

Simple antitumor model compounds for cross-conjugated cyclopentenone prostaglandins

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Experimental section

General methods

Solvents were purified and dried before use by standard procedures. Anhydrous THF was distilled from sodium–benzophenone. CH₂Cl₂, EtOAc and petroleum ether were distilled from CaH₂. CH₂Cl₂ was also distilled over phosphorus pentoxide. Reagents were generally the best quality commercial grade and were used without further purification unless otherwise indicated. All reactions were carried in oven-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) using Sorbfil STC-1A (silica gel 5–17 μm) 110 μm layer precoated foil plates. Visualization of the developed chromatograms was performed by staining with ethanol solution of *p*-anisaldehyde and the following heating. Column chromatography was carried out using Silica 60 silica gel 0.04–0.063 mm. Infrared spectra were recorded on a Shimadzu ‘Prestige-21’ spectrometer as nujol mulls or as neat thin films on KBr plates and were reported in cm⁻¹. ¹H and ¹³C NMR spectra were recorded using a Bruker Avance-III 500 spectrometer at operating frequency 500.13 MHz for ¹H and 125.47 MHz for ¹³C in CDCl₃ (Aldrich Chemical Company, spectra grade). Chemical shifts are reported in δ units (parts per million, ppm) downfield from tetramethylsilane (TMS) as the internal reference. Splitting patterns are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), m (multiplet). Mass spectra were recorded using a Shimadzu LCMS QP-2010EV APCI spectrometer.

General procedure for the thia-Michael reactions

Mono-adducts 3a, 3b, 6 and 8

To a stirred solution of dienone **1** (166.2 mg, 1 mmol) in an appropriate solvent (THF or CH₂Cl₂, 30 ml), mercaptan (1.1 mmol) and triethylamine (304 mg, 0.42 ml, 3 mmol) were added at room temperature.

Bis-adducts 2a–c, 7, 9a and 9b

To a stirred solution of dienone **1** (166.2 mg, 1 mmol) in an appropriate solvent (THF or CH₂Cl₂, 50 ml), mercaptan (5 mmol) and triethylamine (10 mmol) were added at room temperature.

Then the reaction was monitored by TLC. After completion the reaction mixture was evaporated *in vacuo*. The crude product was purified by flash column chromatography using petroleum ether–EtOAc.

Methyl (1*R**,2*R**,5*R**)-[5-(ethylthio)-2-[(ethylthio)methyl]-3-oxocyclopentyl]acetate **2a**.

Colorless oil, R_f 0.71 (petroleum ether–EtOAc, 7 : 3)

^1H NMR (500.13 MHz, CDCl_3) δ : 1.21 (t, J 7.4 Hz, 3H, Me), 1.25 (t, J 7.4 Hz, 3H, Me), 2.28 (dd, J 18.6, 10.6 Hz, 1H, $\text{H}4'$), 2.41 (dddd, J 10.9, 5.5, 4.1, 1.2 Hz, 1H, $\text{H}2'$), 2.48 (dddd, J 10.9, 10.3, 5.5, 5.1 Hz, 1H, $\text{H}1'$), 2.50 (q, J 7.4 Hz, 2H, SCH_2), 2.58 (q, J 7.4 Hz, 2H, SCH_2), 2.72 (dd, J 15.8, 5.5 Hz, 1H, CH_2CO_2), 2.80 (dd, J 13.4, 5.5 Hz, 1H, CH_2S), 2.80 (dd, J 15.8, 5.5 Hz, 1H, CH_2CO_2), 2.83 (ddd, J 18.6, 7.6, 1.2 Hz, 1H, $\text{H}4'$), 2.86 (dd, J 13.4, 4.1 Hz, 1H, CH_2S), 3.12 (ddd, J 10.6, 10.3, 7.6 Hz, 1H, $\text{H}5'$), 3.68 (s, 3H, OMe).

^{13}C NMR (125 MHz, CDCl_3) δ : 14.67 (C8), 14.96 (C10), 25.13 (C9), 27.28 (C7), 30.19 (C6), 35.31 (C2), 43.01 (C1'), 43.08 (C5'), 46.55 (C4'), 51.75 (OMe), 53.99 (C2'), 172.31 (C1), 214.40 (C3').

IR (KBr) ν_{max} : 2967, 2928, 2872, 1741, 1437, 1263, 1171, 1148 cm^{-1} .

ESI m/z : 229 $[\text{M} - \text{EtSH}]^+$ (100%), 199 $[\text{M} - \text{EtSH} - \text{C}_2\text{H}_6]^+$ (60%), 167 $[\text{M} - 2\text{EtSH}]^+$ (95%).

Methyl (1R*,2R*,5S*)-{5-(ethylthio)-2-[(ethylthio)methyl]-3-oxocyclopentyl}acetate 2b.

Colorless oil, R_f 0.71 (petroleum ether–EtOAc, 7 : 3).

^1H NMR (500.13 MHz, CDCl_3) δ : 1.21 (t, J 7.4 Hz, 3H, Me), 1.22 (t, J 7.4 Hz, 3H, Me), 2.33 (dt, J 11.1, 5.0 Hz, 1H, $\text{H}2'$), 2.36 (dd, 2J 13.0, 4.8 Hz, 1H, CH_2S), 2.48 (q, J 7.2 Hz, 2H, SCH_2), 2.57 (dd, J 18.5, 2.8 Hz, 1H, $\text{H}4'$), 2.61 (dd, J 18.5, 5.6, 1.2 Hz, 1H, $\text{H}4'$), 2.71 (dd, J 16.9, 5.3 Hz, 1H, $\text{H}-\text{CH}_2\text{CO}_2$), 2.78 (dd, J 16.9, 9.4 Hz, 1H, CH_2CO_2), 2.80 (q, J 6.8 Hz, 2H, SCH_2), 2.93 (dddd, J 11.1, 9.4, 5.8, 5.3 Hz, 1H, $\text{H}1'$), 2.95 (dd, 2J 13.0, 10.0 Hz, 1H, CH_2S), 3.70 (s, 3H, OMe), 3.76 (ddd, J 5.8, 5.6, 2.9 Hz, 1H, $\text{H}5'$).

^{13}C NMR (125 MHz, CDCl_3) δ : 14.54 (Me), 16.64 (Me), 25.55 (SCH_2), 27.36 (SCH_2), 29.98 (CH_2), 34.58 (SCH_2), 41.08 (C1), 42.92 (C5), 46.56 (C4), 51.19 (C2), 51.79 (OMe), 172.42 (CO_2), 215.40 (CO).

IR (KBr) ν_{max} : 2964, 2926, 2872, 1740, 1436, 1262, 1165 cm^{-1} .

ESI m/z : 291 $[\text{M}+\text{H}]^+$ (8%), 229 $[\text{M} - \text{EtSH}]^+$ (55%), 199 $[\text{M} - \text{EtSH} - \text{C}_2\text{H}_6]^+$ (80%), 167 $[\text{M} - 2\text{EtSH}]^+$ (100%).

Methyl (1R*,2S*,5R*)-5-{(ethylthio)-2-[(ethylthio)methyl]-3-oxocyclopentyl}acetate 2c.

Colorless oil, R_f 0.71 (petroleum ether–EtOAc, 7 : 3)

^1H NMR (500.13 MHz, CDCl_3) δ : 1.23 (t, J 6.8 Hz, 3H, Me), 1.25 (t, J 6.9 Hz, 3H, Me), 2.23 (dd, J 16.0, 9.0 Hz, 1H, CH_2CO_2), 2.24 (dd, J 16.2, 10.0 Hz, 1H, CH_2S), 2.26 (dd, J 16.2, 8.0 Hz, 1H, $\text{H}4'$), 2.52 (q, J 6.8 Hz, 2H, SCH_2), 2.61 (dd, J 16.0, 3.0 Hz, 1H, CH_2CO_2), 2.63 (dd, J 16.2, 4.3 Hz, 1H, SCH_2), 2.64 (q, J 6.9 Hz, 2H, SCH_2), 2.68 (dd, J 16.2, 3.6 Hz, 1H, $\text{H}4'$), 2.89 (dddd, J 9.9, 8.0, 5.6, 3.6 Hz, 1H, $\text{H}1'$), 3.11 (ddd, J 10.1, 8.0, 4.4 Hz, 1H, $\text{H}2'$), 3.35 (ddd, J 8.0, 3.6, 3.5 Hz, 1H, $\text{H}5'$), 3.69 (s, 3H, OMe).

^{13}C NMR (125 MHz, CDCl_3) δ : 14.59 (Me), 14.68 (Me), 25.55 (SCH_2), 26.73 (SCH_2), 32.83 (CH_2S), 40.68 (C1'), 41.78 (C5), 43.01 (C4), 48.92 (C2), 51.89 (OMe), 172.36 (CO_2), 215.29 (CO).

Methyl (1R*,5S*)- and (1R*,5R*)-{5-[(ethylthio)methyl]-4-oxocyclopent-2-en-1-yl}acetates 3a and 3b, respectively.

Colorless oil, **3a** : **3b** 4:1, R_f 0.7 (petroleum ether–EtOAc, 7 : 3) total yield 61%.

IR (KBr) ν_{max} : 3077, 2954, 2928, 1713, 1707, 16.82, 1589, 1434, 1363, 1262, 1170, 793 cm^{-1} .

ESI m/z : (APCI): 229 $[\text{M}+\text{H}]^+$ and 227 $[\text{M}-\text{H}]^-$ (100%).

Compound 3a

Colorless oil, R_f 0.7 (7:3, petroleum ether/EtOAc)

^1H NMR (500.13 MHz, CDCl_3) δ : 1.23 (t, J 7.4 Hz, 3H, Me), 2.27 (ddd, J 2.8, 4.0, 6.8 Hz, 1H, H5'), 2.50 (m, 3H), 2.65 (dd, J 8.6, 13.0 Hz, 1H, CH_2), 2.72 (dd, J 6.2, 15.9 Hz, 1H, CH_2), 3.01 (dd, J 4.0, 13.1 Hz, 1H, CH_2), 3.25 (tt, J 6.2, 2.3 Hz, 1H, H1'), 3.69 (s, 3H, OMe), 6.18 (dd, J 1.9, 5.8 Hz, 1H, H2'), 7.65 (dd, J 2.3, 5.8 Hz, 1H, H3').

^{13}C NMR (75.47 MHz, CDCl_3) δ : 14.64 (Me), 26.77 (SCH_2), 32.16 (C2), 37.94 (CH_2S), 50.62 (C5'), 51.77 (OMe), 133.50 (C3'), 165.77 (C2'), 171.73 (C1'), 208.58 (C4').

Compound 3b

^1H NMR (500.13 MHz, CDCl_3) δ : 1.25 (t, J 7.4 Hz, 3H, Me), 3.70 (s, 3H, OMe), 6.20 (dd, J 1.7, 5.7 Hz, 1H, H3'), 7.75 (dd, J 1.7, 5.7 Hz, 1H, H2').

^{13}C NMR (75.47 MHz, CDCl_3) δ : 14.61 (Me), 26.66 (SCH_2), 30.94 (CH_2), 34.36 (SCH_2), 40.68 (C1'), 47.96 (C5'), 50.62 (OMe), 129.94 (C3'), 166.28 (C2'), 171.90 (C1), 208.50 (C4).

Methyl ({[(1R*,2S*)-2-(2-methoxy-2-oxoethyl)-5-oxocyclopent-3-en-1-yl]methyl}thio)acetate 6.

Colorless oil, R_f 0.52 (petroleum ether–EtOAc, 1 : 1).

^1H NMR (500.13 MHz, CDCl_3) δ : 2.33 (ddd, J 2.8, 4.2, 8.4 Hz, 1H, H5), 2.54 (dd, J 8.2, 16.1 Hz, 1H, CH_2), 2.72 (dd, J 6.5, 16.1 Hz, 1H, CH_2), 2.82 (dd, J 8.4, 13.1 Hz, 1H, CH_2S), 3.11 (dd, J 4.2, 13.0 Hz, 1H, CH_2S), 3.23 (dddd, 3J 8.2, 6.5, 2.8 Hz; 4J 2.4, 2.0 Hz, 1H, H1), 3.27 (s, 2H, CH_2), 3.65 (s, 3H, OMe), 3.70 (s, 3H, OMe), 6.20 (dd, J 2.0, 5.7 Hz, 1H, H2'), 7.67 (dd, J 2.4, 5.7 Hz, 1H, H3').

^{13}C NMR (75.47 MHz, CDCl_3) δ : 33.33 (CH_2), 34.41 (CH_2), 37.51 (CH_2), 43.48 (C1), 50.46 (C5), 51.50 (OMe), 51.91 (OMe), 133.57(C3), 165.75 (C2), 170.59 (CO_2), 171.65 (CO_2), 208.04 (CO).

IR (KBr) ν_{max} : 2998, 2924, 1755, 1738, 1729, 1703, 1694, 1436, 1300, 1280, 1197, 1165, 1136, 1011 cm^{-1} .

ESI m/z : 273 $[\text{M}+\text{H}]^+$ (100%); 271 $[\text{M}-\text{H}]^-$ (100%).

Methyl [{[(1R*,2R*,3R*)-2-(2-methoxy-2-oxoethyl)-3-{[2-methoxy-2-oxoethyl]thio}methyl]-4-oxocyclopentyl]thio}acetate 7.

Colorless oil, R_f 0.7 (petroleum ether–EtOAc, 1 : 1).

^1H NMR (500.13 MHz, CDCl_3) δ : 2.28 (dd, J 10.2, 18.8 Hz, 1H, CH_2CO_2), 2.48 (m, 2H), 2.72 (dd, J 5.0, 16.0 Hz, 1H, CH_2S), 2.80 (dd, J 4.5, 16.0 Hz, 1H, CH_2S), 2.90 (dd, J 7.8, 18.8 Hz, 1H, CH_2CO_2), 2.95 (d, J 4.4 Hz, 2H, H– CH_2S), 3.23 (s, 2H, S– CH_2CO_2), 3.29 (s, 2H, S– CH_2CO_2), 3.68 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.72 (s, 3H, OMe).

^{13}C NMR (75.47 MHz, CDCl_3) δ : 30.99 (CH_2), 32.97(CH_2), 34.72(CH_2), 35.04 (CH_2), 42.77 (C2), 43.85 (C1), 51.82 (OMe), 52.45 (OMe), 52.58 (OMe), 54.09 (C5), 45,86 (CH_2), 170.60 (CO_2), 170.65 (CO_2), 172.04 (CO_2), 213.17 (CO).

IR (KBr) ν_{max} : 3000, 2954, 2925, 1732, 1437, 1282, 1161, 1008 cm^{-1} .

ESI m/z : 396 $[\text{M} + \text{H}_2\text{O}]^+$ (50%), 273 $[\text{M} - \text{SCH}_2\text{CO}_2\text{Me}]^+$ (30%), 208 (100%), 167 $[\text{M} - 2\text{HSCH}_2\text{CO}_2\text{Me}]^+$ (100%); 379 $[\text{M} + \text{H}]^-$ (10%), 303 $[\text{M} - \text{H} - \text{MeCO}_2\text{Me}]^-$ (100%), 179 (100%).

Methyl (1R*,5S*)-[4-oxo-5-[(phenylthio)methyl]cyclopent-2-en-1-yl]acetate 8.

Colorless oil, R_f 0.56 (petroleum ether–EtOAc, 7 : 3).

¹H NMR (500.13 MHz, CDCl₃) δ : 2.31 (dt, *J* 9.6, 3.5 Hz, 1H, H1), 2.43 (dd, *J* 8.9, 16.1 Hz, 1H, CH₂CO₂), 2.75 (dd, *J* 5.8, 16.1 Hz, 1H, CH₂CO₂), 2.91 (dd, *J* 9.6, 13.3 Hz, 1H, CH₂S), 3.25 (m, 1H, H1), 3.52 (dd, *J* 3.8, 13.3 Hz, 1H, CH₂S), 3.70 (s, 3H, OMe), 6.17 (dd, *J* 1.5, 5.7 Hz, 1H, H3), 7.17 (1H, Ph), 7.26 (2H, Ph), 7.35 (2H, Ph), 7.67 (dd, *J* 2.2, 5.7 Hz, 1H, H2).

¹³C NMR (75.47 MHz, CDCl₃) δ : 129.49 (2CH–Ar), 129.02 (2CH–Ar), 34.83 (CH₂), 37.90 (CH₂), 43.84 (C1), 50.12 (C5), 51.82 (OMe), 126.48 (CH–Ar), 133.44 (C3), 135.35 (C_q–Ar), 165.79 (C2), 171.63 (CO₂), 208.10 (CO).

IR (KBr) ν_{max} : 3068, 2952, 1736, 1733, 1706, 1699, 1585, 1481, 1436, 1264, 1171, 1025, 724, 691 cm⁻¹.

ESI *m/z*: 208 [M]⁺ (20%), 167 [M–SPh]⁺ (100%).

Methyl (1R*,2R*,5R*)- and (1R*,2S*,5S*)-{5-phenylthio-3-oxo-2-[(phenylthio)methyl]cyclopentyl}acetate **9a and **9b**, respectively.**

Colorless oil, (**9a**) : (**9b**) 4:1, *R_f* 0.65 (petroleum ether–EtOAc, 7 : 3), yield 81%.

IR (KBr) ν_{max} : 3057, 2950, 2942, 2850, 1740, 1583, 1480, 1438, 1171, 741, 692 cm⁻¹.

ESI *m/z*: 386 [M]⁺ (20%), 277 [M–SPh]⁺ (40%), 208 [M–SPh–CO₂Me]⁺ (100%).

Compound 9a

¹H NMR (500.13 MHz, CDCl₃) δ : 2.20 (dd, *J* 10.2, 18.8 Hz, 1H, C4), 2.45–2.55 (m, 2H, H4, CH₂CO₂), 2.75 (dd, *J* 5.5, 16.2 Hz, 1H, CH₂CO₂), 2.76–2.80 (m, 2H, H2, H1), 2.84 (dd, *J* 4.7, 16.2 Hz, 1H, CH₂CO₂), 3.07 (dd, *J* 6.4, 13.8 Hz, 1H, CH₂S), 3.35 (dd, *J* 3.8, 13.8 Hz, 1H, CH₂S), 3.49 (ddd, *J* 7.8, 10.0, 14.7 Hz, 1H, H5), 3.65 (s, 3H, OMe), 7.23–7.45 (m, 10H, 2Ph).

¹³C NMR (75.47 MHz, CDCl₃) δ : 33.03 (CH₂), 35.24 (OCH₂), 43.26 (CH), 45.43 (CH₂), 46.15 (CH), 51.75 (OMe), 53.40 (CH), 133.44 (C_q–Ph), 172.12 (CO₂), 128.14, 126.58 (CH–Ph), 129.21, 129.04 (CH–Ph), 129.84 (2CH–Ph), 213.31 (CO).

Compound 9b

¹H NMR (500.13 MHz, CDCl₃) δ : 3.15 (dd, *J* 6.2, 13.7 Hz, 1H, CH₂), 3.37 (dd, *J* 4.0, 13.6 Hz, 1H, CH₂), 3.62 (s, 3H, OMe), 4.27 (ddd, *J* 3.0, 5.4, 8.2 Hz, 1H, H5).

¹³C NMR (75.47 MHz, CDCl₃) δ : 32.91 (CH₂), 35.57 (CH₂), 41.64 (CH), 45.44 (CH₂), 46.08 (CH₂), 46.09 (CH), 50.69 (CH), 51.76 (OMe), 128.1, 129.12, 132.14, 4 132.44 (CH–Ph), 135.60 (C_q–Ph), 174.13 (CO₂), 214.24 (CO).

General Procedure for the mCPBA oxidation of sulfides

1. Unsuccessful attempt to obtain sulfoxides.

mCPBA (569.5 mg, 3.3 mmol) was added at –30°C to a stirred solution of **3a** (290.4 mg, 1 mmol, in CH₂Cl₂ (30 ml)). The reaction was monitored by TLC and, after its completion, the reaction mass was held at –30 °C for 1 h, then rapidly filtered through a Schott filter to remove the excess of mCPBA. The precipitate was washed with a small amount of cooled CH₂Cl₂, and the filtrate was evaporated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether–EtOAc) to afford 50 mg of compound **1** and 104 mg of oily compound **5**.

Methyl (1R*,5S*)-{5-[(ethylsulfonyl)methyl]-4-oxocyclopent-2-en-1-yl}acetate **5.**

Colorless oil, *R_f* 0.35 (petroleum ether–EtOAc, 7 : 3).

^1H NMR (500.13 MHz, CDCl_3) δ : 1.20 (t, J 7.5 Hz, 3H, Me), 2.57 (dd, J 16.6, 9.2 Hz, 1H, H2), 2.68 (dt, J 10.3, 3.0 Hz, 1H, H5'), 2.95 (dd, J 13.9, 10.3 Hz, 1H, CH_2SO_2), 3.03 (dd, J 16.6, 5.0 Hz, 1H, H2), 3.08 (q, J 7.5, 2H, CH_2), 3.40 (dddd, 3J 2.3, 3.0, 5.0, 9.2, 4J 1.9 Hz, 1H, H1), 3.55 (dd, J 13.9, 3.0 Hz, 1H, CH_2SO_2), 3.70 (s, 3H, OMe), 6.27 (dd, J 1.9, 5.8 Hz, 1H, H3'), 7.78 (dd, J 2.3, 5.8 Hz, 1H, H2').

^{13}C NMR (125 MHz, CDCl_3) δ : 6.74 (Me), 36.78 (C2), 43.97 (C1), 44.42 (C5), 48.57 (CH_2), 51.91 (OMe), 52.19 (CH_2SO_2), 132.63 (C3), 166.61 (C2), 171.75 (C1), 206.48 (C4).

IR (KBr) ν_{max} : 2980, 2952, 2850, 1731, 1710, 1438, 1304, 1276, 1207, 1130, 829 cm^{-1} .

ESI m/z : 287 $[\text{M} + \text{H}_2\text{O}]^+$ (65%), 261 $[\text{M} + \text{H}]^+$ (95%), 199 $[\text{M} - \text{SCH}_2\text{Me}]^+$ (100%), 167 $[\text{M} - \text{SO}_2\text{CH}_2\text{Me}]^+$ (65%).

ESI m/z : 291 $[\text{M} - \text{H}]^-$ (3%), 259 $[\text{M} - \text{H} - \text{MeOH}]^-$ (100%), 231 $[\text{M} - \text{H} - \text{MeOH} - \text{CH}_2\text{CH}_2]^-$ (25%).

2. Preparation of sulfones.

A solution of sulfide (1 mmol) and mCPBA (3 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature for 2 h and then the reaction mixture was treated in the manner described above for the sulfoxides.

Methyl (1R*,5S*)-[4-oxo-5-[(phenylsulfonyl)methylcyclopent-2-en-1-yl]acetate (10).

Colorless wax, R_f 0.23 (petroleum ether–EtOAc, 7 : 3).

^1H NMR (500.13 MHz, CDCl_3) δ : 2.58 (dd, J 9.56, 16.6 Hz, 1H, CH_2CO_2), 2.65 (td, J 2.5, 10.1 Hz, 1H, H5'), 3.05 (dd, J 10.1, 14.0 Hz, 1H, CH_2SO_2), 3.20 (dd, J 4.5, 16.6 Hz, 1H, CH_2CO_2), 3.47 (dddd, J 2.5, 1.9, 4.5, 2.2, 9.5 Hz, 1H, H1), 3.65 (dd, J 2.4, 14.0 Hz, 1H, CH_2SO_2), 3.70 (s, 3H, OMe), 6.23 (dd, J 1.9, 5.7 Hz, 1H, H3'), 7.57 (t, 2H, Ph), 7.68 (m, 1H, Ph), 7.80 (dd, J 2.3, 5.7 Hz, 1H, H2'), 7.93 (d, J 7.9 Hz, 2H, Ph).

^{13}C NMR (75.47 MHz, CDCl_3) δ : 36.87 (CH_2), 43.97 (CH), 44.71 (CH), 51.90 (OMe), 57.11 (CH_2SO_2), 127.90, (2CH–Ph), 129.51, (2CH–Ph), 132.59 (CH–Ph), 134.12 (C3'), 139.09 (C_q–Ph), 166.67 (C2'), 171.77 (CO₂), 206.22 (CO).

IR (KBr) ν_{max} : 3068, 2954, 2925, 1738, 1729, 1706, 1695, 1447, 1305, 1085, 748 cm^{-1} .

ESI m/z : 309 $[\text{M} + \text{H}]^+$ (100%), 208 $[\text{M} - \text{C}_6\text{H}_6 - \text{MeOH}]^+$ (20%), 167 $[\text{M} - \text{SO}_2\text{C}_6\text{H}_5]^+$ (20%).

Biological assays

Culture conditions and treatments.

HEK293 (human embryonic kidney 293 cells) MCF-7 (human breast adenocarcinoma), A549 (human lung carcinoma) and SH-SY5Y (human neuroblastoma) cell lines were purchased from the Russian Cell Culture Collection (Institute of Cytology, Russian Academy of Science, Saint Petersburg, Russia). Cells were maintained in Dulbecco's modified Eagle's medium (DMEM, Invitrogen, USA) supplemented with 2 mM L-glutamine (Sigma-Aldrich, UK), 10% fetal bovine serum (FBS; Invitrogen, USA) and 50 mg ml^{-1} gentamicin sulfate (Invitrogen, USA) at 37 °C and 5% CO_2 . All compounds were dissolved in DMSO (Sigma-Aldrich, UK) to 100 mM stock solutions and diluted in complete DMEM immediately before addition to the assay plates. DMSO was maintained at a final concentration of 0.1%.

Cell viability

Cells were cultured at appropriate density in 96-well plates (2×10^4 cells/well for HEK293; 1.2×10^4 cells/well for A549; 1.2×10^4 cells/well for MCF-7; 3×10^4 cells/well for SH-SY5Y) and

allowed to grow for 24 h. Thereafter, the cells were treated with test compounds at final concentrations of 1, 10 and 100 μM for 48 h and cell viability was determined by conventional MTT assay following manufacturer's instruction using a Perkin-Elmer 2300 EnSpire® Multimode Plate Reader (USA) at 540 nm. Experiments were repeated independently three times in triplicate and data were expressed as MTT reduction relative to control (*i.e.* cells treated with 0.1% DMSO). The dose of the compound that inhibited 50% cell viability (IC_{50} value) was calculated using nonlinear regression analysis (GraphPad Prism v.5.02, GraphPad Software Inc., USA). The viability of control cells was set as 100%, and the viability in the experimental groups was calculated by comparing the optical density reading with the control.

Statistical analysis

All results were expressed as mean values \pm standard error of the mean (SEM). Differences between experimental groups were analyzed by one-way ANOVA followed by the Dunnett's post-hoc test.

NMR data

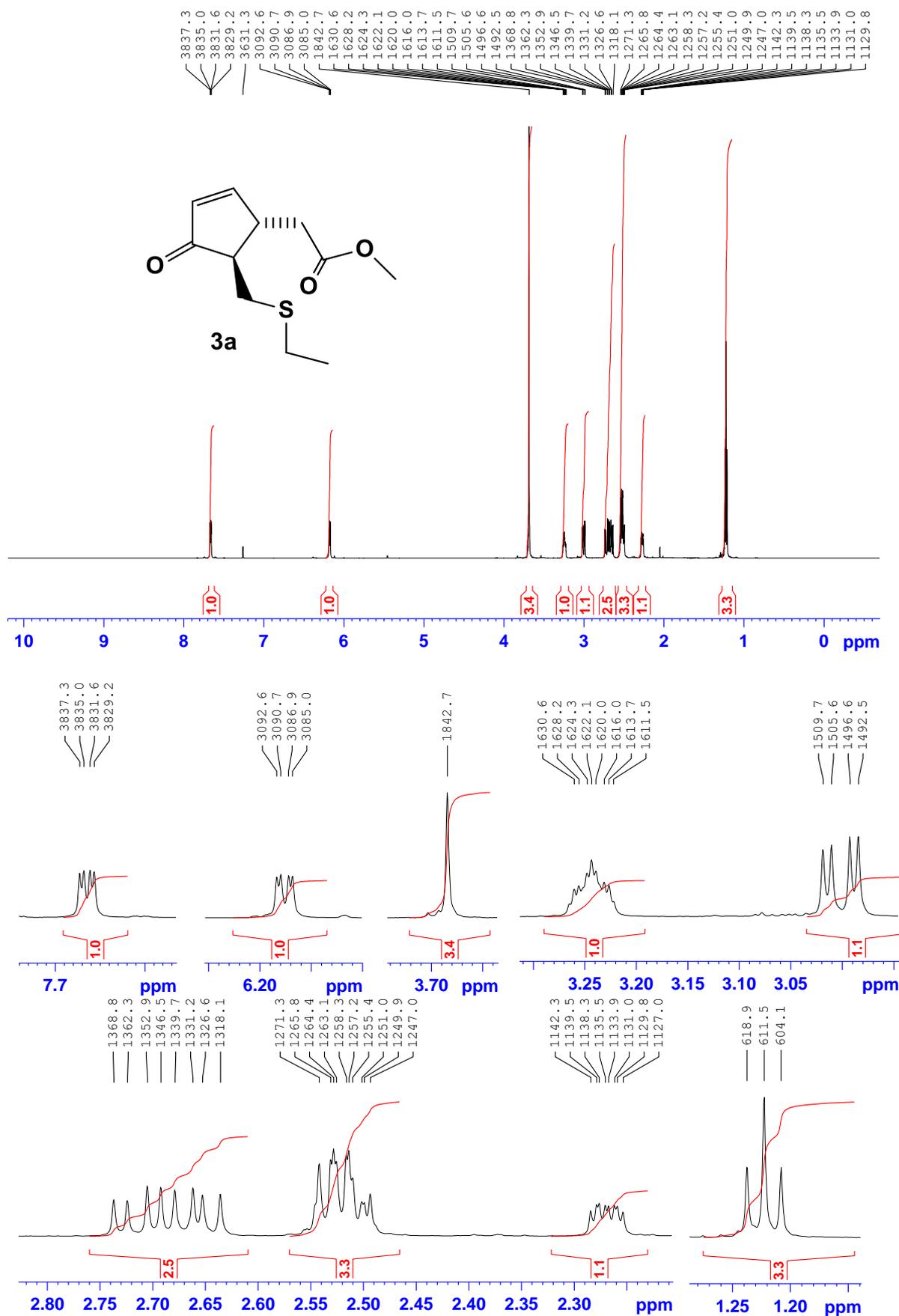


Figure S1 ¹H NMR spectra of compound **3a** in CDCl₃: (top) complete and (bottom) detailed spectrum.

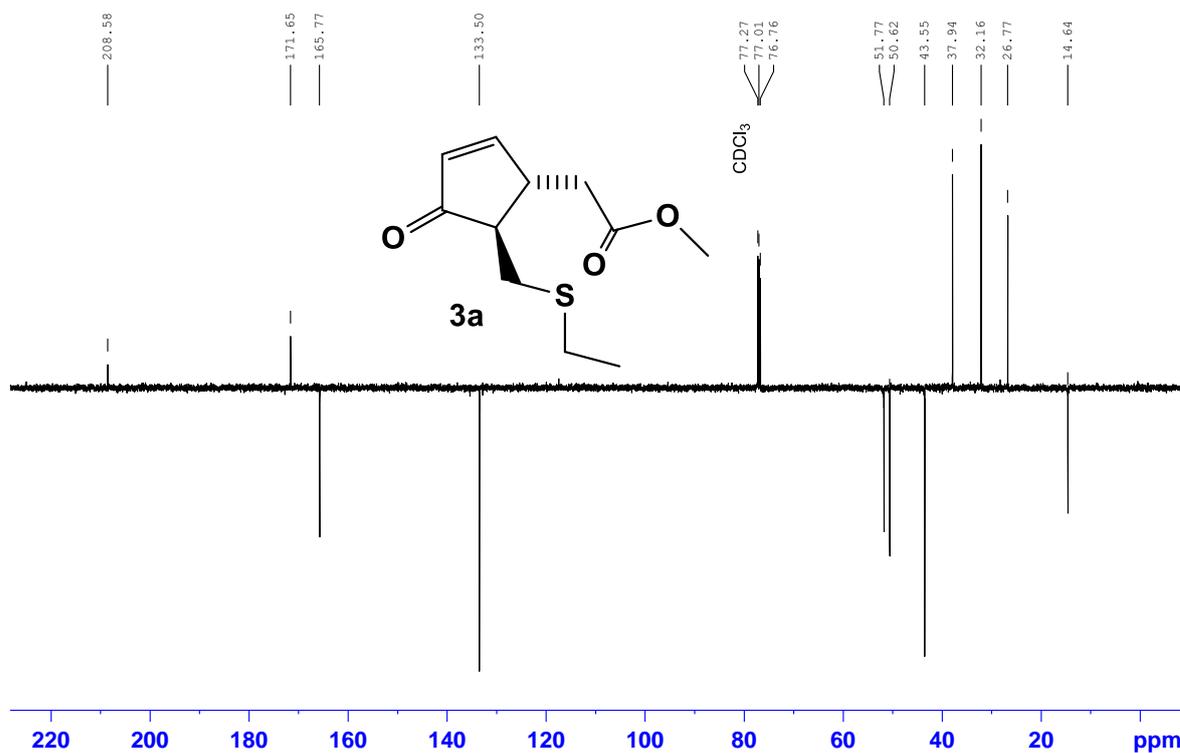


Figure S2 Complete ¹³C{¹H} *J*-modulated spin-echo NMR spectrum of compound **3a** in CDCl₃.

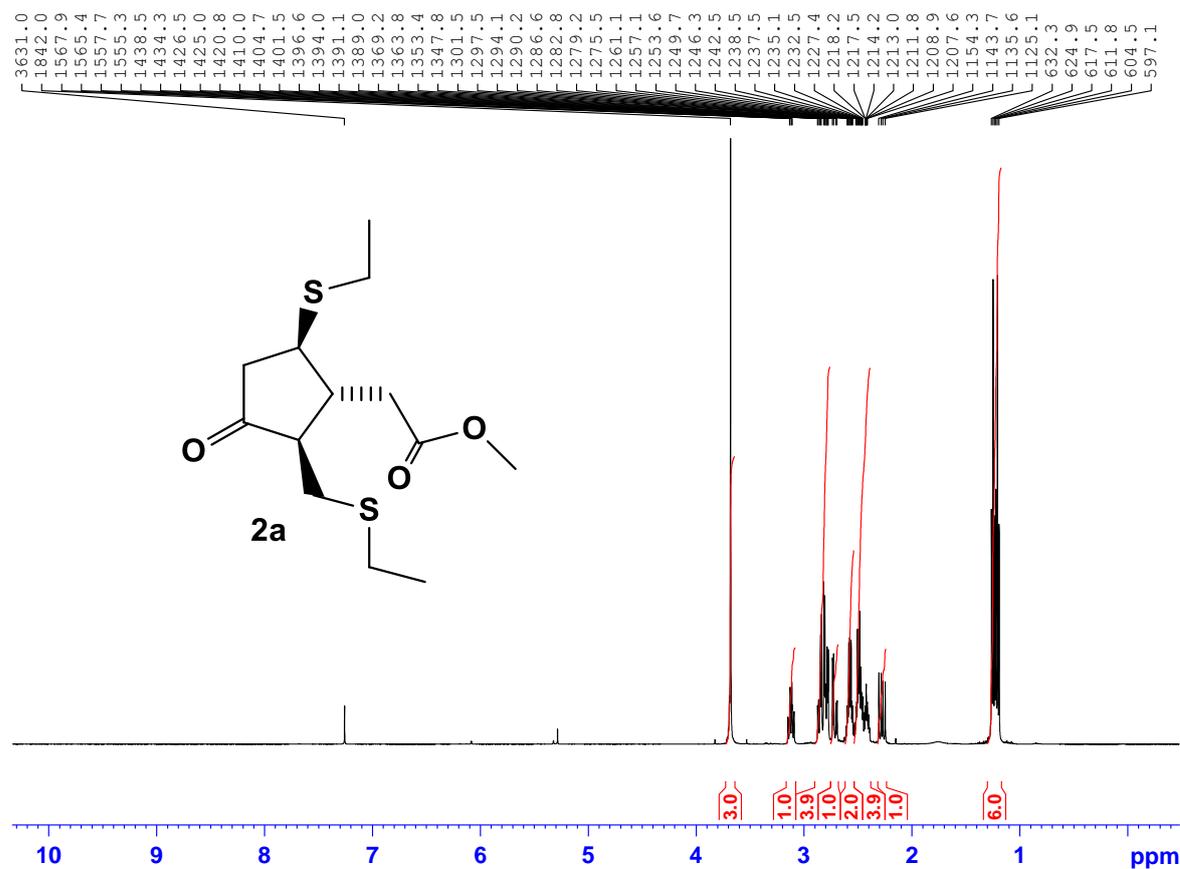


Figure S3 Complete ¹H NMR spectrum of compound **2a** in CDCl₃.

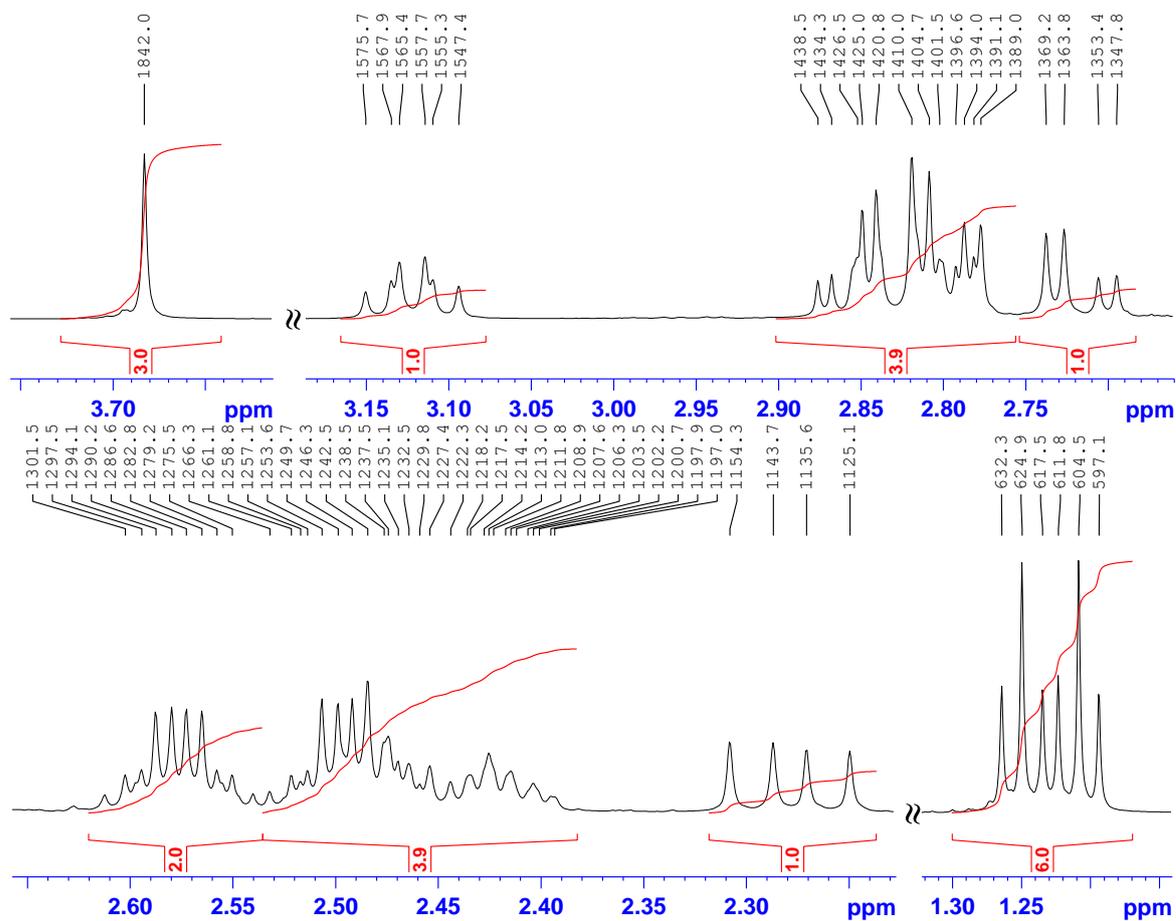


Figure S4 Detailed ^1H NMR spectrum of compound **2a** in CDCl_3 .

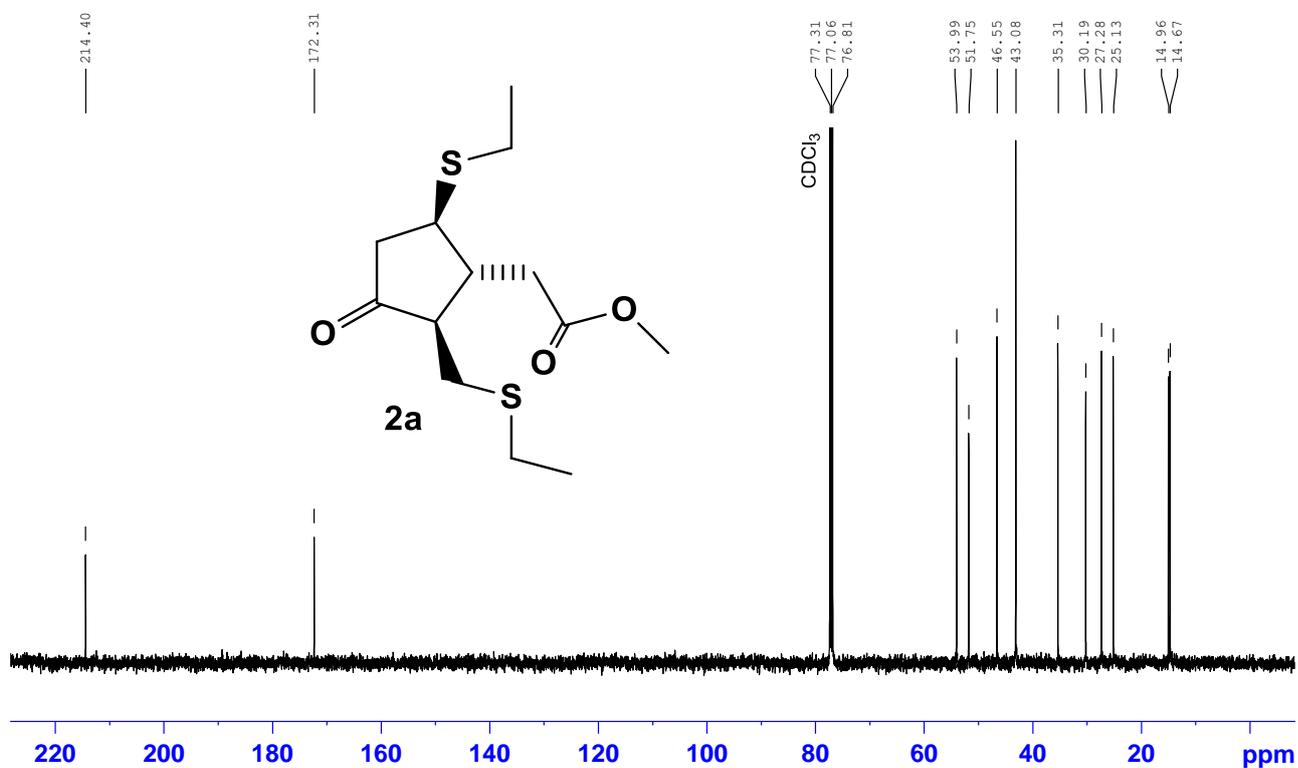


Figure S5 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **2a** in CDCl_3 .

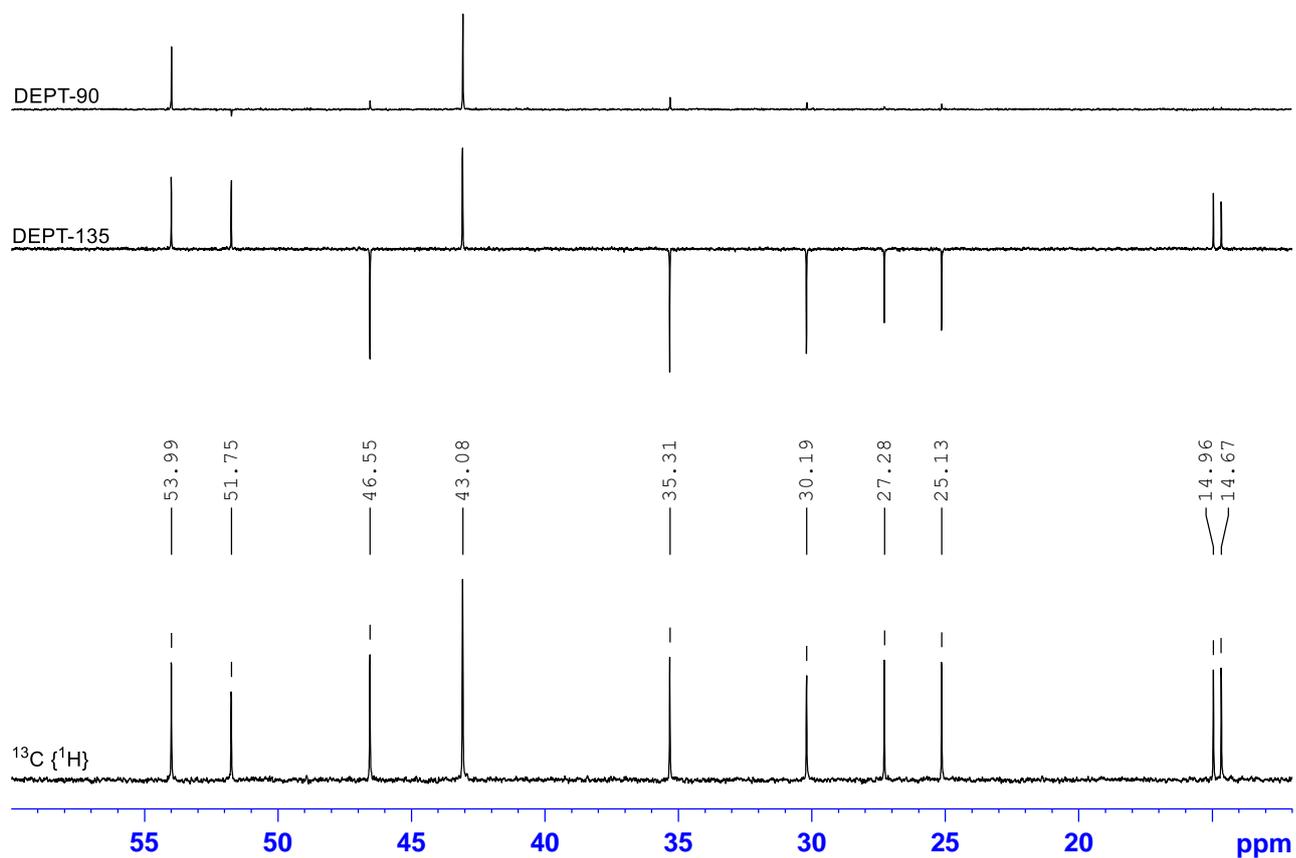


Figure S6 Downfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR, DEPT-135 and DEPT-90 spectra of compound **2a** in CDCl_3 .

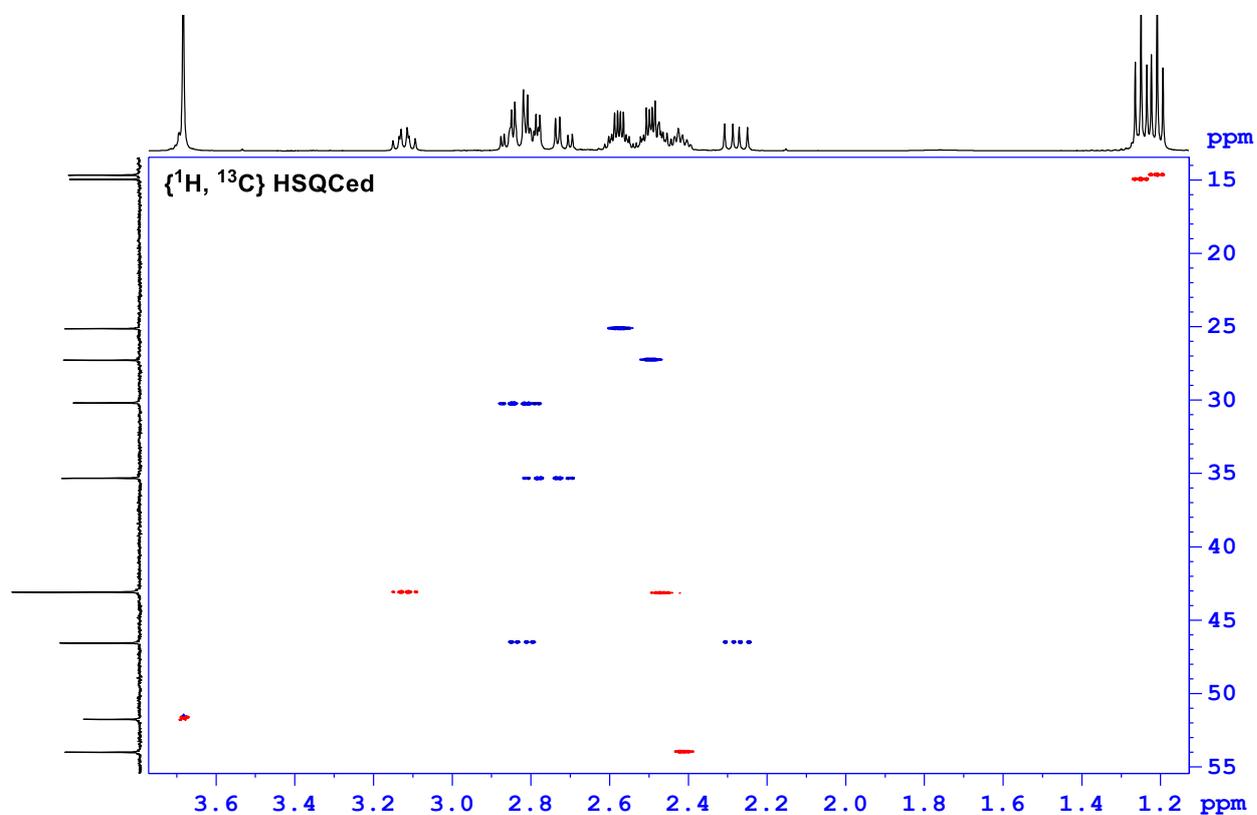


Figure S7 Downfield area of $\{^1\text{H}$, $^{13}\text{C}\}$ HSQC multiplicity edited NMR spectrum of compound **2a** in CDCl_3 .

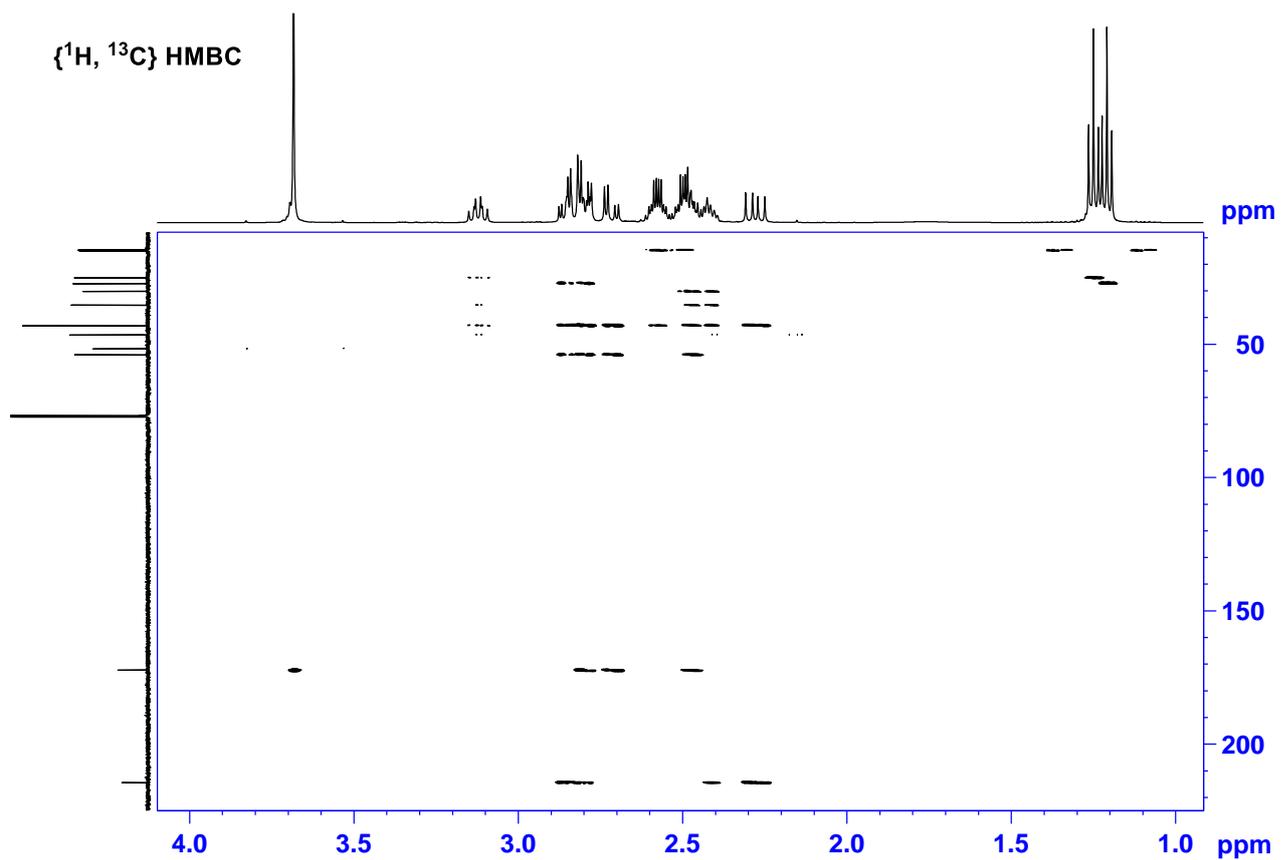


Figure S8 Complete $\{^1\text{H}, ^{13}\text{C}\}$ HMBC NMR spectrum of compound **2a** in CDCl_3 .

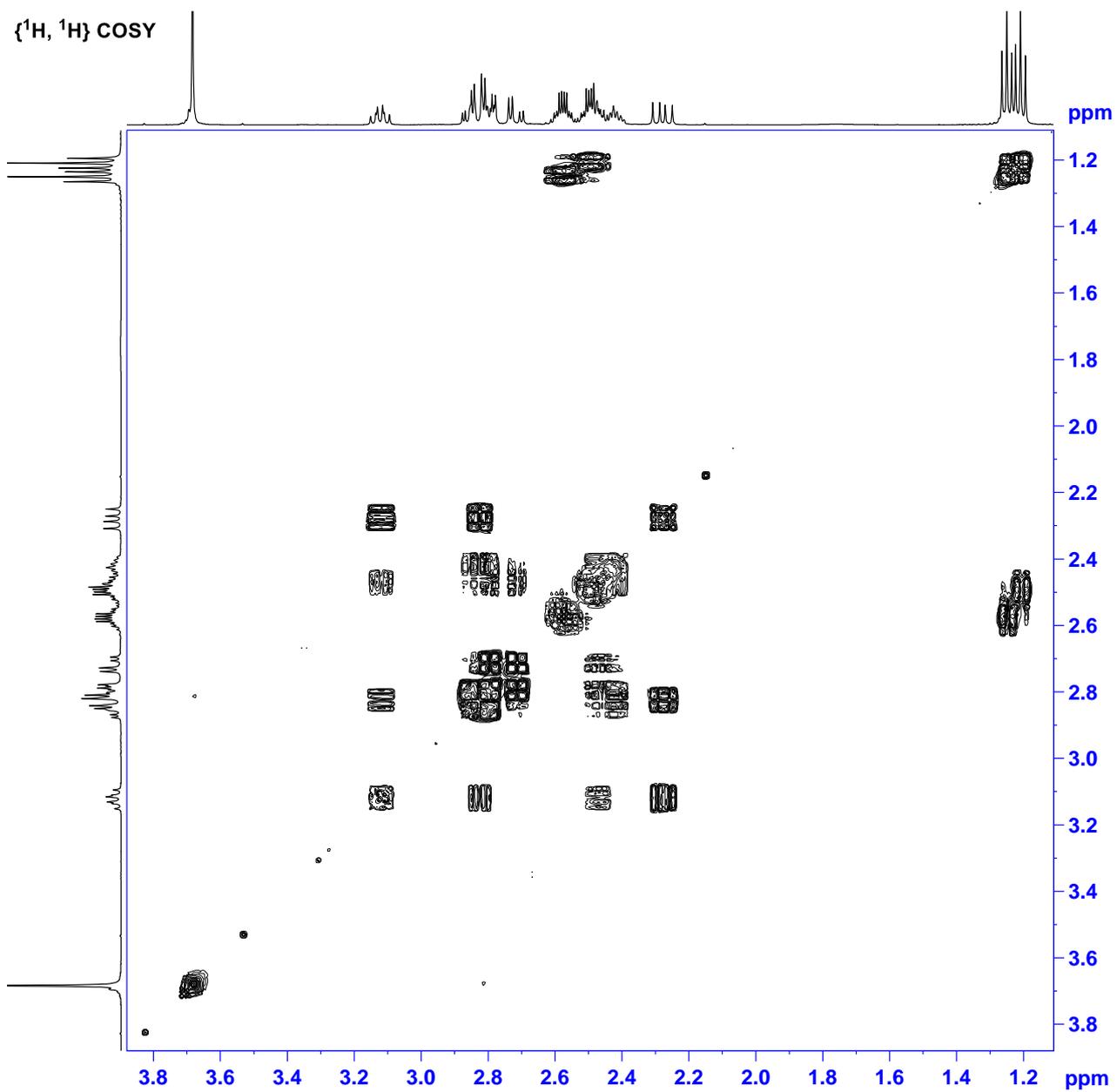


Figure S9 Complete $\{^1\text{H}, ^1\text{H}\}$ COSY NMR spectrum of compound **2a** in CDCl_3 .

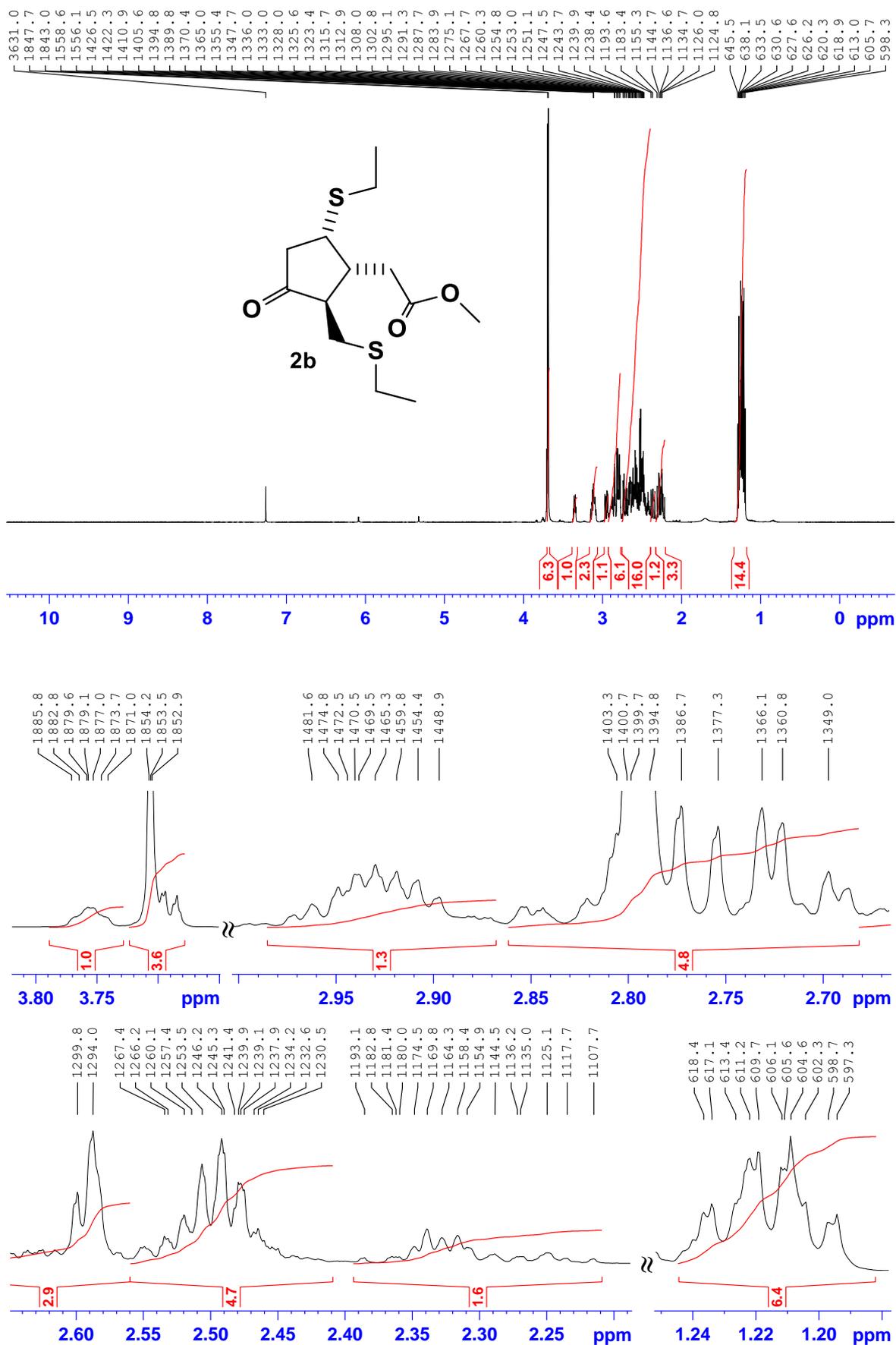


Figure S10 ¹H NMR spectra of compound **2b** in CDCl₃: (top) complete and (bottom) detailed spectrum.

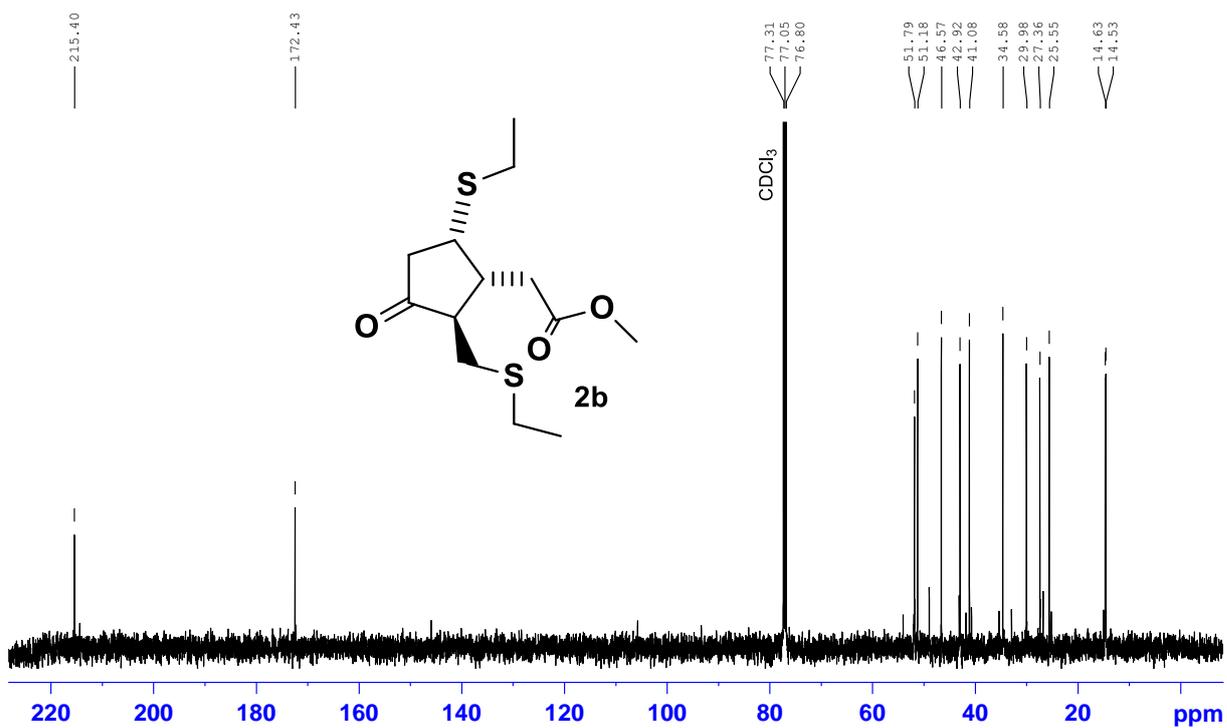


Figure S11 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **2b** in CDCl_3 .

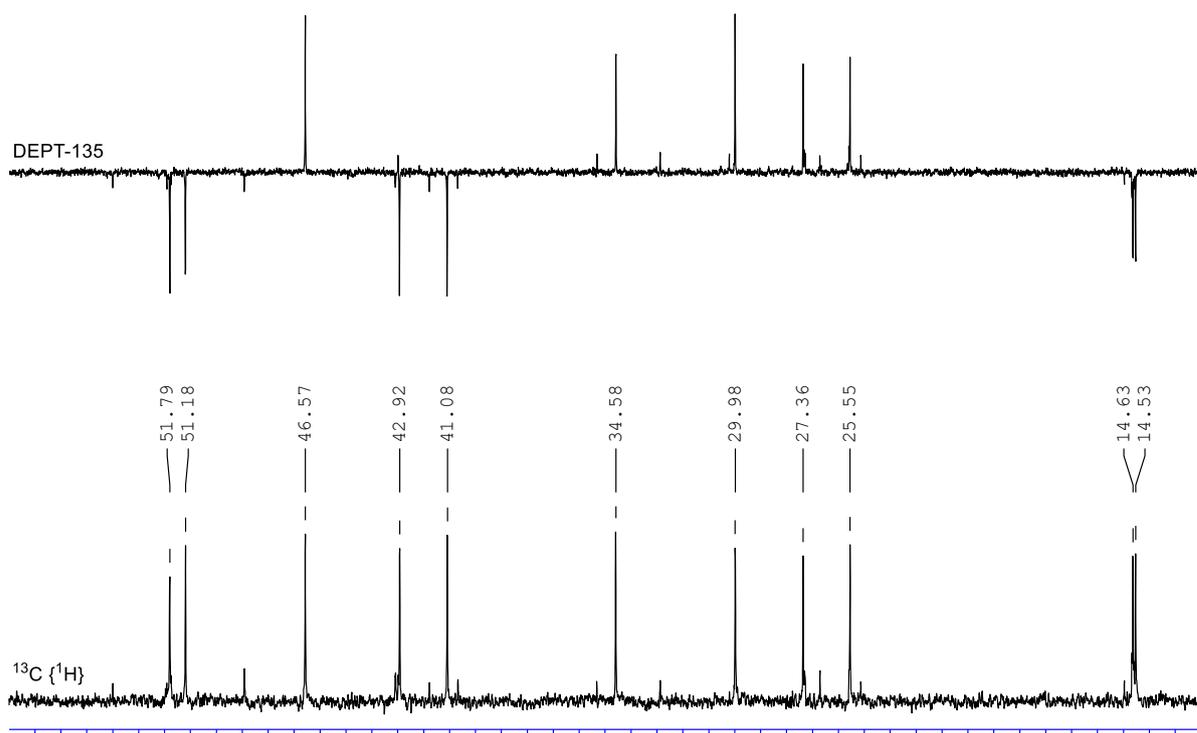


Figure S12 Downfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR and DEPT-135 spectra of compound **2b** in CDCl_3 .

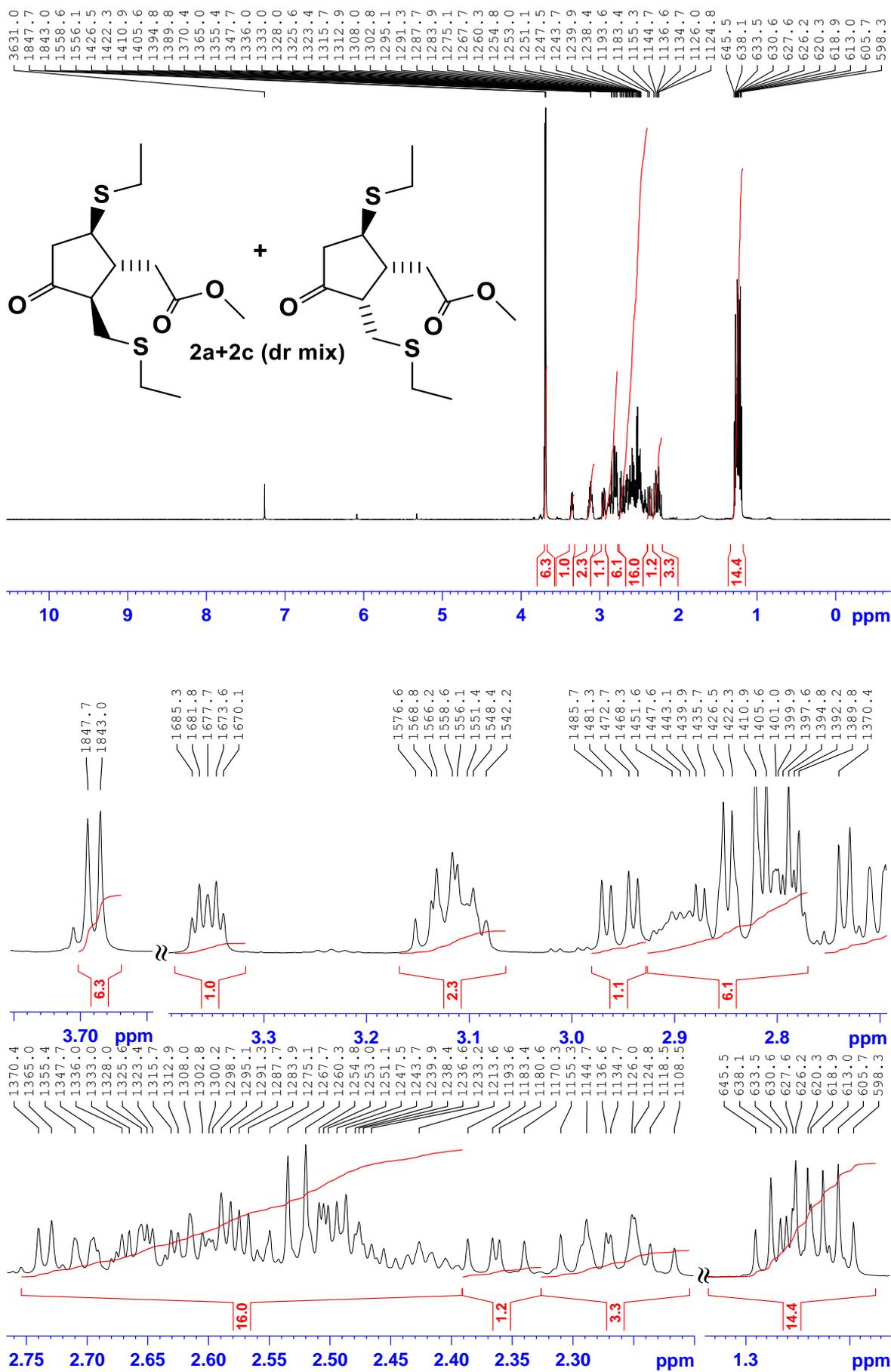
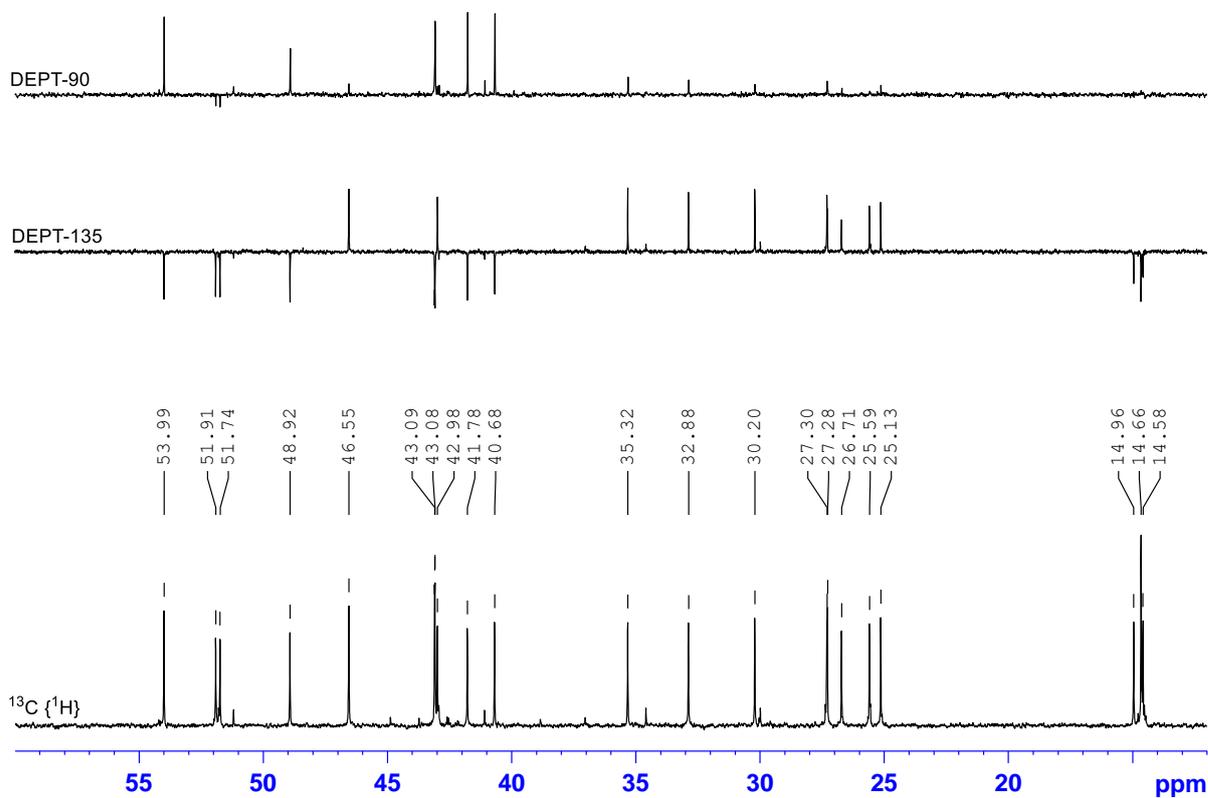
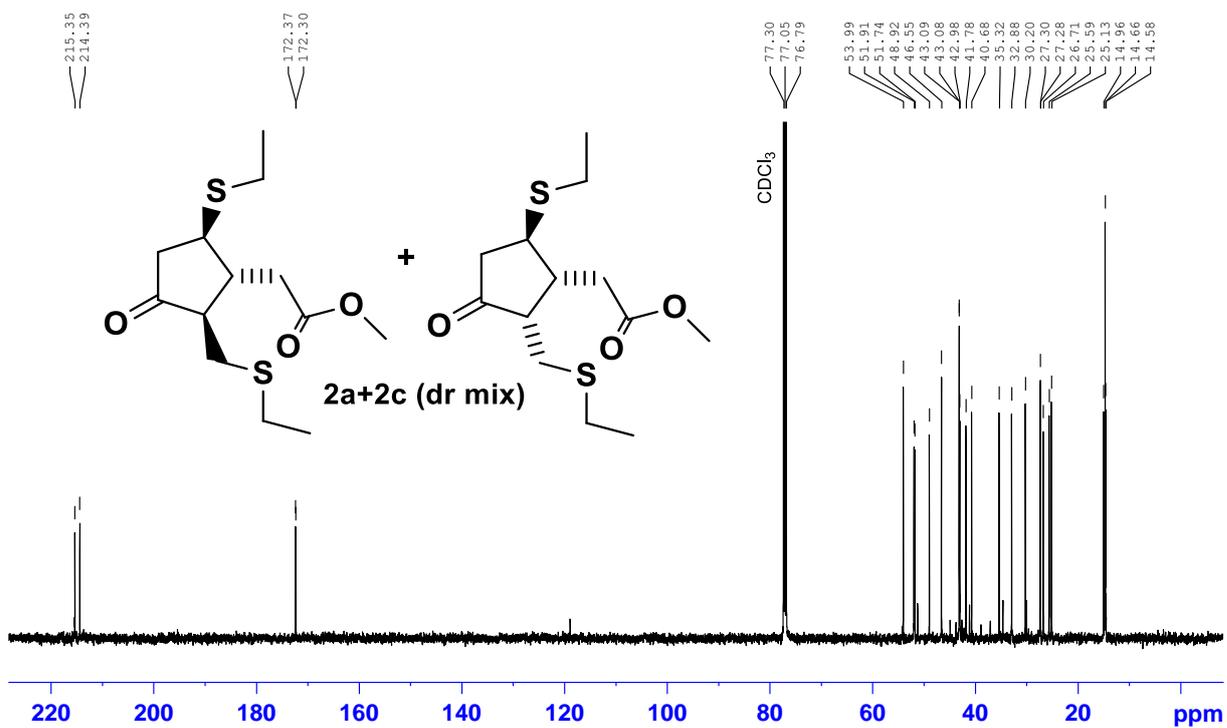


Figure S13 ¹H NMR spectra of mixture of compounds **2a,c** in CDCl₃: (top) complete and (bottom) detailed spectrum.



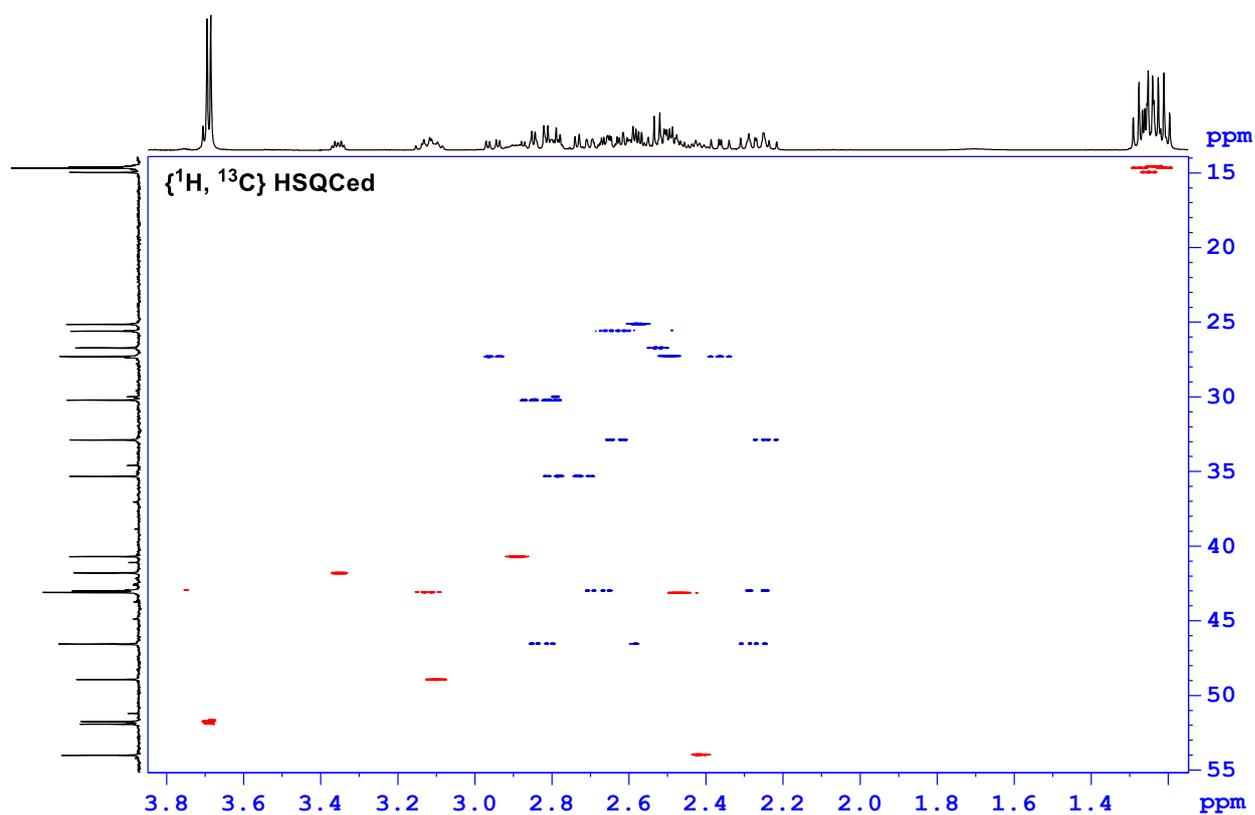


Figure S16 Downfield area of $\{^1\text{H}, ^{13}\text{C}\}$ HSQC multiplicity edited NMR spectrum of mixture of compounds **2a,c** in CDCl_3 .

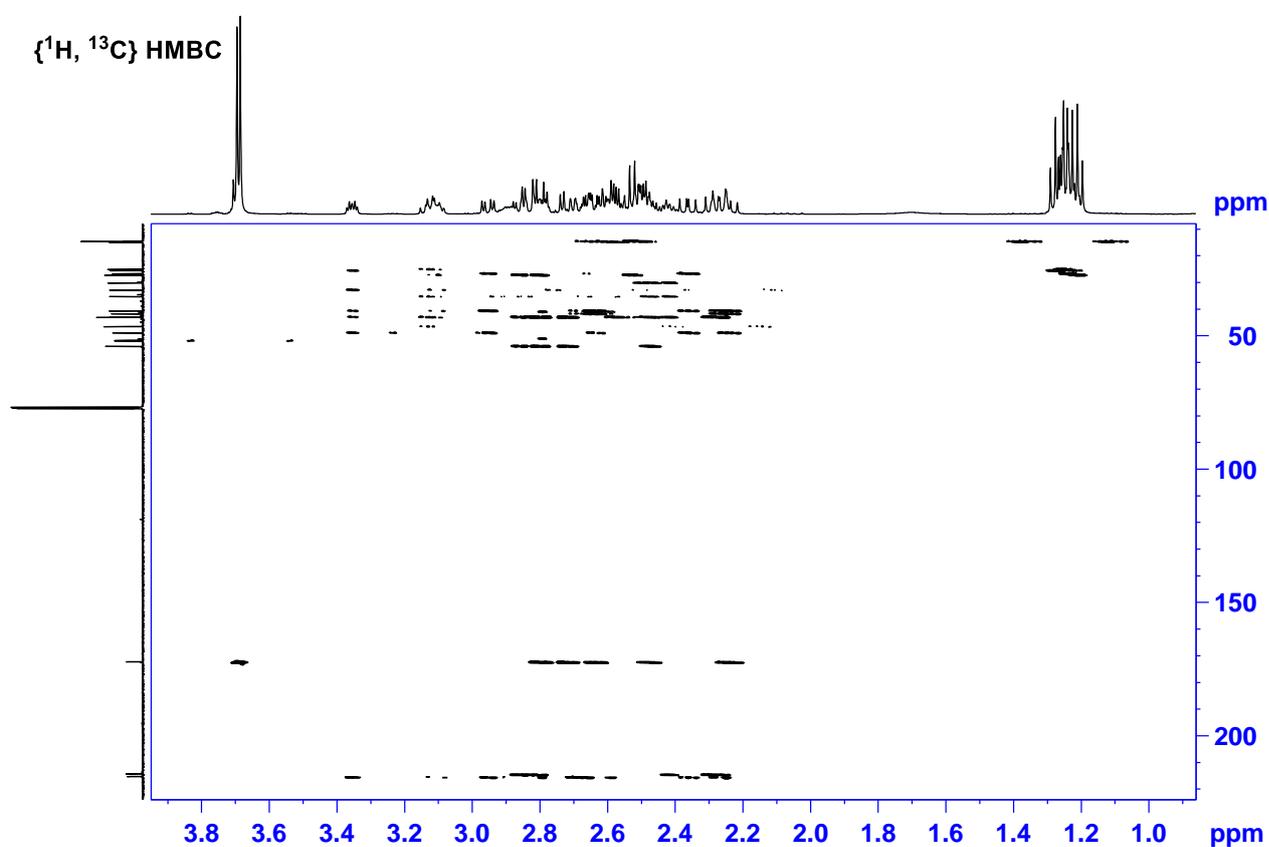


Figure S17 Complete $\{^1\text{H}, ^{13}\text{C}\}$ HMBC NMR spectrum of mixture of compounds **2a,c** in CDCl_3 .

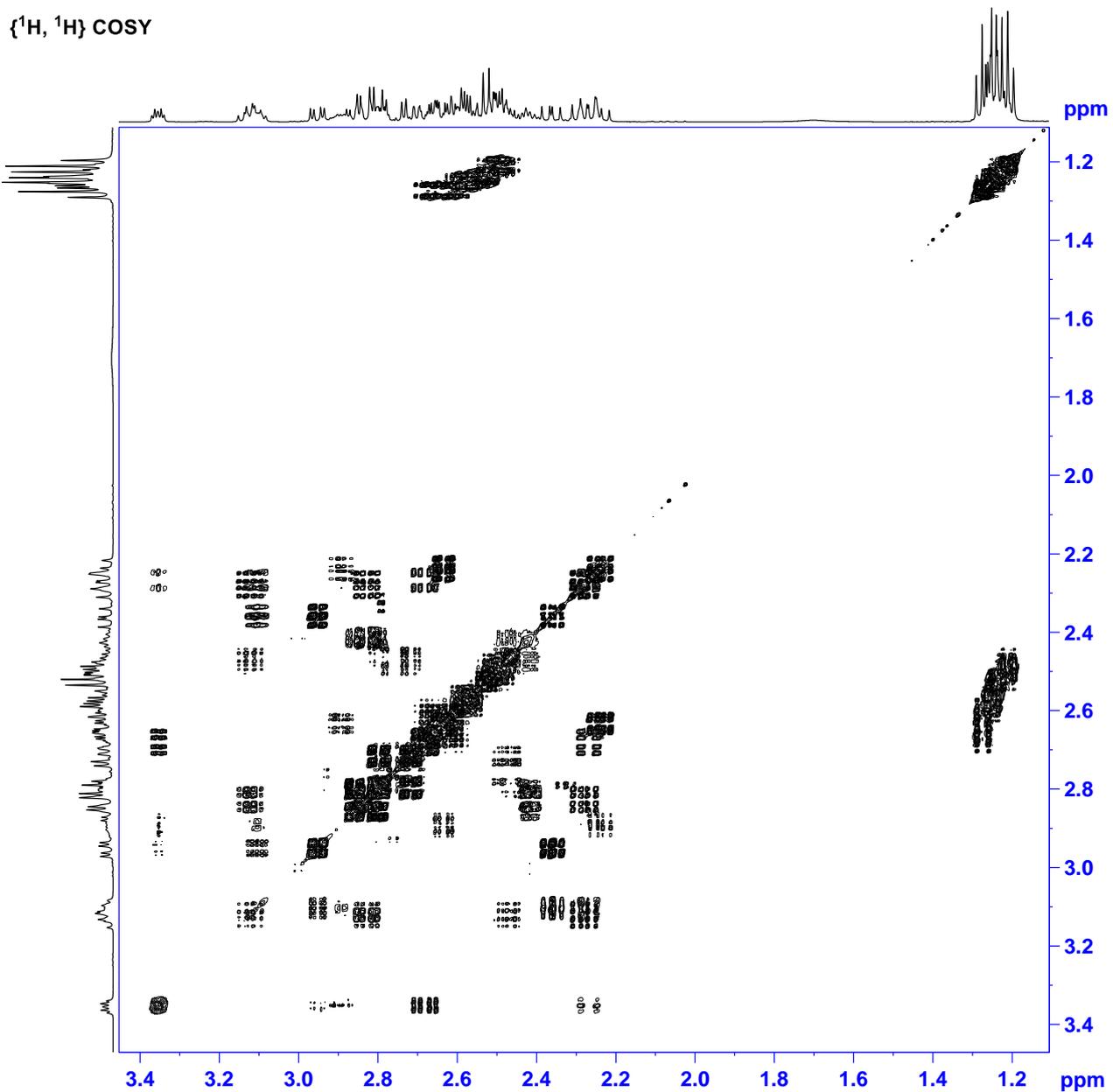


Figure S18 Complete $\{^1\text{H}, ^1\text{H}\}$ COSY NMR spectrum of mixture of compounds **2a,2c** in CDCl_3 .

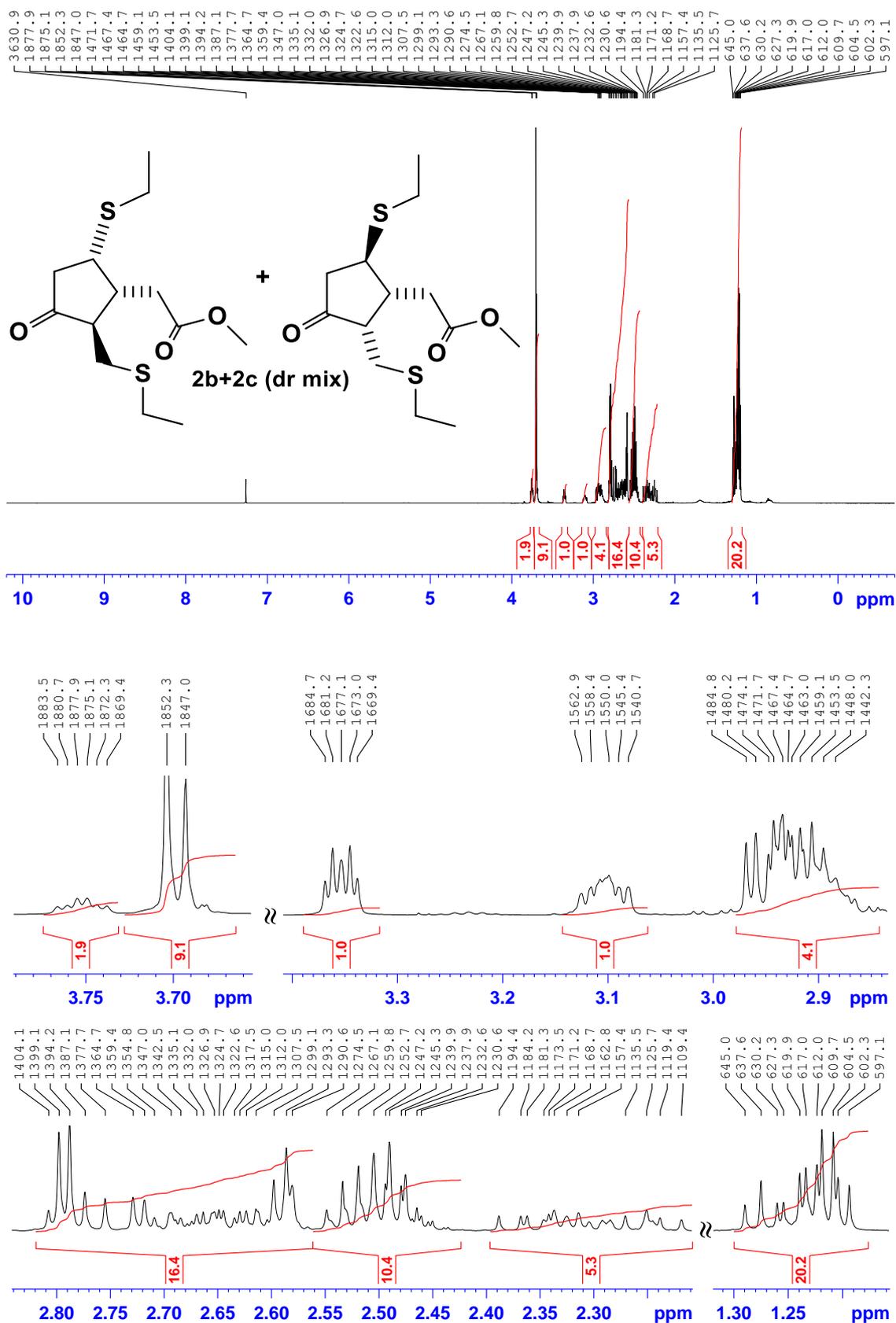


Figure S19 ^1H NMR spectra of mixture of compounds **2b,c** in CDCl_3 : (top) complete and (bottom) detailed spectrum.

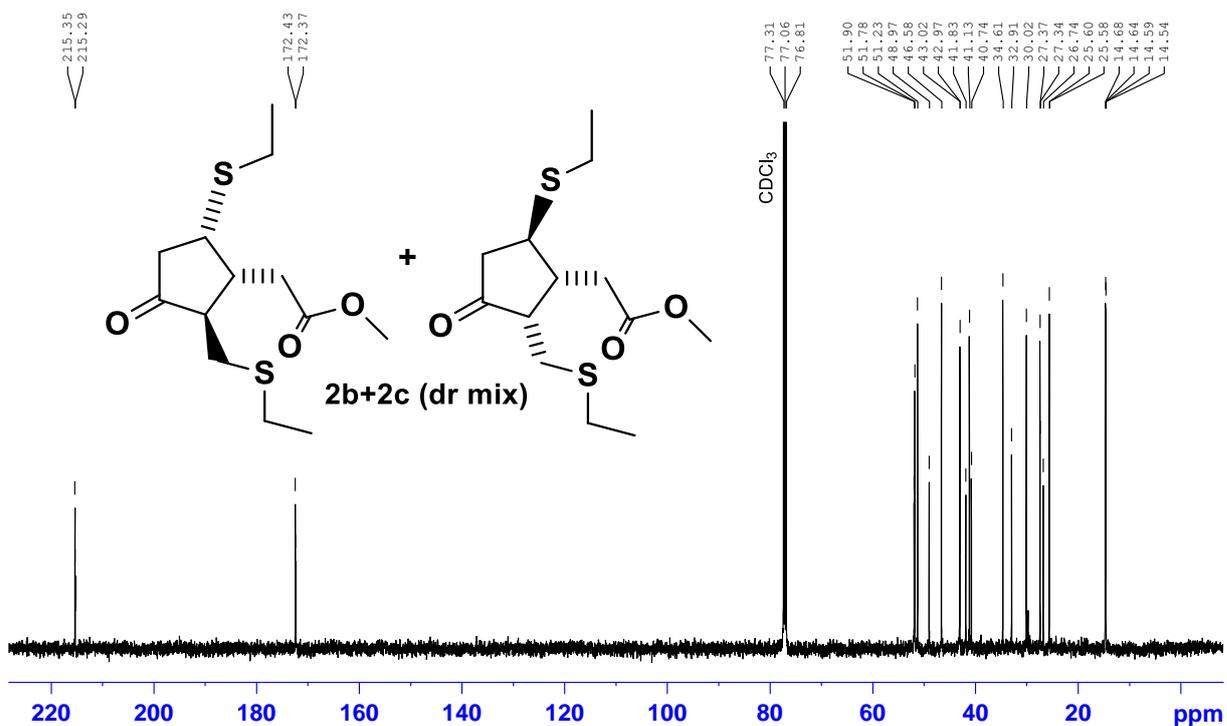


Figure S20 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of mixture of compounds **2b,c** in CDCl_3 .

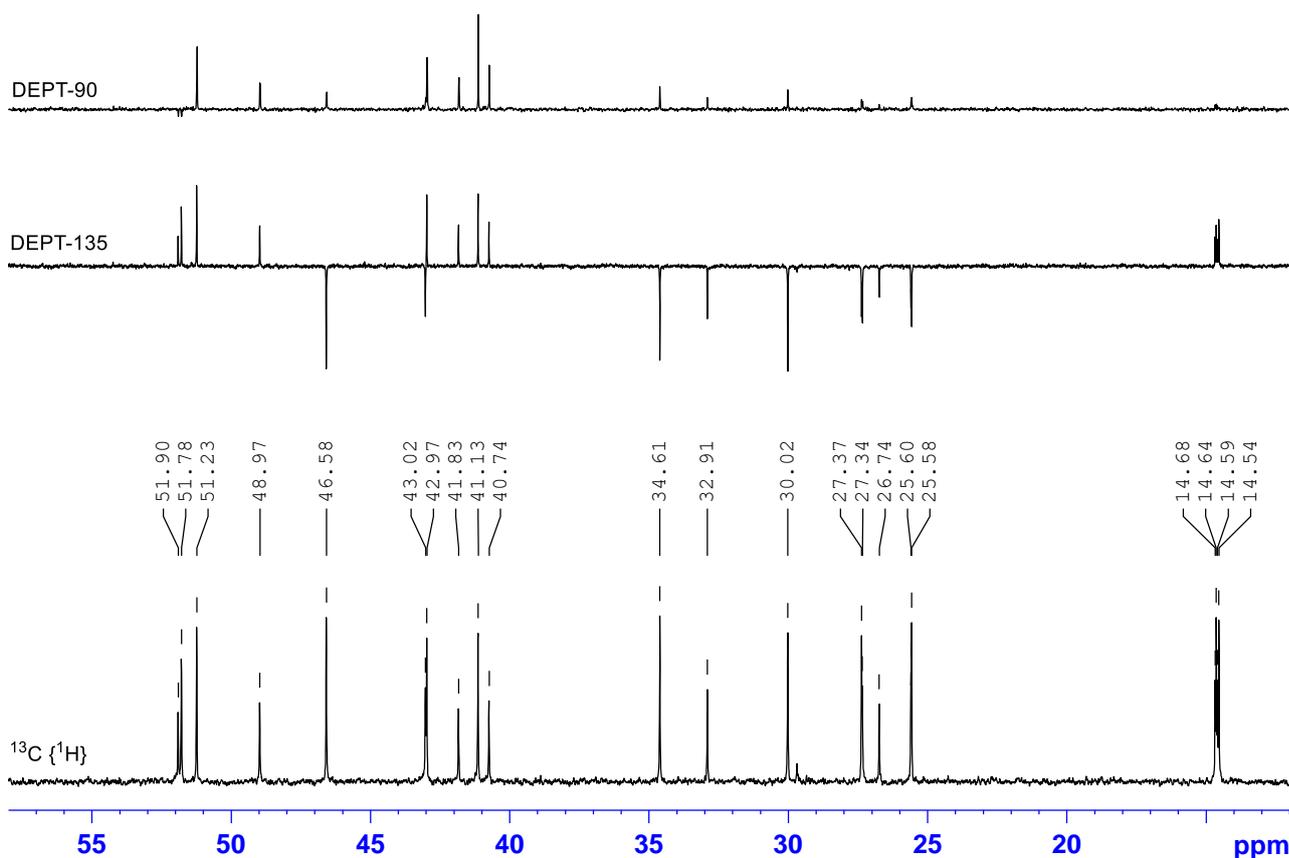


Figure S21 Downfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR, DEPT-135 and DEPT-90 spectra of mixture of compounds **2b,c** in CDCl_3 .

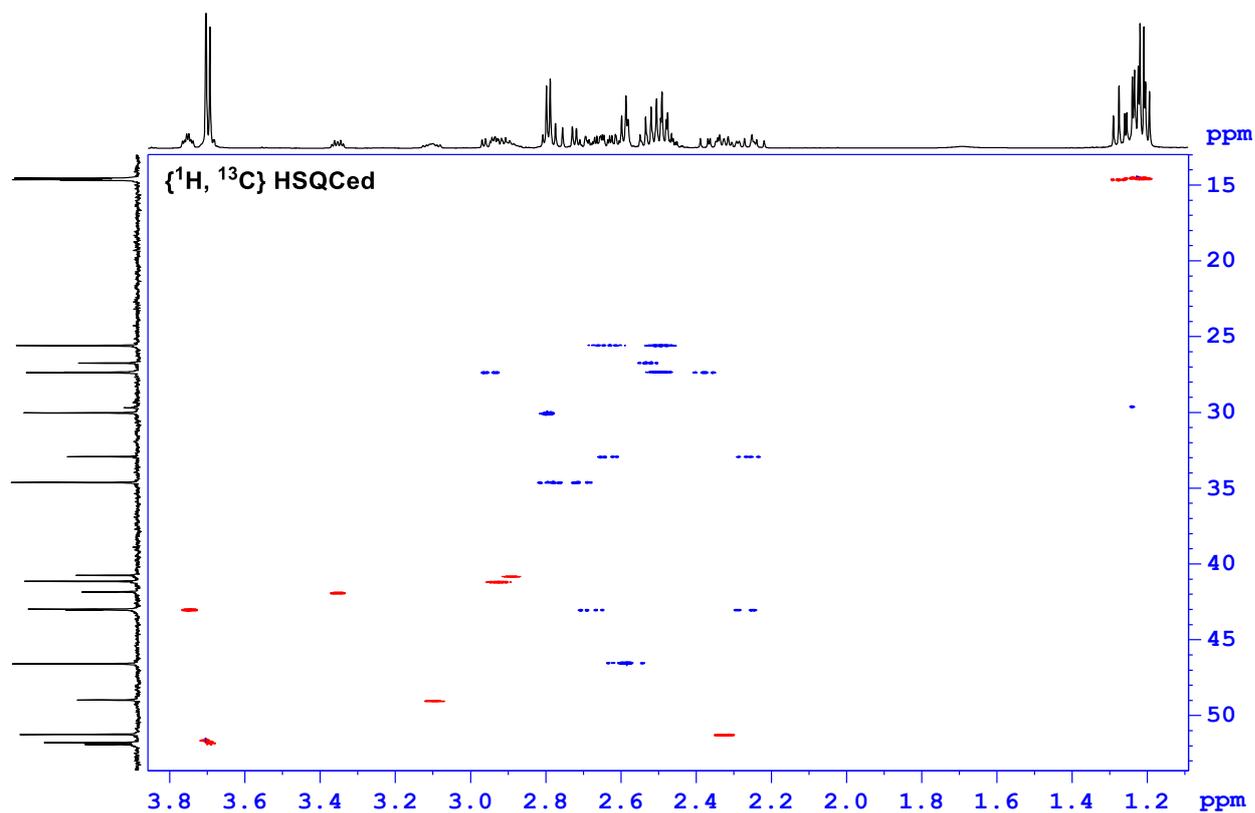


Figure S22 Downfield area of {¹H, ¹³C} HSQC multiplicity edited NMR spectrum of mixture of compounds **2b,c** in CDCl₃.

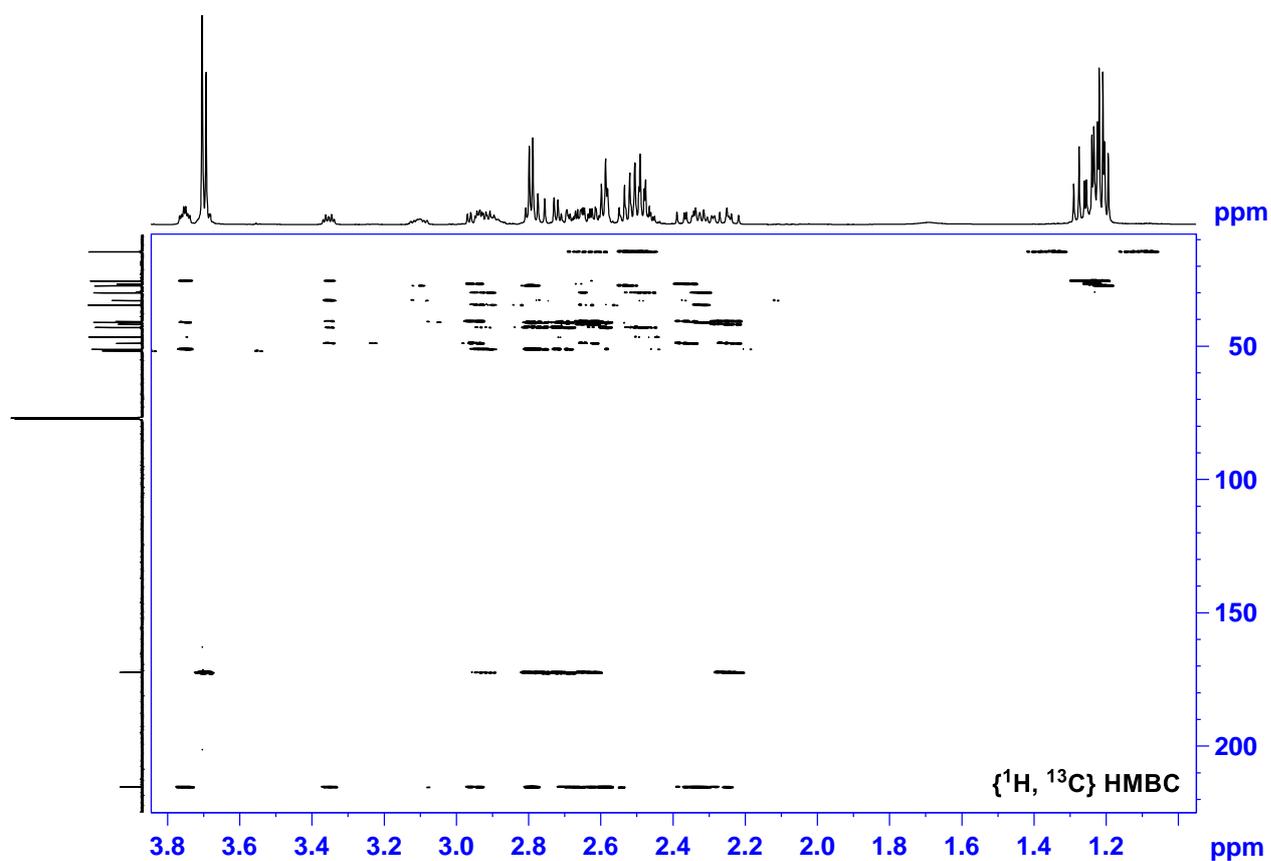


Figure S23 Complete {¹H, ¹³C} HMBC NMR spectrum of mixture of compounds **2b,c** in CDCl₃.

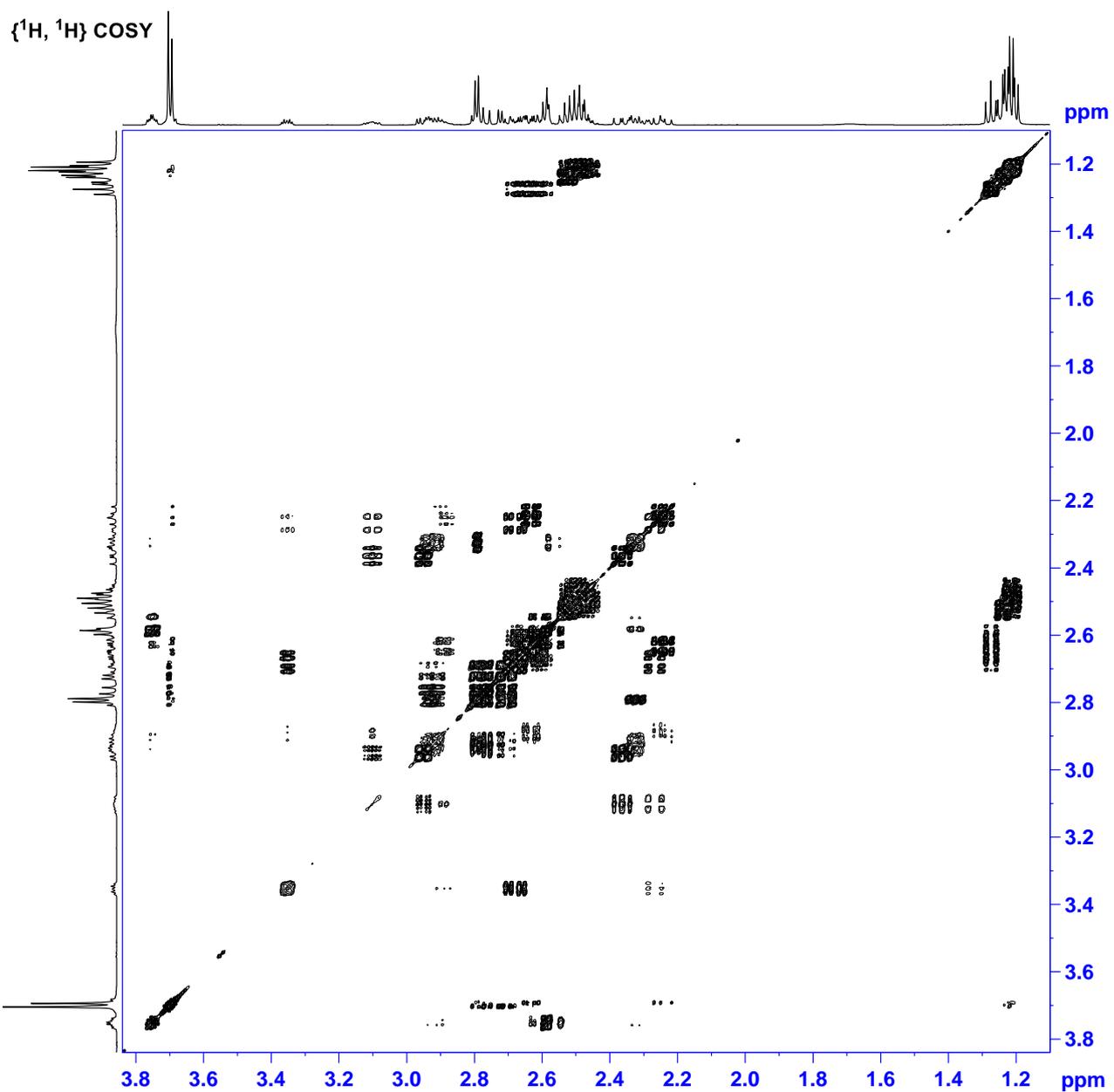


Figure S24 Complete $\{^1\text{H}, ^1\text{H}\}$ COSY NMR spectrum of mixture of compounds **2b,c** in CDCl_3 .

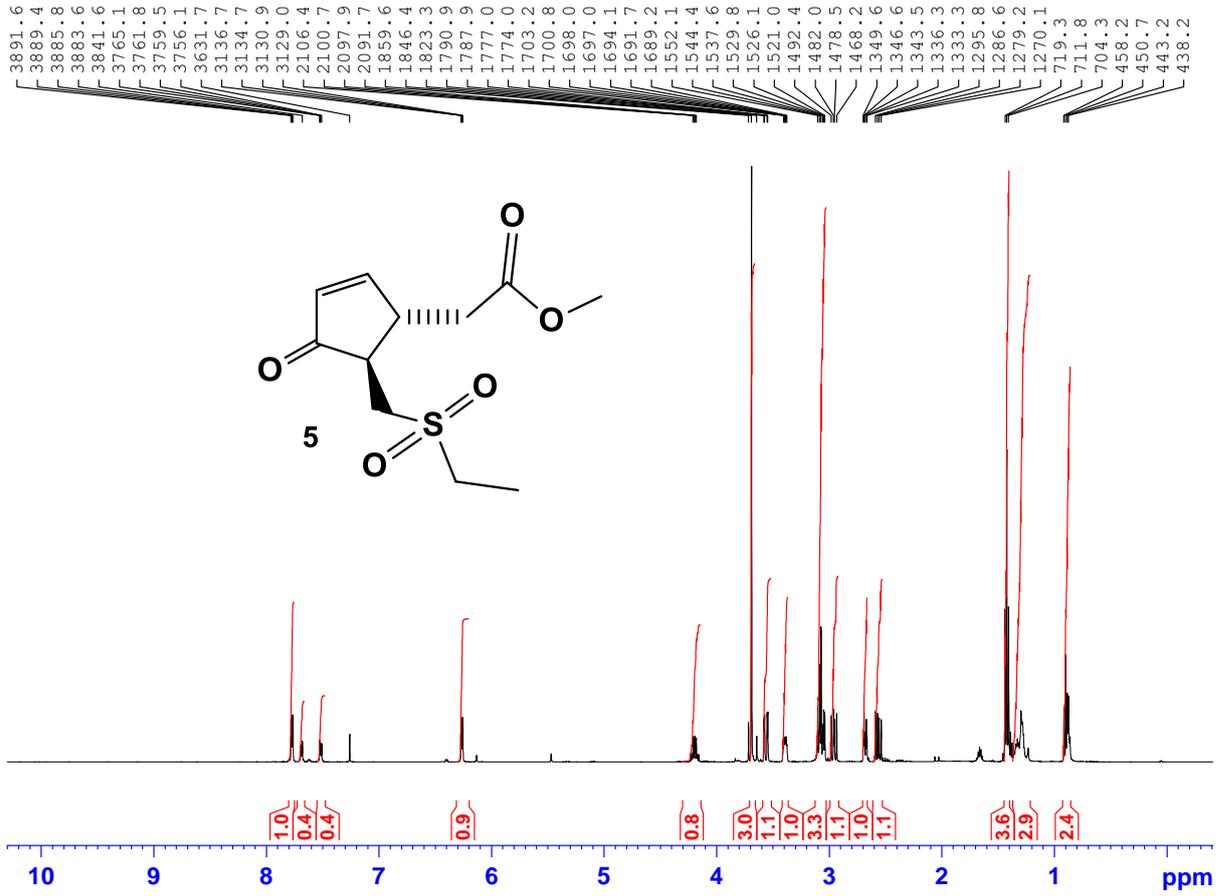


Figure S25 Complete ¹H NMR spectrum of compound 5 in CDCl₃.

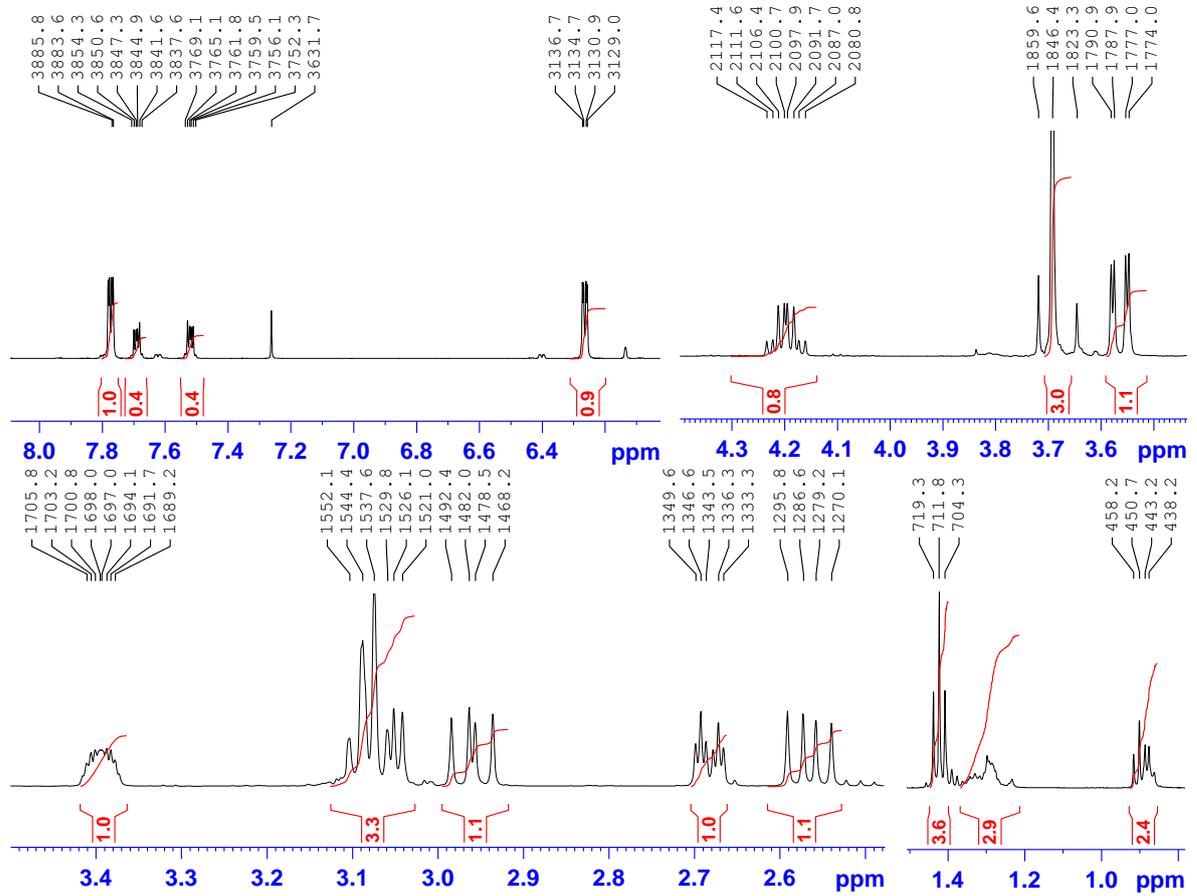


Figure S26 Detailed ¹H NMR spectrum of compound 5 in CDCl₃.

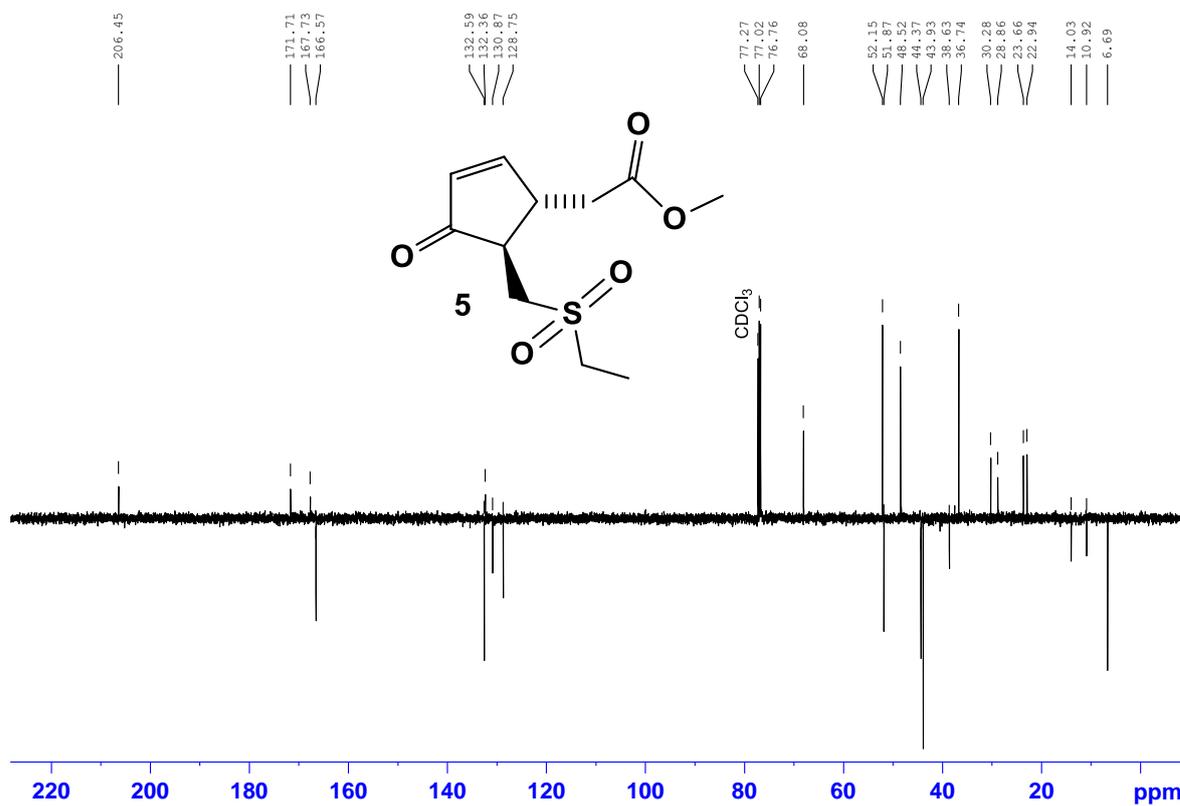


Figure S27 Complete $^{13}\text{C}\{^1\text{H}\}$ *J*-modulated spin-echo NMR spectrum of compound **5** in CDCl_3 .

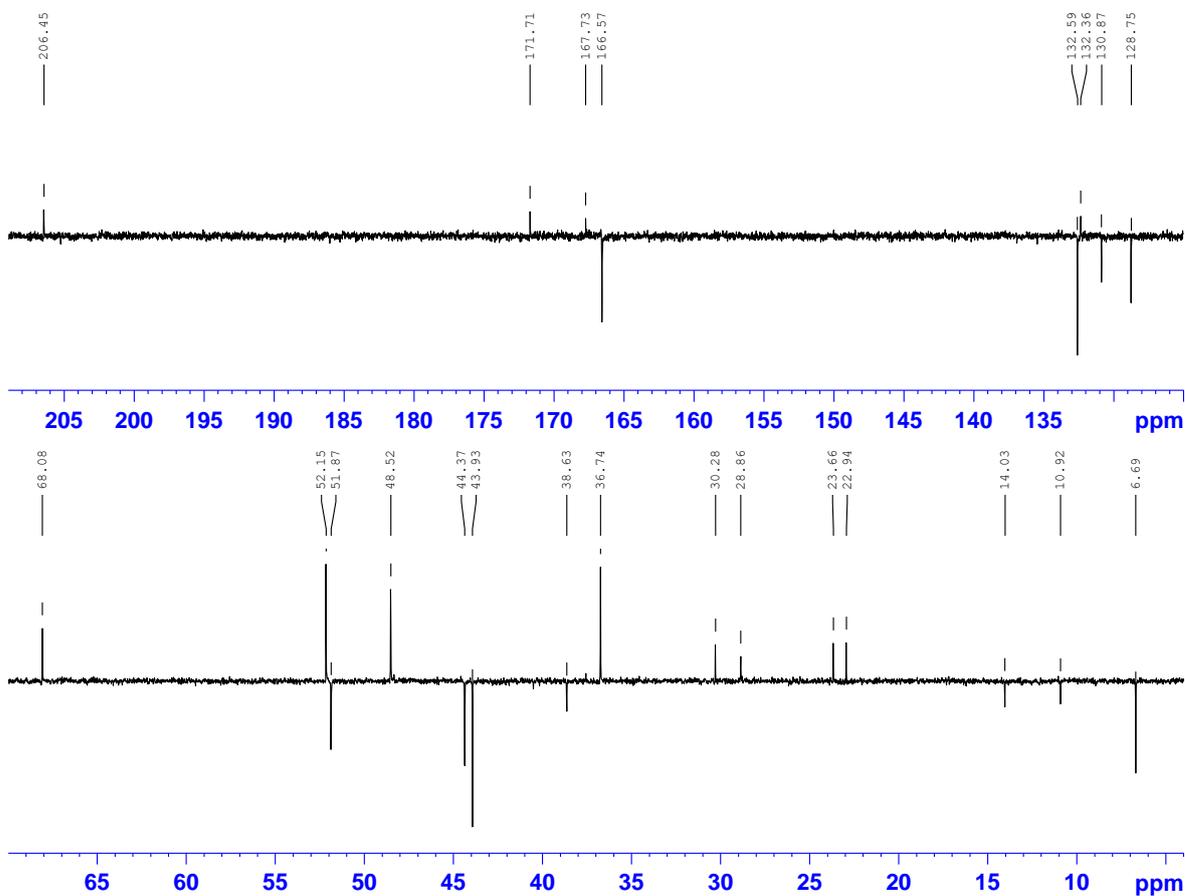


Figure S28 Detailed $^{13}\text{C}\{^1\text{H}\}$ *J*-modulated spin-echo NMR spectrum of compound **5** in CDCl_3 .

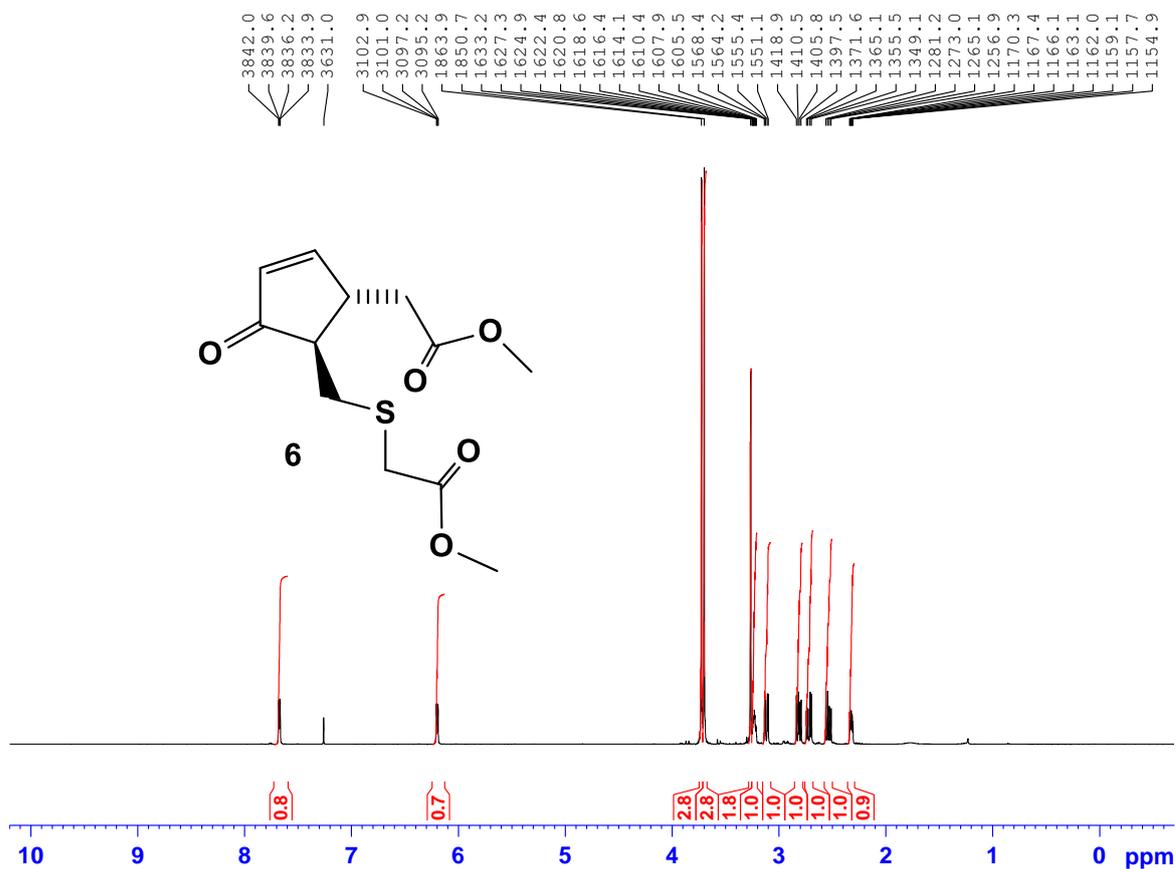


Figure S29 Complete ^1H NMR spectrum of compound 6 in CDCl_3 .

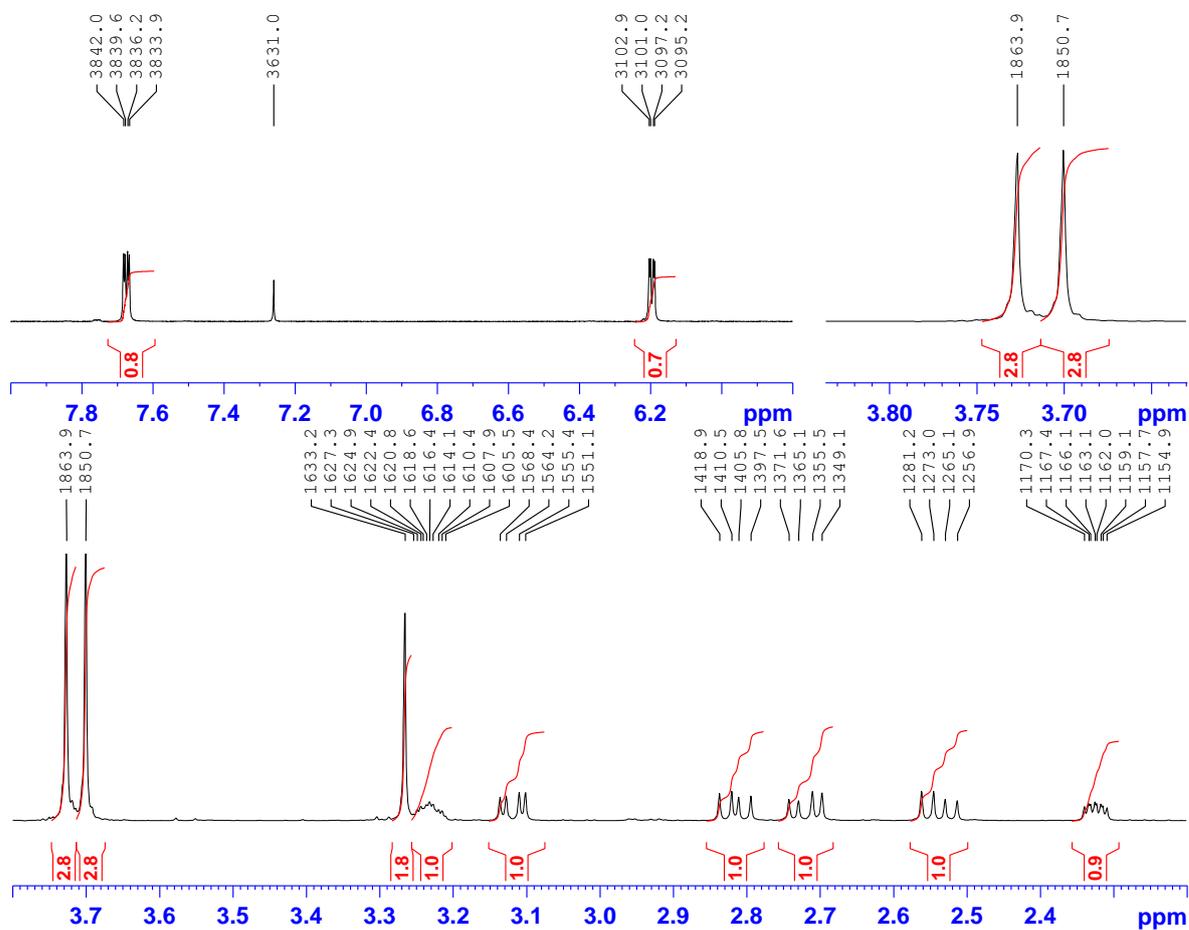


Figure S30 Detailed ^1H NMR spectrum of compound 6 in CDCl_3 .

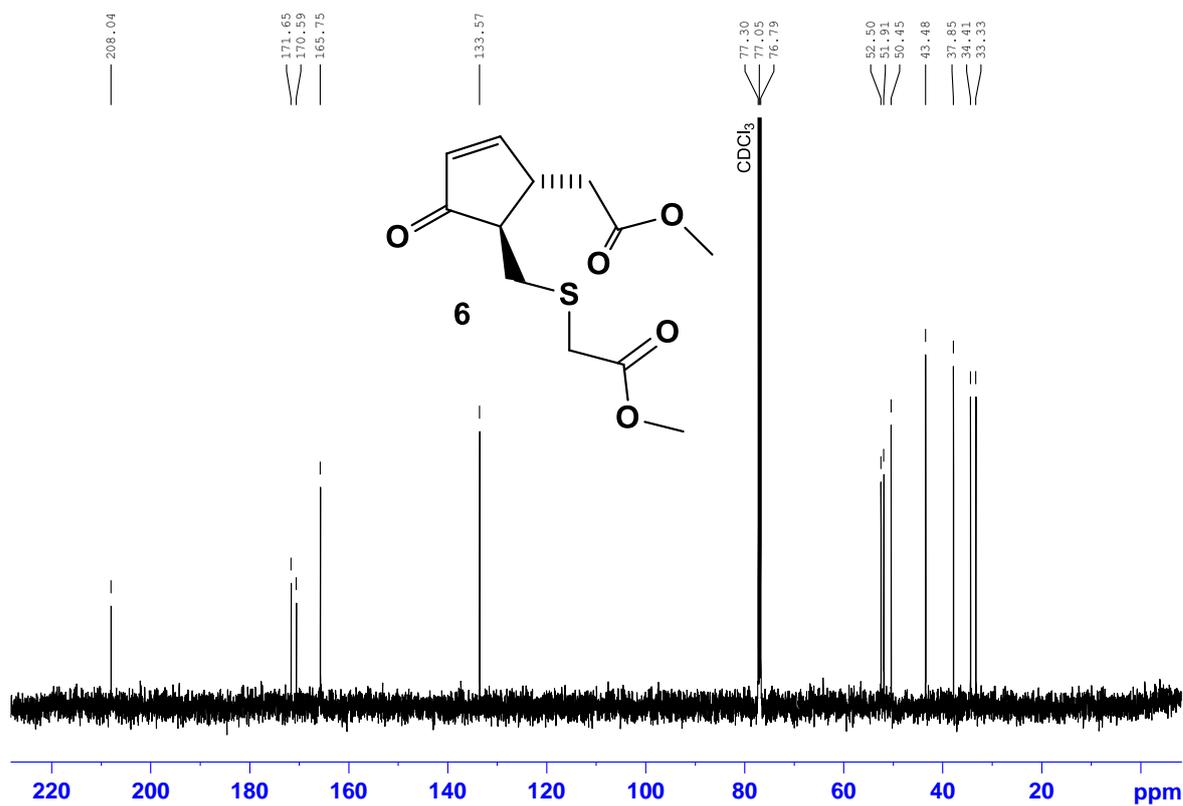


Figure S31 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound 6 in CDCl_3 .

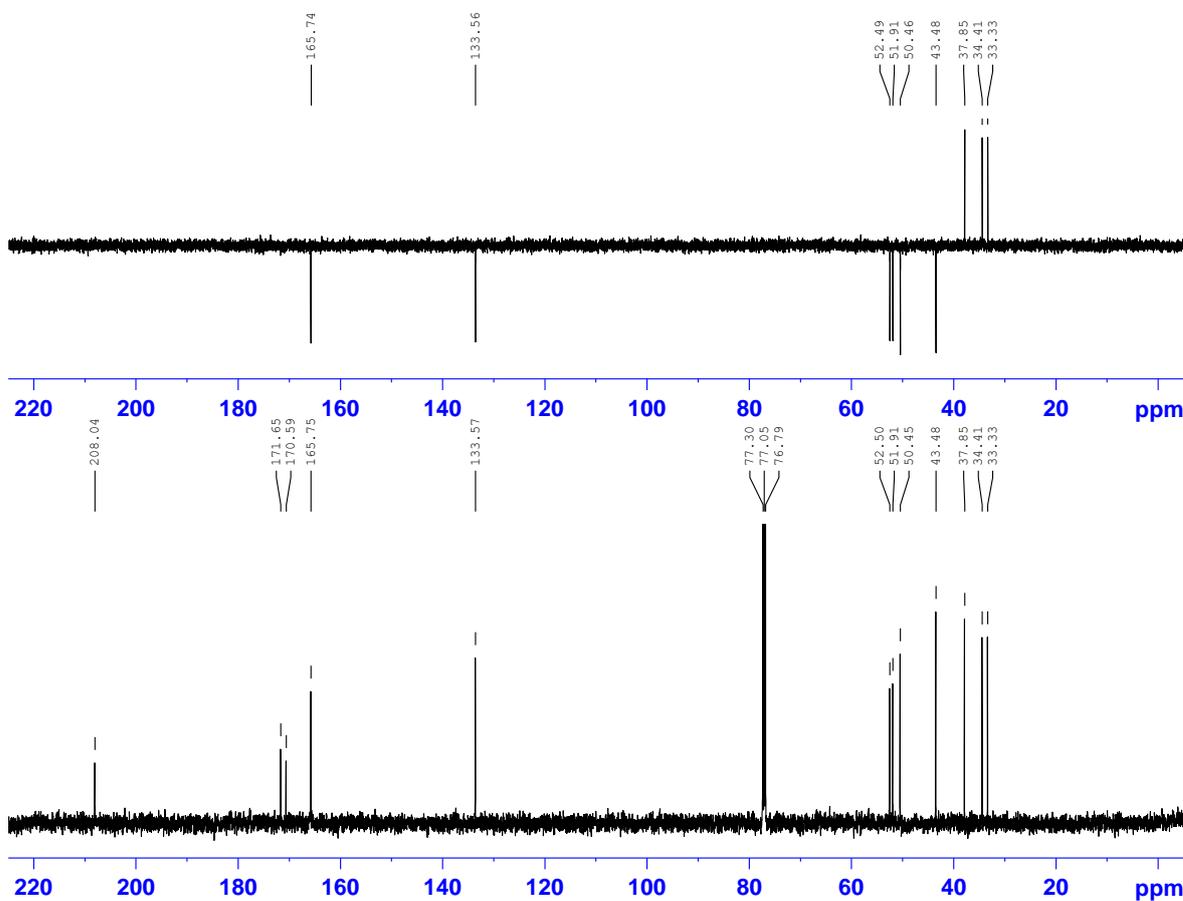


Figure S32 $^{13}\text{C}\{^1\text{H}\}$ NMR and DEPT-135 spectra of compound 6 in CDCl_3 .

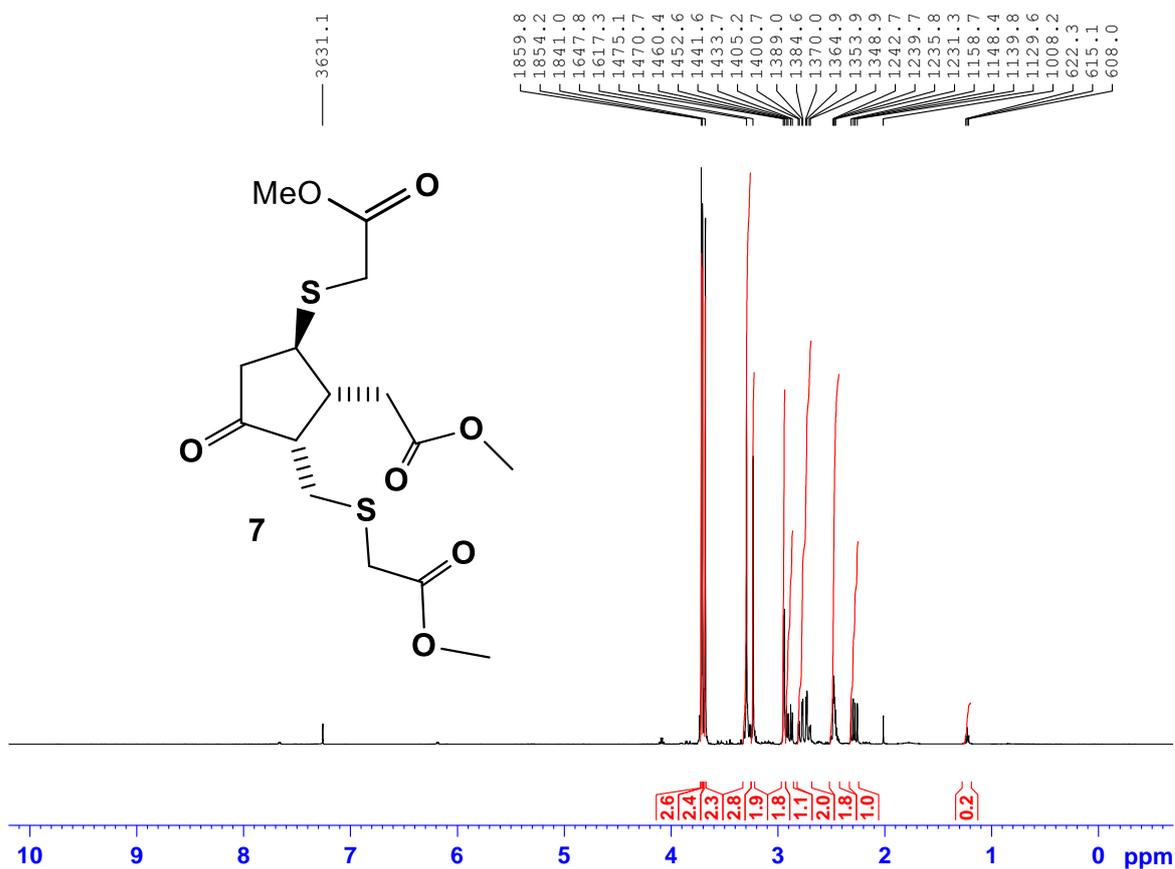


Figure S33 Complete ^1H NMR spectrum of compound 7 in CDCl_3 .

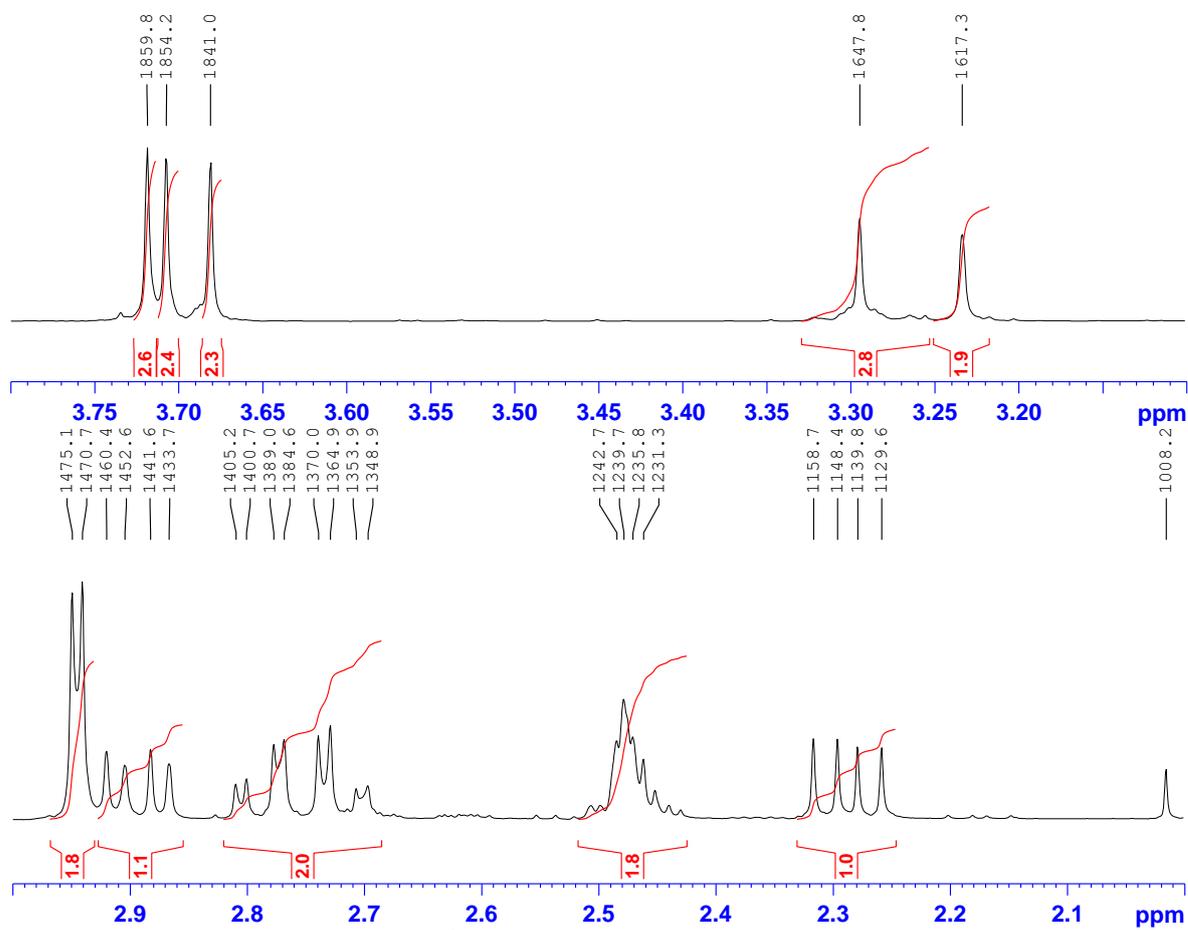


Figure S34 Detailed ^1H NMR spectrum of compound 7 in CDCl_3 .

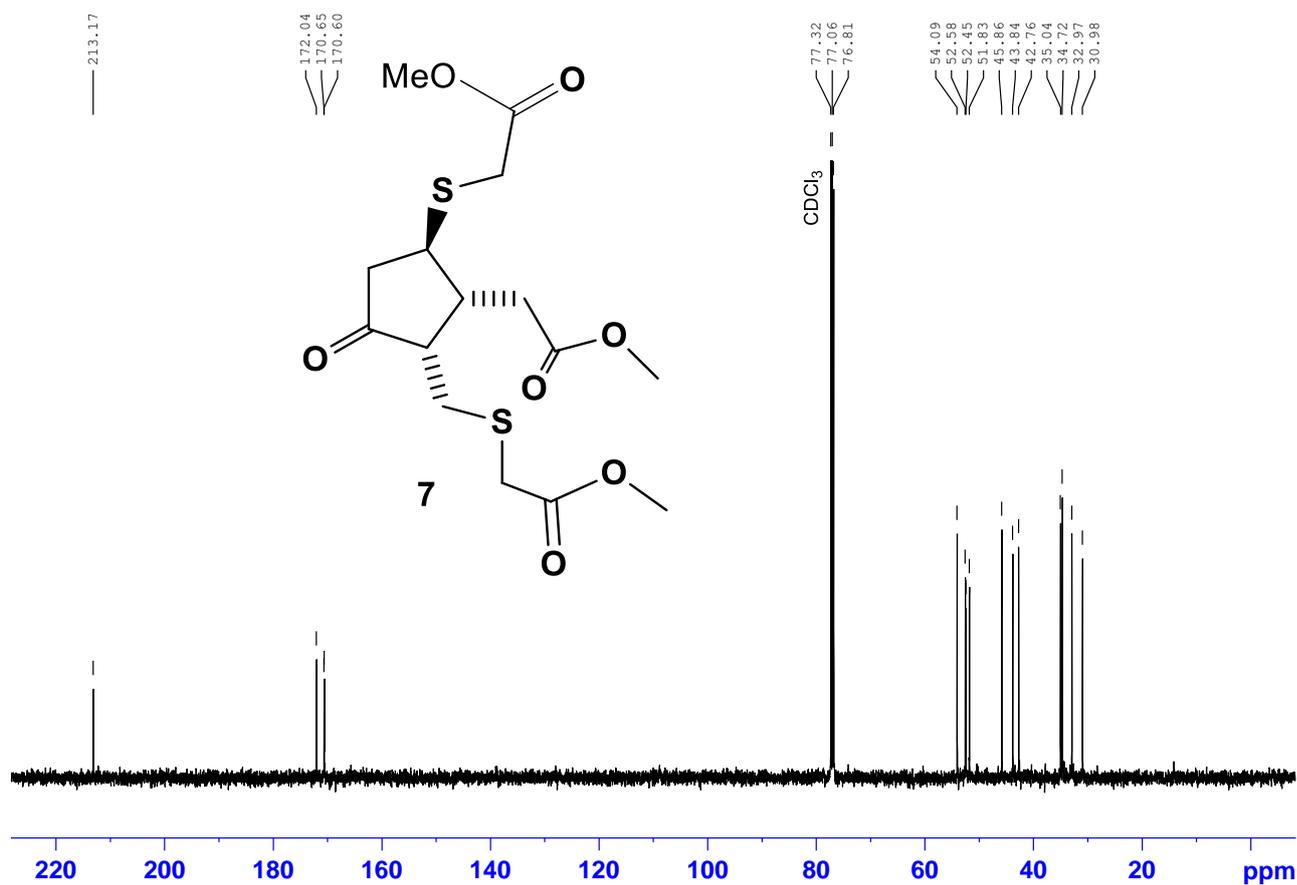


Figure S35 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound 7 in CDCl₃.

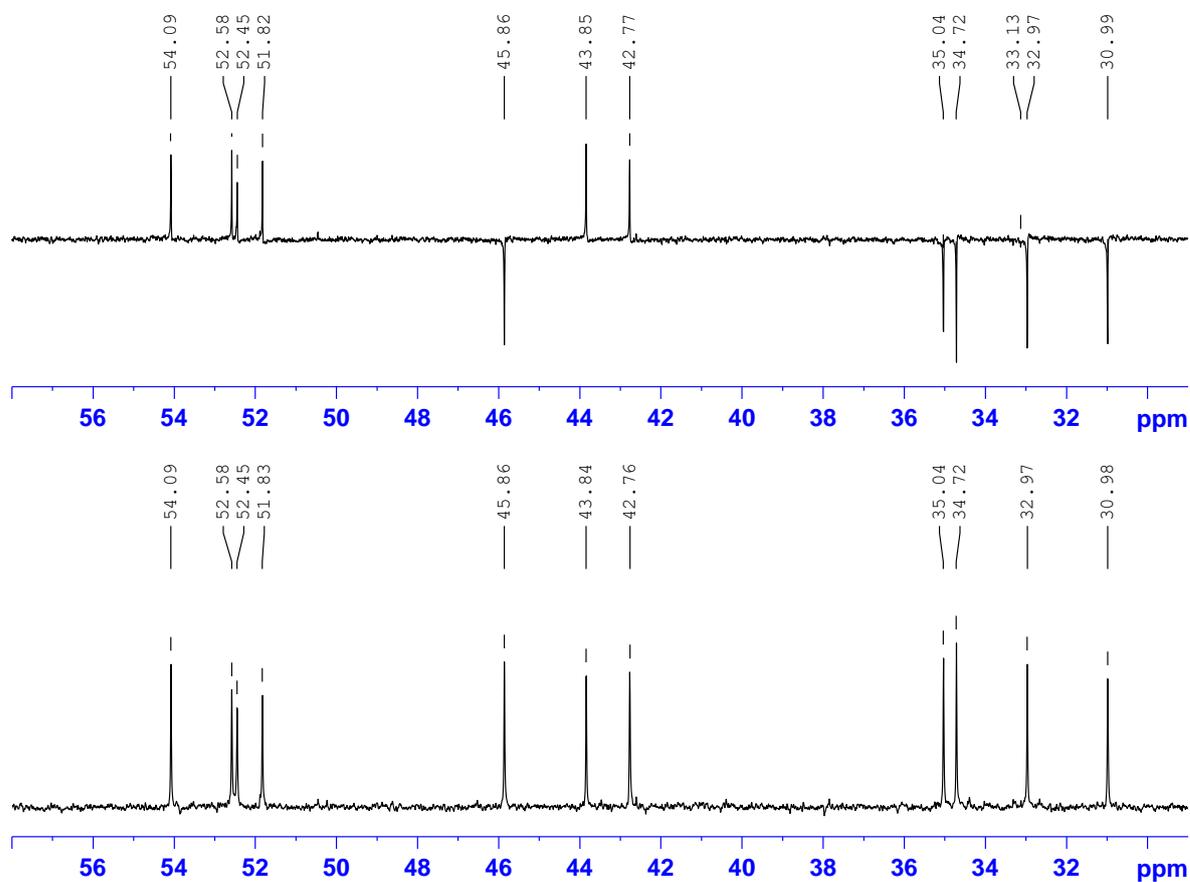


Figure S36 Upfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR and DEPT-135 spectra of compound 7 in CDCl₃.

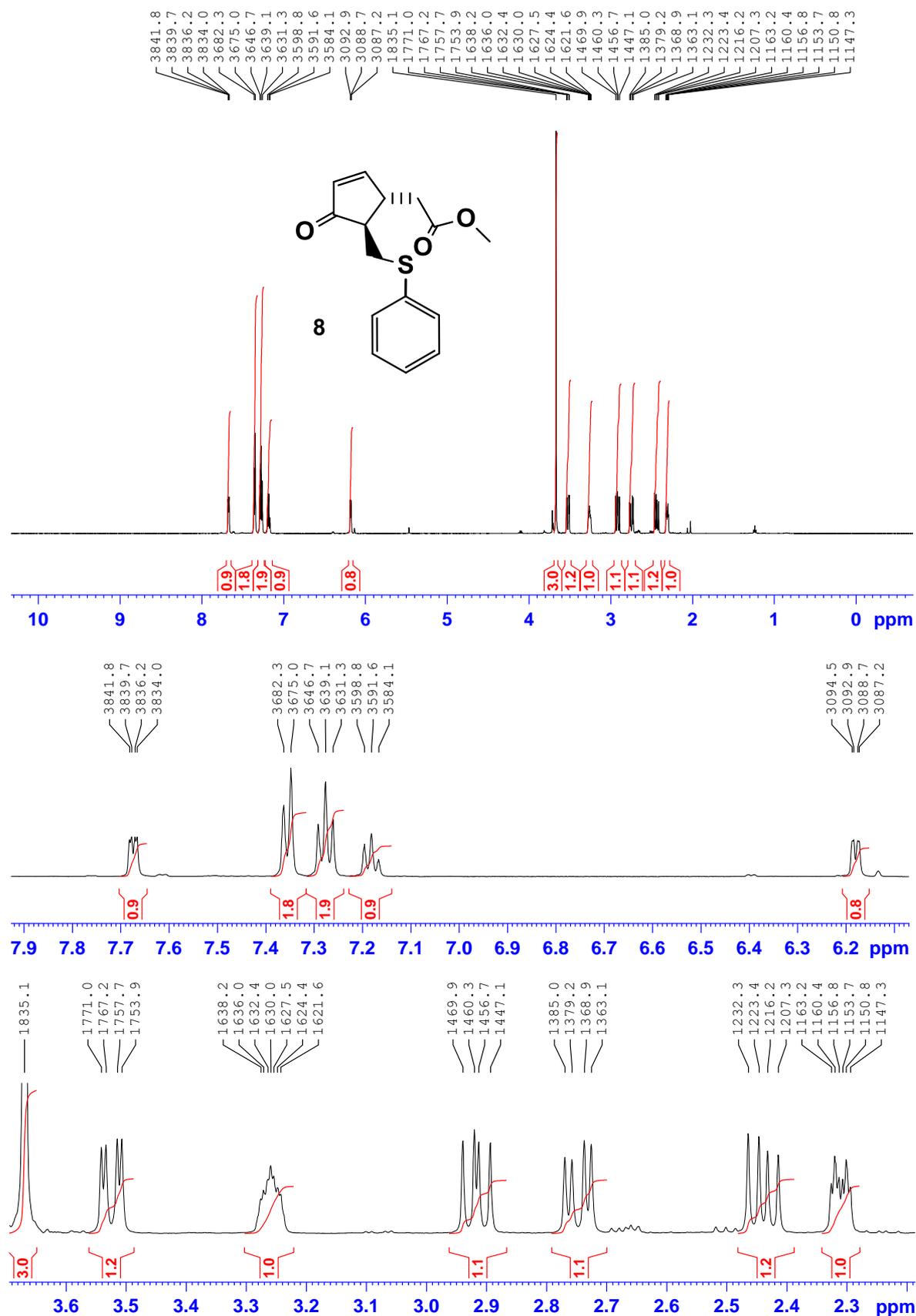


Figure S37 ^1H NMR spectra of compound **8** in CDCl_3 : (top) complete and (bottom) detailed spectrum.

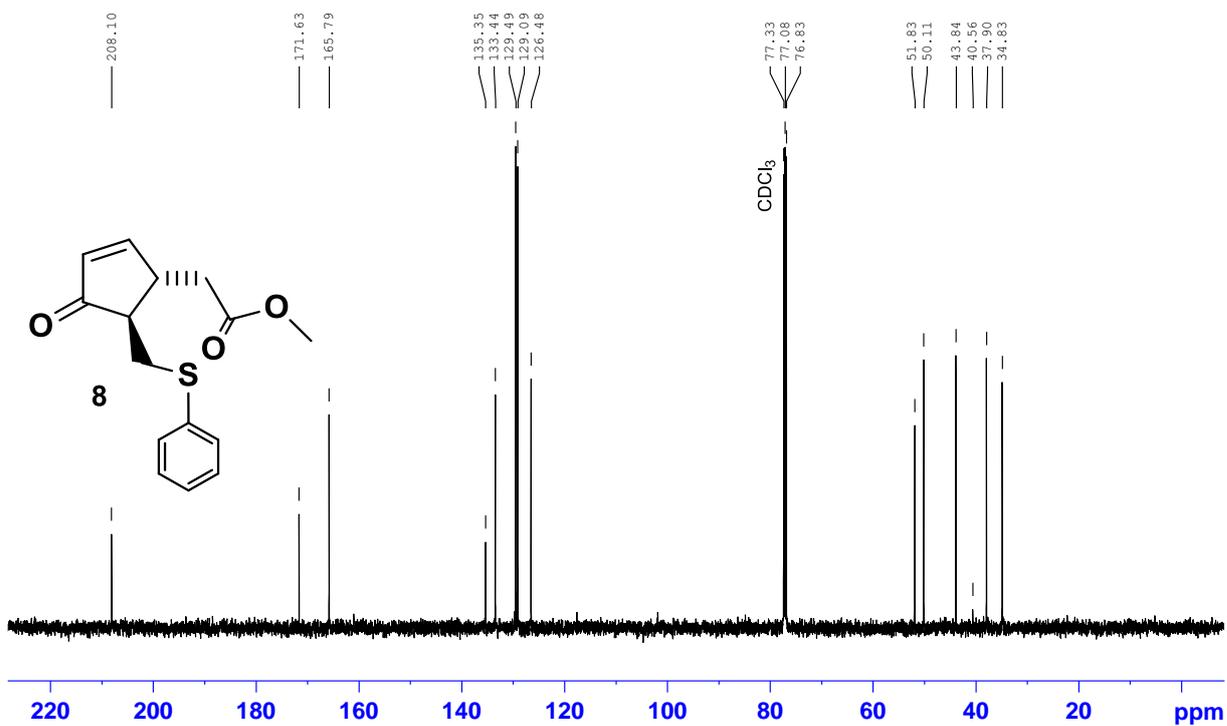


Figure S38 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **8** in CDCl_3 .

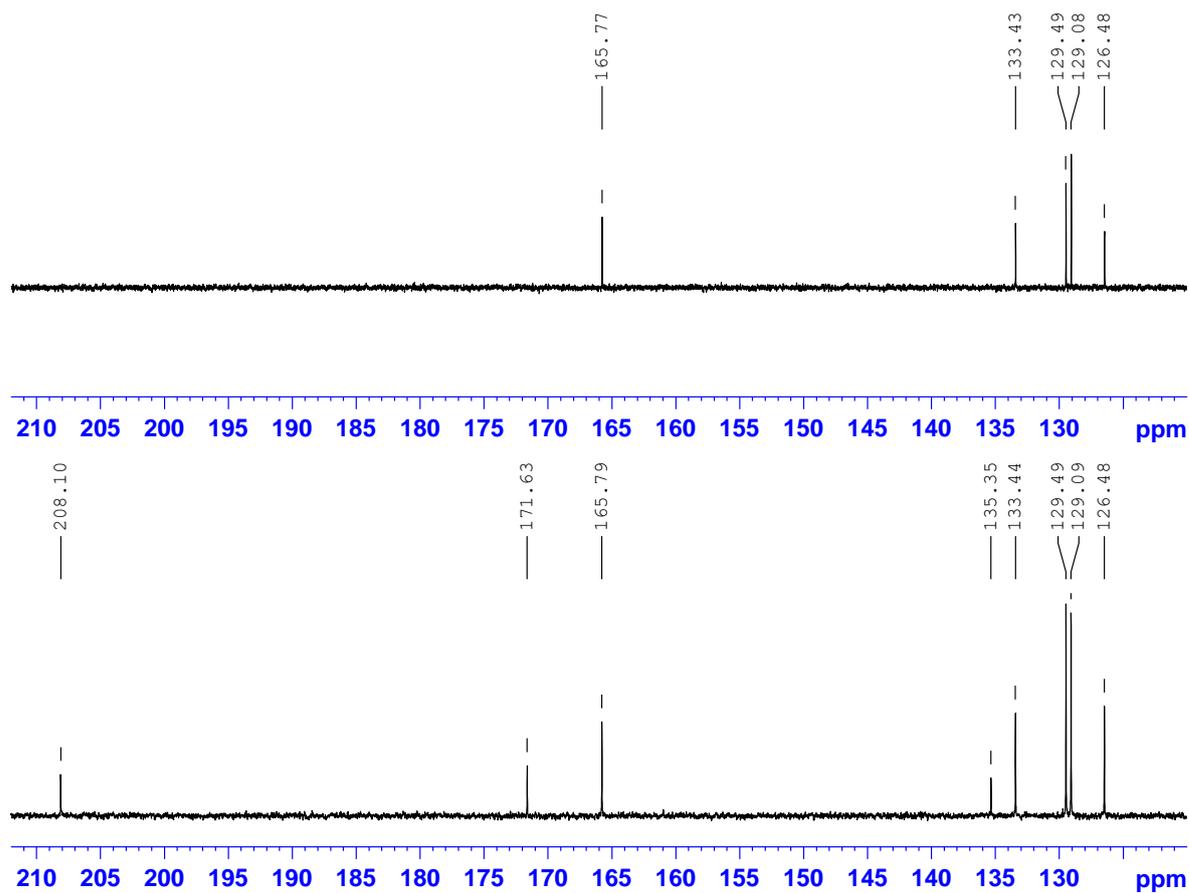


Figure S39 Downfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR and DEPT-135 spectra of compound **8** in CDCl_3

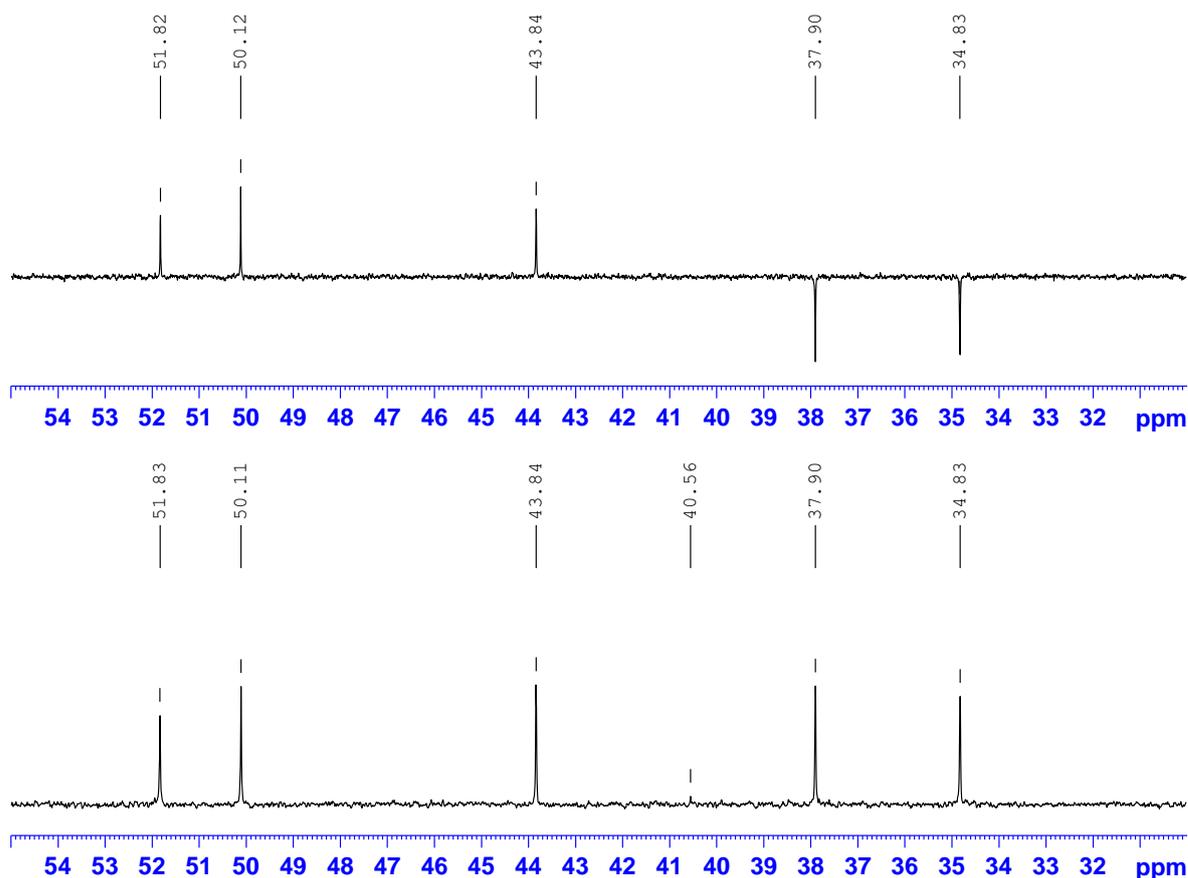


Figure S40 Upfield area of ¹³C{¹H} NMR and DEPT-135 spectra of compound **8** in CDCl₃

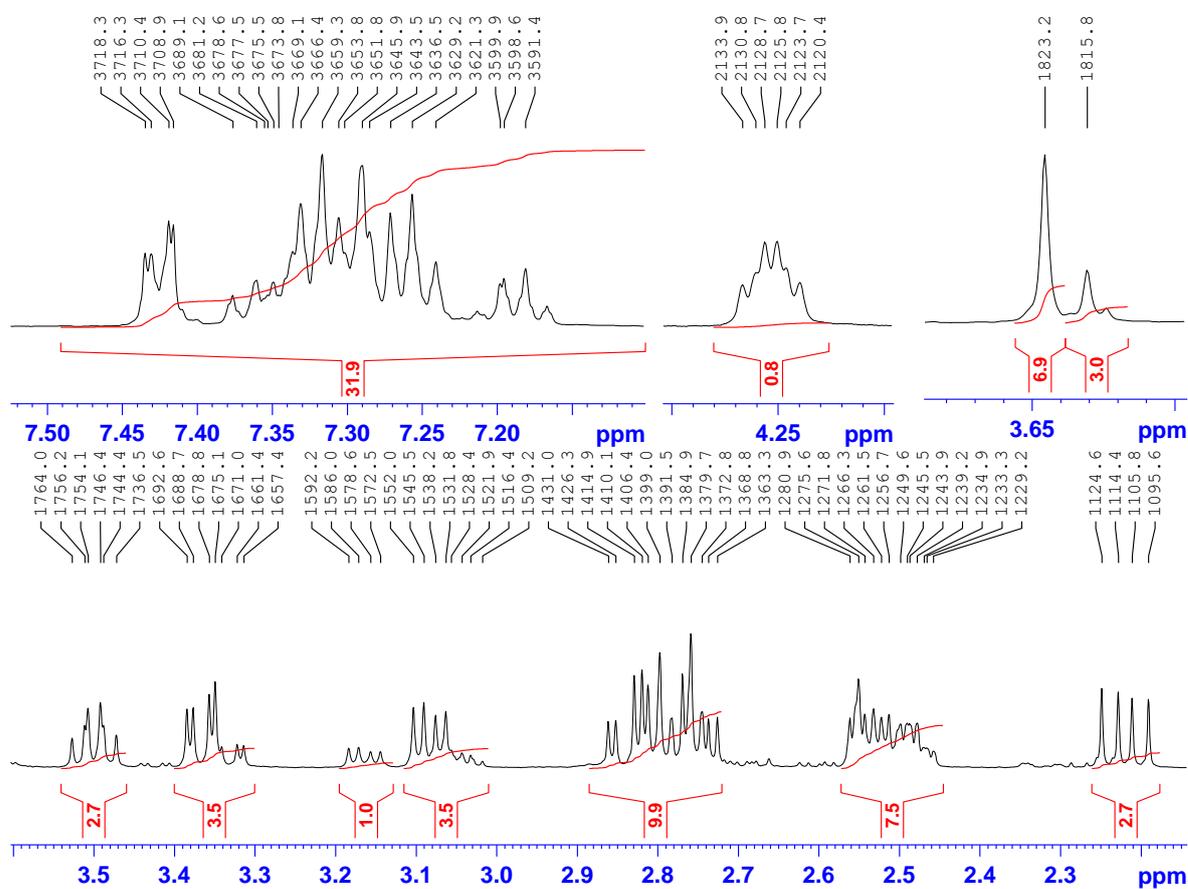


Figure S41 Detailed ¹H NMR spectrum of mixture of compounds **9a,b** in CDCl₃.

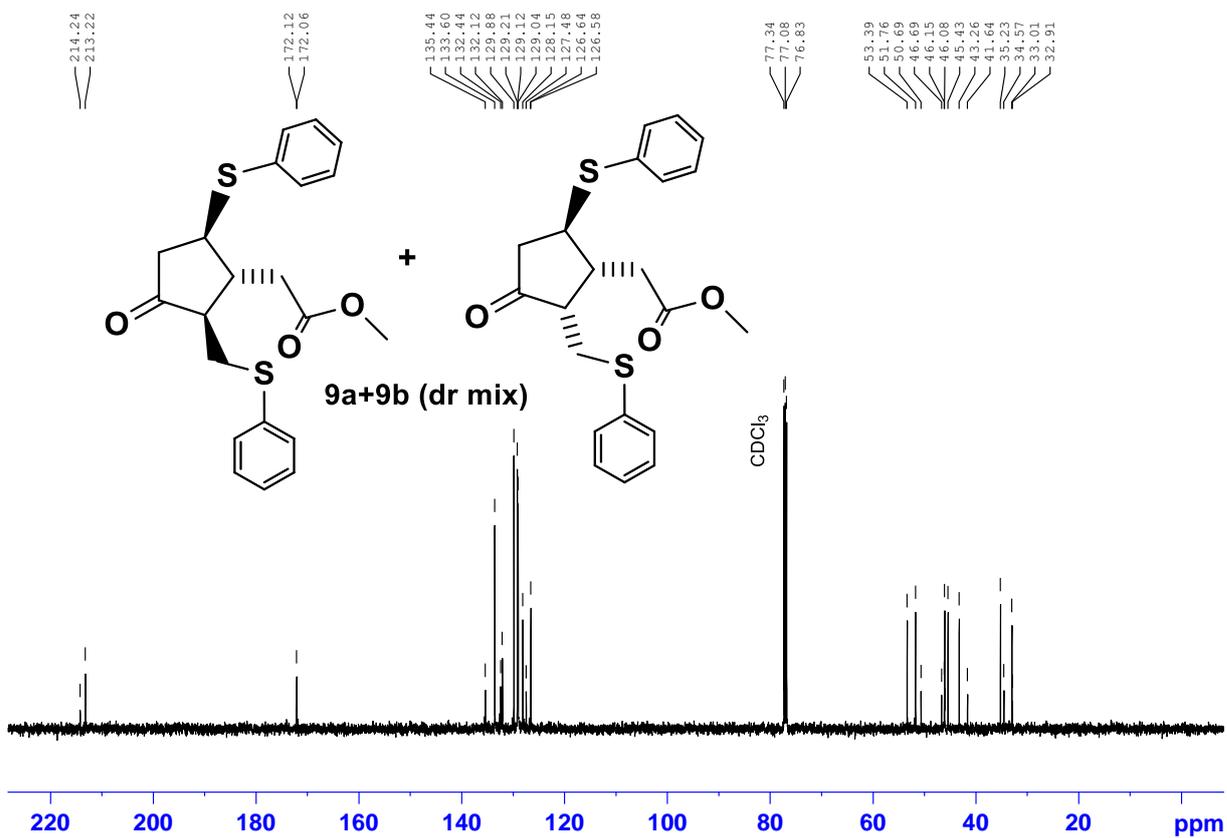


Figure S42 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of mixture of compounds **9a,b** in CDCl_3 .

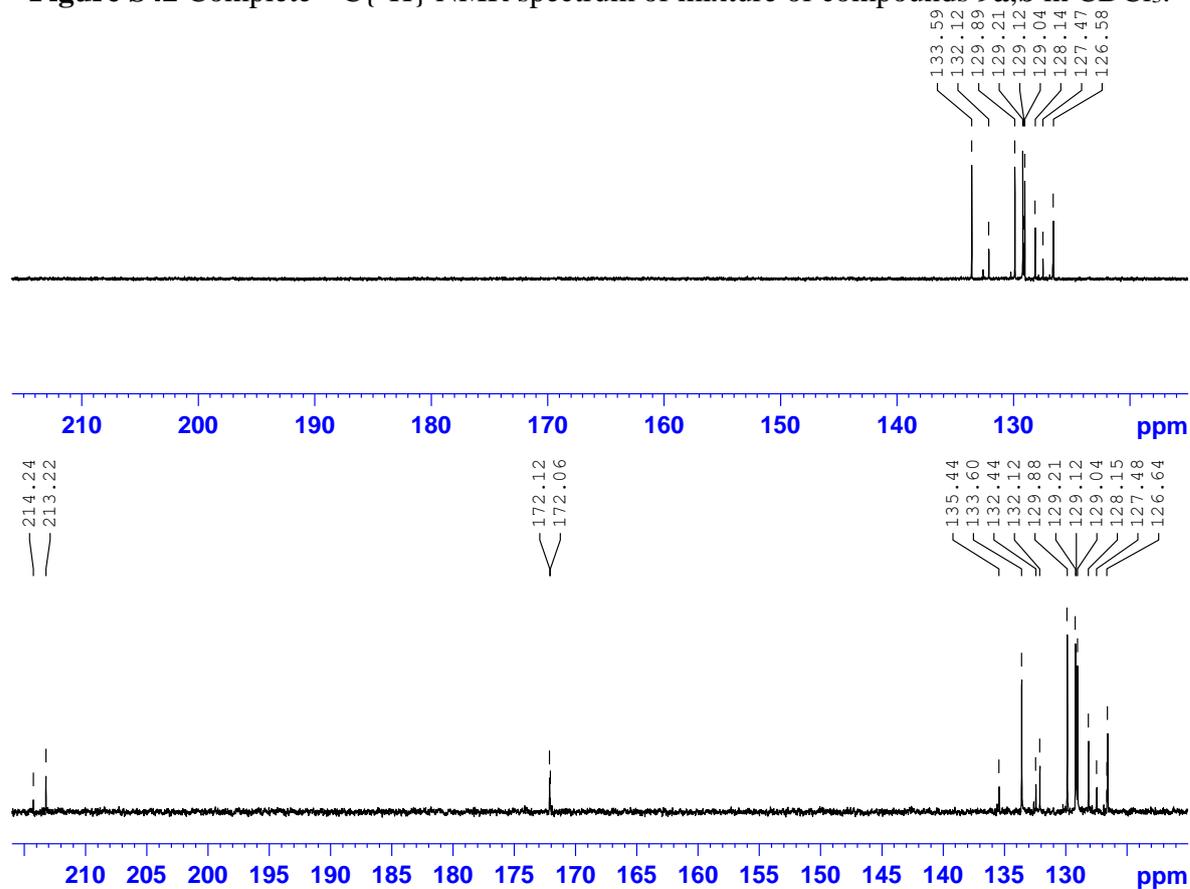


Figure S43 Downfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR and DEPT-135 spectra of mixture of compounds **9a,b** in CDCl_3 .

- S33 -

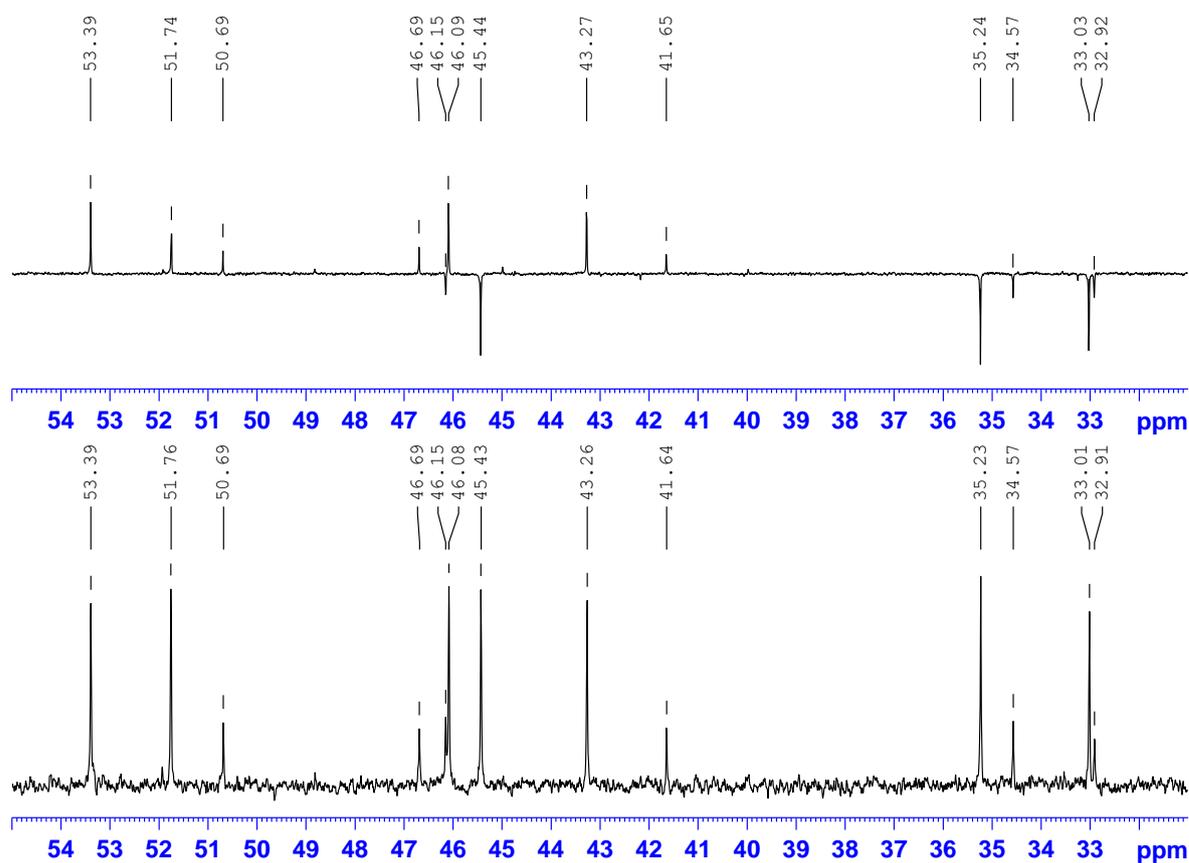


Figure S44 Upfield area of $^{13}\text{C}\{^1\text{H}\}$ NMR and DEPT-135 spectra of mixture of compounds **9a,b** in CDCl_3 .

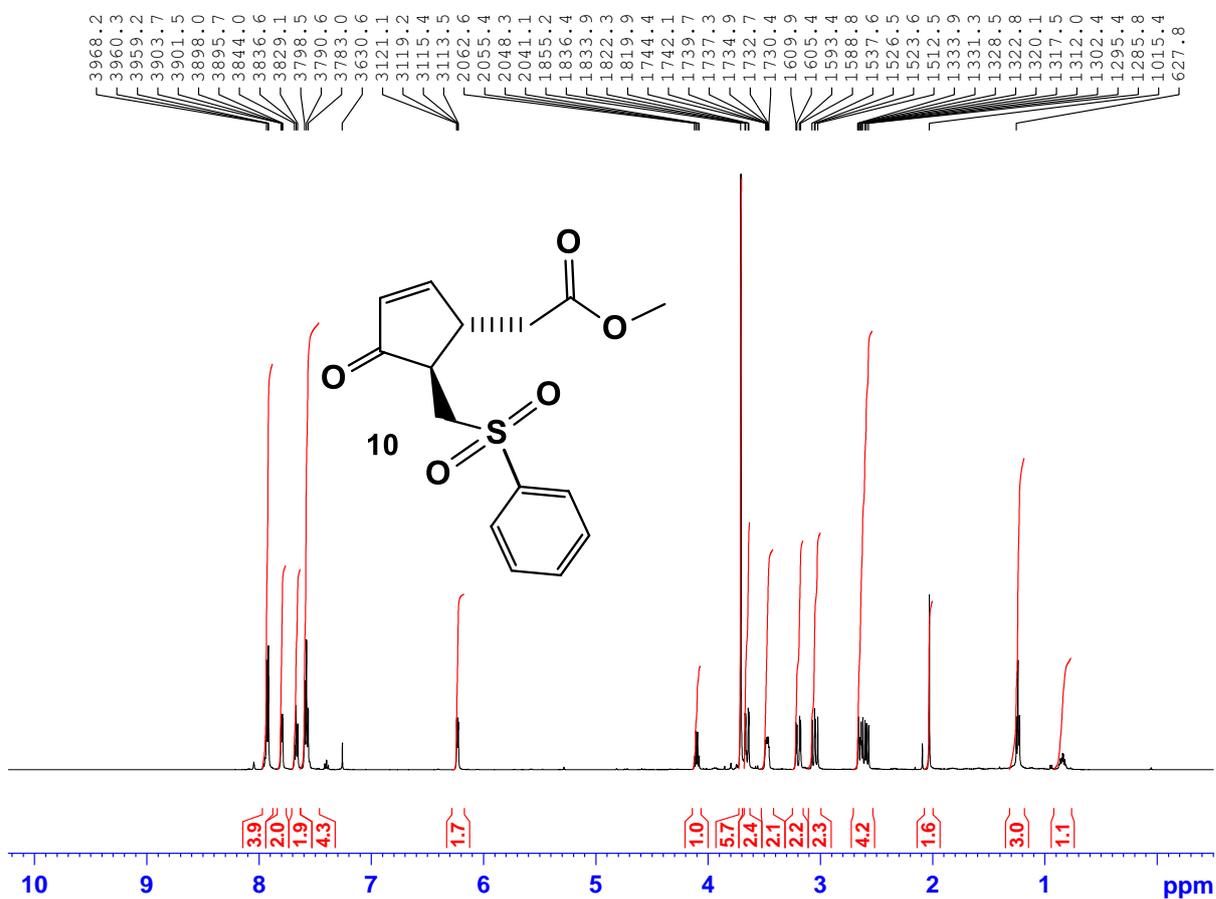


Figure S45 Complete ^1H NMR spectrum of compound **10** in CDCl_3 .

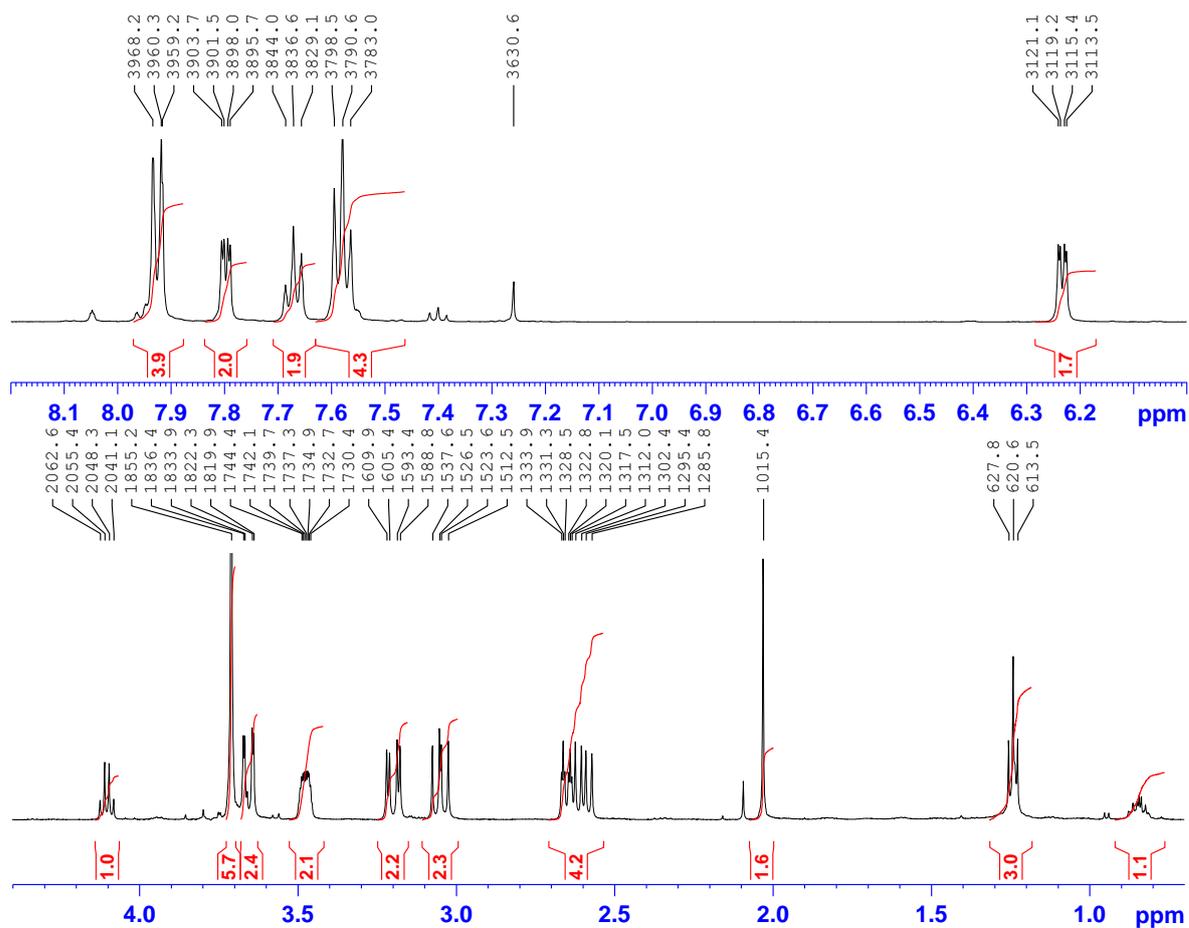


Figure S46 Detailed ^1H NMR spectrum of compound **10** in CDCl_3 .

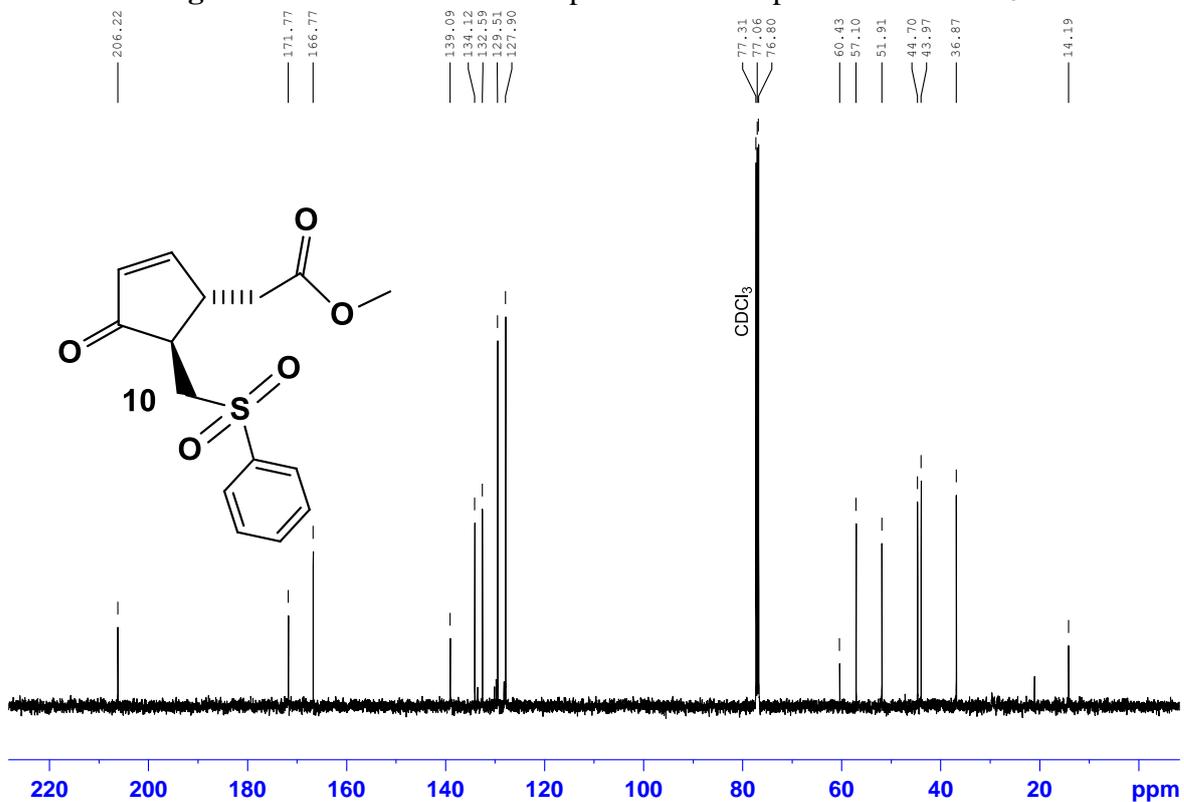


Figure S47 Complete $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of compound **10** in CDCl_3 .

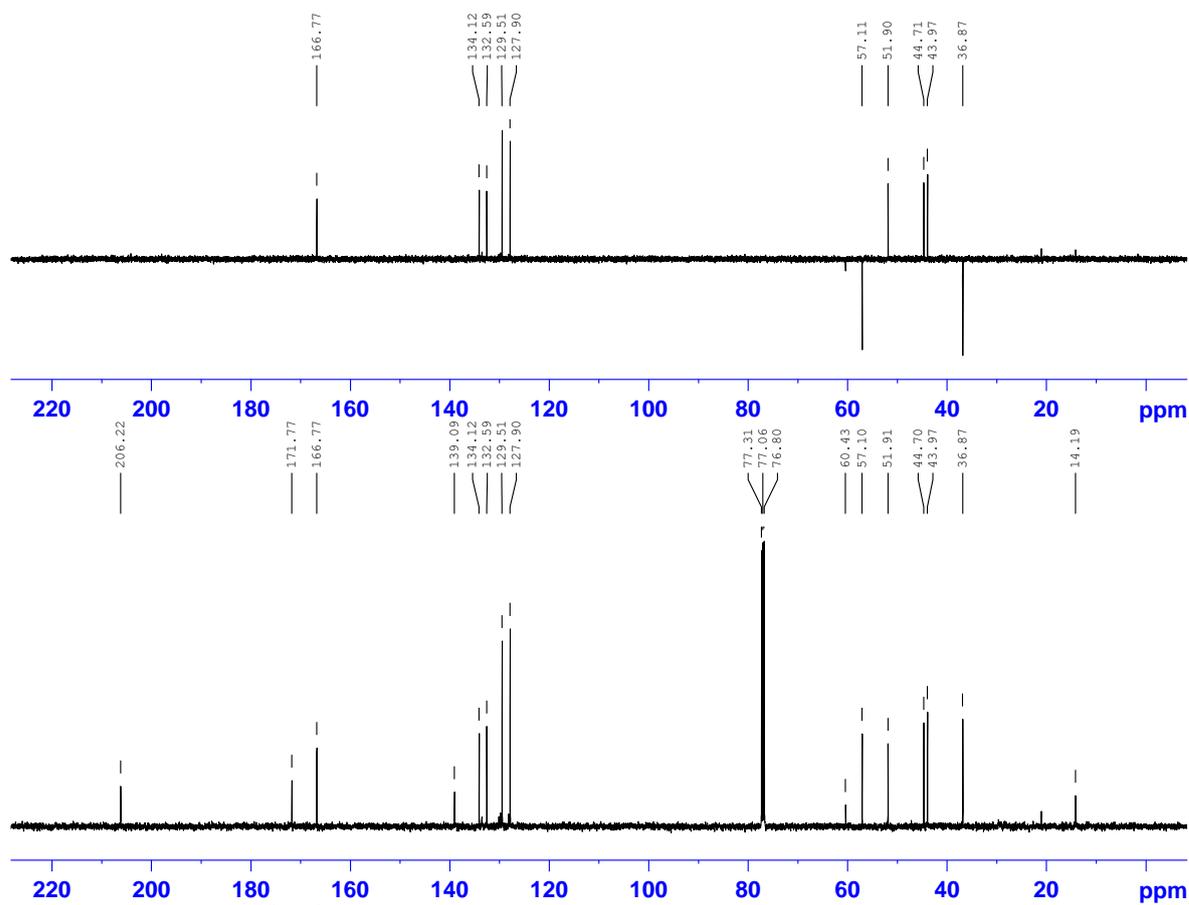


Figure S48 ¹³C{¹H} NMR and DEPT-135 spectra of compound 10 in CDCl₃.