
Supporting Information

Highly Enantioselective Synthesis of Chiral γ -Lactams by Rh-Catalyzed Asymmetric Hydrogenation

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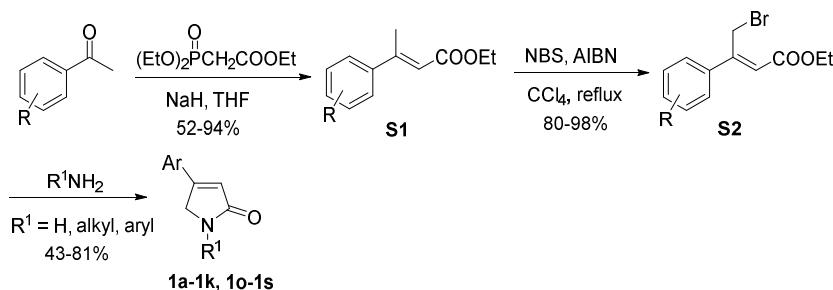
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1. General Information

Unless otherwise mentioned, all experiments were carried out under an atmosphere of argon in a glovebox or using standard Schlenk techniques. Solvents were dried with standard procedures and degassed with N₂. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 300-400 mesh). NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz for ¹H NMR, 101 MHz for ¹³C NMR or a Bruker DPX 500 spectrometer at 500 MHz for ¹H NMR, 126 MHz for ¹³C NMR. Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me₄Si and solvent signals (Me₄Si, 0 ppm for ¹H NMR in CDCl₃ or DMSO-d₆; 77.0 ppm in CDCl₃ or 39.5 ppm in DMSO-d₆ for ¹³C NMR). HPLC analysis was carried out on Agilent 1200 Series instrument using chiral columns.

2. General Procedure for the Synthesis of Substrates

2.1 General Procedure A: synthesis of substrates **1a-1k** and **1o-1s**.¹



To a suspension of NaH (3.0 g, 125 mmol) in THF (100 mL), a solution of ethyl(diethoxyphosphoryl) acetate (10.5 mL, 60 mmol, 1.2 equiv) in THF (20 mL) was added dropwise at 0 °C. After 1 h, acetophenone (50 mmol, 1.0 equiv) was added to the reaction mixture, and the mixture was then stirred for 24 h at rt. After the reaction was completed, water (5 mL) was added to quench the reaction and the organic layer was extracted with ethyl acetate, dried over Na₂SO₄ and evaporated. The residue was further purified by column chromatography on silica gel using the mixture of hexane and ethyl acetate as the eluent (hexane : EtOAc = 30 : 1 to 20 : 1), affording α,β -unsaturated ester **S1** in 52-94% yields.

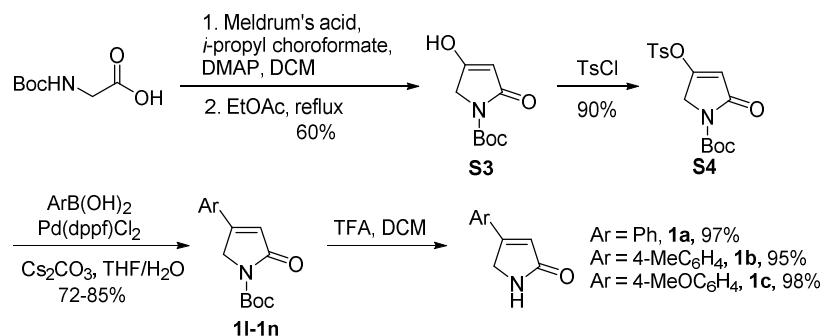
A solution of **S1** (30 mmol), NBS (36 mmol, 1.2 equiv) and AIBN (1.2 mmol, 0.04 equiv) in dry CCl₄ (degassed, 80 mL) was refluxed under nitrogen atmosphere for 20 h. Then the reaction mixture was cooled to room temperature and filtered to remove the formed succinimide during the reaction. The filtrate was concentrated under reduced pressure to afford the crude product, which was further purified by column chromatography on silica gel to give pure **S2** in 80-98% yields

(hexane : EtOAc = 30 : 1 to 20 : 1).

To a solution of **S2** (10 or 5 mmol) in 20 mL of ethanol, a solution of ammonia in methanol (7 M, 10 mL) was dropwise added and the resulting mixture was stirred at rt for 18 h. The mixture was concentrated and the desired products **1a-1k** were purified by recrystallization or column chromatography in 43-81% yield.

To a stirred solution of **S2** (10 mmol) in toluene (30 mL) was added alkyl amine or aniline (or their solution) (21 mmol, 2.1 equiv) with stirring. Stirring was continued for 24 h at rt and then heated to 50 °C for 2 h. The reaction mixture was diluted at rt with ethyl acetate (50 mL) and washed with HCl aqueous solution (5%, 5 mL), NaOH aqueous solution (2%, 10 mL) and water (10 mL), successively. After drying over Na₂SO₄, the solvent was evaporated and the residue was purified by column chromatography on silica gel followed with recrystallization to give the pure products (**1o-1s**) in 45-67% yield.

2.2 General Procedure B: synthesis of substrates **1l-1n**,^{2,3} and an alternative way to substrates **1a-1c**.²



To a stirring solution of Boc-Gly-OH (3.00 g, 17.1 mmol) in dry methylene chloride (36 mL) at 0 °C under argon, Meldrum's acid (2.97 g, 20.6 mmol, 1.2 equiv) and DMAP (5.24 g, 42.8 mmol, 2.5 equiv) were added. A solution of isopropyl chloroformate in toluene (25.7 mL, 25.7 mmol, 1.5 equiv) was then dropwise added, and the resulting mixture was stirred for 3 h at 0 °C. The mixture was washed twice with KHSO₄ aqueous solution (15%, 30 mL), and the organic layer was extracted with EtOAc and dried over MgSO₄. The solution was concentrated and the residue was refluxed in ethyl acetate (340 mL) for 1 h. The solvent was then removed under reduced pressure and the crude product was recrystallized in ethyl acetate to give a crystalline solid of compound **S3** in 60% yield.

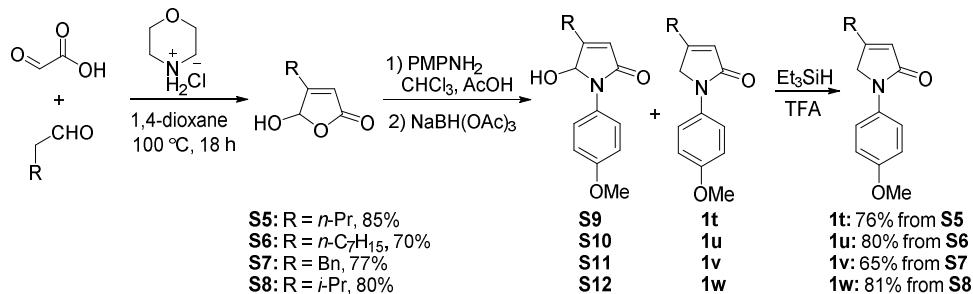
Under an argon atmosphere, compound **S3** (1.00 g, 5.02 mmol) was dissolved in CH₂Cl₂ (50 mL)

mL). *p*-Toluenesulfonyl chloride (0.958 g, 5.02 mmol, 1.0 equiv) and DIPEA (1.75 mL, 10.04 mmol, 2.0 equiv) were added to this solution, and the resulting mixture was stirred for 6 h at rt. The reaction mixture was successively washed with HCl aqueous solution (5%, 5 mL), NaHCO₃ aqueous solution (5%, 10 mL) and saturated NaCl aqueous solution (10 mL). The organic layer was then extracted with CH₂Cl₂, dried over MgSO₄ and filtered. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel using the mixture of ethyl acetate and hexane as eluent (hexane : EtOAc = 1 : 4) to give compound **S4** (90% yield) as a white solid.

Tosylate **S4** (2.0 mmol) and boronic acid (3.0 mmol, 1.5 equiv) were dissolved in THF (20 mL). To this solution was added Pd(dppf)Cl₂ (82 mg, 0.10 mmol, 0.05 equiv) and subsequently a solution of cesium carbonate (1.96 g, 6.0 mmol, 2.0 equiv) in water (2 mL). The reaction mixture was stirred at rt for 40 min and then heated to reflux for 11-23 h until TLC showed complete conversion of the starting material. The reaction mixture was then filtered through a short plug of celite with the aid of ethyl acetate. The filtrate was concentrated and the crude material was dissolved in ethyl acetate (80 mL). The organic layer was washed with saturated Na₂CO₃ aqueous solution (40 mL), brine (2 x 40 mL), and dried over Na₂SO₄. Removal of the solvent under reduced pressure gave a crude material, which was further purified by flash chromatography (EtOAc : CH₂Cl₂ = 5 : 95 to 8 : 92), providing the desired product **1l-1n** in 72-85% yields.

An alternative way to substrates 1a-1c: To a stirred solution of compound **1l-1n** (1.0 mmol) in CH₂Cl₂ (4 mL) was added TFA (4 mL) at rt. The reaction mixture was stirred for 15-60 min until TLC showed complete conversion of the starting material. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and the solvent was removed in vacuo. Purification of the crude material by flash chromatography (EtOAc) gave the desired product **1a-1c** in 95-98% yield.

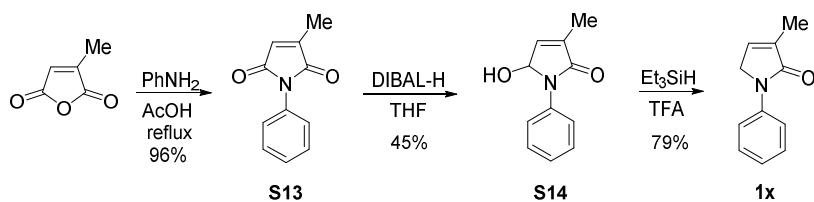
2.3 General Procedure C: synthesis of substrates **1t-1w**.^{4,5}



Morpholine hydrochloride (2.47 g, 20 mmol) was added to a solution of glyoxylic acid (2.96 g, 20 mmol, 50 w/w% in H₂O) in 20 mL of dioxane. A solution of aldehyde (20 mmol) in 5 mL of dioxane was added dropwise via syringe, and the resulting solution was stirred at rt for 2 h and then heated to 100 °C for overnight. The reaction mixture was evaporated and extracted with EtOAc (3 x 10 mL), and the combined organic layers were then washed with saturated NaHCO₃ (aq), brine, dried over MgSO₄, and concentrated. The residue was purified by column chromatography to obtain compounds **S5-S8** (70-85%) as pale yellow oils.

To a solution of **S5-S8** (3.0 mmol) in chloroform (30 mL) was slowly added *p*-anisidine (4.5 mmol) at rt before cooling to 0 °C. Acetic acid (17 µL, 0.3 mmol,) was then added and the reaction mixture was stirred at rt for 1 h. Sodium triacetoxyborohydride (954 mg, 4.5 mmol) was slowly added and the resulting mixture was kept stirring at rt overnight. Water (5 mL) was added to the reaction mixture and the organic layer was extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : EtOAc = 2 : 1) to give a mixture of hydroxylactam (**S9-S12**, respectively) and desired products (**1t-1w**, respectively). Et₃SiH (1.05 g, 9 mmol) was added dropwise to a solution of the above inseparable mixture in 5 mL of TFA. The resulting mixture was stirred at rt for 2 h. The reaction was then quenched by pouring into 10 mL of ice water, and the organic phase was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ solution (3 x 10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The pure products **1t-1w** (65-81% yields for 2 steps) were finally obtained upon purification by column chromatography on silica gel (hexane : EtOAc = 2 : 1).

2.4 General Procedure D: synthesis of substrates **1x**.^{6,7}



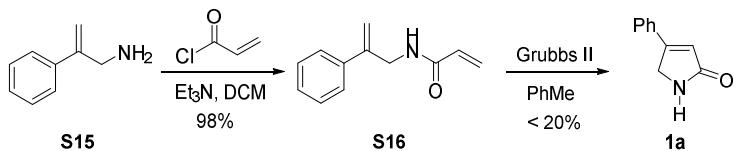
A mixture of citraconic anhydride (5.0 mmol), aniline (5.5 mmol) and acetic acid (15 mL) was refluxed overnight until TLC showed complete conversion of the anhydride. Then the reaction mixture was concentrated under reduced pressure, and the resulting residue was separated by column chromatography (hexane : EtOAc = 6 : 1) to give the product **S13** (910 mg, 96% yield).

To a solution of **S13** (2.0 mmol) in THF was added DIBAL-H (2.0 mmol, 1.5 M in PhMe) dropwise at 0 °C, and the reaction mixture was allowed to warm to rt slowly. The reaction was quenched with ice water at 0 °C before TLC showed complete conversion of **S13**. The mixture was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated to give a crude product, which was purified by column chromatography to give the hydroxylactam **S14** (170 mg, 45% yield).

Et₃SiH (121 mg, 1 mmol) was added dropwise to a solution of the hydroxylactam **S14** (95 mg, 0.5 mmol) in 1 mL of TFA at 0 °C. The resulting mixture was stirred at rt for 2 h. The reaction was quenched by pouring into 5 mL of ice water, and extracted with CH₂Cl₂ (3 x 10 mL). The organic layer was washed with saturated NaHCO₃ solution (2-3 times), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The pure product **1x** (70 mg, 79%) was obtained upon purification by column chromatography on silica gel (hexane : EtOAc = 5 : 1).

2.5 Attempt to synthesis **1a** through ring-closing metathesis.⁸

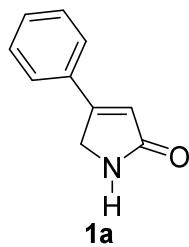
The model substrate **1a** could also be easily achieved via ring-closing metathesis from readily available intermediate **S15**. However, the yield of the ring-closing step was not satisfied in our hand due to the lack of methathesis catalysts. Other NH free lactams could be potentially synthesized in the same way.



3. General Procedure for the Asymmetric Hydrogenation

In a glovebox, a solution of ZhaoPhos (9.6 mg, 0.011 mmol) and Rh(NBD)₂BF₄ (3.7 mg, 0.01 mmol) in 1.0 mL anhydrous CH₂Cl₂ was stirred at room temperature for 40 min. 50 uL of the resulting solution was transferred by micro syringe into a vial charged with a solution of **1** (0.1 mmol) in 0.9 mL anhydrous CH₂Cl₂. The vial was transferred into an autoclave, which was then filled with 60 atm of H₂. The mixture was stirred at 35 °C (temperature of the oil bath) for 48-72 h. The solution was passed through a short column of silica gel (about 4 cm) to remove the metal residue and the filtrate was concentrated. The products were pure enough for NMR and HPLC analysis.

4. Characterization Data

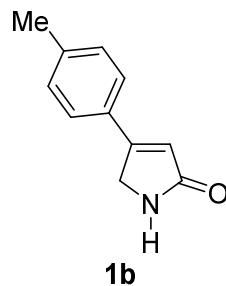


Chemical Formula: C₁₀H₉NO

Molecular Weight: 159.19

4-Phenyl-1,5-dihydro-2H-pyrrol-2-one (1a): Following the general procedure A, the known compound **1a**^{1,2} (1.02 g, 64%) was obtained as a brown solid. ¹H NMR (500 MHz, CDCl₃): δ 7.91 (br s, 1H), 7.54-7.48 (m, 2H), 7.45-7.38 (m, 3H), 6.44 (s, 1H), 4.44 (s, 2H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 175.6, 157.5, 131.8, 130.2, 128.9, 125.9, 120.1, 48.4 ppm.

Compound **1a** could also be prepared through N-Boc deprotection of **1l** in 97% yield.

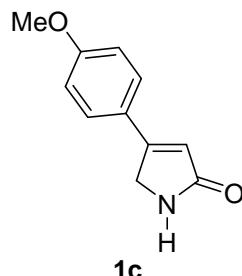


Chemical Formula: C₁₁H₁₁NO

Molecular Weight: 173.22

4-(*p*-Tolyl)-1,5-dihydro-2H-pyrrol-2-one (1b): Following the general procedure A, the unknown compound **1b** (0.61 g, 70%) was obtained as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.14 (br s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.46 (s, 1H), 4.35 (s, 2H), 2.24 (s, 3H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 173.9, 157.1, 139.8, 129.4, 129.4, 126.1, 119.4, 47.6, 21.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₂NO⁺ (M+H)⁺: 174.0913; found: 174.0912.

Compound **1b** could also be prepared through N-Boc deprotection of **1m** in 95% yield.

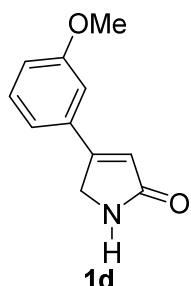


Chemical Formula: C₁₁H₁₁NO₂

Molecular Weight: 189.21

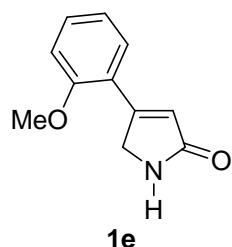
4-(4-Methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1c): Following the general procedure A, the known compound **1c**² (0.58 g, 61%) was obtained as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.07 (br s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.38 (s, 1H), 4.34 (s, 2H), 3.80 (s, 3H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 174.0, 160.6, 156.8, 127.8, 124.7, 118.1, 114.2, 55.3, 47.6 ppm.

Compound **1c** could also be prepared through N-Boc deprotection of **1n** in 98% yield.



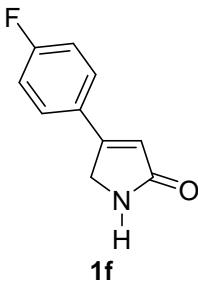
Chemical Formula: C₁₁H₁₁NO₂
Molecular Weight: 189.21

4-(3-Methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1d): Following the general procedure A, the unknown compound **1d** (0.67 g, 71%) was obtained as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 7.72 (br s, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.12-7.08 (m, 1H), 7.03-7.01 (m, 1H), 6.98-6.94 (m, 1H), 6.42 (q, *J* = 1.4 Hz, 1H), 4.42 (t, *J* = 1.4 Hz, 2H), 3.85 (s, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 175.4, 159.9, 157.4, 133.2, 130.0, 120.4, 118.3, 115.4, 111.7, 55.3, 48.4 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₂NO₂⁺ (M+H)⁺: 190.0863; found: 190.0861.



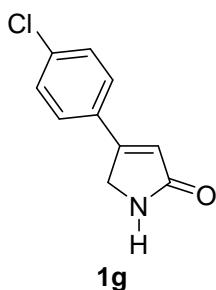
Chemical Formula: C₁₁H₁₁NO₂
Molecular Weight: 189.21

4-(2-Methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1e): Following the general procedure A, the unknown compound **1e** (0.53 g, 56%) was obtained as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 7.82 (br s, 1H), 7.43-7.34 (m, 2H), 7.02-6.97 (m, 2H), 6.66 (q, *J* = 1.4 Hz, 1H), 4.48 (t, *J* = 1.4 Hz, 2H), 3.90 (s, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 176.1, 158.0, 154.2, 131.1, 127.9, 123.0, 120.8, 120.6, 111.4, 55.3, 50.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₂NO₂⁺ (M+H)⁺: 190.0863; found: 190.0861.



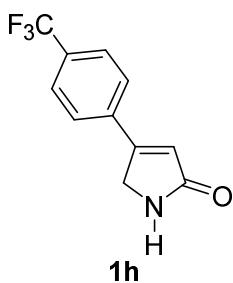
Chemical Formula: C₁₀H₈FNO
Molecular Weight: 177.18

4-(4-Fluorophenyl)-1,5-dihydro-2H-pyrrol-2-one (1f): Following the general procedure A, the unknown compound **1f** (0.61 g, 69%) was obtained as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.20 (br s, 1H), 7.77-7.69 (m, 2H), 7.33-7.26 (m, 2H), 6.52 (s, 1H), 4.37 (s, 2H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 173.6, 163.0 (d, *J*_{C-F} = 247.4 Hz), 155.9, 128.8 (d, *J*_{C-F} = 2.9 Hz), 128.6 (d, *J*_{C-F} = 8.7 Hz), 120.3 (d, *J*_{C-F} = 1.3 Hz), 115.9 (d, *J*_{C-F} = 21.8 Hz), 47.6 ppm. HRMS-ESI (*m/z*): Calculated for C₁₀H₉FNO⁺ (M+H)⁺: 178.0663; found: 178.0662.



Chemical Formula: C₁₀H₈CINO
Molecular Weight: 193.63

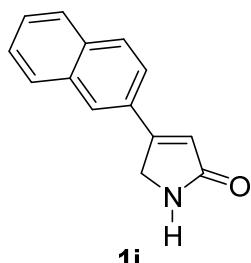
4-(4-Chlorophenyl)-1,5-dihydro-2H-pyrrol-2-one (1g): Following the general procedure A, the known compound **1g**² (0.42 g, 43%) was obtained as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.24 (br s, 1H), 7.73-7.66 (m, 2H), 7.54-7.48 (m, 2H), 6.58 (q, *J* = 1.5 Hz, 1H), 4.37 (t, *J* = 1.5 Hz, 2H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 173.5, 155.7, 134.5, 131.0, 128.9, 128.0, 121.2, 47.5 ppm.



Chemical Formula: C₁₁H₈F₃NO
Molecular Weight: 227.19

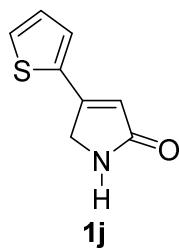
4-(4-(Trifluoromethyl)phenyl)-1,5-dihydro-2H-pyrrol-2-one (1h): Following the general

procedure A, the unknown compound **1h** (0.82 g, 72%) was obtained as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.36 (br s, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 1.4 Hz, 1H), 4.44 (s, 2H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 173.2, 155.4, 136.0, 129.7 (q, *J*_{C-F} = 32.0 Hz), 127.0, 125.7 (q, *J*_{C-F} = 3.8 Hz), 124.0 (q, *J*_{C-F} = 272.4 Hz), 123.0, 47.6 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₉F₃NO⁺ (M+H)⁺: 228.0631; found: 228.0630.



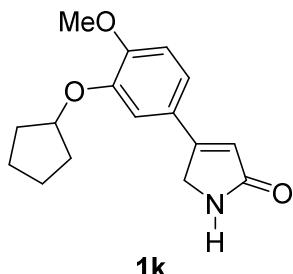
Chemical Formula: C₁₄H₁₁NO
Molecular Weight: 209.25

4-(Naphthalen-2-yl)-1,5-dihydro-2H-pyrrol-2-one (1i): Following the general procedure A, the unknown compound **1i** (0.85 g, 81%) was obtained as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.26 (br s, 1H), 8.18 (s, 1H), 8.01-7.92 (m, 3H), 7.86 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.60-7.55 (m, 2H), 6.68 (q, *J* = 1.2 Hz, 1H), 4.53 (s, 2H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 173.7, 156.9, 133.5, 132.8, 129.6, 128.5, 128.4, 127.7, 127.1, 126.8, 125.4, 123.9, 121.0, 47.7 ppm. HRMS-ESI (*m/z*): Calculated for C₁₄H₁₂NO⁺ (M+H)⁺: 210.0913; found: 210.0911.



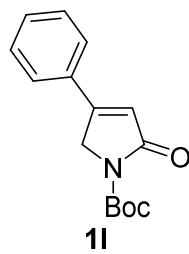
Chemical Formula: C₈H₇NOS
Molecular Weight: 165.21

4-(Thiophen-2-yl)-1,5-dihydro-2H-pyrrol-2-one (1j): Following the general procedure A, the unknown compound **1j**² (0.39 g, 47%) was obtained as a brown solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.13 (br s, 1H), 7.72 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.46 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.21 (d, *J* = 1.4 Hz, 1H), 4.35 (s, 2H); ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆): δ 173.4, 150.9, 135.5, 128.9, 128.4, 127.5, 118.7, 48.1 ppm.



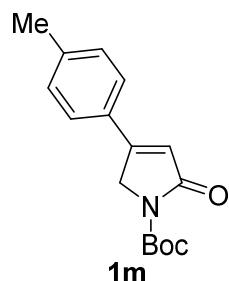
Chemical Formula: C₁₆H₁₉NO₃
Molecular Weight: 273.33

4-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1k): Following the general procedure A, the known compound **1k**⁹ (1.02 g, 75%) was obtained as a pale yellow solid.
¹H NMR (500 MHz, CDCl₃): δ 7.81 (br s, 1H), 7.08-7.01 (m, 2H), 6.87 (d, J = 8.3 Hz, 1H), 6.29 (s, 1H), 4.85-4.78 (m, 1H), 4.41 (s, 2H), 3.88 (s, 3H), 2.01-1.79 (m, 6H), 1.70-1.58 (m, 2H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 175.8, 157.5, 151.9, 147.7, 124.7, 118.9, 118.0, 112.5, 111.5, 80.6, 55.9, 48.4, 32.7 (2C), 24.0 (2C) ppm. HRMS-ESI (m/z): Calculated for C₁₆H₂₀NO₃⁺ (M+H)⁺: 274.1438; found: 274.1436.



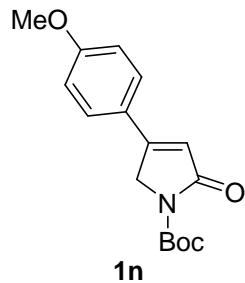
Chemical Formula: C₁₅H₁₇NO₃
Molecular Weight: 259.31

Tert-butyl 2-oxo-4-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (1l): Following the general procedure B, the known compound **1l**² (0.37 g, 72%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.57-7.53 (m, 2H), 7.49-7.43 (m, 3H), 6.42 (t, J = 1.4 Hz, 1H), 4.70 (d, J = 1.4 Hz, 2H), 1.60 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 169.2, 156.0, 149.6, 131.2, 130.8, 129.1, 126.2, 119.7, 83.0, 51.0, 28.1 ppm.



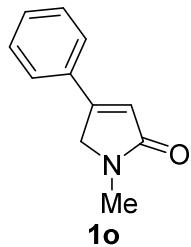
Chemical Formula: C₁₆H₁₉NO₃
Molecular Weight: 273.33

Tert-butyl 2-oxo-4-(p-tolyl)-2,5-dihydro-1H-pyrrole-1-carboxylate (1m): Following the general procedure B, the unknown compound **1m** (0.40 g, 74%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.36 (s, 1H), 4.68 (d, *J* = 1.3 Hz, 2H), 2.41 (s, 3H), 1.59 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 169.4, 156.1, 149.7, 141.8, 129.8, 128.1, 126.1, 118.7, 82.9, 51.0, 28.1, 21.5 ppm. HRMS-ESI (*m/z*): Calculated for C₁₆H₂₀NO₃⁺ (M+H)⁺: 274.1438; found: 274.1434.



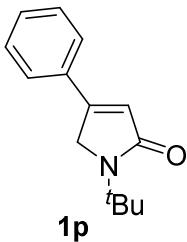
Chemical Formula: C₁₆H₁₉NO₄
Molecular Weight: 289.33

Tert-butyl 4-(4-methoxyphenyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (1n): Following the general procedure B, the known compound **1n**² (0.49 g, 85%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.50 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.29 (s, 1H), 4.66 (s, 2H), 3.87 (s, 3H), 1.59 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 169.5, 161.9, 155.7, 149.7, 127.8, 123.4, 117.4, 114.5, 82.8, 55.4, 50.9, 28.1 ppm.



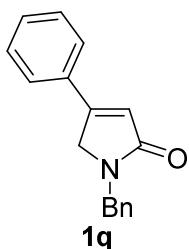
Chemical Formula: C₁₁H₁₁NO
Molecular Weight: 173.22

1-Methyl-4-phenyl-1,5-dihydro-2H-pyrrrol-2-one (1o): Following the general procedure A, the known compound **1o**¹ (0.23 g, 67%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.50-7.45 (m, 2H), 7.44-7.37 (m, 3H), 6.42 (s, 1H), 4.33 (s, 2H), 3.09 (s, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 171.6, 153.7, 131.7, 130.0, 128.9, 125.5, 120.4, 54.2, 28.9 ppm.



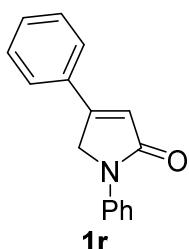
Chemical Formula: C₁₄H₁₇NO
Molecular Weight: 215.30

1-(Tert-butyl)-4-phenyl-1,5-dihydro-2H-pyrrol-2-one (1p): Following the general procedure A, the unknown compound **1p** (0.24 g, 55%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.50-7.45 (m, 2H), 7.43-7.35 (m, 3H), 6.35 (s, 1H), 4.39 (s, 2H), 1.52 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 171.9, 152.7, 132.0, 129.8, 128.9, 125.5, 122.4, 53.9, 50.8, 28.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₄H₁₈NO⁺ (M+H)⁺: 216.1383; found: 216.1383.



Chemical Formula: C₁₇H₁₅NO
Molecular Weight: 249.31

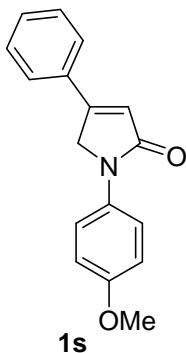
1-Benzyl-4-phenyl-1,5-dihydro-2H-pyrrol-2-one (1q): Following the general procedure A, the known compound **1q**¹⁰ (0.31 g, 62%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.46-7.42 (m, 2H), 7.40-7.33 (m, 5H), 7.31-7.27 (m, 3H), 6.49 (t, *J* = 1.4 Hz, 1H), 4.70 (s, 2H), 4.23 (d, *J* = 1.4 Hz, 2H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 171.6, 154.4, 137.2, 131.7, 130.2, 128.9, 128.8, 128.0, 127.6, 125.7, 120.1, 51.7, 46.0 ppm.



Chemical Formula: C₁₆H₁₃NO
Molecular Weight: 235.29

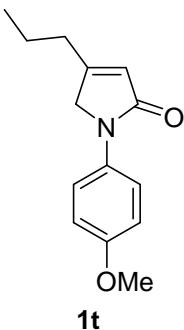
1,4-Diphenyl-1,5-dihydro-2H-pyrrol-2-one (1r): Following the general procedure A, the known compound **1r**¹¹ (0.24 g, 51%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.78 (d, *J* = 8.6 Hz, 2H), 7.60-7.55 (m, 2H), 7.50-7.44 (m, 3H), 7.43-7.37 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.53 (s, 1H), 4.79 (s, 2H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 170.3, 153.5, 139.2, 131.3,

130.6, 129.1 (4C), 125.9 (2C), 124.0, 121.4, 118.7 (2C), 52.7 ppm. HRMS-ESI (*m/z*): Calculated for C₁₆H₁₄NO⁺ (M+H)⁺: 236.1070; found: 236.1069.



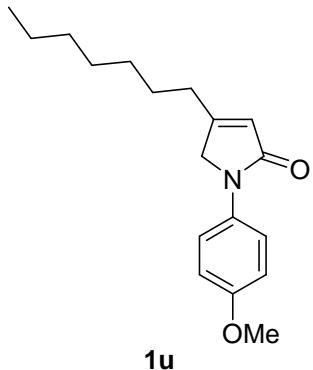
Chemical Formula: C₁₇H₁₅NO₂
Exact Mass: 265.11

1-(4-Methoxyphenyl)-4-phenyl-1,5-dihydro-2H-pyrrol-2-one (1s): Following the general procedure A, the known compound **1s**¹ (0.24 g, 45%) was obtained as a yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 7.67-7.63 (m, 2H), 7.58-7.54 (m, 2H), 7.48-7.43 (m, 3H), 6.97-6.91 (m, 2H), 6.53 (s, 1H), 4.77 (s, 2H), 3.82 (s, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 170.1, 156.3, 153.2, 132.4, 131.4, 130.4, 129.1, 125.8, 121.3, 120.8, 114.3, 55.4, 53.1 ppm. HRMS-ESI (*m/z*): Calculated for C₁₇H₁₆NO₂⁺ (M+H)⁺: 266.1176; found: 266.1173.



Chemical Formula: C₁₄H₁₇NO₂
Exact Mass: 231.13

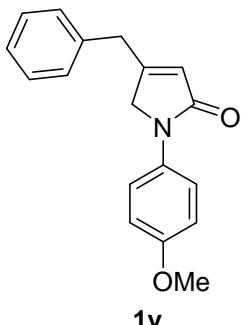
1-(4-Methoxyphenyl)-4-propyl-1,5-dihydro-2H-pyrrol-2-one (1t): Following the general procedure C, the unknown compound **1t** (0.53 g, 76%) was obtained as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.56 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.93 (s, 1H), 4.25 (s, 2H), 3.79 (s, 3H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.70-1.58 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 170.5, 158.8, 156.0, 132.5, 122.8, 120.5, 114.1, 55.4, 55.2, 31.5, 20.9, 13.7 ppm. HRMS-ESI (*m/z*): Calculated for C₁₄H₁₈NO₂⁺ (M+H)⁺: 232.1332; found: 232.1330.



Chemical Formula: C₁₈H₂₅NO₂

Molecular Weight: 287.40

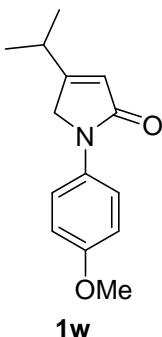
4-Heptyl-1-(4-methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1u): Following the general procedure C, the unknown compound **1u** (0.69 g, 80%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.92 (s, 1H), 4.25 (s, 2H), 3.79 (s, 3H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.63-1.54 (m, 2H), 1.41-1.21 (m, 8H), 0.89 (t, *J* = 6.6 Hz, 3H); ¹³C NMR {¹H} (100 MHz, CDCl₃): δ 170.5, 159.0, 156.0, 132.6, 122.7, 120.5, 114.1, 55.4, 55.2, 31.6, 29.5, 29.1, 28.9, 27.6, 22.5, 14.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₈H₂₆NO₂⁺ (M+H)⁺: 288.1958; found: 288.1955.



Chemical Formula: C₁₈H₁₇NO₂

Molecular Weight: 279.34

4-Benzyl-1-(4-methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1v): Following the general procedure C, the unknown compound **1v** (0.54 g, 65%) was obtained as a brown solid. ¹H NMR (500 MHz, CDCl₃): δ 7.51 (d, *J* = 9.0 Hz, 2H), 7.36-7.30 (m, 2H), 7.29-7.24 (m, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.93 (s, 1H), 4.20 (s, 2H), 3.77 (s, 3H), 3.73 (s, 2H); ¹³C NMR {¹H} (100 MHz, CDCl₃): δ 170.0, 157.3, 156.1, 136.8, 132.4, 128.8, 128.7, 127.0, 124.2, 120.6, 114.1, 55.4, 54.7, 36.2 ppm. HRMS-ESI (*m/z*): Calculated for C₁₈H₁₈NO₂⁺ (M+H)⁺: 280.1332; found: 280.1329.

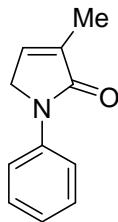


1w

Chemical Formula: C₁₄H₁₇NO₂

Molecular Weight: 231.30

4-Isopropyl-1-(4-methoxyphenyl)-1,5-dihydro-2H-pyrrol-2-one (1w): Following the general procedure C, the unknown compound **1w** (0.56 g, 81%) was obtained as a brown solid. ¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.90 (s, 1H), 4.29 (s, 2H), 3.79 (s, 3H), 2.74-2.62 (m, 1H), 1.22 (s, 3H), 1.21 (s, 3H); ¹³C NMR {¹H} (100 MHz, CDCl₃): δ 170.4, 164.6, 155.9, 132.5, 121.1, 120.5, 114.1, 55.3, 53.7, 28.8, 21.2 ppm. HRMS-ESI (*m/z*): Calculated for C₁₄H₁₈NO₂⁺ (M+H)⁺: 232.1332; found: 232.1332.

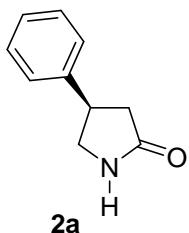


1x

Chemical Formula: C₁₁H₁₁NO

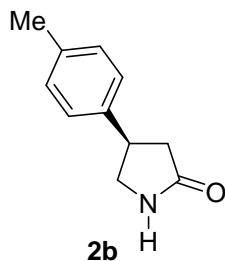
Molecular Weight: 173.22

3-Methyl-1-phenyl-1,5-dihydro-2H-pyrrol-2-one (1x): Following the general procedure D, the known compound **1x**¹² (70 mg, 79%) was obtained as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 7.76-7.72 (m, 2H), 7.39-7.34 (m, 2H), 7.13-7.09 (m, 1H), 6.78-6.76 (m, 1H), 2.28-2.26 (m, 2H), 1.96 (q, *J* = 1.8 Hz, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 170.8, 139.4, 136.6, 134.7, 129.0, 123.8, 118.3, 50.8, 11.3 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₂NO⁺ (M+H)⁺: 174.0913; found: 174.0912.



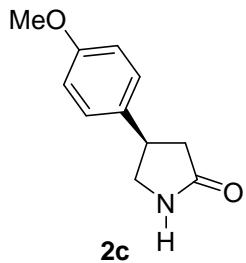
Chemical Formula: C₁₀H₁₁NO
Molecular Weight: 161.20

(R)-4-Phenylpyrrolidin-2-one (2a): White solid, 15.8 mg, 98% yield, 96% ee, $[\alpha]_D^{20} = -27.1$ (*c* 1.00, MeOH) [lit.¹³: $[\alpha]_D^{20} = -31.7$ (*c* 0.29, MeOH) for the *R*-isomer of 93% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.33 (m, 2H), 7.29-7.25 (m, 3H), 6.61 (brs, 1H), 3.79 (t, *J* = 8.8 Hz, 1H), 3.70 (dt, *J* = 16.2, 8.4 Hz, 1H), 3.43 (dd, *J* = 9.3, 7.4 Hz, 1H), 2.74 (dd, *J* = 16.9, 8.9 Hz, 1H), 2.52 (dd, *J* = 16.9, 8.9 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.8, 142.1, 128.8, 127.1, 126.7, 49.5, 40.3, 37.9 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 8.5 min (major), 10.1 min (minor).



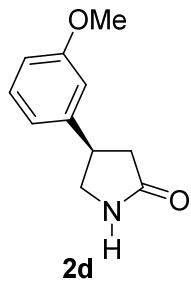
Chemical Formula: C₁₁H₁₃NO
Molecular Weight: 175.23

(R)-4-(*p*-Tolyl)pyrrolidin-2-one (2b): White solid, 16.7 mg, 95% yield, 95% ee, $[\alpha]_D^{20} = -49.5$ (*c* 1.00, MeOH) [lit.¹⁴: $[\alpha]_D^{20} = -44.2$ (*c* 0.5, MeOH)]. ¹H NMR (500 MHz, CDCl₃): δ 7.17-7.13 (m, 4H), 6.80 (br s, 1H), 3.76 (t, *J* = 8.8 Hz, 1H), 3.70-3.61 (m, 1H), 3.40 (dd, *J* = 9.2, 7.8 Hz, 1H), 2.71 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.49 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.34 (s, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.9, 139.0, 136.7, 129.4, 126.6, 49.7, 39.9, 38.0, 21.0 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 95/5; flow = 1.0 mL/min; Retention time: 13.4 min (major), 14.5 min (minor).



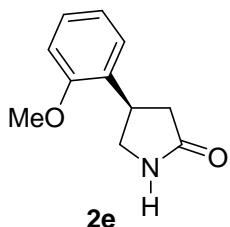
Chemical Formula: C₁₁H₁₃NO₂
Molecular Weight: 191.23

(R)-4-(4-Methoxyphenyl)pyrrolidin-2-one (2c): White solid, 18.0 mg, 94% yield, 96% ee, $[\alpha]_D^{20} = -27.5$ (*c* 1.00, MeOH) [lit.¹⁵: $[\alpha]_D^{25} = -21.0$ (*c* 1.0, MeOH) for the *R*-isomer of 98% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.98 (br s, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.76 (t, *J* = 8.9 Hz, 1H), 3.68-3.60 (m, 1H), 3.38 (dd, *J* = 9.2, 7.7 Hz, 1H), 2.71 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.47 (dd, *J* = 16.8, 8.9 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 178.0, 158.5, 134.1, 127.7, 114.1, 55.2, 49.8, 39.6, 38.2 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 225 nm; *n*-hexane / *i*-propanol = 95/5; flow = 1.0 mL/min; Retention time: 20.6 min (major), 22.3 min (minor).



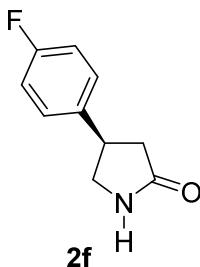
Chemical Formula: C₁₁H₁₃NO₂
Molecular Weight: 191.23

(R)-4-(3-Methoxyphenyl)pyrrolidin-2-one (2d): White solid, 16.4 mg, 86% yield, 95% ee, $[\alpha]_D^{20} = -24.8$ (*c* 1.00, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.28-7.25 (m, 1H), 6.99 (br s, 1H), 6.86-6.80 (m, 3H), 3.81 (s, 3H), 3.78 (t, *J* = 9.0 Hz, 1H), 3.67 (dt, *J* = 16.5, 8.5 Hz, 1H), 3.43 (t, *J* = 8.4 Hz, 1H), 2.73 (dd, *J* = 16.9, 9.0 Hz, 1H), 2.51 (dd, *J* = 16.9, 9.0 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.9, 159.8, 143.7, 129.8, 119.0, 112.8, 112.0, 55.2, 49.4, 40.2, 37.9 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₄NO₂⁺ (M+H)⁺: 192.1019; found: 192.1018. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 11.1 min (major), 13.2 min (minor).



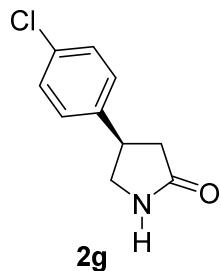
Chemical Formula: C₁₁H₁₃NO₂
Molecular Weight: 191.23

(R)-4-(2-Methoxyphenyl)pyrrolidin-2-one (2e): White solid, 19.0 mg, 99% yield, 92% ee, $[\alpha]_D^{20} = -36.8$ (*c* 1.00, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.27-7.20 (m, 2H), 6.95-6.88 (m, 2H), 6.49 (br s, 1H), 3.96-3.90 (m, 1H), 3.84 (s, 3H), 3.74 (t, *J* = 8.9 Hz, 1H), 3.42 (dd, *J* = 9.1, 7.4 Hz, 1H), 2.68-2.57 (m, 2H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 178.3, 157.3, 129.7, 128.1, 127.4, 120.6, 110.6, 55.2, 48.0, 36.1, 35.3 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₄NO₂⁺ (M+H)⁺: 192.1019; found: 192.1018. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 10.5 min (major), 11.5 min (minor).



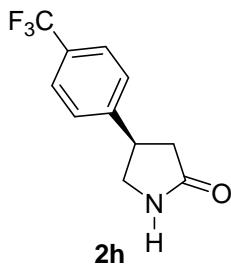
Chemical Formula: C₁₀H₁₀FNO
Molecular Weight: 179.19

(R)-4-(4-Fluorophenyl)pyrrolidin-2-one (2f): White solid, 17.7 mg, 99% yield, 96% ee, $[\alpha]_D^{20} = -26.2$ (*c* 1.00, MeOH) [lit.¹⁵: $[\alpha]_D^{25} = -27.54$ (*c* 1.12, MeOH)]. ¹H NMR (500 MHz, CDCl₃): δ 7.24-7.20 (m, 3H), 7.05-7.01 (m, 2H), 3.84-3.75 (m, 1H), 3.69 (dt, *J* = 16.1, 8.4 Hz, 1H), 3.39 (dd, *J* = 9.2, 7.5 Hz, 1H), 2.74 (dd, *J* = 16.9, 8.9 Hz, 1H), 2.46 (dd, *J* = 16.9, 8.9 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.6, 161.8 (d, *J*_{C-F} = 245.4 Hz), 137.8 (d, *J*_{C-F} = 3.1 Hz), 128.2 (d, *J*_{C-F} = 8.1 Hz), 115.7 (d, *J*_{C-F} = 21.2 Hz), 49.6, 39.6, 38.0 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 8.6 min (major), 10.3 min (minor).



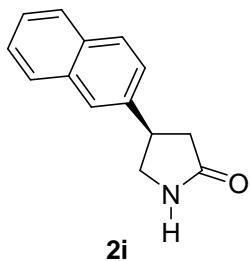
Chemical Formula: C₁₀H₁₀ClNO
Molecular Weight: 195.65

(R)-4-(4-Chlorophenyl)pyrrolidin-2-one (2g): White solid, 19.3 mg, 98% yield, 96% ee, [α]_D²⁵ = −33.4 (c 1.00, EtOH) [lit.¹⁶: [α]_D²⁵ = −39.7 (c 1.00, EtOH) for the *R*-isomer of 99% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.33–7.27 (m, 2H), 7.20–7.18 (m, 2H), 6.65 (br s, 1H), 3.79 (t, *J* = 8.9 Hz, 1H), 3.67 (dt, *J* = 16.0, 8.4 Hz, 1H), 3.39 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.74 (dd, *J* = 17.0, 8.8 Hz, 1H), 2.46 (dd, *J* = 17.0, 8.8 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.5, 140.6, 132.8, 129.0, 128.1, 49.4, 39.6, 37.9 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 9.5 min (major), 11.3 min (minor).



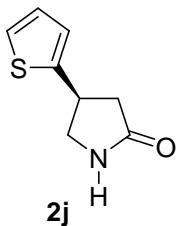
Chemical Formula: C₁₁H₁₀F₃NO
Molecular Weight: 229.20

(R)-4-(4-(Trifluoromethyl)phenyl)pyrrolidin-2-one (2h): White solid, 22.3 mg, 97% yield, 96% ee, [α]_D²⁰ = −22.2 (c 1.00, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.61 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.17 (br s, 1H), 3.84 (t, *J* = 8.6 Hz, 1H), 3.77 (dt, *J* = 15.7, 8.2 Hz, 1H), 3.44 (dd, *J* = 9.3, 6.9 Hz, 1H), 2.79 (dd, *J* = 16.9, 8.5 Hz, 1H), 2.50 (dd, *J* = 16.9, 8.5 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.3, 146.2, 129.5 (q, *J*_{C-F} = 32.5 Hz), 127.1, 125.8 (q, *J*_{C-F} = 3.8 Hz), 124.0 (q, *J*_{C-F} = 272.0 Hz), 49.2, 40.0, 37.7 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₁F₃NO⁺ (M+H)⁺: 230.0787; found: 230.0788. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 7.5 min (major), 9.5 min (minor).



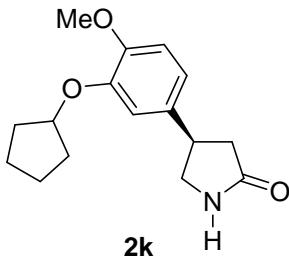
Chemical Formula: C₁₄H₁₃NO
Molecular Weight: 211.26

(R)-4-(Naphthalen-2-yl)pyrrolidin-2-one (2i): White solid, 20.9 mg, 99% yield, 97% ee, [α]_D²⁰ = -48.1 (c 1.00, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.85-7.80 (m, 3H), 7.68 (s, 1H), 7.53-7.43 (m, 2H), 7.40-7.26 (m, 1H), 6.75 (br s, 1H), 3.88-3.84 (m, 2H), 3.55-3.50 (m, 1H), 2.82 (dd, J = 16.7, 8.2 Hz, 1H), 2.62 (dd, J = 16.7, 8.2 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.8, 139.4, 133.3, 132.4, 128.7, 127.6, 126.4, 125.9, 125.3, 124.9, 49.4, 40.3, 37.9 ppm. HRMS-ESI (m/z): Calculated for C₁₄H₁₄NO⁺ (M+H)⁺: 212.1070; found: 212.1068. HPLC: Chiracel AD-H Column (250 mm); detected at 220 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 10.0 min (major), 10.7 min (minor).



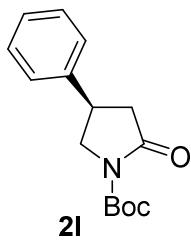
Chemical Formula: C₈H₉NOS
Molecular Weight: 167.23

(R)-4-(Thiophen-2-yl)pyrrolidin-2-one (2j)¹⁷: White solid, 16.2 mg, 97% yield, 97% ee, [α]_D²⁰ = -26.7 (c 1.00, MeOH). ¹H NMR (500 MHz, CDCl₃): δ 7.20 (dd, J = 5.0, 0.7 Hz, 1H), 6.98-6.94 (m, 1H), 6.91 (d, J = 3.3 Hz, 1H), 6.64 (br s, 1H), 3.96 (dt, J = 16.4, 8.4 Hz, 1H), 3.80 (t, J = 8.8 Hz, 1H), 3.46 (dd, J = 9.3, 7.8 Hz, 1H), 2.78 (dd, J = 16.8, 8.7 Hz, 1H), 2.54 (dd, J = 16.8, 8.7 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.1, 145.1, 127.0, 123.9, 123.9, 50.0, 38.9, 36.1 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 230 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 9.8 min (major), 11.1 min (minor).



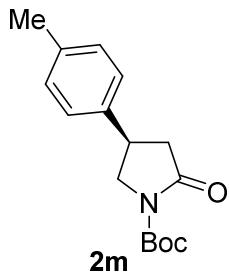
Chemical Formula: C₁₆H₂₁NO₃
Molecular Weight: 275.35

(R)-4-(3-(Cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one (2k): White solid, 27.1 mg, 98% yield, 96% ee, $[\alpha]_D^{25} = -32.5$ (*c* 1.00, MeOH) [lit.¹⁸: $[\alpha]_D^{27} = -33.0$ (*c* 1.00, MeOH) for the *R*-isomer of 99.3% ee]. ¹H NMR (500 MHz, CDCl₃): δ 6.84-6.77 (m, 4H), 4.79-4.75 (m, 1H), 3.83 (s, 3H), 3.76 (t, *J* = 9.0 Hz, 1H), 3.62 (dt, *J* = 16.7, 8.3 Hz, 1H), 3.39 (t, *J* = 8.4 Hz, 1H), 2.71 (dd, *J* = 16.9, 9.0 Hz, 1H), 2.48 (dd, *J* = 16.9, 9.0 Hz, 1H), 1.99-1.78 (m, 6H), 1.67-1.60 (m, 2H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 177.9, 149.1, 147.8, 134.5, 118.7, 113.7, 112.1, 80.5, 56.1, 49.8, 39.9, 38.1, 32.7 (2C), 24.0 (2C) ppm. HRMS-ESI (*m/z*): Calculated for C₁₆H₂₂NO⁺ (M+H)⁺: 276.1594; found: 276.1592. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 95/5; flow = 0.7 mL/min; Retention time: 29.2 min (major), 31.9 min (minor).



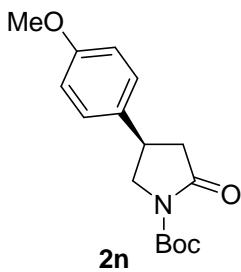
Chemical Formula: C₁₅H₁₉NO₃
Molecular Weight: 261.32

(R)-Tert-butyl 2-oxo-4-phenylpyrrolidine-1-carboxylate (2l): White solid, 25.5 mg, 98% yield, 99% ee, $[\alpha]_D^{20} = -4.3$ (*c* 1.00, CHCl₃) [lit.¹⁸: $[\alpha]_D^{27} = -5.6$ (*c* 0.83, CHCl₃) for the *R*-isomer of 98.2% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.38-7.35 (m, 2H), 7.31-7.24 (m, 3H), 4.17 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.69 (dd, *J* = 10.8, 8.6 Hz, 1H), 3.58-3.49 (m, 1H), 2.90 (dd, *J* = 17.3, 8.5 Hz, 1H), 2.72 (dd, *J* = 17.3, 9.9 Hz, 1H), 1.54 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.1, 149.8, 140.5, 128.9, 127.4, 126.7, 83.0, 53.1, 40.3, 36.4, 28.0 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 95/5; flow = 1.0 mL/min; Retention time: 13.6 min (minor), 14.7 min (major).



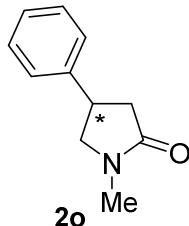
Chemical Formula: C₁₆H₂₁NO₃
Molecular Weight: 275.35

(R)-Tert-butyl 2-oxo-4-(p-tolyl)pyrrolidine-1-carboxylate (2m): White solid, 26.1 mg, 95% yield, 99% ee, $[\alpha]_D^{20} = -0.9$ (*c* 1.00, CHCl₃) [lit.¹⁸: $[\alpha]_D^{27} = -1.3$ (*c* 0.95, CHCl₃) for the *R*-isomer of 98.3% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.17 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 4.14 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.66 (dd, *J* = 10.8, 8.6 Hz, 1H), 3.55-3.45 (m, 1H), 2.87 (dd, *J* = 17.2, 8.5 Hz, 1H), 2.70 (dd, *J* = 17.2, 10.0 Hz, 1H), 2.34 (s, 3H), 1.53 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.2, 149.9, 137.4, 137.1, 129.6, 126.6, 83.0, 53.2, 40.3, 36.0, 28.0, 21.0 ppm. HPLC: Chiracel OD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 0.7 mL/min; Retention time: 19.1 min (major), 22.3 min (minor).



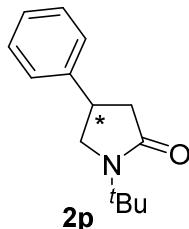
Chemical Formula: C₁₆H₂₁NO₄
Molecular Weight: 291.35

(R)-Tert-butyl 4-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylate (2n): White solid, 24.7 mg, 85% yield, 98% ee, $[\alpha]_D^{20} = -0.5$ (*c* 1.00, CHCl₃) [lit.¹⁸: $[\alpha]_D^{27} = -0.4$ (*c* 0.89, CHCl₃) for the *R*-isomer of 98% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.16 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 4.13 (dd, *J* = 10.5, 8.4 Hz, 1H), 3.81 (s, 3H), 3.64 (t, *J* = 9.5 Hz, 1H), 3.49 (dt, *J* = 17.8, 8.6 Hz, 1H), 2.87 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.68 (dd, *J* = 17.2, 10.1 Hz, 1H), 1.53 (s, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.2, 158.8, 149.9, 132.4, 127.7, 114.3, 83.0, 55.3, 53.3, 40.5, 35.7, 28.0 ppm. HPLC: Chiracel OJ-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 80/20; flow = 0.7 mL/min; Retention time: 20.5 min (minor), 24.9 min (major).



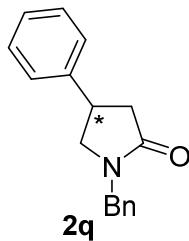
Chemical Formula: C₁₁H₁₃NO
Molecular Weight: 175.23

(–)-1-Methyl-4-phenylpyrrolidin-2-one (2o)¹⁹: Colorless oil, 17.1 mg, 98% yield, 95% ee, [α]_D²⁰ = –42.4 (c 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.36–7.33 (m, 2H), 7.28–7.22 (m, 3H), 3.75 (t, J = 9.0 Hz, 1H), 3.58 (dt, J = 16.2, 8.3 Hz, 1H), 3.41 (dd, J = 9.2, 7.2 Hz, 1H), 2.91 (s, 3H), 2.81 (dd, J = 16.9, 8.3 Hz, 1H), 2.54 (dd, J = 16.8, 8.3 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.9, 142.5, 128.8, 127.0, 126.7, 56.6, 38.8, 37.1, 29.5 ppm. HRMS-ESI (m/z): Calculated for C₁₁H₁₄NO⁺ (M+H)⁺: 176.1070; found: 176.1068. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 90/10; flow = 1.0 mL/min; Retention time: 8.0 min (minor), 8.4 min (major).



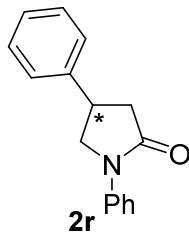
Chemical Formula: C₁₄H₁₉NO
Molecular Weight: 217.31

(–)-1-(Tert-butyl)-4-phenylpyrrolidin-2-one (2p): Colorless oil, 21.2 mg, 98% yield, 97% ee, [α]_D²⁰ = –24.1 (c 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.35–7.32 (m, 2H), 7.27–7.23 (m, 3H), 3.85 (t, J = 7.8 Hz, 1H), 3.47–3.39 (m, 2H), 2.76 (dd, J = 16.8, 8.6 Hz, 1H), 2.54 (dd, J = 16.8, 8.6 Hz, 1H), 1.43 (m, 9H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 174.2, 142.6, 128.8, 126.9, 126.7, 54.1, 53.1, 40.6, 37.0, 27.7 ppm. HRMS-ESI (m/z): Calculated for C₁₄H₂₀NO⁺ (M+H)⁺: 218.1539; found: 218.1538. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; n-hexane / i-propanol = 99/1; flow = 1.0 mL/min; Retention time: 15.8 min (minor), 17.3 min (major).



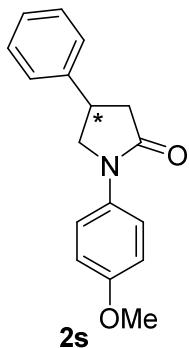
2q
Chemical Formula: C₁₇H₁₇NO
Molecular Weight: 251.33

(+)-1-Benzyl-4-phenylpyrrolidin-2-one (2q)²⁰: White solid, 24.6 mg, 98% yield, 96% ee, [α]_D²⁰ = +30.8 (*c* 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.21 (m, 8H), 7.17-7.16 (m, 2H), 4.56 (d, *J* = 14.6, Hz, 1H), 4.46 (d, *J* = 14.6, Hz, 1H), 3.63 (t, *J* = 9.0 Hz, 1H), 3.54 (dt, *J* = 16.0, 8.2 Hz, 1H), 3.27 (dd, *J* = 9.5, 7.1 Hz, 1H), 2.88 (dd, *J* = 16.8, 8.5 Hz, 1H), 2.62 (dd, *J* = 16.8, 8.5 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.7, 142.2, 136.2, 128.8, 128.7, 128.2, 127.6, 127.0, 126.7, 53.7, 46.6, 38.9, 37.1 ppm. HPLC: Chiracel AD-H Column (250 mm); detected at 210 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 12.3 min (minor), 14.0 min (major).



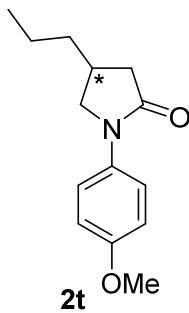
2r
Chemical Formula: C₁₆H₁₅NO
Molecular Weight: 237.30

(+)-1,4-Diphenylpyrrolidin-2-one (2r): White solid, 23.2 mg, 98% yield, 97% ee, [α]_D²⁰ = +10.7 (*c* 1.00, MeOH) ¹H NMR (500 MHz, CDCl₃): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.39-7.25 (m, 7H), 7.16 (t, *J* = 7.3 Hz, 1H), 4.19 (t, *J* = 8.6 Hz, 1H), 3.89 (t, *J* = 8.6 Hz, 1H), 3.70 (dt, *J* = 16.5, 8.3 Hz, 1H), 3.02 (dd, *J* = 17.0, 8.8 Hz, 1H), 2.80 (dd, *J* = 17.0, 8.8 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 172.9, 141.6, 139.1, 128.9 (2C), 127.3, 126.8, 124.6, 119.9, 55.6, 40.3, 37.1 ppm. HRMS-ESI (*m/z*): Calculated for C₁₆H₁₅NO⁺ (M+H)⁺: 238.1226; found: 238.1225. HPLC: Chiracel AD-H Column (250 mm); detected at 245 nm; *n*-hexane / *i*-propanol = 85/15; flow = 1.0 mL/min; Retention time: 11.6 min (minor), 14.8 min (major).



Chemical Formula: C₁₇H₁₇NO₂
Exact Mass: 267.13

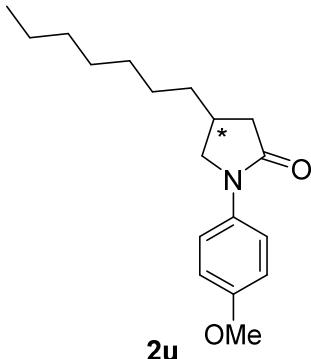
(+)-1-(4-Methoxyphenyl)-4-phenylpyrrolidin-2-one (2s): White solid, 26.4 mg, 99% yield, 96% ee, $[\alpha]_D^{20} = +9.9$ (*c* 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.38-7.35 (m, 2H), 7.30-7.25 (m, 3H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.14 (t, *J* = 8.8 Hz, 1H), 3.85 (t, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.68 (dt, *J* = 16.5, 8.2 Hz, 1H), 2.99 (dd, *J* = 17.0, 8.8 Hz, 1H), 2.77 (dd, *J* = 17.0, 8.8 Hz, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 172.6, 156.6, 141.7, 132.2, 128.9, 127.2, 126.7, 121.8, 114.0, 56.0, 55.4, 40.0, 37.2 ppm. HRMS-ESI (*m/z*): Calculated for C₁₇H₁₈NO⁺ (M+H)⁺: 268.1332; found: 268.1330. HPLC: Chiracel AD-H Column (250 mm); detected at 254 nm; *n*-hexane / *i*-propanol = 80/20; flow = 1.0 mL/min; Retention time: 15.3 min (minor), 22.2 min (major).



Chemical Formula: C₁₄H₁₉NO₂
Exact Mass: 233.14

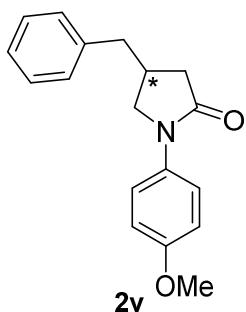
(-)-1-(4-Methoxyphenyl)-4-propylpyrrolidin-2-one (2t): White solid, 22.6 mg, 97% yield, 91% ee, $[\alpha]_D^{25} = -1.9$ (*c* 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.48 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.87 (t, *J* = 8.5 Hz, 1H), 3.79 (s, 3H), 3.46 (t, *J* = 8.2 Hz, 1H), 2.70 (dd, *J* = 16.7, 8.5 Hz, 1H), 2.50-2.39 (m, 1H), 2.27 (dd, *J* = 16.7, 8.2 Hz, 1H), 1.55-1.46 (m, 2H), 1.43-1.37 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.4, 156.4, 132.6, 121.7, 113.9, 55.4, 54.8, 39.0, 36.6, 31.3, 20.5, 14.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₄H₂₀NO⁺ (M+H)⁺: 234.1489; found: 234.1486. HPLC: Chiracel OJ-H Column (250 mm);

detected at 254 nm; *n*-hexane / *i*-propanol = 85/15; flow = 1.0 mL/min; Retention time: 13.0 min (minor), 15.3 min (major).



Chemical Formula: C₁₈H₂₇NO₂
Molecular Weight: 289.42

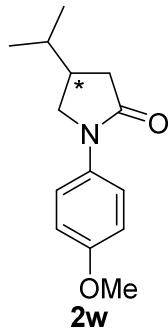
(-)-4-Heptyl-1-(4-methoxyphenyl)pyrrolidin-2-one (2u): White solid, 28.6 mg, 99% yield, 93% ee, $[\alpha]_D^{25} = -1.3$ (*c* 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.50-7.46 (m, 2H), 6.91-6.87 (m, 2H), 3.86 (dd, *J* = 9.4, 7.9 Hz, 1H), 3.79 (s, 3H), 3.45 (dd, *J* = 9.5, 7.1 Hz, 1H), 2.69 (dd, *J* = 16.7, 8.4 Hz, 1H), 2.47-2.37 (m, 1H), 2.27 (dd, *J* = 16.7, 8.1 Hz, 1H), 1.53-1.48 (m, 2H), 1.37-1.23 (m, 10H), 0.89 (t, *J* = 7.1 Hz, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.4, 156.4, 132.6, 121.7, 113.9, 55.4, 54.8, 39.1, 34.4, 31.7, 31.6, 29.5, 29.1, 27.4, 22.6, 14.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₈H₂₈NO₂⁺ (M+H)⁺: 290.2115; found: 290.2110. HPLC: Chiracel OJ-H Column (250 mm); detected at 254 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 10.3 min (minor), 12.3 min (major).



Chemical Formula: C₁₈H₁₉NO₂
Molecular Weight: 281.36

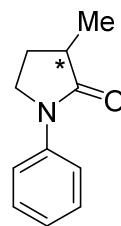
(-)-4-Benzyl-1-(4-methoxyphenyl)pyrrolidin-2-one (2v): White solid, 27.8 mg, 99% yield, 95% ee, $[\alpha]_D^{25} = -29.1$ (*c* 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.46-7.43 (m, 2H), 7.33-7.28 (m, 2H), 7.25-7.21 (m, 1H), 7.20-7.16 (m, 2H), 6.89-6.86 (m, 2H), 3.79-3.76 (m, 1H), 3.77 (s, 3H), 3.52 (dd, *J* = 9.8, 5.6 Hz, 1H), 2.88-2.82 (m, 1H), 2.78-2.66 (m, 3H), 2.40-2.35 (m, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 172.9, 156.4, 138.9, 132.4, 128.64, 128.56, 126.5,

121.7, 113.9, 55.3, 54.0, 40.2, 38.7, 33.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₈H₂₀NO₂⁺ (M+H)⁺: 282.1489; found: 282.1484. HPLC: Chiracel OJ-H Column (250 mm); detected at 254 nm; *n*-hexane / *i*-propanol = 80/20; flow = 1.0 mL/min; Retention time: 25.6 min (minor), 32.2 min (major).



Chemical Formula: C₁₄H₁₉NO₂
Molecular Weight: 233.31

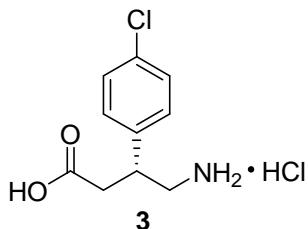
(–)-4-Isopropyl-1-(4-methoxyphenyl)pyrrolidin-2-one (2w): White solid, 22.9 mg, 98% yield, 96% ee, $[\alpha]_D^{25} = -12.0$ (*c* 1.00, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.50-7.47 (m, 2H), 6.91-6.87 (m, 2H), 3.83-3.80 (m, 1H), 3.79 (s, 3H), 3.51 (dd, *J* = 9.3, 8.3 Hz, 1H), 2.64 (dd, *J* = 16.8, 8.6 Hz, 1H), 2.32 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.21-2.12 (m, 1H), 1.70-1.60 (m, 1H), 0.97 (d, *J* = 2.9 Hz, 3H), 0.96 (d, *J* = 2.8 Hz, 3H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 173.5, 156.4, 132.5, 121.7, 113.9, 55.3, 53.3, 38.7, 37.4, 32.4, 20.4, 20.0 ppm. HRMS-ESI (*m/z*): Calculated for C₁₄H₂₀NO₂⁺ (M+H)⁺: 234.1489; found: 234.1486. HPLC: Chiracel OD-H Column (250 mm); detected at 254 nm; *n*-hexane / *i*-propanol = 95/5; flow = 1.0 mL/min; Retention time: 24.8 min (major), 28.9 min (minor).



Chemical Formula: C₁₁H₁₃NO
Molecular Weight: 175.23

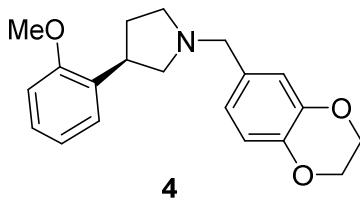
3-Methyl-1-phenylpyrrolidin-2-one (2x): White solid, 17.0 mg, 97% yield, 6% ee. ¹H NMR (500 MHz, CDCl₃): δ 7.65-7.62 (m, 2H), 7.38-7.34 (m, 2H), 7.15-7.11 (m, 1H), 3.80-3.73 (m, 2H), 2.70-2.62 (m, 1H), 2.39-2.33 (m, 1H), 1.80-1.72 (m, 1H), 1.30 (d, *J* = 7.1 Hz, 3H); ¹³C NMR {¹H}

(125 MHz, CDCl₃): δ 176.6, 139.6, 128.7, 124.2, 119.6, 46.6, 38.2, 26.9, 16.1 ppm. HRMS-ESI (*m/z*): Calculated for C₁₁H₁₄NO⁺ (M+H)⁺: 176.1070; found: 176.1068. HPLC: Chiracel OJ-H Column (250 mm); detected at 254 nm; *n*-hexane / *i*-propanol = 90/10; flow = 1.0 mL/min; Retention time: 12.8 min (major), 13.6 min (minor).



Chemical Formula: C₁₀H₁₃Cl₂NO₂
Molecular Weight: 250.12

(R)-Baclofen hydrochloride (3): A mixture of **2g** (52.0 mg) and 6 *N* HCl (1.5 mL) was heated to reflux for 24 h. The solution was cooled and evaporated to dryness under reduced pressure. The residue was dried under vacuum to afford **3** as a white solid, 61.6 mg, 93% yield. $[\alpha]_D^{25} = -3.5$ (*c* 0.65, H₂O), [lit.¹⁸: $[\alpha]_D^{27} = -3.9$ (*c* 0.64, H₂O) for the *R*-isomer of 99% ee]. ¹H NMR {¹H} (500 MHz, D₂O): δ 7.32 (d, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 2H), 3.38-3.23 (m, 2H), 3.14 (t, *J* = 11.4 Hz, 1H), 2.75 (dd, *J* = 16.0, 5.1 Hz, 1H), 2.63 (dd, *J* = 16.0, 8.6 Hz, 1H); ¹³C NMR (125 MHz, D₂O): δ 175.2, 136.9, 133.3, 129.4, 129.2, 43.6, 39.3, 38.1 ppm.



Chemical Formula: C₂₀H₂₃NO₃
Molecular Weight: 325.41

(R)-1-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-3-(2-methoxyphenyl)pyrrolidine (4): LiAlH₄ (38 mg, 1.0 mmol) was slowly added to a solution of compound **2e** (95.6 mg, 0.5 mmol; 92% ee) in THF (5.0 mL). The resulting mixture was refluxed overnight. The mixture was cooled to 0 °C and quenched by successive addition of H₂O, NaOH (15%, aq.), and H₂O (38 μL/38 μL/114 μL, 1 : 1 : 3). The solid residue was filtered and washed with CH₂Cl₂. The filtrate was dried over anhydrous Na₂SO₄, concentrated under reduced pressure and then dried under vacuum, giving the crude pyrrolidine product which was used for the next step without further purification. The crude pyrrolidine and 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (82 mg, 0.5 mmol)

was dissolved in 3 mL of MeOH. NaBH₃CN (126 mg, 1.0 mmol) was added and the reaction mixture was stirred for 4 h at rt. The reaction was then quenched with water and extracted with ethyl acetate. The organic phases were combined, dried, evaporated and the resulting oily residue was further purified by flash chromatography on silica gel using ethyl acetate/hexane/Et₃N (1/2/0.01) as eluents. The product is obtained as colorless oil (124 mg, 76% yield). [α]_D²⁵ = +19.4 (c 1.00, CHCl₃). [lit.²¹: [α]_D²⁰ = -22.2 (c 2.14, CHCl₃) for the S-isomer of 92% ee]. ¹H NMR (500 MHz, CDCl₃): δ 7.31 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.83-6.78 (m, 3H), 4.22 (s, 4H), 3.78 (s, 3H), 3.76-3.69 (m, 1H), 3.57 (d, *J* = 12.8 Hz, 1H), 3.54 (d, *J* = 12.8 Hz, 1H), 2.97 (t, *J* = 8.5 Hz, 1H), 2.81-2.74 (m, 1H), 2.70-2.62 (m, 1H), 2.49 (t, *J* = 8.4 Hz, 1H), 2.32-2.22 (m, 1H), 1.89-1.80 (m, 1H); ¹³C NMR {¹H} (125 MHz, CDCl₃): δ 157.0, 143.1, 142.3, 133.6, 132.8, 127.4, 126.8, 121.7, 120.5, 117.5, 116.8, 110.3, 64.3, 64.3, 60.5, 60.0, 55.3, 54.4, 36.3, 31.8 ppm.

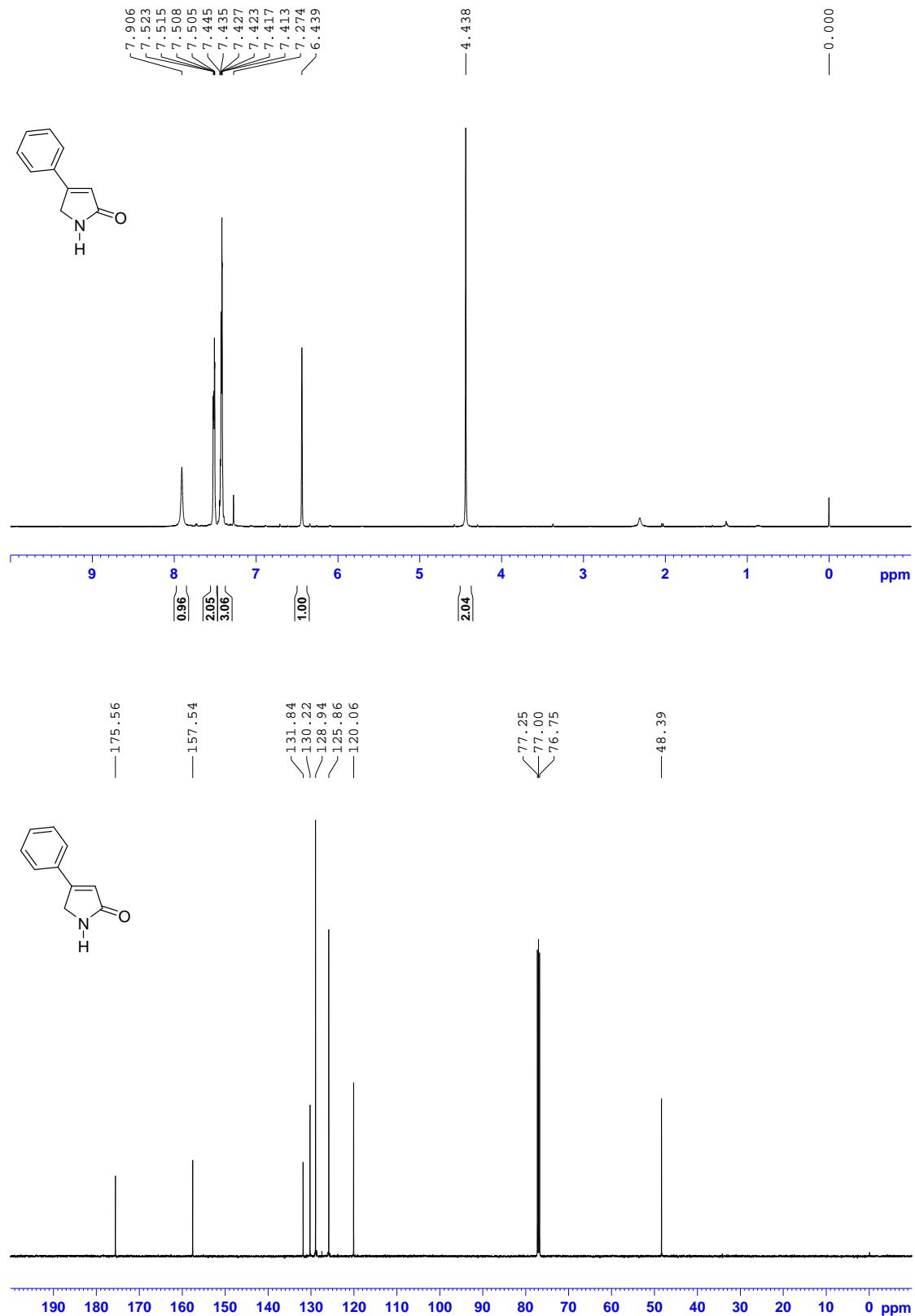
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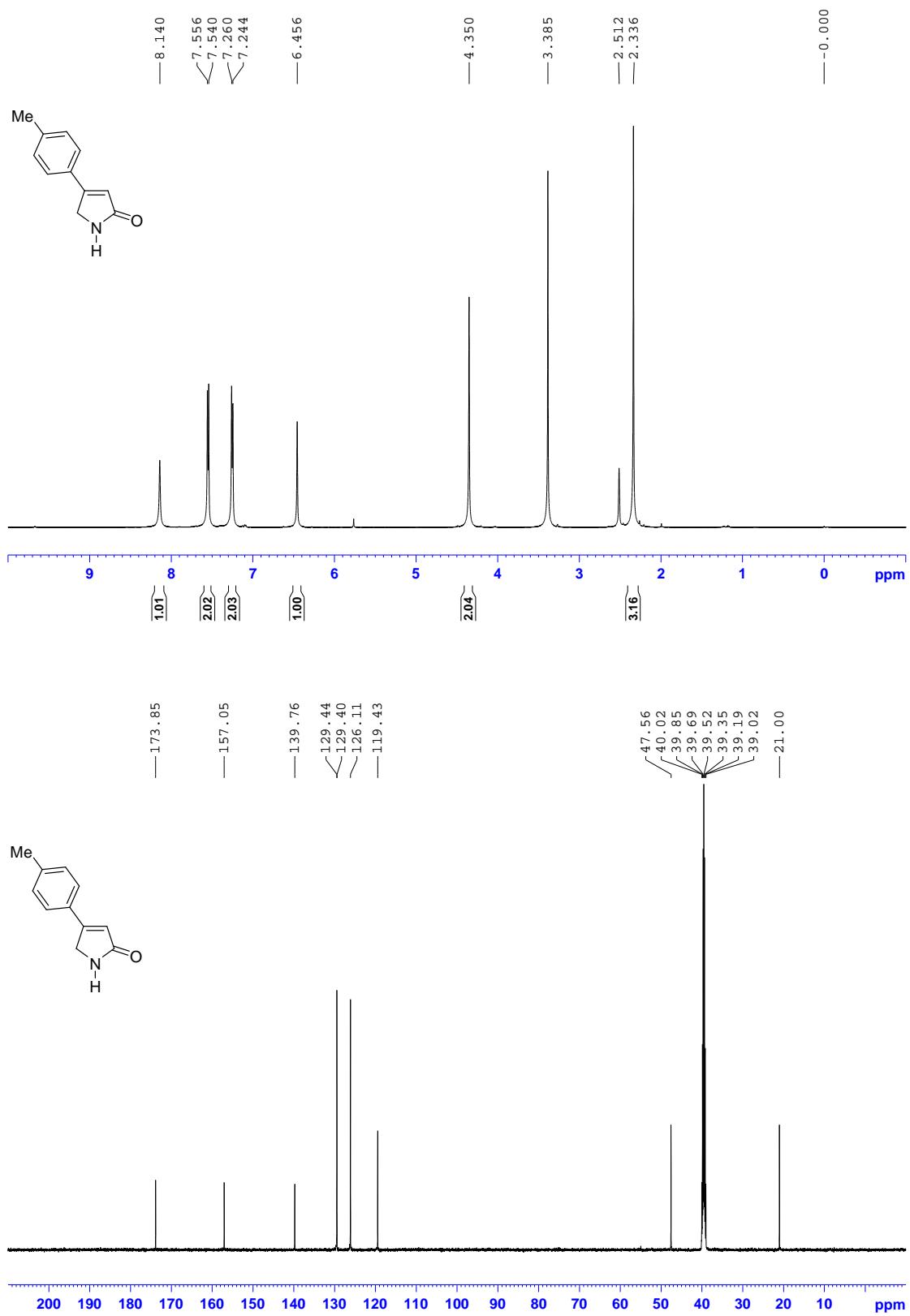
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6. NMR spectra

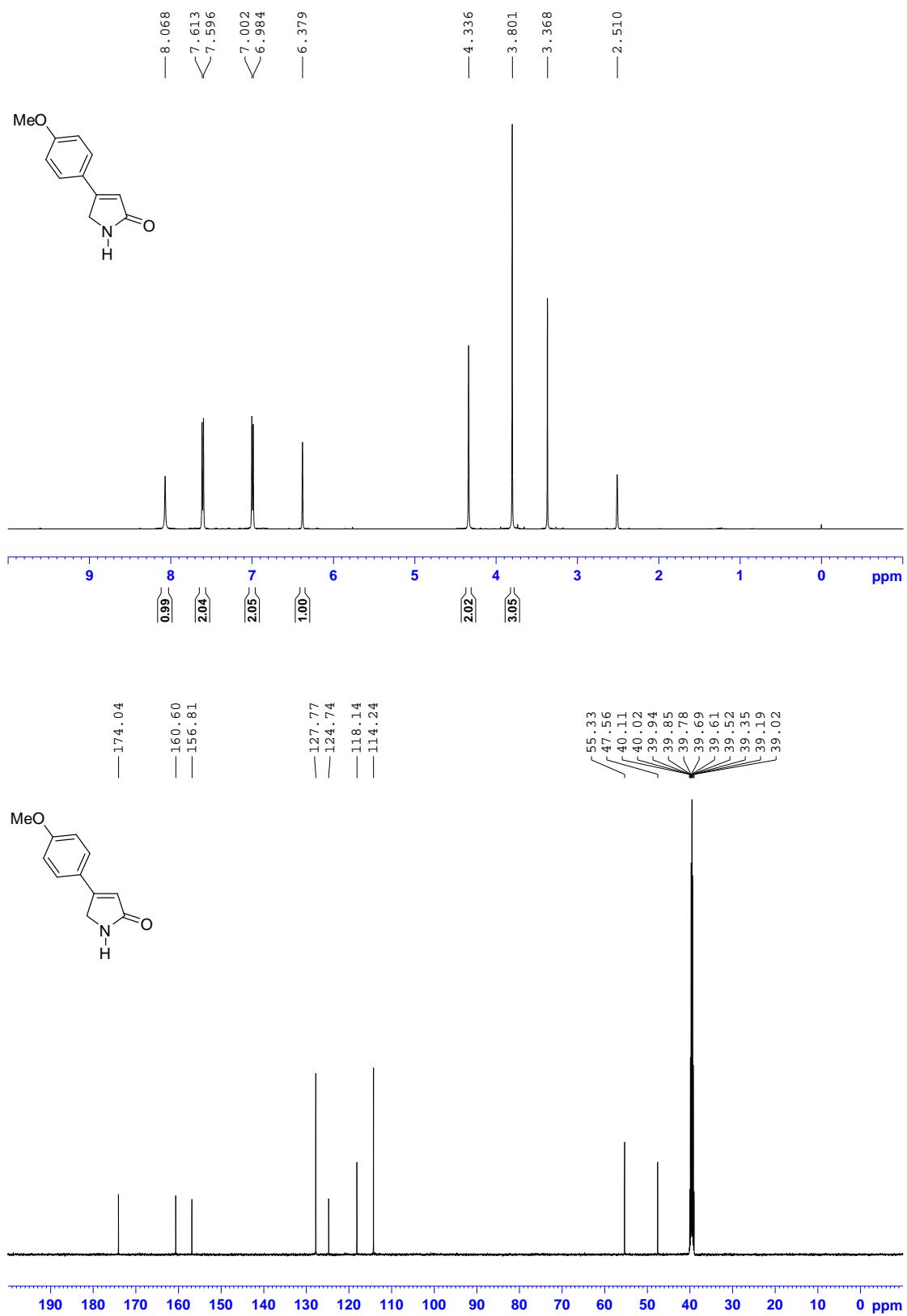
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **1a**:



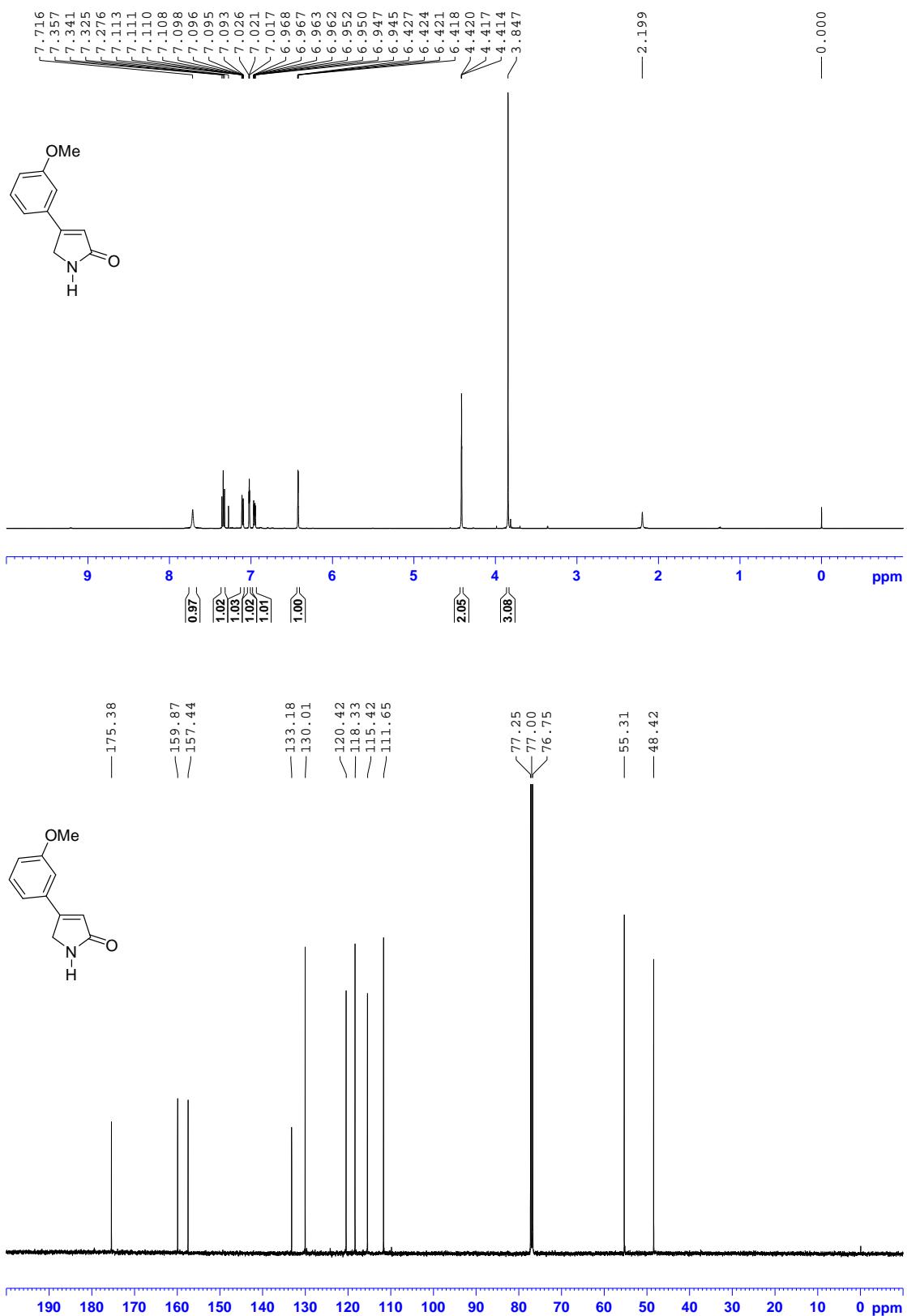
^1H NMR (500 MHz, $\text{DMSO}-d_6$) and ^{13}C NMR { ^1H } (125 MHz, $\text{DMSO}-d_6$) of **1b**:



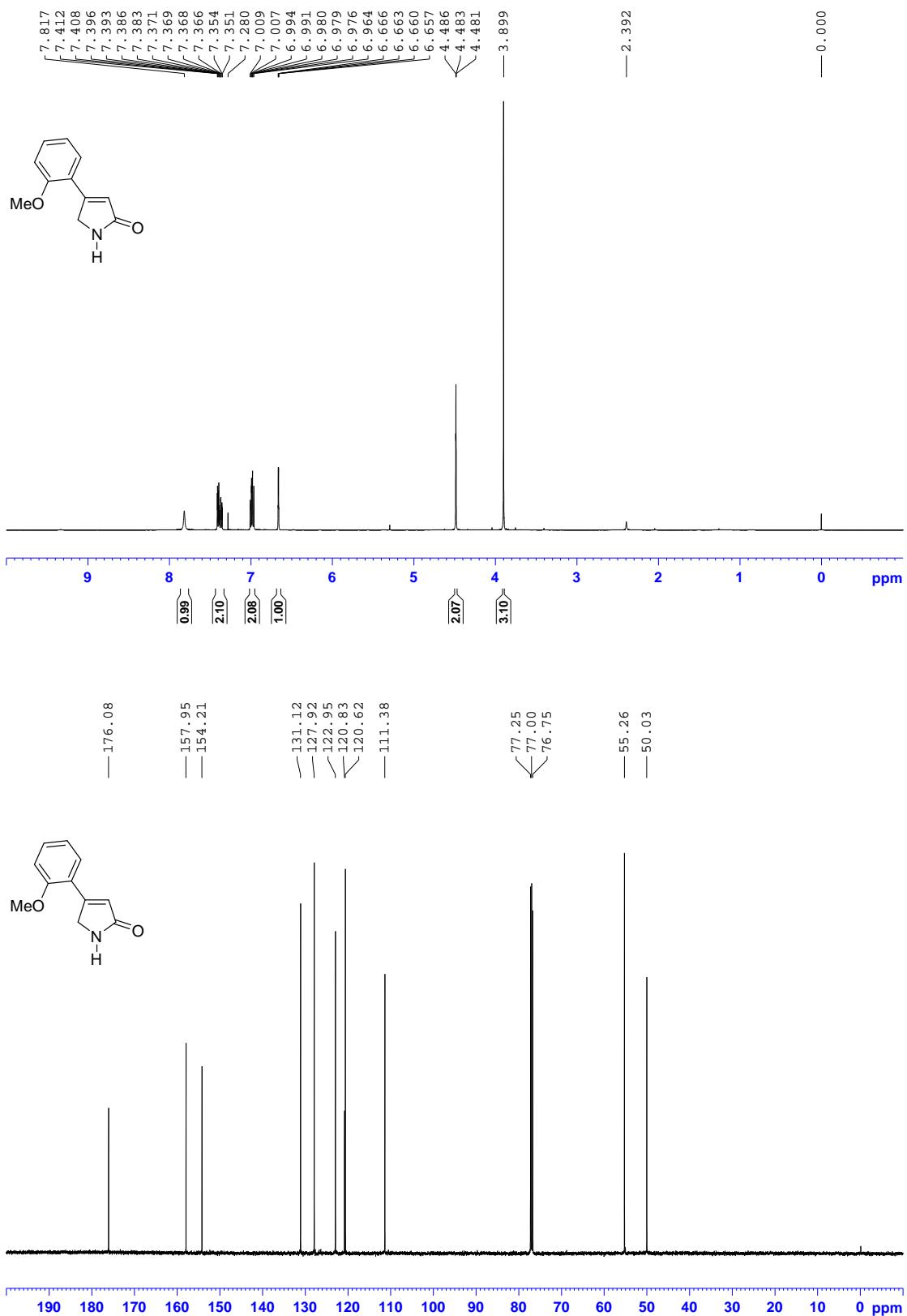
^1H NMR (500 MHz, DMSO- d_6) and ^{13}C NMR { ^1H } (125 MHz, DMSO- d_6) of **1c**:



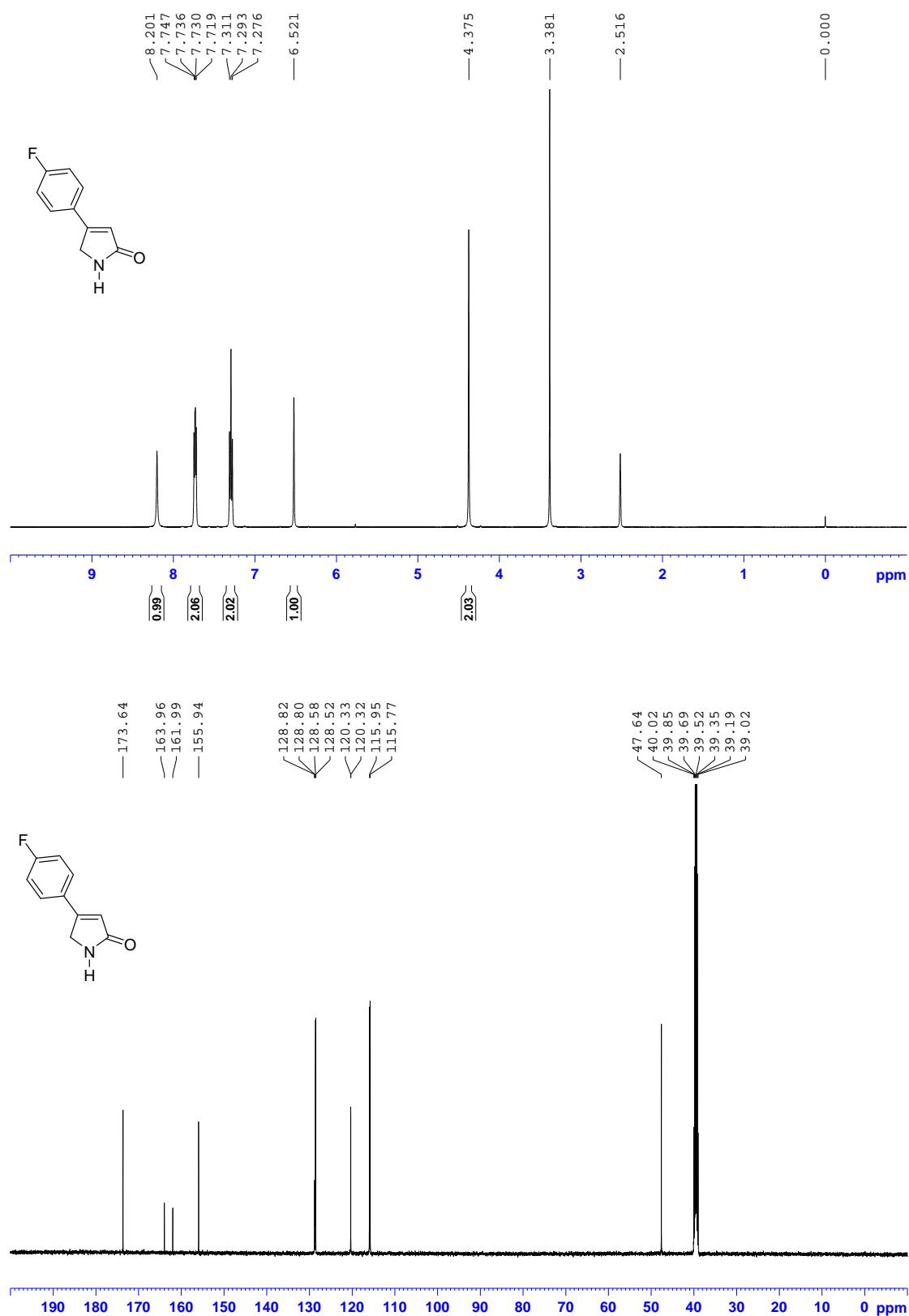
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **1d**:



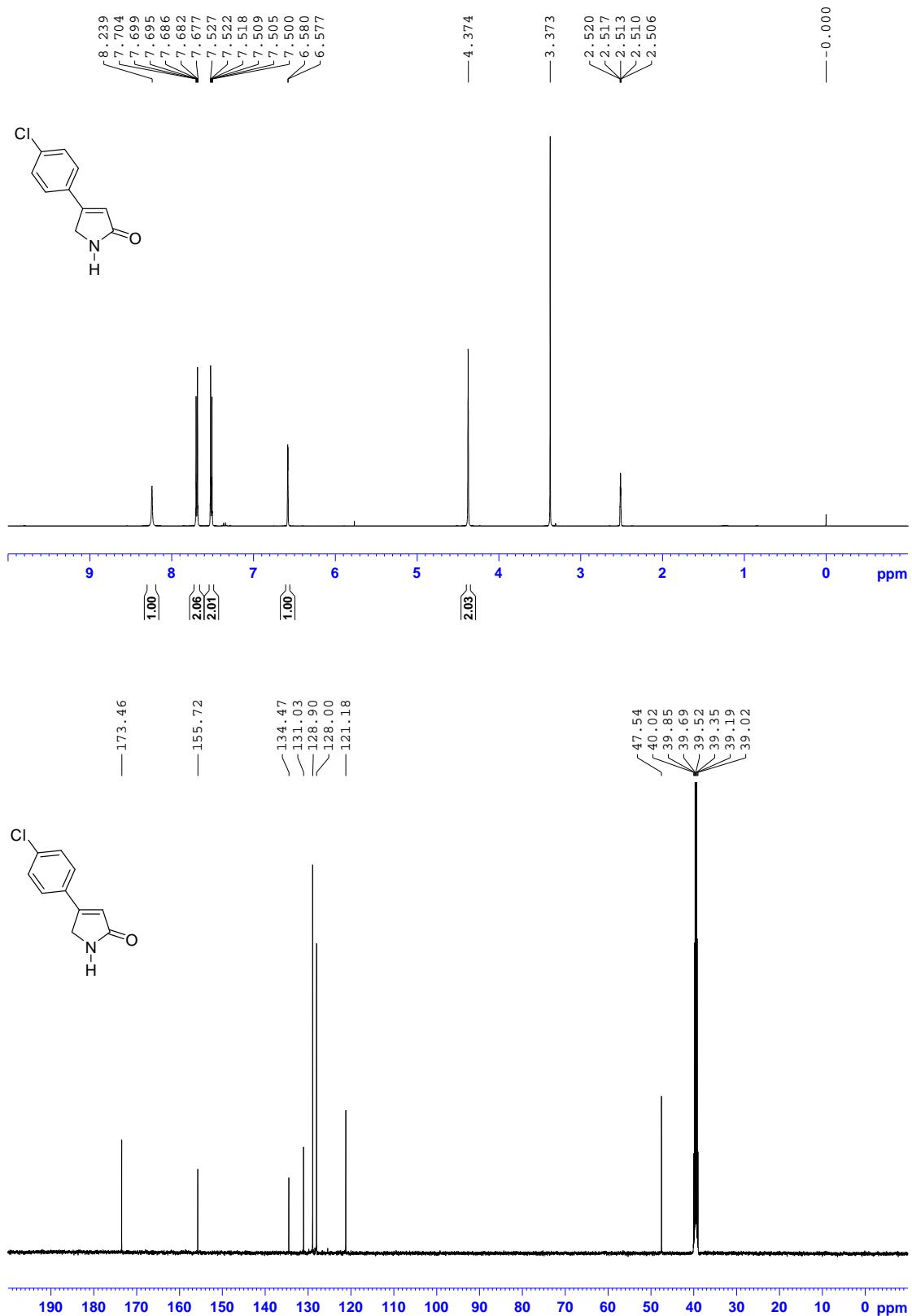
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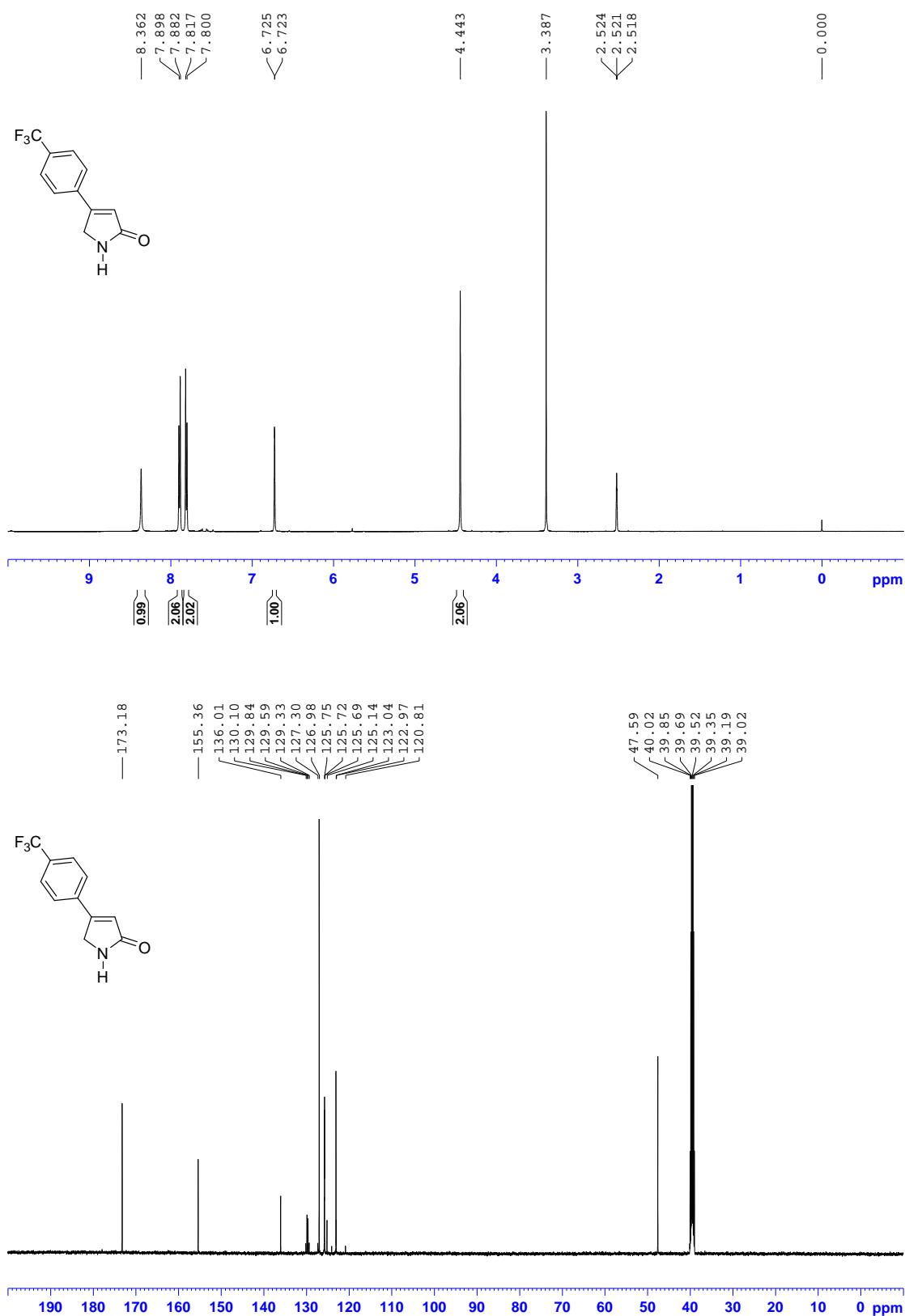
^1H NMR (500 MHz, DMSO- d_6) and ^{13}C NMR { ^1H } (125 MHz, DMSO- d_6) of **1f**:



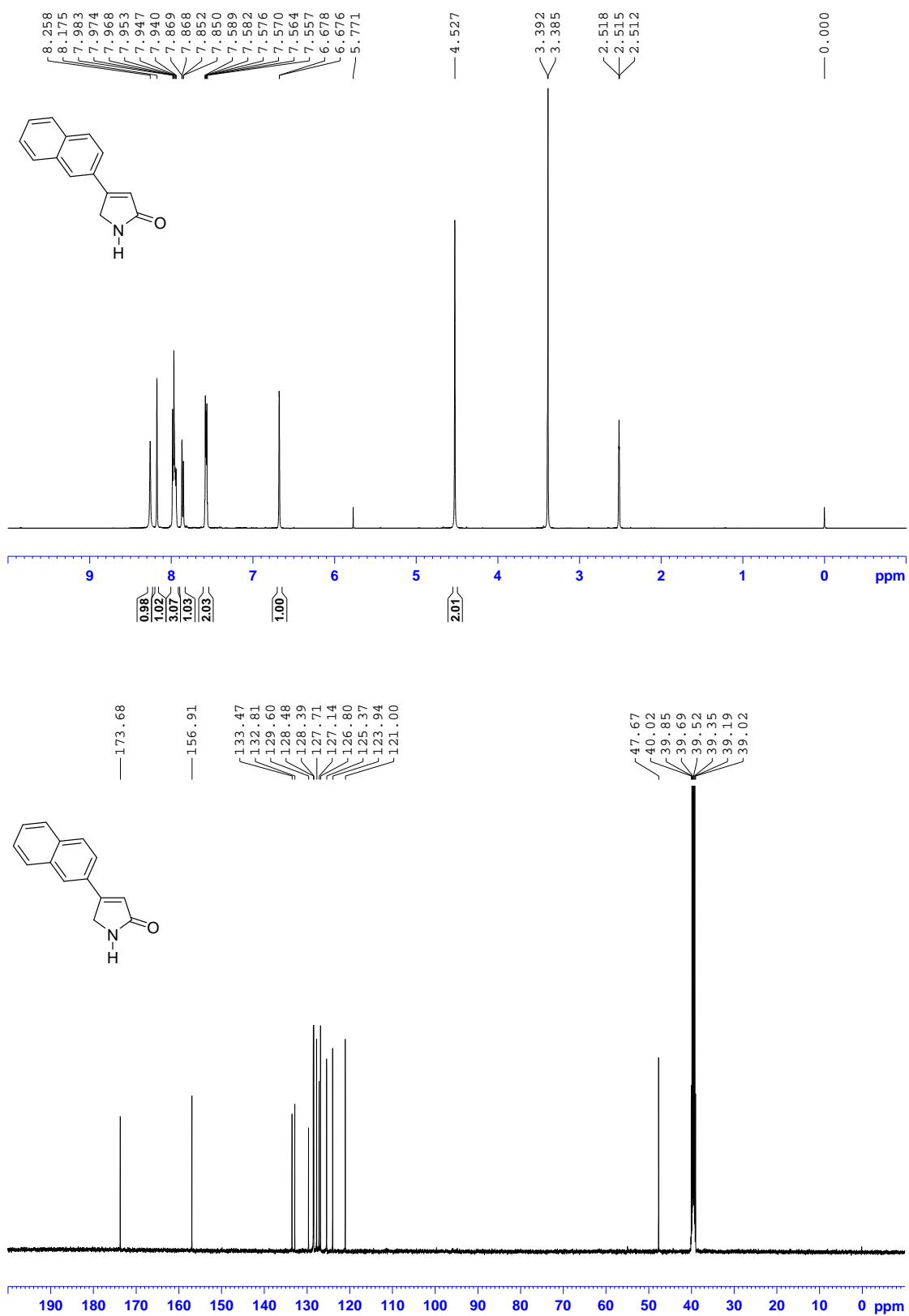
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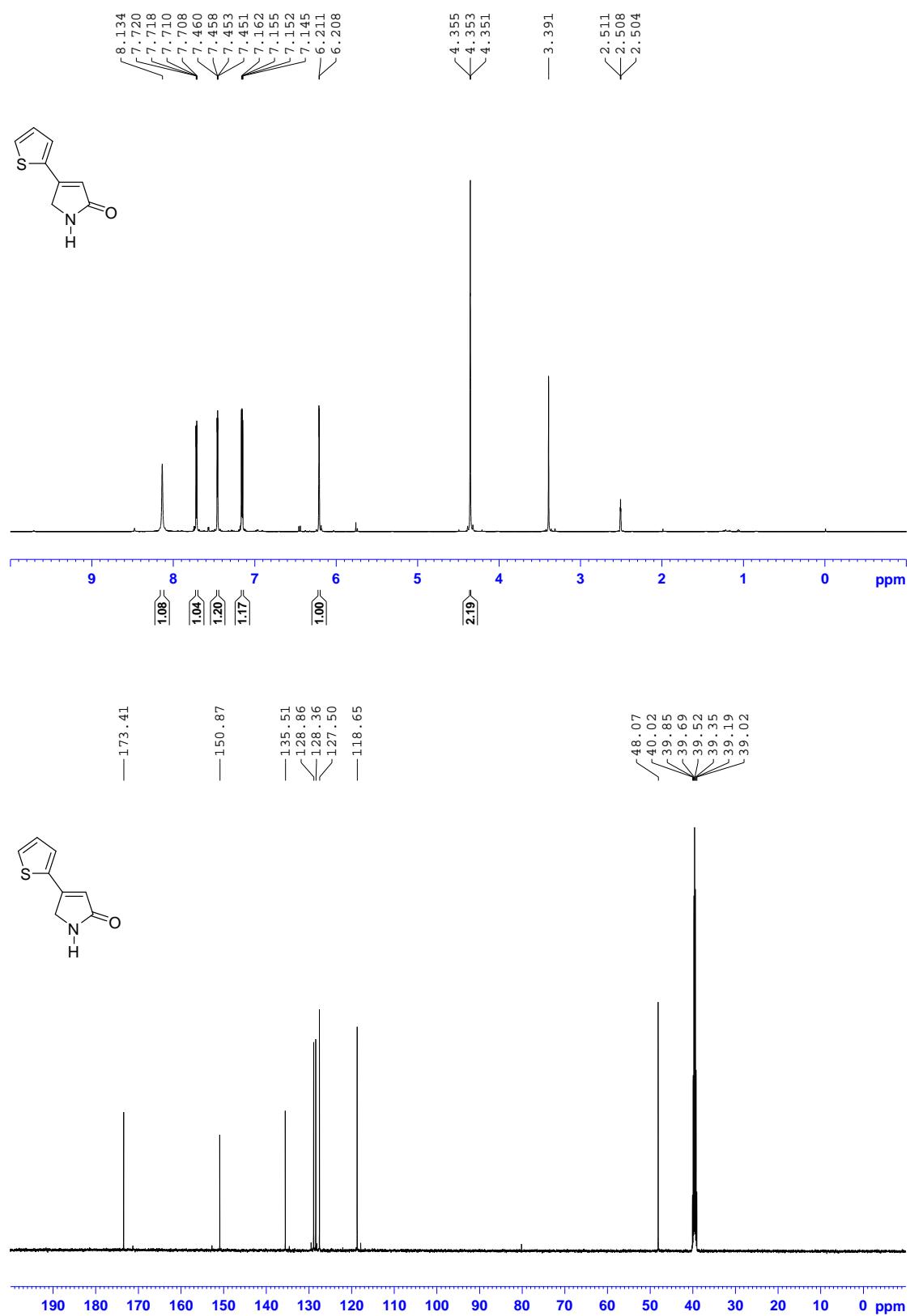
¹H NMR (500 MHz, DMSO-*d*₆) and ¹³C NMR {¹H} (125 MHz, DMSO-*d*₆) of **1h**:



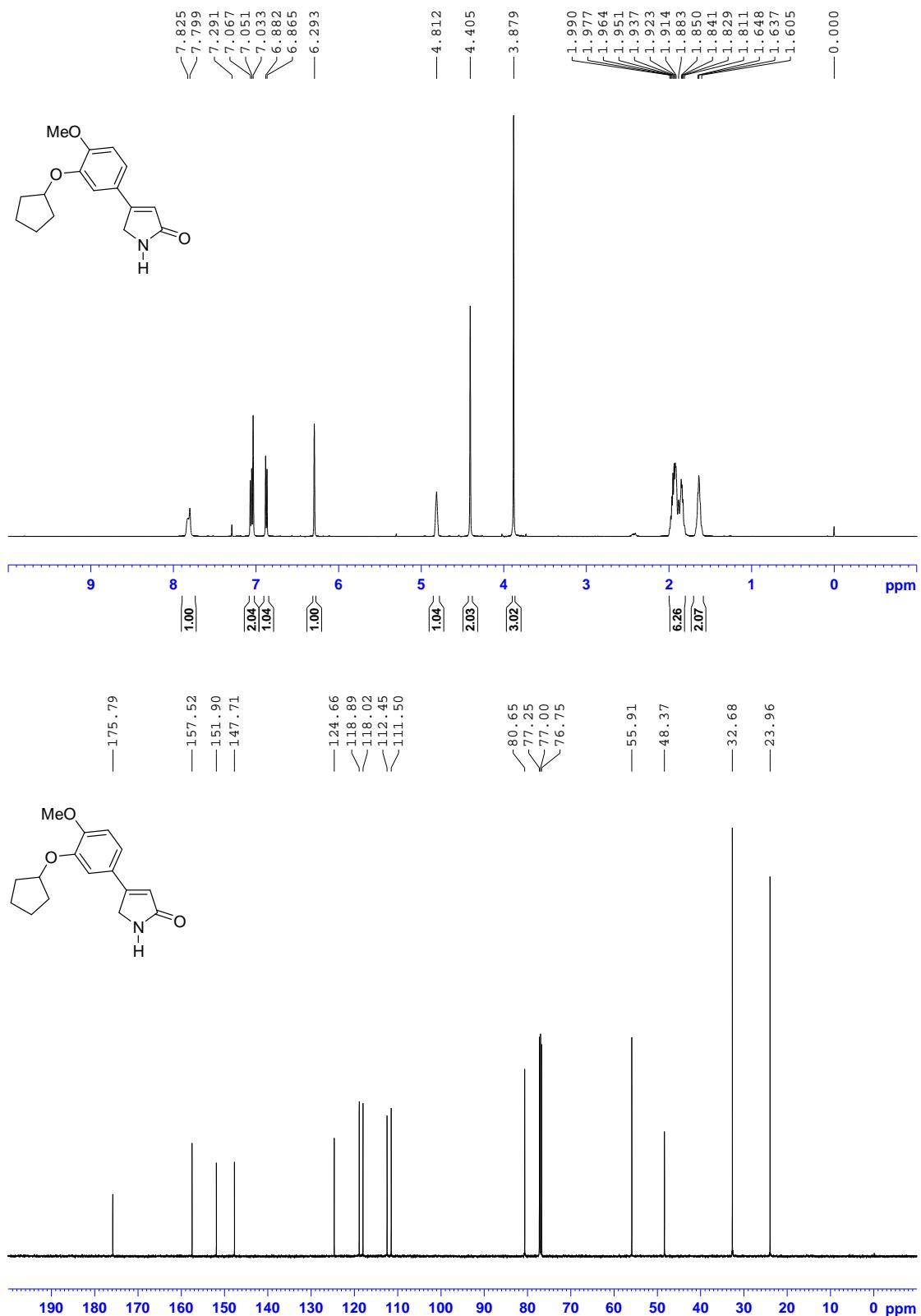
^1H NMR (500 MHz, DMSO- d_6) and ^{13}C NMR { ^1H } (125 MHz, DMSO- d_6) of **1i**:



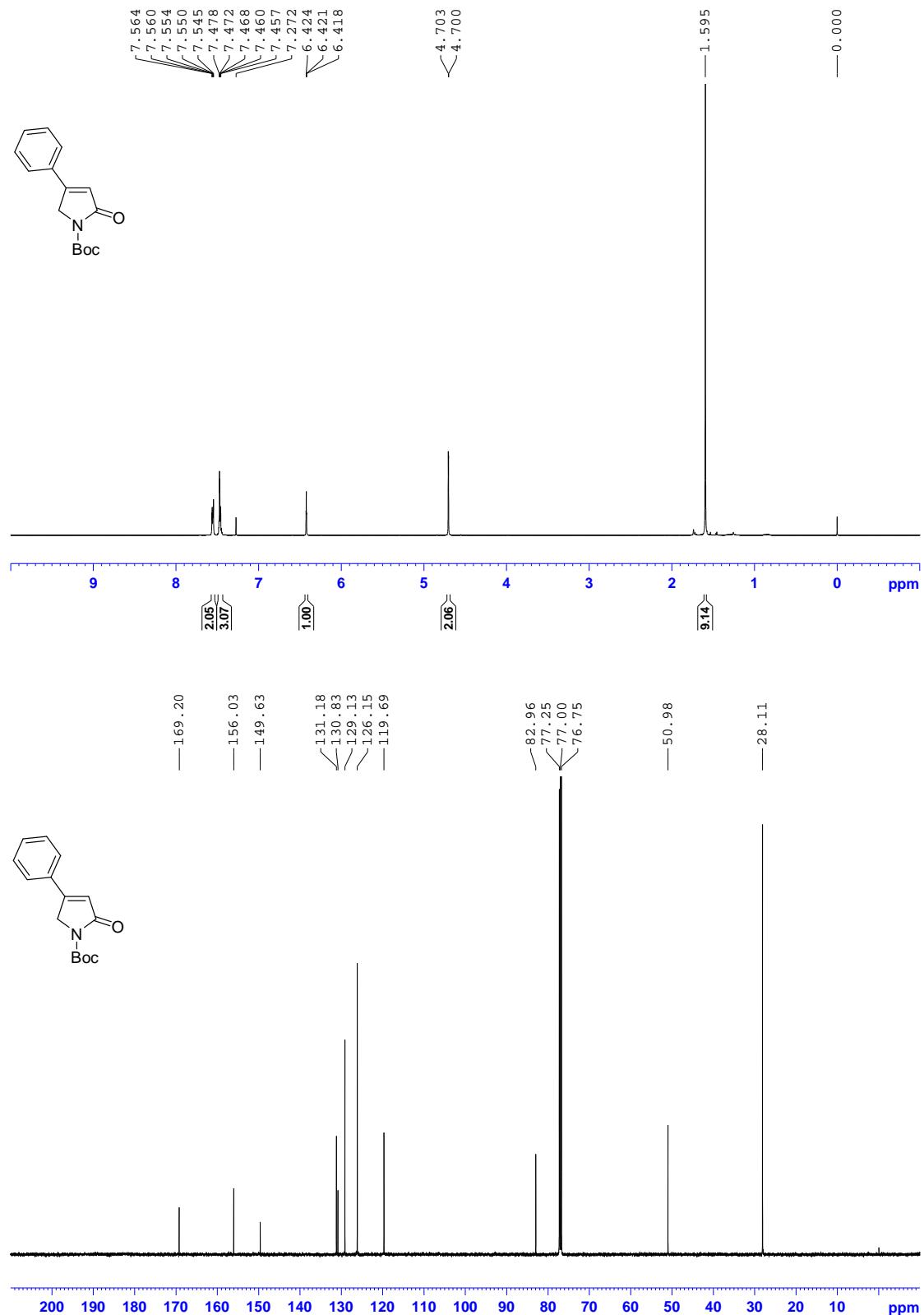
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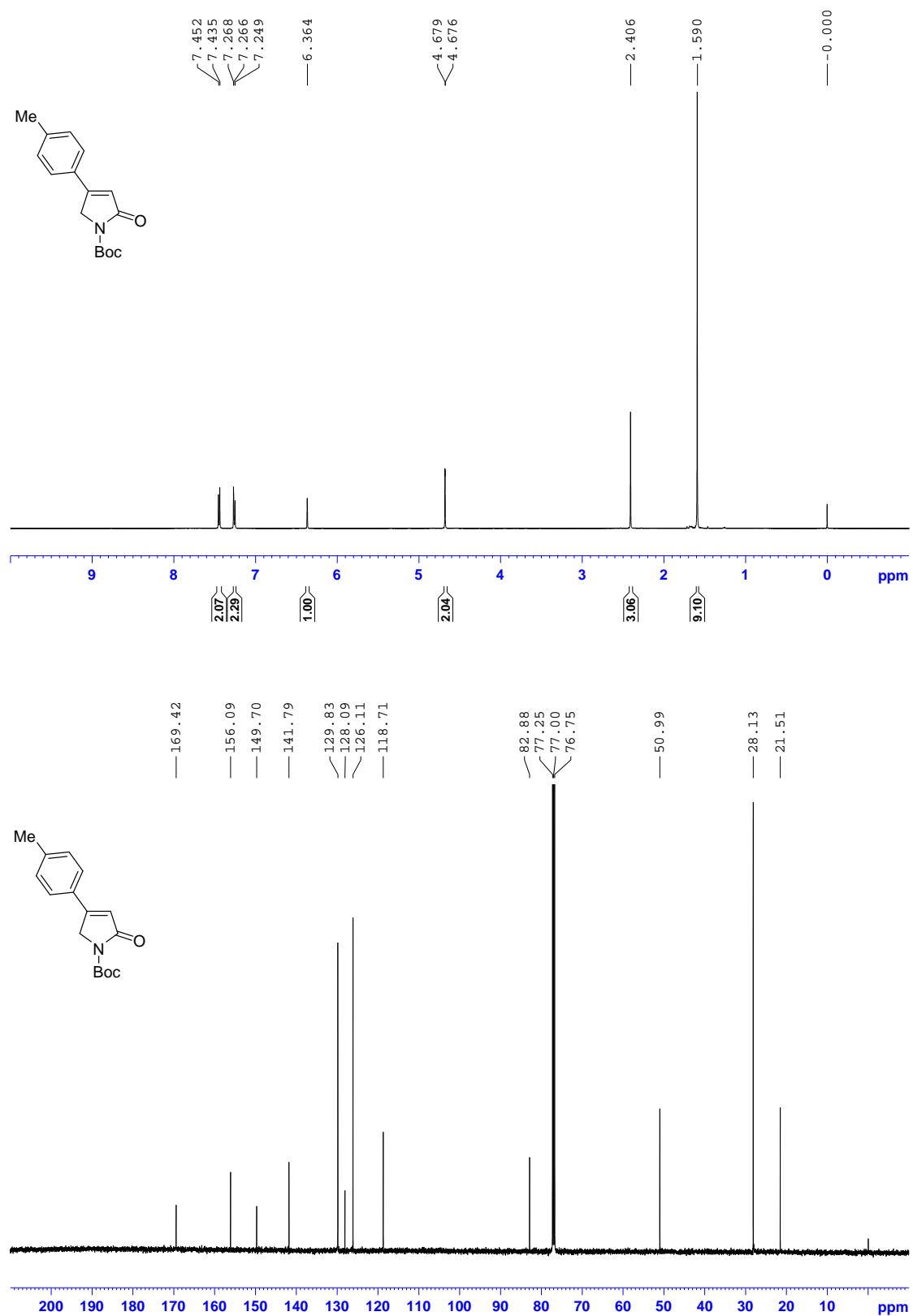
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR $\{\text{H}\}$ (125 MHz, CDCl_3) of **1k**:



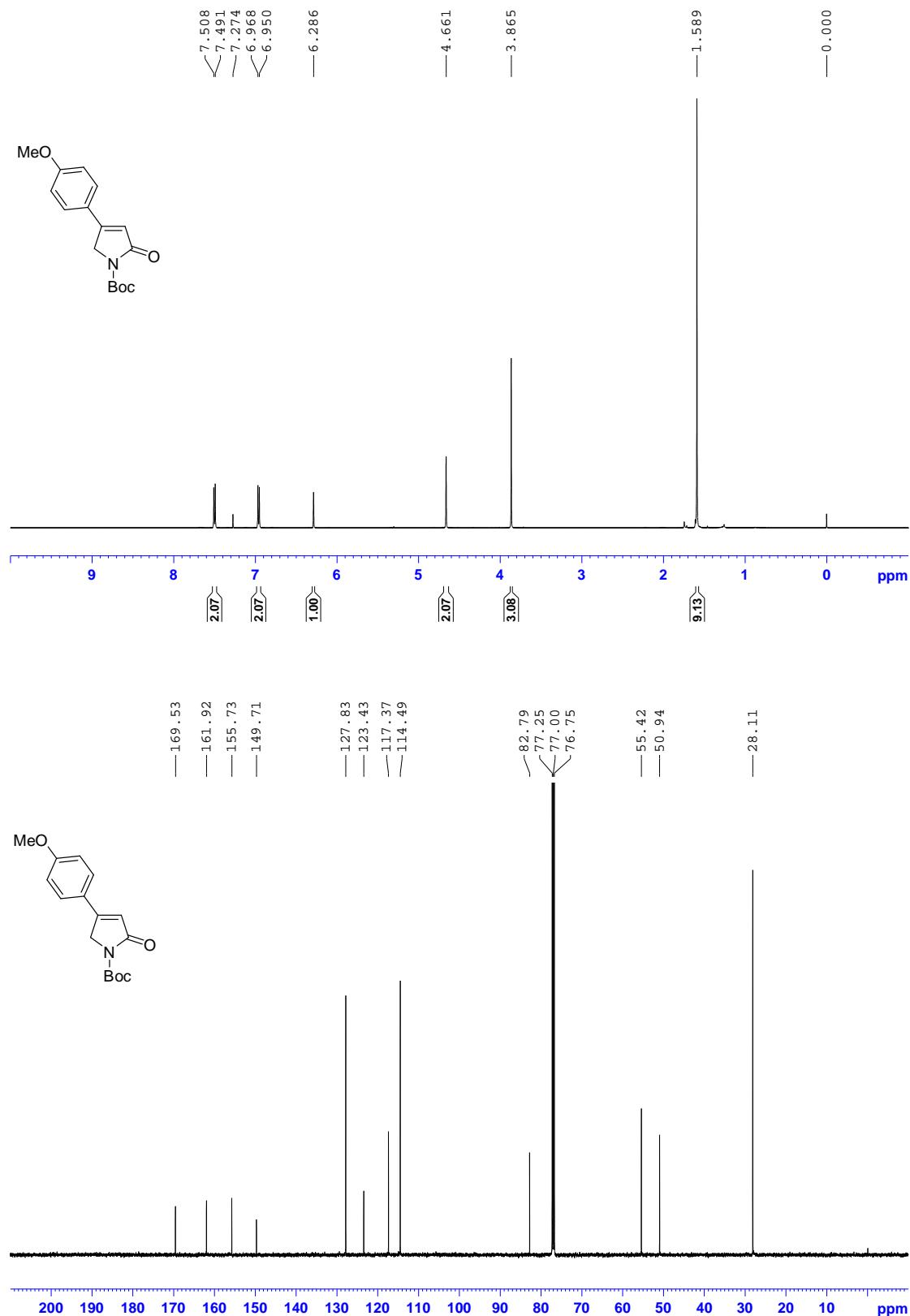
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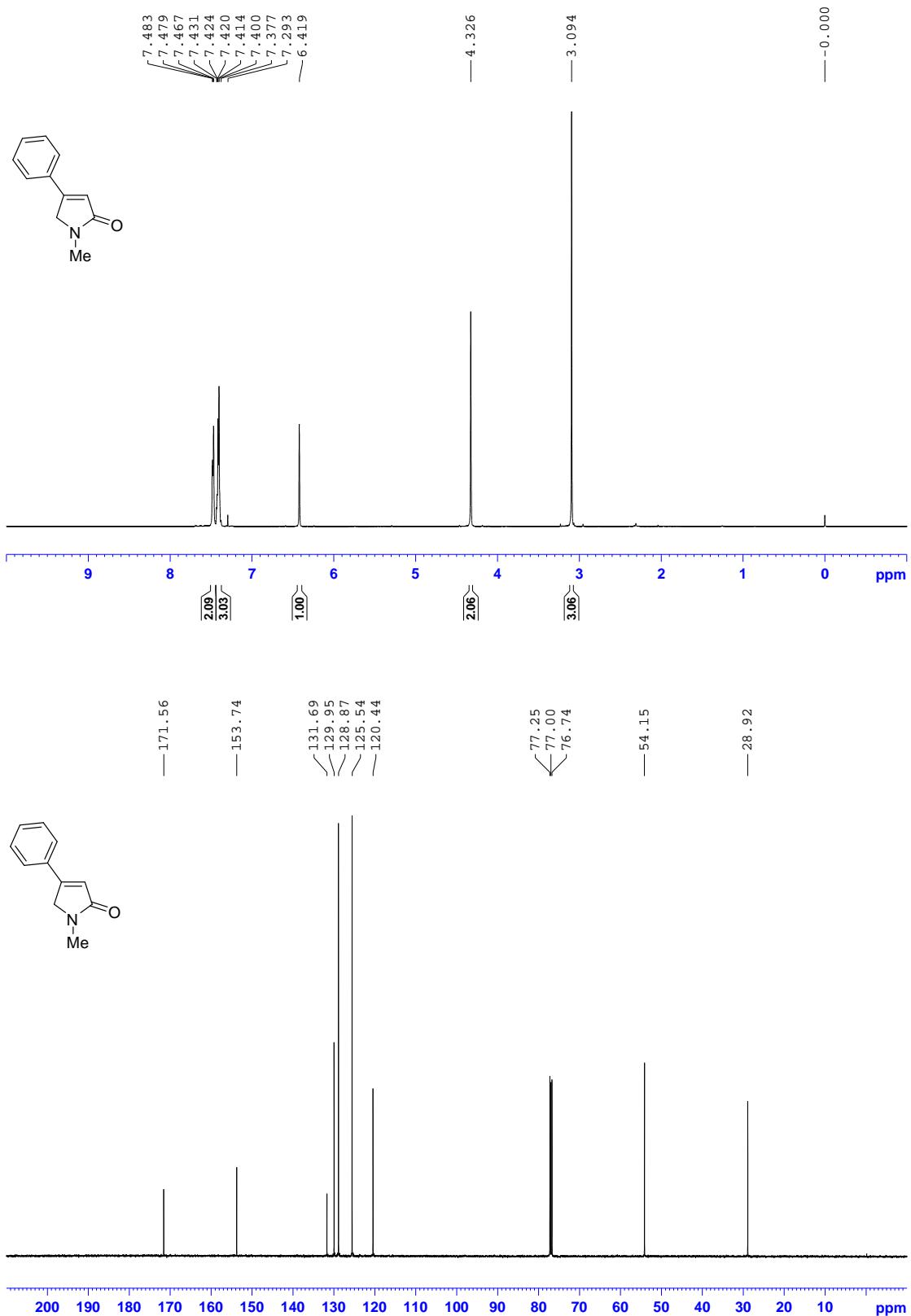
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **1m**:



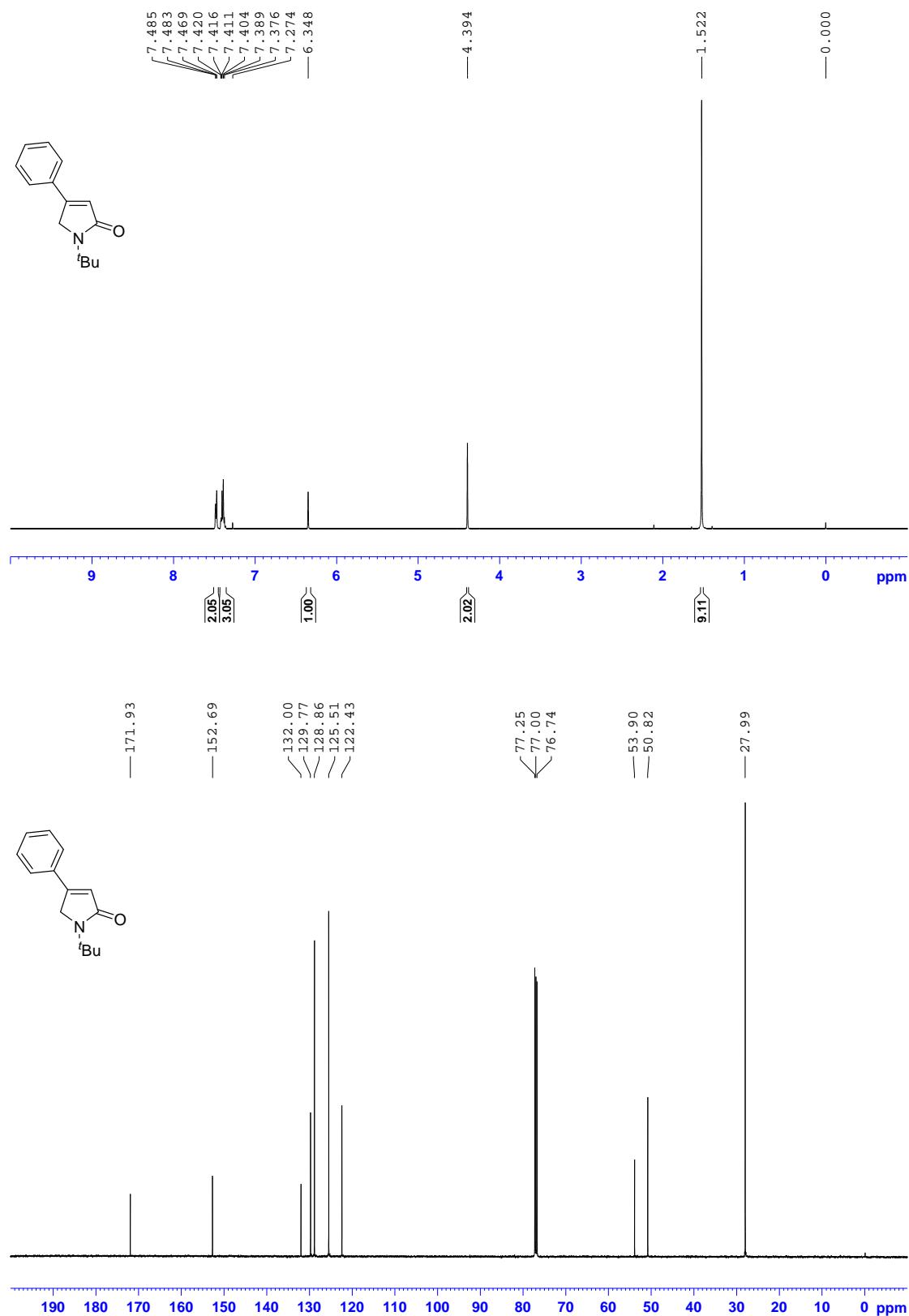
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **1n**:



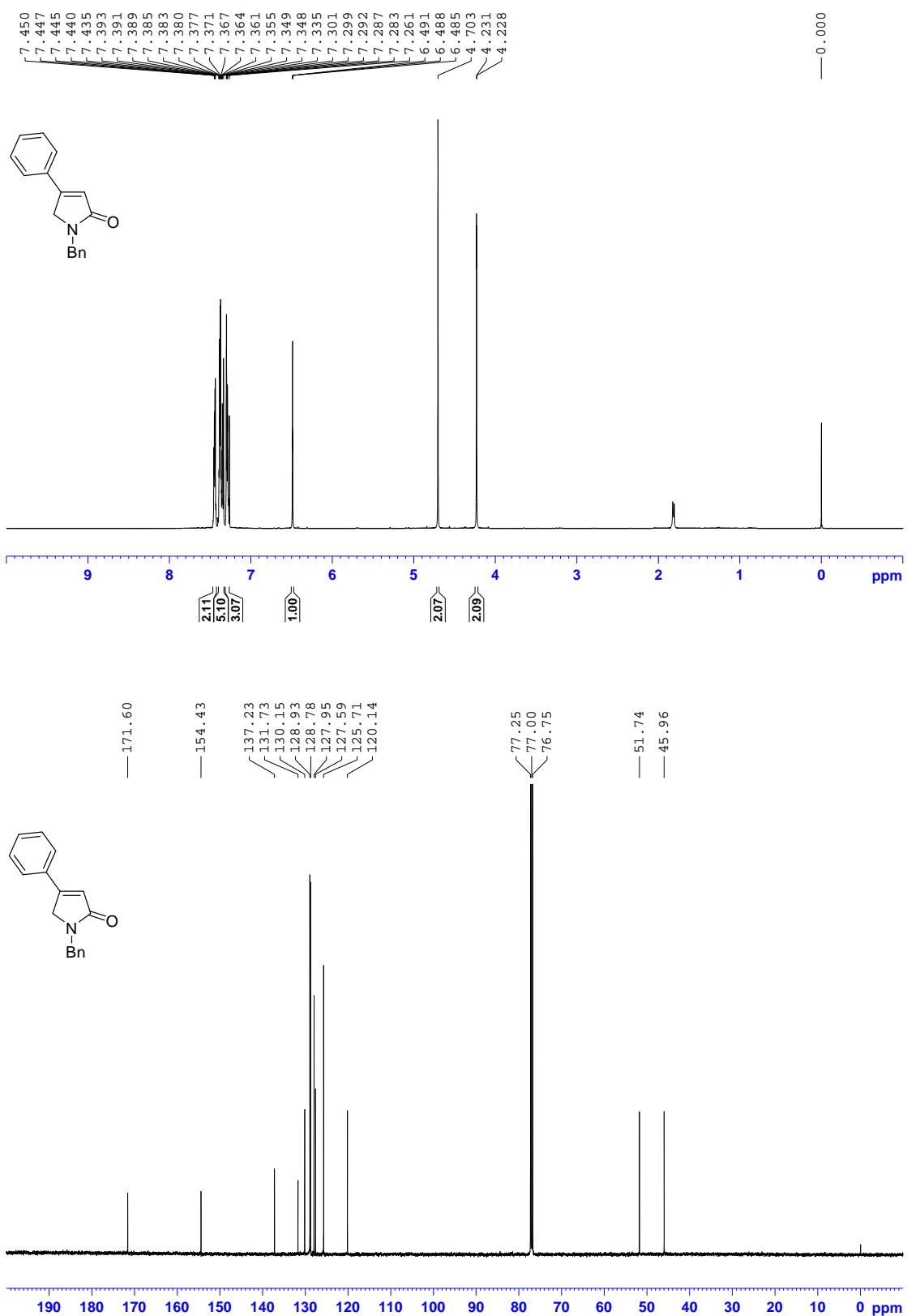
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **1o**:



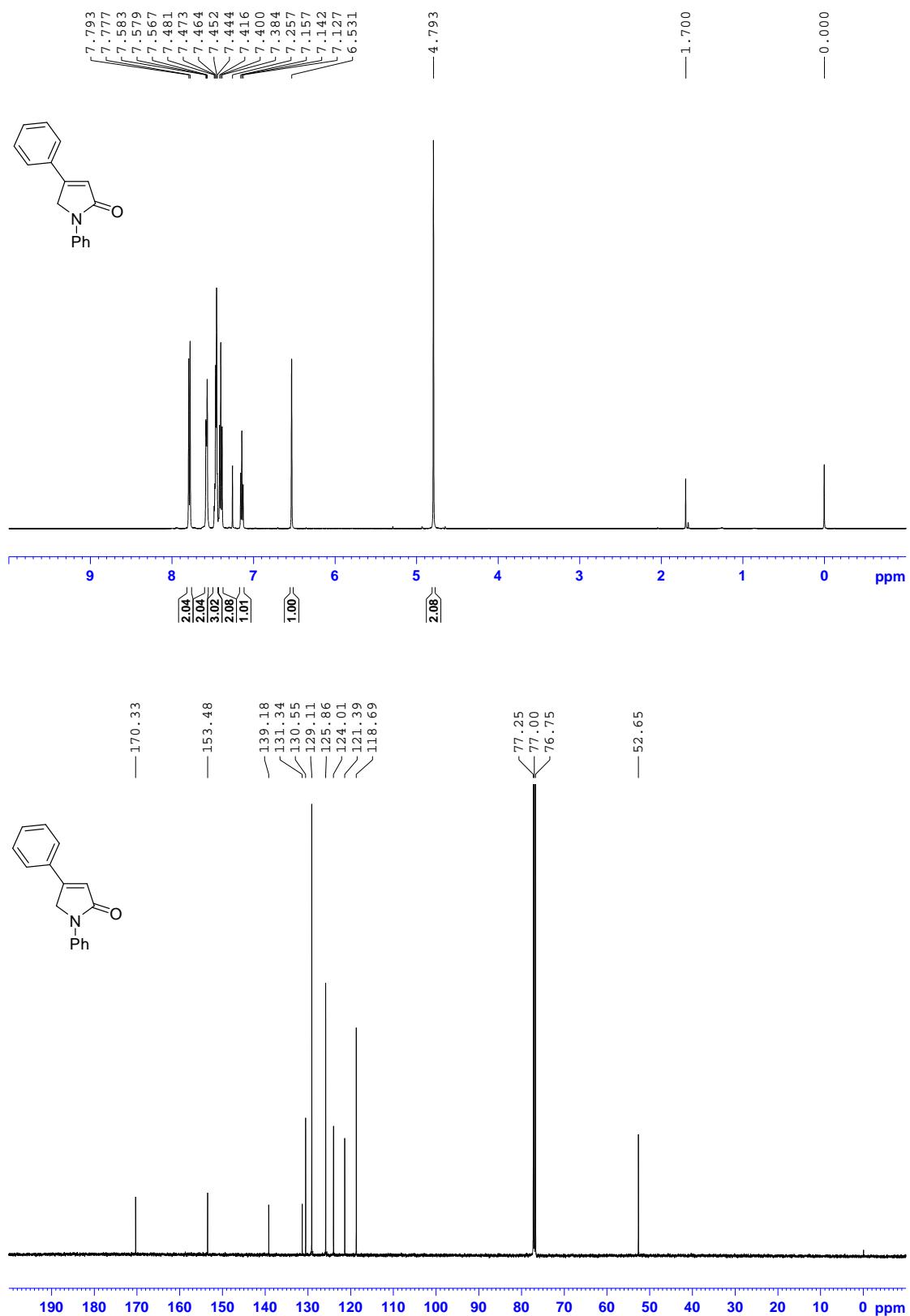
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **1p**:



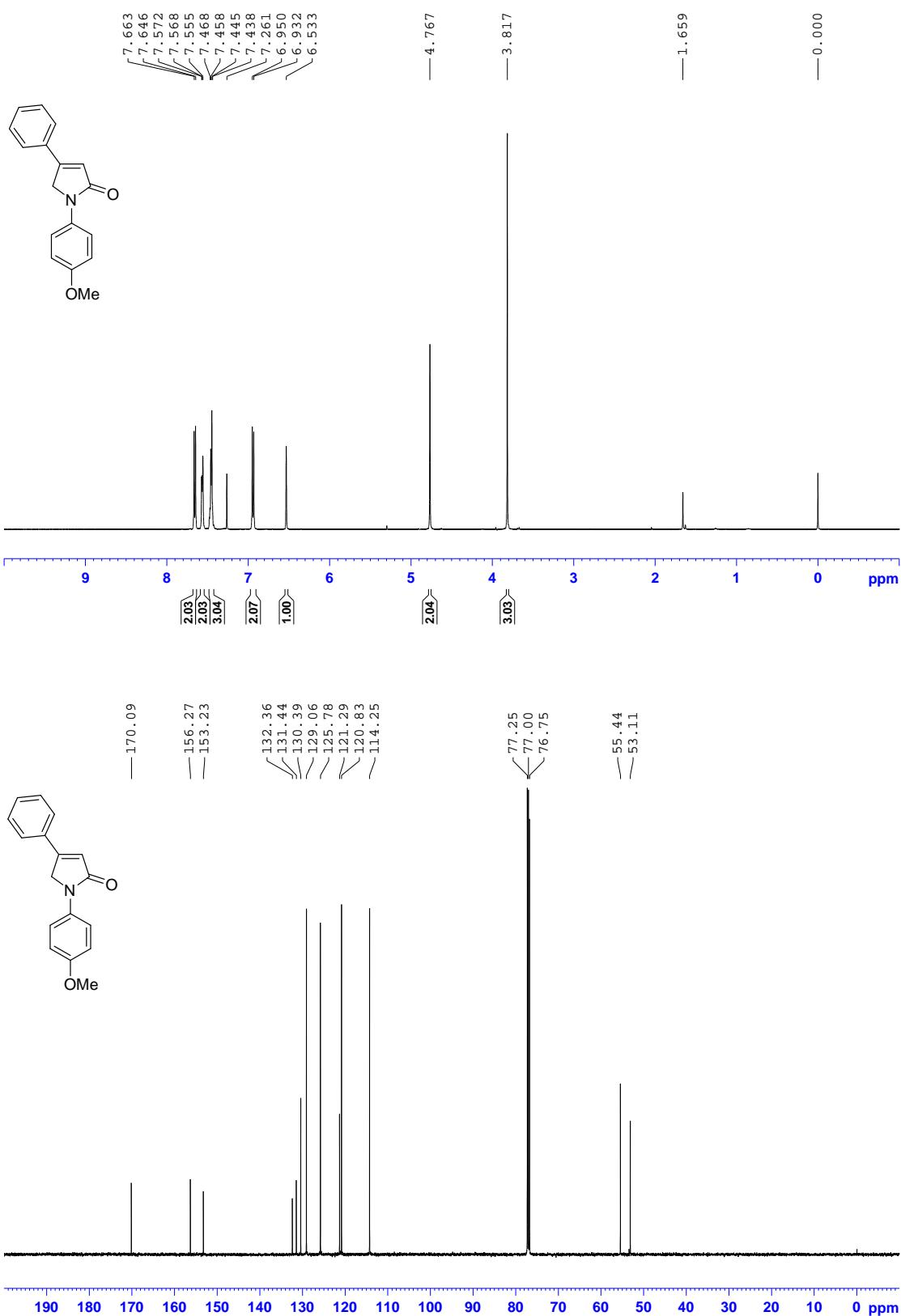
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **1q**:



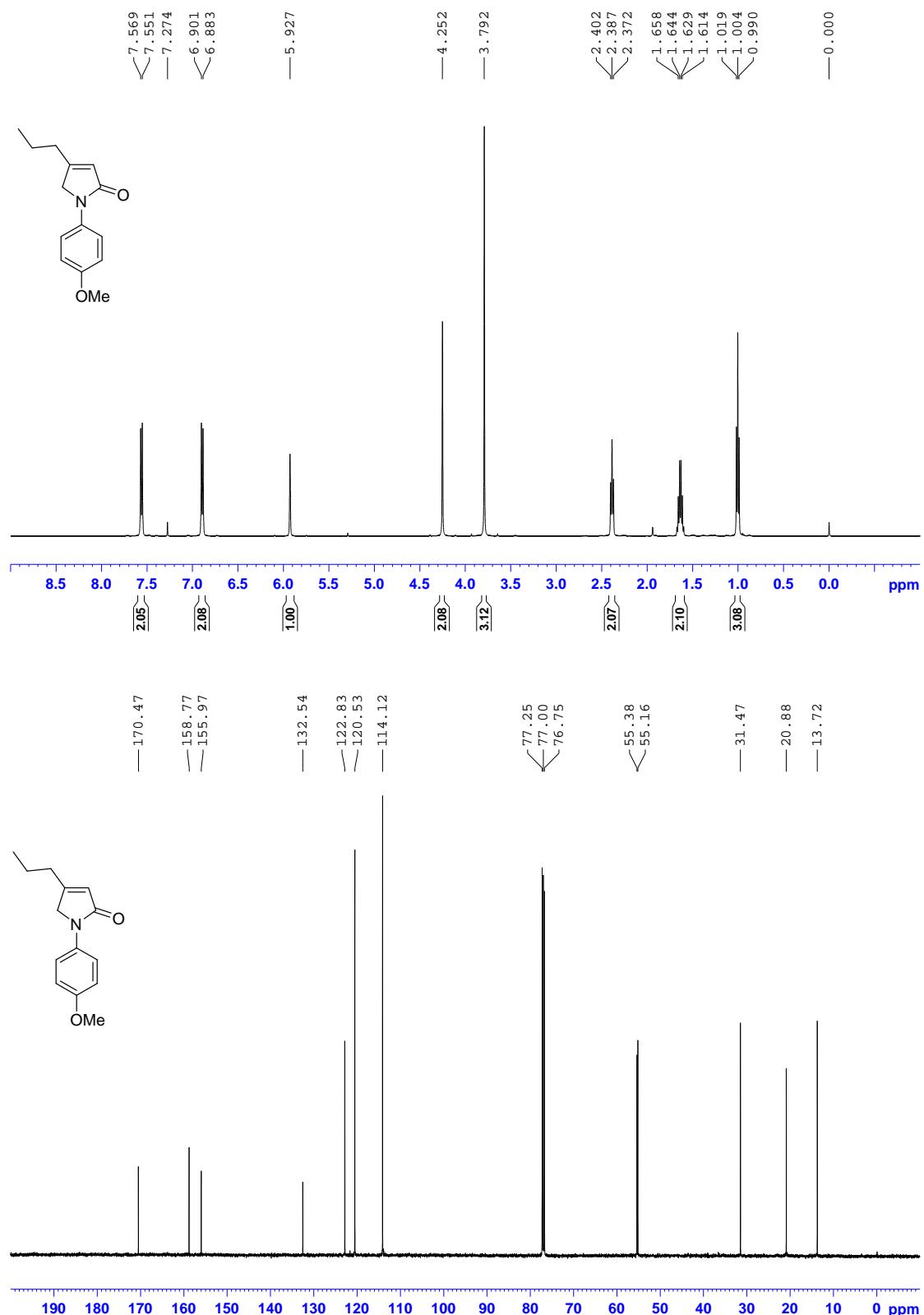
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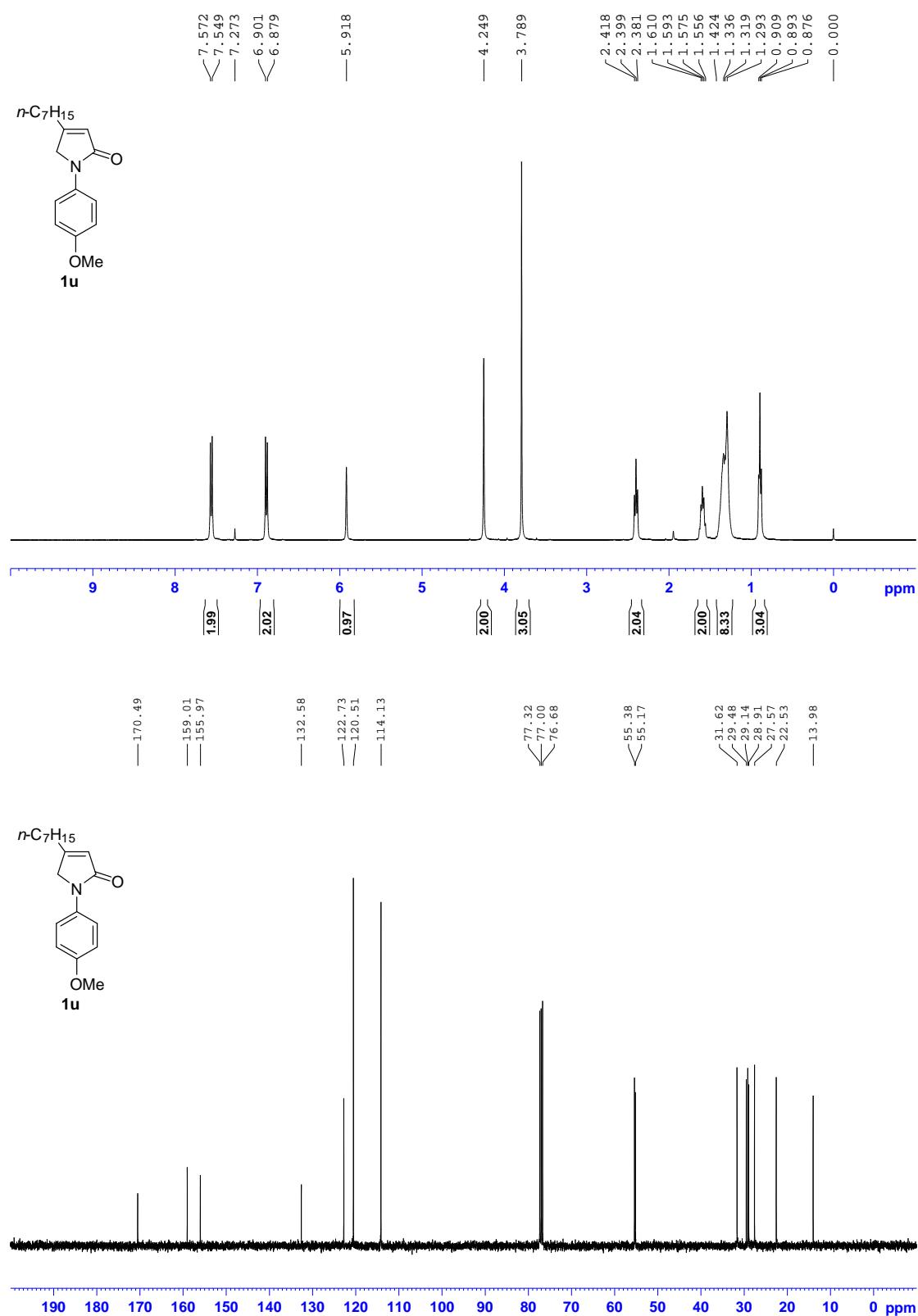
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (^1H) (125 MHz, CDCl_3) of **1s**:



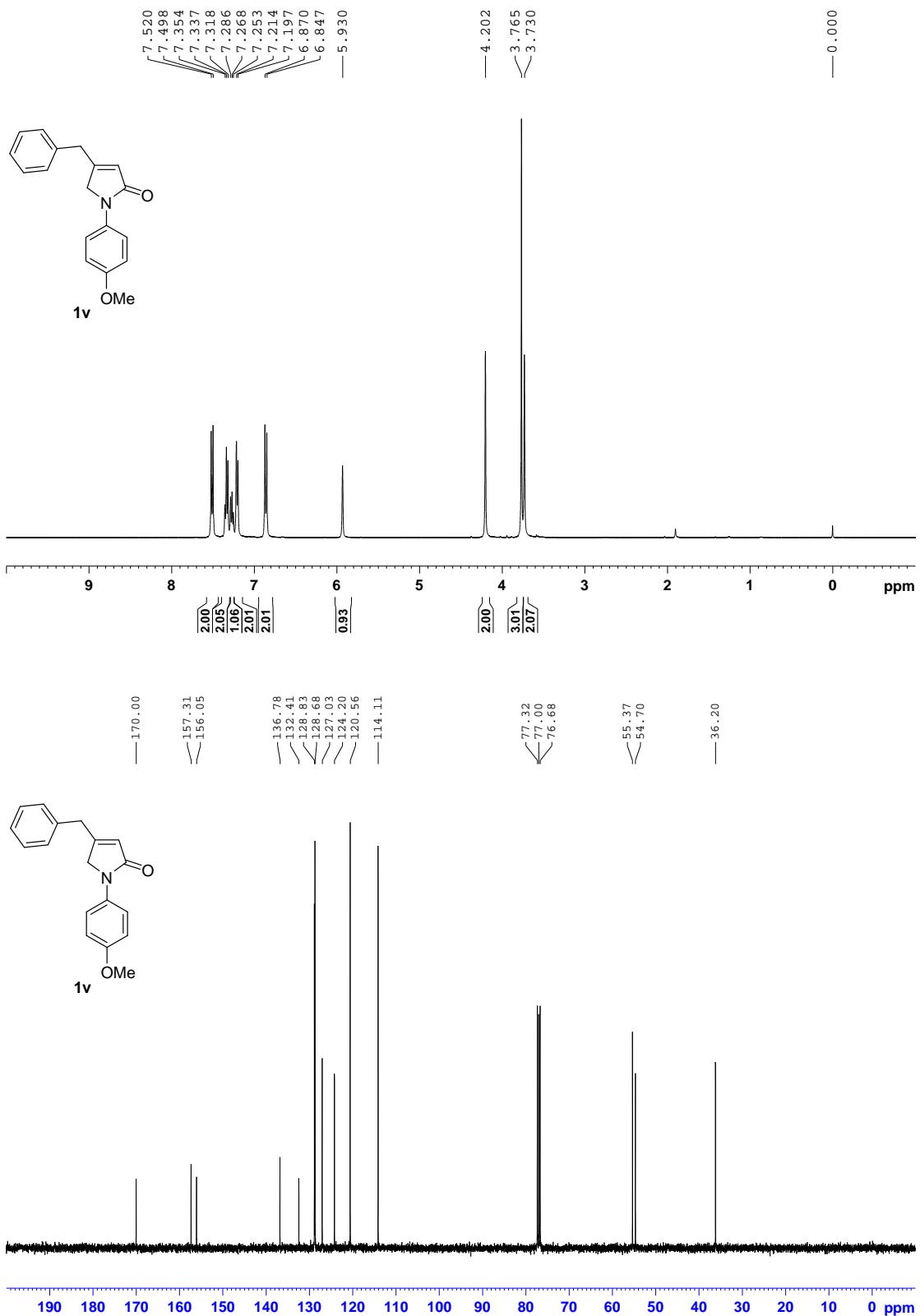
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **1t**:



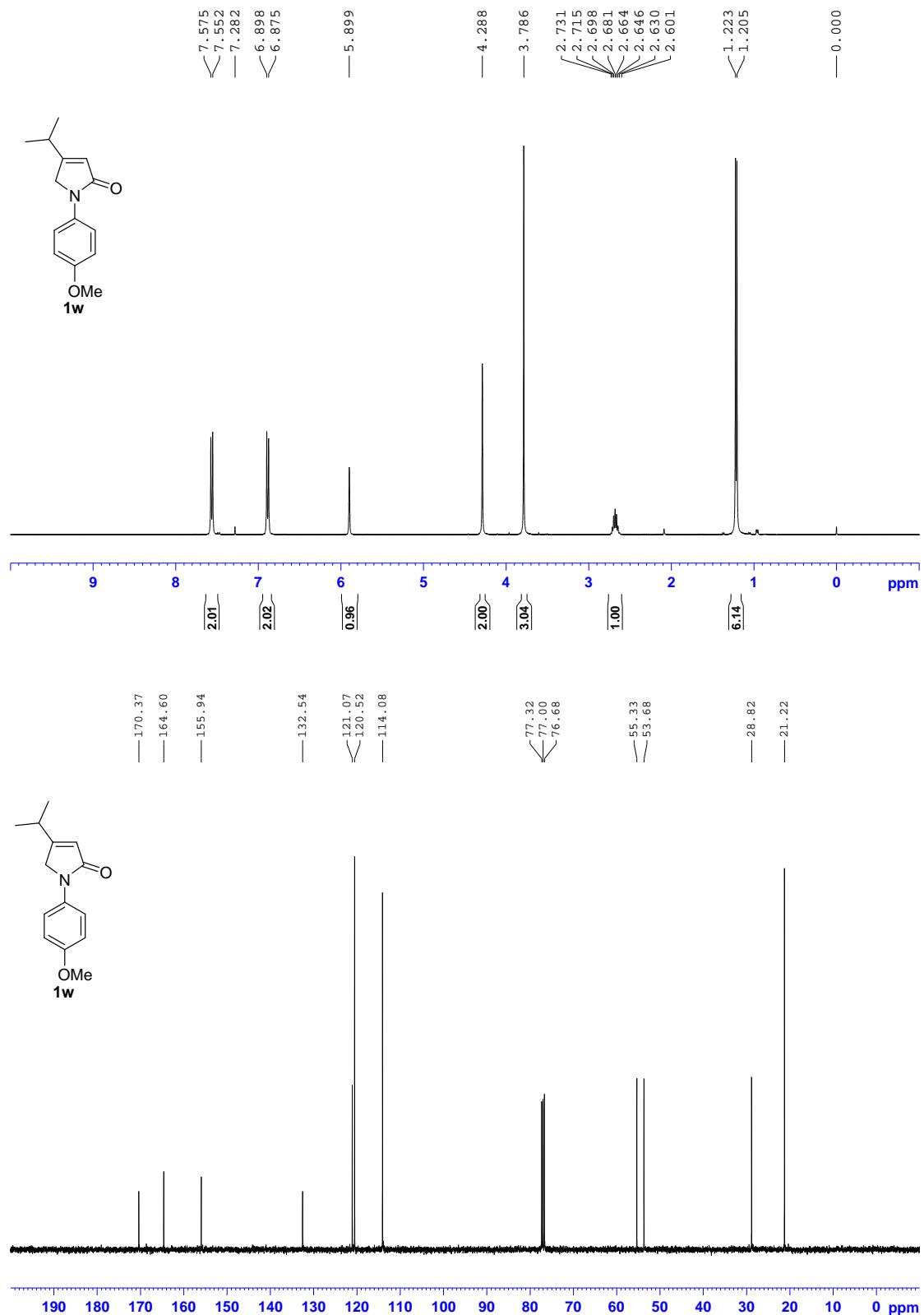
^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR { ^1H } (100 MHz, CDCl_3) of **1u**:



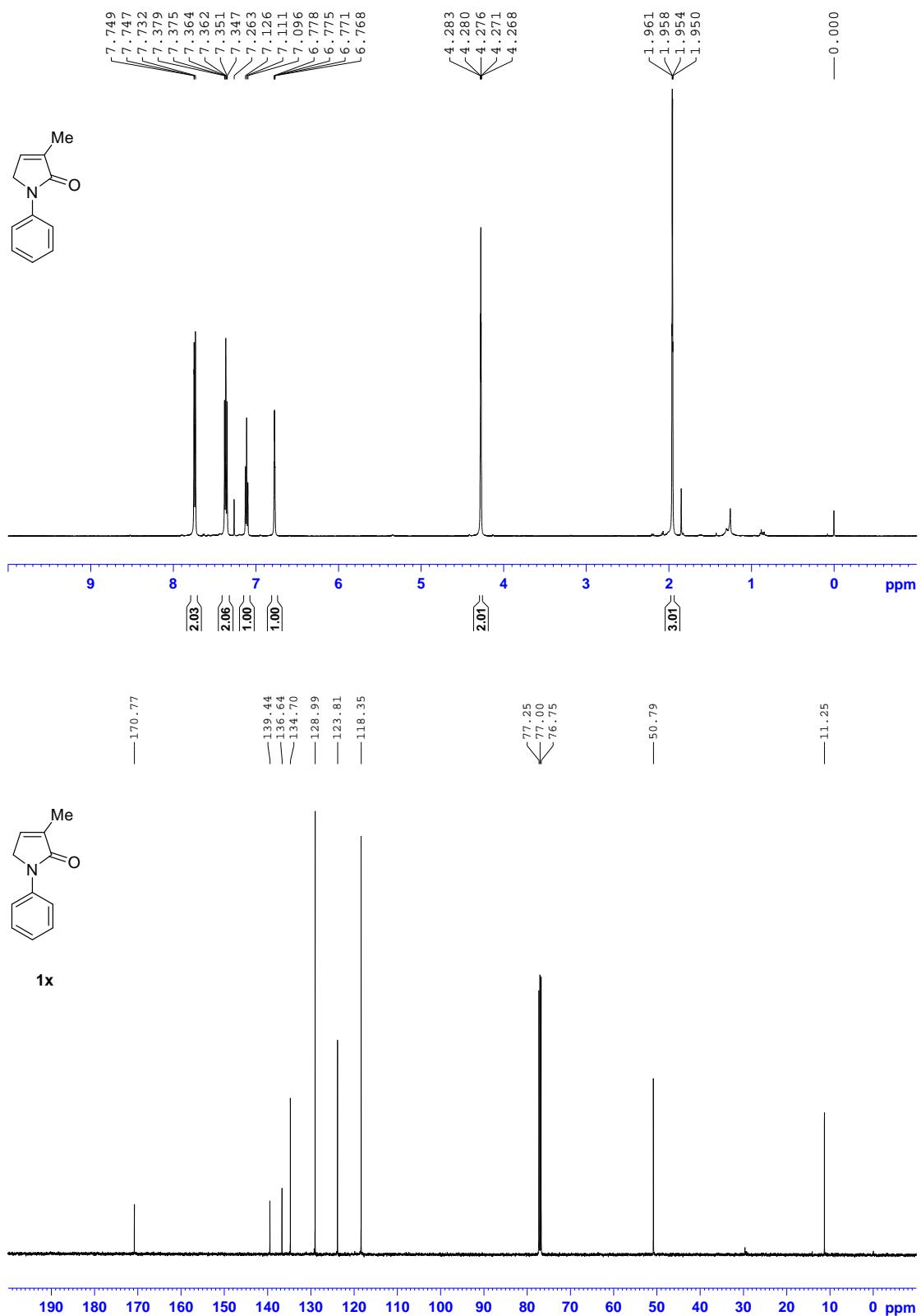
^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR { ^1H } (100 MHz, CDCl_3) of **1v**:



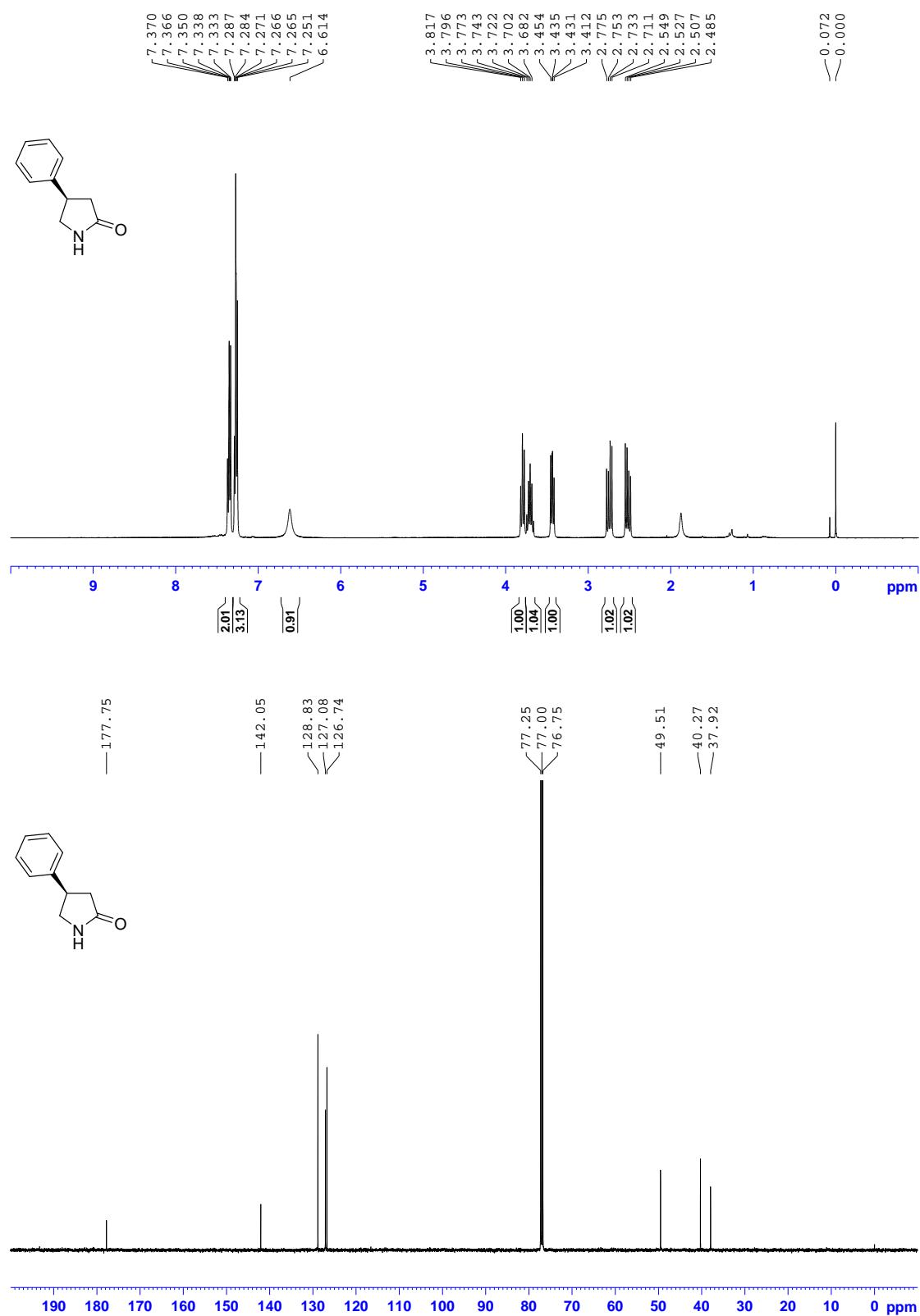
^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR { ^1H } (100 MHz, CDCl_3) of **1w**:



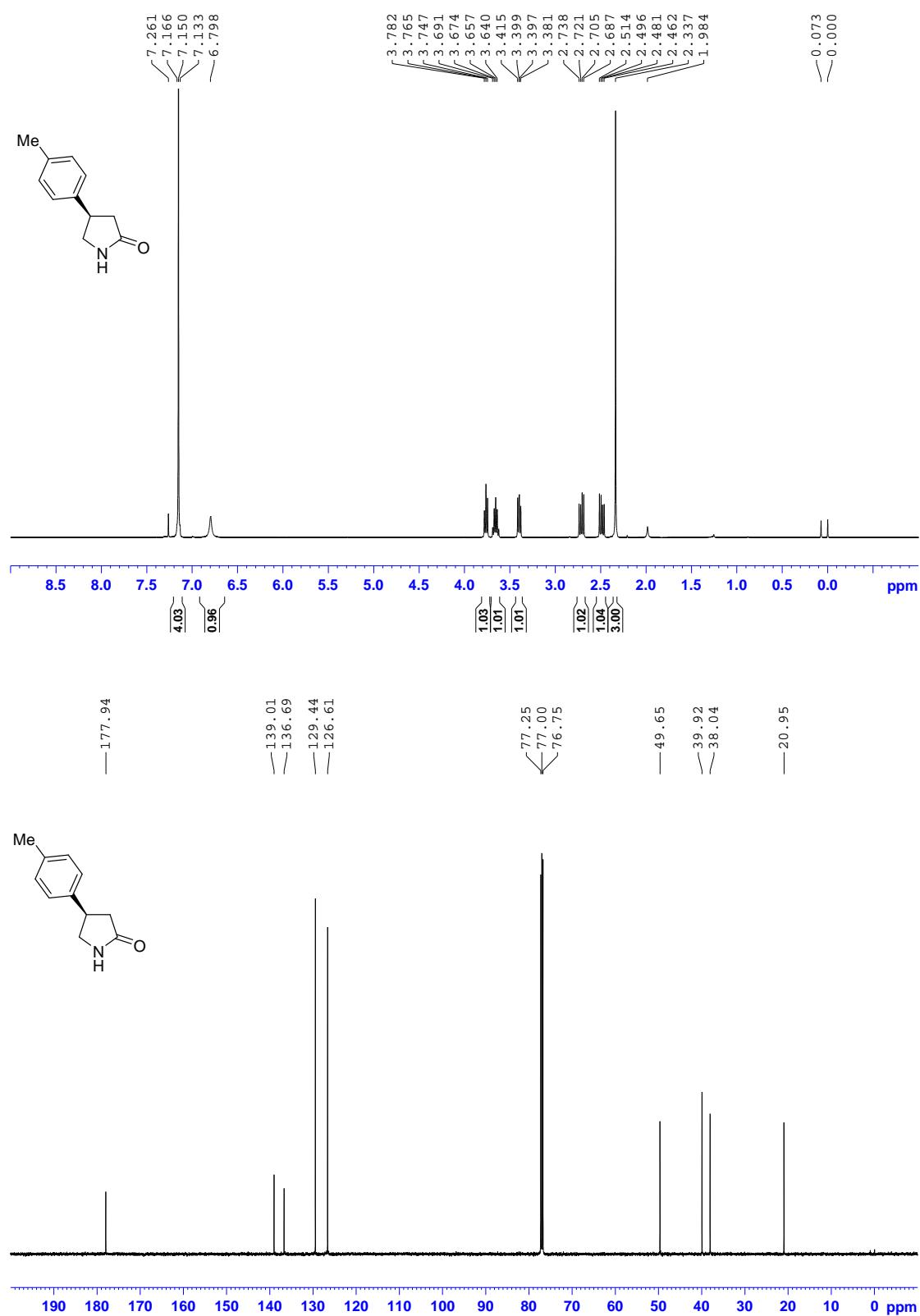
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **1x**:



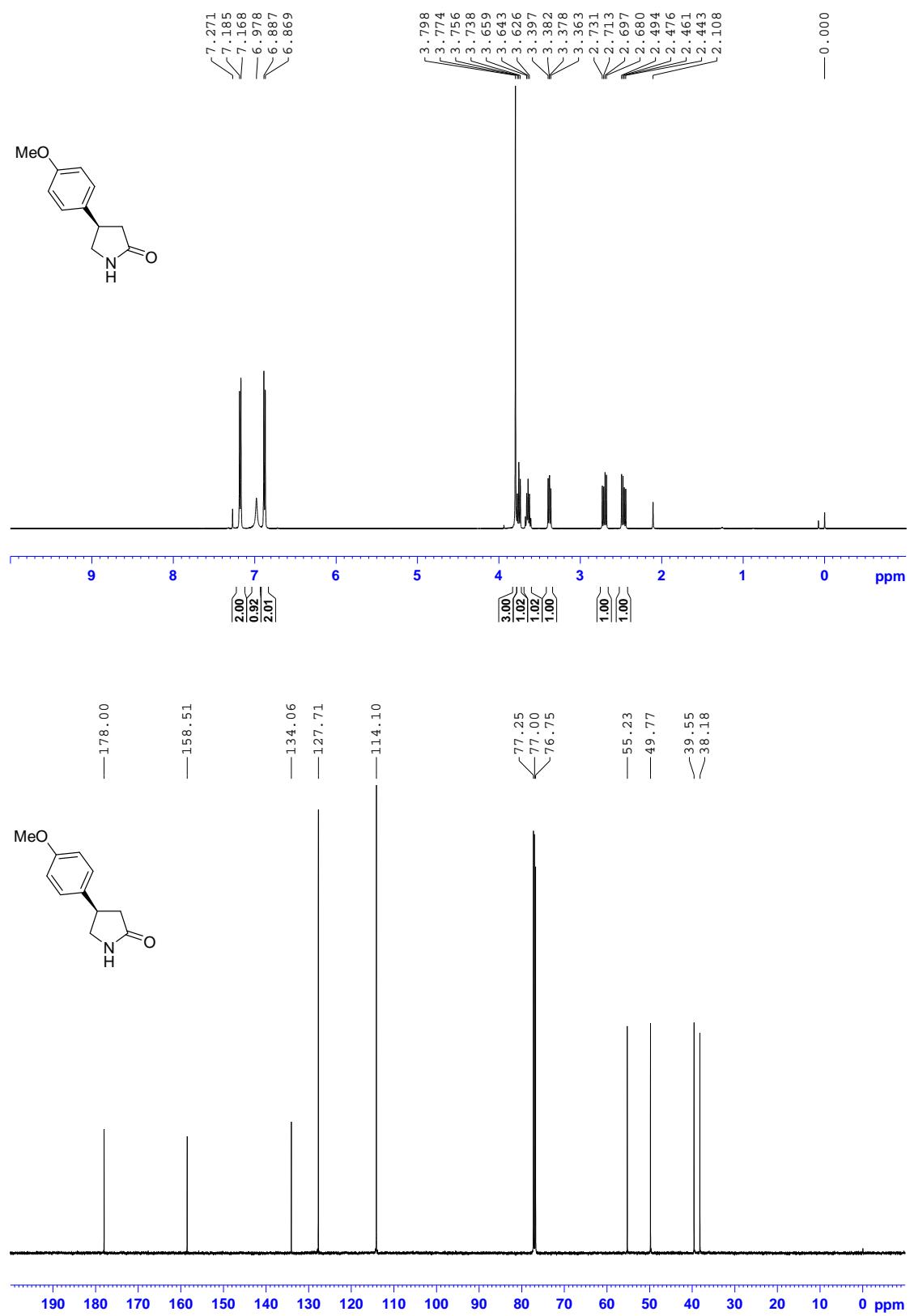
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR $\{\text{H}\}$ (125 MHz, CDCl_3) of **2a**:



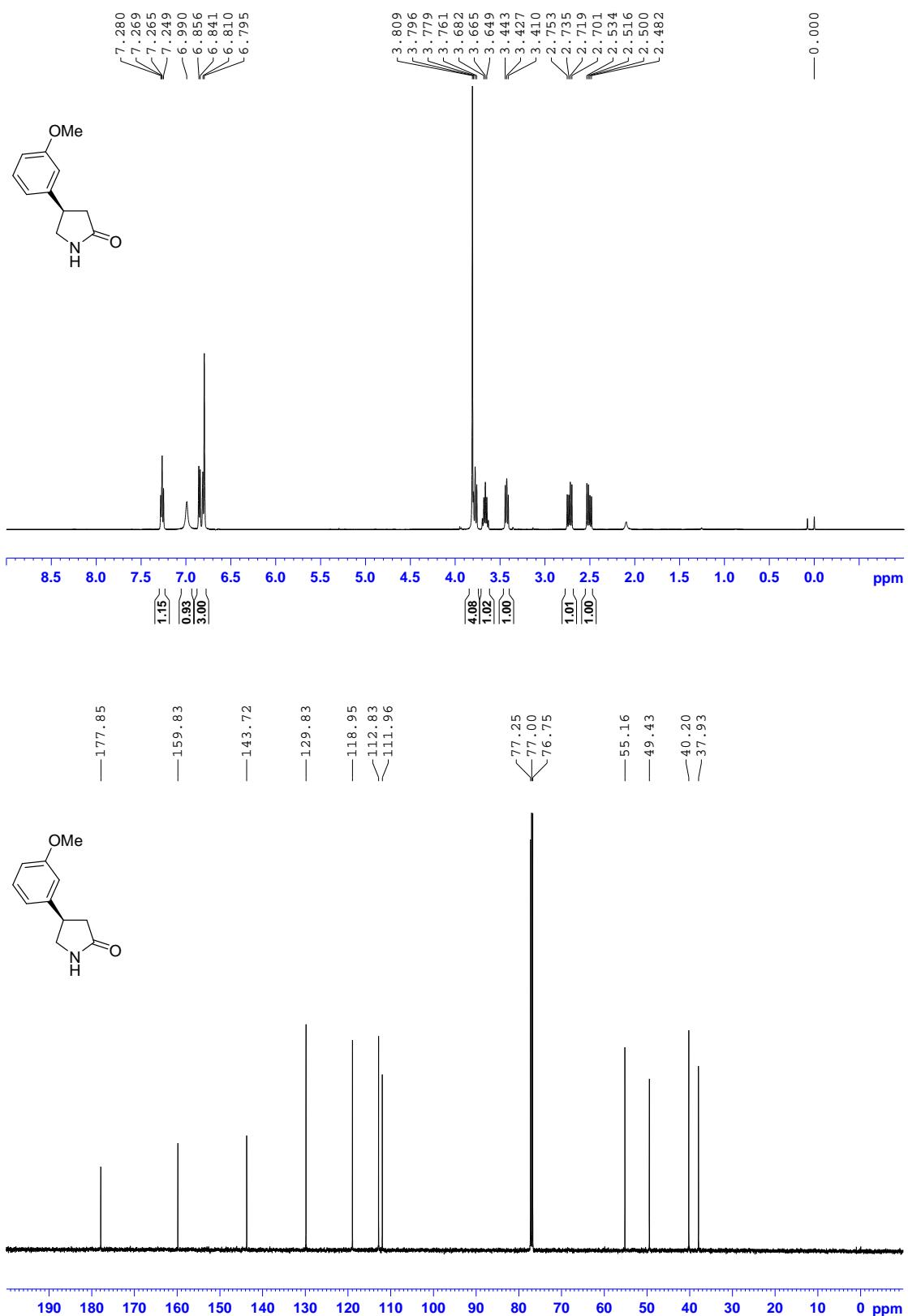
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2b**:



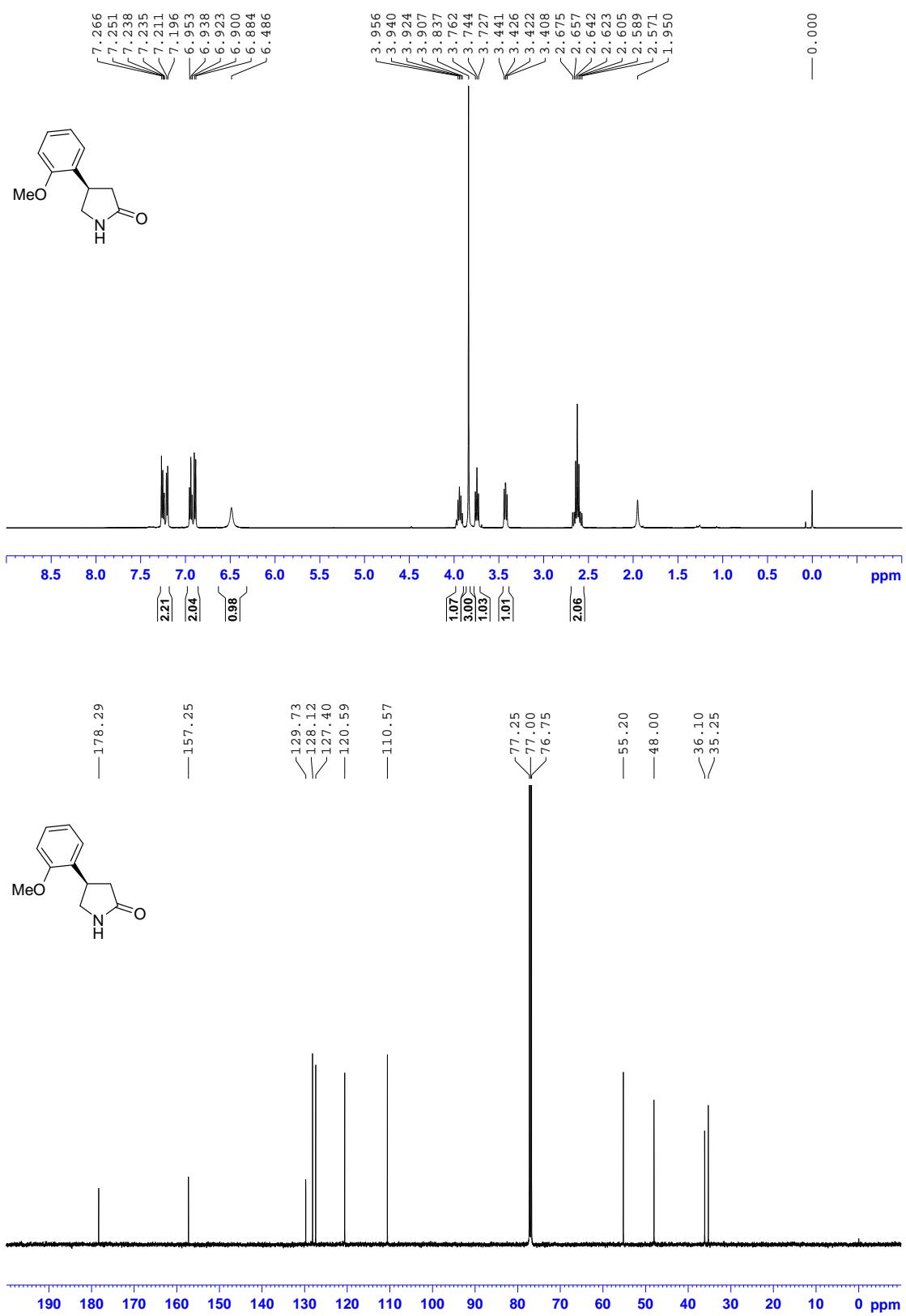
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2c**:



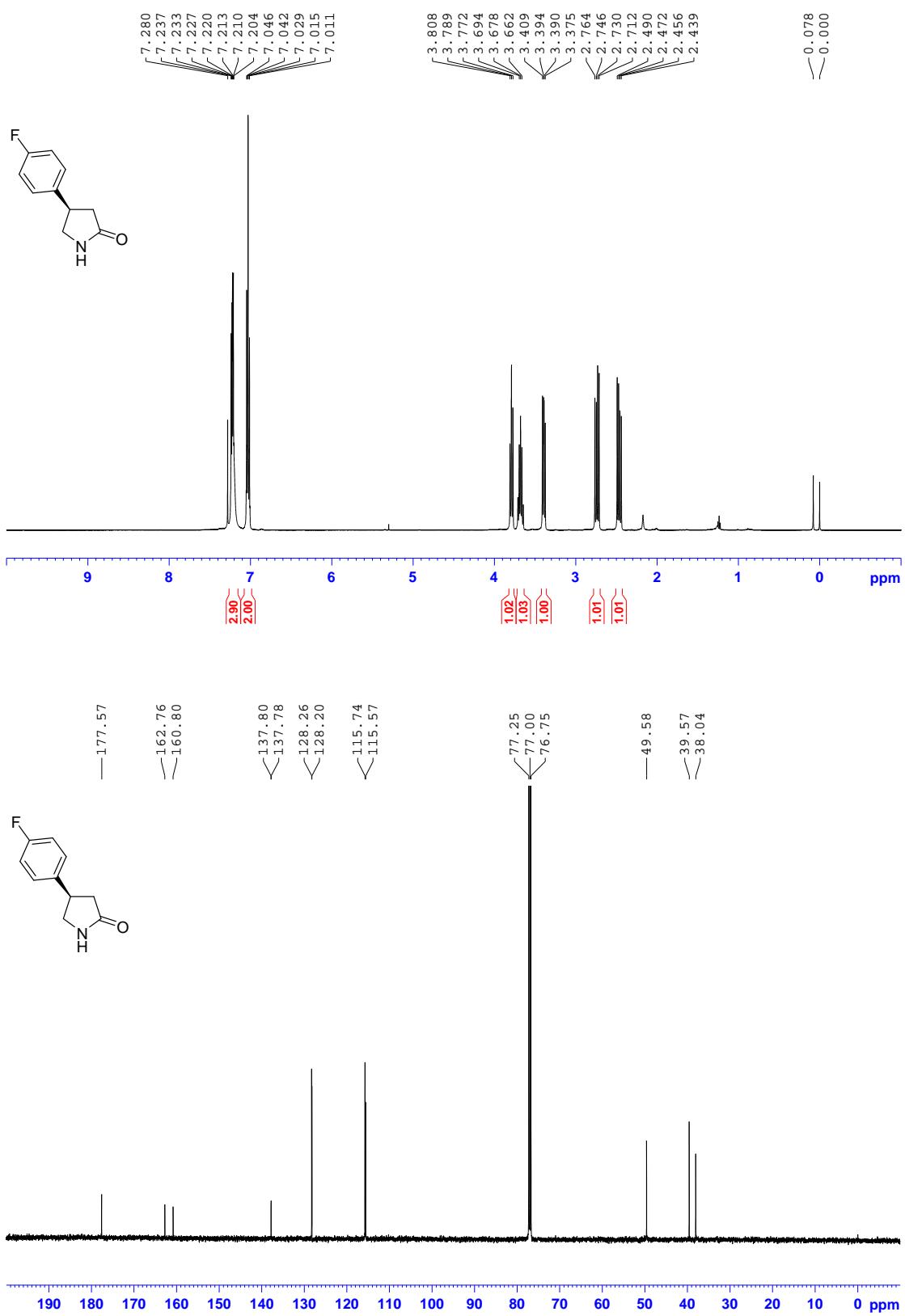
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2d**:



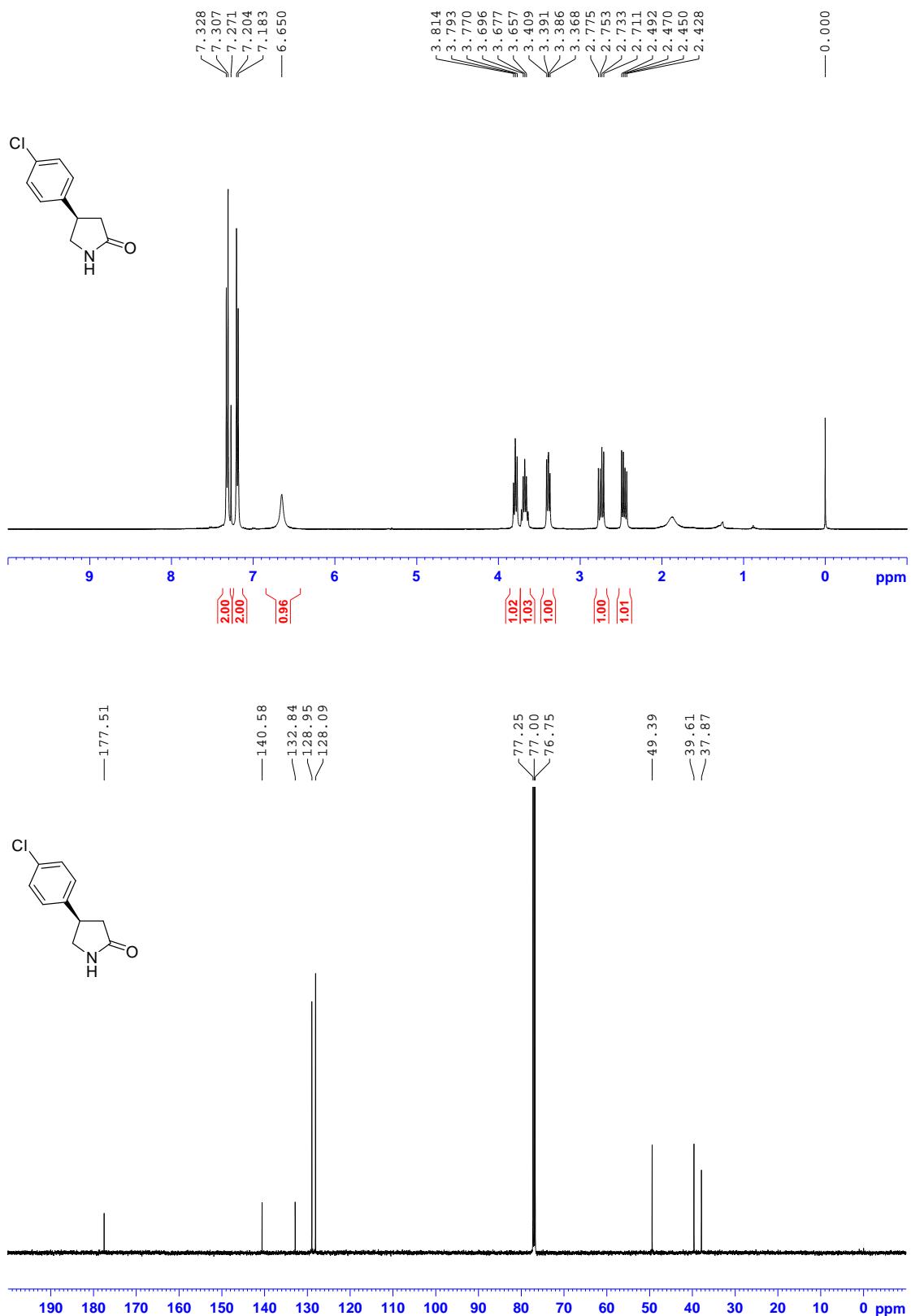
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2e**:



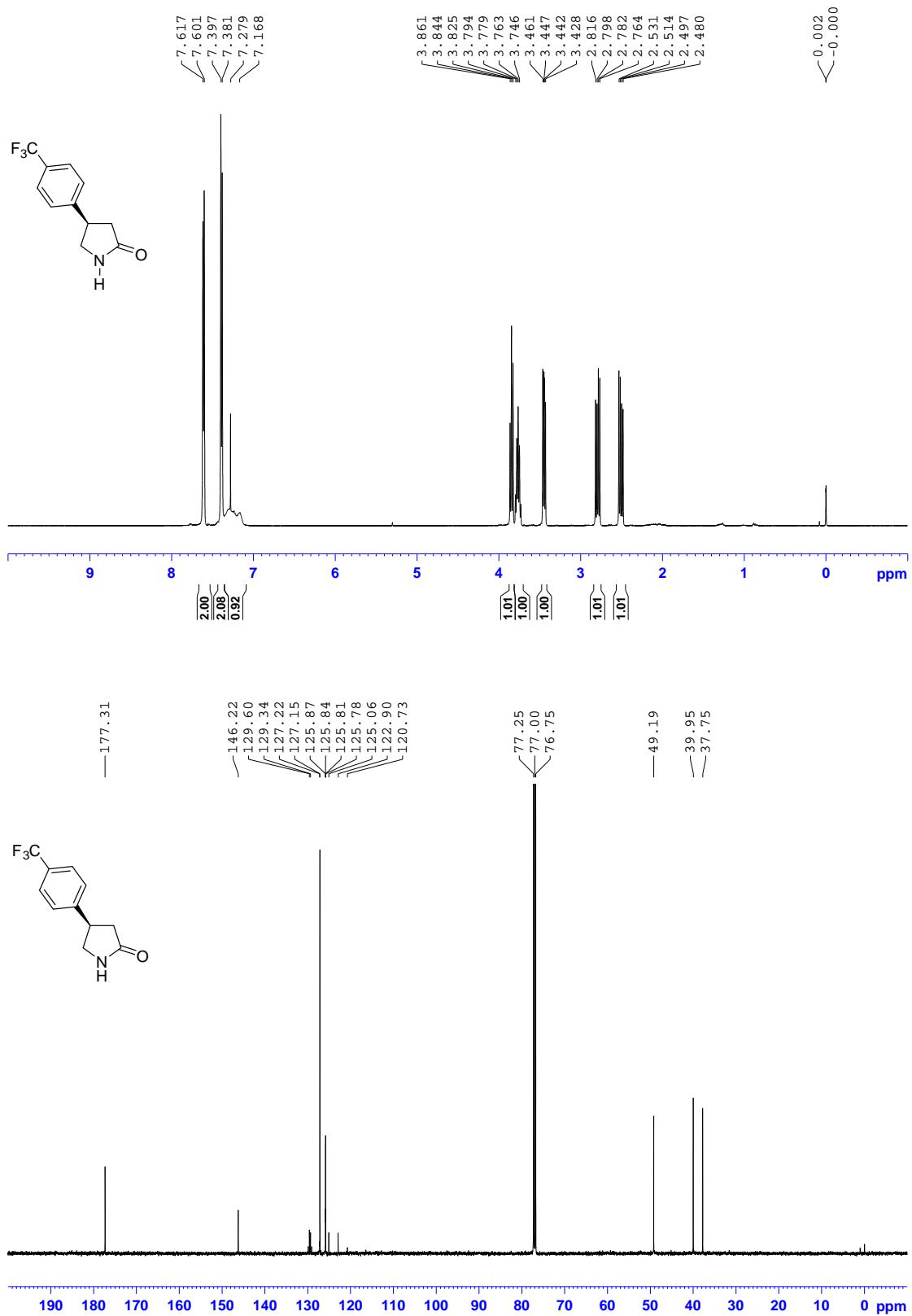
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2f**:



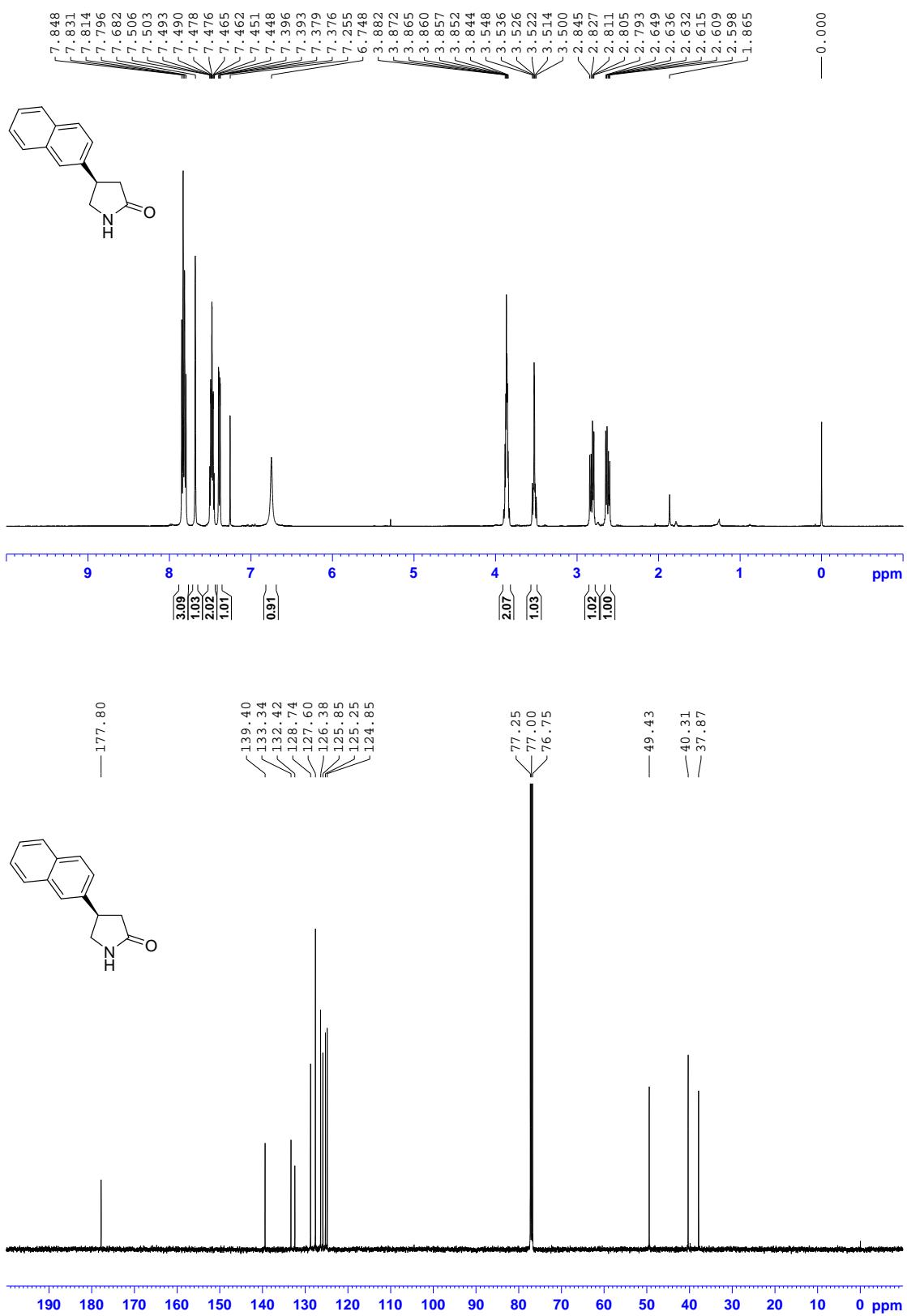
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2g**:



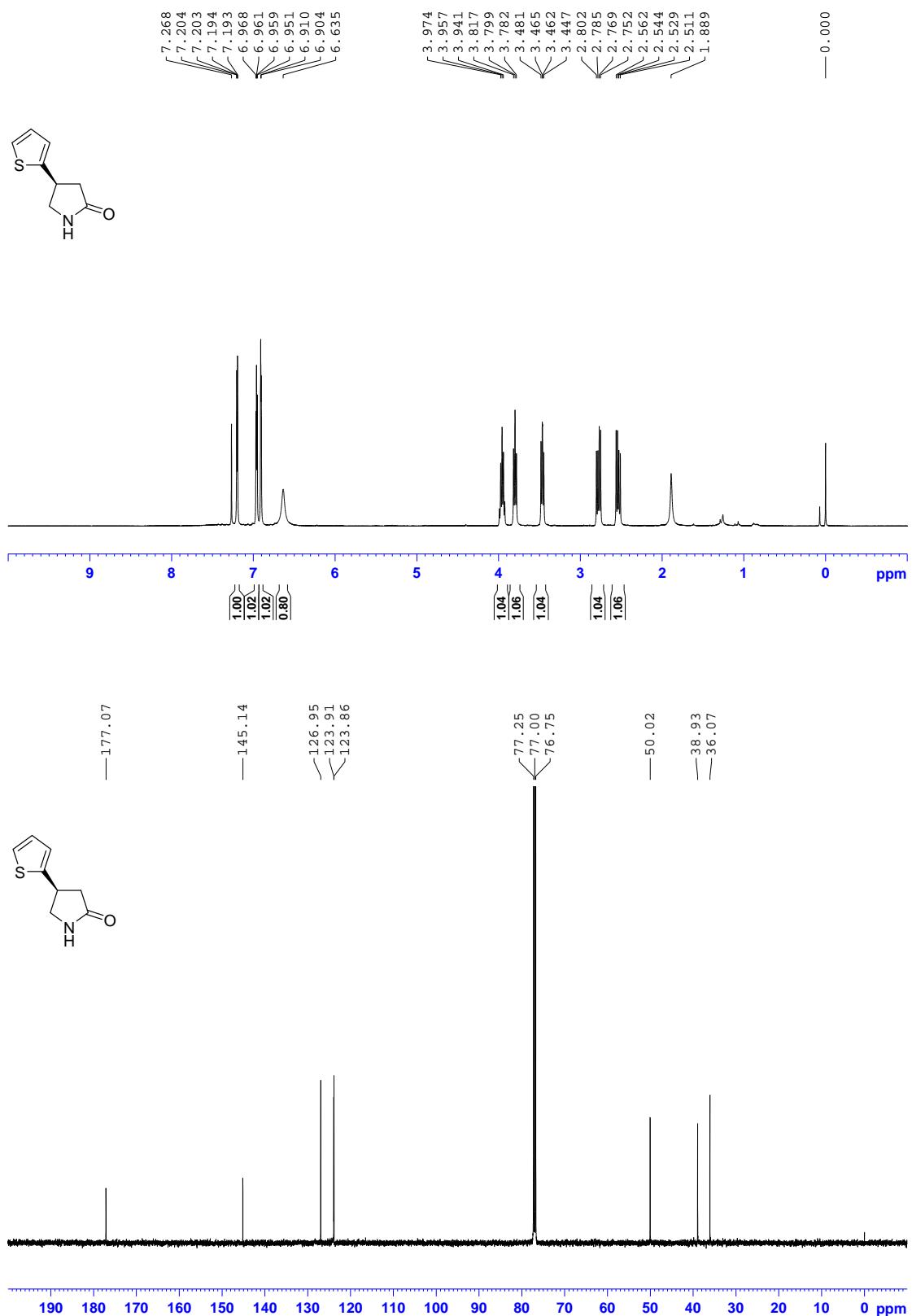
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **2h**:



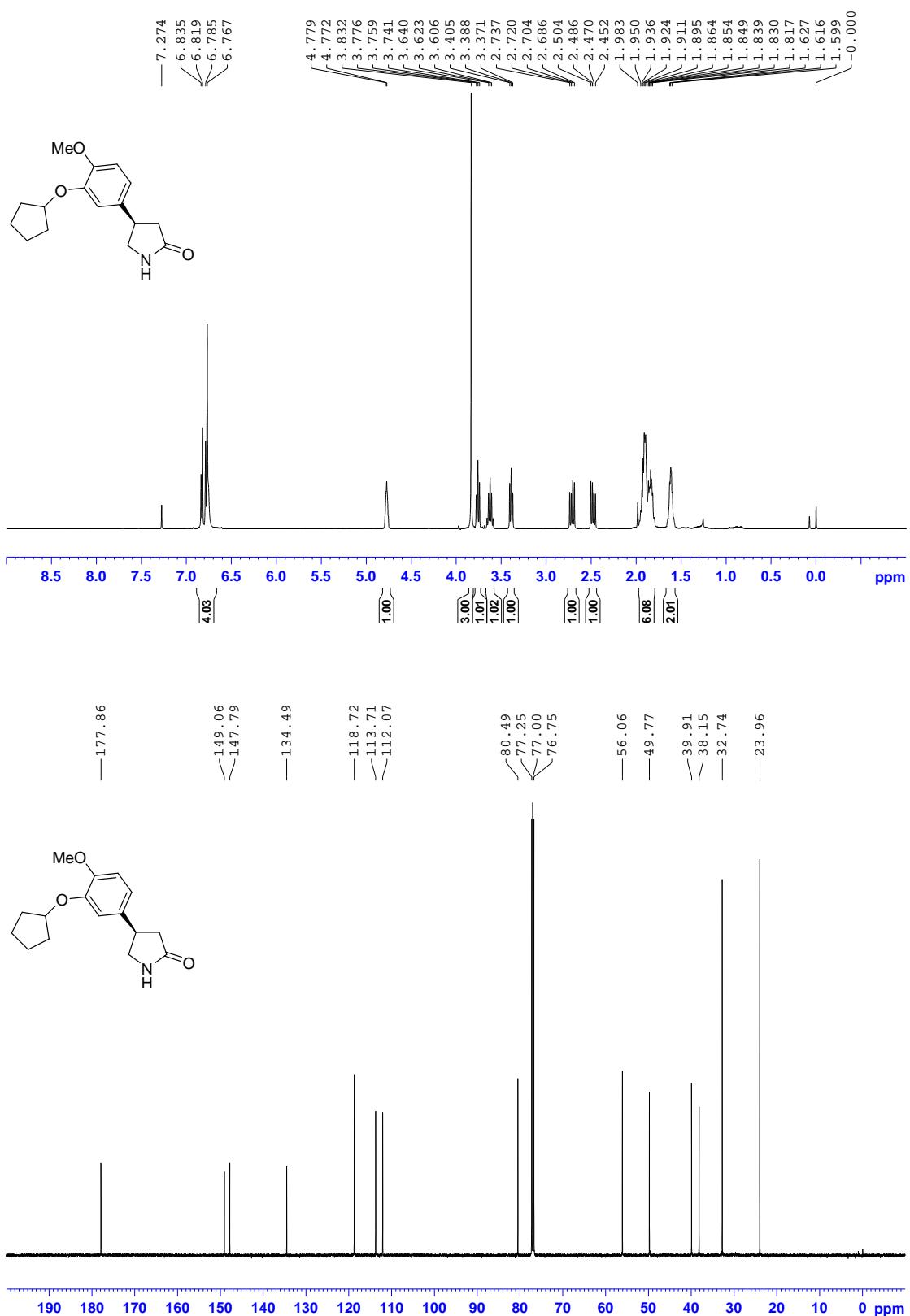
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2i**:



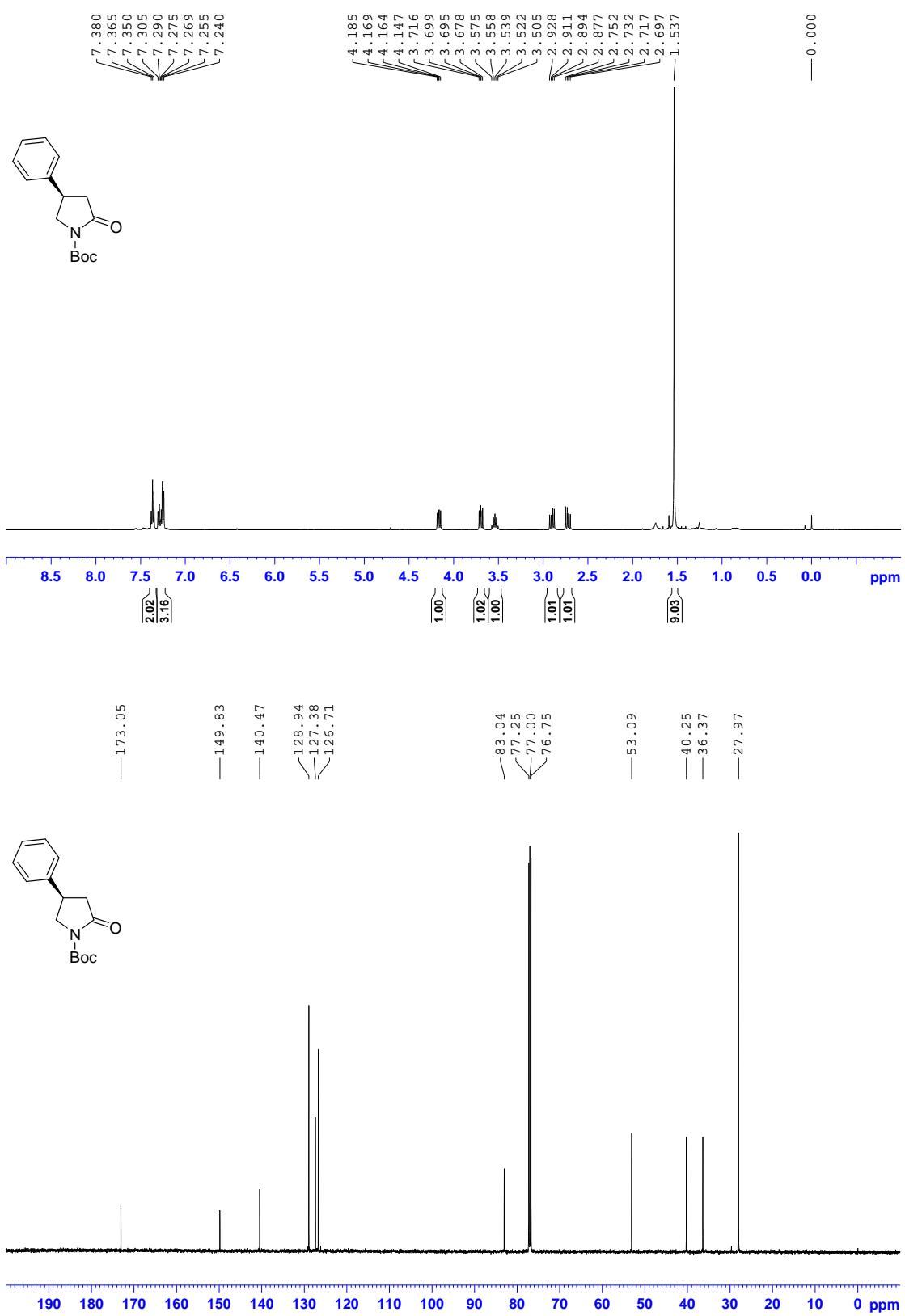
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2j**:



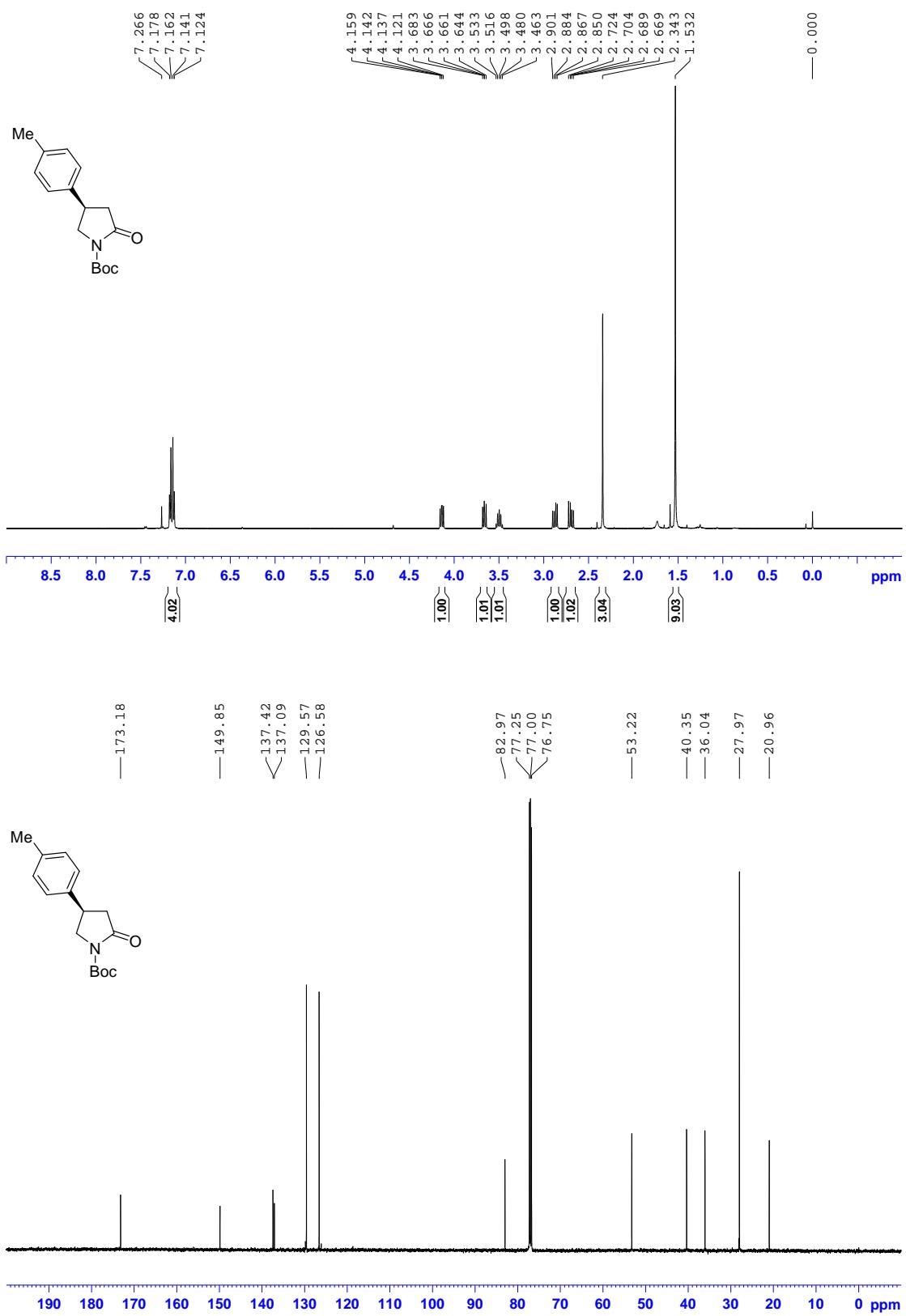
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2k**:



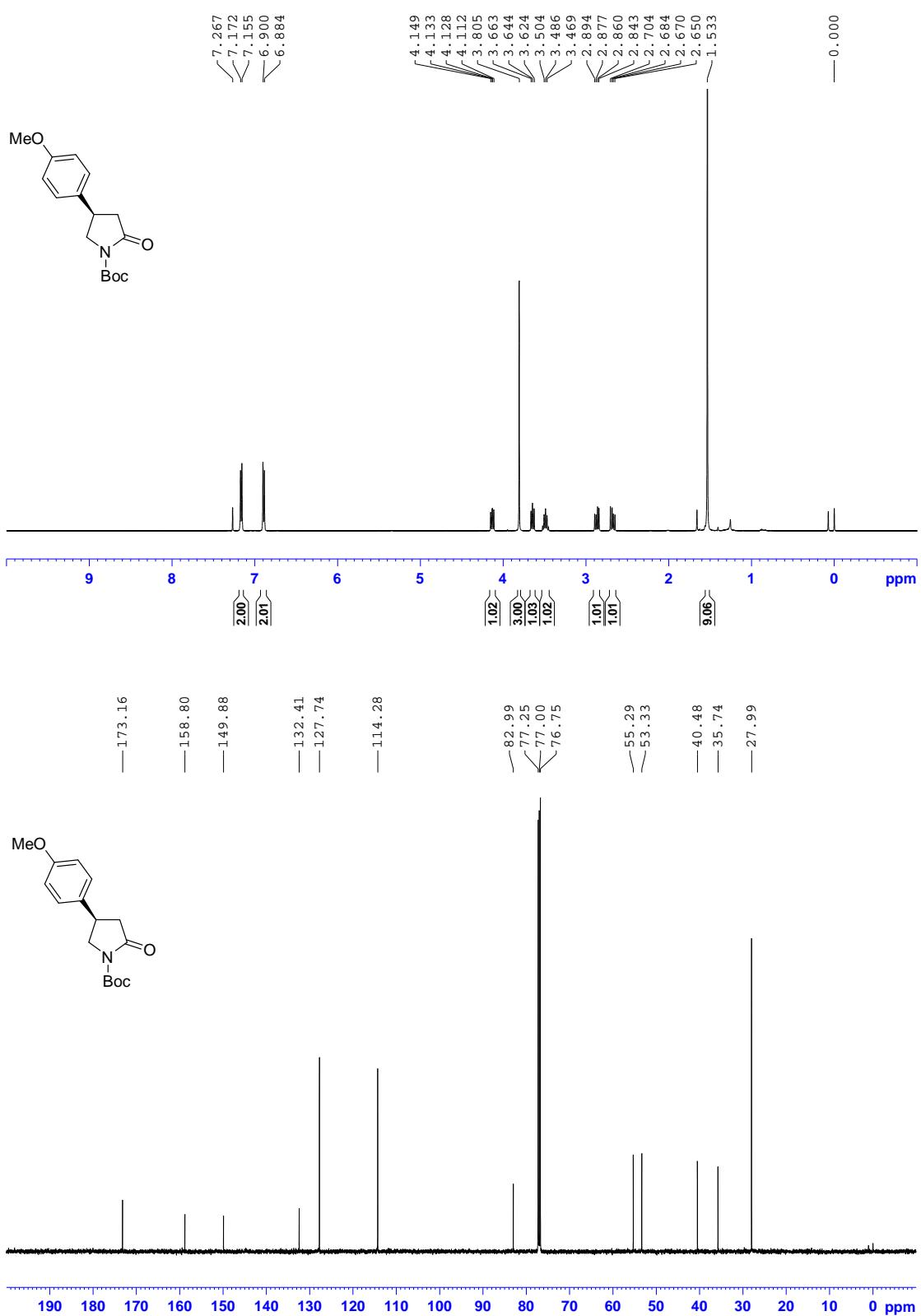
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2l**:



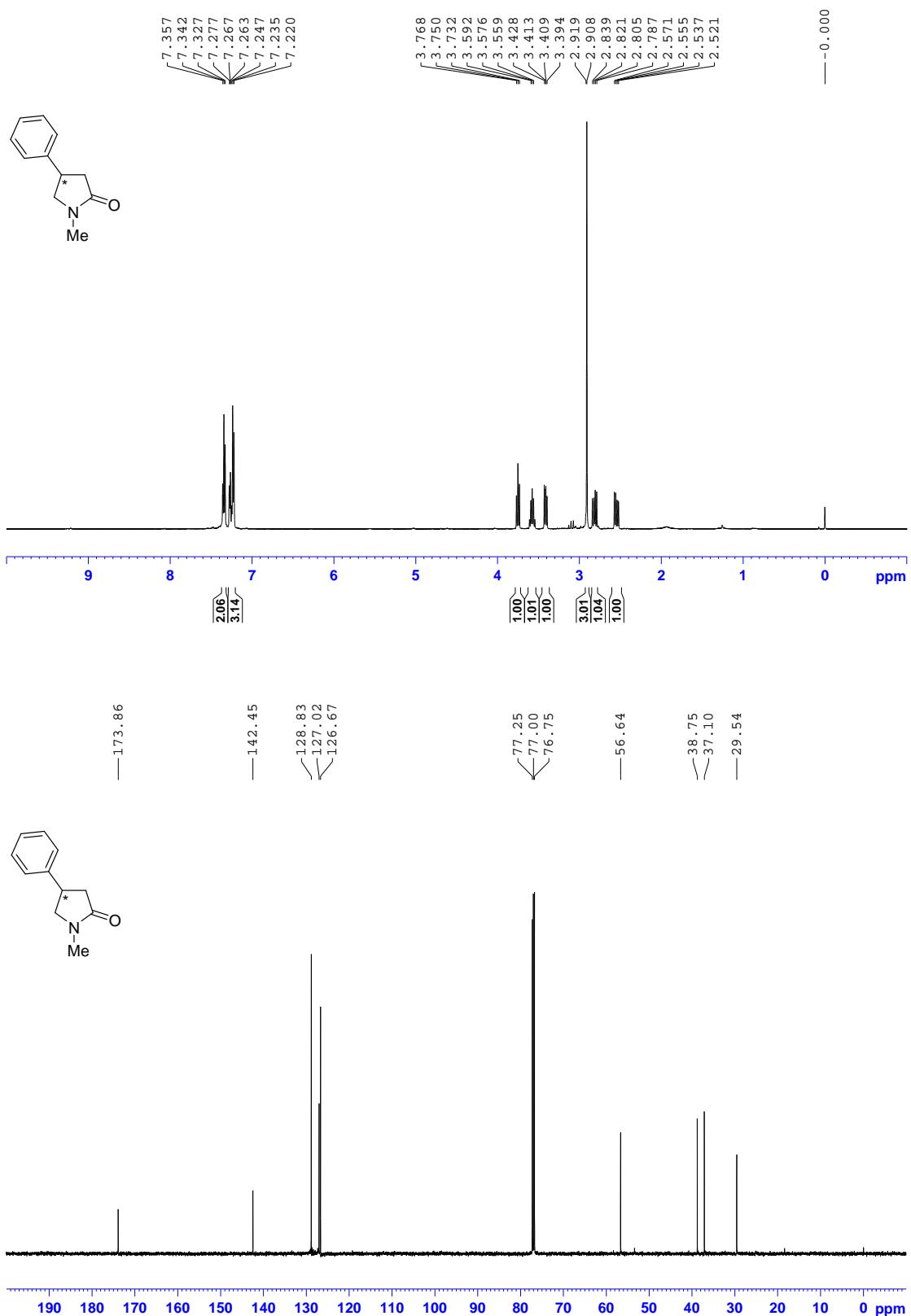
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2m**:



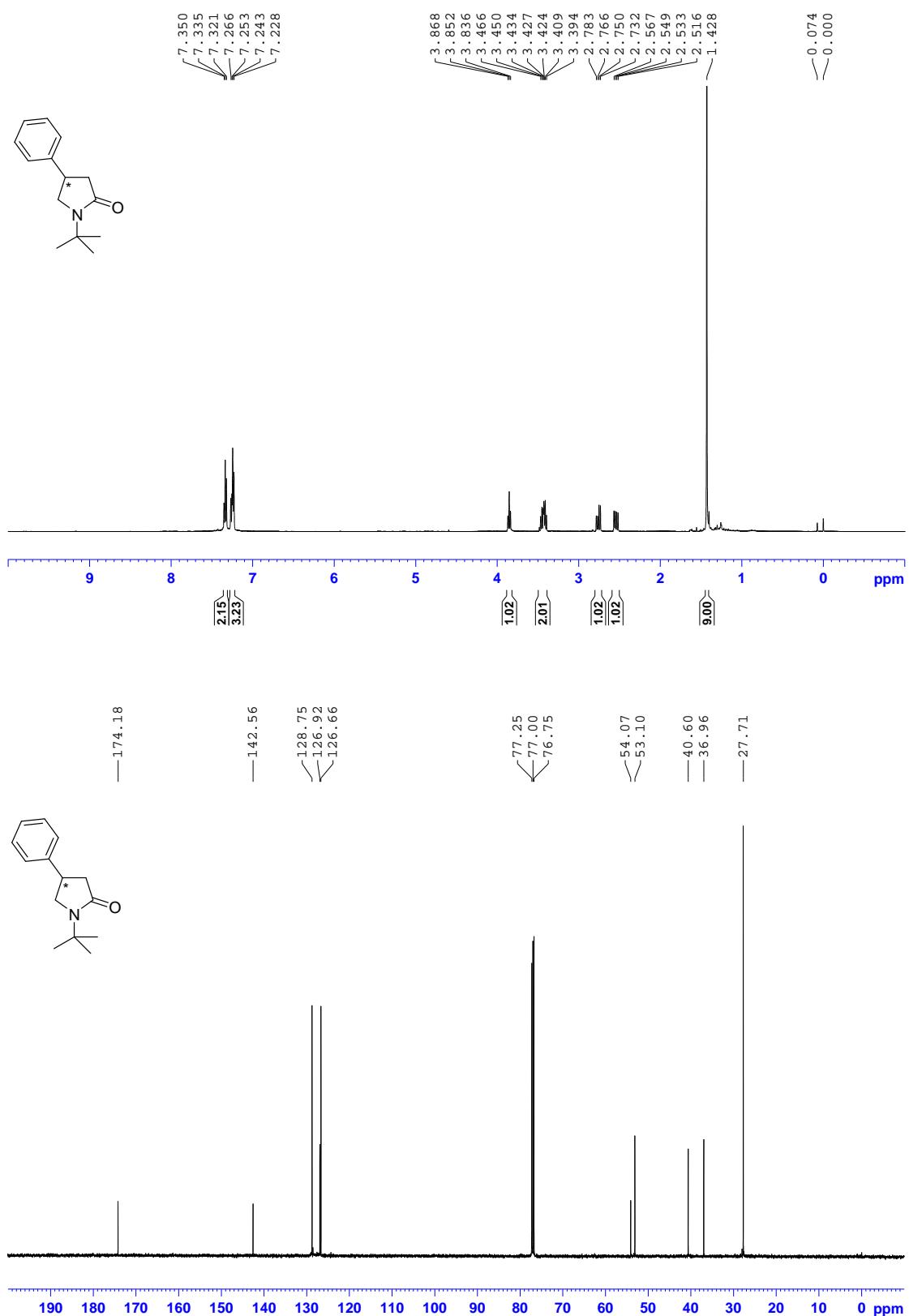
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2n**:



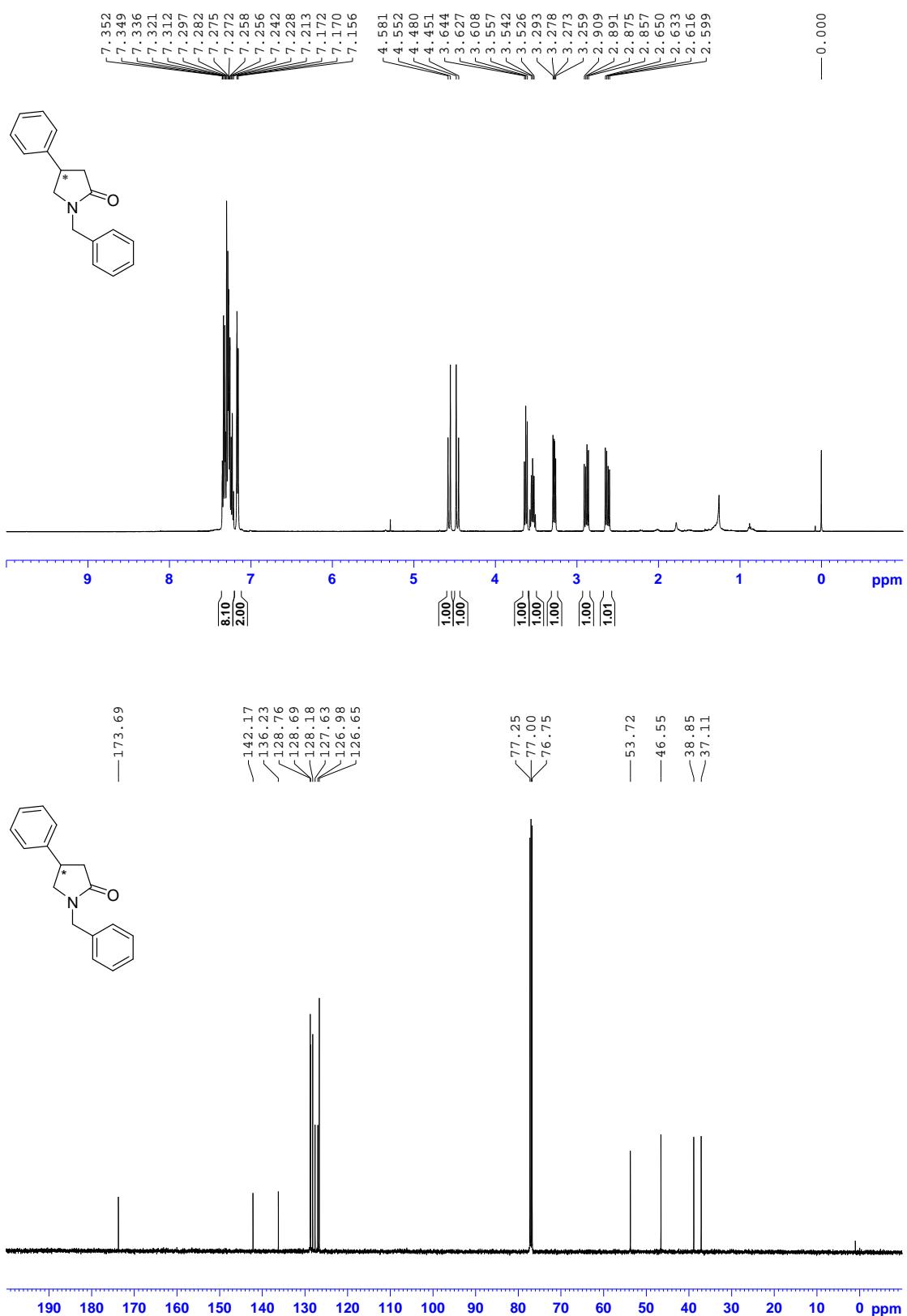
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2o**:



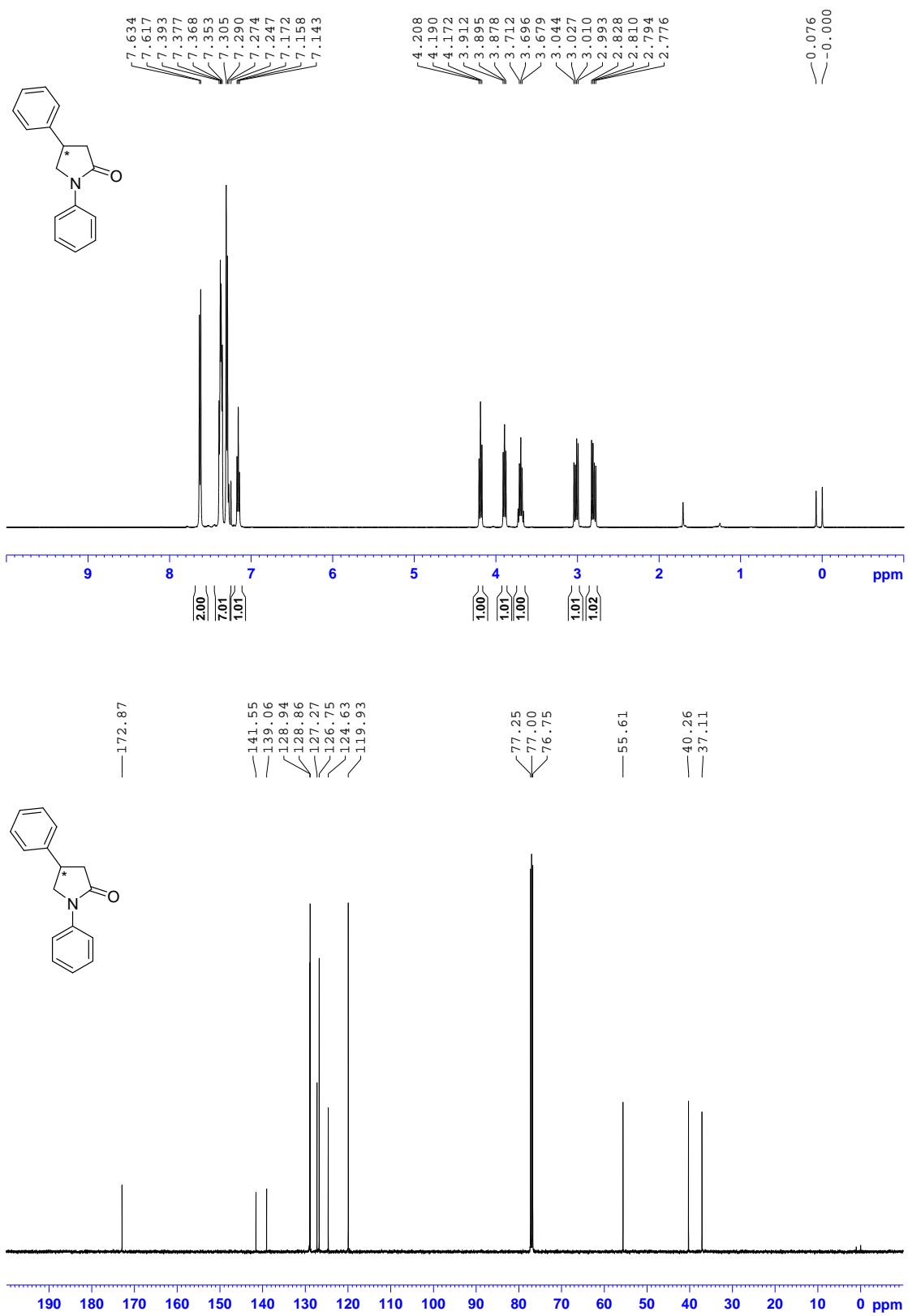
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2p**:



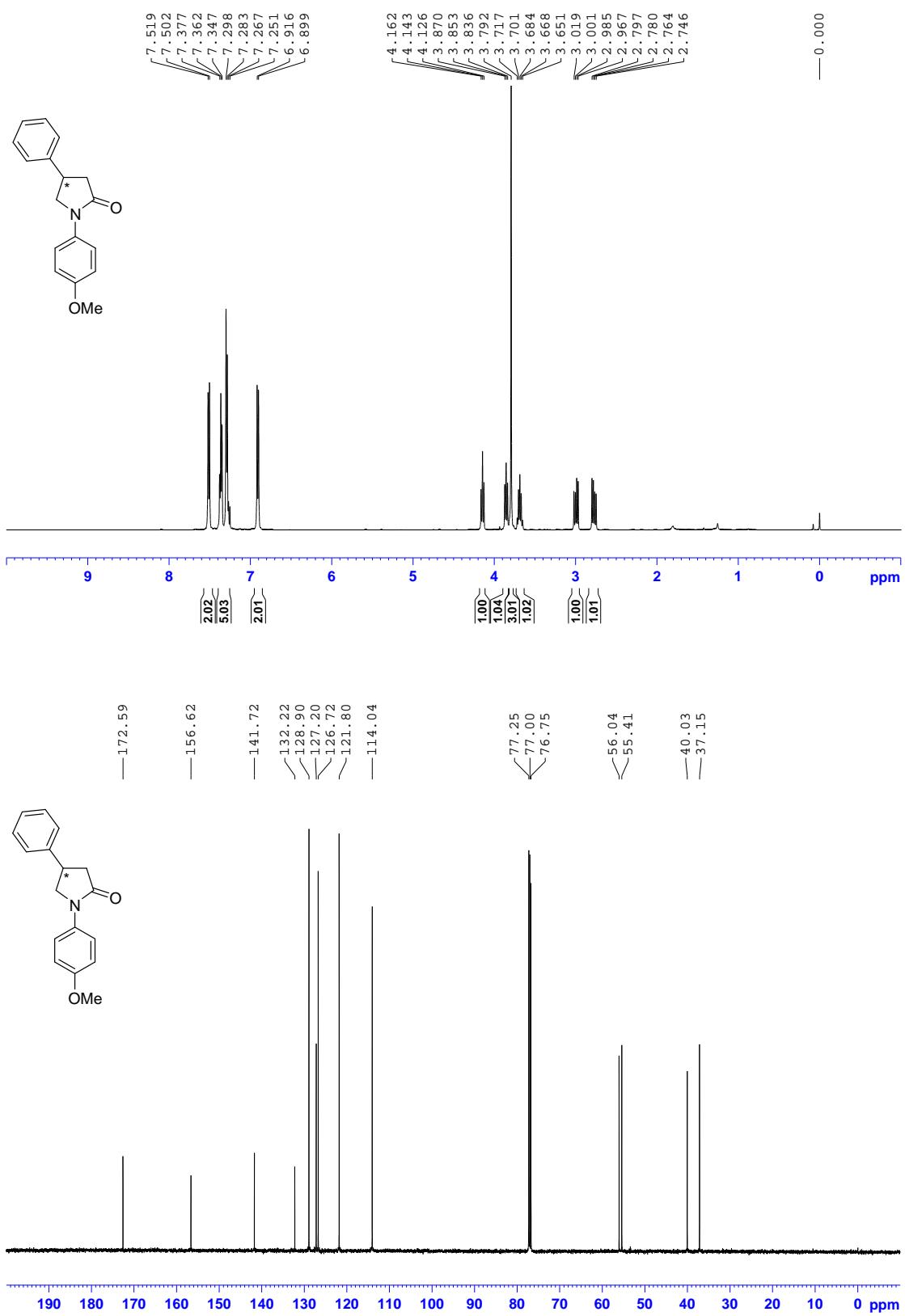
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2q**:



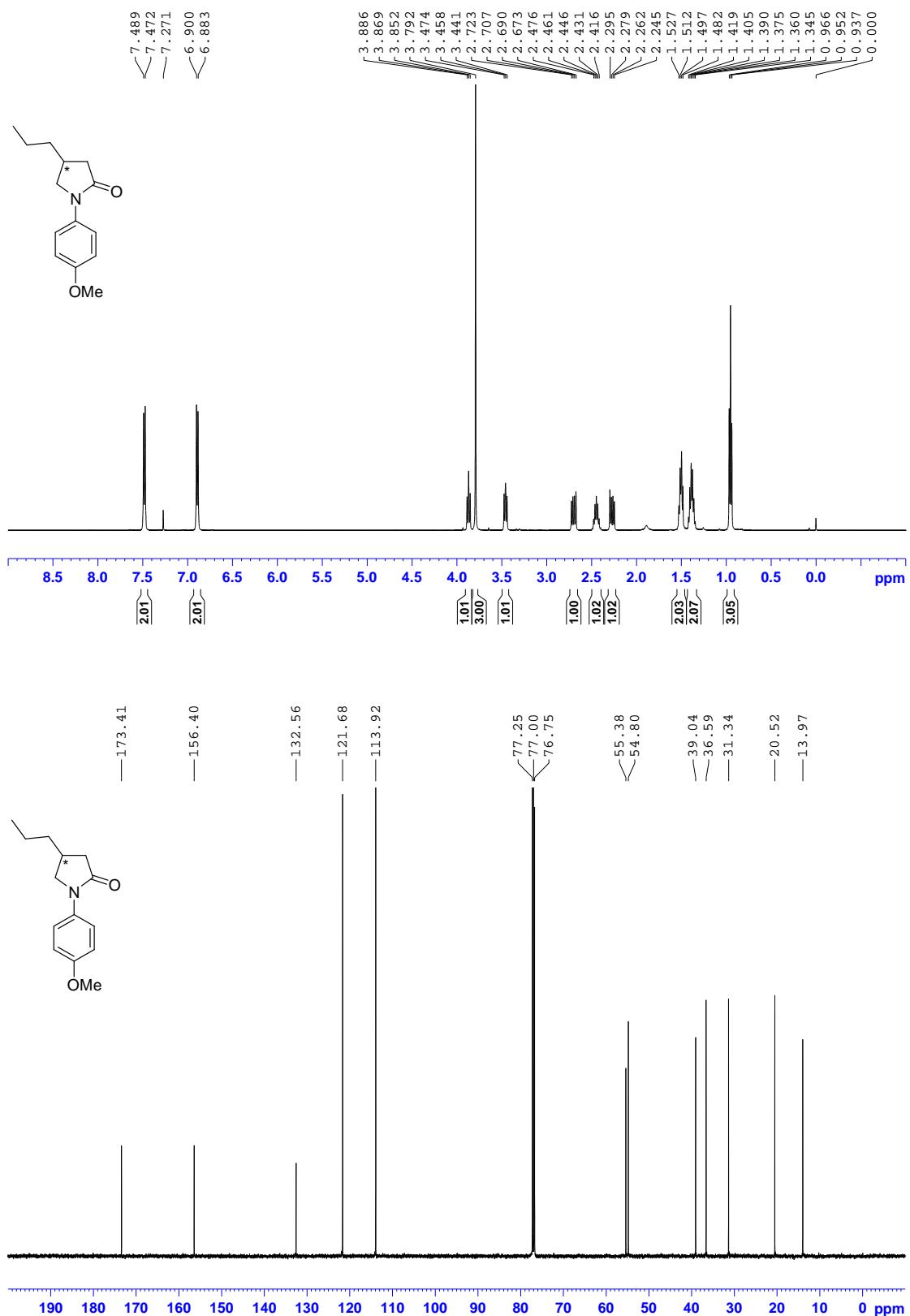
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2r**:



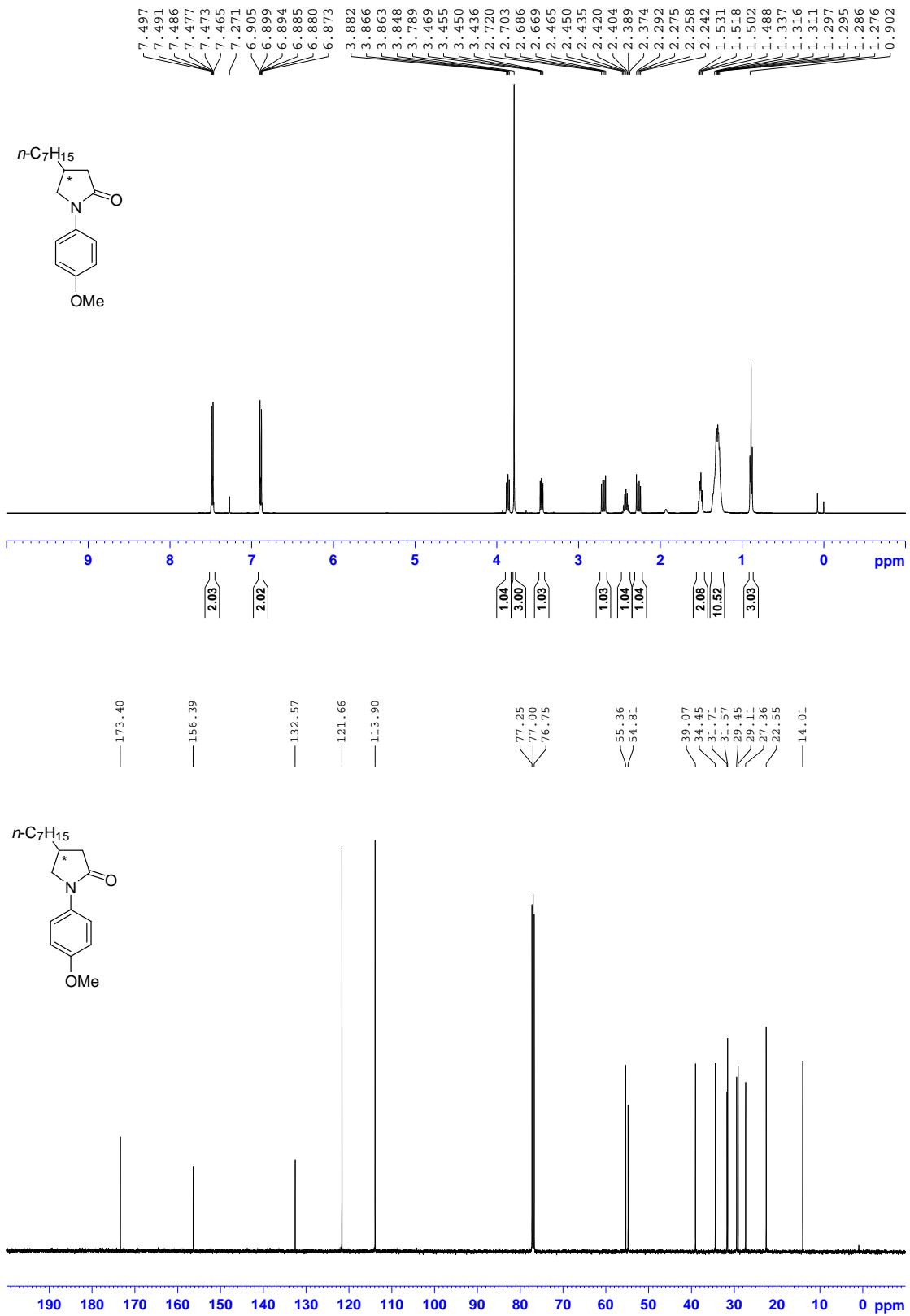
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2s**:



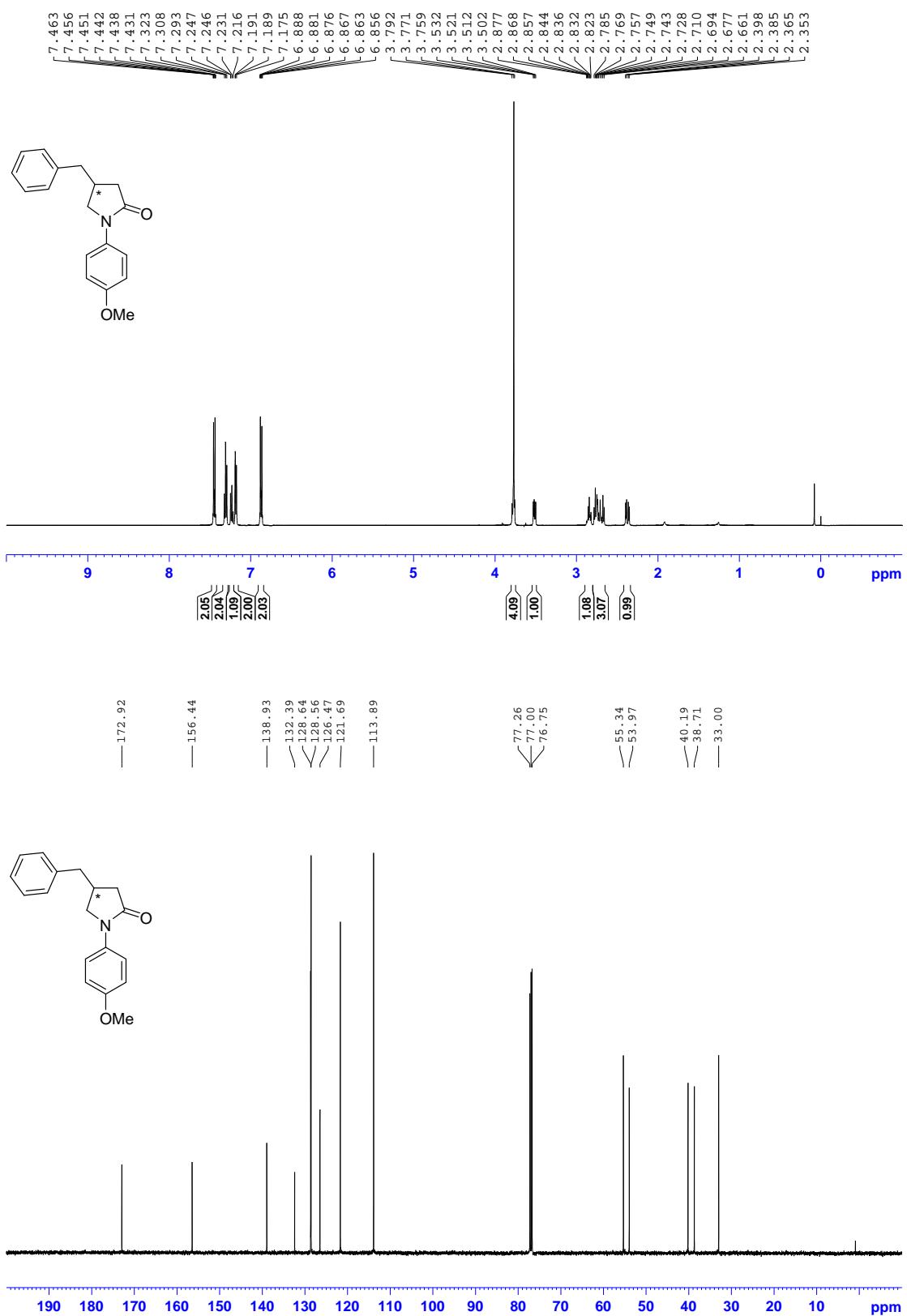
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **2t**:



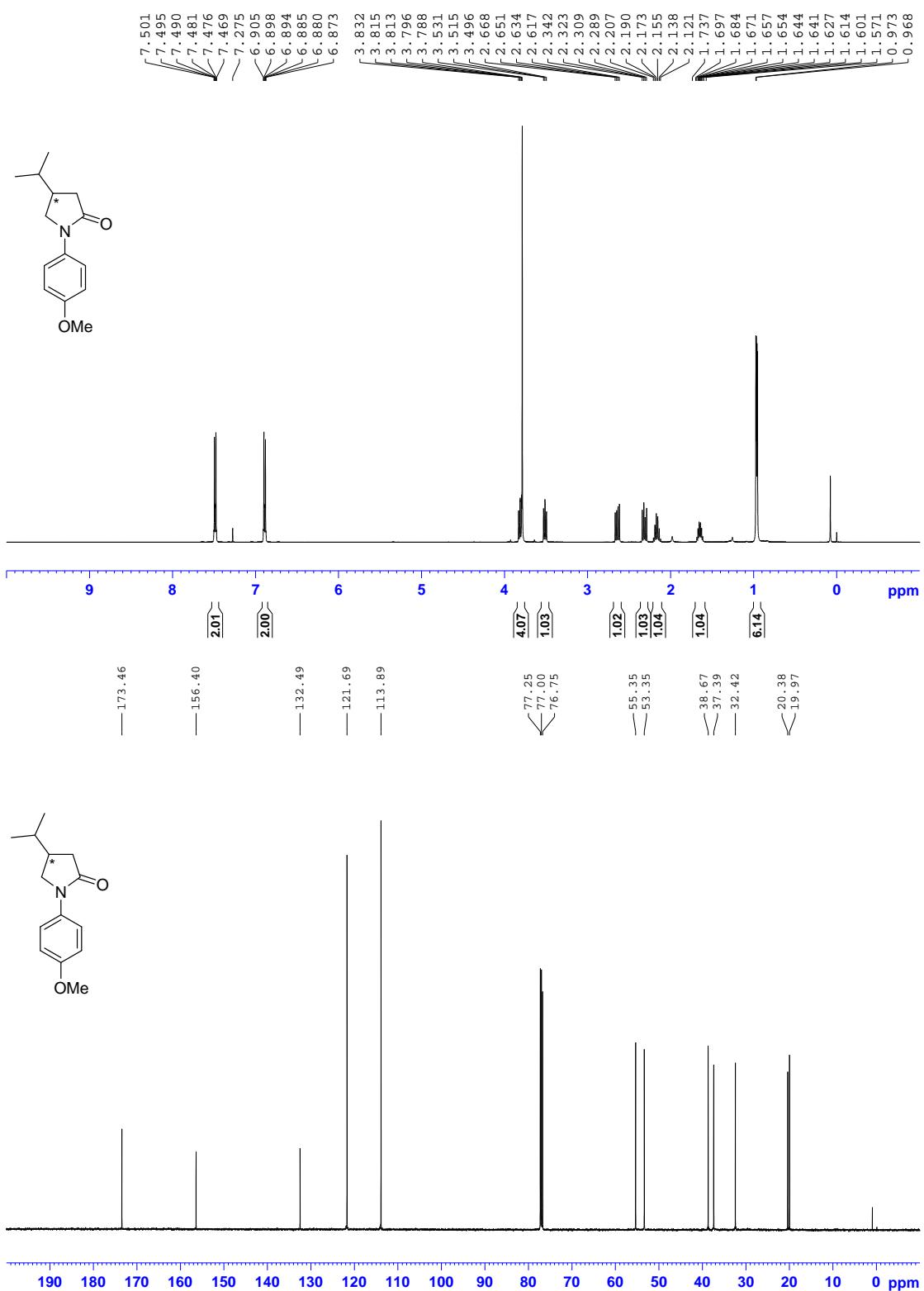
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2u**:



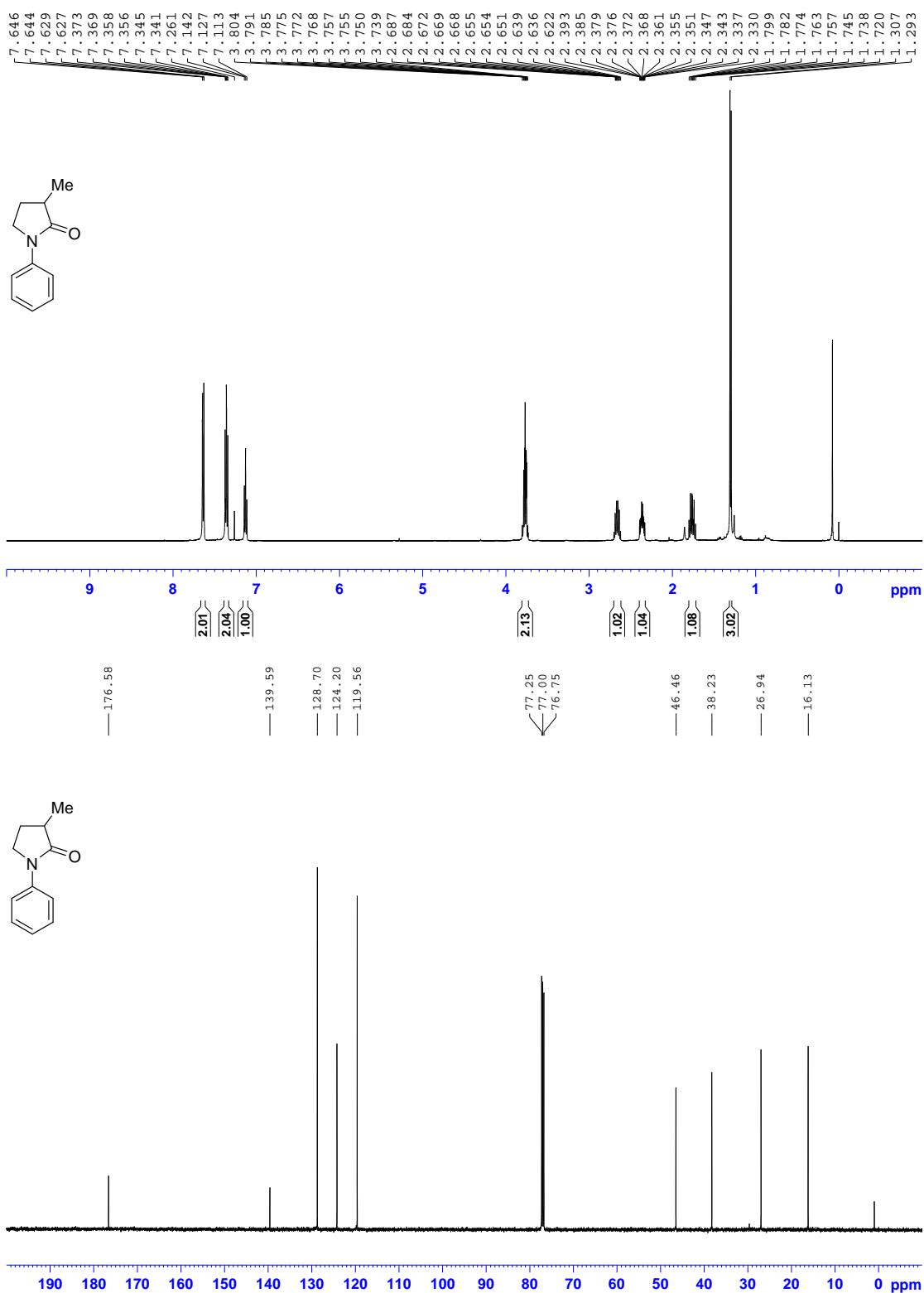
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **2v**:



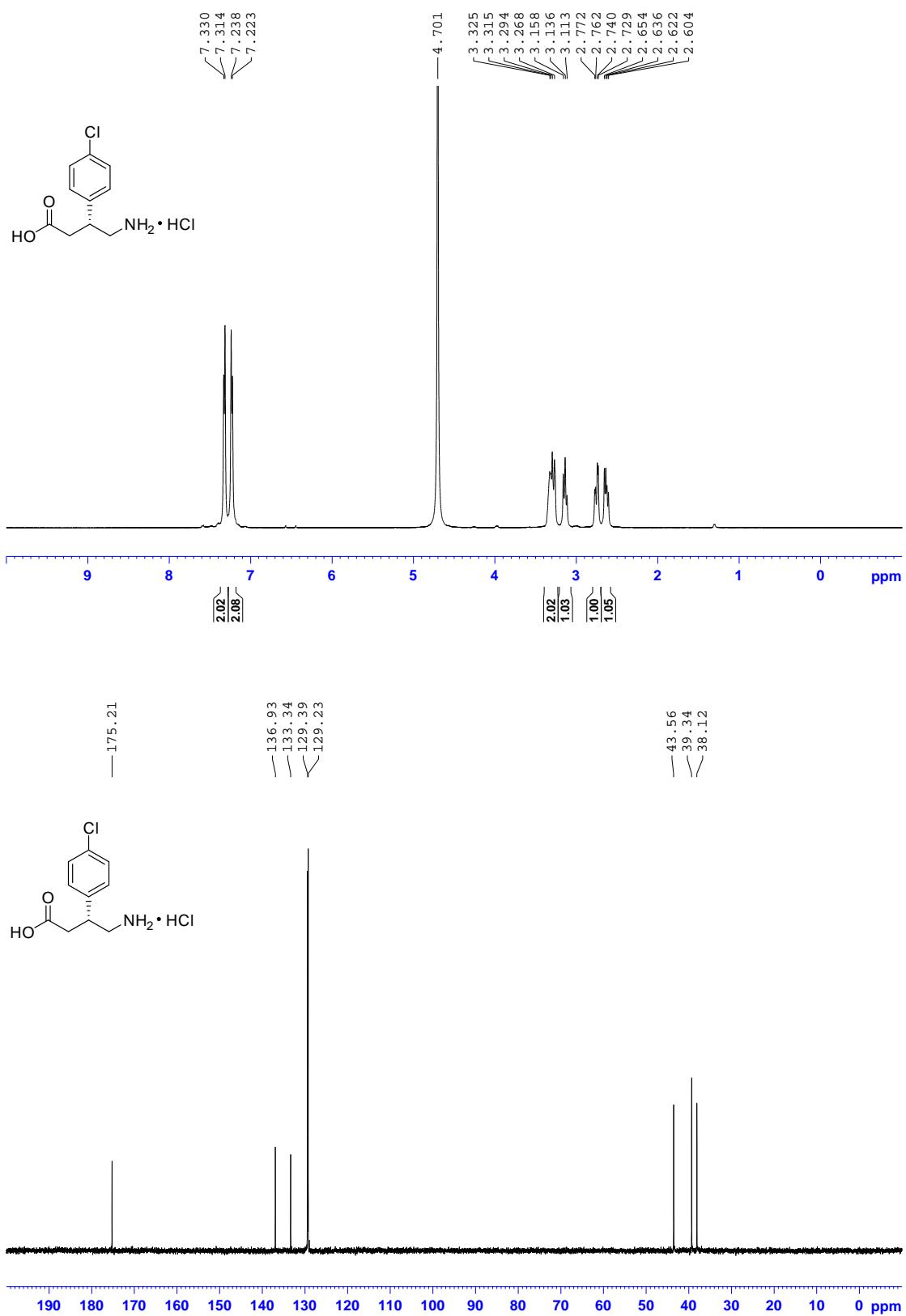
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **2w**:



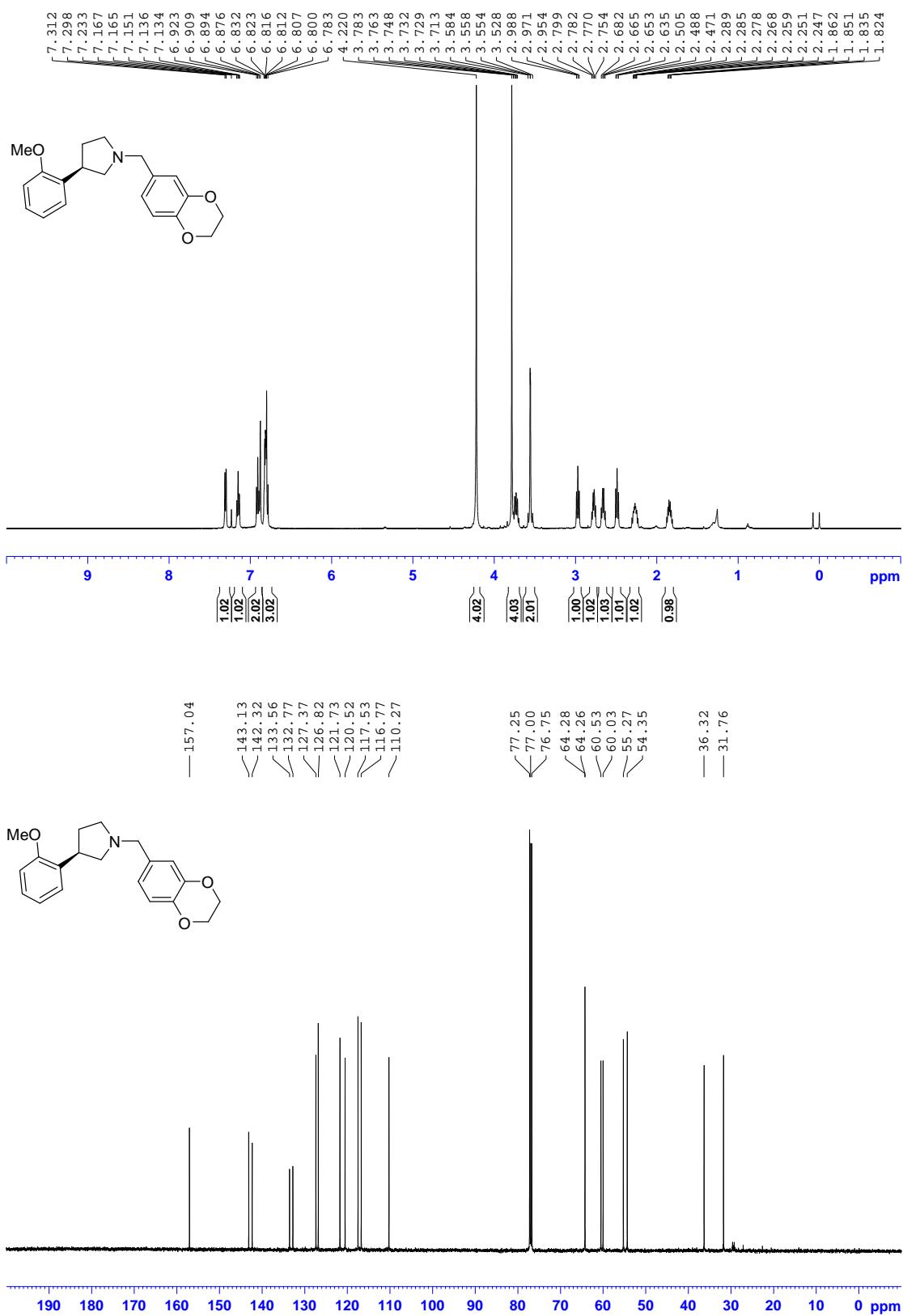
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of *rac*-**2x**:



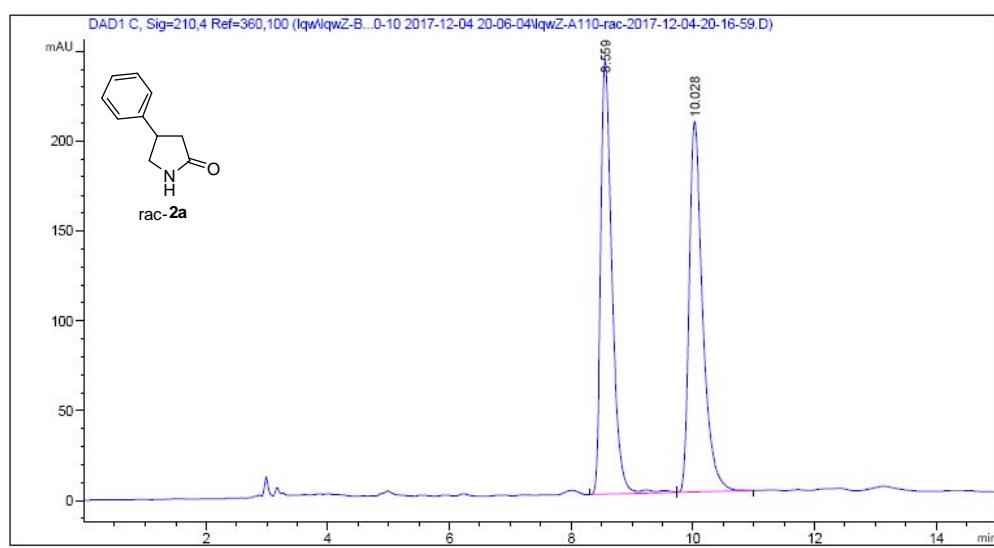
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR { ^1H } (125 MHz, CDCl_3) of **3**:



¹H NMR (500 MHz, CDCl₃) and ¹³C NMR {¹H} (125 MHz, CDCl₃) of **4**:

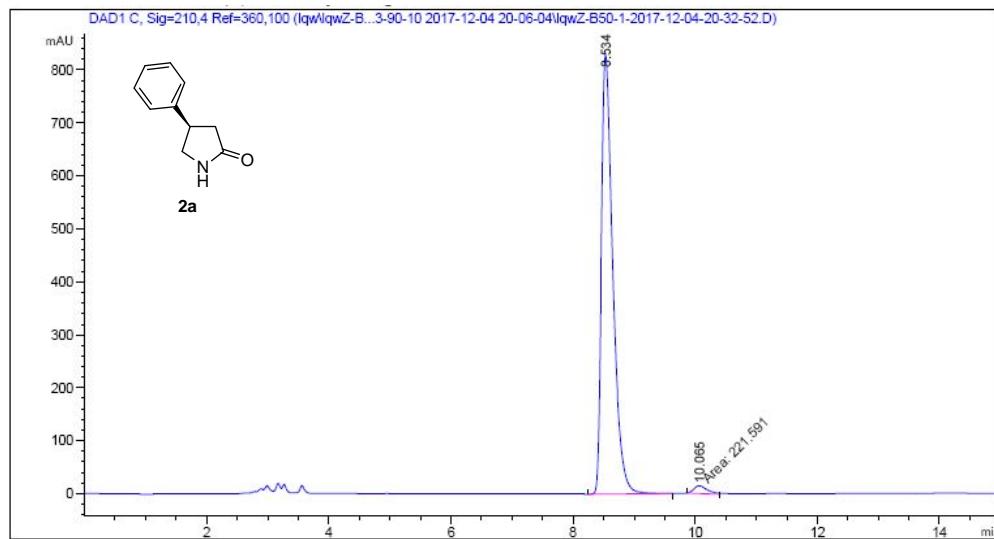


7. HPLC Spectra



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

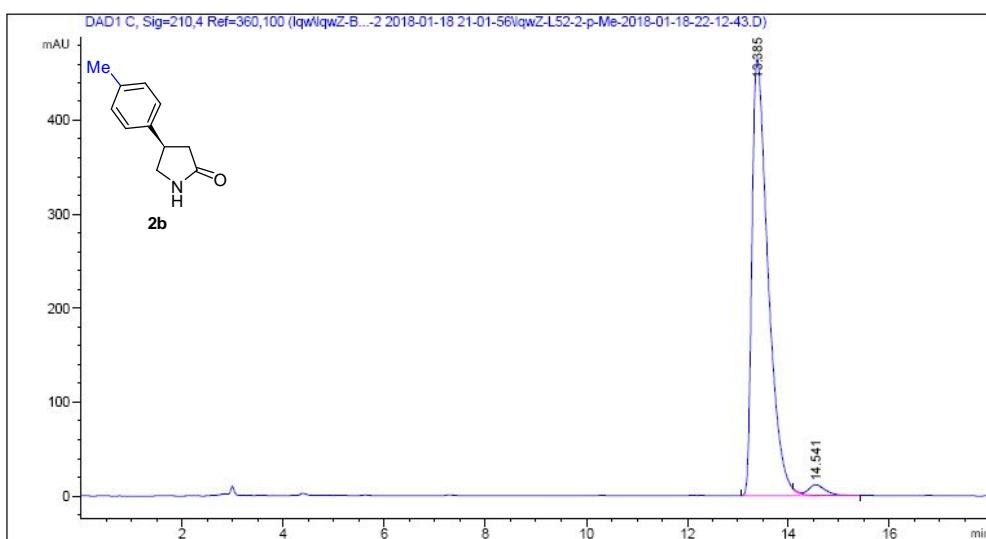
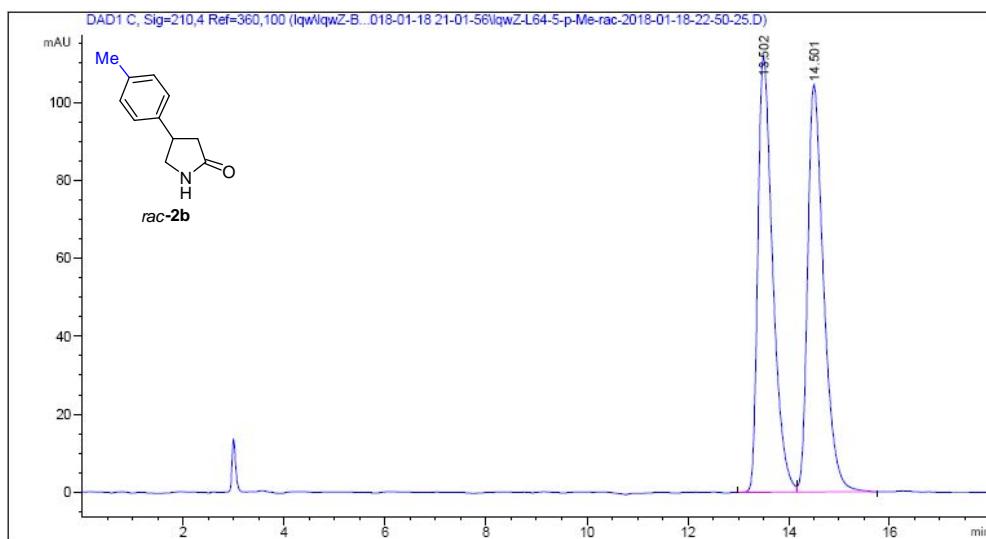
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.559	BV	R	0.1922	3106.58667	241.18594
2	10.028	BB		0.2311	3163.81274	206.13637
Totals :						447.32231

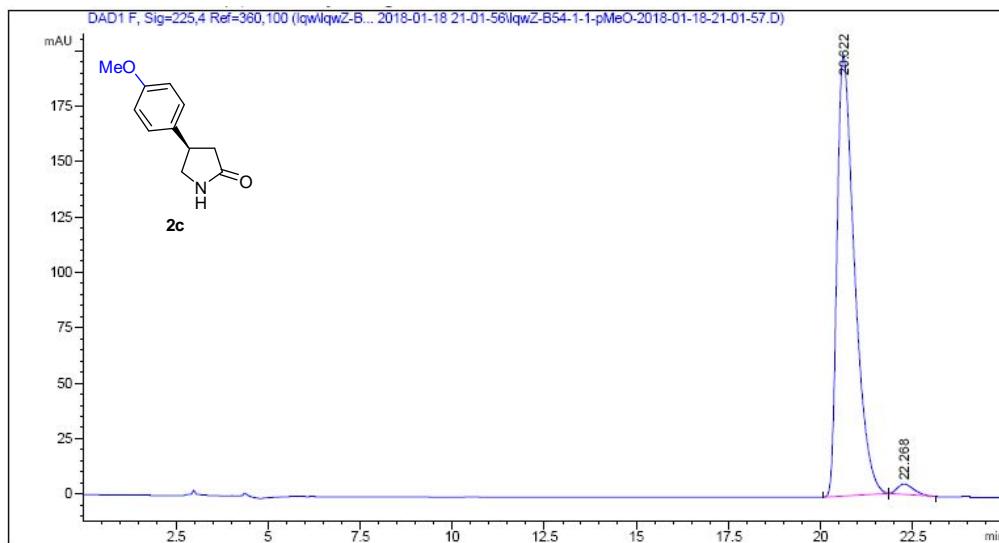
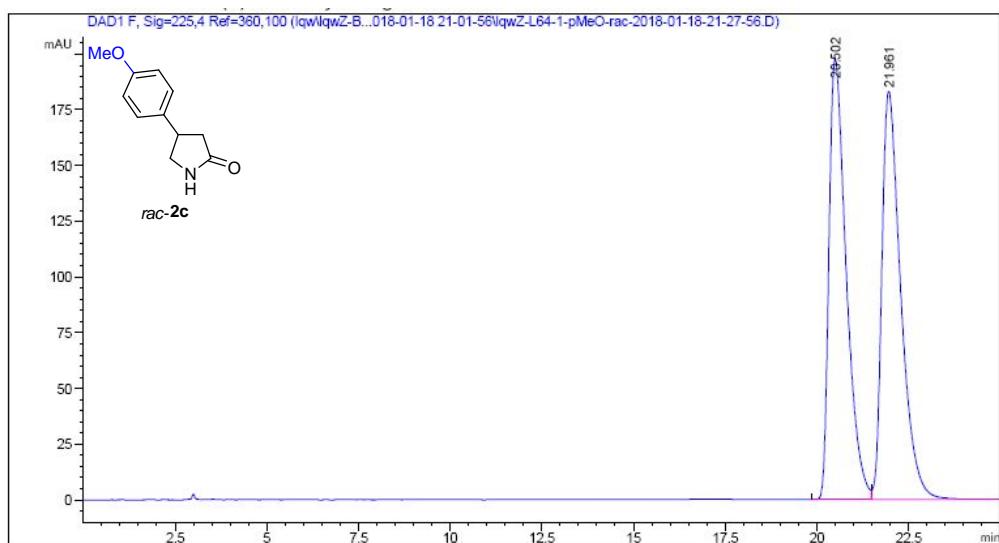


Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.534	BB		0.1948	1.07053e4	828.16925
2	10.065	MM		0.2532	221.59090	14.58555

Totals : 1.09269e4 842.75480

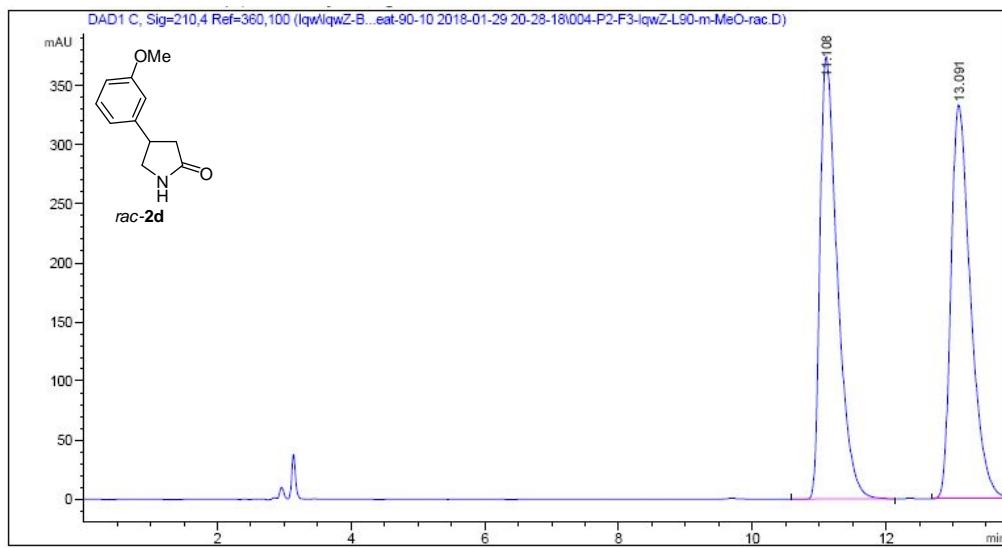




Signal 1: DAD1 F, Sig=225,4 Ref=360,100

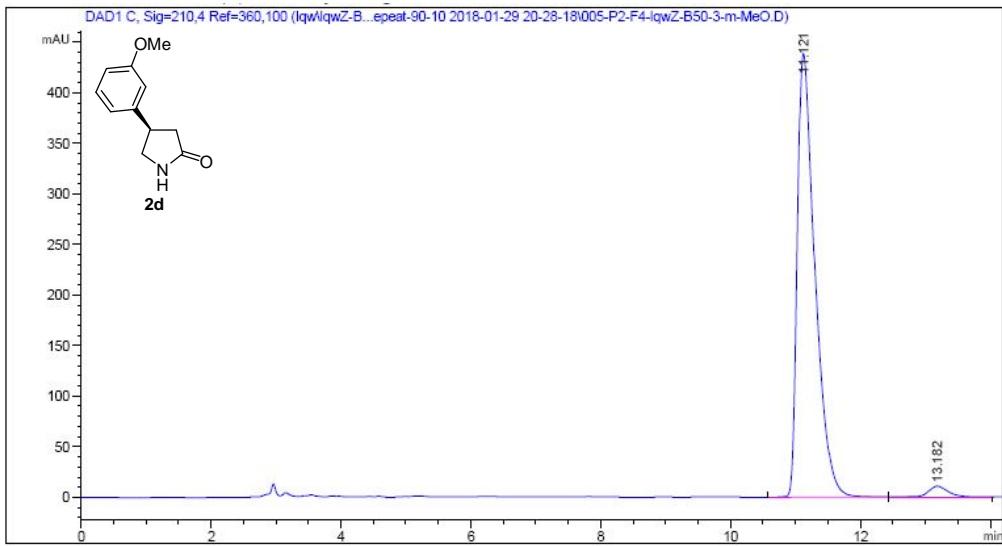
Peak	RetTime	Type	Width	Area	Height	Area %
#	[min]		[min]	[mAU*s]	[mAU]	%
1	20.622	BB	0.5005	6575.64941	198.51378	97.8924
2	22.268	BB	0.4681	141.57372	4.63786	2.1076

Totals : 6717.22313 203.15164



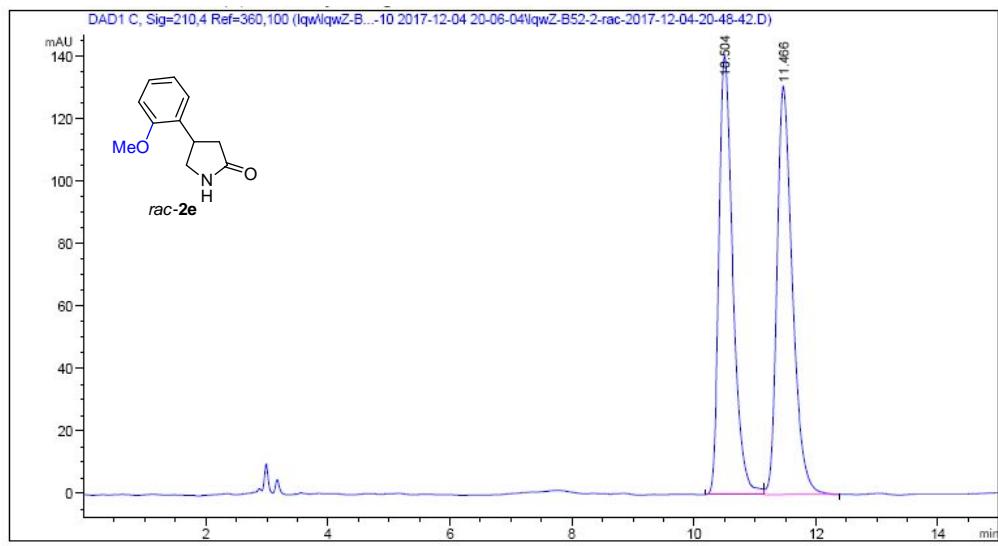
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.108	BB	0.2713	6774.90527	374.13309	49.9904
2	13.091	BBA	0.3093	6777.50586	333.20355	50.0096
Totals :					1.35524e4	707.33664



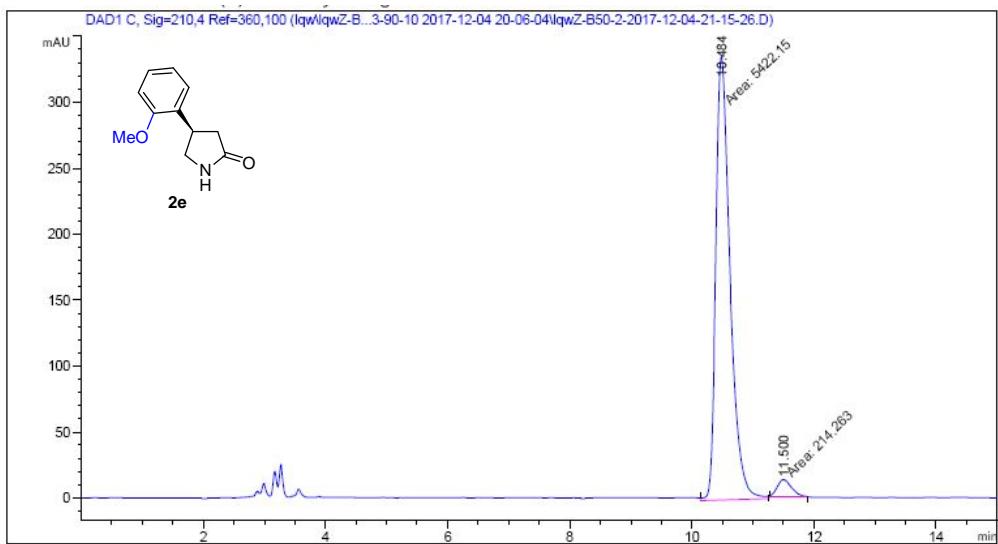
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.121	BB	0.2796	8262.52734	438.92865	97.3897
2	13.182	BB	0.3168	221.46101	10.63998	2.6103
Totals :					8483.98836	449.56863



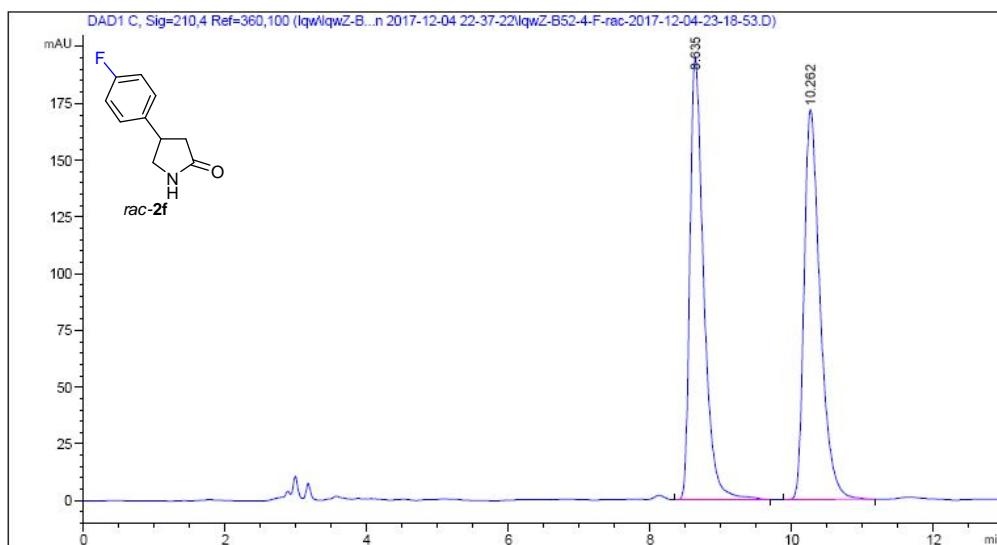
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.504	BV	0.2406	2219.74194	140.25807	49.1084
2	11.466	VB	0.2674	2300.34473	130.66060	50.8916
Totals :					4520.08667	270.91867



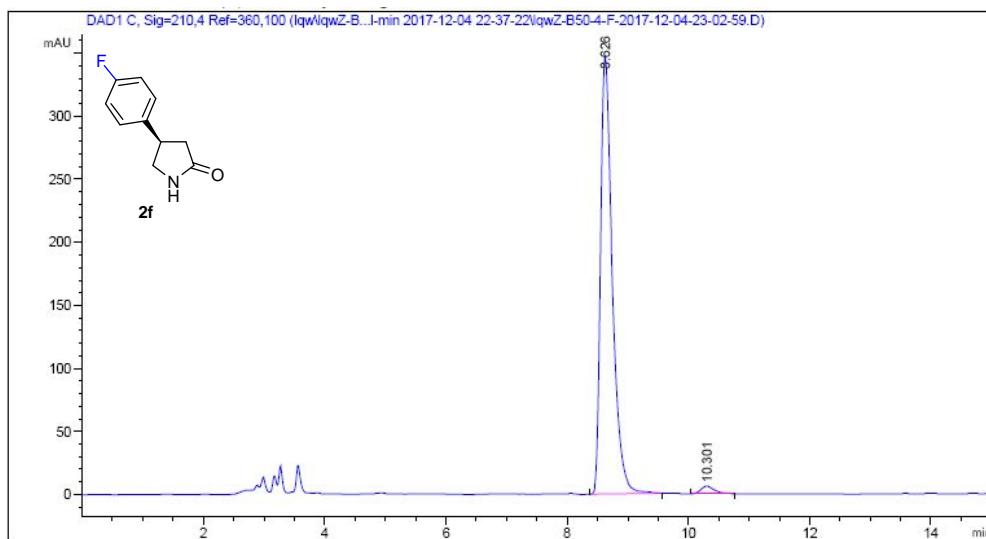
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.484	MM	0.2690	5422.15283	335.92868	96.1986
2	11.500	MM T	0.2747	214.26341	13.00026	3.8014
Totals :					5636.41624	348.92894



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

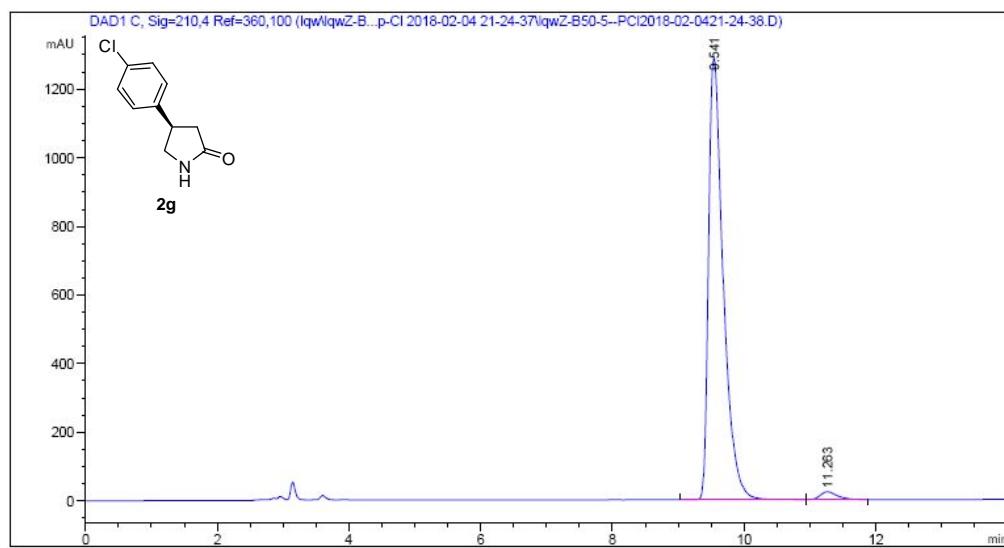
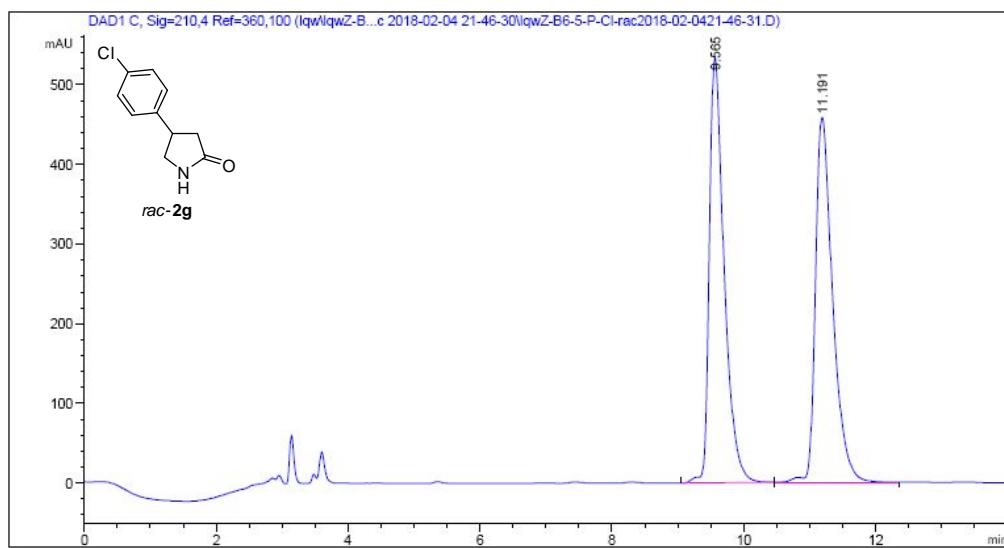
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.635	BB	0.2039	2634.82739	194.66113	49.3243
2	10.262	BB	0.2378	2707.01294	171.86237	50.6757
Totals :					5341.84033	366.52350



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.626	BB	0.2023	4641.90430	346.46350	98.0848
2	10.301	BB	0.2338	90.63592	5.94805	1.9152

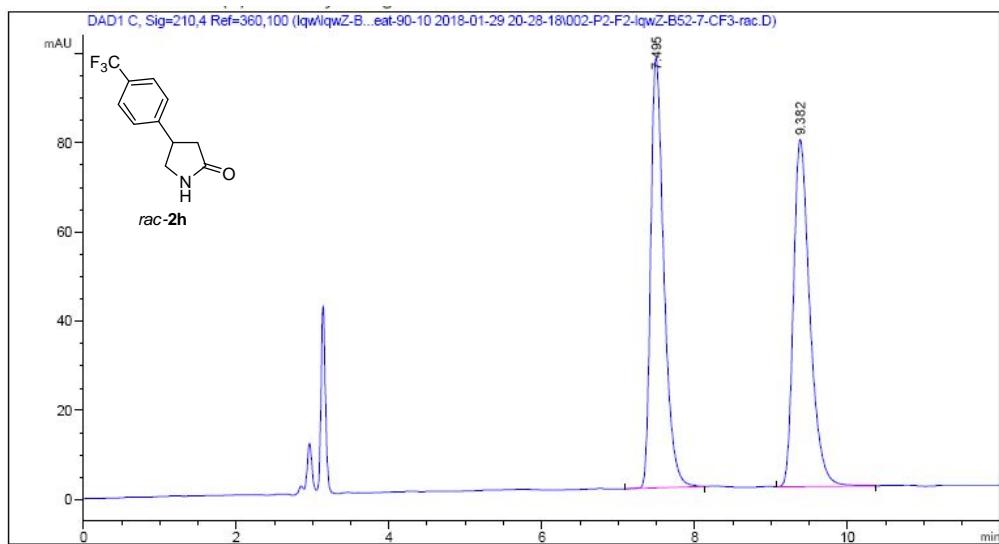
Totals : 4732.54021 352.41155



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

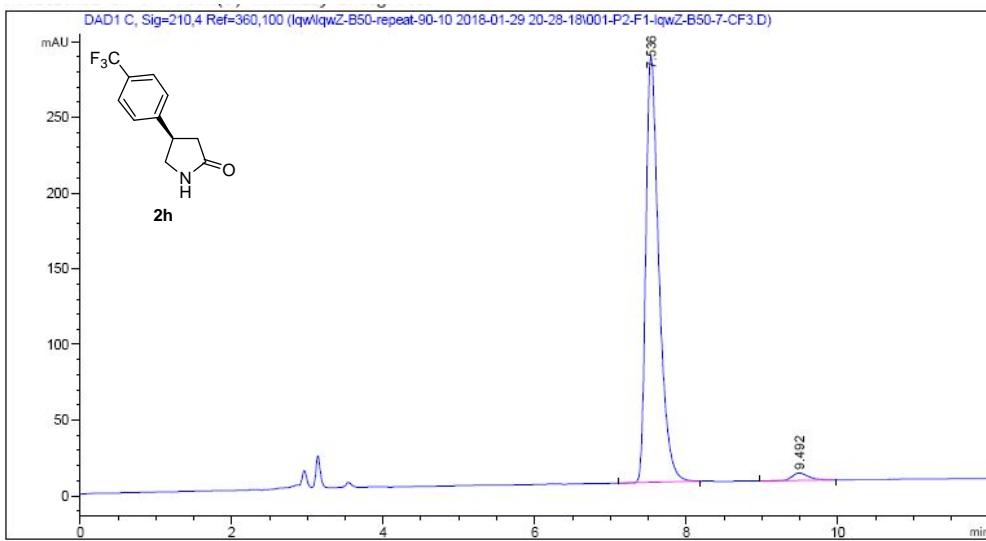
Peak	RetTime	Type	Width	Area	Height	Area %
#	[min]		[min]	[mAU*s]	[mAU]	%
1	9.541	BB	0.2325	1.99141e4	1287.27734	98.0279
2	11.263	BB	0.2701	400.62732	22.45642	1.9721

Totals : 2.03148e4 1309.73376



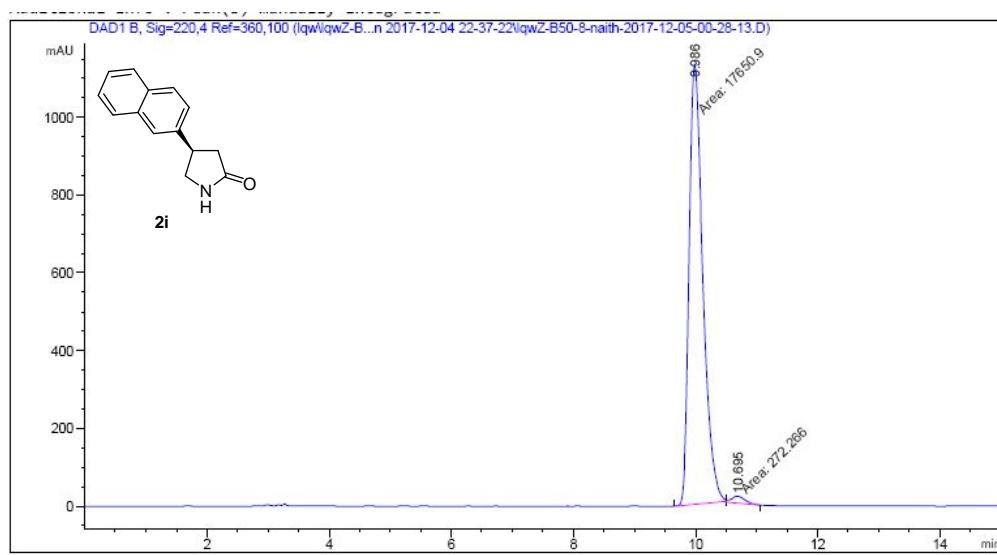
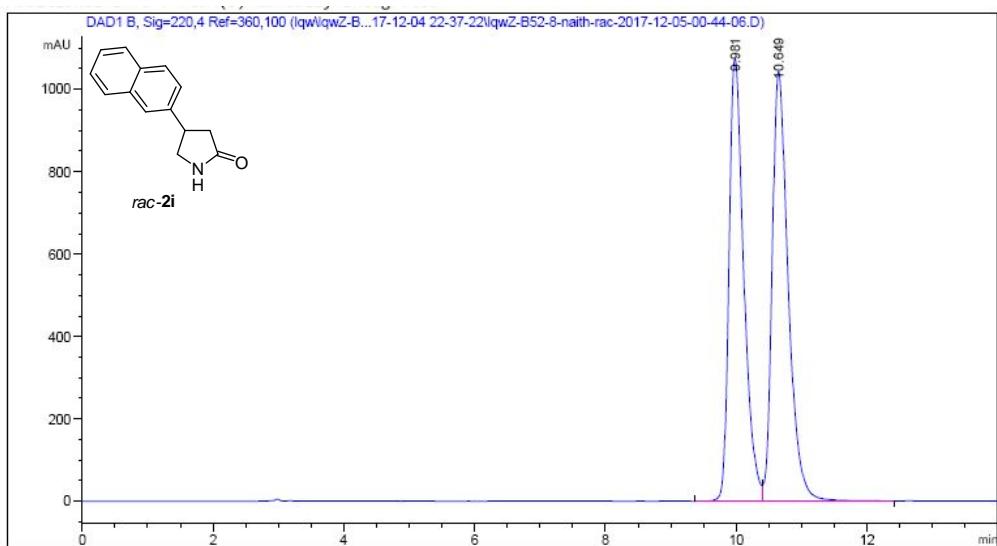
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.108	BB	0.2713	6774.90527	374.13309	49.9904
2	13.091	BBA	0.3093	6777.50586	333.20355	50.0096
Totals :						1.35524e4 707.33664



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

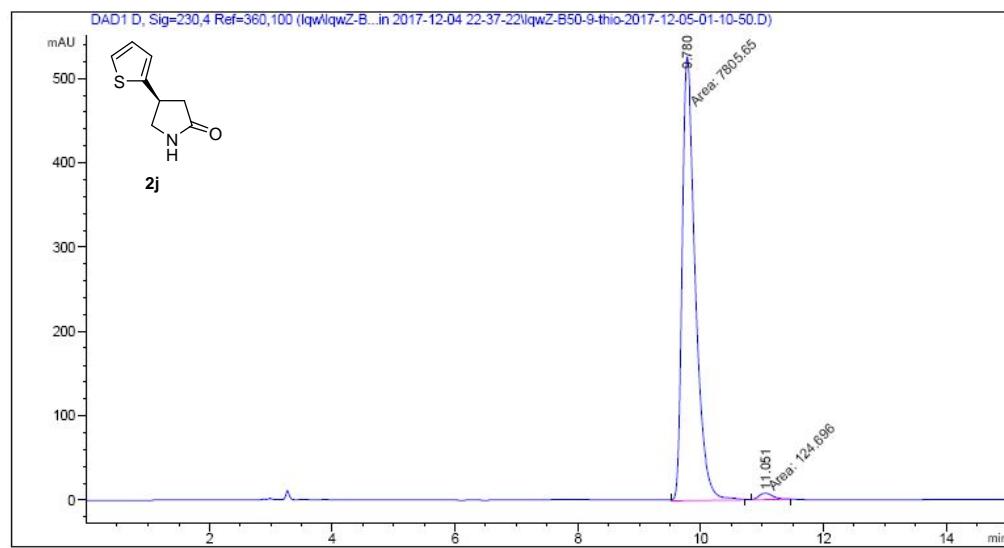
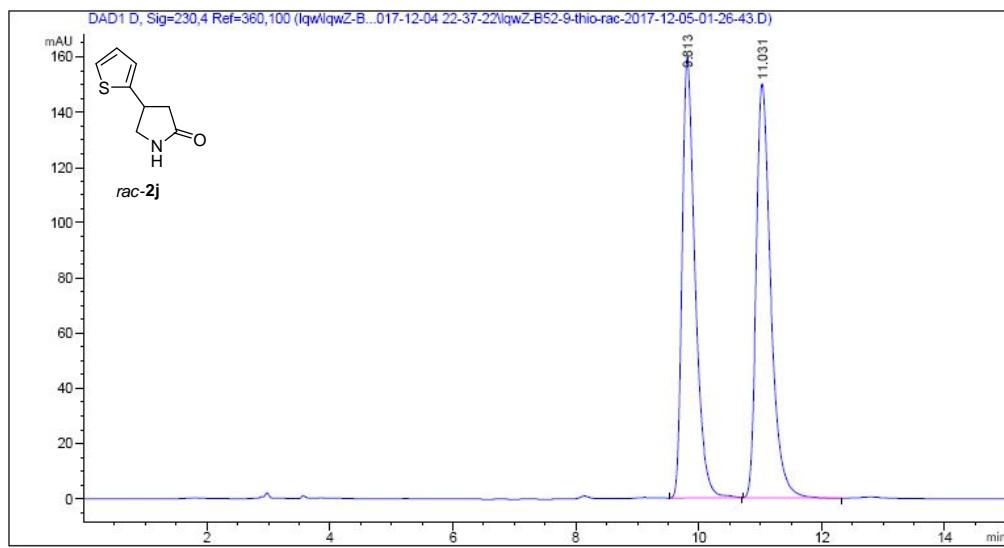
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.536	BB	0.1796	3367.27246	281.37869	97.7809
2	9.492	BB	0.2368	76.41823	4.93234	2.2191
Totals :						3443.69069 286.31103



Signal 1: DAD1 B, Sig=220,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area %
#	[min]		[min]	[mAU*s]	[mAU]	%
1	9.986	MM	0.2605	1.76509e4	1129.43445	98.4809
2	10.695	MM	0.2543	272.26602	17.84383	1.5191

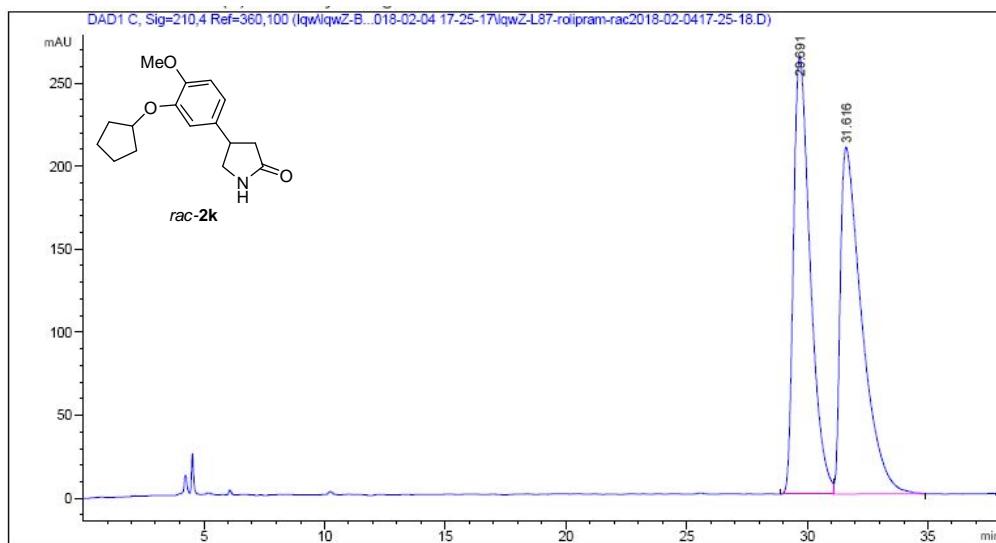
Totals : 1.79231e4 1147.27827



Signal 1: DAD1 D, Sig=230,4 Ref=360,100

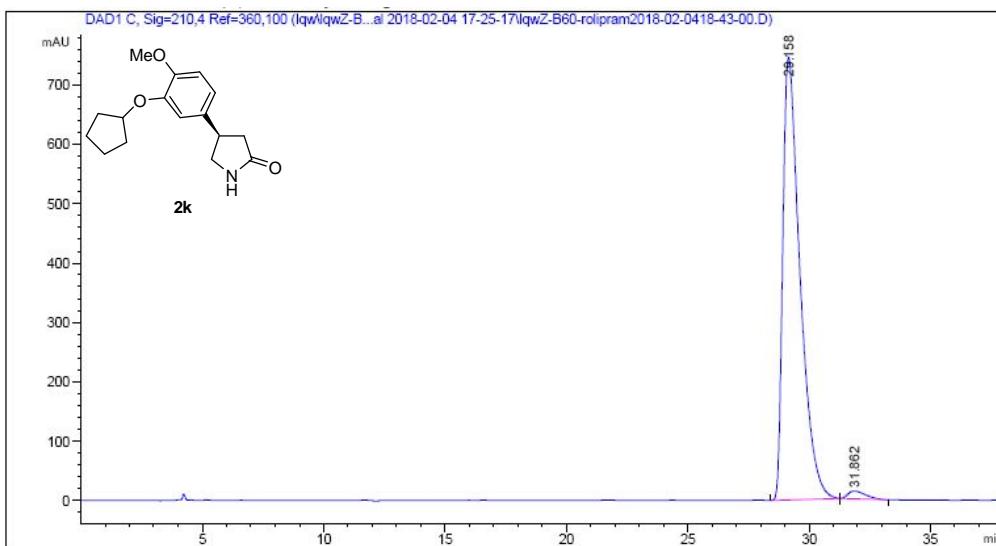
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.780	MM	0.2473	7805.64746	525.95551	98.4276
2	11.051	MM	0.2711	124.69579	7.66535	1.5724

Totals : 7930.34325 533.62085



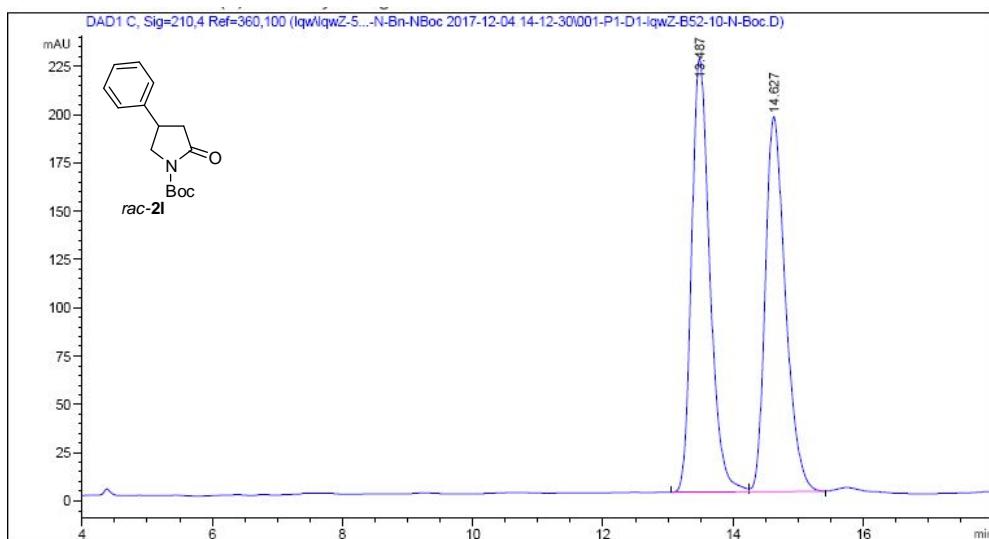
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.691	BV	0.7395	1.27066e4	263.06876	49.5097
2	31.616	VB	0.9311	1.29583e4	208.49011	50.4903
Totals :						2.56649e4 471.55887



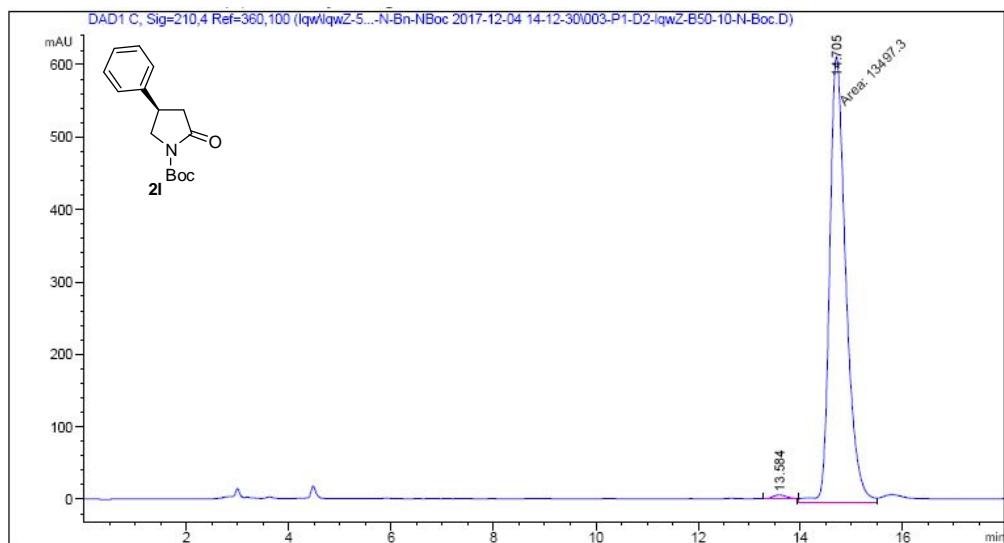
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.158	BB	0.7372	3.66461e4	745.92719	98.2366
2	31.862	BB	0.7802	657.80414	12.91518	1.7634
Totals :						3.73039e4 758.84236



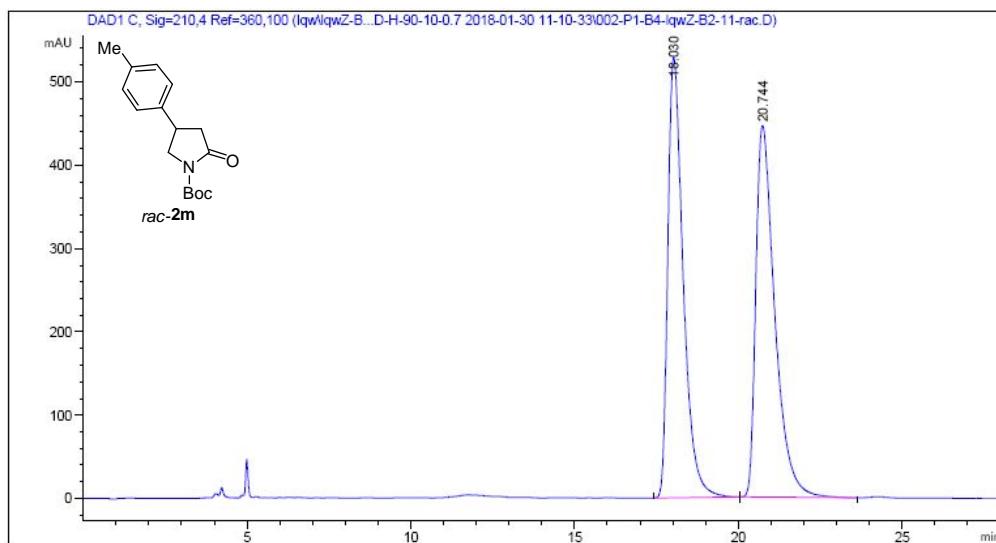
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.487	BV	0.2969	4365.03906	224.39825	51.1178
2	14.627	VB	0.3271	4174.12988	193.97275	48.8822
Totals :					8539.16895	418.37100



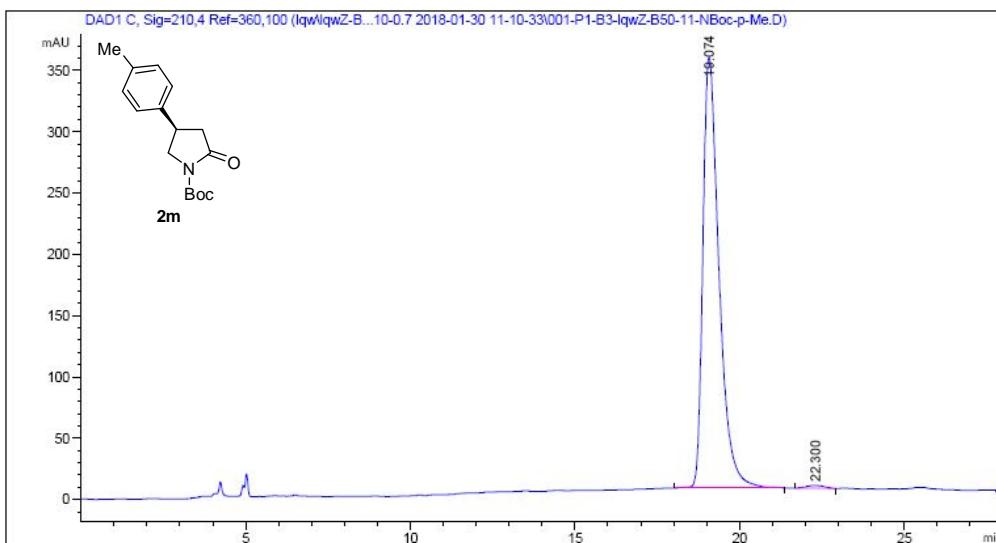
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.584	BB	0.2674	91.51817	5.35428	0.6735
2	14.705	MM	0.3658	1.34973e4	614.97711	99.3265
Totals :					1.35888e4	620.33139



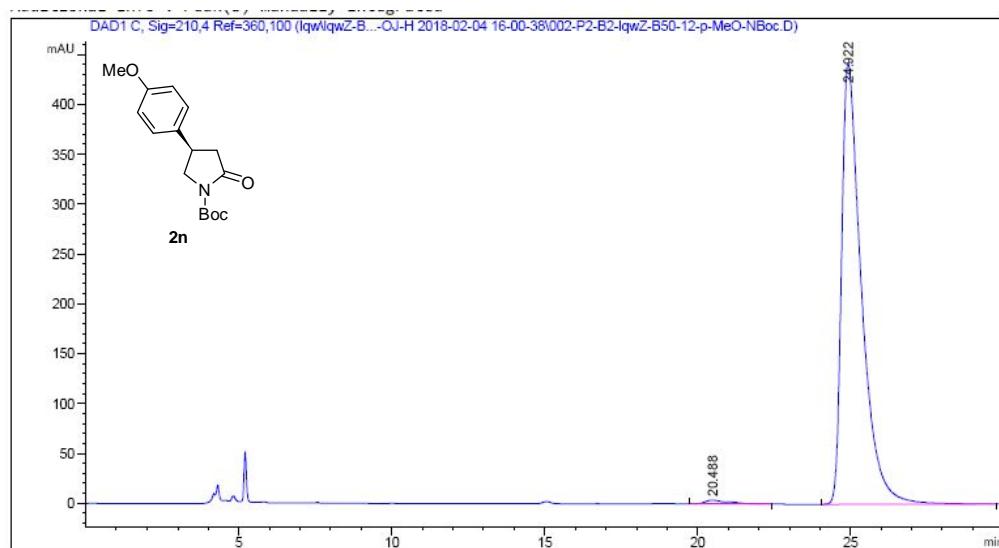
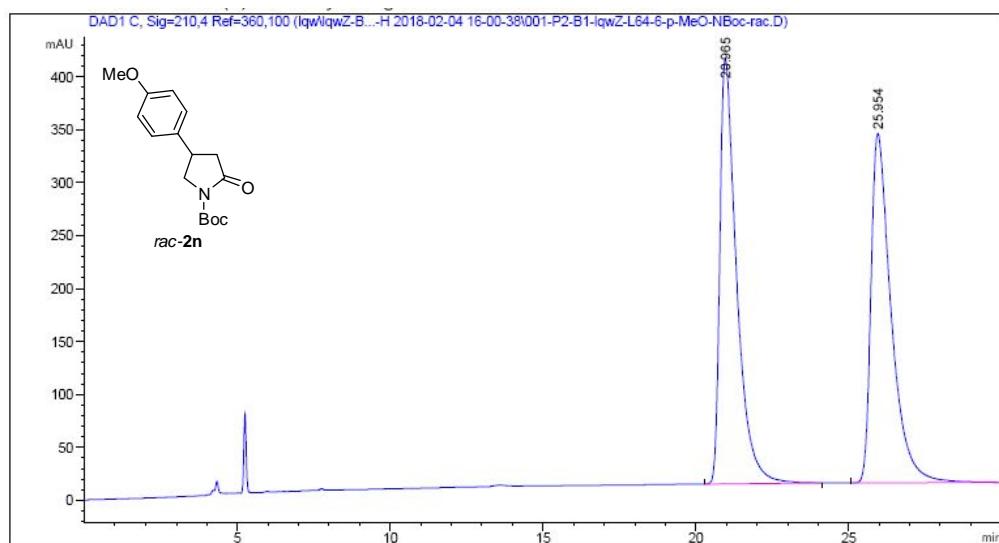
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.030	BB	0.4937	1.71967e4	528.35101	48.9810
2	20.744	BB	0.6049	1.79123e4	445.70758	51.0190
Totals :					3.51090e4	974.05859



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

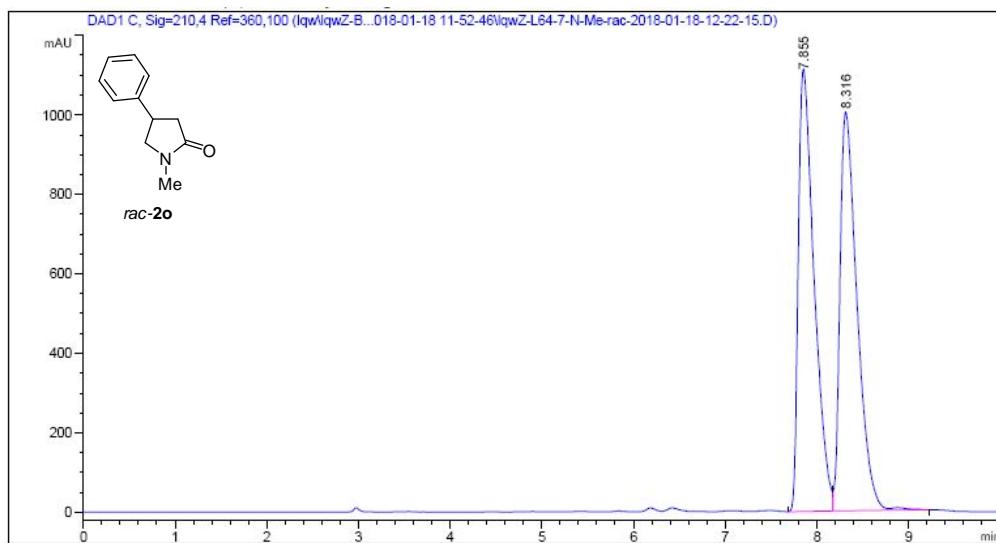
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.074	BB	0.5168	1.19526e4	351.43188	99.3533
2	22.300	BB	0.4444	77.79808	2.22227	0.6467
Totals :					1.20304e4	353.65416



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

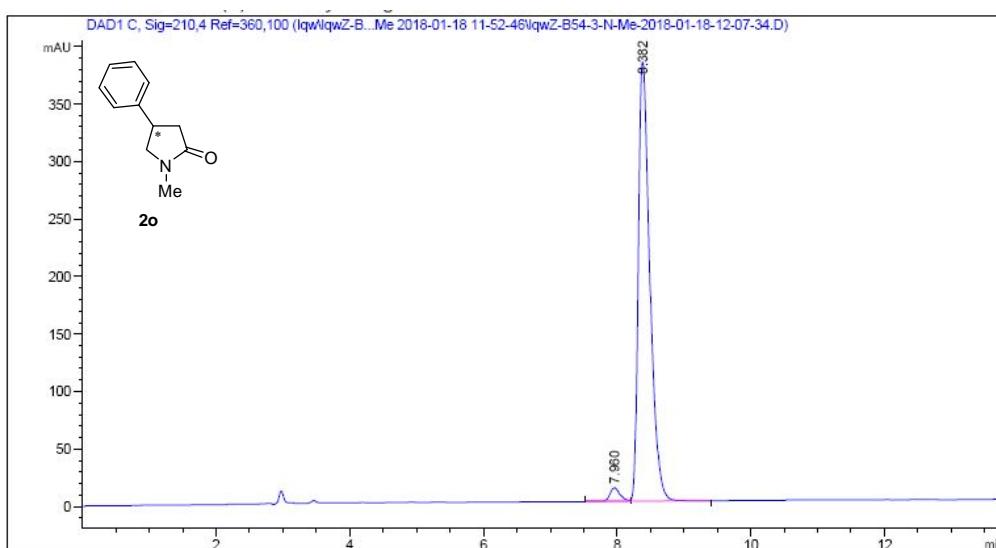
Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	20.488	BB	0.7348	214.59474	3.96915	1.0626
2	24.922	BB	0.6633	1.99797e4	442.06055	98.9374

Totals : 2.01943e4 446.02969



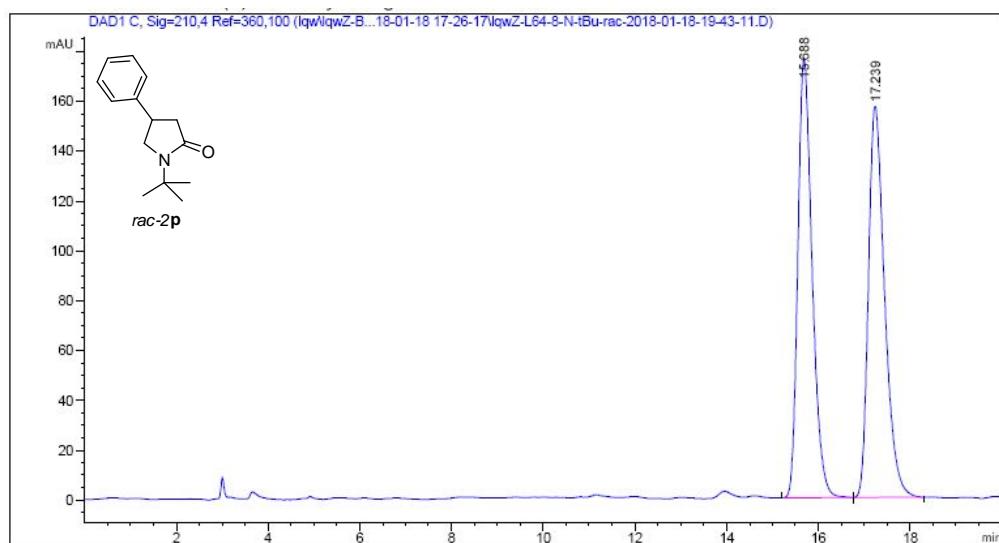
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.855	BV	0.1775	1.33160e4	1113.46008	50.5144
2	8.316	VV R	0.1947	1.30448e4	1003.62549	49.4856
Totals :						2.63607e4 2117.08557



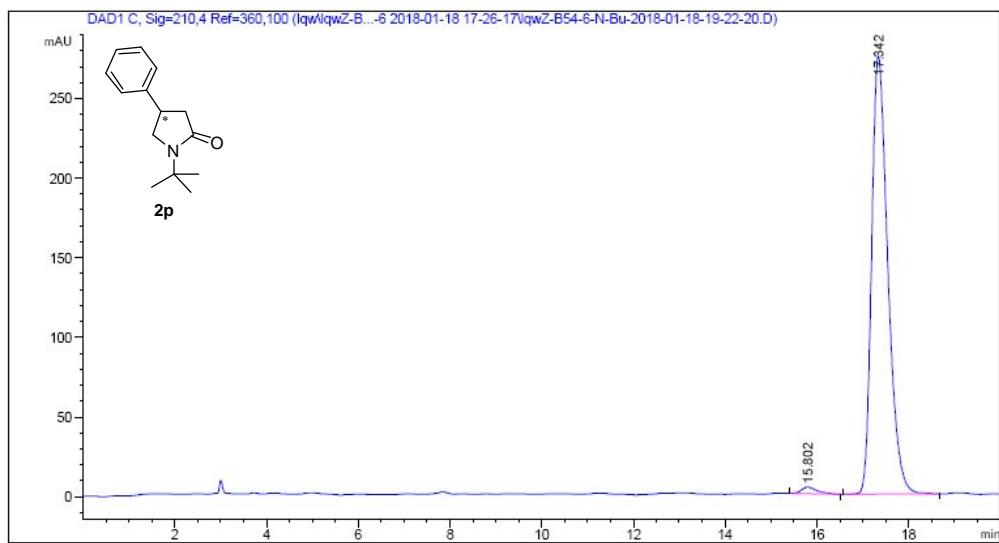
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.960	BV E	0.1579	122.21411	11.69882	2.6101
2	8.382	VB R	0.1814	4560.20801	381.62018	97.3899
Totals :						4682.42212 393.31900



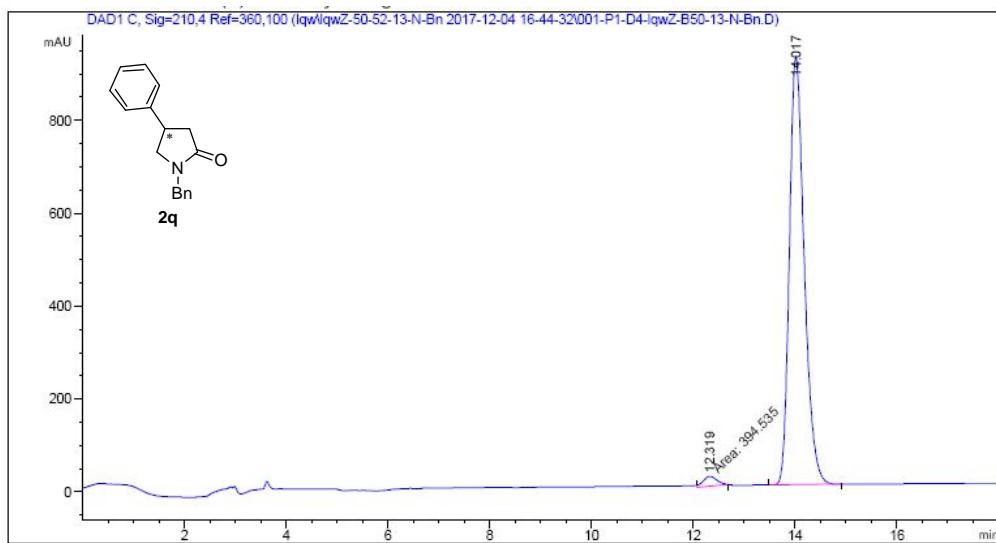
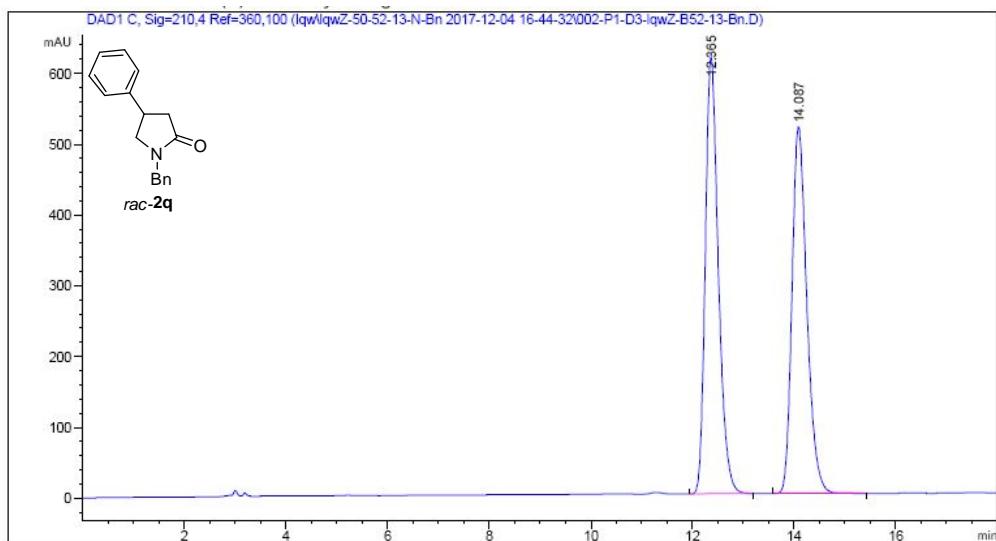
Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.688	BB	0.3307	3814.84253	176.11353	49.8074
2	17.239	BB	0.3717	3844.34106	156.99113	50.1926
Totals :					7659.18359	333.10466



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

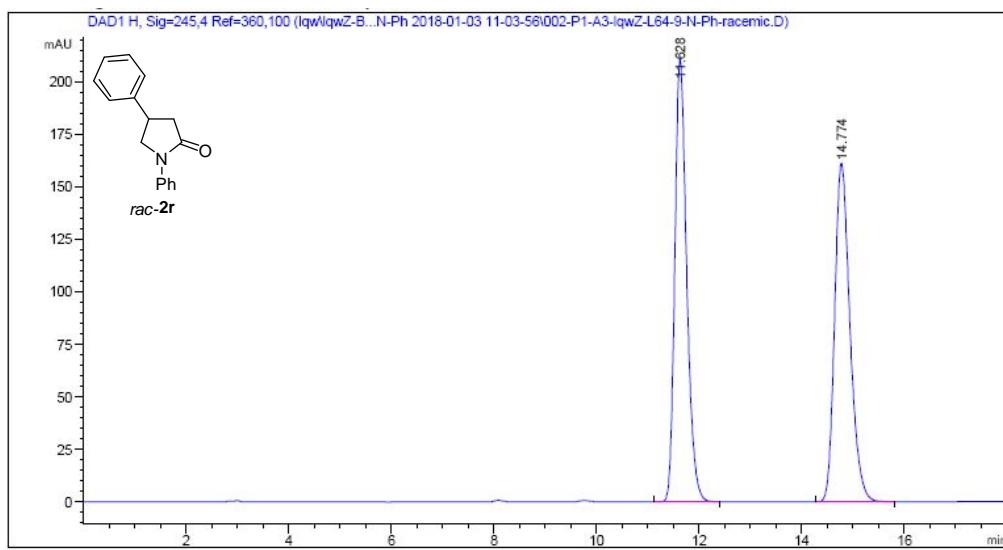
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.802	BB	0.3466	97.37701	4.13728	1.4241
2	17.342	BB	0.3759	6740.52930	275.07278	98.5759
Totals :					6837.90631	279.21006



Signal 1: DAD1 C, Sig=210,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area %
#	[min]		[min]	[mAU*s]	[mAU]	%
1	12.319	MM T	0.3115	394.53540	21.11200	2.0717
2	14.017	BB	0.3079	1.86495e4	922.25934	97.9283

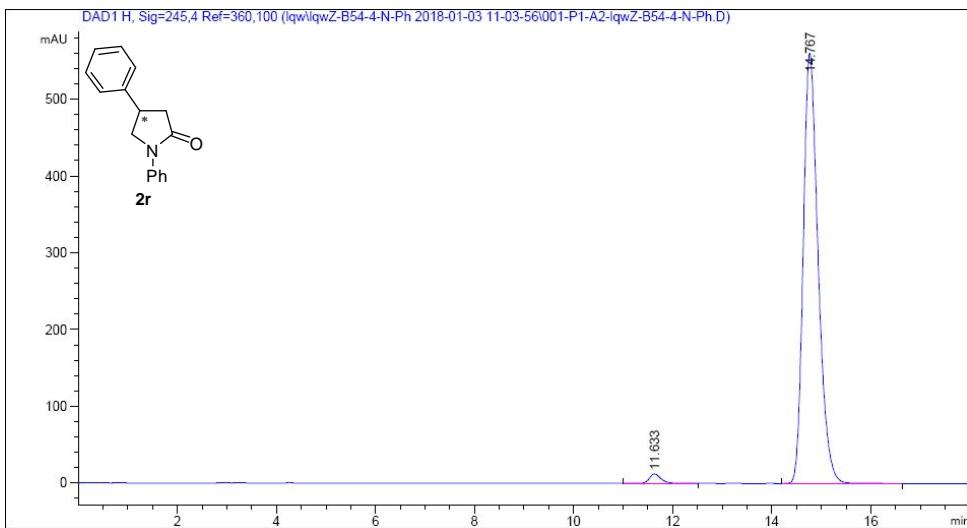
Totals : 1.90441e4 943.37133



Signal 1: DAD1 H, Sig=245,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.628	BB	0.2427	3375.69482	210.90459	50.2870
2	14.774	BB	0.3174	3337.16211	161.26262	49.7130

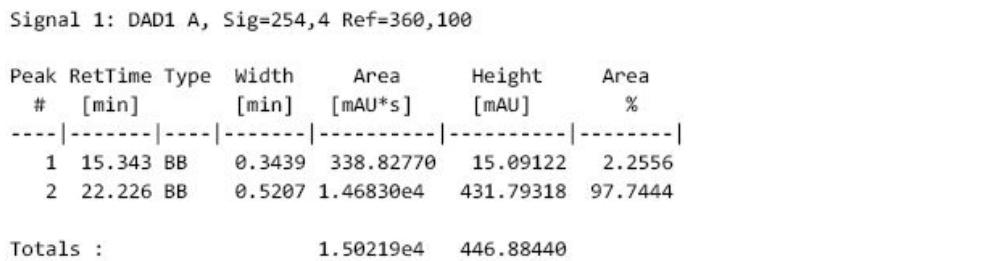
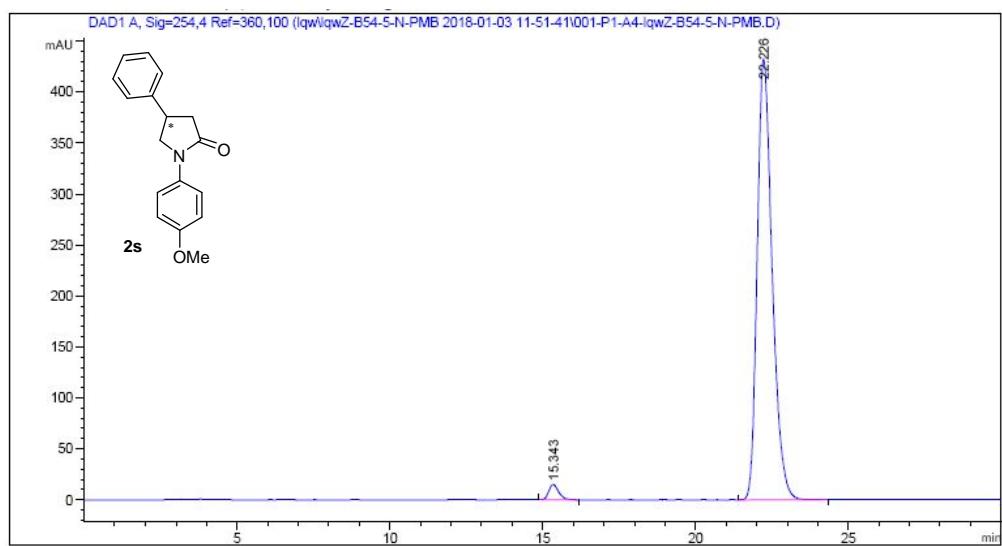
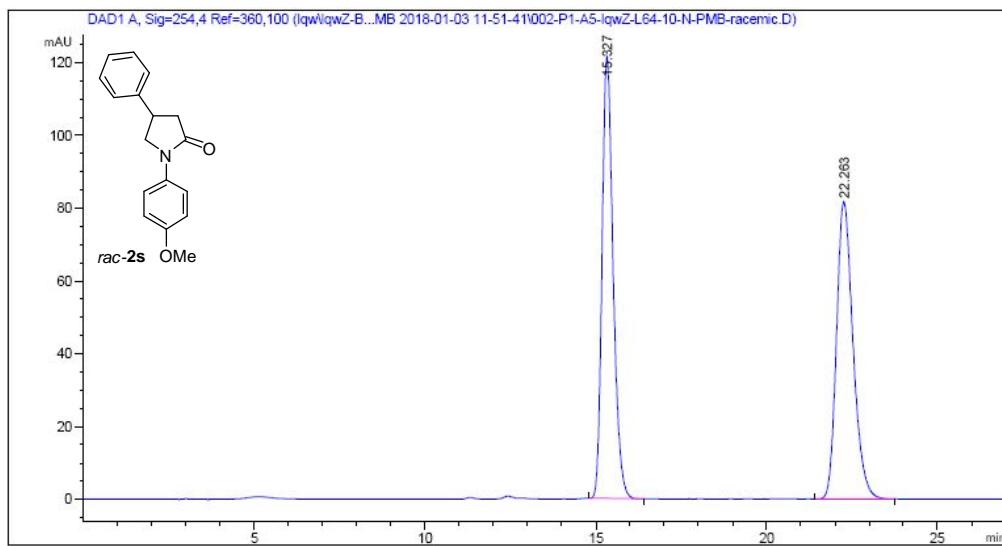
Totals : 6712.85693 372.16721

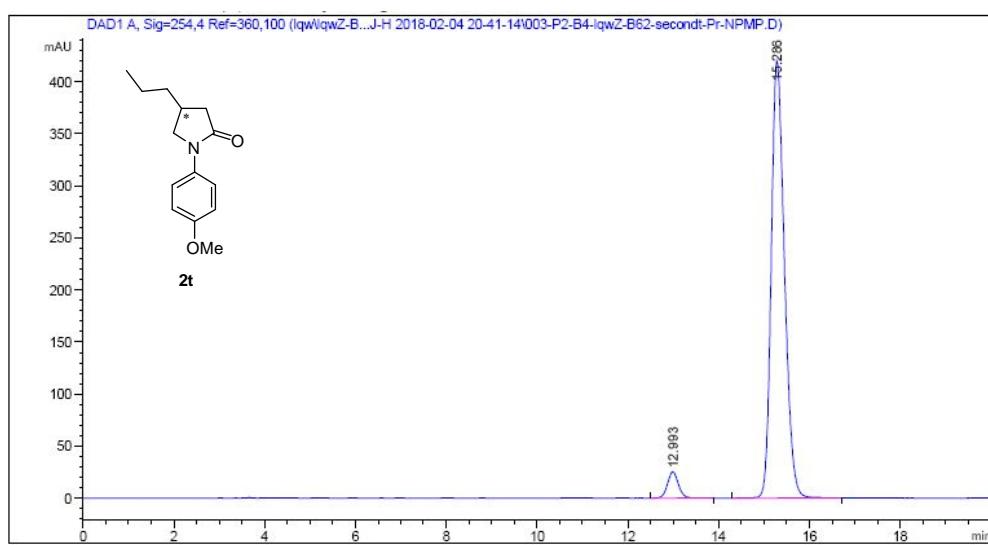
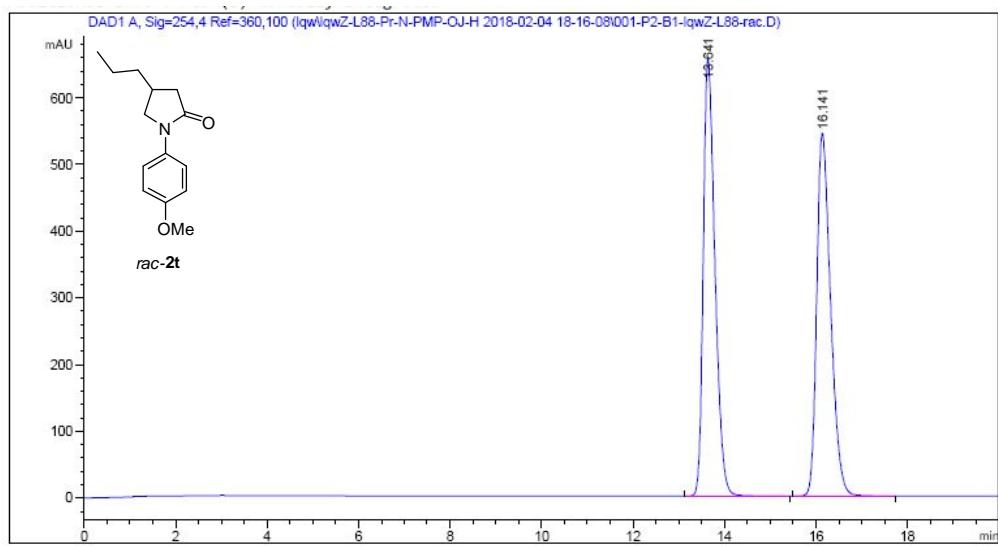


Signal 1: DAD1 H, Sig=245,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.633	BB	0.2472	197.29919	12.16405	1.6610
2	14.767	BB	0.3193	1.16810e4	560.06946	98.3390

Totals : 1.18783e4 572.23351

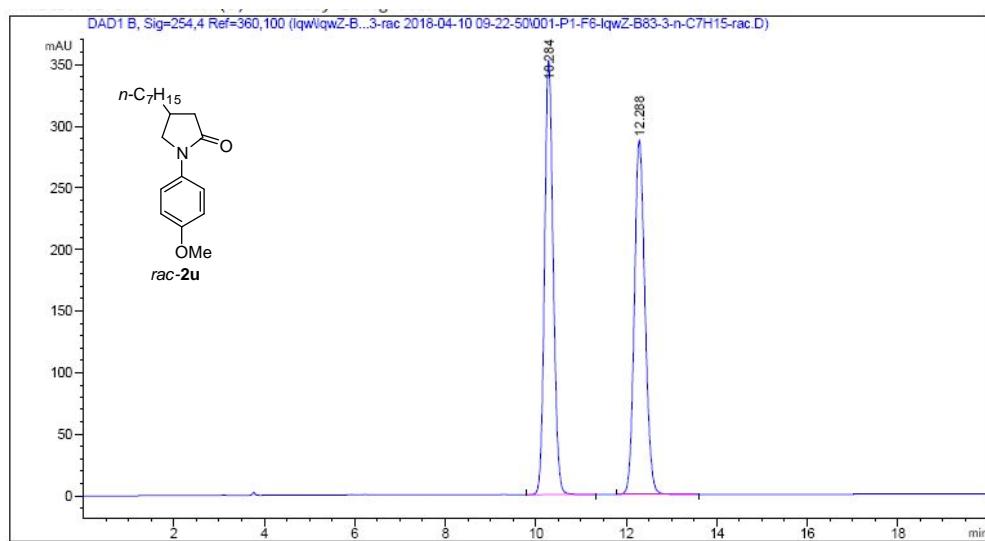




Signal 1: DAD1 A, Sig=254,4 Ref=360,100

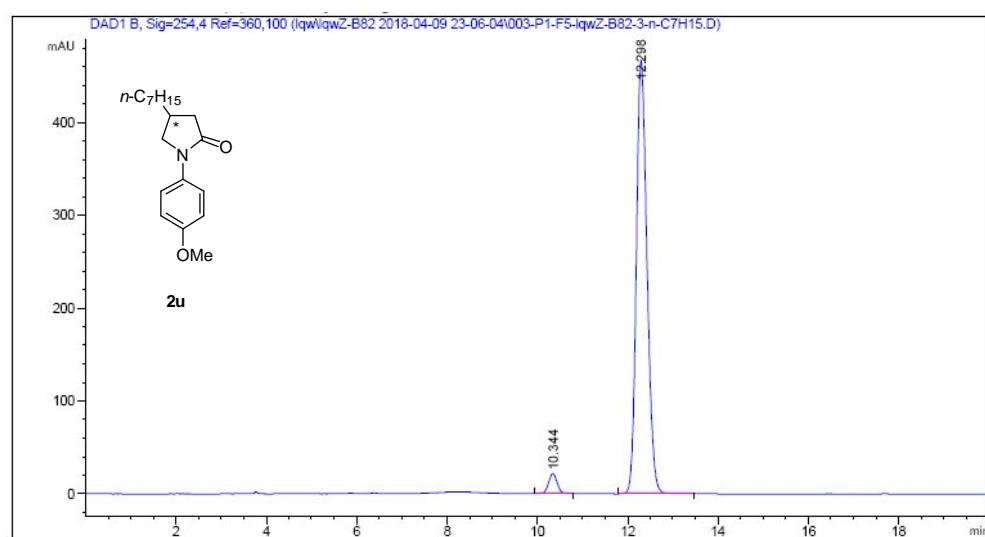
Peak	RetTime	Type	Width	Area	Height	Area %
#	[min]		[min]	[mAU*s]	[mAU]	%
1	12.993	BB	0.2565	418.01108	25.07658	4.7000
2	15.286	BB	0.3095	8475.78027	419.87122	95.3000

Totals : 8893.79135 444.94780



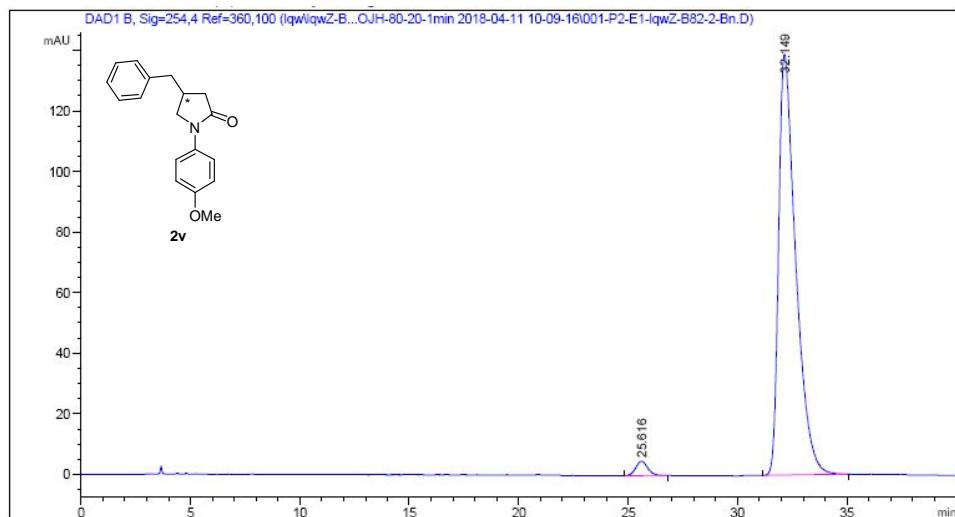
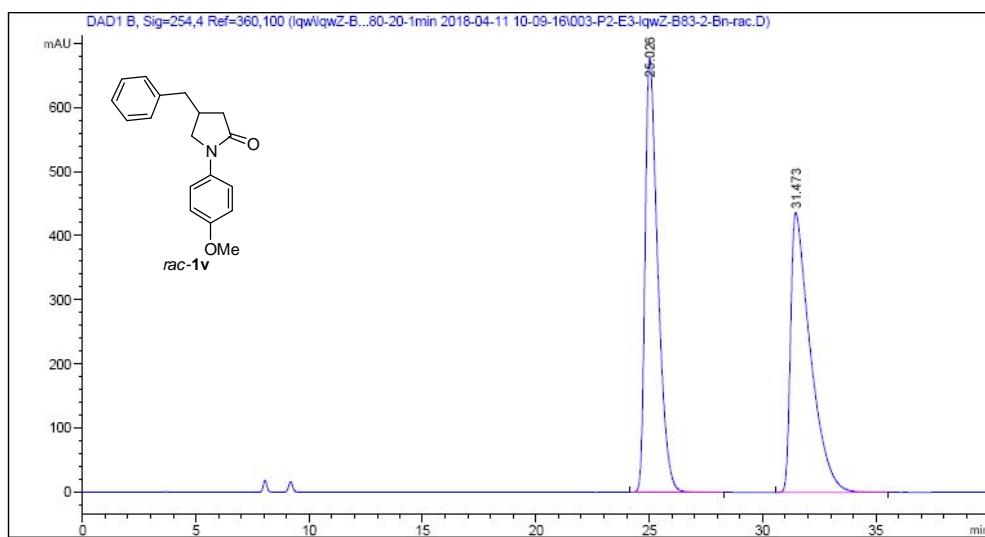
Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.284	BB	0.2048	4675.63916	352.34766	49.9545
2	12.288	BB	0.2520	4684.15576	287.57803	50.0455
Totals :					9359.79492	639.92569



Signal 1: DAD1 B, Sig=254,4 Ref=360,100

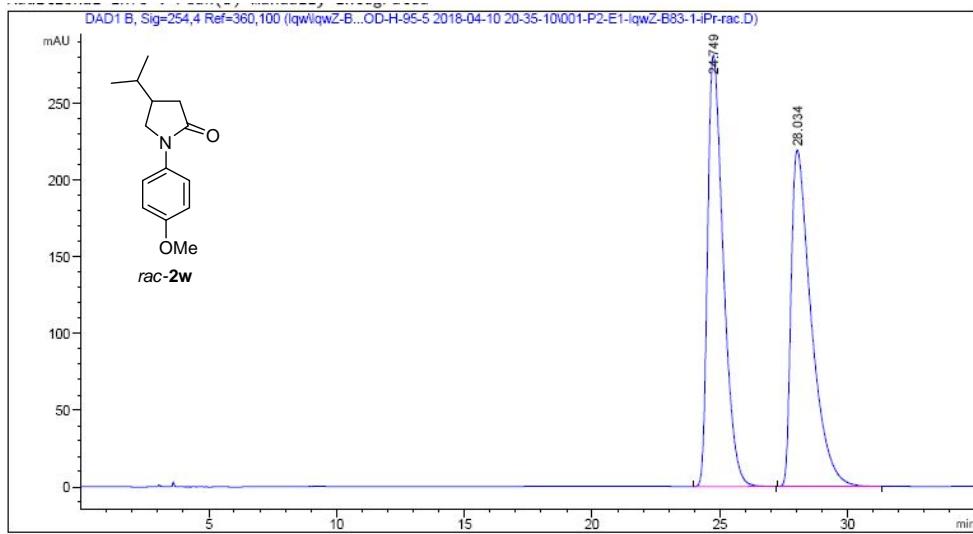
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.344	BB	0.2068	289.24417	21.79973	3.6512
2	12.298	BB	0.2508	7632.66699	466.72543	96.3488
Totals :					7921.91116	488.52516



Signal 1: DAD1 B, Sig=254,4 Ref=360,100

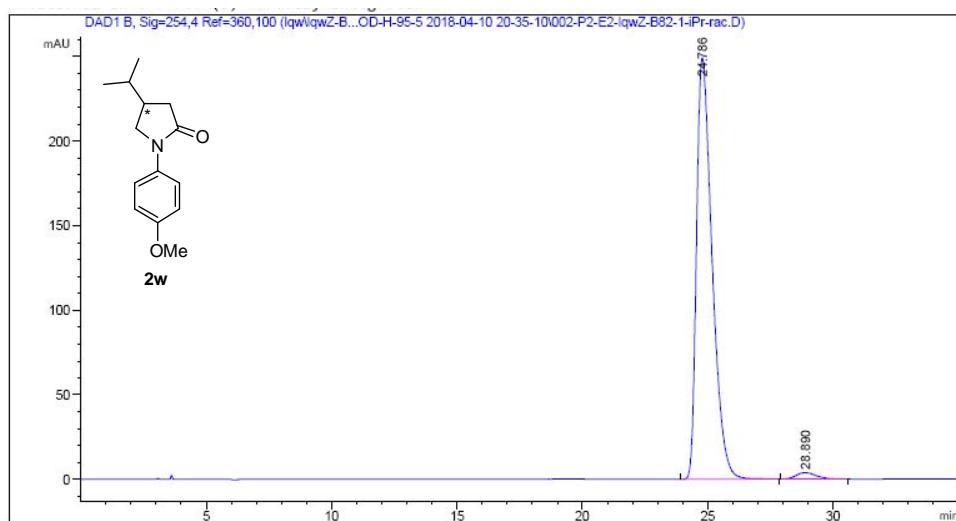
Peak	RetTime	Type	Width	Area	Height	Area %
#	[min]		[min]	[mAU*s]	[mAU]	%
1	25.616	BB	0.5564	177.66013	4.70631	2.2996
2	32.149	BB	0.8039	7547.99219	138.92703	97.7004

Totals : 7725.65231 143.63334



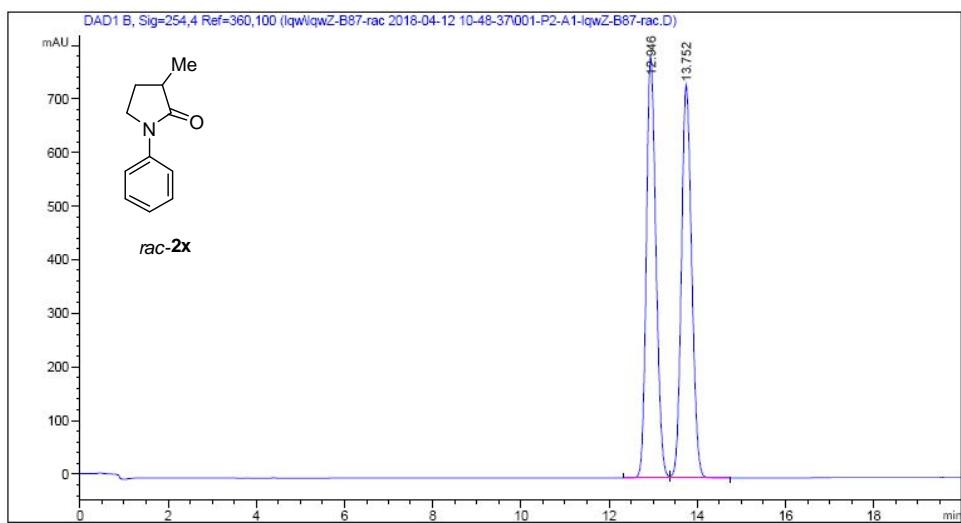
Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.749	BB	0.6512	1.19831e4	281.17130	50.0331
2	28.034	BB	0.8107	1.19673e4	219.28062	49.9669
Totals :					2.39504e4	500.45192



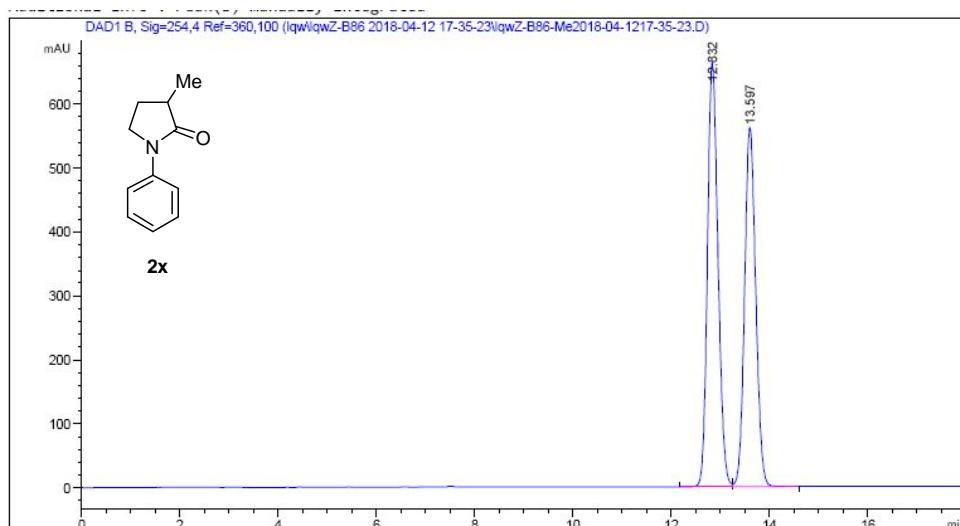
Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.786	BB	0.6595	1.07466e4	249.03342	98.0362
2	28.890	BB	0.6821	215.27481	3.83952	1.9638
Totals :					1.09619e4	252.87293



Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.946	BV	0.2350	1.19363e4	786.80060	50.1942
2	13.752	VB	0.2507	1.18439e4	732.17419	49.8058
Totals :					2.37802e4	1518.97479



Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.832	BV	0.2293	9854.91211	663.40125	52.7688
2	13.597	VB	0.2434	8820.71777	561.13080	47.2312
Totals :					1.86756e4	1224.53204