

Supporting Information

Benzothiazines in Synthesis. Formal Total Synthesis of Pseudopteroxazole

Michael Harmata, Zhengxin Cai and Yugang Chen*

Department of Chemistry, University of Missouri, Columbia, Missouri 65211

Table of Contents

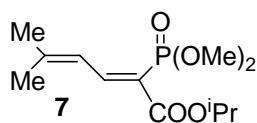
Table of Contents	S1
General	S2
Procedure and analytical data of Compound 7	S3
Procedure and analytical data of Compound 8	S3–S4
Procedure and analytical data of Compound 14	S4
Procedure and analytical data of Compound 15	S5
Procedure Analytical data of the Heck coupling product 16	S6
Spectra (¹ H and ¹³ C NMR) of Compound 7	S7–S8
Spectra (¹ H and ¹³ C NMR) of Compound 8	S9–S10
Spectra (¹ H and ¹³ C NMR) of compound 10	S11–S12
Spectra (¹ H and ¹³ C NMR) of compound 12	S13–S14
Spectra (¹ H and ¹³ C NMR) of compound 16	S15–S16
Spectra (¹ H and ¹³ C NMR) of compound 13	S17–S18
Spectra (¹ H and ¹³ C NMR) of compound 14	S19–S20
Spectra (¹ H and ¹³ C NMR) of compound 15	S21–S22
Spectra (¹ H NMR) of compound 4	S23

General Information:

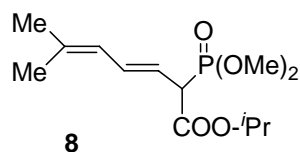
All air and moisture sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. Reactive liquid reagents (LHMDS, etc.) were measured and transferred by gastight syringes through rubber septa. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone ketyl. Toluene was distilled from CaH_2 . The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residue solvents were usually removed under reduced pressure using vacuum pump (approximately 1mm Hg).

Flash chromatographic separations were carried out on silica gel (230-400 mesh) with ACS reagent grade solvents. Analytical thin layer chromatography was performed on glass-backed silica gel plates with F254 indicator. Compounds were visualized under UV light or by developing in iodine, vanillin, phosphomolybdic acid solution or with potassium permanganate solution followed by heating in a hot plate to approximately 350 °C. Melting points were determined with a melting point apparatus.

^1H NMR spectra were recorded in Fourier transform mode at 250, 300 or 500 MHz, respectively, as CDCl_3 solutions with tetramethylsilane ($\delta = 0$ ppm) as the internal standard. ^{13}C NMR spectra were recorded on the same instruments at 62.5, 75 or 125 MHz, respectively, with CDCl_3 ($\delta = 77$ ppm) as the internal reference. ^{31}P NMR spectra were recorded on the same instruments at 101 MHz, respectively, with 85% H_3PO_4 ($\delta = 0$ ppm) as the external standard. Chemical shifts (δ) were reported in parts per million (ppm). Multiplicities were reported as s (singlet), b (broad), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublet), etc. In ^1H NMR spectra of diastereomeric mixtures, the signals for individual isomers were reported when possible. Infrared spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded on a polarimeter with sodium D line at the temperatures as indicated in the experimental for specific compounds. High resolution mass spectra were obtained on a magnetic sector instrument with a resolution greater than 10,000.

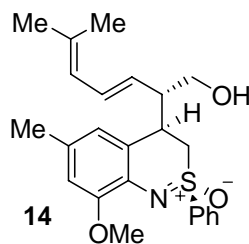


(E/Z)-isopropyl 2-(dimethoxyphosphoryl)-5-methylhexa-2,4-dienoate (7): A mixture of 3-methylbut-2-enal (5 mL, 0.065 mol) and trimethyl phosphonoacetate (5.26 mL, 0.033 mol) in THF (300 mL) with molecular sieves (4 Å) was placed in a 1 L round-bottom flask under an argon atmosphere. To this solution, $\text{Ti}(\text{O}^i\text{Pr})_4$ (29 mL, 0.098 mol) was added. Then TEA (17 mL, 0.13 mol) was added over 30 min, and the mixture was stirred at 0 °C for 7 h. The reaction mixture was poured into 1 N HCl and vigorously stirred at rt for 1 h. It was extracted by ethyl acetate (3x300 mL) and the extract was washed with 300 mL saturated sodium bicarbonate solution and 300 mL brine. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated, affording the product as a mixture of *E/Z* (2:1) isomers (5.82 g, 92%). (*Z*)-isomer: IR (neat): 2978, 2953, 2848, 1699, 1618, 1564, 1250, 1025, 829 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 8.20 (dd, 1 H, $J = 12.5, 44.5$ Hz), 7.22 (dd, 1 H, $J = 1.0, 12.0$ Hz), 5.12 (septet, 1 H, $J = 6.5$ Hz), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.00 (s, 3H), 1.98 (s, 3H), 1.30 (d, 6 H, $J = 6.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.9 (d, $J = 15.0$ Hz), 155.2 (d, $J = 2.5$ Hz), 152.9 (d, $J = 10.0$ Hz), 122.4 (d, $J = 5.0$ Hz), 115.6 (d, $J = 186.0$ Hz), 68.7, 52.6 (d, $J = 5.0$ Hz), 27.6, 21.7 (d, $J = 10.0$ Hz), 19.0; HRMS calcd for $\text{C}_{12}\text{H}_{21}\text{O}_5\text{PNa}$ $[\text{M}+\text{Na}]^+$ 299.1019; Found: 299.1006; ^{31}P NMR (CDCl_3 , 250 MHz) δ 23.4 (85% H_3PO_4 as external standard).



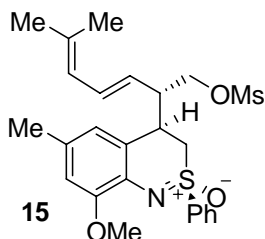
(E)-isopropyl 2-(dimethoxyphosphoryl)-6-methylhepta-3,5-dienoate (8): To a solution of 7 (4.86 g, 0.018 mol) in ether (20 mL) in a 50 mL round-bottom flask, a 0.5 M diazomethane solution in ether (0.088 mL, 0.045 mol) at 0 °C was added dropwise. The reaction was warmed to rt and stirred for 12 h. After the reaction was complete, the solvent was evaporated and the crude product was heated at 100 °C for 1 h. After flash

chromatography with 50% ethyl acetate in hexanes, a colorless oil 4.54 g (84% for two steps) was obtained, the product having only an (*E*) configuration. IR (neat): 2983, 2851, 1728, 1450, 1262, 1102, 1025, 829, 796 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 6.44 (ddd, 1H, $J = 5.0, 11.0, 15.5$ Hz), 5.85 (d, 1H, $J = 11.0$ Hz), 5.65 (ddd, 1H, $J = 7.0, 9.5, 16.0$ Hz), 5.07 (septet, 1H, $J = 6.5$ Hz), 3.81 (d, 3H, $J = 11.0$ Hz), 3.79 (d, 3H, $J = 11.0$ Hz), 3.75 (dd, 1H, $J = 9.5, 24.0$ Hz), 1.78 (s, 3H), 1.76 (s, 3H), 1.28 (d, 3H, $J = 4.5$ Hz), 1.26 (d, 3H, $J = 4.0$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 167.0 (d, $J = 5.0$ Hz), 136.9 (d, $J = 5.0$ Hz), 131.9 (d, $J = 12.5$ Hz), 124.0 (d, $J = 5.0$ Hz), 118.5 (d, $J = 12.5$ Hz), 69.2, 53.7 (d, $J = 7.5$ Hz), 53.4 (d, $J = 7.5$ Hz), 50.6, 49.6 (d, $J = 130.0$ Hz), 25.8, 21.5 (d, $J = 10.0$ Hz), 18.2; HRMS calcd for $\text{C}_{13}\text{H}_{23}\text{O}_5\text{PNa}$ $[\text{M}+\text{Na}]^+$ 313.1175; Found: 313.1171.

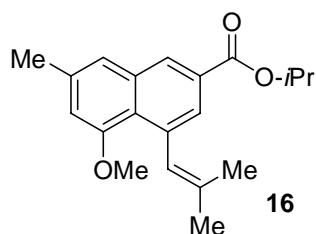


(2*S*,3*E*)-6-Methyl-2-[(2*R*,4*R*)-2-oxido-2-phenyl-3,4-dihydro-2*H*⁴,1-benzothiazin-4-yl]hepta-3,5-dien-1-ol (14**):** To a solution of the ester **13** (383mg, 0.819 mmol) in 8 mL THF, was slowly added 8.19 mL of DIBAL (1M in THF) at 0 °C. After 2 h, it was carefully quenched with ethyl acetate and water. After filtration, followed by washing with 20 mL ethyl acetate, it was concentrated. After flash chromatography (50% ethyl acetate in hexanes), 0.285 g (88%) of **14** was obtained as a semisolid. IR (film): 3448, 2962, 2917, 1577, 1462, 1250, 1102, 1017 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 8.10-8.12 (m, 2H), 7.63-7.66 (m, 1H), 7.54-7.57 (m, 2H), 6.69 (s, 1H), 6.69 (s, 1H), 6.40 (dd, 1H, $J = 11.0, 15.5$ Hz), 5.82 (d, 1H, $J = 10.5$ Hz), 5.51 (dd, 1H, $J = 9.0, 15.5$ Hz), 3.89 (s, 3H, CH_3), 3.69 (ddd, 1H, $J = 4.0, 7.0, 11.0$ Hz), 3.46-3.55 (m, 3H), 2.98-3.13 (m, 1H), 2.32 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.35 (dd, 1H, $J = 4.5, 6.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 152.8, 139.2, 136.1, 133.9, 132.2, 131.0, 130.2, 129.5, 128.4, 125.1, 124.7,

119.1, 111.6, 62.7, 56.2, 50.3, 45.0, 37.5, 26.2, 21.7, 18.6; HRMS calcd for $C_{24}H_{29}NO_3SNa$ $[M+Na]^+$ 434.1760; Found: 434.1751; $[\alpha]_D^{25} = -4.04$ (c 3.02, $CHCl_3$).

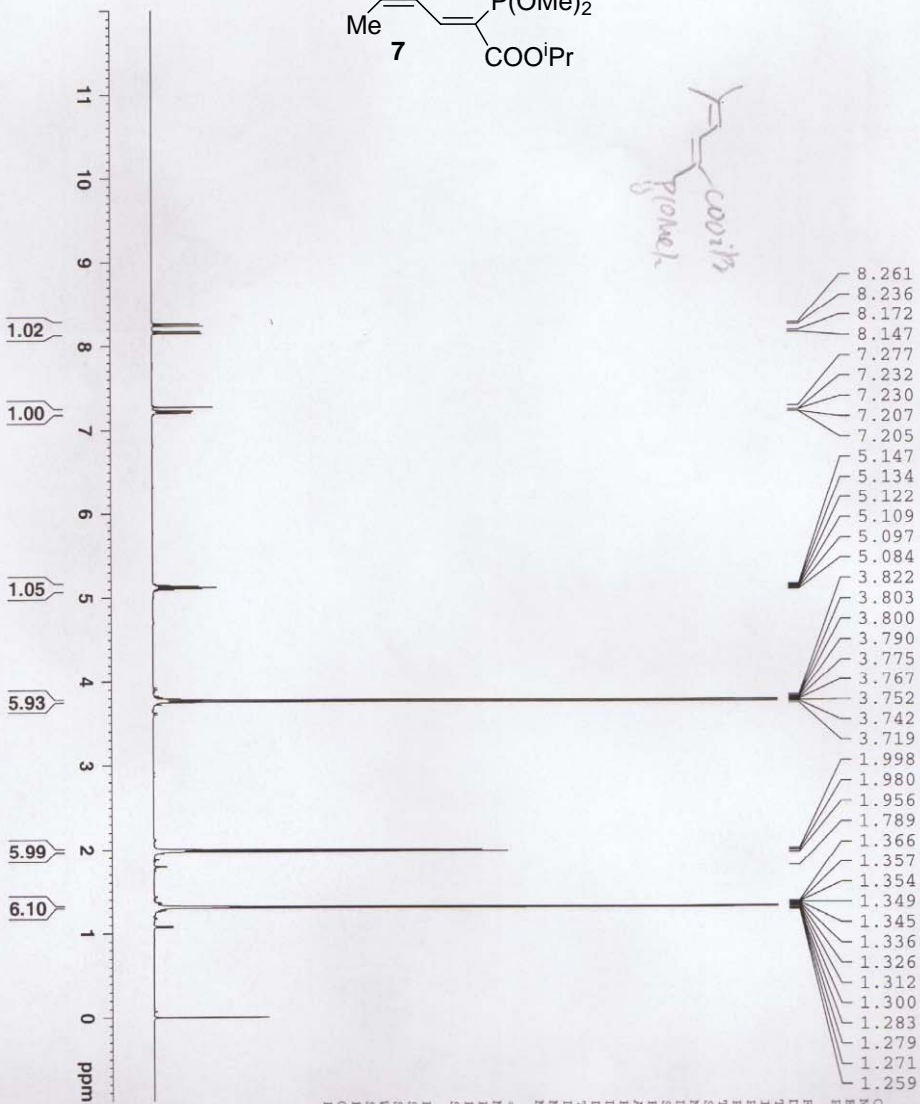
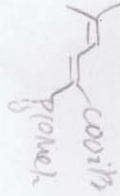
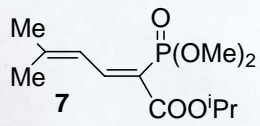


(2*R*,4*R*)-4-[(1*S*,2*E*)-1-Methanesulfonyloxymethyl-5-methyl-2,4-hexadienyl]-3,4-dihydro-8-methoxy-6-methyl-2-phenyl-2γ4-2,1-benzothiazine-2-oxide (15): To a solution of alcohol **14** (48 mg, 0.116 mmol) in 2 mL CH_2Cl_2 was added TEA (33 μ l, 24 mg, 0.24 mmol) and mesyl chloride (14 μ l, 21mg, 0.18 mmol) at 0 °C. The reaction was allowed to reach rt and was stirred for 17 h. It was quenched with 1 mL saturated NH_4Cl , extracted with 2 mL CH_2Cl_2 , washed with 2 mL brine, dried with Na_2SO_4 , and concentrated in vacuo. After chromatography (50% ethyl acetate in hexanes), 45 mg (79%) of **15** was obtained as a white semisolid. IR (film): 3060, 2929, 2226, 1569, 1462, 11348, 1242, 1172, 1103, 964, 833, 731, 682 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, 2H, $J = 7.5$ Hz), 7.66 (dd, 1H, $J = 7.0, 8.0$ Hz), 7.56 (dd, 2H, $J = 8.0, 7.5$ Hz), 6.70 (s, 1H), 6.67 (s, 1H), 6.37 (dd, 1H, $J = 11.0, 15.5$ Hz), 5.80 (d, 1H, $J = 11.0$ Hz), 5.47 (dd, 1H, $J = 7.5, 15.0$ Hz), 4.24 (dd, 1H, $J = 4.5, 10.0$ Hz), 4.05 (dd, 1H, $J = 7.5, 10.0$ Hz), 3.88 (s, 3H), 3.61 (dt, 1H, $J = 11, 5$ Hz), 3.51 (dd, 1H, $J = 4.5, 13.0$ Hz), 3.43 (m, 1H), 3.06 (dd, 1H, $J = 11.5, 12.5$ Hz), 2.90 (s, 3H), 2.33 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7, 138.5, 136.6, 133.8, 131.9, 130.9, 130.2, 129.3, 129.2, 126.0, 124.2, 123.5, 118.8, 111.6, 69.0, 56.0, 49.6, 41.9, 37.3, 37.2, 25.9, 21.4, 18.3; HRMS calcd for $C_{25}H_{31}NO_5S_2Na$ $[M+Na]^+$ 512.1536; Found: 512.1526; $[\alpha]_D^{25} = -13.82$ (c 0.55, $CHCl_3$).



The Heck coupling product **16** is a byproduct that was formed in trace amount under the Buchwald coupling condition indicated in the main text. It was isolated as a colorless oil: IR (neat): 2978, 2917, 1708, 1573, 1454, 1372, 1274, 1221, 1136, 1103 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 8.28 (d, 1H, $J = 1.5$ Hz), 7.67 (s, 1H), 7.30 (s, 1H), 6.94 (s, 1H), 6.73 (d, 1H, $J = 1.0$ Hz), 5.29 (septet, 1H, 6.0 Hz), 3.87 (s, 3H), 1.96 (d, 3H, $J = 1.0$ Hz), 1.71 (d, 3H, $J = 1.5$ Hz), 1.40 (d, 6H, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 166.4, 157.3, 136.1, 135.7, 135.3, 130.9, 128.5, 128.0, 127.7, 126.8, 124.9, 121.6, 110.4, 68.3, 55.9, 26.0, 22.0, 21.7, 19.1; HRMS calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 335.1618; Found: 335.1618.

CAI-PA-conjugated diene-1H NMR

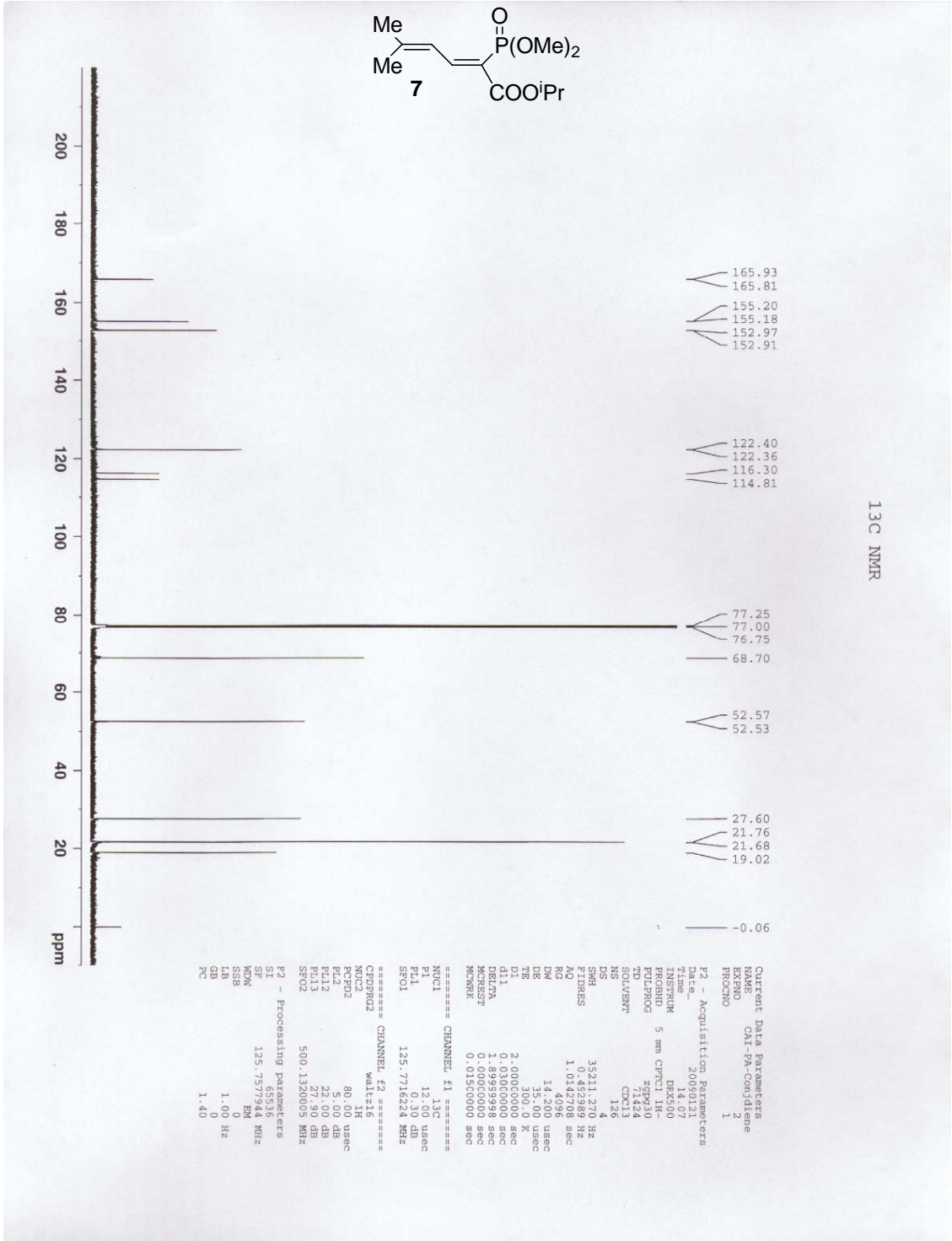


Current Data Parameters
NAME CAI-PA-conjugated diene
EXPNO 1
PROCNO 1

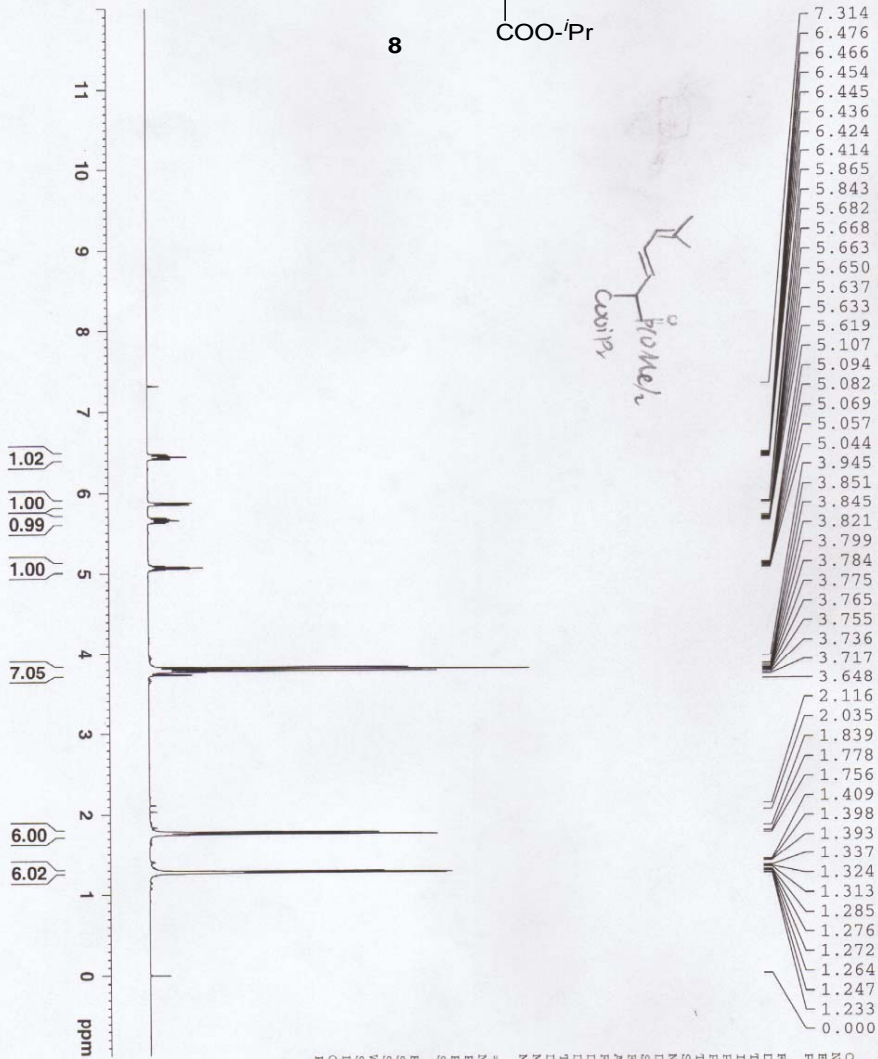
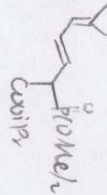
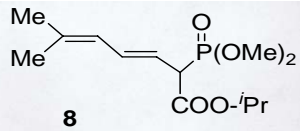
F2 - Acquisition Parameters
Date_ 20090121
Time 14.02
INSTRUM spect
PROBHD 5 mm CPXC-1H-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.15962 Hz
AQ 3.17122 sec
RG 113
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

***** CHANNEL f1 *****
NUC1 1H
P1 8.00 usec
PL1 4.30 dB
SFO1 500.135009 MHz

F2 - Processing parameters
SI 32768
SF 500.130029 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



CAI-PA-4B-Colorless oil-1H NMR

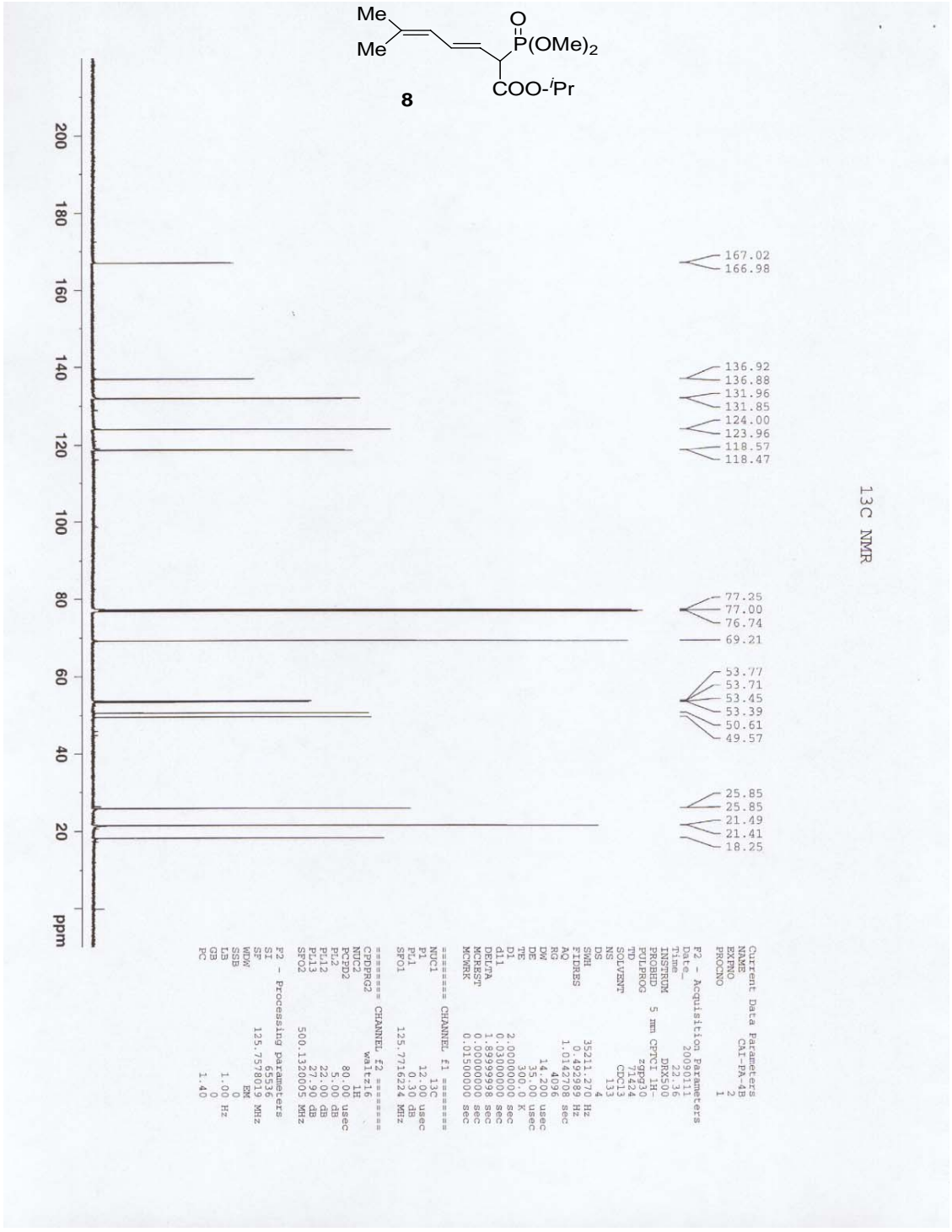


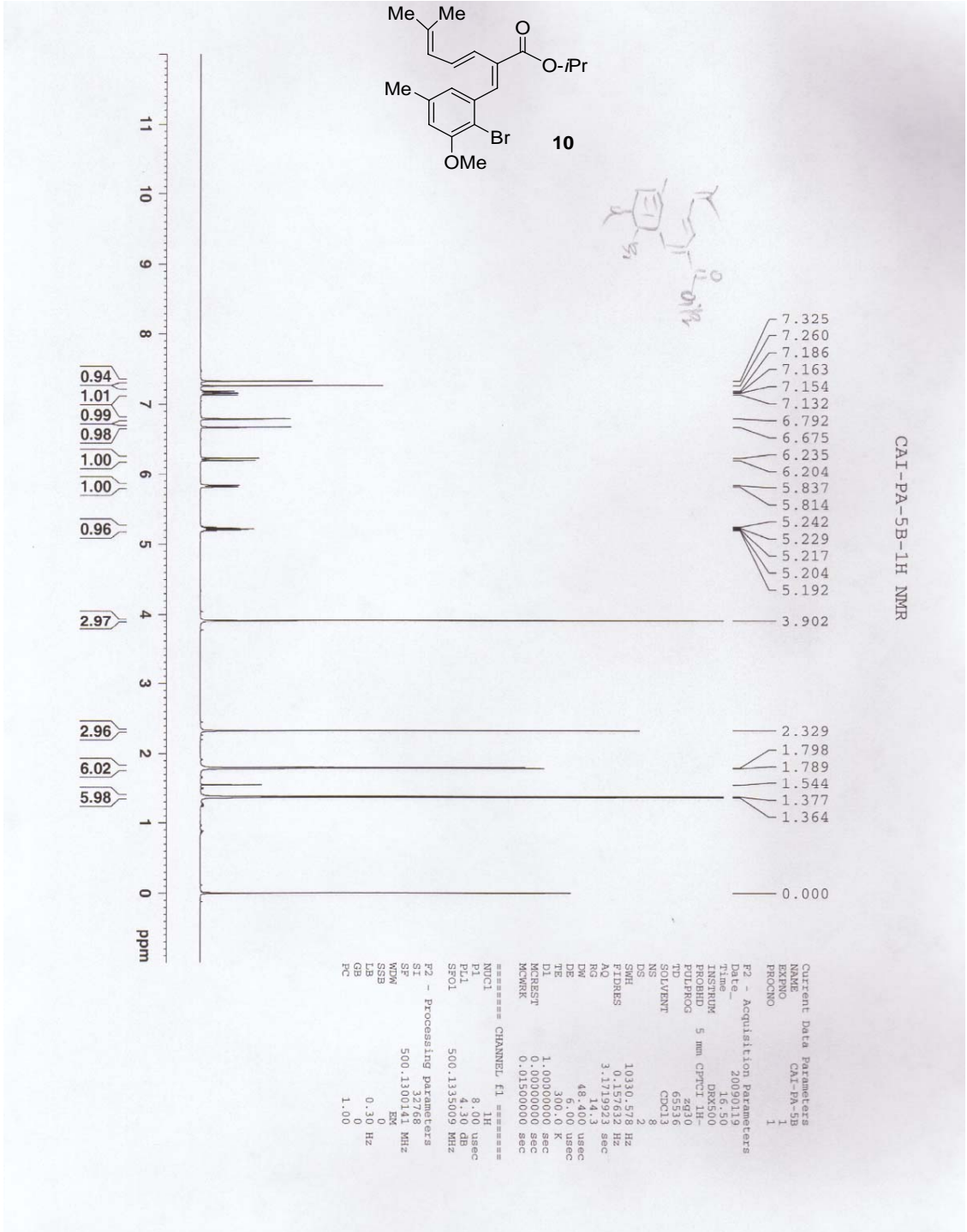
Current Data Parameters
 NAME CAI-PA-4B
 EXPNO 1
 PROCNO 1

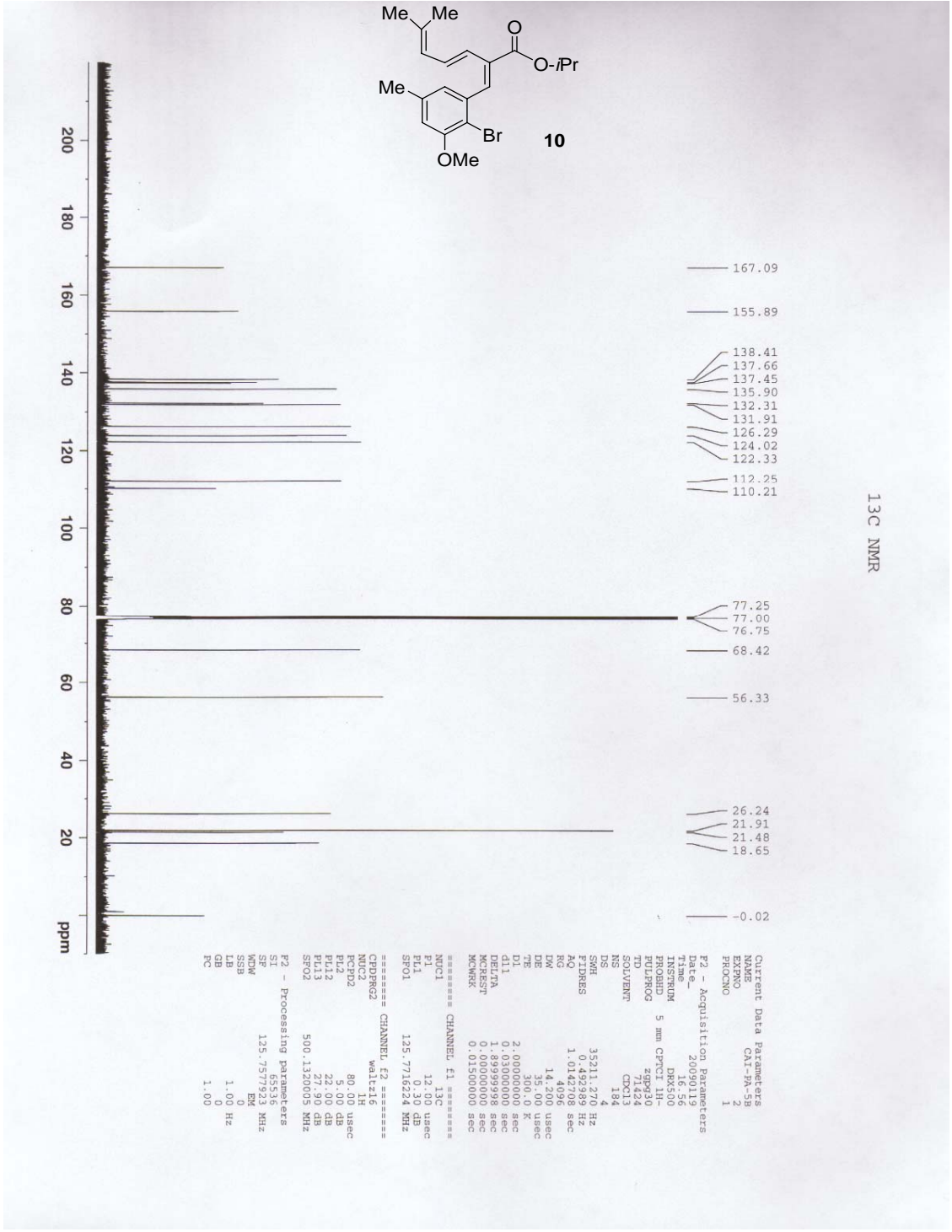
F2 - Acquisition Parameters
 Date_ 20090111
 Time 22.29
 INSTRUM DRX500
 PROBRD 5 mm CPXI 1H-
 PULPROG zgpg30
 T1 6.50
 T12 6.50
 T13 6.50
 SOLVENT CDCl3
 NS 8
 DS 2
 SWH 10330.578 Hz
 FIDRES 0.157632 Hz
 AQ 3.1719922 sec
 RG 653
 DE 48.400 usec
 TE 300.0 K
 D1 1.00000000 sec
 MCREST 0.00000000 sec
 MCWRR 0.01500000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.00 usec
 PL1 4.30 dB
 SFO1 500.1335009 MHz

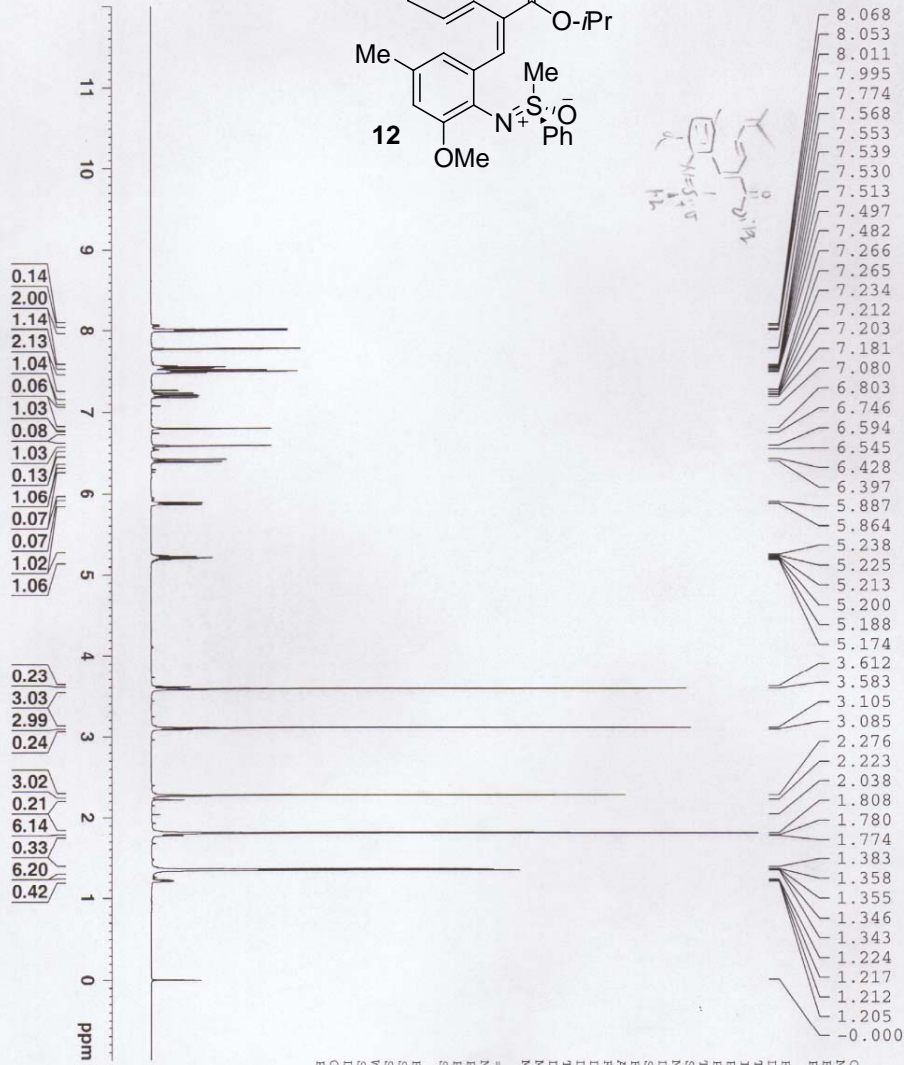
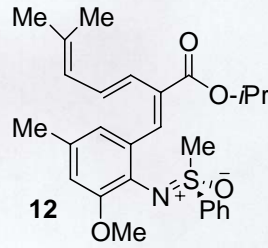
F2 - Processing parameters
 SI 32768
 SF 500.1299870 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00







CAI-IV-SM-MA-1H NMR



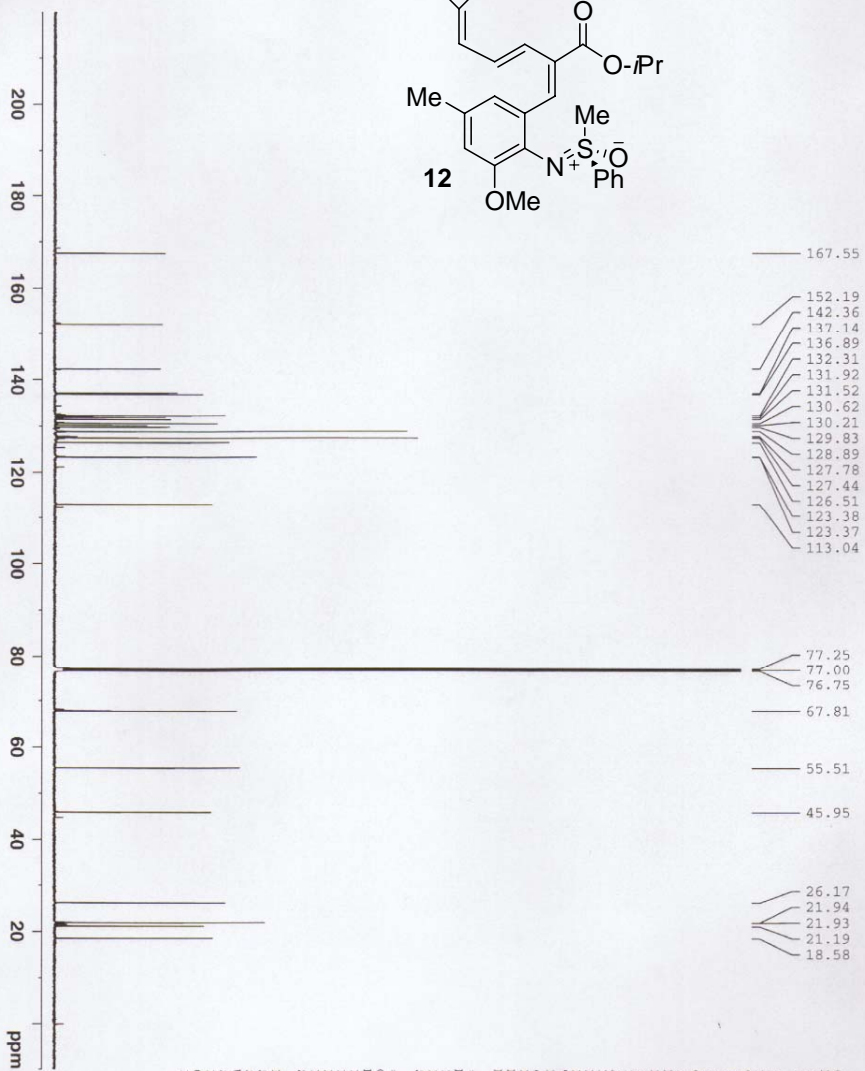
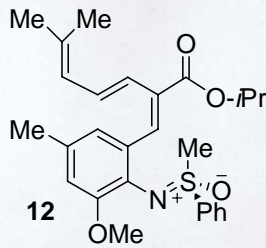
Current Data Parameters
 NAME CAI-IV-PA
 EXPNO 1
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20090113
 Time 14.34
 INSTRUM DRX500
 PROBHID 5 mm CP1H1H-
 PULPROG zgpg30
 TD 2830
 SFO1 500.130013
 SOLVENT CDCl3
 NS 2
 DS 2
 SWH 10330.578 Hz
 FIDRES 0.157632 Hz
 AQ 3.1719223 sec
 RG 5
 DM 48.400 usec
 DE 6.400 usec
 TE 300.0 K
 D1 1.00000000 sec
 MCRRES 0.00000000 sec
 MCWRR 0.01500000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.00 usec
 PL1 4.30 dB
 SFO1 500.1335009 MHz

F2 - Processing parameters
 SI 32768
 SF 500.130013 MHz
 KMDW 0
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

13C NMR



```

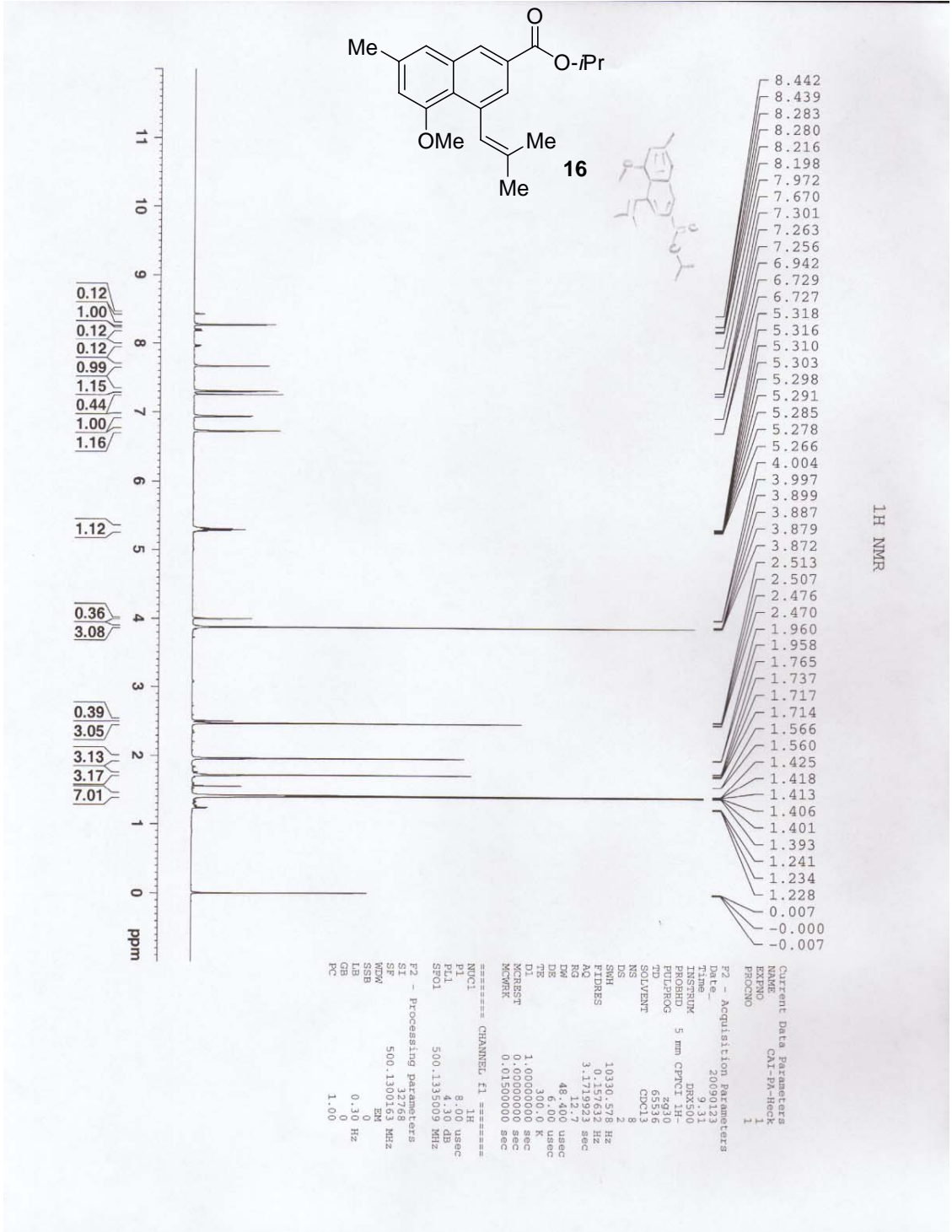
Current Data Parameters
NAME          CH-1V-PR
EXPNO        1
PROCNO       1

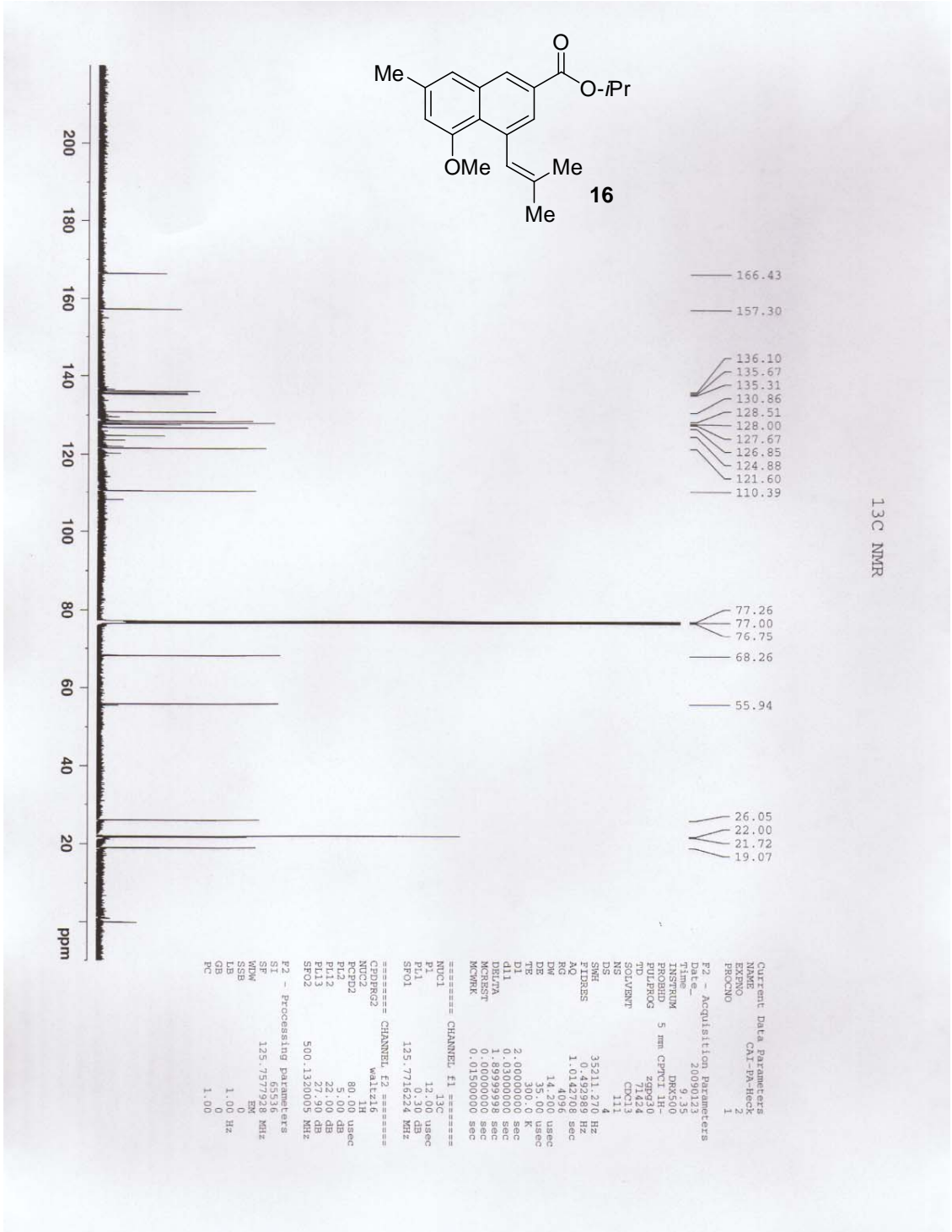
F2 - Acquisition Parameters
Time         20:29:43
Date_       14 41
INSTRUM     DRR500
PROBHD      5 mm CPXI 1H-
PULPROG     zgpg30
SOLVENT     CDCl3
NS          129
DS          4
SWH         35211.270 Hz
FIDRES     0.49289 Hz
AQ         1.014496 sec
RG         4096
DE         14.200 usec
TE         300.0 K
DELTA      2.000000 sec
MCKRESF    1.8999998 sec
MCKMRK     0.01500000 sec

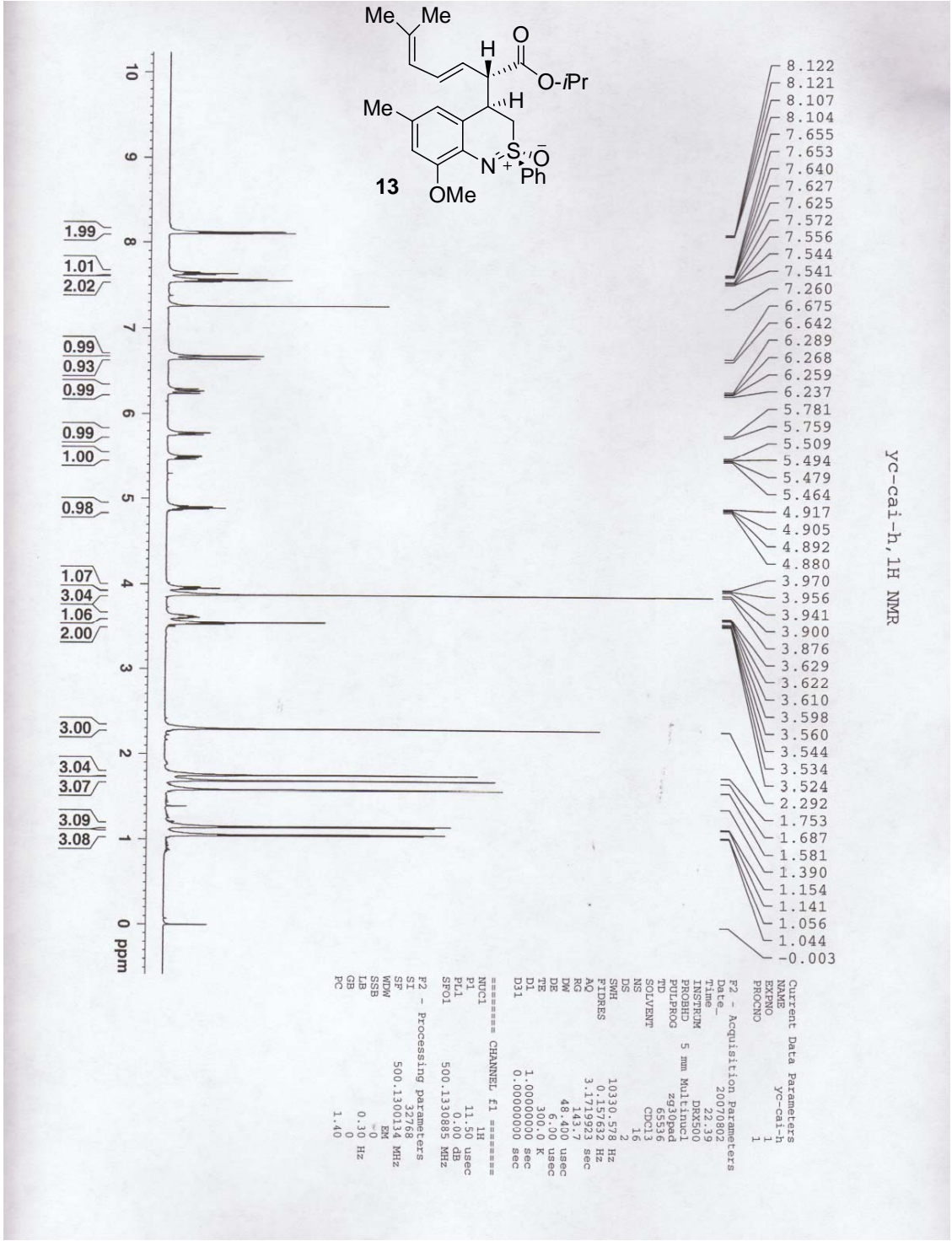
===== CHANNEL f1 =====
NUC1        13C
P1          12.00 usec
PL1         0.30 dB
SFO1       125.7716224 MHz

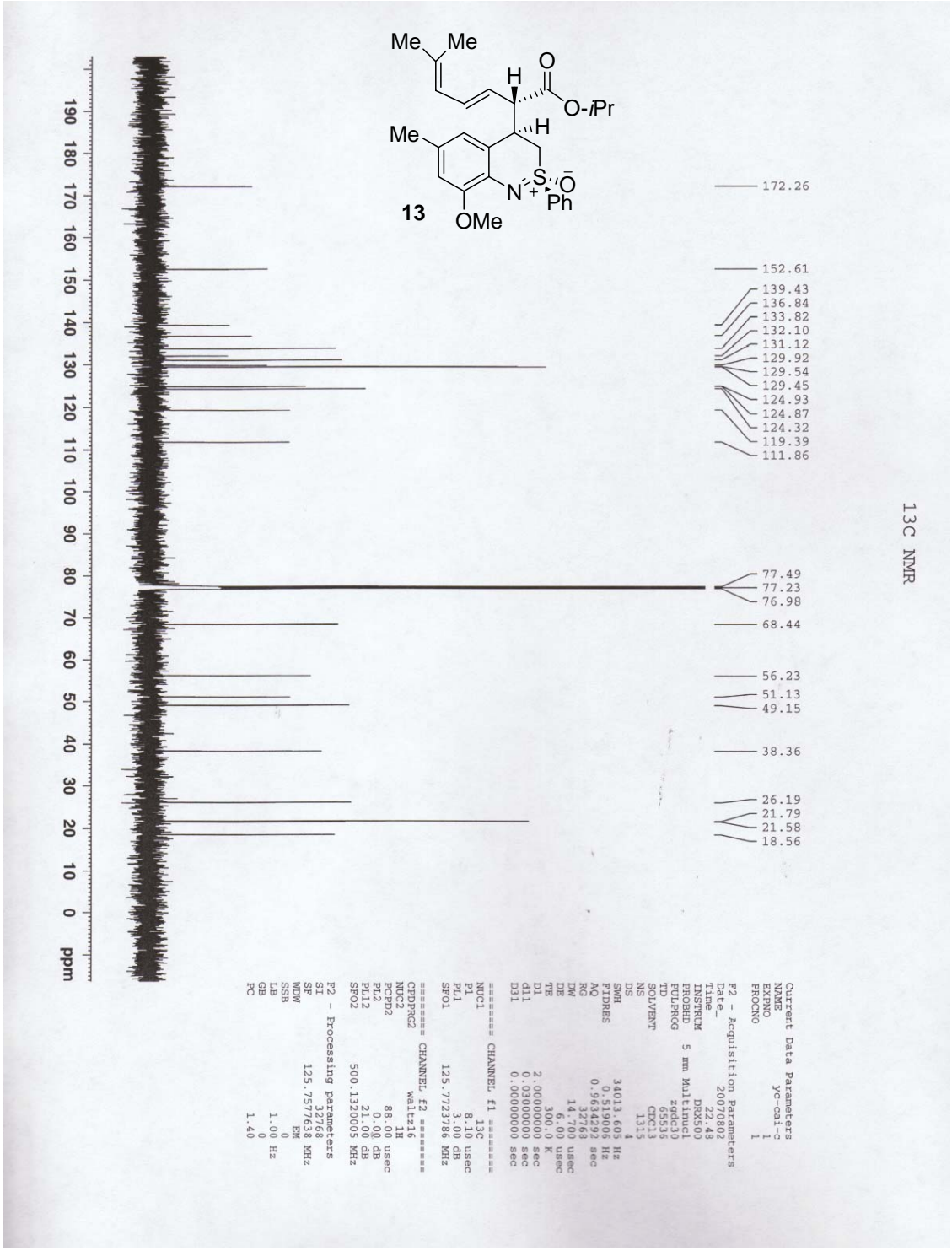
===== CHANNEL f2 =====
CPDPRG2    waltz16
NUC2        1H
PCPD2      80.00 usec
PL2        5.00 dB
PL12       22.00 dB
PL13       22.00 dB
SFO2       500.1320005 MHz

F2 - Processing parameters
SI          65536
SF          125.757809 MHz
WDW         EM
SSB         0
LB          1.00 Hz
GB          0
PC          1.00
  
```

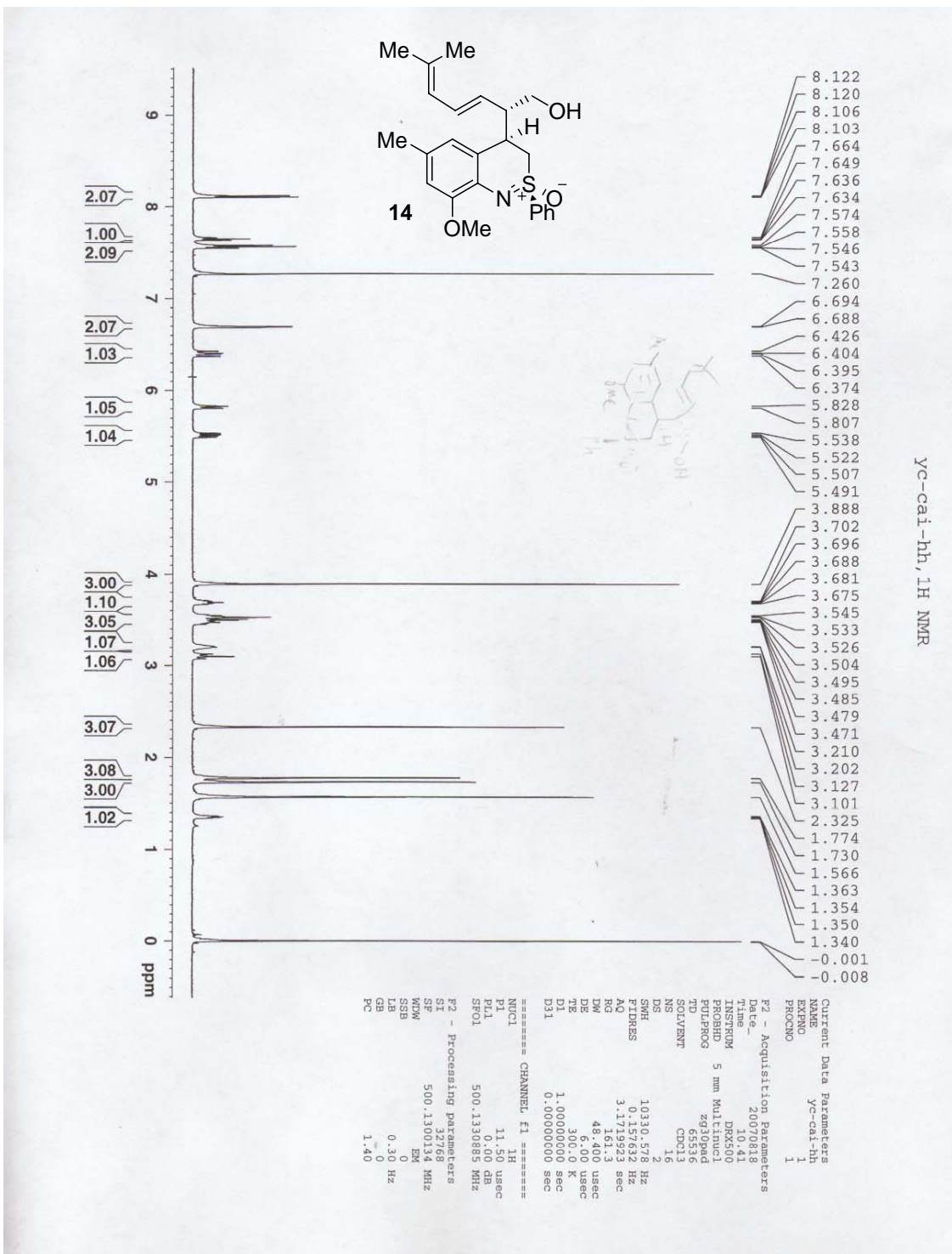




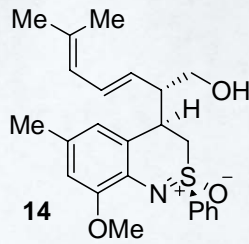
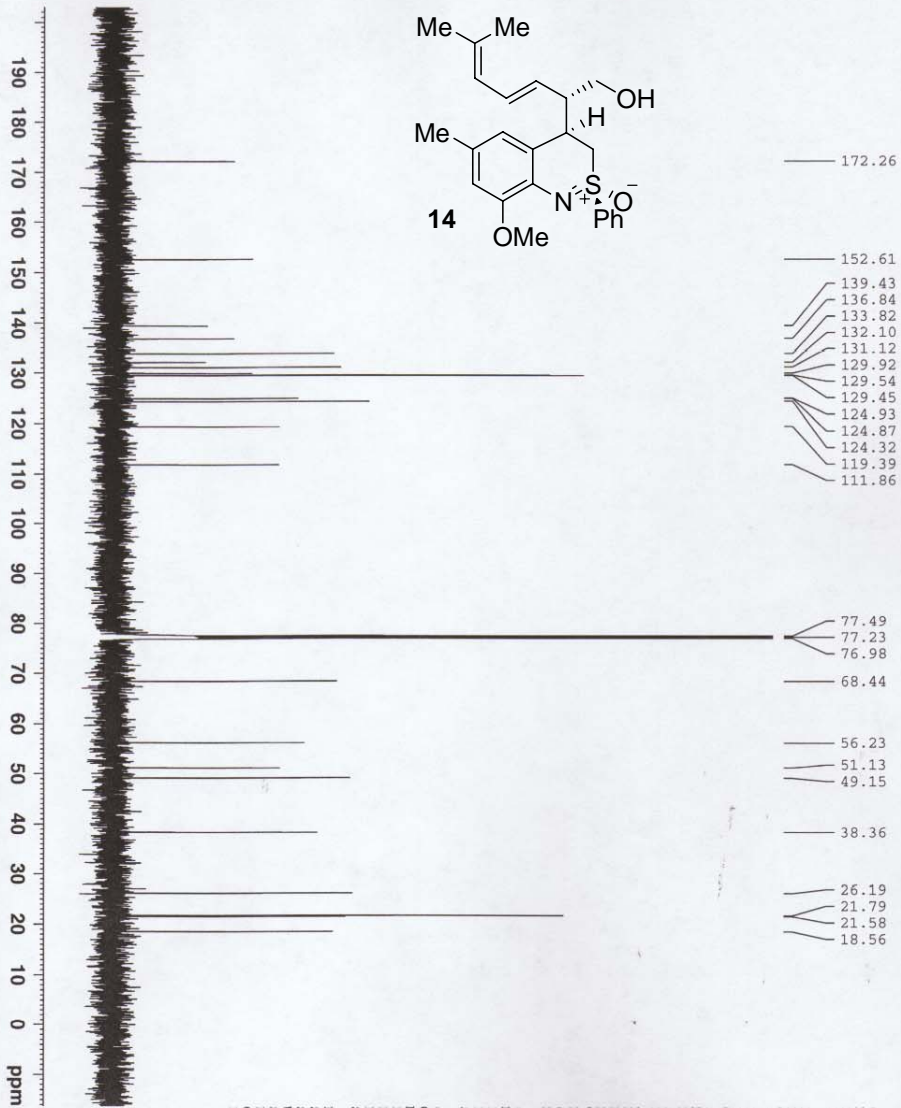




yc-cai-hh, 1H NMR



13C NMR



```

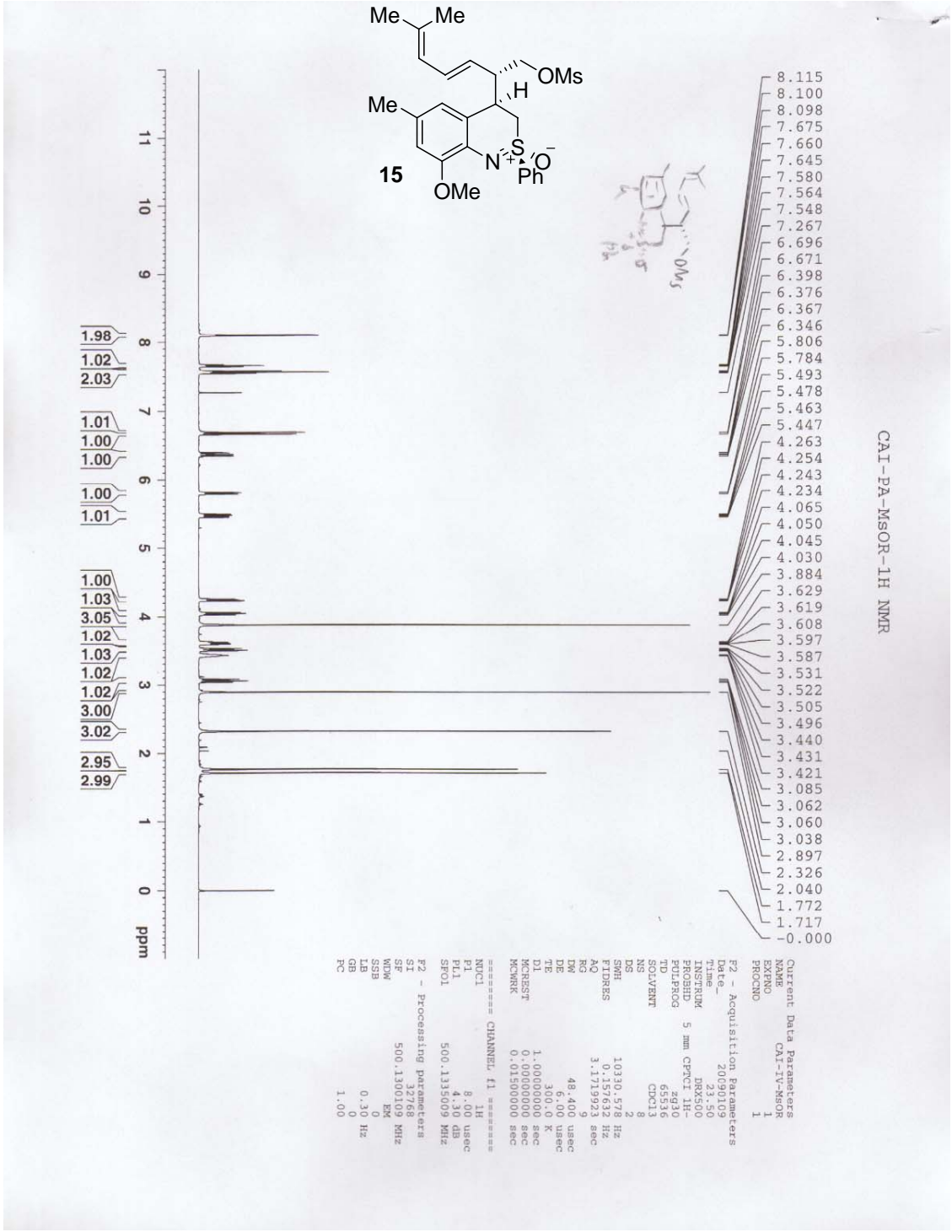
Current Data Parameters
NAME          YC-cal-c
EXPNO        1
PROCNO       1
PROCNAME     1

F2 - Acquisition Parameters
Time_        2007080
Time         22.48
INSTRUM     DRX500
PROBHD      5 mm Multinucl
PULPROG     zgpg30
TD           65536
SOLVENT     CDCl3
NS           1312
DS           4
SWH          34013.605 Hz
FIDRES       0.519006 Hz
AQ           0.9634292 sec
RG           32768
AQ           14.700 usec
DE           6.00 usec
TE           300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
D31          0.00000000 sec

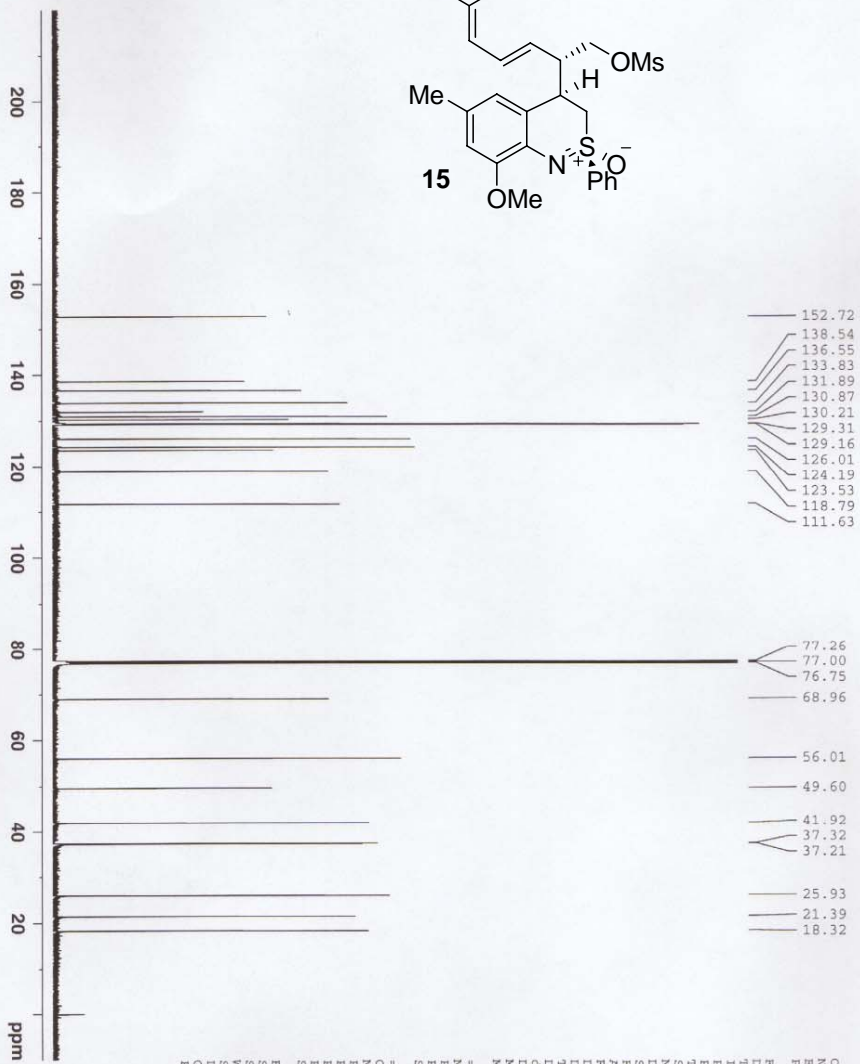
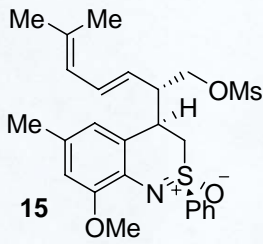
===== CHANNEL f1 =====
NUC1         13C
P1           8.10 usec
PL1          3.00 dB
SFO1        125.7723786 MHz

===== CHANNEL f2 =====
NUC2         13C
P2           88.00 usec
PL2          0.00 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI           32768
SF           125.7577638 MHz
WDW          EM
SSB          0
LB           1.00 Hz
GB           0
PC           1.40
  
```



13C NMR



```

Current Data Parameters
NAME          CN1-1V-M00K
EXPNO         1
PROCNO        1

F2 - Acquisition Parameters
Date_         20090109
Time          12:48
INSTRUM      DDX500
PROBHD       5 mm CPTCI 1H-
PULPROG      zgpg30
TD            71424
SOLVENT      CDCl3
NUC1          13C
NUC2          13C
DS            4
SWH           35211.270 Hz
FIDRES        0.492989 Hz
AQ            1.0142708 sec
RG            14.200
DR            35.00 usec
DE            300.0 K
TE            300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         0.492989 sec
MAGNET        0.00000000 sec
KCMER        0.01500000 sec

===== CHANNEL f1 =====
NUC1          13C
PUL1          12.00 usec
PL1           0.30 dB
SFO1         125.7716224 MHz

===== CHANNEL f2 =====
NAME         waltz16
INSTRUM      IH
PROBHD       80.00 usec
PCPD2        5.00 dB
PL12         22.00 dB
PL13         22.00 dB
PL14         22.00 dB
SFO2         500.1320009 MHz

F2 - Processing parameters
SI            65536
SF            125.7577993 MHz
WDW           EM
SSB           0
LB            1.00 Hz
GB            0
PC            1.00
  
```

