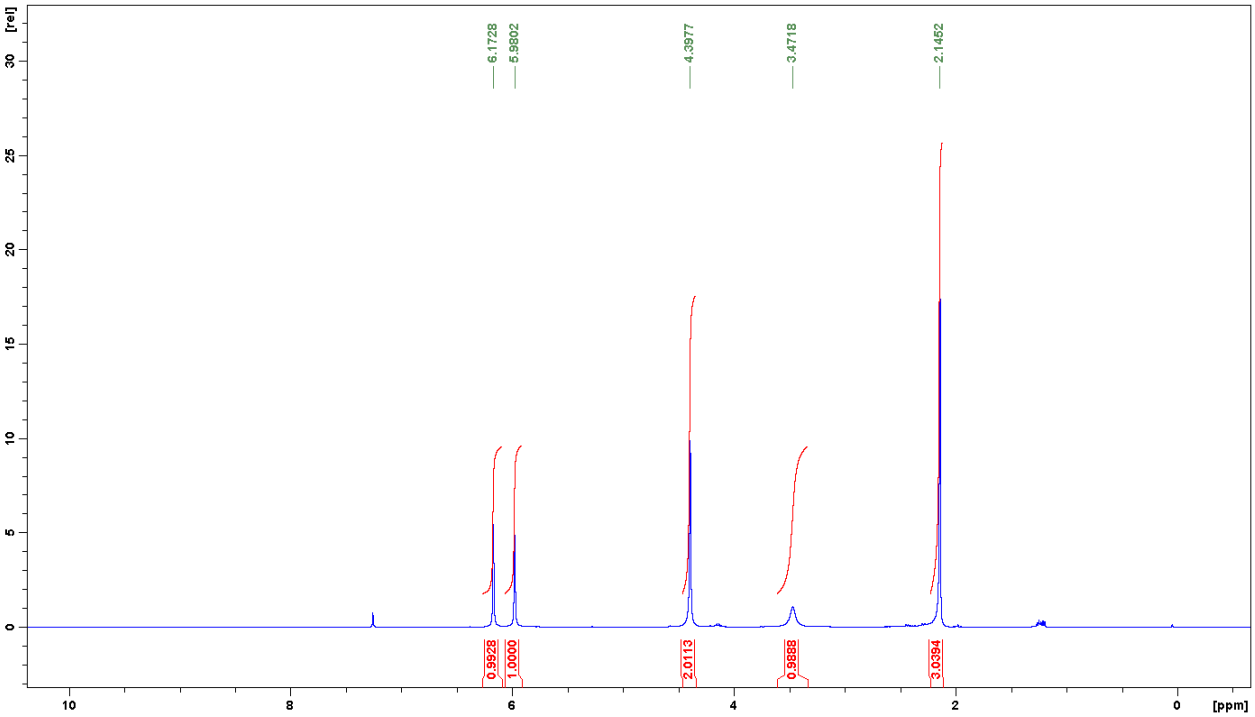
HO
O
O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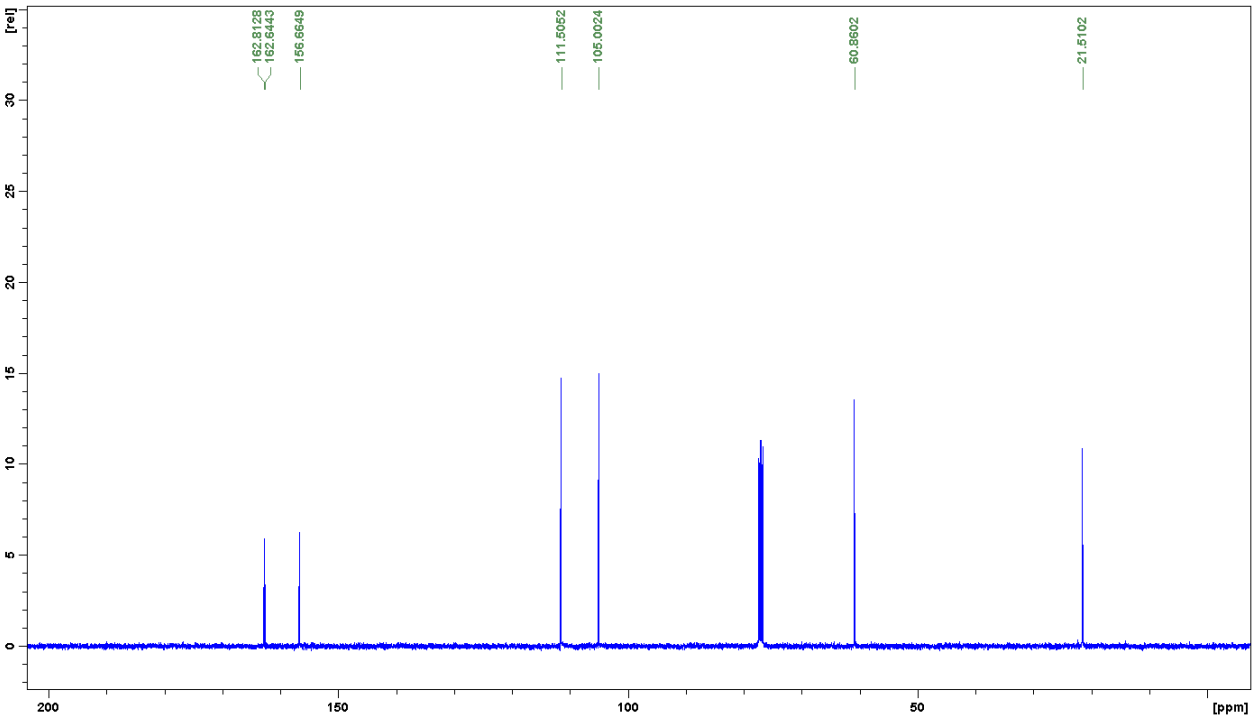
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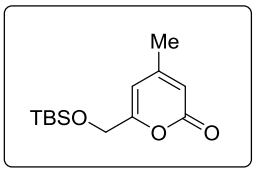
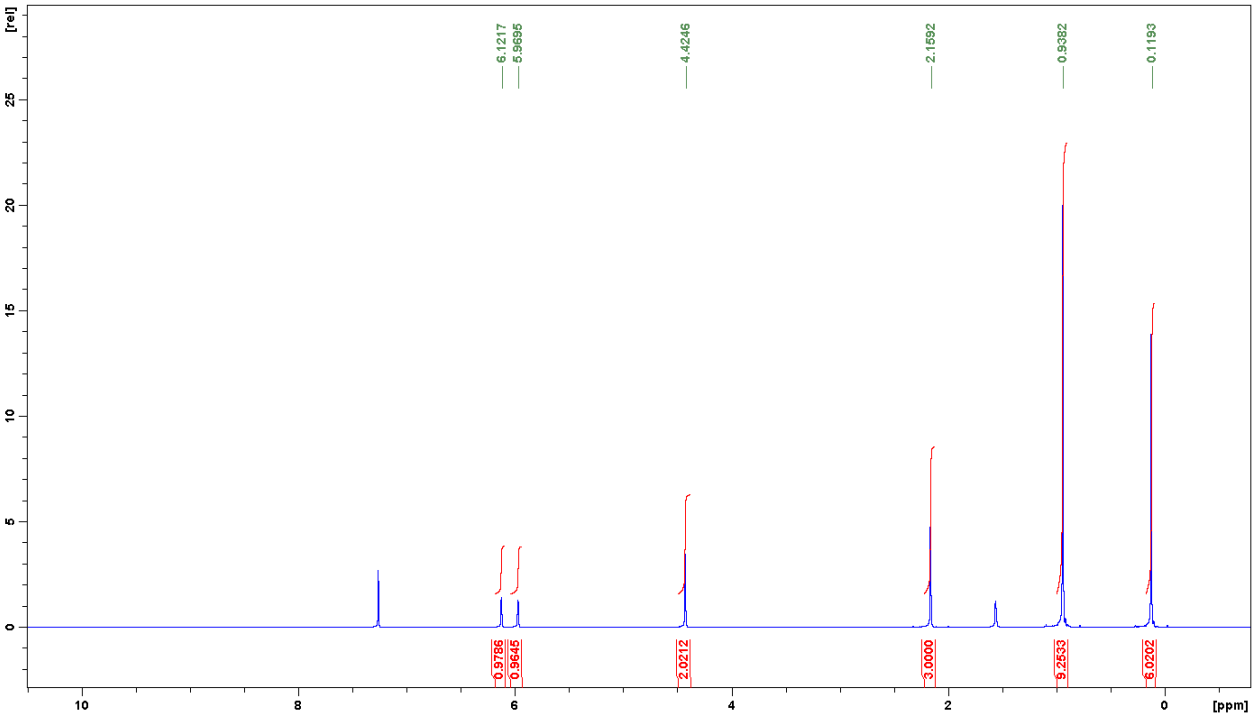

Me
TBSO
O
O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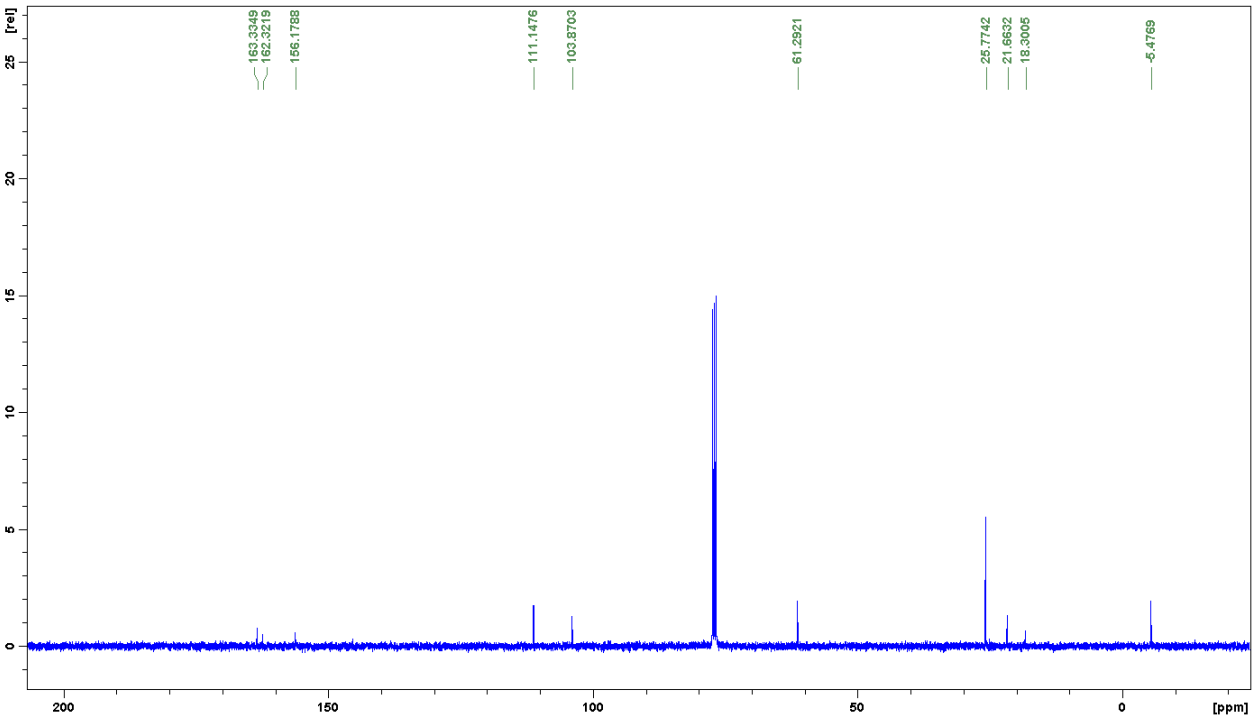
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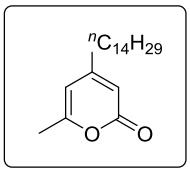
$^{n}C_{14}H_{29}$
O
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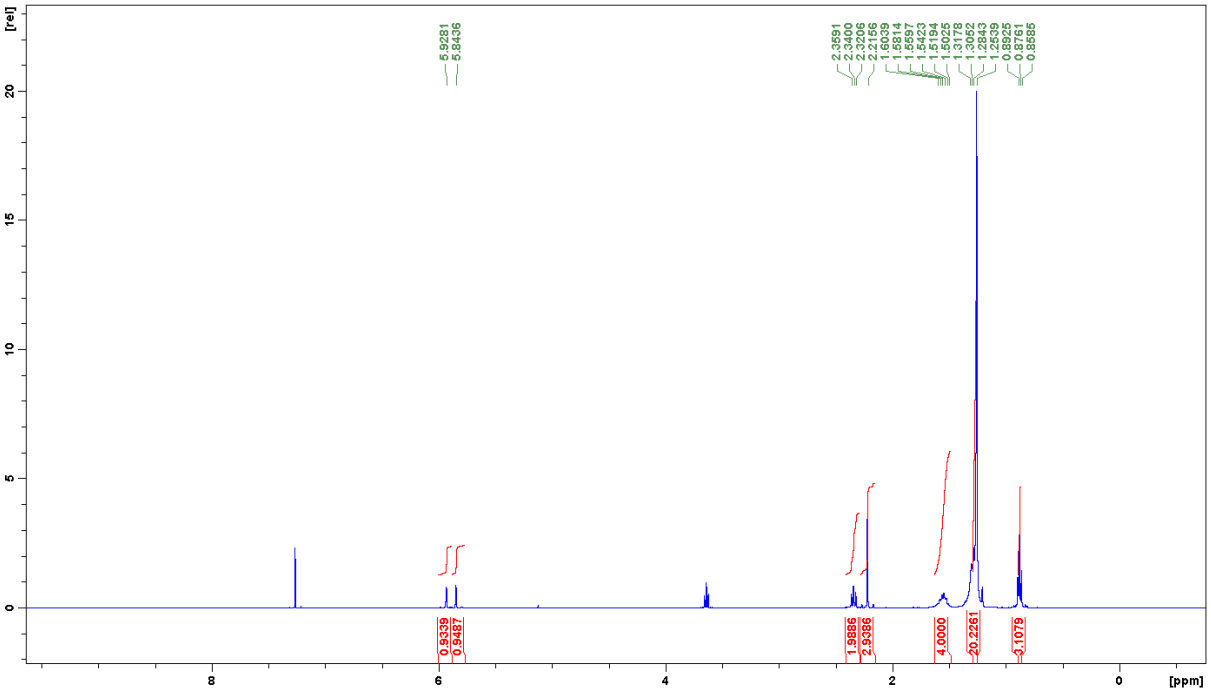
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1.5025
1.3773
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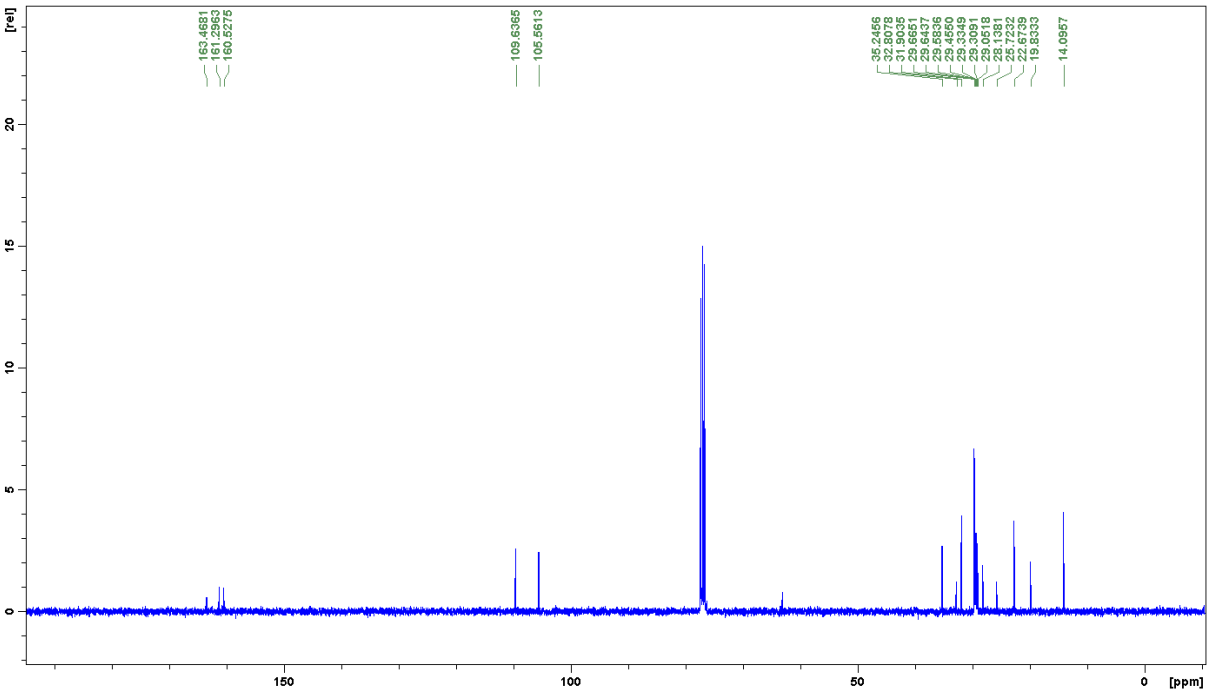
3.1079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29.1513
28.1381
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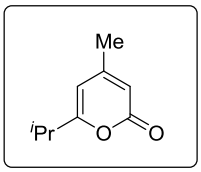
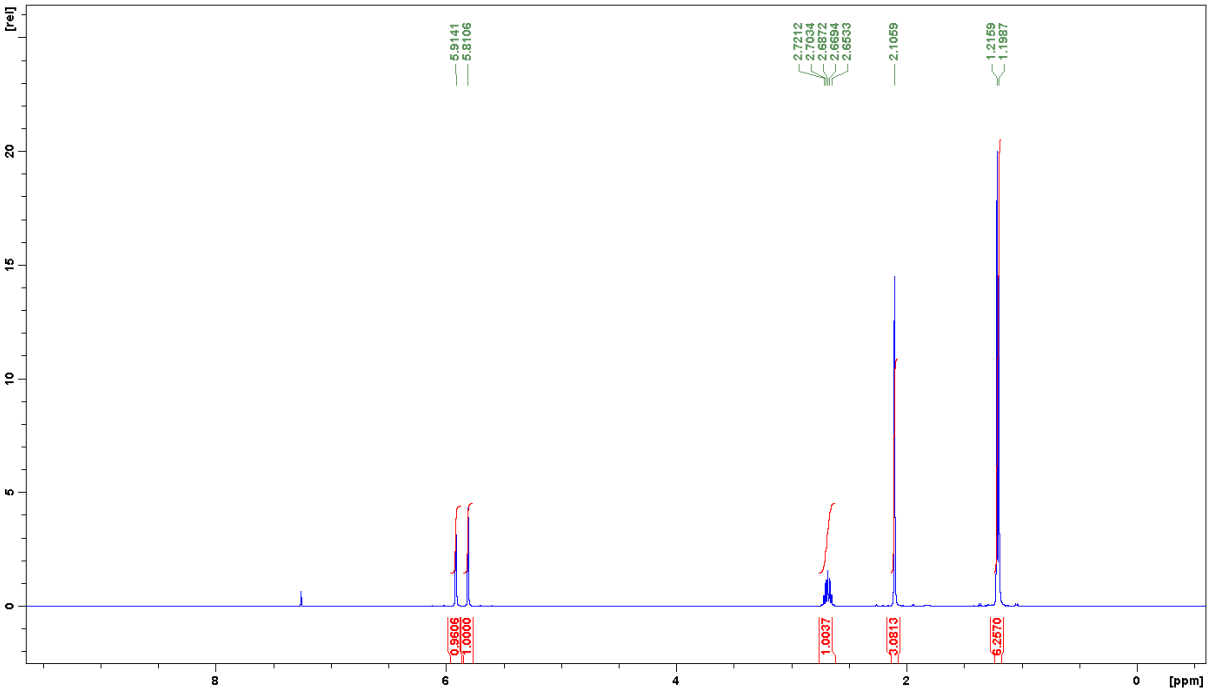

Me
iPr
O
O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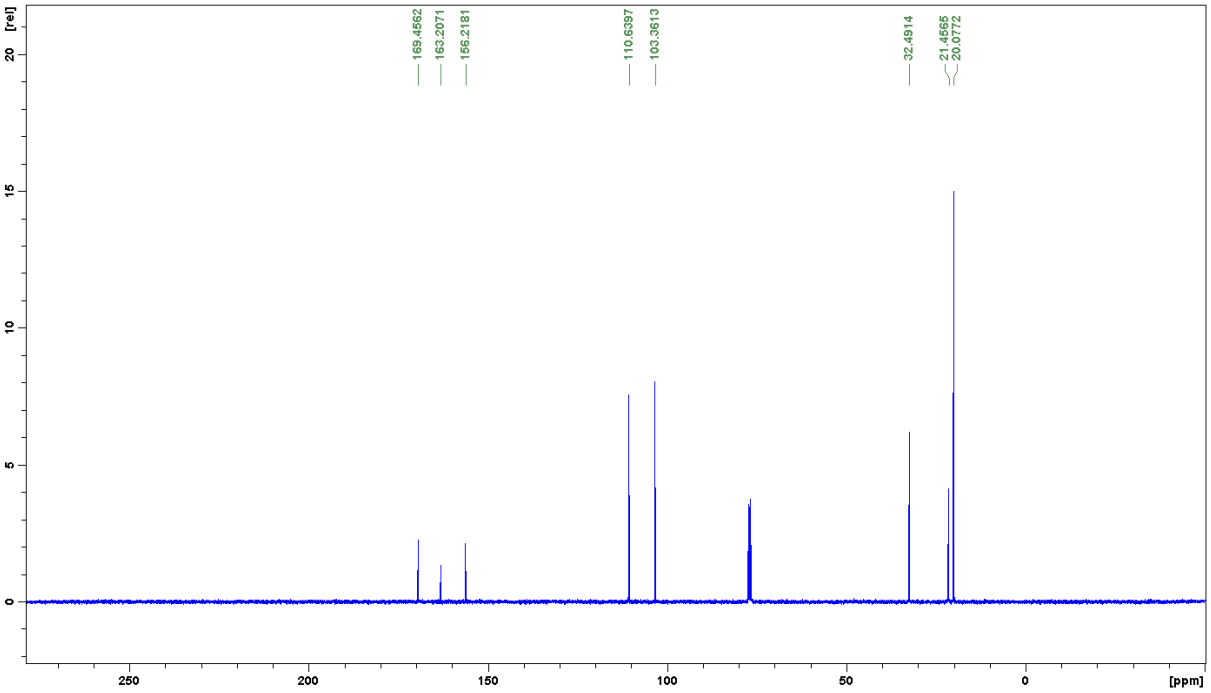
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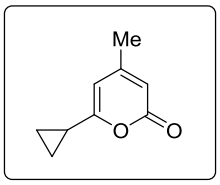
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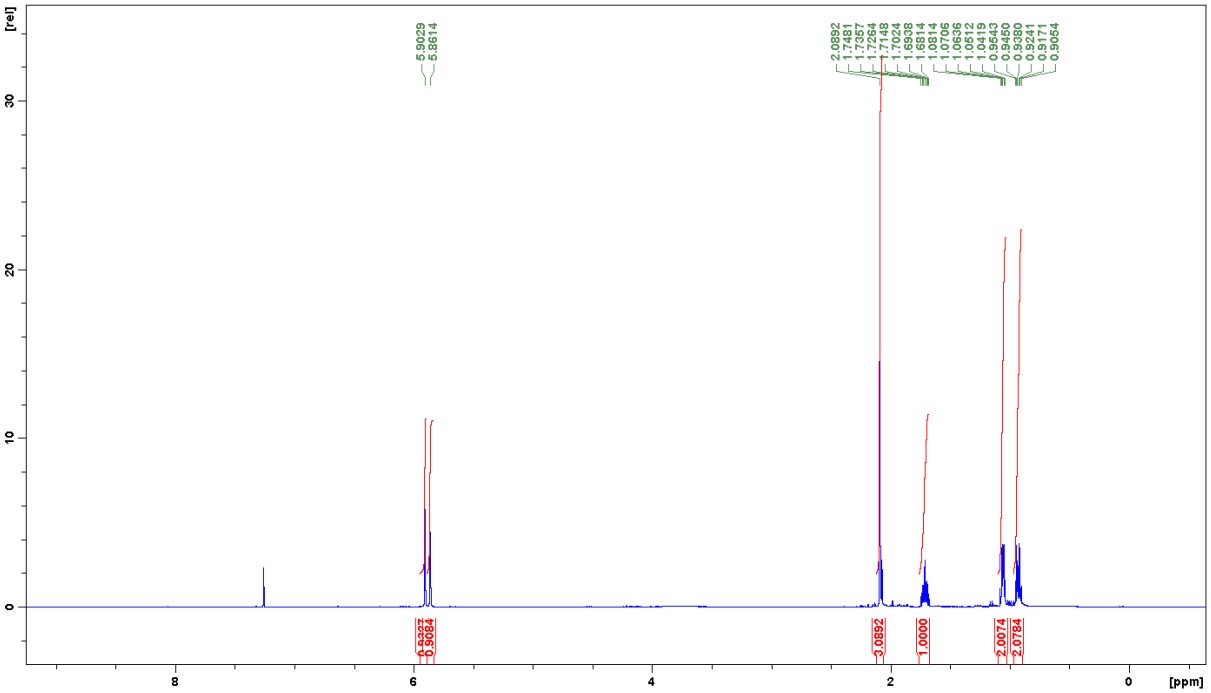
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1.0706
1.0656
1.0512
1.0419
0.9543
0.9450
0.9380
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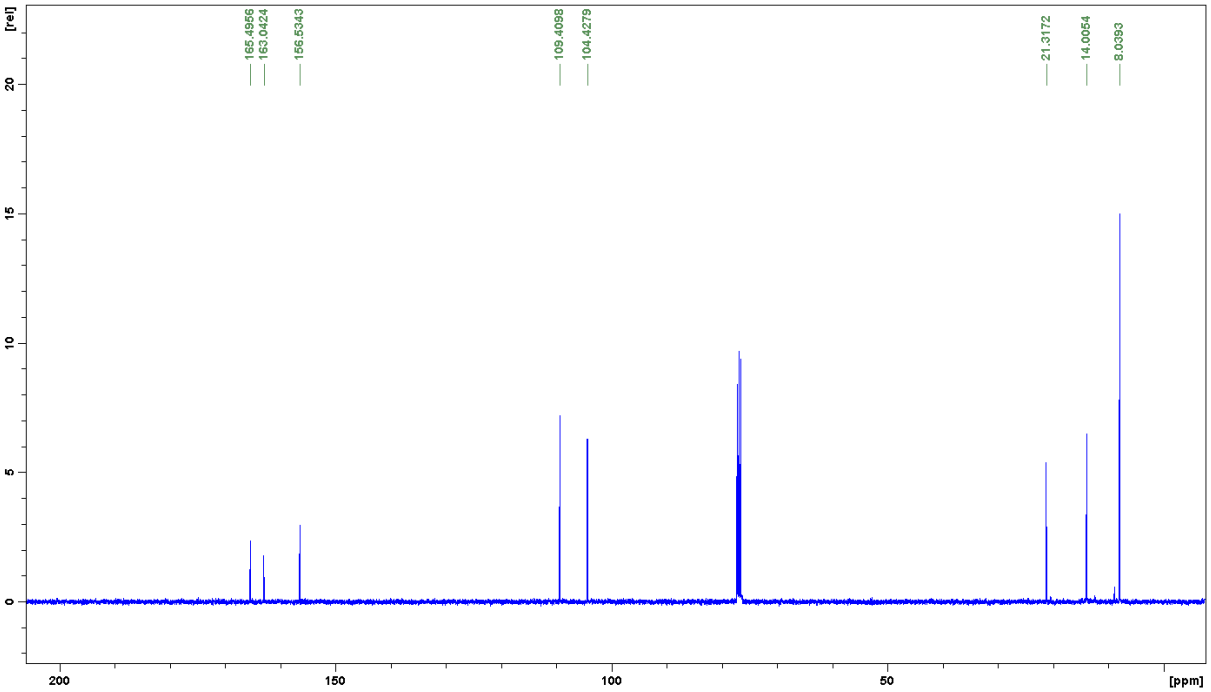
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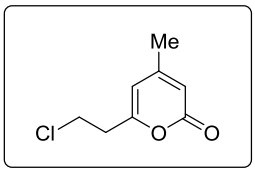
Me
Cl
O
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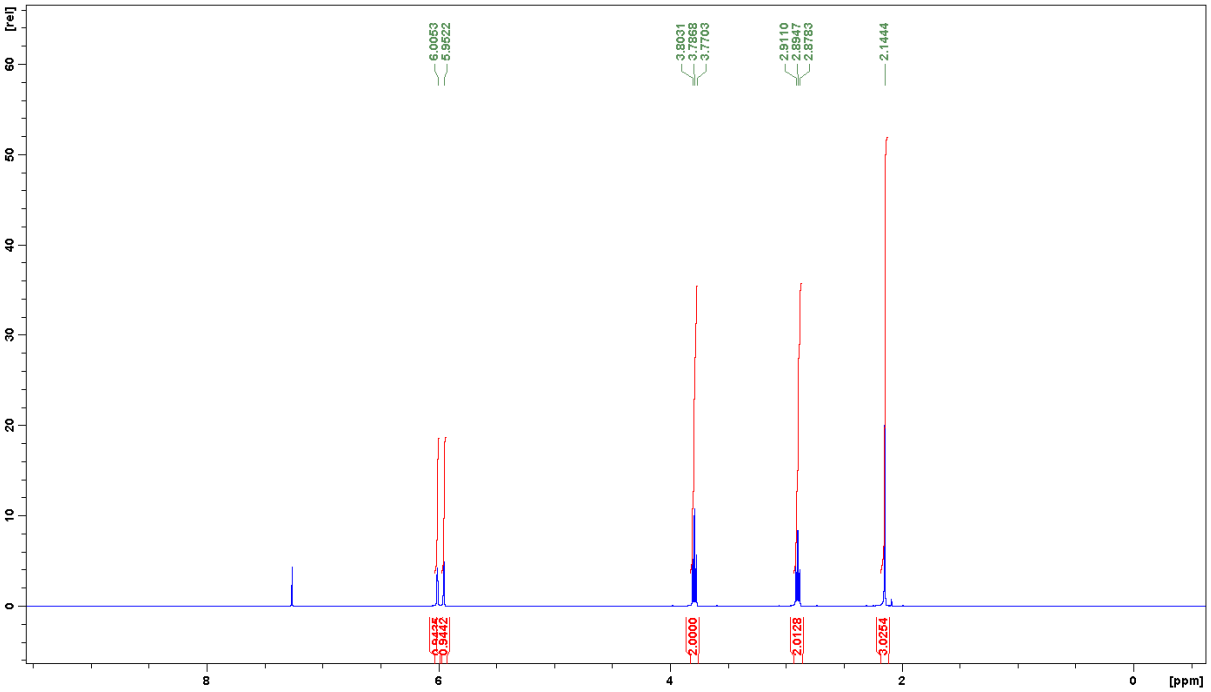
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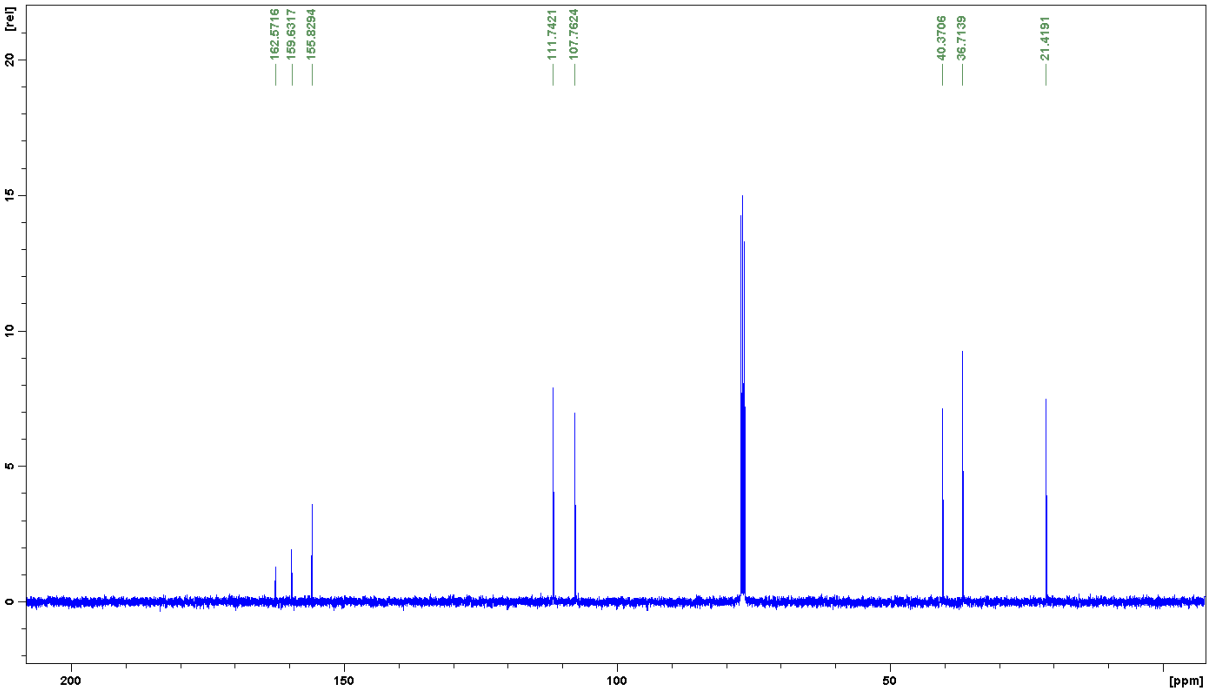
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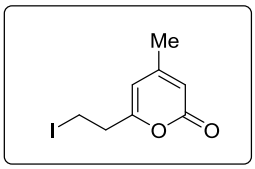
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O
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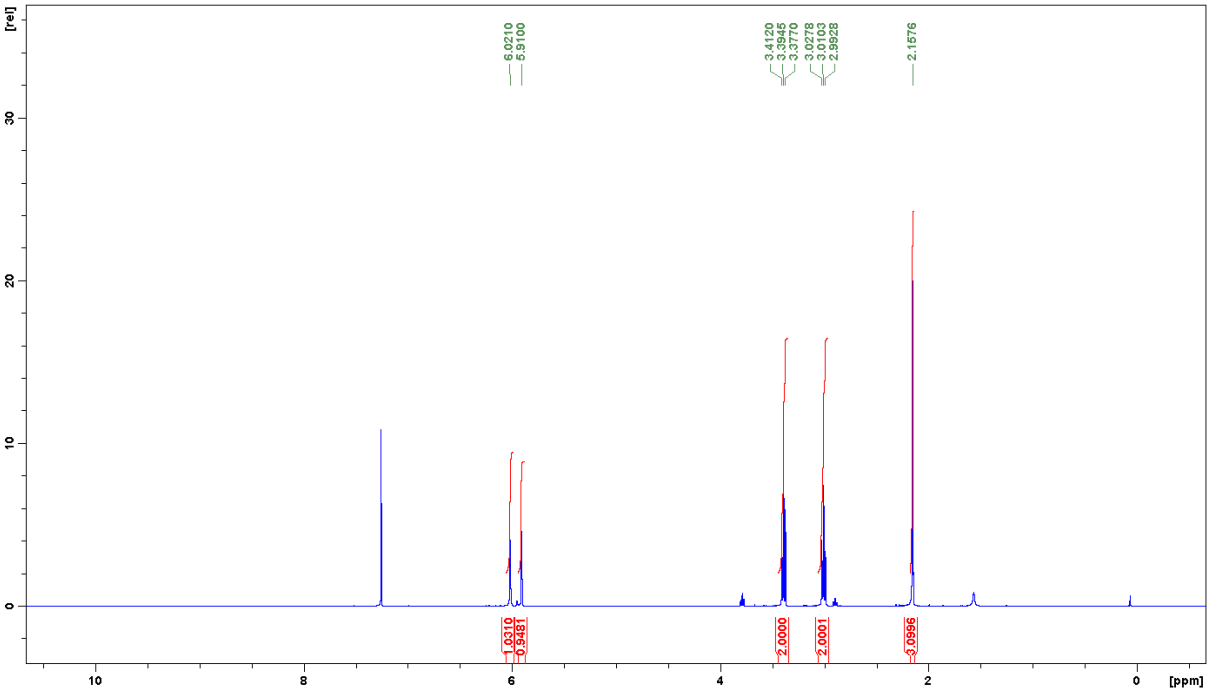
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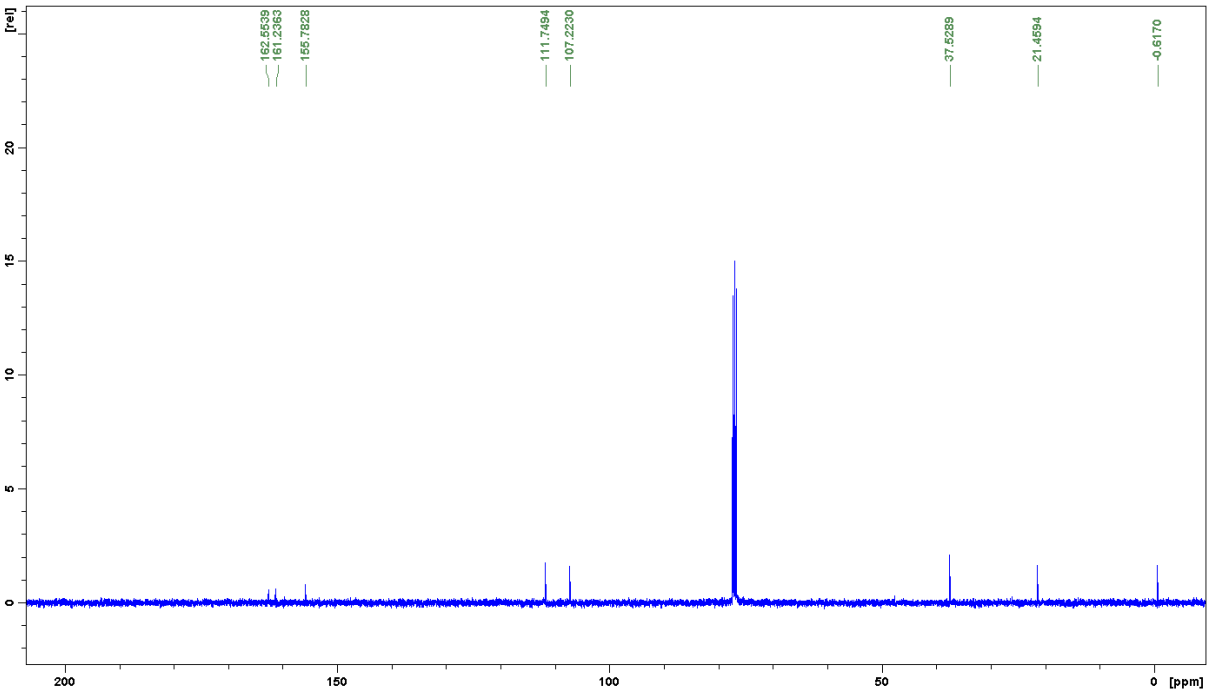
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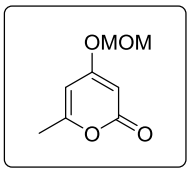
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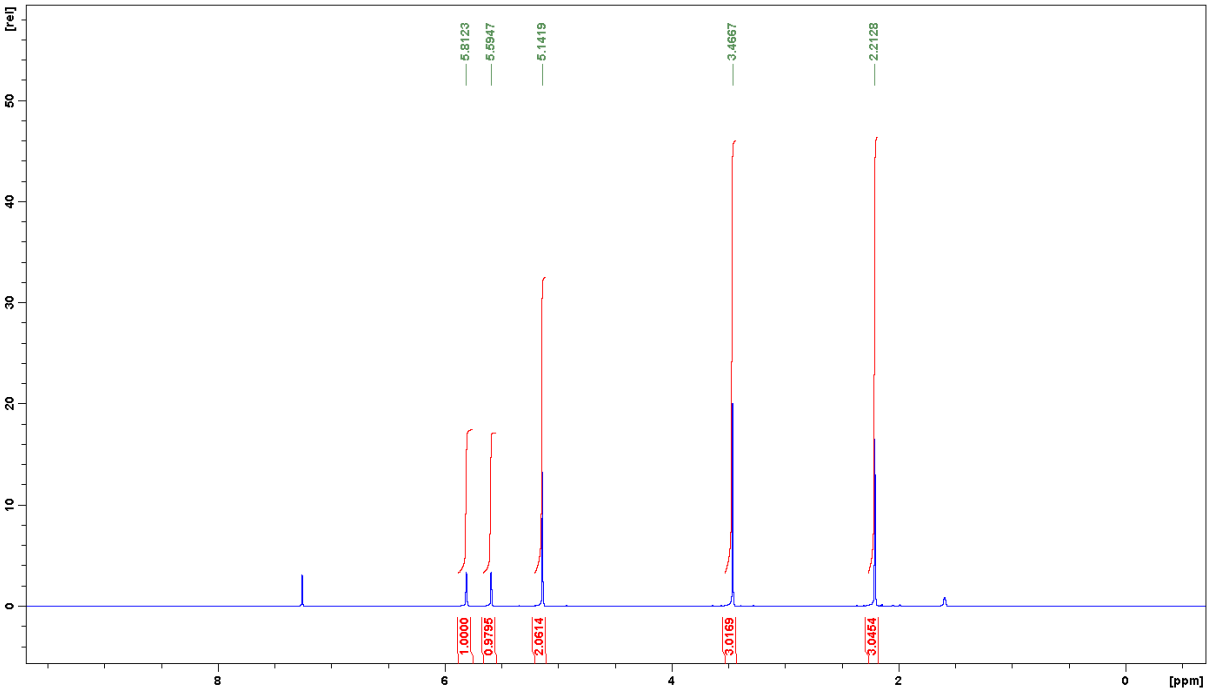
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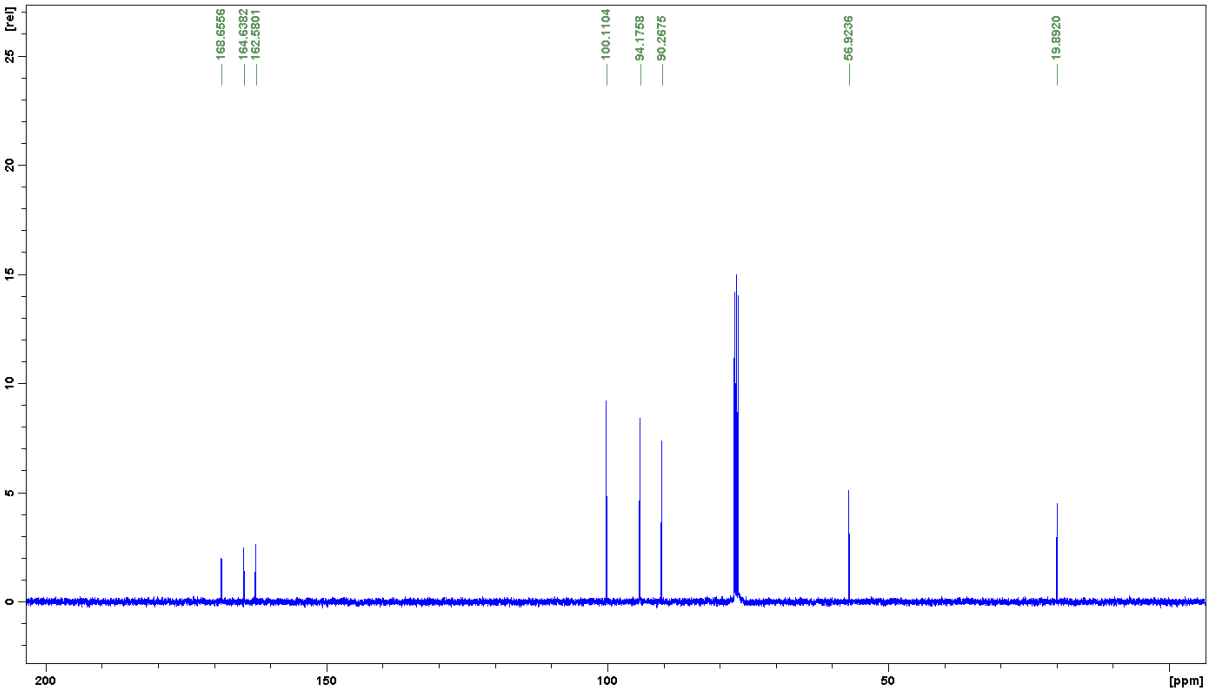
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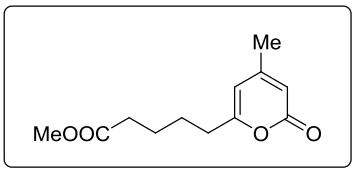
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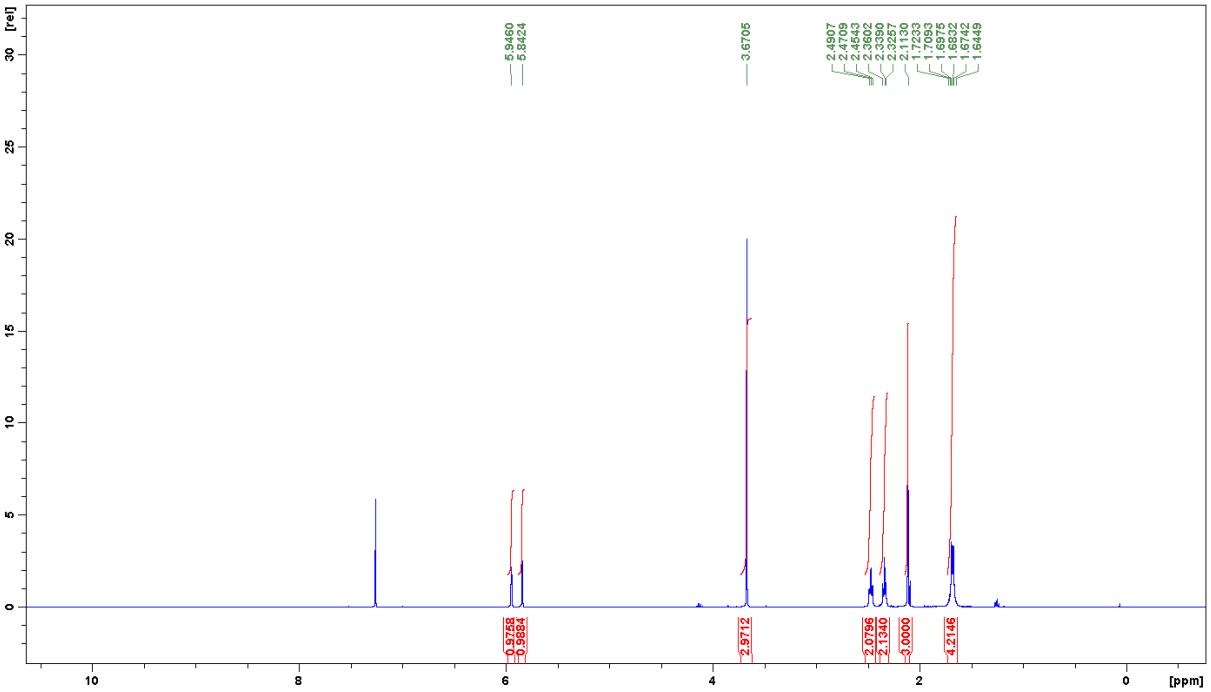
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1.7093
1.6975
1.6832
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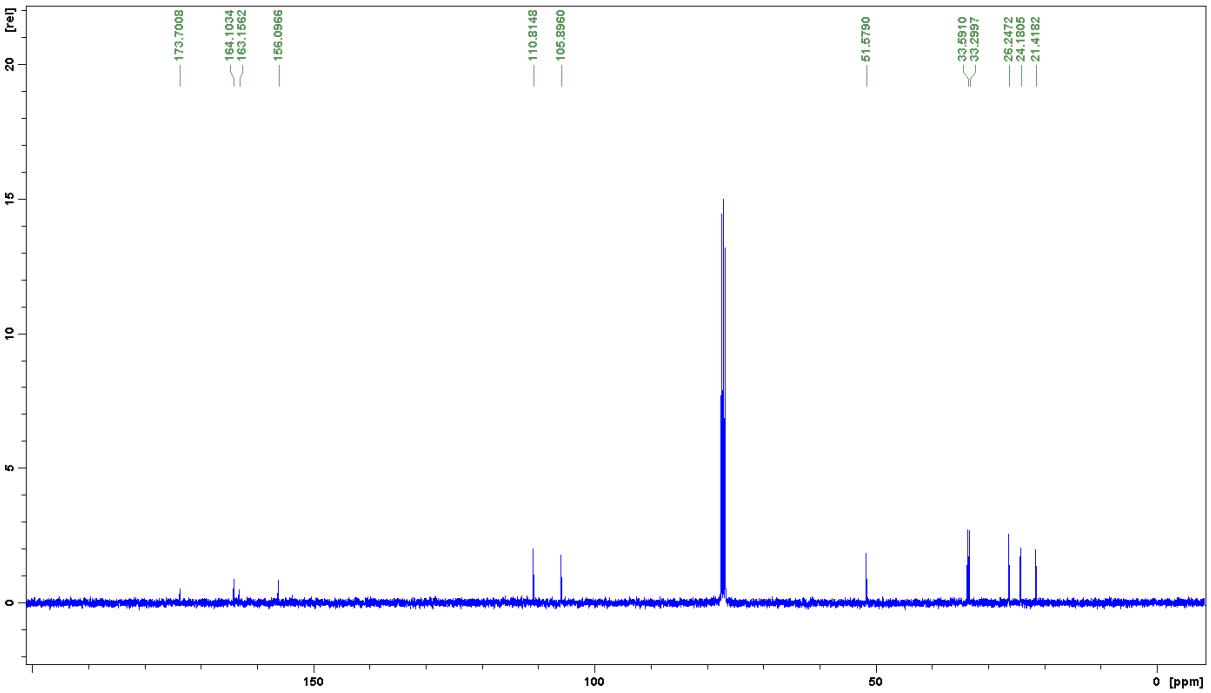
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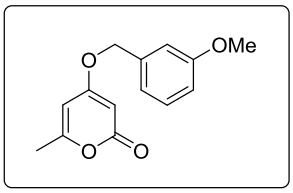
OMe
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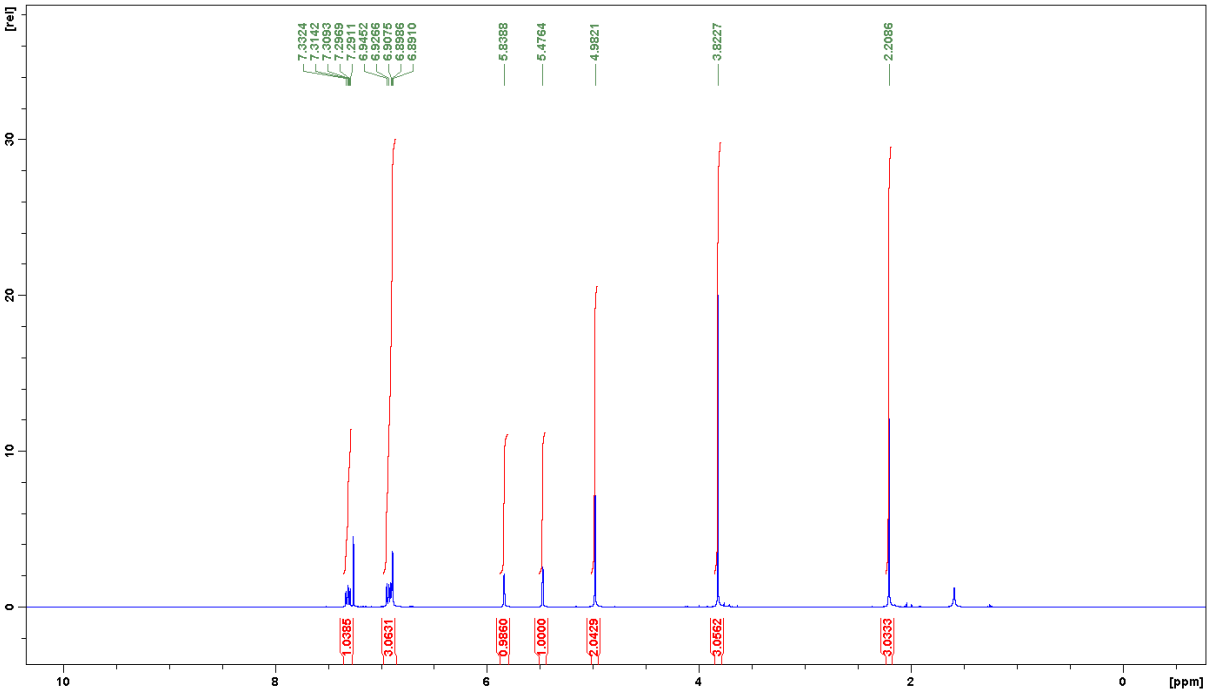
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6.8910
5.8388
5.4764
4.9821
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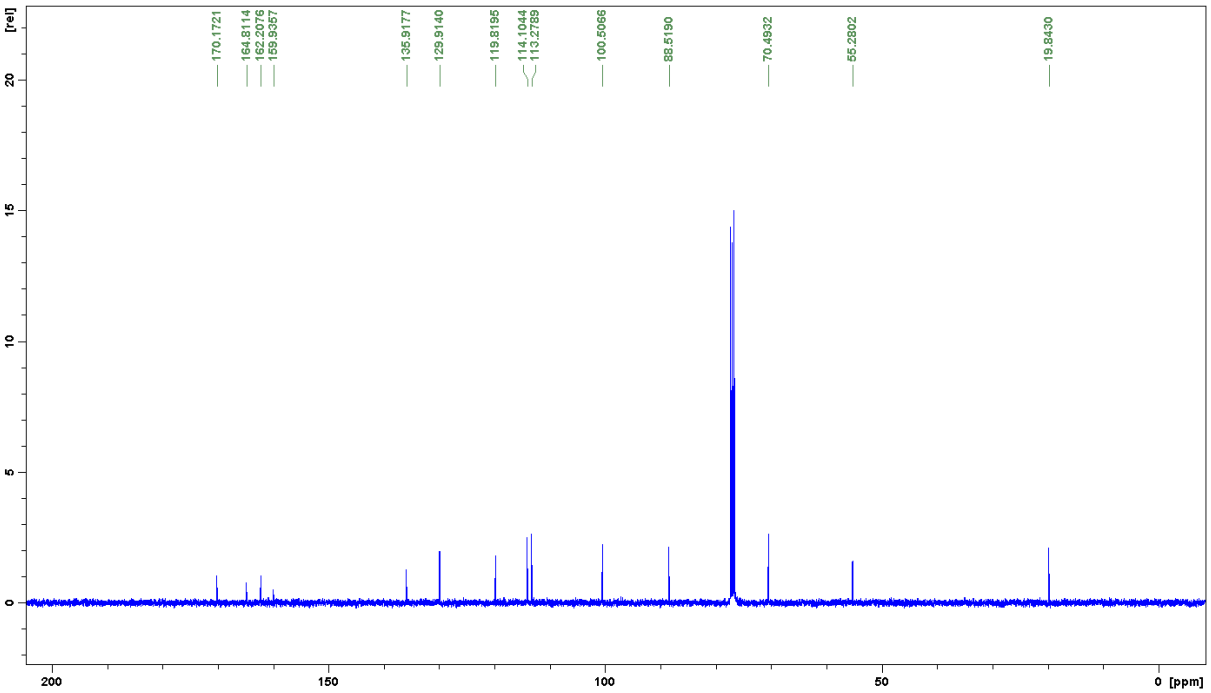
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19.8430
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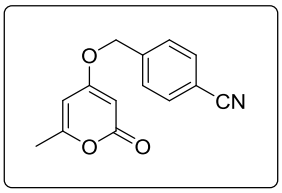
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CN
O
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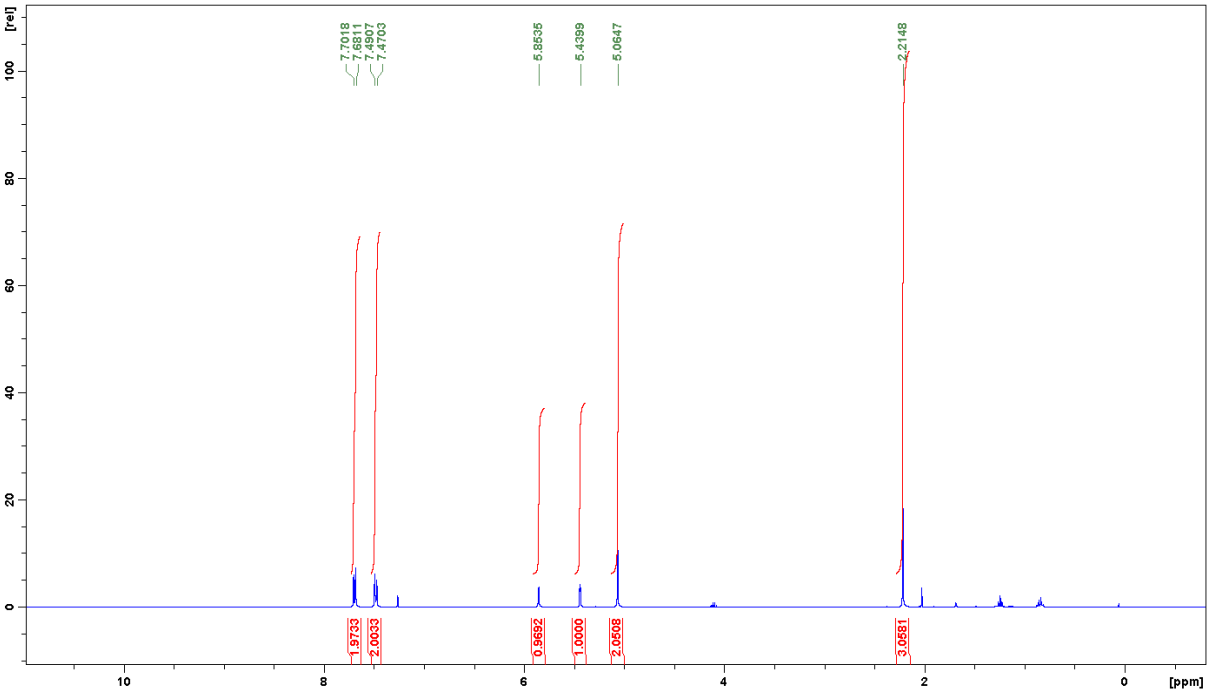
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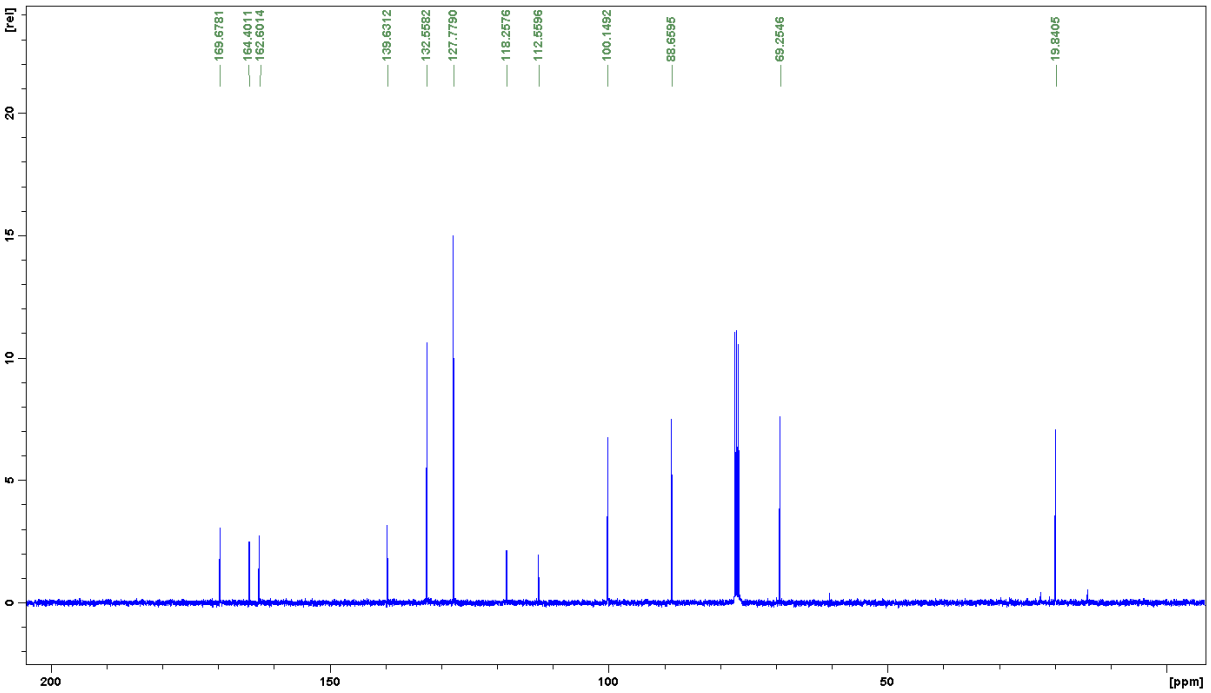
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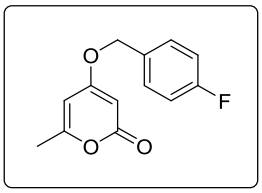
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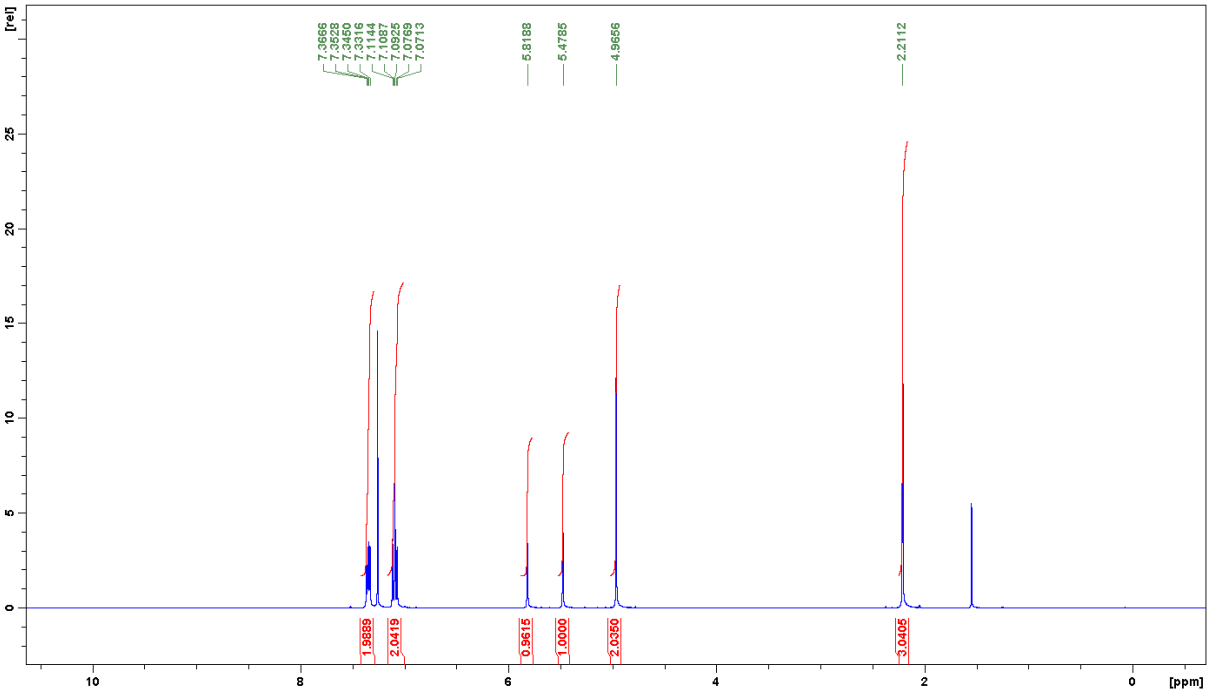
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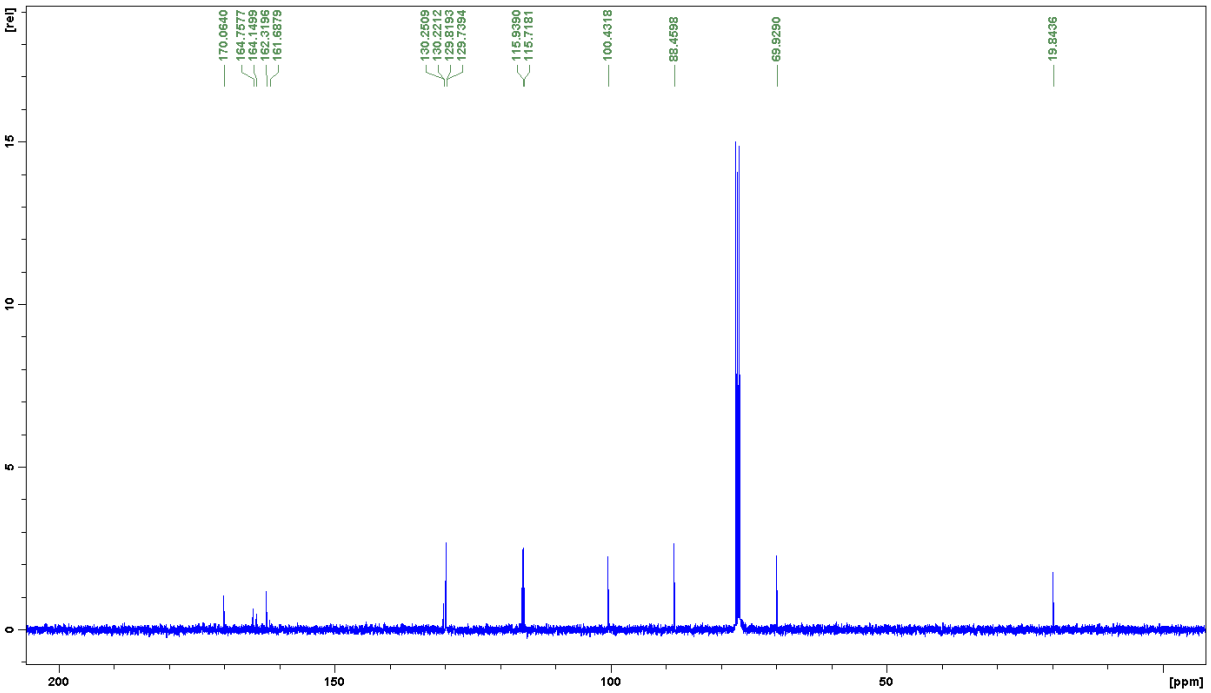
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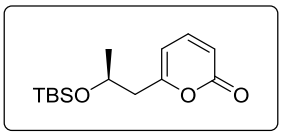
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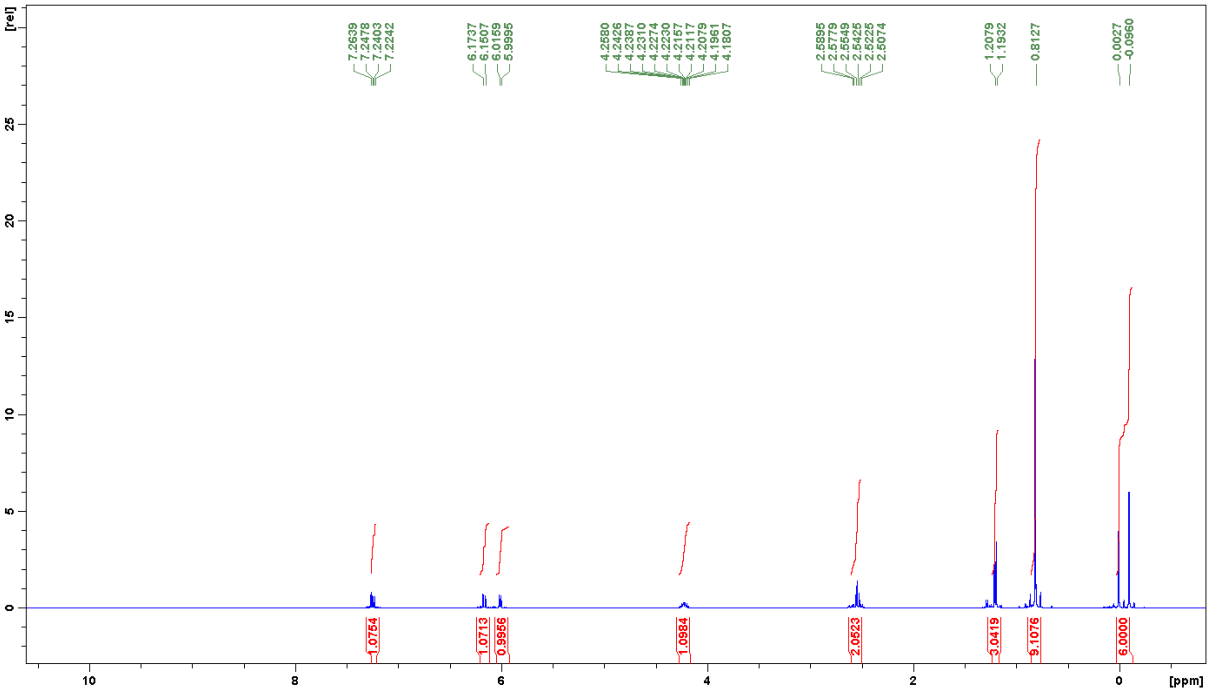
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4.2310
4.2274
4.2230
4.2177
4.2117
4.2079
4.1961
4.1807
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2.5779
2.5649
2.5425
2.5225
2.5074
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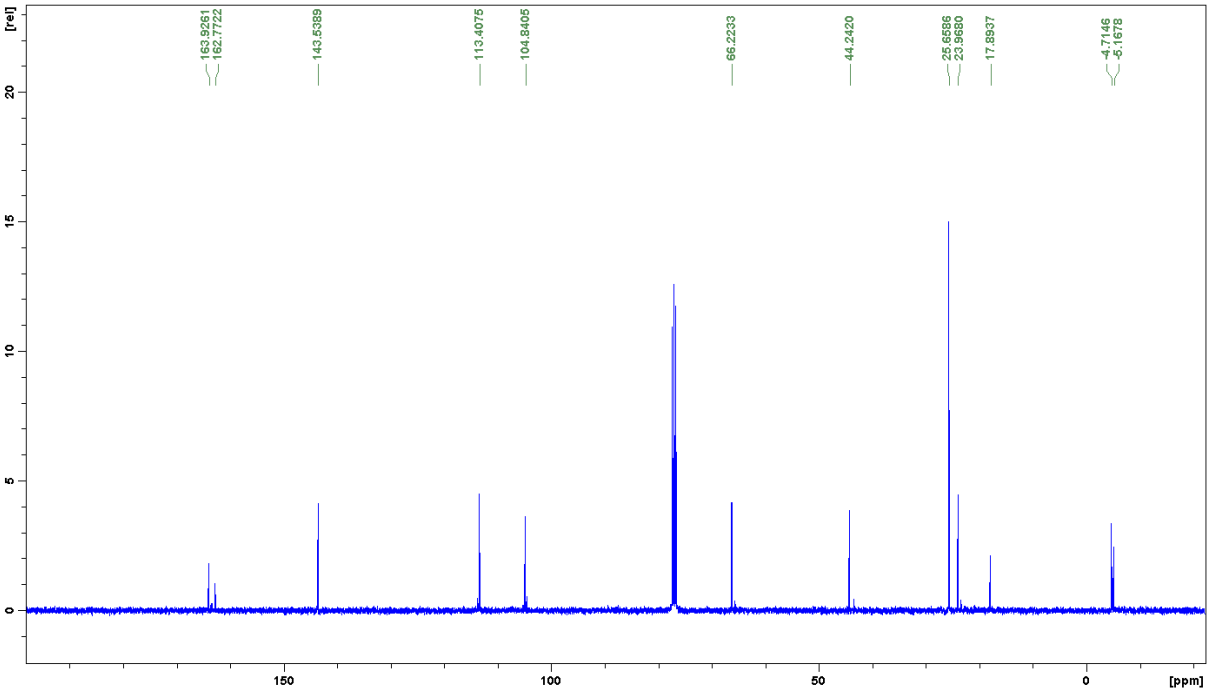
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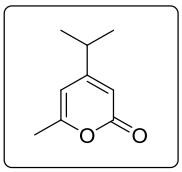

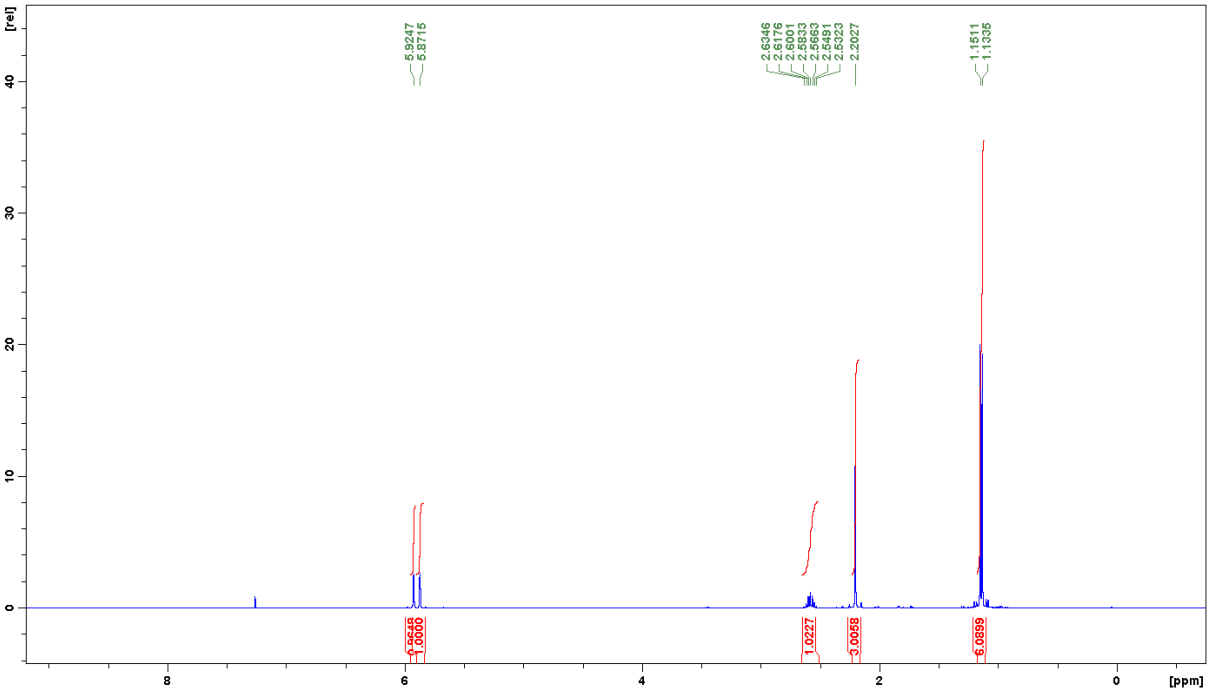
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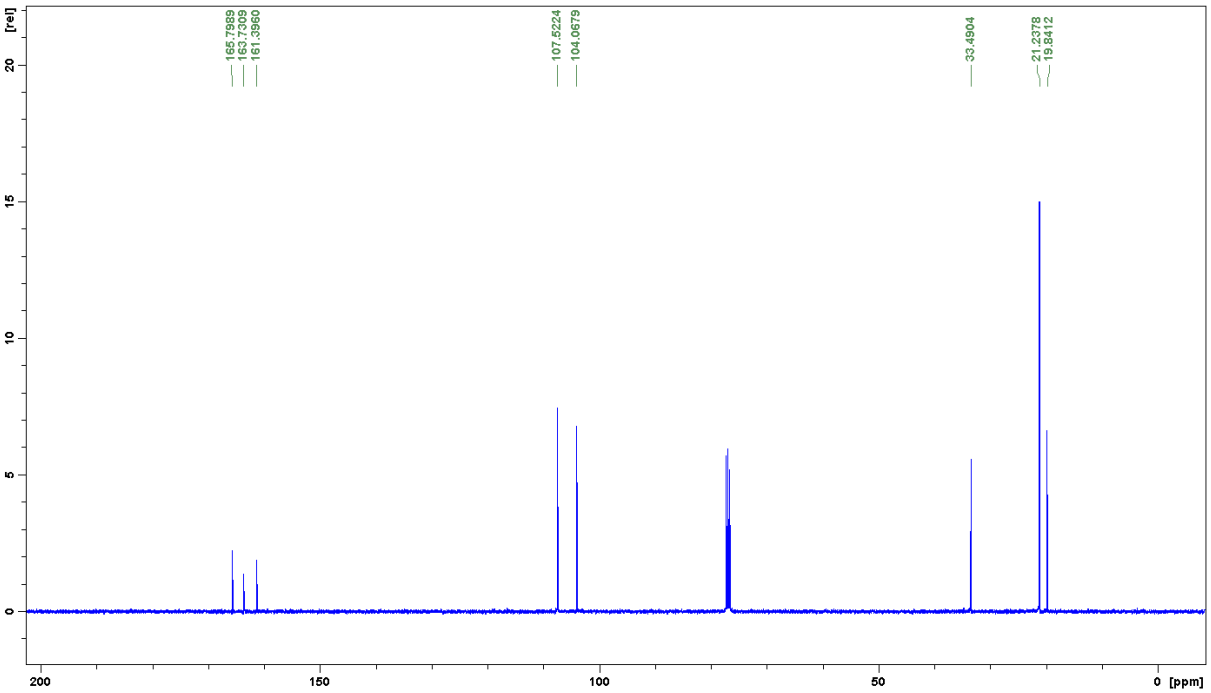
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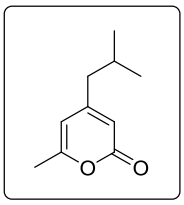

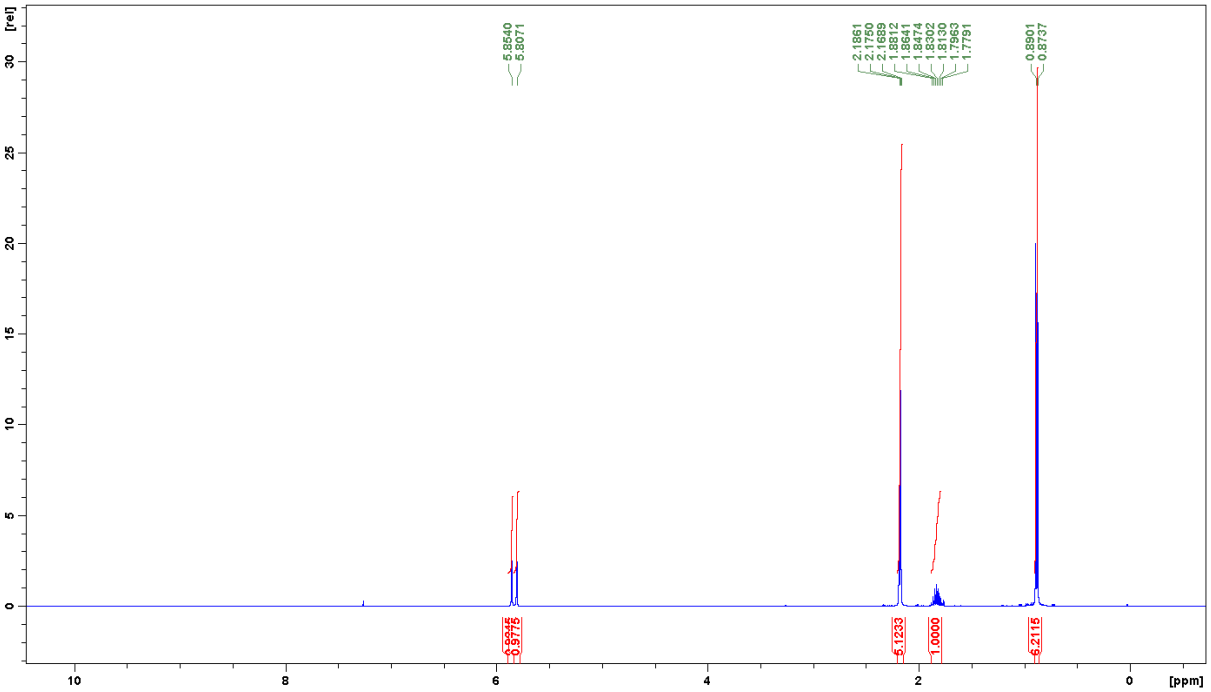
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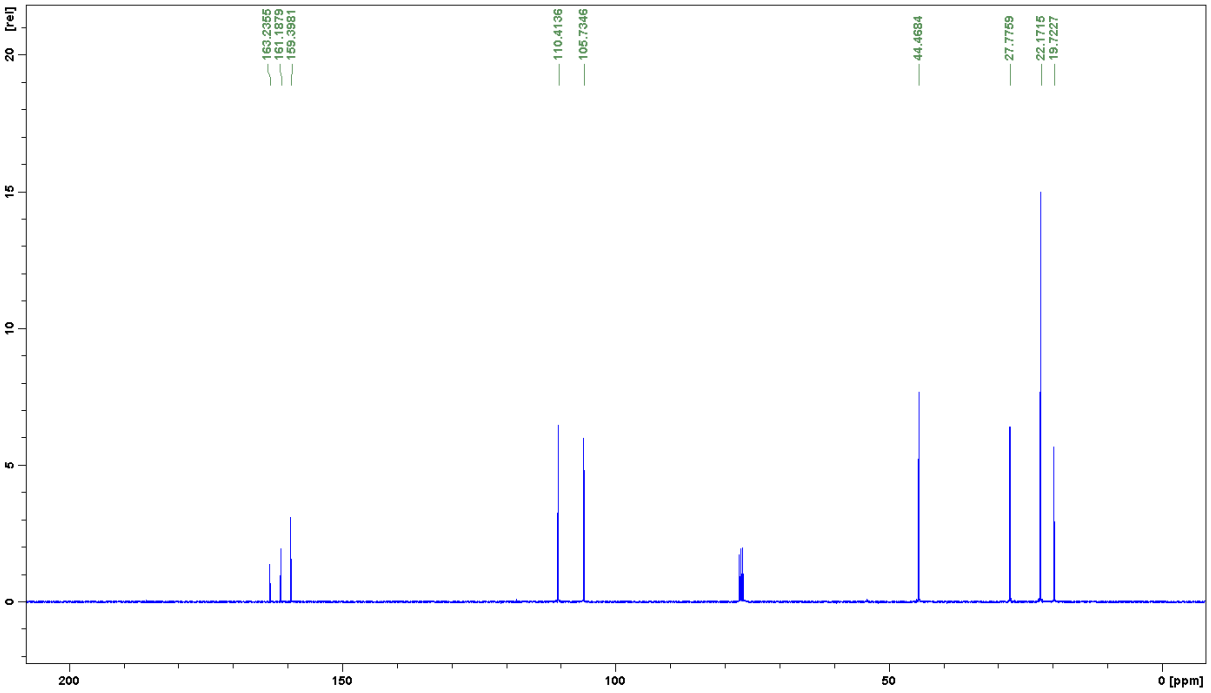
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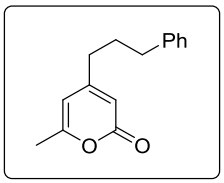
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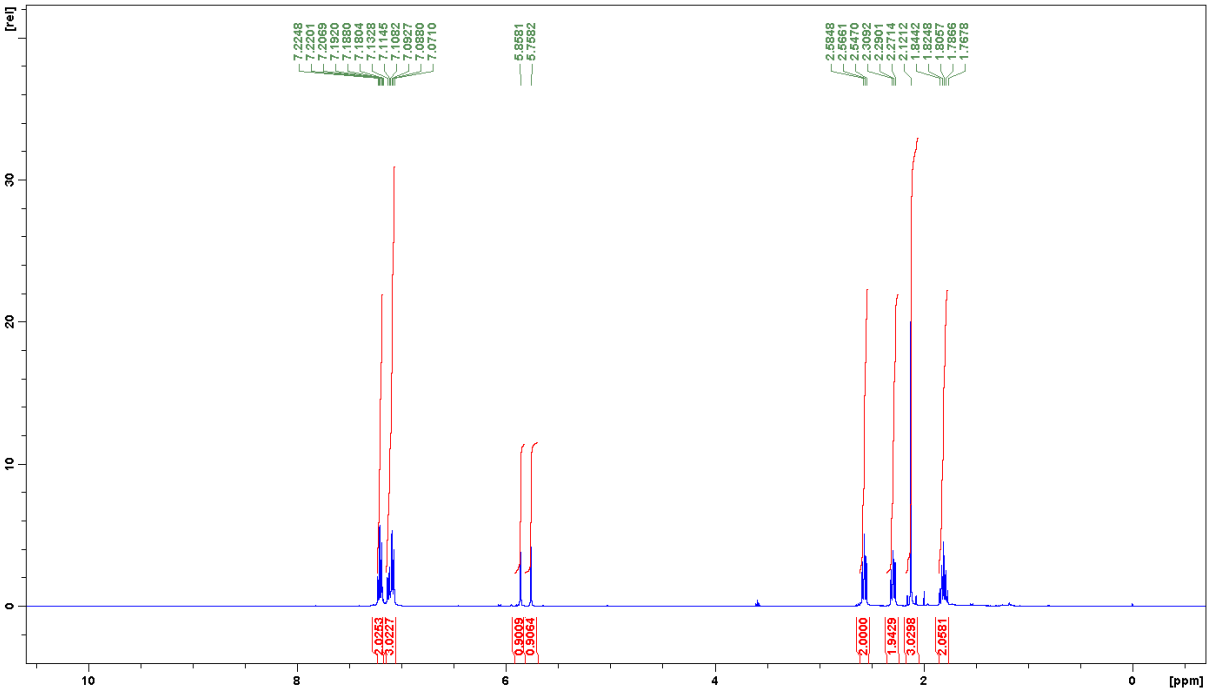
O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7.0710
5.8581
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2.5661
2.5470
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2.2901
2.2714
2.1212
1.9442
1.8248
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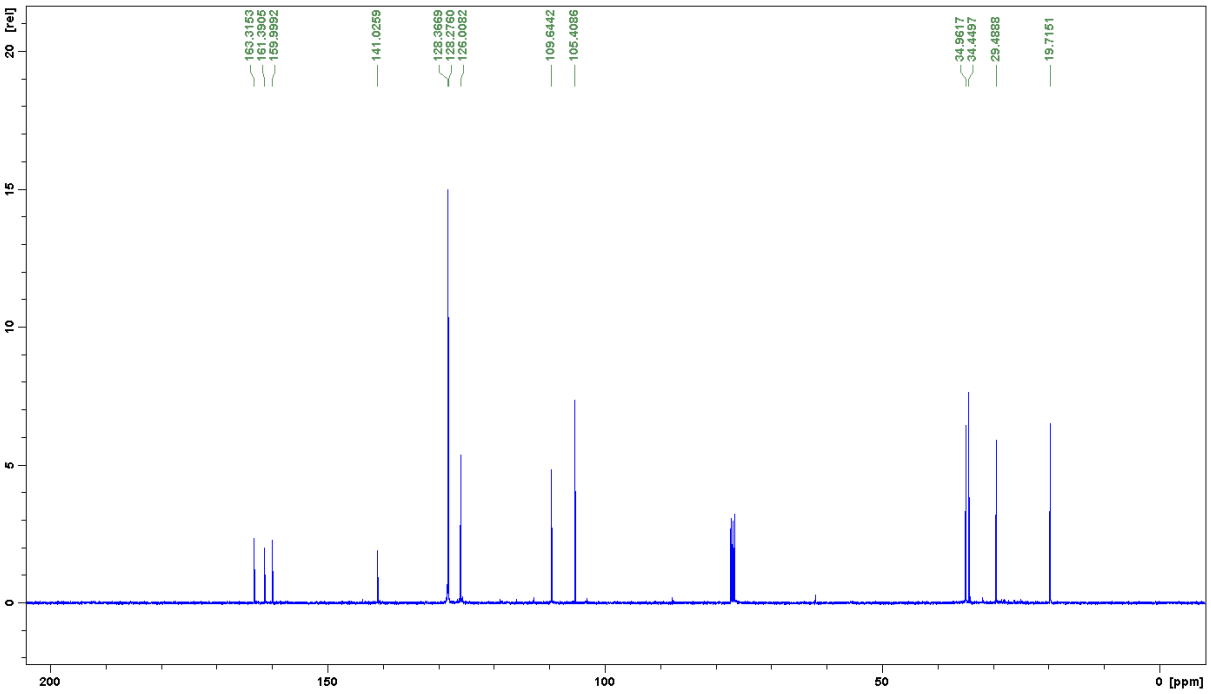
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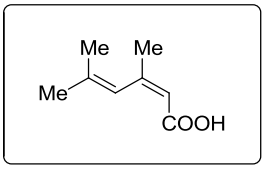
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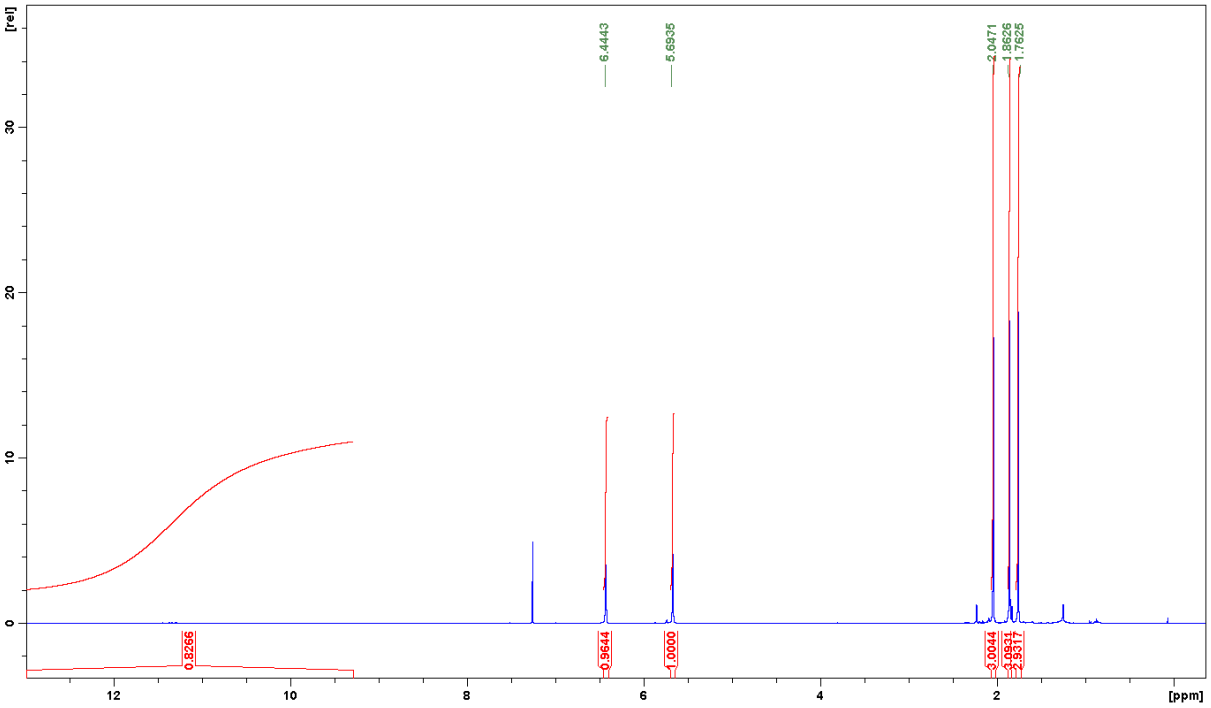
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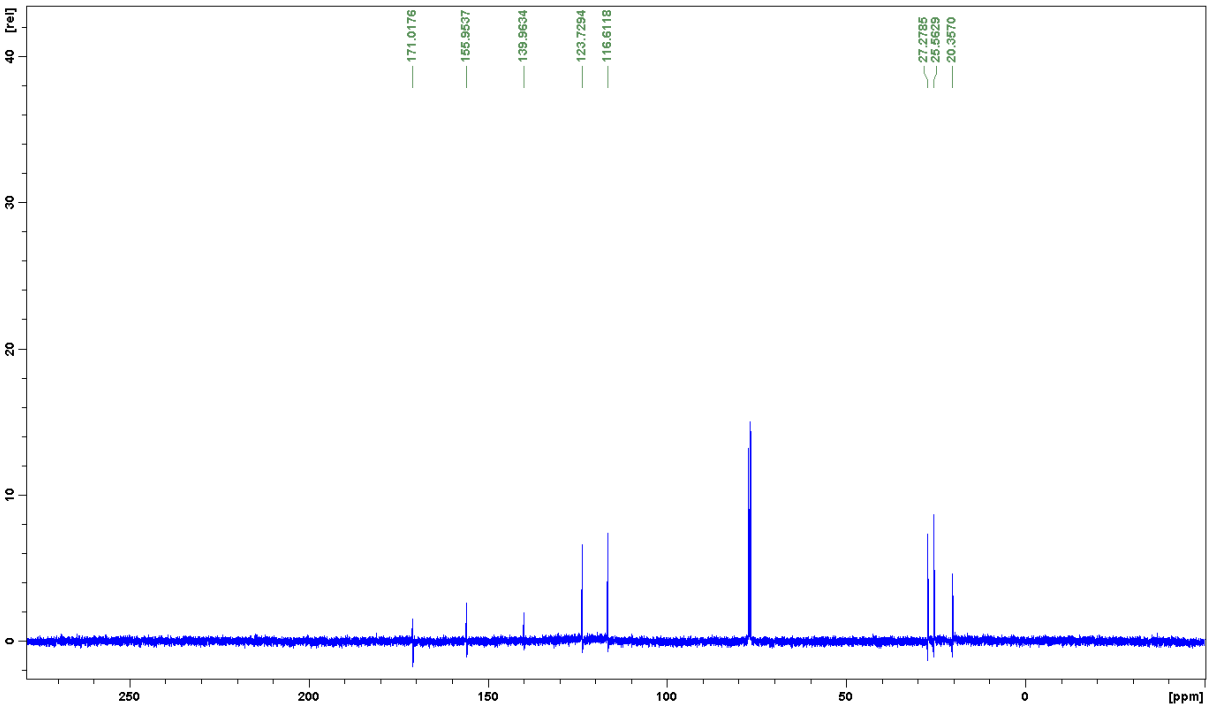
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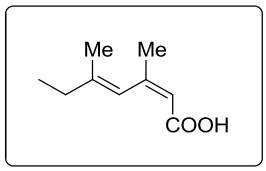
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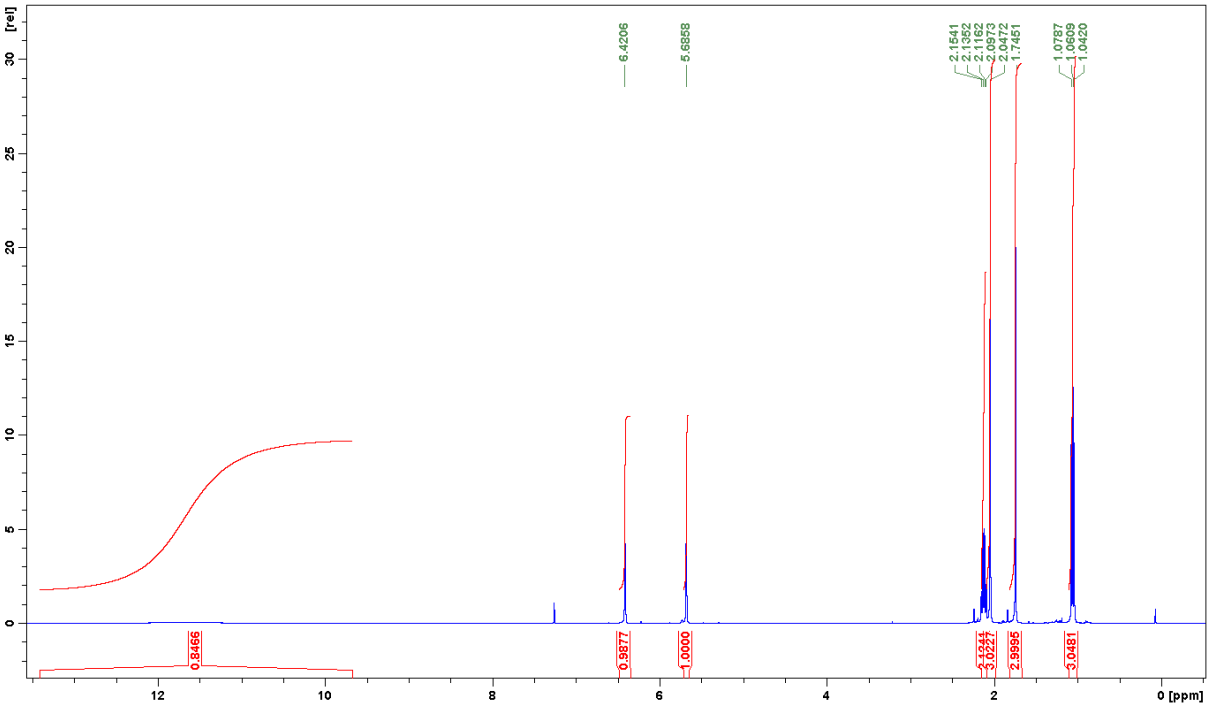
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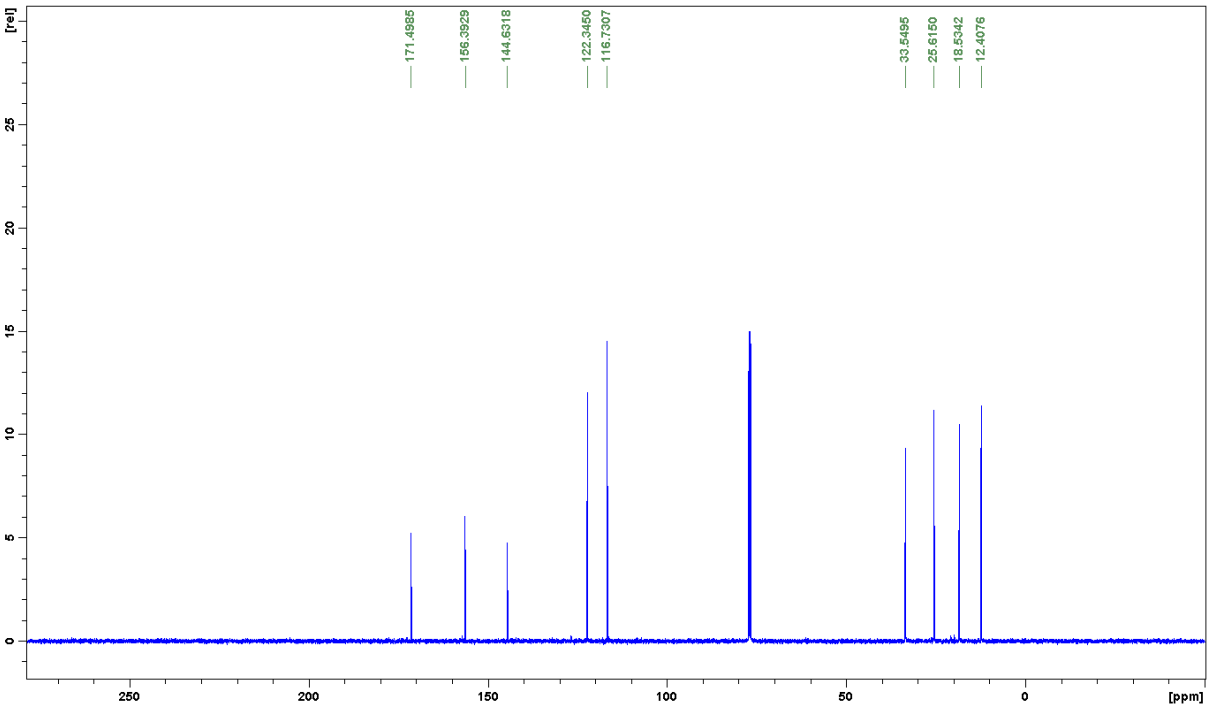
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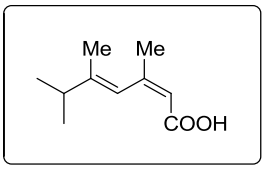
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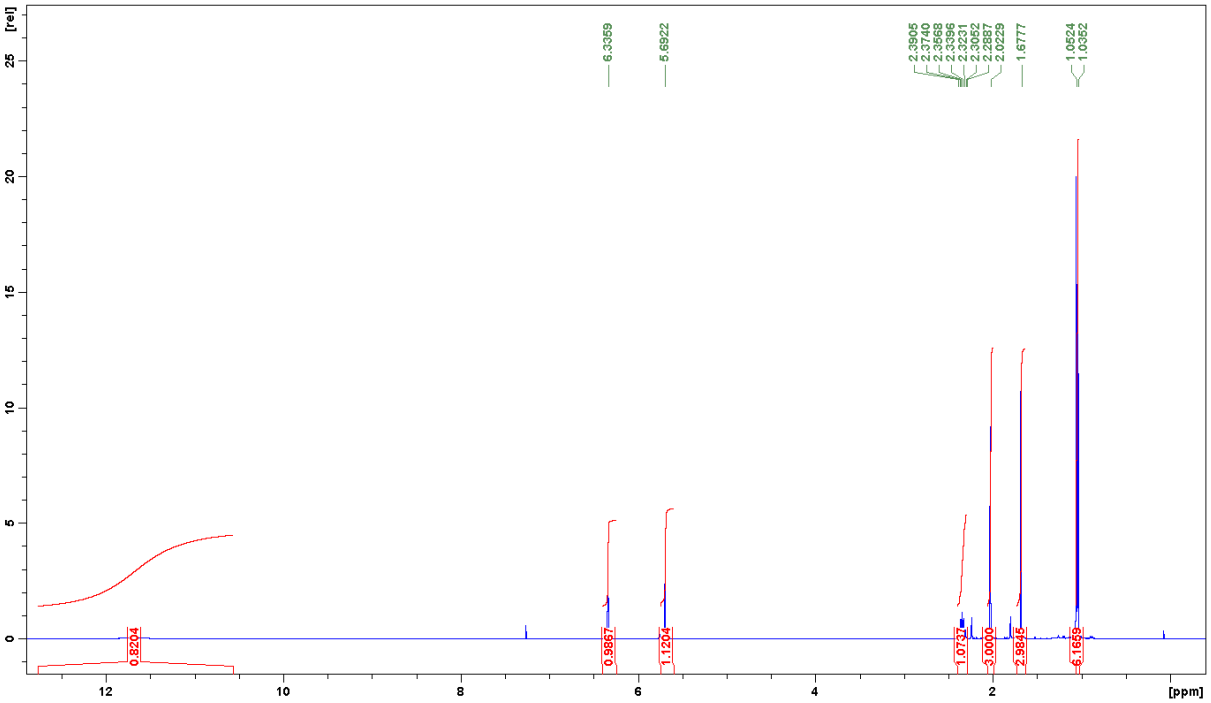
COOH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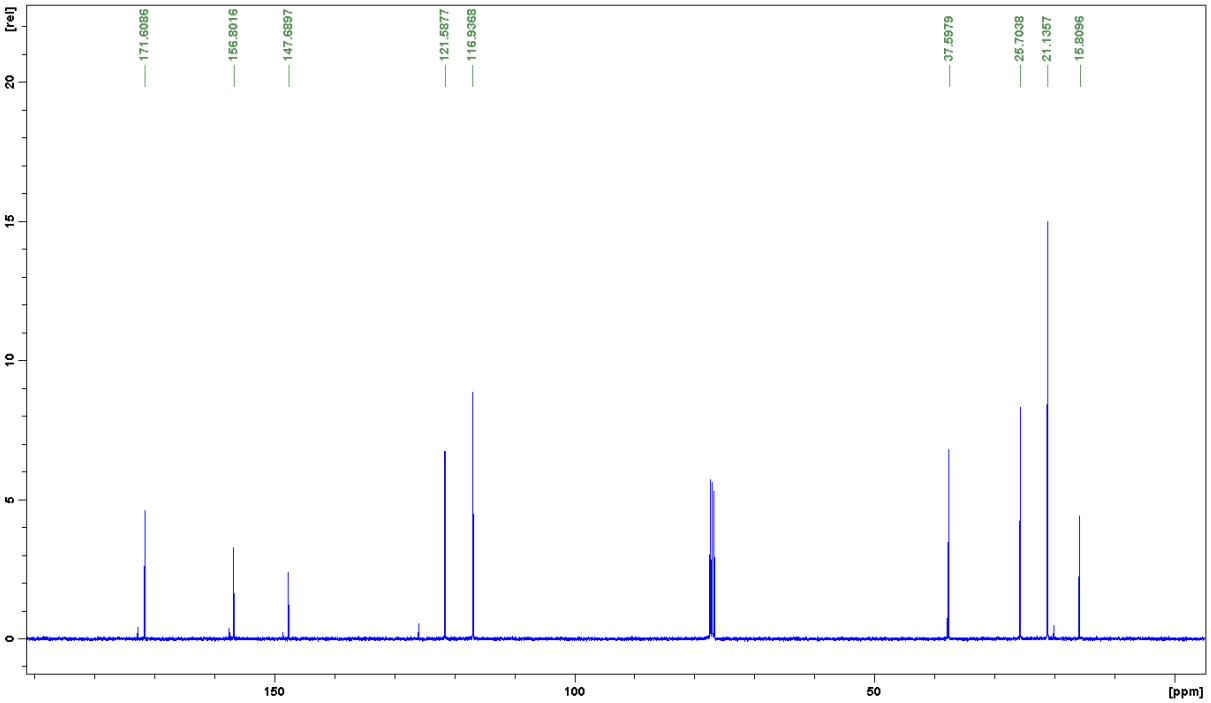
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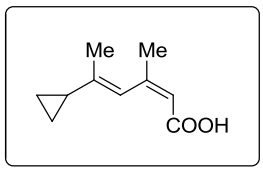
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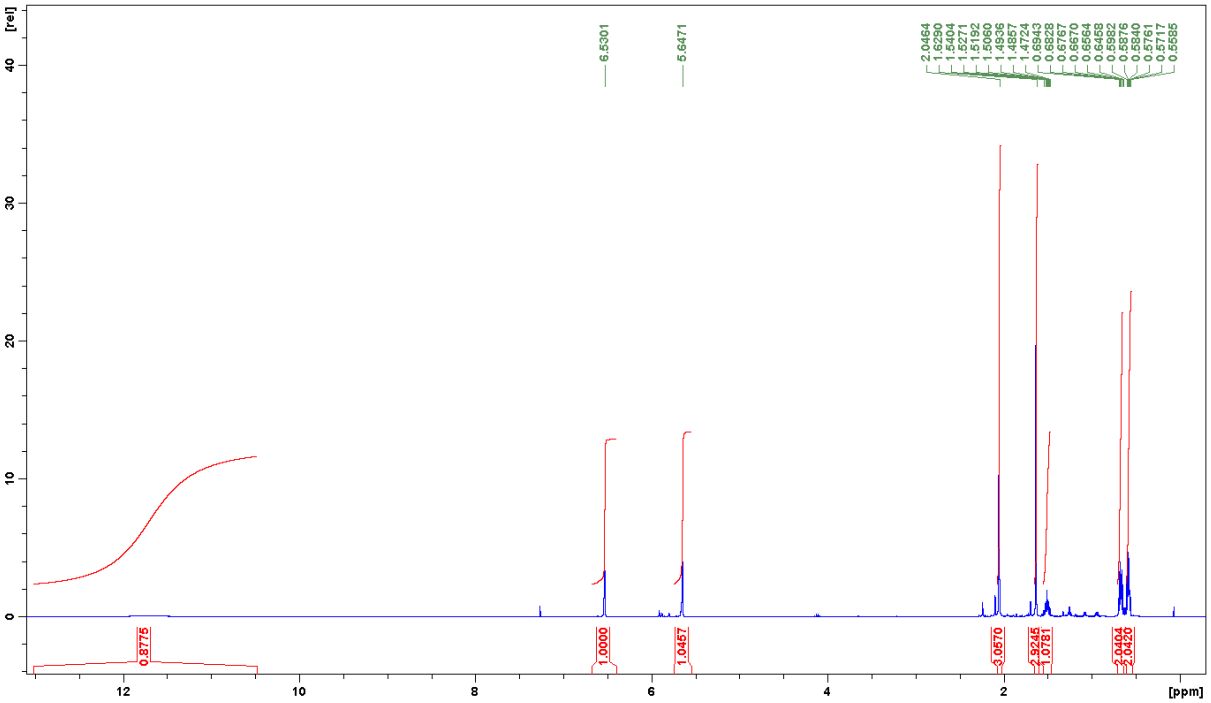
COOH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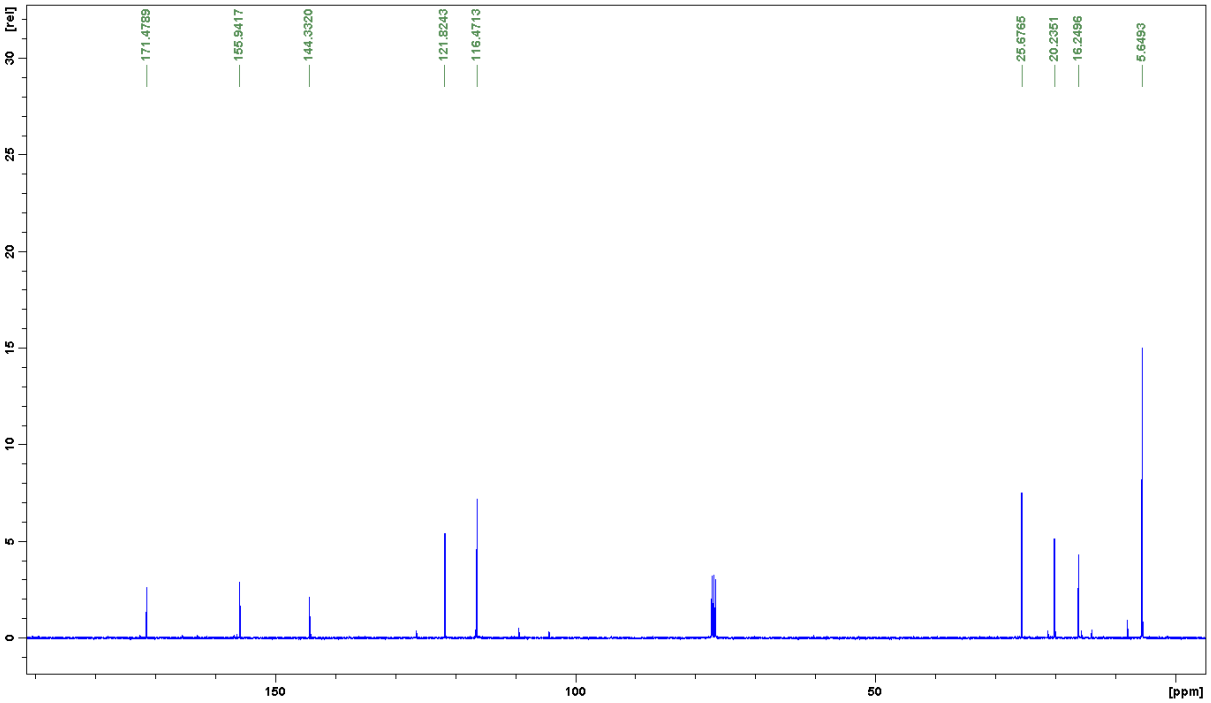
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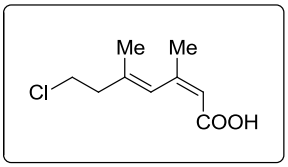
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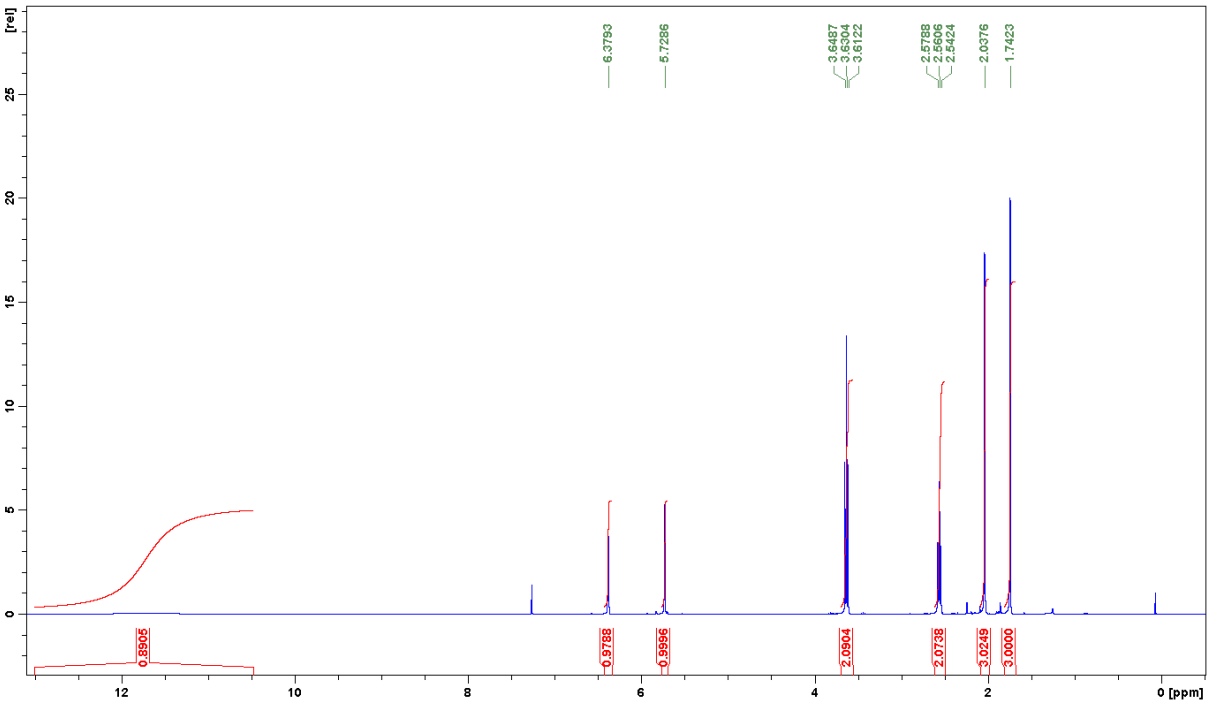
Me
Cl
COOH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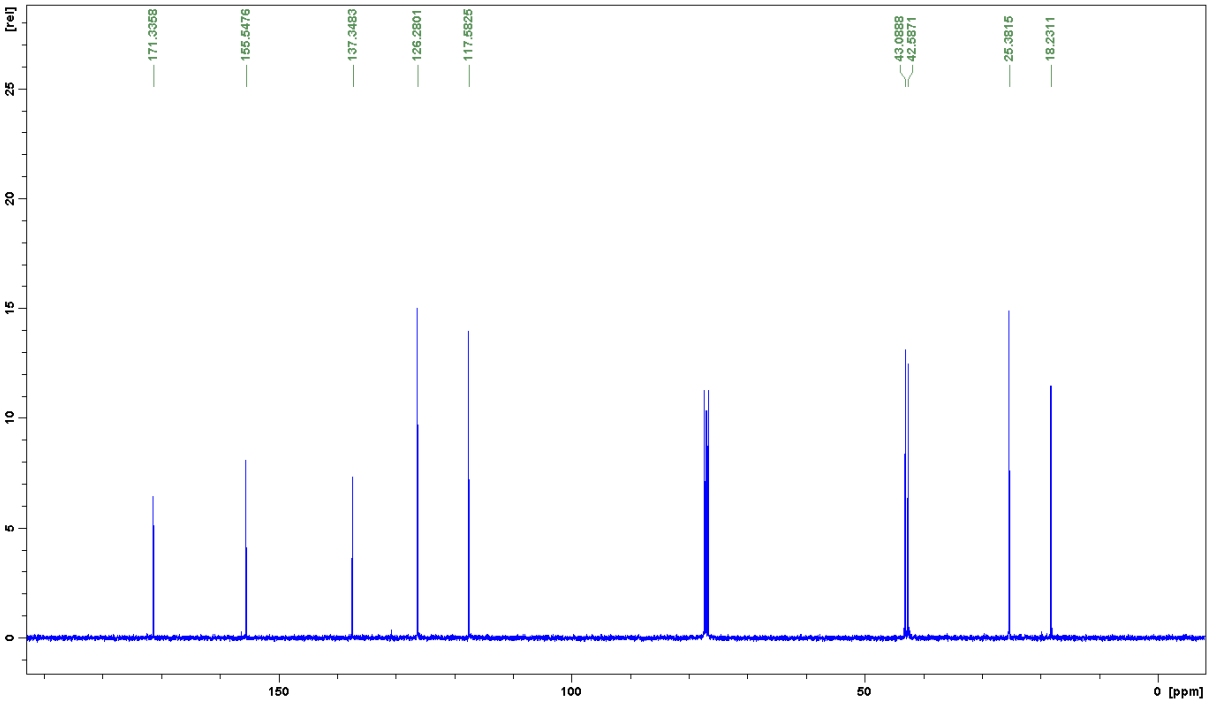
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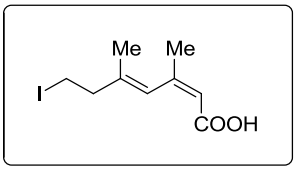
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Me
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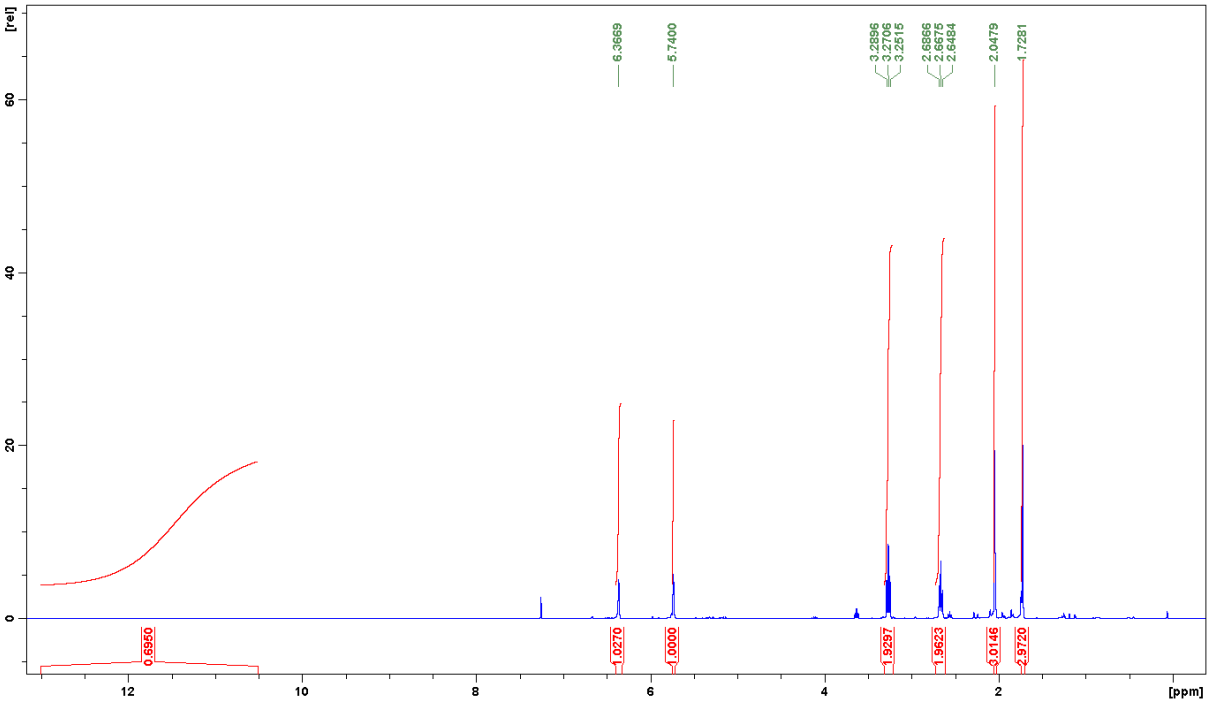
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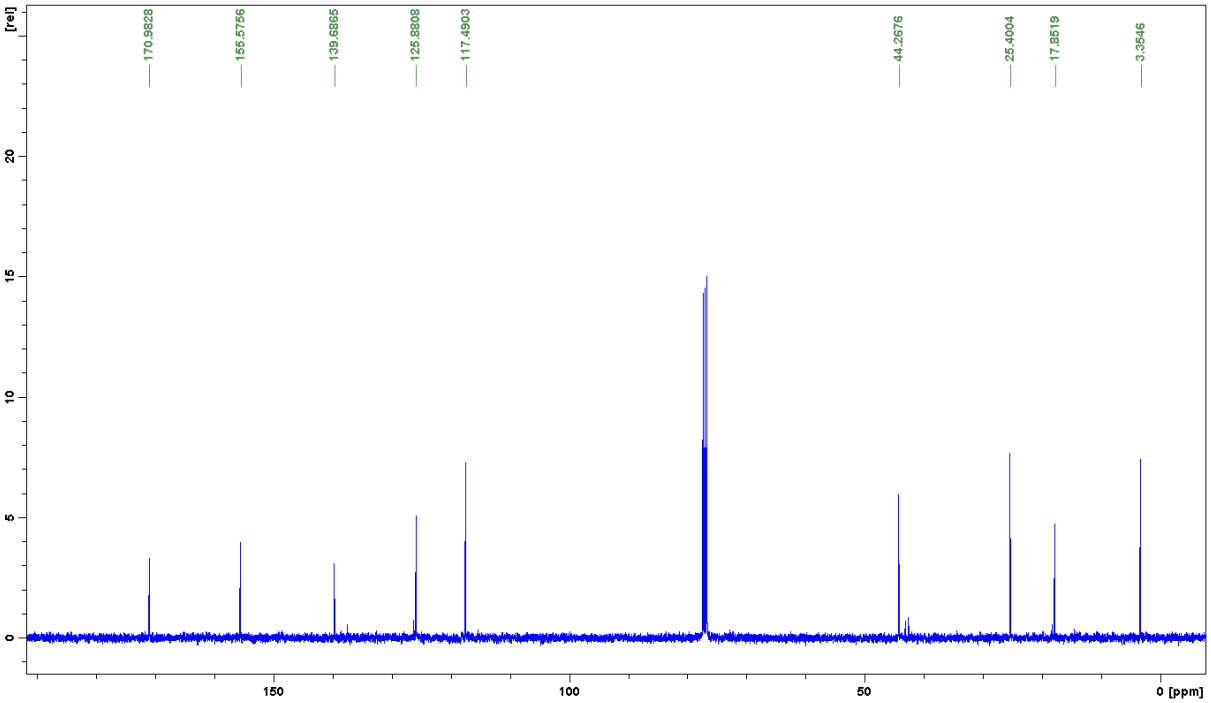
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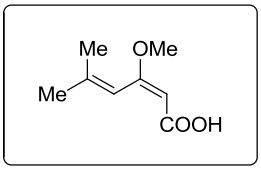
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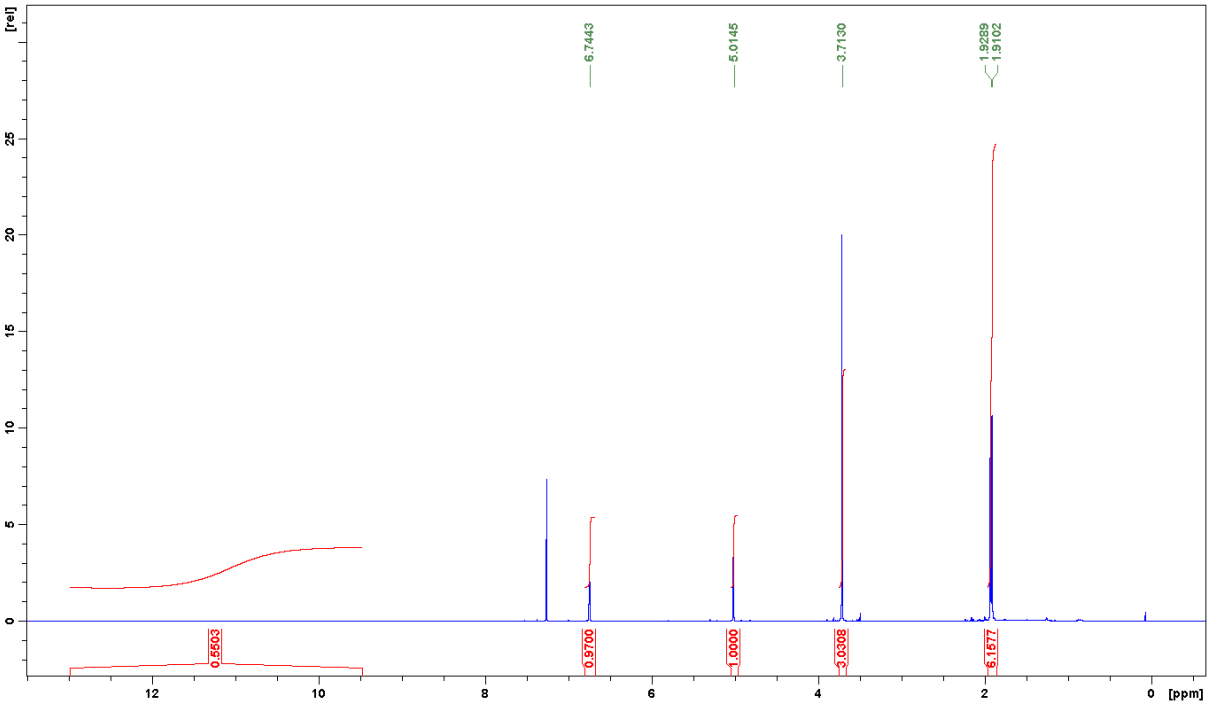
COOH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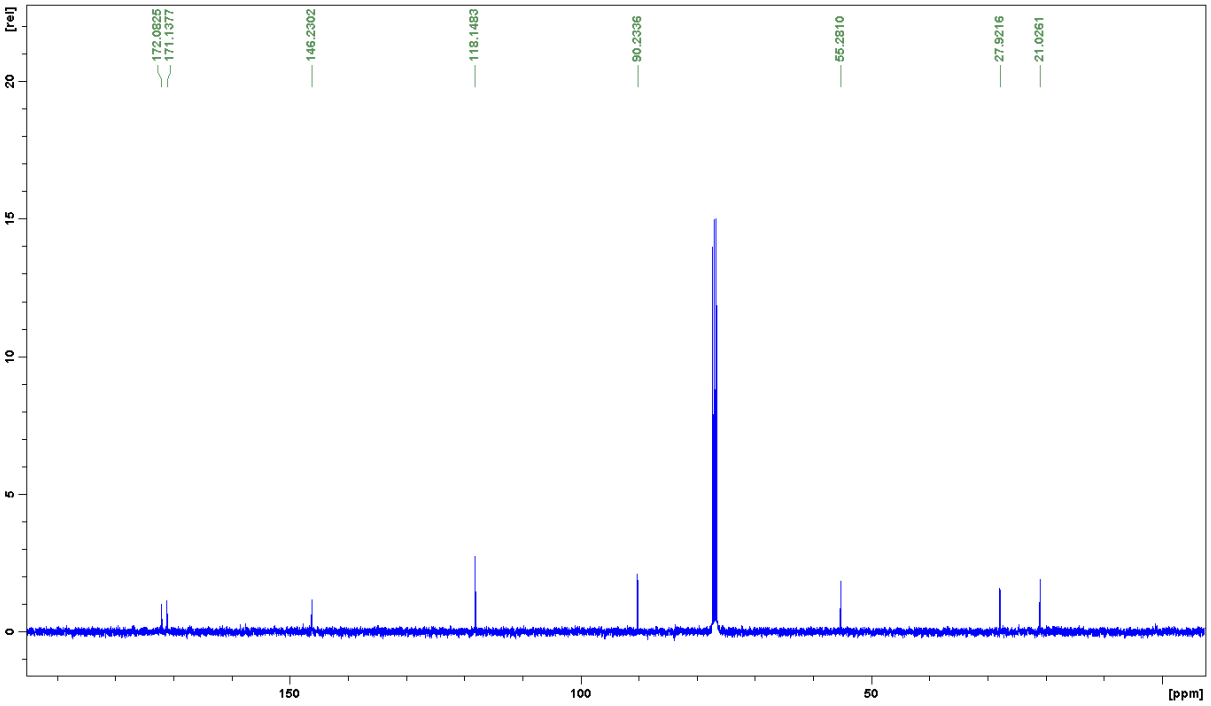
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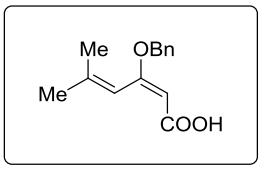
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OBn
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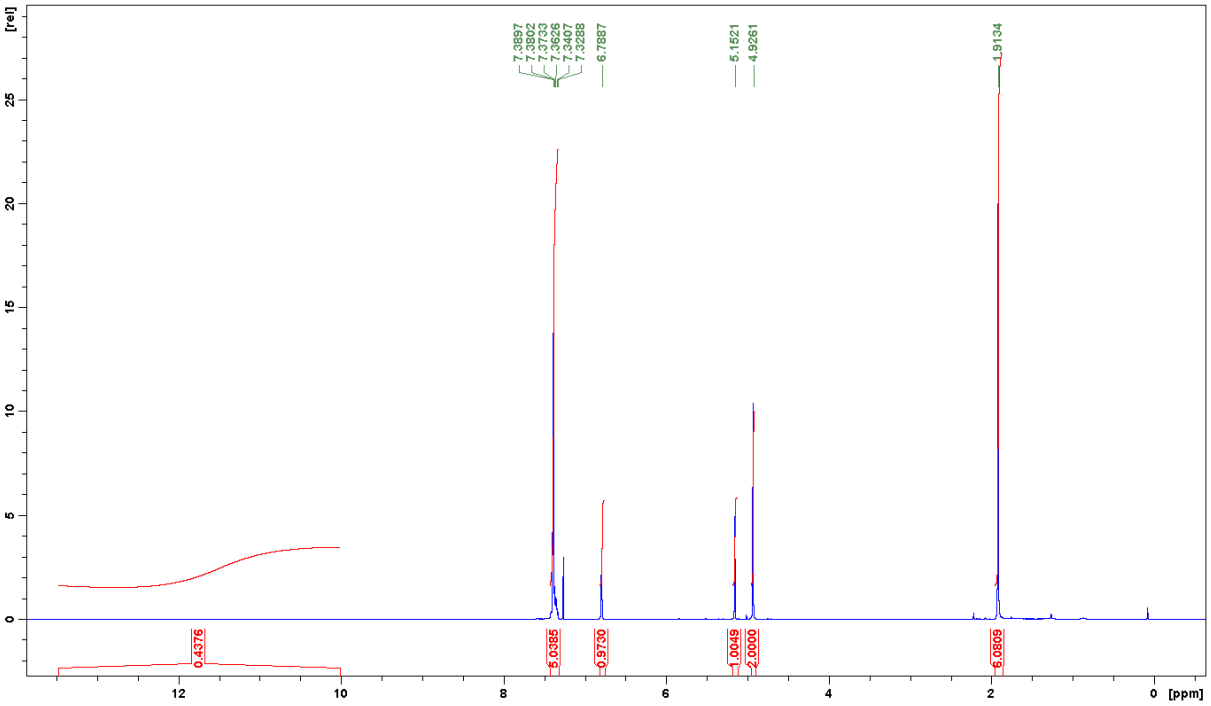
COOH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2.0000
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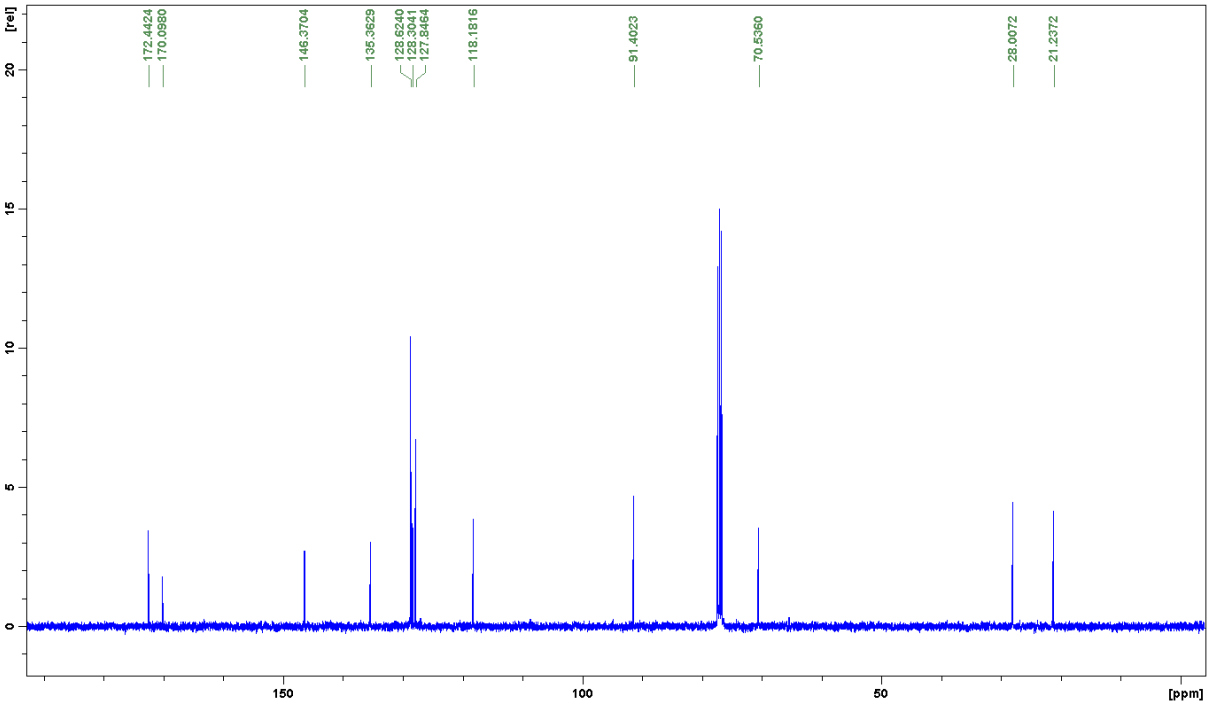
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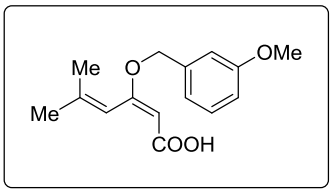
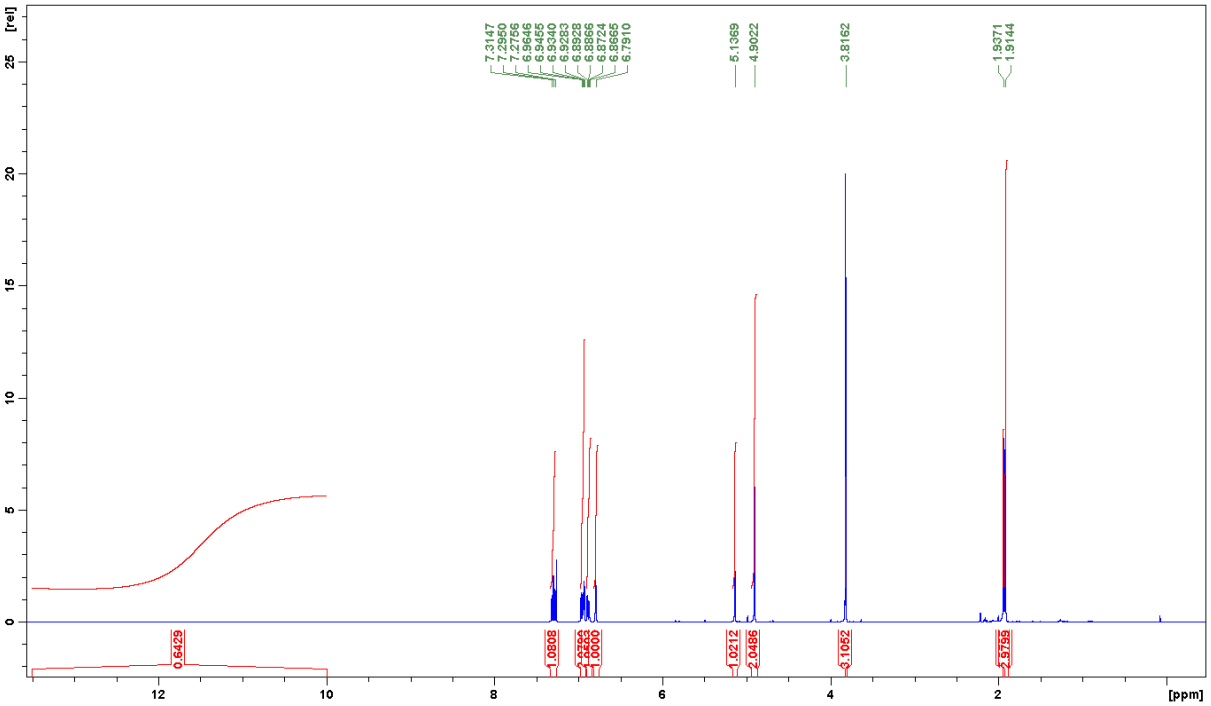

Me
O
OMe
Me
COOH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6.9283
6.8928
6.8866
6.8724
6.8665
6.7910
5.1369
4.9022
3.8162
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1.9144
0.5429
1.0608
1.0212
2.0486
4.1052
2.5759
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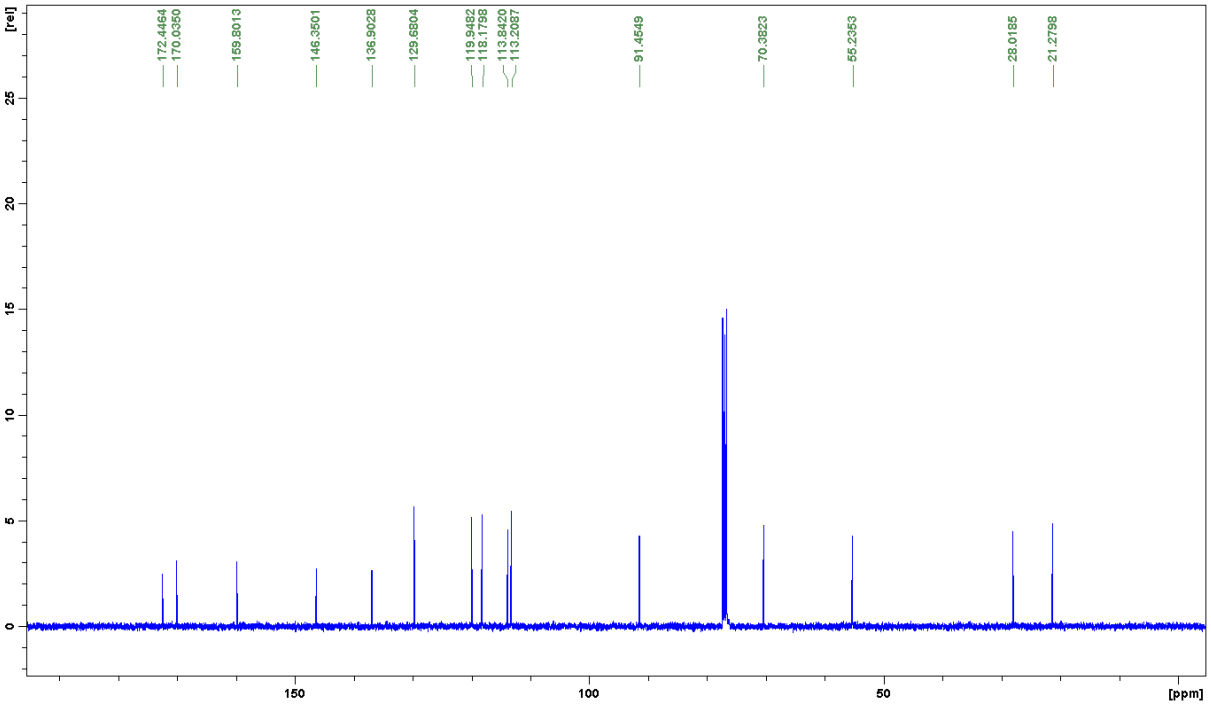
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159.8013
146.3501
135.9028
129.6804
119.9482
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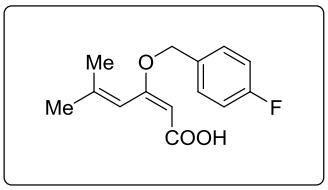
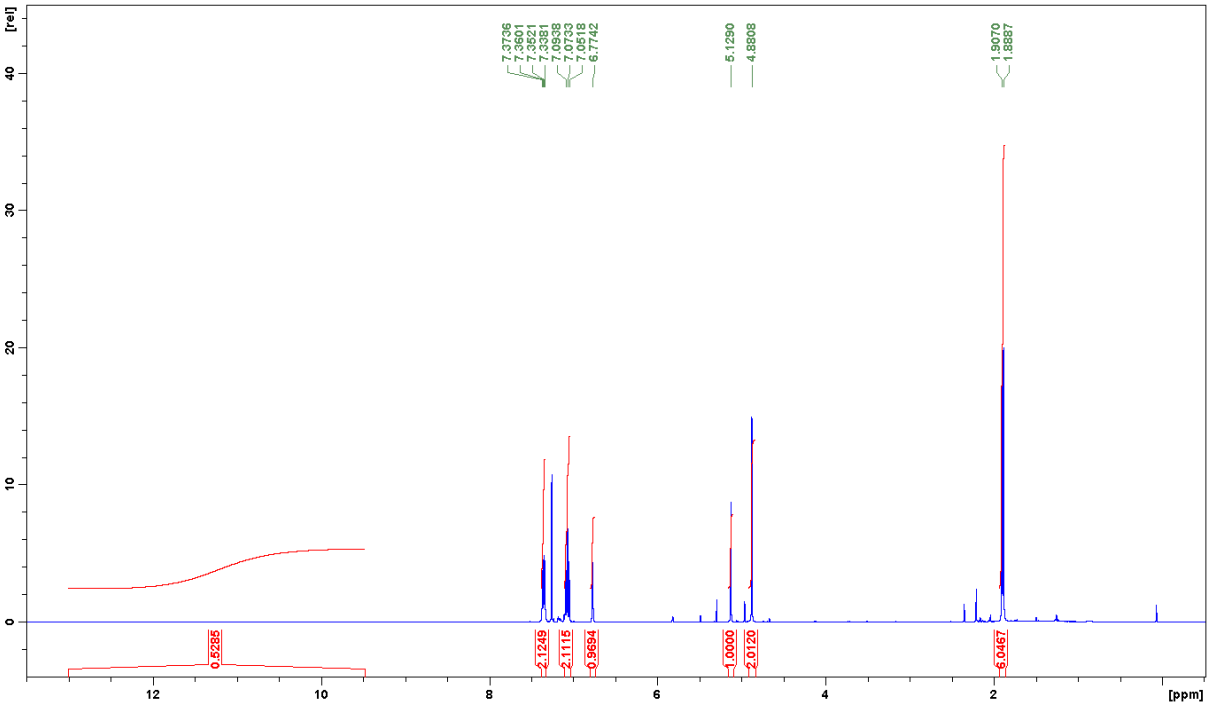
113.8420
113.2087
91.4549
70.3823
55.2353
23.0185
21.2798
[ppm]


Me
O
Me
F
COOH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7.3381
7.0938
7.0733
7.0518
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5.1290
4.8808
1.9070
1.8887
0.5285
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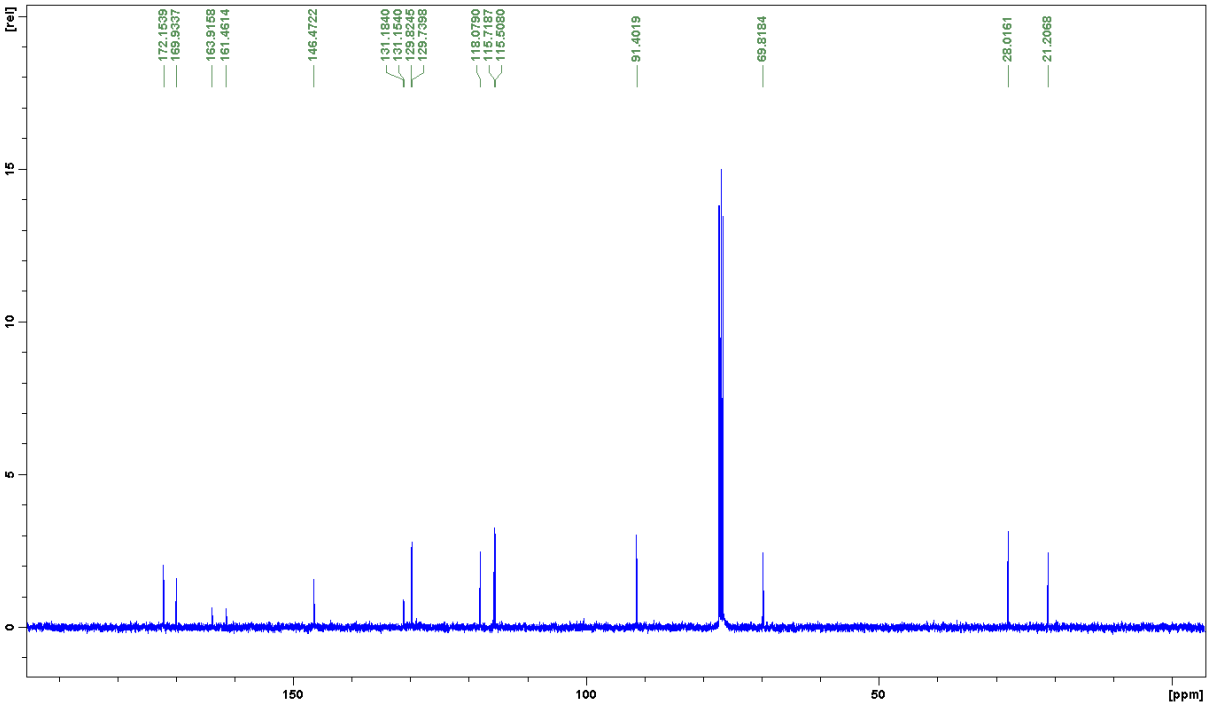
2.1115
0.9694
1.0000
2.0120
6.0467
[ppm]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161.4614
146.4722
131.1840
131.1540
129.8246
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118.0790
115.7187
115.5080
91.4019
69.8184
28.0161
21.2068
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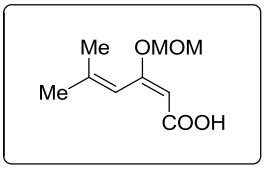
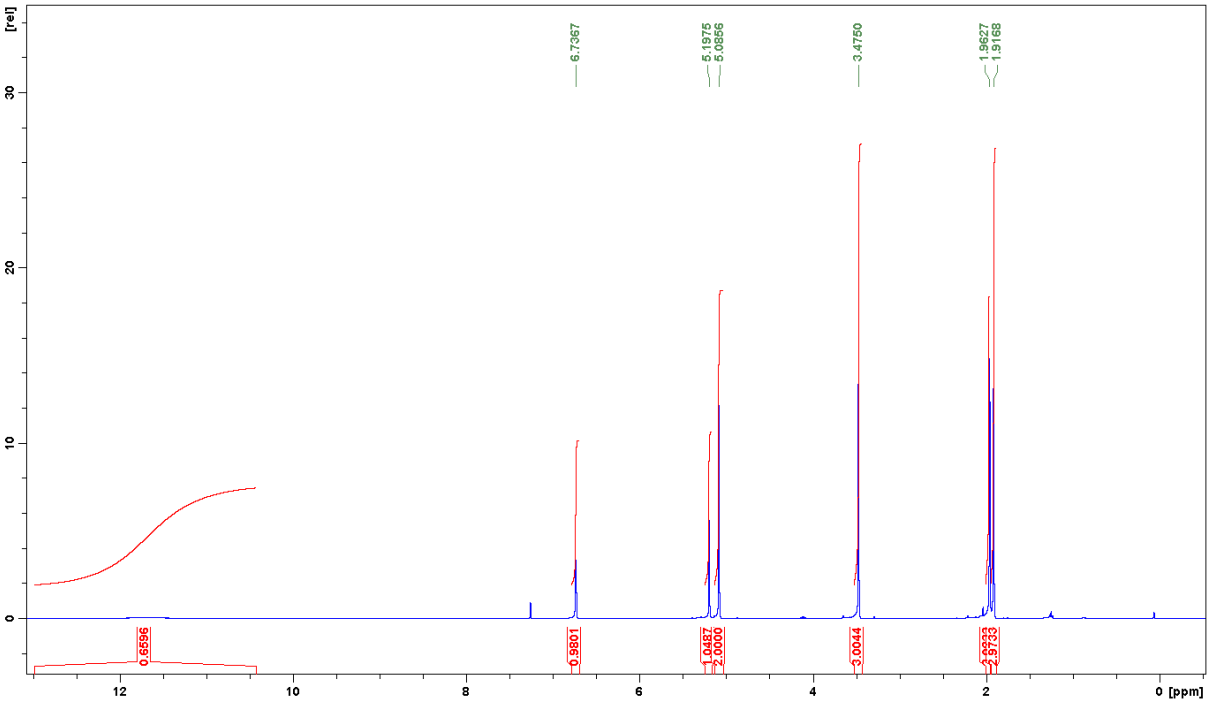

Me
OMOM
Me
COOH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0.9801
1.0487
2.0000
3.0044
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2.9733
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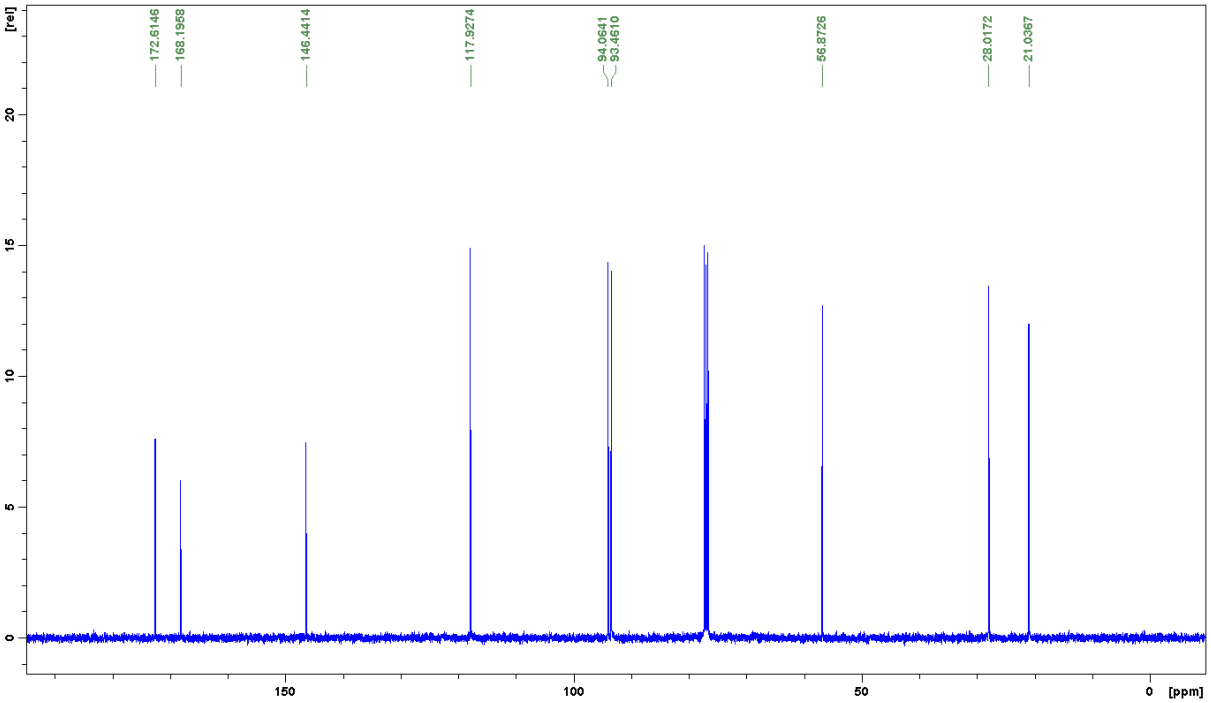
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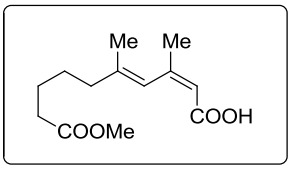
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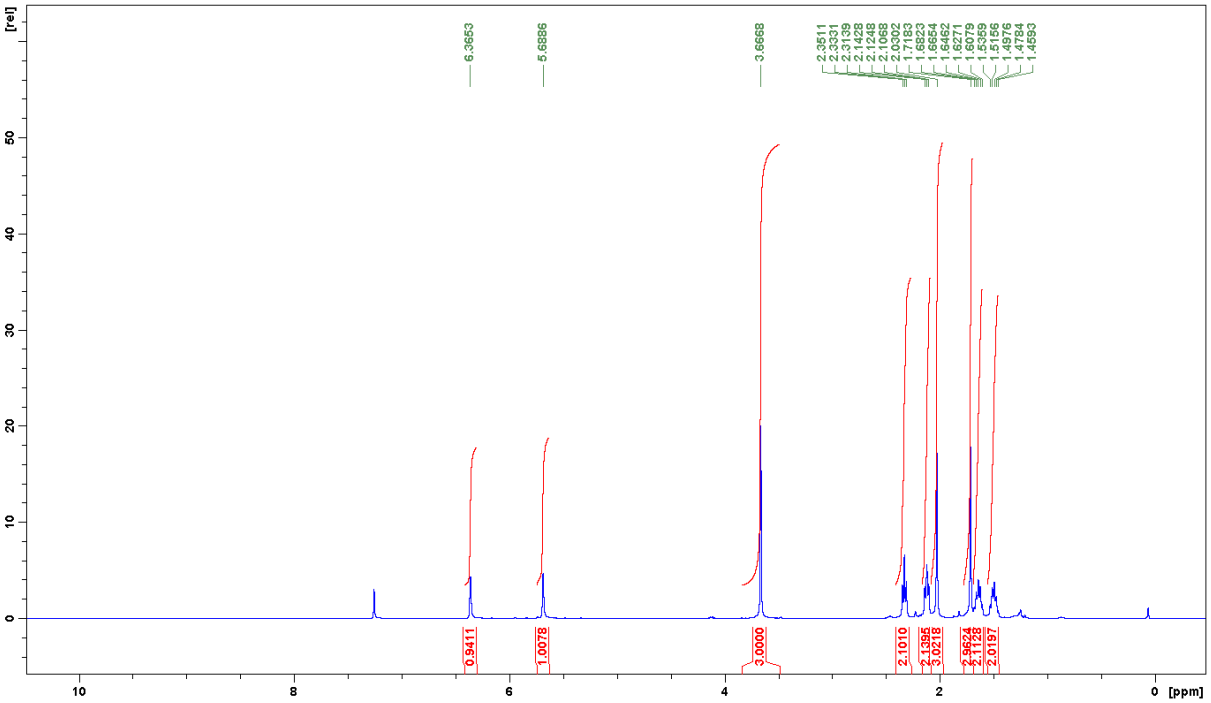
Me
COOMe
COOH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2.1248
2.1068
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1.6823
1.6654
1.6452
1.6271
1.6079
1.5359
1.5156
1.4976
1.4784
1.4593
0.9411
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2.1395
3.0218
2.9624
2.1128
2.0197
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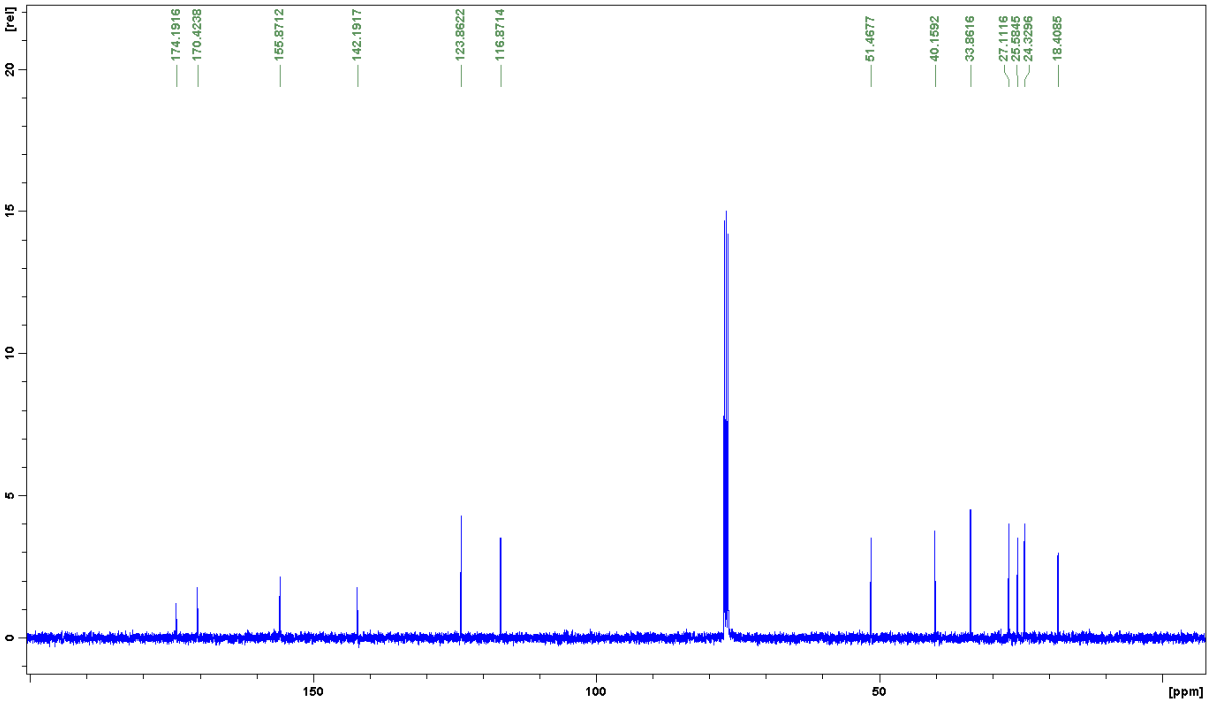
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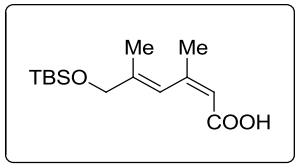
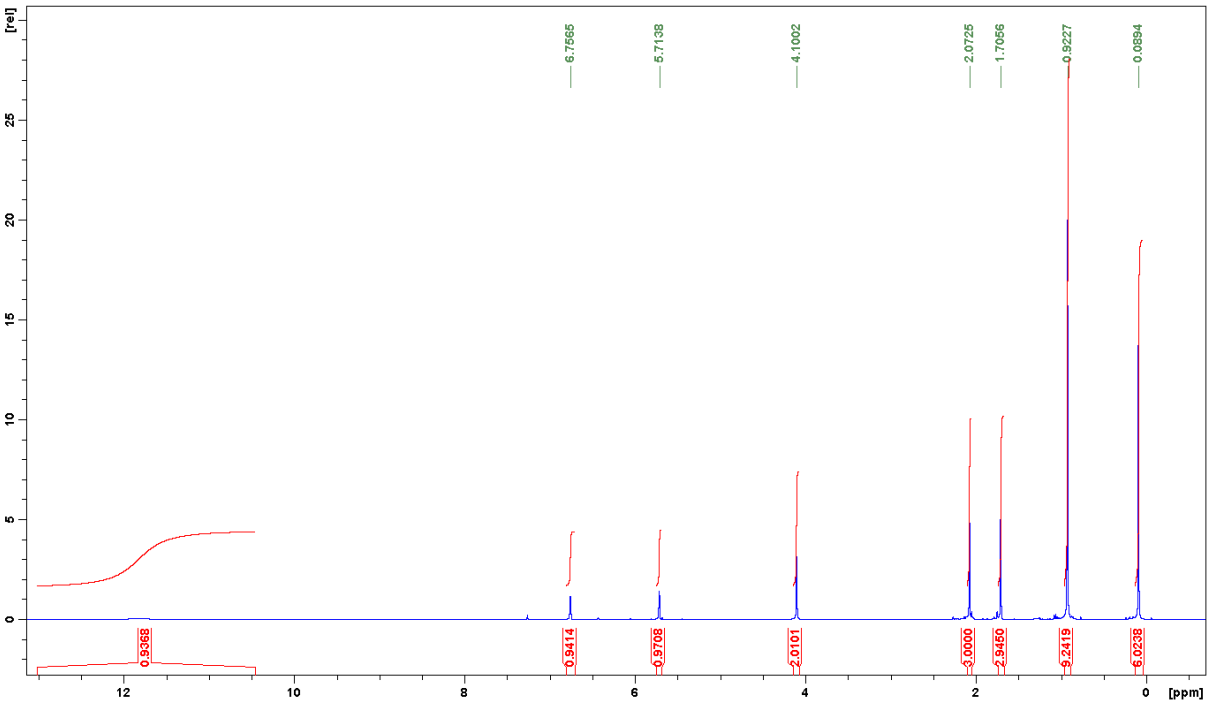
33.8616
27.1116
25.5845
24.3256
18.4085
[ppm]


Me
Me
TBSO
COOH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0.9368
0.9414
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3.0000
2.9450
9.2419
6.0238
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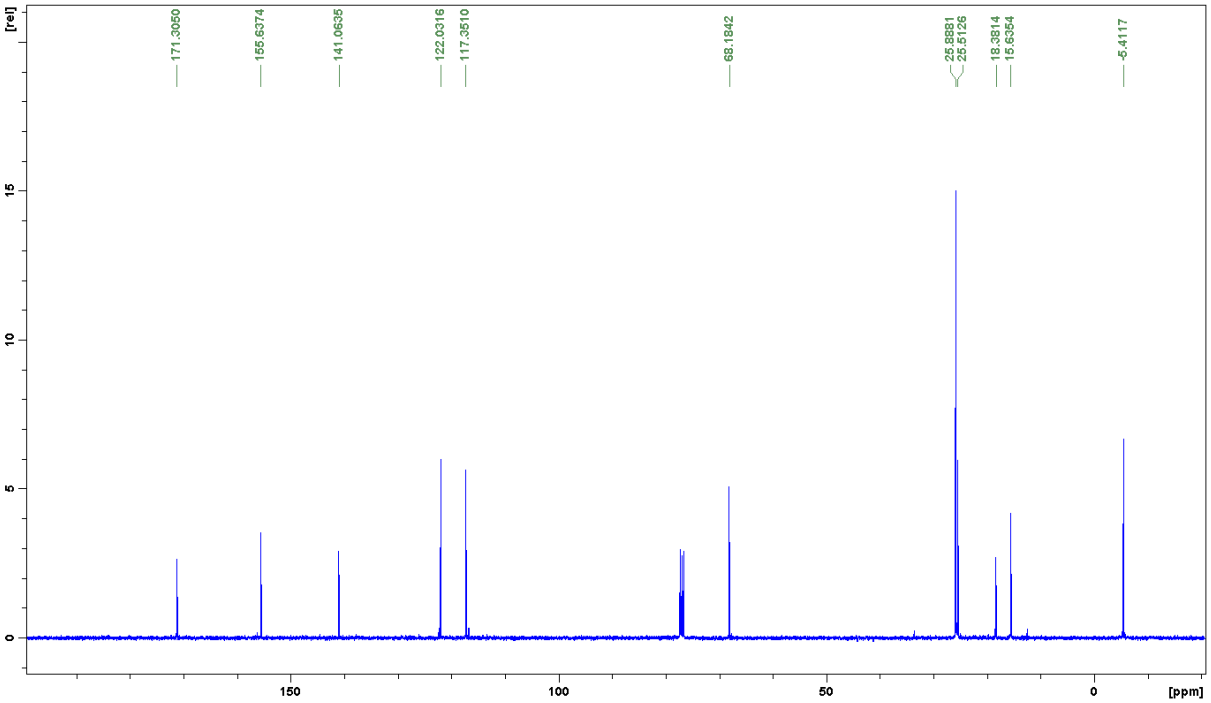
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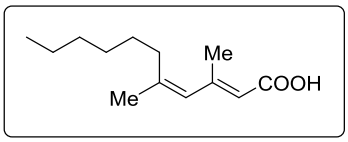
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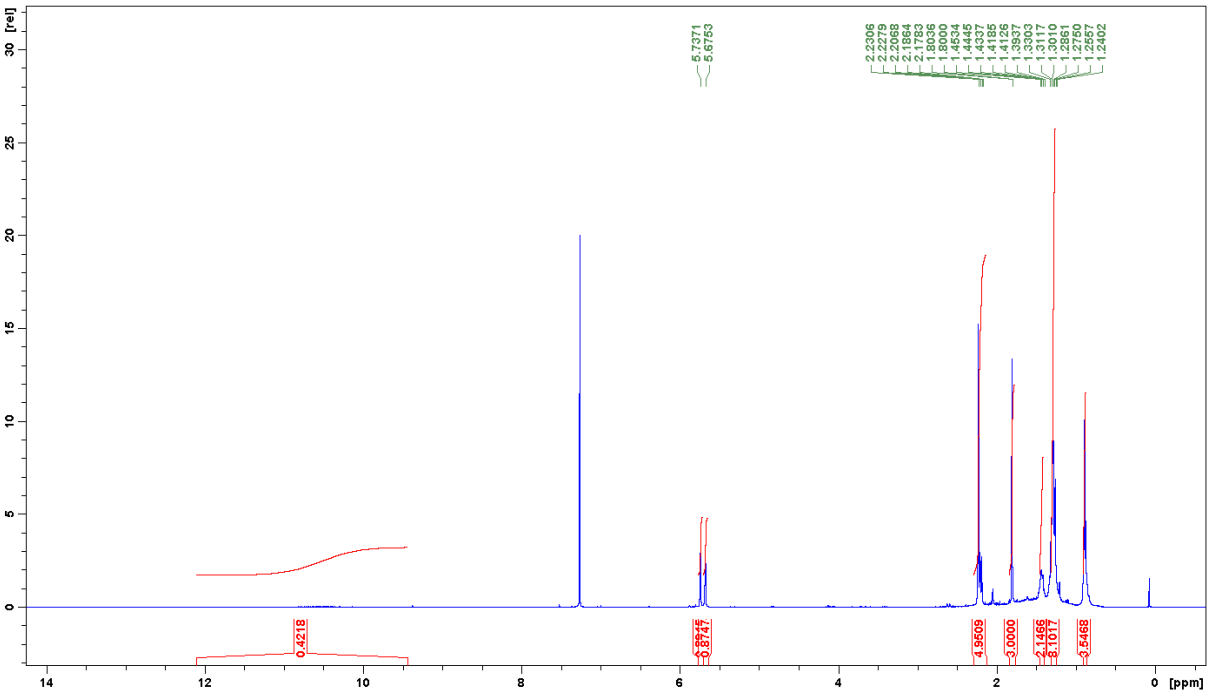
Me
COOH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1.4534
1.4445
1.4337
1.4185
1.4125
1.3937
1.3910
1.3117
1.3010
1.2861
1.2750
1.2557
1.2402
0.4218
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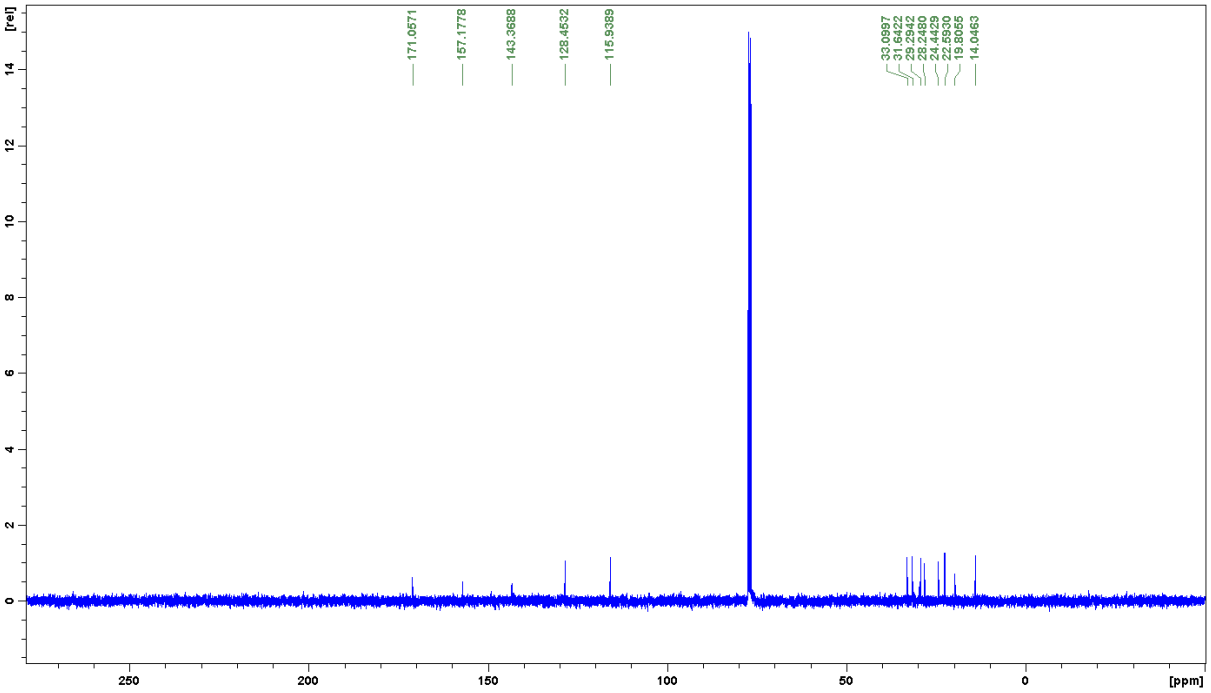
8.1017
3.5468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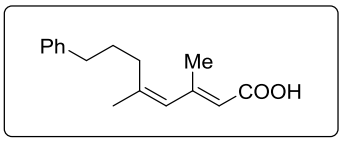
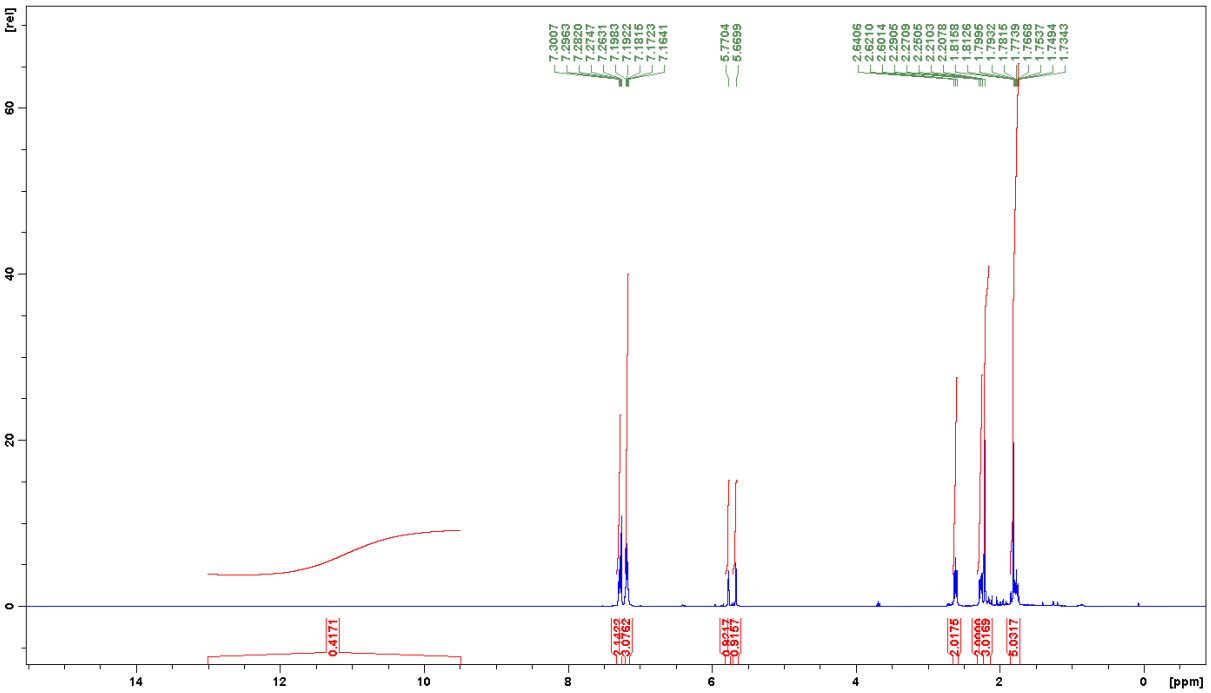
22.5930
19.8055
14.0463


Ph
Me
COOH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5.6699
2.6406
2.6210
2.6014
2.2909
2.2709
2.2505
2.2103
2.2078
1.8158
1.8128
1.7995
1.7932
1.7815
1.7739
1.7683
1.7537
1.7494
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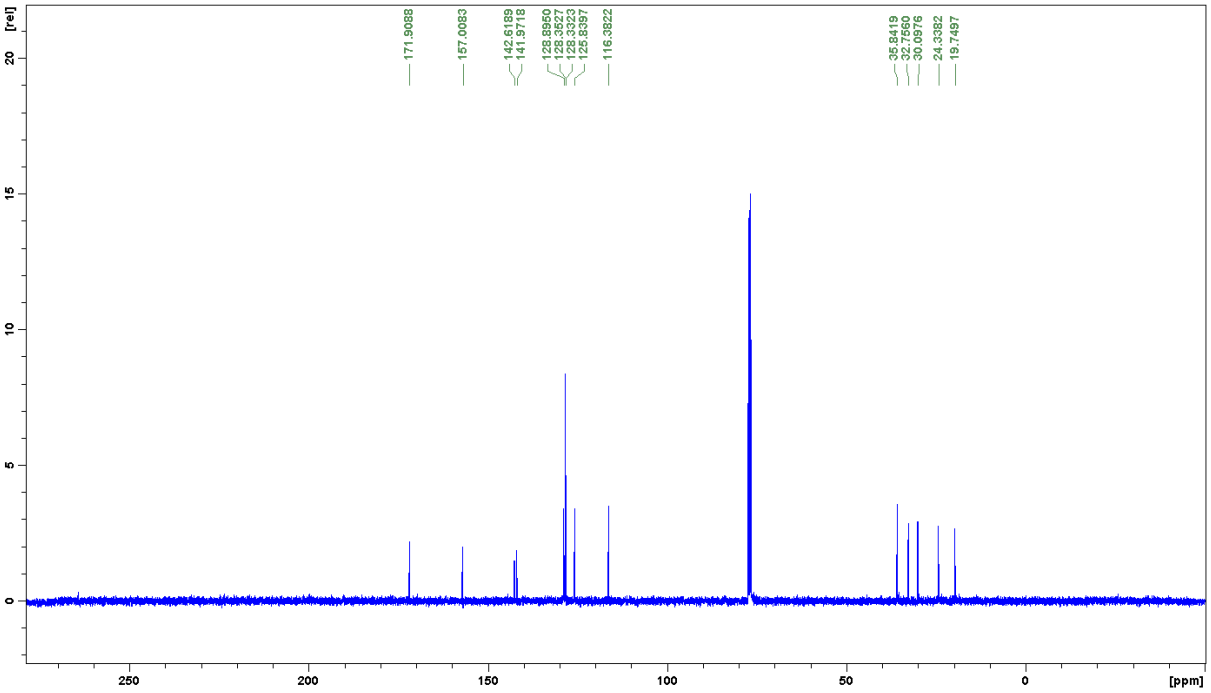
0.9157
2.0175
2.0066
3.0169
6.0317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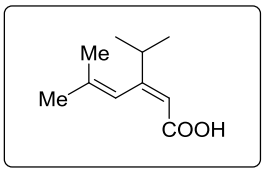
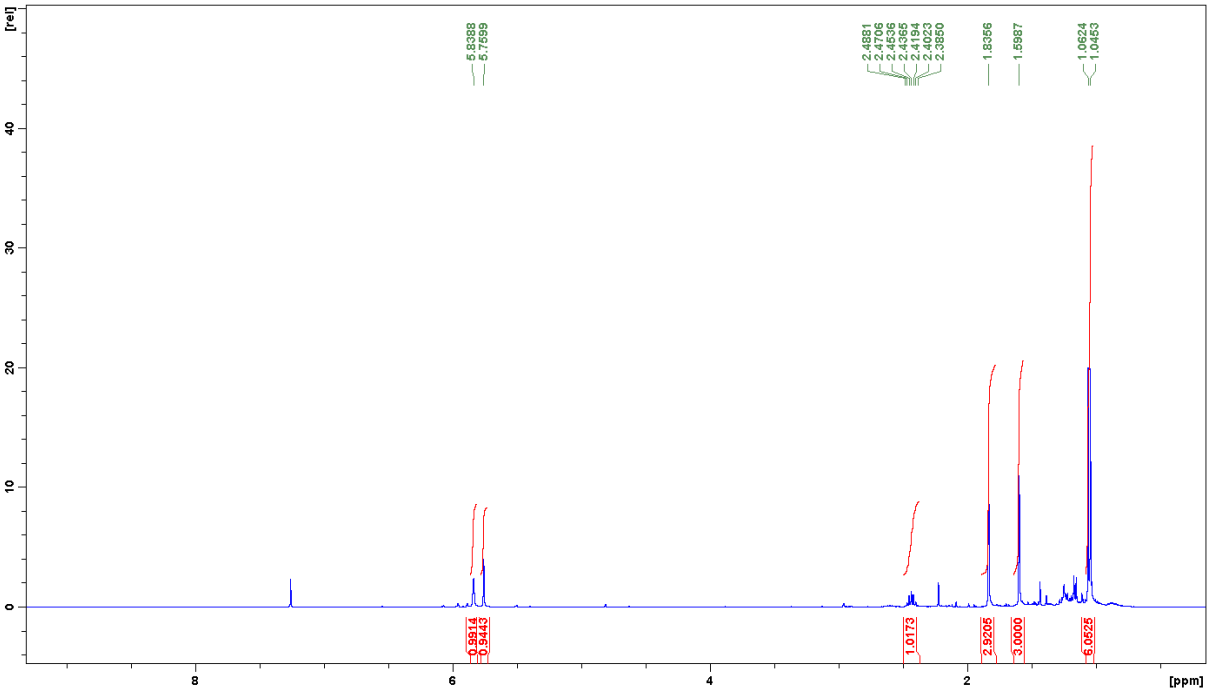
30.0976
24.3382
19.7497


Me
Me
COOH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1.0453
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2.9205
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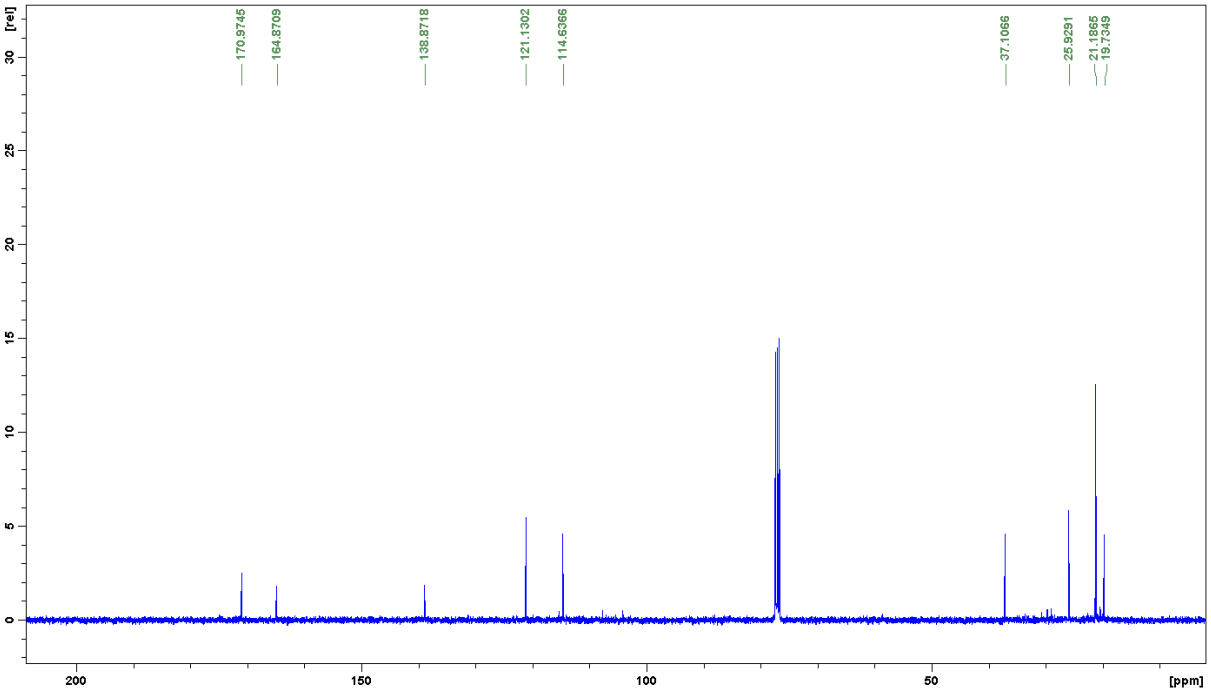
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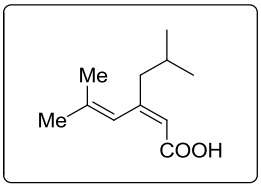
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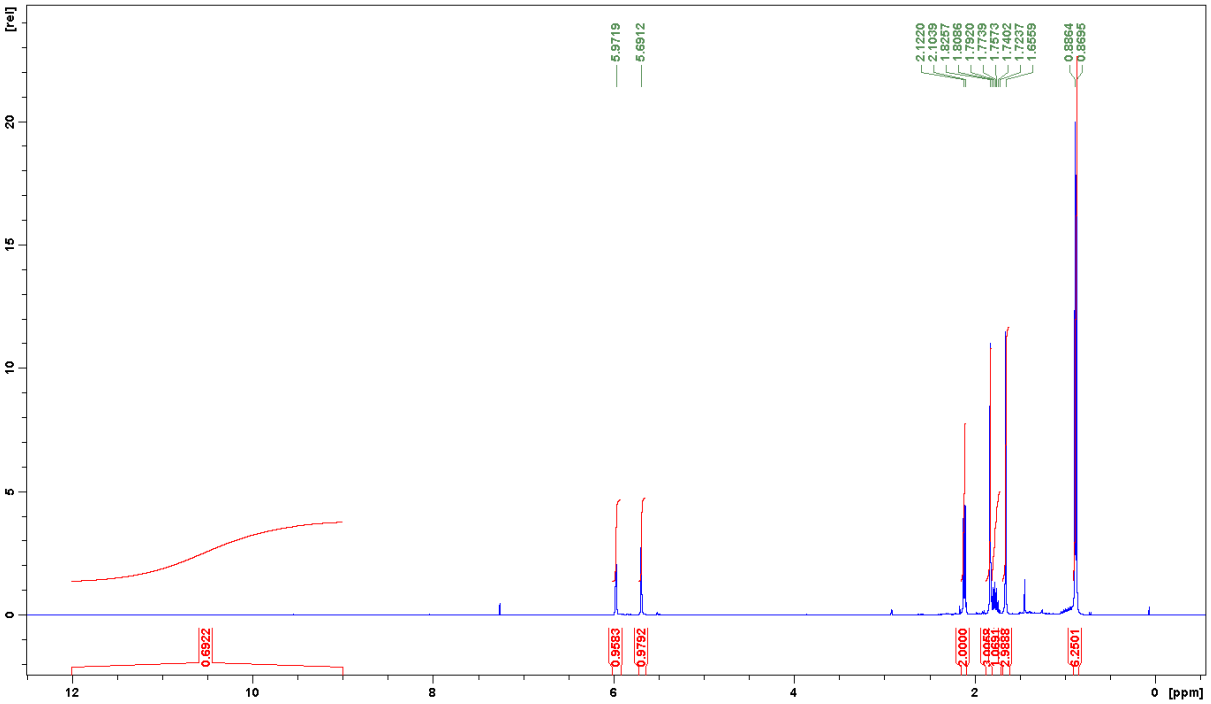
Me
COOH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1.6559
0.8864
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1.0681
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6.2501
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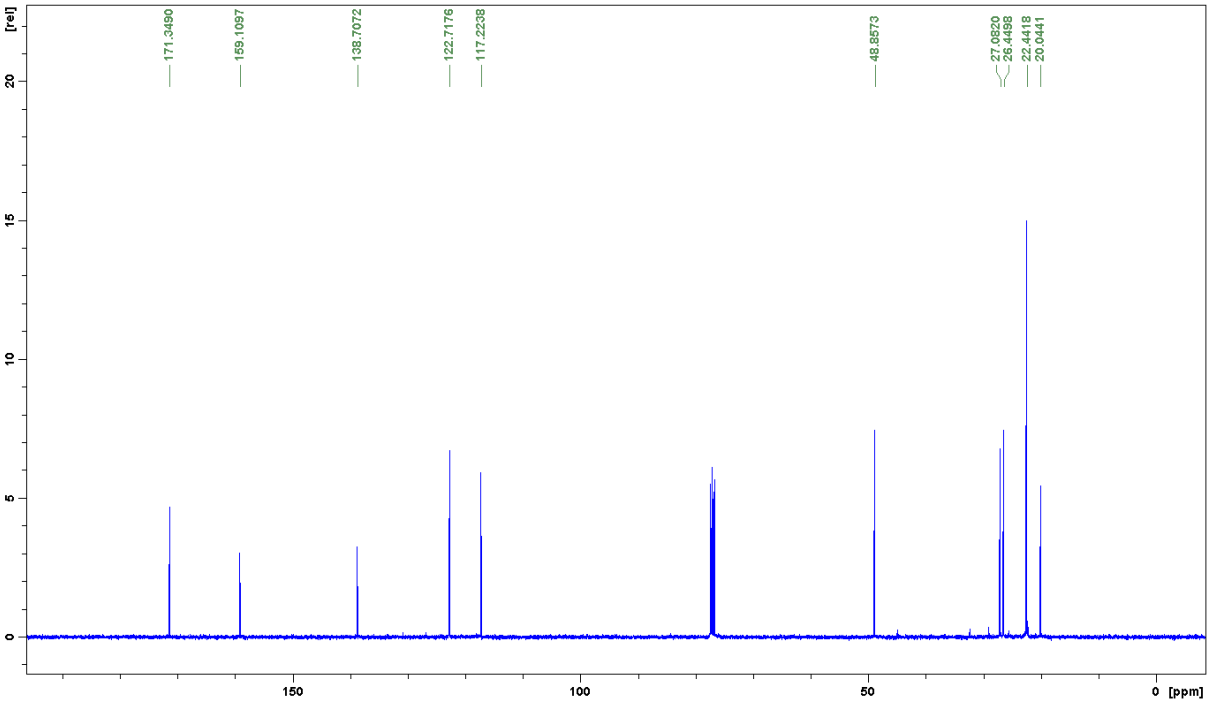
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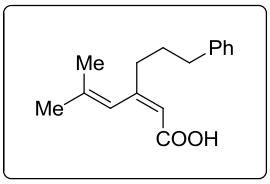
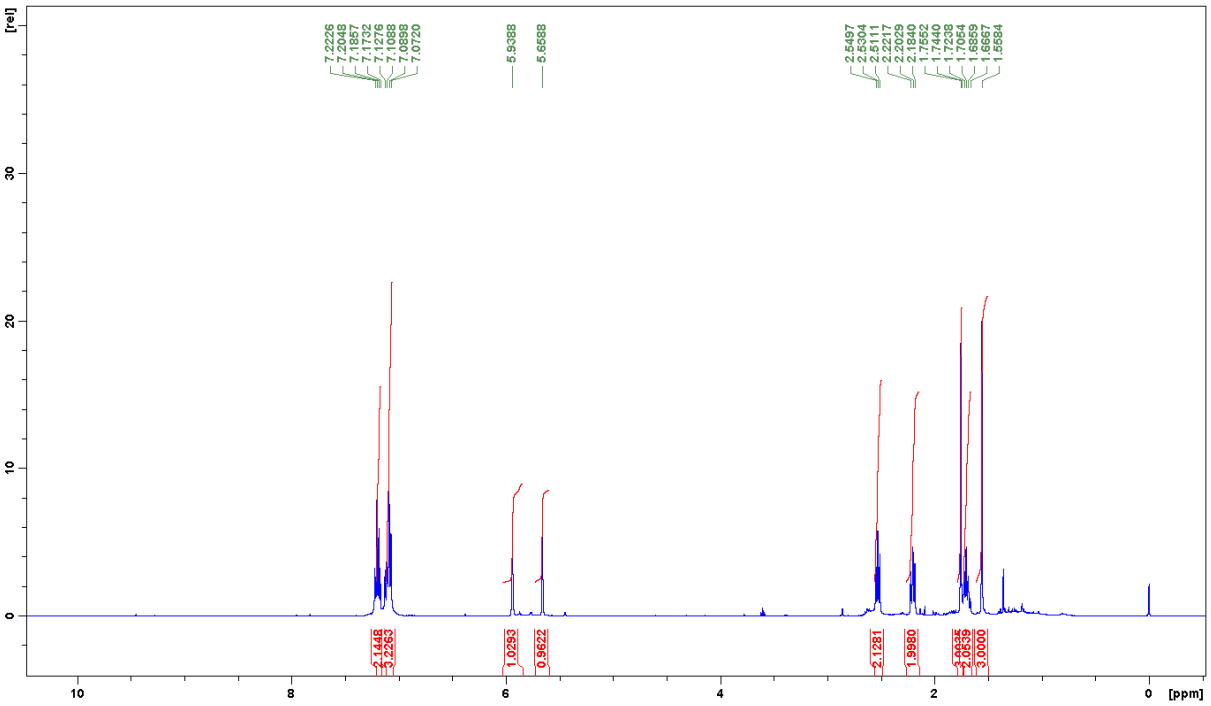

Me
Me
Ph
COOH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5.6588
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2.5304
2.5111
2.2217
2.2029
2.1840
1.7562
1.7440
1.7238
1.7054
1.6859
1.6657
1.6584
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3.0000
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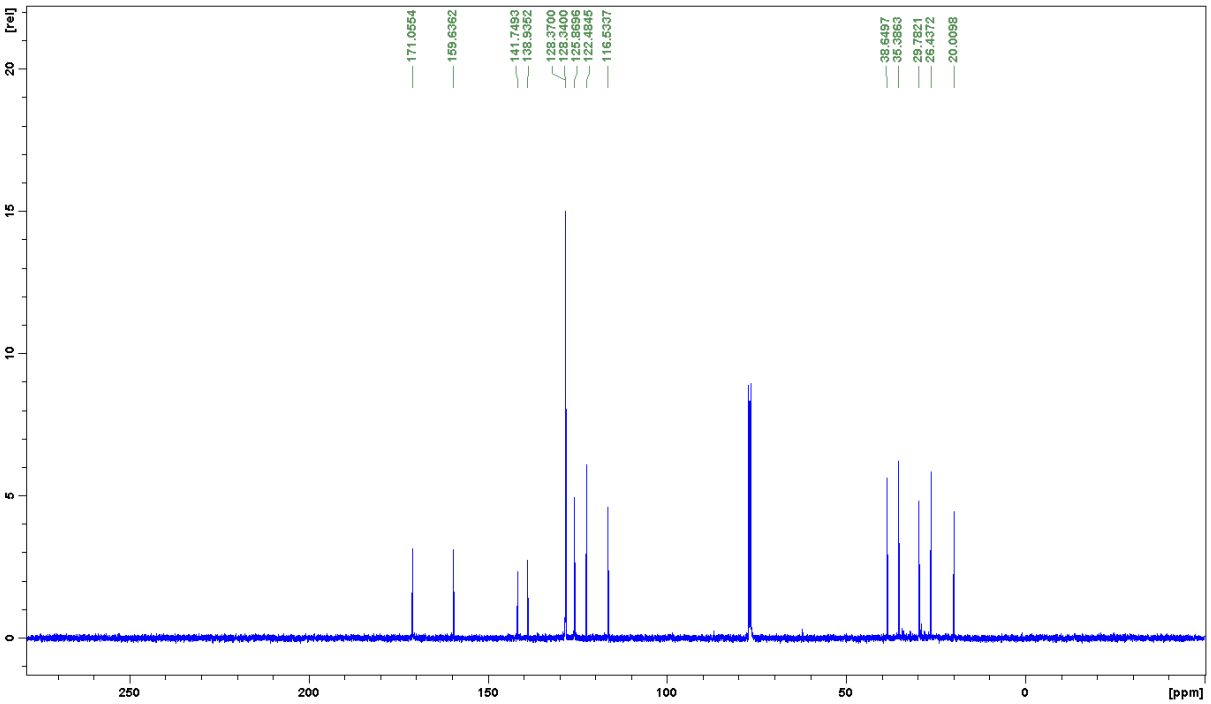
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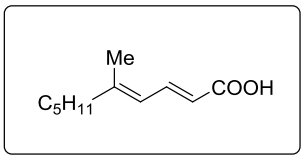
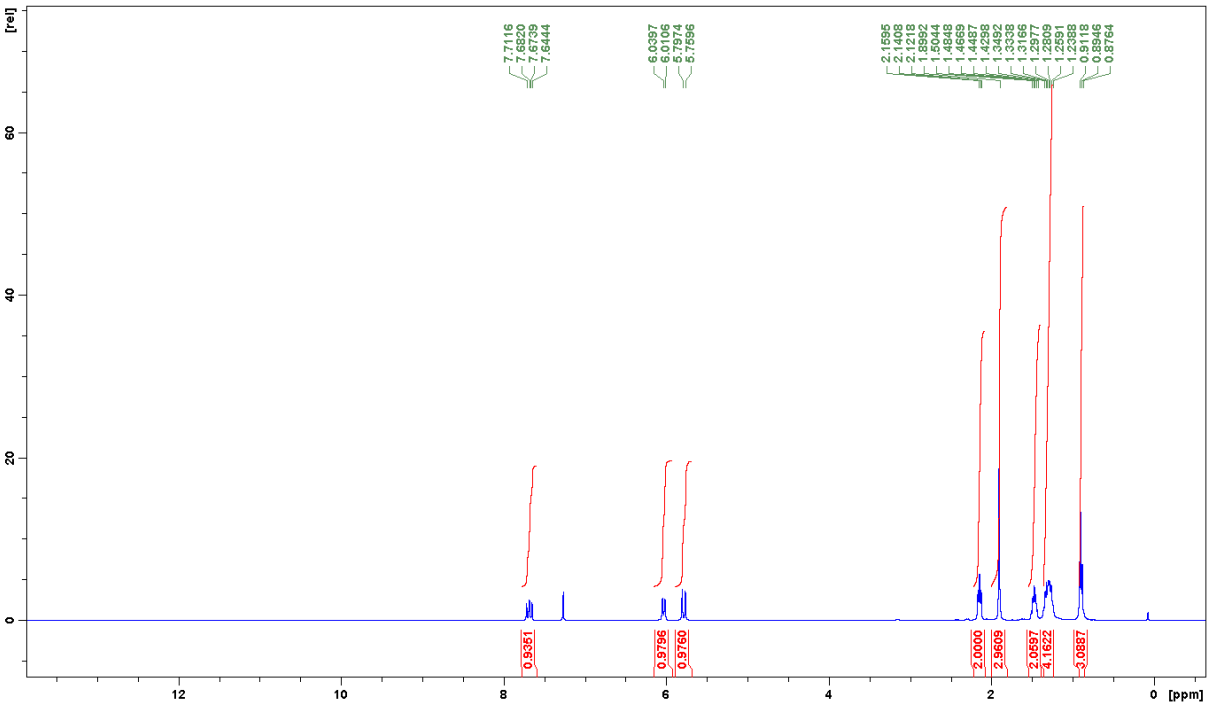
[ppm]


Me
C5H11
COOH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1.4669
1.4497
1.4298
1.3492
1.3338
1.3166
1.2977
1.2809
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1.2388
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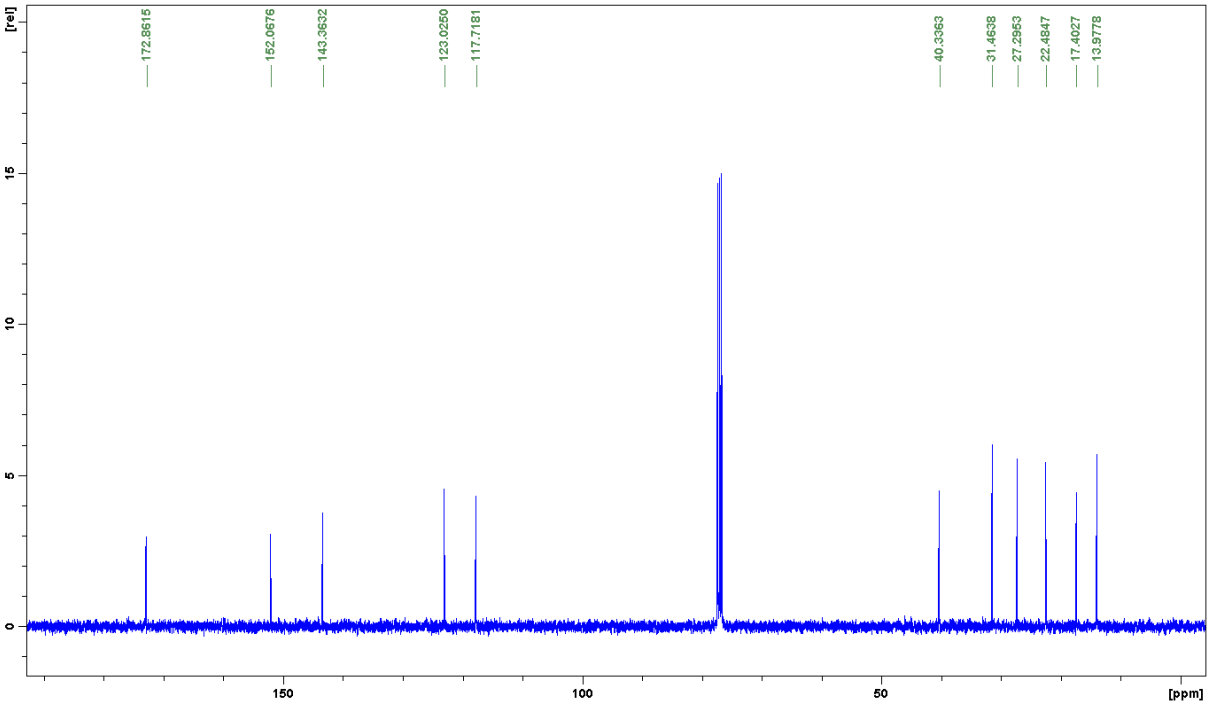
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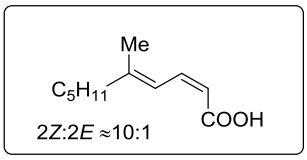
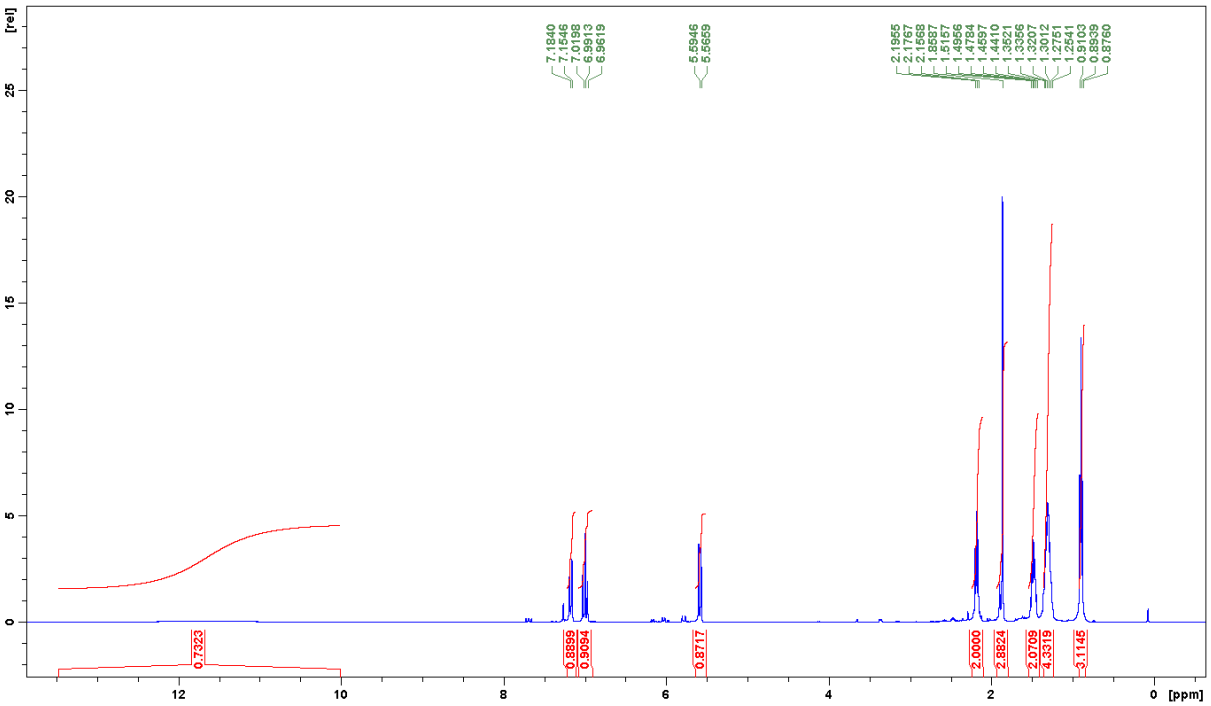
[ppm]


Me
C5H11
COOH
2Z:2E ≈10:1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2.1767
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1.5157
1.4956
1.4794
1.4597
1.4410
1.3521
1.3356
1.3207
1.3012
1.2751
1.2441
0.9103
0.8939
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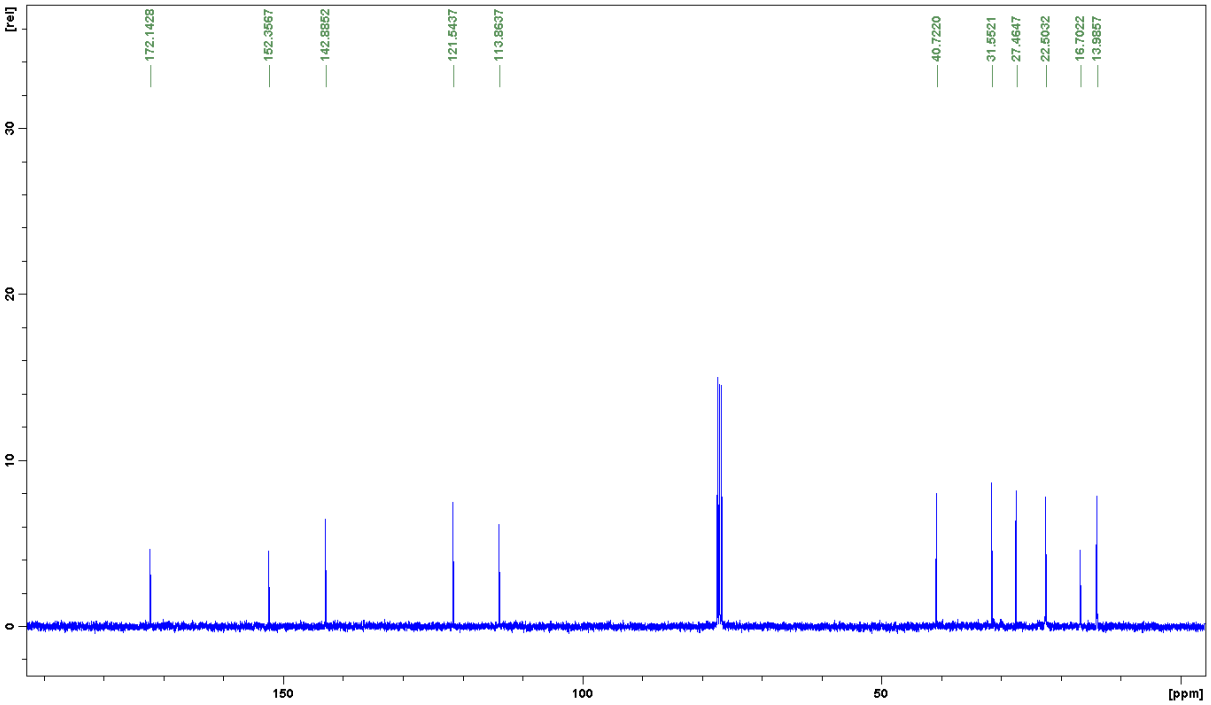
2.0709
4.3319
3.1145
[ppm]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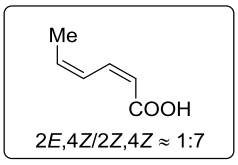
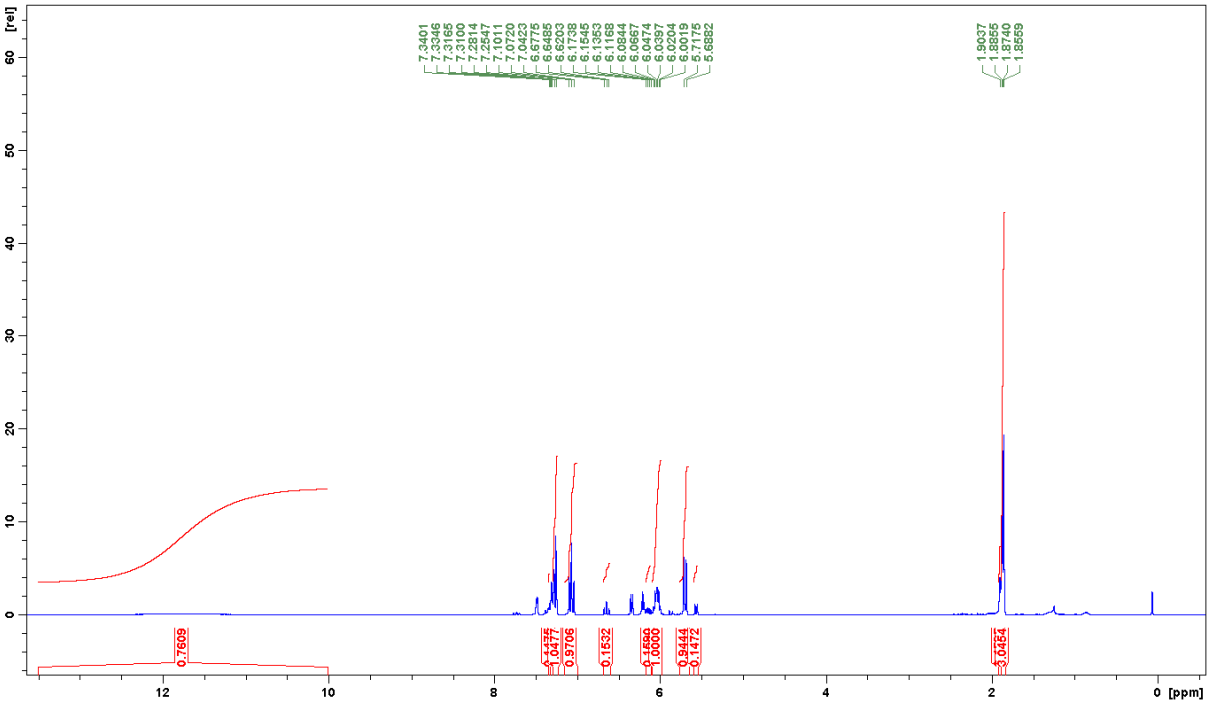
[ppm]


Me
COOH
2*E*,4*Z*/2*Z*,4*Z* ≈ 1:7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7.2547
7.1011
7.0720
7.0423
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6.6485
6.6203
6.1738
6.1545
6.1353
6.1168
6.0944
6.0667
6.0474
6.0397
6.0204
6.0019
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5.6882
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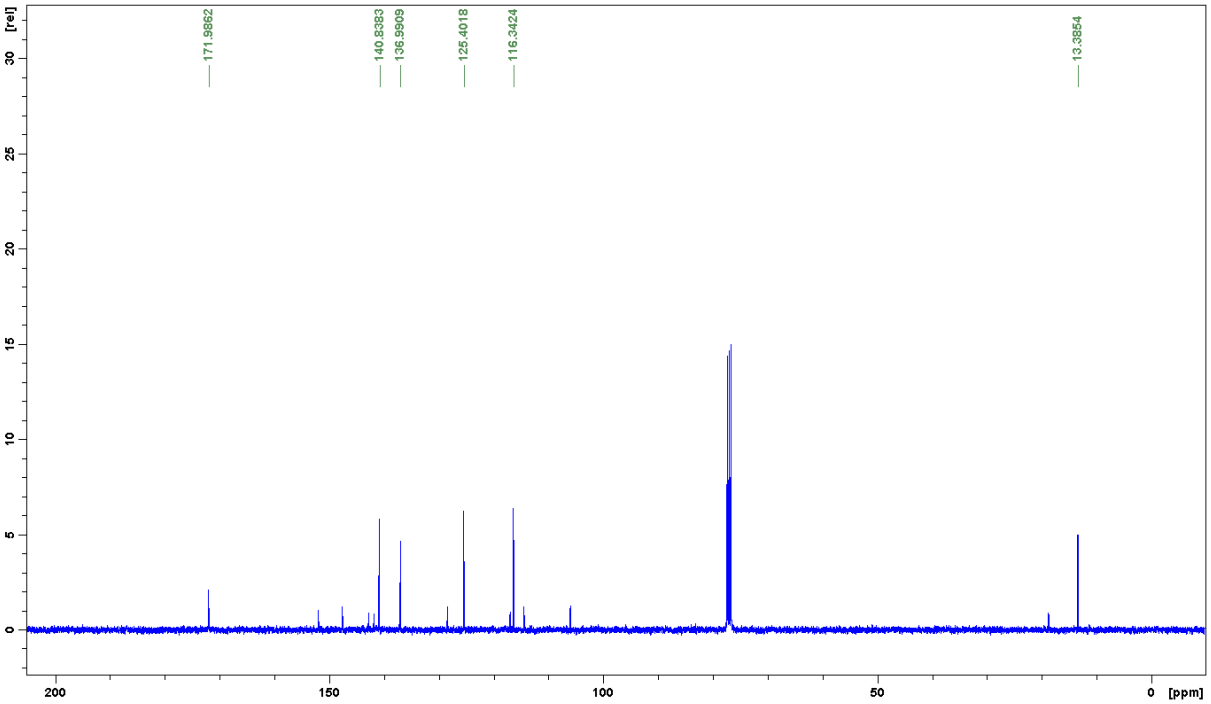
1.8855
1.8740
1.8559
0.7609
1.0477
0.9706
0.1532
1.0000
0.9444
0.1472
3.0454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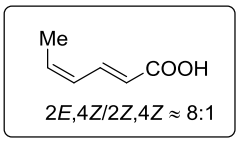
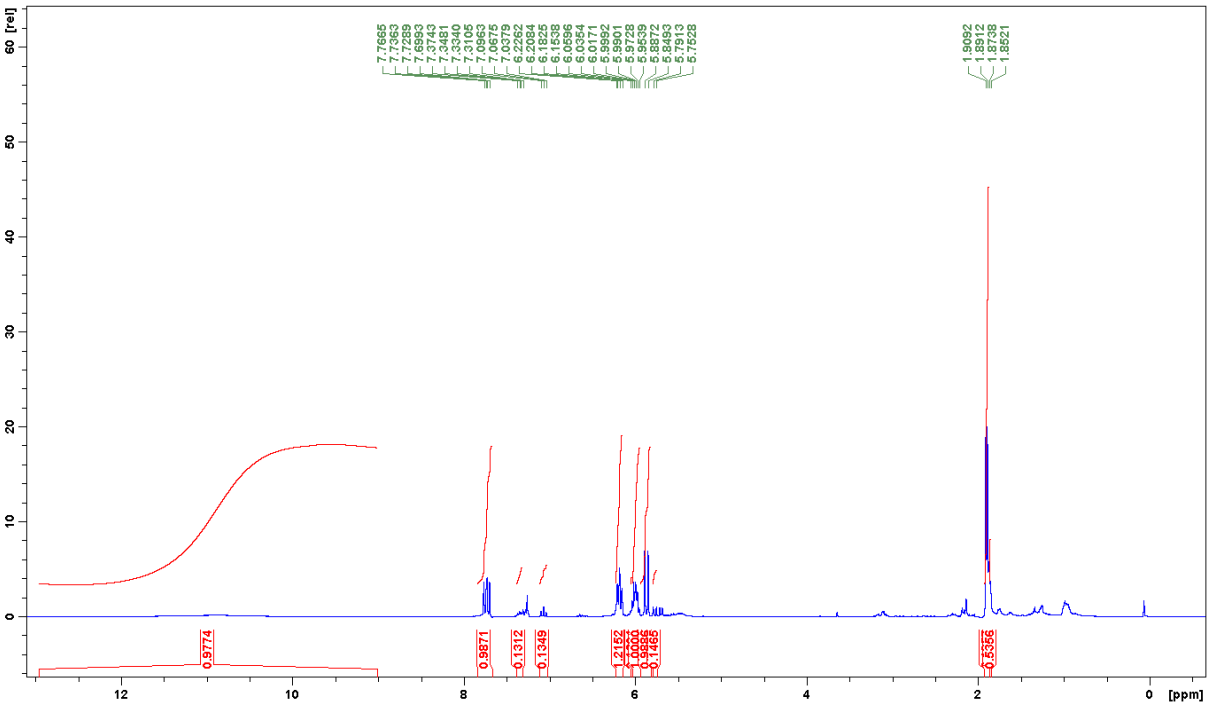
136.9909
125.4018
116.3424
13.3854


Me
COOH

2*E*,4*Z*/2*Z*,4*Z* ≈ 8:1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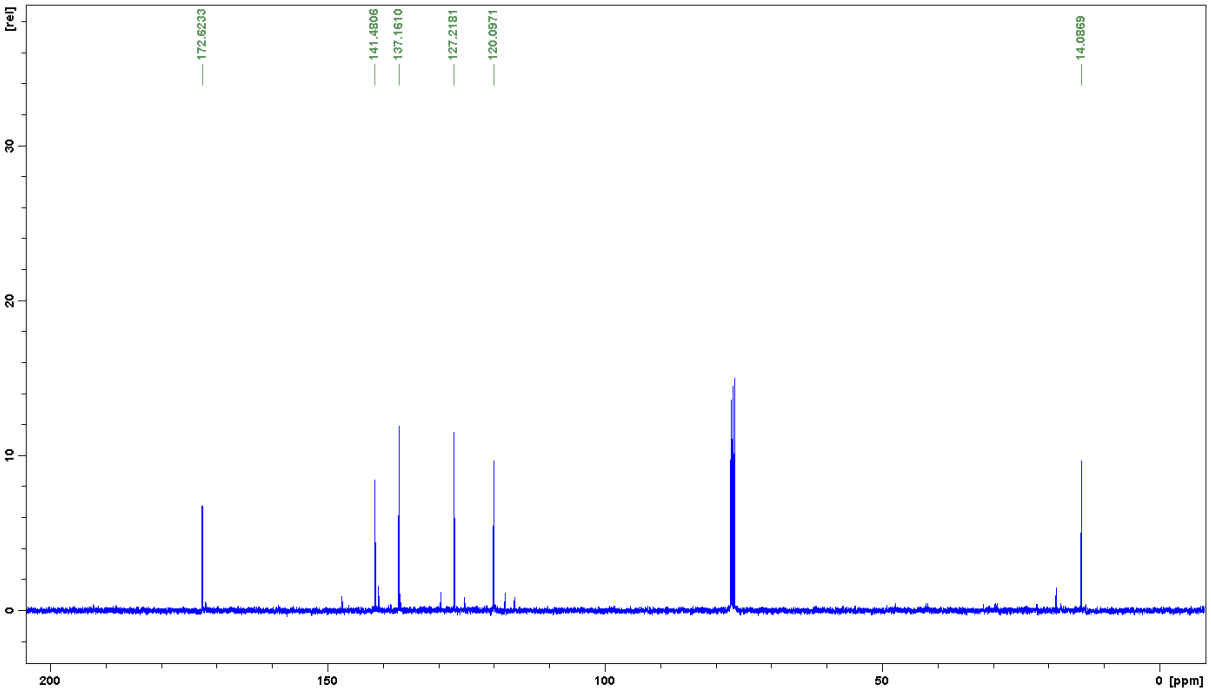
0.9871
0.1312
0.1349
0.1465
0.5356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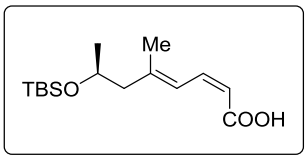
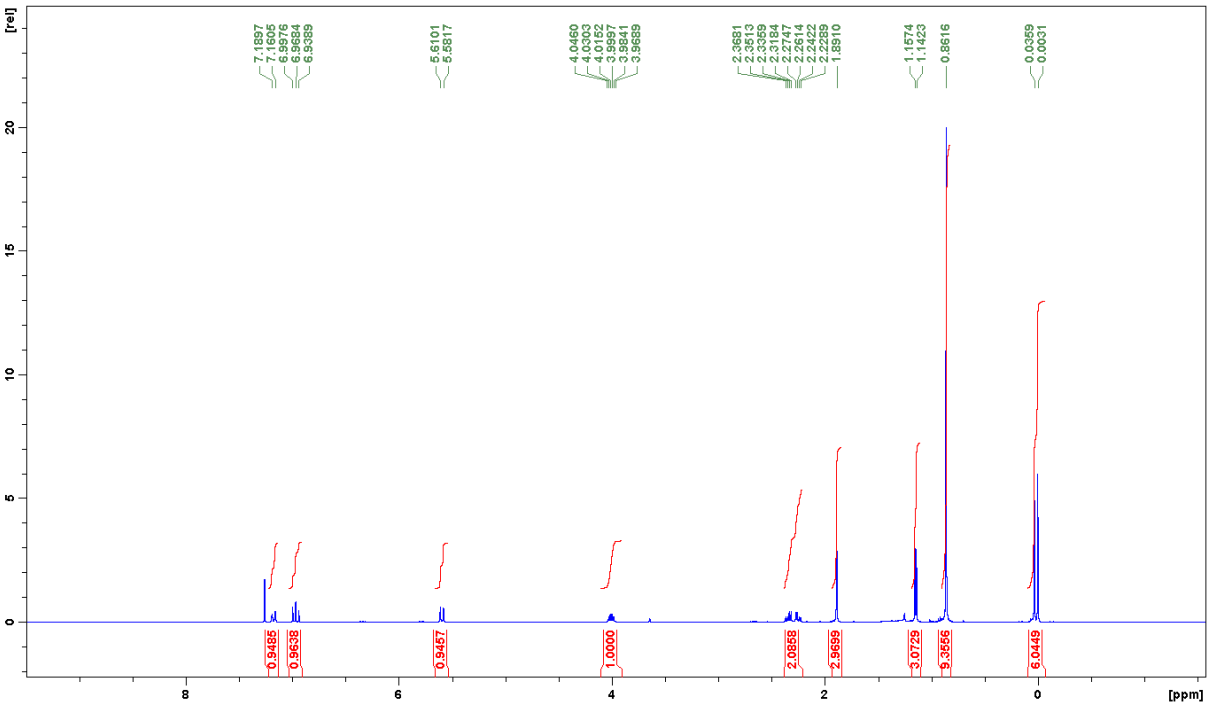
137.1610
127.2181
120.0971
14.0869


Me
TBSO
COOH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7.1605
6.9976
6.9684
6.9389
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5.5817
4.0460
4.0303
4.0152
3.9997
3.9841
3.9689
2.3681
2.3513
2.3359
2.3184
2.2747
2.2614
2.2422
2.2289
1.8910
1.1574
1.1423
0.8616
0.0359
0.0031
0.9485
0.9638
0.9457
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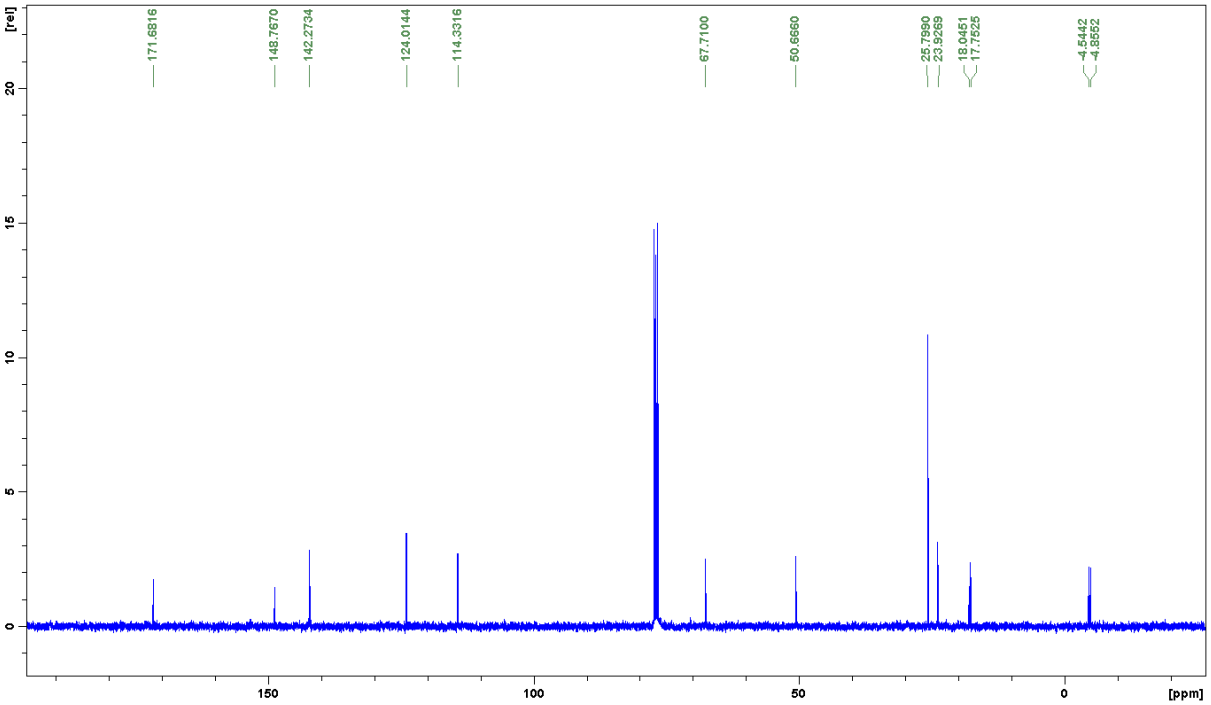
2.0859
2.9659
3.0729
9.3556
6.0449
[ppm]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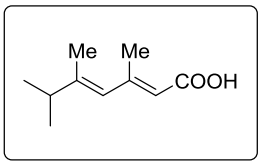
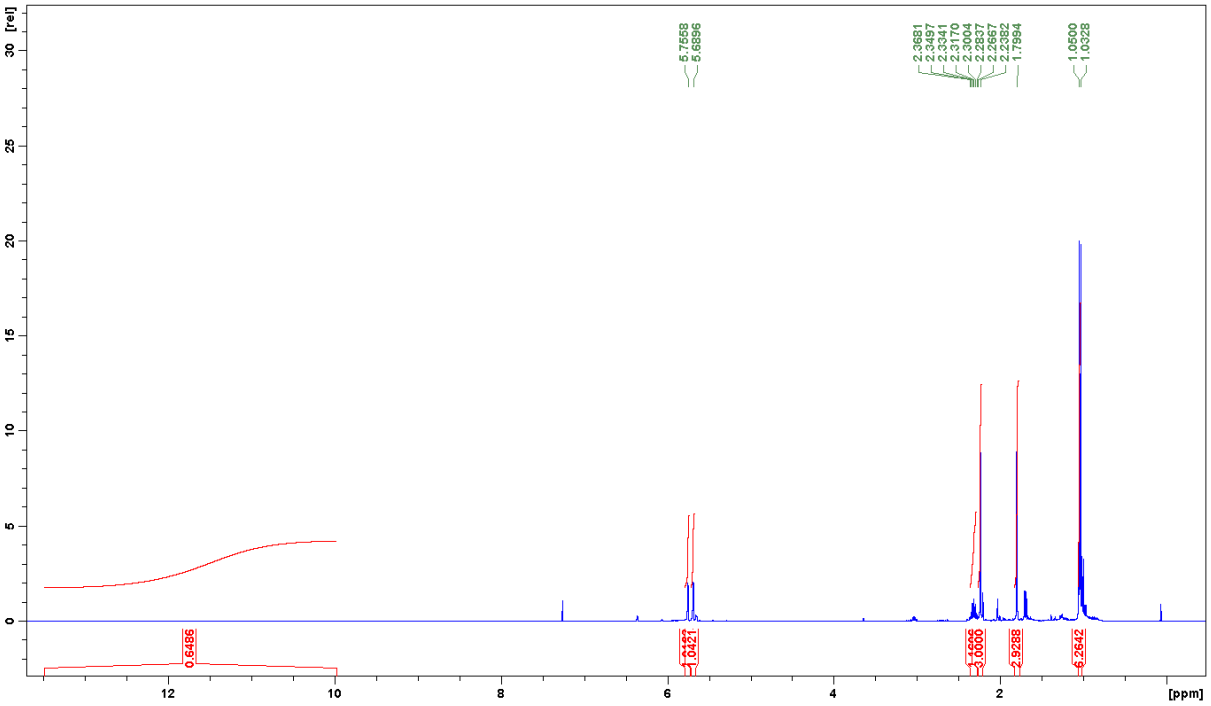
148.7670
142.2734
124.0144
114.3316
67.7100
50.6660
25.7990
23.9269
18.0451
17.7525
-4.5442
-4.8552
[ppm]


Me
Me
COOH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5.6896
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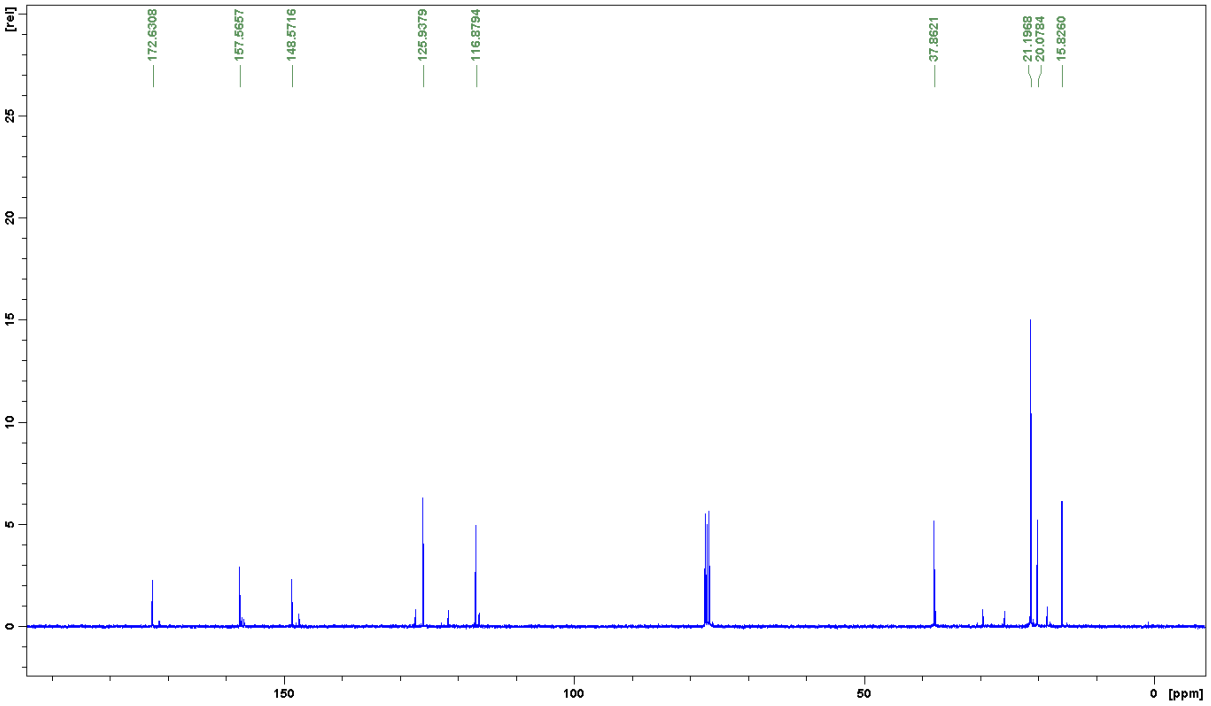
2.3437
2.3341
2.3170
2.3004
2.2837
2.2667
2.2382
1.7994
1.0500
1.0328
0.6486
1.0421
1.0421
1.1666
3.0000
2.9288
6.2642
[ppm]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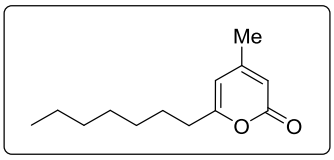
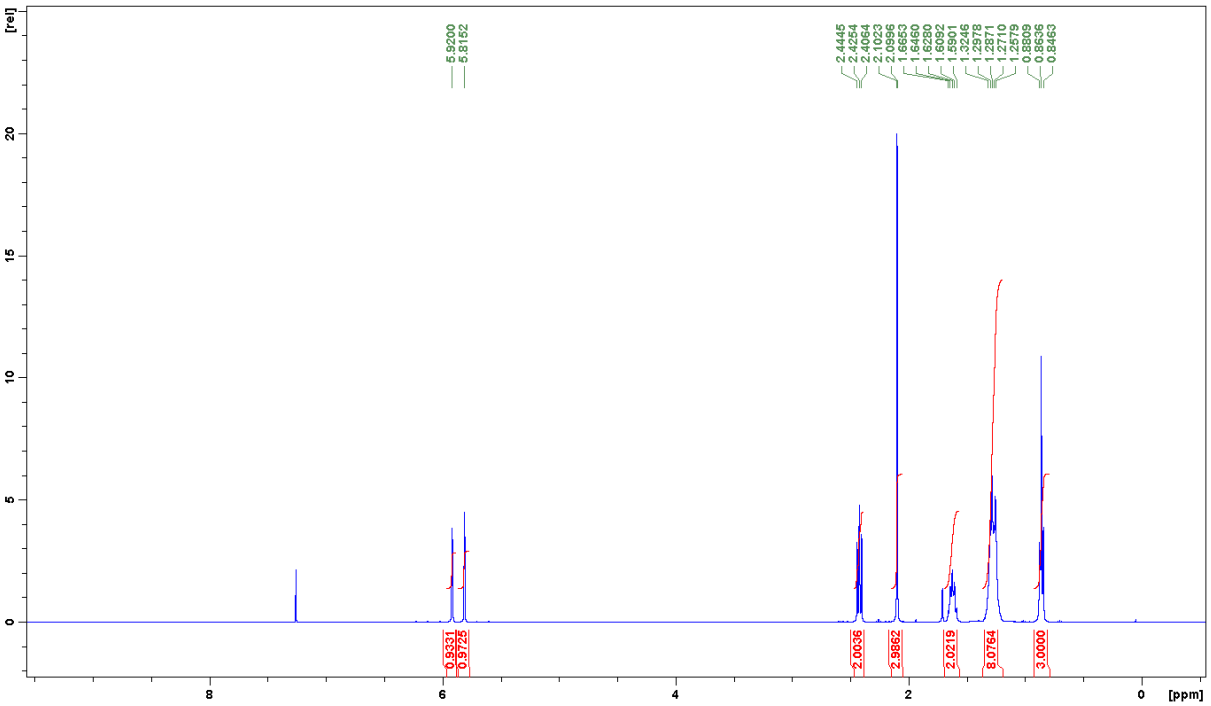

Me
O
O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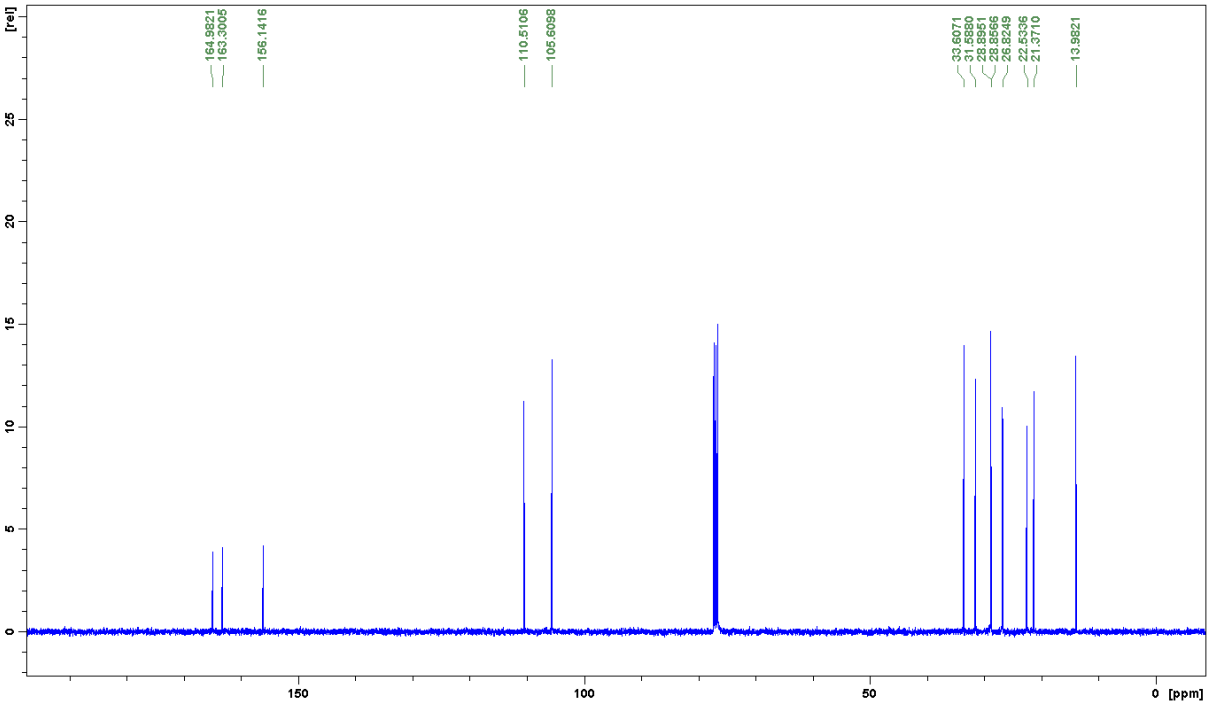
2.4064
2.1023
2.0996
1.6653
1.6450
1.6280
1.6092
1.5901
1.3246
1.2978
1.2871
1.2710
1.2573
0.8809
0.8636
0.8463
0.9331
0.9725
2.0036
2.9862
2.0219
8.0764
3.0000
[ppm]


[rel]
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163.3005
156.1416
110.5106
105.6098
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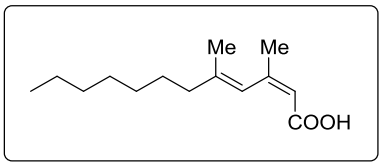
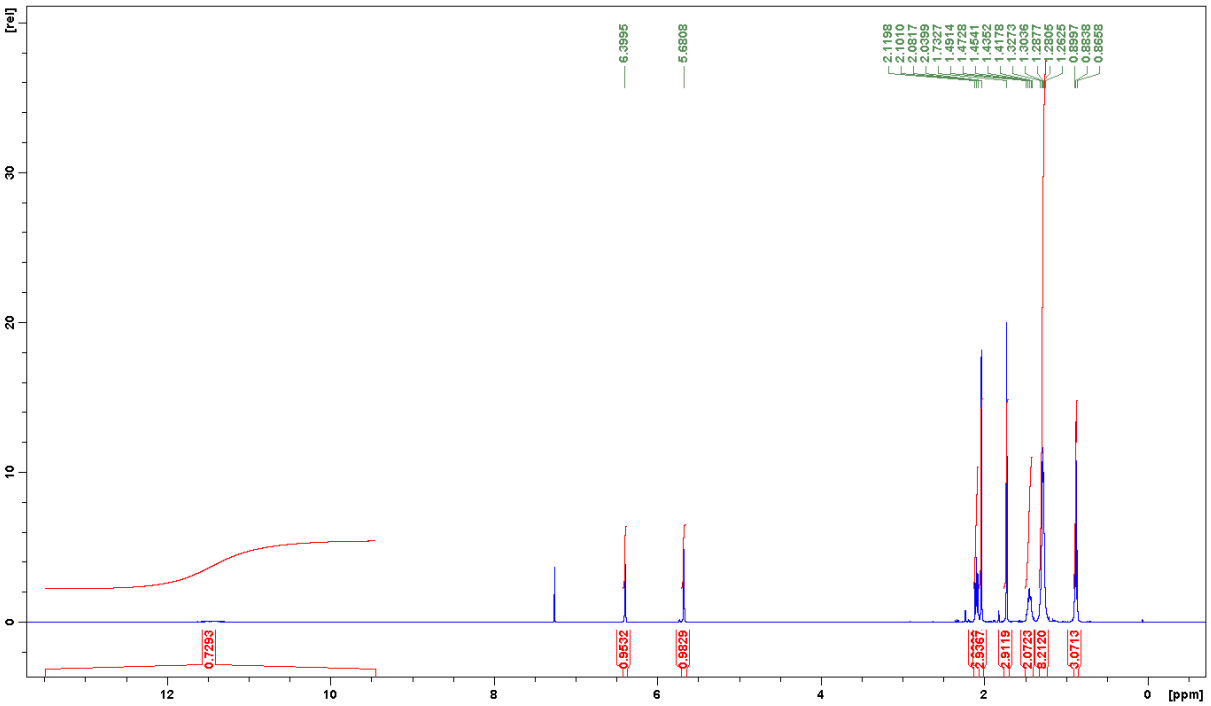
31.5880
28.8951
28.8566
26.8249
22.5336
21.3710
13.9821
[ppm]


Me
Me
COOH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5.6808
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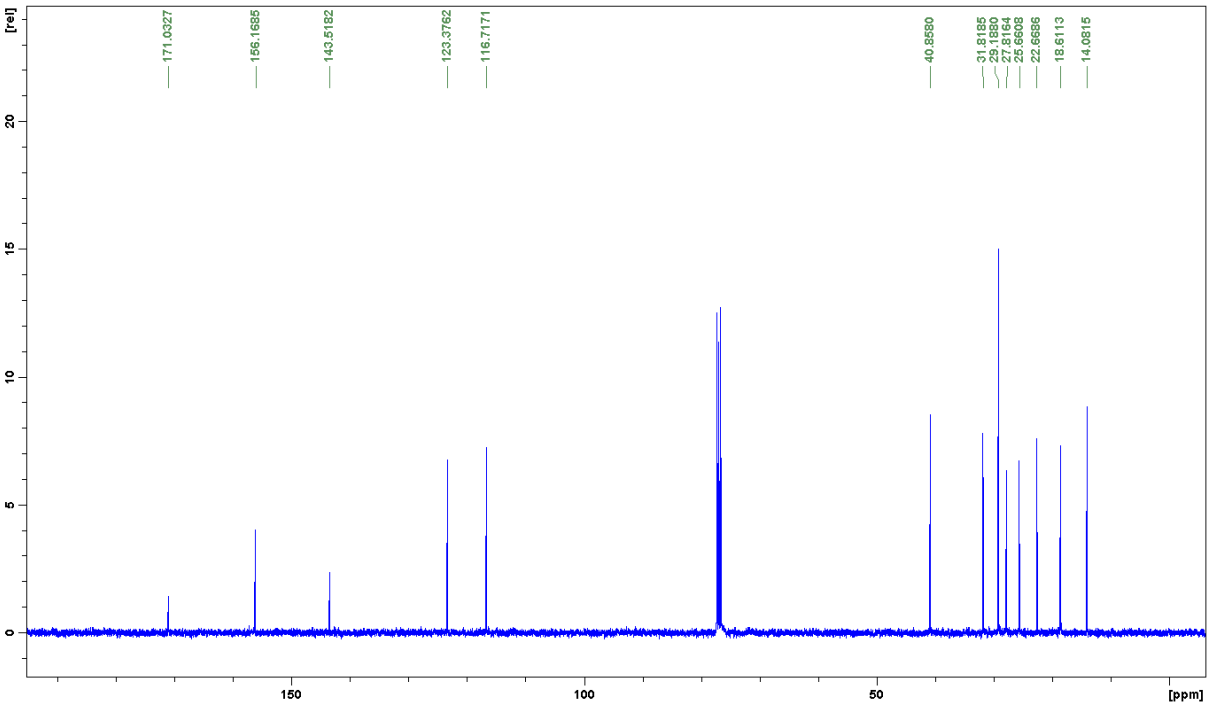
2.1010
2.0817
2.0399
1.7327
1.4914
1.4728
1.4541
1.4352
1.4173
1.3273
1.3036
1.2877
1.2805
1.2625
0.8997
0.8838
0.8658
0.7293
0.9532
0.9829
2.9367
2.9119
2.0723
6.2120
3.0713
[ppm]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116.7171
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29.1880
27.8164
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22.6686
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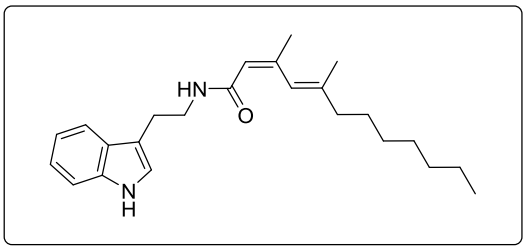
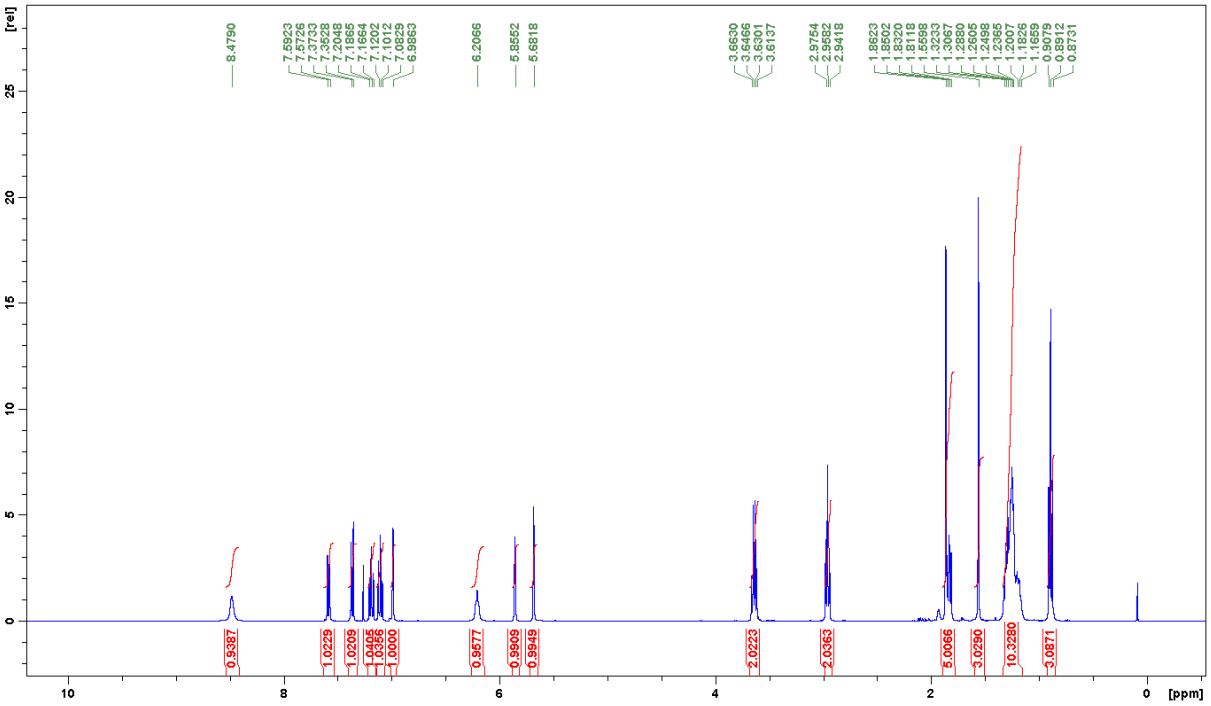
14.0815
[ppm]


HN
O
N
H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7.1664
7.1202
7.1012
7.0829
6.9863
6.2066
5.8552
5.6818
3.6530
3.6466
3.6301
3.6137
2.9754
2.9582
2.9418
1.8623
1.8502
1.8320
1.8118
1.5598
1.3233
1.3067
1.2880
1.2695
1.2508
1.2365
1.2007
1.1826
1.1659
0.9079
0.8912
0.8731
0.9387
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1.0209
1.0406
1.0366
1.0000
0.9577
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0.9949
2.0223
2.0363
5.0066
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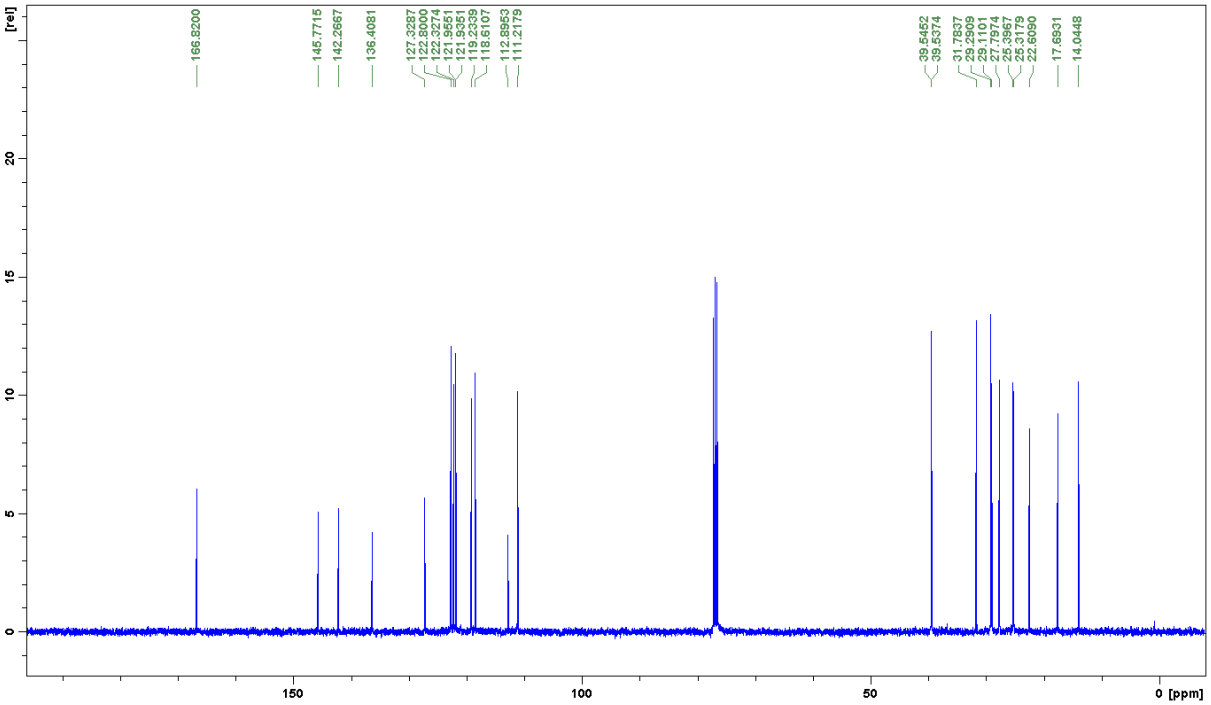
3.0871
[ppm]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145.7715
142.2667
136.4081
127.3287
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112.8953
111.2179
39.5452
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29.2909
29.1101
27.7974
25.3967
25.3179
22.6090
17.6931
14.0448
[ppm]