An Efficient Synthesis of Enantiomerically Pure (*R*)-Pipecolic Acid, (*S*)-Proline and their *N*-Alkylated Derivatives

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SUPPORTING INFORMATION

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General experimental methods

All reactions were carried out under argon with magnetic stirring. All solvents and chemical compounds were purified based on standard procedures. Reagent-grade solvents were used without purification for all extractions and work-up procedures. R_f values refer to TLC on 0.25 mm silica gel plates (60-F_{254}). Flash chromatography (FC) was performed on silica gel 60 (0.040–0.063 mm). IR spectra were acquired on a FT-IR and are reported in wavenumbers

(cm^{-1}) with polystyrene as a standard. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^1H NMR spectra were measured on a 250 or 360 MHz spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 7.27 and D_2O at 4.8 ppm). ^{13}C NMR spectra were measured on a 62.9 or 90.56 MHz spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 77.16 ppm). ^{31}P NMR spectra were recorded on a 101.26 MHz and chemical shifts were quoted relative to internal 85% H_3PO_4 (δ = 0 ppm). High resolution mass spectra were obtained using the following ionization techniques: chemical ionization (CI), electron impact (EI), and electrospray (ES). All new compounds were determined to be >95% pure by ^1H NMR spectroscopy. Optical rotation values were measured on a polarimeter. Samples were inserted into a cell with a path length of 1 dm. Enantiomeric excesses were also performed on a GC chiral column: Cydex B (25 m x 0.25 mm, 140 °C, 1 bar) or β-cyclodextrine DM (40 m x 0.25 mm, 120°C, 1 bar). For more details, see: previous paper.[1]

(2*R*,1'*R*)-5-Hydroxy-2-(1'-phenylethylamino)pentane nitrile [(*R*,*R*)-(+)-5]. Following procedure A in accompanying paper: From 2,3-dihydrofuran **3** (7 g, 100 mmol), (*R*)-α-phenylethylamine (*R*)-**9** (12,1 g, 100 mmol), and NaCN (5.88 g, 120 mmol) in 1 M HCl (100 mL), stirring at rt for 3 days, were obtained 21.80 g of crude desired amino nitrile (*R,R*)-**5**. Crystallisation from ether/pentane afforded 18.85 g (86.5%, in three crops) of pure amino nitrile. Mp 96.0 °C; $[\alpha]_D$ +208.3 (*c* 1.00, $CHCl_3$); R_f = 0.16 (EtOAc/petrol ether: 3/7); IR (neat) 3239, 2225 (CN), 1453 cm^{-1}; Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.35; H, 8.39; N, 12.63. All spectral data are identical with those of antipode (*S,S*)-(−)-**5**, see accompanying paper.

General procedure B: Preparation of cyclic amino nitriles (12/13 and 14/15). To a solution of hydroxyamino nitrile **5** or **6** (2 mmol) in CH_2Cl_2 (15 mL), was successively added at 0 °C, NEt_3 (306 μL, 2.2 mmol) cat. DMAP (60 mg), and mesyl chloride (152 mg, 171 μL, 2.2 mmol). The resulting mixture was stirred at 0 °C for 6 h, and then at rt for 1–2 days to complete reaction as shown by TLC. The mixture, concentrated to dryness, was subjected to chromatography on silica gel to afford pure cyclic amino nitrile **12**/**13** or **14**/**15** as inseparable mixtures of two diastereoisomers.

(2*S,1'*S*)-1-(1'-phenylethyl)pyrrolidine-2-carbonitrile [(2*S*,1'*S*)-12 and (2*R*,1'*S*)-13].**

Following procedure B: From amino nitrile (*S,S*)-**5** (2 mmol), NEt_3 (306 μL), cat. DMAP (60 mg) and MsCl (152 mg). After stirring at 0 °C for 6 h, and then at rt for 30 h, we obtained after FC (eluent EtOAc/petrol ether: 15 → 100%), 330 mg (82%) of nitriles as an inseparable oil mixture of two diastereomers (2*S*,1'*S*)-**12** and (2*R*,1'*S*)-**13** in a 60:40 ratio. R_f = 0.63 (EtOAc/petrol ether: 3/7); IR (neat) 2975, 2222 (CN), 1492, 1454 cm^{-1}; ^1H NMR δ **12**/**13** mixture (60/40): 1.53/1.51 (d, *J* = 6.7 Hz, 3H), 1.68–2.39 (m, 5H, **12**/**13**), 2.47–2.64 (m, 1H, **12**), 2.64–2.77 (m, 1H, **13**), 3.20–3.35 (m, 1H, **12**), 3.48 (dd, *J* = 2.5 Hz, *J* = 5.2 Hz, 1H, **12**), 3.57 (q, *J* = 6.7 Hz, 1H, **13**), 3.65 (q, *J* = 6.7 Hz, 1H, **12**), 4.16 (dd, *J* = 2.1 Hz, *J* = 6.8 Hz, 1H, **13**), 7.20–7.48 (m, 5H, **12**/**13**); ^{13}C NMR δ from **12**/**13** mixture (60:40): 21.6/21.5, 22.9/22.8, 29.2/29.5, 48.5/50.2, 52.9/51.7, 61.3/61.6, 117.7/117.6, 127.0/126.8, 127.3/127.1, 128.5/128.3, 143.7/144.2; MS (EI) *m/z* 200 (M^+, 7), 186 (45), *185* (100), 123 (44), 105 (95), 77 (43); HRMS (EI) calcd for $C_{13}H_{16}N_2$ 200.1313. Found: 200.1314.

(2*R,1'*R*)-1-(1'-phenylethyl)pyrrolidine-2-carbonitrile [(2*R*,1'*R*)-14 and (2*S*,1'*R*)-15].** Following procedure B: From amino nitrile (*R,R*)-**6** (1 mmol), NEt_3 (155 μL), cat. DMAP (30 mg) and MsCl (86 mg). After, stirring at 0 °C for 8 h and at rt for 5 days, and then FC (EtOAc/CH_2Cl_2: 5 → 10%), we obtained 148 mg (69%) of pure cyclic amino nitriles as an inseparable mixture of two diastereomers (2*R*,1'*R*)-**14** and (2*S*,1'*R*)-**15** in a 55:45 ratio. R_f = 0.75 (EtOAc/petrol ether: 3/7); IR (neat) 3401, 2222 (CN), 1454 cm^{-1}; ^1H NMR δ **14**/**15** mixture (55/45): 1.38/1.35 (d, *J* = 6.6 Hz, 3H, **14**/**15**), 1.40–2.08 (m, 6H, **14** and 6H, **15**), 2.16 (dt, *J* = 3.0 Hz, *J* = 12.0 Hz, 1H, **15**), 2.35 (d, *J* = 3.0 Hz, *J* = 12.0 Hz, 1H, **14**), 2.61 (br d, *J* = 12.0 Hz, 1H, **15**), 3.22 (br d, *J* = 12.0 Hz, 1H, **14**), 3.48 (q, *J* = 6.6 Hz, 1H, **15**), 3.54 (q, *J* = 6.6 Hz, 1H, **14**), 3.60 (br s, 1H, **15**), 4.25 (br s, 1H, **14**), 7.14–7.43 (m, 5H **14** and 5H **15**); ^{13}C NMR δ from **14**/**15** mixture (55/45): 20.5/20.7, 21.5/21.0, 25.3/25.1, 28.8/29.2, 45.6/48.1, 51.7/49.6, 63.0/63.1, 117.2/117.0, 127.1/127.2, 127.1/127.5, 128.8/128.5, 143.9/144.7; MS (EI) *m/z* 214 (M^+) (4), *199* (100), 172 (8), 105 (89), 83 (14).

(2*S,1'*S*)-1-(1'-phenylethyl)pyrrolidine-2-carboxamide [(2*S*,1'*S*)-7 and (2*R*,1'*S*)-16].** According to procedure C in accompanying paper: From a mixture of nitrile **12**/**13** (dr: 60:40) (3 mmol), concd H_2SO_4 (18 M, 5 mL), CH_2Cl_2 (10 mL), after stirring at rt for 48 h and FC (twice, eluent, MeOH/EtOAc: 2/98 → 4%), we obtained 338 mg (51.6%) of major (2*S*,1'*S*)-**7**, 225 mg (34.5%) of minor (2*R*,1'*S*)-**16** as an oil, and 33 mg (5%) as mixture of

7/**16**. Data of major (2*S*,1'*S*)-**7** are identical with those noted above.

*Data for (2R,1'S)-**16** minor isomer*: as viscous oil $[\alpha]_D$ +57 (*c* 0.25, $CHCl_3$); R_f = 0.08 (EtOAc/CH_2Cl_2: 3/7); IR (neat): 3420, 3281, 1682, 1453 cm^{-1}; ^1H NMR δ 1.43 (d, *J* = 6.8 Hz, 3H), 1.57–1.85 (m, 2H), 1.85–2.18 (m, 2H), 2.64 (ddd, *J* = 6.3 Hz, *J* = 9.5 Hz, *J* = 10.0 Hz, 1H), 3.00–3.15 (m, 1H), 3.36 (dd, *J* = 3.2 Hz, *J* = 9.5 Hz, 1H), 3.80 (q, *J* = 6.8 Hz, 1H), 5.35 (br s, 1H), 7.10–7.54 (m, 6H). ^{13}C NMR δ 17.5, 24.4, 30.8, 50.1, 61.4, 64.2, 127.1, 127.5, 128.2, 142.9, 179.1. HRMS (EI) calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1422.

(2*R*,1'*R*)-(1'-phenylethyl)piperidine-2-carboxamide [(2*R*,1'*R*)-8 and (2*S*,1'*R*)-17]. According to procedure C in accompanying paper: From a mixture of cyclic nitrile **14**:**15** (dr: 55/45): (2*R*,1'*R*)/(2*S*,1'*R*) (2 mmol), concd H_2SO_4 (18 M, 3 mL), CH_2Cl_2 (7 mL), after stirring at rt for 3 days, and FC (twice, eluent, EtOAc), we obtained 172 mg (37%) of major amide (2*R*,1'*R*)-**8**, 135 mg (29%) as oil of minor amide (2*S*,1'*R*)-**17**, and 14 mg (3%) as mixture. *Data for major amide (2R,1'R)-(+)-**8*** are identical with those described above.

*Data for minor (2S,1'R)-(–)-**17**:* $[\alpha]_D$ –19.0 (*c* 1.00, EtOH), $[\alpha]_D$ –37 (*c* 1.00, $CHCl_3$); R_f = 0.30 (AcOEt/CH_2Cl_2 : 50/50); IR (neat) 3446, 3300, 1676, 1452 cm^{-1}; ^1H NMR ($CDCl_3$): 1.30–2.05 (m, 6H), δ 1.38 (d, *J* = 6.3 Hz, 3H), 2.55–2.85 (m, 2H), 3.34 (dd, *J* = 4.6 Hz, *J* = 7.2 Hz, 1H), 4.02 (q, *J* = 6.3 Hz, 1H), 5.74 (br s, 1H), 6.94 (br s, 1H), 7.12–7.55 (m, 5H); ^{13}C NMR δ 15.1, 22.8, 25.3, 30.0, 44.1, 58.2, 62.8, 127.0, 128.5, 143.7, 177.0; HRMS (EI) calcd for $C_{14}H_{20}N_2O$: 232.1576. Found: 232.1583.

(2*R*,1'*R*)-1-(1'-phenylethyl)piperidine-2-carboxamide [(2*R*,1'*R*)-(+)-8]. Following procedure B: From hydroxy amide (2*R*,1'*R*)-**18** (250 mg, 1 mmol), NEt_3 (155 μL), cat. DMAP (30 mg) and MsCl (76 mg, 86 μL). After stirring at 0 °C for 6 h, then at 40 °C for 2 days, and FC (eluent, MeOH/CH_2Cl_2, 3/97 → 10/90), we obtained 115 mg (50%) of pure cyclic amide (2*R*,1'*R*)-**8**. All spectral data are identical with those described above.

2-Pyrrolidine-2-carboxamide [(*S*)-prolinamide] [(*S*)-(–)-19]. Following procedure D in accompanying paper: From amino amide (2*S*,1'*S*)-**7** (175 mg, 0.8 mmol), EtOH/AcOH : 1/1 (4 mL), and 20% $Pd(OH)_2/C$ (80 mg) stirring at rt for 14 h, gave after FC, 70 mg (77%) of

pure (*S*)-prolinamide **19**.[2] $[\alpha]_D$ – 105 (*c* 2.00, EtOH), $[\alpha]_D$ – 118 (*c* 1.00, $CHCl_3$), mp 95.3 °C ; ref. authentic sample $[\alpha]_D$ –106 (*c* 2.00, EtOH), mp 95–97 °C for compound (*S*); IR (neat): 3389, 3185, 1649, 1396 cm^{-1}; ^1H NMR (CD_3OD): δ 1.40–1.86 (m, 3H), 1.90–2.22 (m, 1H), 2.70–3.06 (m, 2H), 3.61 (dd, *J* = 5.7 Hz, *J* = 8.6 Hz, 1H); ^1H NMR ($CDCl_3$) δ 1.57–1.85 (m, 2H), 1.85–2.04 (m, 1H), 2.04–2.30 (m, 2H), 2.82–3.15 (m, 2H), 3.75 (dd, *J* = 5.2 Hz, *J* = 8.9 Hz, 1H), 5.65 (br s, 1H), 7.45 (br s, 1H); ^{13}C NMR δ: 26.2, 30.6, 47.2, 60.4, 178.8; HRMS (EI): calcd for $C_5H_{10}N_2O$: 114.0793. Found: 114.0796.

General procedure E: aminocarboxylic acid formation. A mixture of amide **19** or **20** (1 mmol) and 6 M HCl (4 mL) was heated to gentle reflux. The reaction was complete within 10 h as shown by TLC. The solution reaction was cooled to rt, and then extracted with ether (5 mL) to remove coloured ether soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure to give amino acids **1a• or 1b•**HCl as a white solid. Recrystallisation from MeOH-ether furnished pure crystalline amino acid•hydrochloride with excellent yield.

To the amino acid salt were added EtOH (3 mL) and propylene oxide (1.5 mL). The mixture was stirred at rt for 5 h, after complete precipitation the organic solvents were removed under reduced pressure to furnish a solid residue. The latter was dissolved in distilled water then filtered through cotton, to give a clean solution, which was concentrated under reduced pressure leading to pure amino acids **1** and **2** with excellent yields.

(*S*)-Proline [(*S*)-(–)-1]. Following procedure E: Amino amide (*S*)-**19** (50 mg, 0.44 mmol), 6 M HCl (6 mL), 10 h at reflux then propylene oxide, gave 46 mg (92%) as a white solid of pure (*S*)-proline **1**. $[\alpha]_D$ –83.2 (*c* 4.00, H_2O), mp 226 °C (dec.); ref. authentic sample $[\alpha]_D$ –84 (*c* 4.00, H_2O), mp 228 °C (decomp.). Its spectral properties were identical to those of an authentic sample.

(*R*)-Pipecolic acid [(*R*)-(+)-2]. Following procedure E: Amino amide (*R*)-**20**[3] (22 mg, 0.17 mmol), 6 M HCl (3 mL), 8 h at reflux, then propylene oxide, gave 20 mg (91%) as a white solid of pure (*R*)-pipecolic acid (*R*)-**2**. $[\alpha]_D$ +26.7 (*c* 1.00, H_2O), mp > 265 °C dec; lit. $[\alpha]_D$ +26.3 (*c* 1.00, H_2O),[4] mp 271 °C dec, $[\alpha]_D$ +25.5 (*c* 1.00, H_2O).[5] Its spectral properties were identical to those

reported in the literature.[4]

References

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(1) Fadel, A.; Khesrani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 305–320.

(2) Roteman, R.; US patent, US 4017513 19770412; *Chem. Abstr*. **1977**, *87*, 39842.

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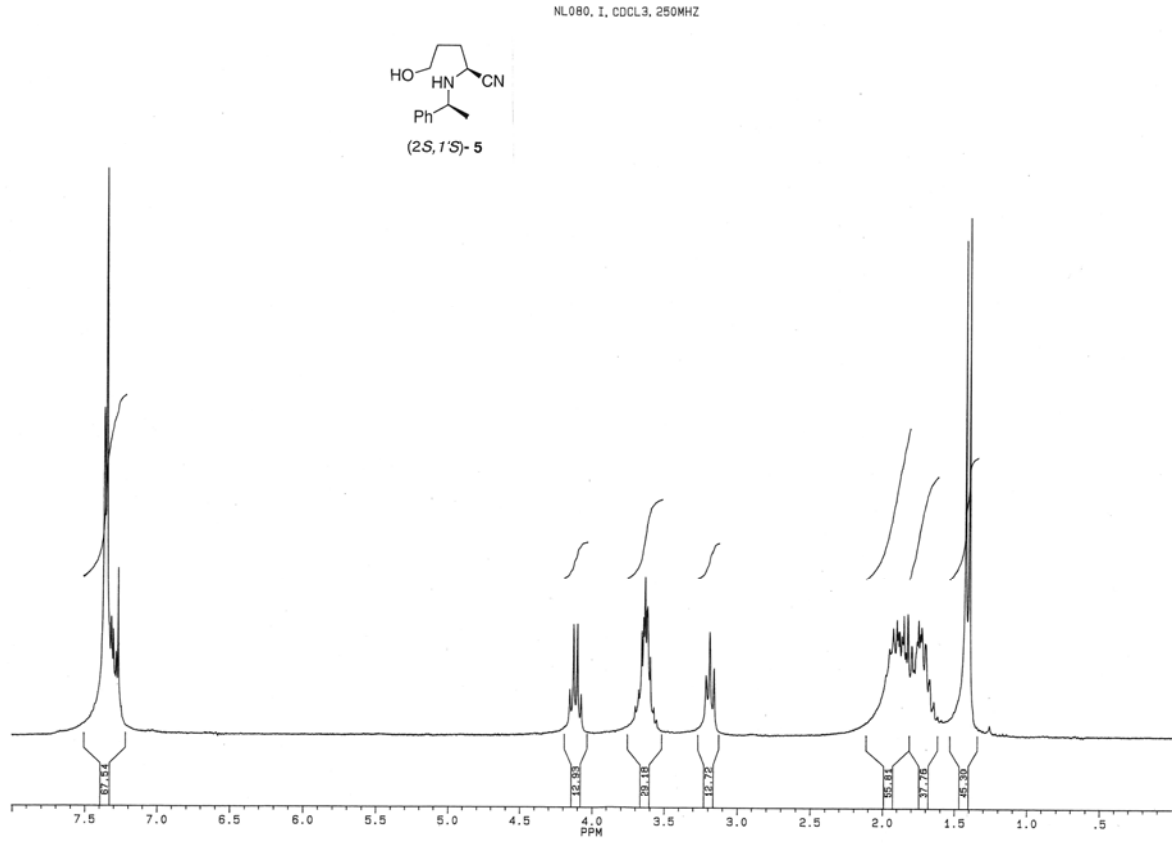
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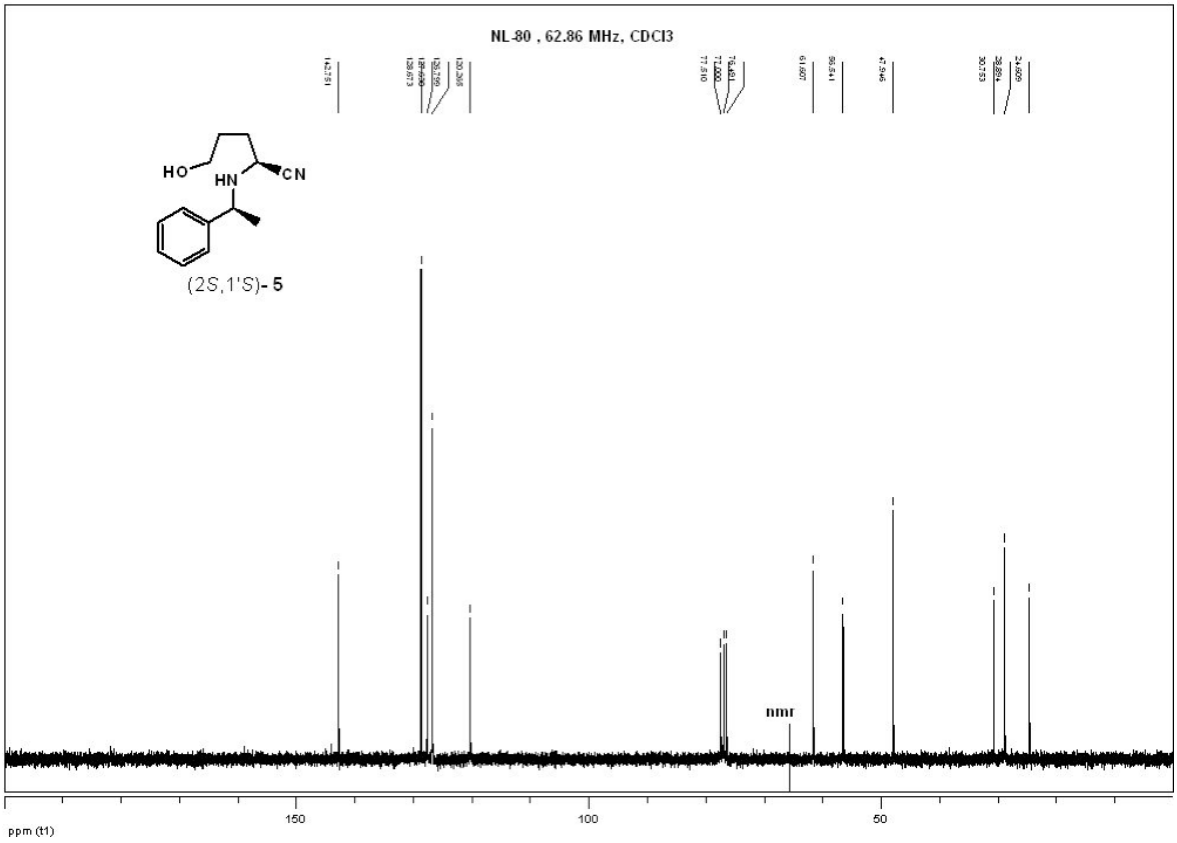
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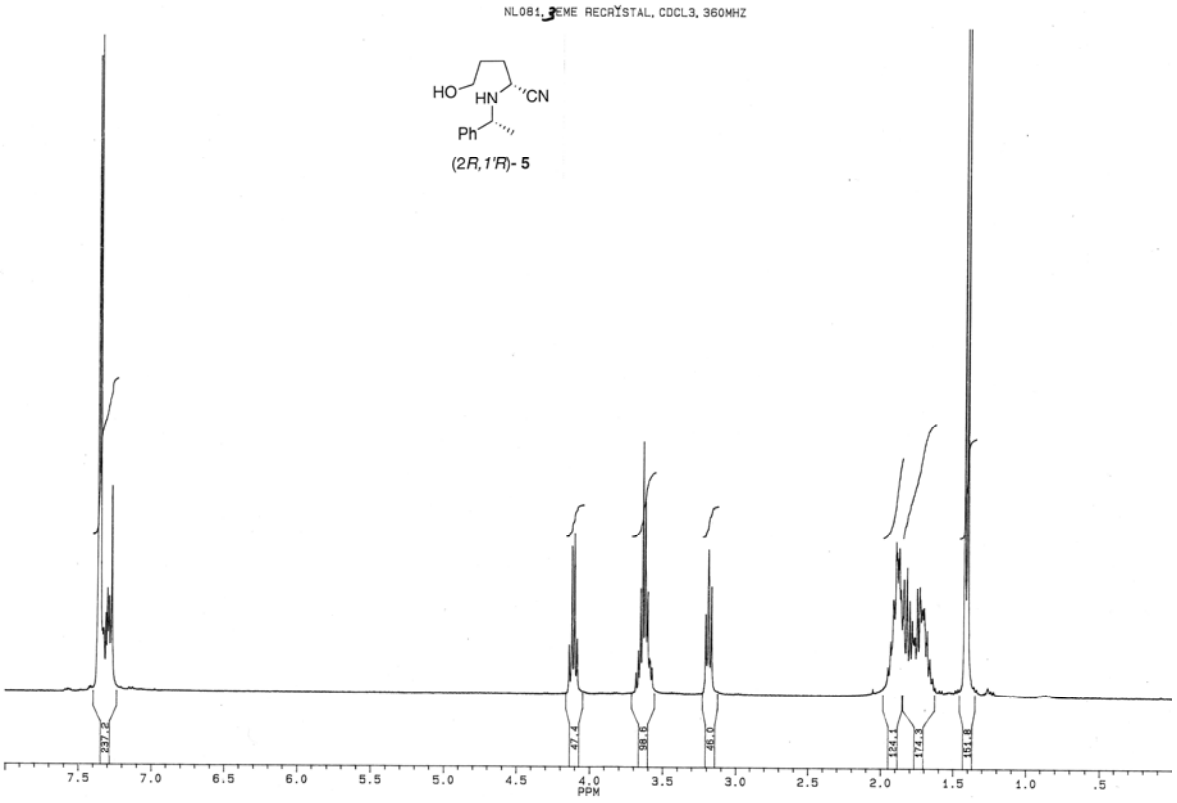
ppm (t1)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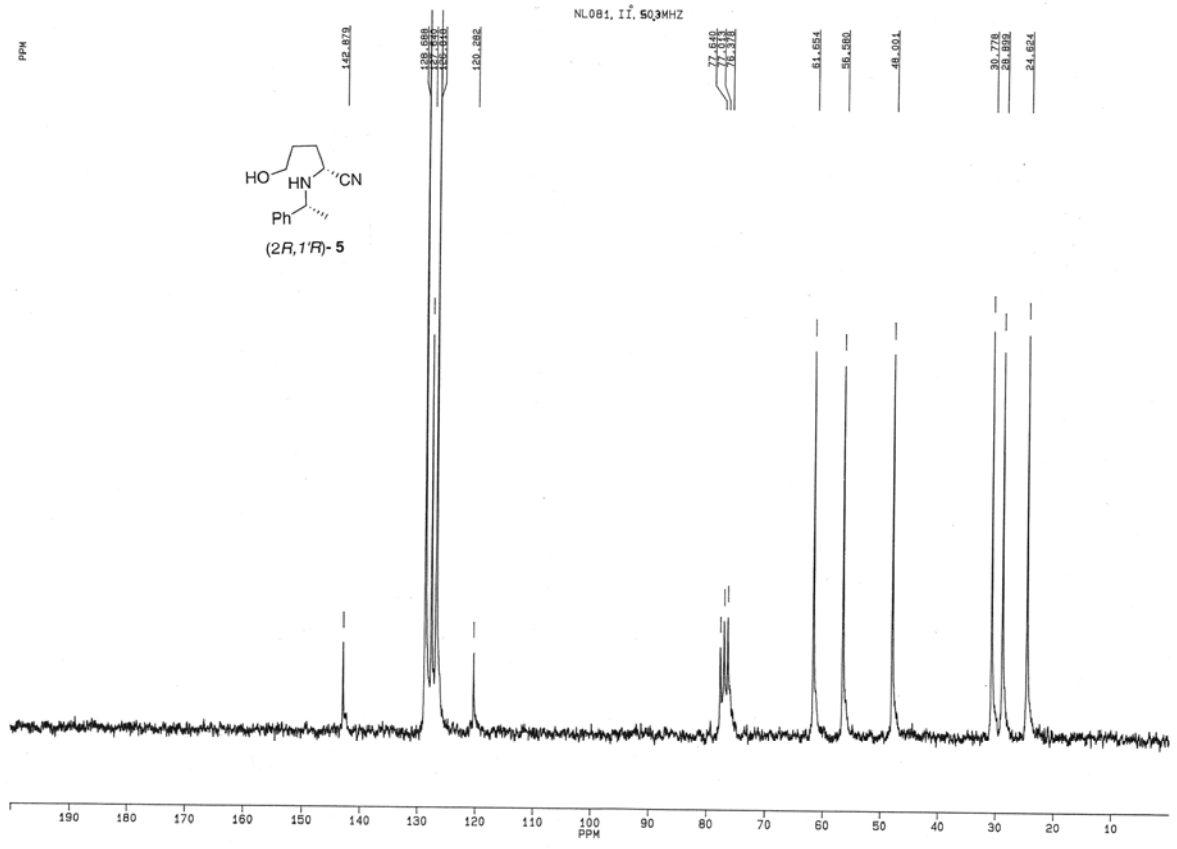
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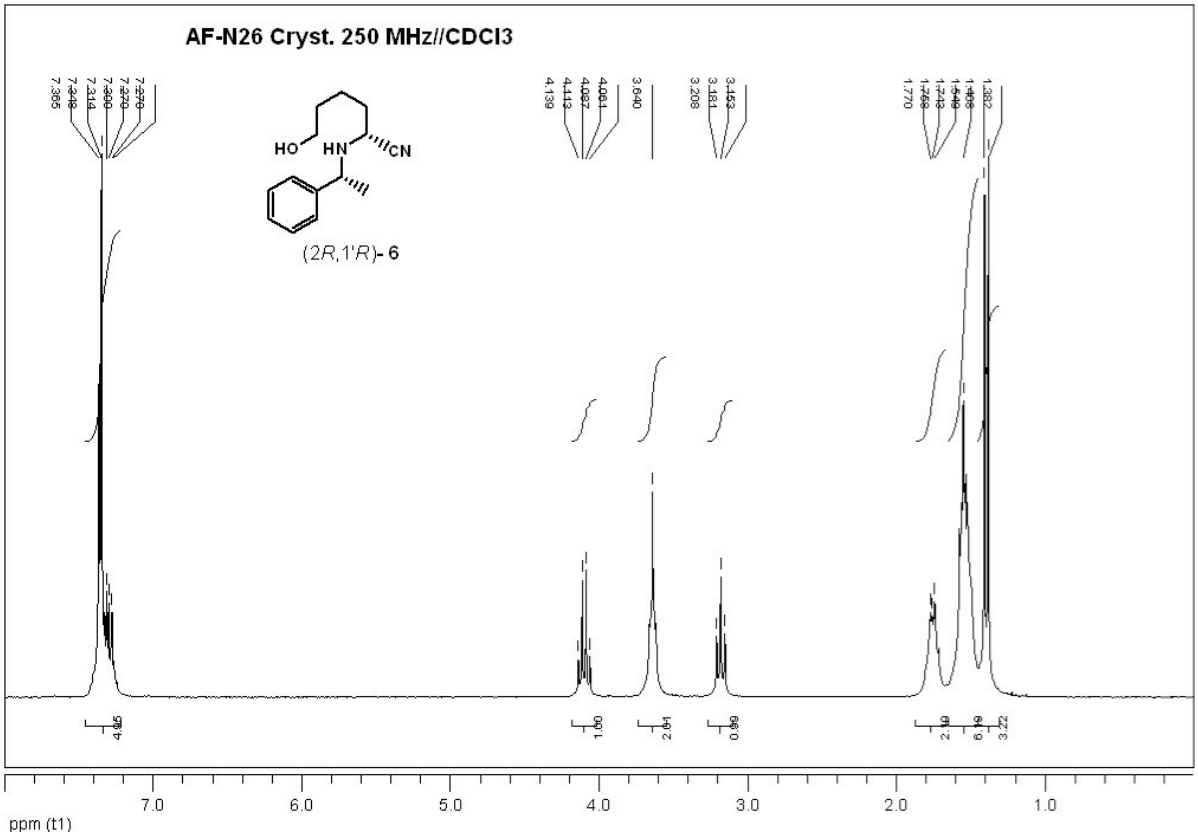
PPM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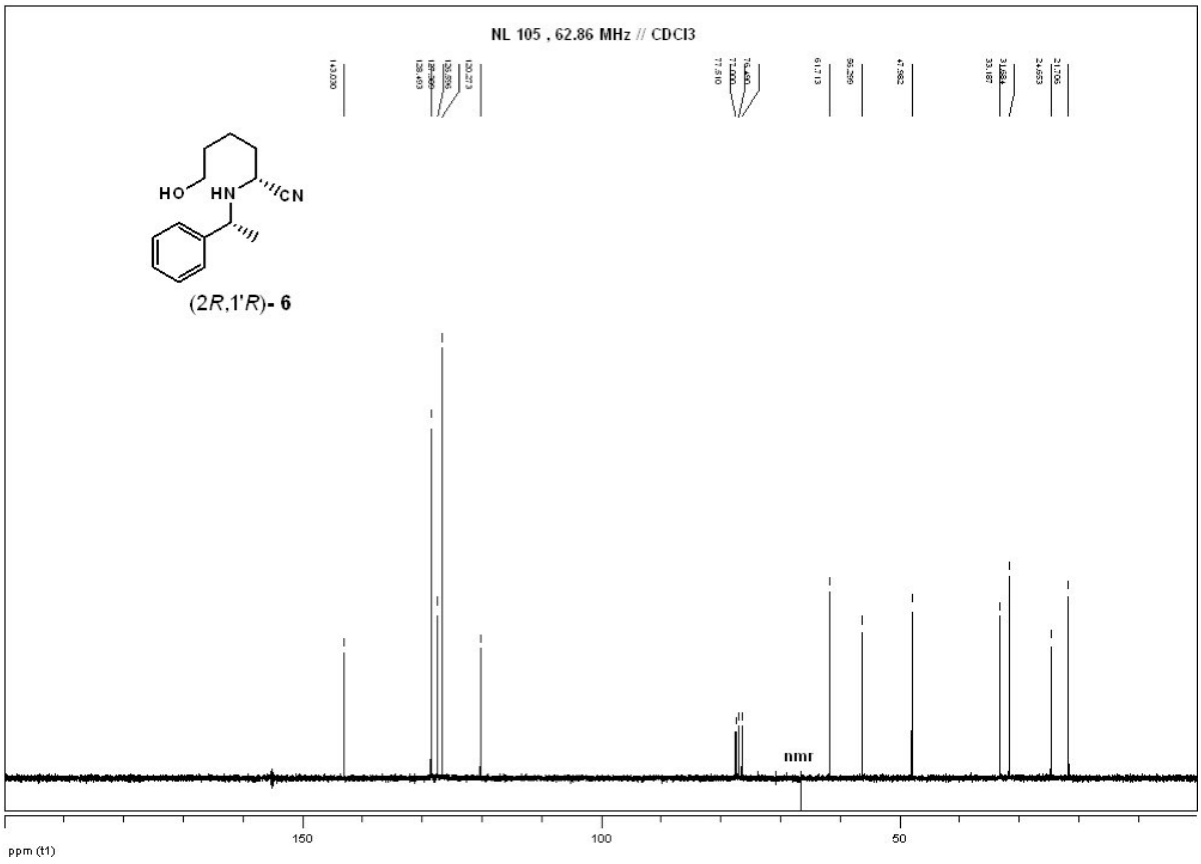
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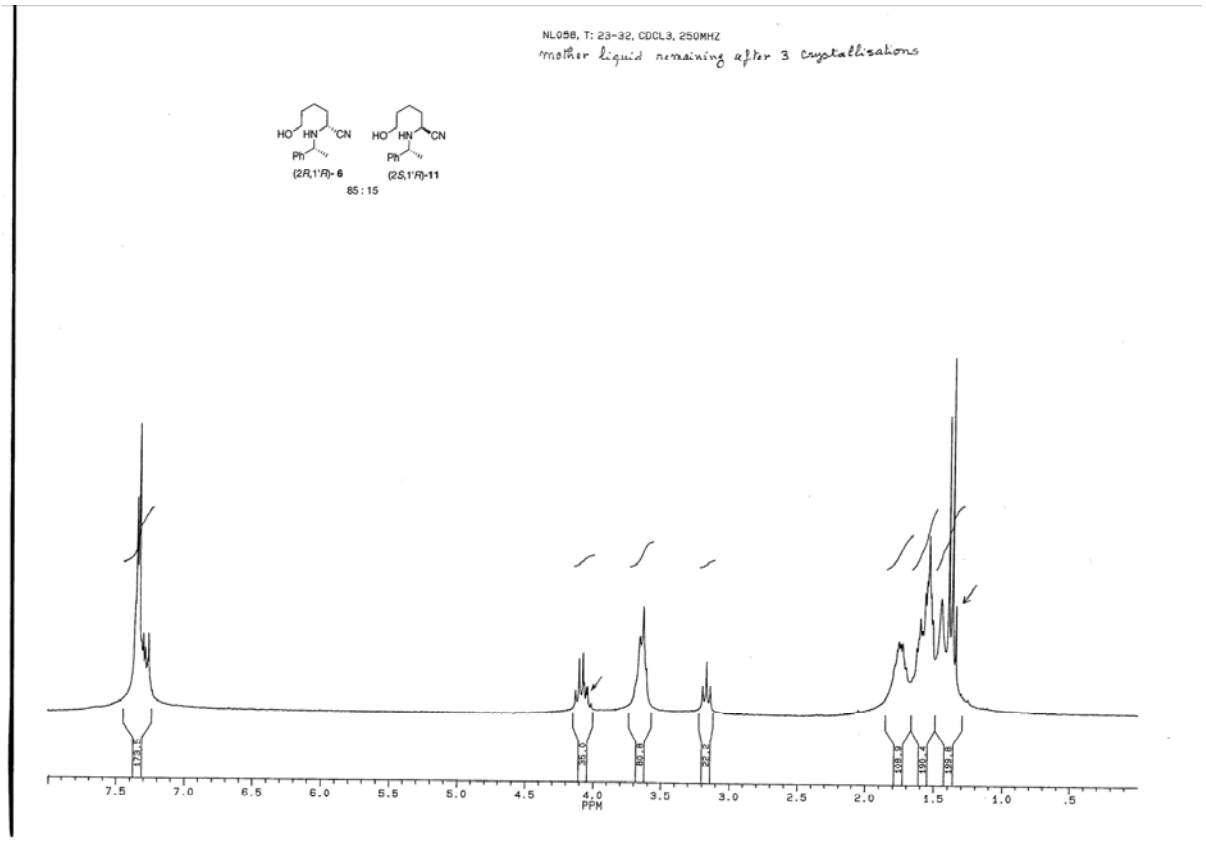
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85 : 15
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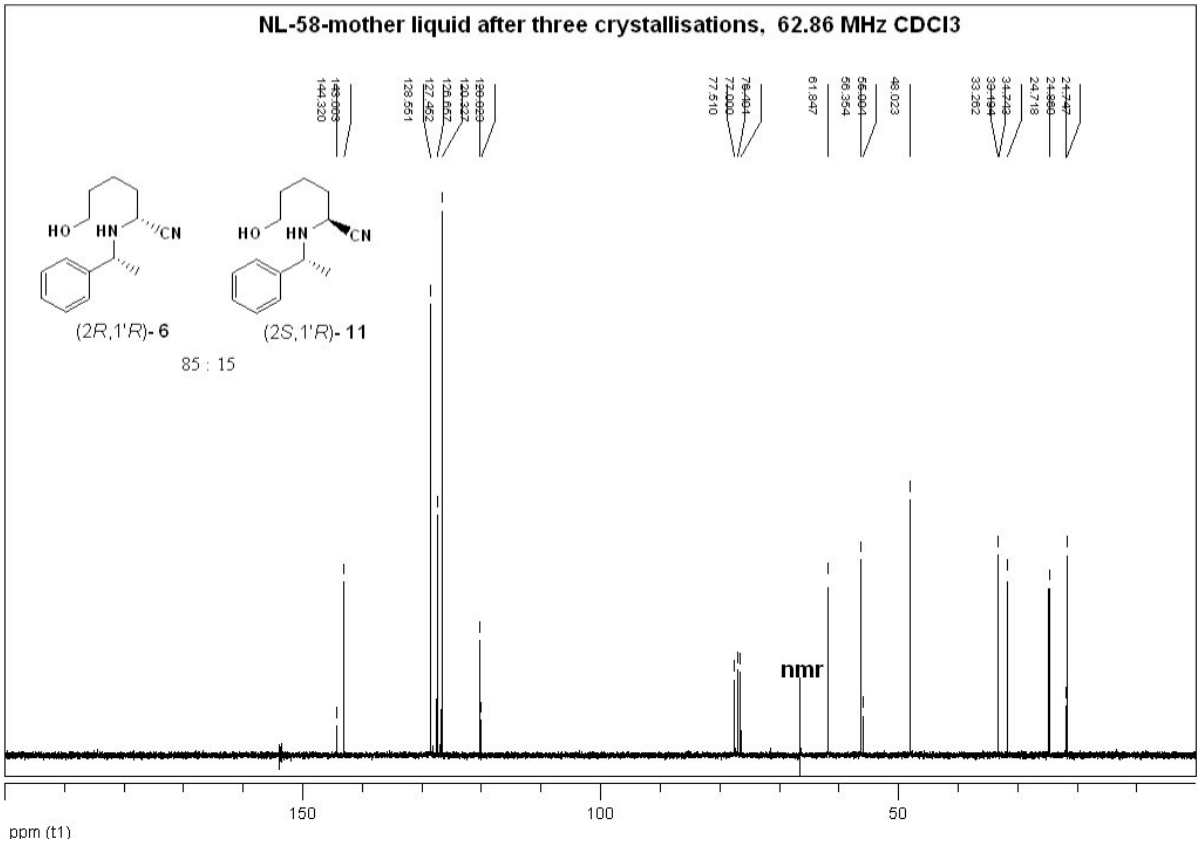
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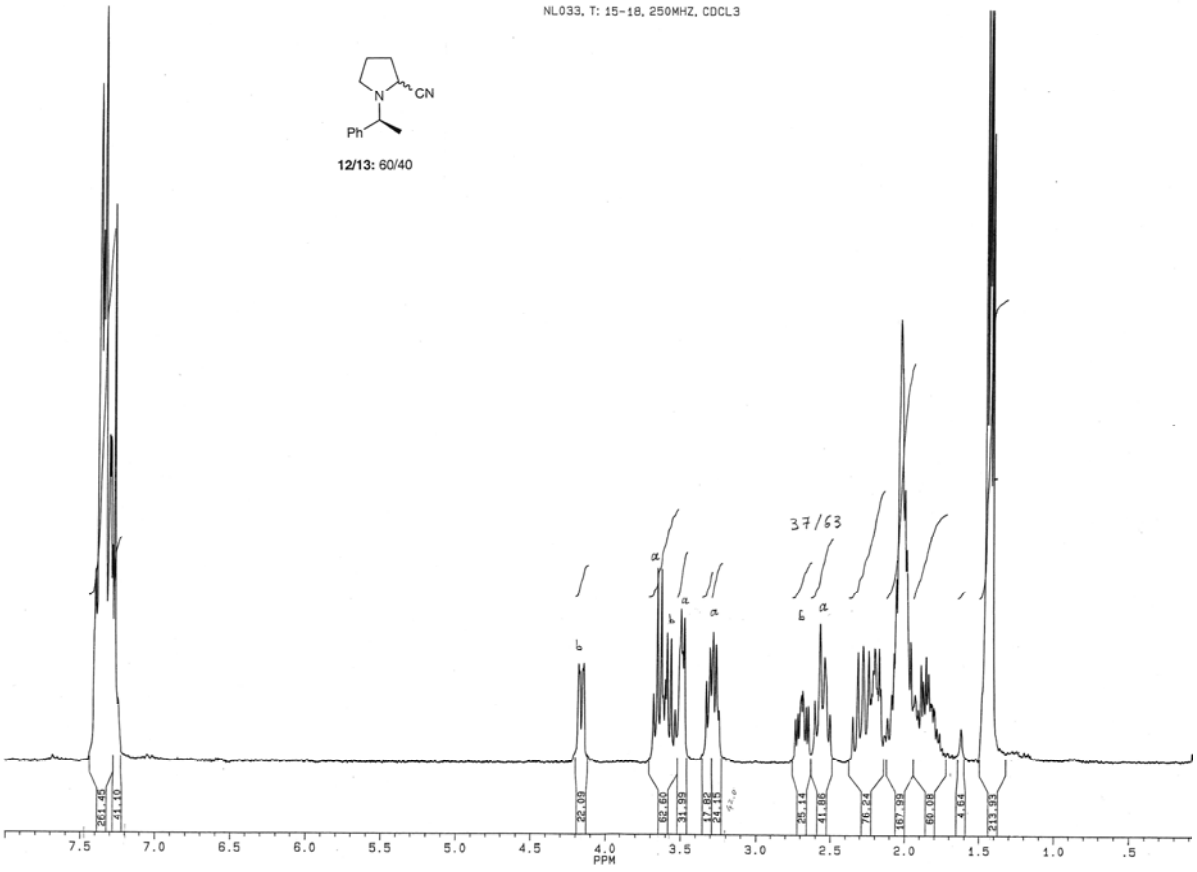
ppm (t1)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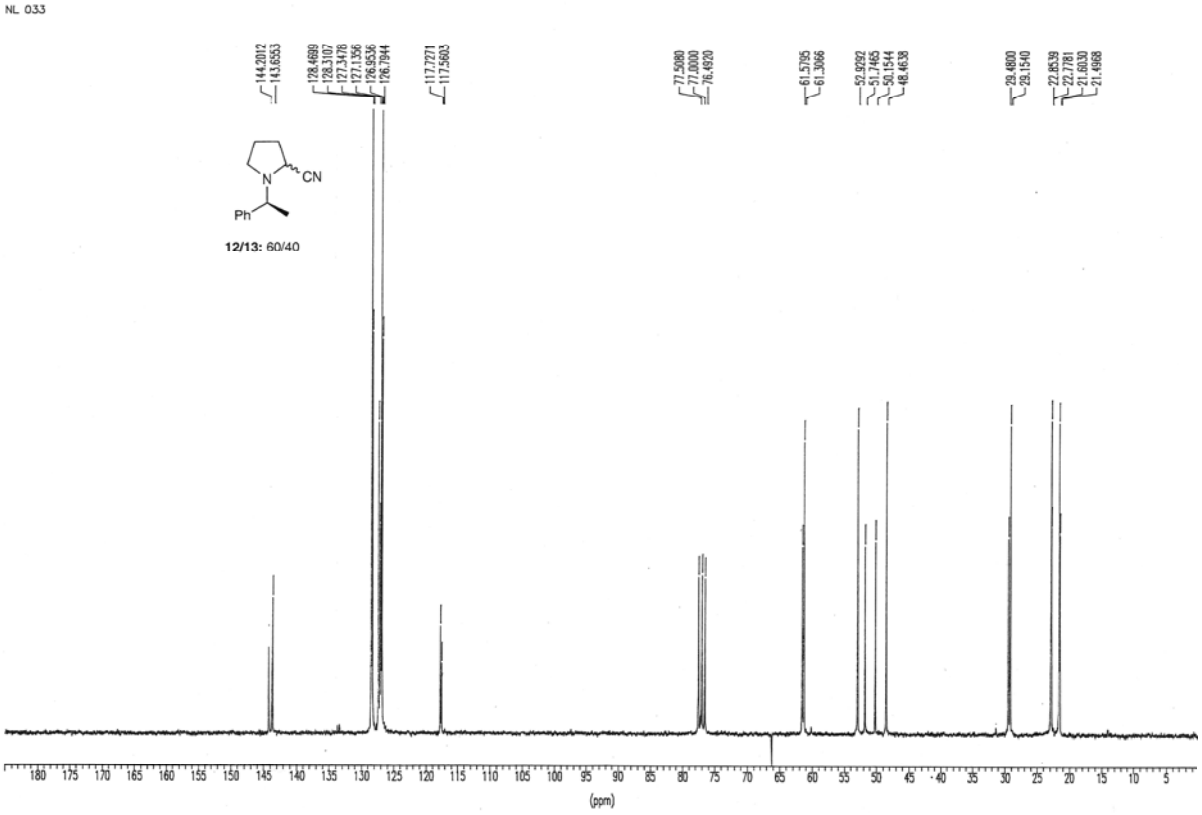
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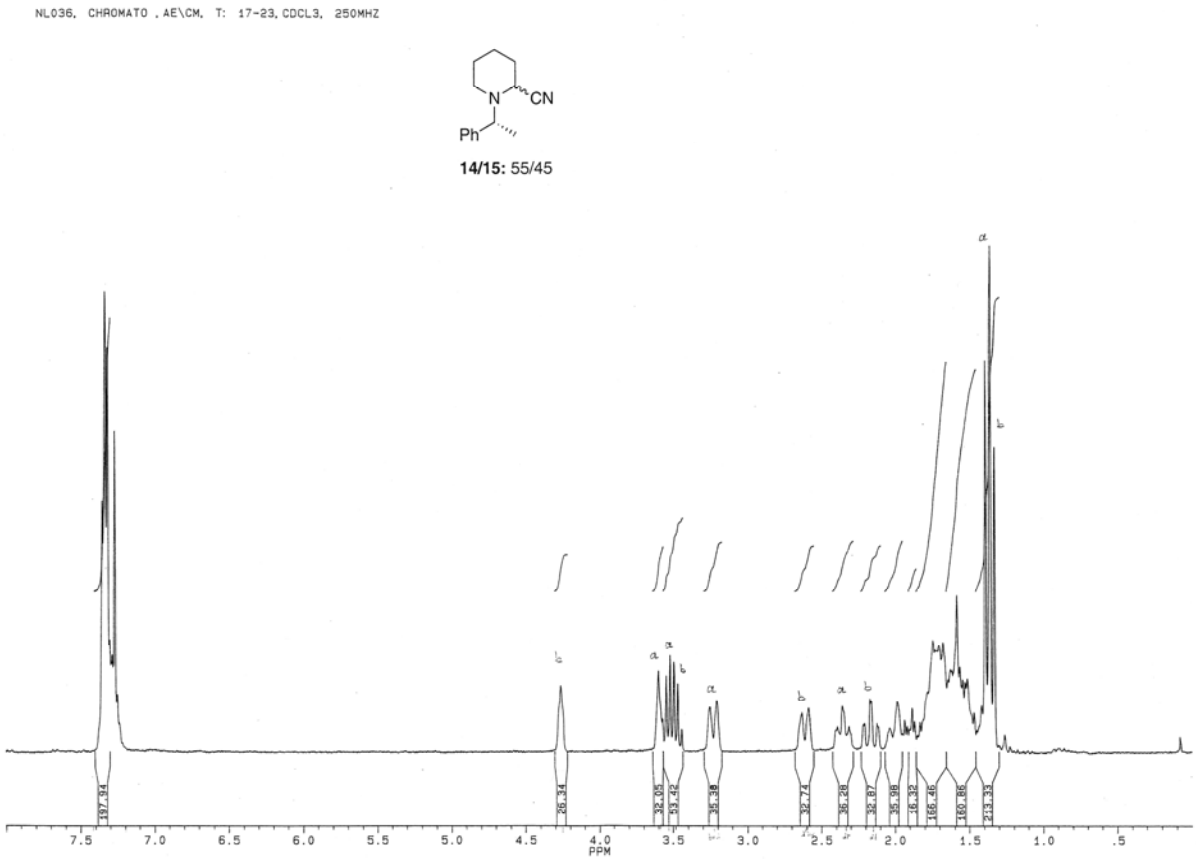
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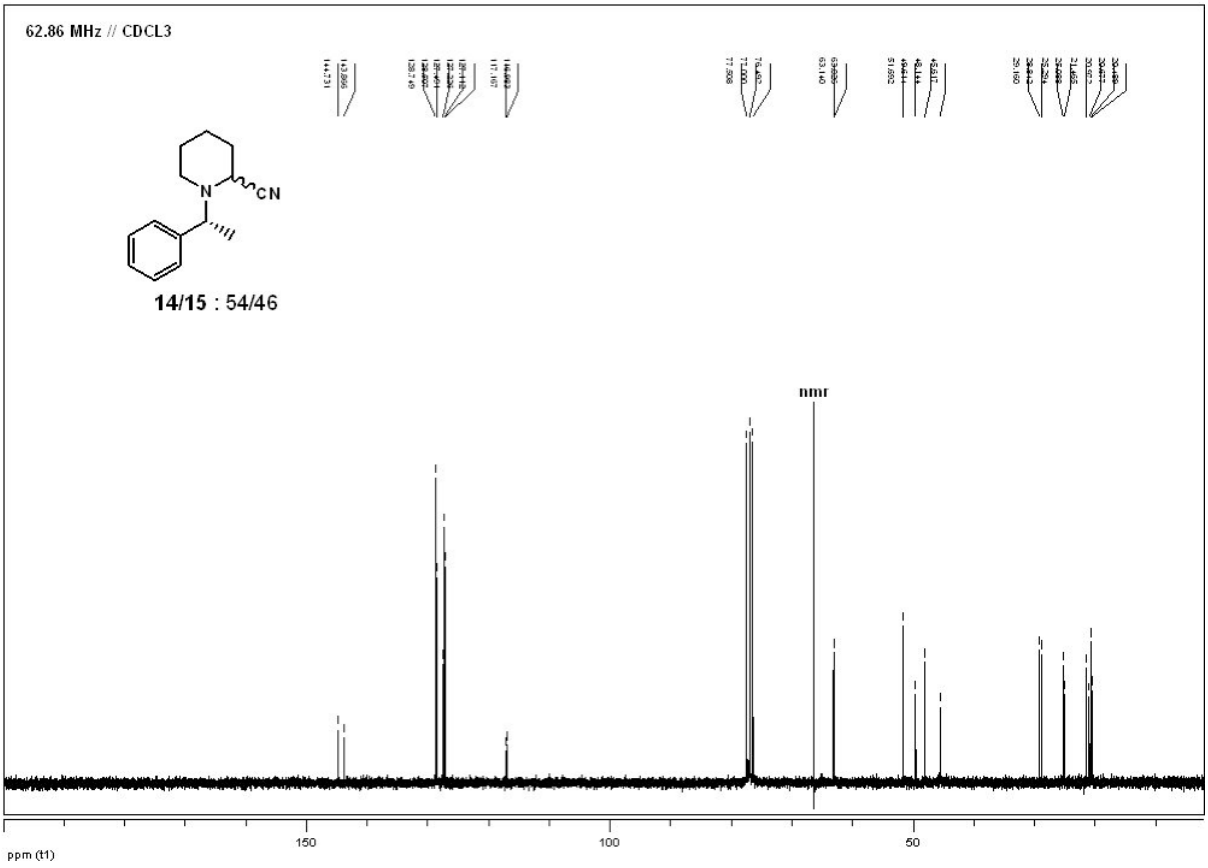
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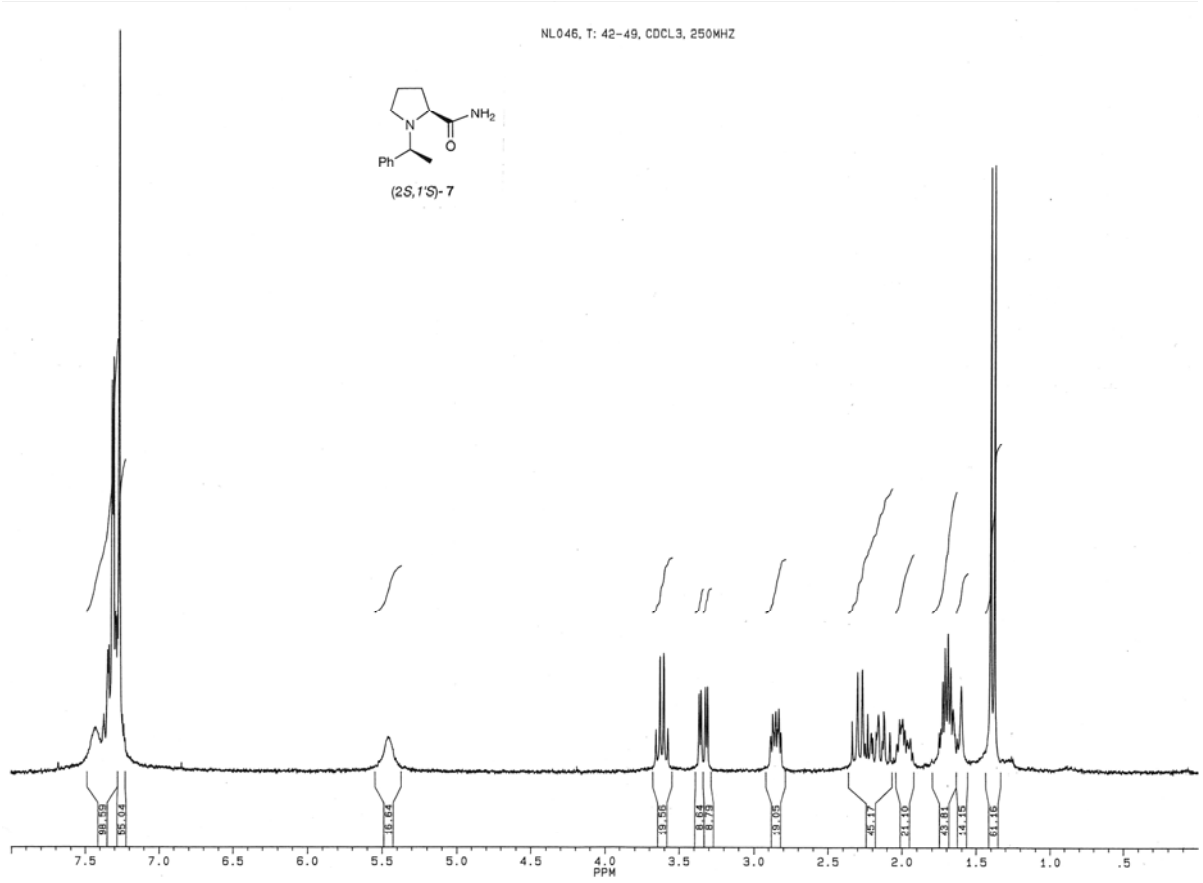
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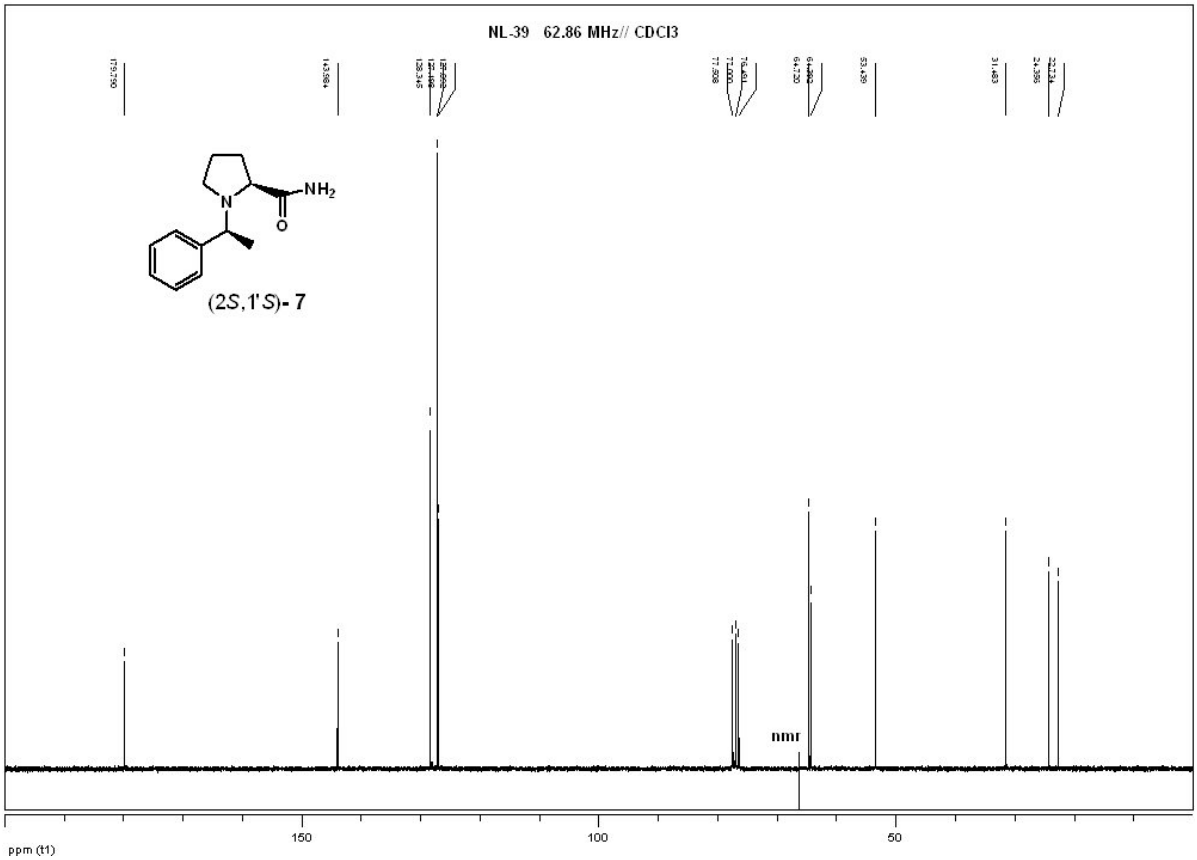
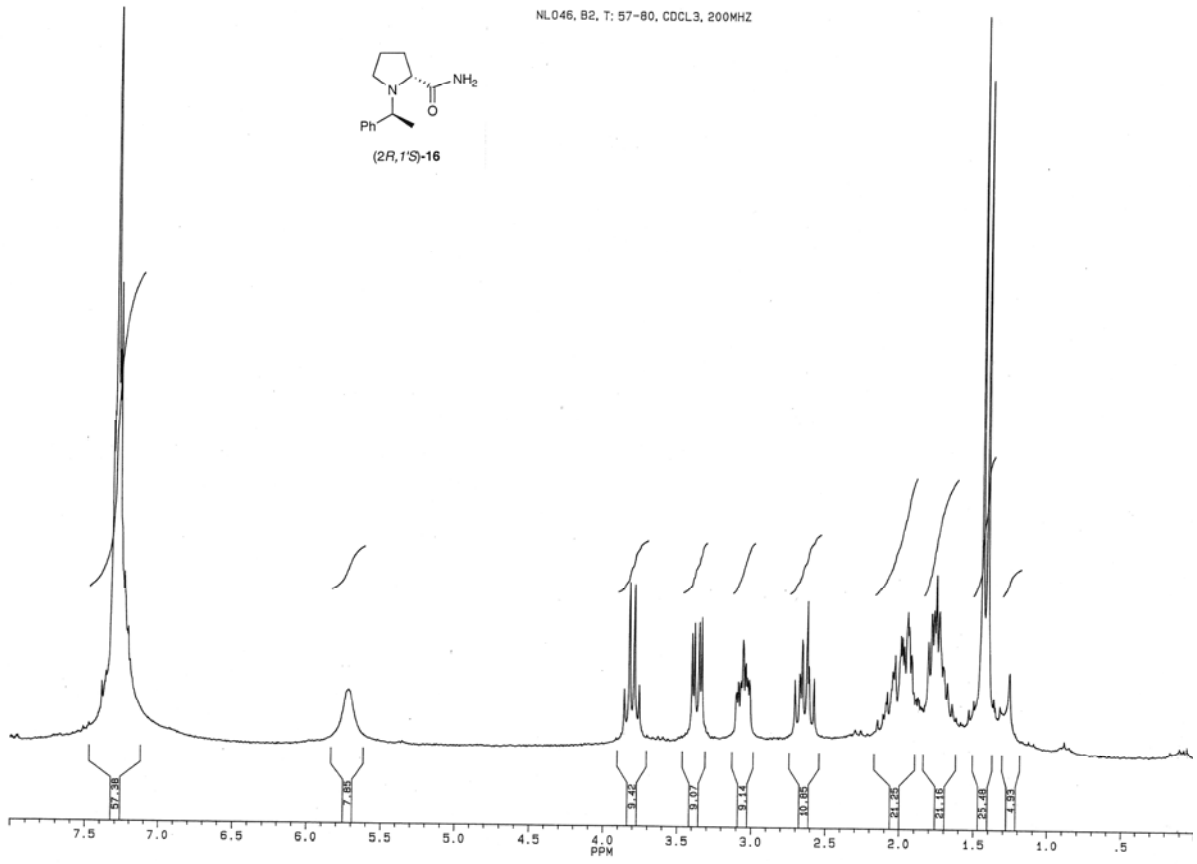
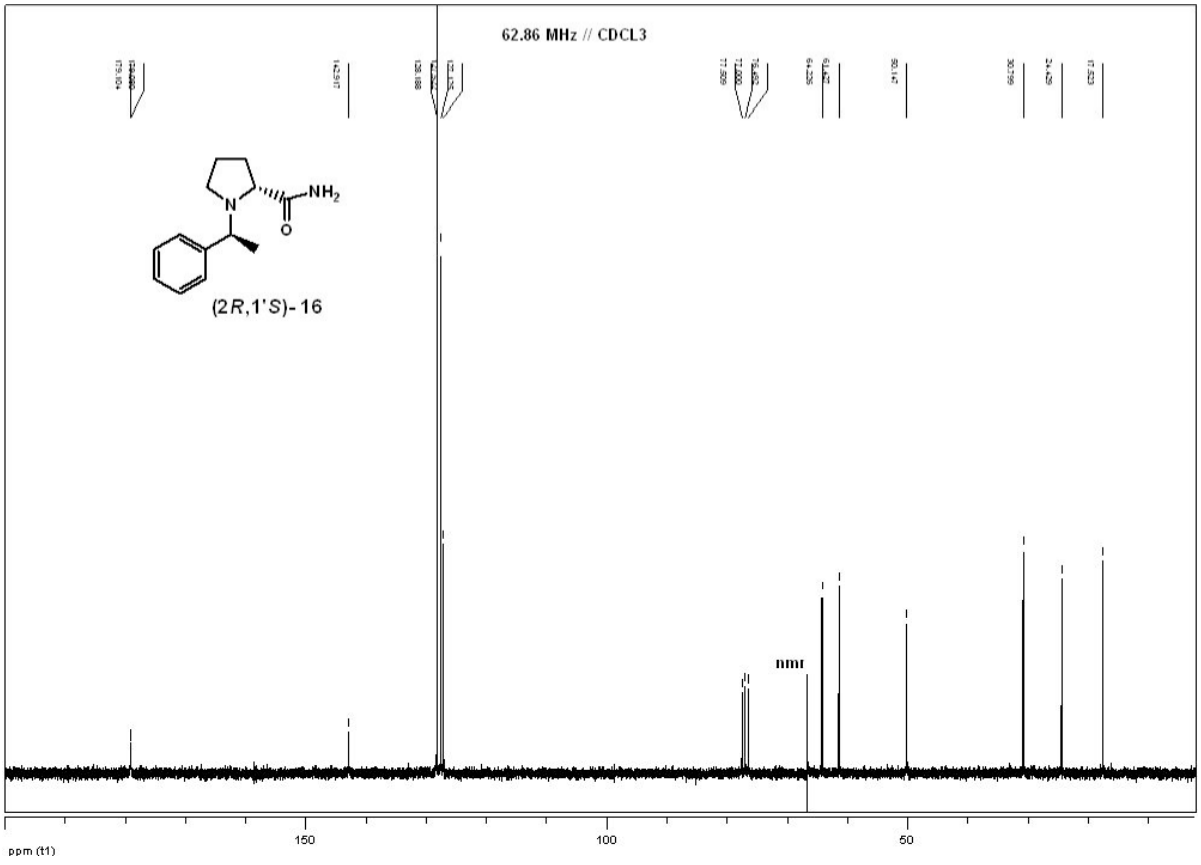
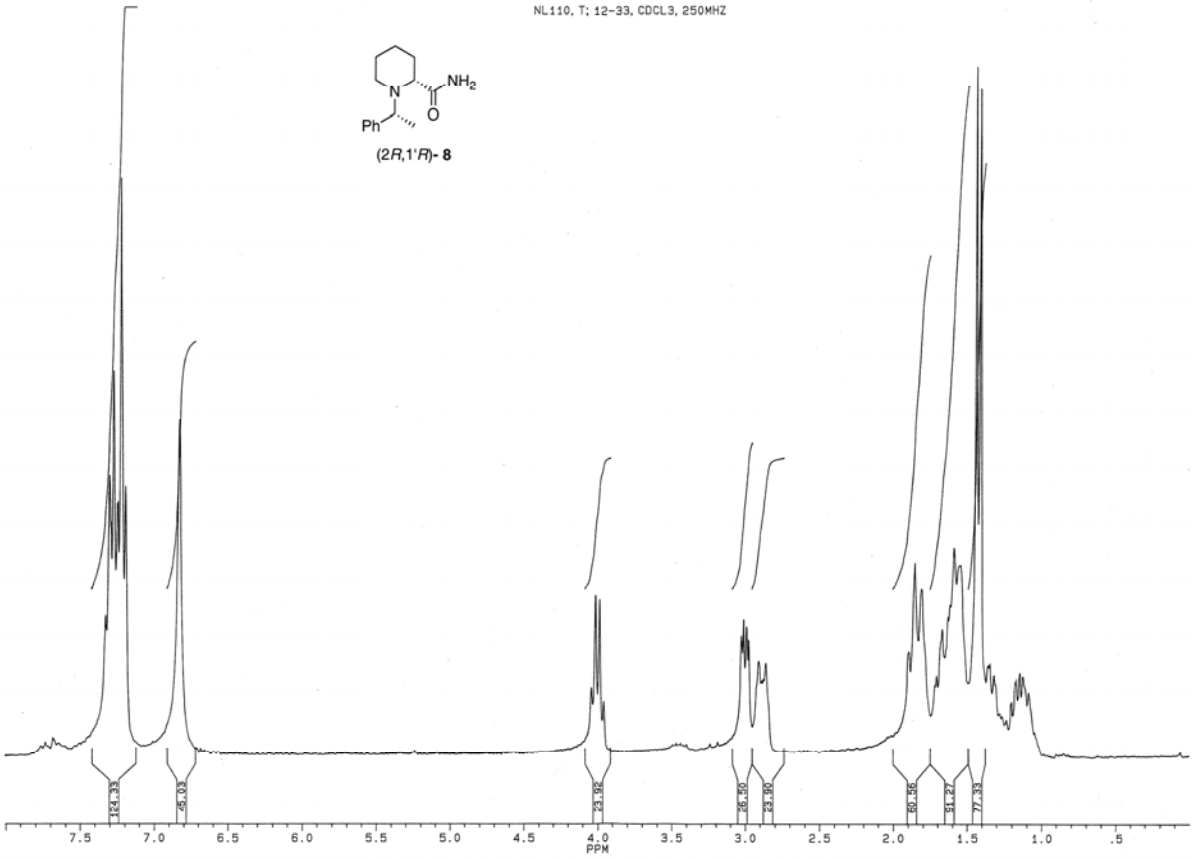
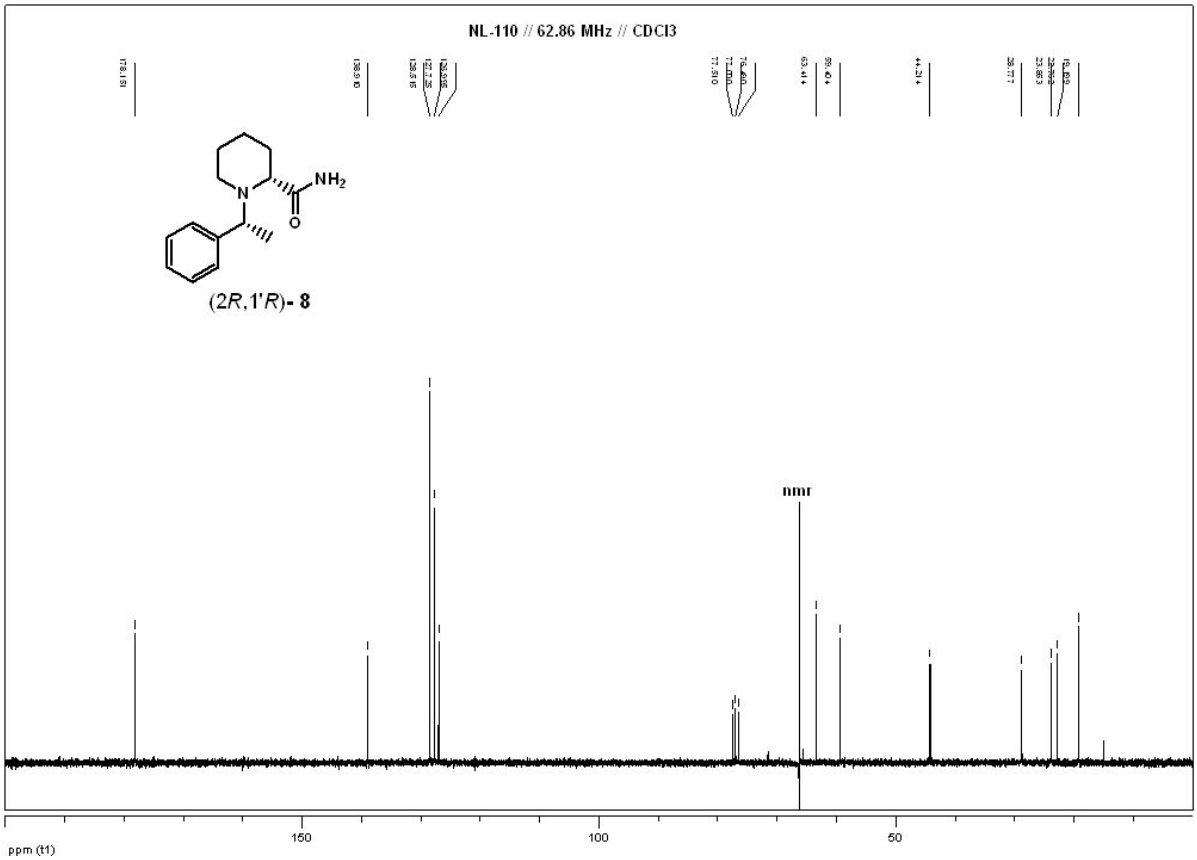
(2S,1'S)- 7
PPM

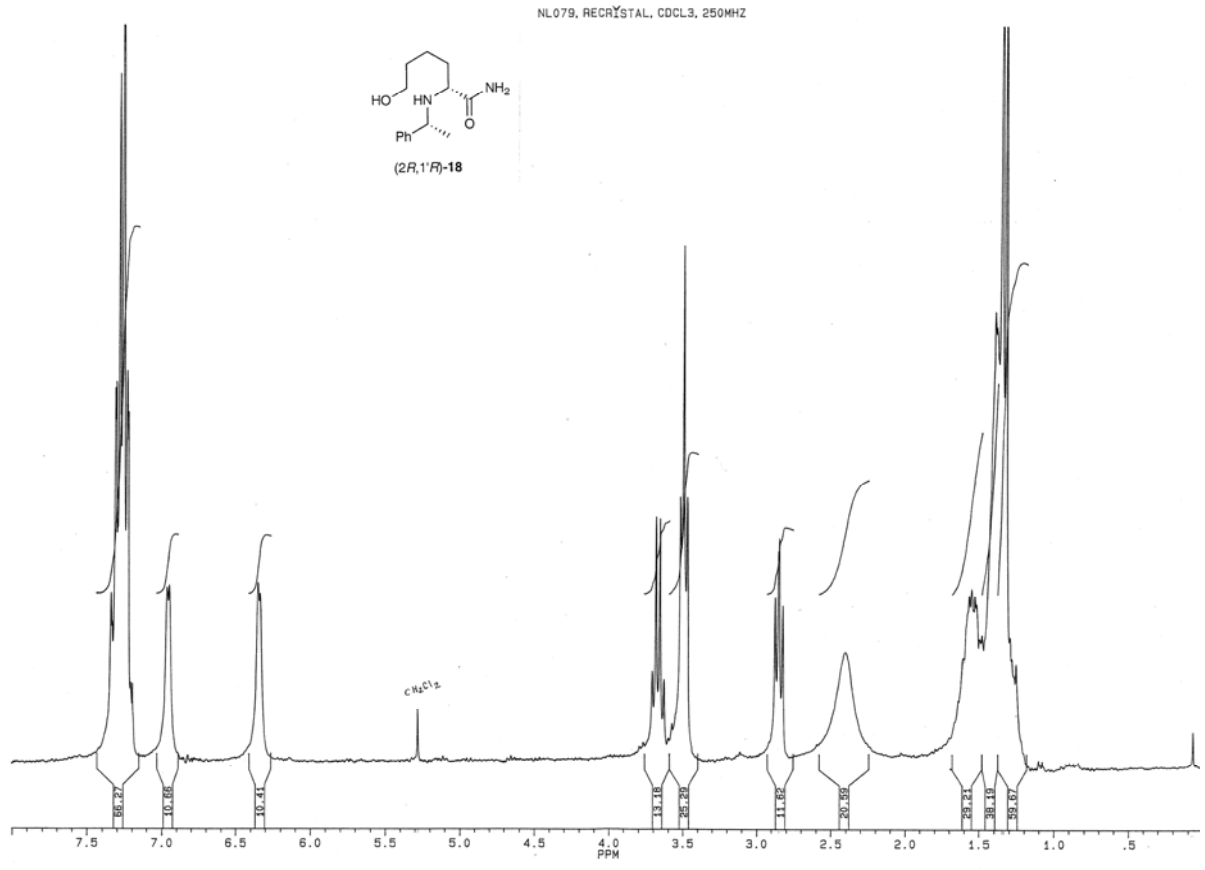

NL-39 62.86 MHz// CDCl3
(2S,1'S)- 7
nmr
ppm (t1)

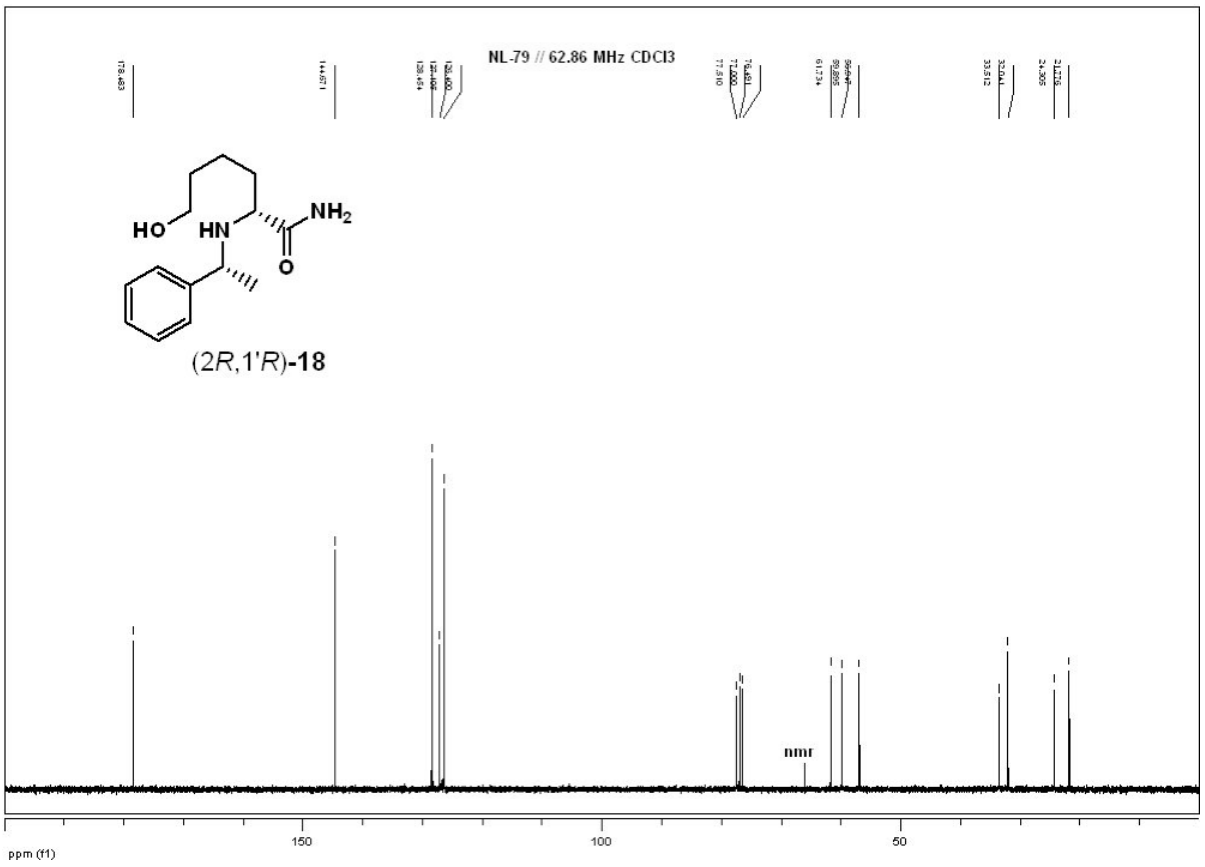

NL046, B2, T: 57-80, CDCL3, 200MHZ
(2R,1'S)-16
PPM

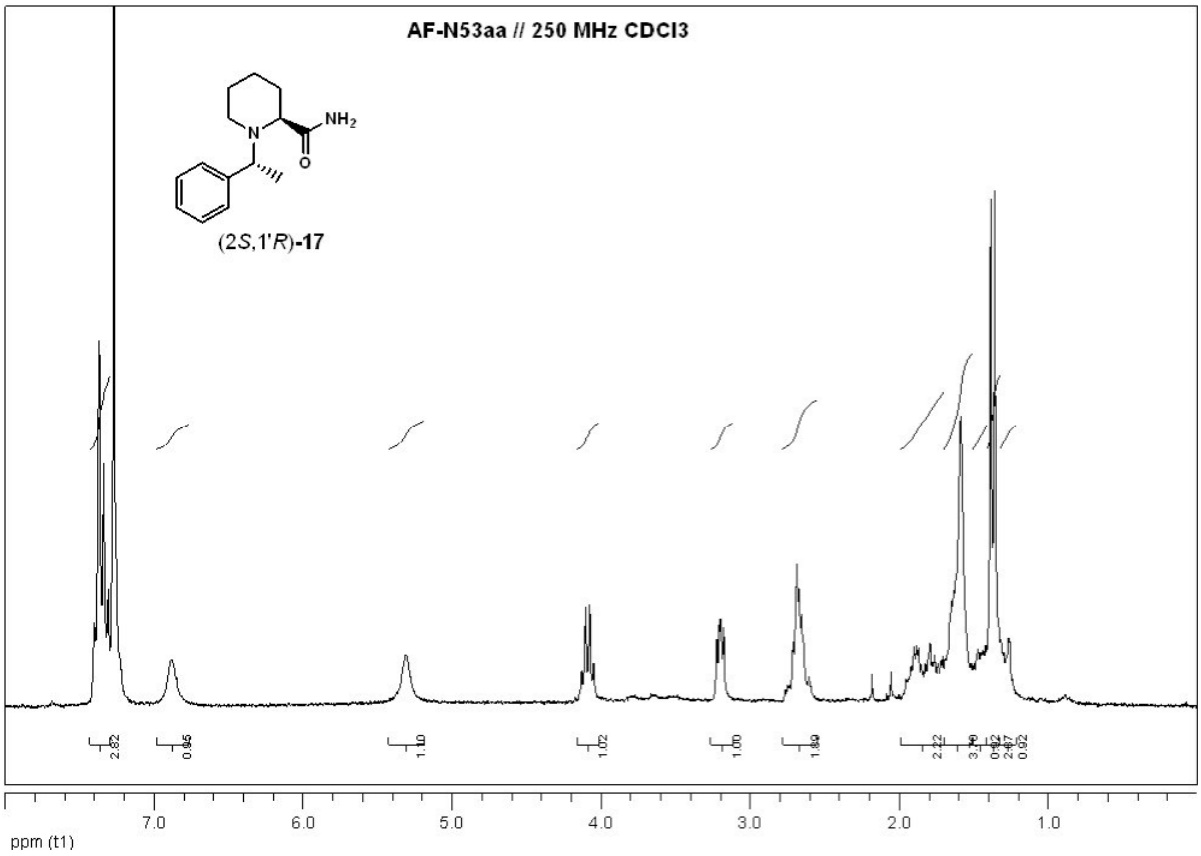

62.86 MHz // CDCL3
(2R,1'S)-16
ppm (t1)

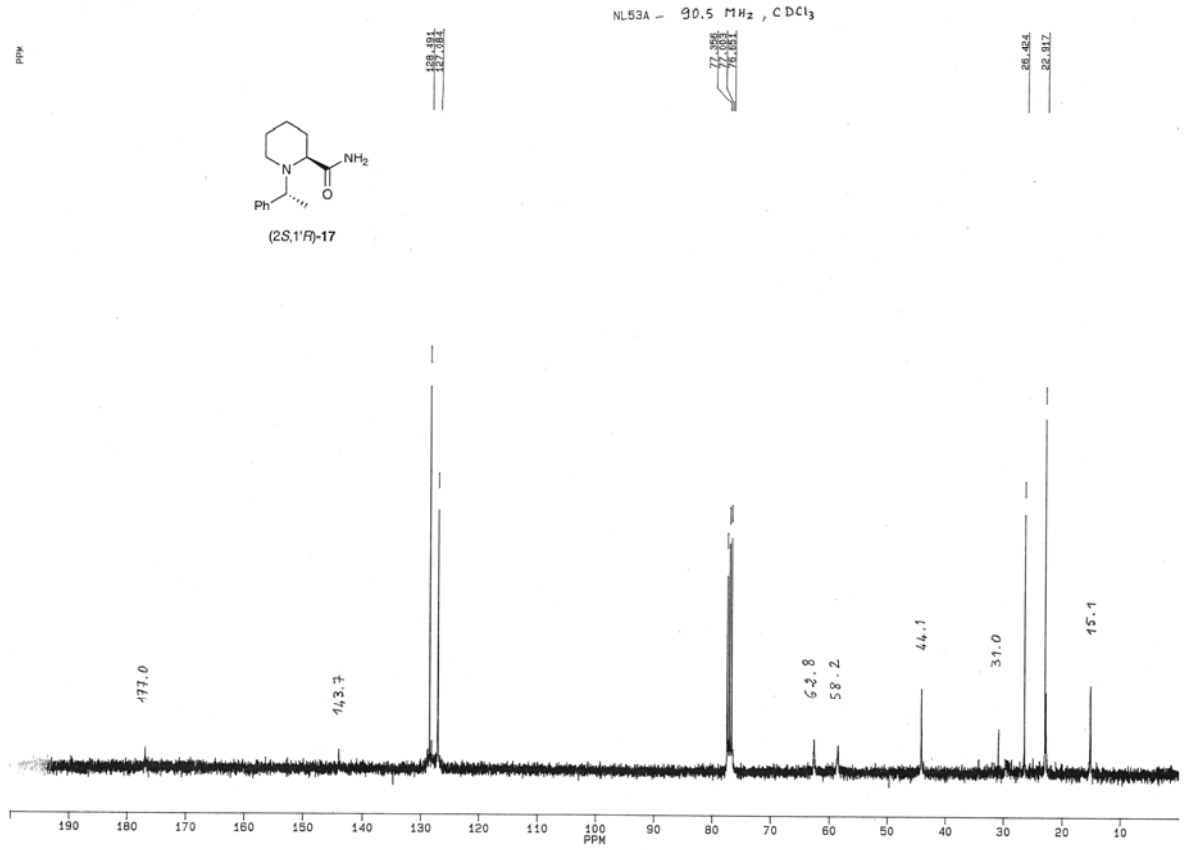

NL110, T; 12-33, CDCL3, 250MHZ
NH2
N
O
Ph
(2R,1'R)- 8
124.33
45.03
24.92
26.50
23.90
60.56
51.27
77.33
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

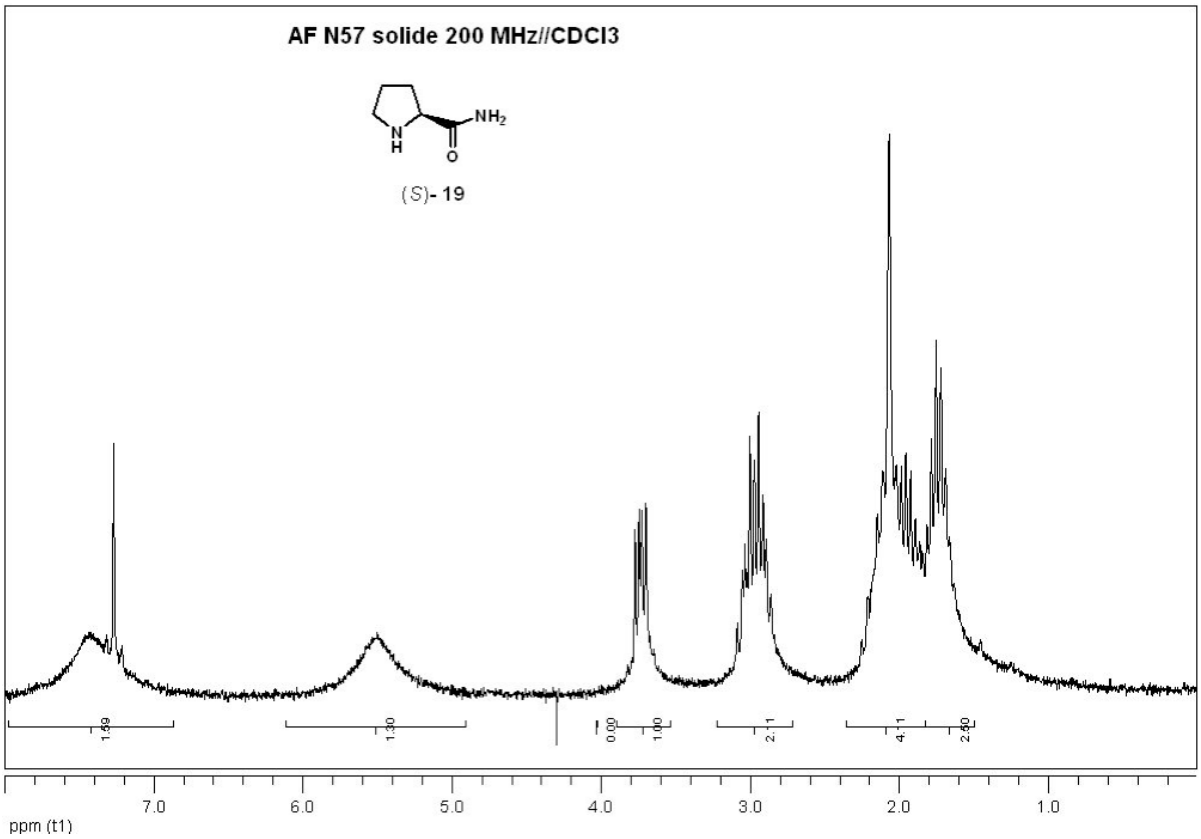

NL-110 // 62.86 MHz // CDCl3
NH2
N
O
(2R,1'R)- 8
nmr
150
100
50
ppm (t1)

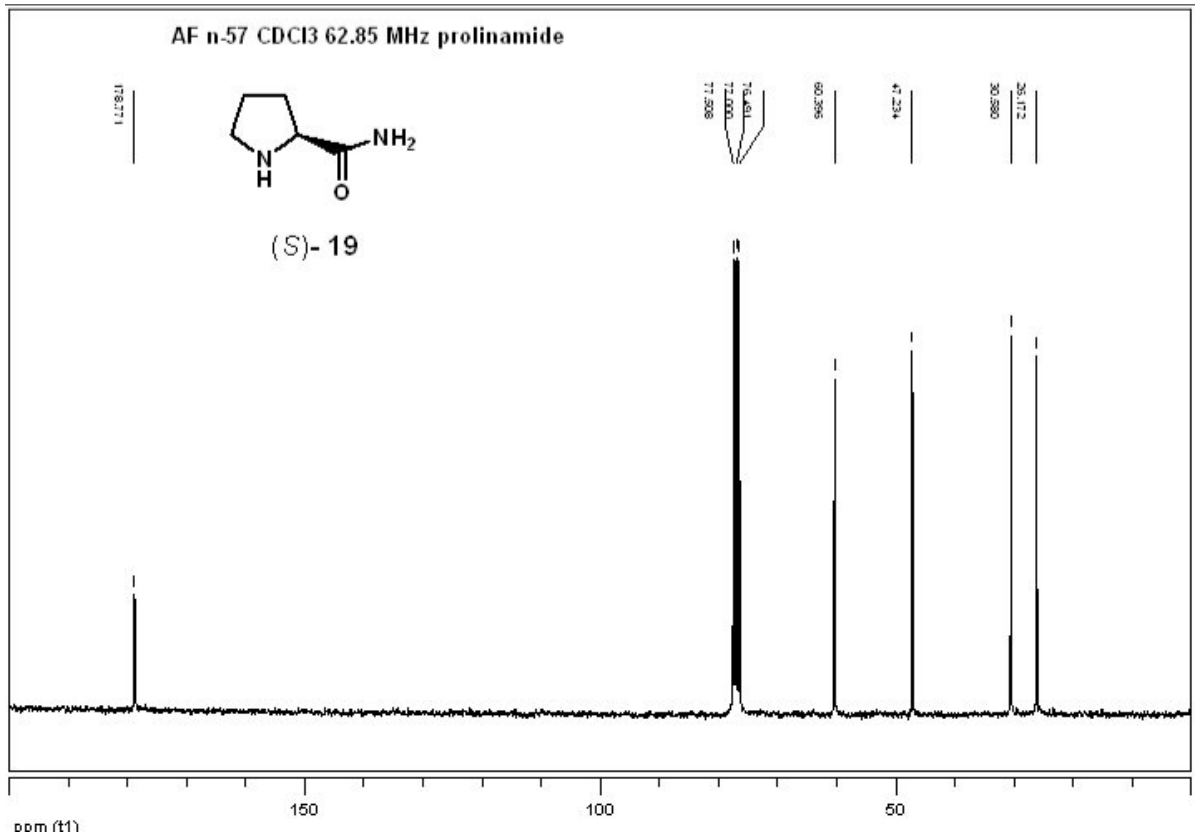

NL079, RECRYSTAL, CDCL3, 250MHZ
HO
HN
NH2
O
Ph
(2R,1'R)-18
CH2Cl2
66.27
10.66
10.41
13.18
25.29
11.62
20.59
23.21
38.19
59.67
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

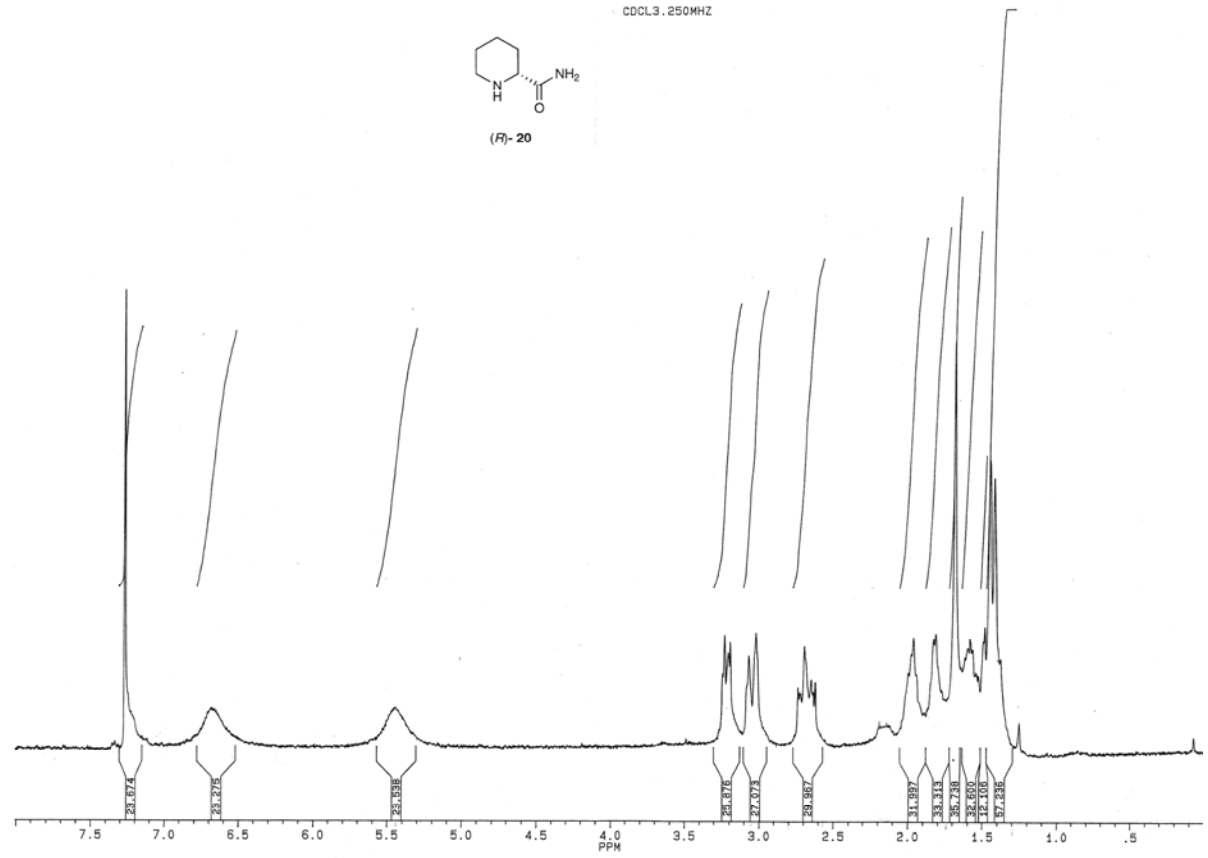

NL-79 // 62.86 MHz CDCl3
HO
HN
NH2
O
(2R,1'R)-18
nmr
150
100
50
ppm (f1)

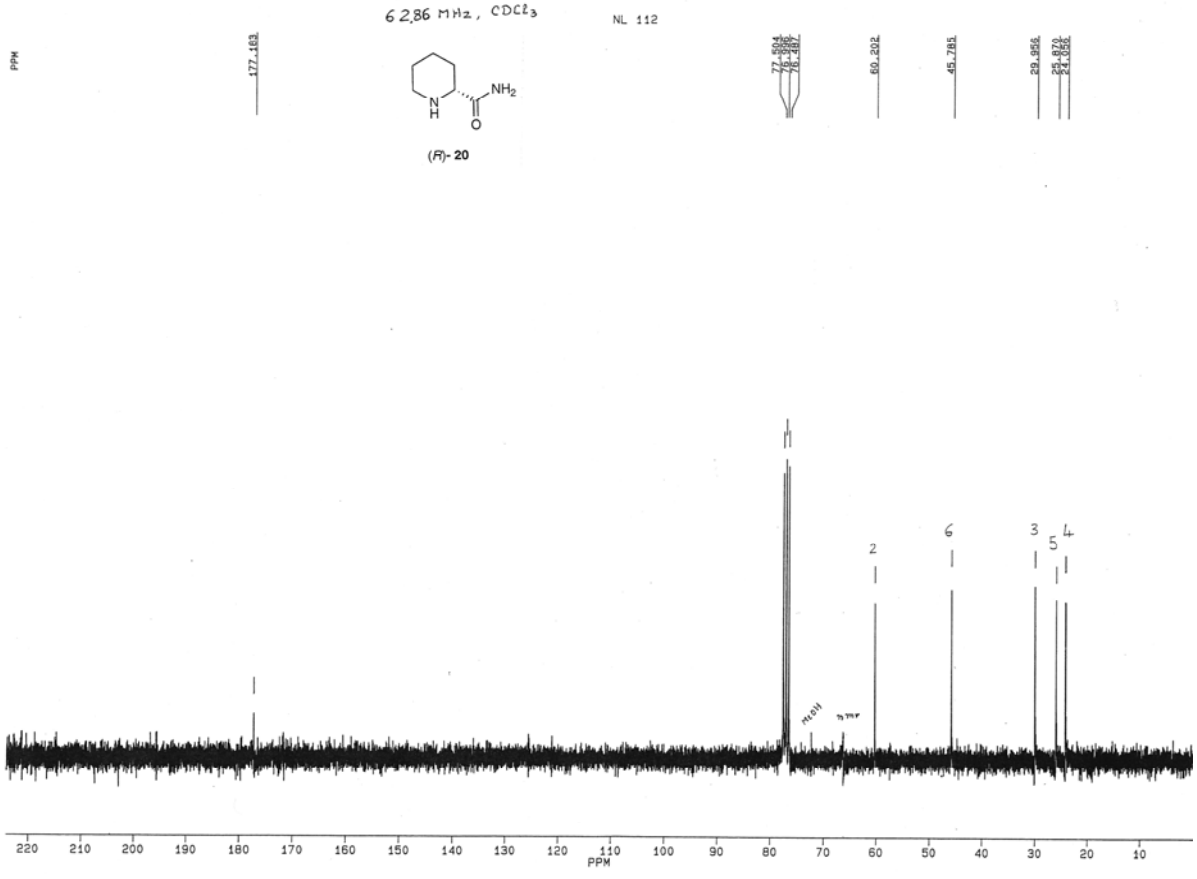

AF-N53aa // 250 MHz CDCl3
NH2
O
(2S,1'R)-17
2.82
0.96
1.10
1.02
1.00
1.80
2.22
3.70
0.92
2.47
0.92
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

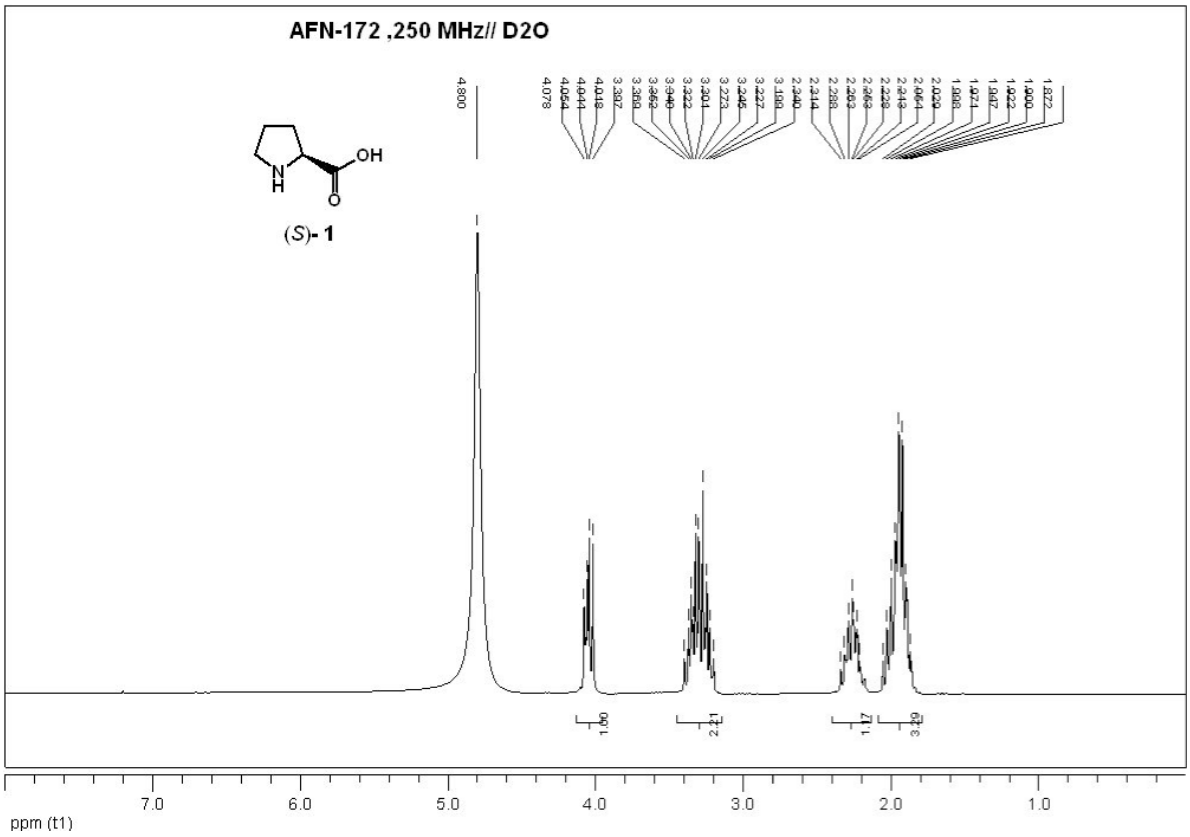

NL53A – 90.5 MHz, CDCl3
128.491
127.984
127.084
77.386
77.061
76.681
26.424
22.917
NH2
O
Ph
(2S,1'R)-17
177.0
143.7
62.8
58.2
44.1
31.0
15.1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
PPM

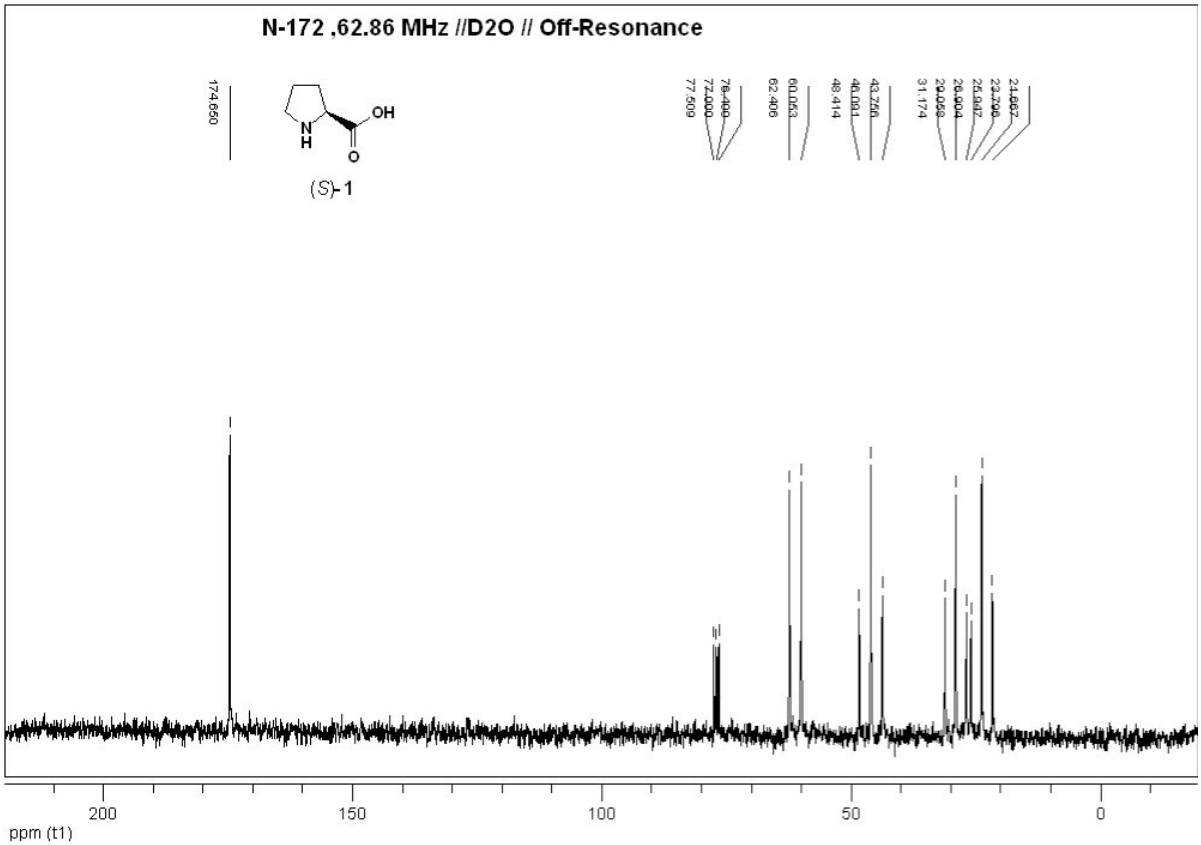

AF N57 solide 200 MHz//CDCl3
NH2
N
H
O
(S)- 19
1.69
1.30
0.00
1.00
2.11
4.11
2.60
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

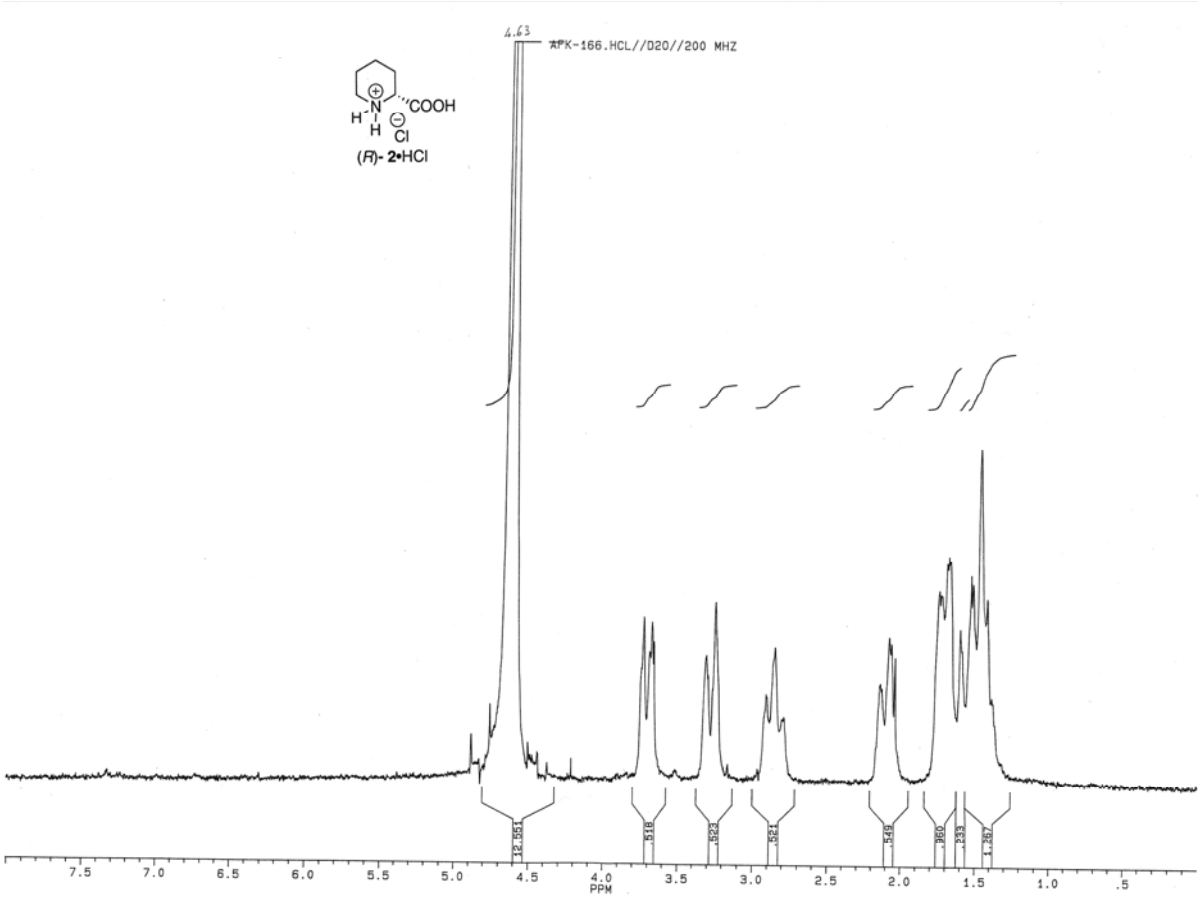

AF n-57 CDCl3 62.85 MHz prolinamide
178.771
77.308
76.491
77.000
60.395
47.234
30.880
25.172
NH2
N
H
O
(S)- 19
150
100
50
ppm (t1)

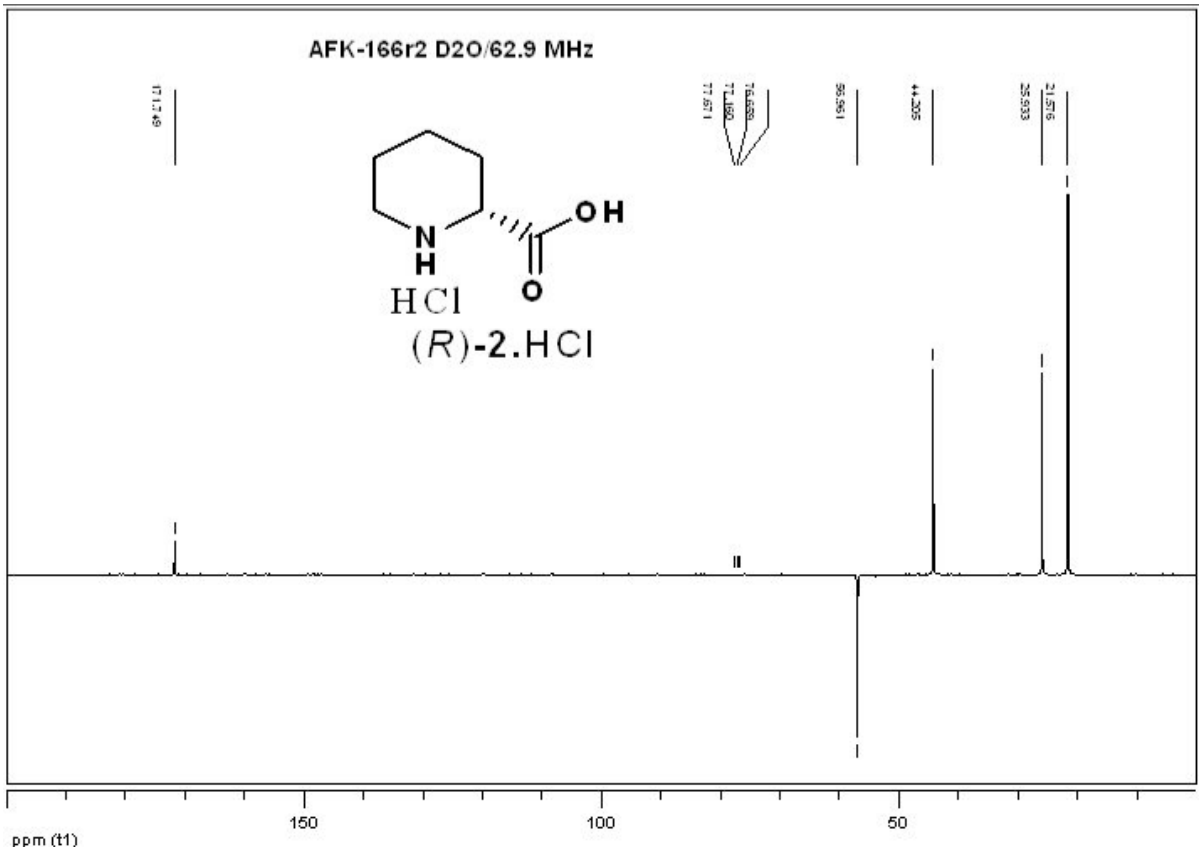

CDCL3.250MHZ
(R)- 20
PPM


62.86 MHz, CDCl3
NL 112
(R)- 20
PPM


AFN-172 ,250 MHz// D2O
(S)- 1
ppm (t1)


N-172 ,62.86 MHz //D2O // Off-Resonance
(S)-1
ppm (t1)


4.63
AFK-166.HCL//D2O//200 MHZ
COOH
Cl
(R)- 2•HCl
12.561
5.18
5.23
5.21
5.49
3.60
3.33
1.267
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM


AFK-166r2 D2O/62.9 MHz
171.749
77.671
76.459
72.160
55.961
44.305
25.933
21.576
OH
N
H
O
HCl
(R)-2.HCl
150
100
50
ppm (t1)