Biomimetic Total Synthesis of (±)-Yezo'otogirin A

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Supporting Information

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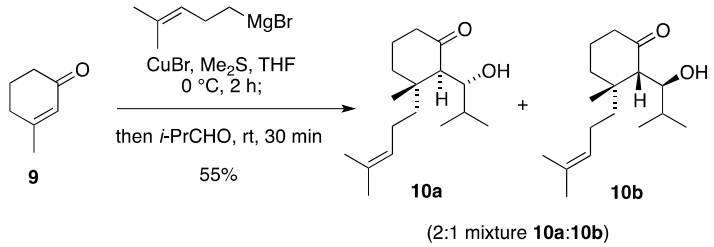
1. General Methods

All chemicals were purchased from commercial suppliers and used as received. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using Merck aluminium sheets silica gel 60 F_{255}. Visualisation was aided by viewing under a UV lamp and staining with CAM stain followed by heating. All R_f values were rounded to the nearest 0.05. Flash chromatography was performed using Davisil (40-63 micron) grade silica gel. Infrared spectra were recorded using a Perkin Elmer Spectrum BX FT-IR system spectrometer as the neat compounds. ^1H and ^{13}C NMR spectra were recorded using a Varian Inova-6000 spectrometer (^1H at 600 MHz, ^{13}C at 150 MHz). The NMR solvent used was $CDCl_3$ unless otherwise specified. ^1H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C NMR are reported in ppm relative to TMS (δ 0.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sxt) sextet, (hept) heptet, and (m) multiplet. All *J* values were rounded to the nearest 0.5 Hz. ESI high resolution mass spectra were recorded on a maXis 3G UHR-Qq-TOF mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) coupled to a Dionex Ultimate 3000 LC system (ThermoFisher).

2. Experimental Procedures

1,3-Hydroxyketone **10a/10b**



To a solution of Mg (550 mg, 22.7 mmol) in anhydrous Et_2O (10 mL) was added 5-bromo-2-methyl-2-pentene (1.34 mL, 9.99 mmol) at room temperature, and the resultant mixture was allowed to stir for 30 min. The mixture was then added to a suspension of CuBr (1.95 g, 13.6 mmol), Me_2S (1.90 mL, 26.0 mmol) and **9** (500 mg, 4.54 mmol) in anhydrous Et_2O (5 mL) at 0 °C and was stirred for 2 h before slowly warming to room temperature. Isobutyraldehyde (1.66 mL, 18.16 mmol) was then added and the mixture was stirred at room temperature for 30 min. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1) to give a 2:1 mixture of **10a** and **10b** (661 mg, 55%) as a colourless oil.

Data for 10a/10b:

R_f = 0.60 (petrol/EtOAc, 3:1)

IR (neat): 3467, 2960, 2928, 2872, 1690, 1452, 1382, 1246 cm^{-1}.

Data for major diastereoisomer 10a:

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.09 (t, *J* = 7.2 Hz, 1H), 3.65 (d, *J* = 10.5 Hz, 1H), 3.37 (dd, *J* = 10.5, 8.9 Hz, 1H), 2.50 (s, 1H). 2.36 – 2.32 (m, 3H), 2.05 – 1.72 (m, 5H), 1.69 (s, 3H), 1.61 (s, 3H), 1.50 – 1.41 (m, 2H), 1.36 – 1.29 (m, 1H), 1.07 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 217.5, 131.7, 124.1, 75.2, 57.5, 43.3, 43.2, 41.5, 37.0, 34.3, 25.7, 23.2, 22.2, 22.1, 20.3, 19.5, 17.6.

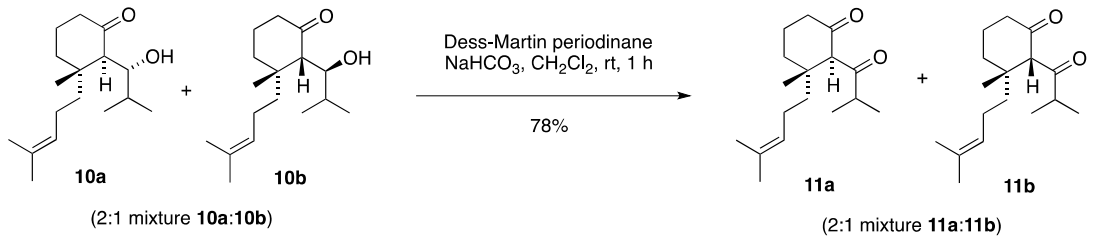
Data for minor diastereoisomer 10b:

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.09 (t, *J* = 7.2 Hz, 1H), 3.95 (d, *J* = 10.2 Hz, 1H), 3.43 (dd, 10.2, 8.4 Hz, 1H), 2.50 (s, 1H), 2.35 – 2.32 (m, 3H), 2.05 – 1.72 (m, 5H), 1.65 (s, 3H), 1.58 (s, 3H), 1.60-1.55 (m, 2H), 1.36 – 1.29 (m, 1H), 1.09 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 7.8 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 216.9, 131.1, 124.6, 75.3, 60.9, 43.3, 43.1, 35.9, 34.5, 34.0, 26.3, 25.7, 22.7, 22.0, 20.1, 19.2, 17.6.

HRMS (ESI): calculated for $C_{17}H_{31}O_2$ 267.2319 $[M+H]^+$, found 267.2314.

1,3-Diketone **11a/11b**



To a solution of hydroxyketone **10a/10b** (660 mg, 2.48 mmol) and $NaHCO_3$ (312 mg, 3.72 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (1.58 g, 3.72 mmol) at room temperature. The mixture was stirred for 1 h, then quenched with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1) to give a 2:1 mixture of **11a** and **11b** (510 mg, 78%) as a colourless oil.

Data for 11a/11b:

R_f = 0.60 (petrol/EtOAc, 5:1)

IR (neat): 2967, 2932, 2875, 1714, 1693, 1466, 1381, 1212 cm^{-1}.

Data for major diastereoisomer 11a:

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.04 (t, *J* = 7.1 Hz, 1H), 3.65 (s, 1H), 2.68 – 2.59 (m, 1H), 2.28 (dt, *J* = 14.3, 4.7 Hz, 2H), 2.14 (dd, *J* = 10.7, 3.3 Hz, 1H), 1.95 − 1.85 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.46 (dt, *J* = 13.8, 4.2 Hz, 1H), 1.40 (d, 4.9 Hz, 1H), 1.31 – 1.19 (m, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 210.3, 208.0, 131.9, 123.8, 72.5, 43.8, 42.0, 39.2, 38.9, 31.2, 25.7, 23.3, 21.7, 21.5, 17.7, 17.6, 17.2

HRMS (ESI): calculated for $C_{17}H_{29}O_2$ 265.2162 $[M+H]^+$, found 265.2157.

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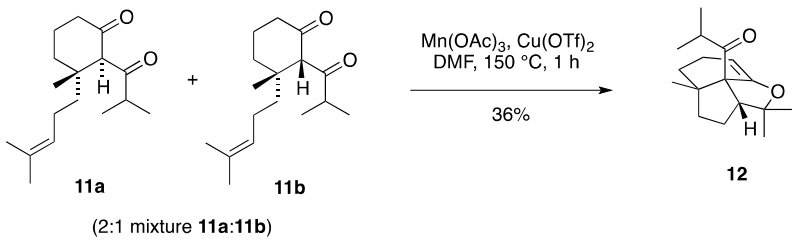
Data for minor diastereoisomer 11b:

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.01 (t, 7.2 Hz, 1H), 3.63 (s, 1H), 2.68 – 2.59 (m, 1H), 2.24 (dt, *J* = 13.2, 4.6 Hz, 2H), 2.12 (dd, *J* = 9.6, 2.4 Hz, 1H), 1.83 – 1. 72 (m, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.43 (dt, *J* = 18.6, 4.2 Hz, 1H), 1.38 (d, *J* = 4.8 Hz, 1H), 1.31 – 1.19 (m, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 210.5, 208.0, 131.7, 124.1, 73.9, 43.7, 42.8, 39.5, 38.9, 31.1, 25.7, 23.8, 22.1, 21.9, 17.9, 17.6, 17.4.

Yezo'otogirin analogue **12**



(2:1 mixture **11a**:**11b**)

$Mn(OAc)_3 \cdot 2H_2O$ (398 mg, 1.51 mmol) and $Cu(OTf)_2$ (275 mg, 0.76 mmol) were added to a solution of **11a/11b** (200 mg, 0.76 mmol) in degassed DMF (20 mL) at room temperature. The reaction mixture was heated to 150 °C and stirred for 1 h. The reaction mixture was then cooled to room temperature and diluted with Et_2O (20 mL) and H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with H_2O (3 x 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 30:1) to give **12** (71 mg, 36%) as a yellow oil.

Data for 12:

R_f = 0.50 (petrol/EtOAc, 9:1)

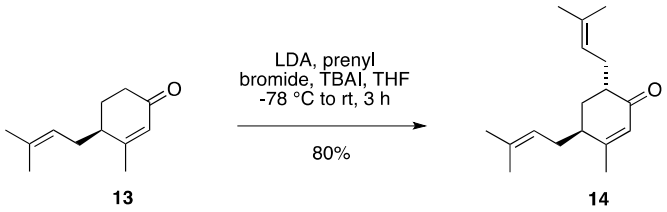
IR (neat): 2973, 2933, 2869, 1690, 1461, 1381, 1264 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.96 (dd, *J* = 4.6, 3.4 Hz, 1H), 3.23 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.18 (hept, *J* = 6.7 Hz, 1H) , 2.35 – 2.22 (m, 2H), 1.89 – 1.78 (m, 3H), 1.72 – 1.67 (m, 2H), 1.58 (dd, *J* = 7.6, 3.0 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 6H), 0.84 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 215.9, 154.7, 97.5, 85.3, 72.4, 51.3, 46.0, 37.7, 37.3, 30.3, 30.0, 25.4, 25.3, 23.9, 21.2, 20.8, 18.0.

HRMS (ESI): calculated for $C_{17}H_{27}O_2$ 263.2006 $[M+H]^+$, found 263.2002.

Ketone **14**



To a solution of **13**[1] (3.10 g, 17.4 mmol) in anhydrous THF (30 mL) at -78 °C was added LDA (2.0 M in THF, 11.5 mL, 23.0 mmol) dropwise over 10 min. The mixture was stirred at -78 °C for a further 30 min. A solution of TBAI (628 mg, 1.74 mmol) and prenyl bromide (3.00 mL, 26.0 mmol) in anhydrous THF (5 mL) was added dropwise and the resultant mixture was stirred at -78 °C for 1 h, then gradually warmed to room temperature and stirred for another 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1) to give **14** (3.43 g, 80%) as a light yellow oil which was a 10:1 inseparable mixture of diastereomers.

Data for 14:

R_f = 0.50 (petrol/EtOAc, 5:1)

IR (neat): 2967, 2914, 2858, 1668, 1440, 1377, 1210 cm^{-1}.

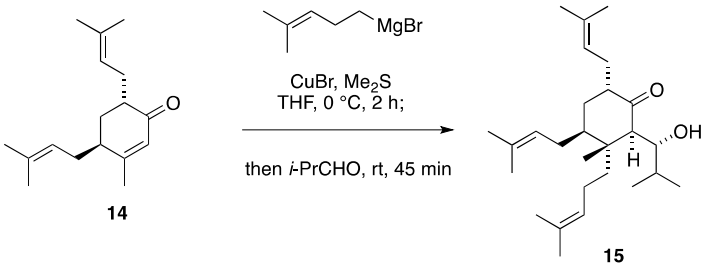
^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.81 (s, 1H), 5.13 – 5.11 (m, 1H), 5.08 – 5.05 (m, 1H), 2.56 – 2.52 (m, 1H), 2.38 – 2.33 (m, 2H), 2.28 – 2.24 (m, 2H), 2.21 – 2.15 (m, 2H), 2.05 – 2.00 (m, 1H), 1.96 (s, 3H), 1.69 (s, 3H), 1.70 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 201.1, 164.5, 133.8, 133.2, 126.5, 122.3, 121.9, 41.9, 39.9, 31.5, 29.8, 28.0, 25.8, 25.8, 22.9, 17.8.

HRMS (ESI): calculated for $C_{17}H_{27}O$ 247.2056 $[M+H]^+$, found 247.2053.

(1) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200.

1,3-Hydroxyketone **15**



To a solution of Mg (248 mg, 10.2 mmol) in anhydrous Et_2O (20 mL) was added 5-bromo-2-methyl-2-pentene (0.54 mL, 4.06 mmol) at room temperature, and the resultant mixture was stirred for 30 min at the same temperature. The mixture was then added to a suspension of CuBr (582 mg, 4.06 mmol), Me_2S (0.30 mL, 4.06 mmol) and **14** (500 mg, 2.03 mmol) in anhydrous THF (20 mL) at 0 °C and was stirred for 2 h before slowly warming to room temperature. Isobutyraldehyde (1.85 mL, 20.29 mmol) was then added and the mixture was stirred at room temperature for 45 min. The mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **15** (412 mg) as a colourless oil, which was used in next step without further purification. A small amount of crude **15** was purified by flash chromatography on SiO_2 (petrol/EtOAc, 50:1 → 20:1) to give **15** as a colourless oil.

Data for 15:

R_f = 0.30 (petrol/EtOAc, 10:1)

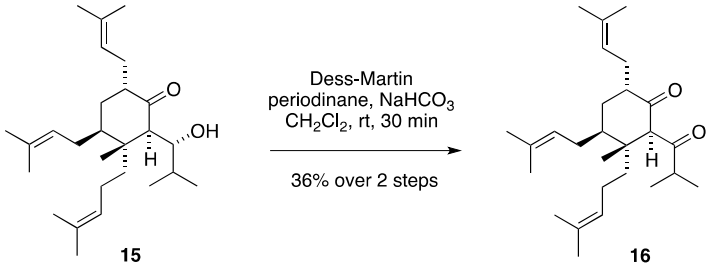
IR (neat): 3518, 2965, 2926, 2869, 1742, 1691, 1449, 1376, 1240 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07 (t, *J* = 5.7 Hz, 2H), 4.98 (t, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 11.5 Hz, 1H), 3.33 (dd, *J* = 11.1, 9.1 Hz, 1H), 2.81 (s, 1H), 2.33 – 2.27 (m, 3H), 2.15 – 2.13 (m, 1H), 2.03 (dt, *J* = 12.7, 9.5 Hz, 1H), 1.97 – 1.93 (m, 1H), 1.87 (dd, *J* = 10.3, 3.8 Hz, 1H), 1.83 – 1.74 (m, 3H), 1.72 (s, 3H), 1.70 (s, 6H), 1.64 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.58 – 1.55 (m, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.98 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ ^{13}C NMR (150 MHz, $CDCl_3$) δ 220.4, 133.1, 131.5, 130.6, 123.7, 122.3, 119.7, 74.7, 50.8, 50.7, 45.4, 37.2, 35.6, 33.1, 31.1, 29.7, 26.5, 24.9, 24.7, 24.7, 20.2, 19.4, 18.8, 17.4, 17.1, 16.9, 16.7.

HRMS (ESI): calculated for $C_{27}H_{47}O_2$ 403.3571 $[M+H]^+$, found 403.3574.

Diketone **16**



To a solution of crude hydroxyketone **15** (412 mg, 1.02 mmol) and $NaHCO_3$ (101 mg, 1.20 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (510 mg, 1.20 mmol) at room temperature. The mixture was stirred for 30 min, and then quenched with saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1) to give diketone **16** (317 mg, 36% over 2 steps) as a colourless oil.

Data for 16:

R_f = 0.30 (Petrol/EtOAc, 10:1)

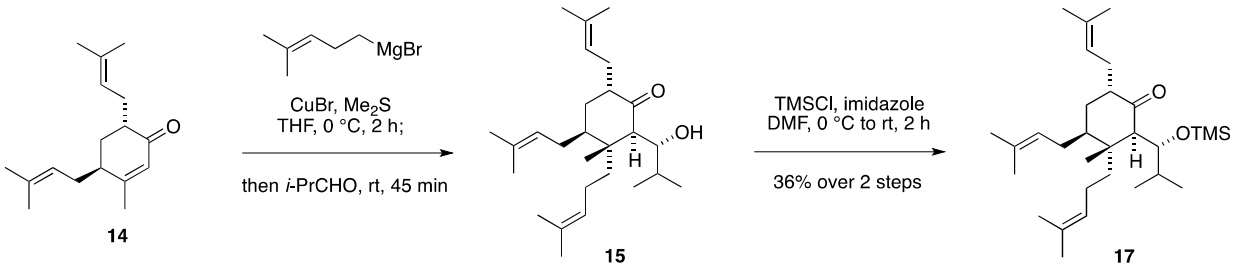
IR (neat): 2964, 2967, 1726, 1697, 1451, 1381 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07 (t, *J* = 7.4 Hz, 1H), 5.04 (t, *J* = 7.2 Hz, 1H), 5.00 (t, *J* = 7.0 Hz, 1H), 3.95 (s, 1H), 2.48 – 2.38 (m, 3H), 2.30 – 2.25 (m, 1H), 2.12 – 2.03 (m, 2H), 1.87 – 1.77 (m, 4H), 1.72 (s, 3H), 1.71 (s, 3H), 1.67 (s, 3H), 1.67 (s, 3H), 1.65 – 1.62 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H), 1.48 – 1.44 (m, 2H), 1.05 (d, *J* = 6. Hz, 3H), 1.05 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 211.4, 210.3, 132.9, 131.8, 130.7, 122.6, 122.1, 119.9, 63.2, 48.8, 44.3, 41.7, 37.0, 36.3, 30.3, 29.6, 25.9, 24.9, 24.7, 24.7, 21.0, 17.4, 17.0, 17.0, 16.7, 16.6.

HRMS (ESI): calculated for $C_{27}H_{45}O_2$ 401.3414 $[M+H]^+$, found 401.3417.

TMS-ether **17**



To a solution of Mg (248 mg, 10.2 mmol) in anhydrous Et_2O (20 mL) was added 5-bromo-2-methyl-2-pentene (0.54 mL, 4.06 mmol) at room temperature, and the resultant mixture was allowed to stir for 30 min at the same temperature. The mixture was then added to a suspension of CuBr (582 mg, 4.06 mmol), Me_2S (0.30 mL, 4.06 mmol) and **14** (500 mg, 2.03 mmol) in anhydrous THF (20 mL) at 0 °C and was stirred for 2 h before slowly warming to room temperature. Isobutyraldehyde (1.85 mL, 20.29 mmol) was then added and the mixture was stirred at room temperature for 45 min. The mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **15** (415 mg) as a colourless oil, which was used in next step without further purification.

TMSCl (336 mg, 3.09 mmol) was added to a suspension of crude **15** (415 mg, 1.03 mmol) and imidazole (351 mg, 5.15 mmol) in DMF (8 mL) at 0 °C, and the resultant mixture was stirred at rt for 2 h. The reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with H_2O (3 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 30:1) to give **17** (350 mg, 36% over 2 steps) as a colourless oil.

Data for 17:

R_f = 0.50 (petrol/EtOAc, 10:1)

IR (neat): 2966, 2916, 2882, 1706, 1449, 1377, 1252 cm^{-1}

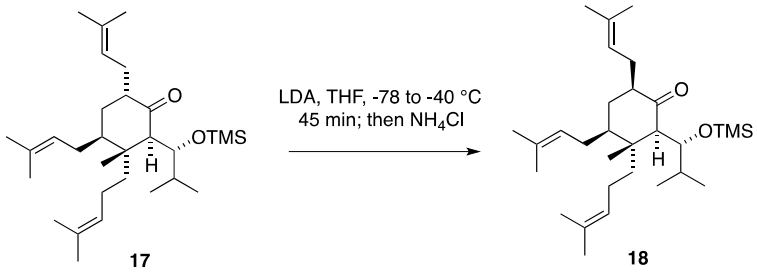
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.06 (t, *J* = 7.7 Hz, 2H), 5.01 (t, *J* = 7.0 Hz, 1H), 3.89 (dd, *J* = 4.6, 2.7 Hz, 1H), 2.72 – 2.69 (m, 1H), 2.36 – 2.32 (overlapped m, 1H), 2.35 (d, *J* = 2.64 Hz, 1H), 2.19 (dd, *J* = 13.6, 5.5 Hz, 1H), 2.02 − 1.83 (m, 5H), 1.78 (dt, *J* = 13.3, 8.5 Hz, 1H), 1.70 (d, *J* = 18.5

Hz, 6H), 1.64 (d, *J* = 19.9 Hz, 6H), 1.58 (d, *J* = 13.8 Hz, 6H), 1.49 – 1.44 (m, 1H), 1.41 – 1.37 (m, 1H), 1.29 − 1.19 (m, 2H), 1.07 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.12 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 214.5, 132.4, 132.3, 131.6, 124.2, 123.8, 122.7, 76.2, 58.4, 46.0, 41.6, 40.9, 40.3, 35.1, 31.7, 28.4, 28.0, 25.9, 25.8, 25.7, 21.8, 20.1, 18.7, 18.2, 18.1, 18.0, 17.8, 1.10.

HRMS (ESI): calculated for $C_{30}H_{55}O_2Si$ 475.3966 $[M+H]^+$, found 475.3969.

TMS-ether **18**



17 18

To a solution of **17** (343 mg, 0.72 mmol) in anhydrous THF (20 mL) at -78 °C was added LDA (2.0 M in THF, 1.07 mL, 2.15 mmol). The resultant mixture was stirred at -78 °C for 15 min and then warmed to -40 °C over 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then passed through a short pad of silica gel with 20:1 petrol/EtOAc as the eluent to remove baseline impurities. The crude product **18** (196 mg) was then obtained as a colourless oil, which was used in the next step without further purification.

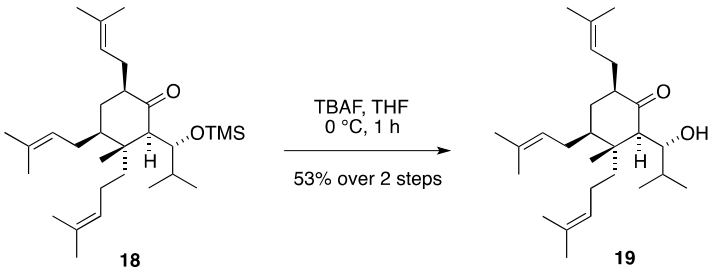
Partial data for 18:

R_f = 0.50 (petrol/EtOAc, 10:1)

IR (neat): 2970, 2916, 1739, 1447, 1374, 1229 cm^{-1}

HRMS (ESI): calculated for $C_{30}H_{55}O_2Si$ 475.3966 $[M+H]^+$, found 475.3968.

1,3-Hydroxyketone **19**



To a solution of crude **18** (196 mg, <0.41 mmol) in anhydrous THF (10 mL) was added TBAF (1.0 M in THF, 0.49 mL, 0.49 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1) to give **19** (154 mg, 53% over 2 steps) as a colourless oil.

Data for 19:

R_f = 0.30 (petrol/EtOAc, 10:1)

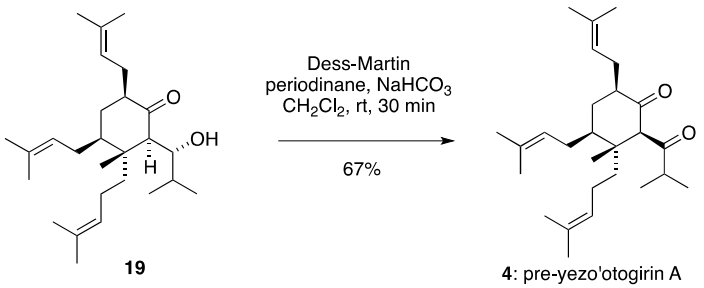
IR (neat): 3529, 1692, 1444, 1382, 1236 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.12 (t, *J* = 6.2 Hz, 1H), 5.08 – 5.03 (m, 2H), 3.99 (d, *J* = 11.3 Hz, 1H), 3.35 (dd, *J* = 11.2, 8.5 Hz, 1H), 2.63 (s, 1H), 2.37 – 2.29 (m, 2H), 2.18 − 2.12 (m, 2H), 2.00 (hept, *J* = 6.2 Hz, 1H), 1.91 – 1.80 (m, 2H), 1.79 – 1.75 (m, 2H), 1.72 (s, 3H), 1.70 – 1.65 (overlapped m, 1H), 1.69 (s, 6H), 1.63 – 1.53 (overlapped m, 2H), 1.60 (s, 6H), 1.60 (s, 3H), 1.18 (q, *J* = 12.5 Hz, 1H), 0.98 (t, *J* = 6.9 Hz, 3H), 0.94 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 218.9, 133.0, 132.6, 131.6, 123.8, 123.3, 121.7, 75.9, 55.6, 52.2, 46.8, 42.9, 36.5, 36.0, 34.5, 27.6, 27.4, 25.9, 25.8, 25.7, 21.2, 20.5, 19.8, 18.5, 17.9, 17.9, 17.7.

HRMS (ESI): calculated for $C_{27}H_{47}O_2$ 403.3571 $[M+H]^+$, found 403.3575.

Pre-yezo'otogirin A (**4**)



To a solution of hydroxyketone **19** (150 mg, 0.37 mmol) and $NaHCO_3$ (37 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (188 mg, 0.44 mmol) at room temperature. The mixture was stirred for 30 min, and then quenched with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 10:1) to give pre-yezo'otogirin A (**4**) (100 mg, 67%) as a colourless oil.

Data for 4:

R_f = 0.50 (petrol/EtOAc, 10:1)

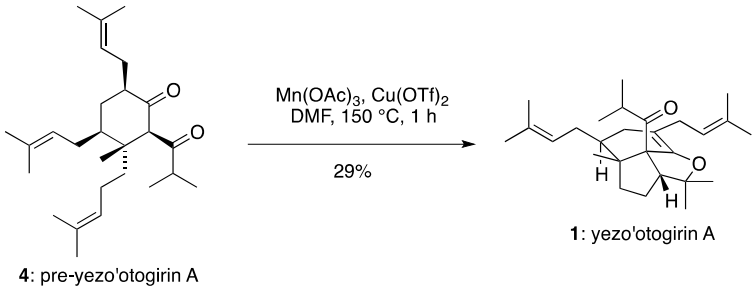
IR (neat): 2969, 2926, 2873, 1724, 1704, 1449, 1378, 1229 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.12 (t, *J* = 7.3 Hz, 1H), 5.08 (t, *J* = 7.3 Hz, 1H), 4.98 (t, *J* = 7.0 Hz, 1H), 3.84 (s, 1H), 2.47 (h, *J* = 9.0 Hz, 1H), 2.40 – 2.32 (m, 2H), 2.15 – 2.10 (m, 2H), 2.07 – 2.00 (m, 1H), 1.96 – 1.91 (m, 1H), 1.82 – 1.75 (m, 2H), 1.73 (s, 3H), 1.69 (s, 3H), 1.68 (m, 1H), 1.66 (s, 3H), 1.60 (s, 6H), 1.57 (s, 3H), 1.50 – 1.46 (m, 2H), 1.18 (q, *J* = 13.2 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 211.1, 210.0, 133.3, 133.0, 131.8, 123.8, 123.2, 121.7, 67.0, 51.3, 45.9, 42.9, 42.6, 36.8, 34.6, 27.7, 27.1, 26.0, 25.9, 25.8, 22.1, 18.7, 18.1, 18.0, 17.82, 17.8, 17.4.

HRMS (ESI): calculated for $C_{27}H_{45}O_2$ 401.3414 $[M+H]^+$, found 401.3417.

Yezo'otogirin A (**1**)



$Mn(OAc)_3 \cdot 2H_2O$ (134 mg, 0.50 mmol) and $Cu(OTf)_2$ (90 mg, 0.25 mmol) were added to a solution of pre-yezo'otogirin A **4** (100 mg, 0.25 mmol) in degassed DMF (20 mL) at room temperature. The reaction mixture was heated to 150 °C and stirred for 1 h. The reaction mixture was then cooled to room temperature and diluted with Et_2O (20 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with H_2O (2 x 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 50:1) to give yezo'otogirin A (**1**) (29 mg, 29%) as a colourless oil.

Data for 1:

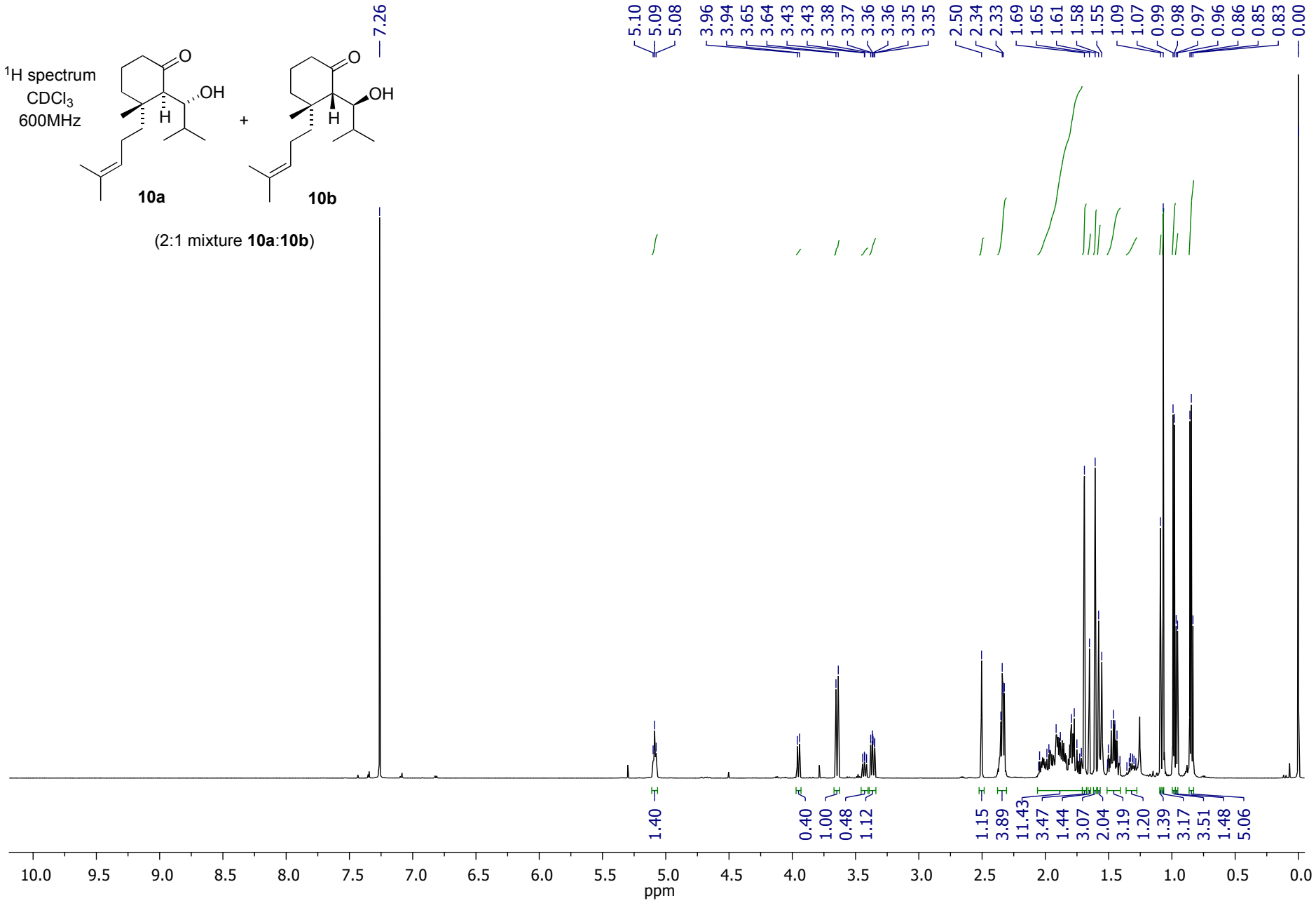
R_f = 0.60 (petrol/EtOAc, 10:1)

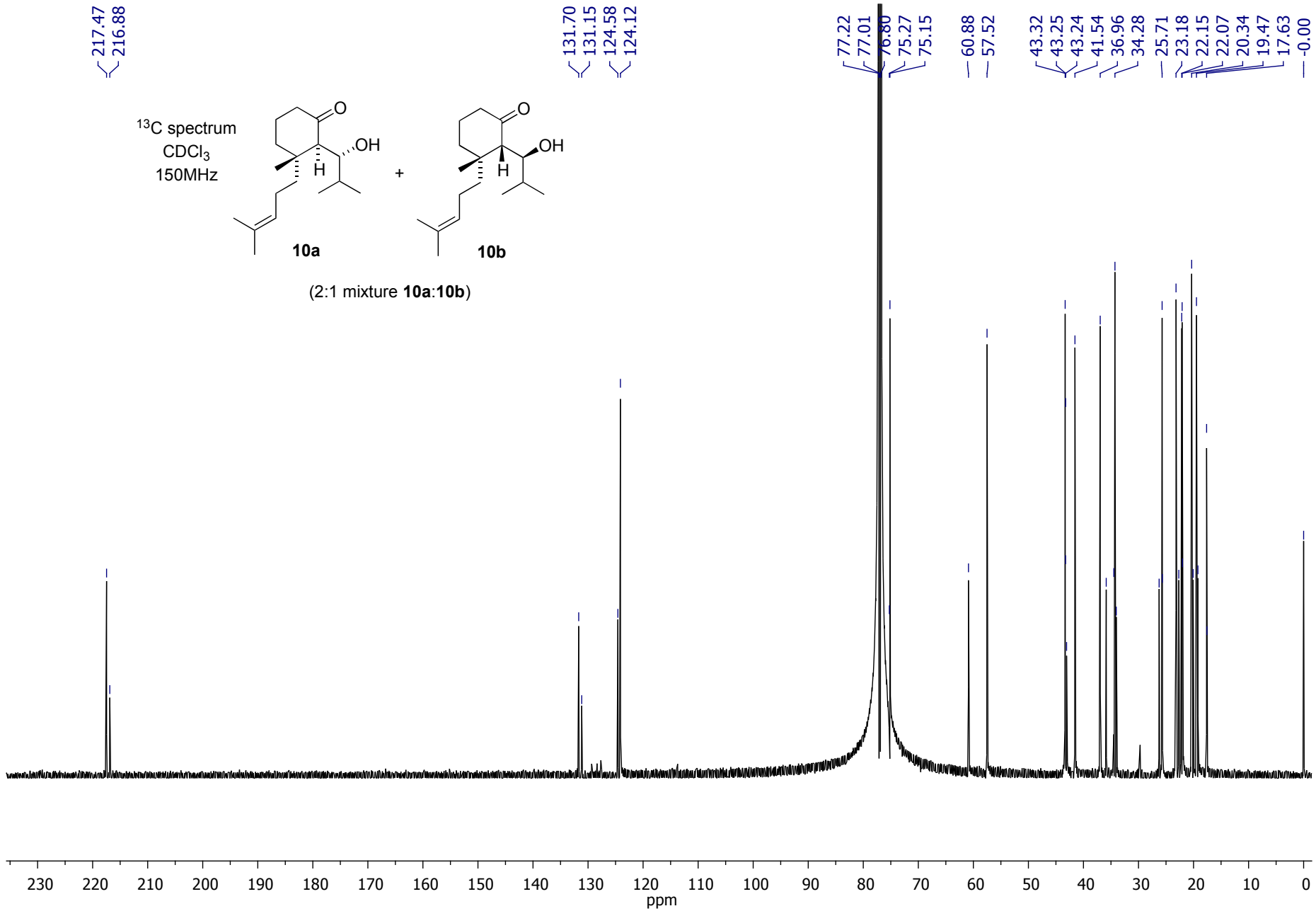
IR (neat): 2970, 2941, 2874, 1739, 1445, 1366, 1217 cm^{-1}

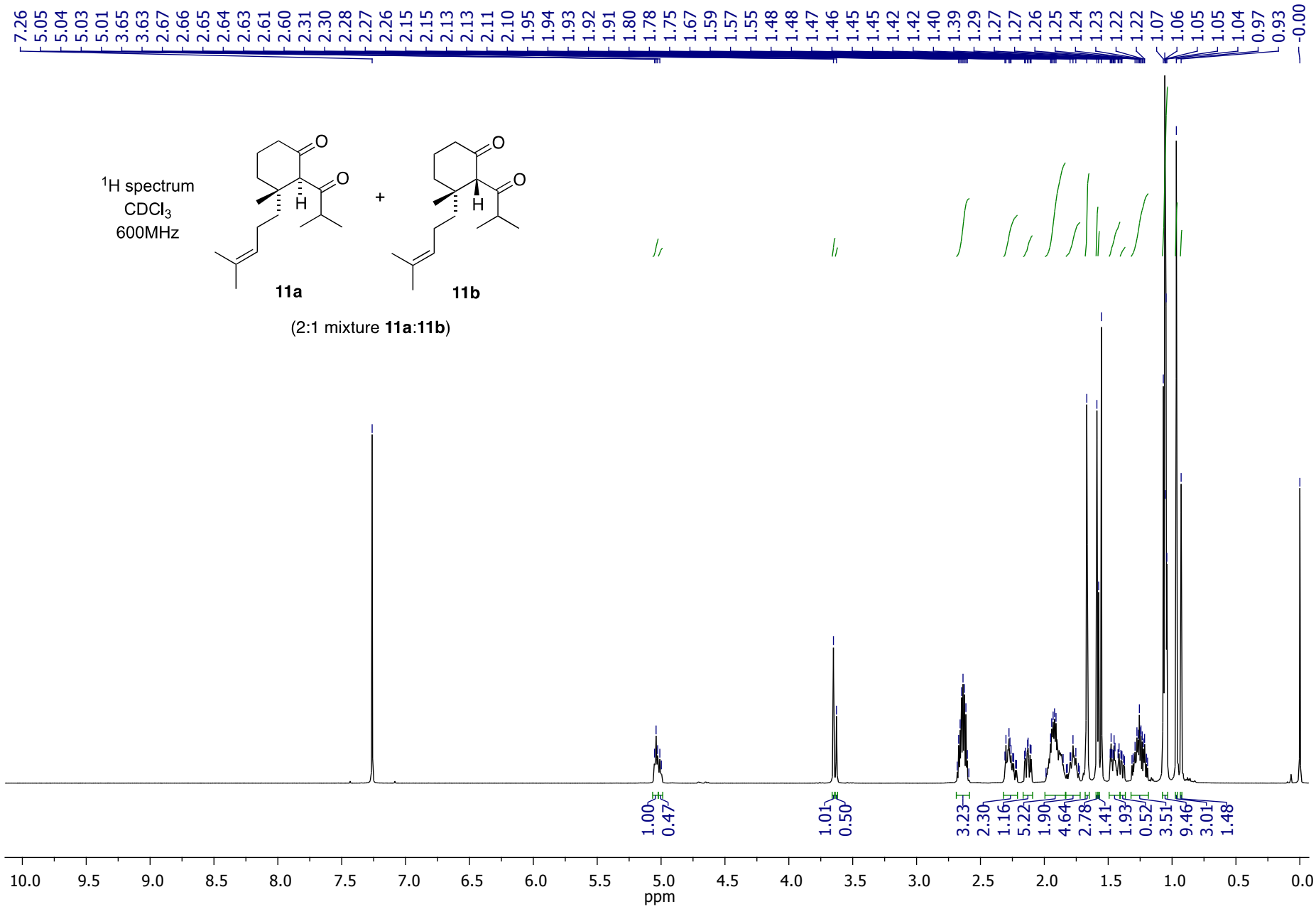
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07 (t, *J* = 7.8 Hz, 1H), 5.06 (t, *J* = 8.4 Hz, 1H), 3.19 (t, *J* = 9.7, 1H), 2.99 (h, *J* = 7.0 Hz, 1H), 2.82 (dd, *J* = 14.2 Hz, 1H), 2.79 (dd, *J* = 7.3 Hz, 1H), 1.94 (dd, *J* = 15.3, 3.1 Hz, 1H), 1.91 – 1.89 (m, 1H), 1.80 (dd, *J* = 14.9, 11.1 Hz, 2H), 1.75 – 1.73 (m, 1H), 1.72 (s, 3H), 1.70 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.56 – 1.52 (m, 2H), 1.38 – 1.33 (m, 1H), 1.19 (s, 3H), 1.17 – 1.15 (m, 1H), 1.14 (s, 3H), 1.03 (d, *J* = 2.4 Hz, 3H), 1.01 (d, *J* = 2.7 Hz, 3H), 0.74 (s, 3H).

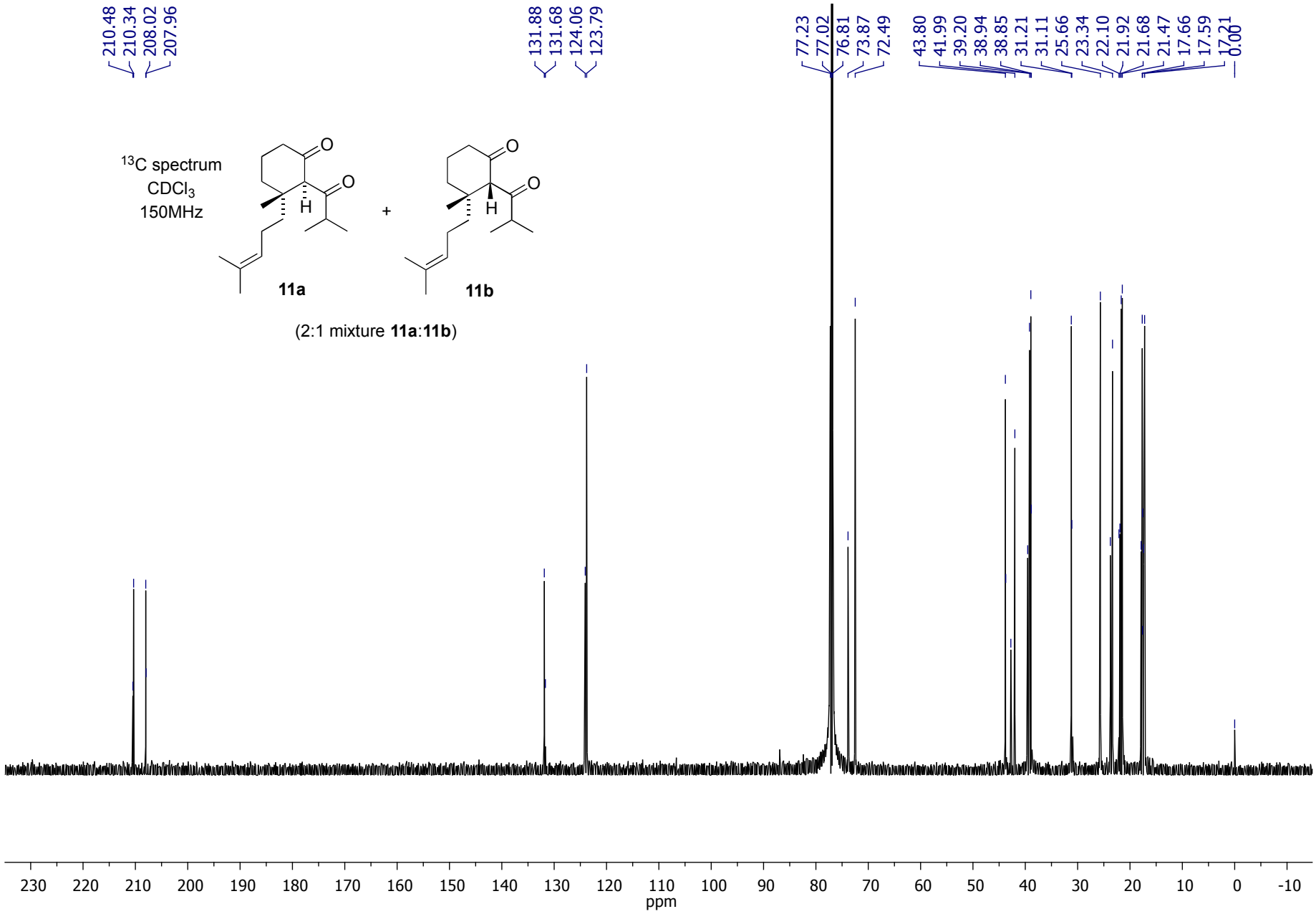
^{13}C NMR (150 MHz, $CDCl_3$): δ 217.4, 149.0, 132.2, 132.0, 124.3, 121.8, 111.4, 83.4, 73.6, 55.0, 48.6, 47.5, 41.3, 37.8, 29.7, 29.5, 29.4, 28.9, 25.9, 25.8, 25.5, 25.3, 21.6, 19.6, 18.3, 17.9, 17.8.

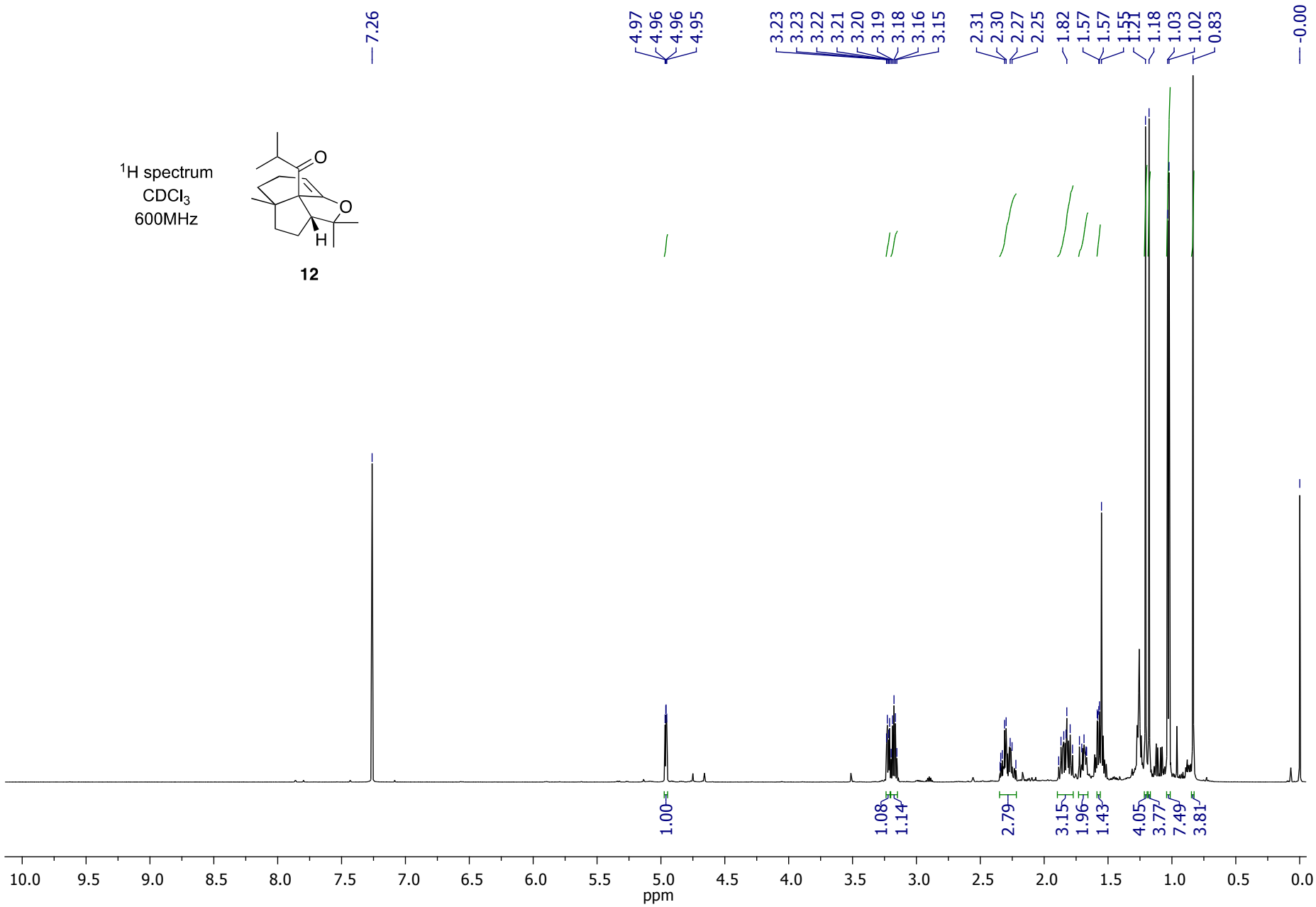
HRMS (ESI): calculated for $C_{27}H_{43}O_2$ 399.3258 $[M+H]^+$, found 399.3256.

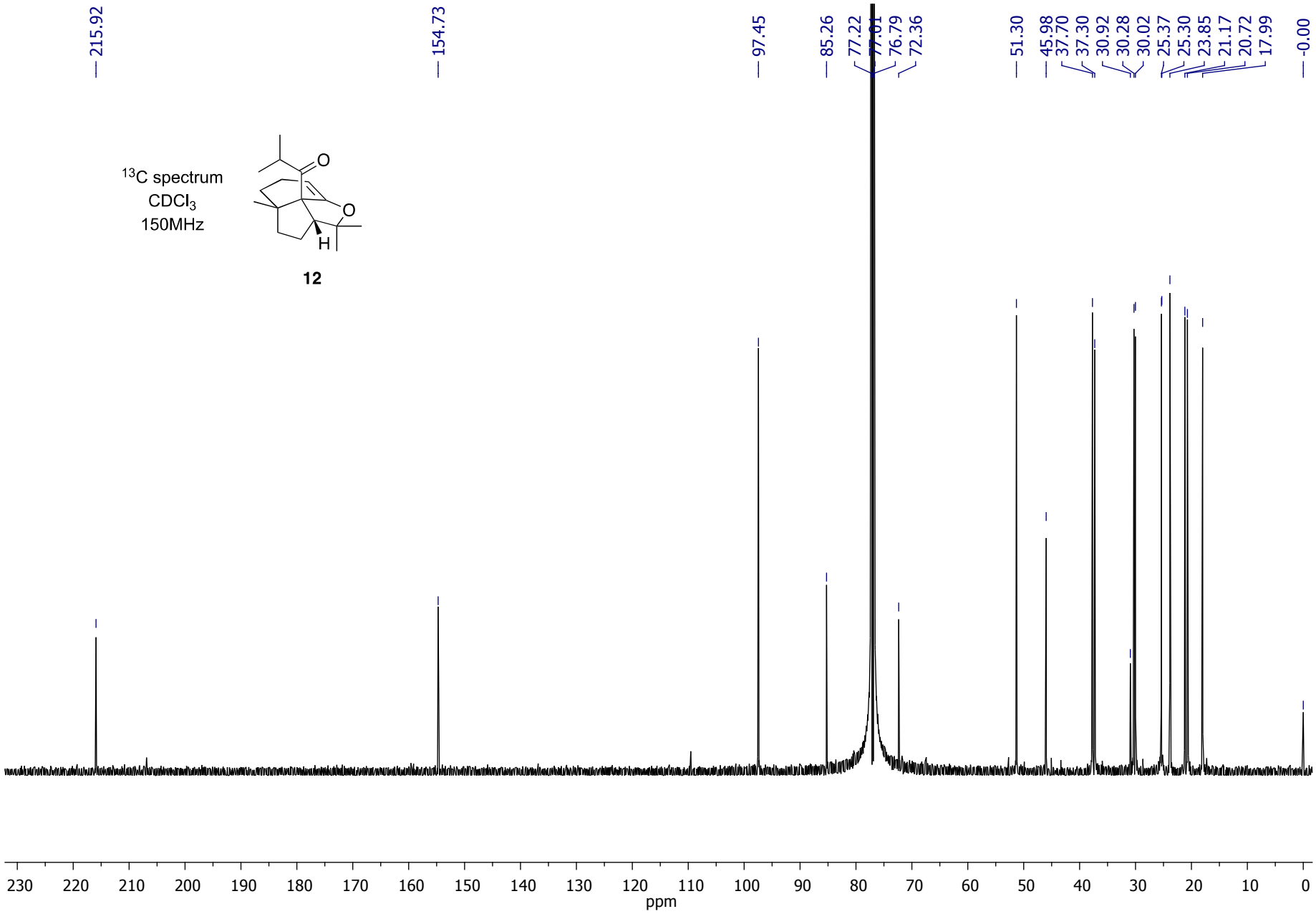

1H spectrum
CDCl3
600MHz
10a
10b
(2:1 mixture 10a:10b)
7.26
5.10
5.09
5.08
3.96
3.94
3.65
3.64
3.43
3.43
3.38
3.37
3.36
3.36
3.35
3.35
2.50
2.34
2.33
1.69
1.65
1.61
1.58
1.55
1.09
1.07
0.99
0.98
0.97
0.96
0.86
0.85
0.83
0.00
1.40
0.40
1.00
0.48
1.12
1.15
3.89
11.43
3.47
1.44
3.07
2.04
3.19
1.20
1.39
3.17
3.51
1.48
5.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

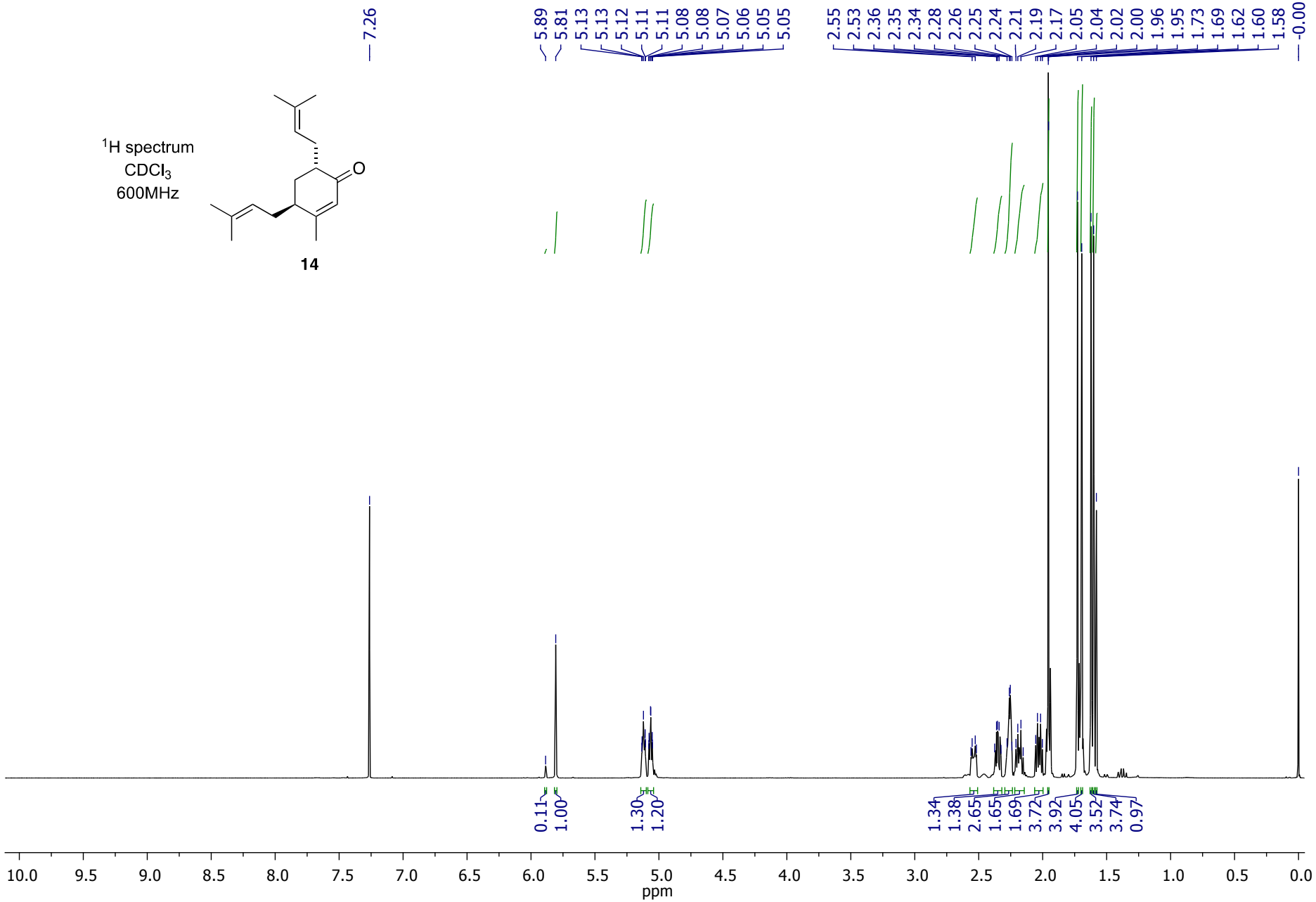

217.47
216.88
131.70
131.15
124.58
124.12
77.22
77.01
76.80
75.27
75.15
60.88
57.52
43.32
43.25
43.24
41.54
36.96
34.28
25.71
23.18
22.15
22.07
20.34
19.47
17.63
-0.00
^{13}C spectrum
$CDCl_3$
150MHz
O
OH
H
+
O
OH
H
10a
10b
(2:1 mixture **10a**:**10b**)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

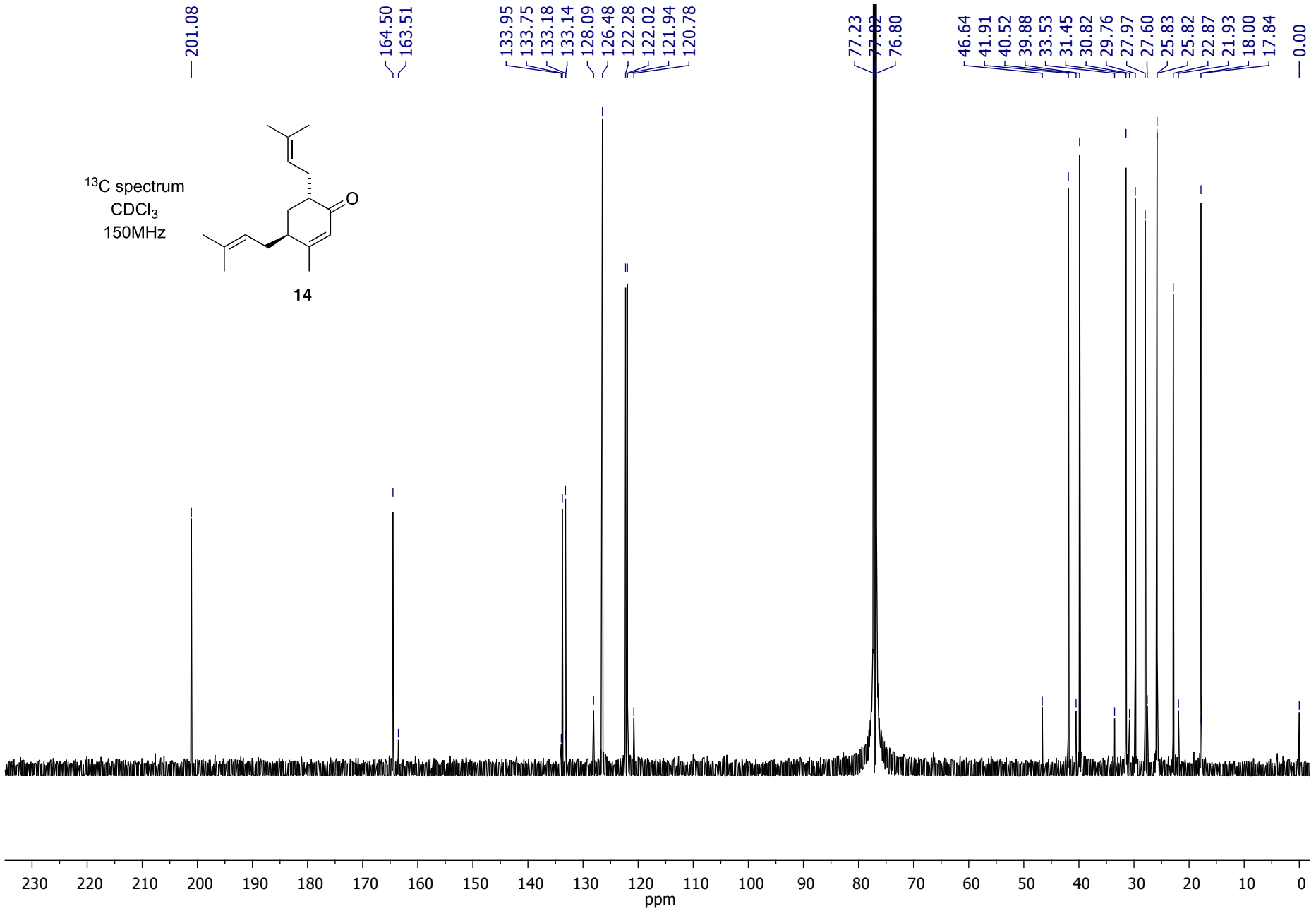

7.26 5.05 5.04 5.03 5.01 3.65 3.63 2.67 2.66 2.65 2.64 2.63 2.61 2.60 2.31 2.30 2.28 2.27 2.26 2.15 2.15 2.13 2.13 2.11 2.10 1.95 1.94 1.93 1.92 1.91 1.80 1.78 1.75 1.67 1.59 1.57 1.55 1.48 1.48 1.47 1.46 1.45 1.45 1.42 1.42 1.40 1.39 1.29 1.27 1.27 1.26 1.25 1.24 1.23 1.22 1.22 1.07 1.06 1.05 1.05 1.04 0.97 0.93 -0.00
1H spectrum
CDCl3
600MHz
O
O
H
+
O
O
H
11a
11b
(2:1 mixture 11a:11b)
1.00 0.47 1.01 0.50 3.23 2.30 1.16 5.22 1.90 4.64 2.78 1.41 1.93 0.52 3.51 9.46 3.01 1.48
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

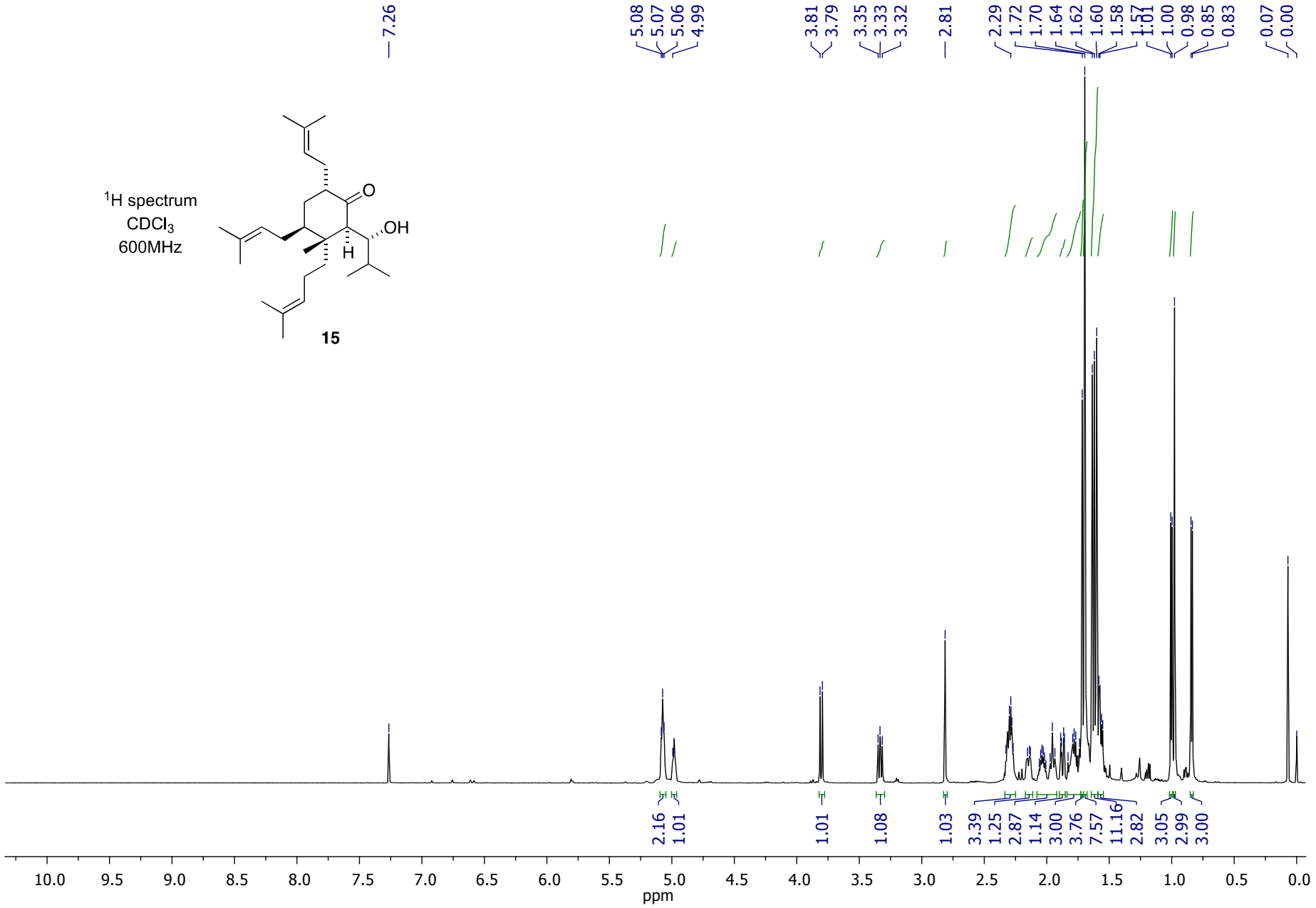

210.48
210.34
208.02
207.96
131.88
131.68
124.06
123.79
77.23
77.02
76.81
73.87
72.49
43.80
41.99
39.20
38.94
38.85
31.21
31.11
25.66
23.34
22.10
21.92
21.68
21.47
17.66
17.59
17.21
0.00
13C spectrum
CDCl3
150MHz
O
O
H
+
O
O
H
11a
11b
(2:1 mixture 11a:11b)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

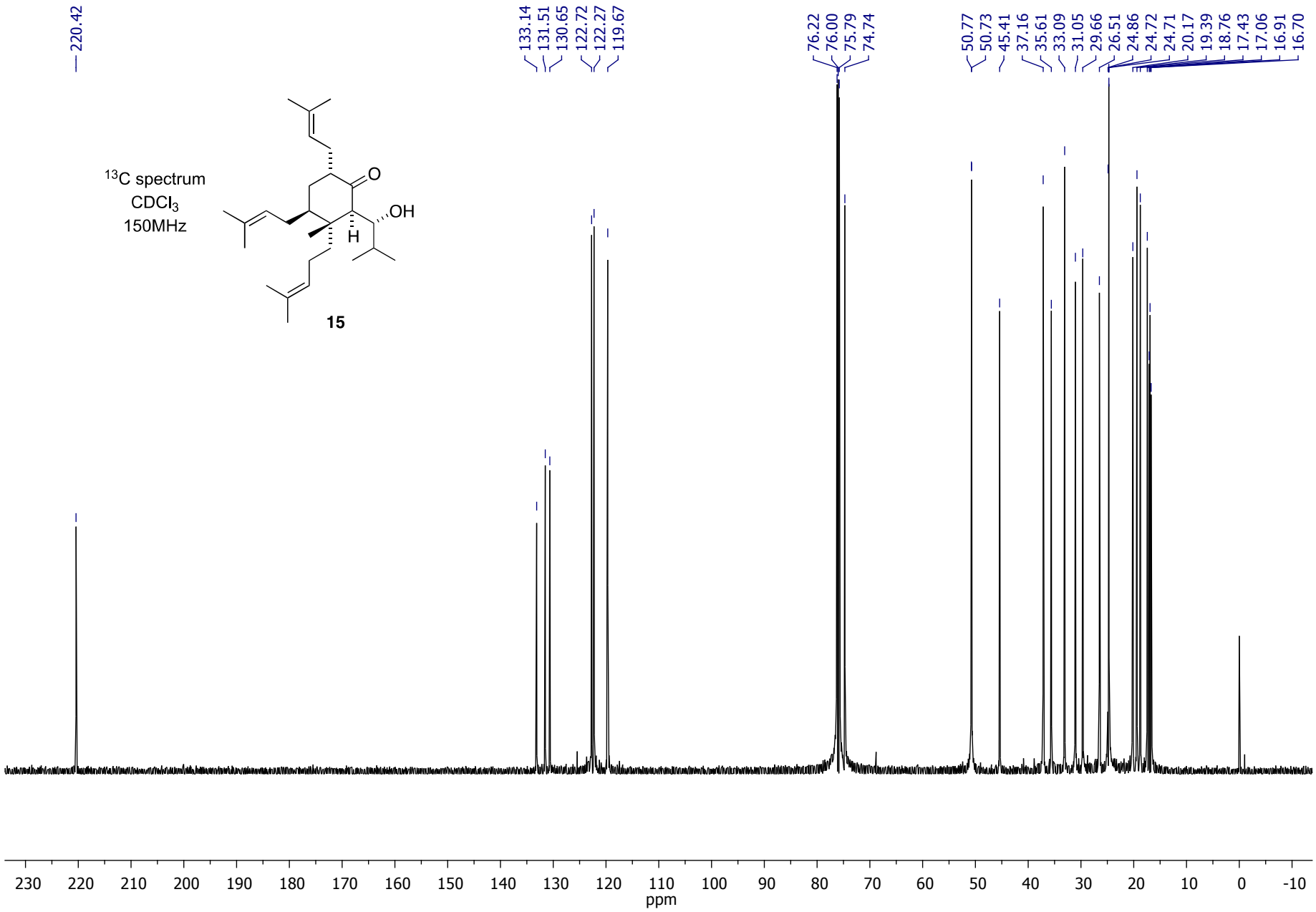

7.26
4.97
4.96
4.96
4.95
3.23
3.23
3.22
3.21
3.20
3.19
3.18
3.16
3.15
2.31
2.30
2.27
2.25
1.82
1.57
1.57
1.55
1.21
1.18
1.03
1.02
0.83
-0.00
1H spectrum
CDCl3
600MHz
O
O
H
12
1.00
1.08
1.14
2.79
3.15
1.96
1.43
4.05
3.77
7.49
3.81
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

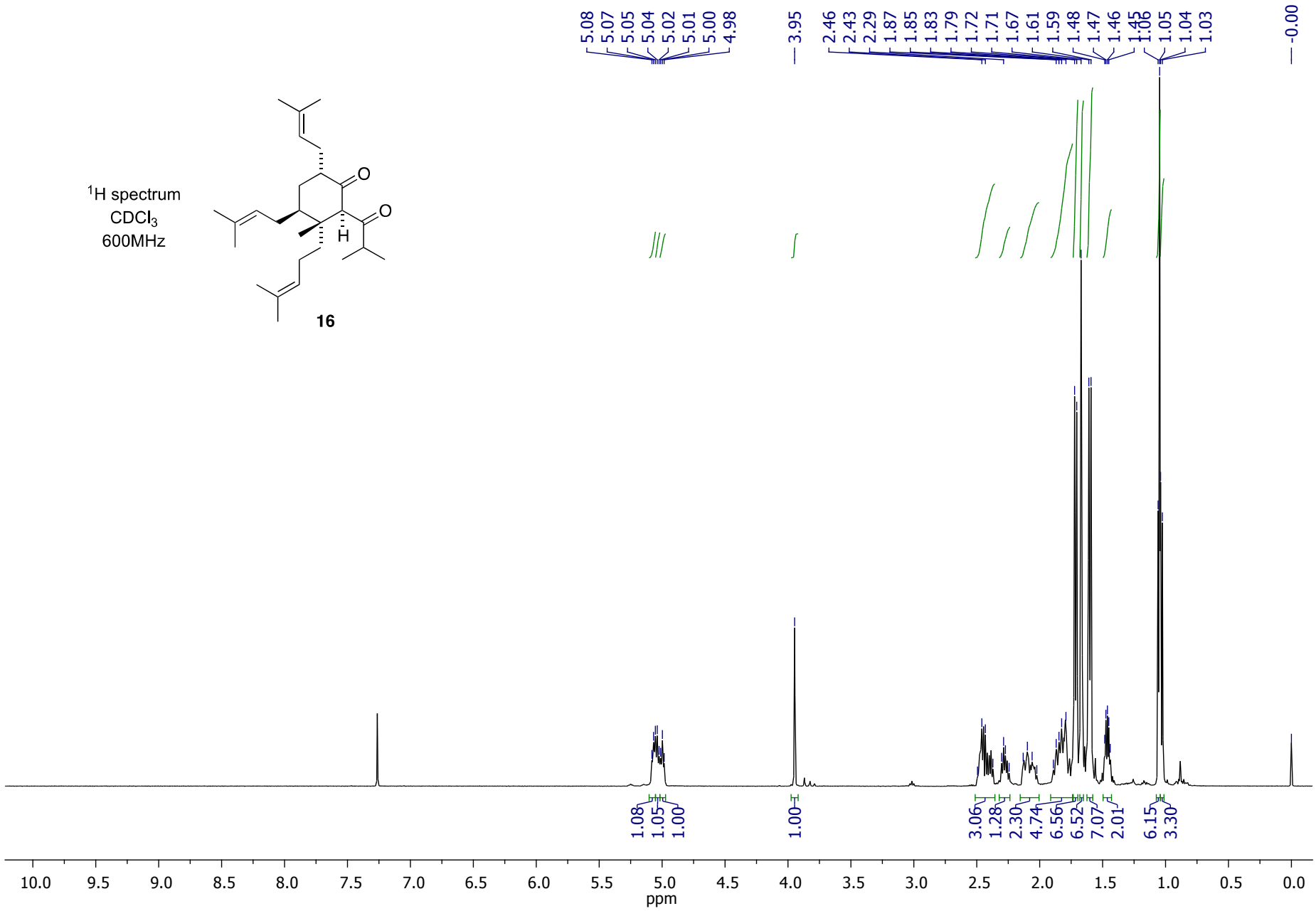

215.92
154.73
97.45
85.26
77.22
77.01
76.79
72.36
51.30
45.98
37.70
37.30
30.92
30.28
30.02
25.37
25.30
23.85
21.17
20.72
17.99
-0.00
^{13}C spectrum
$CDCl_3$
150MHz
O
O
H
12
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

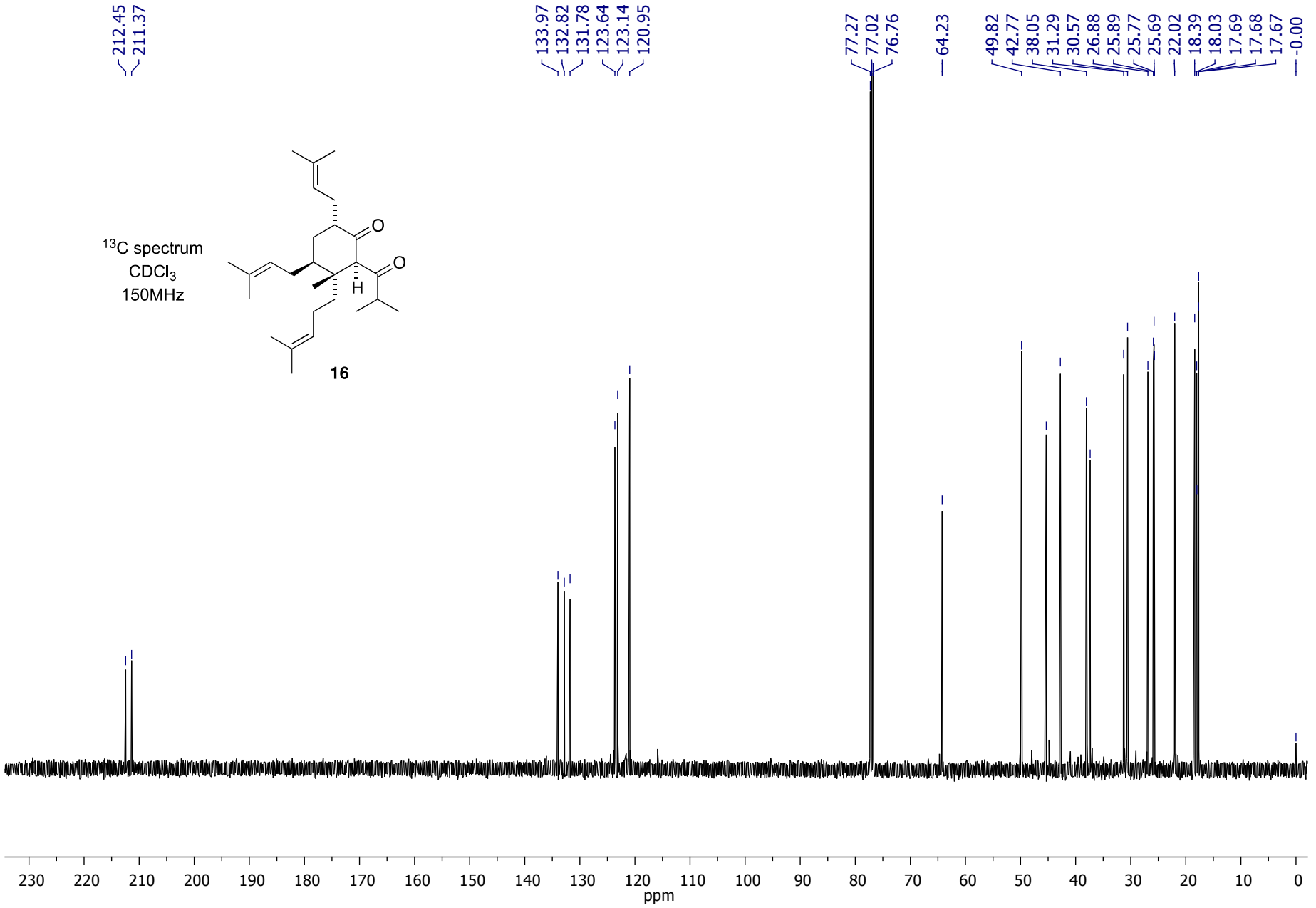

^{1}H spectrum
$CDCl_3$
600MHz
O
14
7.26
5.89
5.81
5.13
5.13
5.12
5.11
5.11
5.08
5.08
5.07
5.06
5.05
5.05
2.55
2.53
2.36
2.35
2.34
2.28
2.26
2.25
2.24
2.21
2.19
2.17
2.05
2.04
2.02
2.00
1.96
1.95
1.73
1.69
1.62
1.60
1.58
-0.00
0.11
1.00
1.30
1.20
1.34
1.38
2.65
1.65
1.69
3.72
3.92
4.05
3.52
3.74
0.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

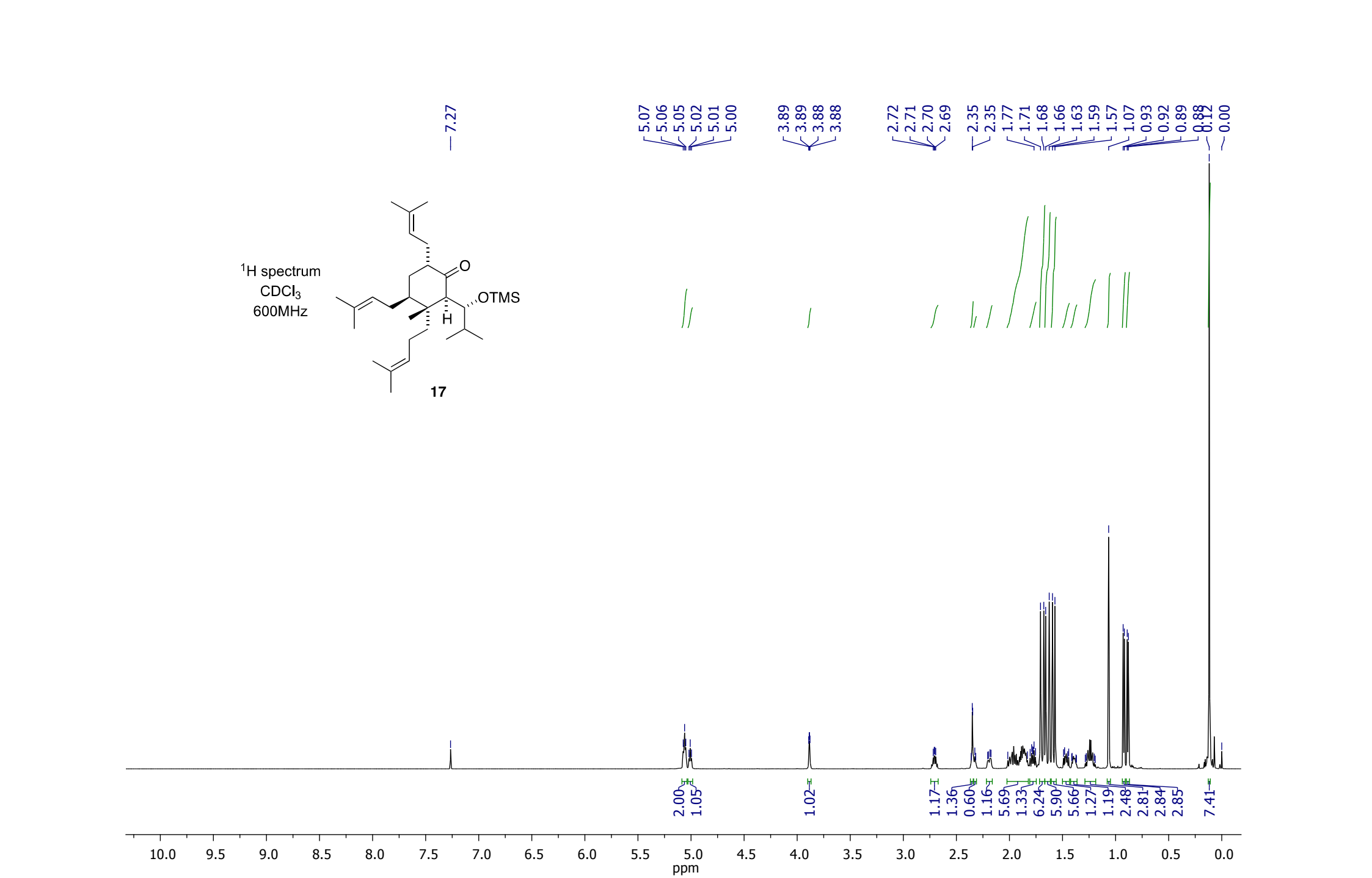

201.08
164.50
163.51
133.95
133.75
133.18
133.14
128.09
126.48
122.28
122.02
121.94
120.78
77.23
77.02
76.80
46.64
41.91
40.52
39.88
33.53
31.45
30.82
29.76
27.97
27.60
25.83
25.82
22.87
21.93
18.00
17.84
0.00
13C spectrum
CDCl3
150MHz
O
14
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

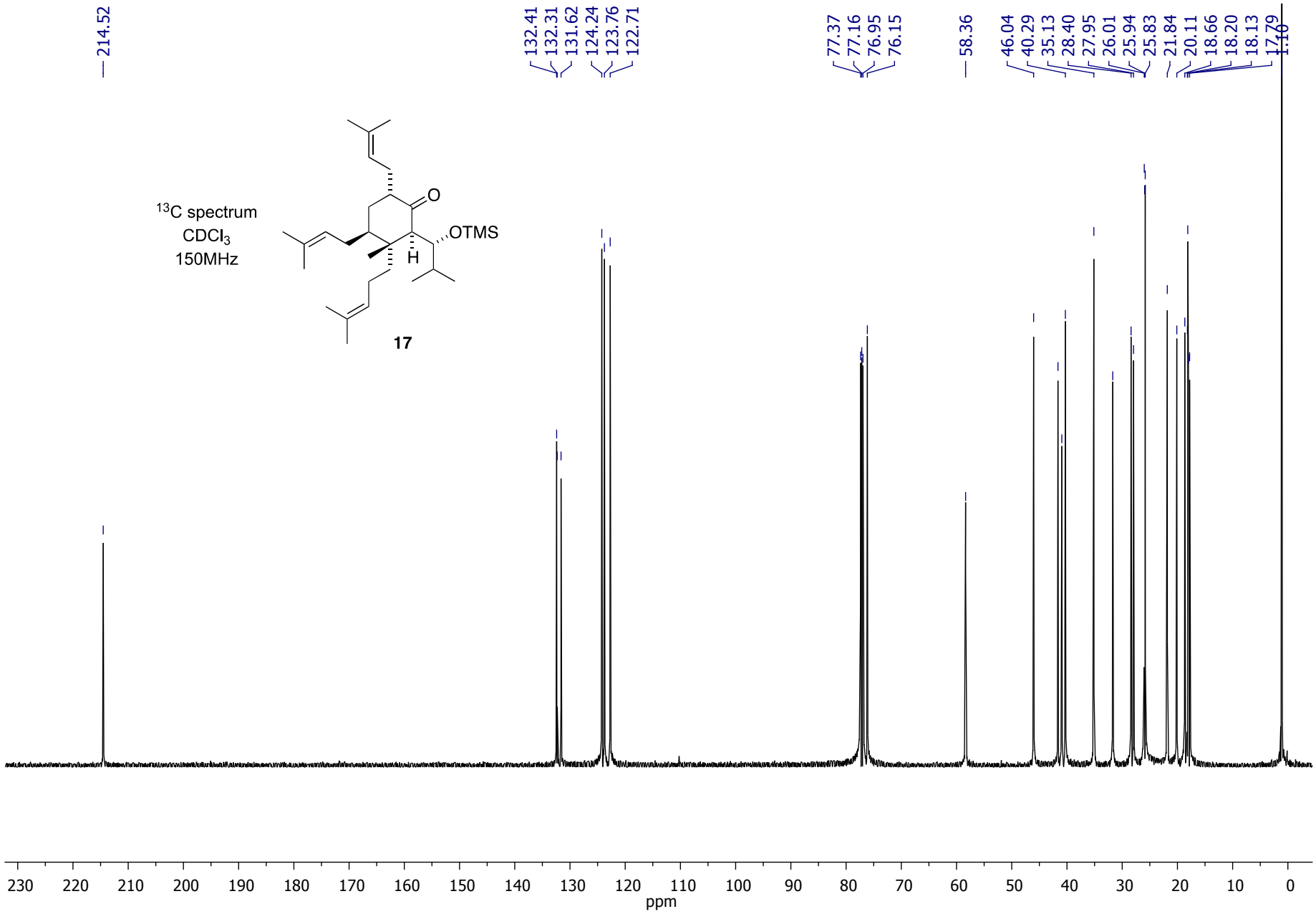

^{1}H spectrum
$CDCl_3$
600MHz
O
OH
H
15
7.26
5.08
5.07
5.06
4.99
3.81
3.79
3.35
3.33
3.32
2.81
2.29
1.72
1.70
1.64
1.62
1.60
1.58
1.57
1.01
1.00
0.98
0.85
0.83
0.07
0.00
2.16
1.01
1.01
1.08
1.03
3.39
1.25
2.87
1.14
3.00
3.76
7.57
11.16
2.82
3.05
2.99
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

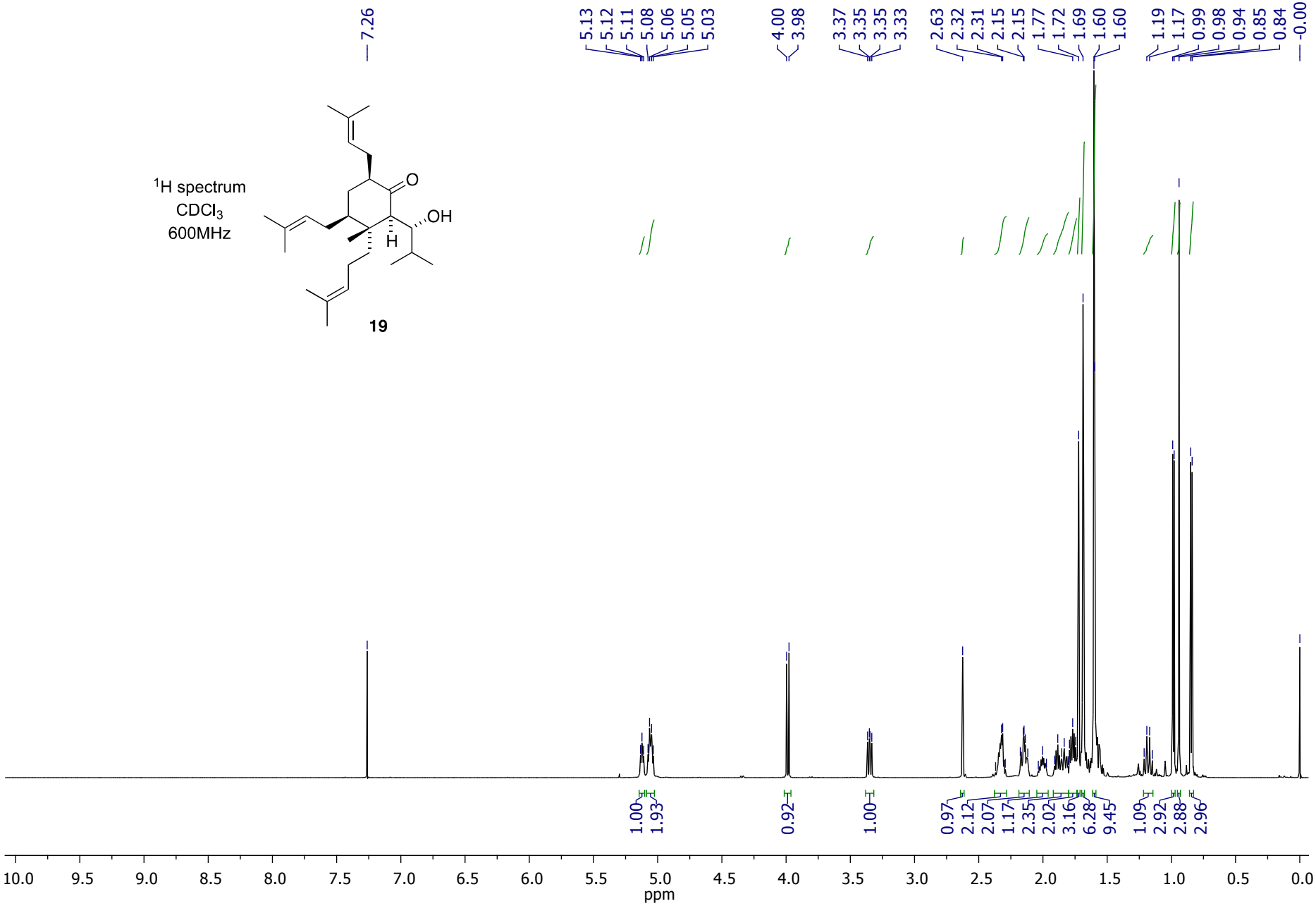

220.42
133.14
131.51
130.65
122.72
122.27
119.67
76.22
76.00
75.79
74.74
50.77
50.73
45.41
37.16
35.61
33.09
31.05
29.66
26.51
24.86
24.72
24.71
20.17
19.39
18.76
17.43
17.06
16.91
16.70
13C spectrum
CDCl3
150MHz
O
OH
H
15
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

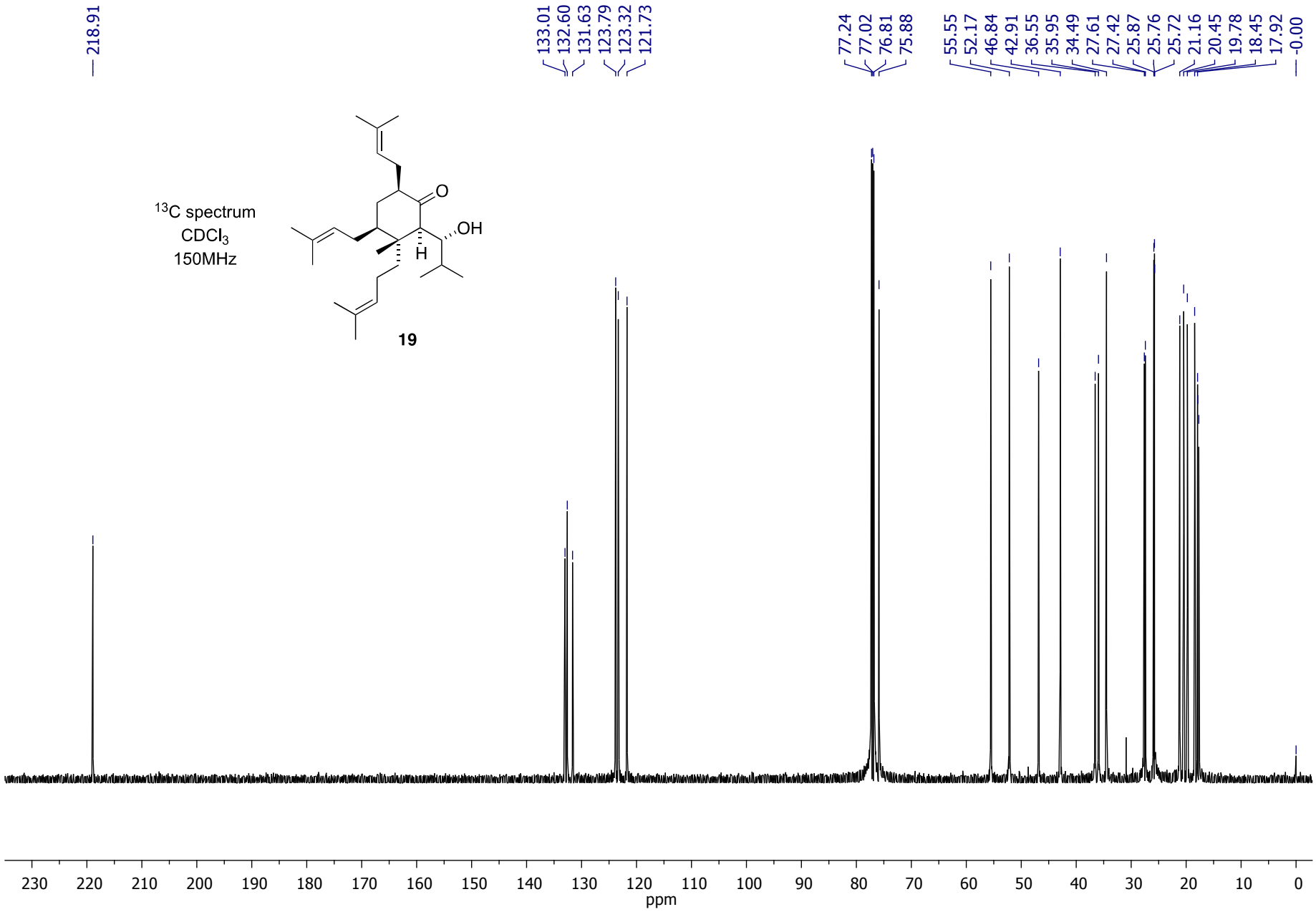

^{1}H spectrum
$CDCl_3$
600MHz
O
O
H
16
5.08
5.07
5.05
5.04
5.02
5.01
5.00
4.98
3.95
2.46
2.43
2.29
1.87
1.85
1.83
1.79
1.72
1.71
1.67
1.61
1.59
1.48
1.47
1.46
1.45
1.06
1.05
1.04
1.03
-0.00
1.08
1.05
1.00
1.00
3.06
1.28
2.30
4.74
6.56
6.52
7.07
2.01
6.15
3.30
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

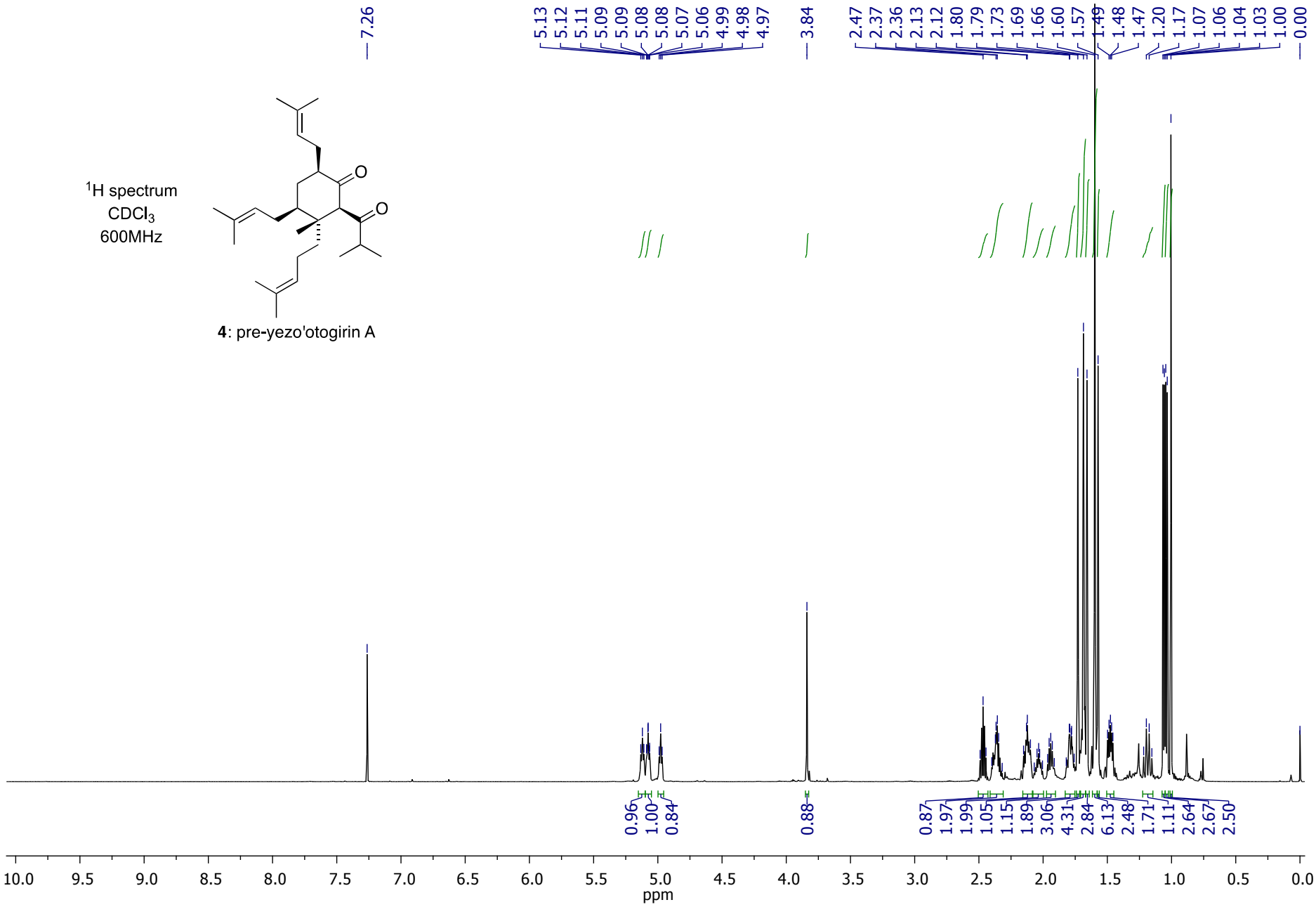

212.45
211.37
133.97
132.82
131.78
123.64
123.14
120.95
77.27
77.02
76.76
64.23
49.82
42.77
38.05
31.29
30.57
26.88
25.89
25.77
25.69
22.02
18.39
18.03
17.69
17.68
17.67
-0.00
13C spectrum
CDCl3
150MHz
O
O
H
16
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

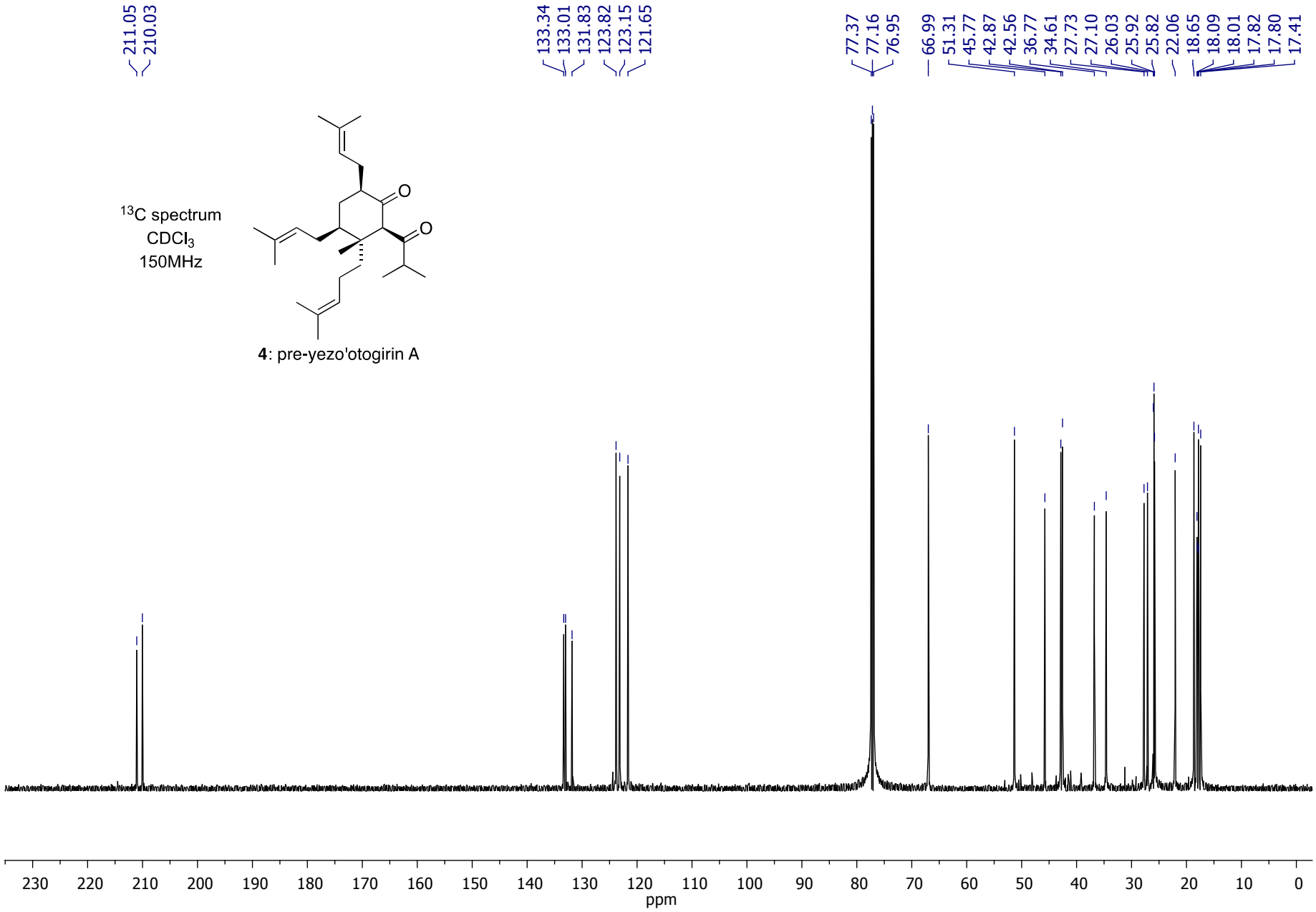

^{1}H spectrum
$CDCl_3$
600MHz
O
OTMS
H
17
7.27
5.07
5.06
5.05
5.02
5.01
5.00
3.89
3.89
3.88
3.88
2.72
2.71
2.70
2.69
2.35
2.35
1.77
1.71
1.68
1.66
1.63
1.59
1.57
1.07
0.93
0.92
0.89
0.88
0.12
0.00
2.00
1.05
1.02
1.17
1.36
0.60
1.16
5.69
1.33
6.24
5.90
5.66
1.27
1.19
2.48
2.81
2.84
2.85
7.41
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


214.52
132.41
132.31
131.62
124.24
123.76
122.71
77.37
77.16
76.95
76.15
58.36
46.04
40.29
35.13
28.40
27.95
26.01
25.94
25.83
21.84
20.11
18.66
18.20
18.13
17.79
1.10
13C spectrum
CDCl3
150MHz
O
OTMS
H
17
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

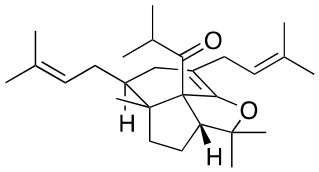

^{1}H spectrum
$CDCl_3$
600MHz
O
OH
H
19
7.26
5.13
5.12
5.11
5.08
5.06
5.05
5.03
4.00
3.98
3.37
3.35
3.35
3.33
2.63
2.32
2.31
2.15
2.15
1.77
1.72
1.69
1.60
1.60
1.19
1.17
0.99
0.98
0.94
0.85
0.84
-0.00
1.00
1.93
0.92
1.00
0.97
2.12
2.07
1.17
2.35
2.02
3.16
6.28
9.45
1.09
2.92
2.88
2.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


218.91
133.01
132.60
131.63
123.79
123.32
121.73
77.24
77.02
76.81
75.88
55.55
52.17
46.84
42.91
36.55
35.95
34.49
27.61
27.42
25.87
25.76
25.72
21.16
20.45
19.78
18.45
17.92
-0.00
13C spectrum
CDCl3
150MHz
O
OH
H
19
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

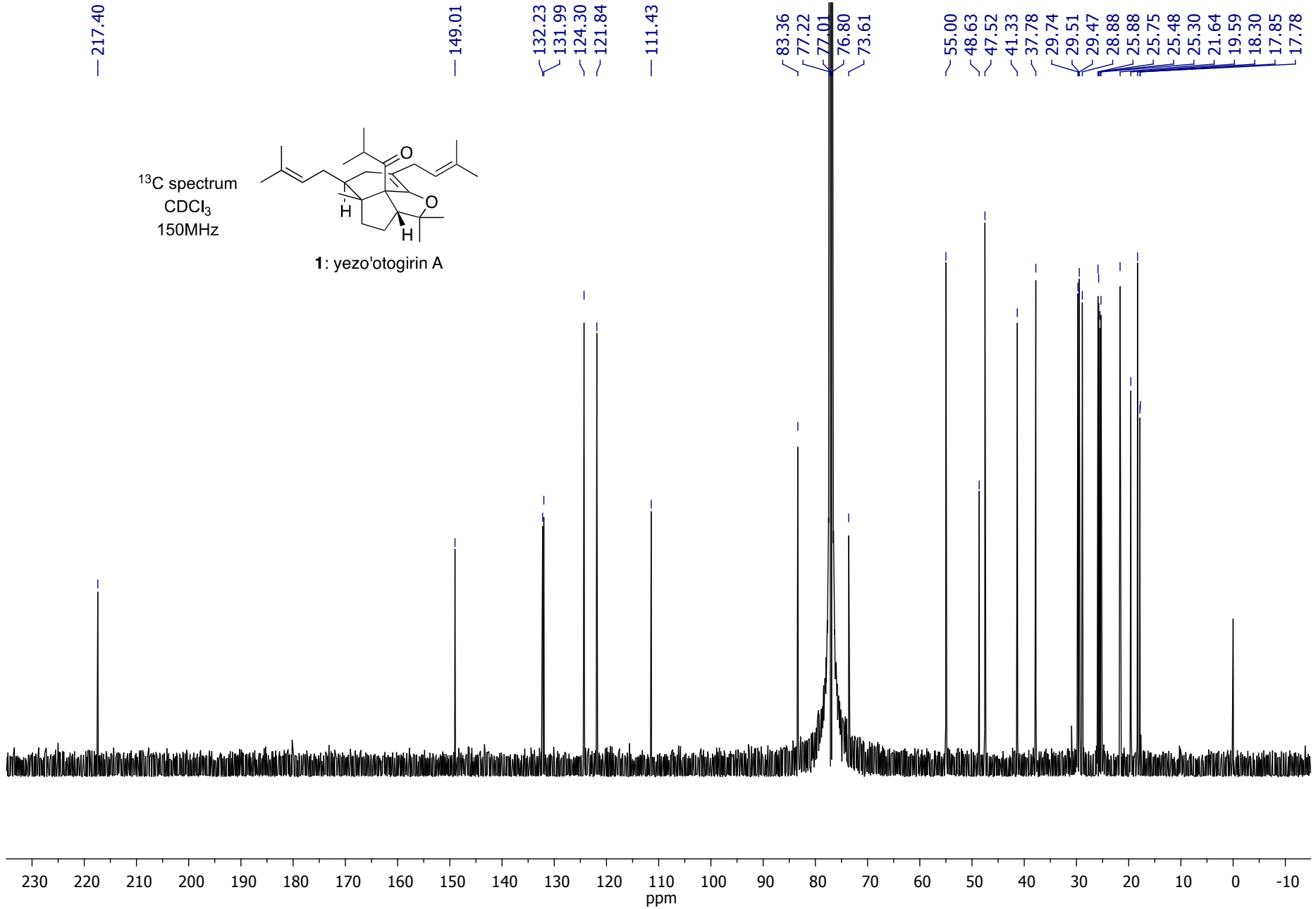

^{1}H spectrum
$CDCl_3$
600MHz
O
O
4: pre-yezo'otogirin A
7.26
5.13
5.12
5.11
5.09
5.09
5.08
5.08
5.07
5.06
4.99
4.98
4.97
3.84
2.47
2.37
2.36
2.13
2.12
1.80
1.79
1.73
1.69
1.66
1.60
1.57
1.49
1.48
1.47
1.20
1.17
1.07
1.06
1.04
1.03
1.00
0.00
0.96
1.00
0.84
0.88
0.87
1.97
1.99
1.05
1.15
1.89
3.06
4.31
2.84
6.13
2.48
1.71
1.11
2.64
2.67
2.50
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


211.05
210.03
133.34
133.01
131.83
123.82
123.15
121.65
77.37
77.16
76.95
66.99
51.31
45.77
42.87
42.56
36.77
34.61
27.73
27.10
26.03
25.92
25.82
22.06
18.65
18.09
18.01
17.82
17.80
17.41
13C spectrum
CDCl3
150MHz
O
O
4: pre-yezo'otogirin A
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

^{1}H spectrum
$CDCl_3$
600MHz



1: yezo'otogirin A


217.40
149.01
132.23
131.99
124.30
121.84
111.43
83.36
77.22
77.01
76.80
73.61
55.00
48.63
47.52
41.33
37.78
29.74
29.51
29.47
28.88
25.88
25.75
25.48
25.30
21.64
19.59
18.30
17.85
17.78
13C spectrum
CDCl3
150MHz
O
H
O
H
1: yezo'otogirin A
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm