Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

SUPPORTING INFORMATION

Continuous Flow Synthesis of Hydroxy Lactones from Alkenoic Acids

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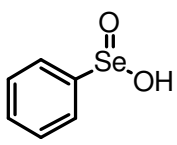
General methods

Unless otherwise noted, chemicals were obtained from commercial suppliers and used without further purification. NMR spectra were recorded on a Bruker AC 400 MHz spectrometer in the indicated solvent. Chemical shifts are reported in parts per million (ppm) and are relative to $CDCl_3$ (7.26 ppm and 77.0 ppm) or to d^6-DMSO (2.49 ppm and 39.7 ppm). The abbreviations used are as follows: s, singlet; brs, broad singlet; d, doublet; dd, double doublet; ddd, doublet of doublet of doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; brm, broad multiplet. With the exception of compounds **5f** and **5l**, all the synthesised substrates, the selenium catalyst and the products have been previously reported and their spectroscopic data obtained in this study are consistent with the literature data.[1-10] For new compounds **5f** and **5l**, high resolution mass spectra (HRMS) were recorded on Agilent 6540-UHD Accurate Mass Q-TOF LC/MS instrument and mass spectrum of the analyte extract ion chromatogram (EIC) was acquired in positive full scan mode (ESI+). A Prevail C18 column (250 x 4.6 mm i.d., 5µm) was used as analytical column for HPLC analysis with DAD detector. A mixture of H_2O/CH_3CN (60:40, v/v) was used as the eluent with a flow rate of 1 mL min^{-1}. IR spectra were recorded on a Jasco FT/IR 410 instrument (KBr). All flow experiments were performed using a commercially available modular Vapourtec R serie equipped with two-loop injection systems (PTFE, 1/16" OD x 0.02" ID, 2 mL each), two integrated HPLC pumps (R2+ pumping module), two external HPLC pumps (Jasco PU-980), a mesoreactor coil (PFA, 1/16" OD x 0.02" ID, 10 mL), two back pressure regulators (BPR, 100 psi, PEEK, 1/16" OD, 1/4"-28), an in-line liquid-liquid separator SEP-10 (Zaiput, Cambridge, MA – USA), tubular mesoreactors (Omnifit Labware DIBA HIT column, L × ID 6.6 mm x 100 mm and 6.6 mm x 150 mm), 3-way hexagonal valves (PTFE, 1/4"-28, 1-4 mm OD, 1.5 mm ID, DIBA), 6-way connector (PTFE, 1/4"-28, 0.5-4 mm OD, 1.5 mm ID, DIBA) and a fraction collector. Thin-layer chromatography was performed using glass plates coated with silica gel 60 F-254. Spots were visualized by UV detector (λ: 254 nm) and/or by staining and worming with potassium permanganate. When required, flash chromatographic purifications were performed using Biotage Isolera™ Prime.

Synthesis of phenylseleninic acid (2)[1]



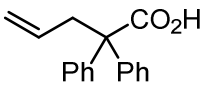
To a solution of $(PhSe)_2$ (2.5 g, 8.01 mmol) in CH_2Cl_2 (6 mL), H_2O_2 (30% wt, 3.3 mL, 31.49 mmol) was added dropwise in 30 min at 0-5 °C. The yellow solution was vigorously stirred at this temperature for 8 h. The white suspension thus obtained was filtered off and the solid was washed with cold H_2O (4 mL) and cold CH_2Cl_2 (7 mL) to afford

phenylseleninic acid (**2**) (2.63 g, 13.91 mmol, 87%) as white solid (m.p.: 124-126 °C, Lit.:[1] 124-125 °C). ^{1}H-NMR (*d*^{6}-DMSO, 400 MHz): δ 7.58-7.60 (m, 3H), 7.81-7.83 (m, 2H). ^{13}C-NMR (*d*^{6}-DMSO, 100.6 MHz): δ 126.3, 129.4, 132.1, 149.2. ^{77}Se-NMR (*d*^{6}-DMSO, 76.3 MHz): δ 1180.40.

Synthesis of alkenoic acids 3k-m[2]

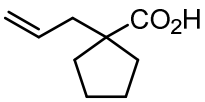
To a solution of freshly distilled *N*,*N*-diisopropylamine (0.85 mL, 6 mmol) in dry THF (1 mL), 2.5 N solution of *n*-BuLi in hexane (2.4 mL, 6 mmol) was added dropwise in 15 min at -78 °C under argon atmosphere. After 1h, the mixture was warmed to -40 °C and, to this solution, a solution of the corresponding acid (1 mmol) in freshly distilled THF (2 mL) was added dropwise at -40 °C in 10 min. The resulting suspension was stirred for 1 h at r.t. and for 30 min at 60 °C. The suspension was cooled to 0 °C and allyliodide (5 mmol, 0.43 mL) was added dropwise. The mixture was stirred at 60 °C for 2 h, then poured into ice-cold water (20 mL) and extracted with Et_2O (3 x 20 mL). The organic phase was acidified (pH 1) with 3N aqueous solution of HCl and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography using Biotage Isolera™ Prime (Cartridge: KP SIL 25 g, Eluent: *n*-hexane/EtOAc from 100:0 to 70:30, v/v).

2,2-diphenylpent-4-enoic acid (3k)[2]



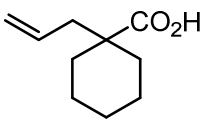
Isolated yield: 65% (165 mg, 0.65 mmol). White solid. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.23 (d, *J*= 6.89 Hz, 2H, 3-C*H*$_2$), 4.97-5.01 (m, 2H, 5-C*H*$_2$), 5.62-5.69 (m, 1H, 4-C*H*), 7.31-7.37 (m, 10H, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 42.3, 60.0, 118.4, 126.9, 127.7, 128.9, 133.7, 141.7, 180.4.

1-allylcyclopentane-1-carboxylic acid (3l)[2]



Isolated yield: 68% (105 mg, 0.68 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.57-1.69 (m, 6H, cyclopent), 2.09-2.13 (m, 2H, cyclopent), 2.39 (d, *J*= 7.16 Hz, 2H, CH_2=CHC*H*$_2$), 5.06-5.11 (m, 2H, C*H*$_2$=CHCH$_2$), 5.73-5.84 (m, 1H, CH_2=C*H*CH$_2$). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 24.9, 35.3, 42.4, 53.2, 117.5, 134.4, 184.4.

1-allylcyclohexane-1-carboxylic acid (3m)[2]



Isolated yield: 71% (120 mg, 0.71 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.25-1.31 (m, 3H, cyclohex), 1.38-1.46 (m, 2H, cyclohex), 1.56-1.60 (m,

3H, cyclohex), 2.04-2.07 (m, 2H, cyclohex), 2.30 (d, *J*= 7.23 Hz, 2H, CH_2=CHCH_2), 5.05-5.08 (m, 2H, CH_2=CHCH_2), 5.73-5.82 (m, 1H, CH_2=C$H$$CH_2$). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 22.8, 25.5, 33.2, 44.2, 46.9, 117.7, 133.1, 183.2.

Protocol and flow-set-up for reaction screening optimization

A solution of **3a** (0.6 mmol, 0.3 M, 2 mL) in EtOAc and a pre-mixed solution (ultrasound, 15 min) of **2** (0.1-0.5 equiv., 0.06-0.3 mmol, 0.03-0.15 M) and H_2O_2 (30% wt, 5 equiv., 3 mmol, 1.5 M) in H_2O/acetone (5:1 v/v, 2 mL) were injected into the loops and pumped with a flow rate of 0.1 or 0.15 mL min^{-1} for each pump (τ= 50 or 33 min). After the injection and switching of the valves into the loops, the solutions were mixed together in a T-junction and flowed through the reactor-coil thermostated (PFA, 1/16" OD x 0.02" ID, 10 mL) at 25 °C. The reactor output was collected, quenched with 10% (w/v) aqueous solution of $NaHSO_3$ (1 mL) and extracted with EtOAc (4 x 10 mL). The organic phase was washed with aqueous saturated solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure (<40 °C) and analyzed by ^{1}H-NMR.

Protocol and flow-set-up for substrate scope

A solution of alkenoic acid **3a-m** (0.6 mmol, 0.3 M, 2 mL) in EtOAc and a pre-mixed solution (ultrasound, 15 min) of **2** (0.3 equiv., 0.18 mmol, 0.09 M), H_2O_2 (30% wt, 5 equiv., 3 mmol, 1.5 M) and HCO_2H (0.1 equiv., 0.06 mmol, 0.03 M) in H_2O/acetone (5:1 v/v, 2 mL) were injected into the loops and pumped with a flow rate of 0.1 mL min^{-1} for each pump (τ= 50 min). After the injection and switching of the valves into the loops, the solutions were mixed together in a T-juction and flowed through the reactor-coil thermostated at 25 °C (PFA, 1/16" OD x 0.02" ID, 10 mL). The reactor output was collected and quenched with an in-line stream of $NaHSO_3$ (10% w/v aqueous solution, 1 mL). After in-line phase separation (liquid-liquid separator SEP-10, Zaiput, Cambridge, MA – USA), the organic phase was flowed with a flow rate of 0.5 mL min^{-1} through a tubular mesoreactor (*Omnifit Labware DIBA HIT column*, L × ID 6.6 mm x 100 mm) packed with alternate layers of Amberlyst A21/silica (2:1 w/w, 4 layers, 300 mg for each layer, Fig. S1). The output was collected, dried over anhydrous Na_2SO_4, concentrated under reduce pressure (<40 °C) and directly characterized by ^{1}H-, ^{13}C-, and 2D-NMR analysis. The separation of the diastereomeric mixtures (Table 2, entries 5 and 8) was performed by automated flash chromatography (Biotage Isolera™ Prime, Cartridge: SNAP KP-SIL 10 g, Eluent: *n*-hexane/EtOAc, from 100:0 to 40:60, v/v).

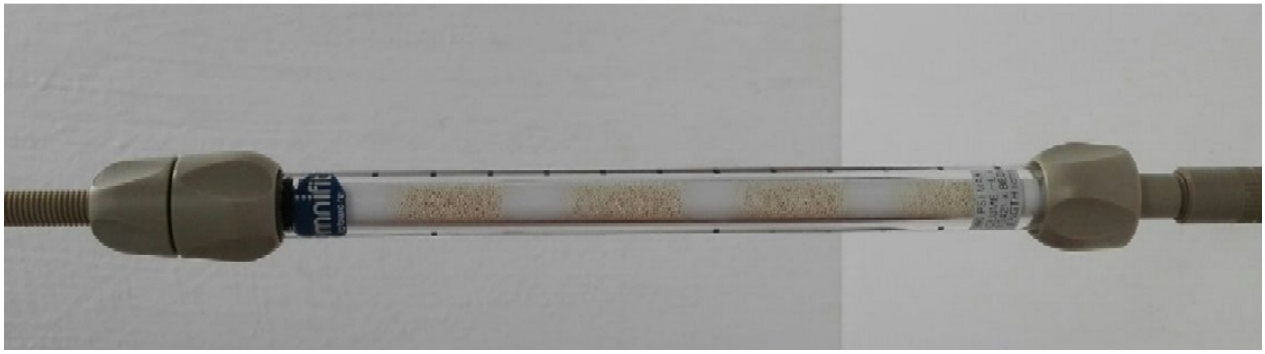
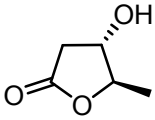


Fig. S1. Omnifit Labware DIBA HIT column for catalyst scavenging.

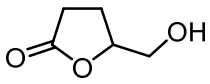
Compounds 5a-m characterization

4-Hydroxy-5-methyl-dihydrofuran-2(3*H*)-one (5a)[3]



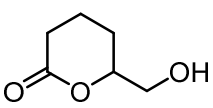
Isolated yield: 85% (59 mg, 0.51 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.38 (d, *J*= 6.62 Hz, 3H, 5-CHC*H*$_3$), 2.24 (brs, 1H, O*H*), 2.53 (dd, J_1= 3.71 Hz, J_2= 17.72 Hz, 1H, 3-C*H*$_{2(A)}$), 2.86 (dd, J_1= 6.49 Hz, J_2= 17.94 Hz, 1H, 3-C*H*$_{2(B)}$), 4.23-4.27 (m, 1H, 4-C*H*), 4.51 (dq, J_1= 2.94 Hz, J_2= 6.62 Hz, 1H, 5-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 18.5, 37.3, 72.8, 84.0, 175.1.

5-Hydroxymethyl-dihydrofuran-2(3*H*)-one (5b)[4]



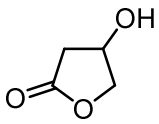
Isolated yield: 80% (56 mg, 0.48 mmol). Colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.18-2.20 (m, 1H, 4-C*H*$_{2(A)}$), 2.28-2.30 (m, 1H, 4-C*H*$_{2(B)}$), 2.57-2.71 (m, 2H, 3-C*H*$_2$), 3.67 (dd, J_1= 4.57 Hz, J_2= 12.54 Hz, 1H, 5-CHC*H*$_{2(A)}$), 3.92 (dd, J_1= 2.72 Hz, J_2= 12.54 Hz, 1H, 5-CHC*H*$_{2(B)}$), 4.64-4.68 (m, 1H, 5-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 23.1, 28.7, 64.0, 80.8, 177.8.

6-Hydroxymethyl-tetrahydro-2*H*-pyran-2-one (5c)[4]



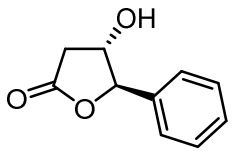
Isolated yield: 74% (57 mg, 0.44 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.71-1.96 (m, 4H, 3-C*H*$_2$ + 4-C*H*$_2$), 2.42-2.48 (m, 1H, 5-C*H*$_{2(A)}$), 2.57-2.62 (m, 1H, 5-C*H*$_{2(B)}$), 3.10 (brs, 1H, O*H*), 3.65 (dd, J_1= 5.45 Hz, J_2= 12.30 Hz, 1H, 6-CHC*H*$_{2(A)}$), 3.76 (dd, J_1= 3.17 Hz, J_2= 12.30 Hz, 1H, 6-CHC*H*$_{2(B)}$), 4.37-4.43 (m, 1H, 6-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 18.2, 23.5, 29.5, 64.6, 81.2, 171.9.

4-Hydroxy-dihydrofuran-2(3*H*)-one (3-BHL) (5d)[4]



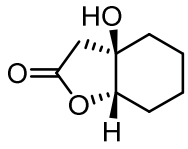
Isolated yield: 79% (48 mg, 0.47 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (brs, 1H, O*H*), 2.54 (dd, J_1= 1.52 Hz, J_2= 17.86 Hz, 1H, 3-$CH_{2(A)}$), 2.77 (dd, J_1= 6.04 Hz, J_2= 17.95 Hz, 1H, 3-$CH_{2(B)}$), 4.32 (d, J= 10.26 Hz, 1H, 5-$CH_{2(A)}$), 4.44 (dd, J_1= 4.46 Hz, J_2= 10.28 Hz, 1H, 5-$CH_{2(B)}$), 4.69-4.72 (m, 1H, 4-*CH*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 37.8, 67.4, 76.2, 176.8.

4-Hydroxy-5-phenyl-dihydrofuran-2(3*H*)-one (5e)[5]



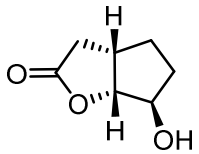
Isolated yield: 71% (76 mg, 0.43 mmol). Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.60 (dd, J_1= 4.26 Hz, J_2= 17.81 Hz, 1H, 3-C$H_{2(A)}$), 2.87 (dd, J_1= 6.51 Hz, J_2= 17.82 Hz, 1H, 3-C$H_{2(B)}$), 3.14 (brs, 1H, O*H*), 4.49 (ddd, J_1= 3.20 Hz, J_2= 3.98 Hz, J_3= 6.42 Hz, 1H, 4-C*H*), 5.39 (d, J= 3.13 Hz, 1H, 5-*CH*), 7.27-7.42 (m, 5H, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 36.9, 74.4, 88.0, 125.0, 128.7, 128.9, 136.7, 175.4.

3a-Hydroxy-hexahydrobenzofuran-2(3*H*)-one (5f)



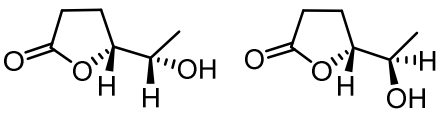
Isolated yield: 92% (86 mg, 0.55 mmol). Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.40-1.44 (m, 2H, 4-CH_2), 1.60-1.71 (m, 4H, 5-CH_2 + 6-CH_2), 1.92-2.14 (m, 2H, 7-CH_2), 2.49-2.70 (m, 2H, 3-CH_2), 4.31 (t, J= 6.59 Hz, 1H, 7a-*CH*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 20.8, 21.5, 28.4, 34.3, 41.8, 74.7, 83.9, 174.9. FT-IR (T%): ν 2932.23 (20.01), 2857.99 (26.42), 2662.25 (64.91), 1759.24 (17.21), 1454.55 (27.02), 1353.78 (28.18), 1248.20 (28.05), 1213.49 (23.88), 1173.95 (21.15), 1062.59 (24.61), 1009.55 (20.05), 948.81 (28.47), 888.06 (28.57), 842.74 (34.29). HRMS (ESI+) m/z $[M+H]^+$ calcd for $C_8H_{12}O_3$ 156.07864; found: 156.07813; Δ= 3.32 ppm; residence time (t_R): 2.055 min.

6-Hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5g)[4]



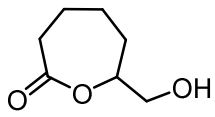
Isolated yield: 76% (65 mg, 0.46 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.48-1.54 (m, 1H, 4-$CH_{2(A)}$), 1.72-1.75 (m, 1H, 5-$CH_{2(A)}$), 1.85-1.88 (m, 1H, 5-$CH_{2(B)}$), 2.19-2.21 (m, 1H, 4-$CH_{2(B)}$), 2.25 (dd, J_1= 2.87 Hz, J_2= 18.61 Hz, 1H, 3-$CH_{2(A)}$), 2.59 (brs, 1H, *OH*), 2.81 (dd, J_1= 10.38 Hz, J_2= 18.56 Hz, 1H, 3-$CH_{2(B)}$), 3.00-3.08 (m, 1H, 3a-*CH*), 4.33 (brs, 1H, 6-*CH*), 4.72 (d, J= 6.90 Hz, 1H, 6a-*CH*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 32.2, 33.0, 37.0, 37.6, 77.6, 91.8, 179.1.

5-(1-hydroxyethyl)Dihydrofuran-2(3*H*)-one (5h, mixture *anti:syn* 80:20)[6]



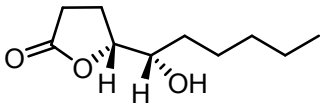
Isolated yield: 78% (60 mg, 0.46 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, *J*= 6.46, 3H, C*H*$_3$, *anti*), 1.25 (d, *J*= 6.08, 3H, C*H*$_3$, *syn*), 2.02-2.08 (m, 2H, 4-C*H*$_2$, *syn*), 2.12-2.30 (m, 2H, 4-C*H*$_2$, *anti*), 2.47-2.64 (m, 4H, 2 x 3-C*H*$_2$, *anti* + *syn*), 2.73 (brs, 2H, 2 x O*H*, *anti* + *syn*), 3.78 (quint, *J*= 6.12 Hz, 1H, C*H*(CH$_3$)OH, *syn*), 4.10-4.12 (m, 1H, C*H*(CH$_3$)OH, *anti*), 4.35 (q, *J*= 6.90 Hz, 1H, 5-C*H*, *syn*), 4.38-4.41 (m, 1H, 5-C*H*, *anti*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 16.9 (*anti*), 17.7 (*syn*), 20.2 (*anti*), 23.3 (*syn*), 27.9 (*anti* + *syn*), 66.5 (*anti*), 69.0 (*syn*), 82.9 (*anti*), 83.5 (*syn*), 176.9 (*syn*), 177.0 (*anti*).

7-(hydroxymethyl)Oxepan-2-one (5i)[7]



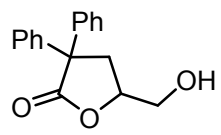
Isolated yield: 67% (58 mg, 0.40 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.44-1.69 (m, 6H, 4-C*H*$_2$ + 5-C*H*$_2$ + 6-C*H*$_2$), 2.38 (t, *J*= 6.98 Hz, 2H, 3-C*H*$_2$), 3.47-3.51 (m, 1H, 7-CHC*H*$_{2(B)}$), 3.62-6.67 (m, 1H, 7-CHC*H*$_{2(A)}$), 3.83 (brs, 1H, O*H*), 4.30-4.34 (m, 1H, 7-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 24.4, 25.0, 31.3, 33.8, 64.9, 78.2, 179.2.

5-(1-hydroxyhexyl)Dihydrofuran-2(3*H*)-one (5j)[8]



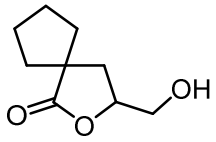
Isolated yield: 82% (92 mg, 0.49 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J*= 6.82 Hz, 3H, $CH_2(CH_2)_3CH_3$), 1.22-1.40 (m, 6H, $CH_2(CH_2)_3CH_3$), 1.50-1.51 (m, 2H, $CH_2(CH_2)_3CH_3$), 2.08-2.14 (m, 1H, 4-C*H*$_{2(A)}$), 2.23-2.28 (m, 1H, 4-C*H*$_{2(B)}$), 2.48-2.58 (m, 2H, 3-C*H*$_2$), 2.76-2.96 (brs, 1H, O*H*), 3.90-3.93 (m, 1H, 5-CHC*H*(OH)), 4.40-4.45 (m, 1H, 5-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 13.9, 20.9, 22.4, 25.2, 28.7, 31.6, 31.8, 71.2, 83.0, 178.0.

5-(hydroxymethyl)-3,3-Diphenyldihydrofuran-2(3*H*)-one (5k)[9]



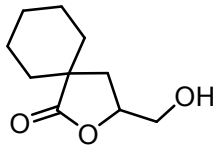
Isolated yield: 78% (125 mg, 0.47 mmol). Pale yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.28-2.32 (m, 1H, 4-C*H*$_{2(A)}$), 2.86-2.99 (m, 1H, 4-C*H*$_{2(B)}$), 3.68 (dd, *J*$_1$= 5.66 Hz, *J*$_2$= 12.34 Hz, 1H, 5-CHC*H*$_{2(A)}$), 3.99 (dd, *J*$_1$= 2.78 Hz, *J*$_2$= 12.38 Hz, 1H, 5-CHC*H*$_{2(B)}$), 4.44-4.56 (m, 1H, 5-*CH*), 7.24-7.38 (m, 10H, Ar). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 46.4, 60.2, 64.8, 82.9, 126.4, 127.4, 127.6, 134.6, 136.8, 172.2.

3-(hydroxymethyl)-2-Oxaspiro[4.4]nonan-1-one (5l)



Isolated yield: 77% (79 mg, 0.46 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.66-2.03 (m, 8H, cyclopent), 2.08-2.19 (m, 2H, 4-*CH*$_2$), 2.73 (brs, 1H, O*H*), 3.64 (dd, J_1= 5.28 Hz, J_2= 12.57 Hz, 1H, 3-CH*CH*$_{2(A)}$), 3.89 (dd, J_1= 2.83 Hz, J_2= 12.58 Hz, 1H, 3-CH*CH*$_{2(B)}$), 4.51-4.55 (m, 1H, 3-*CH*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 25.3, 25.4, 36.8, 37.79, 37.82, 50.1, 63.8, 78.0, 182.6. FT-IR (T%): ν 2957.30 (46.70), 2871.97 (53.78), 1757.80 (33.37), 1447.80 (58.78), 1354.27 (61.03), 1188.90 (45.23), 1055.35 (47.49), 980.63 (59.20), 913.61 (66.95). HRMS (ESI+) m/z $[M+H]^+$ calcd for $C_8H_{12}O_3$ 170.09429; found: 170.09408; Δ= 1.26 ppm; residence time (t_R): 2.663 min.

3-(hydroxymethyl)-2-Oxaspiro[4.5]decan-1-one (5m)[10]



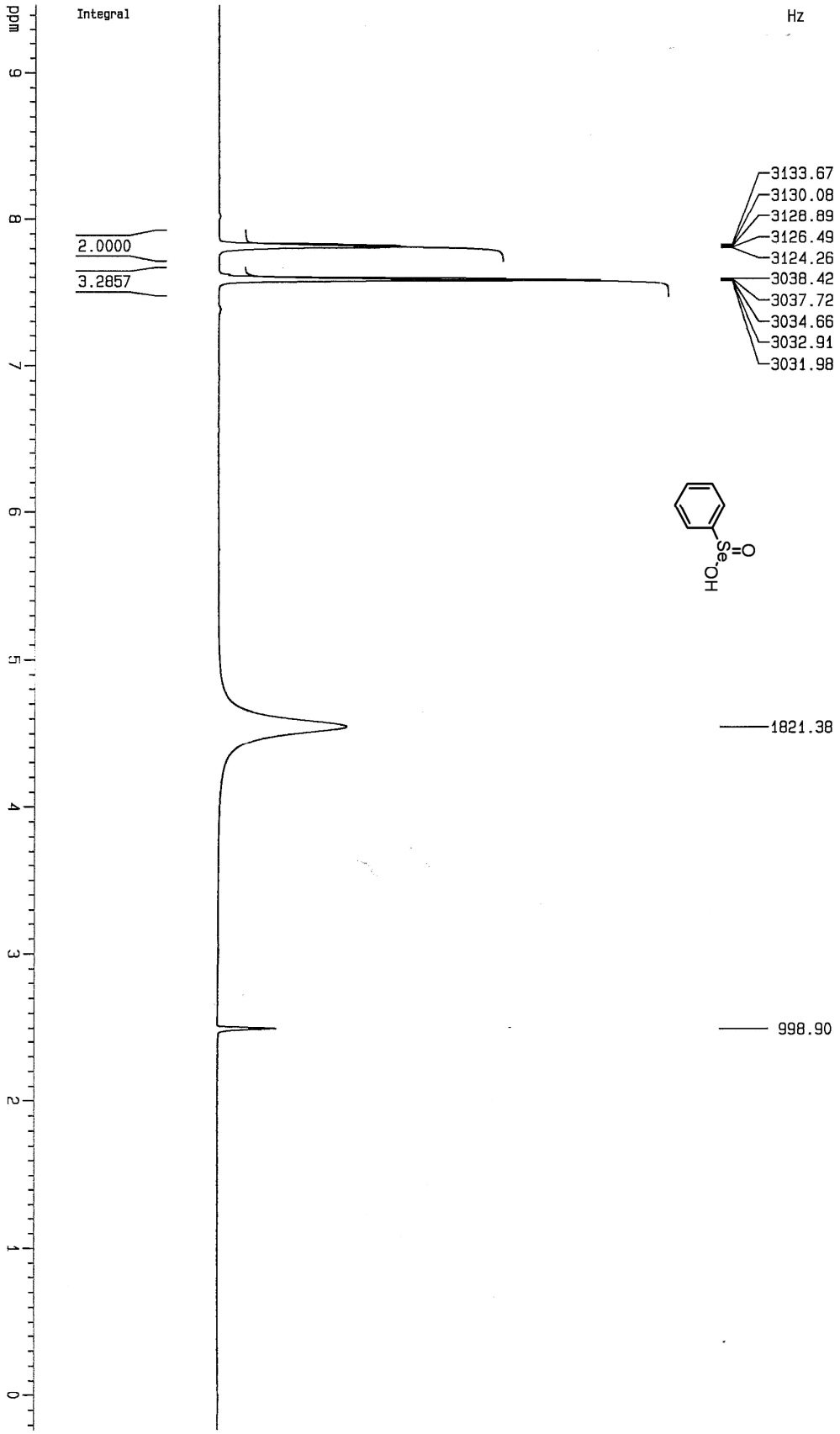
Isolated yield: 76% (85 mg, 0.46 mmol). Colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.25-1.37 (m, 3H, cyclohex), 1.53-1.65 (m, 4H, cyclohex), 1.72-7.77 (m, 3H, cyclohex), 1.89 (dd, J_1= 9.42 Hz, J_2= 12.86 Hz, 1H, 4-*CH*$_{2(A)}$), 2.25 (dd, J_1= 6.92 Hz, J_2= 12.92 Hz, 1H, 4-*CH*$_{2(B)}$), 2.69 (brs, 1H, O*H*), 3.62 (dd, J_1= 5.10 Hz, J_2= 12.57 Hz, 1H, 3-CH*CH*$_{2(A)}$), 3.90 (dd, J_1= 2.78 Hz, J_2= 12.57 Hz, 1H, 3-CH*CH*$_{2(B)}$), 4.52-4.57 (m, 1H, 3-C*H*). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): δ 21.99, 22.0, 32.0, 33.8, 34.0, 44.8, 63.9, 77.6, 181.8.

Scale-up synthesis of 4-hydroxy-dihydrofuran-2(3*H*)-one (3-BHL) (5d)

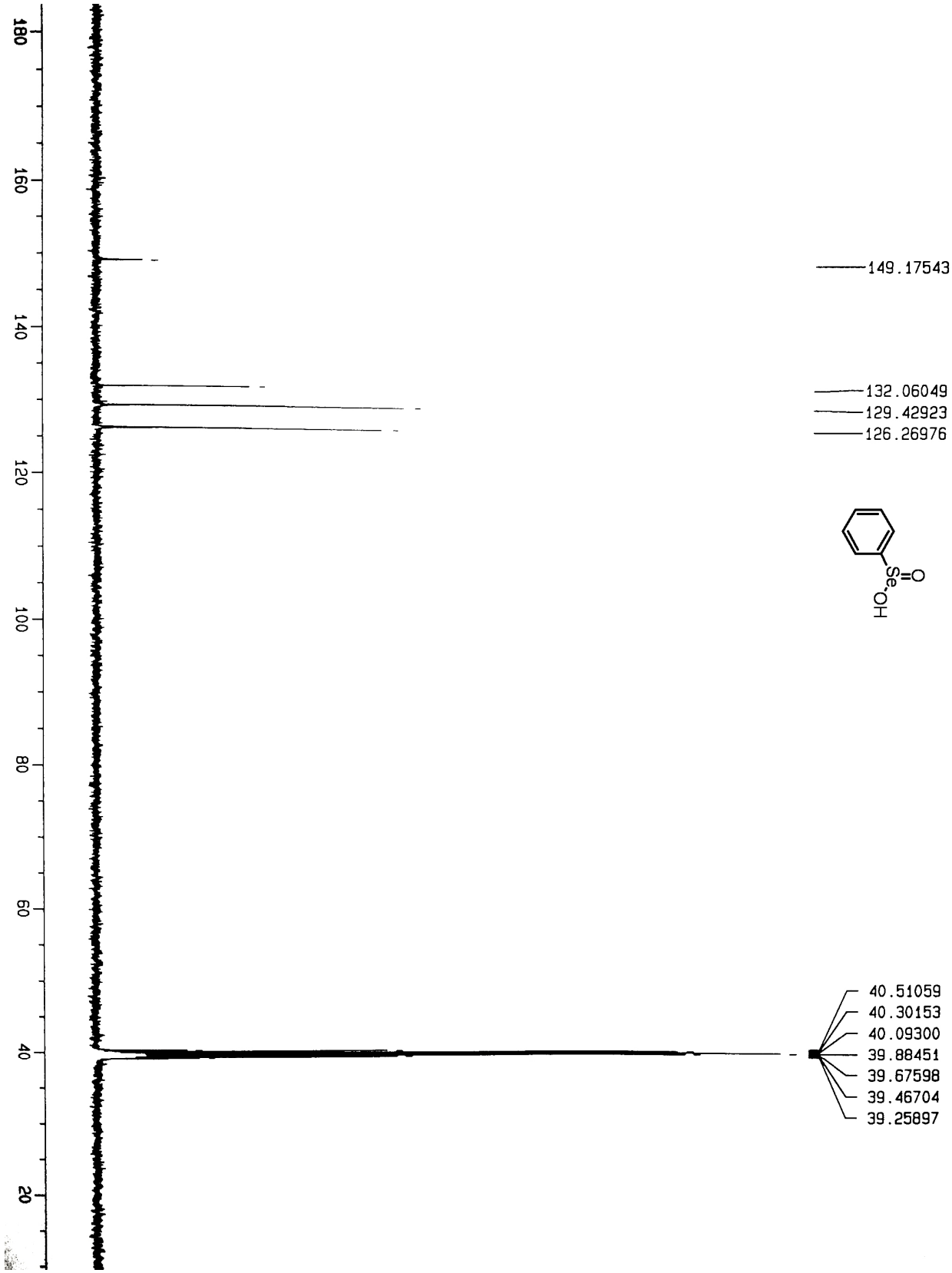
100 mL of a solution of vinylacetic acid (**3d**, 30 mmol, 2.55 mL, 0.3 M) in EtOAc and 100 mL of a pre-mixed solution of phenylseleninic acid (**2**, 0.30 equiv., 9 mmol, 1.7 g), H_2O_2 (30% w/w aqueous solution, 5 equiv., 150 mmol, 15.32 mL) and HCO_2H (0.1 equiv., 3 mmol, 120 µL) in H_2O/acetone (5:1, v/v) were pumped with a flow rate of 0.4 mL min^{-1} for each pump and splitted with a 5-way connector (PTFE, 1/4"-28, 0.5-4 mm OD, 1.5 mm ID, DIBA) through four mesoreactor-coil (PFA, 1/16" OD x 0.02" ID, 10 mL) operating in parallel and thermostated at 25 °C (τ= 50 min for each reactor). After the first 9 mL of dead volume (45 min), the reactor outputs were combined together and collected for 5 h (V= 220 mL). After in-line quenching with 10% w/v aqueous solution of $NaHSO_3$ (20 mL) and phase separation (liquid-liquid separator SEP-10, Zaiput, Cambridge, MA – USA), the organic phase was flowed through a tubular mesoreactor (*Omnifit Labware DIBA HIT column*, L × ID 6.6 mm x 150 mm) packed with alternate layers of Amberlyst A21/silica (2:1 w/w, 4 layers, 450 mg for each layer, loading: 1.3 meq/L corresponding to a total of ~ 6 mmol) with a flow rate of 0.5 mL min^{-1} (τ= 10 min). After 3.5 h, the valve was switched to directed the flow stream

towards a second column. Meanwhile the first A21 packed column was regenerated by flowing a 5% (v/v) ethanolic solution of NH_4OH (50 mL, 0.5 mL min^{-1}). The output was collected for 4 h with a fractions collector affording 4-hydroxy-dihydrofuran-2(3*H*)-one (**5d**) (2.25 g, 22.04 mmol, 74% yield, productivity: 2.45 mmol h^{-1}, 6 g d^{-1}) as colorless oil. For the catalyst recovery, the column was washed with 5% (v/v) ethanolic solution of NH_4OH (50 mL, 0.5 mL min^{-1}). The basic solution was acidified with an in-line stream of 3 N aqueous solution of HCl (50 mL, 0.5 mL min^{-1}) and extracted in-line with a stream of CH_2Cl_2. The organic phase was collected affording pure **2** (1.5 g, 7.93 mmol, 88% recovery) as a white solid.

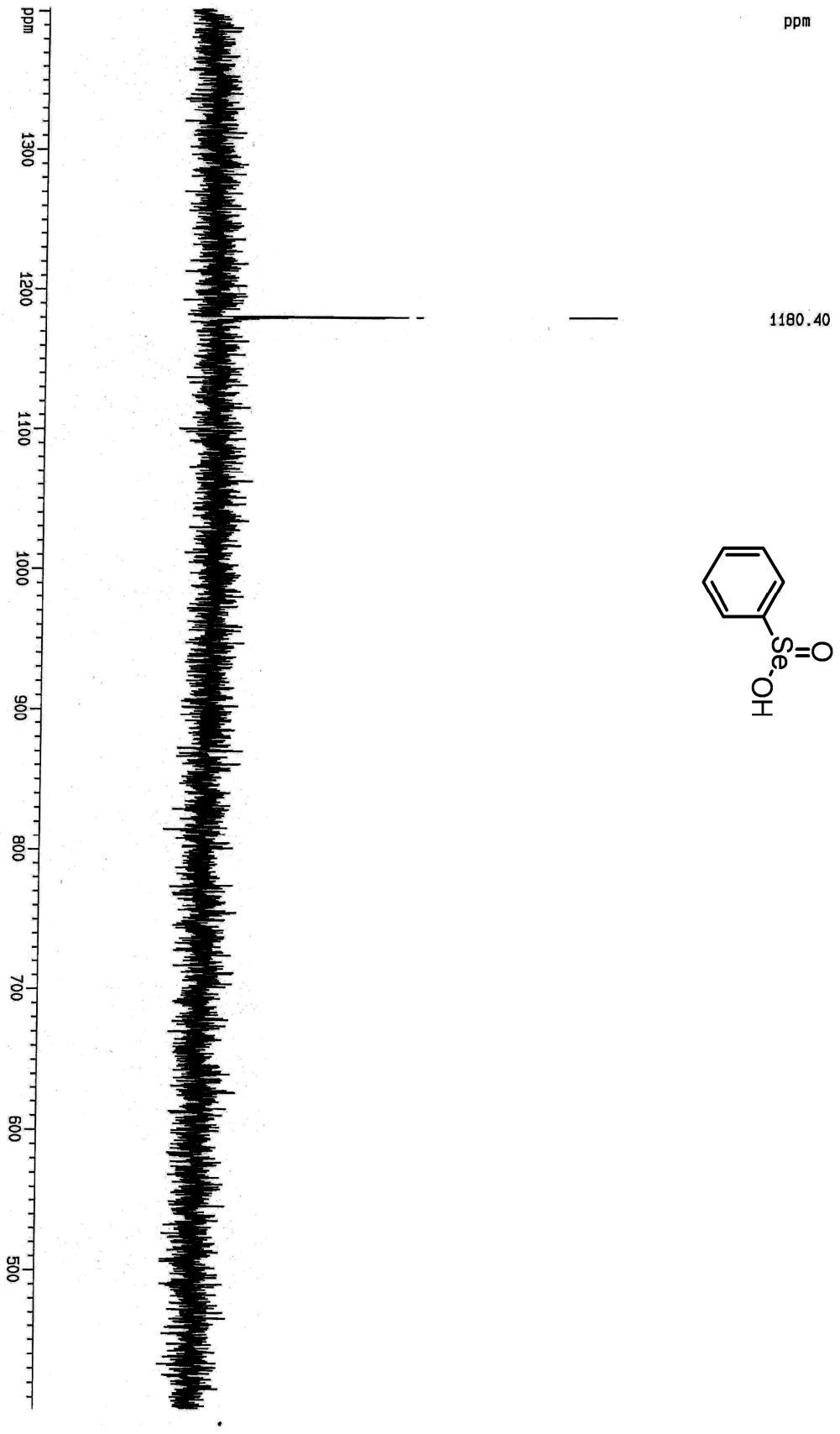
^{1}H-NMR (d^{6}-DMSO, 400 MHz) of phenylseleninic acid (2)



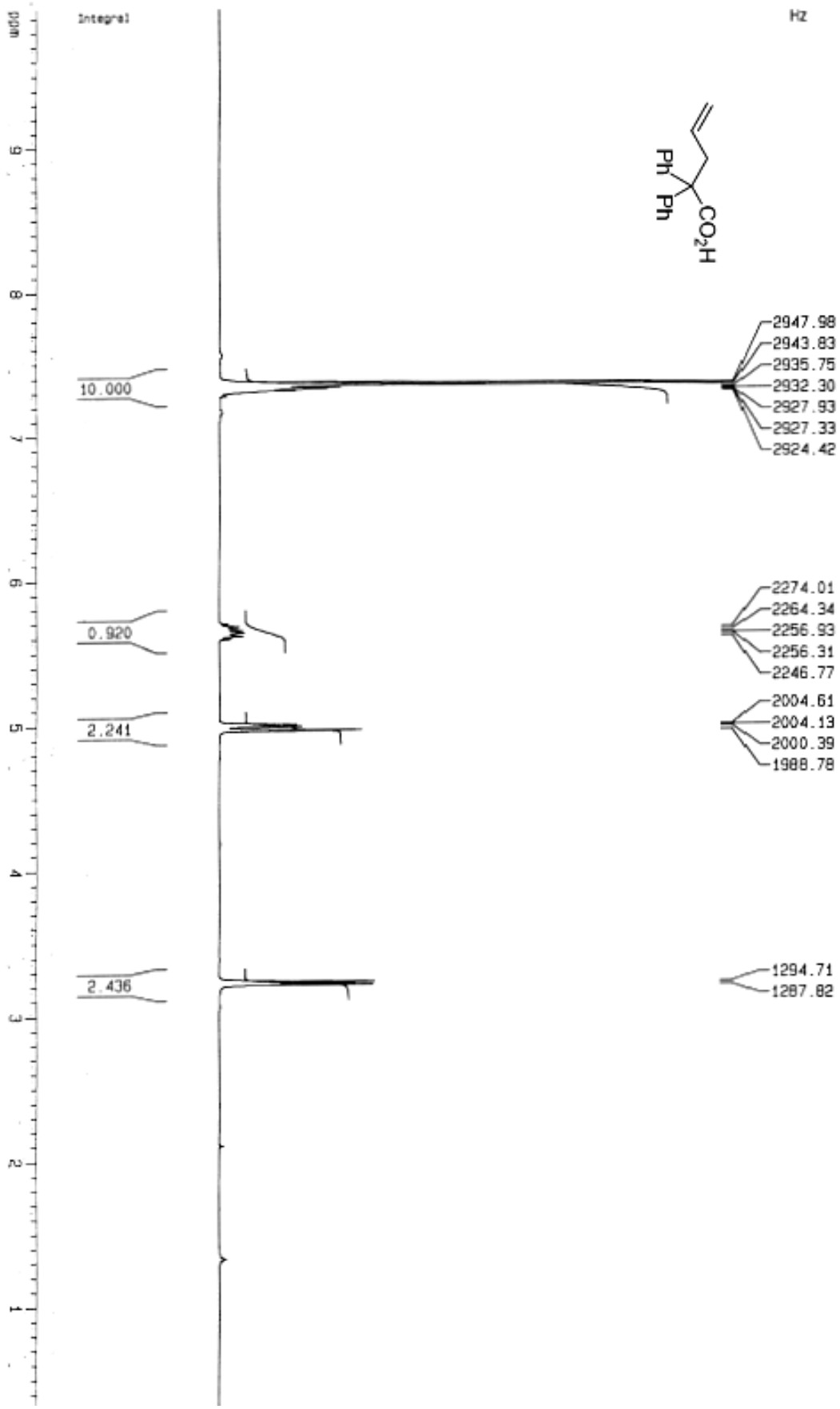
^{13}C-NMR (*d*^{6}-DMSO, 100.6 MHz) of phenylseleninic acid (2)



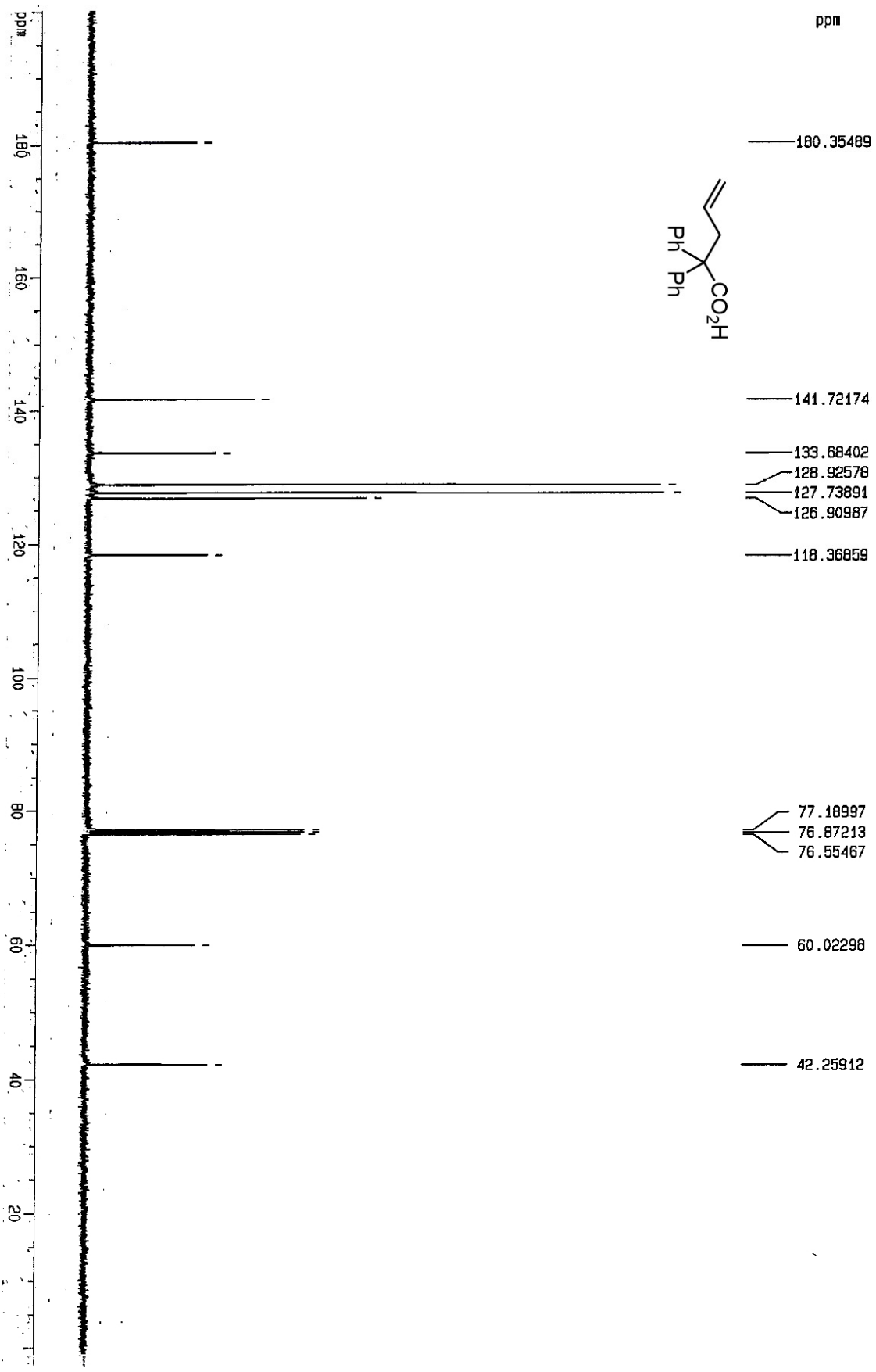
^{77}Se-NMR (*d*^{6}-DMSO, 76.3 MHz) of phenylseleninic acid (2)



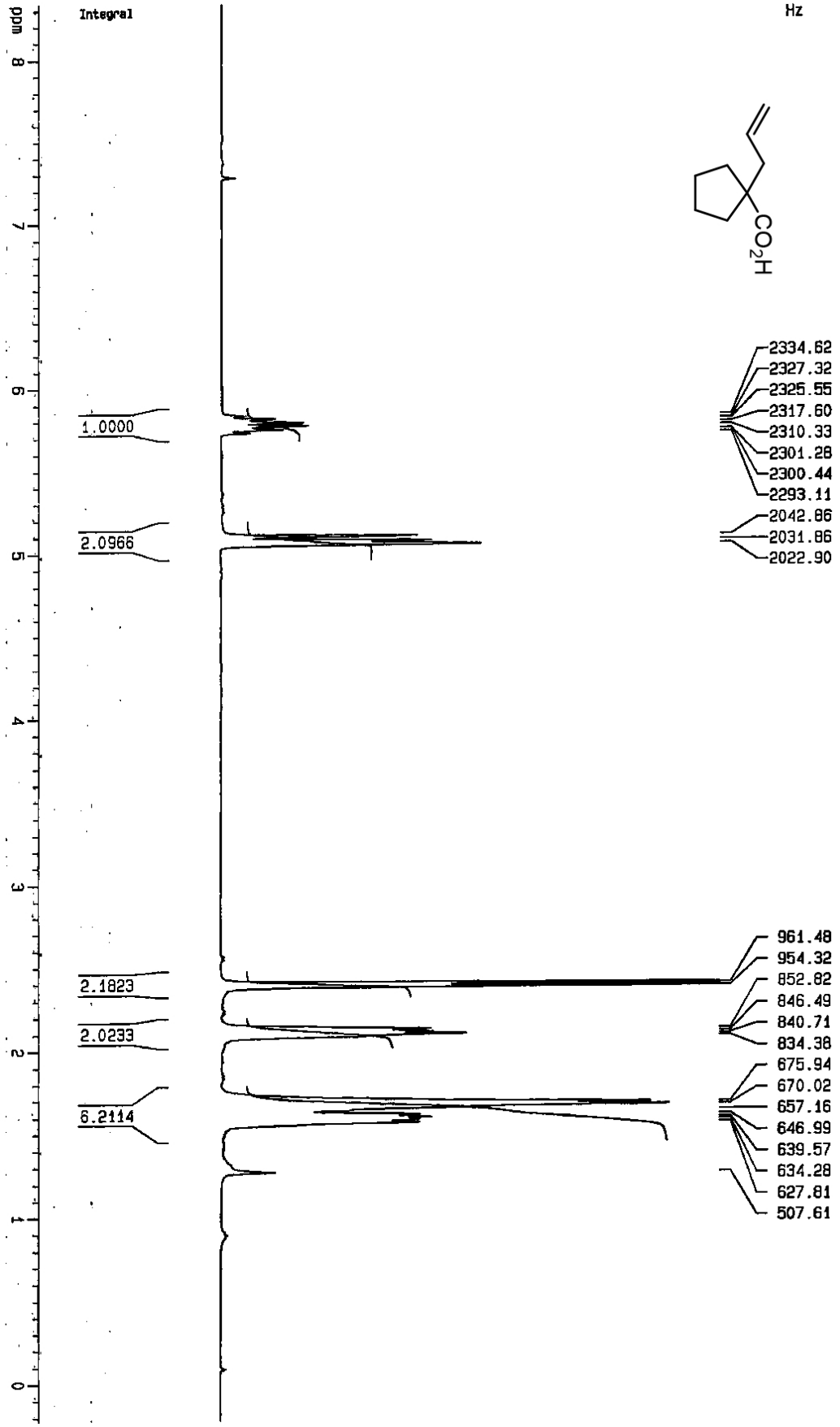
^{1}H-NMR ($CDCl_3$, 400 MHz) of 2,2-diphenylpent-4-enoic acid (3k)



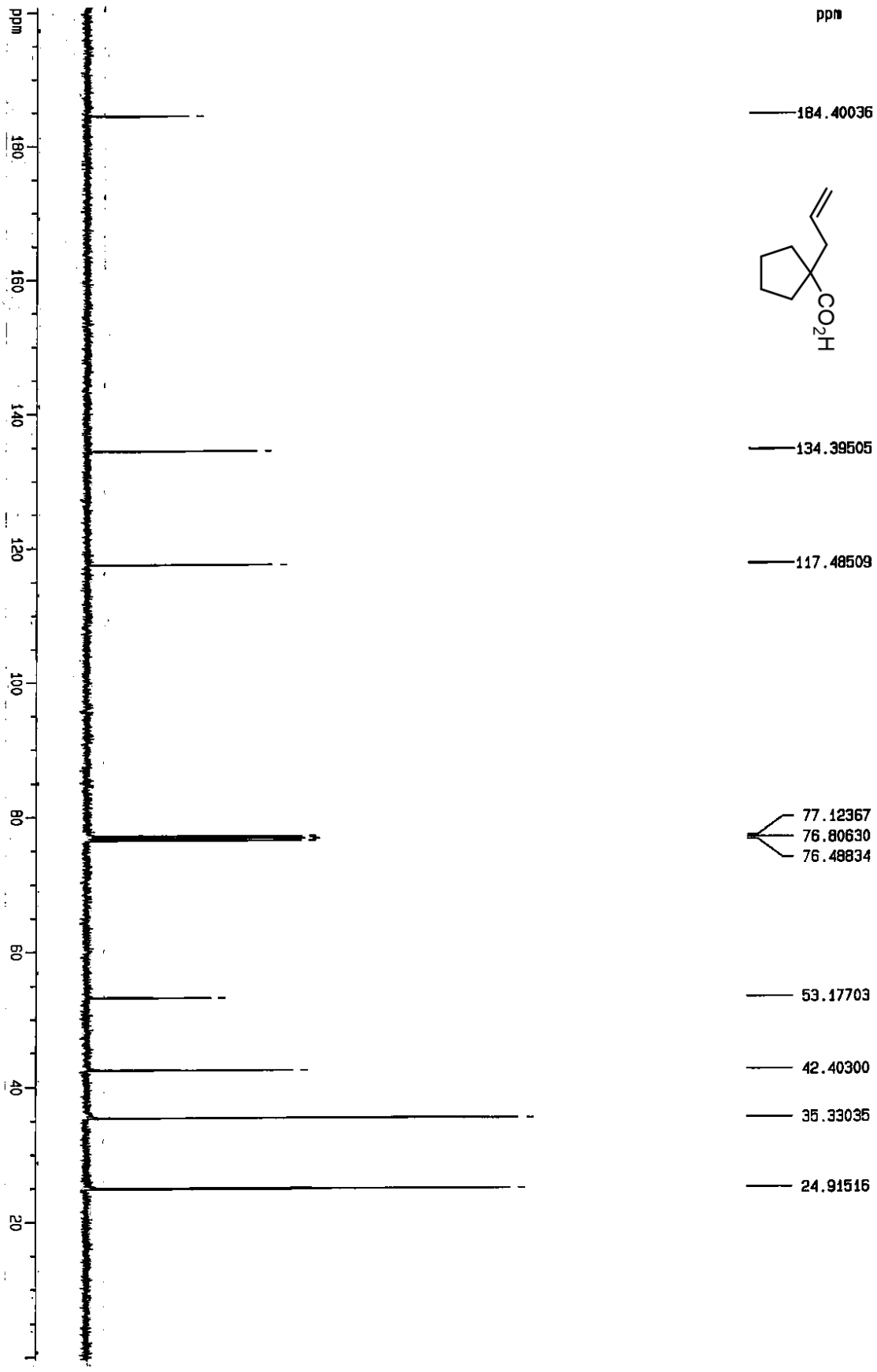
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 2,2-diphenylpent-4-enoic acid (3k)



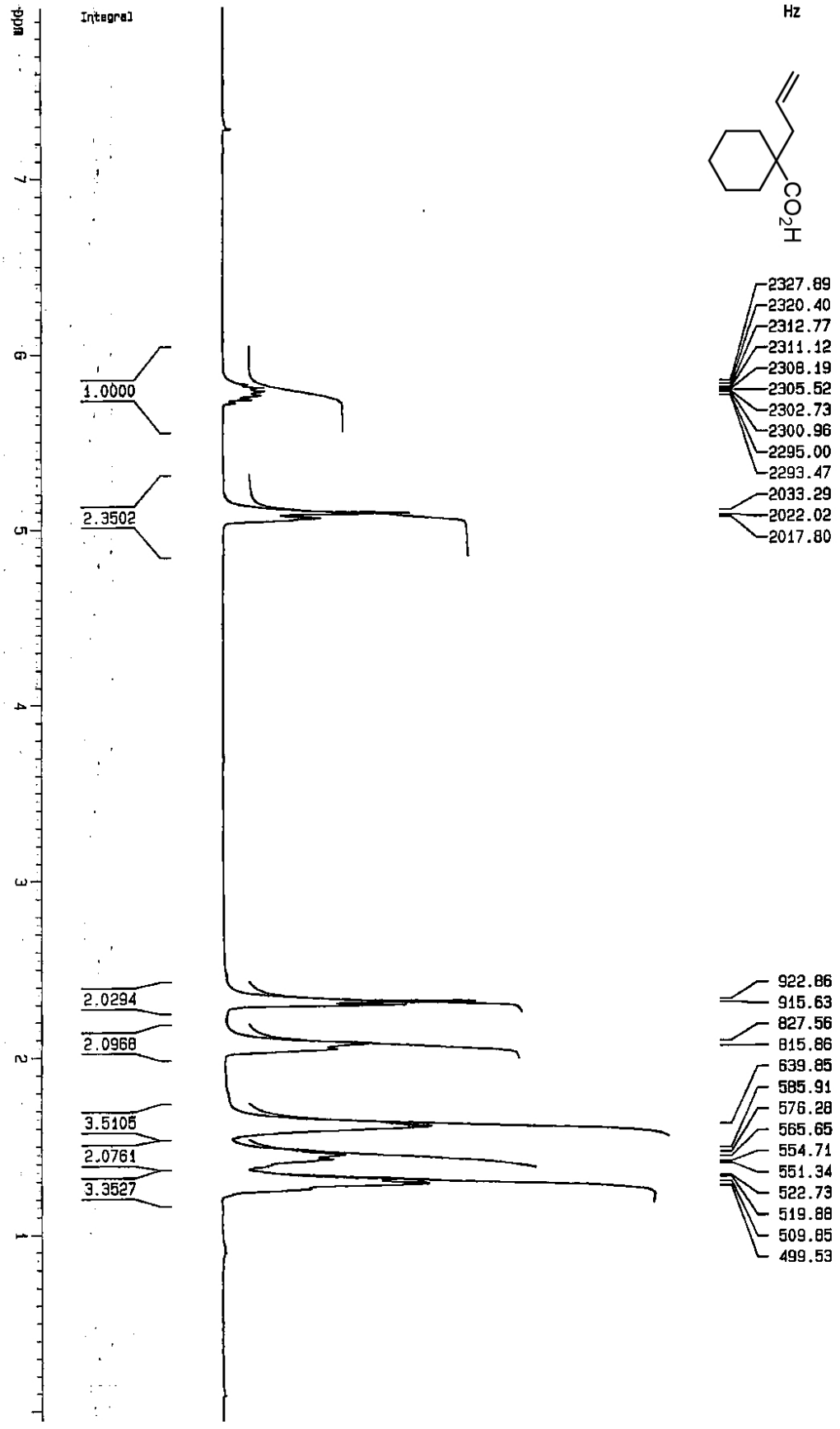
^{1}H-NMR ($CDCl_3$, 400 MHz) of 1-allylcyclopentane-1-carboxylic acid (3l)



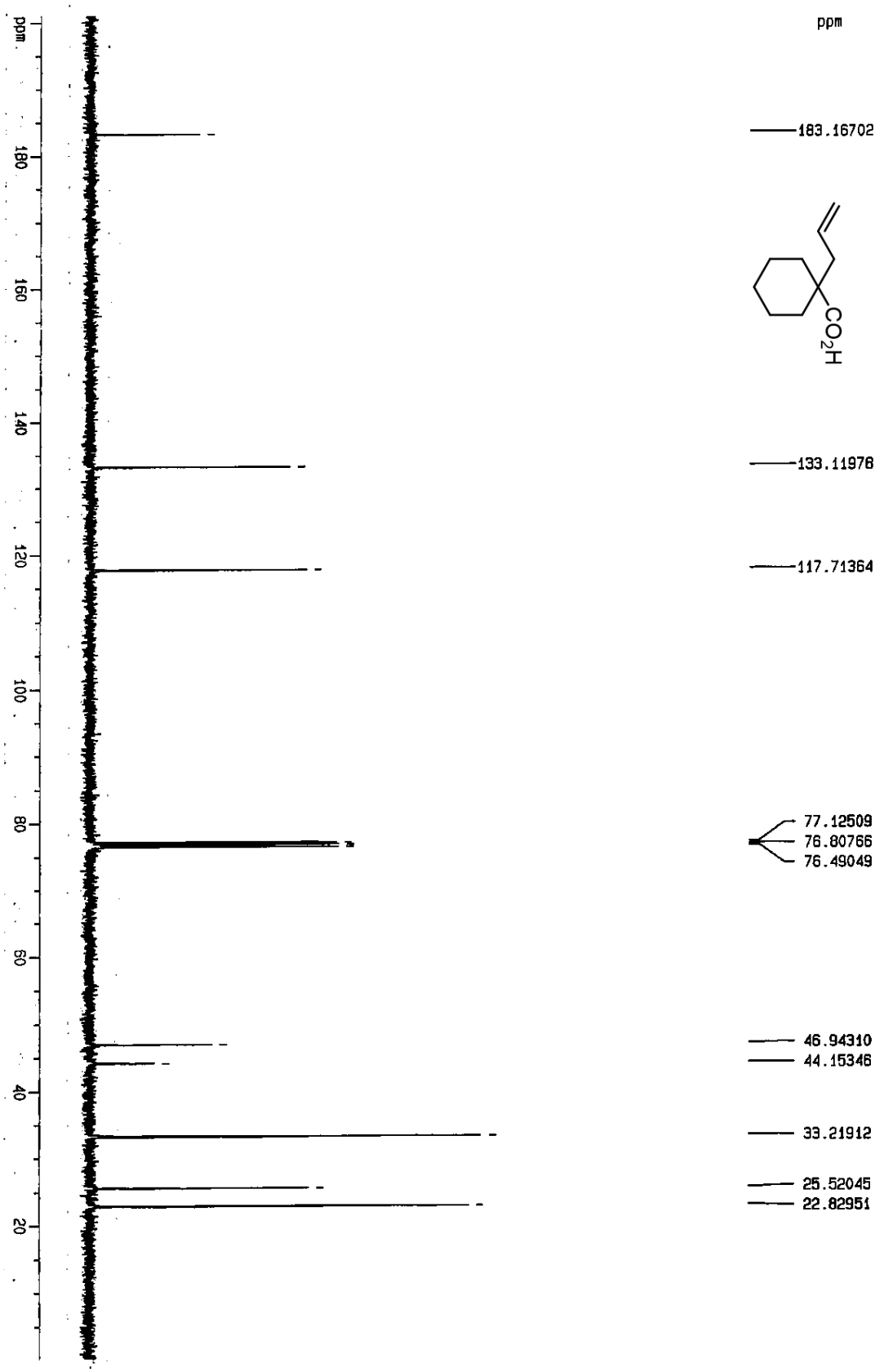
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 1-allylcyclopentane-1-carboxylic acid (3l)



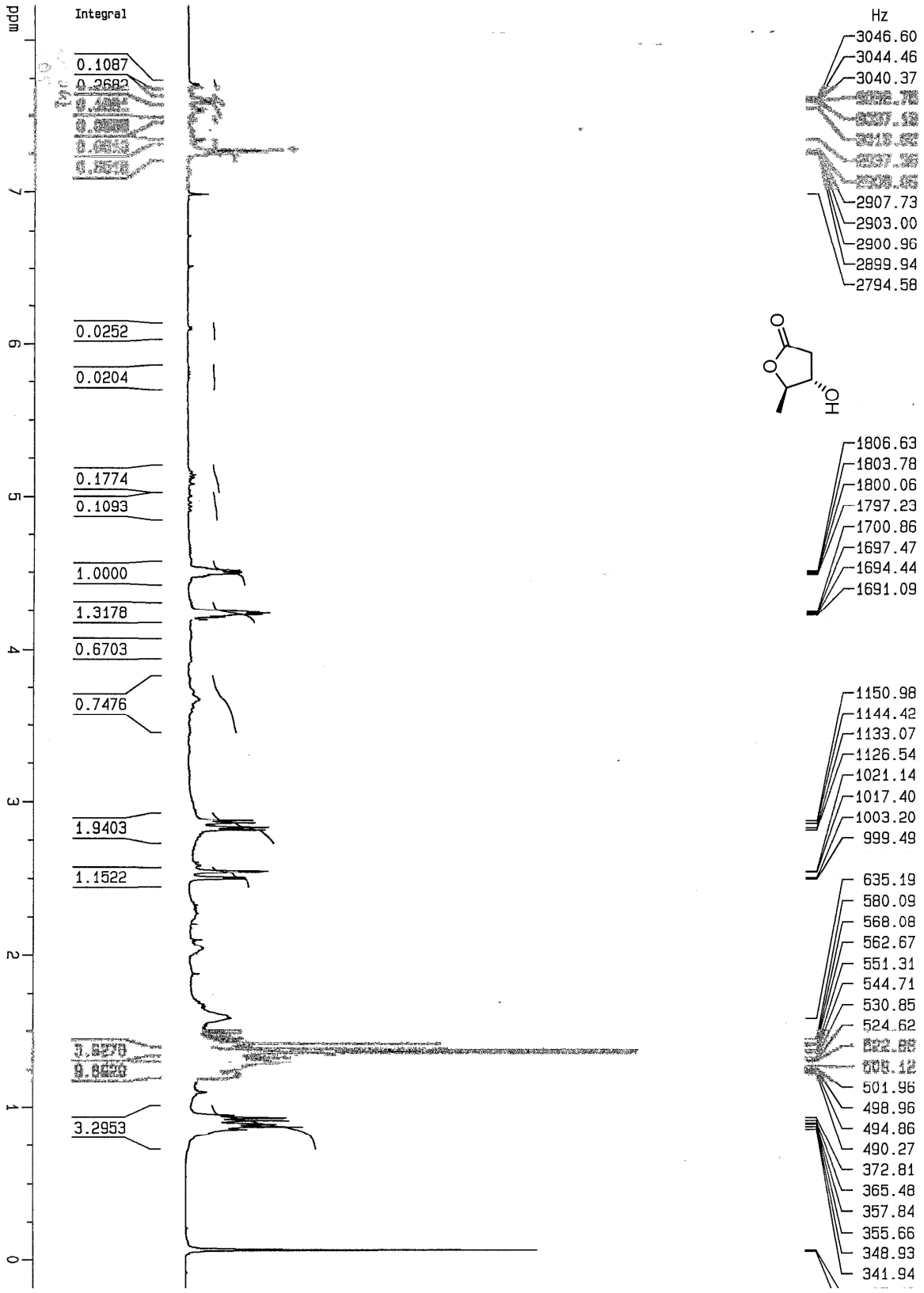
^{1}H-NMR ($CDCl_3$, 400 MHz) of 1-allylcyclohexane-1-carboxylic acid (3m)



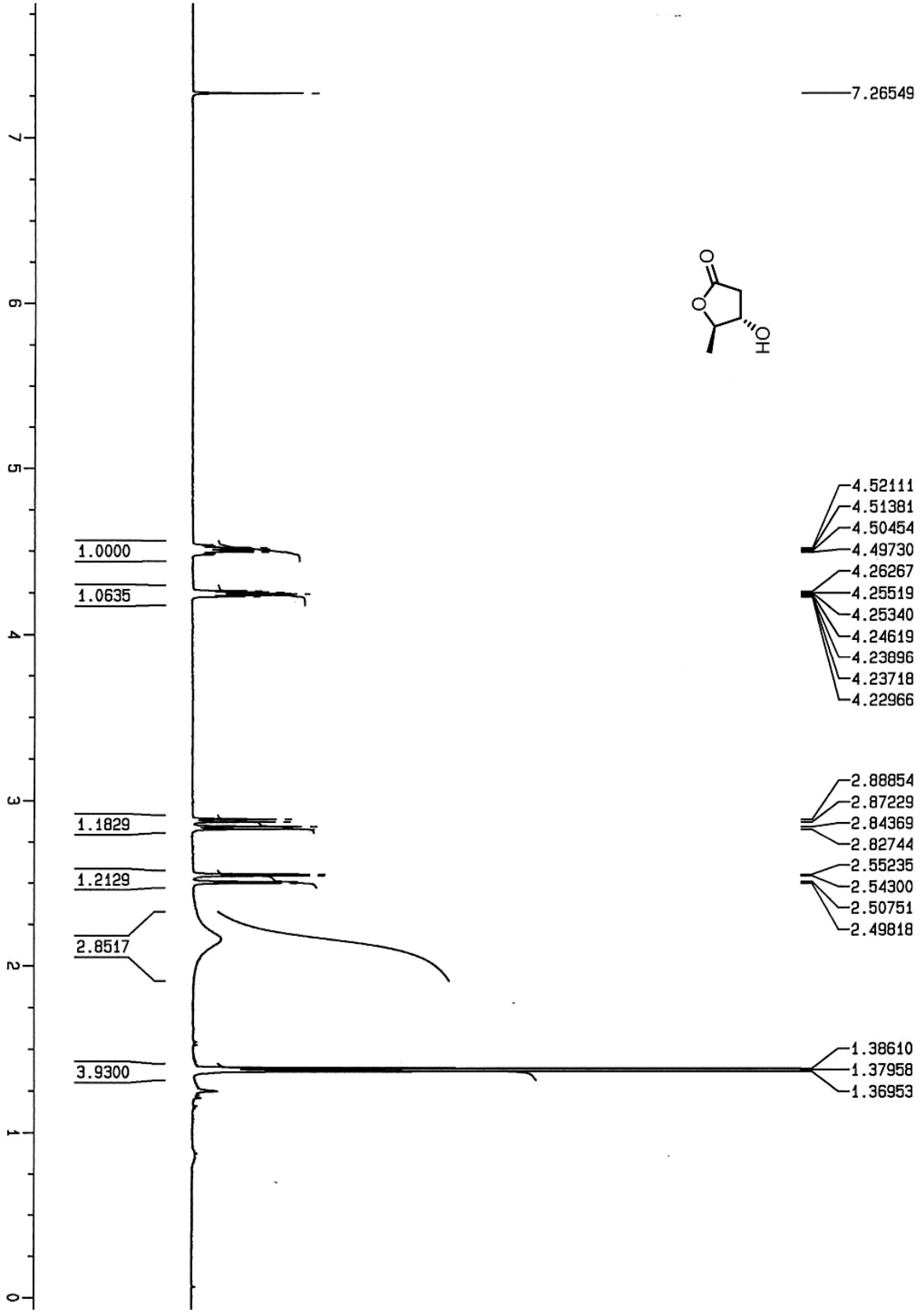
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 1-allylcyclohexane-1-carboxylic acid (3m)



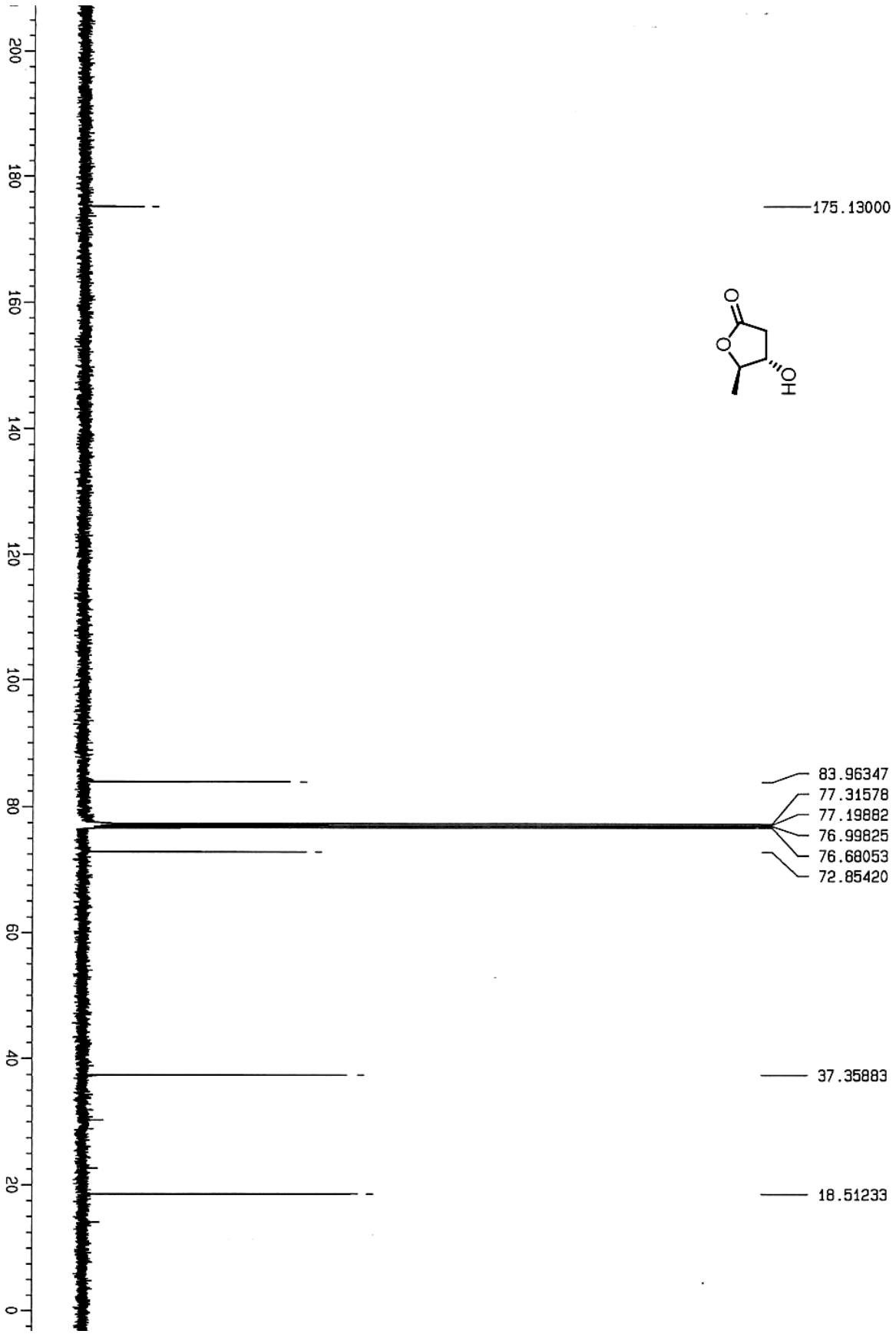
^{1}H-NMR ($CDCl_3$, 400 MHz) of 4-hydroxy-5-methyl-dihydrofuran-2(3*H*)-one (5a) before catalyst scavenging



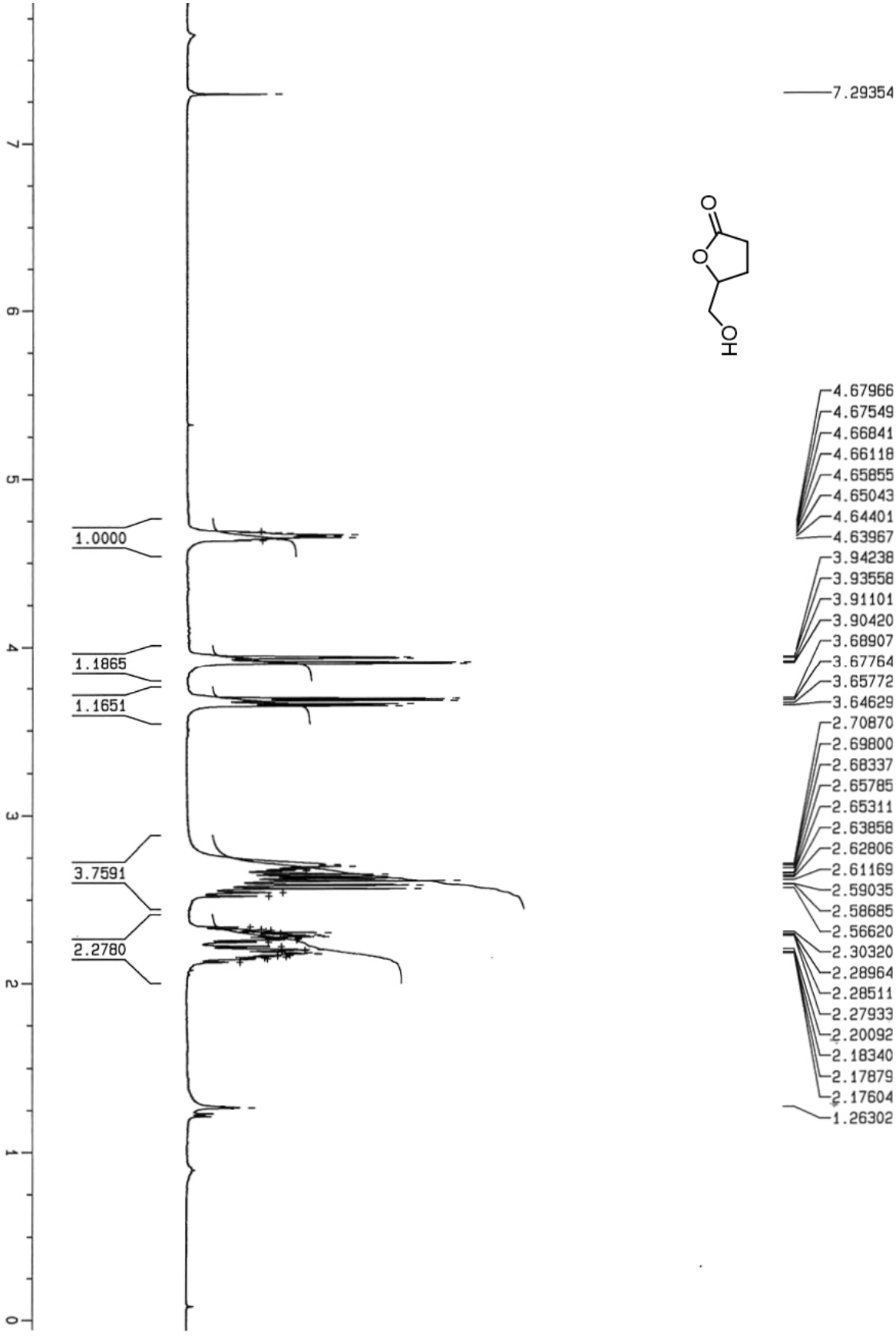
^{1}H-NMR ($CDCl_3$, 400 MHz) of 4-hydroxy-5-methyl-dihydrofuran-2(3*H*)-one (5a) after catalyst scavenging



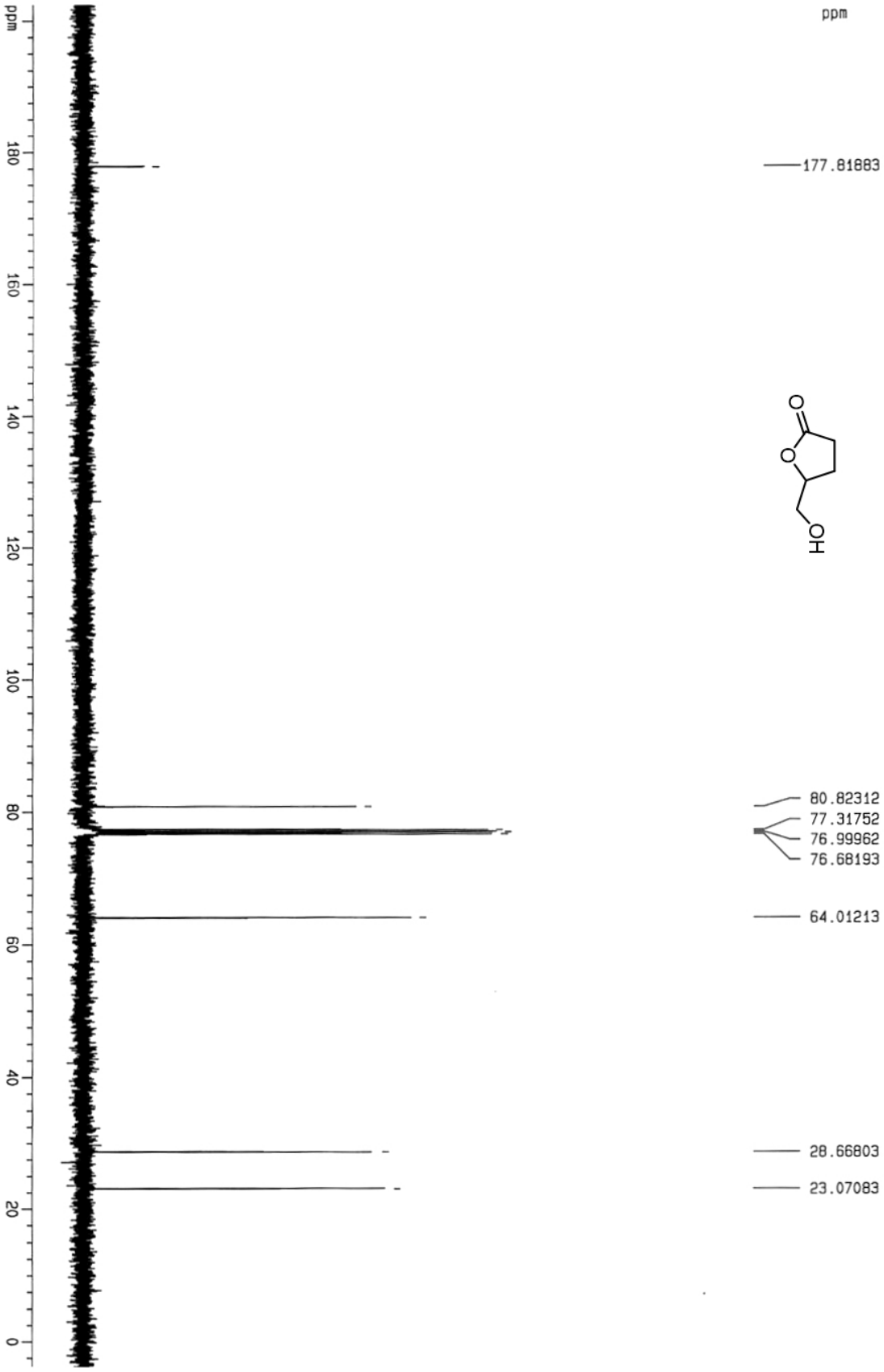
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 4-hydroxy-5-methyl-dihydrofuran-2(3*H*)-one (5a) after catalyst scavenging



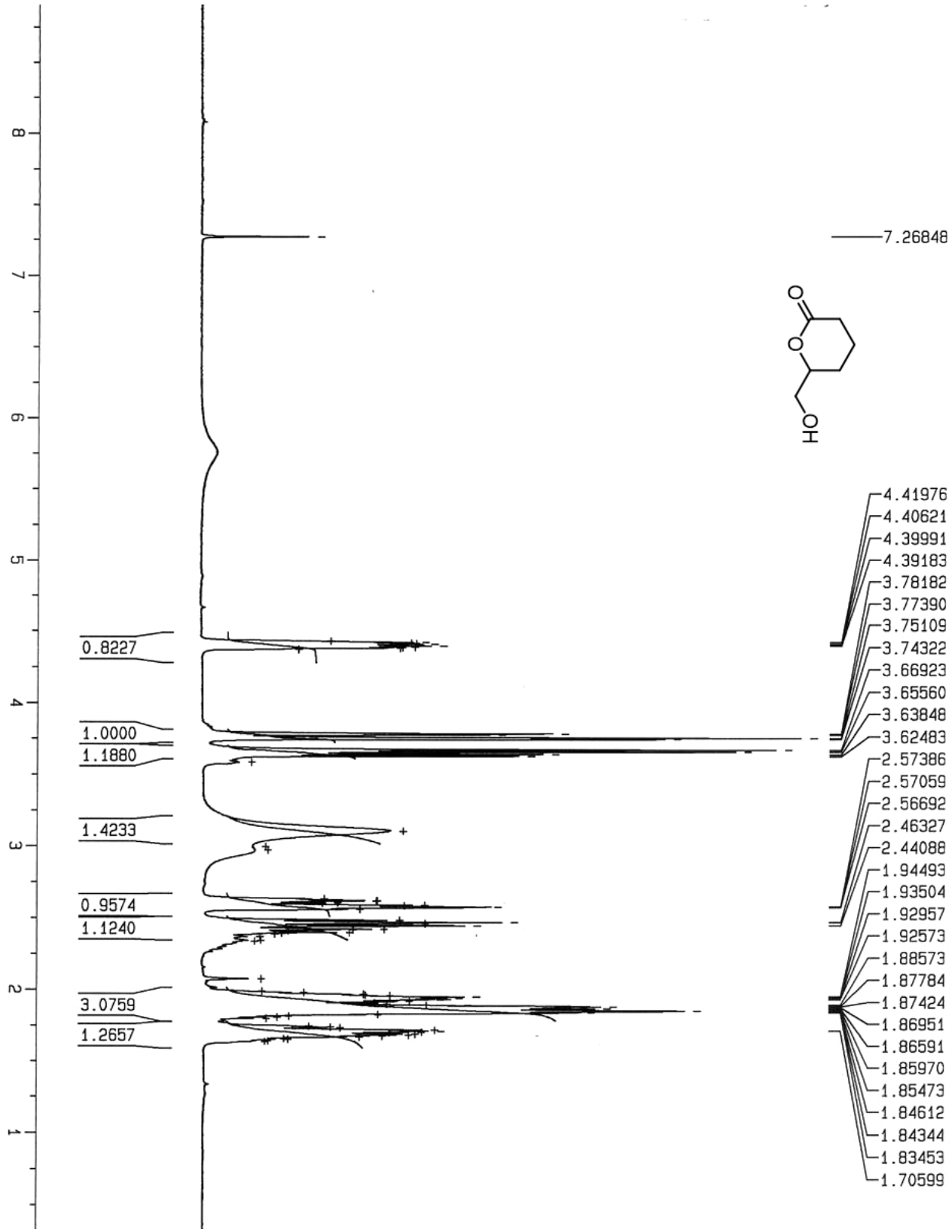
^{1}H-NMR ($CDCl_3$, 400 MHz) of 5-hydroxymethyl-dihydrofuran-2(3*H*)-one (5b)



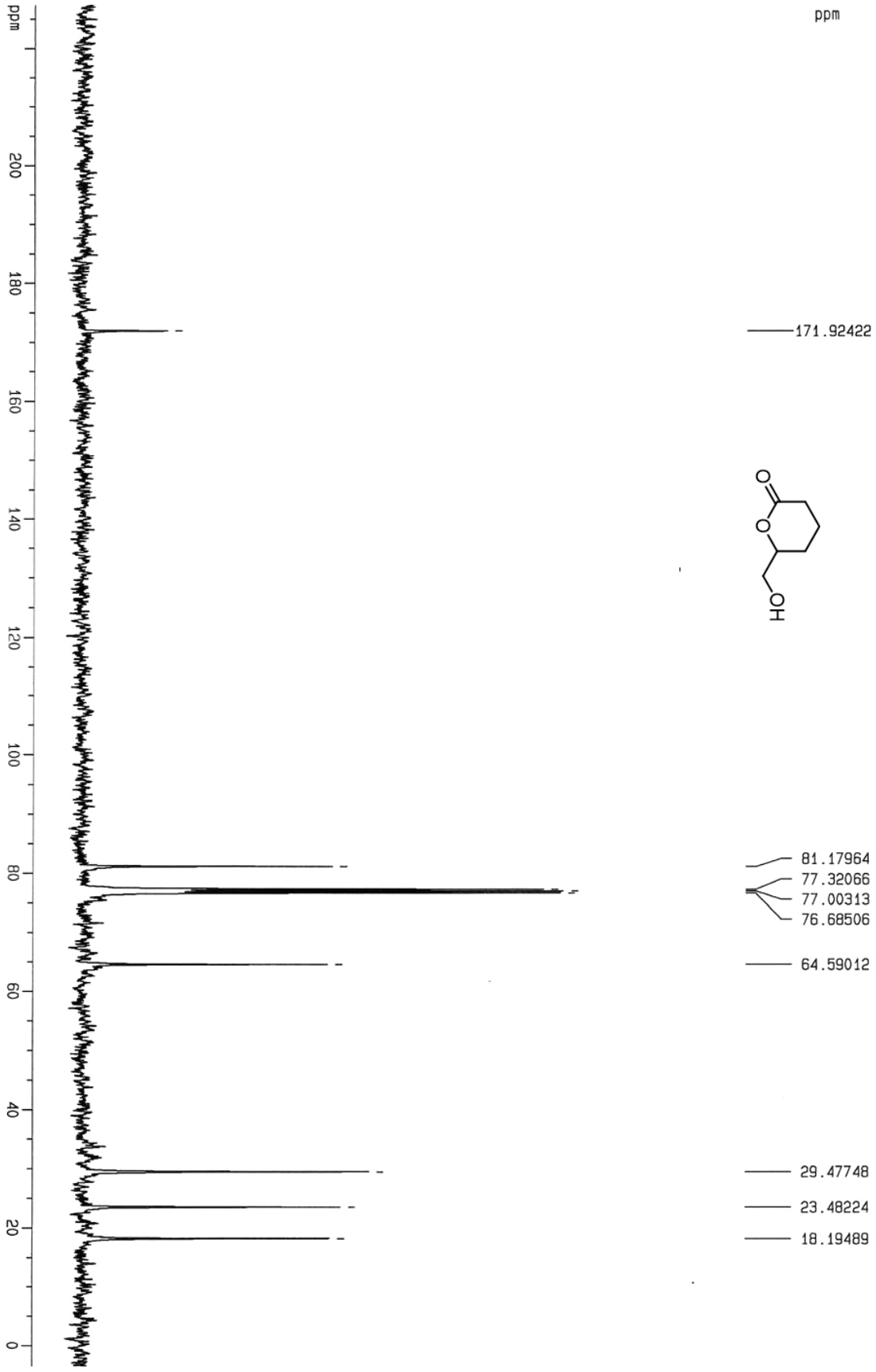
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 5-hydroxymethyl-dihydrofuran-2(3*H*)-one (5b)



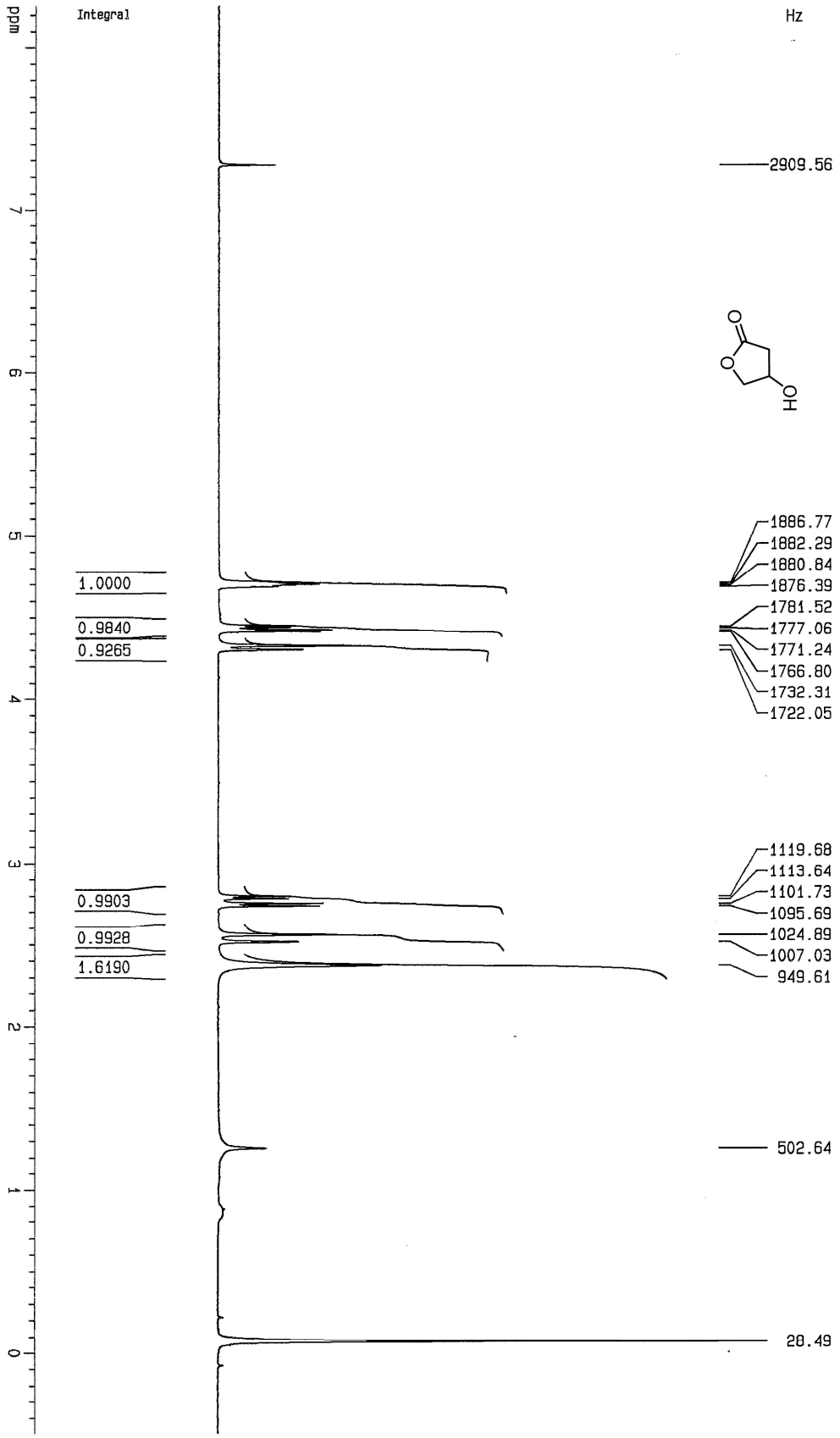
^{1}H-NMR ($CDCl_3$, 400 MHz) of 6-hydroxymethyl-tetrahydro-2*H*-pyran-2-one (5c)



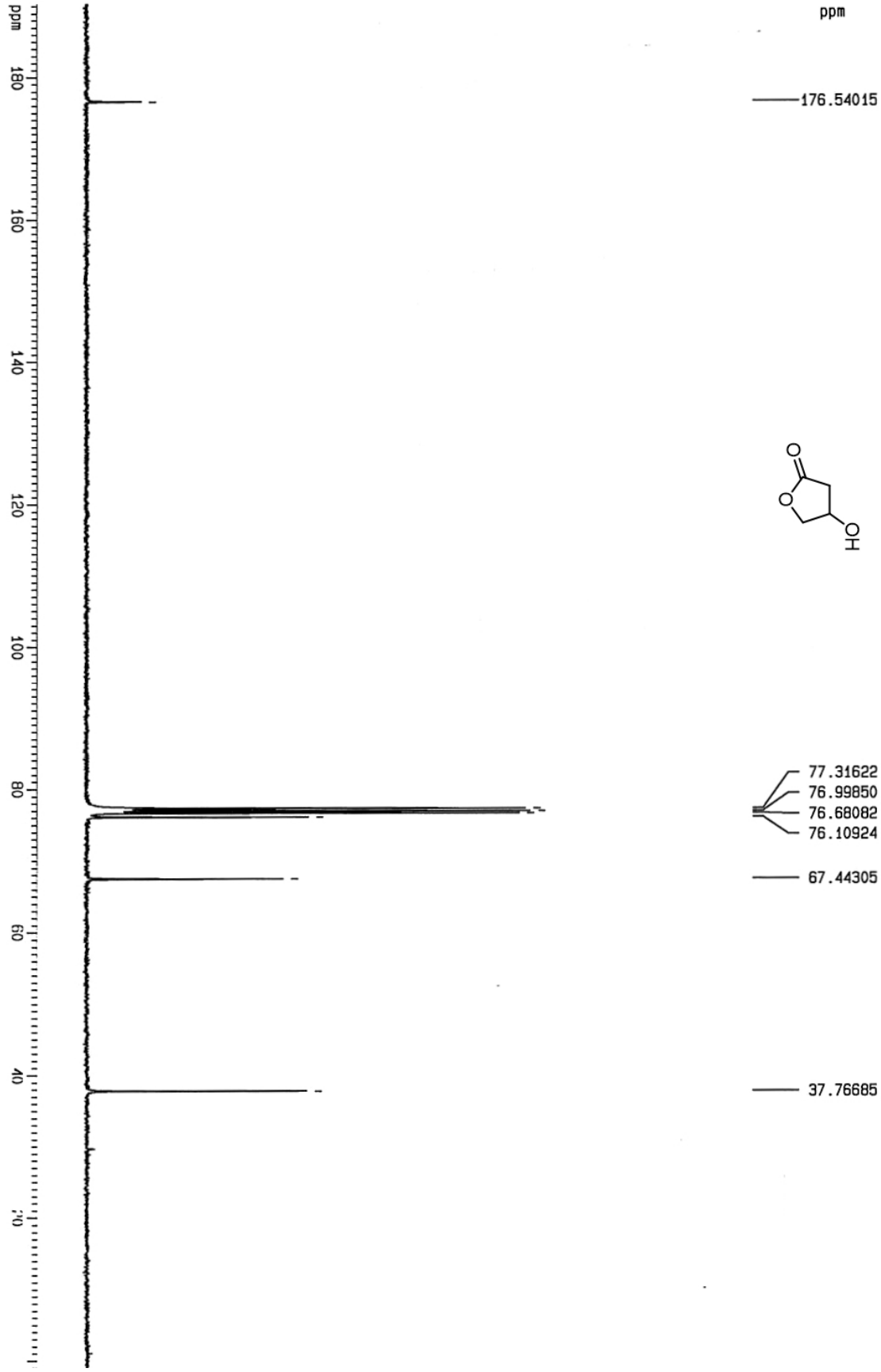
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 6-hydroxymethyl-tetrahydro-2*H*-pyran-2-one (5c)



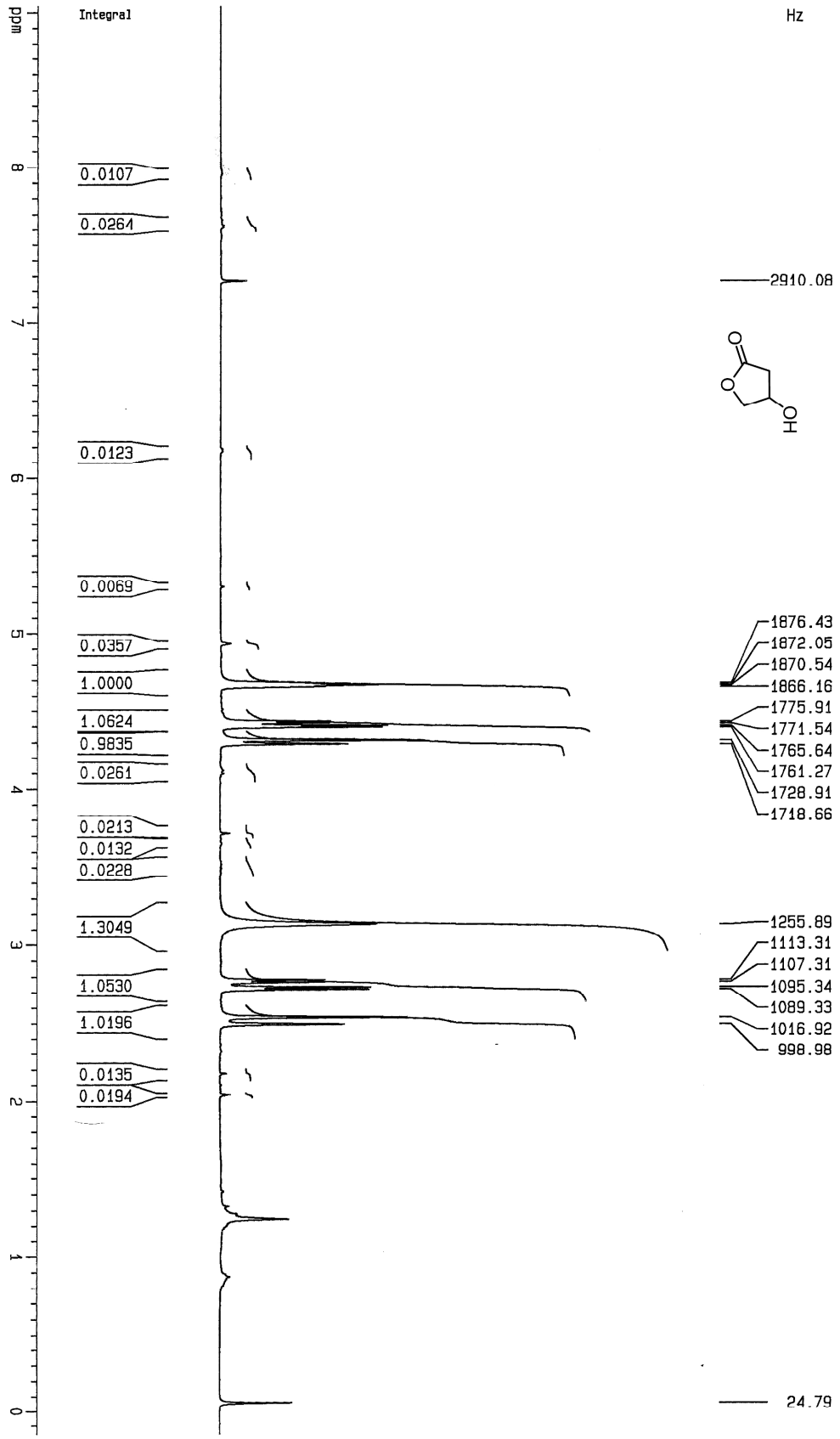
^{1}H-NMR ($CDCl_3$, 400 MHz) of 4-hydroxy-dihydrofuran-2(3*H*)-one (3-BHL) (5d)



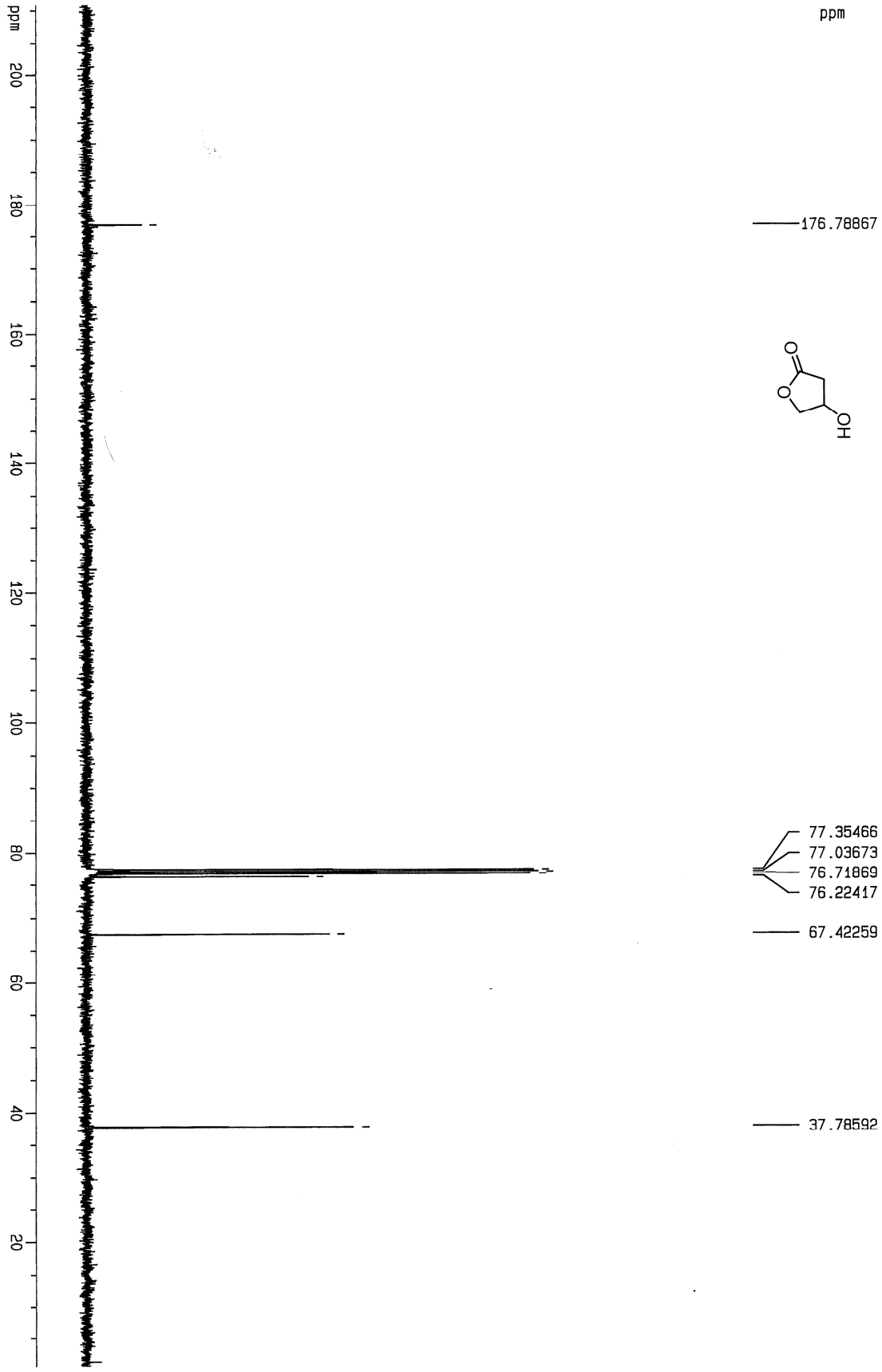
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 4-hydroxy-dihydrofuran-2(3*H*)-one (3-BHL) (5d)



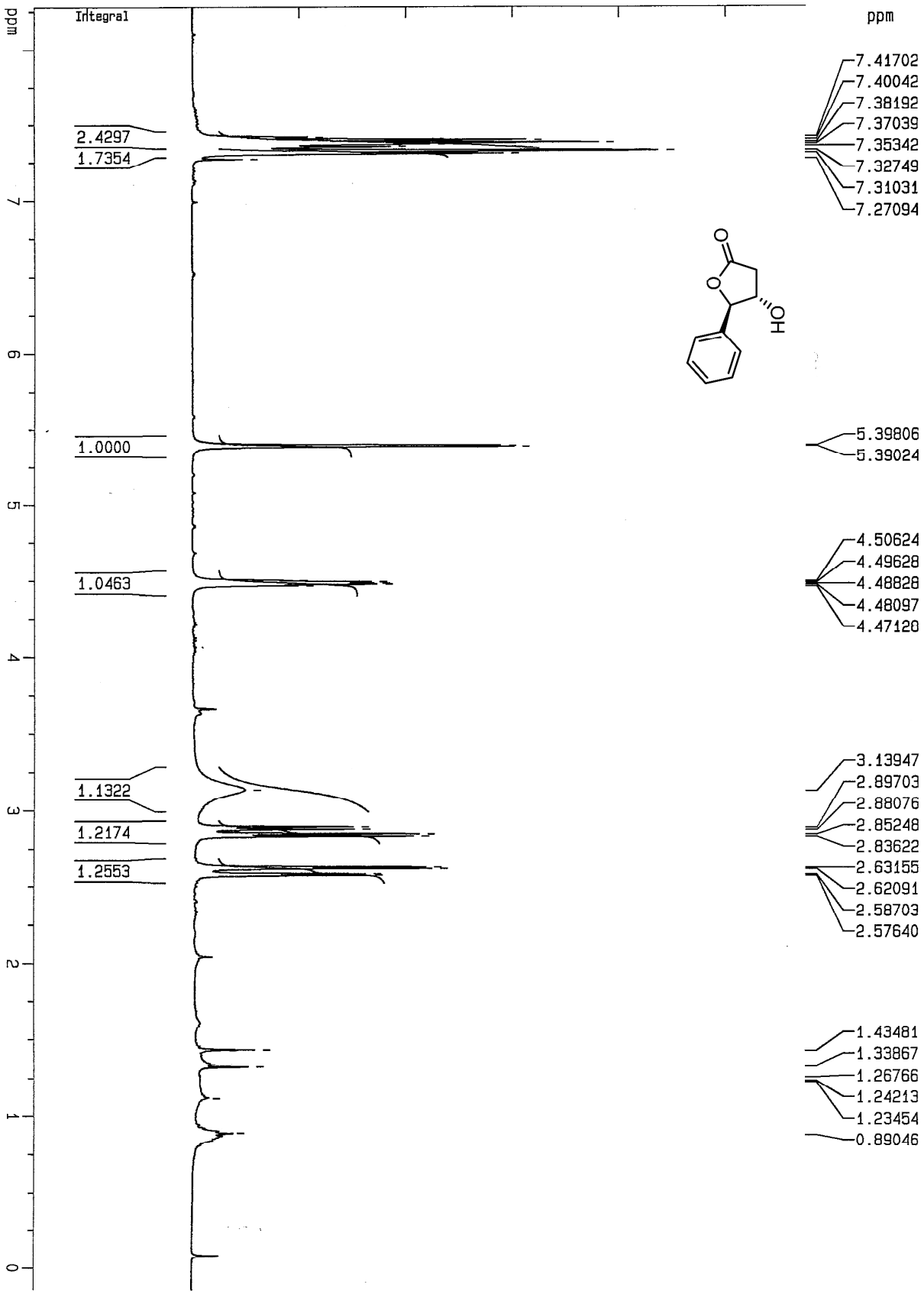
^{1}H-NMR ($CDCl_3$, 400 MHz) of 4-hydroxy-dihydrofuran-2(3*H*)-one (3-BHL) (5d): scale up synthesis



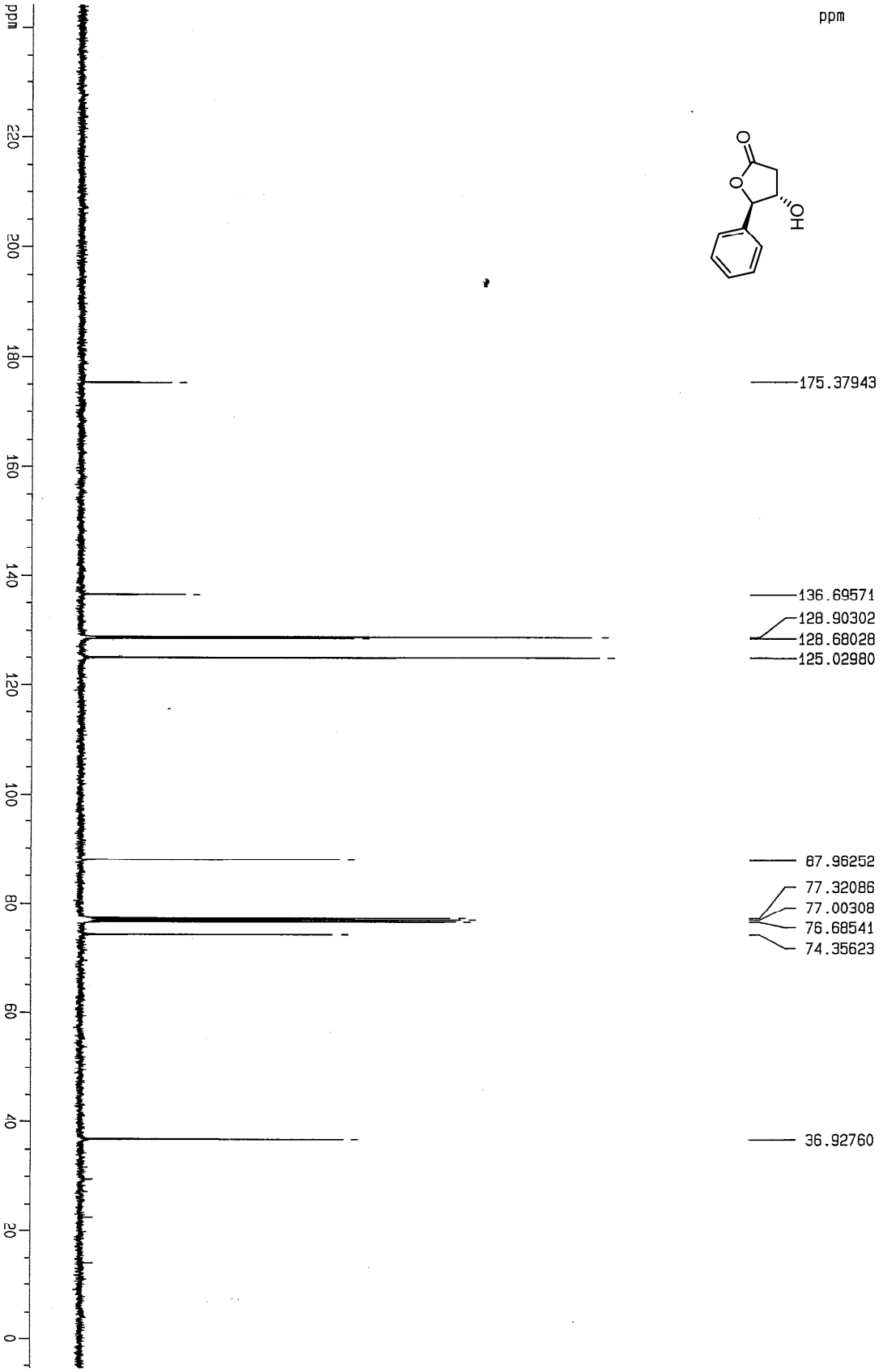
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 4-hydroxy-dihydrofuran-2(3*H*)-one (5d): scale up synthesis



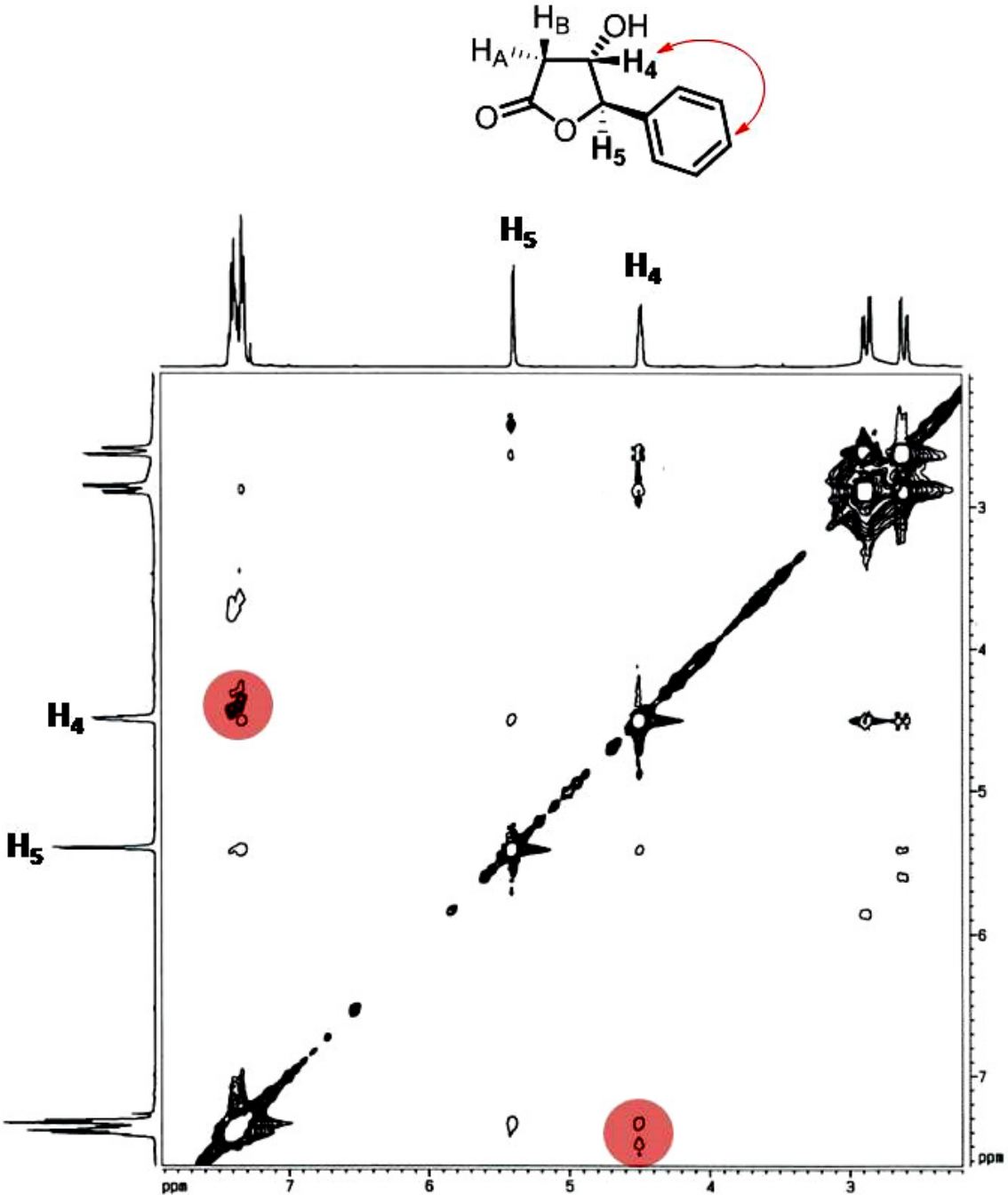
^{1}H-NMR ($CDCl_3$, 400 MHz) of 4-hydroxy-5-phenyl-dihydrofuran-2(3*H*)-one (5e)



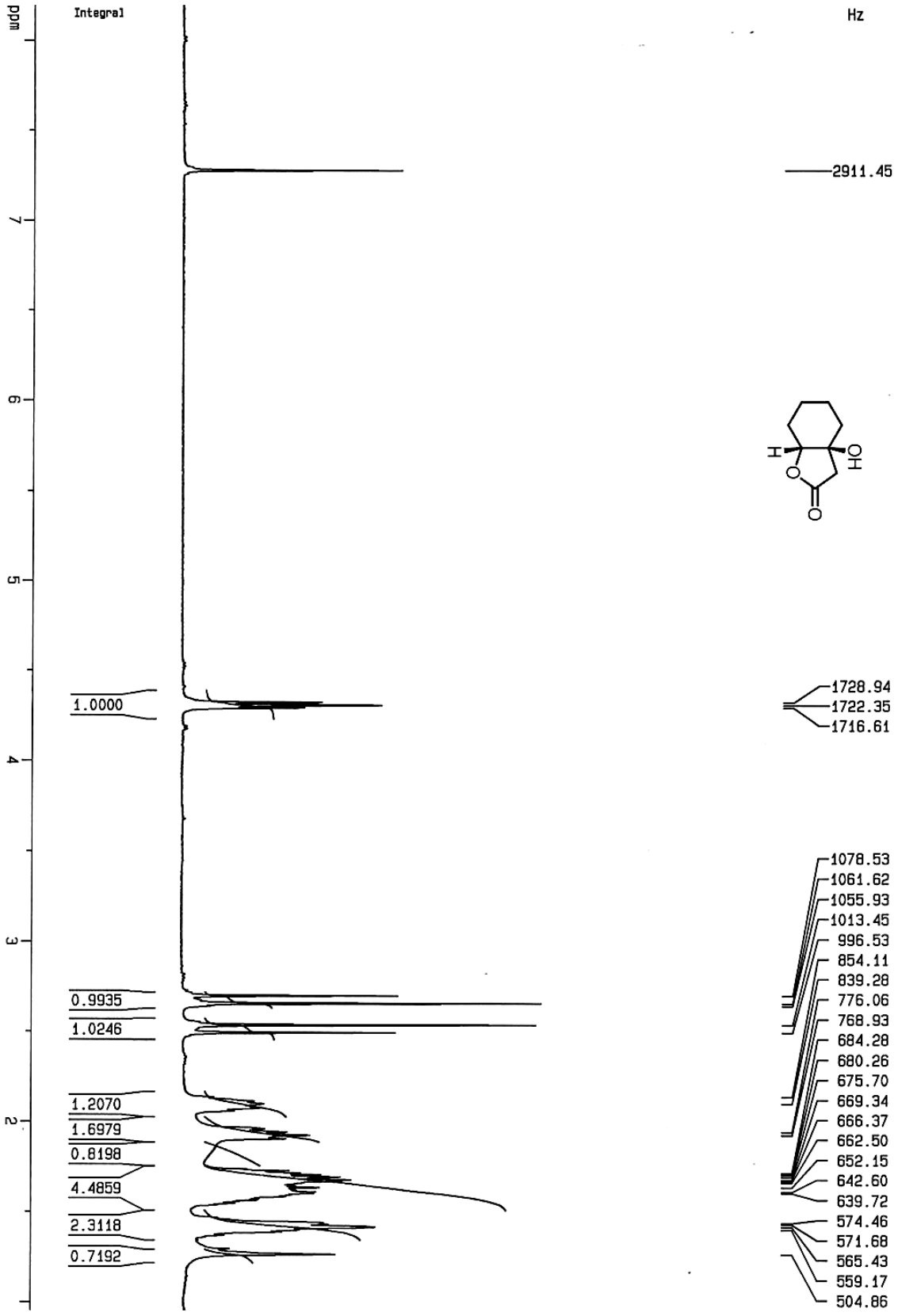
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 4-hydroxy-5-phenyl-dihydrofuran-2(3*H*)-one (5e)



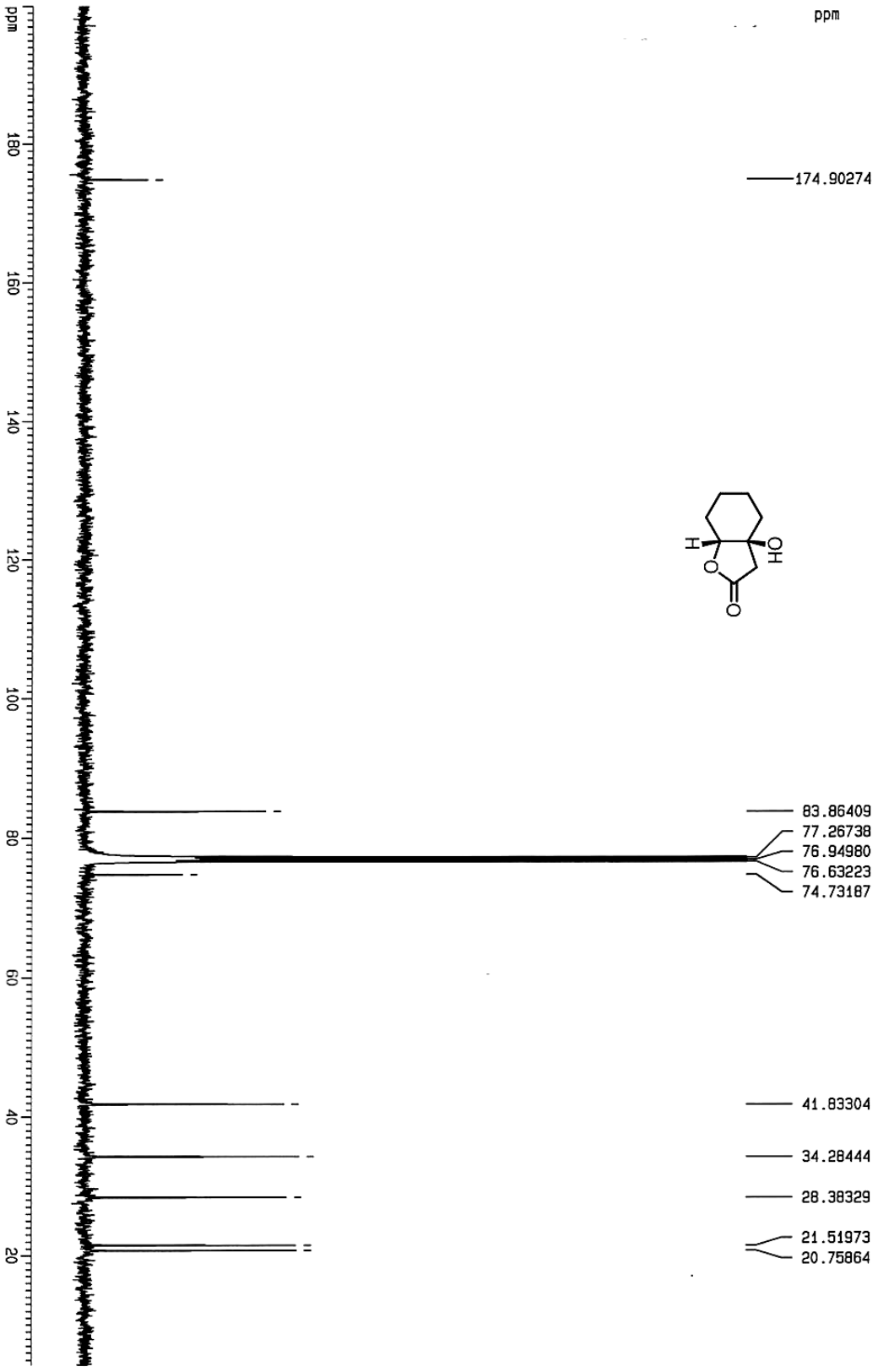
NOESY spectra of 4-hydroxy-5-phenyl-dihydrofuran-2(3*H*)-one (5e)



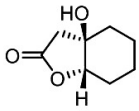
^{1}H-NMR ($CDCl_3$, 400 MHz) of 3a-hydroxy-hexahydrobenzofuran-2(3*H*)-one (5f)



^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 3a-hydroxy-hexahydrobenzofuran-2(3*H*)-one (5f)



HRMS (ESI) of 3a-hydroxy-hexahydrobenzofuran-2(3*H*)-one (5f)

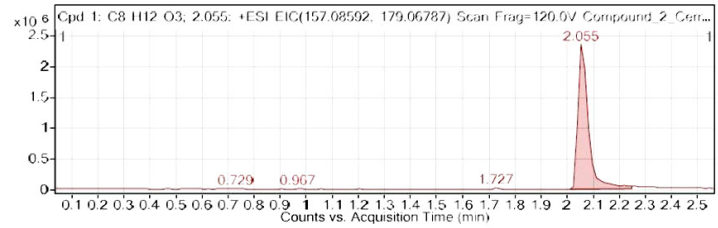


5f

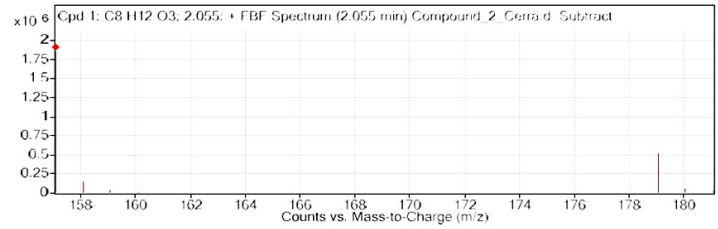
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C8 H12 O3; 2.055	2,055	156,07813	510795	C8 H12 O3	156,07864	-3,32	C8 H12 O3	C8 H12 O3

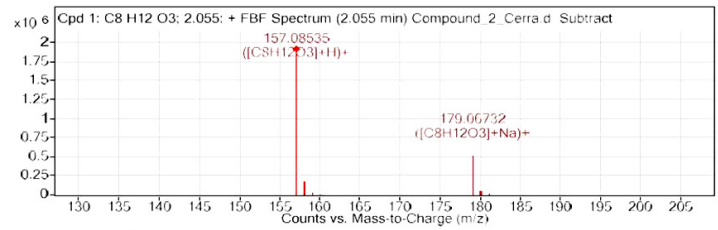
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C8 H12 O3; 2.055	179,06732	2,055	Find By Formula	156,07813



MS Spectrum



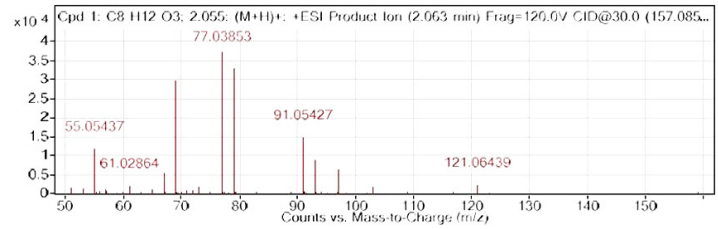
MS Zoomed Spectrum



MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
157,08535	1	1847465,63	C8H12O3	(M+H)+
158,08936	1	147561,2	C8H12O3	(M+H)+
159,09116	1	16662,38	C8H12O3	(M+H)+
160,09293	1	967,11	C8H12O3	(M+H)+
179,06732	1	510795,25	C8H12O3	(M+Na)+
180,07104	1	42812,59	C8H12O3	(M+Na)+
181,07375	1	5933,39	C8H12O3	(M+Na)+

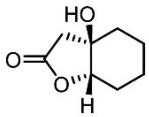
MSMS Spectrum



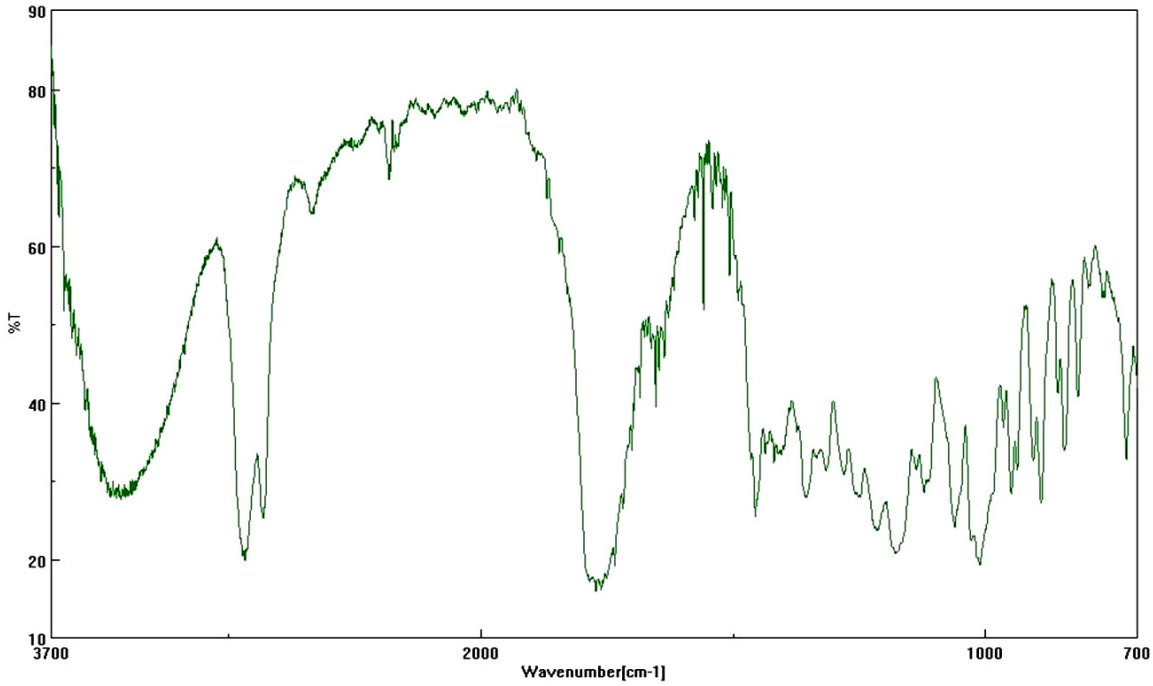
MS/MS Spectrum Peak List

m/z	z	Abund
55,01809	1	6036,3
55,05437	1	11690,01
67,05403	1	5279,23
69,07005	1	29887,84
77,03853	1	37223,56
79,05416	1	32958,09
91,05427	1	14682,47
93,06958	1	8702,7
97,06431	1	6233,18
121,06439		2143,47

FT-IR (KBr) of 3a-hydroxy-hexahydrobenzofuran-2(3*H*)-one (5f)

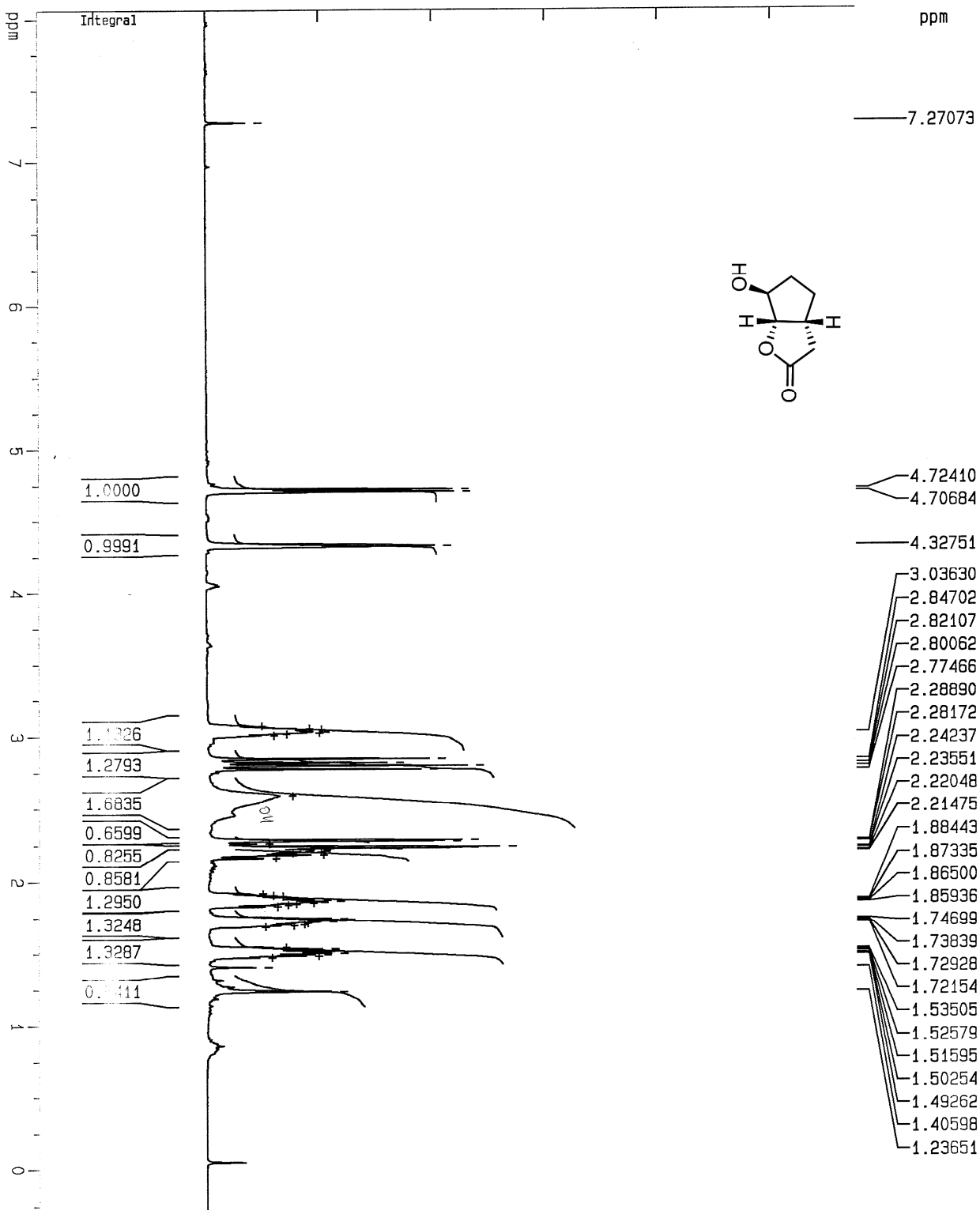


5f

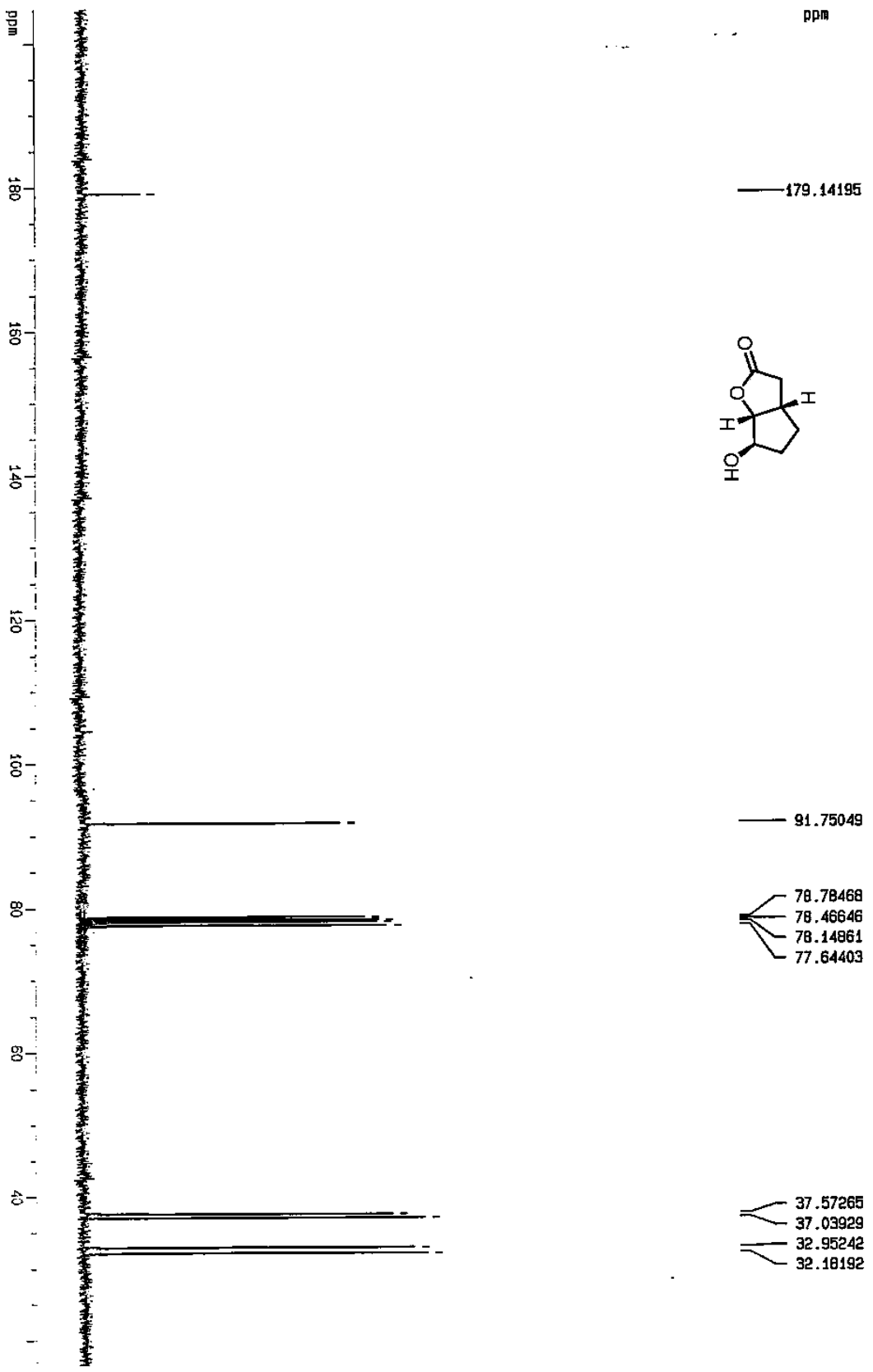


Peak At (Cm^{-1})	%T
2932.23	20.01
2857.99	26.42
2662.25	64.91
1759.24	17.21
1454.55	27.02
1353.78	28.18
1248.20	28.05
1213.49	23.68
1173.95	21.15
1062.59	24.61
1009.15	20.05
948.81	28.47
888.06	28.57
842.74	34.29

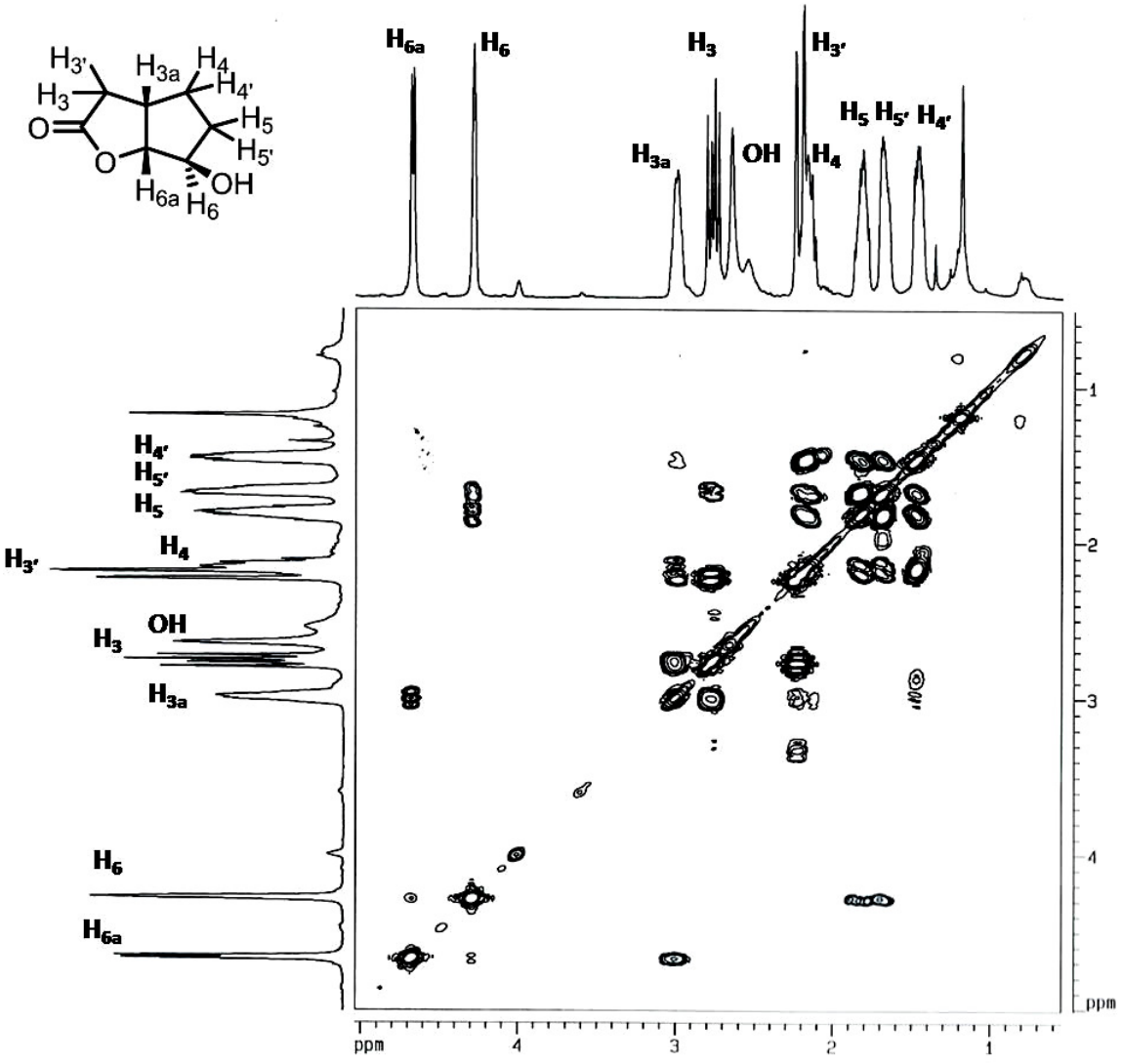
^{1}H-NMR ($CDCl_3$, 400 MHz) of 6-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5g)



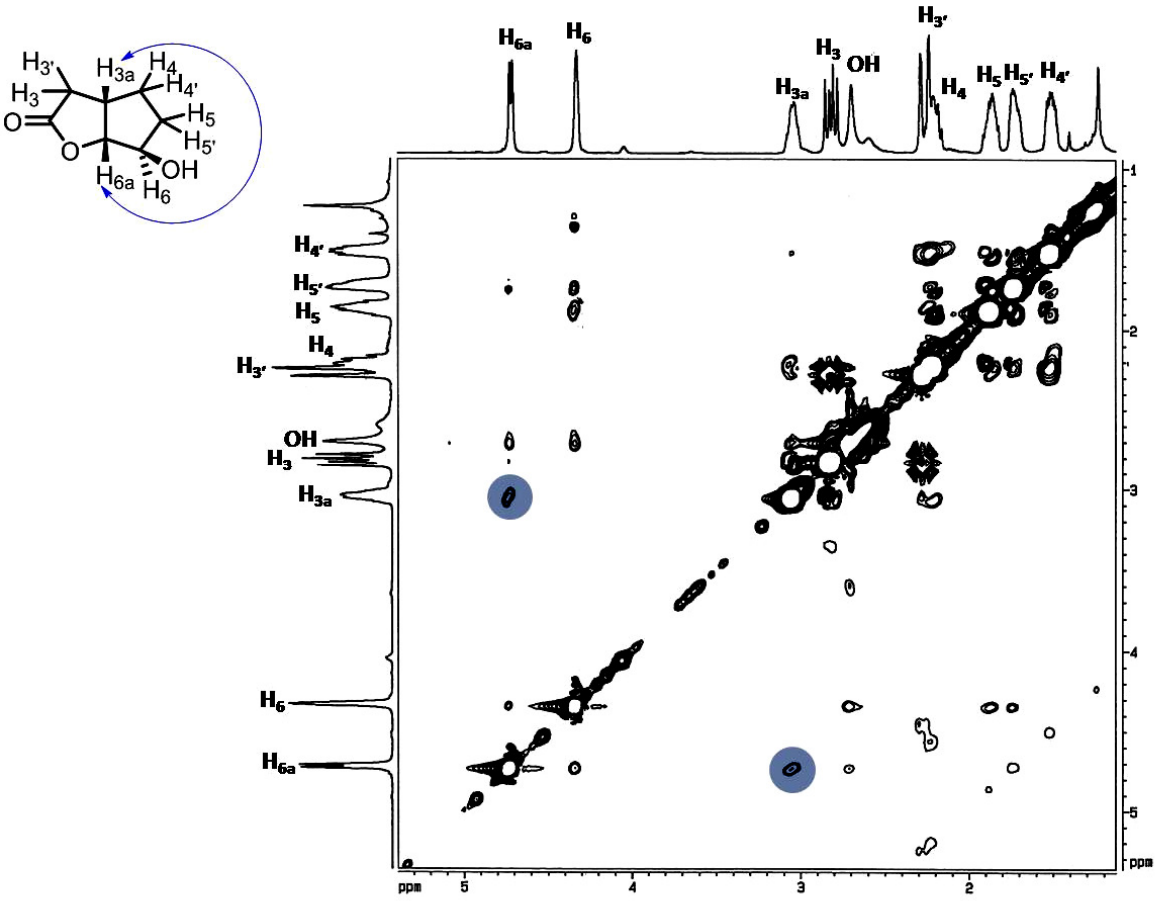
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 6-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5g)



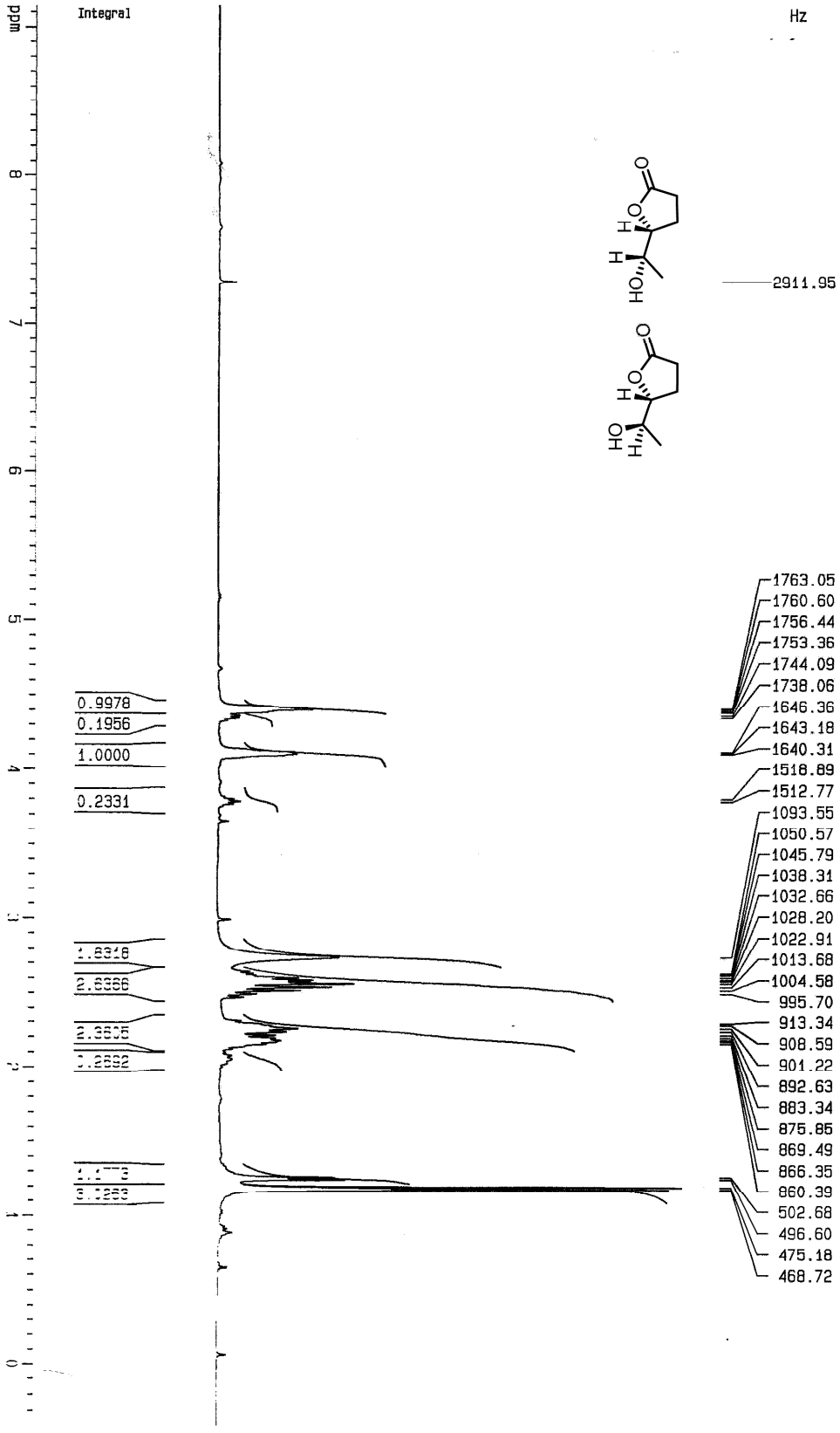
^{1}H,^{1}H-COSY spectra of 6-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5g)



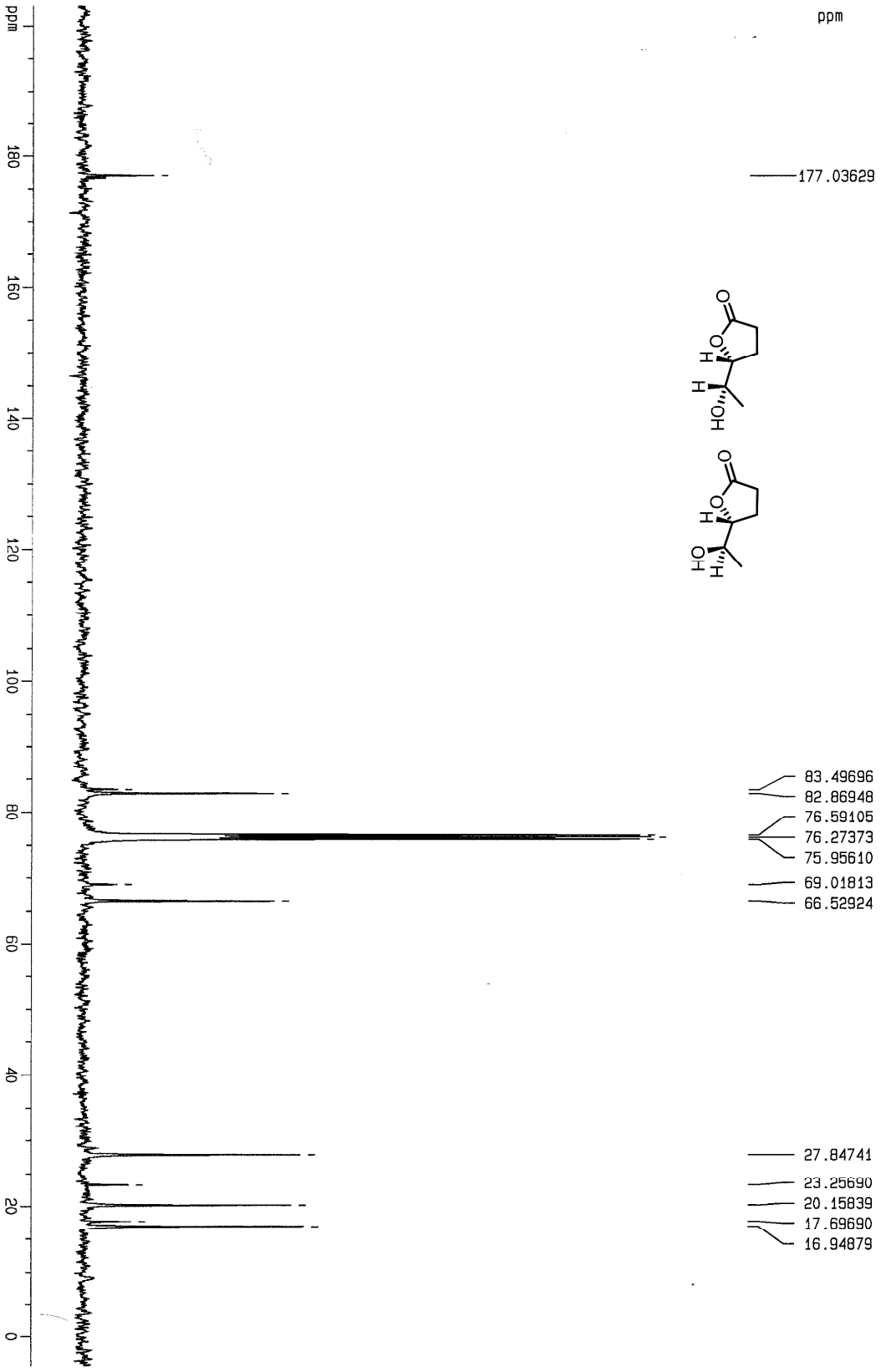
NOESY of 6-hydroxy-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (5g)



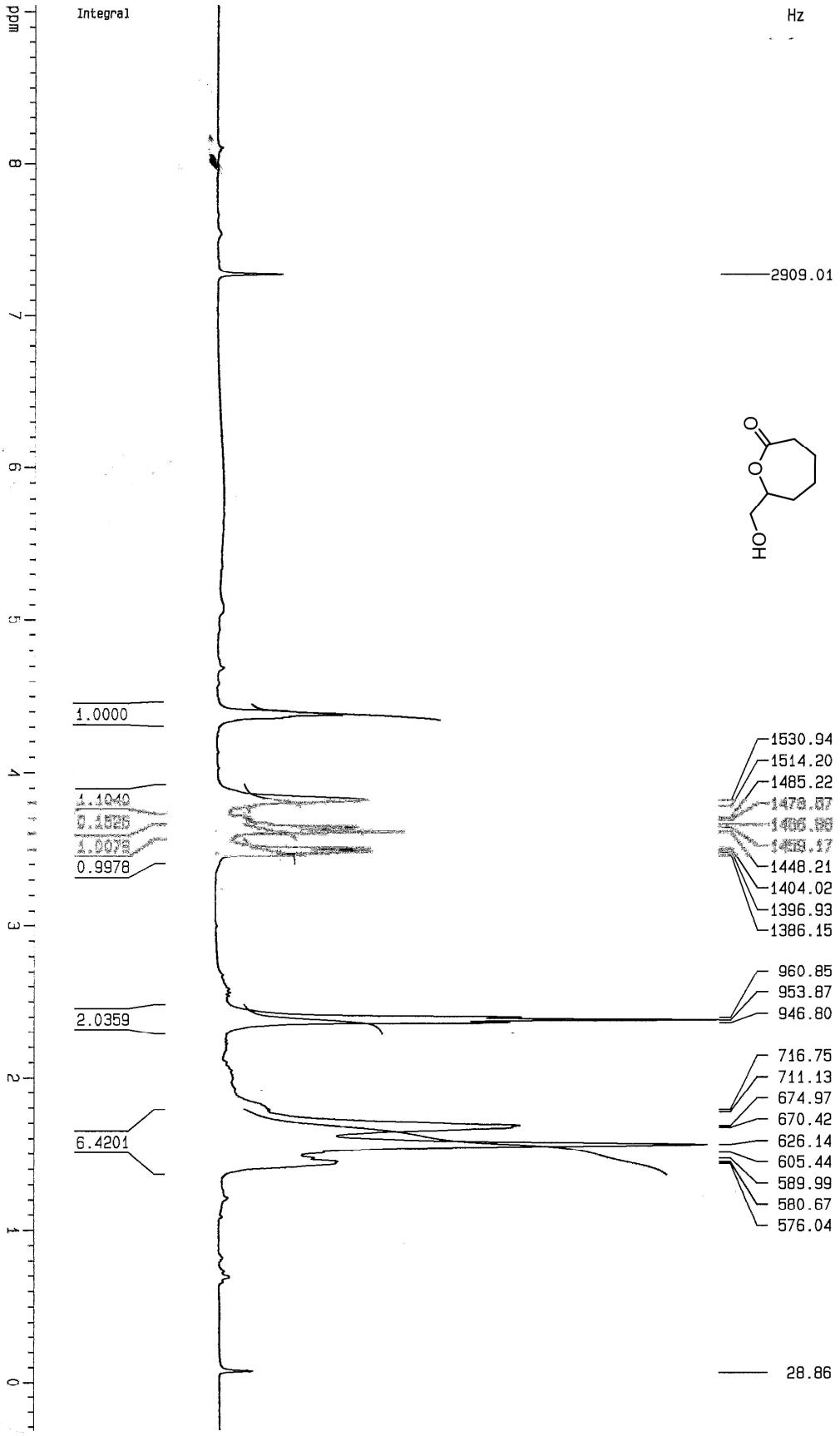
^{1}H-NMR ($CDCl_3$, 400 MHz) of 5-(1-hydroxyethyl)dihydrofuran-2(3*H*)-one (5h, mixture *anti*:*syn* 80:20)



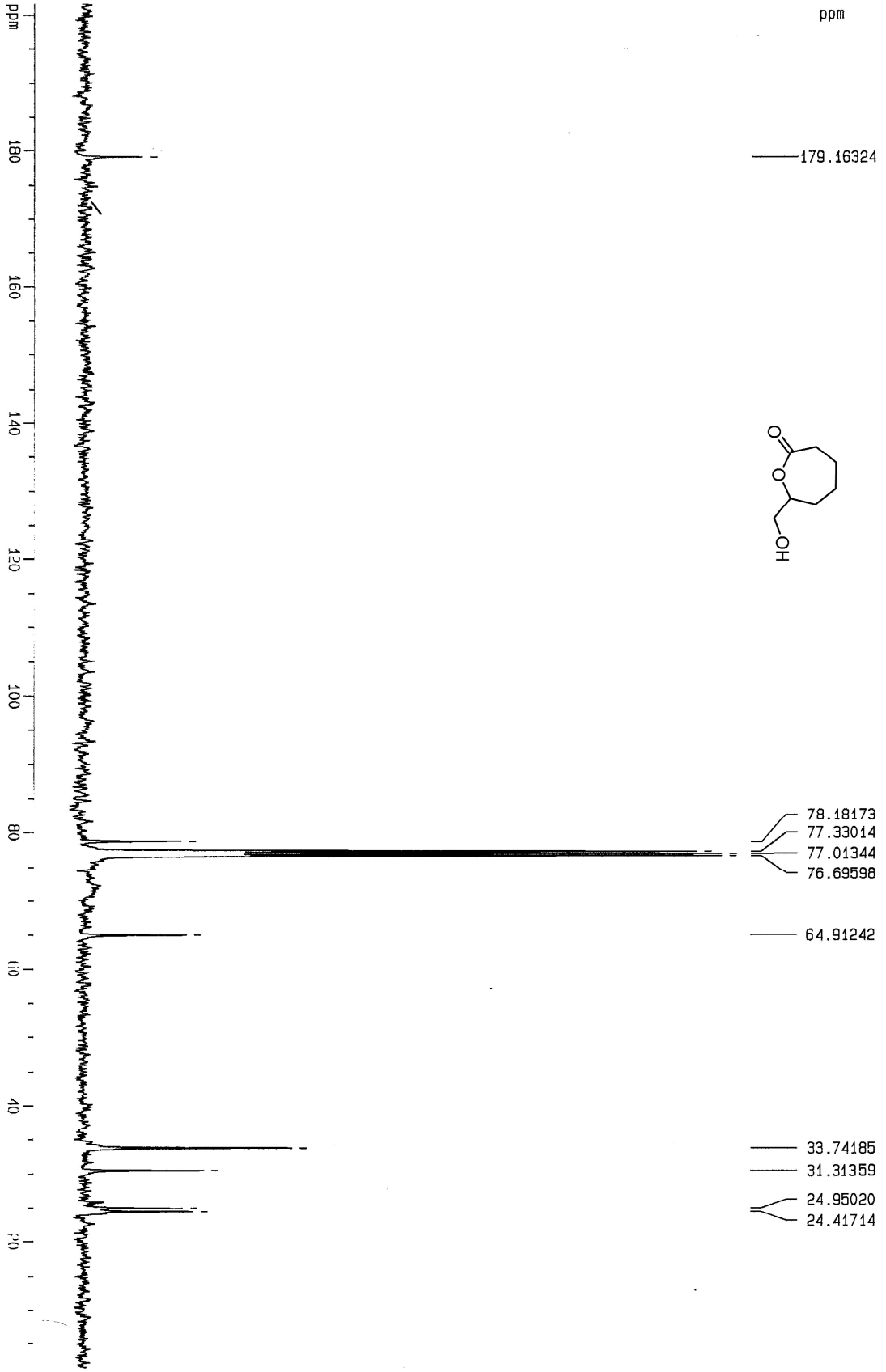
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 5-(1-hydroxyethyl)dihydrofuran-2(3*H*)-one (5h, mixture *anti*:*syn* 80:20)



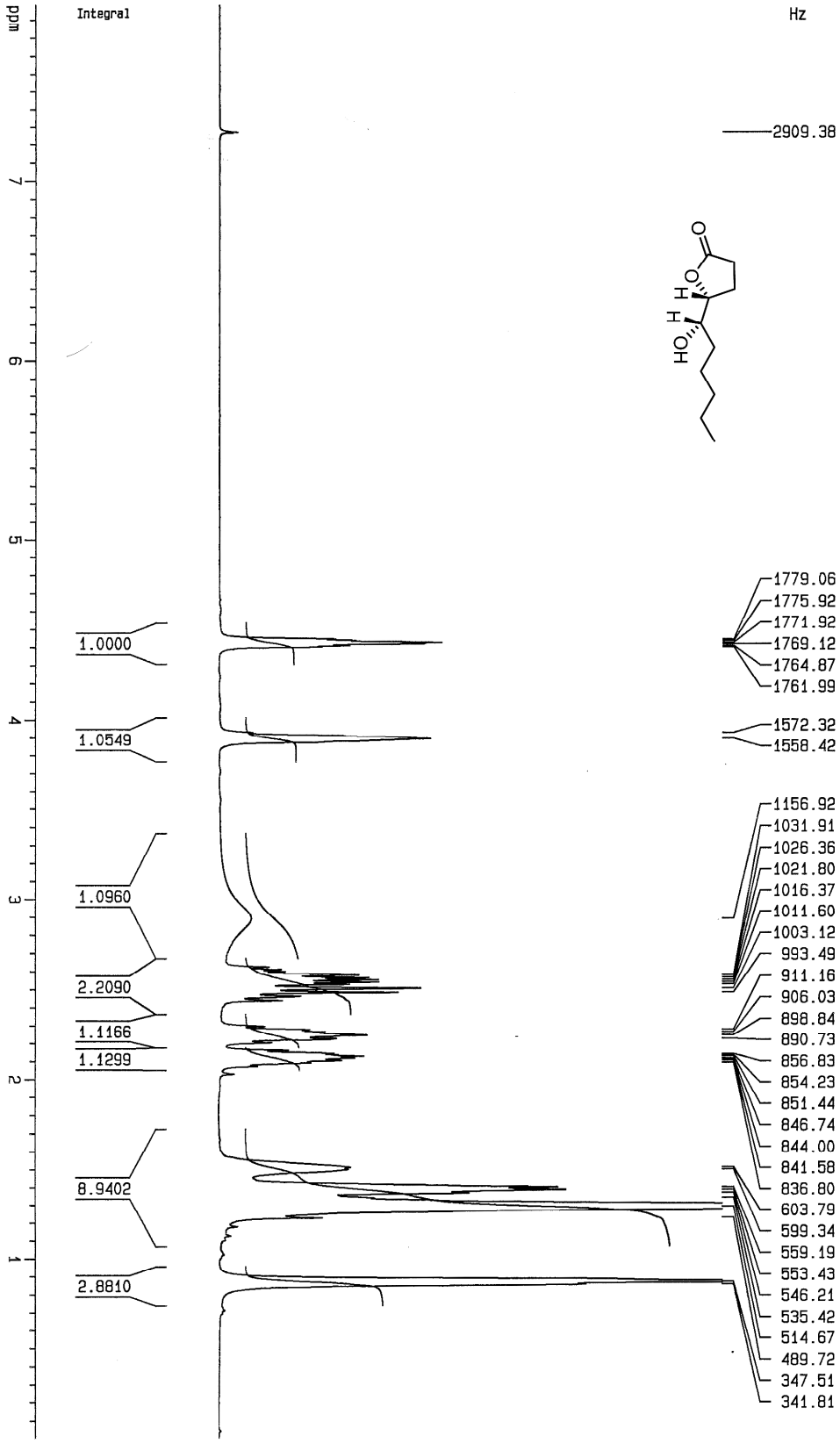
^{1}H-NMR ($CDCl_3$, 400 MHz) of 7-(hydroxymethyl)oxepan-2-one (5i)



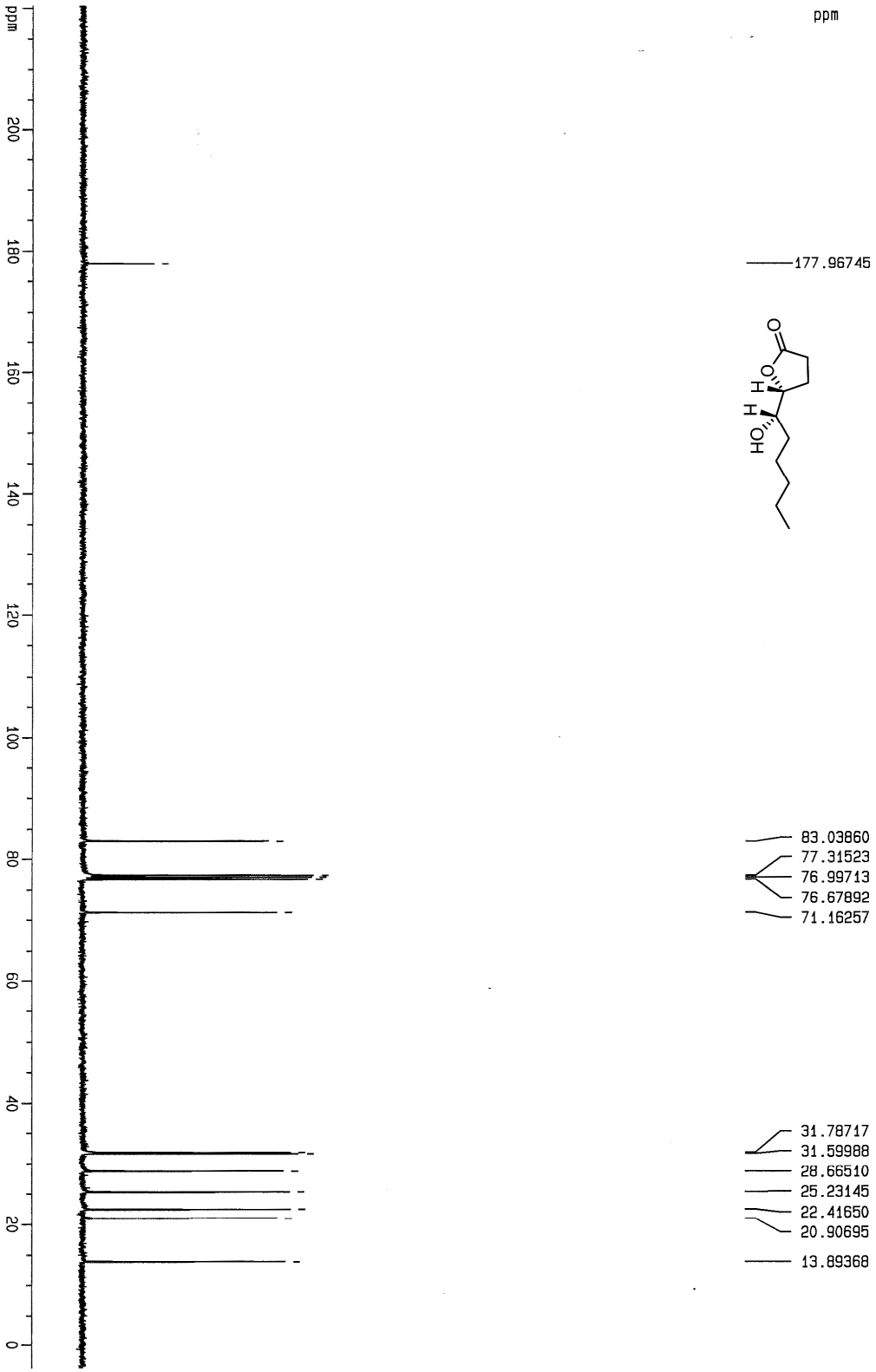
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 7-(hydroxymethyl)oxepan-2-one (5i)



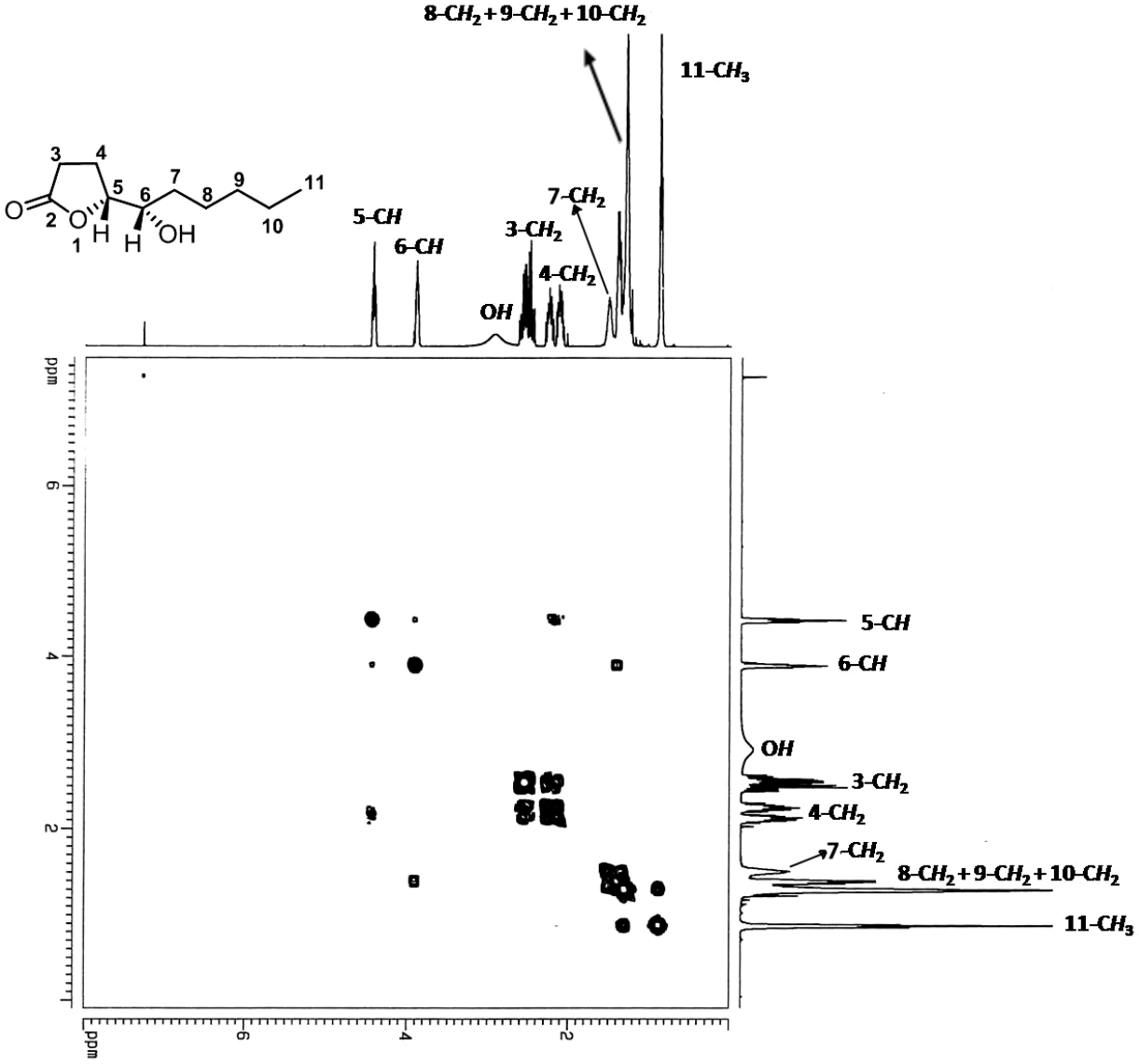
^{1}H-NMR ($CDCl_3$, 400 MHz) of 5-(1-hydroxyhexyl)dihydrofuran-2(3*H*)-one (5j)



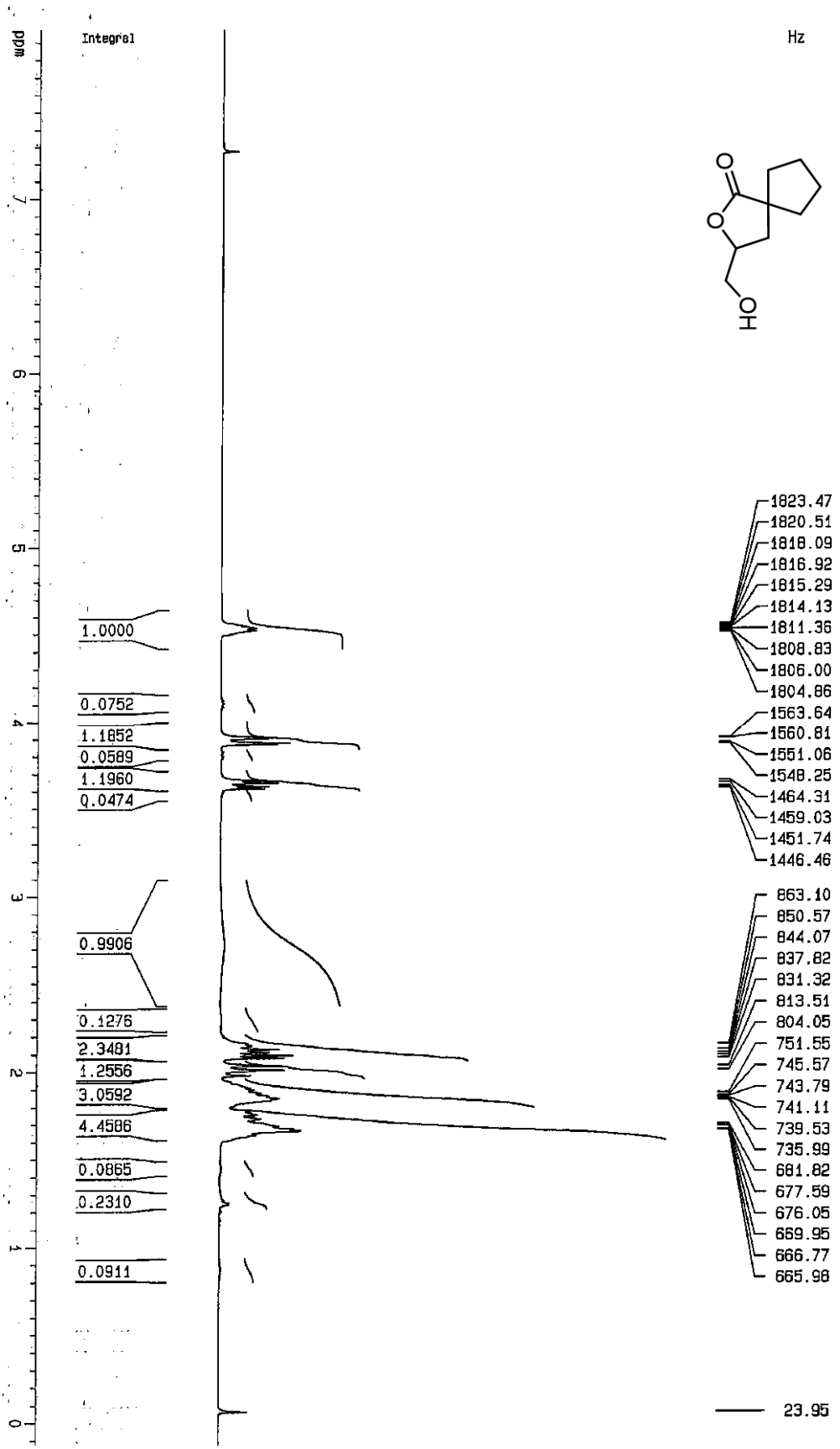
^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 5-(1-hydroxyhexyl)dihydrofuran-2(3*H*)-one (5j)



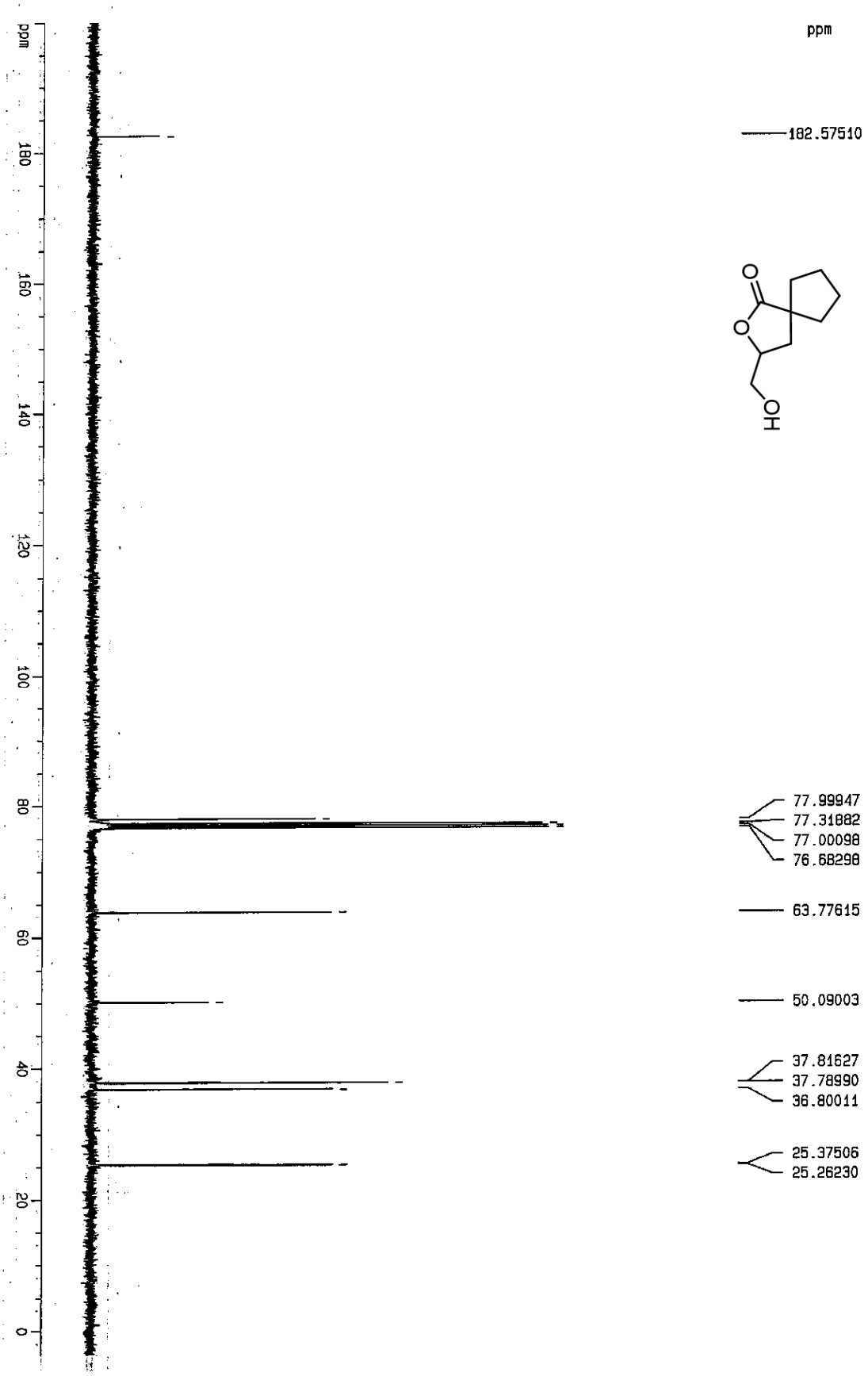
^{1}H,^{1}H-COSY spectra of 5-(1-hydroxyhexyl)dihydrofuran-2(3*H*)-one (5j)



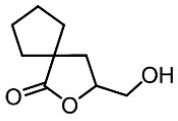
^{1}H-NMR ($CDCl_3$, 400 MHz) of 3-(hydroxymethyl)-2-oxaspiro[4.4]nonan-1-one (5l)



^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 3-(hydroxymethyl)-2-oxaspiro[4.4]nonan-1-one (5l)



HRMS (ESI) of 3-(hydroxymethyl)-2-oxaspiro[4.4]nonan-1-one (5l)

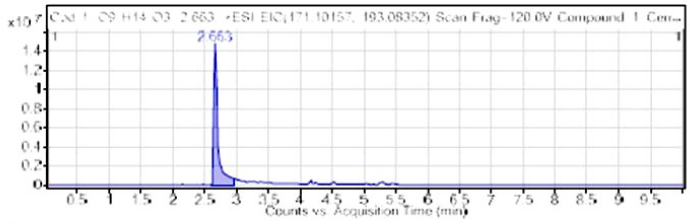


5l

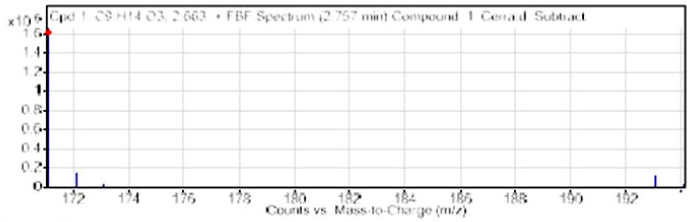
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C9 H14 O3; 2.663	2,663	170,09408	1648115	C9 H14 O3	170,09429	-1,26	C9 H14 O3	C9 H14 O3

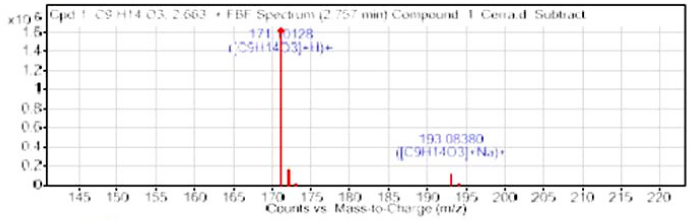
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C9 H14 O3; 2.663	171,10128	2,663	Find By Formula	170,09408



MS Spectrum



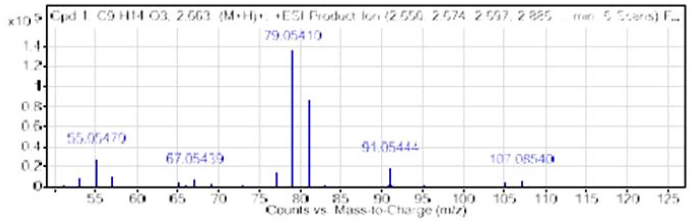
MS Zoomed Spectrum



MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
171,10128	1	1648114,5	C9H14O3	(M+H)+
172,10513	1	133021,42	C9H14O3	(M+H)+
173,10754	1	14910,29	C9H14O3	(M+H)+
193,0838	1	112767,98	C9H14O3	(M+Na)+
194,08706	1	13163,08	C9H14O3	(M+Na)+

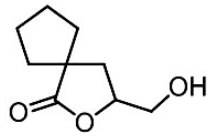
MSMS Spectrum



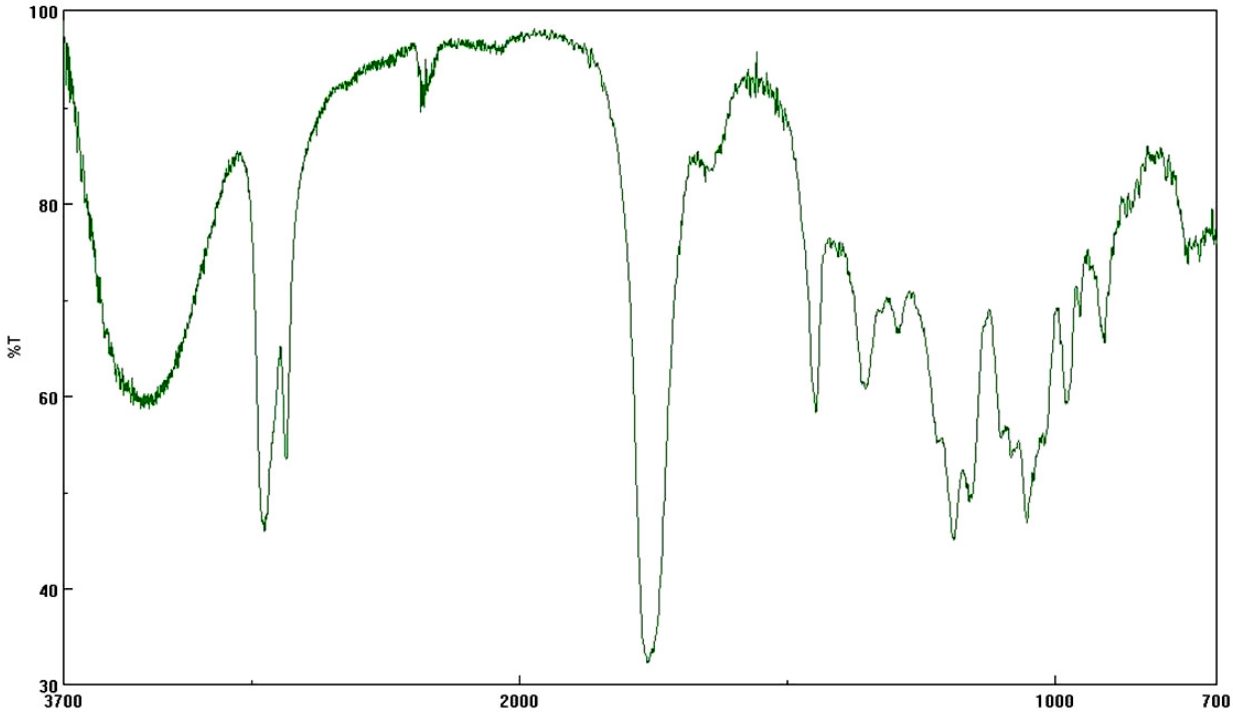
MS/MS Spectrum Peak List

m/z	z	Abund
53,03891	1	7370,54
55,0547	1	26702,07
57,03377	1	8843,78
67,05439	1	6202,29
77,03864	1	12667,83
79,0541	1	135902,41
81,06996	1	85474,53
91,05444	1	17822,12
105,06973	1	4163,24
107,0854	1	5626,47

FT-IR (KBr) of 3-(hydroxymethyl)-2-oxaspiro[4.4]nonan-1-one (5l)

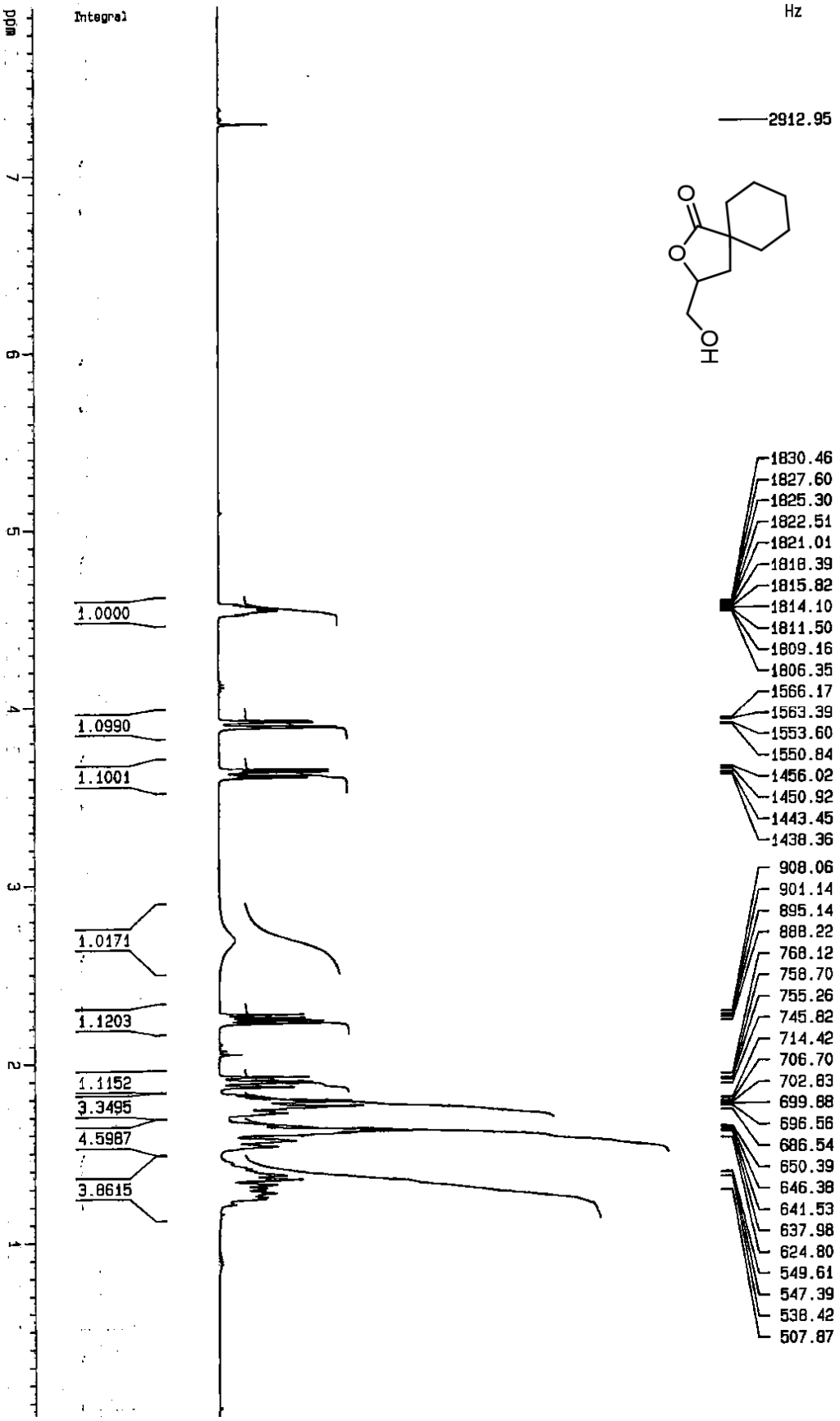


5l

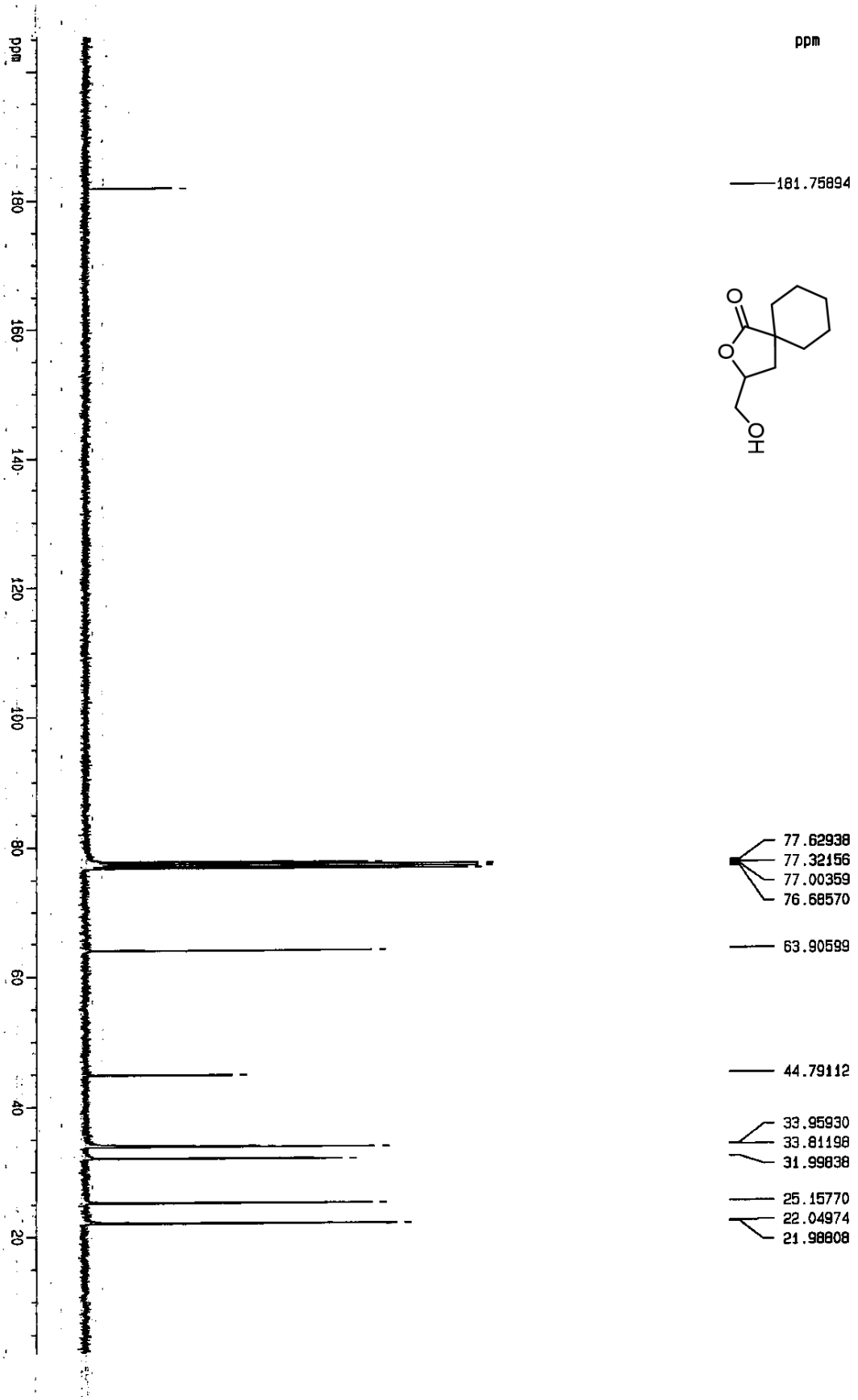


Peak At (Cm^{-1})	%T
2957.30	46.70
2871.97	53.78
1757.80	33.37
1447.80	58.78
1354.27	61.03
1188.90	45.23
1055.35	47.49
980.63	59.20
913.61	66.95

^{1}H-NMR ($CDCl_3$, 400 MHz) of 3-(hydroxymethyl)-2-oxaspiro[4.5]decan-1-one (5m)



^{13}C-NMR ($CDCl_3$, 100.6 MHz) of 3-(hydroxymethyl)-2-oxaspiro[4.5]decan-1-one (5m)



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