

# An Efficient Synthesis of Enantiomerically Pure (*R*)- Pipelicolic 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<sub>254</sub>). 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<sup>-1</sup>) with polystyrene as a standard. Melting points were determined on a capillary melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were measured on a 250 or 360 MHz spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance (CDCl<sub>3</sub> at 7.27 and D<sub>2</sub>O at 4.8 ppm). <sup>13</sup>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<sub>3</sub> at 77.16 ppm). <sup>31</sup>P NMR spectra were recorded on a 101.26 MHz and chemical shifts were quoted relative to internal 85% H<sub>3</sub>PO<sub>4</sub> ( $\delta$  = 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 <sup>1</sup>H 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  $\beta$ -cyclodextrine DM (40 m x 0.25 mm, 120°C, 1 bar). For more details, see: previous paper.<sup>1</sup>

**(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*)- $\alpha$ -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<sub>3</sub>);  $R_f$  = 0.16 (EtOAc/petrol ether: 3/7); IR (neat) 3239, 2225 (CN), 1453 cm<sup>-1</sup>; Anal. Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O: 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<sub>2</sub>Cl<sub>2</sub> (15 mL), was successively added at 0 °C, NEt<sub>3</sub> (306  $\mu$ L, 2.2 mmol) cat. DMAP (60 mg), and mesyl chloride (152 mg, 171  $\mu$ L, 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*<sup>\*</sup>,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<sub>3</sub> (306  $\mu$ L), 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 (*2S,1'S*)-**12** and (*2R,1'S*)-**13** in a 60:40 ratio.  $R_f$  = 0.63 (EtOAc/petrol ether: 3/7); IR (neat) 2975, 2222 (CN), 1492, 1454  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR  $\delta$  **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**); <sup>13</sup>C NMR  $\delta$  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<sup>+</sup>, 7), 186 (45), 185 (100), 123 (44), 105 (95), 77 (43); HRMS (EI) calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub> 200.1313. Found: 200.1314.

**(2*R*<sup>\*,1*R*</sup>)-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<sub>3</sub> (155  $\mu$ L), 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<sub>2</sub>Cl<sub>2</sub>: 5 → 10%), we obtained 148 mg (69%) of pure cyclic amino nitriles as an inseparable mixture of two diastereomers (*2R,1'R*)-**14** and (*2S,1'R*)-**15** in a 55:45 ratio.  $R_f$  = 0.75 (EtOAc/petrol ether: 3/7); IR (neat) 3401, 2222 (CN), 1454  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR  $\delta$  **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**); <sup>13</sup>C NMR  $\delta$  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<sup>+</sup>) (4), 199 (100), 172 (8), 105 (89), 83 (14).

**(2*S*<sup>\*,1*S*</sup>)-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<sub>2</sub>SO<sub>4</sub> (18 M, 5 mL), CH<sub>2</sub>Cl<sub>2</sub> (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 (*2S,1'S*)-**7**, 225 mg (34.5%) of minor (*2R,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<sub>3</sub>);  $R_f = 0.08$  (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>: 3/7); IR (neat): 3420, 3281, 1682, 1453 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  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). <sup>13</sup>C NMR  $\delta$  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<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O: 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<sub>2</sub>SO<sub>4</sub> (18 M, 3 mL), CH<sub>2</sub>Cl<sub>2</sub> (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 (2*R*,1'*R*)-(+)–8* are identical with those described above.

*Data for minor (2*S*,1'*R*)-(–)–17*:  $[\alpha]_D -19.0$  (*c* 1.00, EtOH),  $[\alpha]_D -37$  (*c* 1.00, CHCl<sub>3</sub>);  $R_f = 0.30$  (AcOEt/CH<sub>2</sub>Cl<sub>2</sub> : 50/50); IR (neat) 3446, 3300, 1676, 1452 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.30–2.05 (m, 6H),  $\delta$  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); <sup>13</sup>C NMR  $\delta$  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<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O: 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<sub>3</sub> (155  $\mu$ L), cat. DMAP (30 mg) and MsCl (76 mg, 86  $\mu$ L). After stirring at 0 °C for 6 h, then at 40 °C for 2 days, and FC (eluent, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 3/97  $\rightarrow$  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)<sub>2</sub>/C (80 mg) stirring at rt for 14 h, gave after FC, 70 mg (77%) of

pure (*S*)-prolinamide **19**.<sup>2</sup>  $[\alpha]_D$  – 105 (*c* 2.00, EtOH),  $[\alpha]_D$  – 118 (*c* 1.00, CHCl<sub>3</sub>), 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<sup>–1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  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); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR  $\delta$ : 26.2, 30.6, 47.2, 60.4, 178.8; HRMS (EI): calcd for C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>O: 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<sub>2</sub>O), mp 226 °C (dec.); ref. authentic sample  $[\alpha]_D$  –84 (*c* 4.00, H<sub>2</sub>O), mp 228 °C (decomp.). Its spectral properties were identical to those of an authentic sample.

**(R)-Pipelicolic acid [(R)-(+)-2].** Following procedure E: Amino amide (*R*)-**20**<sup>3</sup> (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*)-pipelicolic acid (*R*)-**2**.  $[\alpha]_D$  +26.7 (*c* 1.00, H<sub>2</sub>O), mp > 265 °C dec; lit.  $[\alpha]_D$  +26.3 (*c* 1.00, H<sub>2</sub>O),<sup>4</sup> mp 271 °C dec,  $[\alpha]_D$  +25.5 (*c* 1.00, H<sub>2</sub>O).<sup>5</sup> Its spectral properties were identical to those

reported in the literature.<sup>4</sup>

## References

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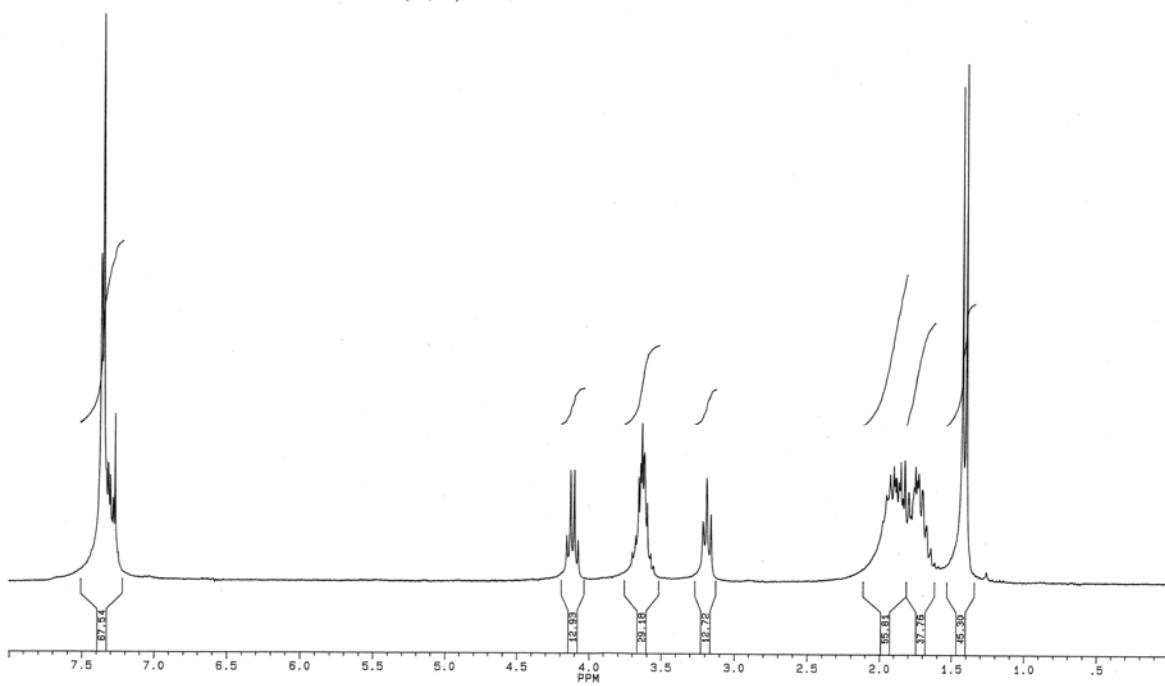
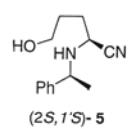
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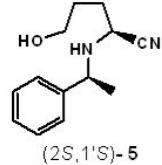
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NL080, I, CDCL3, 250MHZ



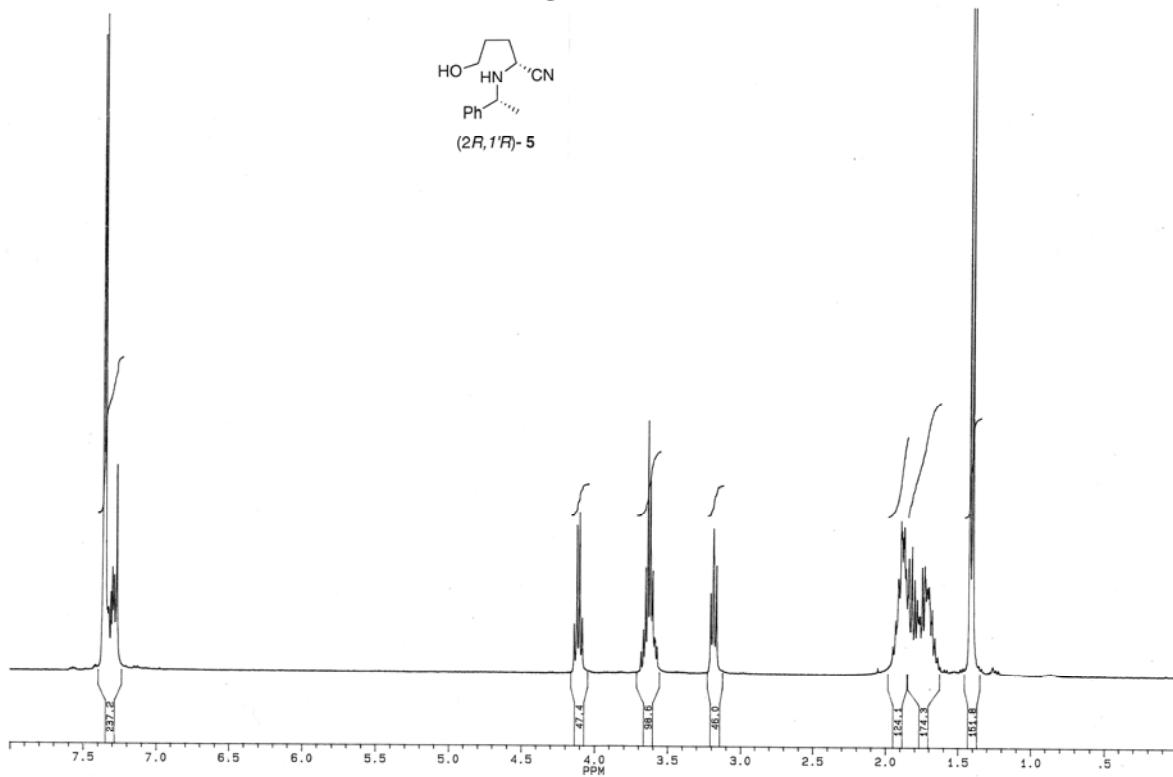
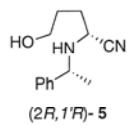
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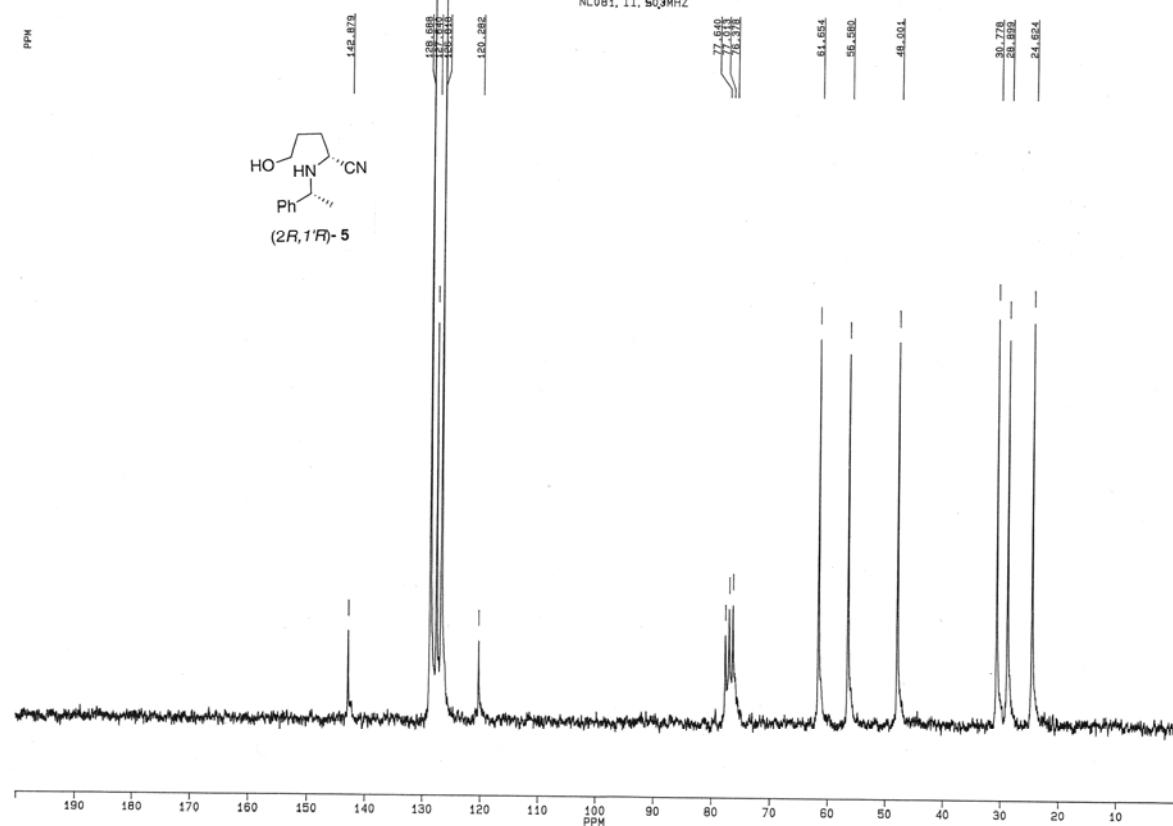
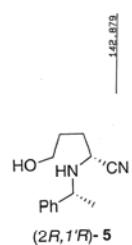
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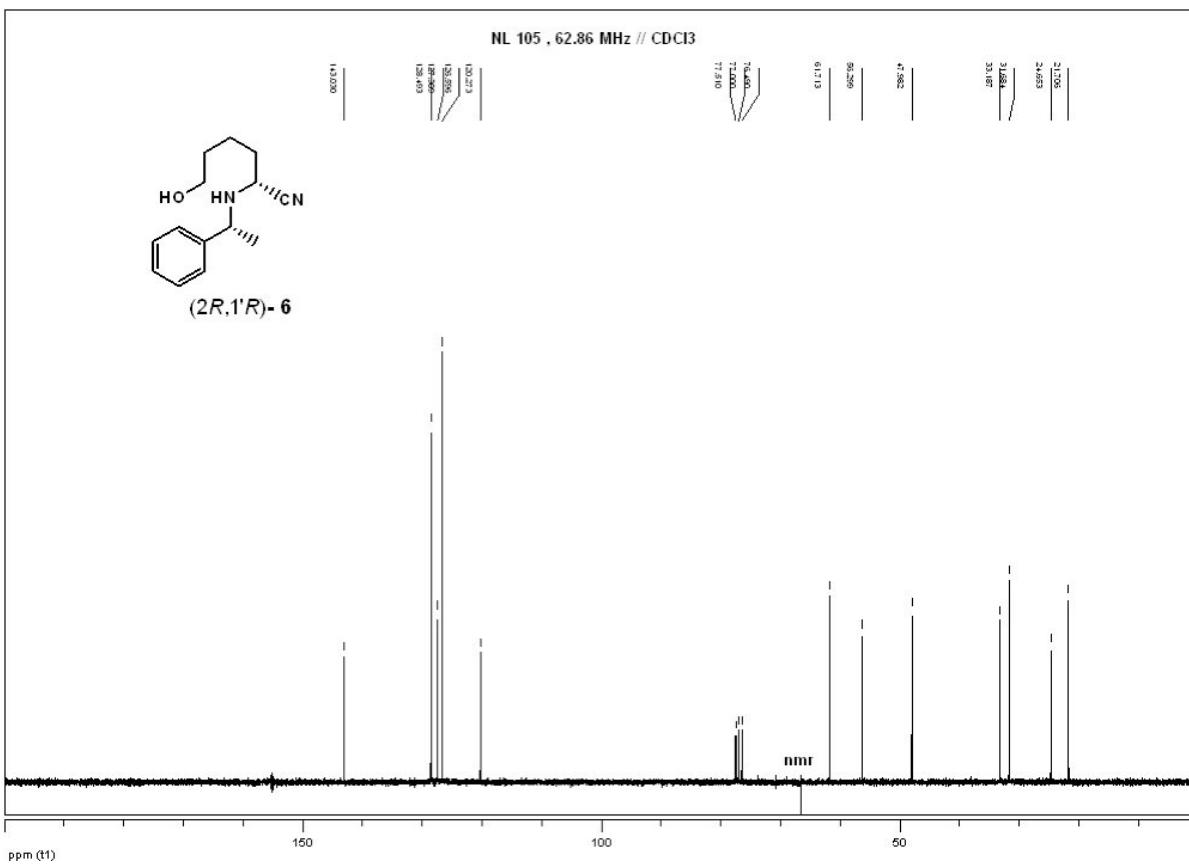
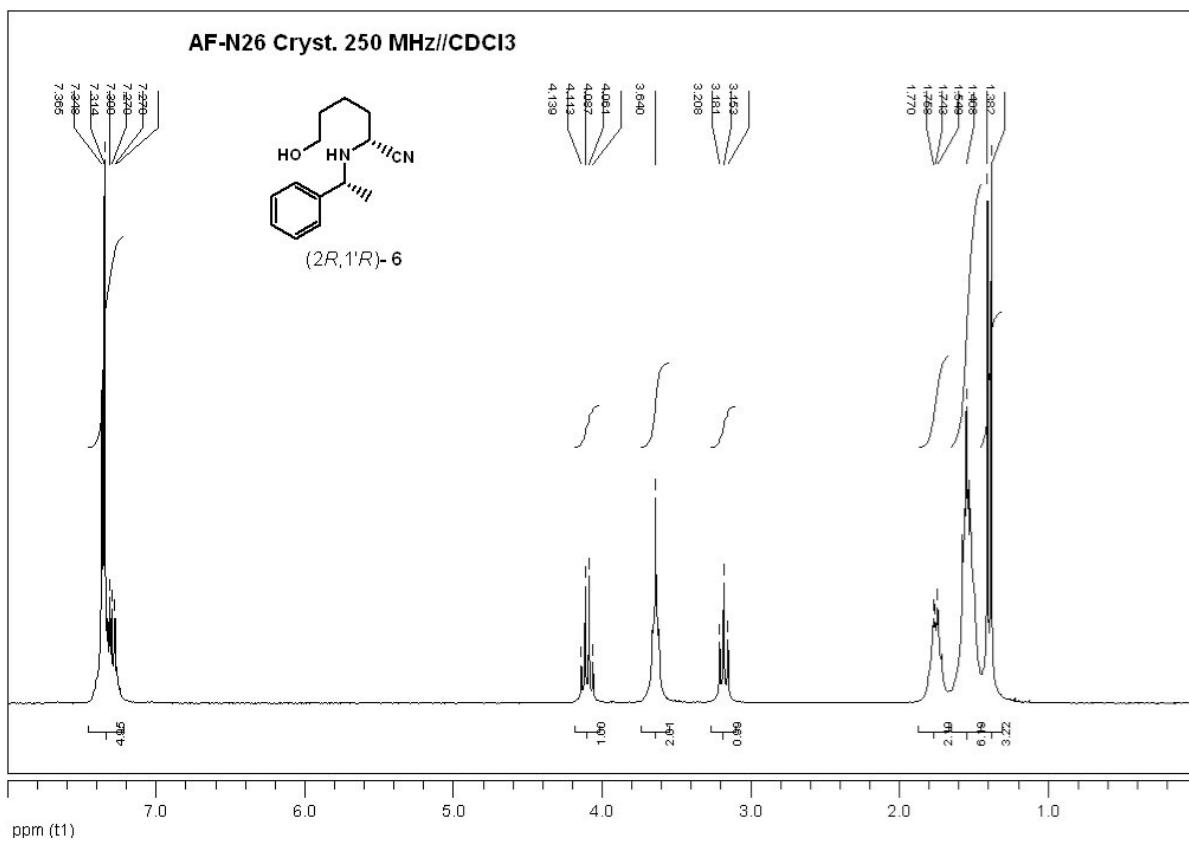
<img alt="Chemical structure of (2S,1'S)-5 and its 13C NMR spectrum. The chemical structure is a cyclopropane ring with a hydroxymethyl group (CH2OH) at the 2-position, a cyano group (CN) at the 1-position, and a 1-phenylpropyl group at the 1'-position. The 13C NMR spectrum shows peaks for the cyclopropane ring carbons (142.7 ppm, 129.3 ppm, 128.7 ppm, 126.9 ppm, 126.7 ppm, 126.5 ppm, 126.3 ppm, 126.1 ppm), the phenyl ring carbons (129.1 ppm, 128.9 ppm, 128.7 ppm, 128.5 ppm, 128.3 ppm, 128.1 ppm, 127.9 ppm, 127.7 ppm, 127.5 ppm, 127.3 ppm, 127.1 ppm, 126.9 ppm, 126.7 ppm, 126.5 ppm, 126.3 ppm, 126.1 ppm, 125.9 ppm, 125.7 ppm, 125.5 ppm, 125.3 ppm, 125.1 ppm, 124.9 ppm, 124.7 ppm, 124.5 ppm, 124.3 ppm, 124.1 ppm, 123.9 ppm, 123.7 ppm, 123.5 ppm, 123.3 ppm, 123.1 ppm, 122.9 ppm, 122.7 ppm, 122.5 ppm, 122.3 ppm, 122.1 ppm, 121.9 ppm, 121.7 ppm, 121.5 ppm, 121.3 ppm, 121.1 ppm, 120.9 ppm, 120.7 ppm, 120.5 ppm, 120.3 ppm, 120.1 ppm, 119.9 ppm, 119.7 ppm, 119.5 ppm, 119.3 ppm, 119.1 ppm, 118.9 ppm, 118.7 ppm, 118.5 ppm, 118.3 ppm, 118.1 ppm, 117.9 ppm, 117.7 ppm, 117.5 ppm, 117.3 ppm, 117.1 ppm, 116.9 ppm, 116.7 ppm, 116.5 ppm, 116.3 ppm, 116.1 ppm, 115.9 ppm, 115.7 ppm, 115.5 ppm, 115.3 ppm, 115.1 ppm, 114.9 ppm, 114.7 ppm, 114.5 ppm, 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ppm, 15.7 ppm, 15.5 ppm, 15.3 ppm, 15.1 ppm, 14.9 ppm, 14.7 ppm, 14.5 ppm, 14.3 ppm, 14.1 ppm, 13.9 ppm, 13.7 ppm, 13.5 ppm, 13.3 ppm, 13.1 ppm, 12.9 ppm, 12.7 ppm, 12.5 ppm, 12.3 ppm, 12.1 ppm, 11.9 ppm, 11.7 ppm, 11.5 ppm, 11.3 ppm, 11.1 ppm, 10.9 ppm, 10.7 ppm, 10.5 ppm, 10.3 ppm, 10.1 ppm, 9.9 ppm, 9.7 ppm, 9.5 ppm, 9.3 ppm, 9.1 ppm, 8.9 ppm, 8.7 ppm, 8.5 ppm, 8.3 ppm, 8.1 ppm, 7.9 ppm, 7.7 ppm, 7.5 ppm, 7.3 ppm, 7.1 ppm, 6.9 ppm, 6.7 ppm, 6.5 ppm, 6.3 ppm, 6.1 ppm, 5.9 ppm, 5.7 ppm, 5.5 ppm, 5.3 ppm, 5.1 ppm, 4.9 ppm, 4.7 ppm, 4.5 ppm, 4.3 ppm, 4.1 ppm, 3.9 ppm, 3.7 ppm, 3.5 ppm, 3.3 ppm, 3.1 ppm, 2.9 ppm, 2.7 ppm, 2.5 ppm, 2.3 ppm, 2.1 ppm, 1.9 ppm, 1.7 ppm, 1.5 ppm, 1.3 ppm, 1.1 ppm, 0.9 ppm, 0.7 ppm, 0.5 ppm, 0.3 ppm, 0.1 ppm, 0.0 ppm.</p>

NL081,  $\text{CDCl}_3$  RECRYSTAL, 360MHz

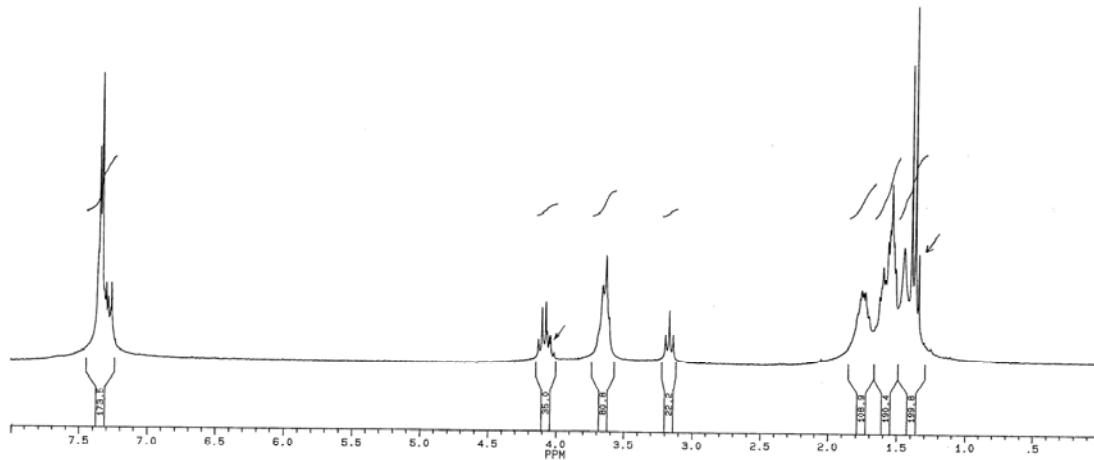
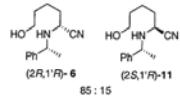


NL081, II, 503MHz

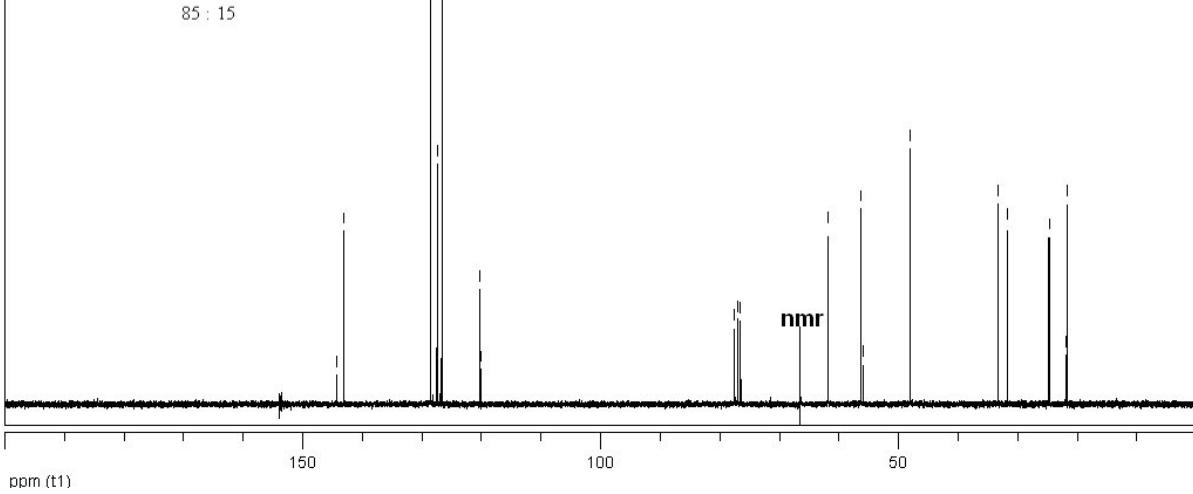
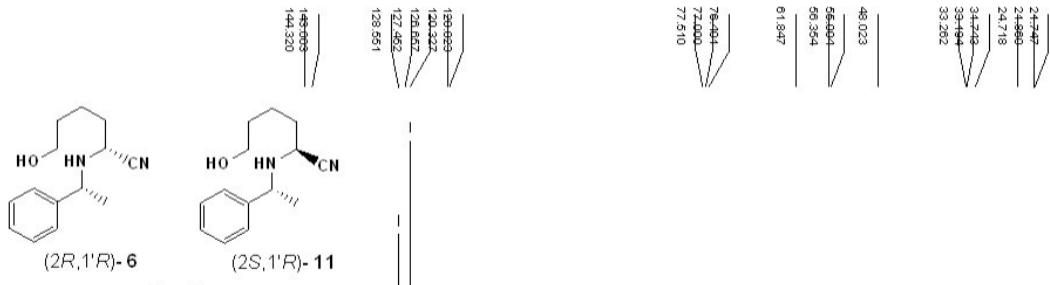




NL05B, T: 23-32, CDCL3, 250MHZ  
mother liquid remaining after 3 crystallizations



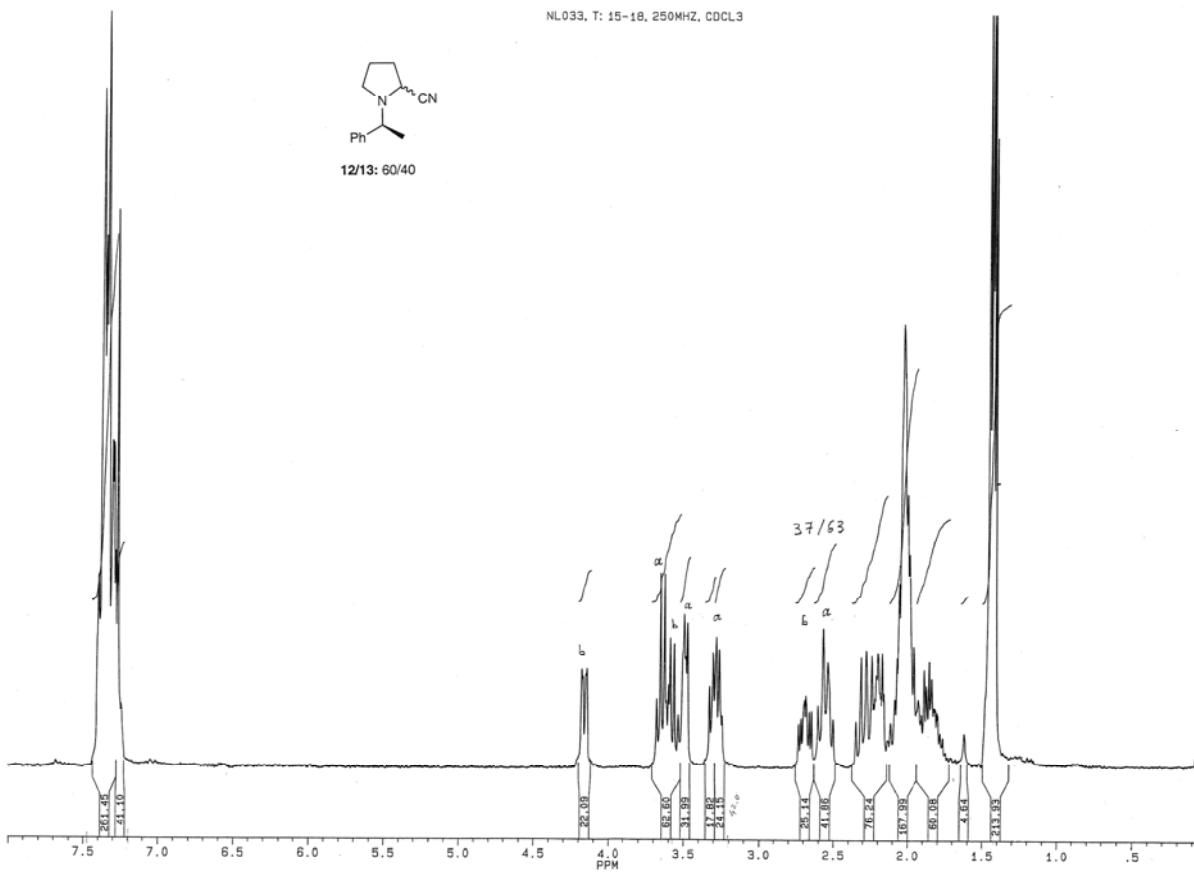
NL-58-mother liquid after three crystallisations, 62.86 MHz CDCl<sub>3</sub>



NL033, T: 15-18, 250MHZ, CDCL3



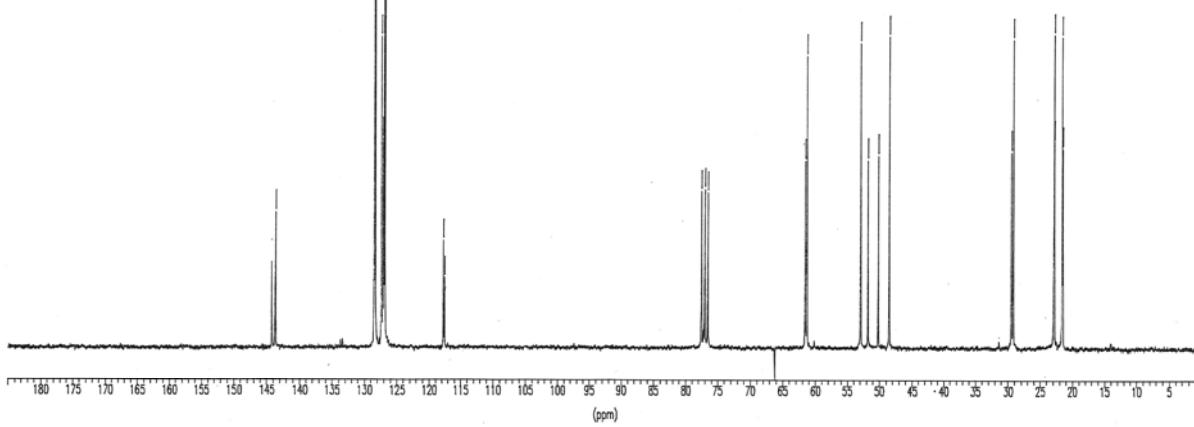
12/13: 60/40



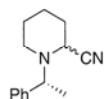
NL 033



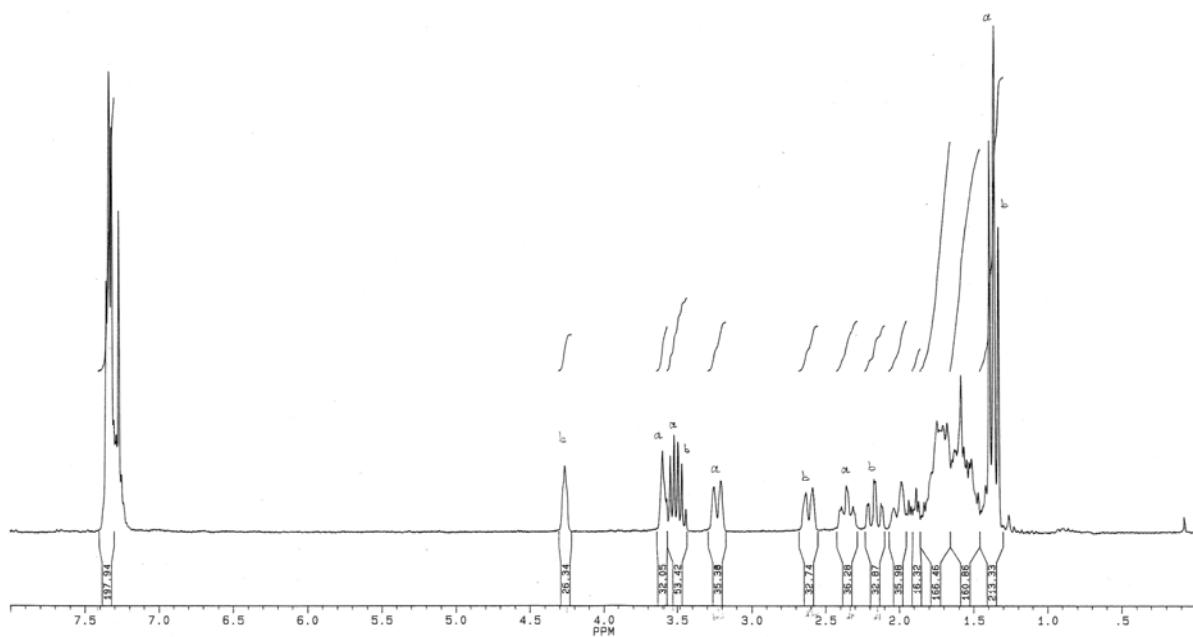
12/13: 60/40



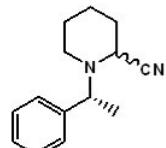
NL036, CHROMATO, AE\CM, T: 17-23, CDCL3, 250MHZ



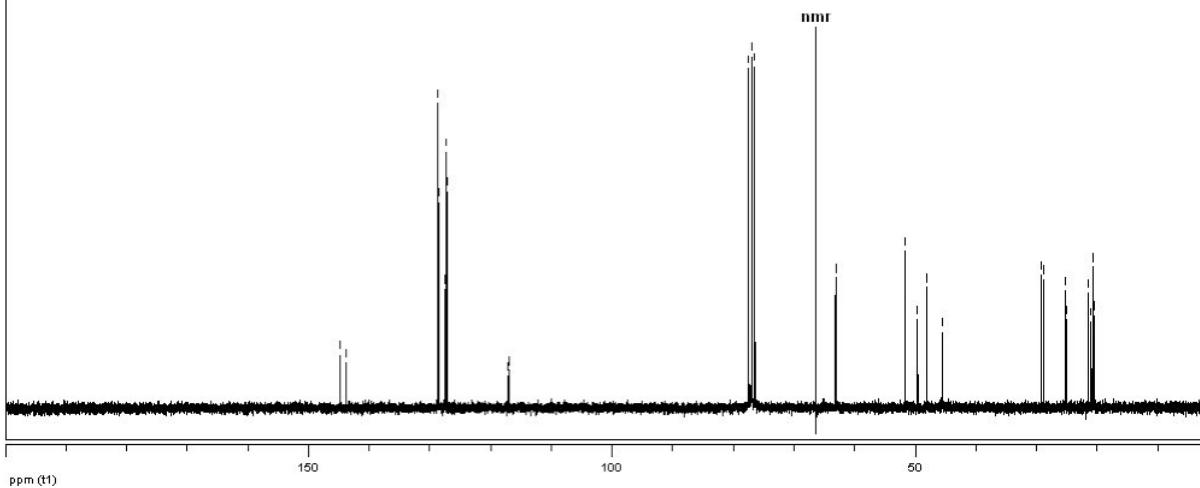
14/15: 55/45

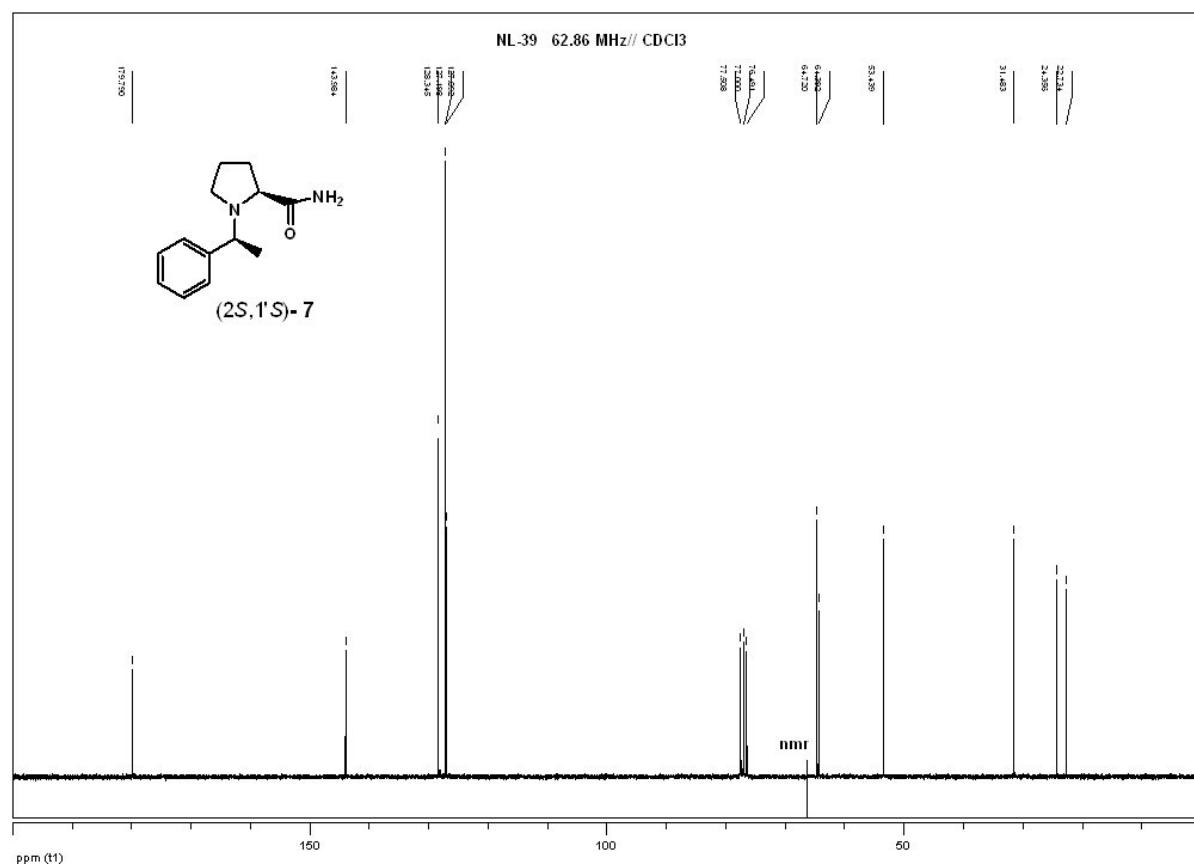
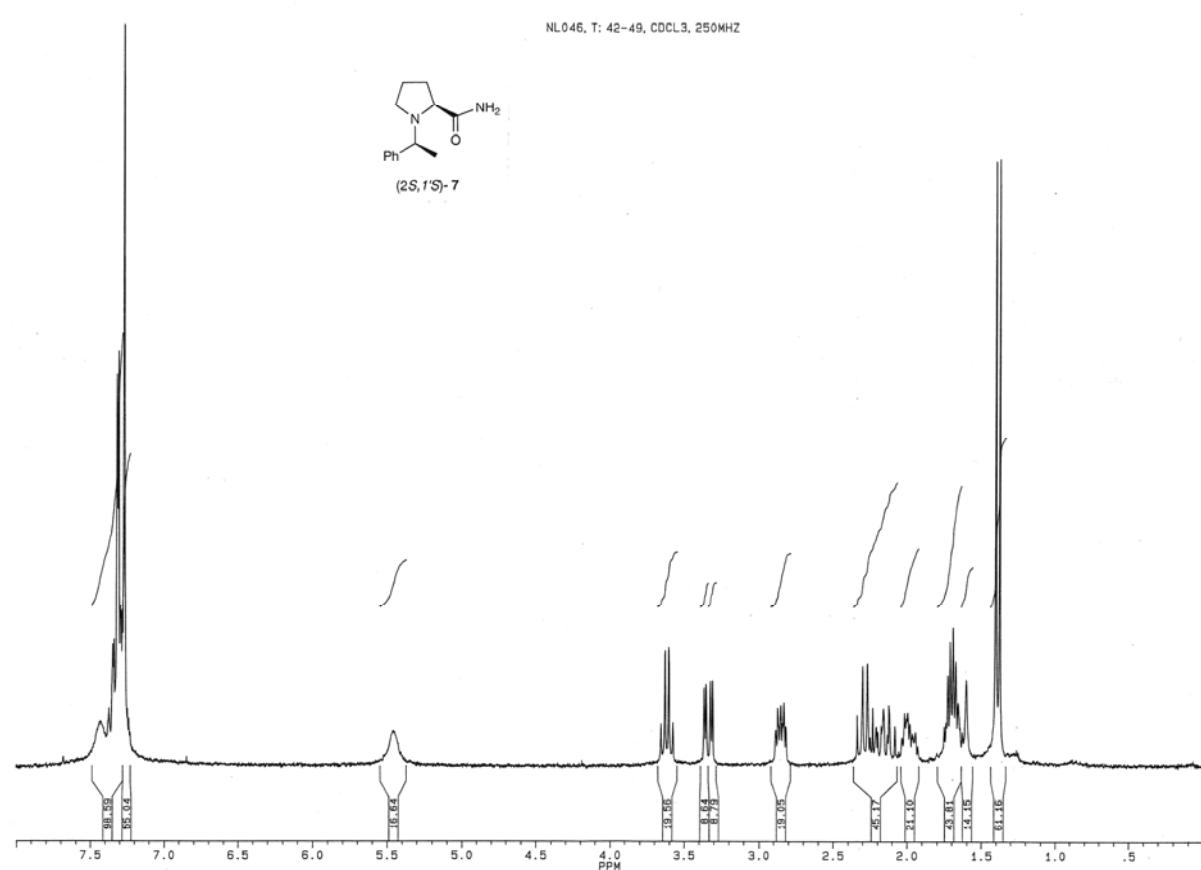


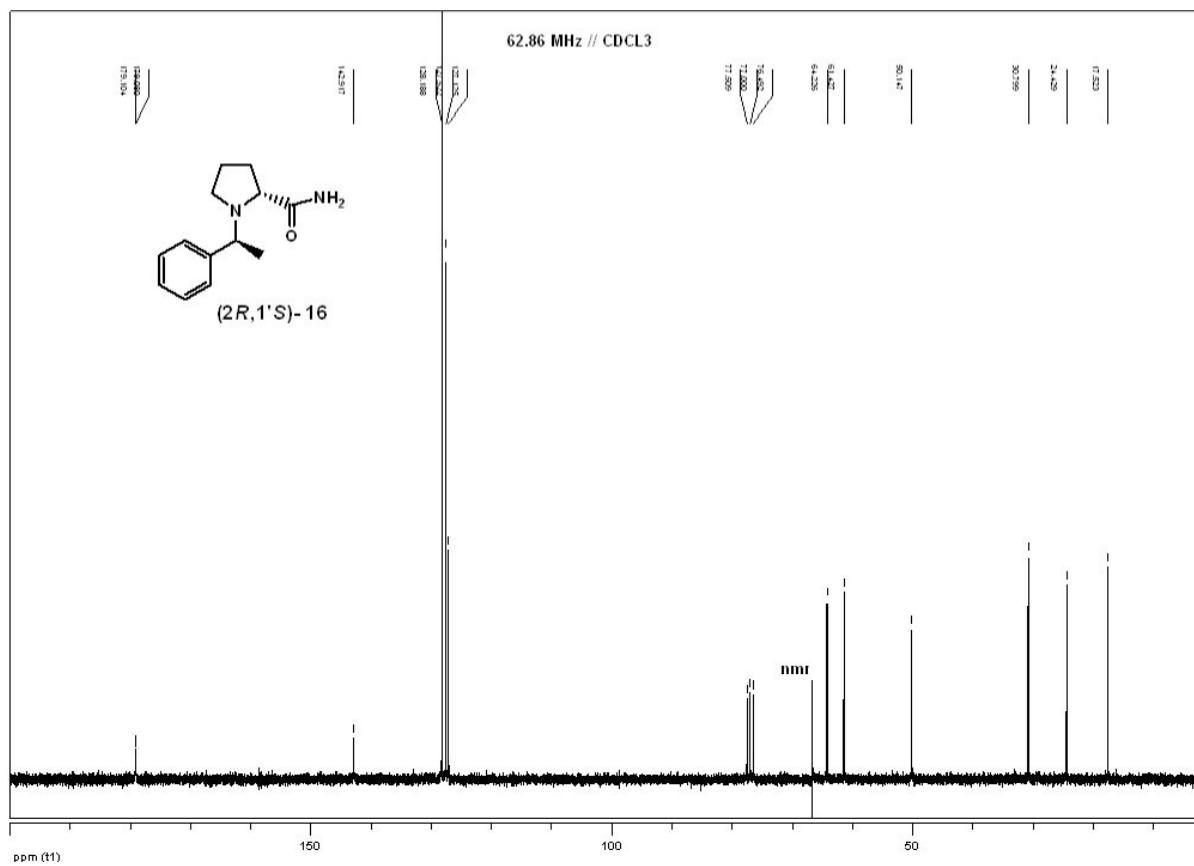
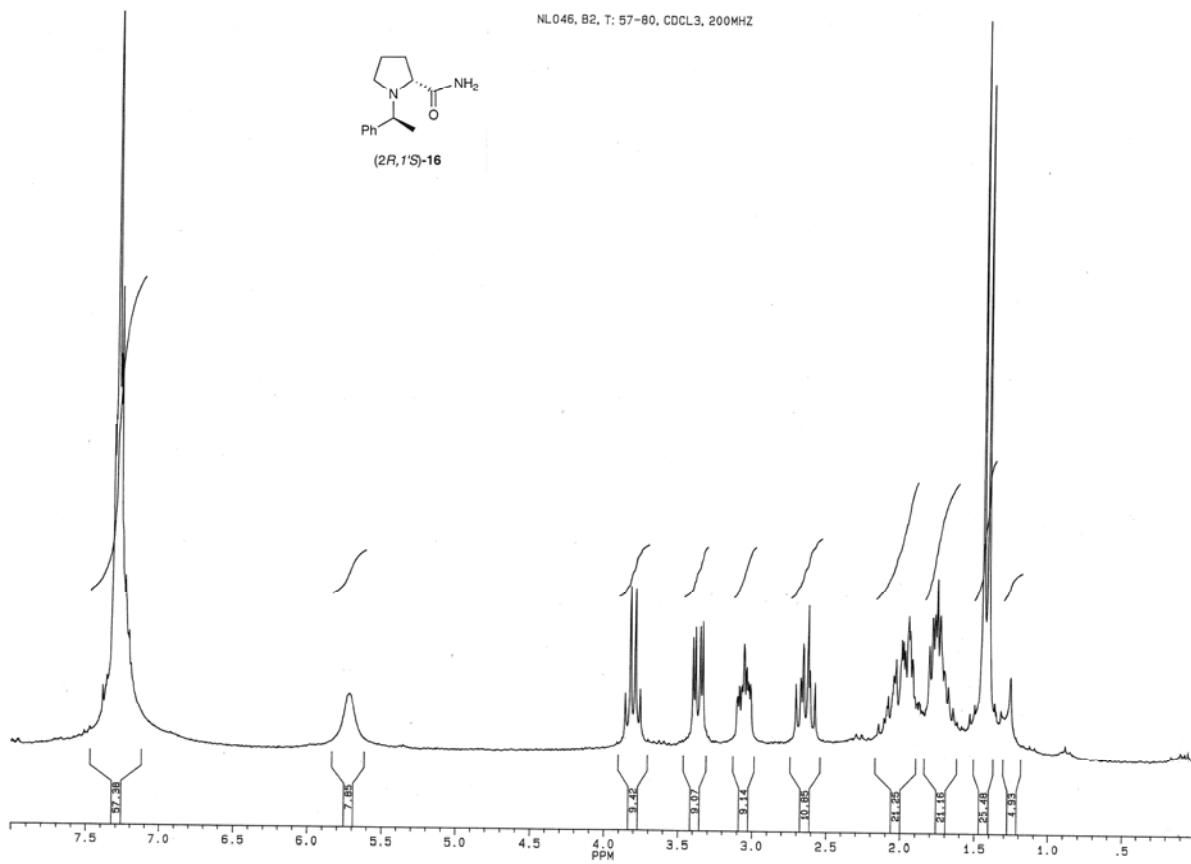
62.86 MHz // CDCL3

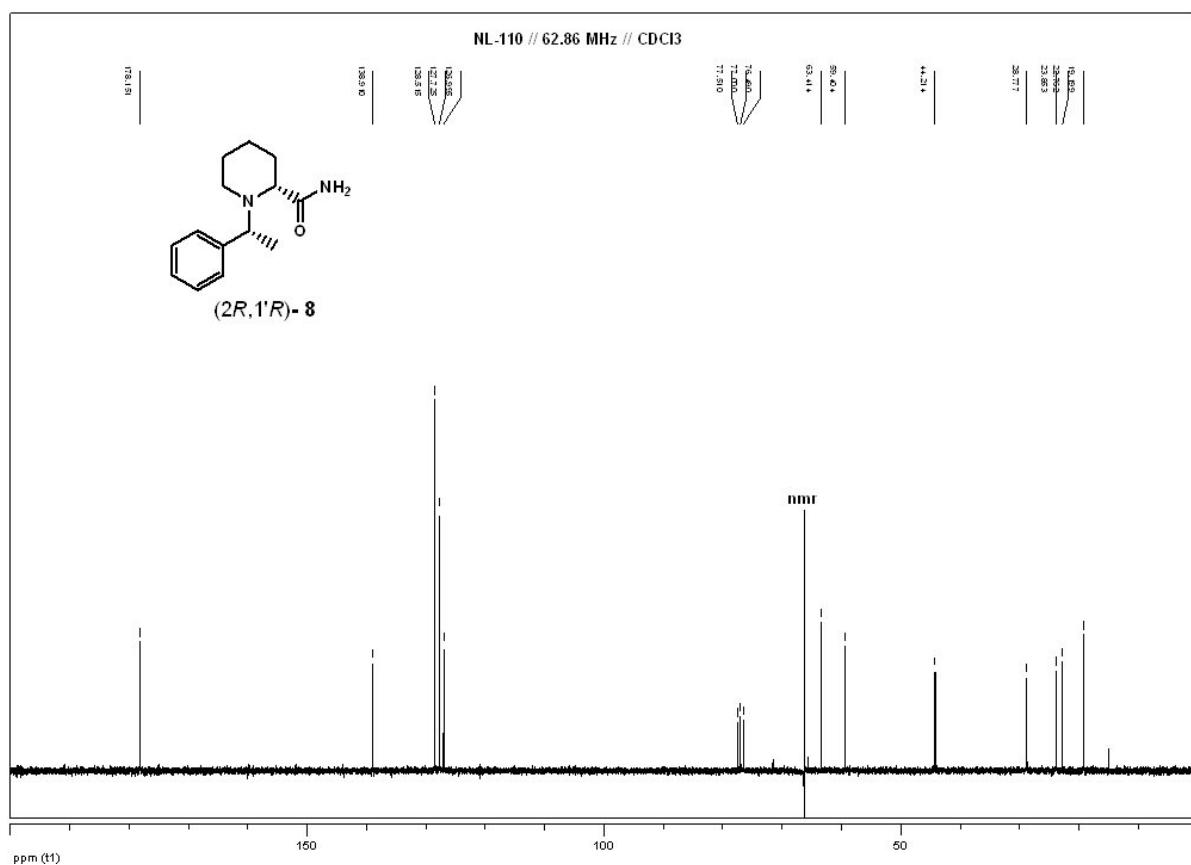
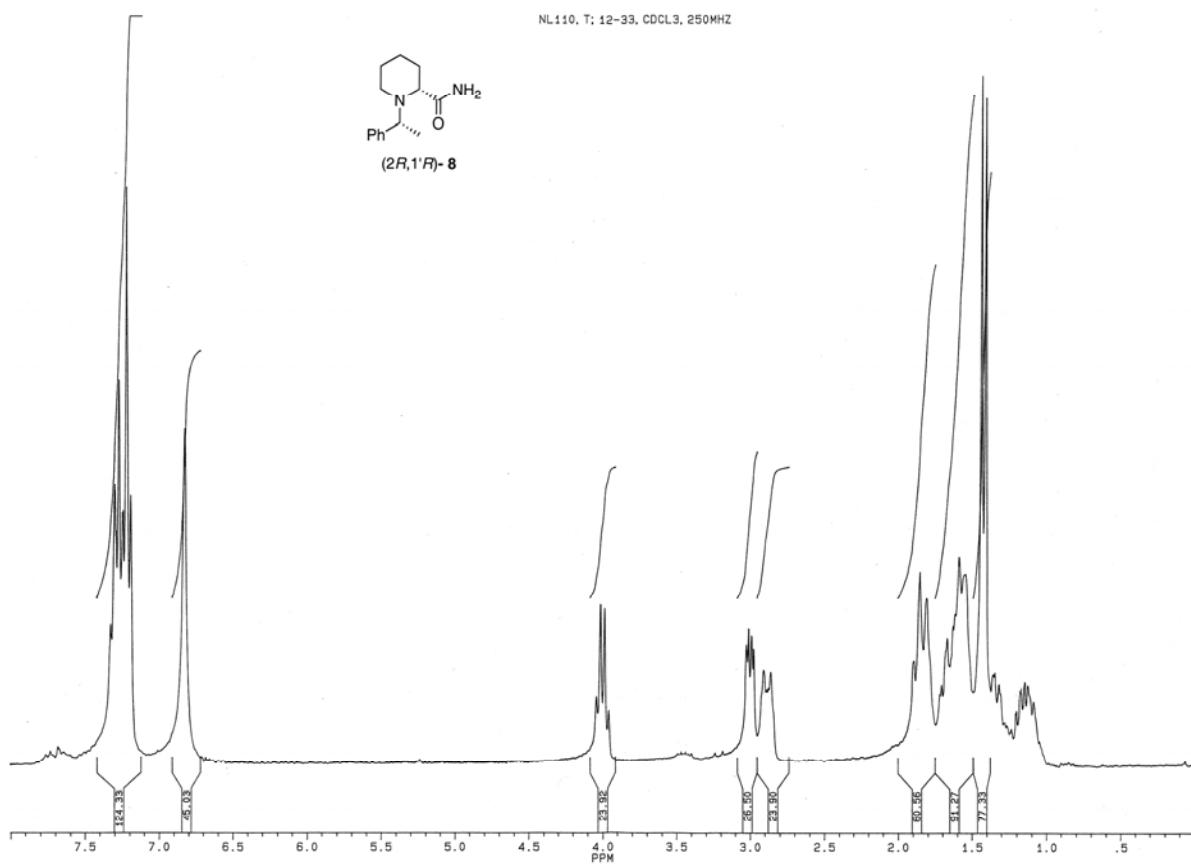


14/15 : 54/46

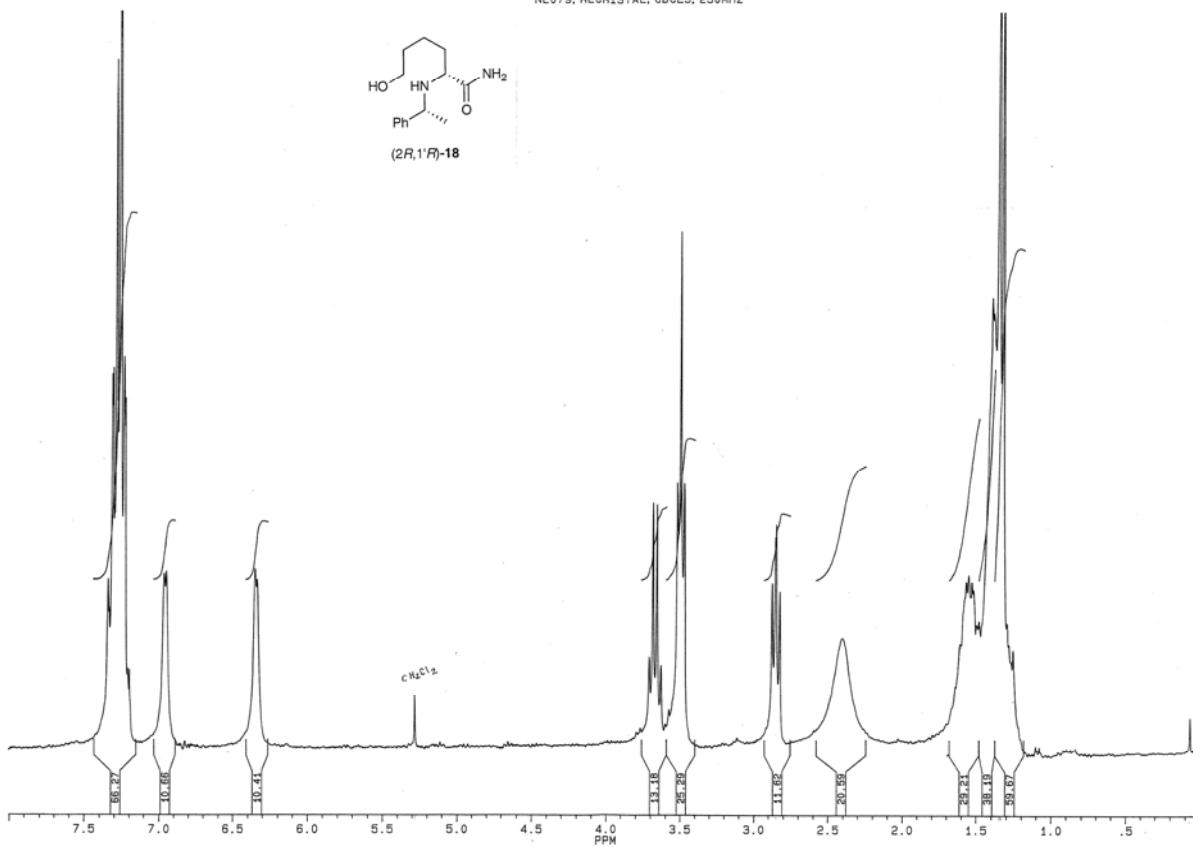
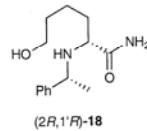




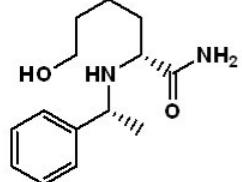




NL079, RECRYSTAL, CDCL3, 250MHZ



NL-79 // 62.86 MHz CDCl3

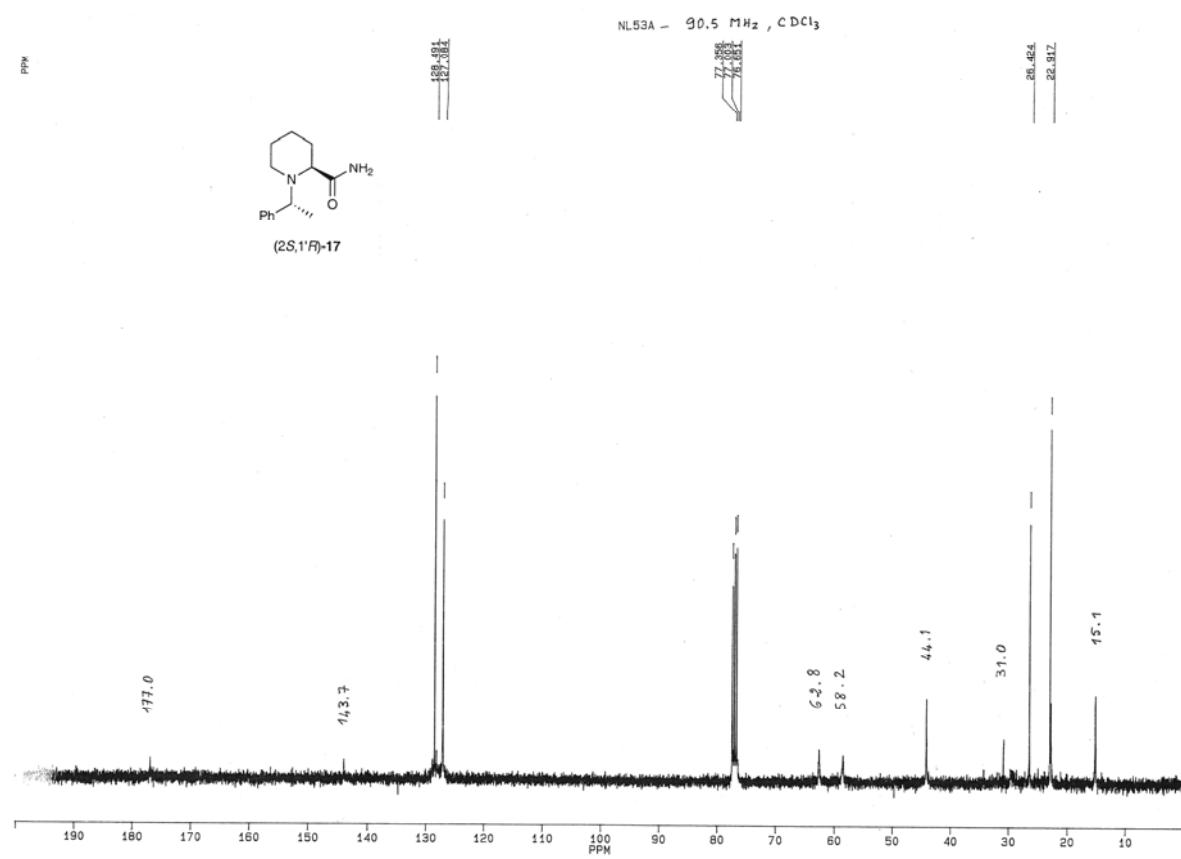
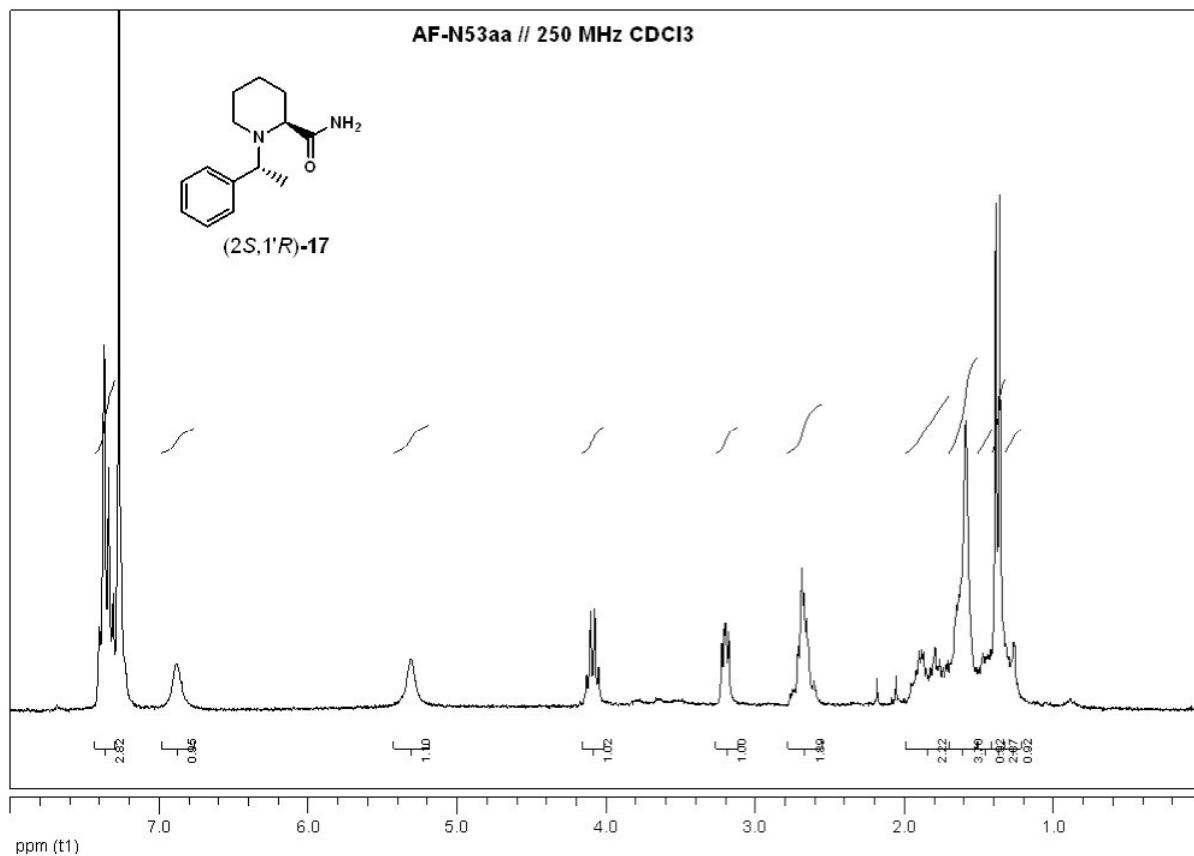


(2*R*,1'*R*)-18

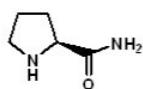
NL-79 // 62.86 MHz CDCl<sub>3</sub>

**(2R,1'R)-18**

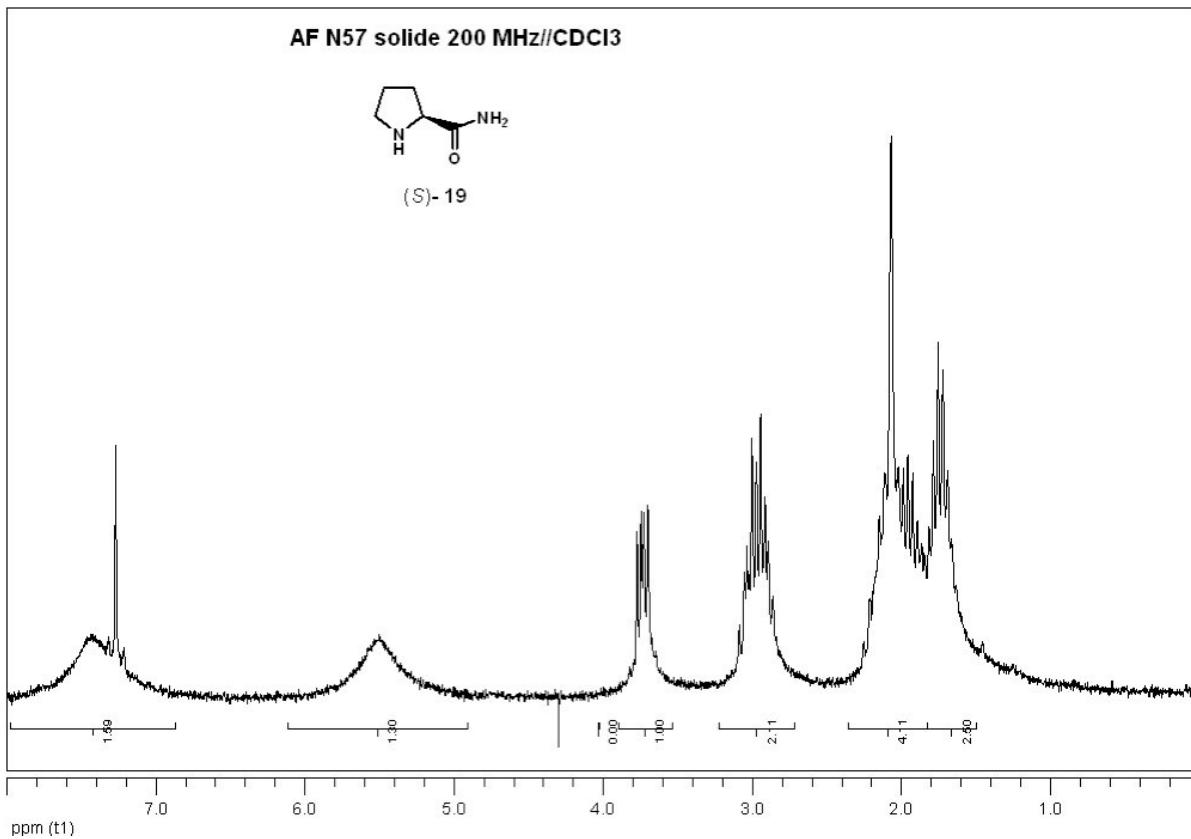
ppm (ppm)



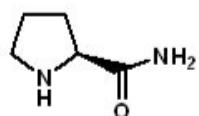
AF N57 solide 200 MHz//CDCl<sub>3</sub>



(S)- 19



AF n-57 CDCl<sub>3</sub> 62.85 MHz prolinamide



(S)- 19

