Oxidative Cyclizations: The Asymmetric Synthesis of (-)-Alliacol A.

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SUPPLEMENTARY MATERIAL

General Information:

Electrolysis reactions were conducted using a model 630 coulometer, a model 410 potentiostatic controller, and a model 420A power supply purchased from the Electrosynthesis Company, Inc. (now Electroytica). Carbon rods, reticulated vitreous carbon (RVC), and platinum electrodes were also purchased from the Electrolytica Co. All glassware was flame dried immediately prior to use and all reactions were conducted under an inert atmosphere. All reagents and solvents were purchased from Aldrich and used without purification unless stated otherwise. Anhydrous methanol was received and stored in Sure/Seal bottles from Aldrich. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and toluene were distilled from calcium hydride. Gravity flow and flash chromatography were carried out using Natland International Corporation Silica gel (200 - 400 mesh). All proton and carbon magnetic resonance spectra were recorded using a Varian Gemini 300, Varian Mercury 300, or Varian Unity 300 spectrometer using $CDCl_3$ as solvent. Chemical shifts are reported downfield from TMS. A mixing time of 600 milliseconds was used for each of the 2D NMR experiments. For the 2D experiments, 2048 data points were taken in t_2 and 200 – 300 data points were taken in t_1. The purity of compounds was established as being greater than 95% using ^1H NMR and ^{13}C NMR. Copies of the spectral data for all new compounds have been included. Infrared spectra (IR) were obtained using a Perkin Elmer Spectrum BS FT-IR System Spectrophotometer. High-resolution electron ionization (FAB) mass spectral data were obtained using a Kratos MS-50 spectrometer with an acceleration voltage of 8 keV. High-resolution electron ionization (EI) mass spectral data were obtained using a Micromass ZAB-SE spectrometer with an ionization voltage of 70 eV and an acceleration voltage of 8 keV. HPLC anaylsis was performed with a Hewlett-Packard Model 1100 machine using a Chiralpak AD column. Polarimetry measurements were obtained with a Perkin Elmer Model 241 Polarimeter.

Experimental details and copies of proton and carbon NMR spectra for the total synthesis of racemic alliacol A can be found in the supplementary material for the preliminary publication (*J. Am. Chem. Soc.* **2003**, *125*, 36.).

Model Studies:

3-(3'-iodopropyl)furan: A 100 mL round-bottom flask was charged with 2.56 g (20.3 mmol) of 3-(3'-hydroxypropyl)furan[7] and placed under vacuum for 4 h. After this period, 20 mL of CH_2Cl_2 and 3.62 mL (3.05 mmol) of 2,6-lutidine were added. The mixture was cooled to 0ºC and then 2.37 mL (3.05 mmol) of MsCl were added and the cooling bath was removed. After 2 h, 17 mL of water were added followed by extraction with 160 mL of diethyl ether. The organic layer was washed with 45 mL each of water and sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated to afford 2.6 g of a pale yellow oil. Chromatography

through silica gel using 3:1:1 hexanes/ethyl ether/methanol as eluant provided the mesylate (4.60 g, 82% yield) as a colorless oil.

To the product synthesized above was added 20 mL of acetone. The mixture was then placed in an ice water bath. After the portion wise addition of 5.36 g (40 mmol) of LiI, the mixture was stirred for 7 h while the temperature was allowed to slowly rise to ambient. The acetone was removed *in vacuo* and then the residue was dissolved in 200 mL ether, washed with water (2x 35 mL) and 5 mL brine, dried over $MgSO_4$, and concentrated to afford a pale yellow oil. Chromatography through silica gel, slurry-packed with 1% TEA in hexanes and eluted with hexanes, provided the iodide (3.99 g, 83% yield) as a colorless oil: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36 (s, 1 H), 7.24 (s, 1 H), 6.26 (s, 1 H), 3.19 (t, J = 8 Hz, 2 H), 2.57 (t, J = 8 Hz, 2 H), 2.05 (qnt, J = 8 Hz, 2 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 143.5, 139.7, 123.4, 111.2, 33.5, 25.8, 6.6. The iodide was carried on without further characterization.

3-(7'-t-Butyldimethylsiloxy-6',6'-dimethyl-5'-oxoheptanyl)furan (9): A 250 mL round-bottom flask was charged with 11 mL of THF and 5.9 mL (42 mmol) of freshly distilled diisopropylamine and then placed under a nitrogen atmosphere and cooled to -78 ºC. Over 2 min, 26 mL of a 1.6 M solution (42 mmol) of n-BuLi in hexanes was added. The cooling bath was removed and then after 30 min the mixture was placed in an ice water bath. To this solution, 9.99 g (43.4 mmol) of 4-t-butyldimethylsiloxy-3,3-dimethylbutanone were added via a syringe over 40 min. The syringe was rinsed with 2 mL of THF. The cooling bath was refreshed with ice and then 10 mL (91.5 mmol) of DMI added. The bath was removed and the reaction stirred for 1h before 2.00 g (8.49 mmol) of iodide in 1.5 mL of THF were added via syringe over 20 min. The syringe was rinsed with 2 mL of THF to ensure complete transfer of the iodide. During the addition, a white precipitate was formed. The amount of this white precipitate increased over the next 40 min. After placing the flask in an ice water bath, 16 mL of sat. NH_4Cl were added and then most of the THF was removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (3x 50 mL) and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford 16.4 g of the crude product. Chromatography through silica gel, slurry-packed with 1% TEA in hexanes and eluted with 3% ether in hexanes, provided the mostly pure ketone. This product was then vacuum distilled using a Kugelrohr apparatus to provide the pure ketone **9** (2.70 g, 94% yield) as a colorless oil: IR(neat) 3473 (s, br), 2963 (s), 2968 (s), 2857 (s), 1768 (w), 1707 (s), 1504 (w), 1463(m), 1379 (m), 1364(m), 1208 (w), 1108(w), 1052 (s), 1032 (s), 726 (w), cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.32 (s, 1 H), 7.17 (s, 1 H), 6.22 (s, 1 H), 3.54 (s, 2 H), 2.50 (t, J = 7 Hz, 2 H), 2.38 (t, J = 7 Hz, 2 H), 1.53 (m, 4 H), 1.03 (s, 6 H), 0.82 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 205.4, 70.8, 49.7, 34.6, 26.0, 22.0, 18.3, -5.5; HRMS (FAB) *m/z* 345.2451 $(M+Li)^+$; calcd for $C_{19}H_{34}O_3SiLi$: 345.2437.

3-(5',7'-bis-t-Butyldimethylsiloxy-6',6'-dimethyl-4'-heptenyl)furan (10): A 50 mL round-bottom flask was charged with 2.70 g (7.98 mmol) of ketone **9**, 15 mL of CH_2Cl_2, and 2.9 mL (23.1 mmol) of freshly distilled triethylamine. The mixture was placed under a nitrogen atmosphere and cooled to –10 ºC. After 5 min had passed, 2.5 mL (10.1 mmol) of TBSOTf were added and the reaction was allowed to stir for 16 h. After cooling the reaction in an ice water bath, 15 mL of sat. aq. $NaHCO_3$ were added, the reaction mixture transferred to a separatory funnel, the layers separated, and the aqueous phase extracted with 3 x 40 mL hexane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford 9.5 g of the crude product. Chromatography through silica gel, slurry-packed with 1% TEA in hexanes and eluted using a solvent gradient from pure hexanes to 3% ether in hexanes, provided silyl enol ether **10** (2.83 g, 78% yield) as a colorless oil: IR(neat) 3548 (w), 2958 (s), 2930 (s), 2857 (s), 1662 (m), 1502 (w), 1461(m), 1359 (m), 1342(m), 1099 (s), 940 (m), 836 (s) cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.35 (s, 1 H), 7.19 (s, 1 H), 6.26 (s, 1 H), 4.44 (t, J = 6 Hz, 1 H), 3.40 (s, 2 H), 2.41 (t, J = 8 Hz, 2 H), 2.37 (qrt, J = 8 Hz, 2 H), 1.57 (qnt, J=8 Hz, 2 H), 1.02 (s, 6 H), 0.96 (s, 8 H), 0.85(s, 10 H), 0.15 (s, 5 H), 0.02 (s, 7 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 155.0, 142.7, 139.0, 125.4, 111.4, 105.4, 69.7, 42.2, 30.8, 26.3, 26.1, 26.0, 24.5, 24.0, 19.4, 18.5, -2.7, -5.2; HRMS (FAB) m/z 459.3292 $(M+Li)^+$; calcd for $C_{25}H_{48}O_3Si_2Li$: 459.3302.

8-(3'-Hydroxy-2',2'-dimethyl-1'-oxopropyl)cyclohexyl[b]furan (12a) and 8-(3'-t-butyl-dimethylsiloxy-2',2'-dimethyl-1'-oxopropyl)cyclohexyl[b]furan (12b): To a 100 mL 3-neck round-bottom flask under nitrogen was added 582 mg (1.28 mmol) of the electrolysis substrate (**10**), 39 mL of CH_2Cl_2, 10 mL of anhydrous MeOH, 0.75 mL (6.4 mmol) of 2,6-lutidine and 2.297 g (21.6 mmol) of $LiClO_4$.

The reaction flask was then fitted with a reticulated vitreous carbon (RVC/ ca. 0.35 cm^3) anode and a carbon rod cathode (6.5 mm diameter). The reaction was then degassed by sonication under nitrogen for 5 min. A constant current of 12.9 mA was then applied to the solution until a total of 262 C (2.12 F/mol) of charge had been passed (about 6 h). At this point, the oxidation was complete as indicated by thin layer chromatography. Toluene sulfonic acid monohydrate (1.236 mg, 6.50 mmol) was then added to the flask and the mixture stirred for an additional 14 h. The reaction was diluted with 360 mL of ethyl ether and then washed with distilled water (3 x 100 mL) followed by 50 mL each of sat. aq. $NaHCO_3$ and brine. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo* to afford 1.7 g of crude oil. Chromatography through silica gel using 1:2 ethyl acetate in hexanes provided the alcohol (159 mg, 56% yield) as a yellow oil and the silyl protected ether (128 mg, 30% yield) as a colorless oil. Characterization data for the alcohol was as follows: IR(neat) 3473 (s, br), 2963 (s), 2968 (s), 2857 (s), 1768 (w), 1707 (s), 1504 (w), 1463(m), 1379 (m), 1364(m), 1208 (w), 1108(w), 1052 (s), 1032 (s), 726 (w), cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.21 (s, 1 H), 6.20 (s, 1 H), 4.23 (t brd, 1 H), 3.73 (d, J = 11.4 Hz, 1 H), 3.56 (d, J = 11.7 Hz, 1 H), 2.49 (m, 2 H), 2.03 (m, 2 H), 1.85 (m, 1 H), 1.66 (m, 1 H), 1.29 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 211.8, 148.2, 141.3, 119.8, 110.7, 69.6, 50.5, 41.6, 28.5, 22.0, 21.7, 21.4, 21.1; HRMS (FAB) m/z 223.1331 (M+H)+; calc'd for $C_{13}H_{19}O_3$: 223.1334. Partial characterization data for the minor silyl ether product (full characterization involved conversion to the deprotected alcohol) were as follows: ^{1}H NMR (300MHz, $CDCl_3$) δ 7.17 (s, 1 H), 6.17 (s, 1 H), 4.24 (t, brd, 1 H), 3.73 (d, J = 9.7 Hz, 1 H), 3.56 (d, J = 9.7 Hz, 1 H), 2.44 (m, 2 H), 1.93 (m, 3 H), 1.62 (m, 1 H), 1.25 (s, 3 H), 1.16 (s, 3 H), 0.84 (s, 9 H) 0.03 (s, 6 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 214.5, 148.8 141.0, 119.2, 110.5, 69.7, 50.4, 41.8, 28.0, 26.0, 22.1, 21.9, 21.8, 18.3, -0.55.

8-(2',2'-Dimethyl-3'-iodo-1'-oxopropyl)cyclohexyl[b]furan (13): A 50 mL round-bottom flask under nitrogen was charged with 1.022 g (3.04 mmol) of PPh_3, 8 mL of toluene, 475 mg (7.13 mmol) of imidazole and 1.110 g (4.37 mmol) of I_2 in that order and then heated to 90ºC. After 10 min, 7 mL of CH_2Cl_2 were added followed by cannulation of 720 mg (3.24 mmol) of **12a** in 6 mL of a 2:1 toluene/CH_2Cl_2 mix. The reaction mixture was refluxed at 115ºC for 18 h, allowed to cool (3 h), diluted with 110 mL of ethyl ether, transferred to a separatory funnel, and washed with 50 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl ether (80 mL) then the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo* to 2.6 g. Chromatography through silica gel, slurry-packed in 1% triethylamine in hexanes, using 10% ethyl acetate in hexanes provided **13** (850 mg, 80% yield) as an extremely pale brown oil: IR(neat) 3401 (w), 3148 (w), 3104 (w), 2963 (s), 2924 (s), 2851 (s), 1709 (s), 1631 (w), 1566 (w), 1502 (m), 1463(m), 1384 (m), 1362 (m), 1329 (w), 1306 (w), 1272 (w), 1231 (w), 1208 (m), 1130 (m), 1110 (m), 1049 (m),951 (w), 884 (m), 730 (m) cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 7.18 (s, 1 H), 6.17 (s, 1 H), 4.00 (t, brd, 1 H), 3.41 (qrt, J = 10.6 Hz, 2 H), 2.46 (m, 2 H), 1.94 (m, 3 H), 1.64 (m, 1 H), 1.42 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 148.0, 141.3, 119.7, 110.5, 48.5, 41.6, 28.2, 25.5, 25.0, 22.1, 21.8, 16.9; HRMS (FAB) m/z 333.0348 (M)+; calcd for $C_{13}H_{18}O_2I$: 333.0352.

$\Delta^{4,11}$-13-Methoxy-8-oxo-4,9-deoxy-10,12-noralliacol (14): A 100 mL round-bottom flask under nitrogen was charged with 158 mg (0.48 mmol) of **13**, 14 mL of THF, and 6 mL of anhydrous MeOH and then stirred at ambient temperature. The resulting solution was treated with 150 mg (0.88 mmol) of $AgNO_3$, stirred 4 h, and quenched with ca. 1 mL of saturated aqueous $NaHCO_3$. The reaction mixture was filtered and the yellow precipitate was washed with 30 mL of ethyl ether. The filtrate was diluted with 200 mL of ether and washed with 3 x 50 mL of water, 35 mL of saturated aqueous $NaHCO_3$, and 20 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield 160 mg of the crude product. Chromatography through silica gel, slurry-packed in 1% triethylamine in hexanes, using 5% ethyl ether in hexanes provided some recovered starting material (26 mg, 16% yield) along with the desired tricyclic product (80 mg, 71% yield, 2.4:1 mixture of acetals) as a clear light brown oil: IR(neat) 3452 (w), 2969 (s), 2930 (s), 2870 (s), 1736 (s), 1672 (w), 1447 (m), 1380 (m), 1363 (m), 1341 (m), 1304 (w), 1254 (w), 1189 (w), 1159 (w), 1100 (m), 1062 (m), 1026 (m), 990 (m), 960 (m), 874 (m), cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 5.75 (s, 0.24 H), 5.57 (s, 0.76 H), 5.44 (s, 0.76 H), 5.42 (s, 0.24 H), 3.43 (s, 2.2 H), 3.32 (s, 0.8 H), 2.60 (d, J = 14.4 Hz, 1 H), 2.43 (m, 0.24 H), 2.28 (m, 1.70 H), 2.11 (t, J = 13.5 Hz, 1 H), 2.00 – 1.80 (m, 3 H), 1.64 (m, 1 H), 1.14 - 1.02 (m, 7 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 223.4, 148.1, 119.0,

107.5, 90.2, 58.7, 55.5, 47.7, 45.6, 27.6, 26.8, 27.0, 26.6, 26.1; HRMS (FAB) m/z 243.1574 (M+Li)+; calcd for $C_{14}H_{20}O_3Li$: 243.1573.

8-(3',3'-dimethyl-4'-methoxy-1--oxobut-3'-enyl)cyclohexyl[b]furan (15): A 50 mL round-bottom flask was charged with 390 mg (1.25 mmol) of **12a**, 11.4 mL of CH_2Cl_2 and 0.28 mL of DMSO. The reaction mixture was cooled to -78ºC and treated with 0.31 mL of freshly distilled oxalyl chloride in a dropwise fashion. The reaction mixture was stirred for 40 min at -78ºC and then 0.8 mL of triethylamine was added, again in a dropwise fashion. The cooling bath was removed and the mixture was allowed to warm over a period of 2 h. The mixture was diluted 3 mL of water and then most of the solvent was removed in vacuo. The crude product was extracted with 3 x 5 mL of ether and the combined organic layers were washed with 3 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford 710 mg of the crude aldehyde used which was used in the following Wittig reaction with no further purification.

A 25 mL round-bottom flask was charged with 1.9 mL (9.0 mmol) of hexamethyldisilizide and 2 mL of THF. The reaction mixture was cooled to -78ºC and treated with 5.4 mL (8.7 mmol) of a 1.6 M solution of n-BuLi in hexanes in a dropwise fashion. The cooling bath was then removed and the reaction mixture was stirred for an additional 50 min. before being used in the following step. At this point, a 100 mL round-bottom flask was charged with 3.09 g (9.0 mmol) of methoxymethyltriphenylphosphonium chloride and 6 mL of THF. The reaction mixture was cooled to -78ºC and treated with the freshly prepared LHMDS solution in a dropwise fashion. The cooling bath was removed and the reaction mixture was allowed to stir for an additional 40 min. The reaction mixture was cooled to -10ºC and treated with a solution of the aldehyde prepared above in 3.5 mL of THF. The reaction mixture was stirred for an additional 12 h then cooled to 0ºC and quenched with 25 mL water. The layers were separated and the organic layer was washed with 15 mL brine. The combined aqueous layers were extracted with ethyl acetate (2 x 40 mL) and then the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 3.1 g of the crude product. Chromatography through silica gel, slurry-packed in 1% TEA in hexanes, using a solvent gradient from pure hexanes to 10% ethyl ether in hexanes provided electrolysis substrate **15** (368 mg, 50% yield) as a colorless oil. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.19 (s, 1 H), 6.48 (d, J = 12 Hz, 0.35 H), 6.20 (s, 1 H), 5.93 (d, J = 8 Hz, 0.65 H), 4.90 (d, J = 12 Hz, 0.35 H), 4.43 (d, J = 12 Hz, 0.65 H), 4.25 (t brd, J = 6 Hz, 1 H), 3.57 (s, 3 H), 2.60 – 2.35 (m, 2 H), 2.10 – 1.80 (m, 3 H), 1.62 (m, 1 H) 1.40 – 1.25 (m, 6 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 148, 141, 119, 111, 109, 107, 61, 56, 48, 43, 29, 27, 25, 21, 20; IR(neat) 2963 (s), 2930 (s), 2851 (s), 1709 (s), 1653 (m), 1460 (m), 1102 (s); HRMS (FAB) *m/z* 255.1571 $(M+Li)^+$; calcd for $C_{14}H_{20}O_3Li$: 255.1572.

$\Delta^{4,11}$-6-Dimethoxymethyl-13-methoxy-8-oxo-4,9-deoxy-10,12-noralliacol (16): A 100 mL 3-neck round-bottom flask was charged with 365 mg (1.47 mmol) of **15**, 48 mL of CH_2Cl_2, 12 mL of anhydrous MeOH, 0.85 mL (7.48 mmol) of 2,6 lutidine and 2.62 g (24.61 mmol) of $LiClO_4$. The reaction flask was fitted with a RVC anode (a cube of ca. 0.5 cm^3) and a carbon rod cathode (6.5 mm diam) and degasses by sonication under nitrogen for 5 min. A current of 19.7 mA was then applied to the solution until a total of 300.7 C (2.1 F/mol) of charge had been passed. The reaction was diluted with 52 mL of ethyl acetate, washed with 20 mL of water, sat. aq. NH_4Cl (2 x 20 mL), and 6 mL brine, and then dried over $MgSO_4$. The crude mixture was concentrated *in vacuo* to afford 0.73 g of a crude product that was chromatographed through silica gel using 1:4 ethyl acetate in hexanes as eluant to provide the tricyclic product **16** (335 mg, 74% yield) as a colorless oil: ^{1}H NMR (300MHz, $CDCl_3$) δ 5.72 (s, 1 H), 5.42 (s, 1 H), 4.65 (d, J= 9 Hz, 1 H), 3.42 (s, 3 H), 3.36 (s, 3 H), 3.28 (s, 3 H), 2.62 (m, 2 H), 2.42 (m, 1 H), 2.18 (m, 1 H), 1.92 (m, 2 H), 1.42 (m, 1 H), 1.27 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 148, 118, 109, 105, 93, 61, 45, 44, 41, 38, 28, 27.5, 27, 26, 21; IR(neat) 3456(w), 2936 (s), 2823 (s), 1737 (s), 1672 (w), 1465 (m); HRMS (FAB) *m/z* 317.1952 $(M+Li)^+$; calcd for $C_{17}H_{26}O_5Li$: 317.1940.

$\Delta^{4,11}$-8β-hydroxy-4,9-deoxy-12-noralliacol (25a) and $\Delta^{4,11}$-8α-hydroxy-4,9-deoxy-12-noralliacol (25b): A 25 mL round-bottom flask was charged with 230 mg (6.03 mmol) of lithium aluminum hydride and 4.6 mL of ether and then placed into an ice water bath. A solution of 685 mg (2.74 mmol) of electrolysis product in 2.3 mL ether was added over 6 min via syringe which was rinsed with 2.3 mL ether. The cooling bath was removed and the reactions was allowed to stir for 90 min. After this period the reaction was carefully treated with 0.23 mL each of chilled water and 3 M NaOH followed by 0.70 mL of chilled water. The mixture was stirred an additional 15 min then filtered. The residue was washed with 30

mL of ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the alcohol product (689 mg, 99%) as viscous oil: ^{1}H NMR (300MHz, $CDCl_3$) δ 5.75 (m, 0.4 H), 5.48 (m, 0.7 H), 5.42 (m, 0.6 H), 5.30 (m, 0.3 H), 4.39 (t brd, 1 H), 3.70 (m, 0.55 H), 3.41 (m, 2.2 H), 3.36 (m, 0.8 H), 2.71 (m, 0.4 H), 2.47 (m, 1 H), 2.18 – 1.36 (m, 7 H), 1.28 - 0.94 (m, 10 H). The product was carried forward without further purification.

A 50 mL round-bottom flask was charged with 1.355 g (5.42 mmol) of the alcohol, 1.330 g (10.9 mmol) of DMAP, 1.8 mL (17.6 mmol) of Ac_2O and 14 mL of CH_2Cl_2. The resulting solution was stirred for 4 h. The mixture was diluted with 75 mL of ether, washed with 60 mL of water, and then the aqueous layer extracted with ether (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, concentrated to remove some of the solvent, filtered through a plug of silica gel with 1:3 ethyl acetate in hexanes, and then concentrated *in vacuo* to afford 1.4 g of the acetylated product.

The crude acetate product was dissolved in 26 mL of acetone and cooled in an ice water bath. Then 3.3 mL of a 1.22 M solution (4.03 mmol) of Jones reagent was added slowly and after 20 min 8.3 mL of iPrOH was added. The mixture was diluted with 100 mL of ether washed with 70 mL of water, and the aqueous layer extracted with ether (2 x 70 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford 1.12 g of the crude lactone.

To remove the acetate protecting group, the crude lactone was dissolved in 36 mL of 10% aqueous methanol then treated with 193 mg (5.75 mmol) of K_2CO_3 and stirred for 12 h. When the reaction was compete, the solvent was removed *in vacuo,* the residue taken up with 35 mL of EtOAc and washed with 15 mL of brine, and then the combined aqueous layer extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford 1.05 g of the crude product. Chromatography through silica gel using 1:1 ethyl acetate in hexanes provided **25a** and **b** (732 mg, 55% from **16**) as a white solid. The isomers were separated as a 1:1.6 mixture. The data for the major isomer **25b** were as follows: ^{1}H NMR (300MHz, $CDCl_3$) δ 5.75 (s, 1 H), 3.80 (d brd, J = 11 Hz, 1 H), 2.77 (d with fine splitting J = 15 Hz, 1 H), 2.35 (t with fine splitting J = 15 Hz, 1 H), 2.24 (d brd, J = 11 Hz, 1 H), 2.13 (d, J = 15 Hz, 1 H), 2.04 (m, 1 H), 1.73 (d, J = 12 Hz, 1 H), 1.68 (d, J = 15 Hz, 1 H), 1.53 (m, 1 H), 1.23 (s, 6 H), 1.08 (d, J = 6 Hz, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 172.5,171.9, 112.4, 97.0, 85.2, 67.6, 49.5, 43.7, 36.3, 33.3, 32.4, 26.6, 25.2, 19.0; HRMS (FAB) m/z 237.1491 (M+H)+; calcd for $C_{14}H_{21}O_3$: 237.1491. In addition, **25b** was characterized using an HMQC experiment to assign proton-carbon correlations and confirm assignment of the signals in the proton NMR and a 2D-COSY experiment in order to accurately identify nuclei that couple to each other. The COSY experiment (spectra below) indicated that there was no coupling between the bridgehead methine at C_9 and the methine at C_8 suggesting that these two methine protons were trans to each other.

Because of difficulties in obtaining pure material (and the overall failure of this particular route to alliacol A), the minor isomer from the reaction sequence was not completely characterized. Instead, a tentative assignment was made by comparing the proton NMR of **25a** to that obtained from **25b**. The H^1 NMR data for **25a** were as follows: ^{1}H NMR (300MHz, $CDCl_3$) δ 5.70 (d, J = 1 Hz, 1H), 4.48 (t, J = 6 Hz, 1H), 2.72 (ddd, J = 13.4 Hz, J = 4.3 Hz, J = 2.4 Hz, 1H), 2.34 (tdd, J_t = 13.4 Hz, J_d = 4.7 Hz, J_d = 1.7 Hz, 1 H), 2.17 (d, J = 15.0 Hz, 1H), 2.09 (m, 1H), 2.00 (app. ddt, J_d = 13.8 Hz, J_d = 5.5 Hz, J_t = 2.4 Hz, 1H), 1.89 (m, 2H), 1.58 (dd, J = 15.0 Hz, J = 1.4 Hz, 1H), 1.23 (s, 3H), 1.19 (d, J = 6 Hz, 3H), 1.17 (s, 3H).

The Asymmeric Synthesis:

*The synthesis of starting material **17** was the same as that reported previously for the racemic synthesis (J. Am. Chem. Soc.* **2003**, *125*, 36*).*

3-(7'-t-Butyldimethylsiloxy-6',6'-dimethyl-3'S-methyl-5'-oxoheptanyl)furan (28): A 500 mL three-necked round-bottom flask was charged with 1.27 g (3.45 mmol) of $Cu(OTf)_2$ (purchased from Strem), placed under vacuum for 40 min, and then backfilled with nitrogen. The flask was placed under an argon atmosphere before adding 250 mL of toluene and 2.49 g of S-(+)-Monophos ligand (again purchased from Strem). The mixture was stirred for 1 h, cooled to -20 ºC, and 3.92 g (11.7 mmol) of **17** in 15 mL of toluene added via syringe. Complete transfer was ensured by washing the syringe with an additional 5 mL of toluene. After 20 min had passed, 19.3 mL of a 2 M solution of Me_2Zn (39.4 mmol) in toluene was added over 12 min. After 30 min, the cooling bath was removed, the reaction mixture stirred for 4.5 h, and an additional 1.20 g (3.45 mmol) of $Cu(OTf)_2$ added. The resulting solution was stirred for 10 h followed by dilution with 500 mL ethyl ether. At this point, the reaction was transferred to a

separatory funnel and carefully quenched with 840 mL of 1.0 M HCl. The aqueous layer was extracted with ethyl ether (2 x 900 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and chromatographed through silica gel using 3% ethyl acetate in hexanes to give **28** (9.13 g, 79 %) as a pale yellow oil: $[\alpha]^{20}$ = -0.3˚(c 1.3, $CHCl_3$); e.e. = 81% (measured with the use of a chiral HPLC column and comparison to the racemic material); IR (neat) 3473 (s, br), 2963 (s), 2968 (s), 2857 (s), 1768 (w), 1707 (s), 1504 (w), 1463(m), 1379 (m), 1364(m), 1208 (w), 1108(w), 1052 (s), 1032 (s), 726 (w), cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.34 (s, 1 H), 7.18 (s, 1 H), 6.24 (s, 1 H), 3.56 (s, 2 H), 2.43 (m, 2 H), 2.08 (m, 1 H), 1.56 (m, 1 H), 1.39 (m, 1 H), 1.06 (s, 6 H), 0.92 (d, J = 7 Hz, 3 H), 0.83 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 214.4, 143.0, 139.0, 125.0, 111.2, 70.2, 49.6, 45.5, 37.3, 28.2, 26.1, 23.0, 22.1, 20.3, 18.4, -5.5; HRMS (EI) *m/z* 295.1724 $(M\text{-}C_4H_9)^+$; calcd for $C_{17}H_{27}O_3Si$: 295.1729.

3-(5',7'-bis-t-Butyldimethylsiloxy-6',6'-dimethyl-3'S-methyl-4'-heptenyl)furan (2*): A 25 mL round-bottom flask was charged with 2.89 g (8.21 mmol) of **28**, 7 mL of $ClCH_2CH_2Cl$, 4.6 mL (32.8 mmol) of freshly distilled TEA, and 5.8 mL (24.6 mmol) of TBSOTf. The mixture was heated to 78 ºC for 36 h and then allowed to cool before 30 mL of sat. aq. $NaHCO_3$ was added. The resulting mixture was transferred to a separatory funnel, diluted with 30 mL of water, and extracted with 3 x 60 mL of hexane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford 6.1 g of the crude product. Chromatography through silica gel, slurry-packed in 1% TEA in hexanes, 1% ethyl acetate in hexanes provided **2*** (3.37 g, 92% yield) as a colorless oil. $[\alpha]^{20}$ = +8.6˚(c 1.0, $CHCl_3$). The rest of the spectral data was identical to that reported earlier for the racemic synthesis.

7S-Methyl-8R-(2',2'-dimethyl-3'-iodo-1'-oxopropyl)cyclohexyl[b]furan (6*): The electrolysis reaction was run in a fashion identical to that reported for the racemic synthesis (and to the electrolysis outlined above for the model studies). All of the spectral data matched that previously reported for the racemic material. For the enantioenriched material: $[\alpha]^{20}$ = +1.6˚(c 1.0, $CHCl_3$).

$\Delta^{4,11}$-1S,5S,9R-13(R,S)-Methoxy-8-oxo-4,9-deoxy-12-noralliacol (21*): In this case, the iodination and subsequent Friedel-Crafts reactions were again done in a fashion identical to that previously reported for the racemic synthesis. The spectral data were identical to the previously reported data for the racemic material. For the enantioenriched material: $[\alpha]^{20}$ = -10.3˚(c 1.1, $CHCl_3$).

$\Delta^{4,11}$-1S,5S,9S-8S-hydroxy-4,9,13-deoxy-12-noralliacol (24*): The Dibal-H reduction was done in a fashion identical to that reported for the racemic synthesis. The spectral data for the product were identical to that reported previously. For the enantioenriched material: $[\alpha]^{20}$ = -19.9˚(c 0.4, $CHCl_3$).

1S,4R,5S,9S-8S-hydroxy-9,13-deoxy-12-noralliacol (26*): Both the epoxidation and reduction steps needed for converting **24*** into **26*** were conducted in a fashion identical to that previously reported for the racemic synthesis. The spectral data for the products for both reactions were also identical to the previously reported data. For the epoxide intermediate: $[\alpha]^{20}$ = -35.8˚(c 1.9, $CHCl_3$). For **26***: $[\alpha]^{20}$ = -8.3˚(c 1.1, $CHCl_3$).

1S,4R,5S,9S-8S-tosyl-9,13-deoxy-12-noralliacol (27*): The tosylation reaction was run in a fashion identical to the racemic synthesis and led to spectral data that matched the previously synthesized material. For the enantioenriched material: $[\alpha]^{20}$ = +3.06˚(c 1.0, $CHCl_3$).

$\Delta^{8,9}$-1S,4R,5S-8,9,13-deoxy-12-noralliacol (23*): As in the previous steps, the elimination reaction was performed in a fashion identical to the racemic synthesis and led to spectral data that matched the previous synthesis. For the enantioenriched material: $[\alpha]^{20}$ = -4.3˚(c 1.0, $CHCl_3$).

1S,4R,5S,8R,9R-13-deoxy-12-noralliacol: A solution of 50 mg (0.23 mmol) of **23*** in 25 mL CH_2Cl_2 was treated with 104 mg (1.23 mmol) of $NaHCO_3$ and cooled to -78ºC. To this solution was added 80 mg (0.46 mmol) of M-CPBA. The temperature was then allowed to rise slowly. After stirring for 4.5 h, 17 mL brine was added, followed by $MgSO_4$. The mixture was filtered through a pad of silica gel, rinsed with MeOH, and concentrated *in vacuo*. Chromatography through silica gel using 20% ethyl acetate in hexanes provided the desired epoxide (47 mg, 86% yield) as a white solid: $[\alpha]^{20}$ = +2.0˚(c 1.0, $CHCl_3$); mp

= 70-71.5ºC, lit.(71.5-73ºC); IR($CHCl_3$) 3480, 1463, 1442, 1380 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 3.82 (dd, J = 8 Hz, J = 6 Hz, 2 H), 3.15 (s, 1 H), 2.07-1.90 (m, 3 H), 1.74 (m, 1 H), 1.65 (m, 1 H), 1.57 (d, J = 10 Hz, 1 H), 1.47 (m, 1 H), 1.17 (d, J = 7.6 Hz, 3 H), 1.10 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 88.6, 78.8, 69.6, 69.3, 63.5, 39.3, 38.3, 37.9, 32.1, 31.4, 25.6, 24.3, 24.0, 16.6; HRMS (EI) *m/z* 223.1336 $(M\text{-}CH_3)^+$; calcd for $C_{13}H_{19}O_3$: 223.1334.

1S,4R,5S,8R,9R-12-noralliacol (29*): To a 25 mL pear-bottom flask containing 32 mg (0.13 mmol) of the epoxide generated in the previous step were added 0.35 mL each of CCl_4, MeCN, and water. The flask was purged with nitrogen and then 74 mg (0.88 mmol) of $NaHCO_3$ and 154 mg (0.72 mmol) of $NaIO_4$ added. The reaction mixture was stirred vigorously and then treated with 12 mg (0.05 mmol) of $RuCl_3 \bullet 3H_2O$. After stirring for 28 h, the reaction was diluted with 3 mL brine and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography through silica gel using 20% ethyl acetate in hexanes provided **29*** (29 mg, 86% yield) as a white solid: $[\alpha]^{20}$ = -5.4˚(c 1.0, $CHCl_3$); mp = 159-160ºC, lit.(160-161ºC); IR($CHC1_3$) 3500, 3030, 1768, 1470 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 3.23 (s, 1 H), 2.79 (d, J = 17.4 Hz, 1 H), 2.56 (d, J = 17.4 Hz, 1 H), 2.00-1.82 (m, 5 H), 1.98 (d, J = 14.2 Hz, 1 H), 1.35-1.28 (m, 1 H), 1.33 (d, J = 14.2 Hz, 1 H), 1.16 (d, J = 7.2 Hz, 3 H), 1.14 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.1, 94.6, 75.8, 69.1, 68.7, 43.1, 41.6, 39.0, 35.5, 31.6, 26.0, 24.4, 24.1, 18.2; HRMS (FAB) *m/z* 253.1430 $(M+H)^+$; calcd for $C_{14}H_{21}O_4$: 253.1440.

(-)-Alliacol A: A 50 mL round-bottom flask was charged with 0.73 mL (4.3 mmol) of 2,2,6,6,-TMP and 6.2 mL of THF. The resulting mixture was cooled to -18ºC. Over a 6 min period, 3.2 mL of 1.34 M solution (4.3 mmol) of n-BuLi in hexanes was added and the cooling bath was maintained at -25ºC. After 30 min had passed, a solution of 65 mg (0.25 mmol) of **29*** and 0.81 mL (4.7 mmol) of HMPA in 2 mL of THF was added over 20 min using a syringe pump. The temperature of the cooling bath was allowed to rise gently to + 10ºC over 1 h and then again cooled to -25ºC before cannulating 800 mg (4.32 mmol) of Eschenmoser's salt in 3.5 mL of THF. The reaction was stirred for 14 h, the reaction then allowed to warm to ambient temperature, and then 15 mL of 10% HCl was added and the solution was extracted with 45 mL EtOAc. The organic layer was washed with 9 mL each sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to 110 mg. Chromatography through silica gel with 30% ethyl acetate in hexanes provided (-)- alliacol A (38 mg, 61% yield) as a white solid: $[\alpha]^{20}$ = -9.6˚(c 1.0, $CHCl_3$); IR ($CHCl_3$) 2951, 1761, 1260, 1125 cm^{-l}; ^1H NMR ($CDCl_3$) δ 6.36 (s, 1 H), 5.90 (s, 1 H), 3.19 (s, 1 H), 1.88 (d, J = 14 Hz, 1 H), 1.21 (d, J = 14 Hz, 1 H), 1.13 (s, 3 H), 1.11 (d, J = 7 Hz, 3 H), 1.09 (s, 3 H); ^{13}C NMR ($CDC1_3$) δ 168.8, 143.0, 124.7, 95.0, 76.7, 69.5, 67.2, 41.8, 39.3, 38.7, 31.6, 26.4, 24.5, 24.2, 19.4; HRMS (FAB) *m/z* 265.1440 $(M+H)^+$; calcd for $C_{15}H_{21}O_4$: 265.1440.

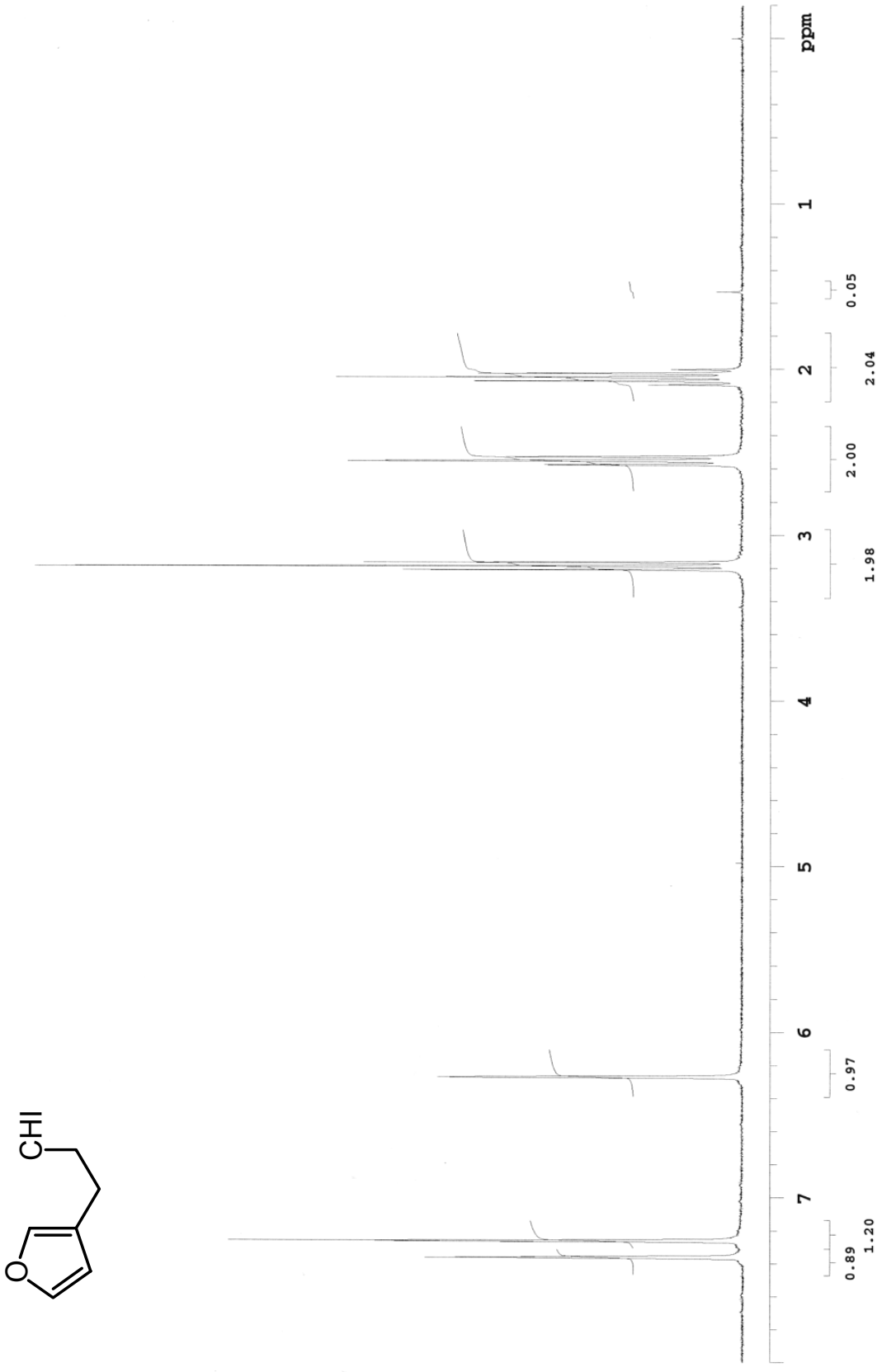


Figure 1: 300 MHz ^{1}H spectrum of 3-(3'-iodopropyl)furan

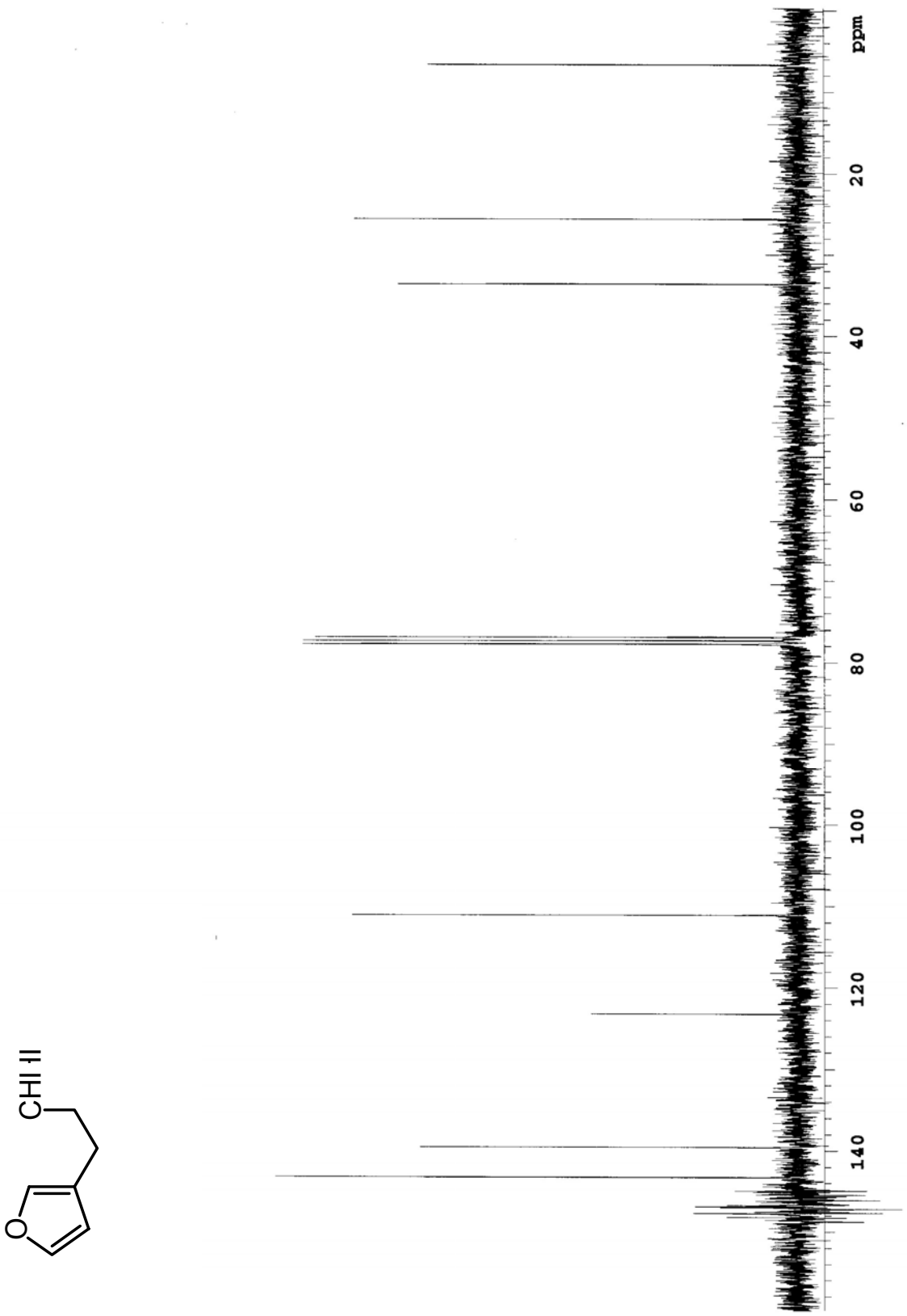


Figure 2:75 MHz ^{13}C spectrum of 3-(3'-iodopropyl)furan

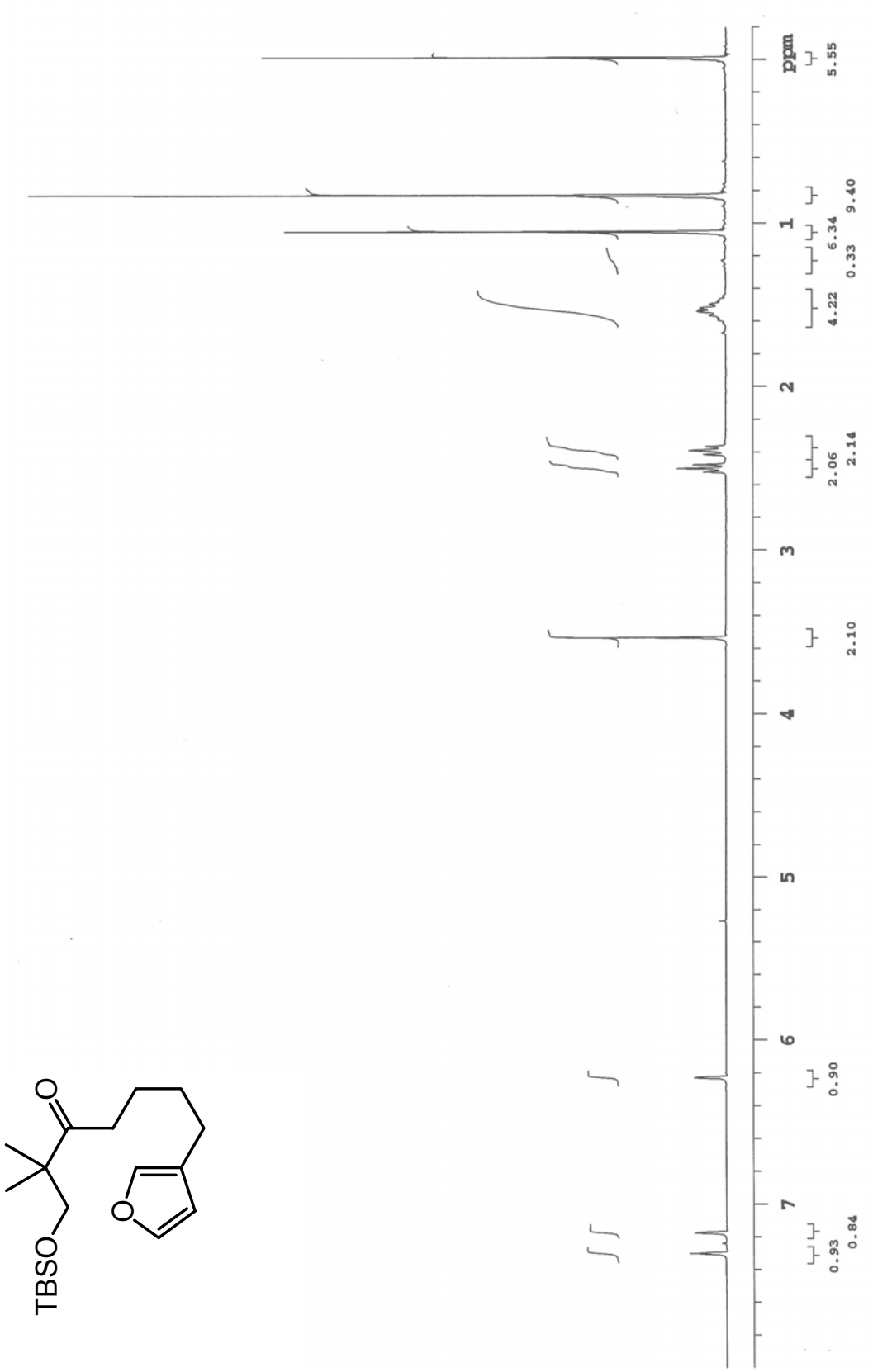


Figure 3: 300 MHz ^{1}H spectrum of **9**

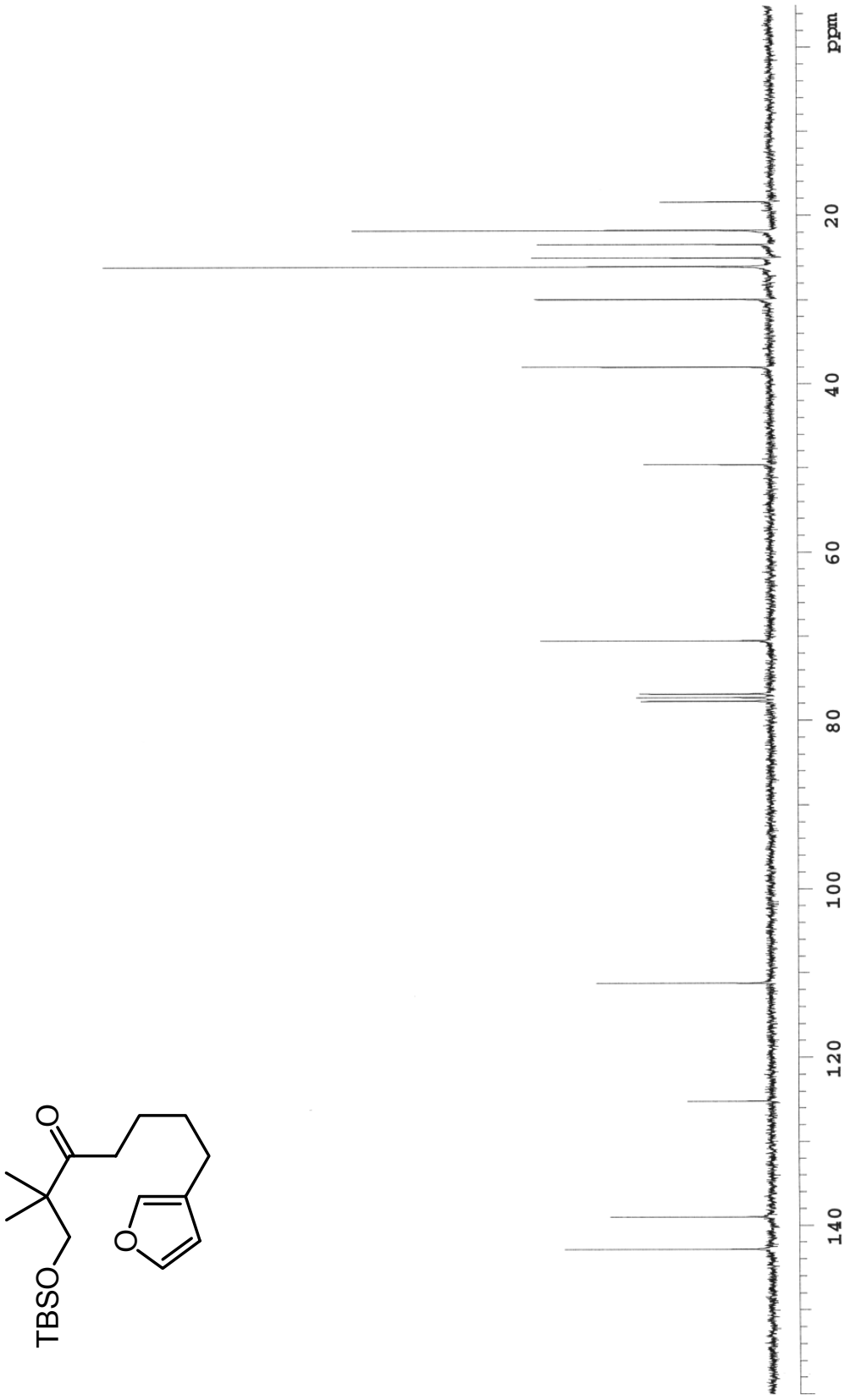


Figure 4: 75 MHz ^{13}C spectrum of **9**

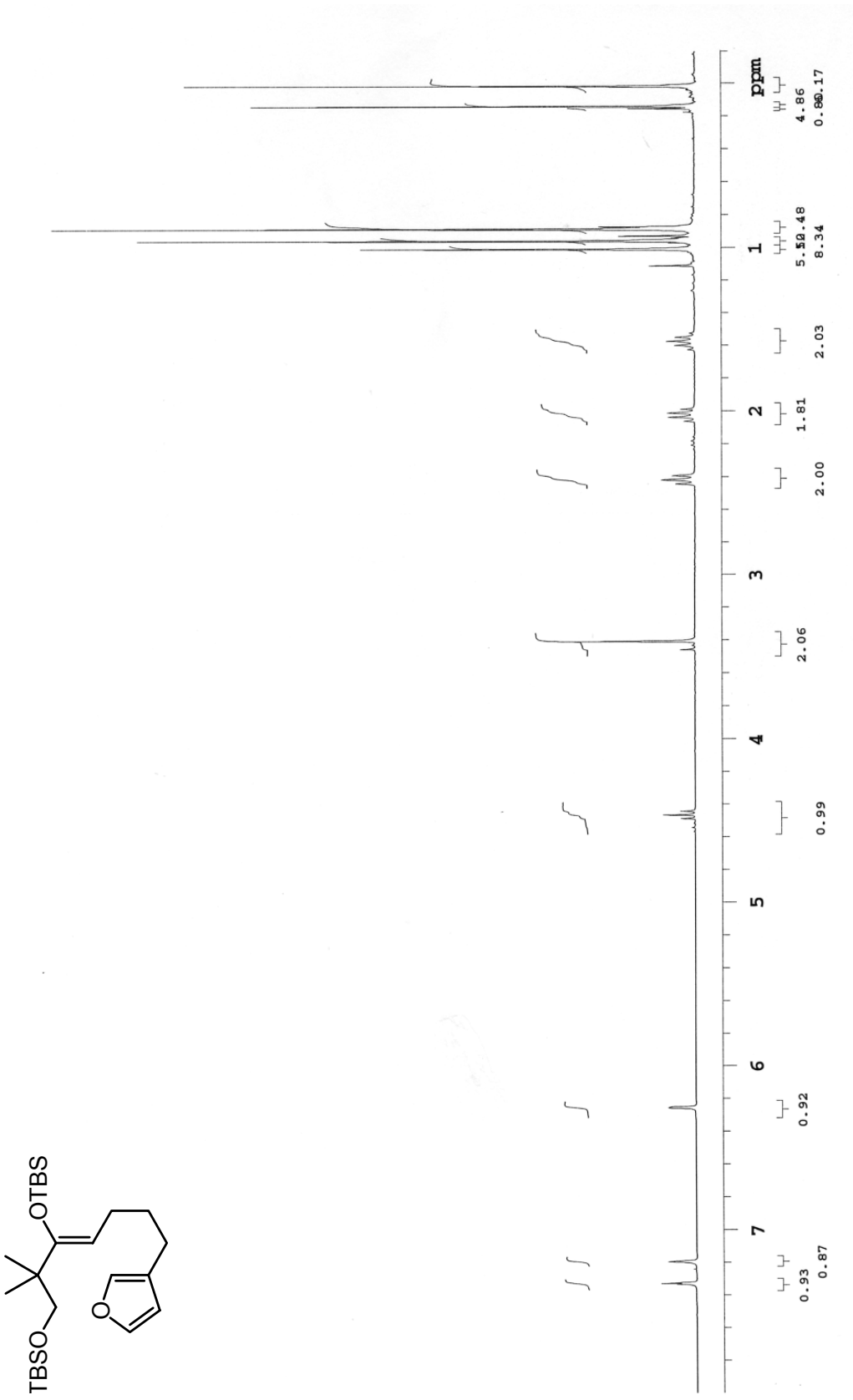


Figure 5: 300 MHz ^{1}H spectrum of **10**

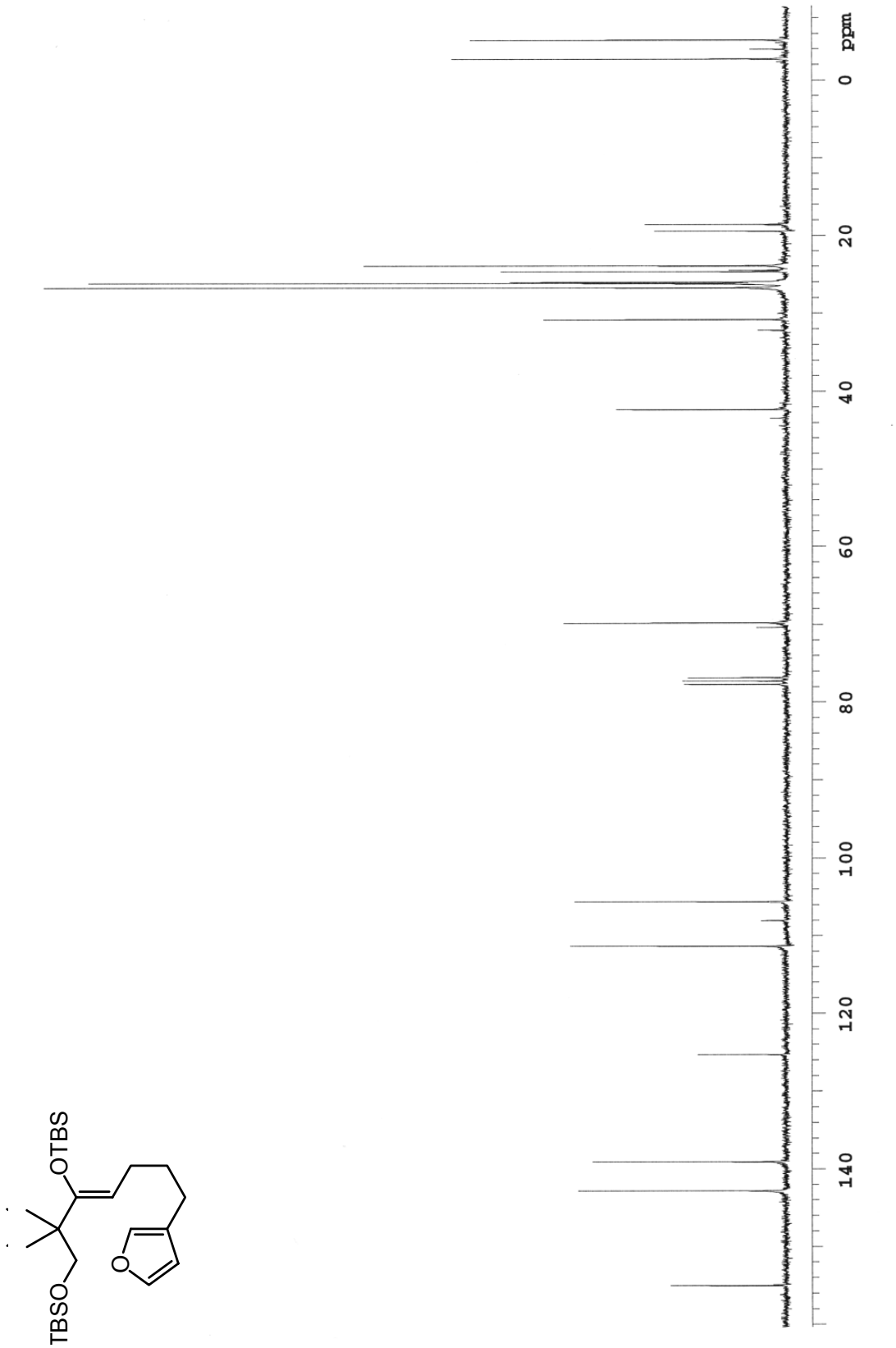


Figure 6: 75 MHz ^{13}C spectrum of **10**

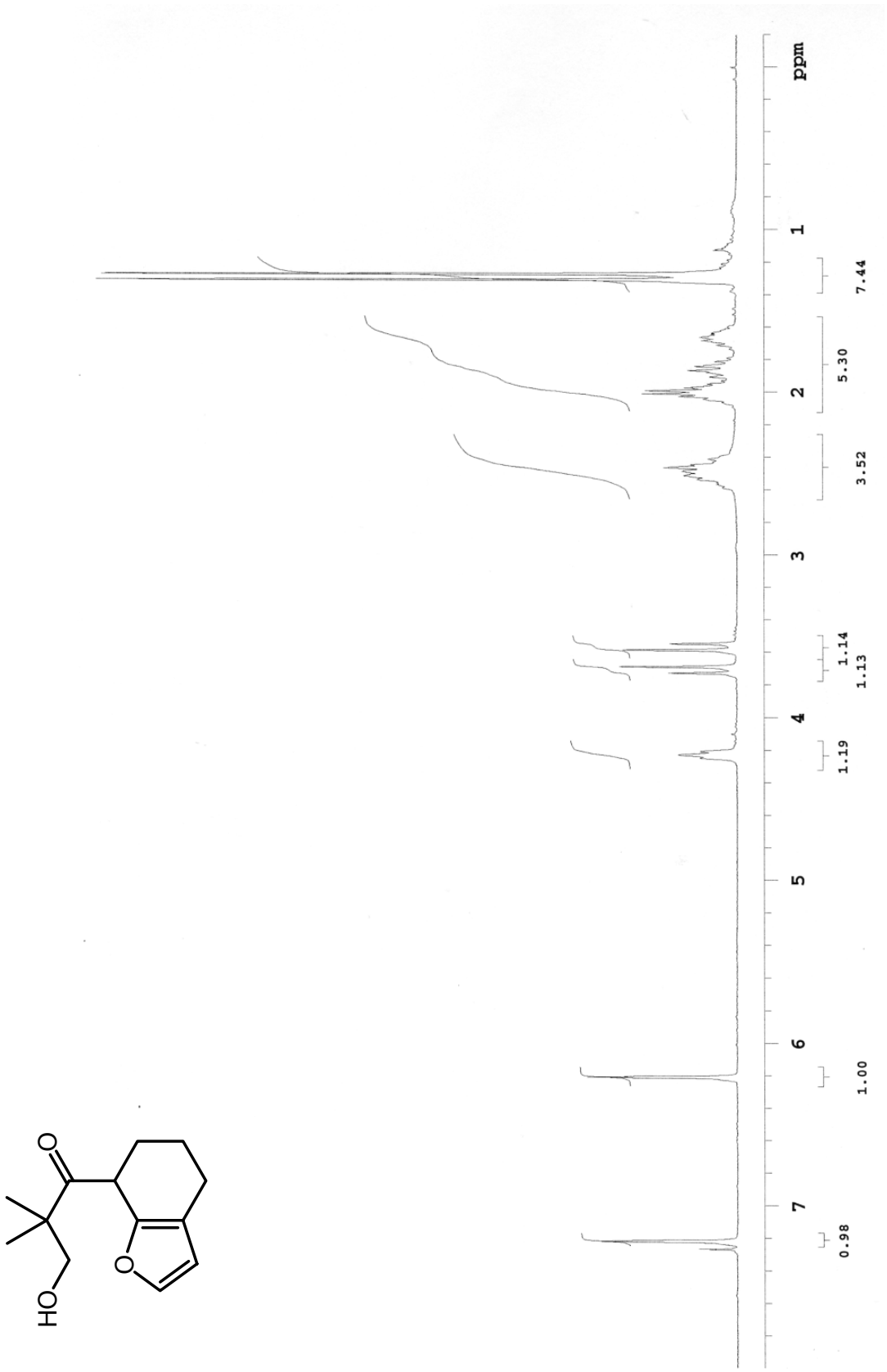


Figure 7: 300 MHz ^{1}H spectrum of **12a**

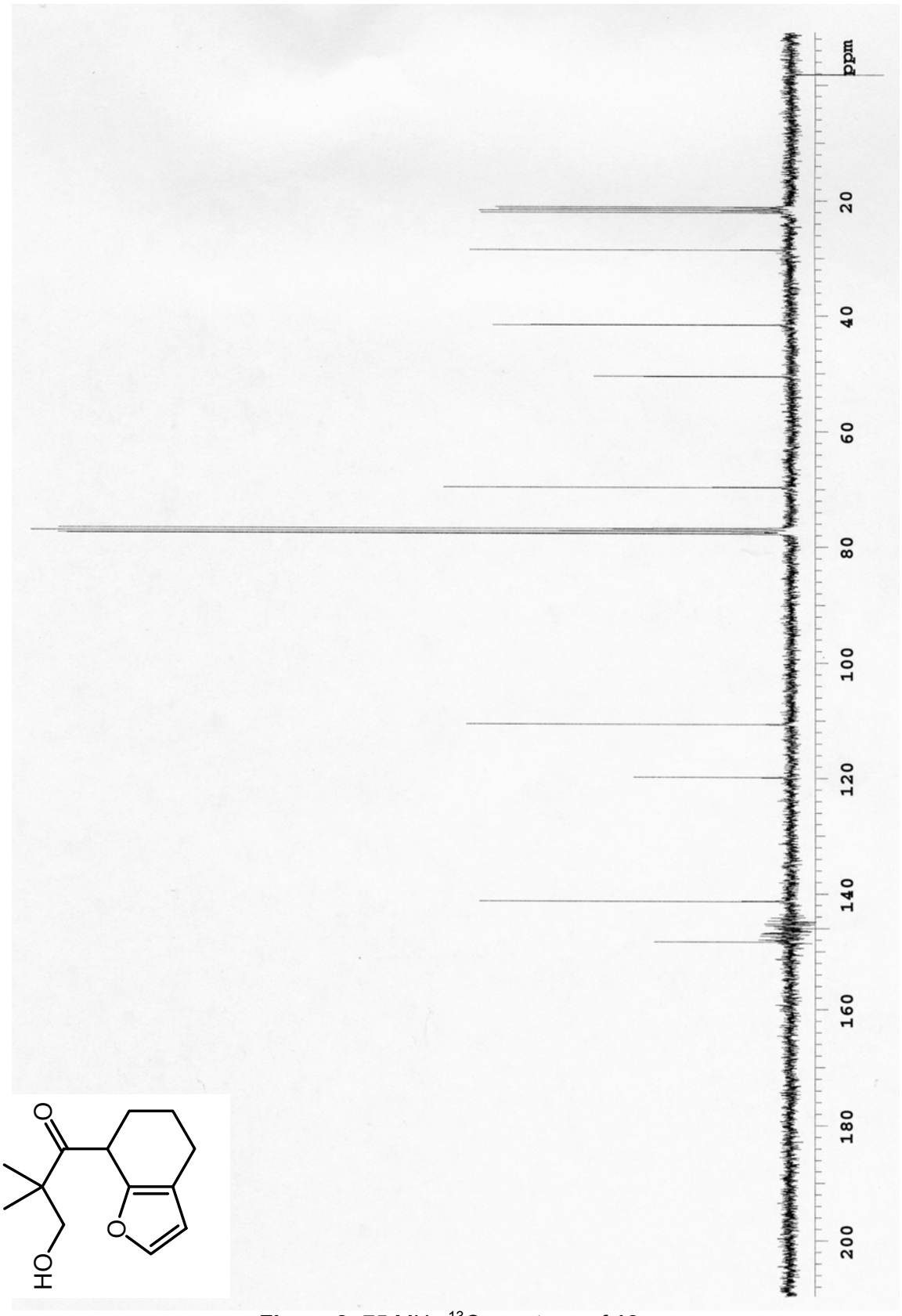


Figure 8: 75 MHz ^{13}C spectrum of **12a**

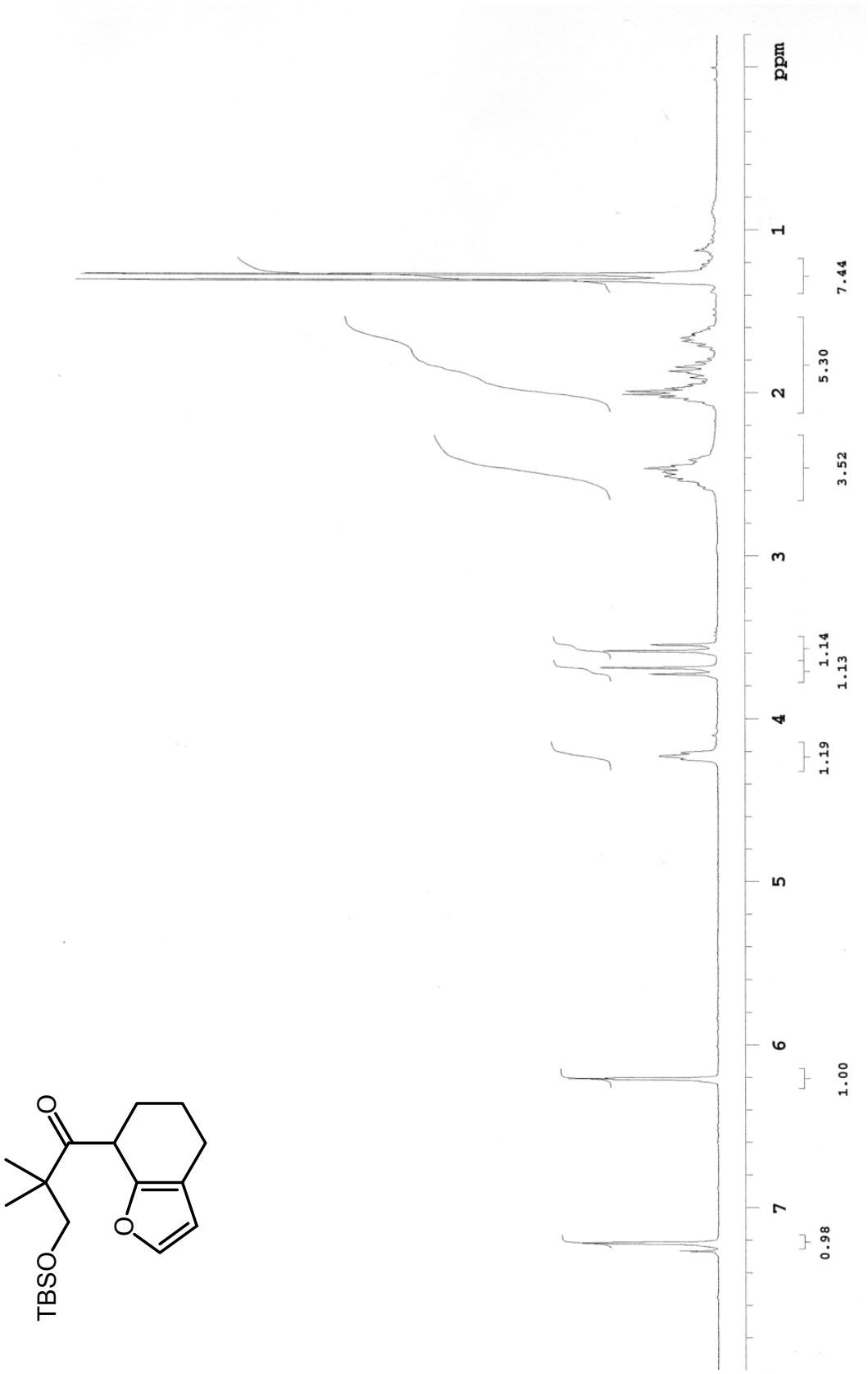


Figure 9: 300 MHz ^{1}H spectrum of **12b**

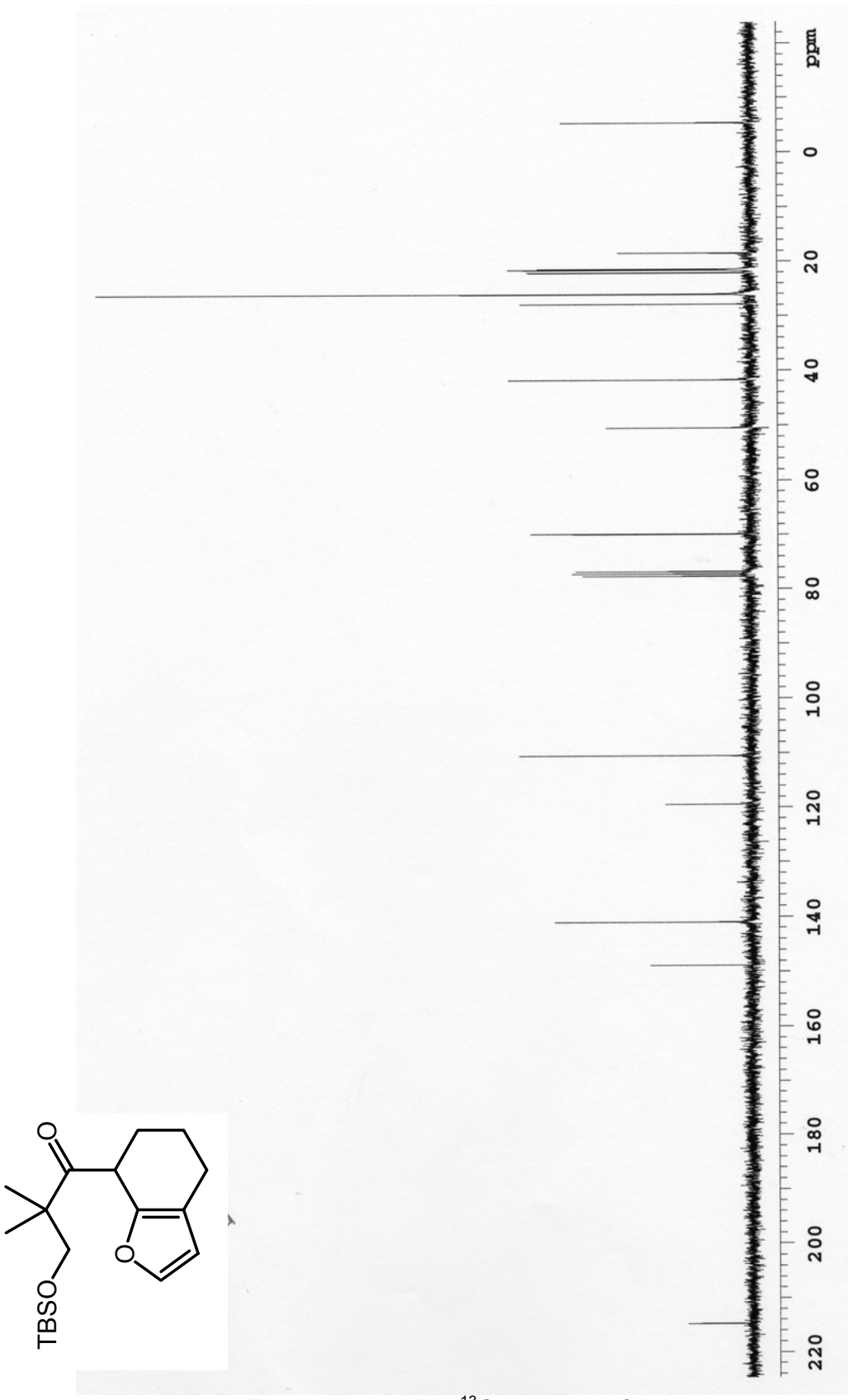


Figure 10: 75 MHz ^{13}C spectrum of **12b**

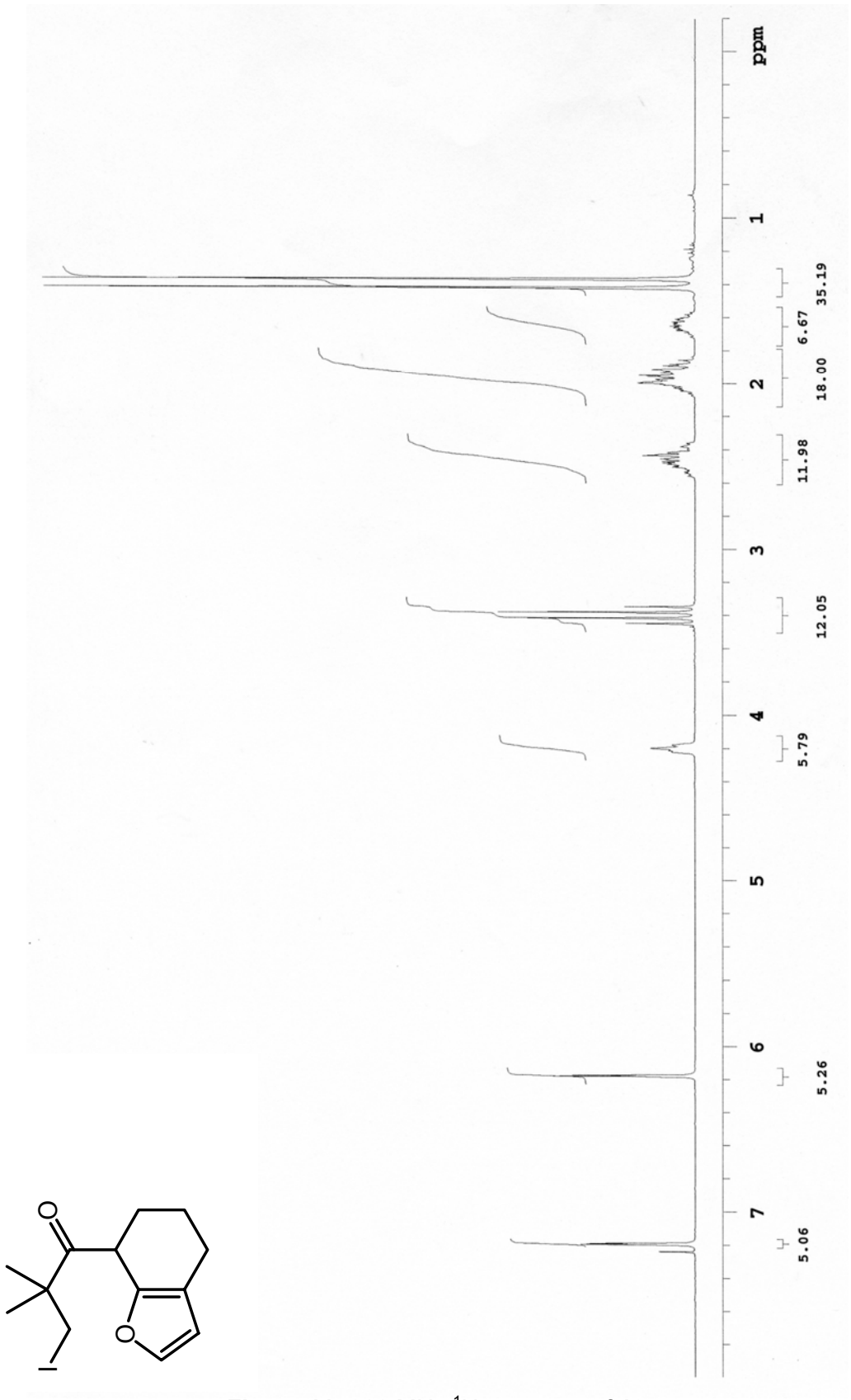


Figure 11: 300 MHz ^{1}H spectrum of **13**

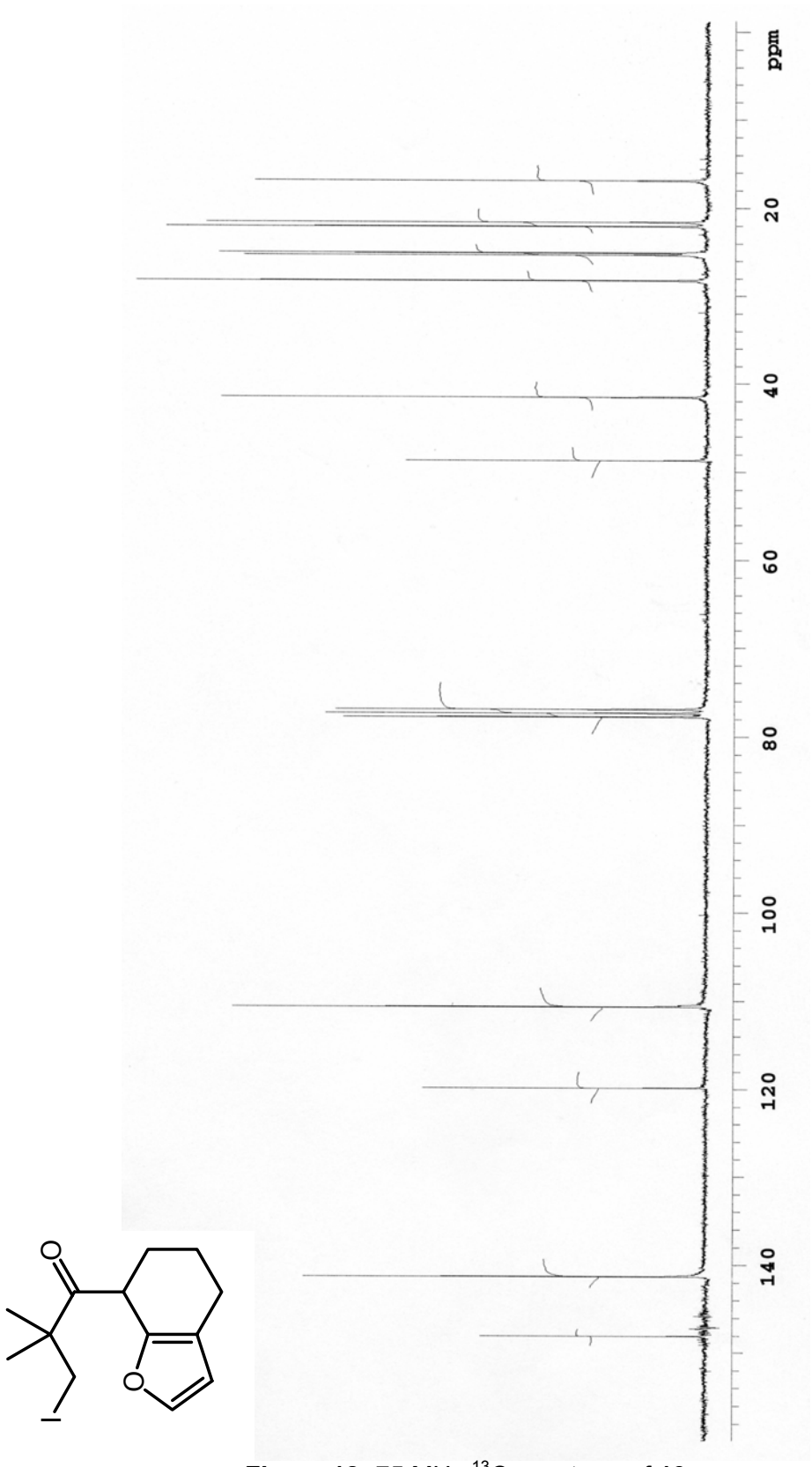


Figure 12: 75 MHz ^{13}C spectrum of **13**

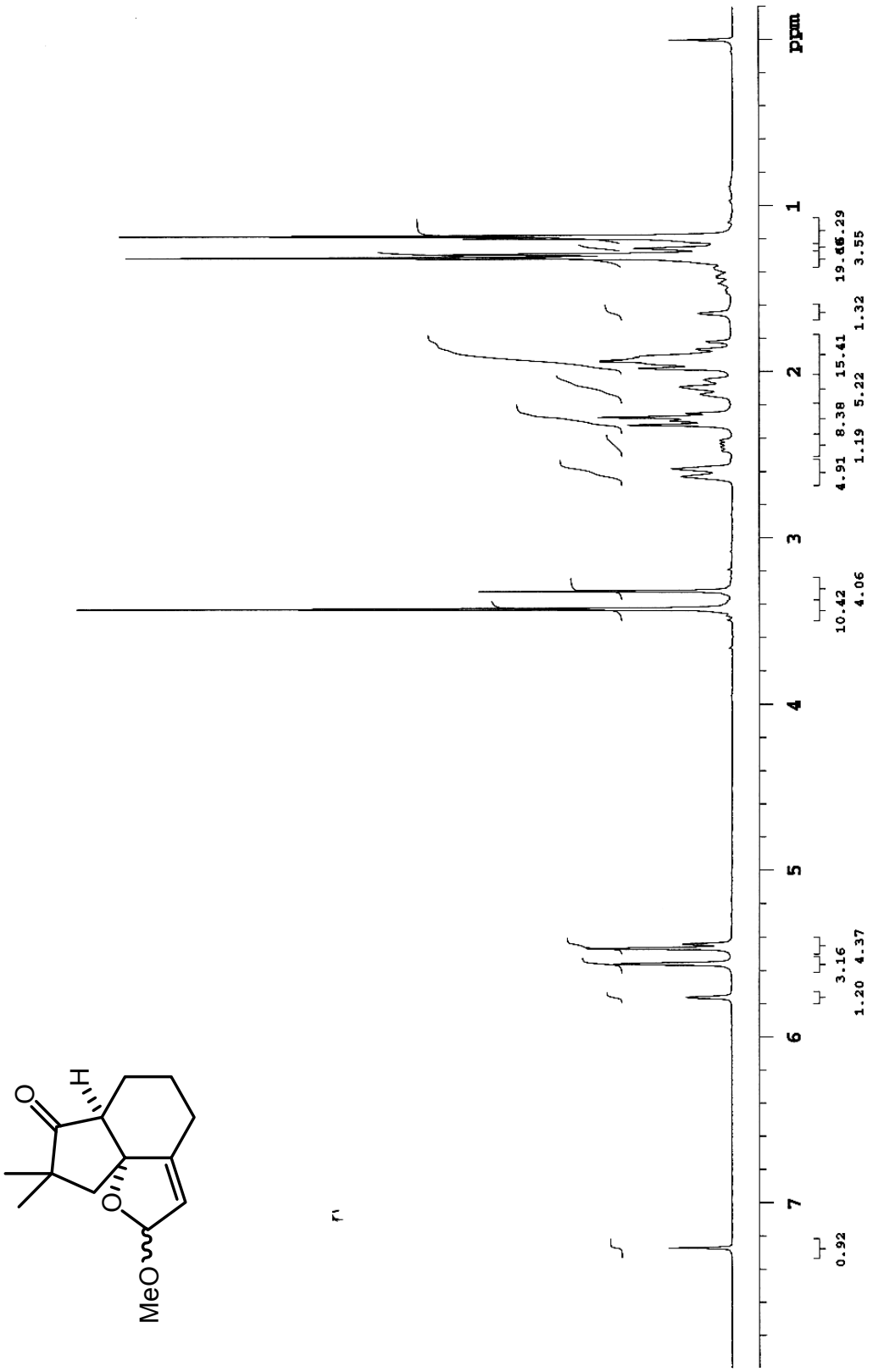


Figure 13: 300 MHz ^{1}H spectrum of **14**

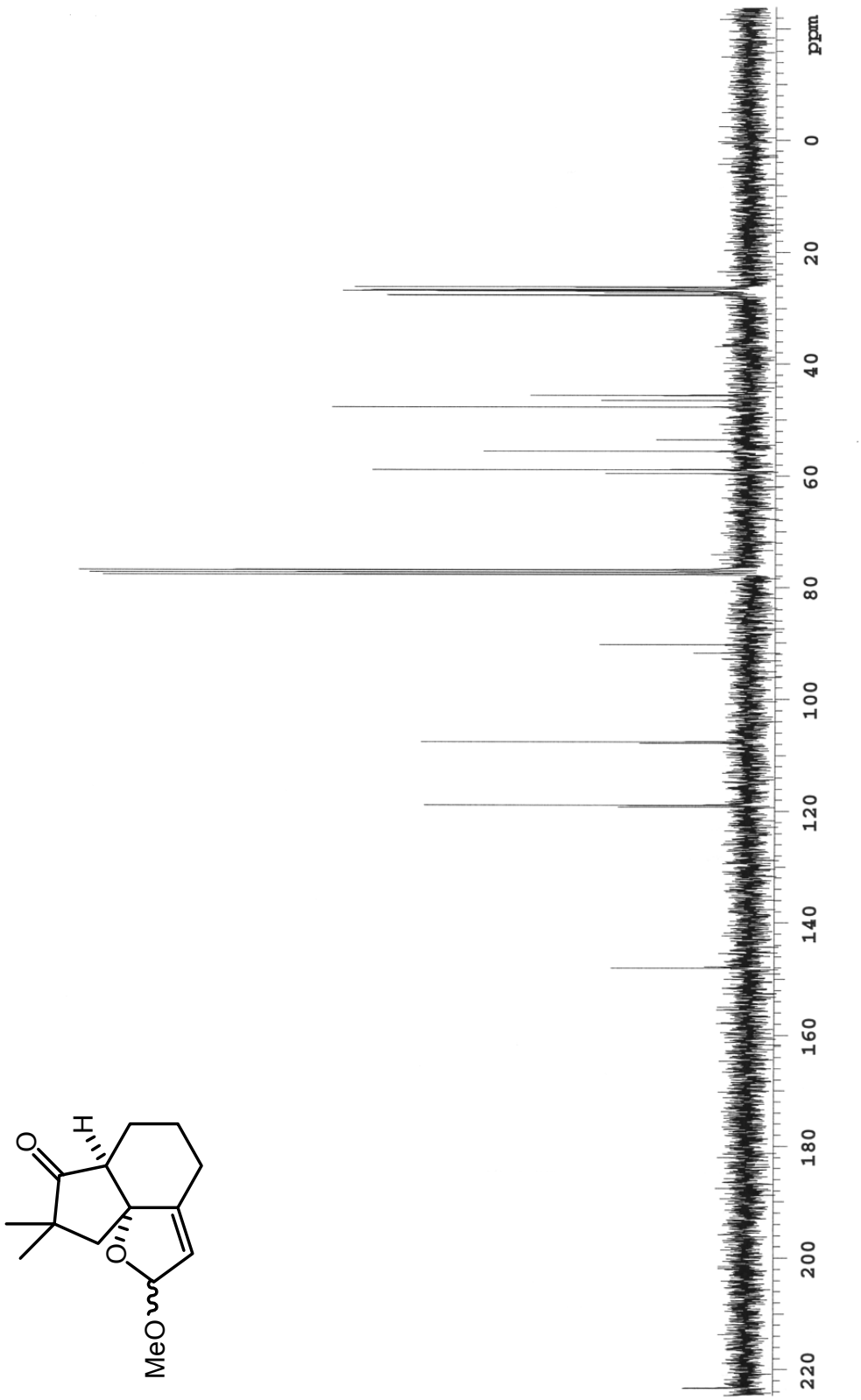


Figure 14:75 MHz ^{13}C spectrum of **14**

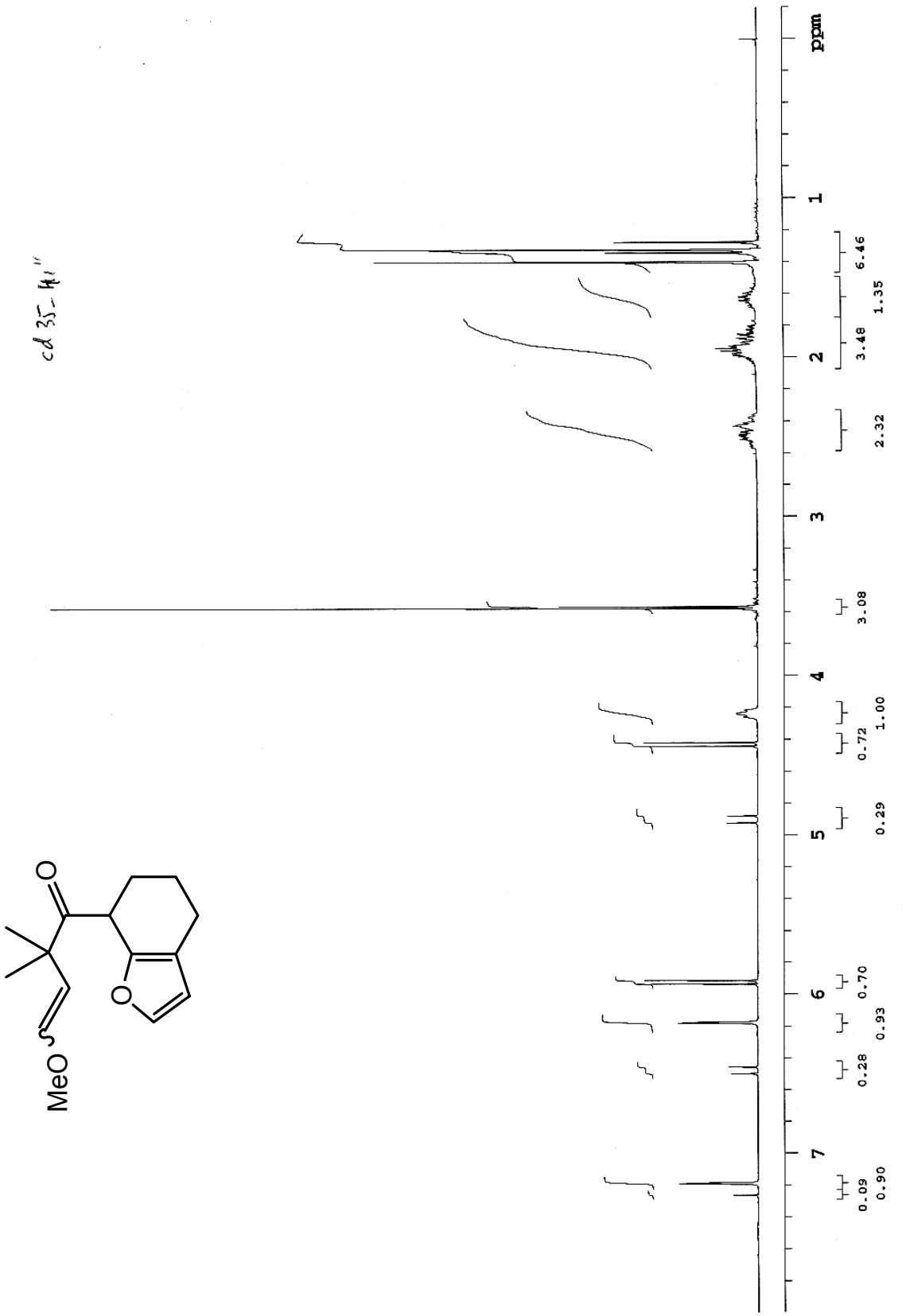


Figure 15: 300 MHz ^{1}H spectrum of **15**

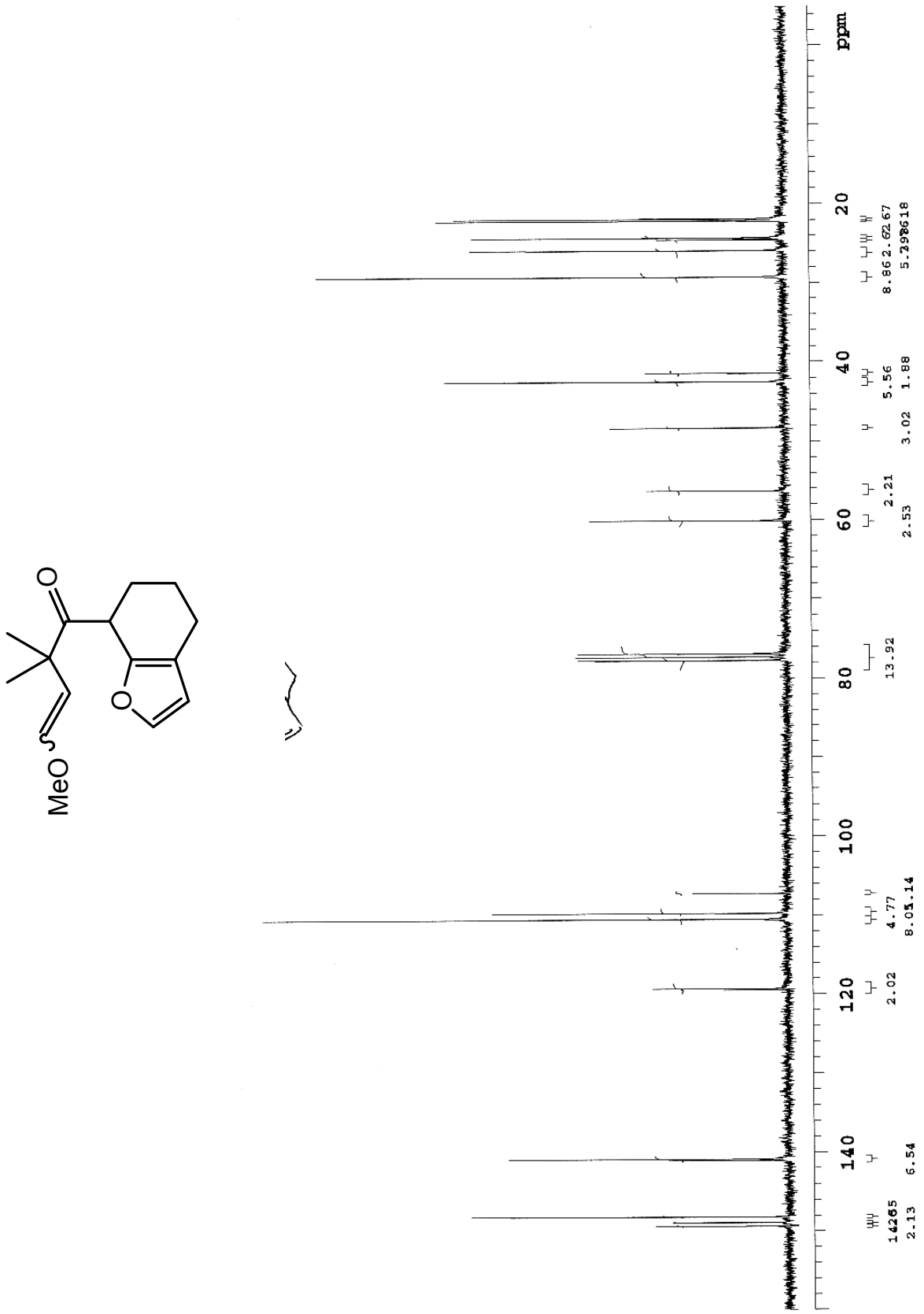


Figure 16: 75 MHz ^{13}C spectrum of **15**

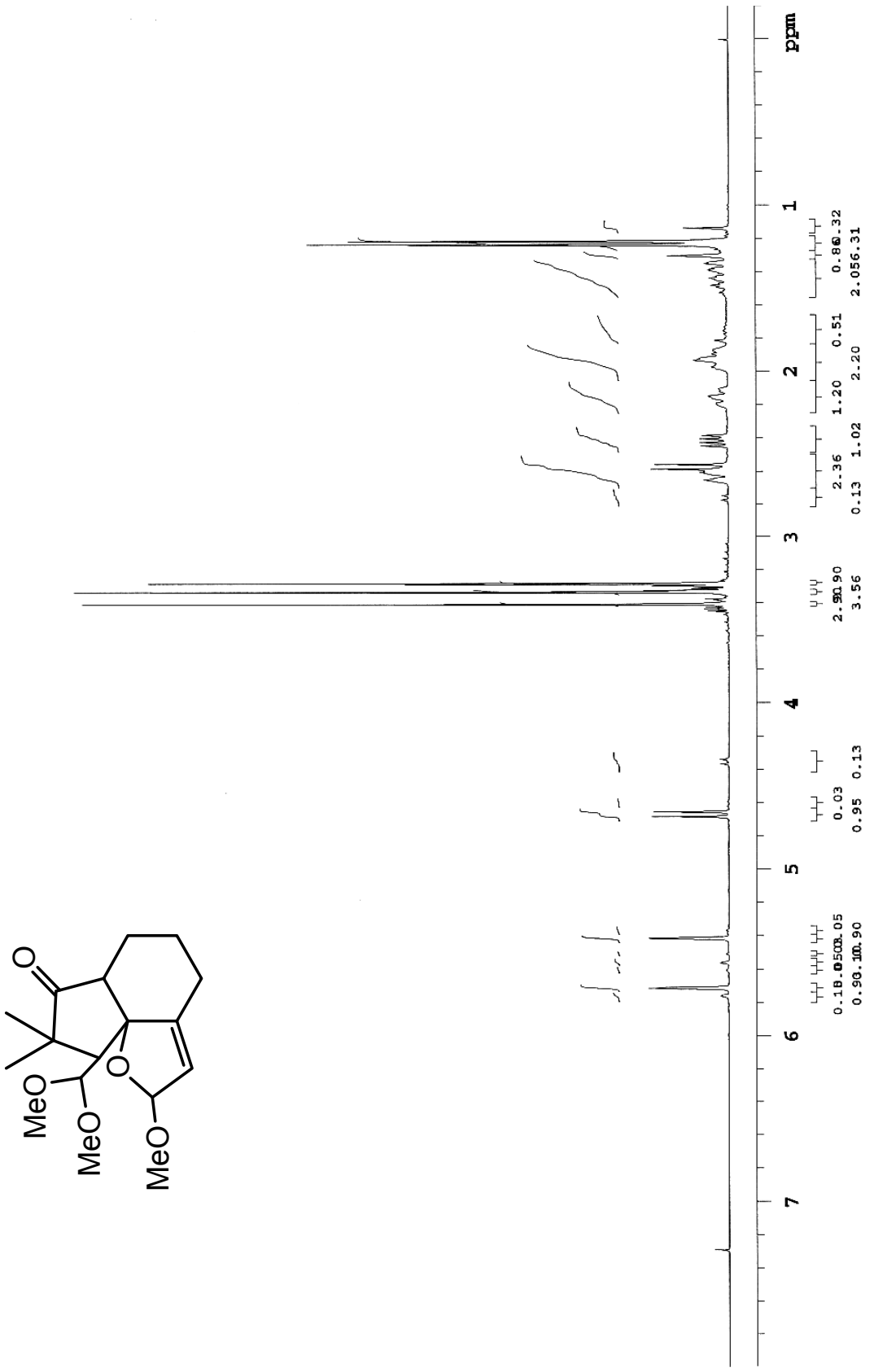


Figure 17: 300 MHz ^{1}H spectrum of **16**

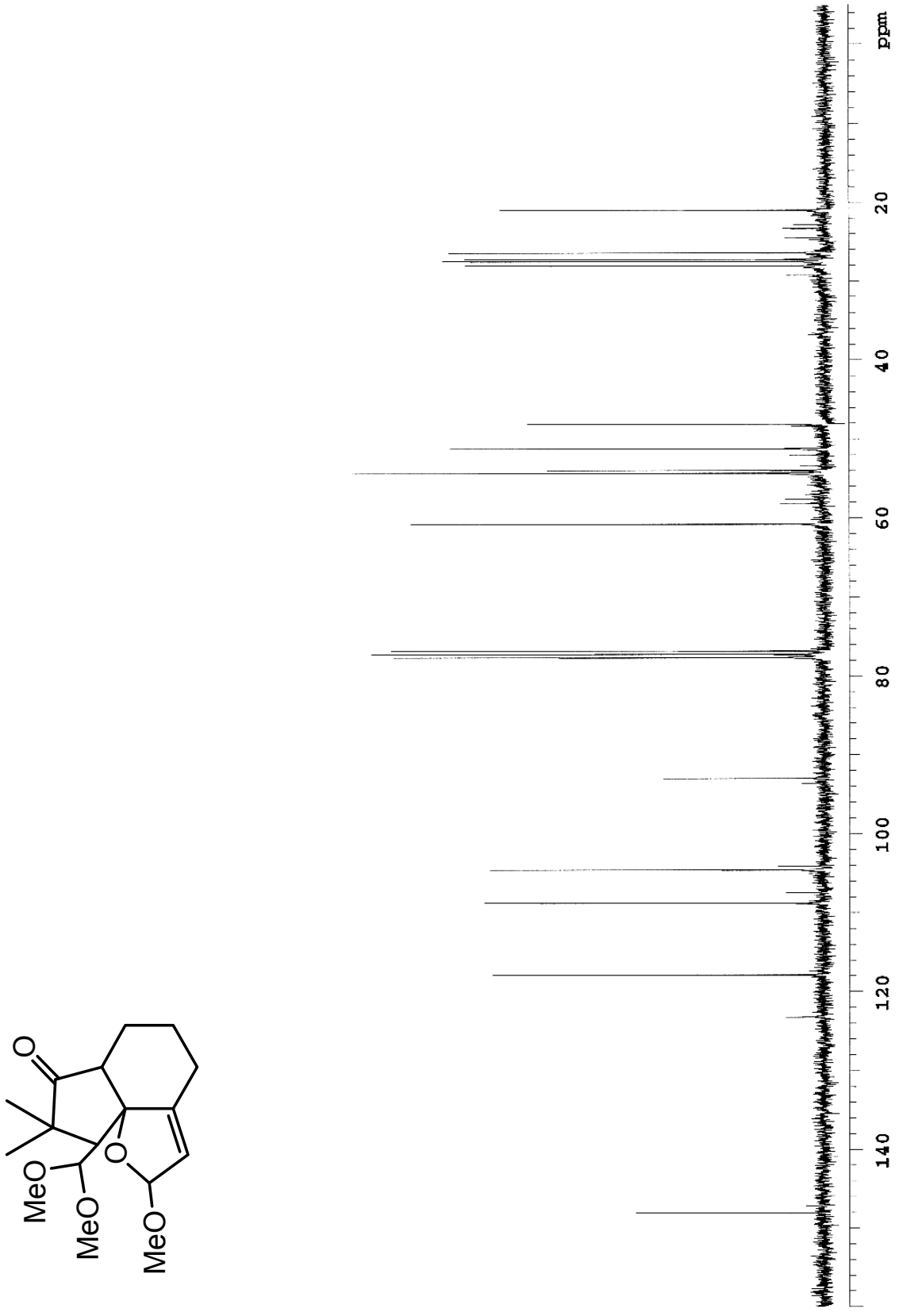


Figure 18: 75 MHz ^{13}C spectrum of **16**

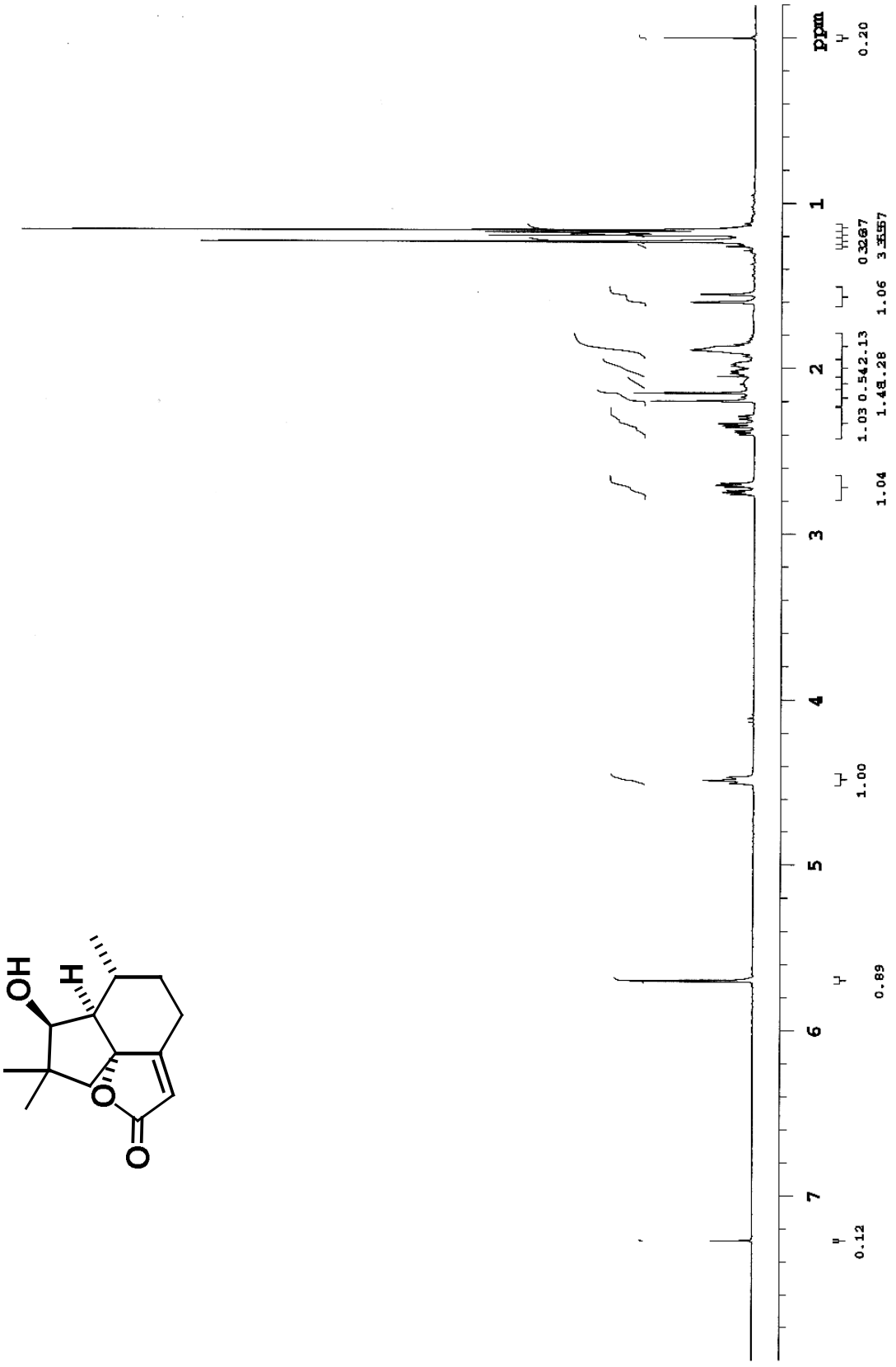


Figure 19: 300 MHz ^{1}H spectrum of **25a**

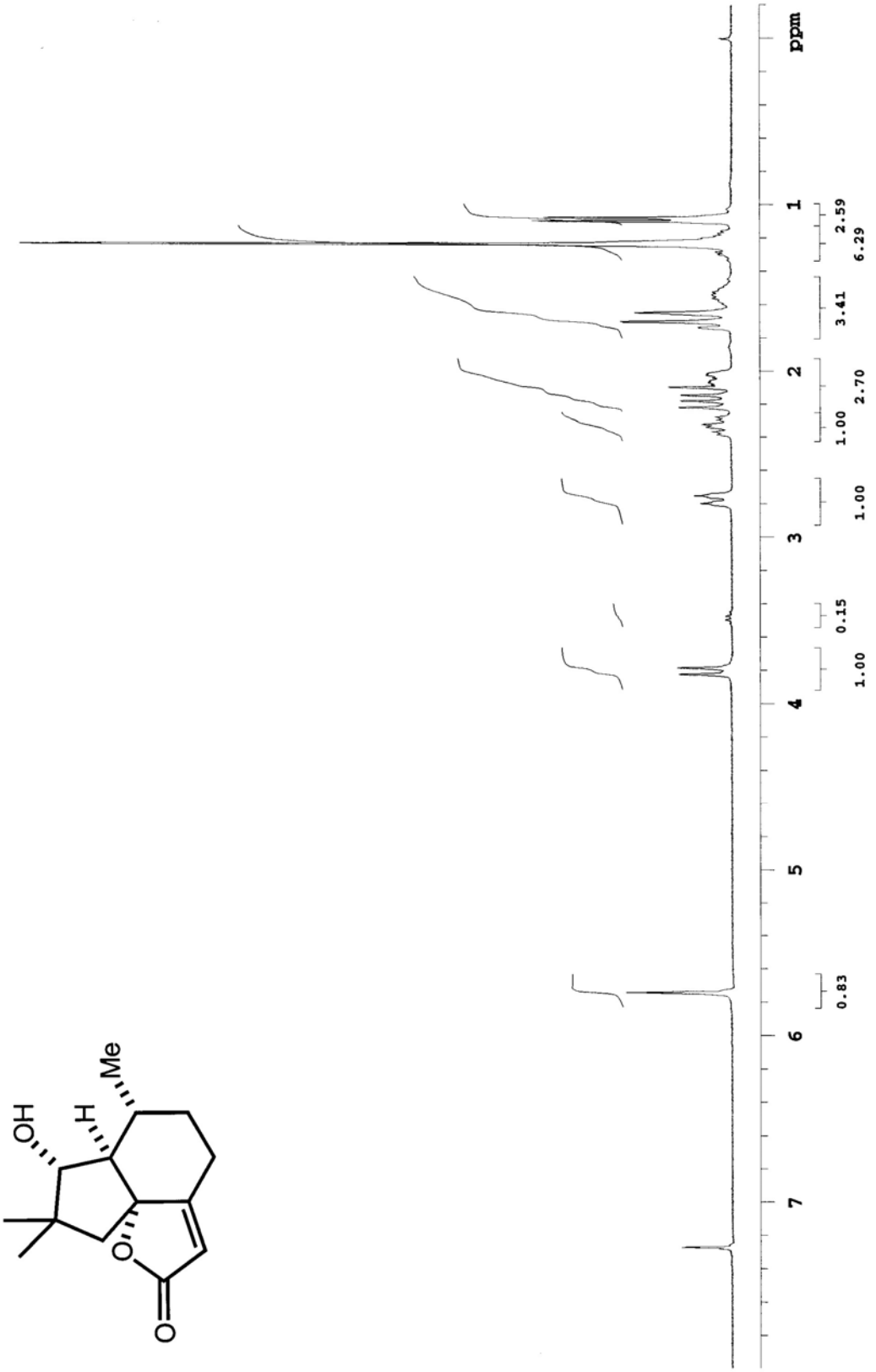


Figure 20:300 MHz ^{1}H spectrum of **25b**

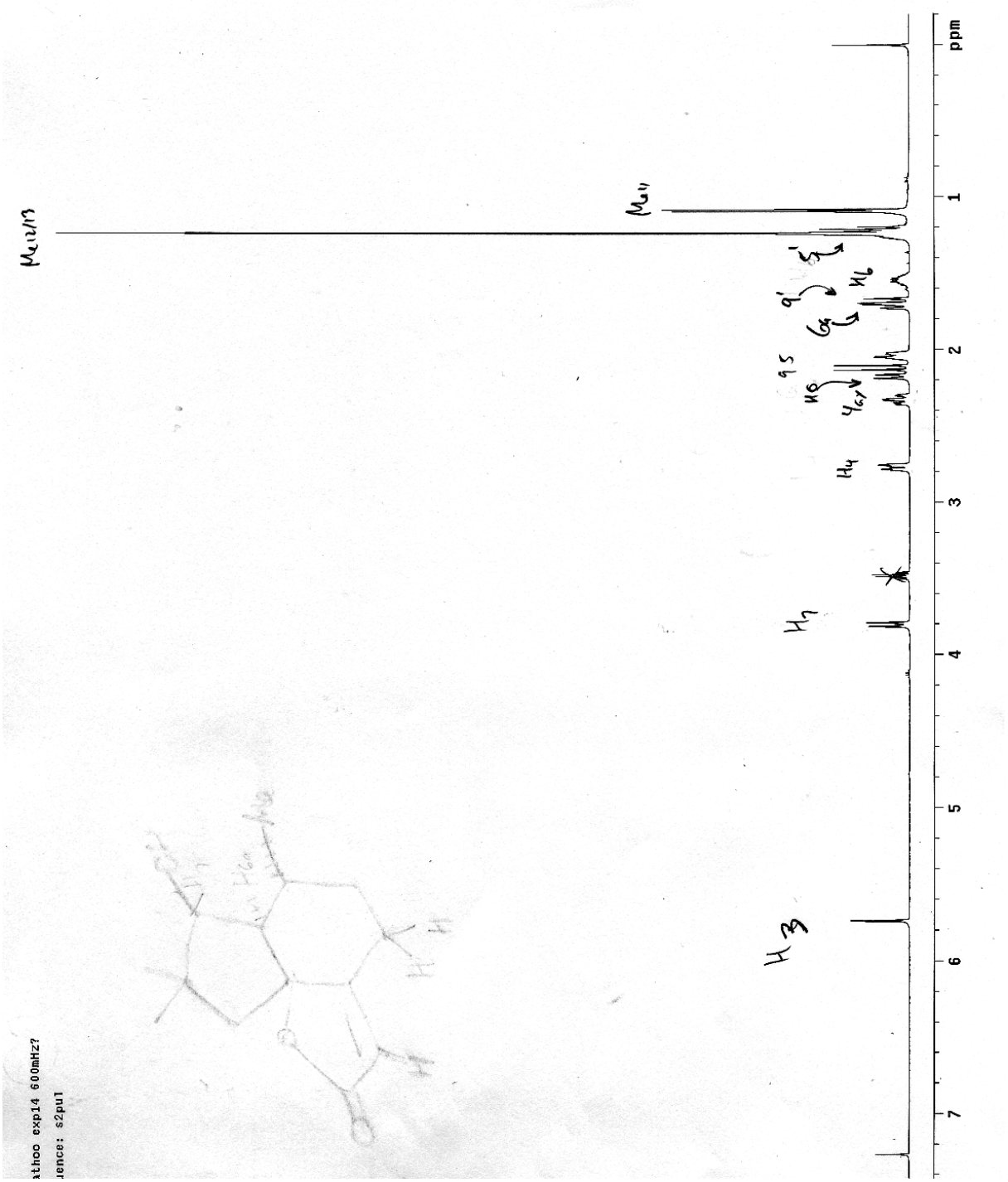
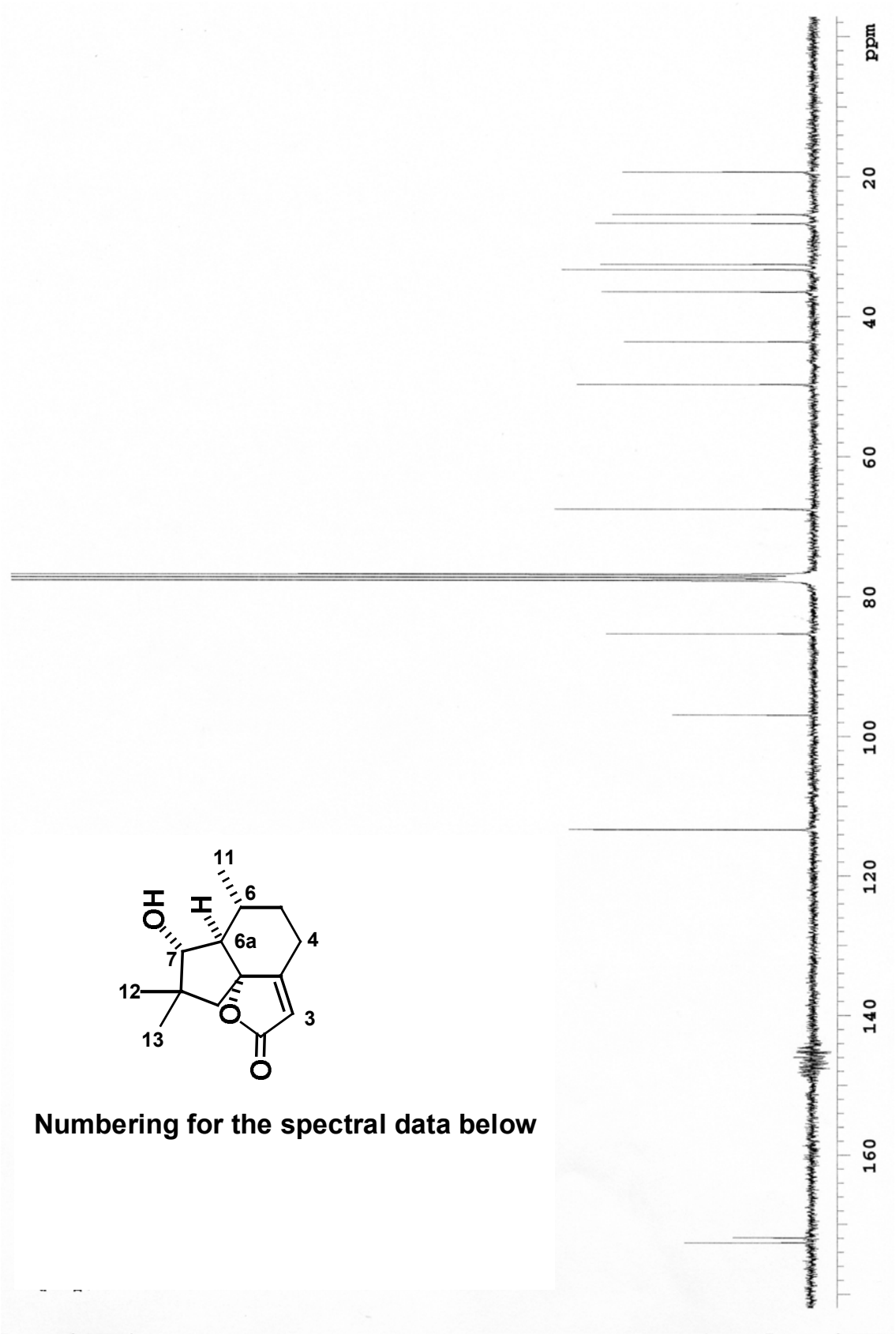


Figure 21: 500 MHz ^{1}H spectrum of **25b**



Numbering for the spectral data below

Figure 22: 75 MHz ^{13}C spectrum of **25b**

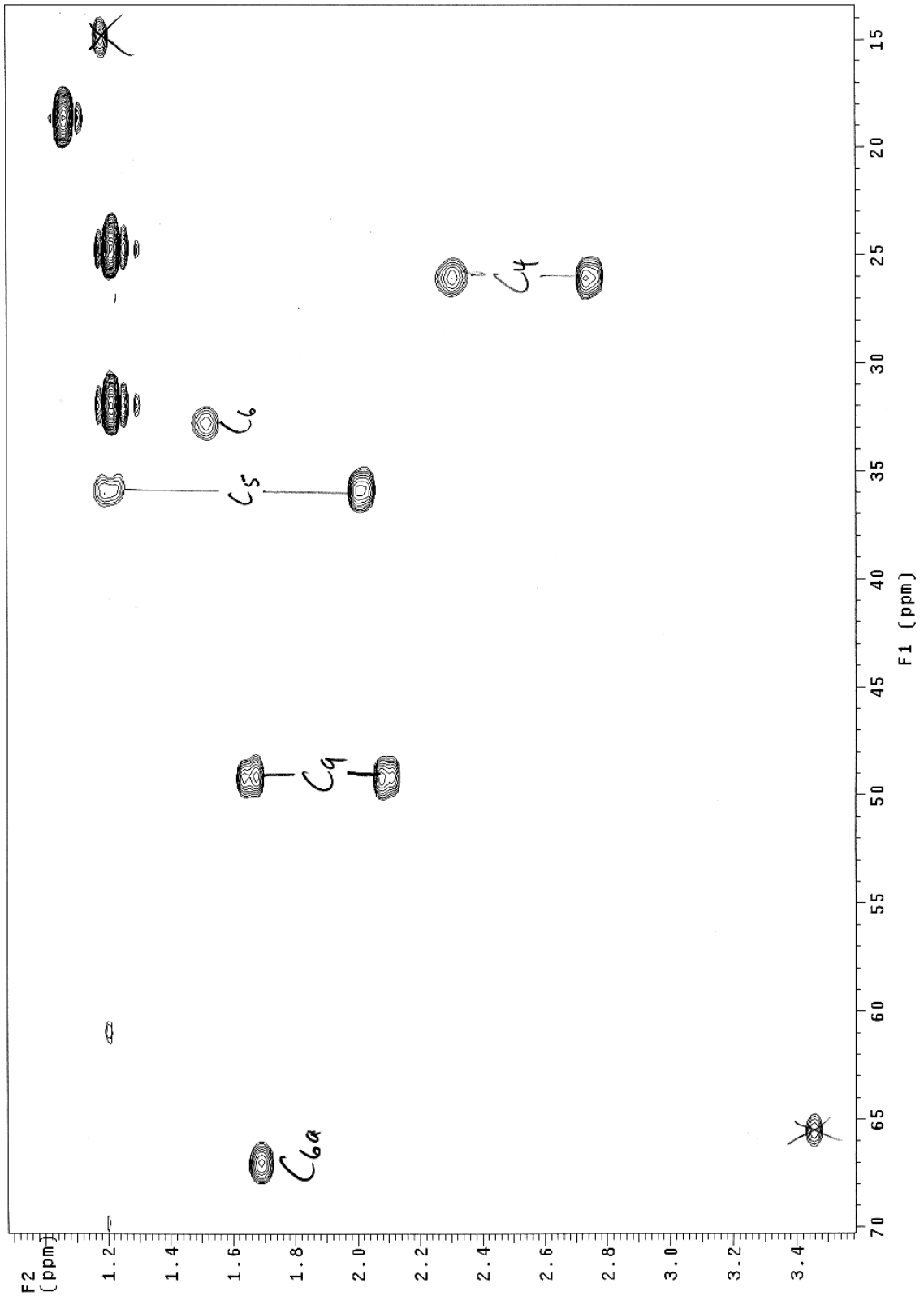


Figure 23: HMQC spectrum of **25b**

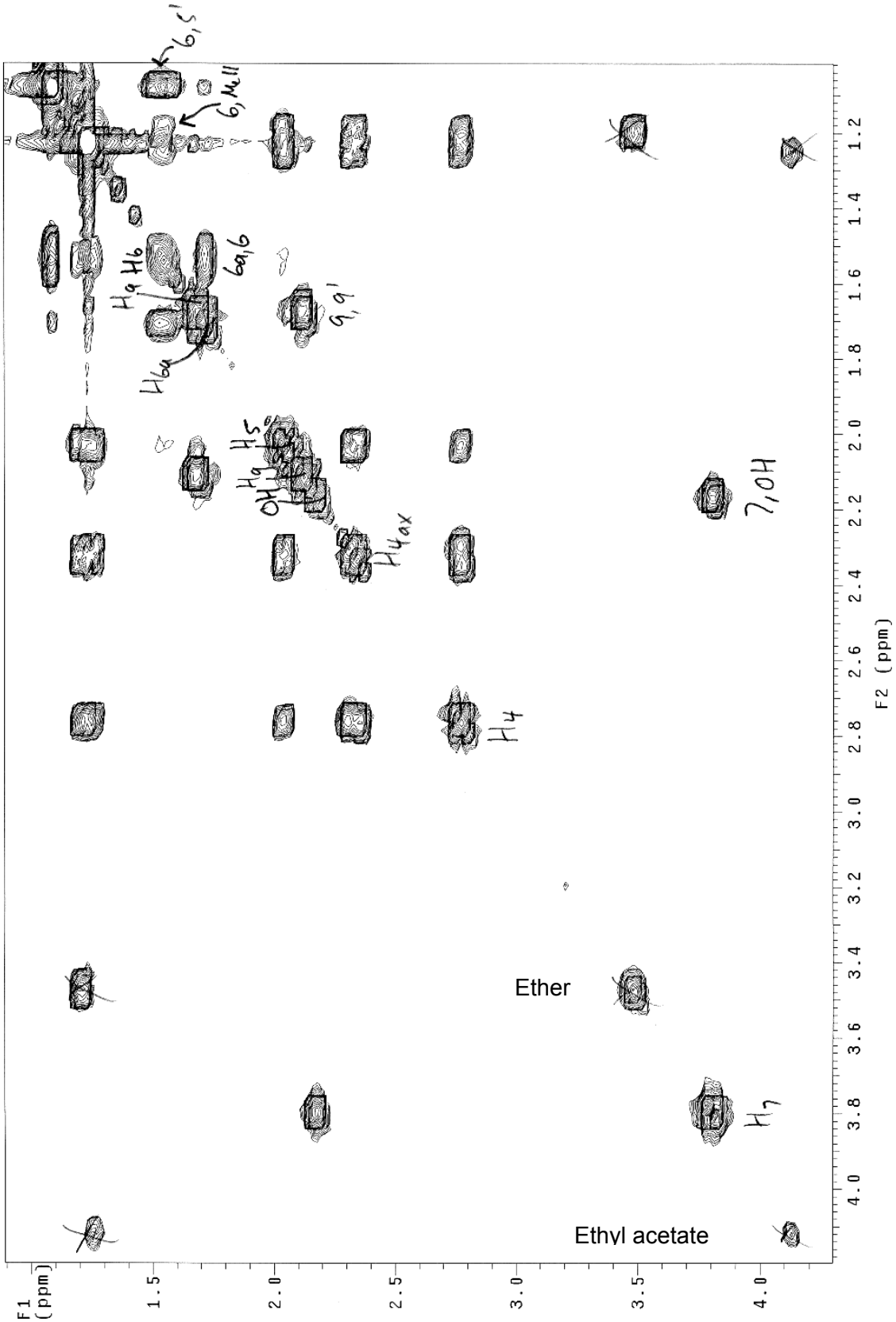


Figure 24:COSY spectrum of 3-**25b**

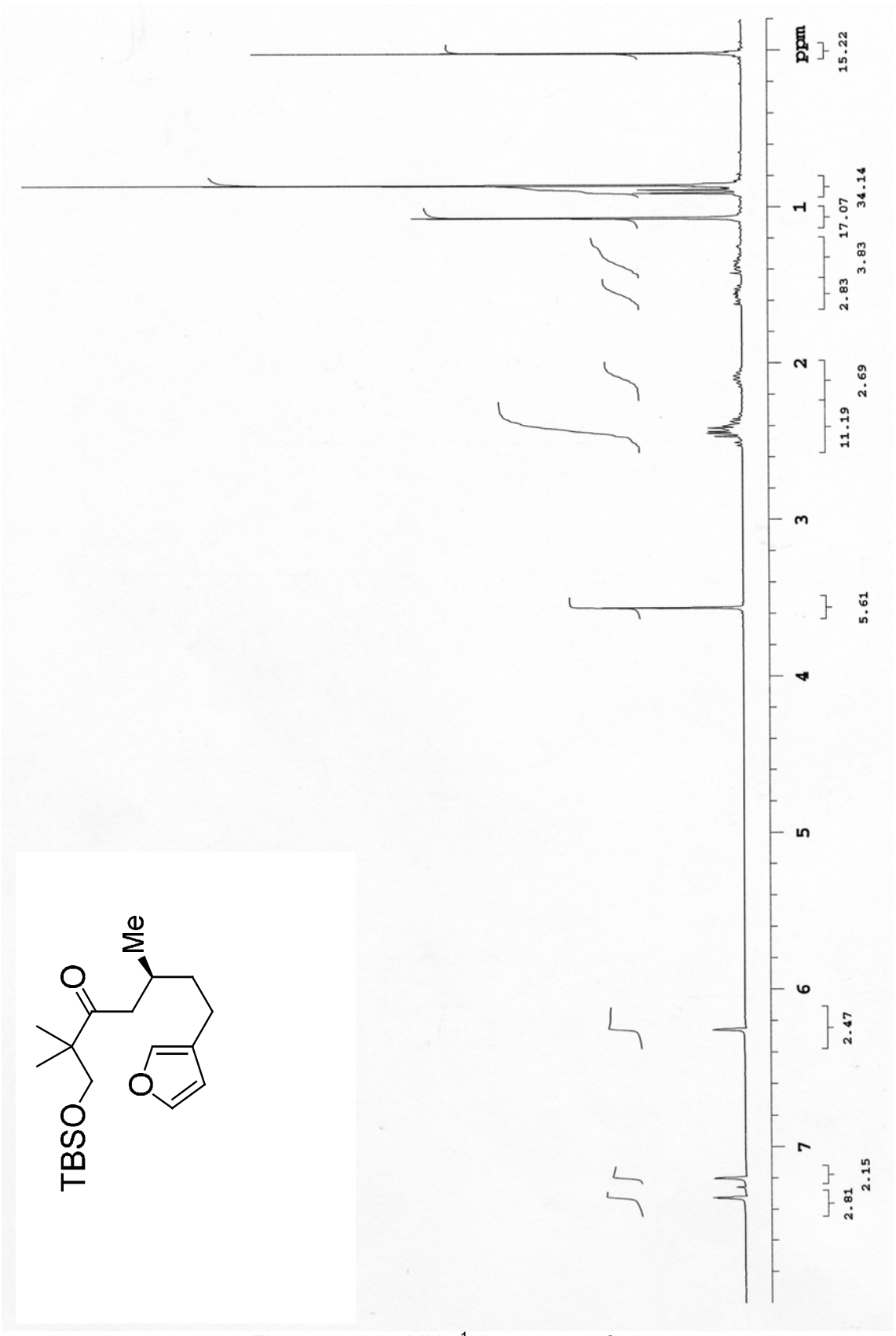


Figure 25:300 MHz ^{1}H spectrum of **28**

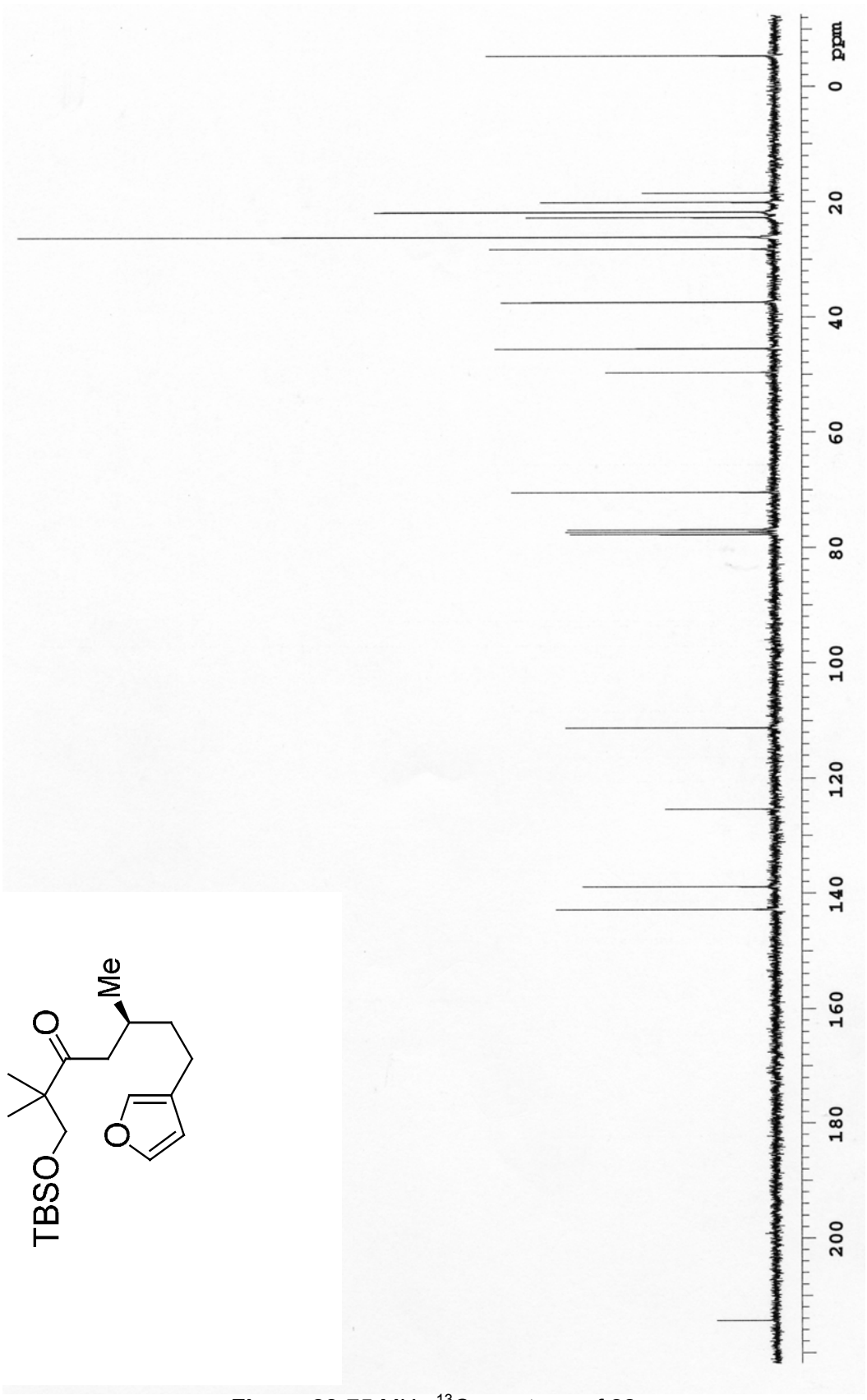


Figure 28:75 MHz ^{13}C spectrum of **28**

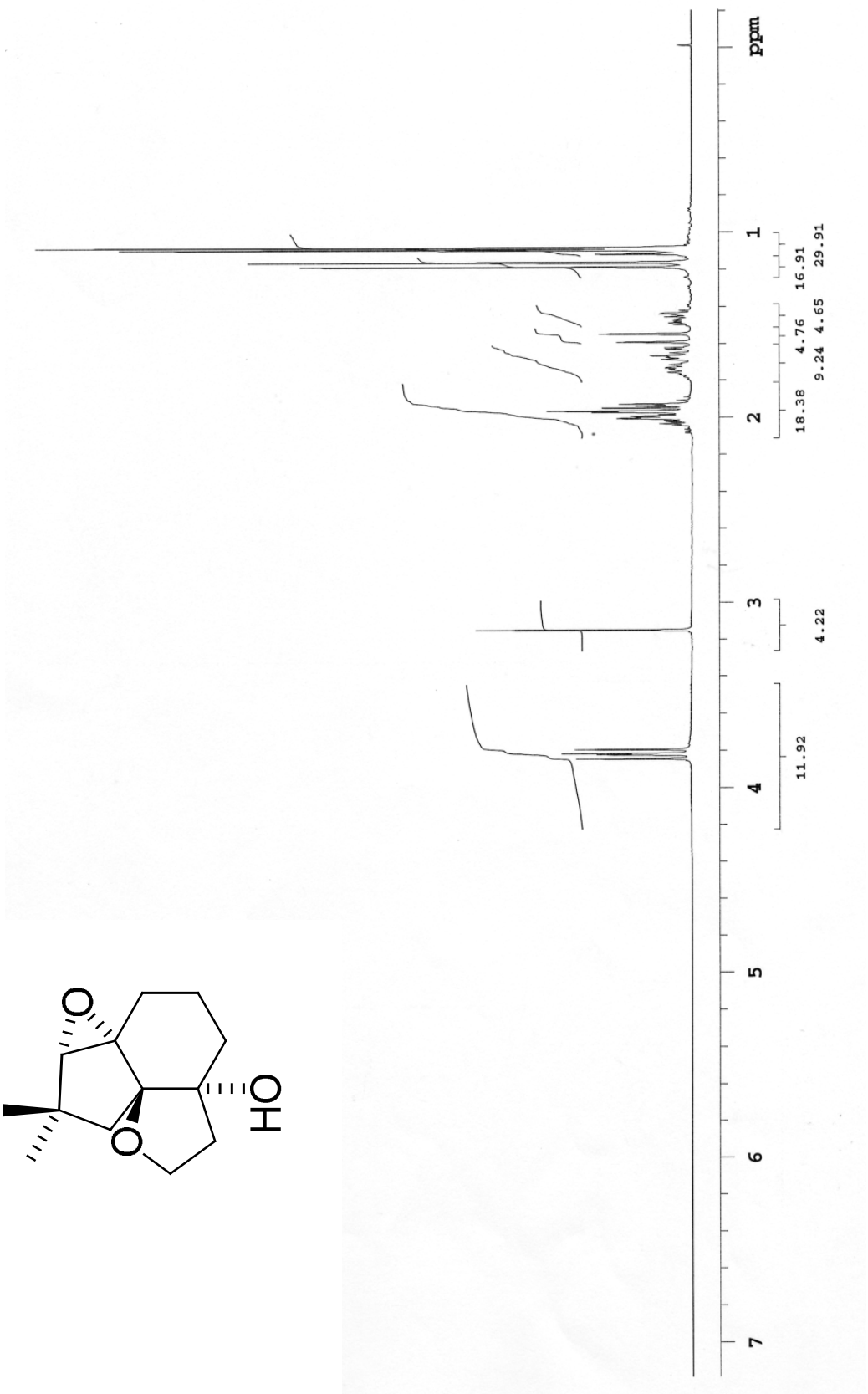


Figure 29:300 MHz ^{1}H spectrum of **1S,4R,5S,8R,9R-13-deoxy-12-noralliacol**

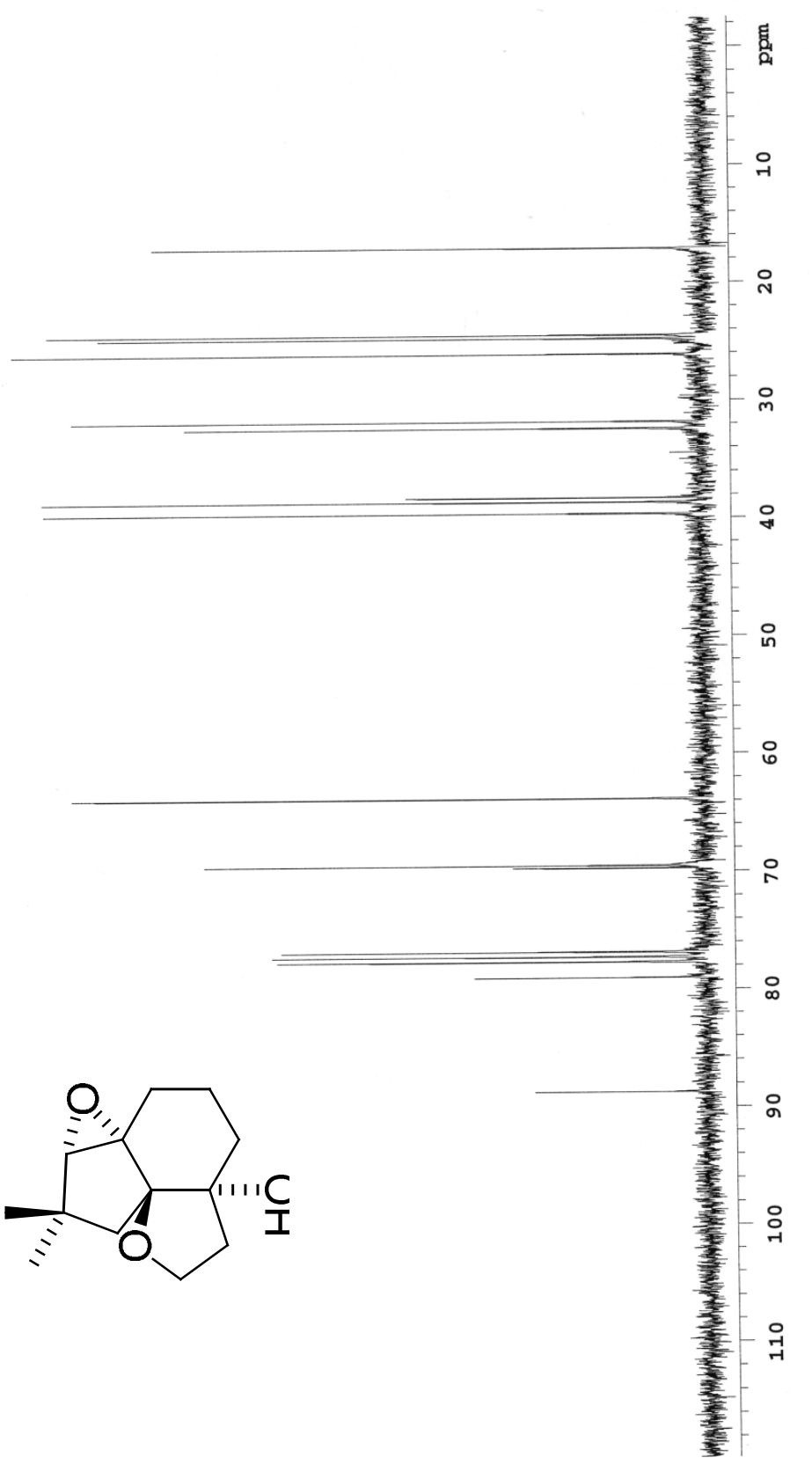


Figure 30: 75 MHz ^{13}C spectrum of **1S,4R,5S,8R,9R-13-deoxy-12-noralliacol**

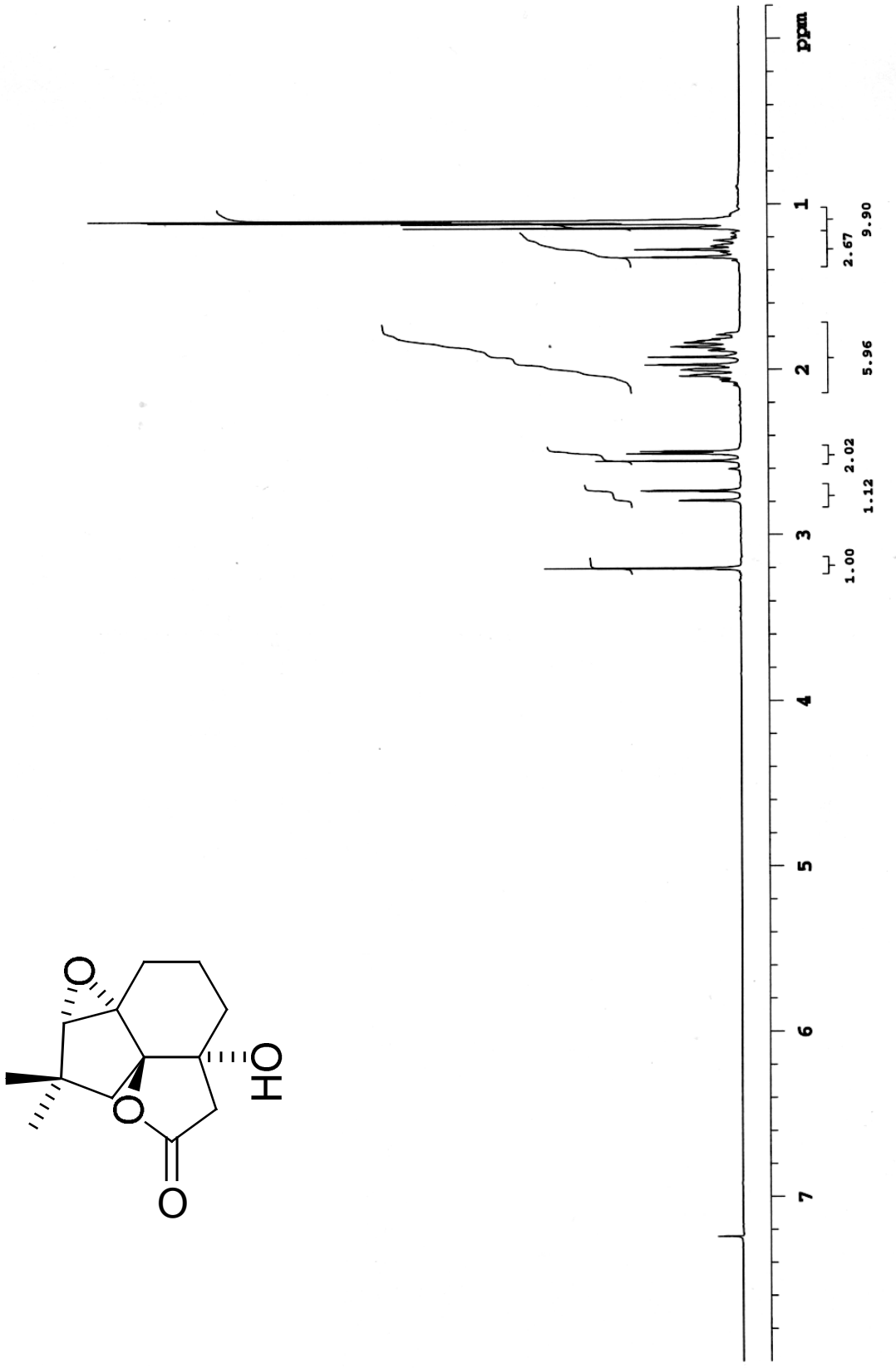


Figure 31: 300 MHz ^{1}H spectrum of **29***

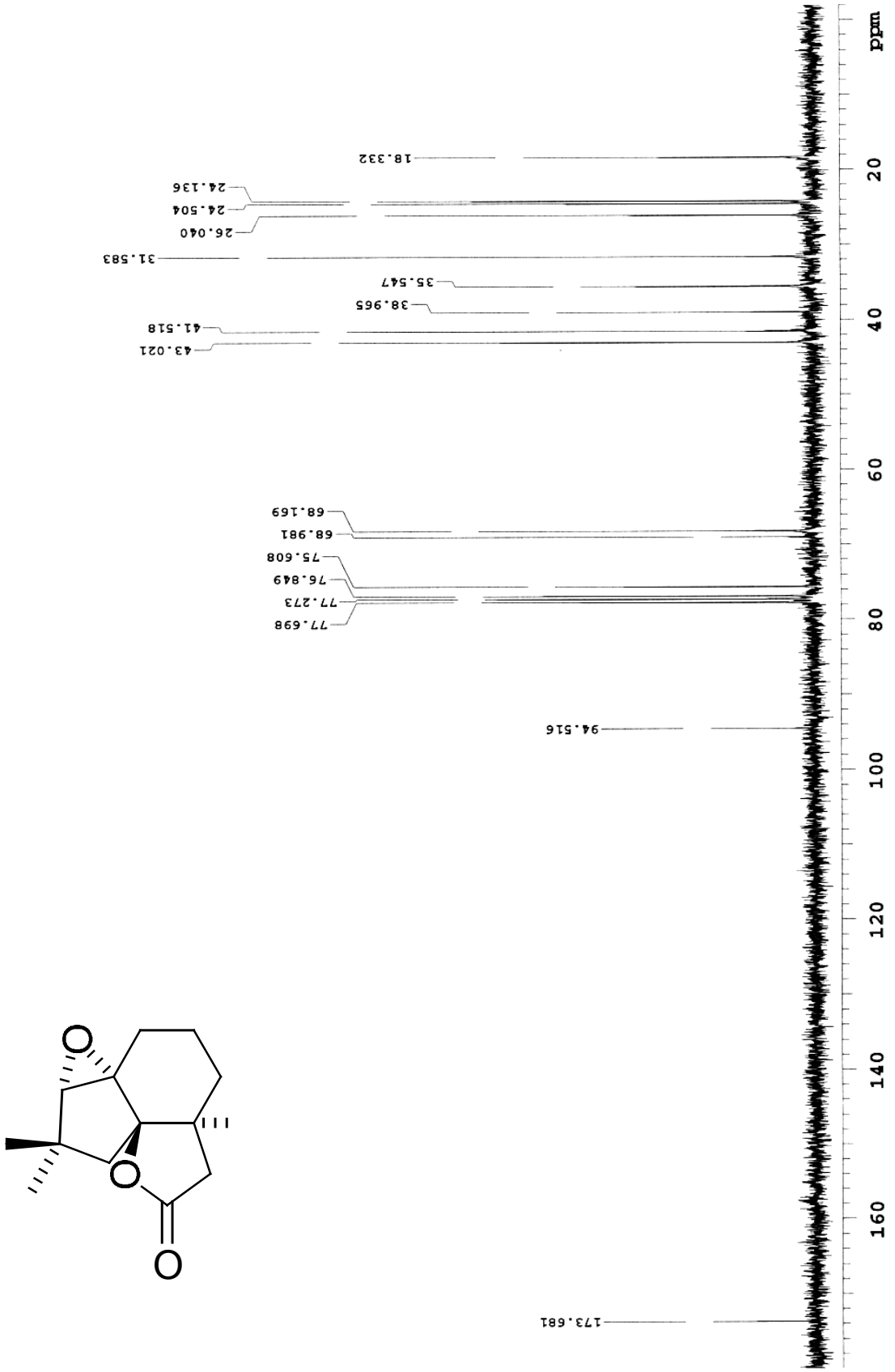


Figure 33:75 MHz ^{13}C spectrum of **29***

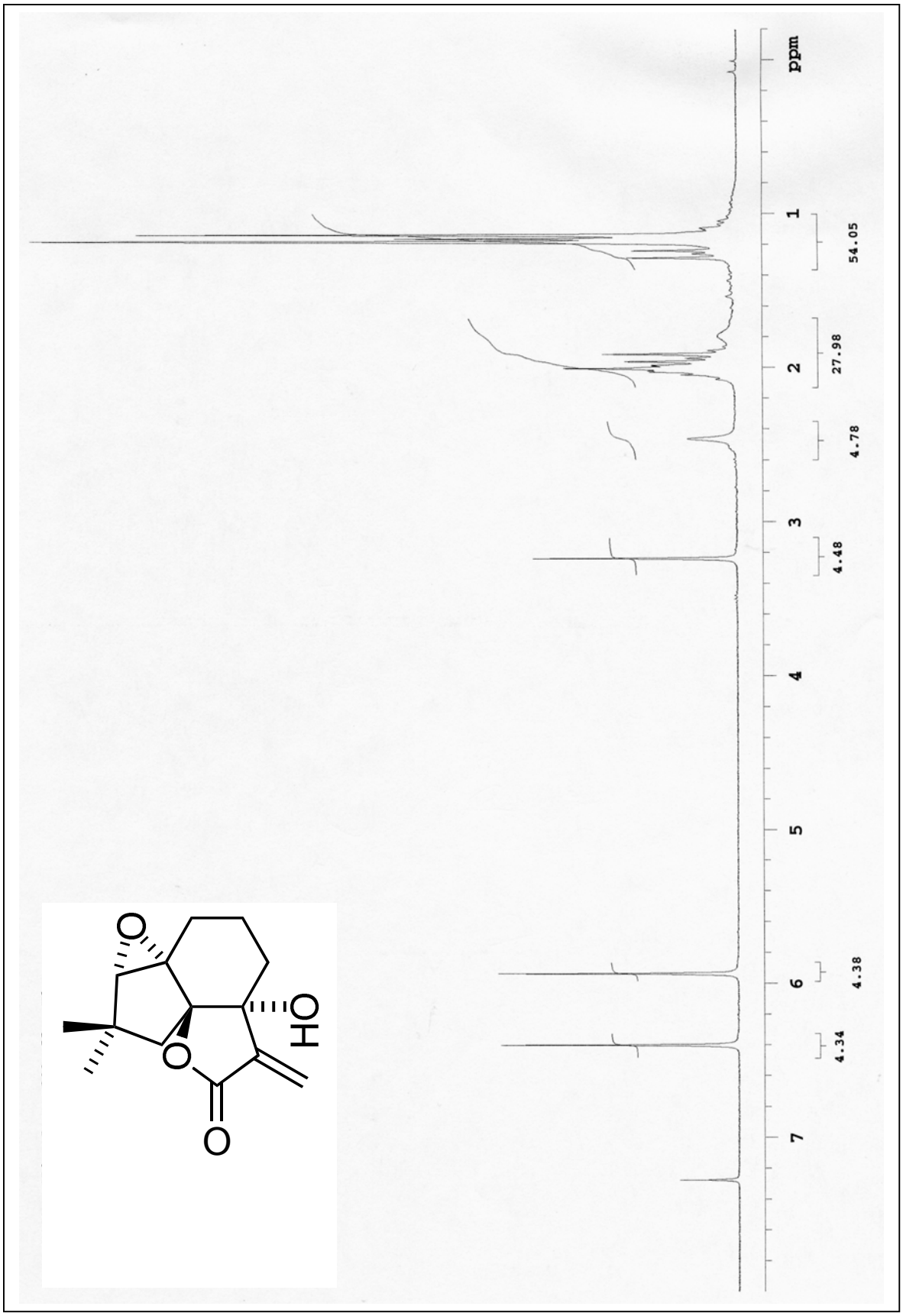


Figure 34: 300 MHz ^{1}H spectrum of **(-)-Alliacol A**

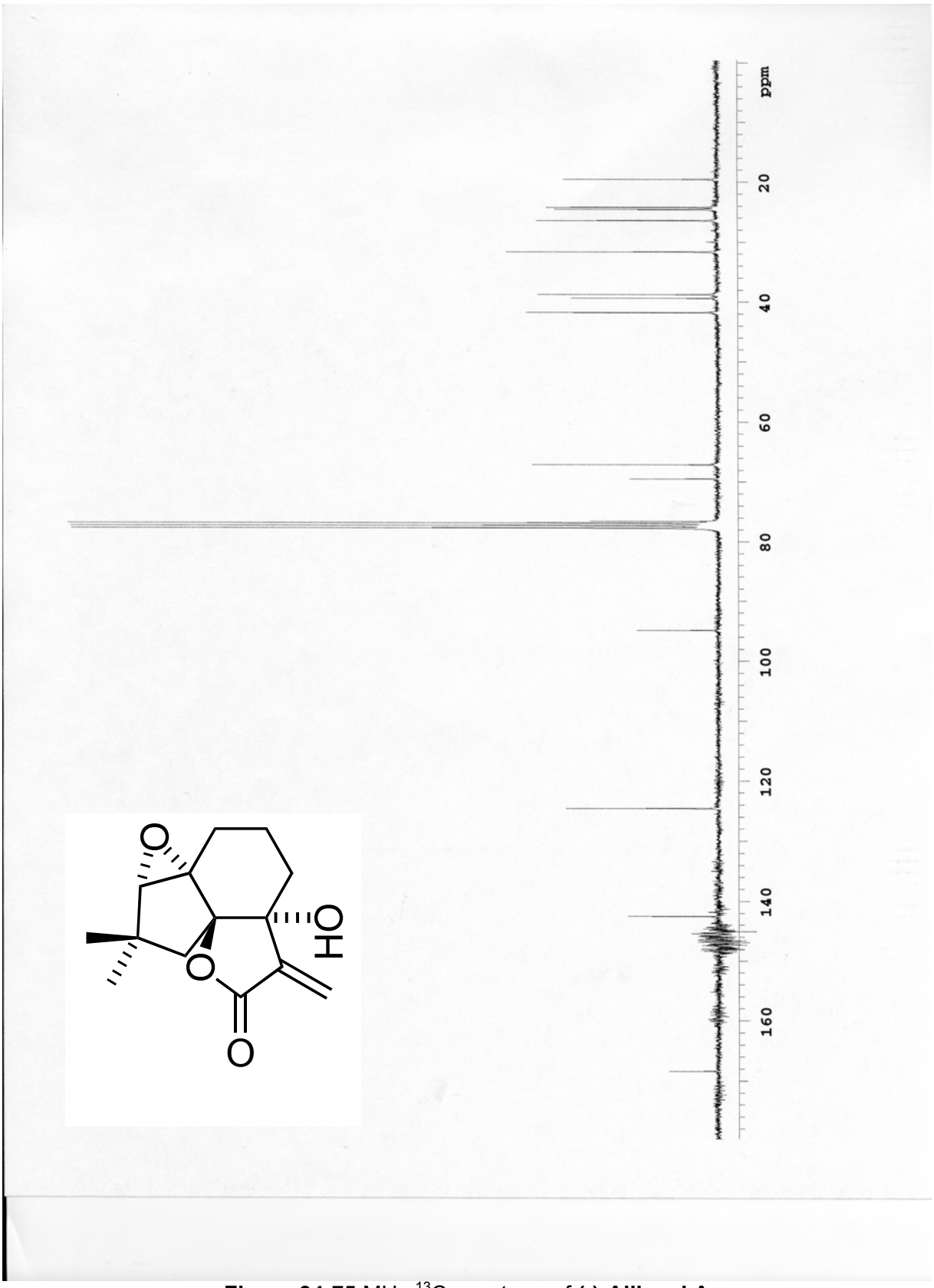


Figure 34:75 MHz ^{13}C spectrum of **(-)-Alliacol A**