



Supporting Information

Enantioselective Nickel-Catalyzed C(sp³)–H Activation of Formamides

*Y.-X. Wang, F.-P. Zhang, H. Chen, Y. Li, J.-F. Li, M. Ye**

Supporting Information

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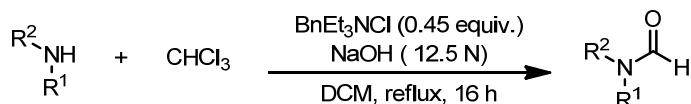
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1. General Information

Unless stated otherwise, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. All solvents were distilled from appropriate drying agents prior to use. All reagents were used as received from commercial suppliers unless otherwise stated. Non-commercially available substrates were synthesized following reported protocols. Melting points were measured on X-4B microscope melting point apparatus and uncorrected. Thin-layer chromatography (TLC) was performed by UV absorbance (254 nm). 200–300 mesh silica gel was used for column chromatography separation. NMR spectra were recorded on Bruker AV 400 spectrometer at 400 MHz (^1H NMR), 100 MHz (^{13}C NMR), 376 MHz (^{19}F NMR) and 162 MHz (^{31}P NMR). Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference (CDCl_3 : $\delta_{\text{H}} = 7.26$ ppm; $\delta_{\text{C}} = 77.16$ ppm). All coupling constants (J values) were reported in Hertz (Hz). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), triplet of doublets (td), quartet (q), and multiplet (m). High resolution mass spectra (HRMS) were recorded on an Agilent 6520 Q-TOF LC/MS with Electron Spray Ionization (ESI) resource. Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1260 with commercial ChiralPak 4.6 × 250 mm columns. Optical rotations were determined by a Rudolph Autopol VI Automatic polarimeter. Single crystal X-ray diffraction data were collected on Rigaku Saturn70 diffractometer.

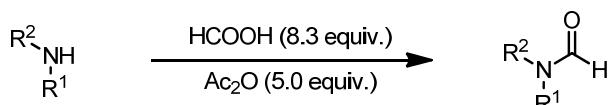
2. General Procedure for Preparation of Formamides

Method A



To a solution of secondary amine (10 mmol, 1.0 equiv.), BnEt_3NCl (1.03 g, 4.5 mmol, 0.45 equiv.) and CHCl_3 (7.3 mL, 92 mmol, 9.2 equiv.) in CH_2Cl_2 (30 mL) was added aqueous NaOH (25 mL, 12.5 M). The resulting mixture was then heated to reflux for 16 h, diluted with H_2O (45 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (3×30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of $\text{EtOAc}/n\text{-hexane}$.

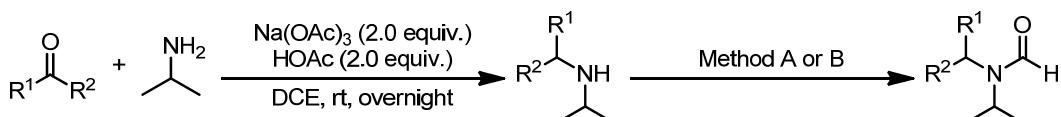
Method B



A mixture of formic acid (3.1 mL, 83 mmol, 8.3 equiv.) and Ac_2O (4.7 mL, 50 mmol, 5.0 equiv.) was stirred at 70 °C for 1 h and then cooled to room temperature. Primary or secondary amine (10 mmol, 1.0 equiv.) was added slowly and the resulting mixture was

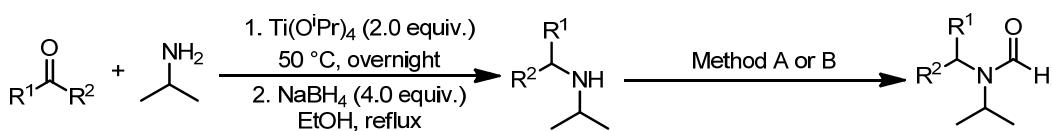
stirred at 50 °C. After the reaction was complete (monitored by TLC), the mixture was concentrated in *vacuo*, neutralized with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc/*n*-hexane.

Method C

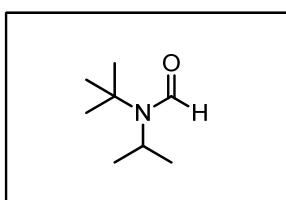


A mixture of aldehyde or ketone (10 mmol, 1.0 equiv.), isopropylamine (0.59 g, 10 mmol, 1.0 equiv.), AcOH (1.14 mL, 20 mmol, 2.0 equiv.) and NaBH(OAc)₃ (4.24 g, 20 mmol, 2.0 equiv.) in DCE (30 mL) were stirred at room temperature overnight, quenched with a solution of NaOH (1M), and stirred for another 30 min. The solution was extracted with DCM (2 × 20 mL), dried over anhydrous Na₂SO₄, filtered, evaporated under vacuum to form the crude secondary amine, which was then subjected to method A or B to give the corresponding formamide.

Method D

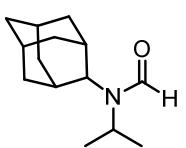


A mixture of isopropylamine (1.18 g, 20 mmol, 2.0 equiv.), aldehyde or ketone (10 mmol, 1.0 equiv.) and Ti(O'Pr)₄ (5.68 g, 20 mmol, 2.0 equiv.) was stirred at 50 °C overnight and then cooled to room temperature. The mixture was diluted with EtOH (20 mL) and NaBH₄ (1.51 g, 40 mmol, 4.0 equiv.) was added slowly. The resulting mixture was heated to reflux for 2 h, cooled to room temperature, quenched with NaOH (4.0 mL, 4N), filtered and concentrated to form the crude secondary amine, which was then subjected to method A or B to give the formamide.



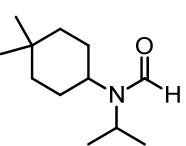
N-tert-Butyl-*N*-isopropylformamide (**1a**)^[1]

Method A. White solid (1.36 g, 95%), m.p. 44–46 °C, inseparable mixture of rotamers. ¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 3.80 – 3.70 (m, 0.05 H), 3.54 – 3.44 (m, 0.95H), 1.41 (d, *J* = 6.8 Hz, 6H), 1.31 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 161.1, 56.4, 47.2, 29.3, 28.9, 25.5, 20.2.



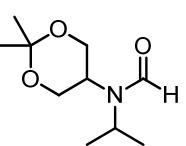
N-(Adamantan-2-yl)-N-isopropylformamide (1b)

Method C (with A). White solid (1.88 g, 85%), m.p. 83–85 °C, inseparable mixture of rotamers. **¹H NMR** (400 MHz, CDCl₃) δ 8.39 (s, 0.85H), 8.37 (s, 0.15H), 3.93 – 3.85 (m, 1H), 3.35 (s, 1H), 2.20 (s, 0.3H), 2.14 (s, 1.7H), 1.97 – 1.85 (m, 6H), 1.84 – 1.76 (m, 2H), 1.73 (s, 2H), 1.63 (d, *J* = 12.8 Hz, 2H), 1.35 (d, *J* = 6.8 Hz, 0.91H), 1.30 (d, *J* = 6.8 Hz, 5.09H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.2, 162.0, 62.1, 59.3, 47.9, 45.1, 38.4, 38.3, 37.5, 37.5, 32.7, 31.5, 31.3, 30.5, 27.5, 27.2, 27.1, 24.6, 19.7. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₄H₂₄NO 222.1852, found 222.1848.



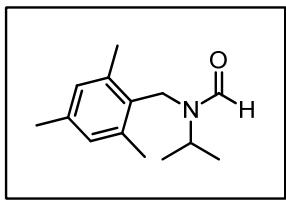
N-(4,4-Dimethylcyclohexyl)-N-isopropylformamide (1c)

Method C (with B). White solid (1.68 g, 85%), m.p. 68–70 °C, inseparable mixture of rotamers. **¹H NMR** (400 MHz, CDCl₃) δ 8.15 (s, 1H), 4.28 – 4.18 (m, 0.52H), 3.71 – 3.61 (m, 0.48H), 3.50 – 3.60 (m, 0.48H), 3.01 – 2.91 (m, 0.52H), 2.03 – 1.85 (m, 1H), 1.75 – 1.62 (m, 1H), 1.61 – 1.49 (m, 1H), 1.47 – 1.29 (m, 3H), 1.28 – 1.19 (m, 5H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 9.2 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 161.8, 161.7, 55.1, 52.6, 47.2, 44.3, 38.9, 38.7, 32.7, 32.6, 29.9, 29.6, 29.5, 25.8, 24.1, 24.0, 23.7, 20.4. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₂H₂₄NO 198.1852, found 198.1850.



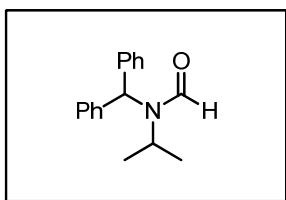
N-(2,2-Dimethyl-1,3-dioxan-5-yl)-N-isopropylformamide (1d)

Method D (with B). White solid (1.21 g, 60%), m.p. 63–65 °C, inseparable mixture of rotamers. **¹H NMR** (400 MHz, CDCl₃) δ 8.49 (s, 0.28H), 8.11 (s, 0.72H), 4.65 – 4.55 (m, 1.6 H), 3.99 – 3.95 (m, 0.7 H), 3.92 – 3.85(m, 0.7 H), 3.84 – 3.78 (m, 0.7 H), 3.66 – 3.62 (m, 1.5H), 3.59 – 3.52 (m, 0.8H), 3.42 – 3.35 (m, 0.4H), 1.55 (s, 2.2H), 1.43 (s, 1.0H), 1.41 (s, 1.0H), 1.39 (s, 2.2H), 1.24 (d, *J* = 6.8 Hz, 4.5H), 1.14 (d, *J* = 6.8 Hz, 1.8H). **¹³C NMR** (100 MHz, CDCl₃) δ 162.8, 161.9, 98.7, 98.2, 64.1, 60.2, 49.9, 46.9, 43.6, 27.2, 24.7, 22.6, 22.2, 20.8, 20.7, 20.4. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₀H₂₀NO₃ 202.1438, found 202.1436.



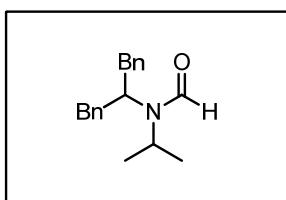
N-Isopropyl-N-(2,4,6-trimethylbenzyl)formamide (1e)

Method C (with B). White solid (2.02 g, 92%), m.p. 75–77 °C, inseparable mixture of rotamers. **¹H NMR** (400 MHz, CDCl₃) δ 8.36 (s, 0.5H), 7.61 (s, 0.5H), 6.86 (d, *J* = 9.2 Hz, 2H), 4.63 (s, 1H), 4.58 – 4.46 (m, 0.5H), 4.25 (s, 1H), 3.24 – 3.08 (m, 0.5H), 2.27 (s, 3H), 2.26 (s, 6H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 161.5, 161.2, 138.2, 138.1, 137.8, 137.4, 129.6, 129.5, 127.3, 47.1, 44.3, 41.8, 39.8, 23.0, 21.0, 21.0, 20.1, 19.7, 19.3. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₄H₂₂NO 220.1696, found 220.1692.



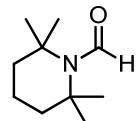
N-Benzhydryl-N-isopropylformamide (1f)

Method C (with B). White solid (2.28 g, 90%), m.p. 78–80 °C, inseparable mixture of rotamers. **¹H NMR** (400 MHz, CDCl₃) δ 8.53 (s, 0.24H), 8.13 (s, 0.76H), 7.41 – 7.25 (m, 7H), 7.17 (d, *J* = 8.0 Hz, 3H), 6.77 (s, 0.24H), 5.77 (s, 0.76H), 4.78 – 4.65 (m, 0.76H), 3.70 – 3.57 (m, 0.24H), 1.20 (d, *J* = 6.8 Hz, 4.62H), 1.18 (d, *J* = 6.8 Hz, 1.38H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.1, 162.1, 140.5, 139.2, 129.0, 128.8, 128.5, 128.3, 127.9, 127.6, 61.5, 60.0, 47.8, 45.1, 24.1, 20.6. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₇H₂₀NO 254.1539, found 254.1534.



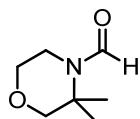
N-(1,3-Biphenylpropan-2-yl)-N-isopropylformamide (1g)

Method C (with B). White solid (2.02 g, 72%), m.p. 81–83 °C, inseparable mixture of rotamers. **¹H NMR** (400 MHz, CDCl₃) δ 8.21 (s, 0.27H), 8.16 (s, 0.73H), 7.34 – 7.24 (m, 4H), 7.23 – 7.15 (m, 5H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.26 – 4.10 (m, 0.27H), 3.80 – 3.51 (m, 0.73H), 3.42 – 3.15 (m, 2.38H), 3.11 – 2.97 (m, 1.62H), 2.97 – 2.89 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 1.63H), 0.68 (d, *J* = 3.4 Hz, 4.37H). **¹³C NMR** (100 MHz, CDCl₃) δ 162.9, 162.3, 139.5, 138.1, 129.5, 129.4, 128.8, 128.5, 127.0, 126.5, 59.4, 44.9, 41.7, 38.1, 22.2, 19.7. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₉H₂₄NO 282.1852, found 282.1847.



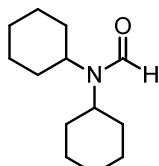
2,2,6,6-Tetramethylpiperidine-1-carbaldehyde (1h)^[2]

Method A. Colorless solid (1.59 g, 94%), m.p. 48–50 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.53 (s, 1H), 1.58 (s, 6H), 1.48 (s, 6H), 1.41 (s, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.7, 55.7, 55.4, 41.4, 40.2, 32.6, 28.1, 16.4.



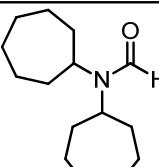
3,3-Dimethylmorpholine-4-carbaldehyde (1i)

Method B. White solid (1.32 g, 92%), m.p. 69–71 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.37 (s, 1H), 3.70 (t, *J* = 4.6 Hz, 2H), 3.62 (t, *J* = 4.8 Hz, 2H), 3.38 (s, 2H), 1.41 (s, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 159.9, 76.6, 67.2, 54.2, 36.3, 23.8. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₇H₁₄NO₂ 144.1019, found 144.1018.



N,N-Dicyclohexylformamide (1j)^[3]

Method B. Colorless oil (1.99 g, 95%). **¹H NMR** (400 MHz, CDCl₃) δ 8.18 (s, 1H), 4.05 – 3.80 (m, 1H), 3.13 – 2.93 (m, 1H), 1.85 – 1.71 (m, 6H), 1.67 – 1.54 (m, 6H), 1.51 – 1.39 (m, 2H), 1.36 – 1.20 (m, 4H), 1.16 – 1.02 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 161.9, 55.0, 52.5, 34.7, 30.4, 26.3, 25.9, 25.4, 25.3.



N,N-Dicycloheptylformamide (1k)^[3]

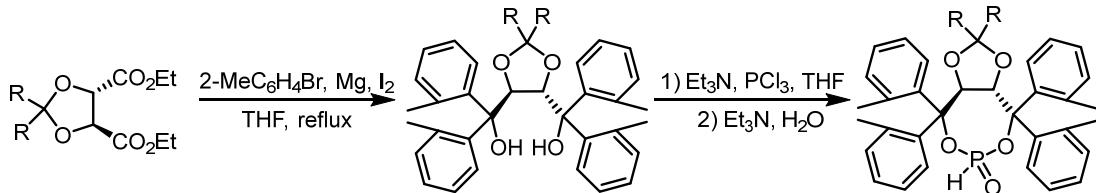
Method B. White solid (2.18 g, 92%), m.p. 49–51 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.11 (s, 1H), 4.00 – 3.80 (m, 1H), 3.30 – 3.16 (m, 1H), 1.94 – 1.81 (m, 4H), 1.75 – 1.65 (m, 8H), 1.64 – 1.55 (m, 4H), 1.54 – 1.39 (m, 8H). **¹³C NMR** (100 MHz, CDCl₃) δ 161.5, 58.2, 55.3, 36.8, 33.0, 27.6, 27.4, 25.6, 25.4.

3. Ligand Synthesis

Phosphite, phosphoramidite and phosphines oxides (PO) ligands were prepared

according to reported procedures in literatures. **L₁-L₃** were prepared according to Tomislav Rovis's method.^[4] **L₄-L₁₁** and **L₁₂-L₁₈** were prepared according to our previous method.^[5,6]

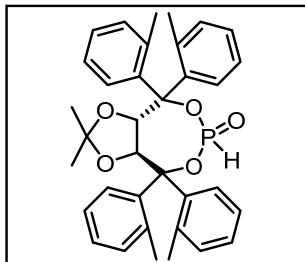
General procedure for the TADDOL-derived SPOs synthesis (**L₆-L₉**)



A solution of (-)-Diethyl L-tartrate (2.06 g, 10 mmol, 1.0 equiv.), ketone (2.0 equiv.) or benzophenone dimethylketal (2.28 g, 1.0 equiv.), and *p*-toluenesulfonic acid (0.34 mg, 0.01 equiv.) in toluene (80 mL) was refluxed overnight, cooled down to room temperature, washed with saturated NaHCO₃ solution and brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, EtOAc/*n*-hexane) to afford the protected (-)-diethyl tartrate.

To a two-neck flask equipped with a magnetic stirring bar and a reflux condenser were added activated magnesium turnings (42.5 mmol, 8.5 equiv.), one grain of I₂ and dry THF (10 mL). Then a portion (2 mL) of the solution of 1-bromo-2-methylbenzene (40 mmol, 8.0 equiv.) in THF (80 mL) was added dropwise to initiate the reaction (warmed by an oil bath). When the brown color disappeared, the remaining solution was added slowly and the reaction mixture was refluxed for 2 h. After cooled down to r.t., the solution was added the protected (-)-diethyl tartrate (5 mmol, 1.0 equiv.) in THF (20 mL) slowly, keeping the internal temperature below the boiling point of the solvent. After complete addition, the reaction mixture was refluxed for 12 h and then cooled down to r.t. Saturated ammonium chloride solution (20 mL), hydrochloric acid (1.0 M, 5 mL) and water (30 mL) were added carefully. The resulting biphasic mixture was extracted with ether (4 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, EtOAc/*n*-hexanes) to obtain the corresponding TADDOL.

To a Schlenk flask charged with the corresponding TADDOL (3.0 mmol, 1.0 equiv.) in dry THF (10 mL) and Et₃N (1.25 mL, 9.0 mmol, 3.0 equiv.) was added a solution of freshly distilled PCl₃ (0.52 mL, 6 mmol, 2.0 equiv.) in dry THF (10 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at the same temperature for 1 h, and to which, were added triethylamine (0.42 mL, 3.0 mmol, 1.0 equiv.) and H₂O (54 μL, 3.0 mmol, 1.0 equiv.) sequentially *via* a syringe at 0 °C. The resulting mixture was warmed to 23 °C and stirred for 1 h. Solid triethylammonium chloride was removed by filtration through a pad of MgSO₄ and the solvent was removed in *vacuo*. The crude product was purified by flash chromatography to afford pure TADDOL-derived secondary phosphine oxides (**L₆-L₉**).

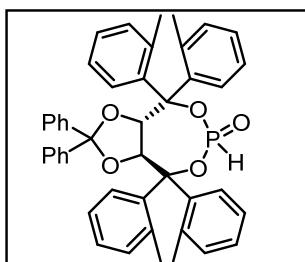


(3a*S*,8a*S*)-2,2-Dimethyl-4,4,8,8-tetra-o-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine 6-oxide (L₆)

White foam solid (1.2 g, 45% of all steps). **¹H NMR (400 MHz, CDCl₃)** δ 8.18 (s, 1H), 7.90 – 7.75 (m, 3H), 7.69 (s, 1H), 7.43 – 7.20 (m, 8H), 7.19 – 7.09 (m, 2H), 7.07 – 6.93 (m, 2H), 5.85 (d, *J* = 24.0 Hz, 2H), 1.97 (s, 6H), 1.57 (s, 6H), 0.47 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 139.9, 139.2, 139.0, 138.5, 136.8, 136.7, 136.6, 136.5, 133.1, 132.6, 129.1, 129.0, 128.6, 128.4, 128.3, 127.1, 125.9, 125.8, 125.7, 125.3, 114.9, 89.2, 89.1, 89.0, 88.9, 80.2, 80.2, 80.1, 80.0, 26.8, 26.4, 23.1, 23.0, 22.9, 21.6.

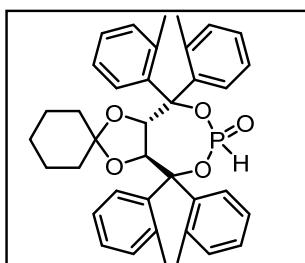
³¹P NMR (162 MHz, CDCl₃) δ -6.34. **HRMS (ESI)** m/z: [M+Na]⁺ calcd. for C₃₅H₃₇NaO₅P 591.2271, found 591.2263.



(3a*S*,8a*S*)-2,2-Diphenyl-4,4,8,8-tetra-o-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine 6-oxide (L₇)

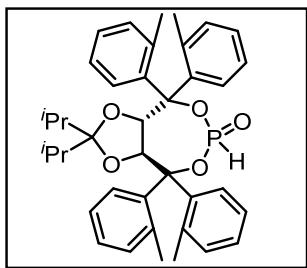
White foam solid (1.4 g, 47% of all steps). **¹H NMR (400 MHz, CDCl₃)** δ 8.17 – 7.55 (m, 4H), 7.40 (q, *J* = 7.4 Hz, 2H), 7.31 (q, *J* = 7.4 Hz, 3H), 7.22 – 6.81 (m, 12H), 6.80 – 5.94 (m, 7H), 6.75 (d, *J*_{P-H} = 723.6 Hz, 1H), 1.90 (s, 6H), 1.45 (s, 3H), 1.42 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 142.2, 141.9, 139.8, 139.7, 139.7, 139.6, 139.3, 139.2, 138.3, 137.5, 136.3, 136.3, 133.3, 133.2, 132.8, 132.7, 129.2, 129.1, 128.4, 128.3, 127.7, 127.6, 127.4, 127.0, 125.8, 125.8, 125.4, 125.3, 124.9, 89.0, 89.0, 89.0, 88.9, 81.4, 81.4, 81.3, 81.3, 27.0, 23.0, 21.6. **³¹P NMR (162 MHz, CDCl₃)** δ -5.5. **HRMS (ESI)** m/z: [M+Na]⁺ calcd. for C₄₅H₄₁NaO₅P 715.2584, found 715.2576.



(3a'*S*,8a'*S*)-4',4',8',8'-Tetra-o-tolyltetrahydrospiro[cyclohexane-1,2'-(1,3)dioxolo[4,5-*e*][1,3,2]dioxaphosphepine] 6'-oxide (L₈)

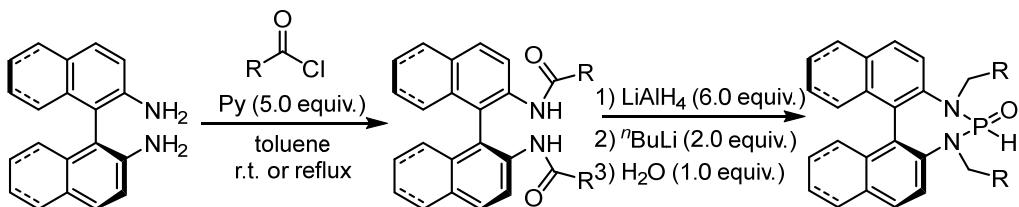
White foam solid (1.2 g, 41% of all steps). **¹H NMR** (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.81 (d, *J* = 6.8 Hz, 3H), 7.45 – 7.26 (m, 5H), 7.25 – 7.17 (m, 3H), 7.13 (dd, *J* = 13.4, 7.2 Hz, 2H), 7.65 – 6.85 (m, 2H), 6.76 (d, *J_{P-H}* = 722.8 Hz, 1H), 6.10 – 5.70 (m, 2H), 1.98 (s, 6H), 1.57 (s, 6H), 1.28 – 1.05 (m, 6H), 0.75 – 0.30 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 139.8, 138.8, 138.8, 138.3, 136.8, 136.7, 133.0, 132.9, 132.6, 132.5, 129.1, 129.0, 128.2, 128.1, 127.2, 127.0, 125.8, 125.7, 125.4, 115.9, 90.0, 90.0, 88.9, 88.9, 79.5, 79.4, 79.3, 79.1, 36.4, 36.2, 24.8, 24.0, 23.9, 23.3, 23.2, 21.6. **³¹P NMR** (162 MHz, CDCl₃) δ -6.20. **HRMS** (ESI) m/z: [M+Na]⁺ calcd. for C₃₈H₄₁NaO₅P 631.2584, found 631.2577.



(3a*S*,8a*S*)-2,2-Diisopropyl-4,4,8,8-tetra-o-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine 6-oxide (L₉)

White foam solid (0.9 g, 26% of all steps). **¹H NMR** (400 MHz, CDCl₃) δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.90 – 7.78 (m, 3H), 7.40 – 7.28 (m, 6H), 7.25 – 7.07 (m, 5H), 6.99 (dd, *J* = 12.8, 7.2 Hz, 2H), 6.58 (d, *J_{P-H}* = 736.4 Hz, 1H), 5.81 (ABd, *J* = 6.6 Hz, 1H), 5.69 (ABd, *J* = 6.6 Hz, 1H), 1.94 (s, 6H), 1.58 (s, 6H), 1.35 – 1.21 (m, 2H), 0.55 (t, *J* = 7.6 Hz, 6H), 0.23 (d, *J* = 6.8 Hz, 3H), 0.19 (d, *J* = 6.4 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 139.9, 139.5, 139.3, 138.6, 137.9, 137.8, 133.6, 133.0, 132.9, 132.5, 129.3, 129.2, 128.2, 128.2, 127.2, 126.9, 125.7, 125.6, 125.6, 125.4, 119.9, 89.7, 89.6, 88.3, 88.3, 78.8, 78.8, 78.6, 78.6, 34.1, 34.0, 23.3, 23.0, 21.7, 21.5, 17.8, 17.8, 16.9, 16.8. **³¹P NMR** (162 MHz, CDCl₃) δ -5.14. **HRMS** (ESI) m/z: [M+Na]⁺ calcd. for C₃₉H₄₅NaO₅P 647.2897, found 647.2891.

General procedure for the BINAM- or H₈-BINAM-derived SPOs synthesis (L₁₉-L₂₂)

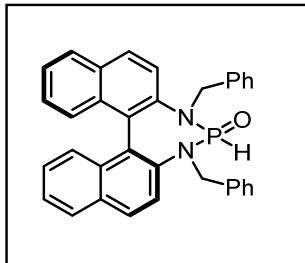


To a solution of (*S*)-[1,1'-binaphthalene]-2,2'-diamine (0.57 g, 2.0 mmol, 1.0 equiv.) or (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diamine (0.58 g, 2.0 mmol, 1.0 equiv.) in dry toluene was added acyl chloride (5.0 mmol, 2.5 equiv.), and pyridine (0.8 mL, 10 mmol). The solution was stirred at corresponding temperature until the completion of the reaction (monitored by TLC). The solvent was removed and the residue was quenched with NaOH (10%, 15 mL) and extracted with ethyl acetate (3× 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, and

concentrated under reduced pressure to give the crude amide product, which can be used without further purification.

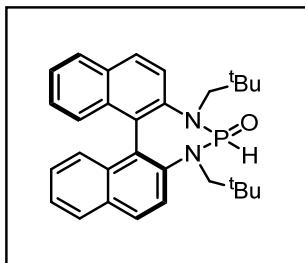
The amide was dissolved in dry THF (30 mL) and cooled to 0 °C. After LiAlH₄ (0.46 g, 12.0 mmol, 6.0 equiv.) was added portionwise, the mixture was stirred at the same temperature for 10 min, and then heated to reflux for 2 hours. After cooling to 0 °C, the mixture was quenched by NaOH (15%, 3 mL), and extracted with Et₂O (3× 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, EtOAc/n-hexane) to afford the reduction diamine product.

To a three-neck Schlenk flask charged with the corresponding substituted diamine (1.0 mmol, 1.0 equiv.) in dry THF (10 mL) was added *n*-BuLi in hexane (2.5 M, 0.8 mL, 2 mmol) within a 10-min period at -78 °C under N₂ atmosphere. The mixture was stirred at the same temperature for 0.5 h before warmed to r.t. for 0.5 h. Then the mixture was cooled to -78 °C again and freshly distilled PCl₃ (95 μL, 1.1 mmol, 1.1 equiv.) was added dropwise. The solution was warmed to r.t. and stirred for 1 h. To the resulting solution were added H₂O (18 μL, 1.0 mmol, 1.0 equiv.) and stirred for 0.5 h. The solvent was removed under reduced pressure and the residues were purified by flash chromatography to afford pure secondary phosphine oxides (**L₁₉**-**L₂₂**).



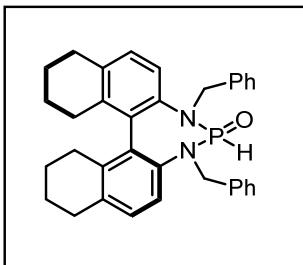
(11b*S*)-3,5-Dibenzyl-3,5-dihydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]diazaphosphepine 4-oxide (L₁₉)

White foam solid (122 mg, 24% of all steps). ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.7 Hz, 1H), 7.87 (dd, *J* = 12.8, 8.6 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.50 (d, *J*_{P-H} = 612.0 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.73 (dd, *J* = 16.6, 7.8 Hz, 2H), 6.63 – 6.46 (m, 8H), 6.45 – 6.38 (m, 2H), 4.96 (dd, *J* = 14.4, 7.6 Hz, 1H), 4.78 – 4.58 (m, 2H), 4.44 (dd, *J* = 14.4, 6.8 Hz, 1H)¹³C NMR (100 MHz, CDCl₃) δ 138.0, 136.9, 136.1, 136.1, 135.6, 132.8, 132.6, 132.3, 131.9, 131.4, 130.8, 129.8, 129.5, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 127.0, 126.6, 126.1, 125.9, 125.7, 125.2, 124.2, 123.6, 51.9, 51.9, 49.7, 49.6. ³¹P NMR (162 MHz, CDCl₃) δ 22.9. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₃₄H₃₈N₂OP 511.1934, found 511.1926.



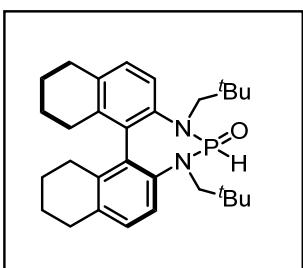
(11b*S*)-3,5-Dineopentyl-3,5-dihydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]diazaphosphepine 4-oxide (L₂₀)

White foam solid (169 mg, 36% of all steps). **¹H NMR (400 MHz, CDCl₃)** δ 7.88 – 7.80 (m, 2H), 7.79 – 7.71 (m, 2H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.18 – 6.99 (m, 4H), 7.02 (d, *J_{P-H}* = 599.6 Hz, 1H), 3.54 – 3.42 (m, 2H), 3.24 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.12 (t, *J* = 15.8 Hz, 1H), 0.16 (s, 18H). **¹³C NMR (100 MHz, CDCl₃)** δ 141.7, 139.5, 139.5, 132.5, 132.3, 131.7, 131.4, 130.8, 129.9, 129.8, 128.3, 128.3, 127.8, 127.7, 126.3, 126.2, 125.5, 125.3, 123.5, 123.1, 59.2, 59.2, 57.4, 57.3, 33.9, 33.9, 33.5, 33.5, 27.5, 27.3. **³¹P NMR (162 MHz, CDCl₃)** δ 27.0. **HRMS (ESI) m/z:** [M+H]⁺ calcd. for C₃₀H₃₆N₂OP 471.2560, found 471.2553.



(11b*S*)-3,5-Dibenzyl-3,5,8,9,10,11,12,13,14,15-decahydronaphtho[2,1-*d*:1',2'-*f*][1,3,2]diazaphosphepine 4-oxide (L₂₁)

White foam solid (93 mg, 18% of all steps). **¹H NMR (400 MHz, CDCl₃)** δ 7.30 (d, *J_{P-H}* = 597.6 Hz, 1H), 7.27 (d, *J* = 9.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.12 – 6.94 (m, 8H), 6.78 (d, *J* = 7.6 Hz, 2H), 6.70 (d, *J* = 7.4 Hz, 2H), 4.85 (dd, *J* = 14.4, 8.0 Hz, 1H), 4.59 – 4.46 (m, 2H), 4.31 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 2H), 2.23 – 2.03 (m, 2H), 1.72 – 1.63 (m, 2H), 1.62 – 1.54 (m, 2H), 1.53 – 1.21 (m, 6H). **¹³C NMR (100 MHz, CDCl₃)** δ 138.5, 138.4, 137.7, 137.5, 137.4, 137.2, 136.8, 136.1, 136.0, 136.0, 135.2, 135.2, 134.7, 134.7, 134.6, 129.1, 128.7, 128.2, 127.9, 127.9, 127.3, 127.0, 123.1, 123.1, 122.6, 122.5, 51.9, 51.8, 49.8, 49.7, 29.8, 29.7, 27.4, 27.2, 22.8, 22.7, 22.6. **³¹P NMR (162 MHz, CDCl₃)** δ 22.9. **HRMS (ESI) m/z:** [M+H]⁺ calcd. for C₃₄H₃₆N₂OP 519.2560, found 519.2555.



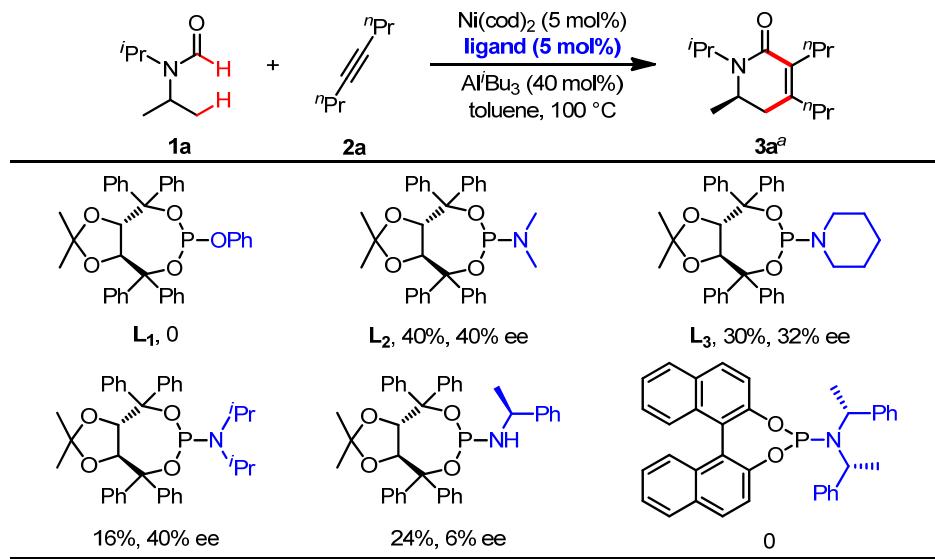
(11b*S*)-3,5-Dineopentyl-3,5,8,9,10,11,12,13,14,15-decahydronaphtho[2,1-*d*:1',2'-*f*][1,3,2]diazaphosphepine 4-oxide (L₂₂)

White foam solid (115 mg, 24% of all steps). **¹H NMR (400 MHz, CDCl₃)** δ 7.26 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J_{P-H}* = 594.0 Hz, 1H), 3.53 – 3.33 (m, 2H), 3.24 – 3.13 (m, 1H), 3.13 – 3.03 (m, 1H), 2.93 – 2.73 (m, 4H), 2.69 – 2.54 (m, 2H), 2.34 – 2.20 (m, 2H), 1.90 – 1.66 (m, 6H), 1.55 – 1.36 (m, 2H), 0.46 (d, *J* = 4.8 Hz, 18H). **¹³C NMR (100 MHz, CDCl₃)** δ 141.1, 138.4, 138.4, 138.0, 137.1, 135.6, 135.5, 135.0, 134.9, 134.7, 133.8, 133.8, 129.0, 129.0,

128.8, 128.7, 122.3, 122.3, 122.0, 121.9, 59.0, 58.9, 57.4, 57.3, 33.8, 33.7, 33.4, 33.3, 29.2, 28.2, 27.7, 27.5, 22.7, 22.6, 22.5, 22.4. **³¹P NMR** (162 MHz, CDCl₃) δ 27.1. **HRMS (ESI)** m/z: [M+H]⁺ calcd. for C₃₀H₄₄N₂OP 479.3186, found 479.3180.

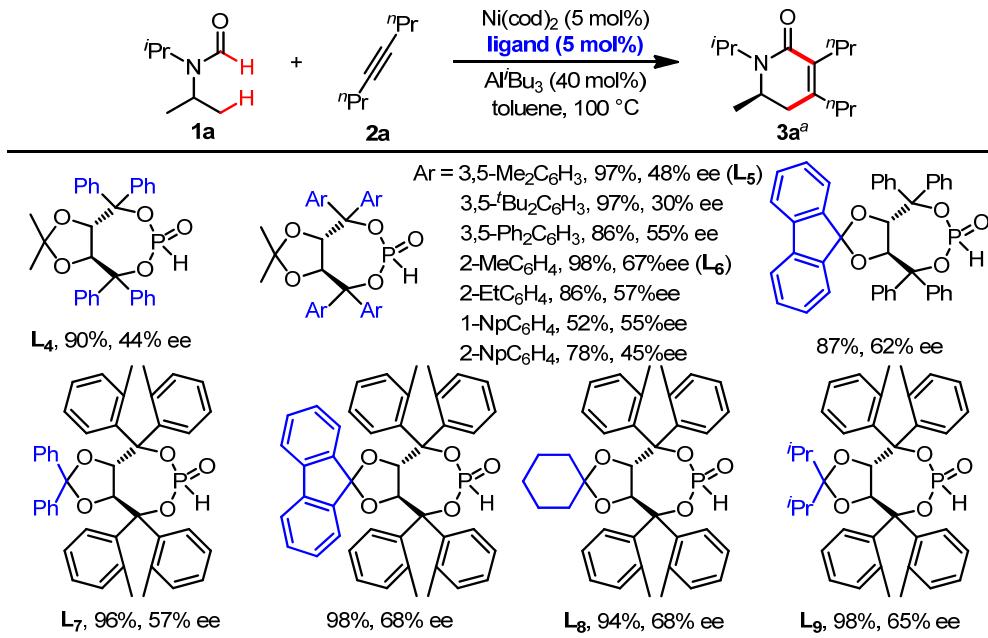
4. Reaction Optimization

Table S1. Chiral Phosphites and Phosphoramidites Effects



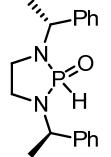
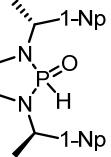
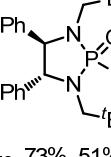
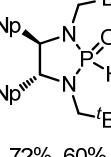
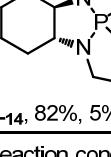
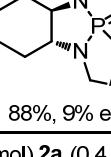
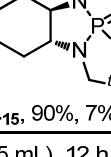
^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), toluene (0.5 mL), 12 h. Yield was determined by ¹H NMR with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC.

Table S2. TADOPOs Effects



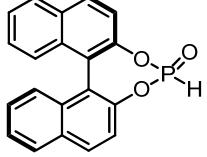
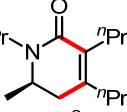
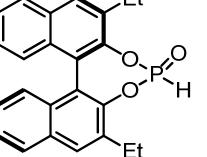
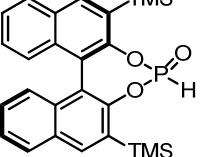
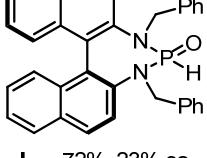
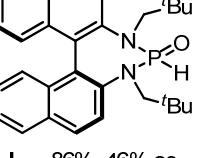
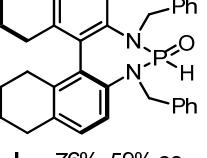
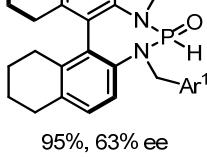
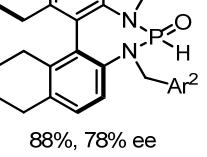
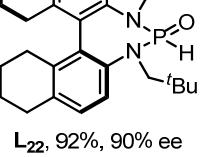
^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) toluene (0.5 mL), 12 h. Yield was determined by ¹H NMR analysis with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC analysis.

Table S3. DAPOs Effects

	
L_{10} , 74%, 6% ee	
	
L_{11} , 74%, 6% ee	
	
84%, 0 ee	
	
L_{13} , 72%, 60% ee	
	
L_{14} , 82%, 5% ee	
	
88%, 9% ee	
	
L_{15} , 90%, 7% ee	

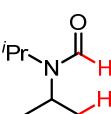
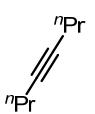
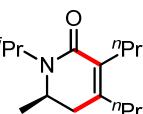
^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) toluene (0.5 mL), 12 h. Yield was determined by ¹H NMR analysis with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC analysis.

Table S4. BINOPOs and BINAPOs Effects

	
L_{16} , 20%, 40% ee	
	
L_{17} , 24%, 67% ee	
	
L_{18} , 68%, 0 ee	
	
L_{19} , 72%, 23% ee	
	
L_{20} , 86%, 46% ee	
	
L_{21} , 76%, 59% ee	
	
95%, 63% ee	
	
88%, 78% ee	
	
L_{22} , 92%, 90% ee	

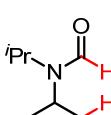
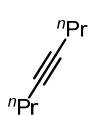
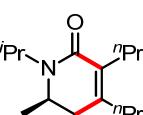
^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) toluene (0.5 mL), 12 h. Yield was determined by ¹H NMR with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC analysis. Ar¹ = 3,5-Me₂C₆H₃. Ar² = 3,5-tBu₂C₆H₃.

Table S5. Lewis Acid Effects

		$\xrightarrow[\text{toluene, } 100^\circ\text{C}]{\text{Ni}(\text{cod})_2 \text{ (5 mol\%)}}, \text{L}_{22} \text{ (5 mol\%)} \text{, L.A. (40 mol\%)}$	
1a	2a		3a^a
entry	L.A.	yield (%)	ee (%)
1	AlMe ₂ Cl	0	--
2	AlMe ₃	36	87
3	AlEt ₃	64	90
4	Al <i>i</i> Bu ₃	92	90
5	MAD	trace	--

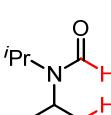
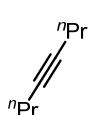
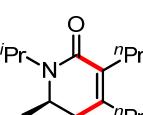
^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) toluene (0.5 mL), 12 h. Yield was determined by ¹H NMR analysis with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC analysis.

Table S6. Temperature Effects

		$\xrightarrow[\text{toluene, T}]{\text{Ni}(\text{cod})_2 \text{ (5 mol\%)}}, \text{L}_{22} \text{ (5 mol\%)} \text{, Al}(\text{iBu})_3 \text{ (40 mol\%)}$	
1a	2a		3a^a
entry	T (°C)	yield (%)	ee (%)
1	60	34	93
2	70	64	92
3	80	92	91
4	90	91	90
5	100	92	90
6	110	92	88

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) toluene (0.5 mL), 12 h. Yield was determined by ¹H NMR analysis with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC analysis.

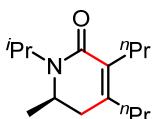
Table S7. Reaction Time Effects

		$\xrightarrow[\text{toluene, } 80^\circ\text{C}]{\text{Ni}(\text{cod})_2 \text{ (5 mol\%)}}, \text{L}_{22} \text{ (5 mol\%)} \text{, Al}(\text{iBu})_3 \text{ (40 mol\%)}$	
1a	2a		3a^a
entry	time (h)	yield (%)	ee (%)
1	1	84	91
2	2	92	91
3	6	92	91
4	12	92	91

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) toluene (0.5 mL). Yield was determined by ¹H NMR analysis with CH₂Br₂ as the internal standard and ee was determined by chiral HPLC analysis.

5. Typical Procedure for Ni-Catalyzed C(sp³)–H Activation

To a 15 mL oven-dried tube were added SPO ligand **L₂₂** (4.8 mg, 5 mol%), Ni(cod)₂ (2.8 mg, 5 mol%), dry degassed toluene (0.5 mL), formamide (0.2 mmol), Al*i*Bu₃ (80 μ L, 40 mol%, 1.0 M in hexane) and alkyne (0.4 mmol) sequentially in an N₂-filled glove-box. The tube was sealed and removed out of the glove-box. After heated at 80 °C in a dry block heater for 2 h, the mixture was cooled to r.t., quenched with 0.1 mL of 5% EDTA disodium salt solution, filtered through a short plug of silica gel (EtOAc as the eluent) and concentrated *in vacuo* to afford the crude product. Further purification by flash column chromatography on silica gel (eluting with EtOAc/*n*-hexane) gave the pure product. Racemic samples of the cyclized products for chiral HPLC analysis were prepared by using *rac*-**L₂₂**.



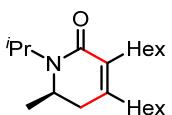
(*R*)-1-Isopropyl-6-methyl-3,4-dipropyl-5,6-dihdropyridin-2(1*H*)-one (**3a**)

Yellow oil (42.7 mg, 90%). **¹H NMR** (400 MHz, CDCl₃) δ 4.80 – 4.67 (m, 1H), 3.64 – 3.54 (m, 1H), 2.57 – 2.43 (m, 2H), 2.23 – 2.05 (m, 3H), 1.92 (d, *J* = 16.4, 1H), 1.49 – 1.32 (m, 4H), 1.21 – 1.09 (m, 9H), 0.96 – 0.87 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.3, 142.0, 130.3, 44.8, 44.4, 35.9, 35.8, 28.6, 23.2, 21.3, 20.7, 20.6, 20.2, 14.4, 14.3. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₅H₂₈NO 238.2165, found 238.2172. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r-minor* = 8.1 min, *t_r-major* = 9.9 min, 91% ee. $[\alpha]_D^{25}$ 111.1 (c 1.0, CHCl₃).



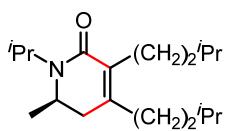
(*R*)-3,4-Diethyl-1-isopropyl-6-methyl-5,6-dihdropyridin-2(1*H*)-one (**3b**)

Colorless oil (34.7 mg, 83%). **¹H NMR** (400 MHz, CDCl₃) δ 4.82 – 4.66 (m, 1H), 3.67 – 3.53 (m, 1H), 2.59 – 2.39 (m, 2H), 2.29 – 2.17 (m, 2H), 2.13 – 2.02 (m, 1H), 1.91 (d, *J* = 16.4 Hz, 1H), 1.14 (dd, *J* = 12.0, 6.4 Hz, 9H), 1.05 – 0.93 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.3, 142.9, 131.0, 44.6, 44.3, 35.3, 26.5, 21.3, 20.6, 20.1, 19.6, 14.6, 11.9. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₃H₂₄NO 210.1852, found 210.1855. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 99:1, 1.0 mL/min, 254 nm, *t_r-minor* = 14.0 min, *t_r-major* = 15.4 min, 93% ee. $[\alpha]_D^{25}$ 110.0 (c 1.0, CHCl₃).



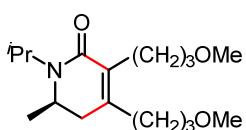
(R)-3,4-Dihexyl-1-isopropyl-6-methyl-5,6-dihydropyridin-2(1H)-one (3c)

Colorless oil (55.3 mg, 86%). **¹H NMR** (400 MHz, CDCl₃) δ 4.81 – 4.65 (m, 1H), 3.63 – 3.53 (m, 1H), 2.56 – 2.42 (m, 2H), 2.23 – 2.02 (m, 3H), 1.91 (d, *J* = 16.4, 1H), 1.42 – 1.22 (m, 16H), 1.19 – 1.10 (m, 9H), 0.92 – 0.79 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.3, 142.0, 130.3, 44.7, 44.4, 35.8, 33.8, 31.8, 31.8, 30.0, 29.7, 29.5, 27.3, 26.6, 22.8, 22.7, 21.3, 20.6, 20.2, 14.2, 14.2. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₂₁H₄₀NO 322.3104, found 322.3111. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 99:1, 1.0 mL/min, 254 nm, *t_r*-minor = 11.6 min, *t_r*-major = 12.5 min, 93% ee. [α]_D²⁵ 96.0 (c 1.0, CHCl₃).



(R)-3,4-Diisopentyl-1-isopropyl-6-methyl-5,6-dihydropyridin-2(1H)-one (3d)

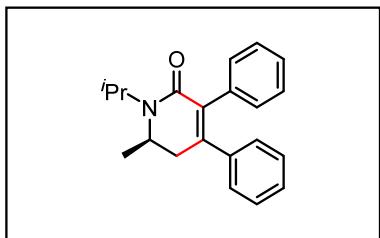
Colorless oil (54.5 mg, 93%). **¹H NMR** (400 MHz, CDCl₃) δ 4.86 – 4.67 (m, 1H), 3.73 – 3.52 (m, 1H), 2.52 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.25 – 2.12 (m, 2H), 2.09 – 1.98 (m, 1H), 1.90 (d, *J* = 16.4 Hz, 1H), 1.65 – 1.45 (m, 2H), 1.33 – 1.21 (m, 4H), 1.15 (q, *J* = 6.6 Hz, 9H), 0.91 (d, *J* = 6.8 Hz, 12H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.3, 142.1, 131.2, 44.6, 44.3, 39.2, 36.5, 35.9, 31.7, 28.6, 28.4, 24.6, 22.6, 22.5, 21.4, 20.6, 20.2. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₉H₃₆NO 294.2791, found 294.2787. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 99:1, 1.0 mL/min, 254 nm, *t_r*-minor = 12.2 min, *t_r*-major = 15.7 min, 93% ee. [α]_D²⁵ 93.9 (c 1.0, CHCl₃).



(R)-1-Isopropyl-3,4-bis(3-methoxypropyl)-6-methyl-5,6-dihydropyridin-2(1H)-one (3e)

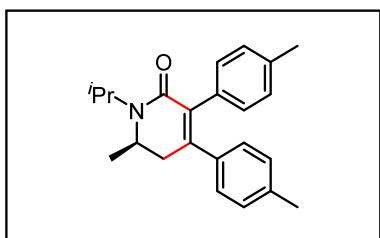
Colorless oil (28.5 mg, 48%). **¹H NMR** (400 MHz, CDCl₃) δ 4.82 – 4.67 (m, 1H), 3.69 – 3.59 (m, 1H), 3.42 – 3.35 (m, 4H), 3.32 (d, *J* = 5.2 Hz, 6H), 2.62 – 2.46 (m, 2H), 2.36 – 2.16 (m, 3H), 1.94 (d, *J* = 16.8 Hz, 1H), 1.76 – 1.60 (m, 4H), 1.23 – 1.09 (m, 9H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.1, 141.9, 130.1, 72.7, 72.3, 58.8, 58.5, 44.9, 44.5, 35.9, 30.3, 29.7, 27.4, 23.1, 21.3, 20.6, 20.2. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for

$C_{17}H_{32}NO_3$ 298.2377, found 298.2370. **HPLC condition:** Chiralpak OD-H column, n -hexane/*i*-PrOH = 97:3, 1.0 mL/min, 254 nm, t_r -minor = 10.3 min, t_r -major = 11.2 min, 90% ee. $[\alpha]_D^{25}$ 36.7 (c 0.5, CHCl₃).



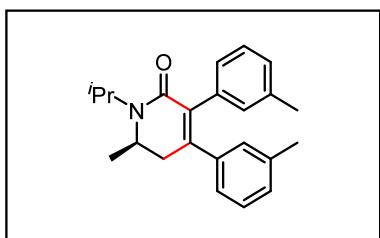
(R)-1-Isopropyl-6-methyl-3,4-diphenyl-5,6-dihydropyridin-2(1H)-one (3f)

White solid (40.9 mg, 67%), m.p. 139–141 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.24 – 7.07 (m, 8H), 7.06 – 6.94 (m, 2H), 4.93 – 4.73 (m, 1H), 3.94 – 3.80 (m, 1H), 3.16 (dd, J = 16.8, 5.8 Hz, 1H), 2.51 (d, J = 16.8 Hz, 1H), 1.48 (d, J = 6.4 Hz, 3H), 1.28 (d, J = 6.4 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.6, 142.8, 140.7, 140.5, 136.4, 132.7, 131.5, 131.1, 128.4, 128.1, 127.6, 127.5, 126.8, 126.7, 125.3, 45.4, 45.1, 38.3, 21.4, 20.6, 20.4. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₂₁H₂₄NO 306.1852, found 306.1853. **HPLC condition:** Chiralpak IA column, n -hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, t_r -minor = 11.4 min, t_r -major = 14.4 min, 92% ee. $[\alpha]_D^{25}$ 124.0 (c 1.0, CHCl₃).



(R)-1-Isopropyl-6-methyl-3,4-di-p-tolyl-5,6-dihydropyridin-2(1H)-one (3g)

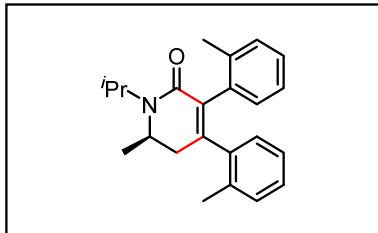
White solid (54.0 mg, 81%), m.p. 128–130 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.09 – 6.95 (m, 6H), 6.94 – 6.87 (m, 2H), 4.92 – 4.76 (m, 1H), 3.93 – 3.76 (m, 1H), 3.11 (dd, J = 16.4, 6.4 Hz, 1H), 2.47 (d, J = 16.4, 1H), 2.26 (s, 6H), 1.44 (d, J = 6.4, 3H), 1.26 (d, J = 6.4, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.9, 142.2, 137.7, 137.3, 136.2, 133.6, 132.1, 130.9, 128.8, 128.4, 128.3, 45.3, 45.0, 38.3, 21.4, 21.3, 21.3, 20.6, 20.3. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₂₃H₂₈NO 334.2165, found 334.2160. **HPLC condition:** Chiralpak IA column, n -hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, t_r -minor = 10.4 min, t_r -major = 16.4 min, 94% ee. $[\alpha]_D^{25}$ 111.7 (c 1.0, CHCl₃).



(R)-1-Isopropyl-6-methyl-3,4-di-*m*-tolyl-5,6-dihydropyridin-2(1H)-one (3h)

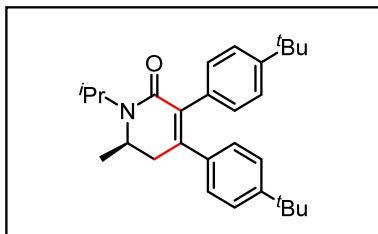
White solid (41.3 mg, 62%), m.p. 104–106 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.07 – 6.99 (m, 2H), 6.98 – 6.88 (m, 3H), 6.87 – 6.81 (m, 2H), 6.78 (d, J = 7.6 Hz, 1H), 4.92 – 4.78 (m, 1H), 3.87 – 3.78 (m, 1H), 3.13 (dd, J = 16.4, 6.0 Hz, 1H), 2.48 (d, J = 16.4,

1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.46 (d, $J = 6.4$ Hz, 3H), 1.46 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 142.6, 140.5, 137.5, 136.9, 136.4, 132.7, 131.6, 128.9, 128.2, 128.1, 127.8, 127.5, 127.4, 125.5, 45.3, 45.0, 38.3, 21.5, 21.4, 21.4, 20.6, 20.4. HRMS (ESI) m/z: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{28}\text{NO}$ 334.2165, found 334.2160. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, $t_{r\text{-minor}} = 9.7$ min, $t_{r\text{-major}} = 11.4$ min, 91% ee. $[\alpha]_D^{25}$ 90.6 (c 1.0, CHCl_3).



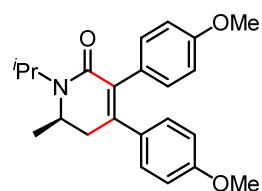
(*R*)-1-Isopropyl-6-methyl-3,4-di-*o*-tolyl-5,6-dihydropyridin-2(1*H*)-one (3i)

White solid (46.0 mg, 69%), m.p. 138–140 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.24 – 6.79 (m, 7H), 6.77 – 6.62 (m, 1H), 4.96 – 4.62 (m, 1H), 3.99 – 3.77 (m, 1H), 3.33 – 3.10 (m, 1H), 2.53 – 2.11 (m, 6H), 1.92 (s, 1H), 1.53 (s, 3H), 1.36 – 1.23 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.4, 144.5, 140.8, 136.5, 134.3, 131.8, 130.4, 130.3, 129.6, 127.3, 127.1, 125.8, 125.4, 125.2, 124.8, 45.9, 45.6, 38.2, 29.8, 21.5, 21.2, 20.9, 20.3. HRMS (ESI) m/z: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{28}\text{NO}$ 334.2165, found 334.2159. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, $t_{r\text{-minor}} = 8.6$ min, $t_{r\text{-major}} = 10.0$ min, 90% ee. $[\alpha]_D^{25}$ −165.6 (c 1.0, CHCl_3).



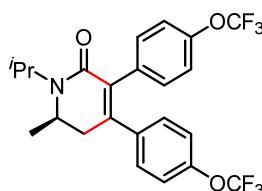
(*R*)-3,4-Bis(4-(*tert*-butyl)phenyl)-1-isopropyl-6-methyl-5,6-dihydropyridin-2(1*H*)-one (3j)

White solid (77.6 mg, 93%), m.p. 191–193 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.16 (t, $J = 8.0$ Hz, 4H), 7.05 (d, $J = 8.4$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 4.91 – 4.74 (m, 1H), 3.91 – 3.78 (m, 1H), 3.11 (dd, $J = 16.8, 6.0$ Hz, 1H), 2.52 (d, $J = 16.4$ Hz, 1H), 1.45 (d, $J = 6.4$ Hz, 3H), 1.30 – 1.18 (m, 24H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 150.5, 149.3, 142.1, 137.6, 133.6, 132.2, 130.7, 128.3, 124.8, 124.5, 45.3, 45.1, 38.2, 34.6, 34.5, 31.4, 31.3, 21.4, 20.6, 20.4. HRMS (ESI) m/z: $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{29}\text{H}_{40}\text{NO}$ 418.3104, found 418.3099. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, $t_{r\text{-minor}} = 8.3$ min, $t_{r\text{-major}} = 11.4$ min, 90% ee. $[\alpha]_D^{25}$ 99.2 (c 1.0, CHCl_3).



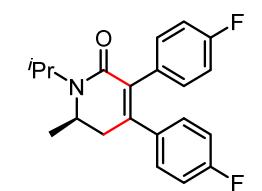
(R)-1-Isopropyl-3,4-bis(4-methoxyphenyl)-6-methyl-5,6-dihydropyridin-2(1*H*)-one (3k)

White solid (57.0 mg, 78%), m.p. 143–145 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 4H), 4.91 – 4.75 (m, 1H), 3.91 – 3.79 (m, 1H), 3.78 – 3.67 (m, 6H), 3.09 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.49 (d, *J* = 16.4 Hz, 1H), 1.44 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.1, 158.8, 158.4, 141.7, 132.9, 132.3, 131.3, 129.9, 129.1, 113.5, 113.2, 55.3, 45.3, 45.0, 38.3, 21.4, 20.6, 20.3. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, *t_r-minor* = 7.7 min, *t_r-major* = 10.5 min, 92% ee. [α]_D²⁵ 116.4 (c 1.0, CHCl₃).



(R)-1-Isopropyl-6-methyl-3,4-bis(4-(trifluoromethoxy)phenyl)-5,6-dihydropyridin-2(1*H*)-one (3l)

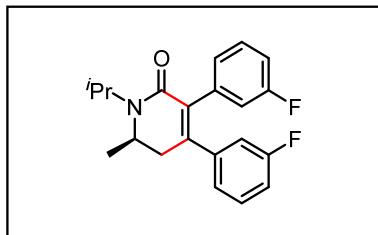
White solid (51.1 mg, 54%), m.p. 77–79 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.13 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 6H), 4.87 – 4.71 (m, 1H), 3.97 – 3.82 (m, 1H), 3.14 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.49 (d, *J* = 16.8 Hz, 1H), 1.46 (d, *J* = 6.4 Hz, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.0, 148.6 (q, *J* = 13.8 Hz), 148.3 (q, *J* = 12.0 Hz), 142.3, 138.6, 134.7, 132.6, 132.2, 129.9, 121.7 (q, *J* = 256.0 Hz), 120.7, 120.2, 119.2 (q, *J* = 256.0 Hz), 45.7, 45.2, 38.3, 21.4, 20.6, 20.4. **¹⁹F NMR** (376 MHz, CDCl₃) δ -57.8, -57.9. **HRMS (ESI) m/z:** [M+H]⁺ calcd. for C₂₃H₂₂F₆NO₃ 474.1498, found 474.1492. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, *t_r-minor* = 8.6 min, *t_r-major* = 13.2 min, 92% ee. [α]_D²⁵ 91.1 (c 1.0, CHCl₃).



(R)-3,4-Bis(4-Fluorophenyl)-1-isopropyl-6-methyl-5,6-dihydropyridin-2(1*H*)-one (3m)

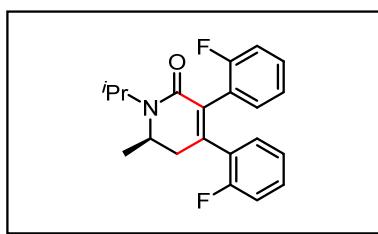
White solid (43.0 mg, 63%), m.p. 126–128 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.87 (t, *J* = 7.8 Hz, 4H), 4.90 – 4.73 (m, 1H),

3.92 – 3.81 (m, 1H), 3.12 (dd, J = 16.8, 6.0 Hz, 1H), 2.47 (d, J = 16.8 Hz, 1H), 1.45 (d, J = 6.4 Hz, 3H), 1.27 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, CDCl_3) δ 163.4, 163.2 (d, J = 9.6 Hz), 160.8 (d, J = 7.2 Hz), 142.2, 136.2 (d, J = 3.2 Hz), 132.8 (d, J = 8.0 Hz), 132.1 (d, J = 3.2 Hz), 131.9, 130.2 (d, J = 8.0 Hz), 115.3 (d, J = 21.4 Hz), 114.7 (d, J = 21.2 Hz), 45.6, 45.1, 38.4, 21.4, 20.6, 20.4. **^{19}F NMR** (376 MHz, CDCl_3) δ -113.4, -115.5. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for $\text{C}_{21}\text{H}_{22}\text{F}_2\text{NO}$ 342.1664, found 342.1660. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, $t_{r\text{-minor}} = 11.8$ min, $t_{r\text{-major}} = 18.0$ min, 95% ee. $[\alpha]_D^{25}$ 147.4 (c 0.5, CHCl_3).



(*R*)-3,4-Bis(3-Fluorophenyl)-1-isopropyl-6-methyl-5,6-dihydropyridin-2(1*H*)-one (3n)

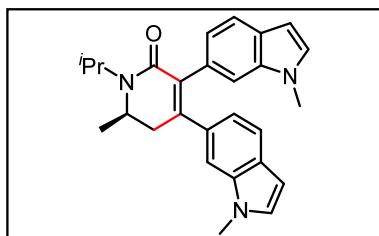
White solid (36.2 mg, 53%), m.p. 63–65 °C. **^1H NMR** (400 MHz, CDCl_3) δ 7.18 – 7.08 (m, 2H), 6.95 – 6.80 (m, 4H), 6.77 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 4.88 – 4.71 (m, 1H), 3.94 – 3.80 (m, 1H), 3.13 (dd, J = 16.8, 6.0 Hz, 1H), 2.46 (d, J = 16.8 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, CDCl_3) δ 163.6 (d, J = 19.4 Hz), 162.9, 161.2 (d, J = 17.6 Hz), 142.3 (d, J = 1.6 Hz), 142.2 (d, J = 7.6 Hz), 138.1 (d, J = 8.2 Hz), 132.3 (d, J = 1.6 Hz), 129.8 (d, J = 8.2 Hz), 129.1 (d, J = 8.2 Hz), 126.8 (d, J = 2.8 Hz), 124.0 (d, J = 2.8 Hz), 118.0 (d, J = 21.6 Hz), 115.1 (d, J = 21.8 Hz), 114.8 (d, J = 21.0 Hz), 114.1 (d, J = 21.0 Hz), 45.6, 45.1, 38.2, 21.3, 20.5, 20.4. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for $\text{C}_{21}\text{H}_{22}\text{F}_2\text{NO}$ 342.1664, found 342.1661. **^{19}F NMR** (376 MHz, CDCl_3) δ -112.7, -114.3. **HPLC condition:** Chiralpak IA-3 column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, $t_{r\text{-minor}} = 10.9$ min, $t_{r\text{-major}} = 12.7$ min, 90% ee. $[\alpha]_D^{25}$ 94.6 (c 1.0, CHCl_3).



(*R*)-3,4-Bis(2-Fluorophenyl)-1-isopropyl-6-methyl-5,6-dihydropyridin-2(1*H*)-one (3o)

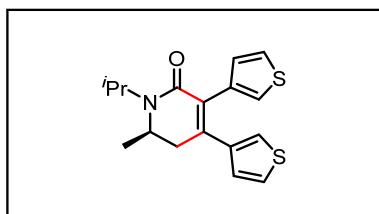
White solid (57.5 mg, 84%), m.p. 136–138 °C. **^1H NMR** (400 MHz, CDCl_3) δ 7.19 – 7.09 (m, 2H), 7.08 – 7.02 (m, 1H), 7.01 – 6.85 (m, 5H), 4.88 – 4.75 (m, 1H), 3.92 – 3.81 (m, 1H), 3.18 (dd, J = 16.8, 6.0 Hz, 1H), 2.43 (d, J = 16.8 Hz, 1H), 1.50 (d, J = 6.6 Hz, 3H), 1.28 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, CDCl_3) δ 162.3, 161.6, 160.7, 159.1, 158.2, 141.0, 132.8, 129.7 (d, J = 7.9 Hz), 129.1 (d, J = 8.1 Hz), 127.7 (d, J = 15.2 Hz), 124.0 (d, J = 16.2 Hz), 123.8 (d, J = 3.2 Hz), 123.3 (d, J = 2.7 Hz), 115.7 (d, J = 21.5 Hz), 115.0 (d, J = 22.2 Hz), 45.6, 45.5, 37.7, 21.3, 20.6, 20.0. **HRMS** (ESI)

m/z: [M+H]⁺ calcd. for C₂₁H₂₂F₂NO 342.1664, found 342.1661. ¹⁹F NMR (376 MHz, CDCl₃) δ -113.6, -114.1. **HPLC condition:** Chiralpak IA-3 column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, *t_r*-minor = 12.0 min, *t_r*-major = 14.1 min, 91% ee. [α]_D²⁵ 25.2 (c 1.0, CHCl₃).



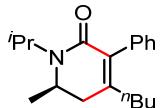
(R)-1-Isopropyl-6-methyl-3,4-bis(1-methyl-1H-indol-6-yl)-5,6-dihydropyridin-2(1H)-one (3p)

White solid (39.5 mg, 48%), m.p. 235–237 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, *J* = 9.6 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.04 – 6.75 (m, 5H), 6.34 (d, *J* = 16.8 Hz, 2H), 4.96 – 4.76 (m, 1H), 3.93 – 3.81 (m, 1H), 3.66 (d, *J* = 11.6, 6H), 3.23 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.62 (d, *J* = 16.4 Hz, 1H), 1.51 (d, *J* = 6.4 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 142.7, 135.8, 135.7, 132.4, 132.1, 129.1, 128.2, 128.1, 128.0, 127.9, 125.3, 123.5, 123.1, 120.6, 110.0, 108.6, 108.2, 101.2, 45.0, 44.9, 39.1, 32.8, 32.8, 21.4, 20.6, 20.3. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₂₇H₃₀N₃O 412.2383, found 412.2380. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, *t_r*-minor = 16.1 min, *t_r*-major = 18.2 min, 93% ee. [α]_D²⁵ 52.8 (c 1.0, CHCl₃).



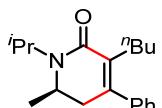
(R)-1-Isopropyl-6-methyl-3,4-di(thiophen-3-yl)-5,6-dihydropyridin-2(1H)-one (3q)

Yellow oil (25.4 mg, 40%). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (dd, *J* = 3.2, 1.2 Hz, 1H), 7.18 (dd, *J* = 4.8, 3.2 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.89 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.59 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.91 – 4.77 (m, 1H), 3.89 – 3.80 (m, 1H), 3.00 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.61 (d, *J* = 17.2, 1H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 163.5, 140.8, 137.2, 136.3, 130.1, 128.0, 126.7, 125.2, 125.0, 124.1, 123.5, 45.3, 44.9, 37.9, 21.3, 20.6, 20.4. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₁₇H₂₀NOS₂ 318.0981, found 318.0978. **HPLC condition:** Chiralpak IA-3 column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, *t_r*-minor = 10.0 min, *t_r*-major = 14.9 min, 90% ee. [α]_D²⁵ 194.6 (c 1.0, CHCl₃).



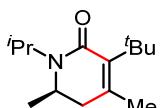
(*R*)-4-Butyl-1-isopropyl-6-methyl-3-phenyl-5,6-dihydropyridin-2(1*H*)-one (3r)

White solid (22.4 mg, 20%), m.p. 73–75 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.42 – 7.34 (m, 2H), 7.33 – 7.26 (m, 1H), 7.22 – 7.14 (m, 2H), 4.91 – 4.76 (m, 1H), 3.78 – 3.64 (m, 1H), 2.92 (dd, *J* = 16.8 Hz, 6.0 Hz 1H), 2.58 – 2.46 (m, 1H), 2.24 (d, *J* = 16.8 Hz, 1H), 2.18 – 2.09 (m, 1H), 1.45 – 1.29 (m, 5H), 1.28 – 1.14 (m, 8H), 0.78 (t, *J* = 7.2, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.2, 141.2, 140.8, 132.4, 128.5, 127.5, 127.4, 44.9, 44.6, 38.7, 31.8, 27.3, 22.9, 21.4, 20.6, 20.3, 14.0. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₉H₂₈NO 286.2165, found 286.2171. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, *t_r*-minor = 7.6 min, *t_r*-major = 10.3 min, 87% ee. [α]_D²⁵ 113.2 (c 0.5, CHCl₃).



(*R*)-3-Butyl-1-isopropyl-6-methyl-4-phenyl-5,6-dihydropyridin-2(1*H*)-one (3r')

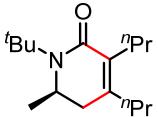
White solid (11.4 mg, 39%), m.p. 52–54 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.22 – 7.14 (m, 2H), 4.84 – 4.69 (m, 1H), 3.83 – 3.69 (m, 1H), 2.72 (dd, *J* = 16.8 Hz, 6.0 Hz 1H), 2.13 (d, *J* = 16.8 Hz, 1H), 2.03 (t, *J* = 7.8 Hz, 2H), 1.45 – 1.30 (m, 5H), 1.28 – 1.12 (m, 8H), 0.78 (t, *J* = 7.2, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.5, 145.1, 136.6, 131.9, 130.1, 127.7, 126.8, 45.0, 44.7, 35.6, 34.2, 29.4, 22.6, 21.3, 20.6, 20.3, 13.9. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₉H₂₈NO 286.2165, found 286.2171. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 97:3, 1.0 mL/min, 254 nm, *t_r*-minor = 12.9 min, *t_r*-major = 13.8 min, 93% ee. [α]_D²⁵ 82.7 (c 1.0, CHCl₃).



(*R*)-3-(Tert-butyl)-1-isopropyl-4,6-dimethyl-5,6-dihydropyridin-2(1*H*)-one (3s)

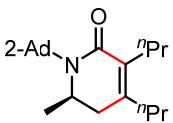
Colorless oil (24.1 mg, 54%). **¹H NMR** (400 MHz, CDCl₃) δ 4.81 – 4.64 (m, 1H), 3.64 – 3.50 (m, 1H), 2.48 – 2.36 (m, 1H), 2.16 (d, *J* = 17.0, 1H), 2.00 (d, *J* = 2.0, 3H), 1.17 (s, 9H), 1.16 – 1.08 (m, 9H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.2, 147.6, 125.5, 44.6, 43.9, 36.4, 34.4, 29.3, 21.3, 20.4, 19.7, 15.5. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for

$C_{14}H_{26}NO$ 224.2009, found 224.2011. **HPLC condition:** Chiralpak IA-3 column, n -hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, t_r -minor = 7.3 min, t_r -major = 8.1 min, 89% ee. $[\alpha]_D^{25}$ 132.4 (c 0.25, CHCl₃).



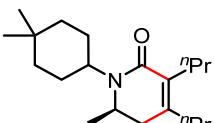
(*R*)-1-(*tert*-Butyl)-6-methyl-3,4-dipropyl-5,6-dihydropyridin-2(1*H*)-one (4a)

Colorless oil (23.1 mg, 46%). **¹H NMR** (400 MHz, CDCl₃) δ 3.96 – 3.84 (m, 1H), 2.58 (dd, J = 16.8, 6.0 Hz, 1H), 2.50 – 2.41 (m, 1H), 2.26 – 1.99 (m, 3H), 1.89 (d, J = 16.8, 1H), 1.46 (s, 9H), 1.45 – 1.35 (m, 4H), 1.13 (d, J = 6.4 Hz, 3H), 0.93 (q, J = 7.8 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.7, 141.4, 131.4, 56.7, 46.9, 36.2, 35.8, 29.4, 28.6, 23.3, 20.7, 19.9, 14.5, 14.4. **HRMS (ESI)** m/z: [M+H]⁺ calcd. for C₁₆H₃₀NO 252.2322, found 252.2319. **HPLC condition:** Chiralpak AD-H column, n -hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, t_r -minor = 5.5 min, t_r -major = 6.7 min, 90% ee. $[\alpha]_D^{25}$ 59.4 (c 1.0, CHCl₃).



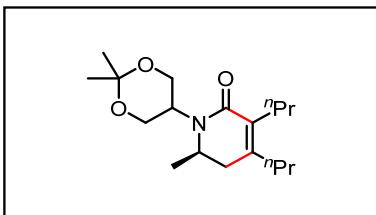
(6*R*)-1-((1*S*,2*R*,5*R*)-Adamantan-2-yl)-6-methyl-3,4-dipropyl-5,6-dihydropyridin-2(1*H*)-one (4b)

White solid (42.8 mg, 65%), m.p. 69–71 °C. **¹H NMR** (400 MHz, CDCl₃) δ 3.65 (s, 1H), 3.33 (s, 1H), 2.45 – 2.23 (m, 2H), 2.18 – 2.05 (m, 2H), 2.04 – 1.93 (m, 3H), 1.92 – 1.84 (m, 2H), 1.82 – 1.64 (m, 5H), 1.63 – 1.31 (m, 10H), 1.26 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 7.8 Hz, 3H), 0.90 (d, J = 7.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.9, 153.4, 131.3, 63.1, 45.2, 38.9, 37.9, 36.8, 36.5, 35.6, 30.9, 30.5, 29.8, 29.6, 27.6, 27.0, 23.6, 23.5, 22.4, 22.3, 15.0, 14.6. **HRMS (ESI)** m/z: [M+H]⁺ calcd. for C₂₂H₃₆NO 330.2791, found 330.2787. **HPLC condition:** Chiralpak IA column, n -hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, t_r -major = 5.8 min, t_r -minor = 6.9 min, 82% ee. $[\alpha]_D^{25}$ 53.6 (c 0.5, CHCl₃).



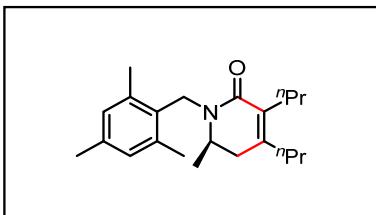
(*R*)-1-(4,4-Dimethylcyclohexyl)-6-methyl-3,4-dipropyl-5,6-dihydropyridin-2(1*H*)-one (4c)

Colorless oil (34.2 mg, 56%). **¹H NMR** (400 MHz, CDCl₃) δ 4.38 – 4.14 (m, 1H), 3.73 – 3.50 (m, 1H), 2.58 – 2.42 (m, 2H), 2.22 – 2.04 (m, 3H), 1.92 (d, J = 16.4 Hz, 1H), 1.70 – 1.54 (m, 3H), 1.51 – 1.27 (m, 9H), 1.15 (d, J = 6.8 Hz, 3H), 0.99 – 0.84 (m, 12H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.3, 141.9, 130.4, 53.7, 45.4, 38.9, 38.7, 35.9, 38.7, 35.9, 35.8, 32.9, 29.7, 28.6, 27.1, 26.3, 24.2, 23.1, 20.7, 20.3. **HRMS (ESI) m/z:** [M+H]⁺ calcd. for C₂₀H₃₆NO 306.2791, found 306.2788. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r*-minor = 11.1 min, *t_r*-major = 18.6 min, 92% ee. [α]_D²⁵ 93.5 (c 1.0, CHCl₃).



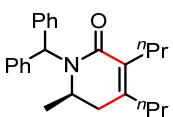
(R)-1-(2,2-Dimethyl-1,3-dioxan-5-yl)-6-methyl-3,4-dipropyl-5,6-dihdropyridin-2(1H)-one (4d)

Colorless oil (46.4 mg, 75%). **¹H NMR** (400 MHz, CDCl₃) δ 4.31 – 4.16 (m, 2H), 4.11 – 3.94 (m, 4H), 2.69 (dd, J = 16.8, 6.2 Hz, 1H), 2.50 – 2.37 (m, 1H), 2.26 – 2.07 (m, 3H), 1.98 (d, J = 16.8 Hz, 1H), 1.52 – 1.31 (m, 10H), 1.25 (d, J = 6.4 Hz, 3H), 0.94 (dt, J = 14.6, 7.2 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.2, 143.6, 129.7, 98.1, 62.6, 61.7, 49.8, 49.3, 36.0, 35.6, 28.5, 24.8, 23.2, 23.2, 20.7, 19.4, 19.4, 14.3. **HRMS (ESI) m/z:** [M+Na]⁺ calcd. for C₁₈H₃₁NNaO₃ 332.2196, found 332.2189. **HPLC condition:** Chiralpak IA-3 column, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, *t_r*-minor = 8.9 min, *t_r*-major = 12.6 min, 92% ee. [α]_D²⁵ 75.7 (c 1.0, CHCl₃).



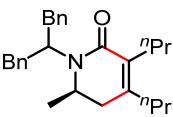
(R)-6-Methyl-3,4-dipropyl-1-(2,4,6-trimethylbenzyl)-5,6-dihdropyridin-2(1H)-one (4e)

Colorless oil (30.1 mg, 46%). **¹H NMR** (400 MHz, CDCl₃) δ 6.85 (s, 2H), 5.29 (d, J = 14.8 Hz, 1H), 4.16 (d, J = 14.8 Hz, 1H), 3.27 – 3.10 (m, 1H), 2.56 – 2.39 (m, 2H), 2.29 (s, 6H), 2.26 (s, 3H), 2.18 – 2.02 (m, 2H), 1.79 (d, J = 16.8 Hz, 2H), 1.50 – 1.35 (m, 4H), 1.09 (d, J = 6.4 Hz, 3H), 1.00 – 0.84 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.5, 142.9, 138.3, 137.0, 131.0, 129.3, 110.1, 46.6, 40.8, 36.0, 34.6, 28.6, 23.3, 21.0, 20.8, 20.2, 17.3, 14.4, 14.3. **HRMS (ESI) m/z:** [M+H]⁺ calcd. for C₂₂H₃₄NO 328.2635, found 328.2630. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r*-minor = 11.5 min, *t_r*-major = 12.3 min, 74% ee. [α]_D²⁵ 66.6 (c 0.5, CHCl₃).



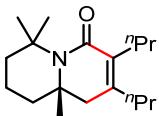
(R)-1-Benzhydryl-6-methyl-3,4-dipropyl-5,6-dihydropyridin-2(1H)-one (4f)

Colorless oil (32.5 mg, 45%). **¹H NMR** (400 MHz, CDCl₃) δ 7.34 – 7.28 (m, 6H), 7.27 – 7.20 (m, 3H), 7.14 (s, 1H), 3.71 – 3.55 (m, 1H), 2.88 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.62 – 2.48 (m, 1H), 2.30 – 2.19 (m, 2H), 2.19 – 2.09 (m, 1H), 1.93 (d, *J* = 16.8 Hz, 1H), 1.55 – 1.08 (m, 5H), 1.02 – 0.88 (m, 6H), 0.56 (d, *J* = 6.4 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.9, 143.3, 140.5, 140.0, 130.7, 130.3, 128.5, 128.4, 127.8, 127.7, 126.9, 60.8, 46.9, 36.1, 35.7, 28.7, 23.2, 20.8, 18.9, 14.5, 14.4. **HRMS (ESI)** m/z: [M+H]⁺ calcd. for C₁₅H₃₂NO 362.2478, found 362.2472. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, *t_r-minor* = 15.4 min, *t_r-major* = 20.1 min, 93% ee. [α]_D²⁵ -100.0 (c 0.5, CHCl₃).



(R)-1-(1,3-Diphenylpropan-2-yl)-6-methyl-3,4-dipropyl-5,6-dihydropyridin-2(1H)-one (4g)

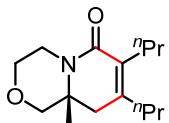
Colorless oil (42.8 mg, 55%). **¹H NMR** (400 MHz, CDCl₃) δ 7.42 – 6.86 (m, 10H), 3.36 (s, 2H), 3.01 (d, *J* = 8.2 Hz, 1H), 2.88 – 2.83 (m, 1H), 2.80 – 2.55 (m, 1H), 2.52 – 2.43 (m, 1H), 2.18 – 2.02 (m, 1H), 2.01 – 1.84 (m, 2H), 1.99 – 1.34 (m, 5H), 1.27 – 1.14 (m, 2H), 0.87 (t, *J* = 7.8 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H), 0.42 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.3, 142.2, 140.1, 130.2, 129.6, 129.4, 128.4, 128.3, 126.3, 126.2, 39.3, 38.7, 35.7, 34.4, 30.4, 28.3, 23.1, 20.5, 18.2, 14.4, 14.1. **HRMS (ESI)** m/z: [M+H]⁺ calcd. for C₂₇H₃₆NO 390.2791, found 390.2787. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r-minor* = 12.4 min, *t_r-major* = 13.5 min, 90% ee. [α]_D²⁵ 38.6 (c 1.0, CHCl₃).



(S)-6,6,9a-Trimethyl-2,3-dipropyl-1,6,7,8,9,9a-hexahydro-4H-quinolizin-4-one (4h)

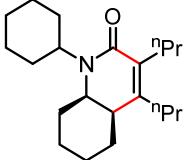
Colorless oil (22.2 mg, 40%). **¹H NMR** (400 MHz, CDCl₃) δ 2.44 – 2.32 (m, 2H), 2.22 – 2.00 (m, 3H), 1.89 (d, *J* = 16.8, 1H), 1.78 – 1.59 (m, 3H), 1.58 (s, 3H), 1.57 – 1.46 (m,

3H), 1.21 (s, 6H), 1.27 – 1.15 (m, 4H), 0.99 – 0.85 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.8, 142.7, 131.2, 55.5, 55.1, 46.3, 42.4, 40.0, 35.5, 32.4, 28.7, 24.5, 24.1, 23.3, 20.6, 16.2, 14.4, 14.2. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₈H₃₂NO 278.2478, found 278.2473. **HPLC condition:** Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r*-major = 5.7 min, *t_r*-minor = 6.2 min, 74% ee. [α]_D²⁵ -54.4 (c 0.5, CHCl₃).



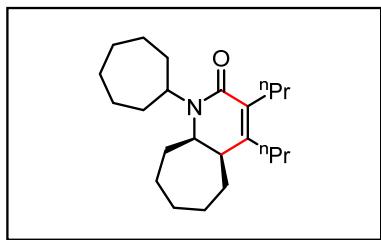
(R)-9a-Methyl-7,8-dipropyl-3,4,9a-tetrahydropyrido[2,1-c][1,4]oxazin-6(1H)-one (4i)

White solid (21.1 mg, 42%), m.p. 56–58 °C. **¹H NMR** (400 MHz, CDCl₃) δ 4.10 – 3.99 (m, 2H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.56 – 3.45 (m, 1H), 3.29 (d, *J* = 11.2 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.45 – 2.35 (m, 1H), 2.34 – 2.19 (m, 3H), 2.18 – 2.09 (m, 1H), 1.91 (d, *J* = 16.8 Hz, 1H), 1.55 – 1.35 (m, 4H), 1.25 (s, 3H), 0.94 (dt, *J* = 14.8, 7.2 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.8, 143.6, 129.1, 67.4, 53.7, 37.1, 37.4, 36.0, 28.6, 23.3, 20.8, 18.9, 14.4, 14.3. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₁₅H₂₆NO₂ 252.1958, found 252.1954. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, *t_r*-minor = 9.2 min, *t_r*-major = 11.9 min, 70% ee. [α]_D²⁵ 62.7 (c 0.5, CHCl₃).



(4aR,8aR)-1-Cyclohexyl-3,4-dipropyl-4a,5,6,7,8,8a-hexahydroquinolin-2(1H)-one (4j)

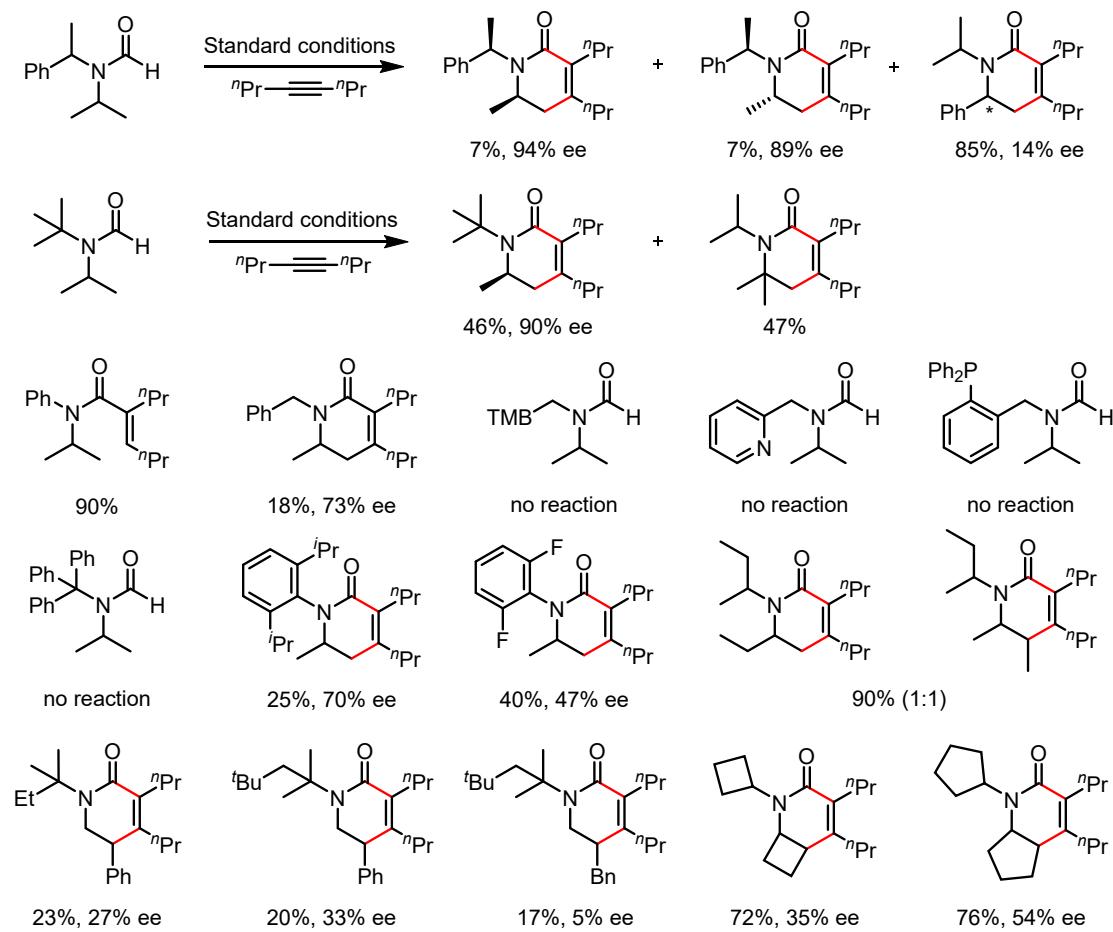
Colorless oil (57.1 mg, 90%). **¹H NMR** (400 MHz, CDCl₃) δ 4.31 – 4.26 (m, 1H), 3.29 – 3.15 (m, 1H), 2.71 – 2.55 (m, 2H), 2.45 – 2.34 (m, 1H), 2.04 – 2.34 (m, 1H), 2.07 – 1.93 (m, 2H), 1.83 – 1.69 (m, 3H), 1.68 – 1.59 (m, 4H), 1.56 – 1.30 (m, 10H), 1.29 – 1.14 (m, 2H), 1.13 – 1.00 (m, 2H), 0.94 – 0.84 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.1, 145.2, 132.1, 53.2, 52.7, 37.7, 31.8, 31.4, 31.2, 28.8, 28.5, 27.7, 26.2, 26.1, 25.7, 25.1, 23.3, 22.2, 22.1, 14.3. **HRMS** (ESI) m/z: [M+H]⁺ calcd. for C₂₁H₃₆NO 318.2791, found 318.2798. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r*-major = 8.7 min, *t_r*-minor = 9.9 min, 85% ee. [α]_D²⁵ -71.3 (c 1.0, CHCl₃).



(4a*R*,9a*R*)-1-Cycloheptyl-3,4-dipropyl-5,6,7,8,9,9a-hexahydro-1*H*-cyclohepta[*b*]pyridin-2(4*aH*)-one (4k)

Colorless oil (65.6 mg, 95%). **¹H NMR** (400 MHz, CDCl₃) δ 4.35 – 4.19 (m, 1H), 3.46 – 3.26 (m, 1H), 2.74 (q, *J* = 6.8 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.36 – 2.23 (m, 1H), 2.19 – 2.09 (m, 1H), 2.08 – 1.98 (m, 1H), 1.97 – 1.91 (m, 1H), 1.90 – 1.80 (m, 2H), 1.78 – 1.54 (m, 11H), 1.53 – 1.18 (m, 12H), 0.89 (q, *J* = 7.2 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.0, 146.6, 130.9, 57.0, 56.8, 40.5, 34.6, 32.9, 31.7, 30.1, 29.5, 28.7, 28.4, 27.7, 27.3, 26.2, 25.6, 25.5, 23.6, 23.3, 22.6, 14.4, 14.3. **HRMS (ESI) m/z:** [M+H]⁺ calcd. for C₂₃H₄₀NO₂ 346.3104, found 346.3101. **HPLC condition:** Chiralpak IA column, *n*-hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, *t_r*-major = 8.7 min, *t_{r-minor = 9.9 min, 85% ee. [α]_D²⁵ -50.4 (c 1.0, CHCl₃).}*

Selected unsuccessful examples:



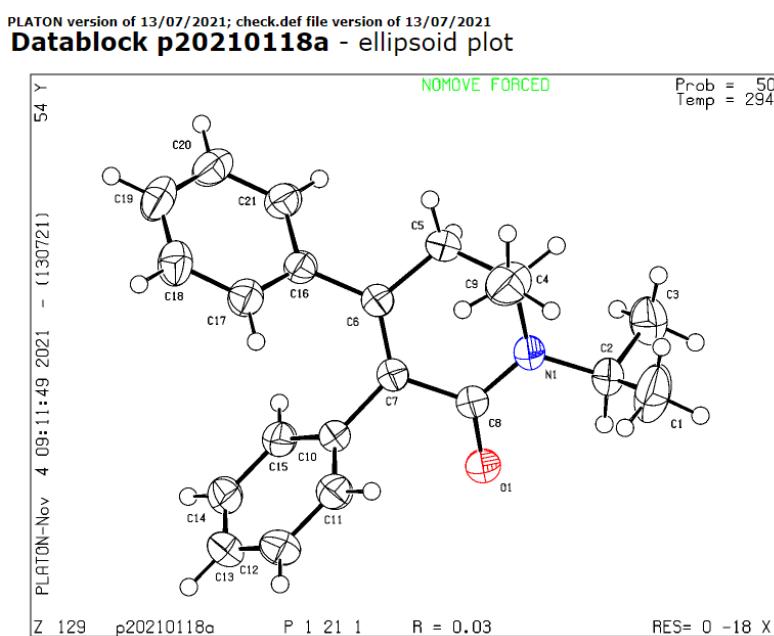
6. Crystal Structure

6.1 Crystal Structure Information of Product 3f

(*R*)-1-Isopropyl-6-methyl-3,4-diphenyl-5,6-dihydropyridin-2(1*H*)-one (3f)

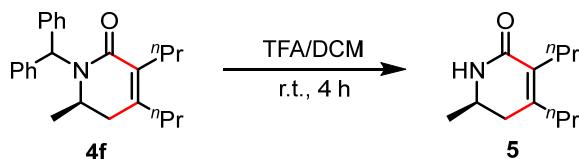
CCDC deposition Number: CCDC 2059806;

Data Block Name: data_p20210118a; Unit Cell Parameters: a 6.18736(4) b 17.86028(10) c 7.67852(5) P21



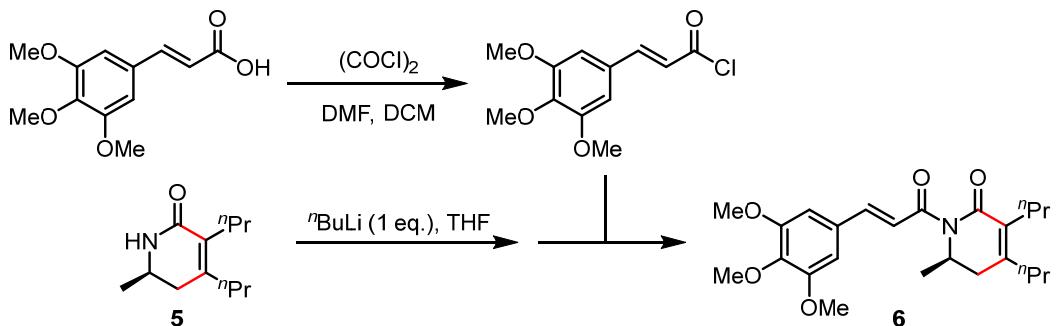
7. Product Transformation

7.1 Deprotection of product 4f



An oven-dried vial was charged with **4f** (0.2 mmol) and TFA/CH₂Cl₂ (1.5 mL, 1:2 v/v). The reaction mixture was stirred at room temperature for 4 h, diluted with CH₂Cl₂ (1 mL) and washed with saturated aqueous Na₂CO₃ (3 × 1 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc/n-hexane) to afford the desired product **5** as a white solid (33.2 mg, 85%). m.p. 42–44 °C. ¹H NMR (400 MHz, CDCl₃) δ 5.56 (s, 1H), 3.65 – 3.48 (m, 1H), 2.41 – 2.30 (m, 1H), 2.30 – 2.04 (m, 5H), 1.55 – 1.32 (m, 4H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.99 – 0.82 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 168.1, 147.6, 129.1, 45.9, 36.7, 35.9, 28.0, 23.2, 21.4, 21.0, 14.3, 14.2. HRMS (ESI) *m/z*: [M+Na]⁺ Calcd. for C₁₂H₂₁NNaO 218.1515; Found 218.1518.

7.2 Synthesis of piperlongumine analog

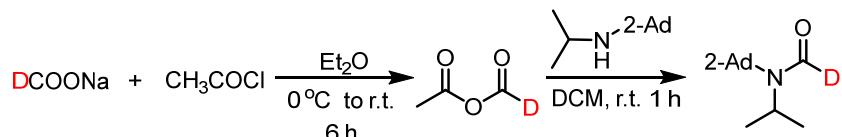


To a solution of carboxylic acid (0.2 mmol, 1.0 equiv.) in anhydrous DCM was added oxalyl chloride (3.0 equiv.) and DMF (1 drop) dropwise sequentially at room temperature in a round bottom flask. The resulting mixture was stirred at room temperature for about 3 h. Then the solvent was removed by rotary evaporation. The residue was concentrated under high vacuum, and used without further purification.

To a flame-dried Schlenk flask charged with **5** (0.2 mmol, 1.0 equiv.) in dry THF (2 mL) was added *n*-BuLi (1.0 equiv., 2.4 M in hexane) dropwise at -78°C under nitrogen atmosphere. After 15 min, a solution of acyl chloride (1.0 equiv.) in dry THF was added dropwise. After 10 min, the reaction was gradually warmed up to room temperature for overnight. Then, the reaction mixture was quenched with saturated ammonium chloride (2 mL) and extracted with ethyl acetate (15 mL). The organic layer was separated and washed with brine (2 × 15 mL). Organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Further purification by column chromatography on silica gel (Hexane/EtOAc) afforded the piperlongumine analog **6** as colorless oil (25.7 mg, 31%). **¹H NMR** (400 MHz, CDCl₃) δ 7.61 (d, *J* = 15.6 Hz, 1H), 7.35 (d, *J* = 15.6 Hz, 1H), 6.78 (s, 2H), 4.89 – 4.74 (m, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 2.75 (dd, *J* = 17.6, 6.2 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.36 – 2.19 (m, 3H), 2.13 (d, *J* = 17.6 Hz, 1H), 1.58 – 1.40 (m, 4H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.97 (dt, *J* = 14.4, 7.4 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 169.3, 166.3, 153.4, 150.7, 142.8, 139.8, 131.1, 130.1, 122.0, 105.6, 76.8, 61.1, 56.3, 47.3, 36.5, 35.0, 28.3, 23.1, 20.8, 18.7, 14.4, 14.4. HRMS (ESI) m/z: [M+Na]⁺ Calcd. for C₂₄H₃₃NNaO₅ 438.2251; Found 438.2255. **HPLC condition:** Chiralpak ODH column, *n*-hexane/*i*-PrOH = 98:2, 0.8 mL/min, 254 nm, *t*_r-minor = 17.629 min, *t*_r-major = 19.843 min, 93% ee. [α]_D²⁵ -25.0 (c 0.2, CHCl₃).

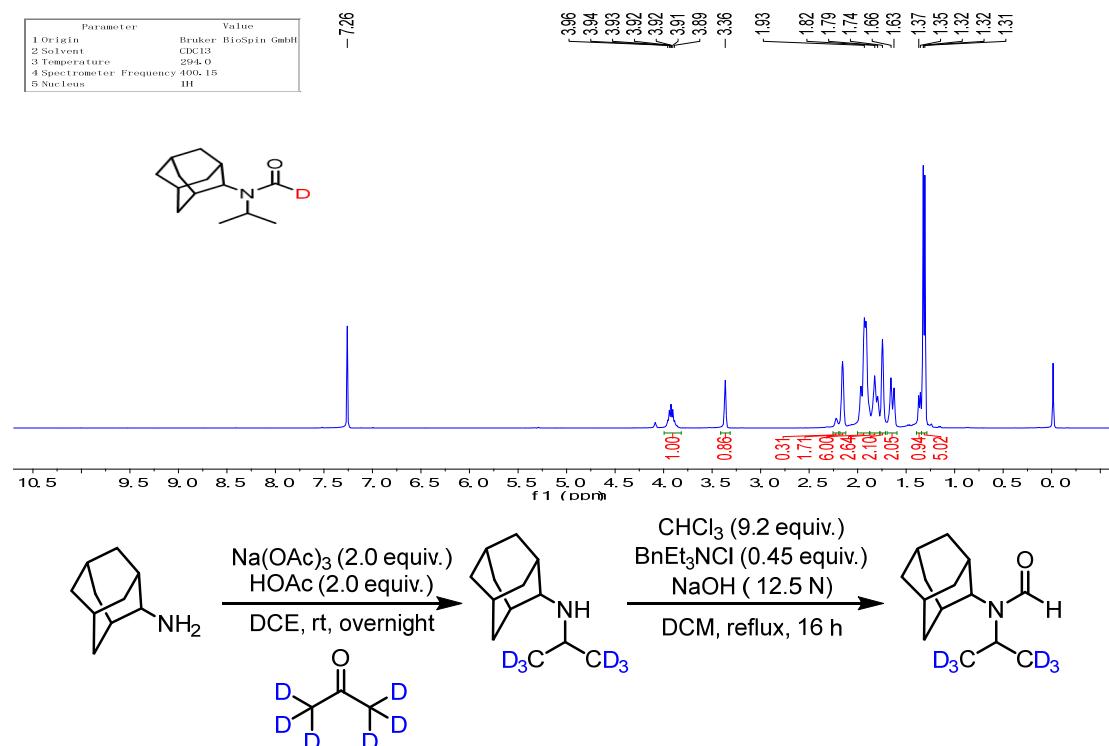
8. Mechanistic Experiments

8.1 Deuterated-substrate preparation



To the solution of sodium formate-*d* (99% D, 0.83 g, 12.0 mmol) in dry Et₂O (5.0 mL) was added acetyl chloride (0.71 mL, 10.0 mmol) slowly (< 25 °C) under N₂ atmosphere. The mixture was stirred at room temperature for 6 h, filtered through a short pad of Celite. The filtrate was evaporated under reduced pressure at low temperature to

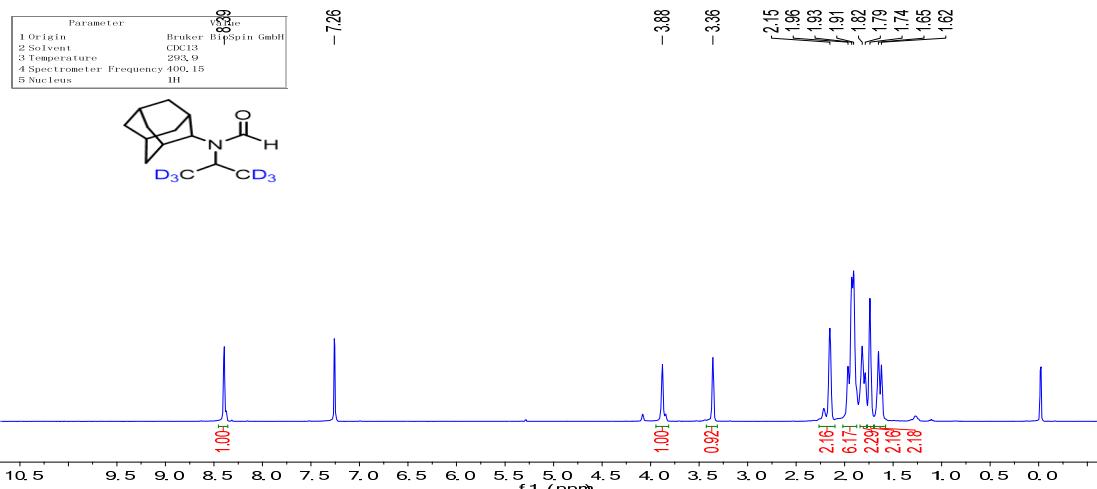
provide acetic formic anhydride-*d*. To a solution of *N*-isopropyladamantan-2-amine (0.97 g, 5.0 mmol, obtained by Method C) in CH₂Cl₂ (10 mL) was added acetic formic anhydride-*d* (0.89 g, 10 mmol), and stirred at r.t. for one hour. The reaction was then quenched with 5 mL of saturated aqueous NaHCO₃, and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (25% EtOAc/n-hexane) to afford the title compound as a white solid (0.94 g, 85% yield after two steps). ¹H NMR (400 MHz, CDCl₃) δ 3.96 – 3.89 (m, 1H), 3.36 (s, 1H), 2.20 (s, 0.3H), 2.14 (s, 1.7H), 1.97 – 1.85 (m, 6H), 1.84 – 1.76 (m, 2H), 1.73 (s, 2H), 1.63 (d, *J* = 12.8 Hz, 2H), 1.35 (d, *J* = 6.8 Hz, 0.94H), 1.30 (d, *J* = 6.8 Hz, 5.02H).



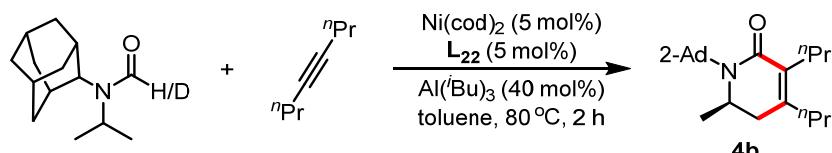
The mixture of adamantan-2-amine (1.51 g, 10 mmol, 1.0 equiv.), propan-2-one-*d*₆ (0.64 g, 10 mmol, 1.0 equiv.), AcOH (1.14 mL, 20 mmol, 2.0 equiv.) and NaBH(OAc)₃ (4.24 g, 20 mmol, 2.0 equiv.) in DCE (30 mL) was stirred at room temperature overnight, quenched with aqueous NaOH (1M), extracted with DCM (2 × 20 mL). The organic phases were dried over anhydrous Na₂SO₄, filtered, and evaporated under vacuum to give crude *N*-(propan-2-yl-1,1,1,3,3,*d*₆)adamantan-2-amine, which was used in the next step without further purification.

To a solution of *N*-(propan-2-yl-1,1,1,3,3,*d*₆)adamantan-2-amine (1.99 g, 10 mmol, 1.0 equiv.), BnEt₃NCl (1.03 g, 4.5 mmol, 0.45 equiv.) and CHCl₃ (7.3 mL, 92 mmol, 9.2 equiv.) in CH₂Cl₂ (30 mL) was added aqueous NaOH (25 mL, 12.5 M). The resulting mixture was then heated to reflux for 16 h, diluted with H₂O (45 mL), and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (25% EtOAc/n-hexane)

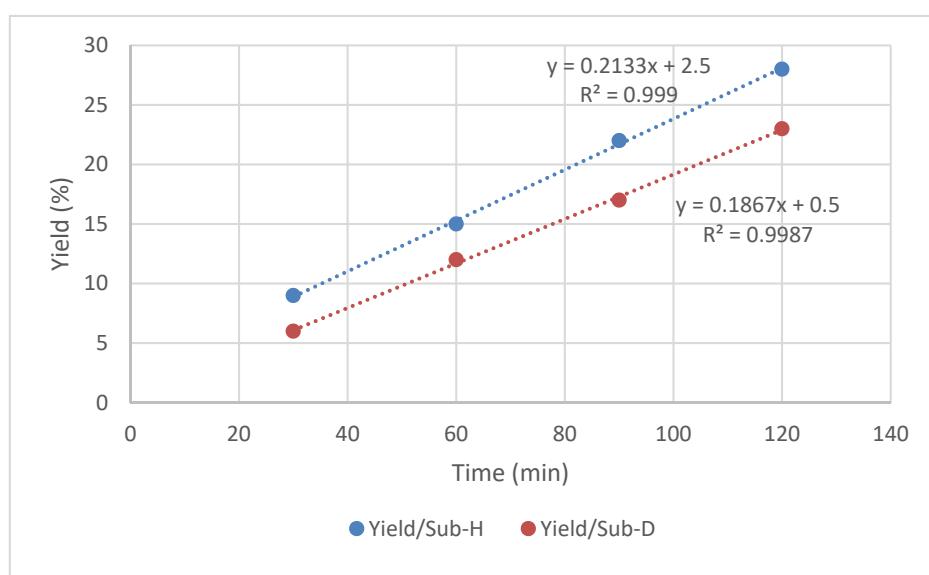
to afford *N*-(adamantan-2-yl)-*N*-(propan-2-yl-1,1,1,3,3,3-*d*₆)formamide as a white solid (1.84 g, 81% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 3.88 (s, 1H), 3.36 (s, 1H), 2.20 (s, 2H), 1.97 – 1.85 (m, 6H), 1.84 – 1.76 (m, 2H), 1.73 (s, 2H), 1.63 (d, *J* = 12.8 Hz, 2H).



8.2 Parallel Reactions for KIE Determination of Formyl Hydride of Formamide

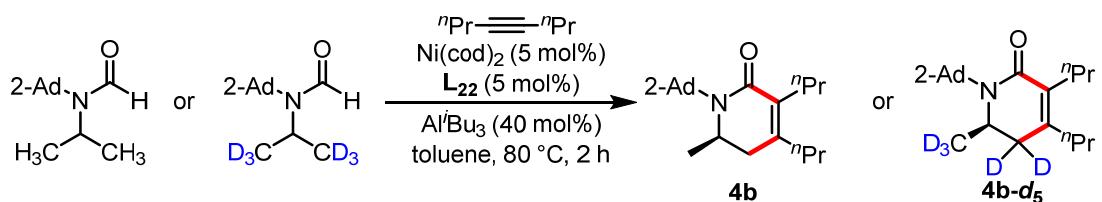


Parallel reactions were set up following the general procedure by using *N*-(adamantan-2-yl)-*N*-isopropylformamide and *N*-(adamantan-2-yl)-*N*-isopropyl formamide-*d* as a substrate respectively. Aliquots were taken at 30 minute intervals for the first two hours. Product yield was determined by ¹H NMR using CH₂Br₂ as an internal standard. Data points represent the average of two runs. The calculated *k*_H/*k*_D = 1.11.

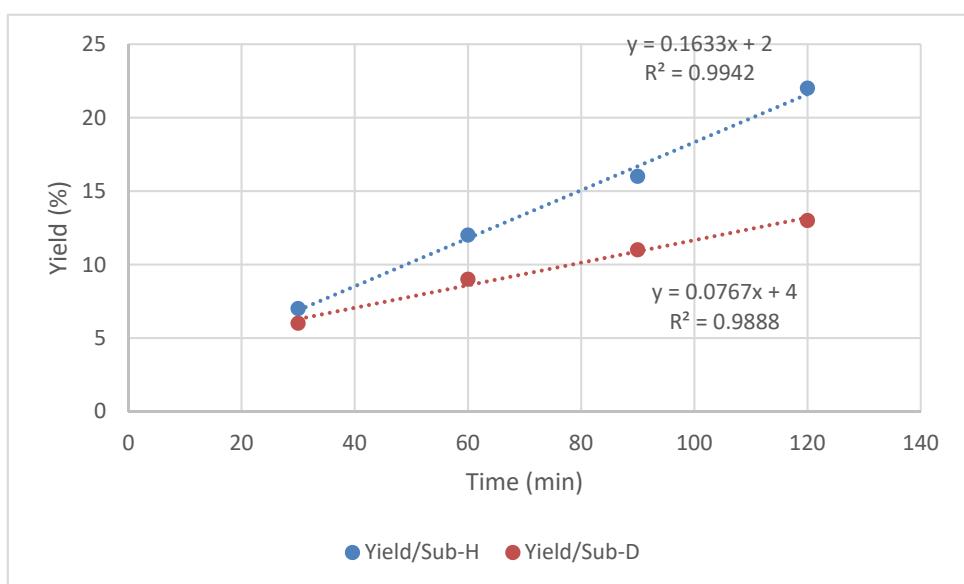


$$\text{KIE} = k_{\text{H}}/k_{\text{D}} = 0.2133 / 0.1867 = 1.14$$

8.3 Parallel Reactions for KIE Determination of Alkyl Hydride of Formamide

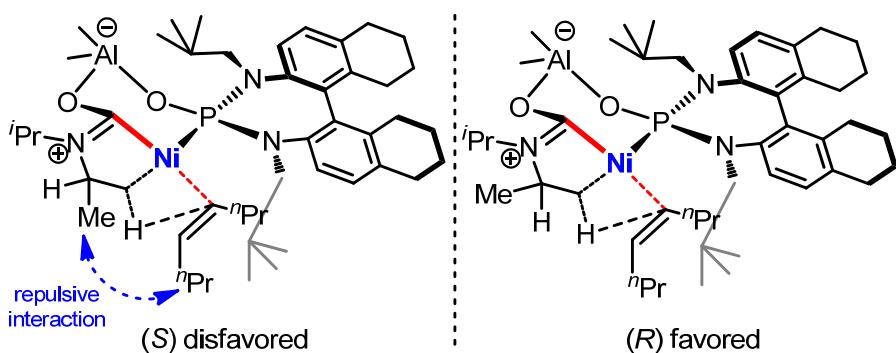


Parallel reactions were set up following the general procedure by using *N*-(adamantan-2-yl)-*N*-isopropyl formamide (0.1 mmol) and *N*-(propan-2-yl-1,1,1,3,3,3-d₆)-adamantan-2-amine (0.1 mmol) as a substrate respectively. Aliquots were taken at 30 minute intervals for the first two hours. Product yield was determined by ¹H NMR using CH₂Br₂ as an internal standard. Data points represent the average of two runs.



$$\text{KIE} = k_{\text{H}}/k_{\text{D}} = 0.1633 / 0.0767 = 2.13$$

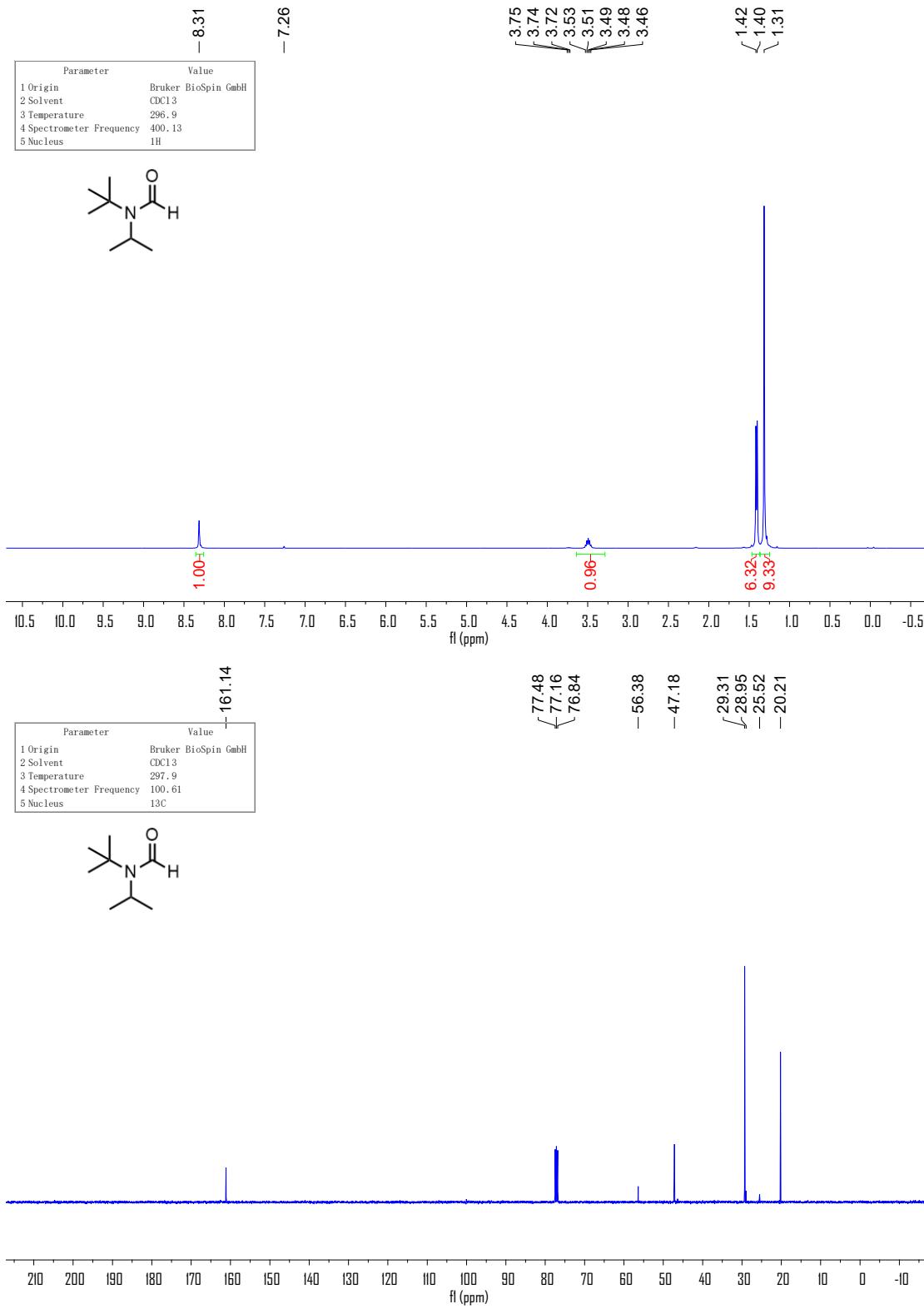
9. Stereochemical model



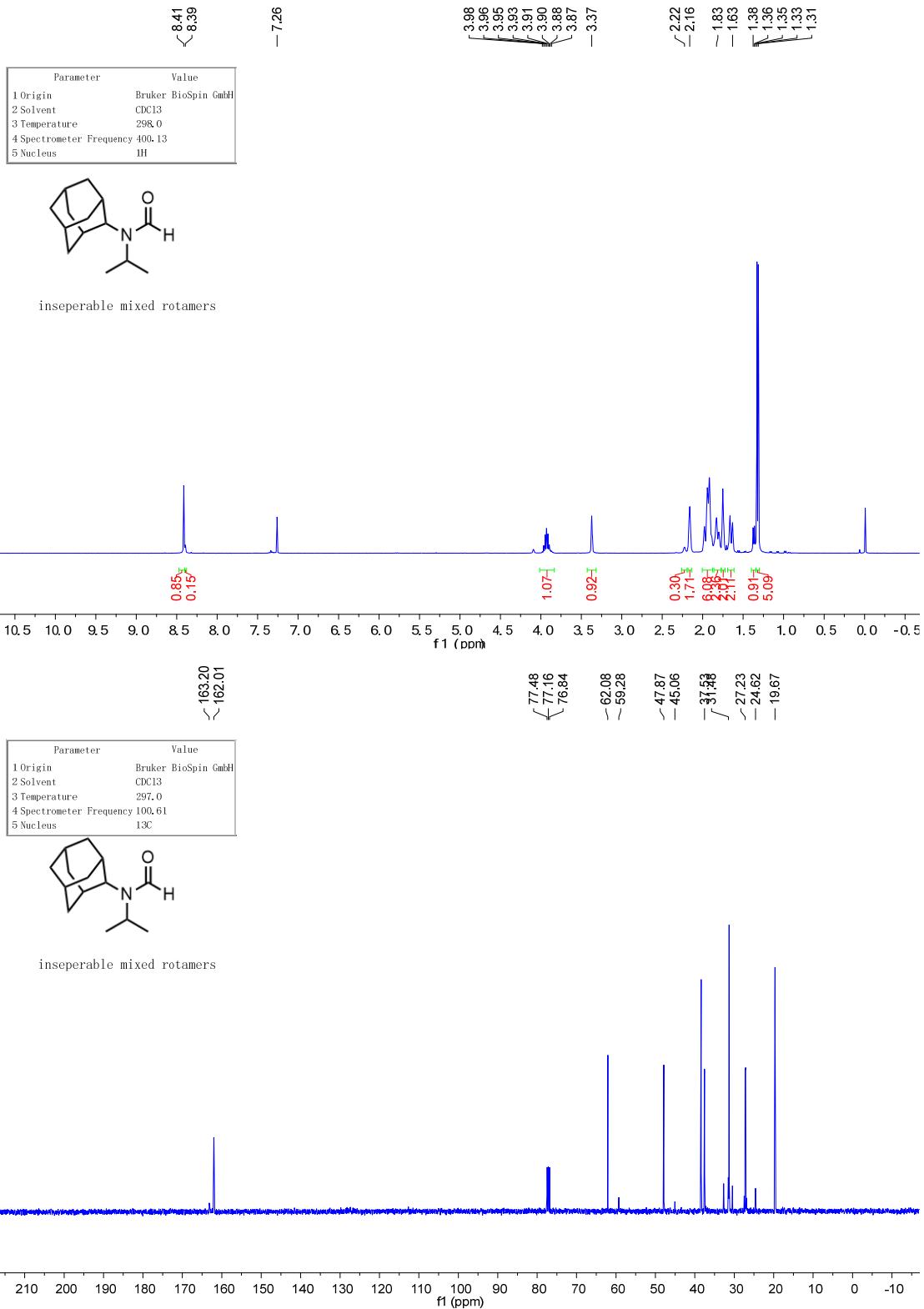
10. Reference

- [1] K. Banert, M. Heck, A. Ihle, J. Kronawitt, T. Pester, T. Shoker, *J. Org. Chem.* **2018**, *83*, 5138.
- [2] P. V. Ilyin, A. S. Pankova, M. A. Kuznetsov, *Synthesis* **2012**, *44*, 1353.
- [3] L. Wallbaum, D. Weismann, D. Löber, C. Bruhn, P. Prochnow, J. E. Bandow, U. Siemeling, *Chem. Eur. J.* **2019**, *25*, 1488.
- [4] R. T. Yu. T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 12370.
- [5] Y.-X. Wang, S.-L. Qi, Y.-X. Luan, X.-W. Han, S. Wang, H. Chen, M. Ye, *J. Am. Chem. Soc.* **2018**, *140*, 5360.
- [6] H. Chen, Y.-X. Wang, Y.-X. Luan, M. Ye, *Angew. Chem., Int. Ed.* **2020**, *59*, 9428.

11. NMR Spectra



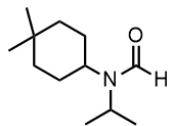
¹H and ¹³C NMR spectra of compound **1a'**



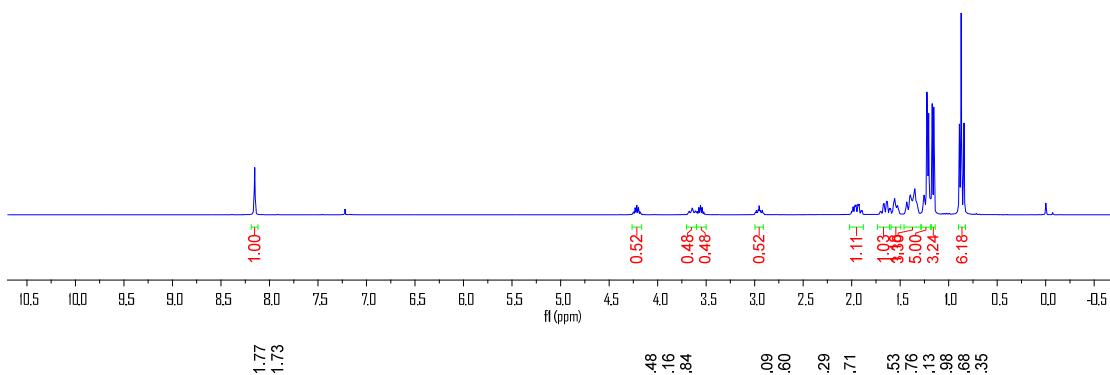
¹H and ¹³C NMR spectra of compound **1b**



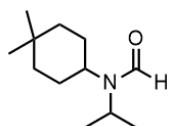
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1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	296.3
4 Spectrometer Frequency	400.13
5 Nucleus	1H



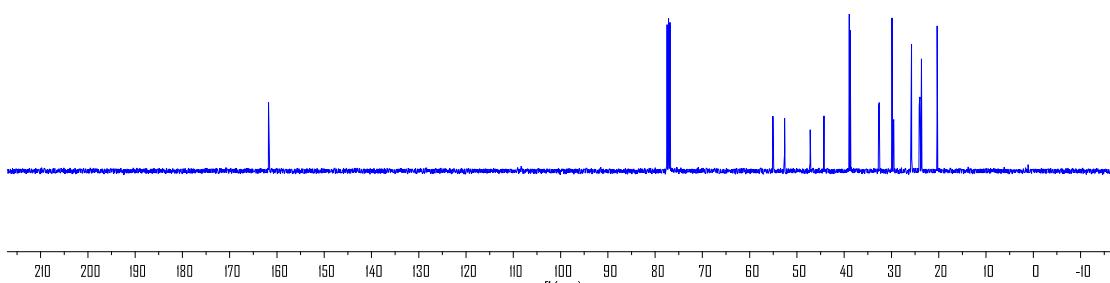
inseperable mixed rotamers



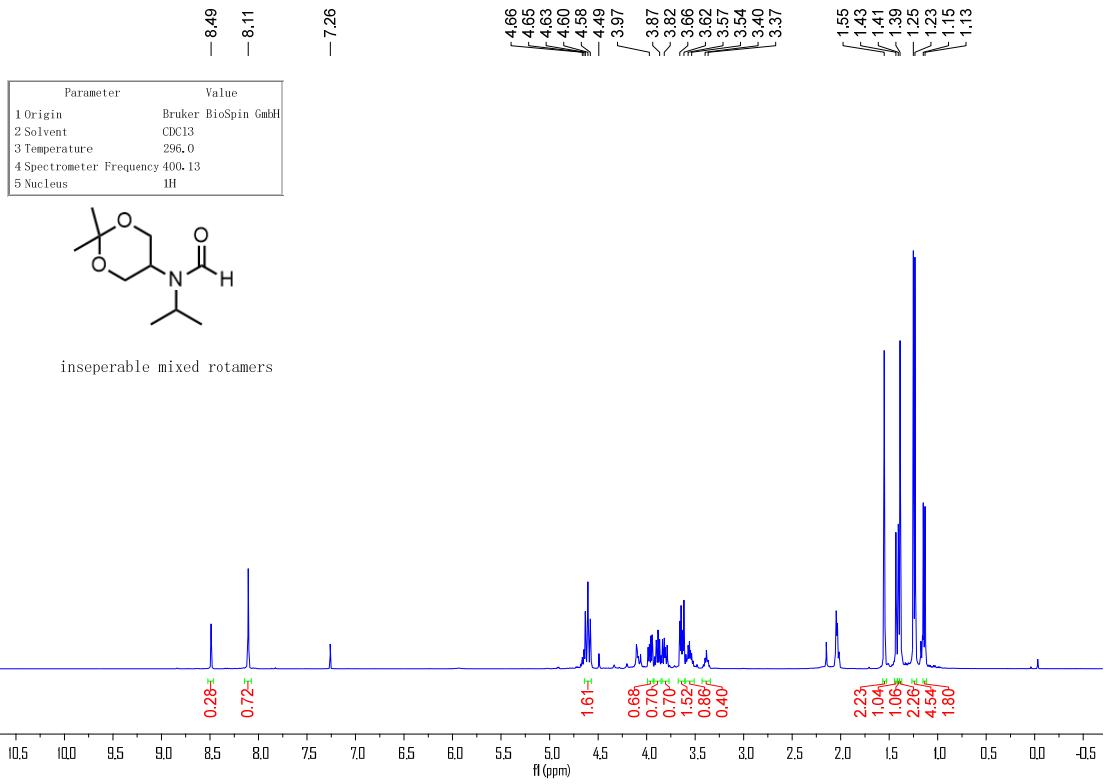
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5 Nucleus	13C



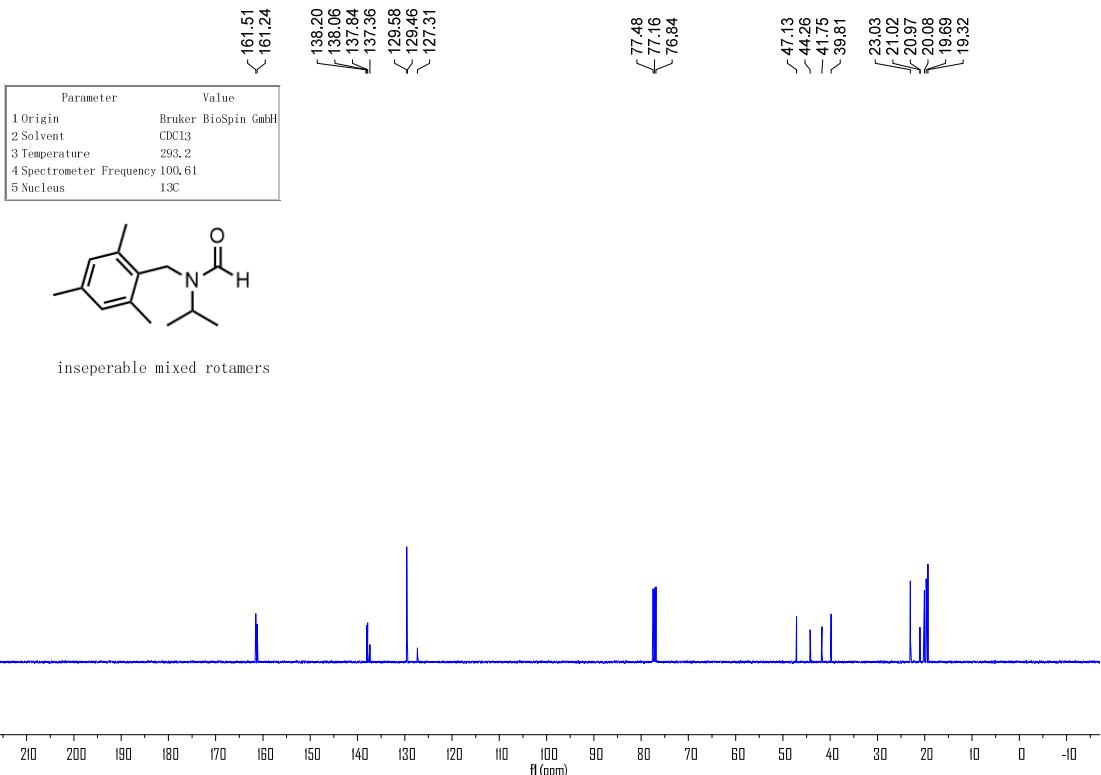
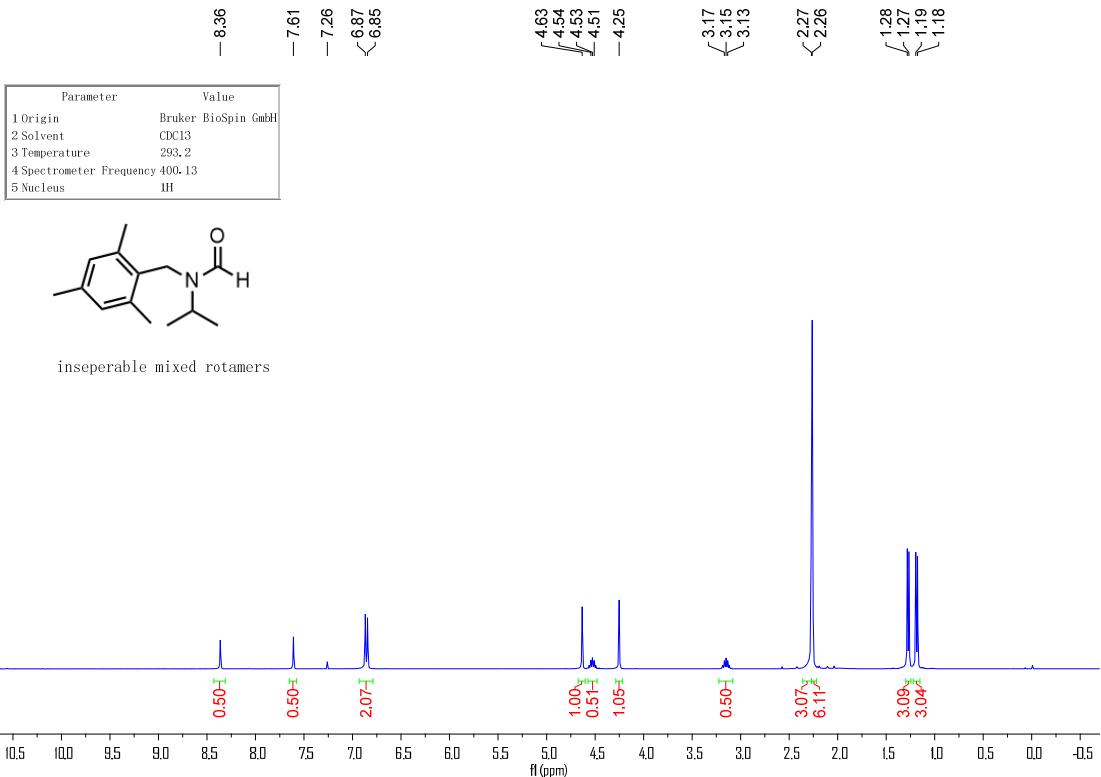
inseperable mixed rotamers



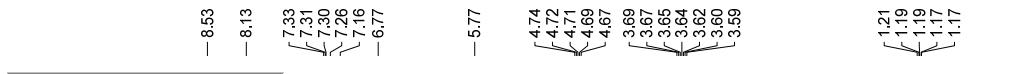
¹H and ¹³C NMR spectra of compound 1c



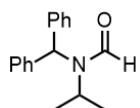
¹H and ¹³C NMR spectra of compound **1d**



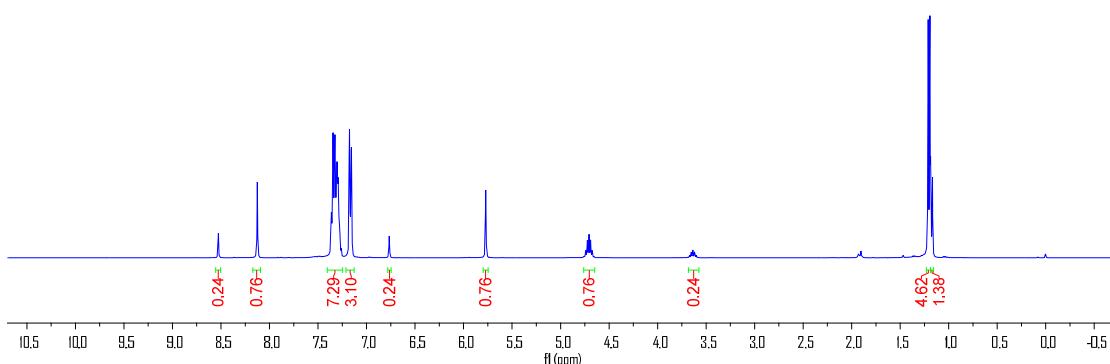
¹H and ¹³C NMR spectra of compound 1e



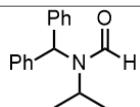
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1 Origin	Bruker BioSpin GmbH
2 Solvent	CDC13
3 Temperature	295.3
4 Spectrometer Frequency	400.15
5 Nucleus	1H



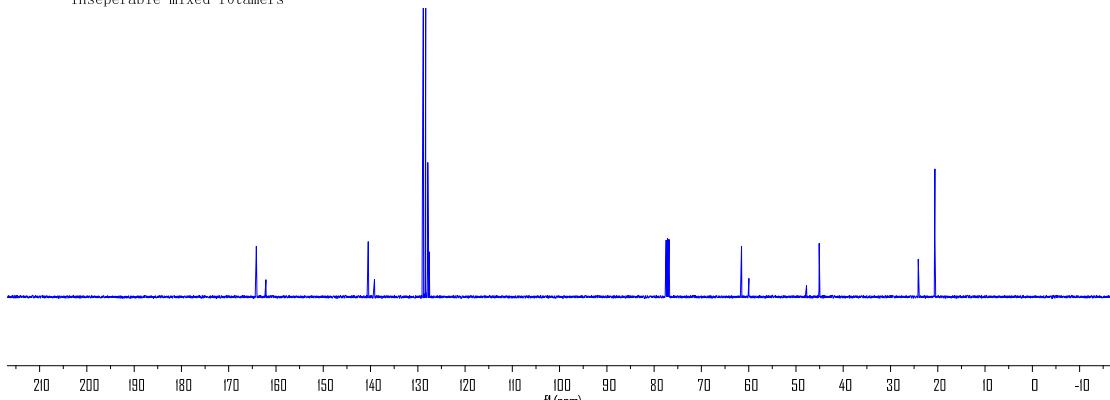
inseperable mixed rotamers



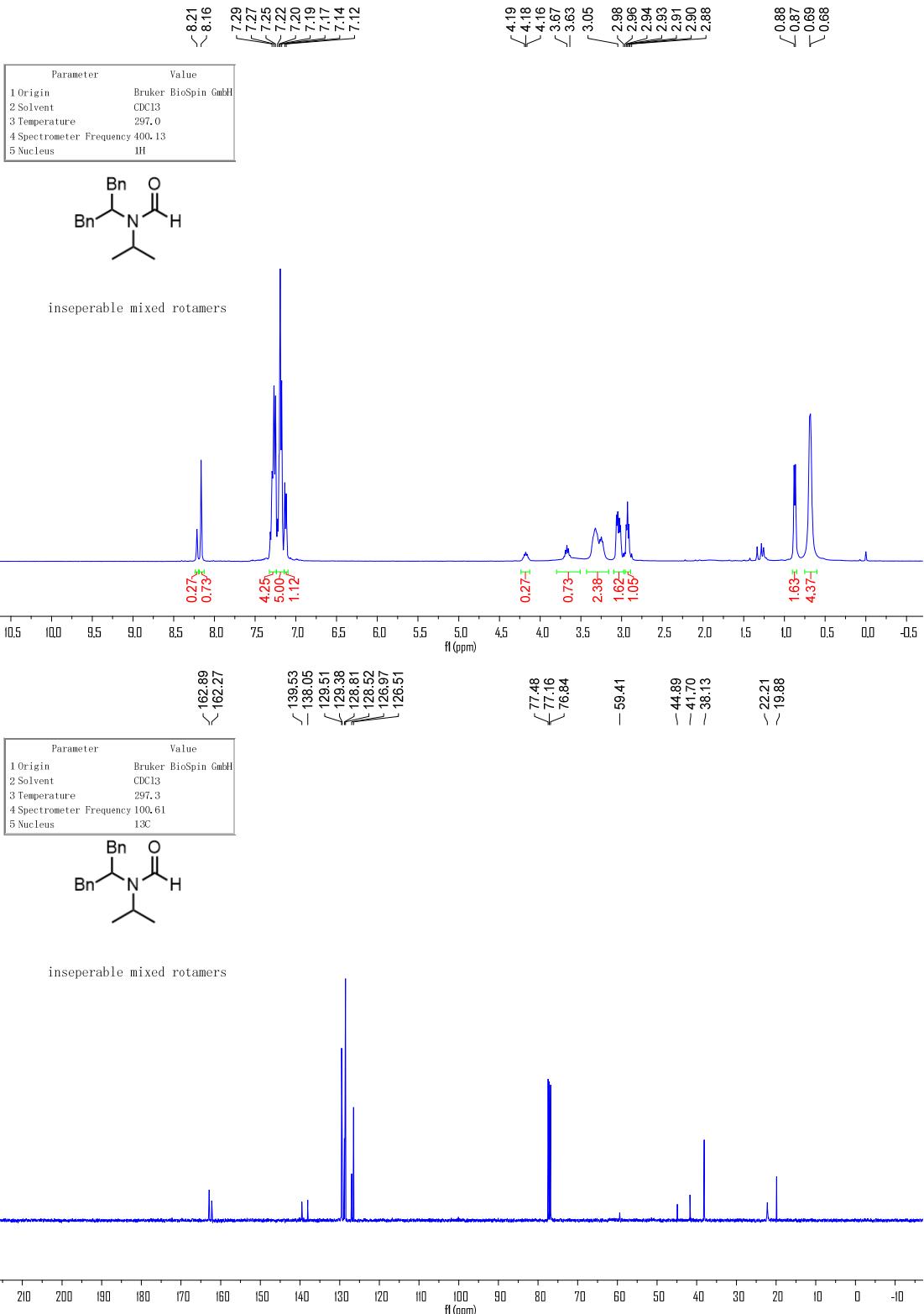
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDC13
3 Temperature	295.7
4 Spectrometer Frequency	100.62
5 Nucleus	¹³ C



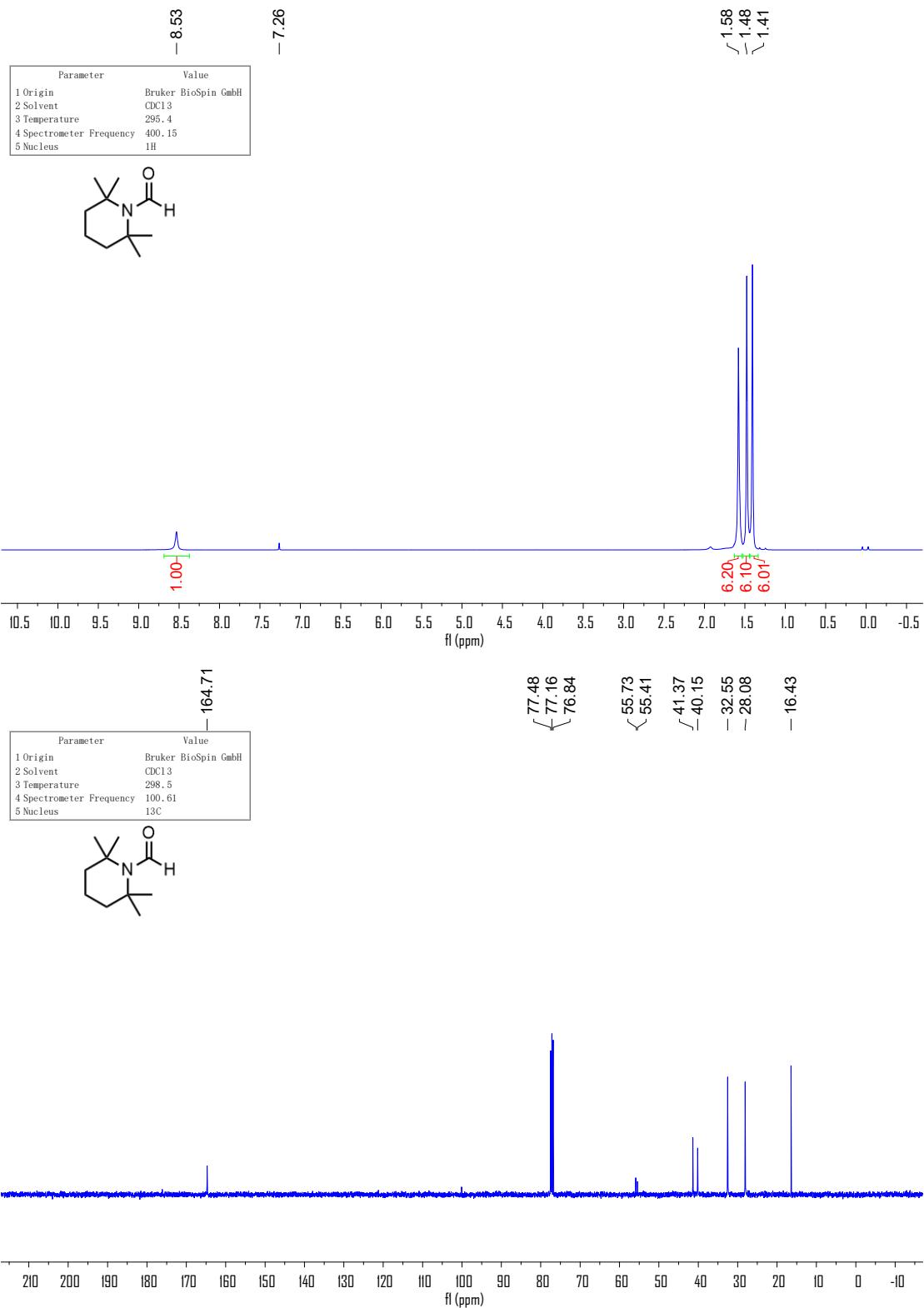
inseperable mixed rotamers



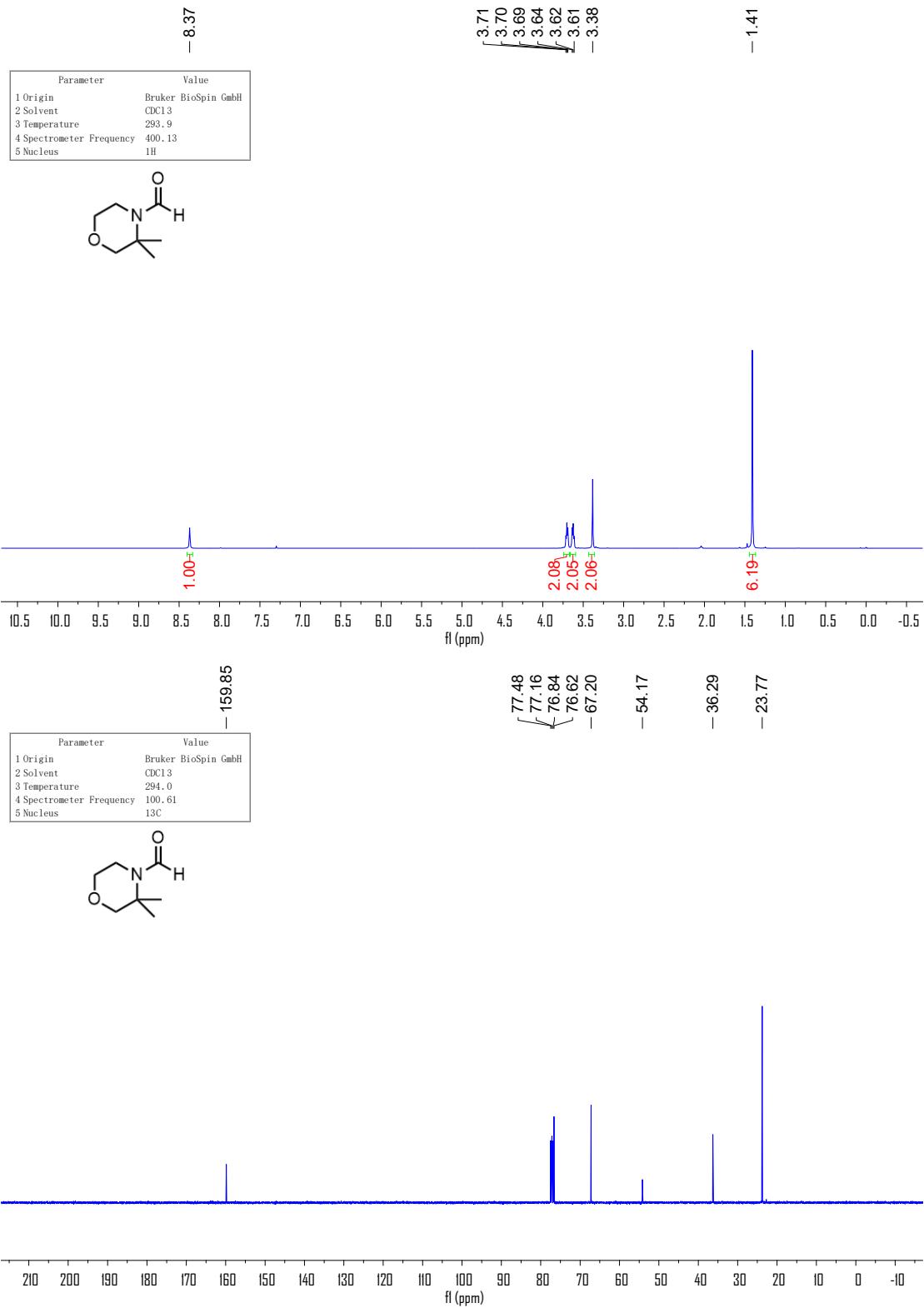
¹H and ¹³C NMR spectra of compound **1f**



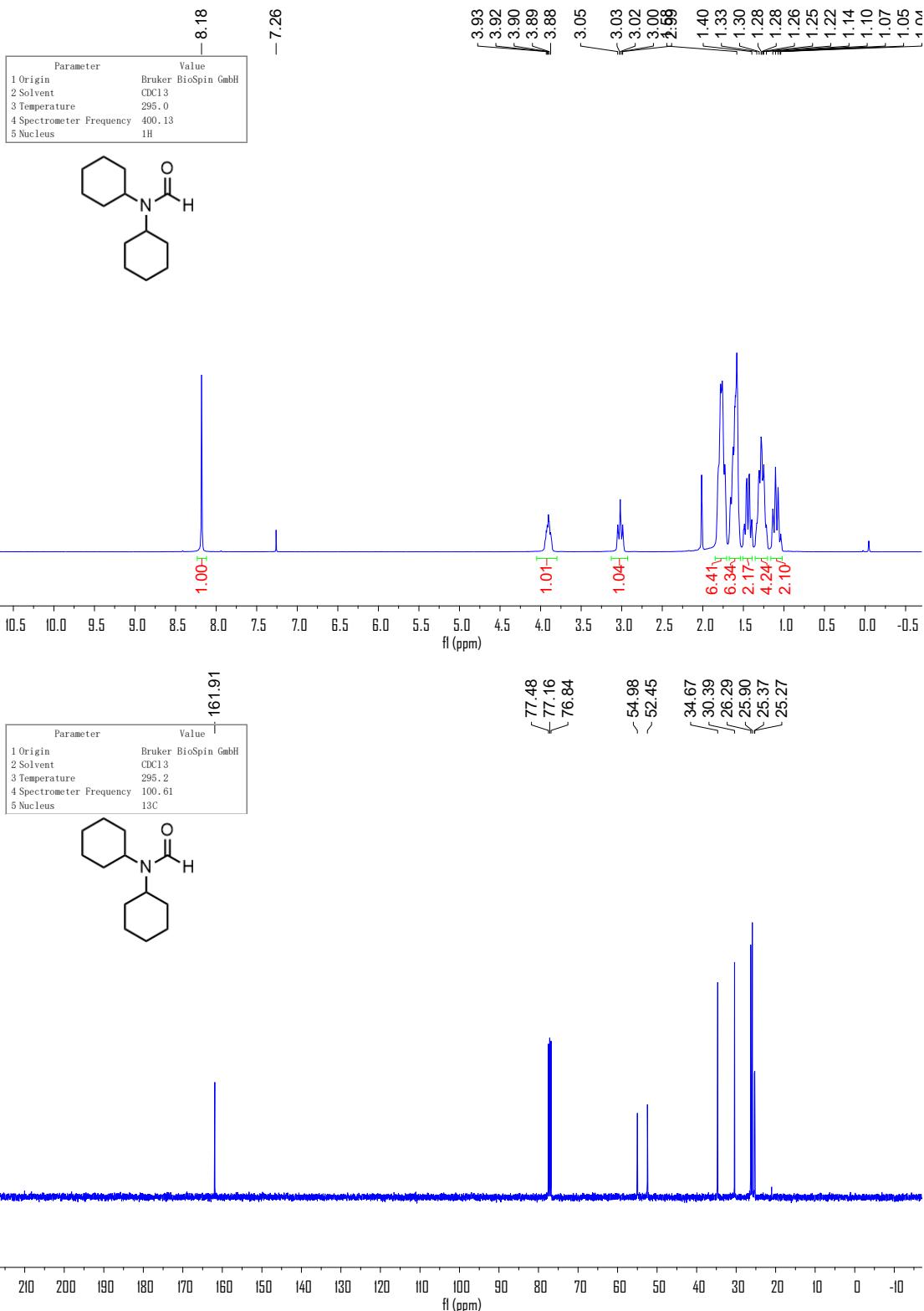
¹H and ¹³C NMR spectra of compound **1g**



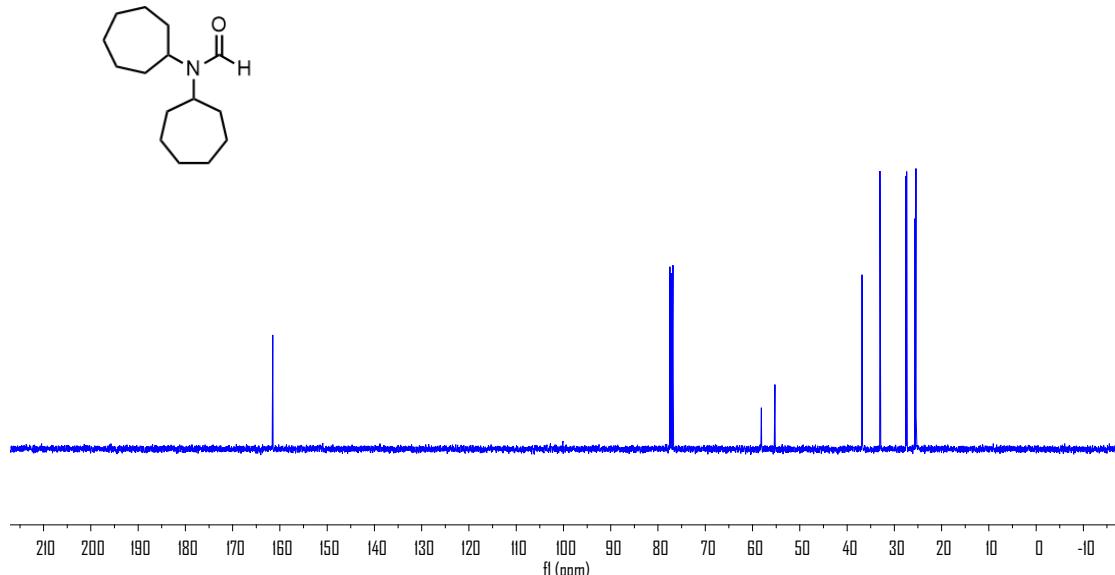
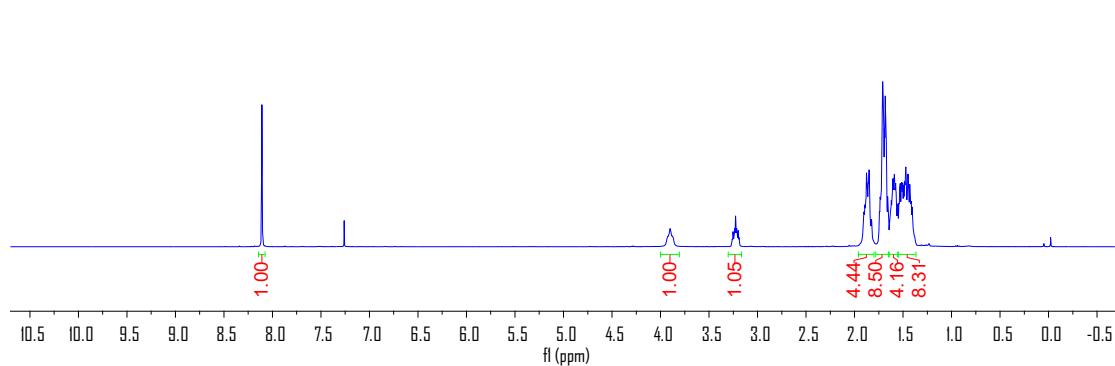
¹H and ¹³C NMR spectra of compound **1h**



¹H and ¹³C NMR spectra of compound **1i**



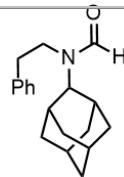
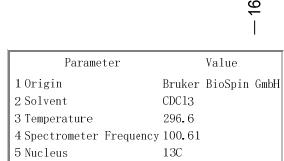
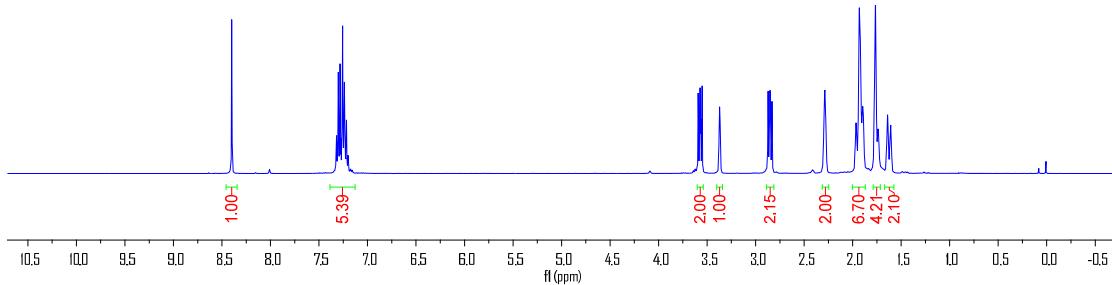
¹H and ¹³C NMR spectra of compound **1j**



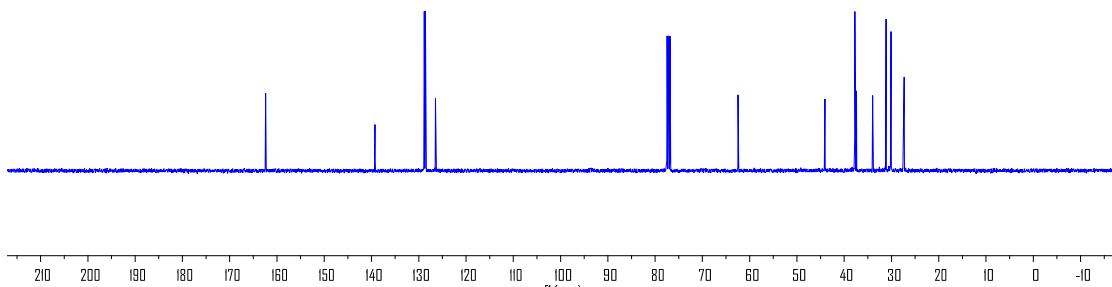
¹H and ¹³C NMR spectra of compound **1k**



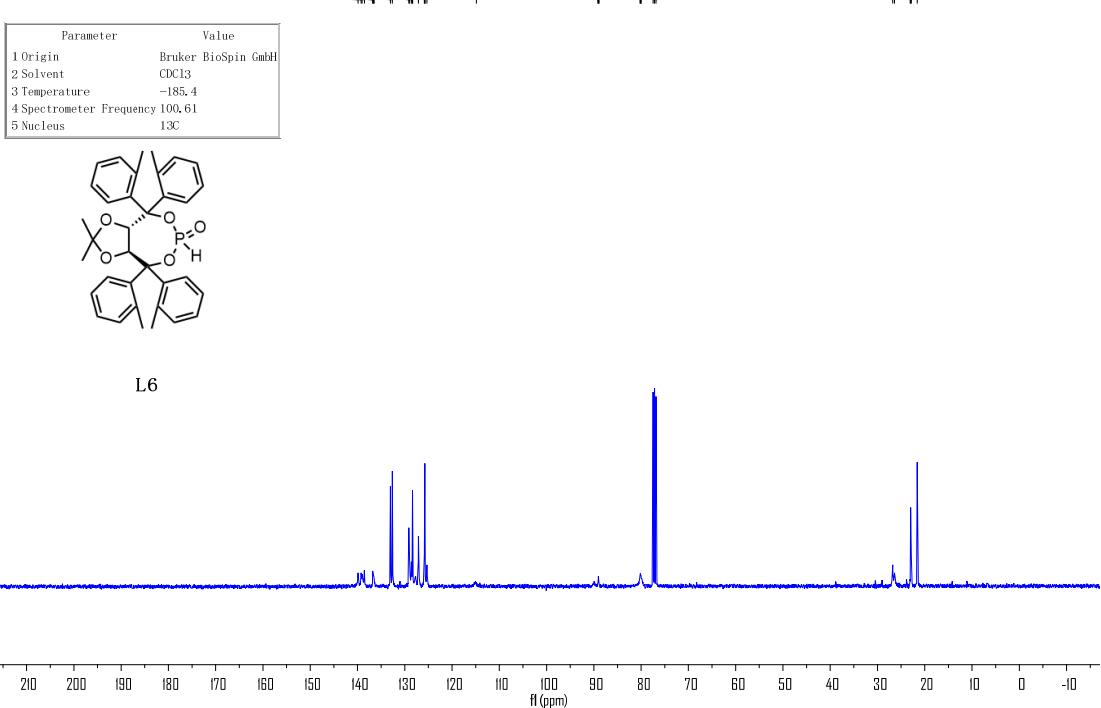
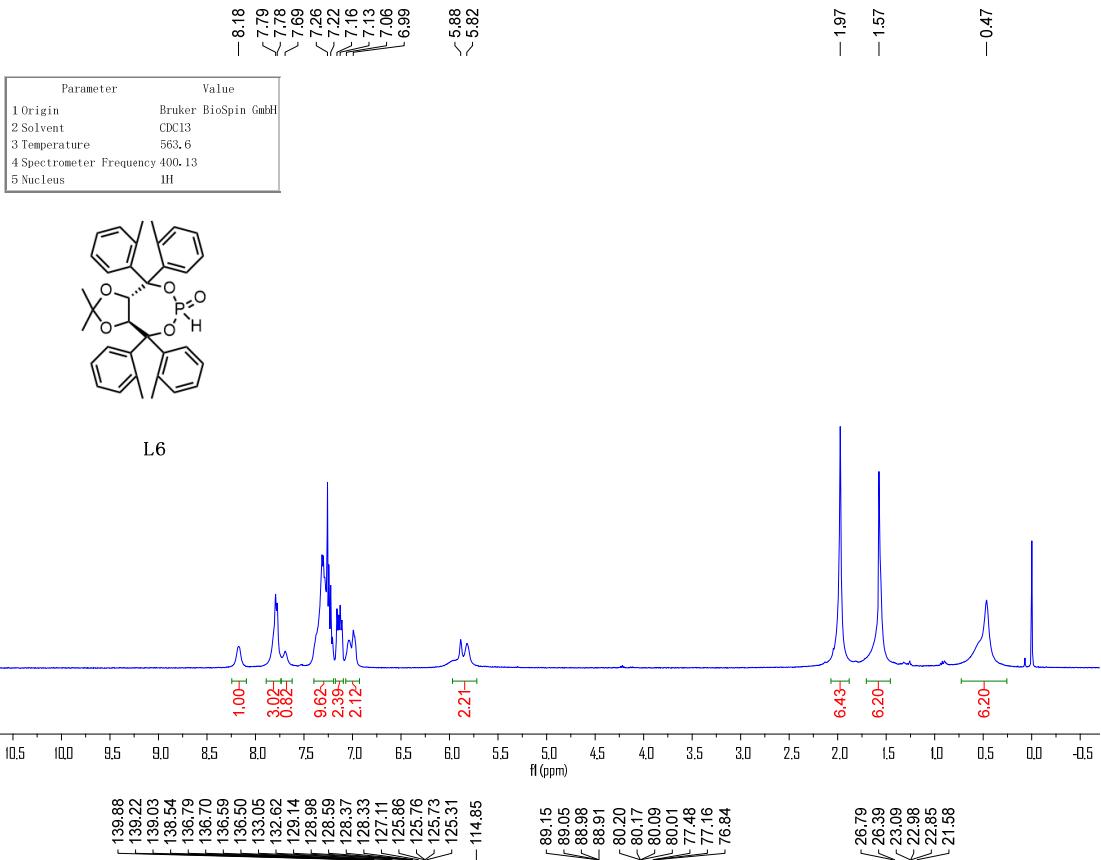
inseperable mixed rotamers



inseperable mixed rotamers

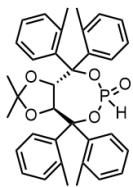


¹H and ¹³C NMR spectra of compound **11**

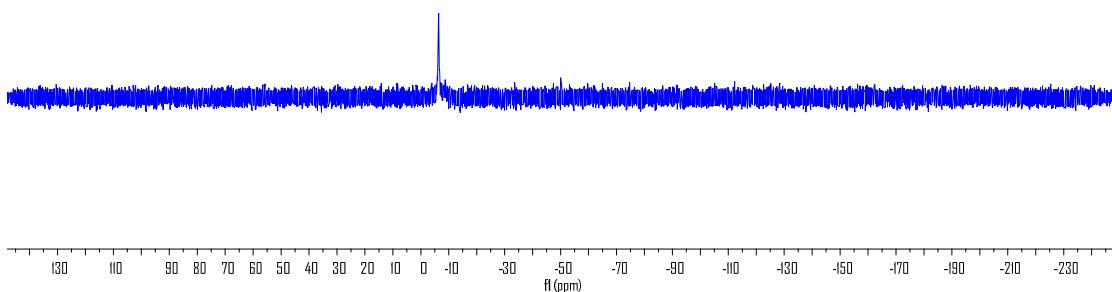


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	522.4
4 Spectrometer Frequency	161.98
5 Nucleus	31P

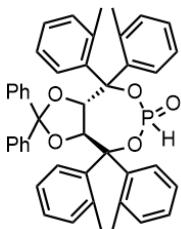
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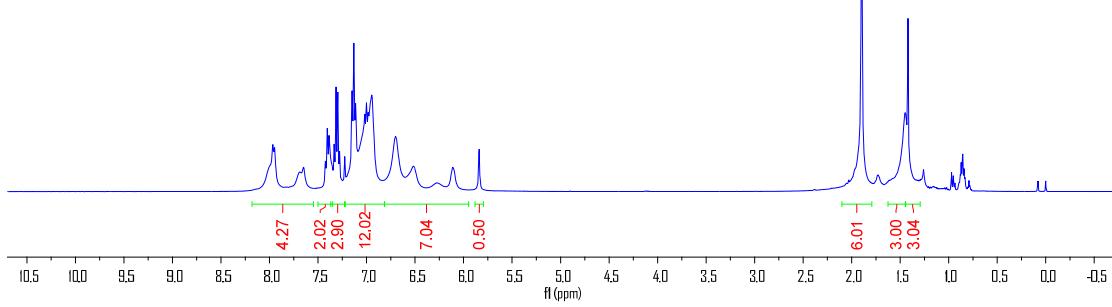
L6



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	294.0
4 Spectrometer Frequency	400.13
5 Nucleus	1H

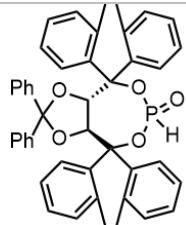


L7

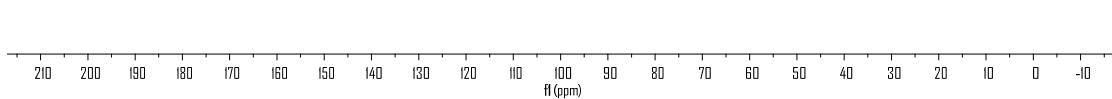




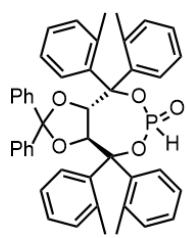
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl_3
3 Temperature	294.1
4 Spectrometer Frequency	100.61
5 Nucleus	^{13}C



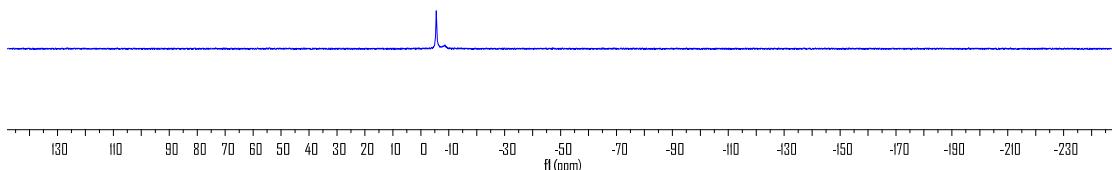
L7

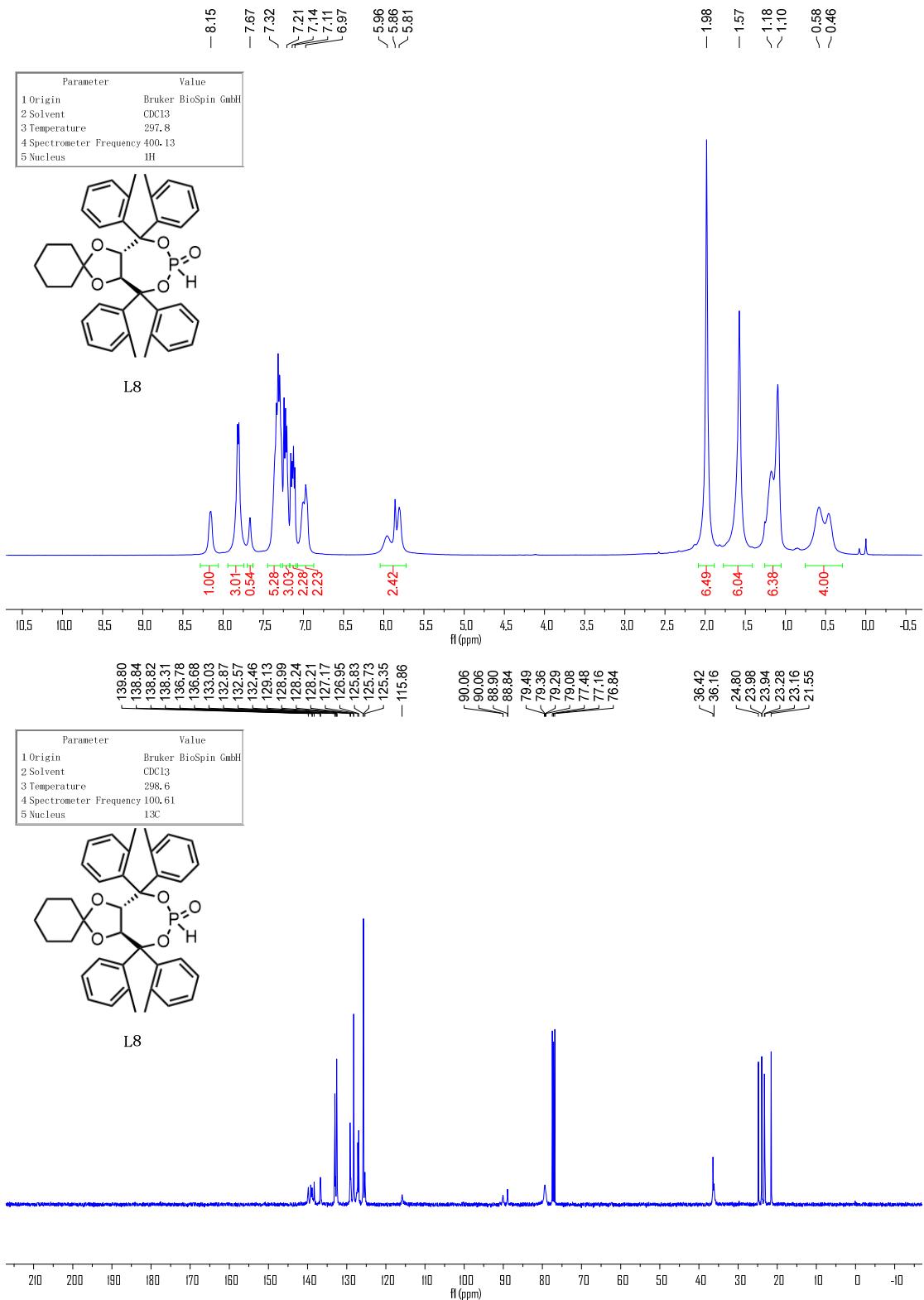


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl_3
3 Temperature	293.9
4 Spectrometer Frequency	161.98
5 Nucleus	^{31}P

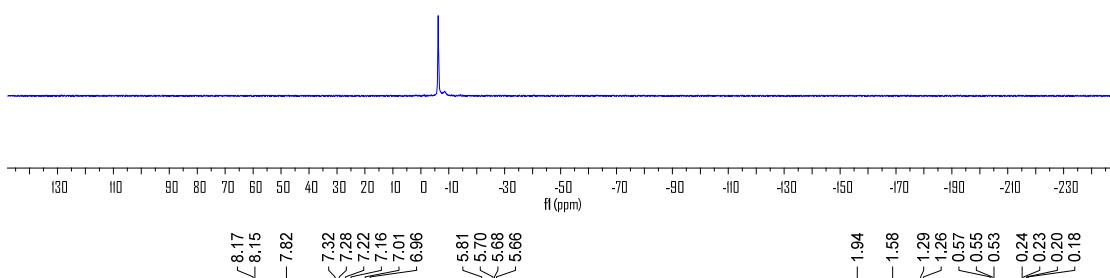
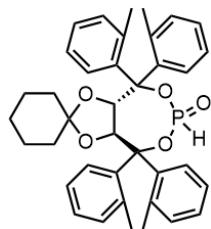


L7

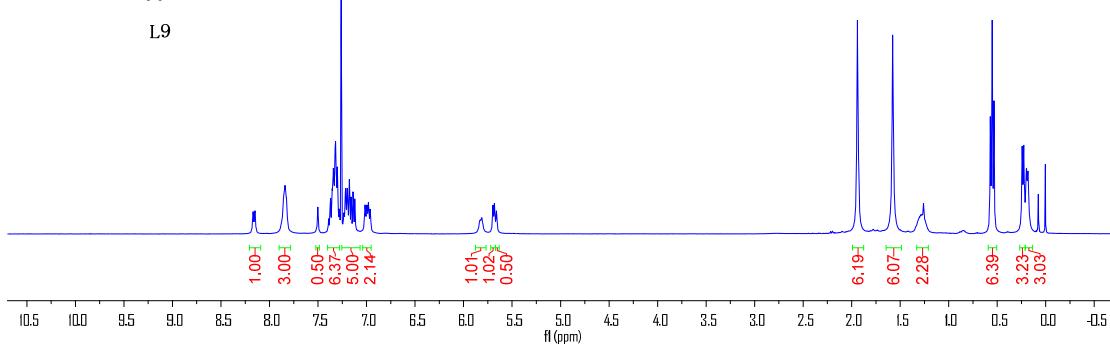
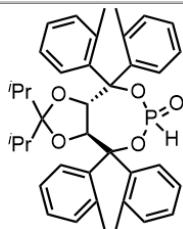


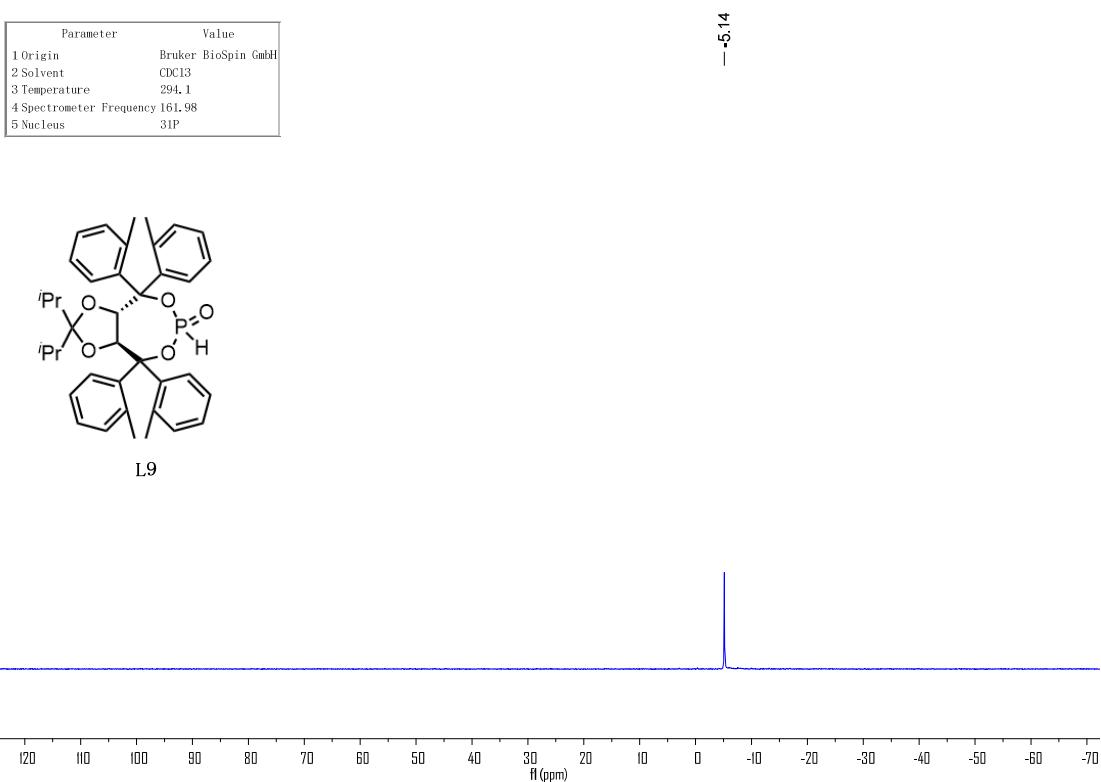
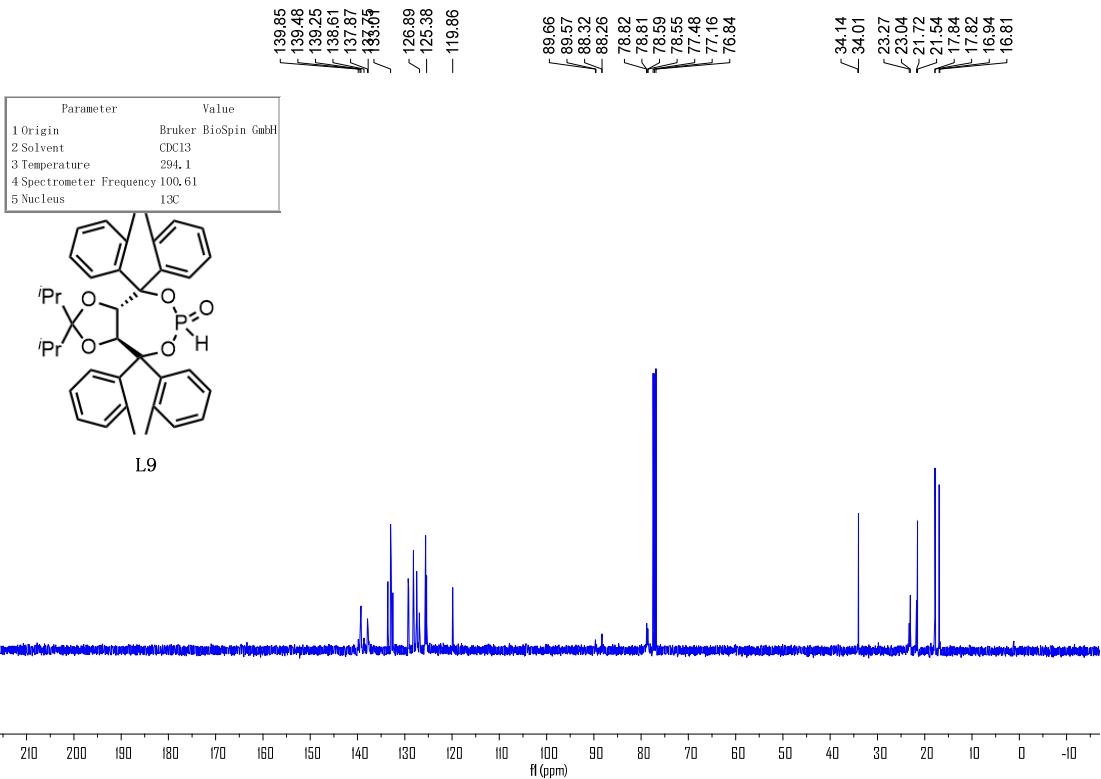


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	294.0
4 Spectrometer Frequency	161.98
5 Nucleus	31P

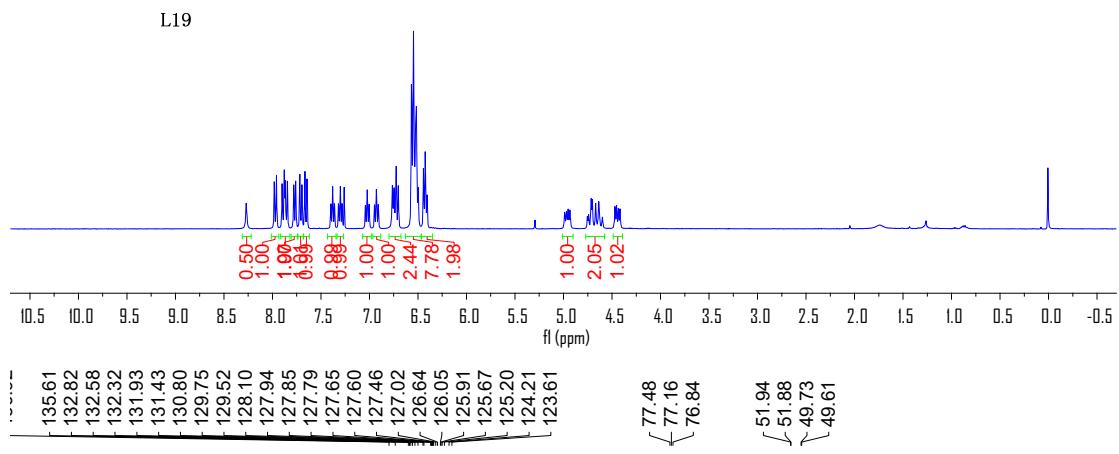
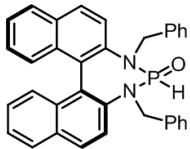


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	297.4
4 Spectrometer Frequency	400.13
5 Nucleus	1H

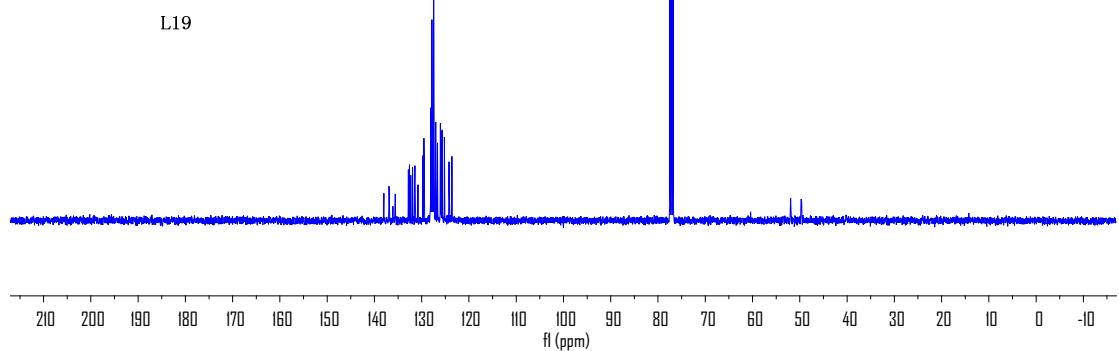
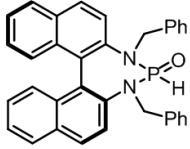




Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDC13
3 Temperature	299.9
4 Spectrometer Frequency	400.13
5 Nucleus	1H

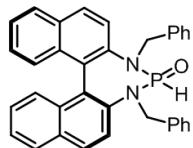


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDC13
3 Temperature	300.2
4 Spectrometer Frequency	100.61
5 Nucleus	13C

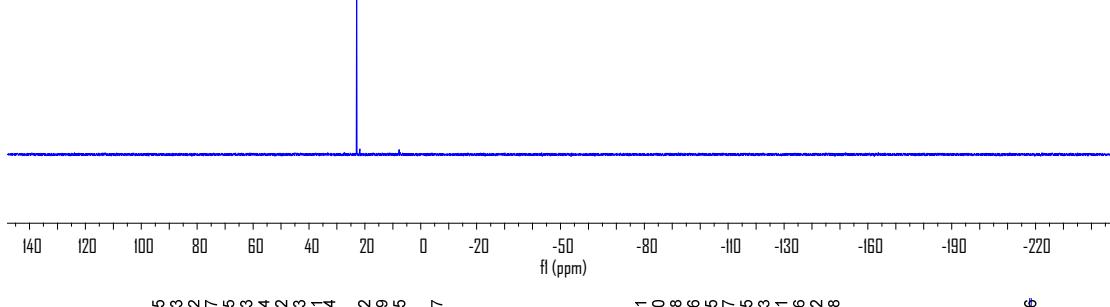


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	300.4
4 Spectrometer Frequency	161.98
5 Nucleus	31P

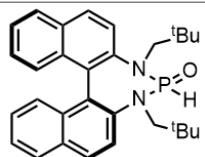
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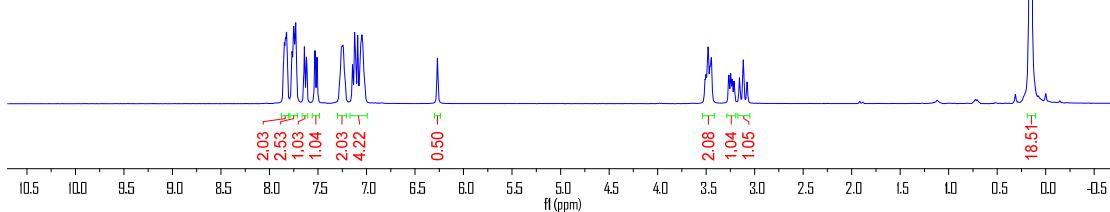
L19



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	300.6
4 Spectrometer Frequency	400.13
5 Nucleus	1H

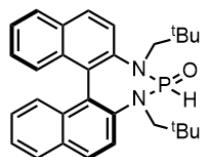


L20

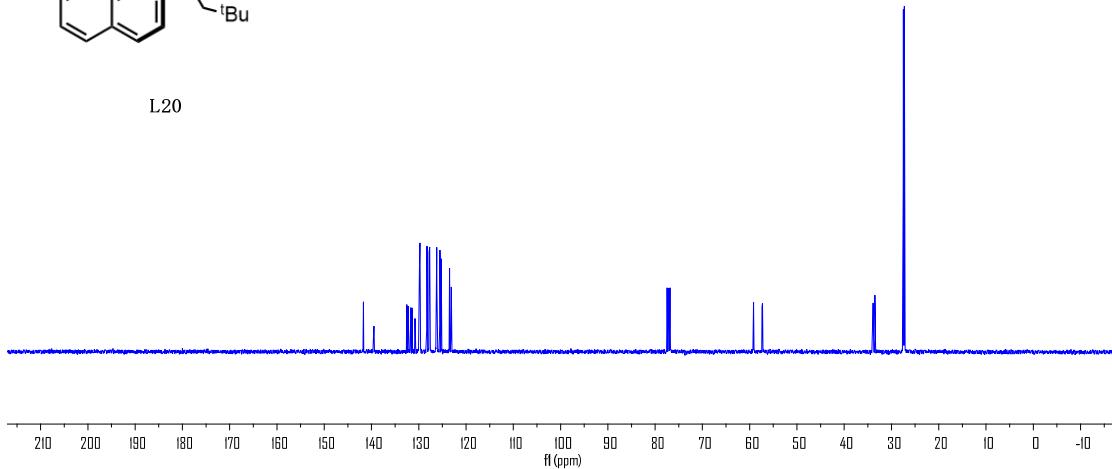


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	300.9
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C

141.72
 ↘ 139.51
 ↘ 139.48
 ↘ 129.76
 ↗ 127.81
 ↗ 127.67
 ↗ 126.29
 ↗ 126.19
 ↗ 125.52
 ↗ 125.25
 ↗ 123.49
 ↗ 123.13

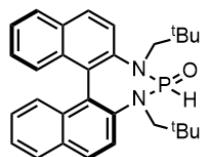


L20

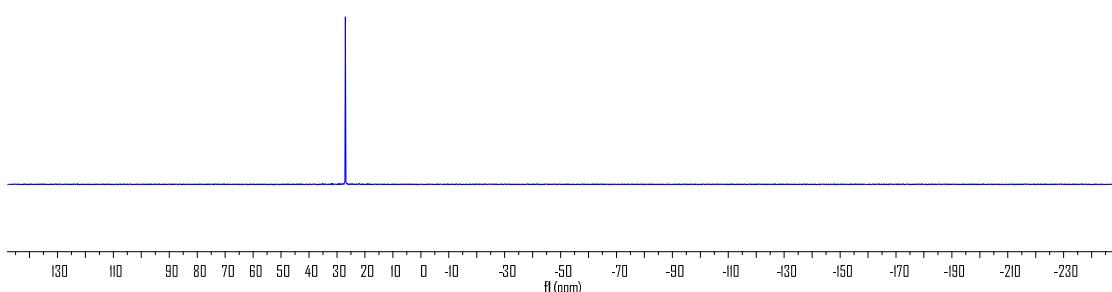


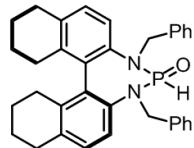
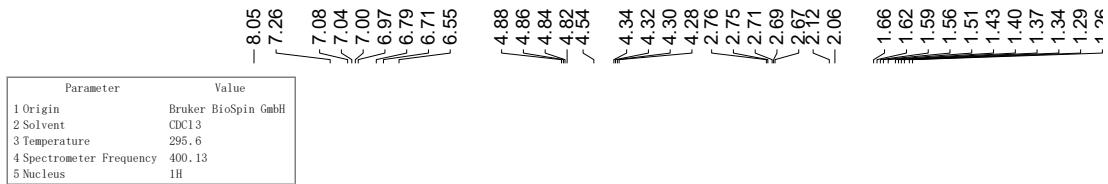
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	300.3
4 Spectrometer Frequency	161.98
5 Nucleus	³¹ P

- 26.98

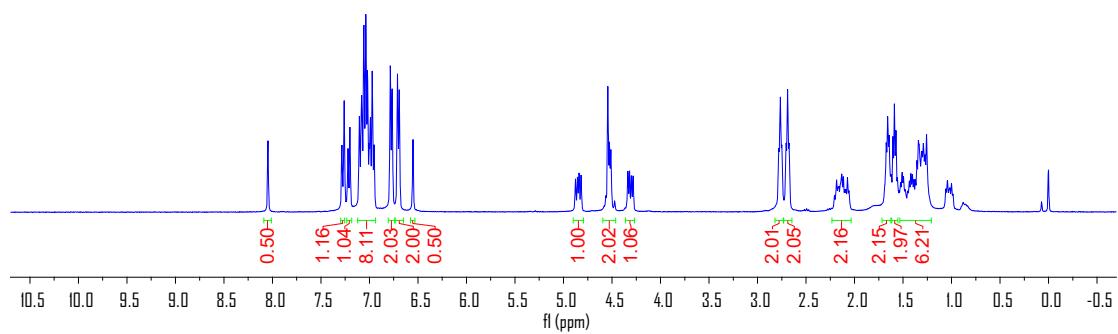


L20

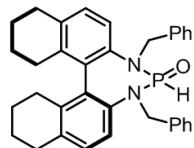




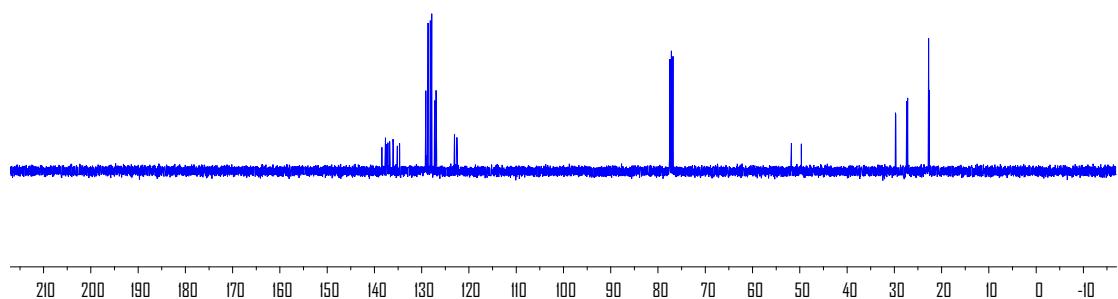
L21



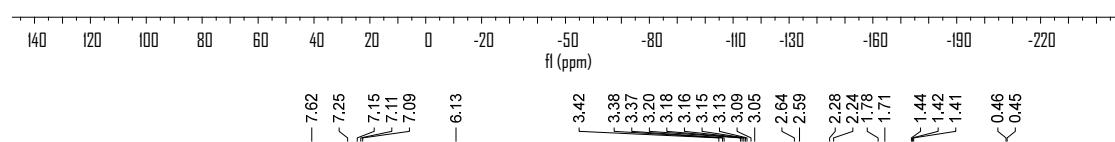
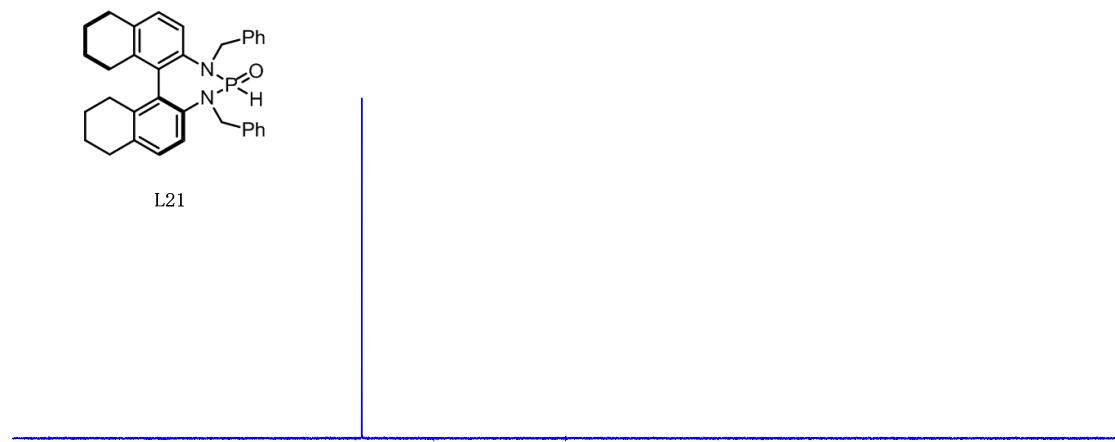
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	298.3
4 Spectrometer Frequency	100.62
5 Nucleus	13C



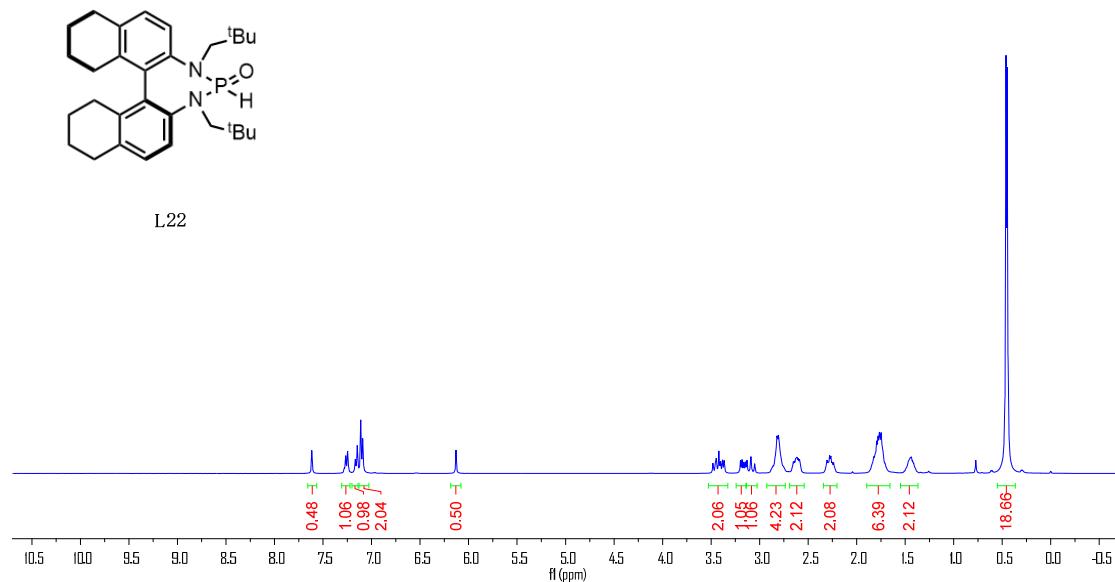
L21

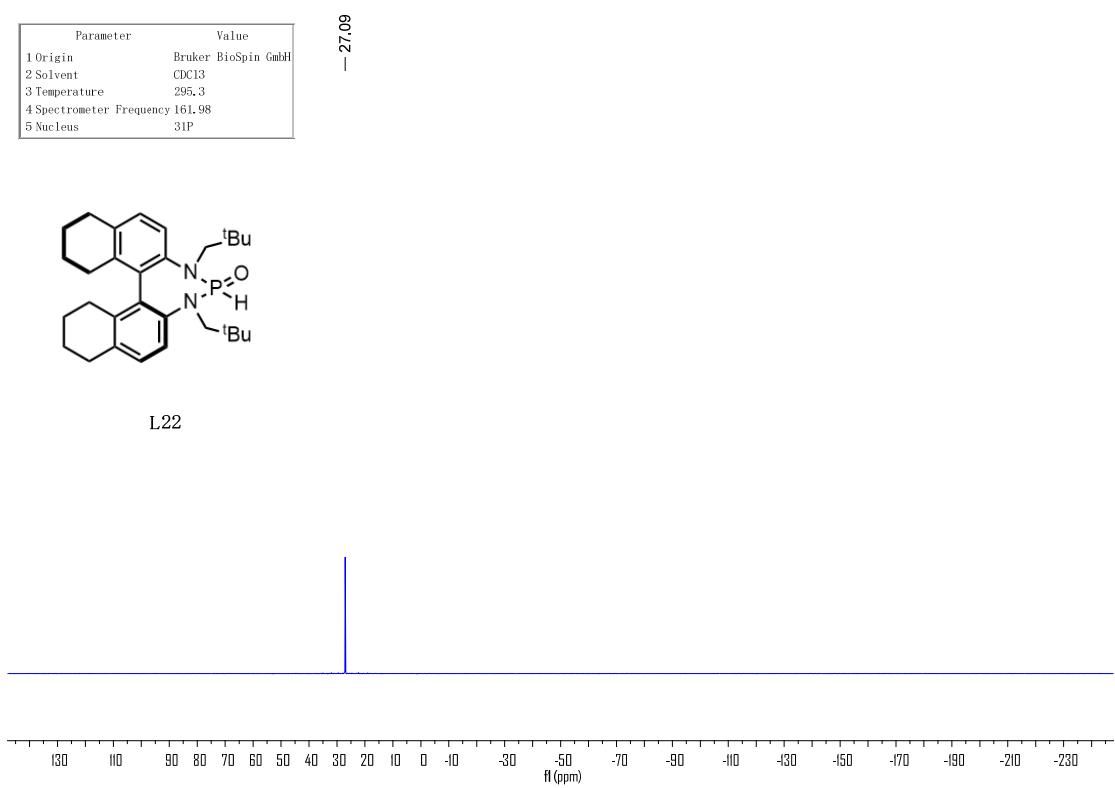
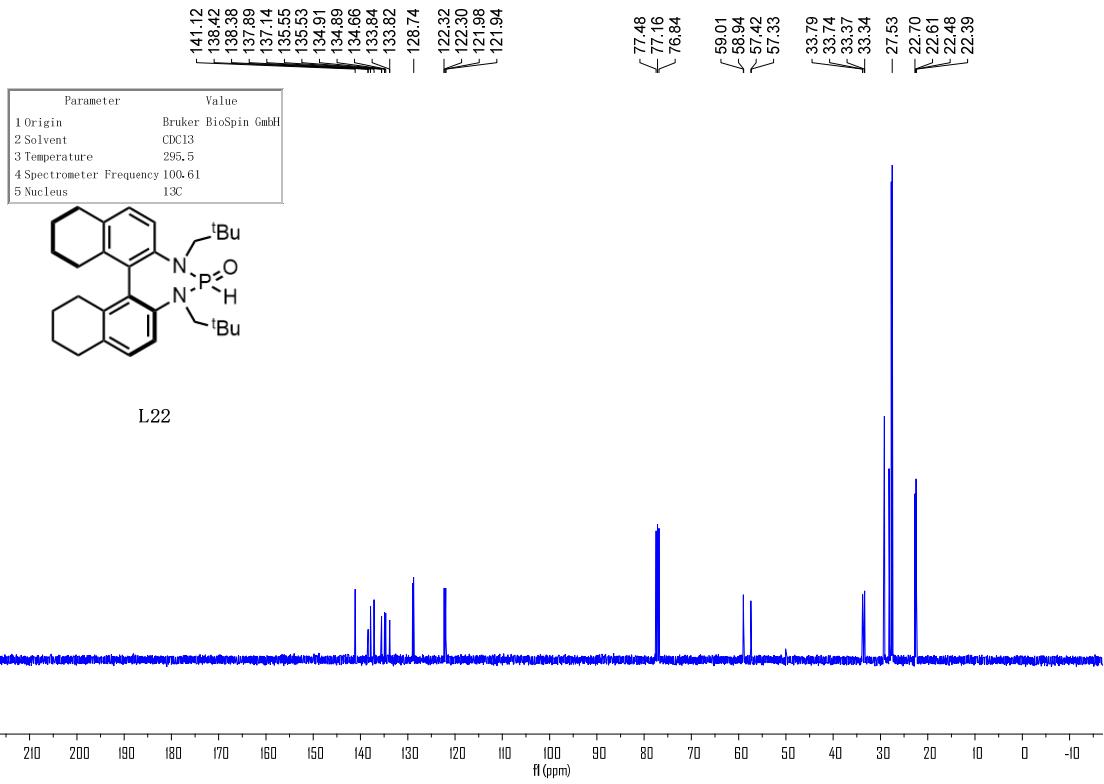


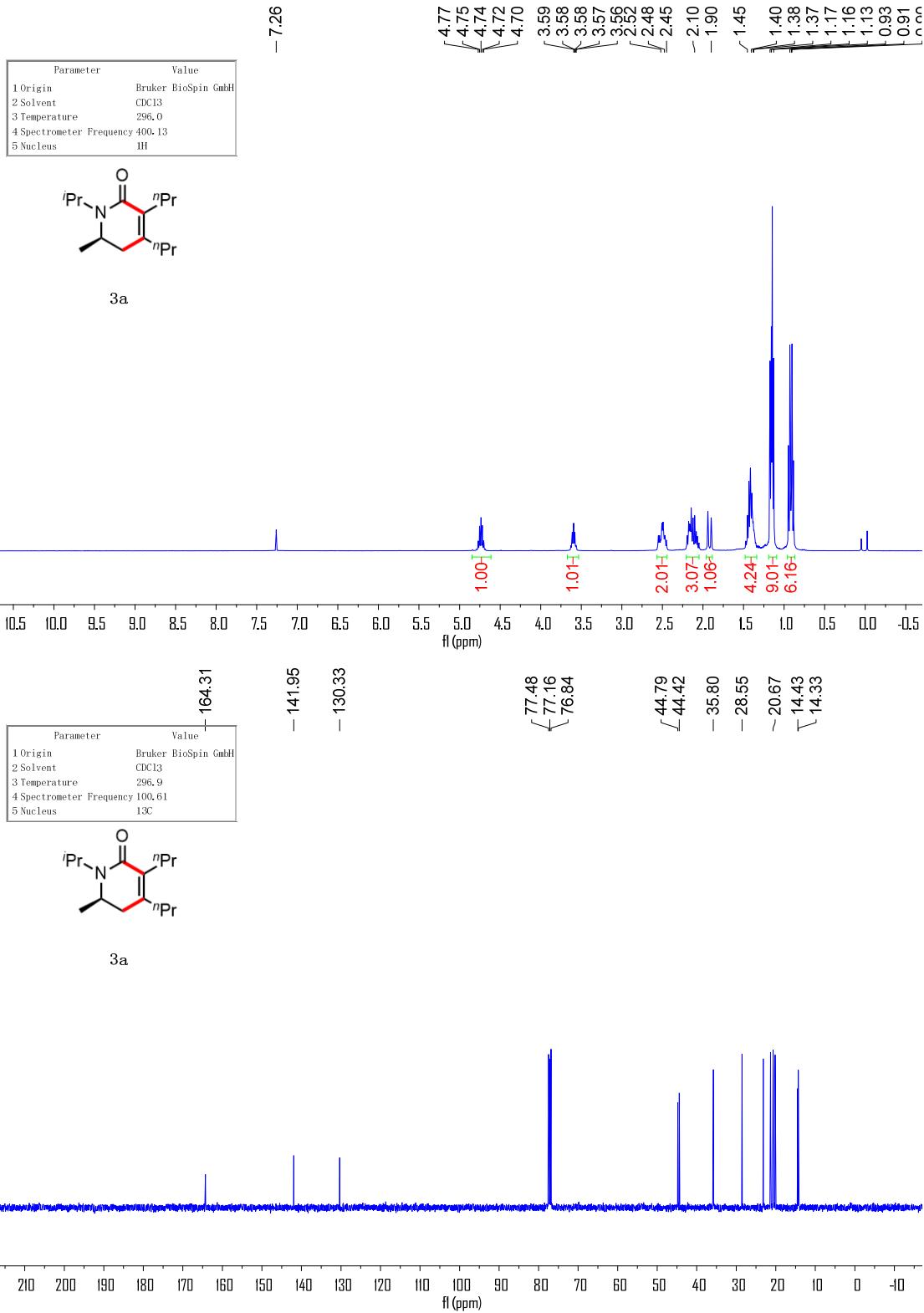
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	298.1
4 Spectrometer Frequency	161.98
5 Nucleus	³¹ P



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.5
4 Spectrometer Frequency	400.13
5 Nucleus	¹ H

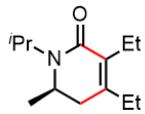
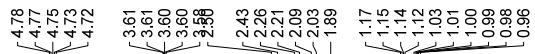




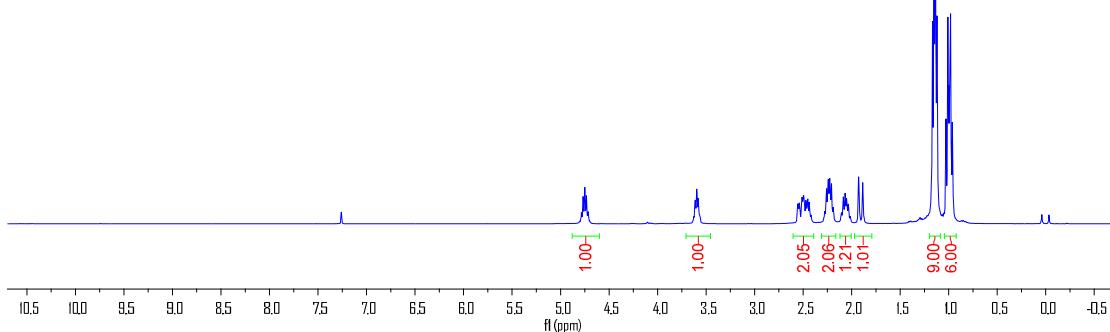


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	293.0
4 Spectrometer Frequency	400.13
5 Nucleus	1H

- 7.26



3b

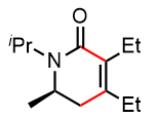


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	293.3
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C

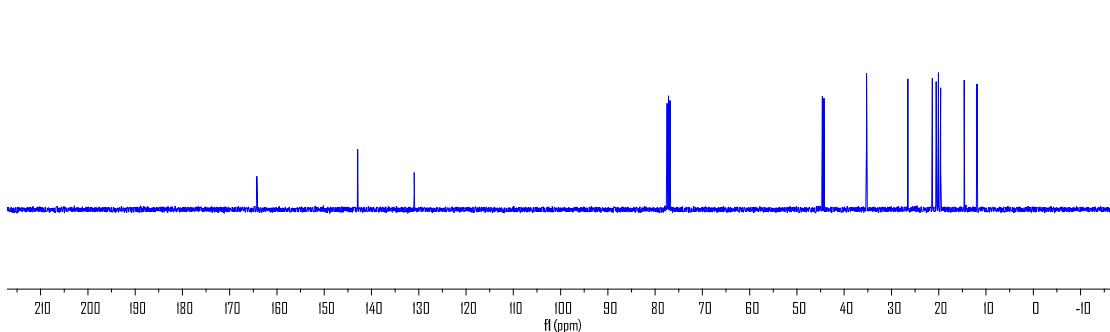
- 164.25

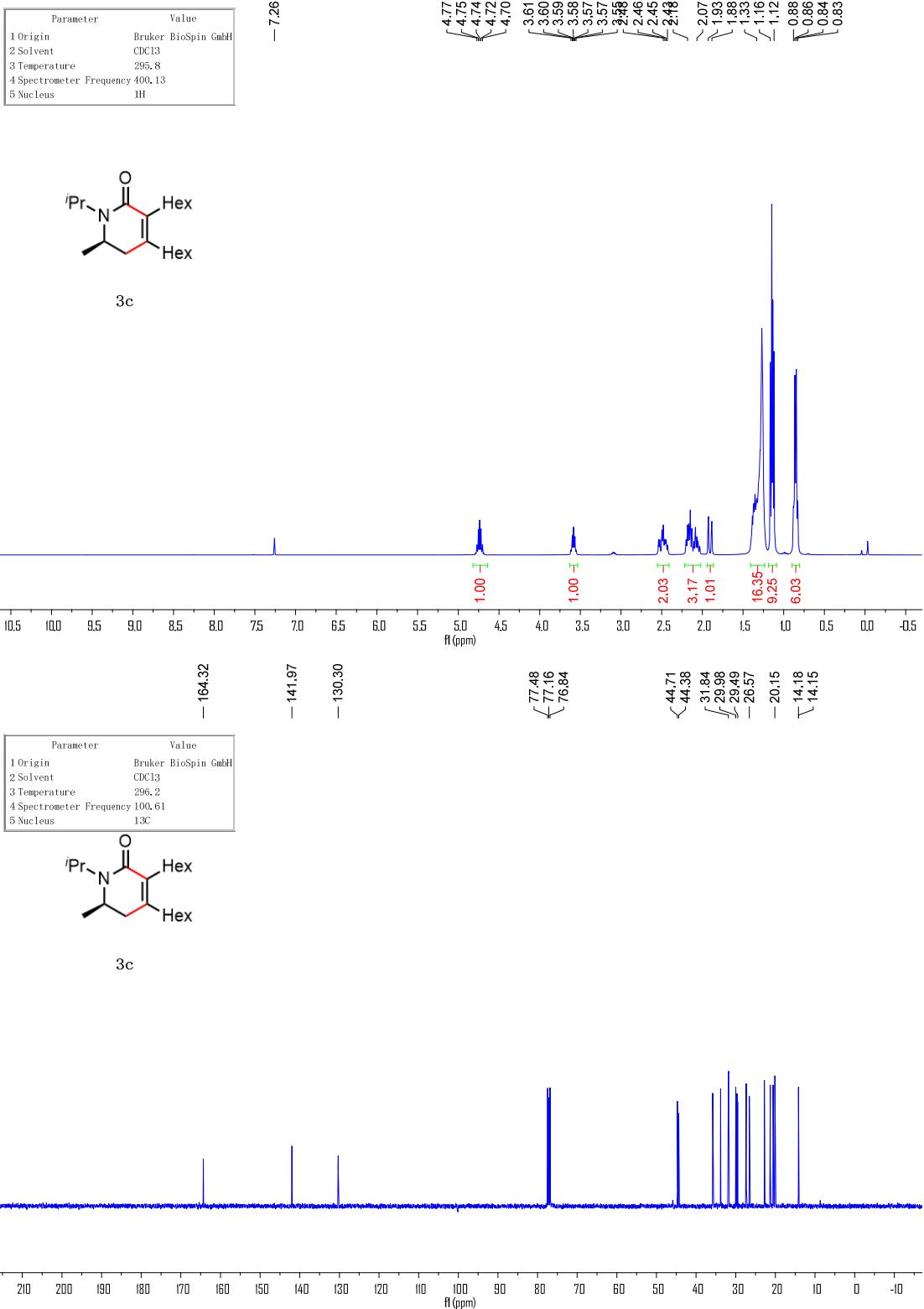
- 142.91

- 130.95



3b





Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-191.5
4 Spectrometer Frequency	400, 13
5 Nucleus	IH

— 7.26

4.79
4.78
4.76
4.74
4.72

3.62
3.60
3.59
3.57
3.56

2.49
2.43
2.22
2.18

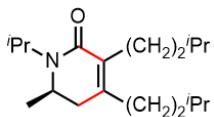
2.14
2.03
1.88

— 1.52

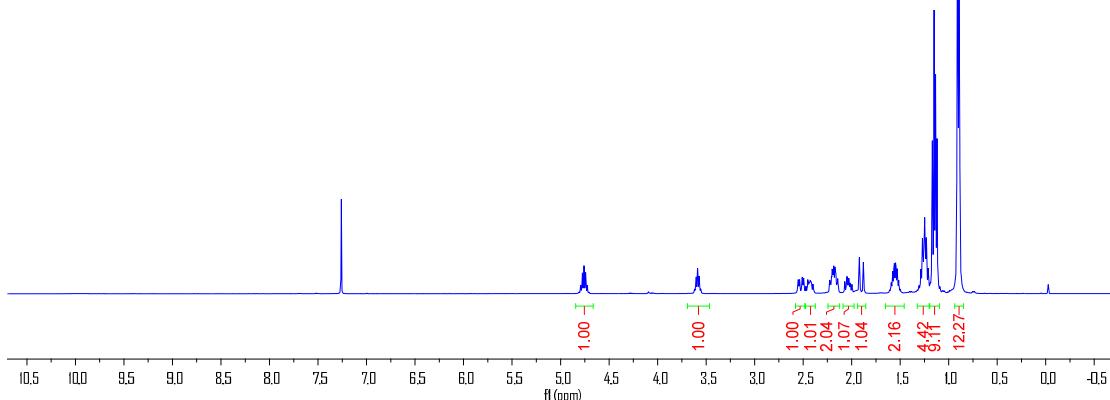
~ 1.15

~ 0.91

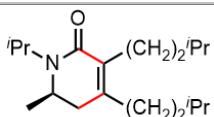
~ 0.90



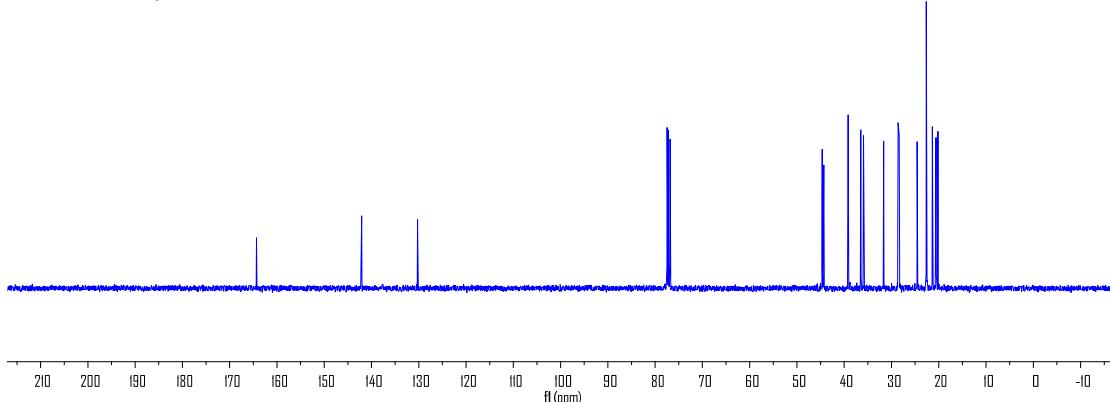
3d



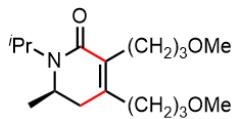
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-191.5
4 Spectrometer Frequency	100, 61
5 Nucleus	¹³ C



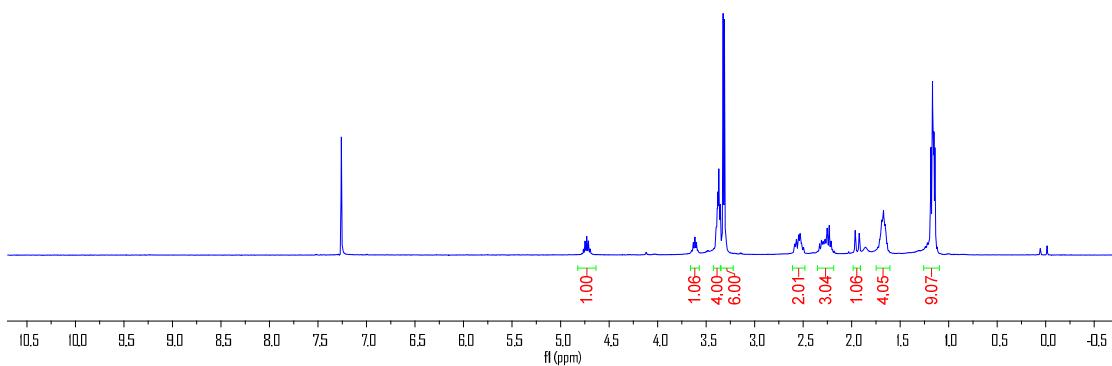
3d



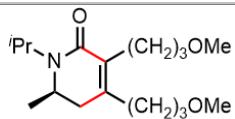
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	297.7
4 Spectrometer Frequency	400.13
5 Nucleus	IH



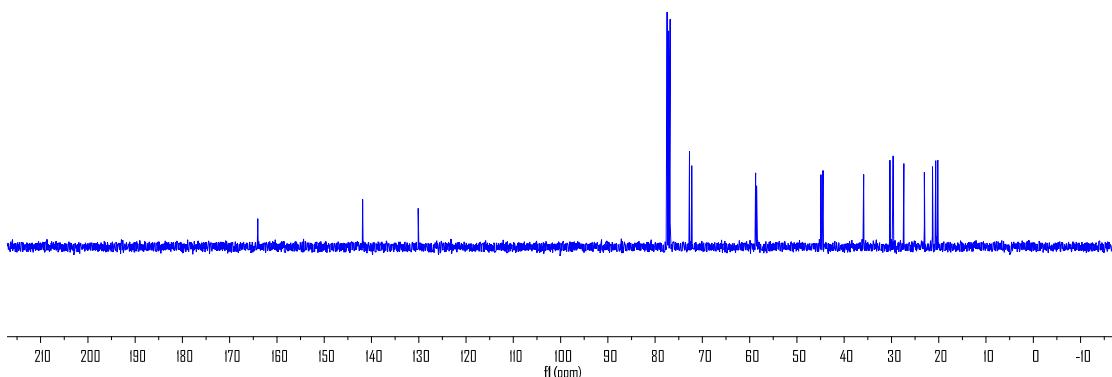
3e



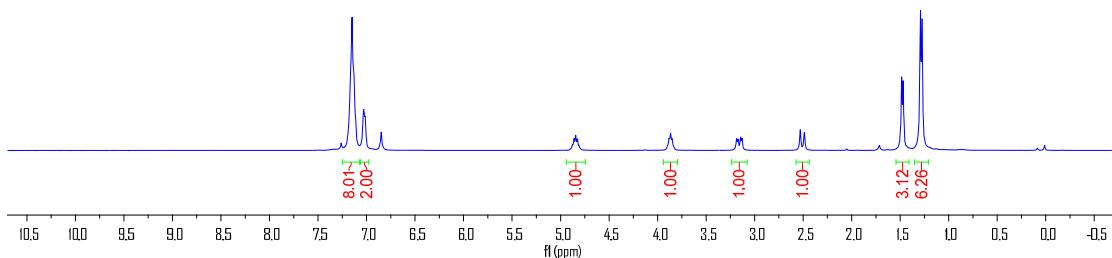
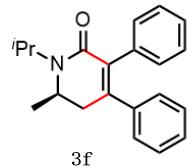
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	297.7
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C



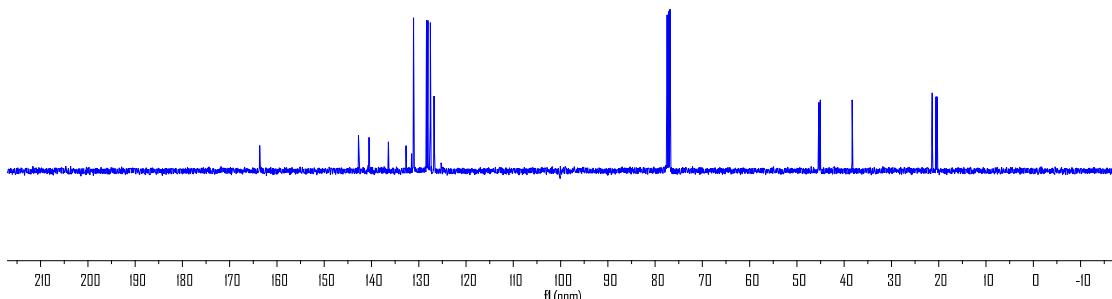
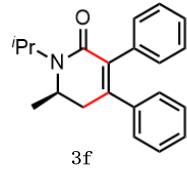
3e



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-197.4
4 Spectrometer Frequency	400.13
5 Nucleus	1H



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-196.1
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C

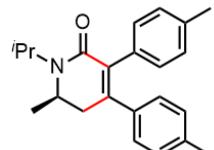


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	294.5
4 Spectrometer Frequency	400.15
5 Nucleus	1H

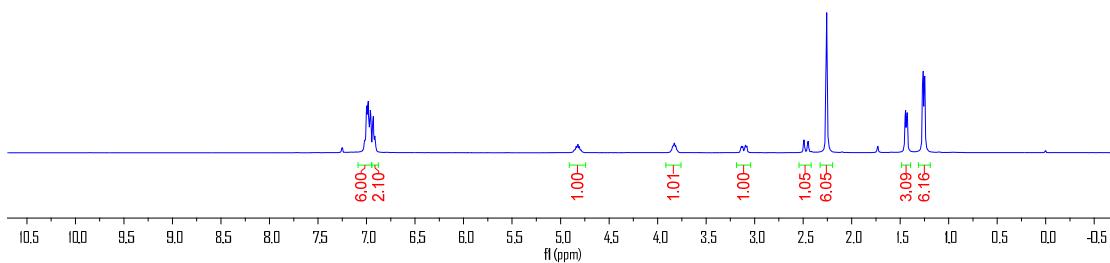
— 7.26
6.98
6.96
6.93
6.93
6.91

4.85
4.84
4.83
4.82
4.81
4.80
4.79

3.84
3.83
3.81
3.14
3.12
3.09
3.08
2.49
2.45
— 2.26



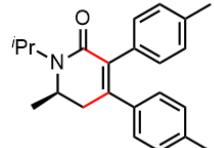
3g



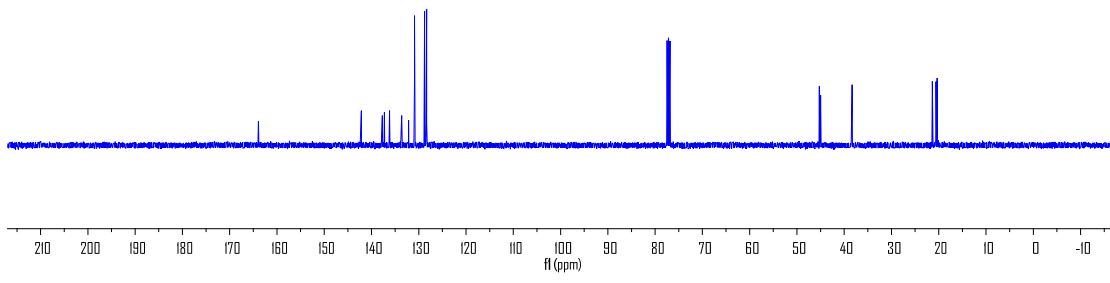
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.0
4 Spectrometer Frequency	100.62
5 Nucleus	13C

— 142.15
— 137.72
— 137.25
— 136.19
— 133.60
— 132.14
— 130.89
— 128.76
— 128.36
— 128.33

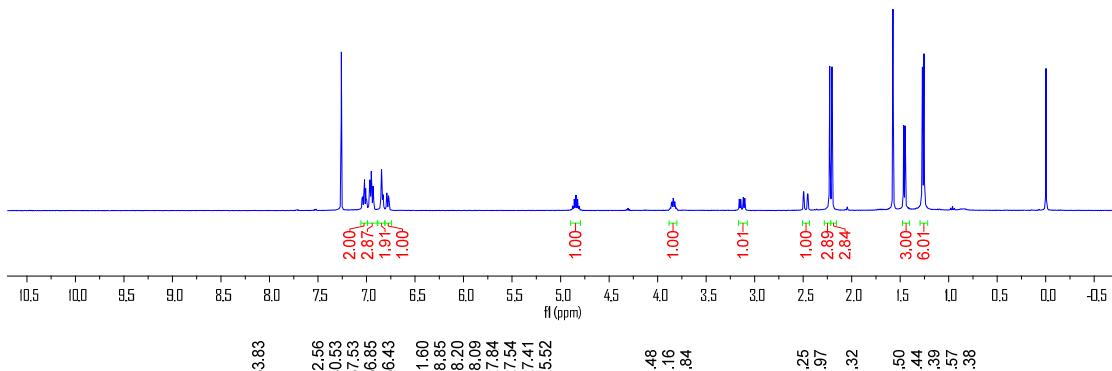
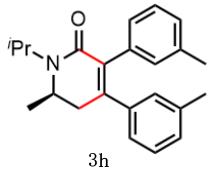
— 77.48
— 77.16
— 76.84
— 45.27
— 44.99
— 38.33



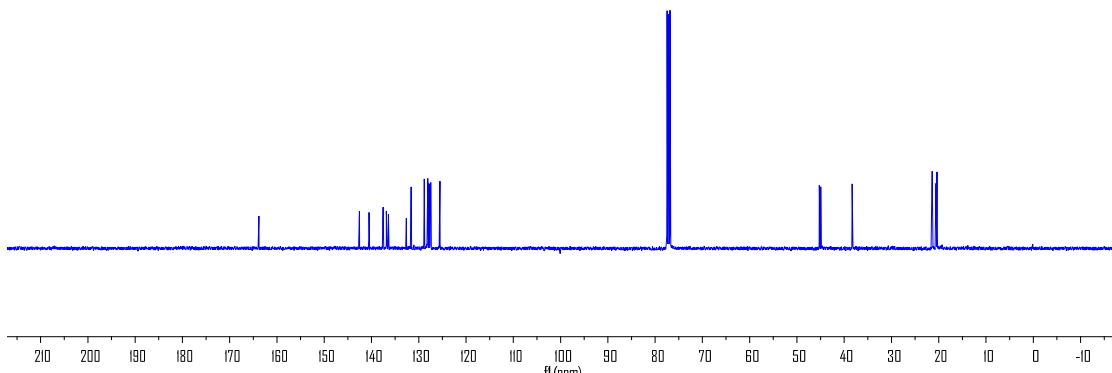
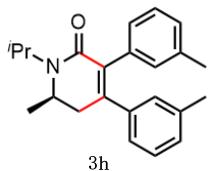
3g

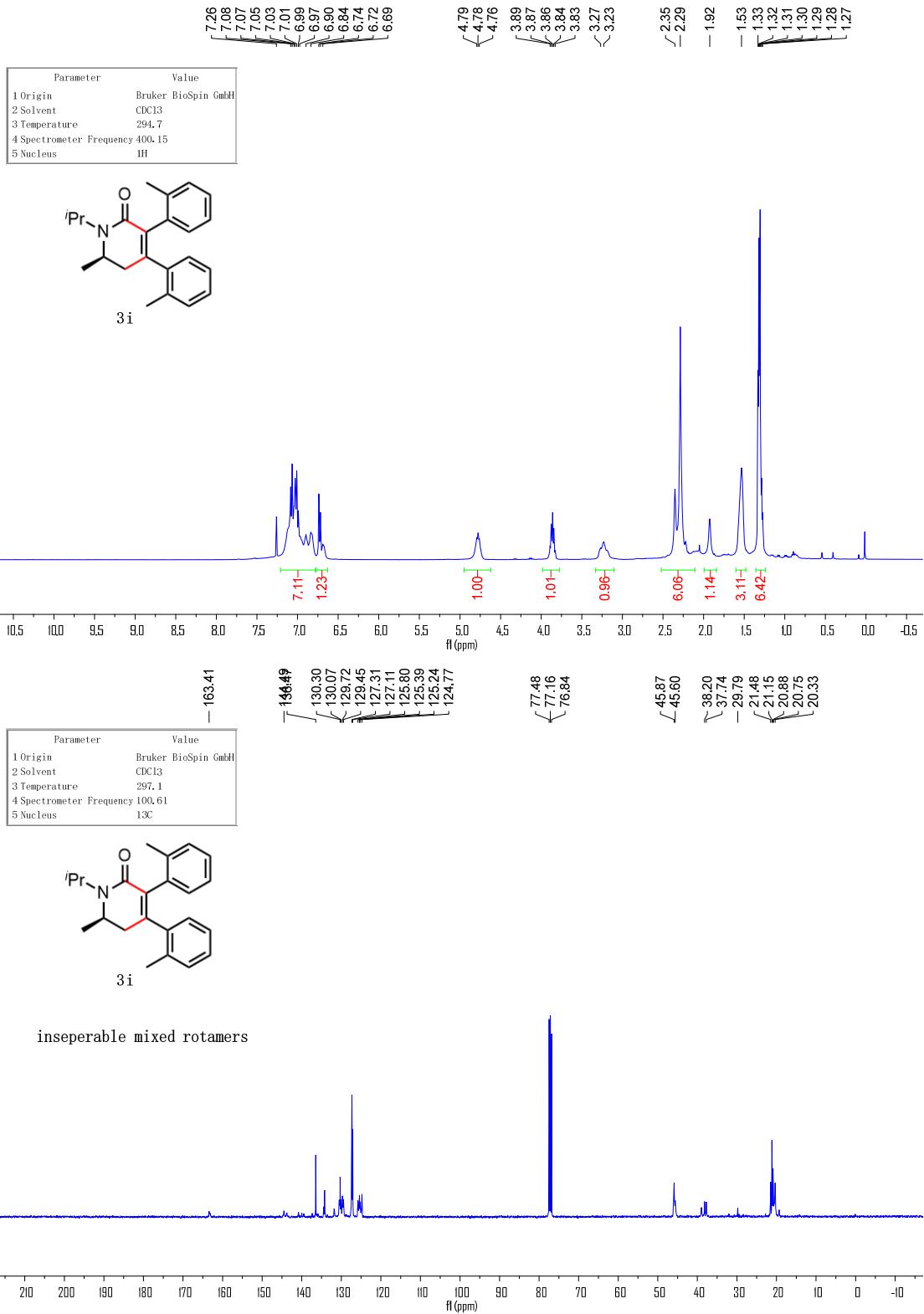


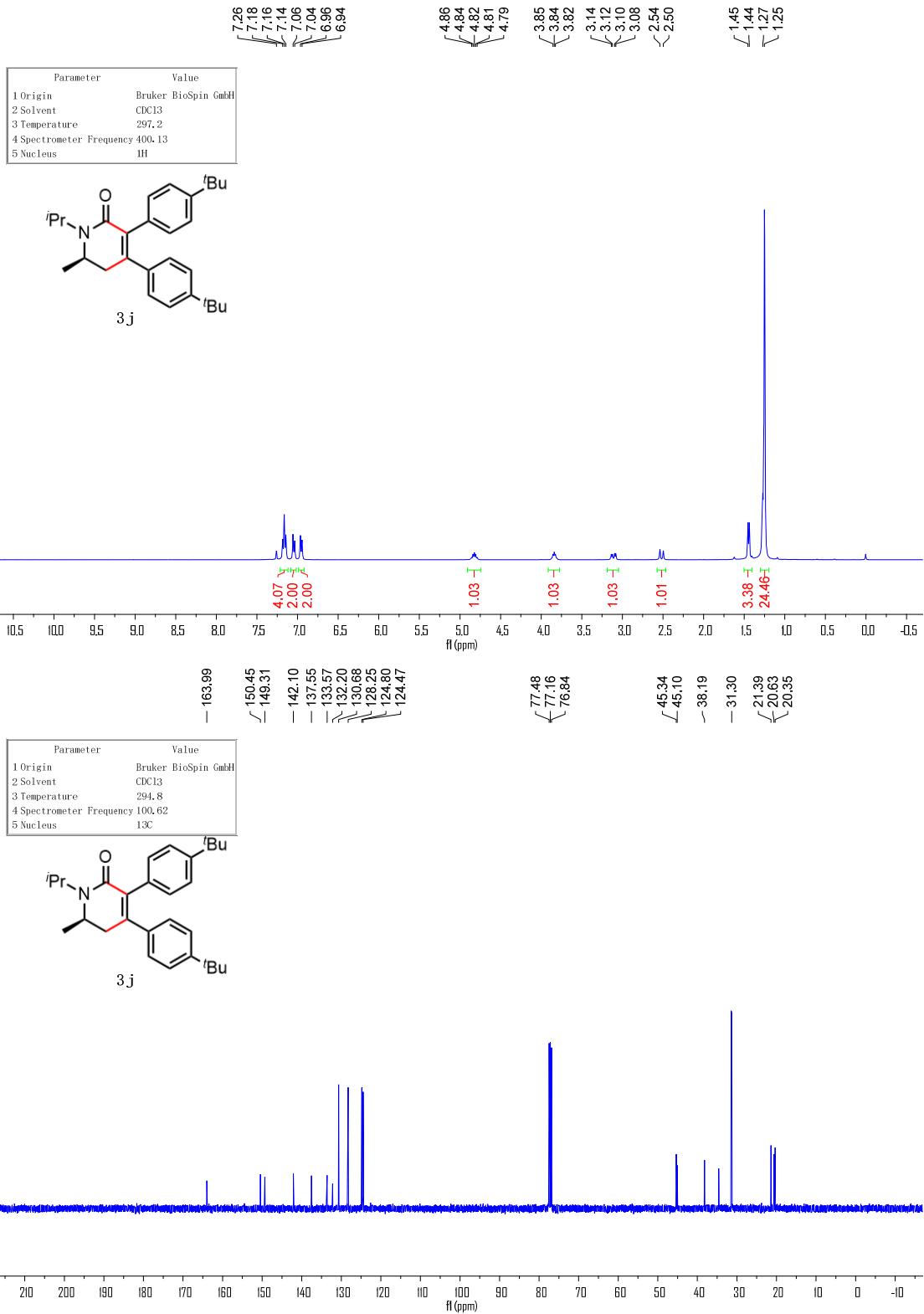
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDC13
3 Temperature	294.6
4 Spectrometer Frequency	400.13
5 Nucleus	1H

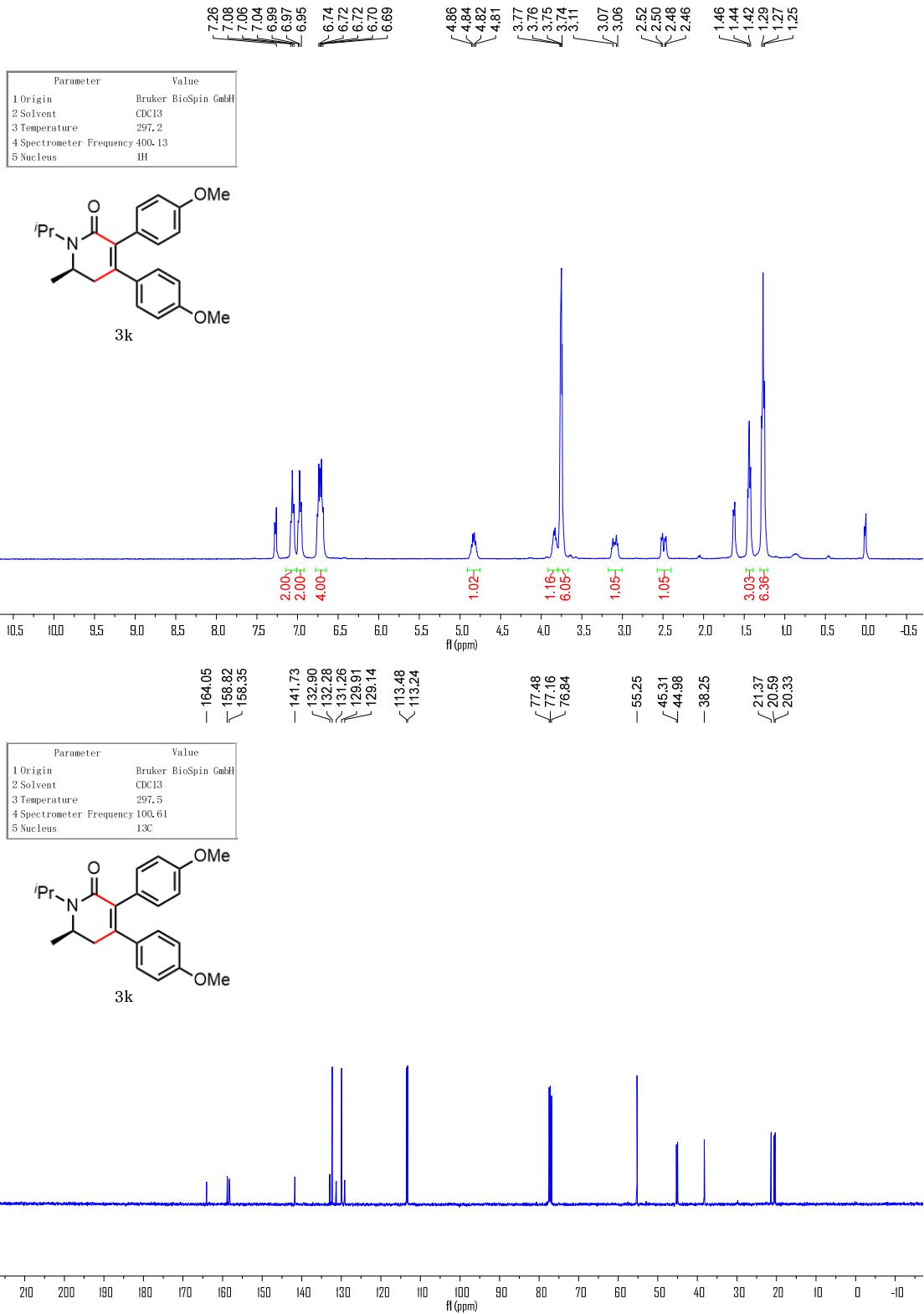


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.0
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C

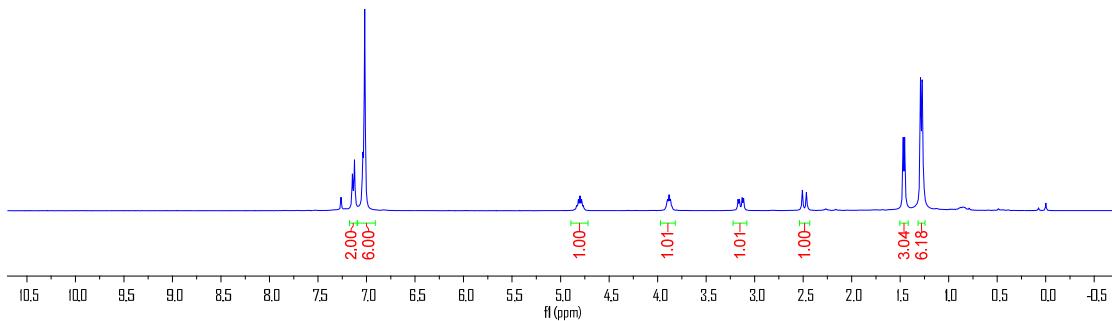
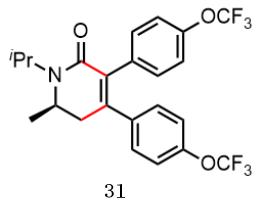




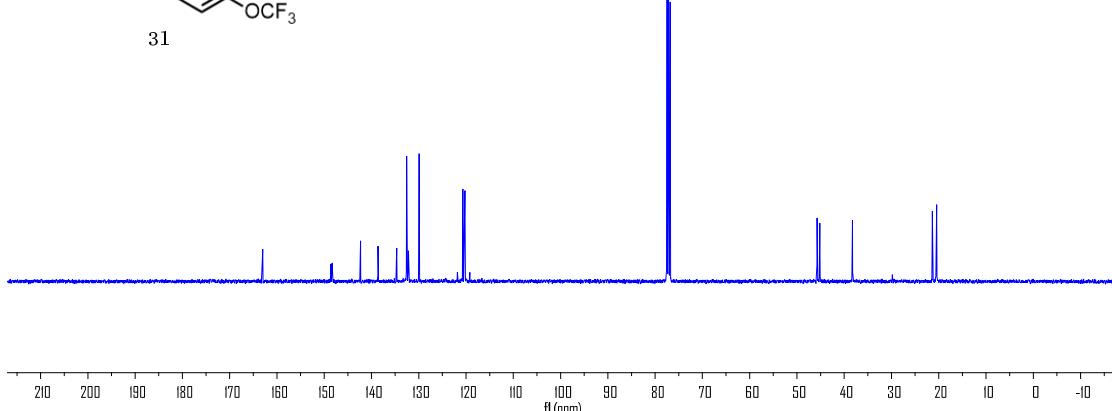
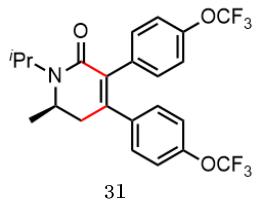




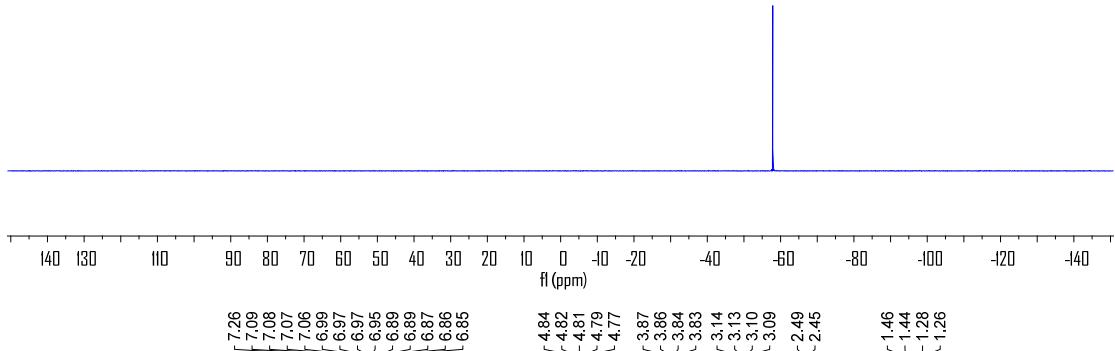
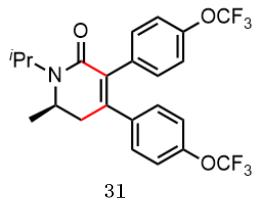
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.6
4 Spectrometer Frequency	400.13
5 Nucleus	1H



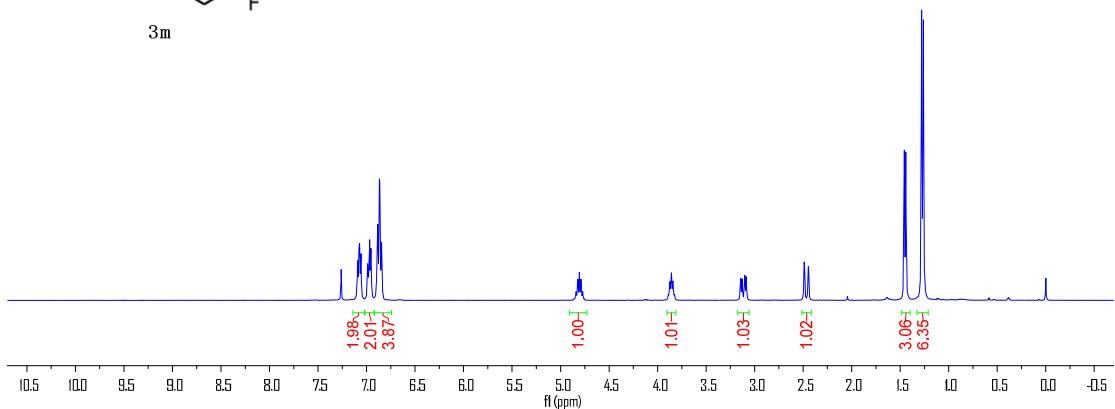
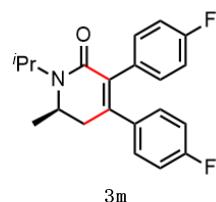
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.9
4 Spectrometer Frequency	100.61
5 Nucleus	13C

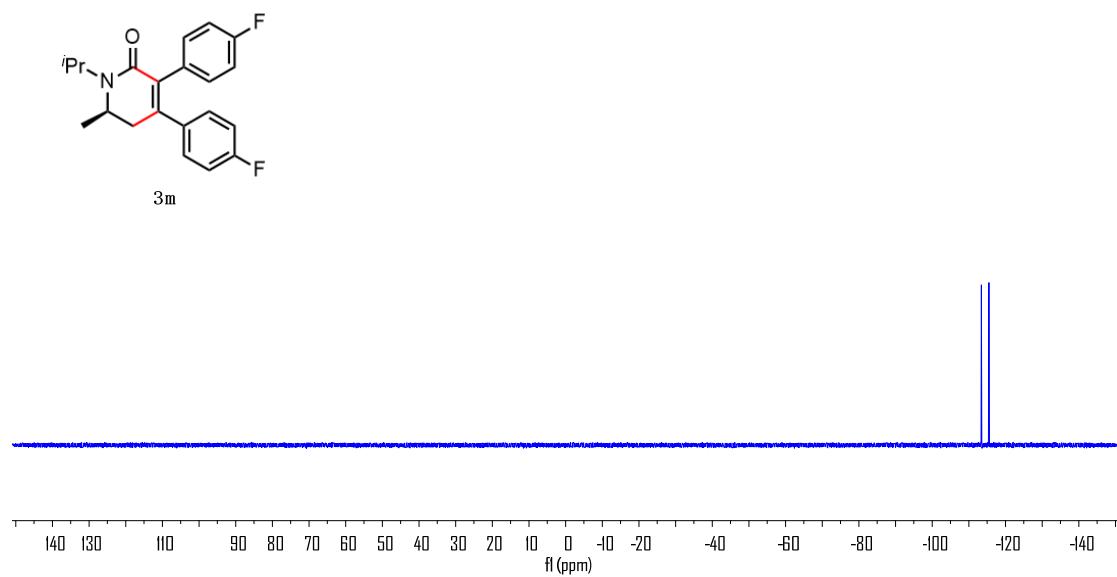
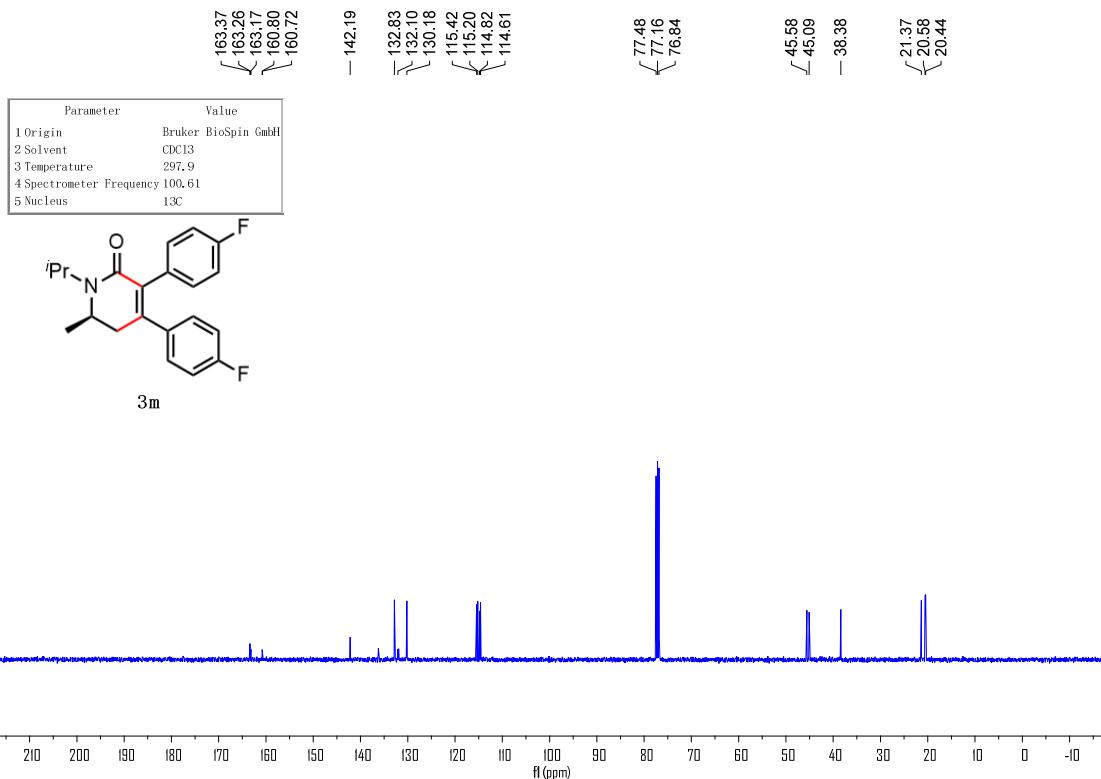


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-547.7
4 Spectrometer Frequency	376.59
5 Nucleus	¹⁹ F

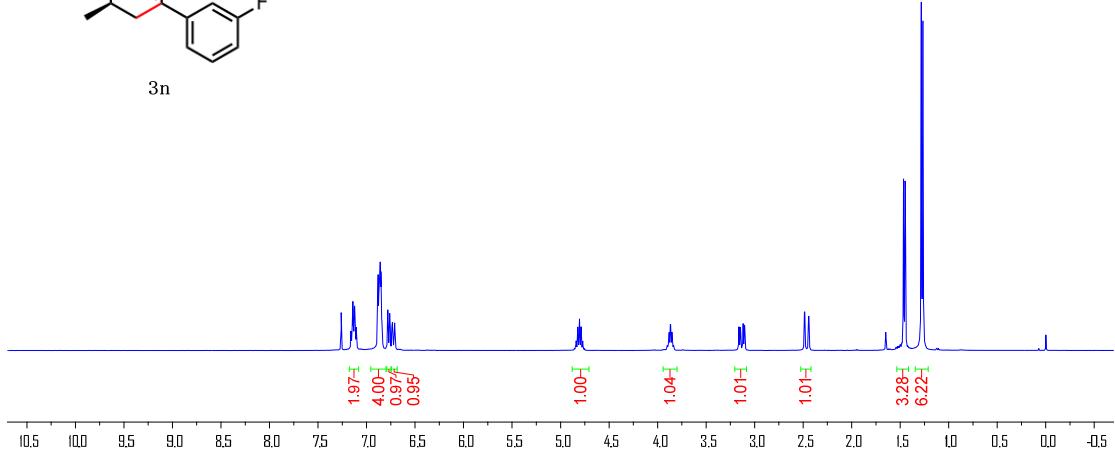


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	297.9
4 Spectrometer Frequency	400.13
5 Nucleus	¹ H

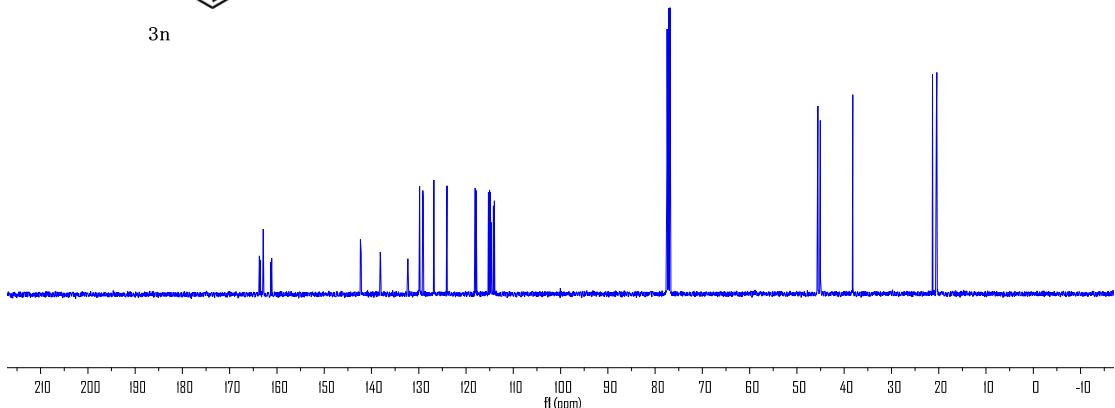
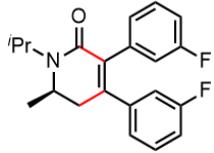




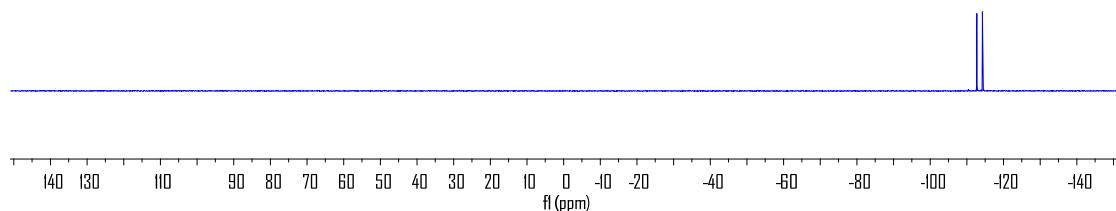
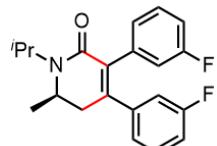
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.6
4 Spectrometer Frequency	400.13
5 Nucleus	^1H



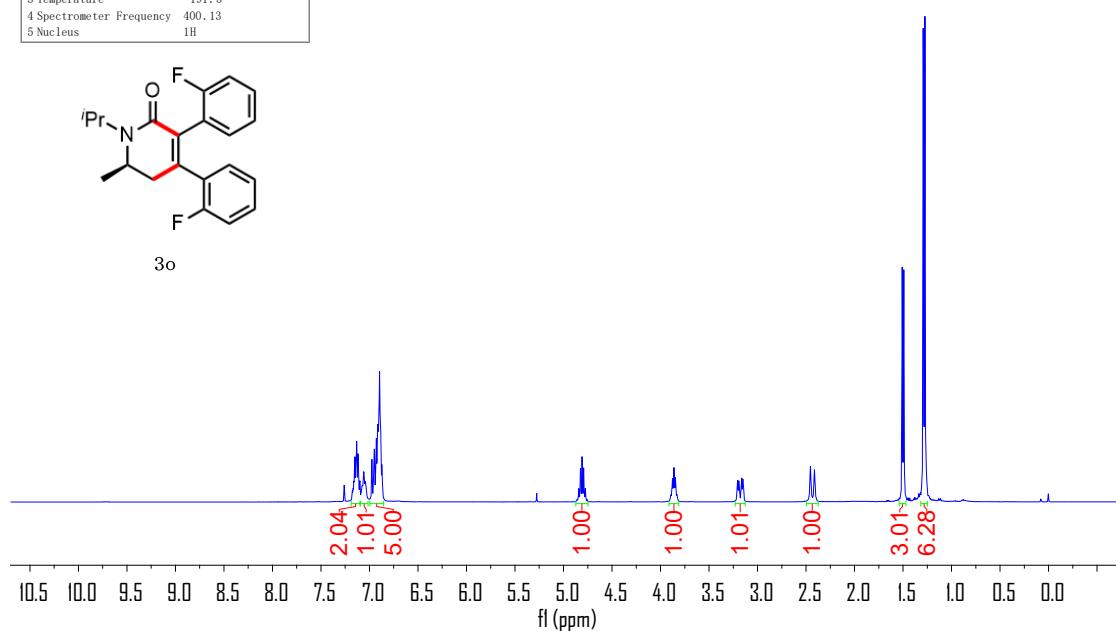
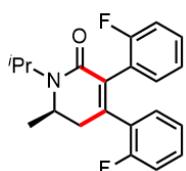
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	315.7
4 Spectrometer Frequency	100.61
5 Nucleus	^{13}C

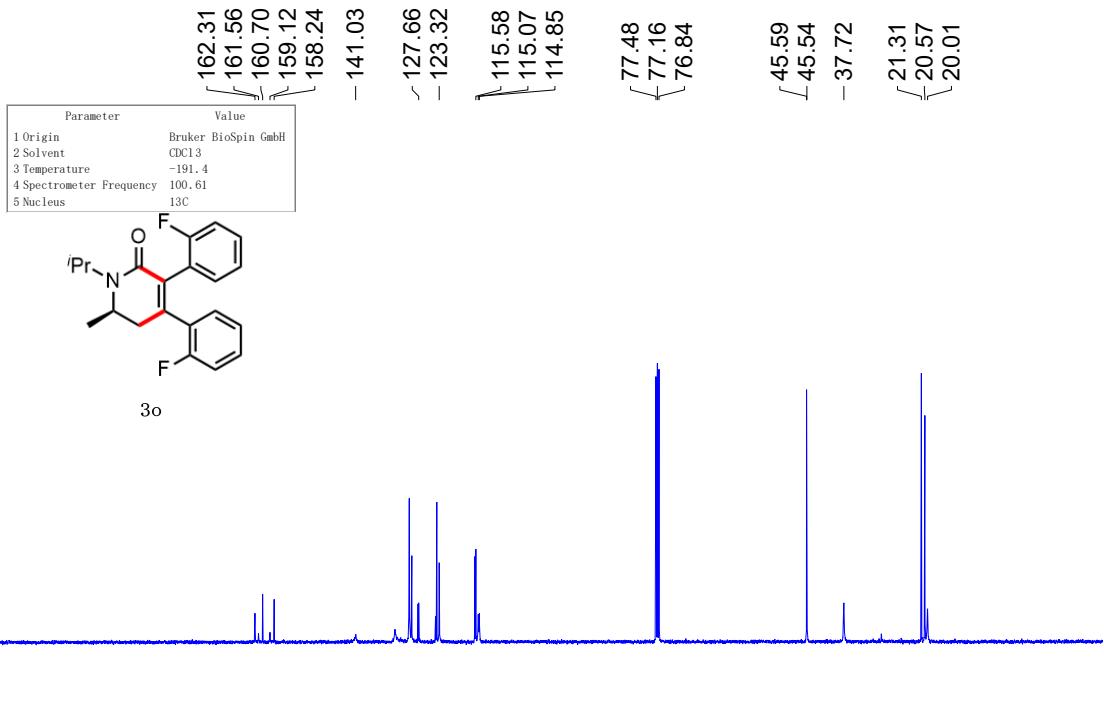


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-547.3
4 Spectrometer Frequency	376.59
5 Nucleus	¹⁹ F



Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-191.5
4 Spectrometer Frequency	400.13
5 Nucleus	¹ H





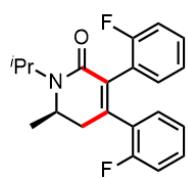
210 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 -10

fl (ppm)

-113.63
-114.10

Parameter Value

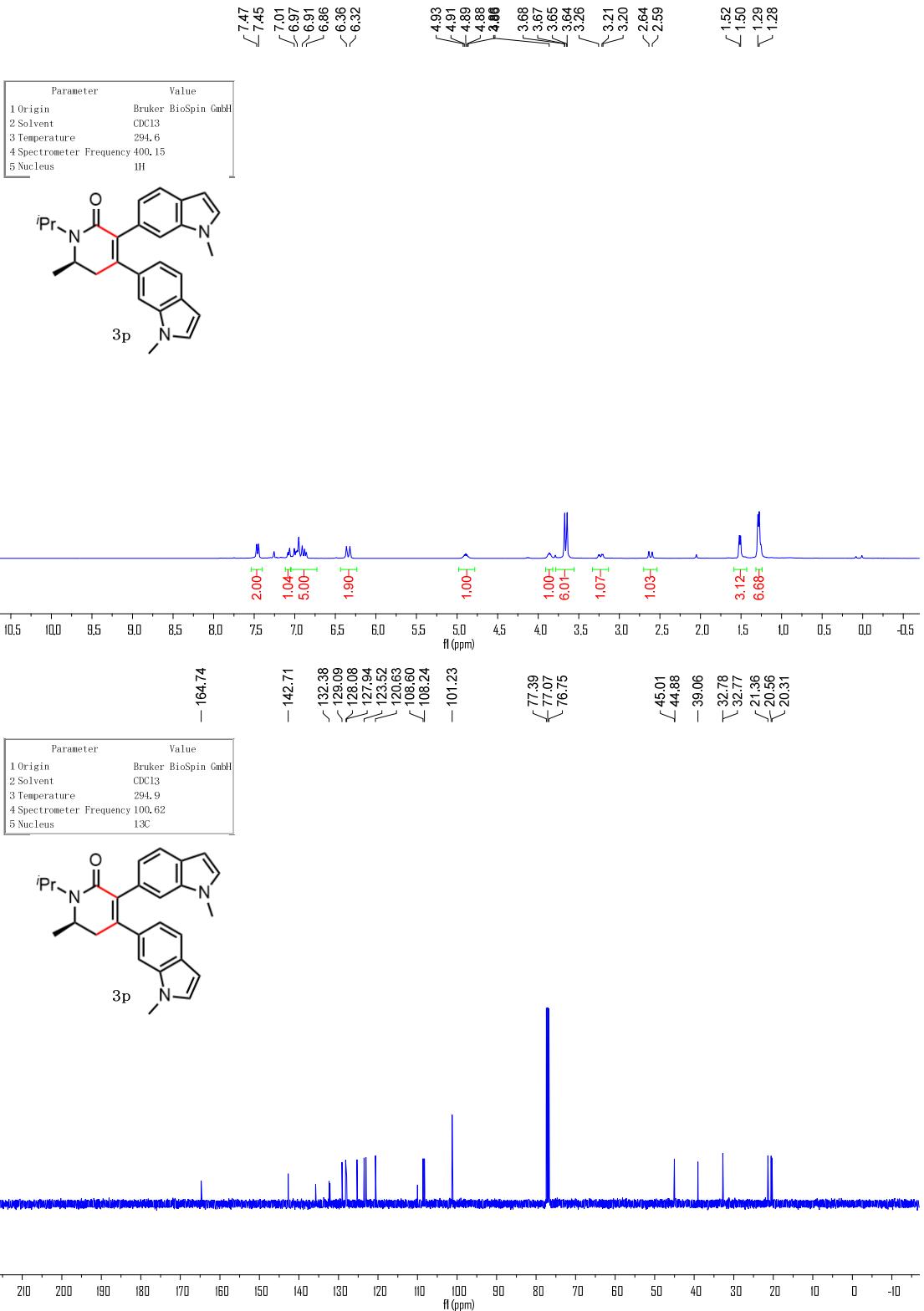
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-541.4
4 Spectrometer Frequency	376.59
5 Nucleus	¹⁹ F

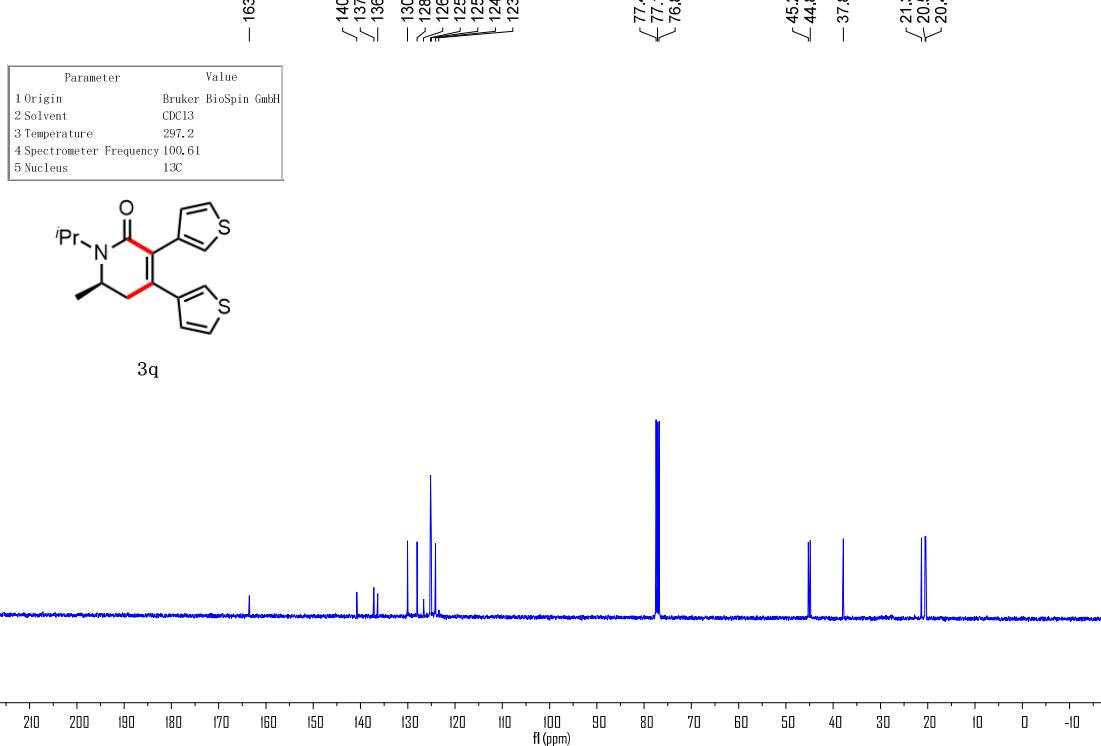
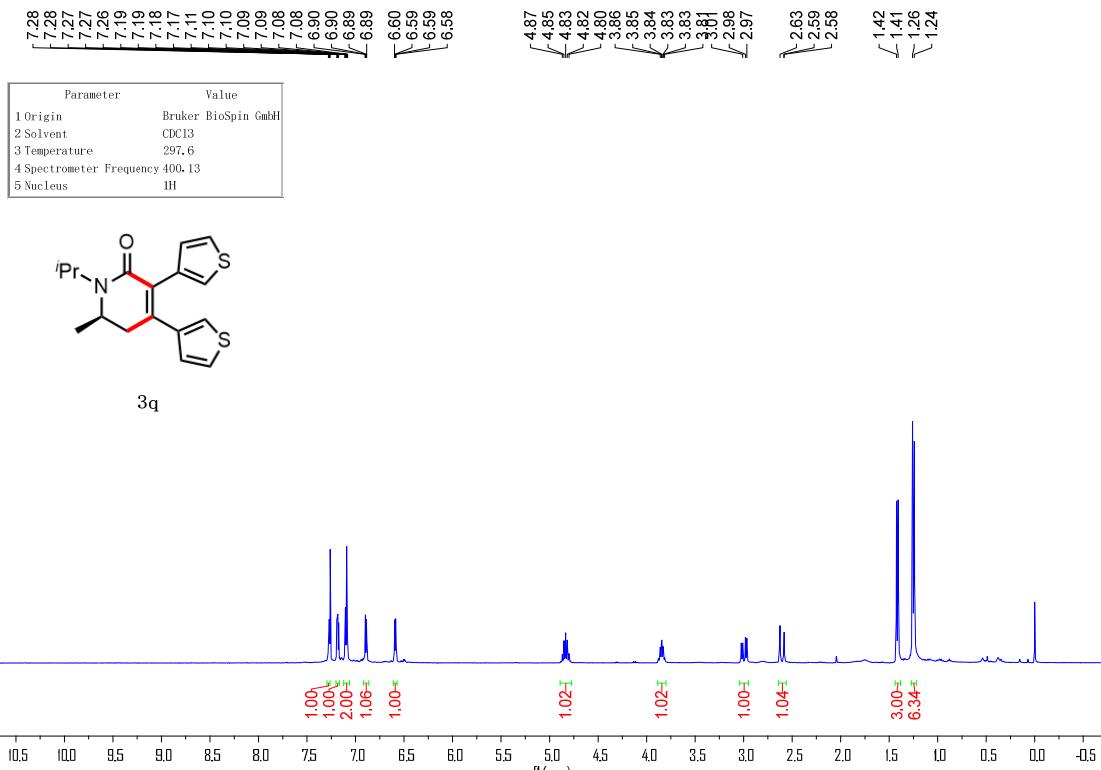


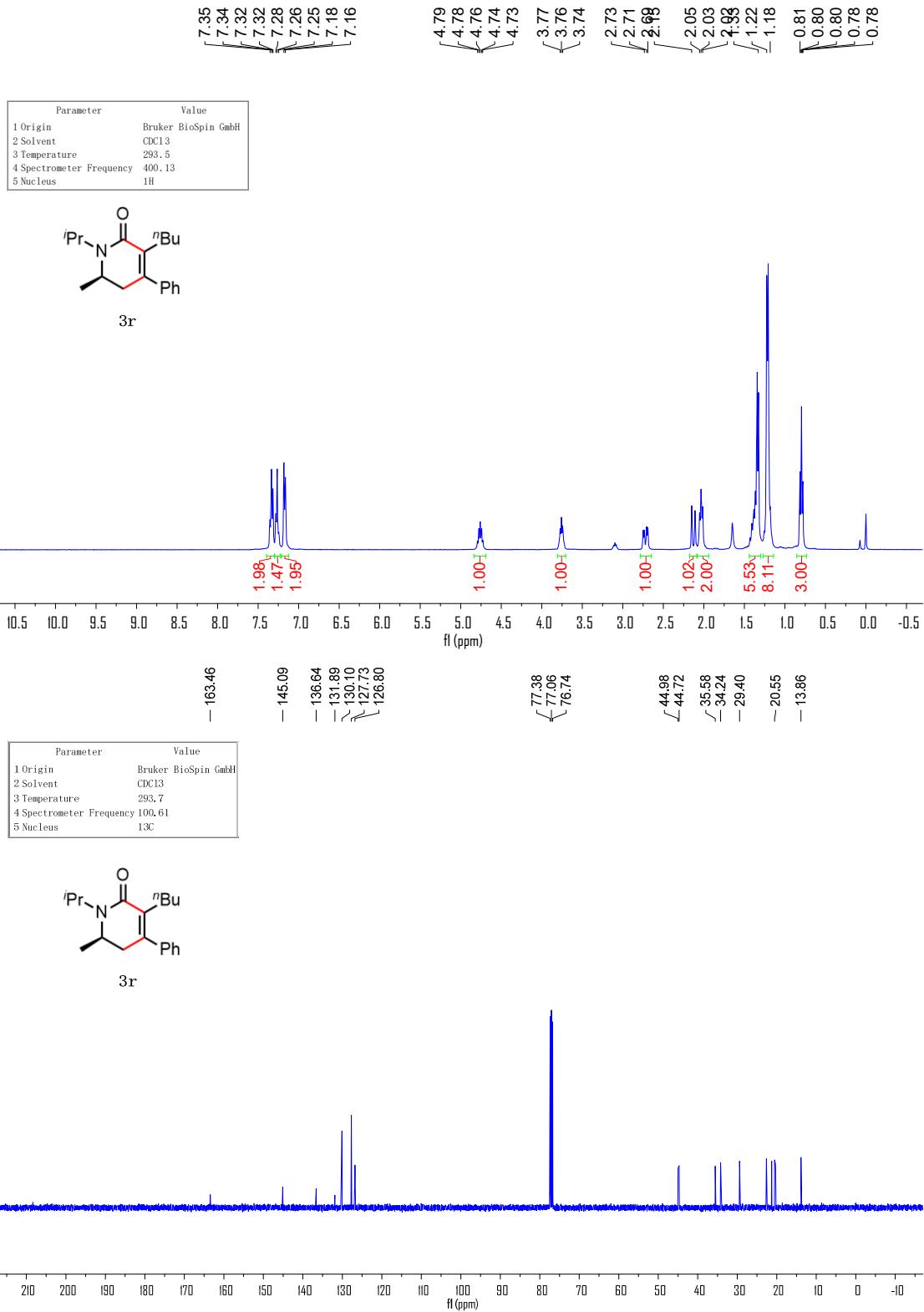
3o

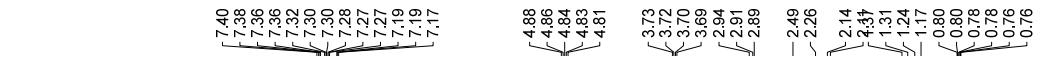
50 130 110 90 70 50 30 10 -20 -40 -60 -80 -100 -120 -140

fl (ppm)

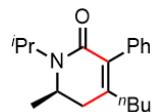




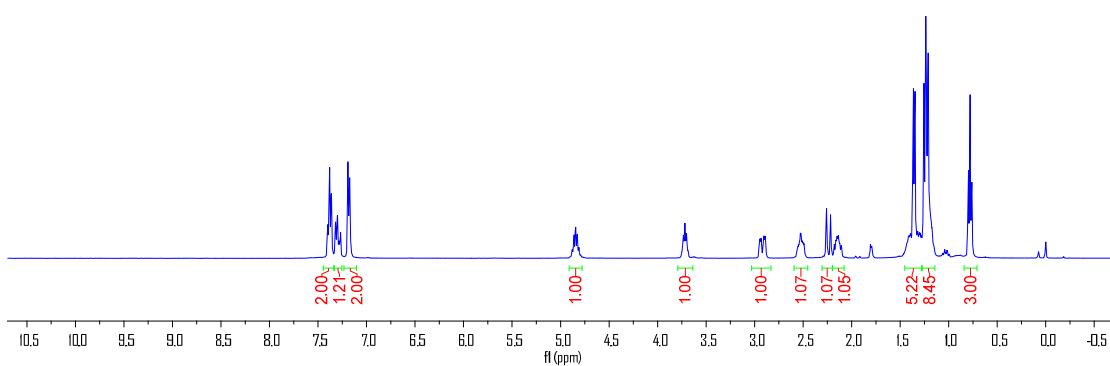




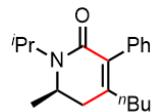
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	292.8
4 Spectrometer Frequency	400.13
5 Nucleus	1H



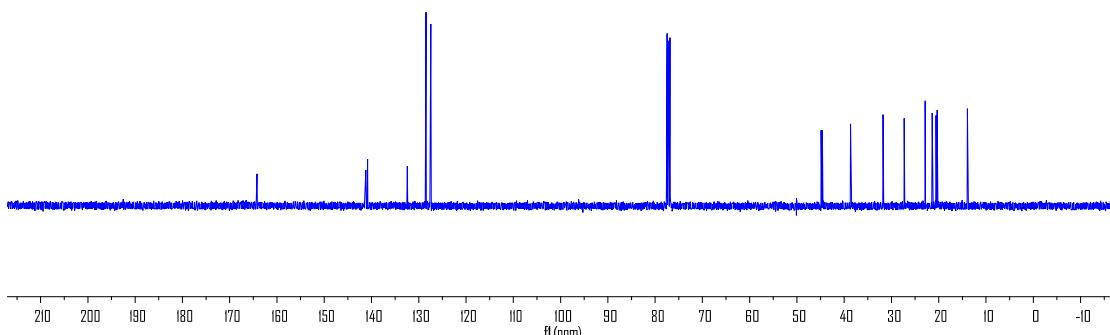
3r'

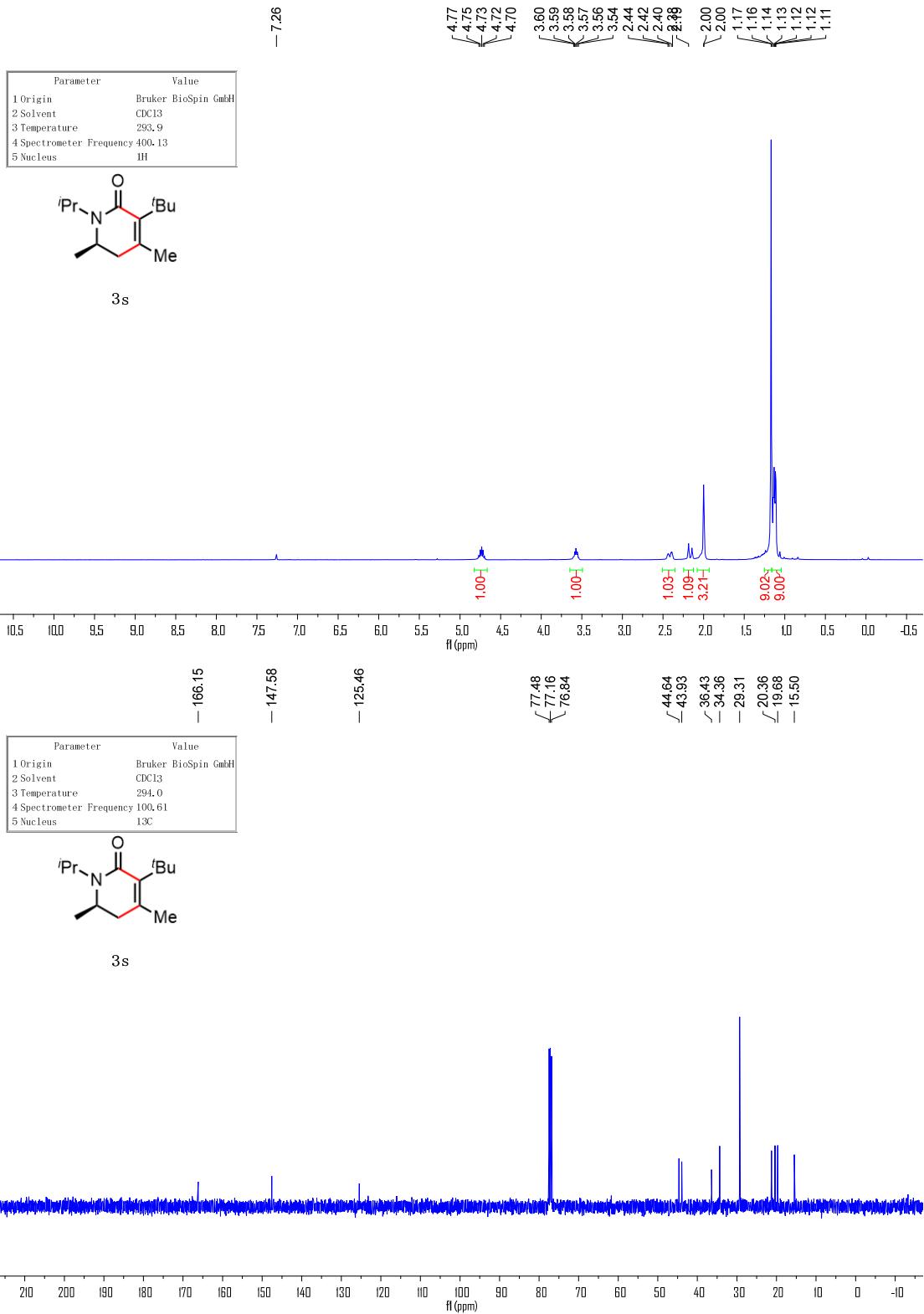


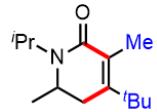
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	293.9
4 Spectrometer Frequency	100.61
5 Nucleus	13C



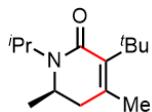
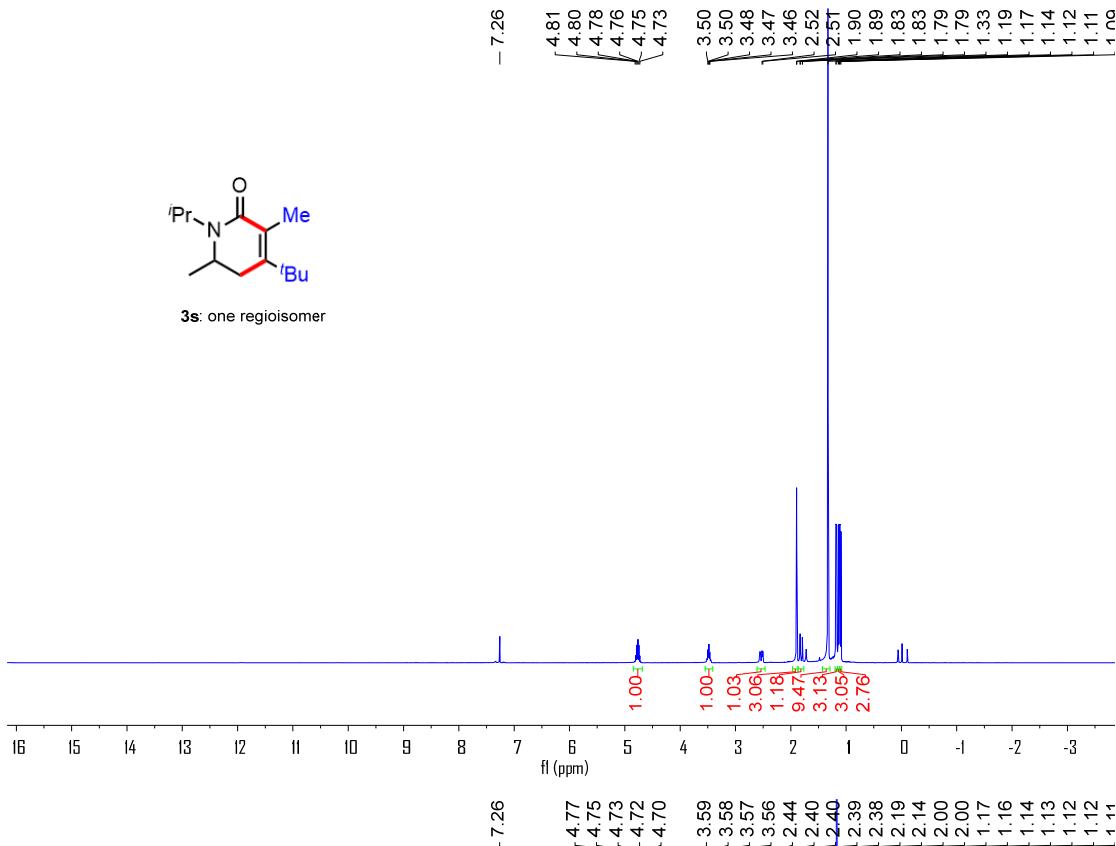
3r'



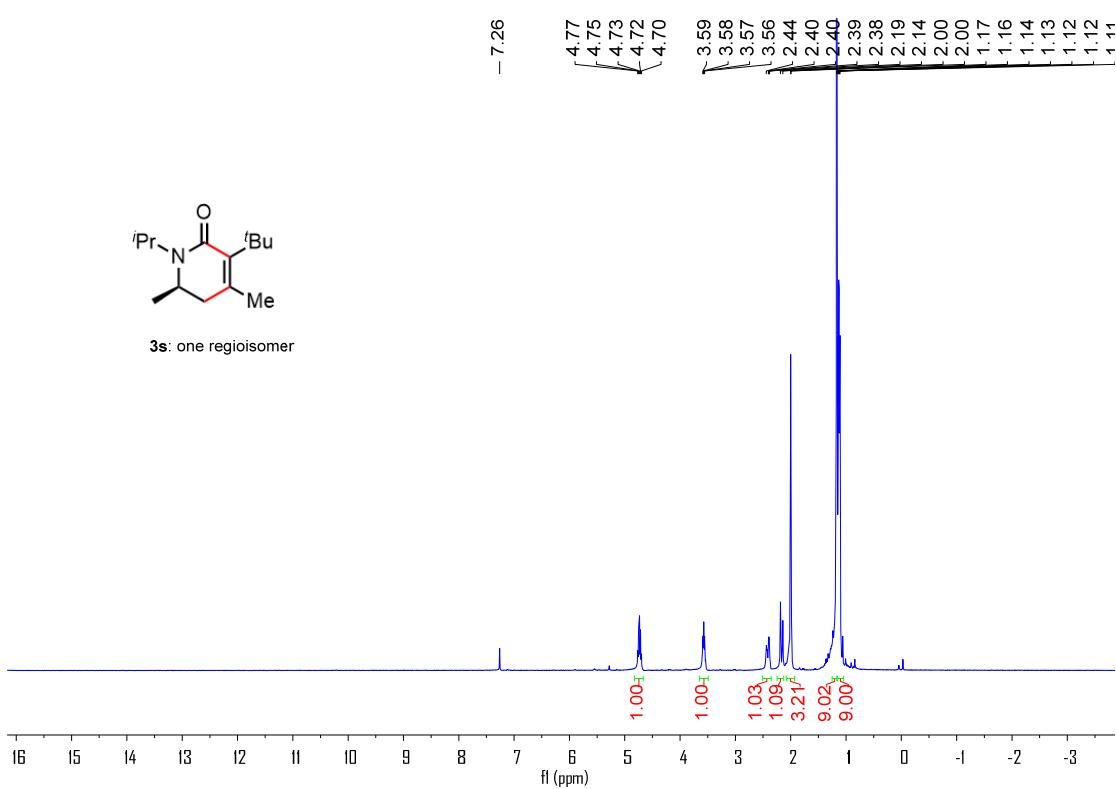


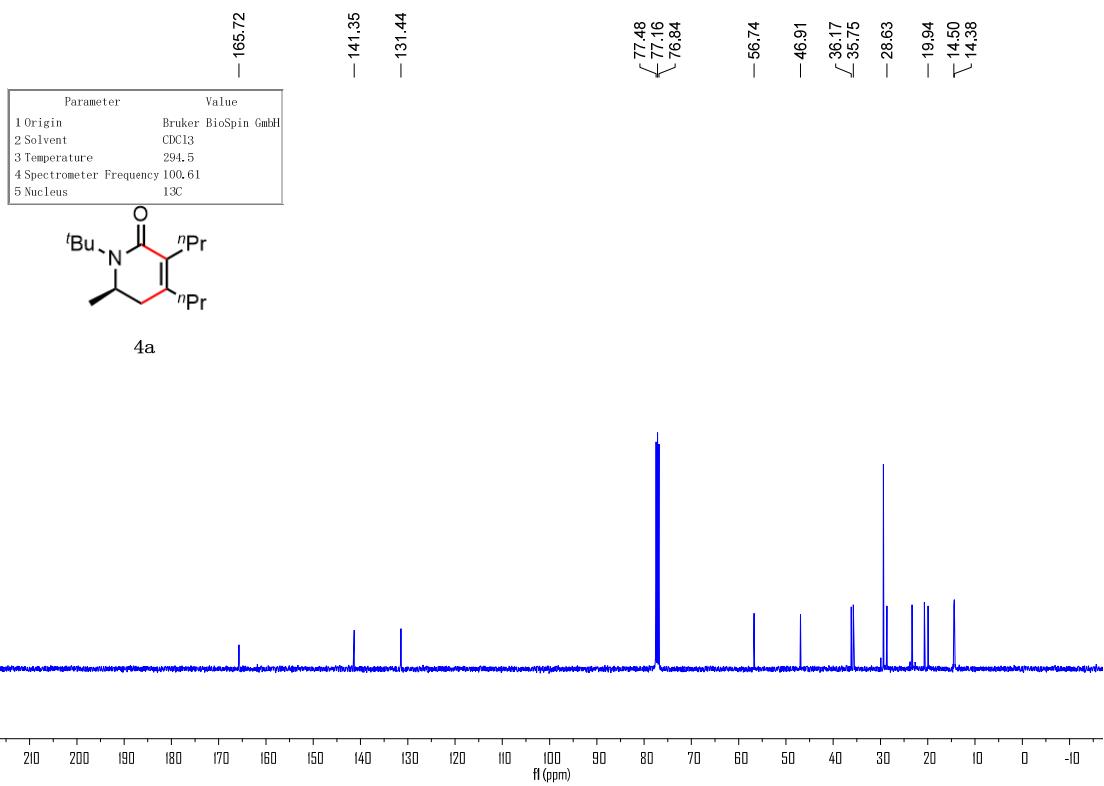
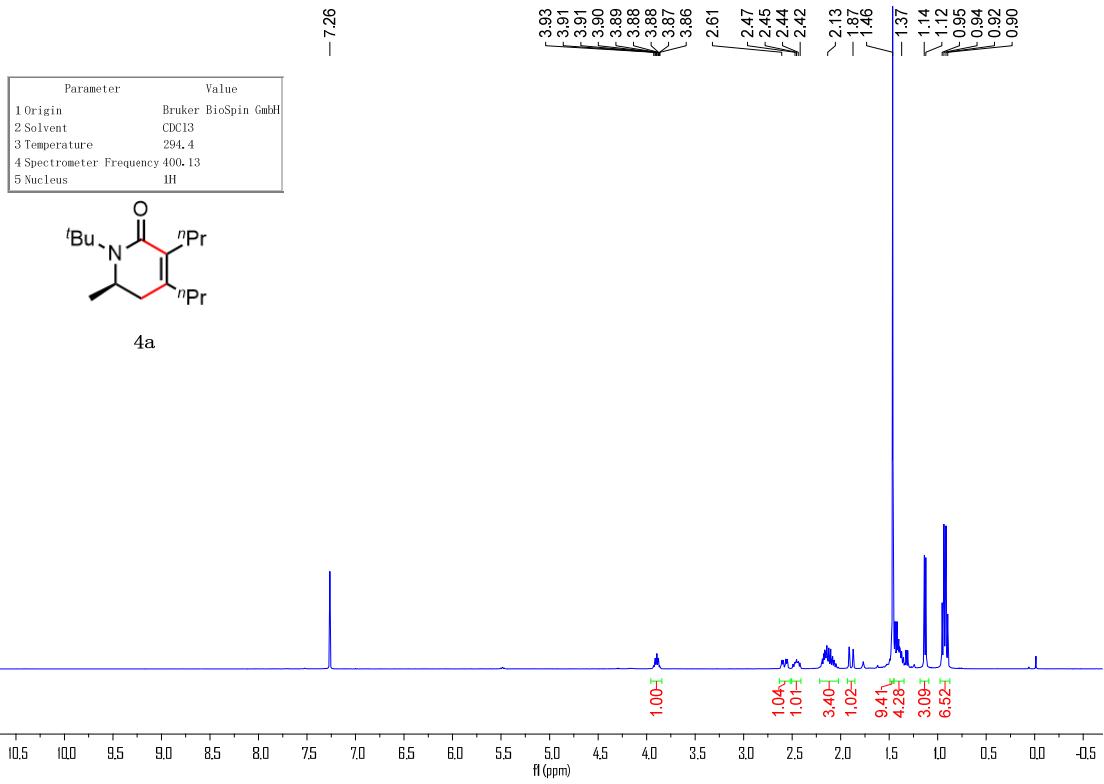


3s: one regioisomer

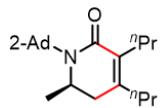


3s: one regioisomer

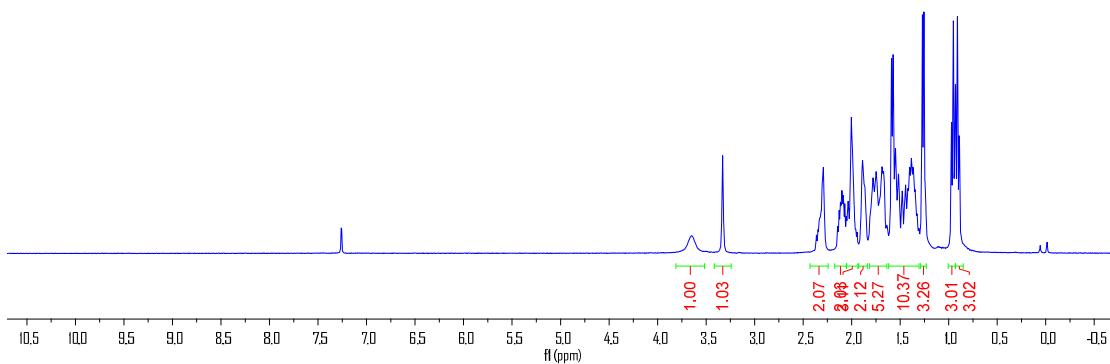




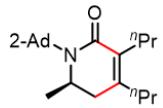
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDC13
3 Temperature	293.8
4 Spectrometer Frequency	400.15
5 Nucleus	1H



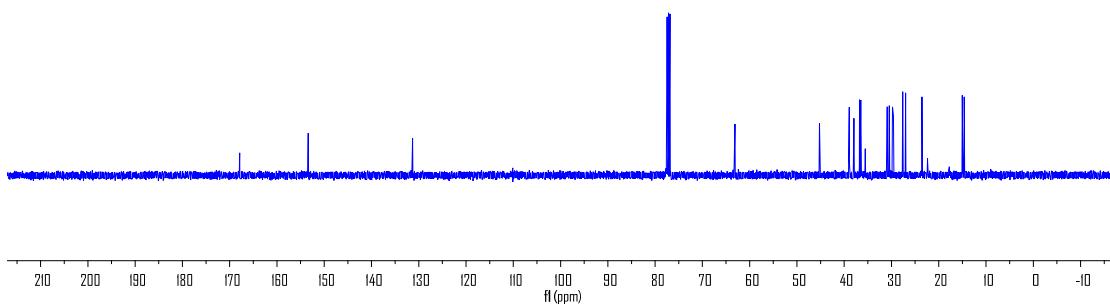
4b

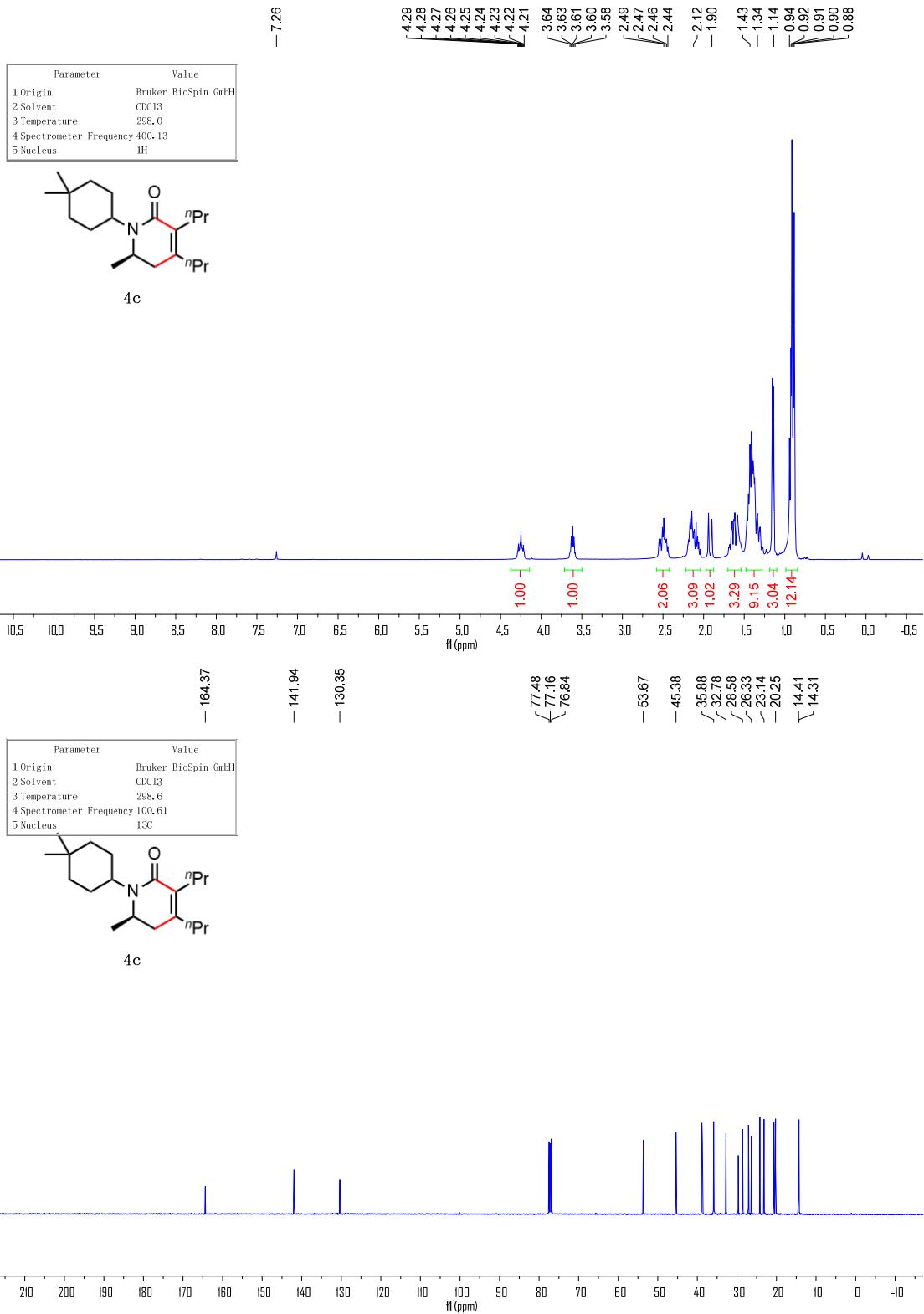


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	294.3
4 Spectrometer Frequency	100.62
5 Nucleus	¹³ C



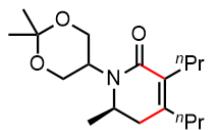
4b



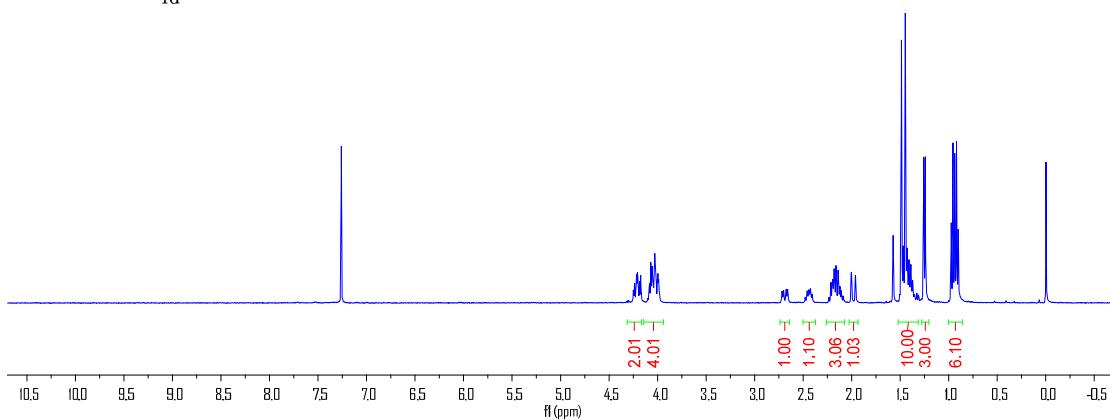




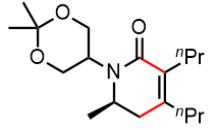
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	296.7
4 Spectrometer Frequency	400.13
5 Nucleus	^H



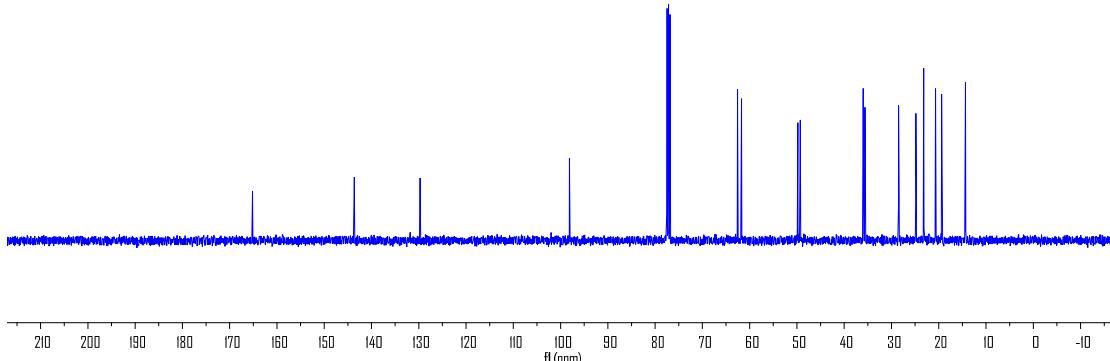
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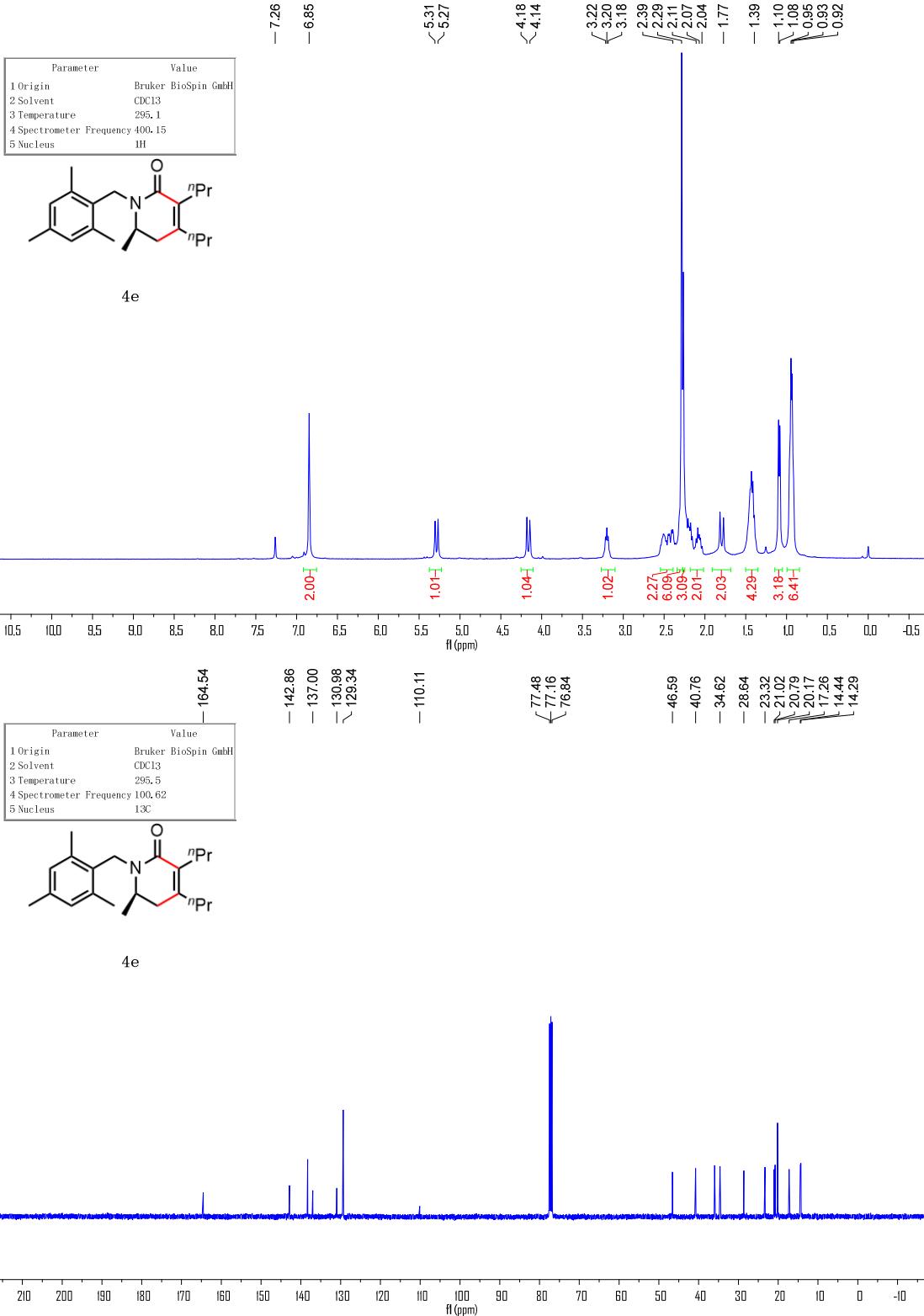


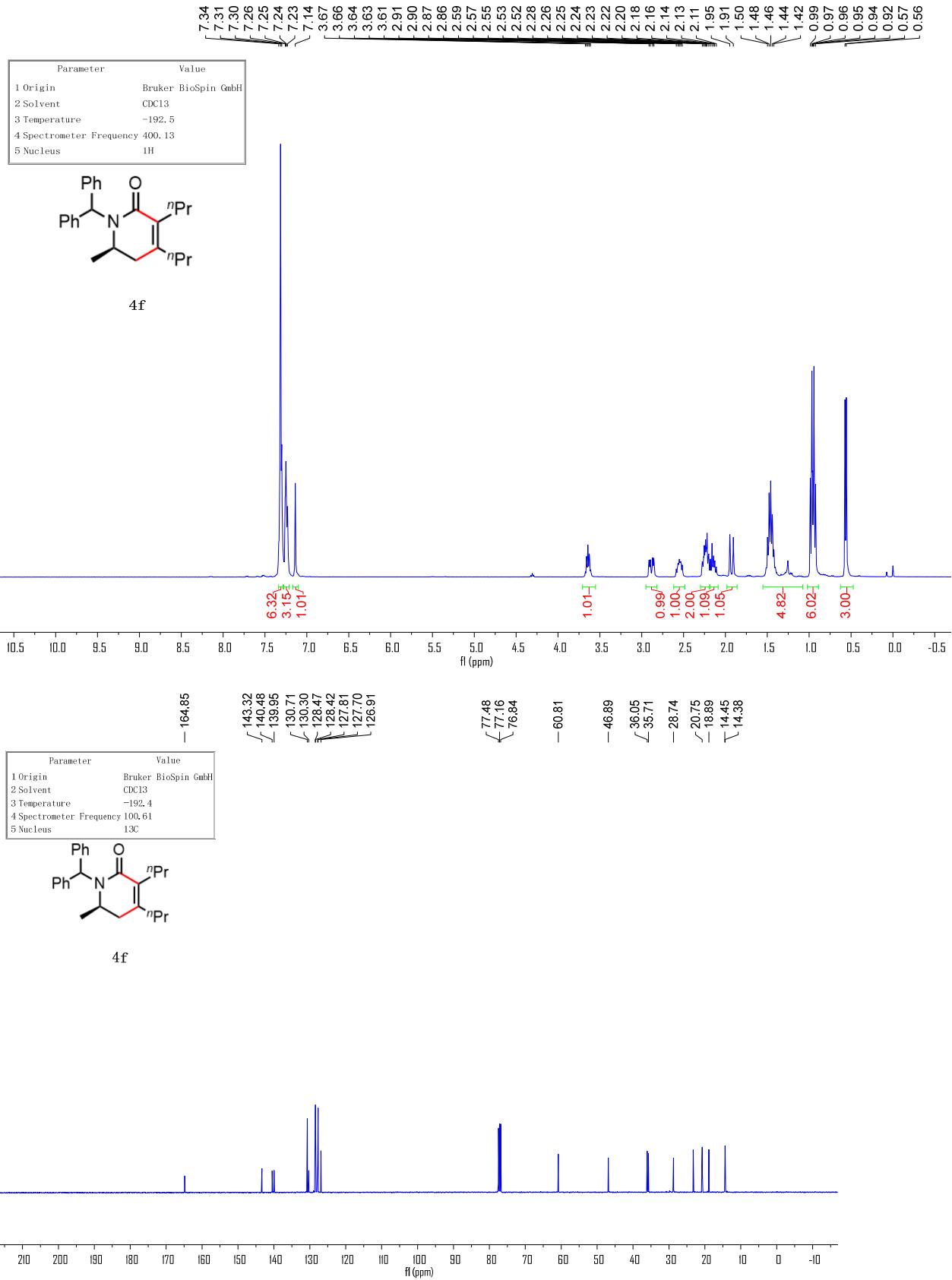
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-192.4
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C

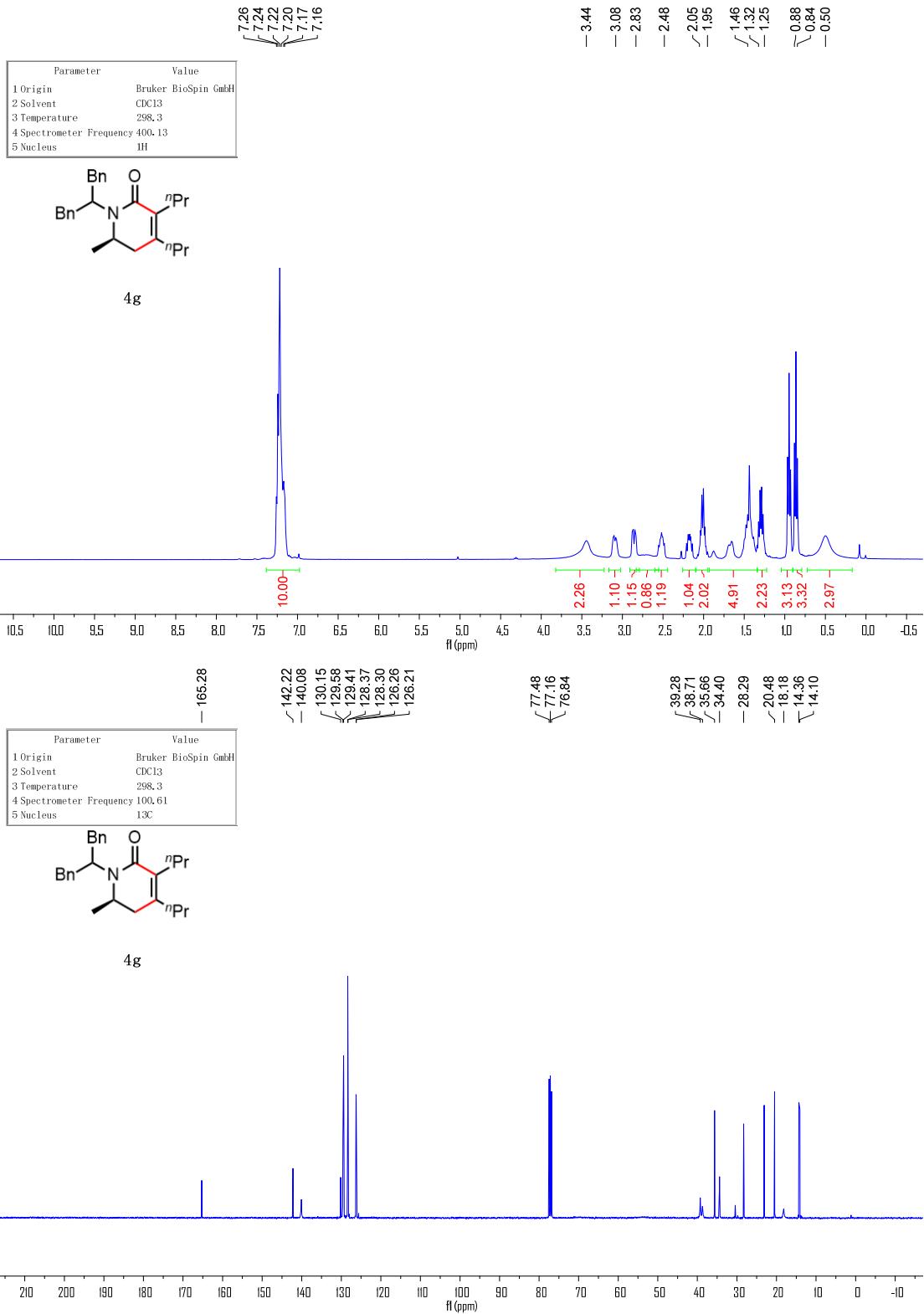


4d



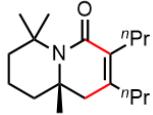




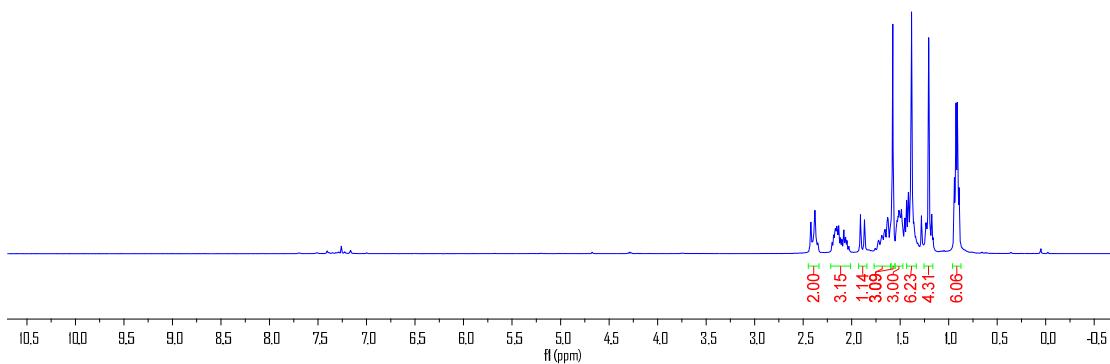




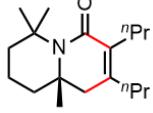
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	293.7
4 Spectrometer Frequency	400.13
5 Nucleus	^H



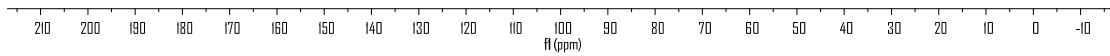
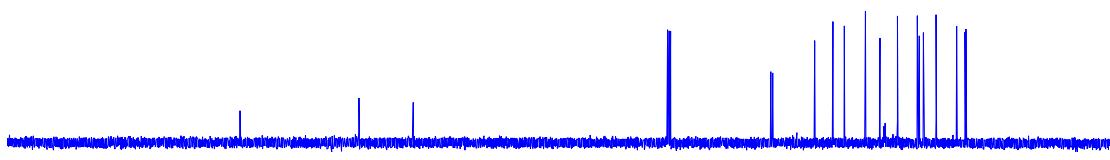
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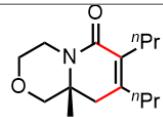
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	293.6
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C



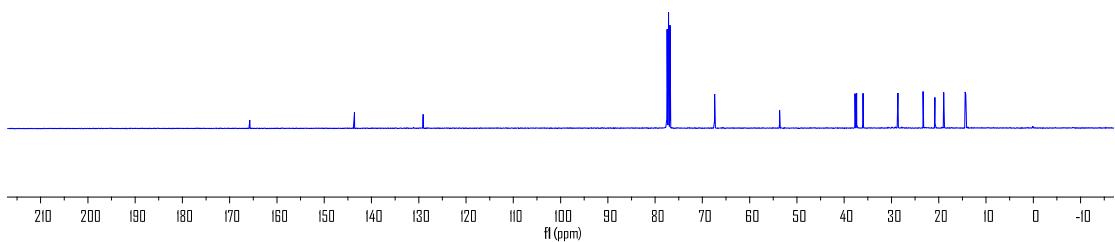
4h



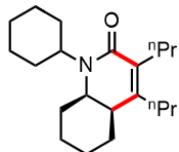
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-191.5
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C



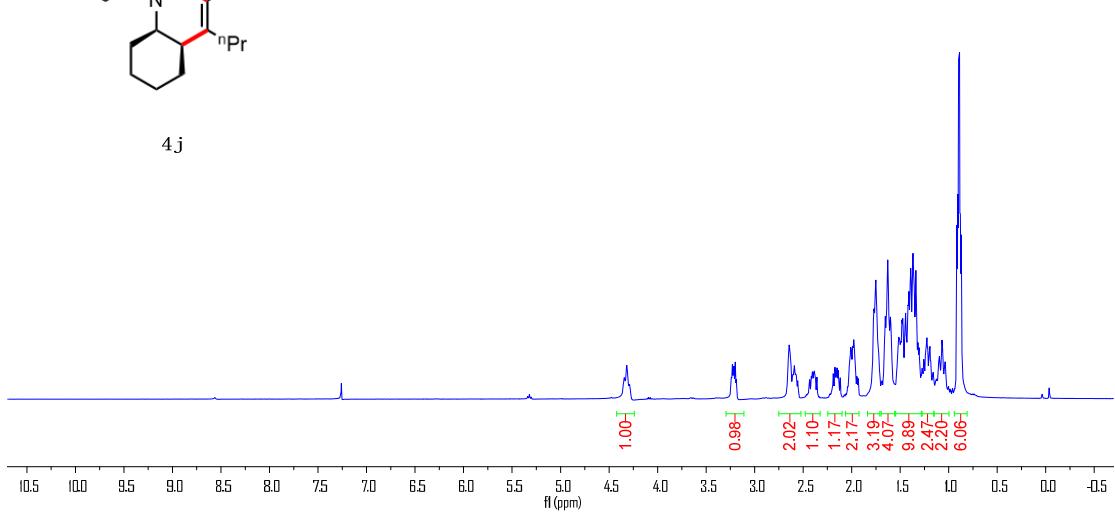
4i



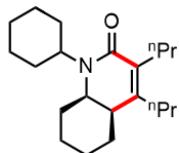
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-547.5
4 Spectrometer Frequency	400.23
5 Nucleus	¹ H



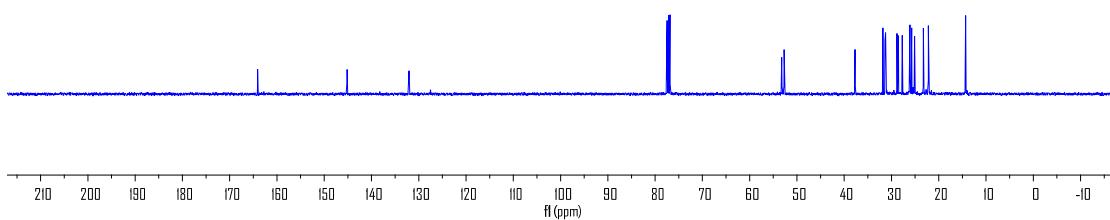
4j



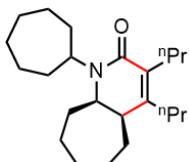
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	-547.7
4 Spectrometer Frequency	100.64
5 Nucleus	¹³ C



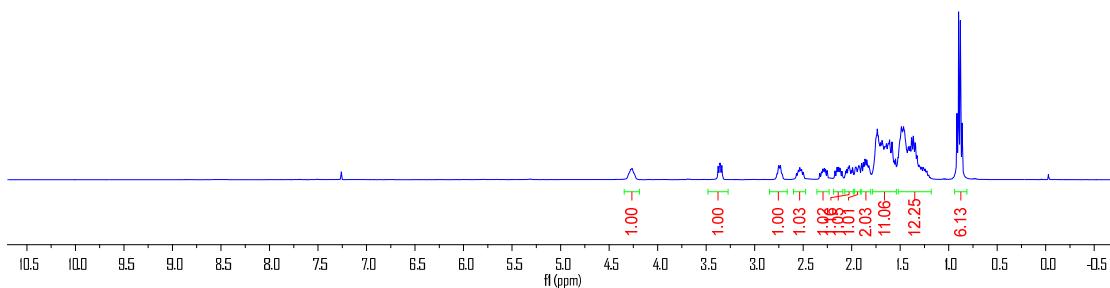
4j



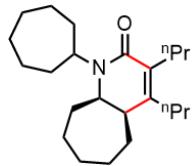
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	293.9
4 Spectrometer Frequency	400.13
5 Nucleus	¹ H



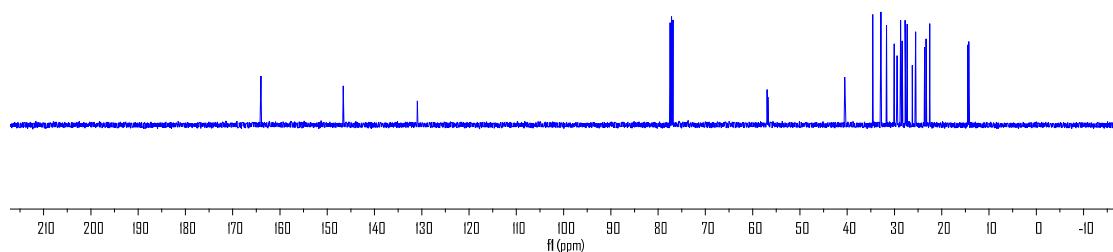
4k



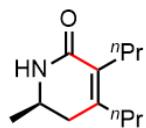
Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	294.2
4 Spectrometer Frequency	100.61
5 Nucleus	¹³ C



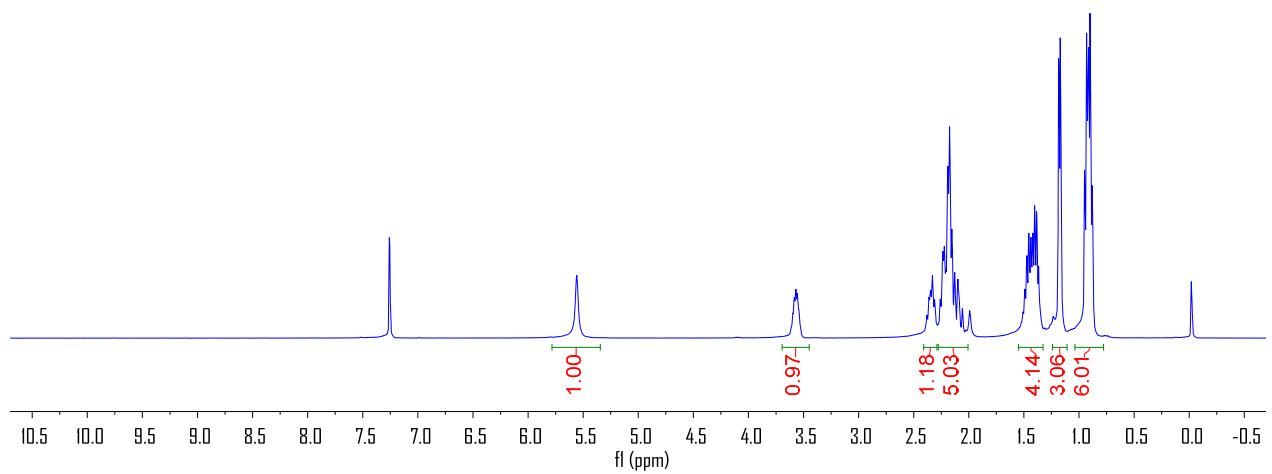
4k

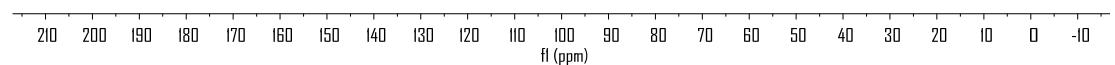
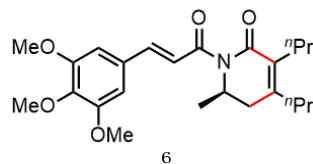
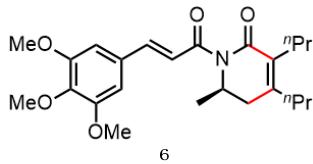
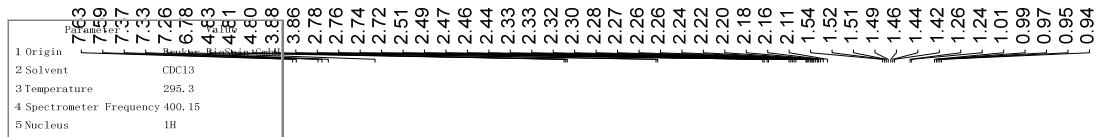


Parameter	Value
1 Origin	Bruker BioSpin GmbH
2 Solvent	CDCl ₃
3 Temperature	295.8
4 Spectrometer Frequency	400.15
5 Nucleus	¹ H

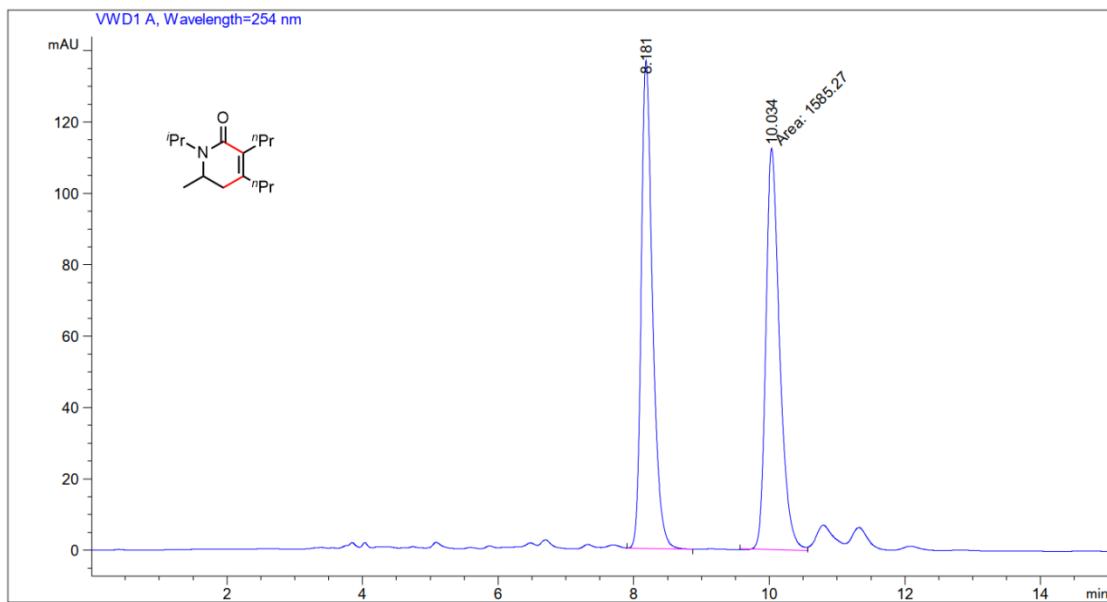


5

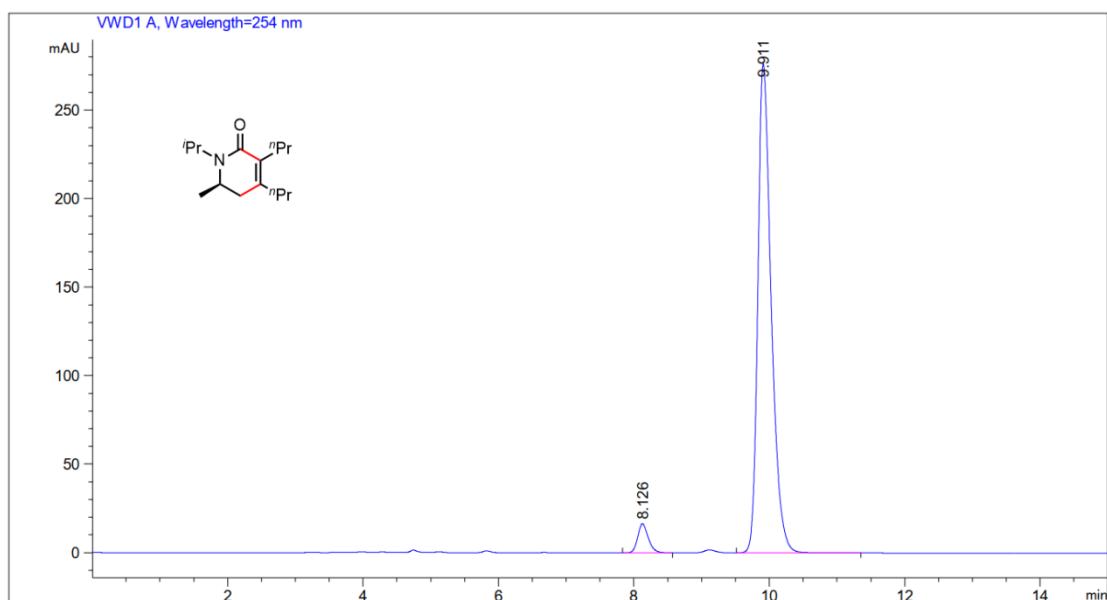




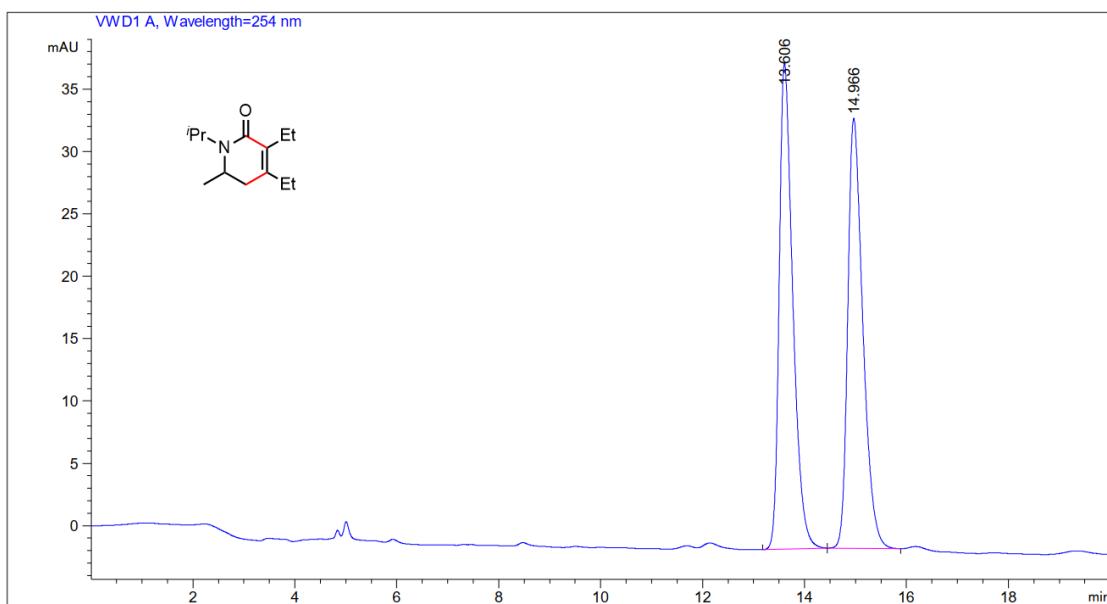
12. HPLC Charts of Chiral Products



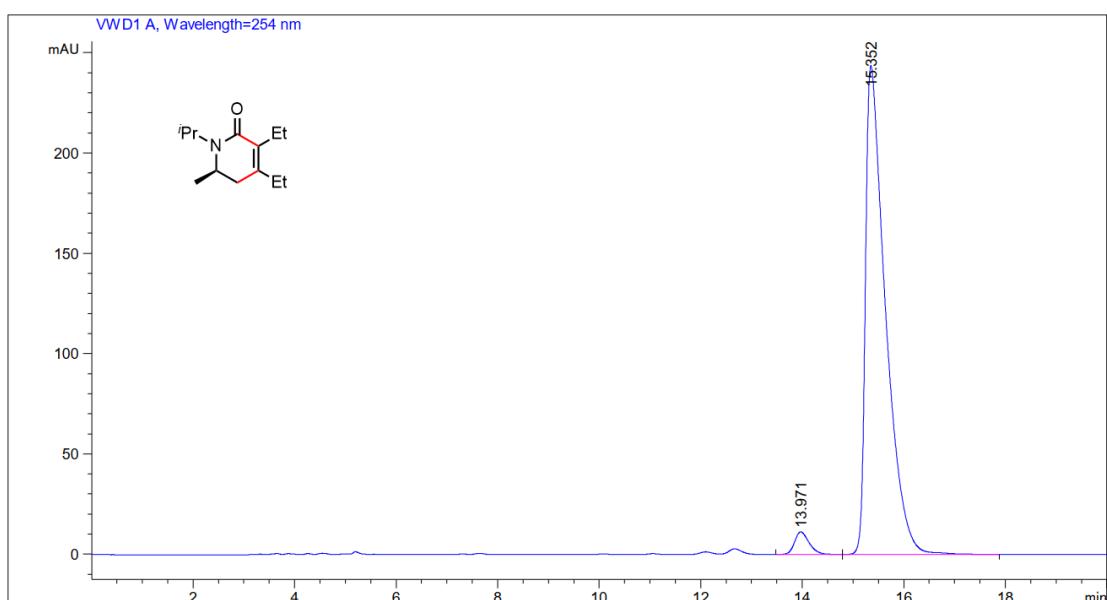
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.181	BB	0.1748	1578.19690	136.63593	49.8882
2	10.034	MM	0.2352	1585.26965	112.34603	50.1118



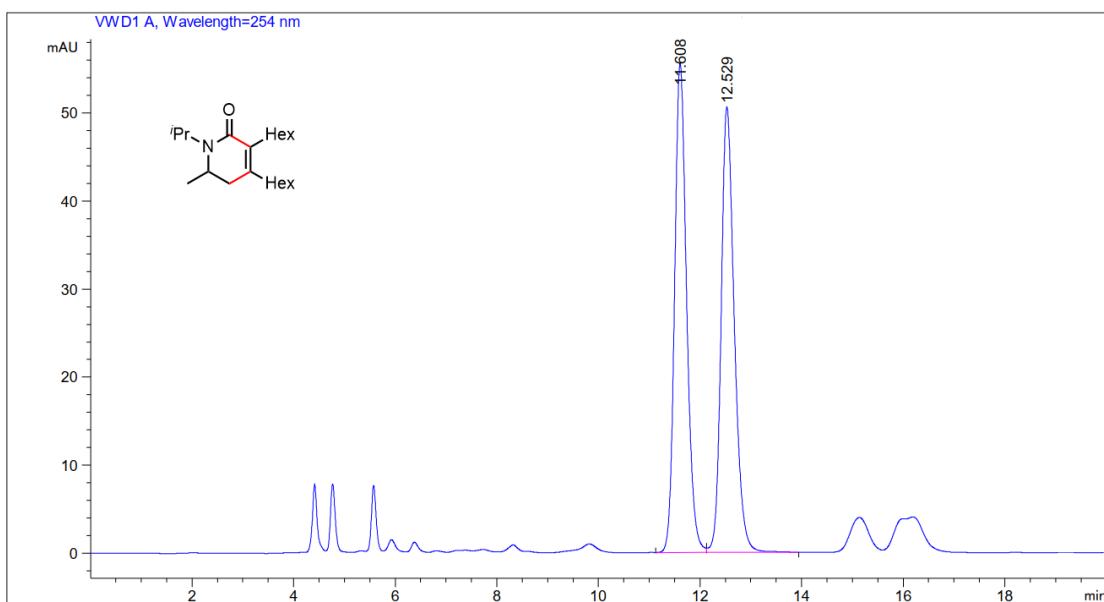
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.126	BB	0.1655	178.44363	16.45618	4.4951
2	9.911	BB	0.2071	3791.28809	276.33911	95.5049



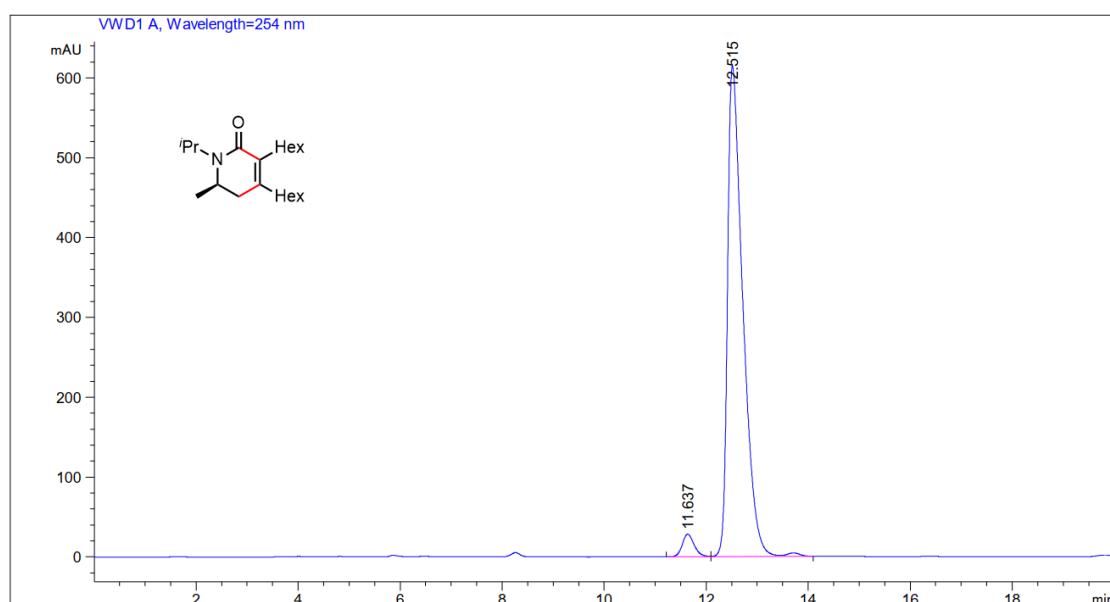
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.606	BB	0.2800	721.18372	38.95485	50.4461
2	14.966	BB	0.3116	708.42889	34.48897	49.5539



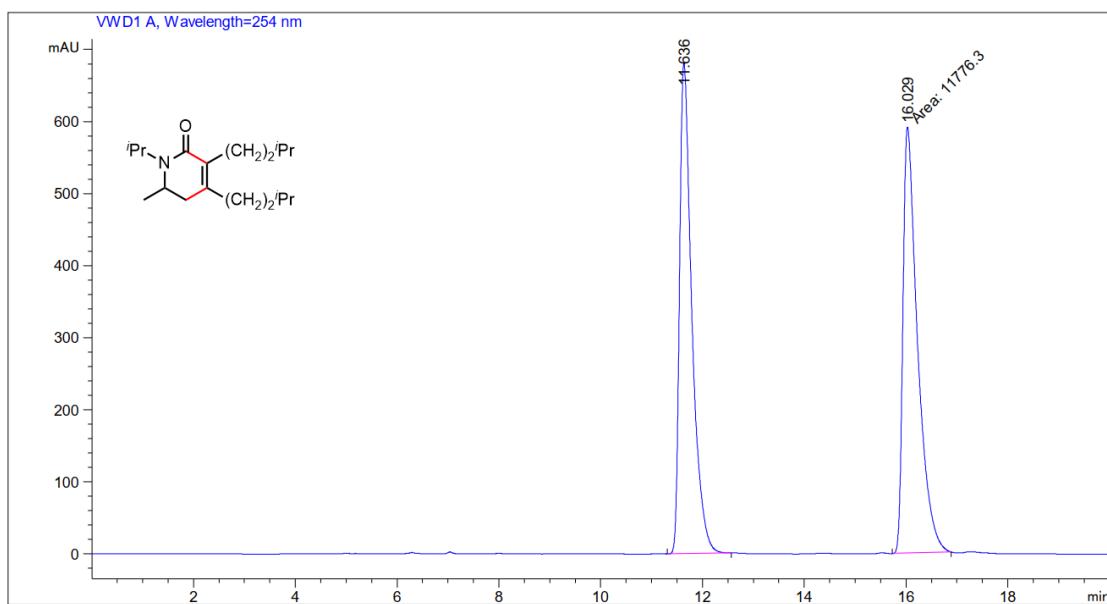
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.971	BB	0.3037	225.70003	11.31668	3.2866
2	15.352	BB	0.4080	6641.52490	243.67752	96.7134



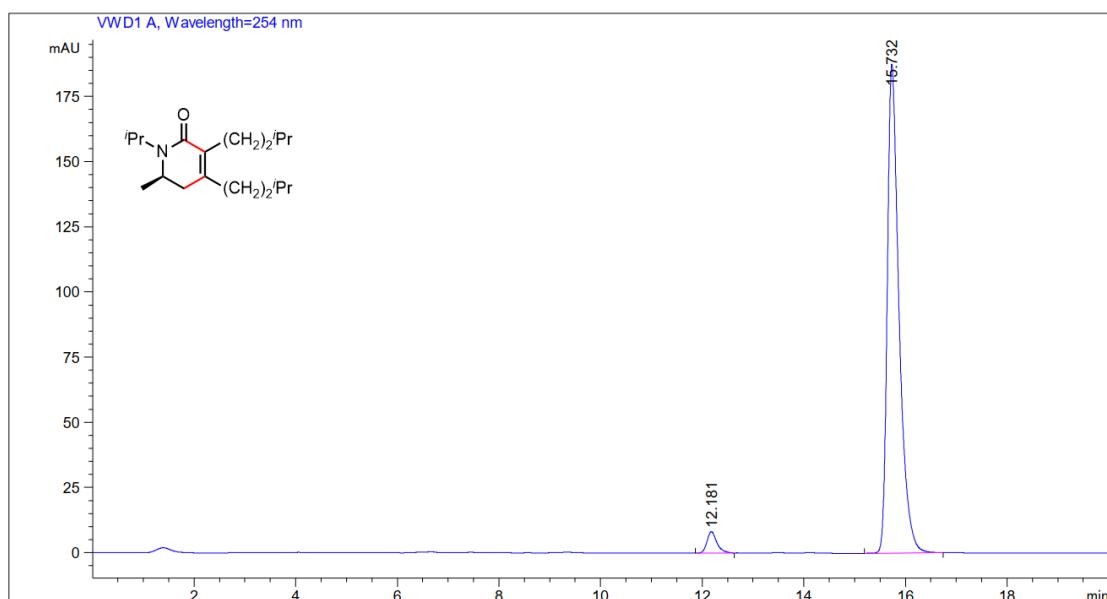
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.608	BV	0.2509	908.60437	55.51854	49.9740
2	12.529	VB	0.2738	909.54871	50.58084	50.0260



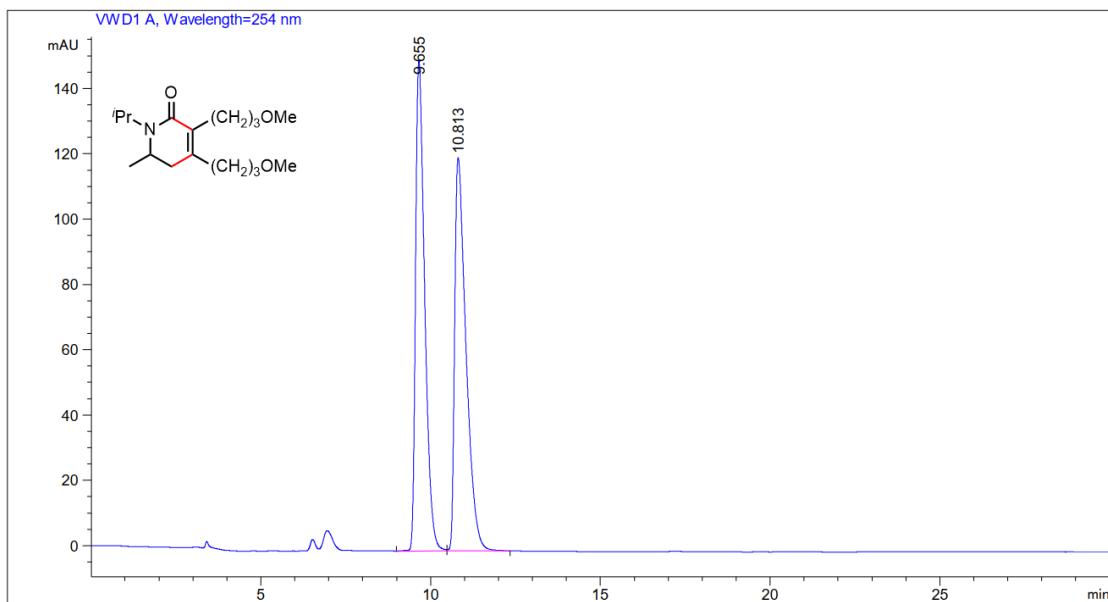
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.637	BV	0.2489	462.41962	28.40645	3.4748
2	12.515	VV R	0.3112	1.28455e4	614.63147	96.5252



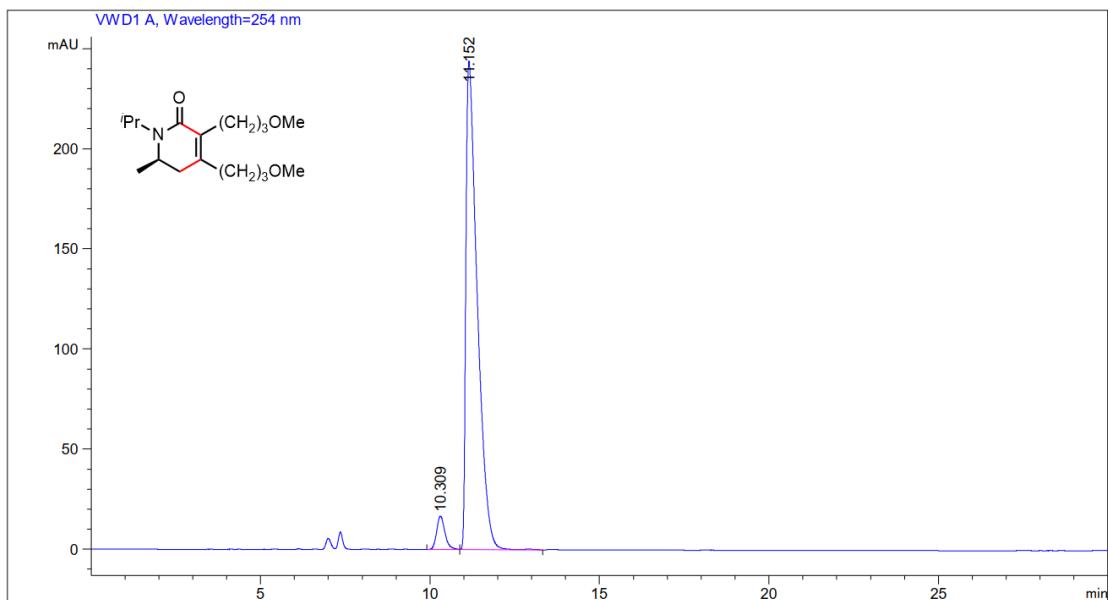
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.636	BB	0.2477	1.14163e4	680.59656	49.2239
2	16.029	MM	0.3319	1.17763e4	591.30249	50.7761



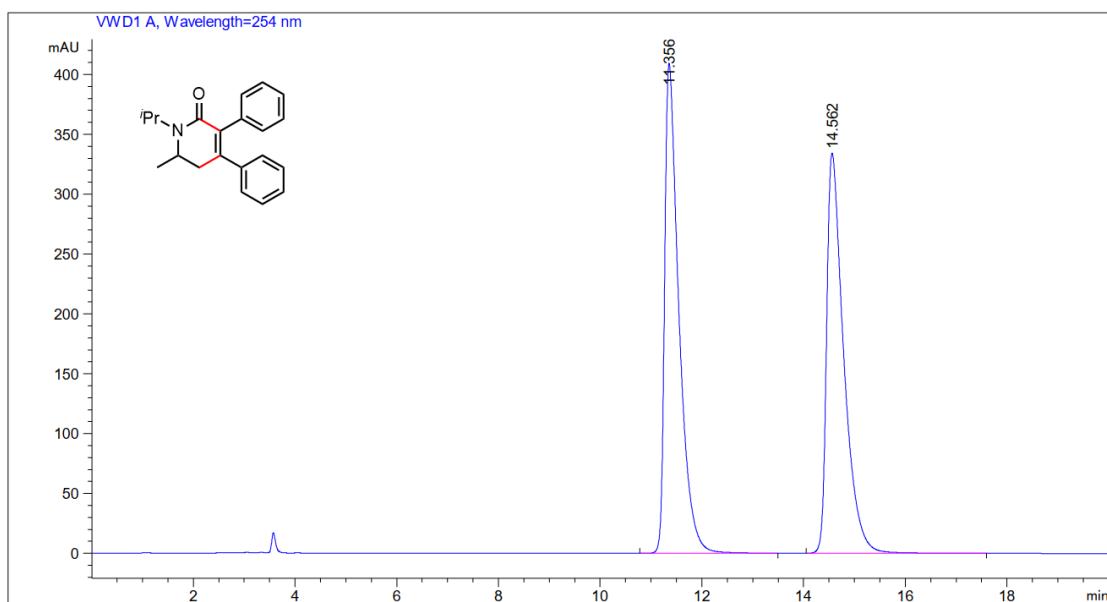
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.181	BB	0.2033	111.23234	8.25198	3.5744
2	15.732	BB	0.2416	3000.66162	187.59151	96.4256



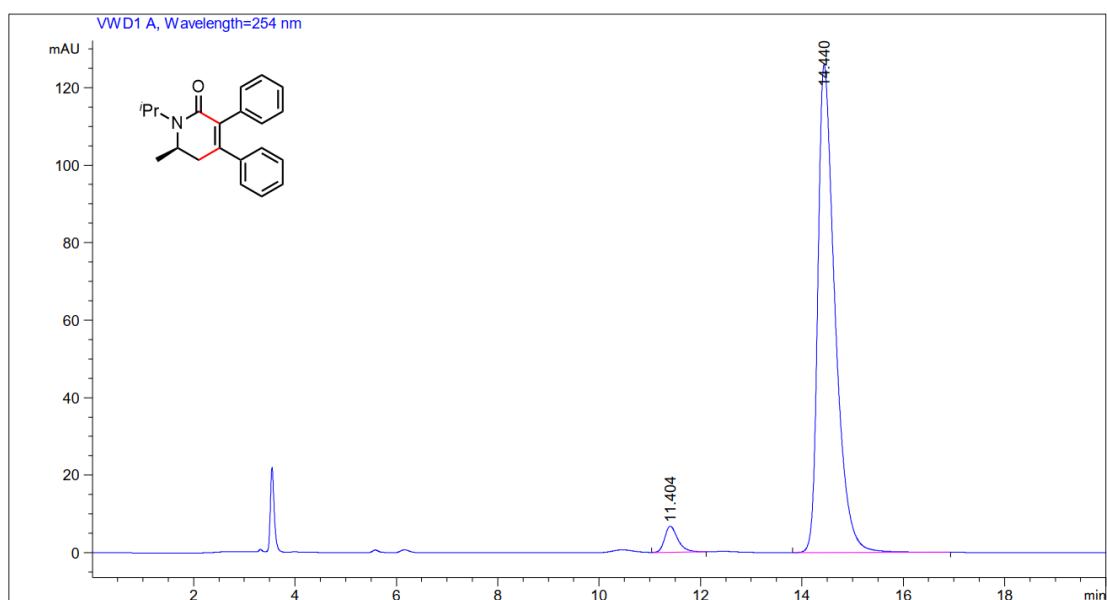
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.655	BV	0.2844	2807.58569	149.97487	50.1279
2	10.813	VB	0.3445	2793.26416	120.45124	49.8721



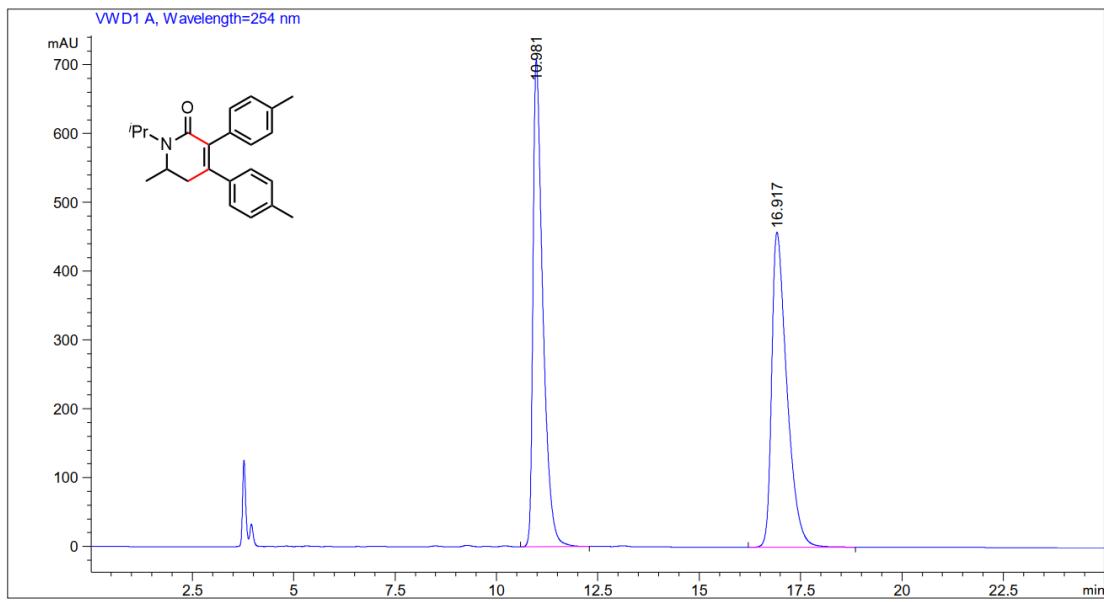
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.309	BV	0.2606	285.36139	16.76467	4.7999
2	11.152	VV R	0.3423	5659.83643	244.05864	95.2001



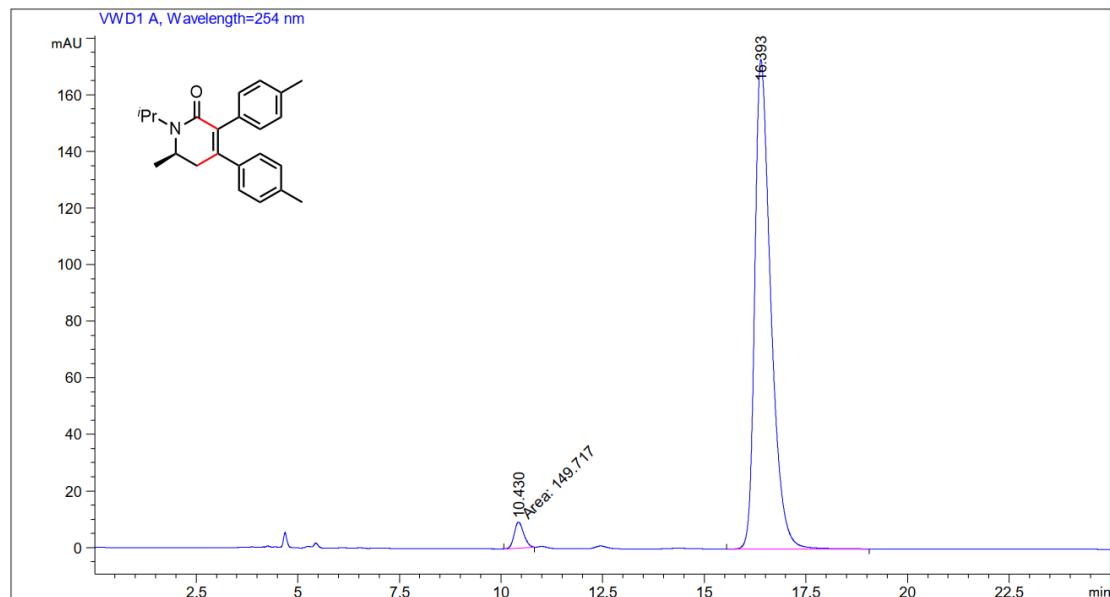
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.356	BB	0.2864	7974.88086	409.20847	50.6457
2	14.562	BB	0.3442	7771.54297	334.29617	49.3543



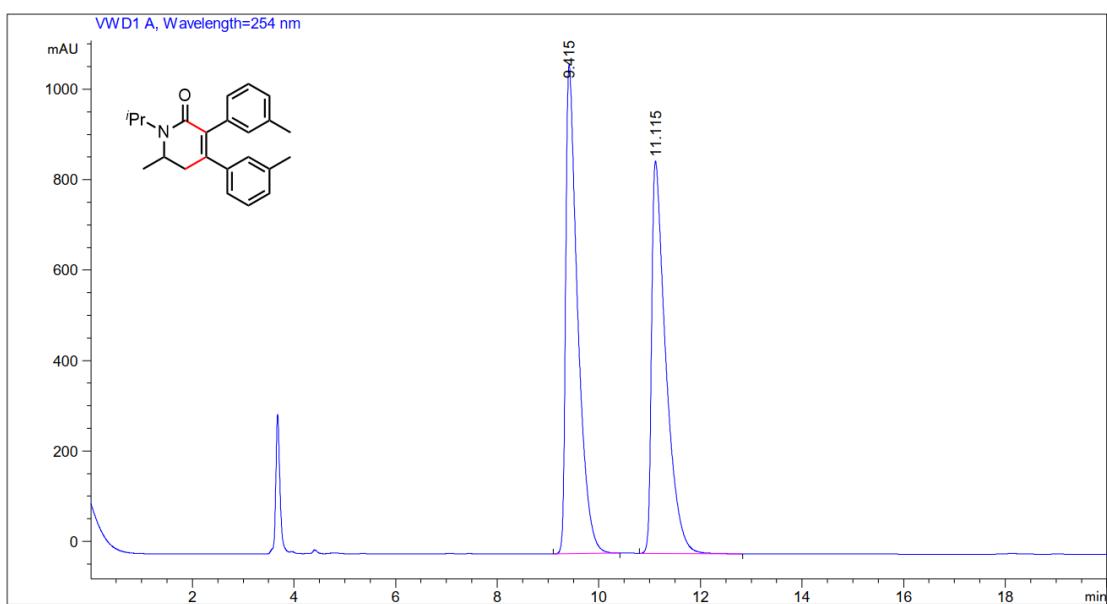
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.404	BB	0.2708	120.55642	6.73466	3.9240
2	14.440	BB	0.3516	2951.76294	125.86121	96.0760



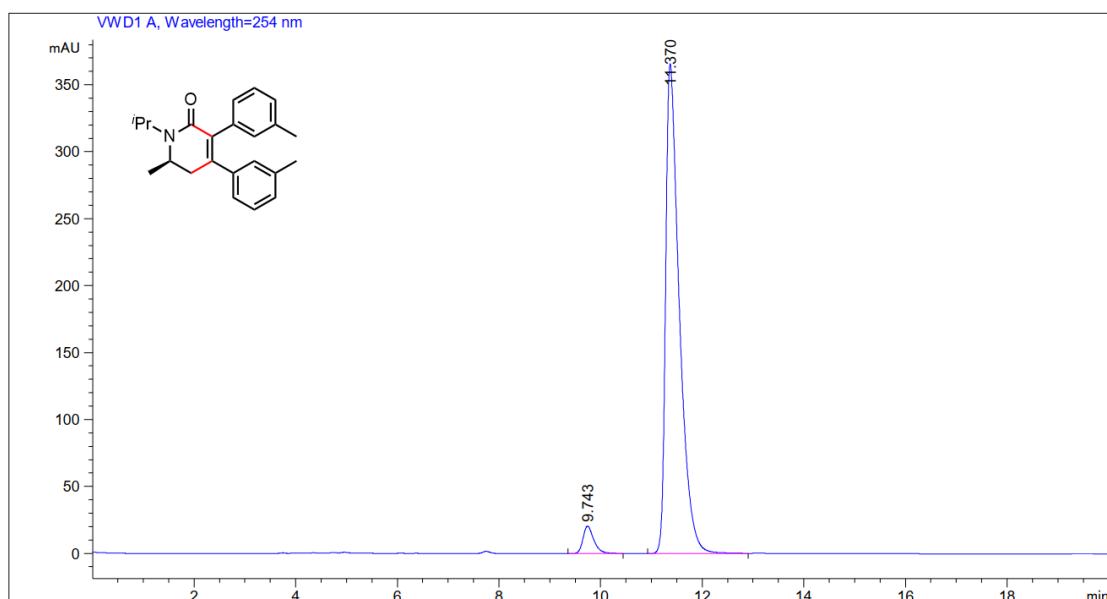
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.981	BB	0.2469	1.19464e4	707.90930	50.0226
2	16.917	BB	0.3870	1.19356e4	458.01645	49.9774



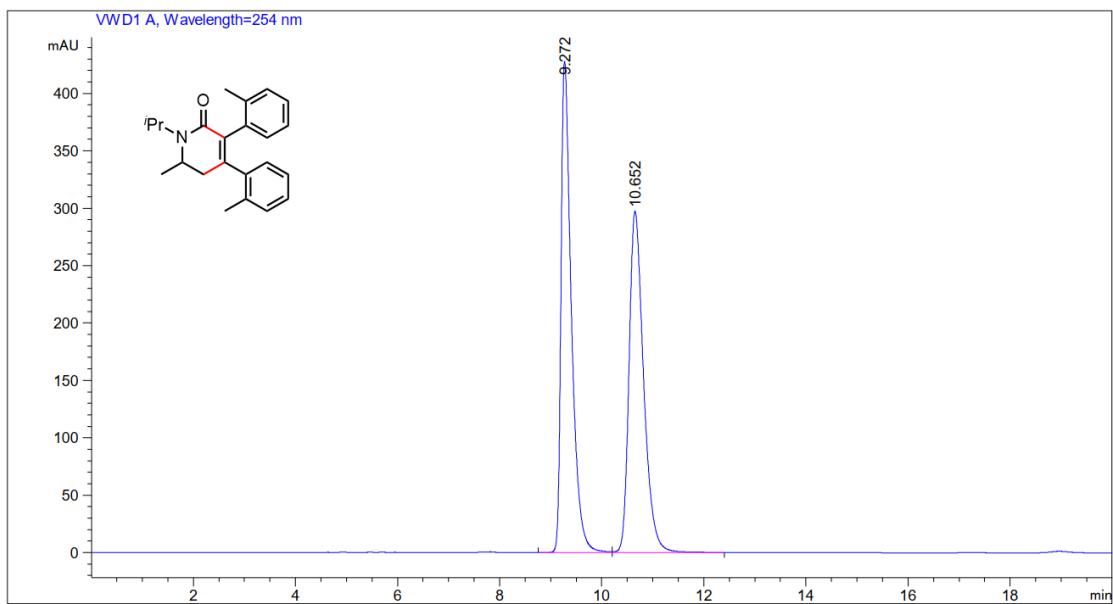
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.430	MM	0.2706	149.71730	9.22245	3.0655
2	16.393	BB	0.4125	4734.15088	172.89500	96.9345



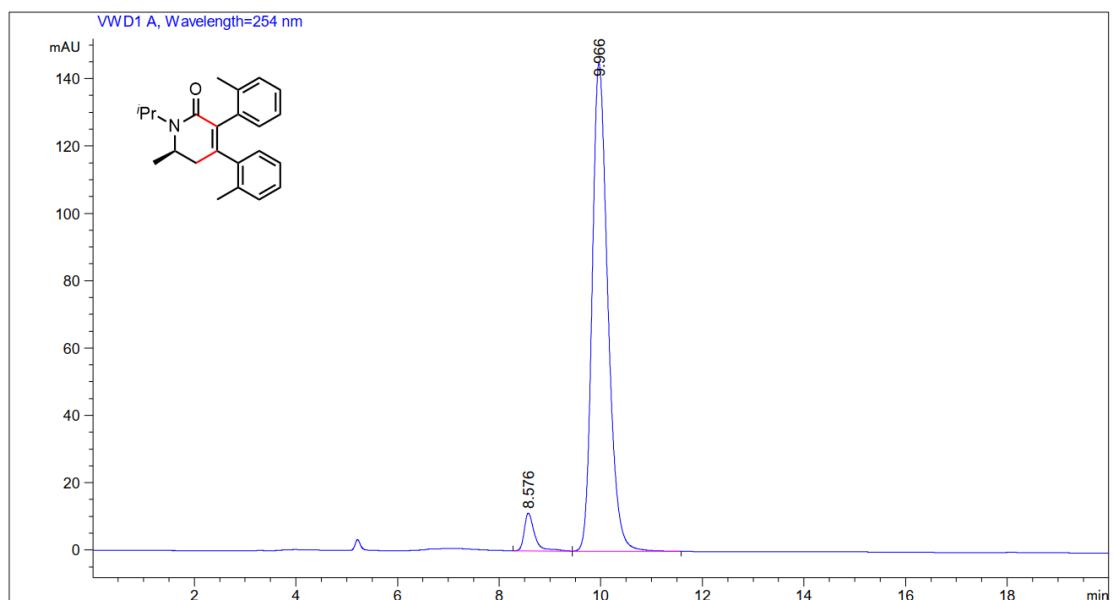
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.415	BB	0.2388	1.76883e4	1081.46387	51.2301
2	11.115	BB	0.2812	1.68389e4	868.43433	48.7699



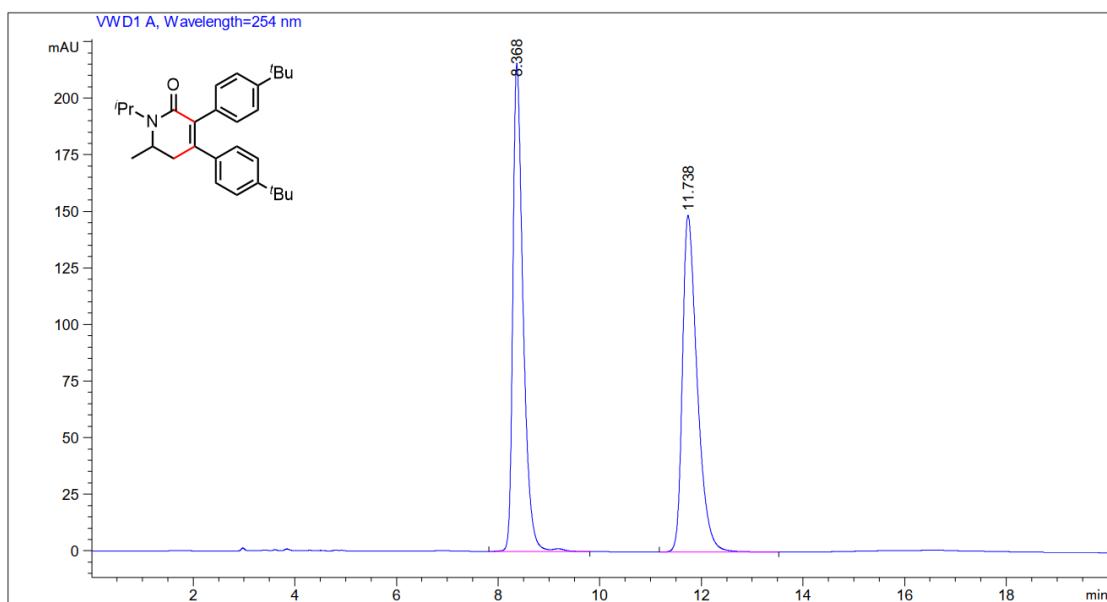
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.743	BB	0.2255	307.08206	20.53567	4.3049
2	11.370	BB	0.2798	6826.30957	365.71463	95.6951



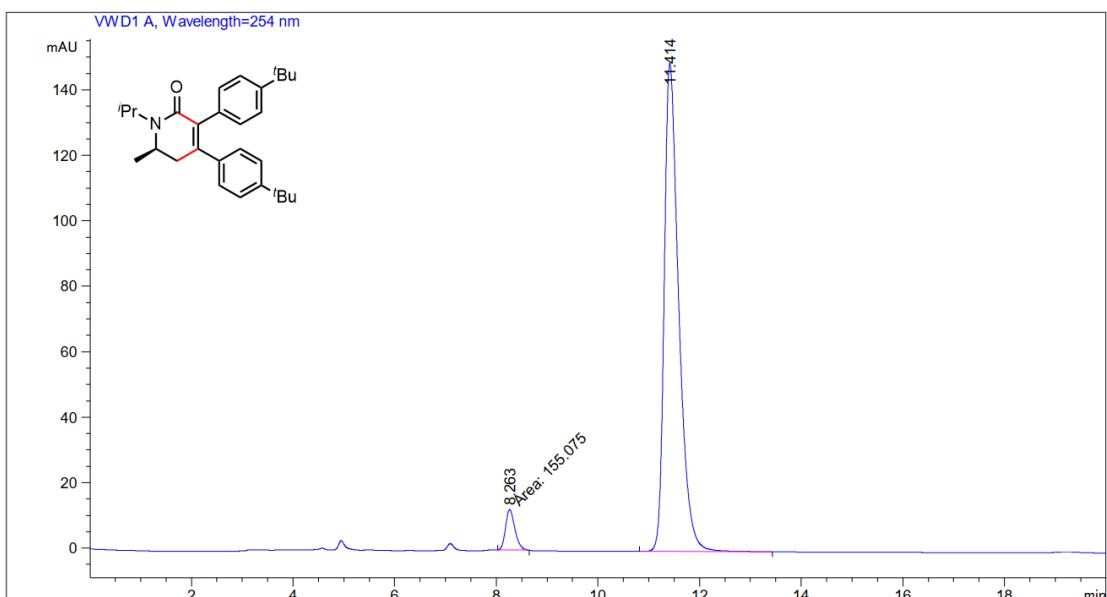
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.272	BV	0.2110	6010.88574	427.65173	50.5881
2	10.652	VB	0.3034	5871.12793	297.23807	49.4119



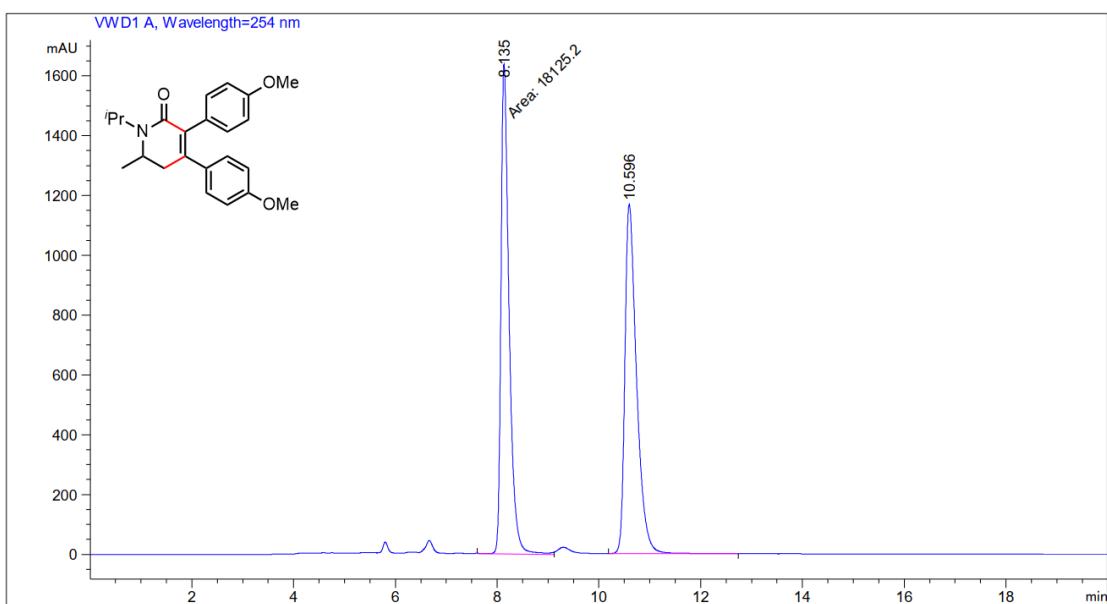
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.576	BB	0.2099	159.02005	11.24816	4.8830
2	9.966	BB	0.3262	3097.61816	144.99127	95.1170



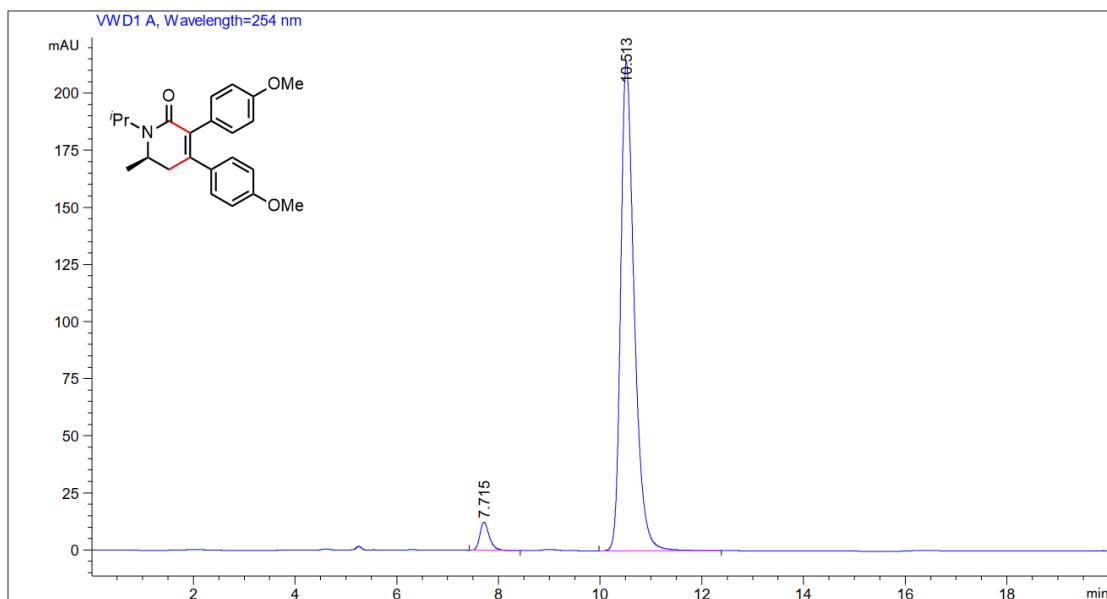
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.368	B V	0.2103	3019.27515	215.64268	50.1197
2	11.738	BB	0.3046	3004.84839	148.78618	49.8803



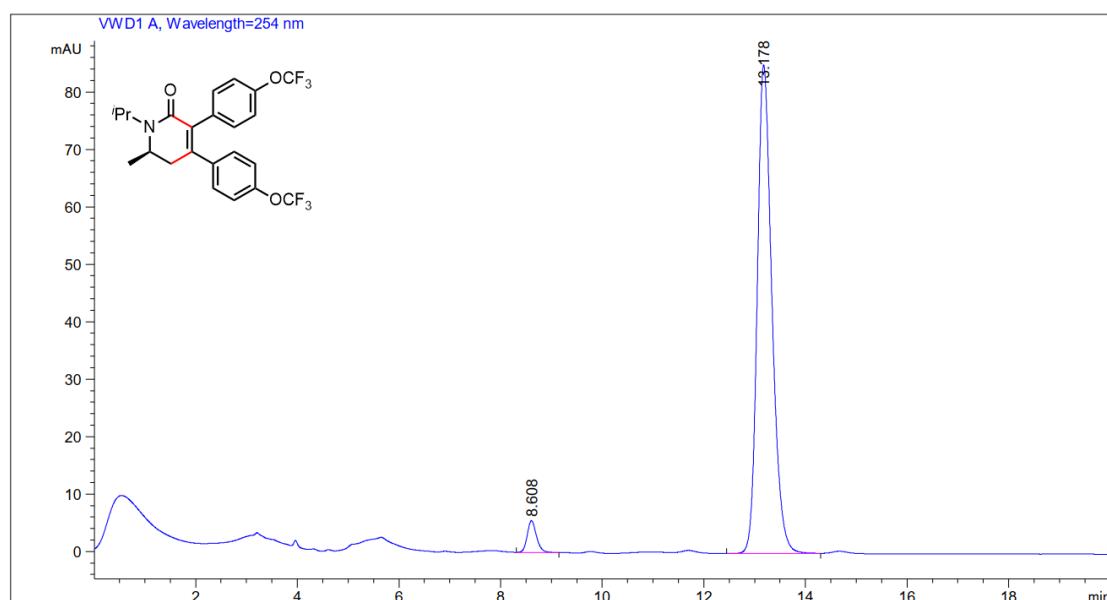
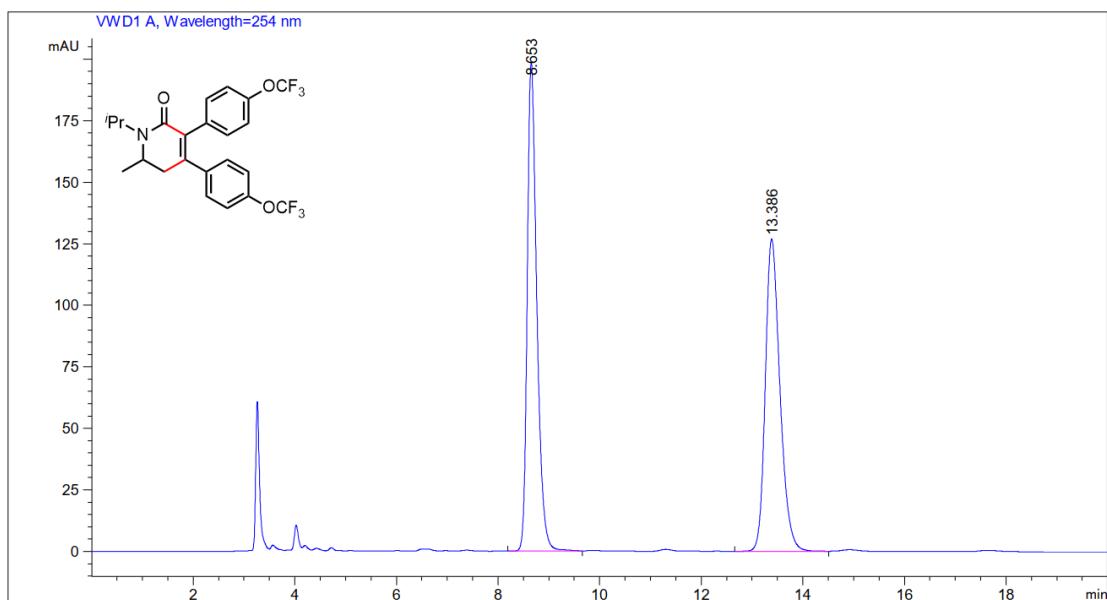
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.263	MM	0.2105	155.07478	12.27703	4.9801
2	11.414	BB	0.2983	2958.80078	149.22462	95.0199



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.135	MM	0.1845	1.81252e4	1637.41821	49.3768
2	10.596	VB	0.2386	1.85827e4	1168.16638	50.6232

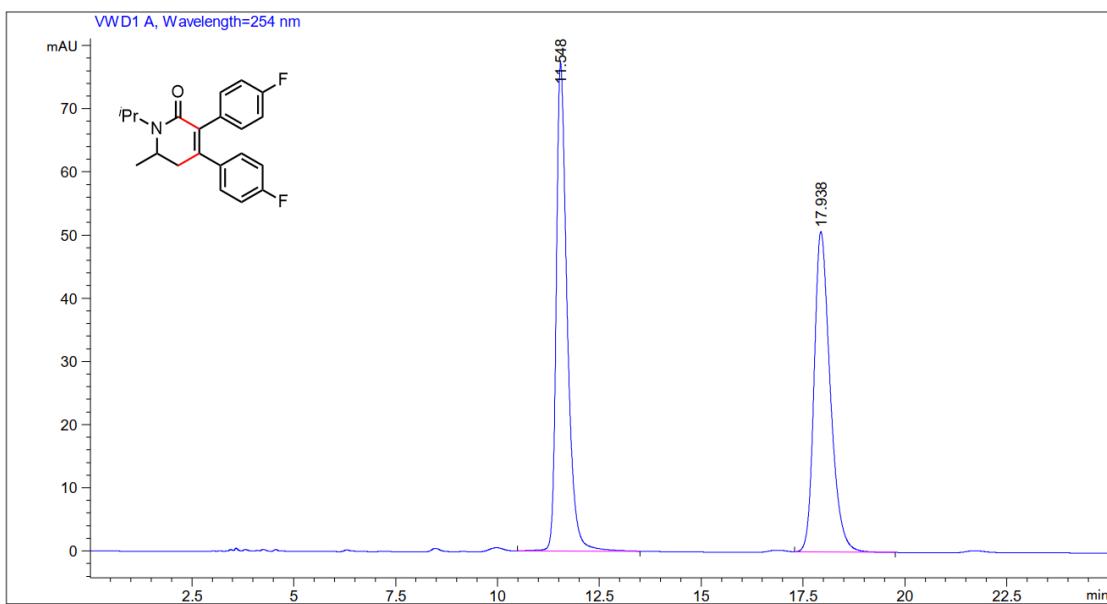


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.715	BB	0.1951	159.69778	12.41482	3.8713
2	10.513	BB	0.2800	3965.47974	214.17451	96.1287

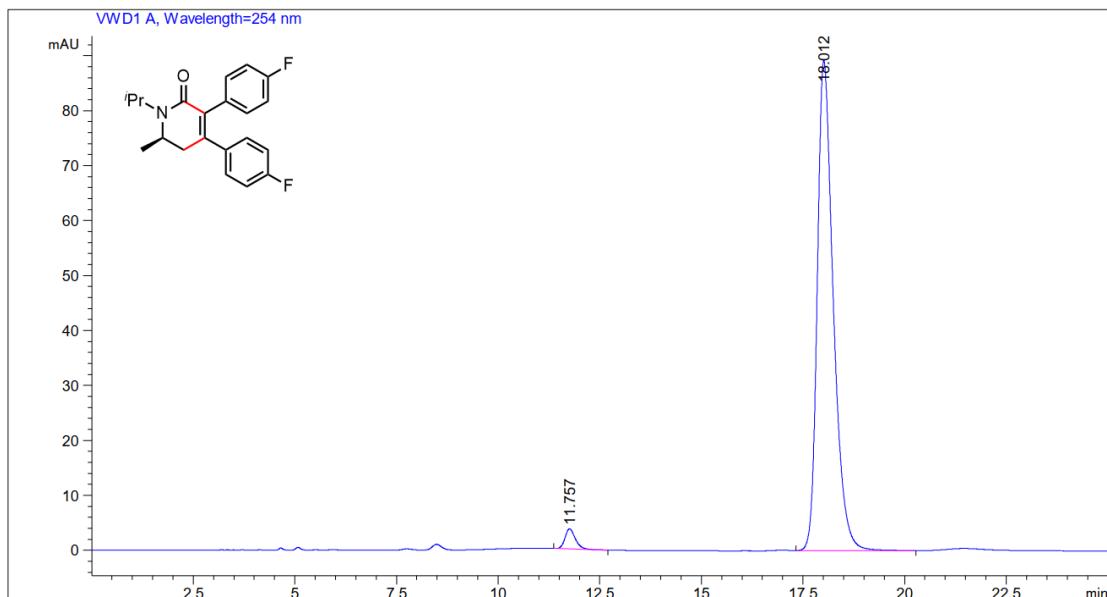


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.653	BB	0.1974	2592.17822	198.46021	50.4908
2	13.386	BB	0.3046	2541.78296	126.96241	49.5092

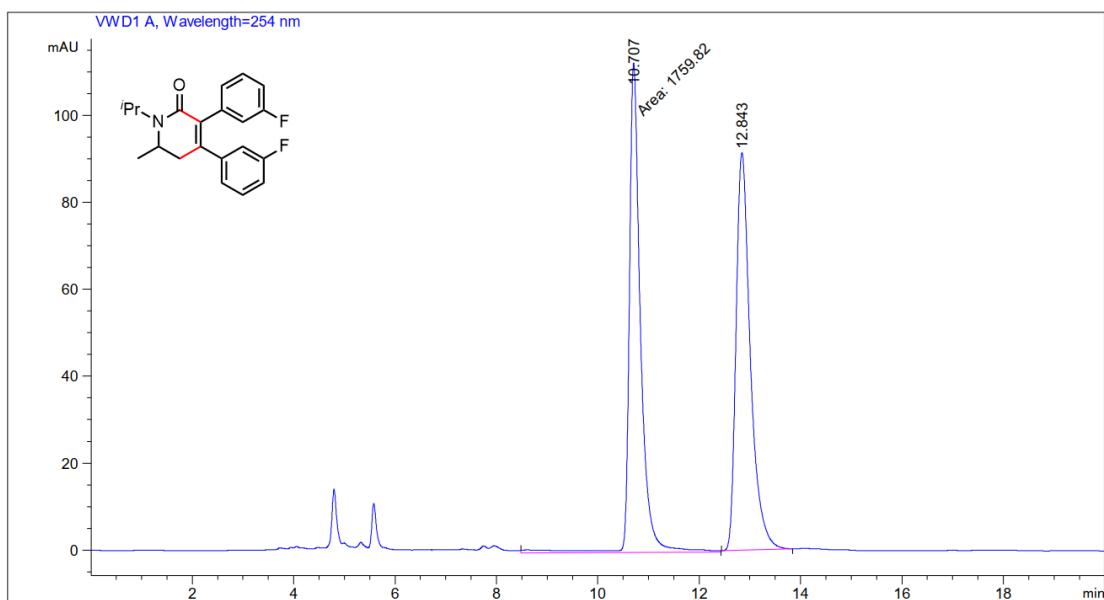
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.608	BB	0.1931	69.76053	5.53299	3.9437
2	13.178	BB	0.3041	1699.12952	85.03091	96.0563



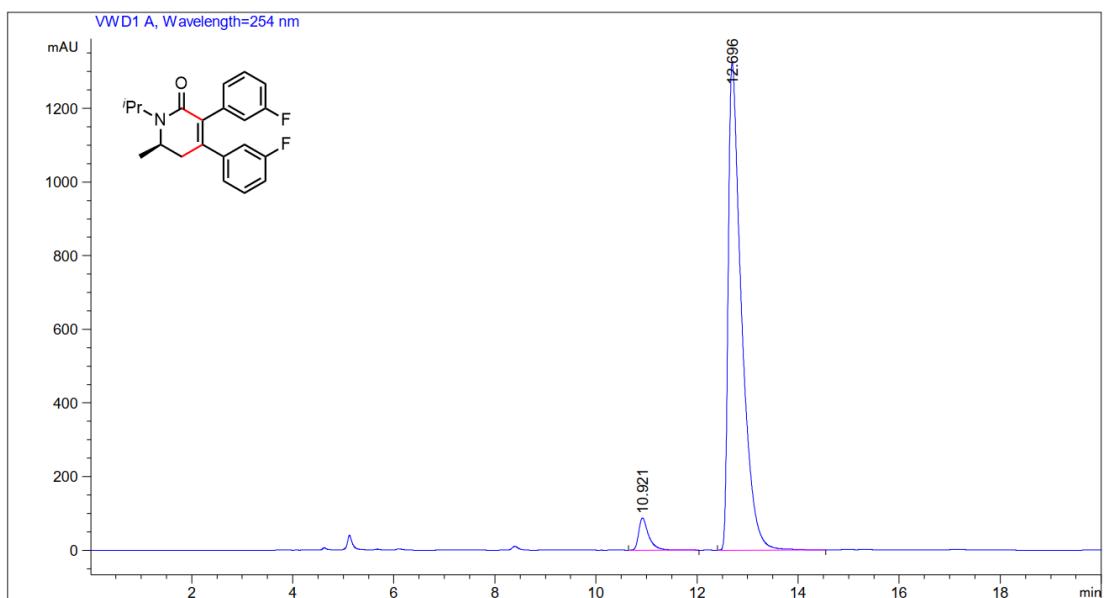
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.548	BB	0.2792	1438.64929	77.28924	50.7753
2	17.938	BB	0.4170	1394.71533	50.69541	49.2247



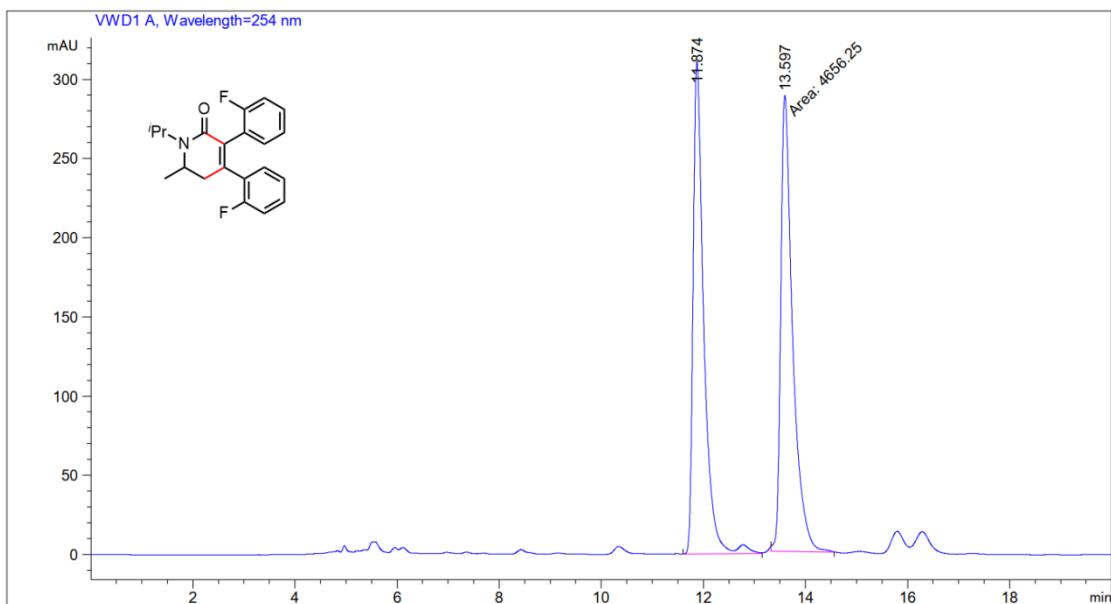
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.757	BB	0.2707	65.17493	3.66090	2.6033
2	18.012	BB	0.4129	2438.39404	89.21936	97.3967



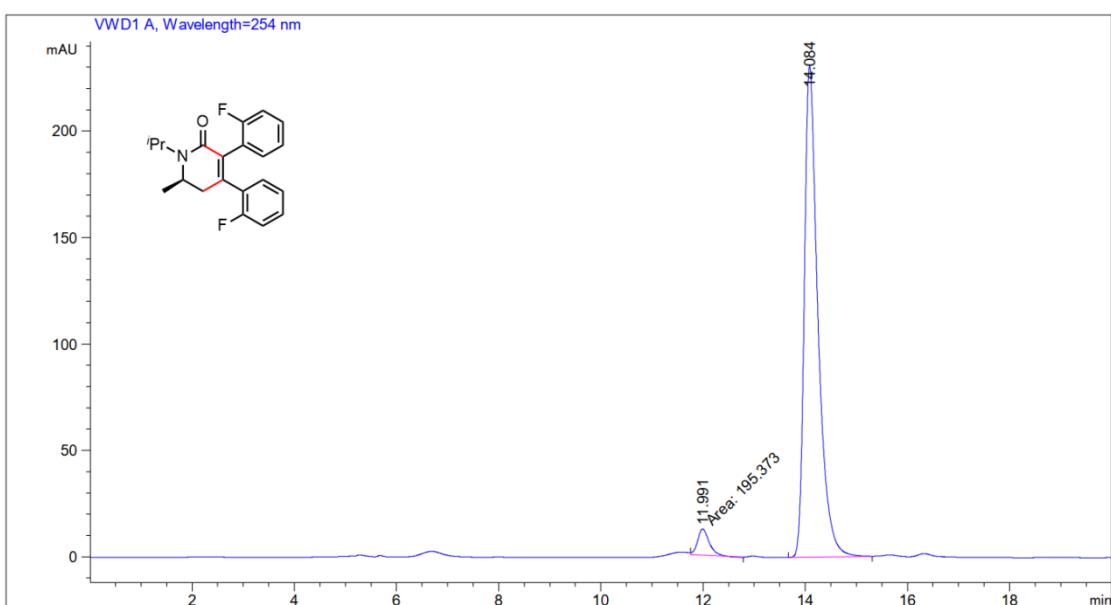
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.707	MM	0.2604	1759.81726	112.61775	49.5921
2	12.843	BB	0.2963	1788.76965	91.41318	50.4079



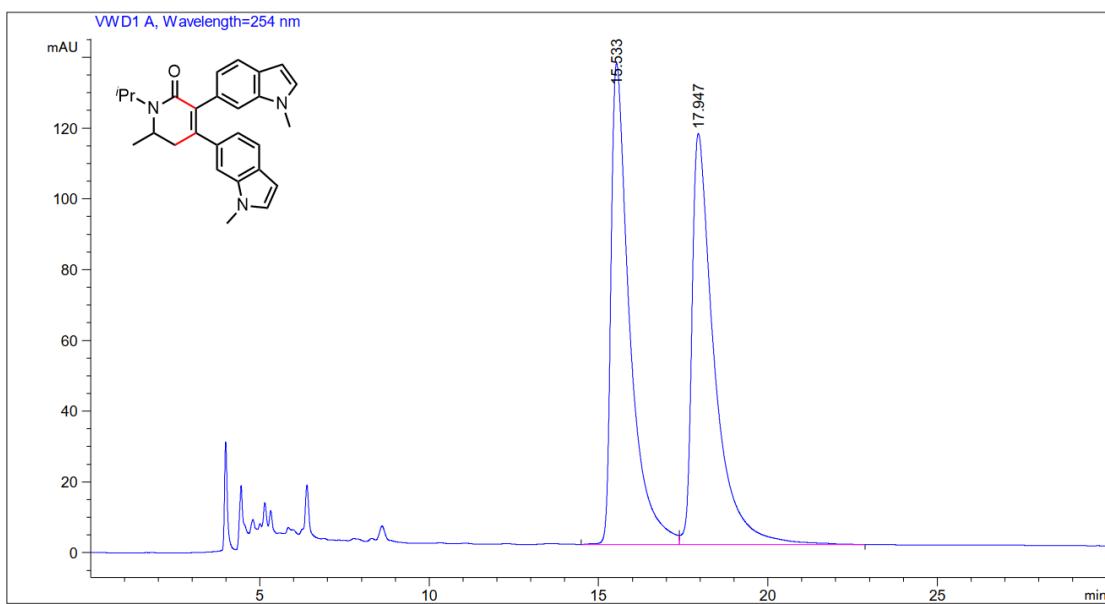
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.921	BB	0.2022	1194.56250	87.52800	4.7036
2	12.696	BB	0.2663	2.42021e4	1323.60791	95.2964



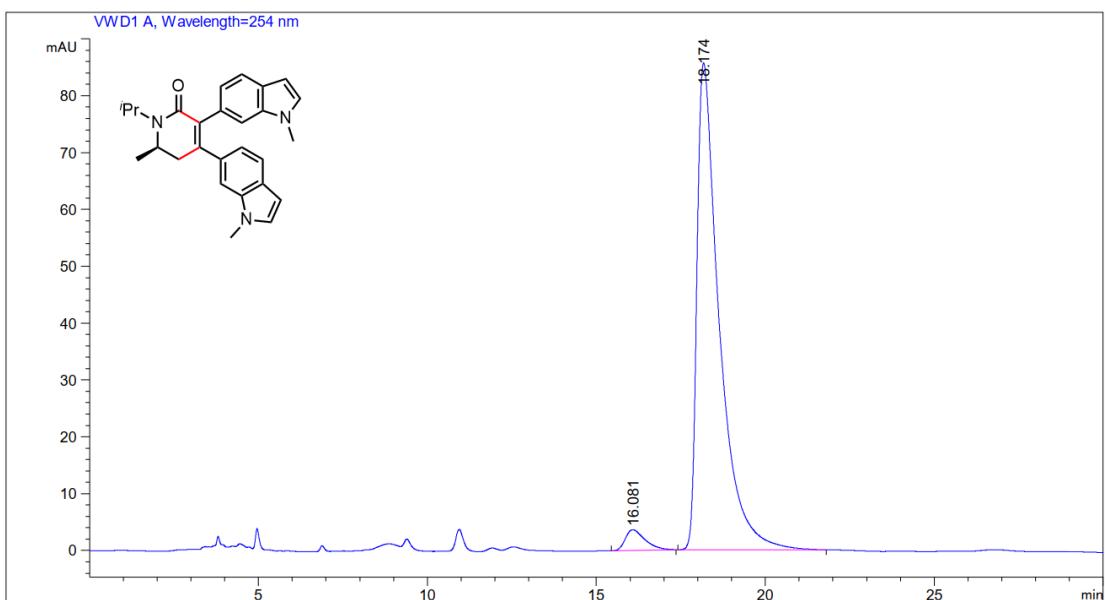
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.874	BV R	0.2121	4528.54980	310.63483	49.3048
2	13.597	MM	0.2694	4656.24805	288.03339	50.6952



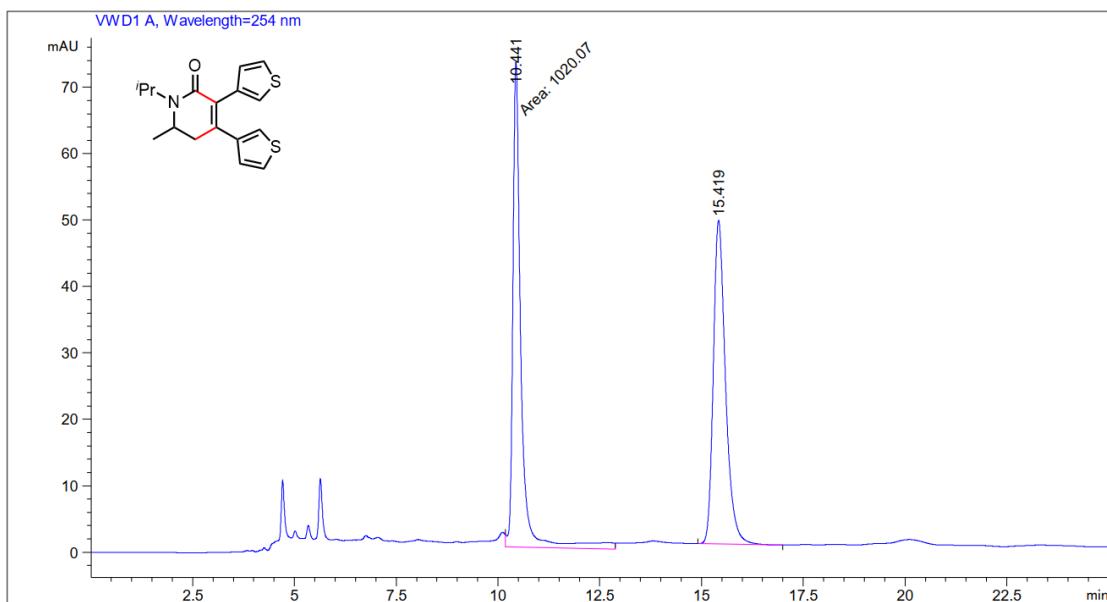
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.991	MM	0.2631	195.37259	12.37577	4.3738
2	14.084	BB	0.2759	4271.52393	230.80164	95.6262



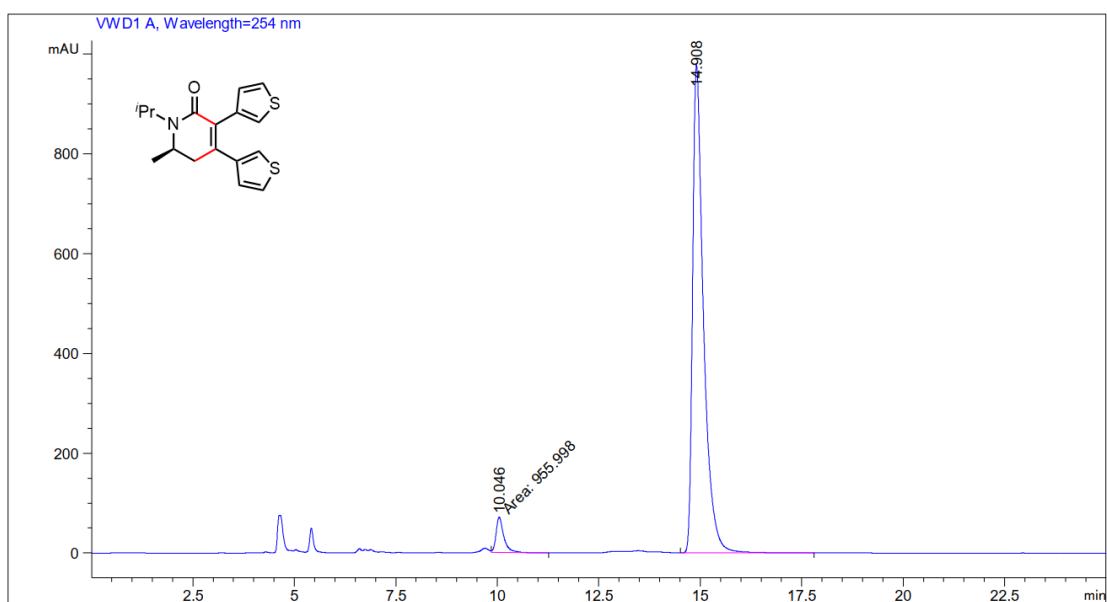
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.533	BV	0.5577	5233.40088	136.07433	49.5768
2	17.947	VB	0.6774	5322.75684	116.19913	50.4232



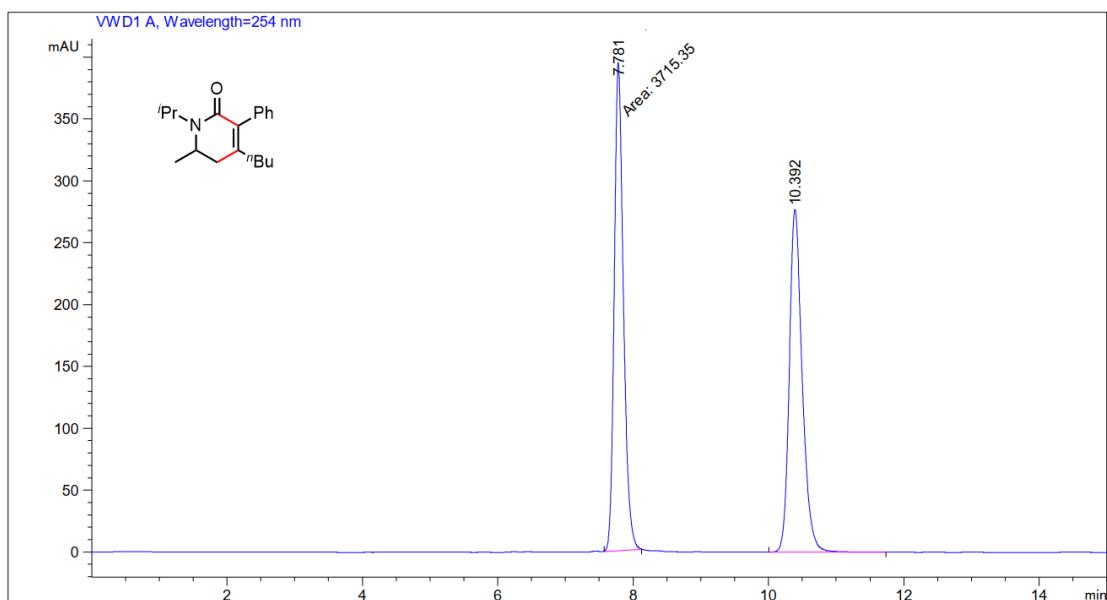
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.081	BB	0.5875	148.01460	3.66252	3.6366
2	18.174	BB	0.6684	3922.17407	85.61866	96.3634



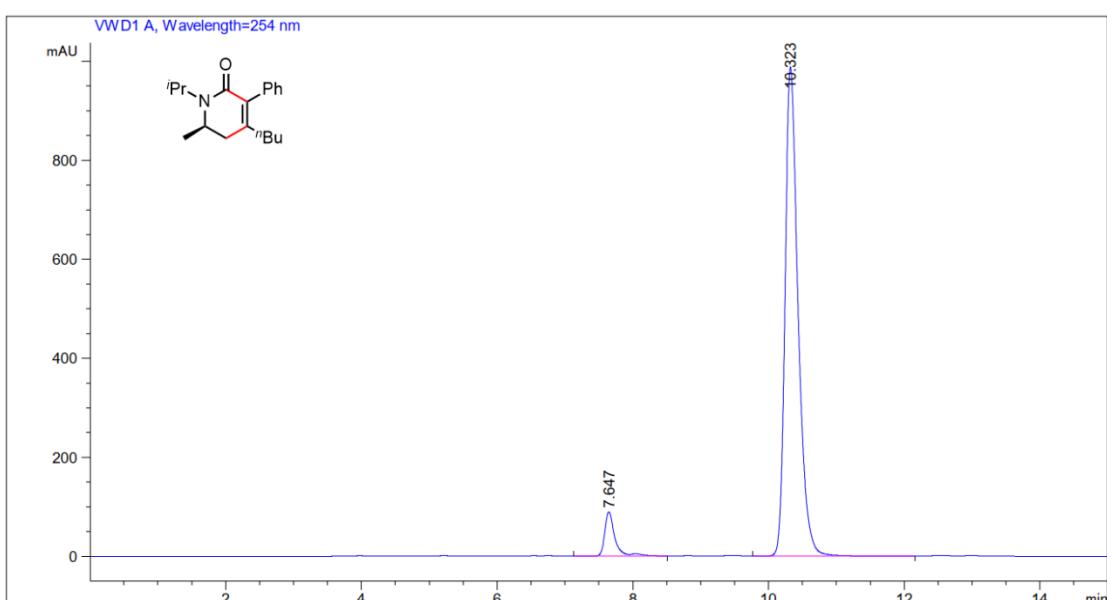
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.441	MM	0.2329	1020.07391	73.00089	50.0849
2	15.419	BB	0.3155	1016.61456	48.71410	49.9151



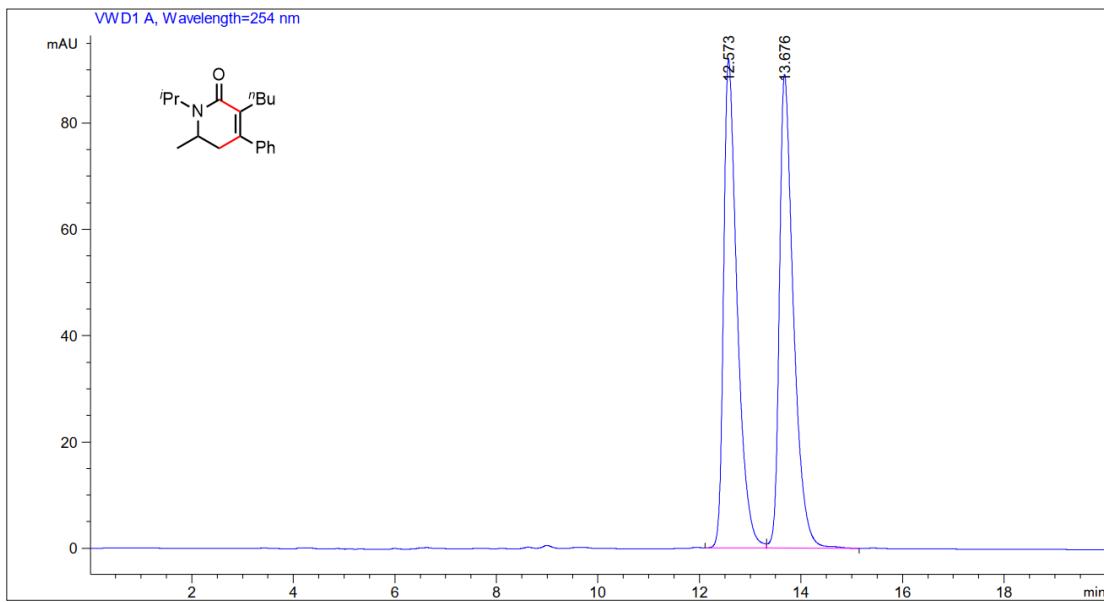
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.046	MM	0.2244	955.99835	71.00436	4.9803
2	14.908	BB	0.2747	1.82396e4	977.65356	95.0197



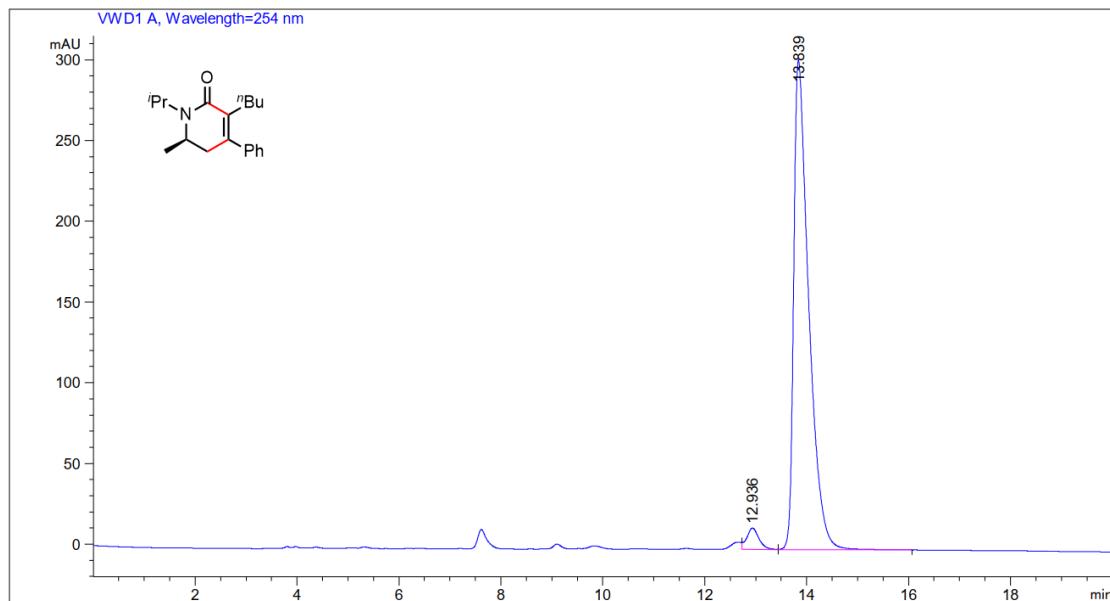
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.781	MM	0.1570	3715.34619	394.33624	50.2850
2	10.392	BB	0.2007	3673.23560	276.97437	49.7150



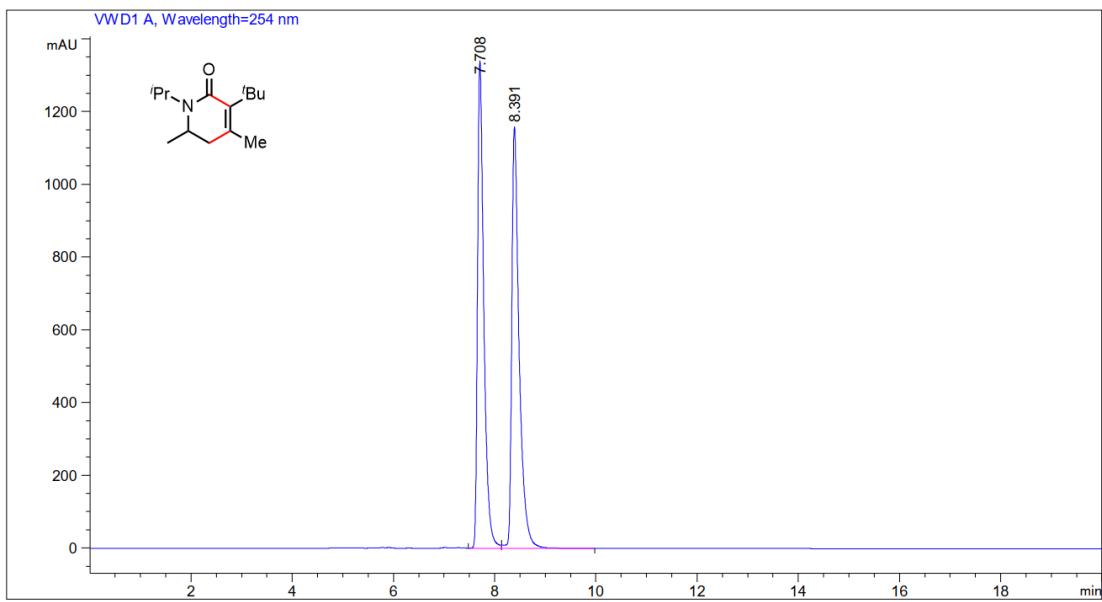
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.647	VV R	0.1470	939.49829	89.45899	6.6544
2	10.323	BB	0.2026	1.31789e4	988.03833	93.3456



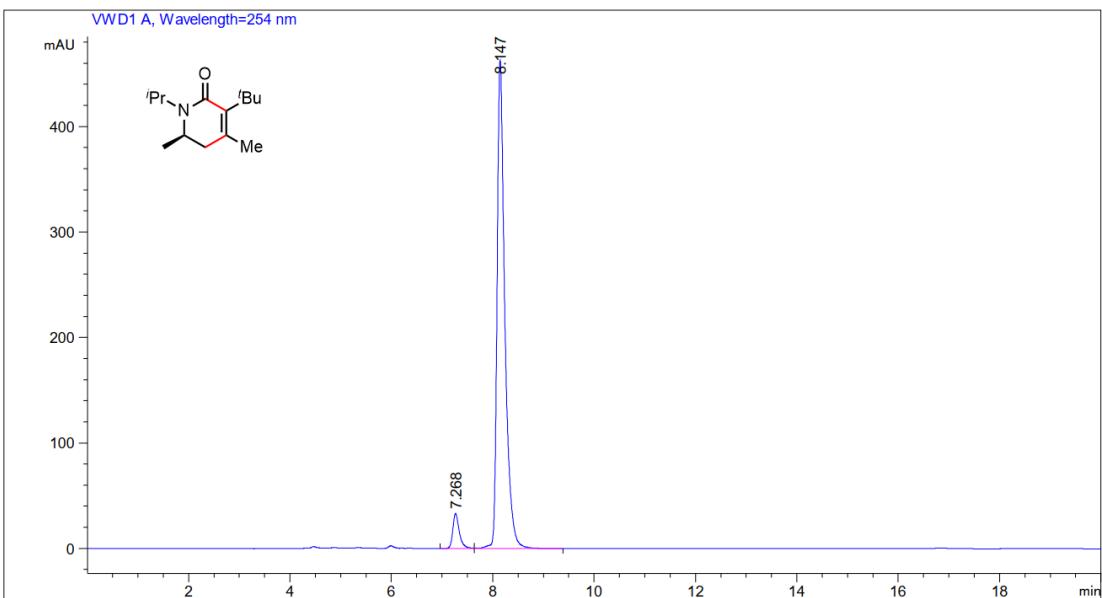
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.573	BV	0.2798	1707.34399	91.86300	49.8252
2	13.676	VB	0.2870	1719.32373	89.16744	50.1748



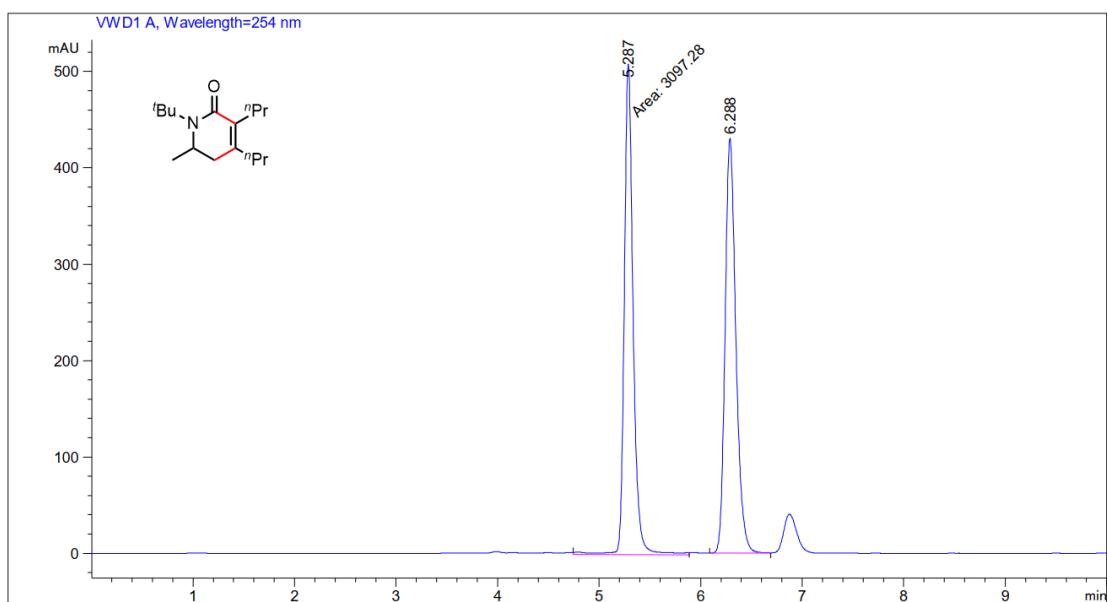
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.936	VV	0.2492	224.76772	13.36400	3.5028
2	13.839	VB	0.3082	6192.01221	303.21664	96.4972



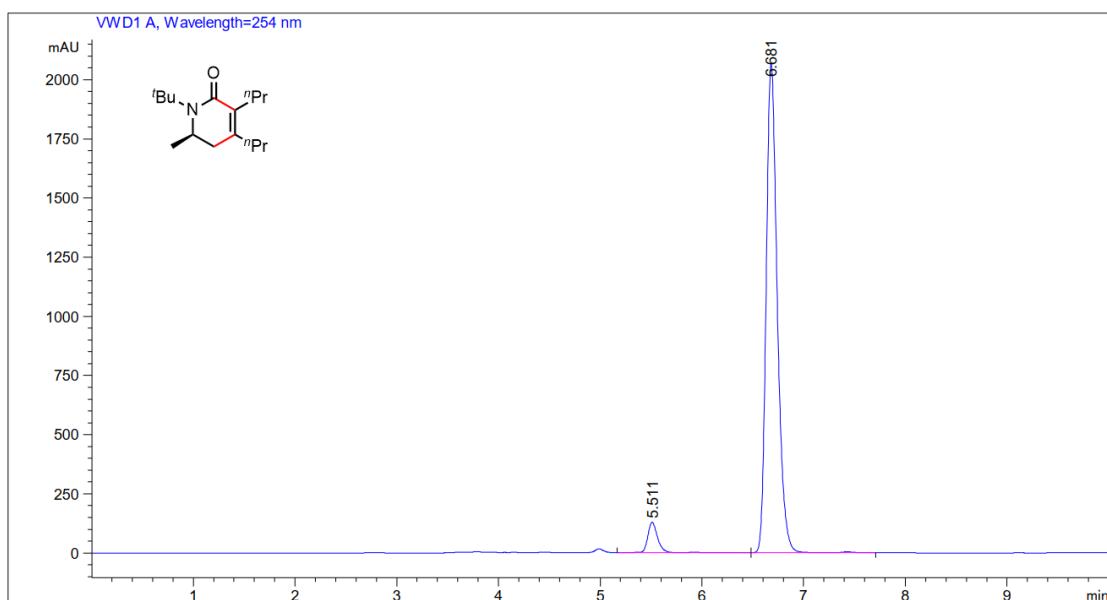
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.708	BV	0.1282	1.15189e4	1340.55432	49.6020
2	8.391	VB	0.1488	1.17037e4	1158.93188	50.3980



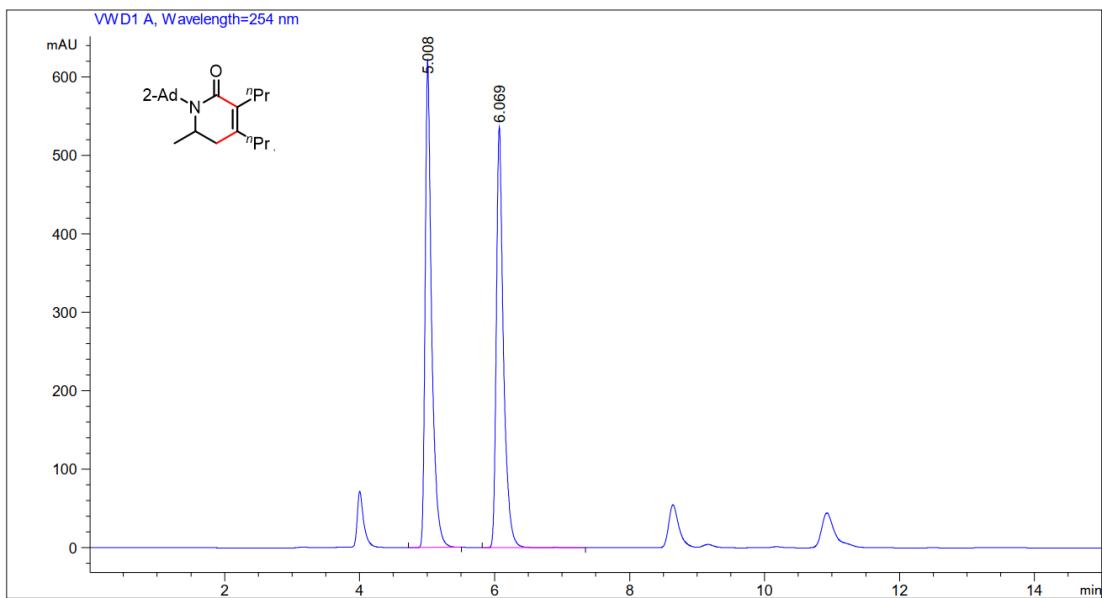
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.268	BV	0.1347	302.16092	33.34755	5.7759
2	8.147	VB	0.1563	4929.25439	462.69647	94.2241



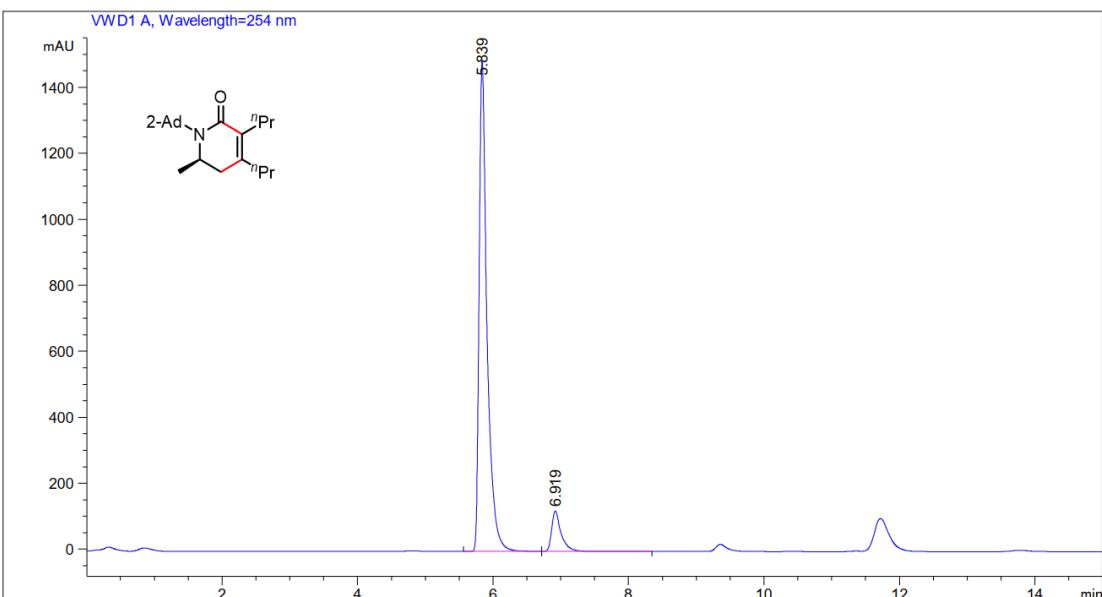
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.287	MM	0.1013	3097.28467	509.33957	49.3942
2	6.288	BV	0.1131	3173.25732	430.14505	50.6058



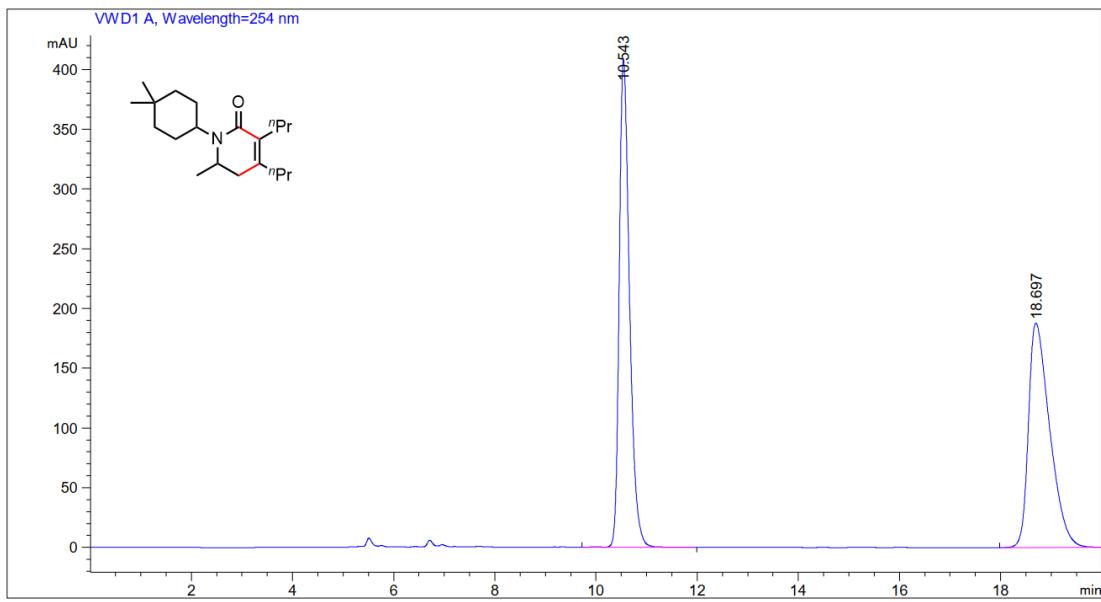
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.511	BV R	0.1015	874.16156	128.71805	5.2940
2	6.681	BV R	0.1161	1.56380e4	2065.92261	94.7060



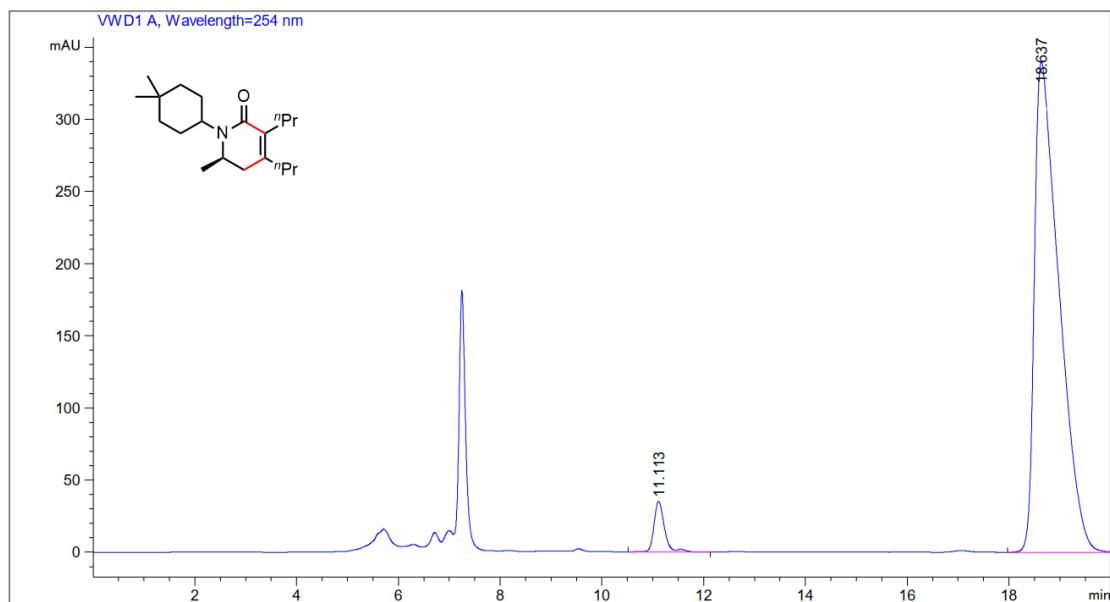
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.008	BB	0.0993	4170.25098	621.04266	51.3177
2	6.069	BV R	0.1090	3956.09106	536.39435	48.6823



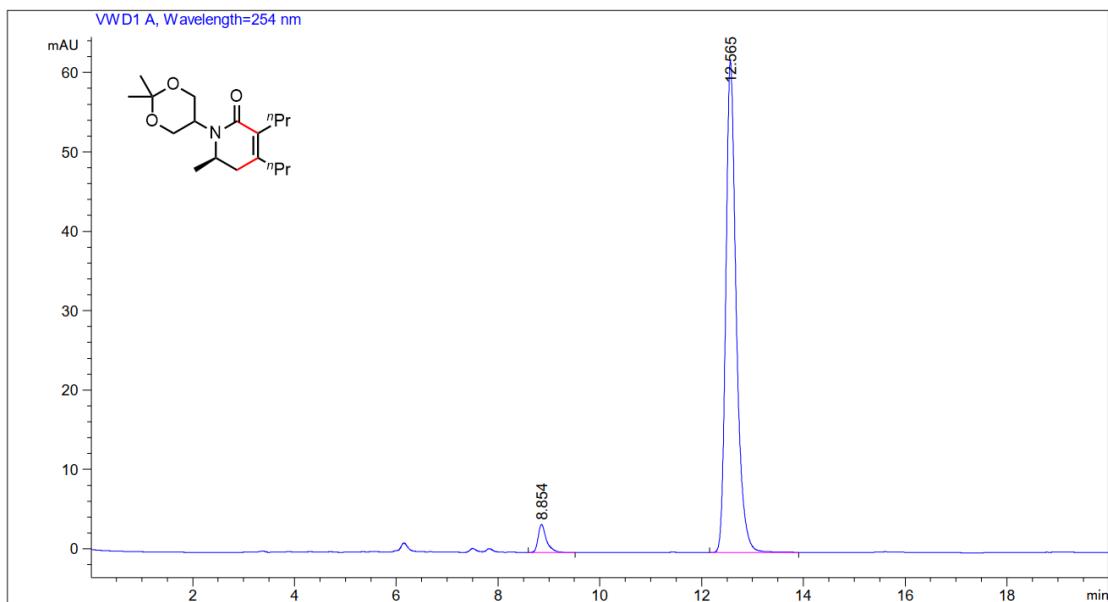
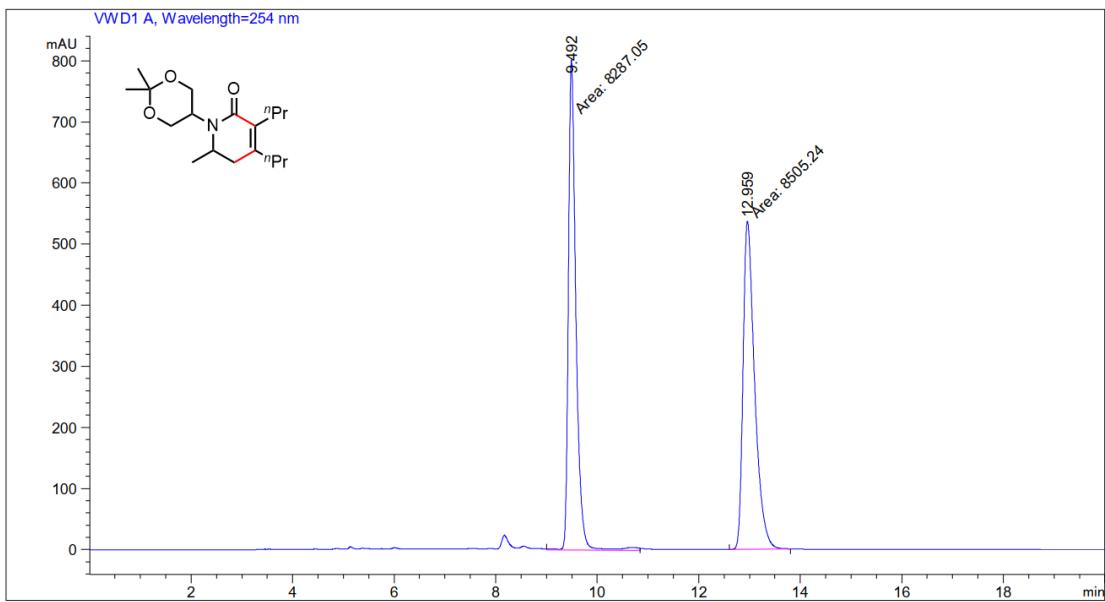
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.839	BB	0.1184	1.20068e4	1483.70850	90.9879
2	6.919	BV R	0.1411	1189.23926	122.65022	9.0121

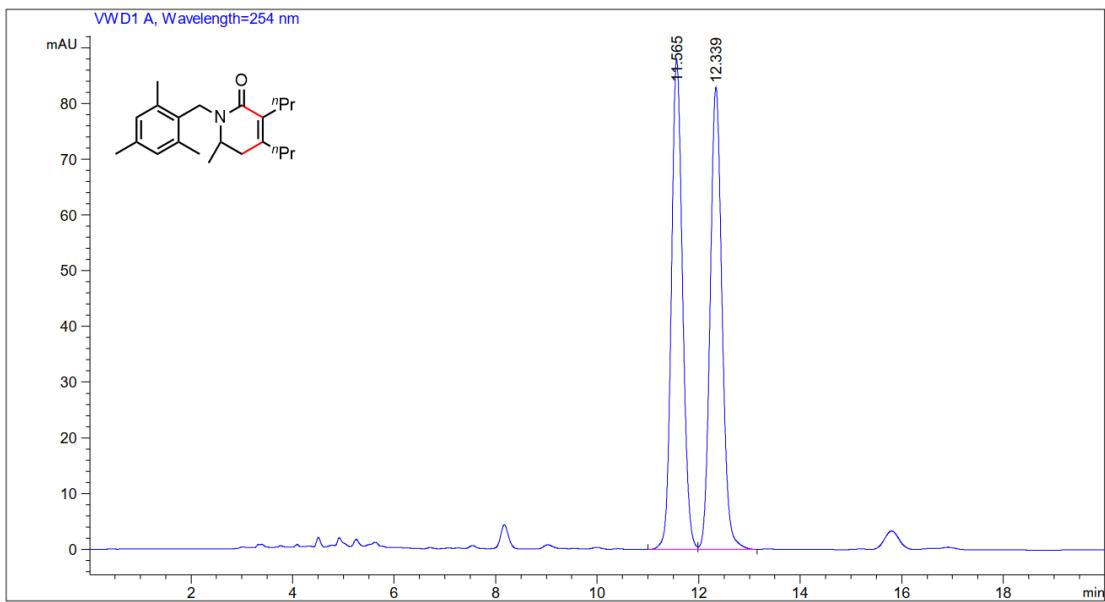


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.543	VB R	0.2171	5777.34473	408.19083	51.2989
2	18.697	BBA	0.4357	5484.77295	187.79933	48.7011

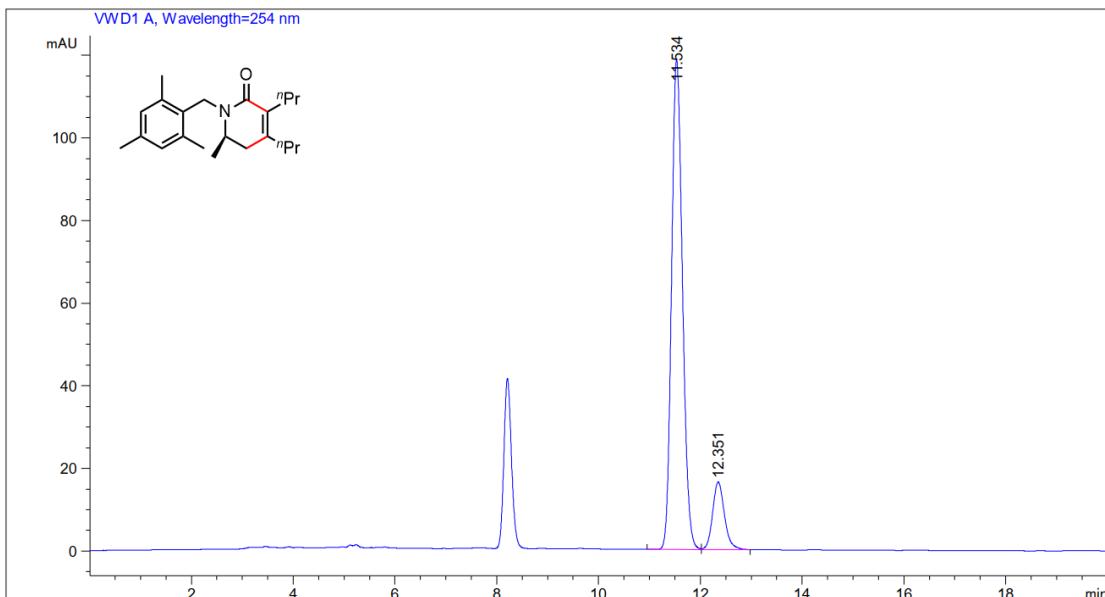


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.113	BV R	0.2127	506.41702	35.17865	4.2574
2	18.637	BBA	0.4719	1.13885e4	339.86777	95.7426

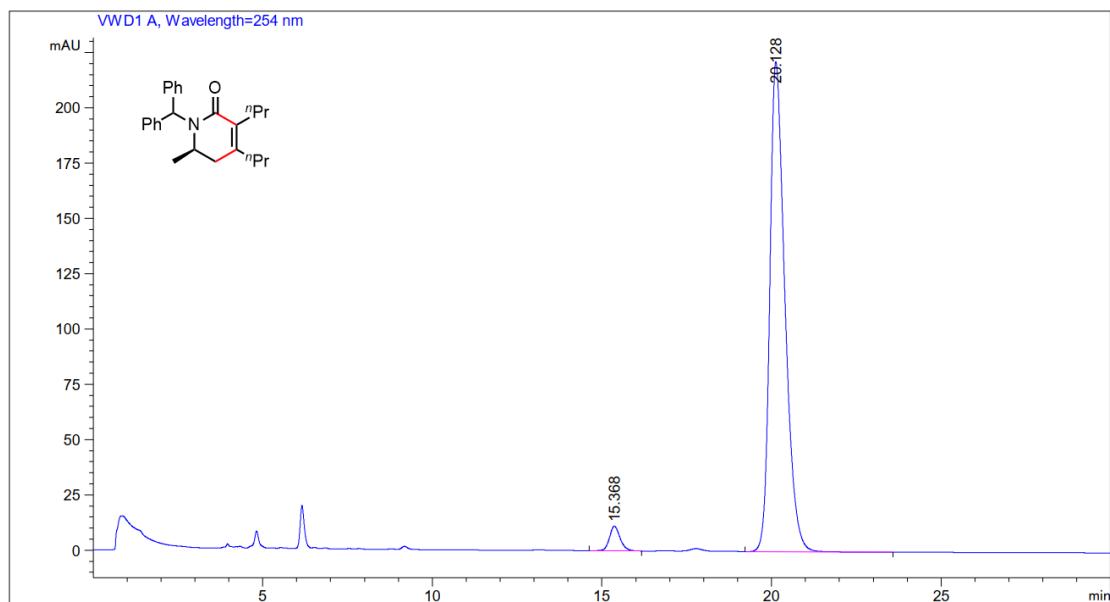
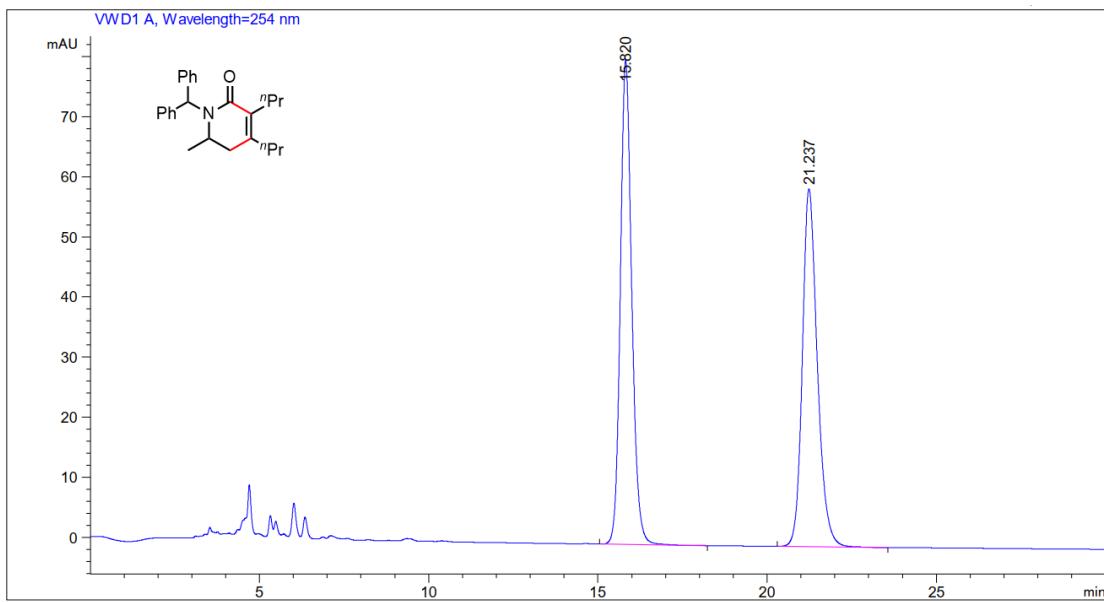


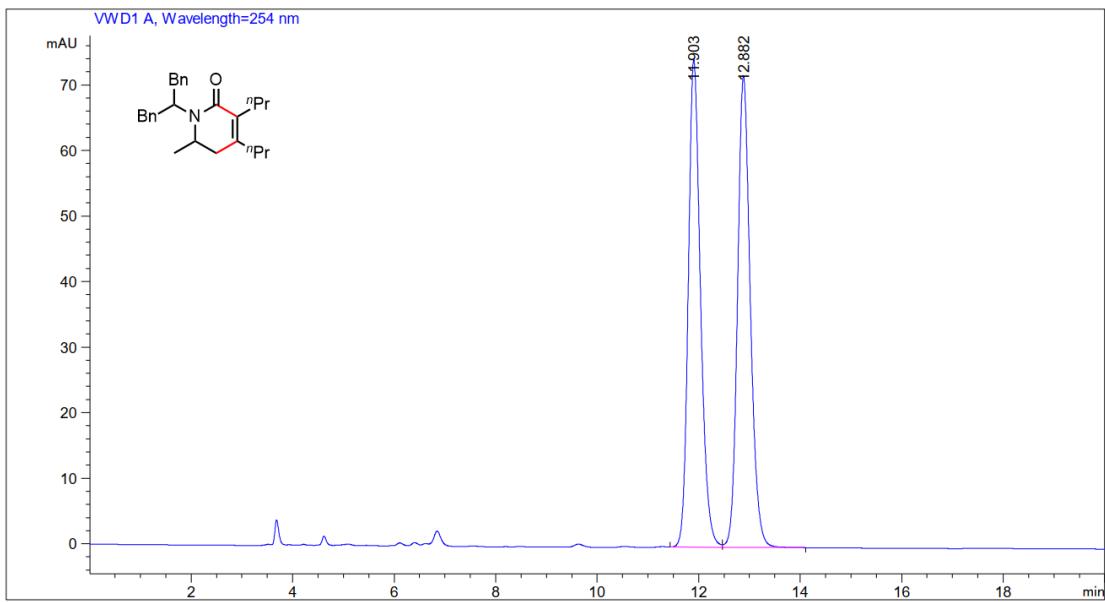


Peak #	RetTime [min]	Type	width [min]	Area [mAU * s]	height [mAU]	Area %
1	11.565	BV	0.2362	1341.75671	87.84230	49.9630
2	12.339	VB	0.2510	1343.74243	82.93308	50.0370

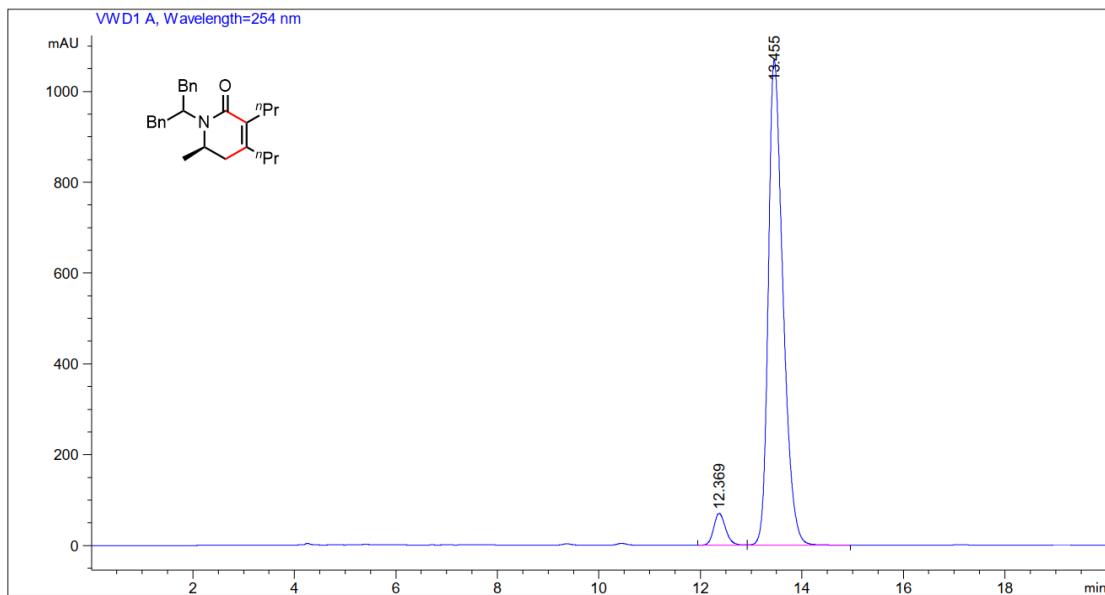


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.534	BV	0.2340	1767.11951	118.51701	86.9820
2	12.351	VB	0.2486	264.47162	16.36062	13.0180

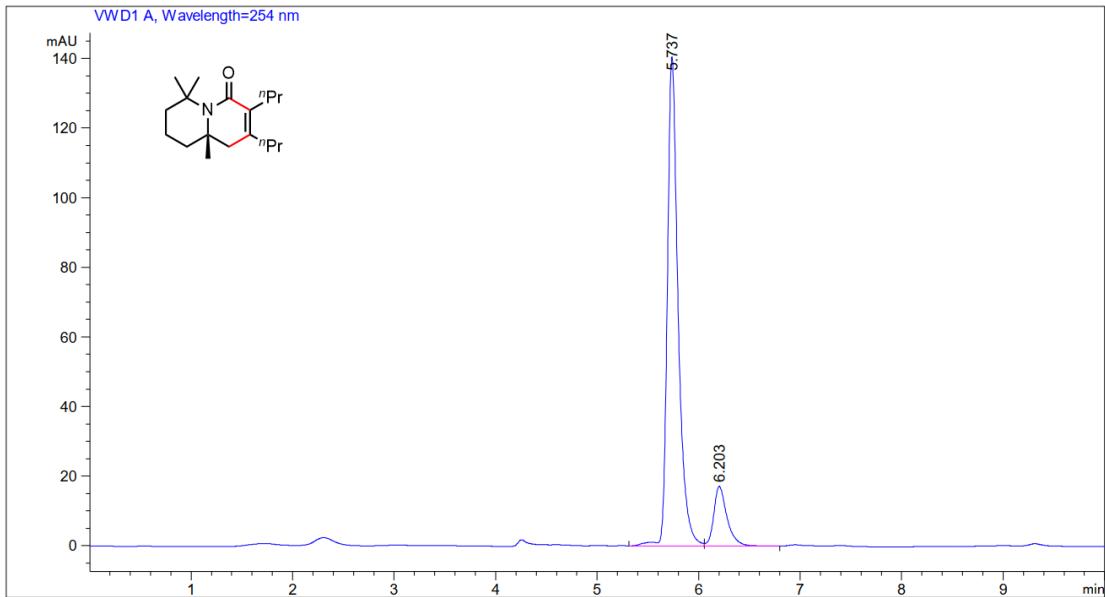
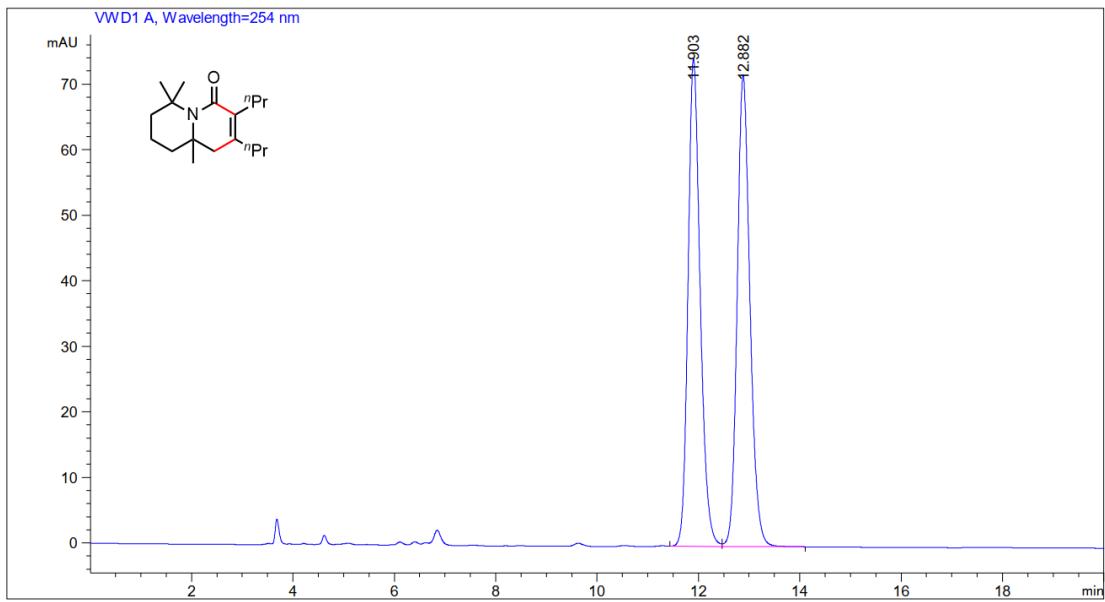


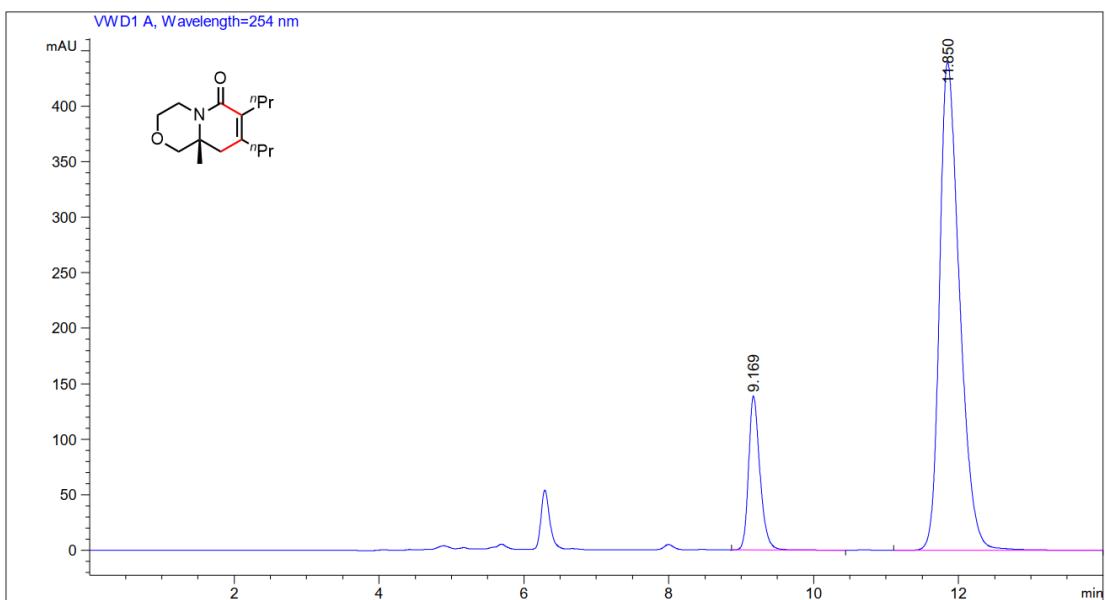
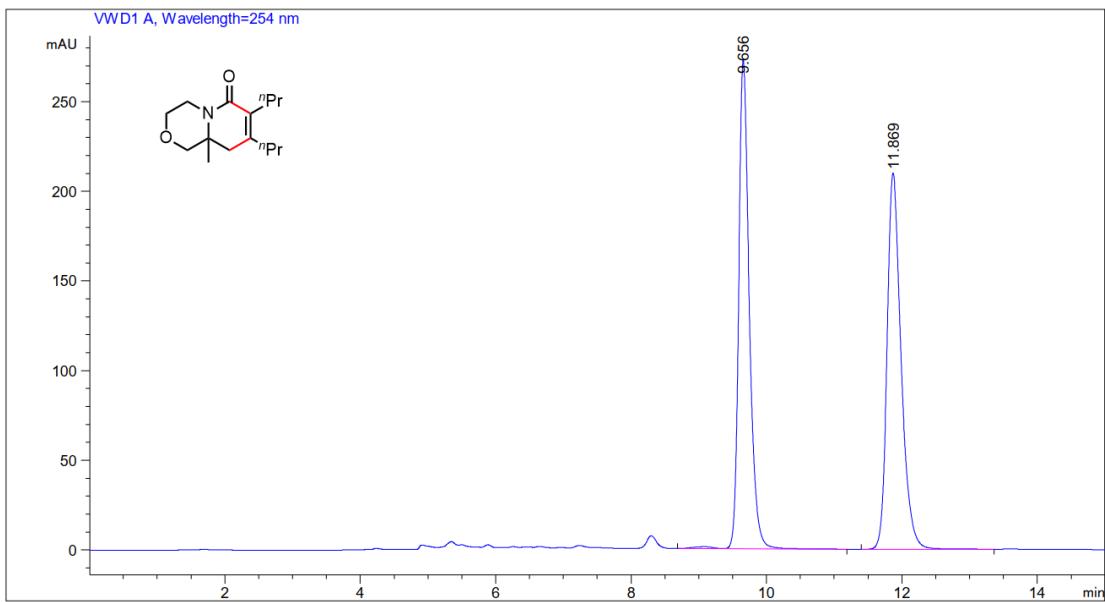


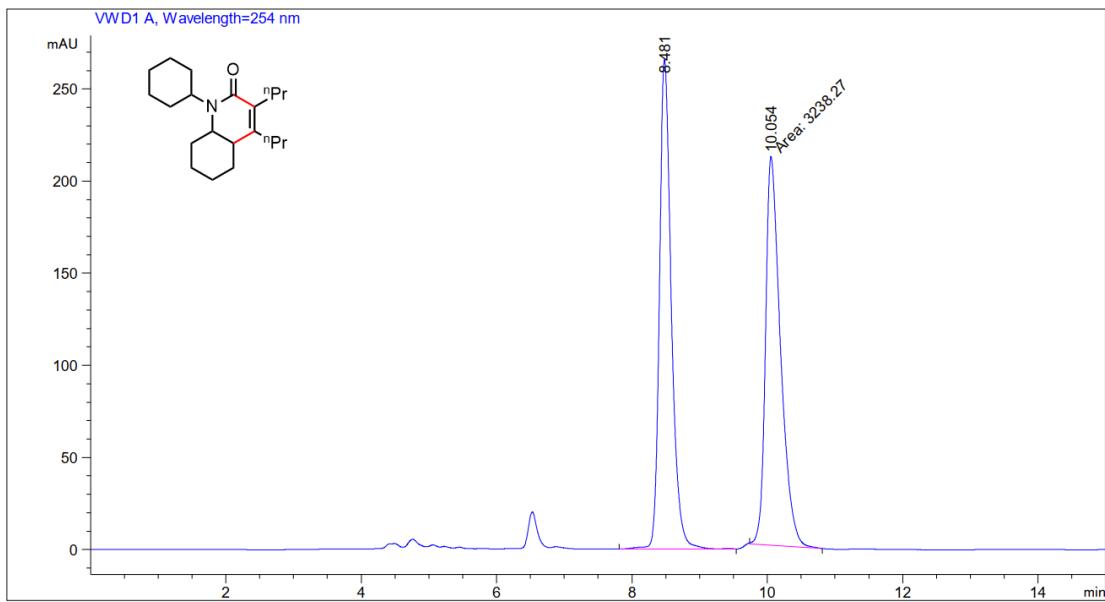
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.903	BV	0.2543	1237.97485	74.34295	49.6544
2	12.882	VB	0.2667	1255.20959	71.88953	50.3456



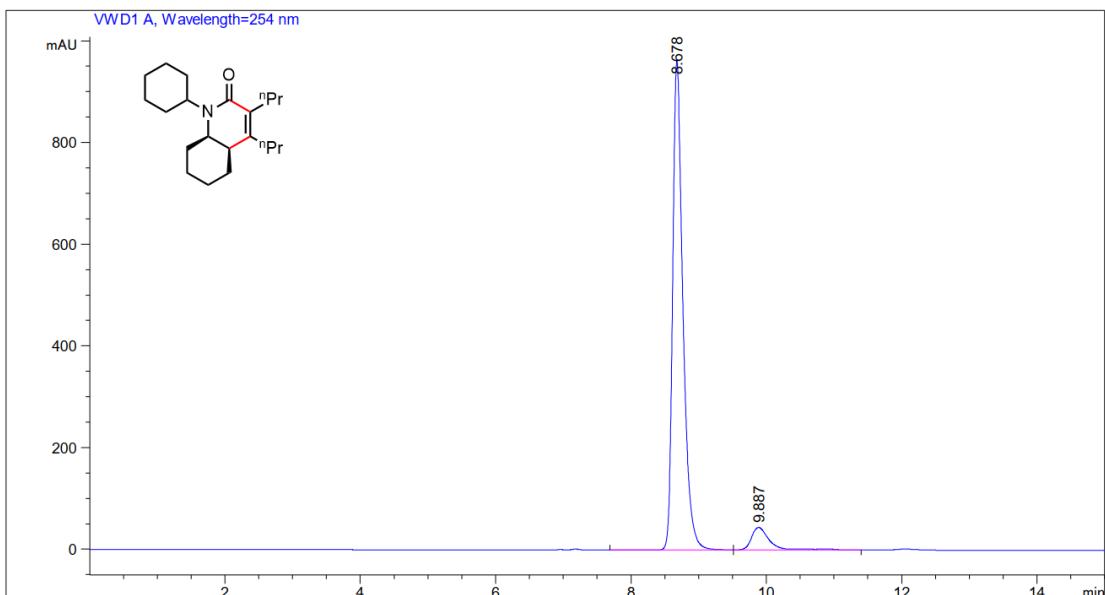
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.369	BV	0.2558	1138.94397	70.02484	5.0415
2	13.455	VB	0.2991	2.14526e4	1069.34180	94.9585



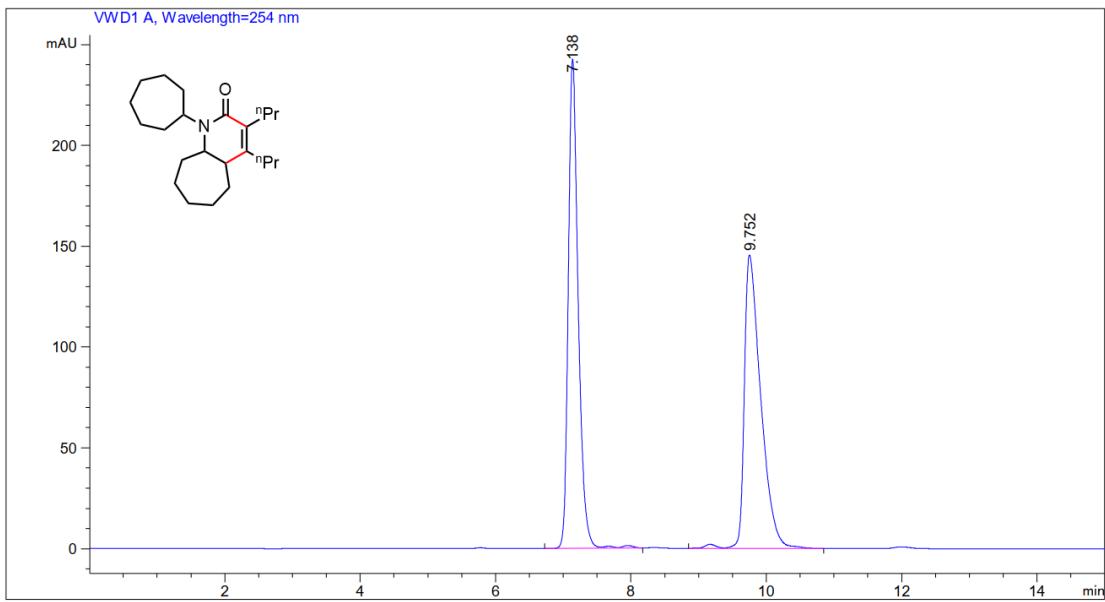




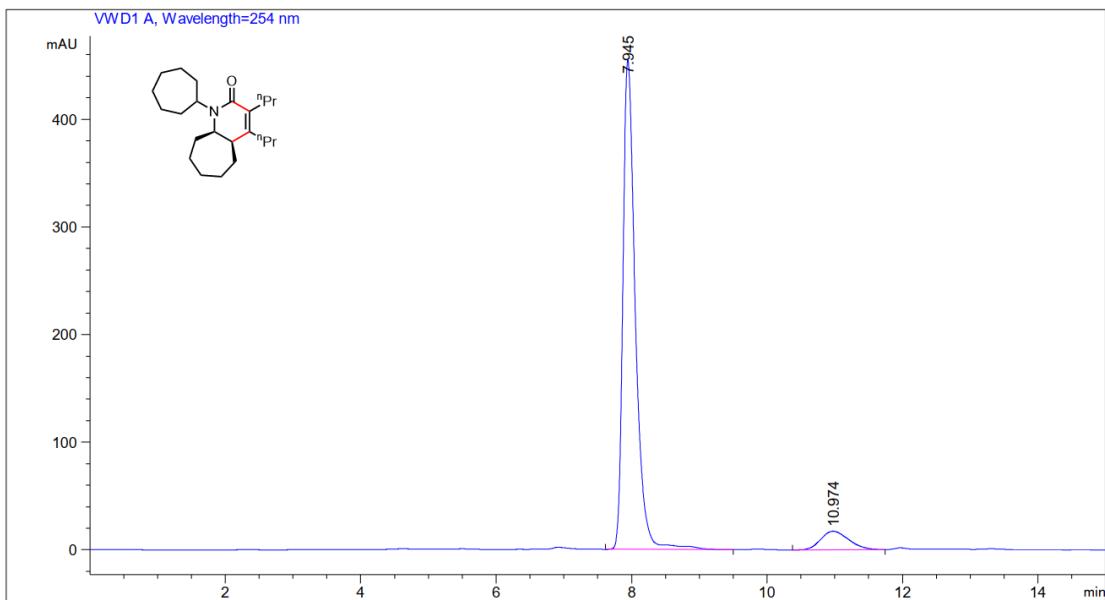
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.481	BV R	0.1840	3233.04565	265.55466	49.9596
2	10.054	MM	0.2557	3238.26904	211.04001	50.0404



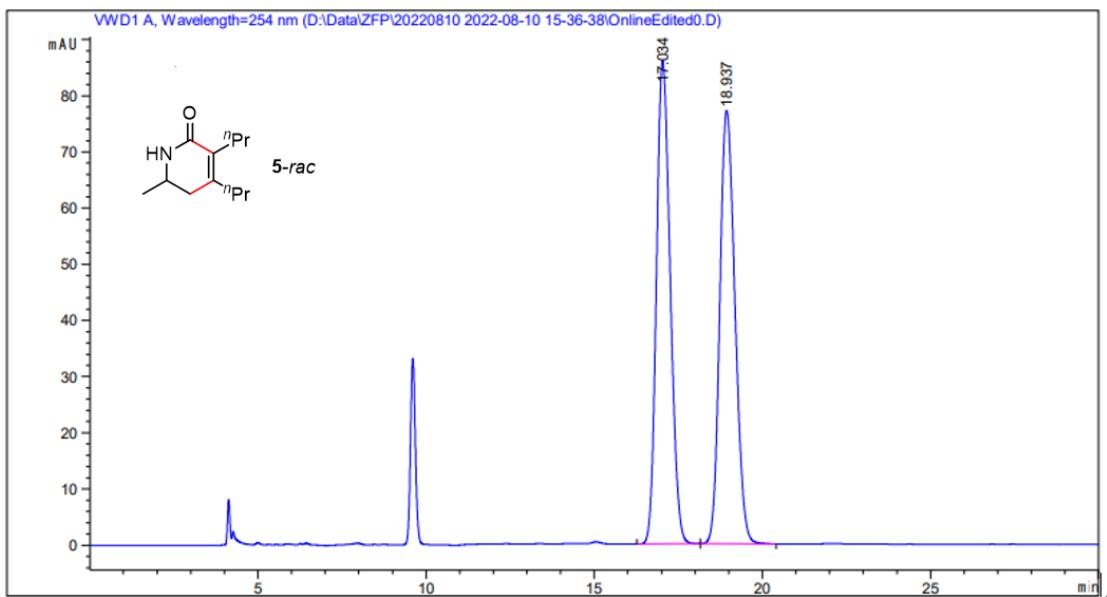
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.678	VB R	0.1578	1.01190e4	961.61035	92.2813
2	9.887	BV R	0.2588	846.38684	44.42161	7.7187



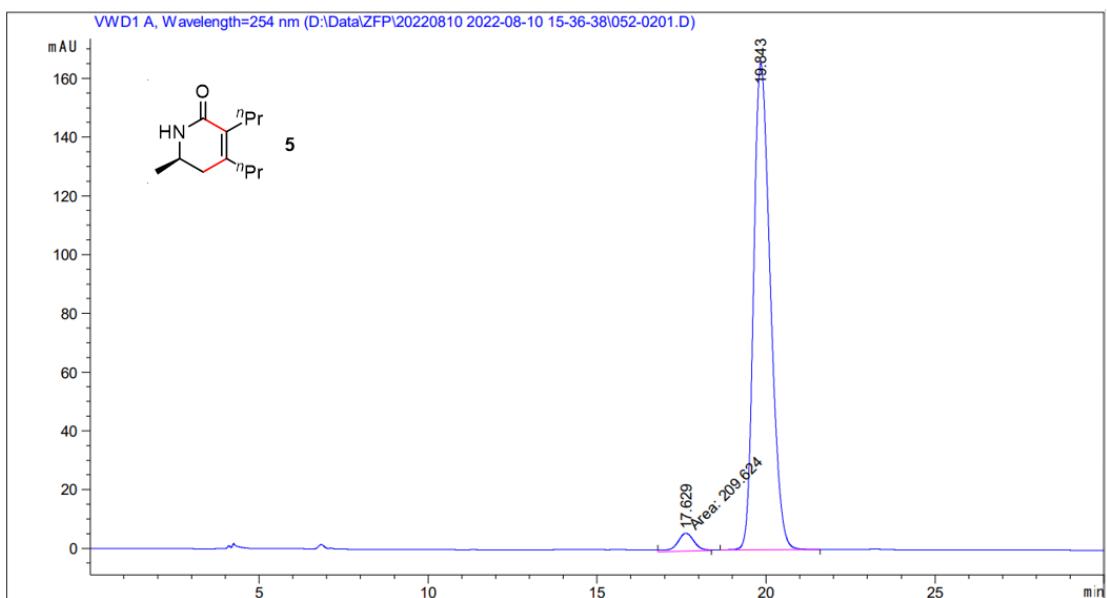
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.138	BV R	0.1539	2473.19604	242.66513	50.1001
2	9.752	VB R	0.2487	2463.31689	145.56787	49.8999



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.945	BV R	0.1910	5812.20508	454.60834	92.2220
2	10.974	BB	0.4396	490.20026	17.19588	7.7780



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.034	BB	0.4468	2439.14185	86.01394	50.2291
2	18.937	BB	0.4937	2416.88892	77.09595	49.7709



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.629	MM	0.5739	209.62392	6.08773	3.5553
2	19.843	BB	0.5312	5686.41650	165.76669	96.4447