

Diastereoselective Synthesis of 2,3,6- Trisubstituted Piperidines

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Nagel, Wendy Simon, Melani Suarez-Contreras, Norma J. Tom and Brian T. O'Neill**

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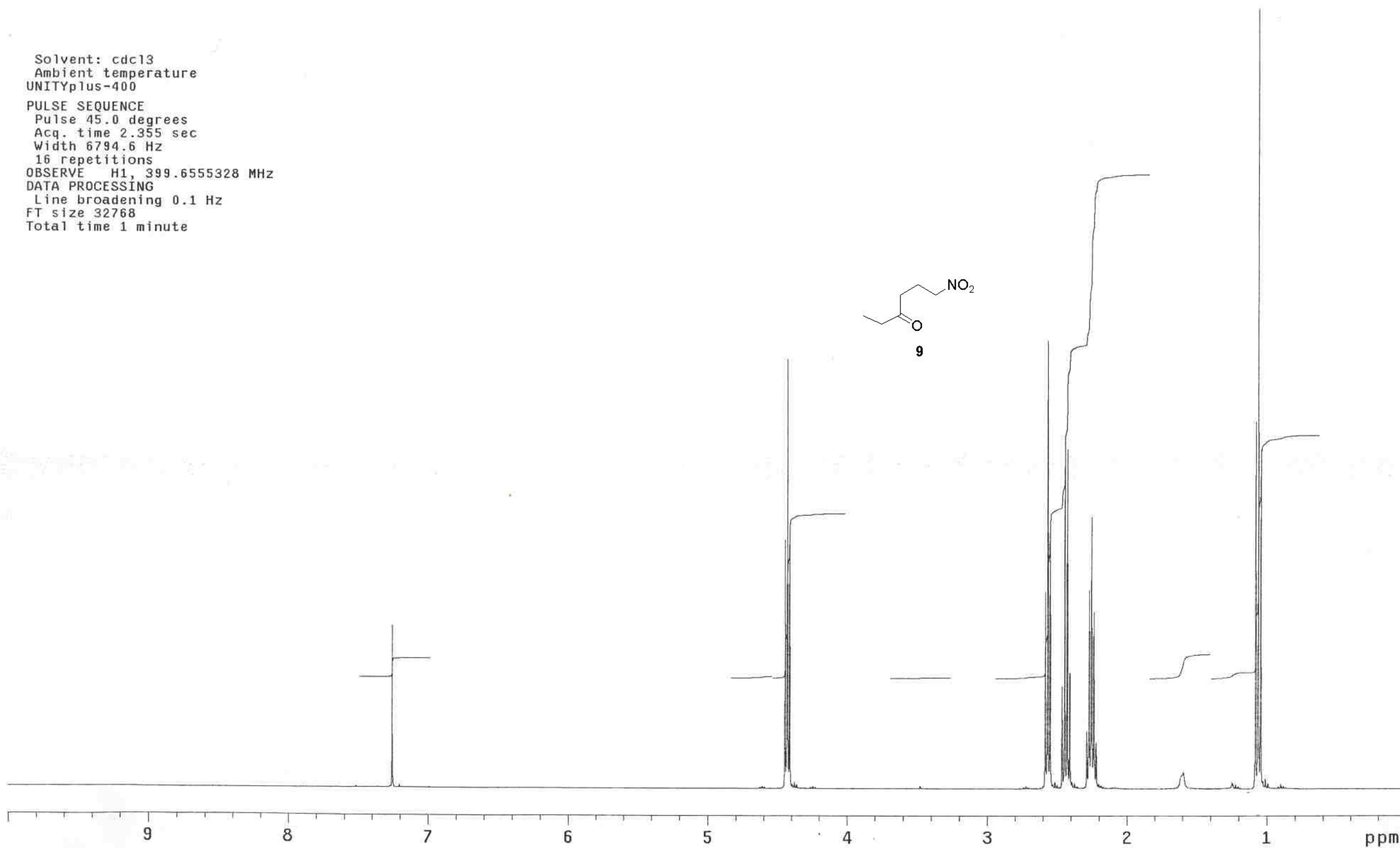
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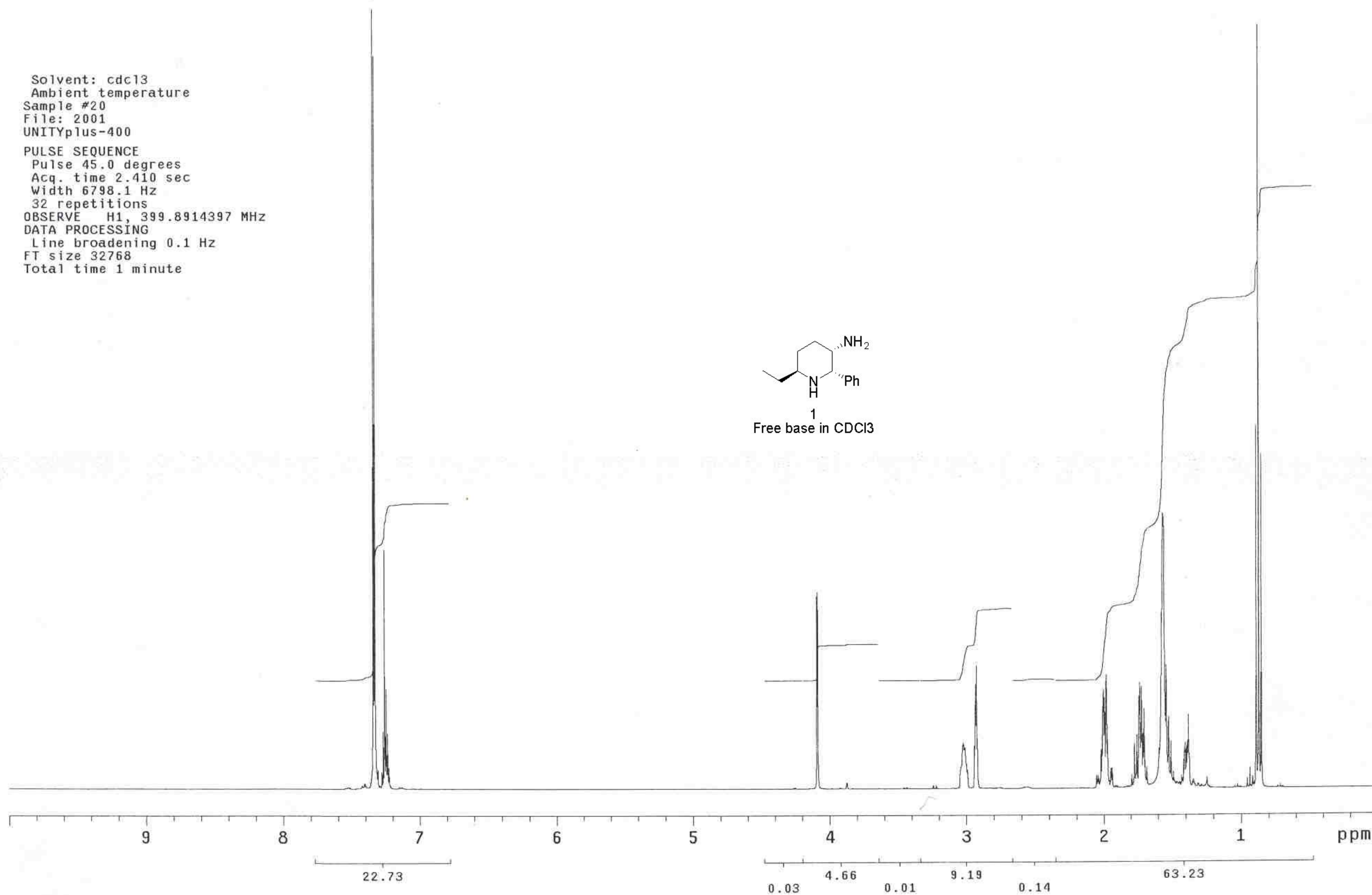
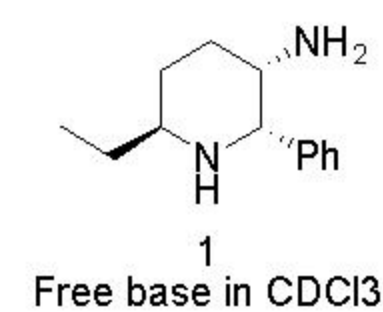
General Experimental Methods.

^1H and ^{13}C NMR spectra are reported in ppm relative to the residual solvent signal. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, comp = complicated pattern due to overlapping resonances, par obsc = partially obscured), coupling constant (J) in Hz, and integration. Low resolution mass spectrometry data was obtained using the chemical ionization method. Infrared spectra are reported as diffuse reflectance (DRIFTS) values. Melting points are reported uncorrected. Solution pH measurements were made with Whatman type CF pH 0-14 indicator paper strips. Inert atmosphere reactions were conducted in oven-dried glassware under an atmosphere of dry nitrogen. Anhydrous solvents and reagents, including 25% sodium methoxide in methanol, were obtained from Aldrich and used without further purification. Two exceptions are ethyl vinyl ketone and methyl vinyl ketone, which were distilled prior to use. Commercial grade Raney® 2800 nickel (Aldrich Catalog #22,167-8) was rinsed with deionized water until the rinse registered a neutral pH. The resultant neutral Raney nickel gave better results for hydrogenation of the nitro group. Some procedures employed fresh Raney nickel, which was prepared as described below. The following protocols include full experimental details for the synthesis of each of the 6-ethyl isomers, and select procedures for the synthesis of various compounds from the 6-methyl series.

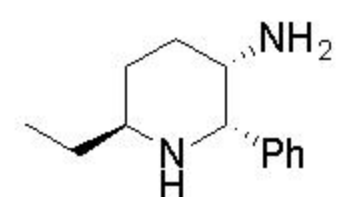
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FT size 32768
Total time 1 minute



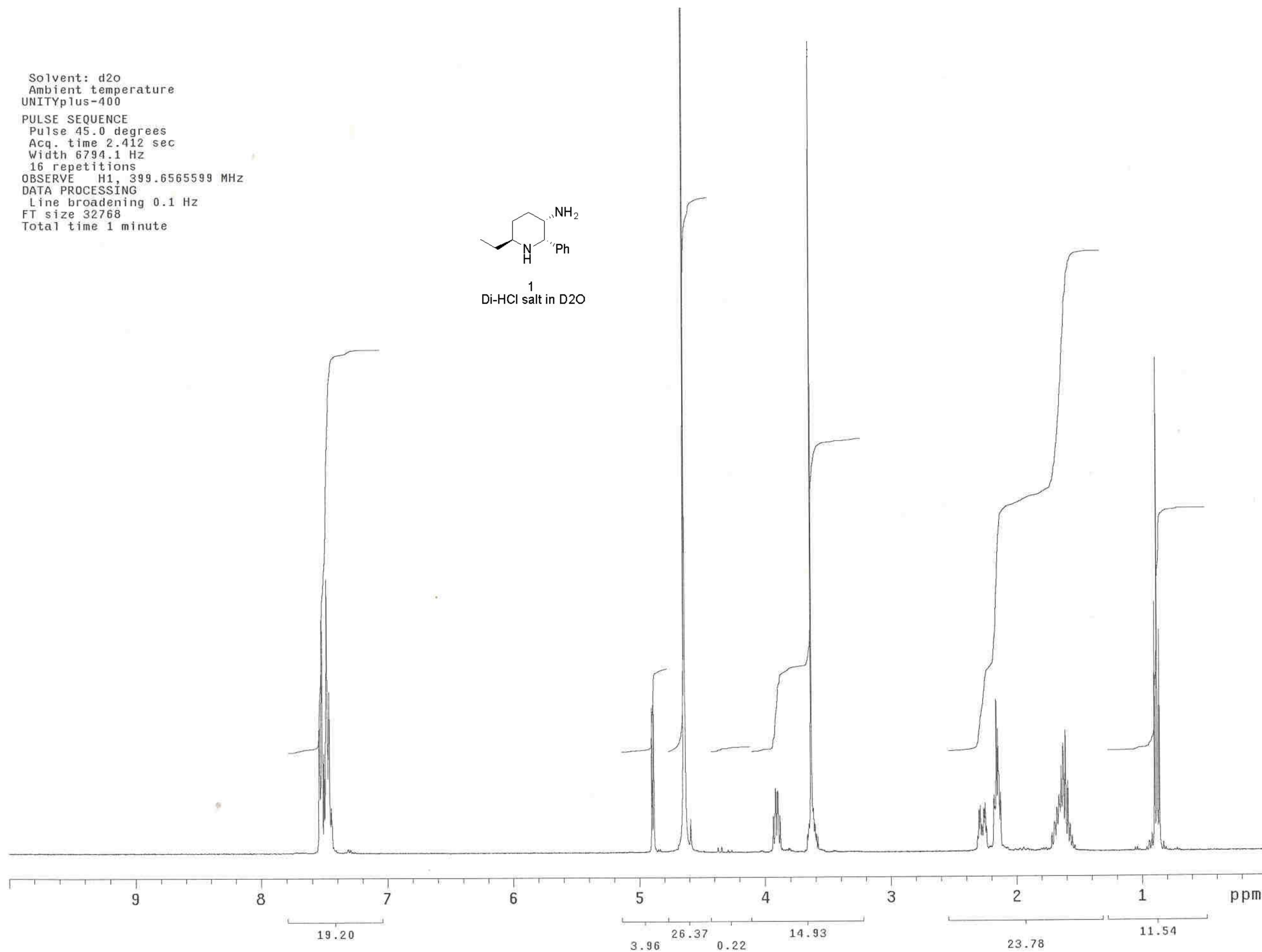
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Acq. time 2.410 sec
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32 repetitions
OBSERVE H1, 399.8914397 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



Solvent: d2o
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.412 sec
Width 6794.1 Hz
16 repetitions
OBSERVE H1, 399.6565599 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



1
Di-HCl salt in D2O



Automation directory: /auto/Automation_data/090205

Pulse Sequence: s2pu1

Solvent: dmsd

Temp. 25.0 C / 298.1 K

Sample #40, user thomas.a.chappie@pfizer.com

File: 4001

INOVA-400 "unityn"

Relax. delay 0.950 sec

Pulse 45.0 degrees

Acq. time 2.562 sec

Width 6394.9 Hz

256 repetitions

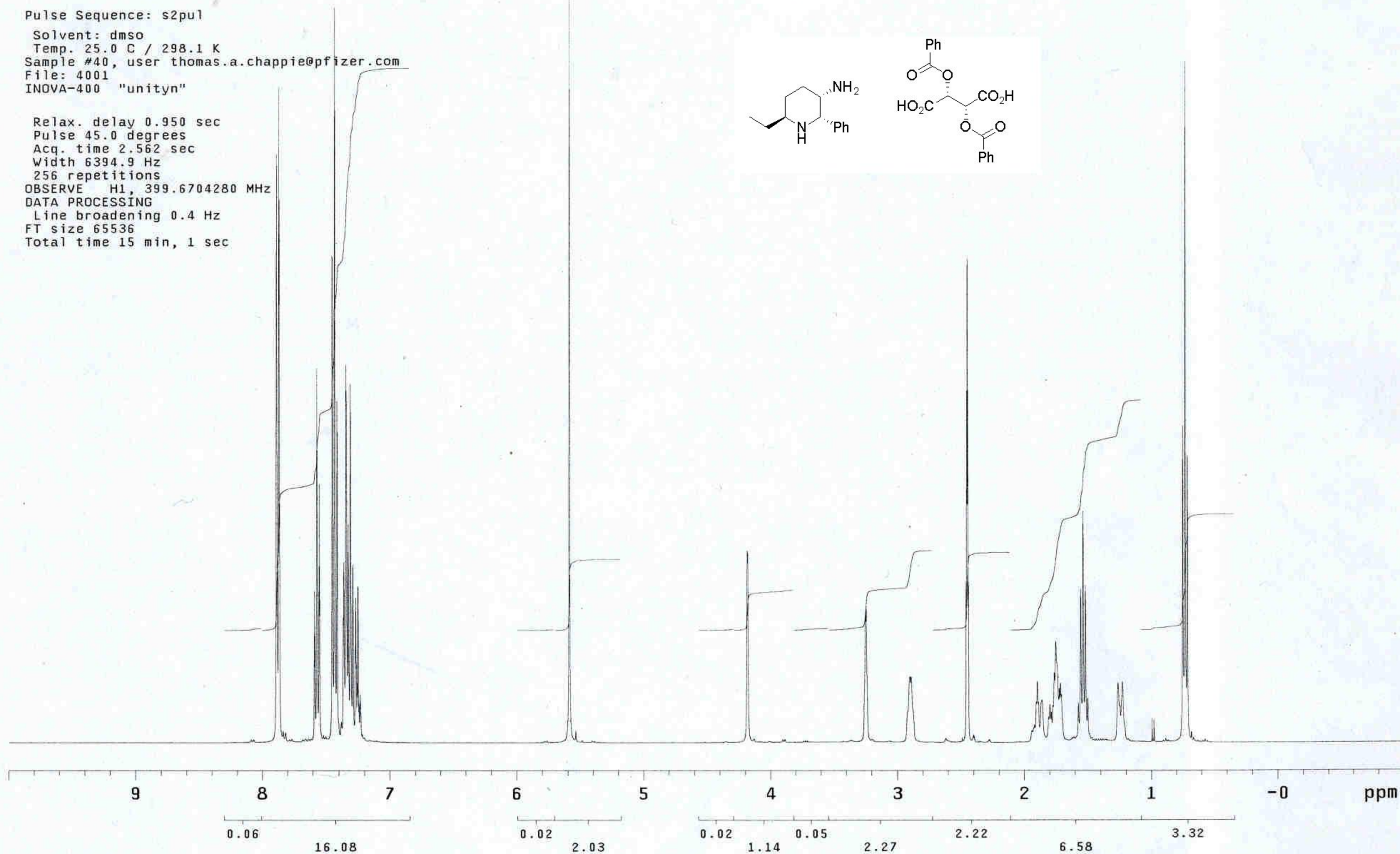
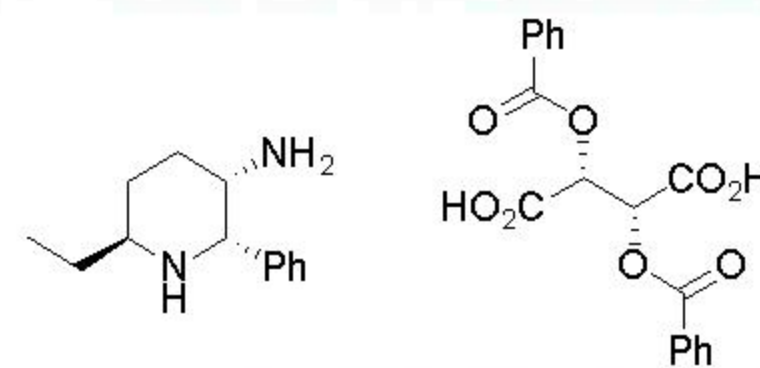
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DATA PROCESSING

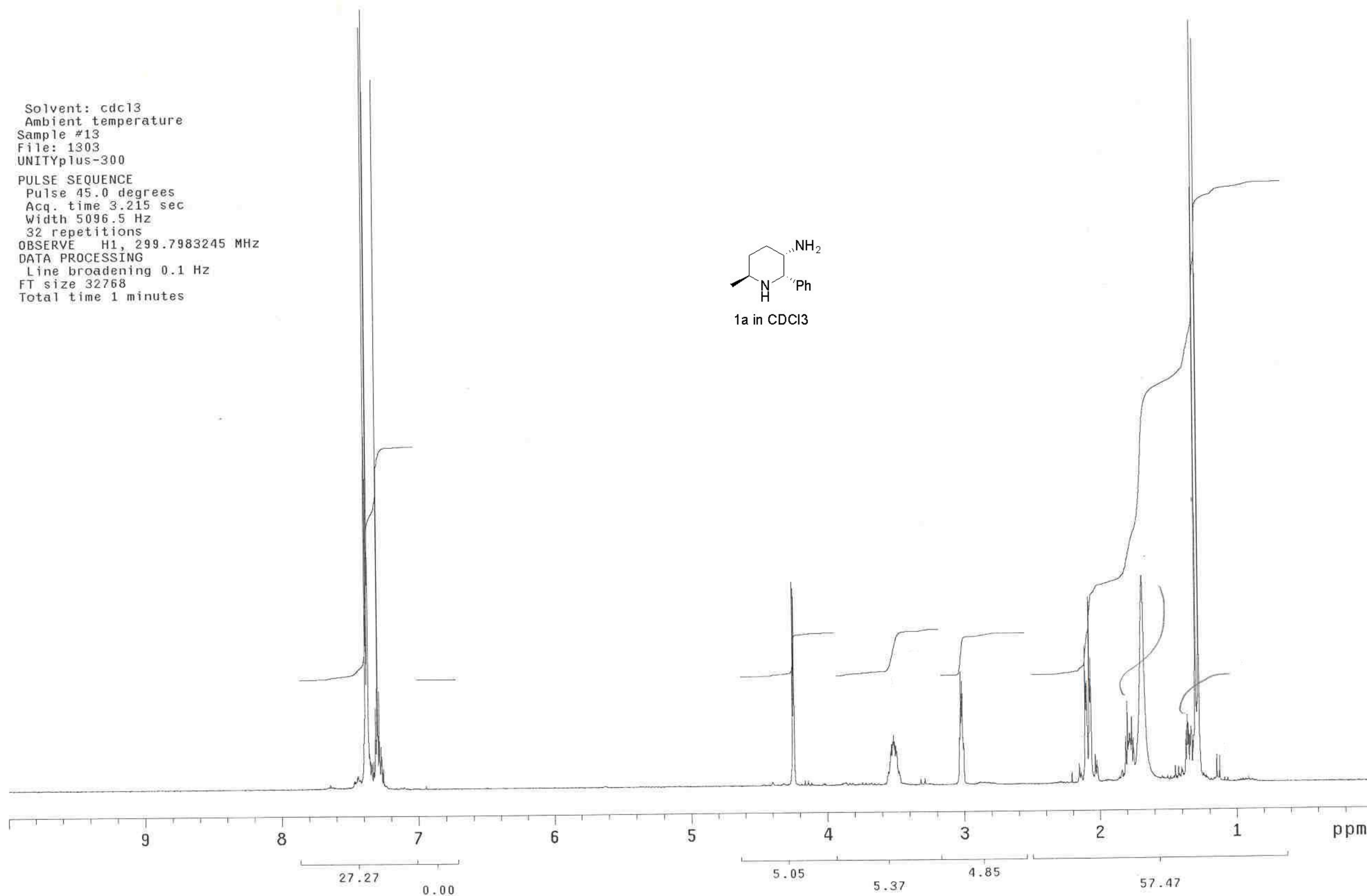
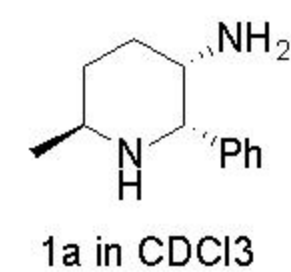
Line broadening 0.4 Hz

FT size 65536

Total time 15 min, 1 sec



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Ambient temperature
Sample #13
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Acq. time 3.215 sec
Width 5096.5 Hz
32 repetitions
OBSERVE H1, 299.7983245 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minutes



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Solvent: d2o

Temp. 25.0 C / 298.1 K

Pulse 45.0 degrees

Acq. time 3.683 sec

Width 6394.9 Hz

16 repetitions

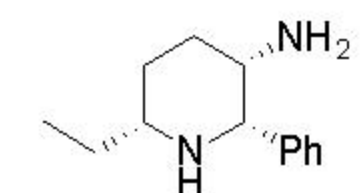
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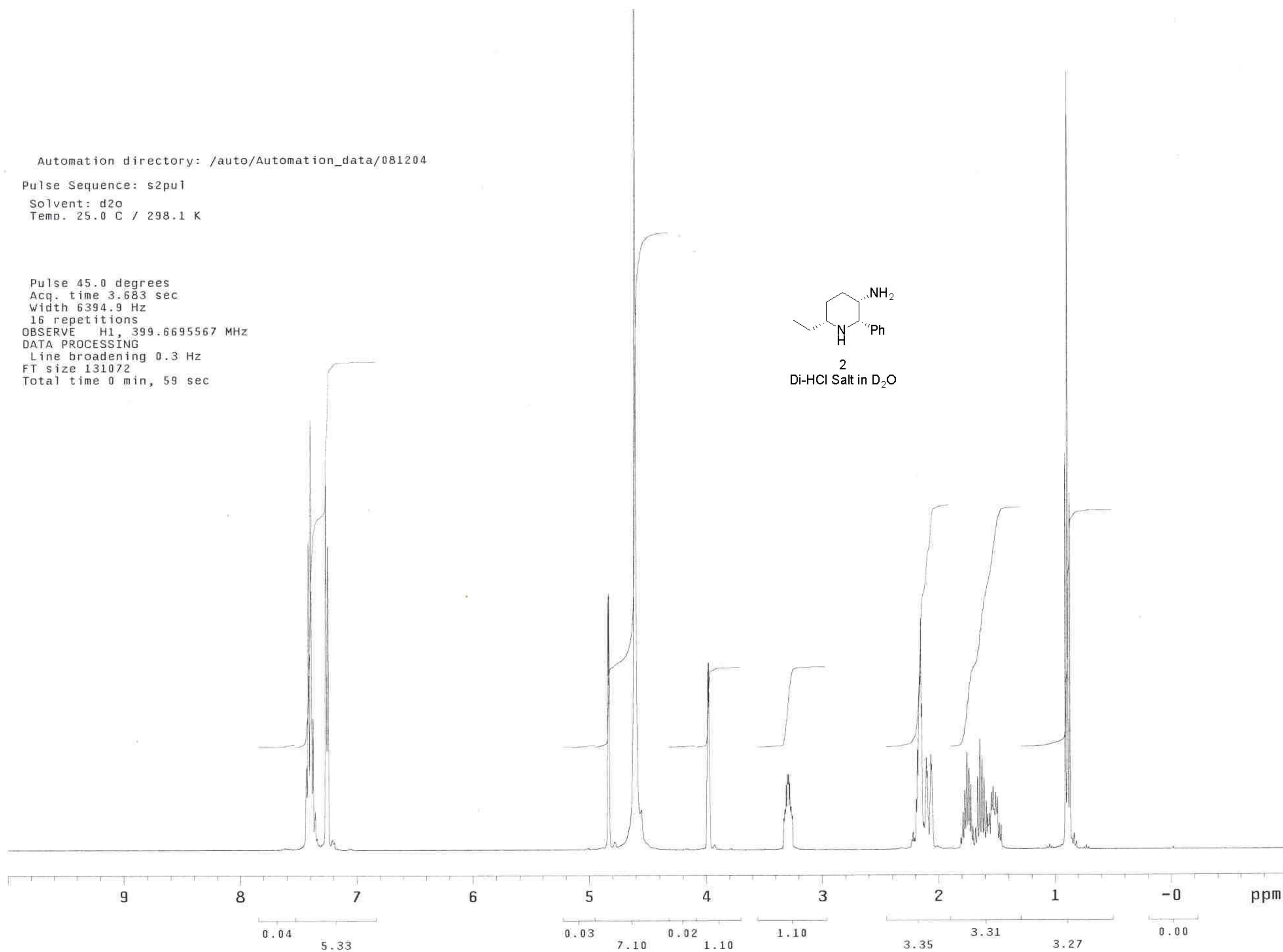
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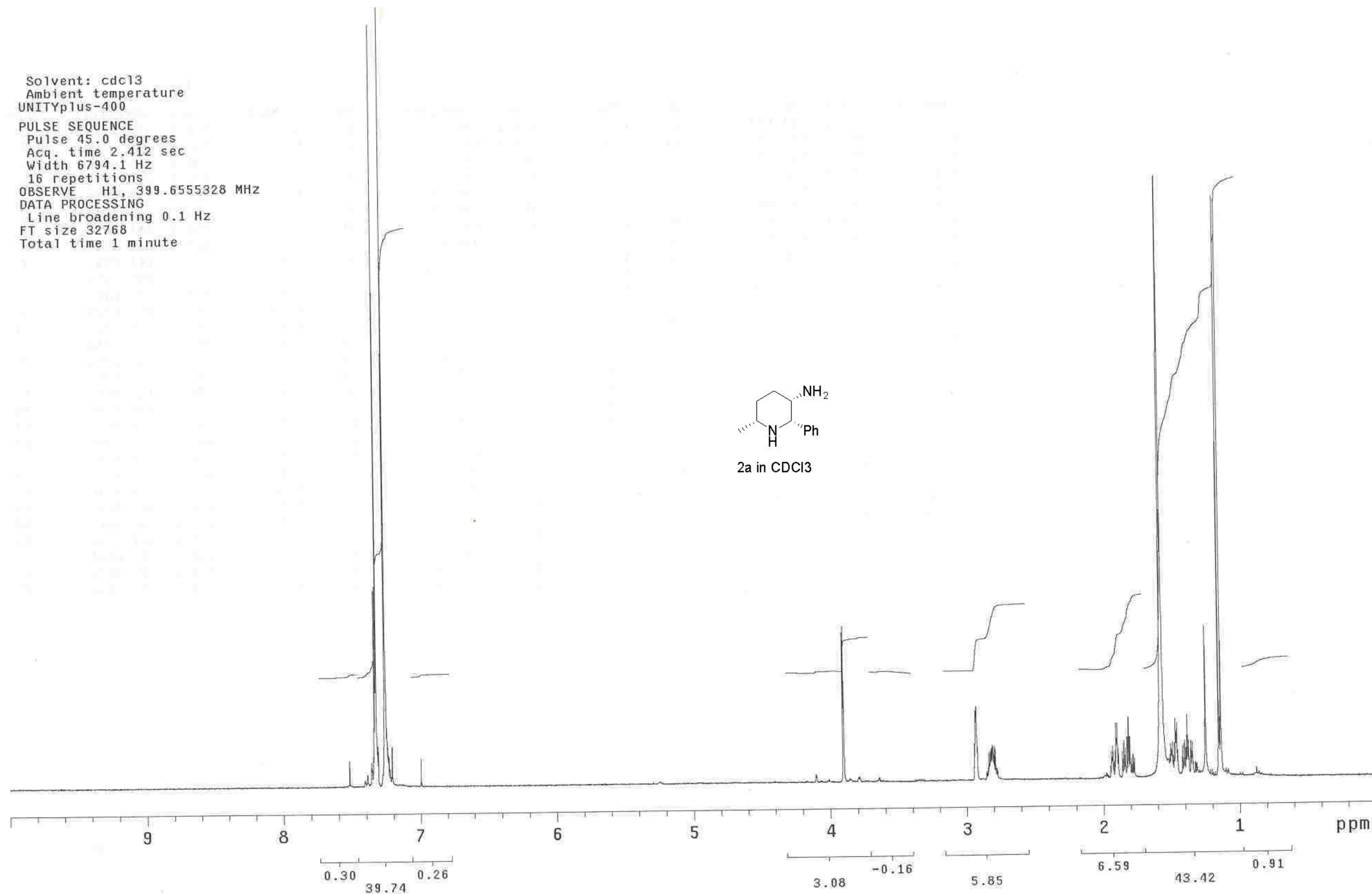
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2
Di-HCl Salt in D₂O



Solvent: cdcl3
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.412 sec
Width 6794.1 Hz
16 repetitions
OBSERVE H1, 399.655328 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



Solvent: cd3od
Ambient temperature
UNITYplus-400

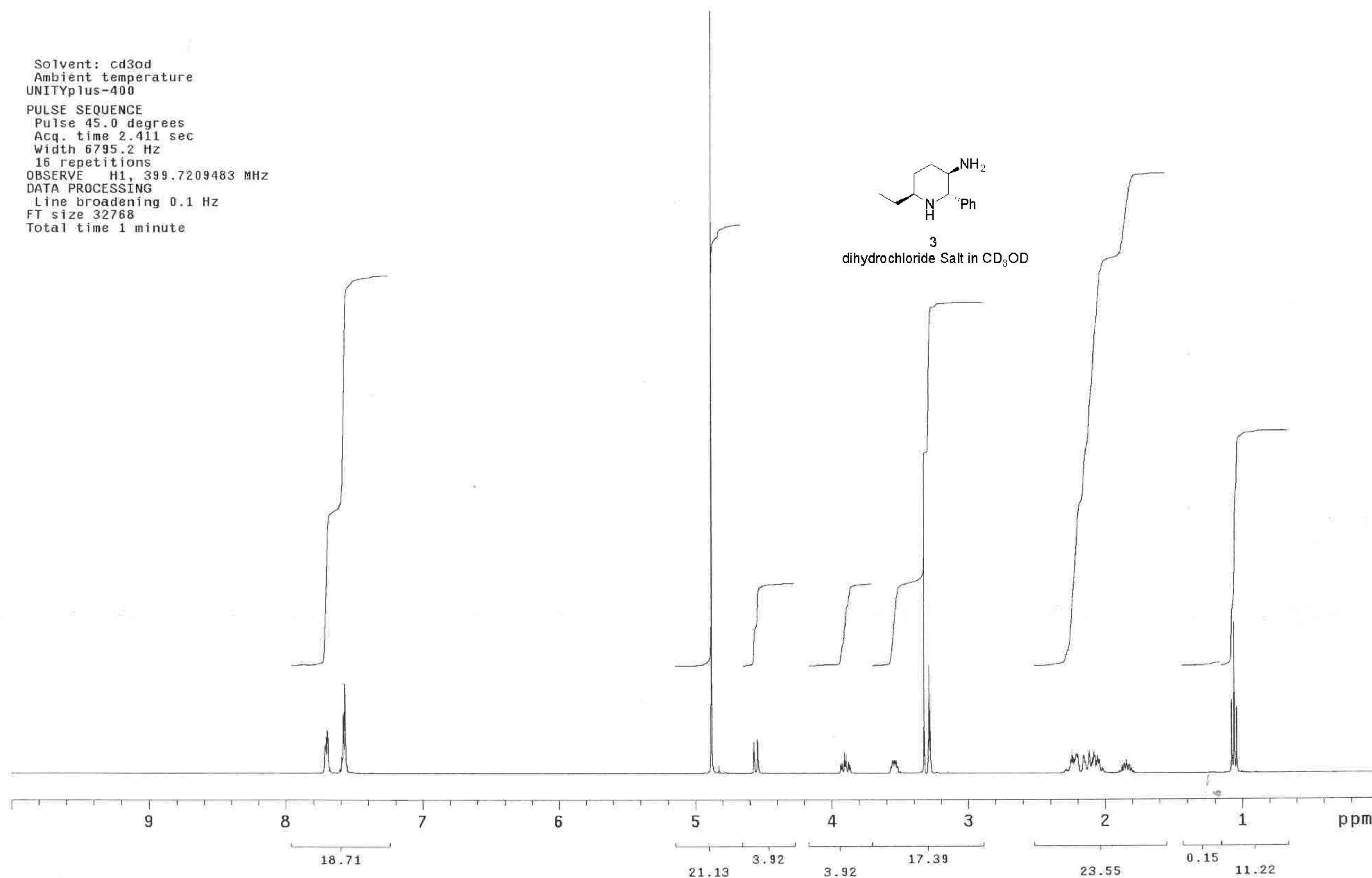
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Pulse 45.0 degrees
Acq. time 2.411 sec
Width 6795.2 Hz
16 repetitions

OBSERVE H1, 399.7209483 MHz

DATA PROCESSING

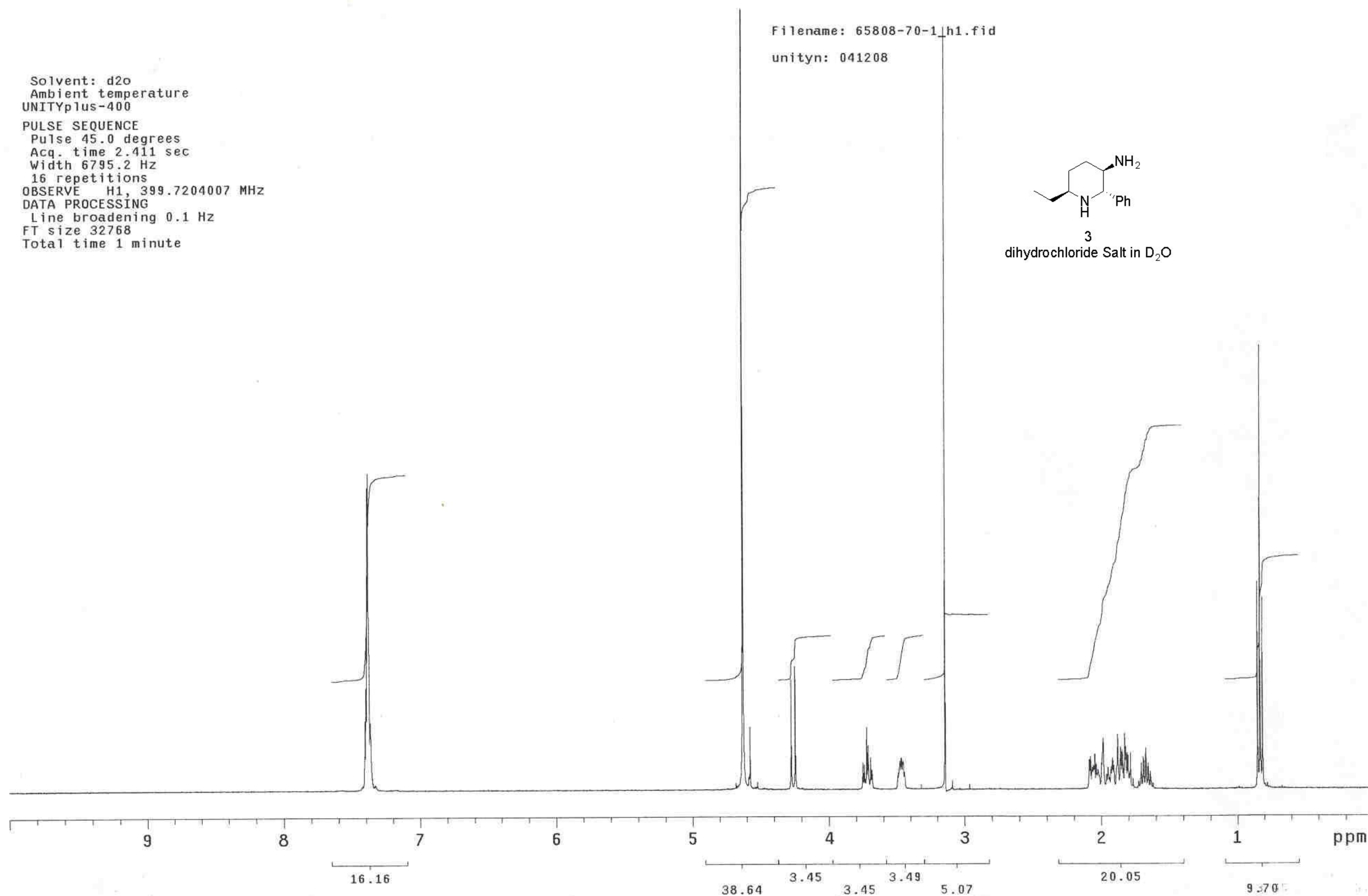
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Total time 1 minute



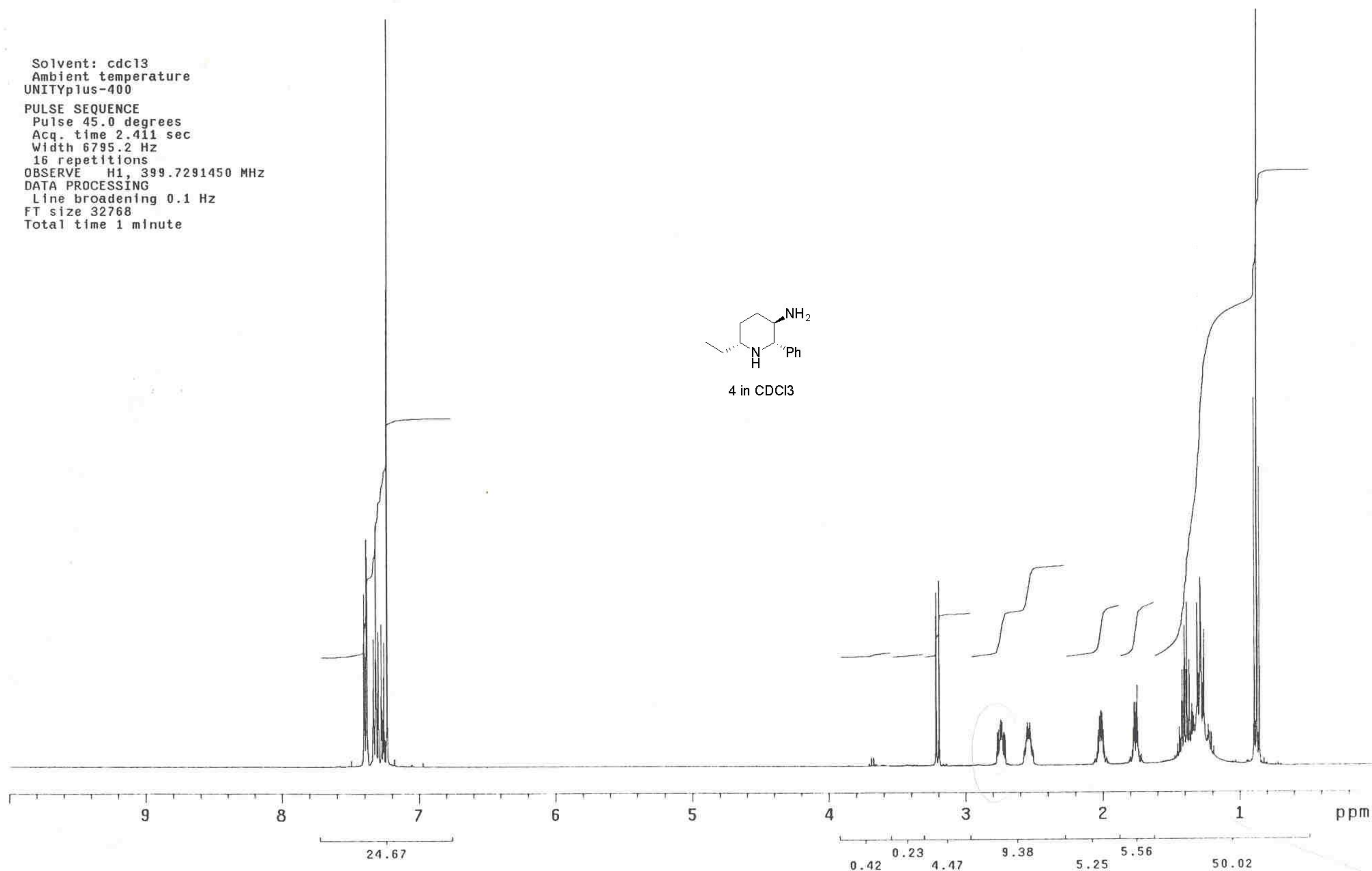
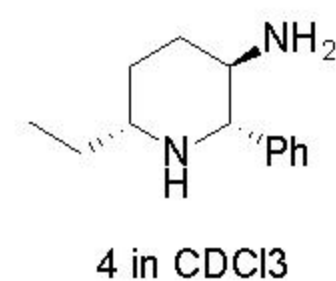
Solvent: d2o
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.411 sec
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16 repetitions
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DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute

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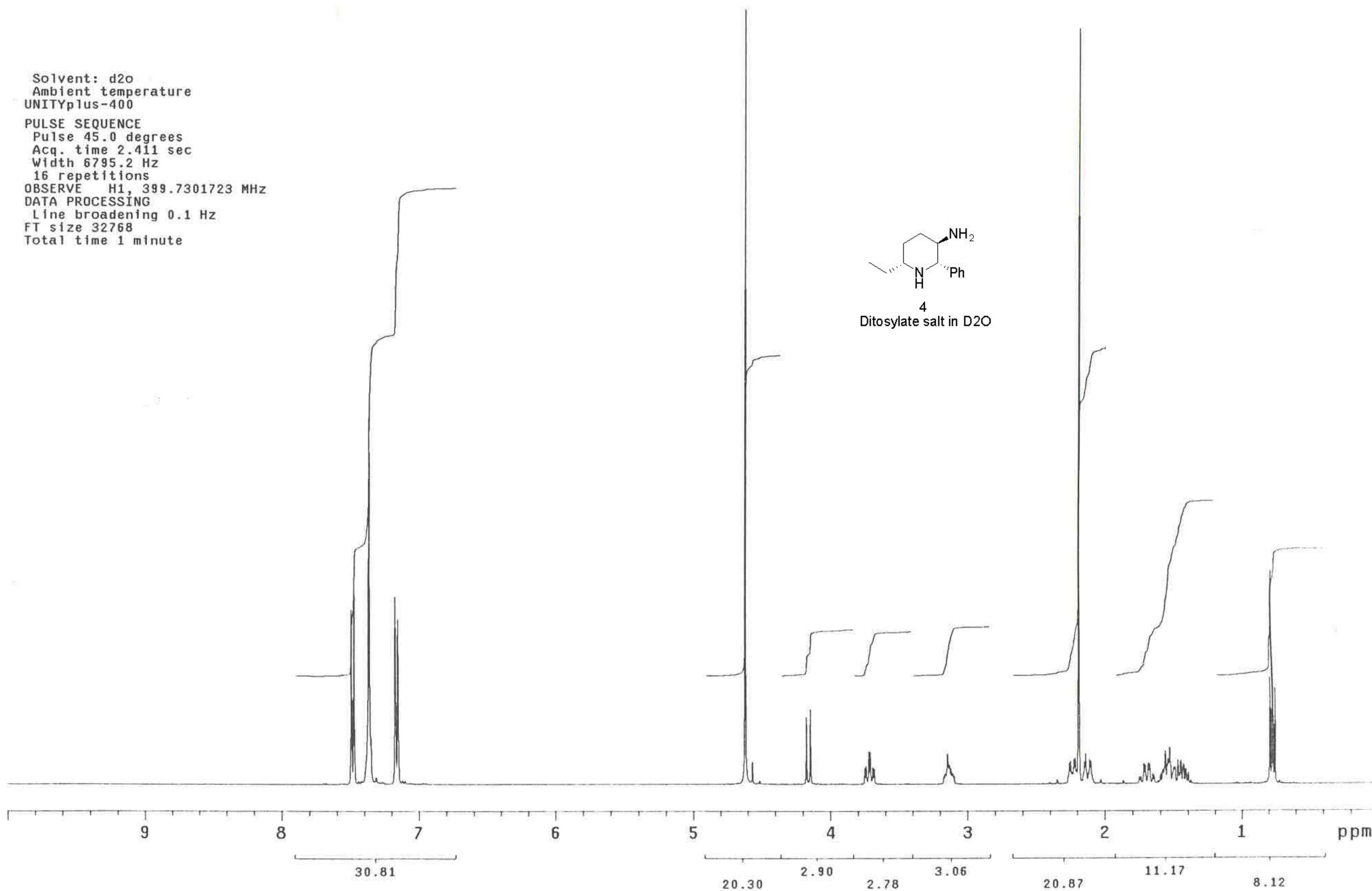
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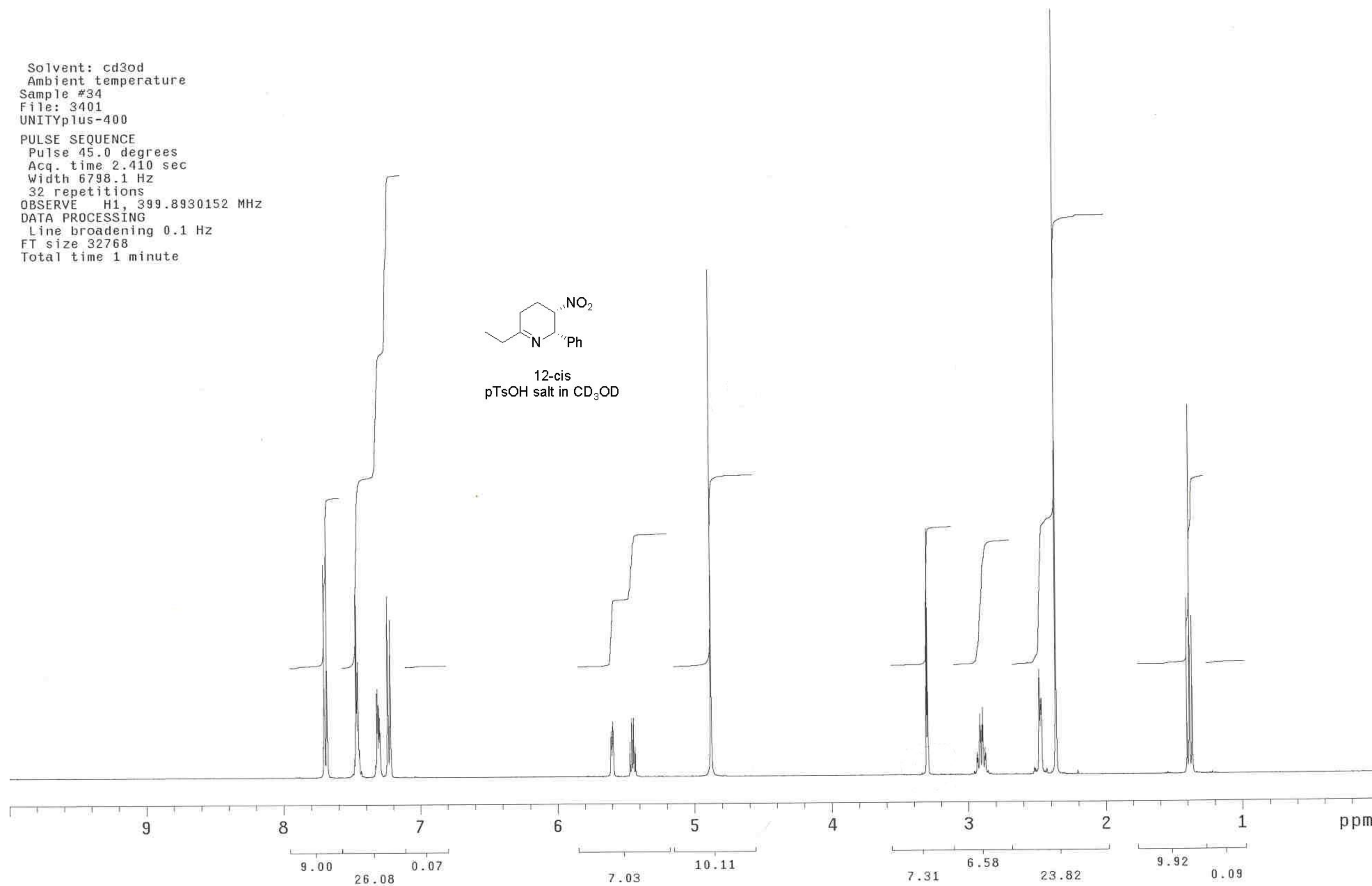
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Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.411 sec
Width 6795.2 Hz
16 repetitions
OBSERVE H1, 399.7291450 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



Solvent: d2o
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.411 sec
Width 6795.2 Hz
16 repetitions
OBSERVE H1, 399.7301723 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



Solvent: cd3od
Ambient temperature
Sample #34
File: 3401
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.410 sec
Width 6798.1 Hz
32 repetitions
OBSERVE H1, 399.8930152 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



Solvent: cd3od
Ambient temperature
UNITYplus-400

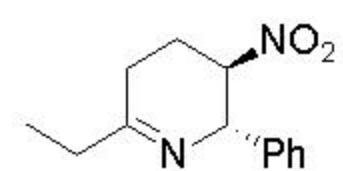
PULSE SEQUENCE

Pulse 45.0 degrees
Acq. time 2.412 sec
Width 6794.1 Hz
16 repetitions

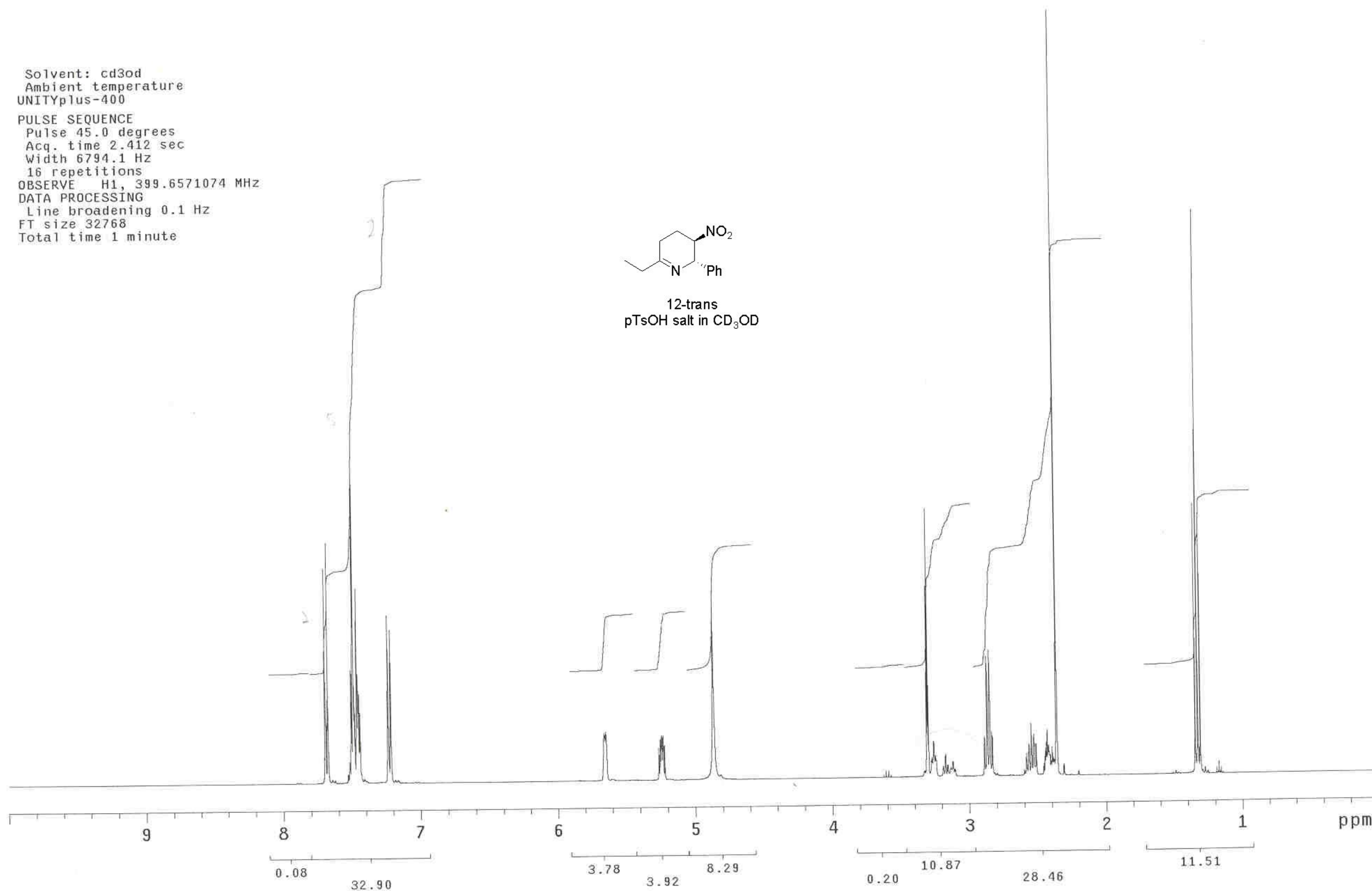
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DATA PROCESSING

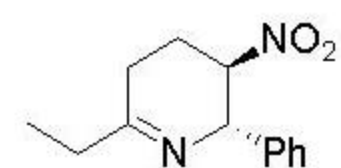
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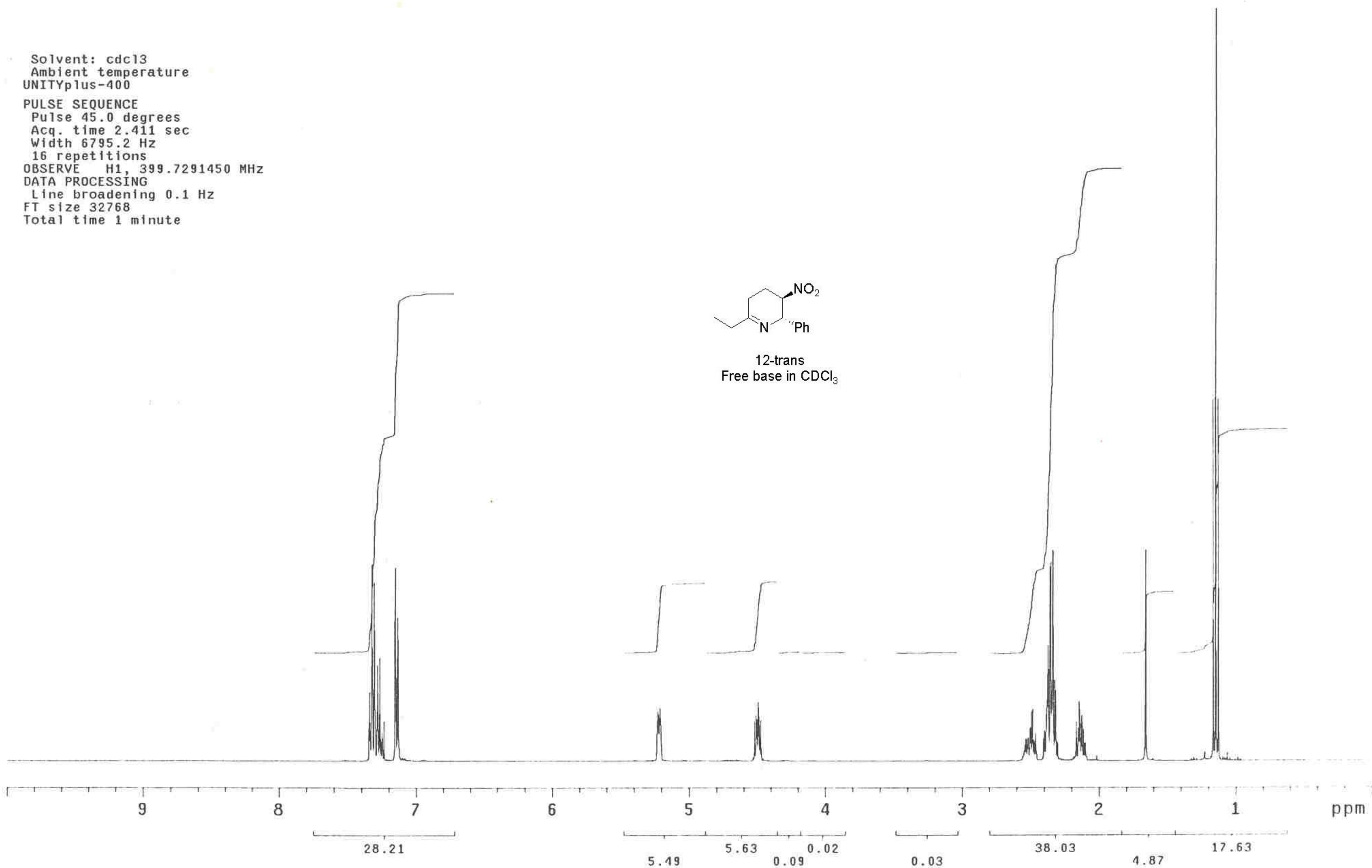
12-trans
pTsOH salt in CD₃OD



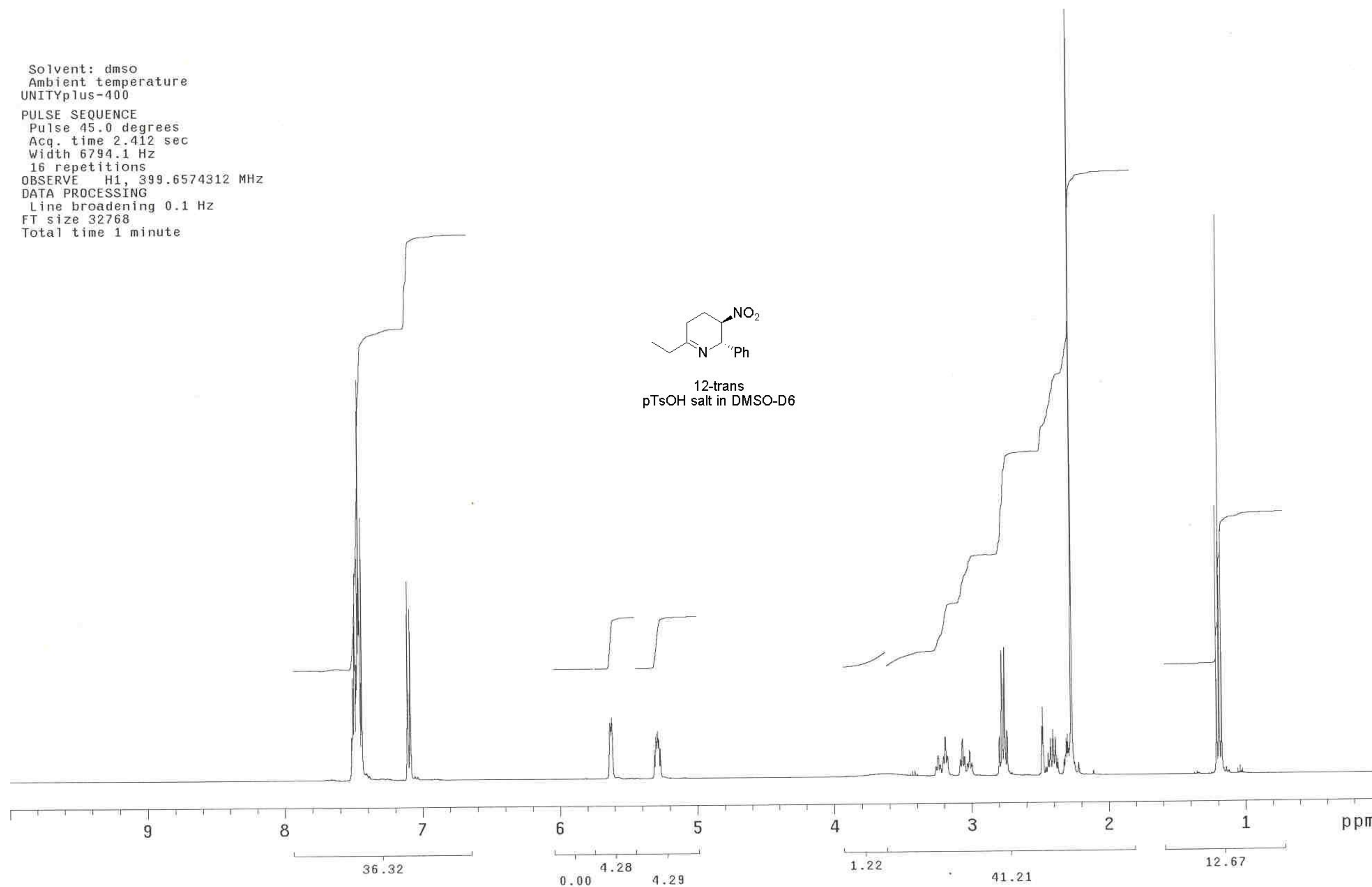
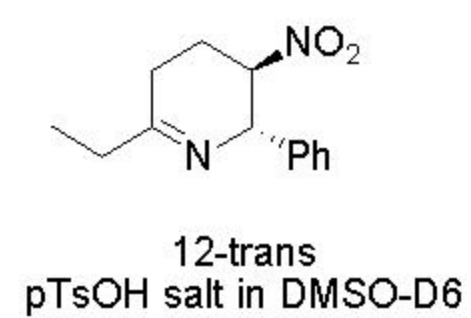
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DATA PROCESSING
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FT size 32768
Total time 1 minute



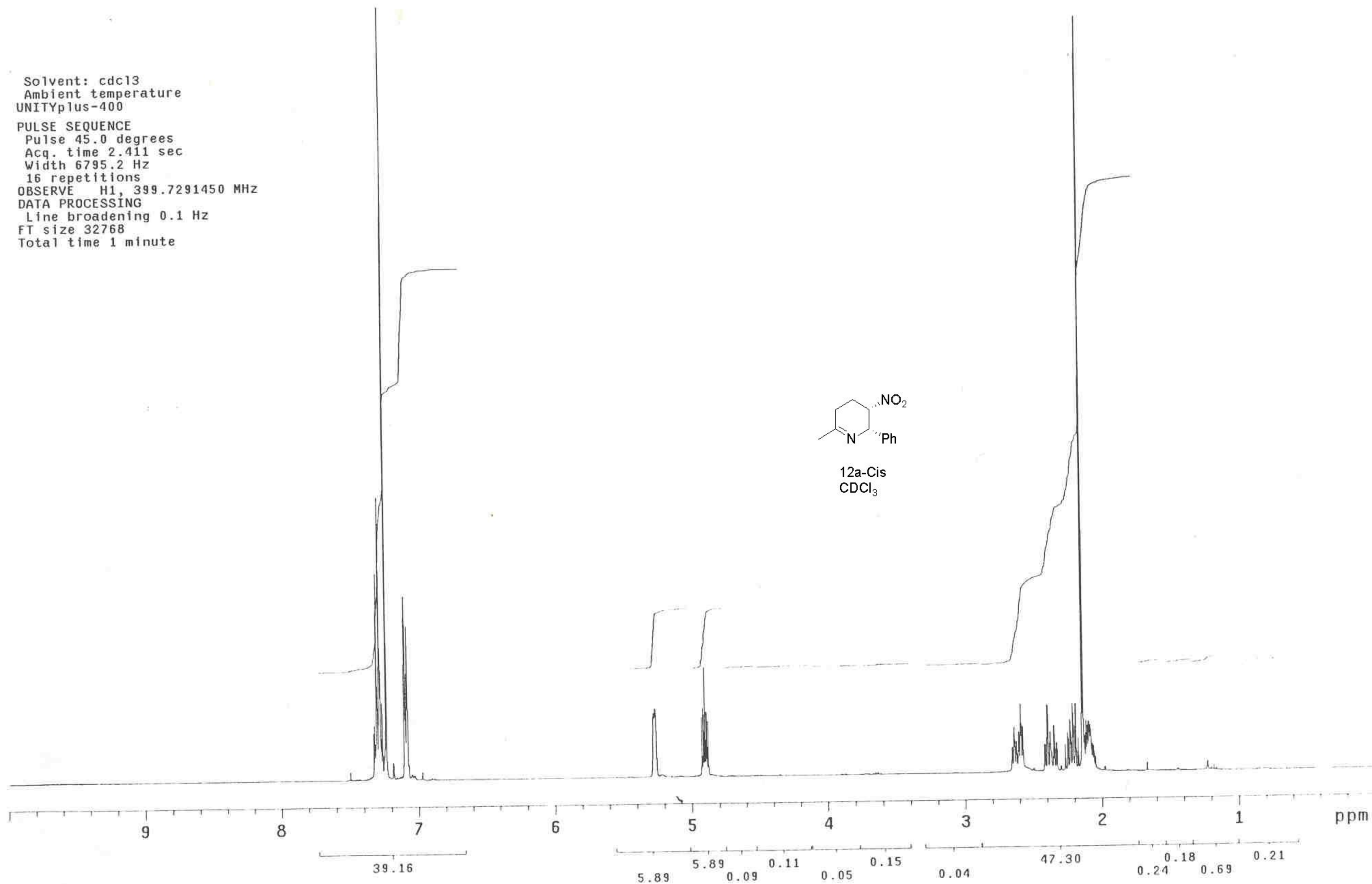
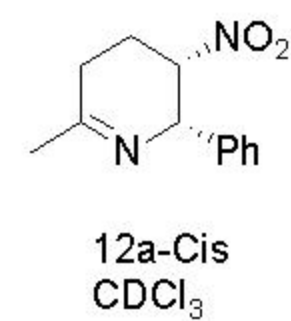
12-trans
Free base in CDCl₃



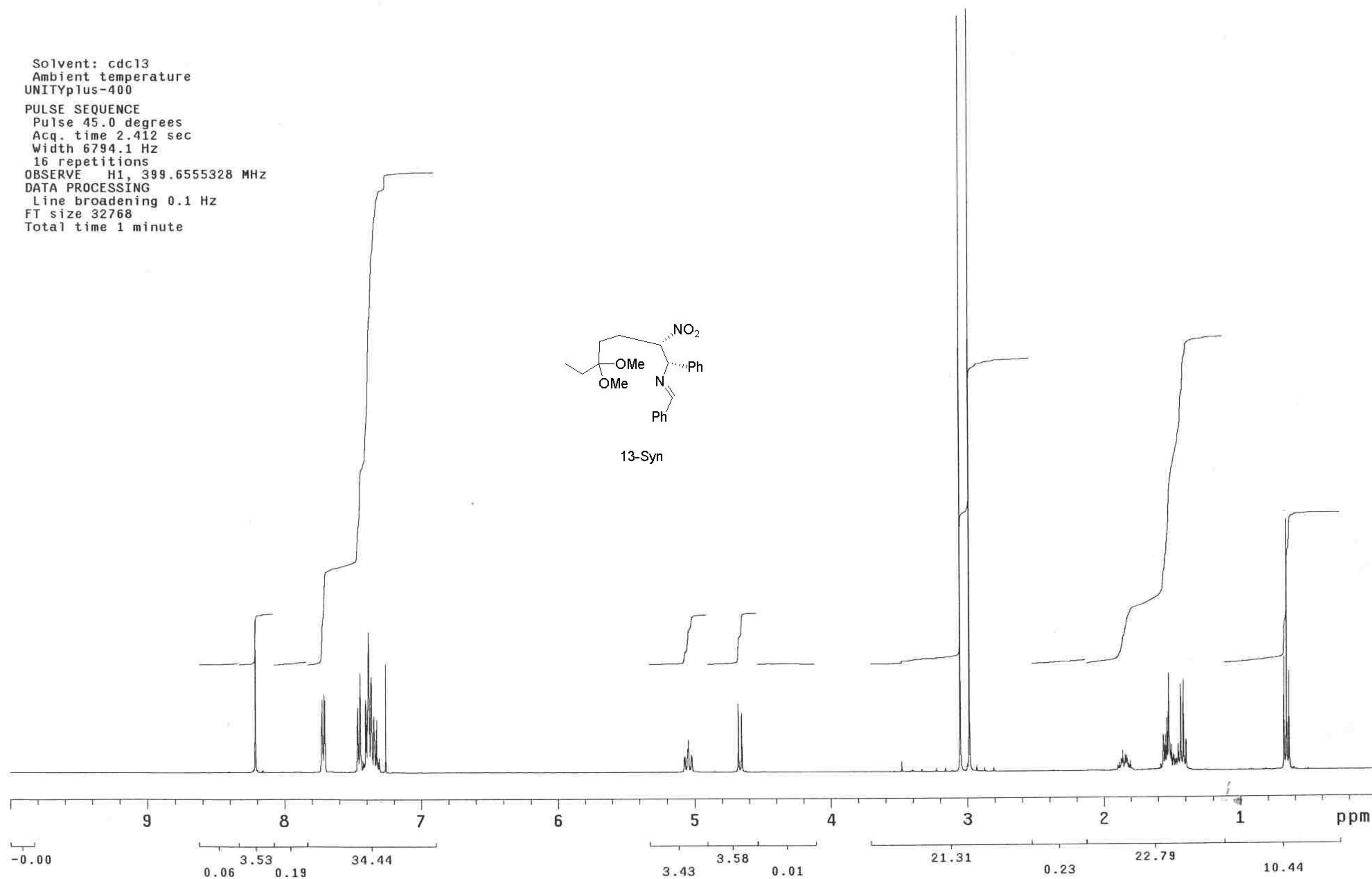
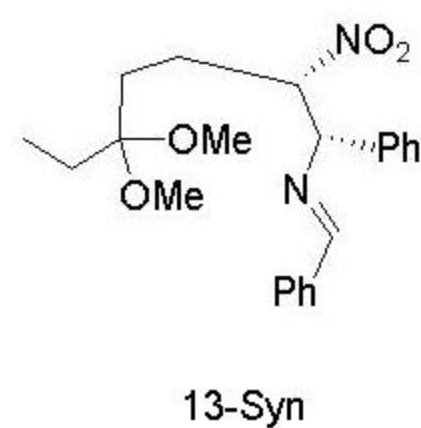
Solvent: dmsO
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
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16 repetitions
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DATA PROCESSING
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FT size 32768
Total time 1 minute



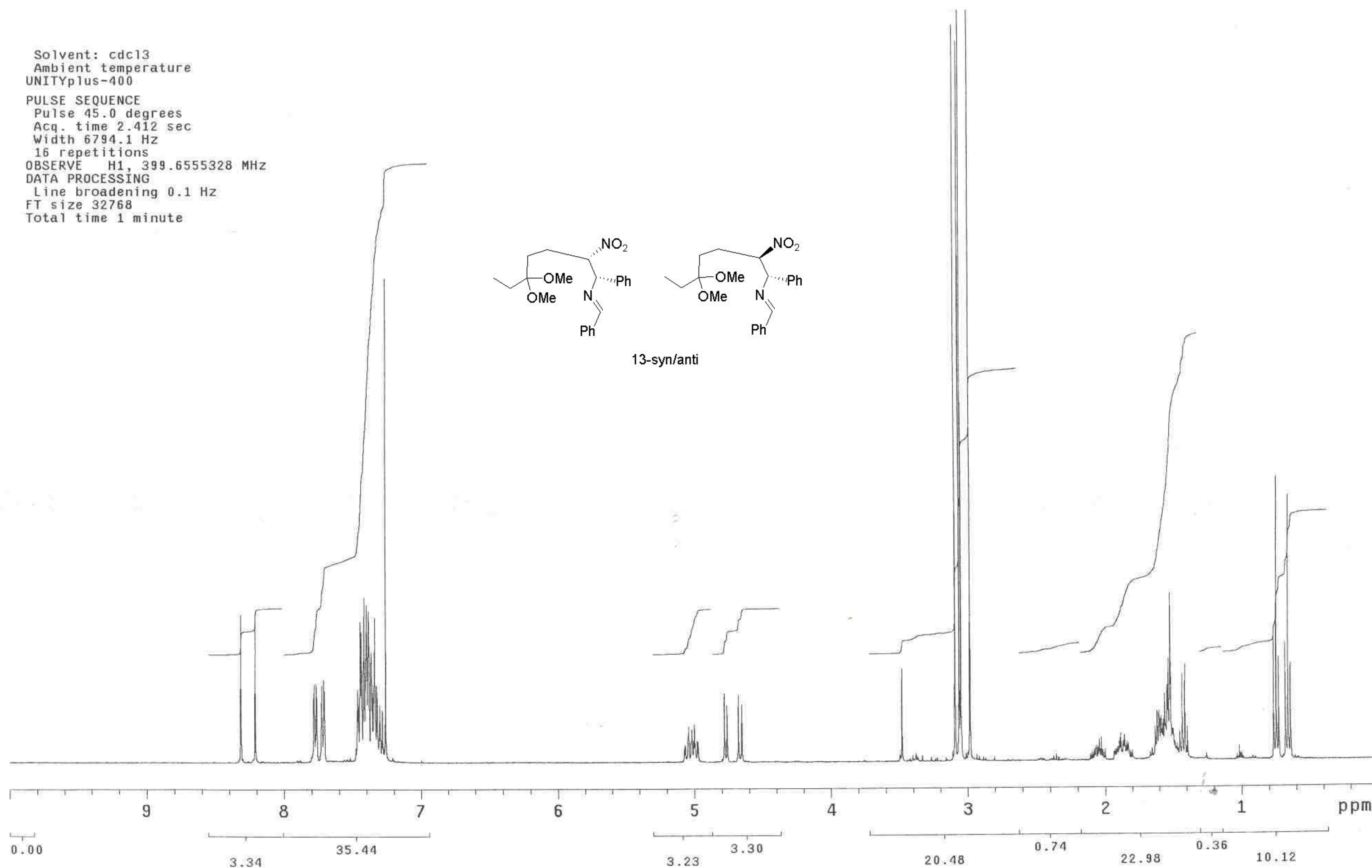
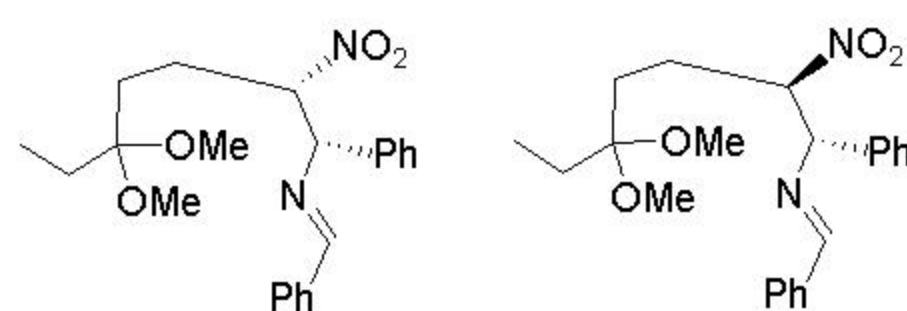
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16 repetitions
OBSERVE H1, 399.7291450 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



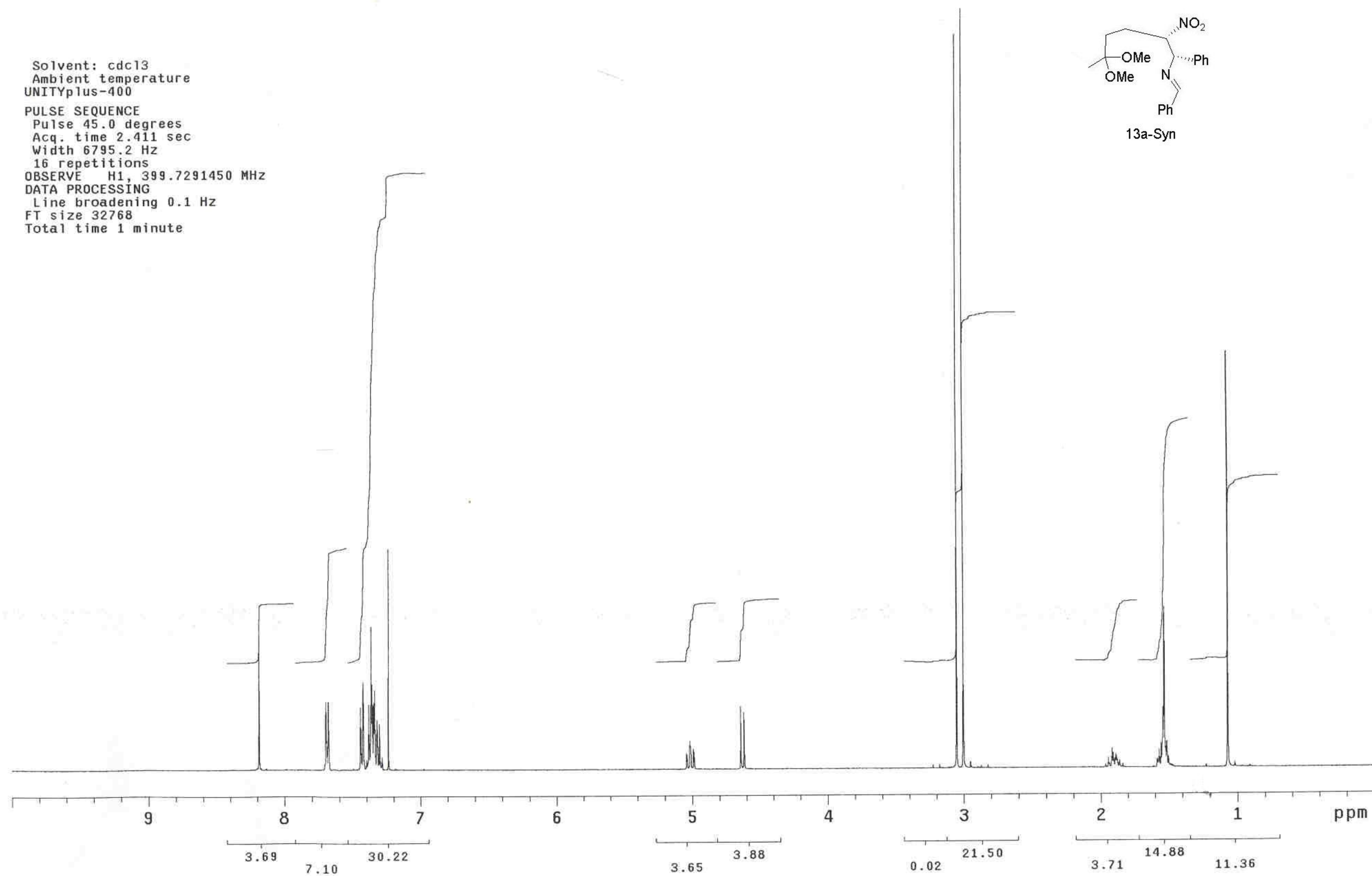
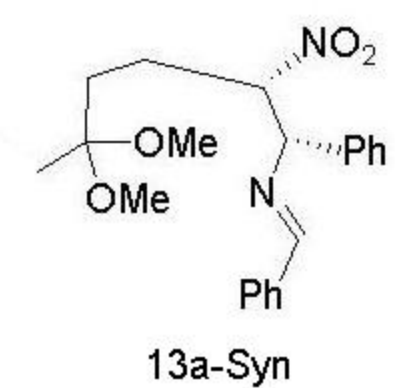
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 Ambient temperature
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 16 repetitions
 OBSERVE H1, 399.655328 MHz
 DATA PROCESSING
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 FT size 32768
 Total time 1 minute



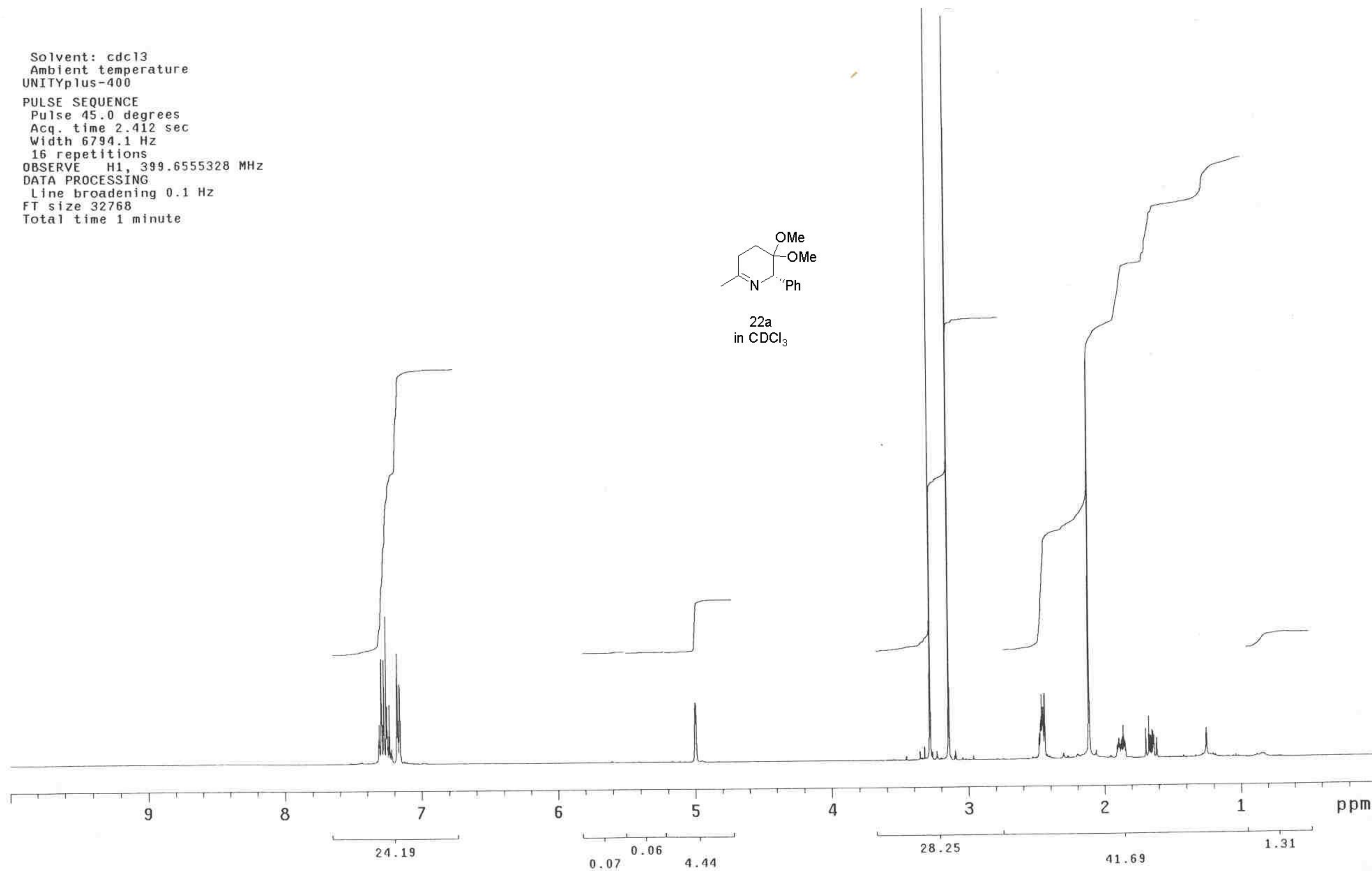
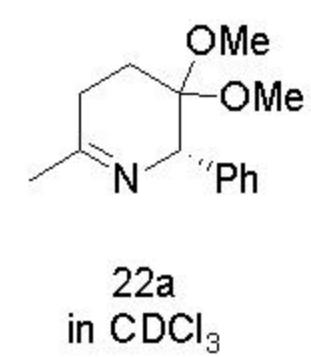
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 DATA PROCESSING
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 FT size 32768
 Total time 1 minute



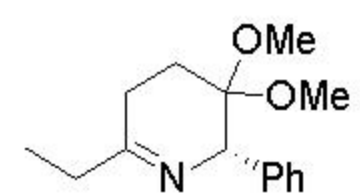
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 DATA PROCESSING
 Line broadening 0.1 Hz
 FT size 32768
 Total time 1 minute



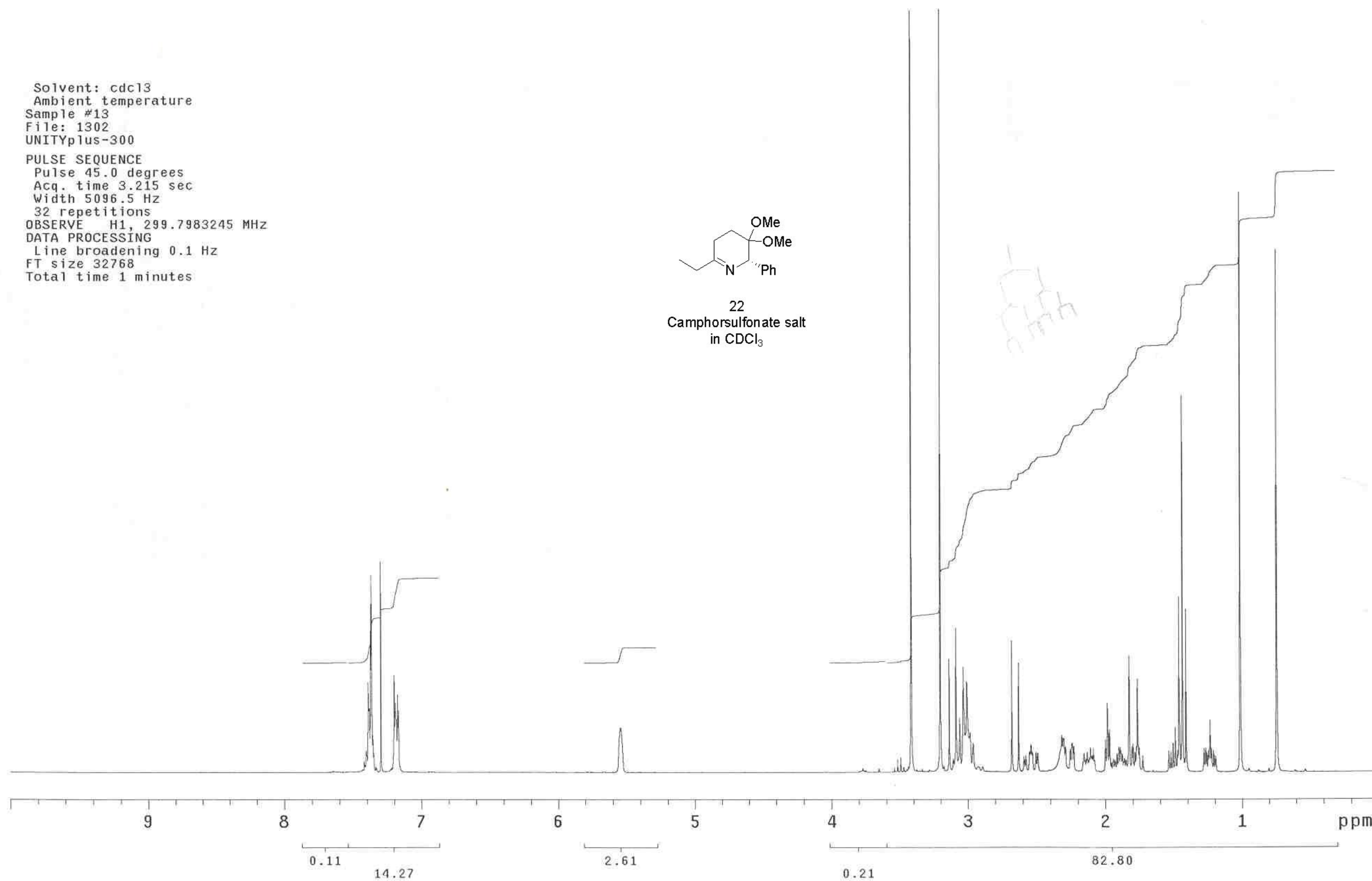
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OBSERVE H1, 399.6555328 MHz
DATA PROCESSING
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FT size 32768
Total time 1 minute



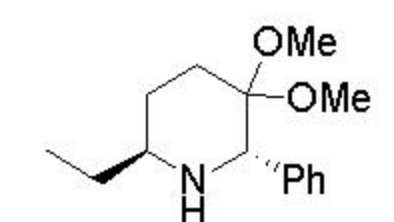
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32 repetitions
OBSERVE H1, 299.7983245 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minutes



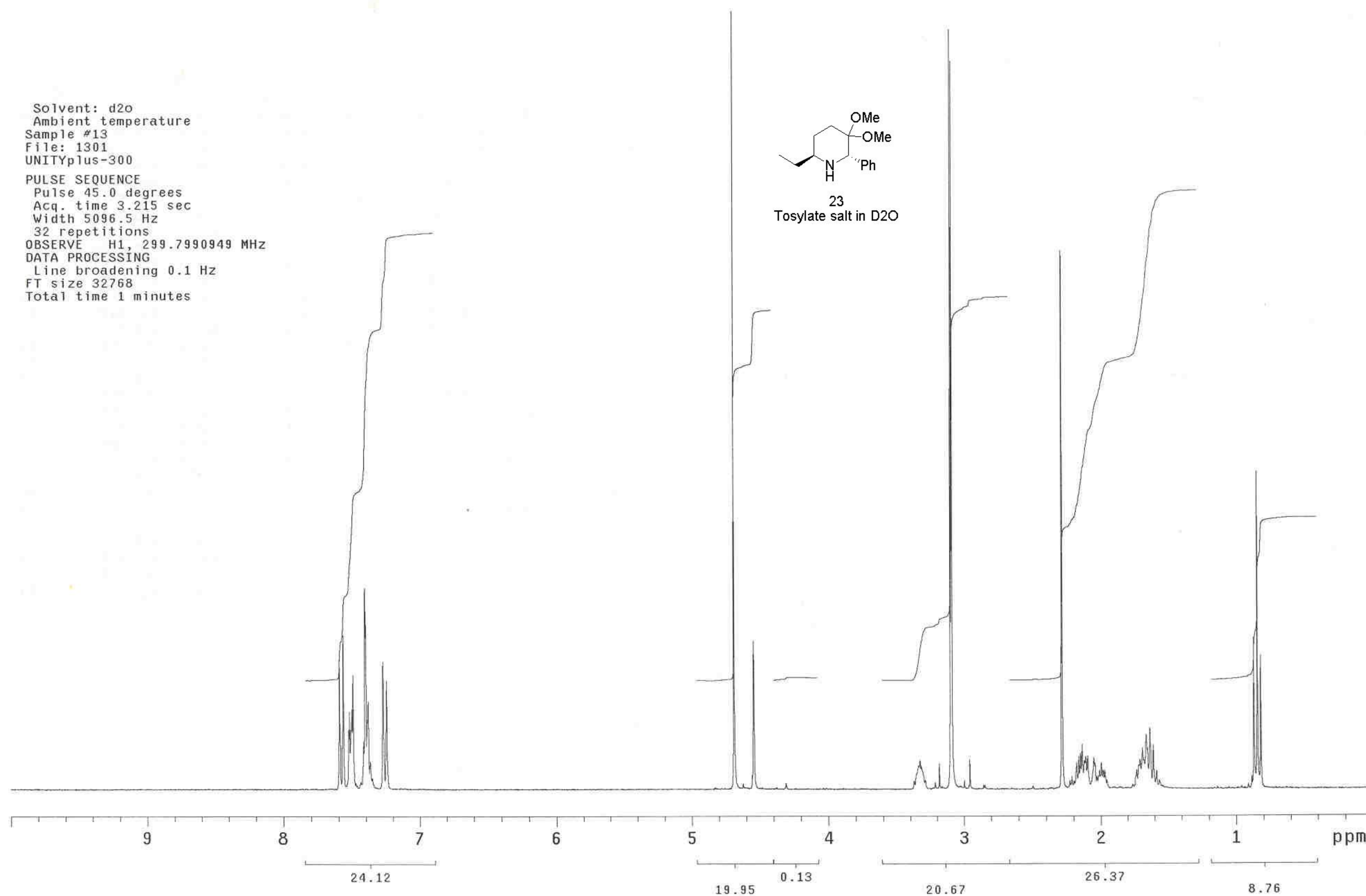
22
Camphorsulfonate salt
in CDCl₃



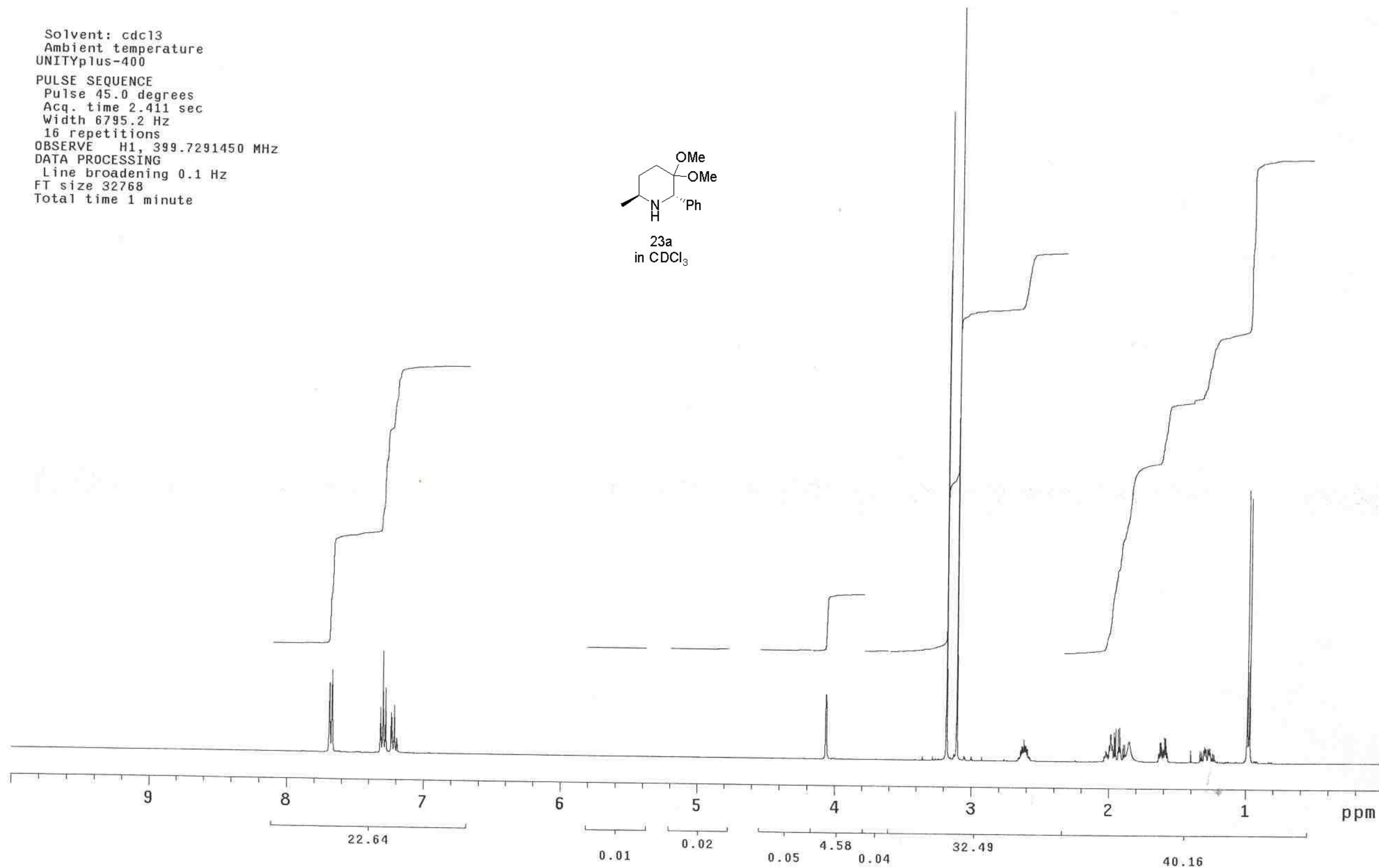
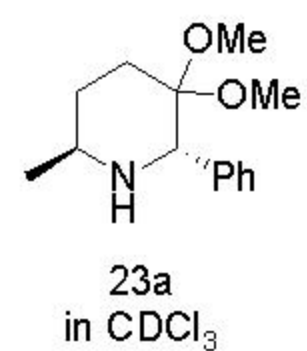
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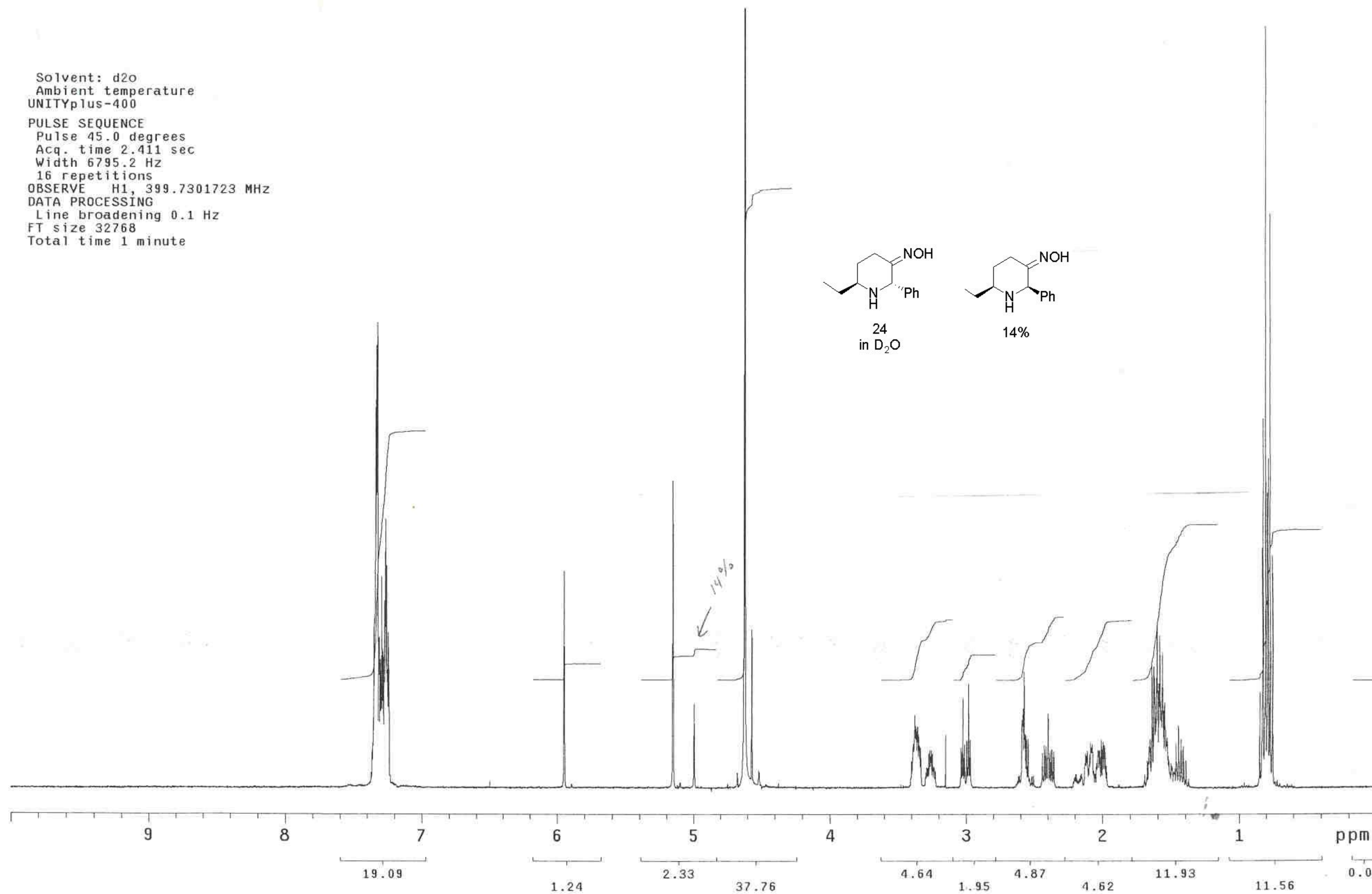
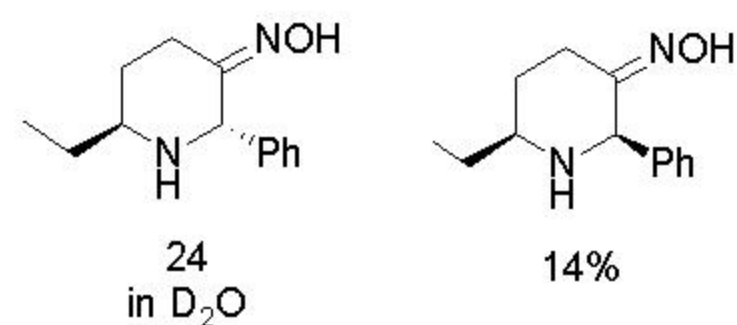
23
 Tosylate salt in D2O



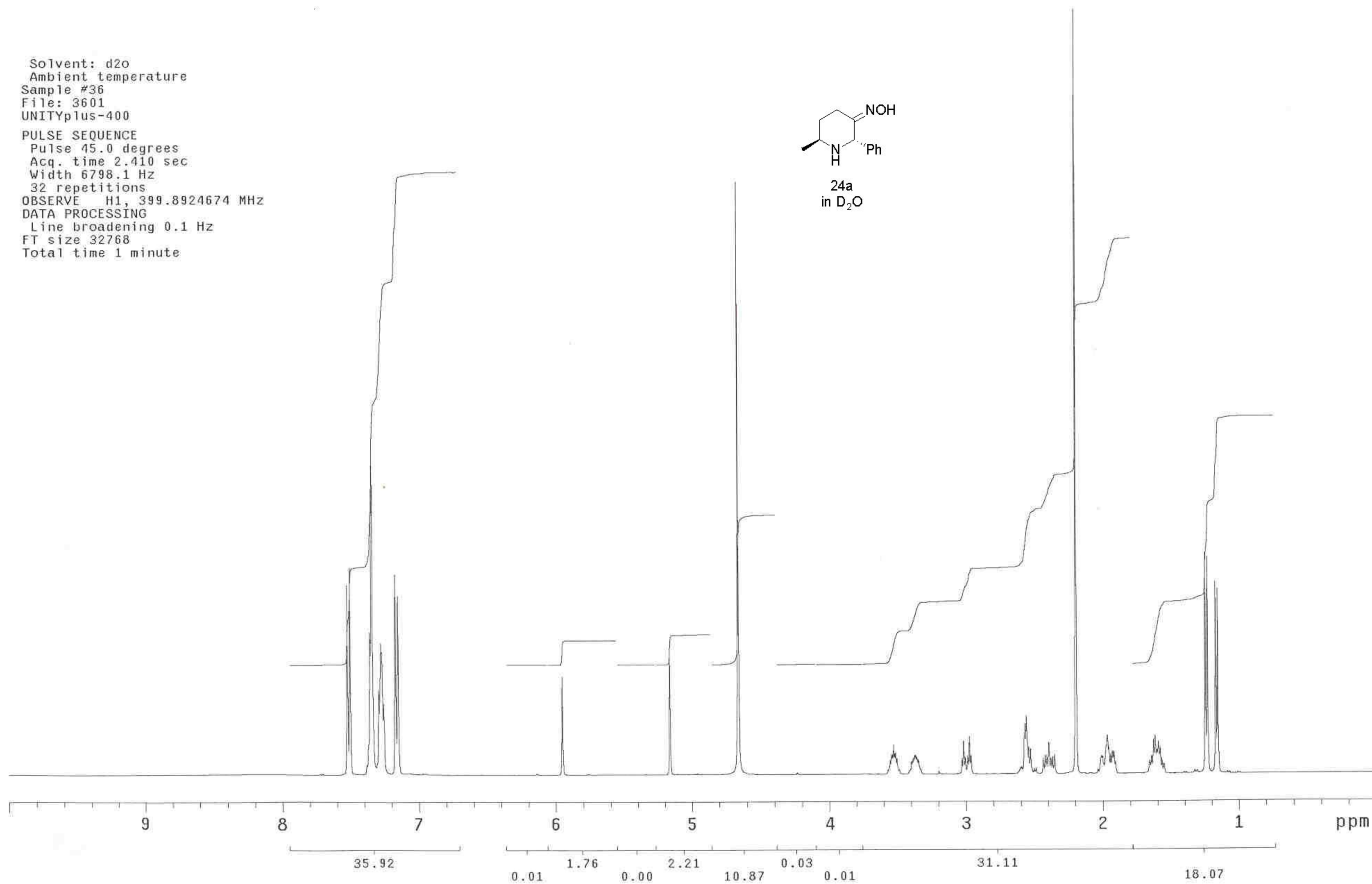
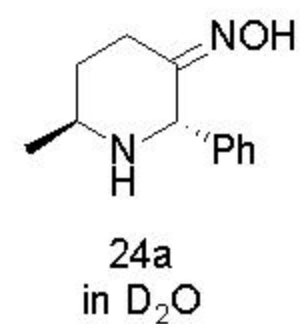
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 Ambient temperature
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 16 repetitions
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 FT size 32768
 Total time 1 minute



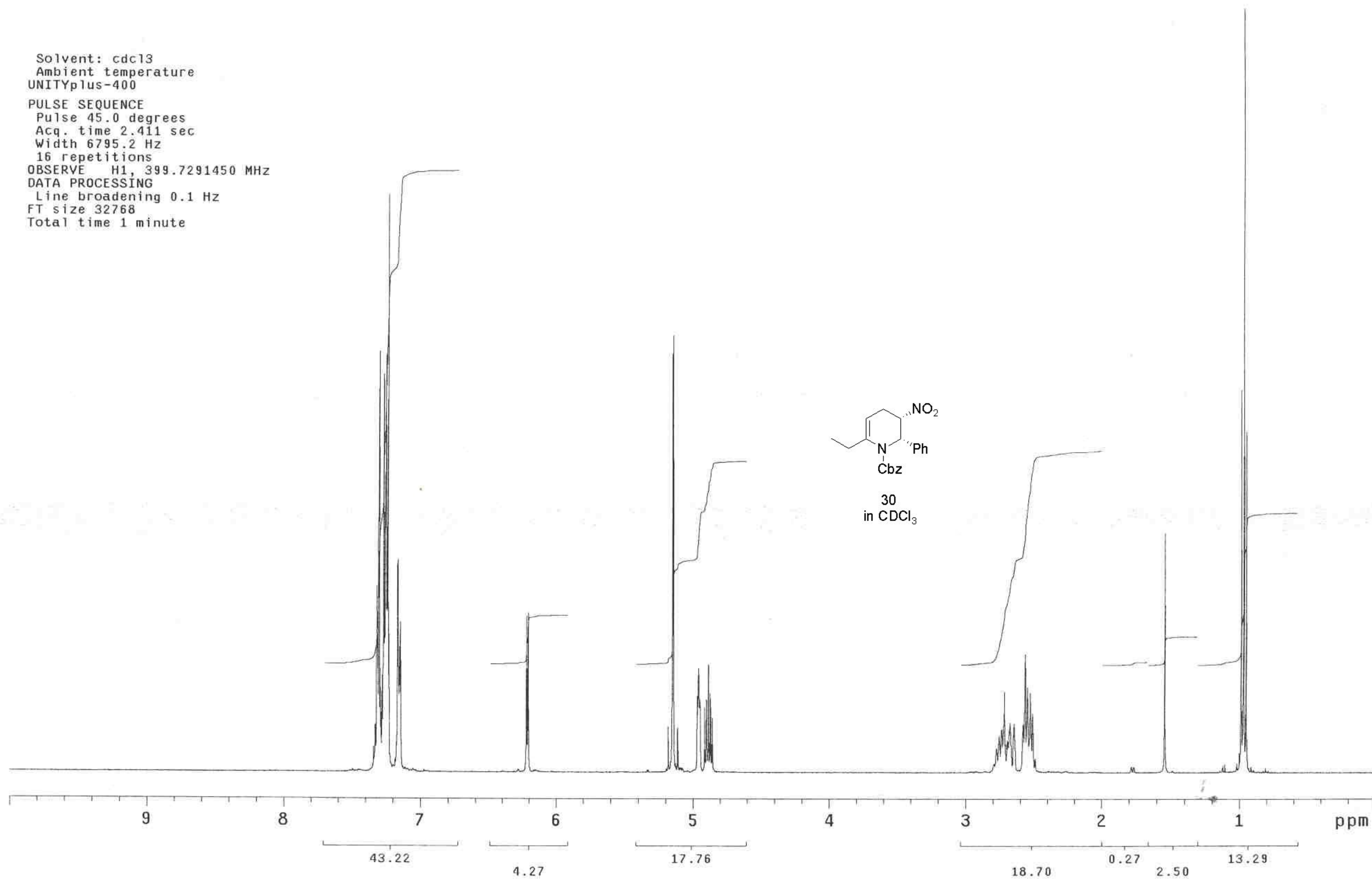
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 DATA PROCESSING
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 FT size 32768
 Total time 1 minute



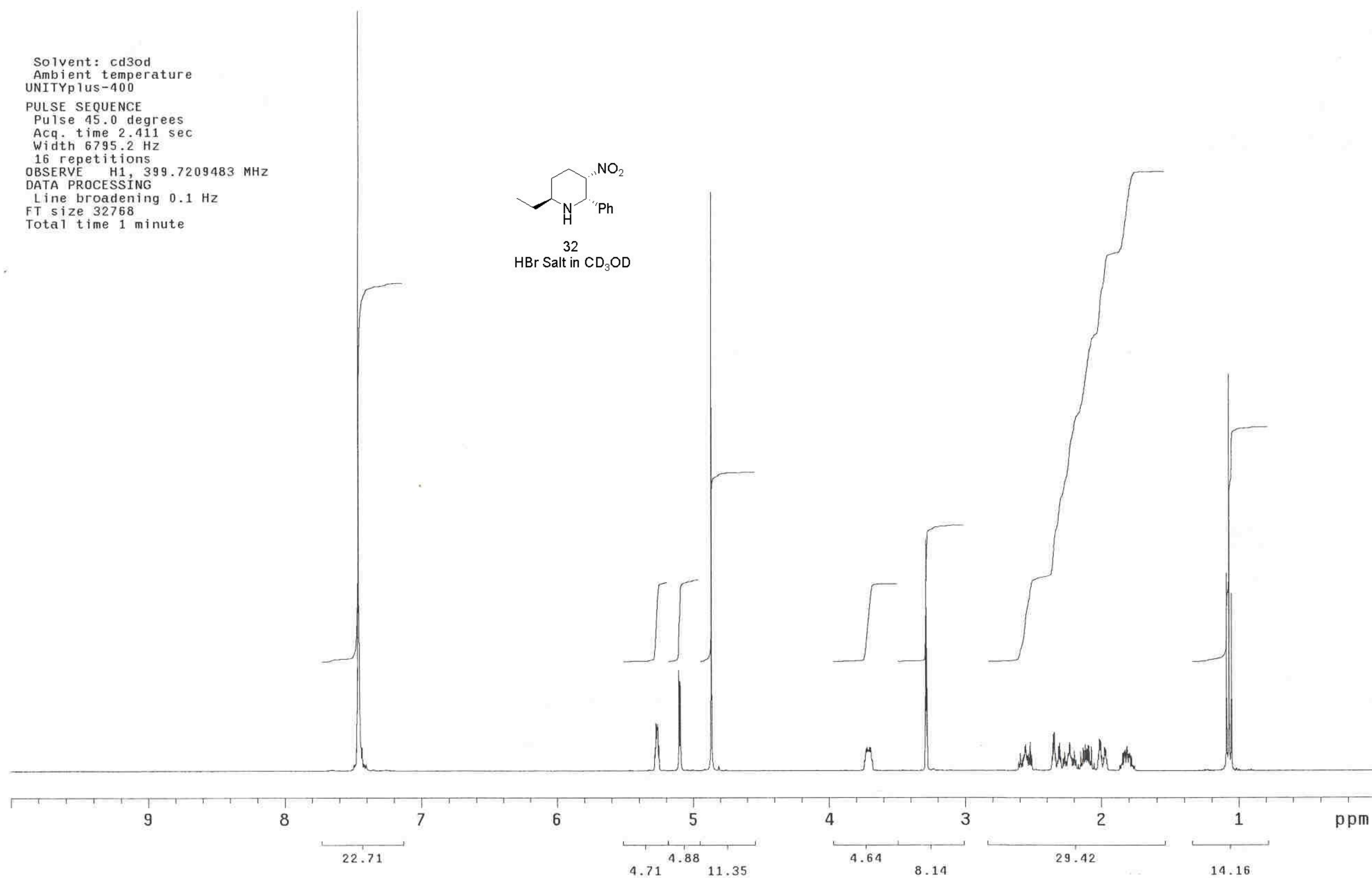
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 Ambient temperature
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 DATA PROCESSING
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 FT size 32768
 Total time 1 minute



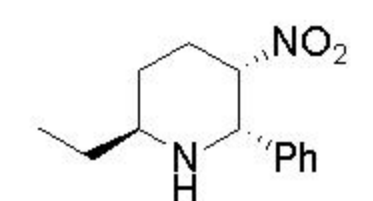
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 PULSE SEQUENCE
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 16 repetitions
 OBSERVE H1, 399.7291450 MHz
 DATA PROCESSING
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 FT size 32768
 Total time 1 minute



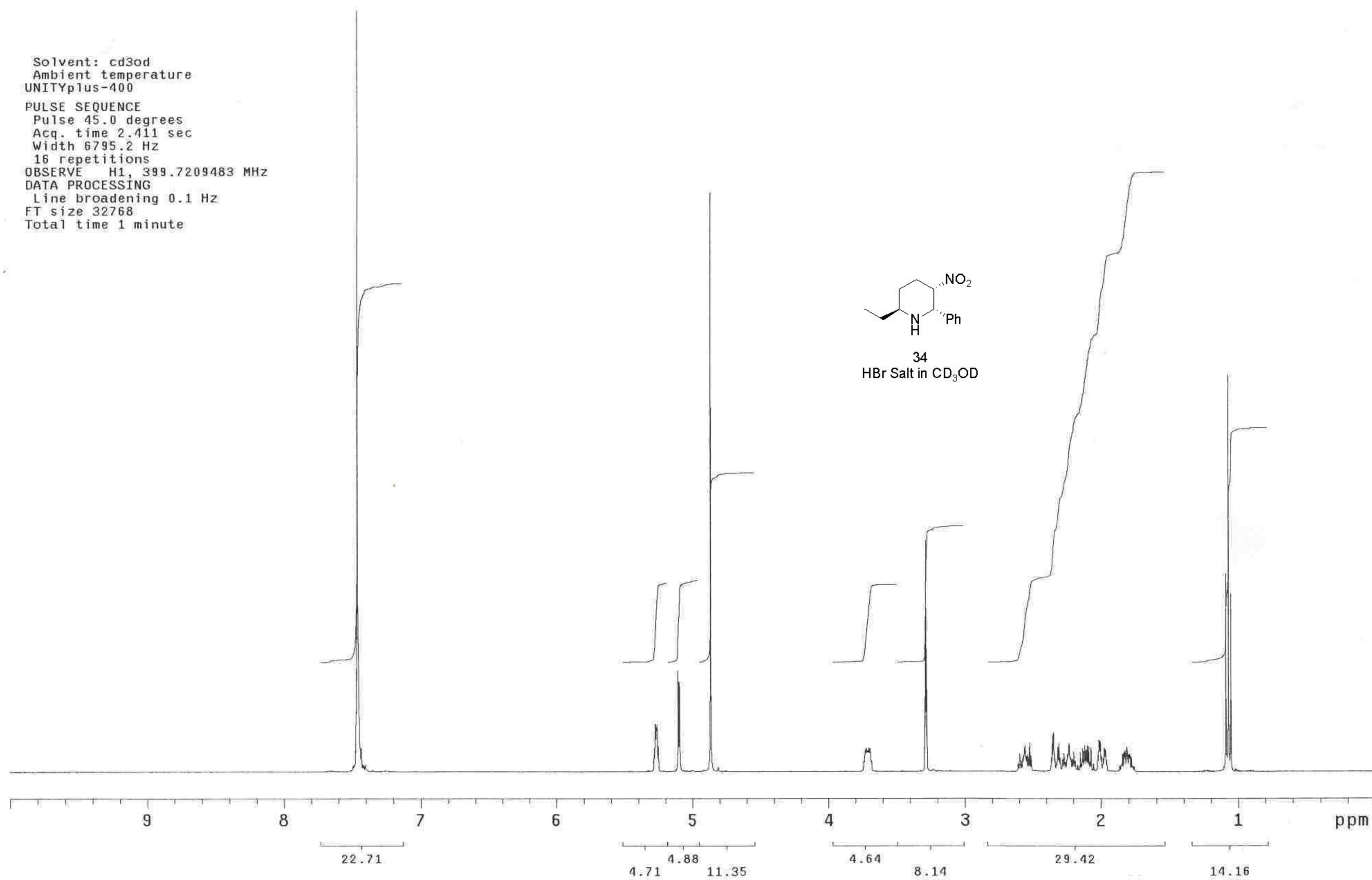
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DATA PROCESSING
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FT size 32768
Total time 1 minute



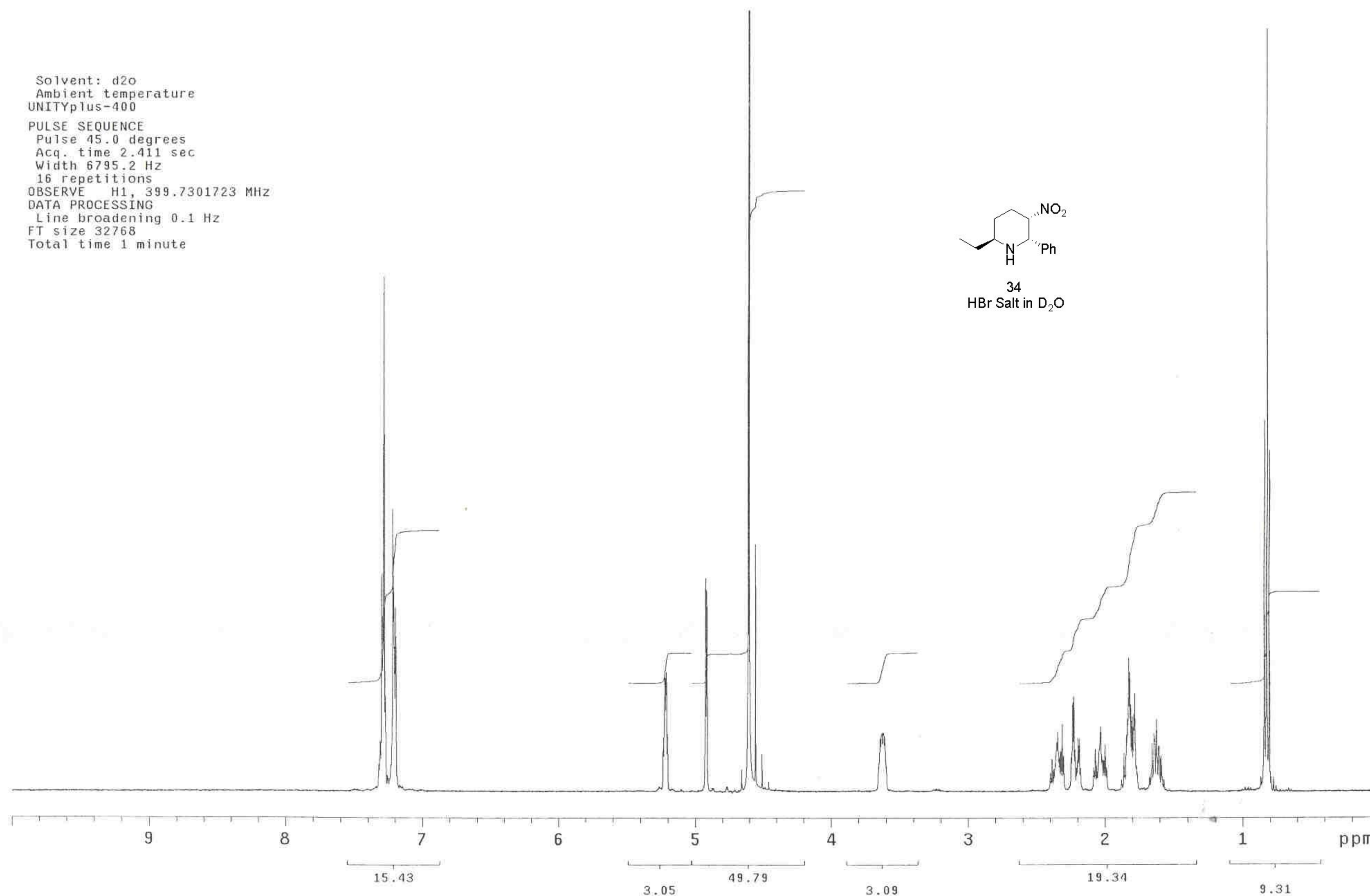
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DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



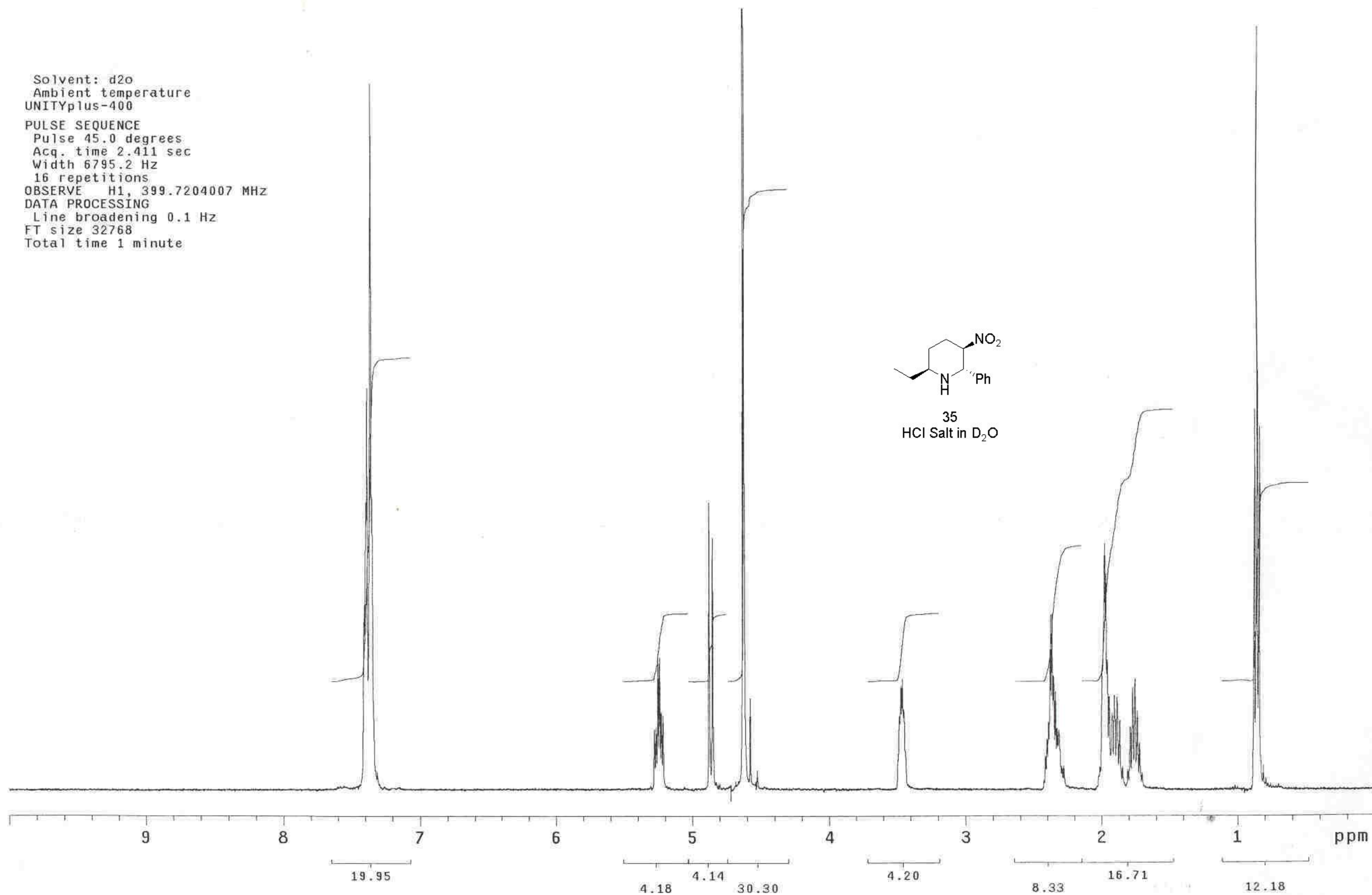
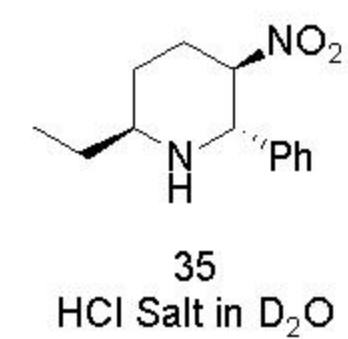
34
HBr Salt in CD₃OD



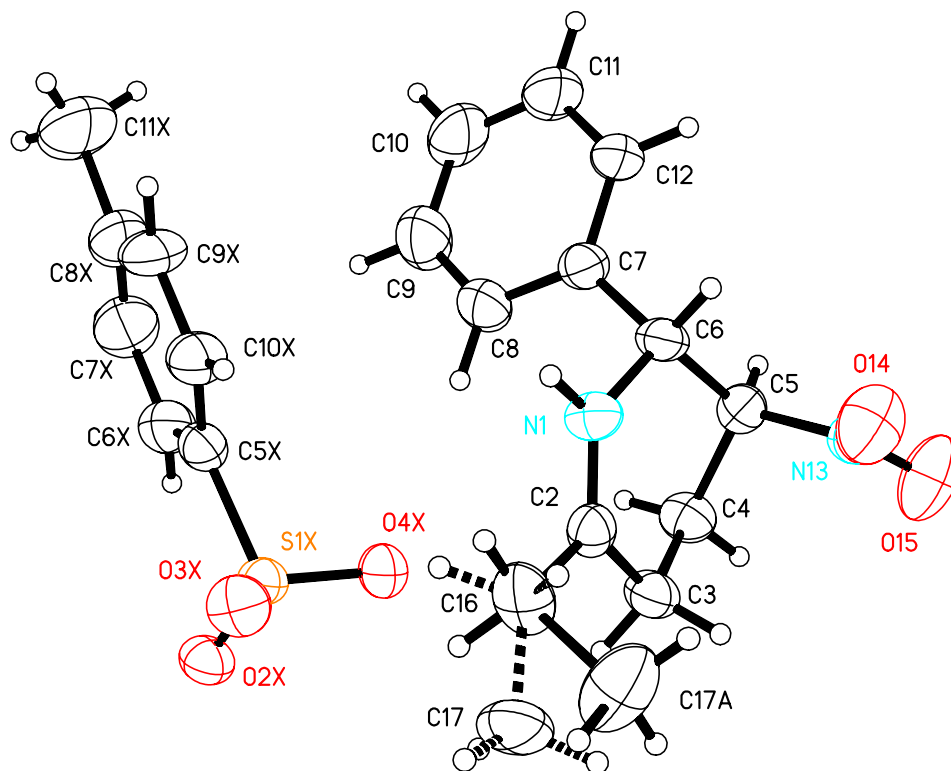
Solvent: d2o
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.411 sec
Width 6795.2 Hz
16 repetitions
OBSERVE H1, 399.7301723 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



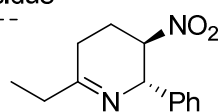
Solvent: d2o
Ambient temperature
UNITYplus-400
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.411 sec
Width 6795.2 Hz
16 repetitions
OBSERVE H1, 399.7204007 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 minute



X-Ray Crystallography ORTEP Diagram for **12-cis**



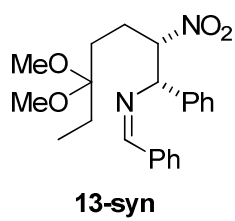
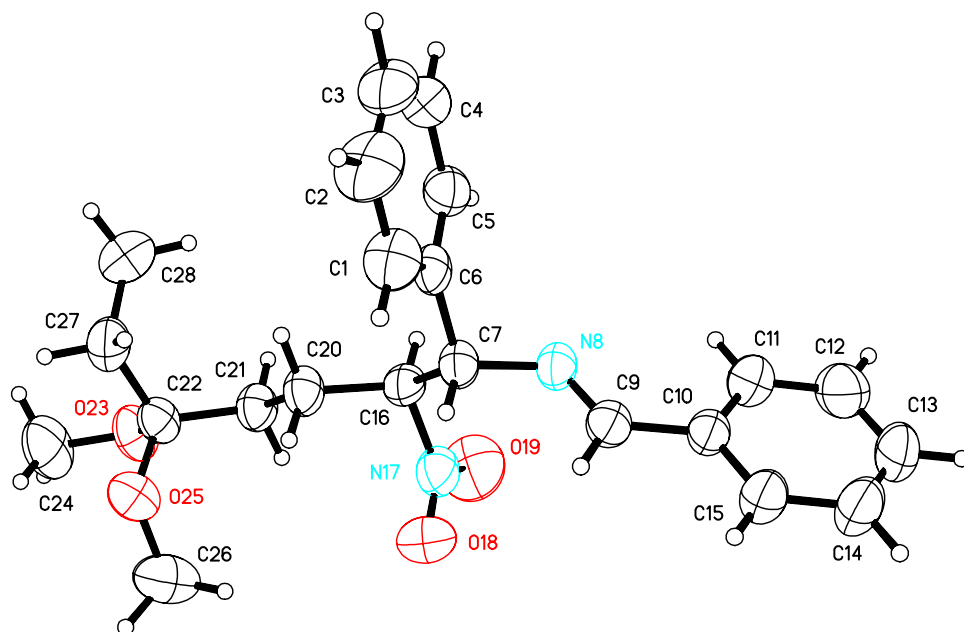
Disorder in ethy residue
shown with -----



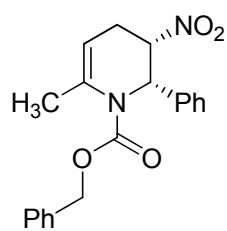
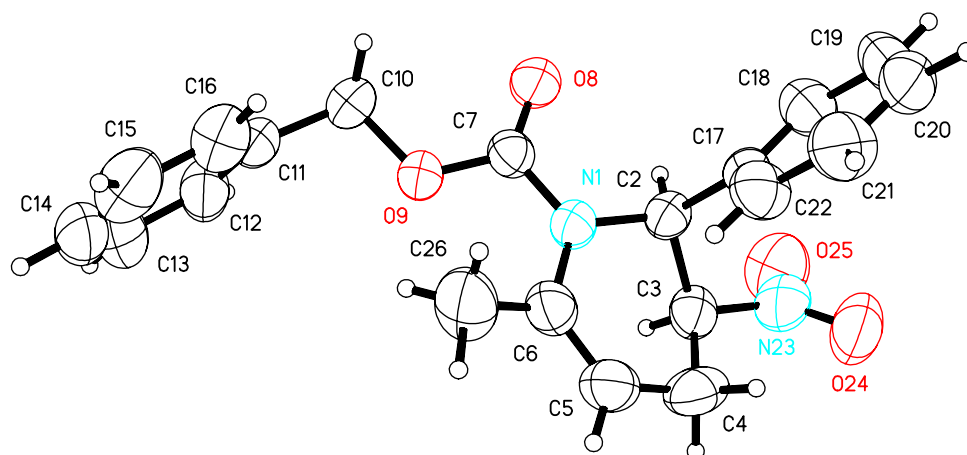
TsOH

12-trans

X-Ray Crystallography ORTEP Diagram for **13-syn**



X-Ray Crystallography ORTEP Diagram for **30a**



30a

X-Ray Crystallography ORTEP Diagram for **34**