Supporting information

Synthesis of α-Keto Aldehydes via Selective Cu(I)-catalyzed Oxidation of α-Hydroxy Ketones

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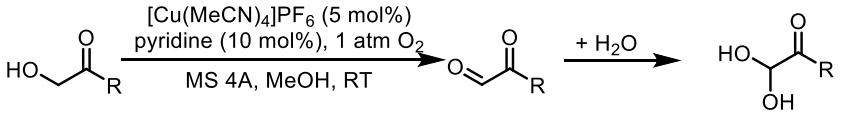
Contents

General Considerations

Commercially available reagents were purchased from Sigma-Alrich, TCI, Strem, or abcr. Solvents used as reaction medium were obtained from Acros Organics and passed through a solvent purification system (MBraun SPS). All solvents used for work-up or column chromatography were purchased from Walter. Neutral NaEDTA solutions were prepared by neutralizing a solution of EDTA in water with NaOH to pH 7. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a 300 MHz or 400 MHz spectrometer (Bruker). Chemical shifts are given in ppm and related to residual solvent peaks.[1] High resolution mass spectroscopy was performed on an Agilent 6210 Time-of-Flight (SICRIT ionization, 15 kHz, 1600 V) or a Thermo Electron MAT 95-XP (EI, 70 eV) apparatus. ATR-IR was measured on a Brucker IR alpha. X-ray diffraction data were collected on a Bruker Kappa APEX II Duo diffractometer. The structure was solved by direct methods (SHELXS-97[2]) and refined by full-matrix least-squares procedures on F^2 (SHELXL-2018[3]). XP (Bruker AXS) was used for graphical representations.

Cu-catalyzed selective oxidation of α-hydroxy-ketones



General Procedure

Unless otherwise mentioned, the preparation of all α-keto aldehydes was performed according to the following procedure: a Schlenk flask was charged with α-hydroxy-ketone (0.50 mmol), $[Cu(MeCN)_4]PF_6$ (5 mol%, 9.0 mg, 0.024 mmol), MS 4A (100 mg), and a magnetic stirring bar. The flask was evacuated for 30 min, brought under a static vacuum, and then charged with oxygen gas from a balloon. Subsequently, dry MeOH (4 mL) and pyridine (10 mol%, 4 µL) were added, and the reaction mixture was stirred at room temperature for 30 min. After the α-hydroxy-ketone had completely converted (the reaction was followed by TLC), the balloon was removed and any remaining oxygen gas was purged from the flask. To isolate the desired product the reaction mixture was henceforth subjected to purification via either purification A or B.

Purification A

The reaction mixture was filtered through filter paper to remove molecular sieves. The obtained solution was diluted with 50 mL dichloromethane (DCM), and then washed with aque-

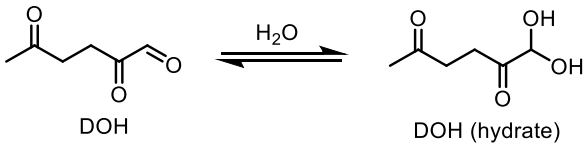
ous NaEDTA solution (0.1%, 10 mL) and brine (10 mL). The organic layer was first dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo*, and thereafter hot water (2 mL) was added to the crude product. After stirring at 100 °C for 10 mins the solution was filtered while being hot. Removal of the water *in vacuo* yielded the desired product.

Purification B

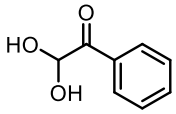
The reaction mixture was filtered through a short pad of silica to remove the molecular sieves and Cu-based catalyst. After removal of the solvent *in vacuo*, the crude product was further purified through column chromatography (silica).

Experimental Data

Most of the obtained α-keto aldehydes were found to be difficult to detect with HRMS (ESI or EI), only compound **4i** afforded a spectrum. In addition, with SICRIT-HRMS the mass spectrum of **4b** was obtained.

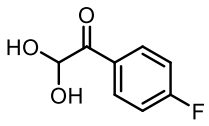


2,5-dioxohexane-1,1-diol (DOH-hydrate). From 1-hydroxyhexane-2,5-dione (**HHD**, 1.0 mmol), using purification B with MeOH/DCM (1:99) as eluent, 112.7 mg (87%) of light yellow-oil was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 4.78 (s, 1H), 3.35 (s, 2H), 2.81-2.87 (m, 2H), 2.72-2.77 (m, 2H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 209.8, 206.9, 98.5, 37.3, 32.1, 29.7. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3411, 2917, 1708, 1407, 1357, 1167, 1076, 978, 835, 538, 416. Anal. Calcd for $C_6H_8O_3$ (aldehyde-form): C, 56.25; H, 6.29. Found: C, 56.12; H, 6.85.



2,2-dihydroxy-1-phenylethan-1-one (4a). From 2-hydroxyacetophenone (**2a**, 1.0 mmol), using purification A, 112 mg (74%) of white solid **4a** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 8.09–8.05 (m, 2H), 7.65–7.60 (m, 1H), 7.54–7.48 (m, 2H), 5.55 (s, 1H). ^{13}C NMR (75 MHz, MeOH- d_4) δ (ppm) 195.7, 135.1, 134.8, 130.5, 129.6, 96.4. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3395, 3351, 1694, 1595, 1445, 1304, 1220, 1109, 1075, 1034, 1022, 1000, 962,

928, 842, 836, 714, 683, 659, 629, 563. The recorded ^{1}H NMR spectrum is in agreement with the one found in literature.[4]



1-(4-fluorophenyl)-2,2-dihydroxyethan-1-one (4b). From 4´-fluoro-2-hydroxyacetophenone (**2b**, 1 mmol), using purification A, 114 mg (75%) of white solid **4b** was obtained. Needle-shaped crystals suitable for X-ray structure analysis were obtained at room temperature, in two days, by layering 2 mL of *n*-pentane over a solution of 10 mg of **4b** in 1 mL acetonitrile. The molecular structure and relevant bond lengths and angles are shown in Figure S1, the refinement parameters in Table S1. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 8.19–8.12 (m, 2H), 7.27–7.19 (m, 2H), 5.49 (s, 1H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 194.3, 167.4 (d, $^{1}J_{C\text{-}F}$ = 254.0 Hz), 133.6 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 131.6, 116.6 (d, $^{2}J_{C\text{-}F}$ = 22.3 Hz), 96.9. ^{19}F NMR (376.5 MHz, MeOH-d_4) δ (ppm) 106.62. HRMS–SICRIT (*m/z*): $[M(diol)\text{-}O+NH_2]^+$ calcd for $C_8H_9FNO_2$ 170.0612; found: 170.0612, $[M(aldehyde)+H]^+$ calcd for $C_8H_6FO_2$ 153.0346; found: 153.0347. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3409, 3371, 1694, 1598, 1508, 1420, 1408, 1298, 1215, 1159, 1113, 1095, 1026, 966, 947, 864, 822, 807, 727, 683, 603, 570. Anal. Calcd for $C_8H_7FO_3$ (hydrate-form): C, 56.48; H, 4.15. Found: C, 56.20; H, 4.10. The recorded ^{1}H NMR spectrum agrees with the one found in literature.[4]

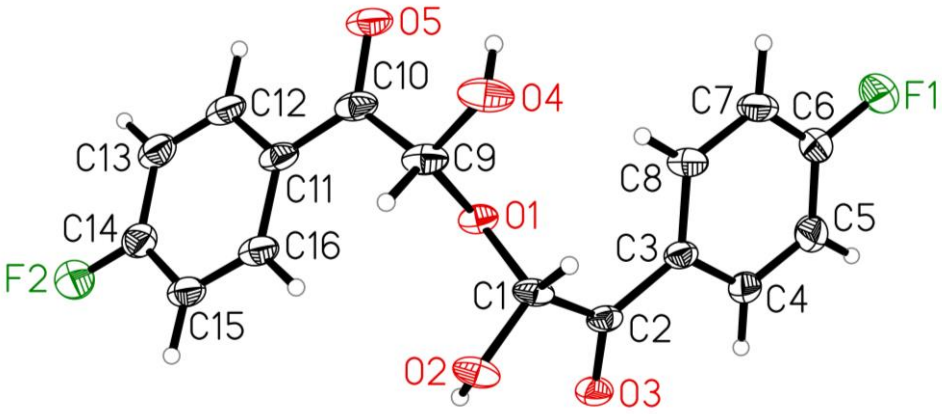
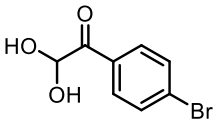


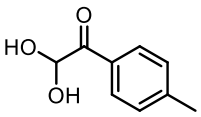
Figure S1. Molecular structure of **4b** with displacement ellipsoids drawn at the 30% probability level. Selected geometrical parameters:

Table S1. Crystal and structure refinement data for **4b**.

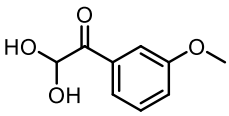
Crystal data	
Chemical formula	$C_{16}H_{12}F_2O_5$
M_r	322.26
Crystal system	monoclinic
Space group	$P2_1/n$
a, *b*, *c* (Å)	17.6167(6), 4.4608(2), 18.2426(6)
β (°)	94.5580(19)
V (Å^3)	1429.05(9)
Z	4
T (K)	150(2)
λ (Å)	1.54178
No. meas. refl.	10907
No. indep. refl.	2527
R_{int}	0.0258
R ($I > 2\sigma(I)$)	0.0333
wR_2 (all data)	0.0914



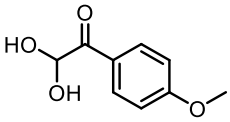
1-(4-bromophenyl)-2,2-dihydroxyethan-1-one (4c). From 1-(4-bromophenyl)-2-hydroxyethan-1-one (**2c**), using purification A, 91 mg (79%) of white crystals of **4c** were obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 8.00–7.96 (m, 2H), 7.70–7.66 (m, 2H), 5.47 (s, 1H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 194.9, 134.0, 132.9, 132.3, 129.7, 97.0. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3421, 3370, 2972, 2518, 1693, 1582, 1563, 1396, 1280, 1222, 1122, 1072, 1025, 1011, 976, 965, 950, 860, 851, 807, 735, 706, 669, 575. The recorded NMR spectra agree with those found in literature.[5]



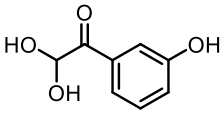
2,2-dihydroxy-1-(*p*-tolyl)ethan-1-one (4d). From 2-hydroxy-1-(*p*-tolyl)ethan-1-one (**2d**), using purification A, 68 mg (82%) of white solid **4d** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.96 (m, 2H), 7.32 (m, 2H), 5.53 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 195.4, 146.2, 132.5, 130.7, 130.3, 96.3, 21.7. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3395, 3341, 1686, 1605, 1224, 1208, 1187, 1107, 1032, 963, 951, 857, 846, 807, 787, 734, 722, 692, 648, 634, 603, 560. The recorded ^{1}H NMR spectra agree with those found in literature.[4]



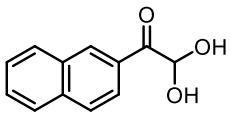
2,2-dihydroxy-1-(3-methoxyphenyl)ethan-1-one (4e). From 2-hydroxy-1-(3-methoxyphenyl)ethan-1-one (**2e**), using purification A, 67 mg (74%) of yellow solid **4e** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.63 (ddd, J = 7.6, 1.5, 1.0 Hz, 1H), 7.55 (dd, J = 2.7, 1.5 Hz, 1H), 7.39 (dd, J = 8.0, 7.9 Hz, 1H), 7.16 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 5.53 (s, 1H), 3.81. ^{13}C-NMR (75 MHz, MeOH-d_4) δ (ppm) 195.5, 161.1, 136.2, 130.7, 123.0, 120.9, 114.9, 96.3, 55.9. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3399, 2940, 2836, 1687, 1596, 1581, 1487, 1456, 1430, 1257, 1204, 1176, 1101, 1037, 989, 882, 783, 699, 679, 614, 564. Anal. Calcd for $C_{18}H_{18}O_7$ (dimer-form): C, 62.42; H, 5.24. Found: C, 62.70; H, 5.18. The recorded ^{1}H NMR spectra agree with those found in literature.[4]



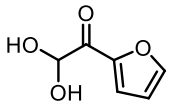
2,2-dihydroxy-1-(4-methoxyphenyl)ethan-1-one (4f). From 2-hydroxy-1-(4-methoxyphenyl)ethan-1-one (**2f**), using purification A, 49 mg (54%) of white solid **4f** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 8.06 (m, 2H), 7.02 (m, 2H), 5.51 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 194.3, 165.8, 133.0, 127.8, 114.9, 96.2, 56.1. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3432, 3416, 1678, 1596, 1509, 1445, 1407, 1310, 1285, 1253, 1170, 1101, 994, 971, 862, 841, 822, 796, 755, 737, 613, 635, 595, 568, 546, 523, 503, 432. Anal. Calcd for $C_9H_8O_3$ (aldehyde-form): C, 65.85; H, 4.91. Found: C, 65.98; H, 4.65. The recorded ^{1}H NMR spectra agree with those found in literature.[4]



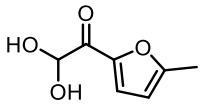
2,2-dihydroxy-1-(3-hydroxyphenyl)ethan-1-one (4g). From 2-hydroxy-1-(3-hydroxyphenyl)ethan-1-one (**2g**), using purification B with ethyl acetate/cyclohexane (1:4) as eluent, 57 mg (68%) of white solid **4g** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.53 (ddd, J = 7.7, 1.6, 1.0 Hz, 1H), 7.46 (ddd, J = 2.6, 1.6, 0.5 Hz, 1H), 7.32 (ddd, J = 8.2, 7.7, 0.4 Hz, 1H), 7.05 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 5.50 (s, 1H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 195.6, 158.9, 136.4, 130.7, 122.0, 121.8, 116.6, 96.2. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3338, 2071, 1686, 1584, 1478, 1450, 1283, 1236, 1193, 1110, 1077, 1018, 989, 883, 816, 783, 757, 702, 677.



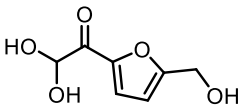
2,2-dihydroxy-1-(naphthalen-2-yl)ethan-1-one (4h). From 2-hydroxy-1-(naphthalen-2-yl)-ethan-1-one (**2h**), using purification A, 73 mg (72%) of white solid **4h** was obtained. ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm) 8.70 (d, J = 1.7 Hz, 1H), 8.06 (m, 2H), 7.94 (m, 2H), 7.65 (m, 1H), 7.59 (m, 1H), 5.70 (s, 1H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 195.8, 137.3, 133.9, 133.0, 132.3, 130.8, 130.0, 129.4, 128.8, 128.0, 125.5, 96.6. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3407, 3365, 2361, 2342, 1691, 1624, 1593, 1507, 1467, 1436, 1387, 1355, 1296, 1268, 1249, 1210, 1038, 1017, 993, 970, 956, 940, 913, 822, 798, 767, 746, 725, 712, 668, 640, 629, 613, 556. The recorded ^{1}H NMR spectra agree with those found in literature.[4]



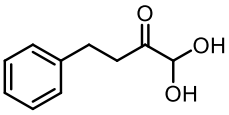
1-(furan-2-yl)-2,2-dihydroxyethan-1-one (4i). From 1-(furan-2-yl)-2-hydroxyethan-1-one (**2i**), using purification A, 53 mg (75%) of yellow oil **4i** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.84 (dd, J = 1.7, 0.7 Hz, 1H), 7.50 (dd, J = 3.6, 0.7 Hz, 1H), 6.67 (dd, J = 3.6, 1.7 Hz, 1H), 5.34 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4) δ (ppm) 184.8, 151.4, 149.5, 122.3, 113.5, 96.4. HRMS–EI (*m/z*): [M]$^{+}$ calcd for $C_6H_4O_3$ 124.0155; found: 124.0156. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3406, 3339, 3130, 1664, 1560, 1460, 1388, 1264, 1127, 1111, 1083, 1067, 1037, 1026, 1015, 966, 910, 981, 851, 842, 821, 771, 756, 710, 614, 589, 571. Anal. Calcd for $C_6H_6O_4$ (hydrate-form): C, 50.71; H, 4.26. Found: C, 50.06; H, 4.03. The recorded ^{1}H NMR spectra agree with those found in literature.[6]



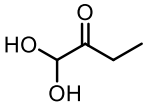
2,2-dihydroxy-1-(5-methylfuran-2-yl)ethan-1-one (4j). From 2-hydroxy-1-(5-methylfuran-2-yl)ethan-1-one (**2j**), using purification A, 58 mg (74%) of yellow oil **4j** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.44 (m, 1H), 6.34 (m, 1H), 5.33 (s, 1H), 2.42 (t, J = 0.7 Hz, 3H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 184.0, 161.0, 150.2, 124.6, 110.4, 96.2, 13.8. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3370, 2921, 1713, 1651, 1507, 1366, 1260, 1207, 1022, 801, 426, 409.



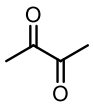
2,2-dihydroxy-1-(5-(hydroxymethyl)furan-2-yl)ethan-1-one (4k). From 2-hydroxy-1-(5-(hydroxymethyl)furan-2-yl)ethan-1-one (**2k**), using purification B without performing column chromatography, 64 mg (74%) of yellow oil **4k** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.46 (m,1H), 6.55 (m, 1H), 5.33 (s, 1H), 4.61 (s, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 184.6, 162.5, 150.8, 123.6, 110.6, 96.4, 57.6. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3367, 2925, 1665, 1584, 1514, 1383, 1300, 1202, 1119, 1016, 912, 806, 754, 578, 504.



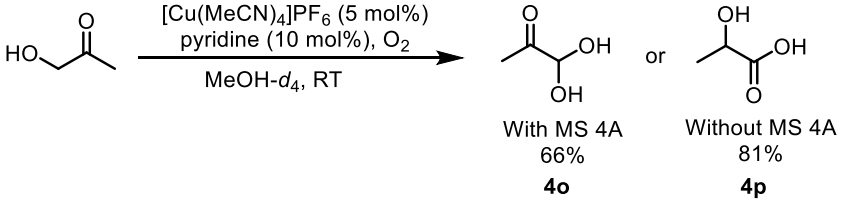
1,1-dihydroxy-4-phenylbutan-2-one (4l). From 1-hydroxy-4-phenylbutan-2-one (**2l**), using purification B with ethyl acetate/cyclohexane (3:17) as eluent, 42 mg (52%) of a light-yellow oil **4l** was obtained. ^{1}H-NMR (300 MHz, MeOH-d_4) δ (ppm) 7.21 (m, 5H), 4.70 (s, 1H), 2.90 (m, 4H). ^{13}C-NMR (75 MHz, MeOH-d_4) δ (ppm) 207.2, 142.5, 129.4, 129.3, 127.0, 98.7, 39.6, 30.0. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3412, 3026, 2931, 1726, 1603, 1496, 1454, 1400, 1281, 1029, 982, 748, 697, 557, 497.



1,1-dihydroxybutan-2-one (4m). A 25 mL Schlenk flask was charged with [Cu(MeCN)$_4$]PF$_6$ (5 mol%, 9.0 mg, 0.024 mmol), MS 4A (100 mg), and a magnetic stirring bar. The flask was evacuated for 30 min, brought under a static vacuum, and then charged with an oxygen gas from a balloon. Subsequently, MeOH-d_4 (4 mL), 1-hydroxybutan-2-one (**2m**, 0.5 mmol, 43 µL), and pyridine (10 mol%, 4 µL) were added and the reaction mixture was stirred at room temperature for 30 min. The balloon was removed after the reaction had finished and any remaining oxygen gas was purged from the flask. Then, EDTA (10 mg) was added, and the reaction mixture was stirred at room temperature for 5 mins. To an aliquot of the reaction mixture internal standard (1,4-dinitrobenzene) was added; ^{1}H NMR analysis of the solution indicated that **4m** was obtained with 57% yield. Because of its relatively low boiling point and its tendency to form polymers upon concentration, an isolated yield of **4o** could not be obtained.[7] ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 4.73 (s, 1H), 2.61 (m, 2H), 1.35 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, MeOH-d_4) δ (ppm) 208.7, 98.6, 31.0, 7.4.

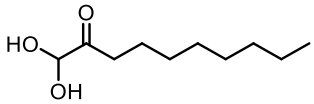


Diketone (4n). 2,3-butanediol (**2n**, 1.00 g, 11.1 mmol) was oxidized according to the general procedure. After maximum conversion was reached the reaction mixture was filtered through filter paper. The filtrate was subsequently diluted with aqueous NaEDTA solution (1%, 100 mL) and extracted DCM (3 x 500 mL). Then, the organic layers were combined and dried over anhydrous $MgSO_4$. The resulting solution was concentrated under reduced pressure (800 bar, 37 °C) to 30 mL. The remaining solvents (DCM and MeOH) were removed through distillation (40–100 °C), yielding **4n** as an orange oil (655 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 197.3, 23.5.



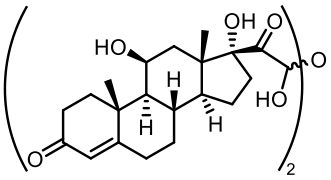
1,1-dihydroxypropan-2-one (4o). From hydroxyacetone (**2o**, 0.5 mmol, 35 µL), using the same method as for product **4m**, **4o** was obtained with 66% yield (det. ^{1}H NMR, *vs.* 1,4-dinitrobenzene). Because of its relatively low boiling point and its tendency of to form polymers upon concentration an isolated yield of **4o** could not be obtained.[7-12] ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 4.70 (s, 1H), 2.17 (s, 3H). The recorded NMR spectrum agrees with that found in literature.[13]

2-hydroxypropanoic acid (4p). From hydroxyacetone (**2p**, 0.5 mmol, 35 µL), using the same method as for product **4m** without adding any molecular sieve, **4p** was obtained with 81% yield (det. ^{1}H NMR,*vs.* 1,4-dinitrobenzene). ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm) 4.25 (q, J = 6.9 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H). The recorded NMR spectrum agrees with that found in literature.[14]



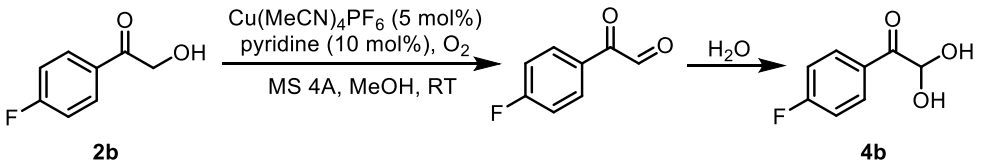
1,1-dihydroxydecan-2-one (4q). From 1-hydroxydecan-2-one (**2q**), using purification B with ethyl acetate/cyclohexane (1:9) as eluent, 31 mg (46%) of colorless oil **4q** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 4.71 (s, 1H), 2.68–2.48 (m, 2H), 2.27 (t, J = 7.3 Hz, 1H),

1.60–1.51 (m, 2H), 1.36–1.26 (m, 10 H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C-NMR (75 MHz, MeOH-d_4) δ (ppm) 208.2, 98.7, 37.8, 33.0, 30.5, 30.3, 24.1, 23.7, 14.4. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 2954, 2922, 2853, 1709, 1465, 1409, 1377, 1070, 987, 722, 467.



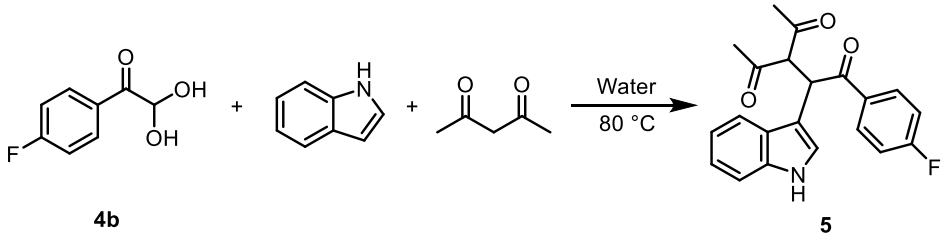
11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-al (4r, mixture of isomers). From hydrocortisone (**2r**), using purification B with ethyl acetate/cyclohexane (1:1) as eluent, 132 mg (73%) of colorless oil **4r** was obtained. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 5.66 (d, J = 1.65 Hz, 1H), 5.20 (d, J = 43.5 Hz, 1H), 4.40–4.37 (m, 1H), 2.73–2.63 (m, 1H), 2.57–2.44 (m, 2H), 2.35–2.18 (m, 3H), 2.09–1.94 (m, 3H), 1.92–1.85 (m, 1H), 1.84–1.66 (m, 3H), 1.57–1.37 (m, 5H), 1.20–1.09 (m, 1H), 1.02–0.97 (m, 1H), 0.92 (d, J = 5.5 Hz, 3H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 207.5, 207.2, 202.4, 176.6, 176.5, 122.5, 94.5, 93.7, 90.0, 89.8, 68.8, 68.6, 57.5, 53.5, 53.1, 49.8, 49.2, 48.7, 40.8, 40.6, 35.8, 35.0, 34.6, 34.3, 34.1, 33.3, 32.8, 32.8, 24.5, 21.4, 18.0, 17.6. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3404, 2926, 2360, 1716, 1650, 1449, 1389, 1338, 1271, 1233, 1187, 1109, 1053, 969, 948, 933, 894, 845, 800, 739, 699, 645, 556, 525, 504, 419. Anal. Calcd for $C_{42}H_{58}O_{11}$ (dimer-form): C, 68.27; H, 7.91. Found: C, 68.18; H, 8.22.

Scale-up Oxidation of 4'-Fluoro-2-Hydroxyacetophenone (2b)



A 1 L Schlenk flask was charged with 4'-fluoro-2-hydroxyacetophenone (**2b**, 64.9 mmol, 10.0 g), a magnetic stirring bar, MS 4A (6.5 g), and $Cu(MeCN)_4PF_6$ (5 mol%, 1.2 g, 3.22 mmol). The flask was evacuated for 1h, brought under a static vacuum, and then charged with an oxygen gas from a balloon. Subsequently, dry MeOH (470 mL) and pyridine (10 mol%, 524 µL, 6.51 mmol) were added, and the reaction mixture was stirred at room temperature for 100 min. After the reaction had finished, the balloon was removed and any remaining oxygen gas was purged from the flask. The reaction mixture was filtered, diluted with DCM (1000 mL) and washed with aqueous NaEDTA solution (1.0%, 100 mL) followed by brine (100 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. Afterwards, hot water (80 mL) was added to the crude product and the solution was stirred for 10 min at 100 °C. Following hot filtration over filter paper, the aqueous solution was left to stand at 8 °C overnight. After this time, white crystals of **4b** (7.4 g, 67%) were collected by filtration.

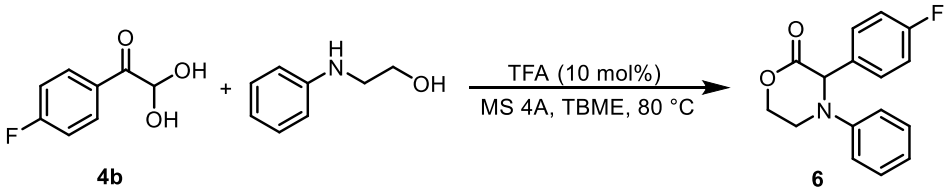
Reaction of 4b with Indole and Acetylacetone



3-acetyl-1-(4-fluorophenyl)-2-(1H-indol-3-yl)pentane-1,4-dione (5). A 4 mL tube was charged with 1-(4-fluorophenyl)-2,2-dihydroxyethan-1-one (**4b**, 1.00 mmol, 170 mg), indole (1.00 mmol, 117 mg), water (2 mL), a magnetic stirring bar, and acetylacetone (1.00 mmol, 102 µL). The reaction mixture was stirred overnight at 80 °C and subsequently extracted with ethyl acetate (2 x 2 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Flash column chromatography of the crude product with ethyl acetate/hexane (1:4) as eluent gave yellow solid **5** (282 mg, 80%). The procedure followed as reported.[15]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.19 (brs, 1H), 8.02–7.96 (m, 2H), 7.73–7.70 (m, 1H), 7.35–7.29 (m, 1H), 7.23–7.14 (m, 2H), 7.08 (d, *J* = 2.6 Hz, 1H), 7.02–6.95 (m, 2H), 5.62 (d, *J* = 11.1 Hz, 1 H), 5.02 (d, *J* = 11.3 Hz, 1H), 2.31 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 203.7, 202.1, 196.3, 165.7 (d, $^{1}J_{C\text{-}F}$ = 167.40 Hz), 136.5, 132.3 (d, $^{4}J_{C\text{-}F}$ = 2.97 Hz), 131.5 (d, $^{3}J_{C\text{-}F}$ = 9.34 Hz), 125.8, 124.0, 122.9, 120.7, 119.0, 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.91 Hz), 111.7, 109.4, 70.3, 45.4, 31.7, 30.4. HRMS–ESI (*m/z*): calcd. for $[C_{21}H_{18}FNO_3Na]^+$ 374.1163; found: 374.1179. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3381, 2360, 2342, 1723, 1697, 1673, 1594, 1505, 1457, 1411, 1353, 1258, 1238, 1155, 1100, 1011, 989, 956, 844, 817, 795, 744, 668, 602, 561, 531, 505, 463, 428.

Reaction of 4b with 2-(Phenylamino)ethan-1-ol

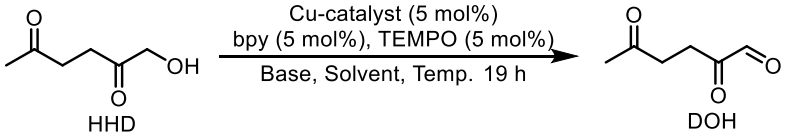


3-(4-fluorophenyl)-4-phenylmorpholin-2-one (6). A 35 mL pressure tube was charged with 1-(4-fluorophenyl)-2,2-dihydroxyethan-1-one (**4b**, 1.1 equiv., 187 mg), MS 4A (300 mg), a magnetic stirring bar, *tert*-butyl methyl ether (8 mL), and 2-(phenylamino)ethan-1-ol (1,0 mmol, 137 mg). The reaction mixture was stirred at 80 °C for 23 hours. After cooling down to room temperature and filtration, the solvent was removed *in vacuo*. Column chromatography of the crude product on silica with ethyl acetate/pentane (1:19) as eluent afforded **6** as yellow solid (259 mg, 96%). The procedure followed as reported.[16]

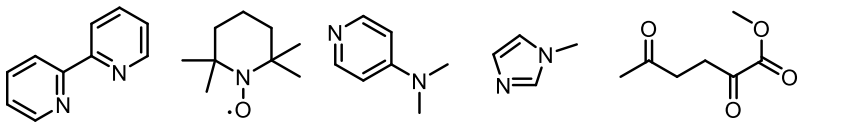
^{1}H NMR (300 MHz, $CDCl_3$) *δ* (ppm) 8.22–8.15 (m, 2H), 7.28–7.16 (m, 4H), 6.83 (dt, *J* = 7.4, 1.05 Hz), 6.53 (d, *J* = 8.7 Hz, 2H), 6.05 (s, 1H), 4.36–4.29 (m, 1H), 4.25–4.18 (m, 1H), 3.81–3.75 (m, 1H), 3.71–3.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 193.3, 166.1 (d, $^{1}J_{C\text{-}F}$ = 255.88 Hz), 145.0, 132.0 (d, $^{3}J_{C\text{-}F}$ = 9.40 Hz), 131.2 (d, $^{4}J_{C\text{-}F}$ = 3.07 Hz), 129.5, 118.5, 116.0 (d, $^{2}J_{C\text{-}F}$ = 21.84 Hz), 113.1, 89.0, 67.0, 47.1. HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{14}FNO_2$ 272.1087; found: 272.1091. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 2921, 2871, 1688, 1592, 1504, 1478, 1411, 1376, 1350, 1333, 1298, 1228, 1195, 1156, 1115, 1068, 1036, 990, 965, 951, 934, 900, 869, 844, 836, 820, 787, 743, 690, 651, 594, 506, 495, 440.

Oxidation of α-hydroxy-ketones under reported conditions

Table S2. Oxidation of HHD via Cu/TEMPO catalyzed oxidation[17, 18]



Entry	Conditions[17, 18]	Results
1	$[Cu(MeCN)_4]BF_4$ (5 mol%), DMAP (10 mol%), MeOH, RT, 19 h	Low conversion and levulinic acid was observed.
2	$[Cu(MeCN)_4]BF_4$ (5 mol%), DMAP (10 mol%), MeOH, 60 °C, 19 h	Low conversion
3	[Cu(MeCN)4]BF_4 (5 mol%), DMAP (10 mol%), MeCN, 60 °C, 19 h	Low conversion and levulinic acid was observed.
4	CuBr (5 mol%), NMI (7 mol%), MeOH, RT, 19 h	Overoxidized product (**MDH** was observed.)
5	$[Cu(MeCN)_4]OTf$ (5 mol%), NMI (7 mol%), MeOH, RT, 19 h	Overoxidized product (**MDH** was observed.)
6	$[Cu(MeCN)_4]BF_4$ (5 mol%), NMI (7 mol%), MeOH, RT, 19 h	Overoxidized product (**MDH** was observed.)
7	$[Cu(MeCN)_4]PF_6$ (5 mol%), NMI (7 mol%), MeOH, RT, 19 h	Overoxidized product (**MDH** was observed.)
8	$CuBr_2$ (5 mol%), NMI (7 mol%), MeOH, RT, 19 h	Overoxidized product (**MDH** was observed.)
9	$Cu(OAc)_2$ (5 mol%), NMI (7 mol%), MeOH, RT, 19 h	Overoxidized product (**MDH** was observed.)
10	$Fe(OAc)_2$ (10 mol%), pyridine (20 mol%), TEMPO (30 mol%), O_2, MeCN, 60 °C	No reaction



General procedure for Table S2 (entry 1-9):

To a 15 mL vial was added Cu-catalyst (5 mol%), bpy (5 mol%, 4 mg), TEMPO (5 mol%, 4 mg), DMAP (10 mol%, 6 mg) or NMI (7 mol%, 3 µL), and solvent (2.5 mL). To the stirred solution was added HHD (0.5 mol, 65 mg). The reaction was stirred at specified solution for 19 hours. The reaction mixture was analyzed through TLC, GC, GC-MS, and NMR. Reaction in entry 10 (Table S2) followed the reported procedure.[18]

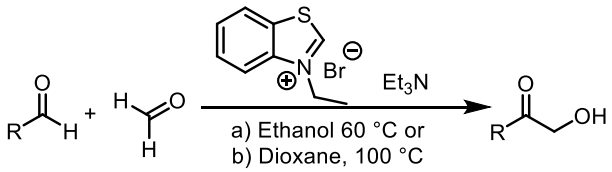
Methyl 2,5-dioxohexanoate (MDH): following the above procedure with 2.0 mmol HHD using $Cu(OAc)_2$ as catalyst in MeOH. After reaction, Column chromatography of the crude product on silica with ethyl acetate/cyclohexane (1:4) as eluent afforded **A** as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.85 (s, 3H), 3.07–3.03 (m, 2H), 2.82–2.78 (m, 2H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 206.1, 192.8, 161.1, 53.1, 37.0, 33.1, 29.7. HRMS–ESI (*m/z*): $[M+Na]^+$ calcd for $C_7H_{10}O_4Na$ 181.0476; found: 181.0476.

Synthetic Details and Characterization Data α-Hydroxy Ketones

General Procedure

The synthesis of the α-hydroxy ketones is described below and in general follows the procedure previously reported in literature.[19]

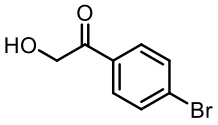


Procedure C: to a 35 mL pressure tube paraformaldehyde (1.0 equiv., 300 mg, 9.99 mmol), 3-ethylbenzothiazolium bromide (10 mol%, 240 mg, 0.983 mmol), ethanol (10 mL), Et_3N (10 mol%, 140 µL, 1.00 mmol), and a magnetic stirring bar were added. Subsequently, 10 mmol of aldehyde was added to the solution. The reaction mixture was stirred at 60°C for 1 day.

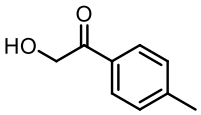
Procedure D: to a 35 mL pressure tube paraformaldehyde (1.0 equiv. 300 mg, 9.99 mmol), 3-ethylbenzothiazolium bromide (10 mol%, 240 mg, 0.983 mmol), dioxane (10 mL), Et_3N (10 mol%, 140 µL, 1.00 mmol), and a magnetic stirring bar were added. Subsequently, 10 mmol aldehyde was added to the solution. The reaction mixture was stirred at 100°C for 2 days.

For both procedures: After cooling down to room temperature the solvent was removed *in vacuo*. After this, the residue was dissolved in ethyl acetate (80 mL), washed with distilled water (2 x 80 mL) and brine (2 x 80 mL). The organic layer was dried over anhydrous Na_2SO_4 followed by removal of the solvent *in vacuo*. To obtain the pure product, the residue was purified by a flash column chromatography.

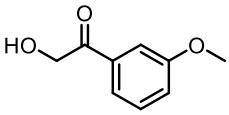
Experimental Data



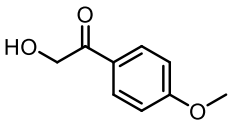
1-(4-bromophenyl)-2-hydroxyethan-1-one (2c). Procedure C with 4-bromobenzaldehyde followed by purification on silica with ethyl acetate/cyclohexane (1:1) yielded a white solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.89–7.85 (m, 2H), 7.71–7.67 (m, 2H), 4.87 (s, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 199.3, 134.6, 133.2, 130.5, 129.6, 66.5. The recorded NMR spectra agree with those found in literature.[20]



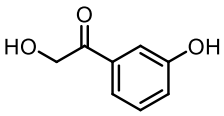
2-hydroxy-1-(*p*-tolyl)ethan-1-one (2d). Procedure C with 4-methylbenzaldehyde followed by purification on silica with ethyl acetate/cyclohexane (3:22) yielded a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.84–7.80 (m, 2H), 7.32–7.28 (m, 2H), 4.85 (d, J = 4.6 Hz, 2H), 3.52 (t, J = 4.7 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 198.1, 145.5, 131.0, 129.7, 127.9, 66.4, 21.9. The recorded NMR spectra agree with those found in literature.[20]



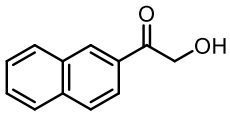
2-hydroxy-1-(3-methoxyphenyl)ethan-1-one (2e). Procedure C with 3-methoxybenzaldehyde followed by purification on silica with ethyl acetate/cyclohexane (3:17) yielded a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47–7.43 (m, 2H), 7.39 (dd, J = 8.0, 8.0 Hz, 1H), 7.15 (ddd, J = 8.0, 2.6, 1.3 Hz, 1H), 4.85 (s, 2H), 3.85 (s, 3H), 3.49 (br s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 198.4, 160.2, 134.8, 130.1, 120.8, 120.2, 112.2, 66.7, 55.6. The recorded NMR spectra agree with those found in literature.[21]



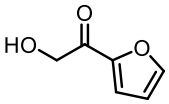
2-hydroxy-1-(4-methoxyphenyl)ethan-1-one (2f). Procedure C with 4-methoxybenzaldehyde followed by purification on silica with ethyl acetate/cyclohexane (3:17) yielded a white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm) 7.96–7.92 (m, 2H), 7.04–7.00 (m, 2H), 4.84 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, MeOH-d_4) δ (ppm) 198.6, 165.7, 131.1, 128.5, 115.1, 66.0, 56.1. The recorded NMR spectra agree with those found in literature.[20]



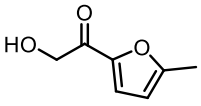
2-hydroxy-1-(3-hydroxyphenyl)ethan-1-one (2g). Procedure C with 3-hydroxybenzaldehyde followed by purification on silica with ethyl acetate/cyclohexane (3:7) yielded a light-yellow solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.43–7.29 (m, 3H), 7.04 (ddd, J = 8.0, 2.6, 1.1 Hz, 1H), 4.85 (s, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 200.1, 159.2, 137.0, 131.0, 121.9, 119.8, 114.9, 66.4. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3427, 3387, 3282, 1681, 1598, 1455, 1406, 1389, 1270, 1244, 1183, 1171, 1104, 1022, 997, 881, 866, 795, 774, 684, 665, 602, 542, 488, 441.



2-hydroxy-1-(naphthalen-2-yl)ethan-1-one (2h). Procedure C with 2-naphthaldehyde followed by purification on silica with ethyl acetate/cyclohexane (3:22) yielded a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 8.38 (s, 1H), 7.96–7.84 (m, 4H), 7.64–7.53 (m, 2H), 4.98 (d, J = 3.7 Hz, 2H), 3.63 (t, J = 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 198.4, 136.2, 132.5, 130.7, 129.7, 129.6, 129.1, 129.0, 128.0, 127.2, 123.1, 65.6. The recorded NMR spectra agree with those found in literature.[20]

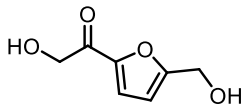


1-(furan-2-yl)-2-hydroxyethan-1-one (2i). Procedure C with furfural followed by purification on silica with ethyl acetate/cyclohexane (3:7) yielded a brown solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.79 (dd, J = 1.7, 0.7 Hz, 1H), 7.39 (dd, J = 3.6, 0.7 Hz, 1H), 6.65 (dd, J = 3.6, 1.7 Hz, 1H), 4.69 (s, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 189.5, 151.9, 148.6, 119.0, 113.4, 65.8. The recorded NMR spectra agree with those found in literature.[22]

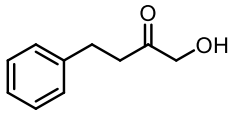


2-hydroxy-1-(5-methylfuran-2-yl)ethan-1-one (2j). Procedure C with 5-methylfurfural followed by purification on silica with ethyl acetate/cyclohexane (1:4) yielded a brown solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.31–7.29 (m, 1H), 6.29–6.27 (m, 1H), 4.64 (s, 2H),

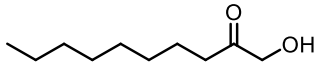
2.38 (s, 3H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 189.0, 160.1, 150.8, 121.4, 110.4, 66.8, 14.0. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3418, 3365, 3120, 2864, 1660, 1586, 1514, 1445, 1404, 1364, 1267, 1245, 1226, 1205, 1116, 1024, 978, 949, 911, 808, 794, 772, 658, 606, 530, 510.



2-hydroxy-1-(5-(hydroxymethyl)furan-2-yl)ethan-1-one (2k). Procedure C with 5-hydroxymethylfurfural followed by purification on silica with ethyl acetate/cyclohexane (1:1) yielded an orange solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ (ppm) 7.35 (d, J = 3.6 Hz, 1H), 6.53 (d, J = 3.6 Hz, 1H), 4.68 (s, 2H), 4.59 (s, 2H). ^{13}C NMR (75 MHz, MeOH-d_4) δ (ppm) 189.4, 161.5, 151.2, 120.2, 110.6, 66.8, 57.5. IR (neat): $\tilde{\nu}_{max}$ (cm^{-1}) 3347, 3131, 3118, 2933, 2888, 1664, 1589, 1523, 1458, 1428, 1332, 1283, 1258, 1205, 1116, 1079, 1028, 998, 968, 914, 833, 773, 670, 528, 479.



1-hydroxy-4-phenylbutan-2-one (2l). Procedure D with 1-hydroxy-4-phenylbutan-2-one followed by purification on silica with ethyl acetate/cyclohexane (1:9) yielded a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.31–7.26 (m, 2H), 7.23–7.14 (m, 3H), 4.18 (s, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 209.0, 140.3, 128.7, 128.3, 126.5, 68.4, 40.0, 29.6. The recorded NMR spectra agree with those found in literature.[20]



1-hydroxydecan-2-one (2q). Procedure D with nonanal followed by purification on silica with ethyl acetate/cyclohexane (1:9) yielded a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.23 (s, 2H), 3.14 (br s, 1H), 2.41 (t, J = 7.5 Hz, 2H), 1.67–1.57 (m, 2H), 1.32–1.24 (m, 10 H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 210.1, 68.2, 38.6, 31.9, 29.4, 29.3, 29.2, 23.9, 22.8, 14.2. The recorded NMR spectra agree with those found in literature.[23]

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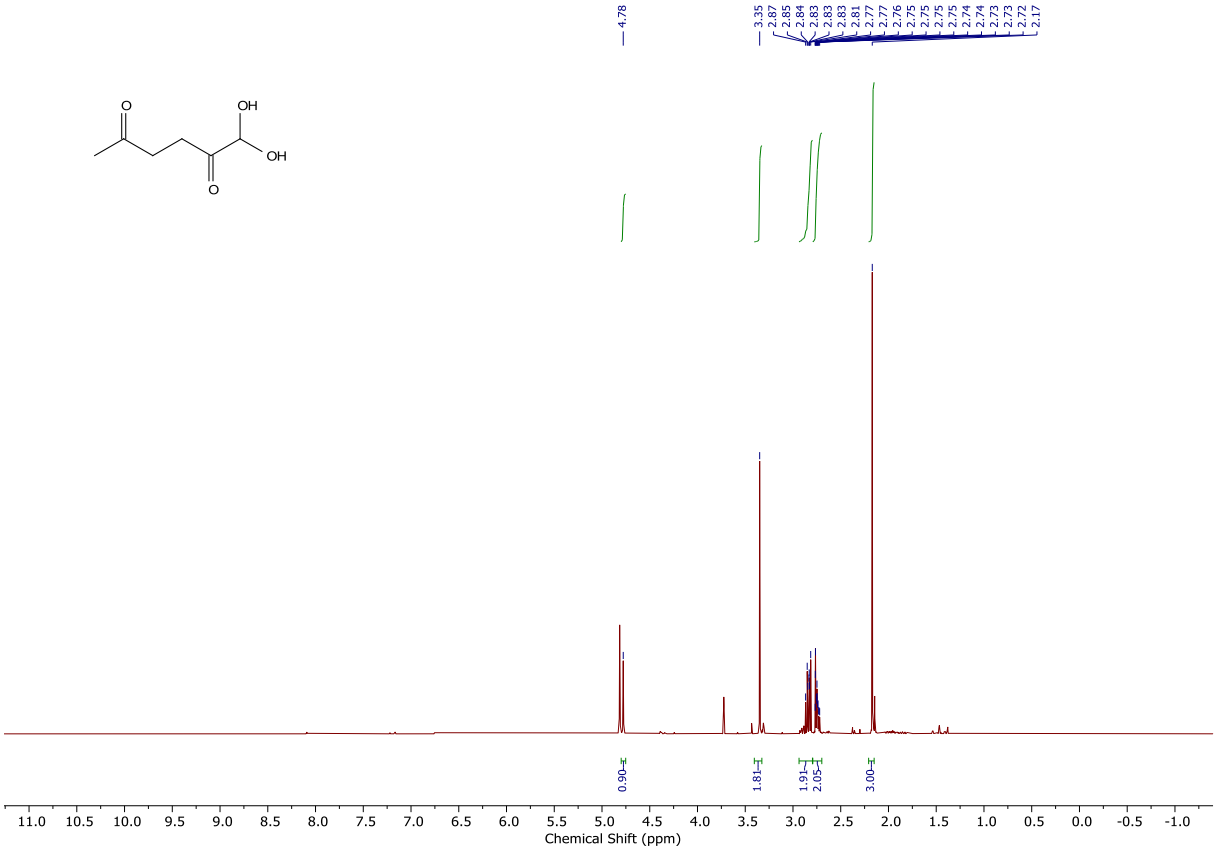
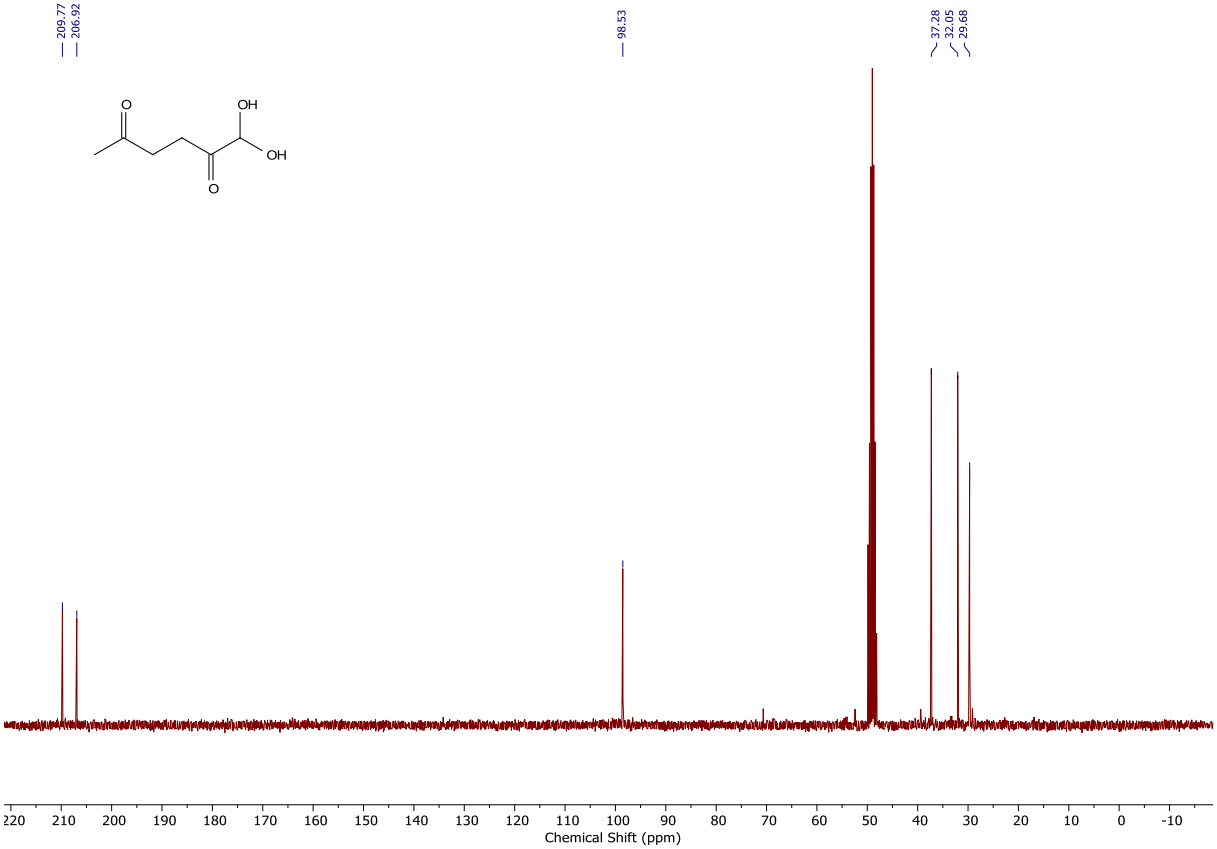
Appendix I: NMR spectra of α-keto aldehydes

^{1}H-NMR (300 MHz, MeOH-d_4)



^{13}C-NMR (75 MHz, MeOH-d_4)



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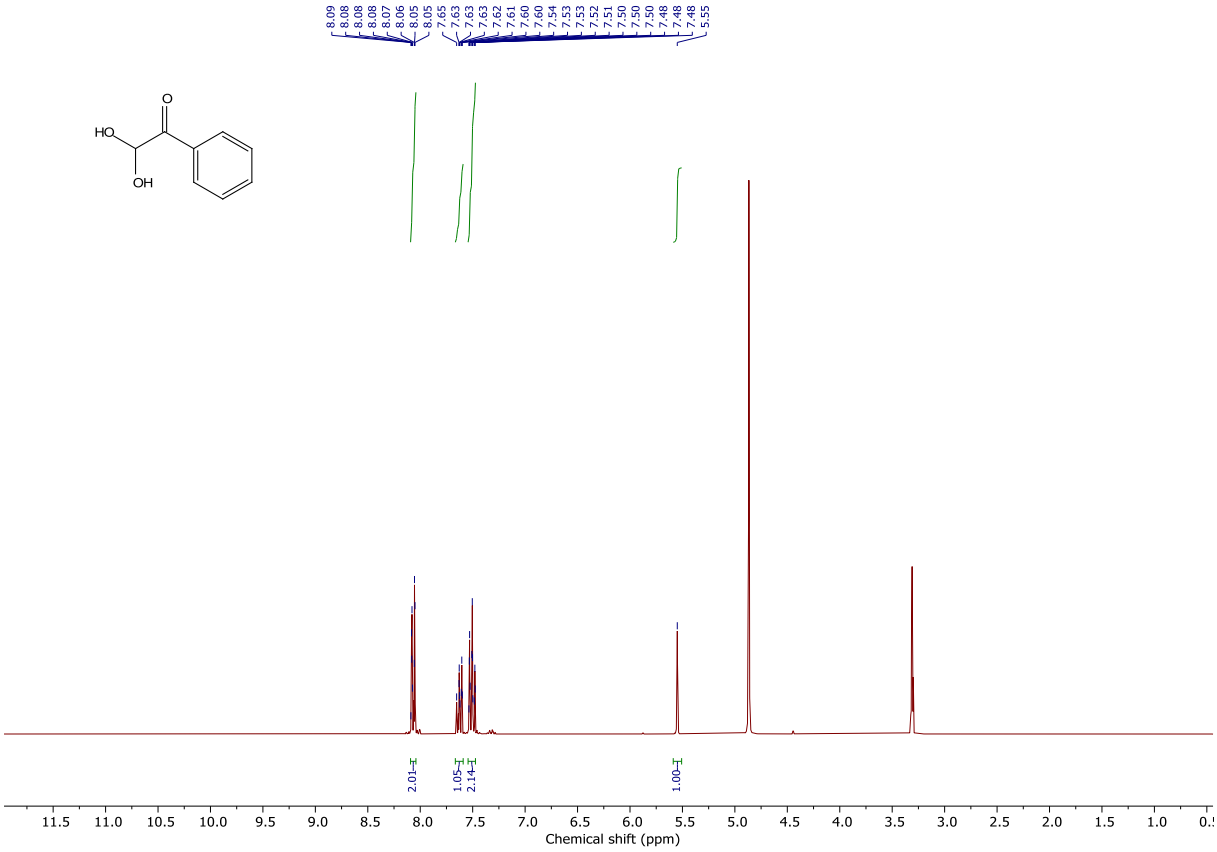

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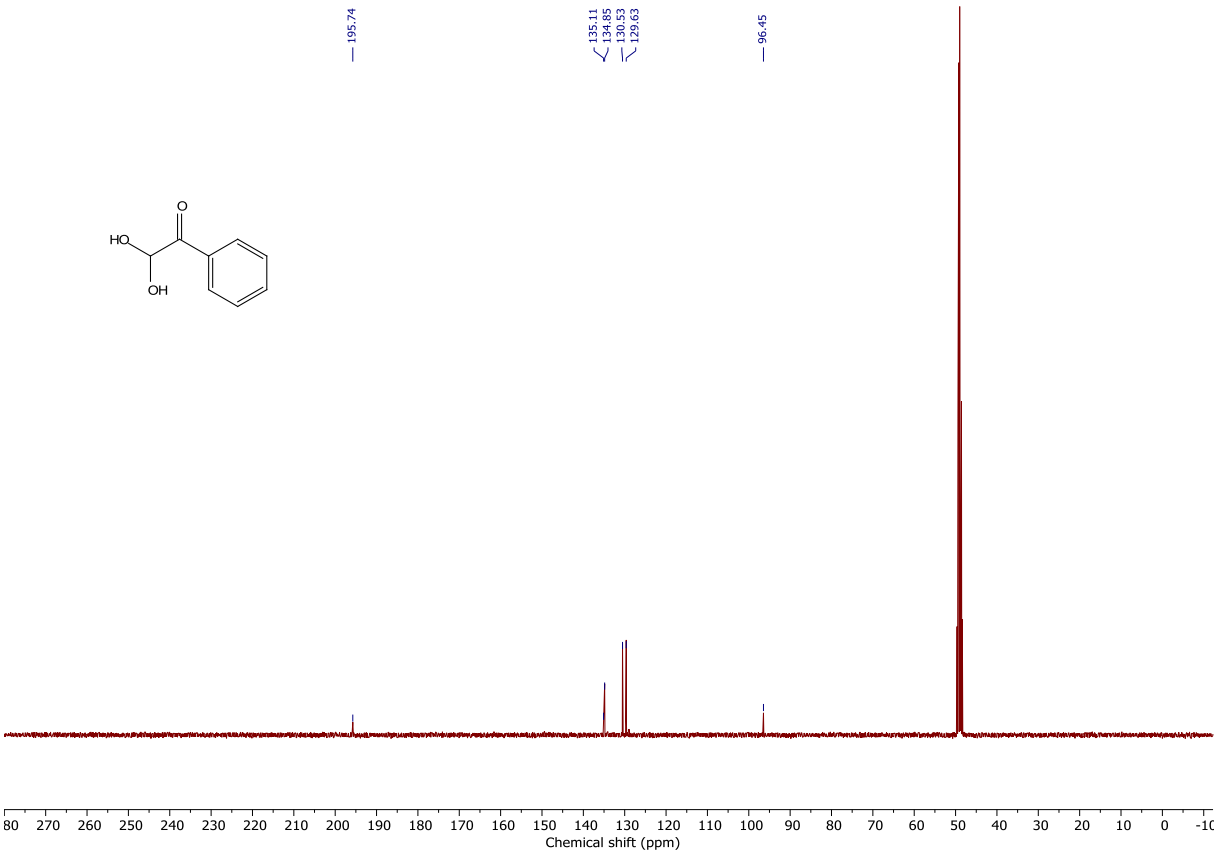

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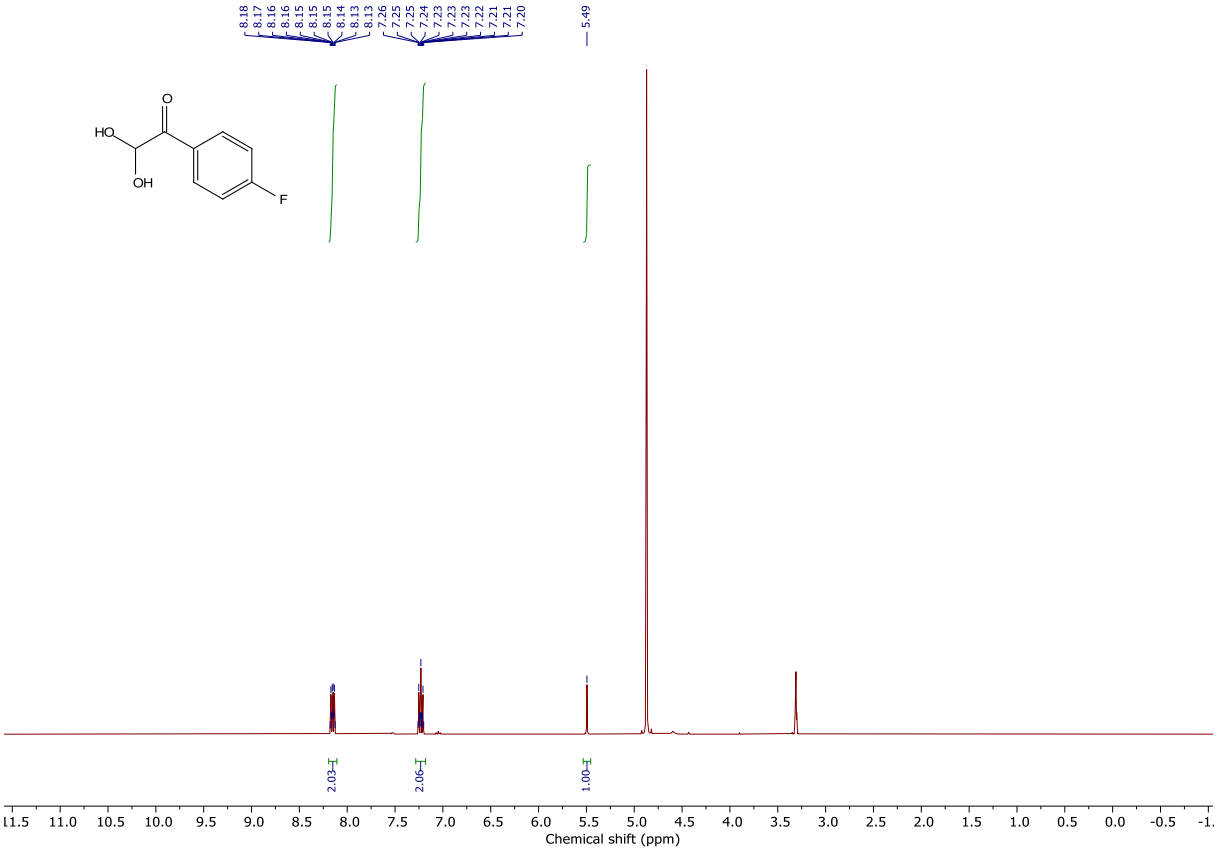

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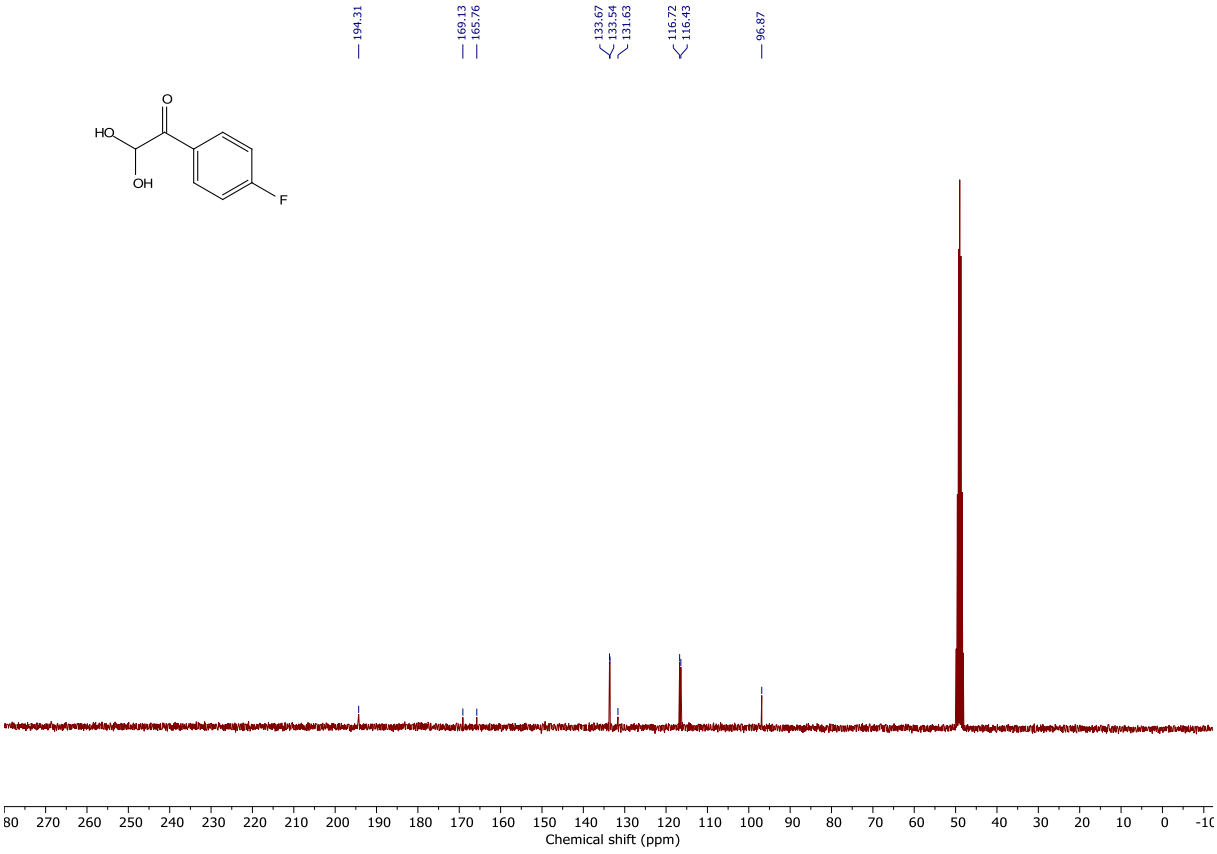

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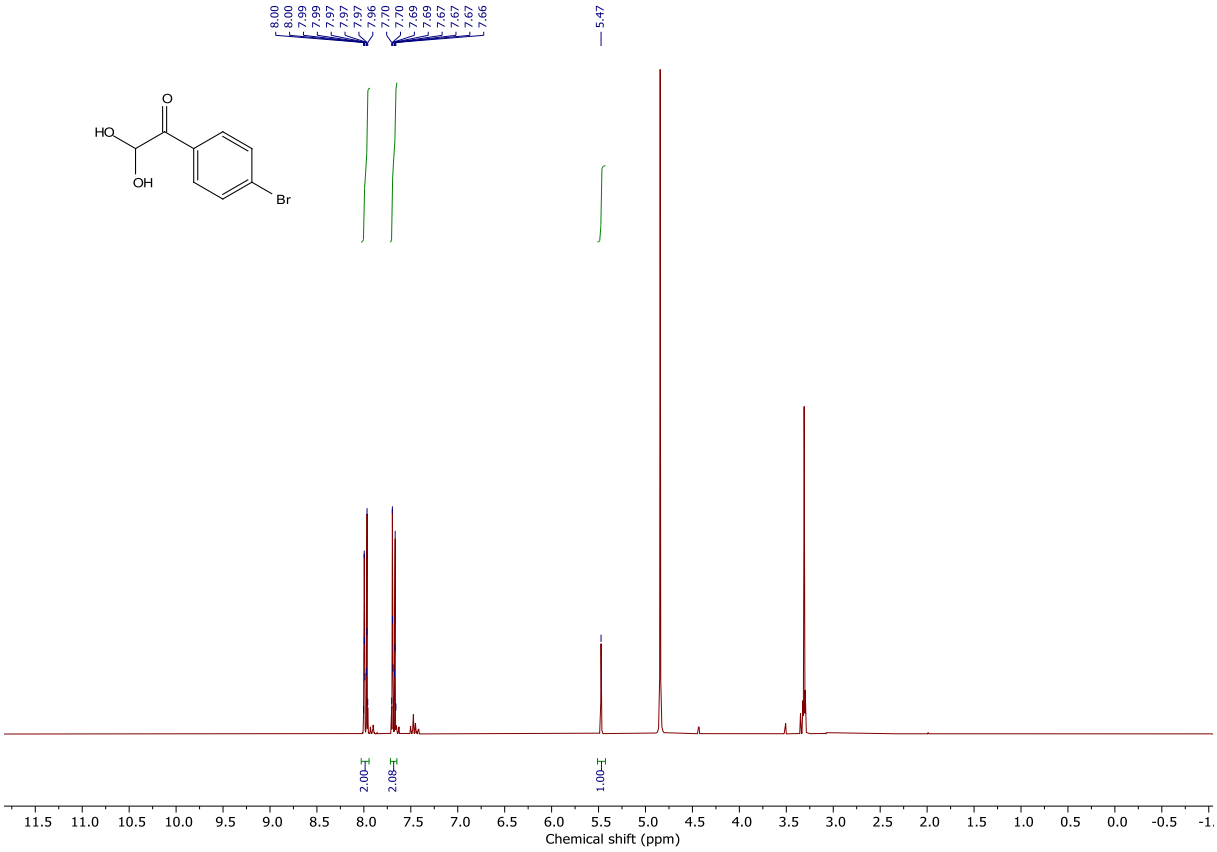

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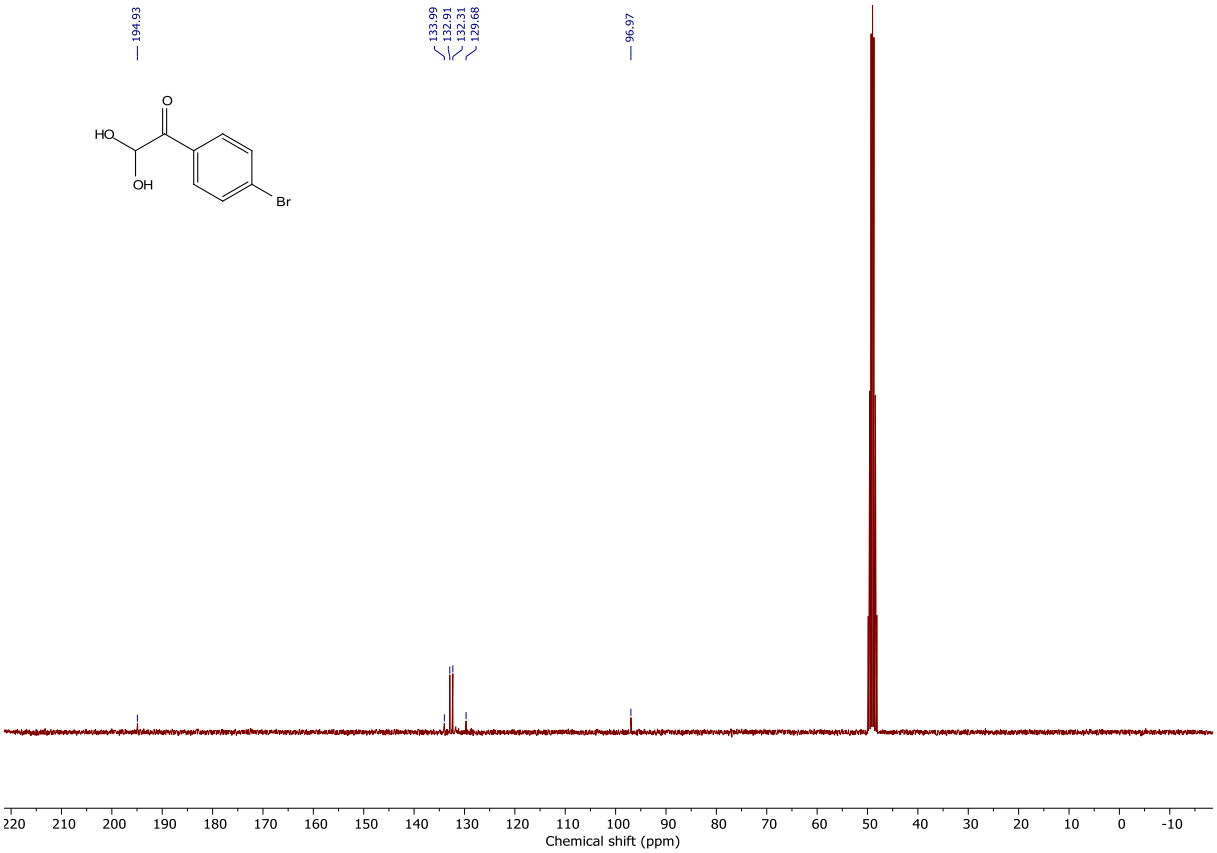

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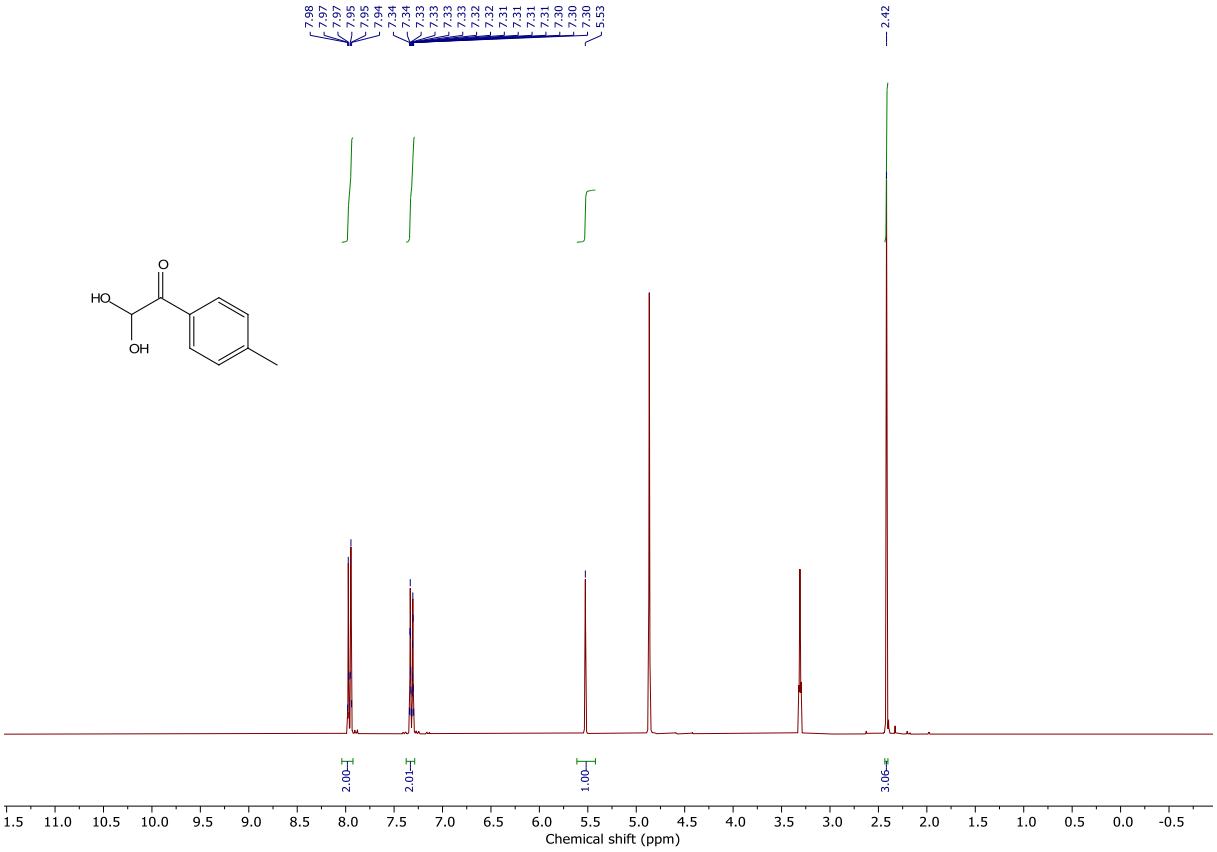

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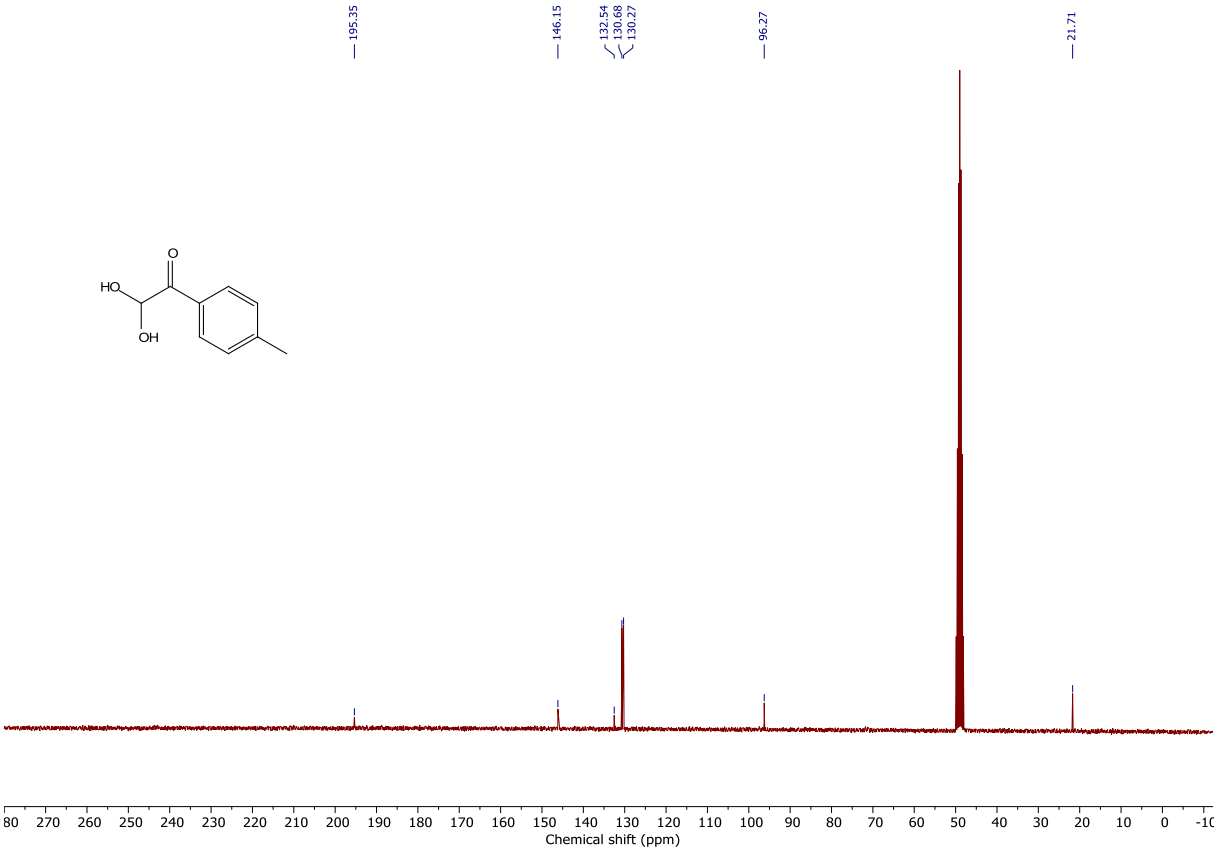

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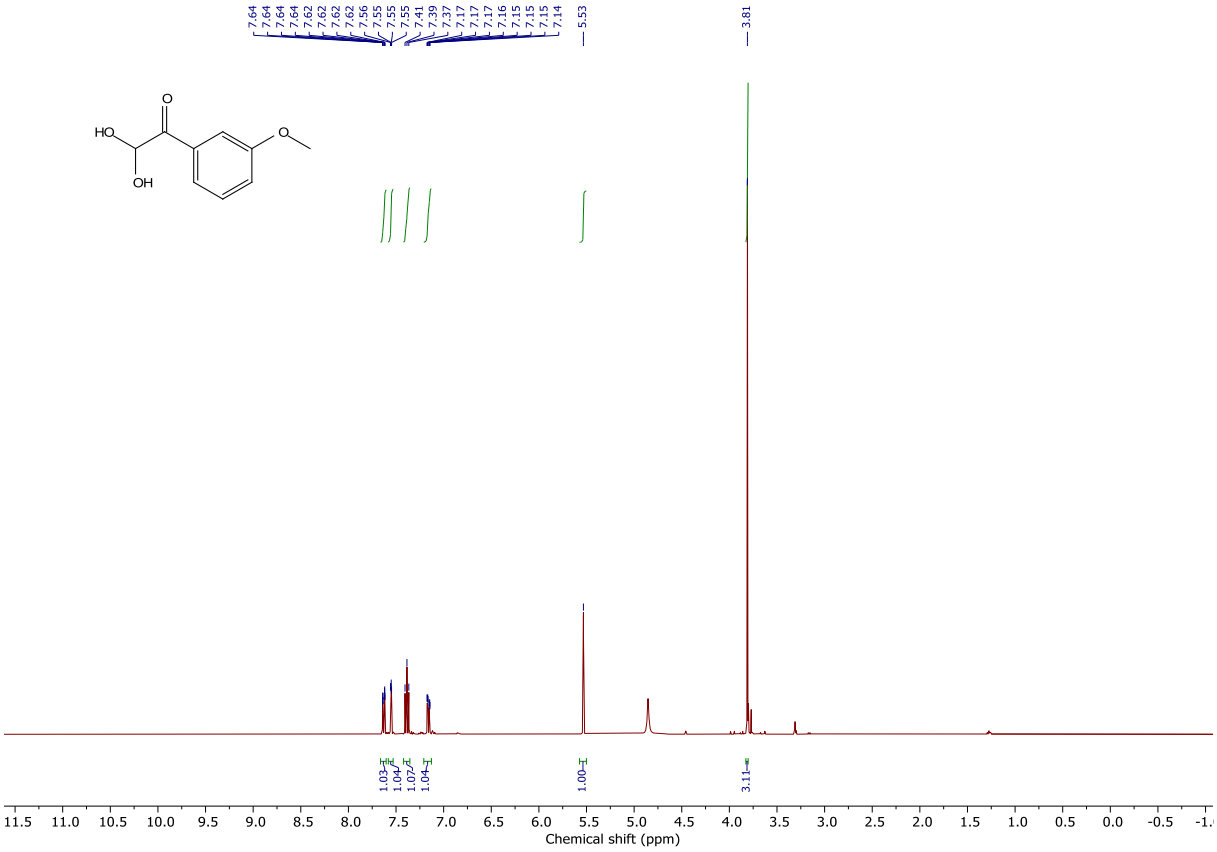

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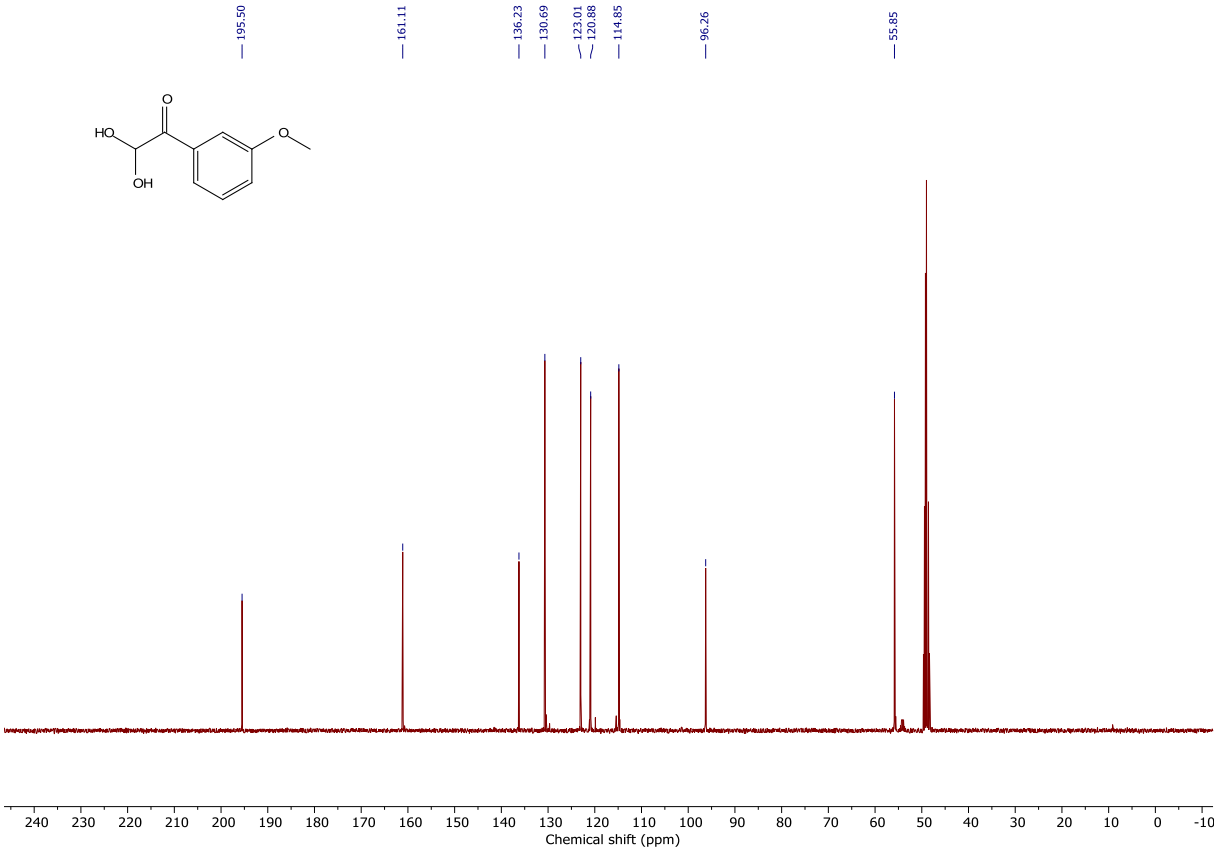

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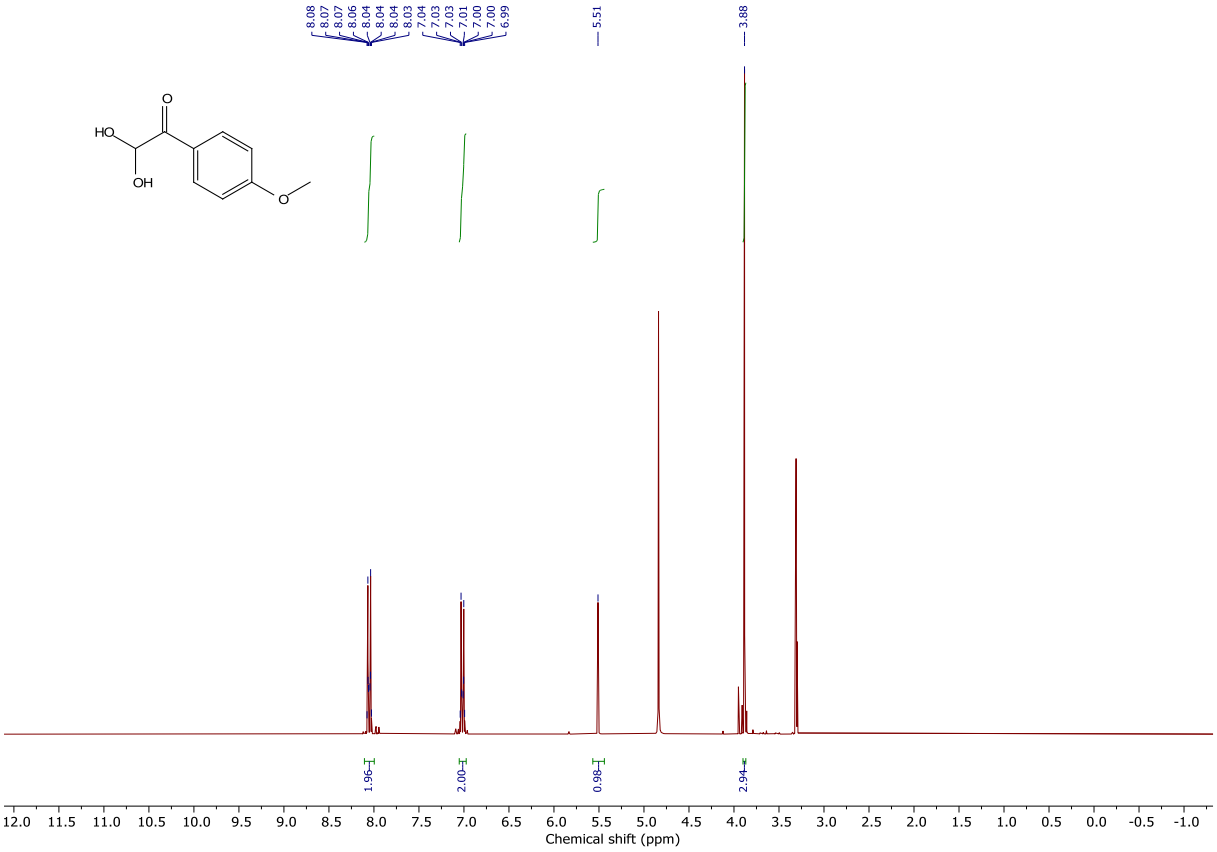

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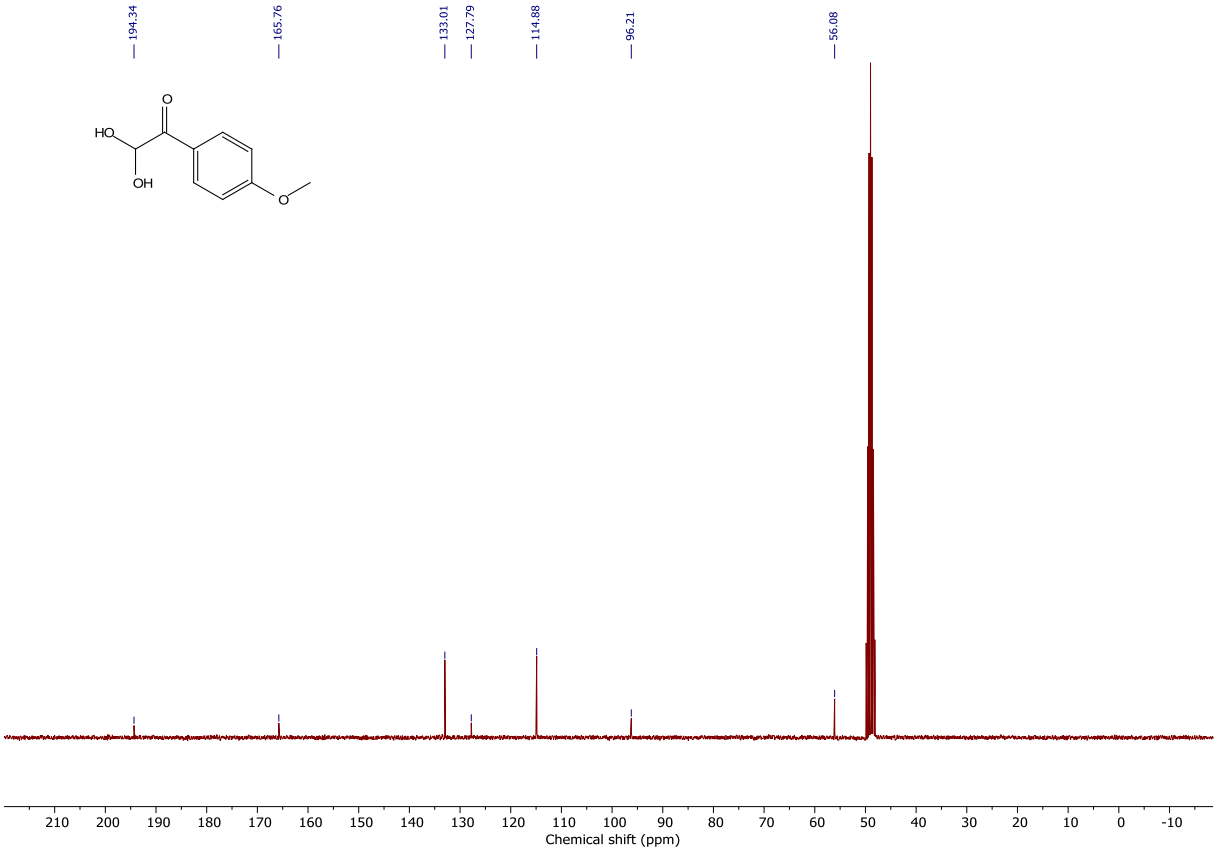

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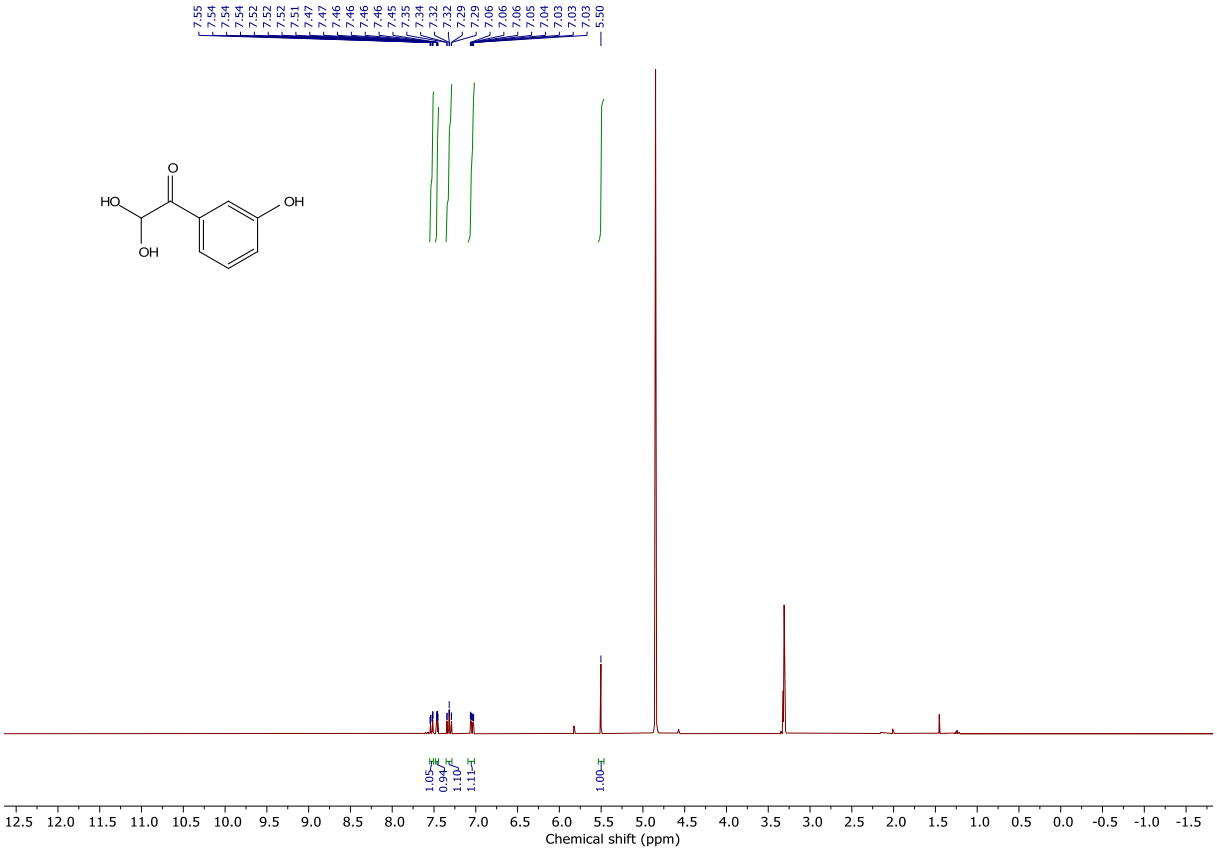

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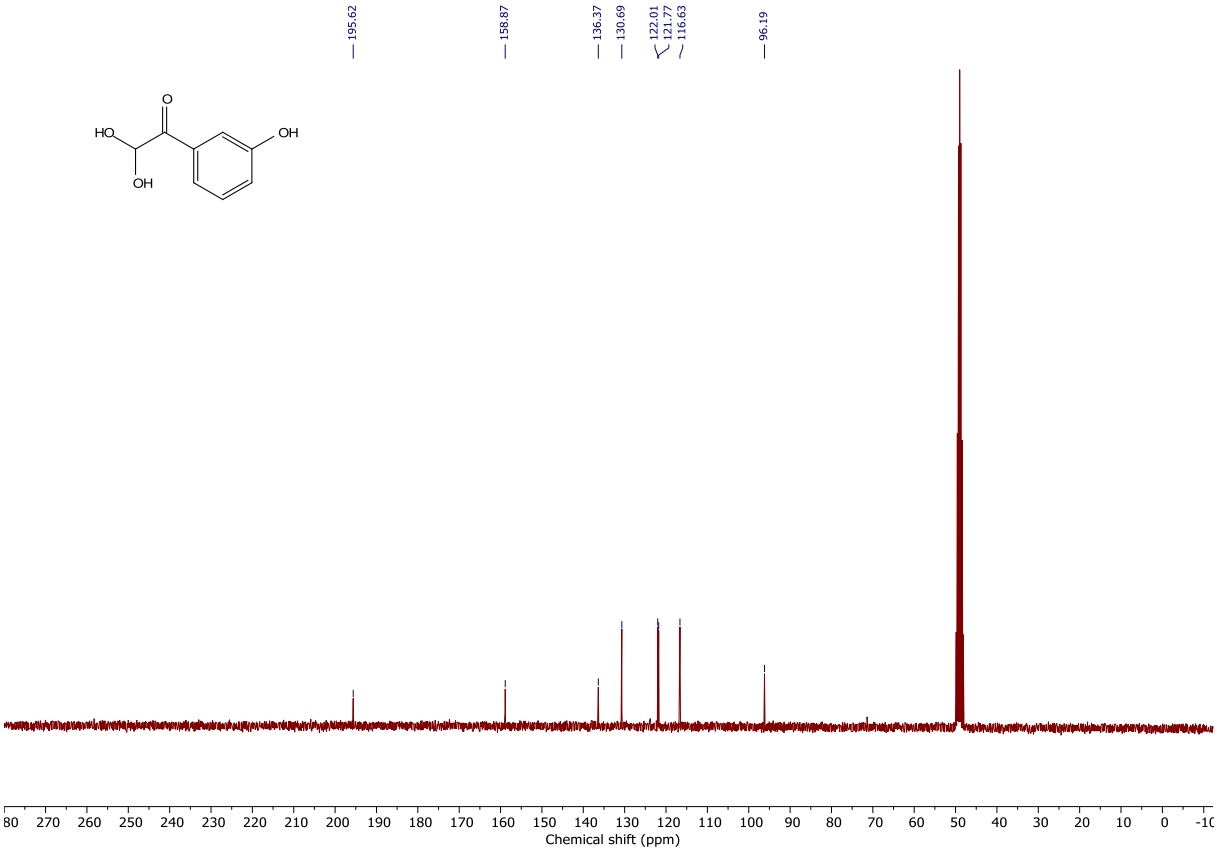

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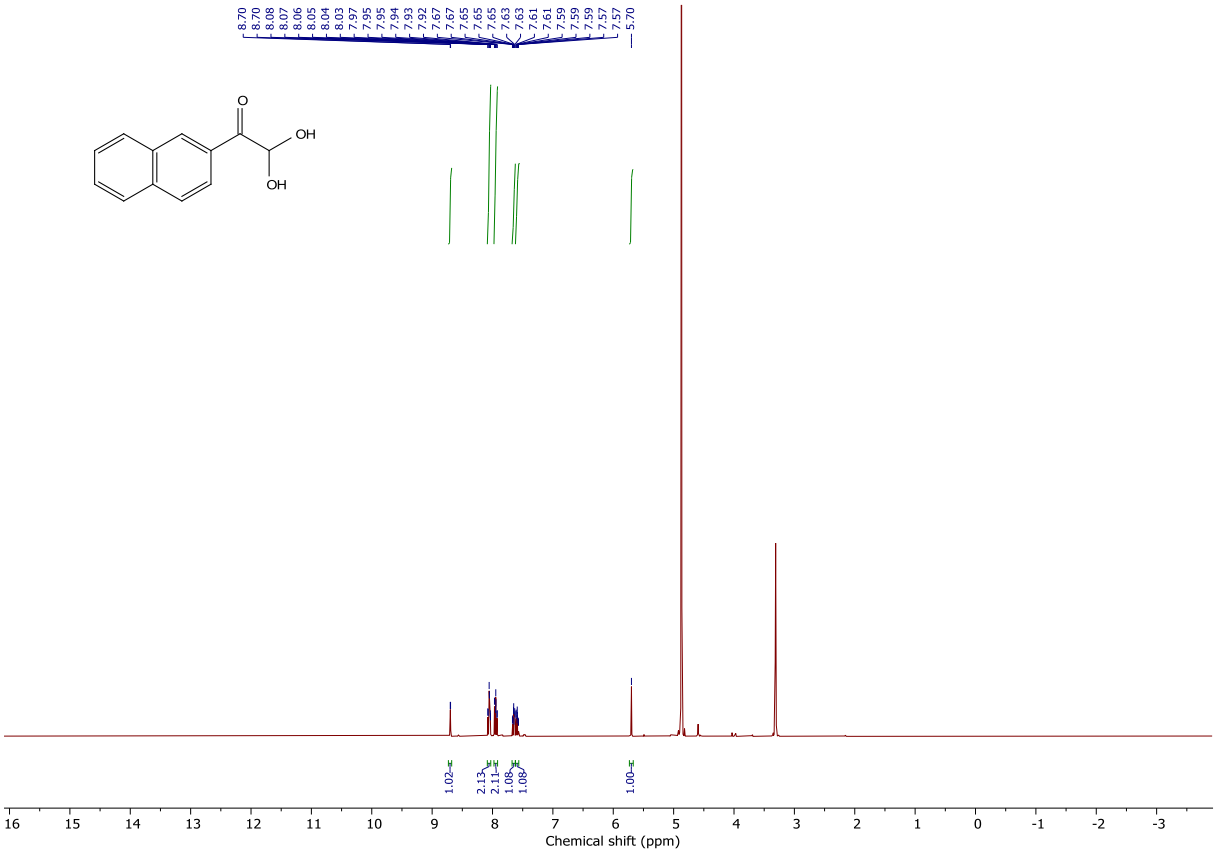

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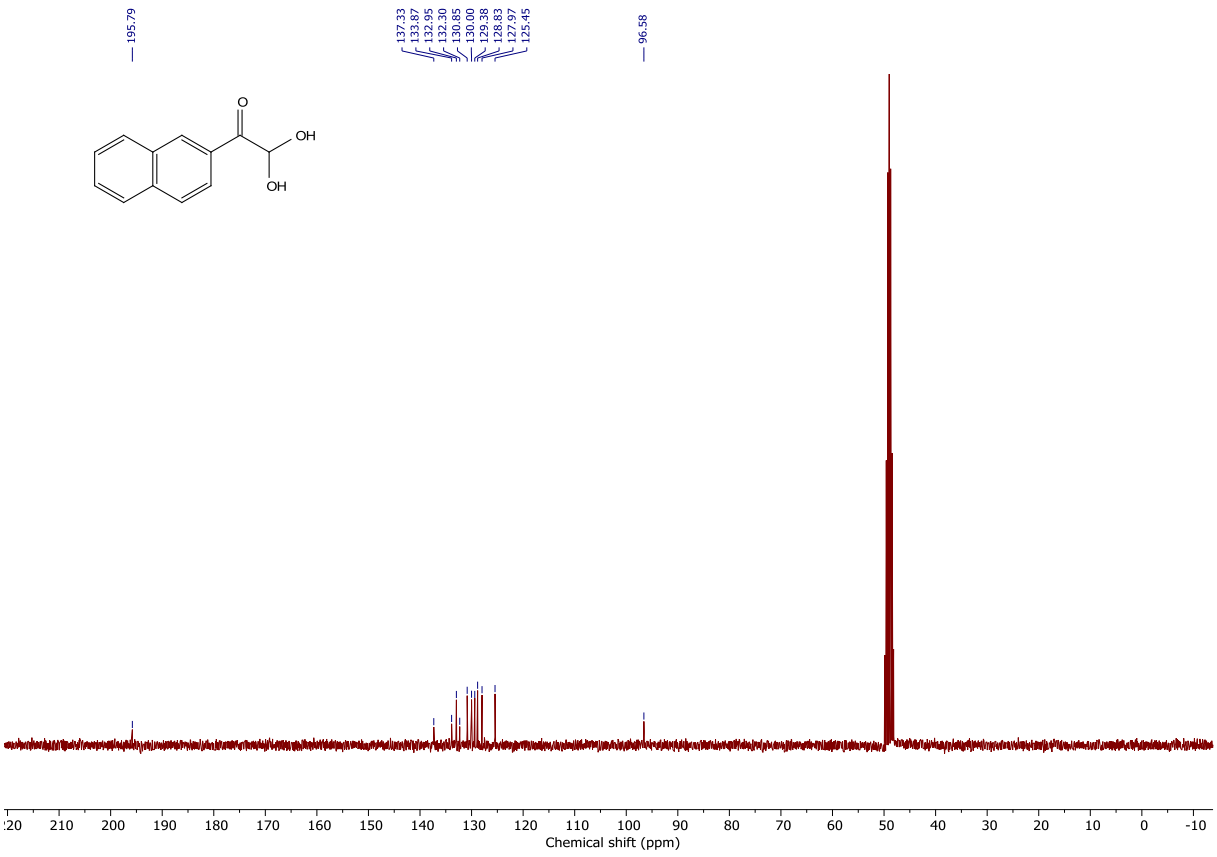

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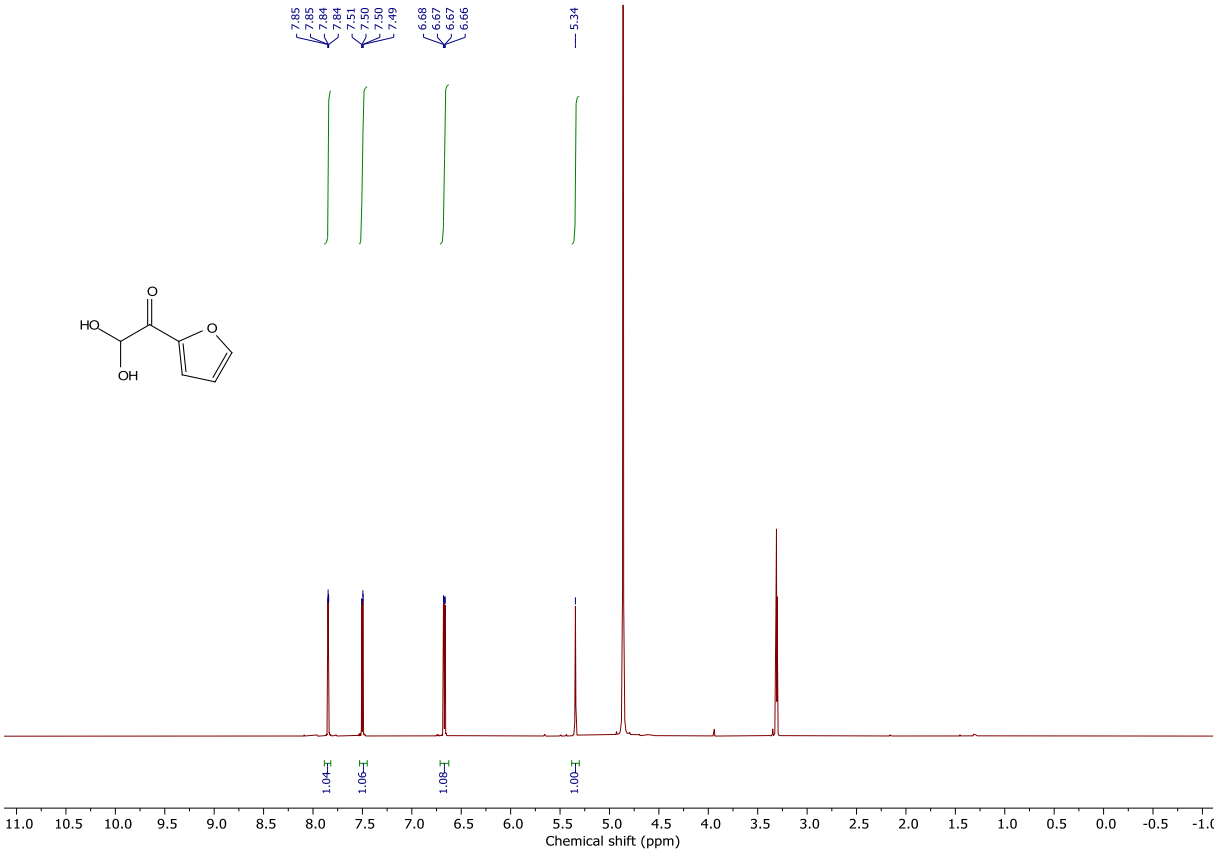

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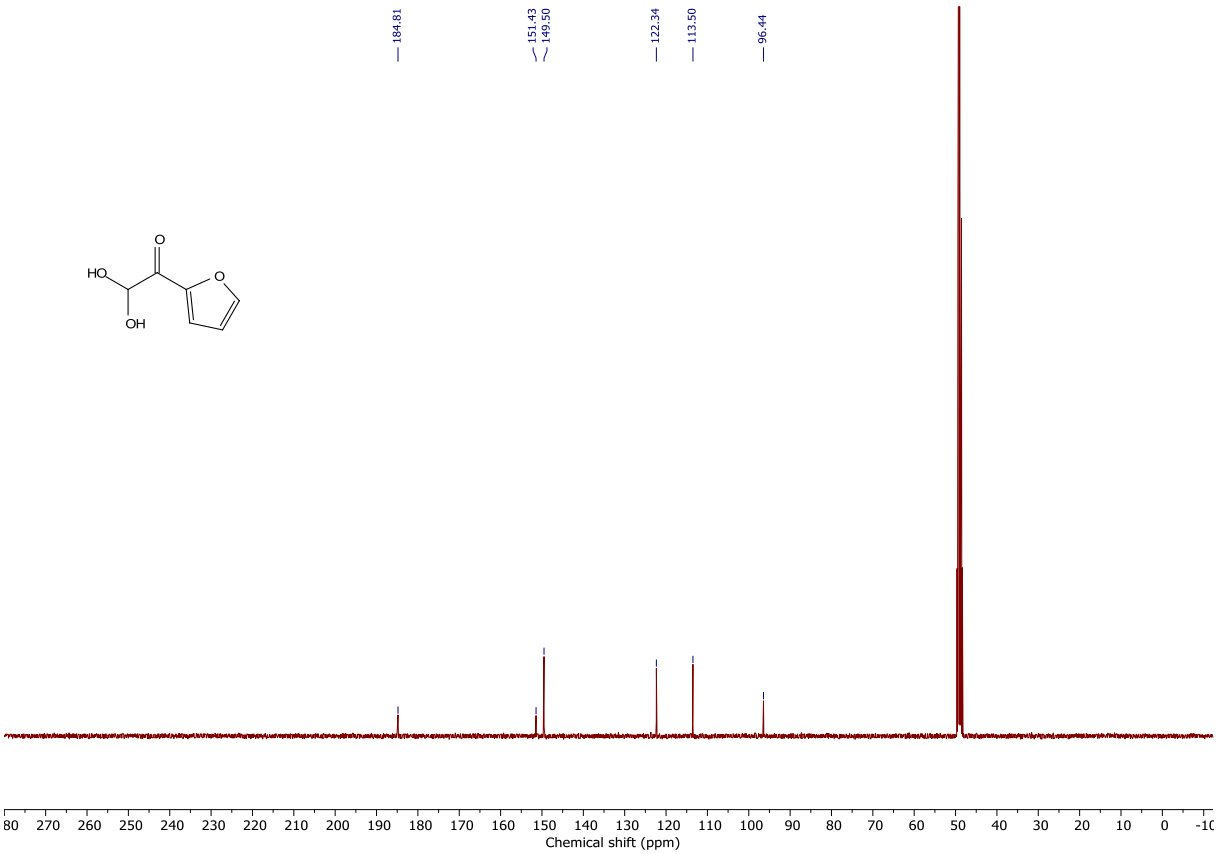

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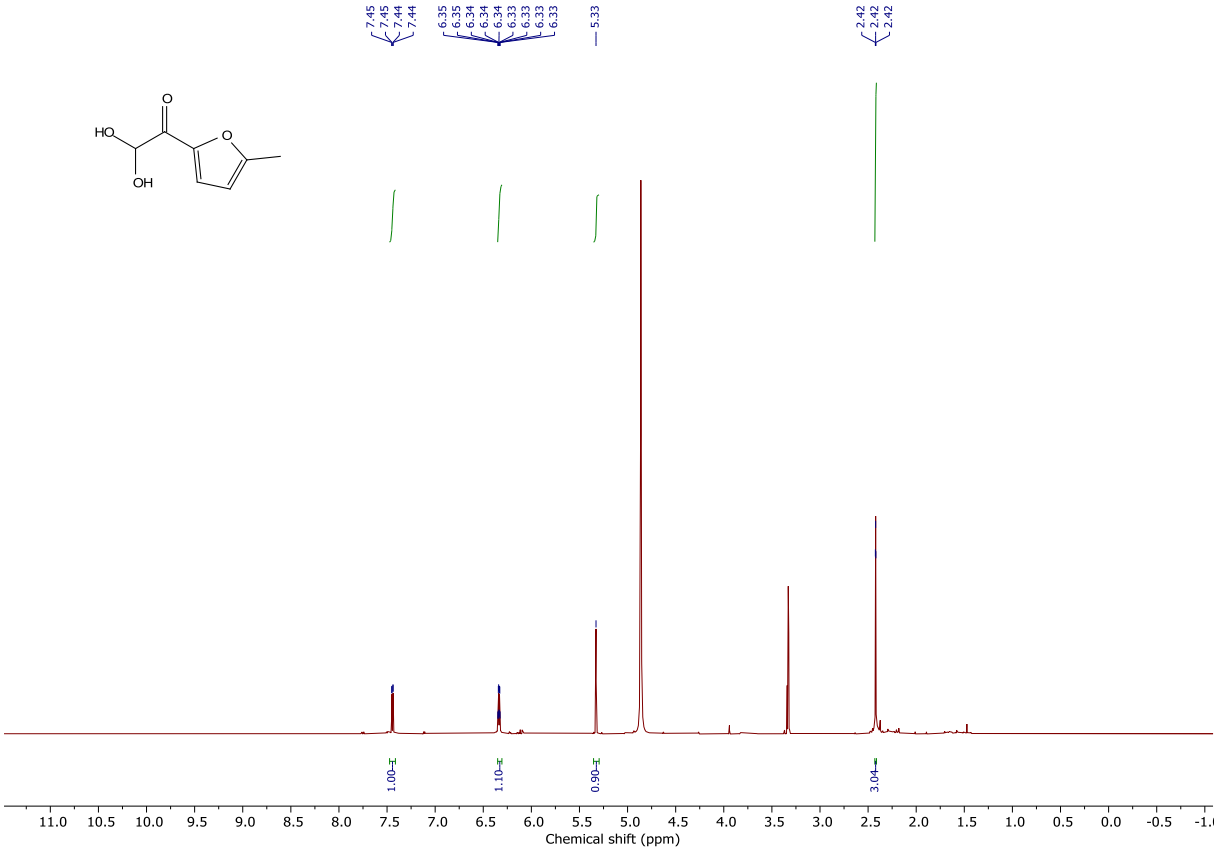

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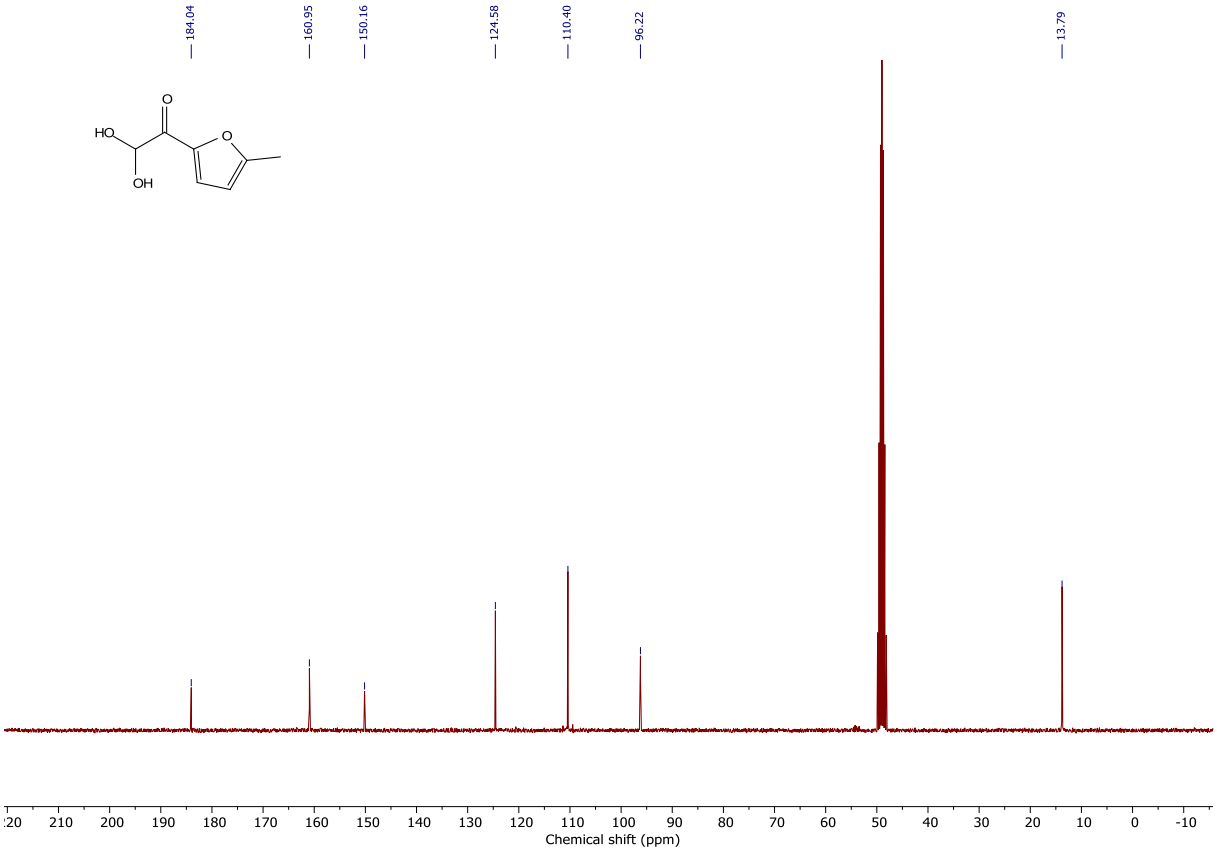

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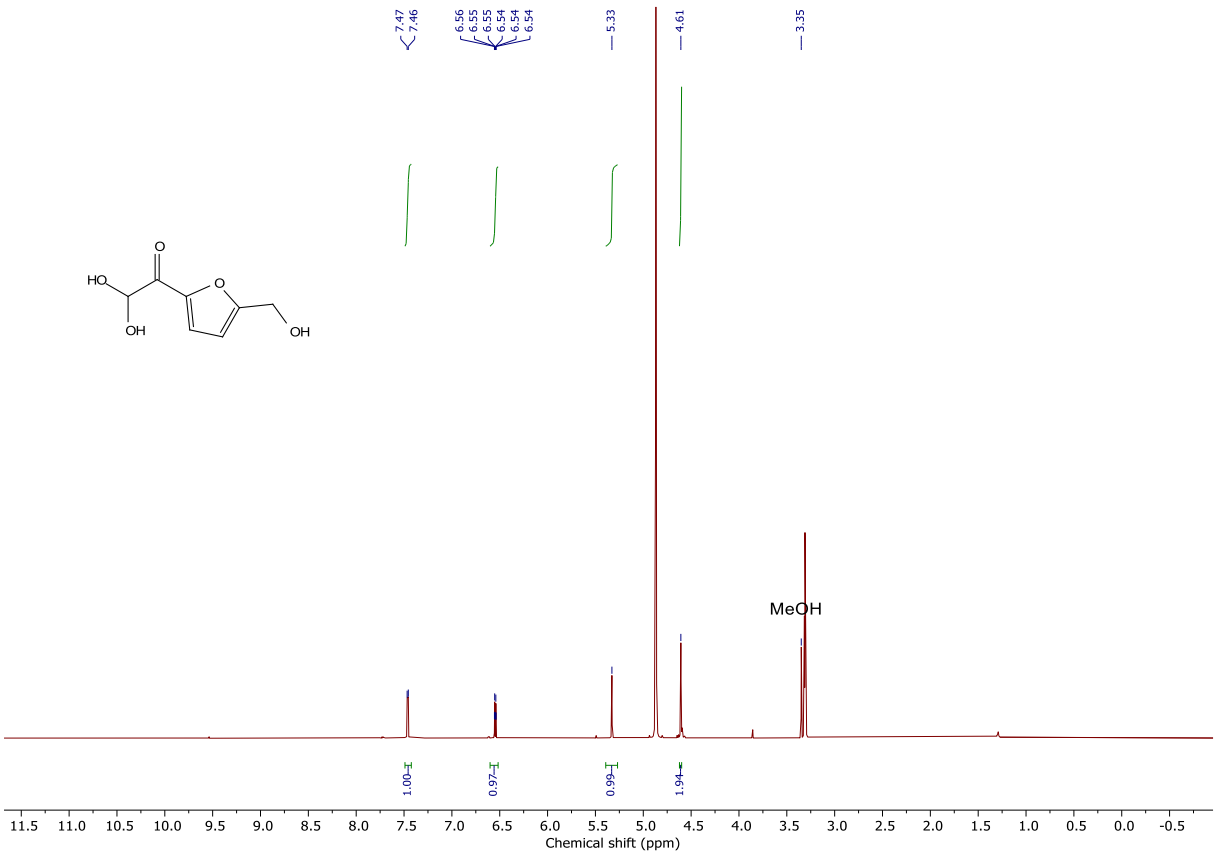

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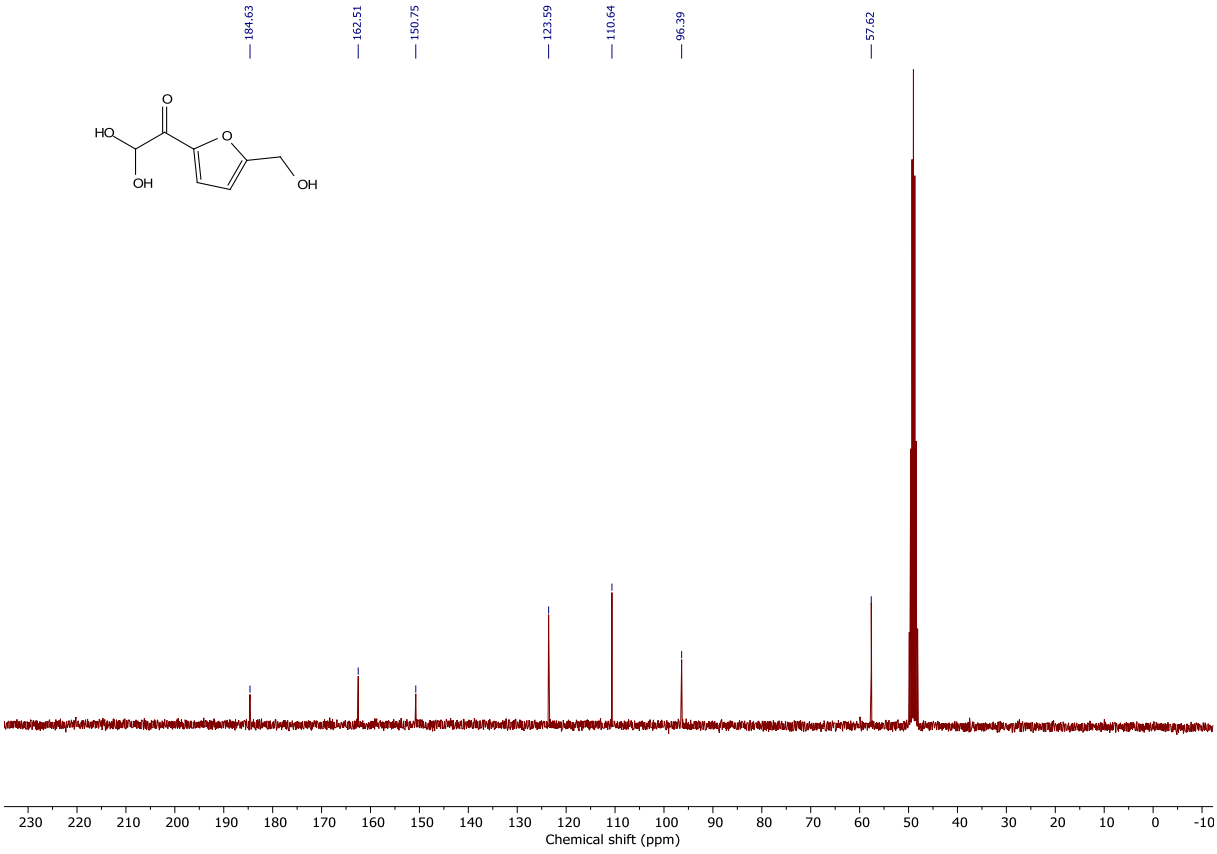

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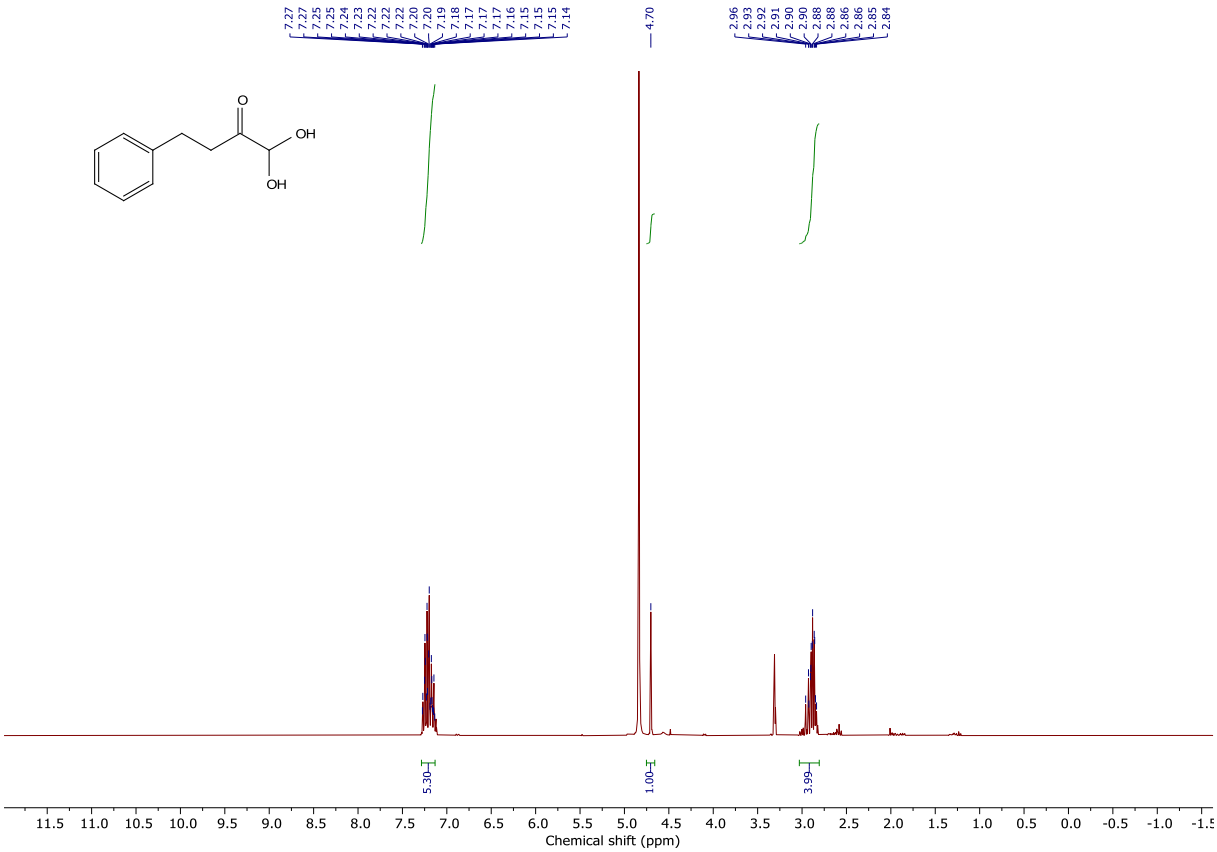

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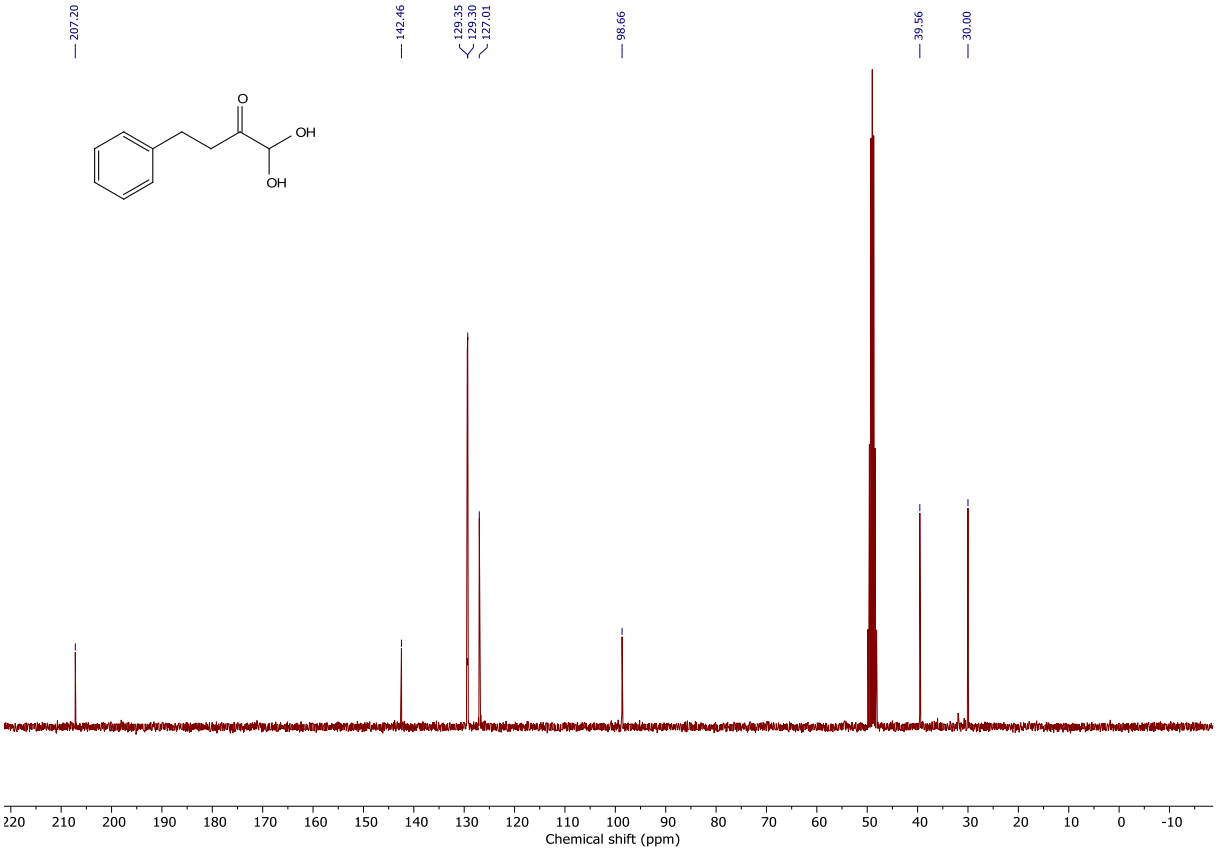

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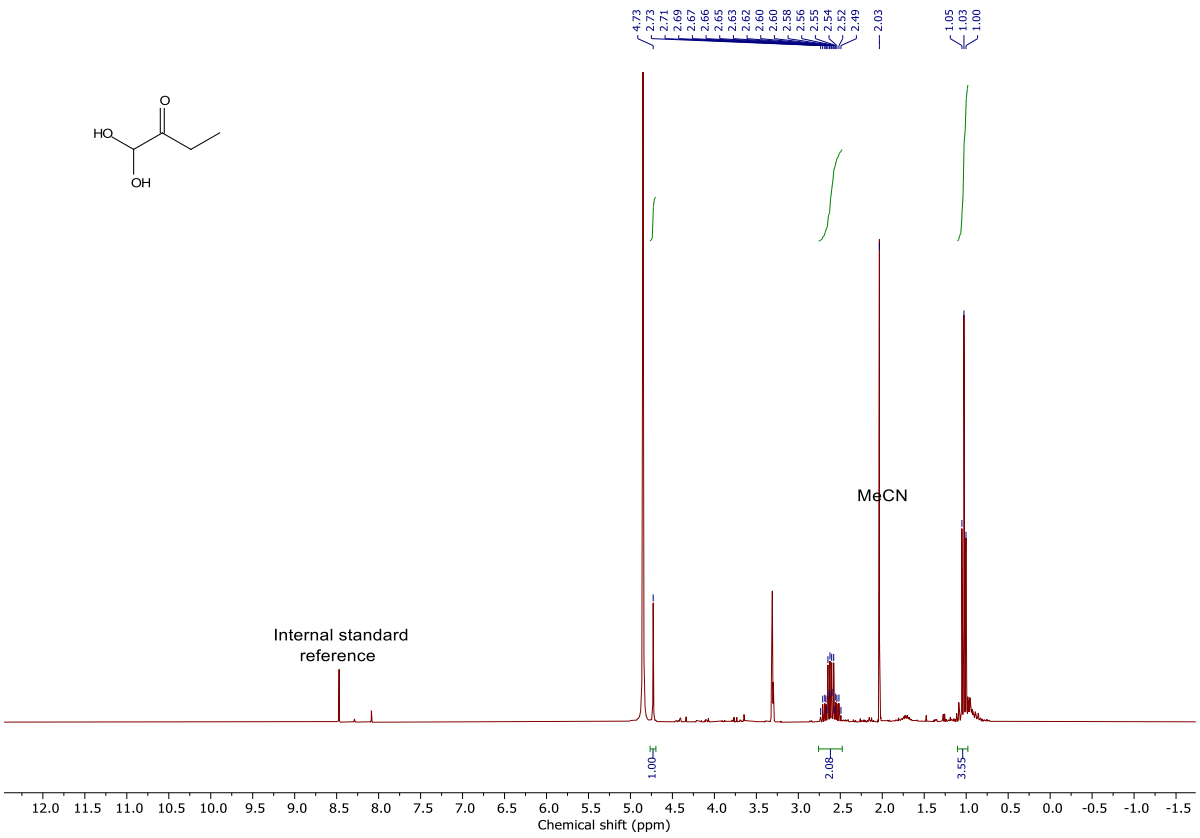

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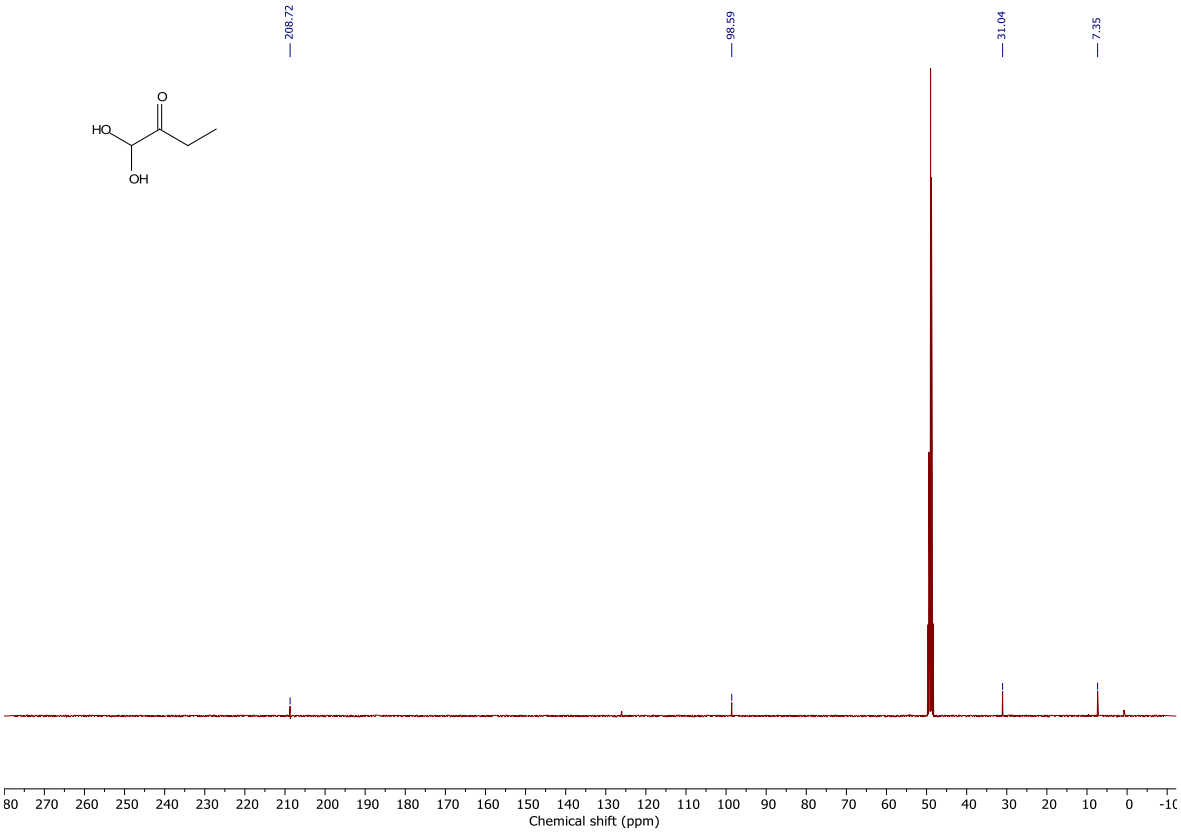

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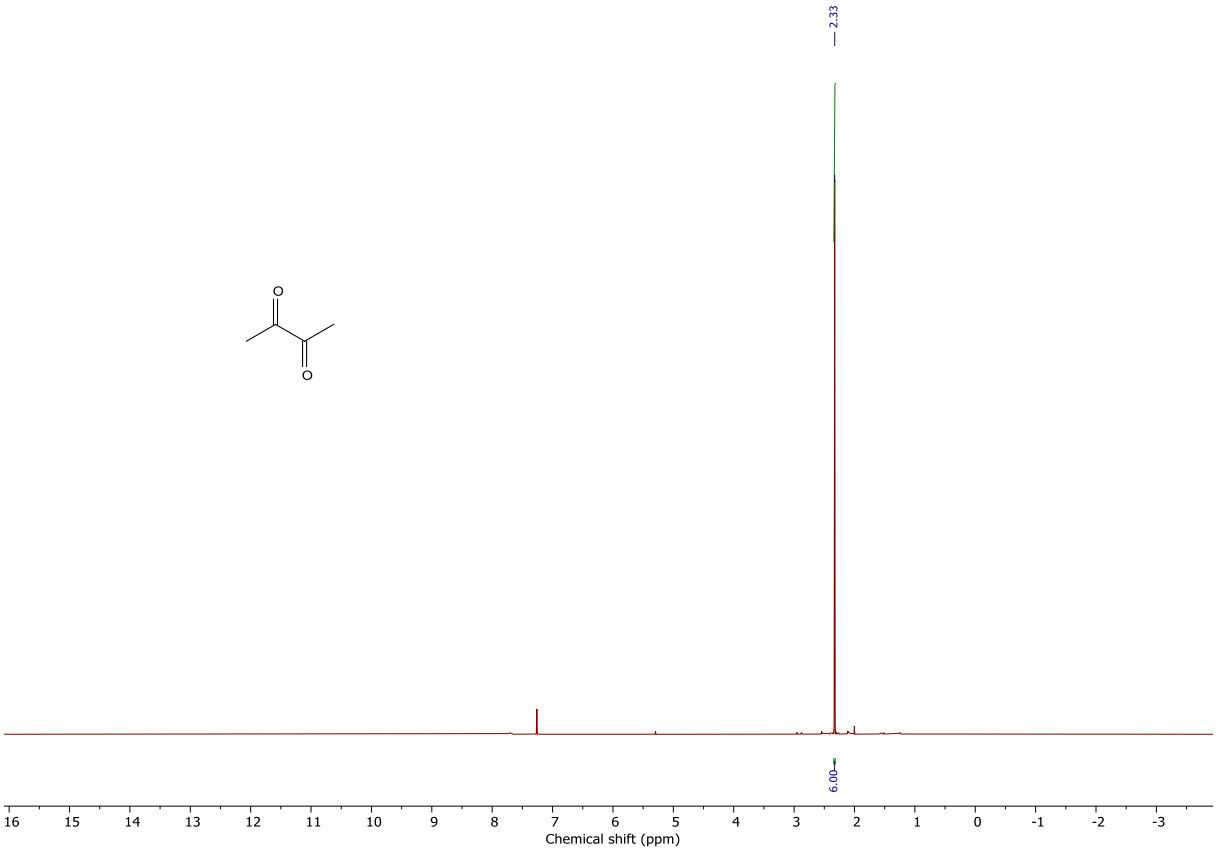

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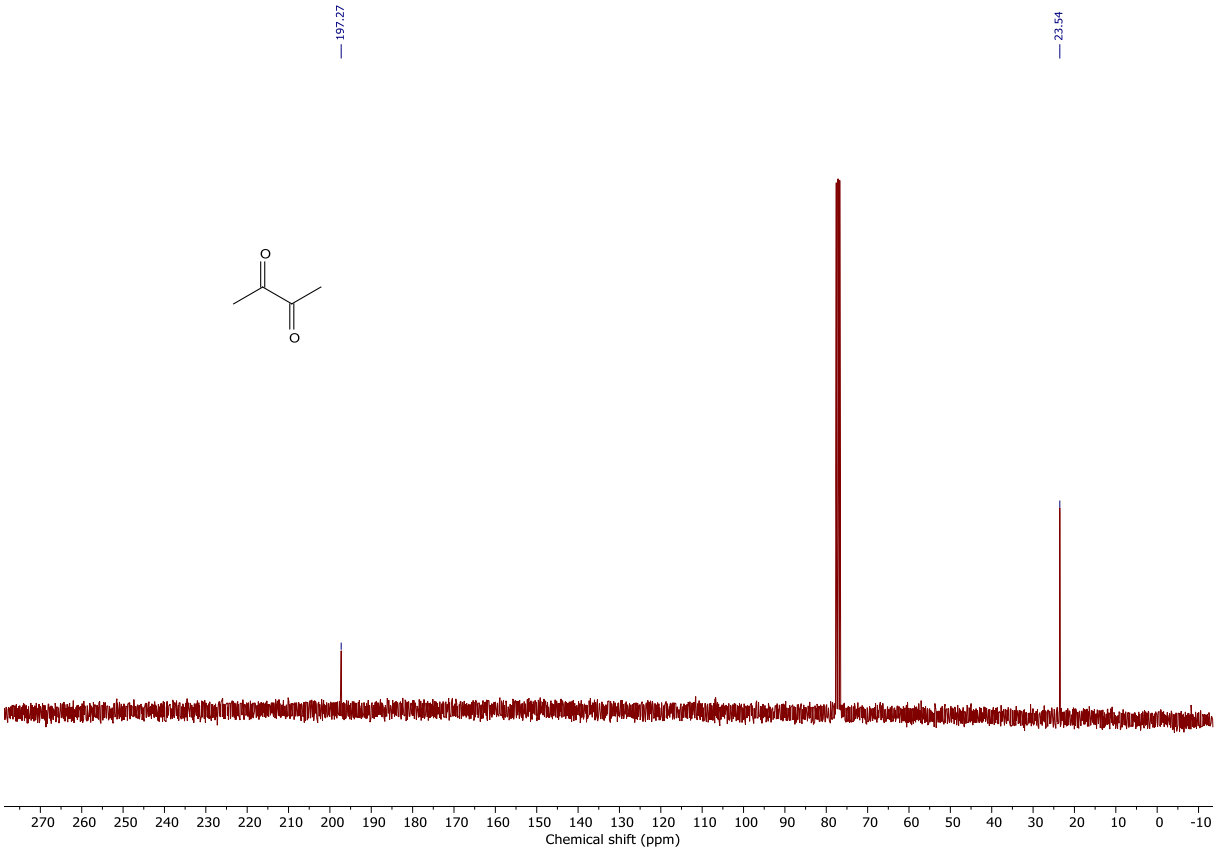

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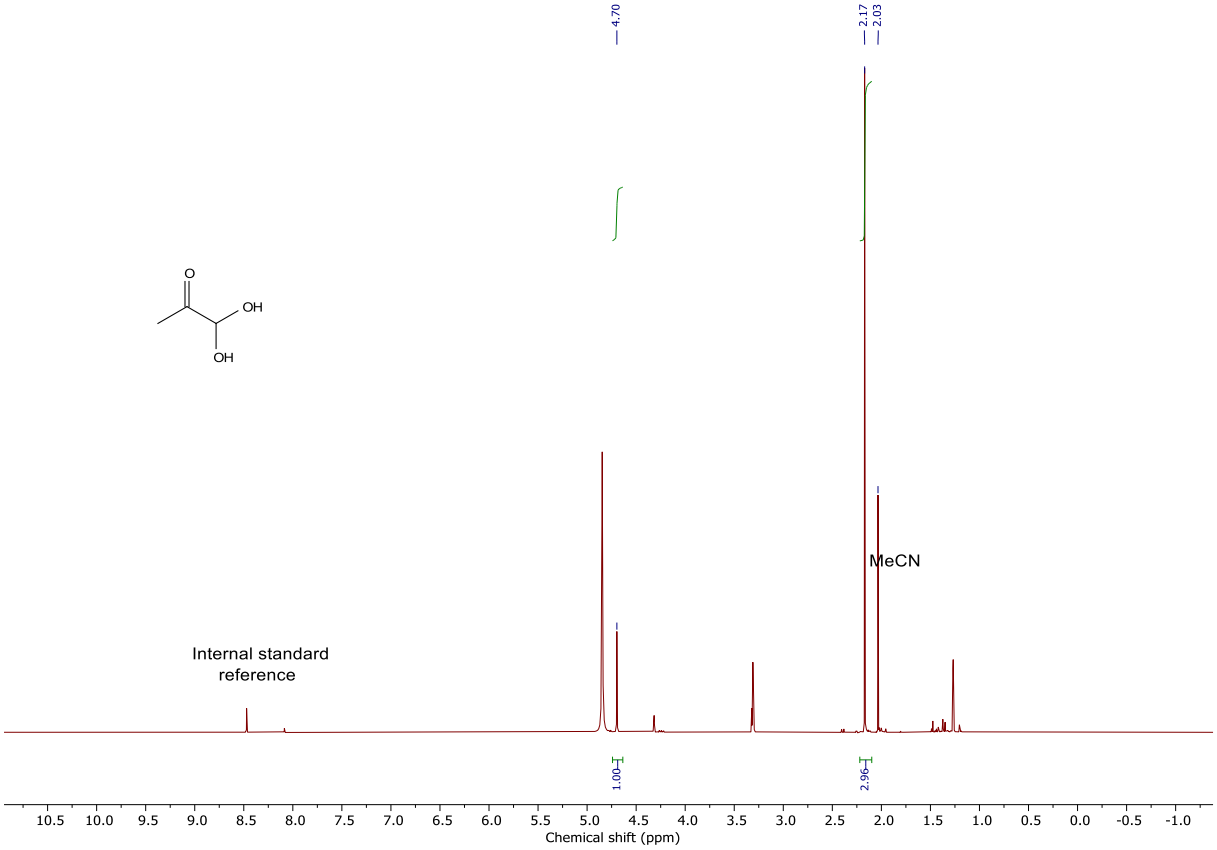

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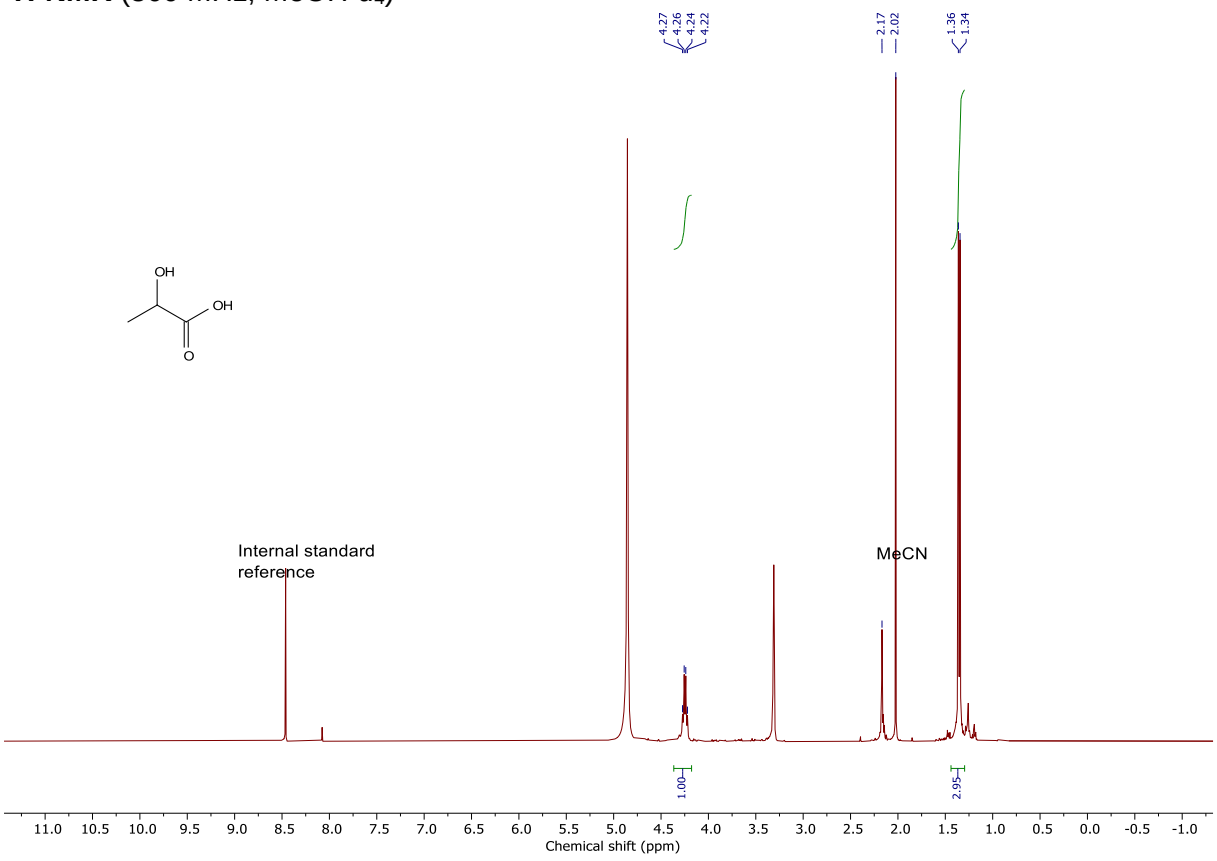

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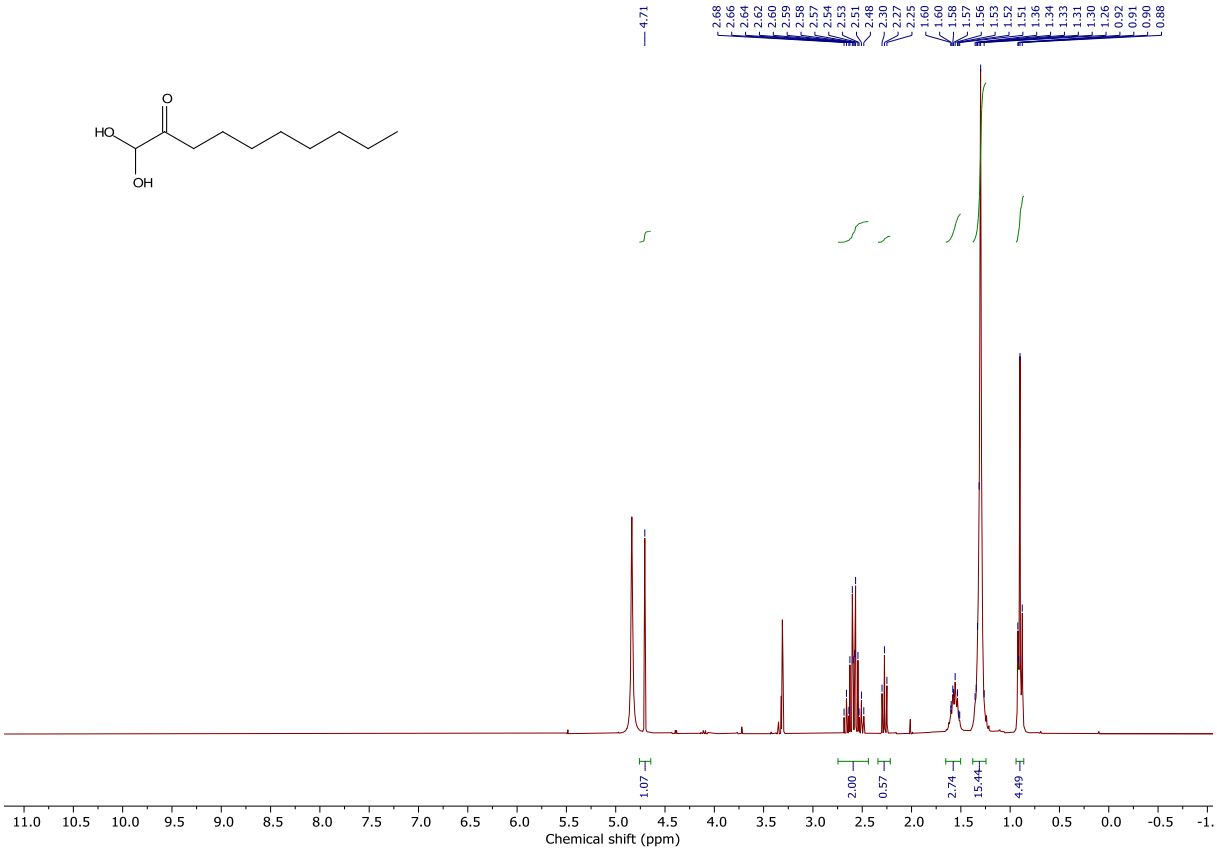

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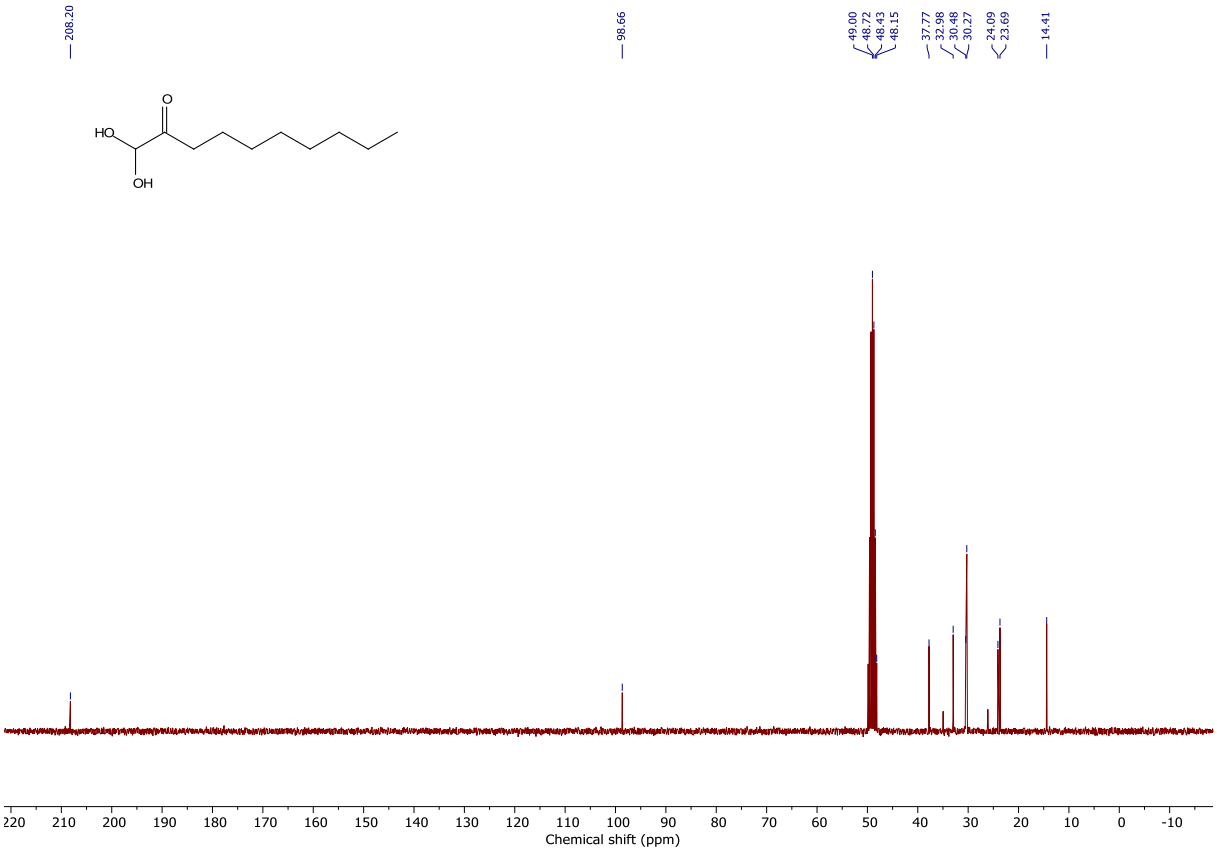

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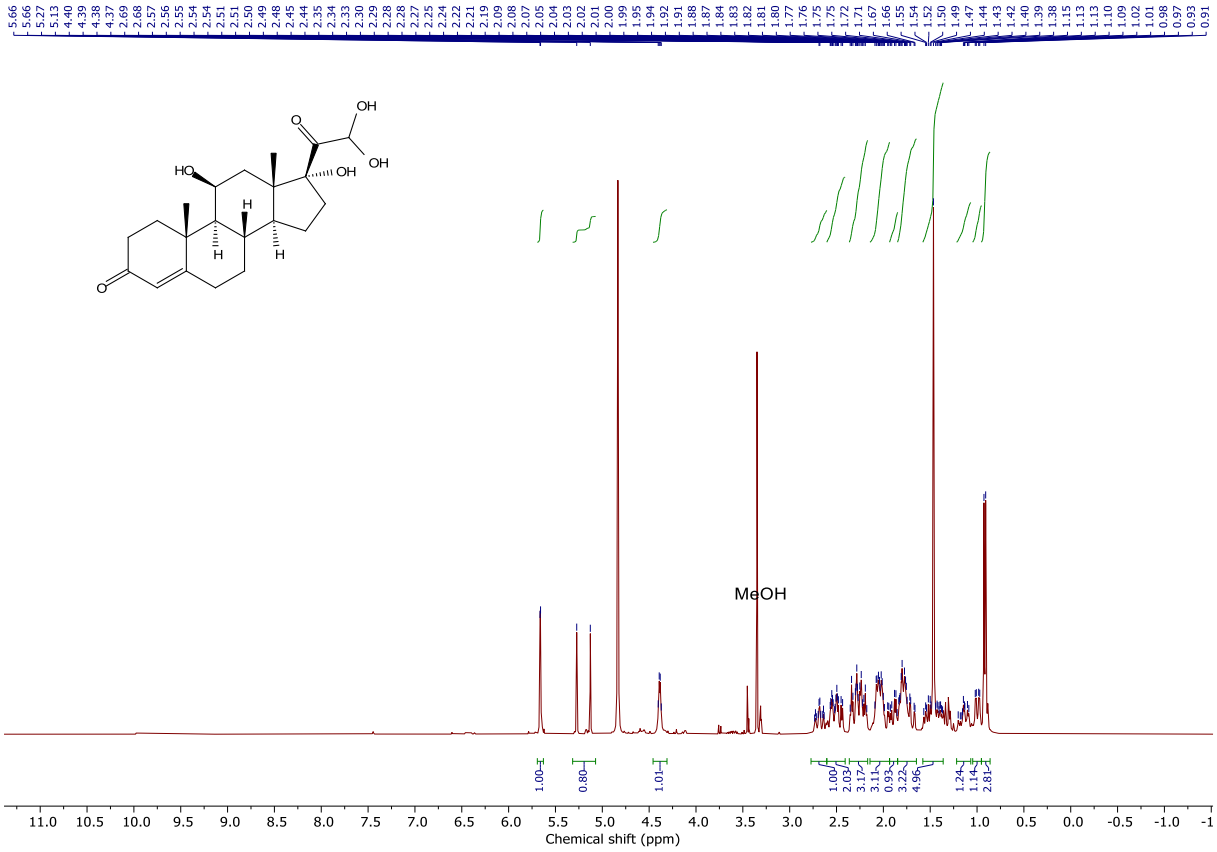
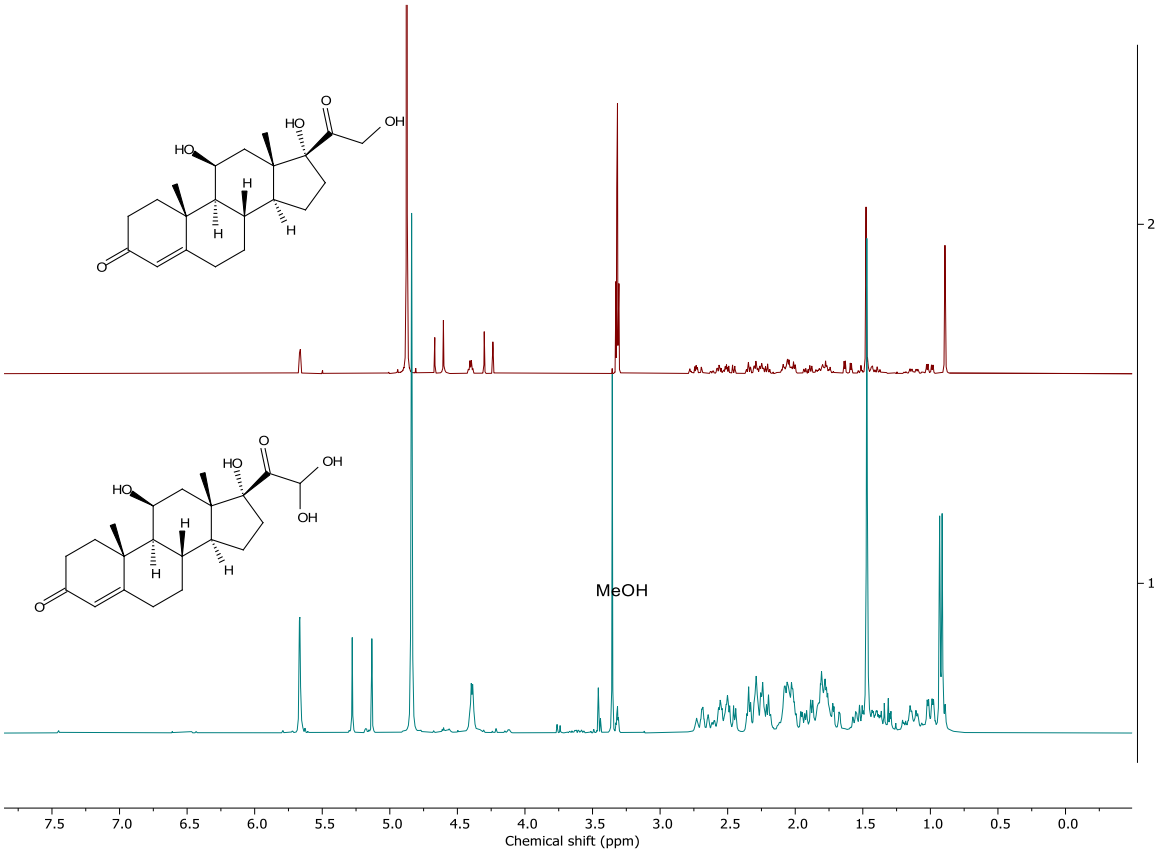


Comparing the product (4r) to hydrocortisone



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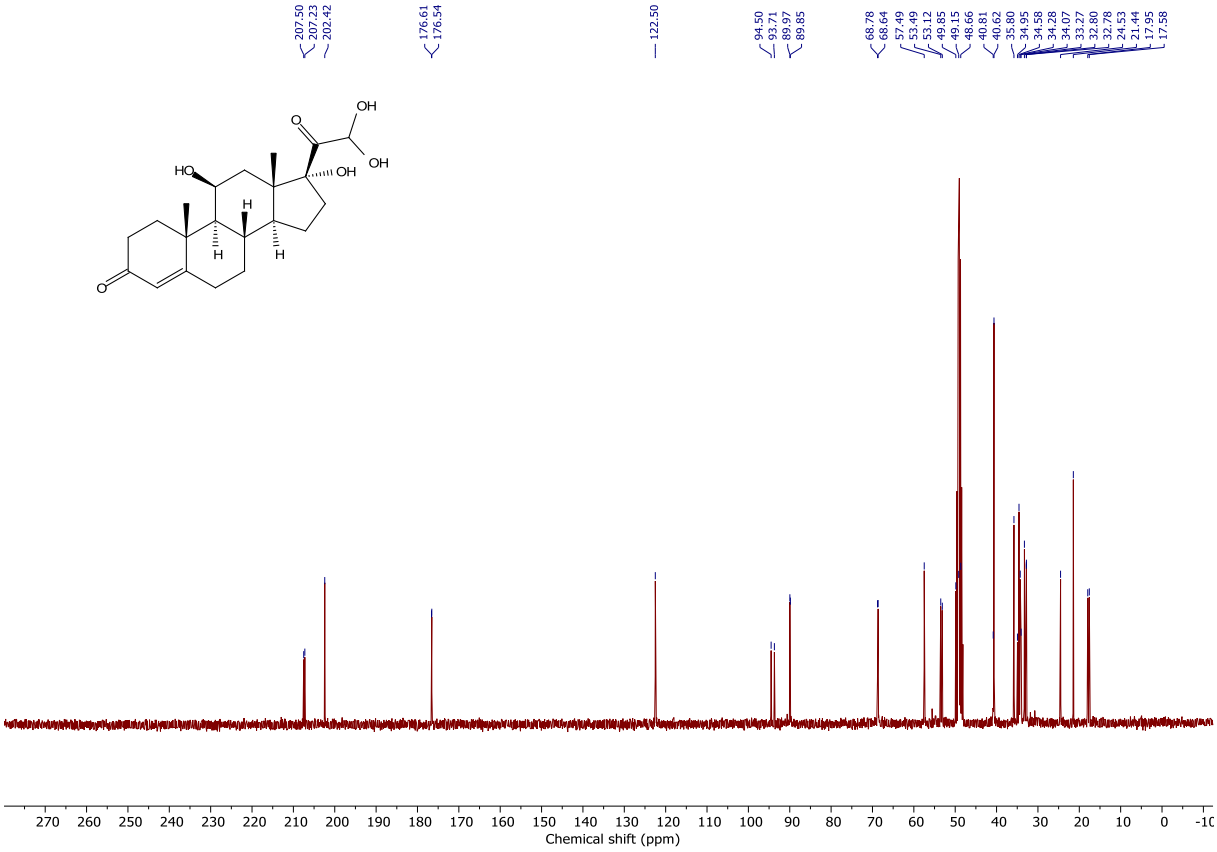
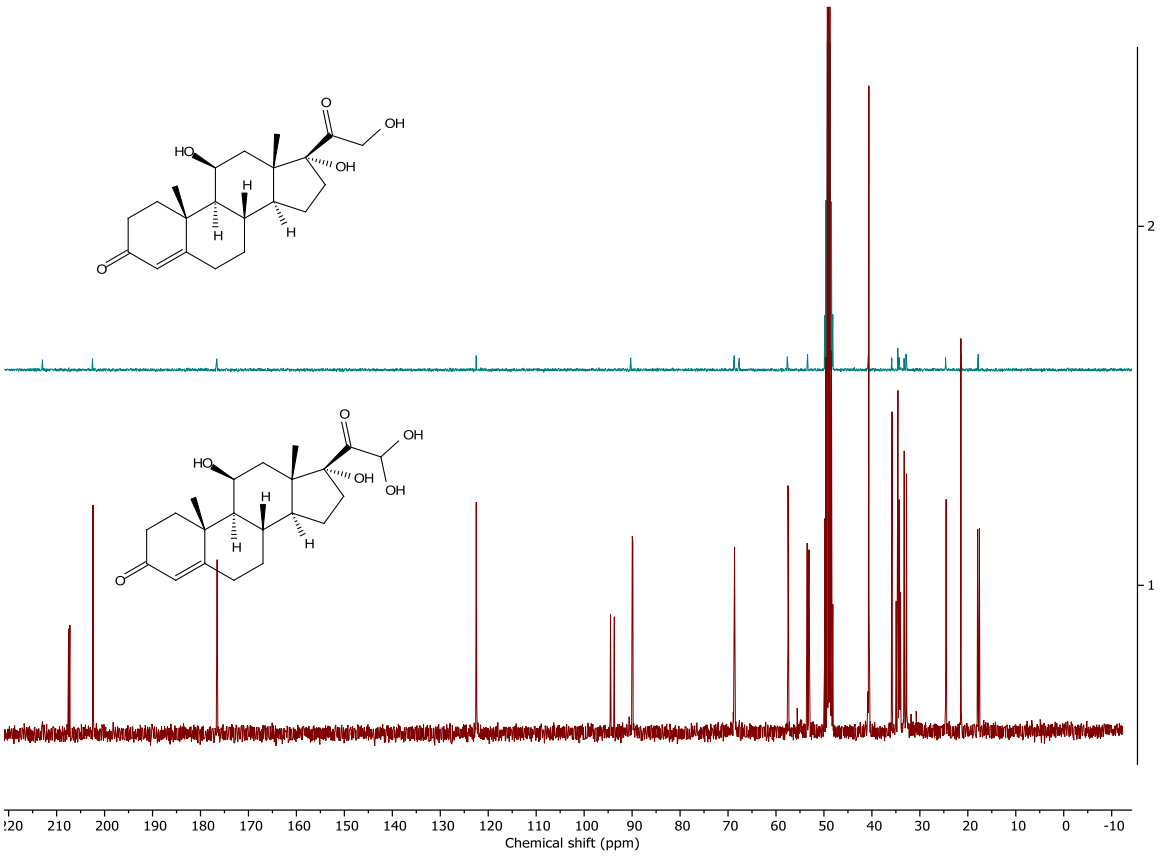
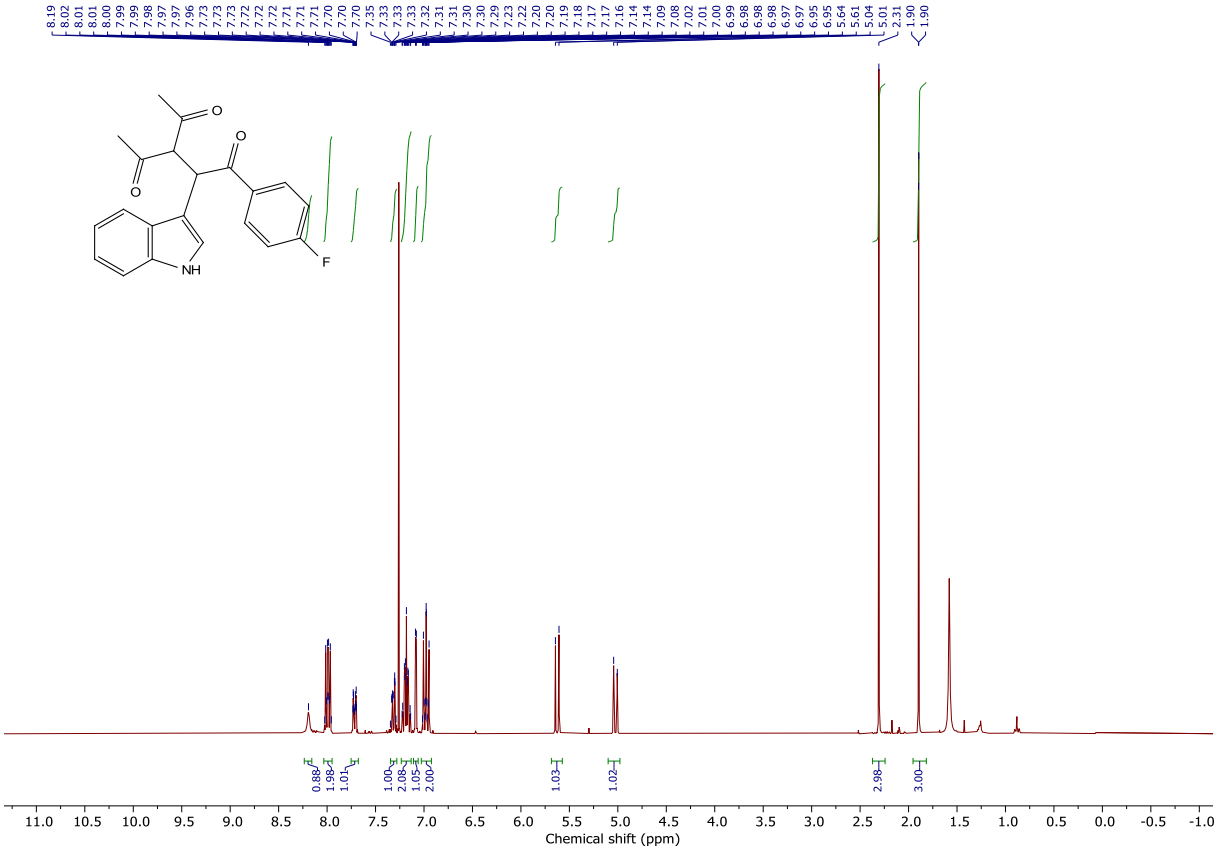


Comparing the product (4r) to hydrocortisone

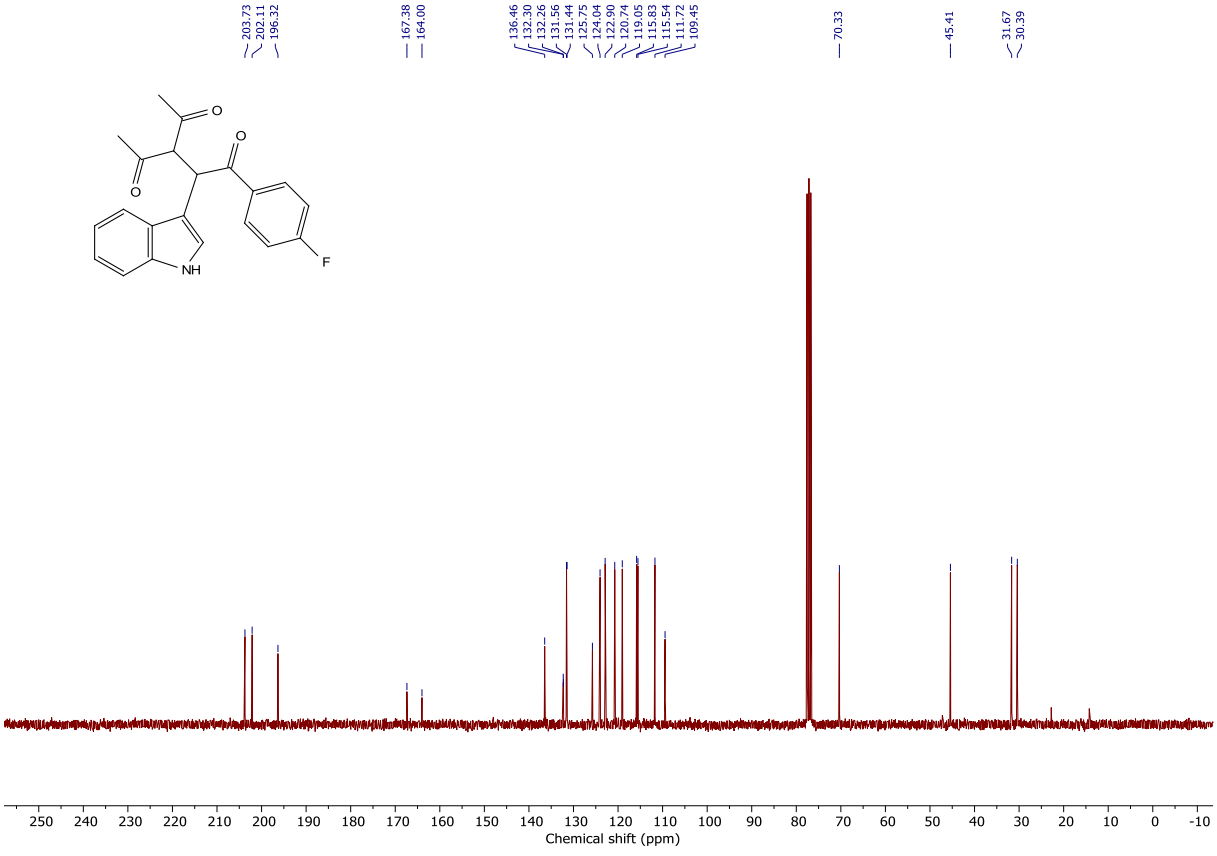


Appendix II: NMR spectra of 4b with Indole and Acetylacetone

^{1}H-NMR (300 MHz, $CDCl_3$)

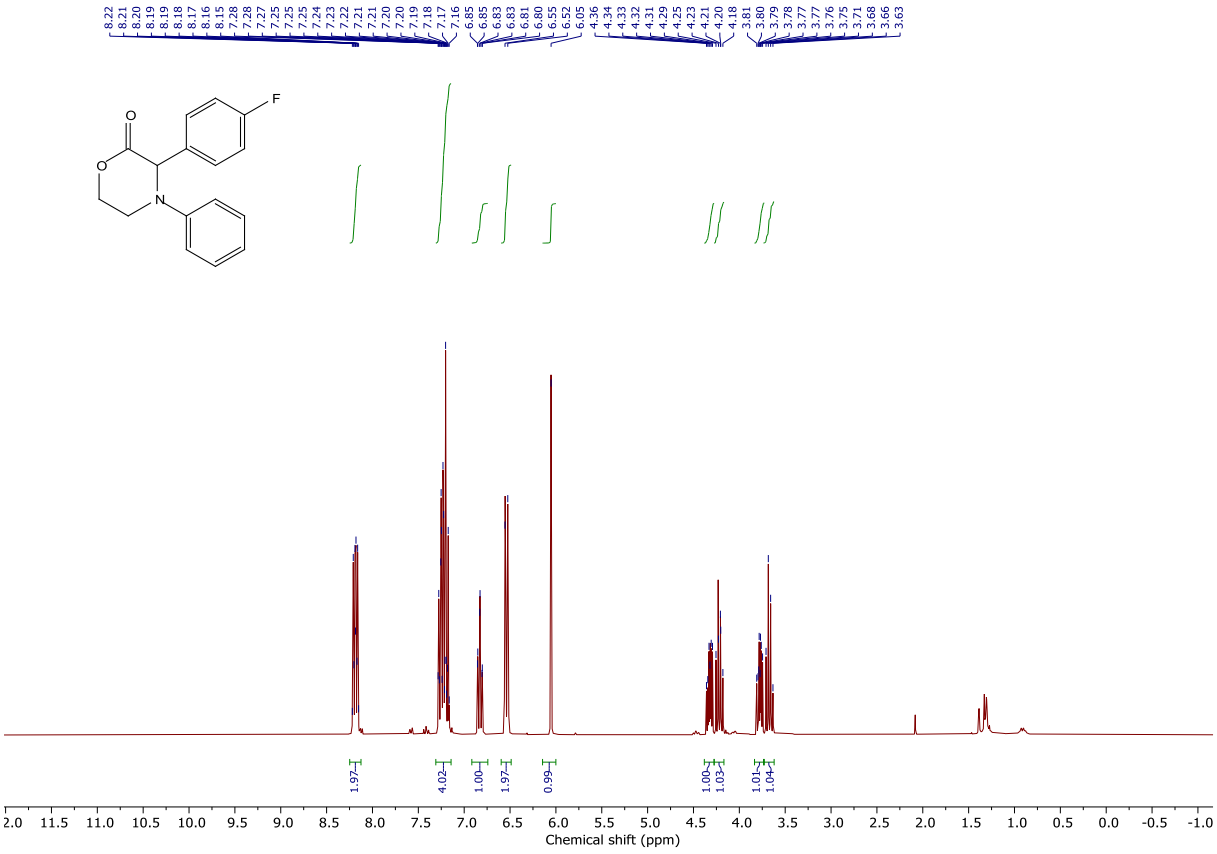


^{13}C-NMR (75 MHz, $CDCl_3$)

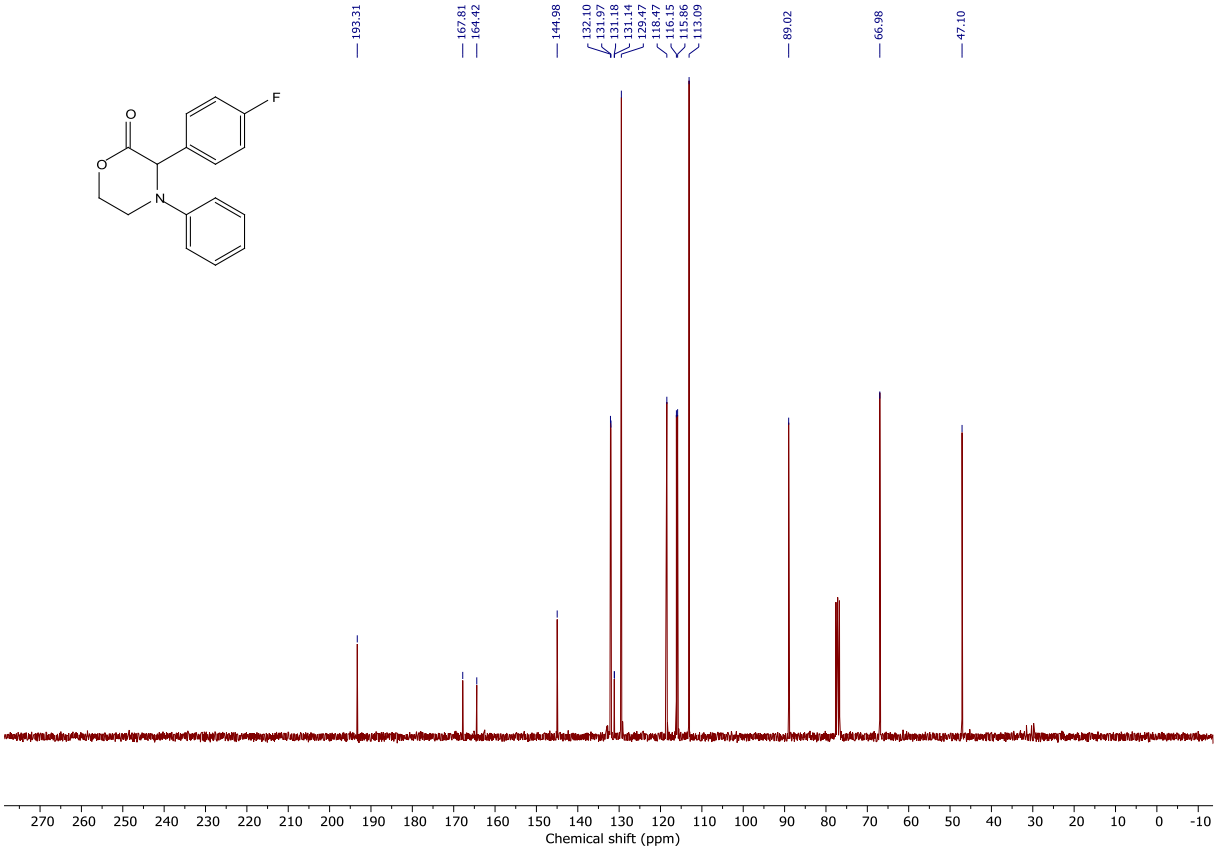


Appendix III: NMR spectra of 4b with 2-(Phenylamino)ethan-1-ol

^{1}H-NMR (300 MHz, $CDCl_3$)

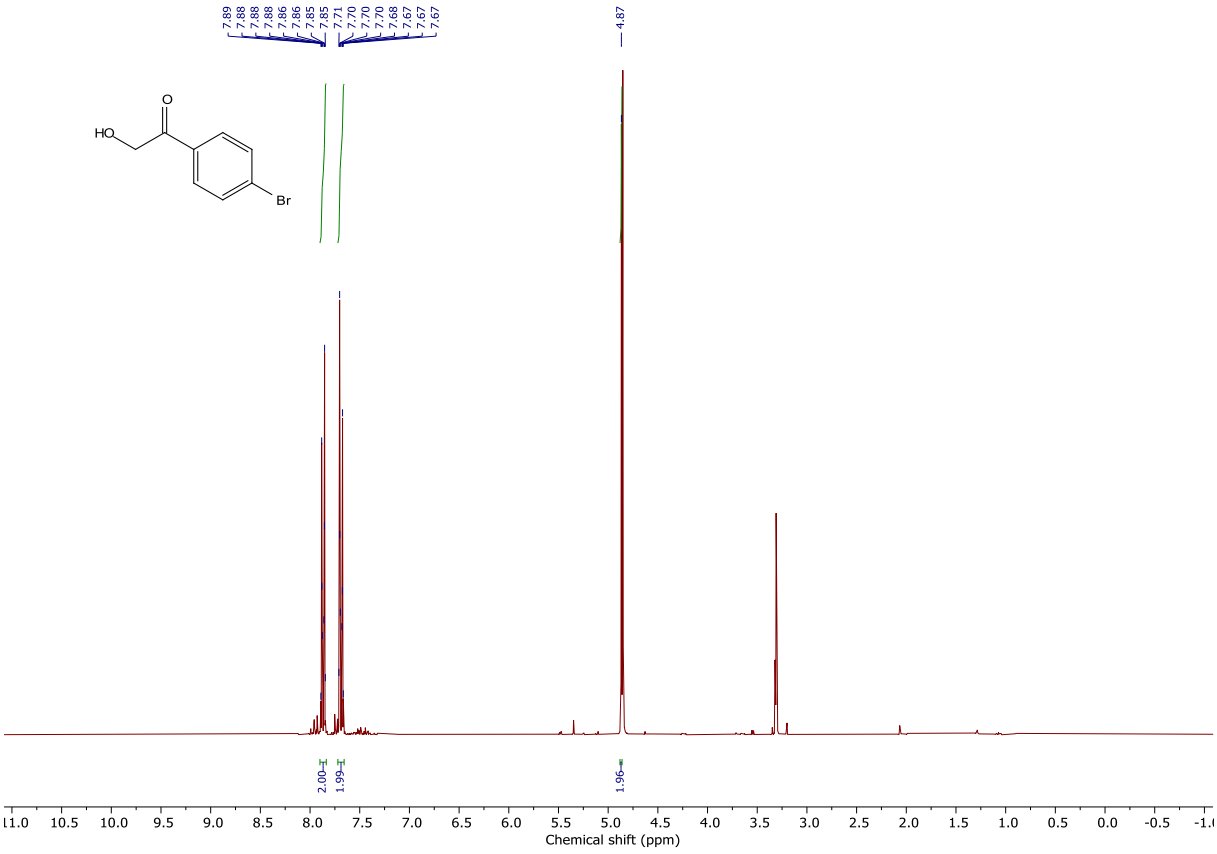


^{13}C-NMR (75 MHz, $CDCl_3$)

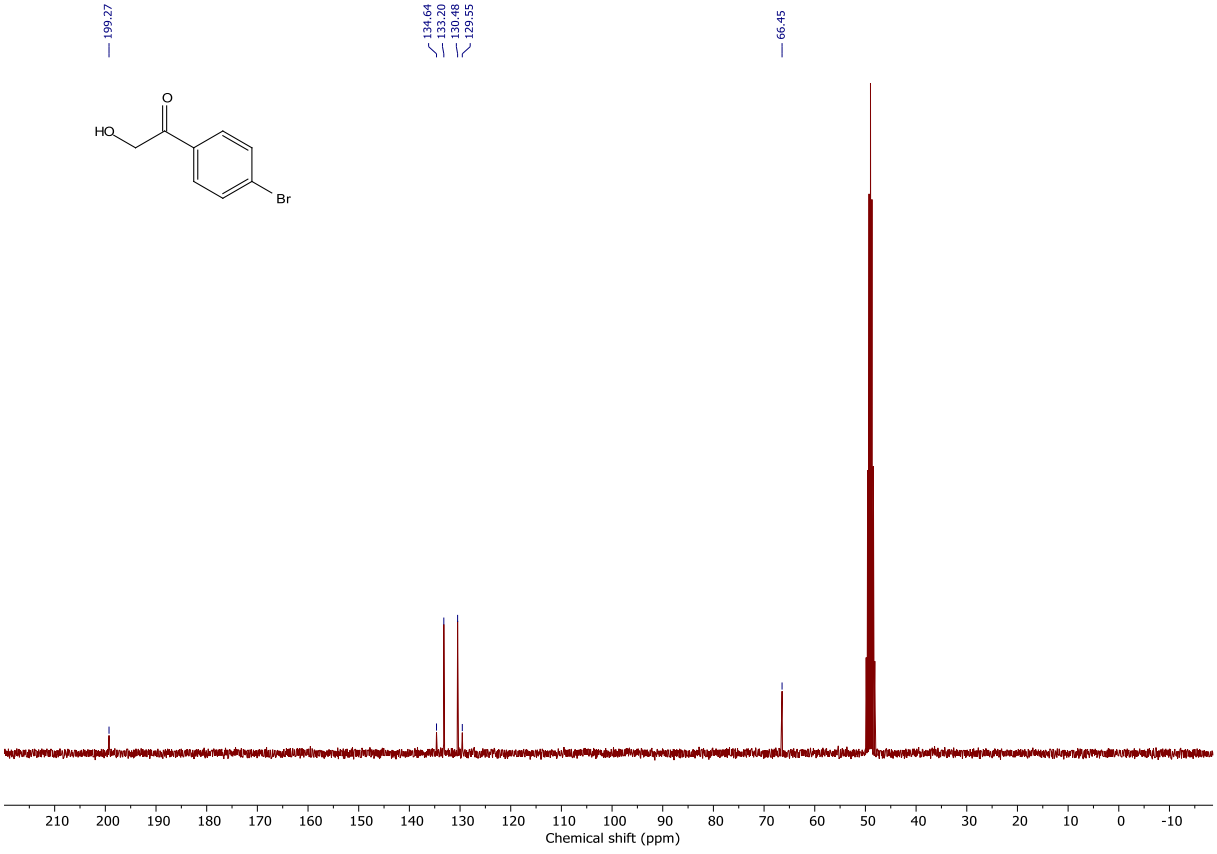


Appendix IV: NMR spectra of α-hydroxy ketones and MDH

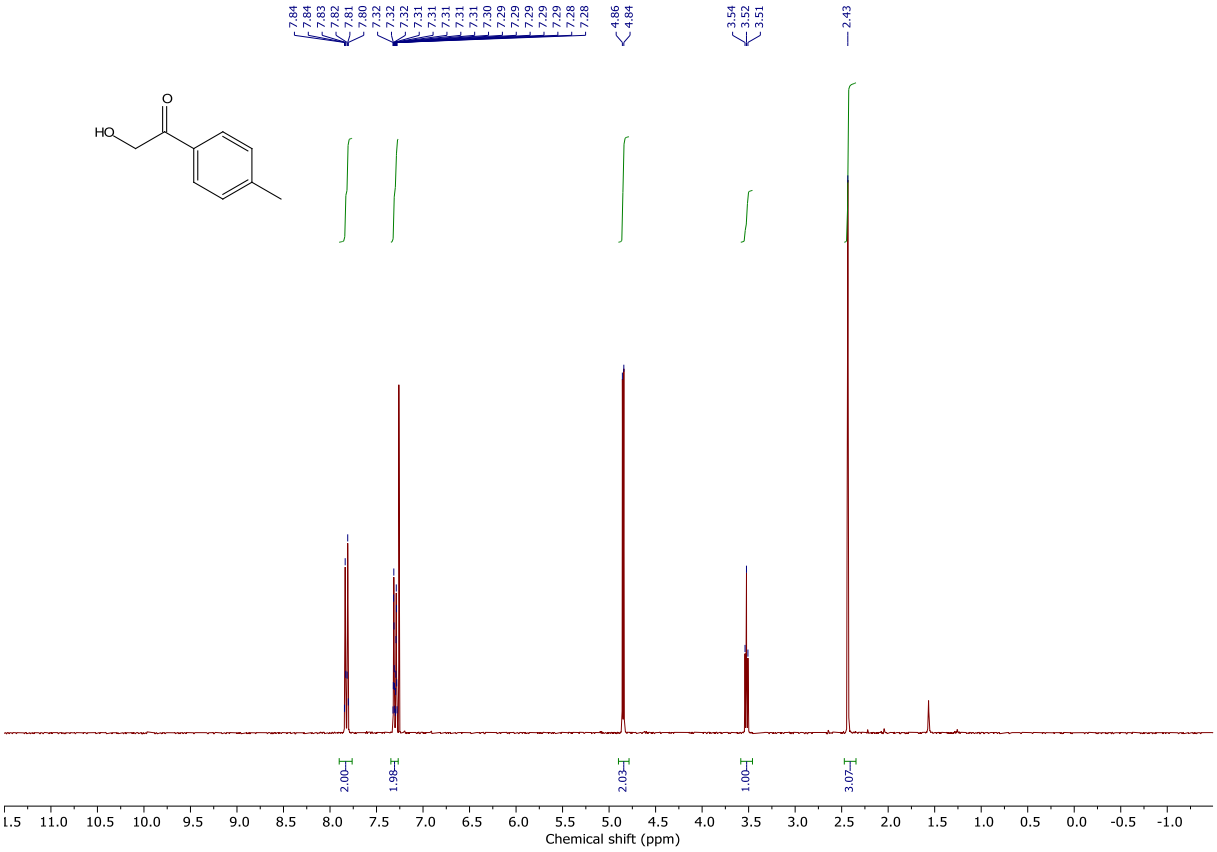
^{1}H-NMR (300 MHz, MeOH-d_4)



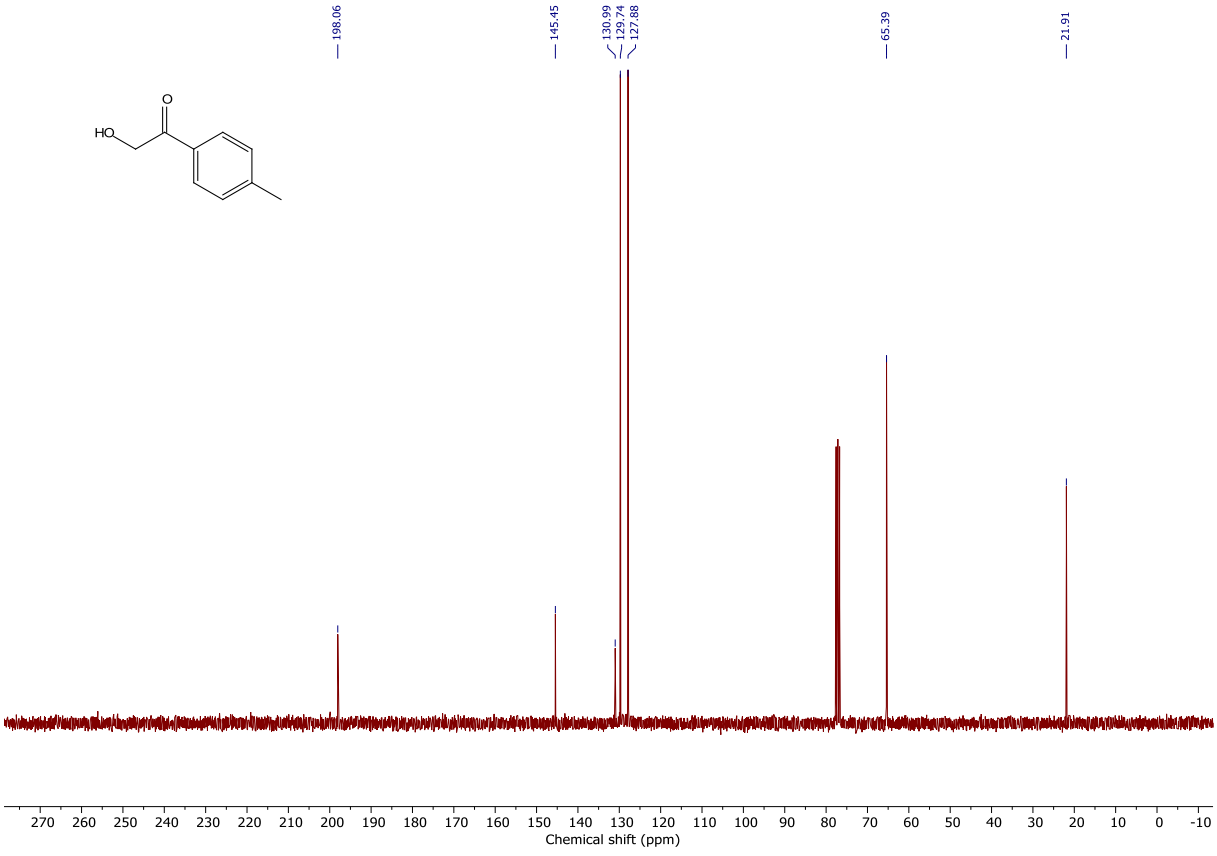
^{13}C-NMR (75 MHz, MeOH-d_4)



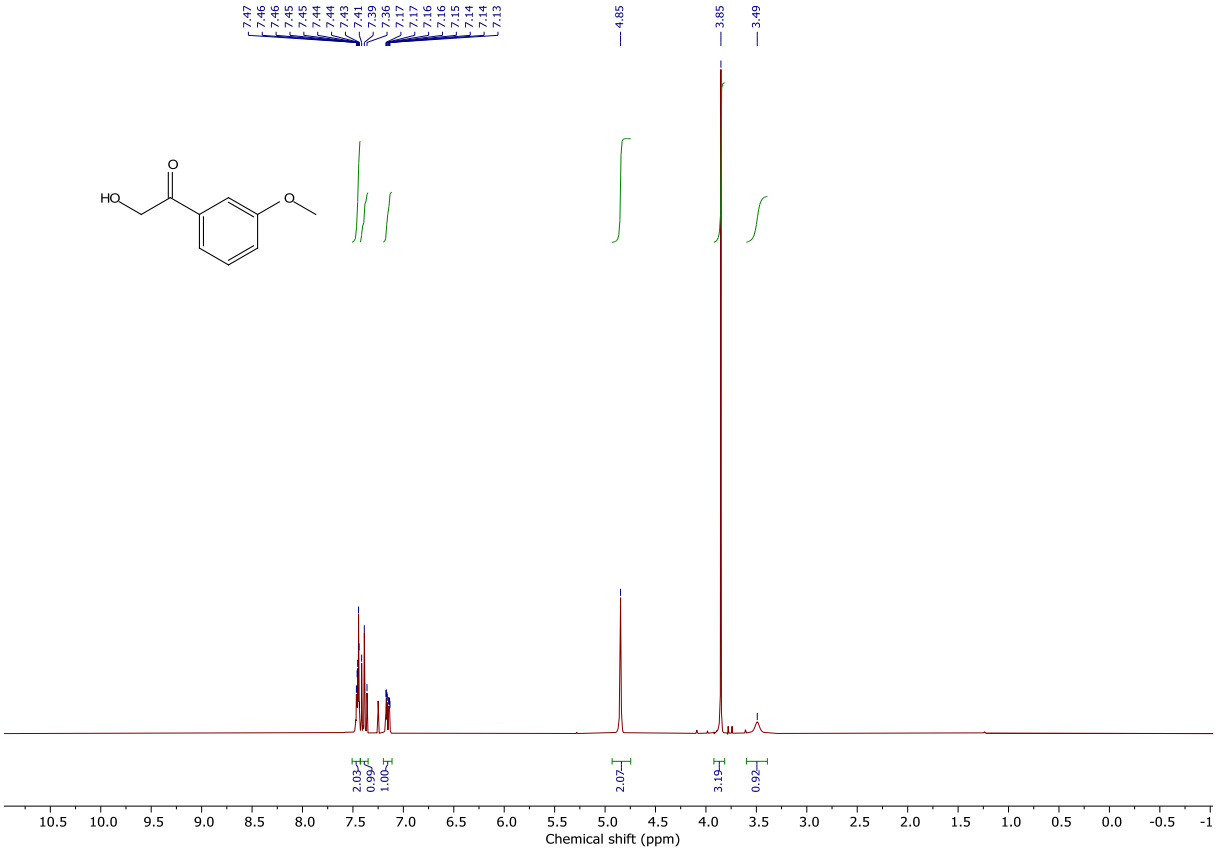
^{1}H-NMR (300 MHz, $CDCl_3$)



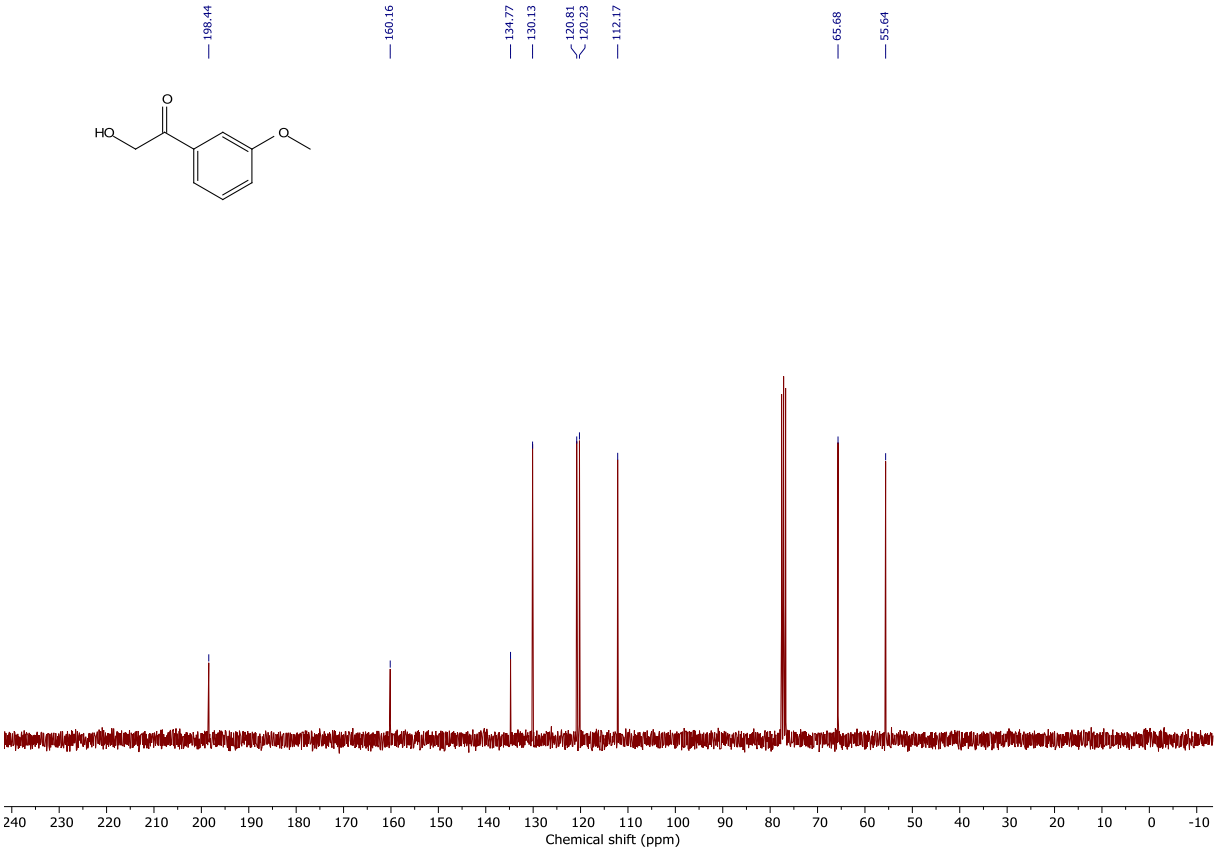
^{13}C-NMR (75 MHz, $CDCl_3$)



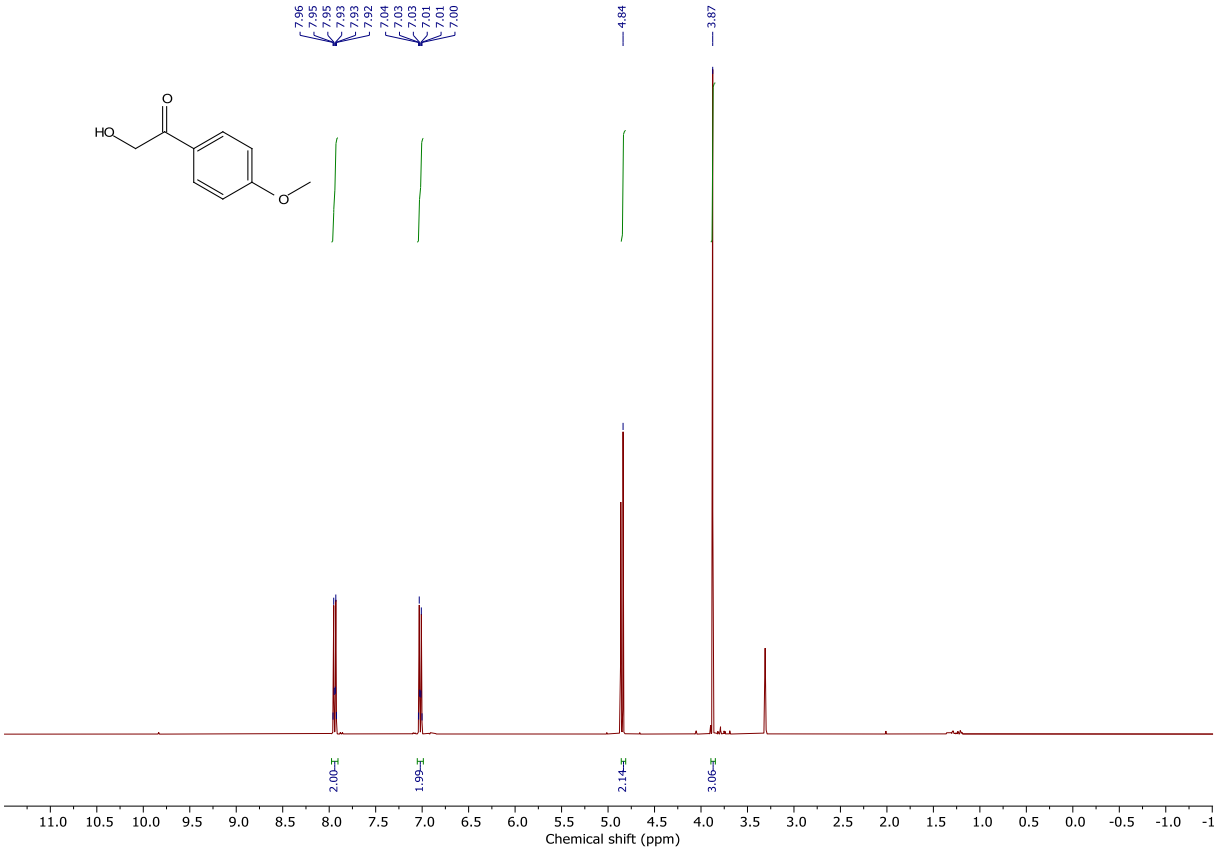
^{1}H-NMR (300 MHz, $CDCl_3$)



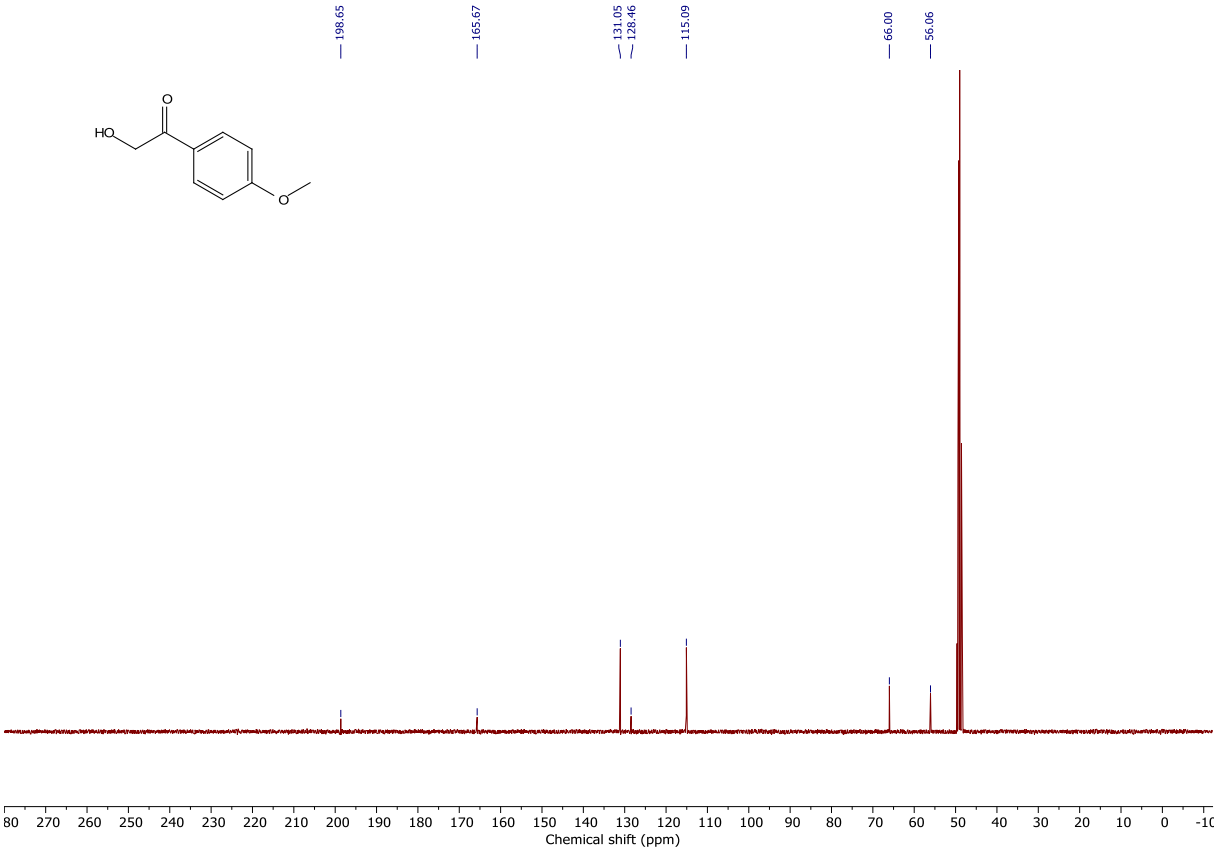
^{13}C-NMR (75 MHz, $CDCl_3$)



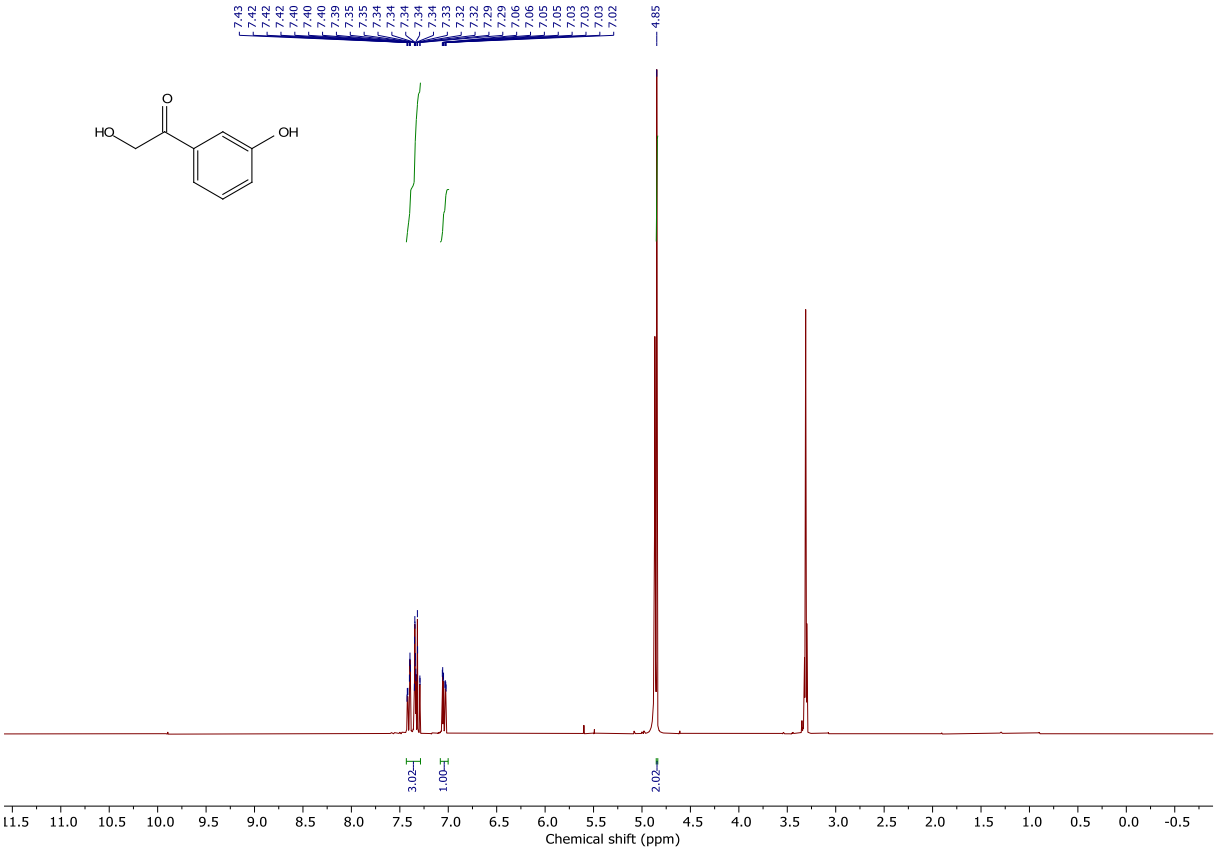
^{1}H-NMR (400 MHz, MeOH-d_4)



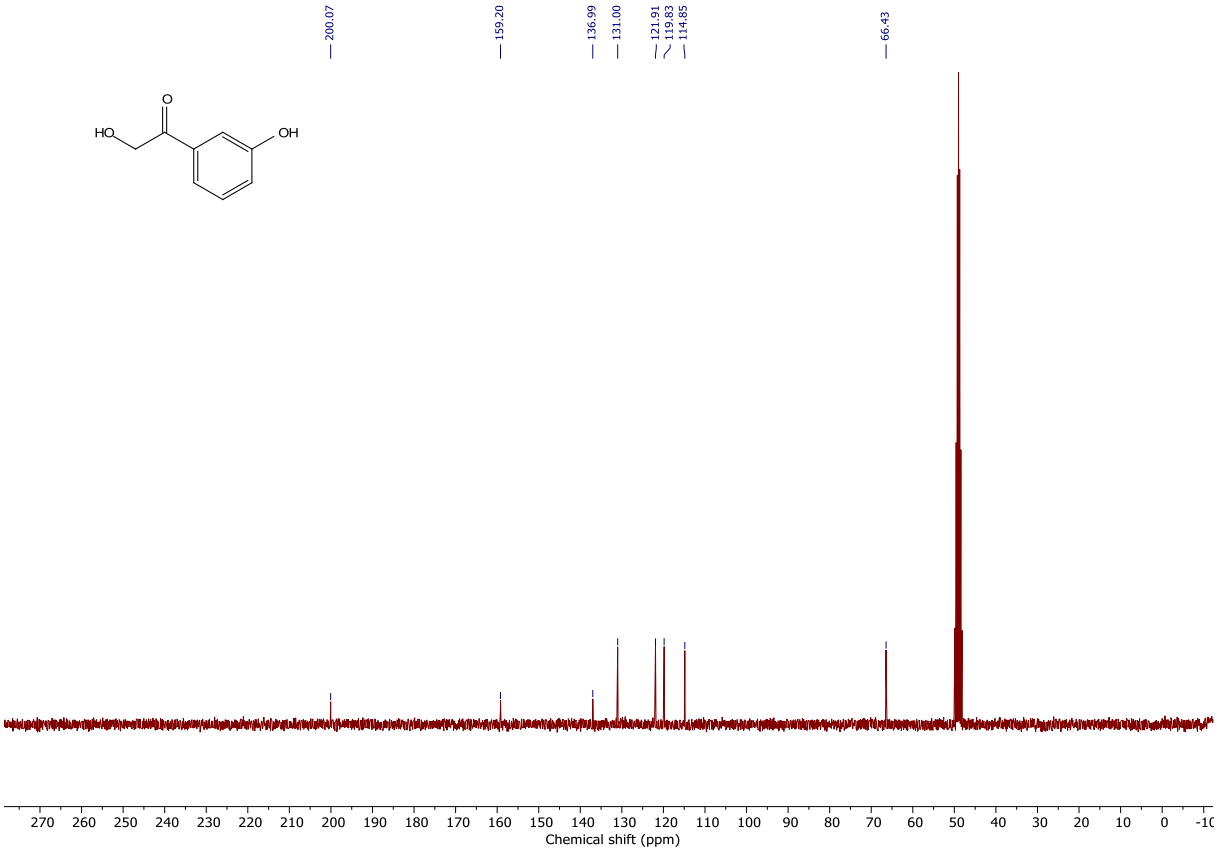
^{13}C-NMR (101 MHz, MeOH-d_4)



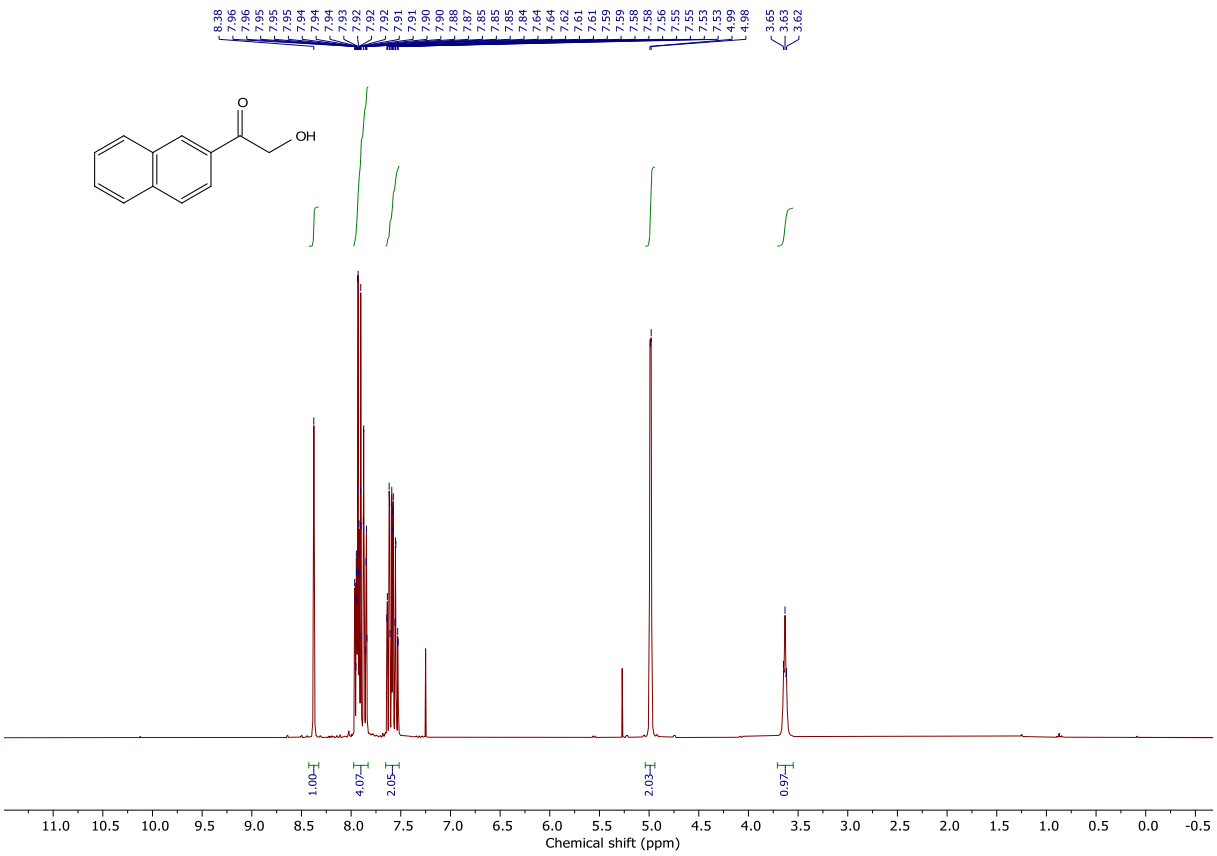
^{1}H-NMR (300 MHz, MeOH-d_4)



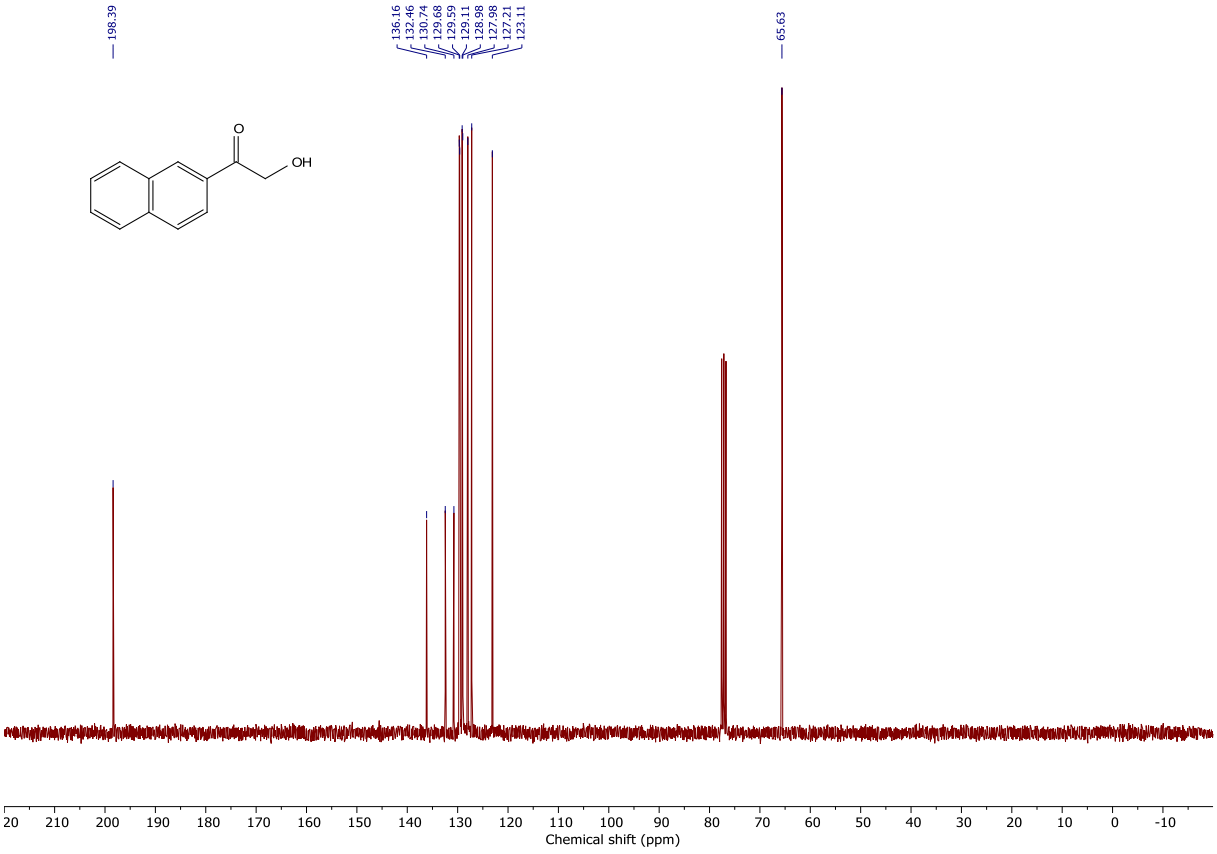
^{13}C-NMR (75 MHz, MeOH-d_4)



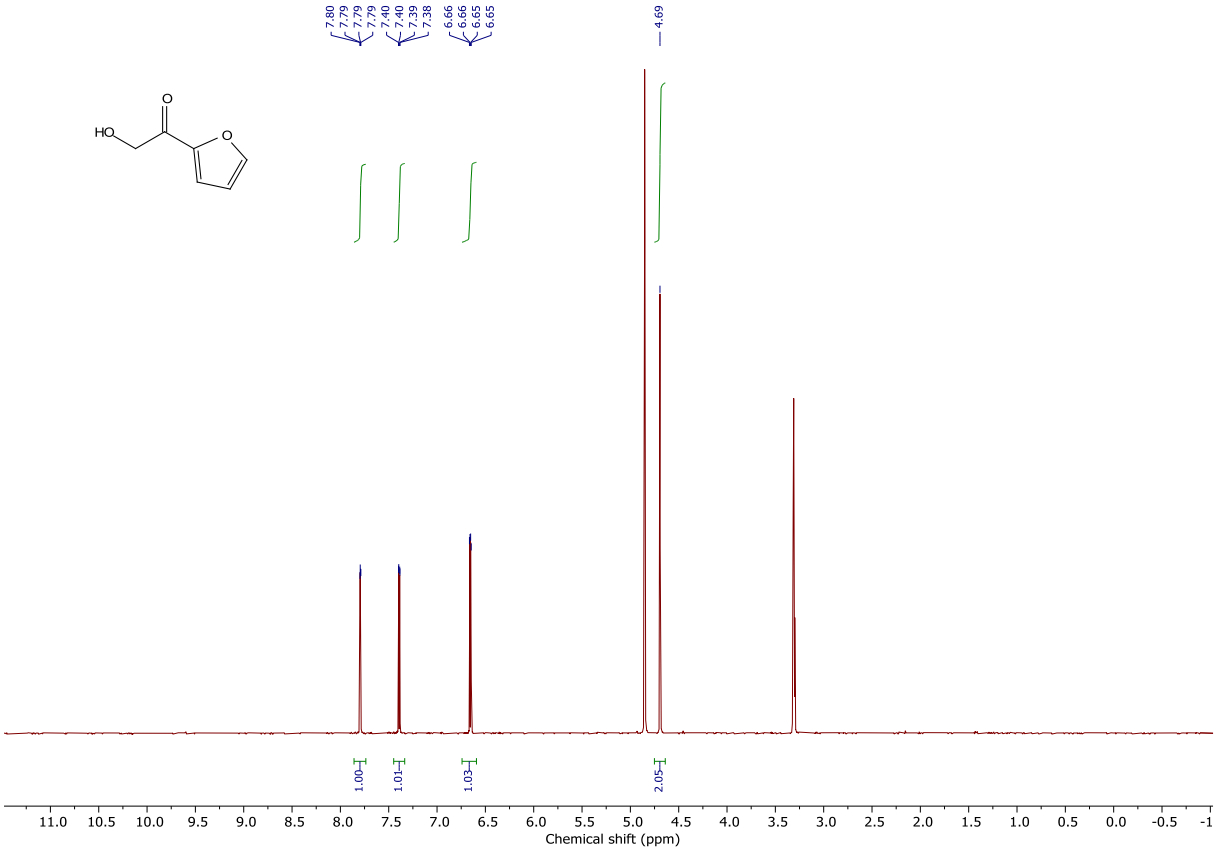
^{1}H-NMR (300 MHz, $CDCl_3$)



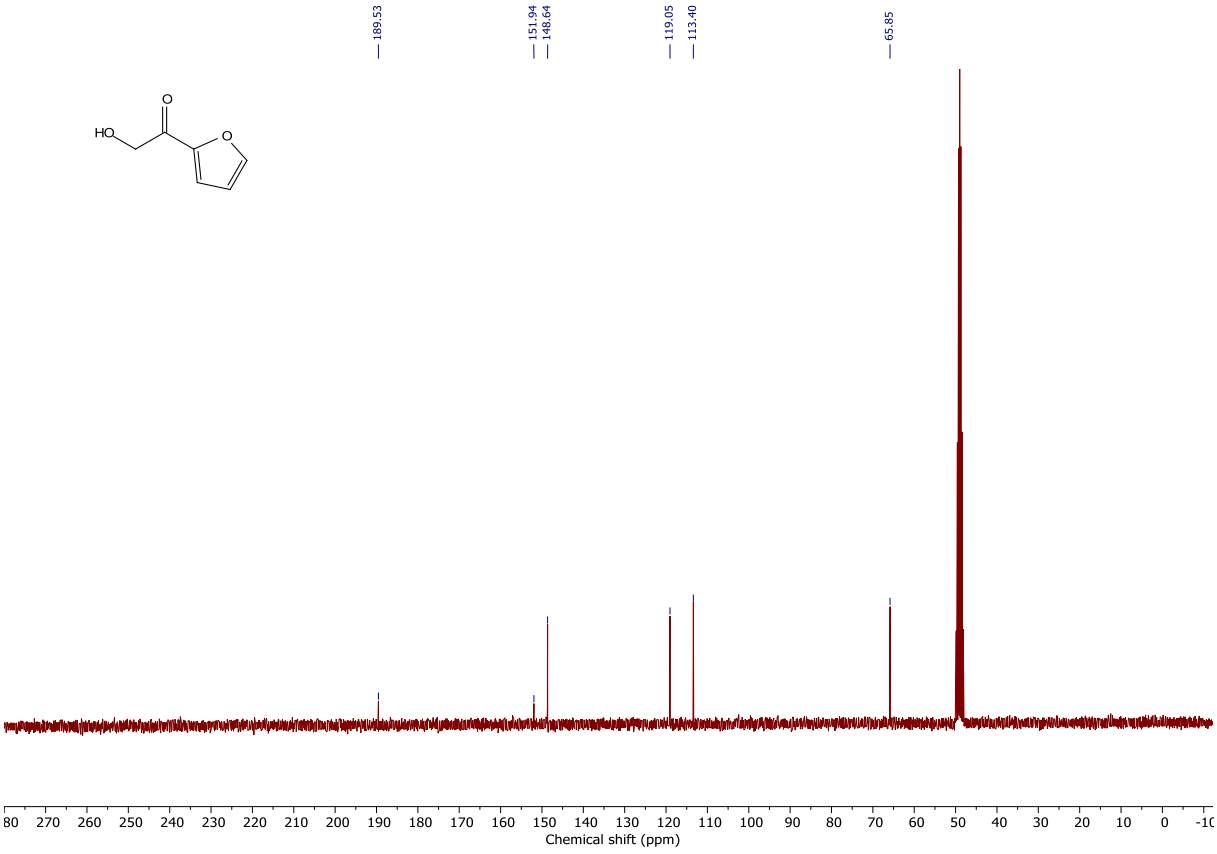
^{13}C-NMR (75 MHz, $CDCl_3$)



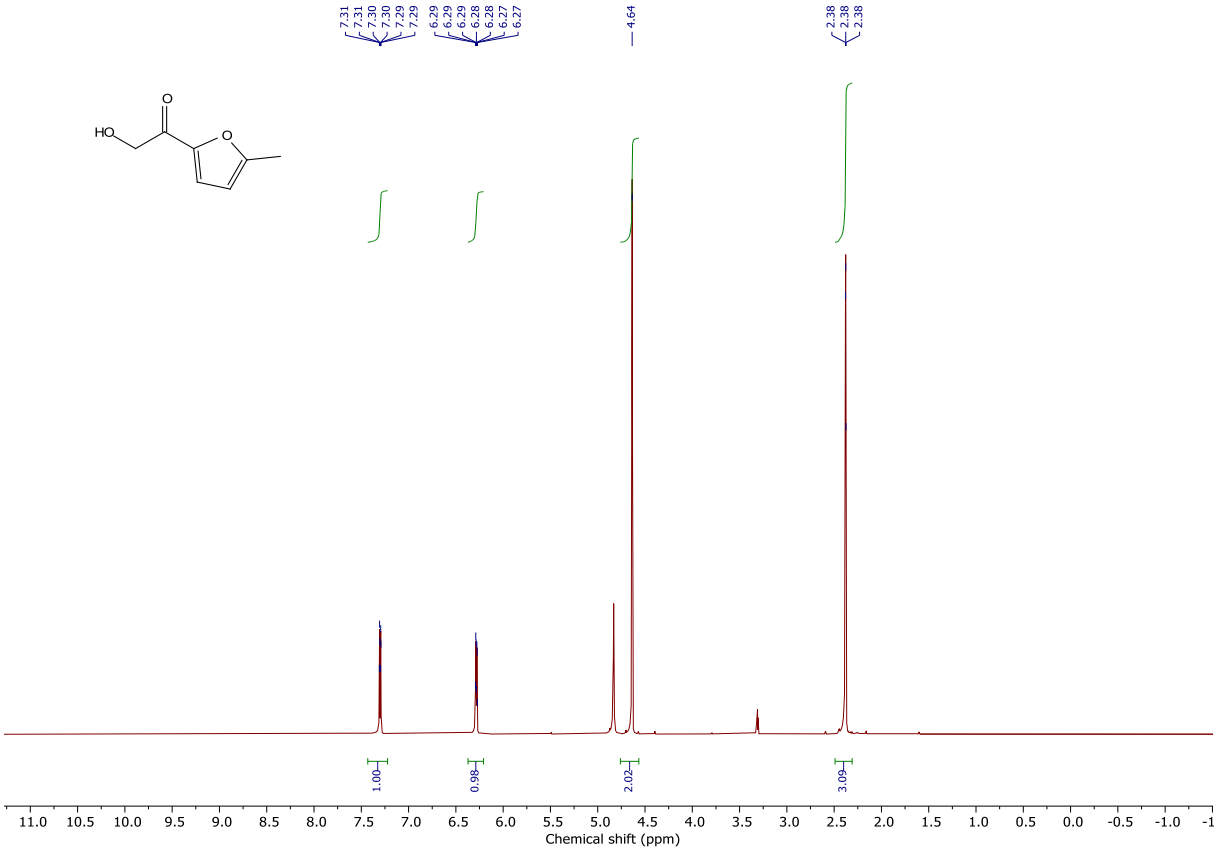
^{1}H-NMR (300 MHz, MeOH-d_4)



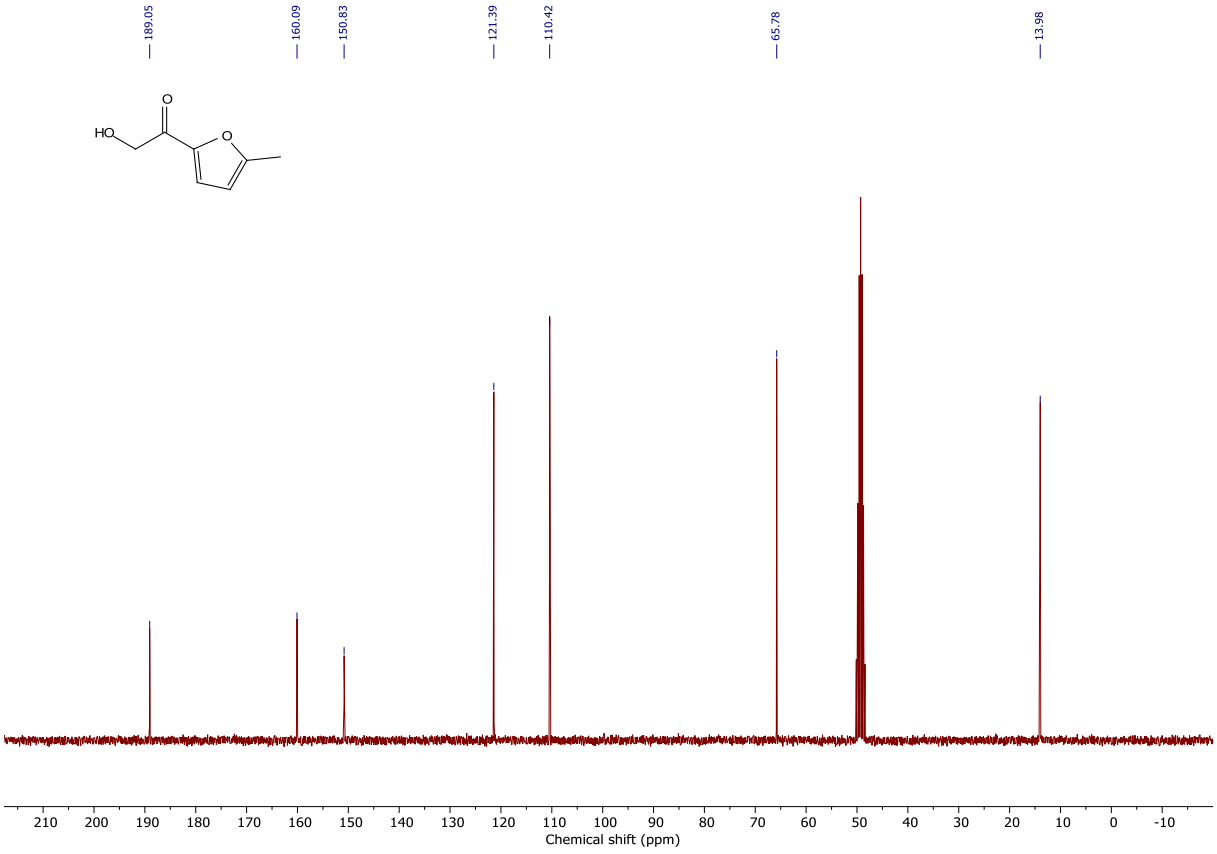
^{13}C-NMR (75 MHz, MeOH-d_4)



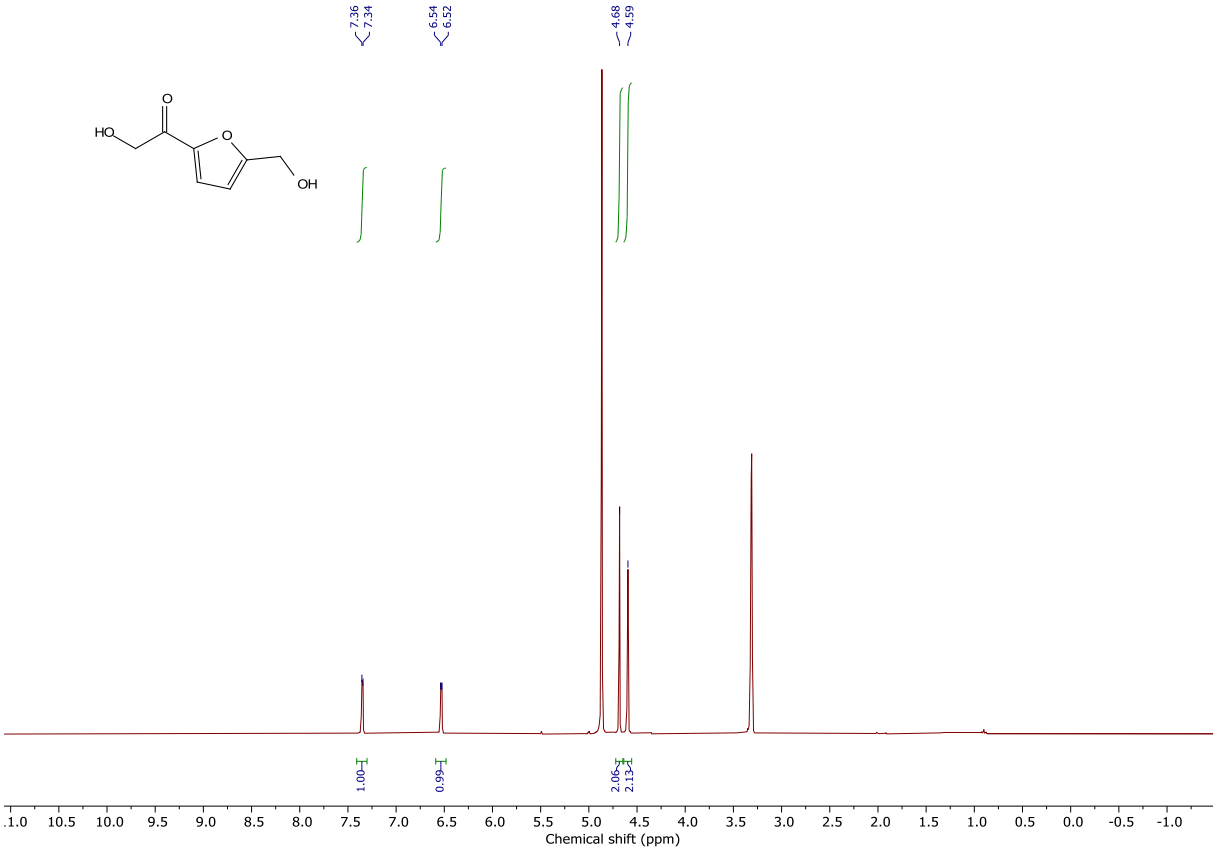
^{1}H-NMR (300 MHz, MeOH-d_4)



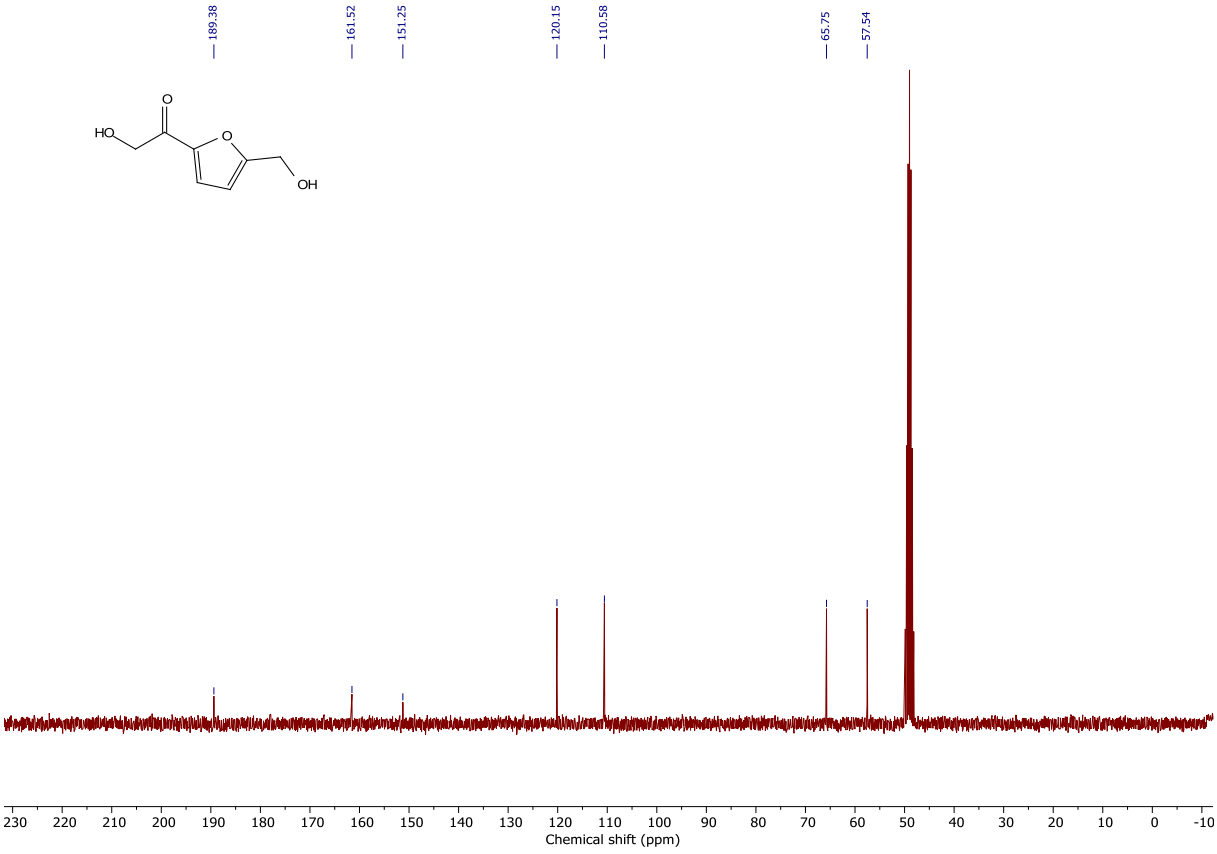
^{13}C-NMR (75 MHz, MeOH-d_4)



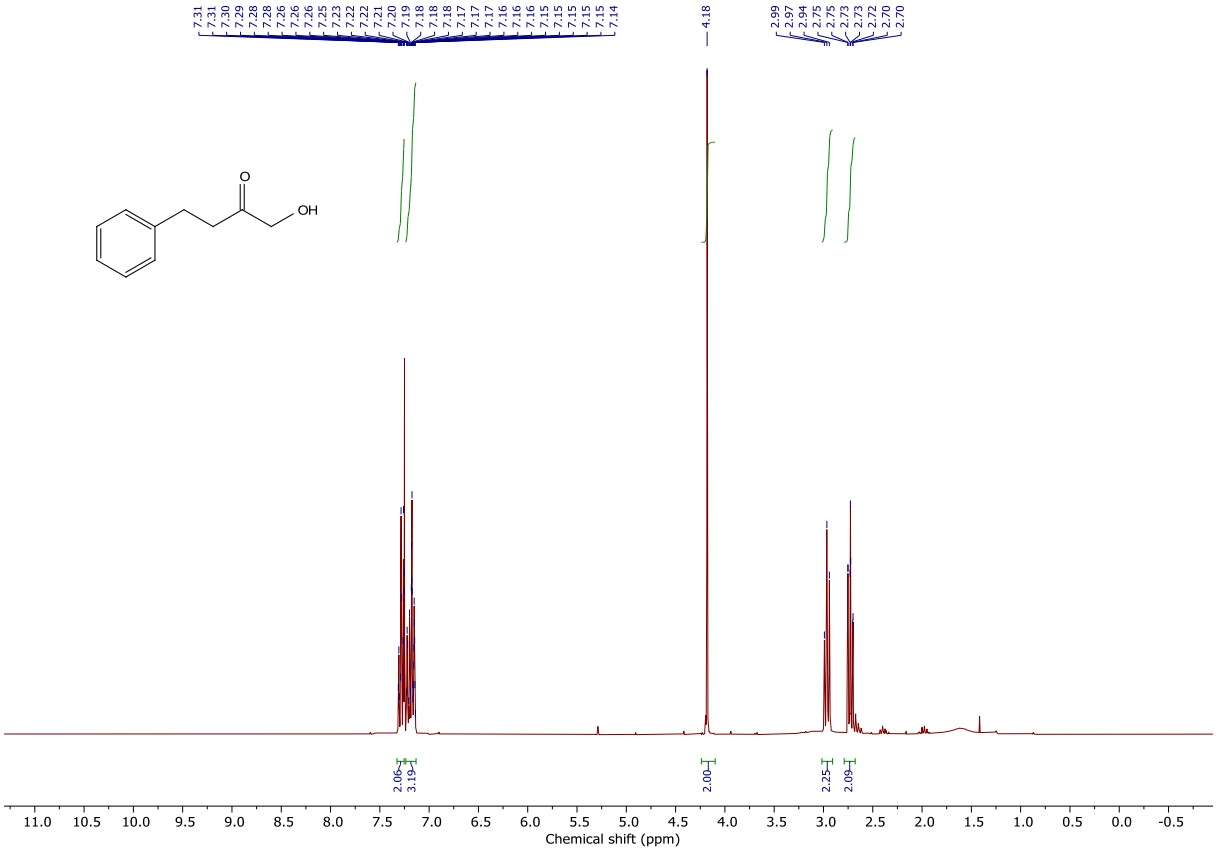
^{1}H-NMR (300 MHz, MeOH-d_4)



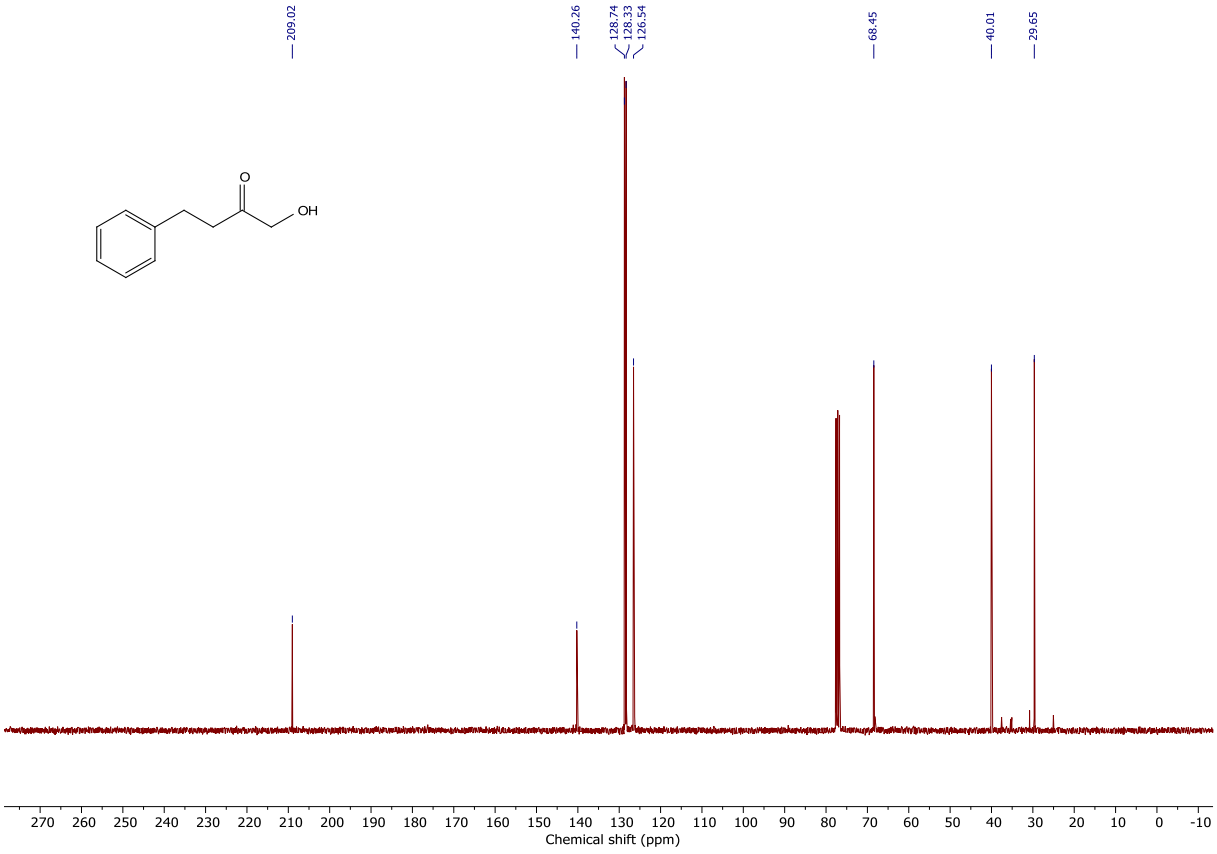
^{13}C-NMR (75 MHz, MeOH-d_4)



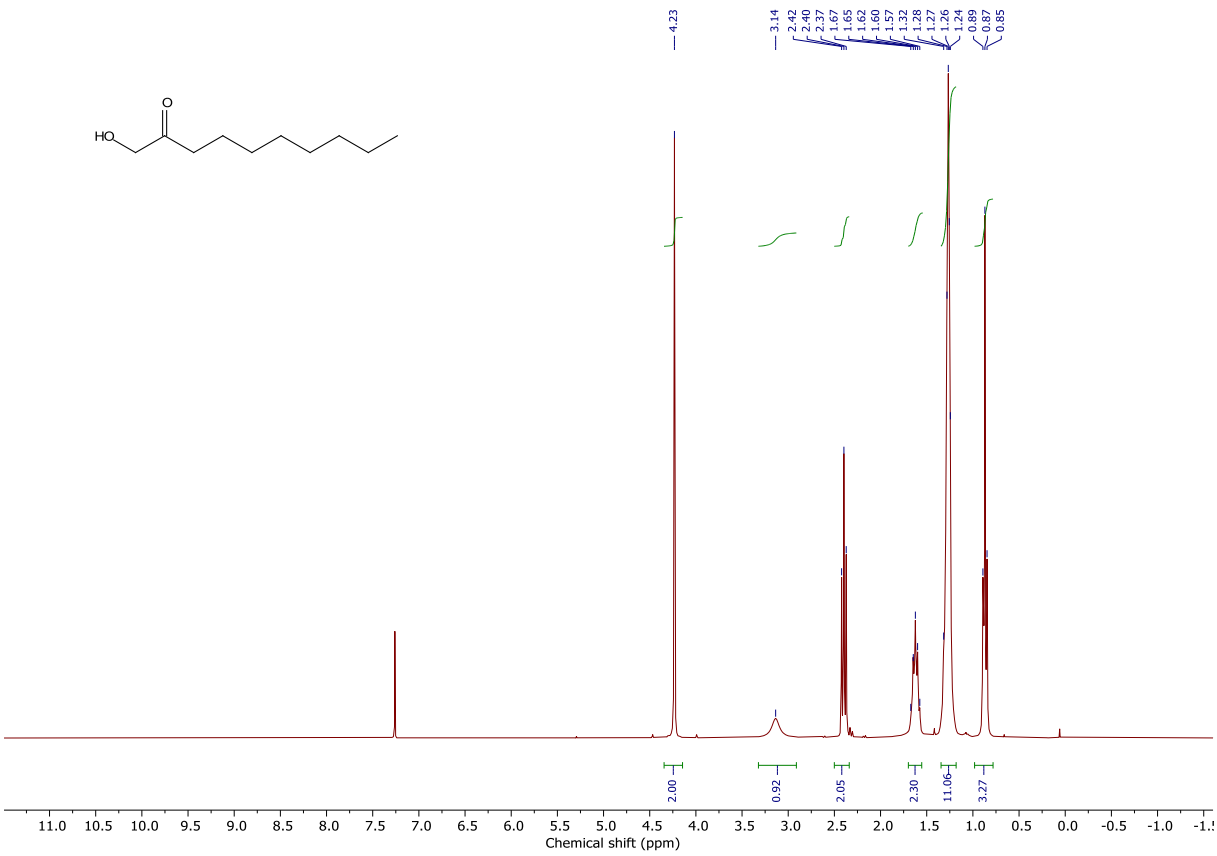
^{1}H-NMR (300 MHz, $CDCl_3$)



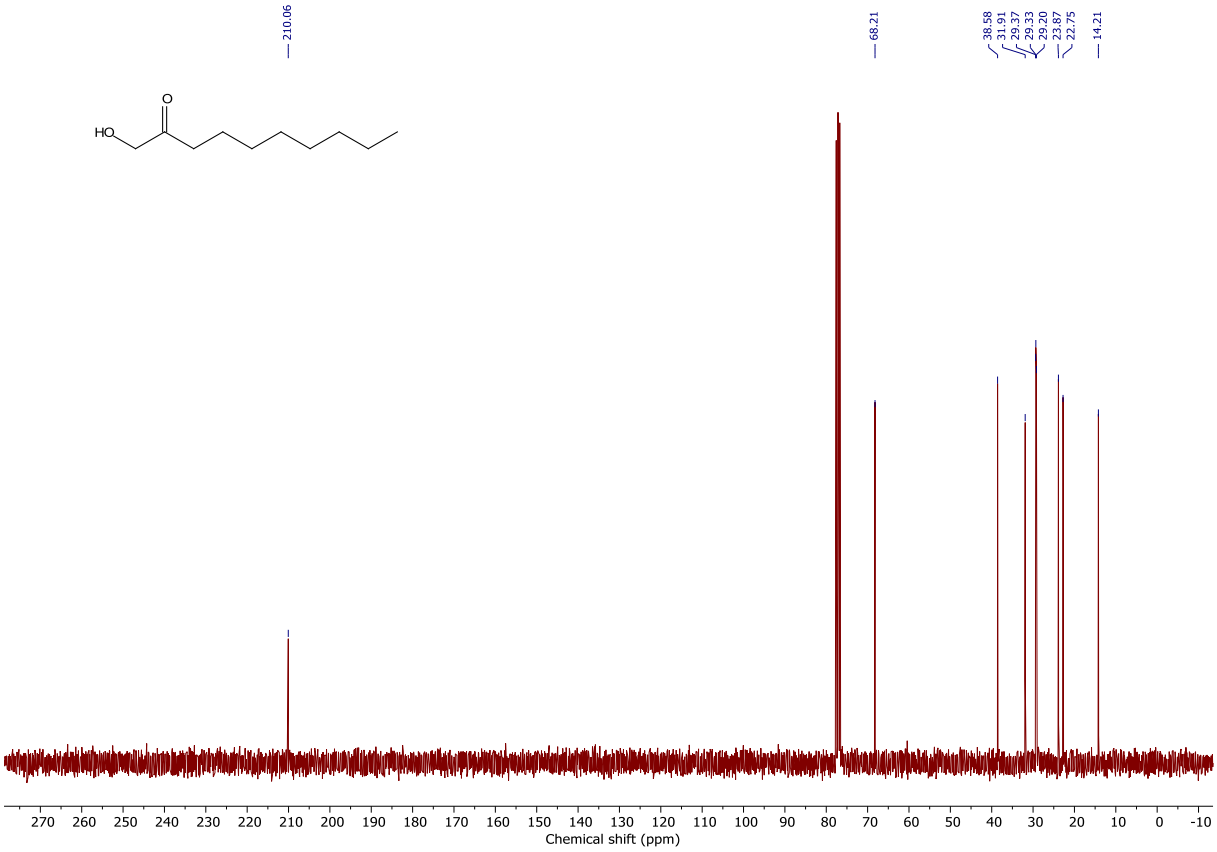
^{13}C-NMR (75 MHz, $CDCl_3$)



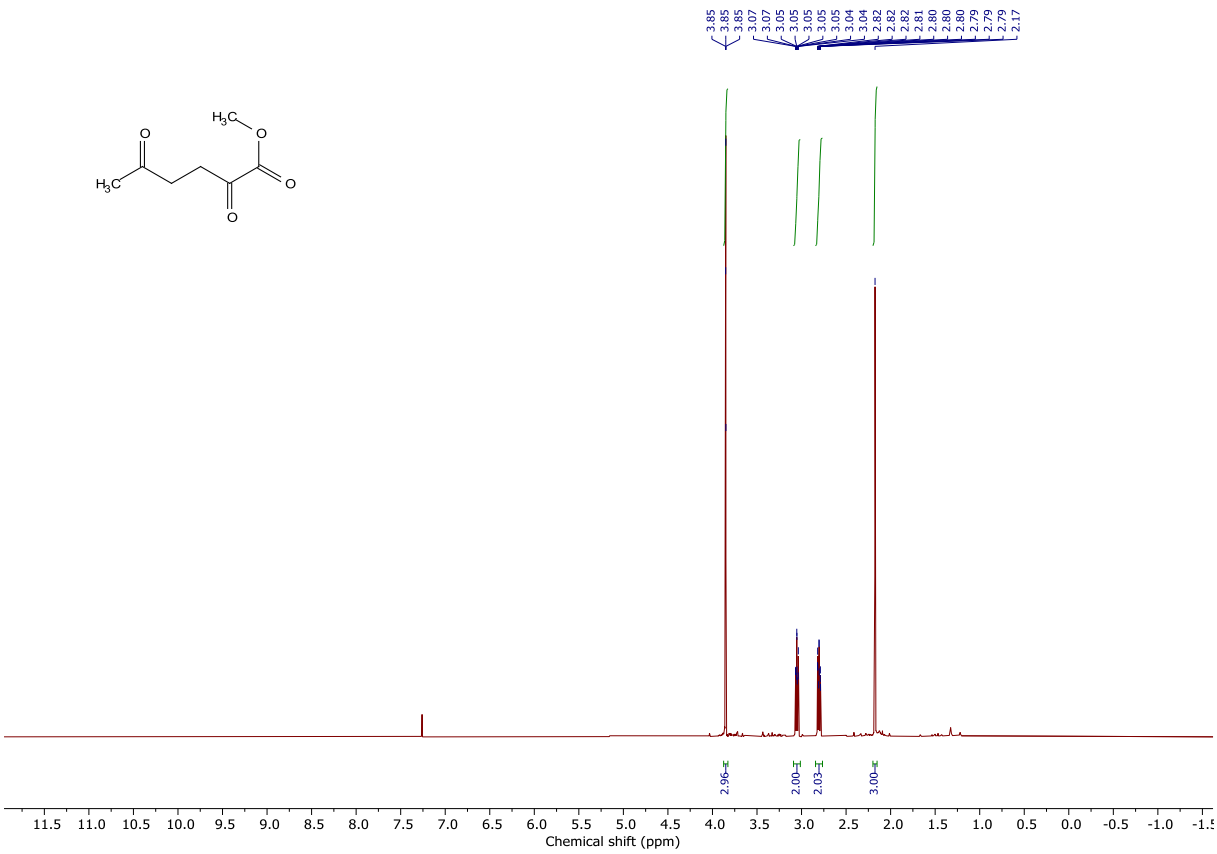
^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C-NMR (75 MHz, $CDCl_3$)



^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C-NMR (75 MHz, $CDCl_3$)