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A Catalytic Asymmetric Synthesis of *N*-Boc- β -Methylphenylalanines

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Supporting Information

Reaction of (2*S,3*R**)-2,3-epoxy-3-phenyl-1-propanol with Me₂CuCNLi₂** A solution of (2*S**,3*R**)-2,3-epoxy-3-phenyl-1-propanol (0.14 g, 0.93 mmol) in ether (3.5 mL) was added *via* canula to a stirred suspension of Me₂CuCNLi₂ prepared *in situ* from CuCN (0.25 g, 2.8 mmol) in ether (30 mL) and MeLi (3.5 mL, 5.6 mmol, 1.6 M in hexane), at -68°C. The mixture was allowed to warm to 0°C, under stirring, during 1h 30 minutes, and then stirred at 0°C for 3h 30 minutes. NH₄Cl saturated aq. sol. and NH₄OH were added to the reaction and the organic layer was extracted with ether. The combined organic phases were dried over MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography yielding 0.09 g (77% yield) of a 1/1 mixture (measured by ¹H-RMN of the corresponding diacetates) of (2*R**,3*S**)-3-phenyl-1,2-butanediol **syn-5** and (1*R**,2*R**)-1-phenyl-2-metil-1,3-propanediol, **syn-11** respectively, along with 0.04 g (71% conversion) of starting material. (1*R**,2*R**)-1-phenyl-2-metil-1,3-propanediol **syn-5**: ¹H-RMN (200 MHz, CDCl₃) δ 0.80 (d, 3H, J=7Hz), 2-2.2 (m, 1H), 3.63 (d, 2H, J=5.6Hz), 4.9 (d, 1H), 7-7.5 (m, 5H) ppm. ¹³C-RMN (50 MHz, CDCl₃) δ 10.6 (CH₃), 41.3 (CH), 66.2 (CH₂), 76.3 (CH), 126.1 (CH), 127.2 (CH), 128.1 (CH), 142 (C) ppm.

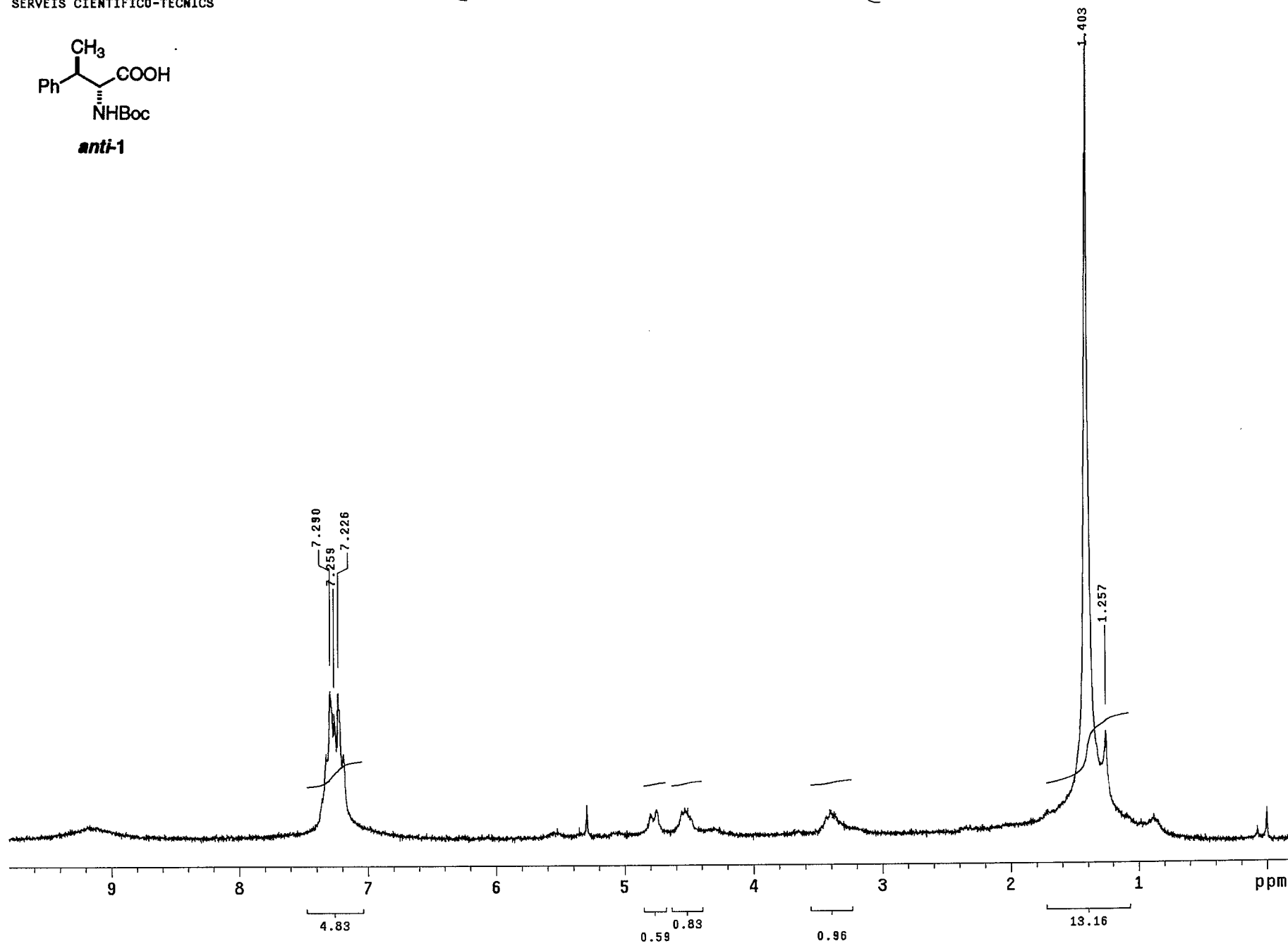
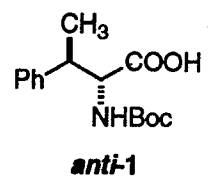
Reaction of (2*S,3*R**)-2,3-epoxy-3-phenyl-1-propanol with Me₃Al:** A solution of (2*S**,3*R**)-2,3-epoxy-3-phenyl-1-propanol (0.09 g, 0.6 mmol) in a mixture 1/1.3 of CH₂Cl₂/hexane (1.6 mL) was added dropwise to a solution of trimethylaluminium (0.9 mL, 2 M in heptane) at -20°C. After stirring for 2 h. at this temperature, the crude was diluted with CH₂Cl₂ and treated with NaF and water. The mixture was stirred for 2 h. at ambient temperature and filtered through Celite®. The organic phase was dried over

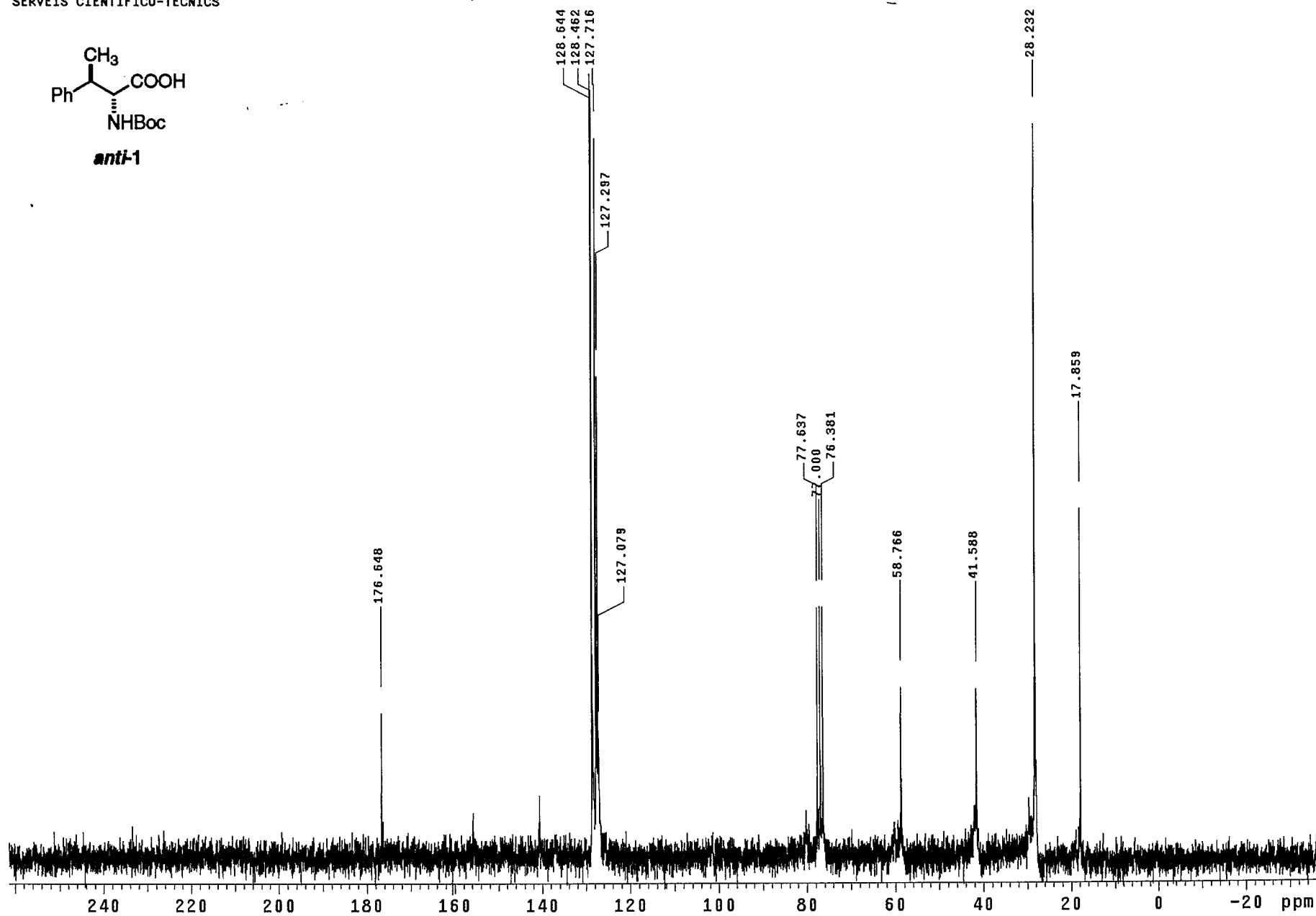
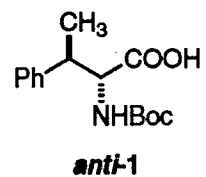
MgSO₄, evaporated and chromatographed yielding 0.08 g (80% yield) of a 2/1 mixture (measured by ¹H-RMN of the corresponding diacetates) of (2*R**,3*R**)-3-phenyl-1,2-butanediol *syn*-**5** and (2*R**,3*S**)-3-phenyl-1,2-butanediol *anti*-**5**, respectively. (2*R**,3*S**)-3-phenyl-1,2-butanediol, *anti*-**5**: ¹H-RMN (200 MHz, CDCl₃) δ 1.35 (d, 3H, J=7Hz), 2.7-2.9 (m, 1H), 3.2-3.9 (m, 3H), 7.1-7.6 (m, 5H) ppm. ¹³C-RMN (50 MHz, CDCl₃) δ 17.5 (CH₃), 42.8 (CH), 65.0 (CH₂), 76.6 (CH), 126.5 (CH), 127.5 (CH), 128.5 (CH), 143.7 (C) ppm.

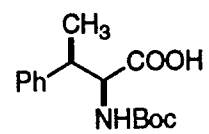
Ethyl (2*R*,3*R*)-2,3-epoxy-3-phenylpropanoate, 12. *cis*-Ethyl cinnamate **13** (1.32 g, 7.5 mmol) and 4-phenyl pyridine *N*-oxide (0.49 g, 2.86 mmol) were dissolved in CH₂Cl₂ (24 mL). (*R,R*)-salen Mn(III) complex (Jacobsen's catalyst²⁰) (0.47 g, 0.74 mmol) was added. The solution was cooled at 0°C and a 0.71 M buffered bleach solution (32 mL, pH=11.3) previously cooled at 0°C was added. The two-phase mixture was vigorously stirred. The reaction was monitored by TLC. Since the reaction rate was slow, additional amounts of catalyst were added. (0.47 g, after 4 h; 0.47 g after 7 h) and the mixture stirred 24 h. The organic phase was separated and filtered through a Celite® pad, washed with water and brine, and dried over Na₂SO₄. The solvent was removed under vacuum, and chromatographed. A 4.3/1 mixture (1.06 g, 79% yield) of *cis*, **12** and *trans* epoxy esters was obtained along with 0.11 g (92 % conversion) of starting material. Ethyl (2*R*,3*R*)-2,3-epoxy-3-phenylpropanoate, **12**: ¹H-RMN (200 MHz, CDCl₃) δ 1.02 (t, 3H, J=7Hz), 3.82 (d, 1H, J=4.6Hz), 4 (q, J=7Hz, 2H), 4.2-4.4 (m, 1H), 7.2-7.5 (m, 5H) ppm. The optical purity of **12** was determined to be 95% ee according to chiral HPLC. Conditions for Chiral HPLC analysis: CHIRALCEL® OD-R column, 25% MeOH/0.5M NaClO₄, 0.5 mL/min.; t_R(2*S*,3*S*):15.1 min., t_R(2*R*,3*R*):16.6 min., t_R(2*R*,3*S*):22.2 min.

Reaction of (2*R*,3*R*)-2,3-epoxy-3-phenylpropanoic acid with Me₂CuLi. To a solution of epoxy ester **12** (0.23 g, 1.2 mmol, 95% ee, contaminated with 15% of its *trans* isomer) in EtOH (1 mL), was added KOH (0.08 g, 1.42 mmol) and the mixture was stirred for 2 h. at 0°C. Ethanol was evaporated and the reaction mixture treated with diethyl ether at 0°C, acidified with 0.1 M HCl, and extracted at 0°C with ether. The combined ethereal phases were dried briefly over Na₂SO₄ and evaporated. The residue was dissolved in ether (12 mL) and added *via* canula to a stirred suspension of Me₂CuLi at 0°C freshly prepared from CuI (0.68 g, 3.6 mmol) in ether (12 mL) and MeLi (4.5 mL, 7.2 mmol, 1.6 M in hexane).

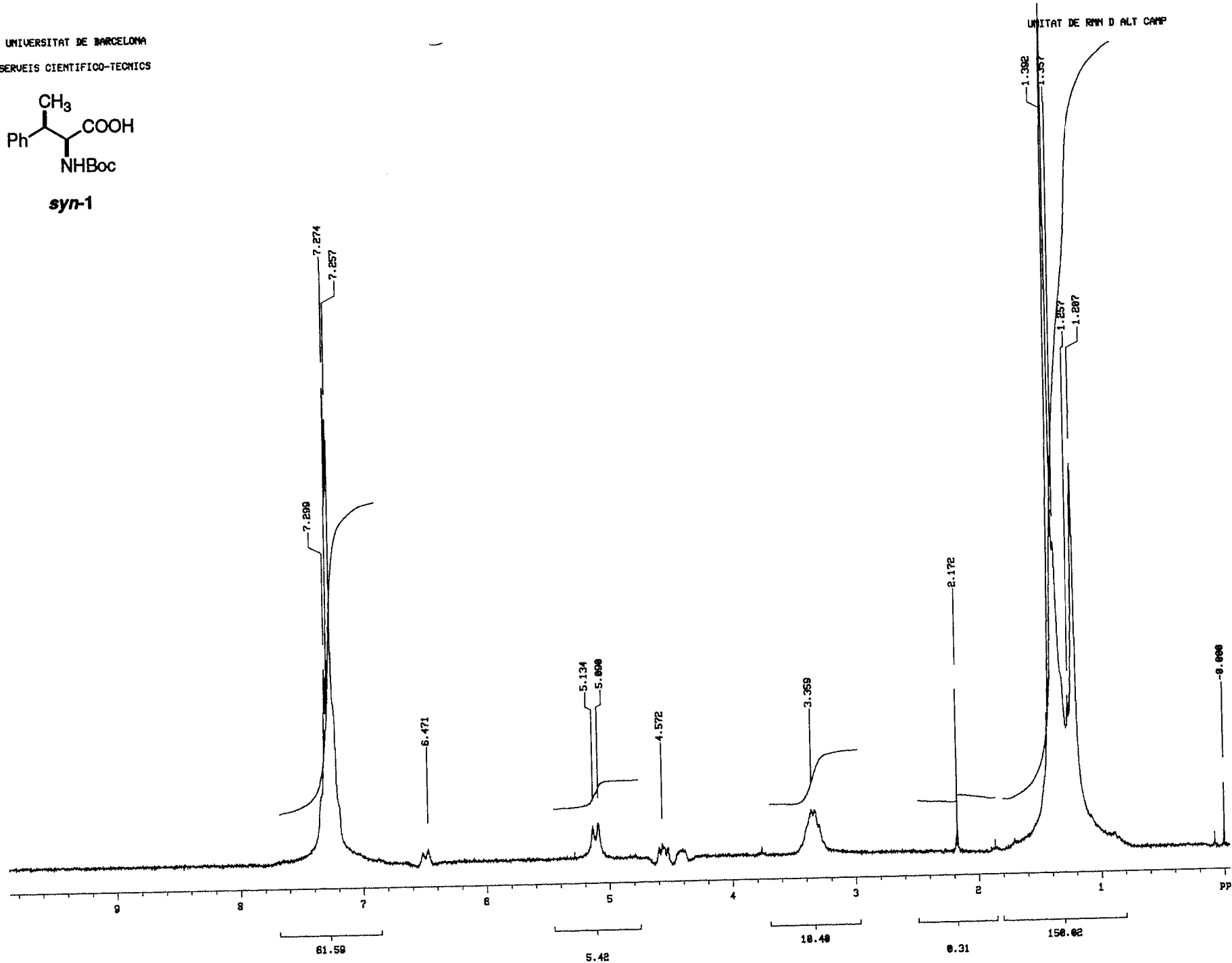
After 3 h. at 0°C, the reaction mixture was acidified with 5% aqueous HCl. The resulting mixture was filtered through a Celite[®] pad and the filtrate extracted with ether. The organic layer was dried over Na₂SO₄ and the solvent was evaporated. The oily residue (0.17 g) was dissolved in dimethylformamide (2 mL), KHCO₃ (0.24 g, 2.4 mmol) and methyl iodide (0.12 mL, 1.92 mmol) were added to the solution and the reaction was stirred at room temperature for 12 h. Water was added and the aqueous layer extracted with ethyl acetate. The combined organic phases were successively washed with a 5% Na₂SO₃ and brine, and dried over MgSO₄. Removal of the solvent gave an oil that was purified by chromatography yielding 0.07 g (30% yield) of a 1.8/1 mixture of the methyl (2*R*,3*S*)-3-phenyl-2-hydroxybutanoate **syn-10** and the methyl (2*R*,3*R*)-3-phenyl-2-hydroxybutanoate **anti-10**, respectively, being the enantiomeric excess of the (2*R*,3*S*) isomer of 87% (by ¹⁹F of its Mosher ester). Methyl (2*R*,3*S*)-3-phenyl-2-hydroxybutanoate, **syn-10**: ¹H-RMN (200 MHz, CDCl₃) δ 1.29 (d, 3H, J=7.4Hz), 2.8 (m, 1H, OH), 3.2-3.4 (m, 1H), 3.75 (s, 3H), 4.3-4.4 (m, 1H), 7.1-7.5 (m, 5H) ppm. ¹³C-RMN (50 MHz, CDCl₃) δ 14.4 (CH₃), 43.3 (CH), 52.5 (CH₃), 75.1 (CH), 126.8 (CH), 127.8 (CH), 128.4 (CH), 140 (C) ppm.

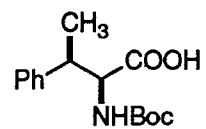




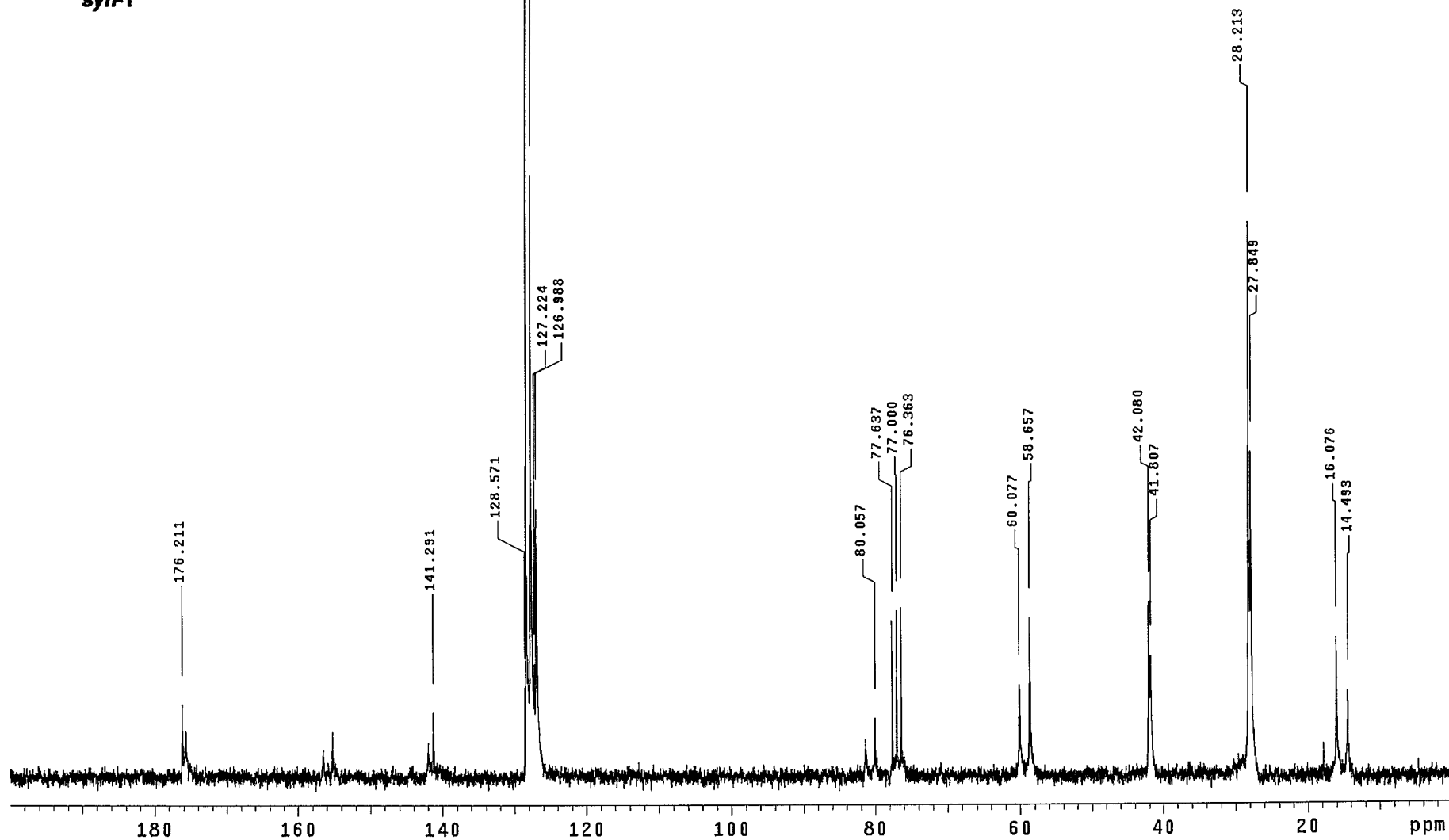


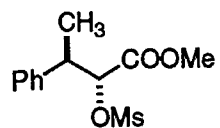
syn-1



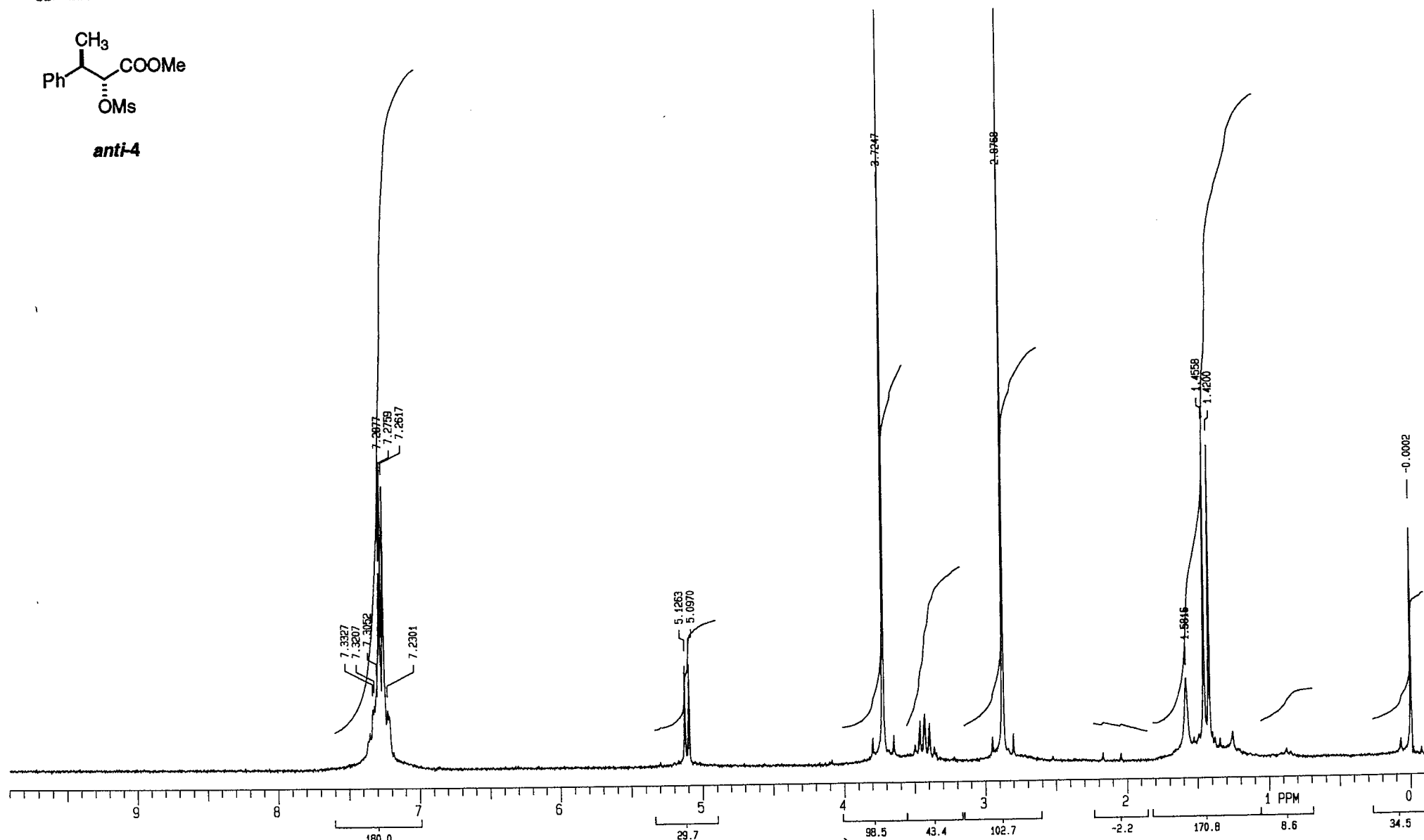


syn-1





anti-4



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3000.3 300.0
1.994 0
15.0 32

1.000 -300.0
NNN 20.0
C 200
0.5

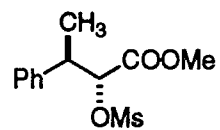
16 ---
--- ---
1999.8 -20.0

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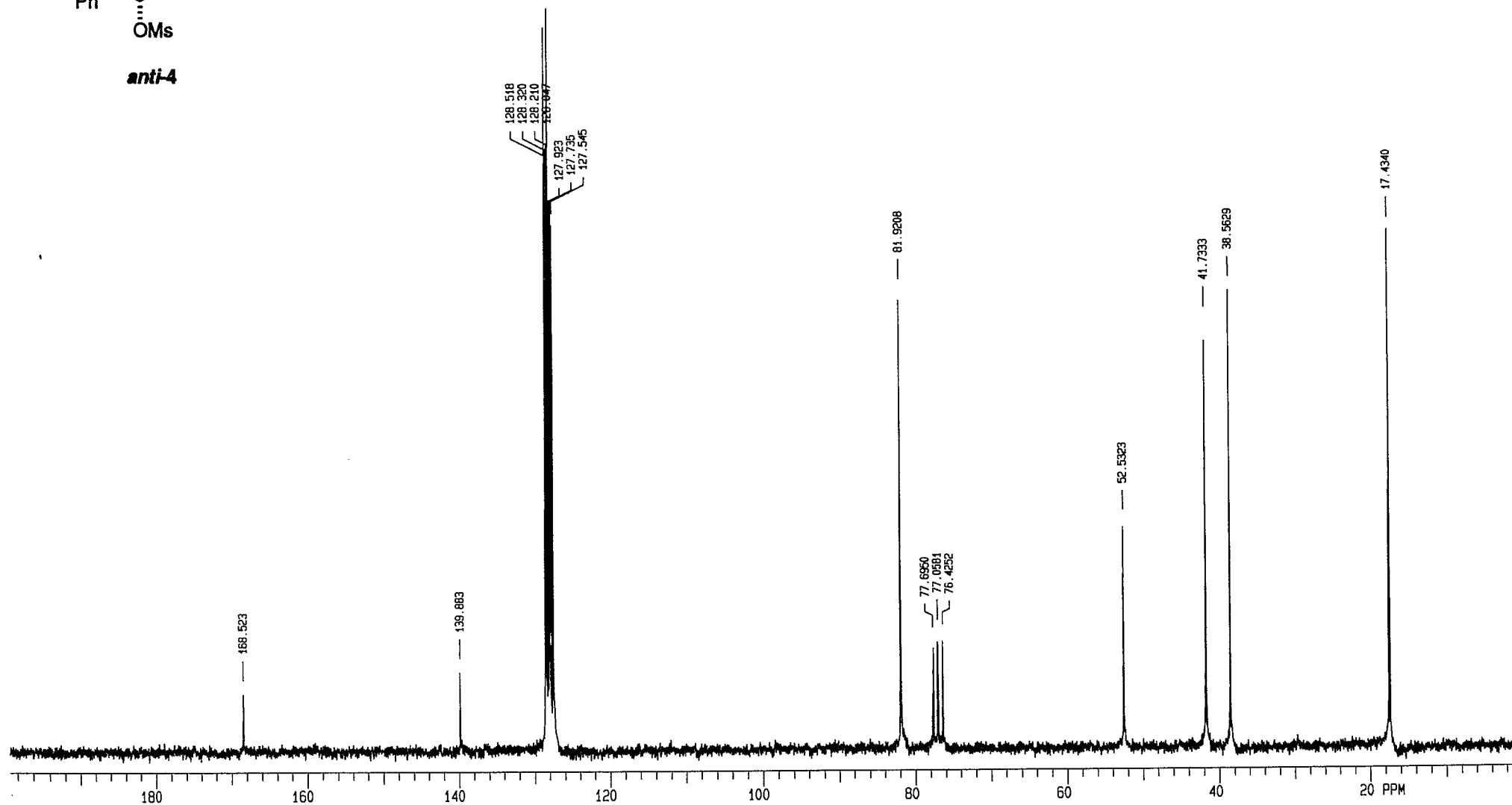
CDCl₃

USER: ARE
ESTE NIREIA

ESTE01
06-17-94
11:37:42
GEMA 200



anti-4



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15.0	2500	29.0	1.0			

S2PUL

USER: ARE

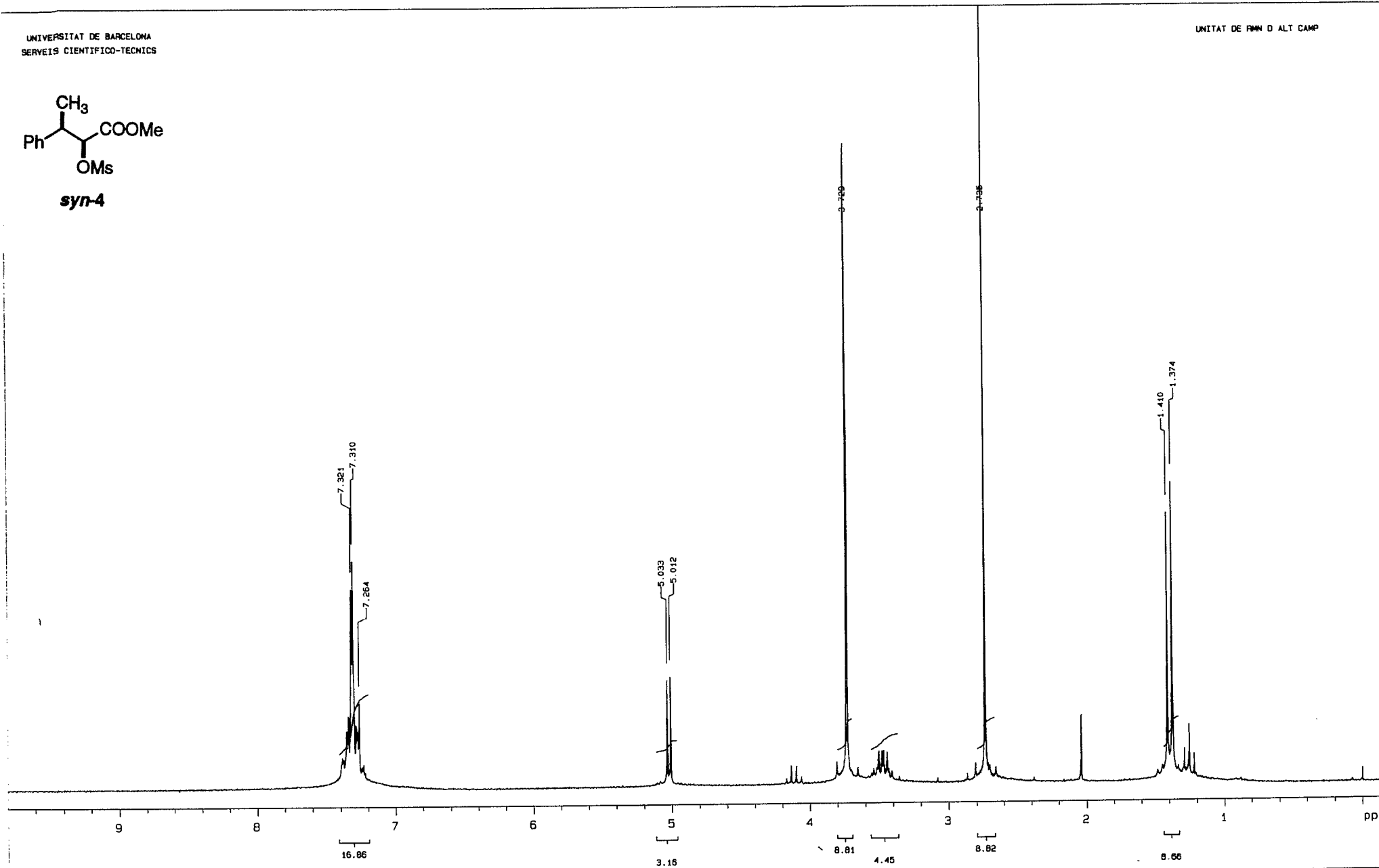
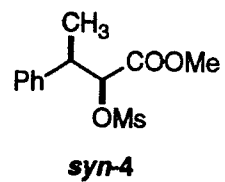
MEES NIREIA

GEMINI-200 13C OBSERVE

CDCL3

MEES01

06-17-94
17:18:24
GEMA 200

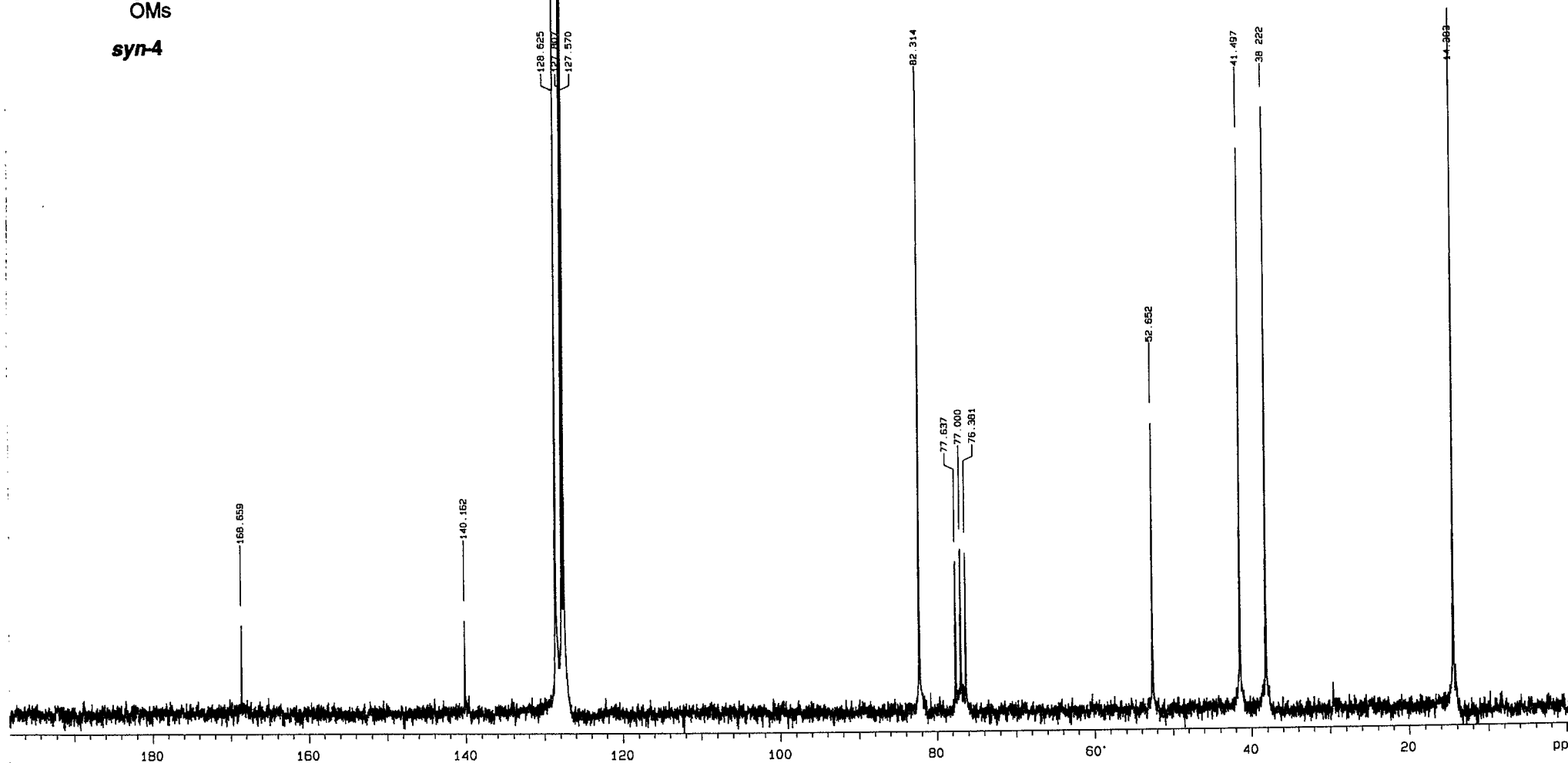
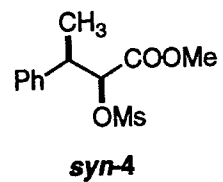


PULSE SEQUENCE
Pulse 15.0 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
16 repetitions

OBSERVE H1, 199.9739341

DATA PROCESSING
FT size 16384

MSM MIREIA
GEMINI-200
usuário: are
fichero: mssm01
fecha: 12-13-95
mssm01.H1
Solvent: cdcl3
Ambient temperature



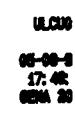
PULSE SEQUENCE
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Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
2500 repetitions

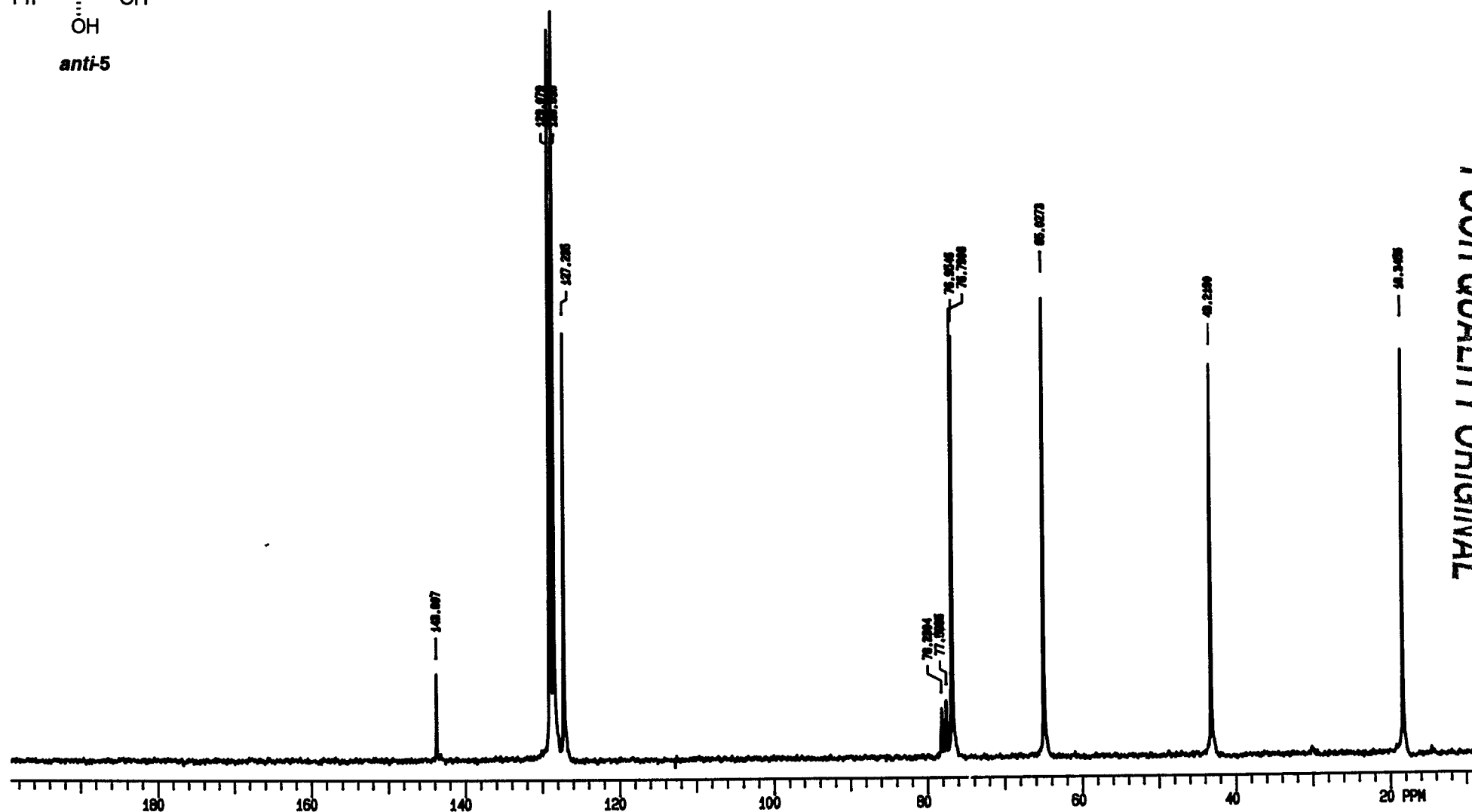
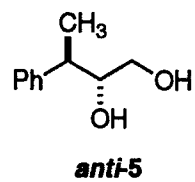
OBSERVE C13, 50.2837529
DECOUPLE H1, 199.9750061
Power 30 dB
continuously on

DATA PROCESSING
Line broadening 1.0 Hz
Ft size 32768

MSM MIREIA

usuario: are
fichero: /mesmo
fecha de realizacion del
espectro:
12/12/97



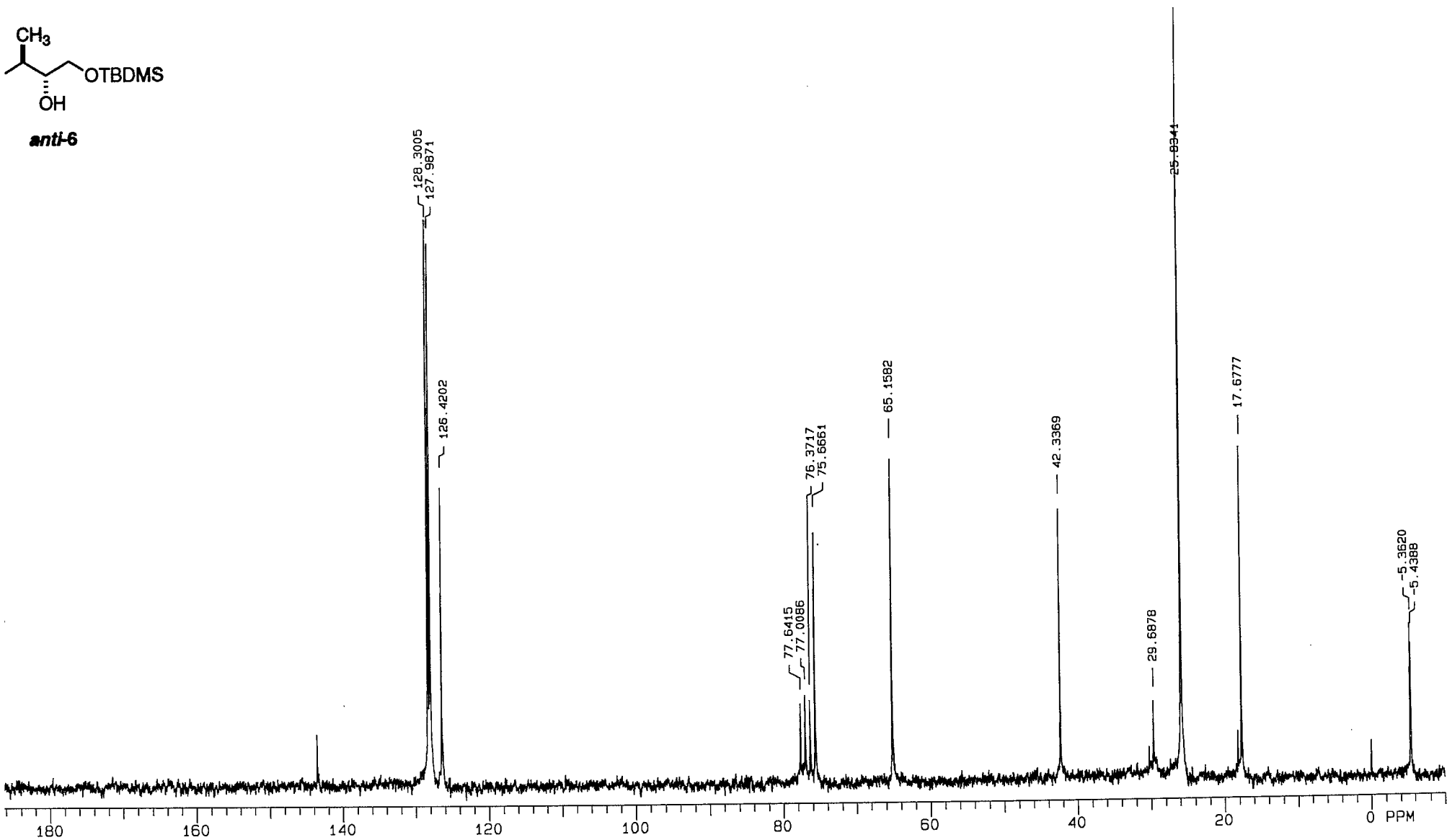
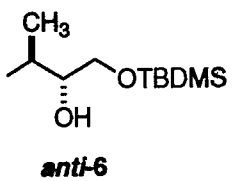


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14002.5	0	YYY	20.0	2.000	---	---	---	NEI
1.004	0.200	S	10000	10057.9	-20.0	---	---	CHIRAL-000 13C OBSERVE
35.0	2000	20.0	1.0	---	---	---	CDCl3	

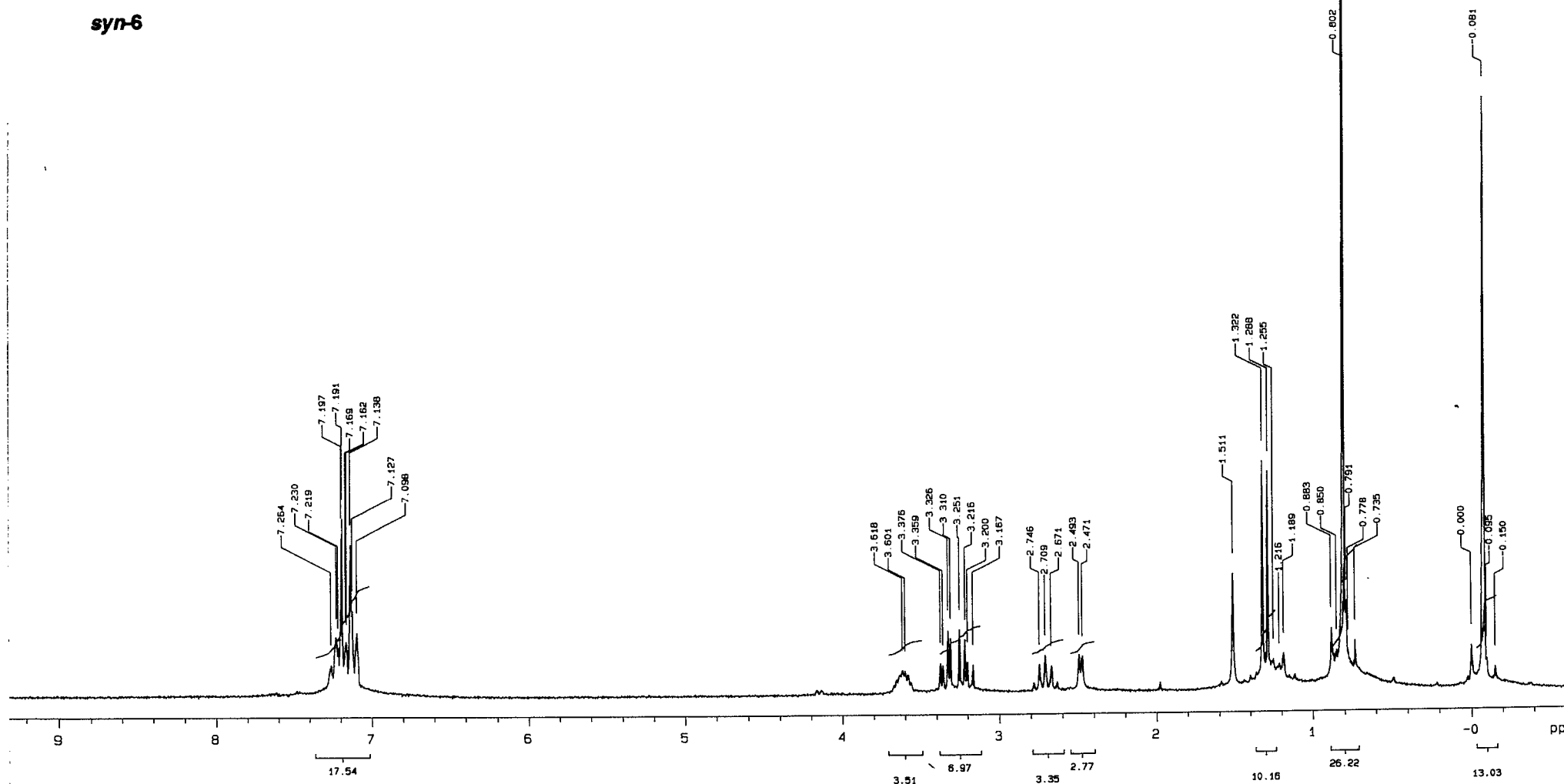
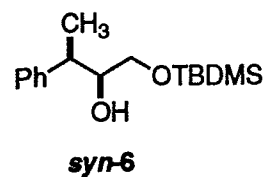
FROM QUALITY ORIGINAL



PAAAC
05-16-9
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GENA 20



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14992.5	0	YYY	20	2.000	---	---		MARR	05-17-94
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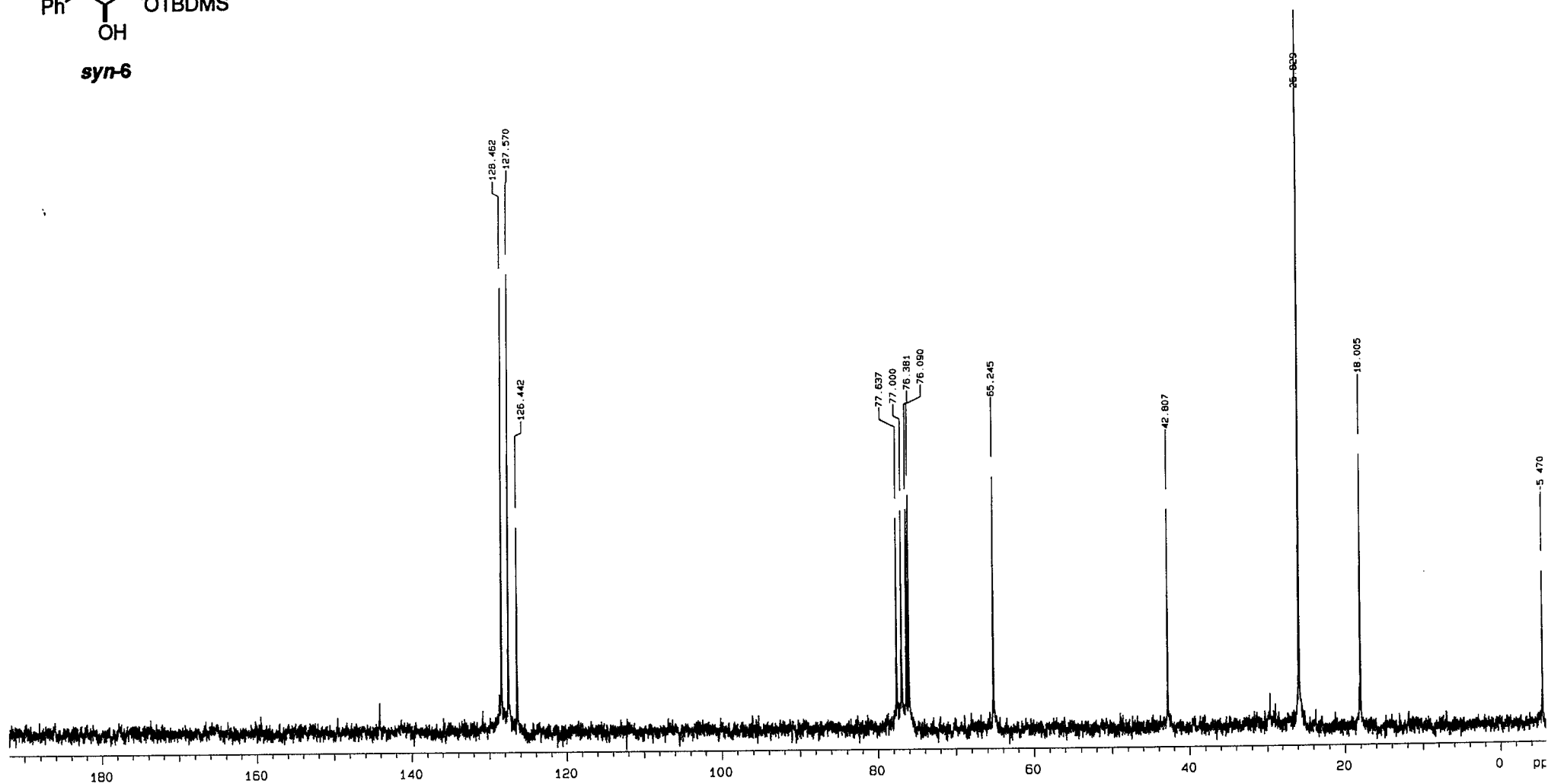
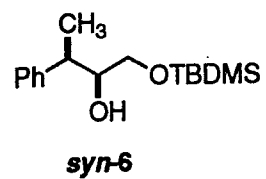


PULSE SEQUENCE
Pulse 46.6 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
32 repetitions

OBSERVE H1. 199.9736437

DATA PROCESSING
FT size 16384

PRIM MIREIA
usuari: are
fitxer: prim01
fecha: 11-16-95
prim01.H1
Solvent: cdcl3
Ambient temperature
Sample #11. user: mester



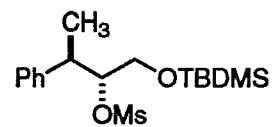
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
5000 repetitions

OBSERVE C13, 50.2837501
DECOUPLE H1, 199.9750061
Power 30 dB
continuously on

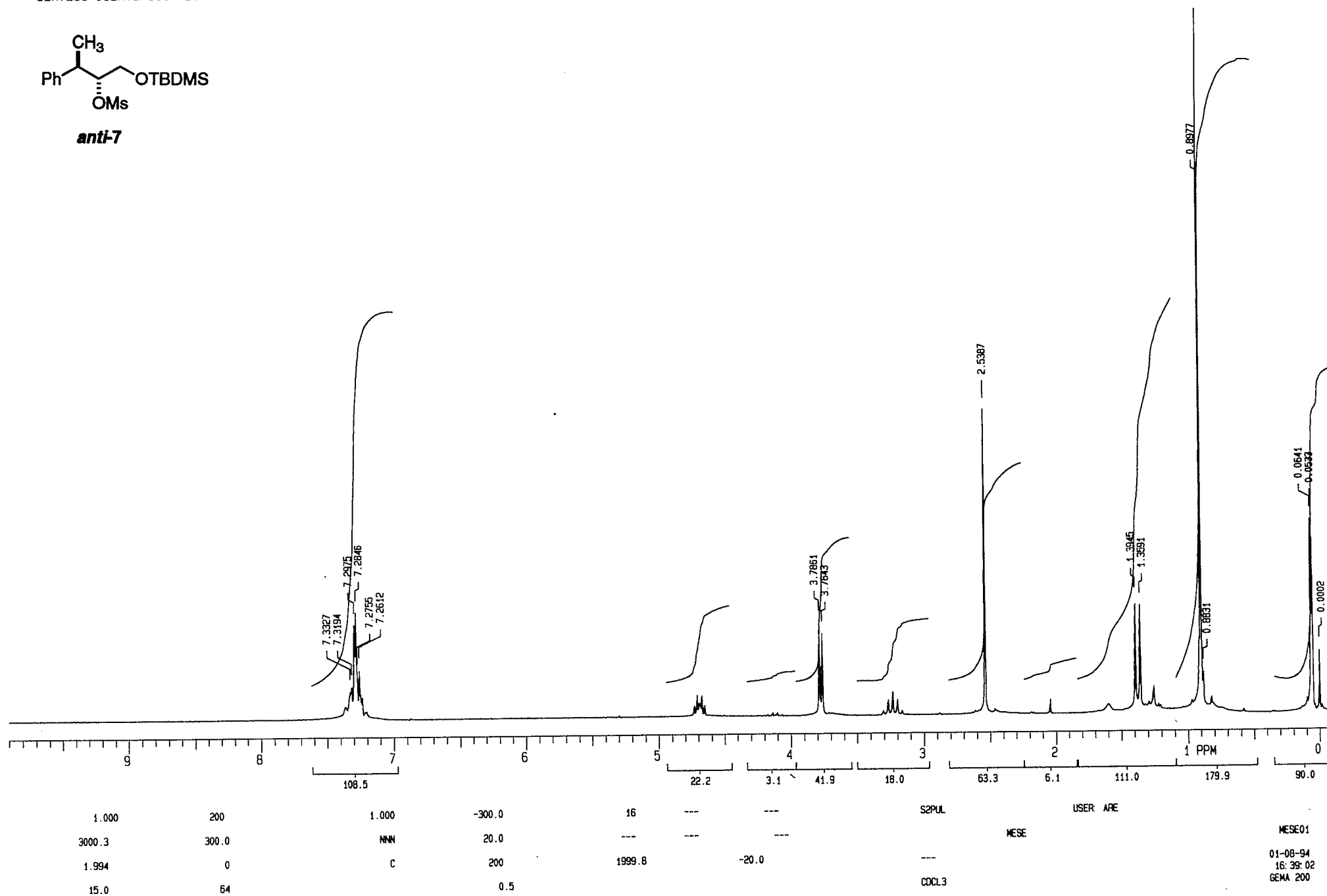
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

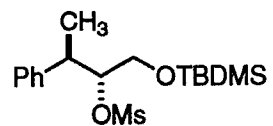
ALCO MIREIA

usuario: are
fitxero: /alco0
fecha de realizacion del
espectro:
Alco Mireia

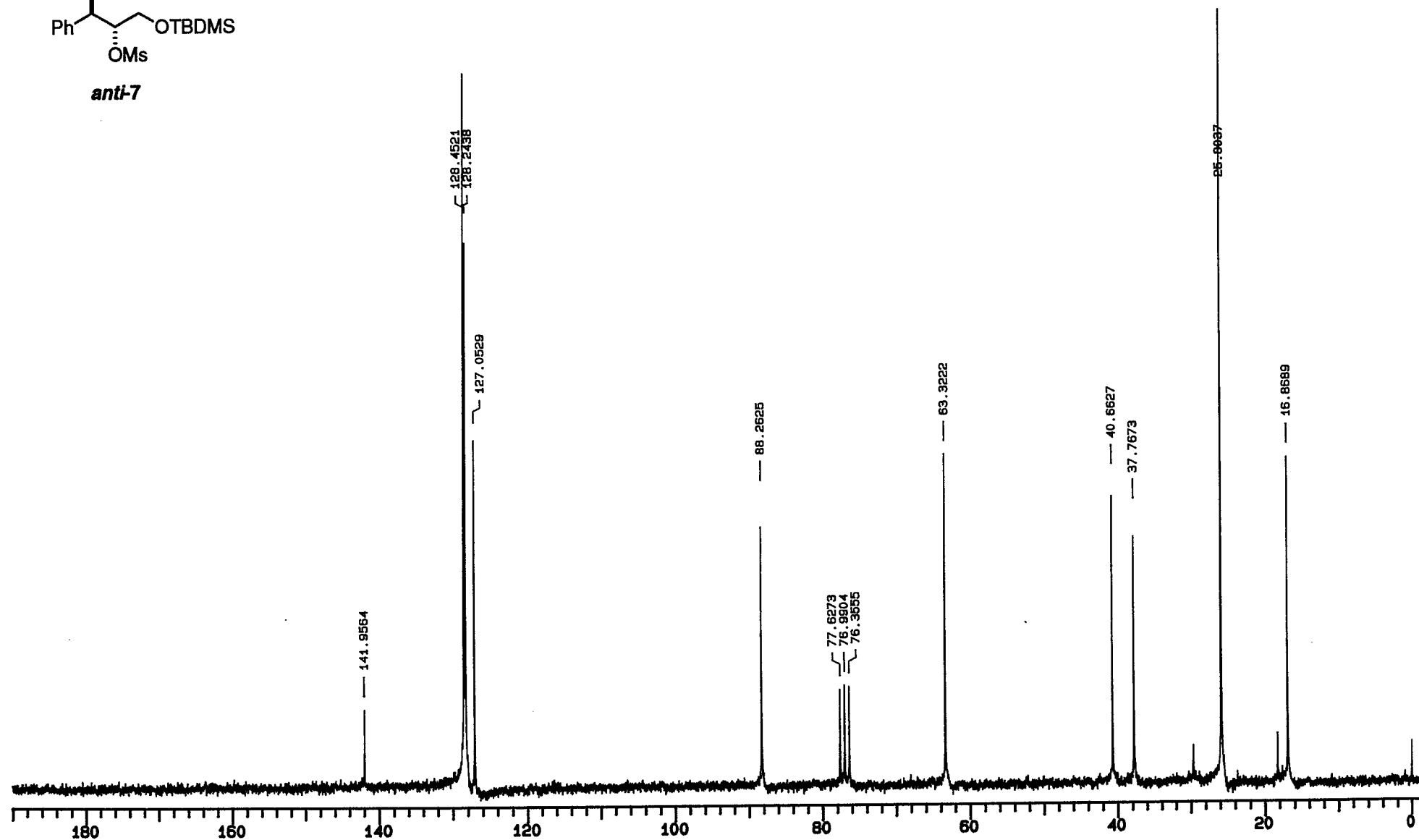


anti-7

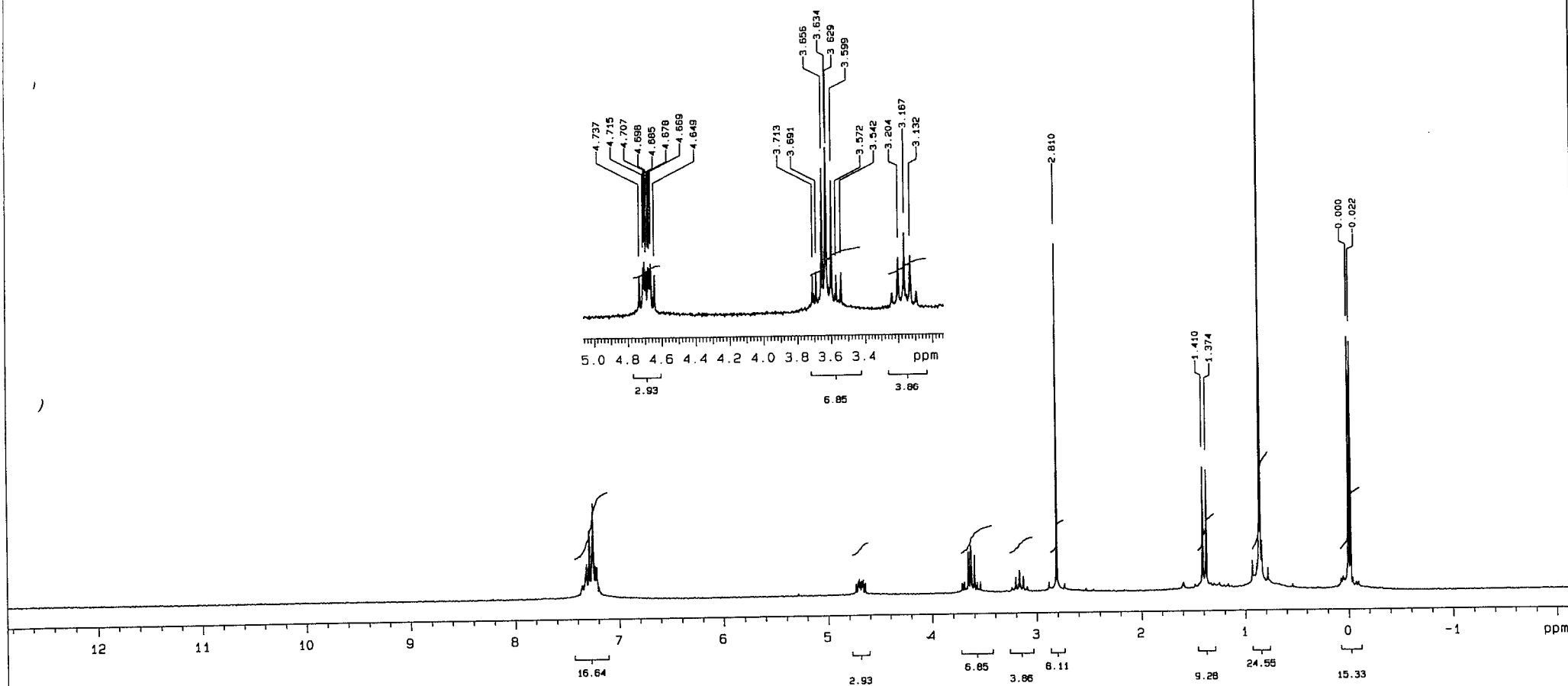
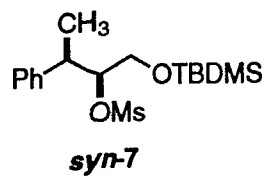




anti-7



13.000	50	1.000	-300.0	32	---	---	32PUL	
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15.0	2500	29.0	1.0				CDCL3	VX

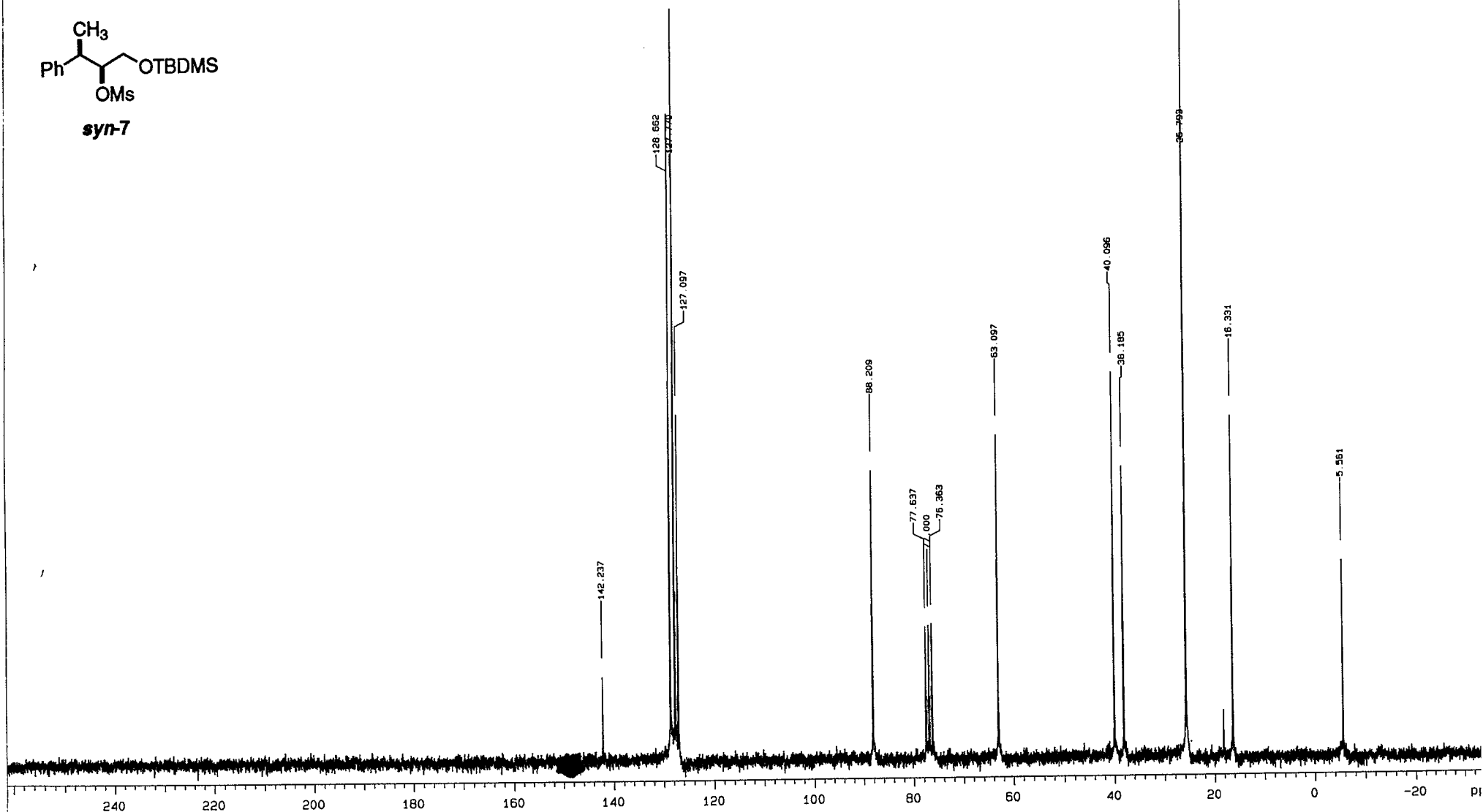
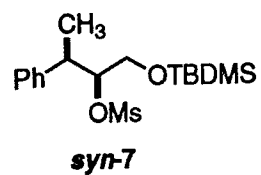


PULSE SEQUENCE
Pulse 15.0 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
16 repetitions

OBSERVE H1, 199.9739367

DATA PROCESSING
FT size 16384

MESILAT MIREIA
GEMINI-200
usuario: are
fichero: mes101
fecha: 11-21-95
mes101.H1
Solvent: cdc13
Ambient temperature



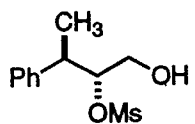
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
2500 repetitions

OBSERVE C13, 50.2837519
DECUPLE H1, 199.9750061
Power 30 dB
continuously on

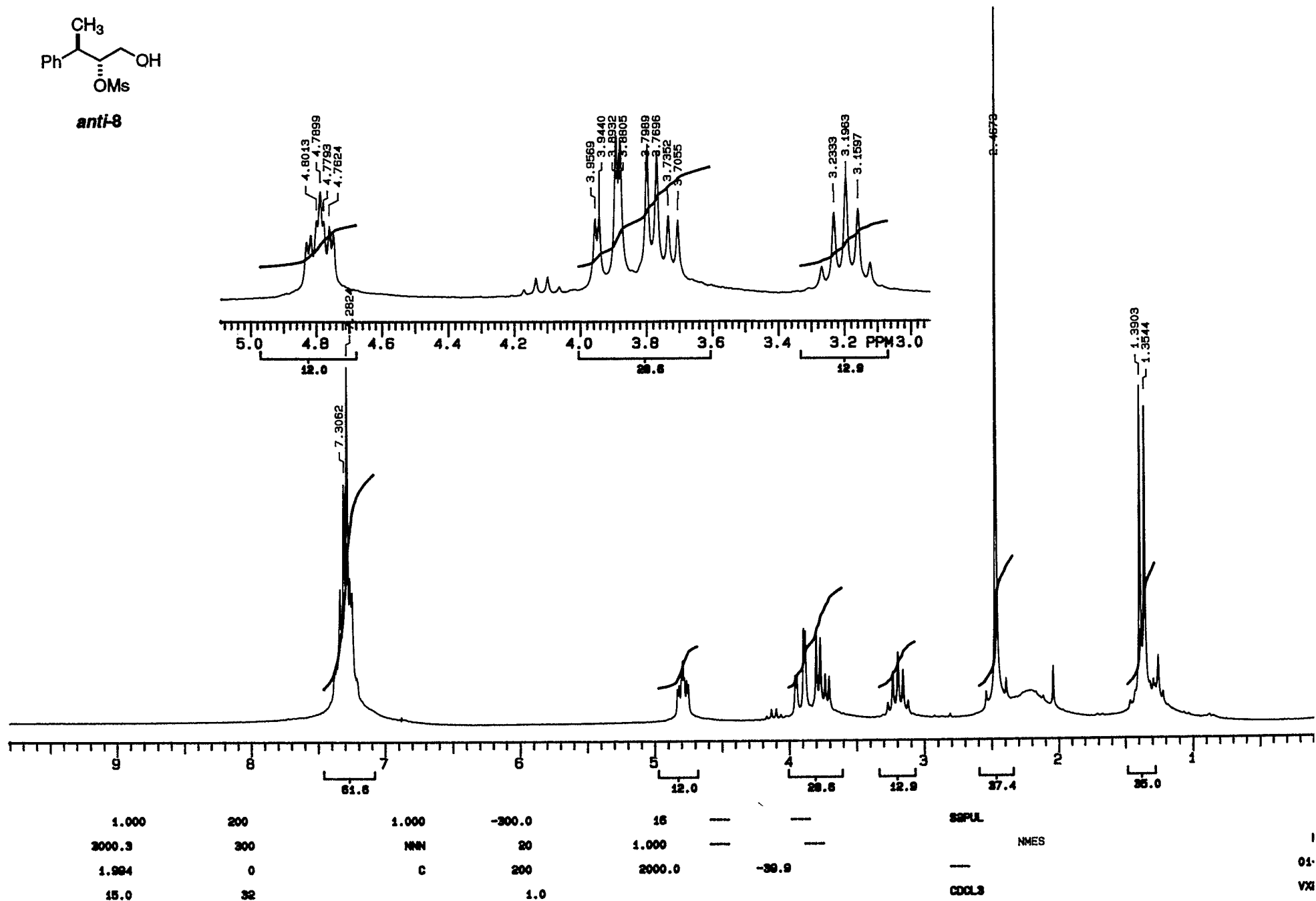
DATA PROCESSING
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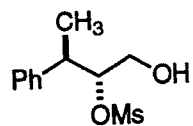
MESILAT MIREIA

usuário: are
fichero: /mes10
fecha de realization del
espectro:
11/02/2006

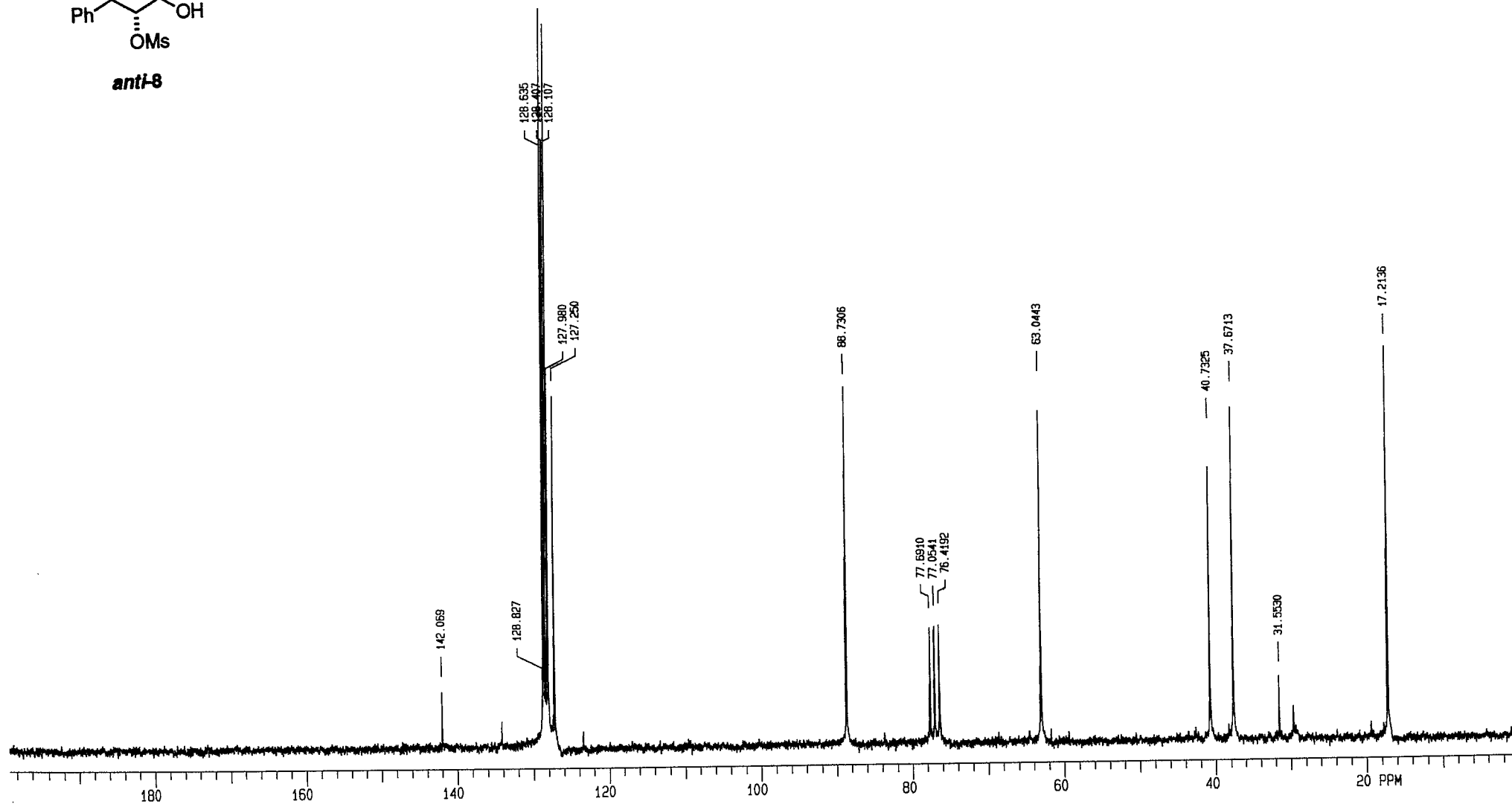


anti-8





anti-8



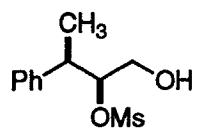
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32	---	---
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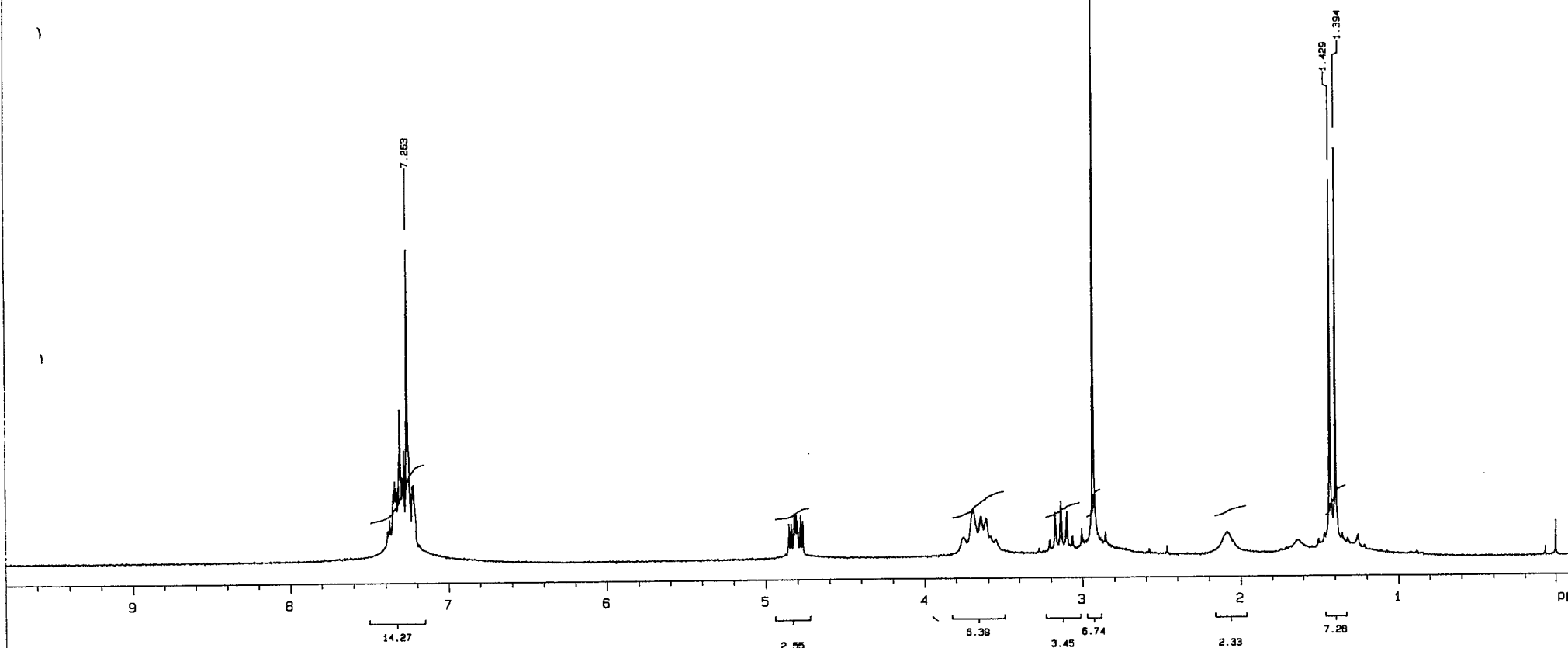
S2PUL
COCL3

USER: ARE
***S
GEMINI-200 13C OBSERVE

***S02
01-04-94
00:46:20
GEMA 200



syn-8

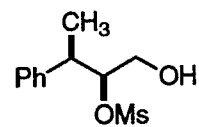


PULSE SEQUENCE
Pulse 48.6 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
32 repetitions

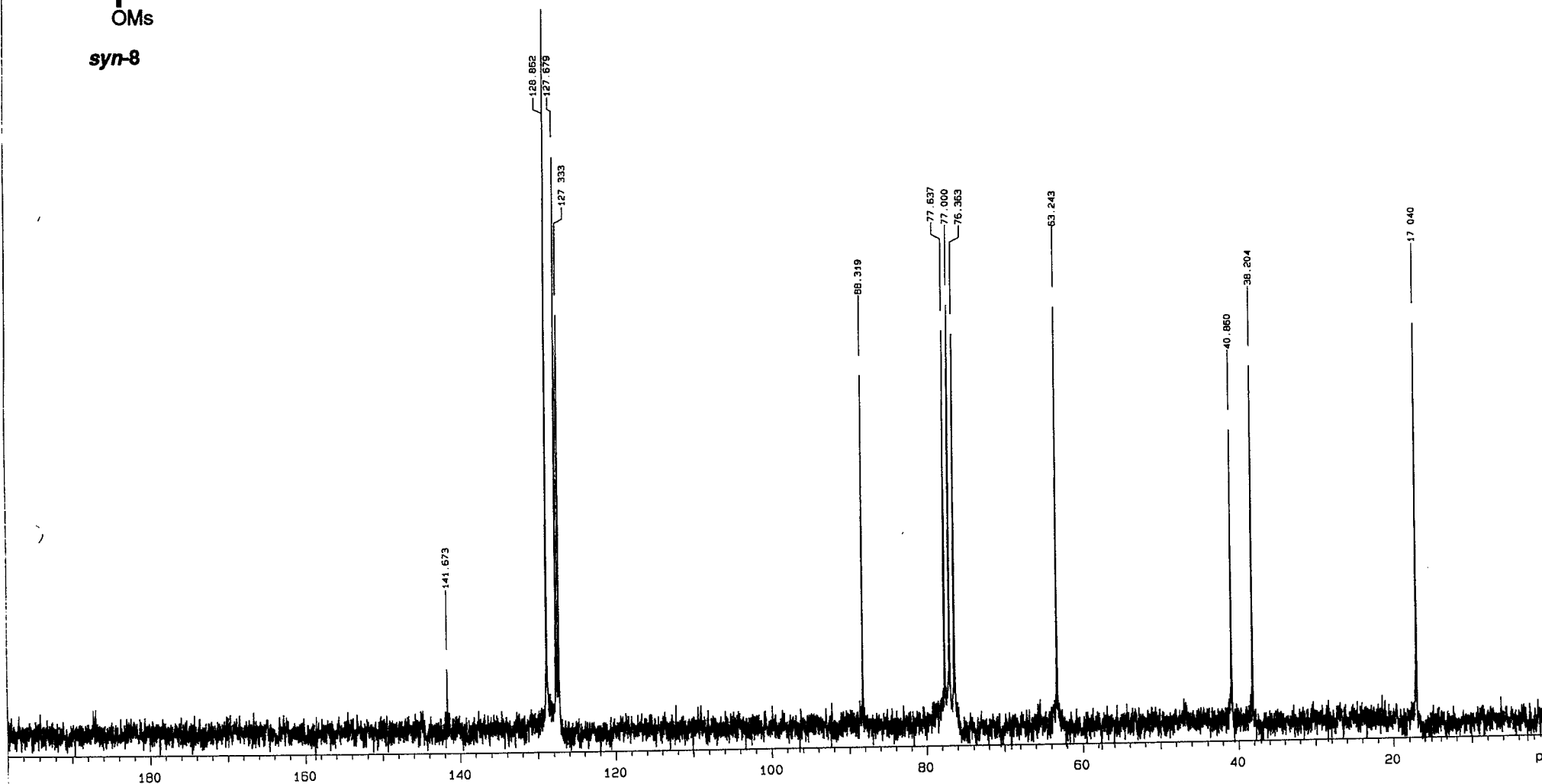
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DATA PROCESSING
FT size 16384

BBBM MIREIA
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fichero: bbbm01
fecha: 11-24-95
bbbm01.H1
Solvent: cdcl3
Ambient temperature
Sample #49 user: mster



syn-8



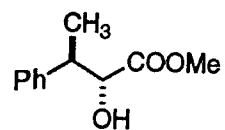
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
5000 repetitions

OBSERVE C13, 50.2837510
DECOUPLE H1, 199.9750051
Power 30 dB
continuously on

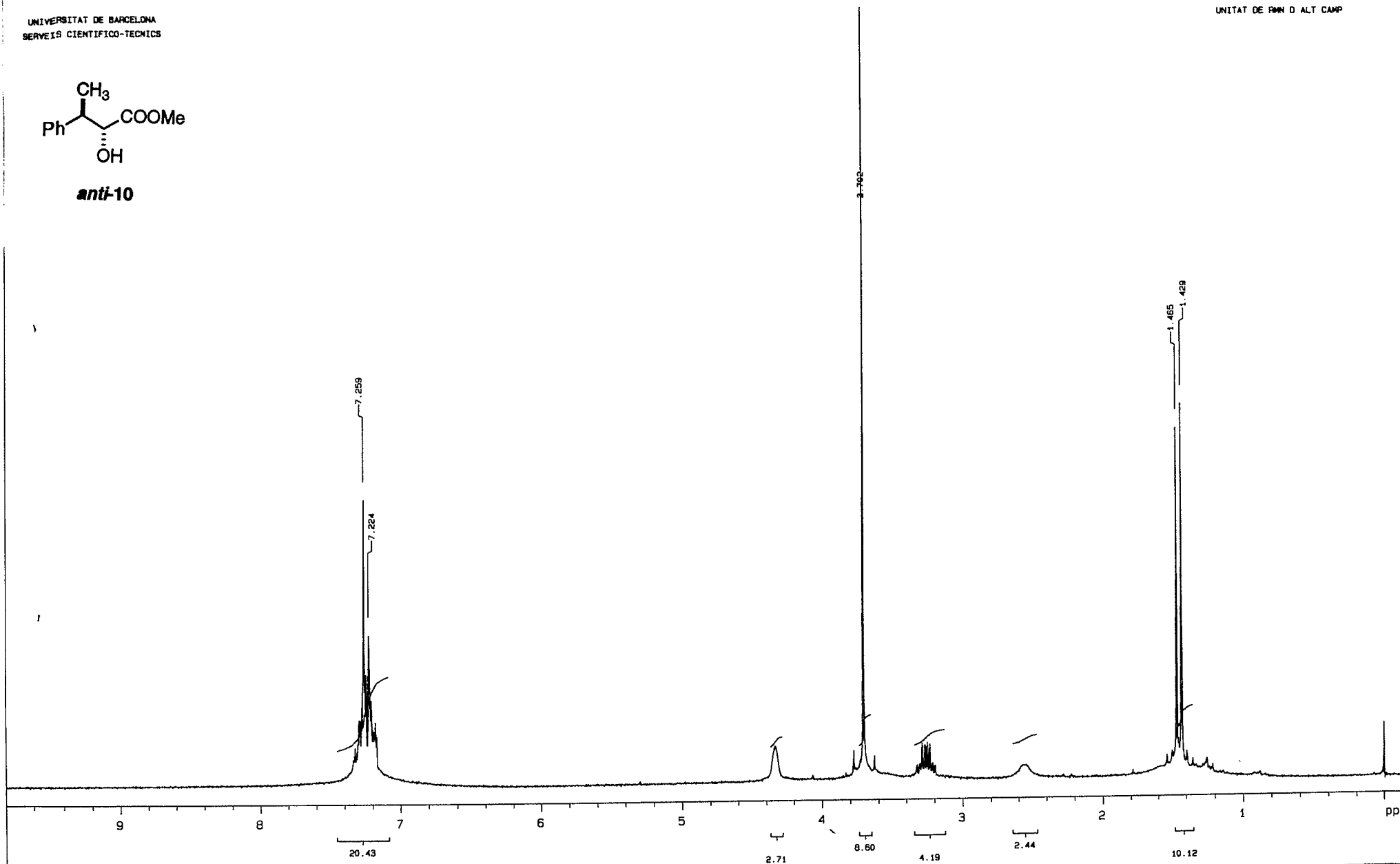
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

DEES MIREIA

usuario: are
fitxero: /dees0
fecha de realizacion del
espectro:
11/02/2005



anti-10

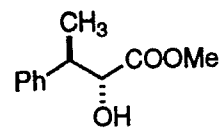


PULSE SEQUENCE
Pulse 45.6 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
32 repetitions

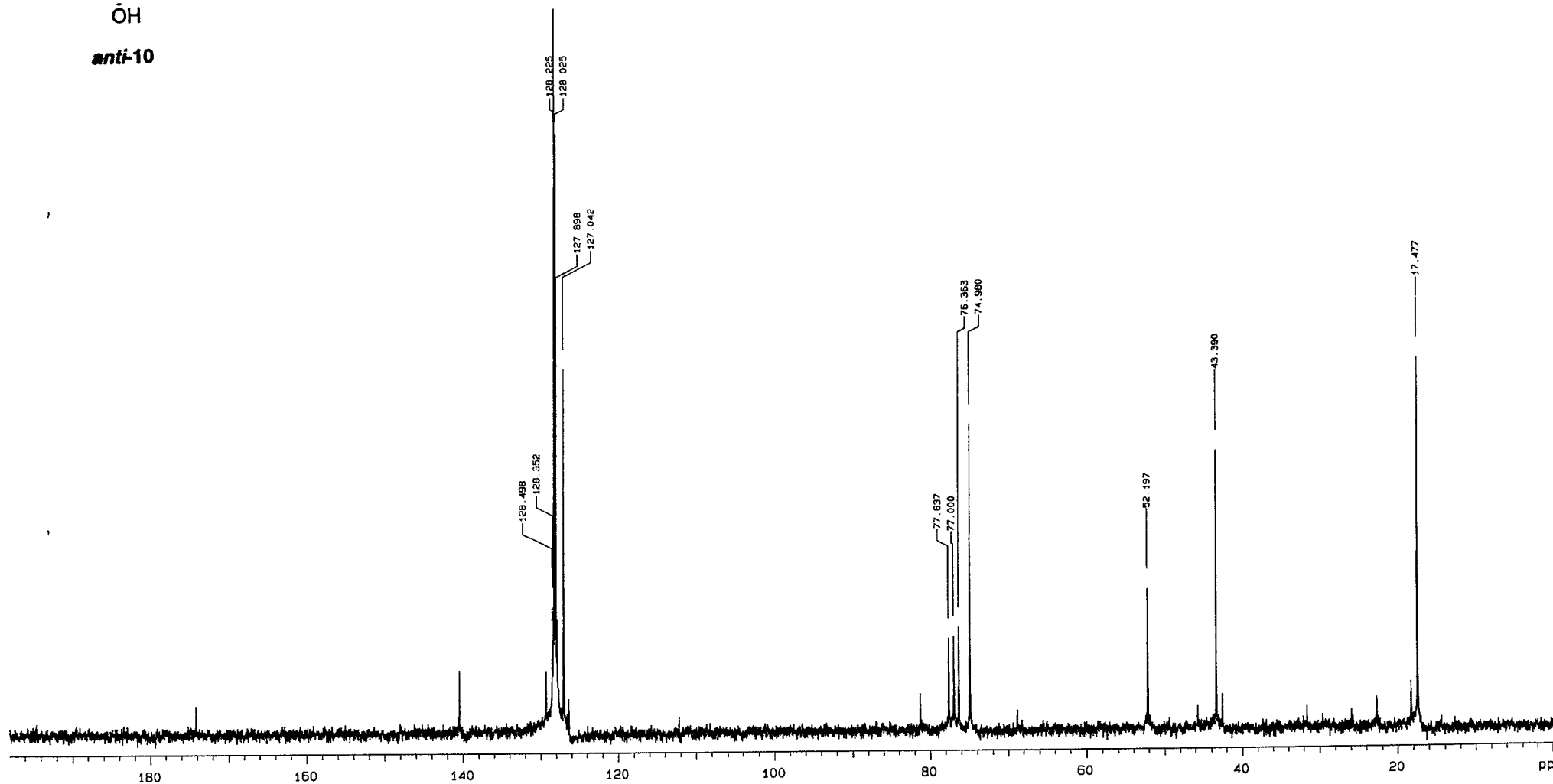
OBSERVE H1, 199.9736301

DATA PROCESSING
FT size 16384

PRPE MIREIA
usuari: are
fichero: prpe01
fecha: 12-14-95
prpe01.H1
Solvent: cdc13
Ambient temperature
Sample #17, user: mester



anti-10



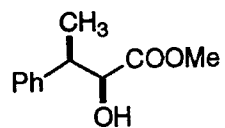
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
2500 repetitions

OBSERVE C13. 50.2637529
DECOUPLE H1. 199.9750061
Power 30 dB
continuously on

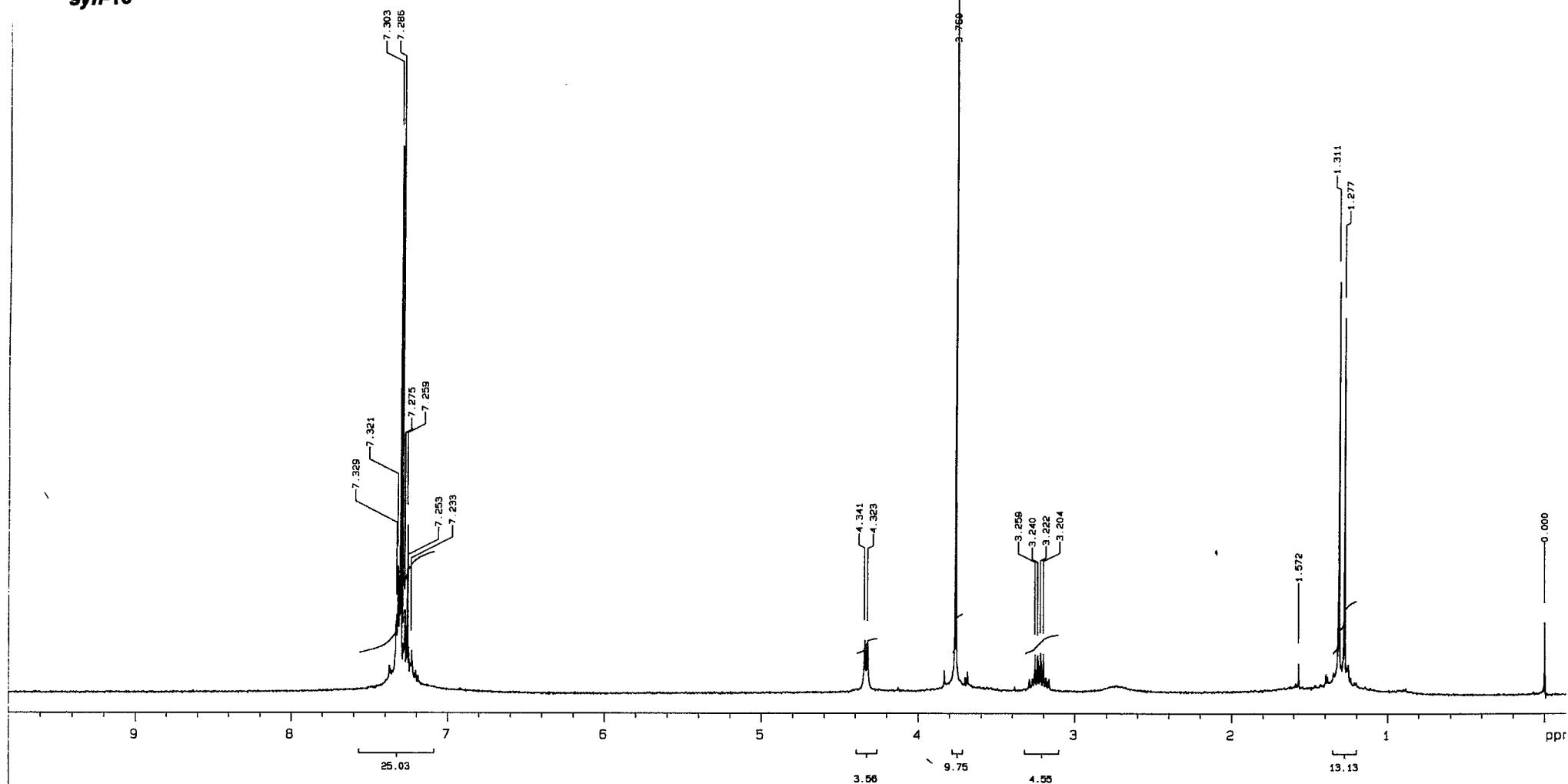
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

OBER MIREIA

usuari: are
fitxer: /ober0
data de realitzaci6 del
espectro:
data de recepci6



syn-10

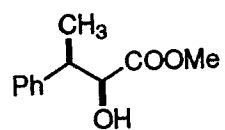


PULSE SEQUENCE
Pulse 46.6 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
32 repetitions

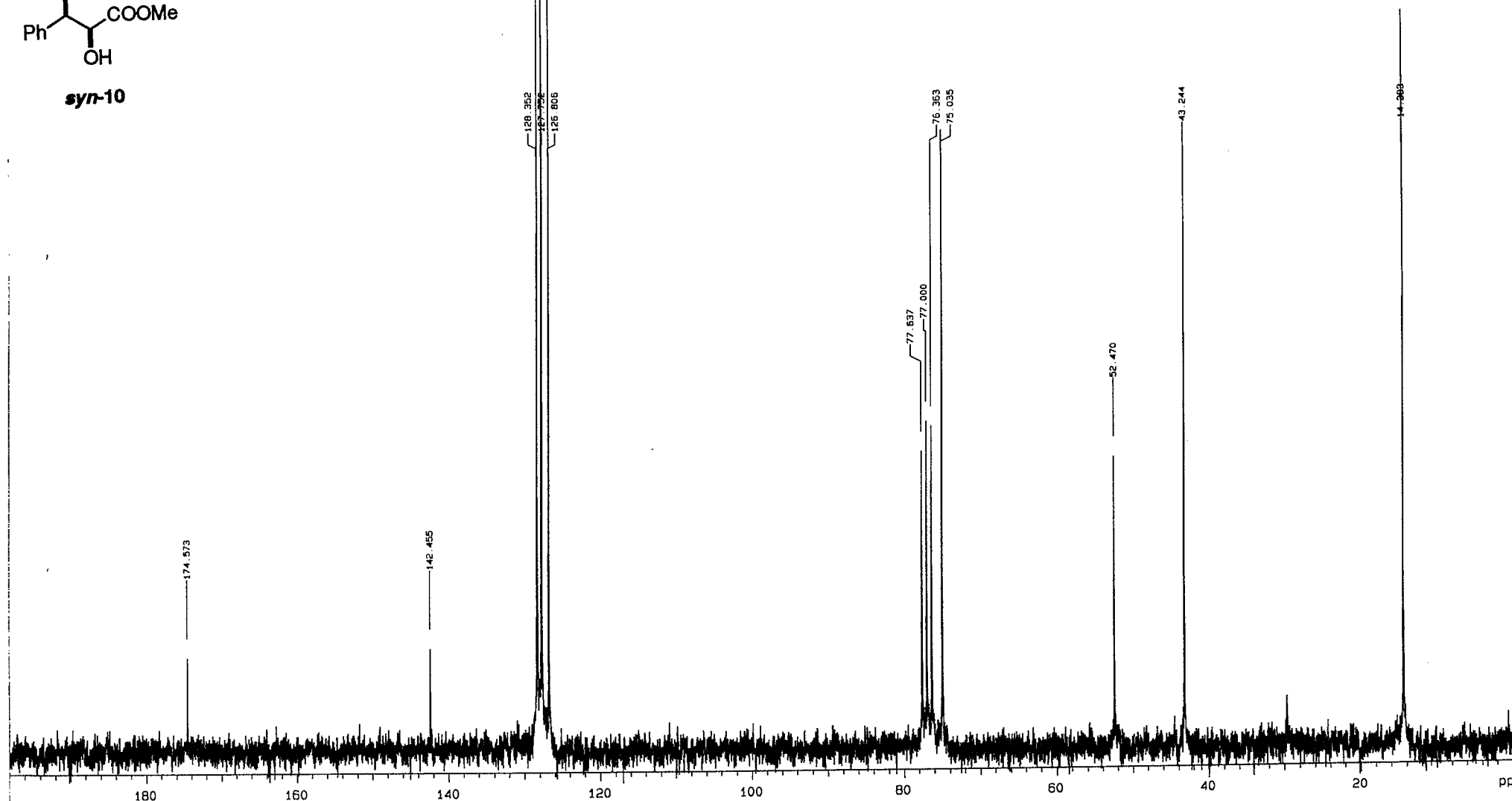
OBSERVE H1, 199.9736301

DATA PROCESSING
FT size 15384

SAPO MIREIA
usuario: are
archivo: sapo01
fecha: 12-05-95
#sapo01.H1
Solvent: cdcl3
Ambient temperature
Sample #20, user master



syn-10



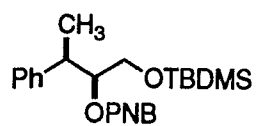
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
2500 repetitions

OBSERVE C13, 50.2837519
DECOUPLE H1, 199.9750061
Power 30 dB
continuously on

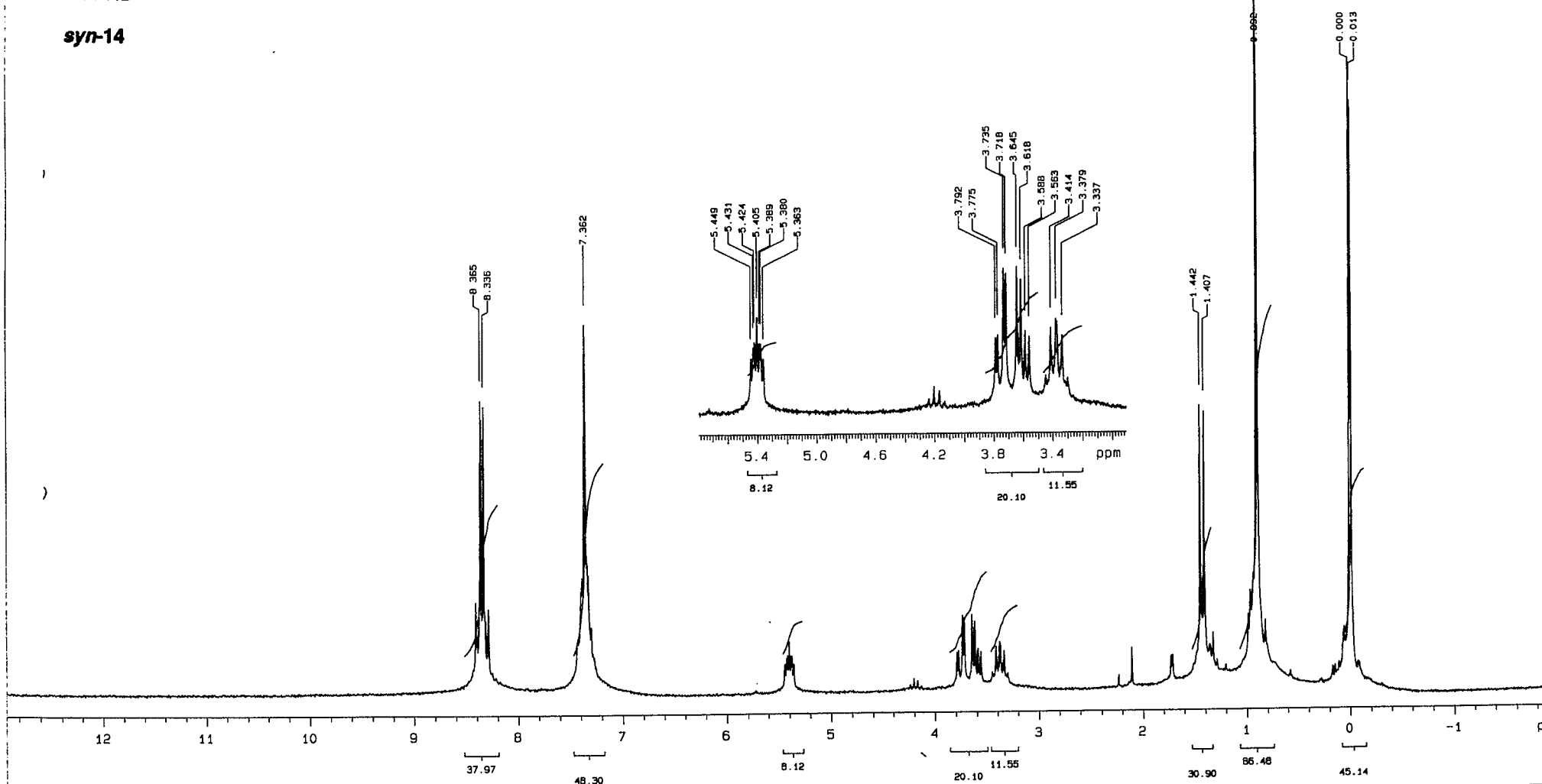
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

SAAP MIRIEA

usuari: arc
fichero: /saap0
fecha de realizacion del
espectro:
12-05-98



syn-14

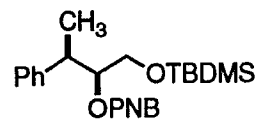


PULSE SEQUENCE
Pulse 15.0 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
16 repetitions

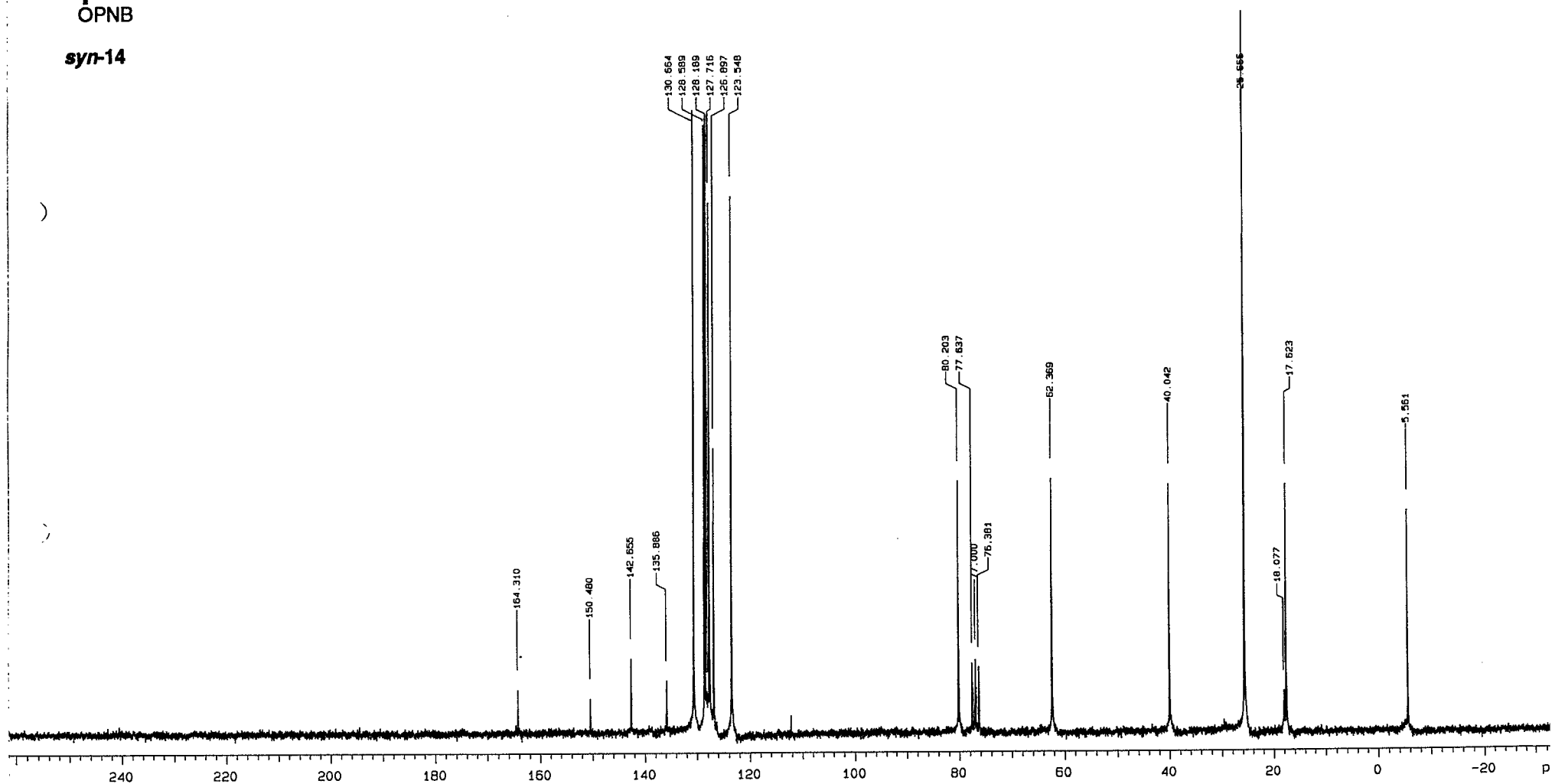
OBSERVE M1, 199.9739224

DATA PROCESSING
FT size 16384

MITS MIREIA
GEMINI-200
usuario: are
fichero: mits01
fecha: 11-14-95
misa01.H1
Solvent: cdc13
Ambient temperature



syn-14



```

PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14992.5 Hz
2500 repetitions

```

```
OBSERVE C13, 50.2837519
DECOUPLE H1, 199.9750061
Power 30 dB
continuously on
```

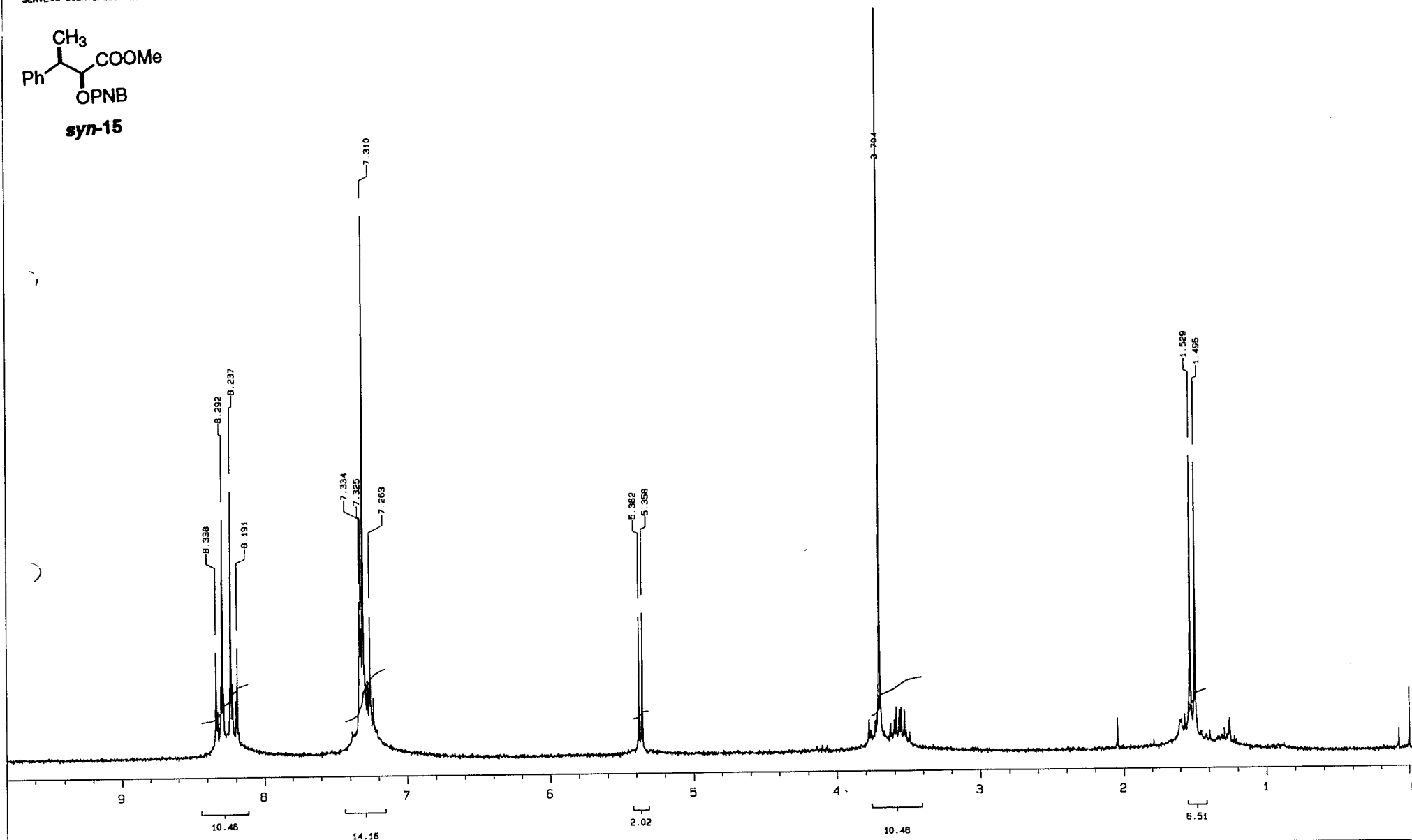
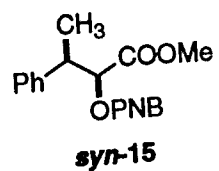
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

MITO MIREIA

```

usuario: are
fichero: /mits0
fecha de realizacion del
espectro:
11/11/95

```

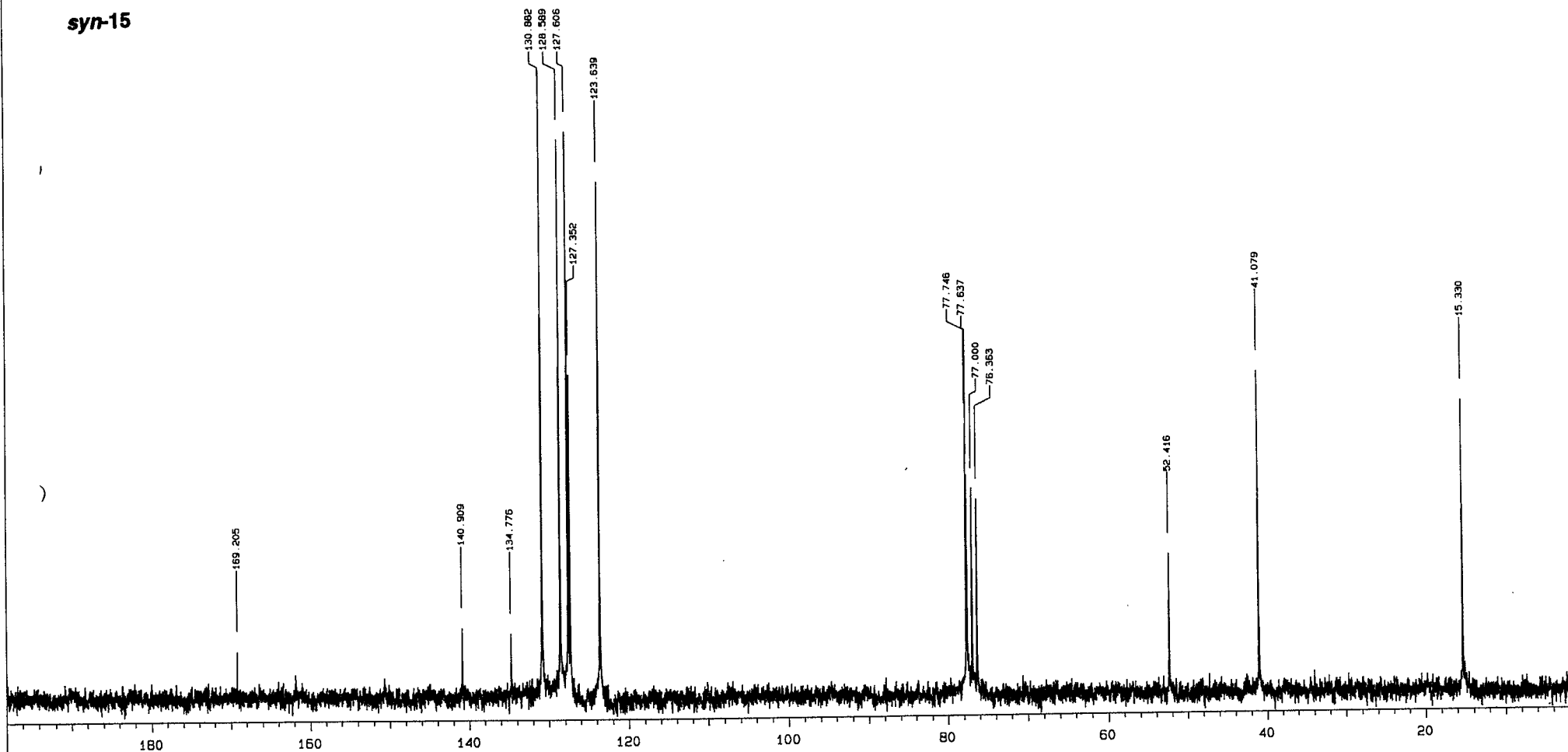
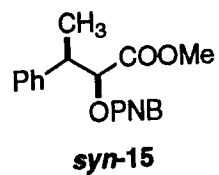



PULSE SEQUENCE
Pulse 15.0 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
16 repetitions

OBSERVE H1, 199.9739349

DATA PROCESSING
FT size 16384

NNNM MIREIA
GEMINI-200
usuário: are
fichero: nnnm01
fecha: 11-26-95
nnnm01.H1
Solvent: cdcl3
Ambient temperature



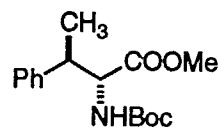
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14892.5 Hz
2500 repetitions

OBSERVE C13, 50.2837510
DECOUPLE H1, 199.9750061
Power 30 dB
continuously on

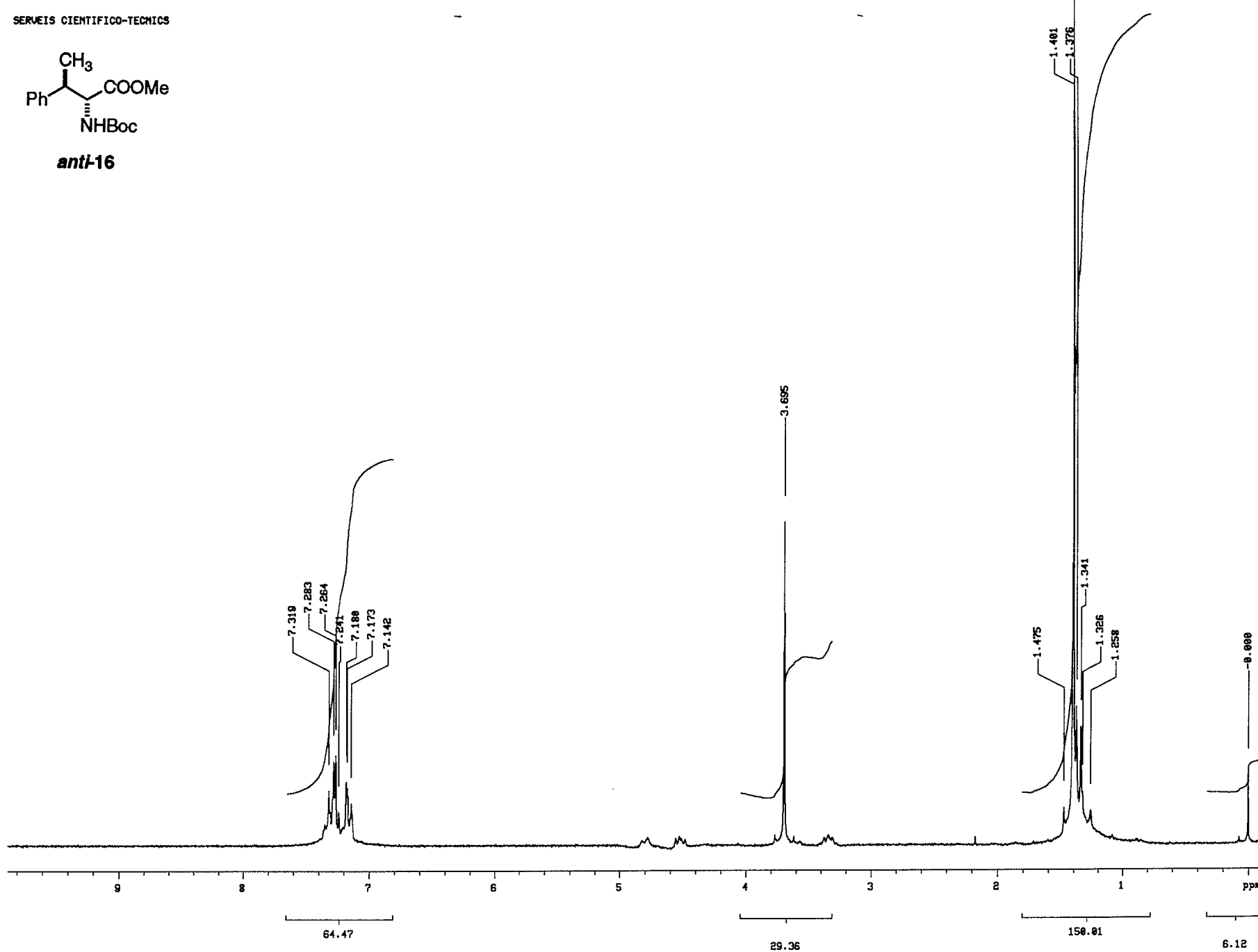
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

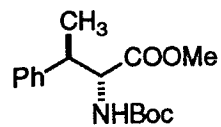
NNNN MIREIA

usuario: are
fichero: /nnmm0
fecha de realizacion del
espectro:
11/02/95

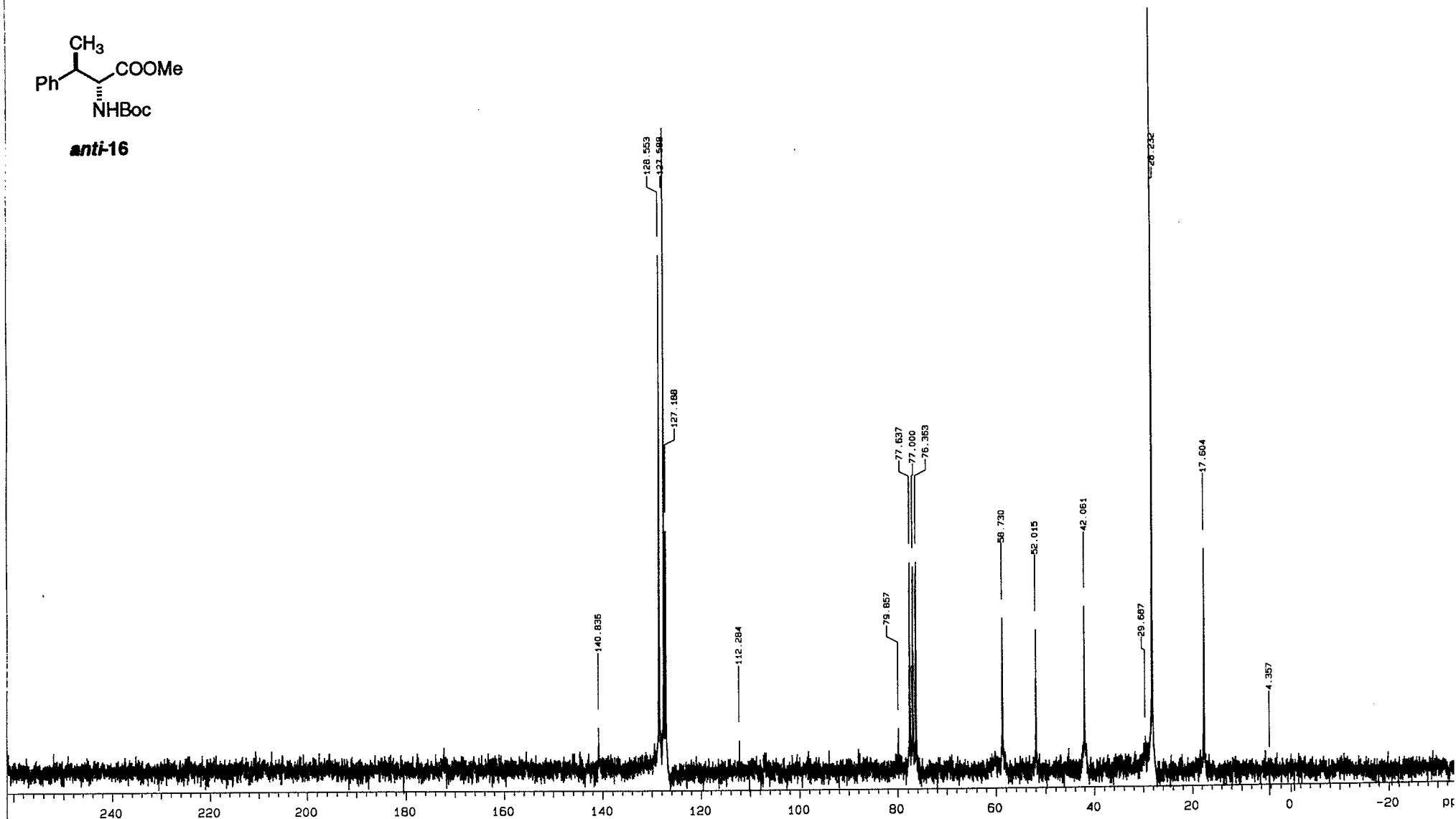


anti-16





anti-16



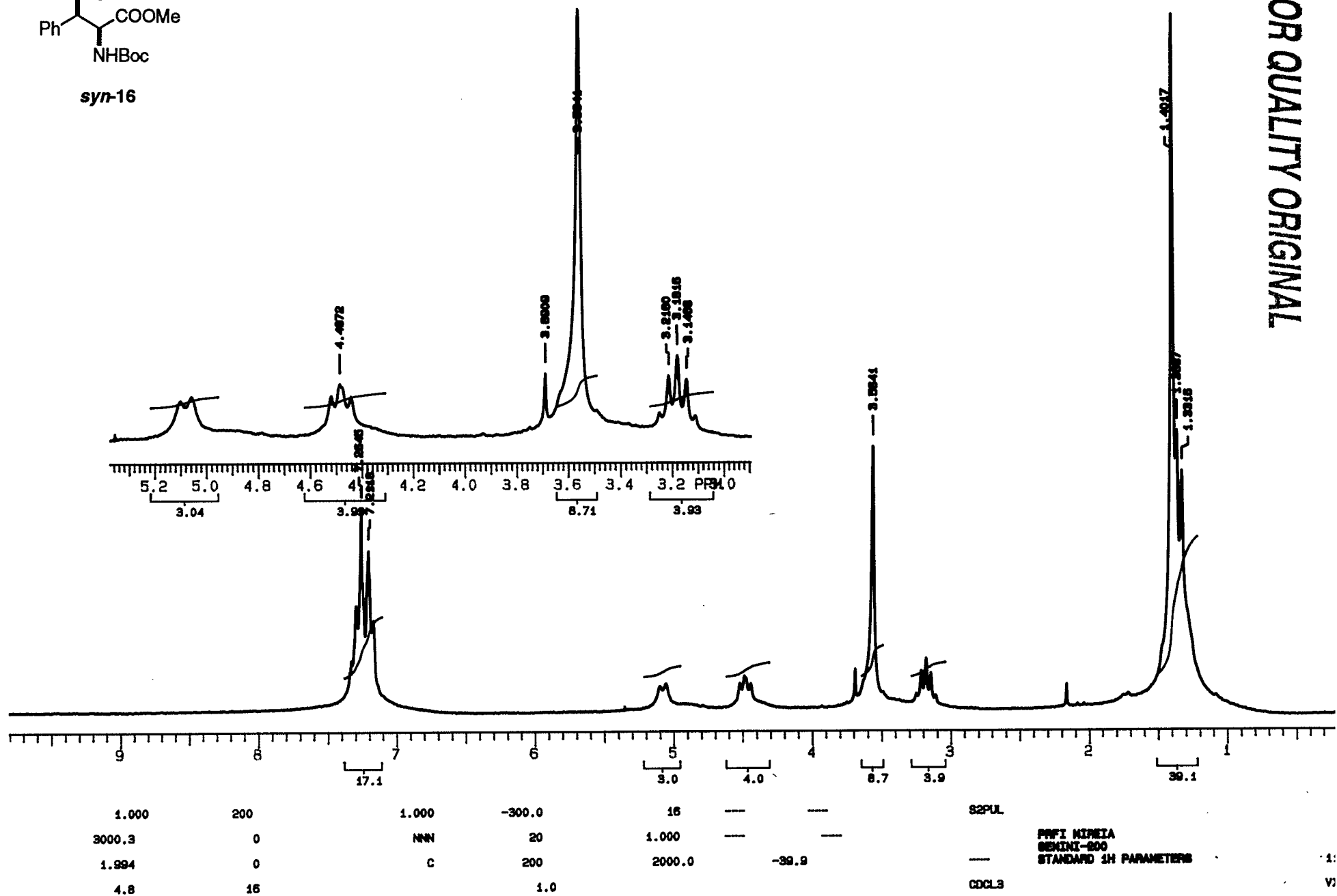
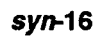
PULSE SEQUENCE
Relax. delay 0.200 sec
Pulse 75.0 degrees
Acq. time 1.001 sec
Width 14882.5 Hz
2500 repetitions

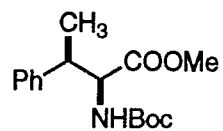
OBSERVE C13, 50.2837510
DECOUPLE H1, 199.9750061
Power 30 dB
continuously on

DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768

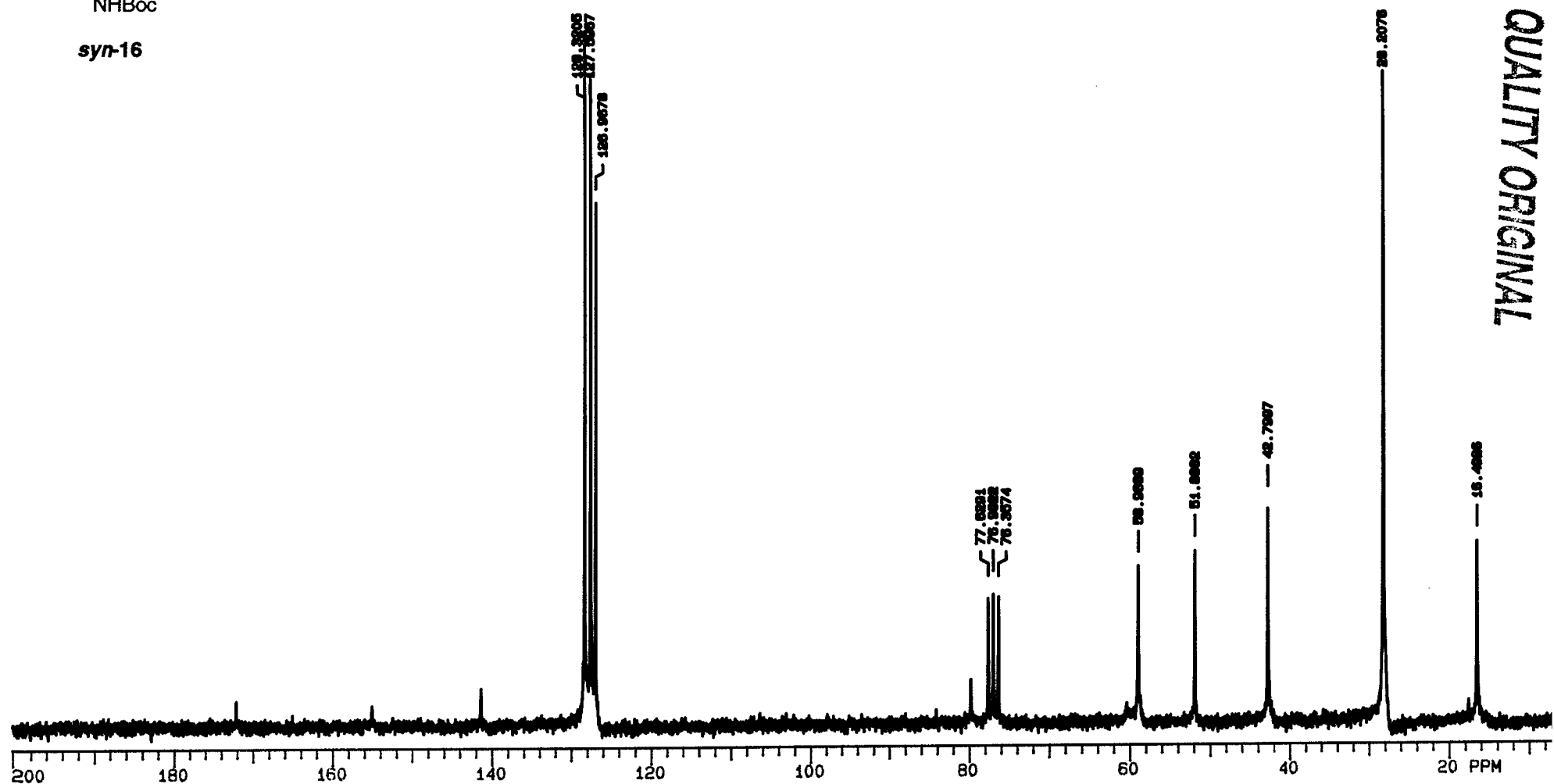
DMET MIREIA

usuario: are
archivo: /dmto
fecha de realizacion del
espectro:
14/12/2006





syn-16



13.000
14992.5
1.001
15.0

50
0
0.200
2500

1.000
YYY
S
29.0

-300.0
20
10500
1.0

32
1.000
10058.1

0

S2PUL
CDCL3

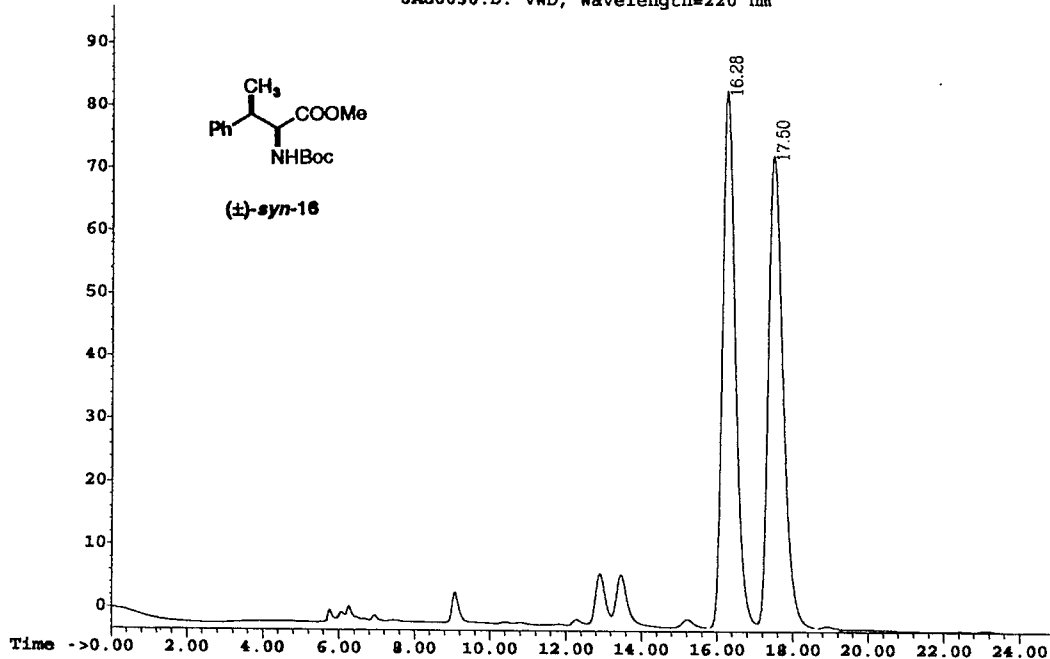
PMFI NIREIA

SEMINI-200 13C OBSERVE

PF
11-1
VXRE

mAU

JAU0030.D: VWD, Wavelength=220 nm

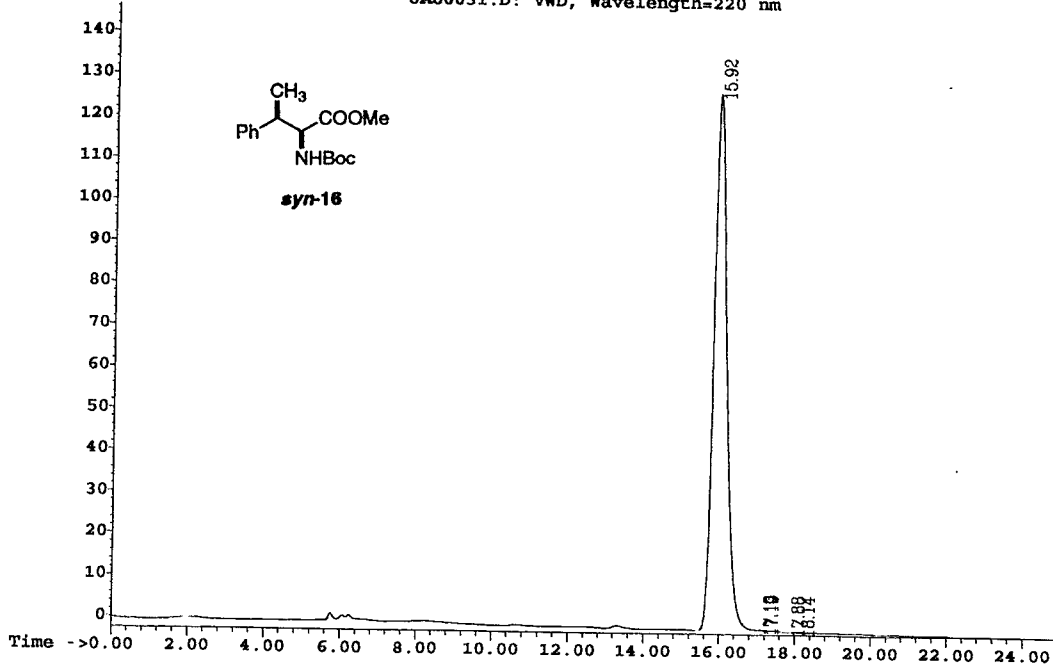


hp 1050

Thu Sep 04 09:43:31 1997

mAU

JAU0031.D: VWD, Wavelength=220 nm

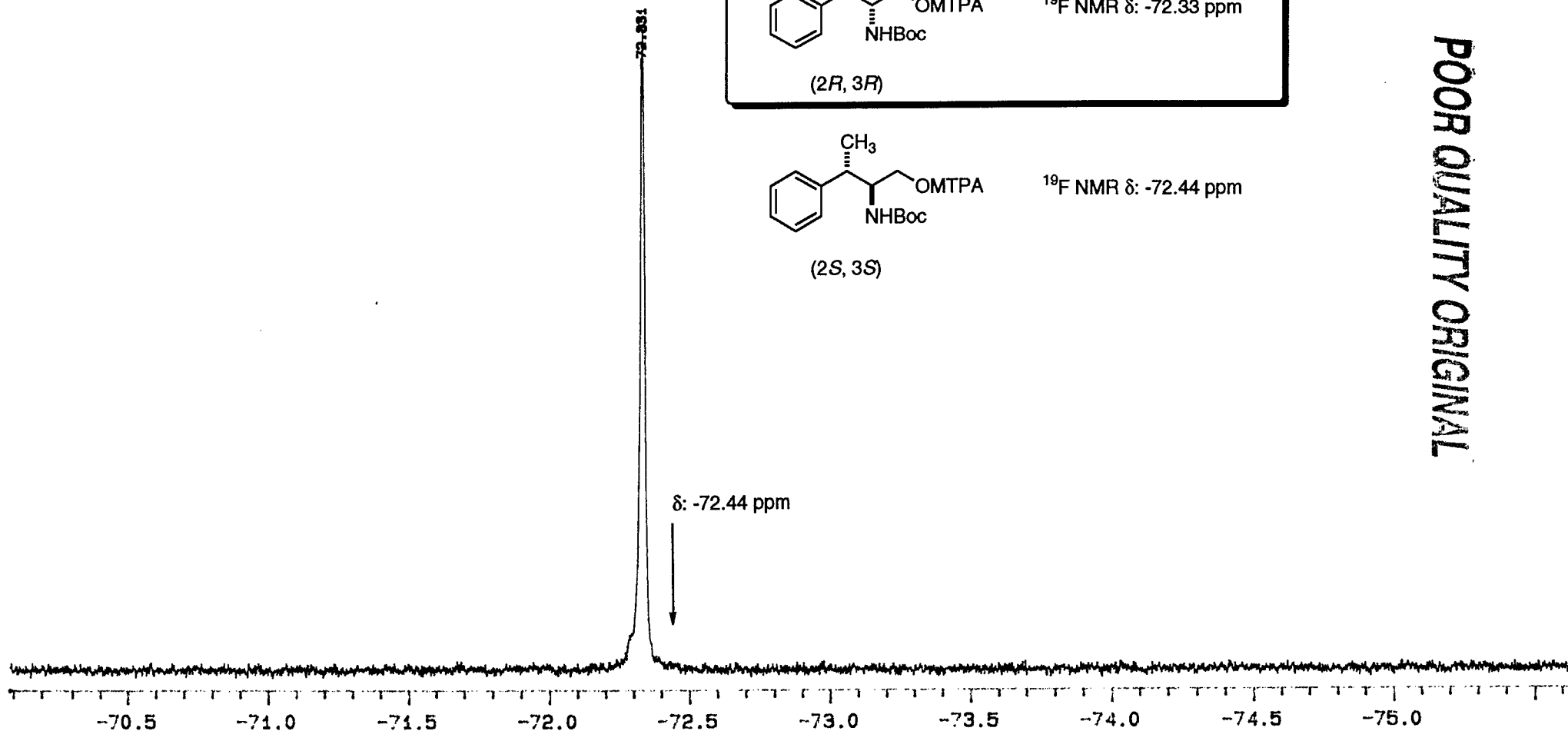
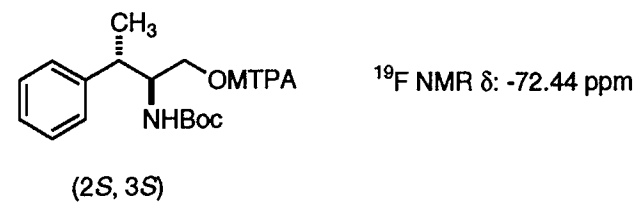
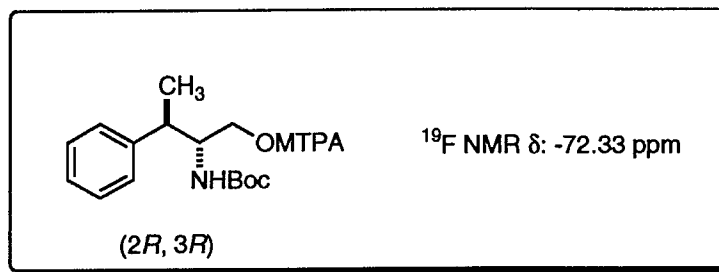


VWD, Wavelength=220 nm

PK#	Ret Time	Area	Height	Type	Width	Area %
1	15.925	3070.322	128.892	VV	0.365	99.4426
2	17.130	3.037	0.425	VV	0.095	0.0984
3	17.187	11.267	0.426	VV	0.441	0.3649
4	17.878	1.389	0.166	VV	0.139	0.0450
5	18.144	1.517	0.129	VV	0.196	0.0491

Total area = 3088

POOR QUALITY ORIGINAL



F19	292.2306	H1	0	not used	s2pu1	
8000.0	8000.5	nm	not used	0.300 not used		19F OBSERVE STANDARD PARAMETERS
2.000	4.000	c	200	1006.6	-21286.7	not used
5.0	44	0	30			CDC13