Synthetic Studies on the *trans*-Chlorocyclopropane Dienyne Side Chain of Callipeltoside-A

Horacio F. Olivo* Francisco Velázquez, and Henrique C. Trevisan

Division of Medicinal and Natural Products Chemistry, College of Pharmacy, and

The Center for Biocatalysis and Bioprocessing,

The University of Iowa, Iowa City, IA 52242

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 points were obtained in a Thomas Hoover Melting Point Apparatus. Melting points reported here are uncorrected. Optical rotations were measured with a Jasco P-1020 polarimeter. Analytical TLC was performed using pre-coated silica gel 60 F_{254} Merck plates.

***tert*-Butyl 2,2-dichlorocyclopropanecarboxylate (2):**

IR υ 2980, 1731, 1368, 1152 cm^{-1}. **^{1}H-NMR** ($CDCl_3$) δ 2.46 (1H, dd, *J* = 9.8, 7.3 Hz), 1.99 (1H, dd, *J* = 7.3, 7.3 Hz), 1.80 (1H, *J* = 9.8, 7.3 Hz), 1.50 (9H, s); **^{13}C-NMR** ($CDCl_3$) δ 165.6 (C), 82.4 (C), 57.5 (C), 34.1 (CH), 27.9 ($3CH_3$), 25.8 (CH_2).

2,2-Dichloro-hydroxymethyl-cyclopropane (3):

R_f = 0.25 (7:3, hexanes/ethyl acetate); **(+)-(*R*)-3:** $[\alpha]^{D}_{27}$ + 4.0 (*c* 1.0, $CHCl_3$); **IR** υ 3335, 2938, 2884, 1430, 1393, 1046 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 3.94 (1H, dd, *J* = 12.2, 5.3 Hz), 3.65, (1H, dd, *J* = 12.2, 8.7 Hz), 1.97 (1H, dddd, *J* = 10.5, 8.7, 7.7, 5.3 Hz), 1.76 (1H, br s), 1.66 (1H, dd, *J* = 10.5, 7.2 Hz), 1.29 (1H, dd, *J* = 7.6, 7.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 62.6 (CH_2), 59.8 (C), 31.8 (CH), 24.7 (CH_2).

***trans*-(*1S,2R*)-2-Chloro-1-hydroxymethyl-cyclopropane (4):**

R_f = 0.3 (7:3, hexanes/ethyl acetate); **(+)-4:** $[\alpha]^{D}_{27}$ + 58 (*c* 1.0, $CHCl_3$); **IR** υ 3334, 2878, 1443, 1271, 1030 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 3.60 (1H, dd, *J* = 12, 6 Hz), 3.51 (1H, dd, *J* = 12, 7 Hz), 2.92 (1H, ddd, *J* = 7.1, 3.6, 3.5 Hz), 1.52 (1H, dddd, *J* = 13, 9.7, 6.4, 3.2 Hz), 1.03 (1H, ddd, *J* = 9.9, 6.3, 3.6 Hz), 0.91 (1H, ddd, *J* = 7.2, 6.5, 6.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 63.5 (CH_2), 30.8 (CH), 24.3 (CH), 13.4 (CH_2).

Enzymatic Resolution of Alcohol **3**:

Dichlorocyclopropyl methanol (**3**), vinyl propionate and petroleum ether were conditioned by adding 10% w/w $Na_2SO_4 \cdot 10H_2O$ and equilibrating overnight to adjust water activity (a_W) to 0.80 (Zacharis, E.; Omar, I.; Partridge, J.; Robb, D. A.; Halling, P. J.; Selection of Salt Hydrate Pairs for Use in Water Control in Enzyme Catalysis in Organic Solvents. *Biotechnology and Bioengineering* **1997**, *55*, 367-374). Lipase from *Candida antarctica* (CAL 435 from Novo Nordisk, 248 mg) was washed with petroleum ether (3 X 1 mL) before adding the reagents. Vinyl propionate (4.38 g, 43.8 mmol) and dichlorocyclopropyl methanol (**3**) (5.18 g, 36.7 mmol) were added to the lipase. The reaction flask was cooled to 0 °C and stirred at 320 rpm. Reaction was monitored by GC analysis. Samples (1 μL) were diluted with 20 μL of acetone and analyzed for conversion and enantiomeric excess on a Chiraldex G-TA capillary column.

When the enantiomeric excess of the non-reacting alcohol reached above 95%, the reaction was stopped by decanting the liquid into a round bottom flask and washing the enzyme with petroleum ether. This enzyme was used several times. A typical reaction profile was 56% conversion and an enantiomeric excess of 74% for the ester product. Solvents were removed under vacuum in a rotavap. The residue was partitioned between 50 mL of methanol-water (1:1) and 25 mL of petroleum ether in a separating funnel. The organic layer was washed with methanol-water (3 X 30 mL). Evaporation of the solvent from the organic layer gave 4.43 g of propionyl ester **5**. Aqueous phases were combined and extracted with petroleum ether (3 X 25 mL). Solvent was removed by distillation using a Vigreaux column, and the water residue was extracted with ethyl acetate (3 X 25 mL). Evaporation of the organic solvent in rotavap gave 1.98 g of alcohol **(+)-3**.

Propionic acid 2,2-Dichlorocyclopropylmethane ester (5):

IR υ 2984, 2945, 1740, 1463, 1181 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 4.33 (1H, dd, *J* = 12, 6 Hz), 4.08 (1H, dd, *J* = 12, 8.5 Hz), 2.39 (2H, q, *J* = 7.6 Hz), 2.0 (1H, m), 1.70 (1H, dd, *J* = 10.5, 7.2 Hz), 1.32 (1H, dd, *J* = 7.5, 7.5 Hz), 1.17 (3H, t, *J* = 7.6 Hz); **^{13}C-NMR** ($CDCl_3$) δ 174.4 (CO), 63.8 (CH_2), 59.4 (C), 28.8 (CH), 27.6 (CH_2), 25.3 (CH_2), 9.2 (CH_3).

Formyl-*trans*-chlorocyclopropane (6):

^{1}H-NMR ($CDCl_3$) δ 9.59 (1H, d, J = 3 Hz), 3.45 (1H, ddd, *J* = 7.7, 5, 3 Hz), 2.37 (1H, ddd, *J* = 12.1, 6, 3 Hz), 1.71 (1H, ddd, *J* = 7.5, 6, 6 Hz), 1.50 (1H, ddd, *J* = 9.4, 6, 5 Hz); **^{13}C-NMR** ($CDCl_3$) δ 198.1 (C), 34.2 (CH), 31.9 (CH), 19.2 (CH_2).

***trans*-2-Chloro-(2',2'-dibromoethynyl)-cyclopropane (7):**

R_f = 0.6 (pentane); **IR** υ 1790, 1280, 938, 782 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 5.84 (1H, d, *J* = 9.0 Hz), 3.10 (1H, ddd, *J* = 7.5, 4.3, 3.1 Hz), 2.03 (1H, dddd, *J* = 9.6, 9.1, 6.3, 3.1 Hz), 1.37 (1H, ddd, *J* = 9.9, 6.6, 4.4 Hz), 1.15 (1H, ddd, *J* = 7.3, 6.4, 6.4 Hz); **^{13}C-NMR** ($CDCl_3$) δ 137.1 (CH), 89.7 (C), 33.0 (CH), 26.0 (CH), 17.5 (CH_2).

***trans*-2-Chlorocyclopropyl acetylene (8):**

^{1}H-NMR ($CDCl_3$) δ 3.18 (1H, m), 1.94 (1H, d, *J* = 2.2 Hz), 1.66 (1H, m), 1.27 (2H, m); **^{13}C-NMR** ($CDCl_3$) δ 83.2 (C), 66.7 (CH), 33.8 (CH), 18.8 (CH_2), 11.0 (CH).

(*E*)-Chloro-4-*trans*-chlorocyclopropyl-but-3-ynene (12):

R_f = 0.5 (pentane); **^{1}H-NMR** ($CDCl_3$) δ 6.46 (1H, d, *J* = 13.7 Hz), 5.86 (1H, dd, *J* = 13.7, 1.9 Hz), 3.17 (1H, m), 1.77 (1H, m), 1.29 (2H, m); **^{13}C-NMR** ($CDCl_3$) δ 130.3 (CH), 113.7 (CH), 91.7 (C), 73.8 (C), 34.2 (CH), 19.3 (CH_2), 11.9 (CH).

(*E*)-*trans*-Chlorocyclopropyl-pent-4-yn-2-enol (13):

R_f = 0.27 (7:3, hexanes/ethyl acetate); **IR** υ 3335, 2864, 2220, 1431, 1257, 1094 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 6.18 (1H, dt, J = 16, 5.3 Hz), 5.68 (1H, ddd, *J* = 16, 3.7, 1.7 Hz), 4.19 (2H, d, *J* = 5.4 Hz), 3.18 (1H, m), 1.78 (1H, m), 1.45 (1H, br s), 1.28 (2H, dd, *J* = 9.2, 6.1 Hz); **^{13}C-NMR** ($CDCl_3$) δ 141.7 (CH), 110.2 (CH), 89.6 (C), 786.6 (C), 62.8 (CH_2), 34.3 (CH), 19.2 (CH_2), 11.9 (CH).

(*E,E*)-*trans*-Chlorocyclopropyl-hepta-6-yn-2,4-dienol (14):

R_f = 0.2 (4:1, hexanes/ethyl acetate); **IR** υ 3361, 3025, 2868, 2213, 1681, 1257 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 6.53 (1H, dd, *J* = 15.5, 10.9 Hz), 6.28 (1H, dd, *J* = 15.3, 10.9 Hz), 5.90 (1H, ddd, *J* = 15.3, 5.3, 5.3 Hz), 5.53 (1H, d, *J* = 15.7 Hz), 4.20 (2H, d, *J* = 5.1 Hz), 3.18 (1H, m), 2.14 (1H, br s), 1.80 (1H, m), 1.29 (2H, m); **^{13}C-NMR** ($CDCl_3$) δ 141.0 (CH), 135.0 (CH), 129.8 (CH), 111.3 (CH), 91.5 (C), 77.8 (C), 62.8 (CH_2), 34.4 (CH), 19.4 (CH_2), 12.2 (CH).

***trans*-Chlorocyclopropylacetylene trimethylstannane (15):**

^{1}H-NMR ($CDCl_3$) δ 3.16 (1H, ddd, *J* = 7.6, 4.1, 3.5 Hz), 1.69 (1H, ddd, *J* = 9.7, 6.3, 3.3 Hz), 1.25 (1H, dd, *J* = 6.1, 6.1 Hz), 1.19 (1H, ddd, *J* = 10.3, 5.7, 4.4 Hz), 0.25 (9H, s); **^{13}C-NMR** ($CDCl_3$) δ 108.8 (C), 81.9 (C), 34.5 (CH), 19.4 (CH_2), 12.5 (CH), -7.5 ($3CH_3$).

(*E,E*)-5-tributylstannyl-penta-2,4-dienoic acid ethyl ester (19):

R_f = 0.2 (95:5, hexanes/ethyl acetate); **IR** υ 2959, 1716, 1626, 1464, 1274 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 7.19 (1H, dd, *J* = 15.4, 10.3 Hz), 6.81 (1H, d, *J* = 18.8 Hz), 6.65 (1H, dd, *J* = 18.8, 10.2 Hz), 5.80 (1H, d, *J* = 15.5 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 1.6-1.4 (6H, m), 1.4-1.2 (6H, m), 1.1-0.8 (15H, m); **^{13}C-NMR** ($CDCl_3$) δ 167.6 (C), 147.3 (CH), 146.5 (CH), 144.4 (CH), 120.1 (CH), 60.4 (CH_2), 29.2 $3CH_2$), 27.4 ($3CH_2$), 14.5 (CH_3), 13.8 ($3CH_2$), 11.6 ($3CH_3$).

(*E,E*)-*trans*-Chlorocyclopropyl-hepta-2,4-dien-6-ynoic acid ethyl ester (20):

R_f = 0.34 (4:1, hexanes/ethyl acetate); **IR** υ 2982, 2210, 1713, 1625 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) δ 7.23 (1H, dd, *J* = 16, 12.1 Hz), 6.58 (1H, dd, *J* = 15.5, 11.4 Hz), 5.91 (1H, d, *J* = 15.4 Hz), 5.89 (1H, dd, *J* = 15.5, 2.1 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 3.21 (1H, m), 1.83 (1H, m), 1.34 (2H, m), 1.29 (3H, t, *J* = 7.2 Hz); **^{13}C-NMR** ($CDCl_3$) δ 166.7 (C), 143.1 (CH), 138.7 (CH), 123.0 (CH), 119.3 (CH), 96.0 (C), 77.5 (C), 60.7 (CH_2), 34.5 (CH), 19.6 (CH_2), 14.4 (CH_3), 12.3 (CH).

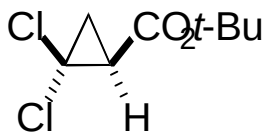
General procedure for the Stille coupling.

A solution of 1,1-dibromoolefin **7** (130 mg, 0.5 mmol) in degassed DMF (2 mL) was transferred by syringe to a 25 mL flask containing vinyl stannane (0.55 mmol) under N_2. *N,N*-Diisopropyl-*N*-ethyl-amine (130 mL, 0.75 mmol) was added by syringe. Tris(dibenzyledeneacetone)-dipalladium (11 mg, 0.012 mmol) and tris(4-methoxyphenyl)-phosphine (26 mg, 0.075 mmol) were added. The mixture was flushed with N_2 and heated to 80 °C. Reaction was monitored by TLC and stopped when no more dibromoolefin was observed. Reaction was diluted in ethyl acetate (20 mL) and filtered thru celite. Solids were washed with ethyl acetate (30 mL). The filtrate was partitioned between ethyl acetate and water (10 mL). The organic layer was washed with water (2 X 10 mL) and dried over MgSO4. The solvent was removed in vacuo and the resideu chromatographed on silica gel.

Synthetic Studies on the *trans*-Chlorocyclopropane Dienyne Side Chain of Callipeltoside-A

Horacio F. Olivo, Francisco Velázquez and Henrique C. Trevisan

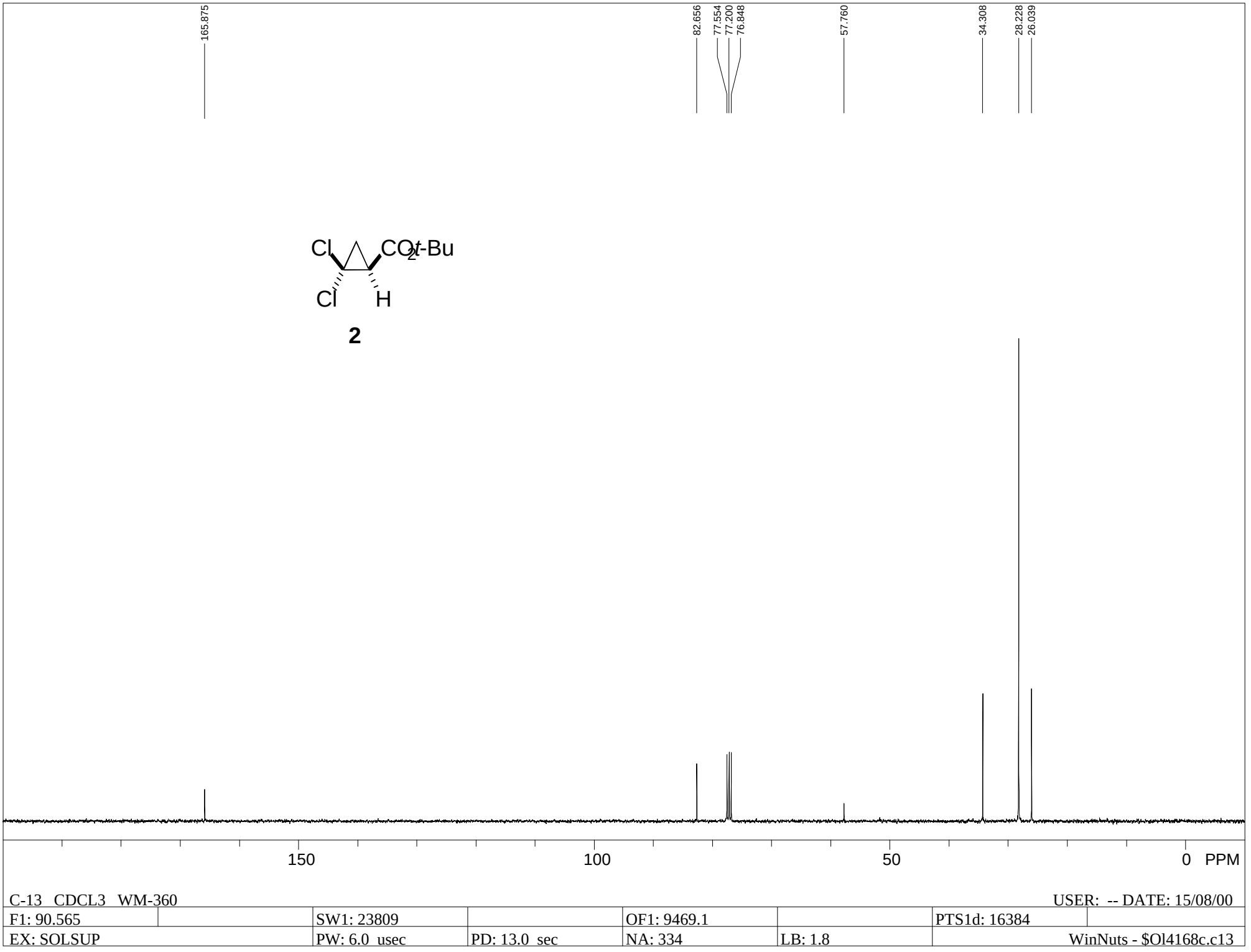
Selected ^{1}H- and ^{13}C-NMR Spectra



2

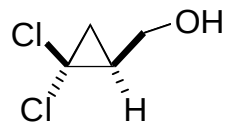
H1 WM-360 CDCl3 USER: -- DATE: 15/08/00

F1: 360.137	SW1: 7246		OF1: 2122.8		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Ol4168c.h1

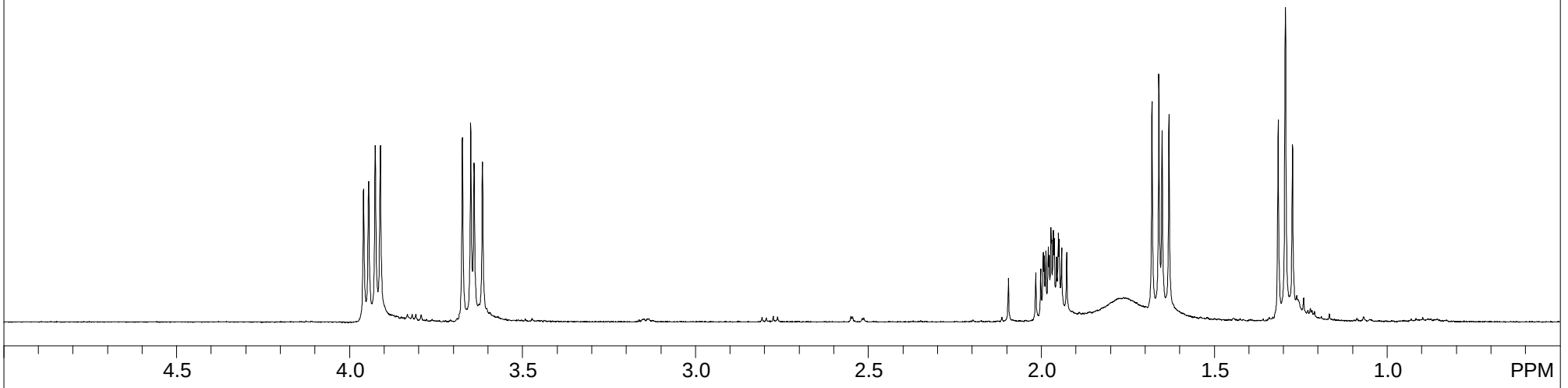


C-13 CDCL3 WM-360 USER: -- DATE: 15/08/00

F1: 90.565	SW1: 23809		OF1: 9469.1		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 334	LB: 1.8	WinNuts - $Ol4168c.c13

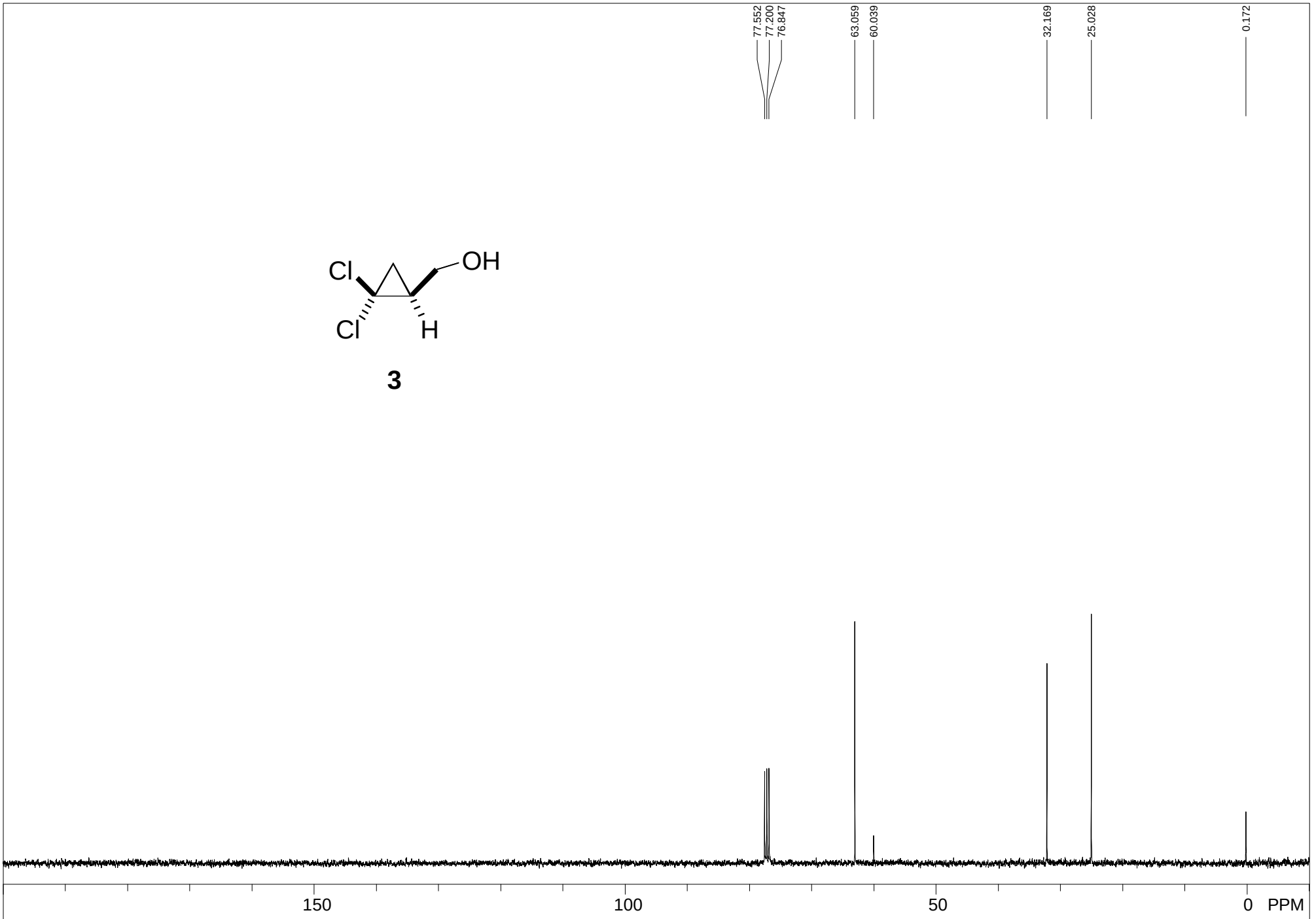


3



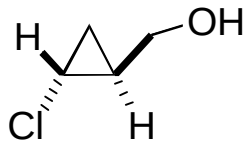
H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 21/12/99

F1: 360.137	SW1: 7246		OF1: 2137.6		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Ol3304c.h1

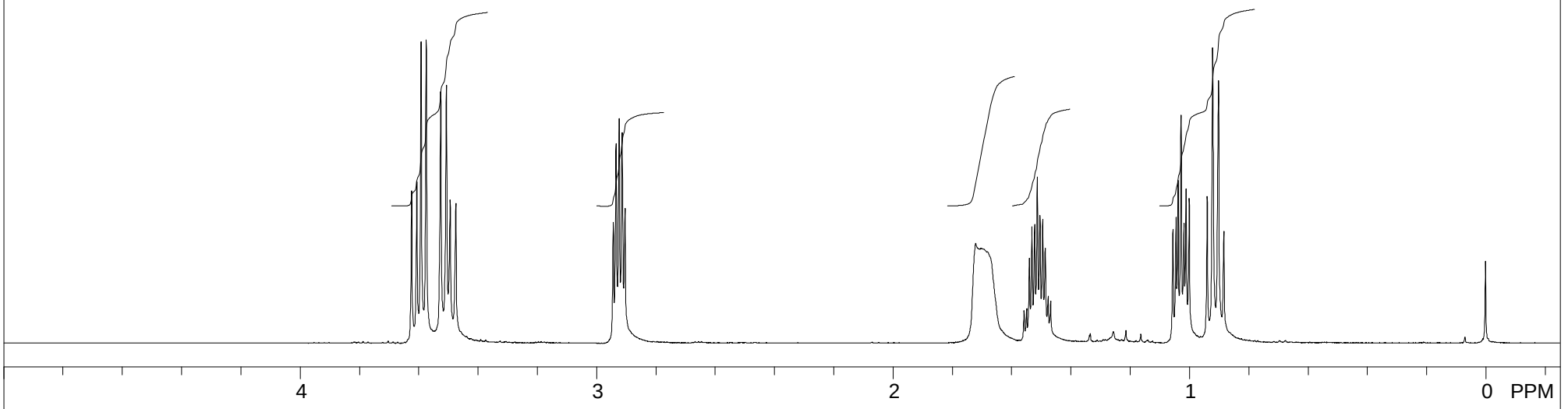


C-13 CDCL3 WM-360 USER: -- DATE: 21/12/99

F1: 90.565	SW1: 23809		OF1: 9468.6		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 200	LB: 1.8	WinNuts - $Ol3304c.c13

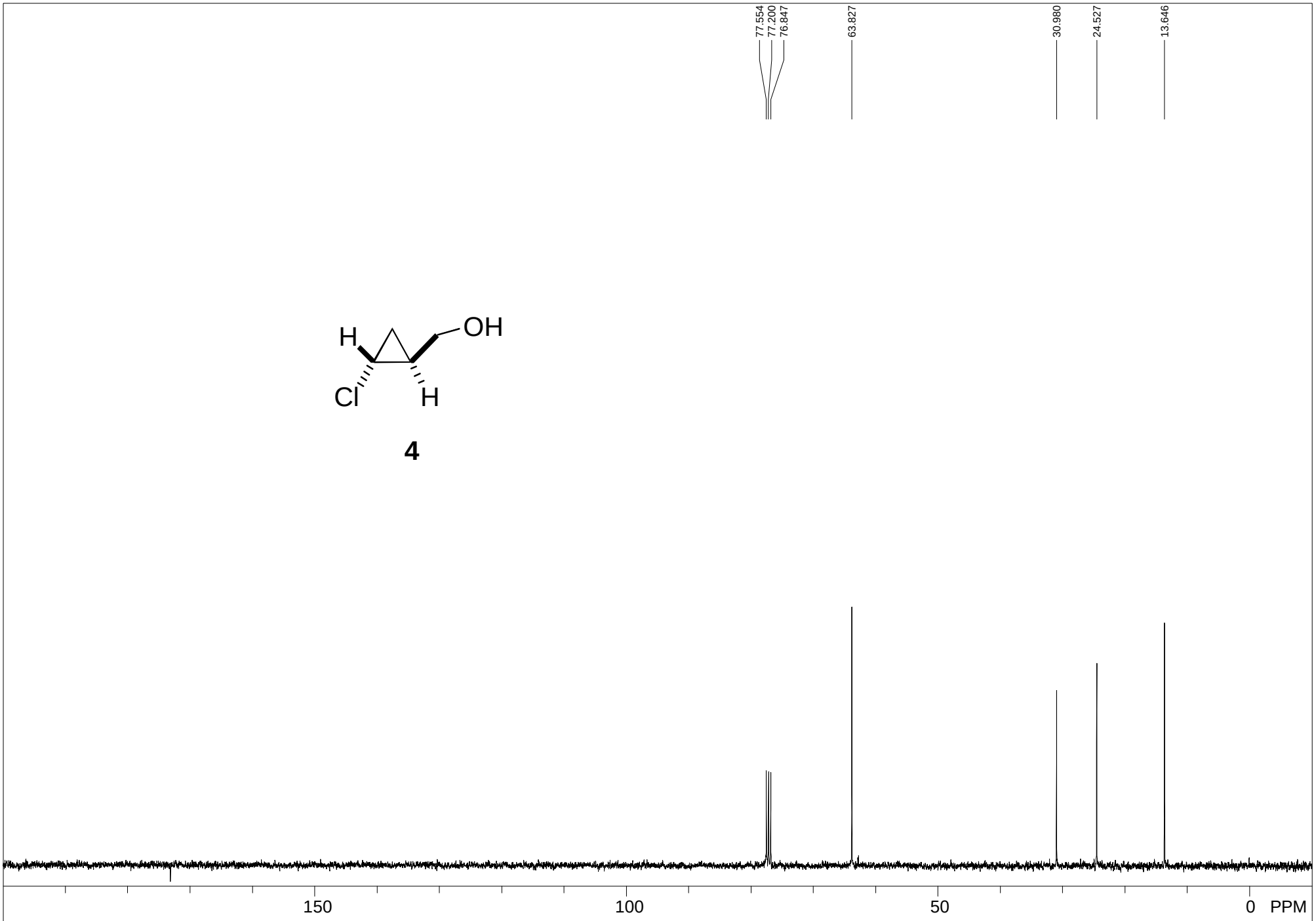


4



H1 WM-360 CDCl3 USER: -- DATE: 12/09/00

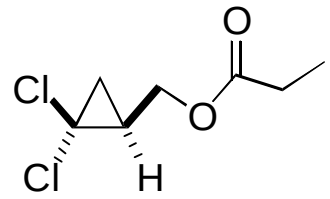
F1: 360.137	SW1: 7246		OF1: 2120.0		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	



4

C-13 CDCL3 WM-360 USER: -- DATE: 18/11/99

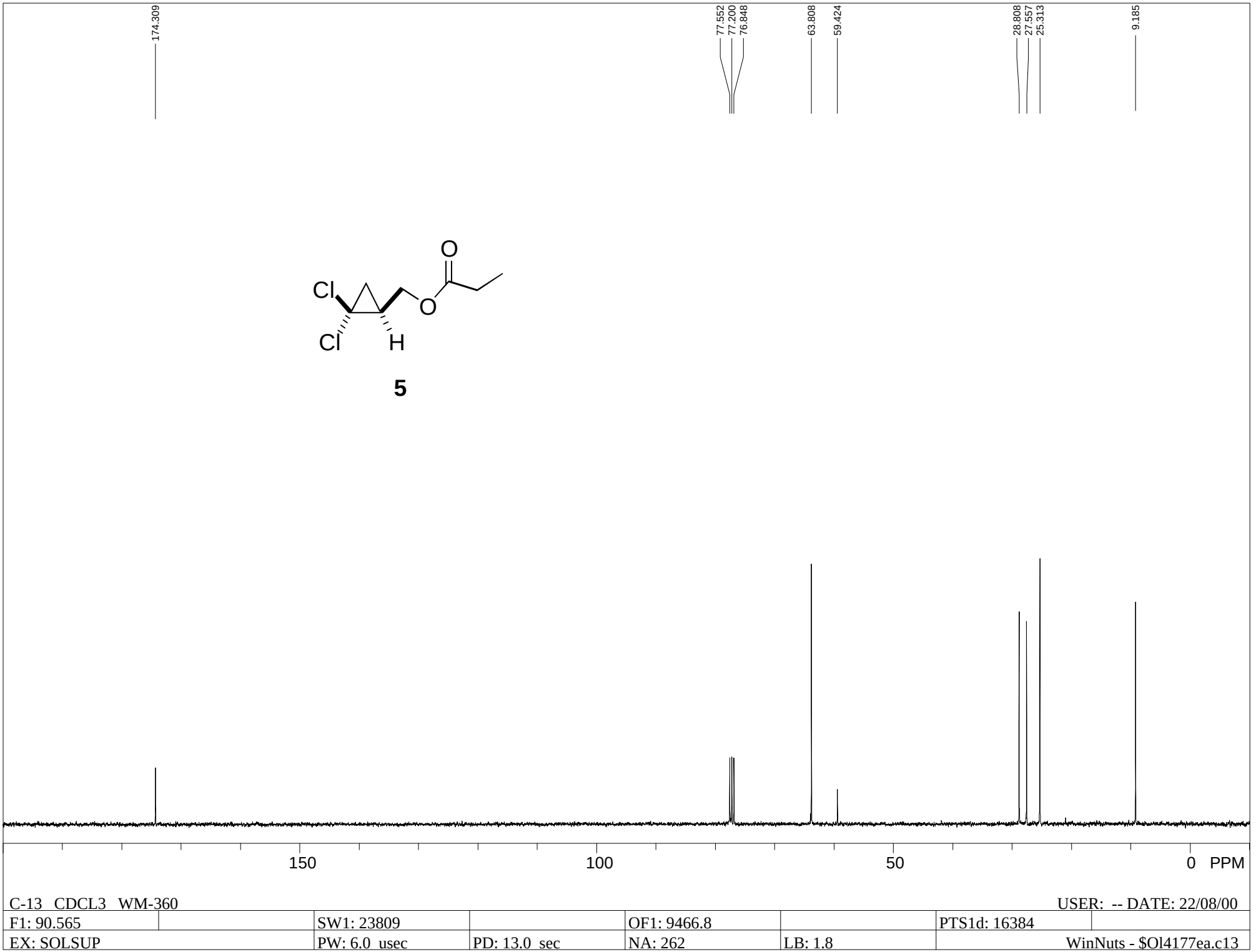
F1: 90.565	SW1: 23809		OF1: 9464.5		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 120	LB: 1.8	WinNuts - $Ol3272.c13



5

H1 WM-360 CDCl3 USER: -- DATE: 22/08/00

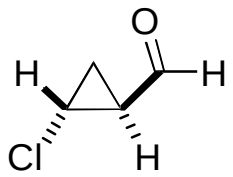
F1: 360.137	SW1: 7246		OF1: 2118.5		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Ol4177ea.h1



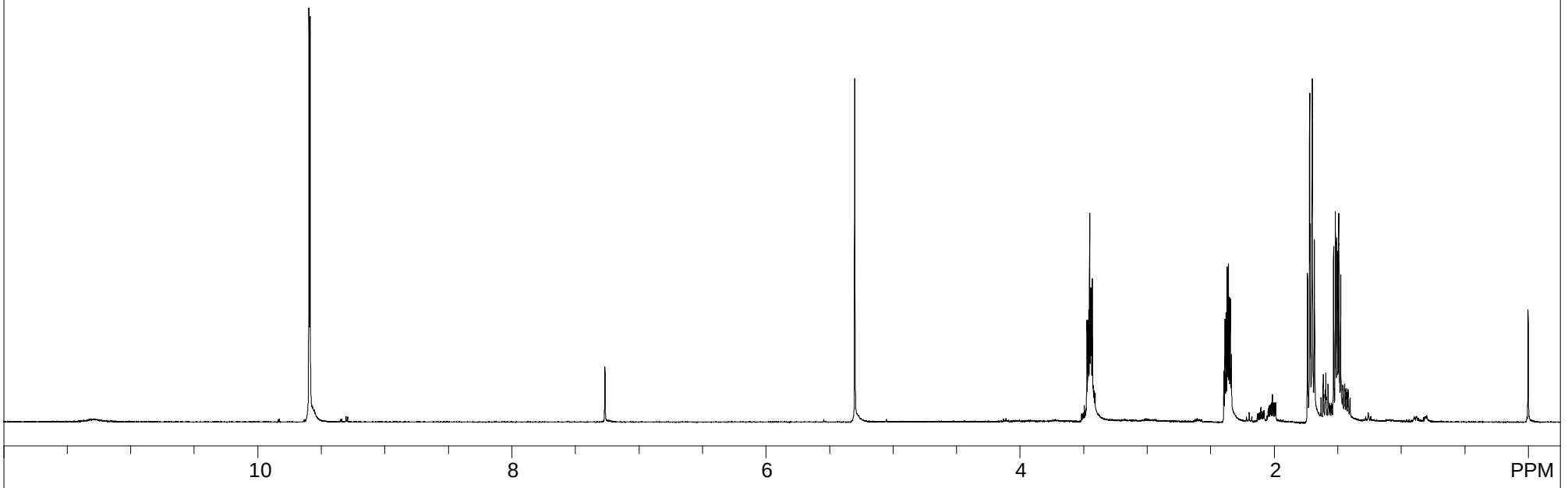
5

C-13 CDCL3 WM-360 USER: -- DATE: 22/08/00

F1: 90.565	SW1: 23809		OF1: 9466.8		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 262	LB: 1.8	WinNuts - $Ol4177ea.c13



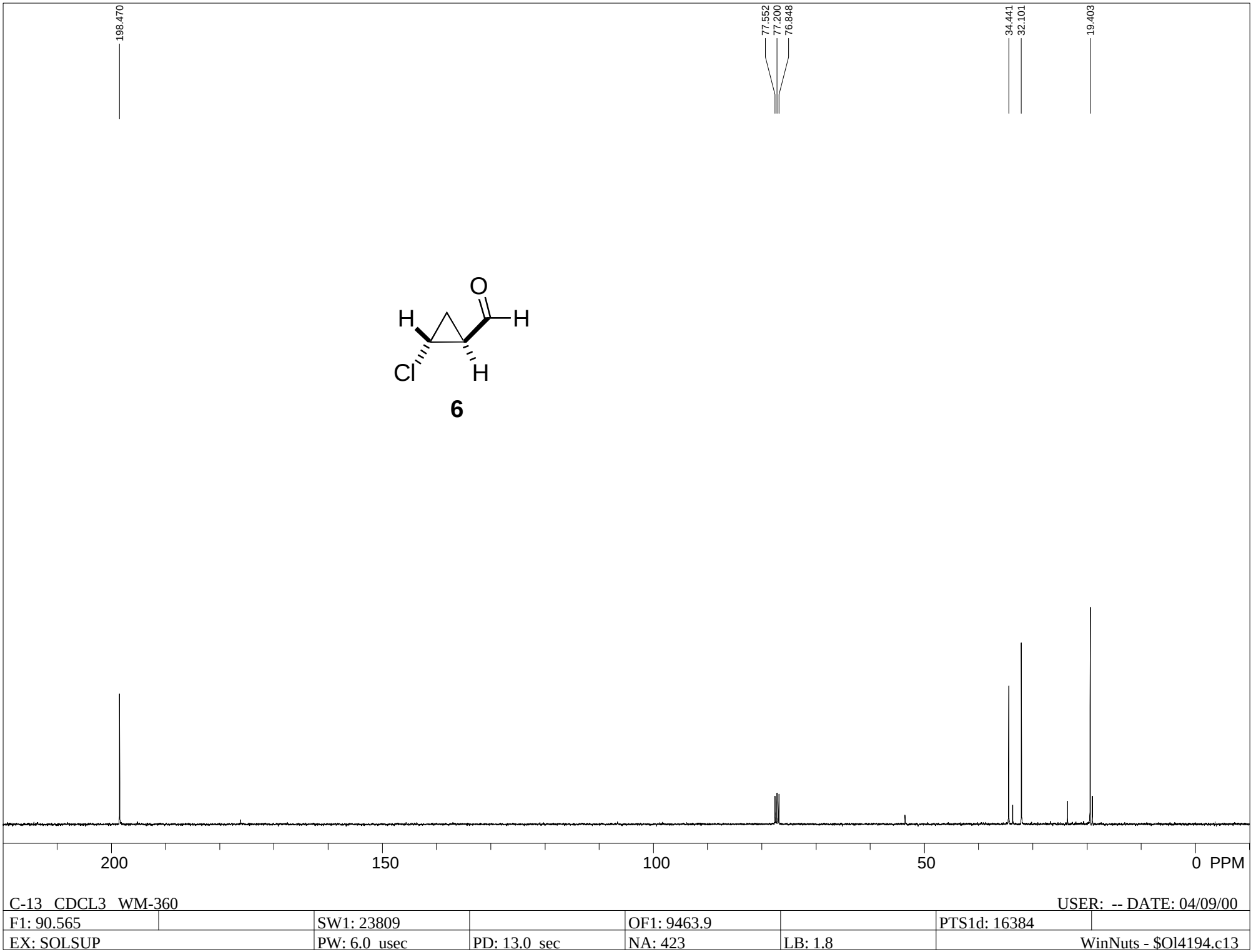
6



aldehyde and some CH2Cl2 imp.

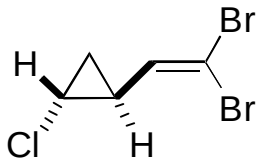
USER: -- DATE: 04/09/00

F1: 360.137		SW1: 7246		OF1: 2119.2		PTS1d: 32768	
EX: ZEGOEMFT		PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2		WinNuts - $Ol4194.h1

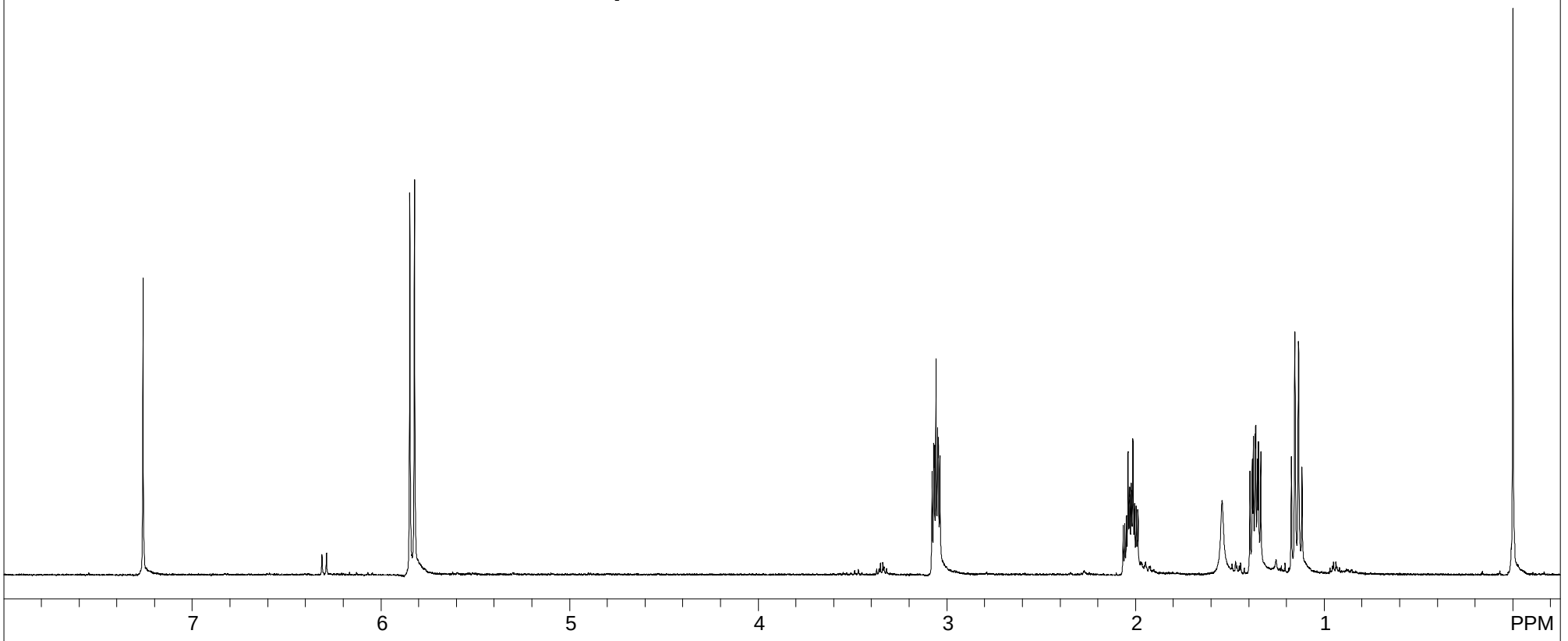


C-13 CDCL3 WM-360 USER: -- DATE: 04/09/00

F1: 90.565	SW1: 23809		OF1: 9463.9		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 423	LB: 1.8	WinNuts - $Ol4194.c13

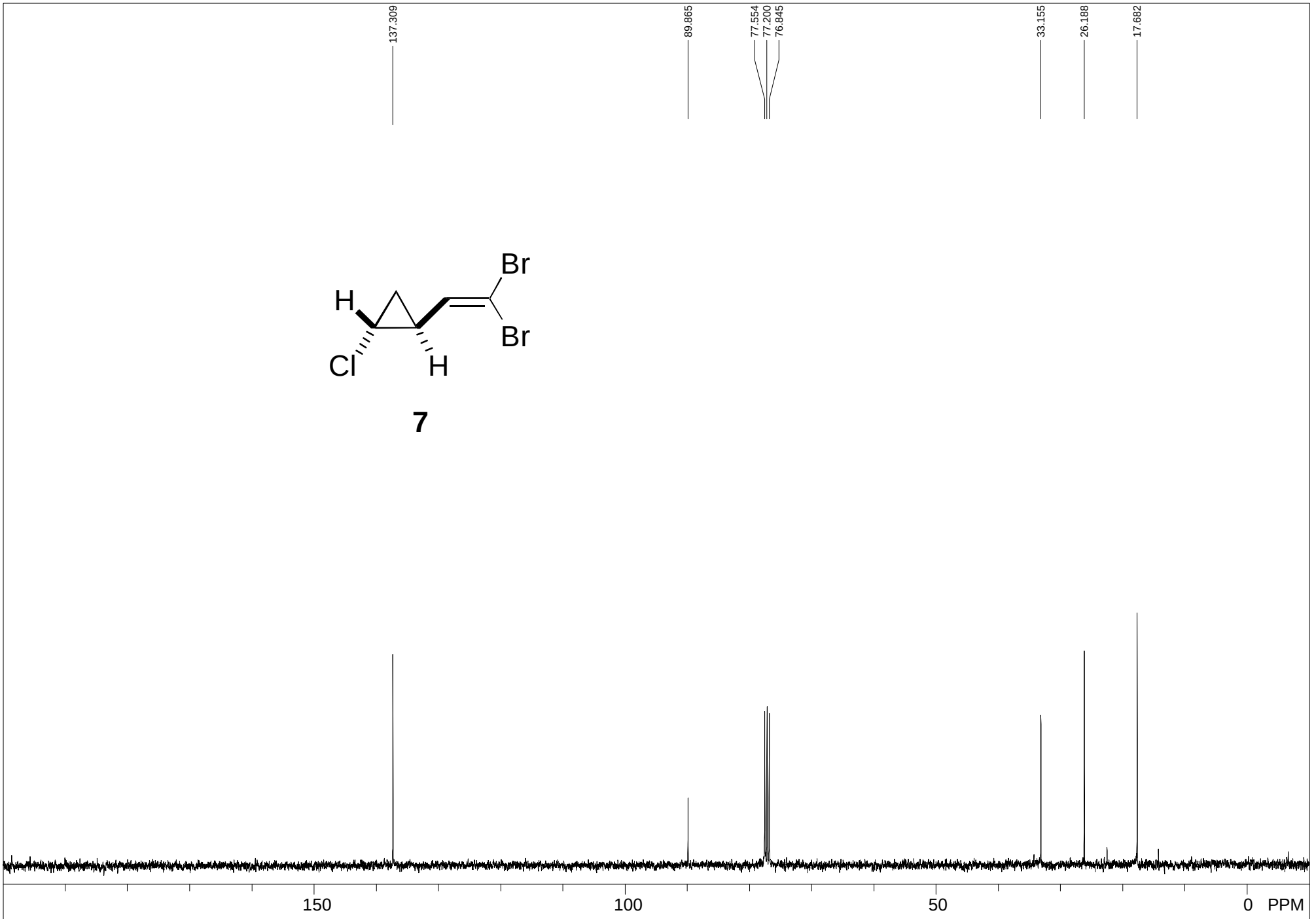


7



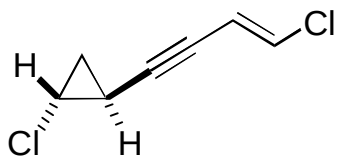
H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 19/12/99

F1: 360.137	SW1: 7246		OF1: 2136.5		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Ol33009.h1

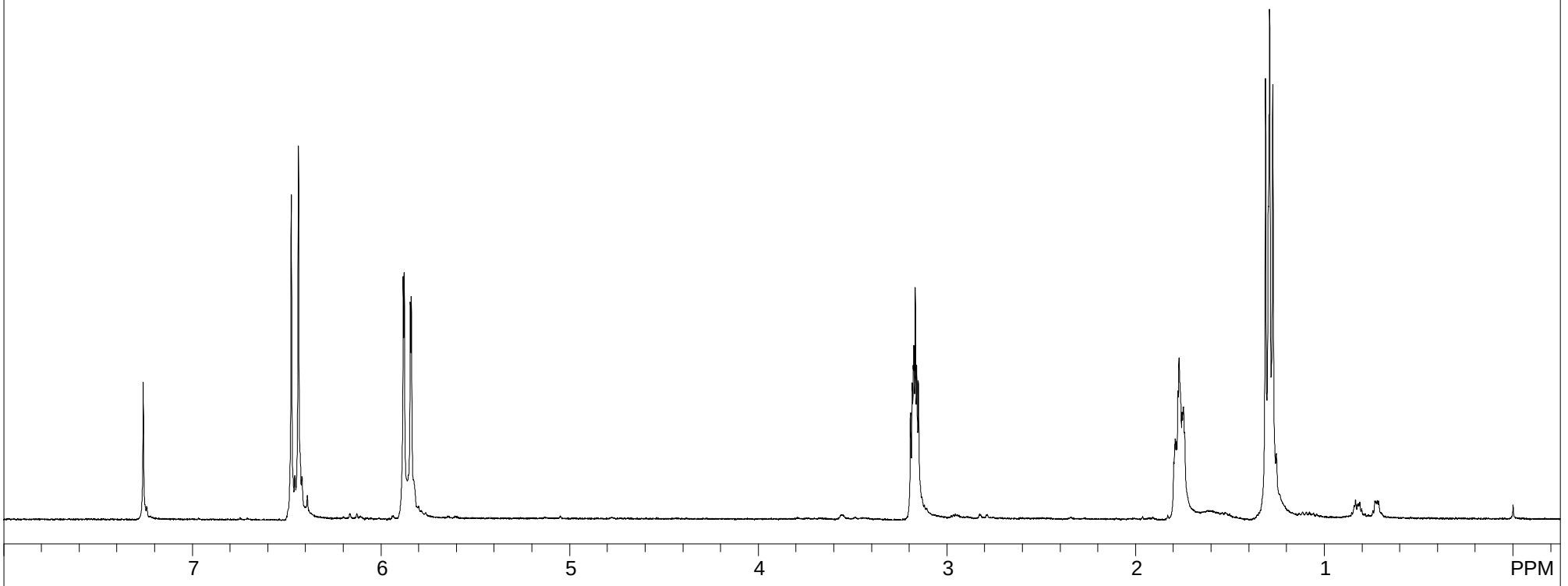


C-13 CDCL3 WM-360 USER: -- DATE: 05/09/00

F1: 90.565	SW1: 23809		OF1: 9469.0		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 300	LB: 1.8	WinNuts - $Ol4196.c13

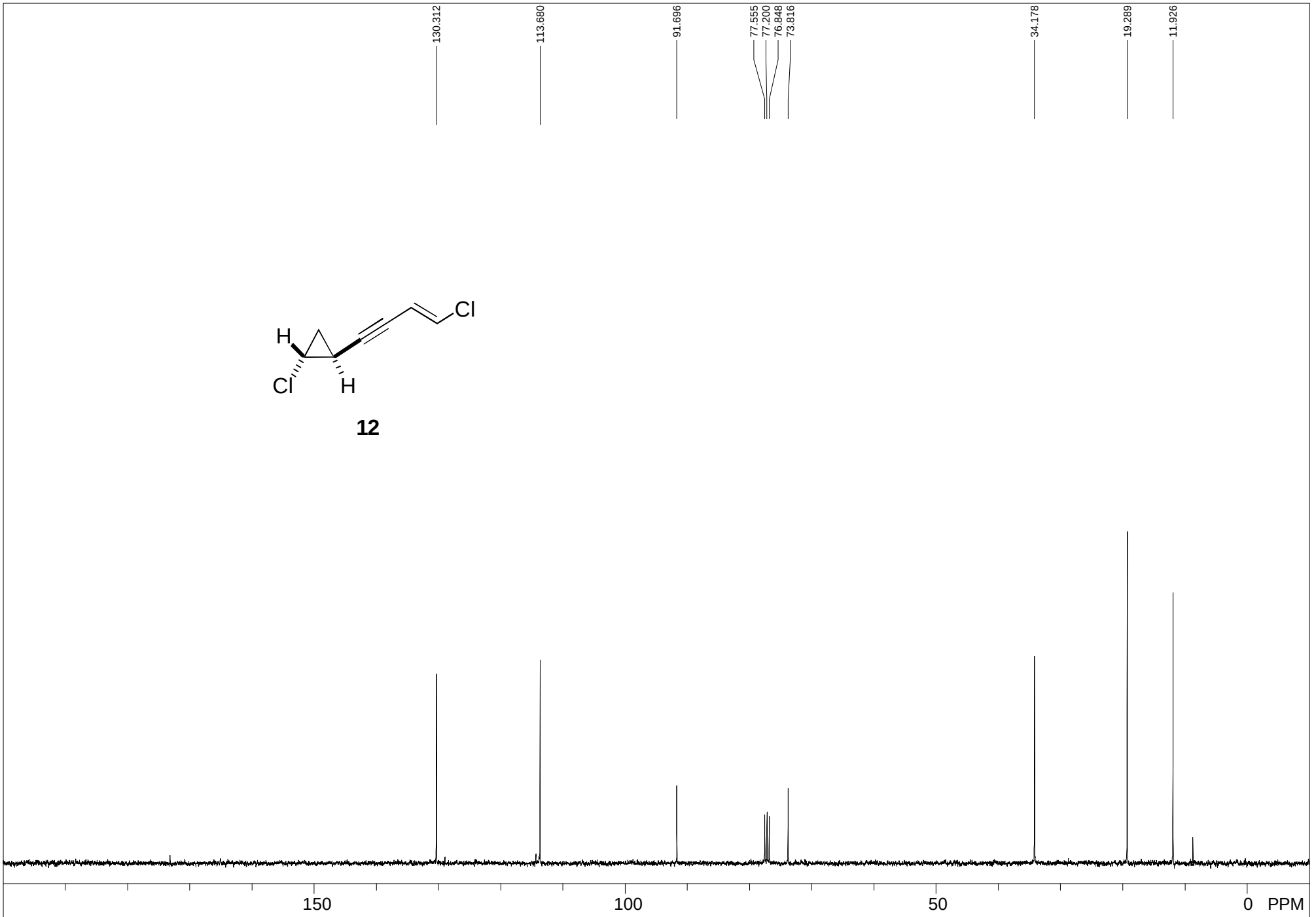


12



H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 21/01/00

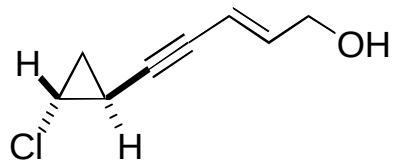
F1: 360.137	SW1: 7246		OF1: 2136.2		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Ol4038b.h1



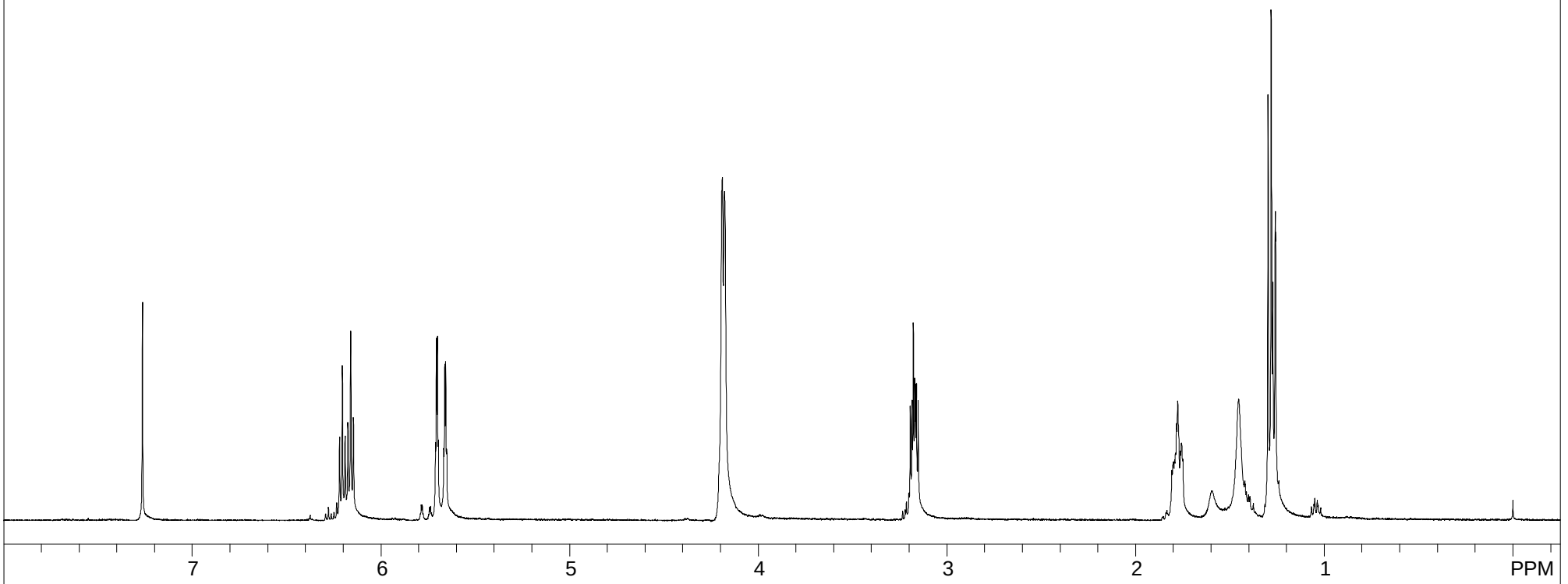
12

C-13 CDCL3 WM-360 USER: -- DATE: 21/01/00

F1: 90.565	SW1: 23809		OF1: 9466.4		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 133	LB: 1.8	WinNuts - $Ol4038b.c13

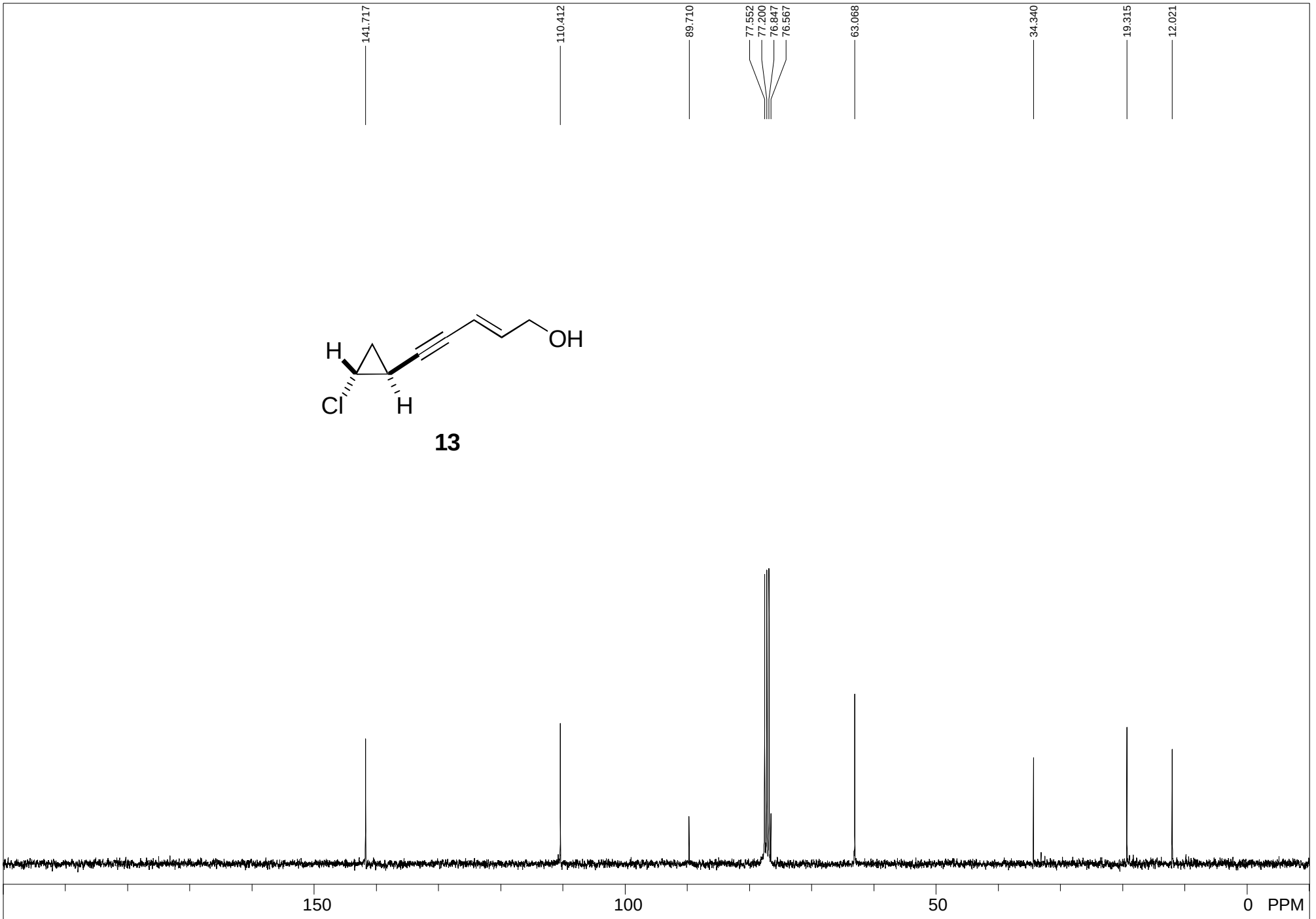


13



H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 13/02/00

F1: 360.137	SW1: 7246		OF1: 2137.6		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Ol4049.h1

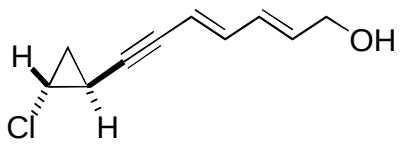


13

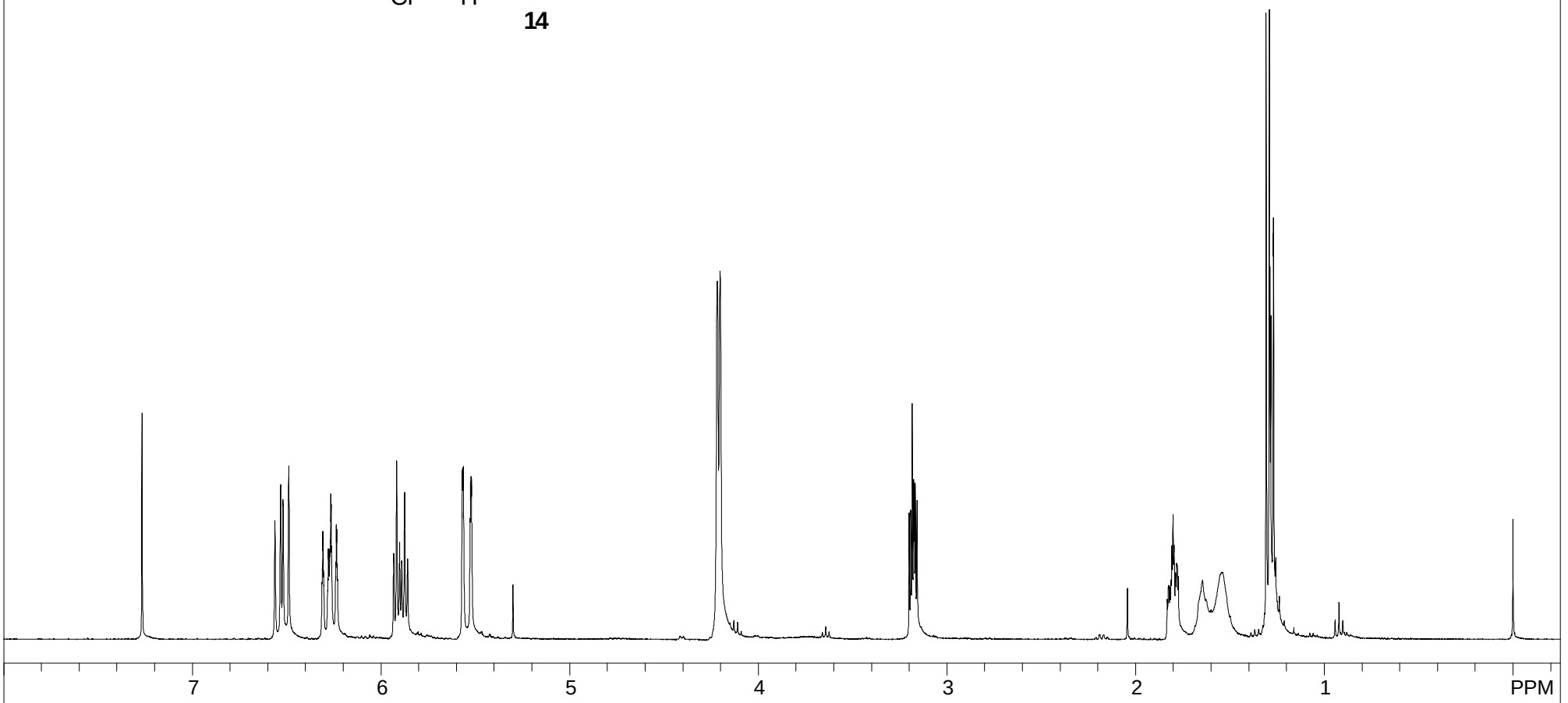
Stille coupling

USER: -- DATE: 26/08/00

F1: 90.565	SW1: 23809		OF1: 9469.8		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 1267	LB: 1.8	WinNuts - $Ol4185a.c13

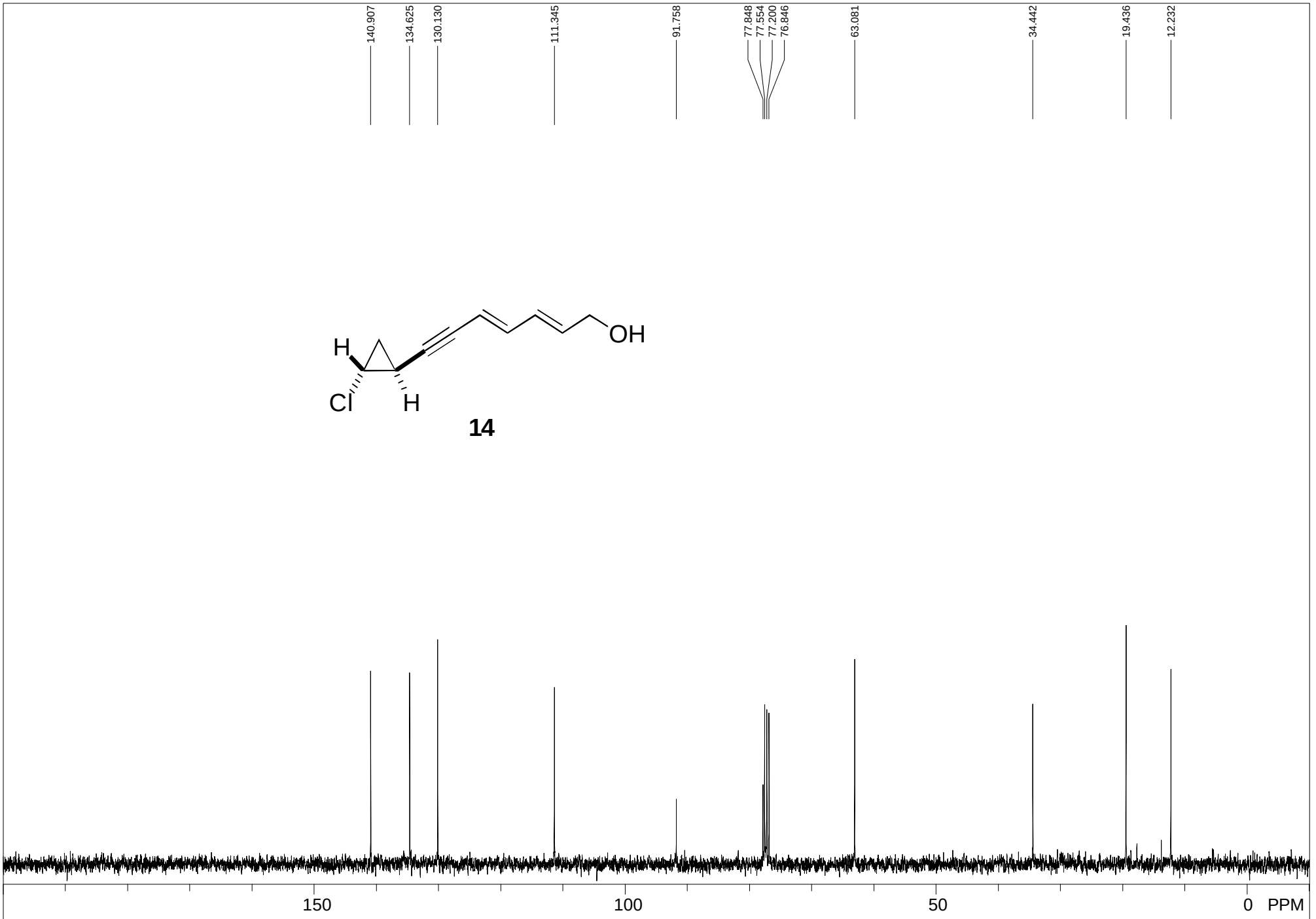


14



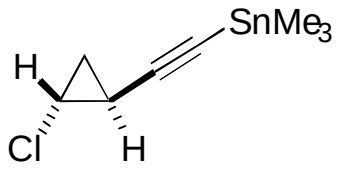
H1 WM-360 CDCl3 USER: -- DATE: 30/09/00

F1: 360.137	SW1: 7246		OF1: 2118.7		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Fv2135aa.h1



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

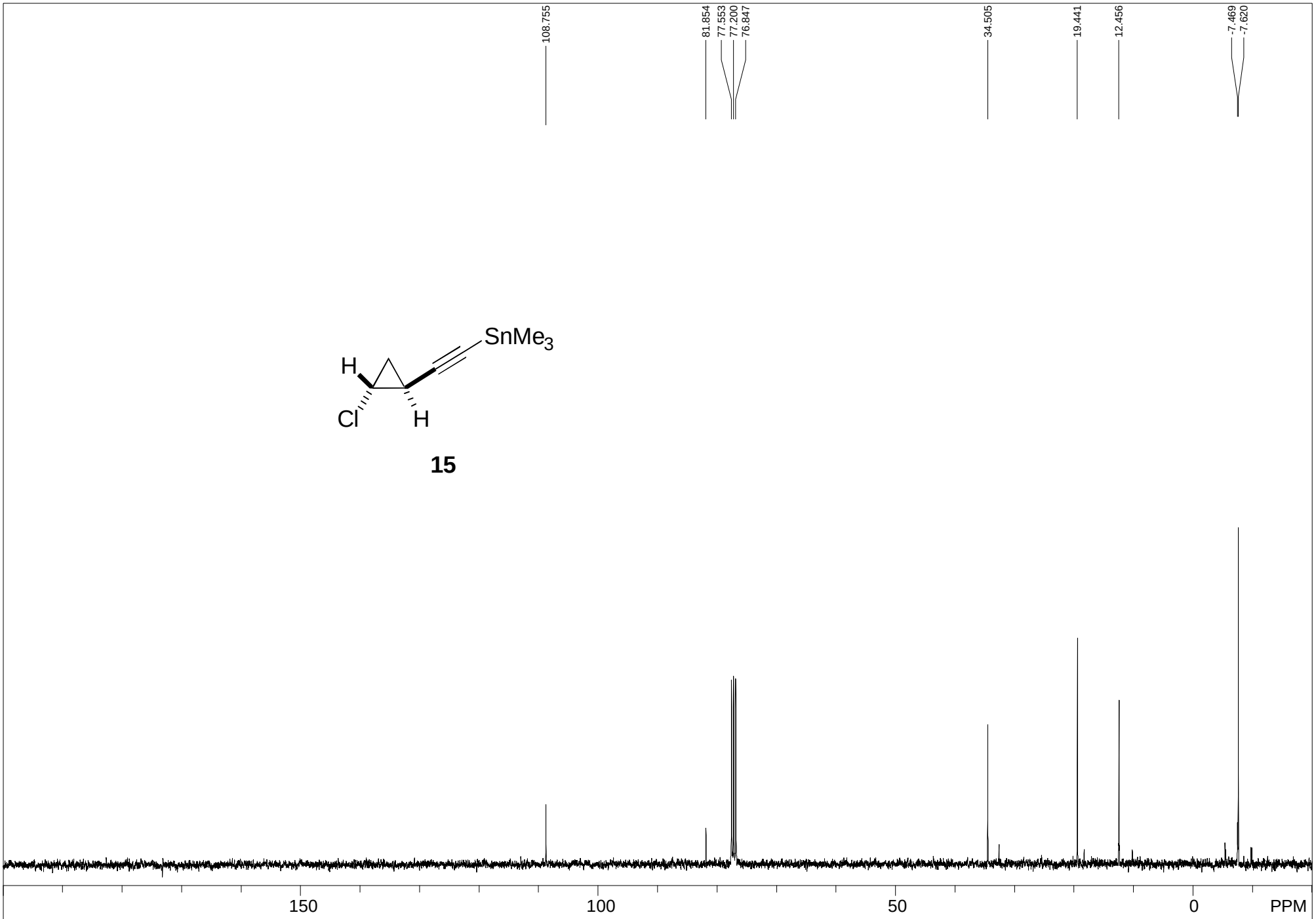
F1: 90.565	SW1: 23809		OF1: 9468.3		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 130	LB: 1.8	WinNuts - $Fv2122aa.c13



15

H1CHLORO.ZZN WM-360 U. of IOWA USER: -- DATE: 10/07/00

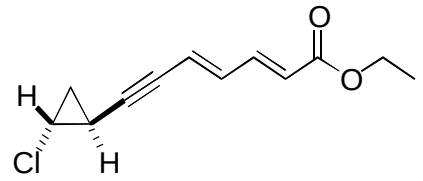
F1: 360.137	SW1: 7246		OF1: 2143.4		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $Fv2063c.h1



15

C-13 CDCL3 WM-360 USER: -- DATE: 10/07/00

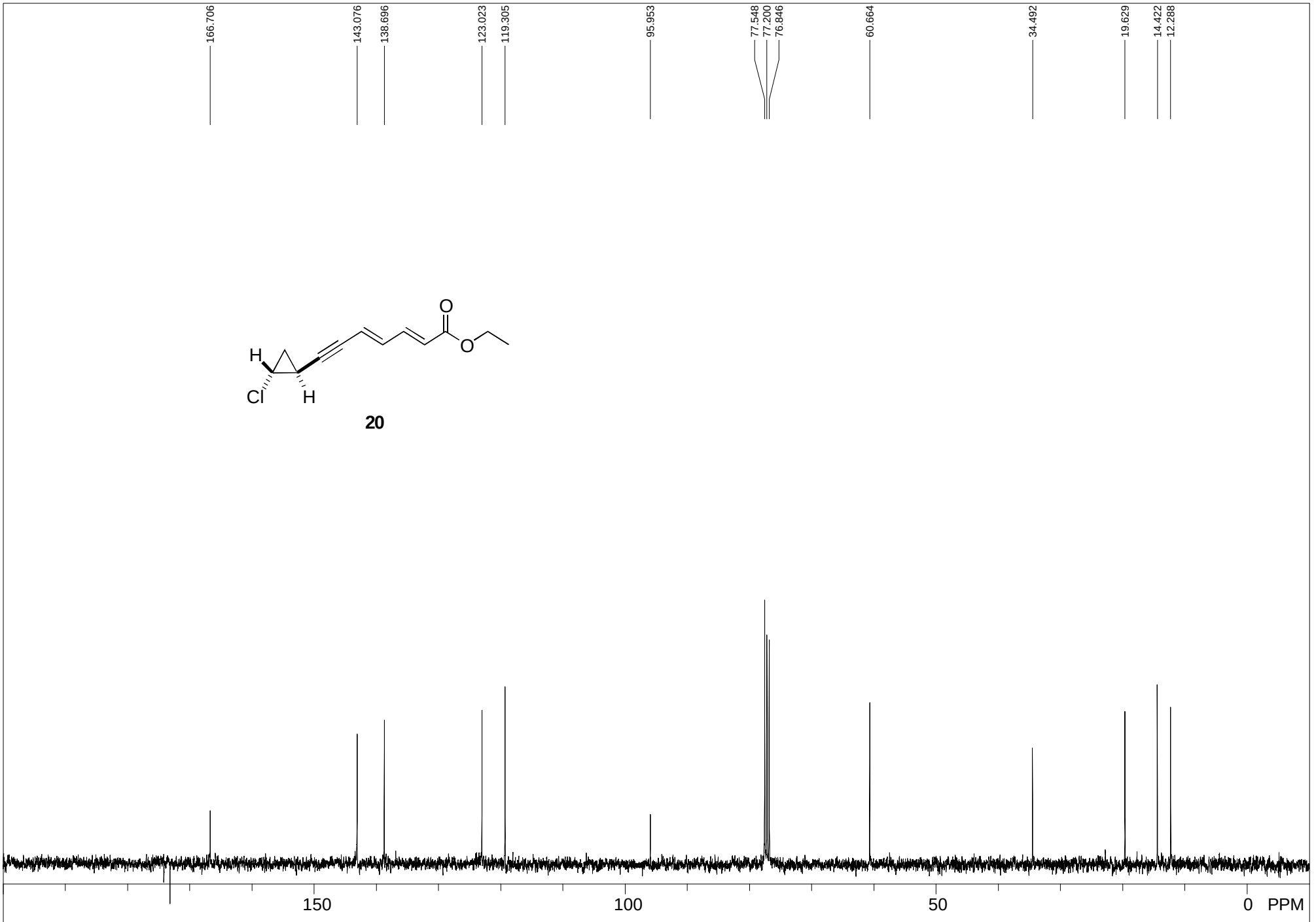
F1: 90.565	SW1: 23809		OF1: 9469.8		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 418	LB: 1.8	WinNuts - $Fv2063c.c13



20

H1 WM-360 CDCl3 USER: -- DATE: 16/09/00

F1: 360.137	SW1: 7246		OF1: 2120.1		PTS1d: 32768
EX: ZEGOEMFT	PW: 6.0 usec	PD: 0.0 sec	NA: 16	LB: 0.2	WinNuts - $F4199.h1



20

C-13 CDCL3 WM-360 USER: -- DATE: 16/09/00

F1: 90.565	SW1: 23809		OF1: 9468.8		PTS1d: 16384
EX: SOLSUP	PW: 6.0 usec	PD: 13.0 sec	NA: 273	LB: 1.8	WinNuts - $F4199.c13