Supporting Information for: A Spontaneous Enzymatically Mediated Dynamic Kinetic Resolution of 8-amino-5,6,7,8-tetrahydroquinoline

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Contents:

S2: General experimental procedures for enzymatic resolution experiments

S3-S5: Chiral GC of racemic **1** (reagent)

S6: ^{1}H NMR of isolated amine (*R*)-**1**

S7-S9: Chiral GC of (*R*)-**1** isolated from acetamide **2** (95.36% ee)

S10-S11: GC of isolated (*R*)-**1** (99.27% pure)

S12: ^{1}H NMR of acetamide **2**.

S13: ^{1}H NMR of ketone **3.**

S14-S16: ^{1}H NMR (d_8 toluene) formation of enamine **4** from ketone **3** and amine **1**

S17-S19: ^{1}H NMR ($CDCl_3$) of enamine **4**

Experimental Section:

General Procedure for Resolution Reaction: To a solution of the amine (**1**) in toluene (0.5M) was added powdered 4Å molecular sieves (50 wt% relative to amine), immobilized *Candida antarctica* Lipase B (Novozym 435: 10-30 wt% relative to amine), ethyl acetate (400 wt% relative to amine). The mixture was then stirred and heated to 50°C under nitrogen. Upon completion, if product isolation was desired, the reaction was cooled to rt, and then filtered through a sintered glass funnel. The filter cake was washed with methanol [to solubilize the acetamide (**2**)], and the filtrate was then concentrated in vacuo. The residue was then purified by silica gel column chromatography, typically using 10% methanol in dichoromethane as an eluent. The enantiomeric excess of the amine was determined by chiral GC by comparison to the retention times of independently prepared enantiomers.

Resolution of 1 (no ketone): Following the general procedure, 5,6,7,8-tetrahydroquinoline (**1**: 1.5 g, 10.1 mmol), toluene (20 mL), ethyl acetate (6 mL), powdered 4Å molecular sieves (750 mg) and Novozym 435 (300 mg) were stirred for 48 hours at 50°C, monitored by GC.

Resolution of 1 (with ketone): Following the general procedure, 5,6,7,8-tetrahydroquinoline (**1**: 1.5g, 10.1 mmol), toluene (20 mL), ethyl acetate (6 mL), powdered 4Å molecular sieves (750 mg), Novozym 435 (300 mg) and ketone (**3**, 74 mg, 0.5 mmol) were stirred at 50°C for 48 hours. The acetamide (*R*)-N-(5,6,7,8-tetrahydroquinolin-8-yl)acetamide [(*R*)-**2**] was isolated in a 78% yield (1.49 g). The acetamide could be hydrolyzed to the (*R*)-amine [(*R*)-**1**] as per established methods[3] in 81% yield, which was measured by chiral GC as 95.4% *ee* (99.3% GC purity).

Analytical Report
Chiral Purity by HPLC

AnorMED

Report By: t.ciofani
Report Generated: 18-Feb-04 8:30

Sample Information

Requesting Chemist	Sample ID
Crawford, Jason	JC-396-23

RACEMIC (1)
(Reagent)
Chiral GC.

Analytical Information

Request Number	Analytical #	Analyst Name	Lab Book Reference
R040217-14	a040288	Travis Ciofani	TC-389-110

Estimated Enantiomeric Excess (EE)

Enantiomer	% Purity	%EE (positive value)
R-isomer		
Mean	50.36	0.72
S-isomer		
Mean	49.64	-0.72

% Purity: CompoundPurity = (Area / Total_Area) * 100
%EE (positive value): EE = (Area / Total_Area * 100) - (100 - (Area / Total_Area * 100))

S-Isomer Results

Injection #	RT, min.	Peak Area	% Total Area
9	26.739	393.351	49.50
11	26.737	400.176	49.57
13	26.737	406.013	49.85
Average	**26.737**	**399.846**	**49.64**
%RSD	**0.01**	**1.59**	**0.38**

% Total Area: CompoundPurity = (Area / Total Area) * 100

R-Isomer Results

Injection #	RT, min.	Peak Area	% Total Area
9	28.593	401.331	50.50
11	28.591	407.108	50.43
13	28.587	408.397	50.15

Injection #	RT, min.	Peak Area	% Total Area
Average	**28.590**	**405.612**	**50.36**
Overall %RS	**0.01**	**0.93**	**0.37**

% Total Area: CompoundPurity = (Area / Total Area) * 100

Analytical Equipment List

Module	Part Number	Serial Number
Instrument: GC1 6890Plus		
68GC	68GC	US00033151
7673	7673	<not available>

Column Configuration

Column Description	Serial Number	Length, mm.	Diameter, mm
HP-5 5% Phenyl Methyl	HP-5 #1	30.0	320.0
CYCLOSILB	CYCLOSILB#2	30.0	250.0

Solvents Used

Solvent A	Solvent B	Solvent C	Solvent D

Data File C:\HPCHEM\1\DATA\Chemstor\1663201\40288F-4.D Sample Name: a040288

JC-396-23: 9.3mg + 1.8mL CH2Cl2

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Injection Date : 2/17/2004 5:56:49 PM Seq. Line : 1
Sample Name : a040288 Location : Vial 8
Acq. Operator : t.ciofani Inj : 4
Inj Volume : 1 µl

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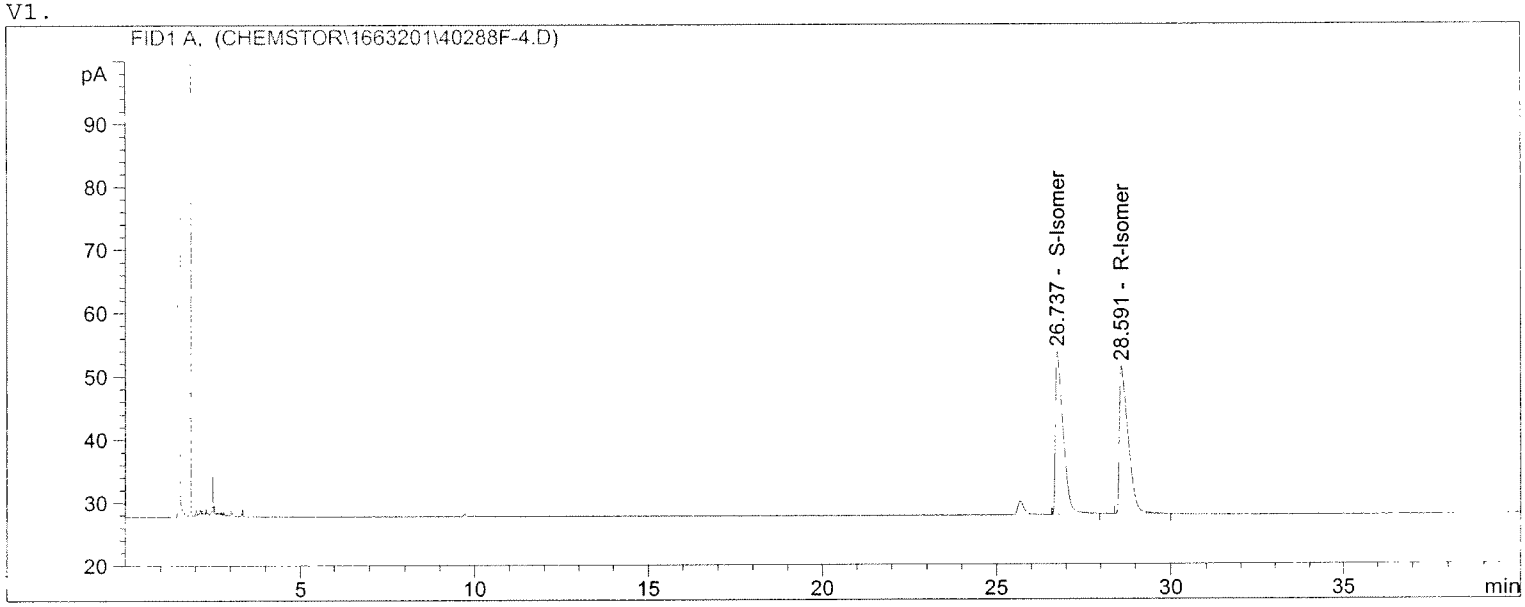
Last changed : 2/9/2004 4:07:33 PM by t.ciofani
Analysis Method : J:\GC\GC1\METHODS\OFFICI~1\AM007V1.M
Last changed : 2/18/2004 8:15:36 AM by t.ciofani
(modified after loading) (Results are from a previously saved Batch)

Chiral Separation of 5,6,7-Tetrahydro-8-amino-quinoline by GC using Cyclosil-B column, AM007.
V1.



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Area Percent Report

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Sorted By : Signal
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Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
1	26.737	PB S	0.2219	400.17551	49.57064	S-Isomer
2	28.591	PP	0.2441	407.10776	50.42936	R-Isomer

Totals : 807.28326

Results obtained with enhanced integrator!

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*** End of Report ***

jc-396-064 isolated THQ-amine from acetamide hydrolysis (crude) proton

R-(1)

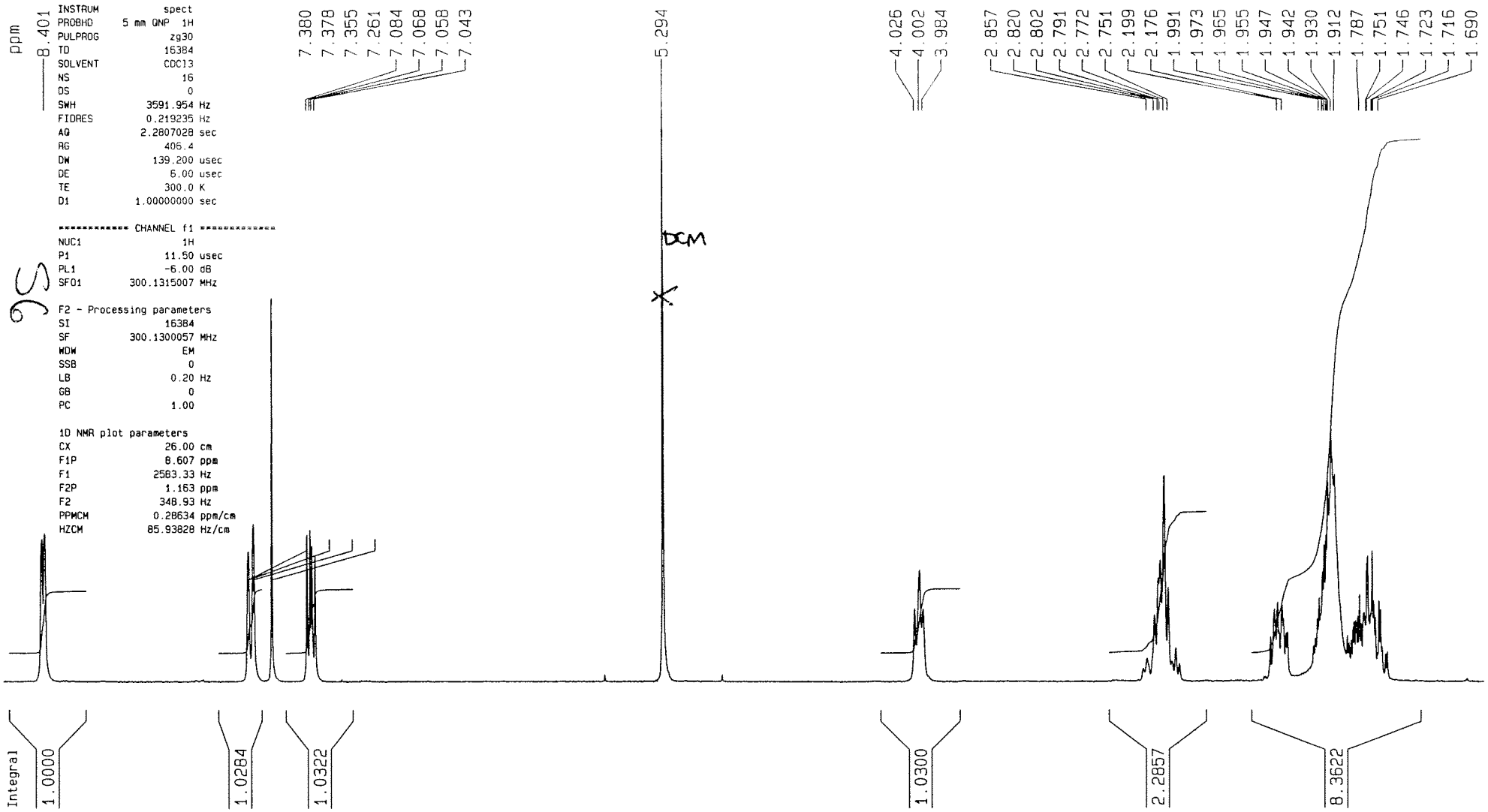
Current Data Parameters
NAME jc-396-064
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040405
Time 15.40
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 406.4
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 8.607 ppm
F1 2583.33 Hz
F2P 1.163 ppm
F2 348.93 Hz
PPMCM 0.28634 ppm/cm
HZCM 85.93828 Hz/cm



Analytical Report
Chiral Purity by GC

AnorMED

Report By: t.ciofani
Report Generated: 7-Apr-04 9:22

Sample Information

R-(1) isolated.
CHIRAL GC

Requesting Chemist	Sample ID
Crawford, Jason	JC-396-064

Analytical Information

Request Number	Analytical #	Analyst Name	Lab Book Reference
R040405-5	A040713	Travis Ciofani	TC-410-2

Estimated Enantiomeric Excess (EE)

Enantiomer	% Purity	%EE (positive value)
R-isomer		
Mean	97.68	95.36
S-isomer		
Mean	2.32	-95.36

% Purity: CompoundPurity = (Area / Total_Area) * 100

%EE (positive value): EE = (Area / Total_Area * 100) - (100 - (Area / Total_Area * 100))

S-Isomer Results

Injection #	RT, min.	Peak Area	% Total Area
9	26.499	37.372	2.24
11	26.479	42.004	2.40
Average	**26.489**	**39.688**	**2.32**
%RSD	**0.05**	**8.25**	**4.77**

% Total Area: CompoundPurity = (Area / Total Area) * 100

R-Isomer Results

Injection #	RT, min.	Peak Area	% Total Area
9	27.688	1630.558	97.76
11	27.664	1710.369	97.60
Average	**27.676**	**1670.464**	**97.68**
Overall %RS	**0.06**	**3.38**	**0.11**

% Total Area: CompoundPurity = (Area / Total Area) * 100

Analytical Equipment List

Module	Part Number	Serial Number
Instrument:		
68GC	68GC	US00033151
7673	7673	<not available>

Column Configuration

Column Description	Serial Number	Length, mm.	Diameter, mm
[redacted] 5% Phenyl Methyl	[redacted] #1	30.0	320.0
CYCLOSILB	CYCLOSILB#1	30.0	250.0

Data File C:\HPCHEM\1\DATA\Chemstor\1920437\40714F-3.D Sample Name: A040713

JC-396-064 (r-isomer), 7.9mg sample + 1.00mL CH2Cl2

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Injection Date : 4/6/2004 6:43:17 PM Seq. Line : 2
Sample Name : A040713 Location : Vial 10
Acq. Operator : t.ciofani Inj : 3
Inj Volume : 1 µl
Acq. Method : J:\GC\GC1\METHODS\OFFICI~1\AM007V1.M
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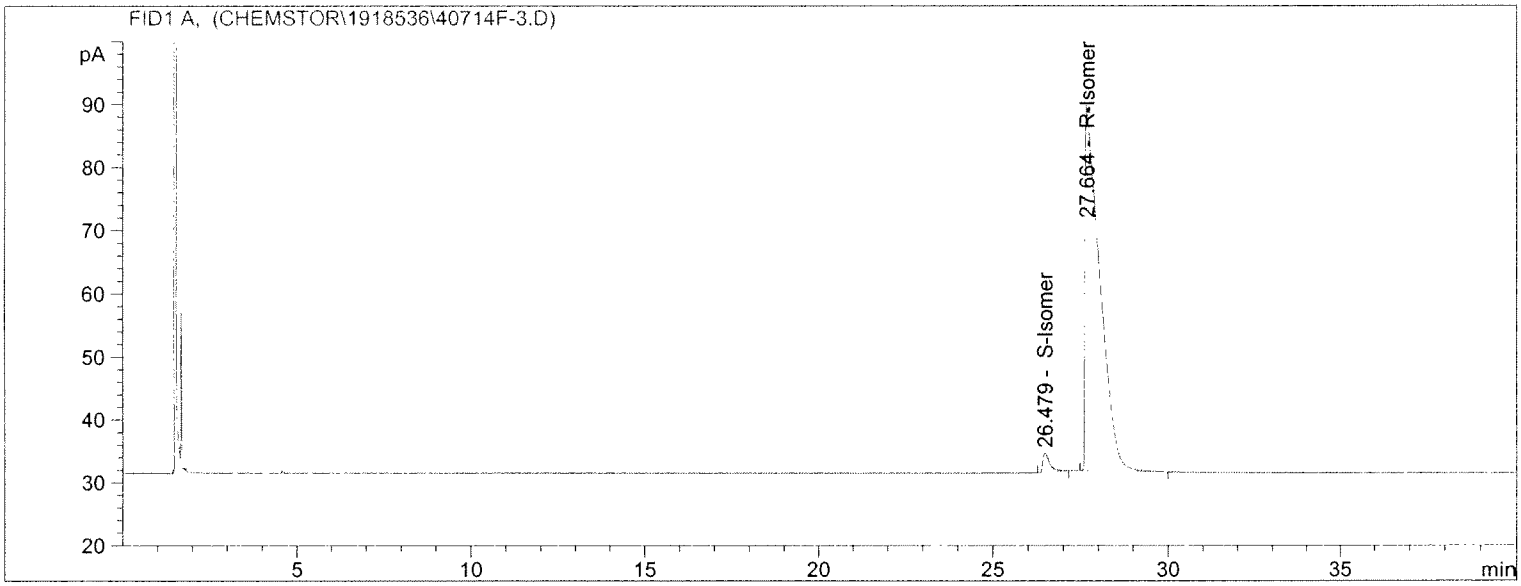
Analysis Method : C:\HPCHEM\1\METHODS\Chemstor\1920374\AM007V1.M
Last changed : 2/9/2004 4:08:36 PM by t.ciofani
Chiral Separation of 5,6,7-Tetrahydro-8-amino-quinoline by GC using Cyclosil-B column, AM007.
V1.



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Area Percent Report

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Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
1	26.479	PB	0.2057	42.00373	2.39696	S-Isomer
2	27.664	BB	0.3803	1710.36926	97.60304	R-Isomer

Totals : 1752.37299

Results obtained with enhanced integrator!
1 Warnings or Errors :

Warning : Calibration warnings (see calibration table listing)

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*** End of Report ***

S9

Analytical Report
Estimated Purity by GC

AnorMED

Report By: t.ciofani
Report Generated: 7-Apr-04 10:59

R-(1)- isolated GC purity

Sample Information

Requesting Chemist	Sample ID
Crawford, Jason	JC-396-064

Analytical Information

Request Number	Analytical #	Analyst Name	Lab Book Reference
R040405-5	A040713	Travis Ciofani	TC-410-2

Estimated Purity

Injection #	RT, min.	Peak Area	% Total Area
19	6.385	1952.993	99.29
20	6.386	1983.066	99.34
21	6.386	1943.934	99.18
Average	**6.385**	**1959.998**	**99.27**
%RSD	**0.01**	**1.05**	**0.08**

% Total Area: CompoundPurity = (Area / Total Area) * 100

Analytical Equipment List

Module	Part Number	Serial Number
Instrument:		
68GC	68GC	US00033151
7673	7673	<not available>

Column Configuration

Column Description	Serial Number	Length, mm.	Diameter, mm
[redacted] 5% Phenyl Methyl Si	[redacted] #1	30.0	320.0
CYCLOSILB	CYCLOSILB#1	30.0	250.0

Data File C:\HPCHEM\1\DATA\Chemstor\1920787\40713B-1.D Sample Name: A040713

JC-396-064, 7.9mg sample + 1.00mL CH2Cl2

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Injection Date : 4/7/2004 9:57:35 AM Seq. Line : 2
Sample Name : A040713 Location : Vial 10
Acq. Operator : t.ciofani Inj : 1
Inj Volume : 1 µl

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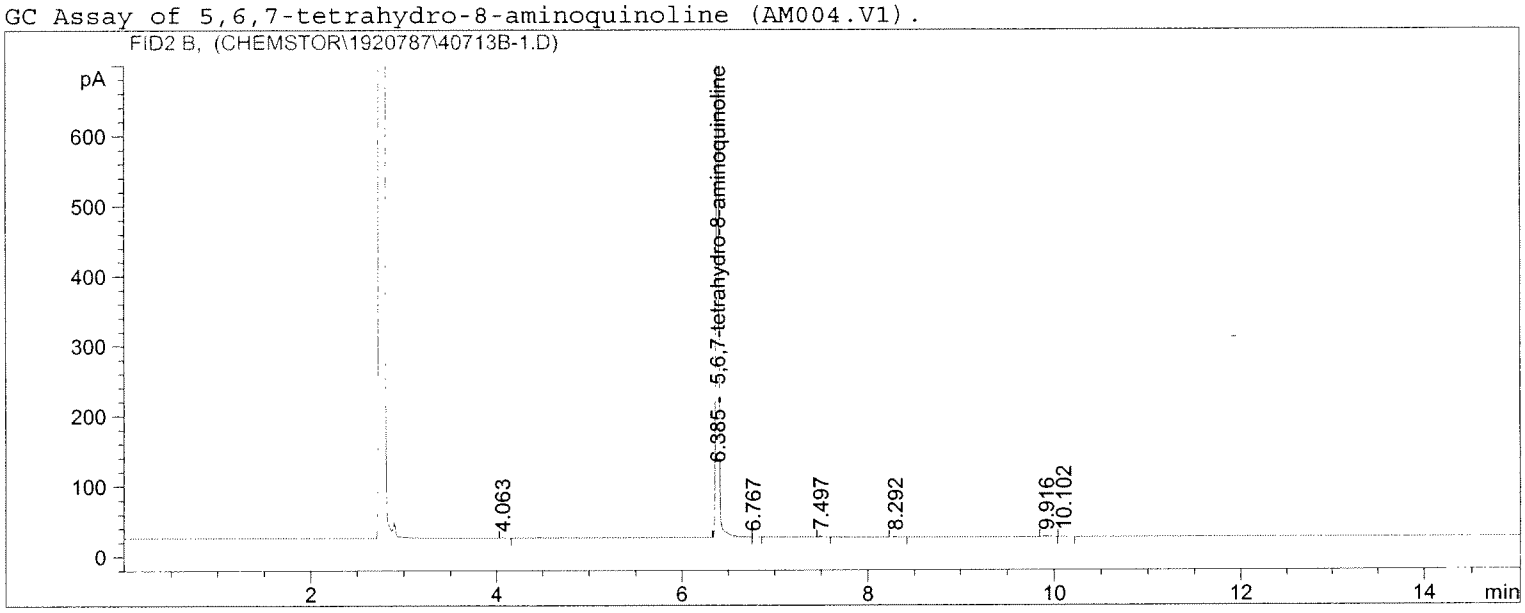
GC Assay of 5,6,7-tetrahydro-8-aminoquinoline (AM004.V1).



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Area Percent Report

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Dilution : 1.0000

Signal 1: FID2 B,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
1	4.063	PB	0.0268	9.54252e-1	0.04851	?
2	6.385	PB	0.0298	1952.99329	99.28598	5,6,7-tetrahydro-8-aminoquinoline
3	6.767	BB	0.0430	1.31677	0.06694	?
4	7.497	PB	0.0360	4.18768	0.21289	?
5	8.292	PB	0.0576	2.68584	0.13654	?
6	9.916	PB	0.0585	3.80694	0.19354	?
7	10.102	BB	0.0560	1.09353	0.05559	?

Totals : 1967.03830

Results obtained with enhanced integrator!

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*** End of Report ***

S11

Current Data Parameters
NAME jc-396-059
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040407
Time 11.06
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 4
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 512
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

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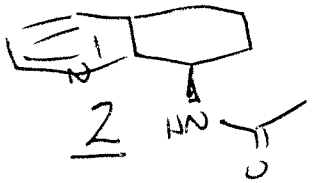
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 10.965 ppm
F1 3290.95 Hz
F2P -1.003 ppm
F2 -301.00 Hz
PPMCM 0.46031 ppm/cm
HZCM 138.15208 Hz/cm

columned acetamide proton



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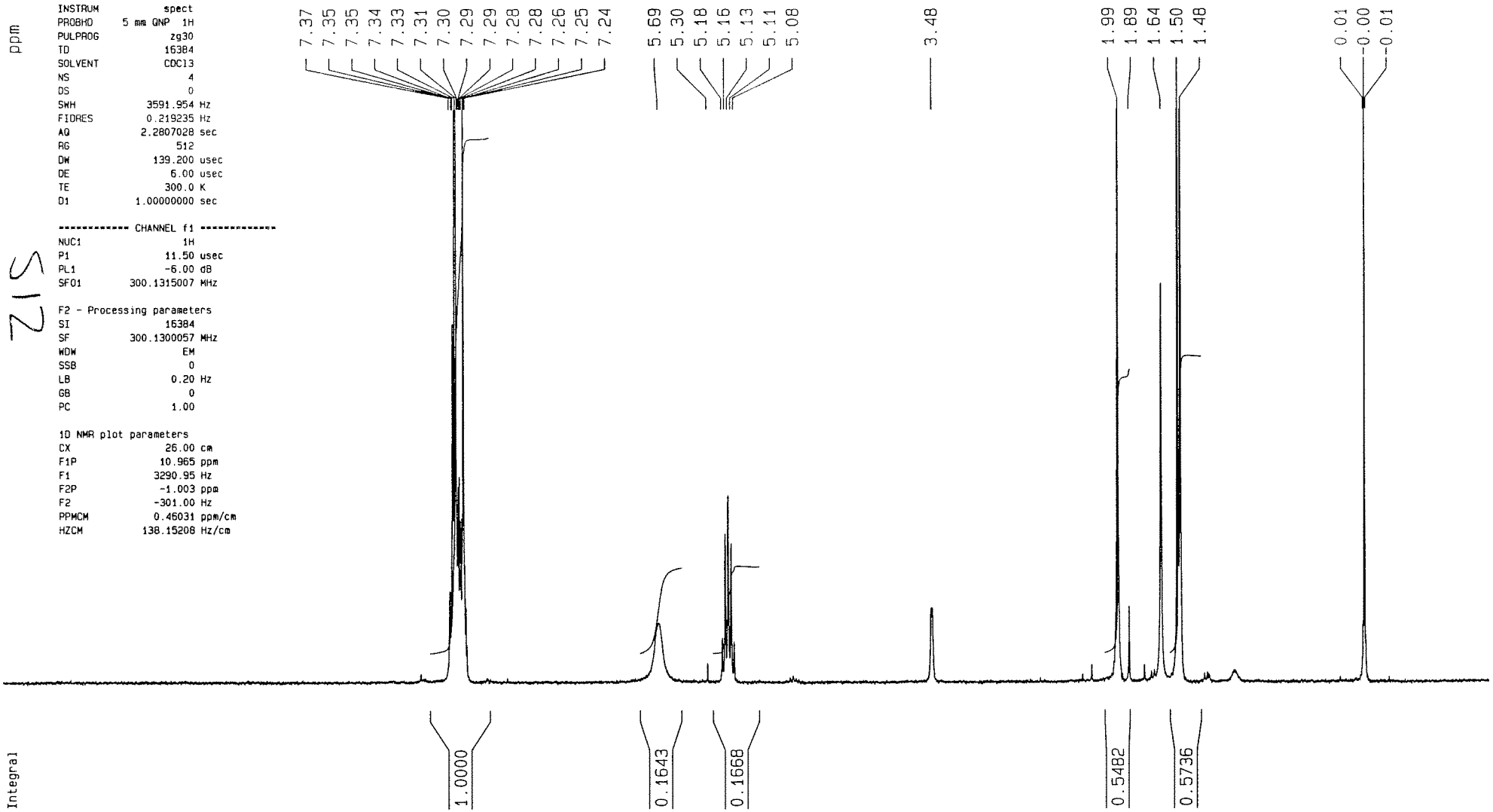

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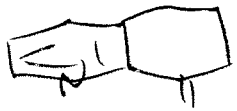

3 0

jc-396-015 crystalline ketone proton

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EXPNO 1
PROCNO 1

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PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 456.1
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TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
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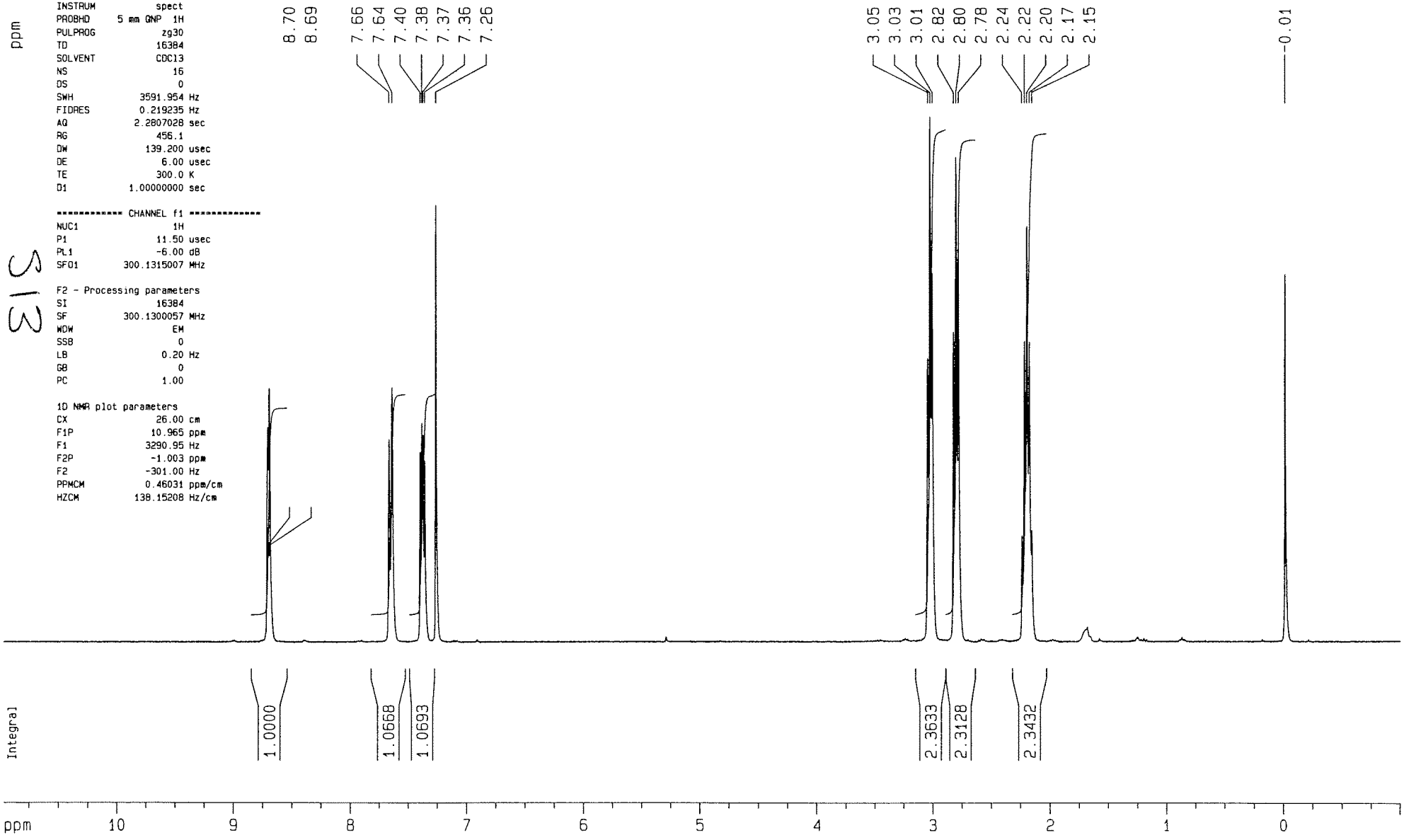
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 10.965 ppm
F1 3290.95 Hz
F2P -1.003 ppm
F2 -301.00 Hz
PPMCM 0.46031 ppm/cm
HZCM 138.15208 Hz/cm

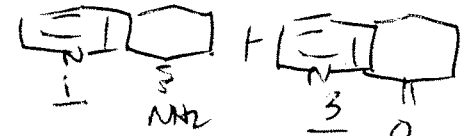


S13

formation of 4

rt aliquot of amine + ketone proton

condensation time = Ø d_8-TOLUENE



in d^8 $PhCH_3$

t = Ø

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EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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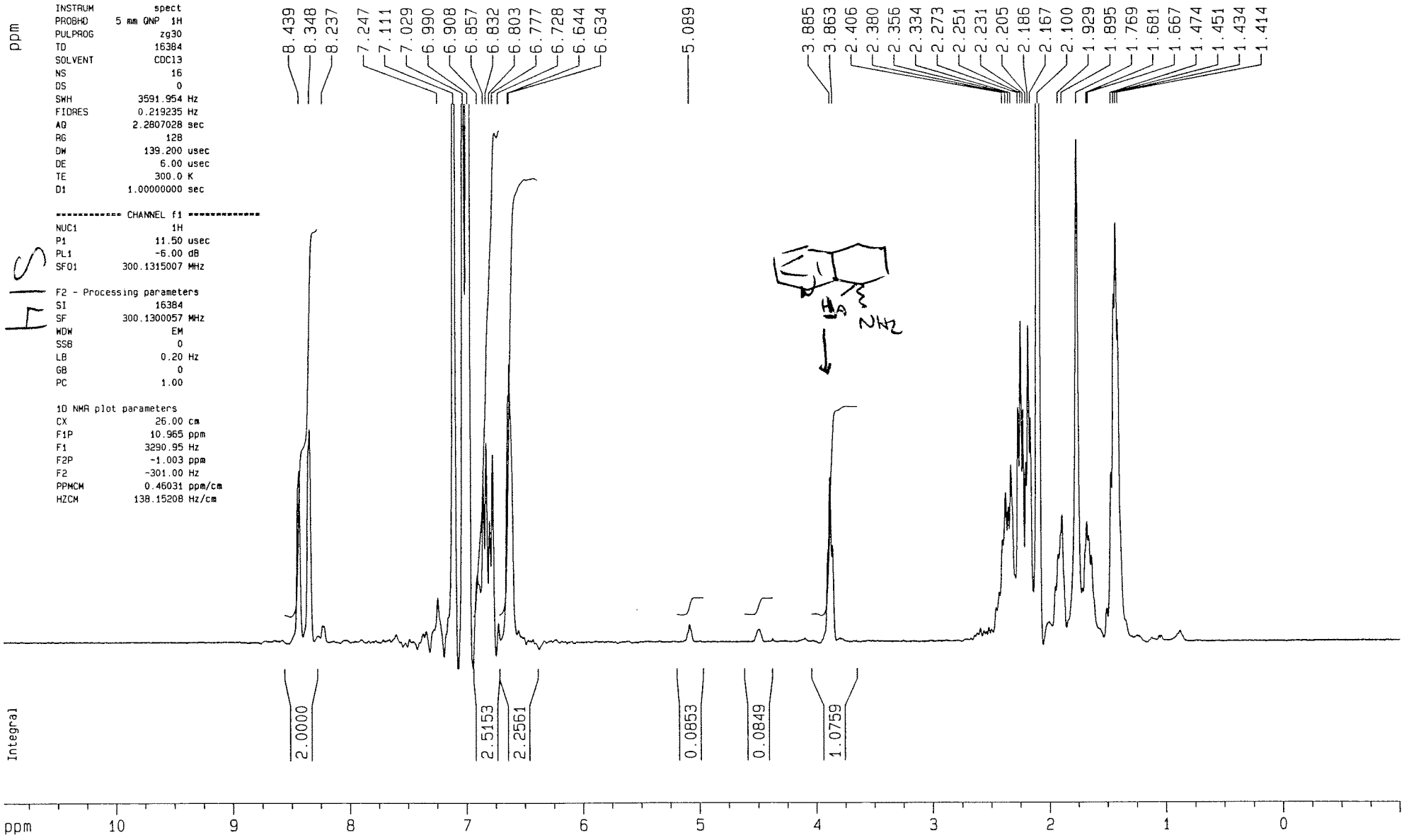
Time 10.52
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 128
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

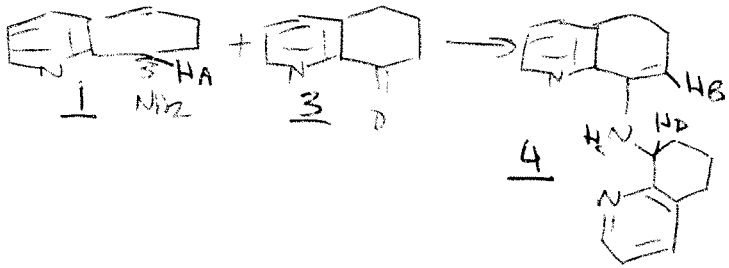
1D NMR plot parameters
CX 26.00 cm
F1P 10.965 ppm
F1 3290.95 Hz
F2P -1.003 ppm
F2 -301.00 Hz
PPMCM 0.46031 ppm/cm
HZCM 138.15208 Hz/cm



formation of 4

amine/ketone condensation 2h@RT proton

d_8 TOLUENE



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NAME jc-396-043
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040227
Time 13.19
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 128
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
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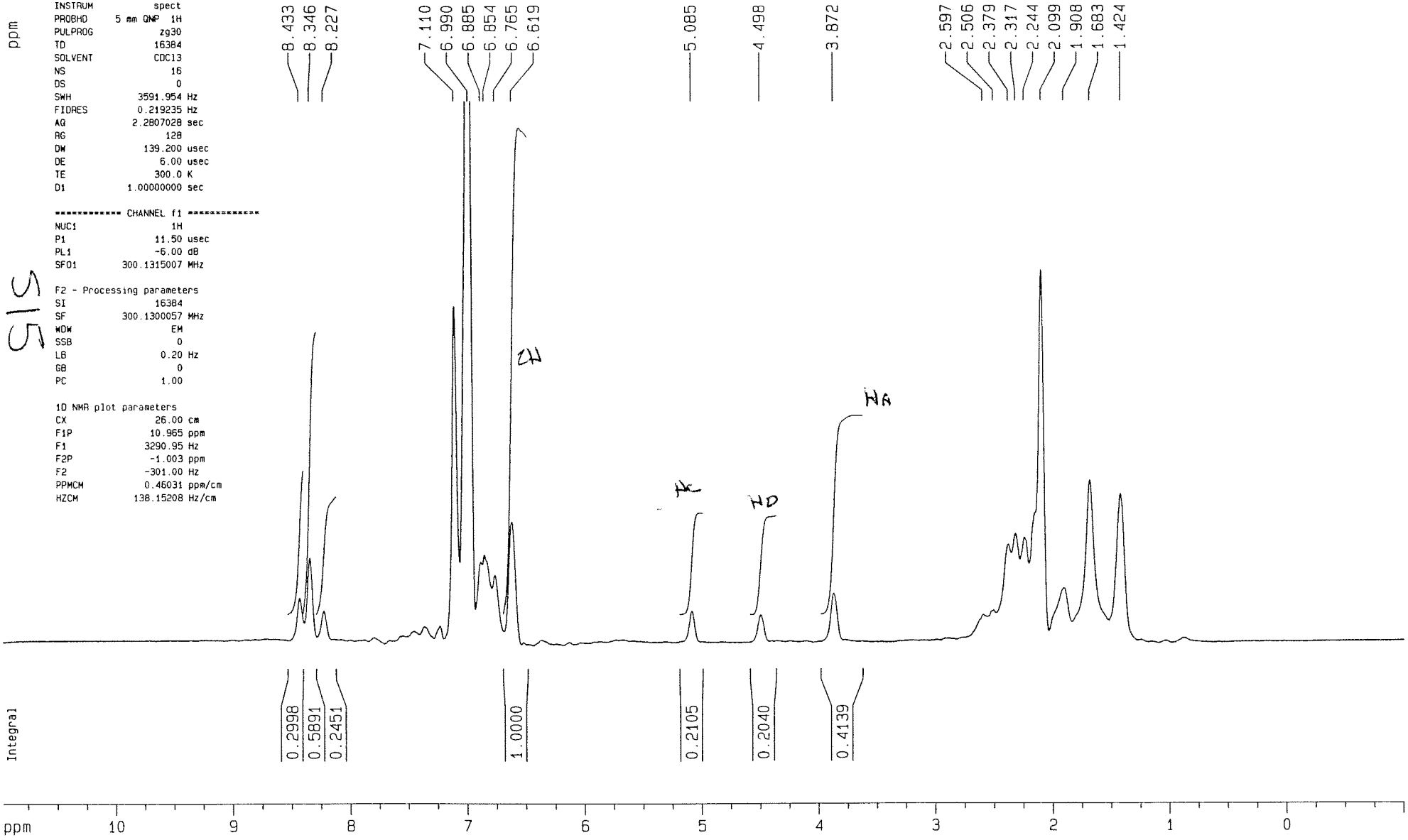
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 10.965 ppm
F1 3290.95 Hz
F2P -1.003 ppm
F2 -301.00 Hz
PPMCM 0.46031 ppm/cm
HZCM 138.15208 Hz/cm



formation of 4

jc-396-043 4.5 hour aliquot proton

d8 TOLUENE

Current Data Parameters
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EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
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Time 15.24
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 128
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
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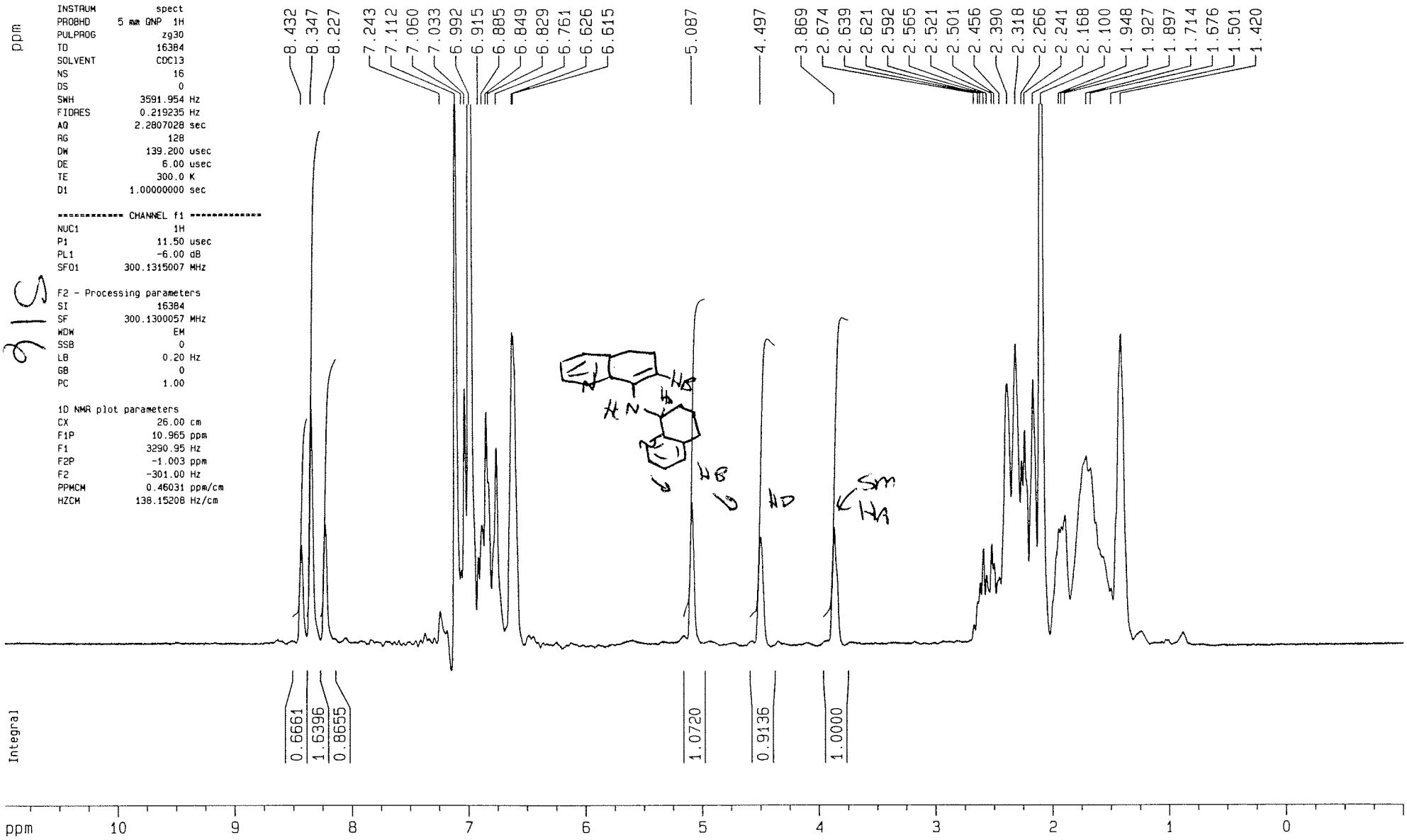
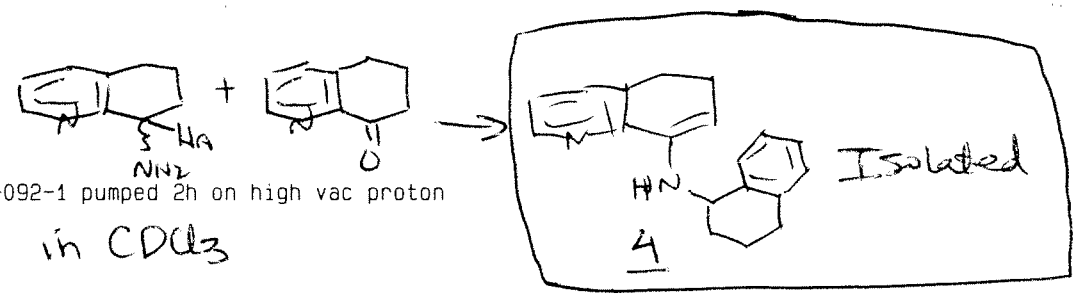
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 10.965 ppm
F1 3290.95 Hz
F2P -1.003 ppm
F2 -301.00 Hz
PPMCM 0.46031 ppm/cm
HZCM 138.15208 Hz/cm



S16



jc-396-092-1 pumped 2h on high vac proton

in $CDCl_3$

Current Data Parameters
NAME jc-396-092
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
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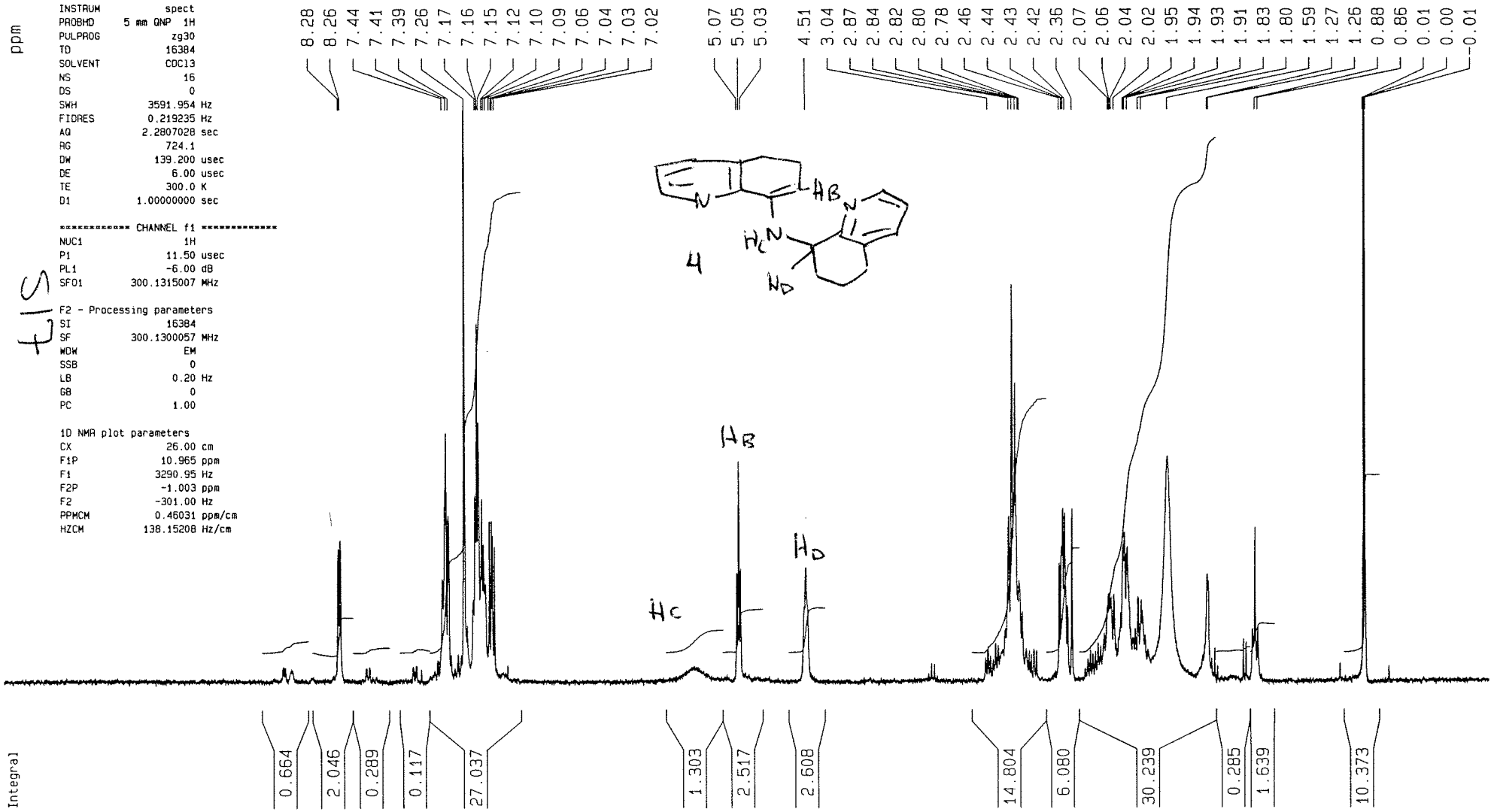
Time 13.25
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 724.1
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 10.965 ppm
F1 3290.95 Hz
F2P -1.003 ppm
F2 -301.00 Hz
PPMCM 0.46031 ppm/cm
HZCM 138.15208 Hz/cm



4 expansion

oil residue (soluble in hex/et2o) proton

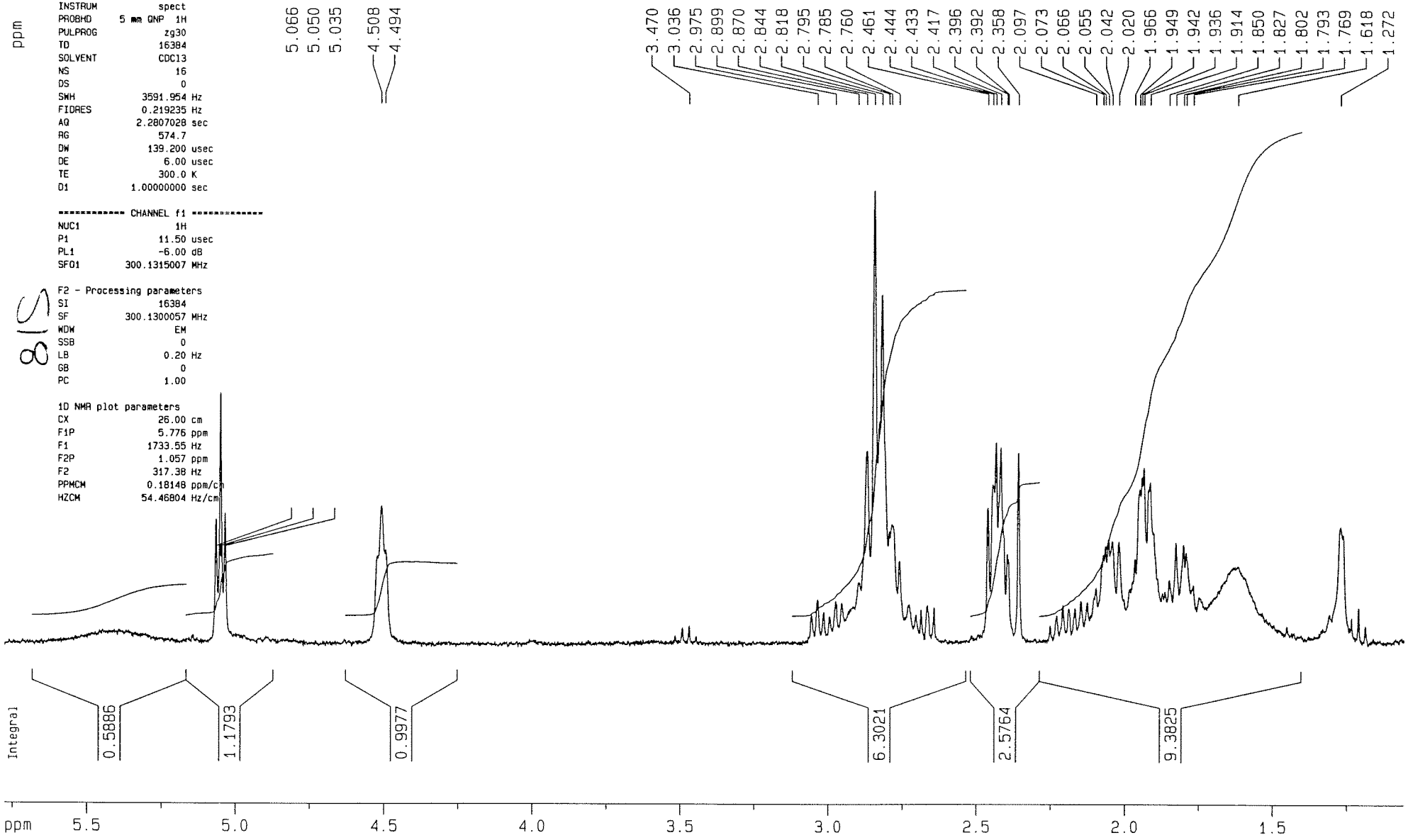
Current Data Parameters
NAME jc-396-092
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040617
Time 10.10
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 574.7
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 5.776 ppm
F1 1733.55 Hz
F2P 1.057 ppm
F2 317.38 Hz
PPMCM 0.18148 ppm/cm
HZCM 54.46804 Hz/cm



8/5/08

4 expansion

oil residue (soluble in hex/et2o) proton

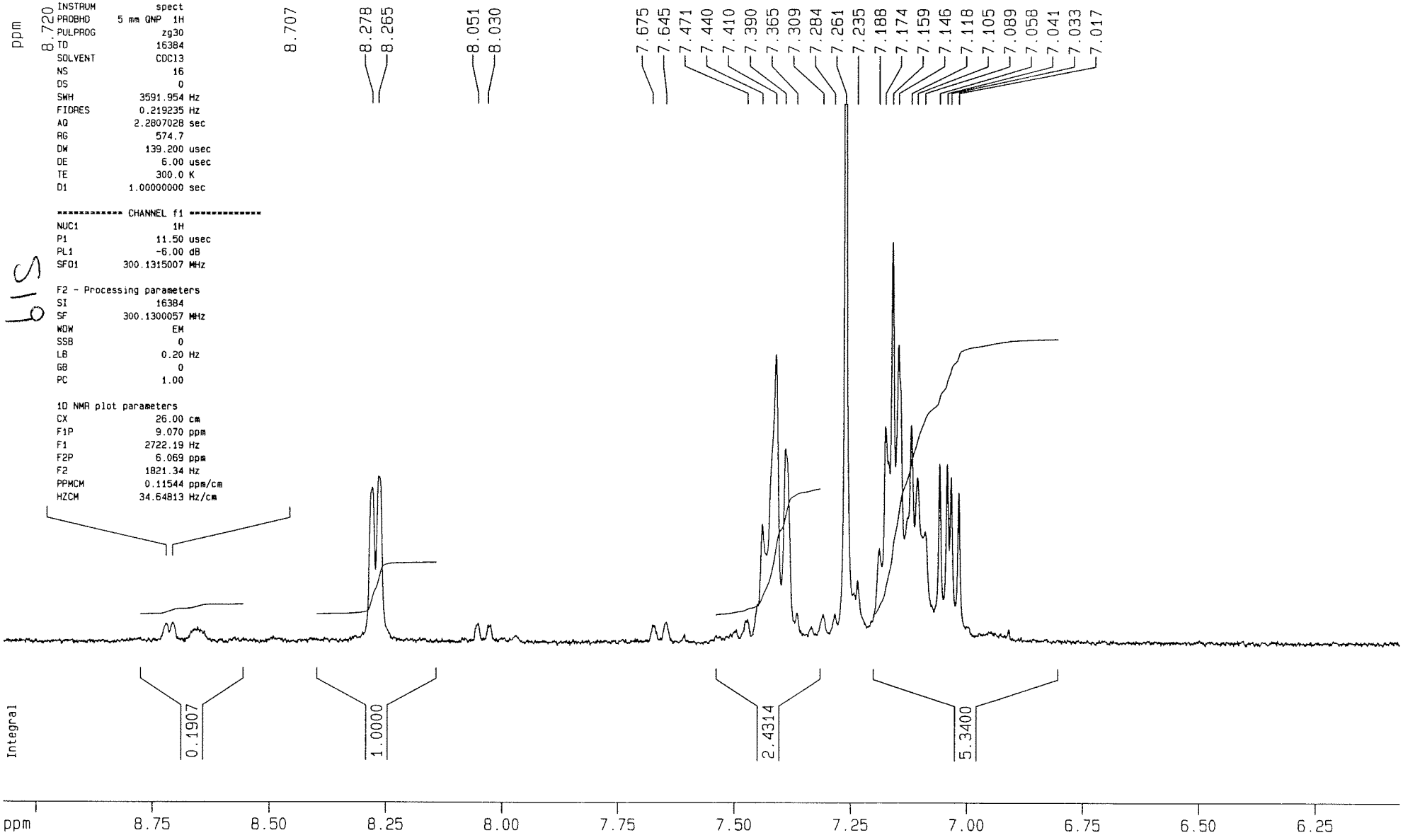
Current Data Parameters
NAME ;c-396-092
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040617
Time 10.10
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.219235 Hz
AQ 2.2807028 sec
RG 574.7
DW 139.200 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 11.50 usec
PL1 -6.00 dB
SFO1 300.1315007 MHz

F2 - Processing parameters
SI 16384
SF 300.1300057 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 26.00 cm
F1P 9.070 ppm
F1 2722.19 Hz
F2P 6.069 ppm
F2 1821.34 Hz
PPMCM 0.11544 ppm/cm
HZCM 34.64813 Hz/cm



S19