First Total Synthesis of type II Abyssomicins: (±)-Abyssomicin 2 and (±)-Neoabyssomicin B

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Supporting Information

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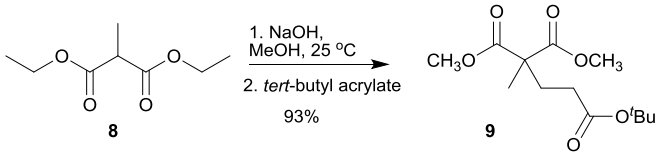
General Methods

All reactions were carried out under anhydrous conditions and an argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, dichloromethane (DCM) from CaH_2, and toluene from sodium. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality from Sigma-Aldrich or Alfa-Aesar and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F254), using UV light as visualizing agent and ethanolic phosphomolybdic acid, *p*-anisaldehyde or potassium permanganate solutions and heat as developing agents. Purifications with flash column chromatography were carried out by using Merck silica gel (60, particle size 0.040–0.063 mm) and elution systems as stated in each experimental procedure. NMR spectra were recorded on Bruker Avance DRX-500 or Bruker Advance II 250 MHz instruments at 25 °C. The following abbreviations were used to explain NMR signal multiplicities: brs: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, h: hexaplet, m: multiplet, dd: doublet of doublets, ddd: doublet of doublets of doublets, dt: doublet of triplets, dq: doublet of quartets. In cases of diastereoisomers, where doublets or triplets overlap, *J* is reported when it is possible to be measured. Assignment of ^{1}H NMR spectra is based on COSY experiments. Samples were dissolved in $CDCl_3$ or CD_3OD at 25 °C. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. Samples were analysed using a MaXis (Bruker Daltonics, Bremen, Germany) time of flight (TOF) mass spectrometer. Samples were introduced to the mass spectrometer via a Dionex Ultimate 3000 autosampler and uHPLC pump. Ultrahigh performance liquid chromatography was performed using a Waters, Acquity UPLC BEH C18 (50 mm x 2.1 mm 1.7 um) column. Gradient elution from 5% acetonitrile (0.2% formic acid) to 100% acetonitrile (0.2% formic acid) was performed over five minutes at 0.6 mL/min. High resolution positive ion electrospray ionisation mass spectra were recorded.

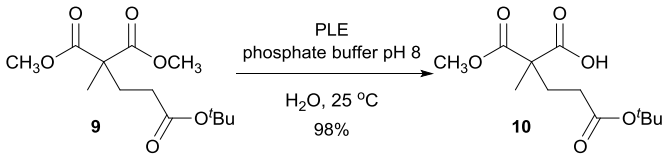
Experimental procedures and data analysis

1-(*tert*-butyl) 3,3-dimethyl butane-1,3,3-tricarboxylate (9):



To a solution of diethyl 2-methylmalonate (**8**) (5.0 g, 28.7 mmol) in MeOH (50 mL) at 25 °C under an argon atmosphere, NaOH (116 mg, 2.9 mmol) was added, and the mixture was allowed to stir for 1 h. Solvent was evaporated *in vacuo*, and *tert*-butyl acrylate (4.42 mL, 30.1 mmol) was added to the residue at 0 °C. The reaction mixture was then allowed to warm up to room temperature and allowed to stir for 30 min and EtOAc (30 mL) and water (20 mL) were added. The organic phase was separated, and the aqueous layer was washed with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. This procedure afforded **9** (7.34 g, 93%) as a pale-yellow oil used in the next step without further purification.[1] R_f = 0.45 (*n*-hexane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 3.69 (s, 6H; CH_3O), 2.25 – 2.17 (m, 2H; -CH_2-), 2.15 – 2.09 (m, 2H; -CH_2-), 1.41 (s, 9H; C(CH_3)$_3$), 1.39 (s, 3H; -C(CH_3)-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 172.4, 172.1, 80.6, 53.1, 52.6, 31.0, 30.8, 28.2, 20.3 ppm.

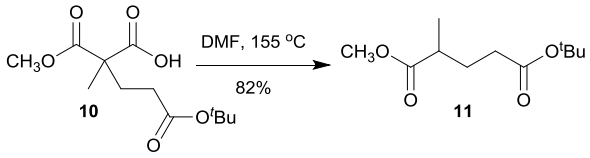
5-(*tert*-butoxy)-2-(methoxycarbonyl)-2-methyl-5-oxopentanoic acid (10):



To a solution of triester **9** (2.3 g, 8.39 mmol) in 1M phosphate buffer (44 mL) at room temperature, Pig Liver Esterase (PLE) (37 mg, 592 units) was added under vigorous stirring. The mixture was allowed to stir for 56 h maintaining the pH ~ 8 of the solution with the aid of 1M aqueous solution of NaOH. The mixture was then basified using aqueous NaOH 1M (8.4 mL) and extracted using Et_2O (2 × 15 mL). The aqueous phase was acidified using aqueous HCl 1M until pH 3 and further extracted with EtOAc (4 × 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 8:2) to afford compound **10** (2.14 g, 98%) as a pale-yellow oil. R_f =0.22 (*n*-hexane/EtOAc 7:3); $[\alpha]_D^{25}$ = + 1.32 (*c* = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 3.77 (s, *J* = 6.0 Hz, 3H; CH_3O-), 2.33 –

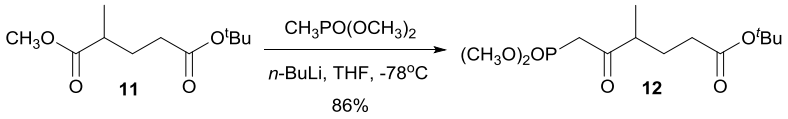
2.24 (m, 2H; -CH_2-), 2.22 – 2.12 (m, 2H; -CH_2-), 1.47 (s, 3H; -C(CH_3)-), 1.44 (brs, 9H; -C(CH_3)$_3$), ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 176.6, 172.6, 172.2, 80.9, 53.0, 31.1, 28.2, 20.6 ppm. HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{12}H_{20}O_6$ 283.1152; found 283.1154.

5-(*tert*-butyl) 1-methyl 2-methylpentanedioate (11):



A solution of **10** (2.0 g, 7.68 mmol) in DMF (46 mL) was heated to 155 °C for 1 h. After the one-hour mark, the solution was allowed to reach room temperature. Water (50 mL) was added to the mixture, and extractions with EtOAc (3 × 50 mL) took place. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 95:5) to afford compound **11** (1.36 g, 82%) as a colourless oil. R_f = 0.82 (*n*-hexane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 3.67 (s, 3H; CH_3O-), 2.56 – 2.41 (m, 1H; -CH(CH$_3$)-), 2.29 – 2.14 (m, 2H; -CH_2COO^{t}Bu), 1.92 (td, *J* = 14.6, 8.0 Hz, 1H; -(CH$_3$)CH-CH_aH$_b$-), 1.73 (dt, *J* = 14.4, 6.7 Hz, 1H; -(CH$_3$)CH-CH$_a$$H_b$-), 1.44 (s, 9H; -C(C$H_3$)$_3$), 1.16 (d, *J* = 7.0 Hz, 3H; -CH(CH_3)-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 176.7, 172.6, 80.5, 51.8, 38.8, 33.3, 28.9, 28.2, 17.2 ppm. HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{11}H_{20}O_4$ 239.1254; found 239.1257.

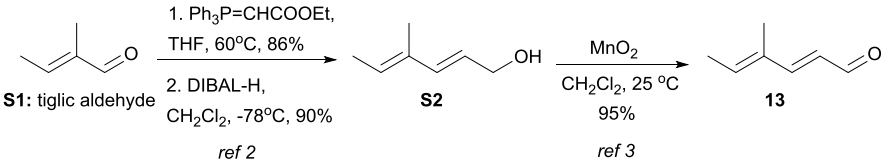
***tert*-butyl 6-(dimethoxyphosphoryl)-4-methyl-5-oxohexanoate (12):**



To a solution of dimethyl methylphosphonate (1.46 mL, 13.5 mmol) in THF (11 mL) at −78°C under an argon atmosphere, a solution of *n*-BuLi (8 mL, 1.6 M solution in *n*-hexane, 12.3 mmol) was added dropwise, and the reaction mixture was allowed to stir for 1.5 h. After the time specified, a solution of **11** (1.2 g, 5.61 mmol) in THF (11 mL) was added dropwise to the mixture, and the reaction was allowed to stir for 3 h at −78°C. Then, the reaction was allowed to reach room temperature and was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was then extracted with EtOAc (4 × 30 mL), and the combined organic extracts were sequentially washed with water (30 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to flash

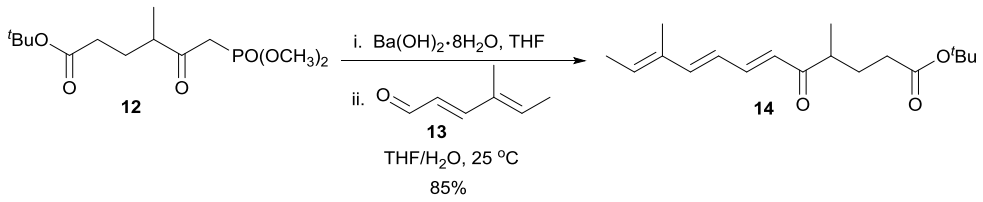
column chromatography (SiO_2, *n*-hexane/EtOAc 7:3 to 6:4) to afford compound **12** (1.49 g, 86%) as a yellow oil. R_f = 0.19 (*n*-hexane/EtOAc 6:4); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 3.78 (d, $J_{H\text{-}P}$ = 11.2 Hz, 6H; CH_3O), 3.16 (d, $J_{H\text{-}P}$ = 22.6 Hz, 2H; -P-CH_2CO), 2.79 (h, J = 6.9 Hz, 1H; -CH(CH_3)-), 2.29 – 2.14 (m, 2H; -CH_2COO^{t}Bu), 1.96 (m, 1H; -(CH_3)CH-CH_aH$_b$-), 1.66 - 1.54 (m, 1H; -(CH_3)CH-CH$_a$$H_b$-), 1.44 (s, 9H; -C(C$H_3$)$_3$), 1.12 (d, J = 7.0 Hz, 3H; -CH(CH_3)-) ppm, ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 205.2 ($J_{C\text{-}P}$ = 6.7 Hz), 172.6, 80.6, 53.2 ($J_{C\text{-}P}$ = 6.8 Hz), 53.1 ($J_{C\text{-}P}$ = 6.8 Hz), 46.5 ($J_{C\text{-}P}$ = 2.0 Hz), 40.4, 39.4, 32.9, 28.2, 27.5, 16.0 ppm; HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{13}H_{25}O_6P$ 331.1281; found 331.1280.

Route for the preparation of aldehyde 13:



Aldehyde **13** was prepared from tiglic aldehyde (**S1**) by a Wittig reaction with PPh_3=CHCOOEt, followed by reduction, to afford alcohol **S2**, and oxidation, according to the depicted route above. This route was based on literature procedures.[2,3] Aldehyde **13** prepared this way was ≥97% *all-trans*. Data for **13**. R_f = 0.62 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 9.54 (d, J = 7.8 Hz, 1H; -CH=O), 7.10 (d, J = 15.5 Hz, 1H; -CH=CH-CHO), 6.17 - 6.00 (d, q overlapping, 2H; CH_3CH=C-; -CH=CH-CHO), 1.85 (d, J = 7.0 Hz, 3H; CH_3CH=C-), 1.80 (brs, 3H; 1.75 (s, 3H; CH_3-C-) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ 194.4, 157.8, 139.0, 134.5, 126.6, 29.8, 15.0, 12.1 ppm.

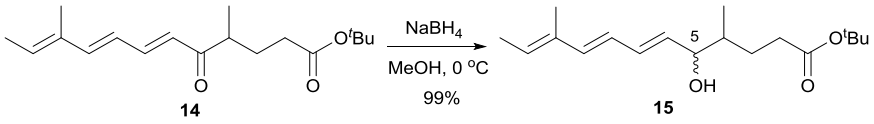
***tert*-butyl (6*E*,8*E*,10*E*)-4,10-dimethyl-5-oxododeca-6,8,10-trienoate (14):**



To a solution of **12** (1.18 g, 3.83 mmol) in THF (32 mL) at 25 °C, $Ba(OH)_2$•$8H_2O$ (2.23 g, 7.07 mmol) was added, and the mixture was allowed stirring for 30 min. Then, the mixture was cooled to 0 °C and a dropwise addition of freshly prepared **13** (633 mg, 5.75 mmol) dissolved in a mixture of THF/H_2O (50 mL, 48:2) was performed. After the addition was complete (ca. 30 min), the reaction was allowed stirring till it reached room temperature where it was allowed to stir for a total of 3 h. The reaction mixture was then quenched with an aqueous

saturated solution of NH_4Cl (20 mL). The mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic extracts were sequentially washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to a flash column chromatography (SiO_2, *n*-hexane/EtOAc 98:2) to afford compound **14** as a yellow oil (950 mg, 85%. ≥ 93% *all-trans*). R_f = 0.78 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.27 (dd, *J* = 15.2, 11.0 Hz, 1H; -C*H*=CH-COCH-), 6.62 (d, *J* = 15.2 Hz, 1H; CH=C*H*-COCH-), 6.35-6.18 (m, 2H;-C*H*=CH-, -CH=C*H*-), 5.80 (q, *J* = 6.5 Hz, 1H; CH_3-C*H*=C-), 2.79 (h, *J* = 6.9 Hz 1H;-CO-C*H*(CH_3)-), 2.19 (m, 2H; -CH_2COO^{t}Bu), 1,96 (m, 1H; -(CH_3)CH-C$H_a$$H_b$-), 1.80-1.76 (d, s, overlapping, *J* = 6.5 Hz, 6H; CH_3-CH=C, CH_3-C=C-), 1.64 (ddt, *J* = 13.1, 8.4, 6.4 Hz, 1H; -(CH_3)CH-C$H_a$$H_b$-), 1.42 (s, 9H; -C(C$H_3$)$_3$), 1.10 (d, *J* = 6.9, Hz, 3H;-CO-CH(CH_3)-) ppm; *Z*-isomer (partial): δ 7.34 (m, 1H; -C*H*=CH-), 7.04 (d, *J* = 15.2 Hz, 1H; -CH=C*H*-), 6.33 (dd, *J* = 15.2, 11.1 Hz, 1H; -C*H*=CH-), 5.67 (q, *J* = 7.4 Hz, 1H; CH_3-C*H*=C-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 203.3, 172.8, 147.2, 144.0, 135.0, 133.3, 127.1, 124.1, 80.4, 43.4, 33.2, 28.4, 28.2, 16.9, 14.5, 12.0 ppm; *Z*-isomer (partial): δ 143.9, 138.7, 130.7, 127.7, 126.7, 20.2, 16.8 ppm; HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{18}H_{28}O_3$ 315.1931; found [*M*+Na]$^+$: 315.1938.

***tert*-butyl (6*E*,8*E*,10*E*)-5-hydroxy-4,10-dimethyldodeca-6,8,10-trienoate (15):**

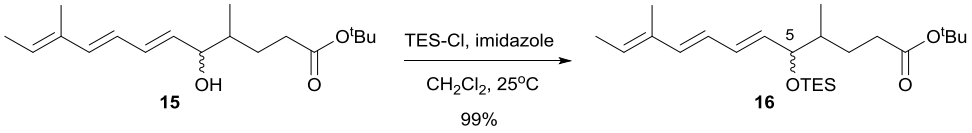


14 **15**

To a solution of **14** (330 mg, 1.13 mmol) in MeOH (5 mL), $NaBH_4$ (47 mg, 1.24 mmol) was added at 0 °C, and the mixture was allowed to stir for 1 h. After the one-hour mark, the reaction mixture was quenched with an aqueous saturated solution of NH_4Cl (4 mL). The aqueous solution was then extracted with EtOAc (4 × 15 mL), and the combined organic extracts were sequentially washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc, 9:1) to afford compound **15** [mixture of diastereoisomers at C-5 (c.a. 1.5:1), 329 mg, 99%] as a pale-yellow oil. R_f =0.42 (*n*-hexane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks reported for all isomers unless defined otherwise)**:** δ 6.31 – 6.21 (m, 2H; -CH=C*H*-C*H*=CH-C(OH)-), 6.17 – 6.08 (m, 1H; -C(CH)$_3$-C*H*=CH-), 5.72 – 5.63 (m, 1H; -CH=C*H*-CH(OH)-), 5.61 (q, *J* = 6.0 Hz, 1H; CH_3-C*H*=C-), 4.04 (t, *J* = 6.0 Hz, 1H; -C*H*(OH)- of major isomer), 3.97 (t, *J* = 6.8 Hz, 1H; -C*H*(OH)- of minor isomer), 2.37 – 2.27 (m, 1H; -C$H_a$$H_b$-COO^{t}Bu), 2.26 – 2.15 (m, 1H; -CH$_a$$H_b$-COO^{t}Bu), 1.90 –

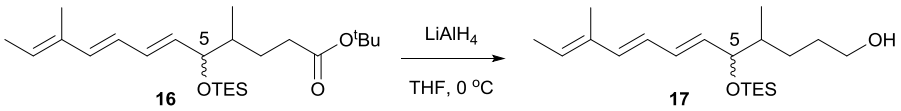
1.77 (m, 1H; -(CH_3)CH-C$H_a$$H_b$-), 1.77 (s, d overlapping, 6H; CH_3-CH=C(CH_3)-), 1.62 – 1.55 (m, 1H; -CH(CH_3)-), 1.44 (s, 9H; -C(CH_3)$_3$), 1.43 – 1.34 (m, 1H; -(CH_3)CH-CH$_a$$H_b$-), 0.91 (d, J = 6.8 Hz, 3H; -CH(CH_3)- of major isomer). 0.88 (d, J = 6.8 Hz, 3H; -CH(CH_3)- of minor isomer) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 173.5, 138.3, 138.1, 134.7, 133.0, 132.8, 132.6, 132.4, 128.1, 128.0, 125.3, 125.35, 76.2, 38.8, 38.8, 33.6, 33.3, 28.3, 27.8, 27.8, 15.1, 14.7, 14.2, 12.1 ppm; HRMS (ESI) m/z: [M+Na]$^+$ calcd. for $C_{18}H_{30}O_3$ 317.2087; found 317.2088.

tert-butyl (6*E*,8*E*,10*E*)-4,10-dimethyl-5-((triethylsilyl)oxy)dodeca-6,8,10-trienoate (16):



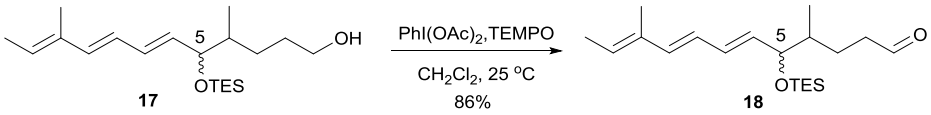
To a solution of **15** (340 mg, 1.15 mmol) in CH_2Cl_2 (12 mL) under an argon atmosphere, were sequentially added imidazole (125 mg, 1.84 mmol) and dropwise TES-Cl (0.27 mL, 1.61 mmol) at 25 °C. After 30 min of stirring, the reaction mixture was quenched with an aqueous saturated solution of $NaHCO_3$ (5 mL) and CH_2Cl_2 was evaporated under reduced pressure. The aqueous solution was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were sequentially washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 98:2) to afford compound **16** [mixture of diastereoisomers at C-5 (c.a. 1.5:1), 465 mg, 99%] as a pale-yellow oil. R_f =0.89 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ 6.26 – 6.06 (m, 3H;-CH=CH-CH=CH-), 5.69 – 5.50 (m, 2H; CH_3-CH=C-, -CH=CH-CH(OTES)-), 4.01 – 3.91 (m, 1H; -CH(OTES)-), 2.27 (ddd, J = 15.4, 9.7, 5.8 Hz, 1H; -C$H_a$$H_b$-COO^{t}Bu), 2.17 (ddt, J = 15.4, 9.5, 6.2 Hz, 1H; -CH$_a$$H_b$-COO^{t}Bu), 1.79 (m, 1H; -(CH_3)CH-C$H_a$$H_b$), 1.77 - 1.71 (s, d overlapping, 6H; -(CH_3)C=C(CH_3)-), 1.53 (m, 1H; -CH(CH_3)-), 1.43 (brs, 9H; -C(CH_3)$_3$), 1.38 - 1.30 (m, 1H; -(CH_3)CH-CH$_a$$H_b$-), 0.97 (t overlapping, 9H; -Si(CH_2CH_3)$_3$), 0.88 - 0.81 (doublets overlapping, 3H; CH(CH_3)-), 0.63 – 0.48 (q overlapping 6H; -Si(C$H_2$$CH_3$)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 173.5, 137.3, 134.8, 134.0, 133.5, 131.7, 131.4, 127.5, 125.7, 80.1, 39.9 (2C), 33.9, 33.8, 28.3 (2C), 28.0, 14.9 (2C), 14.2, 12.1, 7.0, 6.9, 6.6, 5.2 (2C) ppm; HRMS (ESI) m/z: [M+Na]$^+$ calcd. for $C_{24}H_{44}O_3Si$ 431.2952; found 431.2960.

(6*E*,8*E*,10*E*)-4,10-dimethyl-5-((triethylsilyl)oxy)dodeca-6,8,10-trien-1-ol (17)



To a solution of **16** (1.38 g, 3.38 mmol) in dry THF (14 mL) at 0°C, $LiAlH_4$ (257 mg, 6.76 mmol) was added portionwise under argon and the mixture was stirred for 1 h. The reaction was quenched with water (1.2 mL), and an aqueous solution of NaOH 0.5M (1.2 mL), brine (2.2 mL) and Et_2O (28 mL) were added successively. The pale grey dual-layered solution was allowed to stir at 0 °C) until the ether layer turned milky white, then dried over anhydrous Na_2SO_4 and filtered. The solids were washed thoroughly with Et_2O (20 mL), and EtOAc (20 mL) and the combined organic extracts were concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1 to 8:2) to afford compound **17** [mixture of diastereoisomers at C-5 (c.a. 1.5:1), ≥ 93% *all-trans*, 1.12 g, 98%, as a yellow oil. R_f =0.24 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for *all-trans* isomers): δ 6.29 – 6.09 (m, 3H; C*H*=C*H*-C*H*=CH-), 5.63 (m, 2H; CH_3-C*H*=C-, CH=C*H*-CH(OTES)-), 3.97 (m, 1H; -C*H*(OTES)-), 3.63 (t, *J* = 6.5 Hz, 2H; -CH_2OH), 1.80 – 1.70 (s, d overlapping, 6H; CH_3-C=C-, CH_3-CH=C-), 1.69 – 1.46 (m, 4H; -C*H*(CH_3)-C$H_a$$H_b$-C$H_2$-), 1.27 (m, 1H; C*H*($CH_3$)-$CH_aH_b$-), 0.98 – 0.90 (triplets overlapping, 9H; -Si(C$H_2$$CH_3$)$_3$), 0.90-0.82 (doublets overlapping 3H; -CH(CH_3)-), 0.62 – 0.51 (quartets overlapping, 6H; -Si(C$H_2$$CH_3$)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for *all-trans* isomers): δ 137.3, 134.9, 134.0, 133.7, 131.6, 131.4, 127.6, 125.7, 77.6 (2C), 63.5 (2C), 40.1, 30.8 (2C), 28.7, 28.3, 15.5, 15.2, 7.0, 5.2 ppm; HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{20}H_{38}O_2Si$ 361.2533; found 361.2540.

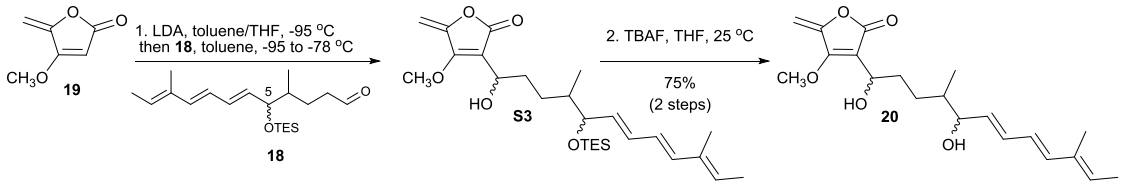
(6*E*,8*E*,10*E*)-4,10-dimethyl-5-((triethylsilyl)oxy)dodeca-6,8,10-trienal (18).



To a solution of **17** (240 mg, 0.71 mmol) in CH_2Cl_2 (4 mL), $PhI(OAc)_2$ (380 mg, 1.18 mmol) and TEMPO (5.6 mg, 0.036 mmol) were added over the course of 40 min, at room temperature under argon, and the mixture was allowed to stir for 2 h. The reaction was quenched with an aqueous saturated solution of $Na_2S_2O_3$ (2 mL) and stirring was continued for 15 min. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed successively with an aqueous saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1) to afford aldehyde **18** [mixture of diastereoisomers at C-5 (c.a. 1.5:1), ≥ 93% *all-trans*, 206 mg, 86%) as a yellow oil. R_f =0.75 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are

reported for *all-trans* isomers): δ 9.75 (m, 1H; -C*H*=O), 6.29 – 6.06 (m, 3H;-C*H*=C*H*-C*H*=CH-), 5.72 – 5.53 (m, 2H; CH_3-C*H*=C-, CH=C*H*-CH(OTES)-), 4.05 – 3.88 (m, 1H; -C*H*(OTES)-), 2.54 – 2.29 (m, 2H; -CH_2-CH=O), 1.85 (m, 1H; -(CH_3)CH-C$H_a$$H_b$-), 1.80 – 1.66 (s, doublet overlapping, 6H; -(CH_3)C=CH-, CH_3-CH=C-), 1.47 – 1.30 (m, 1H; -(CH_3)CH-$CH_a$$H_b$-), 0.98 – 0.91 (triplets overlapping, 9H; -Si(CH_2CH_3)$_3$), 0.89 – 0.80 (doublets overlapping, 3H; -CH(CH_3)-), 0.64 – 0.44 (quartets overlapping, 6H; -Si(C$H_2$$CH_3$)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for *all-trans* isomers): δ 203.0, 137.6 (2C), 134.8, 134.2, 133.5, 133.3, 131.9, 131.8, 127.8 (2C), 125.5, 77.6, 42.3, 42.1, 39.8, 24.8 (2C) 15.4, 15.3, 14.2, 13.3, 12.1, 7.0, 5.2 (2C) ppm; HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{20}H_{36}O_2Si$ 359.2377; found 359.2379.

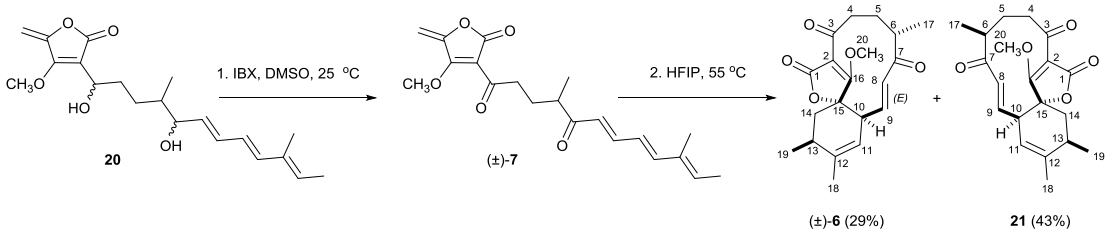
3-((6*E*,8*E*,10*E*)-1,5-dihydroxy-4,10-dimethyldodeca-6,8,10-trien-1-yl)-4-methoxy-5-methylenefuran-2(5*H*)-one (20):



A freshly prepared solution of LDA resulted from mixing *i*-Pr_2NH (1.72 mL, 1.22 mmol) in toluene (5.4 mL) and *n*-BuLi (0.74 mL, 1.6M solution in *n*-hexane, 1.18 mmol) for 1 h at 0°C under argon. The solution was then cooled to −95°C, and a solution of 4-methoxy-5-methylenefuran-2(5*H*)-one (**19**) (136 mg, 1.08 mmol) in a mixture of THF (7.6 mL) and toluene (2.4 mL) was added. The resulting mixture was stirred for 6 min at −95 °C. A solution of aldehyde **18** (120 mg, 0.360 mmol) in toluene (3.6 mL) was added dropwise with stirring and temperature was gradually increased to −78 °C during 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and warmed at 25 °C. The mixture was extracted with EtOAc (4 × 15 mL), and the combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to a flash column chromatography (SiO_2, *n*-hexane/ EtOAc 9:1) to yield the corresponding coupling product **S3** as an inseparable mixture with excess of 4-methoxy-5-methylenefuran-2(5*H*)-one (**19**) which was used in the next step without further purification. R_f =0.39 (*n*-hexane/EtOAc 8:2). To a solution of the above mixture in THF (2 mL), TBAF (1.26 mL, 1M solution in THF, 1.26 mmol) was added at 0 °C. The reaction was allowed to warm at 25 °C. After stirring for 2 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (6 mL) and extracted with EtOAc (4 × 10 mL). The combined organic

extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude mixture was subjected to a flash column chromatography (SiO_2, *n*-hexane/ EtOAc 8:2 to 6:4) to afford diol **20** (mixture of diastereoisomers (c.a. 1:1:1.5:1), *all-trans* ≥ 84%, 94 mg, 75%) as a yellow oil. R_f = 0.18 (*n*-hexane/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for *all-trans* isomers): δ 6.28 – 6.07 (m, 3H; -C*H*=C*H*-C*H*=CH-), 5.78 – 5.53 (m, 2H; -CH=C*H*-CH(OH), CH_3-C*H*=C), 5.07 (brs, 2H; CH_2=C-), 4.82 – 4.71 (m, 1H; -C*H*(OH)-tetronate), 4.15 (singlets overlapping, 3H; CH_3O-), 4.07 – 3.91 (m, 1H; -C*H*(OH)-), 3.12 – 2.92 (m, 1H; -CH(OH)-CH_aH$_b$-), 1.95 – 1.84 (m, 1H; -CH(OH)-CH$_a$$H_b$-), 1.78 – 1.70 (s, d overlapping, 6H; -(CH_3)C=CH-, CH_3-CH=C-), 1.68 – 1.60 (m, 1H; -C*H*(CH_3)-), 1.49 – 1.32 (m, 1H; -CH_aH$_b$-CH(CH_3)-), 1.18 – 1.08 (m, 1H; -CH$_a$$H_b$-CH($CH_3$)-), 0.95 – 0.84 (doublets overlapping, 3H; -CH(CH_3)-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C (peaks reported for all isomers): ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ 169.7, 161.1, 149.5, 138.5, 138.3, 134.7, 133.0, 132.9, 132. 8, 132.7, 132.5 (2C), 128.5, 128.3, 128.2, 125.1, 107.4, 107.3, 93.5, 88.4, 66.8, 66.6, 60.5, 38.9, 38.8, 38.7, 35.5, 35.4, 35.2 (2C), 29.8, 29.2 (2C), 29.1, 29.0, 23.3, 22.8, 20.7, 20.4, 15.5, 15.4, 15.1, 15.0, 14.2, 13.3, 12.1 ppm; HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{20}H_{28}O_5$ 371.1829; found 371.1832.

Oxidation of diol 20 to diketone (±)-7 and IMDA to (±)-6 and 21 via a two-step procedure.



A. Oxidation of 20 to diketone ((±)-7): To a solution of **20** (300 mg, 0.86 mmol) in DMSO (10 mL) , IBX (0.71 g, 2.58 mmol) was added, at room temperature, under argon and the mixture was stirred for 3 h (a direct conversion of **20** to (±)-**7** was observed by TLC). Et_2O (20 mL) was added and the mixture was poured in water (20 mL). The organic phase was separated and the aqueous layer was washed with Et_2O (3 × 20 mL). An aqueous saturated solution of $NaHCO_3$ was added to the combined organic extracts with vigorous stirring until pH ~ 8-9. The organic phase was separated, and the aqueous layers were washed with Et_2O (2 × 30 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, and partially concentrated *in vacuo*. A small amount was subjected to a short flash column chromatography (SiO_2, *n*-hexane/EtOAc/Et_3N 95:5:0.1 to 85:15:0.1) to afford diketone (±)-**7** (*all-trans* ≥ 84%) as a pale-yellow oil for analytical purposes. Data for (±)-**7***: R_f* =0.56 (*n*-

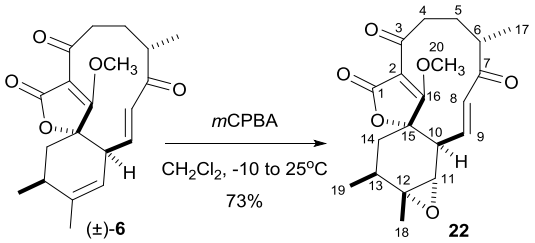
hexane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for *all-trans* isomer): δ 7.34 (dd, *J* = 15.3, 11.1 Hz, 1H; -C*H*=CH-CO-), 7.06 (d, *J* = 15.2 Hz, 1H; -(CH_3)C=C*H*-), 6.34 (dd, *J* = 15.2, 11.1 Hz, 1H;-CH=C*H*-CH=CH-) , 6.28 (d, *J* = 15.4 Hz, 1H; -CH=C*H*-CO-), 5.69 (q, *J* = 7.3 Hz, 1H; (CH_3)C*H*=C-), 5.27 (d, *J* = 2.7 Hz, 1H; -C=CH_aH_b), 5.21 (d, *J* = 2.8 Hz, 1H; -C=CH_aH_b), 4.16 (s, 3H; CH_3O-), 3.07 – 2.91 (m, 2H; -CH_2CO-), 2.83 (h, *J* = 6.9 Hz, 1H; -(CH_3)C*H*CO-), 2.03 (dtt, *J* = 11.0, 7.9, 5.6 Hz, 1H; -CH_aH$_b$-CH_2CO-), 1.86 (brs, 3H; -(CH_3)C=CH-), 1.81 (d, *J*=7.3 Hz, 3H; (CH_3)CH=C-), 1.73 (ddt, *J* = 10.2, 8.4, 6.3 Hz, 1H; -CH_aH_b-CH_2CO-), 1.16 (d, *J* = 7.0 Hz, 3H; -(CH_3)CHCO-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for *all-trans* isomer): δ 203.3, 196.4, 168.1, 166.6, 149.1, 147.3, 144.1, 144.0, 138.8, 133.3, 130.7, 127.6, 127.0, 126.6, 124.1, 96.1, 96.0, 77.16, 63.4, 43.7, 43.6, 40.6, 31.1, 29.9, 27.1, 27, 20.2, 17.2, 17.1, 14.6, 13.7, 12.0 ppm; HRMS (ESI) *m*/*z*: [*M*+Na]$^+$ calcd. for $C_{20}H_{24}O_5$ 367.1516; found 367.1521. **B. IMDA of** (±)-**7 to** (±)-**6 and 21.** HFIP (80 mL) was added to the organic extracts of the above prepared (±)-**7**, the mixture was purged with argon, and residual Et_2O was removed by distillation. The mixture was then allowed to stir for 16 h at 55 °C, under argon and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1 to 8:2) to afford an inseparable mixture of compounds (±)-**6** and **21** in ~ 1:1.6 ratio, assigned by ^{1}H NMR. The two isomers were separated by preparative thin layer chromatography (SiO_2, *n*-hexane/EtOAc 9:1, 5-fold development and then *n*-hexane/EtOAc 8:2, 5-fold development). Compound (±)-**6** (85.3 mg, 29% from **20**) was isolated as a ~5:1 inseparable mixture with a by-product, formed during purification with this procedure, as assigned by the comparison of ^{1}H NMR spectra of the mixture of (±)-**6**/**21** before preparative TLC and the purified compounds (±)-**6** and **21**. The structure of this by-product could not be fully assigned and crystallization of (±)-**6** was not possible. Nevertheless, ^{1}H, ^{13}C NMR and ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC spectra indicated the absence of the double bond $\Delta^{8\text{-}9}$, the existence of a CH_3O- group, and the cyclohexene moiety, and the appearance of a peak at ~11.5 ppm presumably corresponding to an enol. Similar patterns of peaks have been observed in abyssomicin D analogues,[4] however, further structure elucidation was not possible due to overlaps with the peaks of (±)-**6**. Compound **21** was isolated as a white solid (128 mg, 43% from **20**), and it was recrystallized by dissolution with EtOAc and slow crystallization at 25 °C for X-ray analysis.

Data for (±)-**6:** R_f =0.23 (*n*-hexane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.21 (d, *J* = 16.5 Hz, 1H; H-8), 5.98 (dd, *J* = 16.5, 10.3 Hz, 1H; H-9), 5.26 (brs, 1H; H-11), 4.13 (brs, 3H; CH_3-20), 3.32 (m, 1H; H-10), 3.03 (m, 1H; H-4a), 2.82 (m, 1H; H-6), 2.53 – 2.33 (m, 3H; H-13, H-4b, H-14a), 2.12) (m, 1H; H-5a), 1.85 (dd, *J* = 14.5, 4.7 Hz, 1H; H-14b), 1.78 (brs, 3H; H-18),

1.63 (m, 1H; H-5b), 1.17 (d, *J* = 7.3 Hz, 3H; CH_3-19), 1.10 (d, *J* = 6.6 Hz, 3H; CH_3-17) ppm ; ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): *δ* 214.4 (C-3), 204.8 (C-7), 198.8 (C-1), 178.7 (C-16), 141.9 (C-9), 141.7 (C-12), 133.5 (C-8), 118.1 (C-11), 108.6 (C-2), 85.9 (C-15), 63.4 (C-20), 48.2 (C-10), 43.5 (C-6), 41.4 (C-4), 37.0 (C-14), 32.5 (C-13), 31.0 (C-5), 21.0 (C-18), 19.0 (C-19), 15.6 (C-17) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{24}O_5$ 367.1516; found 367.1523. **Partial data for by-product**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): *δ* 11.77 (-OH), 5.44 (brs, 1H; -CH=C-), 3.63 (brs, CH_3O-), 3.03 (CH-), 2.47 (m, CH), 2.24 (m, CH), 2.16 (m, CH), 0.99 (d, CH_3CH-), 1.10 (d, CH_3CH-) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): *δ* 214.2 (**C**=O), 207.4 (**C**=O), 169.8 (C=**C**OCH_3), 138.2 (**C**=C), 119.1 (**C**=C), 54.0 (**C**-), 52.3 (-**C**H_3O), 45.8, 39.3, 19.4, 19.0 ppm.

Data for 21: R_f =0.23 (*n*-hexane/EtOAc 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): *δ* 6.44 (d, *J* = 16.6 Hz, 1H; H-8), 6.38 (dd, *J* = 16.6, 7.1 Hz, 1H; H-9), 5.38 (brs, 1H; H-11), 3.88 (s, 3H; CH_3-20), 3.41 (m, 1H; H-10), 2.97 (m, 1H; H-4b), 2.89 (m, 1H; H-6), 2.48 (q, *J* = 7.0 Hz, 1H; H-13), 2.37 (m, 1H; H-4a), 2.33 (dd, *J* = 14.3 Hz, 7.0 Hz, 1H; H-14a), 2.01 (m, 1H; H-5a), 1.84 -1.75 (dd, s overlapping, 5H; H-14b, H-18, H-5b), 1.15 (d, *J* = 7.2 Hz, 3H; H-19), 1.10 (d, *J* = 6.7 Hz, 3H; H-17) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): *δ* 204.6 (C-7), 198.2 (C-3), 179.4 (C-16), 169.5 (C-1), 142.2 (C-9), 142.1 (C-12), 132.8 (C-8), 118.4 (C-11), 106.8 (C-2), 86.0 (C-15), 61.9 (C-20), 45.8 (C-10), 45.2 (C-6), 43.0 (C-4), 37.8 (C-14), 32.2 (C-13), 29.6 (C-5), 21.0 (C-18), 18.8 (C-19), 16.1 (C-17) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{24}O_5$ 367.1516; found 367.1521.

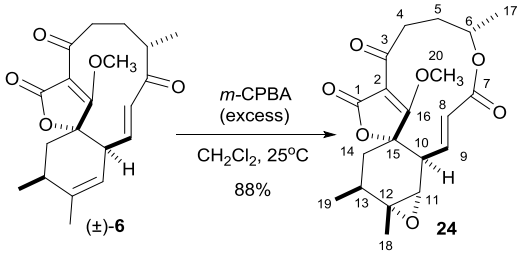
Epoxide 22.



To a solution of (±)-**6** (30 mg, 0.087 mmol) in CH_2Cl_2 (3 mL) at -10 °C, *m*-CPBA (43 mg, 0.174 mmol) was added portionwise, and the solution was stirred for 2 hours, warmed to 25 °C, and left to stir for additional 2 hours. The reaction mixture was quenched with a saturated aqueous solution of Na_2SO_3 (5 mL) and stirred vigorously for 30 minutes. The mixture was then extracted with Et_2O (5 × 5 mL) and the organic extracts were washed with a saturated solution of $NaHCO_3$ (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 8:2 to 7:3) to afford epoxide **22** (23 mg, 73%) as a

pale-yellow oil. R_f =0.24 (*n*-hexane/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.25 (d, *J* = 16.3 Hz, 1H; H-8), 6.06 (dd, *J* = 16.3, 10.5 Hz, 1H; H-9), 4.21 (s, 3H; CH_3-20), 3.03 (m, 1H; H-4a), 2.86 (m, 2H; H-10, H-11) 2.79 (h, *J* = 6.3 Hz, 1H; H-6), 2.45 (ddd, *J* = 15.8, 9.7, 3.8 Hz, 1H; H-4b), 2.19 – 2.07 (m, 3H; H-5a, H-13, H-14a), 1.83 (dt, *J* = 11.9, 6.5 Hz, 1H; H-14b), 1.64 (dtd, *J* = 14.9, 7.4, 4.1 Hz, 1H; H-5b), 1.31 (brs, 3H; CH_3-18), 1.17 (d, *J* = 6.2 Hz, 3H; CH_3-19), 1.12 (d, *J* = 6.1 Hz, 3H; CH_3-17) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ 204.1 (C-7), 198.41 (C-3), 177.9 (C-16), 169.3 (C-1), 138.6 (C-9), 134.6 (C-8), 109.0 (C-2), 85.9 (C-12), 63.9 (C-20), 60.5 (C-15), 59.9 (C-11), 49.2 (C-10), 43.8 (C-6), 41.5 (C-4), 35.7 (C-14), 32.2 (C-13), 30.7 (C-5), 18.3 (C-18), 17.3 (C-19), 15.6 (C-17) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{24}O_6$ 383.1465; found 383.1469.

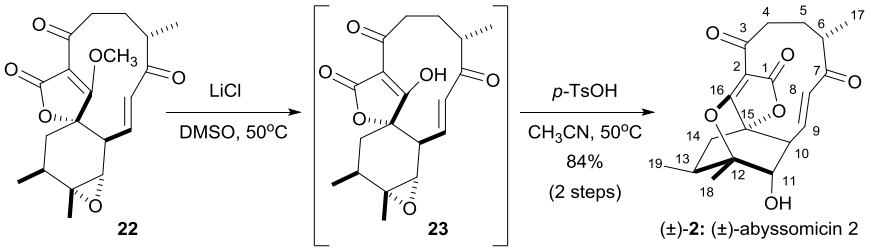
Epoxide lactone 24.



To a solution of (±)-**6** (15 mg, 0.044 mmol) in CH_2Cl_2 (1.5 mL) at -10 °C, *m*-CPBA (87 mg, 0.348 mmol) was added portionwise, and the solution was left to stir for 1 hour, warmed to room temperature, and stirred for additional 4 hours. The reaction mixture was then quenched with the addition of a saturated solution of Na_2SO_3 (5 mL) and left to stir vigorously for 30 minutes. The mixture was then extracted with Et_2O (5 × 5 mL) and the organic extracts were washed with a saturated solution of $NaHCO_3$ (10 mL). The combined organic layers were consecutively dried over anhydrous Na_2SO_4, filtered through cotton and concentrated in vacuo. The crude mixture was subjected to a gradient flash column chromatography (SiO_2, n-Hexane/EtOAc 8:2 to 7:3) to afford epoxide-lactone **24** (14 mg, 88%) as a pale-yellow oil. R_f =0.30 (*n*-hexane/EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.55 (dd, *J* = 16.5, 7.2 Hz, 1H; H-9), 6.05 (d, *J* = 16.5, 1.3 Hz, 1H; H-8), 5.20 (m, 1H; H-6), 3.98 (s, 3H; CH_3-20), 3.62 (ddd, *J* = 13.0, 5.9, 3.7 Hz, 1H; H-4a), 2.97 (d, *J* = 3.0 Hz, 1H; H-11), 2.93 (dd, *J* = 7.3, 3.3 Hz, 1H; H-10), 2.37 (ddd, *J* = 12.6, 10.8, 4.6 Hz, 1H; H-4b), 2.20 – 2.09 (m, 2H; H-13, H-14a), 1.99 - 1.84 (m, 2H; H-5), 1.78 (m, 1H; H-14b), 1.32 (s, 3H; CH_3-18), 1.30 (d, *J* = 6.6 Hz, 3H; CH_3-17), 1.16 (d, *J* = 6.9 Hz, 3H; CH_3-19) ppm; ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): 199.4 (C-3), 180.0 (C-16), 166.2 (C-7), 142.2 (C-9), 124.6 (C-8), 85.4 (C-12), 69.7 (C-6), 62.8 (C-20), 60.8 (C-15), 58.6 (C-11), 46.4 (C-10), 36.7 (C-14), 33.5 (C-4), 32.2 (C-13), 30.8 (C-5), 18.6 (C-17 or C-18), 18.0 (C-17 or

C-18), 17.3 (C-19) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{24}O_7$ 399.1414; found 399.1414.

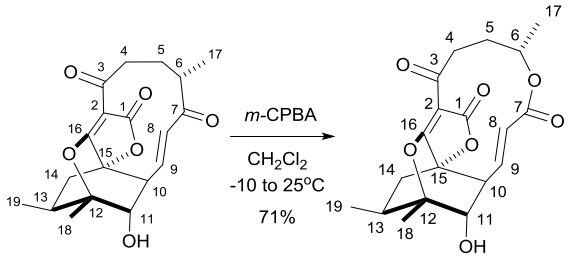
(±)-Abyssomicin 2 ((±)-2):



To a solution of the epoxide **22** (22 mg, 0.061 mmol) in DMSO (1.5 mL), LiCl (26 mg, 0.61 mmol) was added, under argon and the solution was stirred at 50 °C for 2 hours (during this time demethylation of **22** to **23** was observed with a 100% conversion monitored by TLC). After the two-hour mark, the reaction mixture was allowed to warm at room temperature and quenched with a mixture of AcOH/EtOAc (1:5 v/v) until a pH 3-4. The mixture was evaporated *in vacuo* until the excess AcOH/EtOAc was removed. To the crude residue, MeCN (3.5 mL) and *p*-TsOH (14 mg, 0.073 mmol) were added, and the mixture was stirred at 50 °C for 2 hours under argon. The reaction mixture was quenched with water (15 mL) and extracted with EtOAc (10 × 5 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The crude residue was purified by preparative TLC (SiO_2, *n*-hexane/EtOAc 6:4, 8-fold development) to yield the racemic abyssomicin 2 ((±)-**2**) (18 mg, 84%) as a pale-yellow oil. R_f =0.41 (*n*-hexane/EtOAc, 4:6); ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ 6.31 (dd, *J* = 16.8, 6.6 Hz, 1H; H-9), 6.03 (d, *J* = 16.8 Hz, 1H; H-8), 3.87 (d, *J* = 2.3 Hz, 1H; H-11), 3.15 (dd, *J* = 6.7, 2.4 Hz, 1H; H-10), 3.06 (ddd, *J* = 13.6, 5.1, 3.9 Hz, 1H; H-4a), 2.75 (dd, *J* = 12.6, 10.9 Hz, 1H; H-14a), 2.65 (m, 1H; H-13), 2.44 (dt, *J* = 6.5, 4.0 Hz, 1H; H-6), 2.38 (td, *J* = 13.2, 4.4 Hz, 1H; H-4b), 1.86 (dddd, *J* = 16.3, 12.6, 3.9, 3.9 Hz, 1H; H-5a), 1.61 (s, 3H; CH_3-18), 1.58 (m, 1H; H-5b), 1.50 (dd, *J* = 12.6, 2.7 Hz, 1H; H-14b), 1.08 (d, *J* = 6.9 Hz, 3H; CH_3-19) 1.06 (d, *J* = 6.5 Hz, 3H; CH_3-17) ppm; ^{13}C NMR (63 MHz, CD_3OD, 25 °C): δ 205.9 (C-7), 196.5 (C-3), 185.8 (C-16), 171.4 (C-1), 137.8 (C-9), 136.3 (C-8), 105.0 (C-2), 90.4 (C-12), 81.7 (C-15), 75.4 (C-11), 52.4 (C-10), 43.5 (C-6), 42.6 (C-4), 35.3 (C-14), 31.2 (C-5), 29.7 (C-13), 19.7 (C-18), 16.4 (C-19), 16.1 (C-17) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{22}O_6$ 369.1309; found 369.1308.

(±)-Neoabyssomicin B ((±)-3).

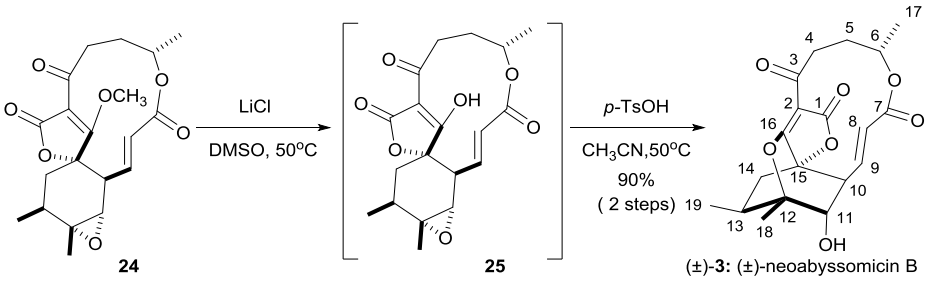
Method A. From abyssomicin 2 ((±)-2).



(±)-**2:** (±)-abyssomicin 2 (±)-**3:** (±)-neoabyssomicin B

To a solution of abyssomicin 2 ((±)-**2**) (5.0 mg, 0.014 mmol) in CH_2Cl_2 (0.5 mL) at -10°C, *m*CPBA (28 mg, 0.115 mmol) was added portionwise, the solution was left to stir for 1 hour, warmed at room temperature, and left to stir for additional 4 hours. The reaction mixture was quenched with the addition of a saturated aqueous solution of Na_2SO_3 (2 mL) and the mixture was vigorously stirred for 30 minutes. The mixture was extracted with Et_2O (2 × 5 mL) and the organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (5 mL). The combined organic layers were consecutively dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was subjected to a preparative TLC (SiO_2, *n*-hexane/EtOAc 6:4, 8-fold development) to afford the racemic neoabyssomicin B ((±)-**3**), (3.7 mg, 71%) as a colorless oil.

Method B. From epoxide 24.

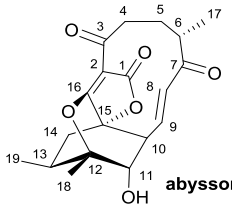


24 **25** (±)-**3:** (±)-neoabyssomicin B

To a solution of epoxide **24** (16 mg, 0.043 mmol) in DMSO (1 mL), LiCl (18 mg, 0.43 mmol) was added. The solution was allowed to stir at 50 °C for 2 hours under argon (methoxy group deprotection of **24** achieved with a 100% conversion to the intermediate **25** was monitored by TLC). After the two-hour mark, the reaction mixture was allowed to reach room temperature and quenched with a mixture of AcOH/EtOAc (1:5) until a pH~3-4. Then, the mixture was evaporated *in vacuo* until the excess AcOH/EtOAc was removed. MeCN (2.4 mL) and *p*-TsOH (4 mg, 0.021 mmol) were added to the crude residue, and the mixture was allowed to stir at 50 °C for 2 hours under argon. After the two-hour mark, water (10 mL) was added and the mixture was extracted with EtOAc (5 × 5 mL). The combined organic extracts,

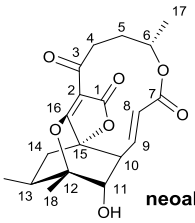
were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude residue, was purified with a preparative TLC protocol (SiO_2, *n*-hexane/EtOAc 6:4, 8-fold development) to yield the racemic neoabyssomicin B ((±)-**3**) (14 mg, 90%) as a colorless oil. R_f =0.34 (*n*-hexane/EtOAc, 4:6); ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ 6.56 (dd, *J* = 16.5, 6.2 Hz, 1H; H-9), 6.19 (d, *J* = 16.7 Hz, 1H; H-8), 4.45 (m, 1H; H-6), 3.99 (d, *J* = 2.8 Hz, 1H; H-11), 3.47 (ddd, *J* = 13.9, 6.7, 3.4 Hz, 1H; H-4a), 3.15 (dd, *J* = 6.0, 2.6 Hz, 1H; H-10), 2.77 (dd, *J* = 12.6, 10.9 Hz, 1H; H-14a), 2.64 (m, 1H; H-13), 2.14 (m, 1H; H-4b), 1.94 (m, 1H; H-5a), 1.85 (m, 1H; H-5b), 1.61 (s, 3H; CH_3-18), 1.44 (dd, *J* = 12.6, 3.1 Hz, 1H; H-14b), 1.33 (d, *J* = 6.1 Hz, 3H; CH_3-17), 1.06 (d, *J* = 7.1 Hz, 3H; CH_3-19); ^{13}C NMR (63 MHz, CD_3OD, 25 °C): δ 196.6 (C-3), 187.6 (C-16), 171.3 (C-1), 169.1 (C-7), 142.9 (C-9), 125.4 (C-8), 102.8 (C-2), 90.8 (C-12), 81.1 (C-15), 74.7 (C-6), 74.2 (C-11), 51.9 (C-10), 37.7 (C-4), 35.9 (C-14), 34.7 (C-5), 29.7 (C-13), 19.6 (C-18), 18.9 (C-17), 16.4 (C-19) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{22}O_7$ 385.1258; found 385.1263.

Table S1. Comparison of ^{1}H NMR (600 MHz, CD_3OD) and ^{13}C NMR (151 MHz, CD_3OD) of the natural abyssomicin 2 (**2**)[5] with the ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (63 MHz, CD_3OD) of the synthetic (±)-**2** prepared in this work.



Position	δ^{1}H (natural **2**) (mult., *J* (Hz))	δ^{13}C (natural)[6]	δ^{1}H ((±)-**2**) (mult., *J* (Hz))	δ^{13}C ((±)-**2**)	$\Delta\delta^{1}$H ($\delta_{(\pm)\text{-}2}$-δ_2)	$\Delta\delta^{13}$C ($\delta_{(\pm)\text{-}2}$-δ_2)
1	-	171.4	-	171.4	-	0
2	-	105.0	-	105.0	-	0
3	-	196.5	-	196.5	-	0
4	3.06 (ddd, 13.6, 5.1, 3.9)	42.6	3.06 (ddd, 13.6, 5.1, 3.9)	42.6	0	0
	2.38 (ddd, 13.6, 12.6, 4.5)		2.38 (td, 13.2, 4.4)		0	
5	1.86 (dddd, 16.3, 12.5, 3.9, 3.9)	31.2	1.86 (dddd, 16.3, 12.6, 3.9, 3.9)	31.2	0	0
	1.58 (dddd, 15.3, 4.7, 4.7, 4.7)		1.58 (m)		0	
6	2.44 (dqd, 6.9, 5.5, 2.6)	43.5	2.44 (dt, 6.5, 4.0)	43.5	0	0
7	-	205.9	-	205.9	-	0
8	6.03 (d, 16.7)	136.3	6.03 (d, 16.8)	136.3	0	0
9	6.31 (dd, 16.7, 6.7)	137.8	6.31 (dd, 16.8, 6.6)	137.8	0	0
10	3.15 (dd, 6.7, 2.3)	52.4	3.15 (dd, 6.7, 2.4)	52.4	0	0
11	3.87 (d, 2.3)	75.4	3.87 (d, 2.3)	75.4	0	0
12	-	90.4	-	90.4	-	0
13	2.64 (dqd, 10.9, 7.1, 2.8)	29.7	2.65 (m)	29.7	+0.1	0
14	2.75 (dd, 12.6, 10.9)	35.3	2.75 (dd, 12.6, 10.9)	35.3	0	0
	1.50 (dd, 12.6, 2.7)		1.50 (dd, 12.6, 2.7)		0	
15	-	81.7	-	81.7	-	0
16	-	185.8	-	185.8	-	0
17	1.06 (d, 6.5)	16.1	1.06 (d, 6.5)	16.1	0	0
18	1.61, s	19.7	1.61 (s)	19.7	0	0
19	1.07 (d, 6.9)	16.4	1.08 (d, 6.9)	16.4	-0.1	0

Table S2. Comparison of ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) of the natural neoabyssomicin B (**3**)[6] with the ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (63 MHz, CD_3OD) of the synthetic (±)-**3** prepared in this work.



neoabyssomicin B

Position	δ^{1}H (natural **3**) (mult., *J* (Hz))	δ^{13}C (natural **3**)	δ^{1}H ((±)-**3**) (mult., *J* (Hz))	δ^{13}C ((±)-**3**)	$\Delta\delta^{1}$H ($\delta_{(\pm)\text{-}3}$-δ_{3})	$\Delta\delta^{13}$C ($\delta_{(\pm)\text{-}3}$-δ_{3})
1	-	171.5	-	171.3	-	-0.2
2	-	102.9	-	102.8	-	-0.1
3	-	196.7	-	196.6	-	-0.1
4	3.46 (ddd, 13.5, 6.5, 3.5)	37.8	3.47 (ddd, 13.9, 6.7, 3.4)	37.7	+0.01	-0.1
	2.14 (m)		2.14 (m)		0	
5	1.94 (m)	34.8	1.94 (m)	34.7	0	-0.1
	1.84 (m)		1.85 (m)		0	
6	4.44 (m)	74.8	4.45 (m)	74.7	+0.01	-0.1
7	-	169.2	-	169.1	-	-0.1
8	6.20 (d, 16.5)	125.5	6.19 (d, 16.7)	125.4	-0.01	-0.1
9	6.57 (dd, 16.5, 6.0)	143.1	6.56 (dd, 16.5, 6.2)	142.9	-0.01	-0.2
10	3.16 (dd, 6.0, 2.0)	52.0	3.15 (dd, 6.0, 2.6)	51.9	-0.01	-0.1
11	3.99 (d, 2.0)	74.4	3.99 (d, 2.8)	74.2	0	-0.2
12	-	90.9	-	90.8	-	-0.1
13	2.64 (m)	29.8	2.64 (m)	29.7	0	-0.1
14	2.77 (dd, 12.4, 11.0)	36.0	2.77 (dd, 12.6, 10.9)	35.9	0	-0.1
	1.44 (dd, 12.5, 3.0)		1.44 (dd, 12.6, 3.1)		0	
15	-	81.3	-	81.1	-	-0.2
16	-	187.7	-	187.6	-	-0.1
17	1.33 (d, 6.0)	19.1	1.33 (d, 6.1)	18.9	0	-0.2
18	1.61 (s)	19.8	1.61 (s)	19.6	0	-0.2
19	1.06 (d, 7.0)	16.6	1.06 (d, 7.1)	16.4	0	-0.2

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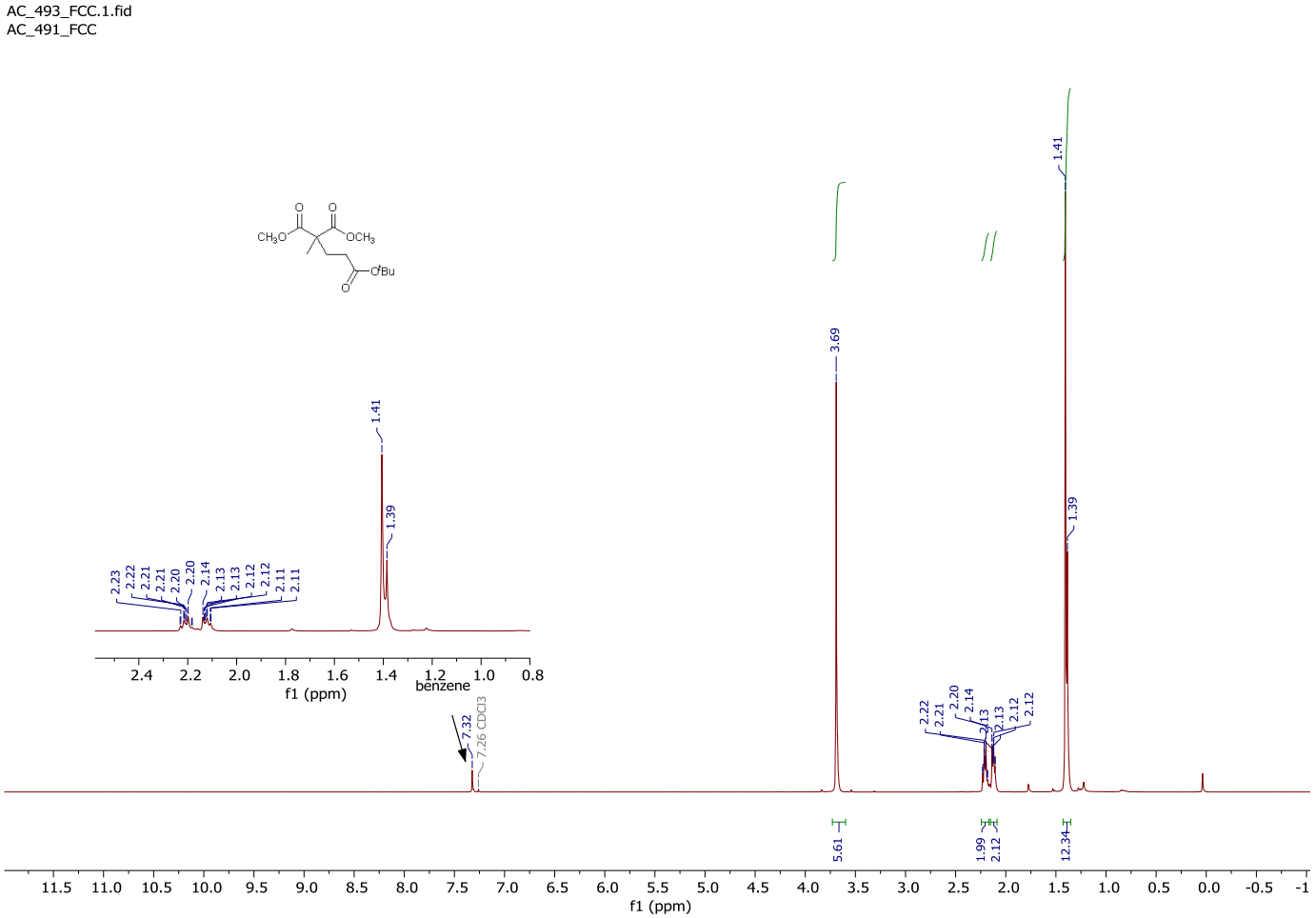
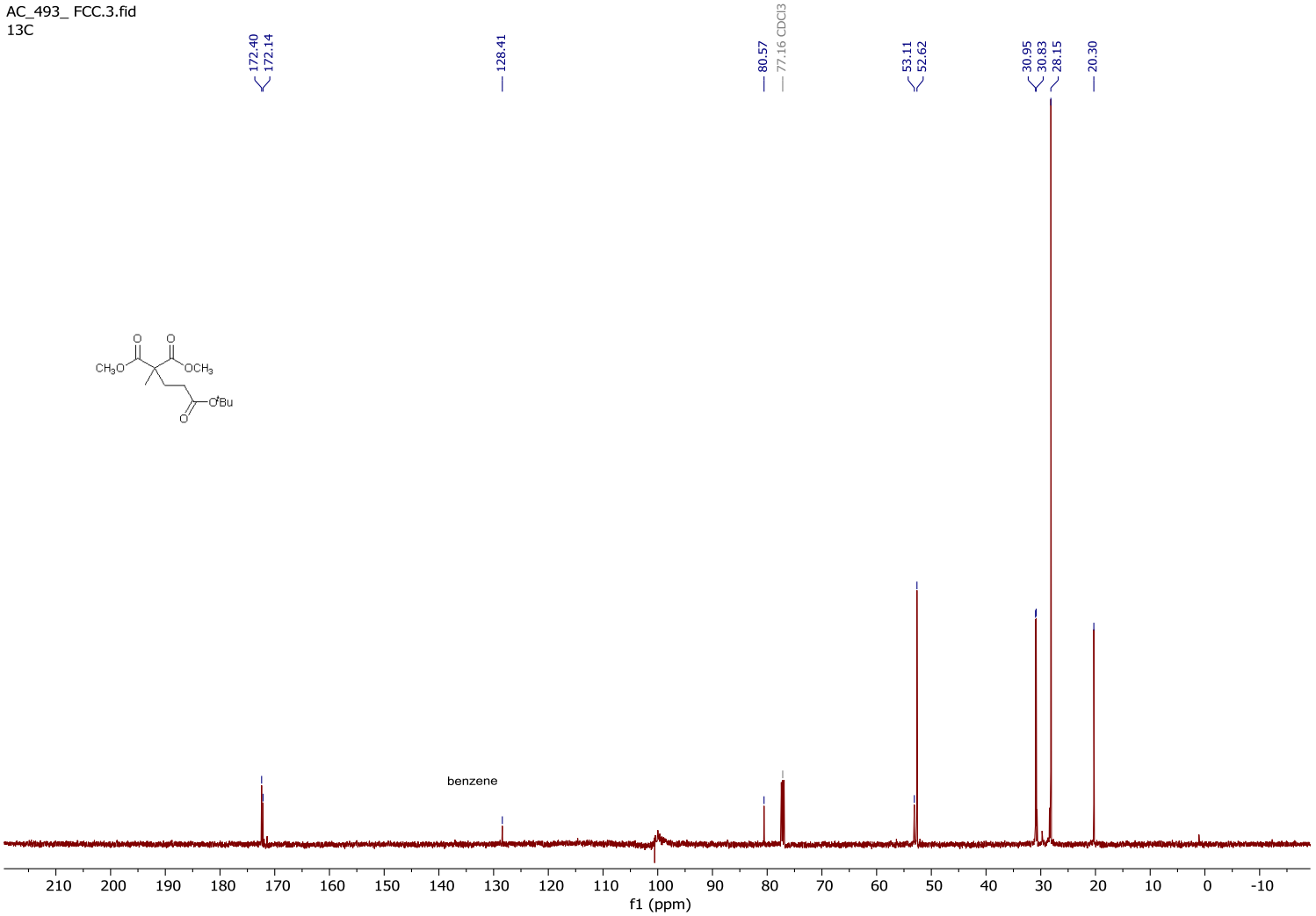
NMR spectra

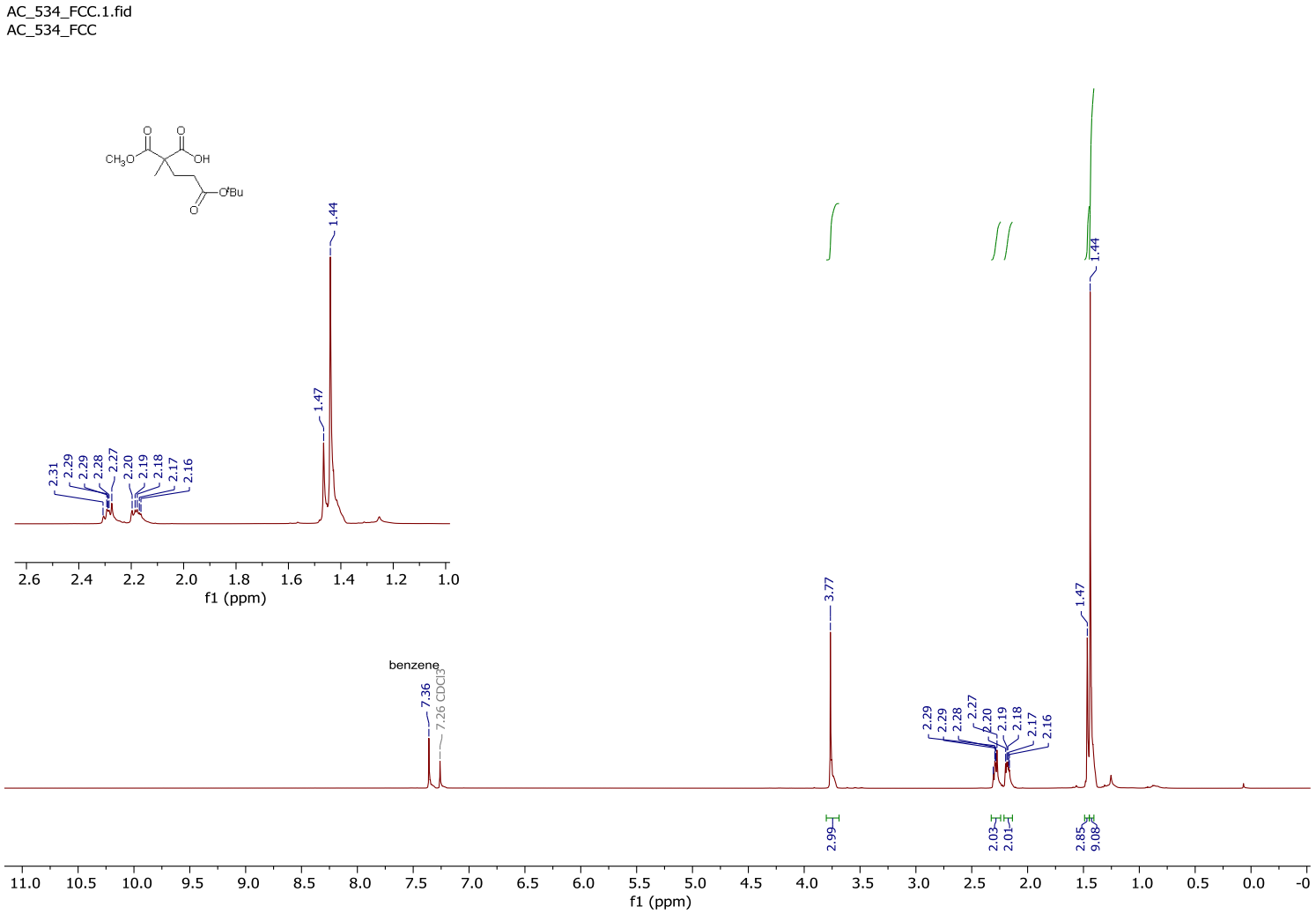
^{1}H NMR (500 MHz, $CDCl_3$) of compound **9**



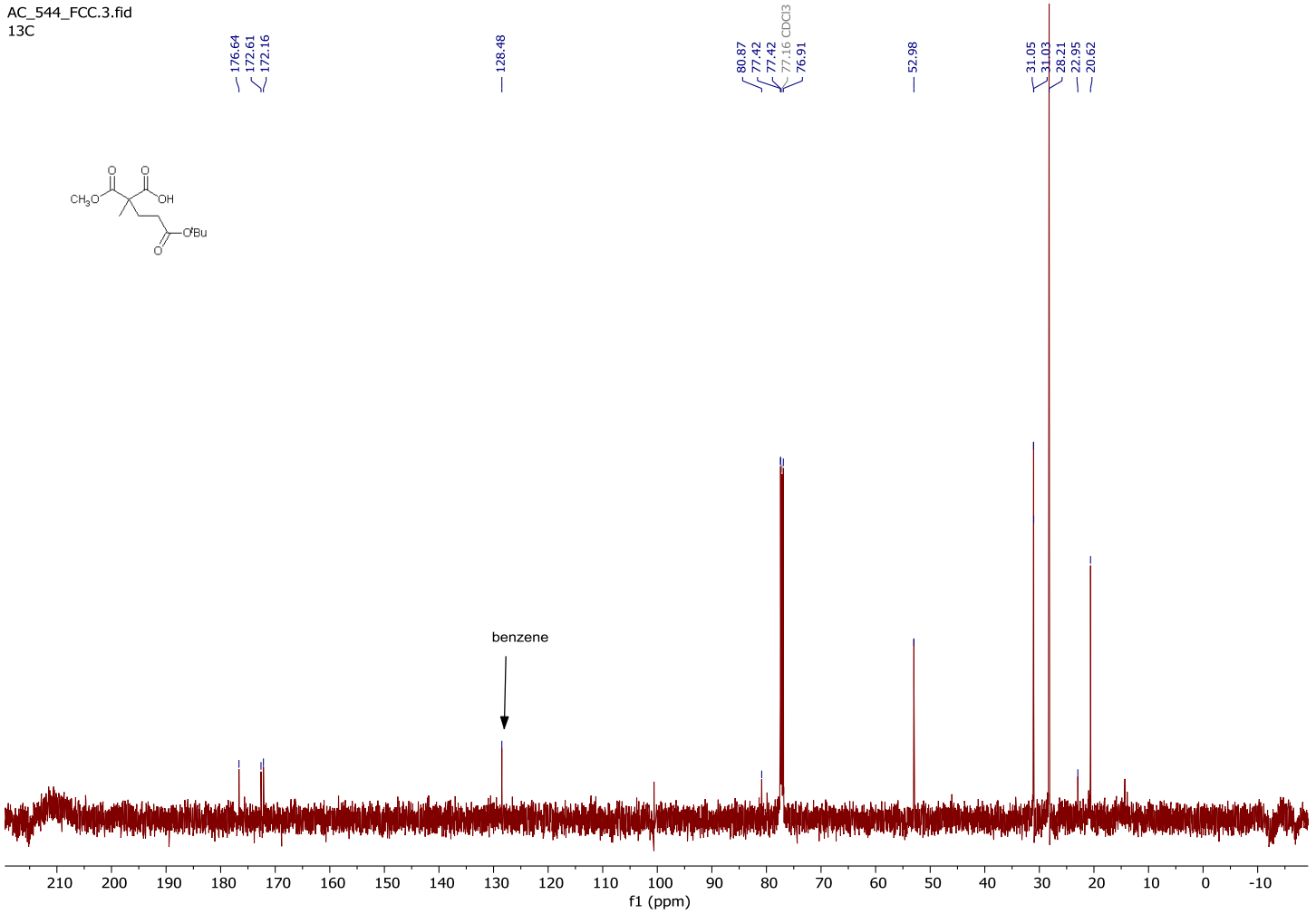
^{13}C NMR (125 MHz, $CDCl_3$) of compound **9**



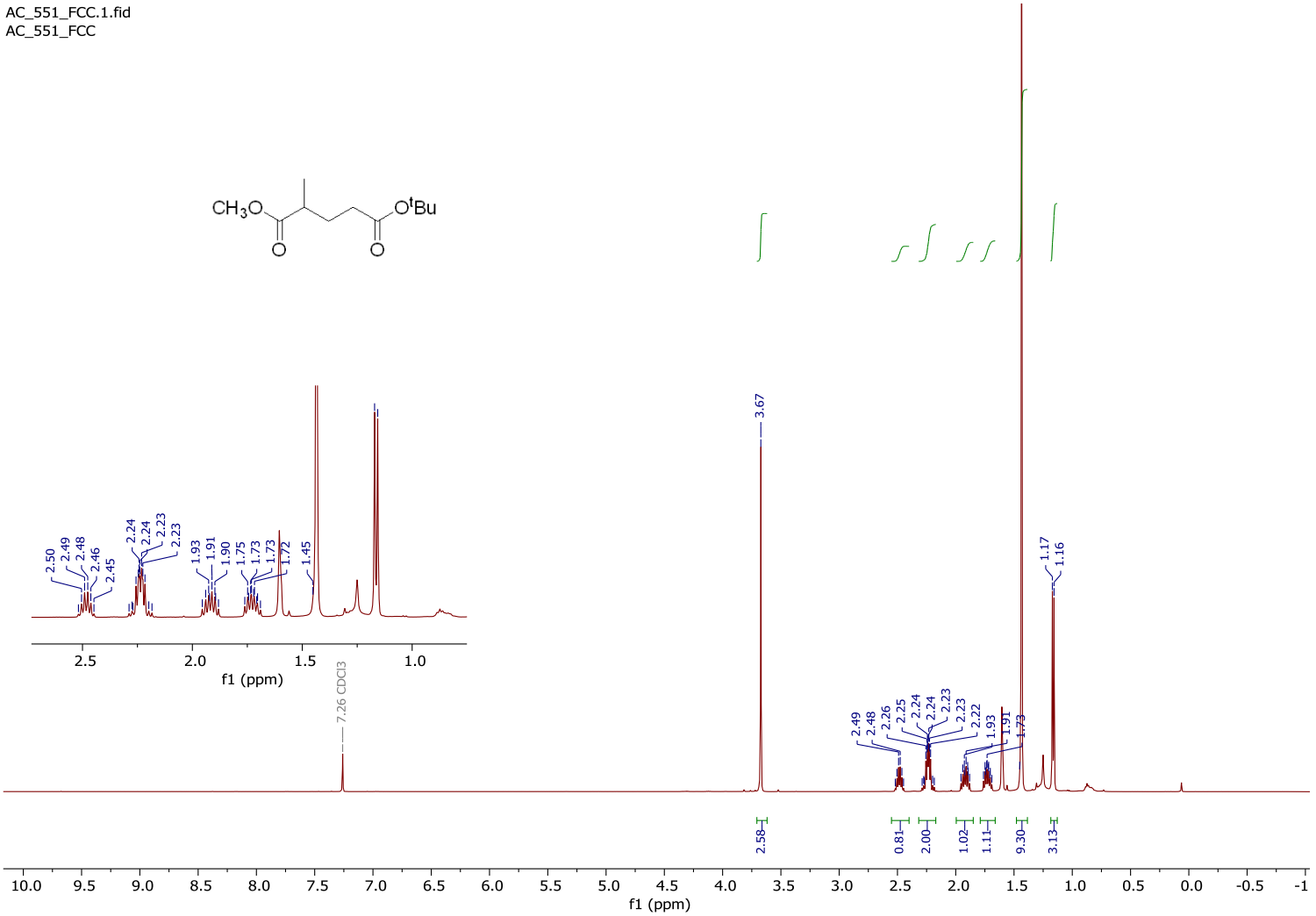
^{1}H NMR (500 MHz, $CDCl_3$) of compound **10**



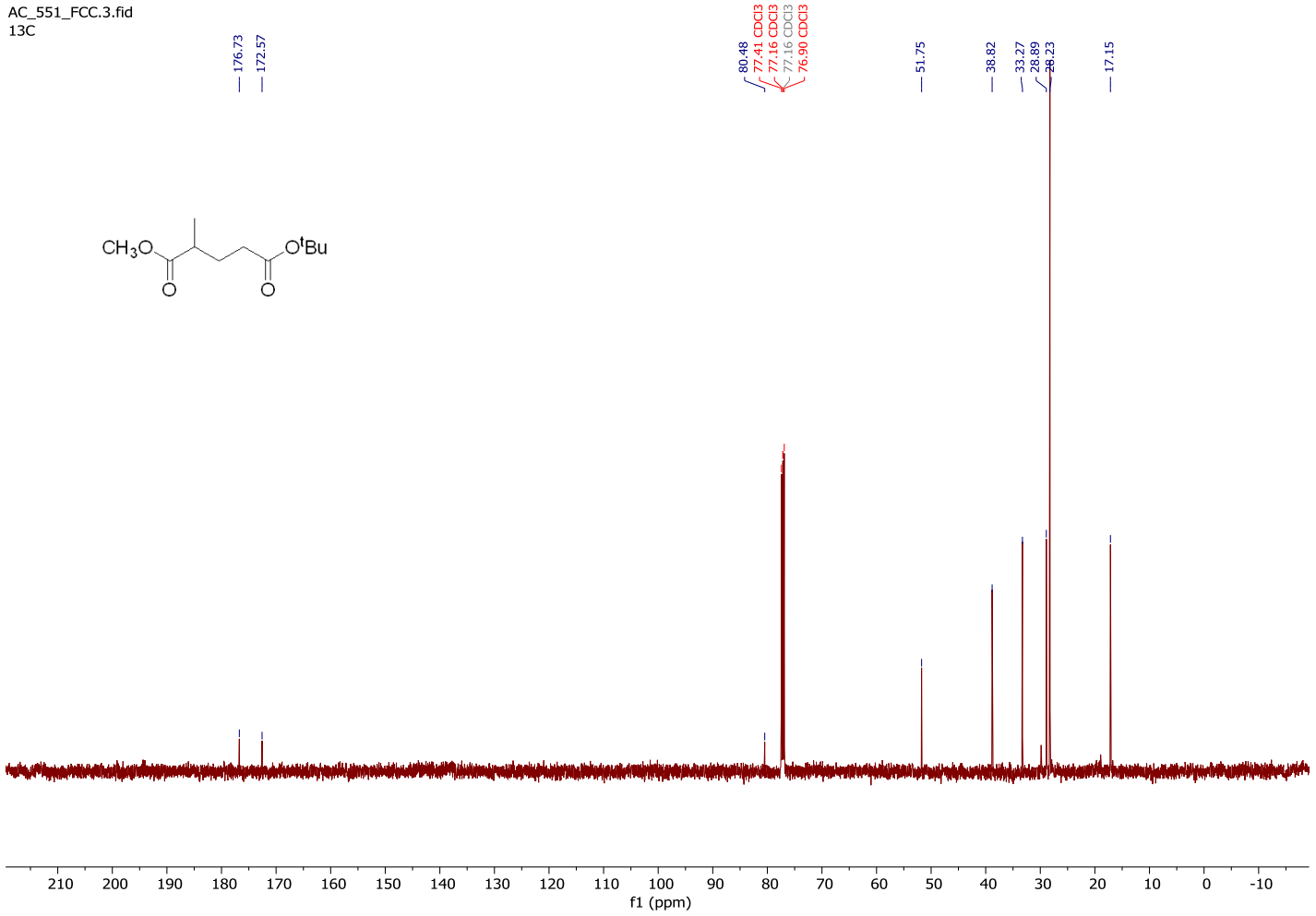
^{13}C NMR (125 MHz, $CDCl_3$) of compound **10**



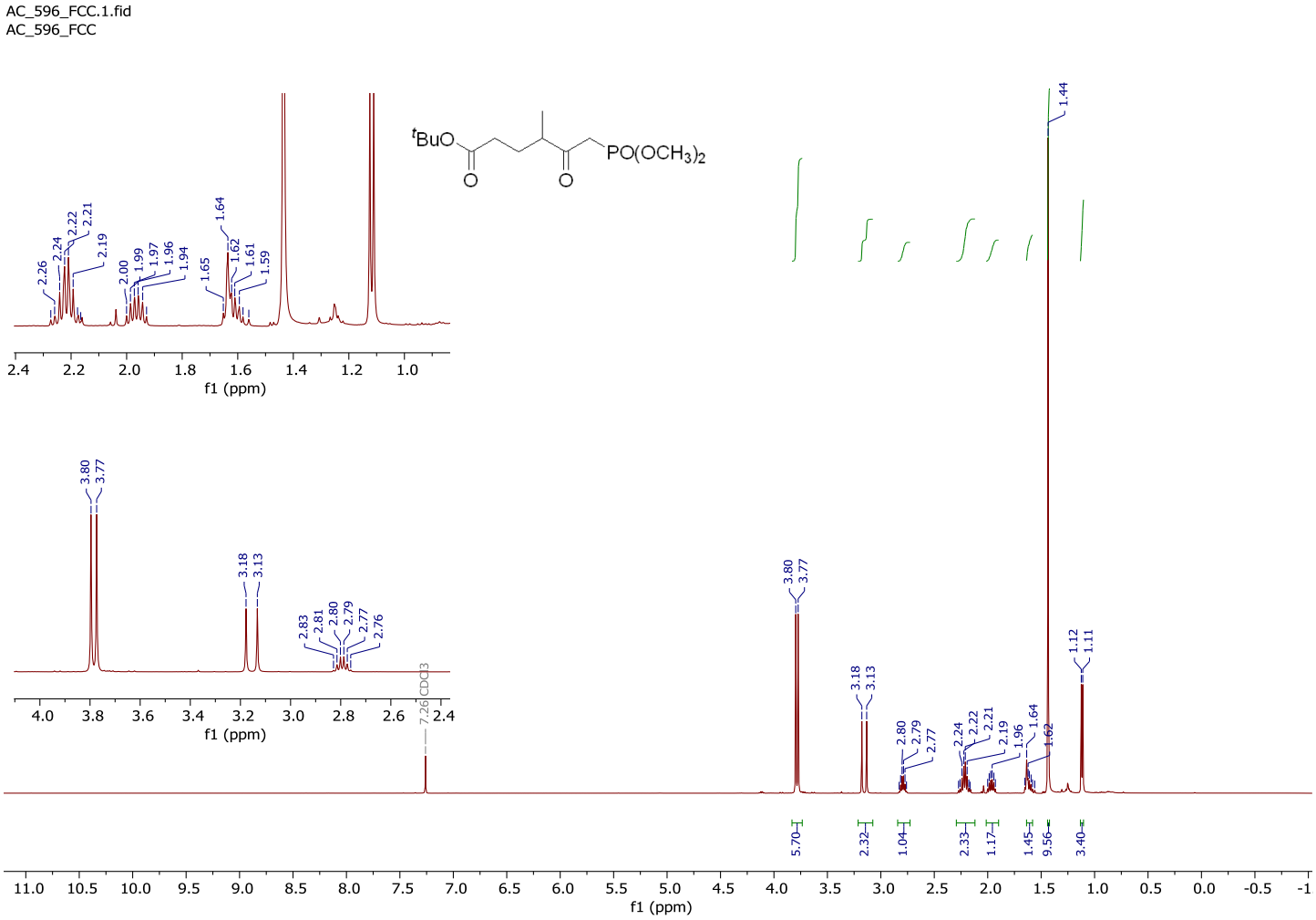
^{1}H NMR (500 MHz, $CDCl_3$) of compound **11**



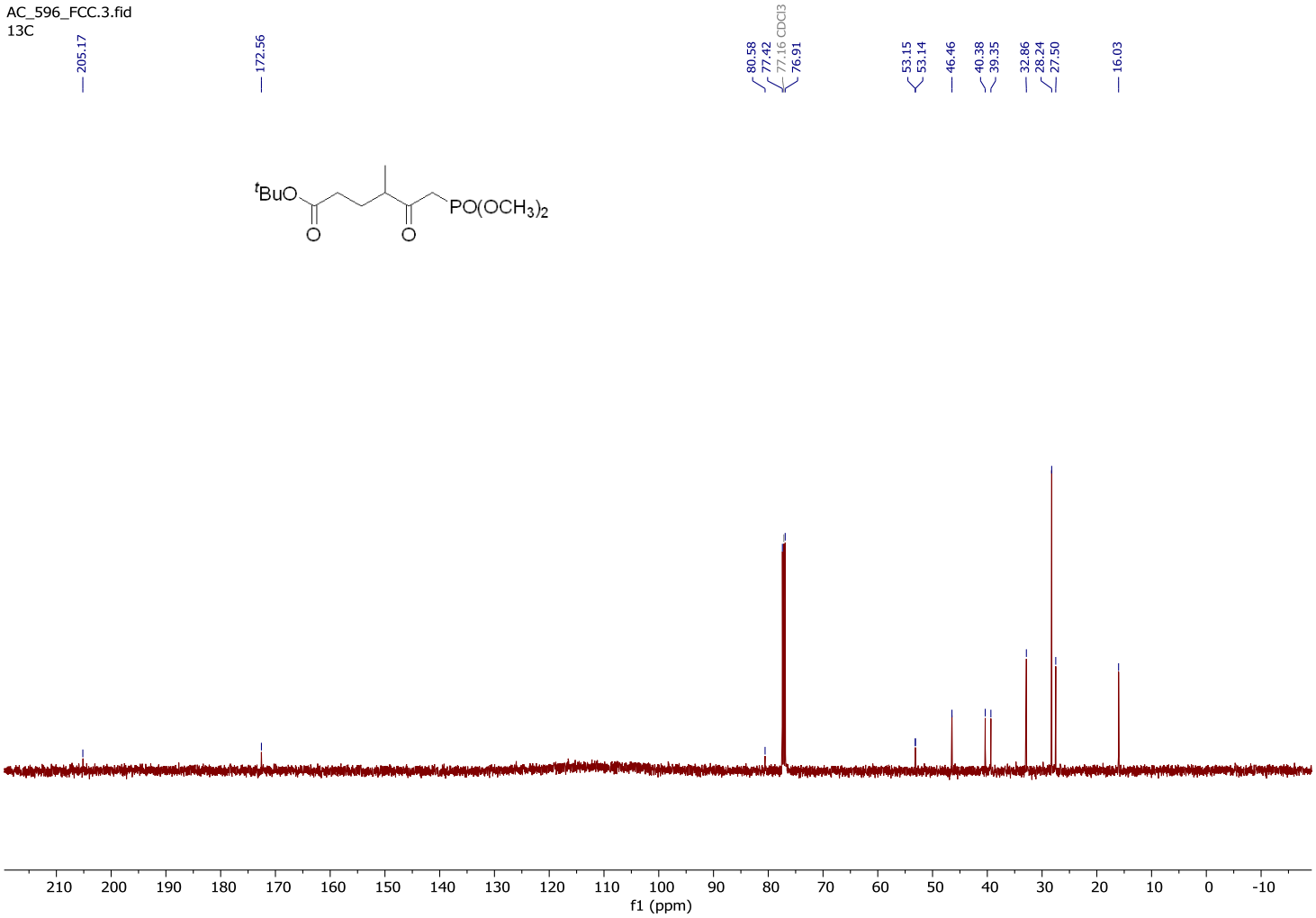
^{13}C NMR (125 MHz, $CDCl_3$) of compound **11**



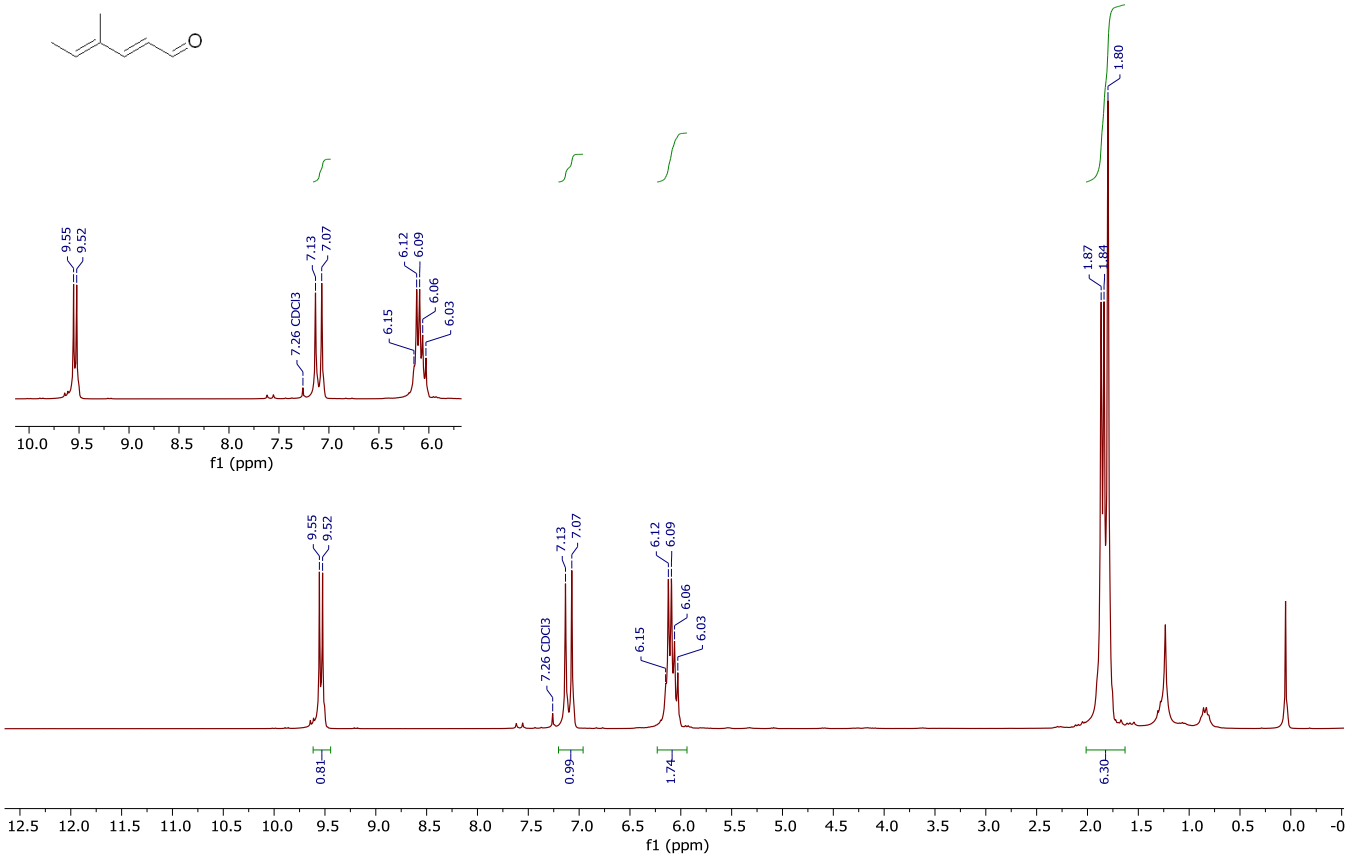
^{1}H NMR (500 MHz, $CDCl_3$) of compound **12**



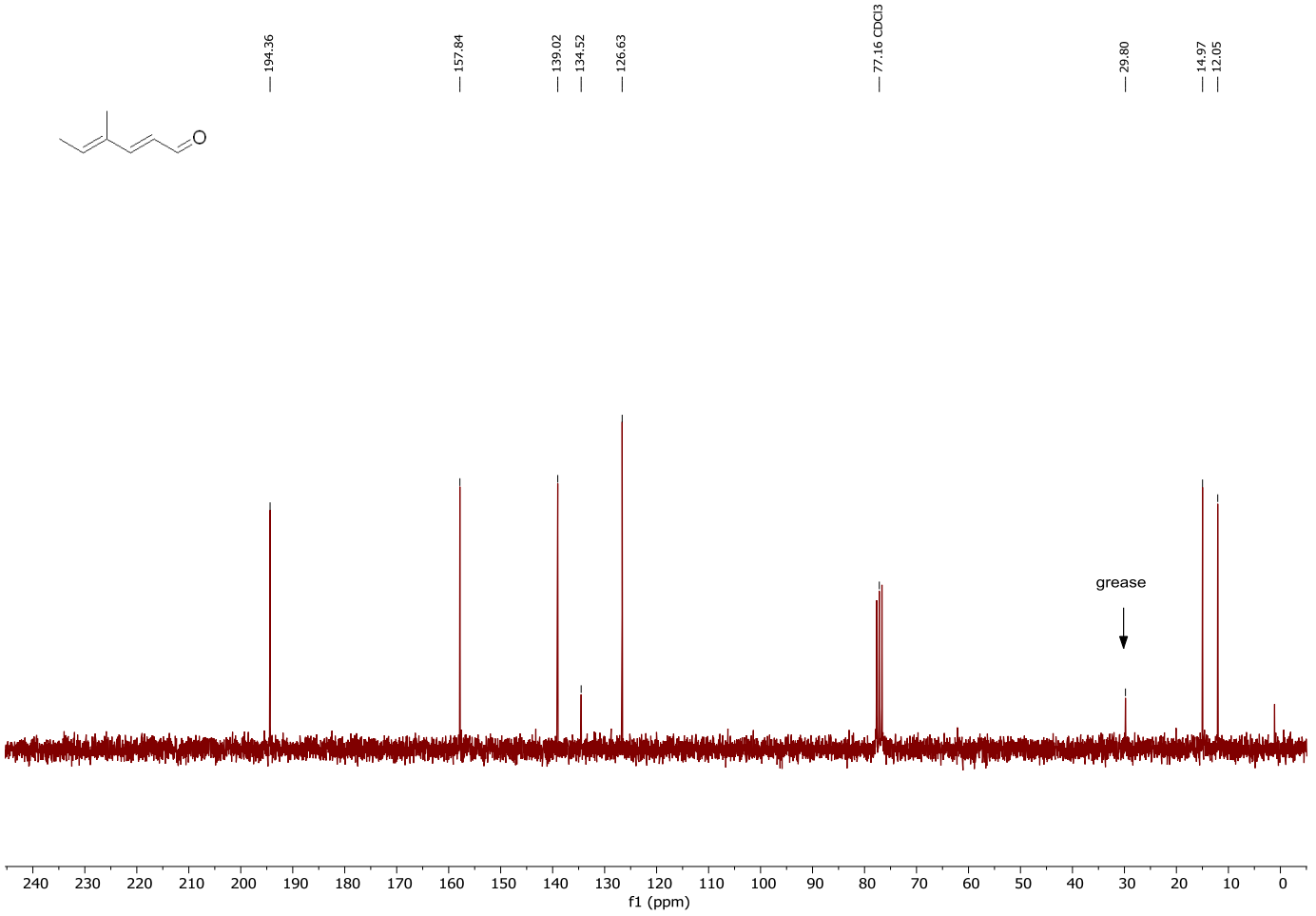
^{13}C NMR (125 MHz, $CDCl_3$) of compound **12**



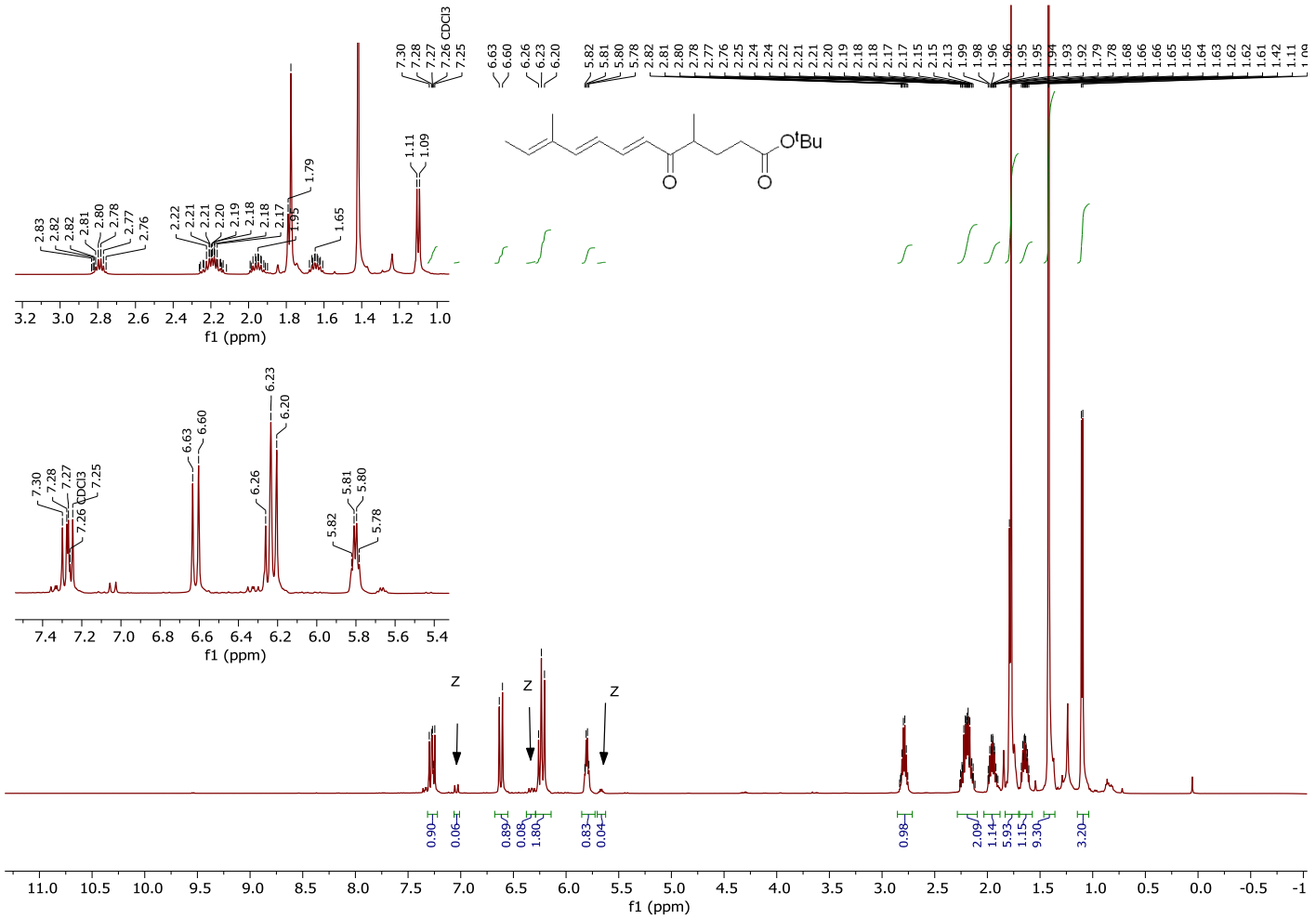
^{1}H NMR (250 MHz, $CDCl_3$) of compound **13**



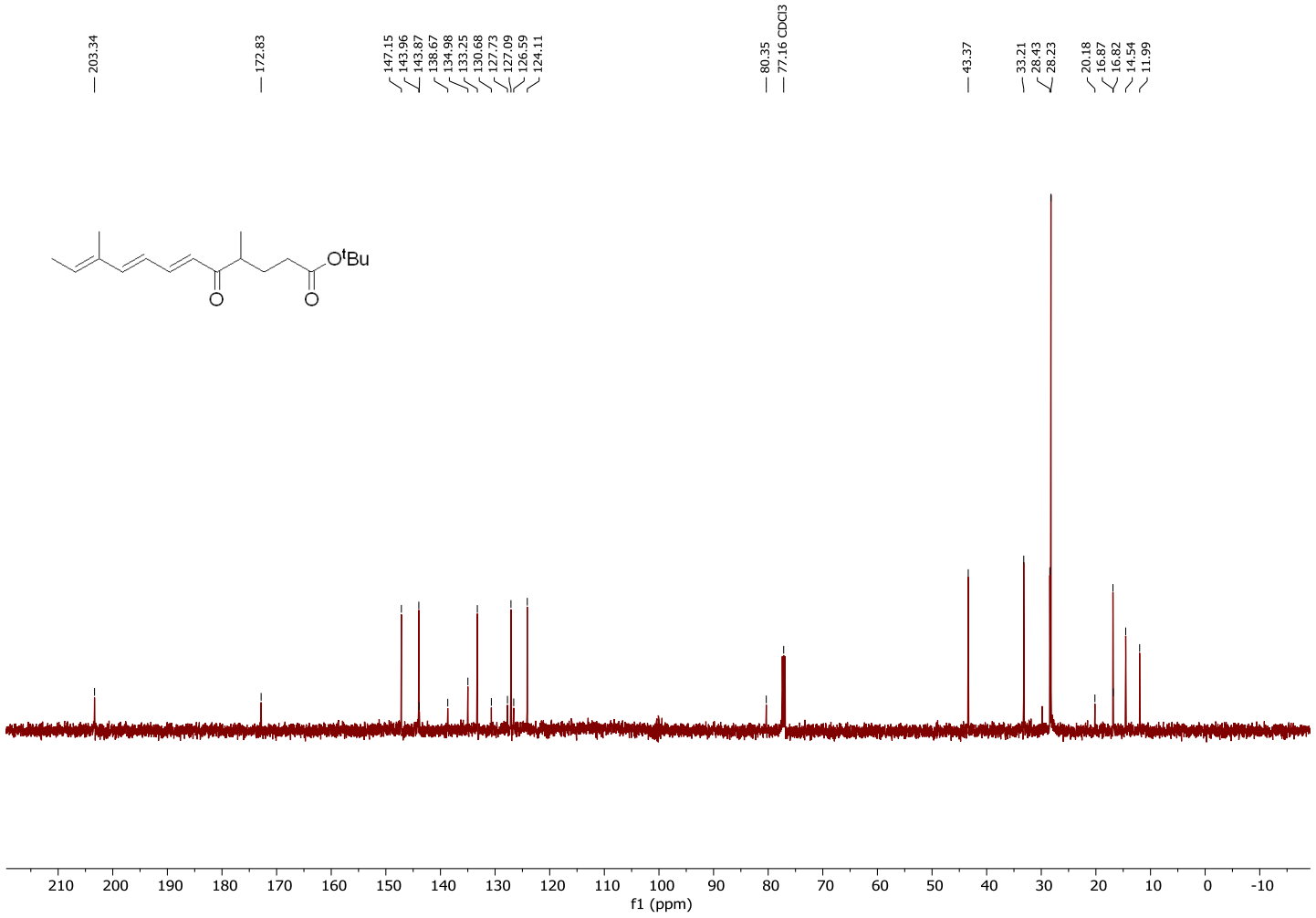
^{13}C NMR (63 MHz, $CDCl_3$) of compound **13**



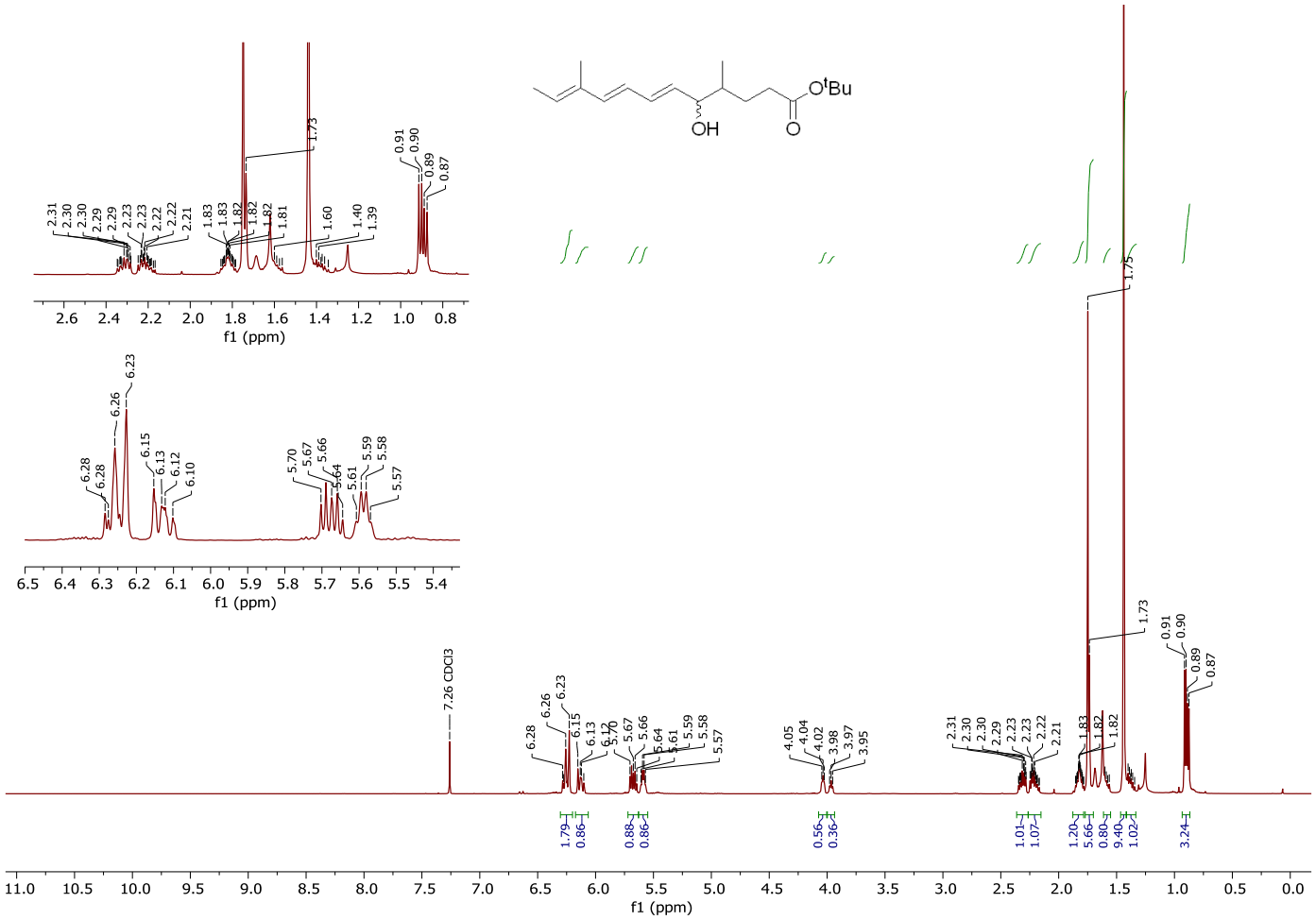
^{1}H NMR (500 MHz, $CDCl_3$) of compound **14**



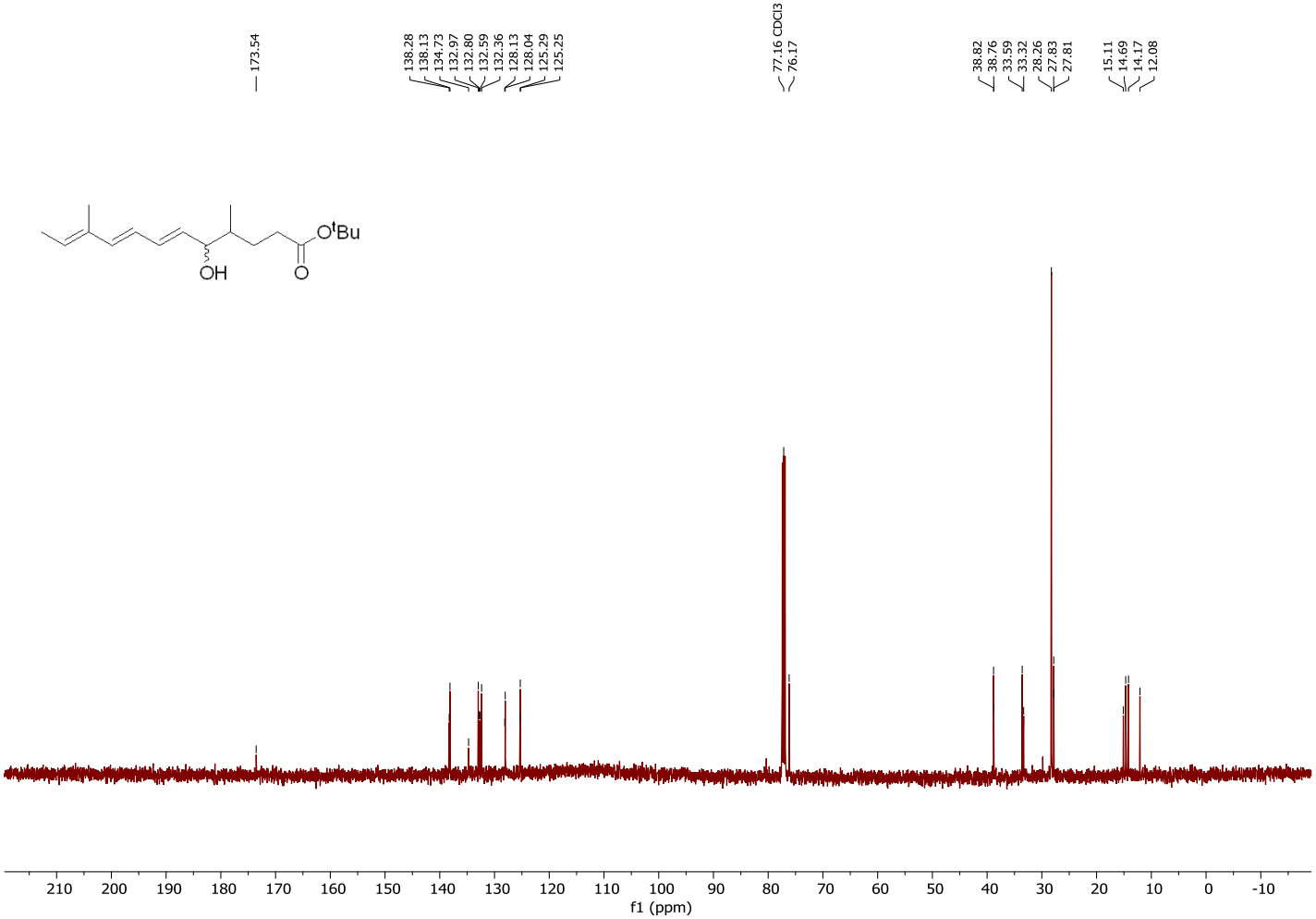
^{13}C NMR (125 MHz, $CDCl_3$) of compound **14**



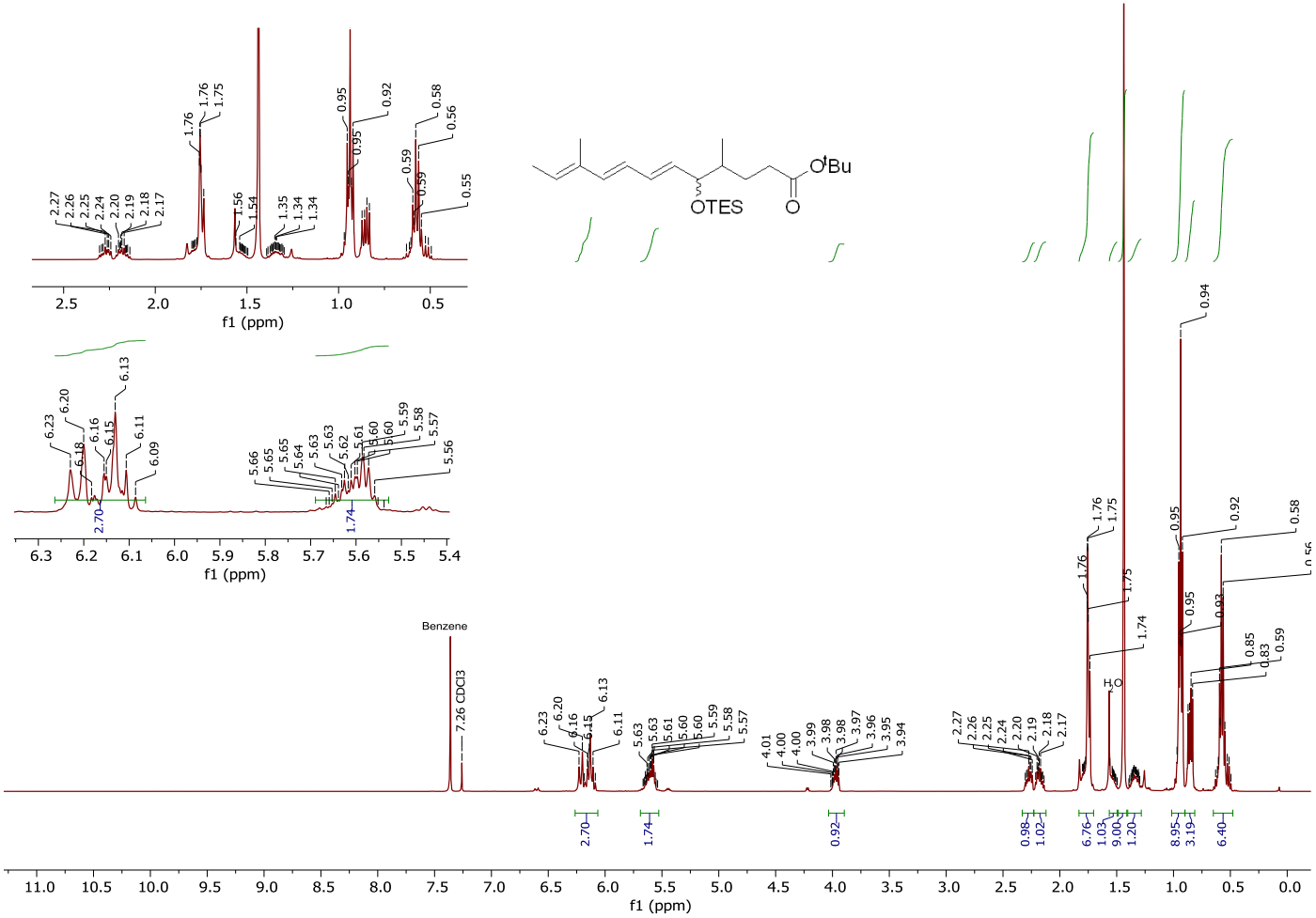
^{1}H NMR (500 MHz, $CDCl_3$) of compound **15**



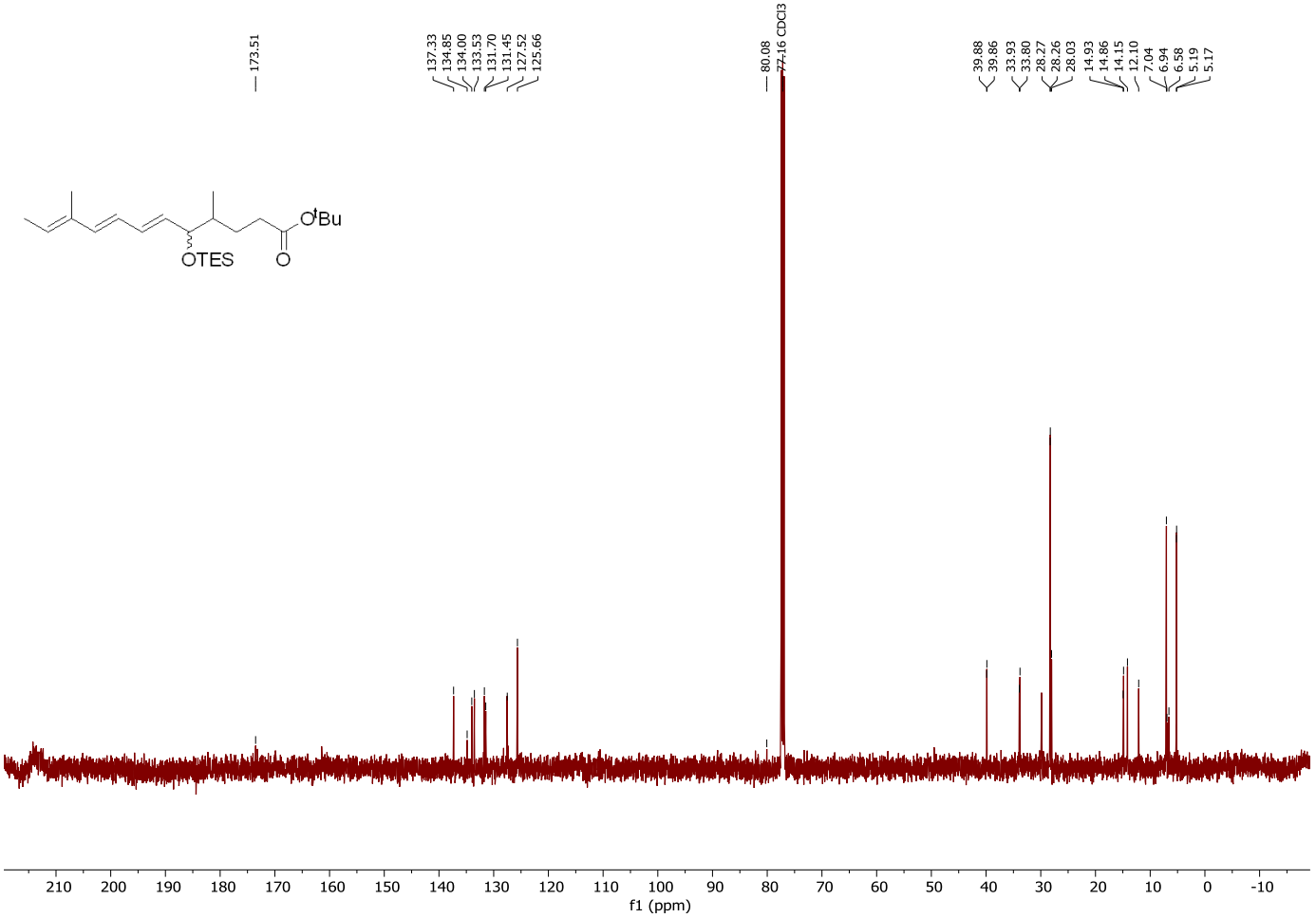
^{13}C NMR (125 MHz, $CDCl_3$) of compound **15**



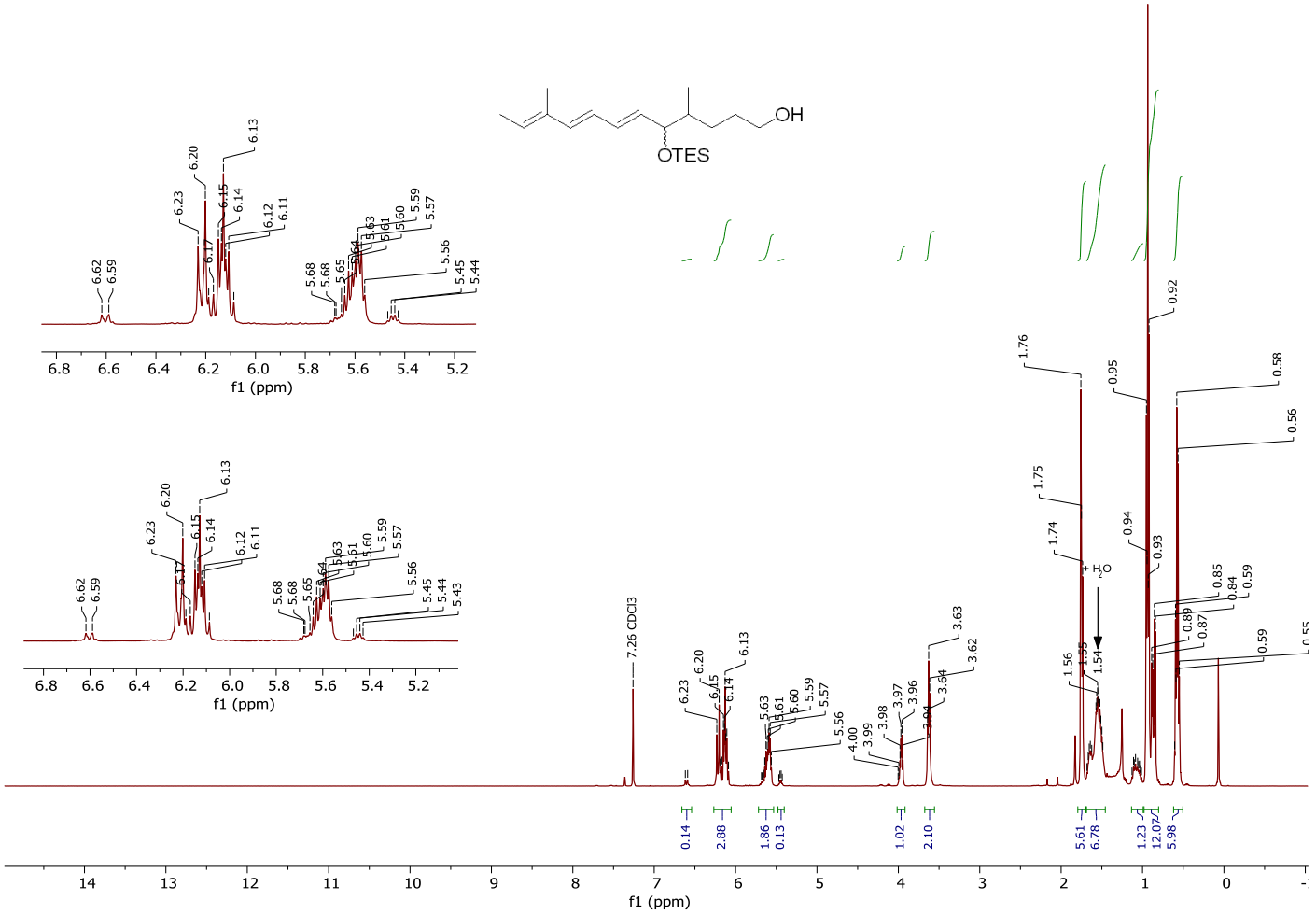
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16**



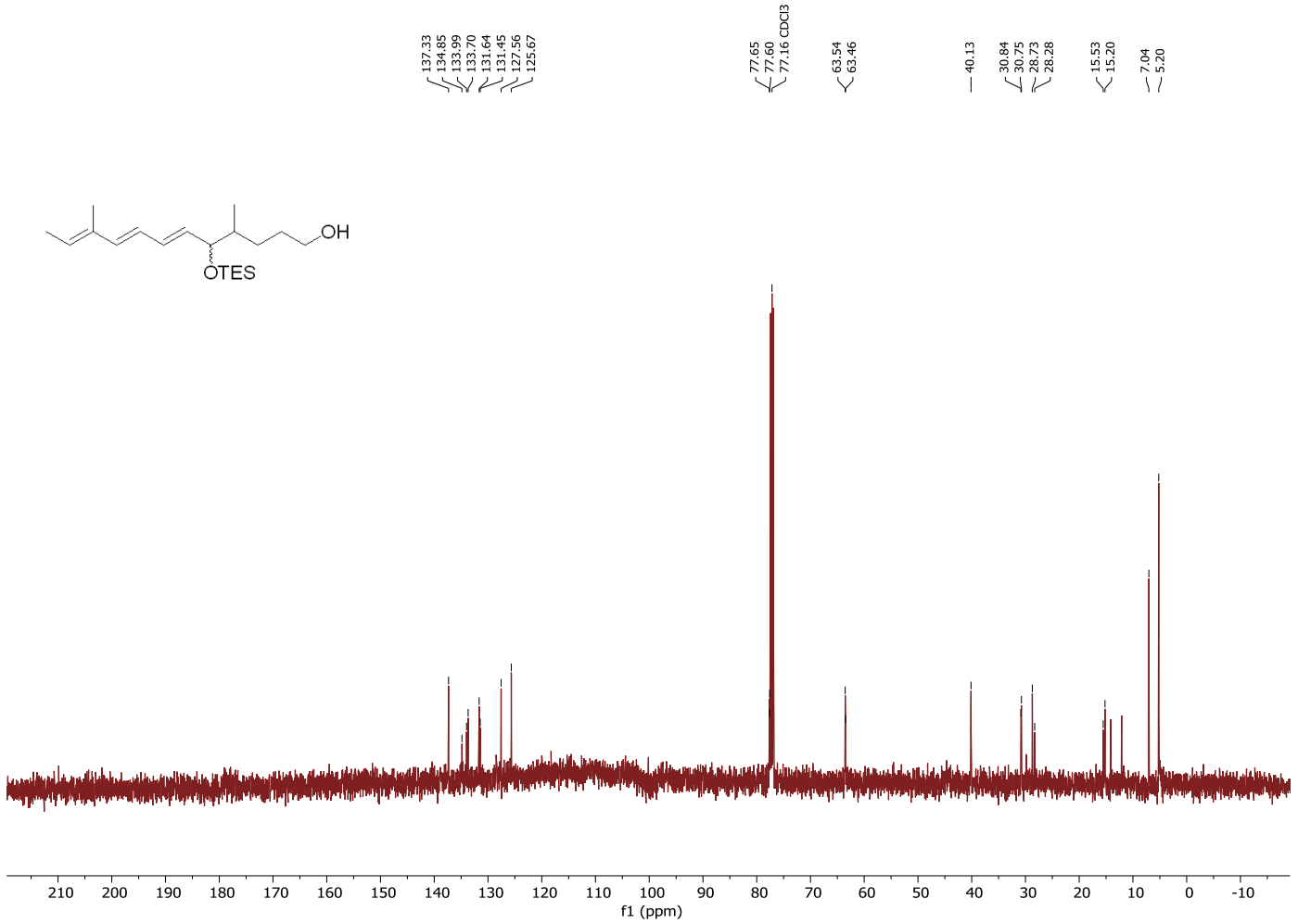
^{13}C NMR (125 MHz, $CDCl_3$) of compound **16**



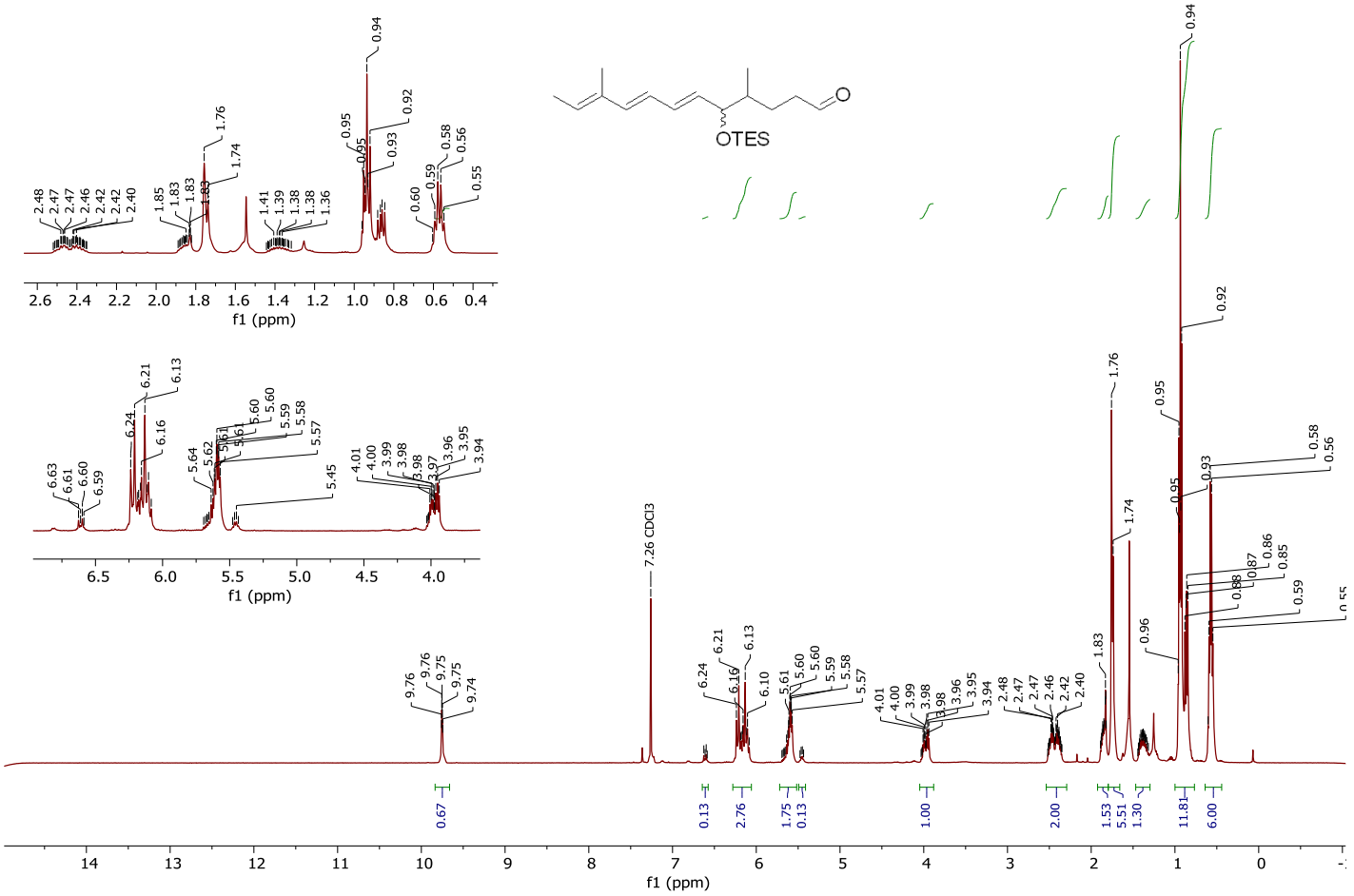
^{1}H NMR (500 MHz, $CDCl_3$) of compound **17**



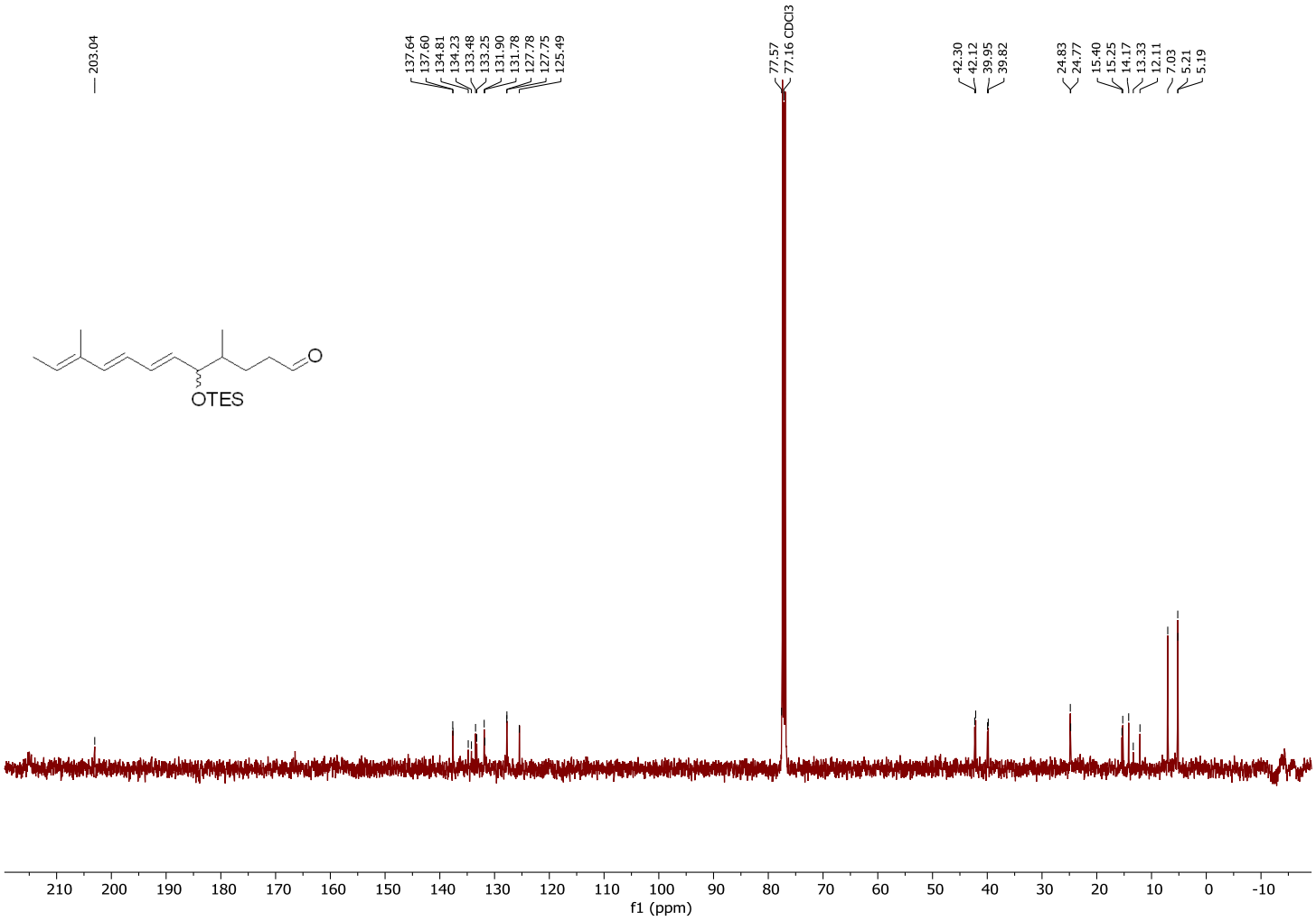
^{13}C NMR (125 MHz, $CDCl_3$) of compound **17**



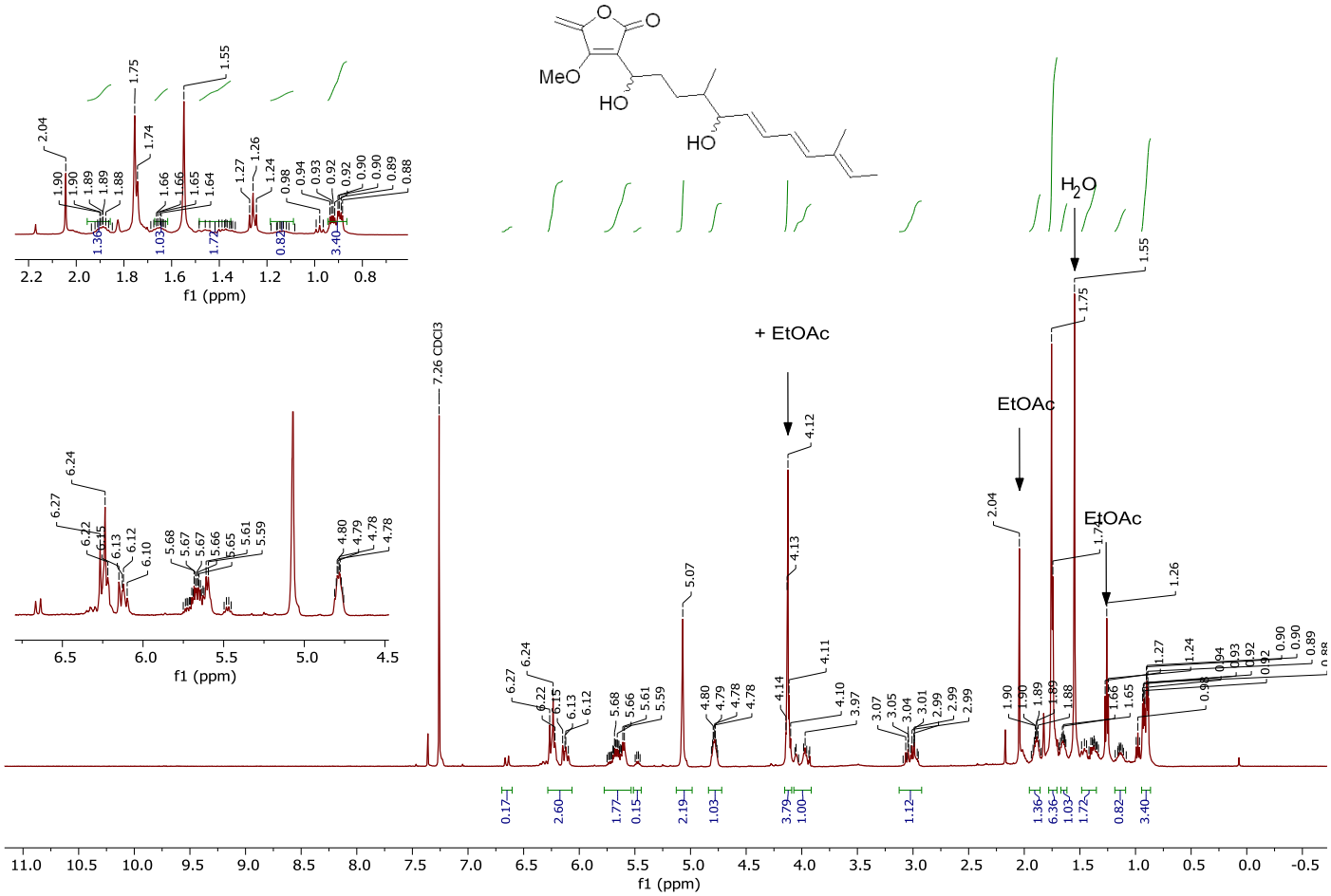
^{1}H NMR (500 MHz, $CDCl_3$) of compound **18**



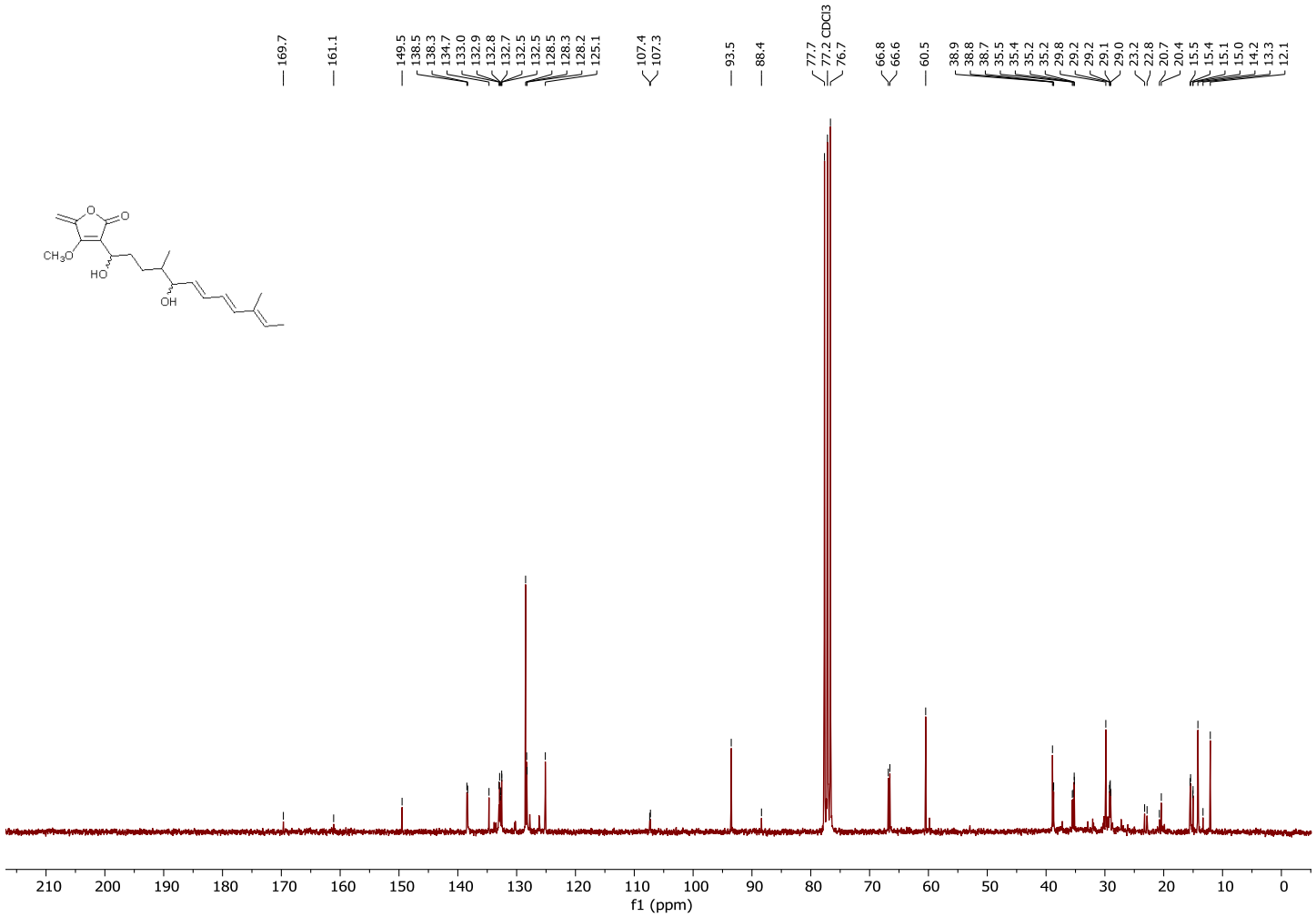
^{13}C NMR (125 MHz, $CDCl_3$) of compound **18**



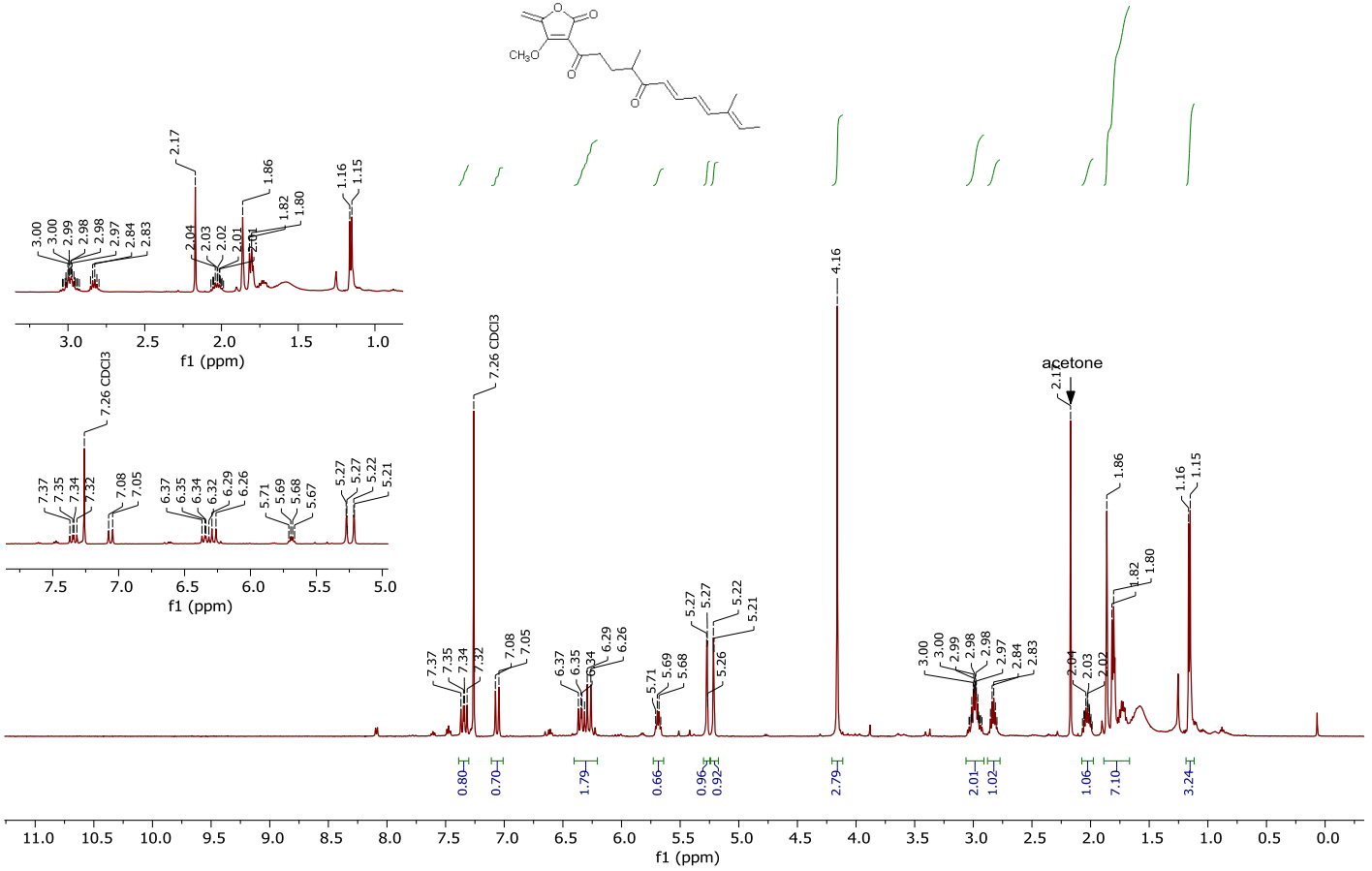
^{1}H NMR (500 MHz, $CDCl_3$) of compound **20**



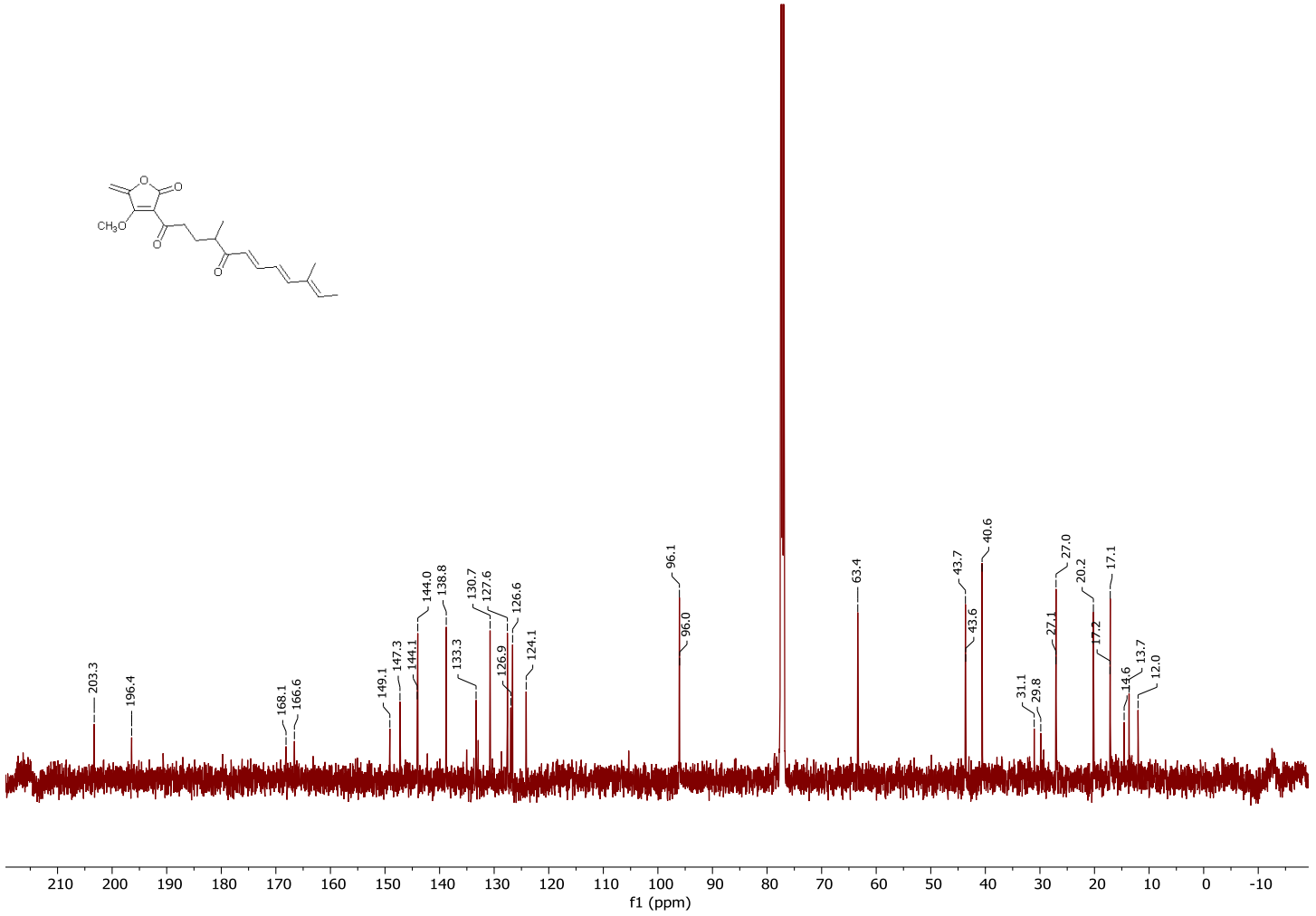
^{13}C NMR (63 MHz, $CDCl_3$) of compound **20**



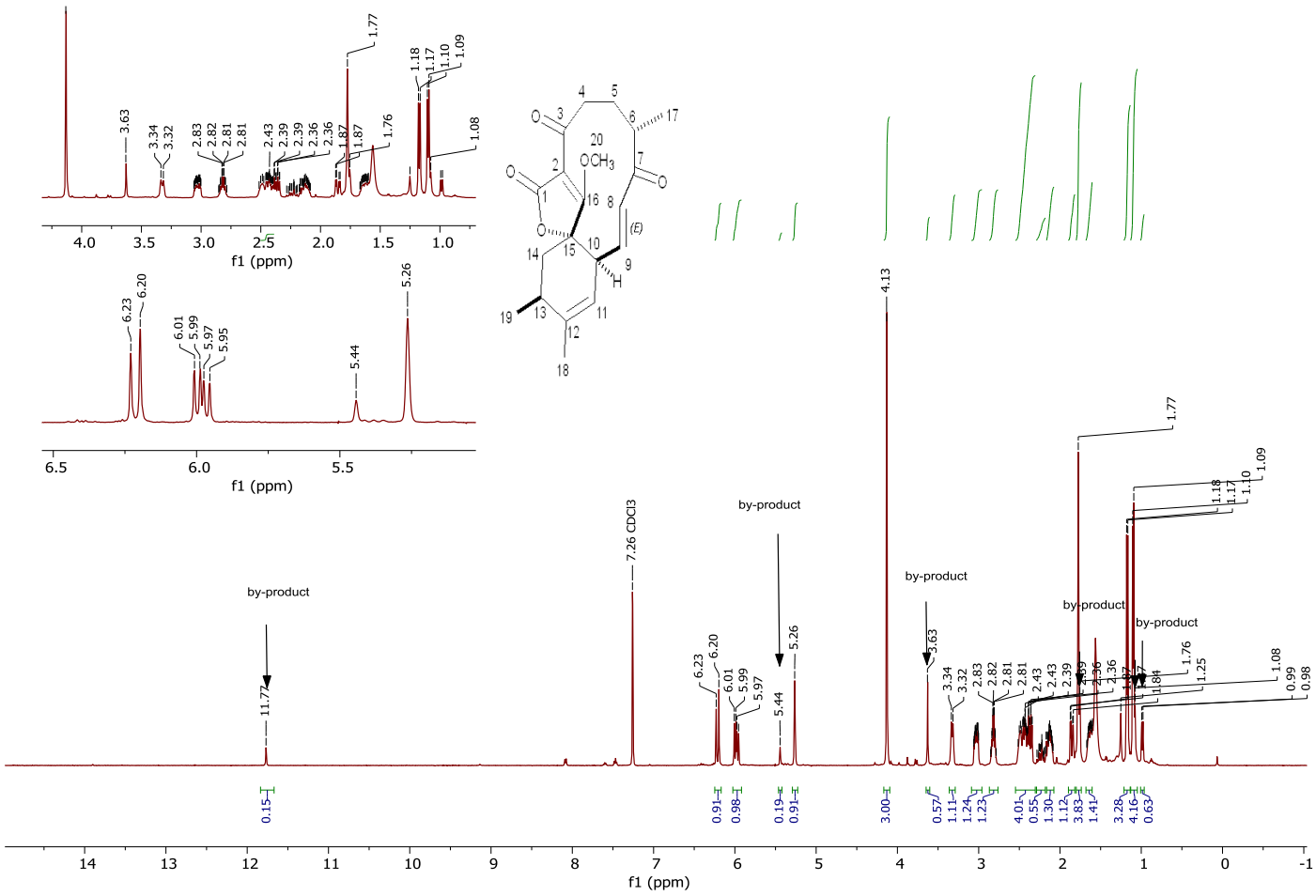
^{1}H NMR (500 MHz, $CDCl_3$) of compound (±)-**7**



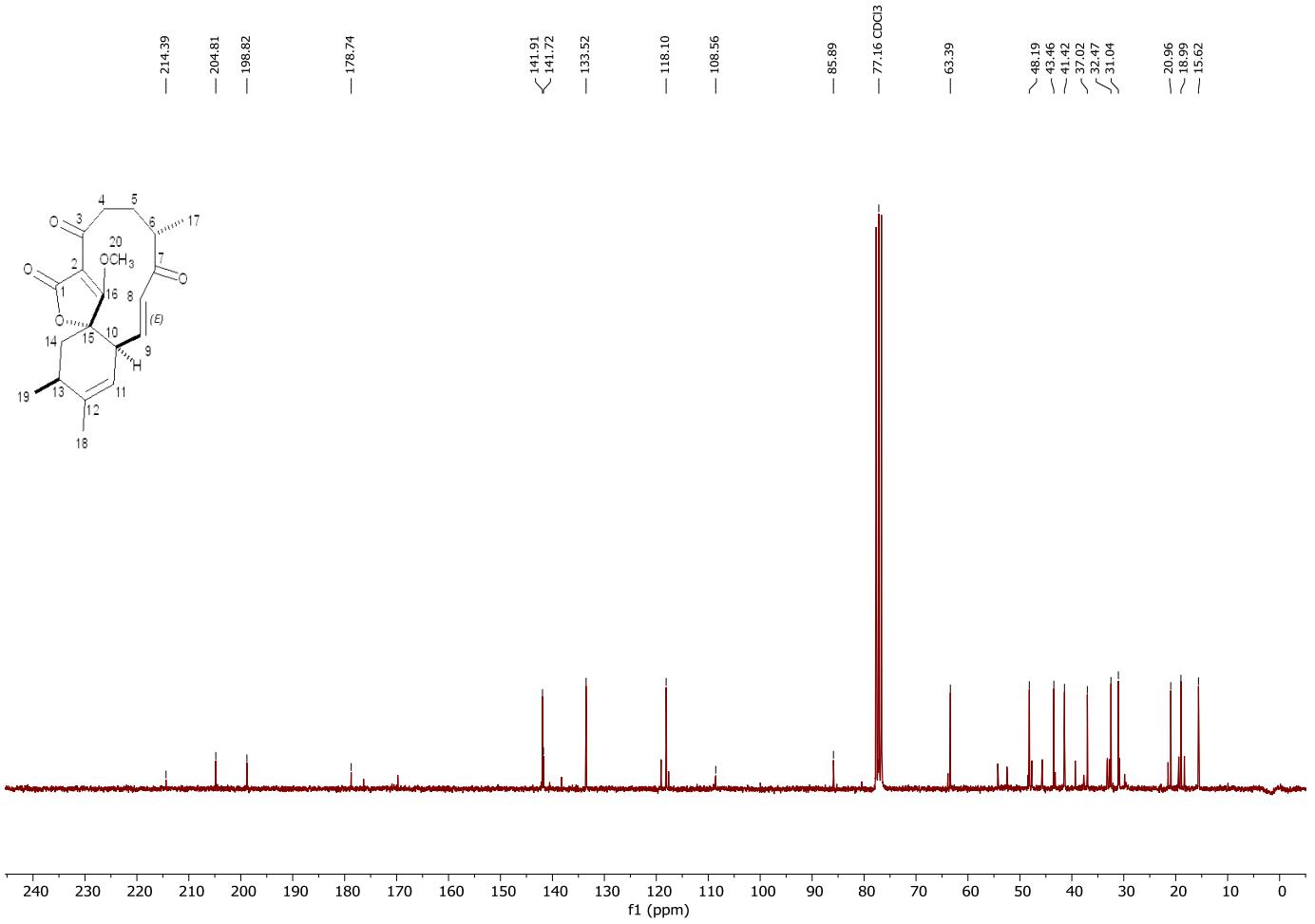
^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**7**



^{1}H NMR (500 MHz, $CDCl_3$) of compound (±)-**6**

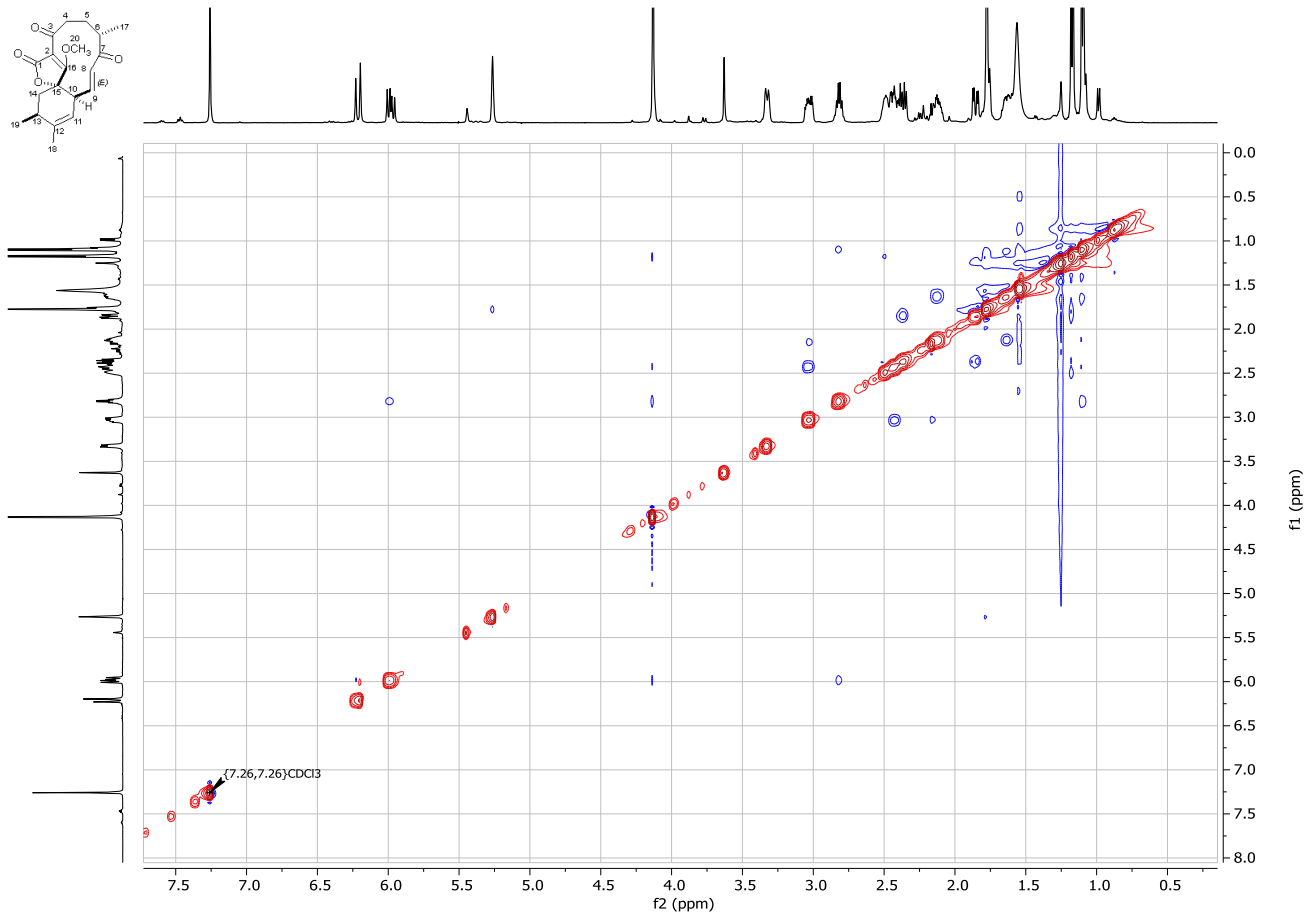


^{13}C NMR (125 MHz, $CDCl_3$) of compound (±)-**6**

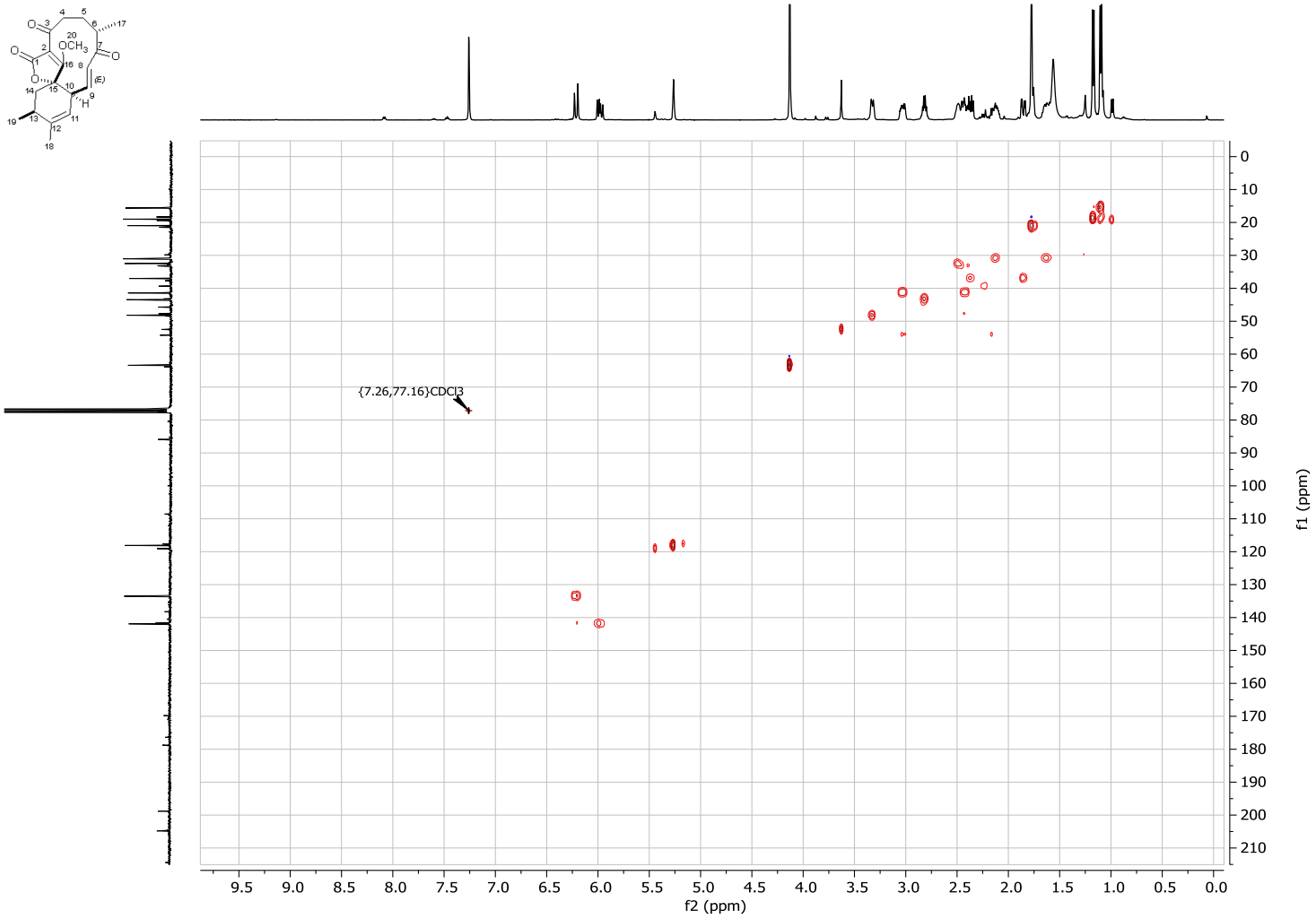


^{1}H-^{1}H COSY of compound (±)-**6**

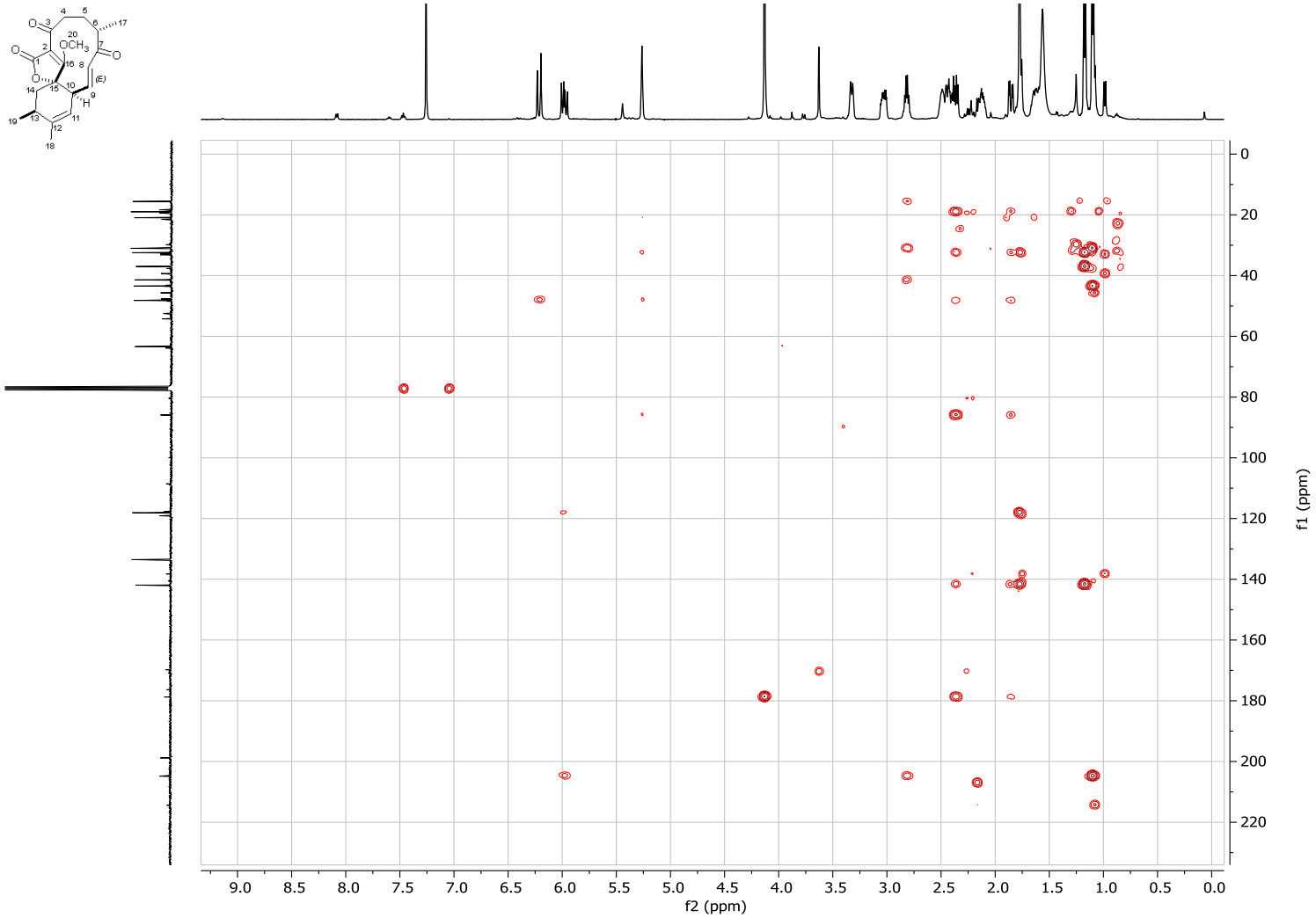
^{1}H-^{1}H NOESY of compound (±)-**6**



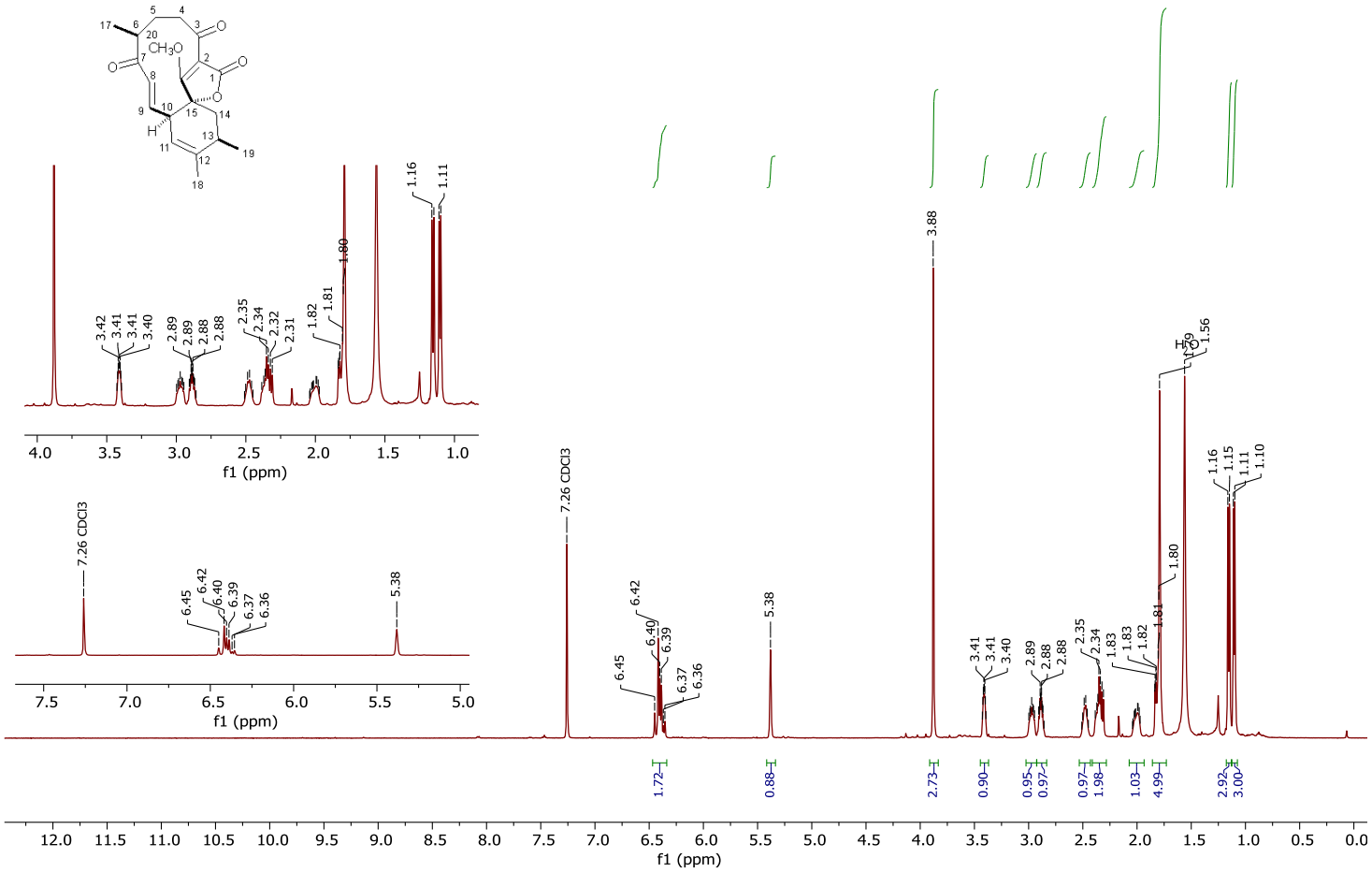
^{1}H-^{13}C HSQC of compound (±)-**6**



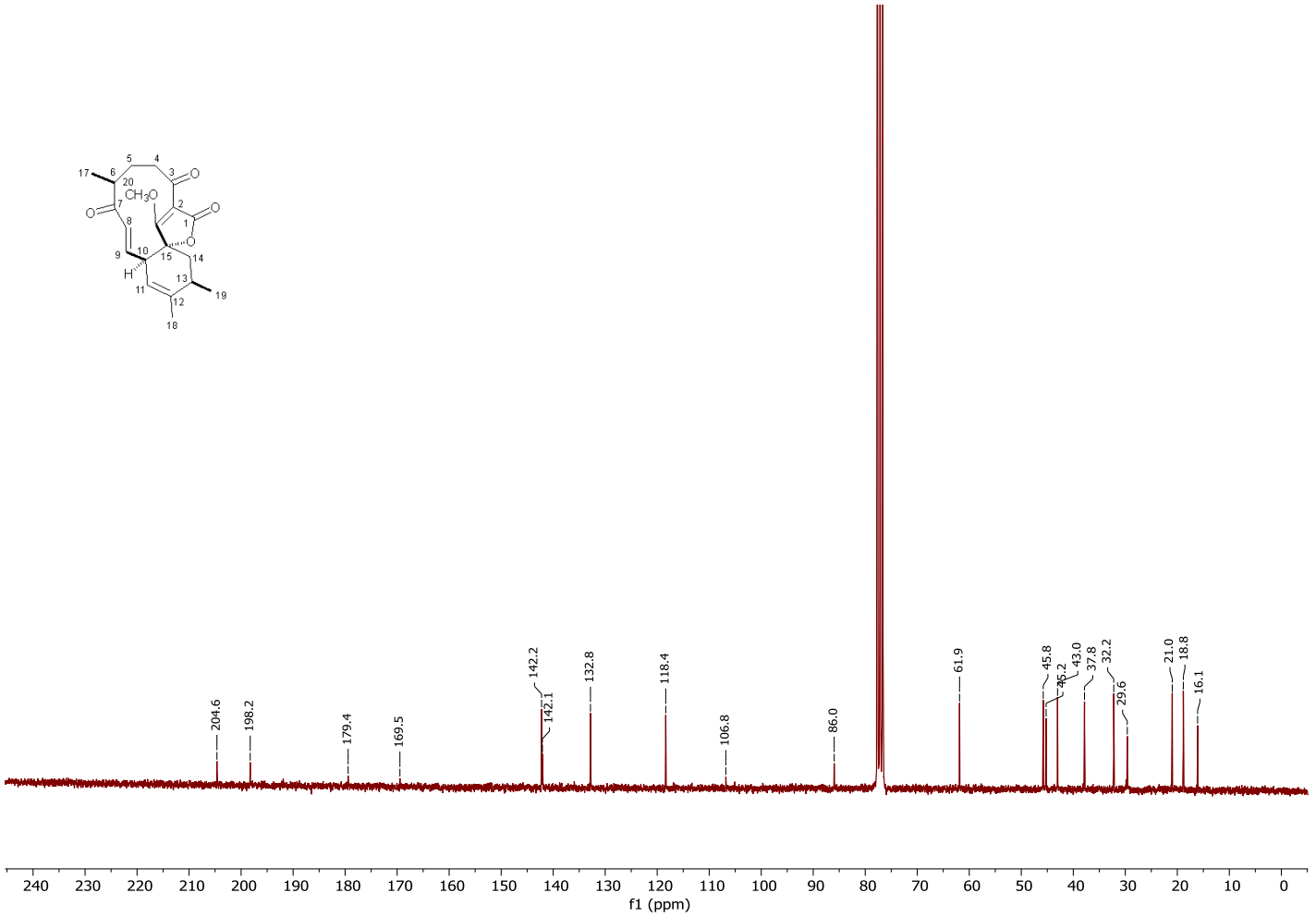
^{1}H-^{13}C HMBC of compound (±)-**6**



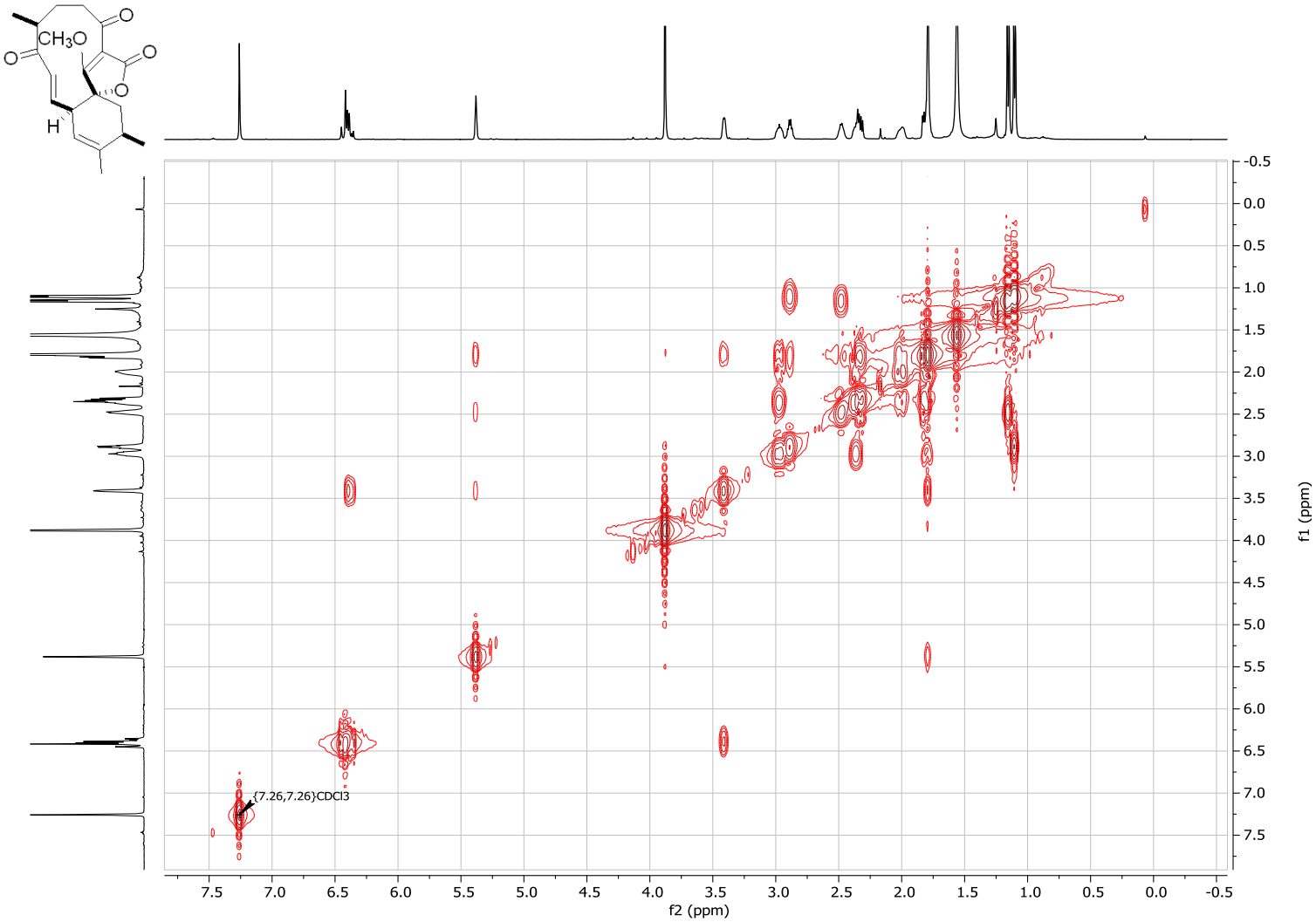
^{1}H NMR (500 MHz, $CDCl_3$) of compound **21**



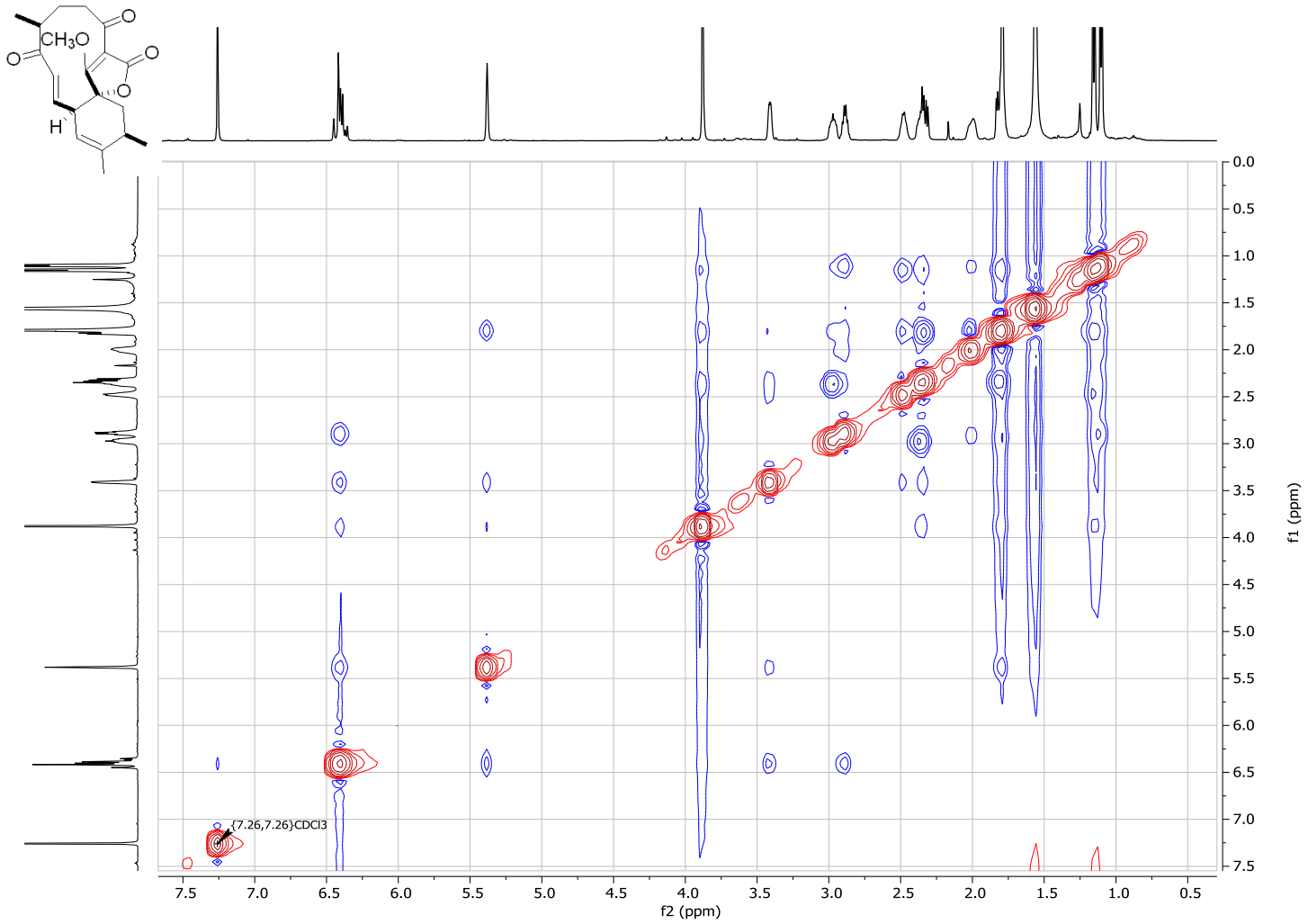
^{13}C NMR (125 MHz, $CDCl_3$) of compound **21**



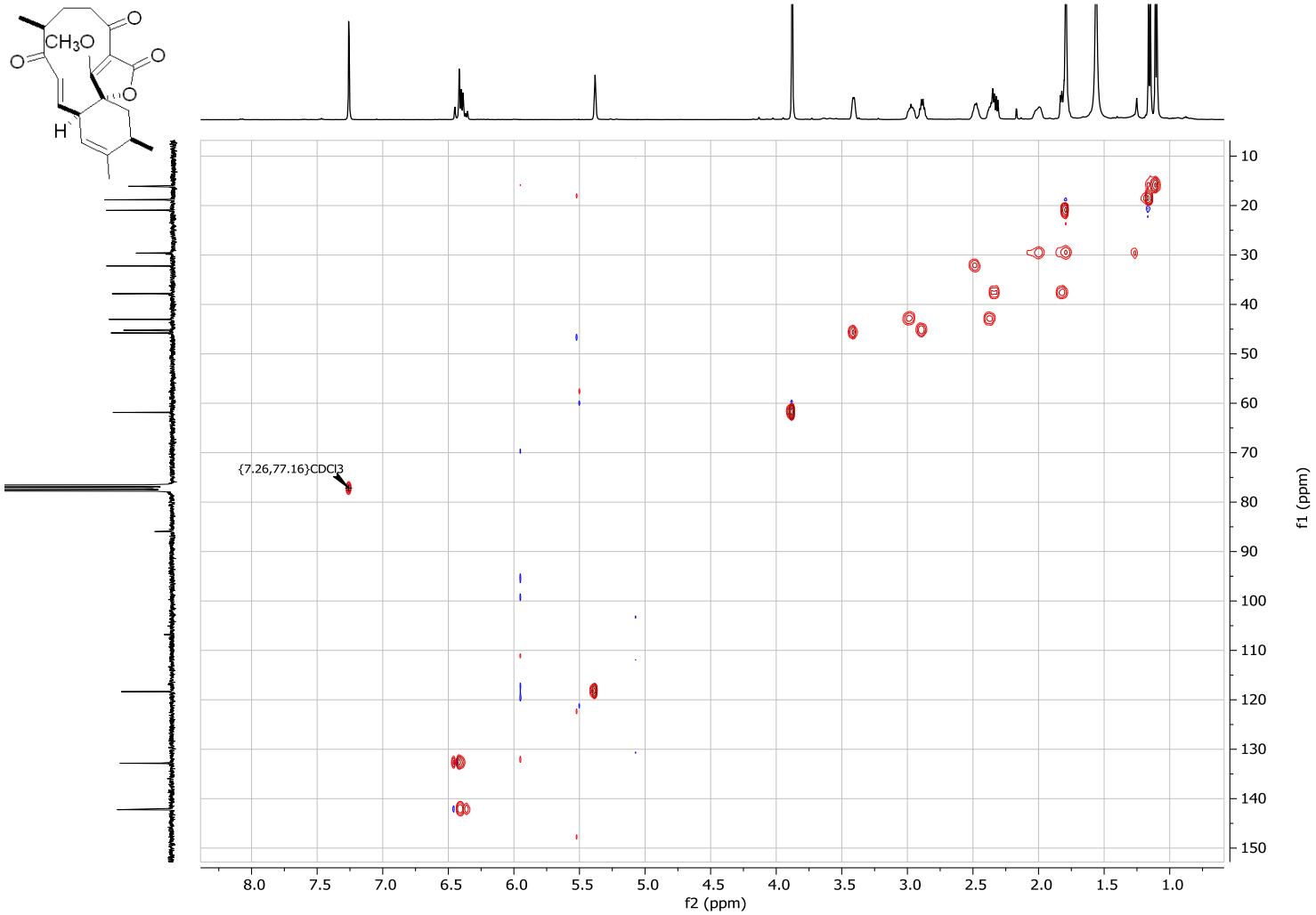
^{1}H-^{1}H COSY of compound **21**



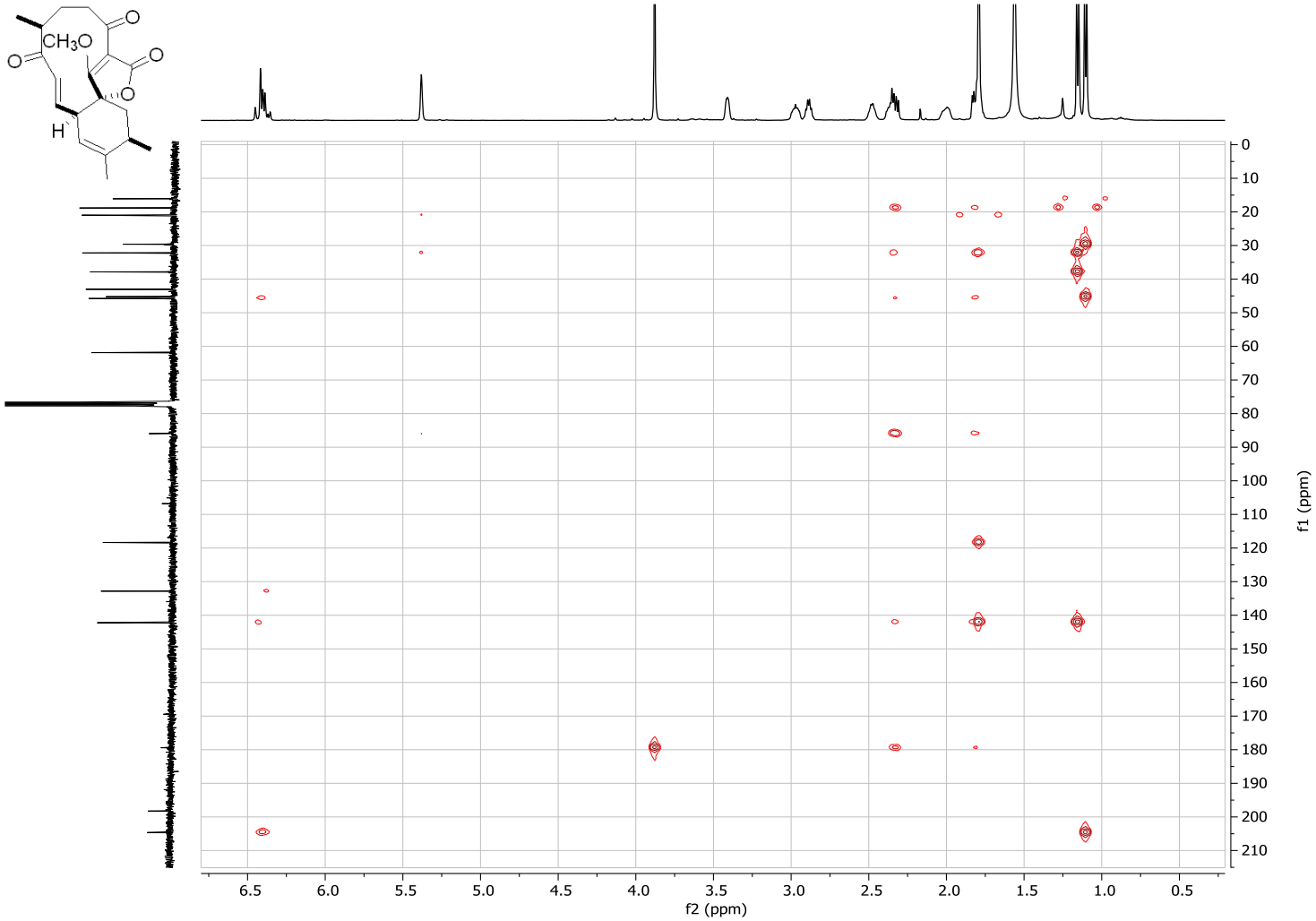
^{1}H-^{1}H NOESY of compound **21**



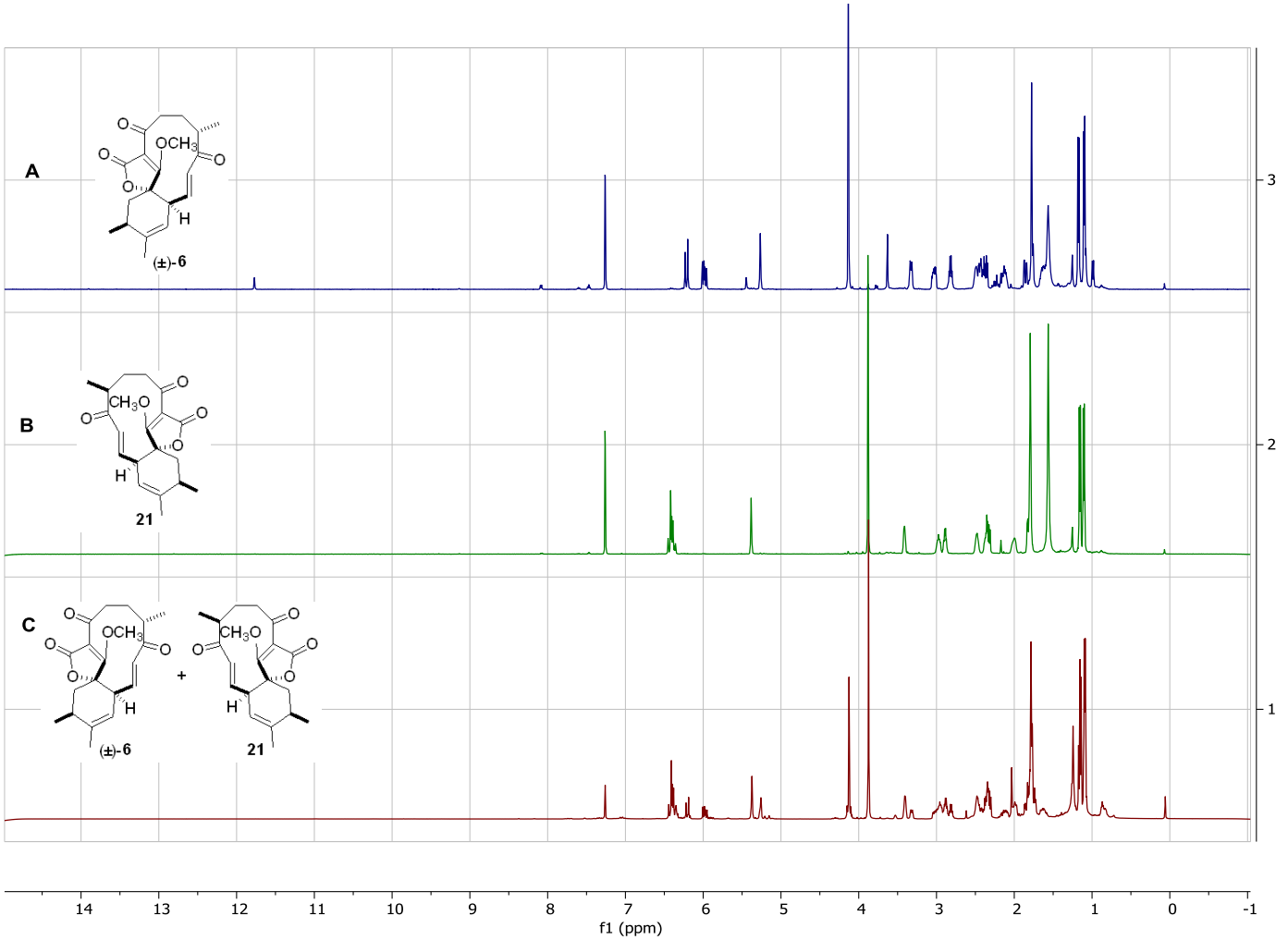
^{1}H-^{13}C HSQC of compound **21**



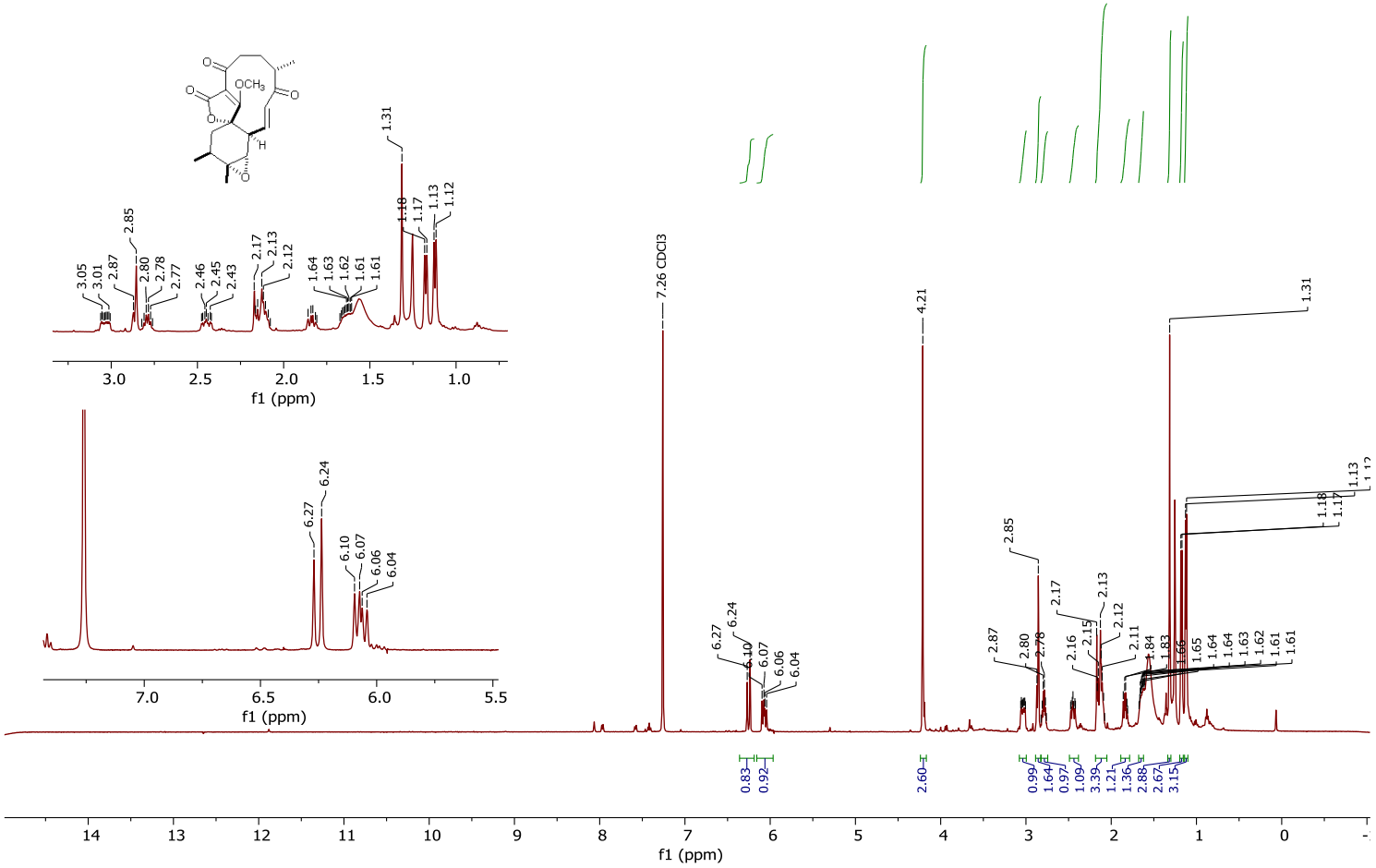
^{1}H-^{13}C HMBC of compound **21**



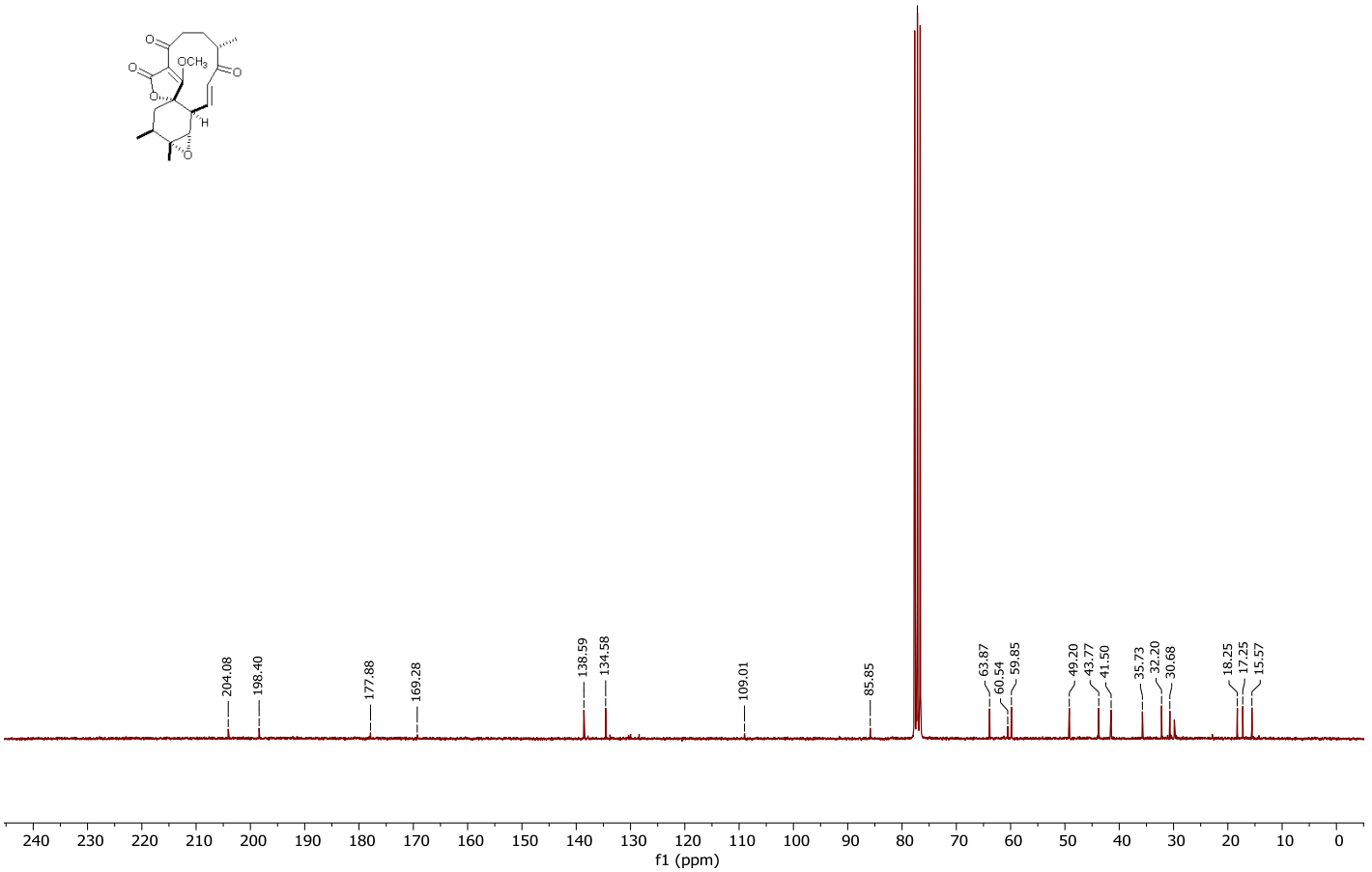
Comparison of ^{1}H NMR spectra of purified compounds (±)-**6** (A) and **21** (B) and the mixture (±)-**6**/**21** (C) before preparative thin layer chromatography.



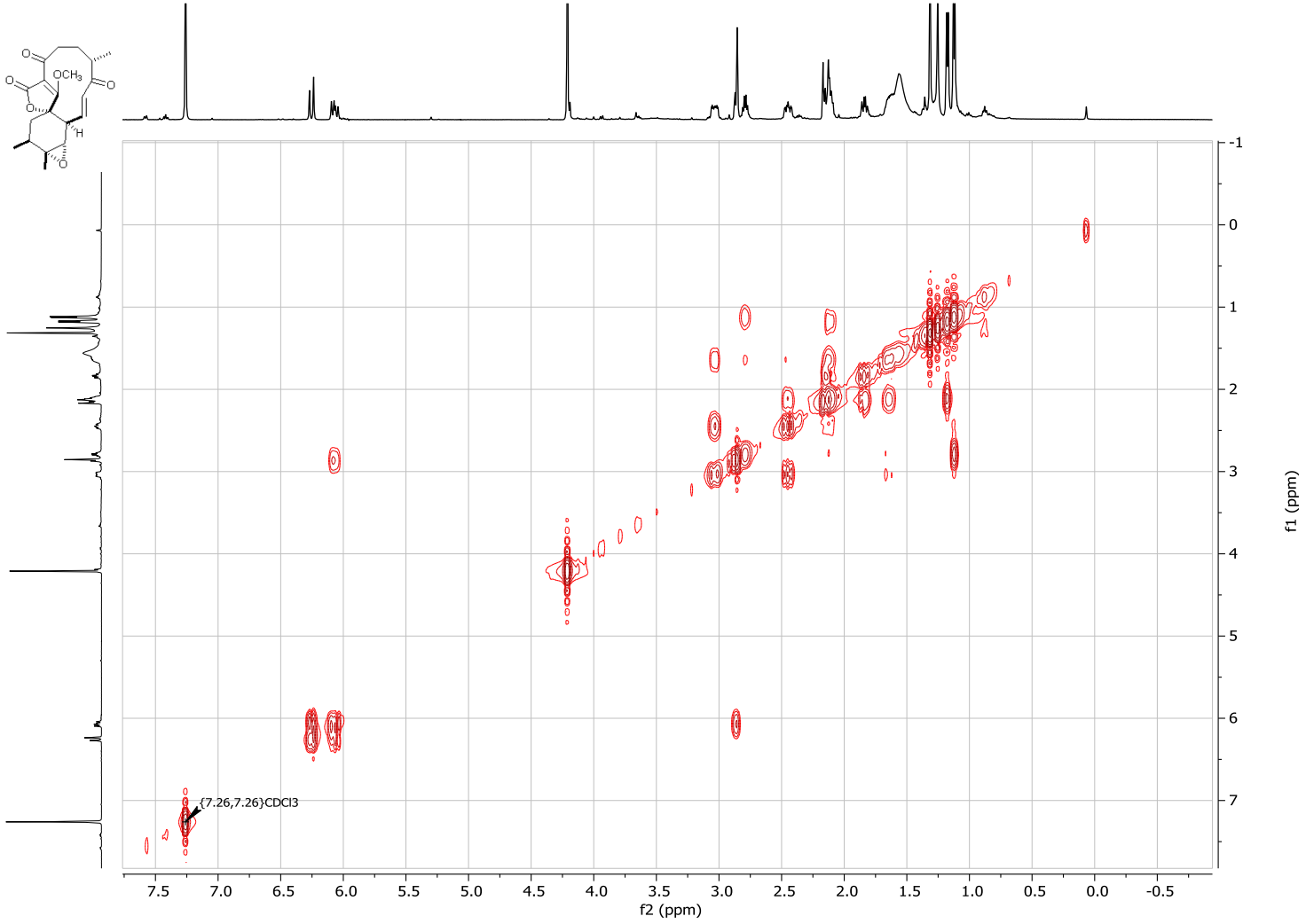
^{1}H NMR (500 MHz, $CDCl_3$) of compound **22**



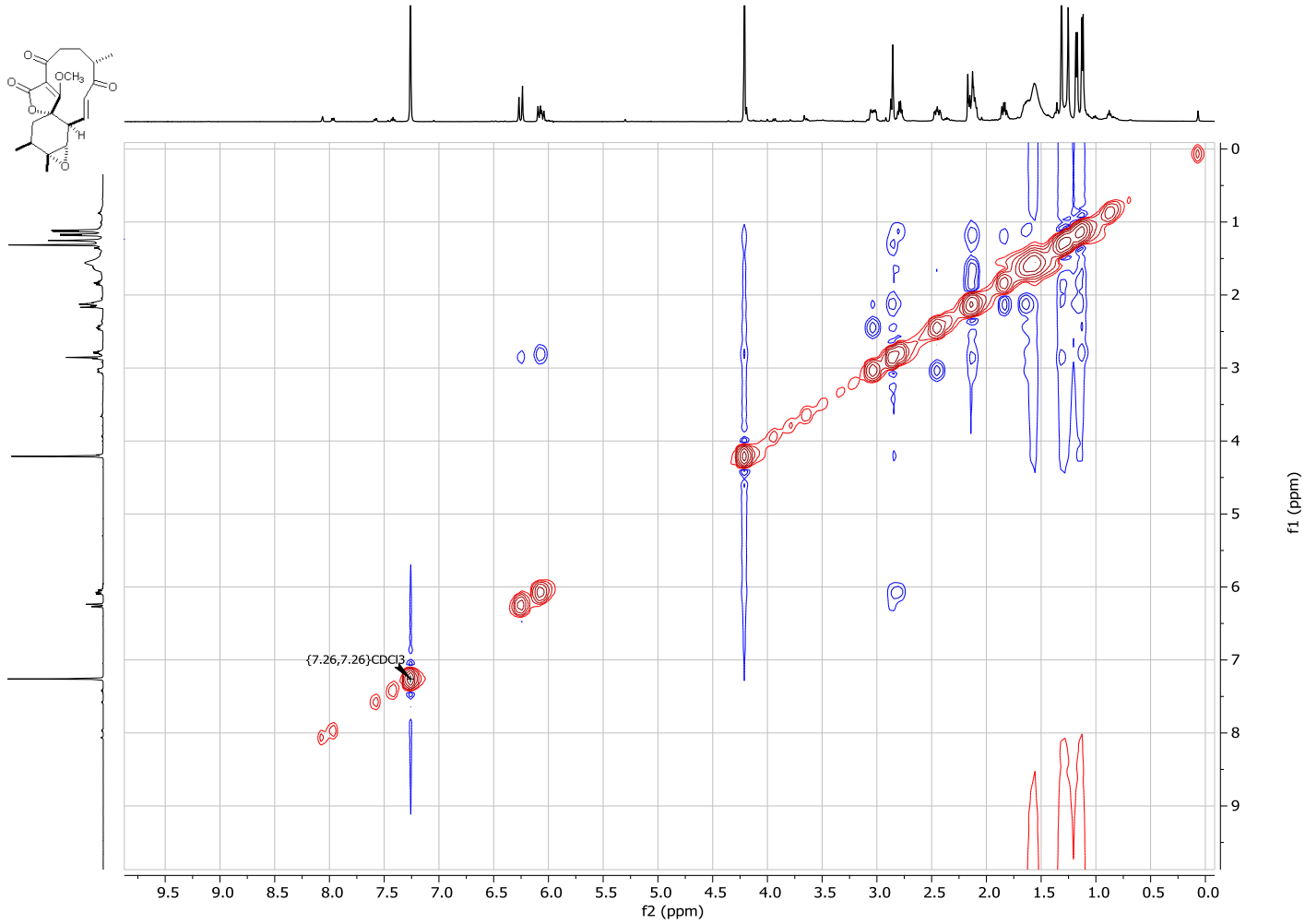
^{13}C NMR (125 MHz, $CDCl_3$) of compound **22**



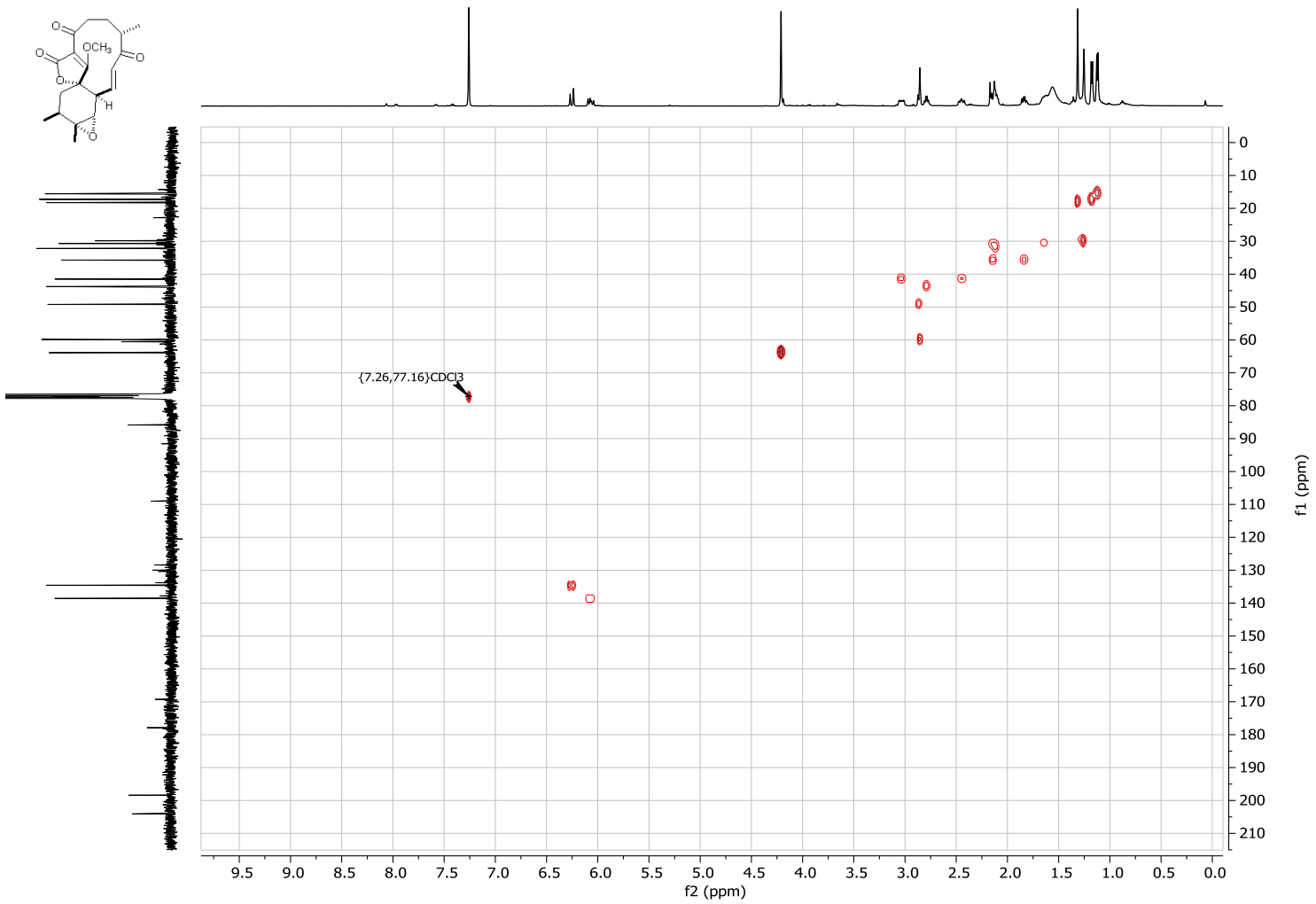
^{1}H-^{1}H COSY of compound **22**



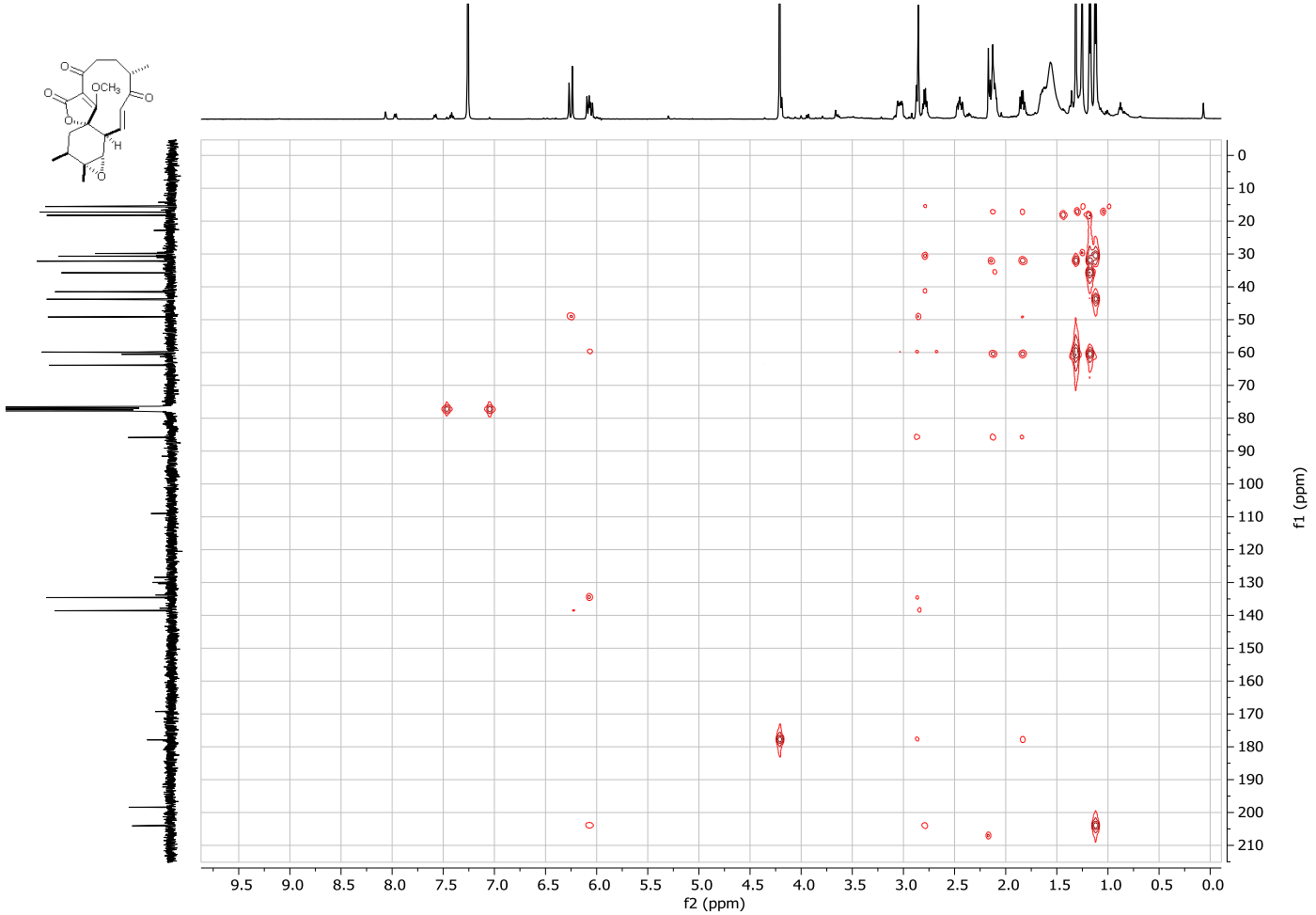
^{1}H-^{1}H NOESY of compound **22**



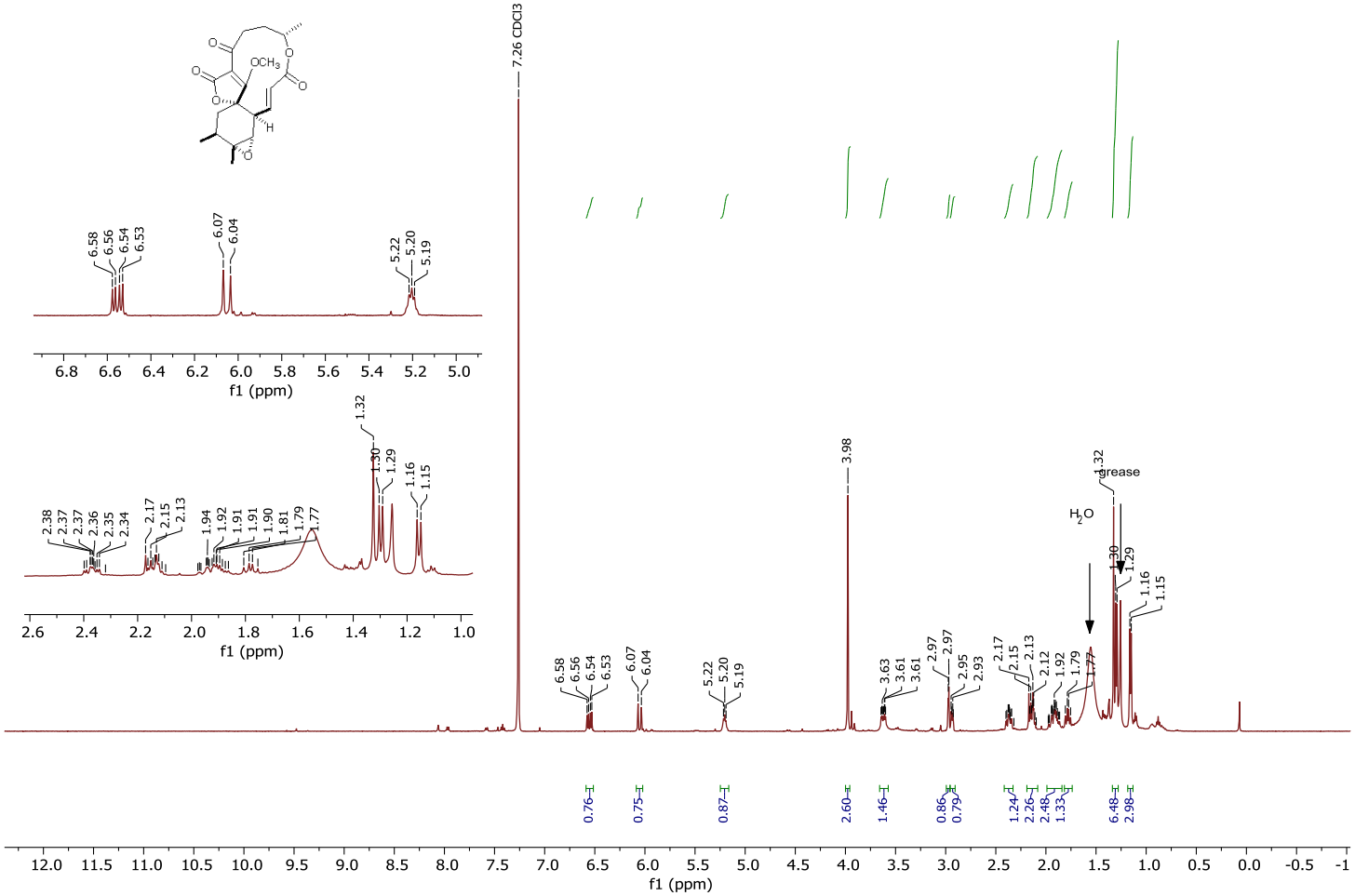
^{1}H-^{13}C HSQC of compound **22**



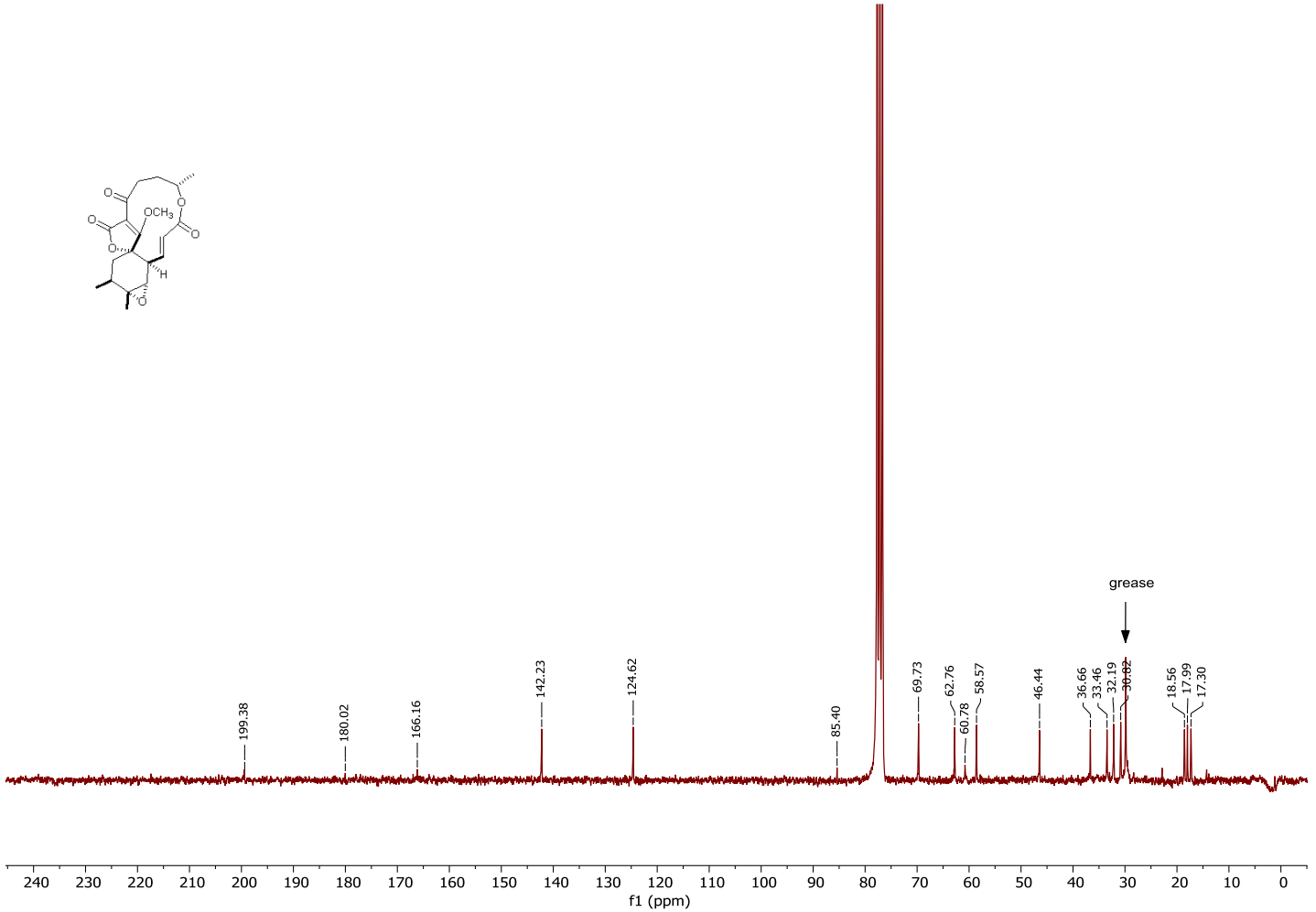
^{1}H-^{13}C HMBC of compound **22**



^{1}H NMR (500 MHz, $CDCl_3$) of compound **24**

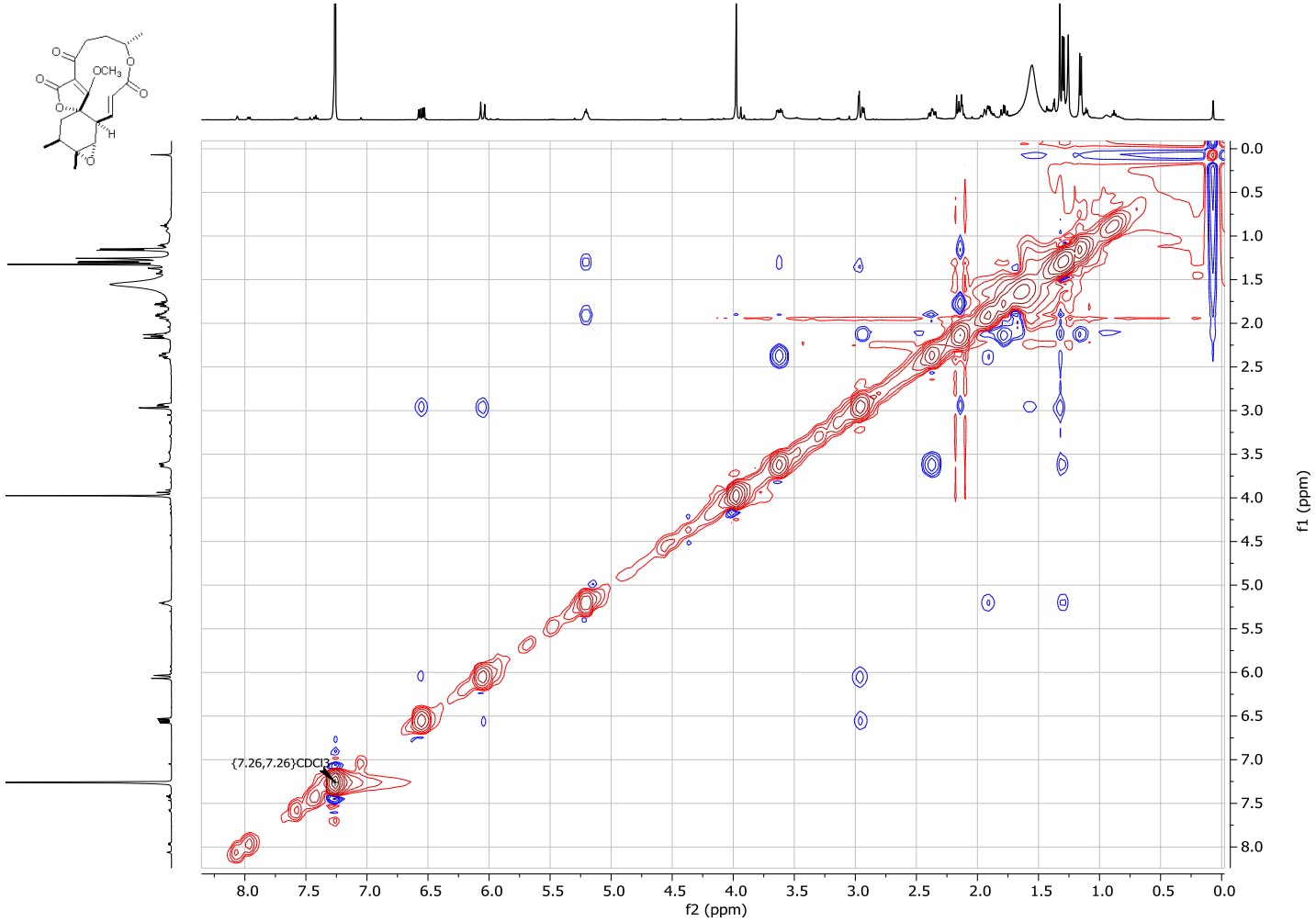


^{13}C NMR (63 MHz, $CDCl_3$) of compound **24**

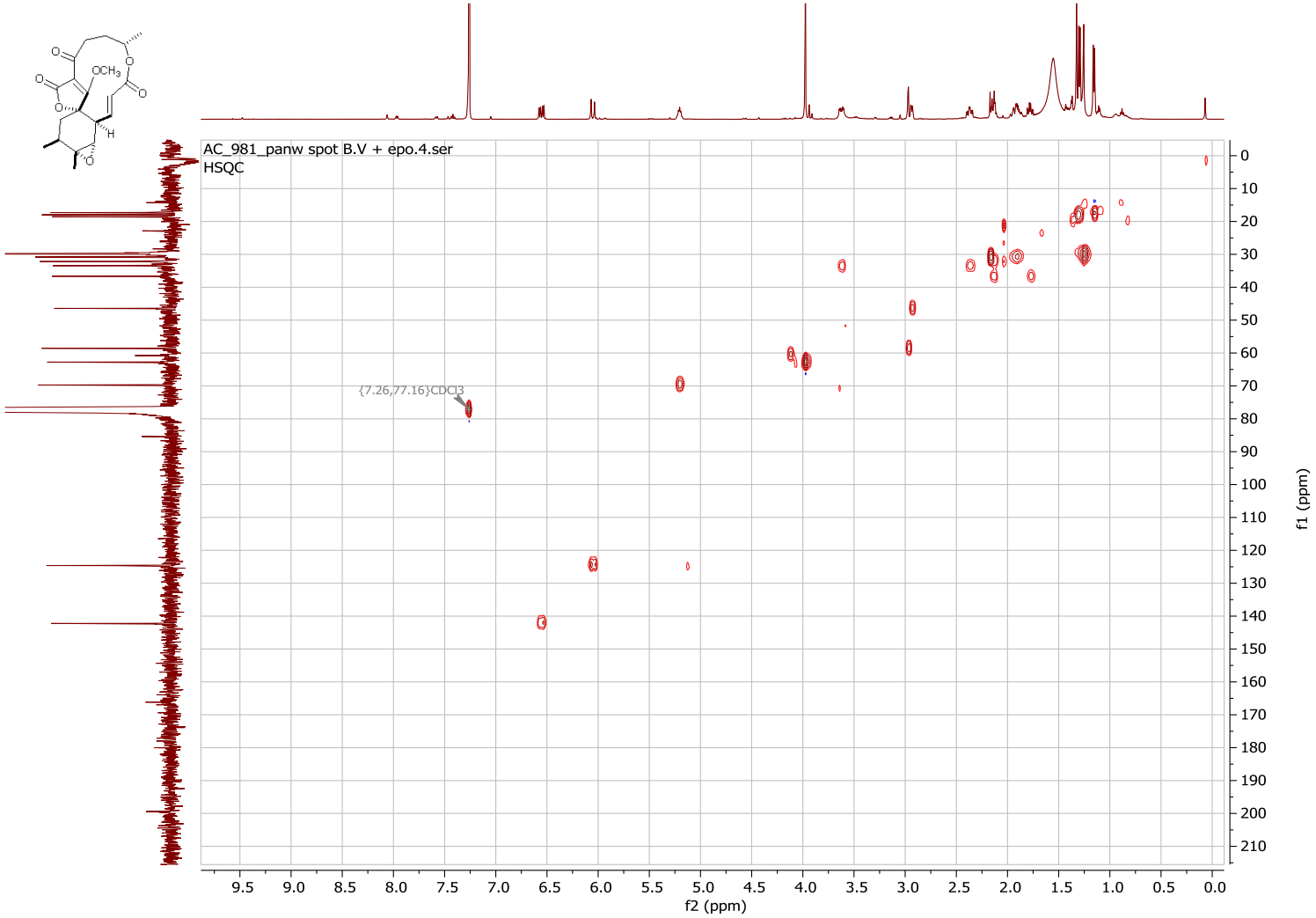


^{1}H-^{1}H COSY of compound **24**

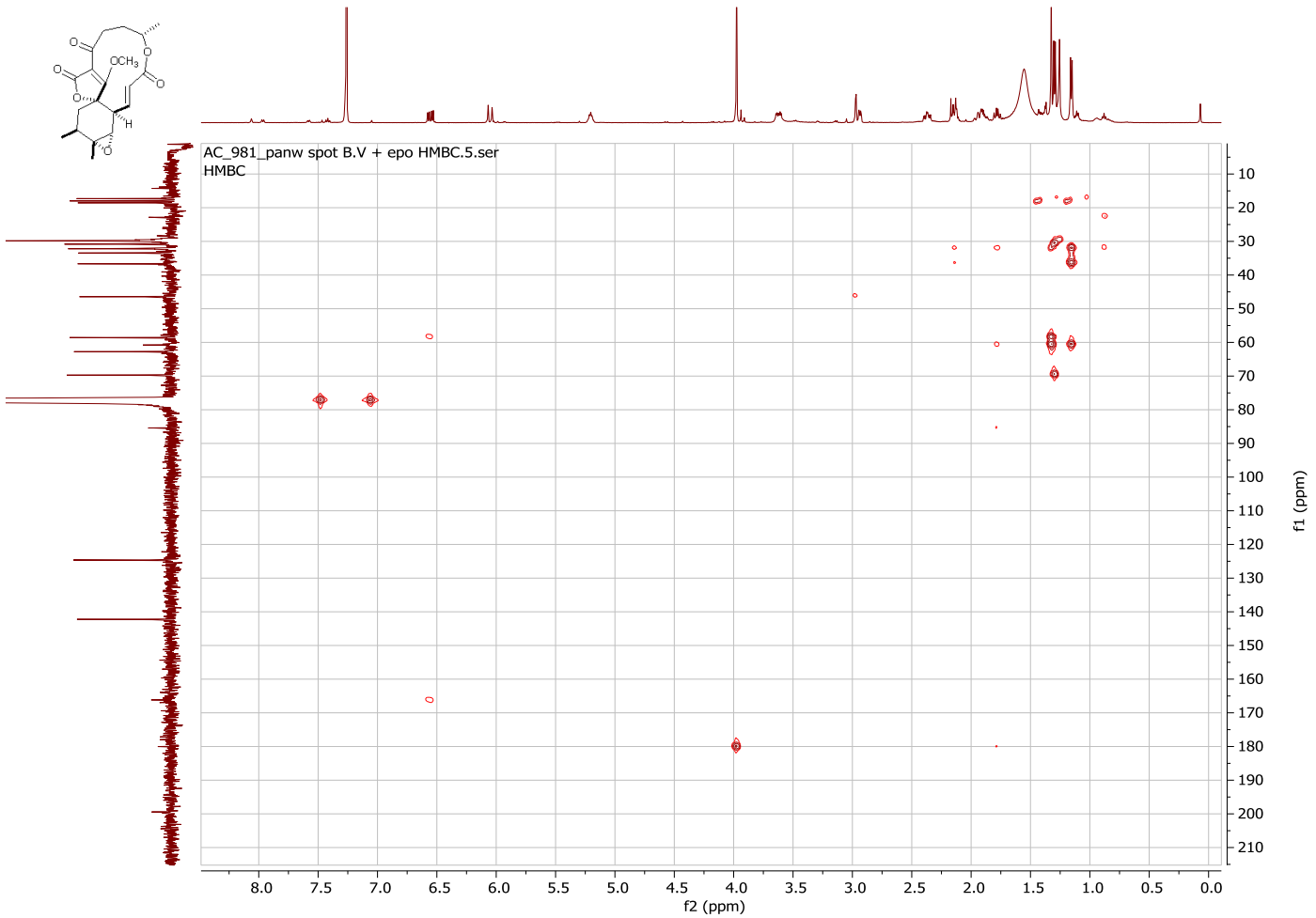
^{1}H-^{1}H NOESY of compound **24**



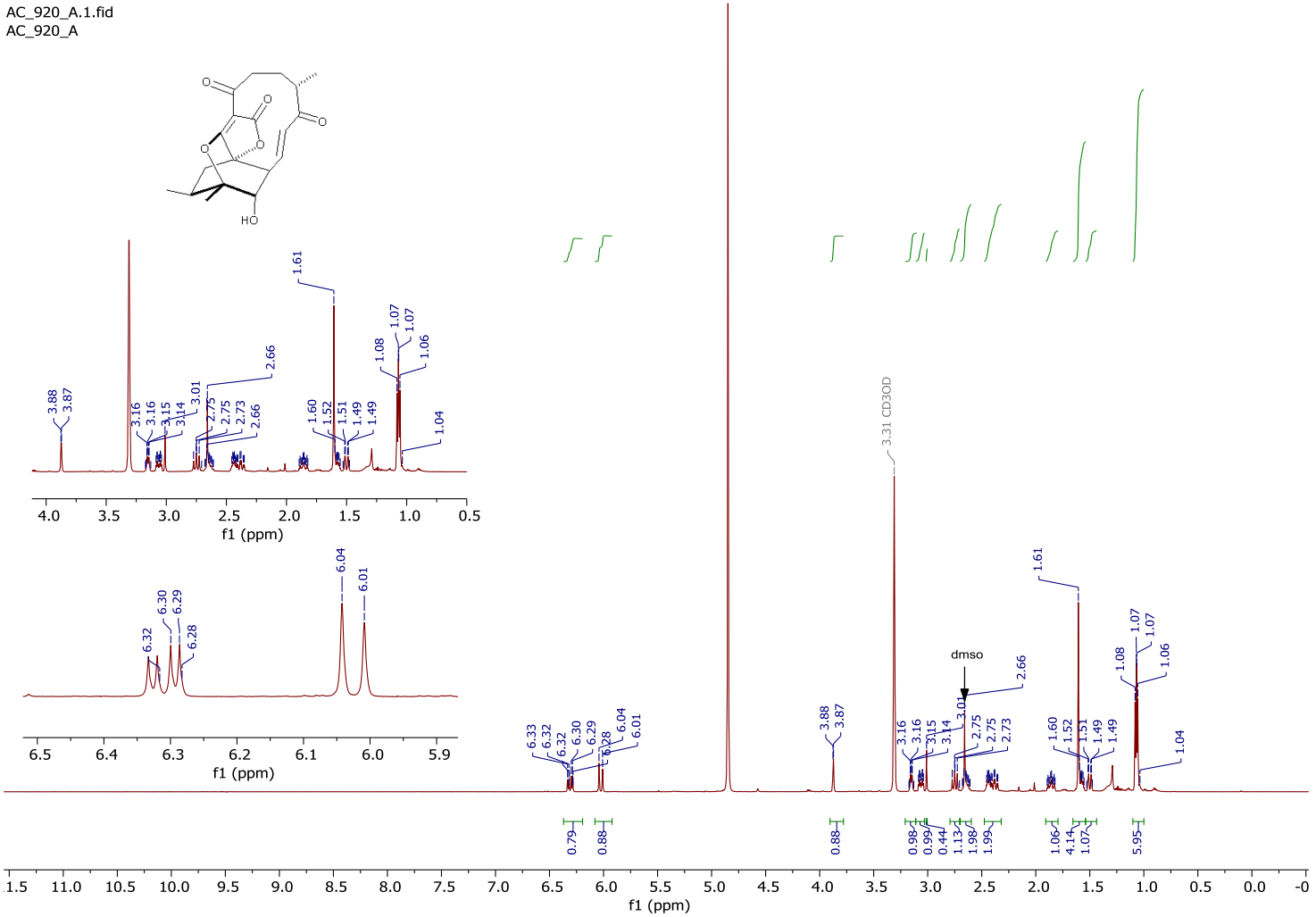
^{1}H-^{13}C HSQC of conpound **24**



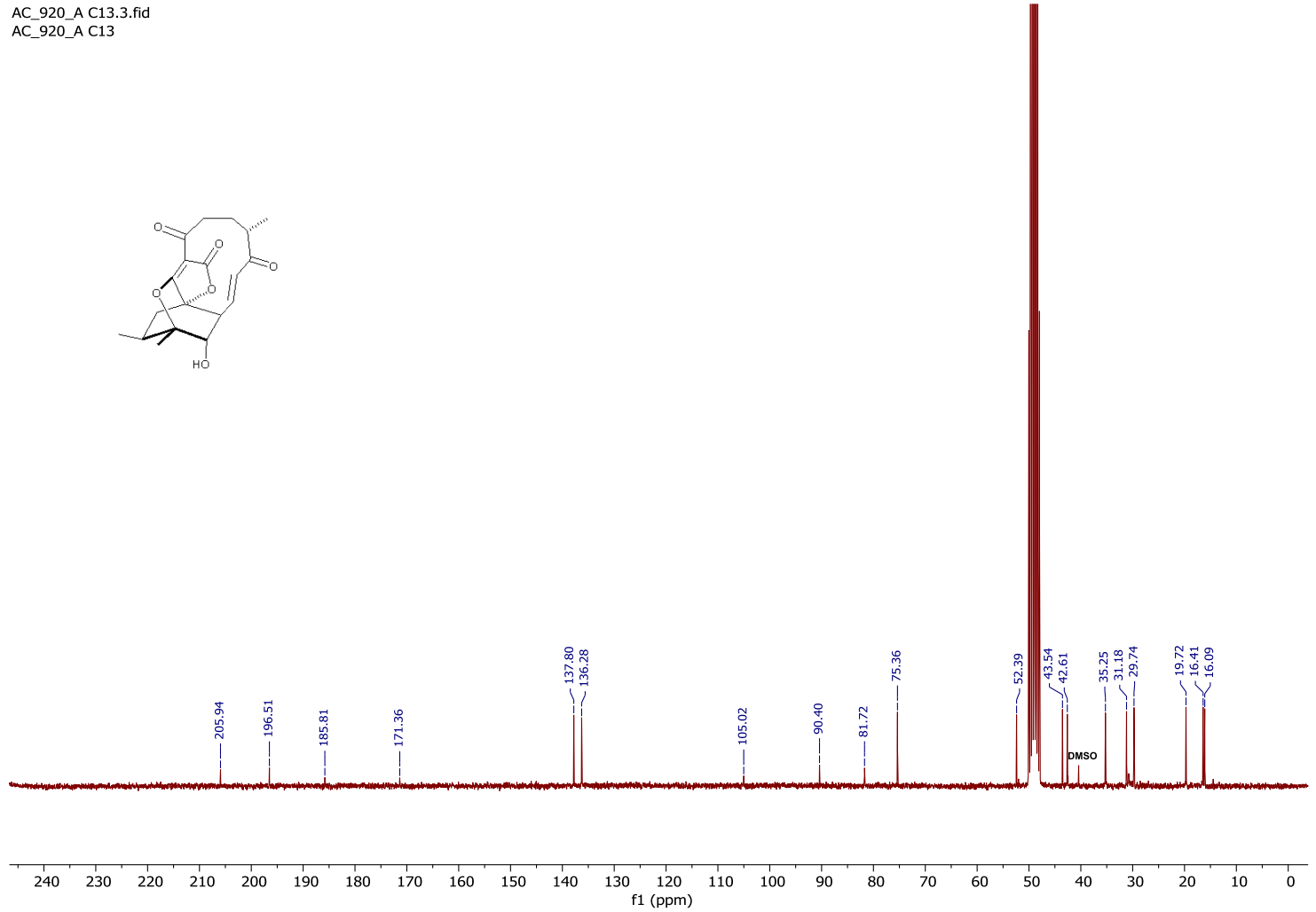
^{1}H -^{13}C HMBC of compound **24**



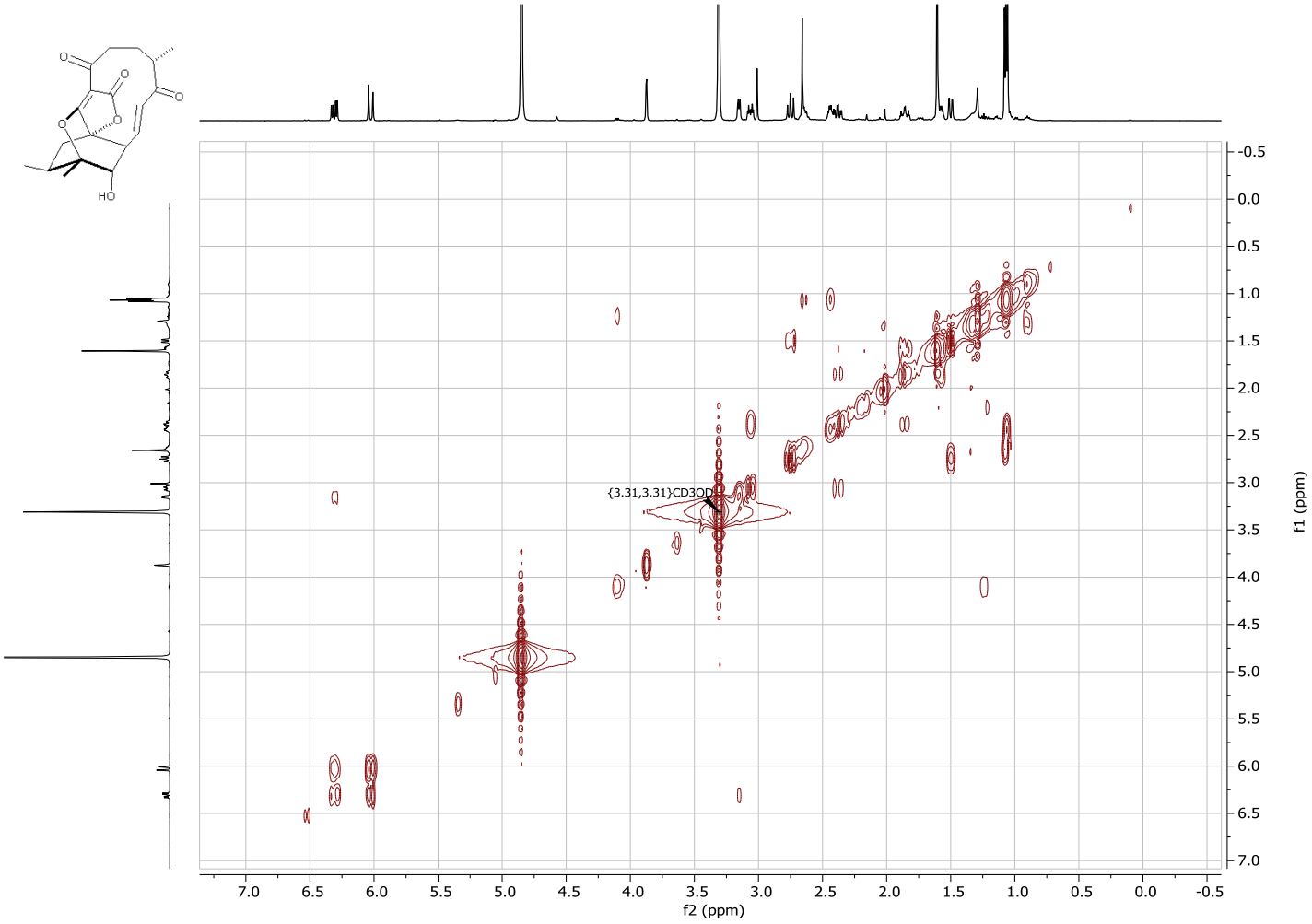
^{1}H NMR (500 MHz, CD_3OD) of abyssomicin 2 ((±)-**2**)



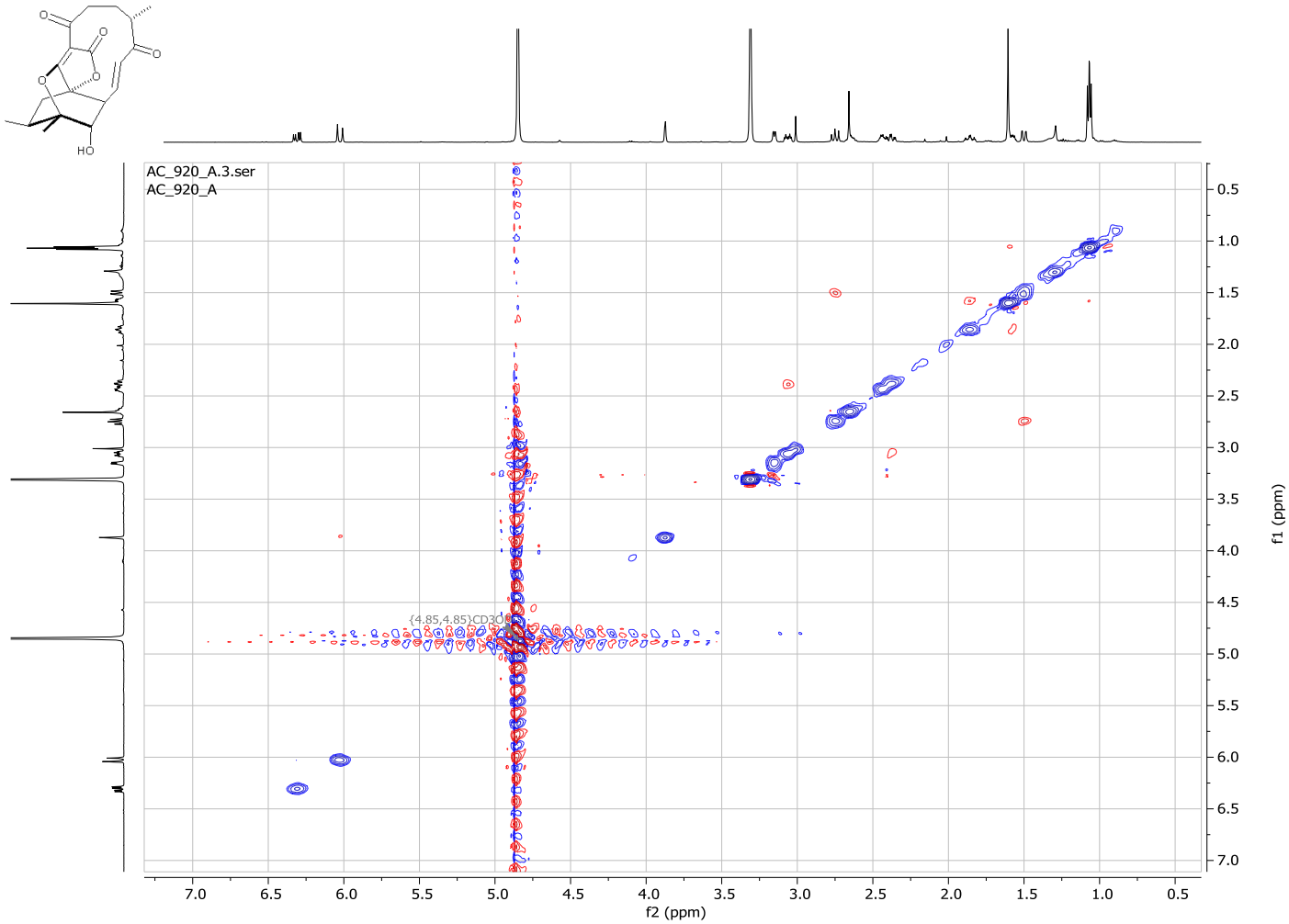
^{13}C NMR (63 MHz, CD_3OD) of abyssomicin 2 ((±)-**2**)



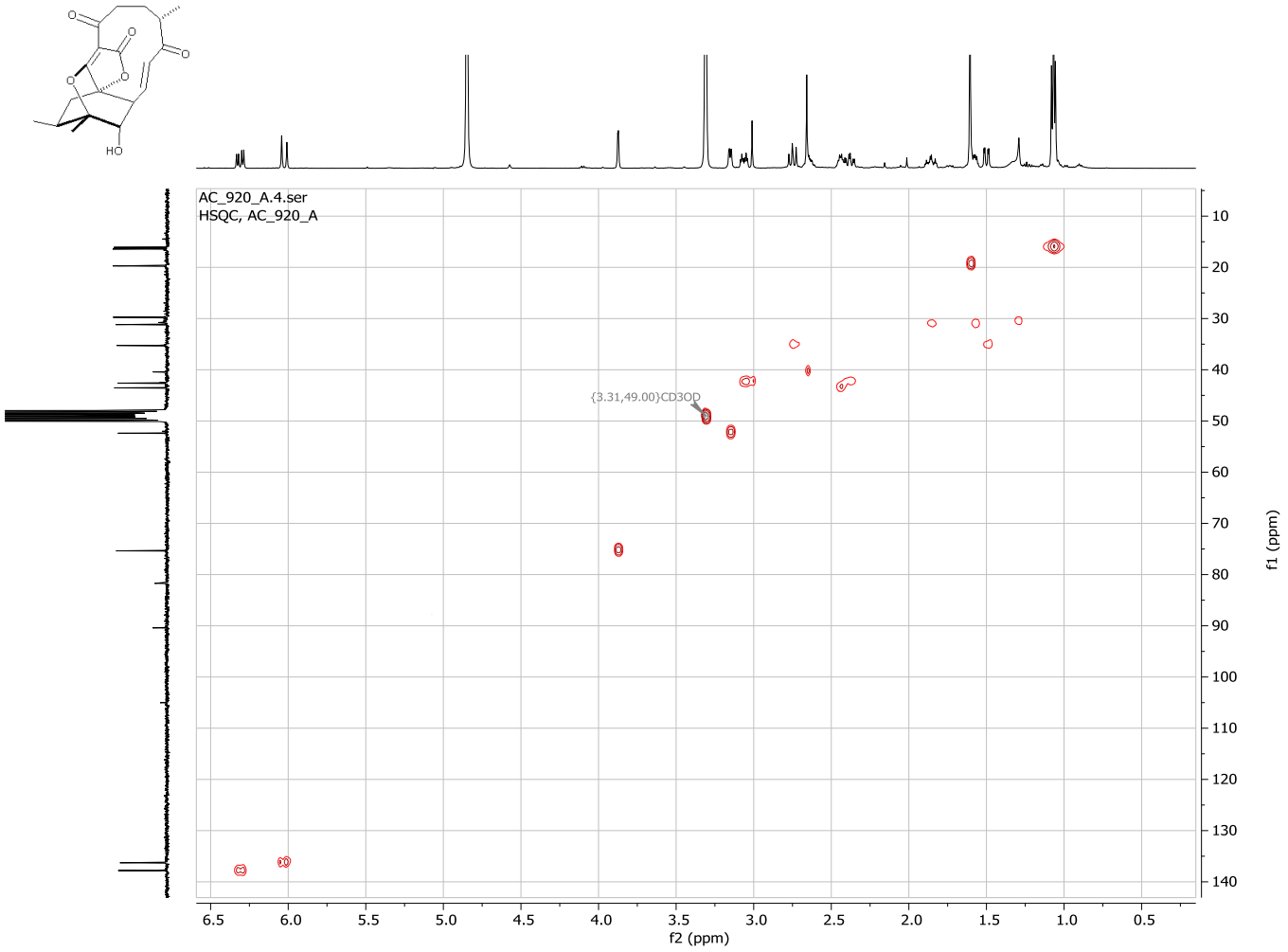
^{1}H-^{1}H COSY of abyssomicin 2 ((±)-**2**)



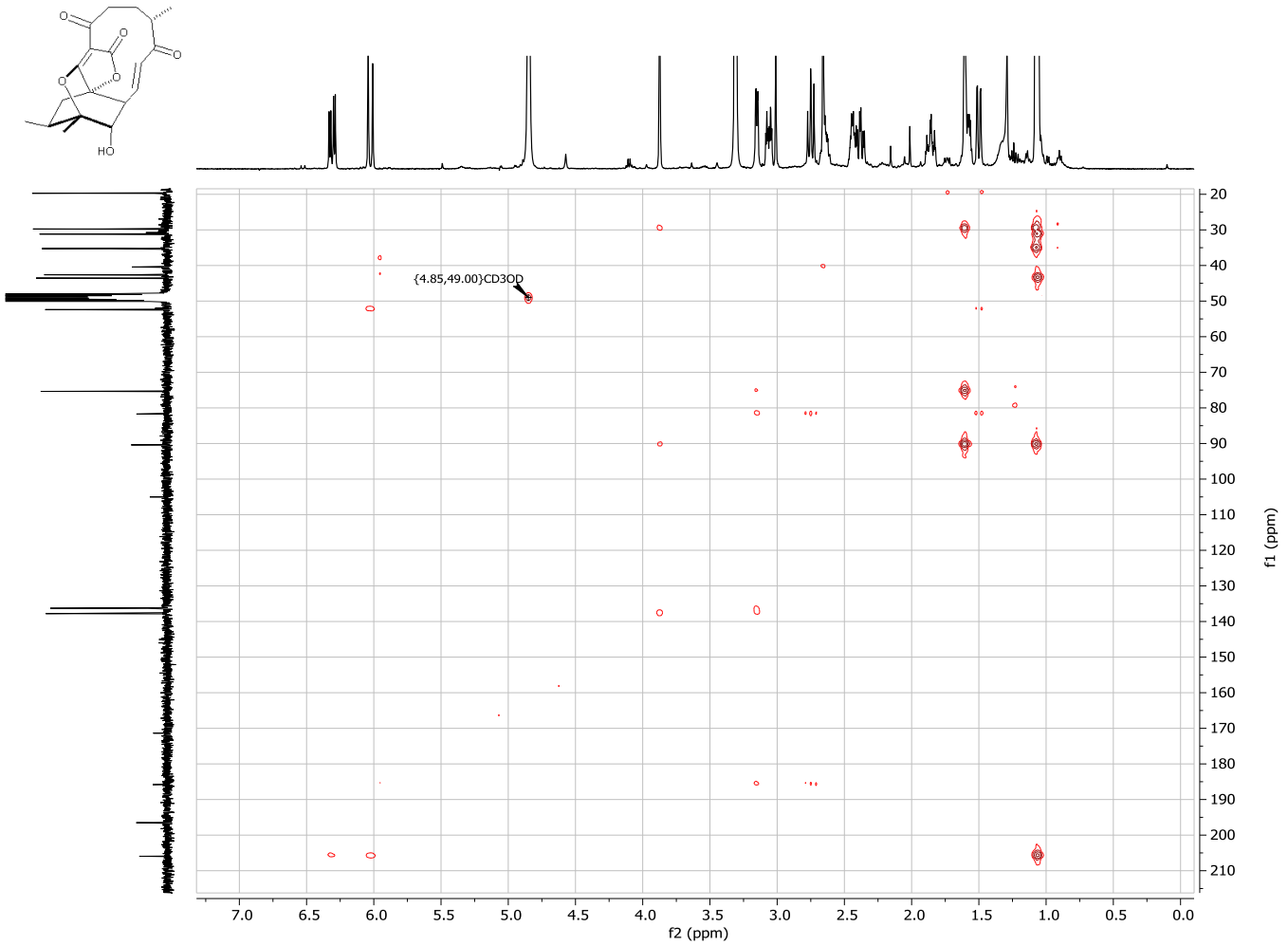
^{1}H-^{1}H NOESY of abyssomicin 2 ((±)-**2**)



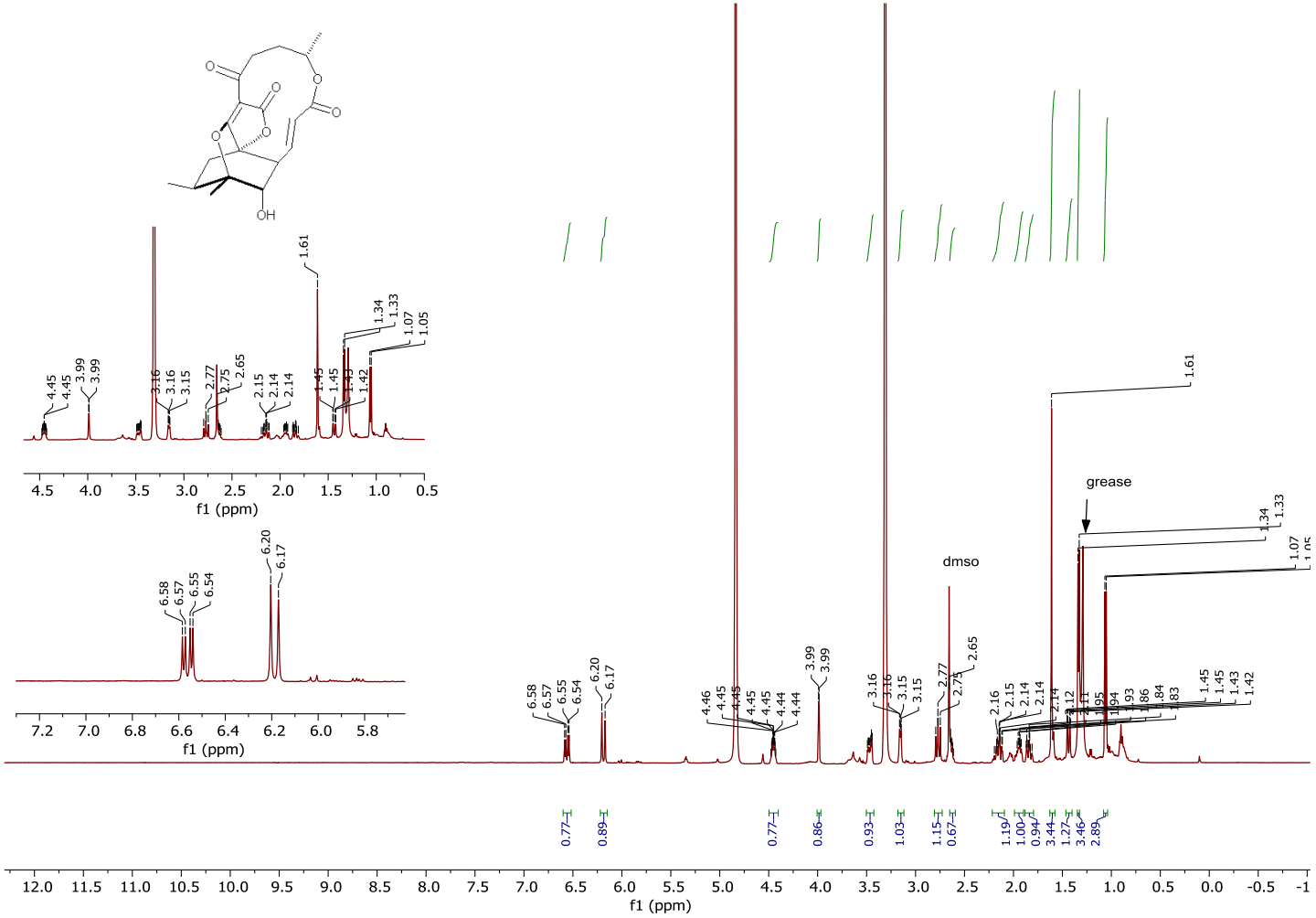
^{1}H-^{13}C HSQC of abyssomicin 2 ((±)-**2**)



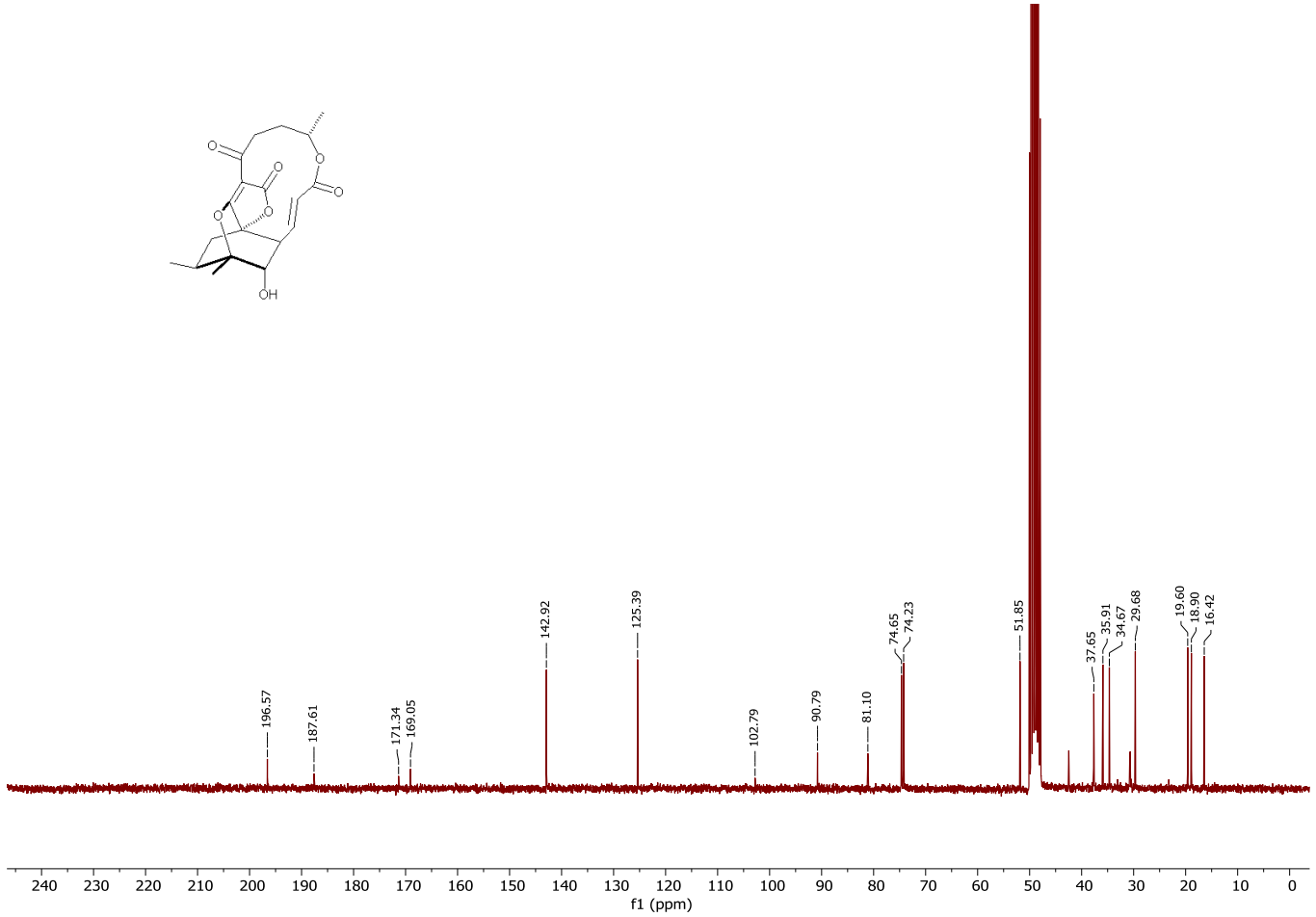
^{1}H-^{13}C HMBC of of abyssomicin 2 ((±)-**2**)



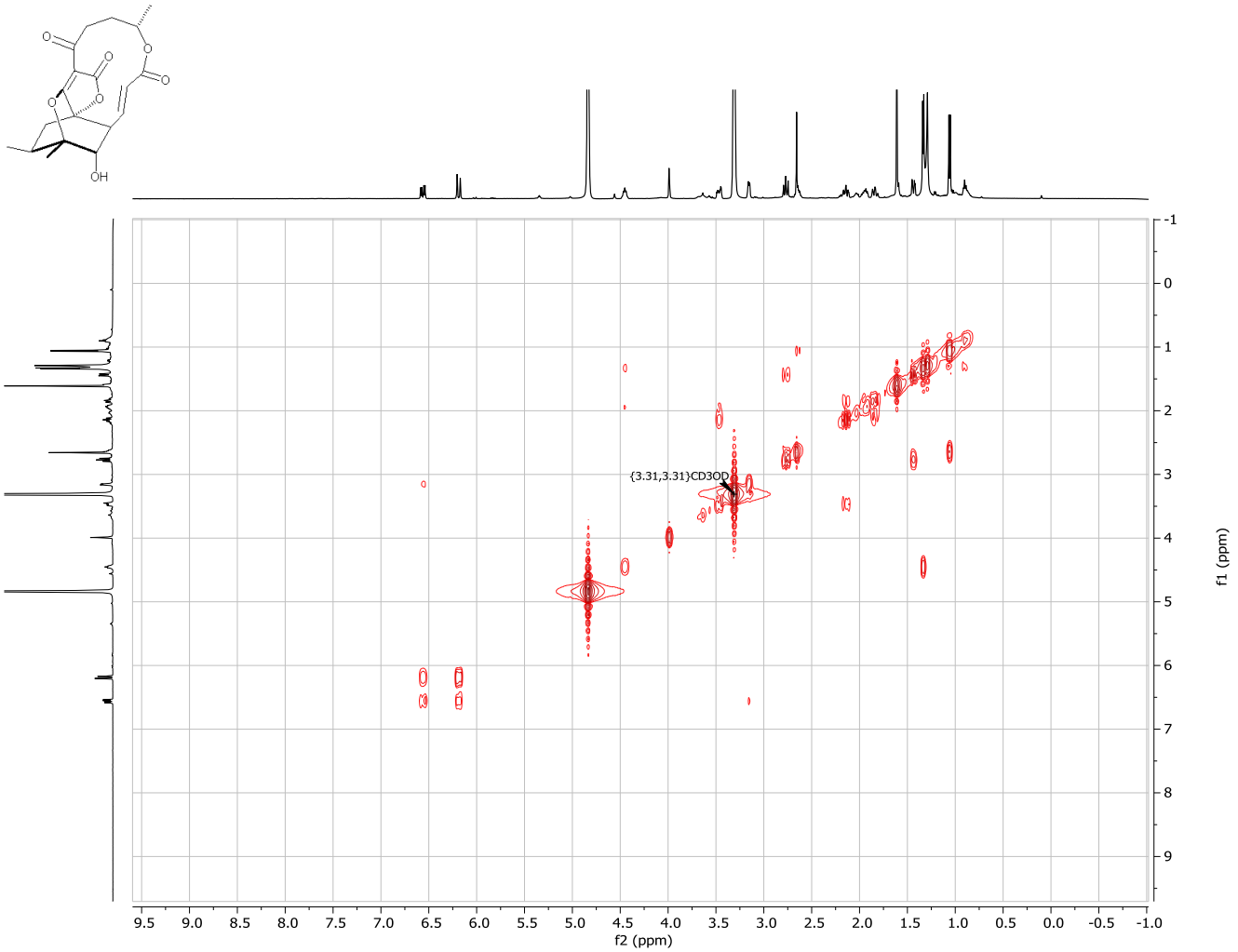
^{1}H NMR (500 MHz, CD_3OD) of neoabyssomicin B ((±)-**3**)



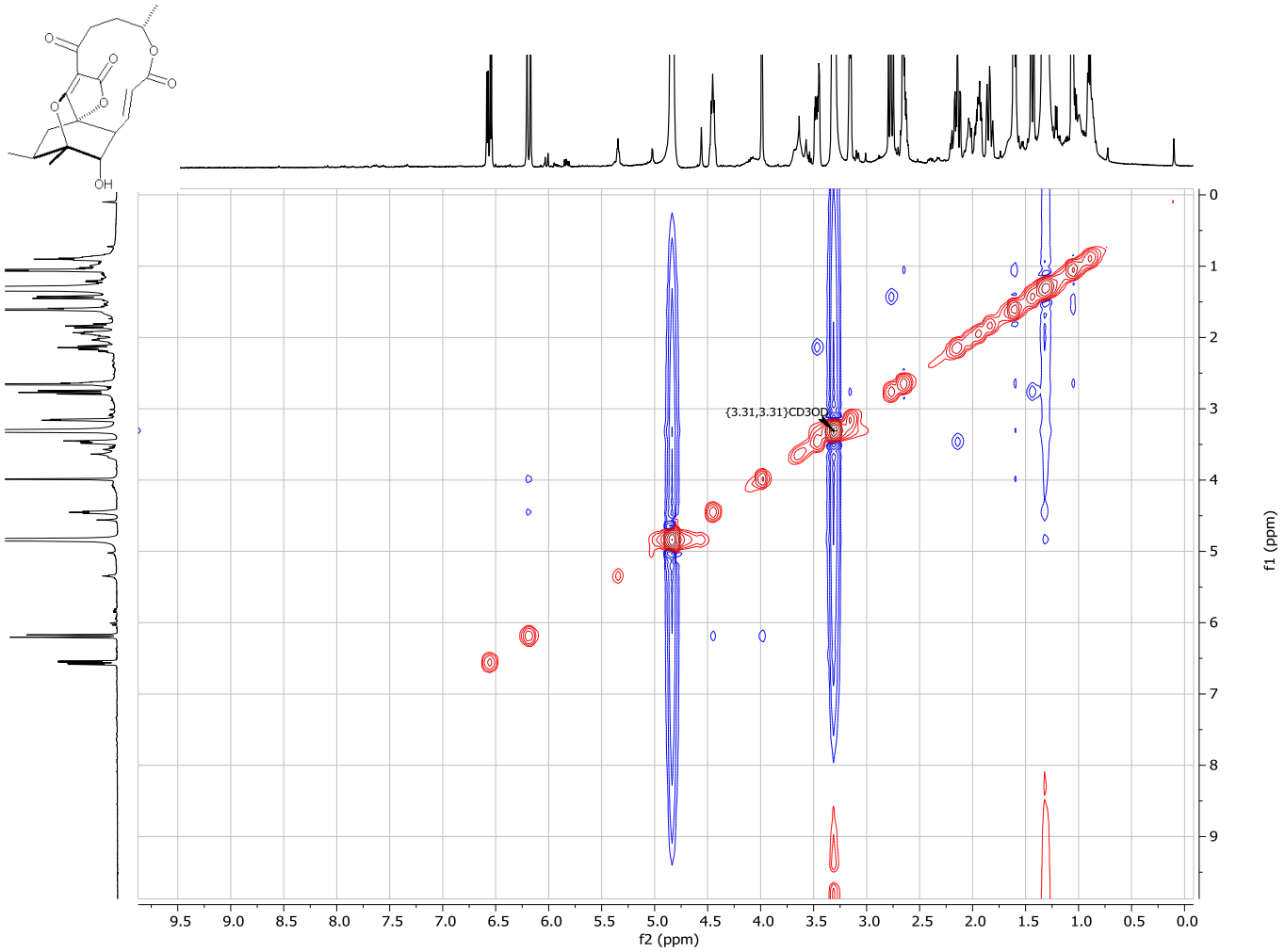
^{13}C NMR (125 MHz, CD_3OD) of neoabyssomicin B ((±)-**3**)



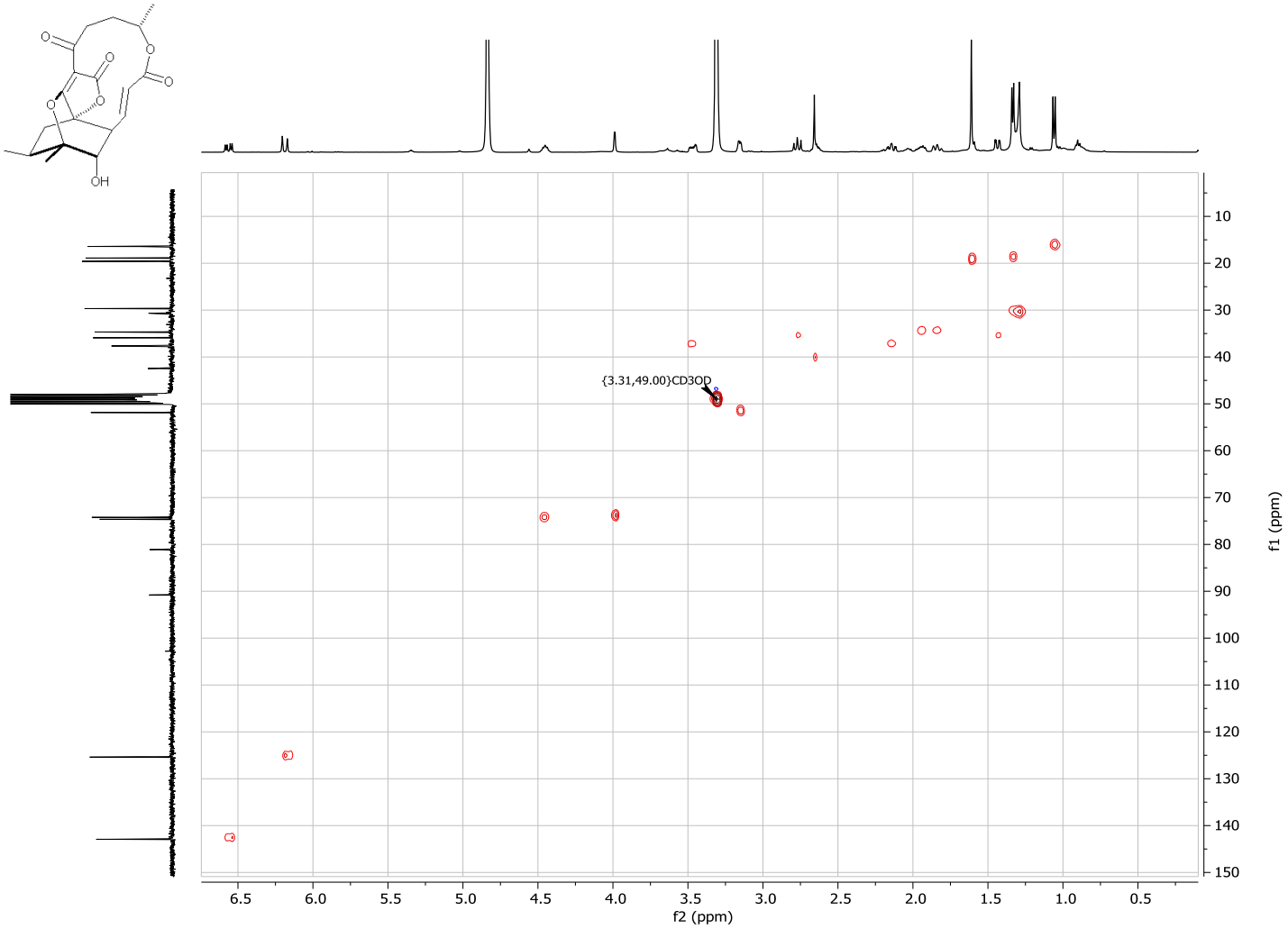
^{1}H-^{1}H COSY of neoabyssomicin B ((±)-**3**)



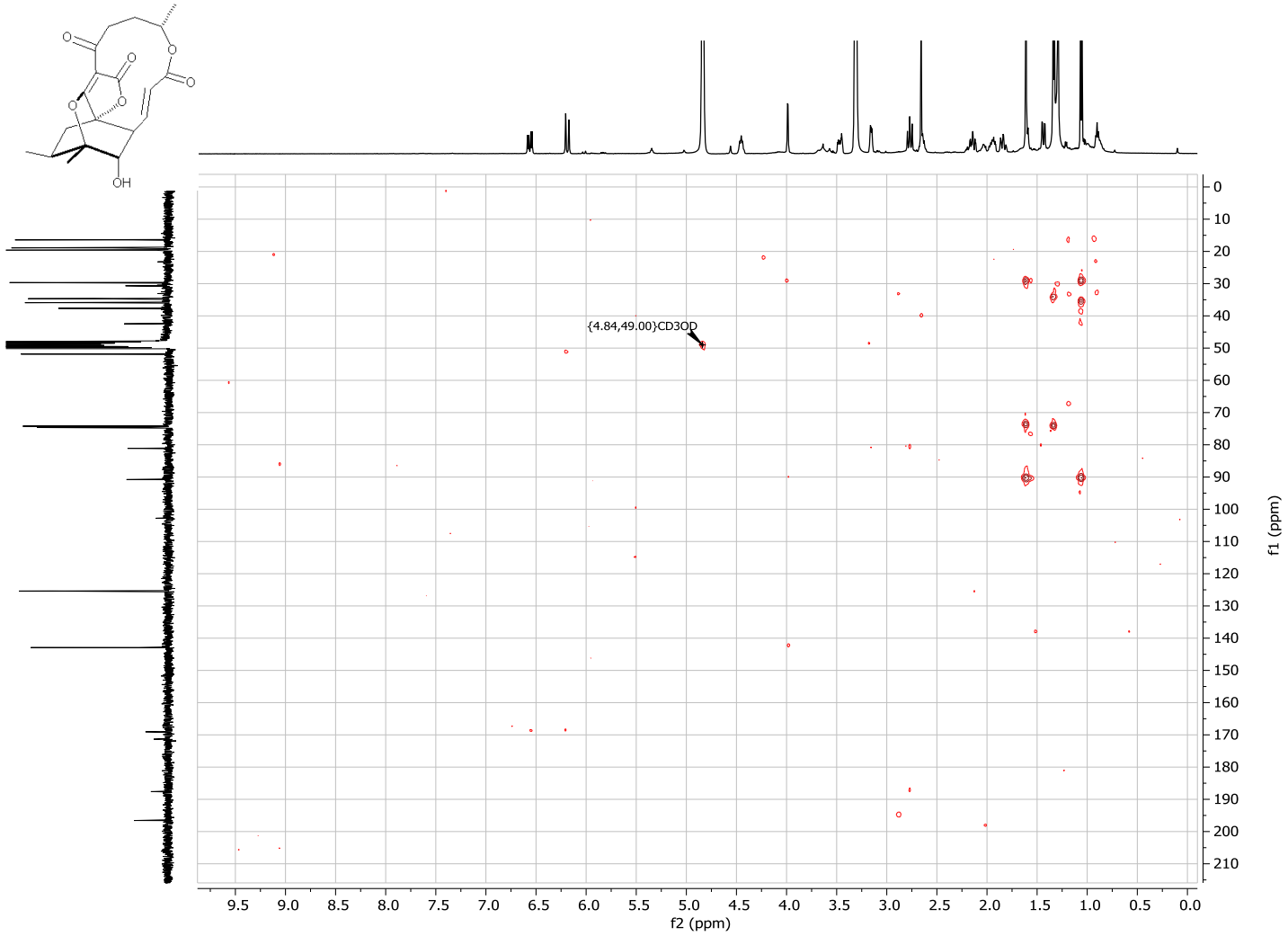
^{1}H-^{1}H NOESY of neoabyssomicin B ((±)-**3**)



^{1}H-^{13}C HSQC of neoabyssomicin B ((±)-**3**)



^{1}H-^{13}C HMBC of neoabyssomicin B ((±)-**3**)



X-ray Crystal Structure Determination.

Slow crystallization from ethyl acetate yielded colorless prismatic crystals. A crystal with approximate dimensions 0.10×0.22×0.38 mm was taken from the mother liquor and immediately cooled to -113 °C. Diffraction measurements were made on a Rigaku R-AXIS SPIDER Image Plate diffractometer using graphite monochromated Mo Kα radiation. Data collection (ω-scans) and processing (cell refinement, data reduction and Empirical absorption correction) were performed using the CrystalClear program package[i]. Important crystallographic data are listed in Table 1. The structure was solved by direct methods using SHELXS v.2013/1 and refined by full-matrix least-squares techniques on F^2 with SHELXL ver.2014/6[ii] Further experimental crystallographic details for **21**: $2\theta_{max}$ = 54 °; reflections collected/unique/used, 18828/3801 [R_{int} = 0.0897]/3801; 322 parameters refined; $(\Delta/\sigma)_{max}$ = 0.001; $(\Delta\rho)_{max}$/($\Delta\rho)_{min}$ = 0.239/-0.252 e/Å^3; *R*1/w*R*2 (for all data), 0.0941/0.1577. All hydrogen atoms were located by difference maps and were refined isotropically. All non-hydrogen atoms were refined anisotropically. Plots of the structure were drawn using the Diamond 3 program package.[iii]

Table 1. Crystallographic data for complex **21**.

Formula	$C_{20}H_{24}O_5$
Fw	344.39
Space group	*Pbca*
a (Å)	12.1705(9)
b (Å)	16.4186(10)
c (Å)	17.4433(10)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	3485.6(4)
Z	8
T (ºC)	-113
Radiation	Mo Kα
ρ_{calcd} (g cm^{-3})	1.313
μ (mm^{-1})	0.094
Reflections with $I>2\sigma(I)$	2466
R_1[a]	0.0528
wR_2[a]	0.1308
CSD deposition number	2250166

[a] $w=1/[\sigma^2(F_o^2)+(\alpha P)^2+bP]$ and $P = [\max(F_o^2,0)+2F_c^2]/3$, a = 0.0898, b = 1.6671, $R_1 = \Sigma(||F_o|-|F_c||)/\Sigma(|F_o|)$ and $wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

References

[i] Rigaku/MSC (2005). *CrystalClear*. Rigaku/MSC Inc., The Woodlands, Texas, USA.

[ii] (a) Sheldrick, G. M. (2008). Acta Cryst. A64, 112-122. (b) Sheldrick, G. M. (2015). Acta Cryst. C71, 3-8.

[iii] DIAMOND – Crystal and Molecular Structure Visualization, Ver. 3.1, Crystal Impact, Rathausgasse 30, 53111, Bonn, Germany.