Molecules **2010**, *15*

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Supporting Information

Synthesis of Lasofoxifene, Nafoxidine and Their Positional Isomers via the Novel Three-Component Coupling Reaction

Kenya Nakata, Yoshiyuki Sano and Isamu Shiina *

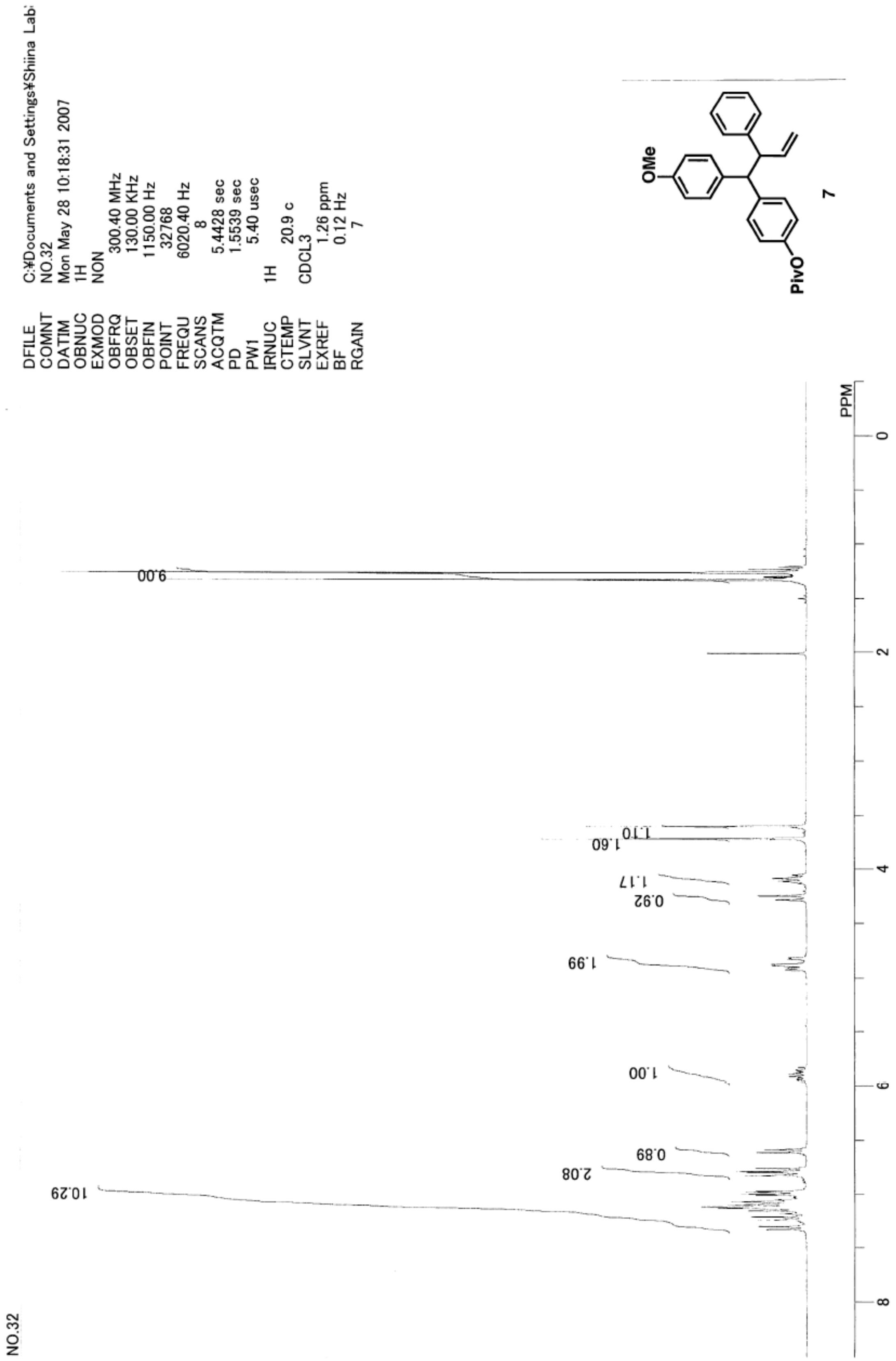
Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

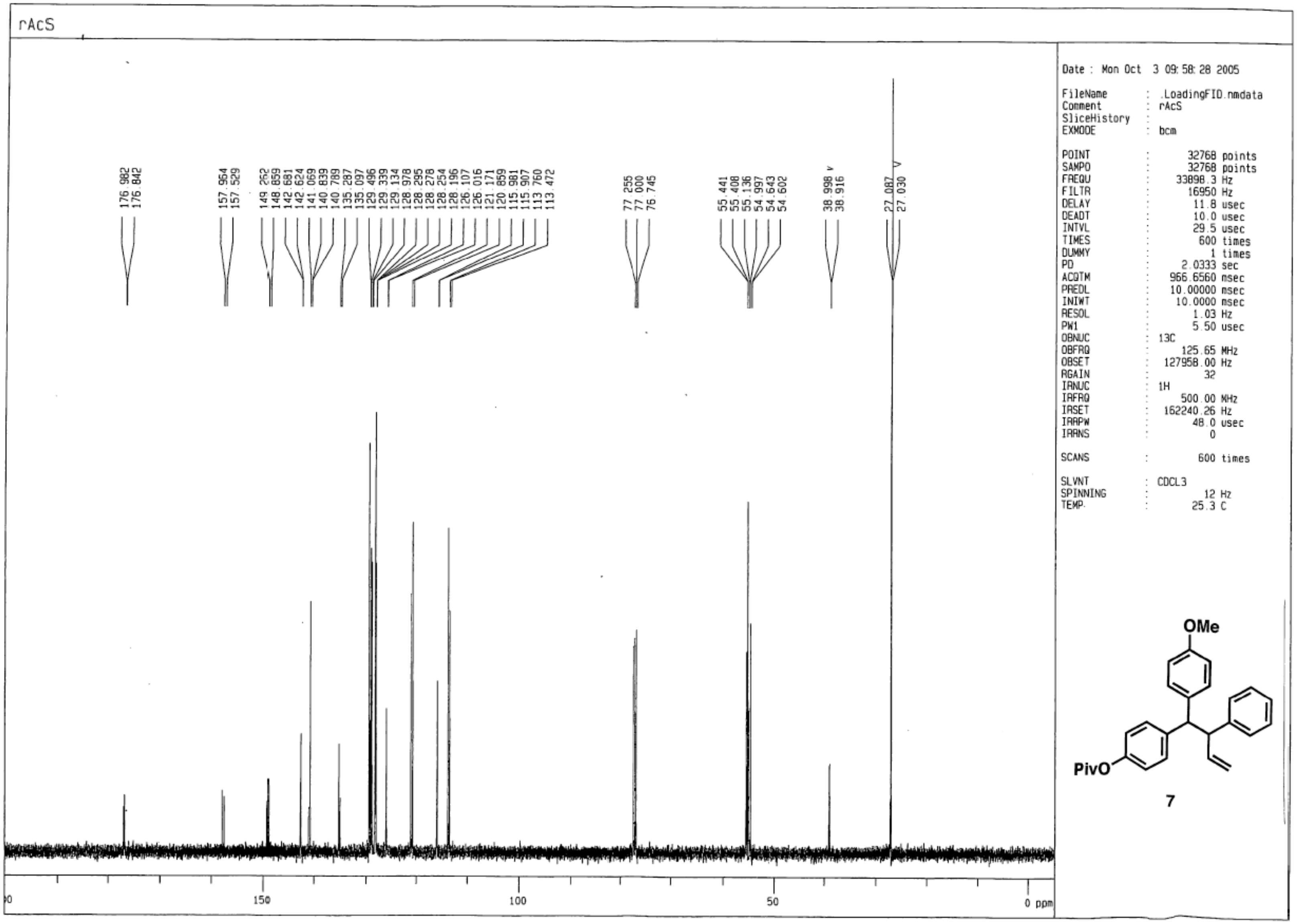
* Author to whom correspondence should be addressed; E-Mail: shiina@rs.kagu.tus.ac.jp;
Fax: +81-3-3260-5609.

Received: 21 August 2010; in revised form: 13 September 2010 / Accepted: 20 September 2010/ Published: 28 September 2010

Supplementary Material

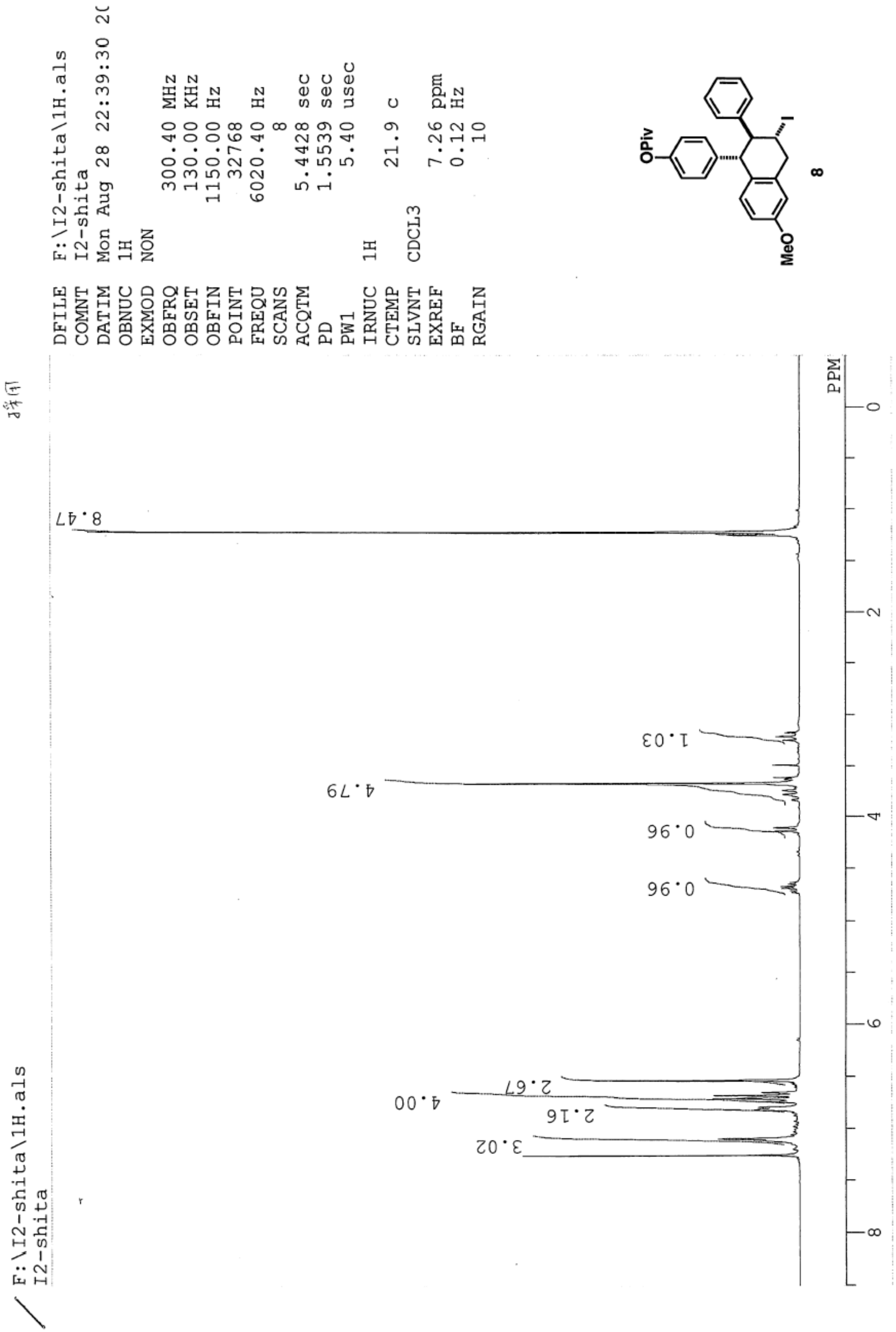
S2-25 ^{1}H and ^{13}C NMR Spectroscopic Data of Compounds


DFILE C:¥Documents and Settings¥Shiina Lab
COMNT NO.32
DATIM Mon May 28 10:18:31 2007
OBNUC 1H
EXMOD NON
OBFRQ 300.40 MHz
OBSET 130.00 KHz
OBFIN 1150.00 Hz
POINT 32768
FREQU 6020.40 Hz
SCANS 8
ACQTM 5.4428 sec
PD 1.5539 sec
PW1 5.40 usec
IRNUC 1H
CTEMP 20.9 c
SLVNT CDCL3
EXREF 1.26 ppm
BF 0.12 Hz
RGAIN 7
OMe
PivO
7
NO.32
9.00
1.10
1.60
1.17
0.92
1.99
1.00
0.89
2.08
10.29
PPM
0
2
4
6
8



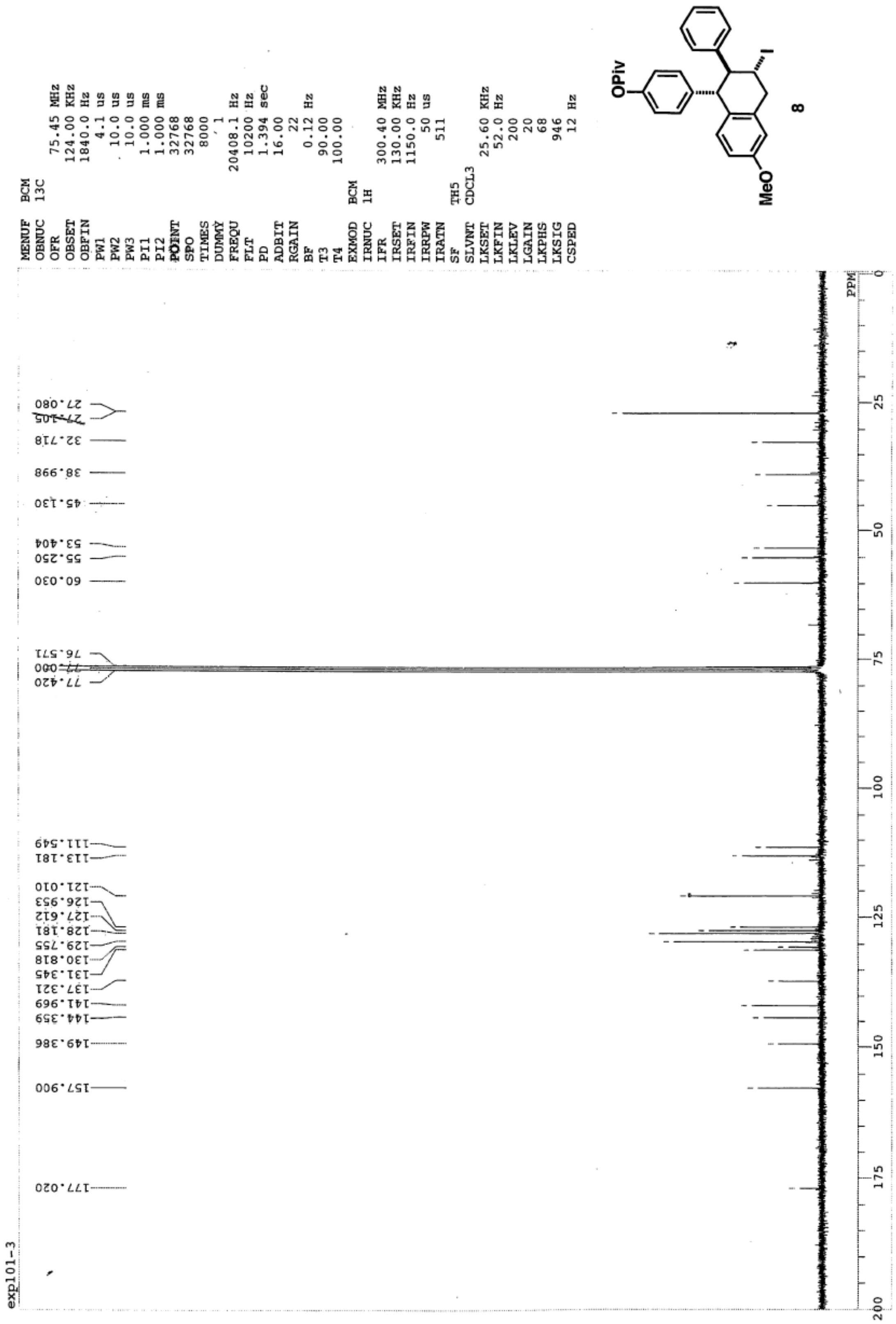
```
Date : Mon Oct  3 09:58:28 2005

FileName       : .LoadingFID.nmdata
Comment        : rAcS
SliceHistory   :
EXMODE         : bcm

POINT          :      32768 points
SAMPO          :      32768 points
FREQU          :    33898.3 Hz
FILTR          :      16950 Hz
DELAY          :       11.8 usec
DEADT          :       10.0 usec
INTVL          :       29.5 usec
TIMES          :        600 times
DUMMY          :          1 times
PD             :     2.0333 sec
ACQTM          :   966.6560 msec
PREDL          :   10.00000 msec
INIWT          :    10.0000 msec
RESOL          :       1.03 Hz
PW1            :       5.50 usec
OBNUC          : 13C
OBFRQ          :     125.65 MHz
OBSET          :  127958.00 Hz
RGAIN          :         32
IRNUC          : 1H
IRFRQ          :     500.00 MHz
IRSET          :  162240.26 Hz
IRRPW          :       48.0 usec
IRRNS          :          0

SCANS          :        600 times

SLVNT          : CDCL3
SPINNING       :         12 Hz
TEMP.          :       25.3 C
```

7



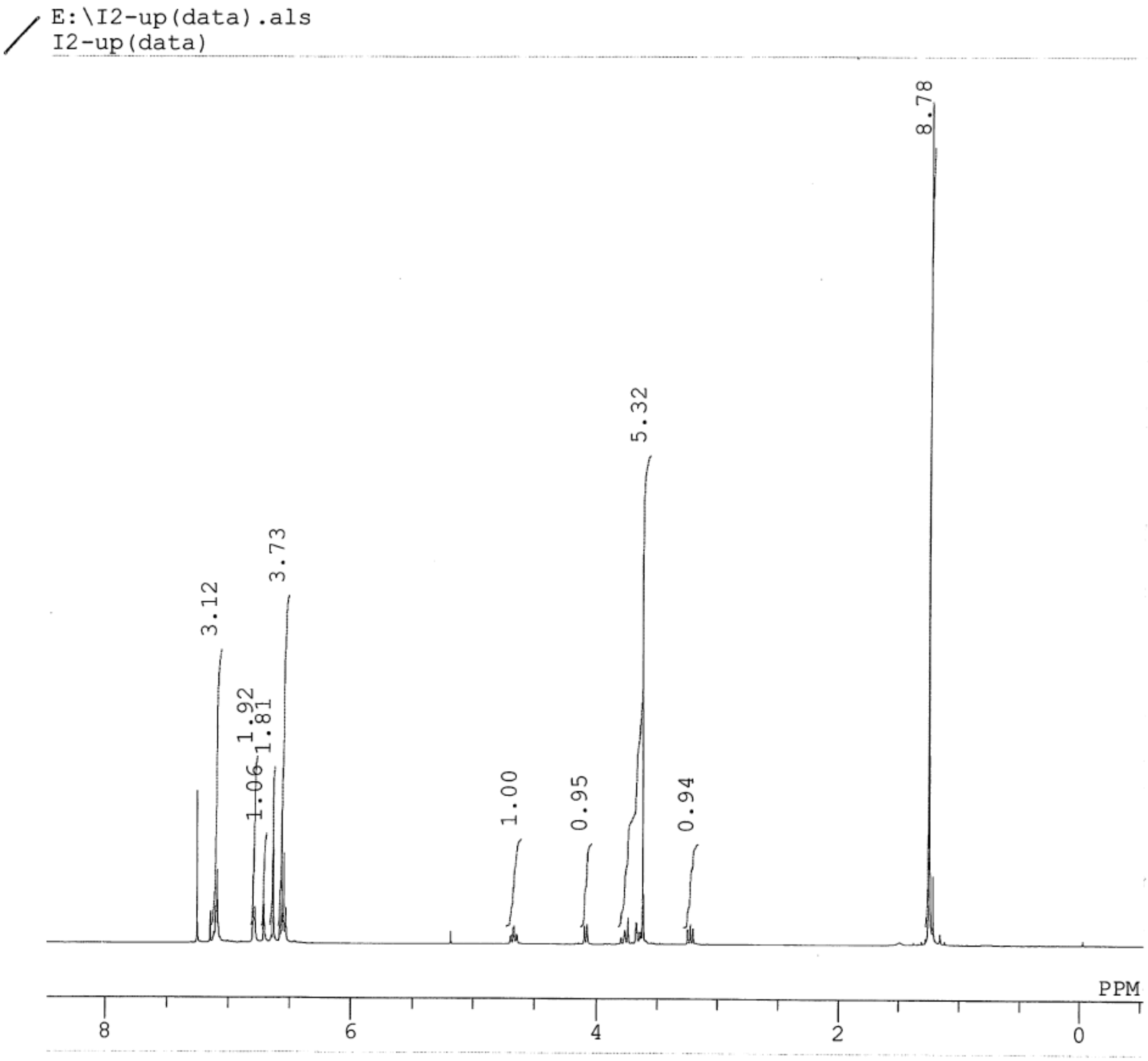
F:\I2-shita\1H.als
I2-shita

```
DFILE  F:\I2-shita\1H.als
COMNT  I2-shita
DATIM  Mon Aug 28 22:39:30 2(
OBNUC  1H
EXMOD  NON
OBFRQ       300.40 MHz
OBSET       130.00 KHz
OBFIN      1150.00 Hz
POINT        32768
FREQU      6020.40 Hz
SCANS            8
ACQTM       5.4428 sec
PD          1.5539 sec
PW1           5.40 usec
IRNUC  1H
CTEMP         21.9 c
SLVNT  CDCL3
EXREF         7.26 ppm
BF            0.12 Hz
RGAIN           10
```

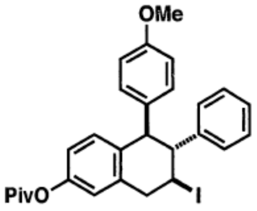

MENUF BCM
OBNUC 13C
OFR 75.45 MHz
OBSET 124.00 KHz
OBFIN 1840.0 Hz
PW1 4.1 us
PW2 10.0 us
PW3 10.0 us
PI1 1.000 ms
PI2 1.000 ms
POINT 32768
SPO 32768
TIMES 8000
DUMMY 1
FREQU 20408.1 Hz
FLT 10200 Hz
PD 1.394 sec
ADBIT 16.00
RGAIN 22
BF 0.12 Hz
T3 90.00
T4 100.00
EXMOD BCM
IRNUC 1H
IFR 300.40 MHz
IRSET 130.00 KHz
IRFIN 1150.0 Hz
IRRPW 50 us
IRATN 511
SF TH5
SLVNT CDCL3
LKSET 25.60 KHz
LKFIN 52.0 Hz
LKLEV 200
LGAIN 20
LKPHS 68
LKSIG 946
CSPED 12 Hz
27.080
27.105
32.718
38.998
45.130
53.404
55.250
60.030
76.571
77.000
77.420
111.549
113.181
121.010
126.953
127.612
128.181
129.755
130.818
131.345
137.321
141.969
144.359
149.386
157.900
177.020
exp101-3
PPM
0
25
50
75
100
125
150
175
200

OPiv
MeO
I

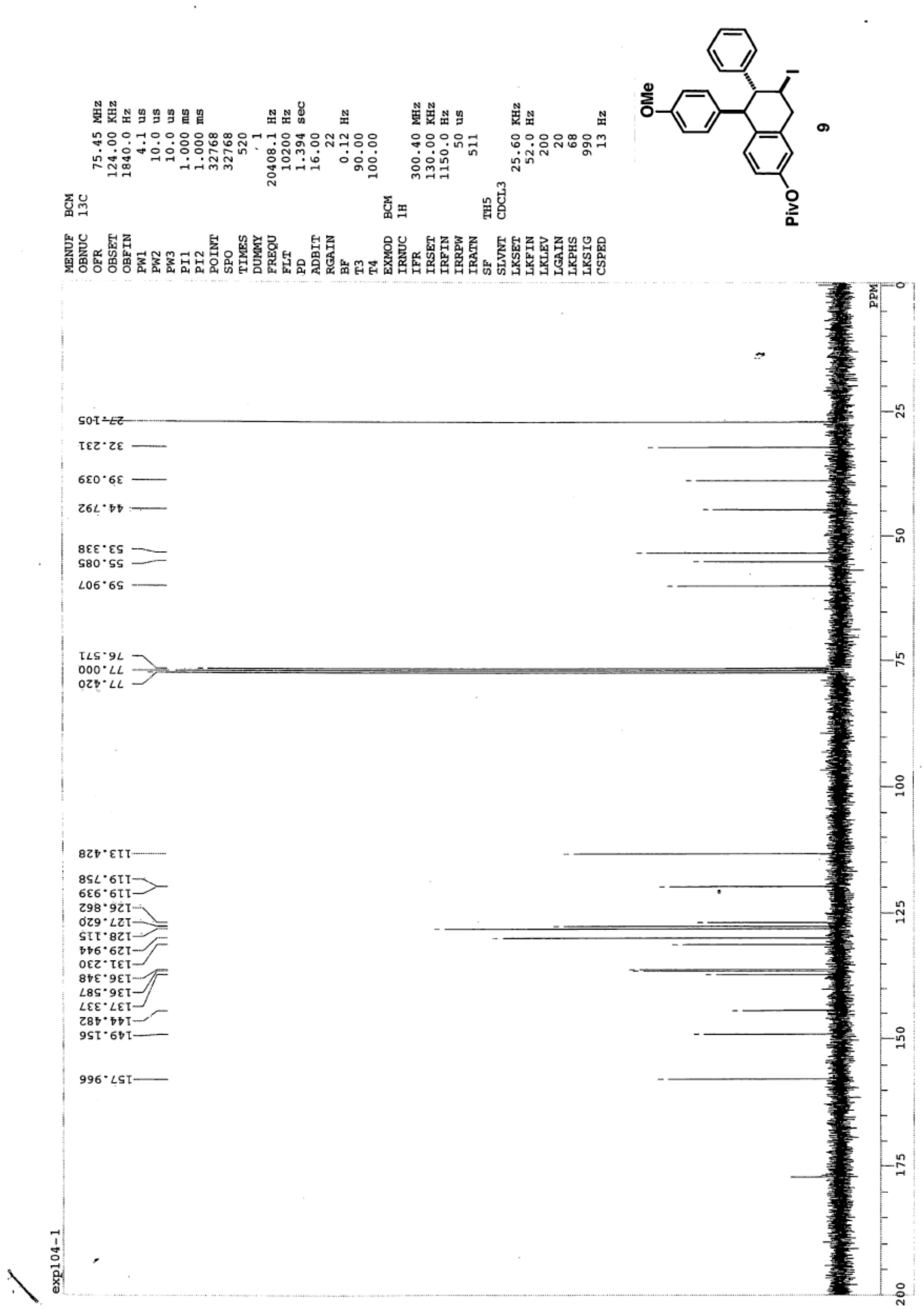
8



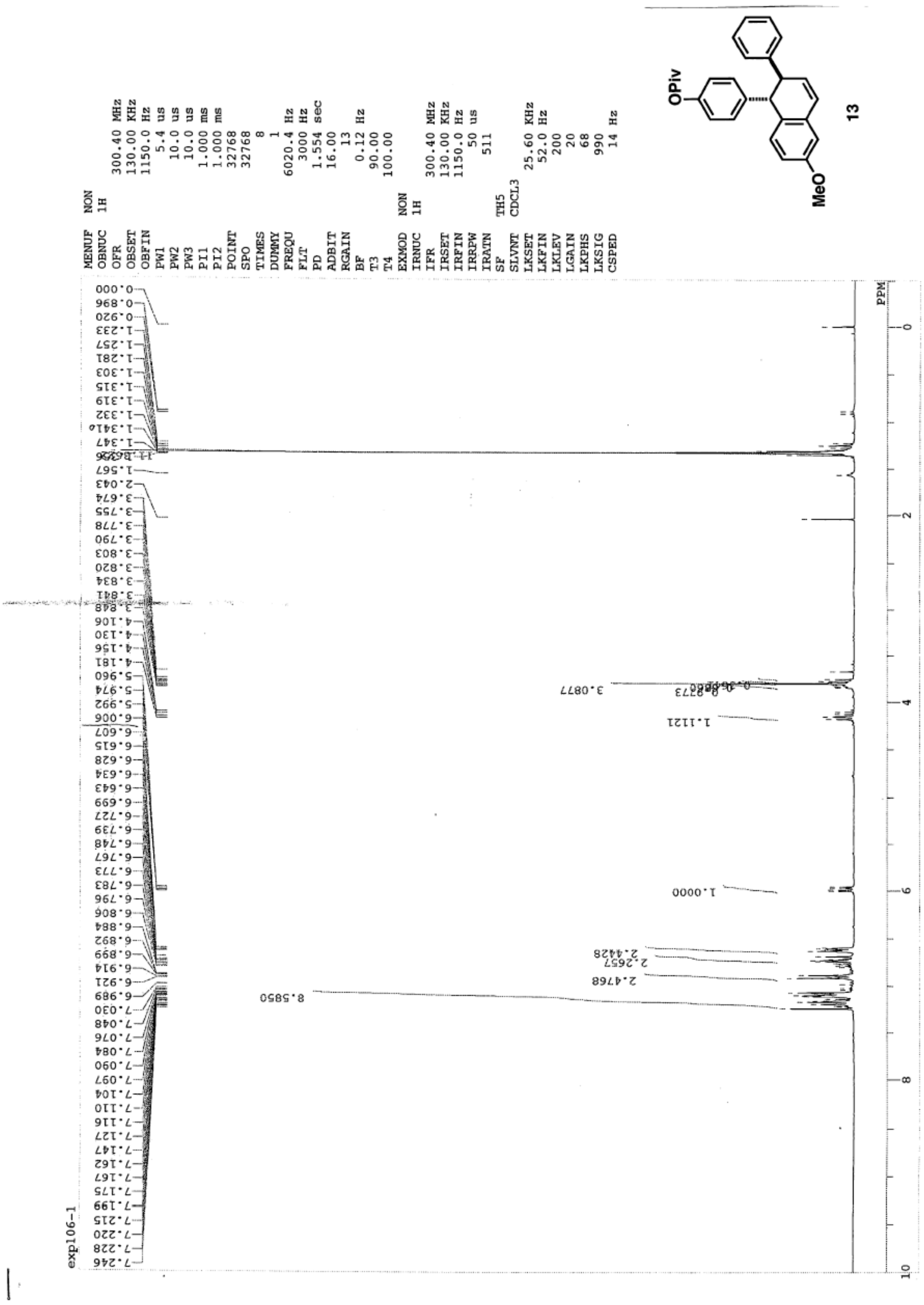
```
DFILE   E:\I2-up(data).als
COMNT   I2-up(data)
DATIM   Wed Sep 20 21:23:47 2(
OBNUC   1H
EXMOD   non
OBFRQ         500.00 MHz
OBSET           0.00 KHz
OBFIN      162160.00 Hz
POINT          32768
FREQU       10000.00 Hz
SCANS              8
ACQTM         3.2768 sec
PD            3.7232 sec
PW1             6.15 usec
IRNUC   1H
CTEMP           23.4 c
SLVNT   CDCL3
EXREF           7.26 ppm
BF              0.12 Hz
RGAIN             15
```



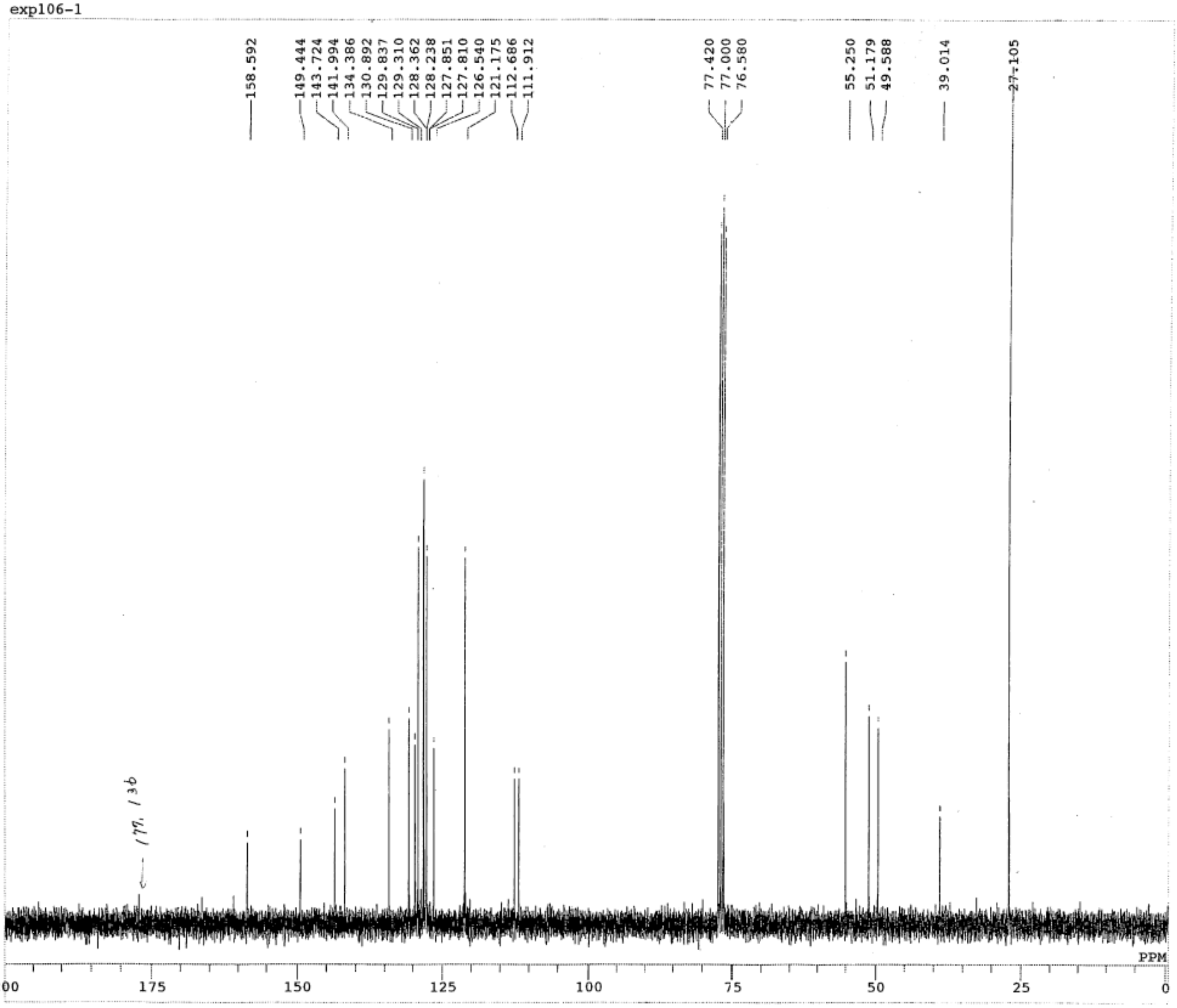
9


exp104-1
MENUF BCM
OBNUC 13C
OFR 75.45 MHz
OBSET 124.00 KHz
OBFIN 1840.0 Hz
PW1 4.1 us
PW2 10.0 us
PW3 10.0 us
PI1 1.000 ms
PI2 1.000 ms
POINT 32768
SPO 32768
TIMES 520
DUMMY 1
FREQU 20408.1 Hz
FLT 10200 Hz
PD 1.394 sec
ADBIT 16.00
RGAIN 22
BF 0.12 Hz
T3 90.00
T4 100.00
EXMOD BCM
IRNUC 1H
IFR 300.40 MHz
IRSET 130.00 KHz
IRFIN 1150.0 Hz
IRRPW 50 us
IRATN 511
SF TH5
SLVNT CDCL3
LKSET 25.60 KHz
LKFIN 52.0 Hz
LKLEV 200
LGAIN 20
LKPHS 68
LKSIG 990
CSPED 13 Hz
27.105
32.231
39.039
44.792
53.338
55.085
59.907
76.571
77.000
77.420
113.428
119.758
119.939
126.862
127.620
128.115
129.944
131.230
136.348
136.587
137.337
144.482
149.156
157.966
PPM
0
25
50
75
100
125
150
175
200
OMe
PivO
I

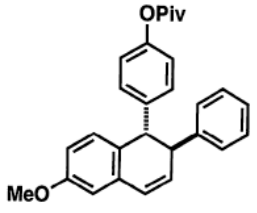
9


exp106-1
MENUF NON
OBNUC 1H
OFR 300.40 MHz
OBSET 130.00 KHz
OBFIN 1150.0 Hz
PW1 5.4 us
PW2 10.0 us
PW3 10.0 us
PI1 1.000 ms
PI2 1.000 ms
POINT 32768
SPO 32768
TIMES 8
DUMMY 1
FREQU 6020.4 Hz
FLT 3000 Hz
PD 1.554 sec
ADBIT 16.00
RGAIN 13
BF 0.12 Hz
T3 90.00
T4 100.00
EXMOD NON
IRNUC 1H
IFR 300.40 MHz
IRSET 130.00 KHz
IRFIN 1150.0 Hz
IRRPW 50 us
IRATN 511
SF TH5
SLVNT CDCL3
LKSET 25.60 KHz
LKFIN 52.0 Hz
LKLEV 200
LGAIN 20
LKPHS 68
LKSIG 990
CSPED 14 Hz
0.000
0.896
0.920
1.233
1.257
1.281
1.303
1.315
1.319
1.332
1.341
1.347
1.567
2.043
3.674
3.755
3.778
3.790
3.803
3.820
3.834
3.841
3.848
4.106
4.130
4.156
4.181
5.960
5.974
5.992
6.006
6.607
6.615
6.628
6.634
6.643
6.699
6.727
6.739
6.748
6.767
6.773
6.783
6.796
6.806
6.884
6.892
6.899
6.914
6.921
6.989
7.030
7.048
7.076
7.084
7.090
7.097
7.104
7.110
7.116
7.127
7.147
7.162
7.167
7.175
7.199
7.215
7.220
7.228
7.246
3.0877
0.8273
1.1121
1.0000
2.4428
2.2657
2.4768
8.5850
PPM
0
2
4
6
8
10
OPiv
MeO
13

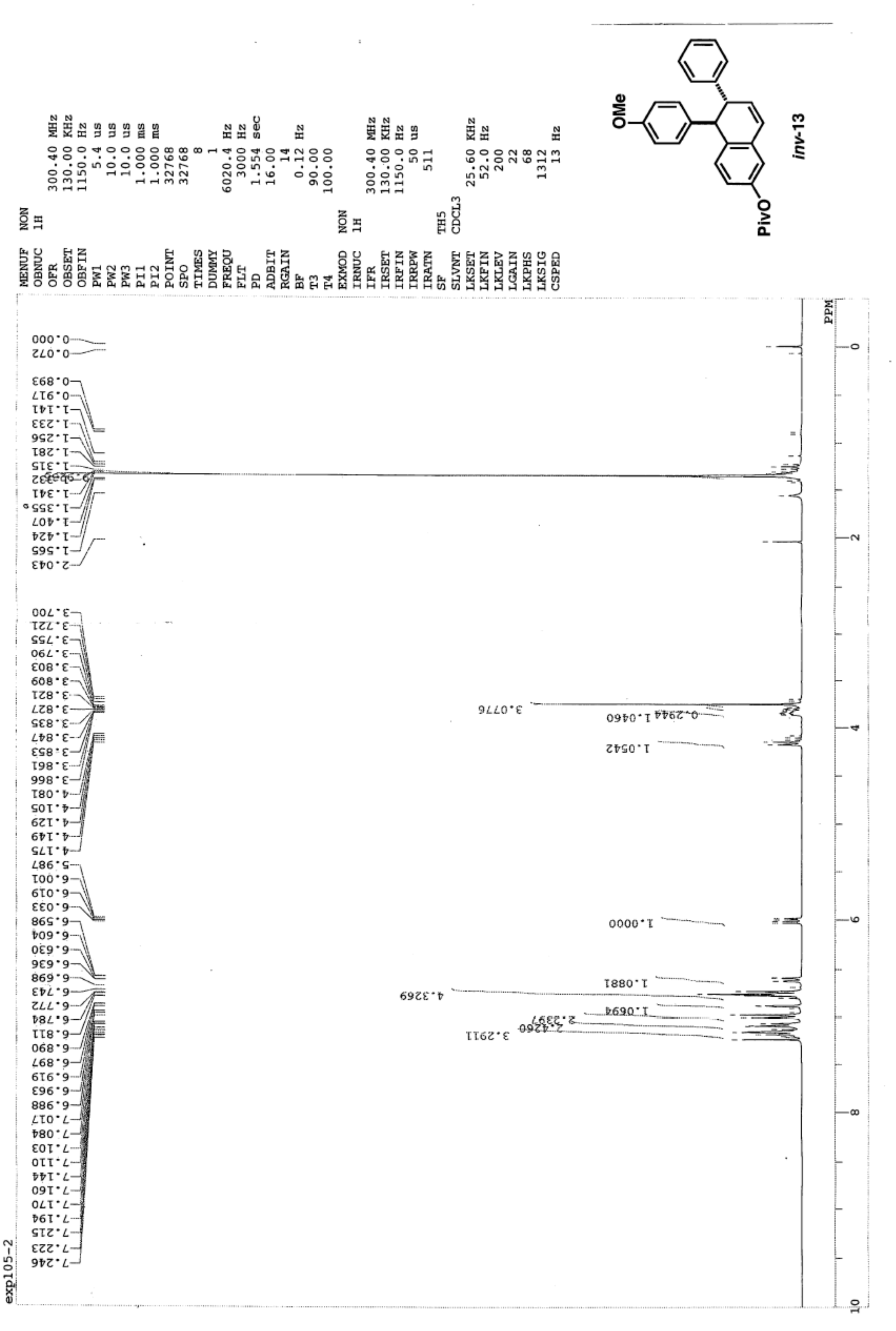
exp106-1



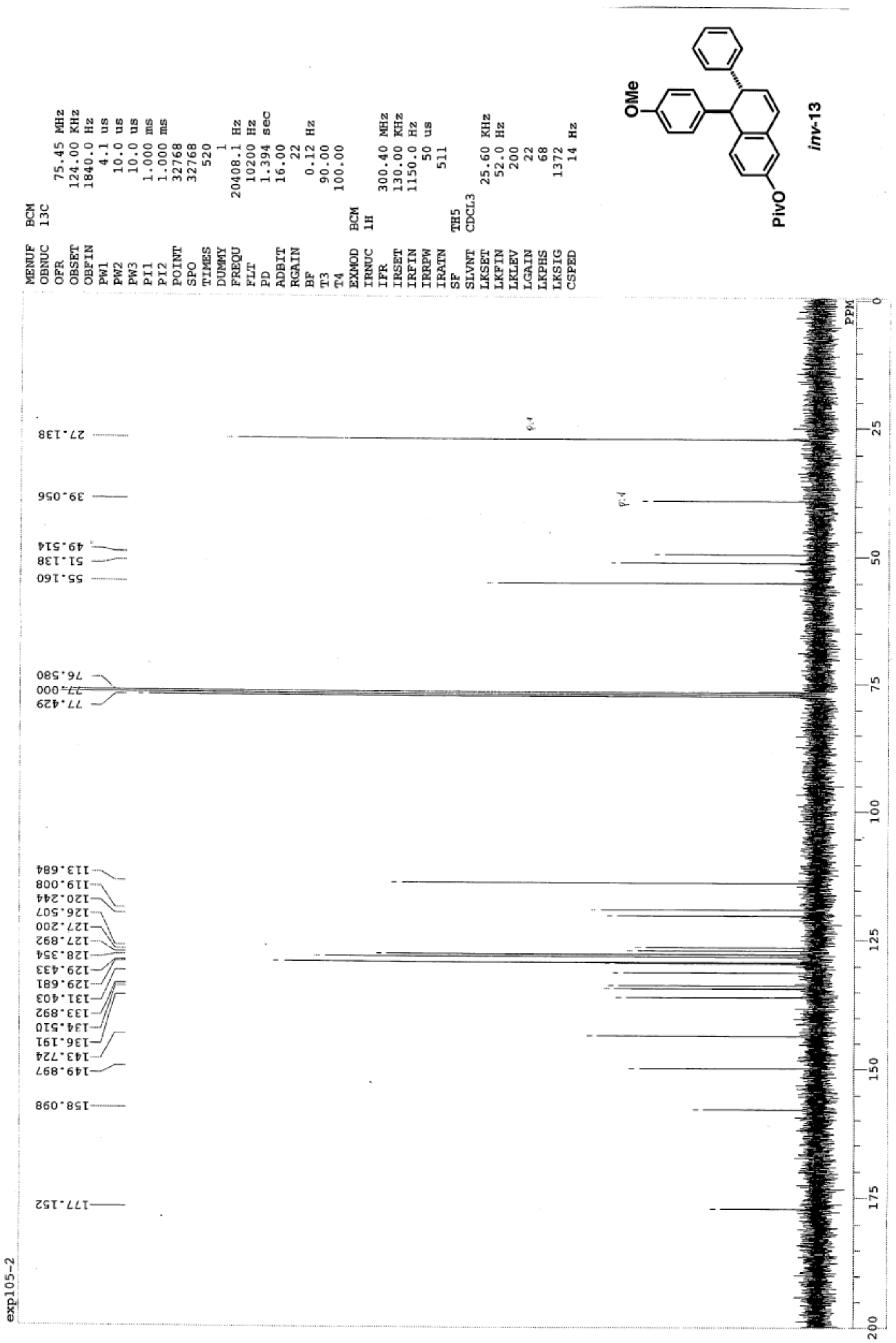
```
MENUF   BCM
OBNUC   13C
OFR          75.45 MHz
OBSET       124.00 KHz
OBFIN       1840.0 Hz
PW1            4.1 us
PW2           10.0 us
PW3           10.0 us
PI1          1.000 ms
PI2          1.000 ms
POINT        32768
SPO          32768
TIMES          520
DUMMY            1
FREQU      20408.1 Hz
FLT          10200 Hz
PD           1.394 sec
ADBIT        16.00
RGAIN           22
BF            0.12 Hz
T3           90.00
T4          100.00
EXMOD   BCM
IRNUC   1H
IFR         300.40 MHz
IRSET       130.00 KHz
IRFIN       1150.0 Hz
IRRPW           50 us
IRATN          511
SF      TH5
SLVNT   CDCL3
LKSET        25.60 KHz
LKFIN         52.0 Hz
LKLEV          200
LGAIN           20
LKPHS           68
LKSIG          961
CSPED           13 Hz
```

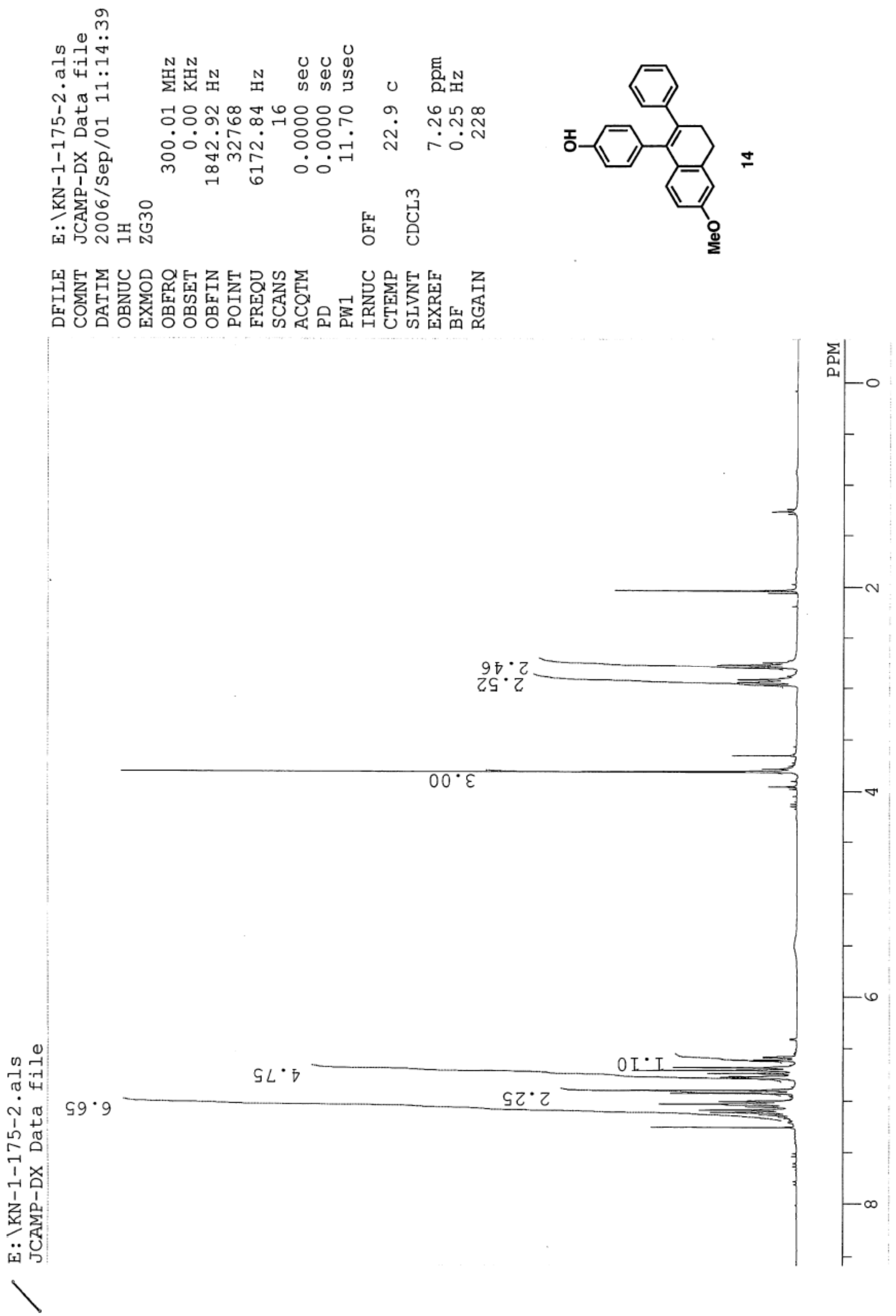


13


exp105-2
MENUF NON
OBNUC 1H
OFR 300.40 MHz
OBSET 130.00 KHz
OBFIN 1150.0 Hz
PW1 5.4 us
PW2 10.0 us
PW3 10.0 us
PI1 1.000 ms
PI2 1.000 ms
POINT 32768
SPO 32768
TIMES 8
DUMMY 1
FREQU 6020.4 Hz
FLT 3000 Hz
PD 1.554 sec
ADBIT 16.00
RGAIN 14
BF 0.12 Hz
T3 90.00
T4 100.00
EXMOD NON
IRNUC 1H
IFR 300.40 MHz
IRSET 130.00 KHz
IRFIN 1150.0 Hz
IRRPW 50 us
IRATN 511
SF TH5
SLVNT CDCL3
LKSET 25.60 KHz
LKFIN 52.0 Hz
LKLEV 200
LGAIN 22
LKPHS 68
LKSIG 1312
CSPED 13 Hz
0.000
0.072
0.893
0.917
1.141
1.233
1.256
1.281
1.315
1.332
1.341
1.355
1.407
1.424
1.565
2.043
3.700
3.721
3.755
3.790
3.803
3.809
3.821
3.827
3.835
3.847
3.853
3.861
3.866
4.081
4.105
4.129
4.149
4.175
5.987
6.001
6.019
6.033
6.598
6.604
6.630
6.636
6.698
6.743
6.772
6.784
6.811
6.890
6.897
6.919
6.963
6.988
7.017
7.084
7.103
7.110
7.144
7.160
7.170
7.194
7.215
7.223
7.246
3.0776
0.2944
1.0460
1.0542
1.0000
1.0881
4.3269
1.0694
2.3397
2.4260
3.2911
OMe
PivO
PPM
0
2
4
6
8
10

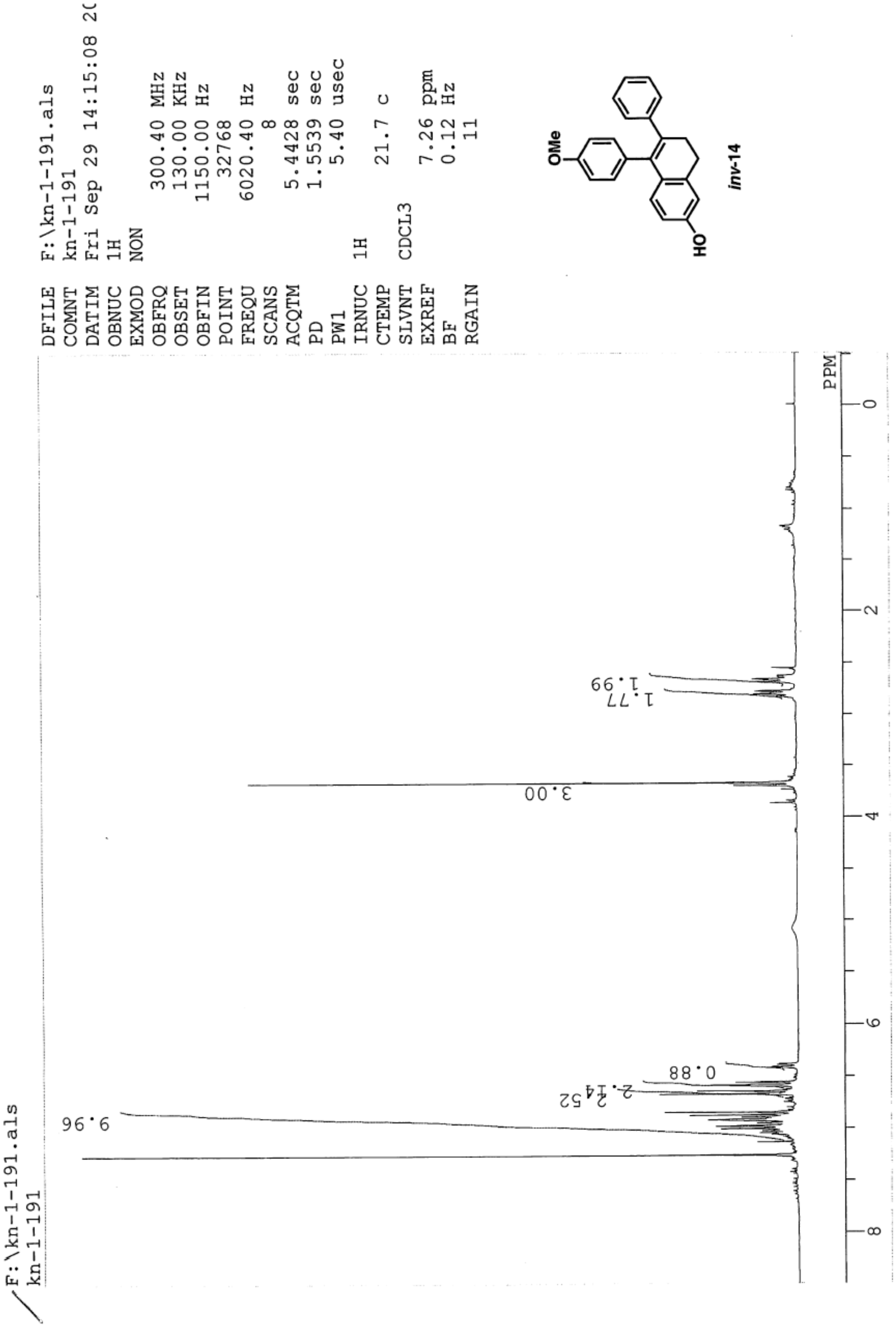
inv-13


exp105-2
MENUF BCM
OBNUC 13C
OFR 75.45 MHz
OBSET 124.00 KHz
OBFIN 1840.0 Hz
PW1 4.1 us
PW2 10.0 us
PW3 10.0 us
PI1 1.000 ms
PI2 1.000 ms
POINT 32768
SPO 32768
TIMES 520
DUMMY 1
FREQU 20408.1 Hz
FLT 10200 Hz
PD 1.394 sec
ADBIT 16.00
RGAIN 22
BF 0.12 Hz
T3 90.00
T4 100.00
EXMOD BCM
IRNUC 1H
IFR 300.40 MHz
IRSET 130.00 KHz
IRFIN 1150.0 Hz
IRRPW 50 us
IRATN 511
SF TH5
SLVNT CDCL3
LKSET 25.60 KHz
LKFIN 52.0 Hz
LKLEV 200
LGAIN 22
LKPHS 68
LKSIG 1372
CSPED 14 Hz
27.138
39.056
49.514
51.138
55.160
76.580
77.000
77.429
113.684
119.008
120.244
126.507
127.200
127.892
128.354
129.433
129.681
131.403
133.892
134.510
136.191
143.724
149.897
158.098
177.152
PPM
0
25
50
75
100
125
150
175
200
OMe
PivO
inv-13

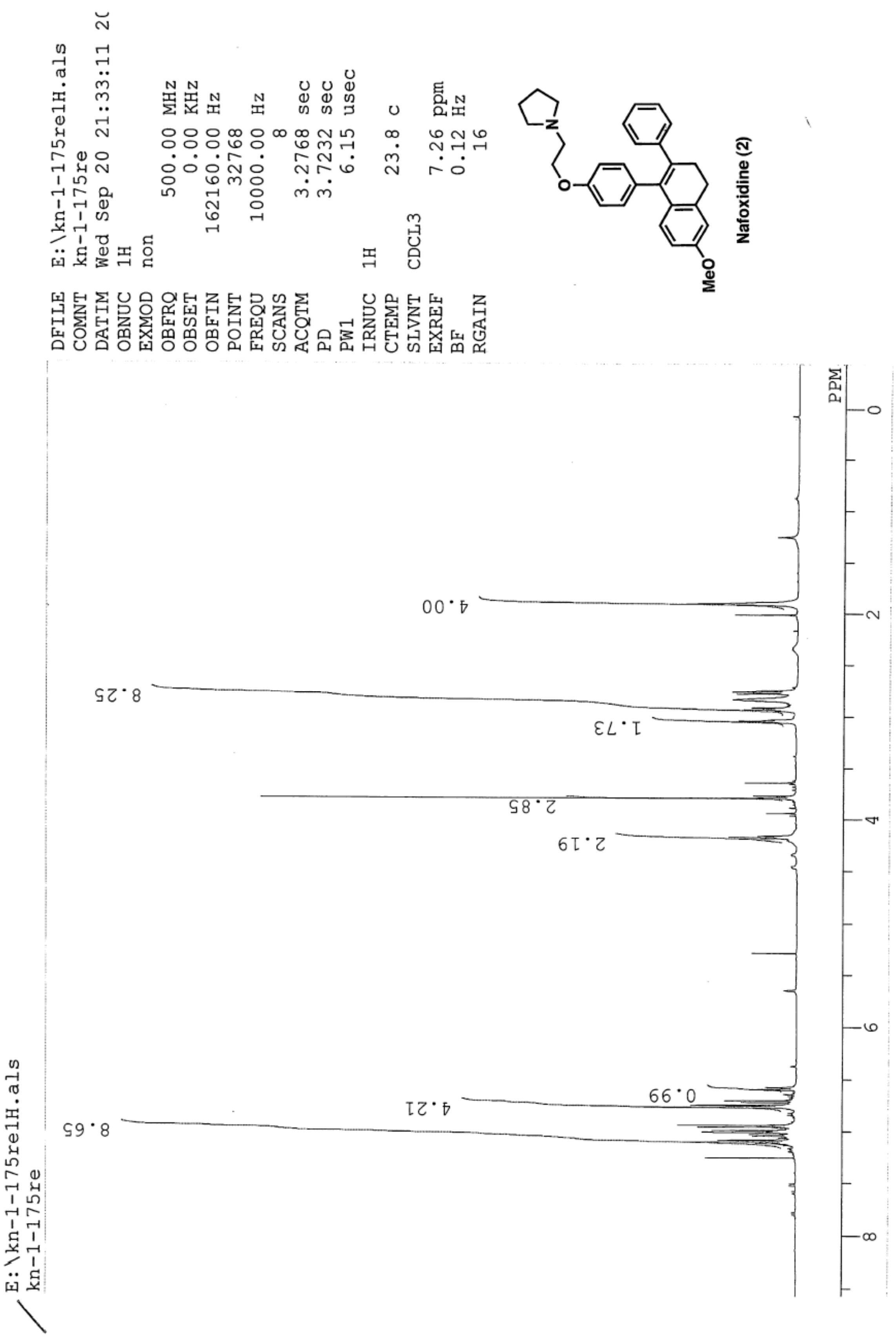


```
DFILE  E:\KN-1-175-2.als
COMNT  JCAMP-DX Data file
DATIM  2006/Sep/01 11:14:39
OBNUC  1H
EXMOD  ZG30
OBFRQ     300.01 MHz
OBSET       0.00 KHz
OBFIN    1842.92 Hz
POINT      32768
FREQU    6172.84 Hz
SCANS         16
ACQTM     0.0000 sec
PD        0.0000 sec
PW1        11.70 usec
IRNUC  OFF
CTEMP       22.9 c
SLVNT  CDCL3
EXREF       7.26 ppm
BF          0.25 Hz
RGAIN        228
```

14



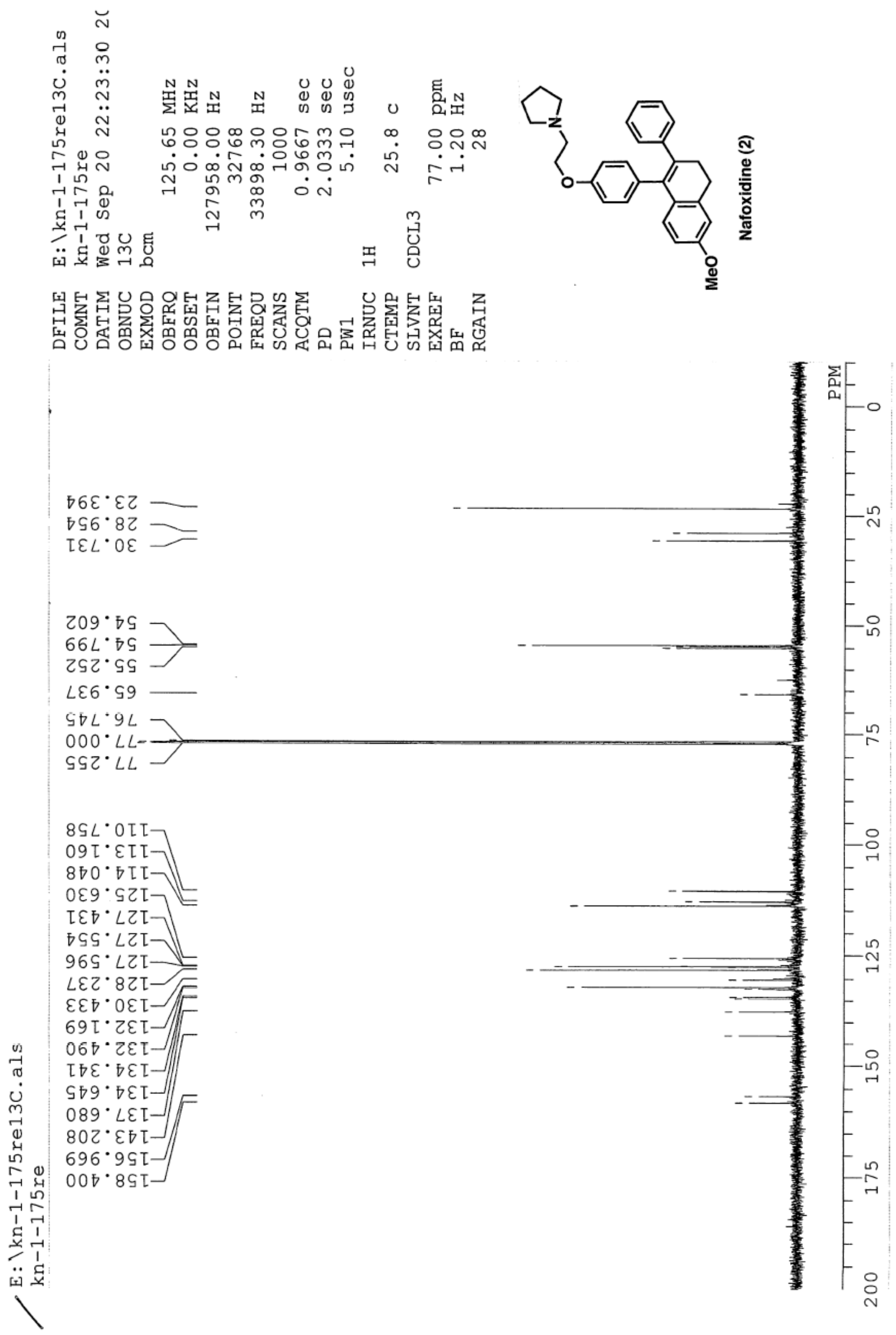
```
DFILE  F:\kn-1-191.als
COMNT  kn-1-191
DATIM  Fri Sep 29 14:15:08 2
OBNUC  1H
EXMOD  NON
OBFRQ     300.40 MHz
OBSET     130.00 KHz
OBFIN    1150.00 Hz
POINT      32768
FREQU    6020.40 Hz
SCANS          8
ACQTM     5.4428 sec
PD        1.5539 sec
PW1         5.40 usec
IRNUC  1H
CTEMP       21.7 c
SLVNT  CDCL3
EXREF       7.26 ppm
BF          0.12 Hz
RGAIN         11
```



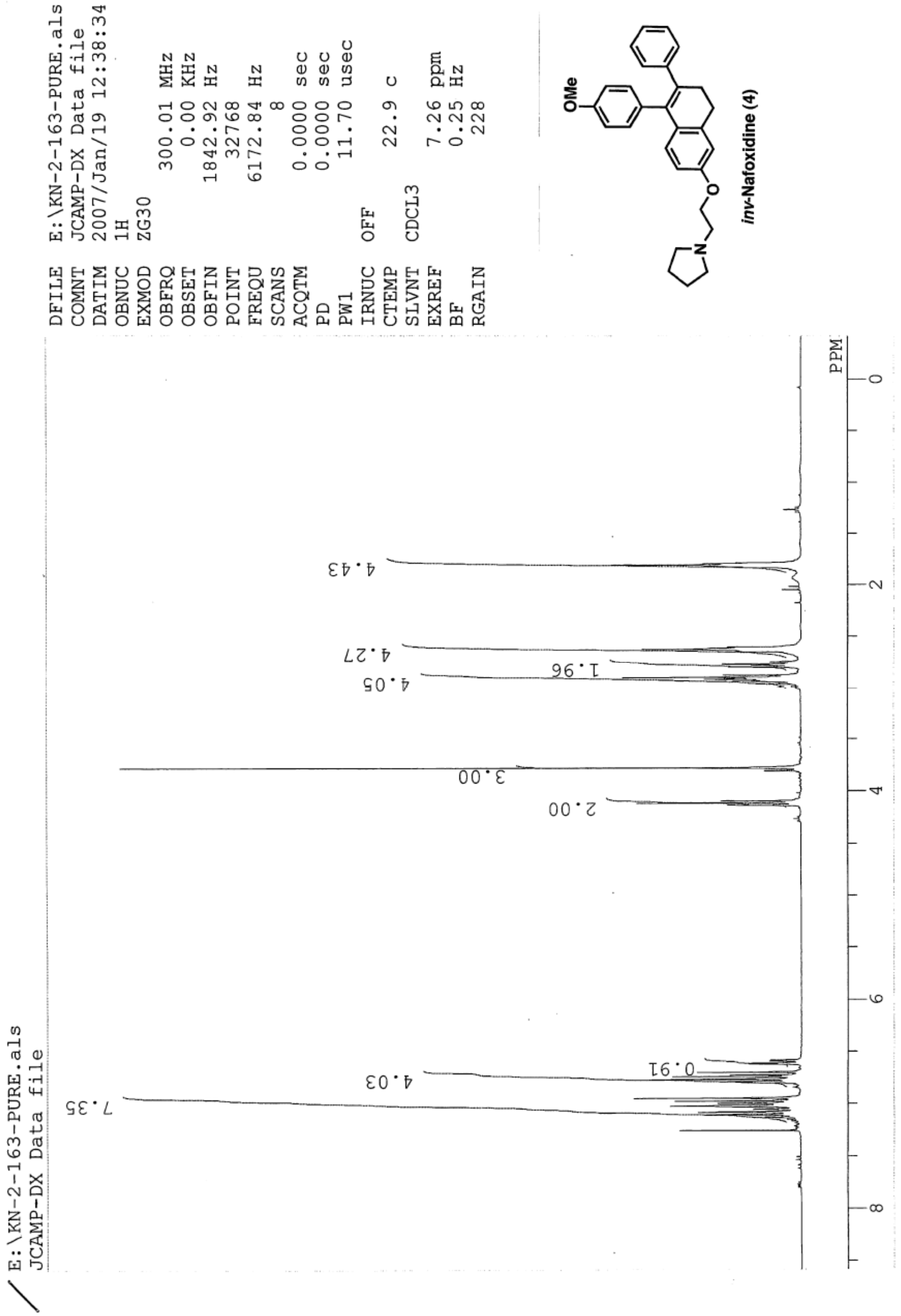
E:\kn-1-175re1H.als
kn-1-175re

DFILE	E:\kn-1-175re1H.als
COMNT	kn-1-175re
DATIM	Wed Sep 20 21:33:11 2
OBNUC	1H
EXMOD	non
OBFRQ	500.00 MHz
OBSET	0.00 KHz
OBFIN	162160.00 Hz
POINT	32768
FREQU	10000.00 Hz
SCANS	8
ACQTM	3.2768 sec
PD	3.7232 sec
PW1	6.15 usec
IRNUC	1H
CTEMP	23.8 c
SLVNT	CDCL3
EXREF	7.26 ppm
BF	0.12 Hz
RGAIN	16

Nafoxidine (2)



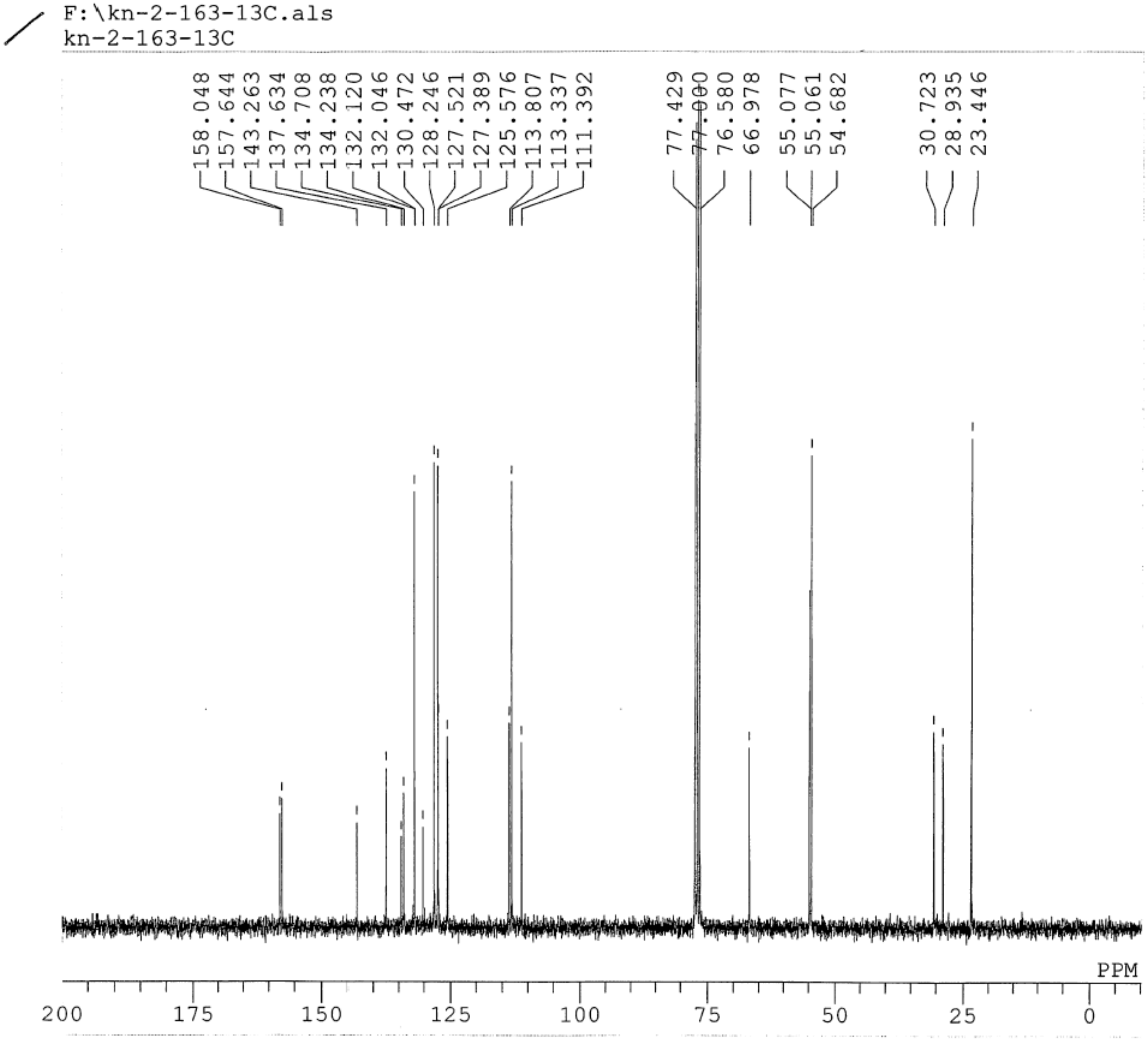
Nafoxidine (2)



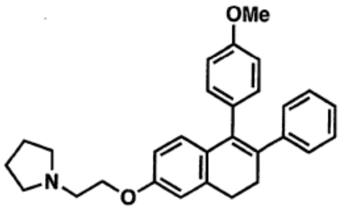
E:\KN-2-163-PURE.als
JCAMP-DX Data file

```
DFILE   E:\KN-2-163-PURE.als
COMNT   JCAMP-DX Data file
DATIM   2007/Jan/19 12:38:34
OBNUC   1H
EXMOD   ZG30
OBFRQ          300.01 MHz
OBSET            0.00 KHz
OBFIN         1842.92 Hz
POINT           32768
FREQU         6172.84 Hz
SCANS               8
ACQTM          0.0000 sec
PD             0.0000 sec
PW1             11.70 usec
IRNUC   OFF
CTEMP            22.9 c
SLVNT   CDCL3
EXREF            7.26 ppm
BF               0.25 Hz
RGAIN             228
```

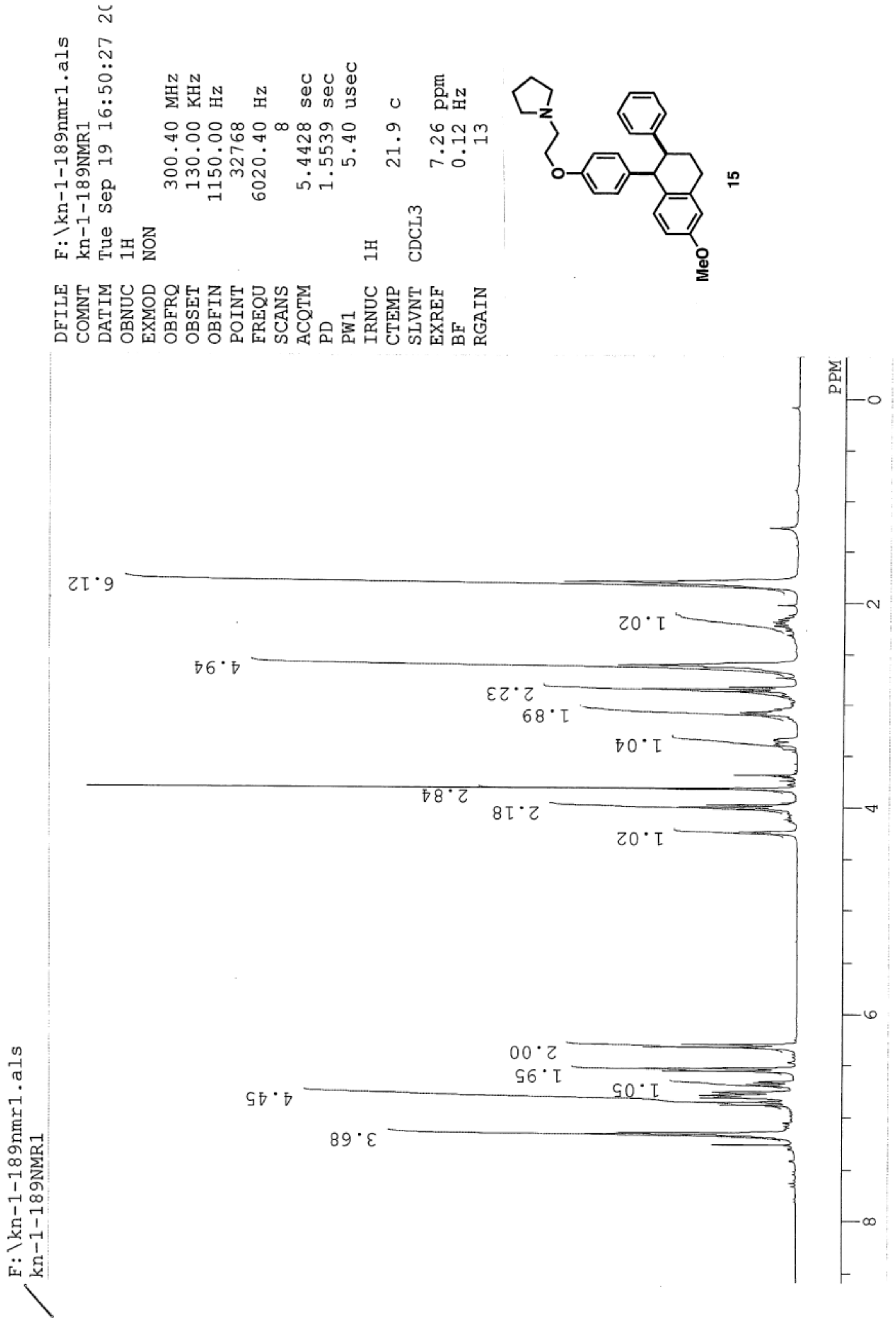
inv-**Nafoxidine (4)**

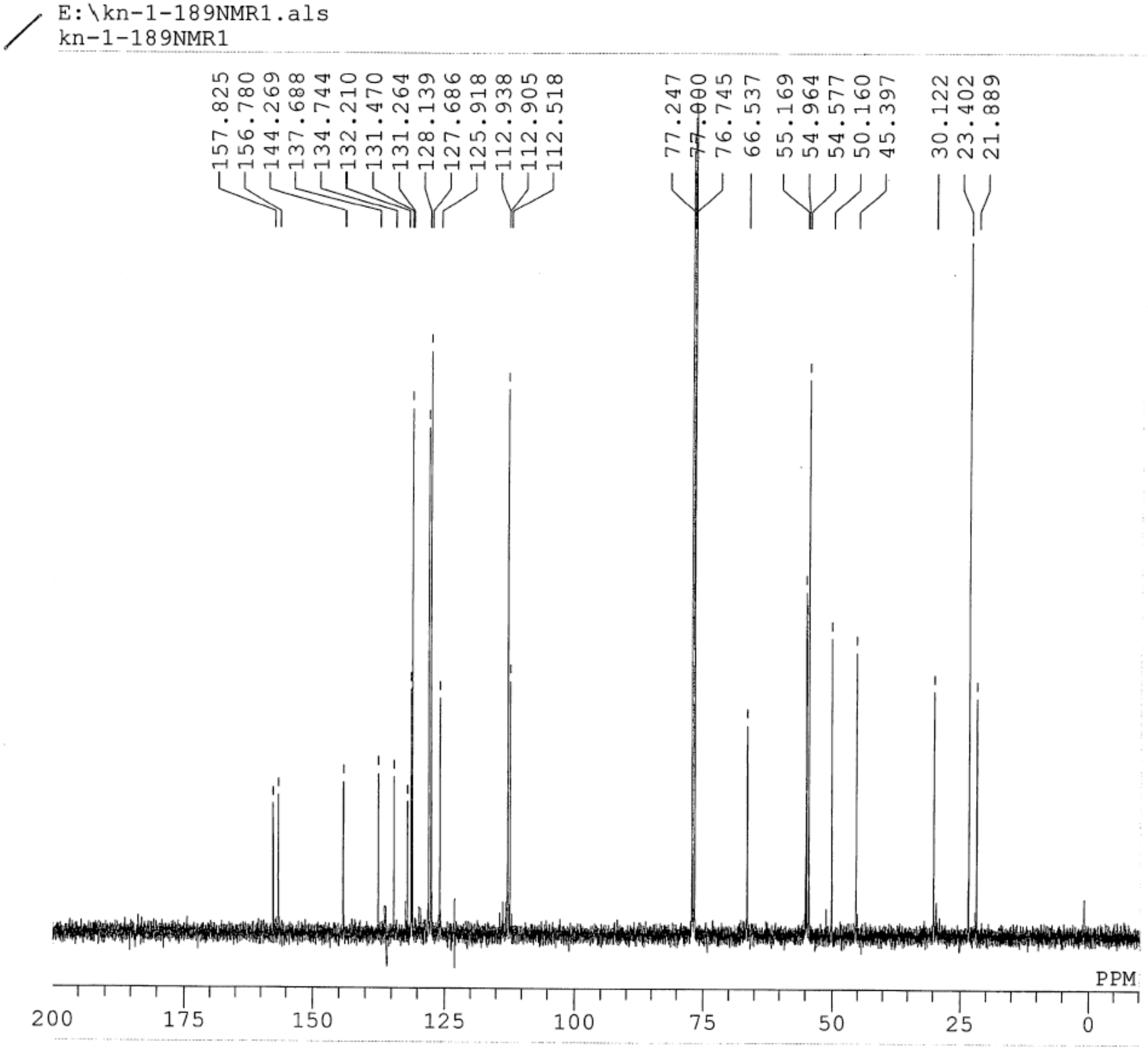


```
DFILE   F:\kn-2-163-13C.als
COMNT   kn-2-163-13C
DATIM   Sat Jan 20 10:30:10 2(
OBNUC   13C
EXMOD   BCM
OBFRQ          75.45 MHz
OBSET         124.00 KHz
OBFIN        1840.00 Hz
POINT          32768
FREQU       20408.10 Hz
SCANS            640
ACQTM         1.6056 sec
PD            1.3944 sec
PW1             4.10 usec
IRNUC   1H
CTEMP           20.6 c
SLVNT   CDCL3
EXREF          77.00 ppm
BF              1.20 Hz
RGAIN             22
```

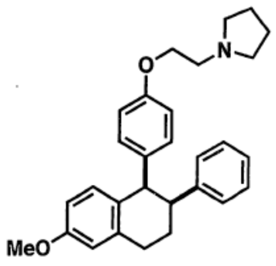


***inv*-Nafoxidine (4)**

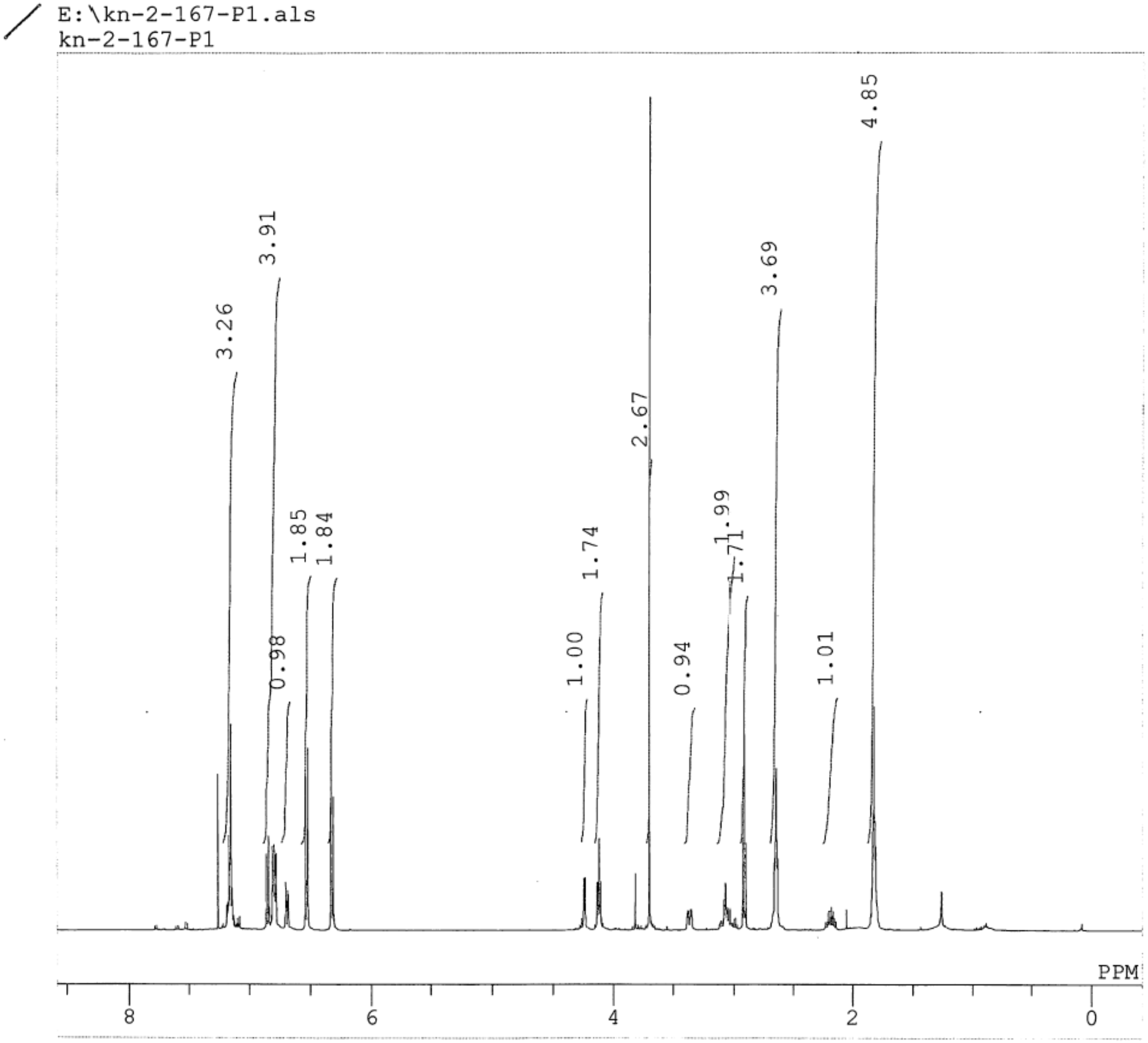

DFILE F:\kn-1-189nmr1.als
COMNT kn-1-189NMR1
DATIM Tue Sep 19 16:50:27 2
OBNUC 1H
EXMOD NON
OBFRQ 300.40 MHz
OBSET 130.00 KHz
OBFIN 1150.00 Hz
POINT 32768
FREQU 6020.40 Hz
SCANS 8
ACQTM 5.4428 sec
PD 1.5539 sec
PW1 5.40 usec
IRNUC 1H
CTEMP 21.9 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 13
F:\kn-1-189nmr1.als
kn-1-189NMR1
MeO
O
N
15
6.12
1.02
4.94
2.23
1.89
1.04
2.84
2.18
1.02
2.00
1.95
1.05
4.45
3.68
PPM
0
2
4
6
8



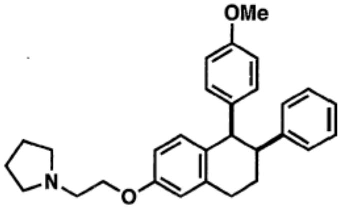
```
DFILE   E:\kn-1-189NMR1.als
COMNT   kn-1-189NMR1
DATIM   Thu Sep 21 16:04:46 2(
OBNUC   13C
EXMOD   bcm
OBFRQ         125.65 MHz
OBSET           0.00 KHz
OBFIN      127958.00 Hz
POINT          32768
FREQU       33898.30 Hz
SCANS            500
ACQTM         0.9667 sec
PD            2.0333 sec
PW1             5.10 usec
IRNUC   1H
CTEMP           25.9 c
SLVNT   CDCL3
EXREF          77.00 ppm
BF              1.20 Hz
RGAIN             30
```



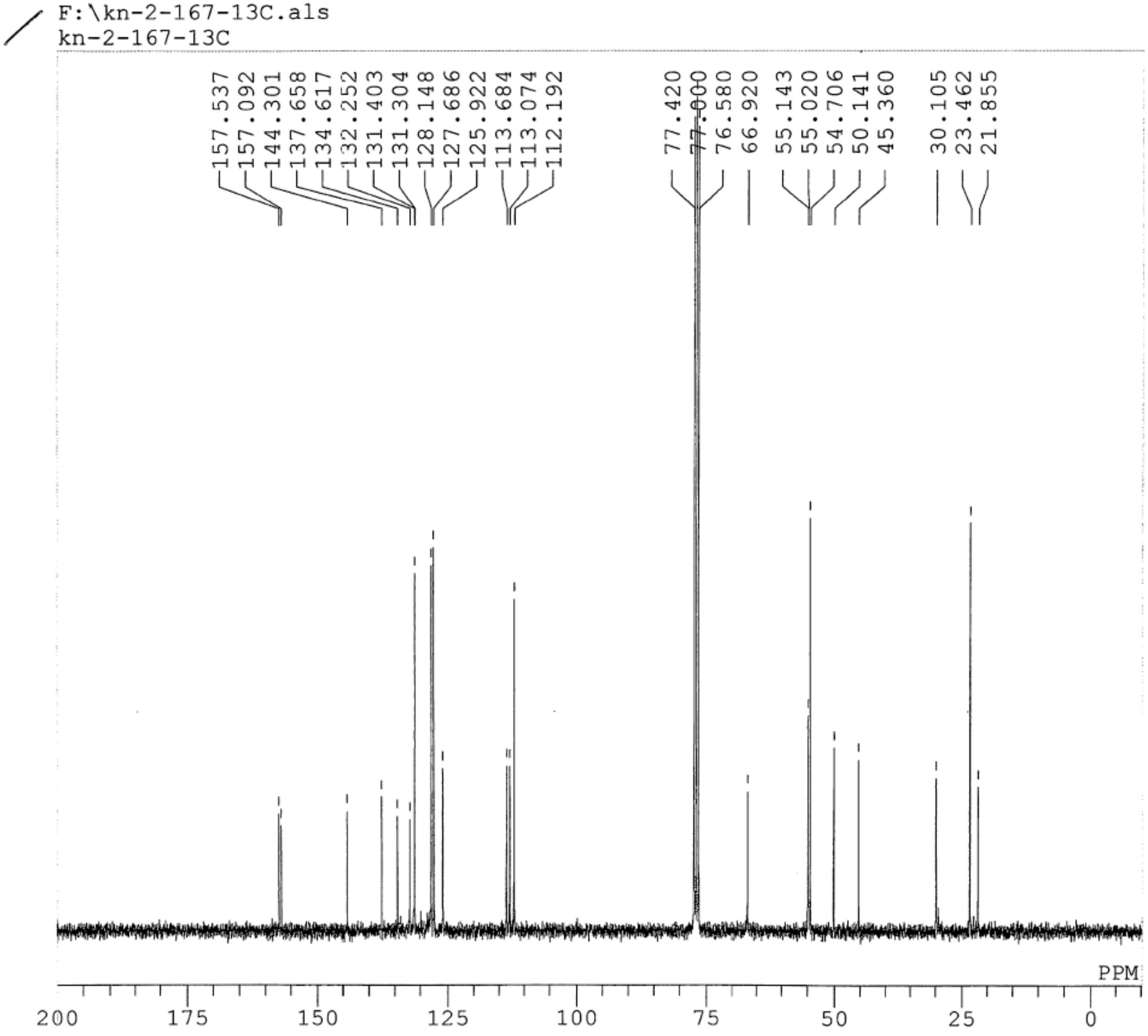
15



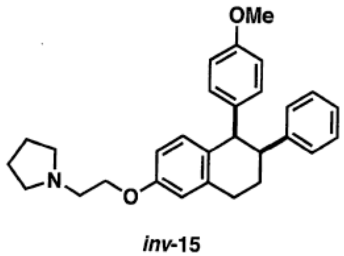
```
DFILE  E:\kn-2-167-P1.als
COMNT  kn-2-167-P1
DATIM  Wed Jan 24 15:54:53 2(
OBNUC  1H
EXMOD  non
OBFRQ        500.00 MHz
OBSET          0.00 KHz
OBFIN     162160.00 Hz
POINT         32768
FREQU      10000.00 Hz
SCANS             8
ACQTM        3.2768 sec
PD           3.7232 sec
PW1            5.95 usec
IRNUC  1H
CTEMP          22.4 c
SLVNT  CDCL3
EXREF          7.26 ppm
BF             0.12 Hz
RGAIN            16
```



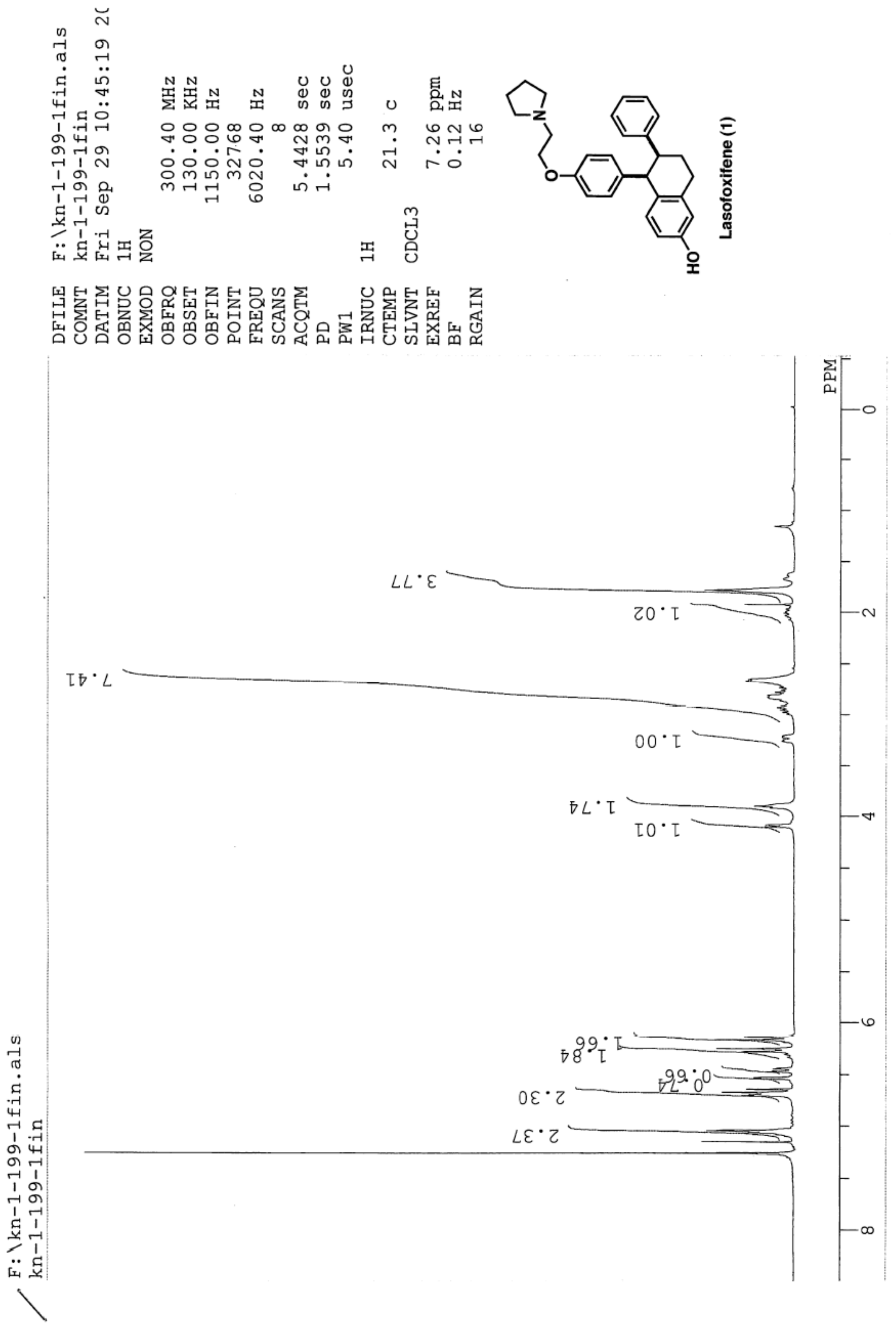
***inv*-15**



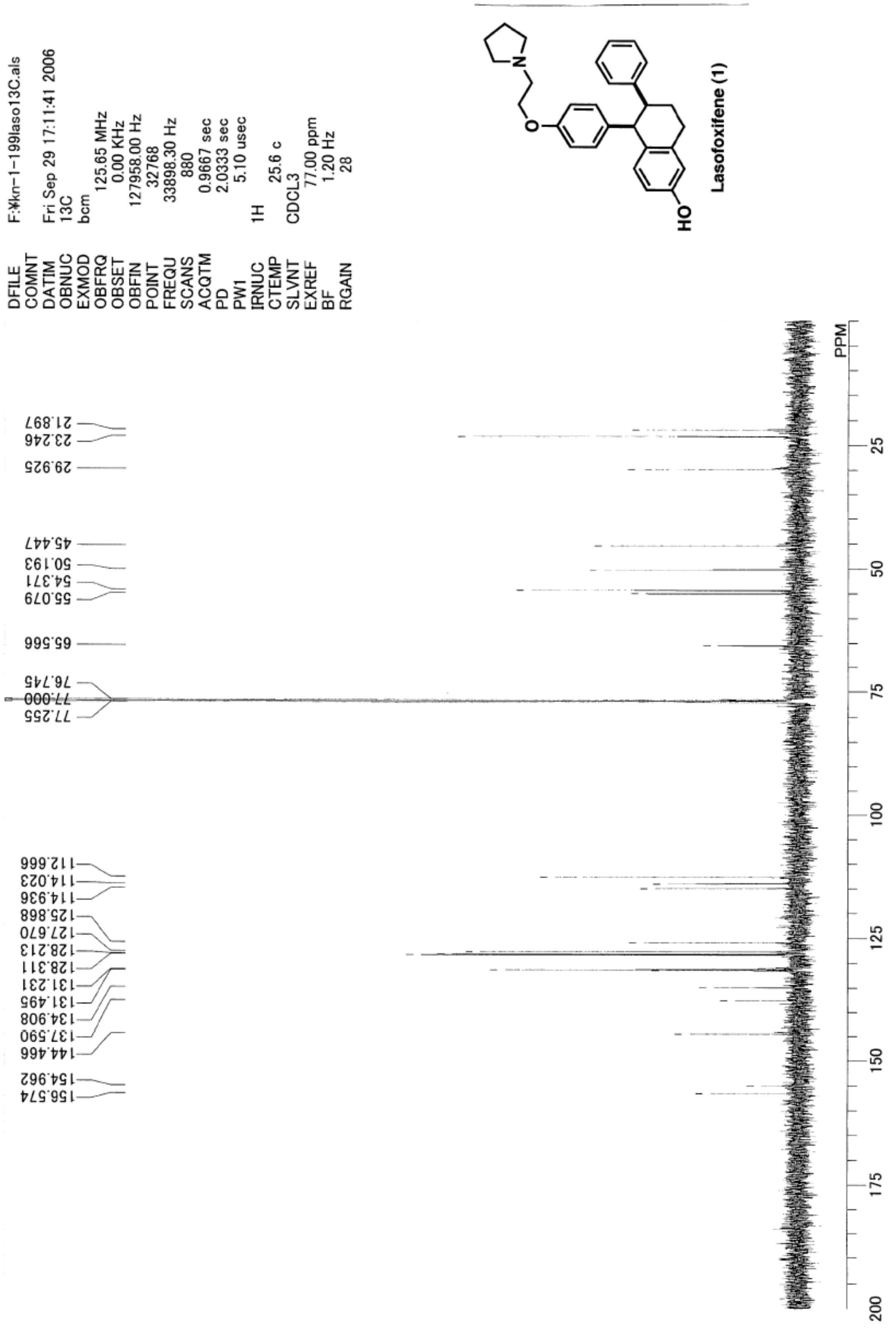
```
DFILE   F:\kn-2-167-13C.als
COMNT   kn-2-167-13C
DATIM   Wed Jan 24 18:18:50 2(
OBNUC   13C
EXMOD   BCM
OBFRQ          75.45 MHz
OBSET         124.00 KHz
OBFIN        1840.00 Hz
POINT          32768
FREQU       20408.10 Hz
SCANS            900
ACQTM         1.6056 sec
PD            1.3944 sec
PW1             4.10 usec
IRNUC   1H
CTEMP           20.7 c
SLVNT   CDCL3
EXREF          77.00 ppm
BF              1.20 Hz
RGAIN             22
```



inv-**15**

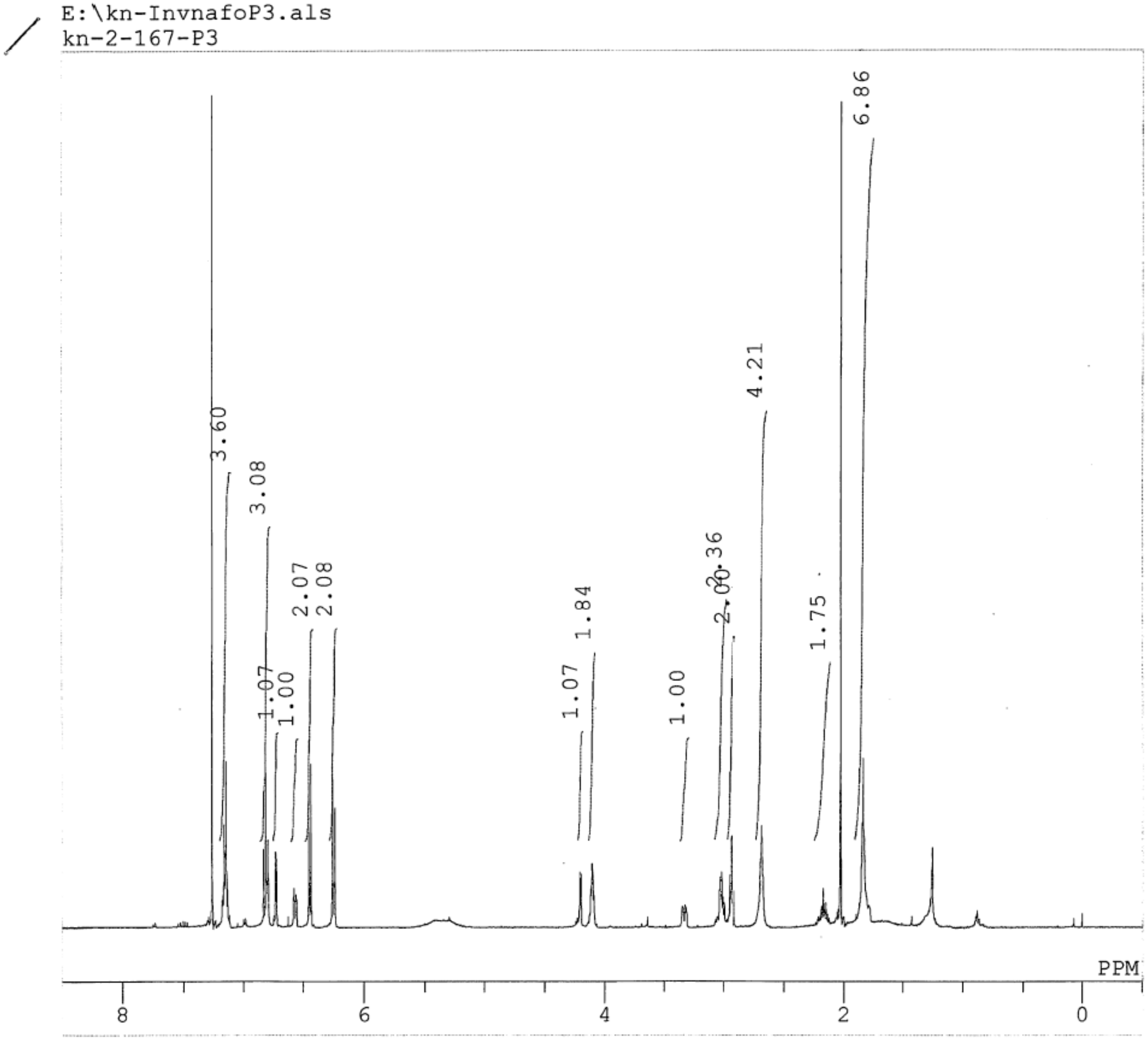


Lasofoxifene (1)

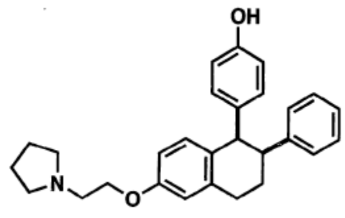


DFILE	F:¥kn-1-199laso13C.als
COMNT	
DATIM	Fri Sep 29 17:11:41 2006
OBNUC	13C
EXMOD	bcm
OBFRQ	125.65 MHz
OBSET	0.00 KHz
OBFIN	127958.00 Hz
POINT	32768
FREQU	33898.30 Hz
SCANS	880
ACQTM	0.9667 sec
PD	2.0333 sec
PW1	5.10 usec
IRNUC	1H
CTEMP	25.6 c
SLVNT	CDCL3
EXREF	77.00 ppm
BF	1.20 Hz
RGAIN	28

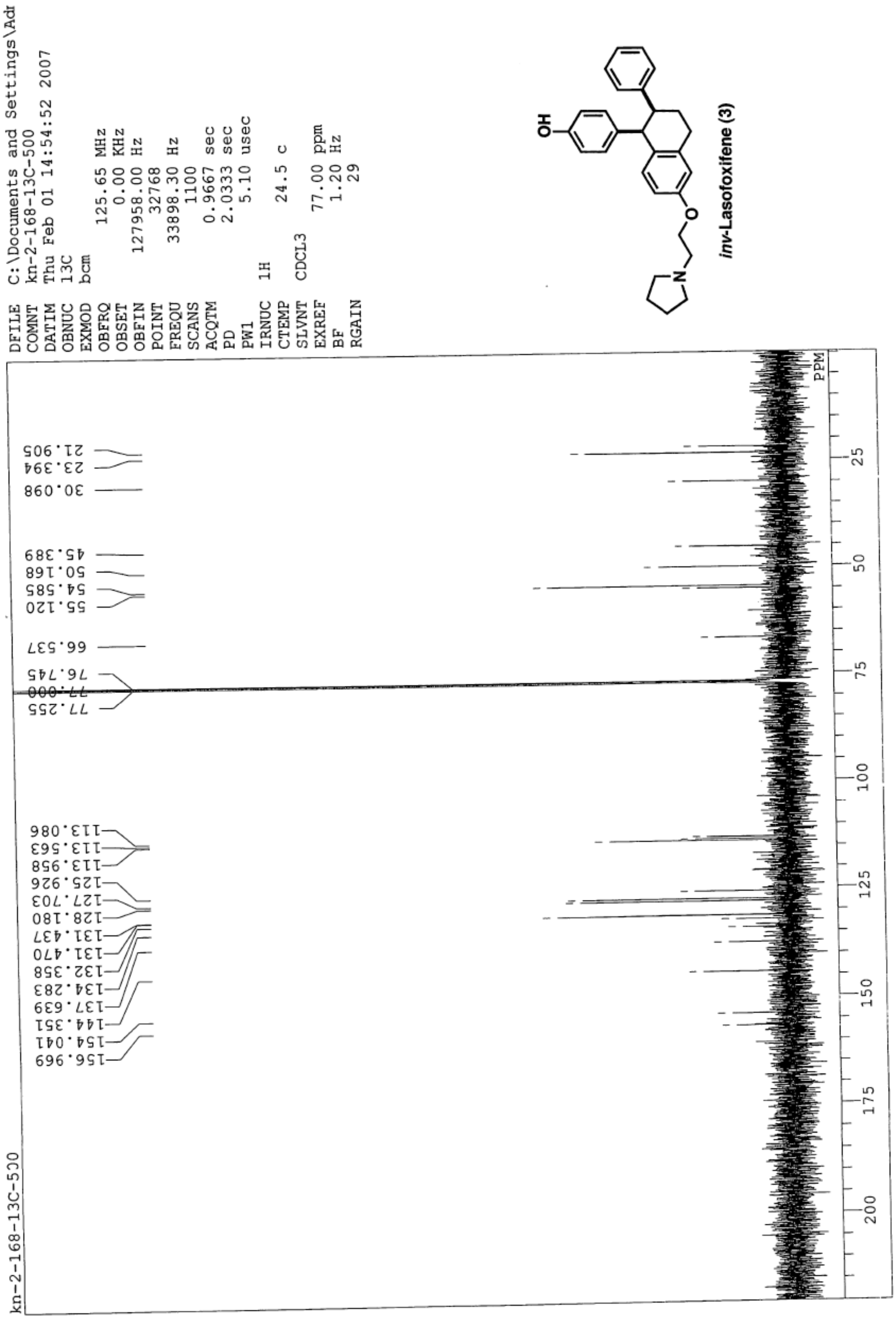
Lasofoxifene (1)



```
DFILE  E:\kn-InvnafoP3.als
COMNT  kn-2-167-P3
DATIM  Sat Jan 27 15:16:36 2(
OBNUC  1H
EXMOD  non
OBFRQ        500.00 MHz
OBSET          0.00 KHz
OBFIN     162160.00 Hz
POINT         32768
FREQU      10000.00 Hz
SCANS             8
ACQTM        3.2768 sec
PD           3.7232 sec
PW1            5.95 usec
IRNUC  1H
CTEMP          22.3 c
SLVNT  CDCL3
EXREF          0.00 ppm
BF             0.12 Hz
RGAIN            23
```



***inv*-Lasofoxifene (3)**



***inv*-Lasofoxifene (3)**