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Asymmetric synthesis of 3-prenyl-substituted pyrrolidin-2-ones

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Contents

1. General remarks

Commercially available reagents were used without further purification. The solvents were purified by standard procedures. Reactions were monitored by thin layer chromatography using silica plates and stained with iodine. Chromatographic purification was performed on silica gel (Acros 0.035–0.070). The NMR ^{1}H and ^{13}C spectra were recorded by Bruker AM 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C acquisitions) in $CDCl_3$. The chemical shifts of ^{1}H and ^{13}C were measured relative to Me_4Si or $CDCl_3$ respectively. The high resolution mass spectra (HR-MS) were measured by Bruker microTOF II with electrospray ionization (ESI).

2. Synthesis and characterization of compounds 3 - 11 and 5'-11'

Pyrrolidin-2-ones 3a-c (General procedure)

Nitro esters **2a-c** (4 mmol) and $NiCl_2 \cdot 6H_2O$ (0.96 g, 4 mmol) were dissolved in MeOH (15 mL). The $NaBH_4$ (0.92 g, 24.1 mmol) was added to the resulting solution with stirring in small portions at 0-5 ºC and the reaction mixture was stirred at ambient temperature for 3 h. The mixture was cooled to 0-5 ºC, another portion of $NaBH_4$ (0.92 g, 24.1 mmol) was added and the mixture was stirred overnight at ambient temperature. Saturated aqueous NH_4Cl (15 mL) was added, the heterogeneous mixture was filtered and the filtrate was extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure (10 torr). The residue was purified by column chromatography (silica gel, *n*-hexane / EtOAc, 3 : 1) to afford pyrrolidin-2-ones **3a-c**.[1,2]

*Methyl (3S,4R)-2-oxo-4-phenylpyrrolidine-3-carboxylate (**3a**)*. Colorless solid, 0,62 g (71 %), mp 120-123 ºC (lit.[3] 94-96 ºC for (*3R*,*4S*)-**3a**); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.43-3.52 (m, 1H), 3.61 (d, *J* 9.6 Hz, 1H), 3.80 (s, 3H), 3.84-3.87 (m, 1H), 4.11-4.19 (m, 1H), 6.66 (s, 1H), 7.27-7.40 (m, 5H).

*Methyl (3S,4R)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-oxopyrrolidine-3-carboxylate (**3b**)*; Colorless solid, 0,88 g (66 %), mp 138-140 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58-1.69 (m, 2H), 1.79-2.00 (m, 6H), 3.39-3.45 (m, 1H), 3.56 (d, *J* 9.7Hz, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 3.77-3.84 (m, 1H), 4.01-4.10 (m, 1H), 4.76-4.77 (m, 1H), 6.77-6.86 (m, 3H), 6.93 (s, 1H). (spectral data for (*3R*,*4S*)-**3b** are reported in[4])

*Methyl (3S,4S)-4-isobutyl-2-oxopyrrolidine-3-carboxylate (**3c**).* Colorless solid; 0,55 g (69 %), mp 66-68 ºC (lit.[4] no data); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88-0.92 (m, 6H), 1.30-1.59 (m, 3H), 2.90-3.00 (m, 2H), 3.08 (d, *J* 8 Hz, 1H), 3.51-3.57 (m, 1H), 3.79 (s, 3H), 6.92 (s, 1H).

C-Alkylation products 5a-c and 5c' (General procedure)

Pyrrolidin-2-one **3a-c** (4.0 mmol) was added to a stirred boiling suspension of sodium metal (92 mg, 4.0 mmol) in dry toluene (10 mL) under argon atmosphere. Then, a solution of alkylating agent **4a** or **4b** (4.4 mmol) in toluene (2 mL) was added dropwise to the reaction mixture with the rate maintaining moderate boiling and the mixture was further refluxed for 5-12 h (TLC-monitoring). The mixture was cooled to ambient temperature and diluted with water (5 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were successively washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure (10 torr) and the residue was purified by column chromatography (silica gel, *n*-hexane / EtOAc from 9 : 1 to 2 : 1) to afford corresponding alkylation product **5a-c** or **5c'**.

*Methyl (4R)-3-(3-methylbut-2-enyl)-2-oxo-4-phenylpyrrolidine-3-carboxylate (**5a**)*. Colorless oil. Yield 0.34 g (59%), from 2 mmol of **3a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.79 (s, 3H), 1.81 (s, 3H), 2.72 (d, *J* 7.5Hz, 2H), 3.49 (s, 3H), 3.57-3.62 (m, 1H), 3.74-3.94 (m, 2H), 5.13 (t, *J* 7.3Hz, 1H), 6.67 (br. s, 1H), 7.17 (d, *J* 6.8Hz, 2H), 7.28-7.38 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.4, 26.1, 29.5, 44.8, 46.8, 51.9, 60.9, 118.6, 127.8, 128.1, 128.6, 136.1, 136.6, 170.4, 175.5; HRMS (ESI), m/z: 288.1595 $[M+H]^+$ (calc. for $C_{17}H_{22}NO_3^+$, m/z: 288.1594).

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*Methyl (4R)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-(3-methylbut-2-enyl)-2-oxopyrrolidine-3-carboxylate (**5b**).* Colorless oil, 0.35 g (58%) from 1.5 mmol of **3b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61-1.70 (m, 2H), 1.79 (s, 3H), 1.80 (s, 3H), 1.86-1.90 (m, 6H), 2.72 (d, *J* 7.9Hz, 2H), 3.51 (s, 3H), 3.48-3.72 (m, 2H), 3.84 (s, 3H), 3.82-3.88 (m, 1H), 4.72-4.80 (m, 1H), 5.12 (t, *J* 7.2Hz, 1H), 6.45 (br. s, 1H), 6.69-6.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5, 24.0, 24.0, 26.2, 29.5, 32.9, 32.9, 45.0, 46.3, 52.0, 56.0, 60.7, 80.8, 111.9, 115.7, 118.8, 120.3, 128.8, 135.9, 147.6, 149.8, 170.5, 175.5; HRMS (ESI), m/z: 402.2270 $[M+H]^+$ (calc. for $C_{23}H_{32}NO_5^+$, m/z: 402.2275).

*Methyl (4S)-4-isobutyl-3-(3-methylbut-2-enyl)-2-oxopyrrolidine-3-carboxylate (**5c**).* Colorless oil, 0.57 g (53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82-0.89 (m, 6H), 1.07-1.29 (m, 2H), 1.45-1.54 (m, 1H), 1.63 (s, 3H), 1.70 (s, 3H), 2.51-2.66 (m, 3H), 3.05-3.11 (m, 1H), 3.35-3.41 (m, 1H), 3.71 (s, 3H), 5.03 (t, *J* 7.5Hz, 1H), 6.38 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.2, 21.6, 23.8, 25.9, 29.5, 38.4, 39.2, 41.3, 46.0, 52.1, 58.5, 118.9, 135.8, 171.4, 176.4; HRMS (ESI), m/z: 268.1903 $[M+H]^+$ (calc. for $C_{15}H_{26}NO_3^+$, m/z: 268.1907).

*Methyl (4S)-4-isobutyl-3-((E)-3,7-dimethylocta-2,6-dienyl)-2-oxo-pyrrolidine-3-carboxylate (**5c'**).* Colorless oil, 0.77 g (57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.85-0.92 (m, 6H), 1.11-1.73 (m, 12H), 2.06 (m, 4H), 2.56-2.71 (m, 3H), 2.95-3.14 (m, 1H), 3.36-3.44 (m, 1H), 3.75 (s, 3H), 5.08-5.11 (m, 2H), 6.21 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5, 17.8, 21.7, 23.8, 26.0, 26.6, 29.3, 32.6, 38.4, 39.2, 40.1, 46.0, 52.1, 58.5, 119.0, 124.2, 131.5, 139.5, 171.4, 176.2; HRMS (ESI), m/z: 336.2529 $[M+H]^+$ (calc. for $C_{20}H_{34}NO_3^+$, m/z: 336.2533).

4-Prenyl-substituted pyrrolidin-2-ones 6a-c and 6c' (General procedure)

Solid KOH (0.13 g, 2.40 mmol) was added to a stirred solution of diester **5a-c** or **5c'** (0.80 mmol) in methanol (2 mL) / water (0.3 mL) and the reaction mixture was refluxed for 10-18 h (TLC control). The MeOH was evaporated under reduced pressure (10 torr) and the residue was diluted with water (10 mL). Neutral impurities were removed by extraction with diethyl ether (2 x 5 mL). Then, the aqueous layer was acidified to pH 5 with diluted HCl and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to afford the corresponding carboxylic acid which was subjected to thermal decarboxylation without further purification. For that, the acid was dissolved in toluene and the resulting solution was refluxed for 6-8 h (TLC control). The reaction mixture was concentrated under reduced pressure (10 torr) and the residue was purified by column chromatography (silica gel, *n*-hexane / EtOAc 3 : 1 to 1 : 10) to afford corresponding pyrrolidin-2-one **6a-c** or **6c'**.

*3-(3-Methylbut-2-enyl)-4-phenylpyrrolidin-2-one (**6a**).* Colorless solid, 120 mg (66%), m.p. 57-60 ºC. Mixture of (3*S*,4*R*)- *and* (3*R*,4*R*)-diastereomers, *dr* 70 : 30; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59 (s, 3H), 1.66 (s, 3H), 2.31-2.43 (m, 2H), 2.65-2.80 (m, 1H), 3.31-3.81 (m, 3H), 4.99 (t, *J* 7.3Hz, 0.3H), 5.07 (t, *J* 7.2Hz, 0.7H), 6.33 (br. s, 1H), 7.20-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.6, 18.0, 24.7, 25.8, 27.3, 43.8, 46.0, 46.6, 47.5, 48.4, 48.9, 120.5, 121.5, 127.1, 127.3, 127.5, 128.0, 128.1, 128.6, 128.6, 128.8, 128.9, 128.9, 133.1, 134.1, 140.5, 141.8, 179.2; HRMS (ESI), m/z: 230.1542 $[M+H]^+$ (calc. for $C_{15}H_{20}NO^+$, m/z: 230.1539). According to HPLC (OJ, *n*-hexane/*i*-PrOH 95:5, 1 ml/min, 220 nm; retention times for major diastereomer: t_{major} = 8.7 min; t_{minor} = 10.2 min; for minor diastereomer: t_{major} = 7.1 min; t_{minor} = 7.5 min) enantiomeric purity for major diastereomer was 94% *ee*.

*4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3-(3-methylbut-2-enyl)pyrrolidin-2-one (**6b**).* Colorless solid, 110 mg (64%) from 0.5 mmol of **5b**. Mixture of diastereomers, *dr* 60 : 40. The diastereomers was separated by column chromatography (silica gel, *n*-hexane / EtOAc 1 : 1) and further crystallized from *n*-hexane / Et_2O.

(3*S*,4*R*)-**6b** (major isomer). Colorless solid, 50 mg (29% from **5b**), m.p. 94-97 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59 (s, 3H), 1.59-1.69 (m, 2H), 1.66 (s, 3H), 1.79-1.90 (m, 6H), 2.39 (m, 2H), 2.59-2.66 (m, 1H), 3.21-3.35 (m, 2H), 3.61-3.66 (m, 1H), 3.85 (s, 3H), 4.76-4.78 (m, 1H), 5.07

(t, *J* 7.1Hz, 1H), 6.49 (br. s, 1H), 6.76-6.85 (3H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.1, 24.1, 25.9, 27.3, 32.9, 45.6, 48.3, 48.6, 56.3, 80.8, 112.5, 114.7, 119.8, 120.6, 134.0, 134.1, 148.0, 149.4, 178.8; HRMS (ESI), m/z: 344.2214 $[M+H]^+$ (calc. for $C_{21}H_{30}NO_3^+$, m/z: 344.2220). According to HPLC (OJ, *n*-hexane/*i*-PrOH 95:5, 1 ml/min, 220 nm; t_{minor} = 9.5 min; t_{major} = 12.4 min) enantiomeric purity of the product was 91% *ee*.

(3*R*,4*R*)-**6b** (minor isomer). Colorless solid, 30 mg (18% from **5b**). m.p. 98-101ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 3H), 1.60-1.63 (m, 2H), 1.63 (s, 3H), 1.77-1.89 (m, 6H), 2.32-2.37 (m, 1H), 2.67-2.75 (m, 2H), 3.48-3.52 (m, 1H), 3.58-3.63 (m, 1H), 3.73-3.79 (m, 1H), 3.84 (s, 3H), 4.73-4.74 (m, 1H), 5.01 (t, *J* 6.8Hz, 1H), 6.24 (br. s, 1H), 6.71-6.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.7, 24.1, 24.2, 24.7, 25.8, 32.9, 32.9, 43.5, 45.6, 47.5, 56.2, 80.7, 112.2, 115.2, 120.1, 121.7, 132.9, 133.0, 147.7, 149.2, 179.6; HRMS (ESI), m/z: 344.2214 $[M+H]^+$ (calc. for $C_{21}H_{30}NO_3^+$, m/z: 344.2220). According to HPLC (OJ, *n*-hexane/*i*-PrOH 95:5, 1 ml/min, 220 nm; t_{major} = 7.5 min; t_{minor} = 9.3 min) enantiomeric purity of the product was 92% *ee*.

*4-Isobutyl-3-(3-methylbut-2-enyl)pyrrolidin-2-one (**6c**).* Colorless oil, 125 mg (75%), mixture of (3*S*,4*S*)- and (3*R*,4*S*)-diastereomers, *dr* 75 : 25. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.94 (m, 6H), 1.23-1.75 (m, 9H), 2.04-2.55 (m, 4H), 2.88-2.93 (m, 0.75H), 3.00-3.05 (m, 0.25H), 3.22-3.47 (m, 1H), 5.12-5.17 (m, 1H), 6.22 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 21.9, 22.0, 23.5, 23.6, 24.5, 25.9, 25.9, 26.0, 27.9, 36.4, 36.9, 37.5, 43.9, 45.0, 46.0, 46.8, 47.7, 121.2, 121.6, 132.9, 133.7, 180.0; HRMS (ESI), m/z: 210.1855 $[M+H]^+$ (calc. for $C_{13}H_{24}NO^+$, m/z: 210.1852). According to HPLC (AD-H, *n*-hexane/*i*-PrOH 9:1, 1 ml/min, 220 nm; retention times for major diastereomer: t_{minor} = 7.0 min; t_{major} = 7.6 min; for minor diastereomer: t_{major} = 7.8 min; t_{minor} = 8.2 min) enantiomeric purity for major diastereomer was 72% *ee*.

*4-Isobutyl-3-((E)-3,7-dimethylocta-2,6-dienyl)pyrrolidin-2-one (**6c'**).* Colorless oil, 150 mg (68%), mixture of (3*S*,4*S*)- *and* (3*R*,4*S*)-diastereomers, *dr* 95 : 5. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 6H), 1.26-1.71 (m, 12H), 1.95-2.47 (m, 8H), 2.88-2.93 (m, 0.95H), 3.01-3.06 (m, 0.05H), 3.32-3.46 (m, 1H), 5.07-5.17 (m, 2H), 6.10 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3, 17.7, 22.0, 22.4, 23.4, 23.5, 23.7, 24.3, 25.7, 25.9, 26.7, 27.7, 37.3, 37.5, 39.9, 43.9, 46.8, 47.7, 109.8 (=$\underline{C}H_2$), 121.0, 121.5, 121.8, 124.3, 131.4, 131.6, 137.2, 180.2; HRMS (ESI), m/z: 278.2469 $[M+H]^+$ (calc. for $C_{18}H_{32}NO^+$, m/z: 278.2478). According to HPLC (AD-H, *n*-hexane / *i*-PrOH 9:1, 1 ml/min, 220 nm; retention times for major diastereomer: t_{minor} = 14.4 min; t_{major} = 16.1 min) enantiomeric purity for major diastereomer was 69% *ee*.

Carbamates 7 and 7'

Triethylamine (49 mg, 0.48 mmol), DMAP (15 mg, 0.12 mmol) and Boc_2O (105 mg, 0.48 mmol) were successively added to a stirred solution of pyrrolidin-2-one **6c** or **6c'** (0.24 mmol) in dry dichloromethane (1 mL). The resulting mixture was stirred overnight at ambient temperature. The solvent was evaporated and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc from 3:1 to 1:10).

*tert-Butyl 4-isobutyl-3-(3-methylbut-2-enyl)-2-oxopyrrolidine-1-carboxylate (**7**).* Colorless oil, 74 mg (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 6H), 1.18-1.70 (m, 18H), 2.00-2.40 (m, 4H), 3.13-3.19 (m, 1H), 3.81-3.87 (m, 1H), 5.10-5.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 21.9, 23.6, 25.8, 27.4, 28.1, 29.7, 33.5, 43.2, 50.2, 50.6, 82.7, 120.7, 134.0, 150.5, 175.5; HRMS (ESI), m/z: 332.2193 $[M+Na]^+$ (calc. for $C_{18}H_{31}NNaO_3^+$, m/z: 332.2196).

*tert-Butyl 4-isobutyl-3-((E)-3,7-dimethylocta-2,6-dienyl)-2-oxopyrrolidine-1-carboxylate (**7'**).* Colorless oil, 90 mg (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.94 (m, 6H), 1.21-1.70 (m, 21H), 2.01-2.43 (m, 8H), 3.13-3.19 (m, 1H), 3.81-3.87 (m, 1H), 5.07-5.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3, 17.7, 21.9, 23.6, 25.7, 26.6, 27.2, 27.9, 28.1, 33.4, 39.8, 43.2, 50.2,

50.5, 82.7, 120.5, 124.2, 131.4, 137.6, 150.4, 175.4; HRMS (ESI), m/z: 400.2809 $[M+Na]^+$ (calc. for $C_{23}H_{39}NNaO_3^+$, m/z: 400.2822).

N-Alkylation products 8 – 11 and 8' – 11' (General procedure)

The 60 % suspension of NaH in mineral oil (19 mg, 0.48 mmol) was added to a stirred solution of pyrrolidin-2-one **6c** or **6d** (0.24 mmol) in dry THF (1 mL) and the resulting mixture was stirred under argon atmosphere for the 1 h. Then a solution of the corresponding alkylating agent (0.29 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred overnight at ambient temperature (TLC control). The reaction mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (4 x 5 mL). The combined extracts were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure (10 torr) and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 5 : 1) to afford *N*-alkylated product **8 – 11 or 8' – 11'**.

*4-Isobutyl-1-methyl-3-(3-methylbut-2-enyl)pyrrolidin-2-one (**8**).* Colorless oil, 47 mg (87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.83-0.90 (m, 6H), 1.14-1.67 (m, 9H), 2.01-2.40 (m, 4H), 2.79-2.98 (m, 4H), 3.27-3.40 (m, 1H), 5.05-5.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.9, 22.0, 23.3, 25.8, 25.9, 28.5, 29.7, 34.6, 44.2, 48.5, 54.2, 121.3, 133.4, 176.1; HRMS (ESI), m/z: 246.1817 $[M+Na]^+$ (calc. for $C_{14}H_{25}NNaO^+$, m/z: 246.1828).

*4-Isobutyl-1-methyl-3-((E)-3,7-dimethylocta-2,6-dienyl)pyrrolidin-2one (**8'**).* Colorless oil, 58 mg (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 6H), 1.23-1.71 (m, 12H), 2.01-2.46 (m, 8H), 2.83-2.92 (m, 4H), 3.37-3.43 (m, 1H), 5.07-5.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3, 17.7, 21.9, 23.4, 25.7, 25.9, 26.7, 28.4, 29.7, 34.6, 39.9, 44.2, 48.5, 54.2, 109.8 (=$\underline{C}H_2$), 121.1, 124.3, 131.3, 137.1, 176.1; HRMS (ESI), m/z: 314.2451 $[M+Na]^+$ (calc. for $C_{19}H_{33}NNaO^+$, m/z: 314.2454).

*4-Isobutyl-1,3-bis(3-methylbut-2-enyl)pyrrolidin-2-one (**9**).* Colorless oil. Yield 46 mg (69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.81-0.89 (m, 6H), 1.17-1.71 (m, 15H), 2.01-2.38 (m, 4H), 2.77-2.83 (m, 1H), 3.29-3.35 (m, 1H), 3.84 (d, *J* 7.2 Hz, 2H), 5.08-5.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 17.9, 22.0, 23.4, 25.7, 25.8, 25.9, 28.5, 34.6, 40.2, 44.1, 48.7, 51.2, 118.8, 121.4, 133.3, 136.7, 175.5; HRMS (ESI), m/z: 278.2487 $[M+H]^+$ (calc. for $C_{18}H_{32}NO^+$, m/z: 278.2478).

*4-Isobutyl-1-(3-methylbut-2-enyl)-3-((E)-3,7-dimethylocta-2,6-dienyl)pyrrolidin-2one (**9'**).* Colorless oil, 51 mg (62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86-0.94 (m, 6H), 1.16-1.76 (m, 18H), 1.94-2.45 (m, 8H), 2.79-2.85 (m, 1H), 3.31-3.37 (m, 1H), 3.86 (d, *J* 7.1 Hz, 2H), 5.10-5.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3, 17.7, 17.9, 22.2, 23.0, 25.7, 25.9, 26.1, 26.7, 28.4, 34.7, 39.9, 40.2, 44.2, 48.8, 51.3, 109.8(=$\underline{C}H_2$), 118.9, 121.2, 124.3, 131.4, 136.8, 137.1, 175.6; HRMS (ESI), m/z: 346.3101 $[M+H]^+$ (calc. for $C_{23}H_{40}NO^+$, m/z: 346.3104).

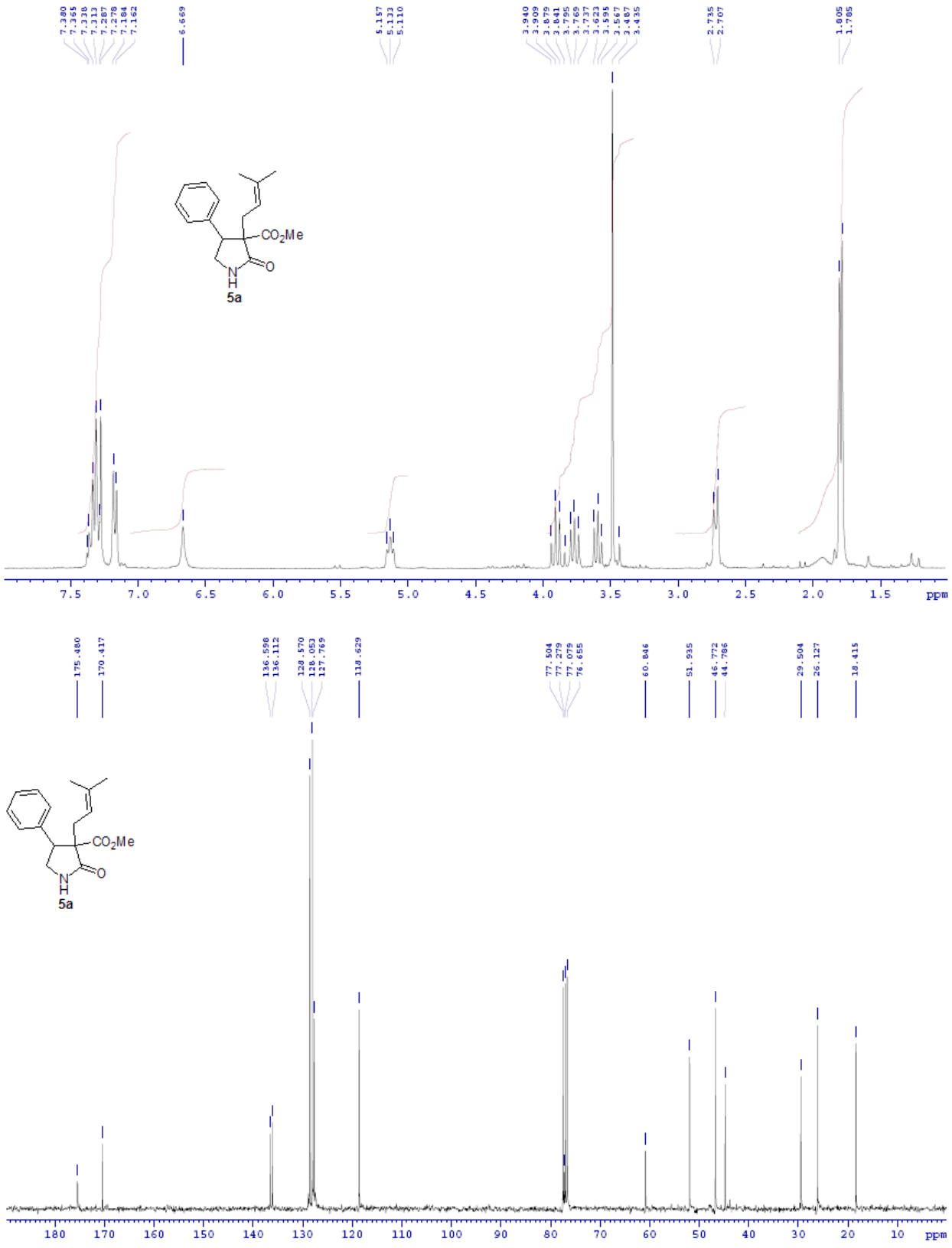
*4-Isobutyl-3-(3-methylbut-2-enyl)-1-((E)-3,7-dimethylocta-2,6-dienyl)pyrrolidin-2-one (**10**).* Colorless oil, 46 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 6H), 1.19-1.83 (m, 18H), 2.05-2.41 (m, 8H), 2.79-2.85 (m, 1H), 3.32-3.38 (m, 1H), 3.89 (d, *J* 7.0 Hz, 2H), 5.06-5.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.2, 17.7, 18.0, 22.1, 23.4, 25.8, 25.9, 26.1, 27.0, 28.6, 34.7, 39.6, 40.1, 44.2, 48.8, 51.2, 118.7, 121.4, 123.9, 131.7, 133.4, 140.2, 175.6; HRMS (ESI), m/z: 368.2931 $[M+Na]^+$ (calc. for $C_{23}H_{39}NNaO^+$, m/z: 368.2924).

*4-Isobutyl-1,3-bis((E)-3,7-dimethylocta-2,6-dienyl)pyrrolidin-2one (**10'**).* Colorless oil, 55 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.91 (m, 6H), 1.18-2.43 (m, 33H), 2.79-2.84 (m, 1H), 3.31-3.37 (m, 1H), 3.89 (d, *J* 7.1 Hz, 2H), 5.09-5.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.2, 16.3, 17.7, 17.7, 22.1, 23.4, 25.7, 25.9, 26.4, 26.7, 28.4, 34.6, 39.6, 39.9, 40.1, 44.2, 48.8, 51.2, 109.8(=$\underline{C}H_2$), 118.8, 121.2, 123.9, 124.3, 131.4, 131.7, 137.1, 140.3, 175.6; HRMS (ESI), m/z: 414.3736 $[M+H]^+$ (calc. for $C_{28}H_{48}NO^+$, m/z: 414.3730).

*Ethyl 2-[4-isobutyl-3-(3-methylbut-2-enyl)-2-oxopyrrolidin-1-yl]acetate (**11**).* Colorless oil, 20 mg (28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.93 (m, 6H), 1.15-1.69 (m, 12H), 1.99-2.48 (m, 4H), 3.00-3.07 (m, 1H), 3.45-3.54 (m, 1H), 3.93-4.21 (m, 4H), 5.07-5.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 17.9, 21.9, 23.3, 25.8, 25.9, 28.3, 34.8, 43.9, 44.2, 48.1, 52.4, 61.2, 121.2, 133.6, 168.8, 176.8; HRMS (ESI), m/z: 296.2227 $[M+H]^+$ (calc. for $C_{17}H_{30}NO_3^+$, m/z: 296.2220).

*Ethyl 2-[4-isobutyl-3-((E)-3,7-dimethylocta-2,6-dienyl)-2-oxopyrrolidin-1-yl]acetate (**11'**).* Colorless oil, 28 mg (32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87-0.94 (m, 6H), 1.16-1.71 (m, 15H), 1.98-2.50 (m, 8H), 3.02-3.07 (m, 1H), 3.46-3.51 (m, 1H), 3.94-4.23 (m, 4H), 5.10-5.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 16.3, 17.7, 22.1, 23.5, 25.9, 26.0, 26.7, 28.3, 36.8, 39.8, 43.9, 44.1, 48.2, 52.4, 62.2, 121.1, 124.4, 131.4, 137.3, 168.8, 176.8; HRMS (ESI), m/z: 364.2843 $[M+H]^+$ (calc. for $C_{22}H_{38}NO_3^+$, m/z: 364.2846).

3. Copies of NMR spectra for compounds 5 - 11 and 5' – 11'



FigureS1 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 5a.

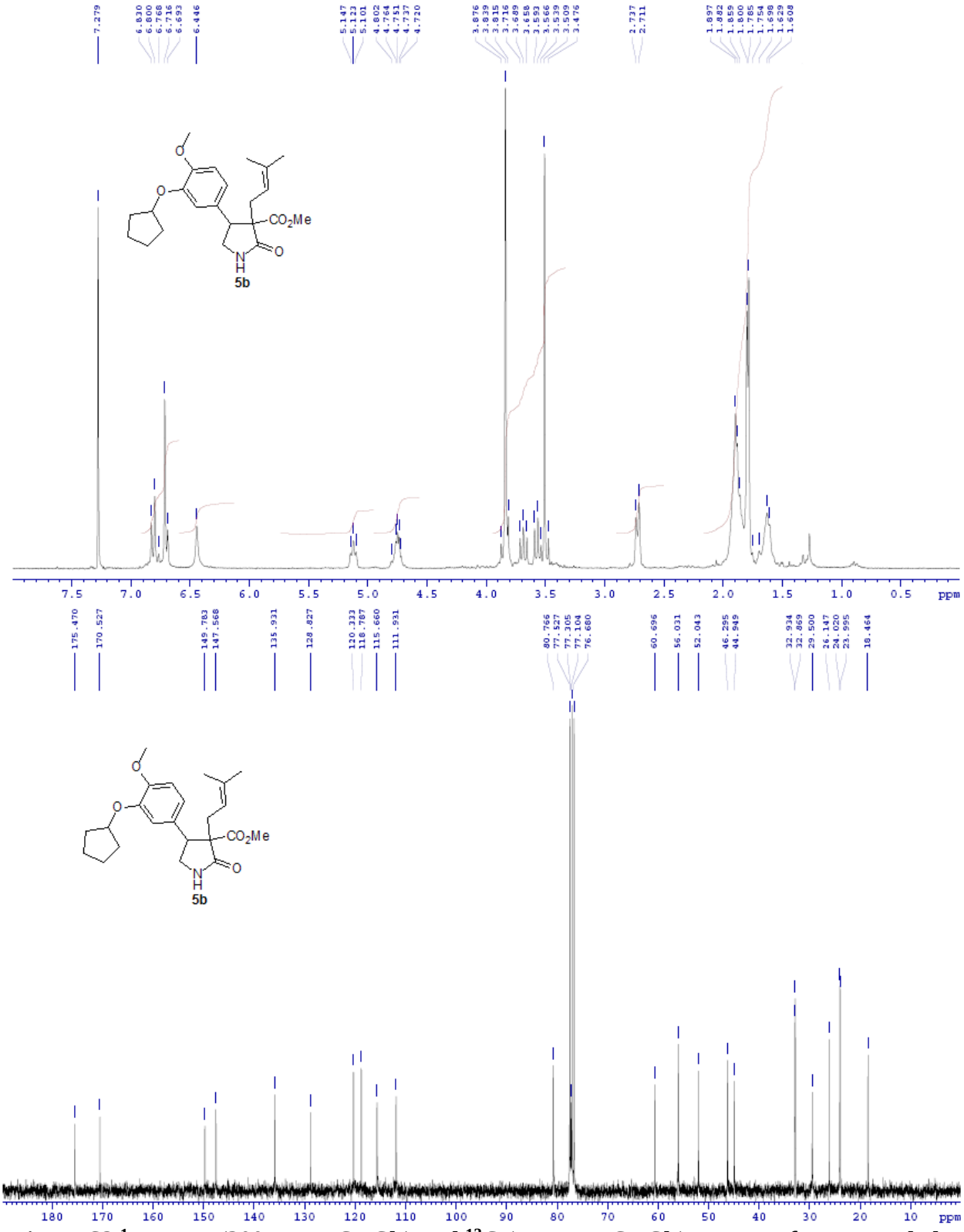


Figure S2 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 5b.

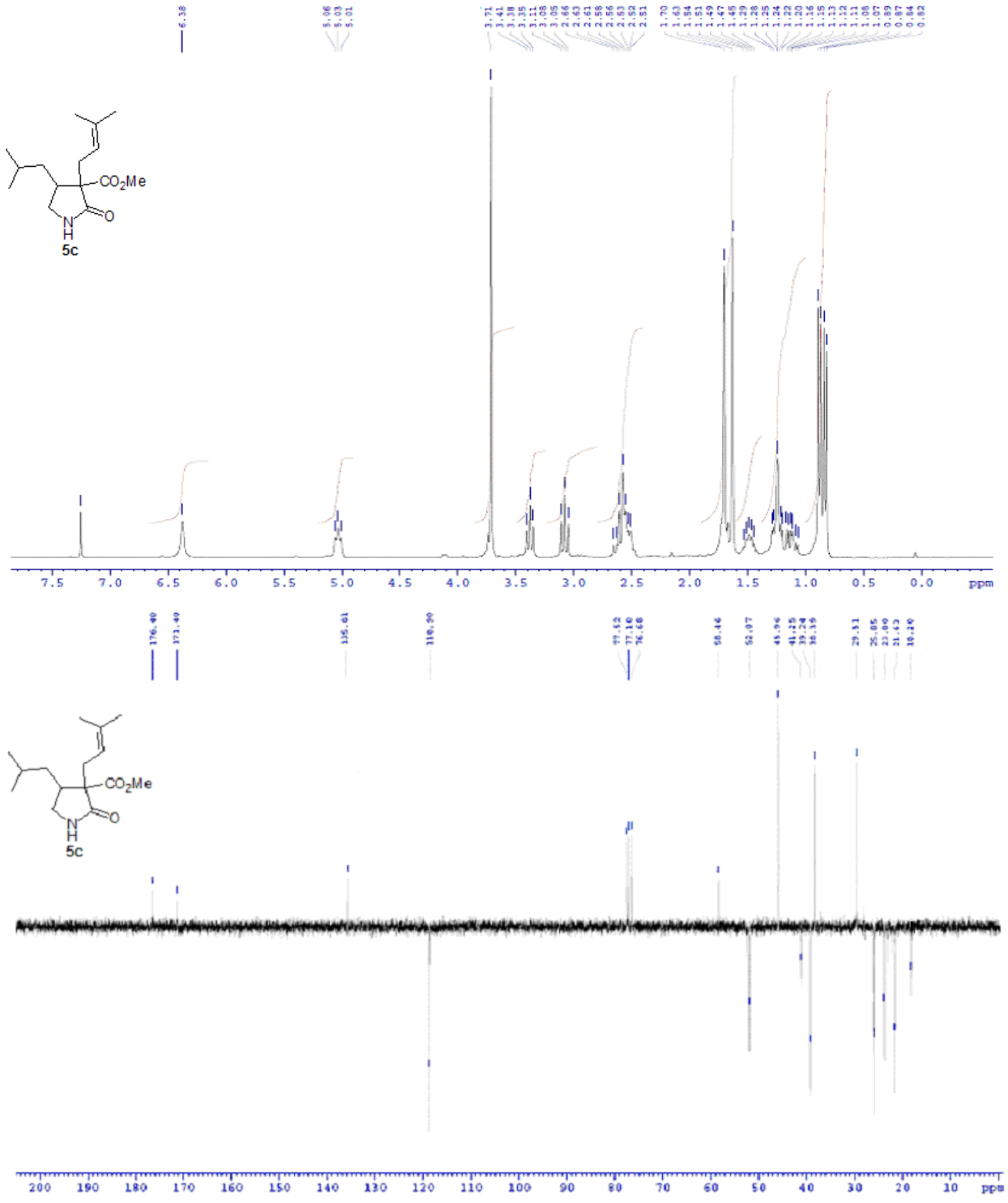


Figure S3 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 5c.

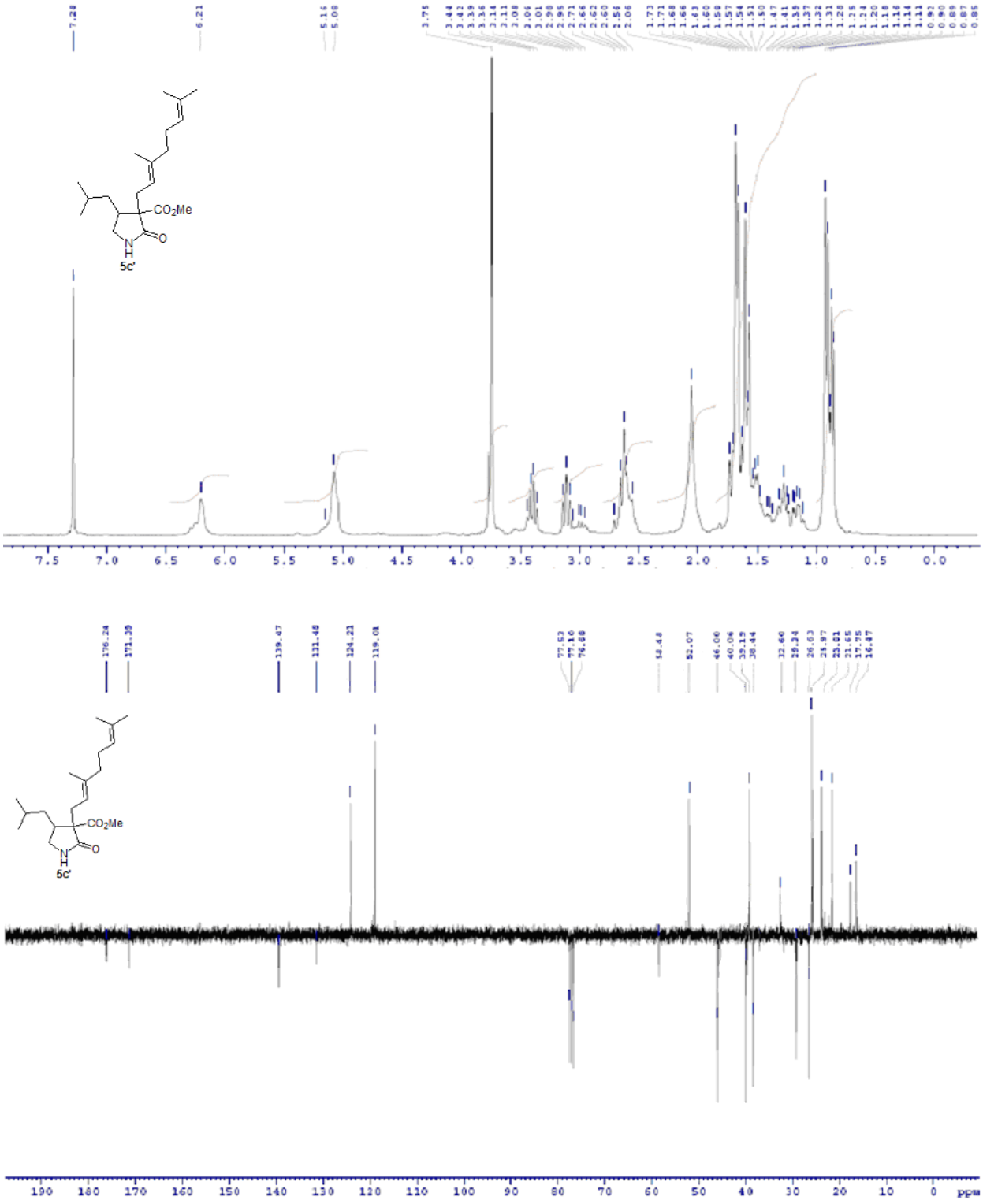


Figure S4 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 5c'.

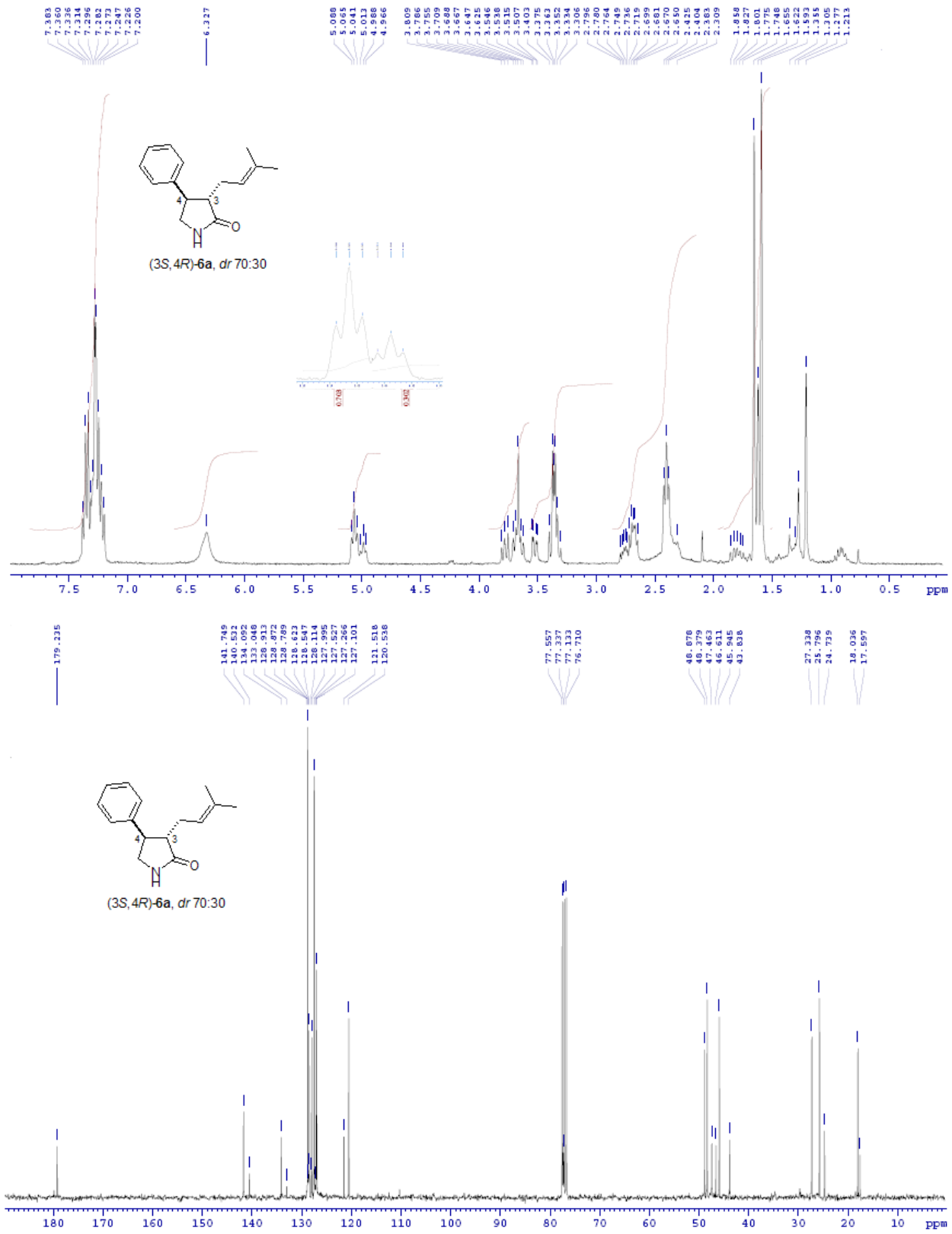


Figure S5 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 6a.

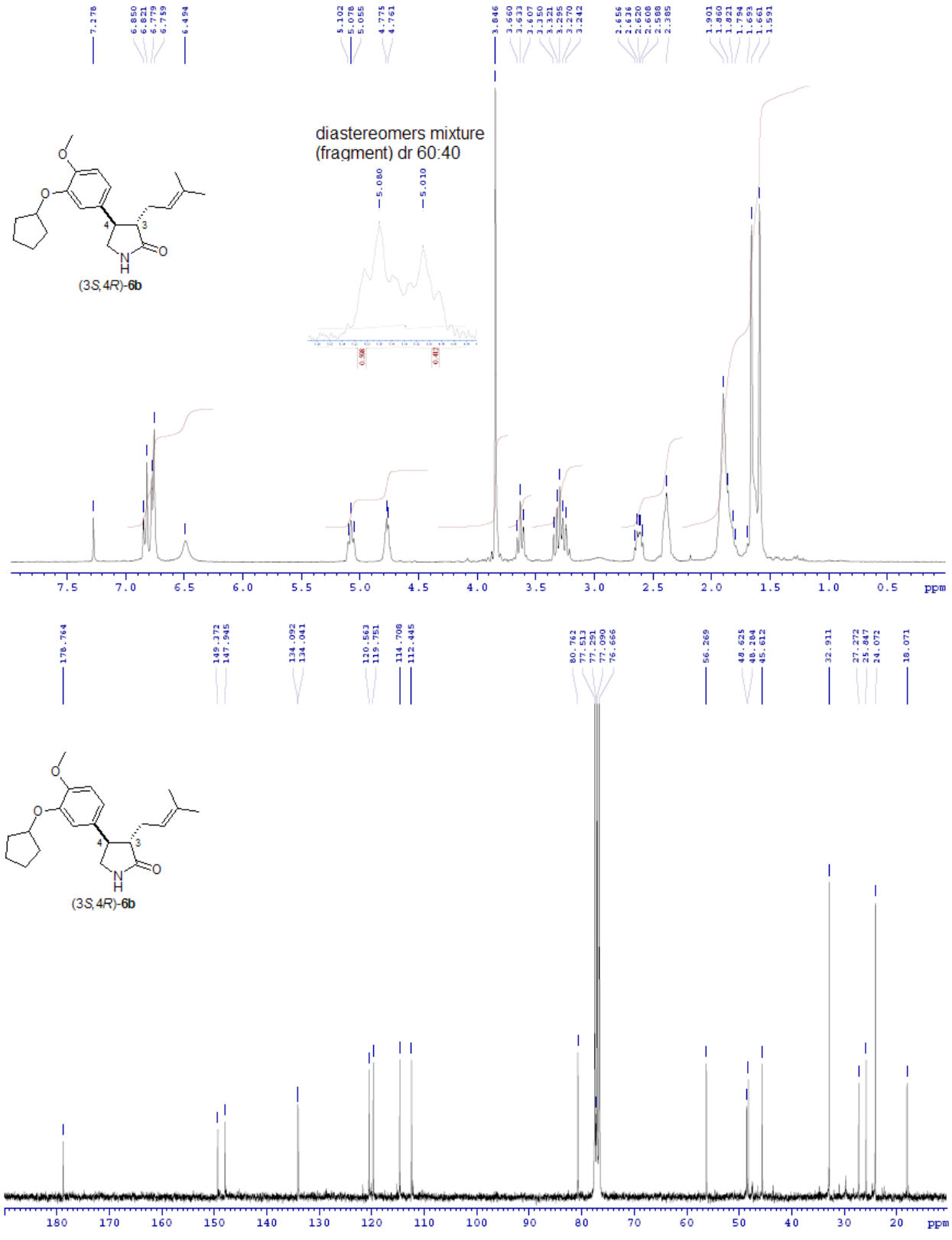


Figure S6 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound (3*S*,4*R*)-6b.

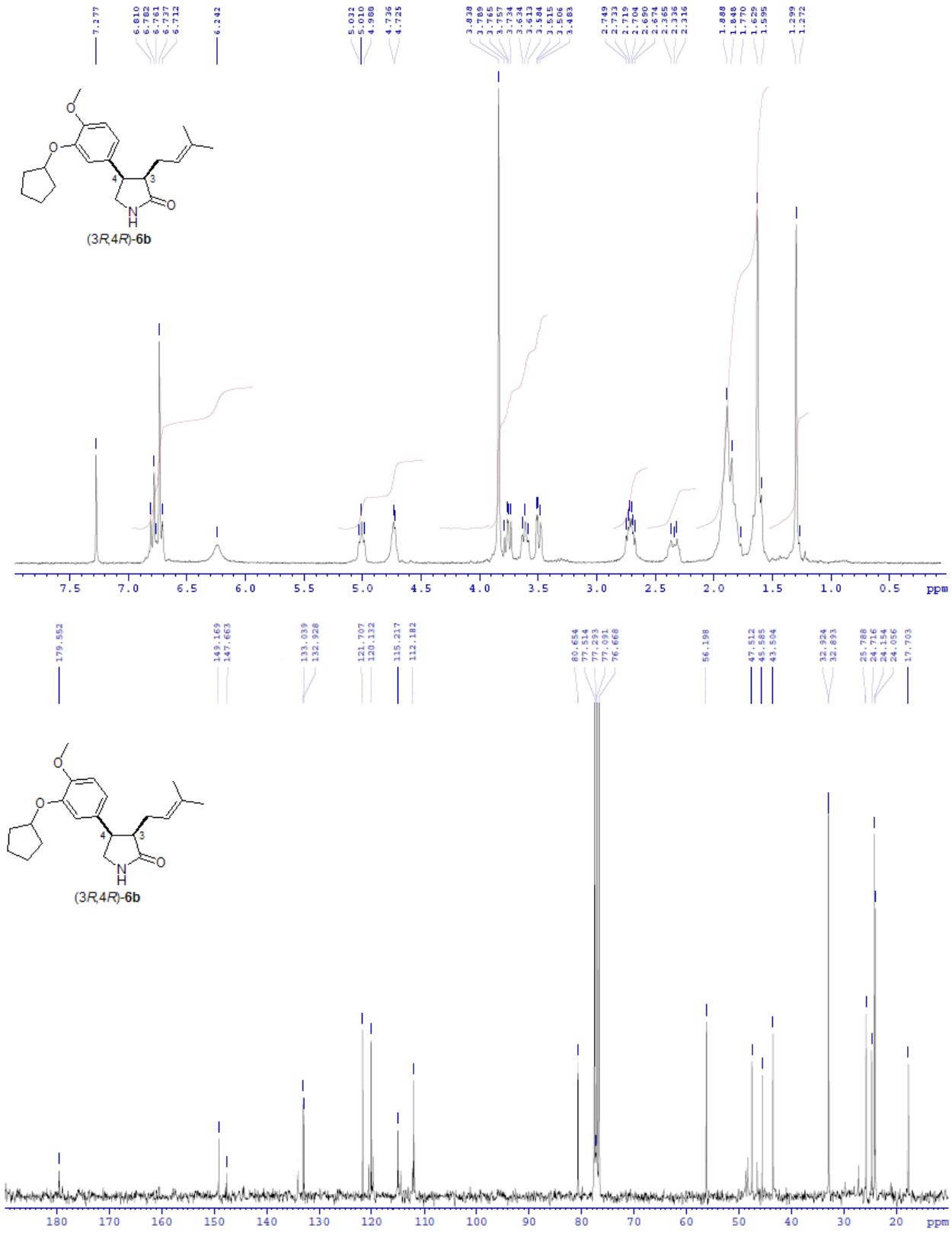


Figure S7 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound (3*R*,4*R*)-6b.

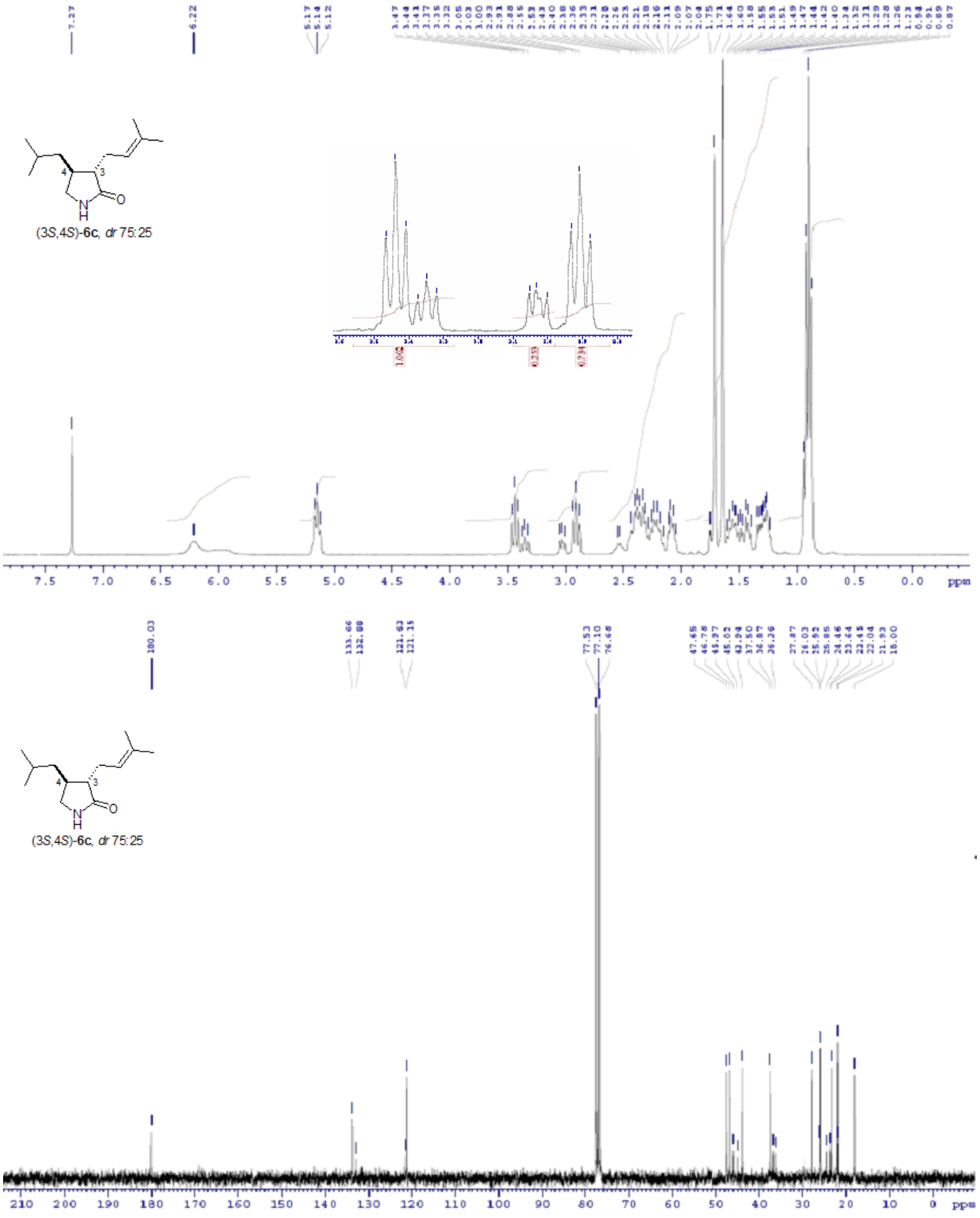


Figure S8 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 6c.

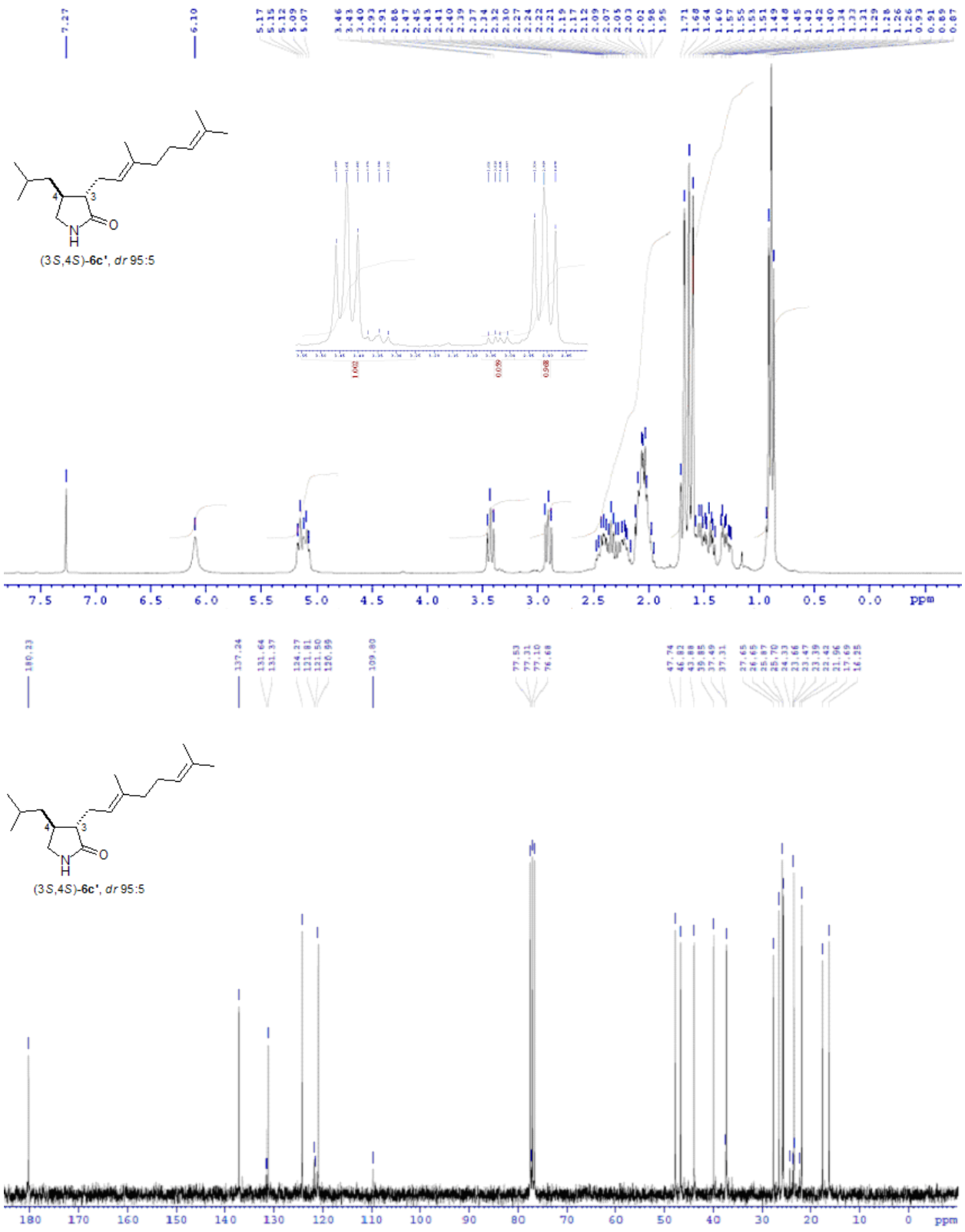


Figure S9 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 6c'.

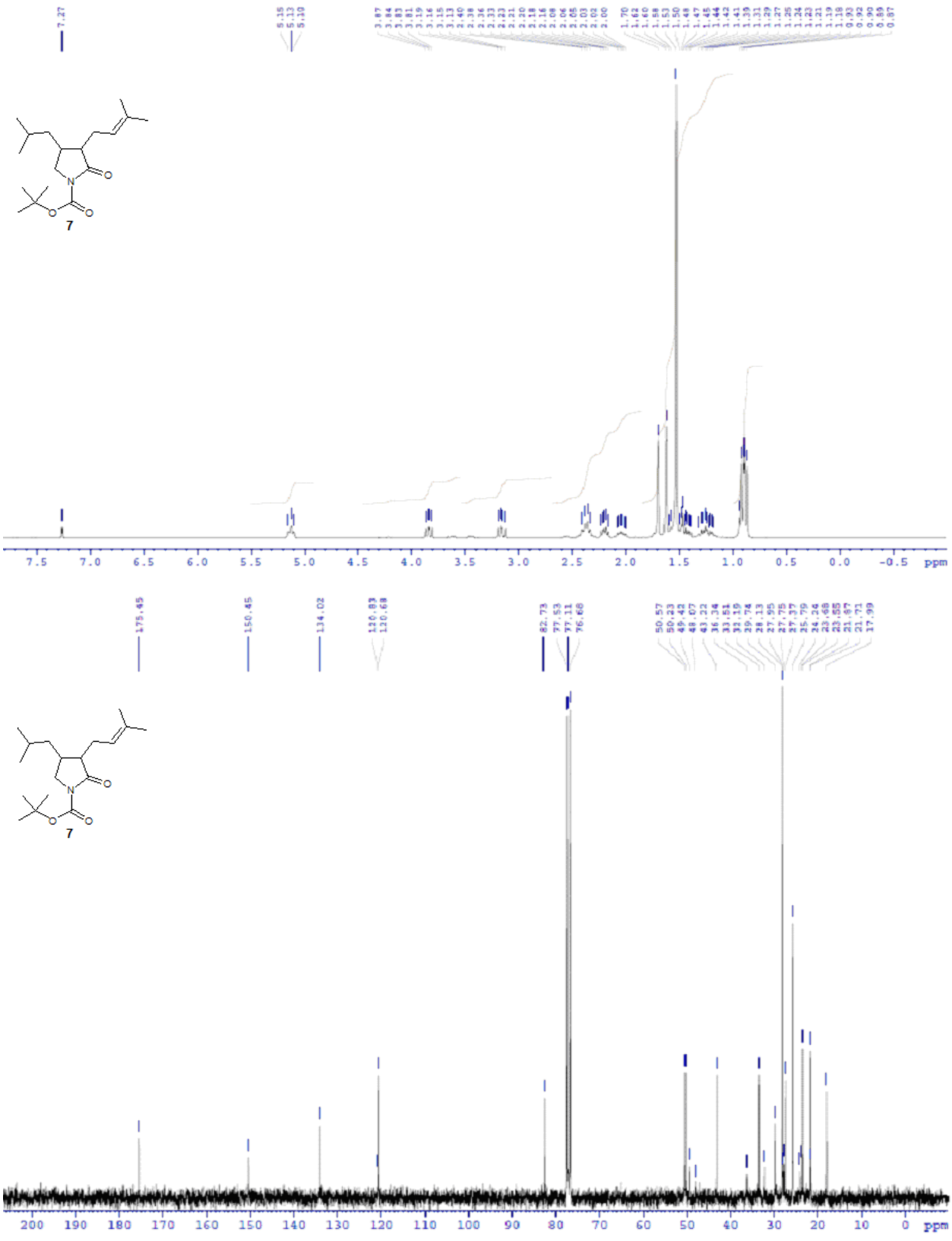


Figure S10 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 7.

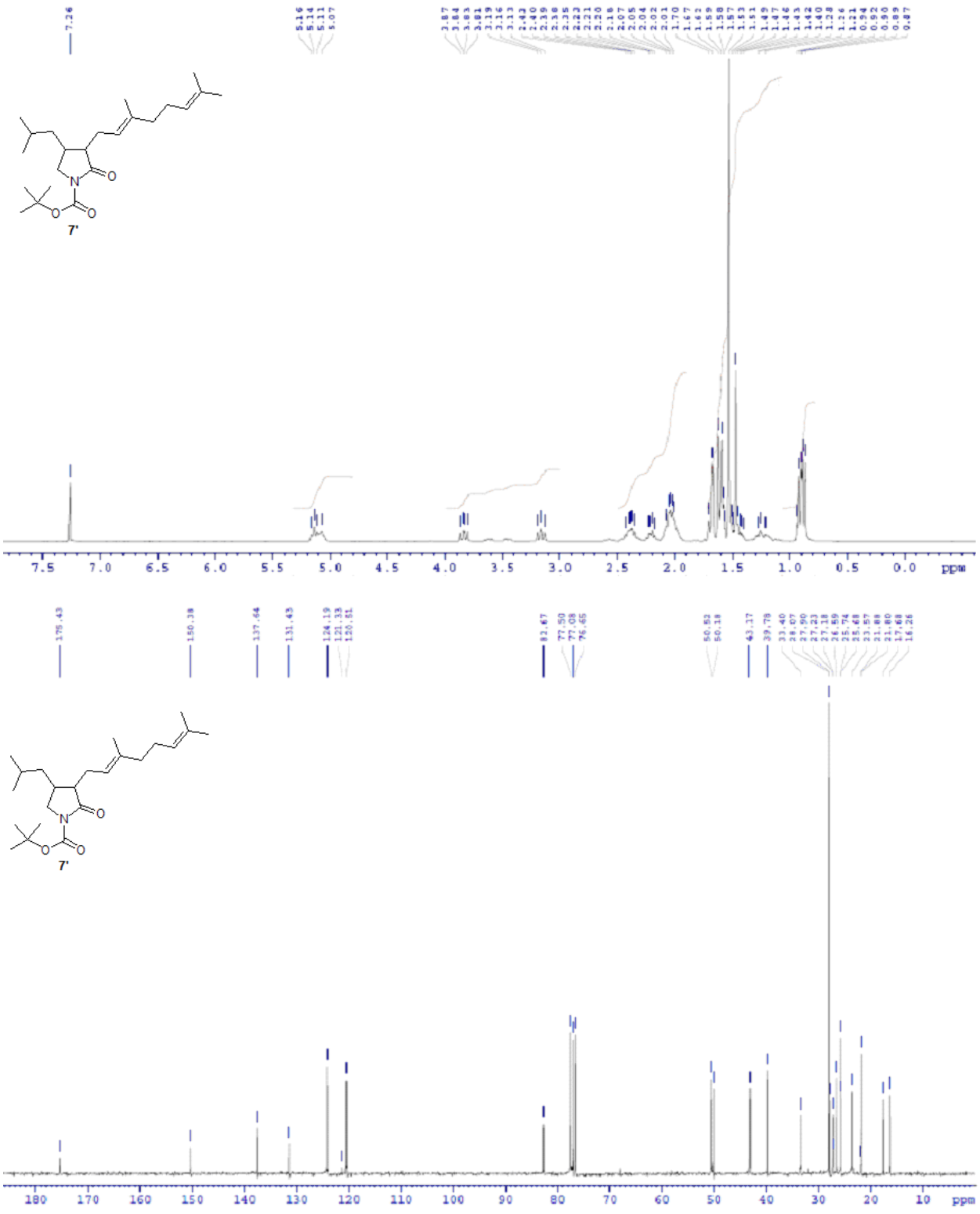


Figure S11 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 7'.

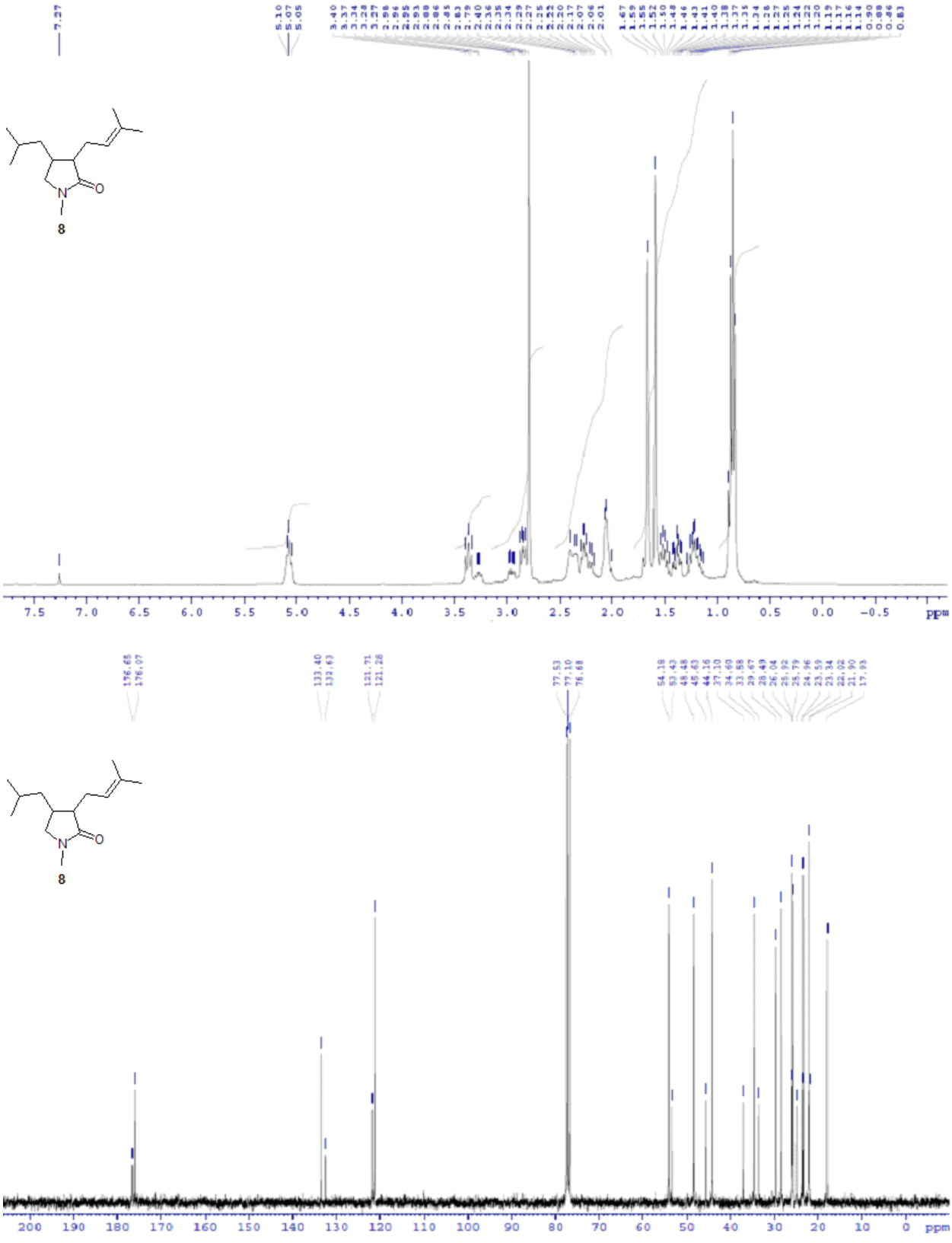


Figure S12 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 8.

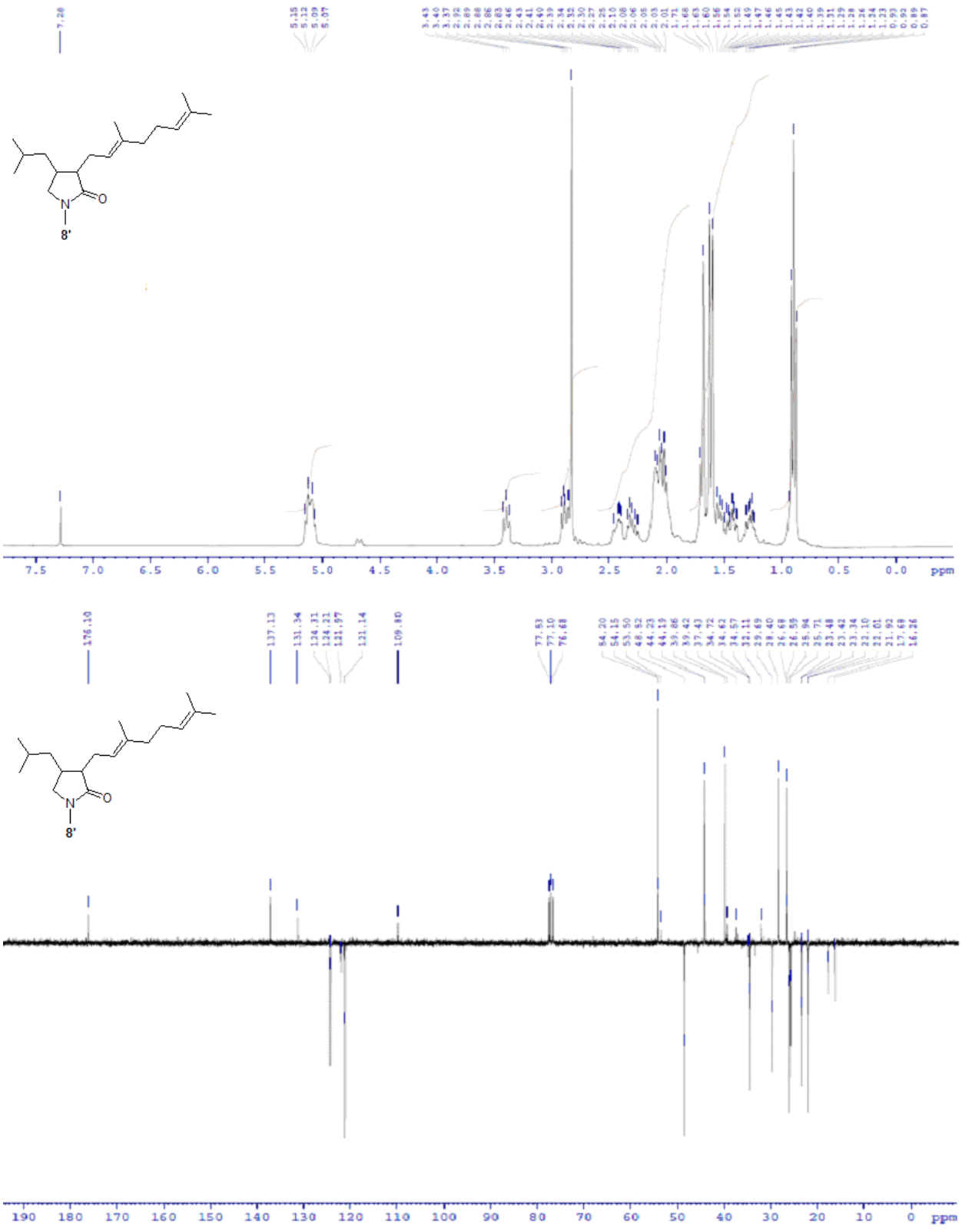


Figure S13 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 8'.

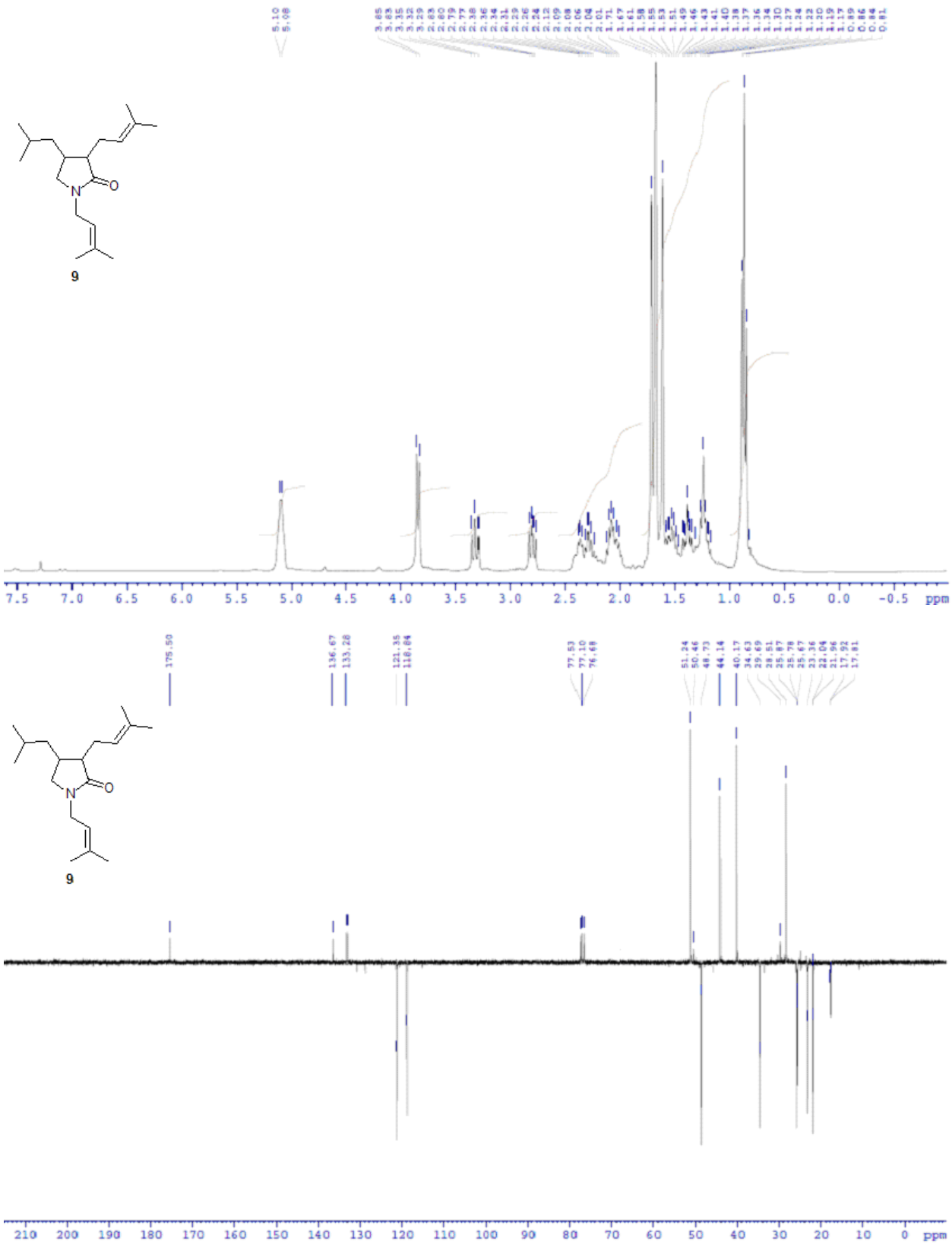


Figure S14 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 9.

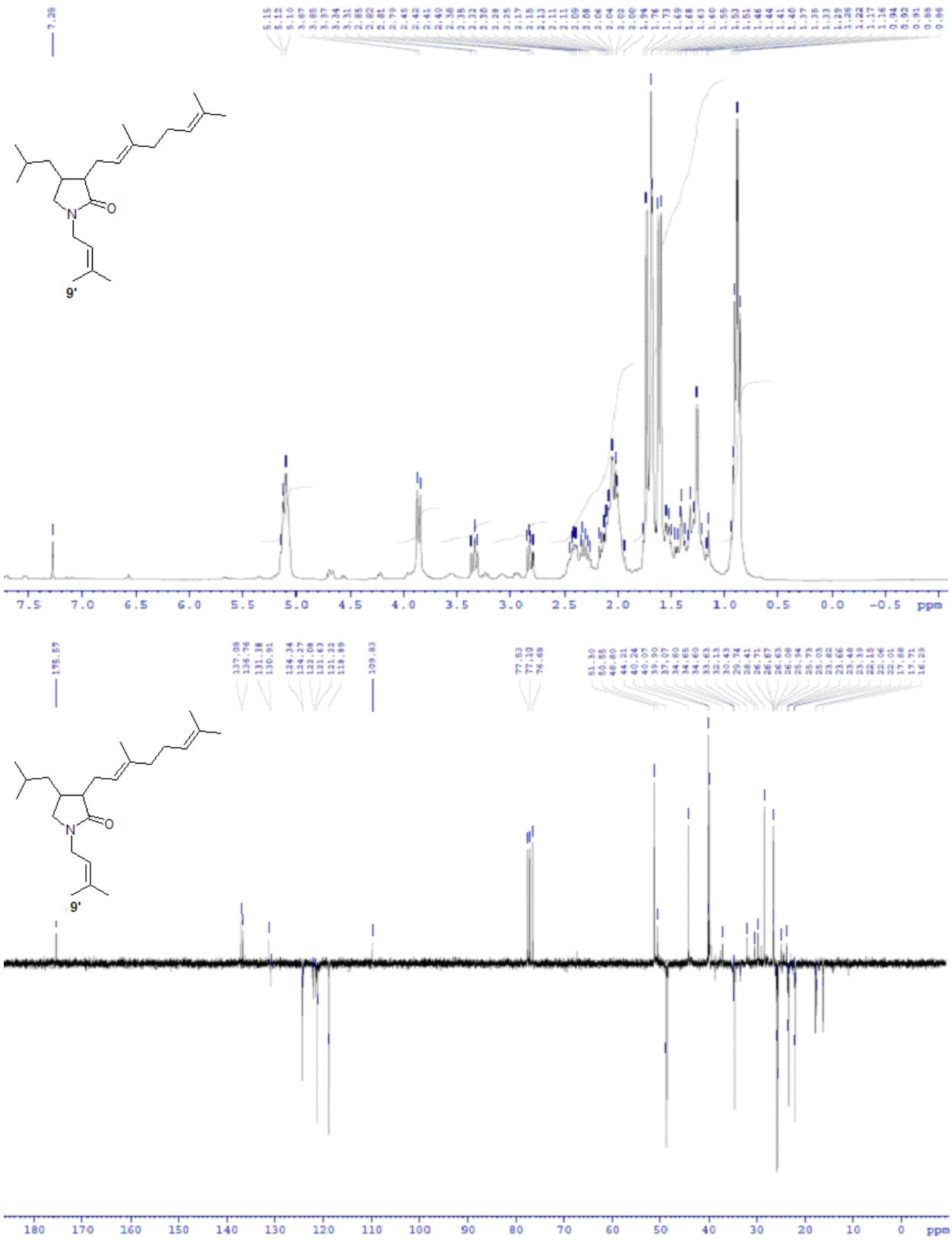


Figure S15 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 9'.

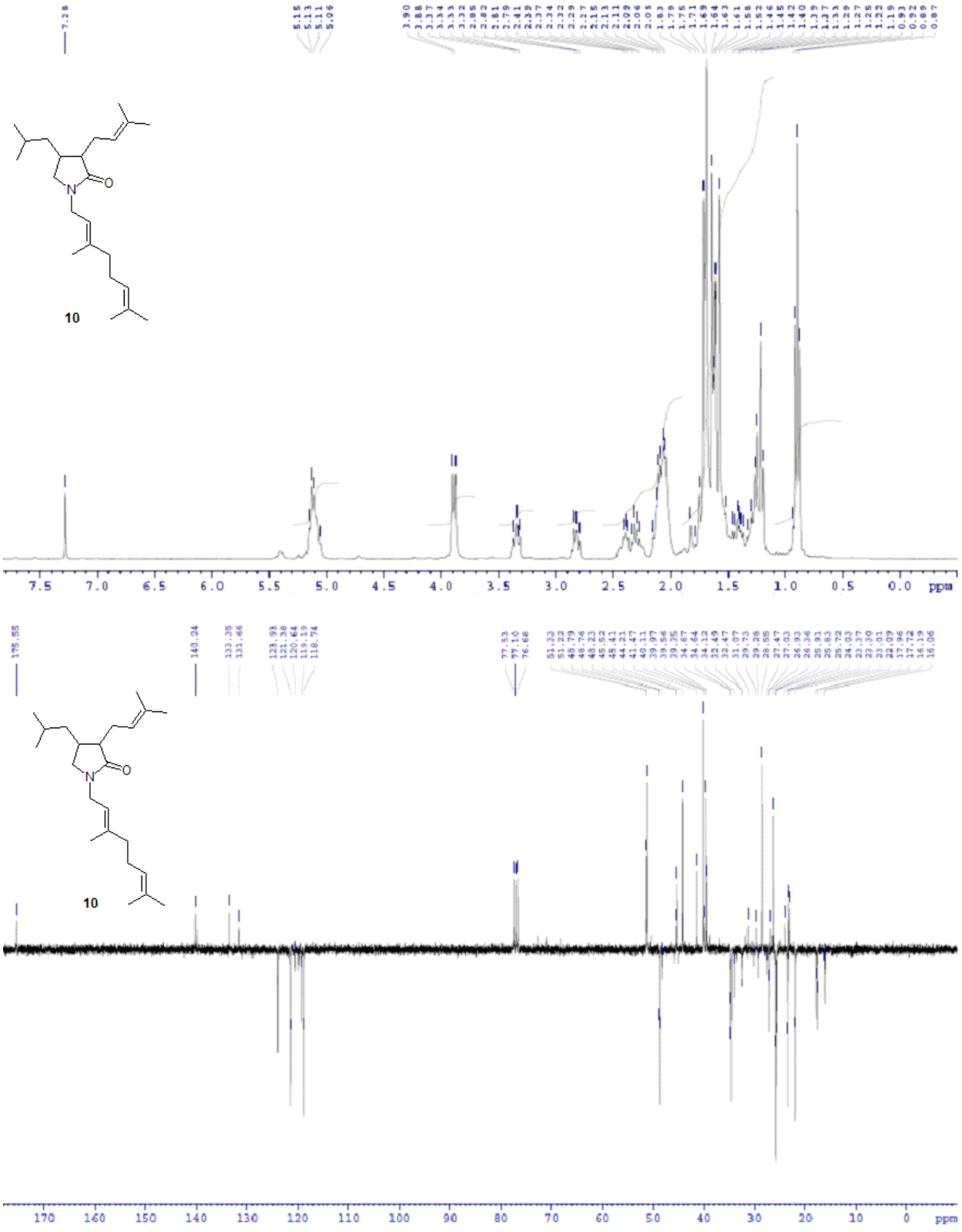


Figure S16 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 10.

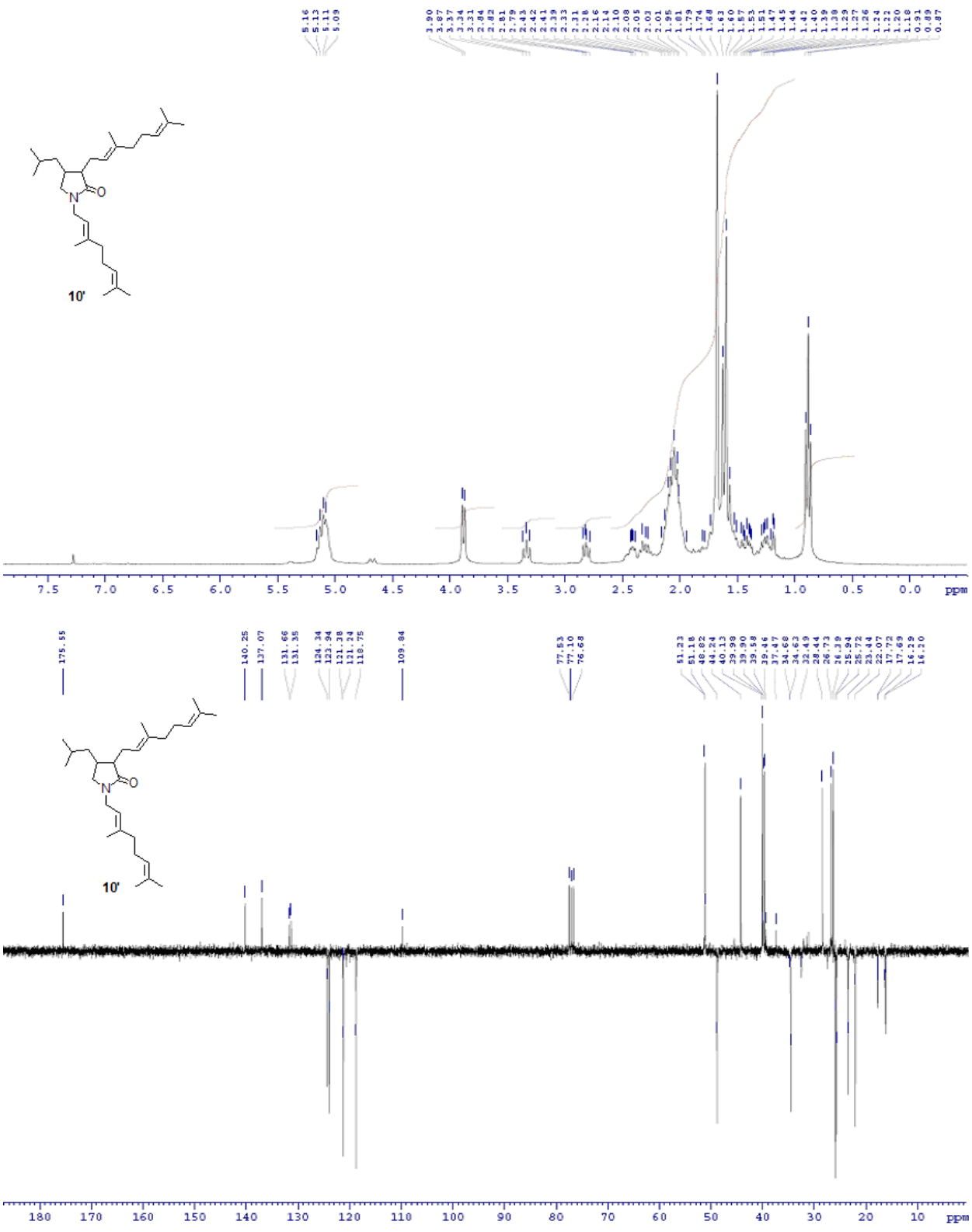


Figure S17 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 10'.

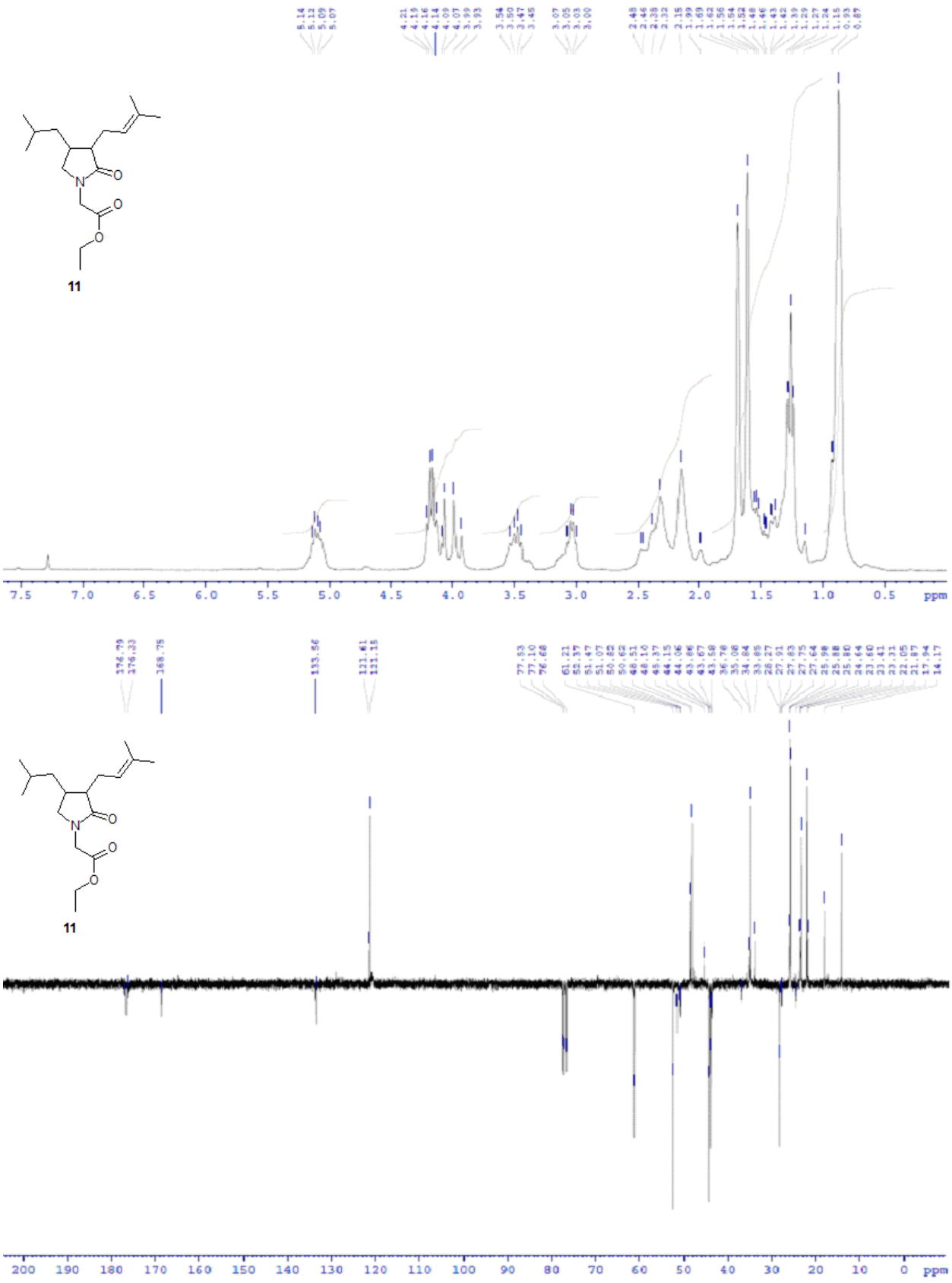


Figure S18 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 11.

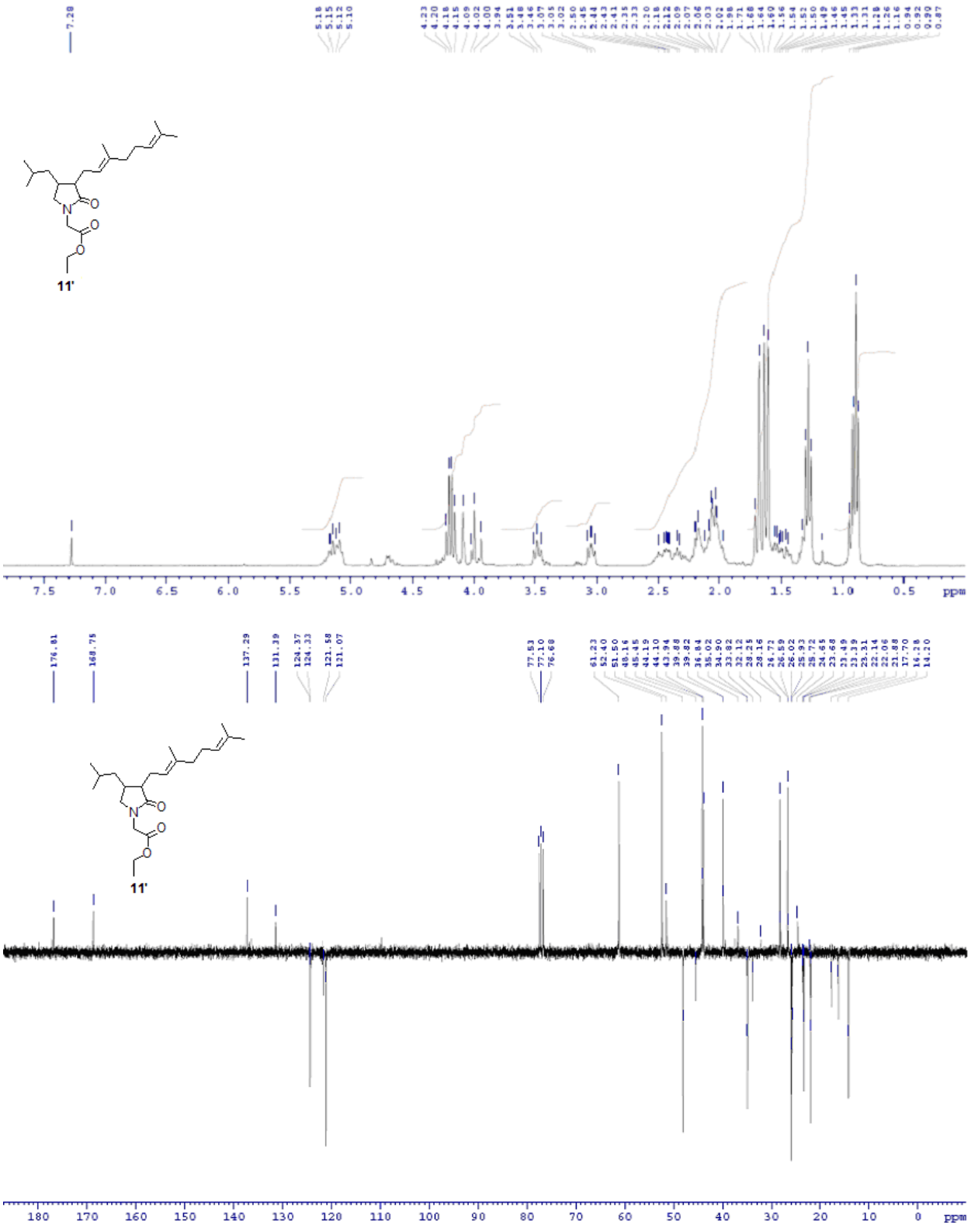


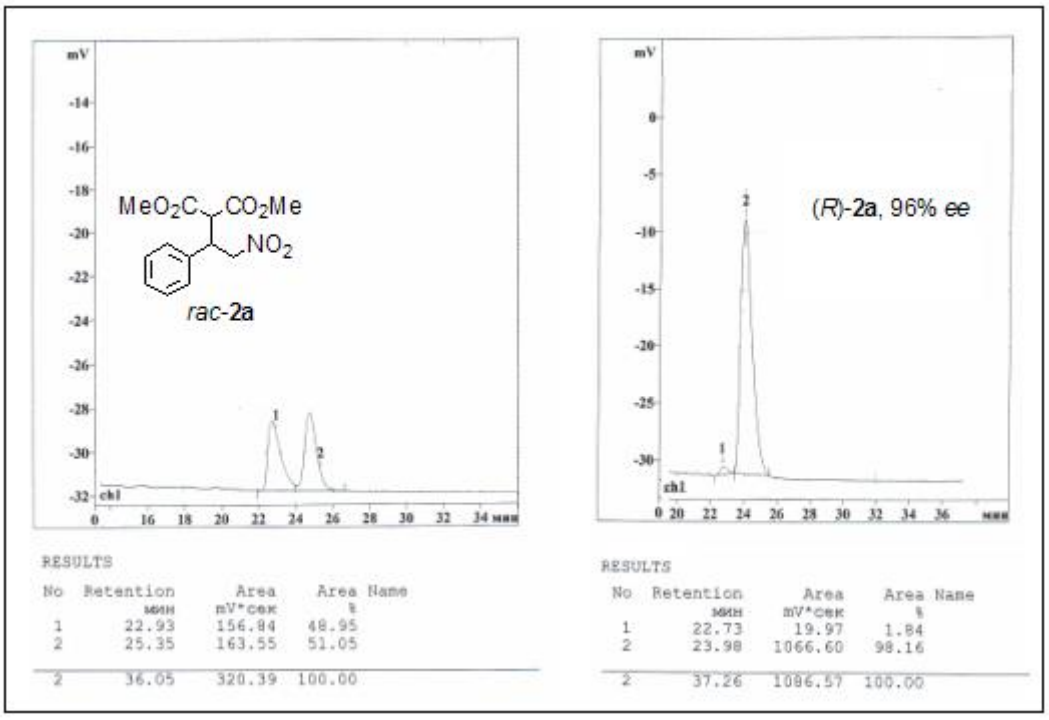
Figure S19 ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C (75 MHz, $CDCl_3$) spectra of compound 11'.

4. X-ray diffraction data for *rac*-6b major diastereomer

Crystals of *rac*-**6b** ($C_{21}H_{29}NO_3$, M = 343.45) are monoclinic, space group $P2_1/n$, at 120 K: a = 12.885(2), b = 6.5217(11), c = 23.341(4) Å, β = 105.094(4)°, V = 1893.7(6) $Å^3$, Z = 4 (Z' = 1), d_{calc} = 1.205 gcm^{-3}, μ(MoKα) = 0.80 cm^{-1}, F(000) = 744. Intensities of 18823 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072Å, ω-scans, 2θ<54°], and 4142 independent reflections [R_{int} = 0.0929] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atom of the NH group was located from the Fourier density synthesis, and the positions of other hydrogen atoms were calculated. All hydrogen atoms were refined in the isotropic approximation in riding model. The refinement converged to wR2 = 0.1706 and GOF = 1.012 for all the independent reflections (R1 = 0.0633 was calculated against F for 2213 observed reflections with I>2σ(I))**.** All calculations were performed using SHELXTL PLUS 5.0.[5] CCDC 1492244 contains the supplementary crystallographic information for ***rac*-6b** major diastereomer**.**

[5] G.M. Sheldrick, *Acta Cryst. A*, 2008, **64**, 112.

5. Copies of HPLC traces for compounds 2a-c, 6a-c, 6c'

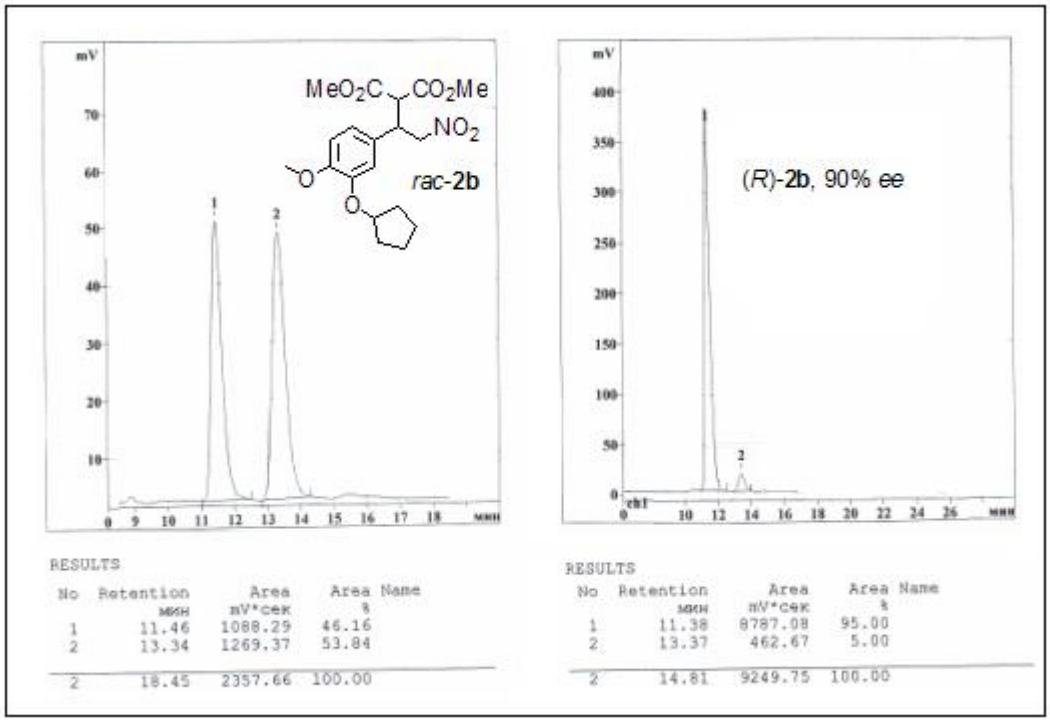


RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	22.93	156.84	48.95	
2	25.35	163.55	51.05	
2	36.05	320.39	100.00	

RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	22.73	19.97	1.84	
2	23.98	1066.60	98.16	
2	37.26	1086.57	100.00	

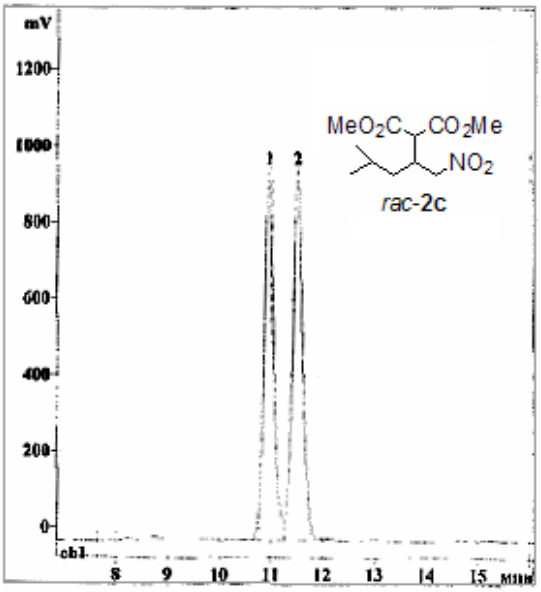


RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	11.46	1088.29	46.16	
2	13.34	1269.37	53.84	
2	18.45	2357.66	100.00	

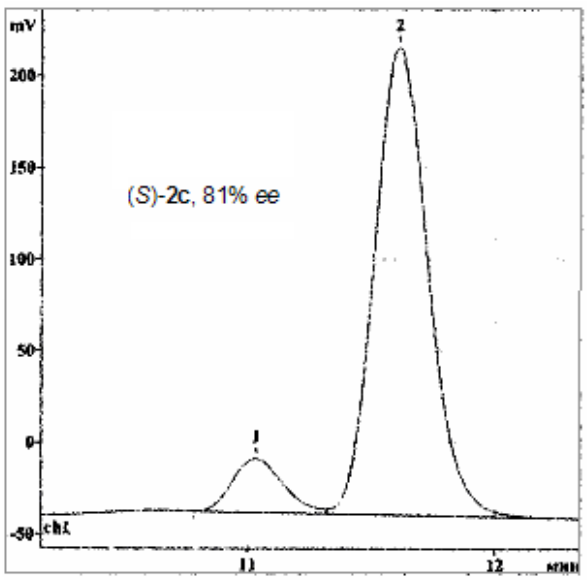
RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	11.38	8787.08	95.00	
2	13.37	462.67	5.00	
2	14.81	9249.75	100.00	



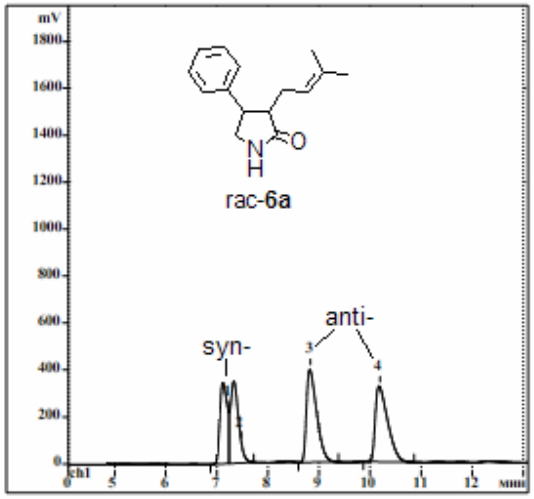
RESULTS

No	Retention мин	Area mV*сек	Area %
1	10.95	12510.40	49.43
2	11.51	12799.55	50.57
2	14.92	25309.95	100.00



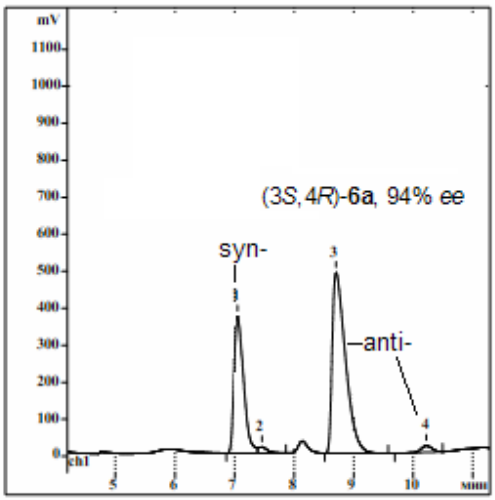
RESULTS

No	Retention мин	Area mV*сек	Area %
1	11.03	410.53	9.70
2	11.61	3821.97	90.30
2	16.07	4232.50	100.00



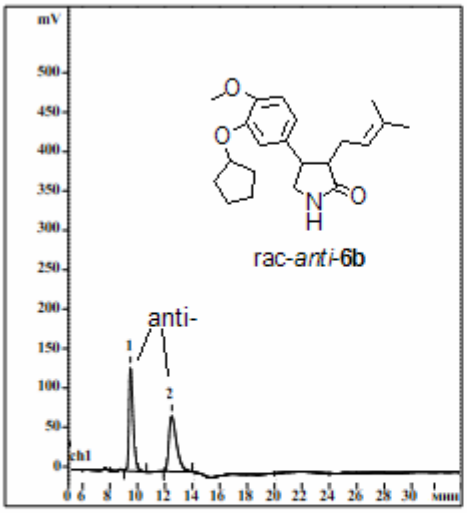
RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	7.235	3518.34	19.10	
2	7.479	3866.74	20.99	
3	8.818	5561.83	30.19	
4	10.17	5477.87	29.73	
4	13.09	18424.78	100.00	



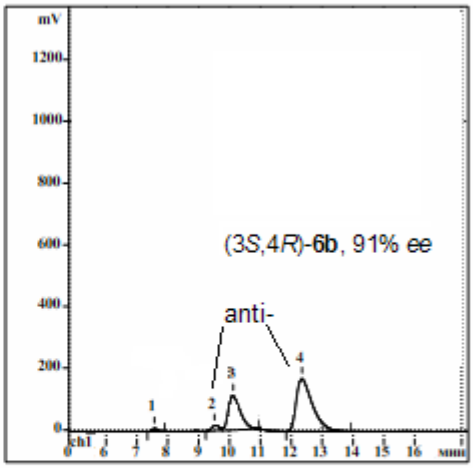
RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	7.048	4150.35	34.19	
2	7.457	172.93	1.42	
3	8.704	7596.26	62.57	
4	10.22	220.92	1.82	
4	12.32	12140.46	100.00	



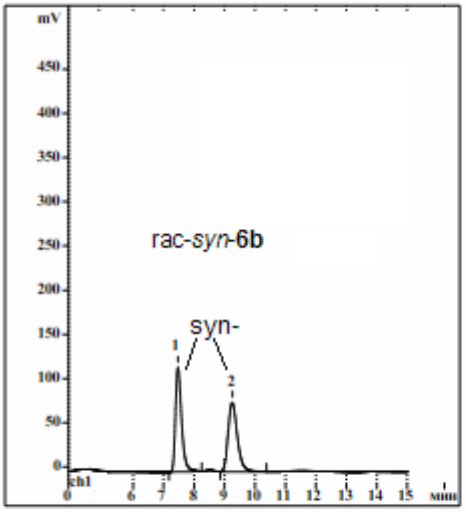
RESULTS

No	Retention Time	Area mV*sec	Area %	Name
1	9.485	2802.47	50.45	
2	12.5	2752.45	49.55	
2	36.49	5554.92	100.00	



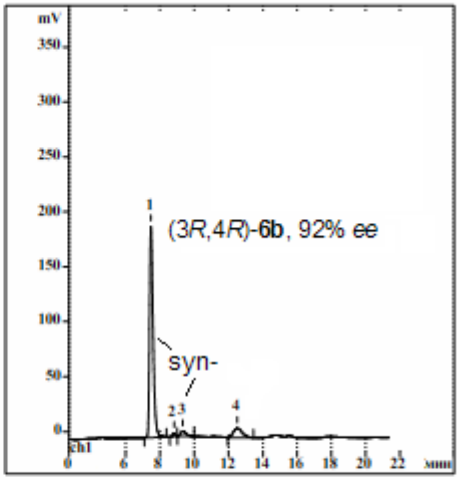
RESULTS

No	Retention Time	Area mV*sec	Area %	Name
1	7.56	129.61	1.33	
2	9.541	289.61	2.98	
3	10.11	3043.38	31.27	
4	12.35	6269.19	64.42	
4	22.21	9731.79	100.00	



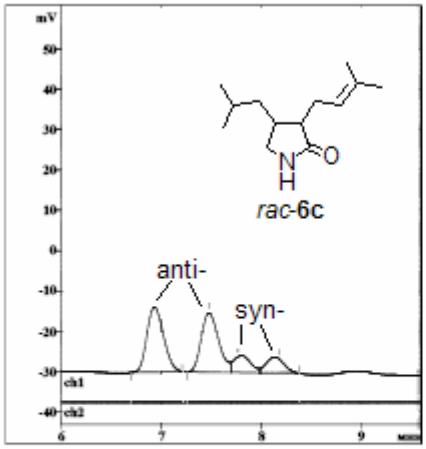
RESULTS

No	Retention Time	Area mV*sec	Area %	Name
1	7.468	1661.30	50.13	
2	9.248	1652.97	49.87	
2	15.02	3314.27	100.00	



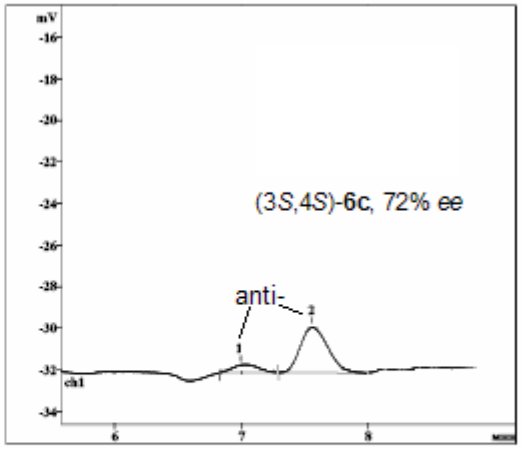
RESULTS

No	Retention Time	Area mV*sec	Area %	Name
1	7.466	2786.47	86.14	
2	8.813	32.90	1.02	
3	9.335	112.17	3.47	
4	12.5	303.19	9.37	
4	21.37	3234.73	100.00	



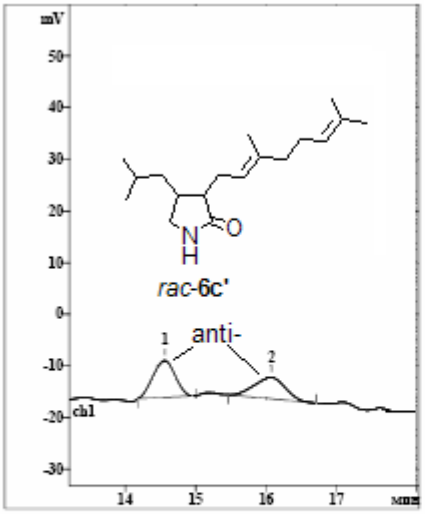
RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	6.929	188.17	40.09	
2	7.476	179.13	38.16	
3	7.764	50.78	10.82	
4	8.182	51.30	10.93	
4	21.81	469.38	100.00	



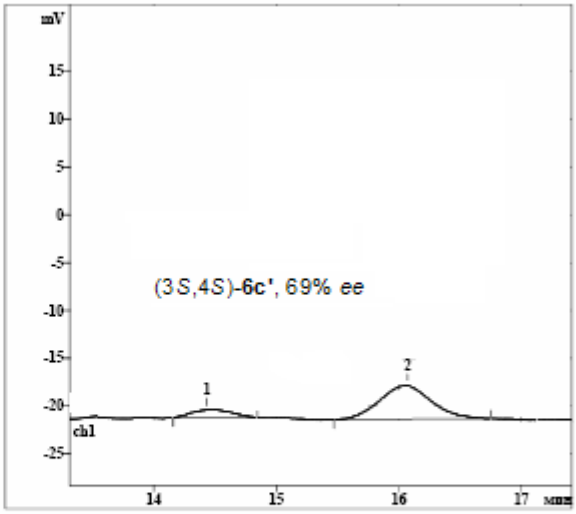
RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	6.985	5.44	14.17	
2	7.563	32.92	85.83	
2	29.13	38.36	100.00	



RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	14.56	156.44	55.48	
2	16.08	125.52	44.52	
2	42.6	281.96	100.00	



RESULTS

No	Retention мин	Area mV*сек	Area %	Name
1	14.43	18.83	15.44	
2	16.06	103.10	84.56	
2	59.6	121.92	100.00	