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of Reliable Methods
for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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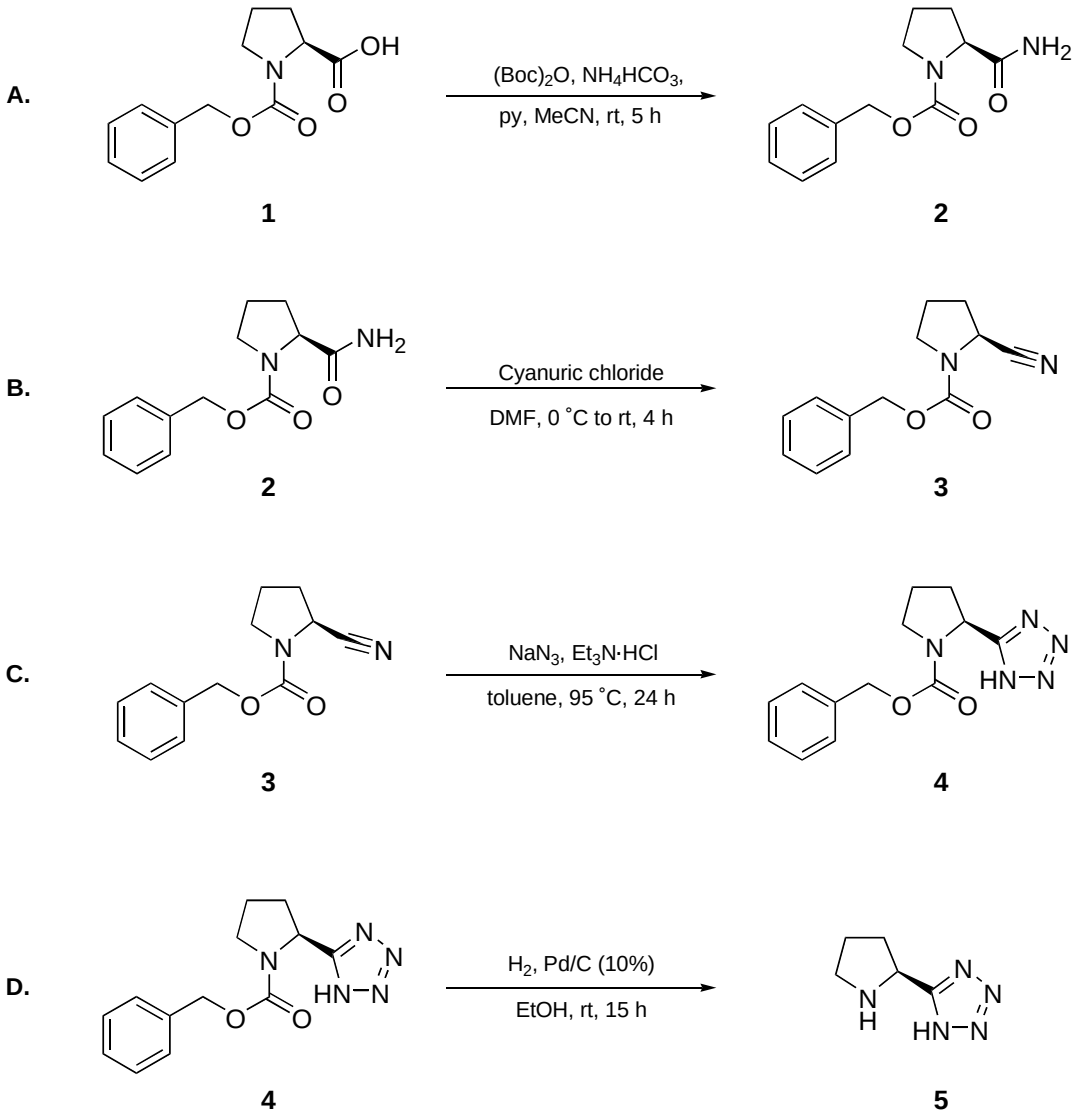
(*S*)-5-PYRROLIDIN-2-YL-1*H*-TETRAZOLE



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1. Procedure

A. *(S)-2-Amido-pyrrolidine-1-carboxylic acid benzyl ester* (**2**). An oven-dried, three-necked, 1-L, round-bottomed flask equipped with an argon inlet, septum, thermocouple and a stirring bar is charged with Cbz-L-proline

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(**1**) (20.0 g, 80.2 mmol) (Note 1), di-*tert*-butyl dicarbonate (22.7 g, 104 mmol, 1.3 equiv) (Note 2), ammonium bicarbonate (7.60 g, 96.2 mmol, 1.2 equiv) (Notes 3 and 4) and acetonitrile (400 mL) (Note 5) under an argon atmosphere. After all reagents are combined, a cloudy, white mixture forms. Pyridine (3.89 mL, 48.1 mmol, 0.6 equiv) (Note 6) is added in one portion via syringe and the mixture is stirred for 5 h at room temperature (Note 7). After complete consumption of the starting material (as monitored by thin layer chromatography, Notes 8 and 9), the reaction mixture is transferred to a one-necked, 1-L, round-bottomed flask and the solvent is removed under reduced pressure with a rotary evaporator (25 °C, 15 mmHg) until approximately 100 mL remains. Ethyl acetate (200 mL) and water (200 mL) are added, the mixture is transferred to a 1-L separatory funnel and the organic phase is separated. The aqueous phase is extracted further with ethyl acetate (2 x 200 mL) and the combined organic phases are washed with brine (200 mL), then are dried ($MgSO_4$, 16 g), filtered, and concentrated under reduced pressure with a rotary evaporator (23-40 °C, 30 mmHg) to give a white solid (Note 10). Recrystallization of the solid from ethyl acetate (Note 11) affords 17.98-18.95 g (90-95%) of **2** as white cubes (Note 12, 13 and 14).

B. *(S)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester* (**3**). An oven-dried, three-necked, 1–L, round-bottomed flask equipped with an argon inlet, septum, thermocouple and a stirring bar is charged with (*S*)-2-amido-pyrrolidine-1-carboxylic acid benzyl ester (**2**) (17.79 g, 71.7 mmol) and *N*,*N*-dimethylformamide (217 mL) (Note 15) under an argon atmosphere, which results in a clear, colorless solution. The solution is cooled in an ice/water bath for 20 min until an internal temperature of 2 °C is reached and cyanuric chloride (8.59 g, 46.6 mmol, 0.65 equiv) (Note 16) is then added in one portion. The reaction mixture is stirred at 4-6 °C (internal temperature) for 1 h, at which point the ice bath is removed and the mixture is allowed to warm to room temperature over 45 min and is stirred for an additional 2.25 h (Note 17). After complete consumption of the starting material (as monitored by thin layer chromatography, Note 18), the mixture is cooled to 5 °C using an ice-water bath and distilled water (200 mL) is added slowly (Note 19). The mixture is transferred to a 1-L separatory funnel and is extracted with ethyl acetate (3 x 200 mL). The combined organic phases are washed with lithium chloride solution (10 wt % in distilled water, 3 x 200 mL, Note 20), then are dried ($MgSO_4$, 18 g), filtered, and concentrated under reduced pressure with a rotary

evaporator (24-40 °C, 30 mmHg) to give a colorless, viscous oil. Suction filtration through a pad of silica (Note 21) affords 16.22 g (97%) of **3** as a colorless oil, which turns to a milky, viscous oil upon storing in the refrigerator (Notes 22, 23 and 24).

C. *(S)-2-(1H-Tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester* (**4**) (Note 25). An oven-dried, single-necked, 250-mL, round-bottomed flask equipped with a gas inlet adaptor and a stirring bar is evacuated and backfilled with argon. The glass Ar adaptor is quickly removed and the flask is charged with (*S*)-2-cyano-pyrrolidine-1-carboxylic acid benzyl ester (**3**) (15.28 g, 66.4 mmol, 1.0 equiv), sodium azide (5.61 g, 86.3 mmol, 1.3 equiv) (Notes 26 and 27), triethylamine hydrochloride (11.9 g, 86.3 mmol, 1.3 equiv) (Notes 28 and 29) and toluene (65 mL) (Note 30) under an argon atmosphere, which results in a white mixture upon stirring. A reflux condenser with an Ar adaptor is fitted to the flask and the reaction mixture is heated to 95 °C (external temperature) in an oil bath for 24 h under an argon atmosphere (Note 31). After complete consumption of starting material (as monitored by thin layer chromatography, Note 32), deionized water (100 mL) is added and the mixture is transferred to a 250-mL separatory funnel. The flask is rinsed with additional toluene (25 mL) and deionized water (25 mL) and the aqueous phase is separated. The organic phase is further washed with water (50 mL) and the combined aqueous extracts are transferred to a 500-mL Erlenmeyer flask and are cooled with stirring in an ice/water bath to 0 °C (external temperature). Sodium nitrite solution (20 wt % aqueous, 21 mL, 61 mmol, Note 33) is added in one portion, followed by dropwise addition of sulfuric acid (20 wt % aqueous, 20 mL, 72 mmol, Note 34) with vigorous stirring until gas evolution ceases (Note 35), the solution is acidic (Note 36) and a sticky orange solid is formed (Note 37). The aqueous mixture is transferred to a 500-mL separatory funnel, the flask is rinsed with ethyl acetate (50 mL) and the aqueous phase is extracted with ethyl acetate (3 x 50 mL) (Note 38). The combined organic extracts are dried ($MgSO_4$, 18 g), filtered, and the solvent is removed under reduced pressure with a rotary evaporator (24-45 °C, 30 mmHg) to afford crude product **4** as a sticky, orange foam (Notes 39, 40 and 41). This material is then used directly in the next step.

D. (S)-5-Pyrrolidin-2-yl-1H-tetrazole (**5**). A 500-mL, single-necked, round-bottomed flask equipped with a stirring bar is charged with a solution of (*S*)-2-(1*H*-tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester (**4**) (15.33 g, 56.1 mmol) in ethanol (255 mL) (Note 42). Palladium-on-carbon

(10 wt %, 1.49 g) (Note 43) is added to the solution under an argon atmosphere. The flask is evacuated and purged with hydrogen gas five times on a hydrogen manifold. The mixture is then stirred under a hydrogen atmosphere at room temperature for 20-24 h (Note 44). After complete conversion (as monitored by thin layer chromatography, Note 45), the catalyst is removed by filtration through Celite using a medium-porosity fritted funnel (Notes 46 and 47), and the Celite is washed sequentially with ethanol (30 mL), acetic acid (10 mL) (Note 48) and water (50 mL), and then again with ethanol (30 mL), acetic acid (10 mL) and water (50 mL) (Note 49). The filtrate is concentrated under reduced pressure with a rotary evaporator (45 °C, 115 mmHg to remove ethanol, then 45 °C, 50 mmHg to remove water, then 45 °C, 22 mmHg to remove acetic acid), and then is dried under vacuum (0.1 mmHg) at room temperature for 13 h in a 50-mL, round-bottomed flask to afford 7.12-7.68 g (91-98%) of crude **5** as a pale brown solid. Ethanol (25 mL) is then added (Note 50) and a reflux condenser is attached to the flask. The suspension is heated in a 90 °C oil bath for 1 h, then is allowed to cool to room temperature before being cooled in the freezer (–23 °C) for 15 h. The precipitate is isolated by suction filtration, then is washed with cold ethanol (2 x 10 mL) (Notes 51 and 52) and then dried in a round bottom flask in a 40 °C oil bath (with a magnetic stirrer) under vacuum (0.1 mmHg) for 5 h, to furnish 6.09-6.94 g (78-89% over two steps) of **5** as a white solid (Notes 53 and 54).

2. Notes

1. Cbz-L-proline (**1**) (>99%) was purchased from Fluka and used as received.

2. The submitters used di-*tert*-butyl dicarbonate (>99%) purchased from Aldrich, whereas the checkers used di-*tert*-butyldicarbonate (97%) from Aldrich and each was used as received.

3. Ammonium bicarbonate (>99%) was purchased from Sigma and used as received.

4. The three solids (Cbz-L-proline (**1**), di-*tert*-butyl dicarbonate and ammonium bicarbonate) may be added in any order prior to the addition of acetonitrile.

5. The submitters used acetonitrile (HPLC grade, 99.99%) purchased from Fisher whereas the checkers used acetonitrile (HPLC grade,

99.99%) from Acros, and the solvent was distilled over calcium hydride prior to use.

6. The submitters used pyridine (99.8%, Sureseal) purchased from Aldrich, which was used as received. The checkers used pyridine purchased from Fisher that was distilled over calcium hydride prior to use.

7. The reaction mixture was a cloudy suspension for the duration of the reaction.

8. The submitters reported that the R_f values of the starting material and product are 0.21 and 0.26 respectively (EtOAc). The checkers found that the use of 99/1 ethyl acetate/acetic acid improved the resolution of the spots on TLC. The R_f values of the starting material and product are 0.36 and 0.30, respectively.

9. The submitters found that prior to work-up of the reaction, there is a UV active impurity, which does not stain in permanganate ($KMnO_4$) or molybdate ($[NH_4]_6Mo_7O_{24}.4H_2O$) dips. R_f = 0.42 (EtOAc). Following work-up, it is no longer present. The checkers did not observe this impurity by TLC.

10. Crude product is usually isolated as a white crystalline solid, but is occasionally a white foam. The checkers had a difficult time solidifying the product initially, but ultimately could do so by scratching the flask and removing excess ethyl acetate under high vacuum (0.05 mmHg, 23 °C) for 6 h.

11. The white solid (19.81 g) was transferred to a 125-mL Erlenmeyer flask and the solids were dissolved in boiling ethyl acetate (60 mL) to give a tan solution. The solution was slowly cooled to room temperature and was allowed to stand overnight. The flask was cooled in an ice/H_2O bath for 1 h prior to collection of the precipitate by suction filtration. The solids were washed with cold ethyl acetate (2 x 10 mL) and then were dried at 23 °C under high vacuum (0.05 mmHg) for 6 h to give 17.98 g (90%) of **2** as white cubes.

12. The submitters purified **2** by chromatography using Breckland Scientific Silica Gel 60 (0.040 – 0.063 mm). The white solid was dissolved in dichloromethane (30 mL) and suction filtered through a pad of silica gel (6 cm diameter by 6 cm height), eluting with ethyl acetate (2.5 L), collecting in 10 x 50-mL round-bottomed flasks followed by 4 x 500-mL round-bottomed flasks. All fractions except fractions one to four were combined. The solvent was removed under reduced pressure with a rotary evaporator (380 mmHg, 30 °C).

13. (*S*)-2-Amido-pyrrolidine-1-carboxylic acid benzyl ester (**2**) has the following physicochemical properties: $[\alpha]_D^{25}$ –100.6 (*c* 0.51, $CHCl_3$); mp 91-93 °C; IR (film) cm^{-1}: 3329 (w), 2976 (w), 2945 (w), 1693 (s), 1674 (s), 1416 (s), 1356 (m), 1240 (w), 1117 (w), 1091 (w); ^1H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 7.23-7.40 (br m, 5 H, PhH), 6.72 (app s), 6.13 (app s), and 5.98 (app s, 2 H, NH_2), 5.08-5.18 (m, 2 H, $PhCH_2$), 4.29-4.34 (m, 1 H, NCH), 3.42-3.53 (m, 2 H, NCH_2), 2.28 (app s), and 2.14 (app s, 2 H, CH_2-CH_2), 1.87-2.03 (m, 2 H, CH_2-CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ: 175.3 and 174.4 ($C(O)NH_2$), 155.9 and 155.0 (C(O)O), 136.3 (Ph), 128.4 (Ph), 128.0 (Ph), 127.8 (Ph), 67.2 ($PhCH_2$), 60.6 and 60.1 (NCH), 47.4 and 46.9 (NCH_2), 31.0 and 28.5 ($NCHCH_2$), 24.4 and 23.5 ($NHCH_2CH_2$); HRMS (ESI) *m/z*: calcd. for $C_{13}H_{16}N_2O_3$ $[M+H]^+$, 249.1239; found $[M+H]^+$, 249.1239. Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.00; H, 6.49; N, 11.31.

14. The enantiomeric composition of **2** was checked by the use of CSP-HPLC: (*R*)-**2**, t_R 14.2 min (<0.1); (*S*)-**2**, t_R 19.5 min (>99.9) (Daicel Chiralpak AD-H, hexane/*i*-PrOH, 90:10, 1.0 mL/min, 210 and 254 nm).

15. *N*,*N*-Dimethylformamide (extra dry with molecular sieves, water <50 ppm) was purchased from Acros and used as received.

16. Cyanuric chloride (>99%) was purchased from Acros and used as received.

17. The reaction mixture changed from a pale yellow solution to a pale yellow suspension when reaction is complete.

18. The reaction was sampled by removing ~200 μL of the reaction mixture and quenching onto water (1 mL). The sample was extracted using ethyl acetate (1 mL). The R_f values of the starting material and product are 0.00 and 0.24 respectively (CH_2Cl_2). The submitters found a volatile minor impurity (R_f = 0.37, CH_2Cl_2), which is removed under vacuum (0.4 mbar) and not seen in the ^1H NMR spectrum of the product. The checkers observed a minor impurity (R_f = 0.05, CH_2Cl_2), which was removed after aqueous work-up.

19. As the water was added, the internal temperature of the mixture increased from 5 °C to 37 °C.

20. LiCl (99+%) was purchased from Sigma and used as received. LiCl (50 g) was dissolved in deionized water (450 g) to make a stock solution.

21. The yellow oil is dissolved in dichloromethane (30 mL) and pushed through a pad of silica gel (6 cm diameter by 6 cm height, 3.5 psi), eluting with dichloromethane (2 L), collecting in 5 x 100-mL Erlenmeyer flasks followed by 3 x 500-mL Erlenmeyer flasks. All fractions except fraction one are combined on the basis of TLC analysis. The solvent is removed under reduced pressure with a rotary evaporator (15 mmHg, 24 °C).

22. Submitters reported that the yellow oil obtained after purification by filtration through silica gel solidified in the freezer after storage for 15 h. Checkers never obtained the product as a solid, even after storage in the freezer for 5 d.

23. (*S*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester (**3**) has the following physicochemical properties: $[\alpha]_D^{25}$ –91.6 (*c* 0.995, $CHCl_3$); IR (film) cm^{-1}: 2958 (m), 2887 (m), 2239 (w), 1709 (s), 1410 (s), 1358 (s), 1267 (s), 1180 (s); ^1H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 7.31-7.42 (m, 5 H, PhH), 5.13-5.22 (m, 2 H, $PhCH_2$), 4.61 (dd, J_1 = 7.6 Hz, J_2 = 2.7 Hz) and 4.55 (dd, 1 H J_1 = 7.6 Hz, J_2 = 2.4 Hz, NCHCN), 3.55-3.63 (m, 1 H, NC<u>H</u>H'), 3.37-3.62 (m, 1 H, NCH<u>H</u>'), 2.00-2.30 (m, 4 H, CH_2CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) (mixture of rotamers) δ: 154.2 and 153.5 (NCO), 135.9 and 135.8 (Ph), 128.4 (Ph), 128.1 (Ph), 128.0 (Ph), 118.8 and 118.6 (NCH<u>C</u>N), 67.7 and 67.5 (Ph<u>C</u>H_2), 47.4 and 46.9 (NCH), 46.2 and 45.8 (NCH_2), 31.6 and 30.7 (NCH_2<u>C</u>H_2), 24.5 and 23.6 (NCH_2<u>C</u>H_2); HRMS (ESI) *m/z*: calcd for $C_{13}H_{14}N_2O_2$ $[M+Na]^+$, 253.0953; found $[M+Na]^+$, 253.0954. Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C,67.53; H, 6.07; N, 12.35.

24. The enantiomeric composition of **3** was checked by the use of CSP-HPLC: (*R*)-**3**, t_R 37.8 min (<0.1); (*S*)-**3**, t_R 41.7 min (>99.9) (Daicel Chiralpak AD-H, hexane/*i*-PrOH, 98:2, 1.0 mL/min, 254 nm).

25. (*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester (**4**) may also be synthesized according to the method found in International Patents WO 2005/014602 A1 and WO 2007/009716.

26. Sodium azide (>99%) was purchased from Sigma-Aldrich and used as received.

27. Sodium azide must be weighed out using a non-metallic spatula in a fume hood.

28. Triethylamine hydrochloride (>99%) was purchased from Fluka and used as received.

29. The three solids ((*S*)-2-cyano-pyrrolidine-1-carboxylic acid benzyl ester (**4**), sodium azide and triethylamine hydrochloride) may be added in any order prior to the addition of toluene.

30. Submitters used toluene (laboratory reagent grade, >99%), which was supplied by Fisher and distilled over calcium hydride prior to use. Checkers used toluene supplied by Fisher (ACS grade) and was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon.

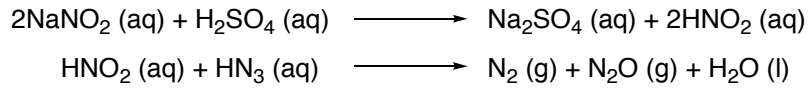
31. Although no problems were encountered during the reaction, it is highly recommended to use a blast shield while heating the reaction.

32. The R_f values of the starting material and product are 0.69 and 0.10, respectively (EtOAc).

33. Sodium nitrite (97+%) was purchased from Sigma-Aldrich as used as received. $NaNO_2$ (40 g) was dissolved in deionized water (200 mL) to make a 2.9 M stock solution.

34. A 3.6 M stock solution of aq. H_2SO_4 was prepared by diluting conc. H_2SO_4 (18 M, 80 mL) with deionized water (320 mL).

35. When nitrous acid reacts with hydrazoic acid, rapid evolution of nitrogen and nitrous oxide gases occurs with concurrent production of water. The highly toxic hydrazoic acid side-product is thus completely and safely quenched under these conditions.



36. The pH of the solution is 5.0 after the addition of acid.

37. Vigorous stirring during the quench is essential to prevent the stirring bar from becoming trapped in the sticky orange solid. An overhead stirrer is recommended for the quench of any reaction using more than 20 g of the (*S*)-2-cyano-pyrrolidine-1-carboxylic acid benzyl ester (**4**) starting material.

38. Care must be taken during the extraction to make sure that the orange solid has dissolved completely.

39. (*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester (**4**) has the following physicochemical properties: $[\alpha]_D^{25}$ –90.7 (*c* 1.29, $CHCl_3$); IR (film) cm^{-1}: 3111 (m), 2982 (m), 2889 (m), 1699 (s), 1422 (s), 1358 (s), 1125 (m), 698 (m); exothermic range: 204-291 °C (maximum: 253

˚C); ^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 7.31-7.35 (m, 3 H, PhH), 7.23 (app s, 1 H, PhH), 7.03 (app s, 1 H, PhH), 5.41-5.42 (m), 5.21 (d, *J* = 12.5 Hz), 5.11-5.16 (m), 5.07 (d, *J* = 12.5 Hz), and 5.02 (d, 3 H, *J* = 12.2 Hz, NCH, $PhCH_2$), 3.59-3.63 (m) and 3.51-3.56 (m, 2 H, NCH_2), 2.65-2.69 (m), 2.19-2.42 (m), 2.05-2.11 (m), and 1.86-2.00 (m, 4 H, CH_2CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) (mixture of rotamers) δ: 156.5, 156.2 and 155.1 (NCO, NCN), 133.6 (Ph), 128.5 (Ph), 128.3 (Ph), 127.7 (Ph), 127.6 (Ph), 68.0 and 67.8 ($PhCH_2$), 52.5 and 51.3 (NCH), 47.2 and 47.0 (NCH_2), 33.0 and 29.7 ($NCHCH_2$), 24.5 and 23.5 (NCH_2CH_2); HRMS (ESI) *m/z* calcd. for $C_{13}H_{16}N_5O_2$, $[M+H]^+$, 274.1304); found: $[M+H]^+$, 274.1309.

40. The submitters determined the enantiomeric purity through the use of CSP-SFC: (*R*)-**4**, t_R 22.4 min (<0.1); (*S*)-**4**, t_R 24.4 min (>99.9) (Daicel Chiralpak AD-H, *i*-PrOH, 10-20% gradient over 20 min followed by 20% isocratic elution, 1.0 mL/min, 200 nm). The checkers employed CSP-SFC under slightly different conditions: (*R*)-**4**, t_R 19.7 min (<0.1); (*S*)-**4**, t_R 21.7 min (>99.9) (Daicel Chiralpak AD, MeOH, 9-12 % (0.1 %/min), 2.7 mL/min, 150 bar, 210 nm).

41. The checkers found that compound **4** solidified to a free-flowing powder (mp 81-84 °C) after concentrating an ethanolic solution and storing the residue at –20 °C for 3 days.

42. Submitters used ethanol (>99.8%) that was purchased from Fluka or VWR and was used as received. Checkers used ethanol purchased from Aldrich and was used as received.

43. Palladium on carbon (10 wt %) was purchased from Aldrich and used as received.

44. Submitters used hydrogen gas contained in a triple-layered balloon and enters the flask via a three-way tap. No pressure is required for this reaction to work. Checkers used a hydrogen gas manifold that allows for the use of 1 atm of hydrogen pressure.

45. The R_f values of the starting material and product are 0.14 and 0.00 respectively (EtOAc). The starting material oxidizes blue in molybdate ($[NH_4]_6Mo_7O_{24}.4H_2O$) whereas the product does not.

46. Submitters used Celite supplied by Aldrich (Celite 521), which was used as received. Checkers used Celite 545 supplied by Fisher, which was used as received.

47. The Celite pad is 6.5 cm diameter by 2.5 cm height.

48. Glacial laboratory reagent grade acetic acid (>99%) was purchased from Fisher Scientific and used as received.

49. The checkers found problems with the filtration on smaller reaction scales. The filter cake must be thoroughly washed with water to completely remove the product from the Celite.

50. Prior to the addition of ethanol, any lumps of crude material formed are crushed to a powder.

51. The ethanol is cooled in an ice/water bath for 20 min, prior to being used to wash the (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole product (**5**).

52. To obtain the yield quoted, it is imperative that the amount of ethanol used for washing is not exceeded from that stated.

53. (*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole (**5**) has the following physicochemical properties: $[\alpha]_D^{25}$ –8.5 (*c* 1.04, MeOH); IR (film) cm^{-1}: 2966 (s), 2165 (s), 1927 (w), 1625 (s), 1460 (s), 1411 (s), 1325 (s), 1207 (m), 1117 (s), 1044 (s); exothermic range: 269-365 °C (maximum: 275 °C); ^{1}H NMR (500 MHz, d_6-DMSO) δ: 9.41 (br s, 1 H, NH), 4.77 (app t, 1 H, *J* = 7.5 Hz, NHC<u>H</u>), 3.23-3.35 (m, 2 H, NHC<u>H</u>$_2$), 2.31-2.33 (m, 1 H, NCHCH<u>H</u>'), 2.10-2.17 (m, 1 H, NHCHC<u>H</u>H'), 1.99-2.04 (m, 2 H, NHCH$_2$C<u>H</u>$_2$); ^{13}C NMR (126 MHz, d_6-DMSO) δ: 157.8 (NHCH<u>C</u>), 55.0 (NHCH), 44.7 (NHCH$_2$), 30.0 (NHCH<u>C</u>H$_2$), 23.2 (NHCH$_2$<u>C</u>H$_2$); HRMS (ESI) *m/z*: calcd for $C_5H_9N_5$ $[M+Na]^+$, 162.0756: found: $[M+Na]^+$, 162.0748. Anal. Calcd. for $C_5H_9N_5$: C, 43.15; H, 6.52; N, 50.33. Found: C, 42.83; H, 6.46; N, 50.01.

54. The enantiomeric purity of the (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**5**), was checked by conversion to (*S*)-2-(1*H*-tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester (**4**) using the following procedure: In a flame-dried, 50-mL, 3-necked, round-bottomed flask equipped with a argon inlet, septum, thermocouple and a stir bar was charged (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**5**) (209 mg, 1.50 mmol). Dry dichloromethane chloride (11 mL) and benzyl chloroformate (222 μL, 1.58 mmol, 1.05 equiv) were added. The resulting suspension was cooled to 1 °C (internal) using an ice/water bath and pyridine (0.36 mL, 3.0 mmol, 3.0 equiv) was added dropwise (temperature was maintained below 5 °C). The resulting solution was stirred at 1-3 °C for 2 h before the ice bath was removed and the solution was allowed to room temperature and was stirred at 23 °C for 3 h. The solution was then diluted with ethyl acetate (100 mL) and was transferred to a 250-mL separatory funnel. The solution was washed with 1 N HCl (3 x 30 mL), brine (40 mL), then was dried ($MgSO_4$, 5 g) and filtered. The filtrate was concentrated in vacuo (30 mmHg, 25 °C) to give a colorless oil. Purification of the oil by flash column chromatography (silica

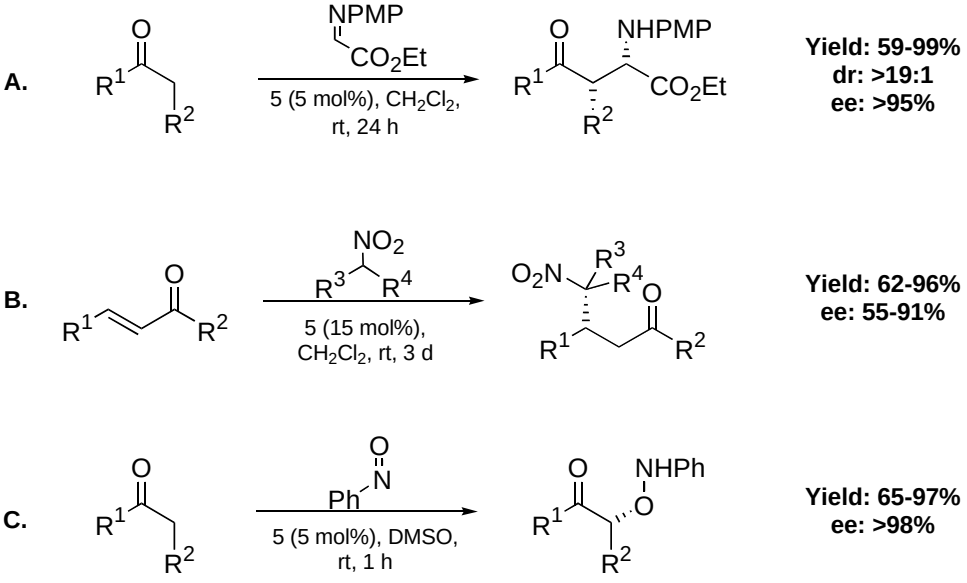
gel, EtOAc/MeOH, 93/7) afforded 390 mg (95%) of (*S*)-2-(1*H*-tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester (**4**) as a sticky, white foam. The enantiomeric composition was checked by the use of CSP-SFC. (*R*)-**4**, t_R 22.4 min (<0.1); (*S*)-**4**, t_R 24.4 min (>99.9); (Daicel Chiralpak AD-H, *i*-PrOH, 10-20% gradient over 20 min followed by 20% isocratic elution, 1.0 mL/min, 200 nm). The checkers employed CSP-SFC under slightly different conditions: (*R*)-**4**, t_R 19.7 min (<0.1); (*S*)-**4**, t_R 21.7 min (>99.9) (Daicel Chiralpak AD, MeOH, 9-12 % (0.1 %/min), 2.7 mL/min, 150 bar, 210 nm).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

(*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole (**5**) is a novel proline-derived organocatalyst that was developed by the Ley group[4,5] and others[6,7] almost simultaneously. Its utility has been proven in several reaction processes, including the Mannich (A, Scheme)[4,5] and aldol reactions,[6-8] addition of ketones to nitro-olefins,[5,9] nitroalkanes/malonates to enones (B)[10-12] and α-oxyamination (C)[13-15] among others.[16-27]



The preparation of **5** shown here is a variant of those which already exist,[5,8,13,28-35] and offers the following advantages:

1) The procedures can all be carried out safely, on large scale without detriment to the yields.
2) The azide cyclization procedure avoids the generation of explosive ammonium azide during the reaction.
3) The hydrogenation protocol avoids the use of a 9/1 acetic acid:water mixture as the solvent and the concurrent extended (3 d) reaction time.
4) Product is obtained that requires very little purification.

This preparation can also be used to obtain the enantiomer of the desired product, (*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole.[36]

1. Process R & D, Chemical and Analytical Development, Novartis Pharmaceuticals Corporation, 4002 Basel, Switzerland.
2. Provided the preparation method for (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**5**), together with the analytical data for (*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester (**4**) and (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**5**).
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16. For recent reviews on the use of (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**5**) in organic synthesis, see: (a) Longbottom, D. A.; Franckevičius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichimica Acta* **2007**, *in press*; (b) Longbottom, D. A.; Franckevičius, V.; Ley, S. V. *Chimia* **2007**, *5*, 247-256; (c) Limbach, M. *Chem. Biodiv.* **2006**, *2*, 119-133.
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36. (*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazole has the same physical properties as the (*S*)-enantiomer, aside from the optical rotation, which is equal and opposite: $[\alpha]_D^{25}$ +9 (*c* 1.0, MeOH). The enantiomeric composition was checked by the use of CSP-SFC. (*R*)-**4**, t_R 22.4 min (>99.9); (*S*)-**4**, t_R 24.4 min (<0.1); (Daicel Chiralpak AD-H, *i*-PrOH, 10-20% gradient over 20 min followed by 20% isocratic elution, 1.0 mL/min, 200 nm)

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole: 2*H*-Tetrazole, 5-[(2*S*)-2-pyrrolidinyl]-; (33878-70-5)
(*S*)-2-Amido-pyrrolidine-1-carboxylic acid benzyl ester: 1-Pyrrolidinecarboxylic acid, 2-(aminocarbonyl)-, phenylmethyl ester, (2*S*)-; (34079-31-7)
Cbz-L-proline: 1,2-Pyrrolidinedicarboxylic acid, 1-(phenylmethyl) ester, (2*S*)-; (1148-11-4)
Di-*tert*-butyl dicarbonate: Dicarbonic acid, C,C'-bis(1,1-dimethylethyl) ester; (24424-99-5)
(*S*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester: 1-Pyrrolidinecarboxylic acid, 2-cyano-, phenylmethyl ester, (2*S*)-; (63808-36-6)
Cyanuric chloride: 2,4,6-Trichloro-1,3,5-triazine; (108-77-0)
(*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester: 1-Pyrrolidinecarboxylic acid, 2-(2*H*-tetrazol-5-yl)-, phenylmethyl ester, (2*S*)-; (33876-20-9)
Sodium azide; (26628-22-8)
Triethylamine hydrochloride: Ethanamine, *N*,*N*-diethyl-, hydrochloride (1:1); (554-68-7)

Steven V. Ley received his PhD from Loughborough University in 1972, after which he carried out post-doctoral research with Professor Leo Paquette at Ohio State University, followed by Professor Derek Barton at Imperial College London. In 1975, he joined that Department as a lecturer and became Head of Department in 1989. In 1992, he moved to the 1702 BP Chair of Organic Chemistry at the University of Cambridge and became a Fellow of Trinity College. He was elected to the Royal Society in 1990 and was President of the Royal Society of Chemistry (RSC) 2000-02. Steve has been the recipient of many prizes and awards including the Yamada-Koga Prize, Nagoya Gold Medal, ACS Award for Creative Work in Synthetic Organic Chemistry and the Paul Karrer Medal.

Valentina Aureggi was born 1977 in Como, Italy. She obtained her Diploma in 1999 and MSci degree in 2003 at Insubria University. During this five-year course of study, her final year project was carried out at the University of Neuchâtel, investigating the synthesis of amido silyloxy dienes under the supervision of Professor Reinhard Neier. Following this, she obtained her PhD in 2007 under the supervision of Professor Gottfried Sedelmeier in the Department of Process Research and Development of Novartis Pharma in Basel. She is currently pursuing post-doctoral research in Professor Mark Lautens's group at the University of Toronto.

Vilius Franckevičius was born in 1983 in Kaunas, Lithuania. He studied Natural Sciences at the University of Cambridge, where he undertook his final year project on the development of new organocatalysts under the supervision of Professor Steven V. Ley, and subsequently obtained his MSci degree in Natural Sciences (Chemistry) in 2005 (Fitzwilliam College). He is currently a PhD student in the Ley group where he is involved in the application of organocatalytic methodology in natural product synthesis.

Matthew O. Kitching was born in 1983 in Wolverhampton, England. He completed his undergraduate degree in Natural Science at the University of Cambridge in 2005. Following this, he joined Professor Steven V. Ley's group as a summer project student where he worked on development of new organocatalytic species, including the pyrrolidinyl tetrazole. After completing his MSci degree in Natural Sciences (Chemistry) at the University of Cambridge, working with Dr. Jane Clarke on protein thermodynamic stability and its relationship to disease, he returned to Professor Steven V. Ley's group for his PhD as part of the Innovative Technology Centre studying microencapsulated palladium catalysts.

Deborah A. Longbottom received her undergraduate degree from the University of Durham in 1997 and, following a year working in the pharmaceutical industry, came to Cambridge to carry out her PhD under the guidance of Professor Steven V. Ley. In 2002, she pursued post-doctoral research with K. C. Nicolaou and returned to the Ley Group early in 2004. Her research interests have encompassed both natural product synthesis, e.g. polyenoyltetramic acids and depsipeptides, and method development e.g. novel uses of the Burgess reagent and organocatalytic methodologies. Currently, she is a senior research associate in the Ley group. As of October 2007, she will hold a joint position between the Department of Chemistry and Homerton College, Cambridge, with an additional By-fellowship at Churchill College.

Alexander J. Oelke was born in 1980 in Reinbek, Germany. He studied chemistry at the University of Hamburg, where he obtained his Diploma in 2006 under the supervision of Professor Chris Meier and in collaboration with Professor Steven V. Ley for the development of an organocatalytic tandem procedure for the synthesis of chiral pyridazine derivatives. He is currently a PhD student in the Ley group at the University of Cambridge, where he is involved in the application of organocatalytic methodology in natural product synthesis.

Gottfried Sedelmeier was born in 1948 in Schallstadt, Germany. He studied Chemistry at the University of Freiburg, where he obtained his PhD in 1979 under the supervision of Professor Horst Prinzbach. He then joined the Process Research Department of Ciba-Geigy Pharma (now Novartis) in Basel, where he has worked until the present. Since 1991, he has also held a Lectureship position at the University of Freiburg, where he teaches on the subject of Industrial Pharmaceutical Chemistry and in 2003, he became an honorary Professor at that same institution.

As an undergraduate student at Illinois Wesleyan University, Russell Smith performed organic research for four years. His undergraduate advisor, Dr. Ram S. Mohan, sparked his love for organic chemistry and experimentation and he graduated with a BS degree with Research Honors in 2004. He joined the research group of Scott Denmark at the University of Illinois, where his current project is studying the use of aryl silanolates in cross-coupling reactions to form biaryl compounds. When not in lab, he enjoys spending time with his wife, Lindsay, and dog, Lucky. He is a football fanatic and cannot wait until fall every year.

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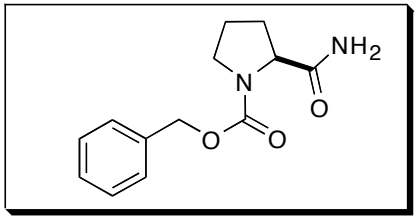

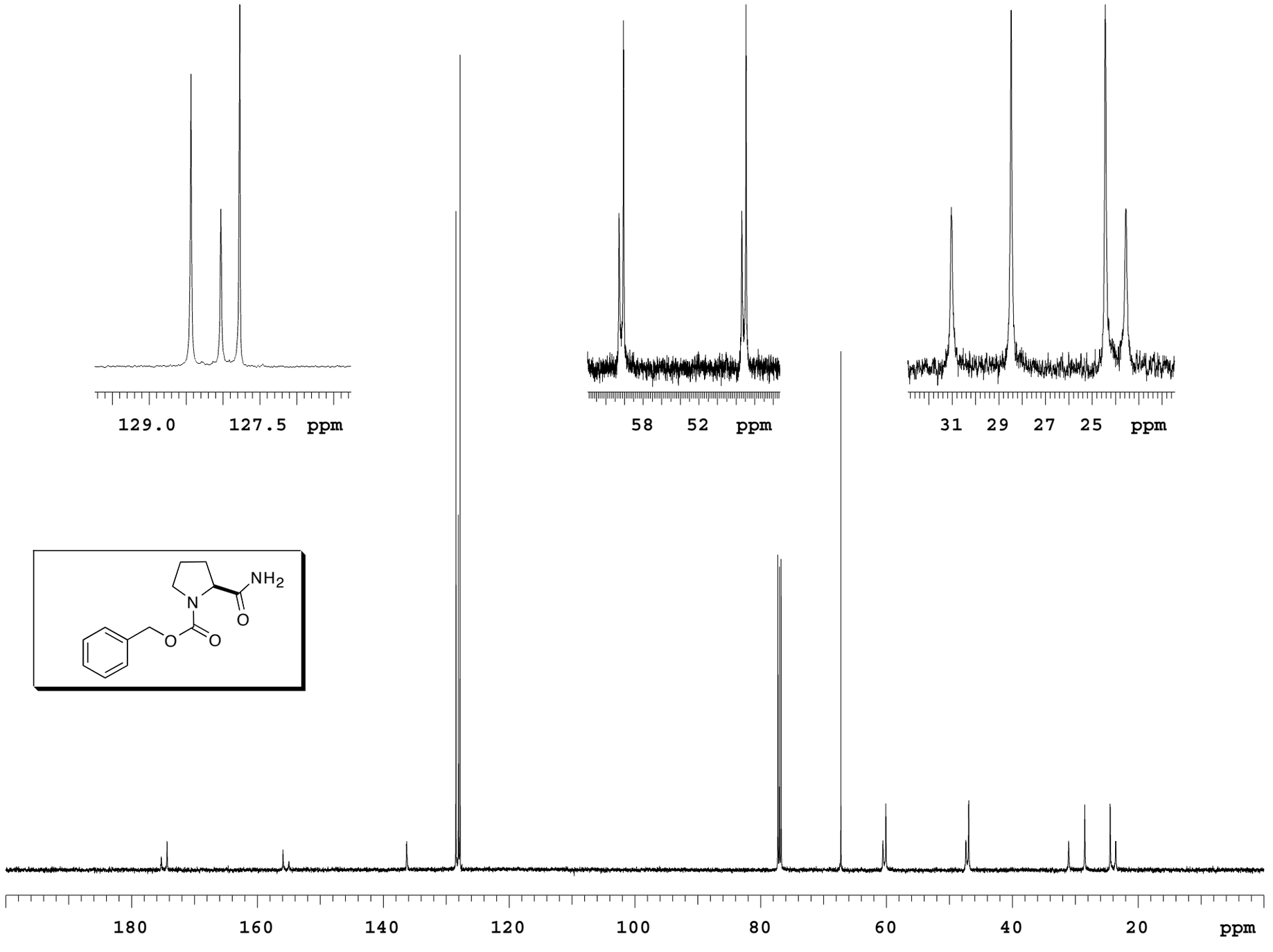
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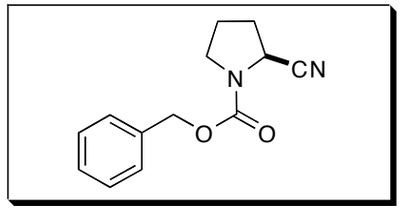

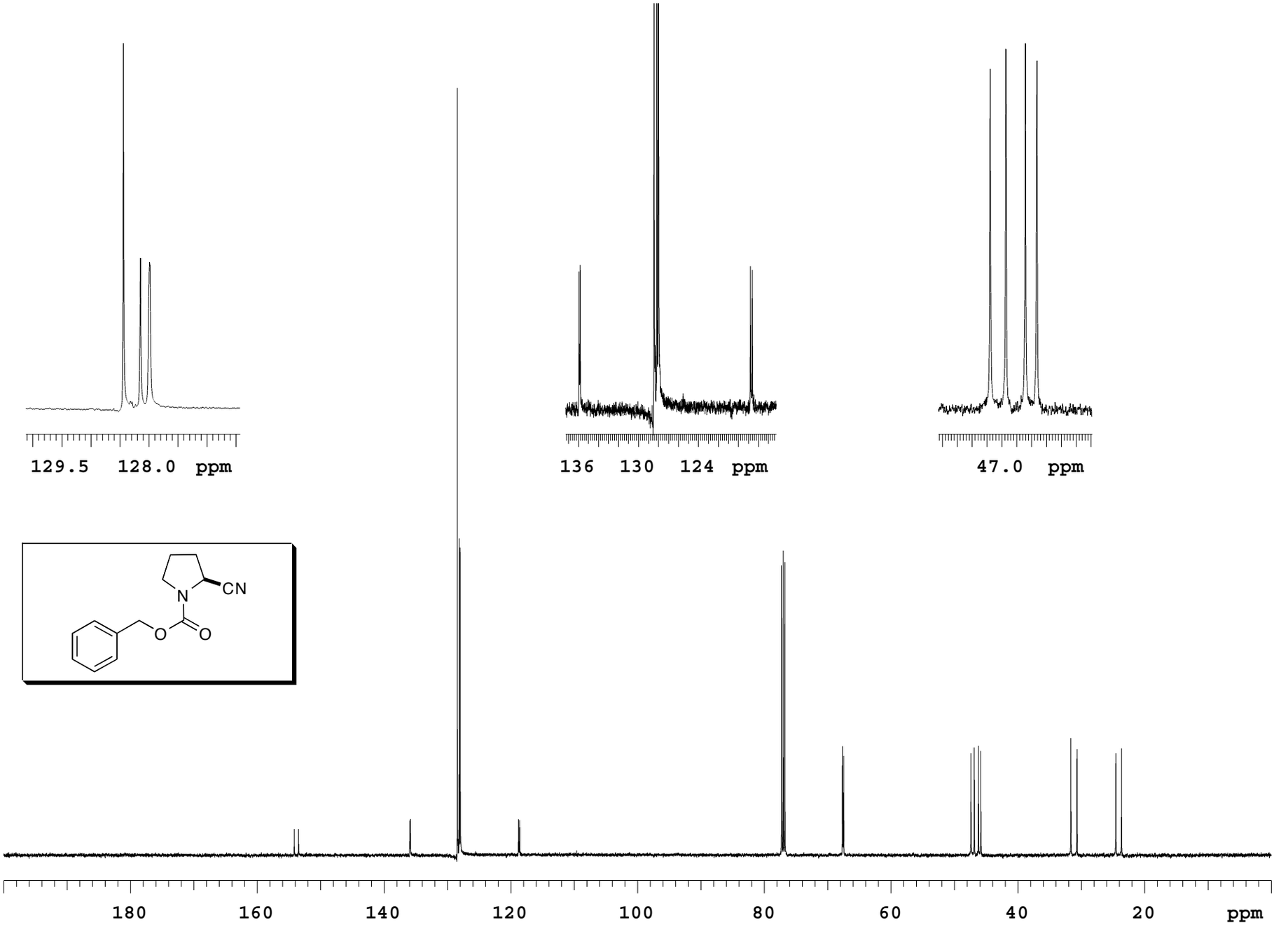
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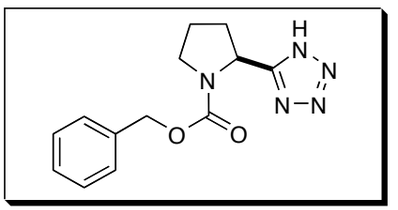

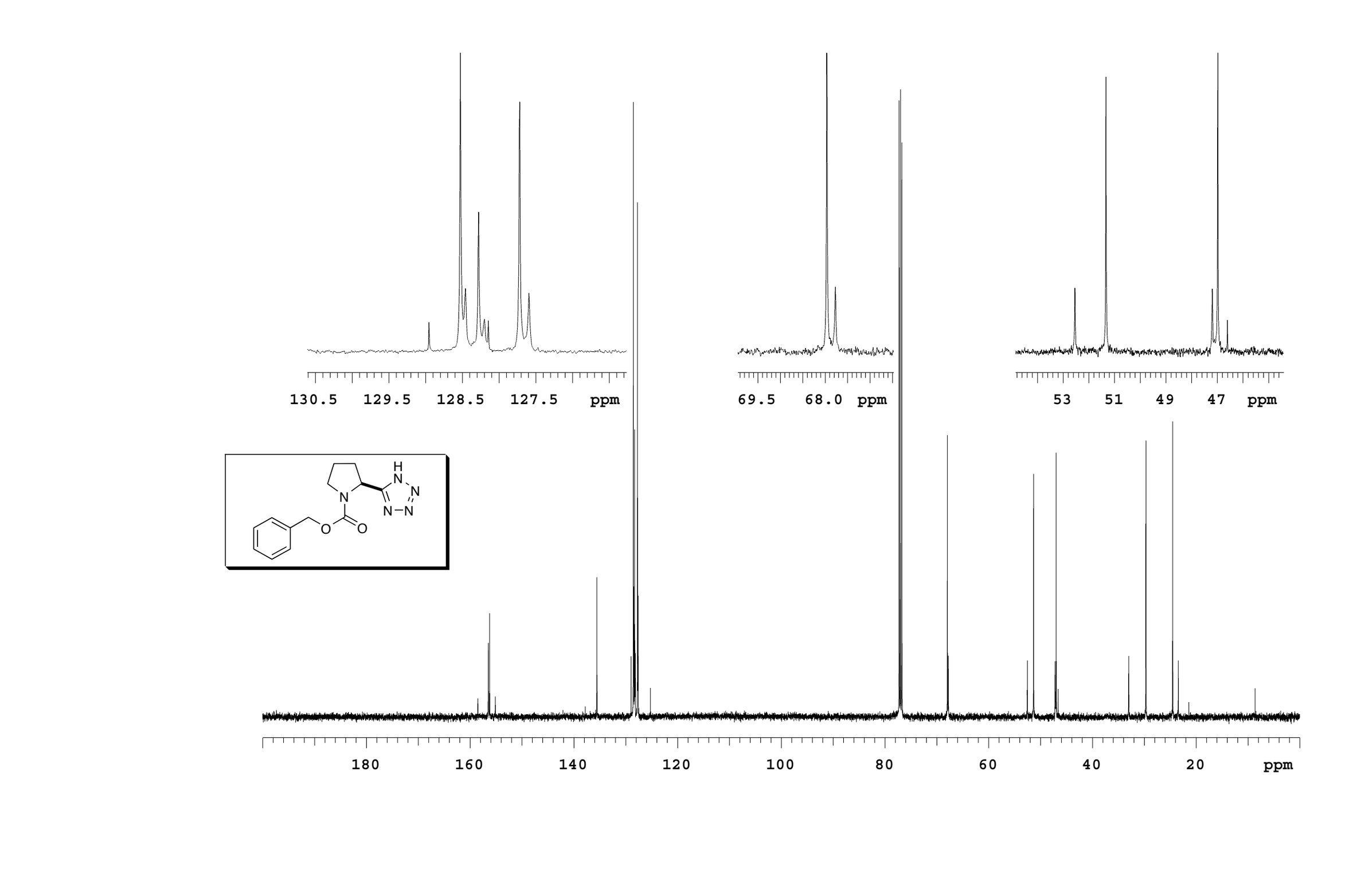
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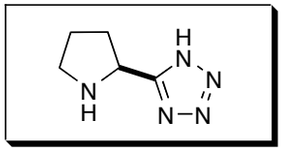

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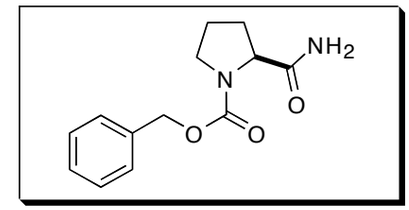
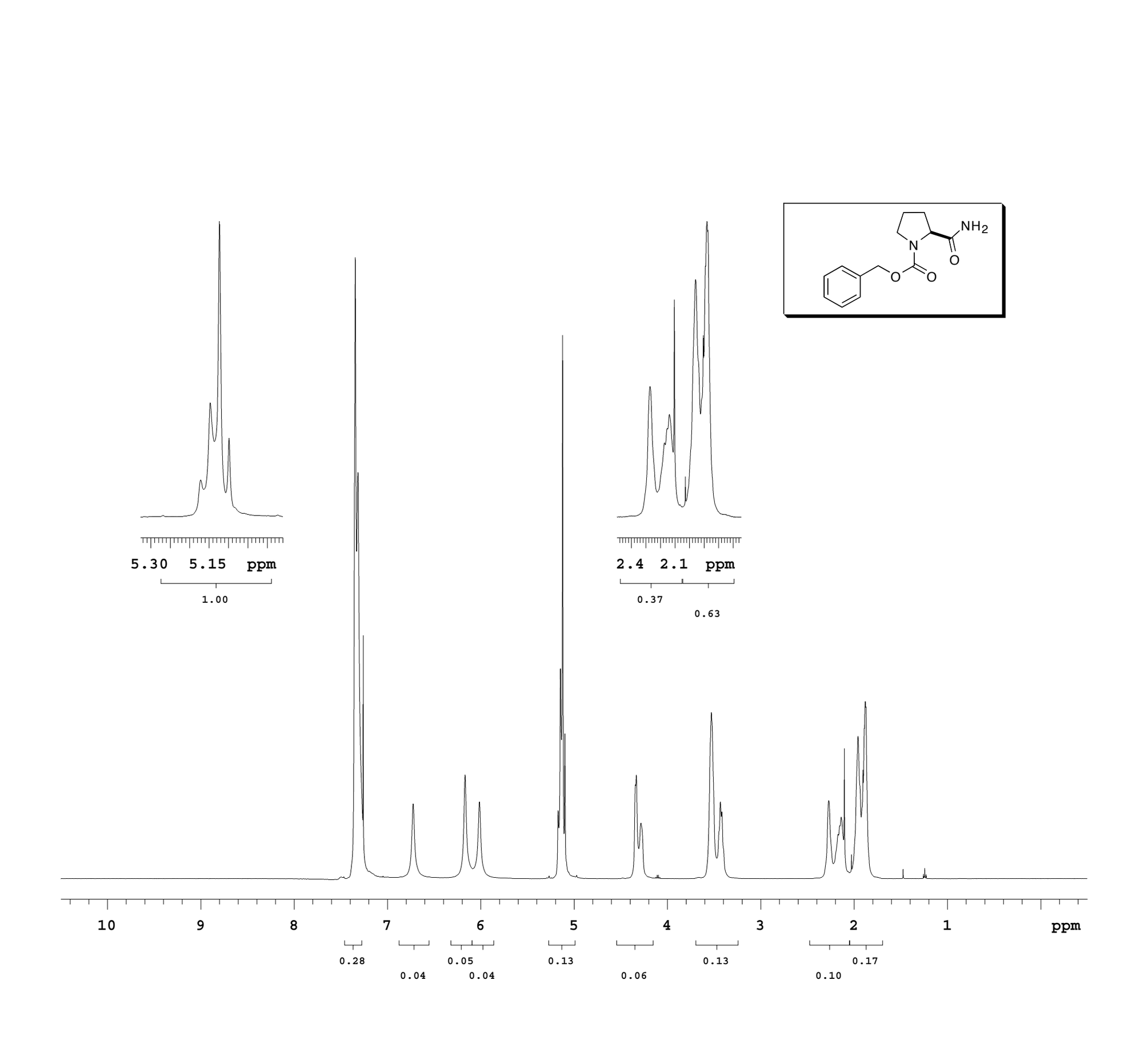
sw	7024.9	dfrq2	0
fb	4000	dn2	
bs	4	dpwr2	1
tpwr	63	dof2	0
pw	6.5	dm2	n
d1	0	dmm2	c
tof	2.0	dmf2	200
nt	16	dseq2	
ct	16	dres2	1.0
alock	n	homo2	n
gain	not used	PROCESSING	
FLAGS		lb	0.30
il	n	wtfile	
in	n	proc	ft
dp	y	fn	not used
hs	nn	math	f
DISPLAY			
sp	-250.0	werr	
wp	5496.6	wexp	
vs	230	wbs	
sc	0	wnt	
wc	250		
hzmm	21.99		
is	610.01		
rfl	4642.5		
rfp	3627.8		
th	7		
ins	1.000		
ai	ph		

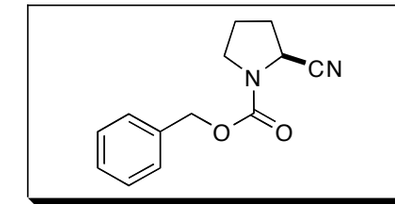


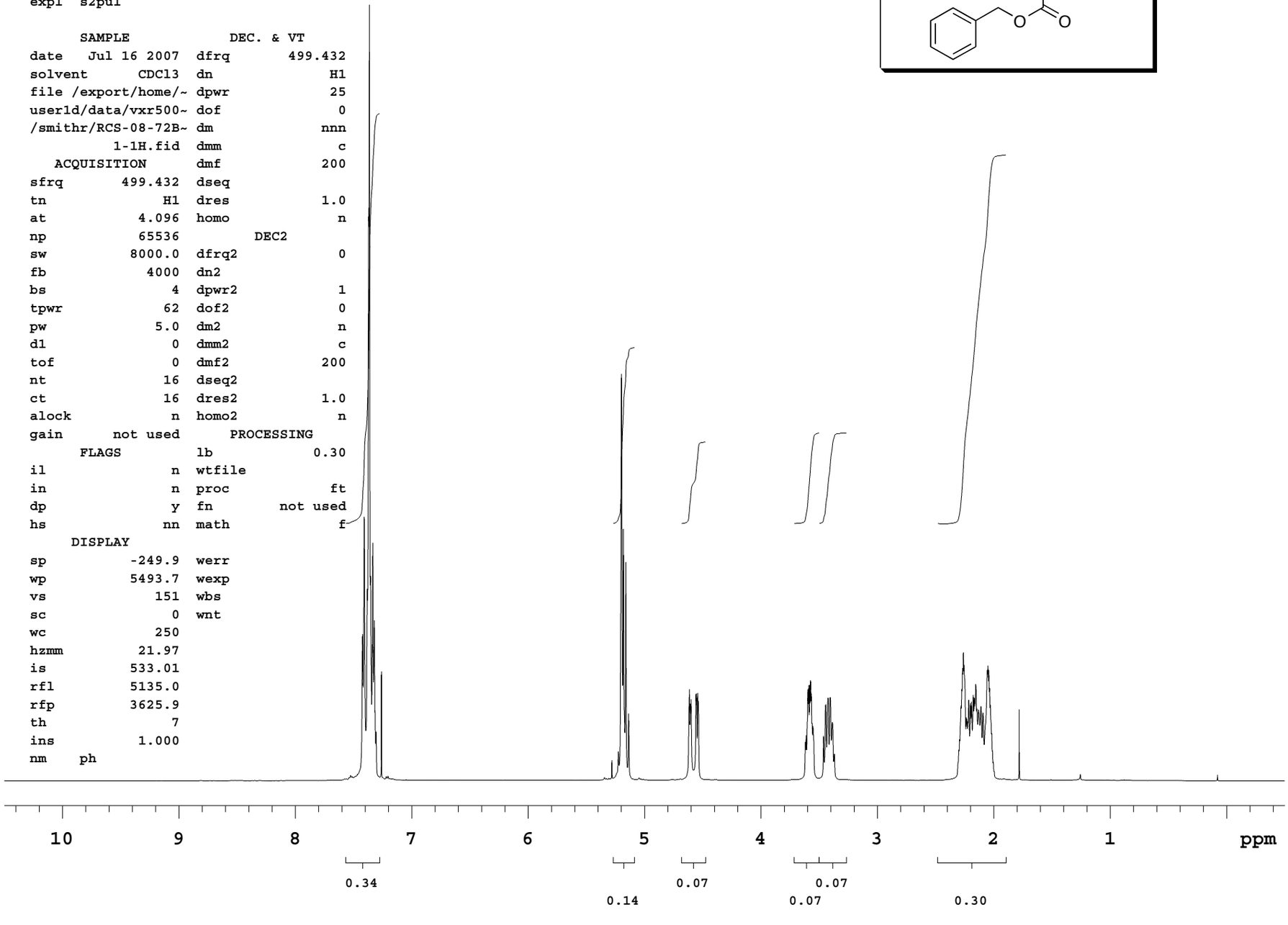

NH2
N
O
O
O
5.30 5.15 ppm
1.00
2.4 2.1 ppm
0.37
0.63
10 9 8 7 6 5 4 3 2 1 ppm
0.28
0.04
0.05
0.04
0.13
0.06
0.13
0.17
0.10

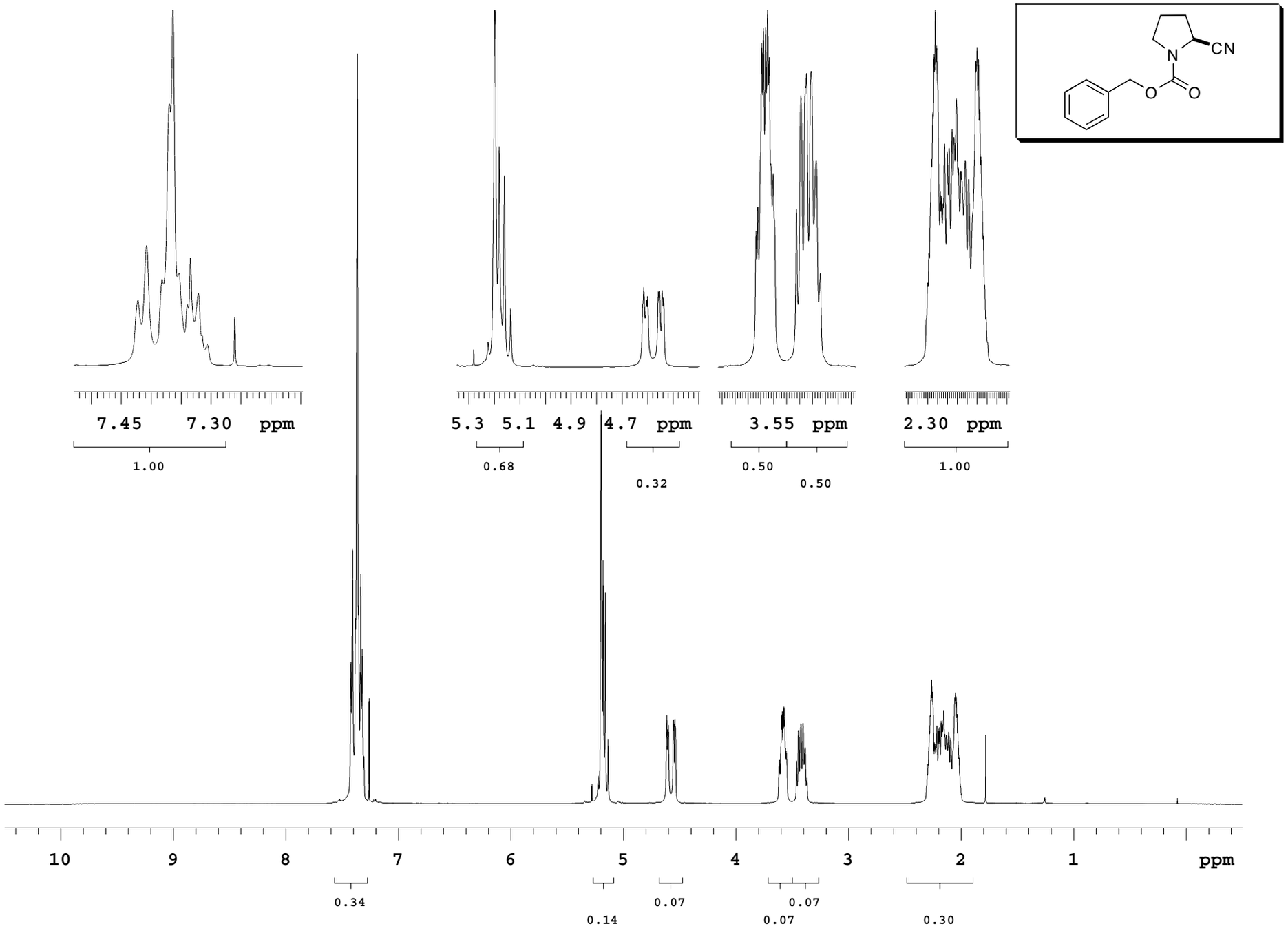
RCS-08-72B1-1H

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jul 16 2007	dfrq	499.432
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	25
user1d	/data/vxr500~	dof	0
/smithr/RCS-08-72B~		dm	nnn
	1-1H.fid	dmm	c
ACQUISITION		dmf	200
sfrq	499.432	dseq	
tn	H1	dres	1.0
at	4.096	homo	n
np	65536	DEC2	
sw	8000.0	dfrq2	0
fb	4000	dn2	
bs	4	dpwr2	1
tpwr	62	dof2	0
pw	5.0	dm2	n
d1	0	dmm2	c
tof	0	dmf2	200
nt	16	dseq2	
ct	16	dres2	1.0
alock	n	homo2	n
gain	not used	PROCESSING	
FLAGS		lb	0.30
il	n	wtfile	
in	n	proc	ft
dp	y	fn	not used
hs	nn	math	f
DISPLAY			
sp	-249.9	werr	
wp	5493.7	wexp	
vs	151	wbs	
sc	0	wnt	
wc	250		
hzmm	21.97		
is	533.01		
rfl	5135.0		
rfp	3625.9		
th	7		
ins	1.000		
nm	ph		



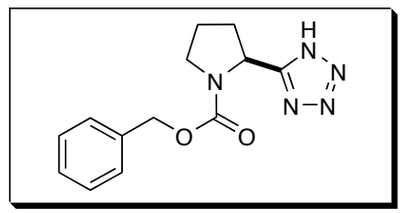


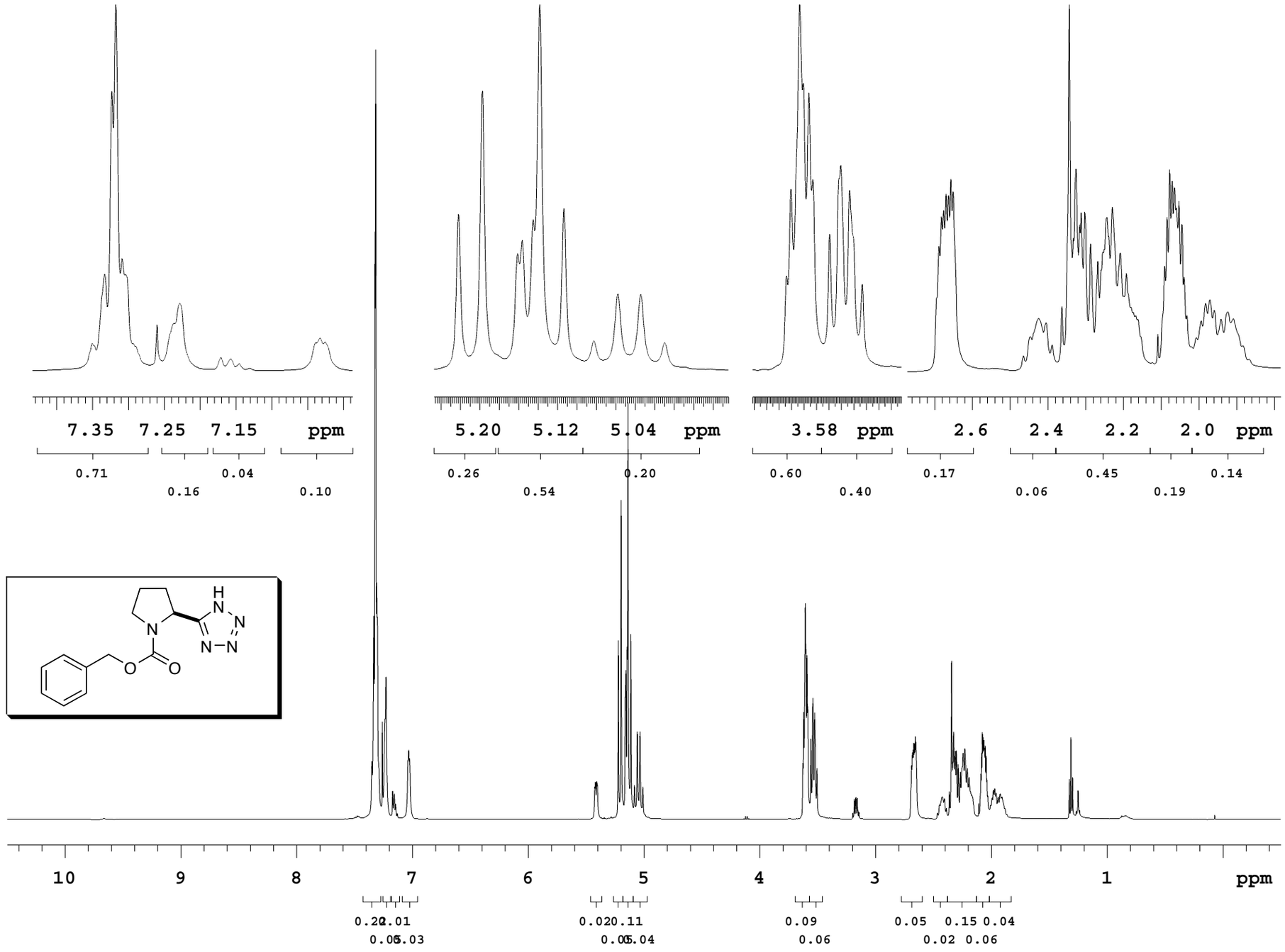

CN
N
O
O
7.45
7.30
ppm
1.00
5.3
5.1
4.9
4.7
ppm
0.68
0.32
3.55
ppm
0.50
0.50
2.30
ppm
1.00
10
9
8
7
6
5
4
3
2
1
ppm
0.34
0.14
0.07
0.07
0.07
0.30

RCS-08-84A1-1H

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jul 24 2007	dfrq	500.070
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	18
user1d	/data/ui500n~	dof	0
b/smithr	/RCS-08-84~	dm	nnn
	A1-1H.fid	dmm	c
ACQUISITION		dmf	200
sfrq	500.070	dseq	
tn	H1	dres	1.0
at	4.096	homo	n
np	65536	DEC2	
sw	8000.0	dfrq2	0
fb	4000	dn2	
bs	16	dpwr2	1
tpwr	55	dof2	0
pw	7.7	dm2	n
d1	0	dmm2	c
tof	0	dmf2	200
nt	16	dseq2	
ct	16	dres2	1.0
alock	n	homo2	n
gain	not used	PROCESSING	
FLAGS		lb	0.30
il	n	wtfile	
in	n	proc	ft
dp	y	fn	not used
hs	nn	math	f
DISPLAY			
sp	-250.1	werr	
wp	5500.7	wexp	
vs	121	wbs	
sc	0	wnt	
wc	250		
hzmm	22.00		
is	842.92		
rfl	5140.9		
rfp	3630.5		
th	7		
ins	1.000		
ai	ph		

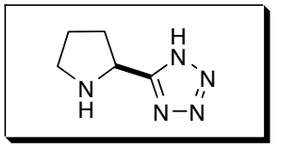


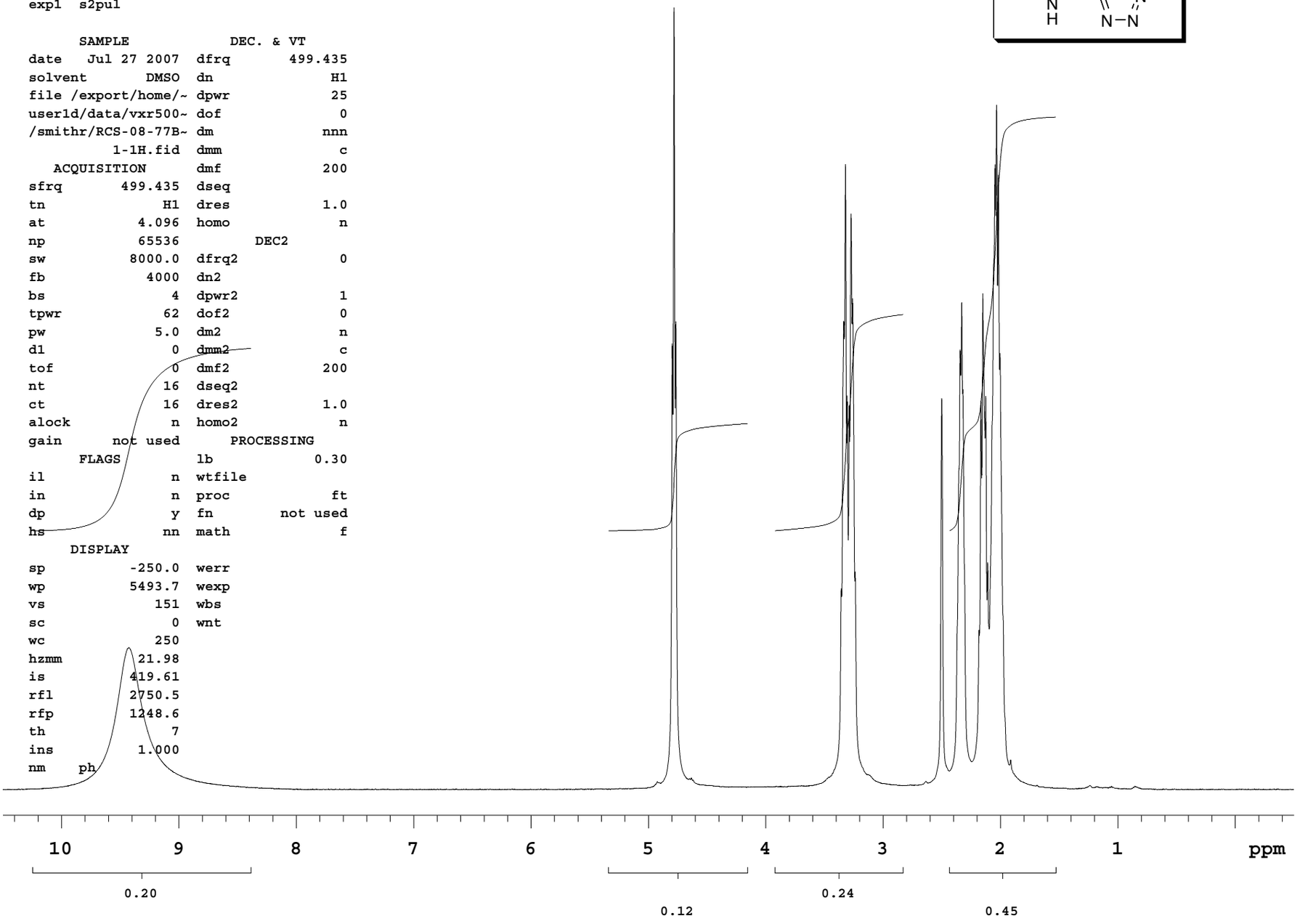

7.35 7.25 7.15 ppm
0.71 0.16 0.04 0.10
5.20 5.12 5.04 ppm
0.26 0.54 0.20
3.58 ppm
0.60 0.40
2.6 2.4 2.2 2.0 ppm
0.17 0.06 0.45 0.19 0.14
H
N
N
N
N
N
O
O
10 9 8 7 6 5 4 3 2 1 ppm
0.20 2.01 0.06 5.03
0.02 0.11 0.05 5.04
0.09 0.06
0.05 0.15 0.04 0.02 0.06

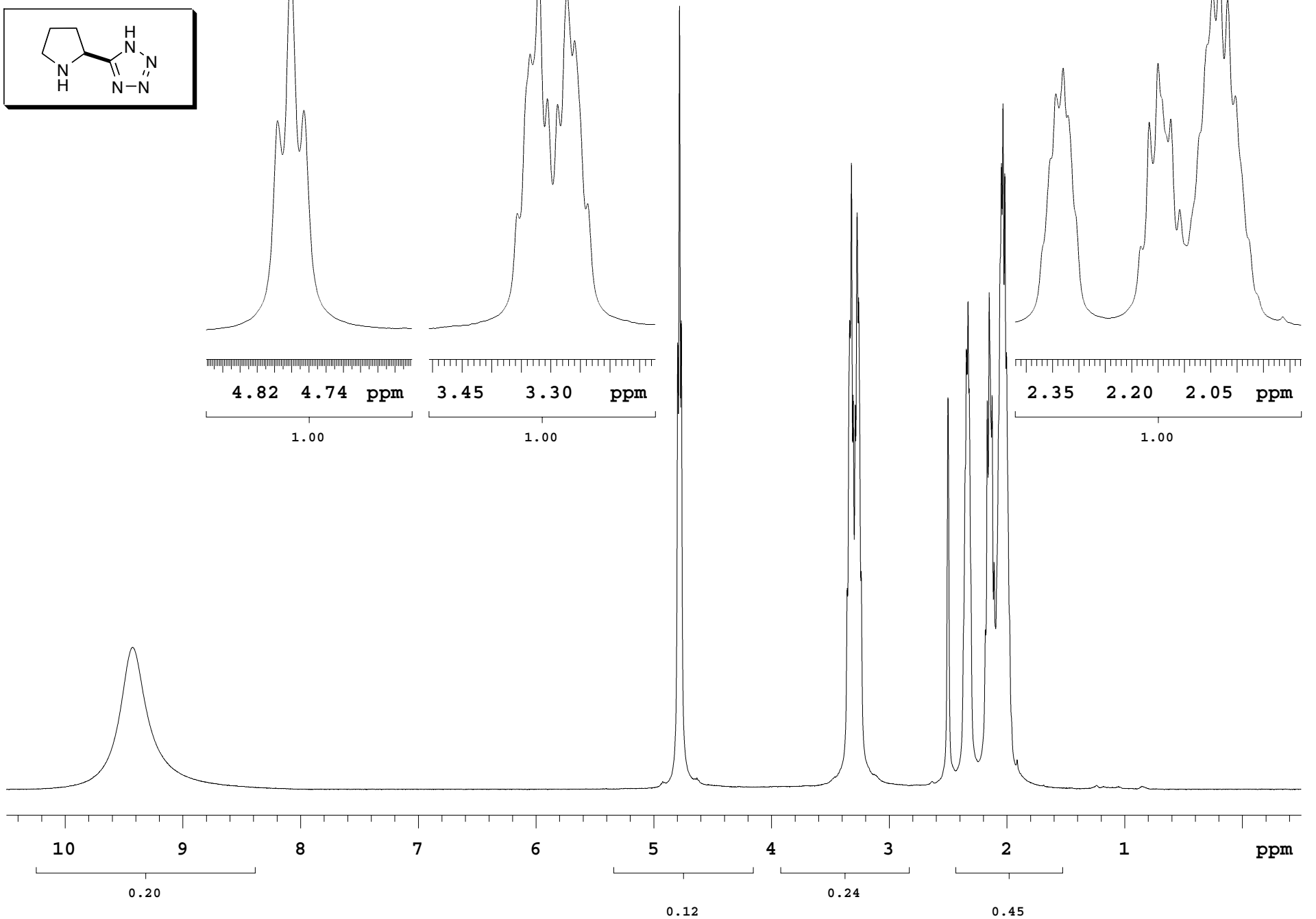
RCS-08-77B1-1H

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jul 27 2007	dfrq	499.435
solvent	DMSO	dn	H1
file	/export/home/~	dpwr	25
	user1d/data/vxr500~	dof	0
	/smithr/RCS-08-77B~	dm	nnn
	1-1H.fid	dmm	c
ACQUISITION		dmf	200
sfrq	499.435	dseq	
tn	H1	dres	1.0
at	4.096	homo	n
np	65536	DEC2	
sw	8000.0	dfrq2	0
fb	4000	dn2	
bs	4	dpwr2	1
tpwr	62	dof2	0
pw	5.0	dm2	n
d1	0	dmm2	c
tof	0	dmf2	200
nt	16	dseq2	
ct	16	dres2	1.0
alock	n	homo2	n
gain	not used	PROCESSING	
FLAGS		lb	0.30
il	n	wtfile	
in	n	proc	ft
dp	y	fn	not used
hs	nn	math	f
DISPLAY			
sp	-250.0	werr	
wp	5493.7	wexp	
vs	151	wbs	
sc	0	wnt	
wc	250		
hzmm	21.98		
is	419.61		
rfl	2750.5		
rfp	1248.6		
th	7		
ins	1.000		
nm	ph		






4.82 4.74 ppm
1.00
3.45 3.30 ppm
1.00
2.35 2.20 2.05 ppm
1.00
10 9 8 7 6 5 4 3 2 1 ppm
0.20
0.12
0.24
0.45