SYNTHESIS OF THE C1-C9 FRAGMENT OF CALLIPELTOSIDE-A

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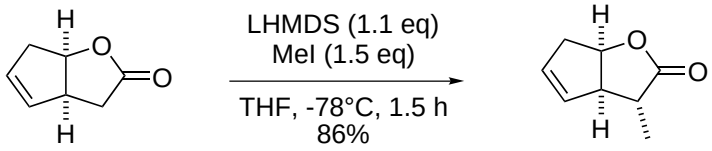
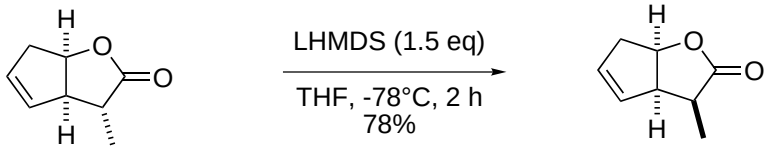
Supplementary Material

General procedures. Both ^{1}H and ^{13}C NMR spectra were obtained using a Bruker WM-360 spectrometer, using TMS as internal reference in $CDCl_3$. Carbon multiplicities were determined using DEPT experiment. IR spectra were recorded using a Nicolet 210 spectrometer. Melting and boiling points reported here are uncorrected. Melting points were obtained in a Thomas Hoover Melting Point Apparatus. Optical rotations were measured with a Jasco P-1020 polarimeter. Analytical TLC was performed using pre-coated silica gel 60 F_{254} Merck plates. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN).



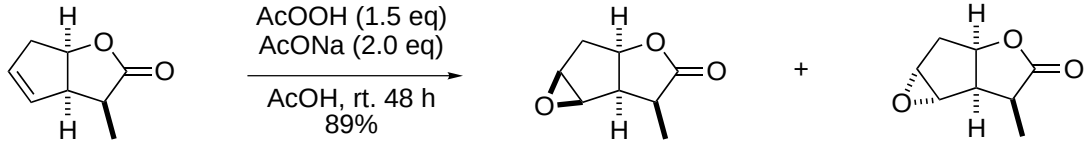
4 **6**

(1*R*,4*R*,5*R*)-4-methyl-2-oxabicyclo[3.3.0]-oct-6-en-3-one (6). To a well stirred solution of (1*R*,5*S*)-lactone **4** (10.0 g, 80.5 mmol, [α]= + 102 (*c* 1.0, CH_3OH)) in dry THF mantained at –78 °C was added LHMDS (1.1 eq, 88.6 mmol) over a period of 30 min. After addition was completed reaction was stirred for 1h. Methyl iodide (2.0 eq, 22.86 g, 161.1 mmol) dissolved in 10 mL of dry THF was added to the enolate solution held at –60 °C. Reaction was stirred at -60°C until TLC showed that there was no more starting material left (approx 1h). Reaction was diluted with 400 mL of ether and poured into a separatory funnel containing 200 mL of sat. solution of ammonium chloride. Aqueous layer was saturated with sodium chloride and extracted with ether (2 x 100 mL), EtOAc (1 x 100 mL), and dichloromethane (1 x 100 mL). Combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed *in vacuo* to give an oily residue which was chromatographed on a silica gel column (6 x 18 cm). Elution of the column with a mixture of ethyl acetate-hexane (3.5:6.5) gave the product as a clear oil: yield 9.56 g (86%); **TLC**: R_f = 0.36 (ethyl acetate-hexane, 3:7, $KMnO_4$); **[α]=** + 90 (*c* 1.0, CH_3OH); **^{1}H-NMR** ($CDCl_3$): δ 5.77 (dd, *J* = 2.3, 5.7 Hz, 1H), 5.61 (dd, *J* = 2.3, 5.7 Hz, 1H), 5.15 (m, 1H), 3.15 (m, *J* = 1.9, 3.7 Hz, 1H), 2.67 (broad s, 2H), 2.55 (qd, *J* = 1.8, 7.6 Hz, 1H), 1.38 (d, *J* = 7.6 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 180.4 (C), 131.1 (CH), 129.6 (CH), 81.5 (CH), 53.9 (CH), 40.0 (CH), 39.4 (CH_2), 17.5 (CH_3) ppm.



6 **7**

(1*R*,4*S*,5*R*)-4-methyl-2-oxabicyclo[3.3.0]-oct-6-en-3-one (7). LHMDS (1.1 eq, 102.3 mmol) was added over a period of 20 min to a well stirred solution of lactone **6** (9.42 g, 68.2 mmol) in 100 mL of dry THF mantained at -78 °C. Reaction was stirred for approximately 2 h. Approximately 10 mL of the enolate solution were taken out from the reaction flask and poured very slowly, avoiding any disturbance, into a tube containing 10 mL of sat. ammonium chloride and 20 mL of ether. The tube was carefully tighten with a cap and stirred vigorously (the procedure described above was repeated as many times as needed to quench the rest of the enolate solution). All the fractions obtained were combined and layers separated. Aqueous layer was saturated with sodium chloride and extracted with ether (2 x 100 mL) and dichloromethane (2 x 100 mL). Combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed *in vacuo* and the residue was chromatographed in a silica gel column (6.5 x 18 cm). Elution of the column with a mixture of hexane-AcOEt (7:3) gave the product (17:1 mixture of epimers, **7**:**6**): yield 7.34 g (78%); **TLC**: R_f = 0.34 (ethyl acetate-hexane, 3:7, $KMnO_4$); **[α]=** + 95 (*c* 1.0, CH_3OH);**^{1}H-NMR** ($CDCl_3$): δ 5.83 (m, 1H), 5.66 (m, 1H), 5.02 (m, 1H), 3.54 (m, 1H), 2.84 (dq, *J* = 1.7, 7.3 Hz, 1H), 2.70 (broad s, 2H), 1.27 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 178.8 (C), 130.6 (CH), 127.3 (CH), 80.6 (CH), 50.5 (CH), 39.6 (CH_2), 37.3 (CH), 11.9 (CH_3) ppm.



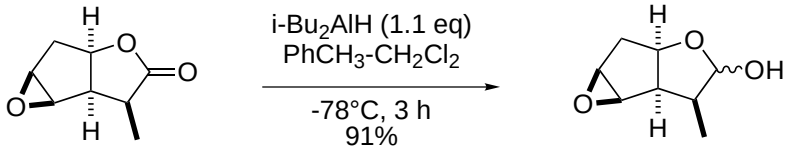
7 **endo-8** **exo-8**

(1*R*,4*S*,5*R*,6*R*,7*S*)-6,7-epoxy-4-methyl-2-oxabicyclo[3.3.0]-octan-3-one (*endo*-8) and (1*R*,4*S*,5*R*,6*S*,7*R*)-6,7-epoxy-4-methyl-2-oxabicyclo[3.3.0]-octan-3-one (*exo*-8). Unsaturated lactone **7** (6.62 g, 48.0 mmol) was dissolved in 50 mL of glacial acetic acid. Sodium acetate (2 eq, 96.0 mmol, 7.86 g) was added followed by the addition dropwise of 32% peracetic acid (1.5 eq, 72.0 mmol, 17.1 g soln 32%). Reaction was stirred for 48h at room temperature. Reaction was diluted with 500 mL of ethyl acetate and treated with aqueous solution of sodium sulfite (12.6 g in 400 mL of water). Sodium bicarbonate was added to neutralize some of the acetic acid present. Aqueous layer was back extracted with EtOAc (4 x 100 mL). Combined organic layers were treated with 50 mL of brine

solution and dried over sodium sulfate. Solvent was removed *in vacuo* and the residual acetic acid was coevaporated with benzene. The oily residue was dried in high vaccum overnight. The epoxides were separated in a silica gel column (6.5 x 15 cm). Elution of the column with 1.6 L of a mixture of ethyl acetate-hexane (8:2) gave the pure epoxides (6.3:1 mixture, ***endo*-8**:***exo*-8**): yield 6.58 g (89%);

For epoxide ***endo*-8**: **mp** 56-57 ^{o}C; **TLC**: R_f = 0.18 (EtOAc-hexane, 7:3, $KMnO_4$); **[α]=** + 108 (*c* 1.0, CH_3OH); **^{1}H-NMR** ($CDCl_3$): δ 4.85 (t, *J* = 6.7 Hz, 1H), 3.66 (brod s, 1H), 3.59 (broad s, 1H), 3.02 (td, *J* = 1.5, 7.1 Hz, 1H), 2.82 (dq, *J* = 1.5, 7.3 Hz, 1H), 2.50 (d, *J* = 16.0 Hz, 1H), 2.11 (ddd, *J* = 1.4, 6.7, 16.0 Hz, 1H), 1.43 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 178.5 (C), 80.4 (CH), 59.5 (CH), 57.8 (CH), 45.3 (CH), 35.7 (CH), 34.3 (CH_2), 11.6 (CH_3) ppm. **IR** (KBr): 2978, 1748, 1174 cm^{-1}; ***Elem Anal***: Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 61.99; H, 6.65.

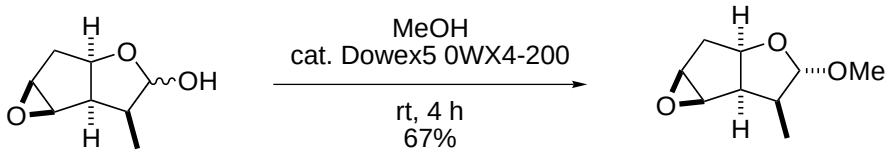
For epoxide ***exo*-8**: **TLC**: R_f = 0.45 (EtOAc-hexane, 7:3, $KMnO_4$); **^{1}H-NMR** ($CDCl_3$): δ 4.79 (td, *J* = 2.5, 6.5 Hz, 1H), 3.63 (broad s, 1H), 3.57 (broad d, *J* = 2.2 Hz, 1H), 3.12 (dd, *J* = 6.5, 10.6 Hz, 1H), 2.88 (dq, *J* = 7.7, 10.5 Hz, 1H), 2.50 (dd, *J* = 6.6, 15.8 Hz, 1H), 2.05 (dt, *J* = 2.4, 15.8 Hz, 1H), 1.36 (d, *J* = 7.7 Hz, 3H). **^{13}C-NMR** ($CDCl_3$): 179.1 (C), 83.4 (CH) , 58.5 (CH), 57.7 (CH), 44.4 (CH), 36.2 (CH), 35.4 (CH_2), 12.5 (CH_3) ppm.



endo-8 **9**

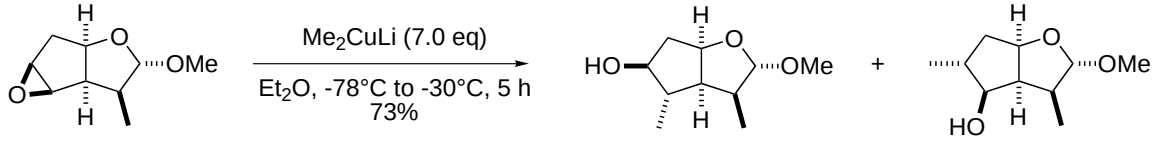
(1*R*,4*S*,3*RS*,5*R*,6*R*,7*S*)-6,7-epoxy-4-methyl-2-oxabicyclo[3.3.0]-octan-3-ol (9): To a well stirred solution of *endo*-epoxylactone **8** (3.41 g, 22.2 mmol) in 100 mL of freshly distilled toluene (distilled from CaH) and 20 mL of freshly distilled dichloromethane (distilled from CaH) at – 78 ^{o}C, was added DIBAL (1.1 eq, 24.4 mmol, 1.5M in toluene) over a period of 15 min. Reaction was stirred for 3h at – 78 ^{o}C. Reaction mixture was quenched by addition of methanol (2.34 g, 73.1 mmol) in 10 mL of benzene. Reaction was warmed-up to room temperature and stirred for 30 min. Water (1.31 g, 73.1 mmol) was added and the mixture was stirred for further 20 min. Reaction was diluted with 300 mL of methanol and filtered through a short path of celite to remove the aluminum salts. Filtrate cake was washed 3 times with 30 mL of methanol each time. Solvent was removed *in vacuo* and the residue was chromatographed in a silica gel column (4.5 x 14 cm). Elution of the column with a mixture of EtOAc-hexane (7:3) gave the product as a white solid: yield 3.47 g (91%) yield: **mp** 76-77 ^{o}C; **TLC**: R_f 0.21 (EtOAc-hexane, 8:2, $KMnO_4$); **IR** (KBr): 3316, 2960, 2924, 1464, 1122, 1045, 990 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) for

major compound: δ 5.09 (dd, *J* = 5.3, 1.9 Hz, 1H), 4.70 (t, *J* = 7.5 Hz, 1H), 3.72 (broad s, 1H), 3.54 (broad d, *J* = 1.7 Hz, 1H), 2.89 (td, *J* = 1.7, 7.9 Hz, 1H), 2.54 (qd, *J* = 1.4, 7.1 Hz, 1H), 2.33 (d, *J* = 16.0 Hz, 1H), 2.12 (ddd, *J* = 1.7, 7.6, 16.0 Hz, 1H), 1.20 (d, *J* = 7.1 Hz, 3H); **^{13}C-NMR** ($CDCl_3$) for major compound: 101.4 (CH), 83.9 (CH), 63.1 (CH), 59.2 (CH), 48.5 (CH), 39.7 (CH), 37.1 (CH_2), 11.0 (CH_3) ppm; ***Elem Anal***: Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.84; H, 7.82.



9 **10**

(1*R*,3*S*,4*S*,5*R*,6*R*,7*S*)-3-methoxy-4-methyl-2-oxabicyclo[3.3.0]-octane (10): Lactol **9** (772 mg, 4.94 mmol) was dissolved in 20 mL of methanol and stirred with a catalytic amount of DOWEX 50WX4-200 (10% w/w) at room temperature for 4 hours. Reaction was diluted with 200 mL of ether and washed with satd sodium bicarbonate (1 x 50 mL, 1 x 20 mL) and brine. Organic layer was dried over sodium sulfate and solvent removed *in vacuo*. Purification of the product was done in a silica gel column (4.5 x 10 cm). Elution of the column with a mixture of EtOAC-hexane (4:6) gave the product as a clear oil: yield 563 mg (67%); **TLC**: R_f 0.40 (EtOAc-hexane, 7:3, $KMnO_4$); **IR** (KBr): 2931, 2833, 1460, 1389, 1193, 1120, 1054, 850 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 4.72 (d, *J* = 5.0 Hz, 1H), 4.70 (t, *J* = 6.5 Hz, 1H), 3.56 (broad s, 1H), 3.45 (broad s, 1H), 3.38 (s, 3H), 2.73 (td, *J* = 1.6, 5.2 Hz, 1H), 2.34 (m, *J* = 7.3, 5.2 Hz, 1H), 2.27 (d, *J* = 15.7 Hz, 1H), 1.95 (ddd, *J* = 1.7, 6.7, 15.7 Hz, 1H), 1.29 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 112.6 (CH), 82.0 (CH), 59.1 (CH), 58.1 (CH), 56.0 (CH_3), 48.7 (CH), 41.4 (CH), 35.2 (CH_2), 13.3 (CH_3) ppm. ***Elem Anal***: Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.33; H, 8.51.



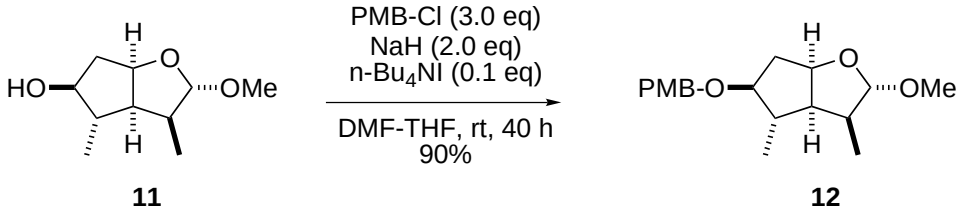
10 **11** **regio-11**

(1*R*,3*S*,4*S*,5*R*,6*S*,7*S*)-7-hydroxy-3-methoxy-4,6-dimethyl-2-oxabicyclo[3.3.0]-octane (11), and (1*R*, 3*S*,4*S*,5*R*,6*S*,7*R*)-6-hydroxy-3-methoxy-4,7-dimethyl-2-oxabicyclo[3.3.0]-octane (*regio*-11): To a well stirred suspension of copper iodide (7.0 eq, 28.8 mmol, 5.43 g) in 120 mL of freshly distilled ether (distilled from potassium) at – 20 °C was added MeLi (14.0 eq, 57.5 mmol, 1.4 M soln in ether) over a period of 15 min. Organocuprate was stirred for 15 min at – 20 °C and then it was cooled to – 78 °C. Epoxyacetal **10** (700 mg, 4.11 mmol) dissolved in 10 mL of freshly distilled ether was

added and temperature was gradually increased to – 30 °C. Reaction was stirred at – 30 °C for further 5 hours. Reaction was diluted with 200 mL of ether and poured into a separatory funnel containing 100 mL of sat. ammonium chloride. Aqueos layer was back extracted with ether (4 x 100 mL) and EtOAc (1 x 80 mL). Combined organic layers were treated with 100 mL of brine and dried over sodium sulfate. Solvent was removed *in vacuo* and the products were separated using a silica gel column (3.5 x 12.5 cm). Elution of the column with a mixture of EtOAc-hexane (7:3) gave the pure alcohols (16:1 mixture, **11**:***regio*-11**): yield 555 mg (73%);

For alcohol **11**: **TLC**: R_f 0.33 (EtOAc-hexane, 7:3, $KMnO_4$); **IR** (NaCl): 3422, 2962, 2831, 1459, 1378, 1252, 1195, 1104, 1013, 961 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 4.65 (d, *J* = 3.5 Hz, 1H), 4.53 (ddd, *J* = 2.5, 3.3, 5.9 Hz, 1H), 3.71 (broad s, 1H), 3.36 (s, 3H), 2.36 (ddq, *J* = 3.5, 7.5, 15.3 Hz, 1H), 2.25 (dt, *J* = 6.3, 14.0 Hz, 1H), 2.13 (m, *J* = 6.3, 8.1 Hz, 2H), 1.91 (ddq, *J* = 6.8, 7.5, 14.4 Hz, 1H), 1.79 (ddd, *J* = 2.9, 3.3, 14.1 Hz, 1H), 1.11 (d, *J* = 7.4 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 112.6 (CH), 82.3 (CH), 80.6 (CH), 55.5 (CH_3), 52.2 (CH), 42.3 (CH), 41.9 (CH), 40.5 (CH_2), 18.8 (CH_3), 13.7 (CH_3) ppm; ***Elem Anal***: Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.45; H, 9.85.

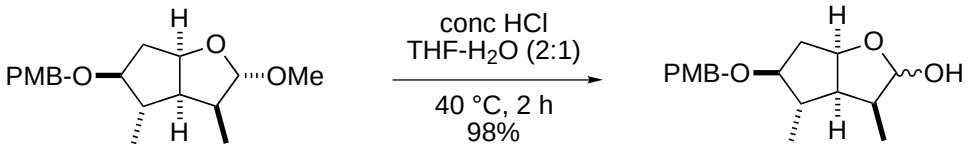
For alcohol ***regio*-11**: **TLC**: R*f* 0.50 (EtOAc-hexane, 7:3, $KMnO_4$); **IR** (NaCl): 3464, 2933, 2830, 1458, 1376, 1196, 1100, 1044, 969 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 4.68 (d, *J* = 3.8 Hz, 1H), 3.78 (dd, *J* = 6.2, 11.2 Hz, 1H), 3.37 (s, 3 H), 2.67 (dd, *J* = 5.8, 14.0 Hz, 1H), 2.41 (qd, *J* = 7.4, 3.8 Hz, 1H), 2.26 (m, 1H), 2.13 (dd, *J* = 8.1, 14.4 Hz, 1H), 1.82 (d, *J* = 7.8 Hz, 1H), 1.53 (ddd, *J* = 5.2, 6.5, 14.6 Hz, 1H), 1.31 (d, *J* = 7.4 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 113.0 (CH), 83.2 (CH), 80.5 (CH), 55.8 (CH_3), 50.4 (CH), 42.9 (CH), 42.6 (CH), 37.5 (CH_2), 19.5 (CH_3), 13.3 (CH_3) ppm.



11 **12**

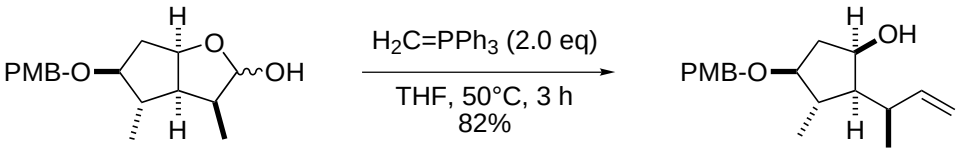
(1*R*,3*S*,4*S*,5*R*,6*S*,7*S*)-3-methoxy-4,6-dimethyl-7-[4-methoxybenzyloxy]-2-oxabicyclo[3.3.0]-octane (12): Sodium hydride (2.0 eq, 6.3 mmol) was washed with hexane to remove mineral oil under N_2 atmosphere. A catalytic amount of tetrabutylammonium iodide (0.1 eq, 0.315 mmol, 116.3 mg) was added together with 15 mL of DMF. The suspension was stirred at 0 °C and treated with alcohol **11** (587 mg, 3.15 mmol) dissolved in 8 mL of dry THF. Reaction was stirred at 0 °C for 40 min followed by the addition of *p*-methoxybenzyl chloride (3.0 eq, 9.45 mmol, 1.48 g). Reaction was allowed to warm-up to room temperature and stirred for 40 h. Reaction was diluted with 150 mL of ether and treated with 50 ml of sat. sodium bicarbonate. Aqueous

layer was back extracted with ether (2 x 50 mL). Combined organic layers were treated with brine and dried over sodium sulfate. Solvent was removed under reduced pressure and the oily residue was purified in a silica gel column (4.5 x 16 cm). Elution of the column with a mixture of EtOAc-hexane (1:4) gave the product as a colorless oil: yield 867 mg (90%); **TLC**: R_f 0.27 (EtOAc-hexane, 1:4, $KMnO_4$); **IR** (NaCl): 2960, 2932, 2835, 1612, 1513, 1462, 1248, 1100, 1035, 821 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.64 (d, *J* = 3.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.40 (dt, *J* = 6.8, 4.4 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 3.8 (s, 3H), 3.42 (dt, *J* = 8.4, 7.1 Hz, 1H), 3.35 (s, 3H), 2.35 (dt, *J* = 13.6, 7.0 Hz, 1H), 2.27 (ddd, *J* = 3.6, 7.3, 14.7 Hz, 1H), 2.09 (m, 1H), 1.95 (m, *J* = 6.5 Hz, 1H), 1.67 (ddd, *J* = 4.4, 8.4, 13.0 Hz, 1H), 1.07 (d, *J* = 7.4 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 159.3 (C), 130.92 (C), 129.4 (2CH), 113.9 (2CH), 112.6 (CH), 86.5 (CH), 81.0 (CH), 71.6 (CH_2), 55.6 (CH_3), 55.4 (CH_3), 50.8 (CH), 42.0 (CH), 39.6 (CH), 37.9 (CH_2), 18.4 (CH_3), 13.6 (CH_3) ppm. ***Elem Anal***: Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.16; H, 8.48.



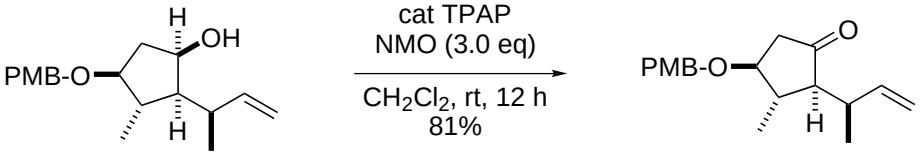
12 **13**

(1*R*,3*RS*,4*S*,5*R*,6*S*,7*S*)-4,6-dimethyl-7-[4-methoxy-benzyloxy]-2-oxabicyclo[3.3.0]-octan-3-ol (13): Methylacetal **12** (34.3 mg, 0.11 mmol) was dissolved in 2.0 mL of THF and 1.0 mL of water. A catalytic amount of *conc* HCl (0.1 mL) was added and reaction was stirred at 40 ^oC until TLC showed no more starting material left (aprox 2h). Reaction was diluted with 30 mL of ether and treated with 20 mL of sat. aq. sodium bicarbonate. Aqueous layer was back extracted with ether (3 x 20 mL) and EtOAc (2 x 15 mL). Combined organic layers were washed with brine and dried over sodium sulfate. Solvent was removed under reduced pressure. No further purification was needed for the product which was obtained as an oil: yield 32 mg (98%); **TLC**: R_f 0.26 (EtOAc-hexane, 1:1, $KMnO_4$); **^{1}H-NMR** for major stereoisomer ($CDCl_3$): δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.08 (br s, 1H); 4.78 (d, *J* = 9.2 Hz, 1H), 4.64 (m, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.63 (dt, *J* = 2.5, 6.0 Hz, 1H), 2.50-1.90 (m, 4H), 1.66 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 10.96 (d, *J* = 7.3 Hz, 3H); **^{13}C-NMR** for major stereoisomer ($CDCl_3$): 159.5 (C), 129.7 (2CH), 129.5 (C), 114.0 (2CH), 102.5 (CH), 88.3 (CH), 85.6 (CH), 70.9 (CH_2), 55.4 (CH_3), 53.6 (CH), 42.2 (CH), 40.0 (CH), 38.7 (CH_2), 21.7 (CH_3), 10.7 (CH_3) ppm. ***Elem Anal***: Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.75; H, 8.46.



13 **14**

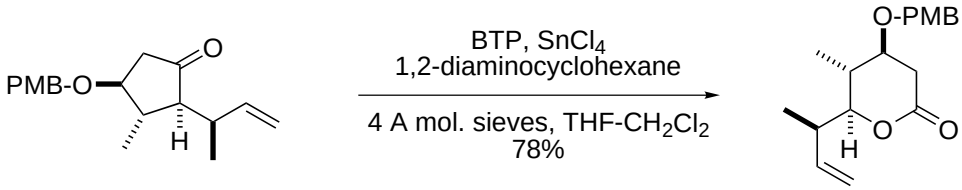
(1*R*,2*S*,3*S*,4*S*)-2-(3*S*-butenyl)-4-[4-methoxy-benzyloxy]-3-methyl-cyclopentanol (14): To a well stirred suspension of methyltriphenylphosphonium bromide (2.0 eq, 1.38 g, 3.87 mmol) in 15 mL of freshly distilled THF (distilled from potassium) mantained at –78 ^{o}C was added MeLi (2.0 eq, 3.87 mmol, 1.4M soln in ether). Temperature was gradually increased to 25^{o}C and ylide was stirred for 30 min. The light yellow solution was recooled and treated with lactol **18** (566.9 mg, 1.93 mmol) dissolved in 4 mL of freshly distilled THF. Reaction was gradually warmed-up to room temperature and then it was placed in an oil bath at 50^{o}C for 12h. Reaction was diluted with 100 mL of ether and washed with 50 mL of water. Aqueous layer was back extracted with ether (3 x 30 mL). Combined organic layers were treated with brine and dried over sodium sulfate. Solvent was removed *in vacuo* and the residue was purified in a silica gel column (3.5 x 13.5 cm). Elution of the column with a mixture of EtOAc-hexane (2:8) gave the product as a colorless oil: yield 460 mg (82%); **TLC**: R_f 0.26 (EtOAc-hexane, 1:9, $KMnO_4$); **IR** (NaCl): 3510, 3072, 2955, 2867, 2836, 1612, 1513, 1462, 1248, 1099, 1074, 1036, 826 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.75 (ddd, *J* = 9.0, 10.0, 17.1 Hz, 1H), 5.04 (ddd, *J* = 2.1, 0.7, 17.0 Hz, 1H), 4.93 (dd, *J* = 2.1, 10.0 Hz, 1H), 4.42 (s, 2H), 4.18 (dt, *J* = 4.2, 10.6 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, *J* = 0.7, 4.8 Hz, 1H), 2.93 (d, *J* = 10.8 Hz, 1H), 2.42 (m, *J* = 6.6, 13.0 Hz, 1H), 2.09 (dd, *J* = 0.7, 14.4 Hz, 1H), 2.01 (q, *J* = 7.2 Hz, 1H), 1.74 (dt, *J* = 4.5, 14.4 Hz, 1H), 1.11 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 159.3 (C), 144.5 (CH), 130.2 (C), 129.3 (2CH), 114.0 (2CH), 113.0 (CH_2), 88.7 (CH), 75.6 (CH), 70.3 (CH_2), 59.1 (CH), 55.4 (CH_3), 42.8 (CH), 40.2 (CH), 38.6 (CH_2), 21.3 (CH_3), 19.8 (CH_3) ppm. ***Elem Anal***: Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.14; H, 9.21.



14 **15**

(2*S*,3*S*,4*S*)-2-(3*R*-butenyl)-3-methyl-4-[4-methoxy-benzyloxy]-cyclopentanone (15): Alcohol **14** (268.9 mg, 0.92 mmol) was dissolved in 10 mL of freshly distilled dichloromethane (distilled from CaH). 4Å molecular sieves, *N*-methylmorpholine-*N*-oxide (3.0 eq, 325.4 mg, 2.77 mmol) and a catalytic amount of tetrapropylammonium

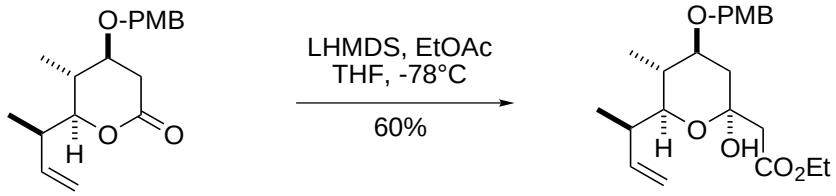
perruthenate (aprox 10 mg) were added and reaction was stirred overnight at room temperature. Reaction was diluted with 100 mL of dichloromethane and filtered thru a short path of celite and fluorosil. Solvent was removed *in vacuo* and the residue was purified in a silica gel column (2.5 x 10 cm). Elution of the column with a mixture of EtOAc-hexane (1:9) gave the product as a colorless oil: yield 214 mg (81%); **TLC**: R_f 0.32 (EtOAc-hexane, 1:9, $KMnO_4$); **IR** (NaCl): 3072, 2962, 2933, 2903, 2871, 1739, 1612, 1513, 1463, 1248, 1096, 820 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.78 (ddd, *J* = 7.7, 10.0, 17.5 Hz, 1H), 5.01 (broad d, *J* = 4.4 Hz, 1H), 4.97 (broad s, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.66 (q, *J* = 7.5 Hz, 1H), 2.72 (m, *J* = 7.1 Hz, 1H), 2.63 (ddd, *J* = 1.1, 6.9, 18.1 Hz, 1H), 2.20 (m, *J* = 6.8, 10.2 Hz, 1H), 2.13 (dd, *J* = 8.3, 18.1 Hz, 1H), 1.80 (ddd, *J* = 1.0, 4.4, 10.2 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): 215.5 (C), 159.4 (C), 141.1 (CH), 130.2 (C), 129.3 (2CH), 114.7 (CH_2), 113.9 (2CH), 80.5 (CH), 71.8 (CH_2), 60.8 (CH), 55.3 (CH_3), 45.2 (CH_2), 39.8 (CH), 37.2 (CH), 18.5 (CH_3), 17.4 (CH_3) ppm. ***Elem Anal***: Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.25; H, 8.53.



15 **16**

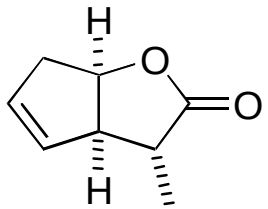
(3*S*,4*R*,5*S*)-6-(3*S*-butenyl)-4-(4-methoxy-benzyloxy)-5-methyl-tetrahydro-pyran-2-one (16): To a mixture of molecular sieves (4Å, 100 mg) and 0.12 mL of a 0.5 M solution of *trans*-1,2-diaminocyclohexane (in THF) in 3 mL of CH_2Cl_2 was added 0.06 mL of 1.0 M solution of $SnCl_4$ (in THF). The resulting white suspension was cooled to 0 °C and 0.38 mL of 1.0 M solution of of bis(trimethylsilyl) peroxide (in CH_2Cl_2) was added. Reaction mixture was stirred for 10 min and then ketone **15** (55 mg, 0.19 mmol) in 3.0 mL of CH_2Cl_2 was added at 0 °C. Reaction was stirred at room temperature for 30 h. Solid sodium sulfite was added and suspension stirred for 1 h. The mixture was filtered through a short path of silica and washed with ethyl acetate. Solvent was removed *in vacuo* and the residue was purified in a silica gel column (1 x 10 cm). Elution of the column with a mixture of EtOAc-hexane (1:4) gave ketone **15** (14.4%) and the product as a colorless oil: yield 46 mg (78%); **TLC**: R_f 0.31 (EtOAc-hexane, 3:7, $KMnO_4$); **IR** (NaCl): 2972, 2936, 1744, 1613, 1514, 1248 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.93 (ddd, *J* = 7.6, 10.0, 17.3 Hz, 1H), 5.05 (broad d, *J* = 4.4 Hz, 1H), 4.97 (broad s, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 3.86 (dd, *J* = 2.8, 10.0 Hz, 3H), 3.80 (s, 3H), 3.48 (dd, *J* = 6.5, 1.0 Hz, 1H), 2.83 (dd, *J* =

5.5, 16.9 Hz, 1H), 2.59 (dd, *J* = 6.5, 16.9 Hz, 1H), 2.50 (m, *J* = 2.8, 6.8, 7.6 Hz, 1H), 1.94 (m, *J* = 6.8, 7.1, 10.0 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): δ 170.8 (CO), 159.5 (C), 140.7 (CH), 129.7 (C), 129.5 (2CH), 115.3 (CH_2), 114.0 (2CH), 85.2 (CH), 76.1 (CH), 70.7 (CH_2), 55.4 (CH_3), 39.4 (CH), 37.0 (CH), 35.6 (CH_2), 14.7 (CH_3), 12.6 (CH_3) ppm. ***Elem Anal***: Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.95; H, 8.16.



16 **17**

[(2*S*,4*S*,5*R*,6*S*)-6-(3*R*-butenyl)-4-(4-methoxy-benzyloxy)-5-methyl-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (17): A well stirred solution of LHMDS (0.93 mL, 1M in THF) in 5 mL of THF was cooled to -78 °C, and added ethyl acetate (0.9 mL, 0.93 mmol) in THF (1 mL). The reaction mixture was stirred for 45 min at -78 °C. Lactone **16** (237 mg, 0.77 mmol) dissolved in 2 mL of THF was added to the ester enolate. Reaction was stirred for 1 h at -78 °C, and temperature was slowly increased to 0 °C. The reaction mixture was diluted with Et_2O and treated with brine solution. The aqueous layer was back extracted with Et_2O (4X10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed *in vacuo* and the residue was purified in a silica gel column (3.5 x 13.5 cm). Elution of the column with a mixture of EtOAc-hexane (1:9) gave the product as a solid: yield 180 mg (60% yield); **mp** 56-58 °C **TLC**: R_f 0.35 (EtOAc-hexane, 1:4, $KMnO_4$); **IR** (NaCl): 3473, 2977, 1708, 1515, 1254, 1176, 1027 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.82 (ddd, *J* =7.2, 10.2, 17.4 Hz, 1H), 4.96 (dt, *J* = 1.3, 17.4 Hz, 1H), 4.91 (ddd, *J* = 0.9, 1.7, 10.3 Hz, 1H), 4.74 (d, *J* = 2.4 Hz, 1H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.37 (d, *J* = 10.9 Hz, 1H),4.18 (dq, *J* = 7.1, 10.8 Hz, 2H), 3.80 (s, 3H), 3.61 (dd, *J* = 2.2, 10.4 Hz, 1H), 3.52 (dt, *J* = 4.6, 10.5 Hz, 1H), 2.62 (d, *J* = 14.8 Hz, 1H), 2.58 (d, *J* = 14.8 Hz, 1H),2.40 (dt, *J* = 1.0, 7.1 Hz, 1H), 2.32 (dd, *J* = 6.8, 7.1, 10.0 Hz, 1H), 1.54 (m, *J* = 6.5, 10.2 Hz, 1H),1.32 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): δ 172.2 (CO), 159.4 (C), 143.1 (CH), 130.94 (C), 129.5 (2CH), 114.0 (2CH), 113.1 (CH_2), 96.2 (C), 77.2 (CH), 76.4 (CH), 71.1 (CH_2), 61.1 (CH_2), 51.5 (CH_3), 45.4 (CH_2), 40.4 (CH_2), 38.8 (CH), 38.0 (CH), 14.4 (CH_3), 12.6 (CH_3), 12.1 (CH_3) ppm. ***Elem Anal***: Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.47; H, 8.37.



6

7 6 5 4 3 2 1 PPM

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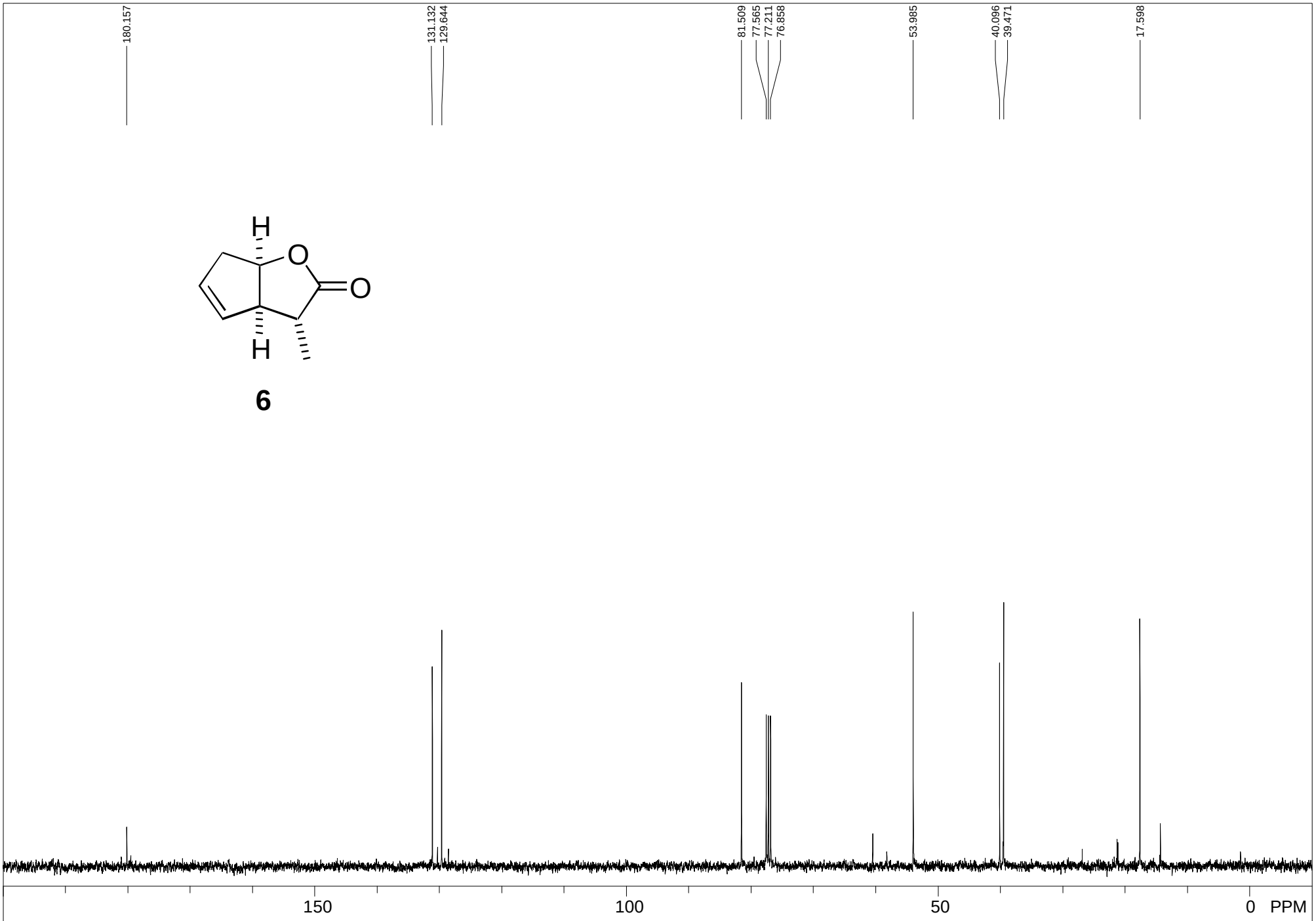

C-13 CDCL3 WM-360 USER: -- DATE: 09/08/99

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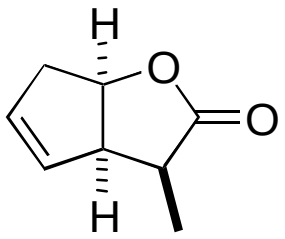

7

endo-methyl bicyclic lactone

USER: -- DATE: 16/08/99

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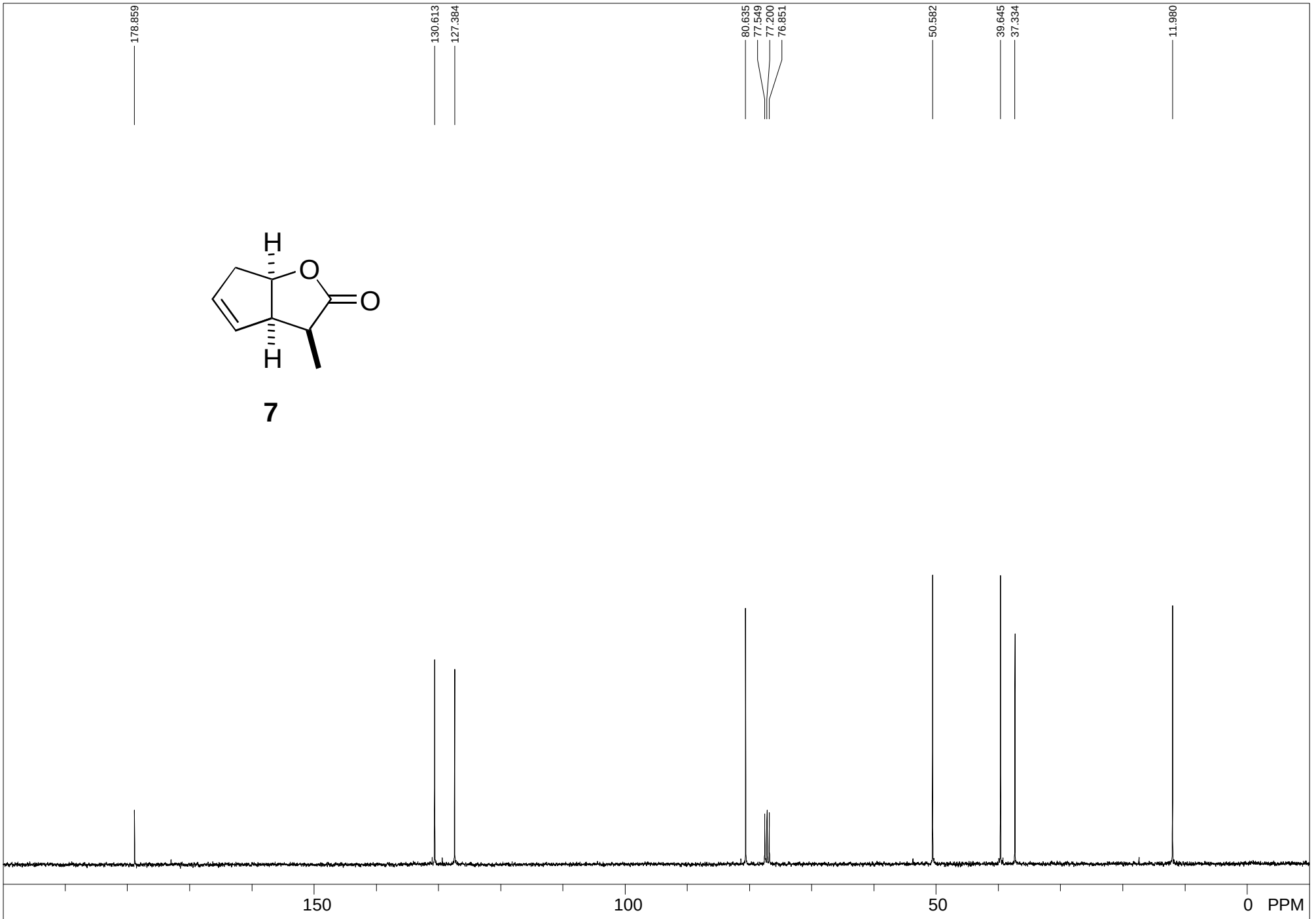

endo-methyl bicyclic lactone

USER: -- DATE: 16/08/99

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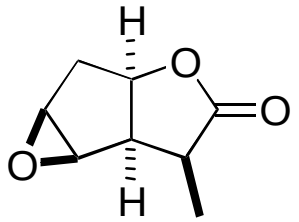

8

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 19/07/99

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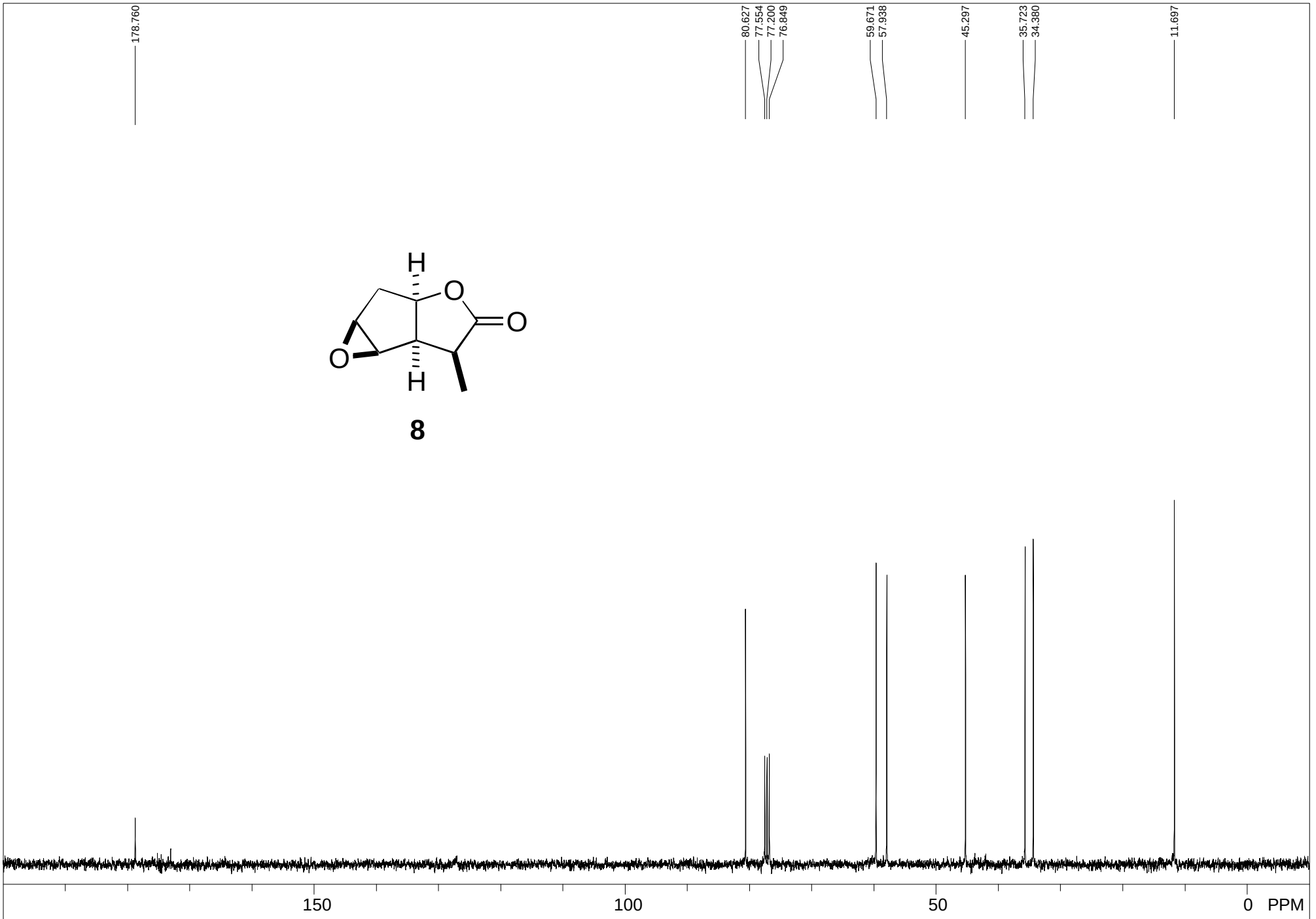

8

C-13 CDCL3 WM-360 USER: -- DATE: 23/08/99

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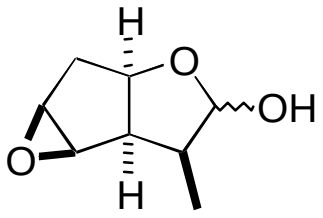

9

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 13/09/99

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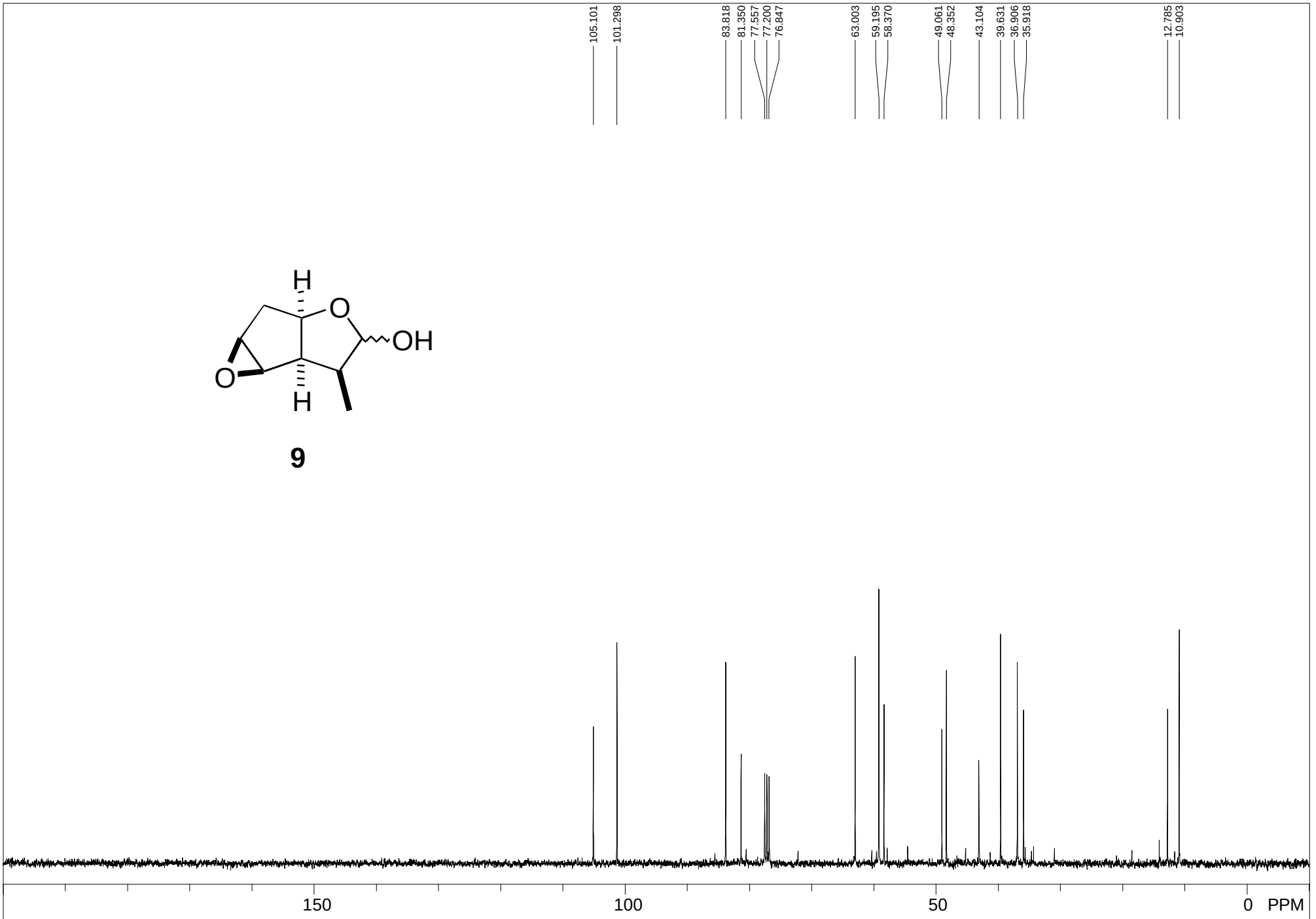

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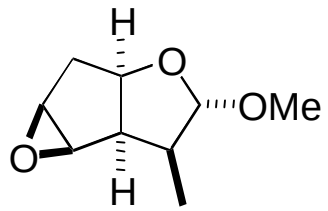

10

7 6 5 4 3 2 1 PPM

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 17/01/00

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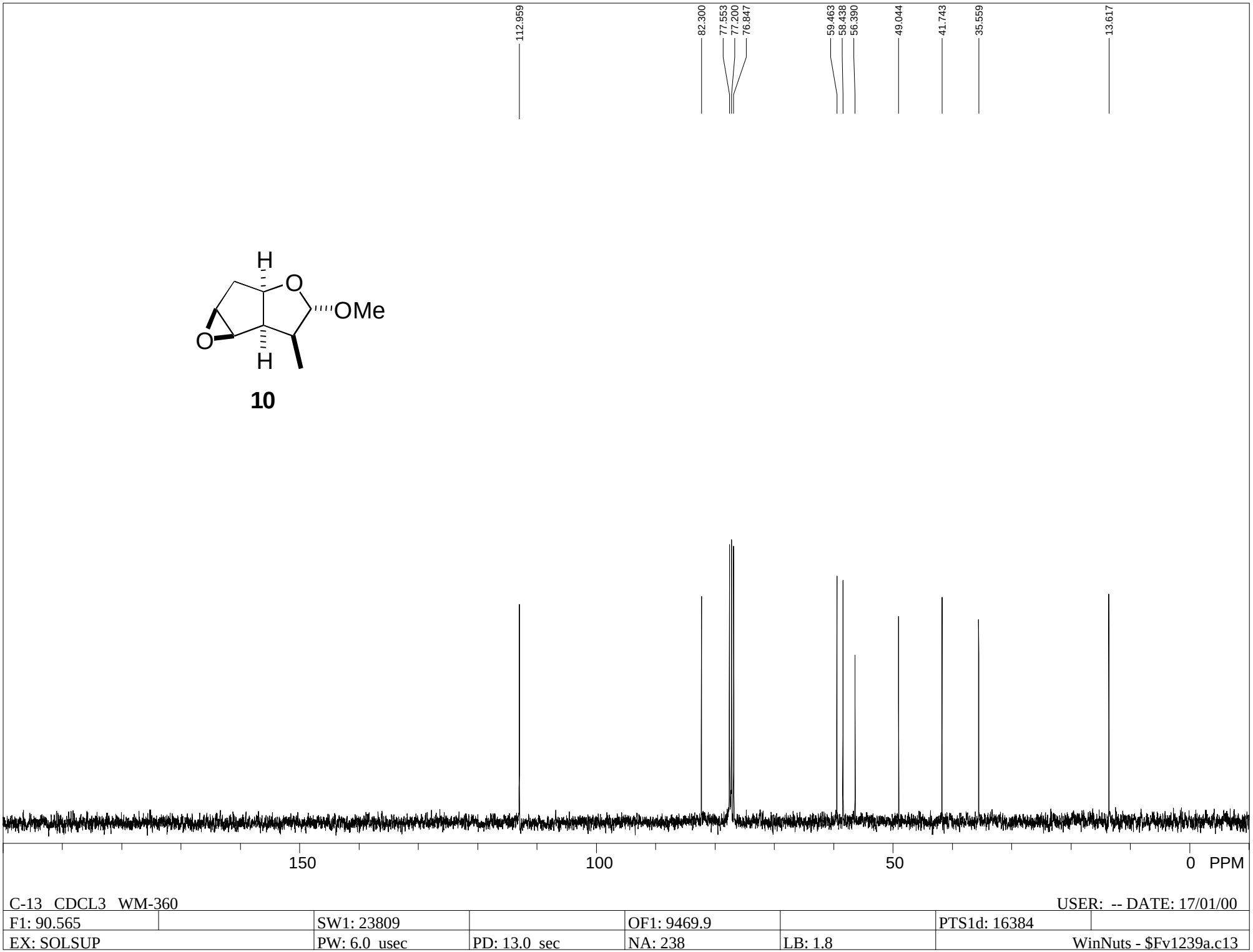

10

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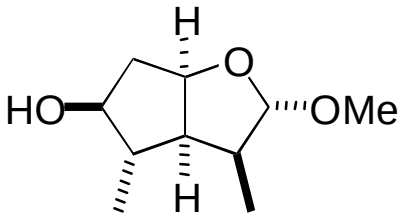

11

7 6 5 4 3 2 1 PPM

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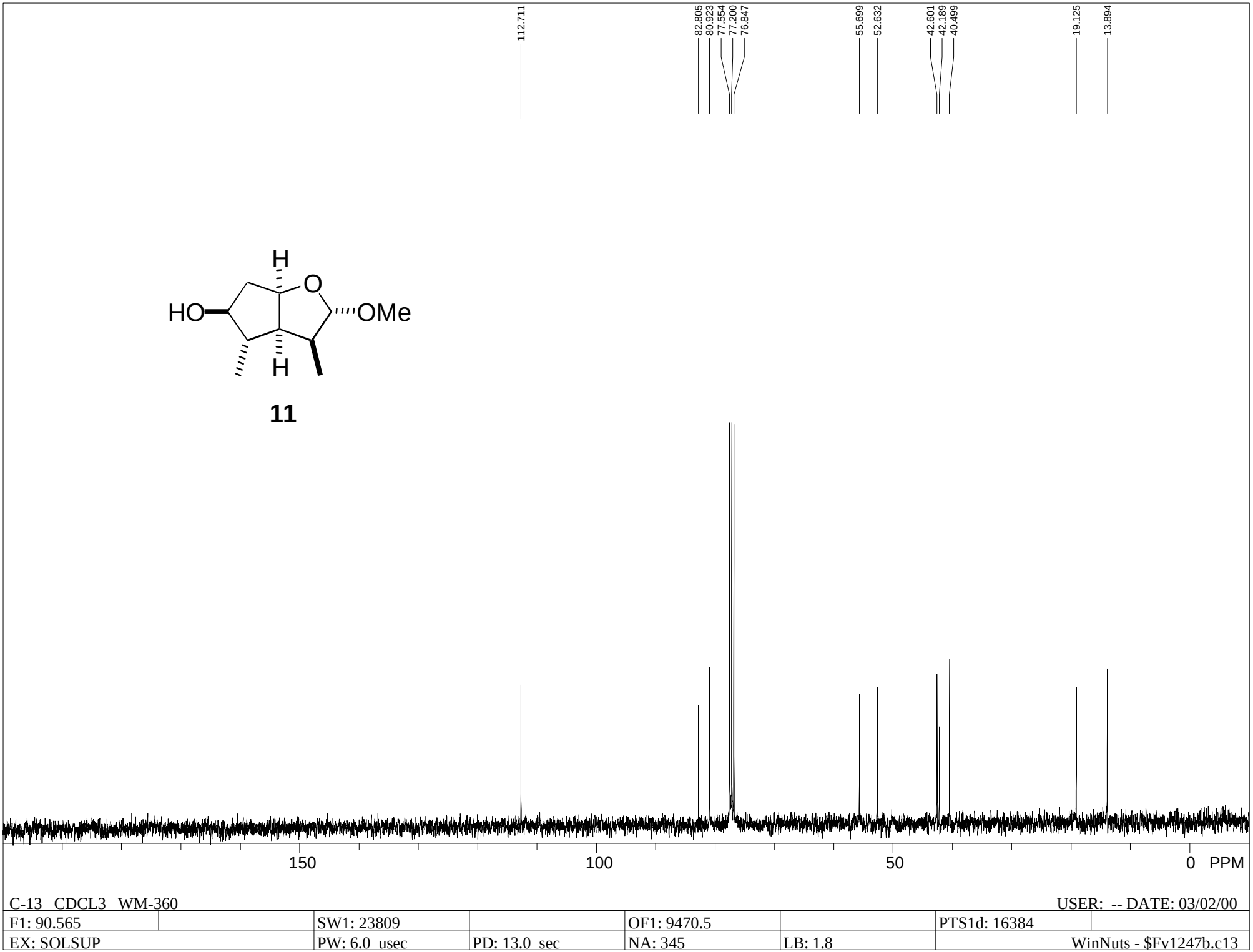

11

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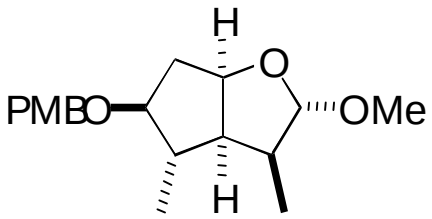

12

7 6 5 4 3 2 1 PPM

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 22/01/00

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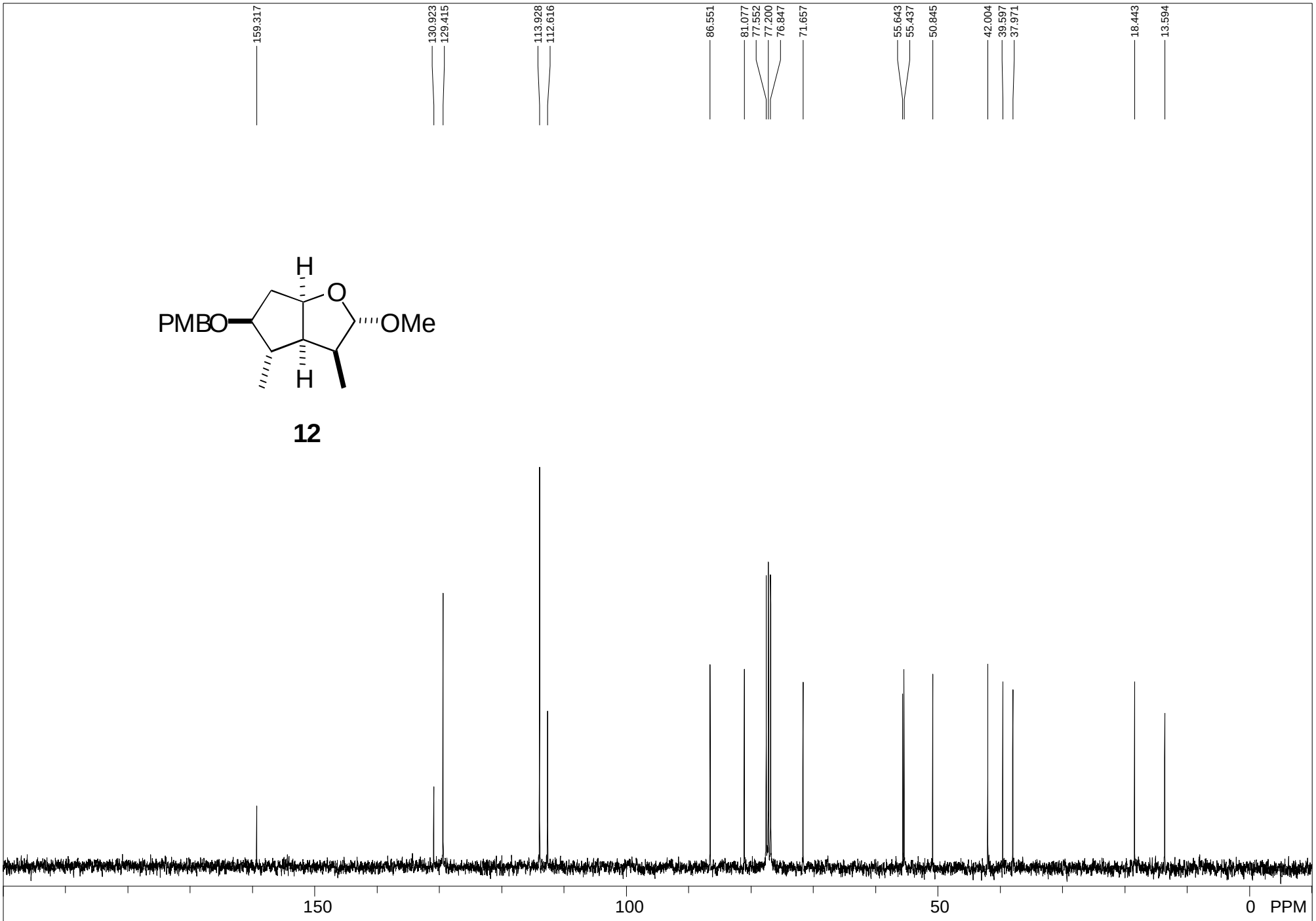

12

C-13 CDCL3 WM-360 USER: -- DATE: 22/01/00

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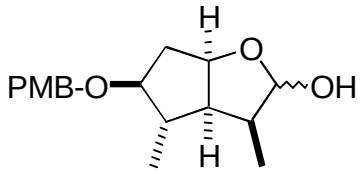

13

7 6 5 4 3 2 1 PPM

compound 13 USER: -- DATE: 27/01/00

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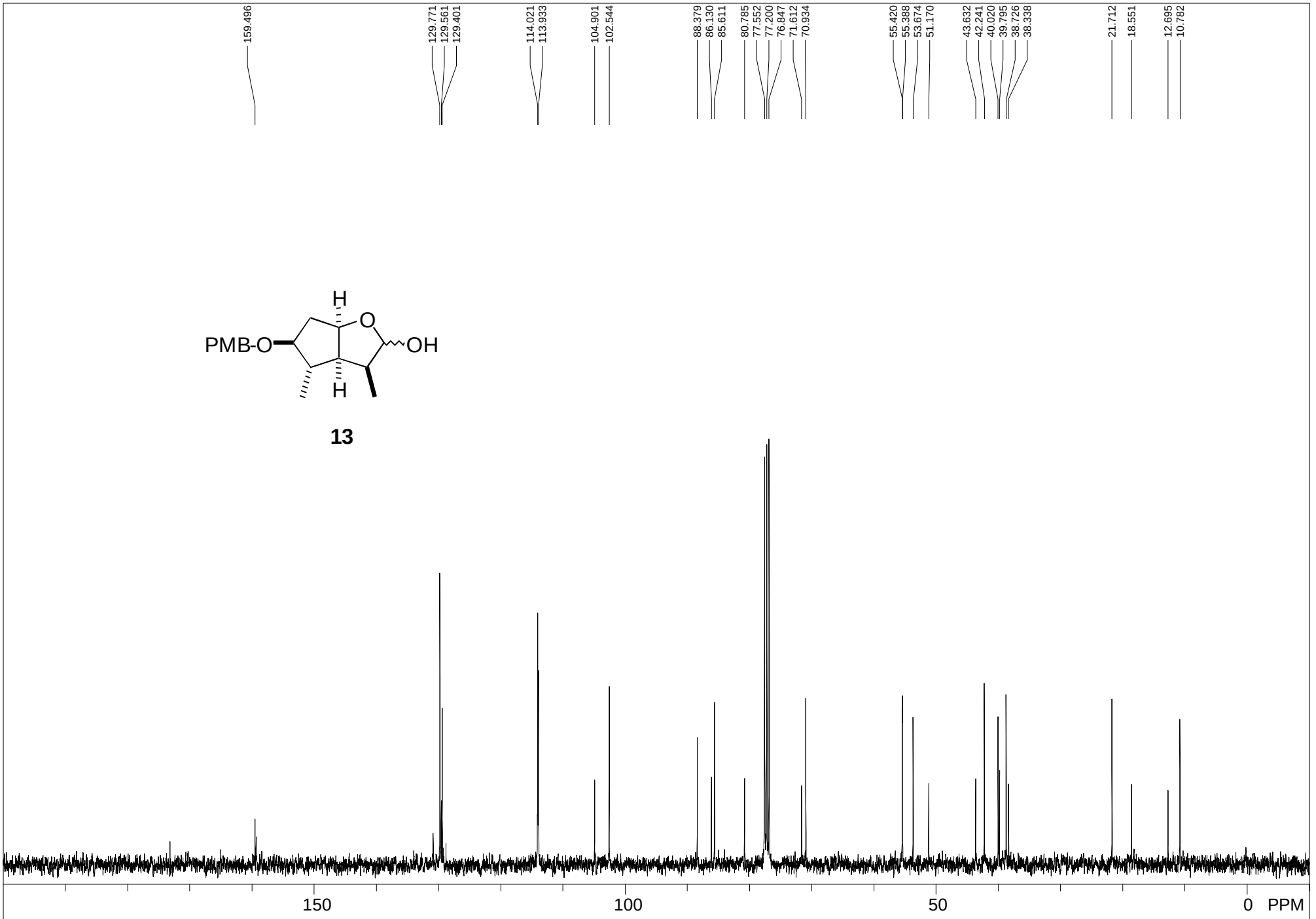

13

C-13 CDCL3 WM-360 USER: -- DATE: 10/02/95

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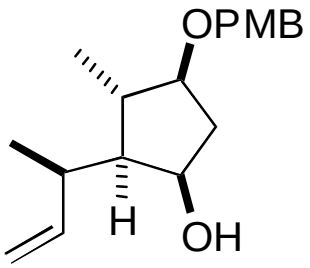
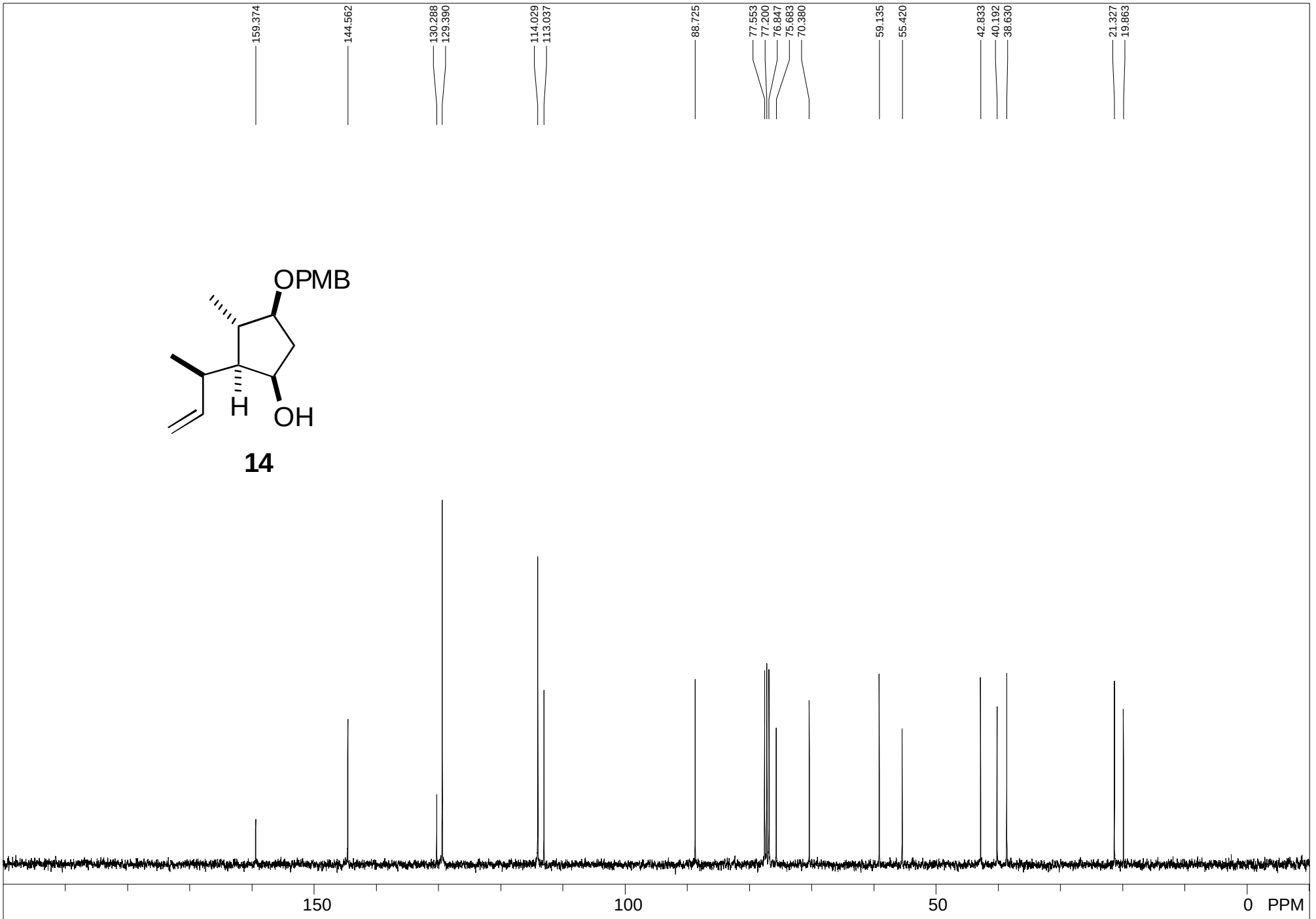


14

7 6 5 4 3 2 1 PPM

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 25/02/00

F1: 360.137	SW1: 7246		OF1: 2135.5		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Fv1271.h1



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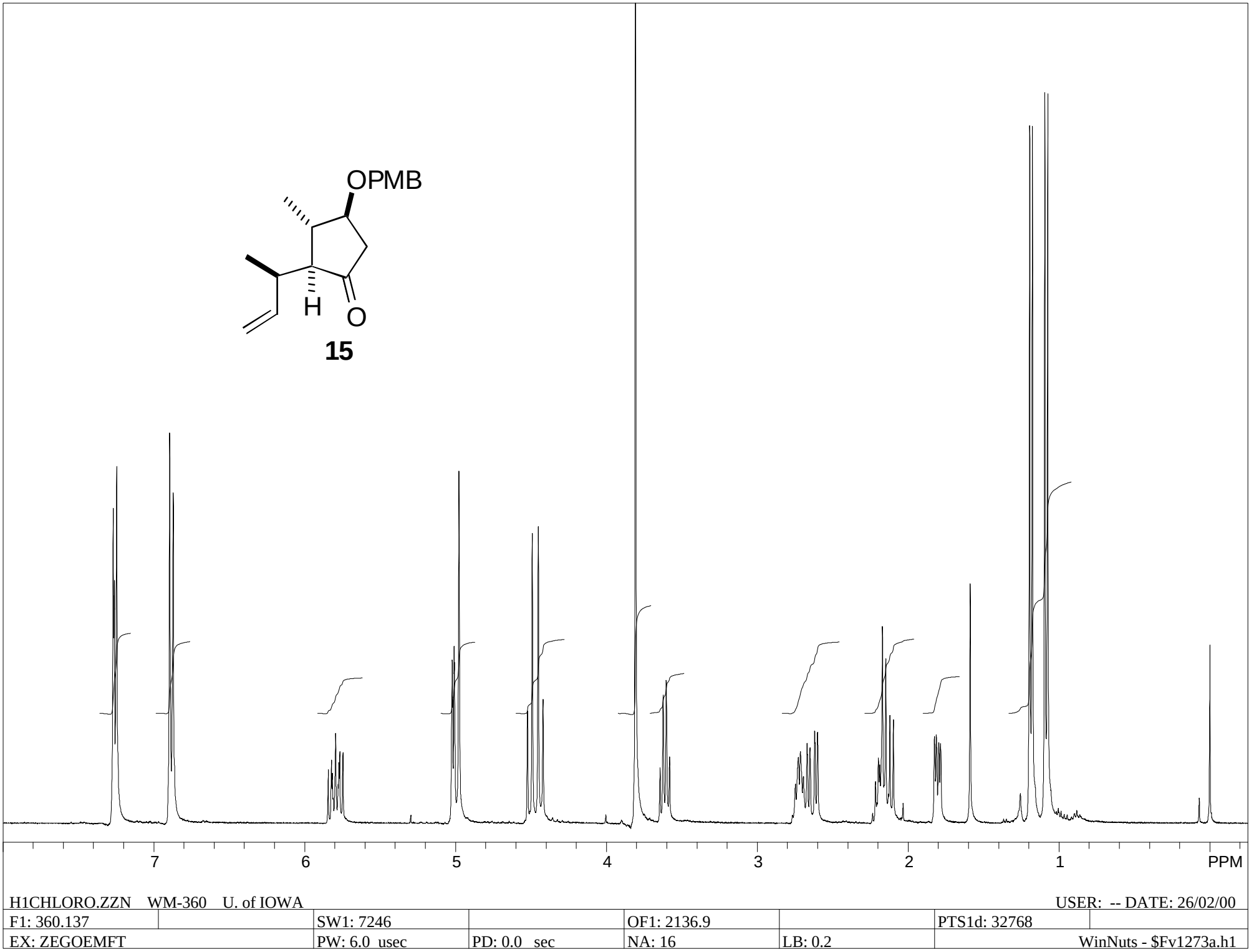
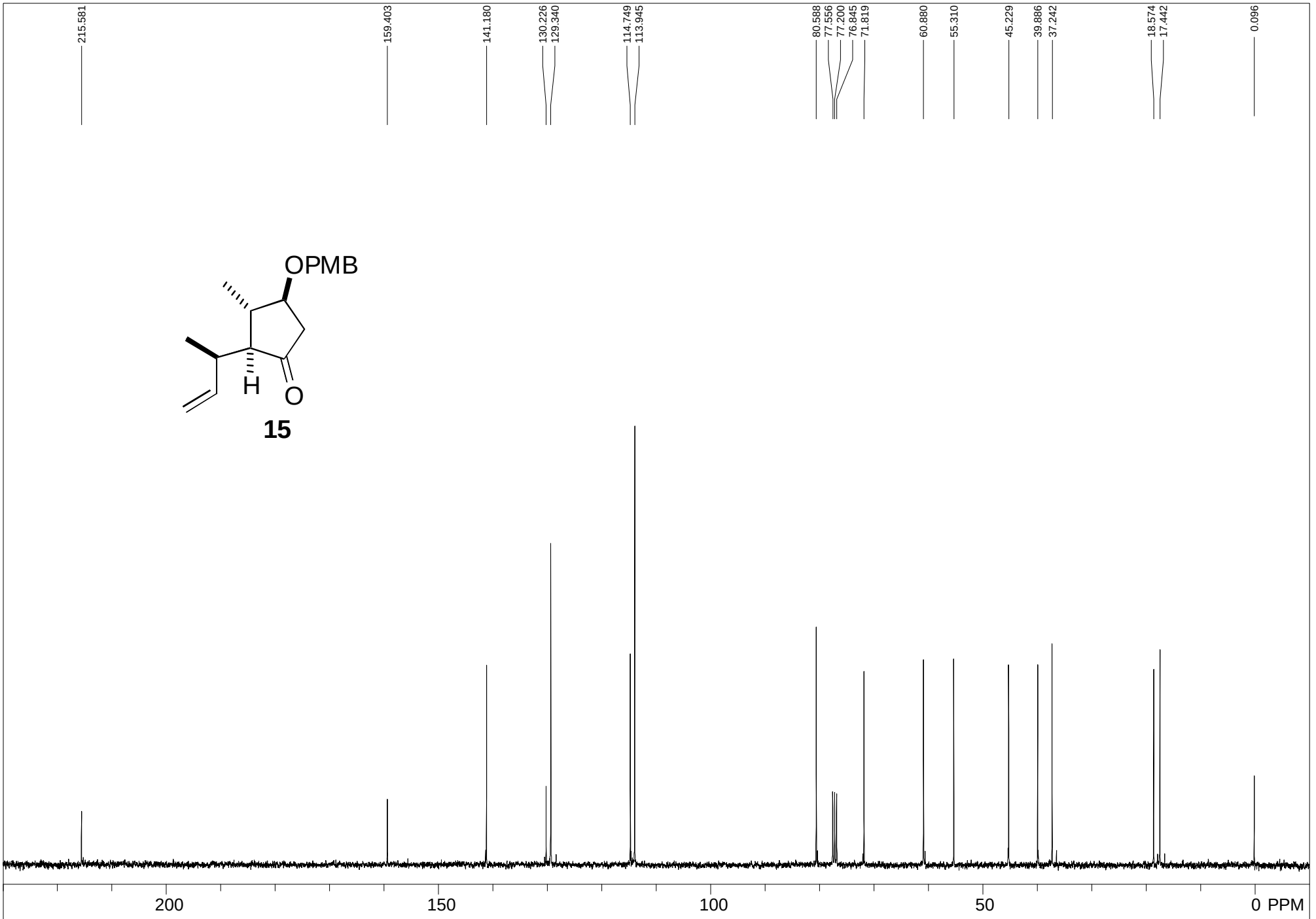
C-13 CDCL3 WM-360 USER: -- DATE: 25/02/00

F1: 90.565	SW1: 23809		OF1: 9468.0		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 335	LB: 1.8	WinNuts - $Fv1271a.c13



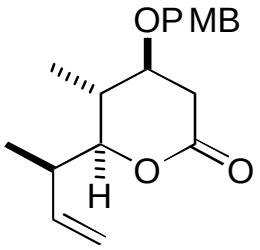
H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 26/02/00

F1: 360.137	SW1: 7246		OF1: 2136.9		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Fv1273a.h1



C-13 CDCL3 WM-360 USER: -- DATE: 03/03/00

F1: 90.565	SW1: 23809		OF1: 9460.3		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 199	LB: 1.8	WinNuts - $Fv1275a.c13



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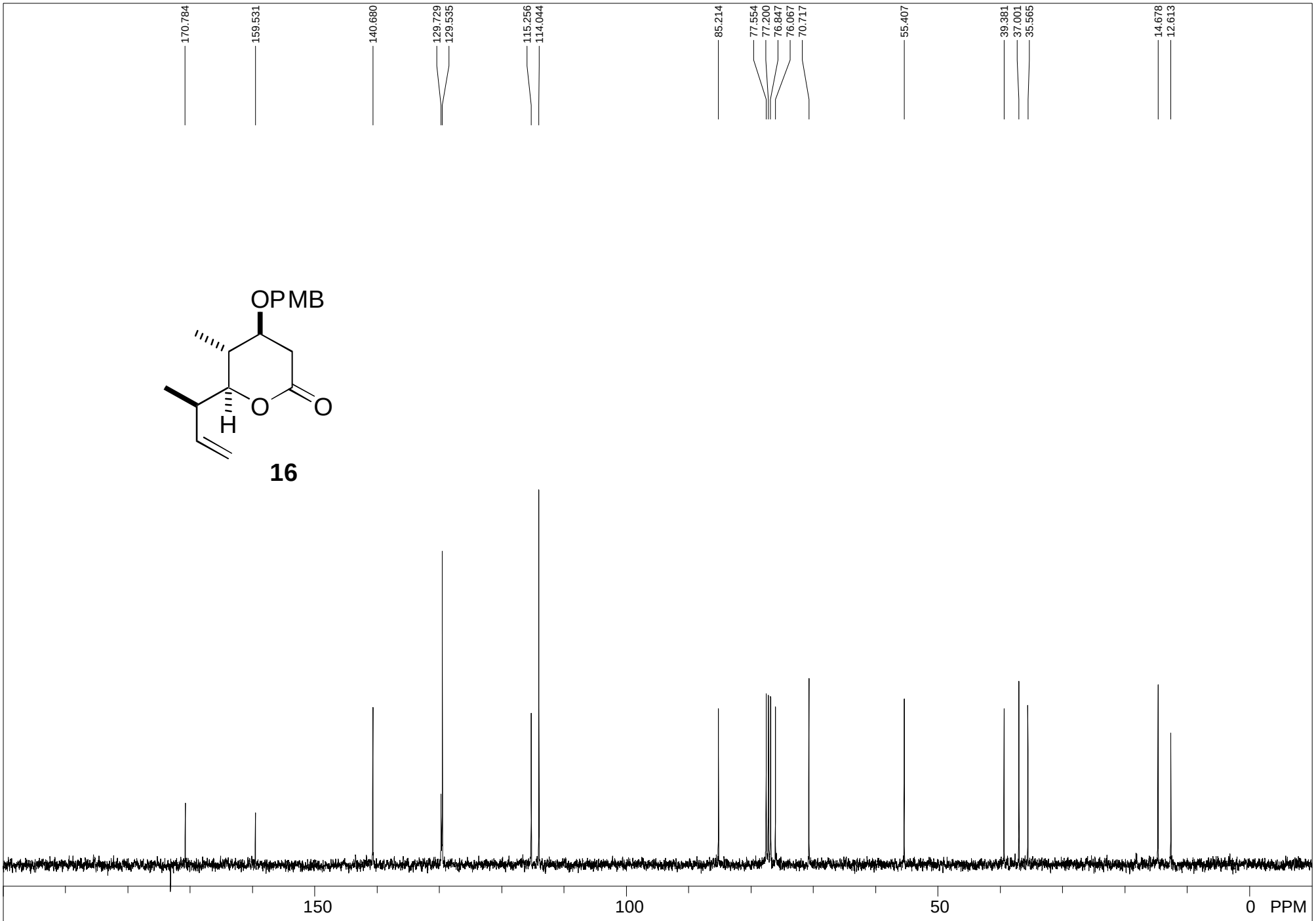
7 6 5 4 3 2 1 PPM

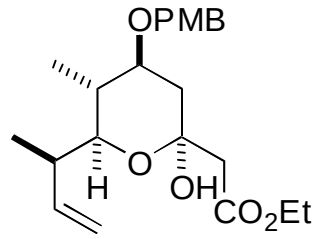
H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 21/03/00

F1: 360.137	SW1: 7246		OF1: 2139.4		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Fv1285b.h1



C-13 CDCL3 WM-360 USER: -- DATE: 21/03/00

F1: 90.565	SW1: 23809		OF1: 9464.4		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 200	LB: 1.8	WinNuts - $Fv1285b.c13

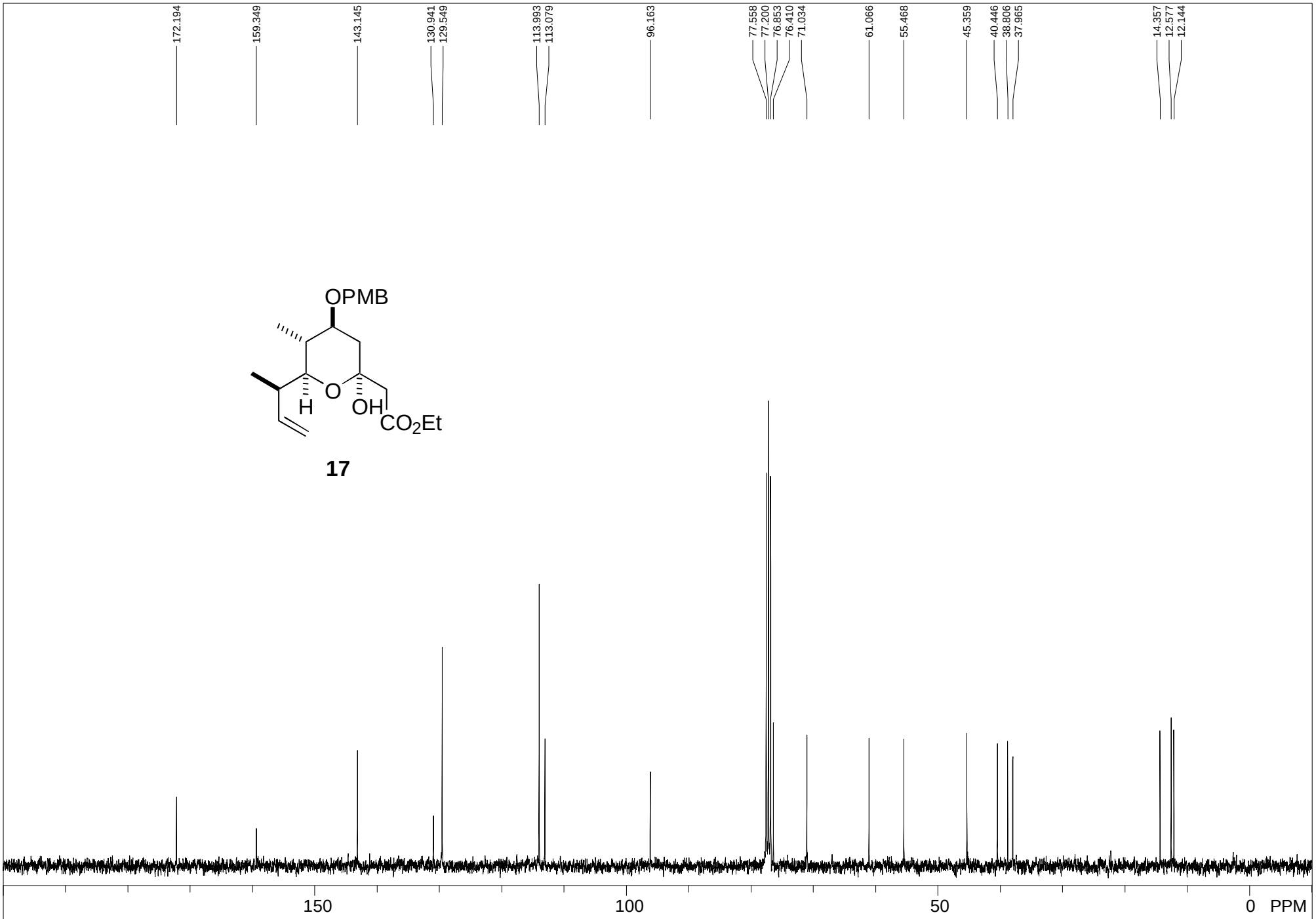


17

7 6 5 4 3 2 1 PPM

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 12/04/00

F1: 360.137	SW1: 7246		OF1: 2136.3		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Fv1299a.h1



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C-13 CDCL3 WM-360 USER: -- DATE: 12/04/00

F1: 90.565	SW1: 23809		OF1: 9470.1		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 640	LB: 1.8	WinNuts - $Fv1299a.c13