

Supporting Information

Pd-Catalyzed C–S Activation/Isocyanide Insertion/Hydrogenation Enables a Selective Aerobic Oxidation/Cyclization

Jian Chang[†], Bangyu Liu[†], Yang Yang[†], and Mang Wang^{*†,‡}

[†]Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Faculty of Chemistry, Northeast Normal University, Changchun 130024, China

[‡]State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, China

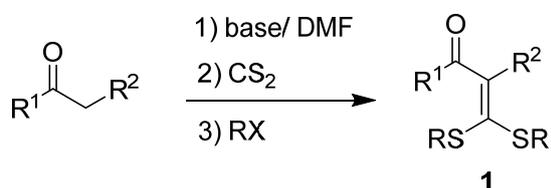
Table of contents

I. General	S2
II. Synthetic procedures/analytical data of compounds 1	S2
III. Synthetic procedures/analytical data of compounds 2, 3, 4a, 5a, 6a, 7	S4
IV. Crystal data and ORTEP drawing of compound 3a	S12
V. Investigations of the reaction mechanism.....	S13
VI. References.....	S16
VII. Copies of ¹ H NMR and ¹³ C NMR spectra of new compounds 1, 2, 3, 4a, 5a, 6a, 7	S17

I. General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H NMR and ^{13}C NMR spectra were recorded at 25°C on a Varian 500 MHz or 400 MHz and 125 MHz, and using TMS as internal standard. High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF II focus spectrometer (ESI). Melting points were uncorrected. DMSO was dried over anhydrous Na_2SO_4 for 48h. Compound **3a** with dimension 0.40 × 0.39 × 0.38 mm was glued on a glass fiber. Data were collected at 293 K using graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) and Bruker APEX CCD area-detector in the range $3.00^\circ < \theta < 25.99^\circ$. Substrates **1** were prepared following the known procedure.¹ **1a**,² **1b**,² **1c**,³ **1e**,² **1i**,⁴ **1j**,⁵ **1k**,⁶ **1l**,¹ **1m**,⁷ **1n**,⁷ **1q**,⁸ are known compounds.

II. Synthetic procedures/analytical data of compounds **1**



General procedure for the synthesis of ketene dithioacetals of 1a-i, 1l-q (taking **1a** as an example): To a well-stirred suspension of 1-(4-fluorophenyl)propan-2-one (6.7 mL, 50 mmol), K_2CO_3 (17.2 g, 125 mmol) and DMF (30 mL) was stirred at room temperature for 0.5 h. Then the reaction mixture was added CS_2 (3.3 mL, 55 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, EtBr (8.2 mL, 110 mmol) was added dropwise within 15 min. The mixture was allowed to warm to room temperature and stirred for 14 h, and then poured into ice-water (80 mL) under stirring and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phase was washed with water (3 × 25 mL), dried over anhydrous MgSO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ ethyl acetate 60/1, v/v) to give 4,4-bis(ethylthio)-3-(4-fluorophenyl)but-3-en-2-one **1a** (12.8 g, 90%) as a yellow solid.

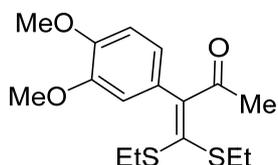
General procedure for the synthesis of ketene dithioacetals 1j: To a well-stirred suspension of anhydrous t-BuOK (4.94 g, 44 mmol) and butan-2-one (1.79 mL, 20 mmol) in 40 mL of anhydrous DMF were added CS_2 (1.32 mL, 20 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 1.5 h, MeI (2.49 mL, 40 mmol) was added dropwise within 30 min. The mixture was allowed to warm to room temperature and stirred for 5 h, and then poured into saturated aqueous NH_4Cl (100 mL) under stirring. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with water (3 × 15 mL), dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate: 80/1, v/v) to give 3-methyl-4,4-bis(methylthio)but-3-en-2-one **1j** (705 mg, 20%) as a light yellow oil.

General procedure for the synthesis of ketene dithioacetals 1k: To a solution of **1m** (1.16 g, 5.0 mmol) in 20 mL of CH_2Cl_2 was added concentrated H_2SO_4 (1.1 mL, 20 mmol) dropwise within 15 min at 0 °C. The mixture

was allowed to warm to room temperature and stirred for 10 h, and then poured onto saturated NaCl ice-water (50 mL) under stirring. The mixture was neutralized with aqueous NaHCO₃, and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate 20/1, V/V) to give 4,4-bis(ethylthio)but-3-en-2-one **1k** (855 mg, 90%) as a white solid.

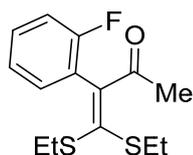
General procedure for the synthesis of ketene dithioacetals 1r: To a stirred solution of **1c** (1.48 g, 5.0 mmol) in 20 mL of CH₂Cl₂ was added concentrated H₂SO₄ (1.1 mL, 20 mmol) dropwise within 15 min at 0 °C. The mixture was allowed to warm to room temperature and stirred for 48 h, and then poured onto saturated NaCl ice-water (50 mL) under stirring. The mixture was neutralized with aqueous NaHCO₃, and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ ethyl acetate 100/1, V/V) to give (2-(4-methoxyphenyl)ethene-1,1-diyl)bis(ethylsulfane) **1'r** (698 mg, 55%) as a colorless liquid. Then to a stirred solution of POCl₃ (0.18 mL, 2.0 mmol) in 5.0 mL anhydrous DMF was added **1'r** (254 mg, 1.0 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight, and then poured onto aqueous K₂CO₃ (15 mL) and stirring for 20 minutes. Then the mixture was neutralized with dilute HCl, and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ ethyl acetate 30/1, V/V) to give 3,3-bis(ethylthio)-2-(4-methoxyphenyl)acrylaldehyde **1r** (225 mg, 80%) as a yellow oil.

3-(3,4-Dimethoxyphenyl)-4,4-bis(ethylthio)but-3-en-2-one (**1d**)



Yellow oil; 81% yield (13.2 g); ¹H NMR (500 MHz, CDCl₃) δ 1.17 (t, *J* = 7.5 Hz, 3H), 1.32 (t, *J* = 7.5 Hz, 3H), 2.30 (s, 3H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.88 (q, *J* = 7.5 Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.86 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 202.0, 149.2, 148.8, 148.5, 133.5, 128.3, 121.8, 111.7, 110.5, 55.8, 55.7, 30.3, 28.3, 27.9, 14.6, 14.5. HRMS (ESI-TOF) calcd for C₁₆H₂₃O₃S₂⁺ ([M+H]⁺) 327.1083, found 327.1081.

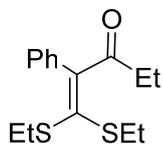
4,4-Bis(ethylthio)-3-(2-fluorophenyl)but-3-en-2-one (**1f**)



Yellow oil; 82% yield (11.6 g); ¹H NMR (500 MHz, CDCl₃) δ 1.15 (t, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7.5 Hz, 3H), 2.29 (s, 3H), 2.66 (q, *J* = 7.5 Hz, 2H), 2.93 (q, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 8.5 Hz, 1H), 7.16 (t, *J* = 8.5 Hz, 1H), 7.25 (t, *J* = 8.5 Hz, 1H), 7.33 (t, *J* = 8.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 199.5, 159.7 (d, *J* = 244 Hz, 1C), 144.1, 140.5, 131.4 (d, *J* = 2.7 Hz, 1C), 130.1 (d, *J* = 7.6 Hz, 1C), 126.0 (d, *J* = 16.7 Hz, 1C), 124.1 (d, *J* = 3.4 Hz,

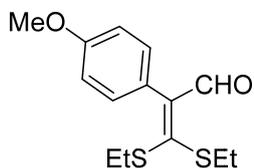
1C), 115.6 (d, $J = 22.0$ Hz, 1C), 30.2, 28.9, 28.7, 14.7, 14.6. **HRMS** (ESI-TOF) calcd for $C_{14}H_{18}FOS_2^+$ ($[M+H]^+$) 285.0778, found 285.0771.

1,1-Bis(ethylthio)-2-phenylpent-1-en-3-one (**1o**)



Light yellow oil; 76% yield (10.6 g); **1H NMR** (400 MHz, $CDCl_3$) δ 1.07 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 7.2$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 2.57 (q, $J = 7.2$ Hz, 2H), 2.66 (q, $J = 7.2$ Hz, 2H), 2.87 (q, $J = 7.2$ Hz, 2H), 7.28-7.38 (m, 5H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.7, 150.1, 136.3, 134.1, 128.9 (2C), 128.2 (2C), 128.0, 35.9, 28.3, 27.9, 14.6, 14.5, 7.9. **HRMS** (ESI-TOF) calcd for $C_{15}H_{21}OS_2^+$ ($[M+H]^+$) 281.1028, found 281.1024.

3,3-Bis(ethylthio)-2-(4-methoxyphenyl)acrylaldehyde (**1r**)

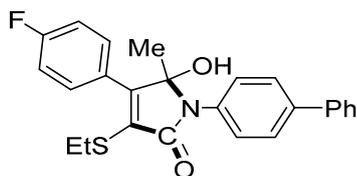


Yellow oil; 80% yield (225 mg) based on **1r**; **1H NMR** (400 MHz, $CDCl_3$) δ 1.16 (t, $J = 7.2$ Hz, 3H), 1.36 (t, $J = 7.2$ Hz, 3H), 2.58 (q, $J = 7.2$ Hz, 2H), 2.99 (q, $J = 7.2$ Hz, 2H), 3.82 (s, 3H), 6.93 (t, $J = 7.2$ Hz, 2H), 7.15 (t, $J = 7.2$ Hz, 2H), 10.40 (s, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 188.9, 159.9, 159.1, 143.9, 131.0 (2C), 127.9, 113.7 (2C), 55.1, 30.2, 28.7, 14.8, 14.4. **HRMS** (ESI-TOF) calcd for $C_{14}H_{19}O_2S_2^+$ ($[M+H]^+$) 283.0821, found 283.0825.

III. Synthetic procedures/analytical data of compound **2a**, **3**, **4a**, **5a**, **6a**, and **7**

General procedure for the synthesis of **2a:** To a dried three-necked flask were added **1a** (142 mg, 0.5 mmol), triphenylsilane (260 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), 4-isocyano-1,1'-biphenyl (269 mg, 1.5 mmol) and DMSO (5.0 mL), respectively, under N_2 . Then the mixture was heated to $90^\circ C$ and stirred for 7 h. After 4-isocyano-1,1'-biphenyl was consumed (monitored by TLC), the reaction mixture was poured into ice water (30 mL), extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with saturated aqueous NaCl (3×15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent, petroleum ether/ ethyl acetate: 25/1, v/v) to give **2a** (90 mg, 43%) as a brown solid. When H_2O (0.5 mL) was added, only trace amount of **2a** was detected with the recovery of **1a** in 95% yield.

1-([1,1'-Biphenyl]-4-yl)-3-(ethylthio)-4-(4-fluorophenyl)-5-hydroxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (**2a**)



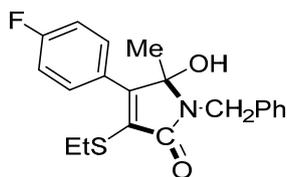
Brown solid; mp 148-149 °C; 43% yield (90 mg); ¹H NMR (500 MHz, CDCl₃) δ 1.22 (t, *J* = 7.5 Hz, 3H), 1.43 (s, 3H), 3.12 (q, *J* = 7.5 Hz, 2H), 3.21 (s, 1H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.58 (s, 4H), 7.84-7.87 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 166.9, 162.9 (d, *J* = 249.1 Hz, 1C), 153.8, 140.1, 139.4, 134.4, 131.1 (d, *J* = 8.1 Hz, 2C), 128.8 (2C), 127.8, 127.4, 127.3 (2C), 127.2, 126.9 (2C), 126.4 (2C), 115.2 (d, *J* = 21.4 Hz, 2C), 91.9, 26.1, 23.4, 14.9. HRMS (ESI-TOF) calcd for C₂₅H₂₃FNO₂S⁺ ([M+H]⁺) 420.1428, found 420.1423.

Synthetic procedures/analytical data of compounds 3

General procedure for the synthesis of 2a', 3a-3j, 3o and 3p (taking 3a as an example): To a dried three-necked flask were added 1a (142 mg, 0.5 mmol), triphenylsilane (156 mg, 0.6 mmol), Pd(PPh₃)₂Cl₂ (17.5 mg, 0.025 mmol), ethyl 2-isocyanoacetate (165 μL, 1.5 mmol) and DMSO (5.0 mL), respectively, under N₂. After the reaction mixture was stirred for 5 minutes at room temperature, H₂O (0.5 mL) was added by using a syringe. Then the mixture was heated to 70°C and stirred for 4 h. After 1a was consumed (monitored by TLC), the reaction mixture was poured into ice water (30 mL), extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 15 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent, petroleum ether/ethyl acetate: 12/1, v/v) to give 3a (152 mg, 86%) as a yellow solid. Generally, the reaction proceeding for longer time or at higher reaction temperature led to the formation of by-product 5a in 5-10% yield or 6a in 10-15% yield.

General procedure for the synthesis of 4a, 3k-3n, 3q (taking 3l as an example): To a dried three-necked flask were added 1l (147 mg, 0.5 mmol), triphenylsilane (260 mg, 1.0 mmol), Pd(PPh₃)₂Cl₂ (35.0 mg, 0.05 mmol), ethyl 2-isocyanoacetate (165 μL, 1.5 mmol) and DMSO (5.0 mL), respectively, under N₂. After the reaction mixture was stirred for 5 minutes at room temperature, H₂O (0.5 mL) was added by using a syringe. Then the mixture was heated to 90°C and stirred for 4 h. After 1l was consumed (monitored by TLC), the reaction mixture was poured into ice water (30 mL), extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 15 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent, petroleum ether/ethyl acetate: 15/1, v/v) to give 3l (167 mg, 92%) as a yellow solid.

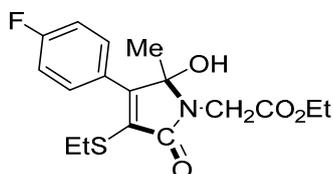
Ethyl2-(4-(ethylthio)-3-(4-fluorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (2a')



Yellow oil; 35% yield (63 mg); ¹H NMR (500 MHz, CDCl₃) δ 1.19 (t, *J* = 7.5 Hz, 3H), 1.24 (s, 3H), 2.98-3.04 (m, 1H), 3.08-3.13 (m, 1H), 3.64 (s, 1H), 4.51 (d, *J* = 15.5 Hz, 1H), 4.79 (d, *J* = 15.5 Hz, 1H), 7.07 (q, *J* = 9.0 Hz, 2H), 7.23-7.25 (m, 1H), 7.29 (q, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 8.5 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 167.5, 162.9 (d, *J* = 248.9 Hz, 1C), 153.8, 138.4, 131.0 (d, *J* = 32.5 Hz, 2C), 128.5 (2C),

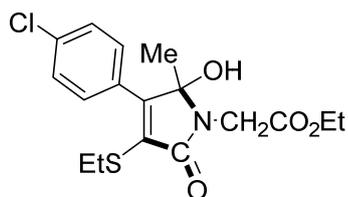
127.8 (d, $J = 14.0$ Hz, 1C), 127.7 (2C), 127.3, 127.2, 115.3 (d, $J = 85.5$ Hz, 2C), 90.5, 42.1, 26.0, 23.8, 15.0. **HRMS** (ESI-TOF) calcd for $C_{20}H_{20}FNNaO_2S^+$ ($[M+Na]^+$) 380.1091, found 380.1093.

Ethyl 2-(4-(ethylthio)-3-(4-fluorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3a**)



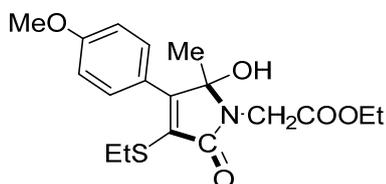
Yellow solid; mp 121-122 °C; 86% yield (152 mg); **¹H NMR** (400 MHz, $CDCl_3$) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.40 (s, 3H), 3.05 (q, $J = 7.2$ Hz, 1H), 3.16 (q, $J = 7.2$ Hz, 1H), 3.51 (s, 1H), 3.93 (d, $J = 18.0$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.49 (d, $J = 18.0$ Hz, 1H), 7.11-7.16 (m, 2H), 7.80-7.84 (m, 2H). **¹³C NMR** (125 MHz, $CDCl_3$) δ 170.8, 167.4, 162.9 (d, $J = 248.7$ Hz, 1C), 154.5, 131.1 (d, $J = 8.1$ Hz, 2C), 127.7 (d, $J = 3.4$ Hz, 1C), 126.6, 115.2 (d, $J = 21.0$ Hz, 2C), 89.6, 62.0, 40.2, 26.1, 22.8, 15.0, 14.0. **HRMS** (ESI-TOF) calcd for $C_{17}H_{20}FNNaO_4S^+$ ($[M+Na]^+$) 376.0989, found 376.0983.

Ethyl 2-(4-(ethylthio)-3-(4-chlorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3b**)



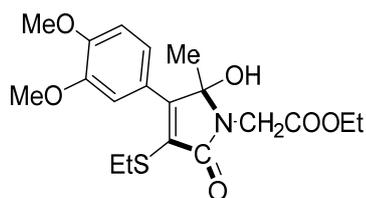
Yellow solid; mp 100-101 °C; 87% yield (161 mg); **¹H NMR** (500 MHz, $CDCl_3$) δ 1.21 (t, $J = 7.5$ Hz, 3H), 1.31 (t, $J = 7.5$ Hz, 3H), 1.39 (s, 3H), 3.02-3.09 (m, 1H), 3.12-3.19 (m, 1H), 3.62 (s, 1H), 3.94 (d, $J = 18.0$ Hz, 1H), 4.24 (q, $J = 7.5$ Hz, 2H), 4.46 (d, $J = 18.0$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.76 (d, $J = 8.5$ Hz, 2H). **¹³C NMR** (125 MHz, $CDCl_3$) δ 171.0, 167.3, 154.1, 135.3, 130.4 (2C), 130.1, 128.5 (2C), 127.4, 89.6, 62.1, 40.4, 26.2, 22.8, 15.1, 14.0. **HRMS** (ESI-TOF) calcd for $C_{17}H_{20}ClNNaO_4S^+$ ($[M+Na]^+$) 392.0694, found 392.0696.

Ethyl 2-(4-(ethylthio)-2-hydroxy-3-(4-methoxyphenyl)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3c**)



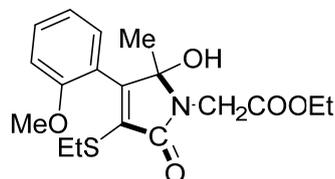
Yellow solid; mp 110-111 °C; 80% yield (146 mg); **¹H NMR** (400 MHz, $CDCl_3$) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.41 (s, 3H), 3.03 (q, $J = 7.2$ Hz, 1H), 3.14 (q, $J = 7.2$ Hz, 1H), 3.54 (s, 1H), 3.85 (s, 3H), 3.94 (d, $J = 18.0$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 4.45 (d, $J = 18.0$ Hz, 1H), 6.96 (dd, $J = 2.0, 6.8$ Hz, 2H), 7.81 (dd, $J = 2.0, 6.8$ Hz, 2H). **¹³C NMR** (125 MHz, $CDCl_3$) δ 171.1, 167.7, 160.3, 155.6, 130.7 (2C), 124.9, 124.0, 113.6 (2C), 89.7, 62.0, 55.2, 40.3, 26.3, 23.1, 15.0, 14.0. **HRMS** (ESI-TOF) calcd for $C_{18}H_{23}NNaO_5S^+$ ($[M+Na]^+$) 388.1189, found 388.1174.

Ethyl 2-(3-(3,4-dimethoxyphenyl)-4-(ethylthio)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3d**)



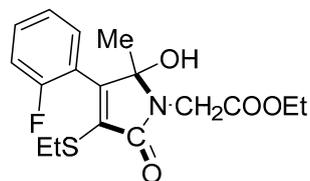
Light yellow solid; mp 134-135 °C; 81% yield (160 mg); **¹H NMR** (400 MHz, CDCl₃) δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 3H), 3.05 (q, *J* = 7.2 Hz, 1H), 3.17 (q, *J* = 7.2 Hz, 1H), 3.56 (s, 1H), 3.91 (s, 3H), 3.93 (s, 3H), 3.95 (d, *J* = 17.6 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.48 (d, *J* = 17.6 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H). **¹³C NMR** (125 MHz, CDCl₃) δ 171.2, 167.7, 155.4, 149.9, 148.3, 125.1, 124.2, 122.7, 112.0, 110.5, 89.8, 62.0, 55.9, 55.8, 40.3, 26.3, 23.1, 15.1, 14.0. **HRMS** (ESI-TOF) calcd for C₁₉H₂₅NNaO₆S⁺ ([M+Na]⁺) 418.1295, found 418.1289.

Ethyl 2-(4-(ethylthio)-2-hydroxy-3-(2-methoxyphenyl)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3e**)



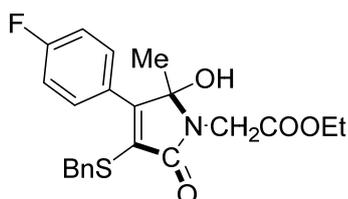
Light yellow solid; mp 120-121 °C; 82% yield (150 mg); **¹H NMR** (500 MHz, CDCl₃) δ 1.16 (t, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 7.5 Hz, 3H), 1.38 (s, 3H), 2.87 (q, *J* = 7.5 Hz, 1H), 2.94 (q, *J* = 7.5 Hz, 1H), 3.68 (s, 1H), 3.83 (s, 3H), 4.04 (d, *J* = 18.0 Hz, 1H), 4.23 (q, *J* = 7.5 Hz, 2H), 4.33 (d, *J* = 18.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.38-7.42 (m, 1H). **¹³C NMR** (125 MHz, CDCl₃) δ 170.1, 167.0, 156.5, 153.4, 130.5 (2C), 130.1, 121.0, 120.8, 111.1, 89.9, 61.6, 55.6, 40.2, 25.1, 22.4, 15.1, 14.1. **HRMS** (ESI-TOF) calcd for C₁₈H₂₃NNaO₅S⁺ ([M+Na]⁺) 388.1189, found 388.1184.

Ethyl 2-(4-(ethylthio)-3-(2-fluorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3f**)



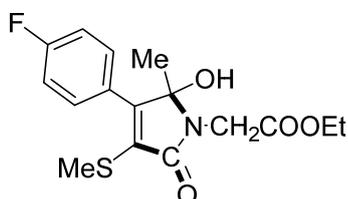
Yellow solid; mp 146-147 °C; 87% yield (154 mg); **¹H NMR** (400 MHz, CDCl₃) δ 1.18 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.39 (s, 3H), 2.92-2.98 (m, 2H), 3.48 (s, 1H), 3.98 (d, *J* = 18.0 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.43 (d, *J* = 18.0 Hz, 1H), 7.14-7.24 (m, 2H), 7.39-7.49 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 170.7, 167.0, 159.4 (d, *J* = 247.0 Hz, 1C), 150.5, 131.2, 131.0 (d, *J* = 8.1 Hz, 1C), 130.3, 124.0 (d, *J* = 3.4 Hz, 1C), 119.6 (d, *J* = 16.1 Hz, 1C), 115.8 (d, *J* = 22.0 Hz, 1C), 89.7, 62.0, 40.4, 25.2, 21.9, 15.0, 14.0. **HRMS** (ESI-TOF) calcd for C₁₇H₂₀FNNaO₄S⁺ ([M+Na]⁺) 376.0989, found 376.0987.

Ethyl 2-(4-(benzylthio)-3-(4-fluorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3g**)



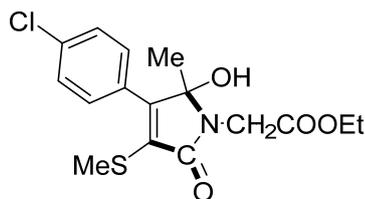
Light yellow solid; mp 138-139 °C; 72% yield (150 mg); **¹H NMR** (400 MHz, CDCl₃) δ 1.29 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 3.59 (s, 1H), 3.99 (d, *J* = 18.0 Hz, 1H), 4.13 (d, *J* = 12.8 Hz, 1H), 4.23-4.31 (m, 3H), 4.42 (d, *J* = 18.0 Hz, 1H), 6.99 (t, *J* = 8.4 Hz, 2H), 7.17-7.25 (m, 5H), 7.41 (dd, *J* = 5.6, 8.4 Hz, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 170.6, 167.5, 163.0 (d, *J* = 249.0 Hz, 1C), 158.5, 137.7, 130.9 (d, *J* = 8.1 Hz, 2C), 129.1 (2C), 128.3 (2C), 127.3 (d, *J* = 3.4 Hz, 1C), 127.1, 125.8, 115.1 (d, *J* = 21.4 Hz, 2C), 89.8, 62.0, 40.2, 36.4, 22.5, 14.1. **HRMS** (ESI-TOF) calcd for C₂₂H₂₂FNNaO₄S⁺ ([M+Na]⁺) 438.1146, found 438.1151.

Ethyl 2-(3-(4-fluorophenyl)-2-hydroxy-2-methyl-4-(methylthio)-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3h**)



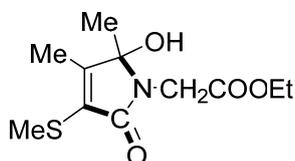
Light yellow solid; mp 125-126 °C; 81% yield (137 mg); **¹H NMR** (400 MHz, CDCl₃) δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.39 (s, 3H), 2.48 (s, 3H), 3.63 (s, 1H), 3.95 (d, *J* = 18.0 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.46 (d, *J* = 18.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 2H), 7.79 (t, *J* = 8.0 Hz, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 171.0, 167.3, 163.0 (d, *J* = 249.0 Hz, 1C), 153.1, 131.1 (d, *J* = 8.1 Hz, 2C), 127.9, 127.7, 115.3 (d, *J* = 21.5 Hz, 2C), 89.6, 62.1, 40.3, 22.8, 15.3, 14.0. **HRMS** (ESI-TOF) calcd for C₁₆H₁₈FNNaO₄S⁺ ([M+Na]⁺) 362.0833, found 362.0823.

Ethyl 2-(3-(4-chlorophenyl)-2-hydroxy-2-methyl-4-(methylthio)-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3i**)



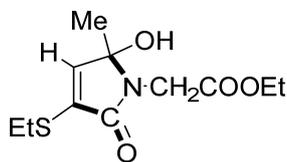
Light yellow solid; mp 119-120 °C; 79% yield (140 mg); **¹H NMR** (500 MHz, CDCl₃) δ 1.31 (t, *J* = 7.5 Hz, 3H), 1.39 (s, 3H), 2.47 (s, 3H), 3.72 (s, 1H), 3.96 (d, *J* = 18.0 Hz, 1H), 4.23 (q, *J* = 7.5 Hz, 2H), 4.42 (d, *J* = 18.0 Hz, 1H), 7.41 (dd, *J* = 2.0 9.0 Hz, 2H), 7.73-7.75 (m, 2H). **¹³C NMR** (125 MHz, CDCl₃) δ 170.7, 167.2, 152.6, 135.2, 130.3 (2C), 130.0, 128.5 (2C), 128.4, 89.6, 62.0, 40.2, 22.7, 15.2, 14.0. **HRMS** (ESI-TOF) calcd for C₁₆H₁₈ClNNaO₄S⁺ ([M+Na]⁺) 378.0537, found 378.0533.

Ethyl 2-(2-hydroxy-2,3-dimethyl-4-(methylthio)-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3j**)



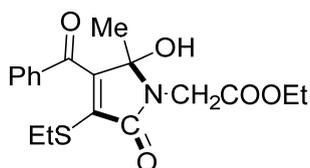
Light yellow oil; 83% yield (108 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.29 (t, $J = 7.2$ Hz, 3H), 1.41 (s, 3H), 2.06 (s, 3H), 3.46 (s, 3H), 3.45 (s, 1H), 3.92 (d, $J = 17.6$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.33 (d, $J = 17.6$ Hz, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.6, 167.6, 158.4, 126.4, 88.8, 61.8, 40.0, 21.3, 15.1, 14.0, 11.1. **HRMS** (ESI-TOF) calcd for $\text{C}_{11}\text{H}_{17}\text{NNaO}_4\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 282.0770, found 282.0774.

Ethyl 2-(4-(ethylthio)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3k**)



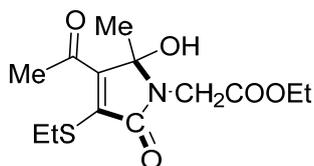
Light yellow oil; 58% yield (75 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.28 (t, $J = 7.2$ Hz, 3H), 1.37 (t, $J = 7.2$ Hz, 3H), 1.49 (s, 3H), 2.86 (q, $J = 7.2$ Hz, 2H), 3.59 (s, 1H), 3.95 (d, $J = 18.0$ Hz, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.26 (d, $J = 18.0$ Hz, 1H), 6.39 (s, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.9, 166.8, 136.7, 136.0, 88.7, 61.6, 39.7, 24.9, 22.6, 13.9, 13.2. **HRMS** (ESI-TOF) calcd for $\text{C}_{11}\text{H}_{17}\text{NNaO}_4\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 282.0770, found 282.0771.

Ethyl 2-(3-benzoyl-4-(ethylthio)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3l**)



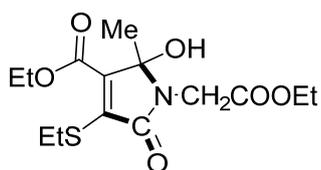
Yellow solid; mp 142-143 °C; 92% yield (167 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.16 (t, $J = 7.2$ Hz, 3H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.62 (s, 3H), 2.93 (q, $J = 7.2$ Hz, 2H), 4.07 (d, $J = 17.6$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 4.30 (d, $J = 17.6$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 2H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.92 (t, $J = 7.6$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 193.2, 169.9, 166.0, 148.8, 136.5, 134.7, 134.3, 129.4 (2C), 128.9 (2C), 89.3, 61.9, 40.2, 25.8, 23.0, 15.0, 14.0. **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{21}\text{NNaO}_5\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 386.1033, found 386.1033.

Ethyl 2-(3-acetyl-4-(ethylthio)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3m**)



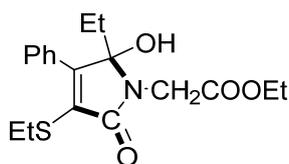
Light yellow oil; 60% yield (90 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.28-1.35 (m, 6H), 1.62 (s, 3H), 2.54 (s, 3H), 3.51 (q, $J = 7.6$ Hz, 2H), 3.80 (s, 1H), 4.04 (d, $J = 18.0$ Hz, 1H), 4.20-4.25 (m, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 194.8, 169.2, 165.0, 144.4, 142.9, 87.8, 61.8, 40.0, 31.1, 25.3, 23.5, 15.5, 14.0. **HRMS** (ESI-TOF) calcd for $\text{C}_{13}\text{H}_{19}\text{NNaO}_5\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 324.0876, found 324.0875.

Ethyl 1-(2-ethoxy-2-oxoethyl)-4-(ethylthio)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**3n**)



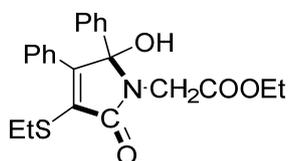
Light yellow oil; 65% yield (108 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.27-1.34 (m, 6H), 1.38 (t, $J = 7.2$ Hz, 3H), 1.66 (s, 3H), 3.39 (s, 1H), 3.48 (q, $J = 7.2$ Hz, 2H), 4.03 (d, $J = 18.0$ Hz, 1H), 4.19-4.24 (m, 3H), 4.31-4.39 (m, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 169.2, 164.7, 162.7, 144.4, 136.4, 87.4, 61.7, 61.2, 40.0, 24.5, 23.0, 15.5, 14.2, 14.0. **HRMS** (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{21}\text{NNaO}_6\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 354.0982, found 354.0981.

Ethyl 2-(2-ethyl-4-(ethylthio)-2-hydroxy-5-oxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3o**)



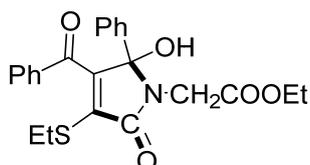
Light yellow solid; mp 90-91 °C; 77% yield (134 mg); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 0.53 (t, $J = 7.5$ Hz, 3H), 1.22 (t, $J = 7.5$ Hz, 3H), 1.32 (t, $J = 7.5$ Hz, 3H), 1.79 (q, $J = 7.5$ Hz, 2H), 3.10 (q, $J = 7.5$ Hz, 2H), 3.64 (s, 1H), 3.77 (d, $J = 18.0$ Hz, 1H), 4.24 (q, $J = 7.5$ Hz, 2H), 4.52 (d, $J = 18.0$ Hz, 1H), 7.40-7.45 (m, 3H), 7.80 (t, $J = 6.5$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.0, 168.2, 154.1, 131.7, 129.3, 128.9 (2C), 128.1 (2C), 127.9, 92.9, 62.0, 40.3, 27.3, 26.1, 15.1, 14.0, 7.0. **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{23}\text{NNaO}_4\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 372.1240, found 372.1234.

Ethyl 2-(4-(ethylthio)-2-hydroxy-5-oxo-2,3-diphenyl-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3p**)



Light yellow solid; mp 83-84 °C; 65% yield (129 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.24 (t, $J = 5.6$ Hz, 3H), 1.27 (t, $J = 5.6$ Hz, 3H), 3.10-3.14 (m, 2H), 3.46 (d, $J = 18.0$ Hz, 1H), 4.19 (q, $J = 5.6$ Hz, 2H), 4.37 (s, 1H), 4.42 (d, $J = 18.0$ Hz, 1H), 7.24-7.32 (m, 6H), 7.38 (d, $J = 6.4$ Hz, 2H), 7.44 (dd, $J = 2.0, 7.0$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.4, 168.1, 156.2, 136.9, 131.3, 129.1, 129.0 (2C), 128.6, 128.5 (2C), 127.8 (2C), 127.0, 126.1 (2C), 92.0, 62.1, 41.0, 26.1, 15.2, 14.0. **HRMS** (ESI-TOF) calcd for $\text{C}_{22}\text{H}_{23}\text{NNaO}_4\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 420.1240, found 420.1244.

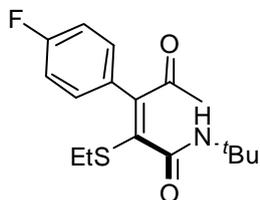
Ethyl 2-(3-benzoyl-4-(ethylthio)-2-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrol-1-yl)acetate (**3q**)



Yellow solid; mp 142-143 °C; 83% yield (176 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.19-1.26 (m, 6H), 3.01 (q, $J = 7.6$ Hz, 2H), 3.63 (d, $J = 17.6$ Hz, 1H), 4.17 (q, $J = 7.6$ Hz, 2H), 4.35 (d, $J = 17.6$ Hz, 1H), 4.77 (s, 1H), 7.30 (m,

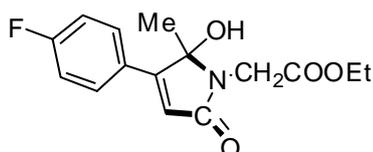
3H), 7.37-7.42 (m, 4H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.68 (d, $J = 7.6$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 192.5, 169.9, 167.0, 148.6, 136.4, 135.9, 134.8, 134.1, 129.2 (2C), 129.0, 128.7 (4C), 126.1 (2C), 91.8, 62.0, 41.2, 25.9, 15.1, 14.0. **HRMS** (ESI-TOF) calcd for $\text{C}_{23}\text{H}_{23}\text{NNaO}_5\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 448.1189, found 448.1183.

(*E*)-*N*-(*tert*-butyl)-2-(ethylthio)-3-(4-fluorophenyl)-4-oxopent-2-enamide (**4a**)



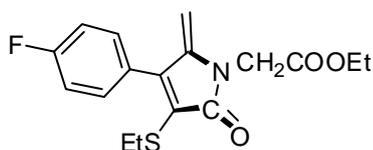
Light yellow oil; 62% yield (100 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.22 (t, $J = 7.2$ Hz, 3H), 1.45 (s, 9H), 2.11 (s, 3H), 2.73 (q, $J = 7.2$ Hz, 2H), 6.22 (s, 1H), 7.11 (t, $J = 8.4$ Hz, 2H), 7.29 (dd, $J = 5.6, 8.4$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 198.6, 164.1, 162.6 (d, $J = 247.1$ Hz, 1C), 142.1, 141.3, 131.7, 130.8 (d, $J = 8.1$ Hz, 2C), 116.0 (d, $J = 21.5$ Hz, 2C), 52.1, 29.5, 28.5 (3C), 26.9, 14.5. **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{22}\text{FNNaO}_2\text{S}^+$ ($[\text{M}+\text{Na}]^+$) 346.1247, found 346.1253.

Ethyl 2-(3-(4-fluorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**5a**)



White solid; mp 169-171 °C; 10% yield (15 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 3H), 1.54 (s, 3H), 3.69 (s, 1H), 3.92 (d, $J = 18.0$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 4.49 (d, $J = 18.0$ Hz, 1H), 6.27 (s, 1H), 7.13 (t, $J = 8.8$ Hz, 2H), 7.83 (dd, $J = 5.6, 8.8$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.2, 169.0, 163.7 (d, $J = 250.0$ Hz, 1C), 160.1, 129.8 (d, $J = 8.1$ Hz, 2C), 127.1, 118.6, 116.0 (d, $J = 21.4$ Hz, 2C), 90.6, 62.1, 39.9, 23.2, 14.1. **HRMS** (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{16}\text{FNNaO}_4^+$ ($[\text{M}+\text{Na}]^+$) 316.0956, found 316.0959.

Ethyl 2-(3-(ethylthio)-4-(4-fluorophenyl)-5-methylene-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**6a**)

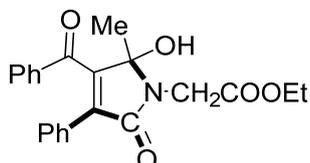


Light yellow oil; 5% yield (9 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 3.10 (q, $J = 7.2$ Hz, 2H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.45 (s, 2H), 4.75 (d, $J = 2.4$ Hz, 1H), 4.78 (d, $J = 2.4$ Hz, 1H), 7.16 (t, $J = 8.4$ Hz, 2H), 7.37-7.41 (m, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 167.9, 166.7, 162.9 (d, $J = 248.0$ Hz, 1C), 144.3, 143.6, 131.5 (d, $J = 8.5$ Hz, 2C), 128.2, 126.9 (d, $J = 3.4$ Hz, 1C), 115.4 (d, $J = 21.9$ Hz, 2C), 94.8, 61.6, 41.1, 25.7, 15.2, 14.1. **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{19}\text{FNO}_3\text{S}^+$ ($[\text{M}+\text{H}]^+$) 336.1064, found 336.1070.

General procedure for the synthesis of 7 (taking **7a** as an example): To a dried sealed tube were added **3I** (109 mg, 0.3 mmol), $\text{Pd}(\text{PPh}_3)_4$ (34.7 mg, 0.03 mmol), CuTc (86 mg, 0.45 mmol), phenylboronic acid (73 mg, 0.6 mmol) and THF (3.0 mL), respectively, under N_2 at room temperature. Then the mixture was heated to 80 °C and

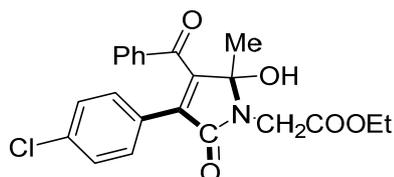
stirred for 32 h. The reaction mixture was poured into ice water (30 mL), extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent, petroleum ether/ethyl acetate: 12/1, v/v) to give ethyl 2-(3-benzoyl-2-hydroxy-2-methyl-5-oxo-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)acetate **7a** (77 mg, 68%) as a white solid.

Ethyl 2-(3-benzoyl-2-hydroxy-2-methyl-5-oxo-4-phenyl-2,5-dihydro-1H-pyrrol-1-yl)acetate (**7a**)



White solid; mp 69-70 °C; 68% yield (77 mg); ¹H NMR (400 MHz, CDCl₃) δ 1.33 (t, *J* = 7.2 Hz, 3H), 1.71 (s, 3H), 3.87 (s, 1H), 4.11 (d, *J* = 18.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.46 (d, *J* = 18.0 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 3H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.44-7.48 (m, 3H), 7.77 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 194.5, 170.6, 167.5, 150.5, 135.3, 134.3, 134.2, 129.5 (2C), 129.3 129.5 (2C), 129.0, 128.6 (2C), 128.2 (2C), 88.7, 62.0, 40.3, 22.8, 14.1. HRMS (ESI-TOF) calcd for C₂₂H₂₁NNaO₅⁺ ([M+Na]⁺) 402.1312, found 402.1300.

Ethyl 2-(3-benzoyl-4-(4-chlorophenyl)-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)acetate (**7b**)



White solid; mp 84-85 °C; 65% yield (81 mg); ¹H NMR (500 MHz, CDCl₃) δ 1.34 (t, *J* = 7.5 Hz, 3H), 1.70 (s, 3H), 3.93 (s, 1H), 4.08 (d, *J* = 18.0 Hz, 1H), 4.27 (q, *J* = 7.5 Hz, 2H), 4.46 (d, *J* = 18.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.34 (t, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 194.3, 170.6, 167.2, 151.1, 135.7, 135.2, 134.5, 132.8, 130.5 (2C), 129.5 (2C), 128.8 (2C), 128.6 (2C), 127.5, 88.7, 62.2, 40.3, 22.7, 14.1. HRMS (ESI-TOF) calcd for C₂₂H₂₀ClNNaO₅⁺ ([M+Na]⁺) 436.0922, found 436.0922.

IV. Crystal data and ORTEP drawing of compound **3a**

Crystal data for **3a**: C₁₇H₂₀FNO₄S, colorless, *M* = 353.40, triclinic, space group P-1, *a* = 8.5007(9) Å, *b* = 10.2500(12) Å, *c* = 11.2985(15) Å, *V* = 896.65(18) Å³, α = 75.804(10), β = 70.345(11), γ = 81.631(9), *Z* = 2, *T* = 293(2) K, *F*(000) = 372, 5666 reflections collected, 3499 unique with *R*(int) = 0.0206, *R*¹ = 0.0532, *wR*² = 0.1505 (*I* > 2σ(*I*)). CCDC 1042264 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

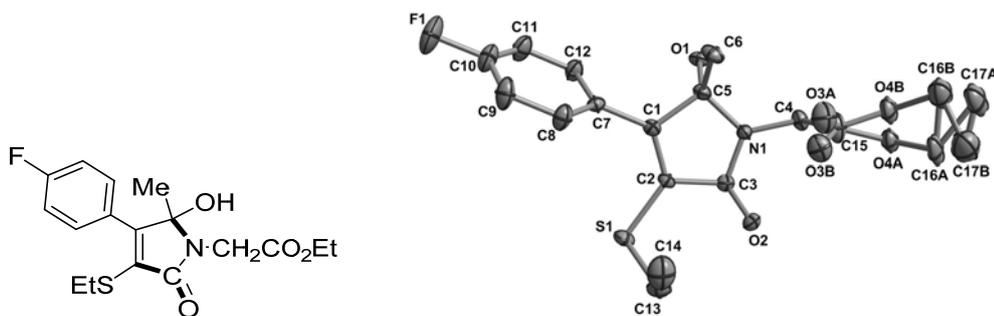


Figure. ORTEP diagram of **3a**.

V. Investigations of the reaction mechanism

To demonstrate the role of both H₂O and O₂, the model reaction was performed with or without H₂O or O₂, respectively. ¹⁸O-Labeled experiments were also included for identifying where the oxygen atom in the amide carbonyl of γ -lactam **3a** originated.

1. The role of H₂O for the reaction:

(a) To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μ L, 0.3 mmol) and dried DMSO (1.0 mL) with 4 Å MS, respectively, under N₂. Then the mixture was heated at 70 °C for 4 h. Almost no reaction was detected under TLC.

(b) To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μ L, 0.3 mmol) and DMSO (1.0 mL), respectively, under N₂. After the reaction mixture was stirred for 5 minutes at room temperature, H₂O (0.1 mL) was added by using a syringe. Then the mixture was heated to 70 °C and stirred for 4 h. **1a** was detected to be consumed almost completely but no **3a** was observed under TLC at this time. Then the reaction was quenched by 0.5 mL of water under N₂ and stirred for additional 1 h. No **3a** was detected under TLC, too.

The above experimental results could demonstrate that water plays a role for Pd-catalyzed cross-coupling of **1a** with isocyanide, but has no effect on the final formation of γ -lactam **3a** from the reaction intermediate.

2. The role of O₂ for the reaction:

(1) To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μ L, 0.3 mmol) and DMSO (1.0 mL), respectively, under N₂. After the reaction mixture was stirred for 5 minutes at room temperature, H₂O (0.1 mL) was added by using a syringe. Then the mixture was heated to 70 °C and stirred for 4 h for the consumption of **1a**. The resulting reaction mixture was stirred under O₂ for additional 1 h. **3a** was detected to be formed along with a consumption of a corresponding intermediate under TLC. The isolated yield of **3a** was 75%.

(2) To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μ L, 0.3 mmol) and DMSO (1.0 mL), respectively, under O₂. After the reaction mixture was stirred for 5 minutes at room temperature, H₂O (0.1 mL) was added by using a syringe. Then the mixture was heated to 70 °C and stirred for 4 h. The reaction occurred and **3a** could be observed under TLC. However, the isolated yield of **3a** is less than 20% with the recovery of **1a** in 50%.

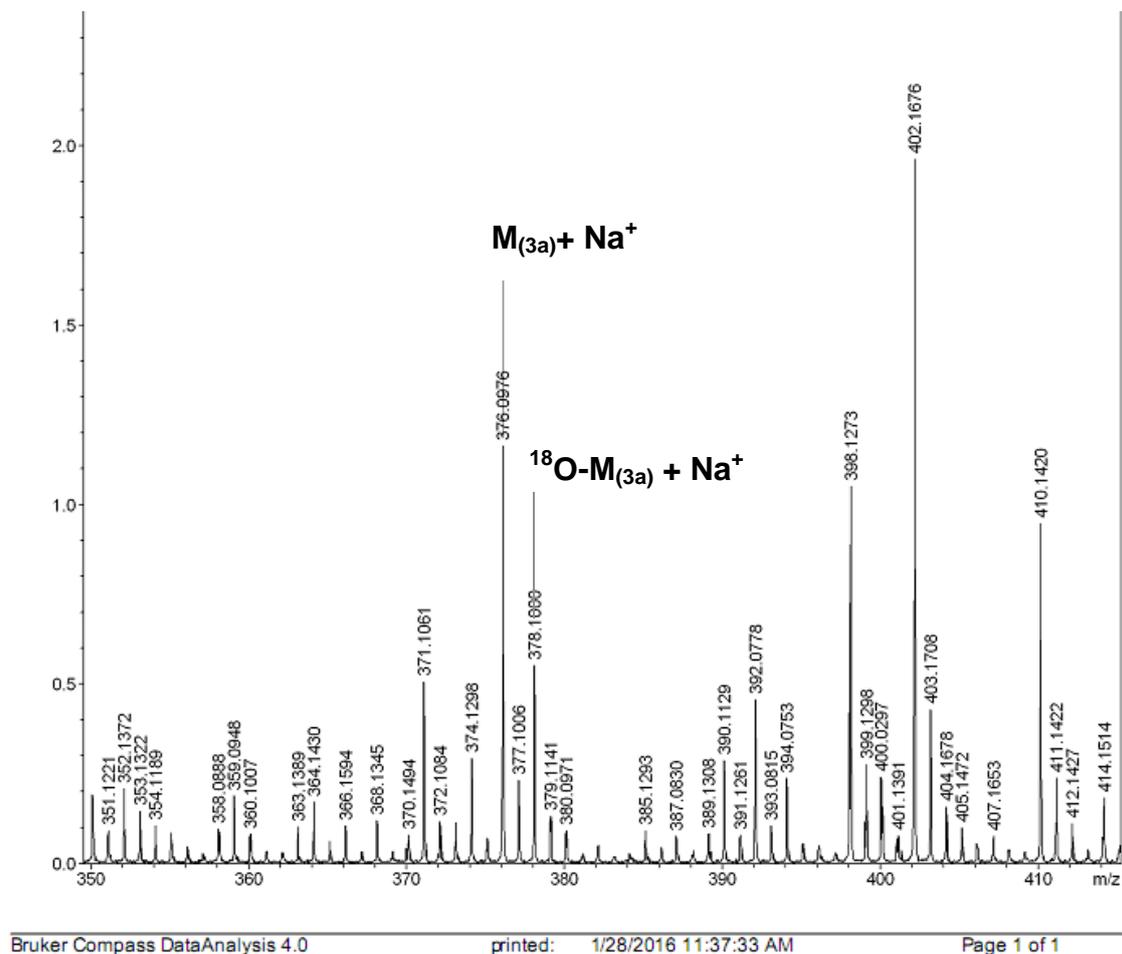
The above experimental results could demonstrate that O₂ plays a role for the final formation of γ -lactam **3a** from a corresponding intermediate, but has a bad effect on Pd-catalyzed cross-coupling of **1a** with isocyanide.

3. ^{18}O -Labeled experiments:

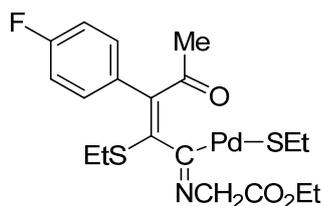
(a) H_2^{18}O -Labeled experiment: To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μL , 0.3 mmol) and DMSO (1.0 mL), respectively, under N_2 . After the reaction mixture was stirred for 5 minutes at room temperature, H_2^{18}O (0.1 mL) was added by using a syringe. Then the mixture was heated to 70 $^\circ\text{C}$ and stirred for 4 h for the consumption of **1a**. After the exchange of N_2 by $^{16}\text{O}_2$, the resulting reaction mixture was stirred under $^{16}\text{O}_2$ for additional 1 h. Samples were then diluted with MeCN prior to the injection into the mass spectrometer. Only ^{16}O -**3a** was detected by HRMS. Additional experiment of the above reaction by quenching with 0.2 mL of H_2^{18}O did not yet afford ^{18}O -**3a**.

(b) $^{18}\text{O}_2$ -Labeled experiment: To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μL , 0.3 mmol) and DMSO (1.0 mL), respectively, under N_2 . After the reaction mixture was stirred for 5 minutes at room temperature, H_2^{16}O (0.1 mL) was added by using a syringe. Then the mixture was heated to 70 $^\circ\text{C}$ and stirred for 4 h for the consumption of **1a**. After the exchange of N_2 by $^{18}\text{O}_2$, the resulting reaction mixture was stirred under $^{18}\text{O}_2$ for additional 1 h. Samples were then diluted with MeCN prior to the injection into the mass spectrometer. Pseudomolecular ion of ^{18}O -**3a** was detected in HRMS spectra ($m/z = 378.1000$, $\text{M}+2+\text{Na}^+$). The above experimental results could demonstrate that the oxygen atom in the amide carbonyl of γ -lactam **3a** originated from O_2 in the air.

HRMS spectrum of the reaction mixture for the $^{18}\text{O}_2$ -labeled experiment:

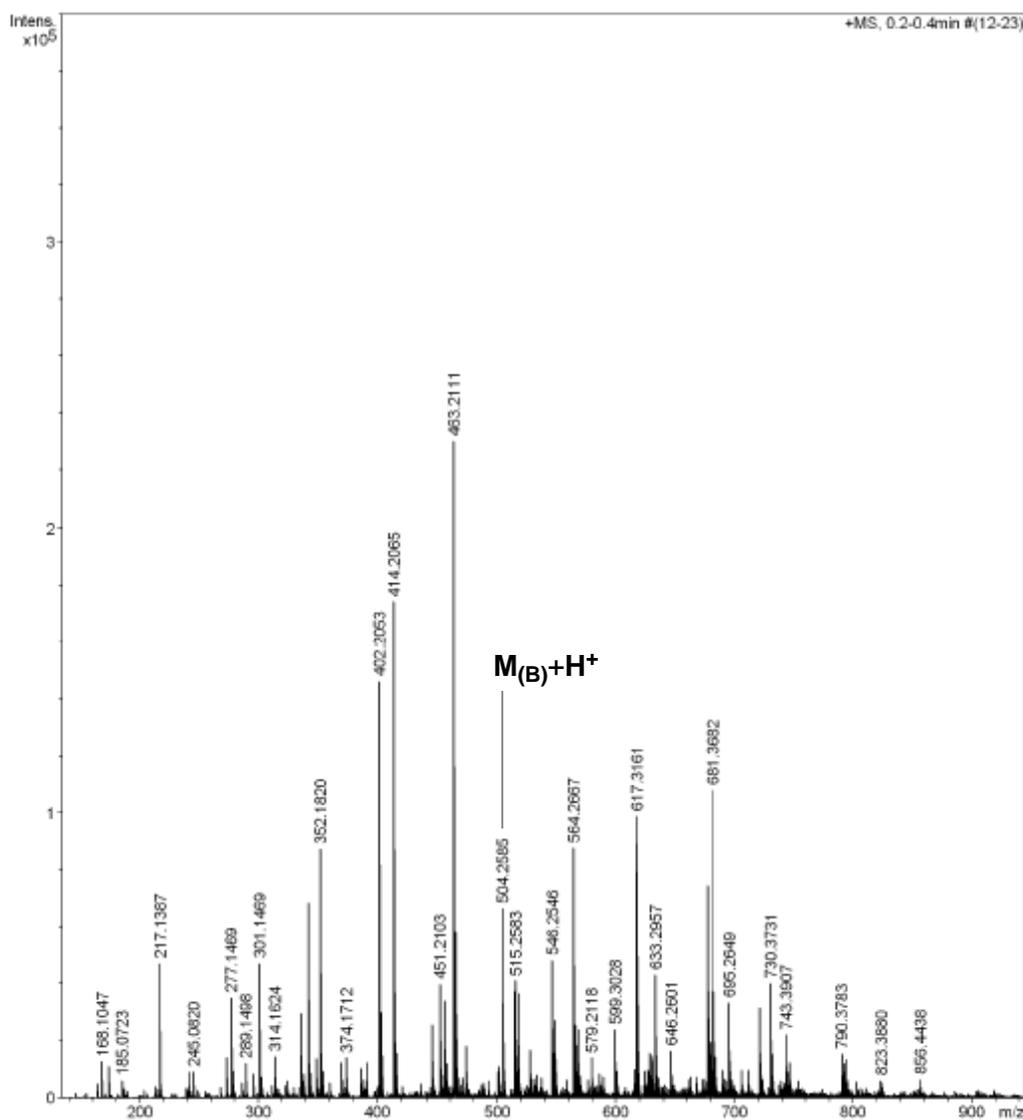


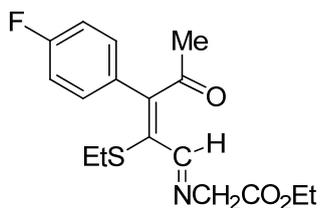
4. HRMS-ESI study of the reaction mixture: To a sealed tube were added **1a** (28.2 mg, 0.1 mmol), triphenylsilane (31.2 mg, 0.12 mmol), Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol), ethyl 2-isocyanoacetate (33 μL, 0.3 mmol) and DMSO (1.0 mL), respectively, under N₂. After the reaction mixture was stirred for 5 minutes at room temperature, H₂O (0.1 mL) was added by using a syringe. Then the mixture was heated to 70°C and stirred for 4 h for the consumption of **1a**. Samples were diluted with MeCN prior to the injection into the mass spectrometer. It was found, among the obtained spectra, that a peak at $m/z = 504.2585$ could be regarded as **B** in HRMS spectrum 1, and the peaks at $m/z = 338.1220$ and 360.1037 could be regarded as **D** in MS spectrum 2.



B(M+H⁺), calculated: 504.0289

HRMS spectrum 1:

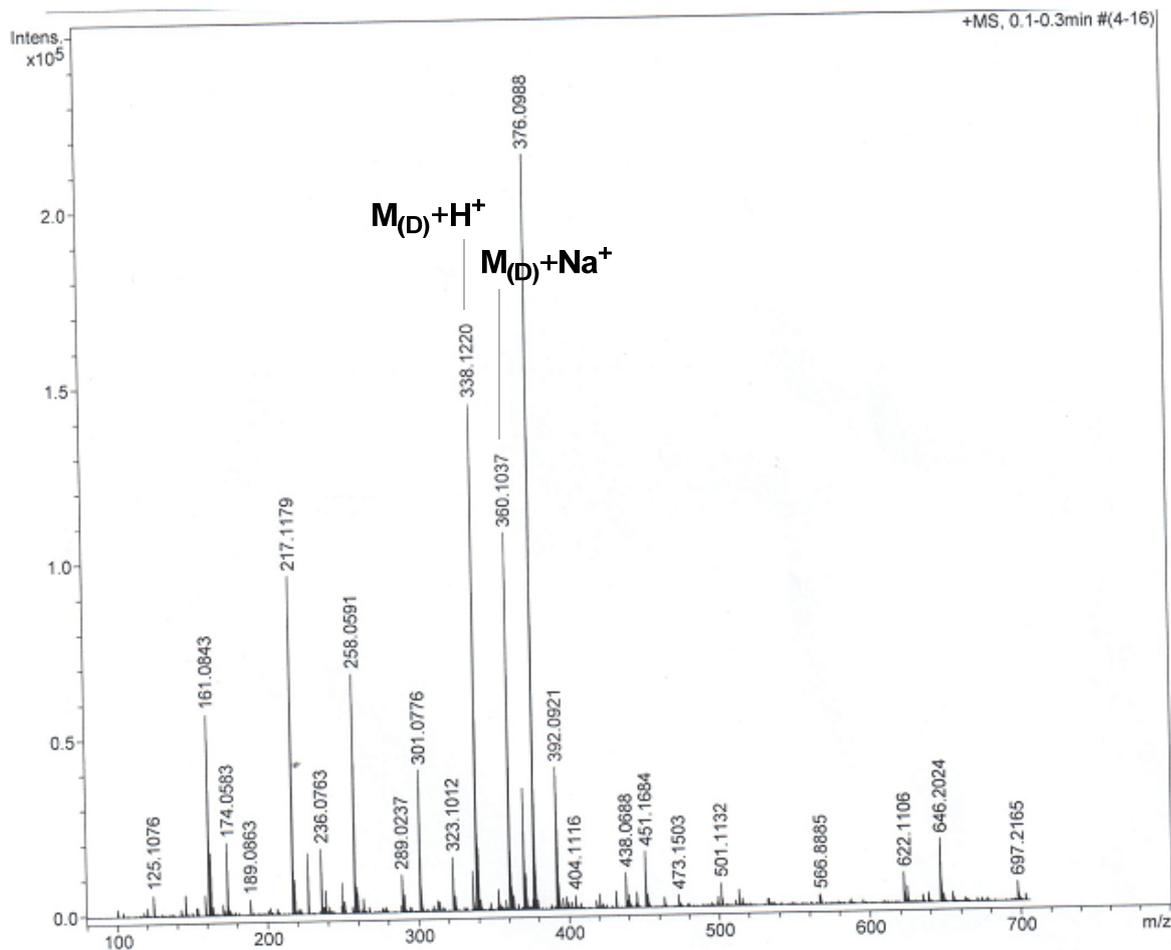




D (M+H⁺), calculated: 338.1221

D (M+Na⁺), calculated: 360.1041

HRMS spectrum 2:



VI. References

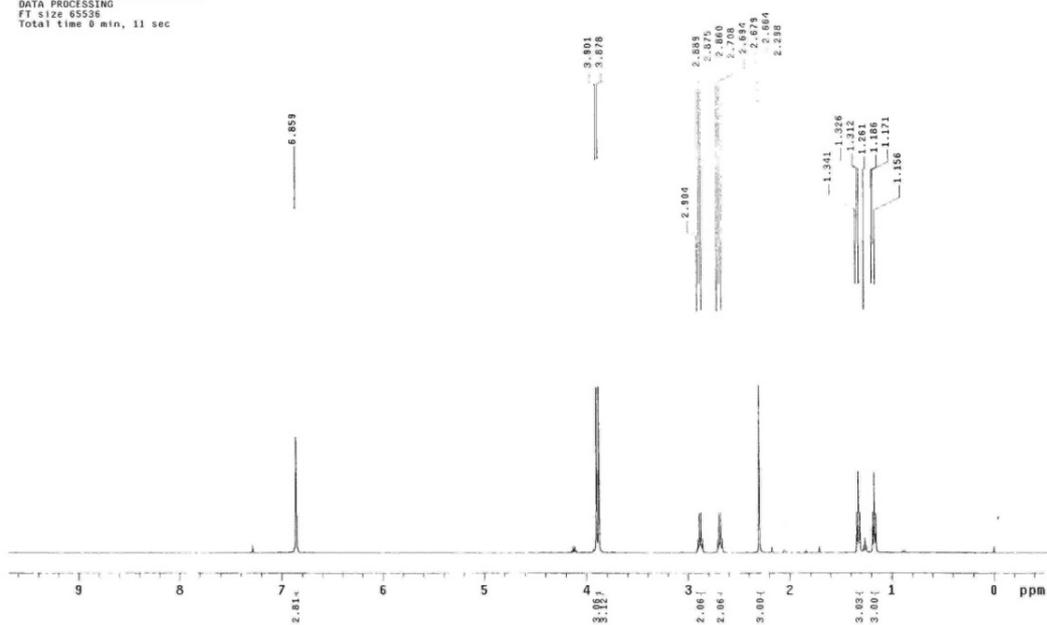
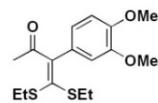
- (1) (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578. (b) Liu, J.; Wang, M.; Li, B.; Liu, Q.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 4401.
- (2) Liu, B.; Zheng, G.; Liu, X.; Xu, C.; Liu, J.; Wang, M. *Chem. Commun.* **2013**, *49*, 2201.
- (3) Zhang, L.; Liang, F.; Cheng, X.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 899.
- (4) Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779.
- (5) Thuillier, A.; Viable, J. *Bull. Soc. Chim. Fr.* **1962**, 2187.
- (6) Sun, S.; Liu, Y.; Liu, Q.; Zhao, Y.; Dong, D. *Synlett*. **2004**, 1731.
- (7) Yin, Y.; Xu, Q.; Yin, G. *J. Jiangxi Normal Univ., Nat. Sci. ED* **2012**, *36*, 412.
- (8) Mashraqui, S. H.; Hariharasubrahmanian, H. *J. Chem. Res., Synop.* **1999**, 492.

VII. Copies of ¹H NMR and ¹³C NMR spectra of new compounds **1**, **2a**, **3**, **4a**, **5a**, **6a**, **7**.

1d

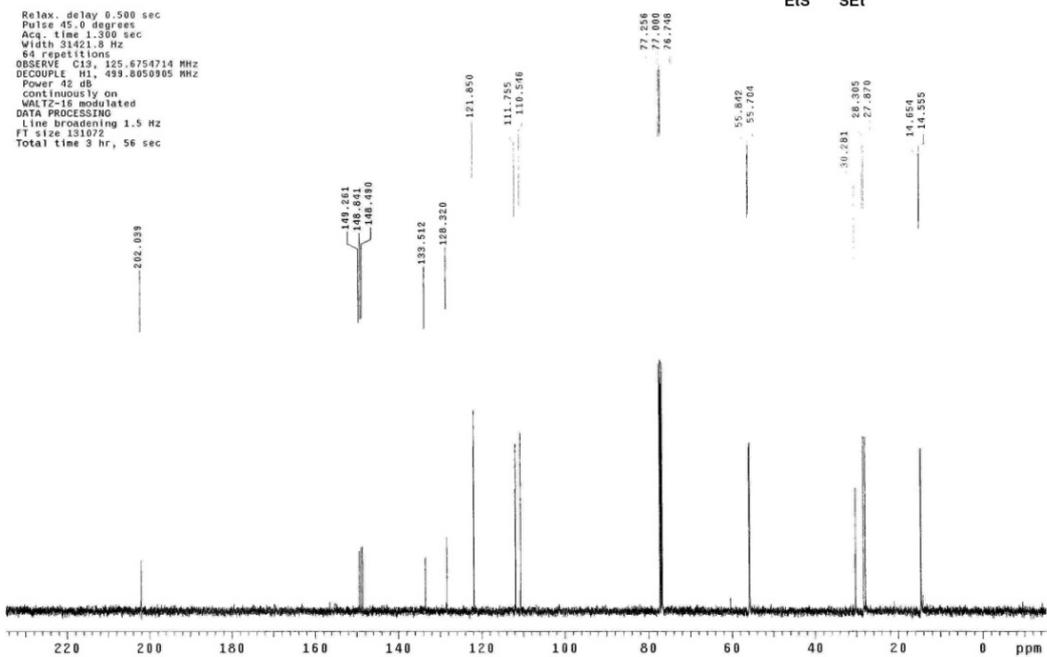
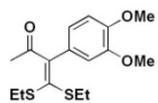
STANDARD PROTON PARAMETERS.

Archive directory: /export/home/ouyy/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: f805
INOVA-500 "NEMO500"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.892 sec
Width 10311.9 Hz
4 repetitions
OBSERVE H1, 499.8025802 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 11 sec



STANDARD CARBON PARAMETERS

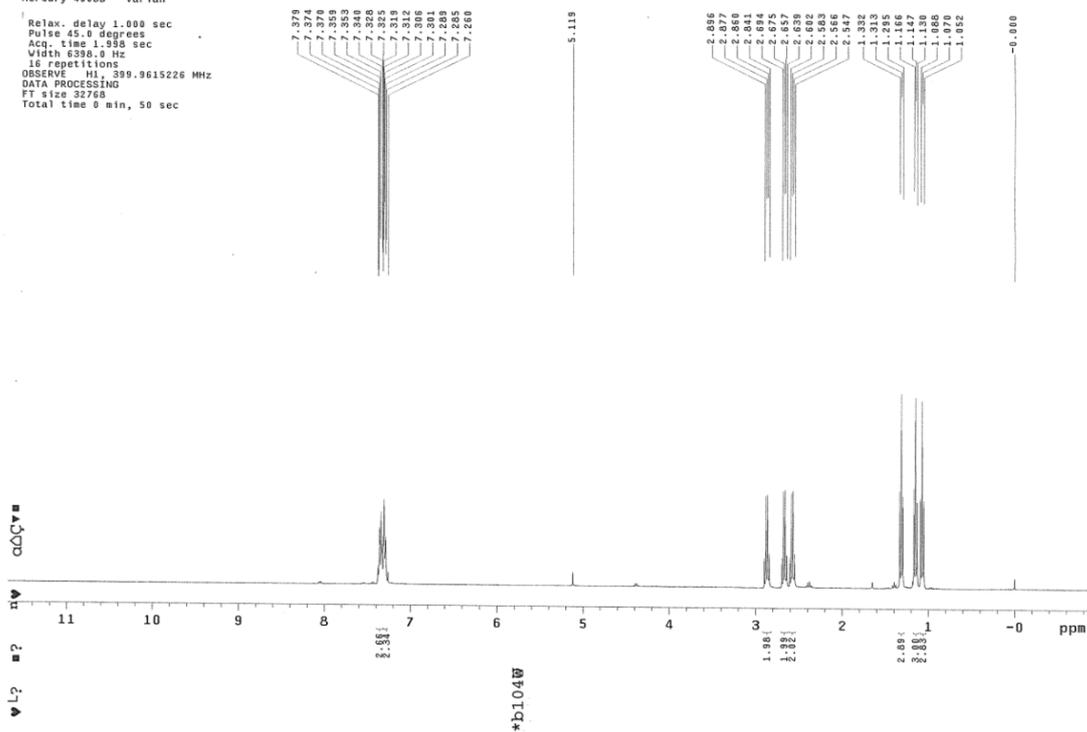
Archive directory: /export/home/ouyy/vnmrsys/data
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: f826
INOVA-500 "NEMO500"
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 1.360 sec
Width 31421.8 Hz
64 repetitions
OBSERVE C13, 125.6754714 MHz
DECOUPLE H1, 499.8050905 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 131072
Total time 3 hr, 56 sec



1o

Std Proton parameters
 Sample directory:
 Pulse Sequence: s2pul
 Solvent: cdc13
 Ambient temperature
 Operator: lpg
 File: c160
 Mercury-400BB "Varian"

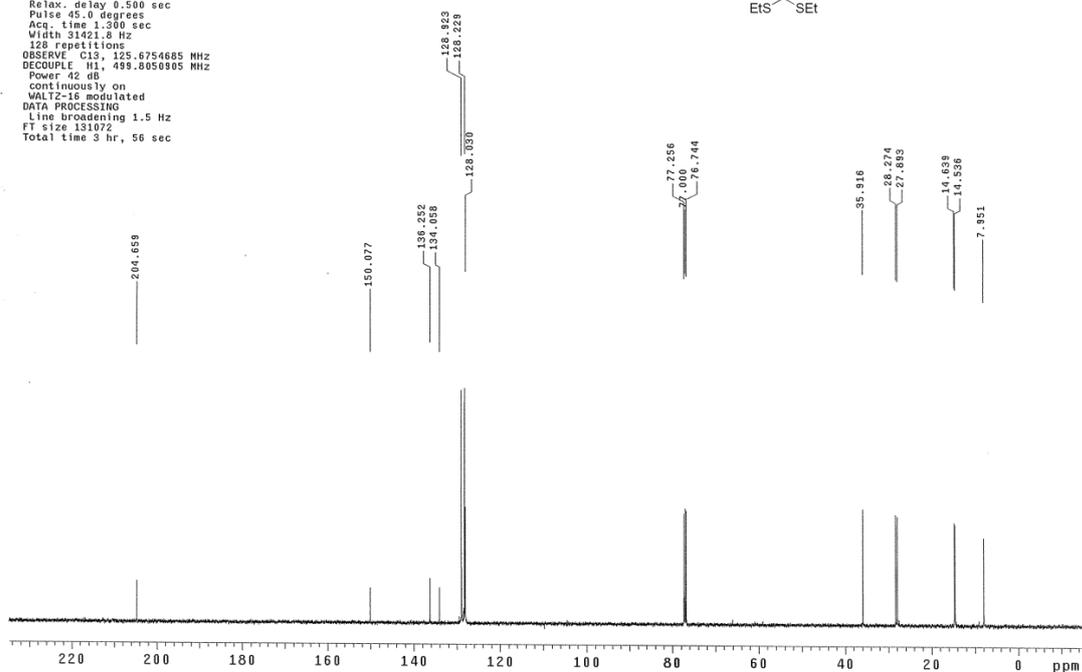
Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 6390.0 Hz
 16 repetitions
 OBSERVE H1 399.9615226 MHz
 DATA PROCESSING
 FT size 32768
 Total time 0 min, 50 sec



STANDARD CARBON PARAMETERS

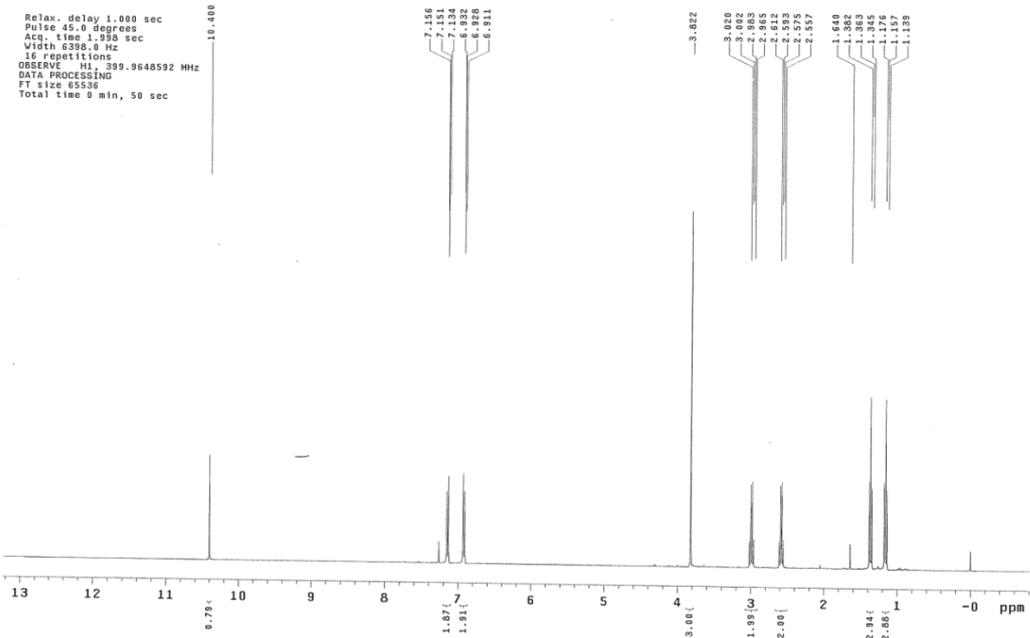
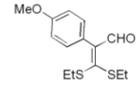
Archive directory: /export/home/ouyy/vnmrsys/data
 Sample directory:
 Pulse Sequence: s2pul
 Solvent: cdc13
 Ambient temperature
 User: 1-14-87
 File: 1648
 INOVA-500 "NENUS00"

Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 31421.8 Hz
 128 Repetitions
 OBSERVE C13 125.6754685 MHz
 DECOUPLE H1 499.8050905 MHz
 Power 42 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.5 Hz
 FT size 131072
 Total time 3 hr, 56 sec



Std Proton parameters
 Sample directory:
 Pulse Sequence: s2pul
 Solvent: cdcl3
 Ambient temperature
 Operator: lps
 File: f351
 Mercury-400BB "varian"

Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.950 sec
 Width 6330.0 Hz
 16 repetitions
 OBSERVE H1, 399.9648592 MHz
 DATA PROCESSING
 FT size 65536
 Total time 0 min, 50 sec

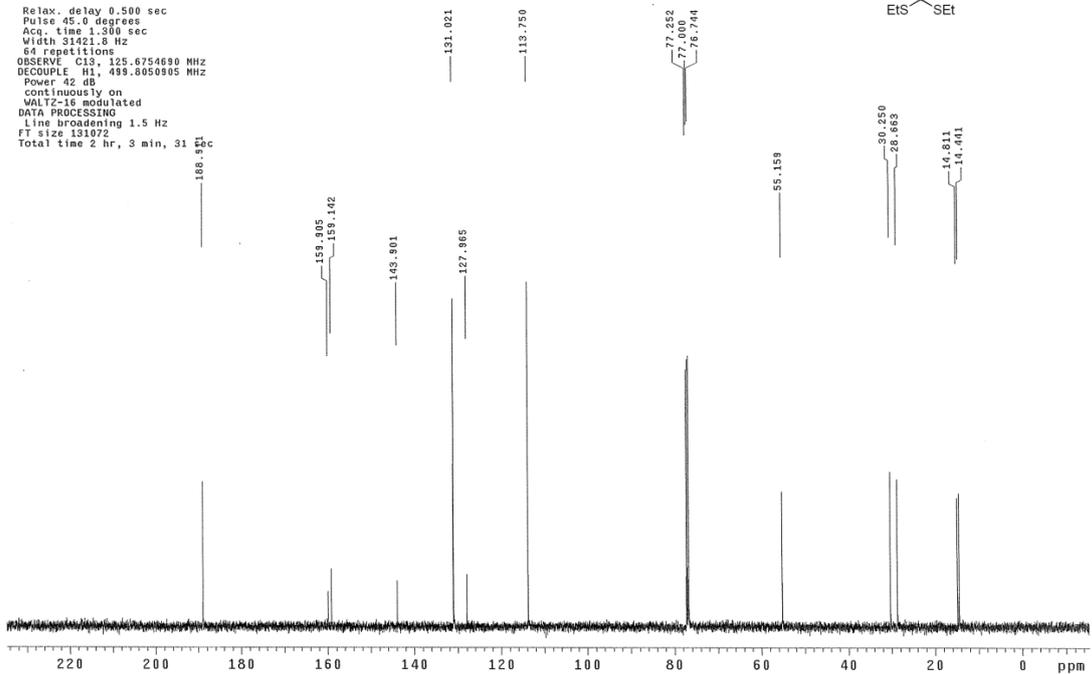
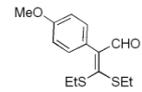


STANDARD CARBON PARAMETERS

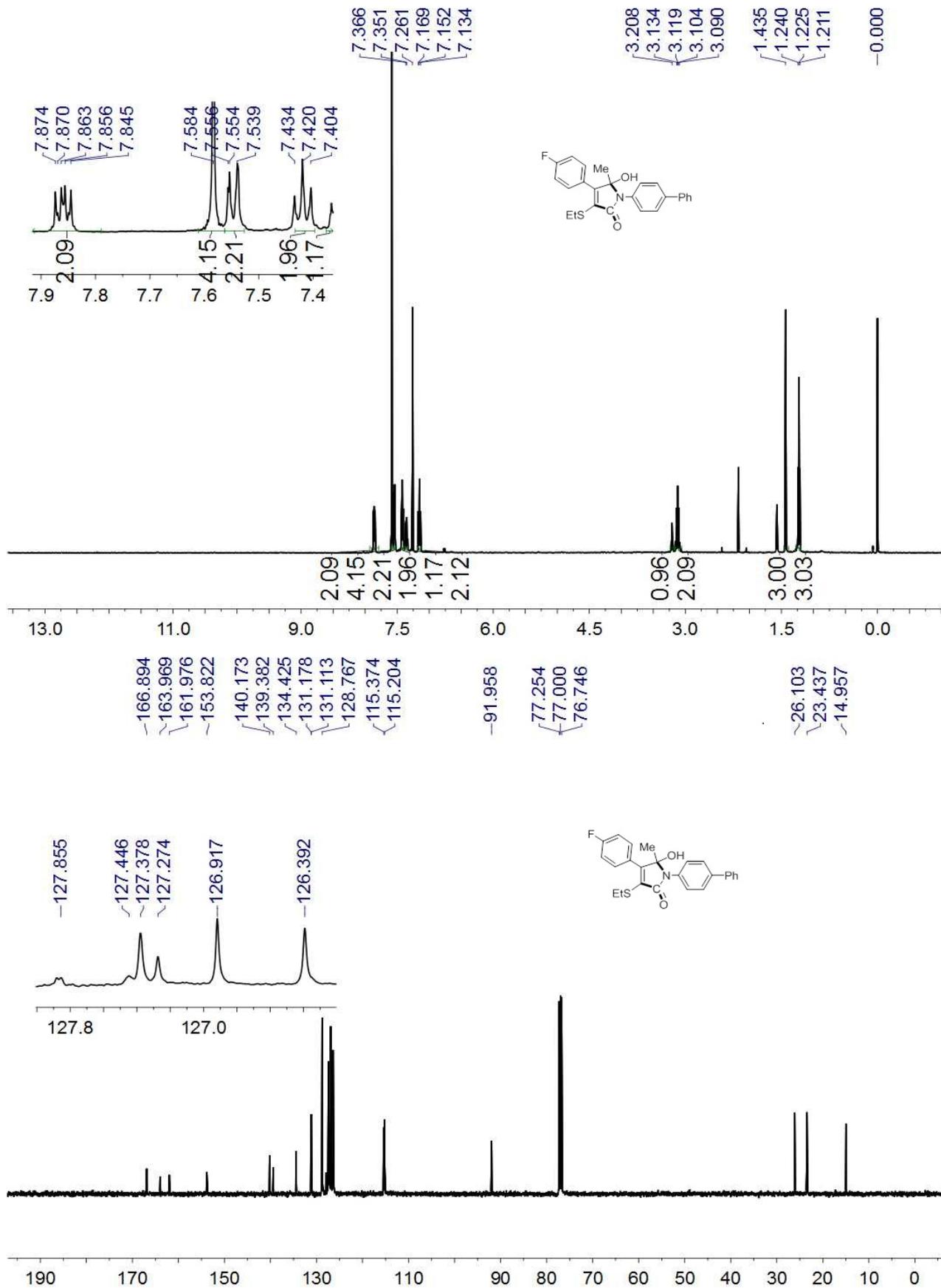
Archive directory: /export/home/ouyy/vnmrsys/data
 Sample directory:

Pulse Sequence: s2pul
 Solvent: cdcl3
 Ambient temperature
 User: 1-14-87
 File: m318
 INOVA-500 "NENU500"

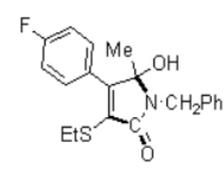
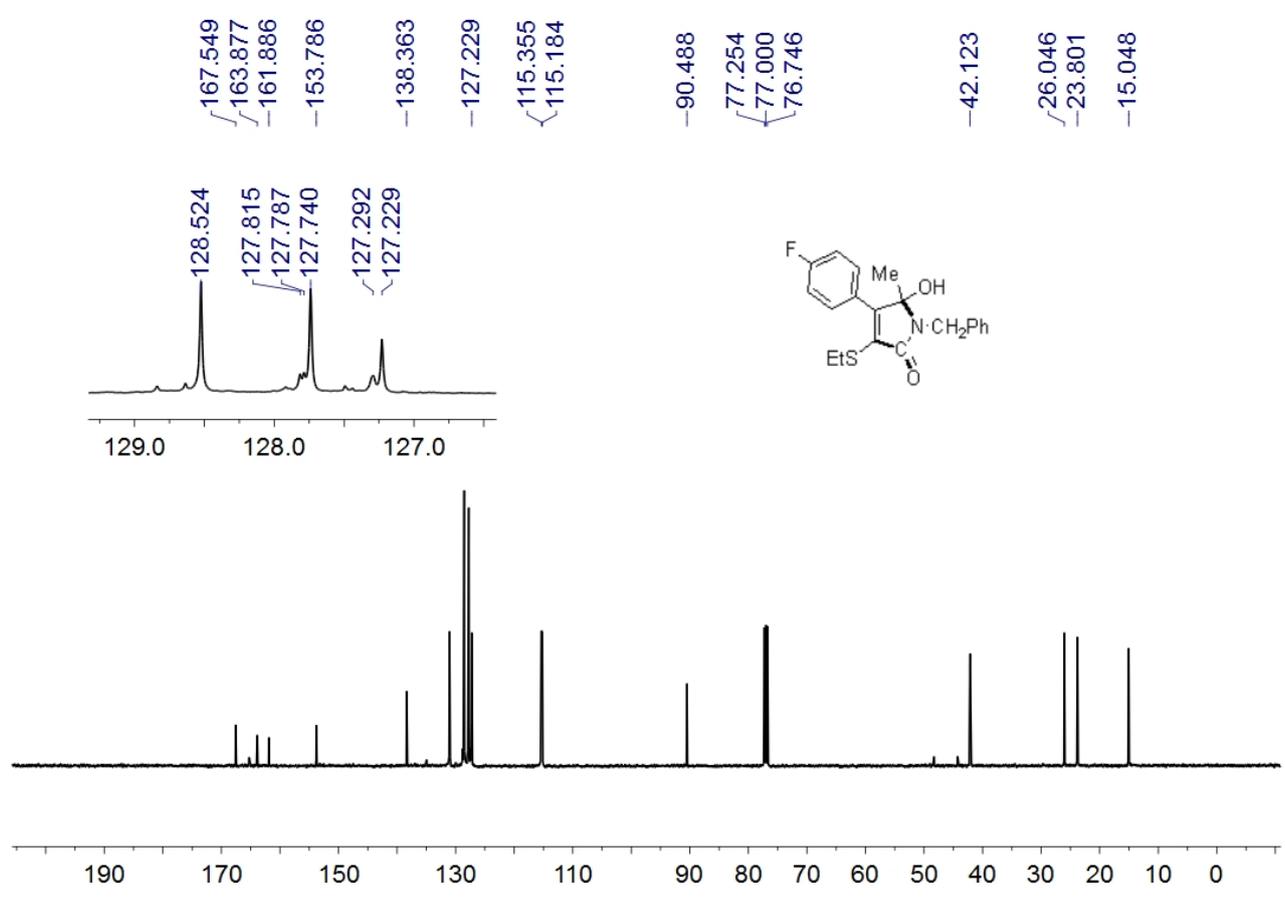
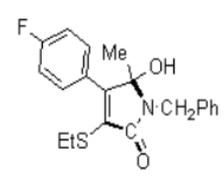
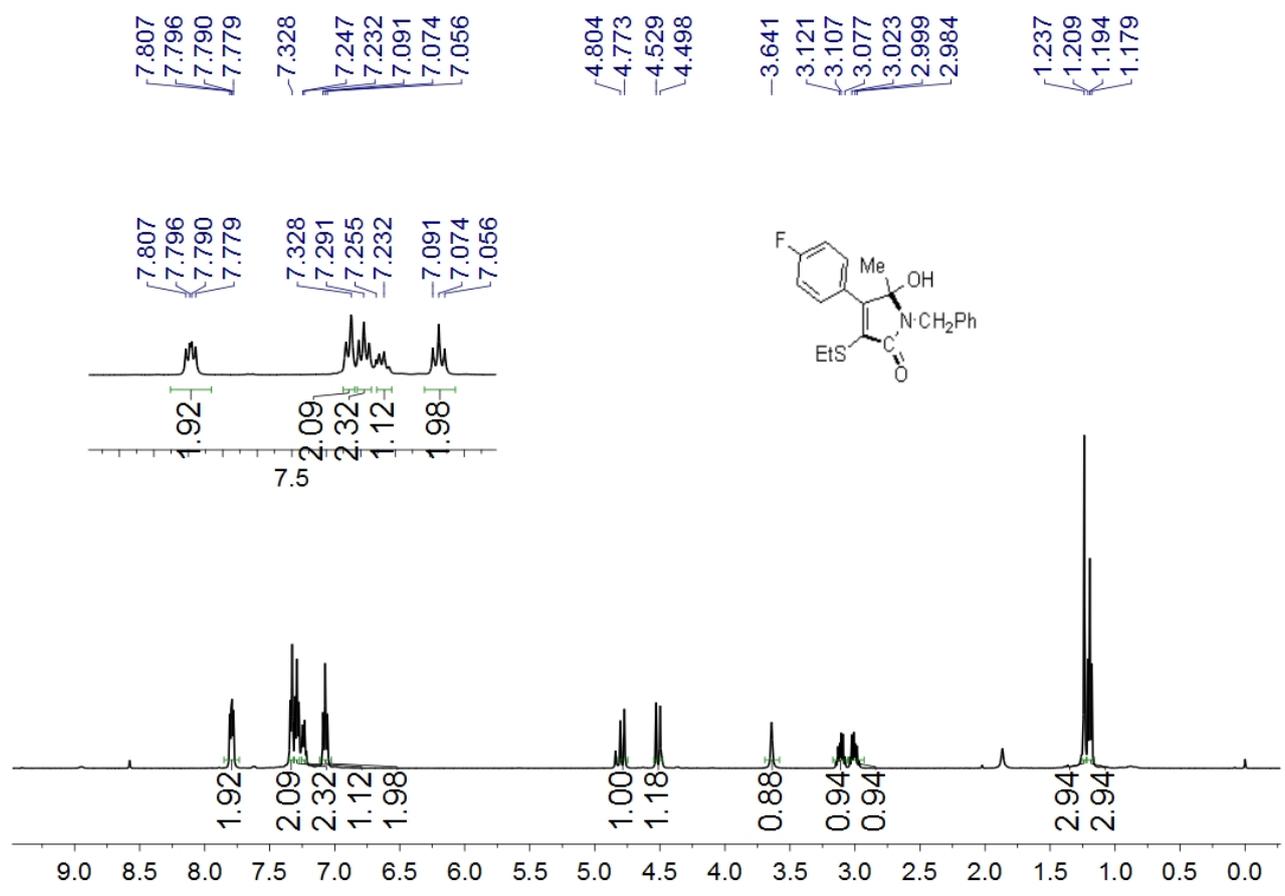
Relax. delay 0.500 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 31421.8 Hz
 64 repetitions
 OBSERVE C13, 125.6754680 MHz
 DECOUPLE H1, 499.8050805 MHz
 Power 42.00
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.5 Hz
 FT size 131072
 Total time 2 hr, 3 min, 31



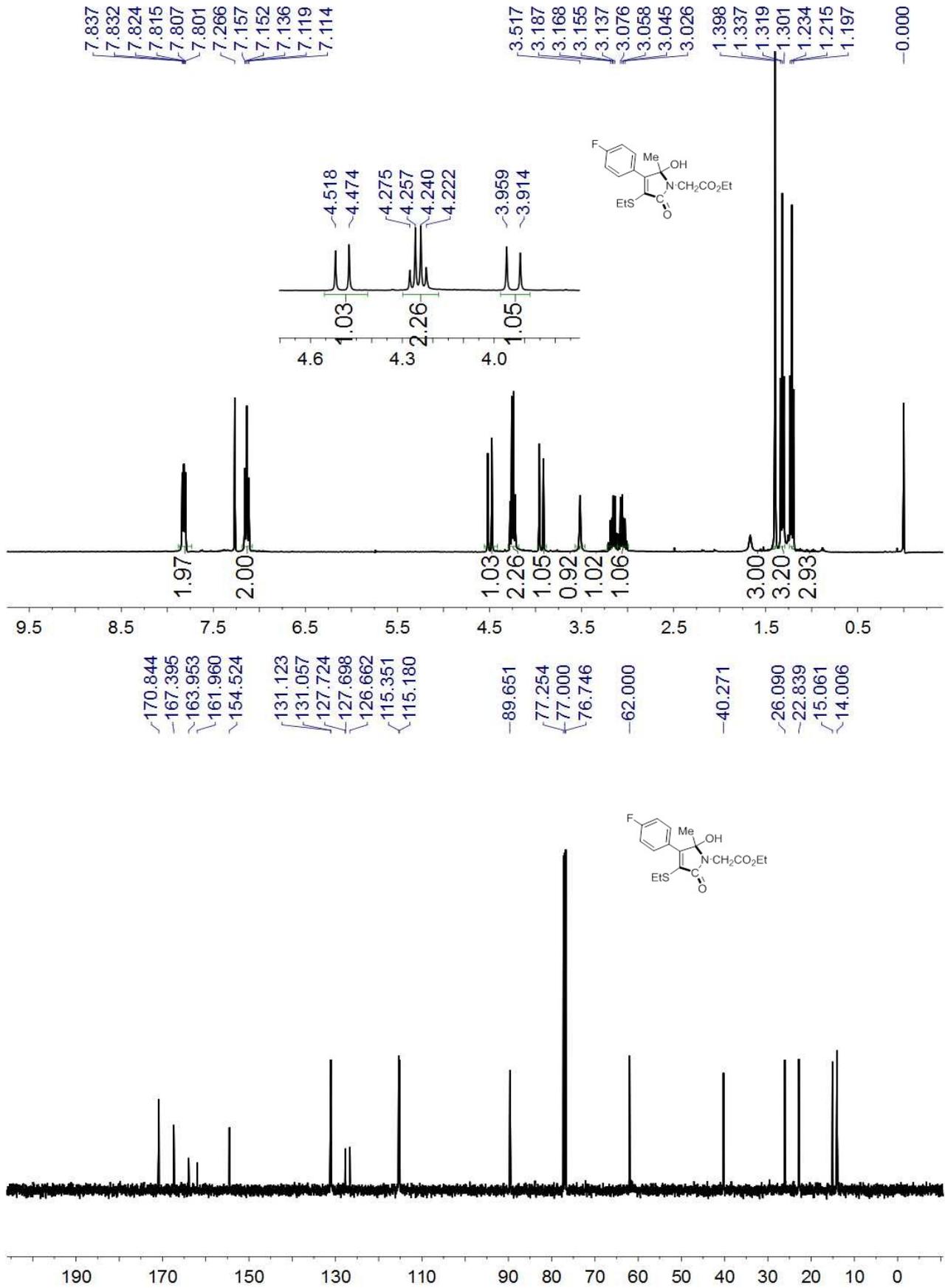
2a



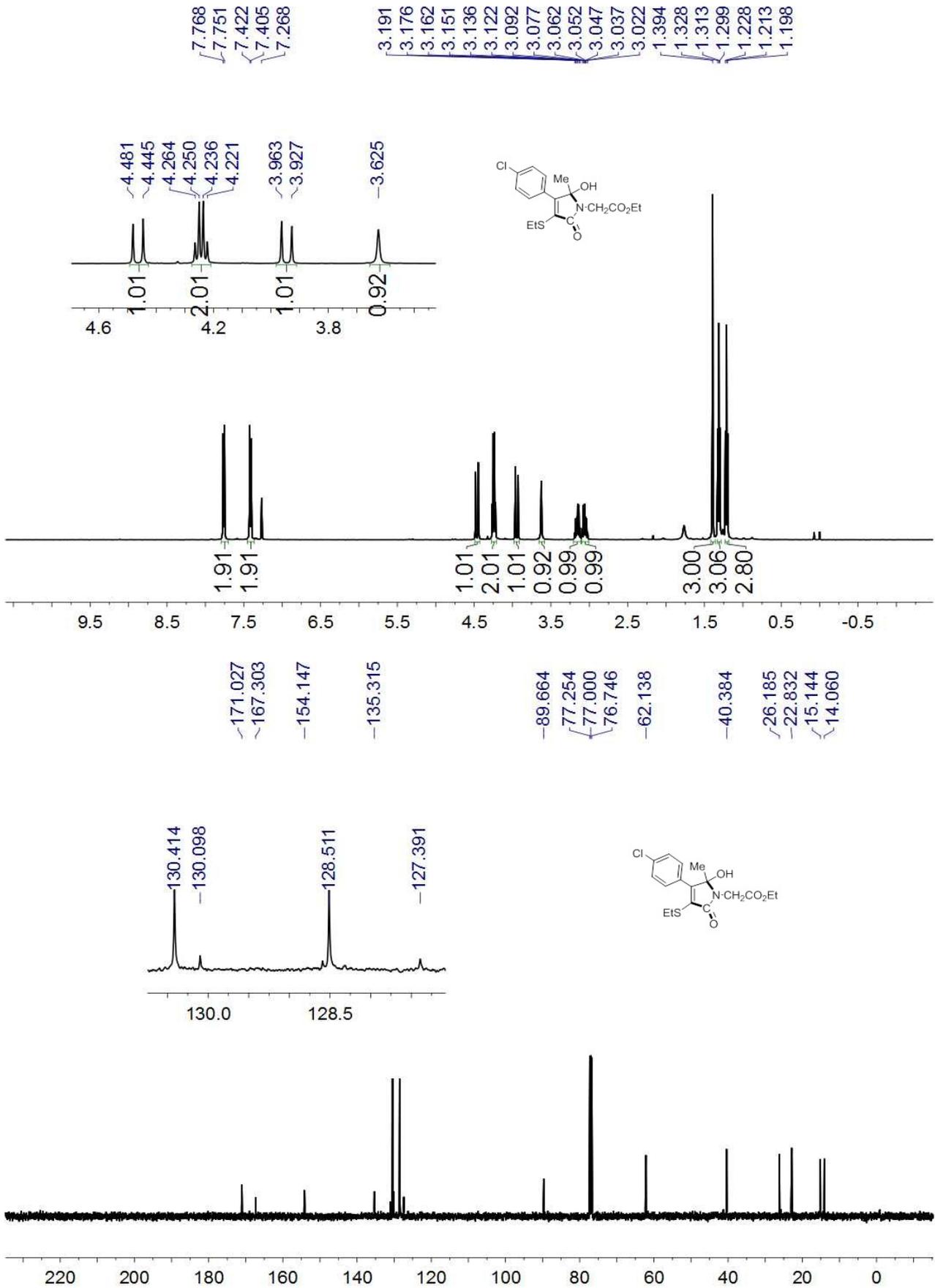
2a'



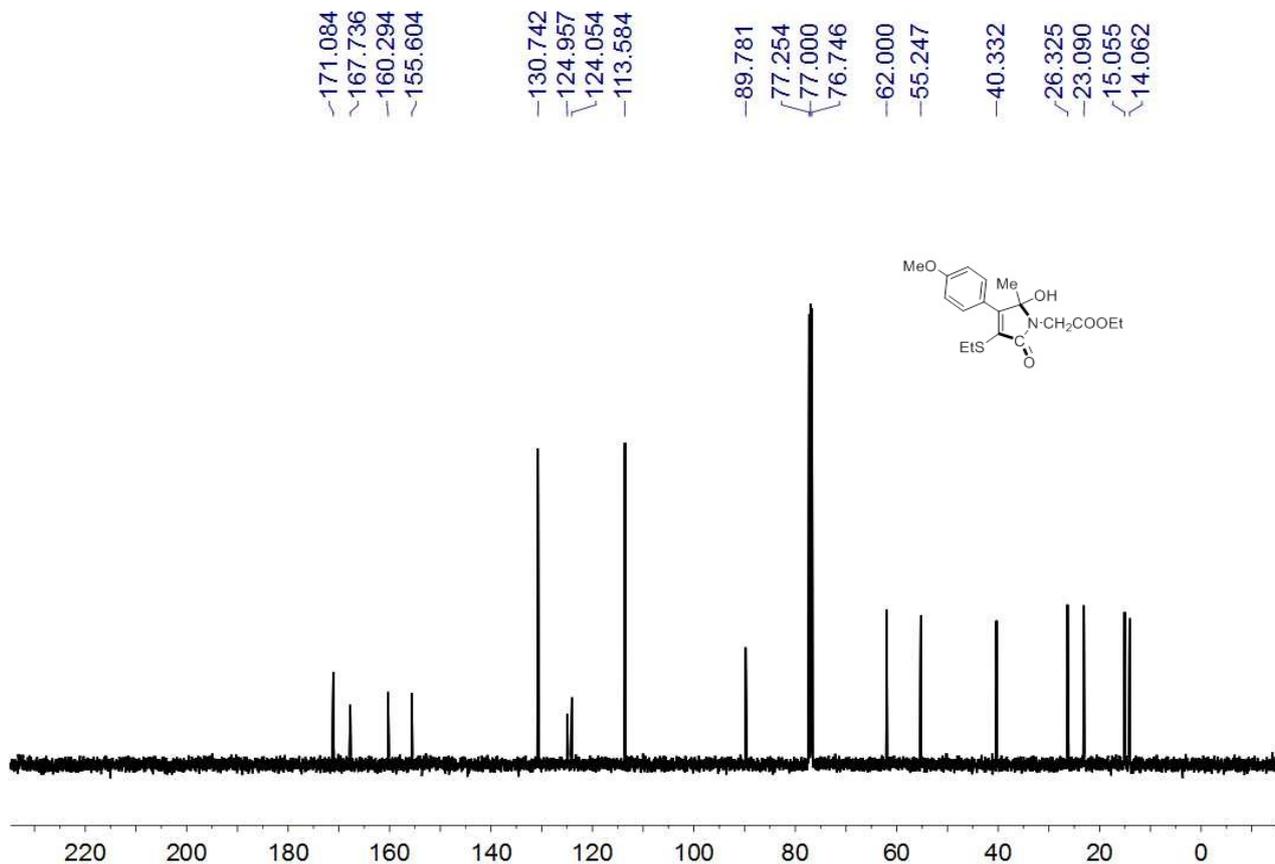
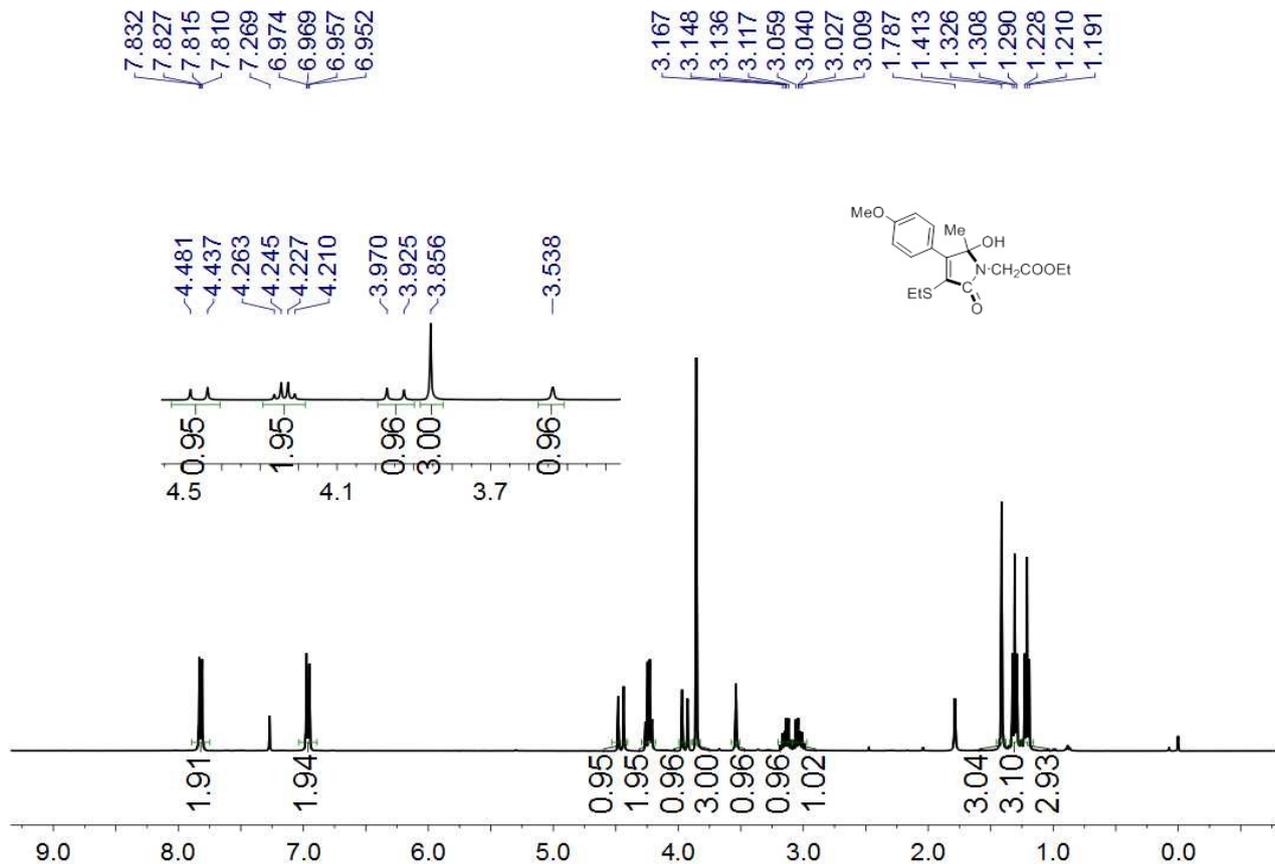
3a



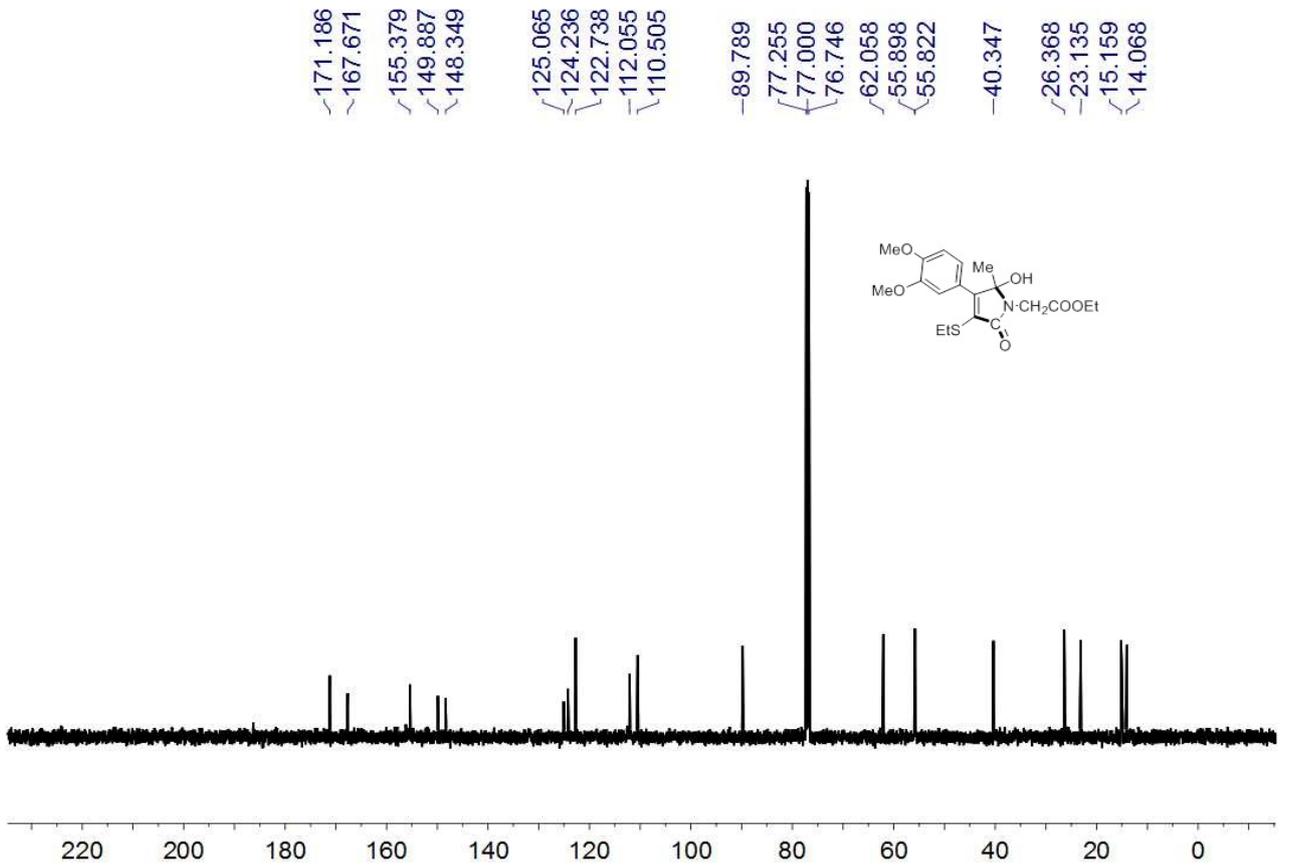
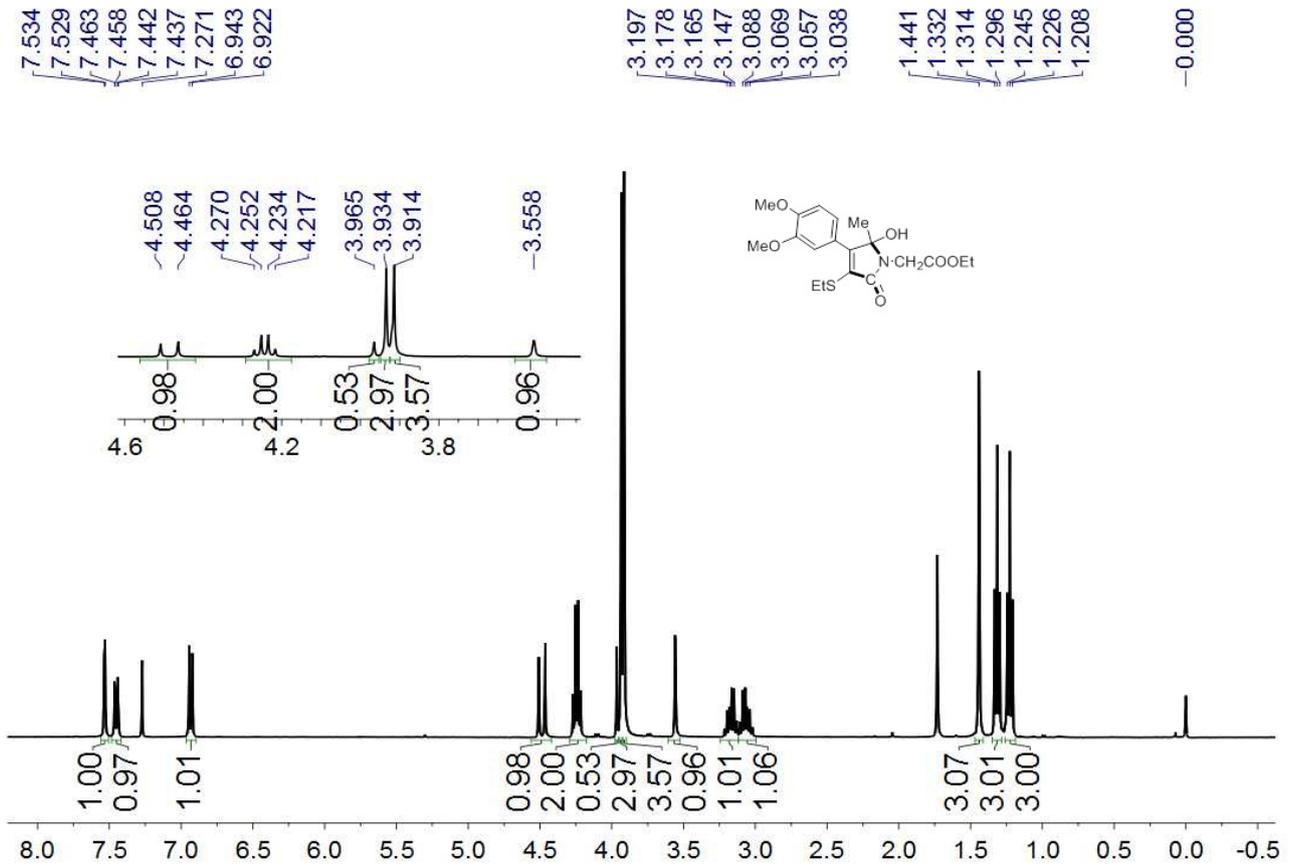
3b



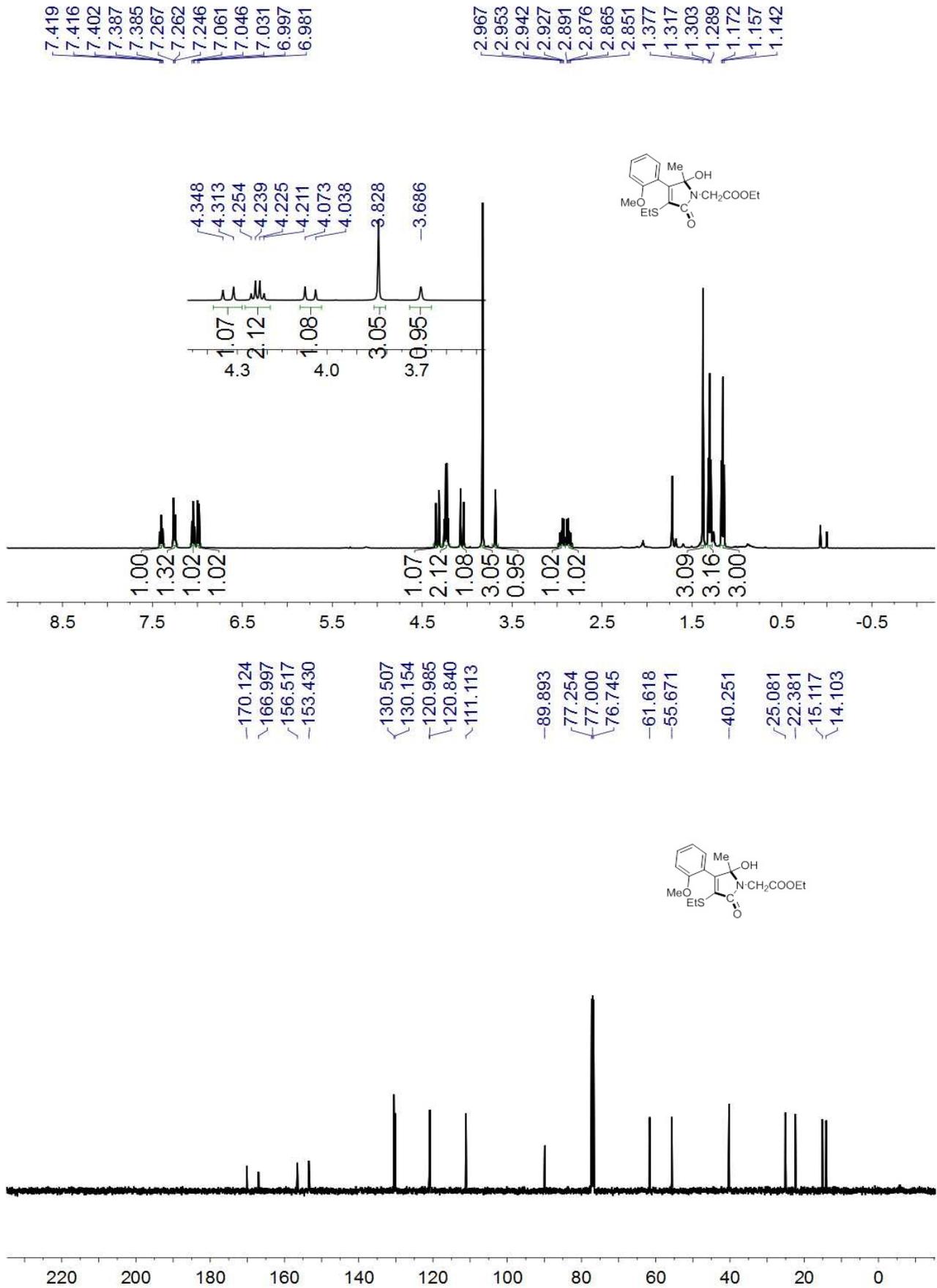
3c



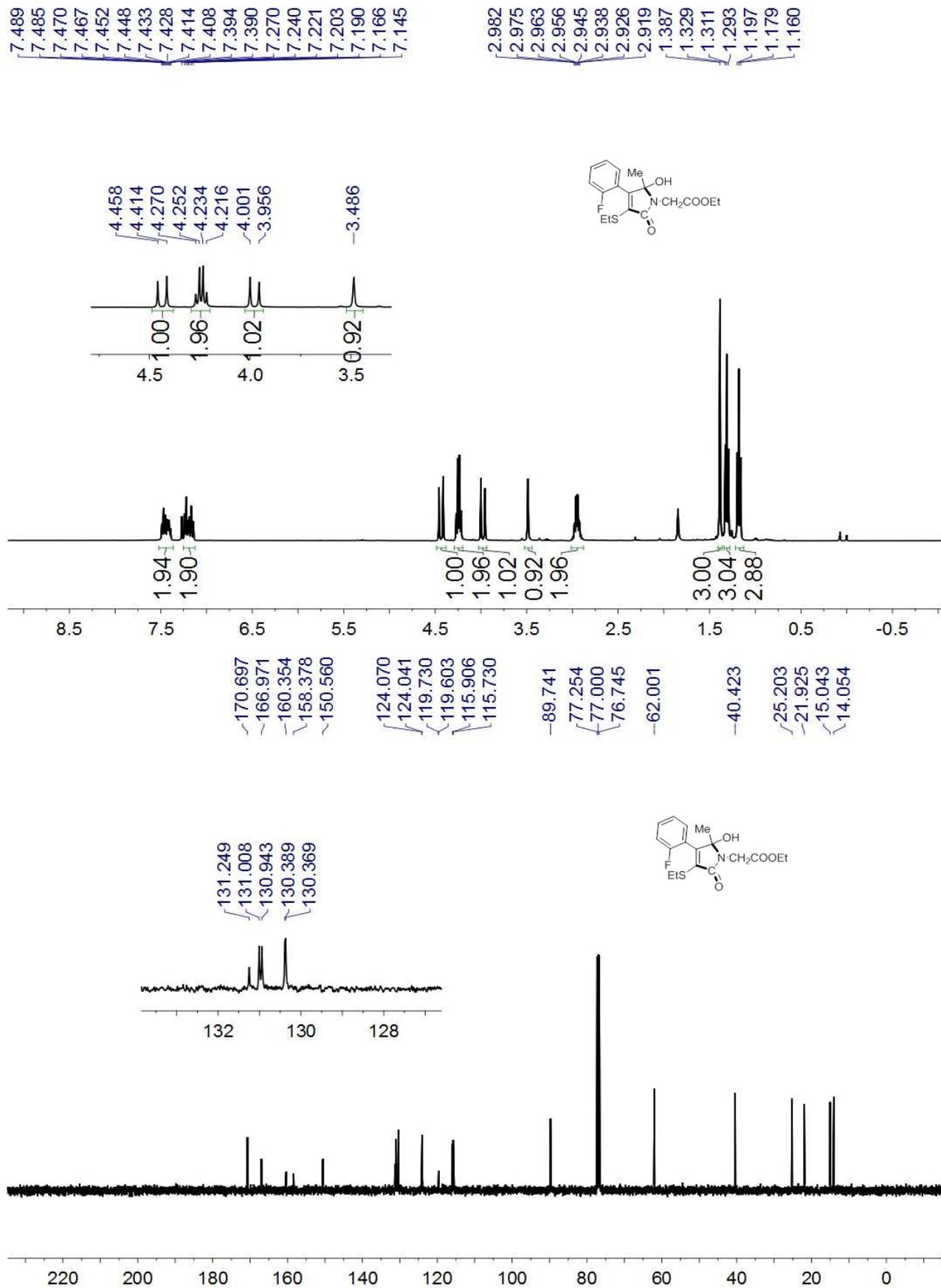
3d



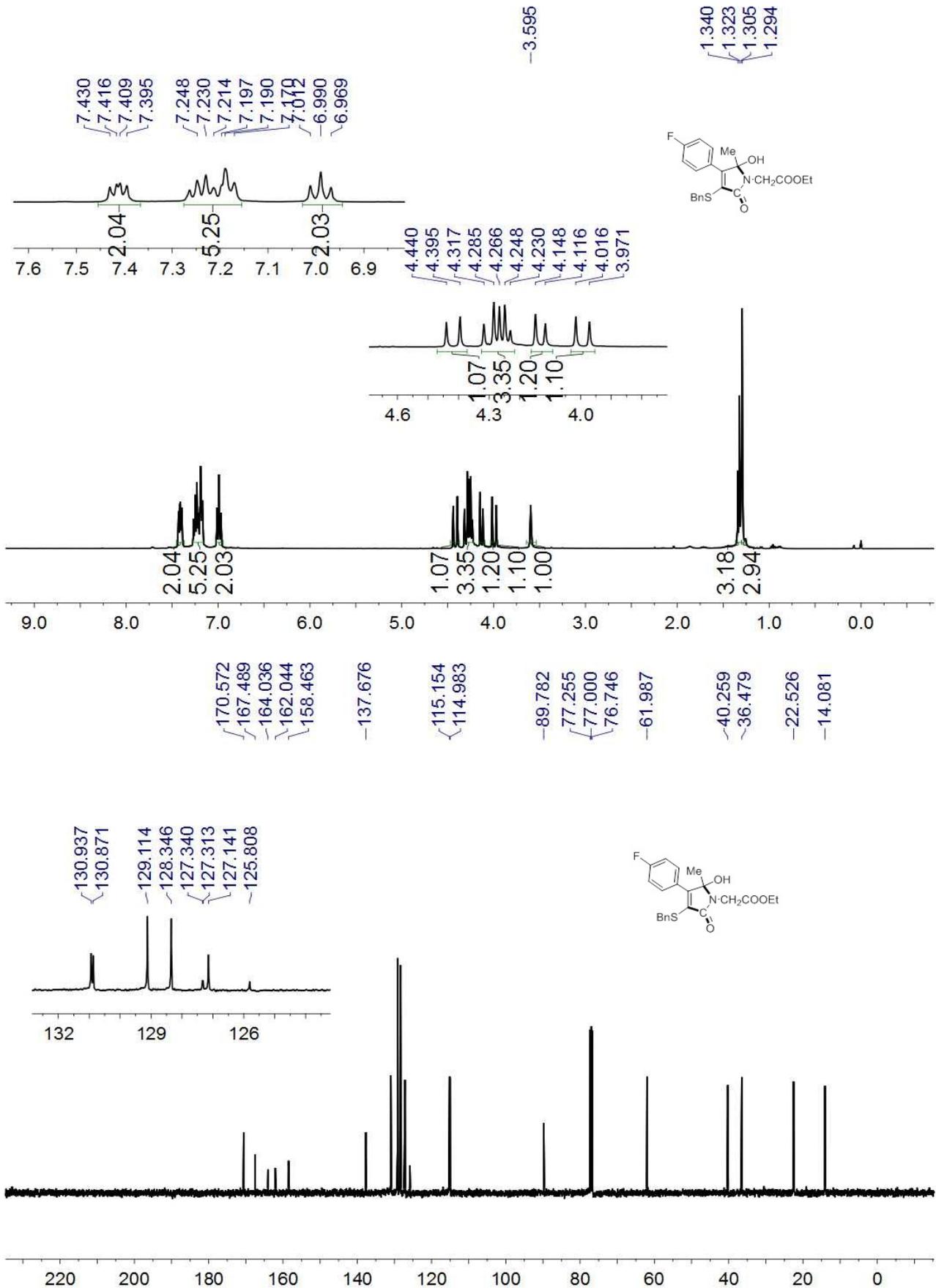
3e



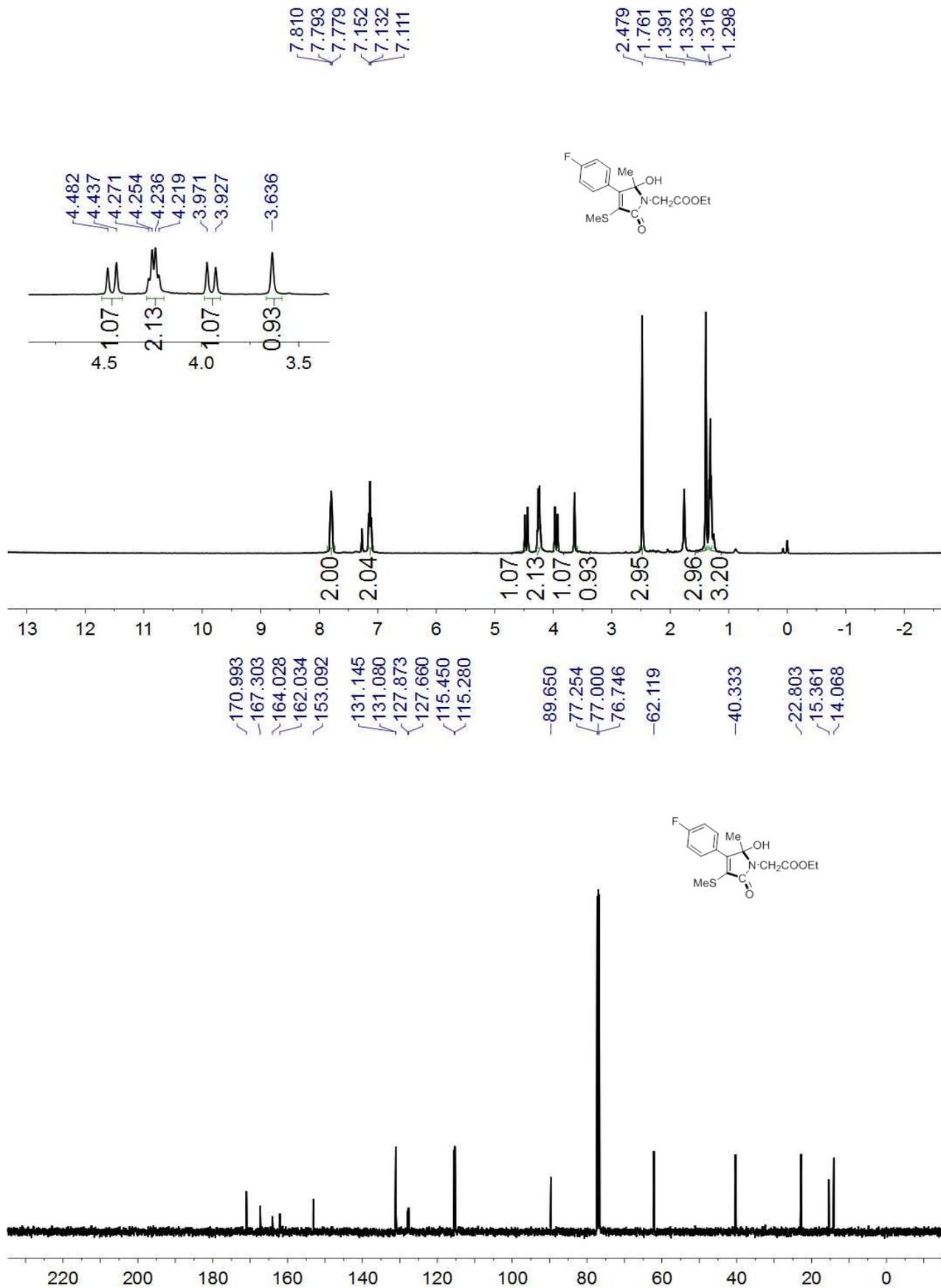
3f



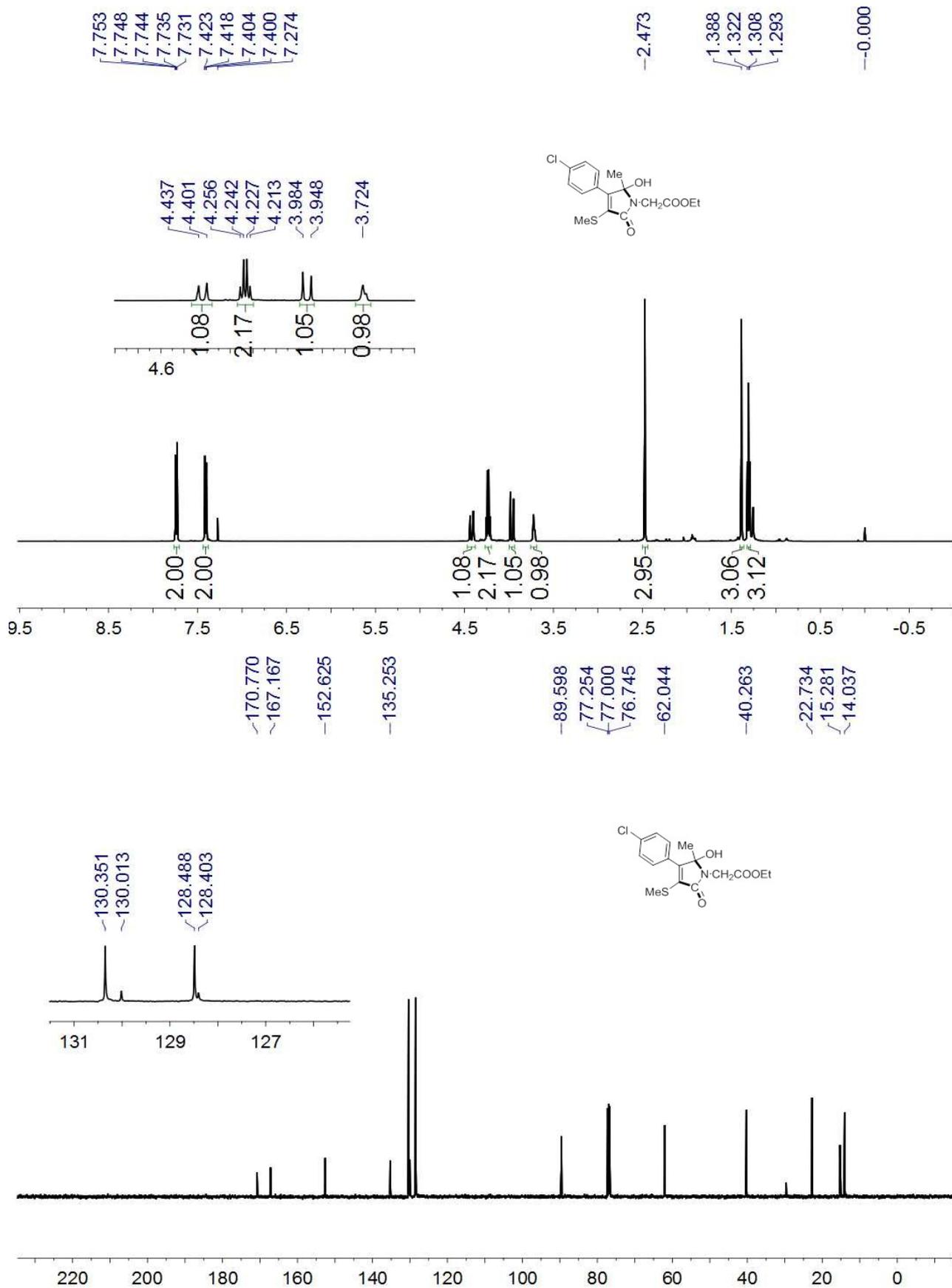
3g



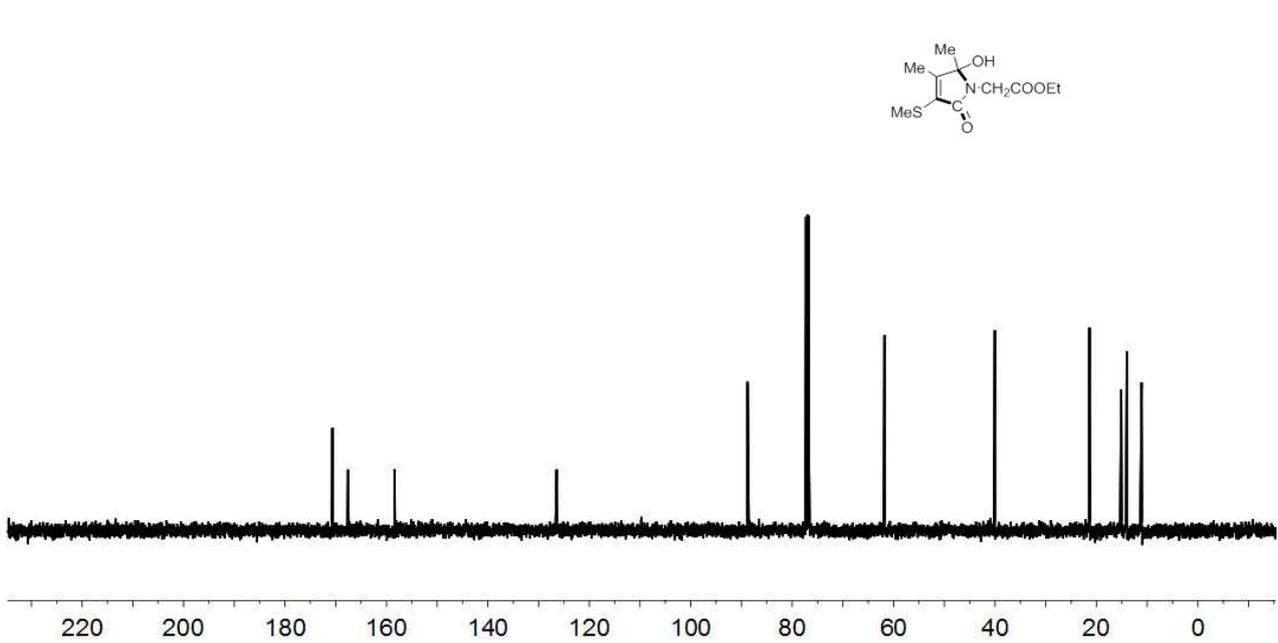
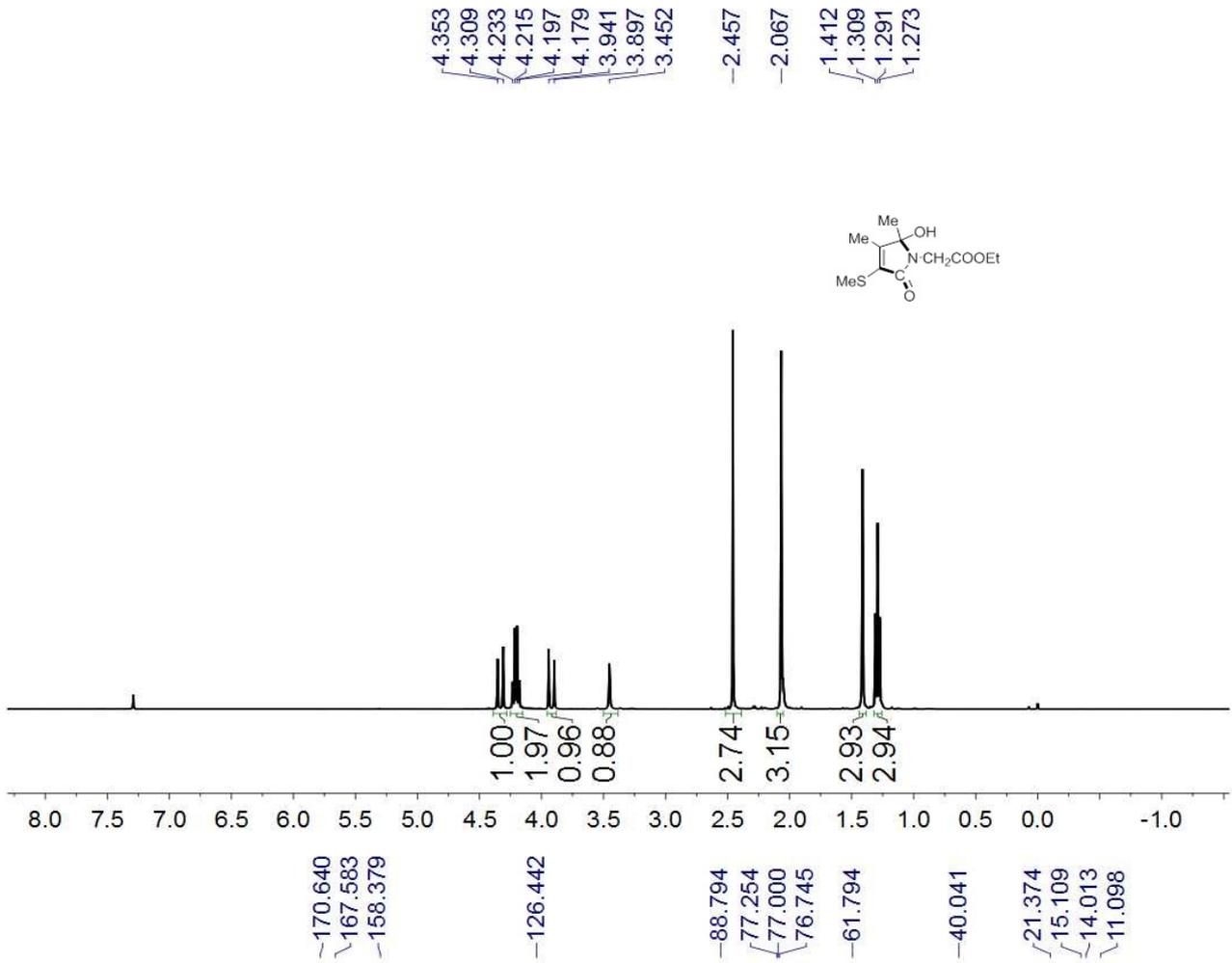
3h



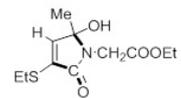
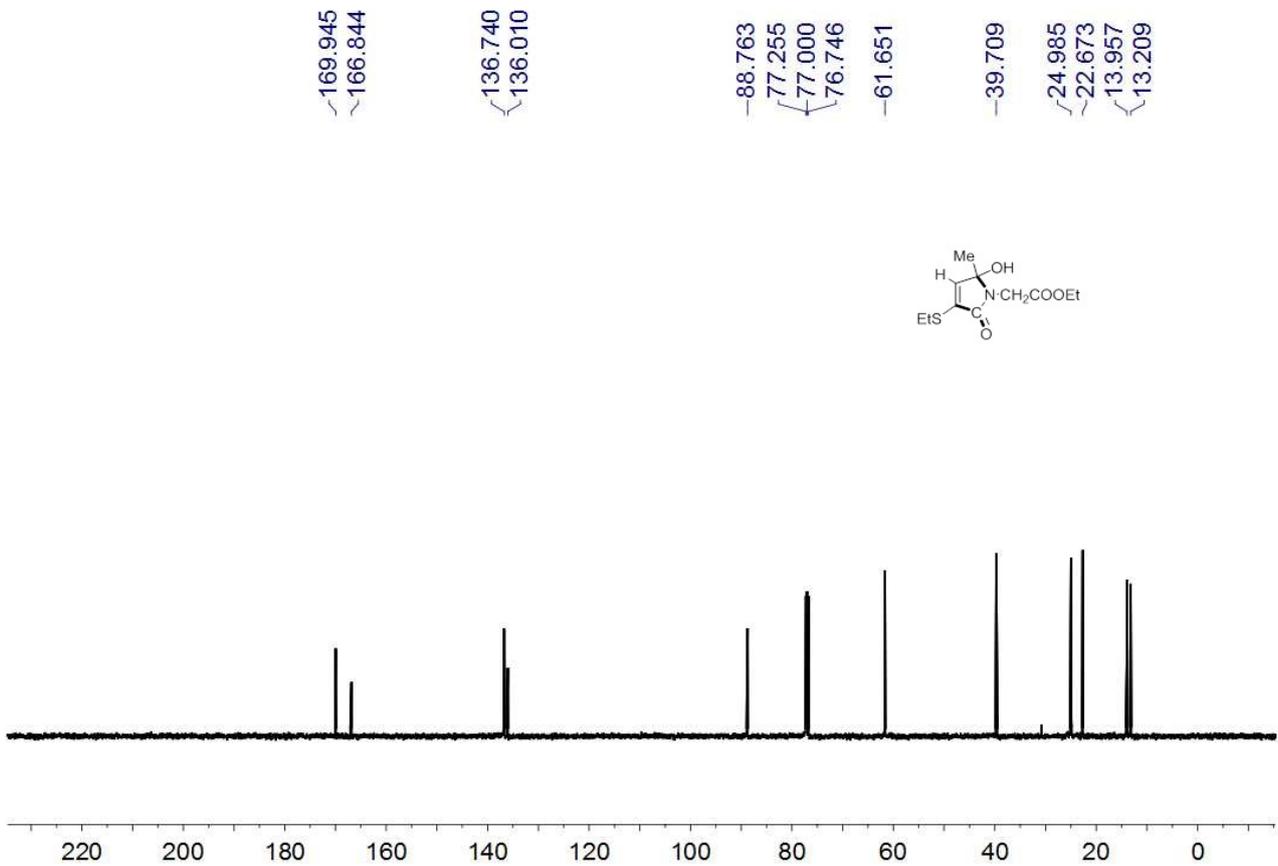
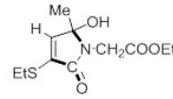
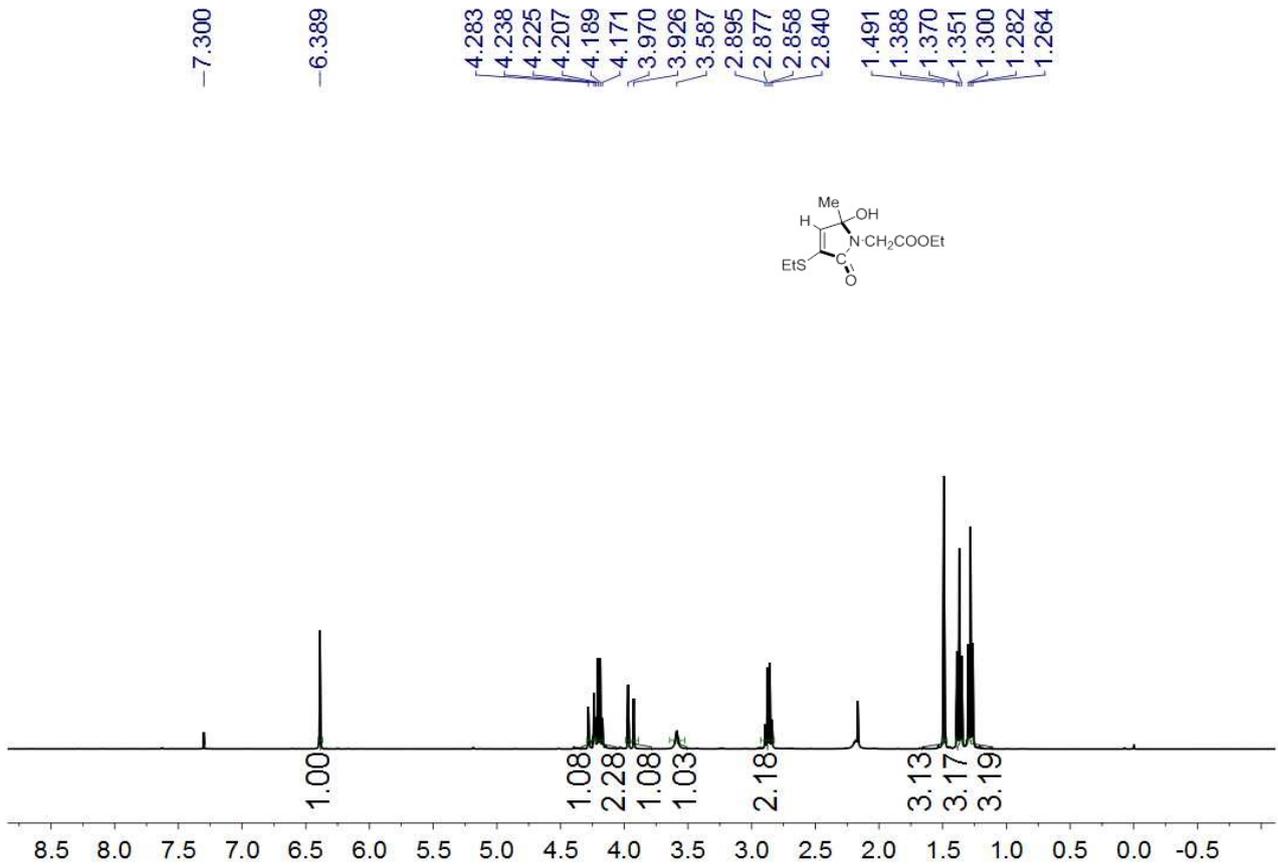
3i



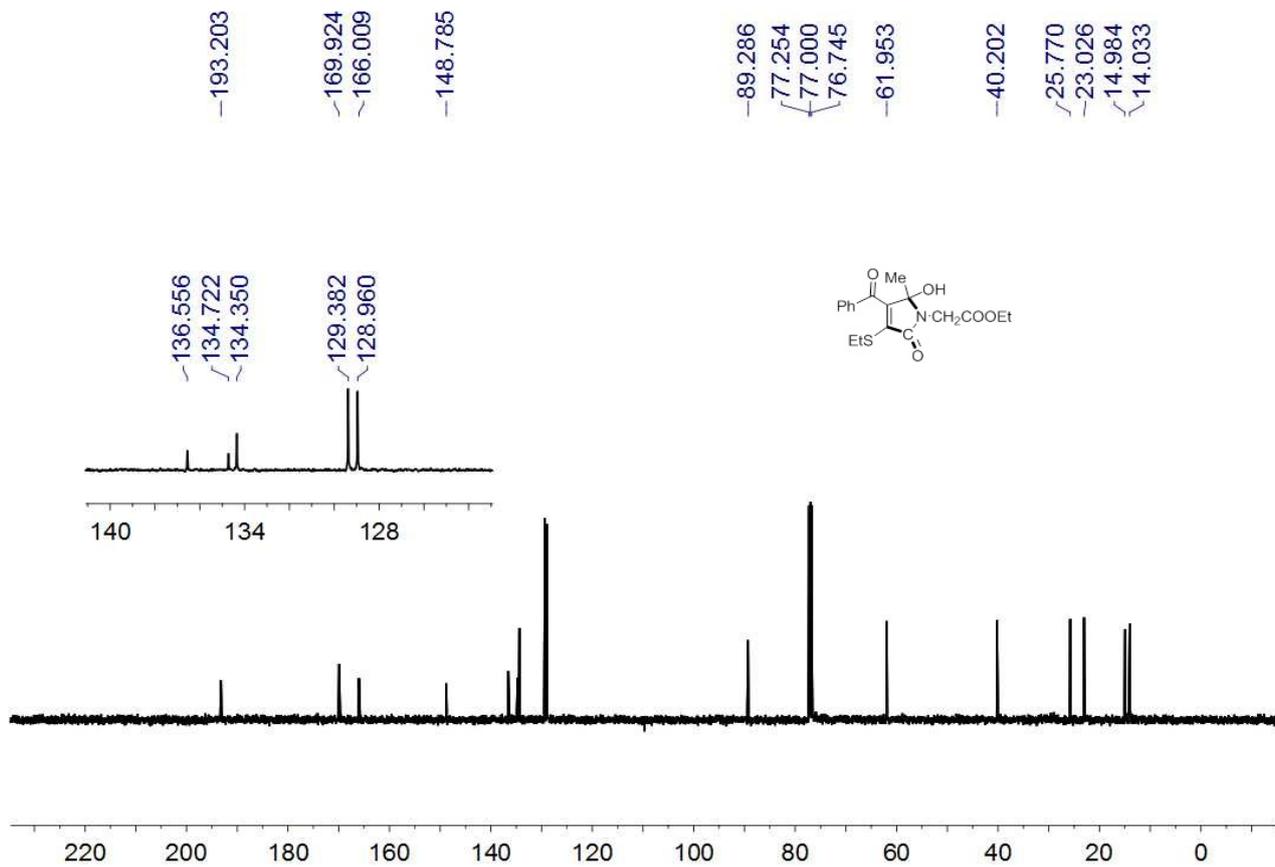
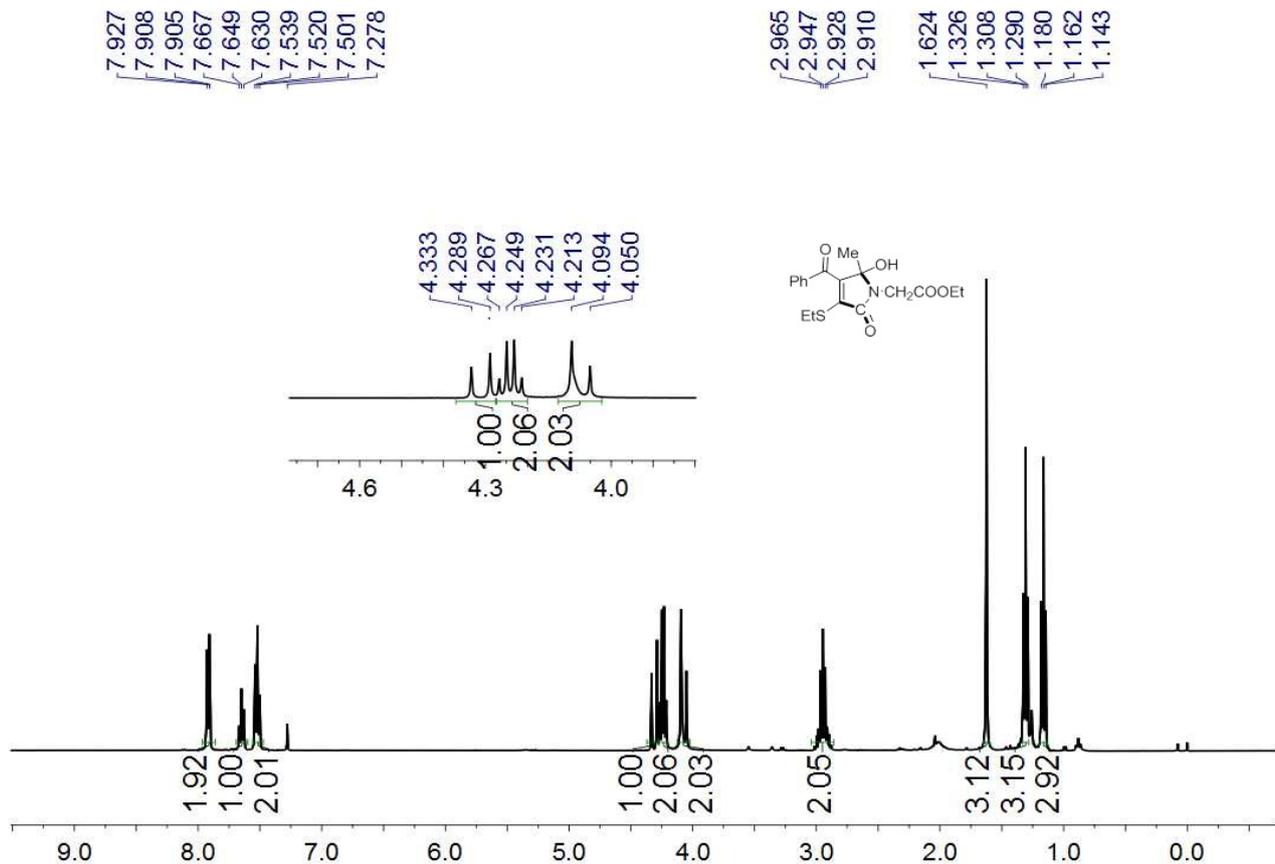
3j



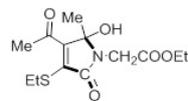
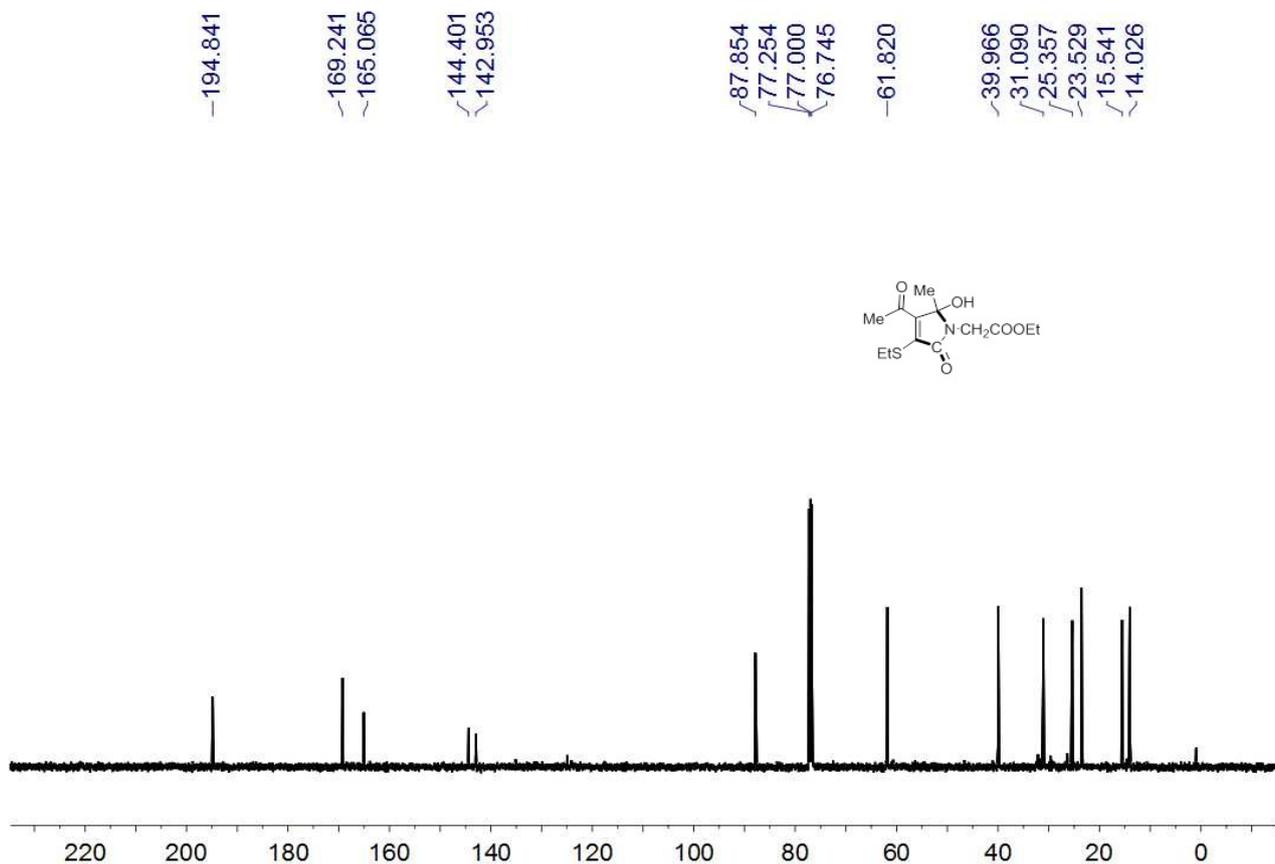
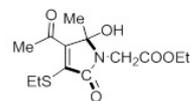
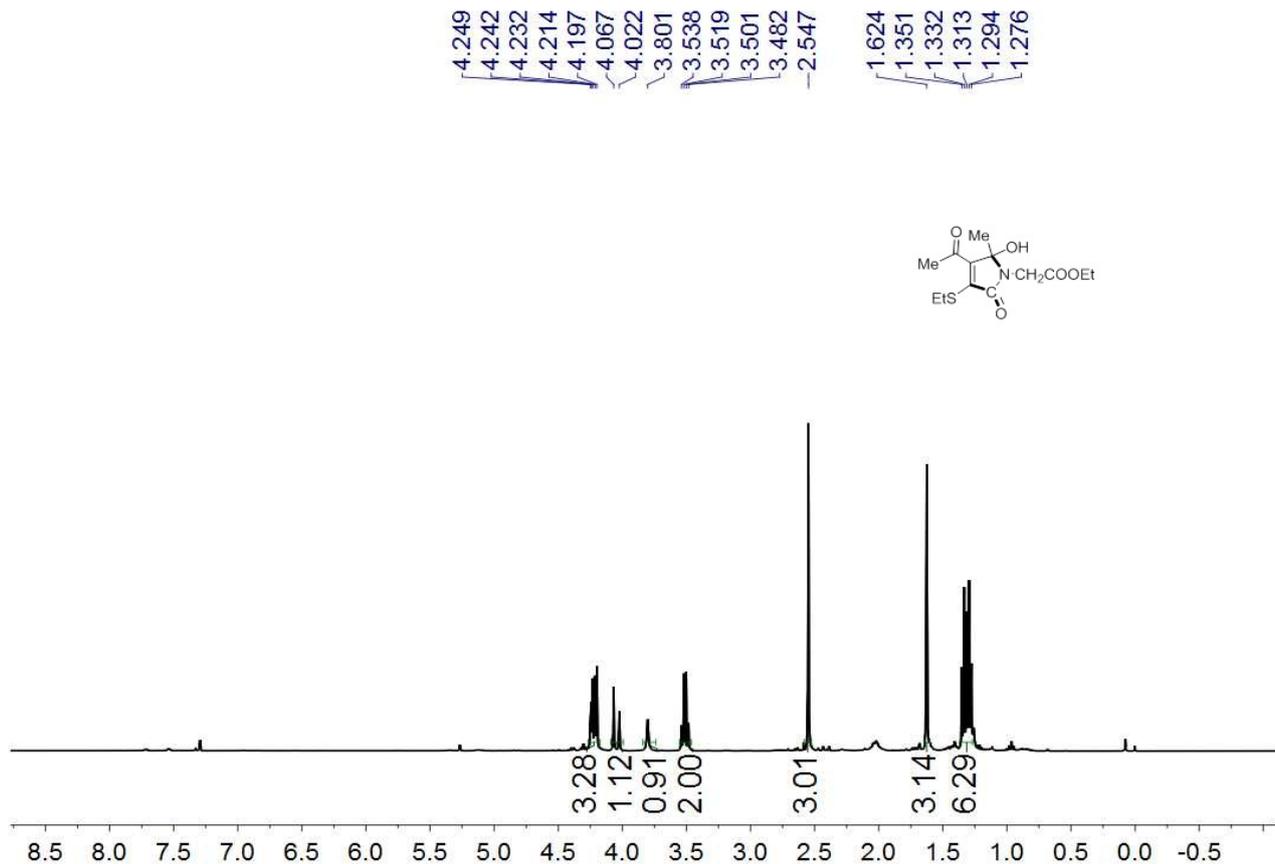
3k



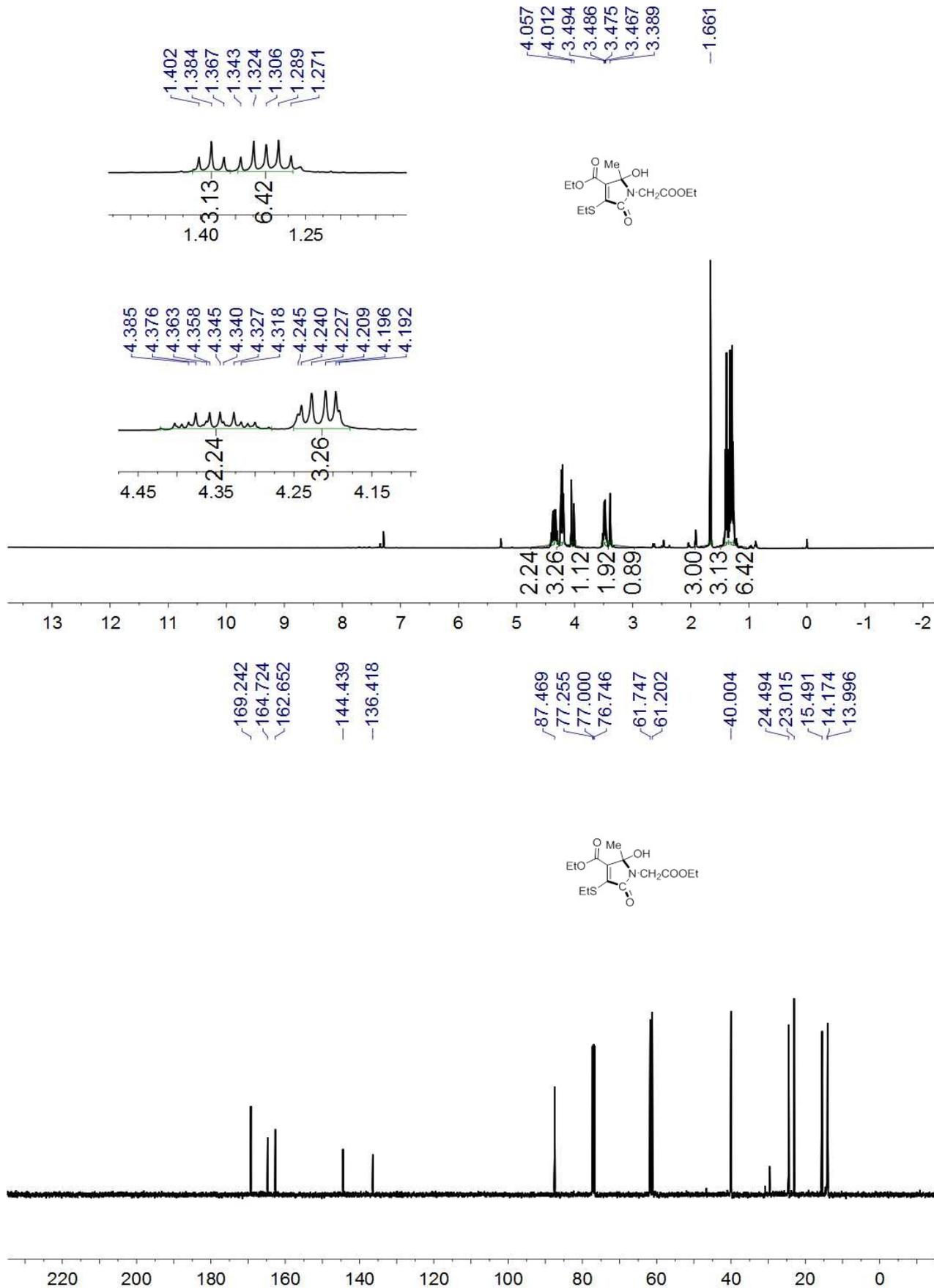
31



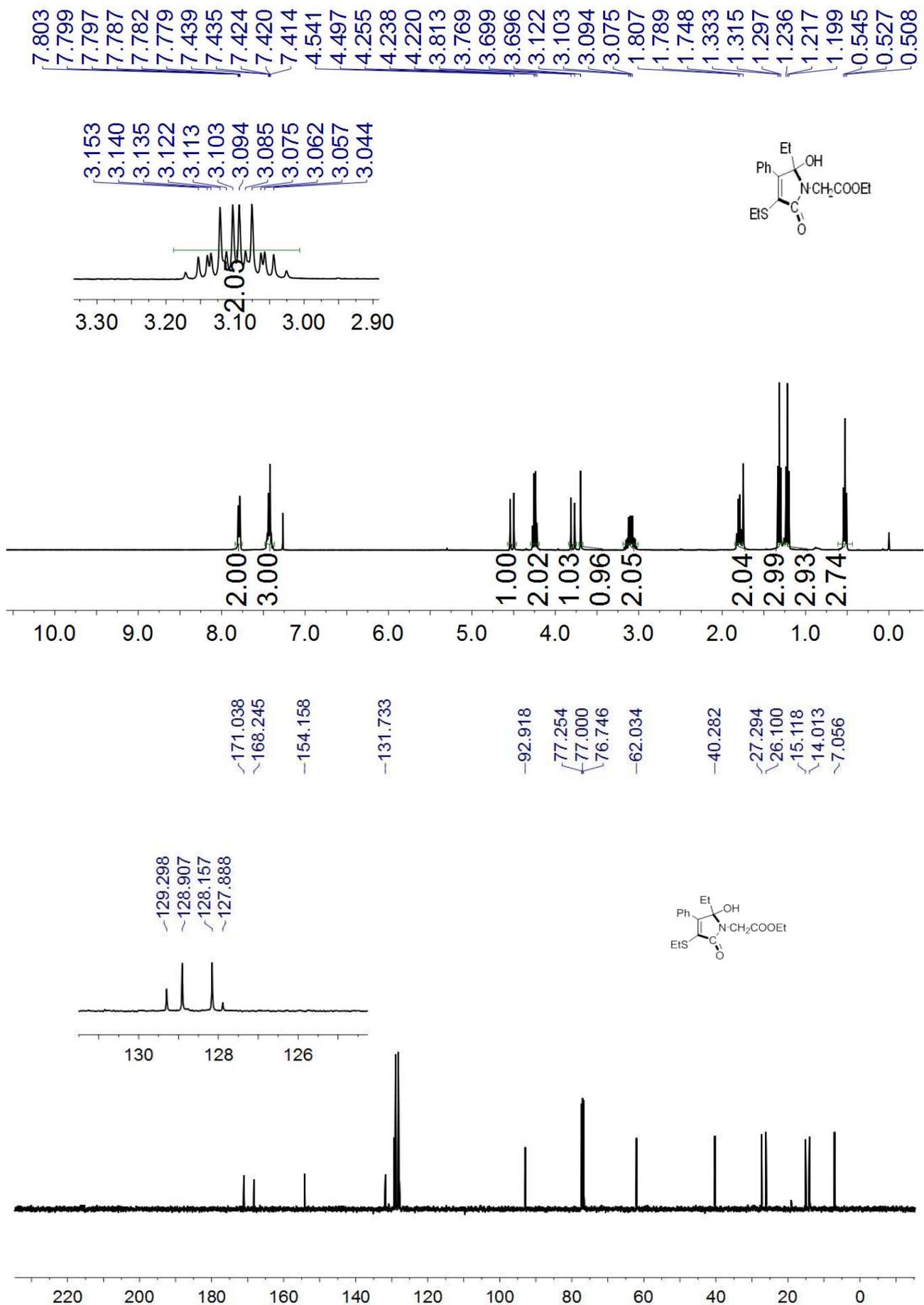
3m



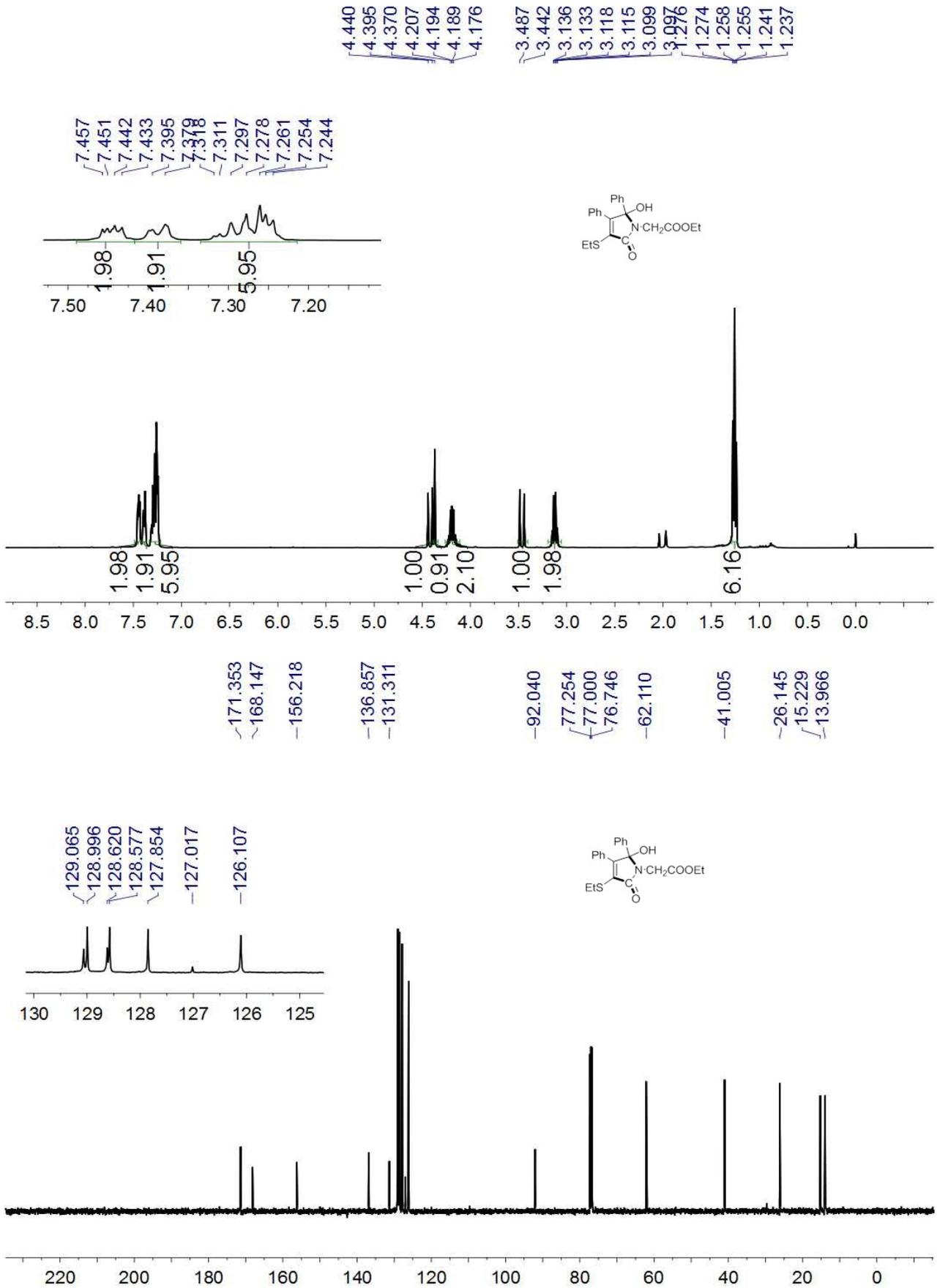
3n



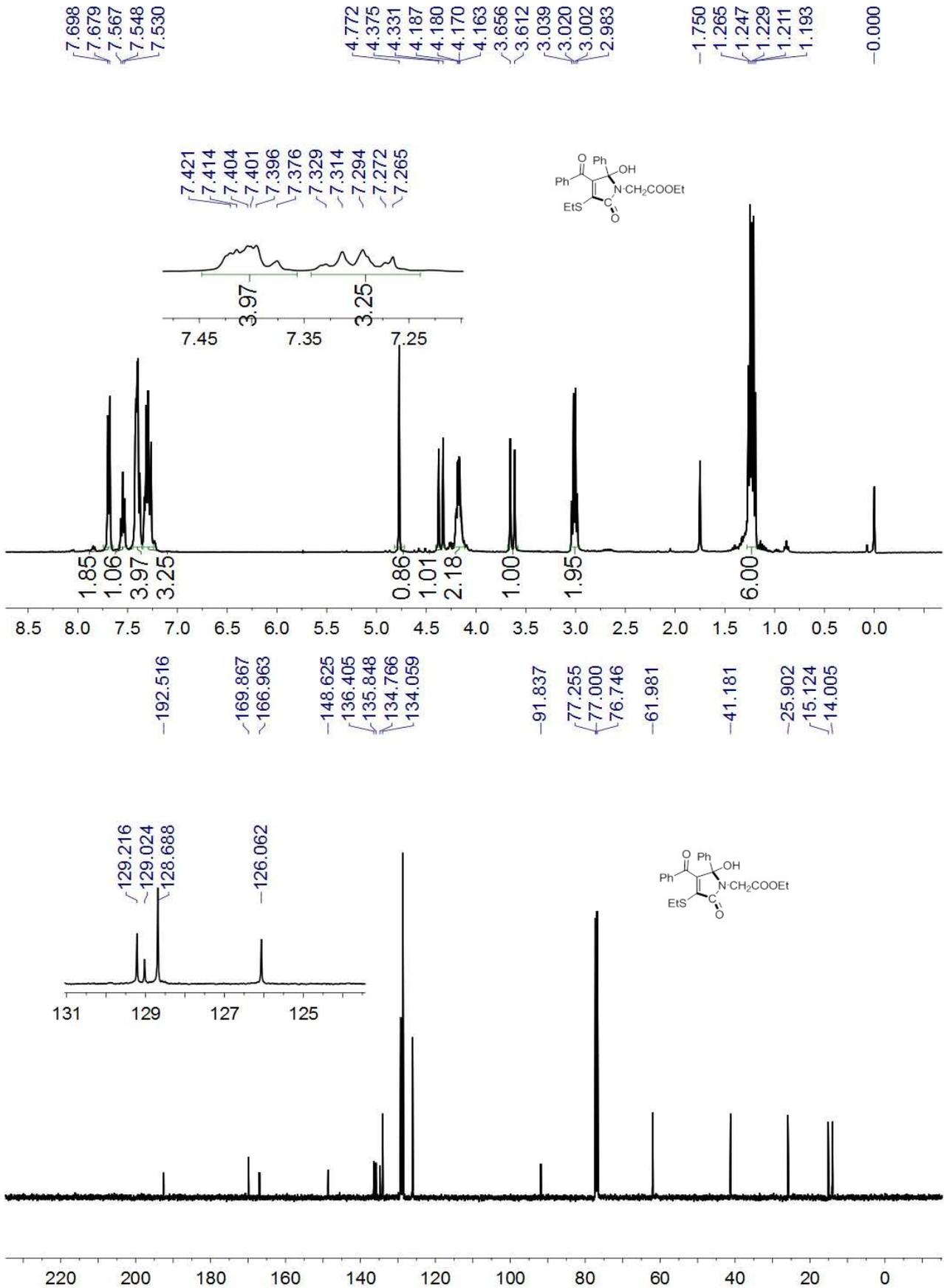
30



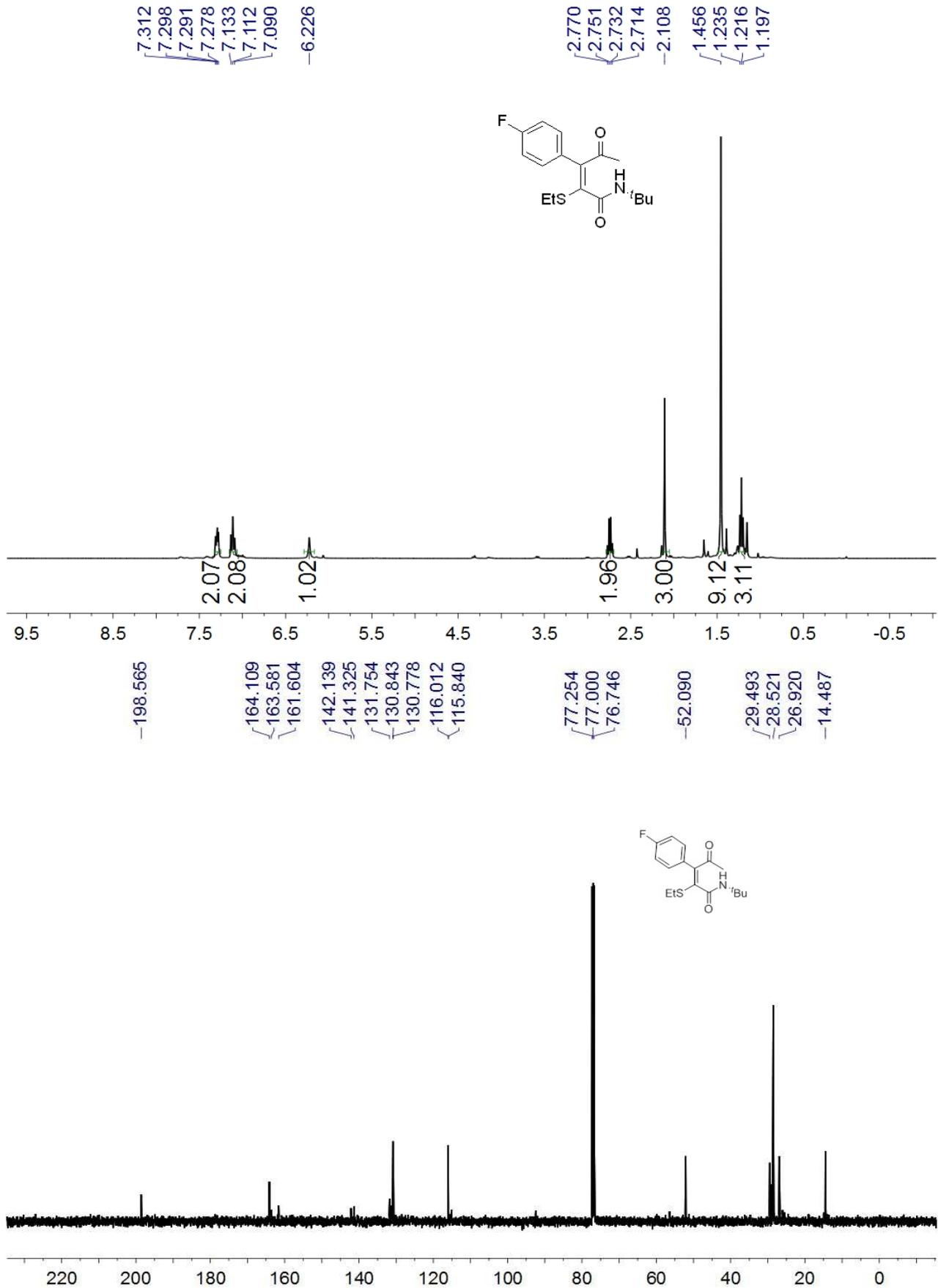
3p



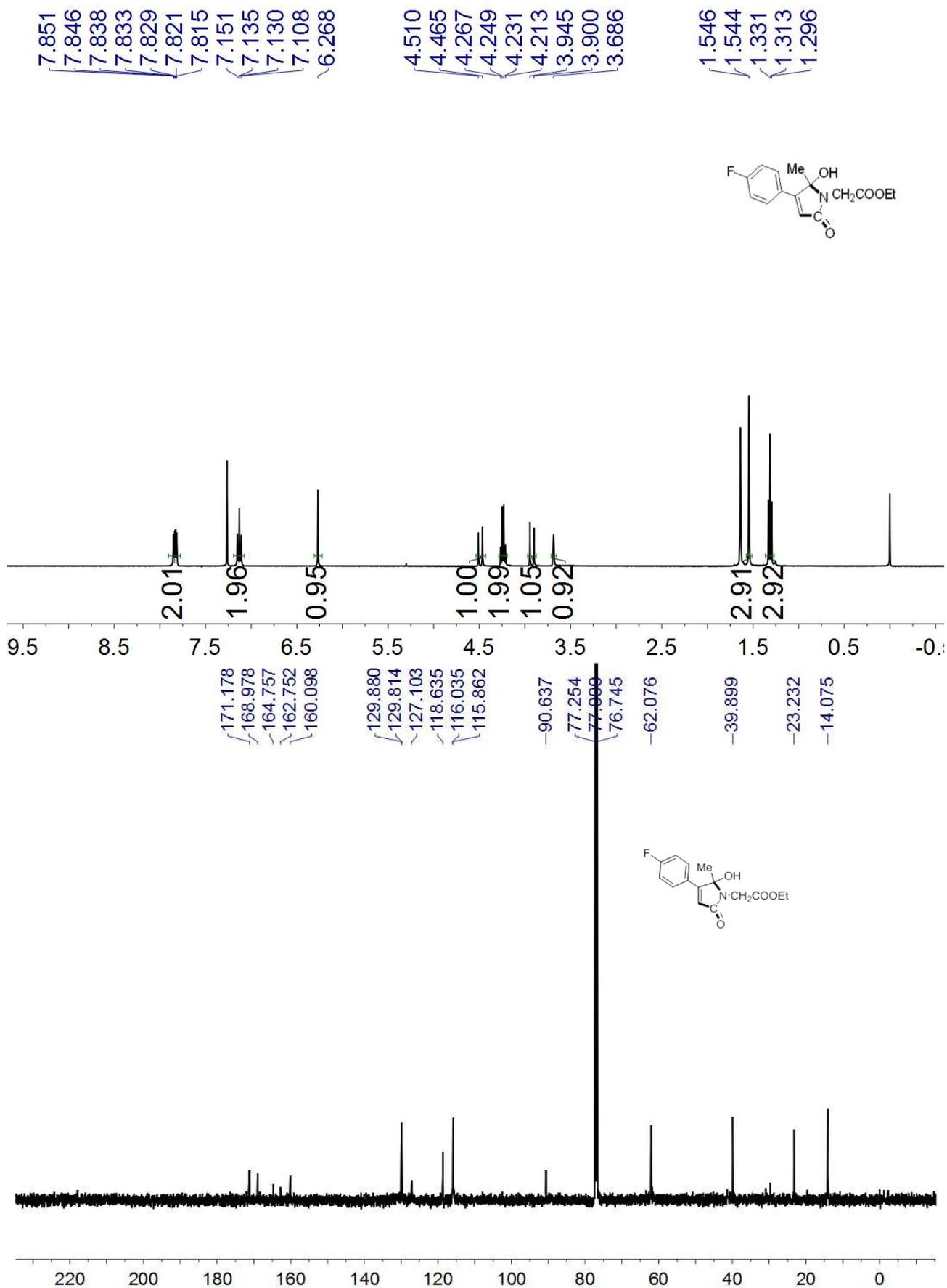
3q



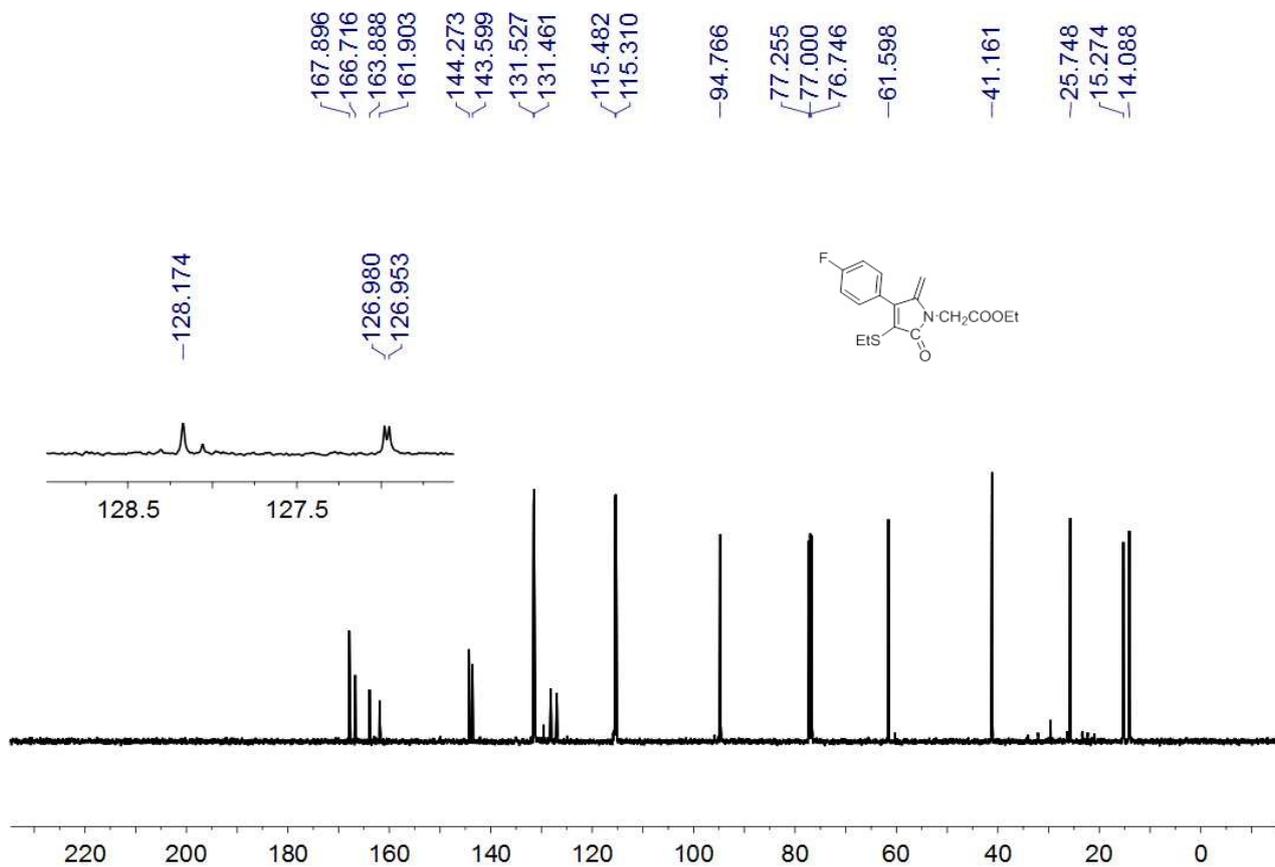
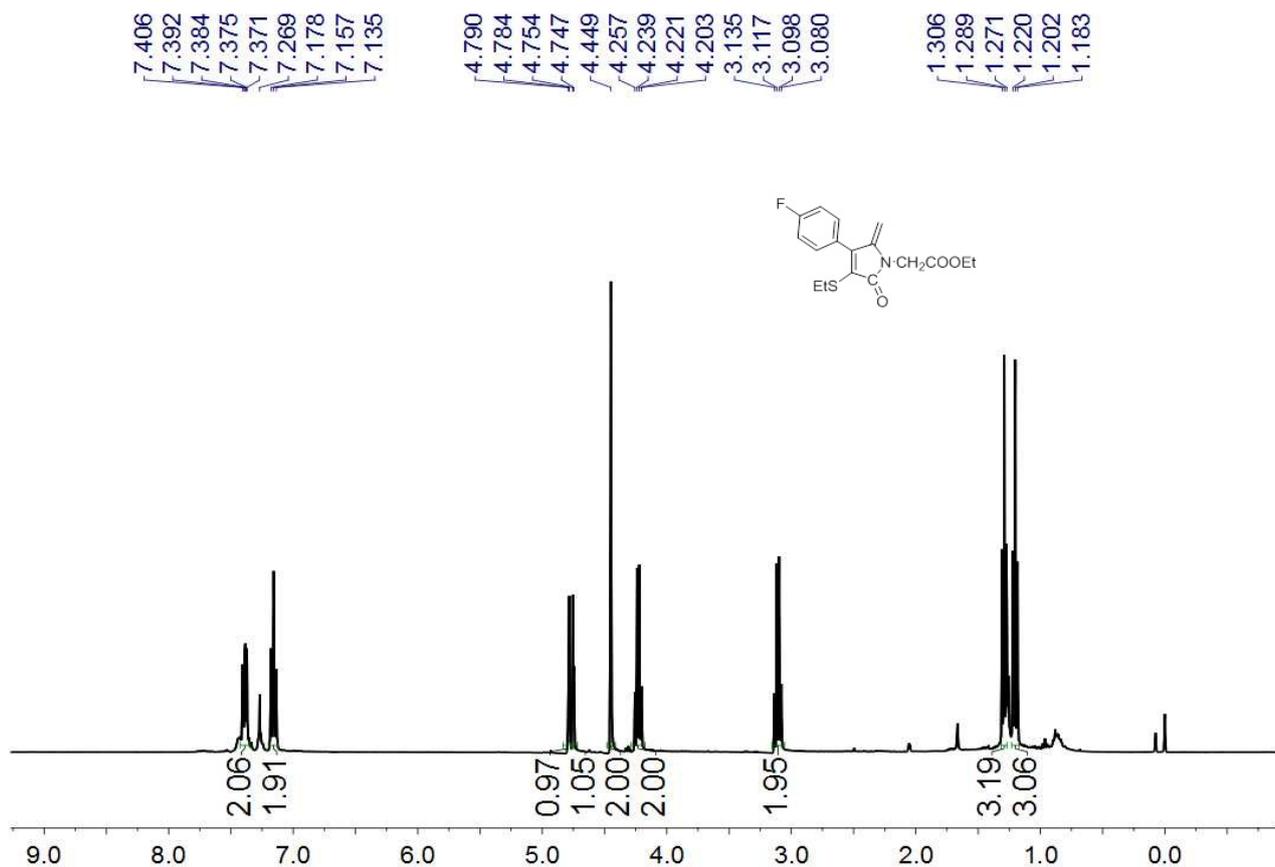
4a



5a



6a



7a

