An Efficient and General Protocol for the Copper-Free Sonogashira Coupling of Aryl Bromides at Room Temperature

Arash Soheili*, Jennifer Albaneze-Walker, Jerry A. Murry, Peter G. Dormer, David L. Hughes

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc.
PO Box 2000, Rahway, NJ 07065

Supporting Information

General Information: Solvents, bases, acetylene, and aryl halides were purchased from Aldrich and used without purification. $(AllylPdCl)_2$ was purchased from Johnson & Matthey and P(*t*-Bu)$_3$ was purchased as a 10 wt% solution in hexanes from Digital Science and Strem Chemicals. P(*t*-Bu)$_3$HBF$_4$ was purchased from Strem Chemicals. All reactions were monitored by HPLC using XTerra column (XTerra RP_{18} 5*u*m) 4.6 x 250 mm, eluent: CH_3CN / 20mM KH_2PO_4 buffer. Initial conditions of 40% CH_3CN with gradient to 80% CH_3CN over 25 min. Flow rate of 1 mL/min with UV detection at 220nm. All ends of reactions were determined by the complete consumption of aryl halide by HPLC. All products conformed to previously published ^{1}H NMR spectra referenced.

Representative Procedure – aryl bromide is a solid (Table 2, Entry 2; 4-Methylbenzoate phenyl acetylene):[1] Reaction time: 23 h. Methyl 4-bromobonzoate (0.46 g, 2.12 mmol) and $(AllylPdCl)_2$ (0.019 g, 0.053 mmol) was added to a dry Schlenk tube and sealed with a rubber septa. The vessel was degassed then backfilled with nitrogen in 3 repetitions followed by addition of acetonitrile (2.5 mL). Then P(*t*-Bu)$_3$ (0.64 mL of a 10 wt% in hexnaes, 0.21 mmol), phenylacetylene (0.26 mL, 2.33 mmol), and piperidine (0.42 mL, 4.24 mmol) were added in that order via a syringe to the stirred reaction mixture. During the reaction, the precipitation of piperidine bromide salt was observed. After completion of reaction, as determined by complete conversion of aryl halide, EtOAc (10 mL) and water (5 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with 2 x 10 mL of EtOAc. The organic layers were combined then washed with brine, dried with sodium sulfate, and concentrated. Purification by flash chromatography (95:5 / Hexanes:EtOAc) furnished the desired product (0.46 g, 92%) as a solid.

Representative Procedure - aryl bromide is a liquid (Table 2, Entry 10; 2,6-Dimethylphenyl phenyl acetylene):[2] Reaction time: < 18 h. $(AllylPdCl)_2$ (0.022 g, 0.061 mmol) was added to a dry Schlenk tube and sealed with a rubber septa. The vessel was degassed then backfilled with nitrogen in 3 repetitions followed by addition of acetonitrile (2.5 mL) and 2,6-bromoxylene (0.45 g, 2.42 mmol). Then P(*t*-Bu)$_3$ (0.73 mL of a 10 wt% in hexanes, 0.24 mmol) and phenylacetylene (0.29 mL, 2.66 mmol) were added in that order via a syringe to the stirred reaction mixture followed immediately by DABCO (0.54 g, 4.84 mmol) under a positive pressure of nitrogen. During the reaction the precipitation of DABCO bromide salt was observed. After completion of reaction, as determined by complete conversion of aryl halide, EtOAc (10 mL) and water (5 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with 2 x 10 mL of EtOAc. The organic layers was combined then washed with brine, dried with sodium sulfate, and concentrated. Purification by flash chromatography (100 % Hexanes) furnished the desired product (0.44 g, 88%) as an oil.

Table 2, Entry 1: 4-phenyl cyclopropylmethanone ethynylferrocene. Reaction time: 16 h. Purification by flash chromatography (95:5 / hexanes:EtOAc to 85:15 / hexanes:EtOAc) furnished the desired product (0.43g, 86%) as a orange solid. ^{1}H NMR (400 MHz, C_6D_6) δ 0.64 (dq, 2H, J = 8.0, 3.6 Hz), 1.31 (dq, 2H, J = 4.4, 3.6 Hz), 2.14 (tt, 1H, J = 8.0, 4.4 Hz), 4.06 (t, 2H, J = 1.8 Hz), 4.18 (s, 5H), 4.60 (2H, t, J = 1.8 Hz), 7.58

(d, 2H, J = 8.4 Hz), 7.90 (d, 2H, J = 8.4 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.7, 17.1, 64.4, 69.1, 70.0, 71.5, 85.2, 92.2, 127.9, 128.5, 131.3, 136.4, 199.7; Anal Calcd for $C_{22}H_{18}FeO$: C, 74.60; H, 5.12; Fe, 15.77. Found: C, 73.96; H, 5.10; Fe, 16.40. m.p. 164 – 165 °C.

Table 2, Entry 3: 4-Acetylphenyl phenyl acetylene.[3] Reaction time: 9 h. Purification by flash chromatography (95:5 / hexanes:EtOAc) furnished the desired product (0.48g, 96%) as a solid.

Table 2, Entry 4: 2-Methyl-4-acetylphenyl-3-butyn-2-ol.[4] Reaction time: 48 h. Purification by flash chromatography (6:4 / hexanes:EtOAc) furnished the desired product (0.40g, 80%) as a oil.

Table 2, Entry 5: 1-Acetylphenyl-1-octyne.[5] Reaction time: <15 h. Purification by flash chromatography (95:5 hexanes:EtOAc) furnished the desired product (0.39g, 78%) as a oil.

Table 2, Entry 6: Diphenyl acetylene.[6] Reaction time: < 15 h. Purified by filteration over a short plug of silica and washing with ~ 600 mL of hexanes. The filterate was concentrated to furnish the desired product (0.43g, 86%) as a solid.

Table 2, Entry 7: 1-Cyclohexene phenyl acetylene.[7] Reaction time: < 20 h. Purified by filteration over a short plug of silica and washing with ~ 500 mL of hexanes. The filterate was concentrated to furnish the desired product (0.48g, 96%) as a solid.

Table 2, Entry 8: 4-Methoxyphenyl phenyl acetylene.[8] Reaction time: 11 h. Purification by flash chromatography (98:2 hexanes:EtOAc) furnished the desired product (0.41g, 82%) as a solid.

Table 2, Entry 9: 1-Cyclohexene-4-methoxyphenyl acetylene.[9] Reaction time: < 20 h. Purification by flash chromatography (99:1 hexanes:EtOAc) furnished the desired product (0.46g, 92%) as a oil.

Table 2, Entry 11: 3-pyridine phenyl acetylene.[10] Reaction time: 48 h. After completion of reaction, as determined by HPLC, EtOAc (10 mL) and water (5 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with 10 mL of EtOAc. The combined organics were then extracted with 3 x 10 mL of 2N HCl and the organic discarded. The combined aqueous was pH adjusted to 7 and extracted with 3 x 10 mL of EtOAc. The combined organics layers were then dried with sodium sulfate and concentrated. Purification by flash chromatography (7:3 hexanes:EtOAc) furnished the desired product (0.42g, 84%) as a solid.

Table 2, Entry 12: 3-pyridine-N-oxide phenyl acetylene. Reaction time: 35 h. Purification by flash chromatography (9:1 /EtOAc:MeOH) furnished the desired product (0.47g, 94%) as a off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.26 (m, 1H), 7.36-7.42 (m, 4H), 7.51-7.56 (d, 2H, J = 6.4 Hz), 8.15-8.18 (d, 2H, J = 6.4 Hz), 8.33 (s,

1H),; ^{13}C NMR (400 MHz, $CDCl_3$): δ 83.0, 94.5, 121.4, 123.5, 125.6, 128.4, 128.5, 131.8, 138.6, 141.0.; Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 78.11; H, 4.59; N, 6.94. m.p. 114 – 115 °C.

Table 2, Entry 13: 3-thiophene phenyl acetylene.[11] Reaction time: < 16 h. Purification by flash chromatography (100% hexanes) furnished the desired product (0.48g, 96%) as a solid.

Table 2, Entry 14: 4-Acetylphenyl phenyl acetylene.[3] Reaction time: 24 h. Phenylacetylene was charged via a syringe pump at a rate of 0.03 mL/h. After completion of reaction, as determined by HPLC, Ether (10 mL) and water (5 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with 2 x 10 mL of Ether. The organic layers were combined then washed with brine, dried with sodium sulfate, and concentrated. Purification by flash chromatography (95:5 / hexanes:EtOAc) furnished the desired product (0.25g, 50%) as a solid.

References:

(1) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873-8879.

(2) Cao, D.; Kolshorn, H.; Meier, H. *Tetrahedron Lett.* **1996**, *37*, 4487-4490.

(3) Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, *7*, 756-757.

(4) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763-1765.

(5) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J.Org.Chem.* **2000**, *65*, 1780-1787.

(6) Katritzky, A. R.; Wang, J.; Karodia, N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4142-4147.

(7) Stille, J. K.; Simpson, J. H. *J. Amer. Chem. Soc.* **1987**, *109*, 2138-2152.

(8) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729-1731.

(9) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91-94.

(10) Bookham, J. L.; Smithies, D. M. *J. Organomet. Chem.* **1999**, *577*, 305-315.

(11) Walsh, C. J.; Mandal, B. K. *J. Org. Chem.* **1999**, *64*, 6102-6105.

Kinetic Data: All reactions were monitored by HPLC using XTerra column (XTerra RP_{18} 5*u*m) 4.6 x 250 mm, eluent: CH_3CN / 20mM KH_2PO_4 buffer. Initial conditions of 40% CH_3CN with gradient to 80% CH_3CN over 10 min. Flow rate of 2.2 mL/min with UV detection at 220nm. All concentrations were determined by comparison of the peak area of substrate to the internal standard of 1,4-di-*t*-butylbenzene.

Typical Procedure: 4-bromoacetophenone (0.452 g, 2.27 mmol), $(AllylPdCl)_2$ (.0166 g, 0.045 mmol), and 1,4-di-*t*-butylbenzene (0.19 g) were charged to a dry Schlenk tube and sealed with a rubber septa. The vessel was degassed then backfilled with nitrogen in 3 repetitions followed by addition of acetonitrile (5.5 mL). Then $P(t\text{-}Bu)_3$ (0.55 mL of a 10 wt% in hexanes, 0.18 mmol) was charged followed by DABCO (0.76 g, 6.81 mmol) under a positive pressure of nitrogen. The reaction is allowed to stir for 1 h at room temperature then phenylacetylene (0.24 g, 2.38 mmol) was charged and the reaction monitored by HPLC.

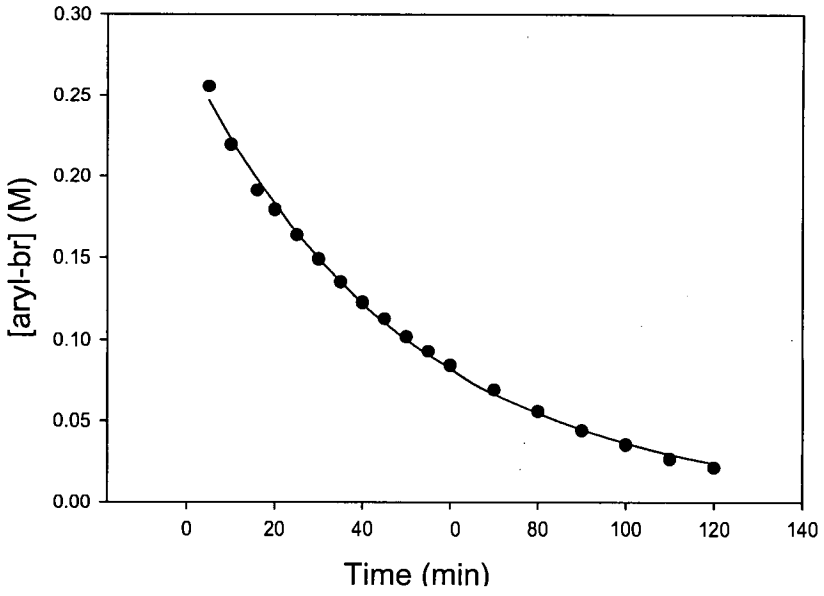


Figure S1. [Bromoacetophenone] versus time in coupling with phenylacetylene

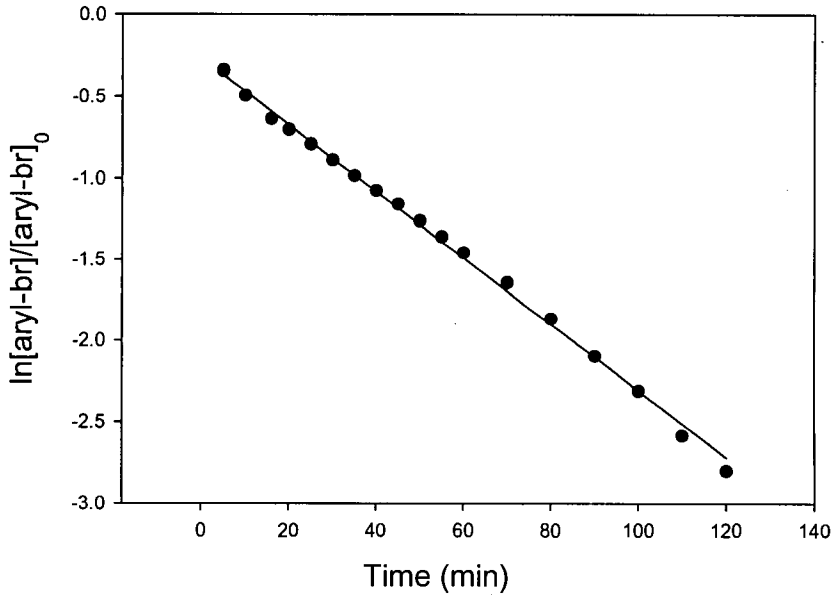
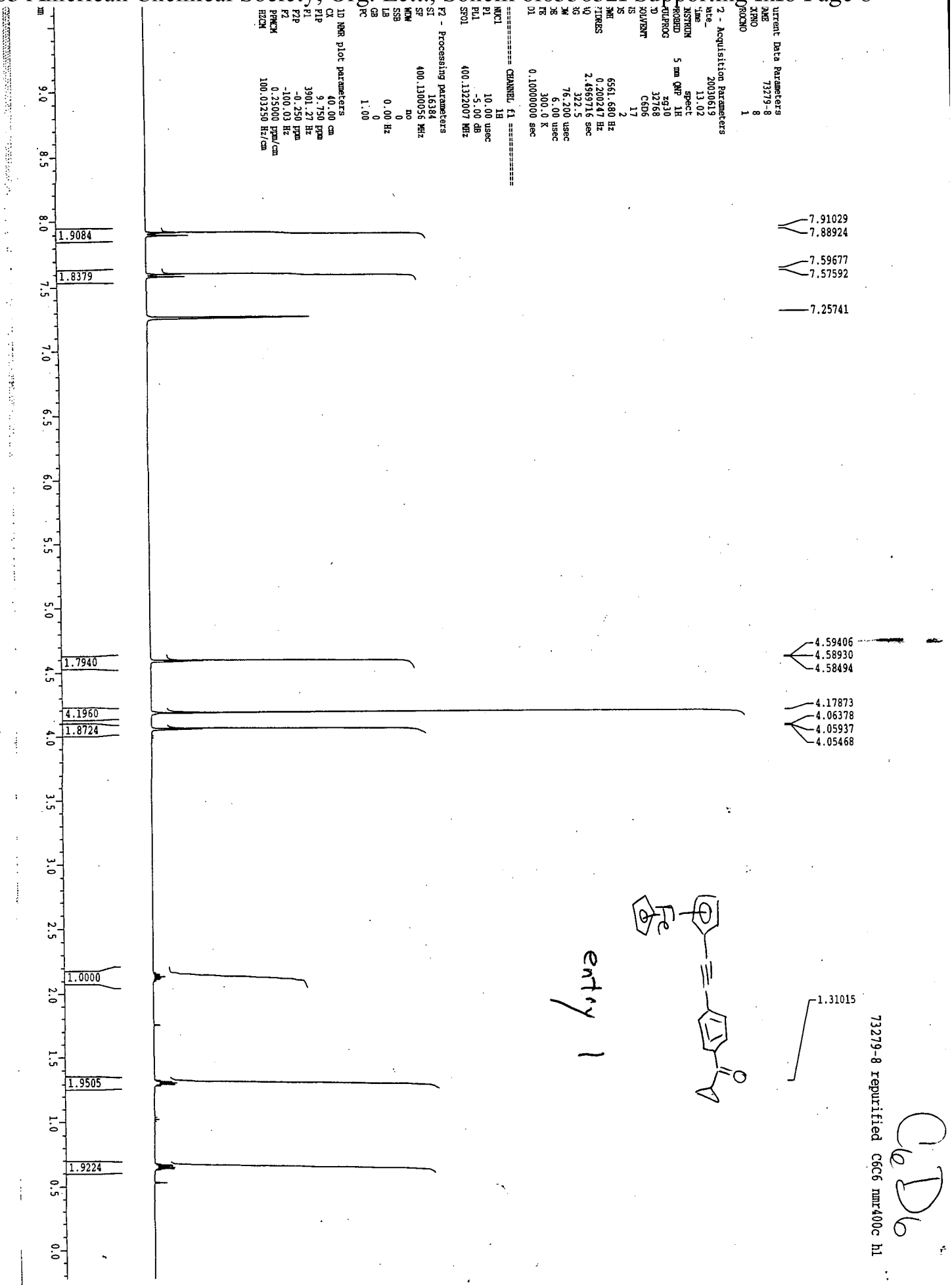
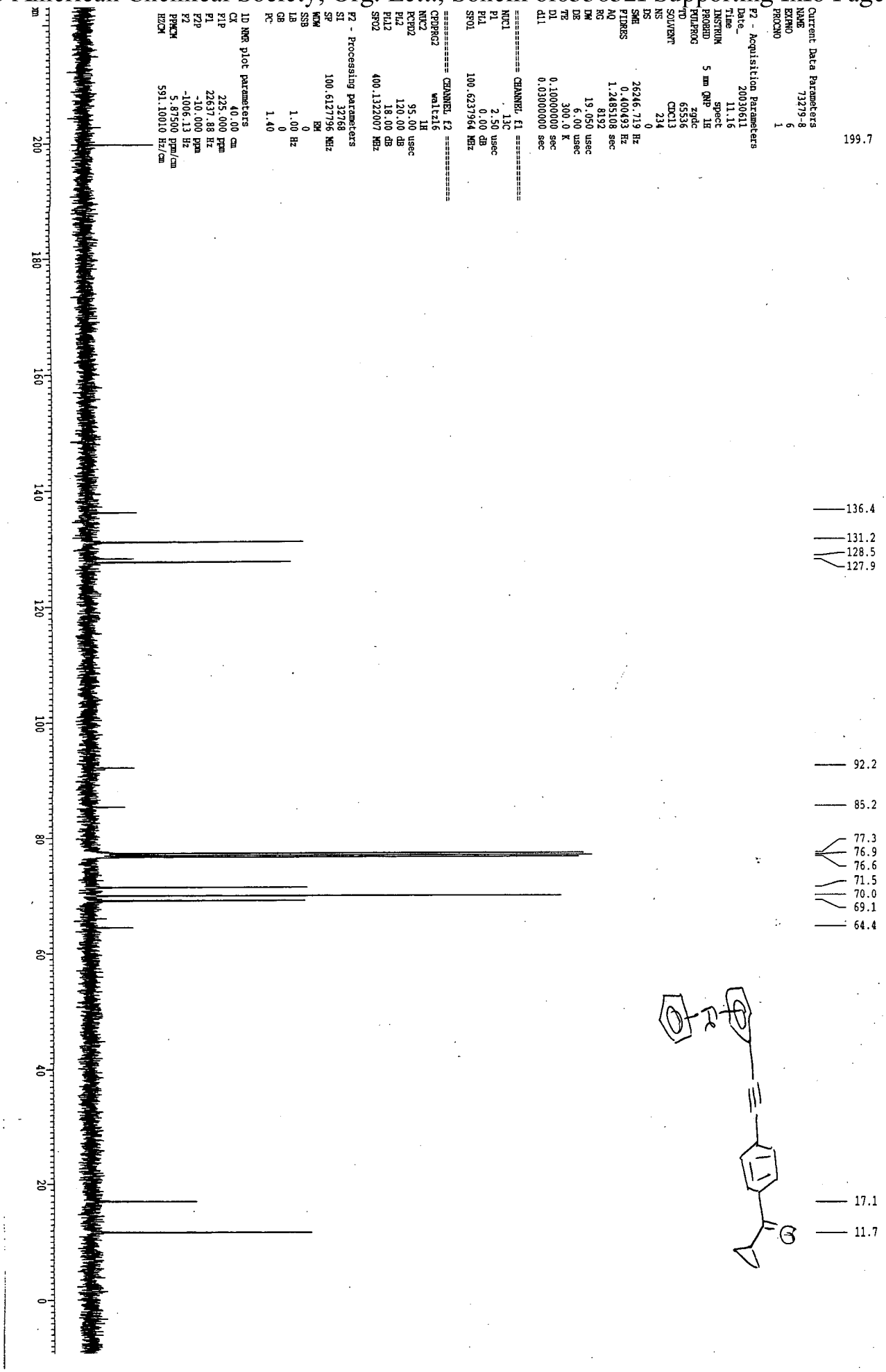


Figure S2. 1st Order Plot of Bromoacetophenone

Table S1. Observed Rates of Reaction with Changing Substrate Concentration

[Aryl-Br] (M)	[PhCCH] (M)	[DABCO] (M)	k_{obs} (s^{-1}) x 10^{-2}
0.360	0.377	0.719	1.33
0.528	0.377	0.719	1.95
0.719	0.377	0.719	2.41
0.943	0.377	0.719	4.17
0.360	**0.719**	0.719	2.02
0.360	**1.079**	0.719	2.75
0.360	**1.439**	0.719	2.78
0.360	0.377	**0.904**	1.47
0.360	0.377	**1.074**	2.04
0.360	0.377	**1.427**	2.07





nmr400c h1

Current Data Parameters
NAME 73243-11
EXPNO 1
PROCNO 1

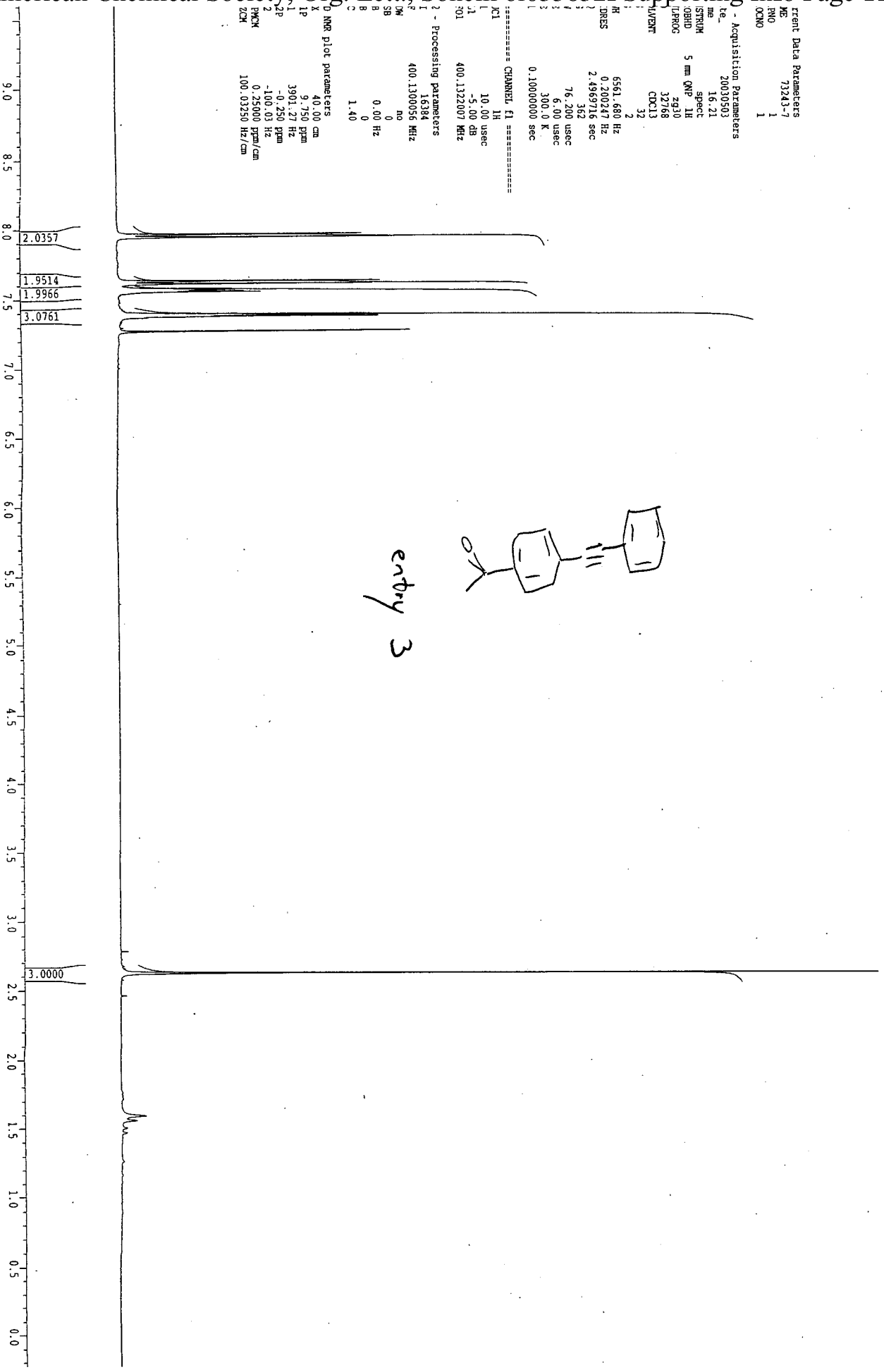
F2 - Acquisition Parameters
Date_ 20030508
Time 13.44
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 6561.680 Hz
FIDRES 0.200247 Hz
AQ 2.4969716 sec
RG 406.4
DW 76.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

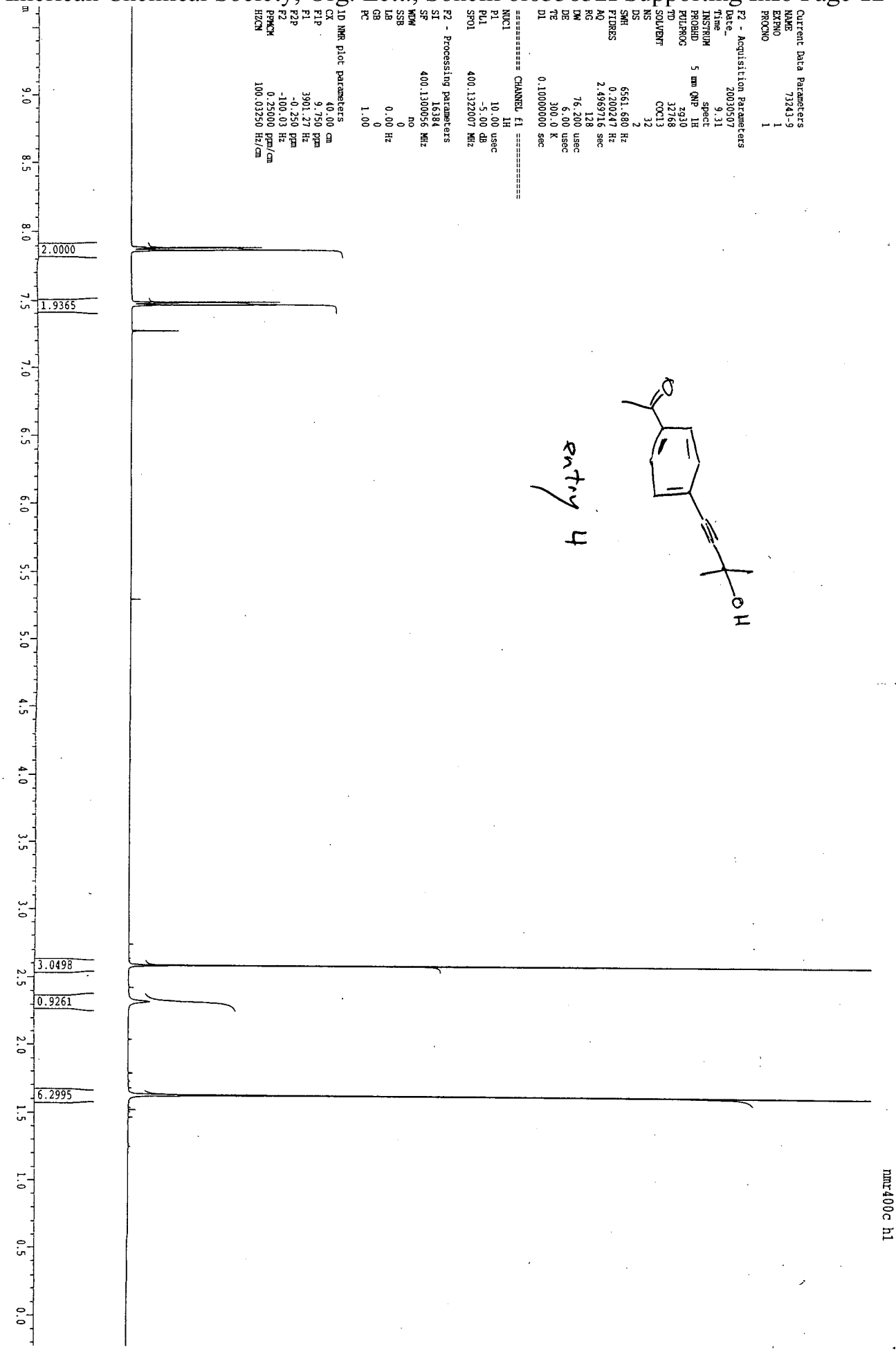
========== CHANNEL f1 ==========
NUC1 1H
P1 10.00 usec
PL1 -5.00 dB
SFO1 400.1322007 MHz

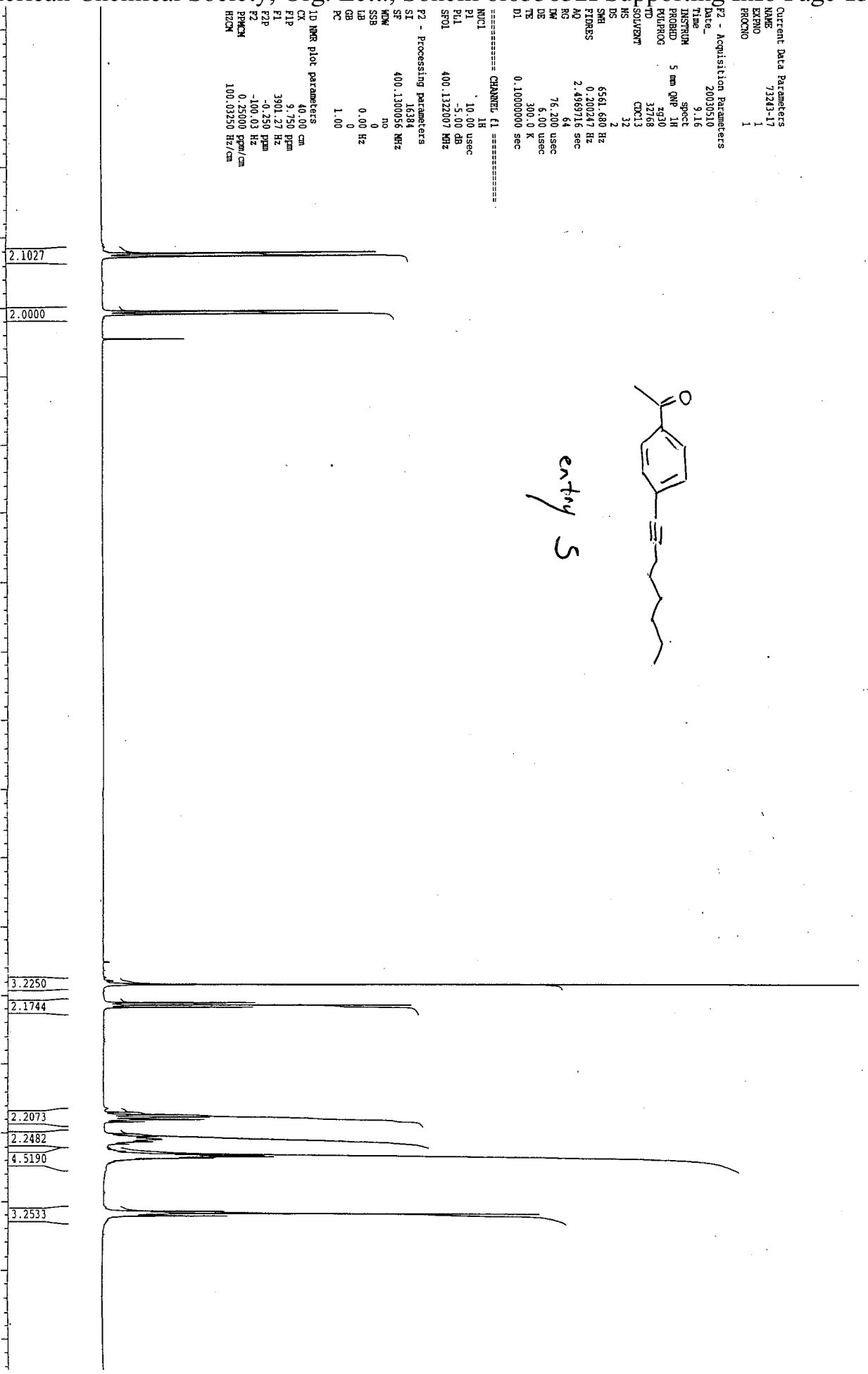
F2 - Processing parameters
SI 16384
SF 400.1300056 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

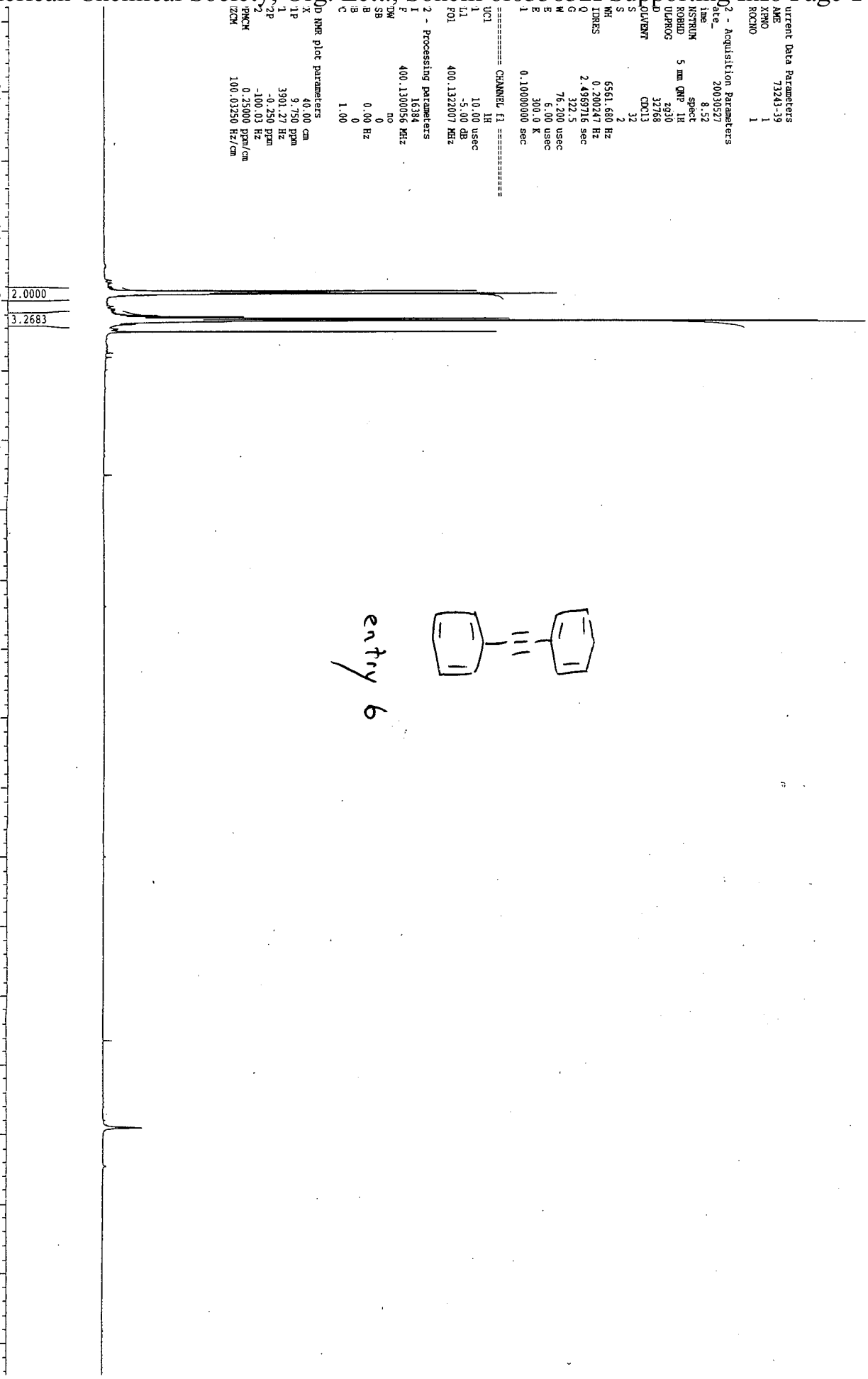
1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3901.27 Hz
F2P -0.250 ppm
F2 -100.03 Hz
PPMCM 0.25000 ppm/cm
HZCM 100.03250 Hz/cm

entry 2

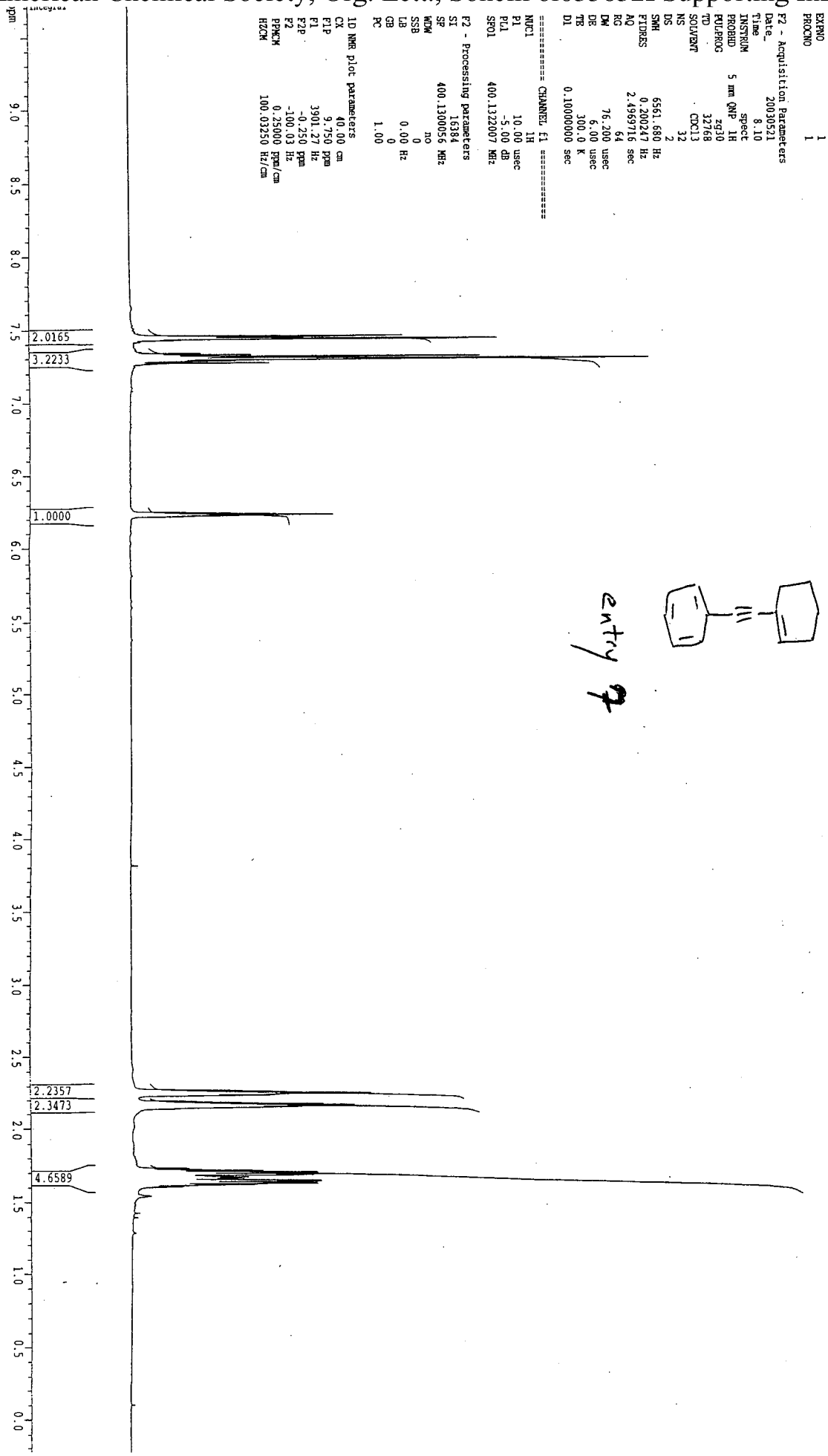


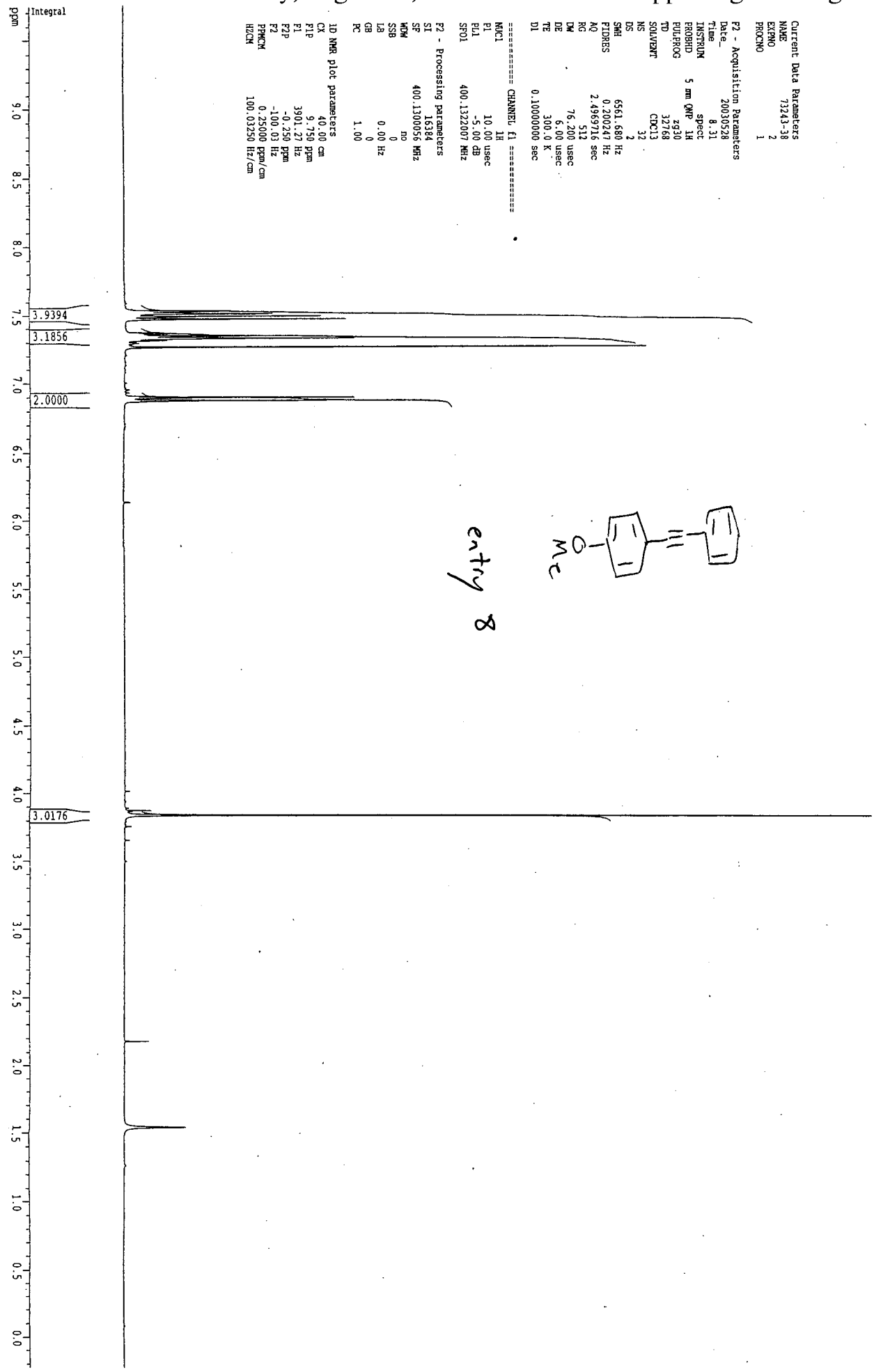


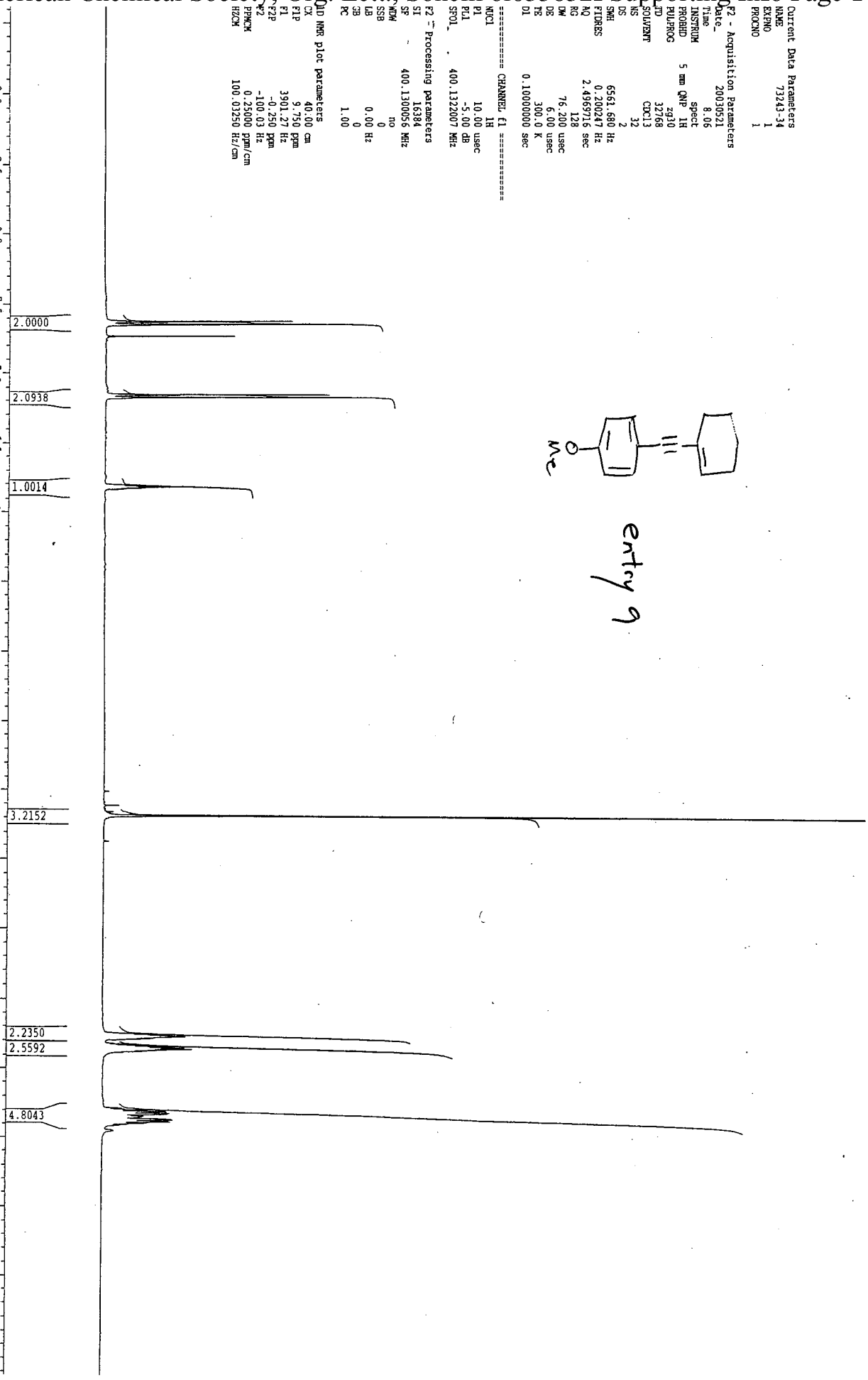


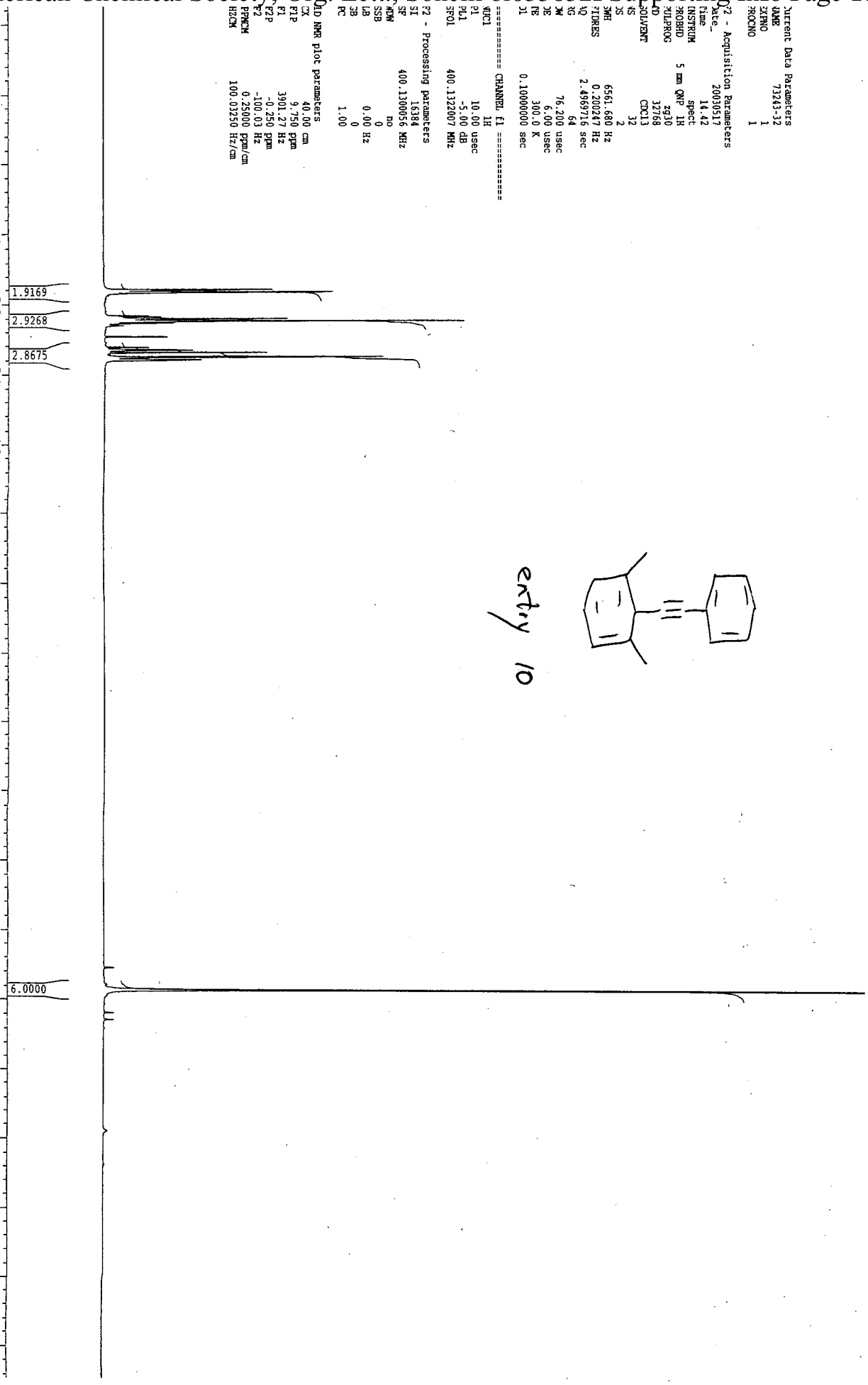


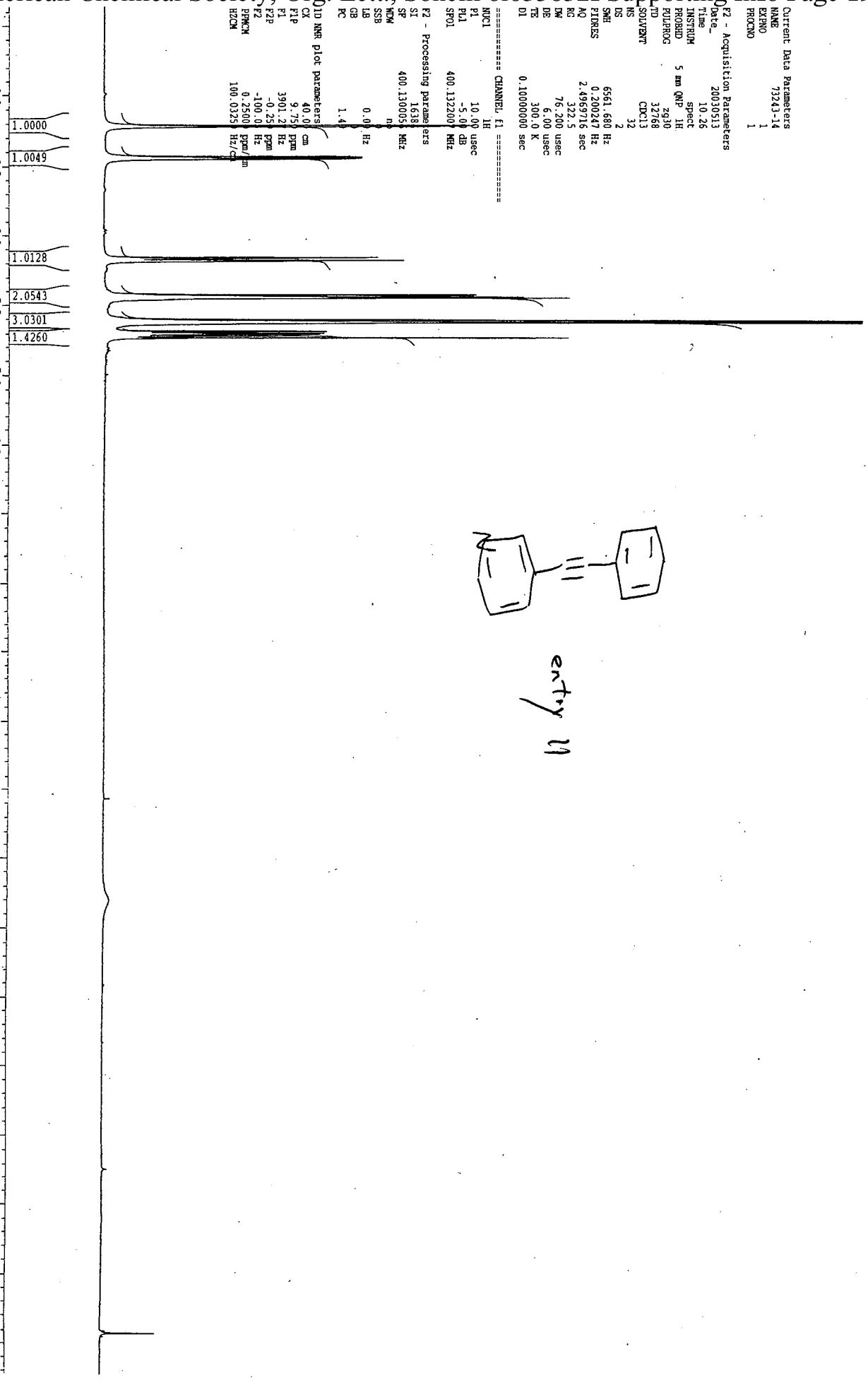

```
current Data Parameters
NAME                 73243-39
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20030527
Time                   8.52
INSTRUM                spect
PROBHD     5 mm QNP 1H
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       32
DS                        2
SWH                6561.680 Hz
FIDRES                0.200247 Hz
AQ                 2.4969716 sec
RG                      322.5
DW                   76.200 usec
DE                    6.00 usec
TE                   300.0 K
D1                 0.10000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     10.00 usec
PL1                    -5.00 dB
SFO1           400.1322007 MHz

F2 - Processing parameters
SI                       16384
SF             400.1300056 MHz
WDW                         no
SSB                          0
LB                    0.00 Hz
GB                           0
PC                    1.00

1D NMR plot parameters
WX                    40.00 cm
F1P                    9.750 ppm
F1                   3901.27 Hz
F2P                   -0.250 ppm
F2                   -100.03 Hz
PPMCM                 0.25000 ppm/cm
HZCM                100.03250 Hz/cm
```











nmr400c h1

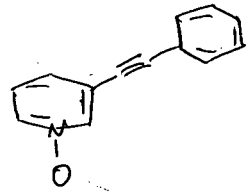
Current Data Parameters
NAME 73243-1c
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030618
Time 11.36
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 6561.680 Hz
FIDRES 0.200247 Hz
AQ 2.4969716 sec
RG 322.5
DW 76.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

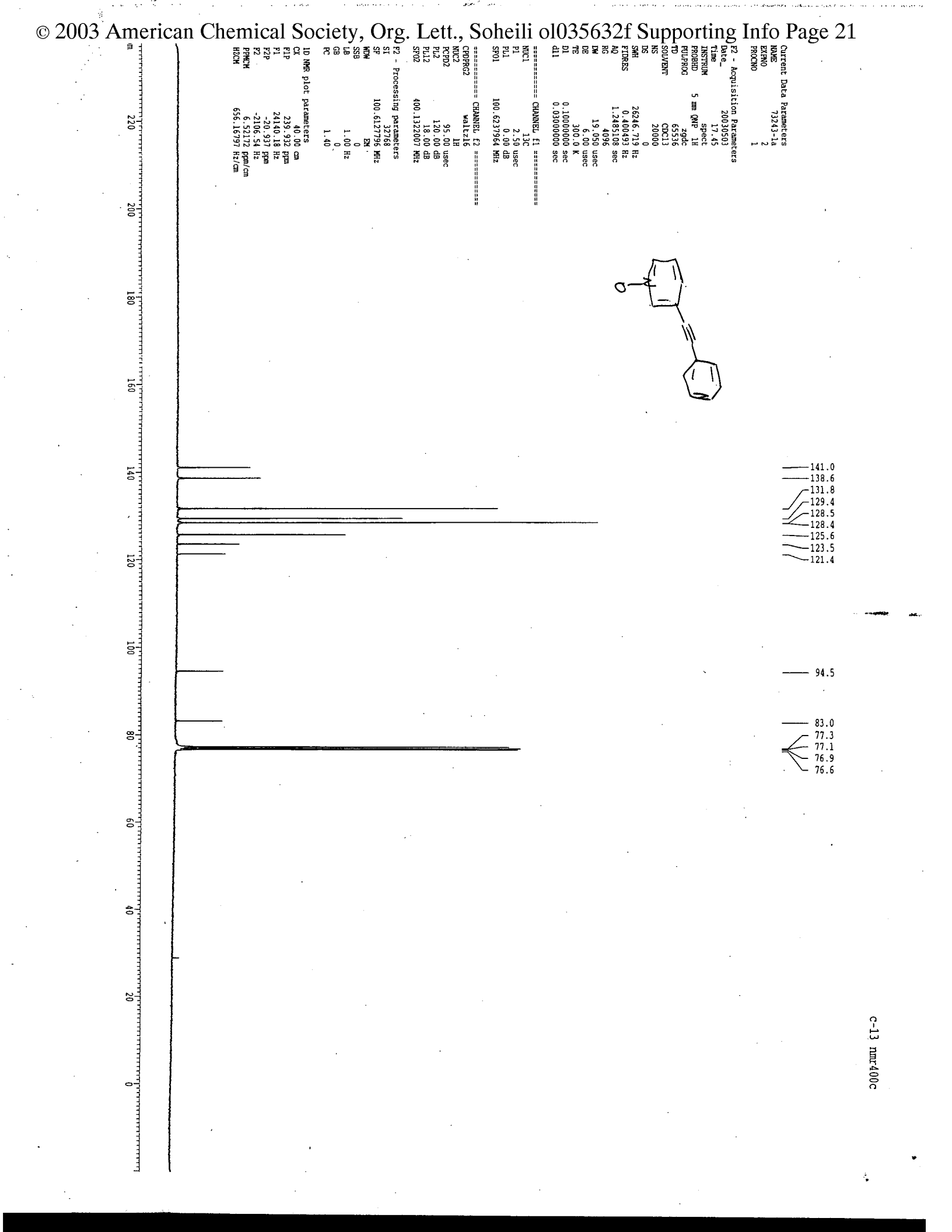
========== CHANNEL f1 ==========
NUC1 1H
P1 10.00 usec
PL1 -5.00 dB
SFO1 400.1322007 MHz

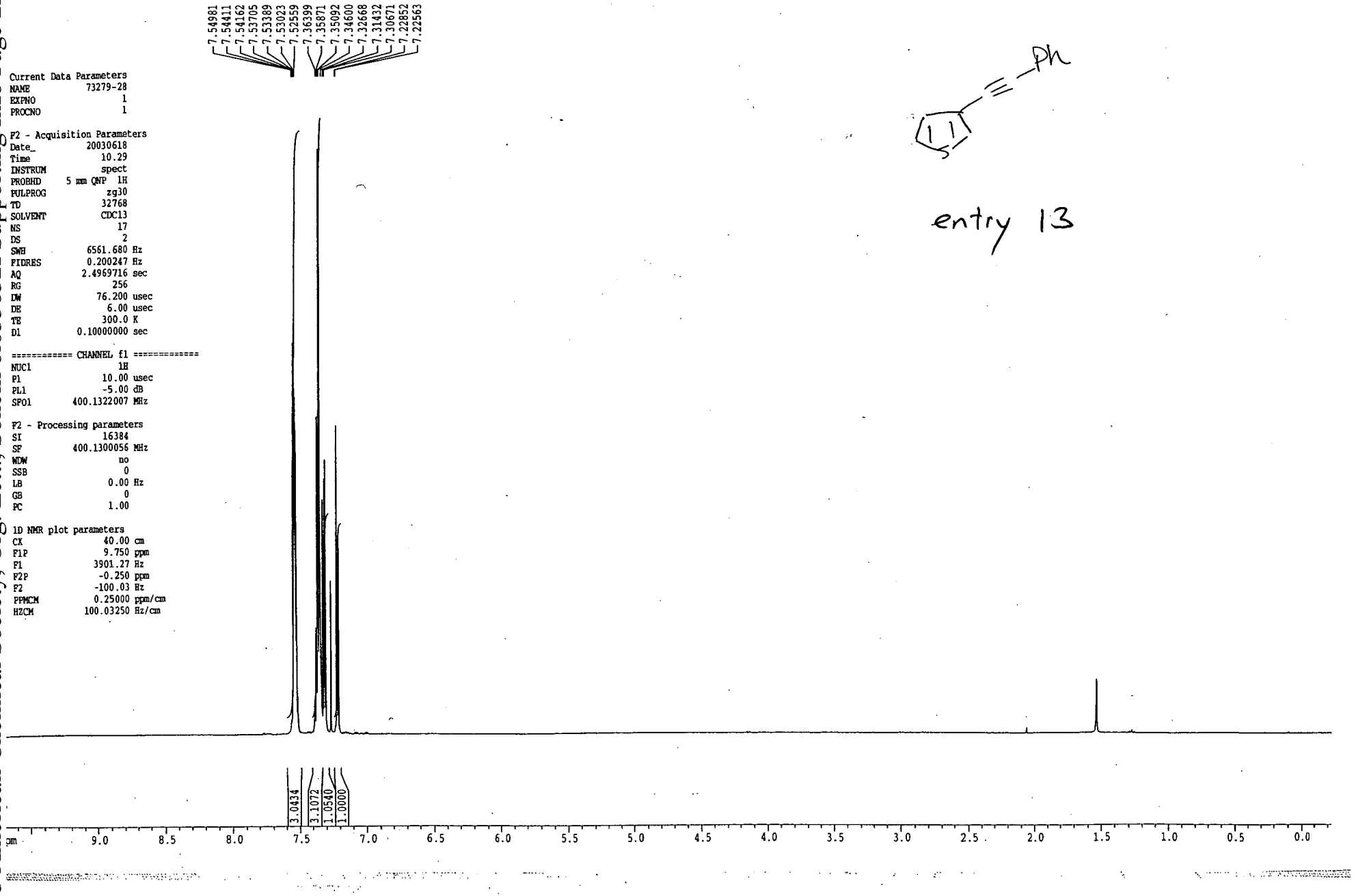
F2 - Processing parameters
SI 16384
SF 400.1300056 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3901.27 Hz
F2P -0.250 ppm
F2 -100.03 Hz
PPMCM 0.25000 ppm/cm
HZCM 100.03250 Hz/cm



entry 12





Current Data Parameters
NAME 73279-28
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030618
Time 10.29
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 17
DS 2
SWH 6561.680 Hz
FIDRES 0.200247 Hz
AQ 2.4969716 sec
RG 256
DW 76.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.00 usec
PL1 -5.00 dB
SFO1 400.1322007 MHz

F2 - Processing parameters
SI 16384
SF 400.1300056 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 40.00 cm
F1P 9.750 ppm
F1 3901.27 Hz
F2P -0.250 ppm
F2 -100.03 Hz
PPMCM 0.25000 ppm/cm
HZCM 100.03250 Hz/cm