

Enantioselective Copper-Catalyzed Conjugate Addition of Dialkylzinc to Nitro-Olefins

Alexandre Alexakis,* Cyril Benhaim

Department of Organic Chemistry, University of Geneva, 30, Quai Ernest Ansermet, 1211 Geneva 2, Switzerland.

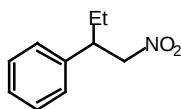
alexandre.alexakis@chiorg.unige.ch

Supplementary material

Experimental procedure, ^1H and ^{13}C spectra, GC chromatograms. This material is available free of charge via Internet at <http://pubs.acs.org>

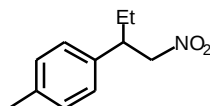
General Procedure for Catalytic Conjugate Addition

To a solution of copper triflate (1.8 mg, 0.005 mmol) in either dry toluene or dry methylene chloride (1.5 ml), at room temperature, under argon, were added two equivalents of ligand (0.01 mmol). The solution was stirred at 25°C for 30 min and then cooled to -40°C. Dialkyl zinc (1.2 mmol, 1.2 ml of 1N sol. in hexane) was added dropwise at such a rate as the temperature did not rise above -30°C. The solution was stirred for 15 min at -30°C. The nitro-olefin (1 mmol) was then added dropwise in 5 min. The reaction mixture was stirred at -30°C for 3h before being quenched by aqueous NH_4Cl . Enantiomeric excess was determined by chiral GC.



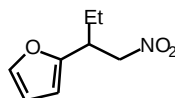
(1-Nitromethyl-propyl)-benzene

enantiomer separation: *Lipodex E*, 25m, $50\text{cm}^3\cdot\text{s}^{-1}$, T° : 100°C, 1°/min, $R_t=13.57\text{min}$ enantiomer(S), $R_t=14.05\text{min}$ enantiomer(R). Purification by Chromatography (pentane : ether, 95/5, $R_f=0.4$), δ_{H} (400 MHz, CDCl_3) 7.2-7.5 (m, 5H, Ph), 4.59 (m, 2H, CH_2NO_2), 3.40 (m, 1H, CH), 1.74 (m, 2H, CH_2CH_3), 0.85 (t, 3H, $J=7.4\text{Hz}$, CH_2CH_3). δ_{C} (100 MHz, CDCl_3) 11.5 (CH_3), 26.1 (CH_2CH_3), 46.0 (CH), 80.8 (CH_2NO_2), 127.3, 128.8, 129.1, 139.2.



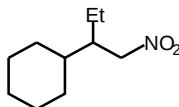
4-Methyl-1-(1-Nitromethyl-propyl)-benzene

enantiomer separation: *LipodexE*, 25m, $50\text{cm}^3\cdot\text{s}^{-1}$, $T^\circ:100^\circ\text{C}$, $1^\circ/\text{min}$, $R_t=13.5\text{min}$ enantiomer(*S*), $R_t=14.1\text{min}$ enantiomer(*R*). Purification by flash Chromatography (pentane : ether, 95/5, $R_f=0.4$), δ_{H} (400 MHz, CDCl_3) 7.17 (d, 2H, Ar), 7.10 (d, 2H, Ar), 4.57 (dd, 2H) 3.35 (m, 1H, CH), 2.40 (s, 3H, $\text{CH}_3\text{-Ar}$), 1.75 (m, 2H, CH_2CH_3), 0.87 (t, 3H, CH_3). δ_{C} (100 MHz, CDCl_3) 11.5 (CH_3), 21.0 (CH_3), 26.2 (CH_2CH_3), 45.8 (CH), 81.3 (CH_2NO_2), 128.1, 130.3, 137.0, 137.9 (Ar).



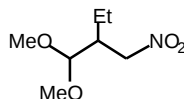
2-(1-Nitromethyl-propyl)-furan

enantiomer separation: *CP chirasil-Dex CB*, 25m, $50\text{cm}^3\cdot\text{s}^{-1}$, $T^\circ:90^\circ\text{C}$, $3^\circ/\text{min}$, $R_t=11.2\text{min}$ enantiomer(*S*), $R_t=11.6\text{min}$ enantiomer(*R*). Purification by flash Chromatography (pentane : ether, 90/10, $R_f=0.8$) yellow oil, δ_{H} (400 MHz, CDCl_3) δ_{H} (400 MHz, CDCl_3) 7.36 (s, 1H, CH=), 6.31 (s, 1H, CH=), 6.15 (s, 1H, CH=), 4.59 (dd, 2H, CH_2NO_2), 3.53 (m, CH), 1.74 (m, 2H, CH_2CH_3), 0.91 (t, 3H, CH_3). δ_{C} (100 MHz, CDCl_3) 11.2 (CH_3) 24.1 (CH_2CH_3), 39.4 (CH), 78.2 (CH_2NO_2), 107.3, 110.2, 142.1, 152.4 (Furyl).



(1-Nitromethyl-propyl)-cyclohexane

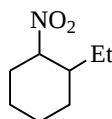
enantiomer separation: *LipodexE*, 25m, $50\text{cm}^3\cdot\text{s}^{-1}$, $T^\circ:90^\circ\text{C}$, $1^\circ/\text{min}$, $R_t=15.28\text{min}$ enantiomer(+), $R_t=15.8\text{min}$ enantiomer(-). Purification by flash Chromatography (pentane : ether, 90/10, $R_f=0.7$), δ_{H} (400 MHz, CDCl_3) 4.32 (dd, 1H, CH_2NO_2), 4.20 (dd, 1H, CH_2NO_2), 1.98 (CH), 1.0-1.7 (m, 13H, cHex.), 0.90 (t, 3H, CH_3). δ_{C} (100 MHz, CDCl_3) 11.3 (CH_3) 21.4 (CH_2CH_3), 26.5 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 38.5 (CH), 77.7 (CH_2NO_2).



1,1-Dimethoxy-2-nitromethyl-butane

enantiomer separation: *LipodexE*, 25m, $50\text{cm}^3\cdot\text{s}^{-1}$, $T^\circ:90^\circ\text{C}$, $1^\circ/\text{min}$, $R_t=9.18\text{min}$ enantiomer(+), $R_t=9.98\text{min}$ enantiomer(-) Purification by flash Chromatography (pentane : ether, 95/5, $R_f=0.3$) yellow oil; δ_{H} (400 MHz, CDCl_3) 4.56 (dd, 1H, CH_2NO_2), 4.31 (dd, 1H, CH_2NO_2), 4.31 (d, 1H, $\text{CH}(\text{OCH}_3)_2$), 3.42 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 2.49 (m, 1H,

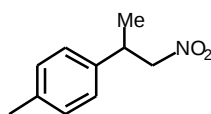
CH) 1.62 (m, 1H, $\underline{\text{CH}_2\text{CH}_3}$), 1.43 (m, 1H, $\underline{\text{CH}_2\text{CH}_3}$), 0.98 (t, $J=7.56\text{Hz}$, 3H, $\text{CH}_2\underline{\text{CH}_3}$), δ_{C} (100 MHz, CDCl_3) 10.9 ($\text{CH}_2\underline{\text{CH}_3}$), 20.5 ($\underline{\text{CH}_2\text{CH}_3}$), 42.0 (CH), 54.7 (OCH_3), 55.9 (OCH_3), 75.2 (CH_2NO_2) 105.3 ($\underline{\text{CH}}(\text{OCH}_3)_2$)



2-Ethyl-1-Nitro-cyclohexane

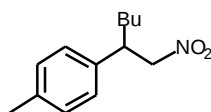
enantiomer separation: *LipodexE*, 25m, $50\text{cm}^3.\text{s}^{-1}$, $T^\circ:60^\circ\text{C}$, $3^\circ/\text{min}$, $R_t=16.16(\text{minor } \underline{\text{trans}})$, 16.37 (major cis), 16.78 (minor cis), 17.12(major trans). Purification by flash Chromatography (pentane : ether, 95/5, $R_f=0.3$) yellow oil; δ_{H} (400 MHz, CDCl_3) 4.64 (m, 1H, (cis CHEt-CHNO_2)), 4.21 (m, 1H, (trans CHEt-CHNO_2)), 2.21 (m, 1H, (trans CHEt-CHNO_2)), 2.11 (m, 1H, (cis CHEt-CHNO_2)), 1.20-2.00 (m, 10H, CH_2), 0.94 (t, 3H, $\text{CH}_2\underline{\text{CH}_3}$) δ_{C} (100 MHz, CDCl_3) 10.2 (CH_3)_{trans}, 11.6 (CH_3)_{cis}, 21.8 (CH_2), 22.1 (CH_2), 24.5 (CH_2), 24.8 (CH_2), 25.2 (CH_2), 26.5 (CH_2), 27.2 (CH_2), 28.9 (CH_2), 31.9 (CH_2), 40.7 (CHEt)_{cis}, 42.1 (CHEt)_{trans}, 86.4 (CHNO_2)_{cis}, 91.1 (CHNO_2)_{trans}.

The mixture of cis and trans (80/20) isomers was treated with 1 equiv. DBU, at r.t., in dry ether. After 30 min the cis/trans ratio was 5/95. The ee value given in the Table is the one obtained after isomerisation.



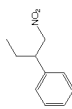
1-Methyl-4-(1-Nitromethyl-ethyl)-benzene

enantiomer separation: *LipodexE*, 25m, $60\text{cm}^3.\text{s}^{-1}$, $T^\circ:100^\circ\text{C}$, $1^\circ/\text{min}$, $R_t=15.57\text{min}$ enantiomer(S), $R_t=16.04\text{min}$ enantiomer(R) Purification by Chromatography (pentane : ether, 90/10, $R_f=0.4$), δ_{H} (400 MHz, CDCl_3) 7.15 (2d, 4H, Ar), 4.52 (m, 2H, CH_2NO_2), 3.60 (m, 1H, CH), 2.34 (s, 3H, $\text{CH}_3\text{-Ar}$), 1.38 (d, $J=4.8\text{Hz}$, 3H, CH_3). δ_{C} (100 MHz, CDCl_3) 18.7 (CH_3), 21.0 ($\text{CH}_3\text{-Ar}$), 38.2 (CH), 82.0 (CH_2NO_2), 126.7, 129.6, 137.2, 137.8 (Ar)



1-Methyl-4-(1-Nitromethyl-pentyl)-benzene

enantiomer separation: *ChirasilDEX G-TA*, 30m, $60\text{cm}^3.\text{s}^{-1}$, $T^\circ:100^\circ\text{C}$, $1^\circ/\text{min}$, $R_t=35.97\text{min}$ enantiomer(S), $R_t=36.22\text{min}$ enantiomer(R). Purification by Chromatography (pentane : ether, 90/10, $R_f=0.4$), δ_{H} (400 MHz, CDCl_3) 7.15 (d, 2H, Ar), 7.08 (d, 2H, Ar), 4.53 (m, 2H, CH_2NO_2) 3.41 (m, 1H, CH) 2.34 (s, 3H, $\text{CH}_3\text{-Ar}$) 1.68 (m, 2H, CH_2) 1.27 (m, 2H, CH_2) 1.19 (m, 2H, CH_2), 0.85 (m, 3H, CH_3) δ_{C} (100 MHz, CDCl_3) 13.8 (CH_3), 21.0 ($\text{CH}_3\text{-Ar}$) 22.4, 29.0, 32.7 (CH_2), 44.0 (CH), 81.1 (CH_2NO_2) 127.3, 129.4, 136.4, 137.1 (Ar).



BENHAIM
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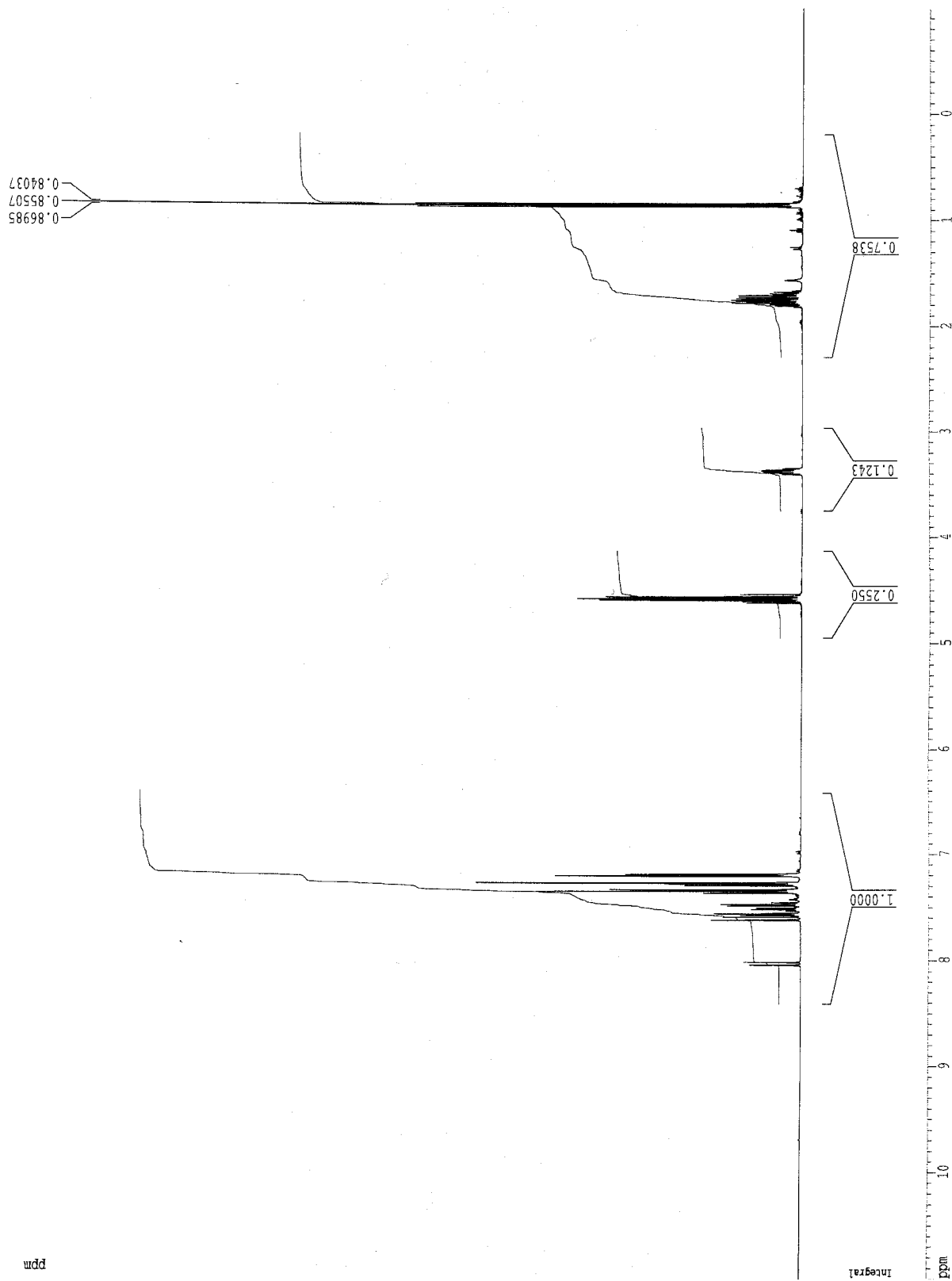
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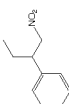
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BENHAIM
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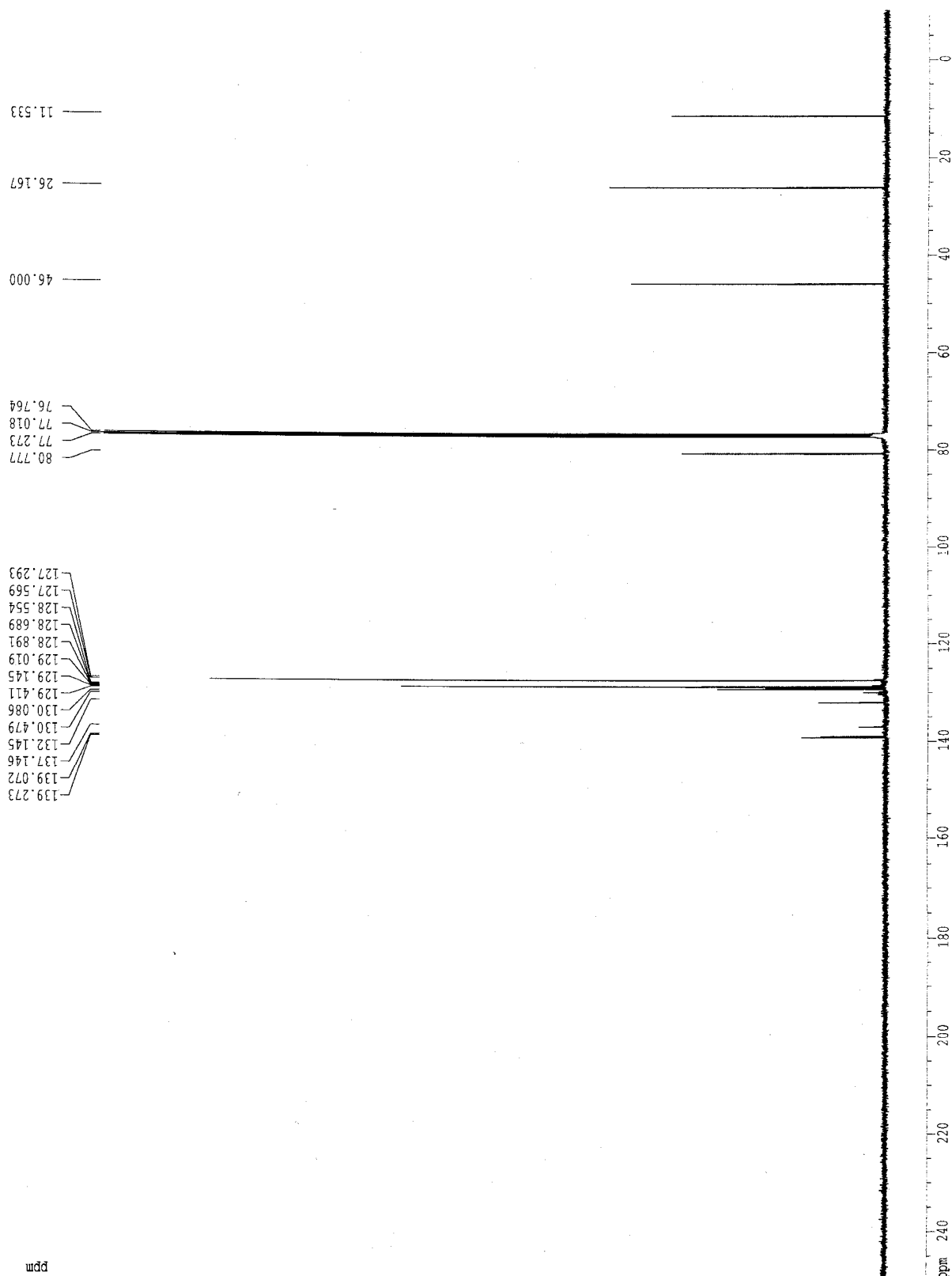
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d11 0.03000000 sec
d12 0.0002000 sec

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PL1 -3.00 dB
SF01 125.7715719 MHz

===== CHANNEL f2 =====
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PL12 15.00 dB
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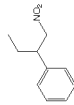
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BENHAIM

C13DEPT135 CDCl3 u guest 3



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EXPNO 12
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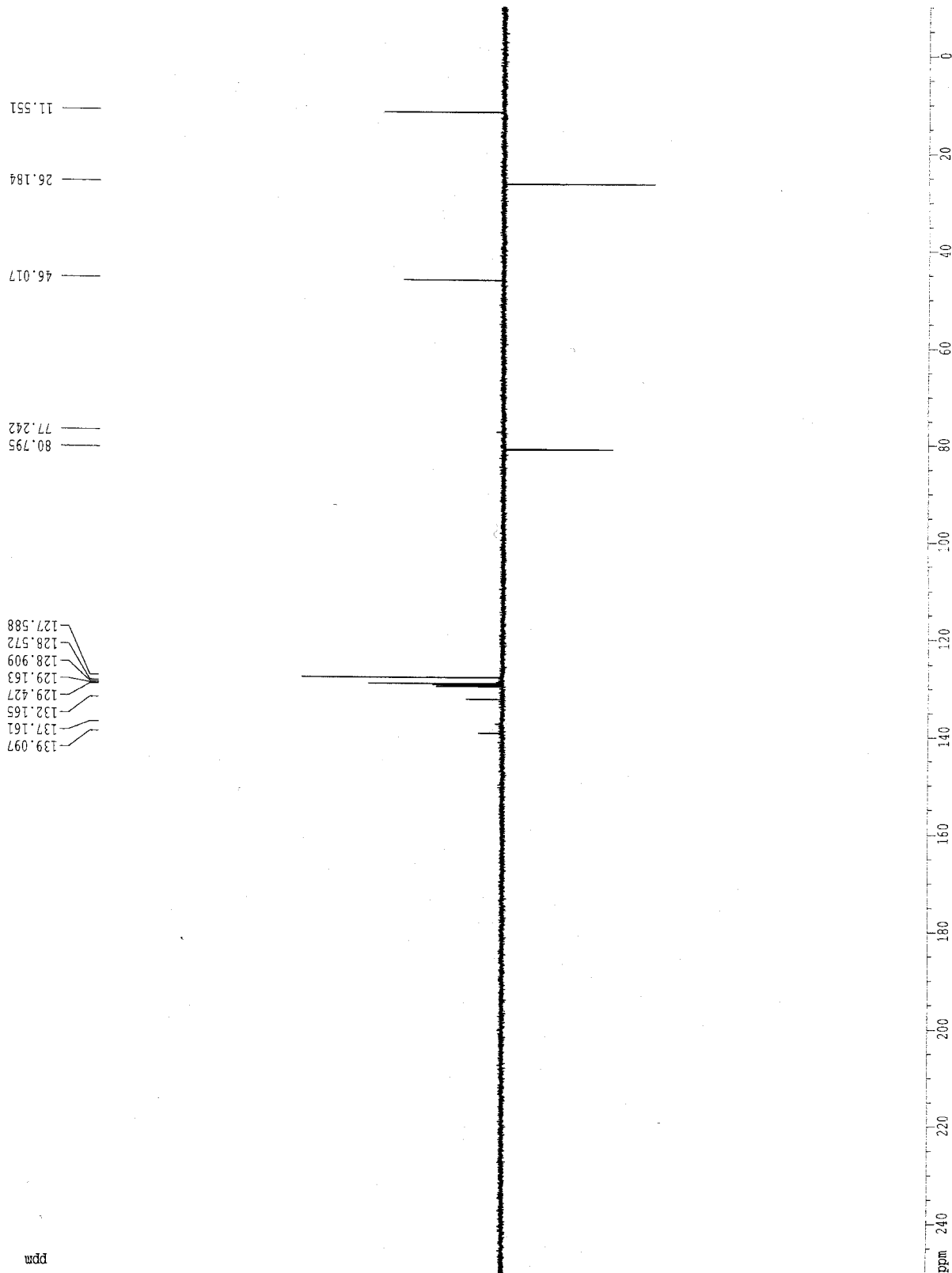
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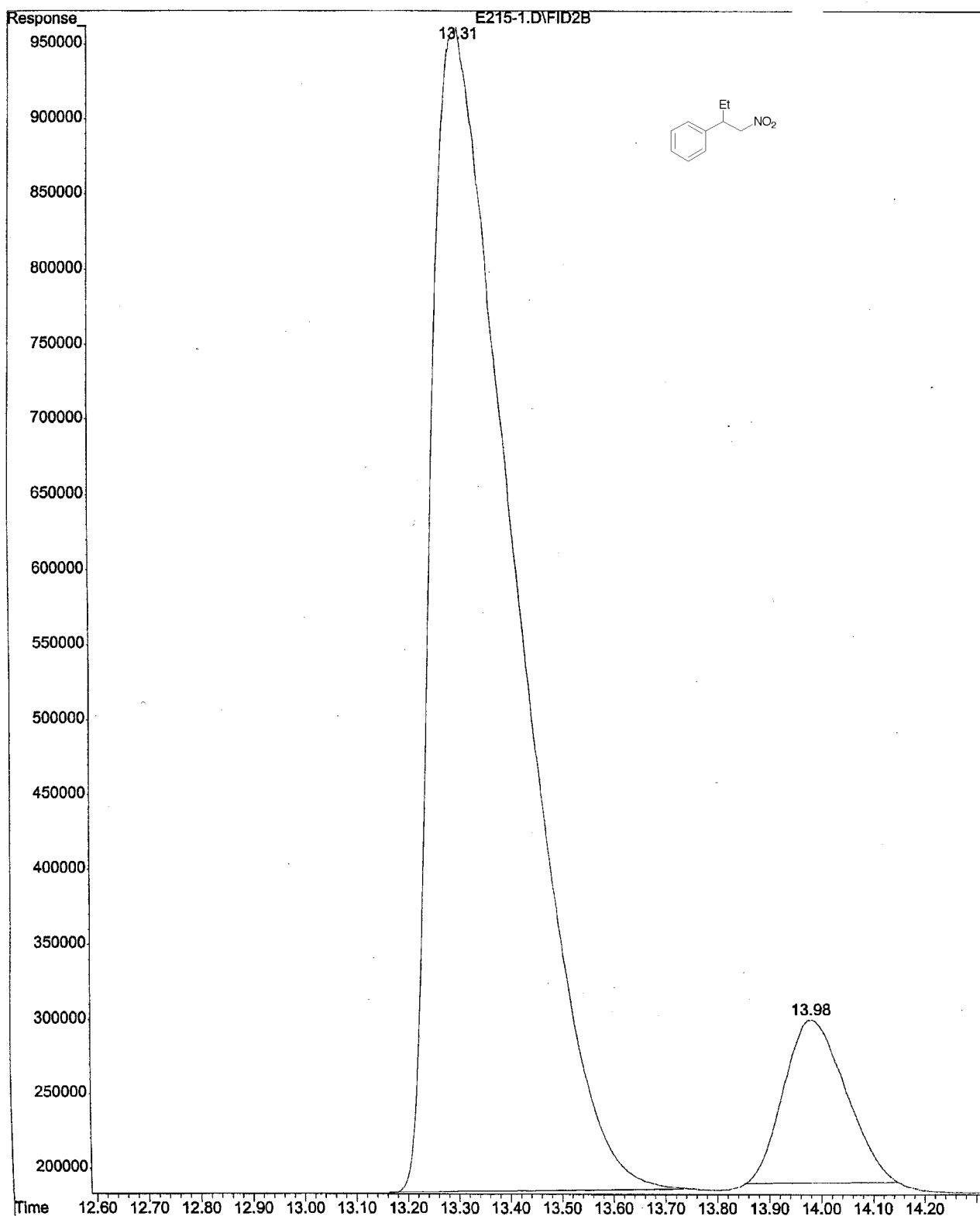
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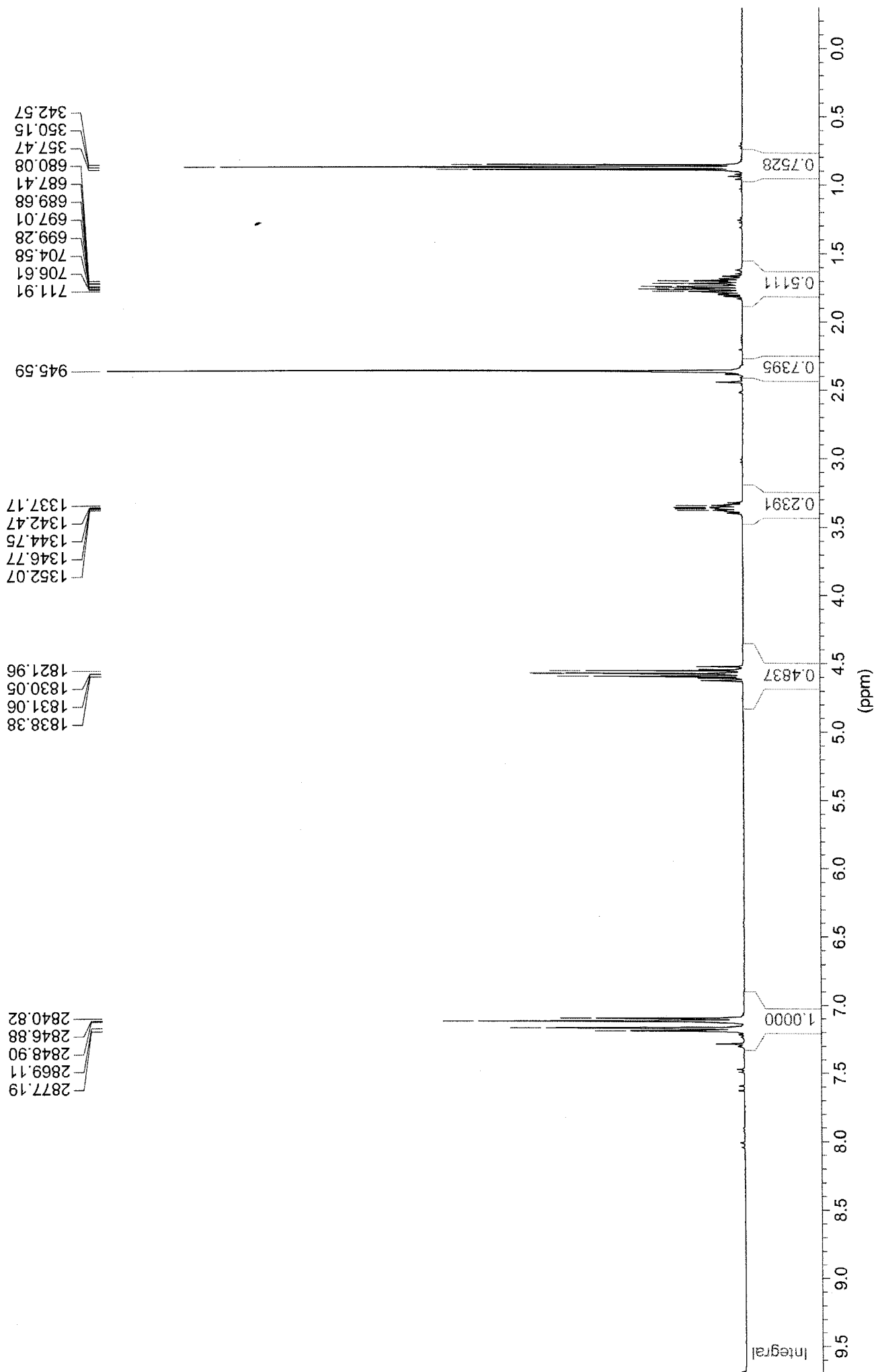
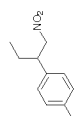
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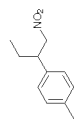
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HZCM 1089.90076 Hz/cm



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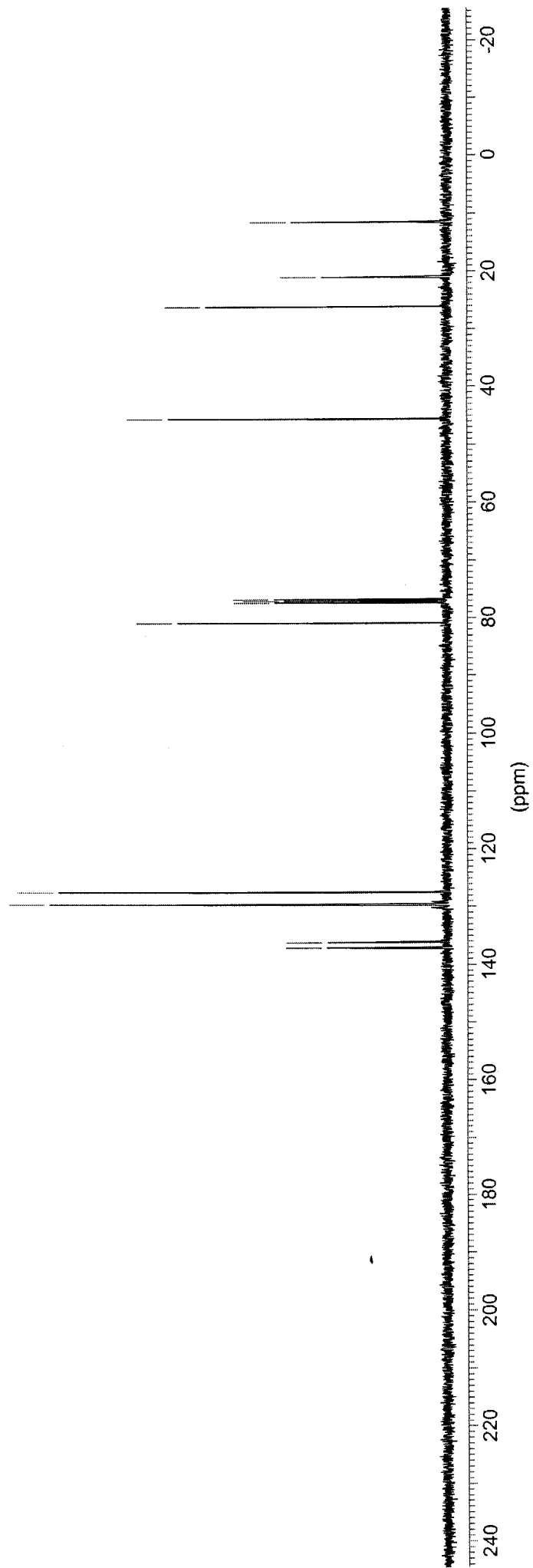
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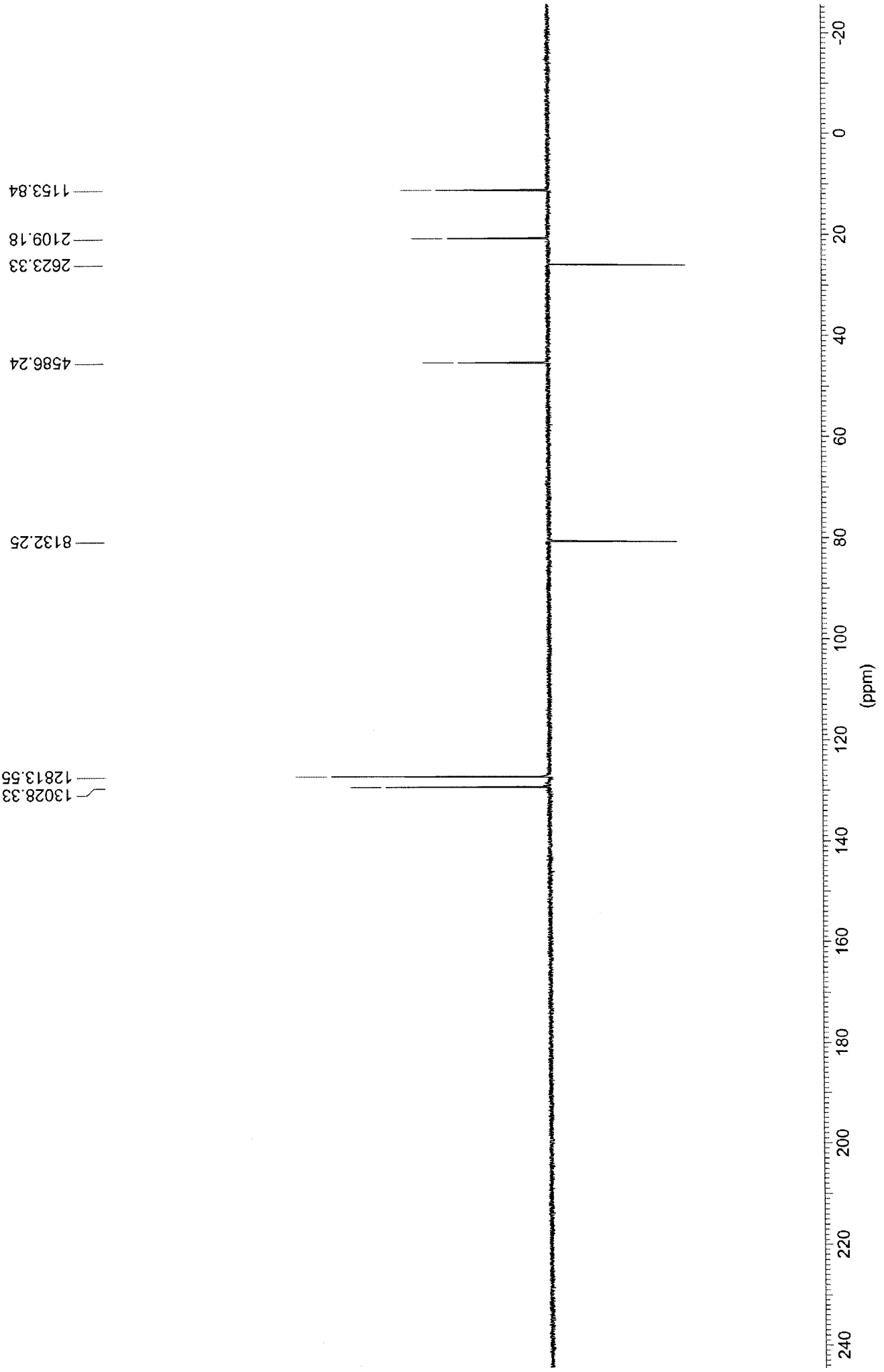
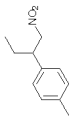
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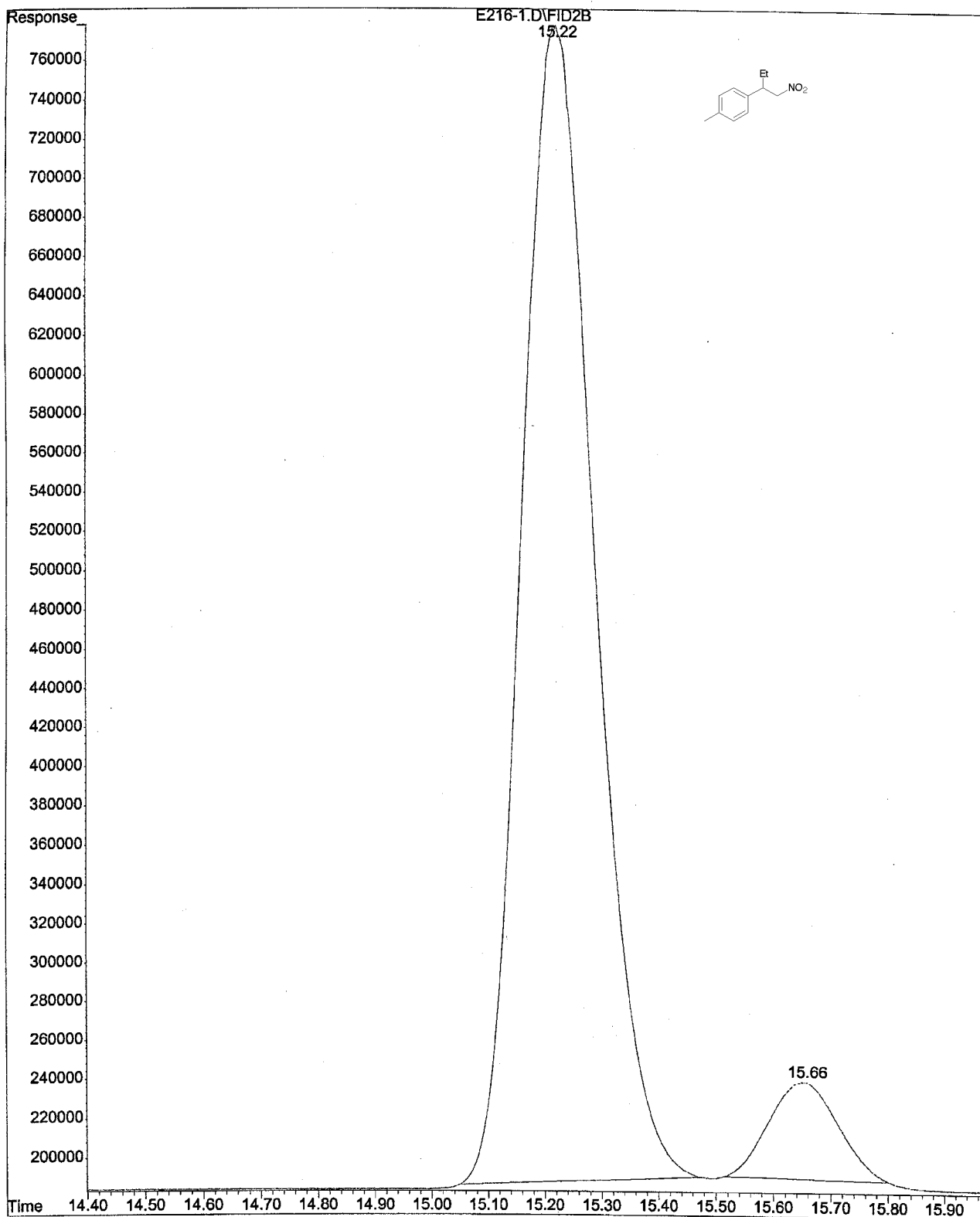
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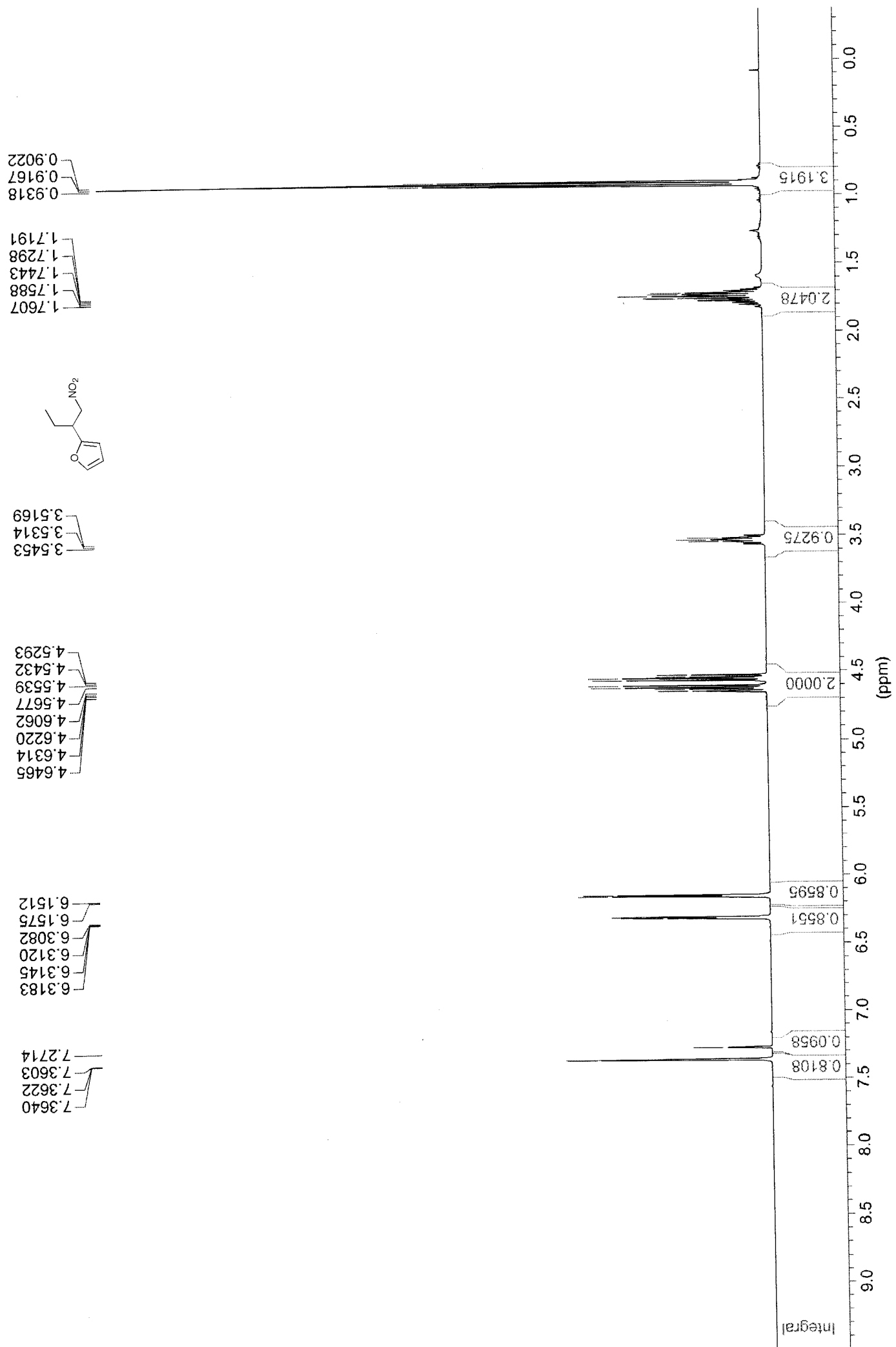
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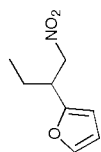




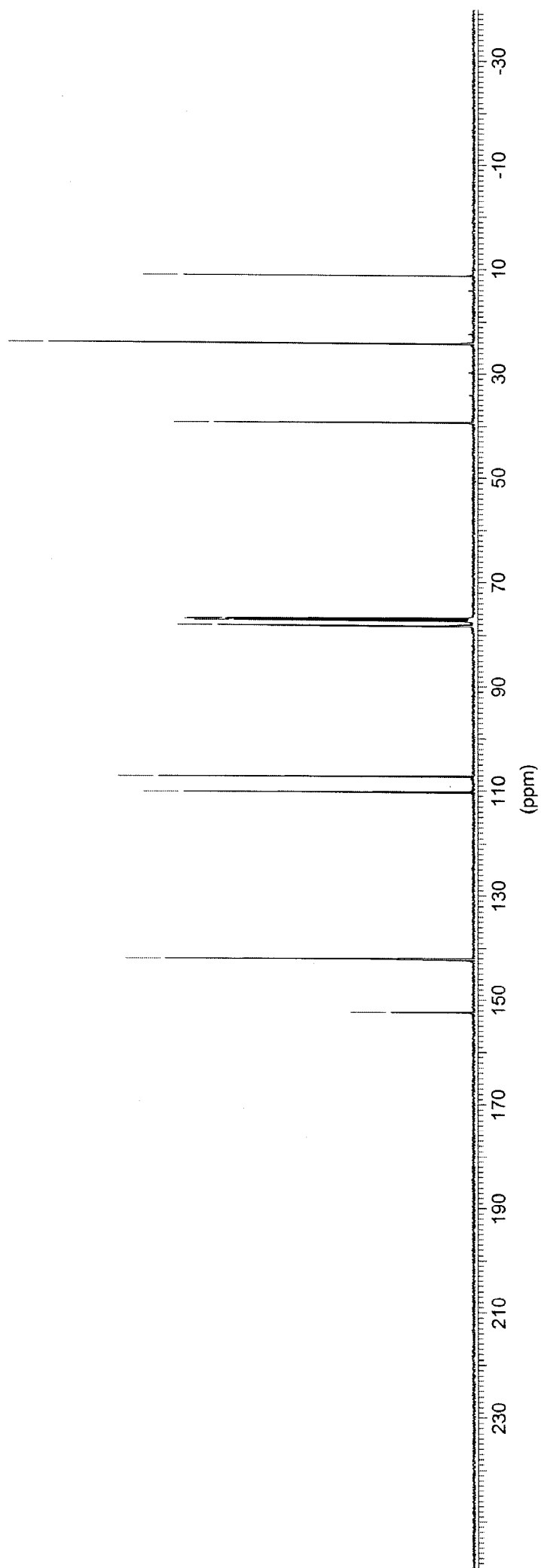
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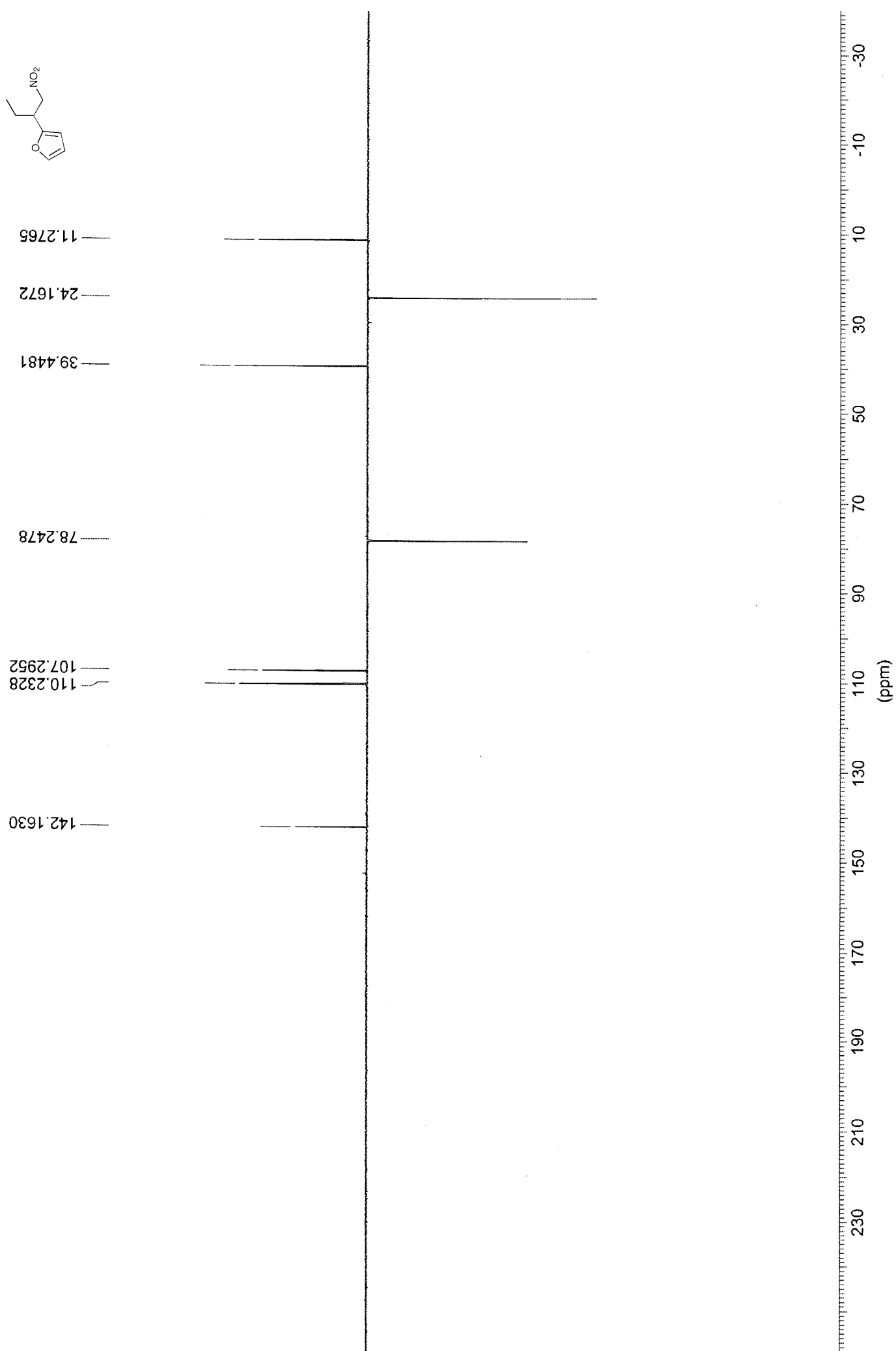
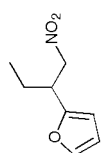




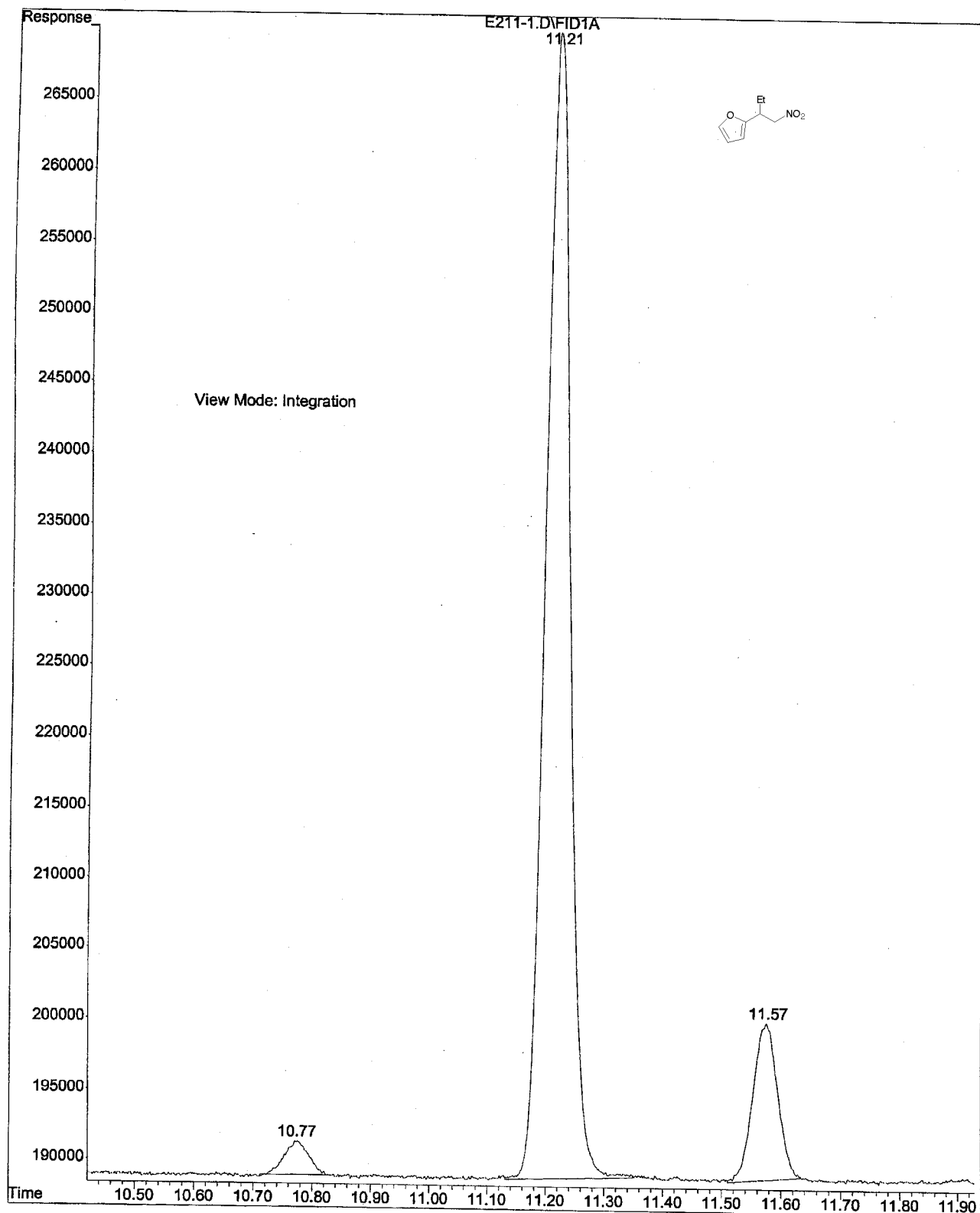


- 11.2512
- 24.1510
- 39.4319
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- 77.0183
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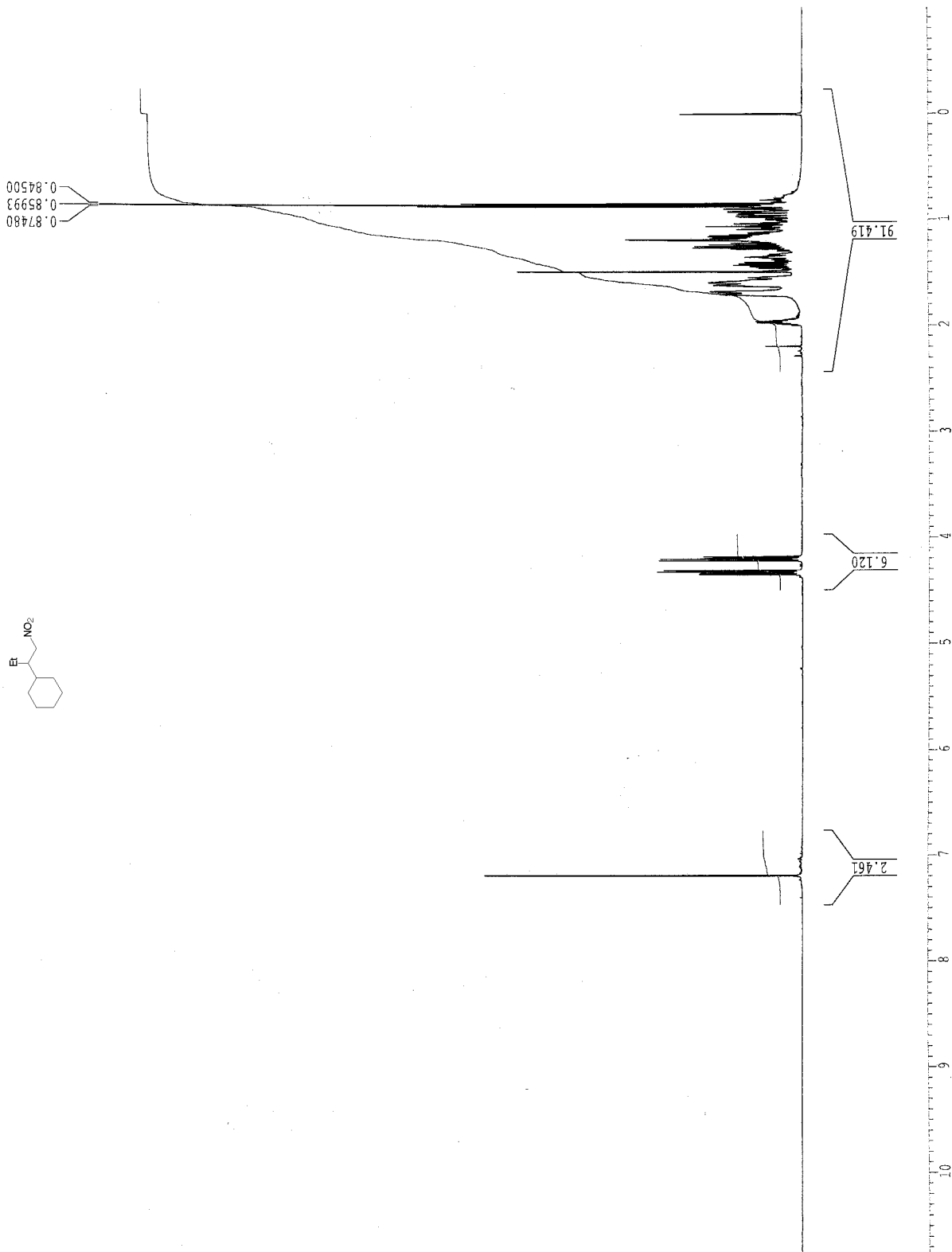
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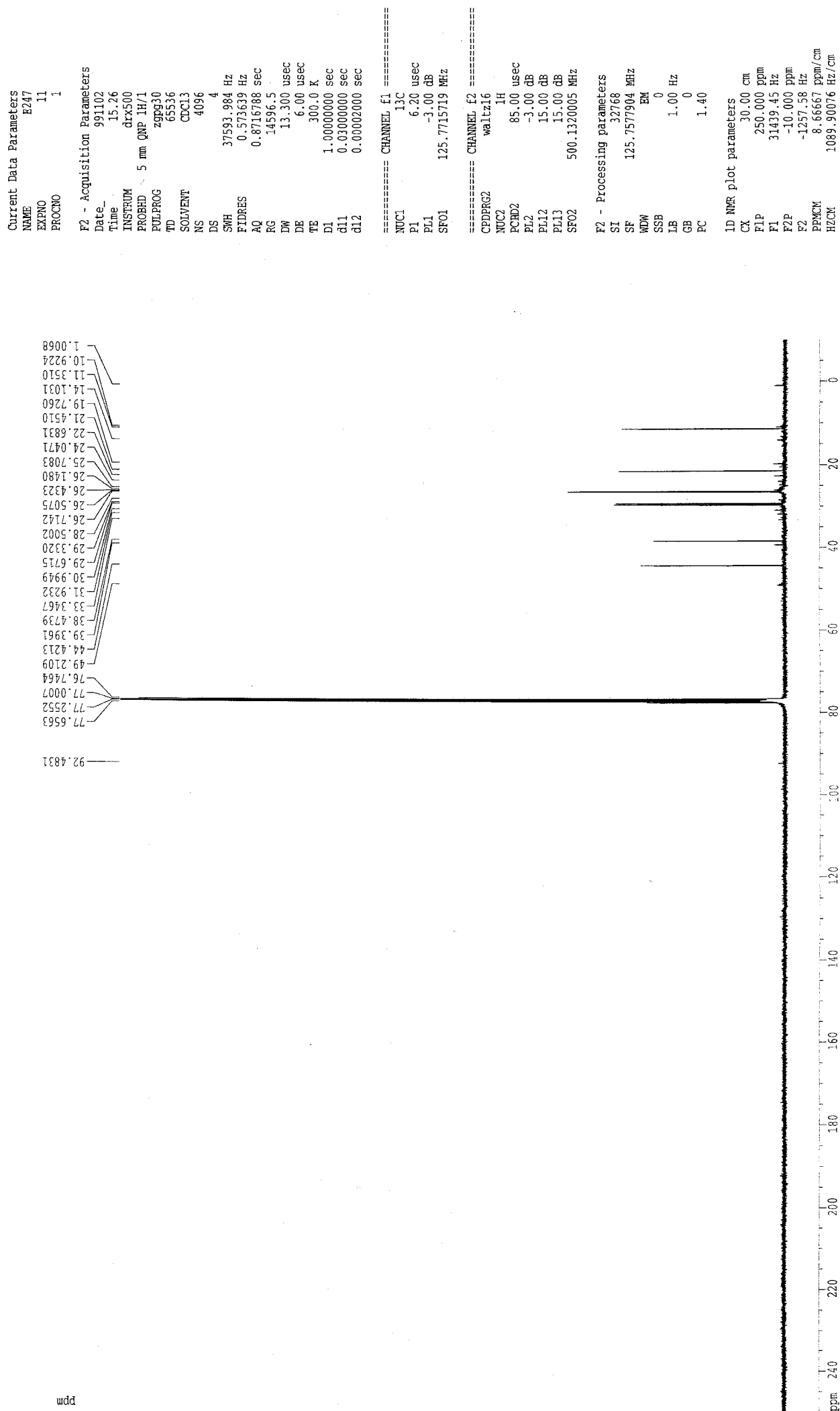
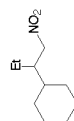
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1D NMR plot parameters

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F1 5501.43 Hz
F2P -1.000 ppm
F2 -500.13 Hz
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HZCM 200.05202 Hz/cm



BENHAIM
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BENHAIM
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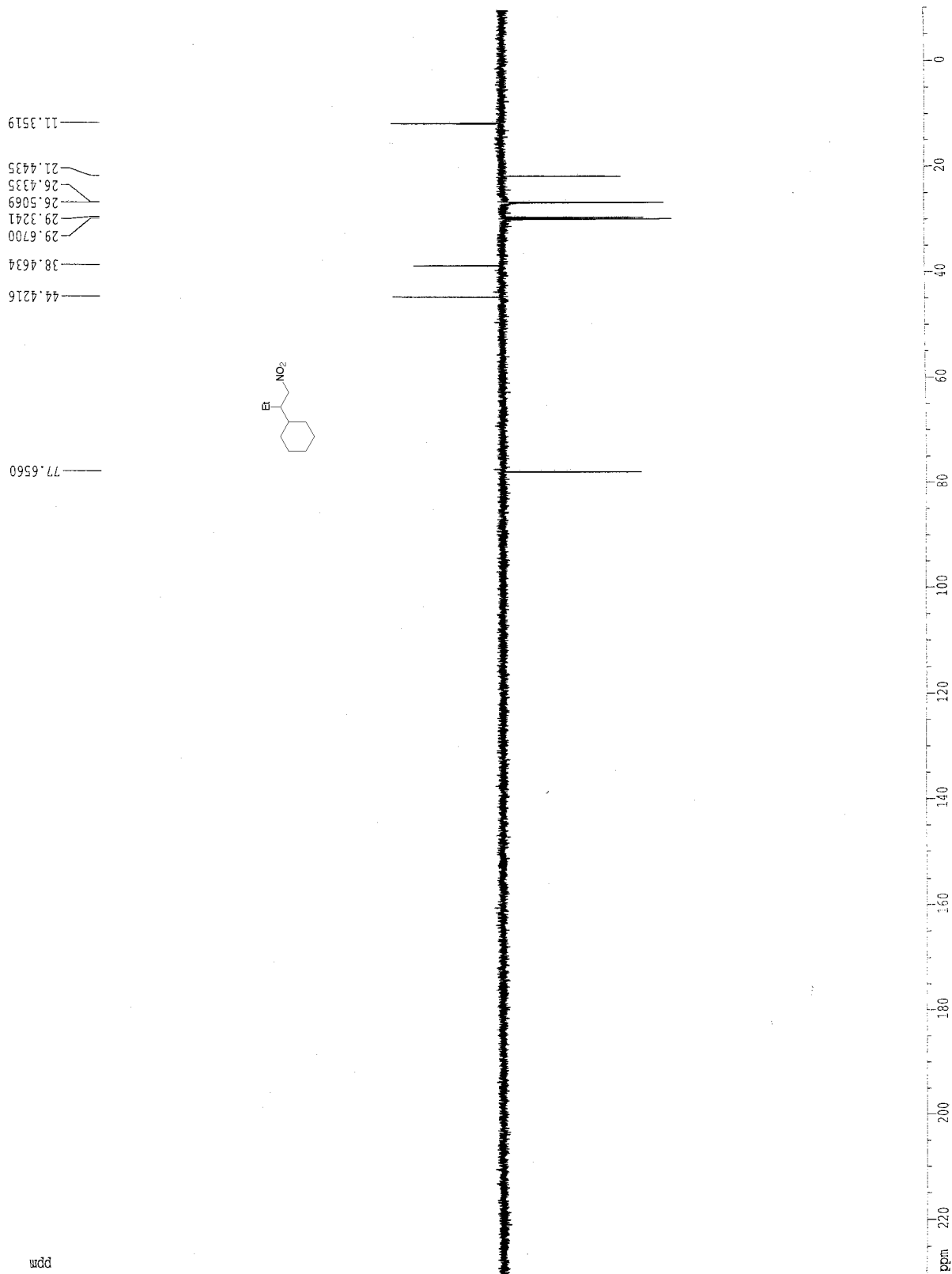
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PL1 -3.00 dB
SFO1 125.7715718 MHz

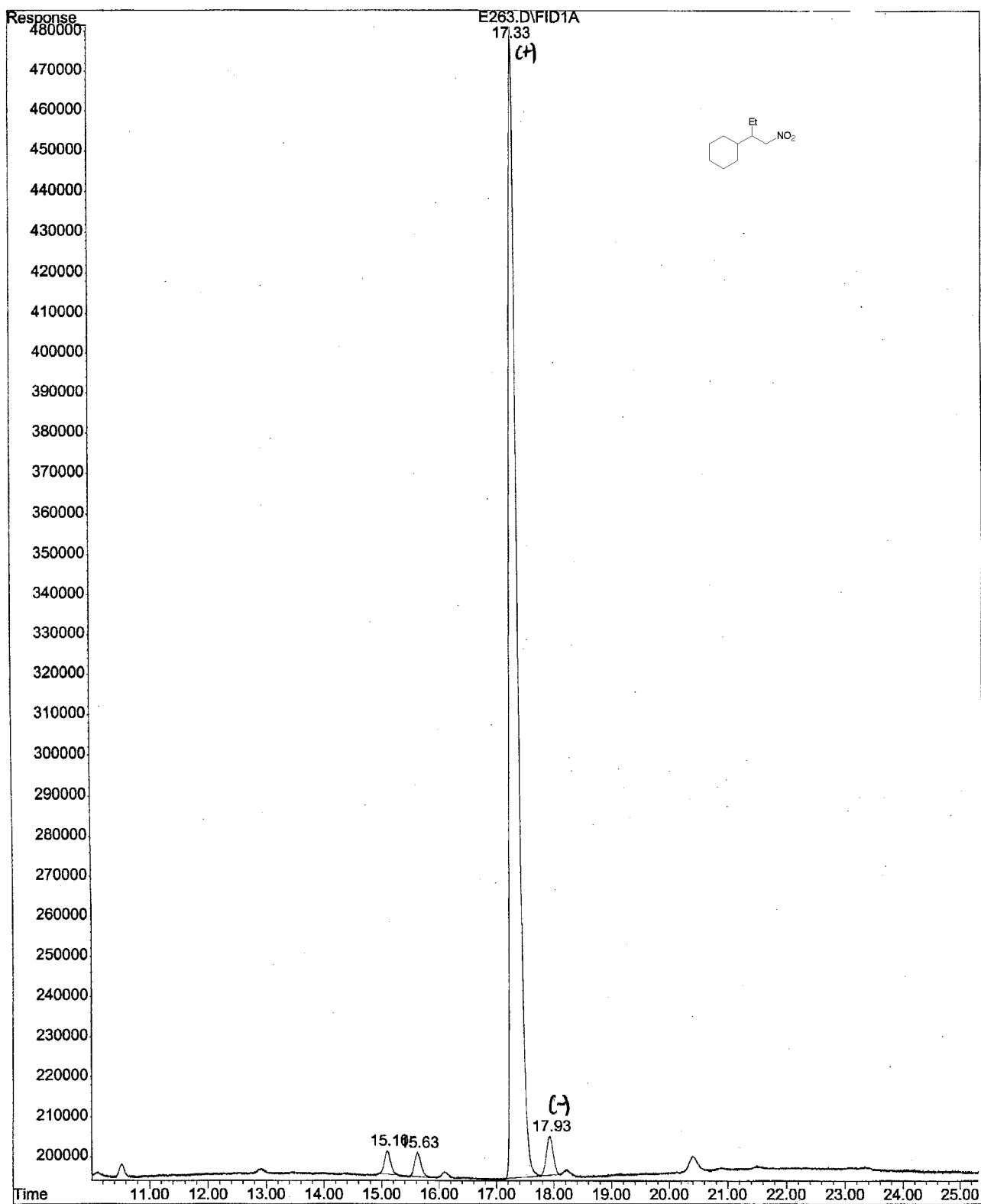
===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
P3 10.60 usec
P4 21.20 usec
PCPD2 85.00 usec
PL2 -3.00 dB
PL12 15.00 dB
SFO2 500.1320005 MHz

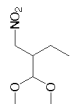
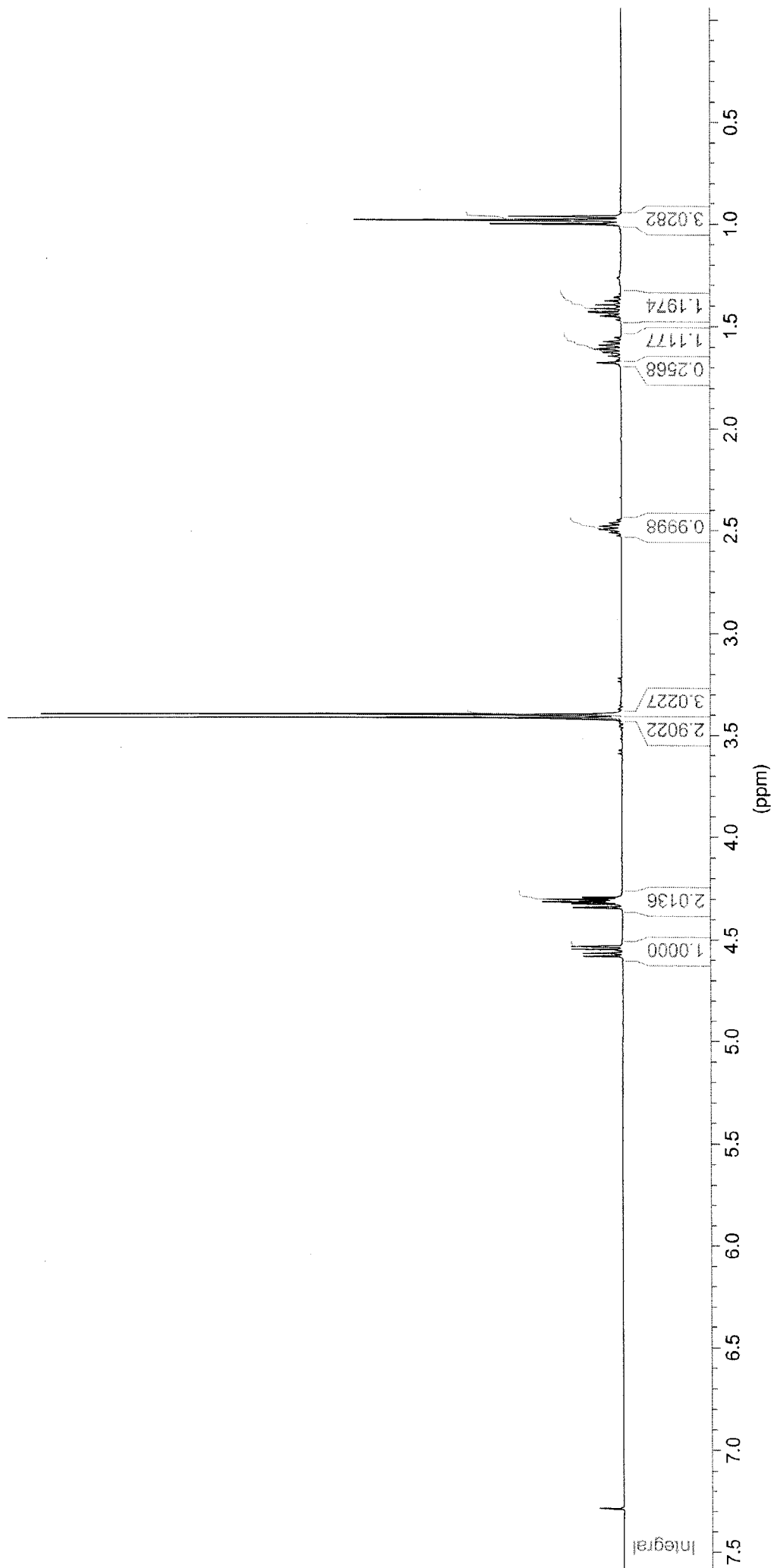
F2 - Processing parameters
SI 32768
SF 125.7577904 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 30.00 cm
F1P 230.000 ppm
F1 28924.29 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 8.00000 ppm/cm
HZCM 1006.06232 Hz/cm



File : C:\HPCHEM\2\DATA\E263.D
Operator : CYRIL
Acquired : 2-15-00 9:38:34 using AcqMethod FRONTVAR.M
Instrument : HP G1530A
Sample Name:
Misc Info :
Vial Number: 1



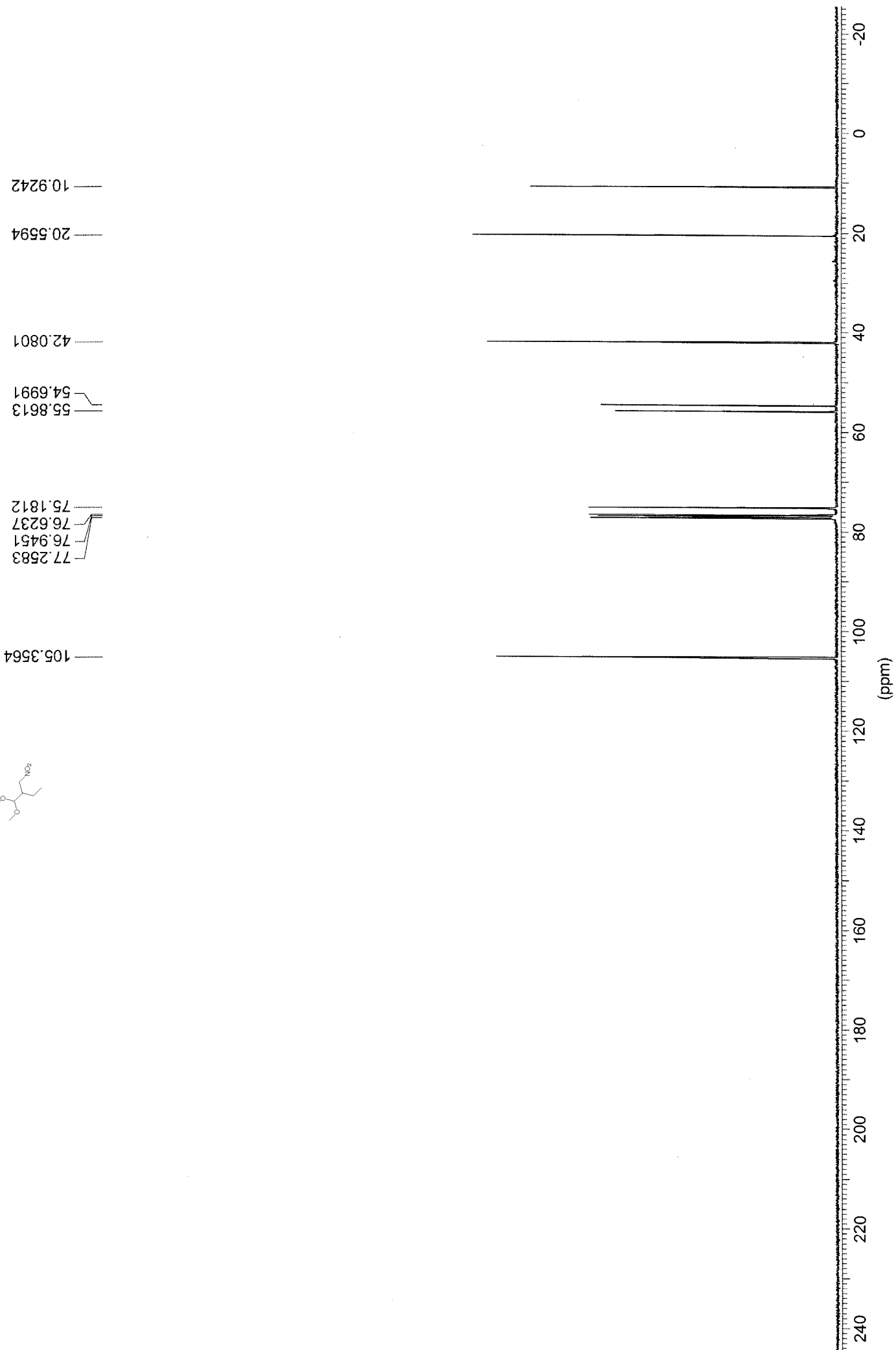


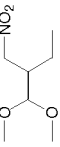
1.6775
1.6283
1.6251
1.6087
1.5929
1.5898
1.5740
1.4490
1.4307
1.4124
1.3947
1.3764
1.0026
0.9837
0.9647

2.4945
2.4806

3.4182
3.4012

4.5812
4.5667
4.5490
4.5345
4.3426
4.3255
4.3160
4.3104
4.3034
4.2933





105.3481

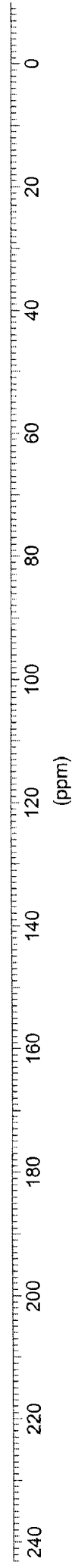
75.1812

55.8778
54.6991

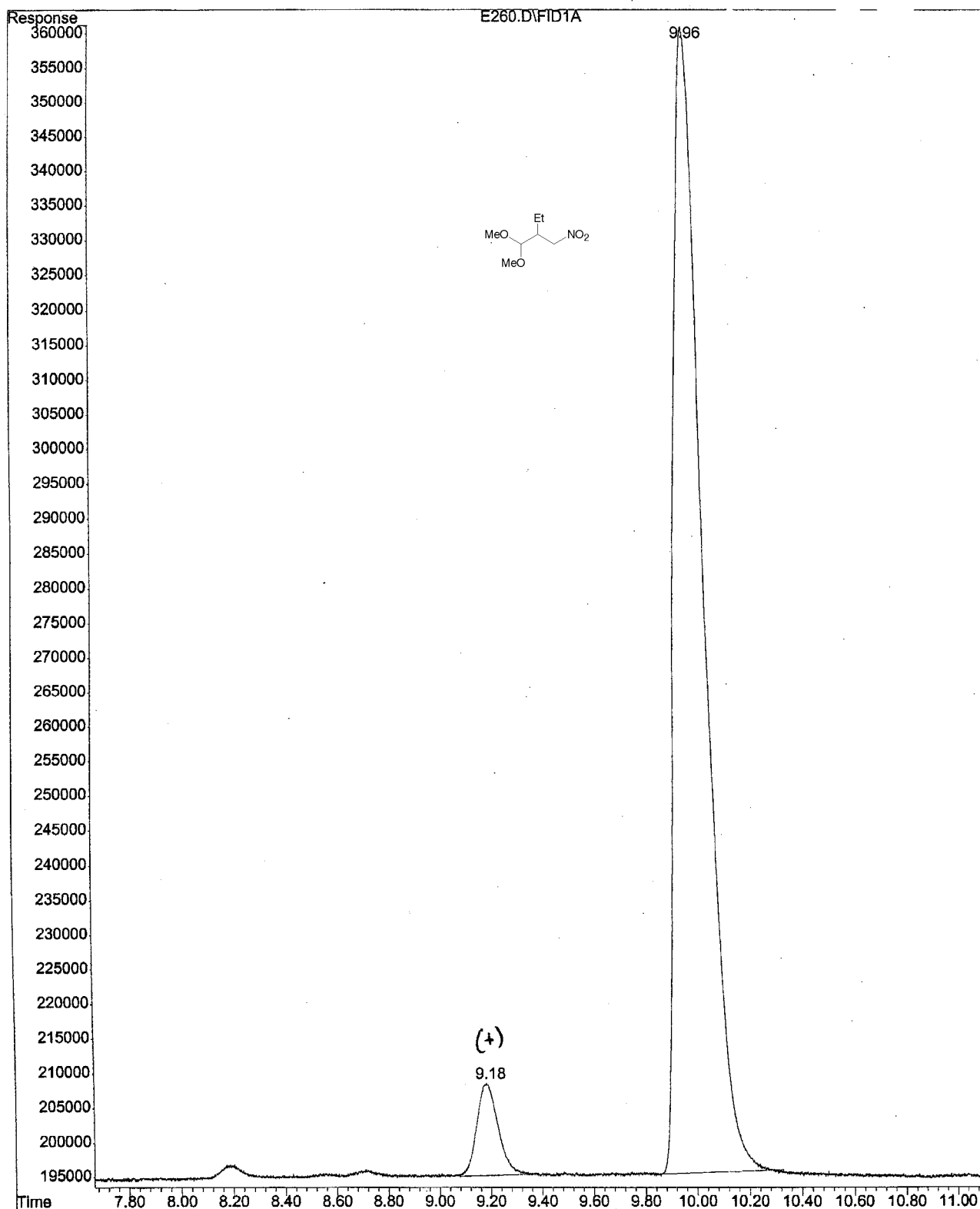
42.0719

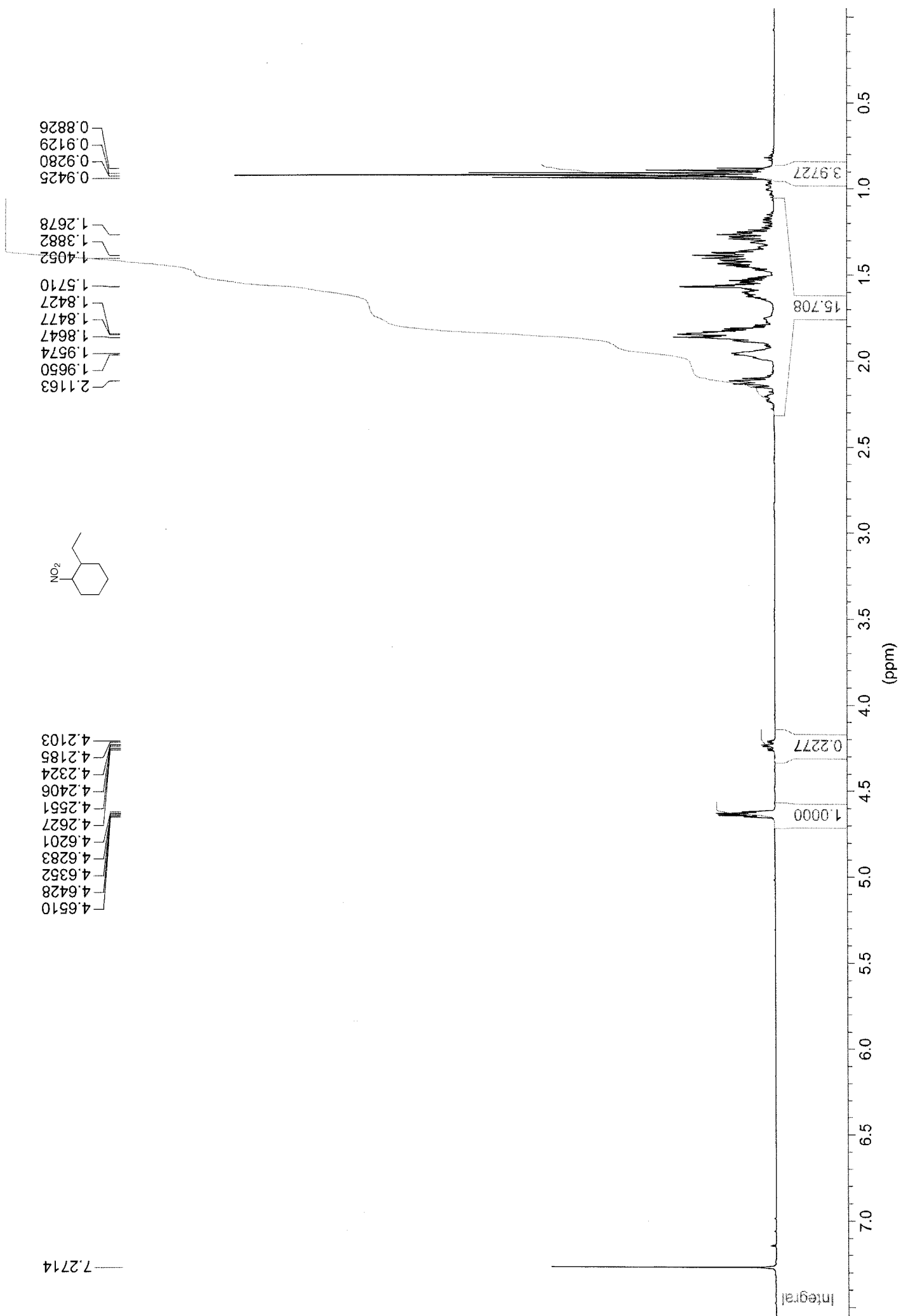
20.5594

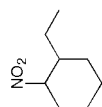
10.9324



File : C:\HPCHEM\2\DATA\E260.D
Operator : CYRIL
Acquired : 2-11-00 10:30:58 using AcqMethod FRONTVAR.M
Instrument : HP G1530A
Sample Name:
Misc Info :
Vial Number: 1







42.1140
40.7365

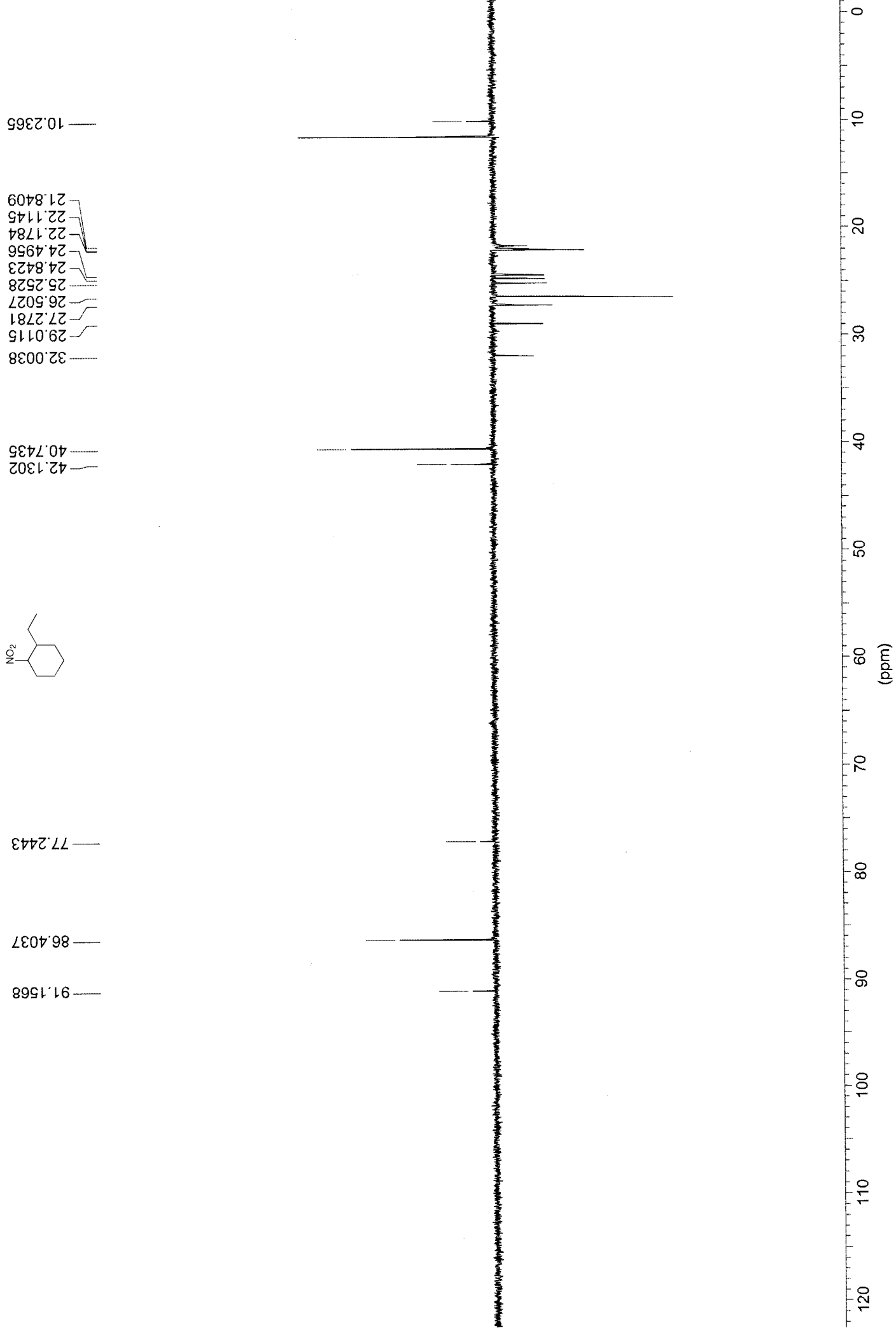
31.9876
28.9953
27.2710
26.4865
25.2366
24.8261
24.4794
22.1622
22.1075
21.8338

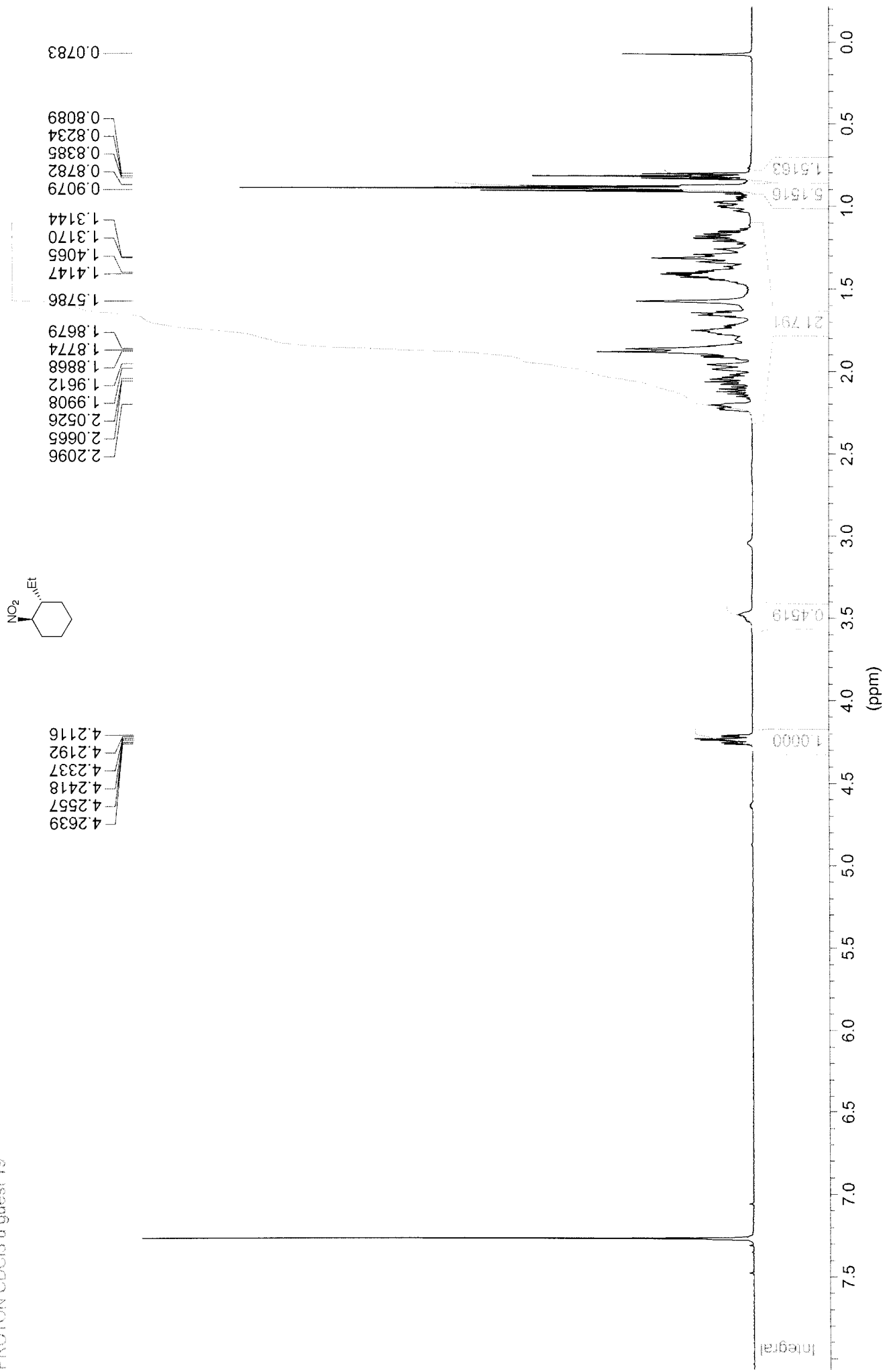
11.6435
10.2203

86.3875

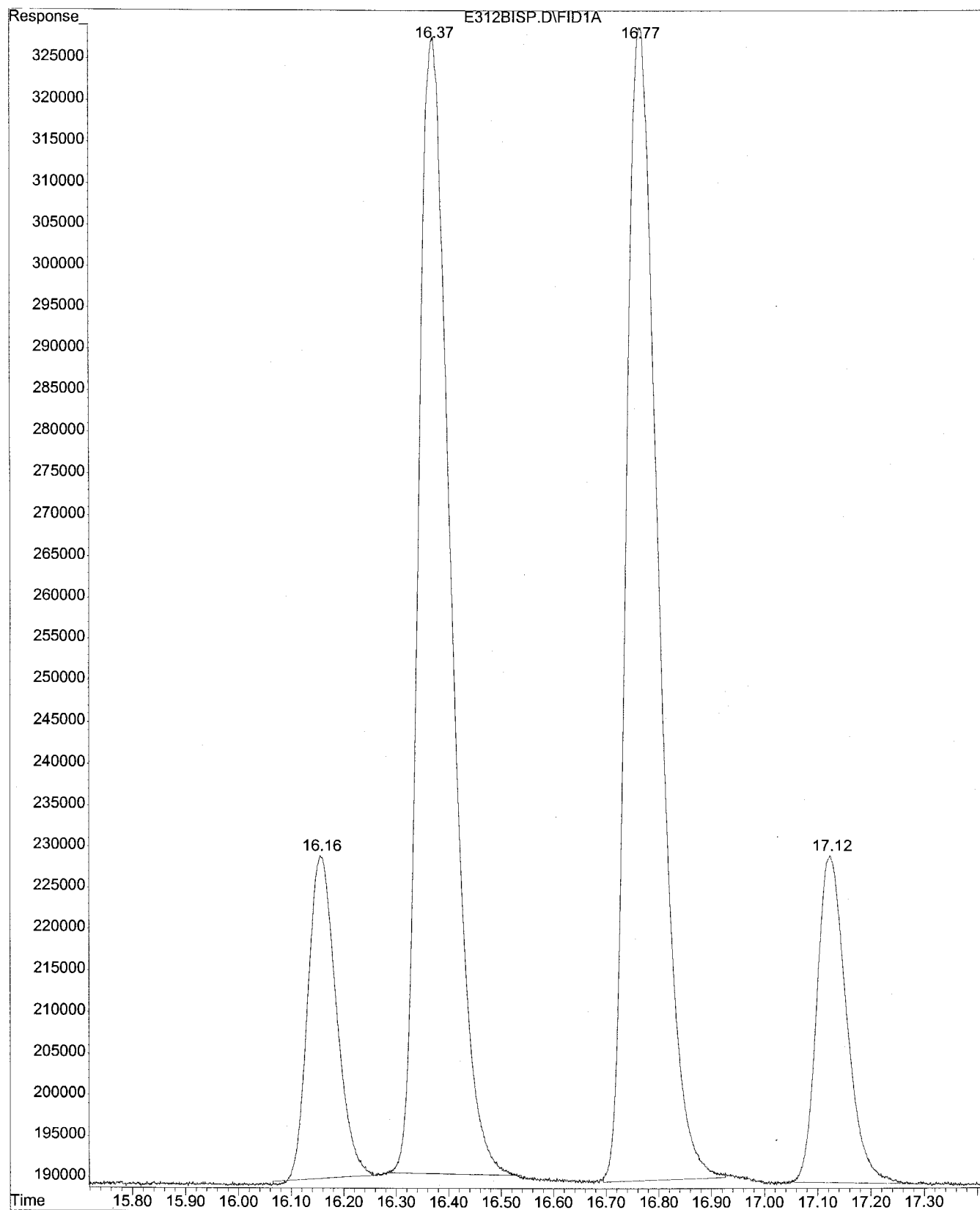
91.1314

(ppm)

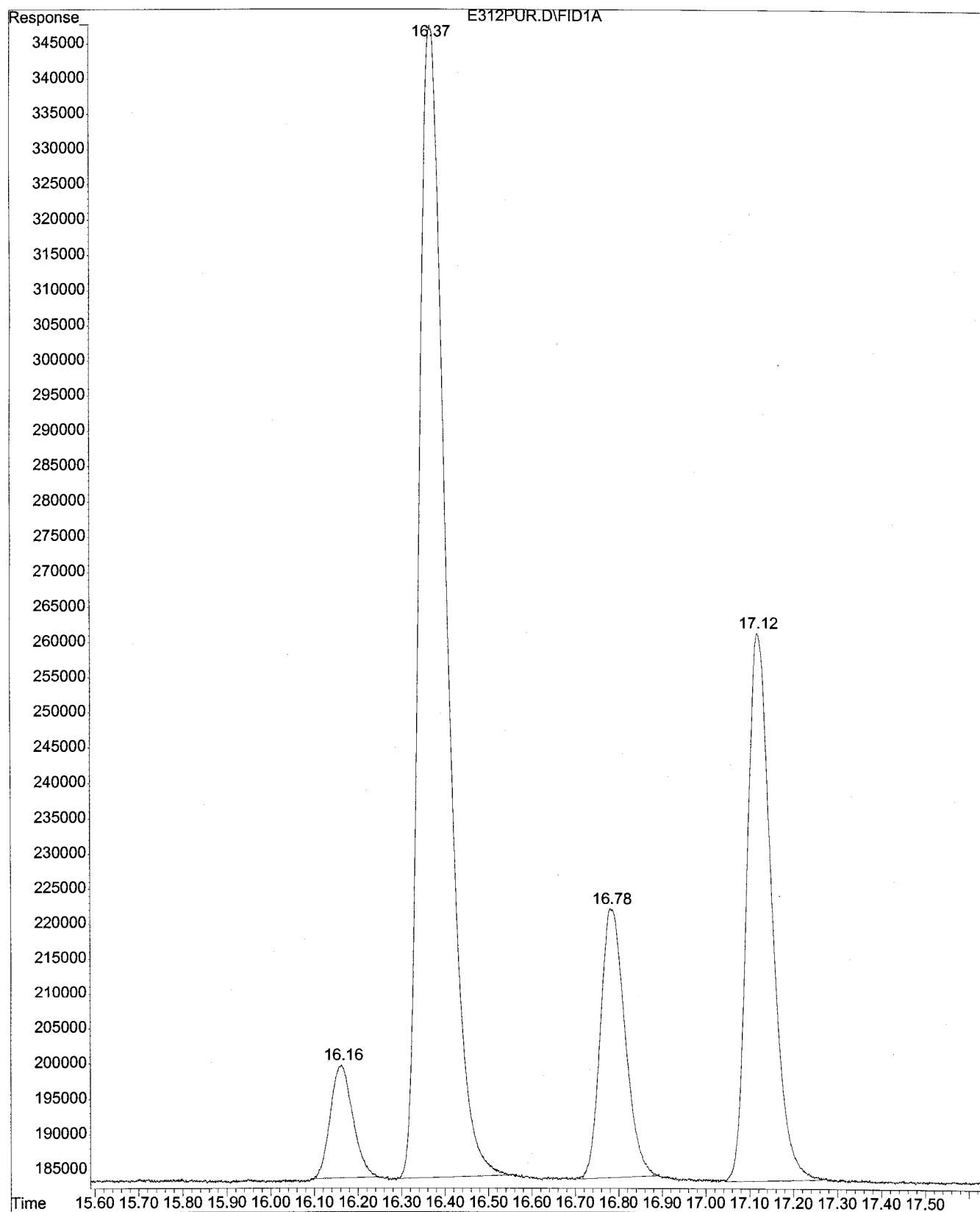


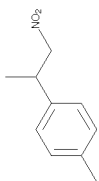


File : C:\HPCHEM\2\DATA\E312BISP.D
Operator : CYRIL
Acquired : 6-23-00 14:42:37 using AcqMethod FRONTVAR.M
Instrument : HP G1530A
Sample Name:
Misc Info : 60-3-130-
Vial Number: 4



File : C:\HPCHEM\2\DATA\E312PUR.D
Operator : CYRIL
Acquired : 6-24-00 16:44:17 using AcqMethod FRONTVAR.M
Instrument : HP G1530A
Sample Name:
Misc Info : 60-3-120-
Vial Number: 8





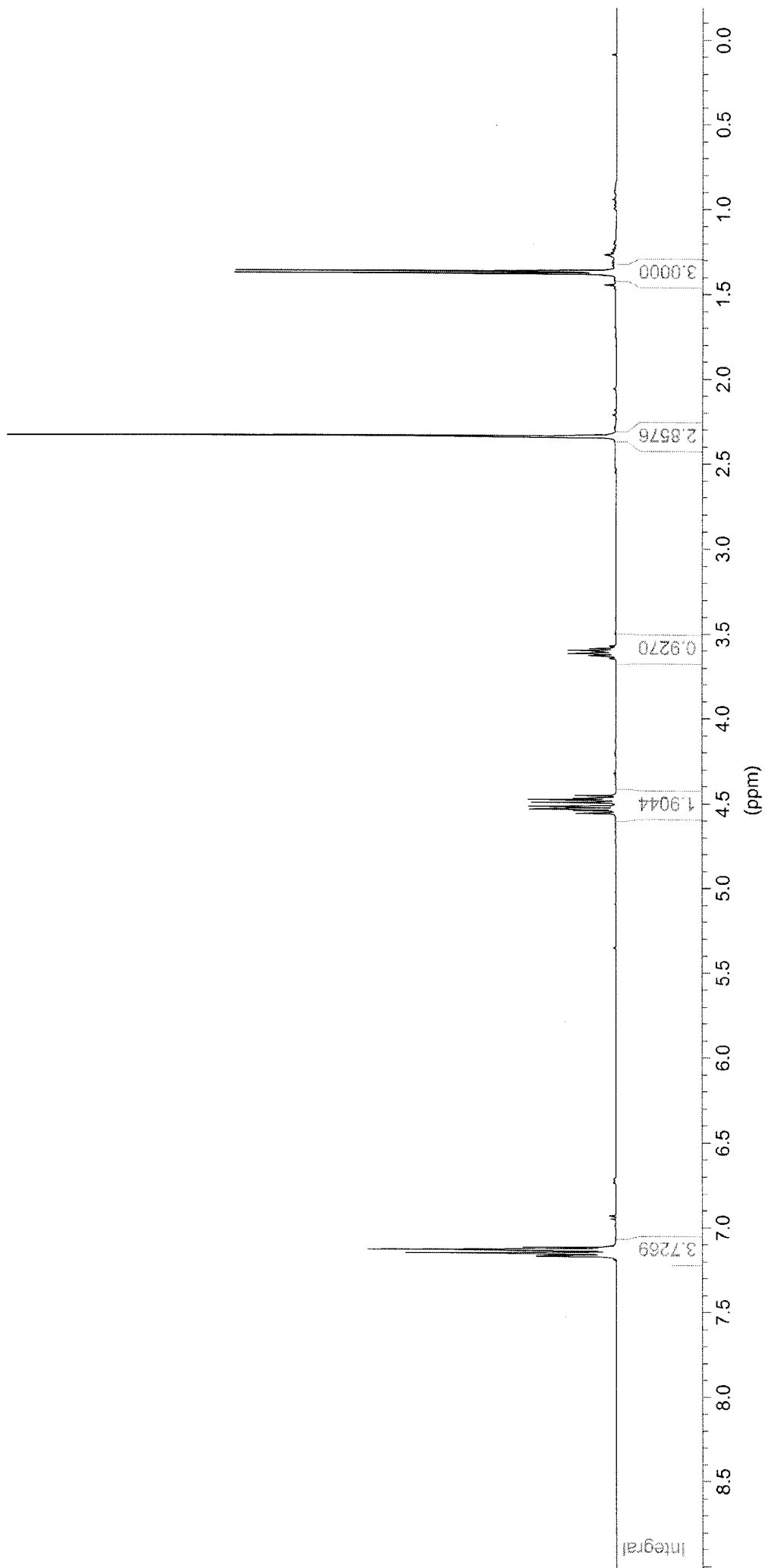
1.3680
1.3819

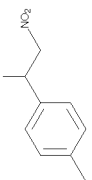
2.3413

3.5882
3.6027
3.6178
3.6323

4.4549
4.4719
4.4789
4.4959
4.5205
4.5350
4.5444
4.5589

7.1188
7.1352
7.1548
7.1712





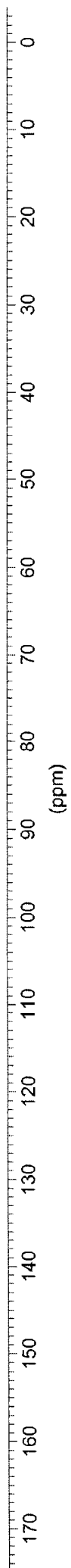
21.0036
18.7502

38.2824

81.9902

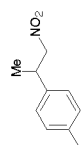
129.6118
126.7381

137.8407
137.2295



21.0198
18.7573

38.2895



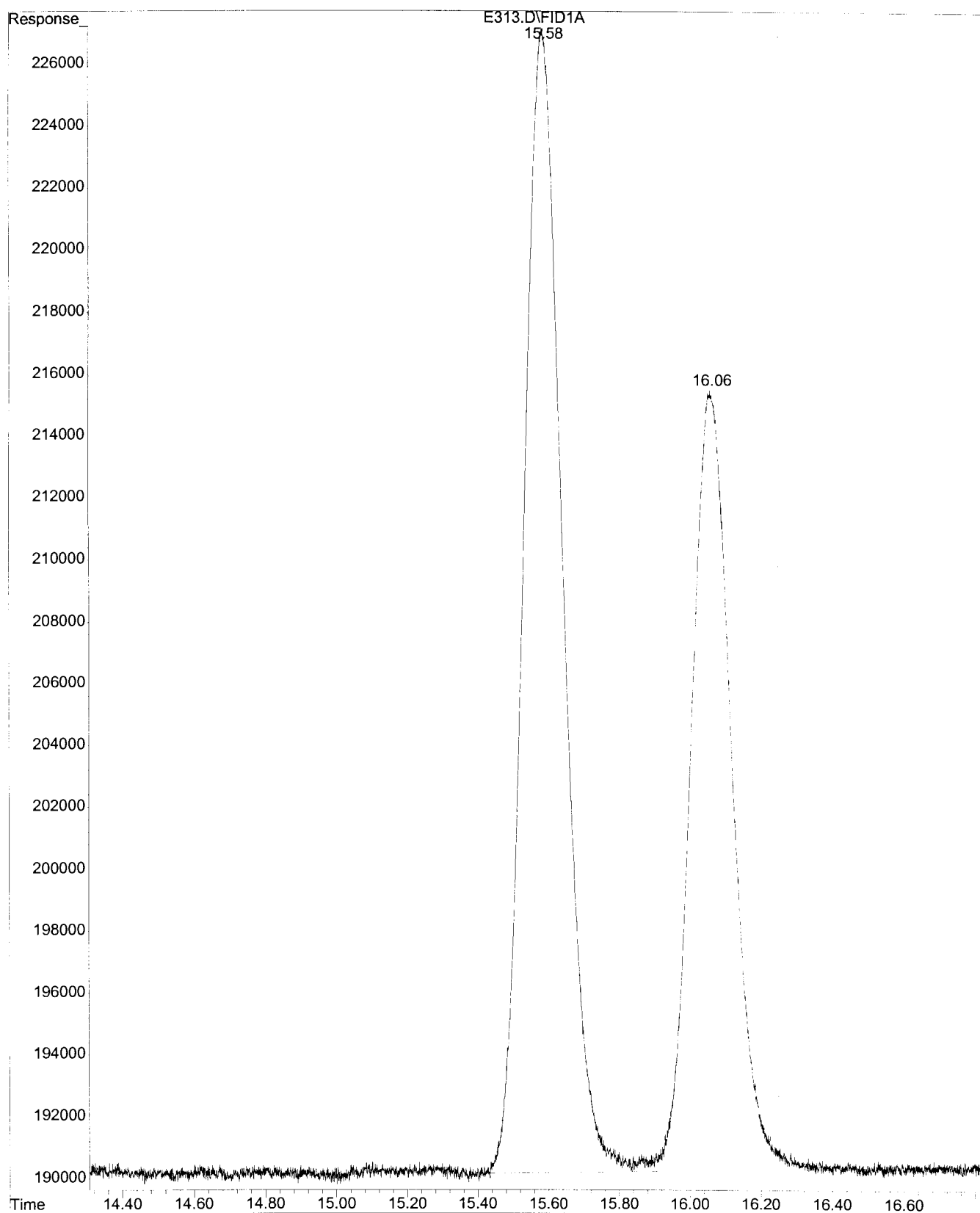
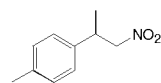
81.9882

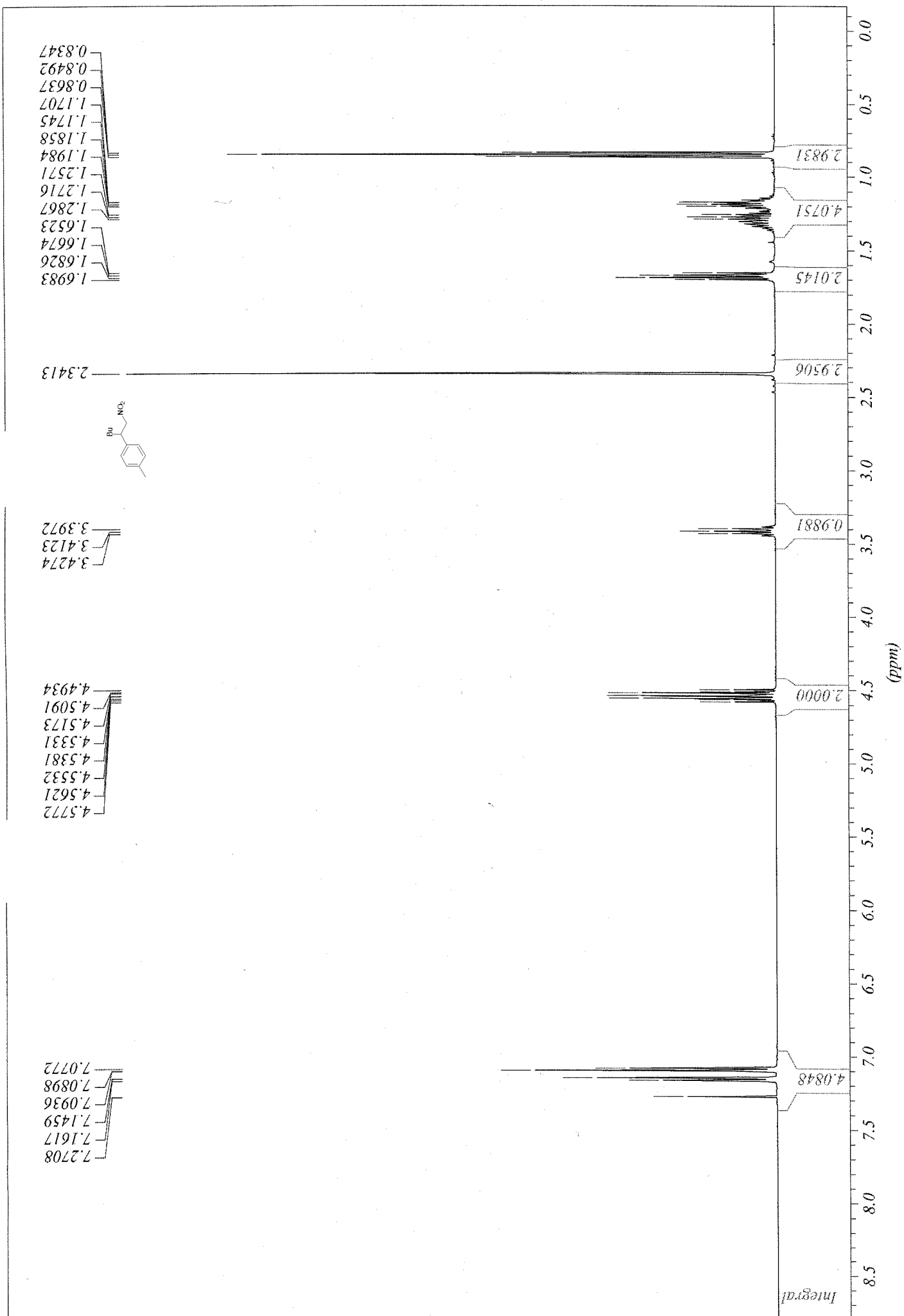
129.1993
126.7544

-30 -10 10 30 50 70 90 110 130 150 170 190 210 230

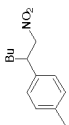
(ppm)

File : C:\HPCHEM\2\DATA\E313.D
Operator : CYRIL
Acquired : 6-23-00 17:15:13 using AcqMethod FRONTVAR.M
Instrument : HP G1530A
Sample Name:
Misc Info : 100-1-120-
Vial Number: 5





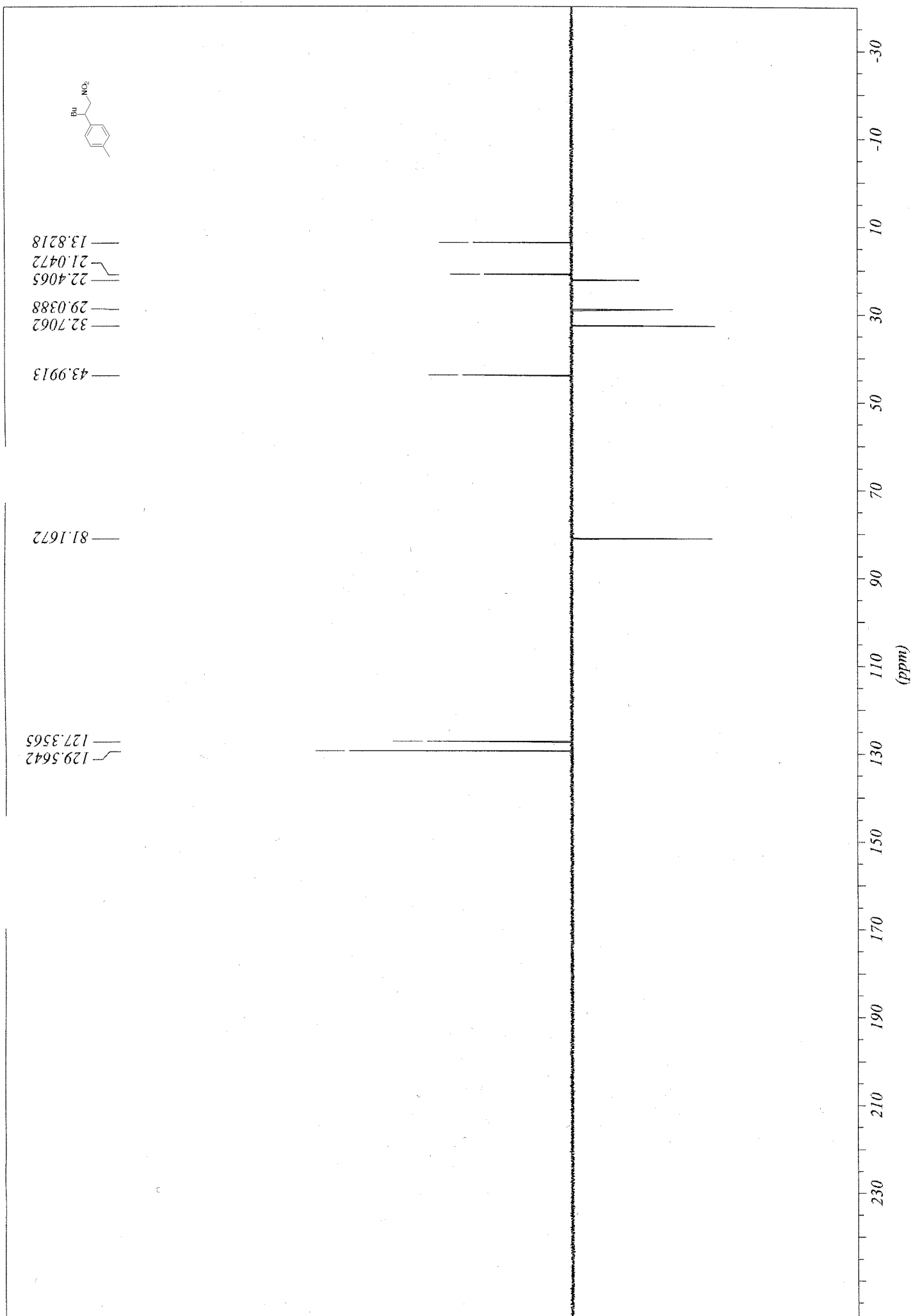
— 13.7965
 — 21.0310
 — 22.3812
 — 29.0226
 — 32.6900
 — 43.9751



— 76.7446
 — 77.0000
 — 77.2555
 — 81.1510

— 127.3311
 — 129.5480
 — 136.4267
 — 137.1383

(ppm)



File : C:\HPCHEM\2\DATA\E278G.D
Operator : Louise
Acquired : 3-29-00 18:25:38 using AcqMethod G-TA-401.M
Instrument : HP G1530A
Sample Name: E278G
Misc Info :
Vial Number: 5

