

Supporting Information

Benzoyl methyl phosphates as efficient reagents in the one-pot tandem approach for the synthesis of 2-phenylbenzimidazoles in water

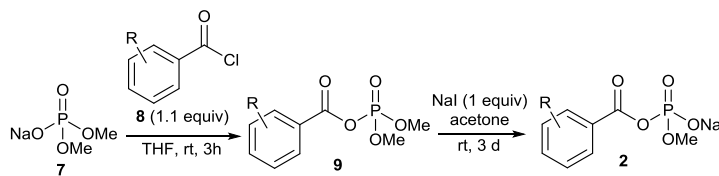
Hidemasa Hikawa,* Maki Imani, Hideharu Suzuki, Yuusaku Yokoyama and Isao Azumaya*

Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Chiba 274-8510, Japan

hidemasa.hikawa@phar.toho-u.ac.jp and isao.azumaya@phar.toho-u.ac.jp

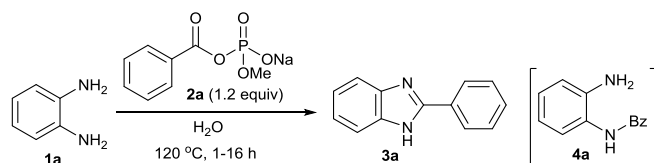
1. Table of contents	S1
2. Table S1. Preparation of benzoyl methyl phosphates 2.	S2
2. Figure 1. Reaction progress.	S3-S5
3. Copies of ¹H and ¹³C NMR spectra of the all compounds	S6-S51

Table S1. Preparation of benzoyl methyl phosphates **2**.



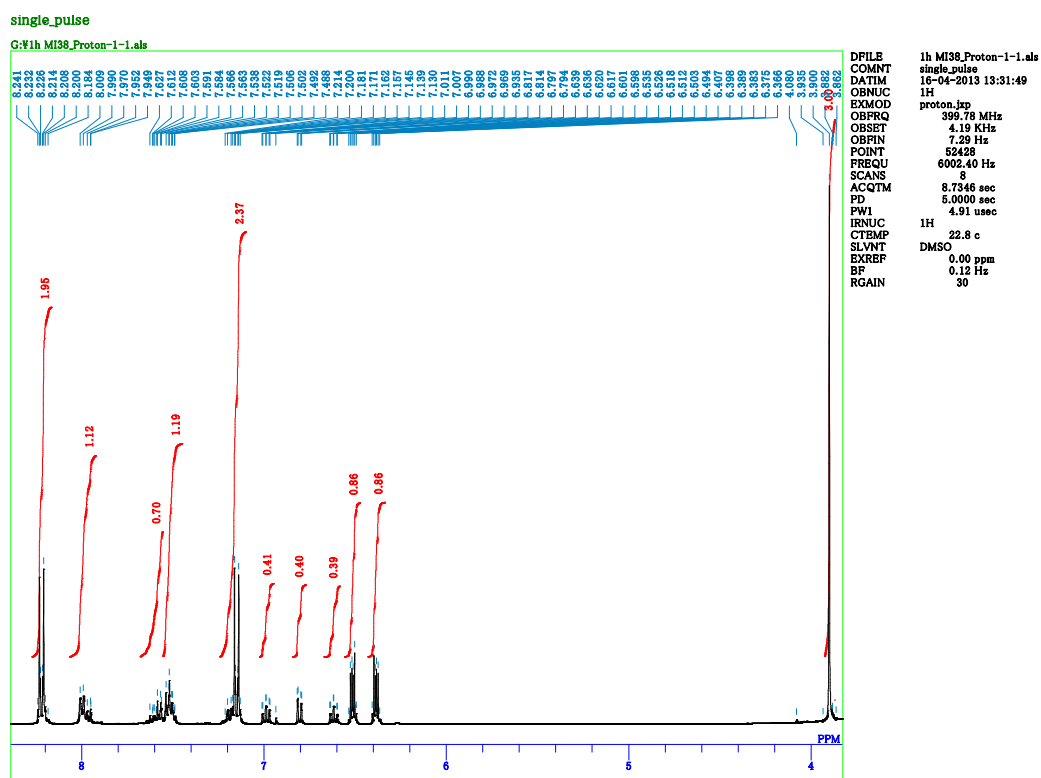
R	benzoyl dimethyl phosphates 9	Yield (%)	benzoyl methyl phosphates 2	Yield (%)
H	9a	87	2a	93
4-OMe	9b	80	2b	90
4-Me	9c	73	2c	95
4-Cl	9d	45	2d	80
4-CN	9e	41	2e	93
2-OMe	9f	66	2f	68
2-F	9g	80	2g	92
2-Cl	9h	46	2h	95
2-I	9i	83	2i	91

Figure 1. Reaction progress.



A mixture of 1,2-phenylenediamine **1a** (54.0 mg, 0.5 mmol) and benzoyl methyl phosphate **2a** (143 mg, 0.6 mmol) in H₂O (2 mL) was heated at 120 °C for 1-16 h in a sealed tube. After the reaction mixture was cooled, *p*-nitroanisole (76.6 mg, 0.5 mmol, internal standard) was added to the reaction mixture, which was extracted with AcOEt. The organic layer was washed with brine, and concentrated in vacuo. The residue was analyzed by ¹H-NMR spectroscopy.

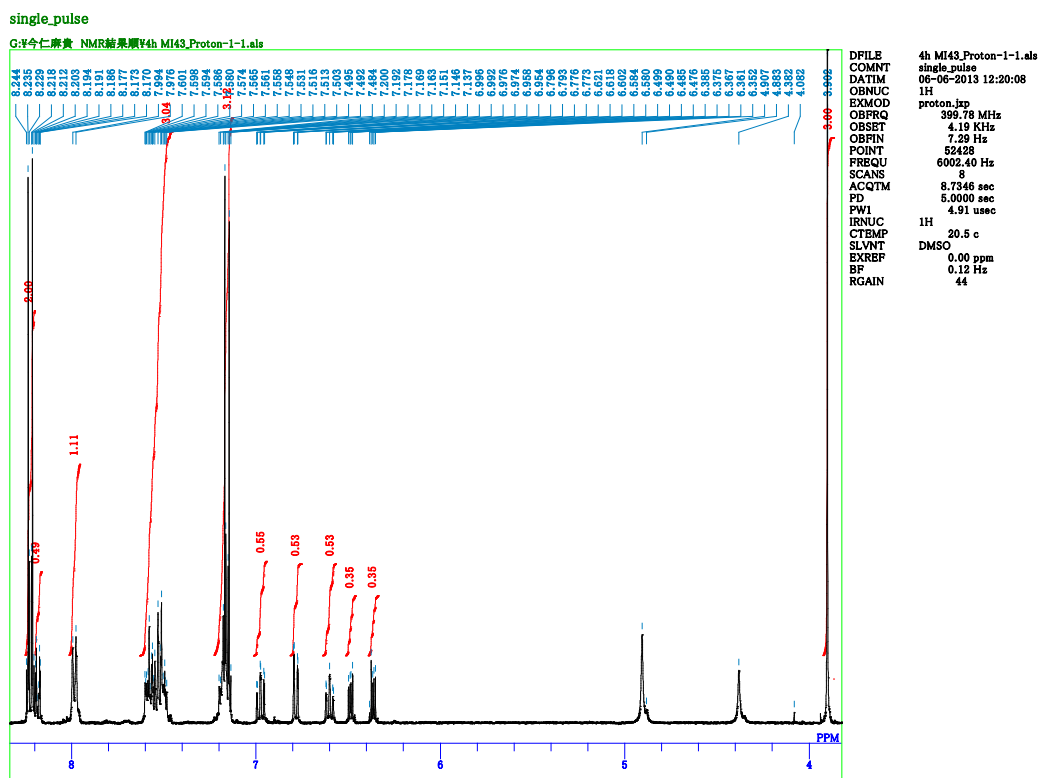
1 h



Conversion yield was calculated by integration.

	SM 1a	Benzimidazole 3a	Benzoyl 4a	<i>p</i> -nitroanisole internal standard
Signal δ	6.5 (Ar- <u>H</u>)	8.2 (Ar- <u>H</u>)	6.8 (Ar- <u>H</u>)	3.9 (-OCH ₃)
Integral value	0.86 (2H)	0 (2H)	0.40 (1H)	3.00 (3H)
Amount (mmol)	0.215	0	0.2	
Calculated ratio	43%	0%	40%	76.6 mg (0.5 mmol)

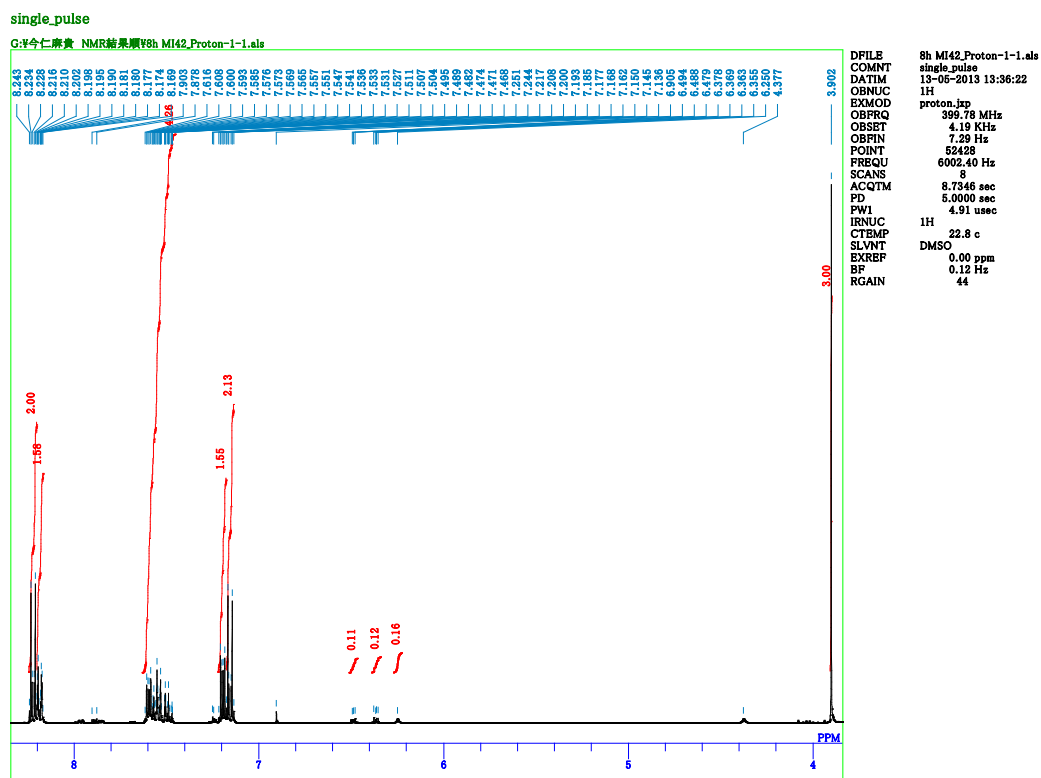
4 h



Conversion yield was calculated by integration.

	SM 1a	Benzimidazole 3a	Benzoyl 4a	<i>p</i> -nitroanisole internal standard
Signal δ	6.5 (Ar- H)	8.2 (Ar- H)	6.8 (Ar- H)	3.9 (-O CH ₃)
Integral value	0.35 (2H)	0.49 (2H)	0.53 (1H)	3.00 (3H)
Amount (mmol)	0.09	0.125	0.265	
Calculated ratio	18%	25%	53%	76.6 mg (0.5 mmol)

8 h

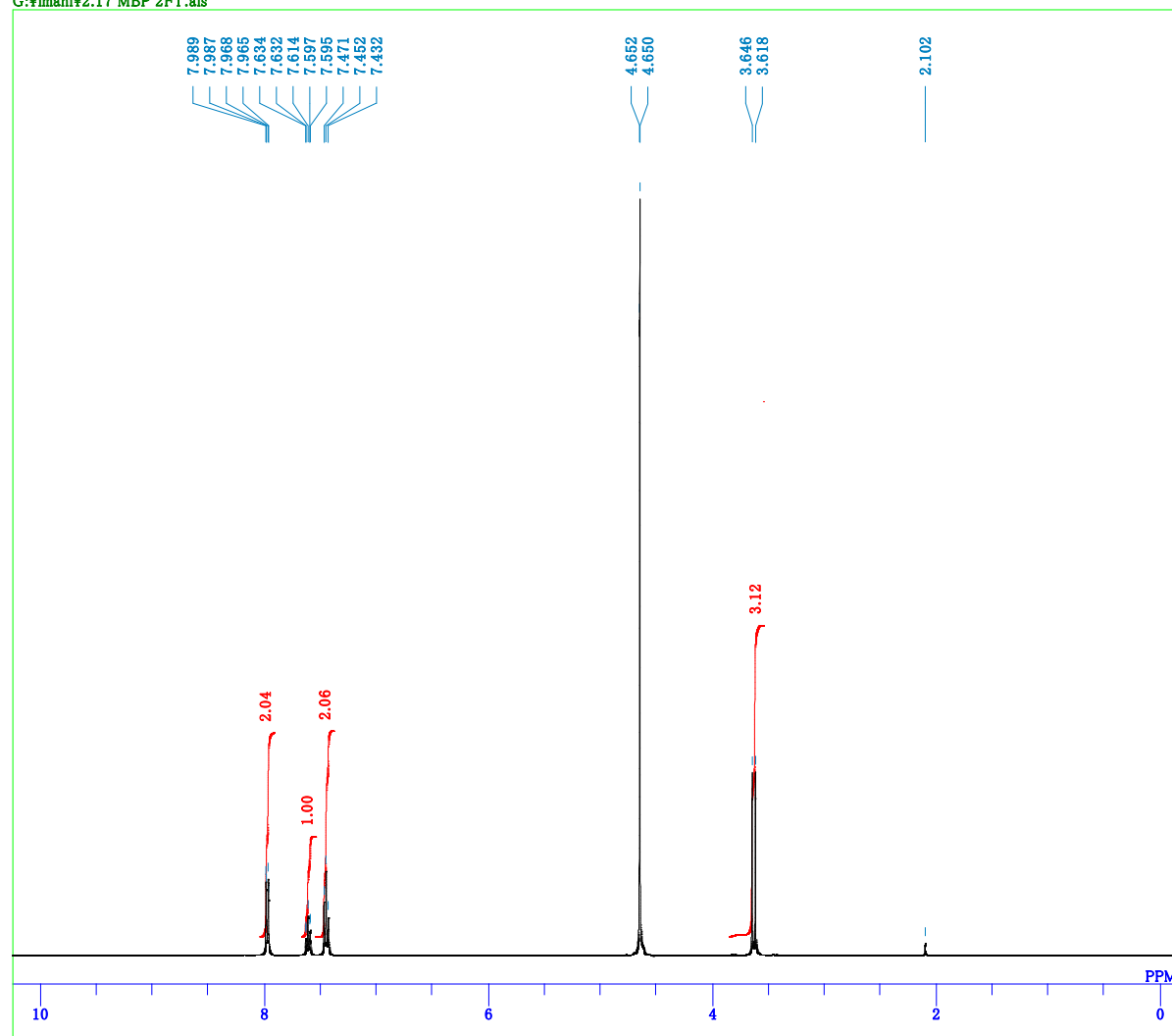


Conversion yield was calculated by integration.

	SM 1a	Benzimidazole 3a	Benzoyl 4a	<i>p</i> -nitroanisole internal standard
Signal δ	6.5 (Ar- <u>H</u>)	8.2 (Ar- <u>H</u>)	6.8 (Ar- <u>H</u>)	3.9 (-OCH ₃)
Integral value	0.11 (2H)	1.58 (2H)	0 (1H)	3.00 (3H)
Amount (mmol)	0.03	0.395	0	
Calculated ratio	6%	79%	0%	76.6 mg (0.5 mmol)

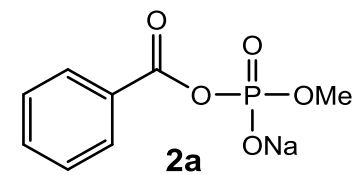
2.17 MBP 2

G:\Yimani\2.17 MBP 2FT.als



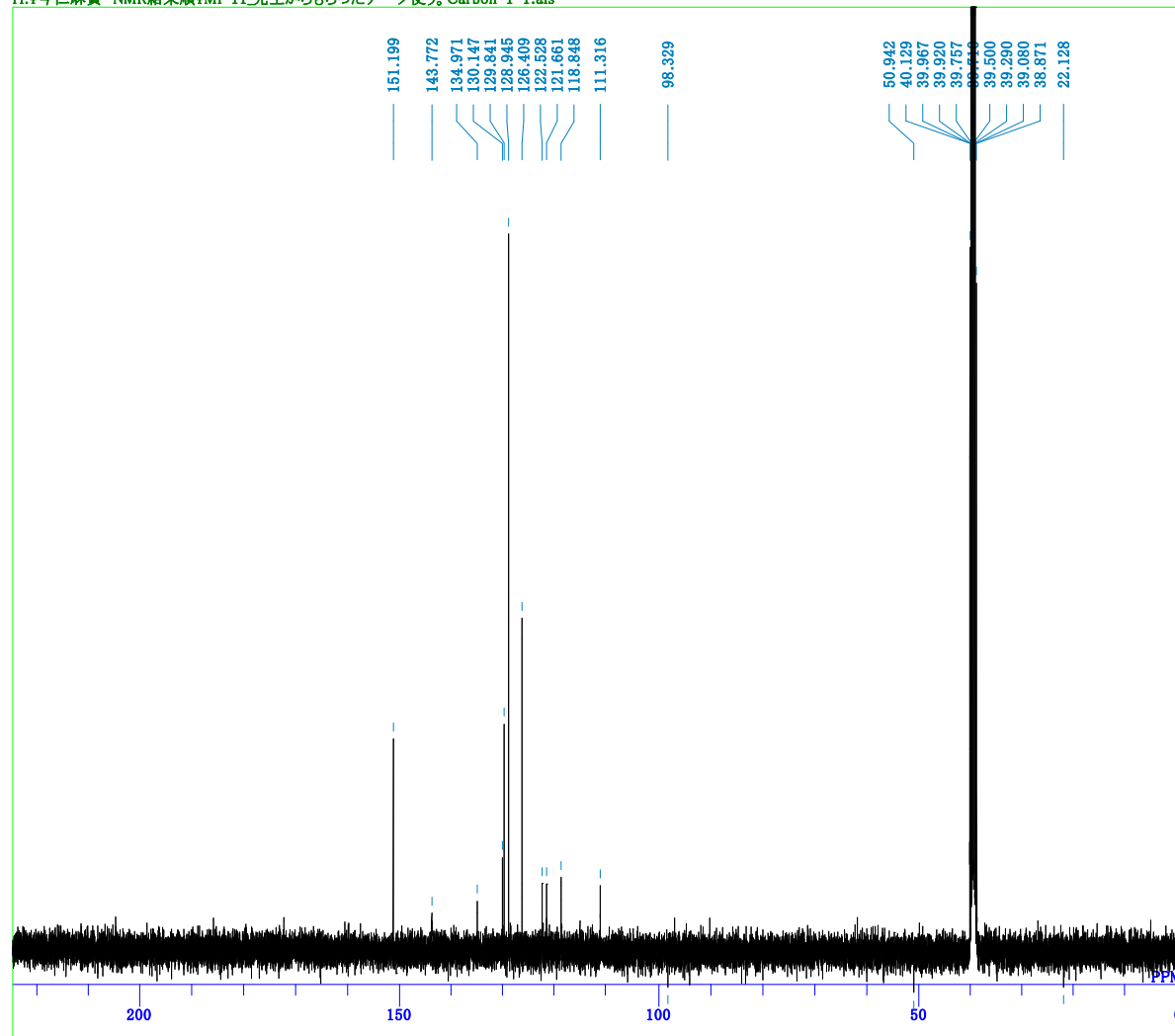
D2O
EXREF
BF
RGAIN
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN
NON
OBFREQ
OBSSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

2.17 MBP 2FT.als
2.17 MBP 2
Fri Feb 17 14:34:39 2012
1H
NON
399.65 MHz
124.00 KHz
11300.00 Hz
65536
6006.01 Hz
8
10.9117 sec
1.0000 sec
5.50 usec
1H
24.7 c
D2O
4.65 ppm
0.50 Hz
19

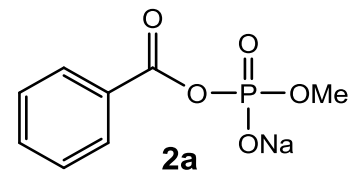


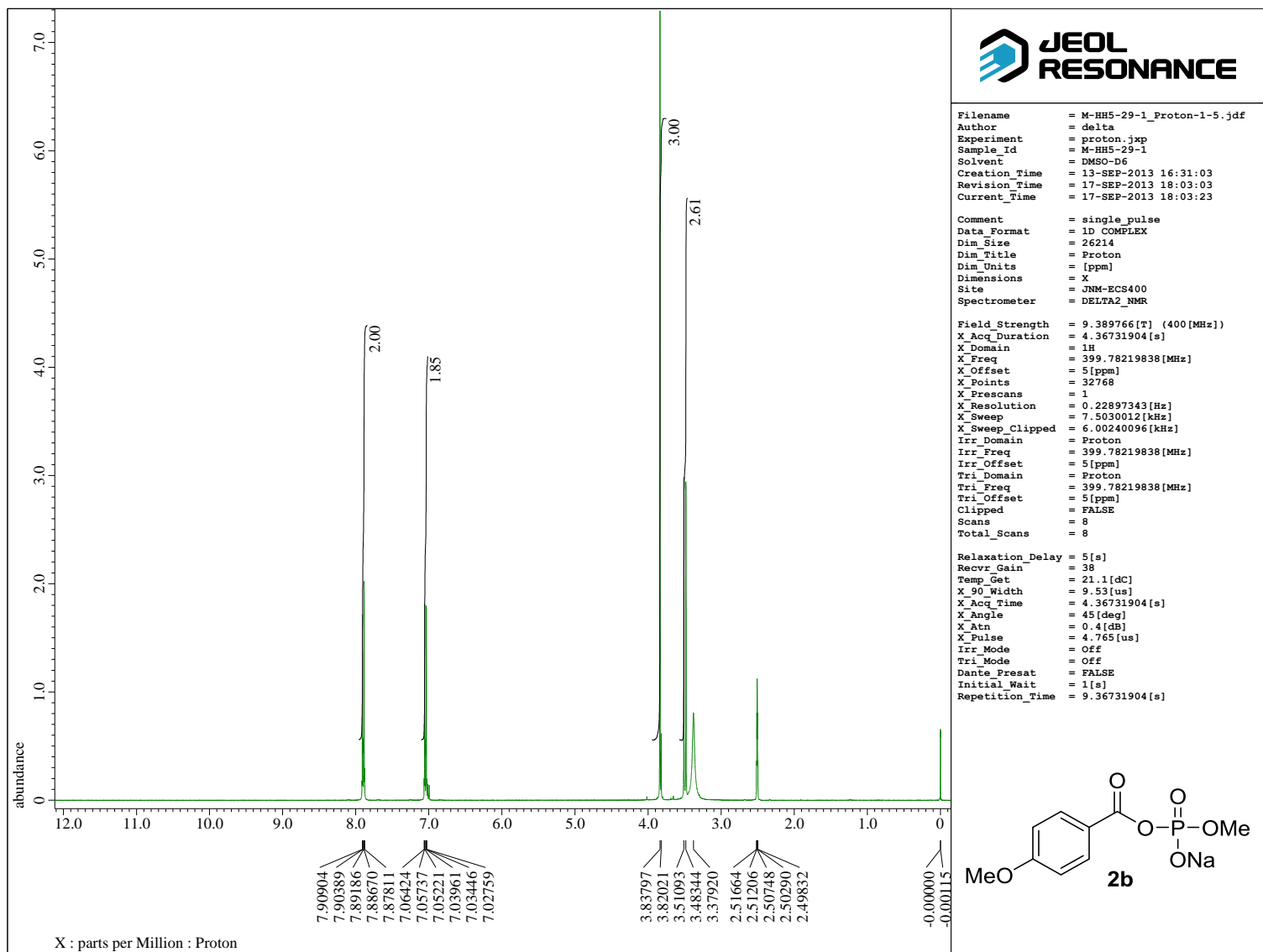
single pulse decoupled gated NOE

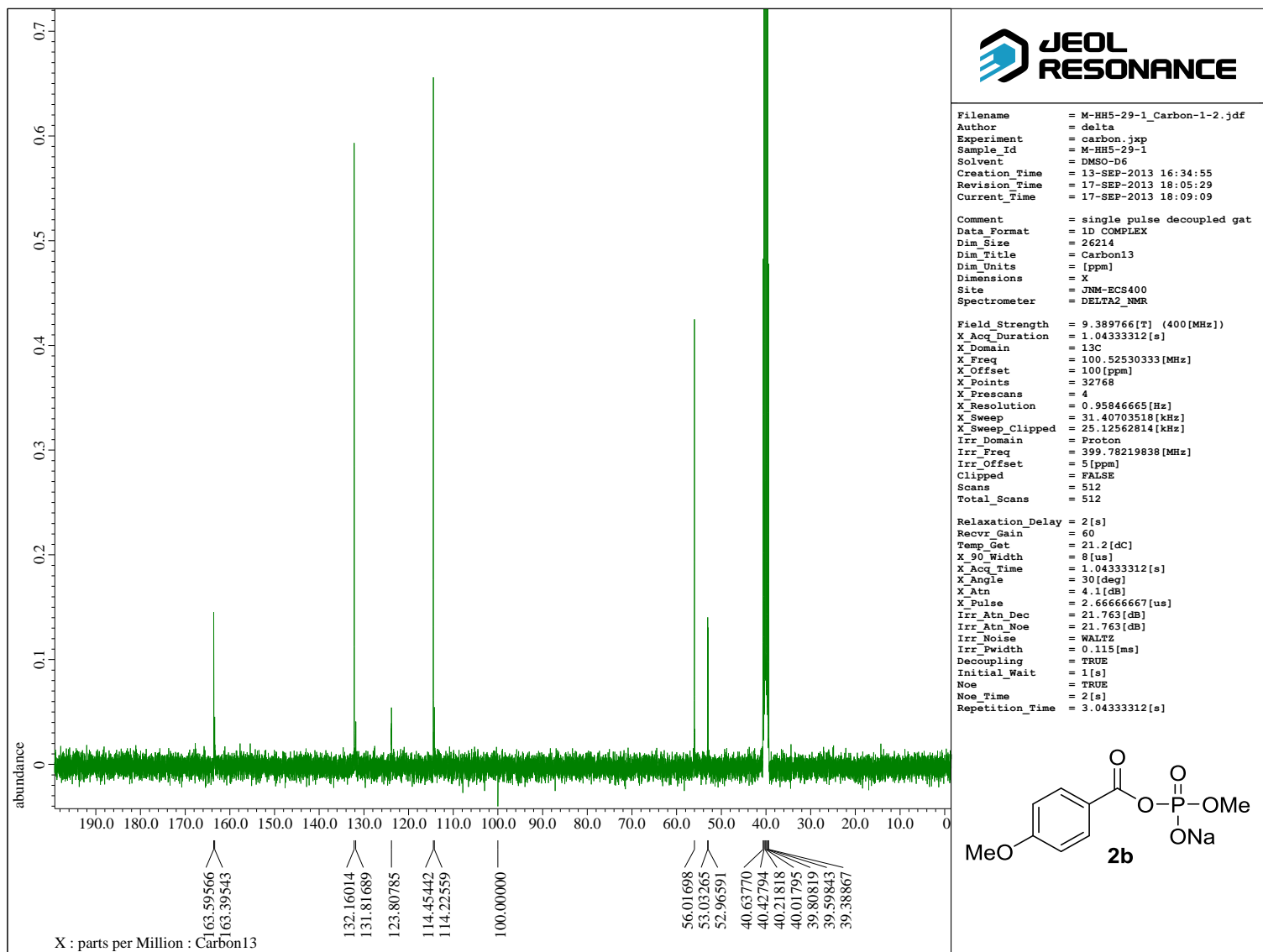
H:¥今仁麻貴 NMR結果順¥MI-11_先生からもらったデータ使う。Carbon-1-1.als



DFILE MI-11_先生からもらったデータ使う。Ca
COMNT single pulse decoupled gated NOE
DATIM 06-03-2013 18:31:55
OBNUC 13C
EXMOD carbon.jxp
OBFKQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 1024
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 23.7 c
SLVNT DMSO
EXREF 39.50 ppm
BF 0.12 Hz
RGAIN 60

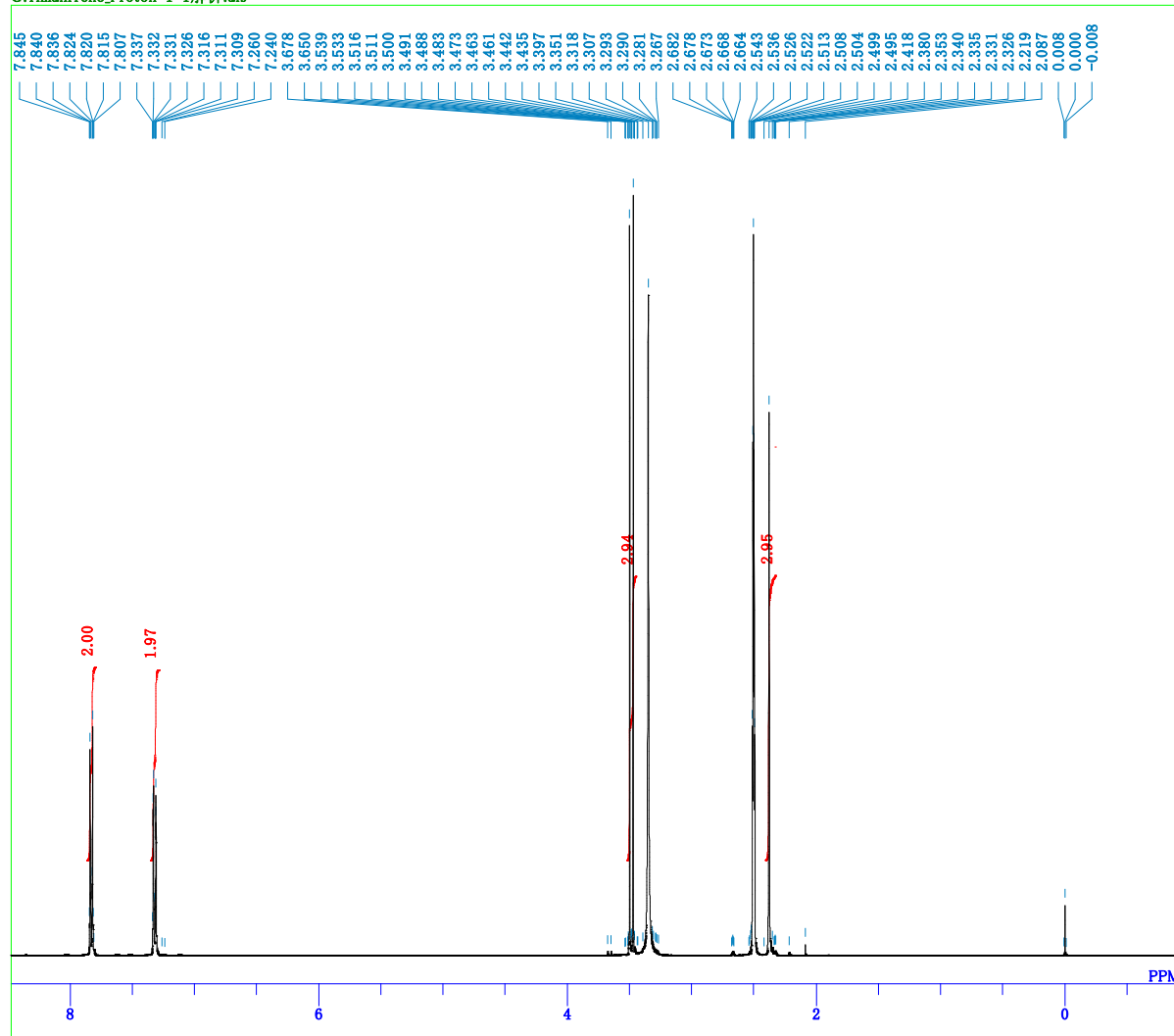




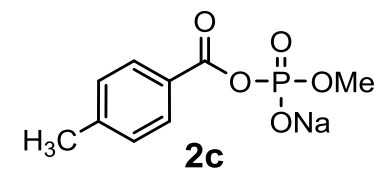


single_pulse

G:\imani\ch3_Proton-1-1解析.als

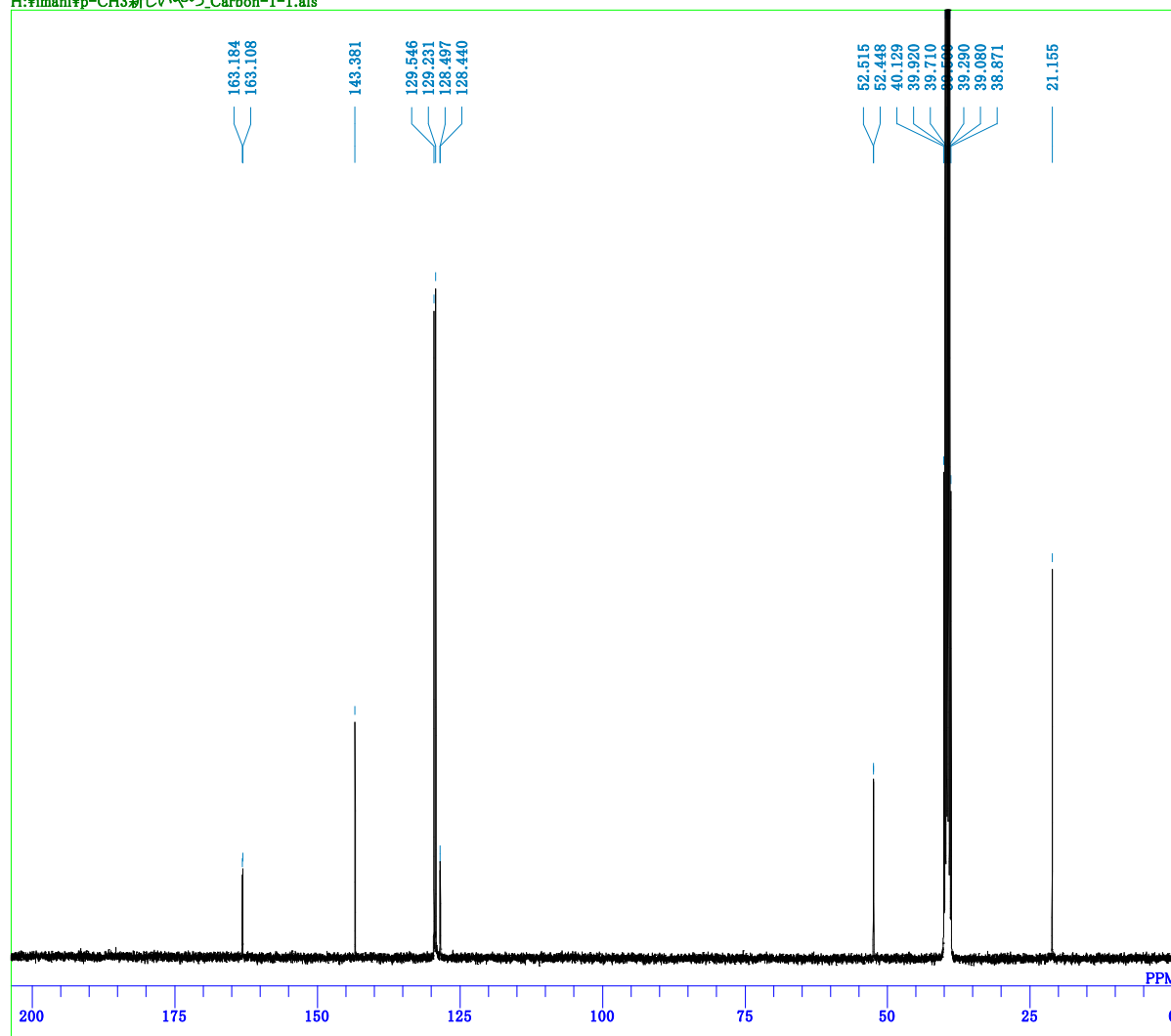


DFILE ch3_Proton-1-1解析.als
COMNT single_pulse
DATIM 22-01-2013 14:09:54
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 22.3 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 42

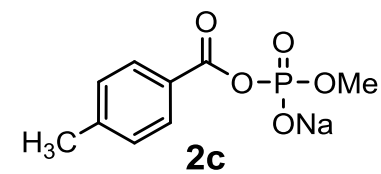


single pulse decoupled gated NOE

H:\imani\p-CH3新しいやつ_Carbon-1-1.als

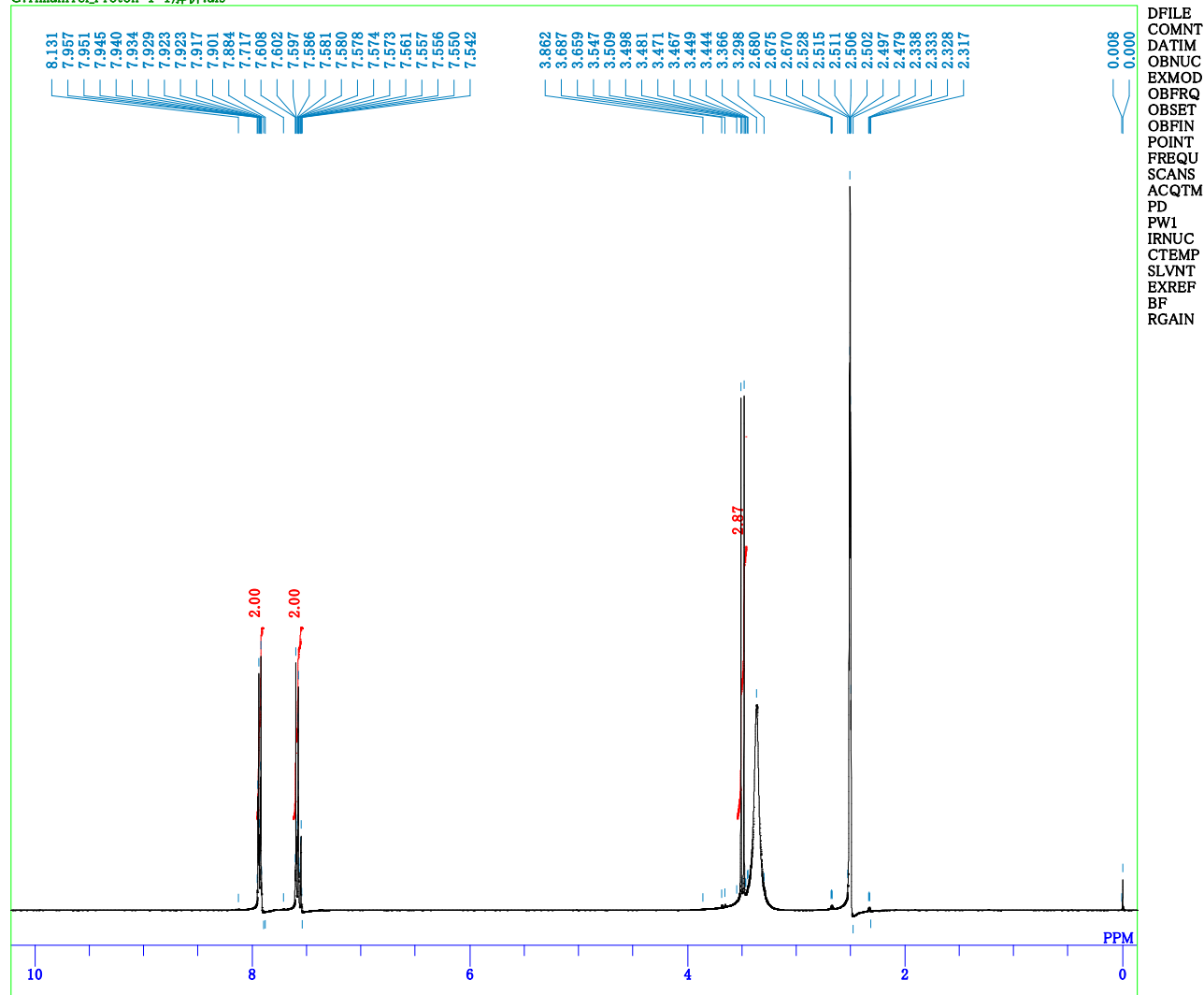


DFILE p-CH3新しいやつ_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 14-08-2013 19:25:47
OBNUC 13C
EXMOD carbon.jp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 3000
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 21.9 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60

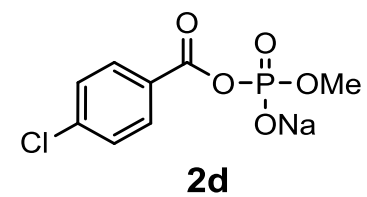


single_pulse

G:\imani\Cl_Proton-1-1解析.als

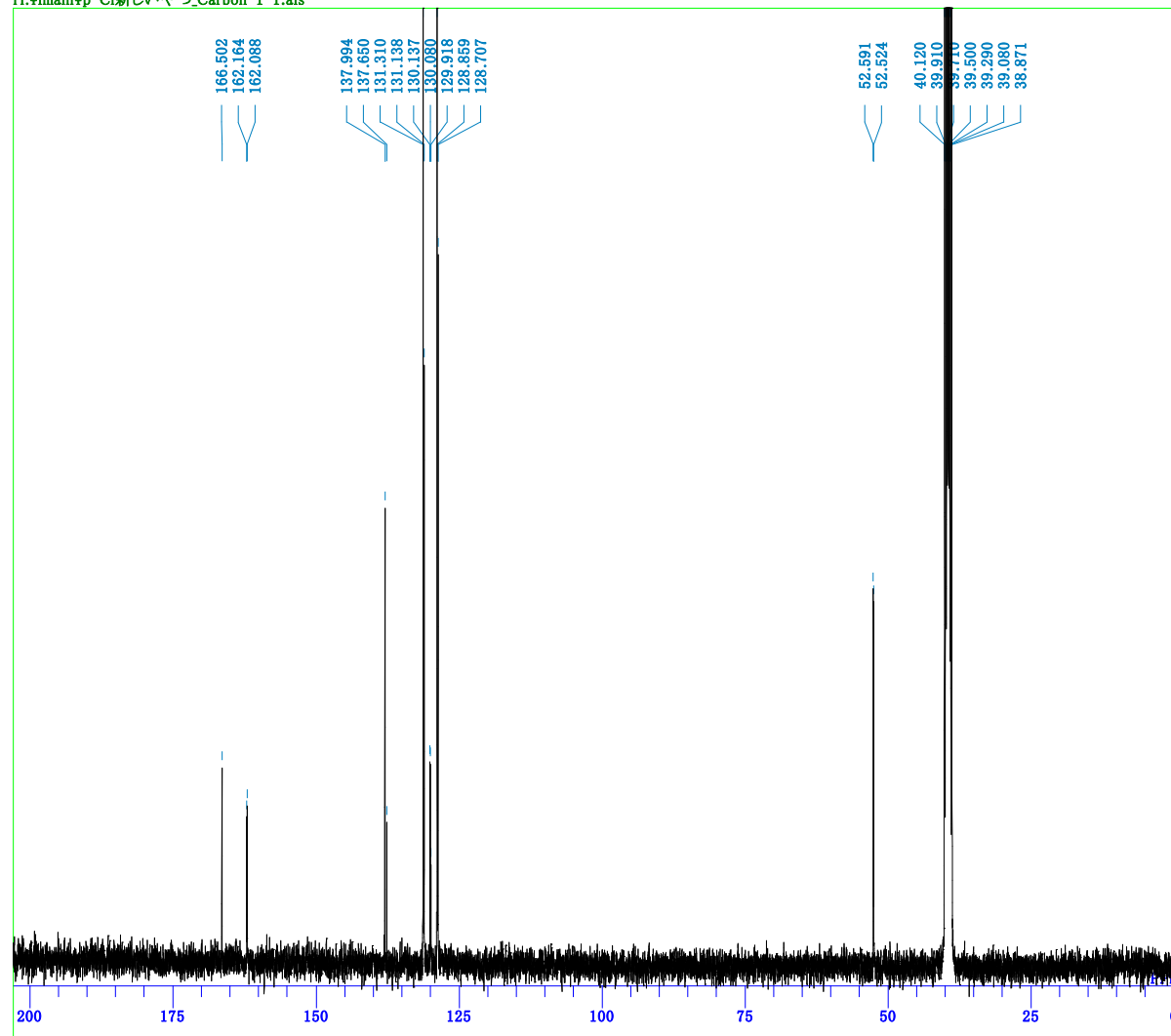


cl_Proton-1-1解析.als
single_pulse
22-01-2013 13:59:59
1H
proton.jxp
399.78 MHz
4.19 KHz
7.29 Hz
52428
6002.40 Hz
8
8.7346 sec
5.0000 sec
4.91 usec
1H
22.3 c
DMSO
0.00 ppm
0.12 Hz
40

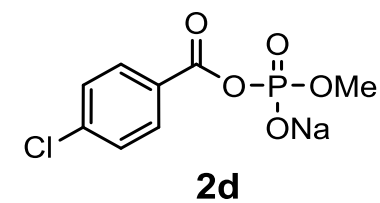


single pulse decoupled gated NOE

H:\imani\p-Cl新しいやつ_Carbon-1-1.als

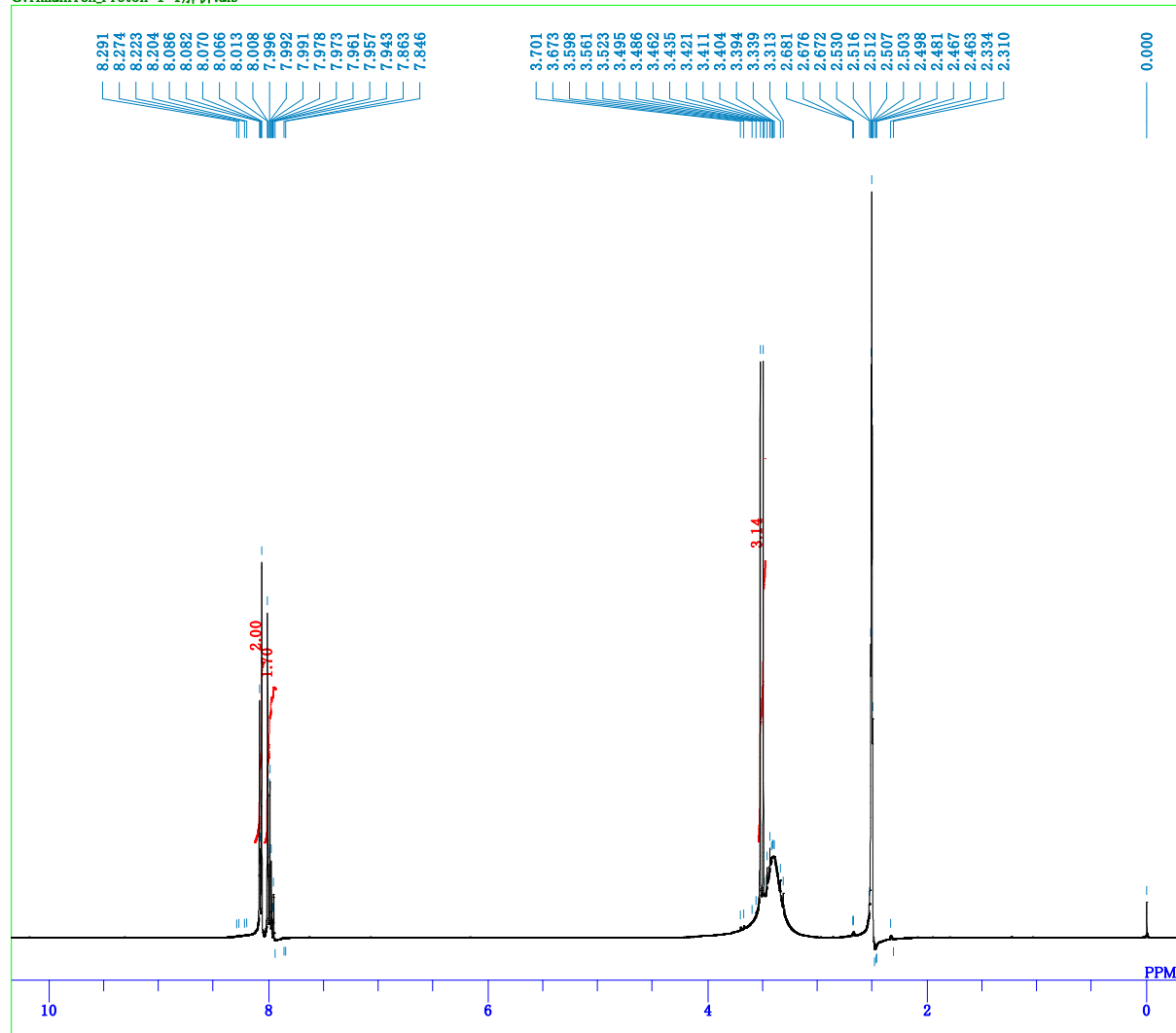


DFILE p-Cl新しいやつ_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 14-08-2013 22:06:12
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 3000
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 22.2 c
DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60

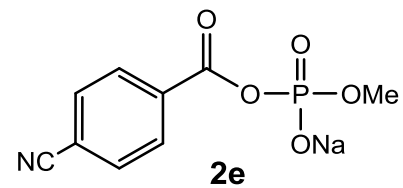


single_pulse

G:\imani\cn_Proton-1-1解析.als

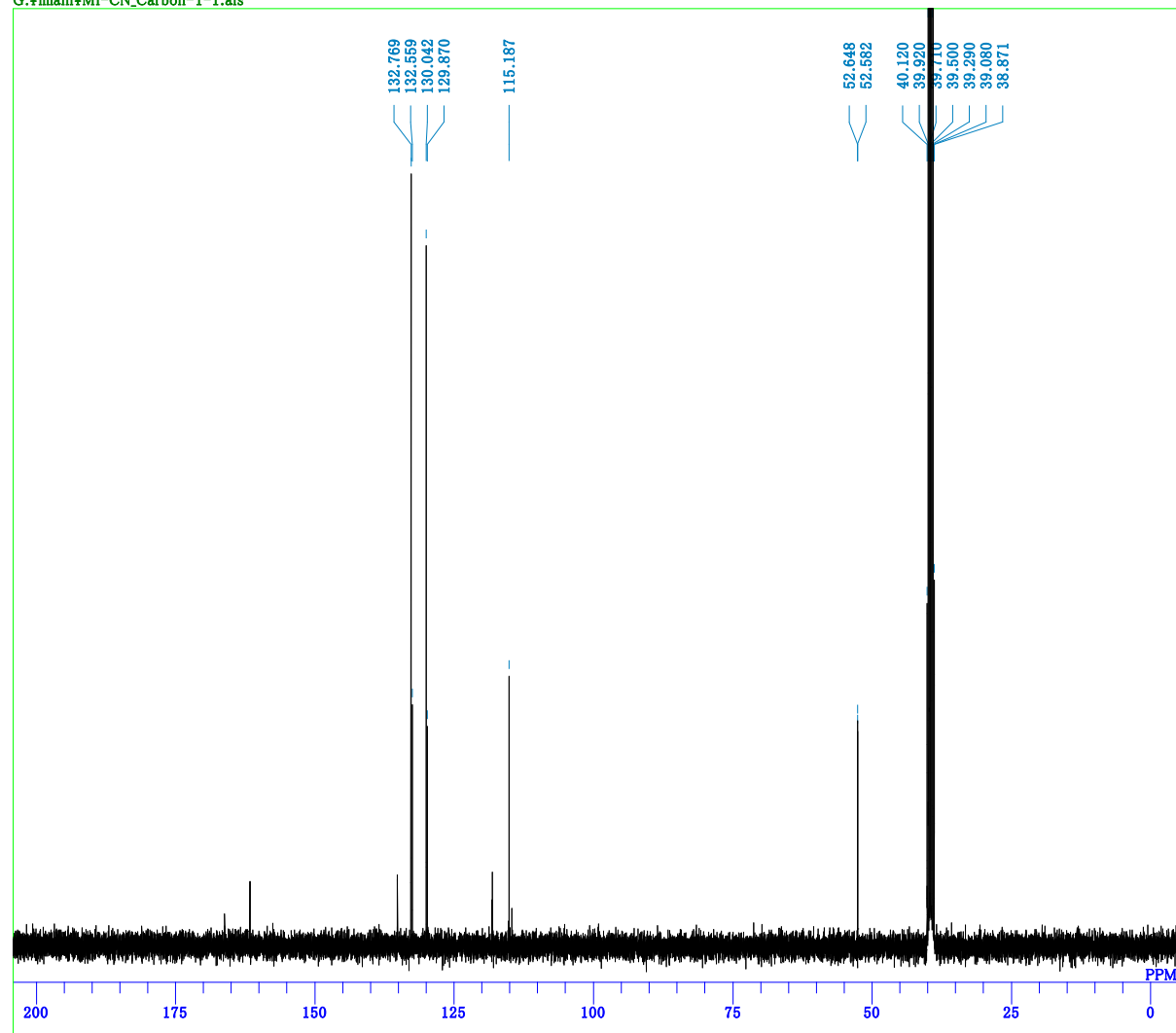


DFILE cn_Proton-1-1解析.als
COMNT single_pulse
DATIM 22-01-2013 14:19:43
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 22.4 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 40

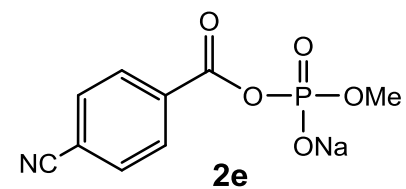


single pulse decoupled gated NOE

G:\imani\MI-CN_Carbon-1-1.als

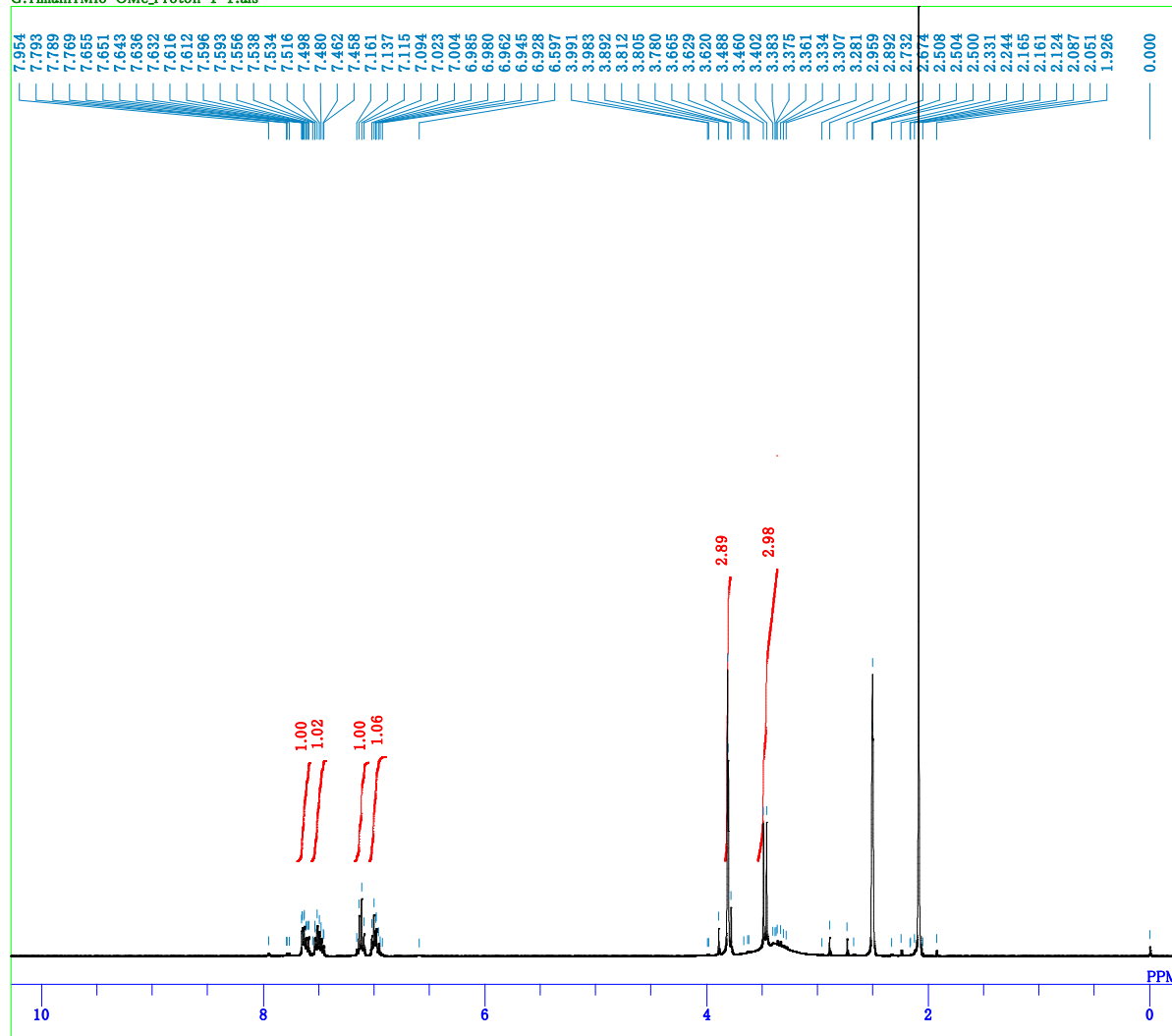


DFILE MI-CN_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 07-03-2013 00:13:37
OBNUC 13C
EXMOD carbon_jrp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 512
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 23.8 c
SLVNT DMSO
EXREF 39.50 ppm
BF 0.12 Hz
RGAIN 60

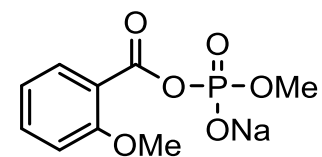


single_pulse

G:\imani\Mlo-OMe_Proton-1-1.als



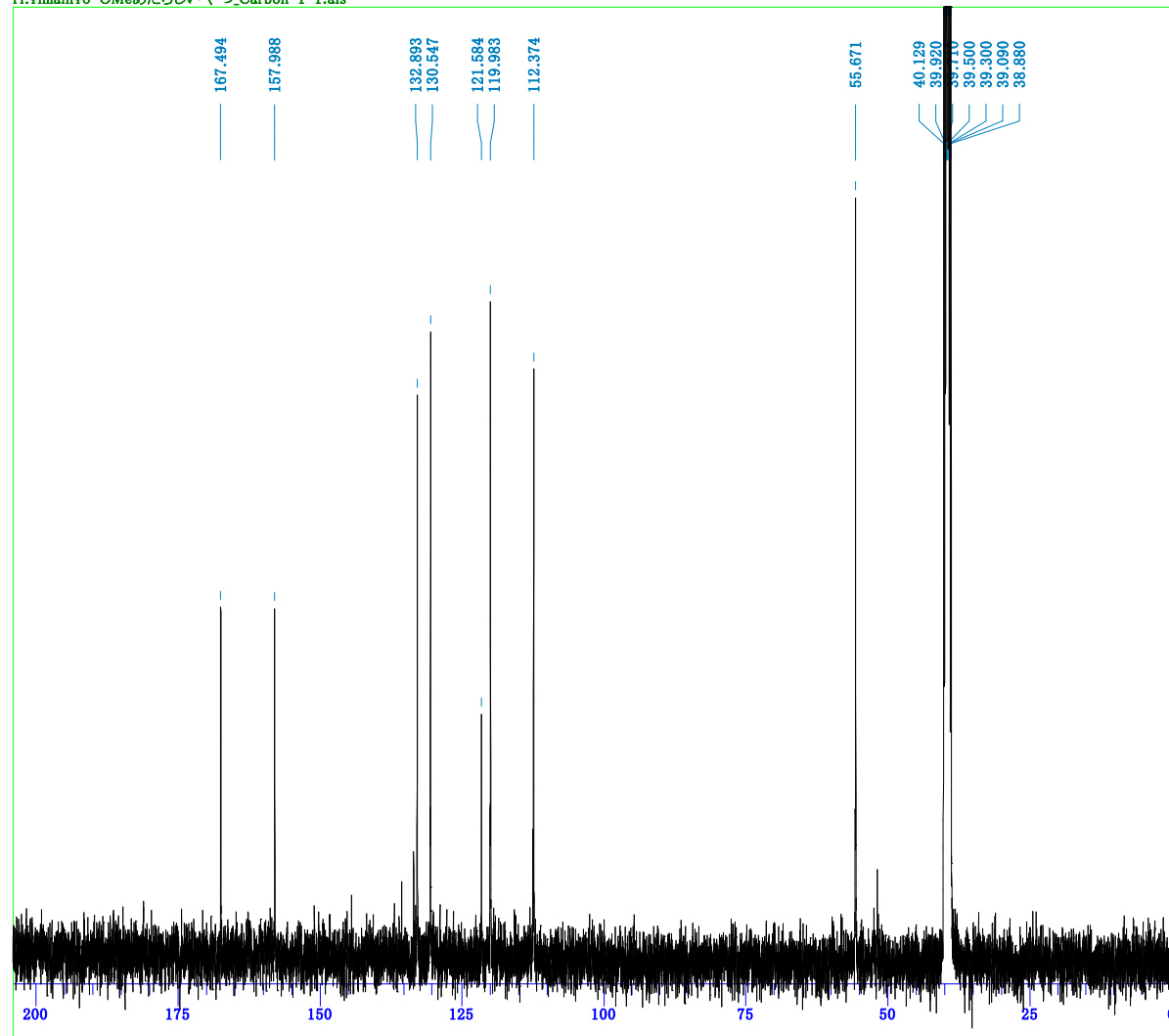
DFILE Mlo-OMe_Proton-1-1.als
COMNT single_pulse
DATIM 07-03-2013 13:44:44
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 23.2 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 38



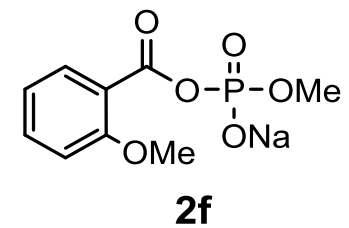
2f

single pulse decoupled gated NOE

H:\Yimani\Yo-OMeあたらしいやつ_Carbon-1-1.als

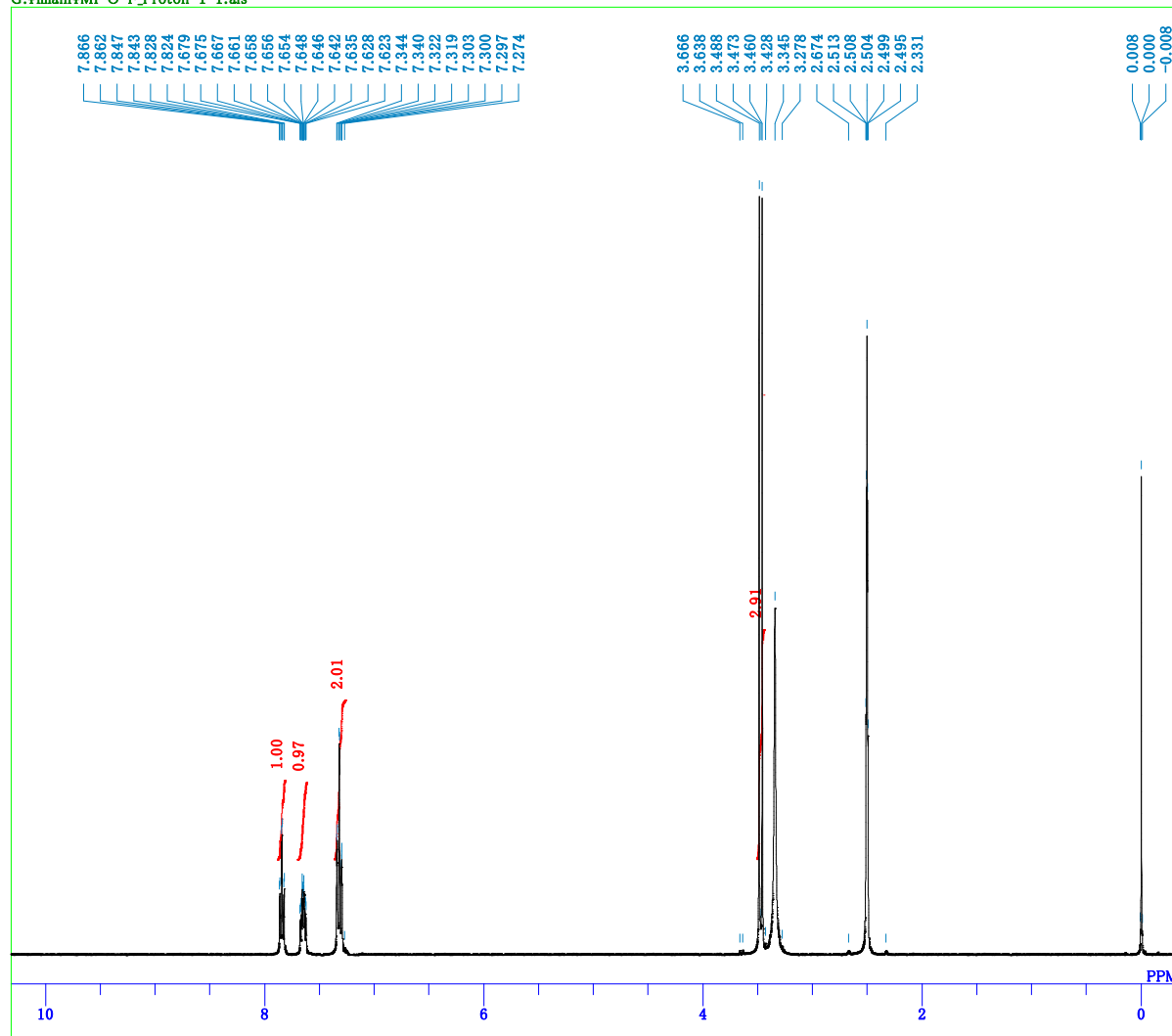


DFILE o-OMeあたらしいやつ_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 15-08-2013 05:06:59
OBNUC 13C
EXMOD carbon.jp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 1024
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 22.6 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60

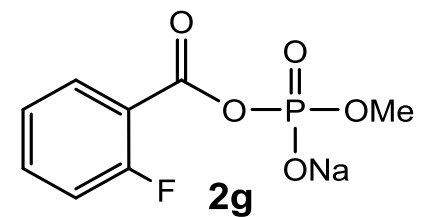


single_pulse

G:\imani\MI-O-F_Proton-1-1.als

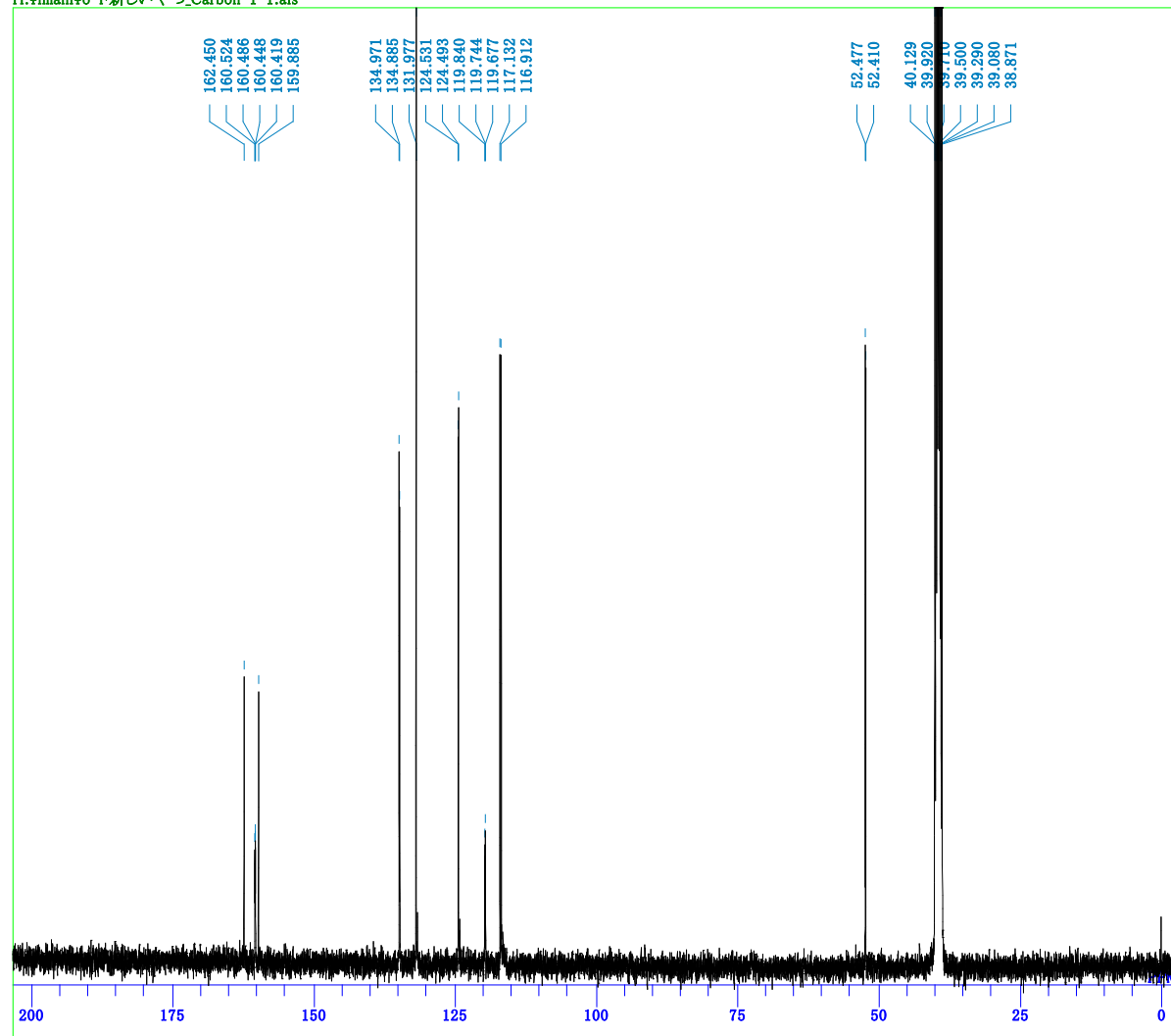


DFILE MI-O-F_Proton-1-1.als
COMNT single_pulse
DATIM 27-06-2013 14:01:21
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 20.6 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 48

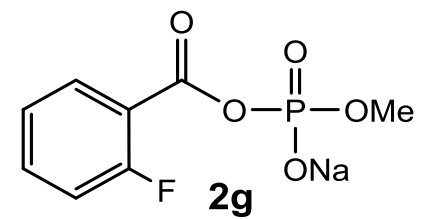


single pulse decoupled gated NOE

H:\Yimani\Fo-F新しいやつ_Carbon-1-1.als

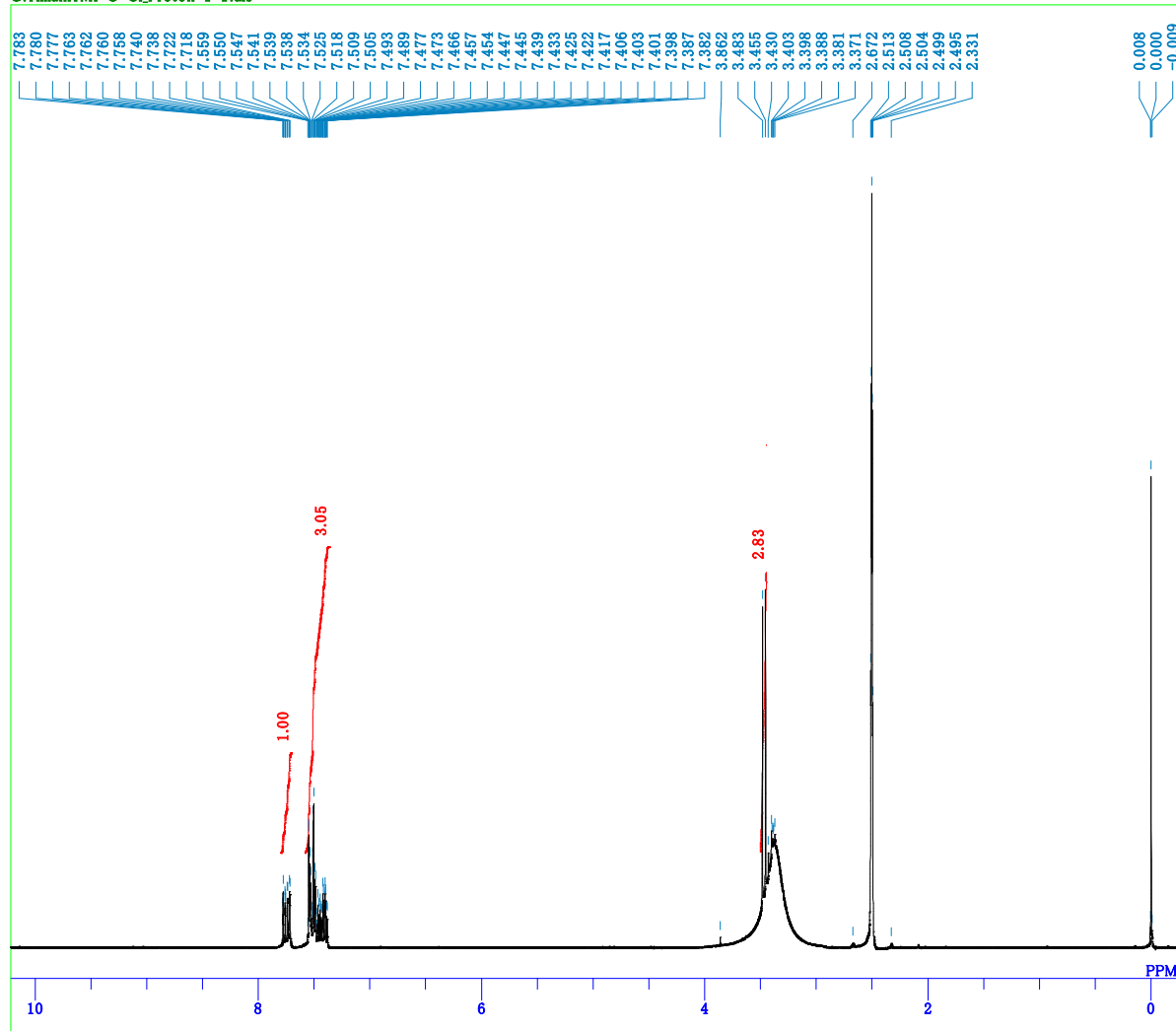


DFILE o-F新しいやつ_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 15-08-2013 00:45:30
OBNUC 13C
EXMOD carbon_jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 5000
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 21.7 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60

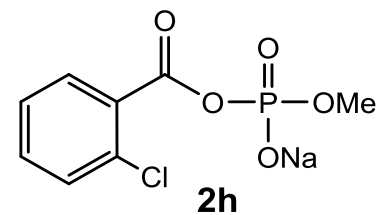


single_pulse

G:\Yimani\MI-O-ClProton-1-1.als

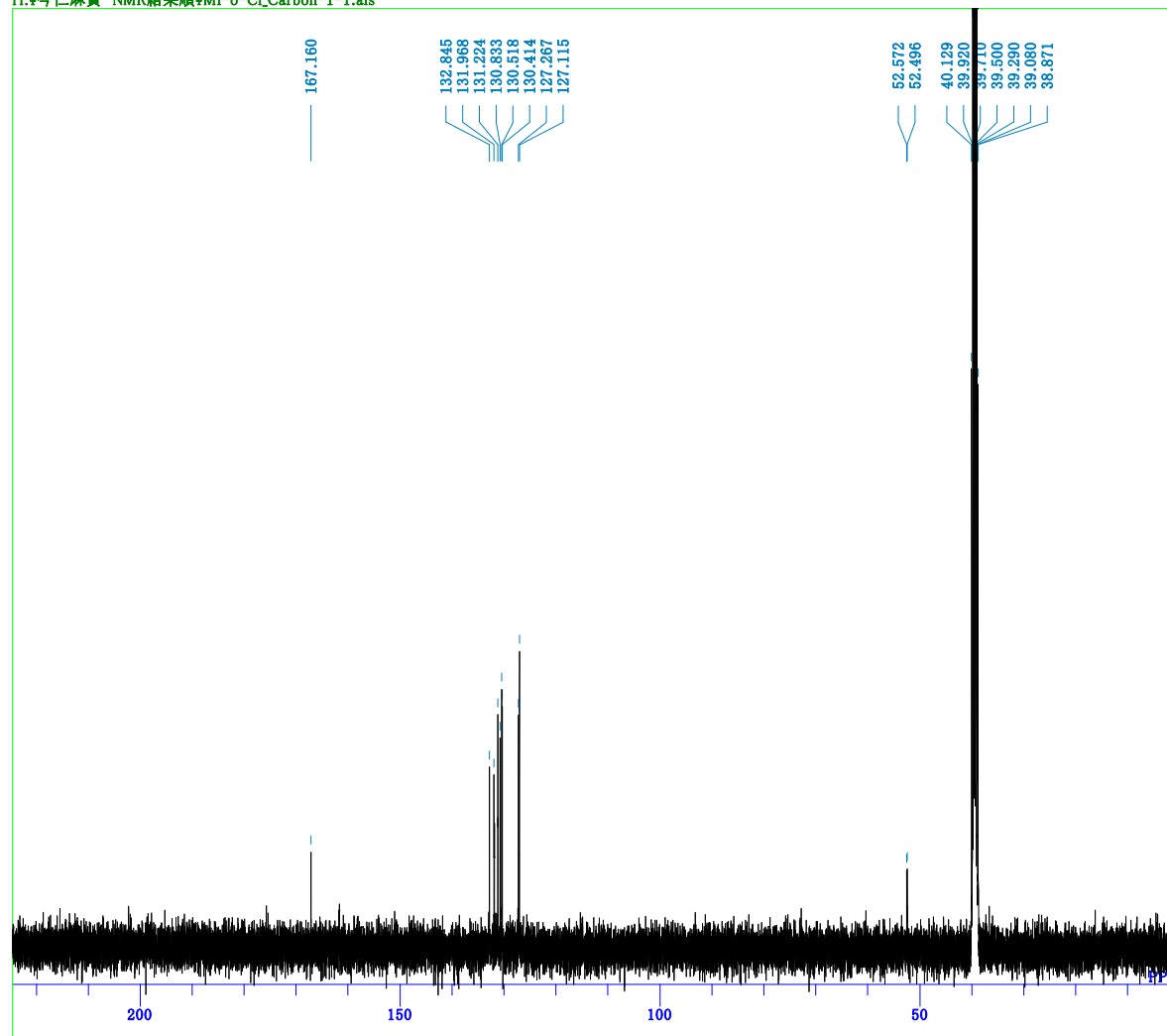


D:\MI-O-ClProton-1-1.als
single_pulse
27-06-2013 14:12:05
1H
proton.jxp
EXMOD 399.78 MHz
OBFRQ 4.19 KHz
OBSET 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 20.5 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 46

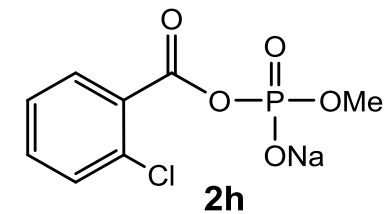


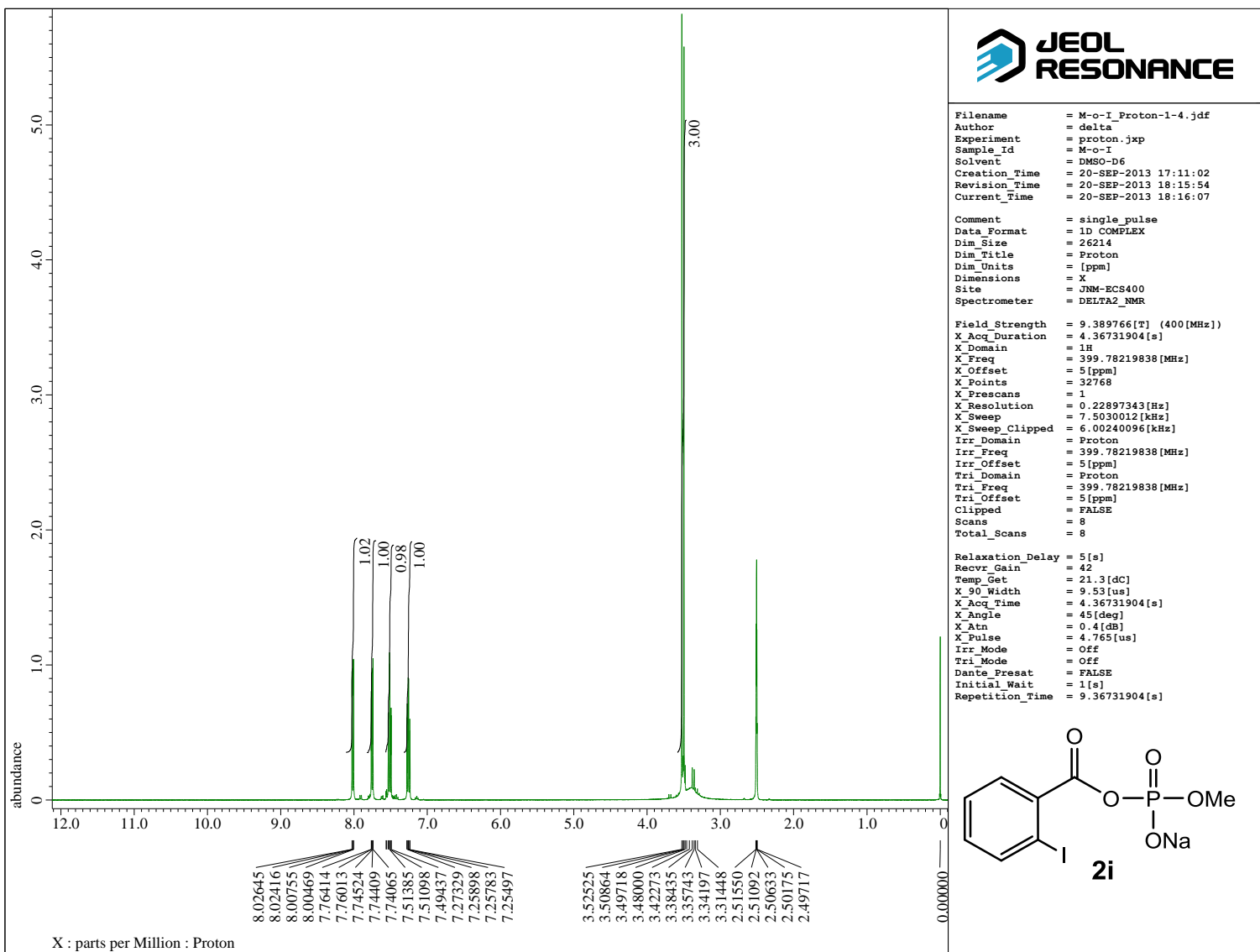
single pulse decoupled gated NOE

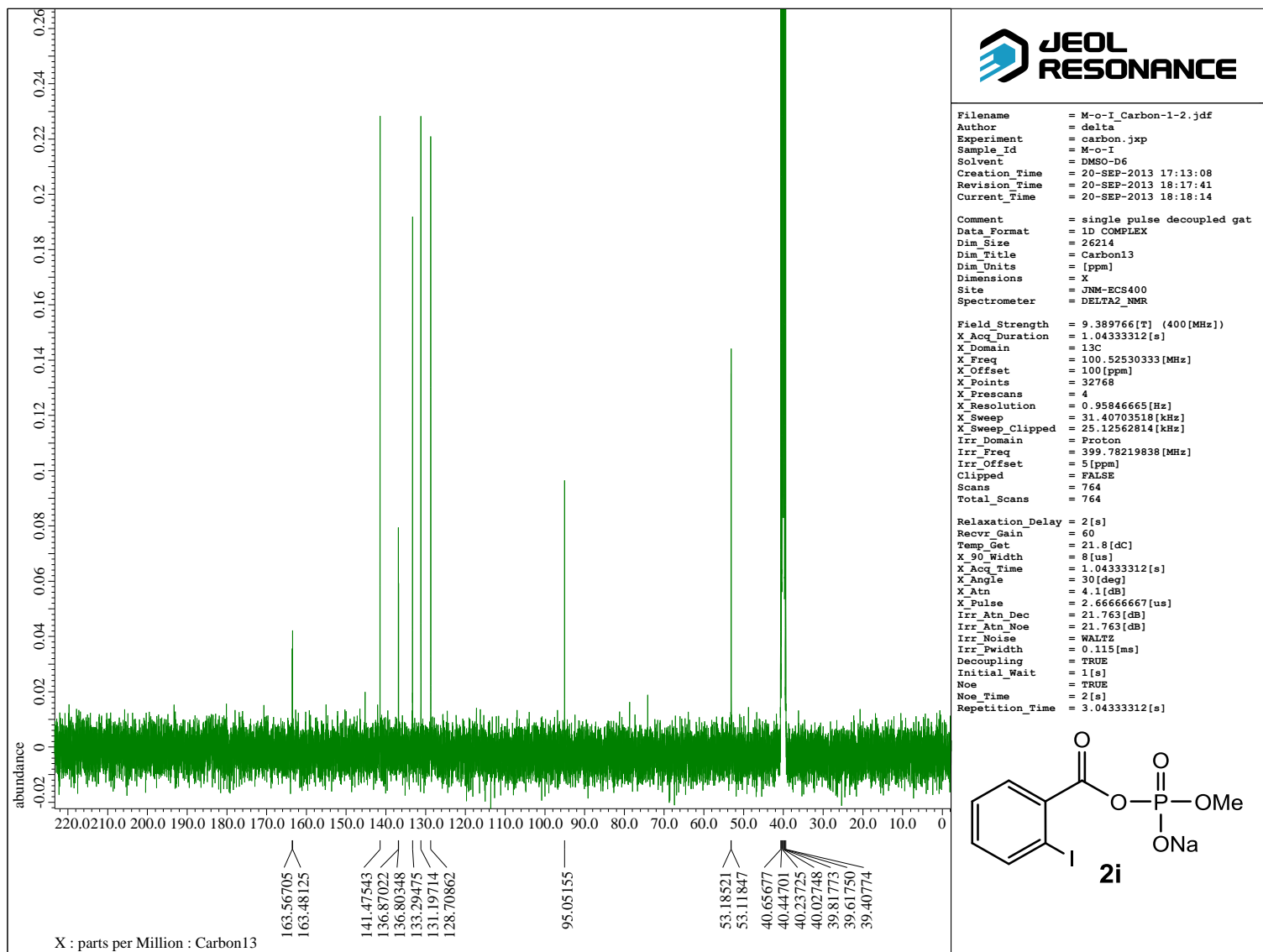
H¹ 今仁麻黄 NMR結果順MI-o-Cl_Carbon-1-1.als



DFILE MI-o-Cl_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 26-06-2013 20:53:12
OBNUC 13C
EXMOD carbon.jpg
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 1024
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 21.7 c
SLVNT DMSO
EXREF 39.50 ppm
BF 0.12 Hz
RGAIN 60

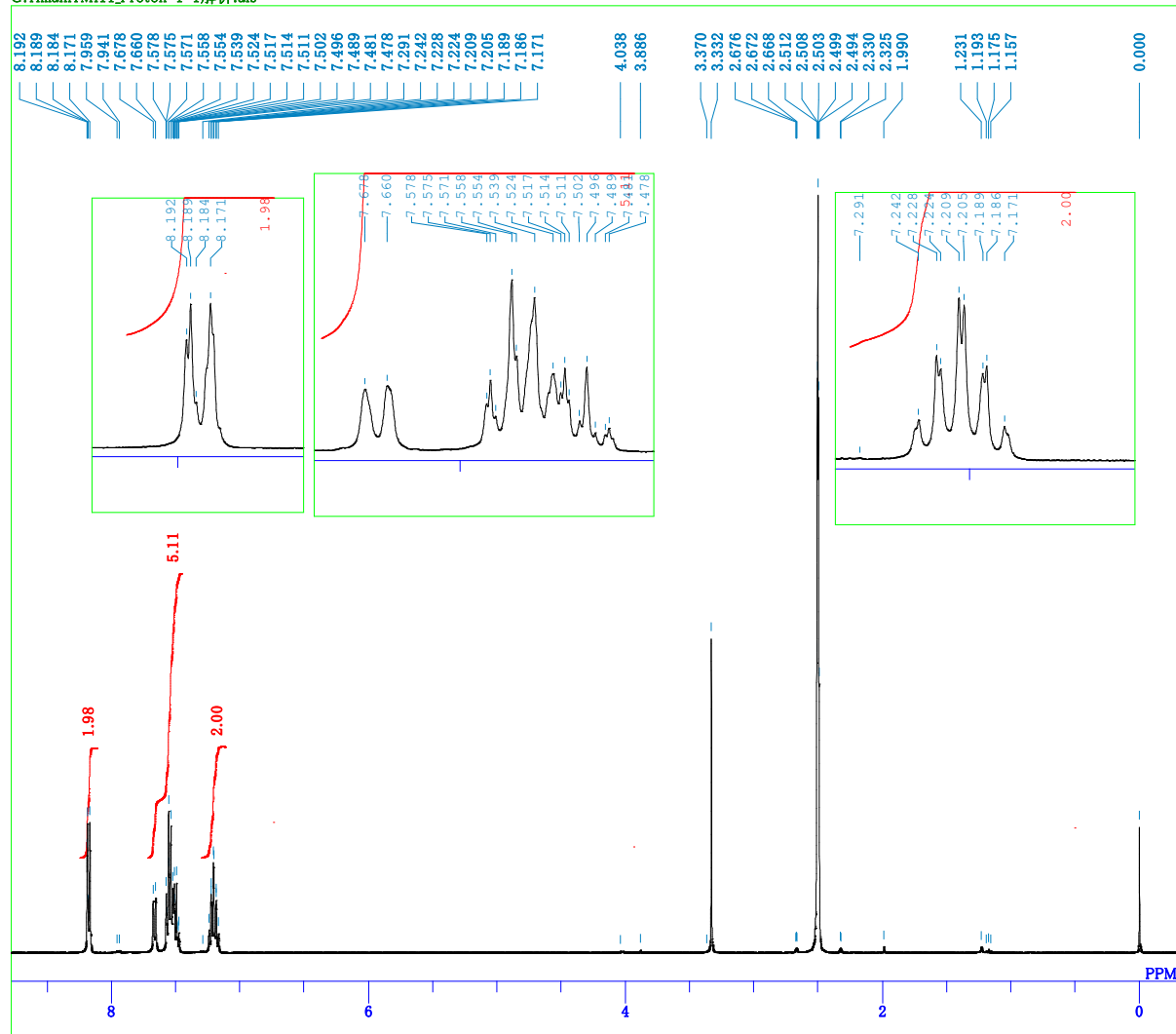




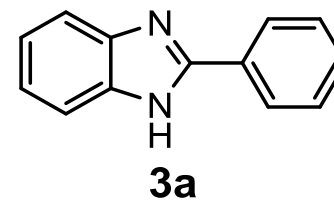


single_pulse

G:\imani\MI11_Proton-1-1解析.als

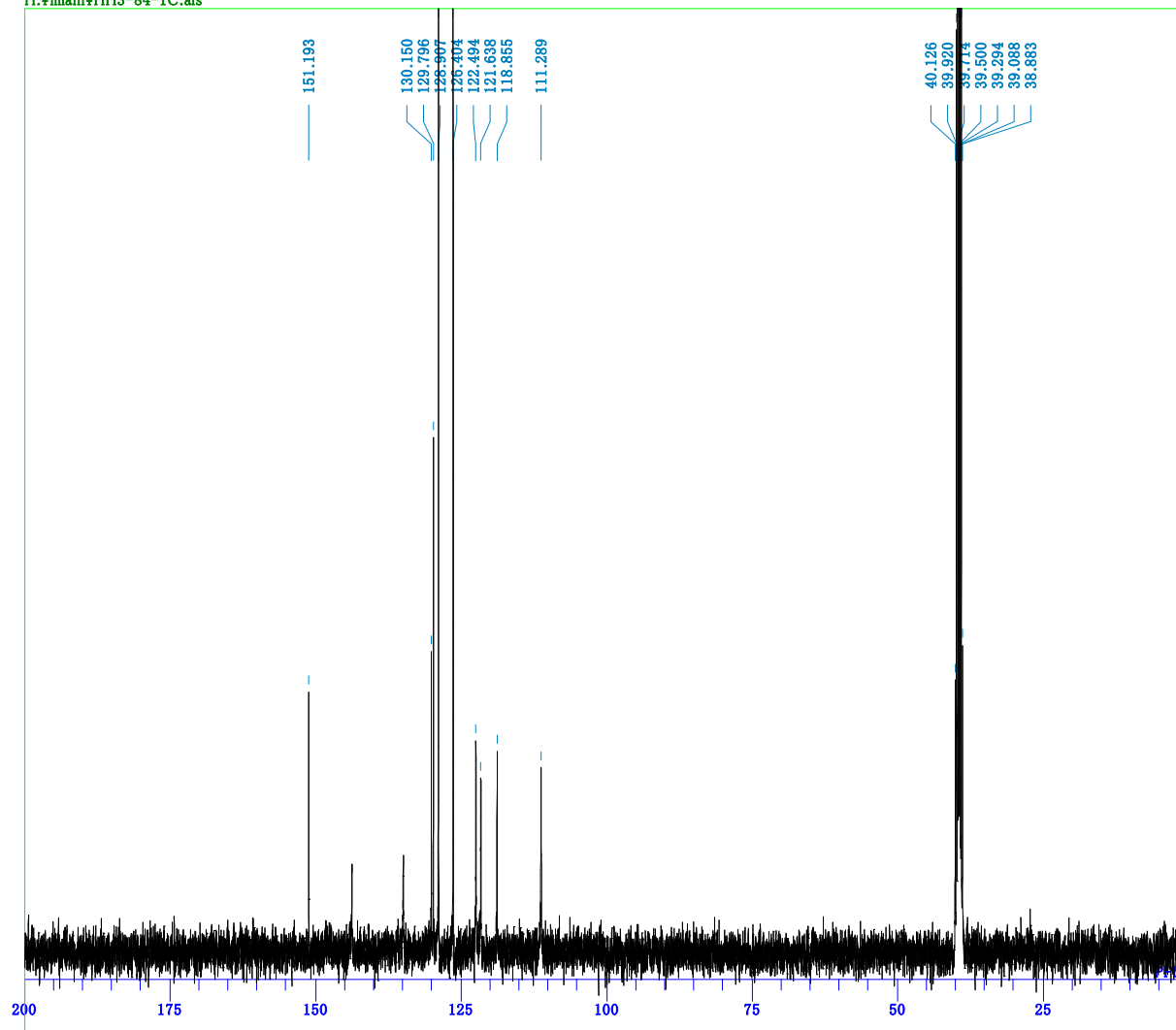


DFILE MI11_Proton-1-1解析.als
COMNT single_pulse
DATIM 11-01-2013 16:54:39
OBNUC 1H
EXMOD proton_jxp
OBFREQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 22.6 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 44

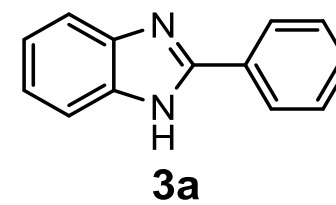


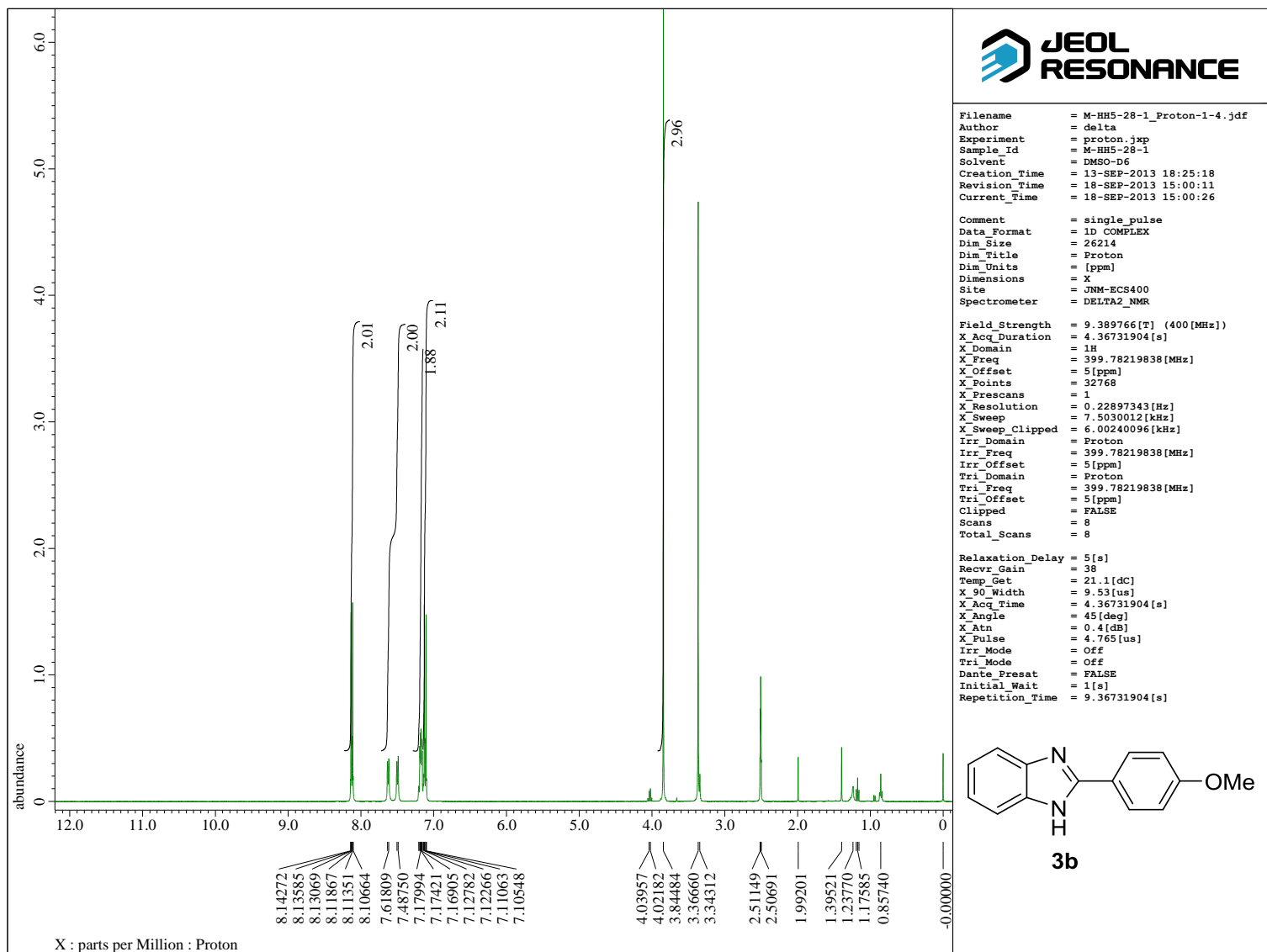
HH3-84-1C

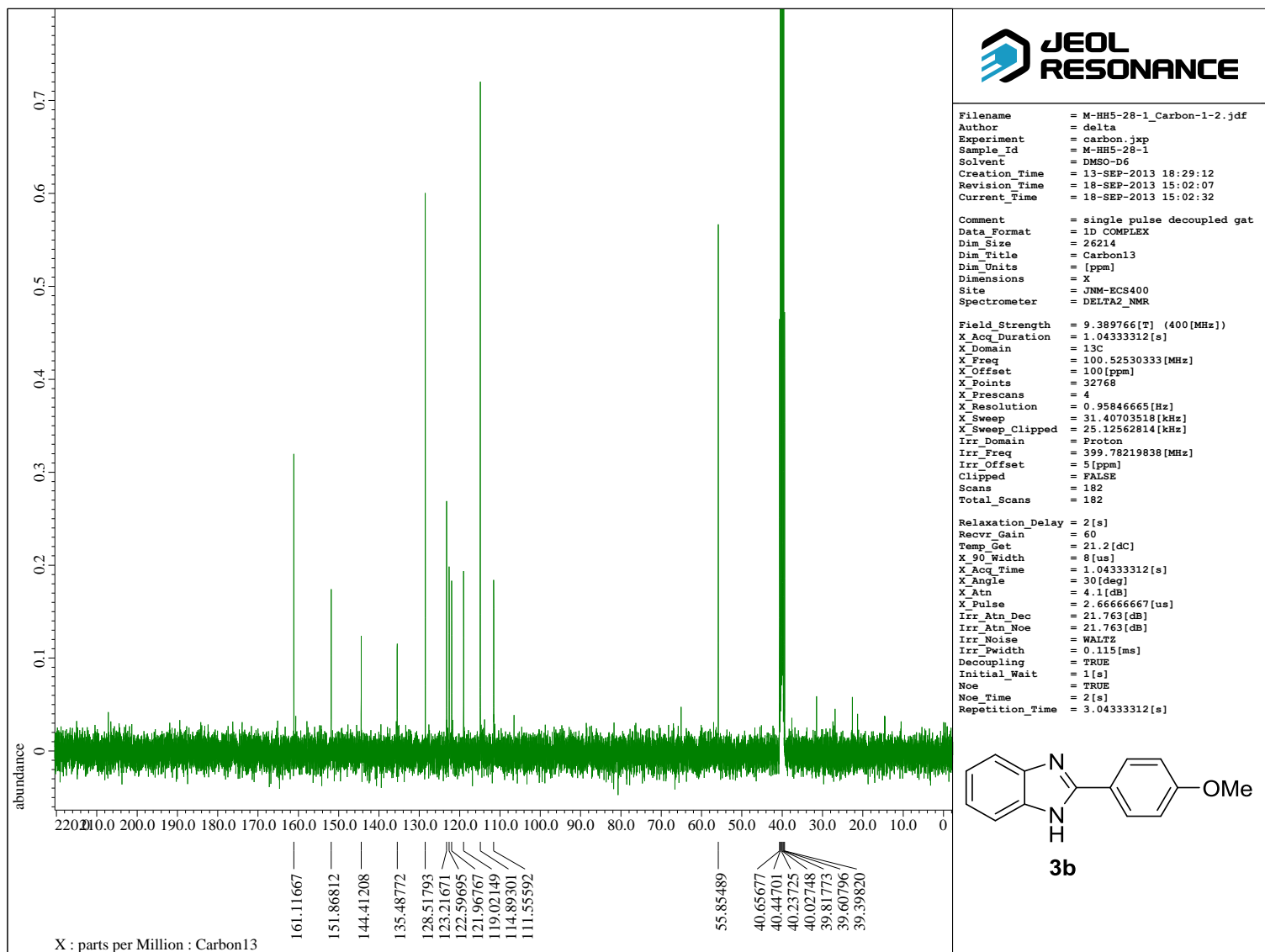
H:\imani\HH3-84-1C.als

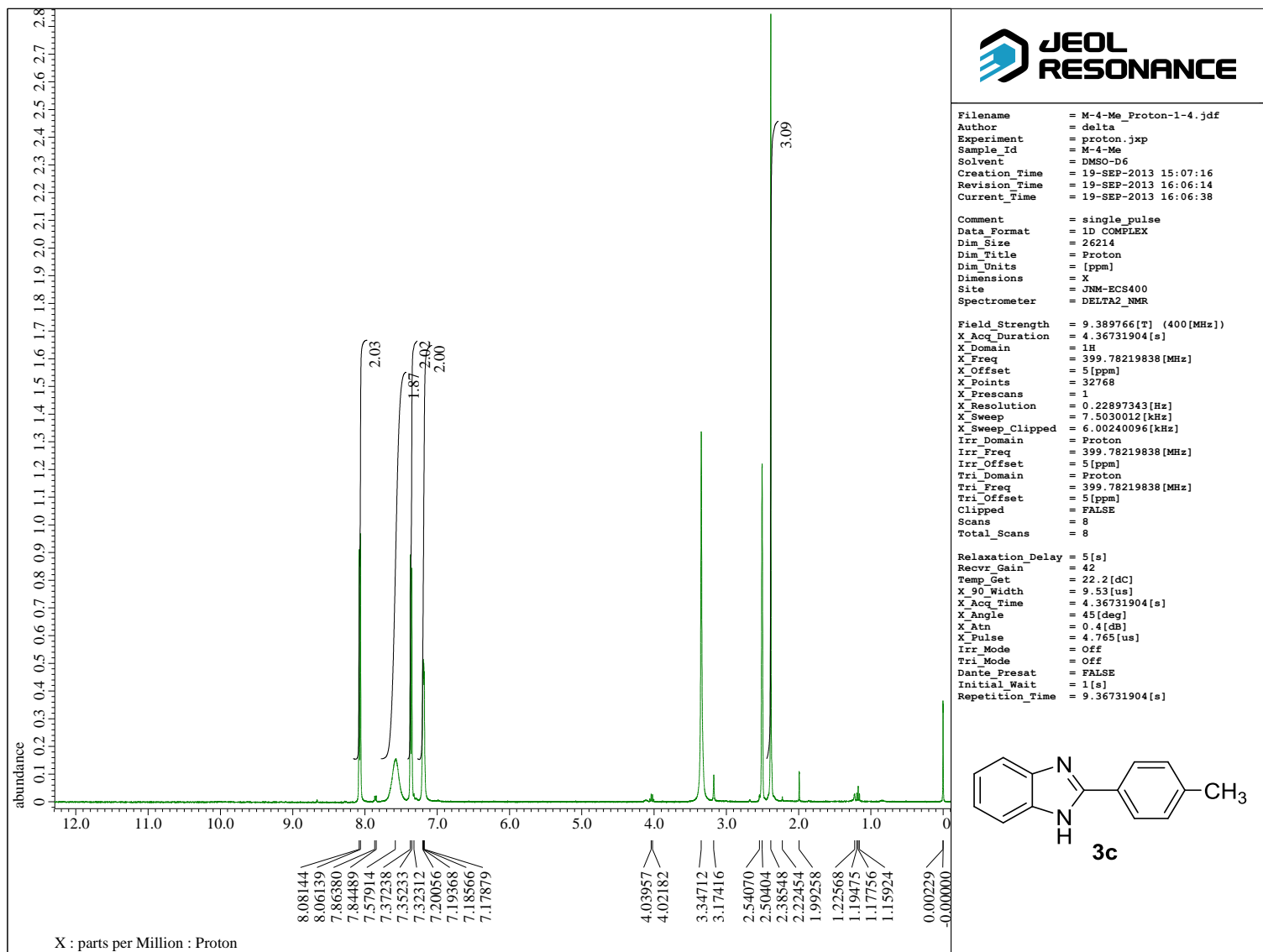


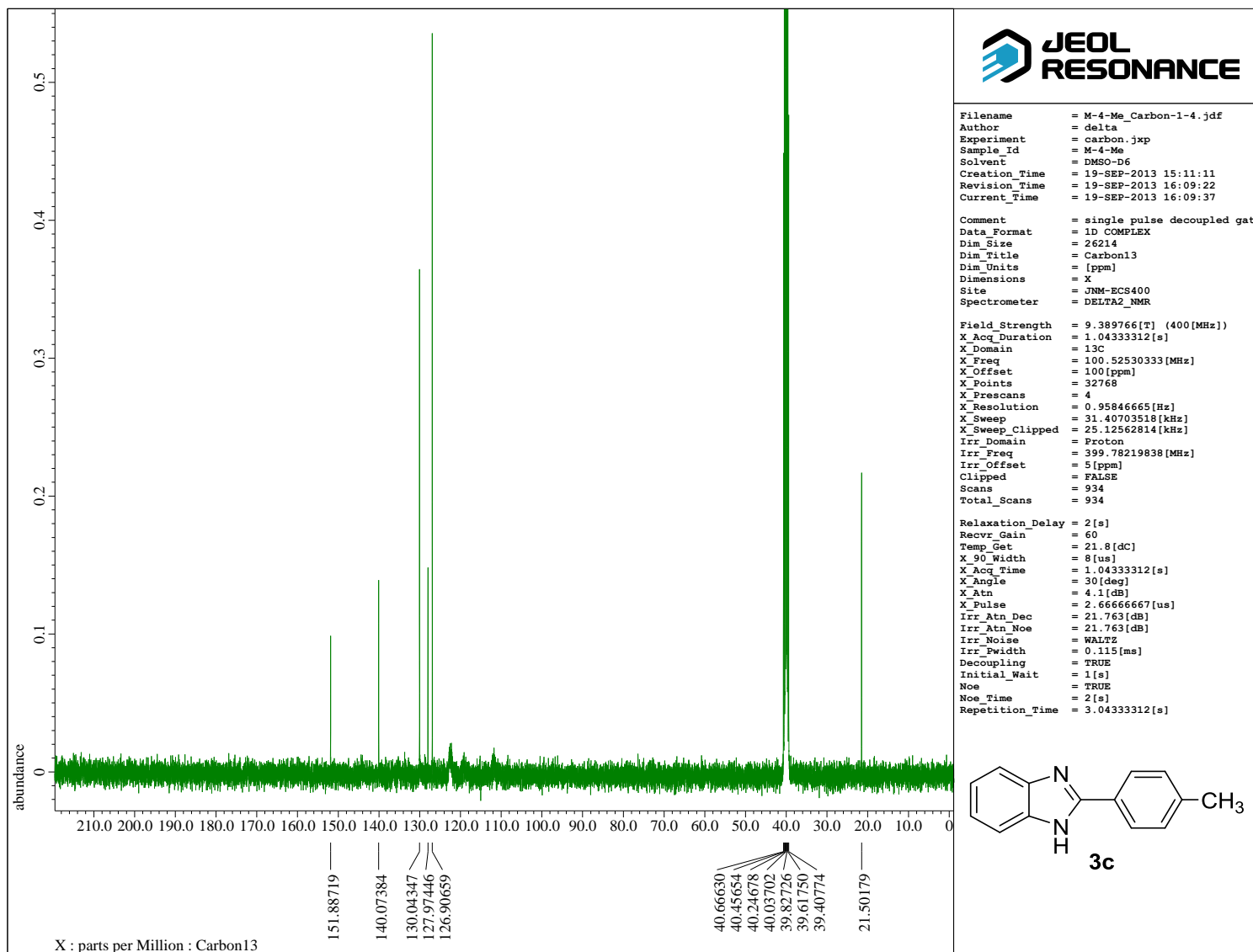
DFILE HH3-84-1C.als
COMNT HH3-84-1C
DATIM Fri Mar 02 09:53:29 2012
OBNUC 13C
EXMOD BCM
OBFRQ 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.00 Hz
POINT 32768
FREQU 27118.64 Hz
SCANS 139
ACQTM 1.2083 sec
PD 1.7920 sec
PW1 4.70 usec
IRNUC 1H
CTEMP 25.1 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 24





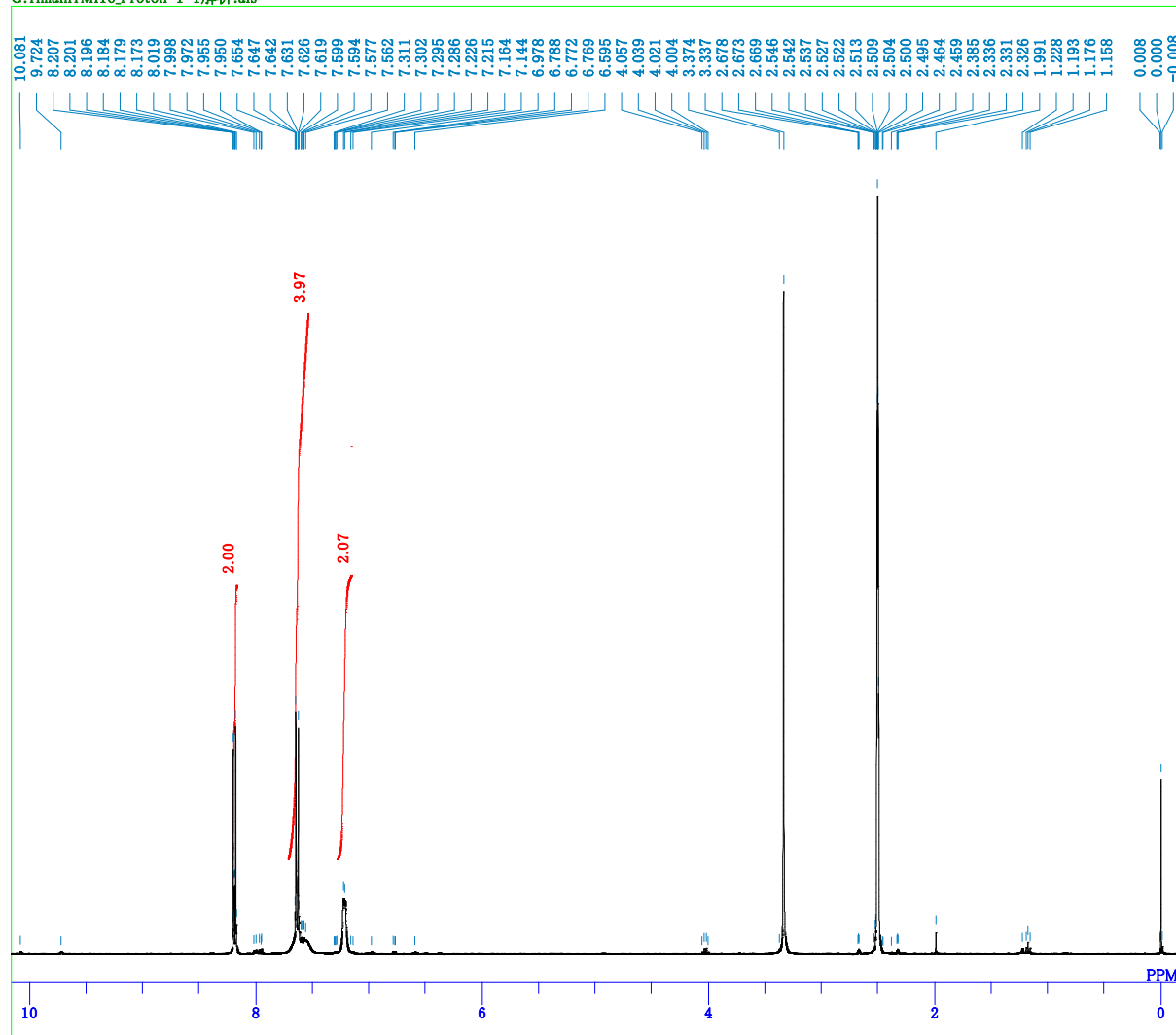




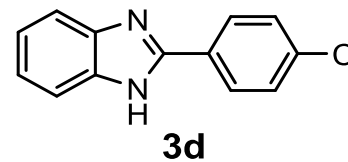


single_pulse

G:\imani\MI16_Proton-1-1解析.als

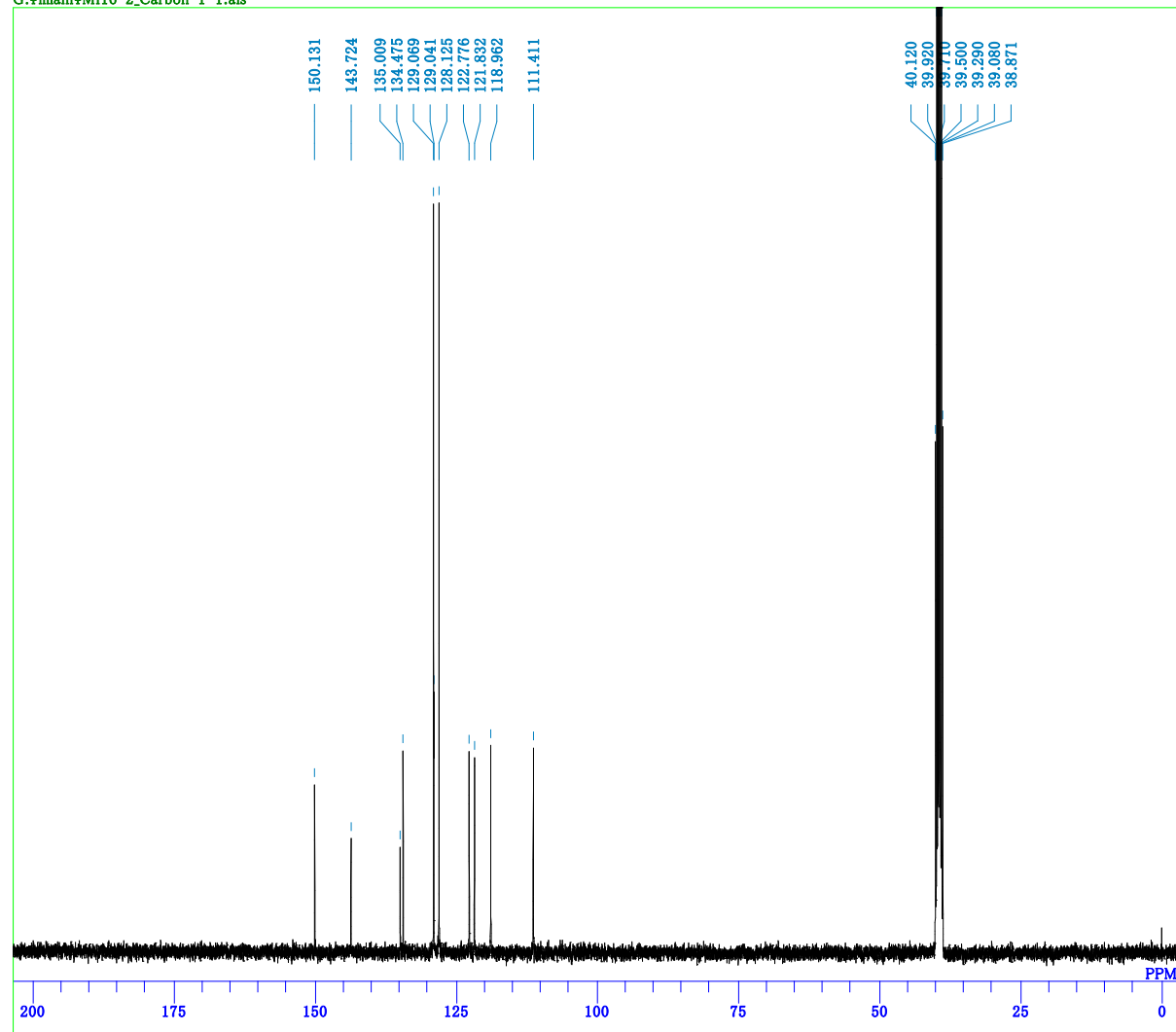


DFILE MI16_Proton-1-1解析.als
COMNT single_pulse
DATIM 05-02-2013 13:16:55
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 22.9 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 44

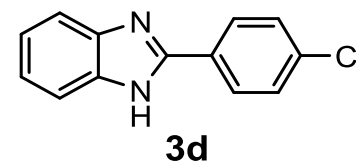


single pulse decoupled gated NOE

G:\fimani\MI16-2_Carbon-1-1.als

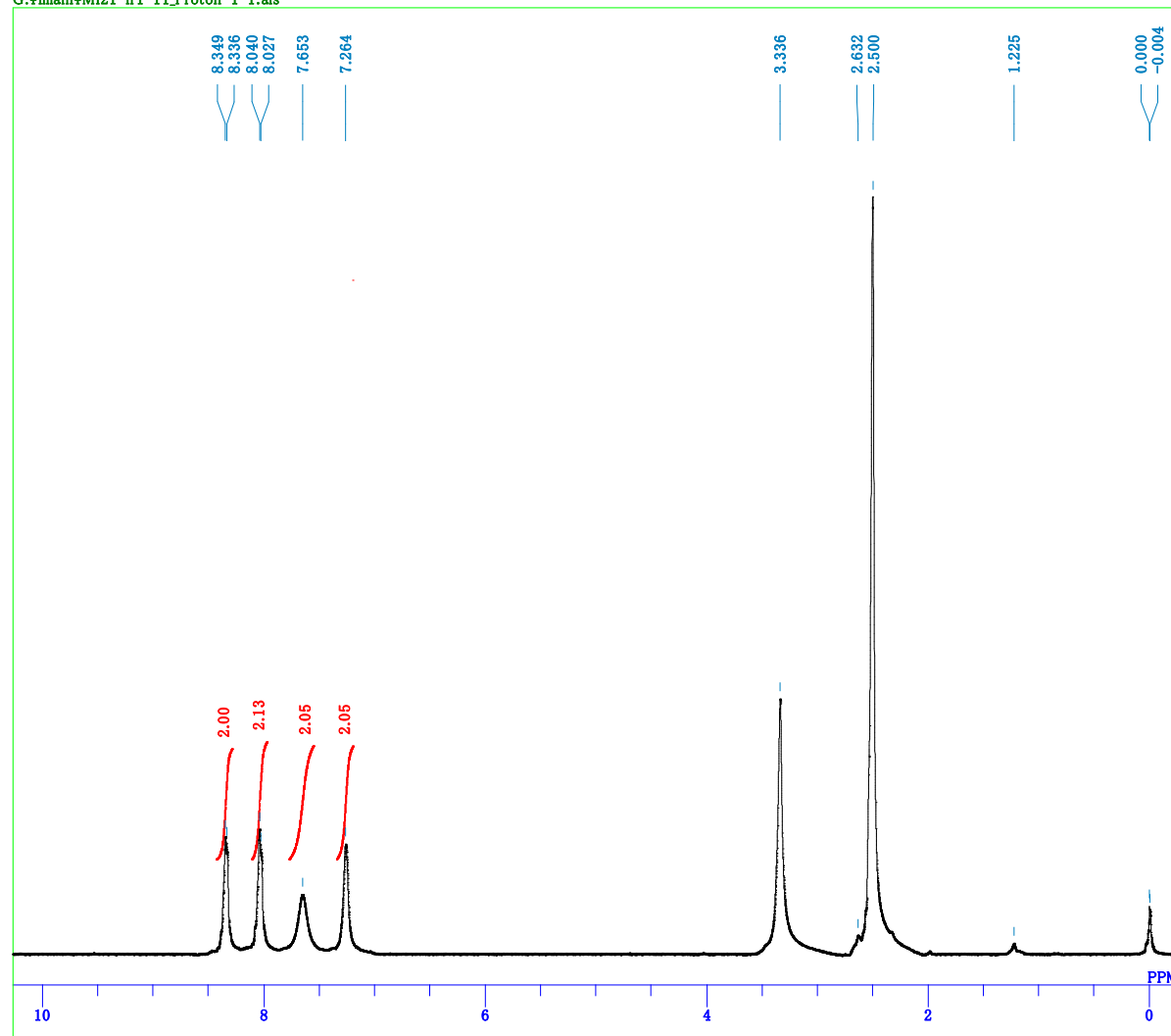


DFILE MI16-2_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 03-07-2013 18:53:40
OBNUC 13C
EXMOD carbon_jrp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 1024
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 21.1 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60

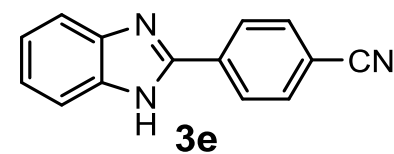


single_pulse

G:\imani\MI21-fr1-11_Proton-1-1.als

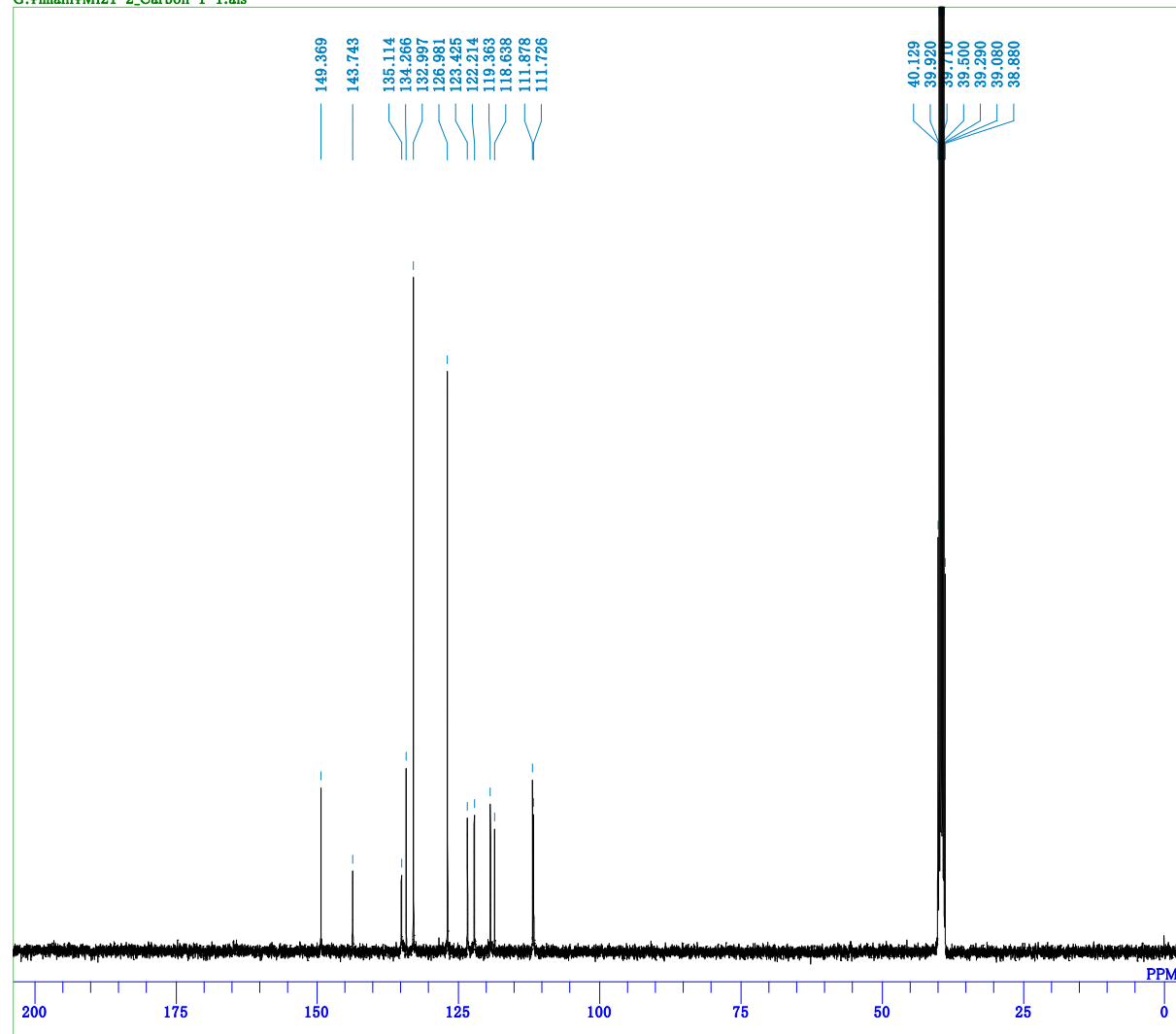


DFILE MI21-fr1-11_Proton-1-1.als
COMNT single_pulse
DATIM 26-02-2013 13:05:35
OBNUC 1H
EXMOD proton.jxp
OBFRQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 21.8 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 44

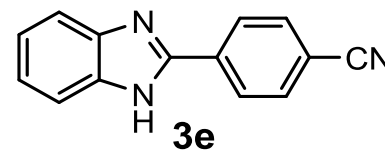


single pulse decoupled gated NOE

G:\imani\MI21-2_Carbon-1-1.als

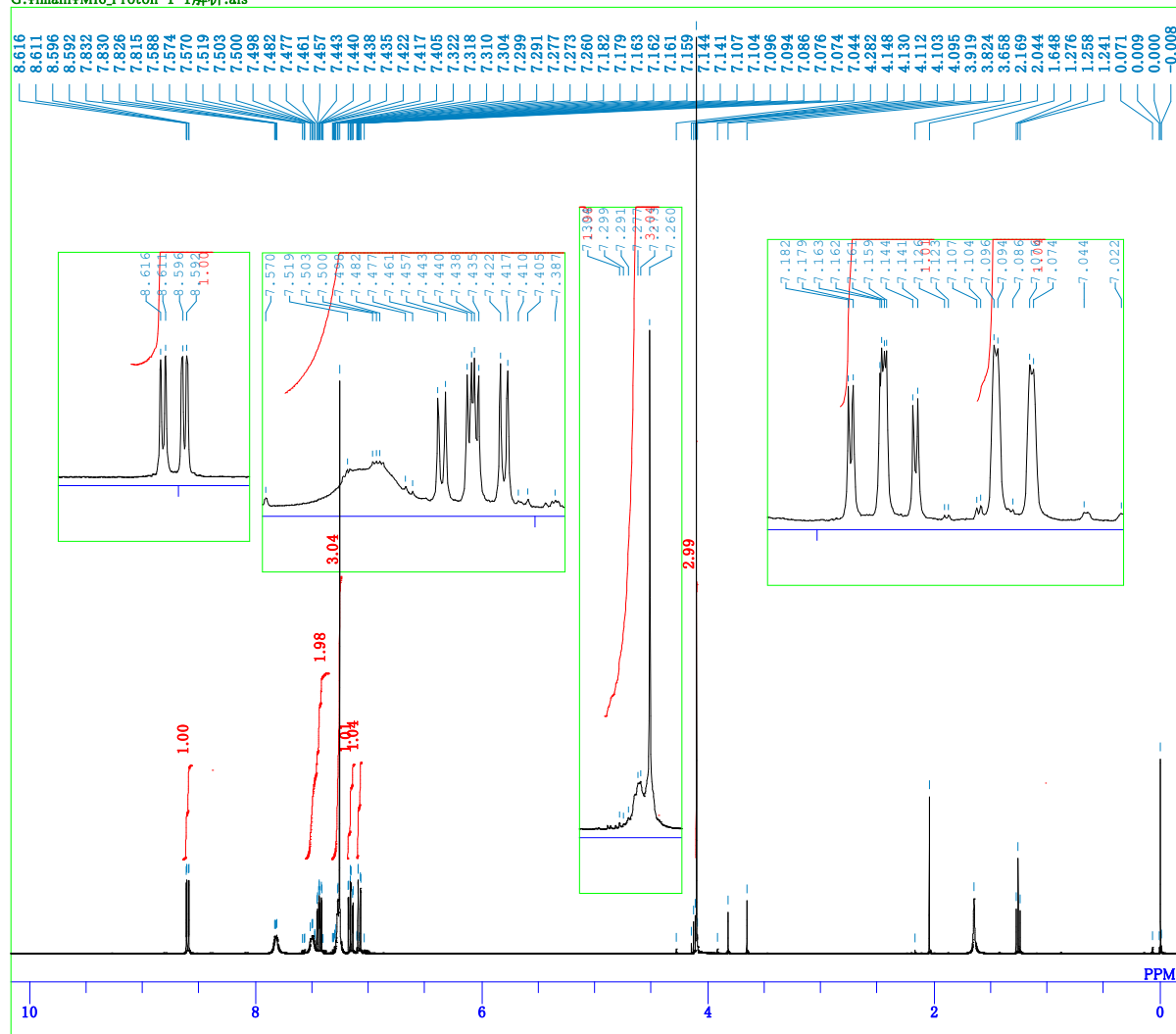


DFILE MI21-2_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 03-07-2013 19:55:09
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 1024
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 21.3 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60



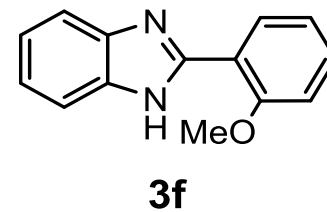
single_pulse

G:\Yimani\MI6_Proton-1-1解析.als



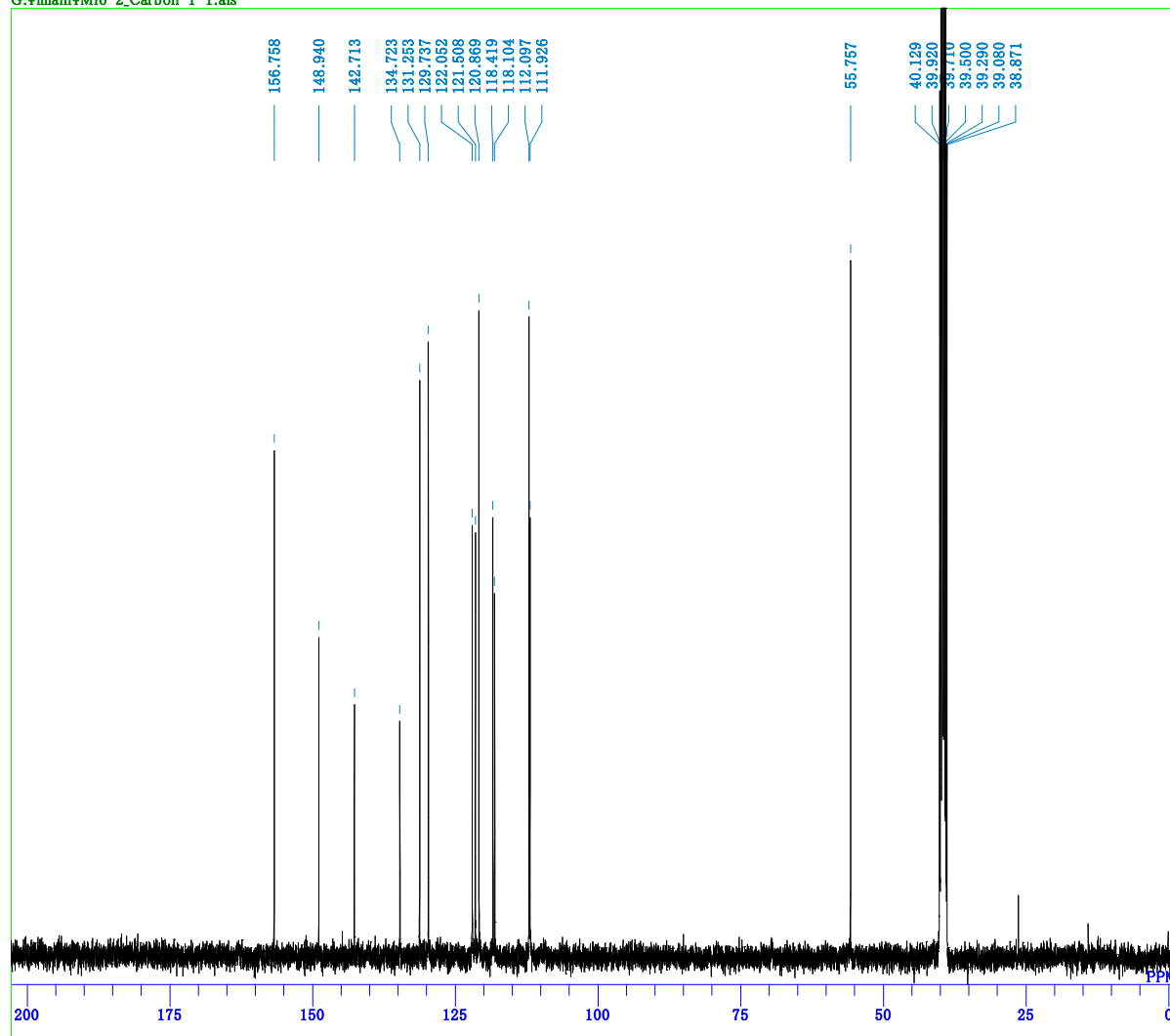
DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFREQ
OBSSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

MI6_Proton-1-1解析.als
single_pulse
13-12-2012 17:15:01
1H
proton.jxp
399.78 MHz
4.19 KHz
7.29 Hz
26214
6002.40 Hz
8
4.3673 sec
5.0000 sec
4.91 usec
1H
23.6 c
CDCl3
0.00 ppm
0.12 Hz
48

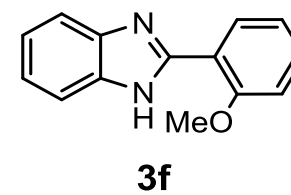


single pulse decoupled gated NOE

G:\fmani\MI6-2_Carbon-1-1.als

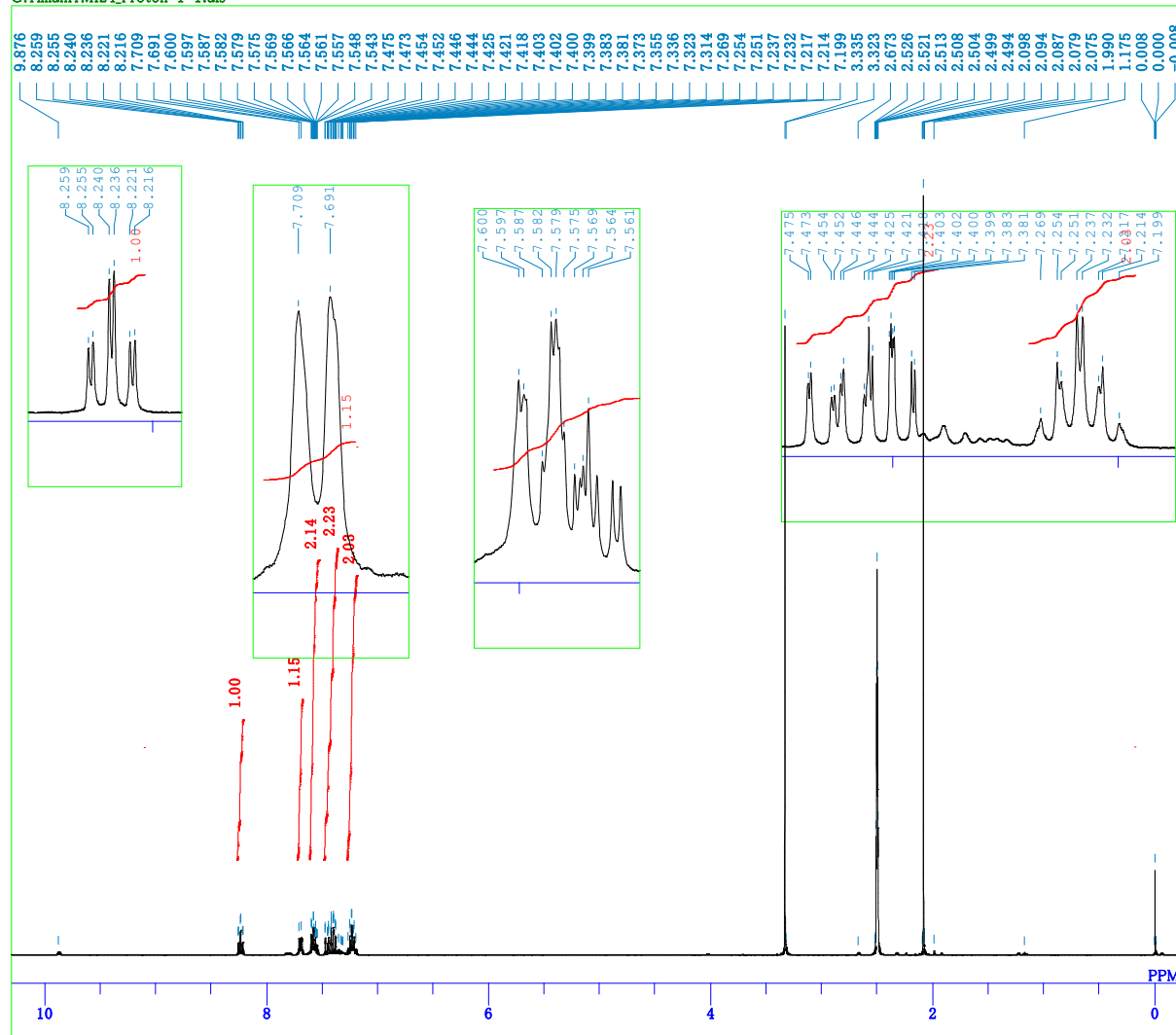


DFILE MI6-2_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 03-07-2013 17:54:41
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 1024
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 21.2 c
SLVNT DMSO
EXREF 39.50 ppm
BF 1.20 Hz
RGAIN 60

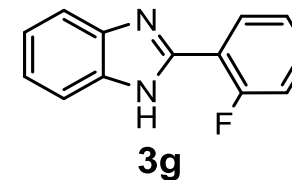


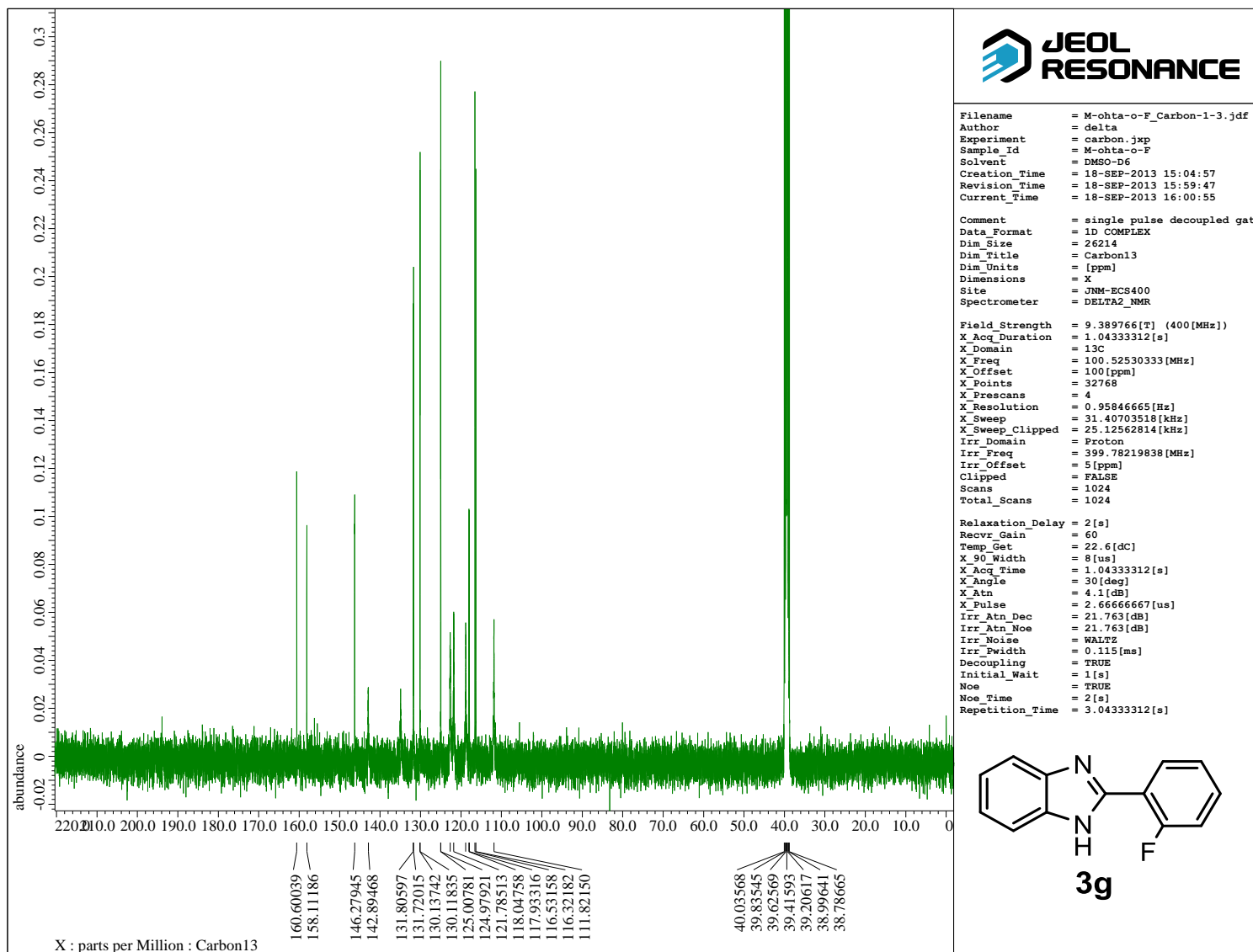
single_pulse

G:\imani\MI24_Proton-1-1.als



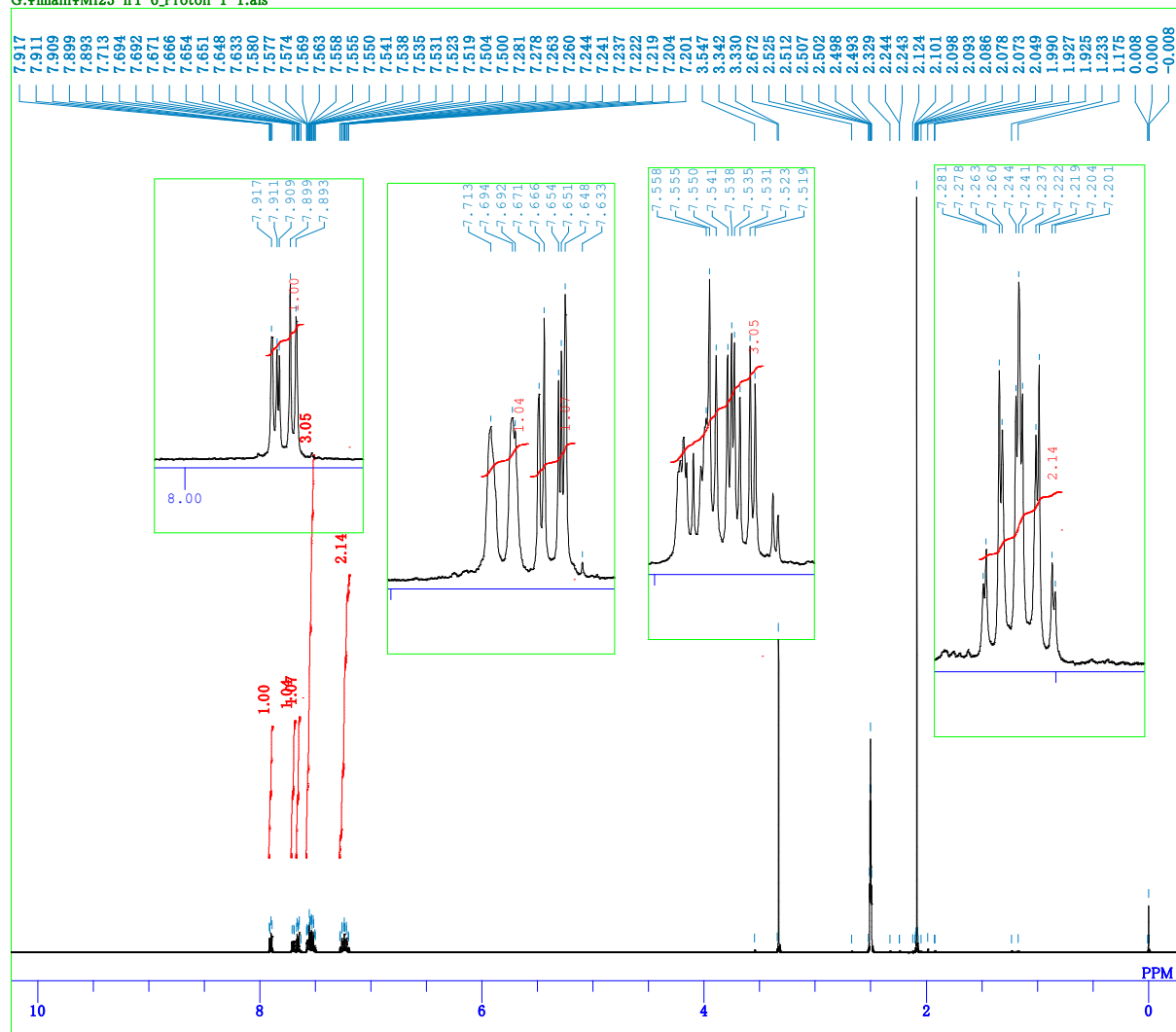
DFILE MI24_Proton-1-1.als
 COMNT single_pulse
 DATIM 07-03-2013 13:24:51
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 399.78 MHz
 OBSETE 4.19 KHz
 OBFIN 7.29 Hz
 POINT 52428
 FREQU 6002.40 Hz
 SCANS 8
 ACQTM 8.7346 sec
 PD 5.0000 sec
 PW1 4.91 usec
 IRNUC 1H
 CTEMP 21.6 c
 SLVNT DMSO
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 46



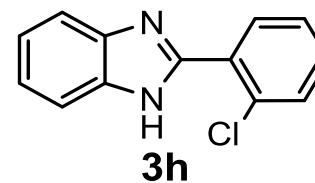


single_pulse

G:\fmani\MI23-fr1-6_Proton-1-1.als

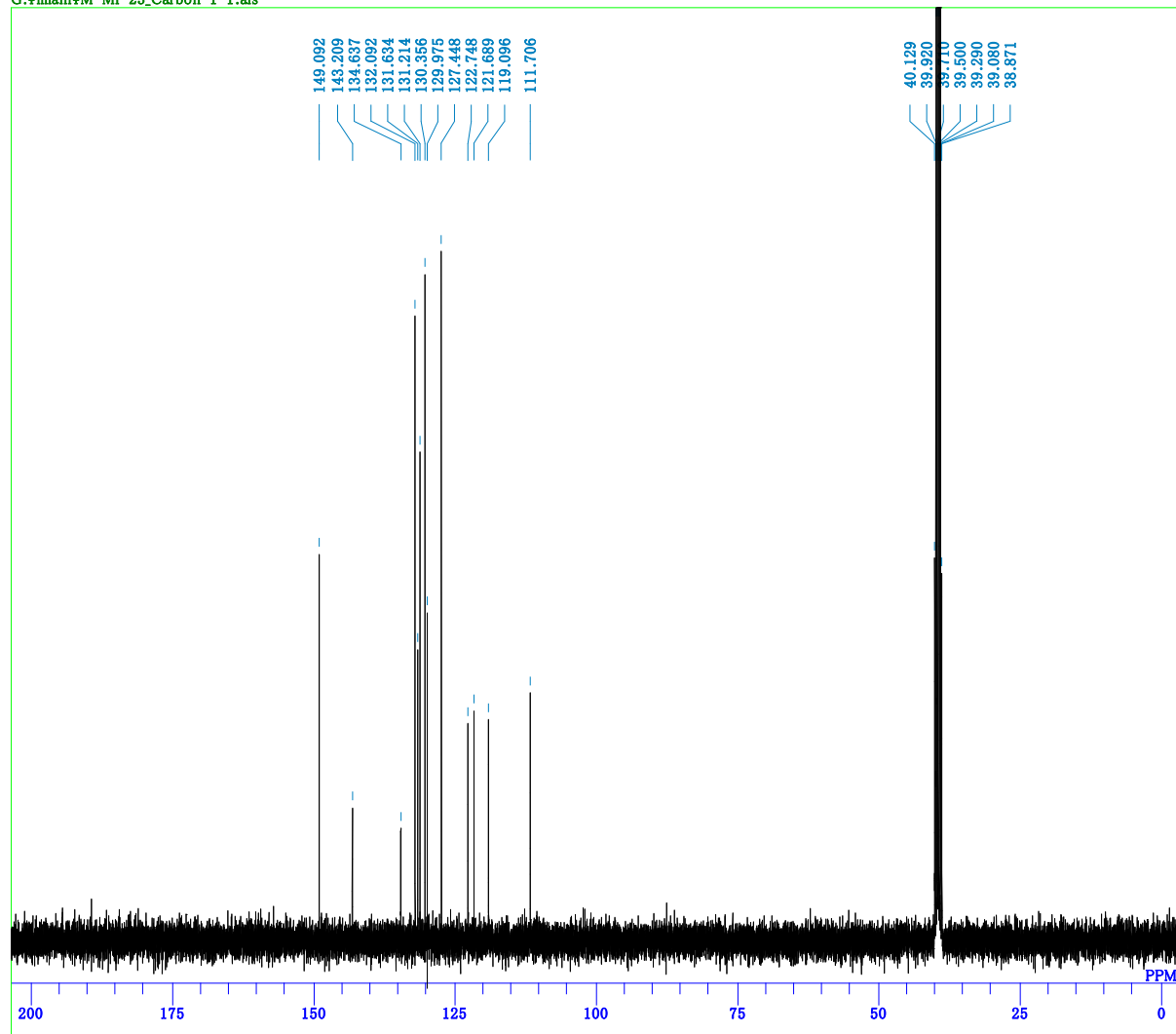


DFILE MI23-fr1-6_Proton-1-1.als
COMNT single_pulse
DATIM 07-03-2013 13:15:58
OBNUC 1H
EXMOD proton.jxp
OBFREQ 399.78 MHz
OBSET 4.19 KHz
OBFIN 7.29 Hz
POINT 52428
FREQU 6002.40 Hz
SCANS 8
ACQTM 8.7346 sec
PD 5.0000 sec
PW1 4.91 usec
IRNUC 1H
CTEMP 22.1 c
SLVNT DMSO
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 44

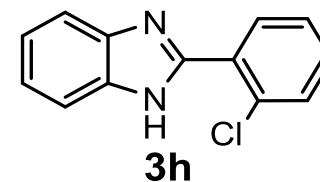


single pulse decoupled gated NOE

G:\imani\M-MI-23_Carbon-1-1.als

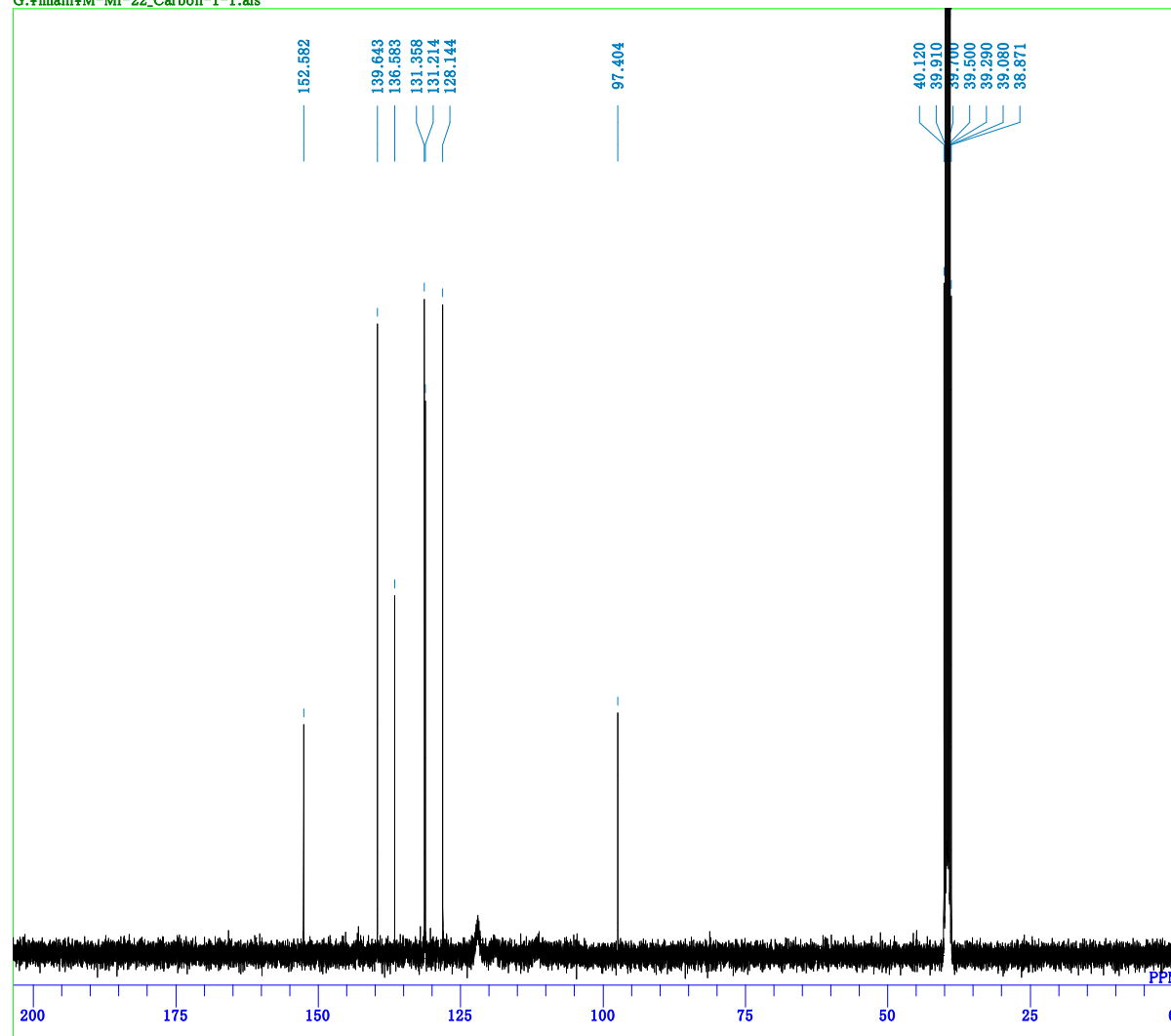


DFILE M-MI-23_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 06-06-2013 09:21:36
OBNUC 13C
EXMOD carbon_jrp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 299
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 20.8 c
SLVNT DMSO
EXREF 39.50 ppm
BF 0.00 Hz
RGAIN 60



single pulse decoupled gated NOE

G:\imani\M-MI-22_Carbon-1-1.als



DFILE M-MI-22_Carbon-1-1.als
COMNT single pulse decoupled gated NOE
DATIM 06-06-2013 06:41:27
OBNUC 13C
EXMOD carbon_jrp
OBFRQ 100.53 MHz
OBSET 5.35 KHz
OBFIN 5.86 Hz
POINT 26214
FREQU 25125.63 Hz
SCANS 3000
ACQTM 1.0433 sec
PD 2.0000 sec
PW1 2.67 usec
IRNUC 1H
CTEMP 20.8 c
SLVNT DMSO
EXREF 39.50 ppm
BF 0.00 Hz
RGAIN 60

