Electronic Supplementary Information (ESI)

First enantiospecific synthesis of marine sesquiterpene quinol akaol A

Enrique Alvarez-Manzaneda,* Rachid Chahboun, Esteban Alvarez, Antonio Fernández, Ramón Álvarez-Manzaneda, Alí Haidour, Jose Miguel Ramos and Ali Akhaouzan

**Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, 18071 Granada, Spain.*

eamr@ugr.es

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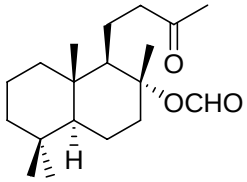
General procedures

All reaction was carried out under argon atmosphere. Dichloromethane (DCM) was dried over calcium hydride, benzene were dried over sodium-benzophenone. Chromatography separations were carried out by flash column on silica gel 60 (230-400 Mesh) or aluminum oxide neutral (50 – 160 μm Mesh) or florisil (100-200 Mesh) using Hexane-Et_2O (H-E) mixture.

Instrumentation**:** Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum Models 782 and 983G spectrophotometers with samples between sodium chloride plates. Data are presented as the frequency of absorption (cm^{-1}). Proton and Carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded on a Varian 400 or 500 spectrometer, chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. Data are presented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = double, t= triplet, m = multiplet J = coupling constant in Hertz (Hz) and the signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations. Infrared (IR) spectra**:** These were recorded as thin films or as solids on PerkinElmer Spectrum Models 782 and 983G spectrophotometers with samples between sodium chloride plates. Only selected absorbancies (νmax) are reported.

Experimental Procedures

(1R,2R,4aS,8aS)-2,5,5,8a-tetramethyl-1-(3-oxobutyl)-decahydronaphthalen-2-yl formate (14).

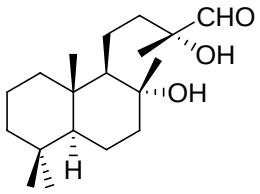


14

A stirred solution of **12** (20 g, 64.93 mmol) and lead (IV) acetate (40 g, 85.7 mmol) in CH_2Cl_2 (500 mL) was slowly bubbled with an O_3/O_2 mixture at 0 ºC, and the course of the reaction was monitored by TLC. When the starting material was consumed (5 h), the solution was flushed with argon and the resulting mixture was filtered through a silica gel (120 g) - sodium bisulfite (10 g, 96.1 mmol) pad and washed with ether (100 mL). The mixture was concentrated in vacuo, and ether (150 mL) was added, the mixture was washed with water (8 x 50 mL), sat. $NaHCO_3$ solution (2 x 20 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give 19.4 g of pure **14** (97%) as a white solid.

Mp 58.5ºC. $[\alpha]_D^{25}$ = - 22.5 (*c* 8.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 2.65 – 2.52 (m, 2H), 2.46 (m, 1H), 2.10 (s, 3H), 1.80 – 1.51 (m, 7H), 1.49 (s, 3H), 1.45 – 1.32 (m, 2H), 1.31 – 1.21 (m, 1H), 1.11 (m, 1H), 1.00 – 0.88 (m, 2H), 0.85 (s, 3H), 0.83 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1 (C), 160.4 (CH), 89.2 (C), 58.2 (CH), 55.7 (CH), 46.5 (CH_2), 41.9 (CH_2), 39.7 ($2CH_2$), 39.7 (C), 33.4 (CH_3), 33.2 (C), 29.9 (CH_3), 21.5 (CH_3), 21.2 (CH_3), 20.1 (CH_2), 19.5 (CH_2), 18.4 (CH_2), 15.6 (CH_3). IR (film) 1718, 1459, 1389, 1364, 1200, 1179, 1126 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{32}O_3Na$ ($M+Na^+$) 331.2249, found: 331.2238.

(R)-2-hydroxy-4-((1R,2R,4aS,8aS)-2-hydroxy-2,5,5,8a-tetramethyl-decahydronaphthalen-1-yl)-2-methylbutanal (13).



13

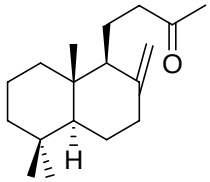
A stirred solution of **12** (1.5 g, 4.87 mmol) in CH_2Cl_2 (20 mL) was slowly bubbled with an O_3/O_2 mixture at -78 ºC and the course of the reaction was monitored by TLC. When the starting material was consumed (1h), the solution was flushed with argon, and triphenylphosphine (1.9 g, 7.29 mmol) was added. The mixture was further stirred for 12h at room temperature and the solvent was removed. Flash chromatography on silica gel (6:4) gave the aldehyde **13** (860 mg, 57%), as a colorless syrup.

$[\alpha]_D^{25}$ = -2.8 (*c* 9.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 3.75 (br s, 1H), 1.91 – 1.80 (m, 4H), 1.77 – 1.50 (m, 5H), 1.49 – 1.27 (m, 4H), 1.28 (s, 3H), 1.24 – 1.13 (m, 2H), 1.13 (s, 3H), 0.88 (m, 1H), 0.86 (s, 3H), 0.78 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0 (CH), 78.4 (C), 74.9 (C), 61.3 (CH), 56.2 (CH), 44.7 (CH_2), 42.1 (CH_2), 39.8 (CH_2), 39.8 (CH_2), 39.4 (C), 33.5 (CH_3), 33.4 (C), 24.4 (CH_3), 22.6 (CH_3), 21.6 (CH_3), 20.64 (CH_2), 18.7 (CH_2), 18.5 (CH_2), 15.4 (CH_3). IR (film) 3413, 1734, 1459, 1388, 1083, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{34}O_3Na$ ($M+Na^+$) 333.2406, found: 333.2393.

Synthesis of methyl ketone 14 from 13.

To a solution of dihydroxy aldehyde **13** (0.5g, 1.61 mmol) in dry CH_2Cl_2 (15 mL) was added lead (IV) acetate (1g, 2.14 mmol) and the reaction mixture was stirred at room temperature for 30 min, at which time TLC showed no starting material. Then, the reaction was quenched with 5% Na_2SO_3 (3 mL), extracted with Et_2O, washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (15% ether/hexanes) to give pure **14** (460 mg, 93%).

4-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)butan-2-one (11).



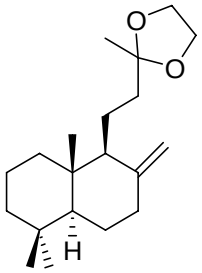
11

A stirred solution of methyl ketone **14** (1.5 g, 4.87 mmol) in collidine (8 mL) was refluxed at 180ºC for 10 h, at which time TLC showed no starting material. Then it was diluted with ether (60 mL) and washed with 1N HCl solution (6 x 15 mL), brine (3 x 10 mL), dried (Na_2SO_4) and concentrated to afford a crude product containing a 6 : 1 mixture of exocyclic and endocyclic trisubstituted regioisomers. The pure ketone **11** (1.04 g, 81%) was obtained, as a colorless syrup, after chromatography of the crude on silica gel (3% ether/hexanes).

$[\alpha]_D^{25}$ = +40.3 (*c* 18.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.43 (s, 1H), 2.59 (m, 1H), 2.48 (m, 1H), 2.37 (ddd, *J* = 12.7, 4.4, 2.5 Hz, 1H), 2.29 (m, 1H), 2.09 (s, 3H), 1.94 (ddd, *J* = 13.0, 9.1, 5.1 Hz, 1H), 1.88 – 1.00 (m, 9H), 1.15 (ddd, *J* =

21.8, 15.3, 9.0 Hz, 1H), 1.87 (m, 1H), 0.86 (s, 3H), 0.79 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5 (C), 148.5 (C), 106.4 (CH_2), 56.5 (CH), 55.7 (CH), 43.1 (CH_2), 42.3 (CH_2), 39.9 (C), 39.1 (CH_2), 38.4 (CH_2), 33.8 (CH_3), 33.7 (C), 30.1 (CH_3), 24.6 (CH_2), 21.8 (CH_3), 19.5 (CH_2), 17.7 (CH_2), 14.4 (CH_3). IR (film) 1718, 1639, 1459, 1363, 1160, 889, 772, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{18}H_{30}ONa$ ($M+Na^+$) 285.2194, found: 285.2205.

2-methyl-2-(2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)ethyl)-1,3-dioxolane (15).



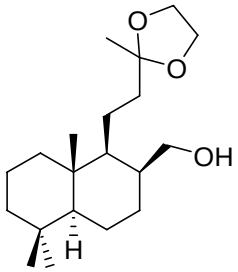
15

To a stirred solution of ketone **11** (1 g, 3.81 mmol) in dry CH_2Cl_2 (5 mL), was added successively ethylene glycol (5 mL) and Iodine (250 mg, 0.98 mmol) and the mixture was stirred at room temperature under an argon atmosphere for 5 h. Then the reaction was worked up by the addition of 5% aqueous sodium bisulfite solution (10 mL), and it was extracted with ether (2 x 30 mL). The organic phase was washed with sat.$NaHCO_3$ solution (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 1.16 g of pure **15** (99%) as a yellow syrup.

$[\alpha]_D^{25}$ = +32.9 (*c* 26.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.54 (s, 1H), 4.14 – 3.69 (m, 4H), 2.36 (br d, *J* = 12.7 Hz, 1H), 1.95 (ddd, *J* = 12.7, 12.7, 5.0 Hz, 1H), 1.86 – 1.65 (m, 4H), 1.62 – 1.44 (m, 4H), 1.42 – 1.33 (m, 3H), 1.33 – 1.31 (m,

2H), 1.30 (s, 3H), 1.21 – 0.87 (m, 1H), 0.86 (s, 3H), 0.79 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7 (C), 110.5 (C), 106.6 (CH), 64.7 (CH_2), 64.7 (CH_2), 57.1 (CH), 55.7 (CH), 42.4 (CH_2), 39.9 (C), 39.3 (CH_2), 38.5 (CH_2), 38.1 (CH_2), 33.8 (CH_3), 33.7 (C), 24.6 (CH_2), 23.9 (CH_3), 21.9 (CH_3), 19.5 (CH_2), 18.0 (CH_2), 14.5 (CH_3). IR (film) 1719, 1643, 1459, 1375, 1221, 1063, 889 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{34}O_2Na$ ($M+Na^+$) 329.2457, found: 329.2464.

((1S,2S,4aS,8aR)-5,5,8a-trimethyl-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-decahydronaphthalen-2-yl)methanol (16).



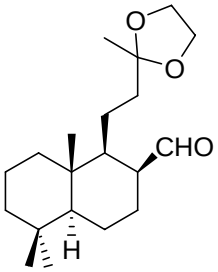
16

1M Borane tetrahydrofuran complex (4.54 mL, 4.54 mmol) was added to a stirred solution of **15** (1 g, 3.27 mmol) in dry THF (25 mL) cooled to 0 ºC. After 1 h, the reaction was allowed to warm to room temperature and stirred for 12 h, at which time TLC showed no starting material. Then the reaction mixtue was cooled to 0 ºC and ethanol (2 mL) was added dropwise, after 5 min, H_2O_2 (4 mL, 30 % aq. solution) and NaOH (4 mL, 4N ethanol solution) were added sequentially. The reaction mixture was allowed to warm to room temperature and stirred for an additional 5 h. The mixture was concentrated in vacuo, ether - water (50:15 mL) was added, and the mixture was washed with brine (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash

chromatography on silica gel (50% ether/hexanes), affording 921 mg of **16** (87%), as white solid.

Mp 82.9ºC. $[\alpha]_D^{25}$ = +32.8 (*c* 14.6, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 – 3.88 (m, 4H), 3.67 (d, *J* = 10.3 Hz, 1H), 3.55 (ddd, *J* = 10.3, 10.3, 2.9 Hz, 1H), 2.02 (ddd, *J* = 13.2, 5.5, 3.0 Hz, 1H), 1.83 (m, 1H), 1.76 (ddd, *J* = 12.8, 12.8, 4.8 Hz, 1H), 1.67 (br d, *J* = 12.8 Hz, 1H), 1.61 – 1.08 (m, 13H), 1.31 (s, 3H), 0.89 (m, 1H), 0.84 (s, 3H), 0.79 (s, 3H), 0.70 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 110.5 (C), 64.7 (2 CH_2), 61.7 (CH_2), 56.7 (CH), 53.4 (CH), 42.2 (CH_2), 39.9 (CH), 39.3 (CH_2), 38.2 (C), 37.9 (CH_2), 33.6 (CH_3), 33.4 (C), 29.5 (CH_2), 23.9 (CH_3), 21.7 (CH_3), 19.7 (CH_2), 18.8 (CH_2), 17.9 (CH_2), 15.9 (CH_3). IR (KBr) 3415, 1464, 1385, 1218, 1064, 1029, 955, 860 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{36}O_3Na$ ($M+Na^+$) 347.2562, found: 347.2553.

(1S,2S,4aS,8aR)-5,5,8a-trimethyl-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-decahydronaphthalene-2-carbaldehyde (17).



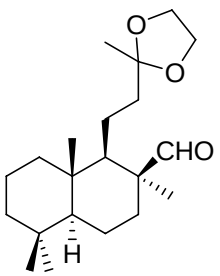
17

Pyridinium dichromate (PDC; 1.16 g, 3.08 mmol) was added to a stirred solution of **16** (0.5 g, 1.54 mmol) in dry CH_2Cl_2 (20 mL) and the mixture was stirred at room temperature under an argon atmosphere for 10 h, at which time TLC showed no remaining starting material. Then, the reaction mixture was worked up by the addition

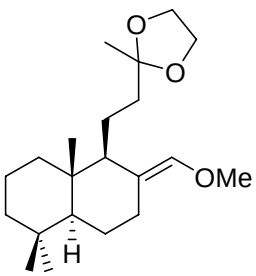
of ether (30 mL), and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether (10 mL). The filtrate was washed with 1N HCl solution (5 mL), brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to yield 462 mg of aldehyde **17**, together with a small quantity of its 8-epimer (5 : 1 ratio) (93%), as a colourless syrup.

$[\alpha]_D^{25}$ = +26.6 (*c* 26.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 4.20 – 3.60 (m, 4H), 2.46 (m, 1H), 2.36 (br d, *J* = 12.0 Hz, 1H), 1.89 (ddd, *J*= 12.0, 12.0, 4.9 Hz, 1H), 1.81 – 1.21 (m, 15H), 1.15 (ddd, *J* = 13.4, 13.4, 3.6 Hz, 1H), 0.97 – 0.87 (m, 2H), 0.84 (s, 3H), 0.77 (s, 3H), 0.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (CH), 110.2 (C), 64.8 (CH_2), 64.8 (CH_2), 56.0 (CH), 54.0 (CH), 47.6 (CH), 42.2 (CH_2), 38.9 (CH_2), 38.8 (C), 38.1 (CH_2), 33.6 (CH_3), 33.4 (C), 26.5 (CH_2), 23.9 (CH_3), 21.7 (CH_3), 19.5 (CH_2), 19.0 (CH_2), 18.8 (CH_2), 15.2 (CH_3). IR (KBr) 1710, 1459, 1376, 1207, 1063, 860, 669 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{34}O_3Na$ ($M+Na^+$) 345.2406, found: 345.2397.

(1R,2S,4aS,8aS)-2,5,5,8a-tetramethyl-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-decahydronaphthalene-2-carbaldehyde (18) and 2-(2-((1R,4aS,8aS,E)-2-(methoxymethylene)-5,5,8a-trimethyl-decahydronaphthalen-1-yl)ethyl)-2-methyl-1,3-dioxolane (19).



18



19

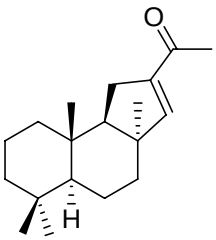
Potassium *tert*-butoxide (63 mg, 0.56 mmol) was added to a stirred solution of **17** (150 mg, 0.47 mmol) in dry benzene (20 mL) under an argon atmosphere. After 5 min methyl iodide (0.1 mL, 1.6 mmol) was added and the reaction mixture was stirred at room temperature for 2 h, at which time TLC showed no starting material. The mixture was concentrated in vacuo to give a crude product, which was dissolved in ether (40 mL) and washed with brine (2 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (10% ether/hexanes), affording 9 mg of **19** (6 %) and 134 mg of pure **18** (85%), as colourless syrups.

18: $[\alpha]_D^{25}$ = -7.0 (*c* 10.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 4.00 - 3.90 (m, 4H), 2.22 (ddd, *J* = 13.4, 3.4, 3.4 Hz, 1H), 1.82 – 1.35 (m, 8H), 1.33 (s, 3H), 1.31 – 1.03 (m, 5H), 1.01 (s, 3H), 0.94 – 0.87 (m, 2H), 0.85 (s, 3H), 0.76 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7 (CH), 109.9 (C), 64.8 ($2CH_2$), 61.1 (CH), 56.0 (CH), 50.0 (C), 43.4 (CH_2), 42.2 (CH_2), 39.6 (C), 38.9 (CH_2), 35.8 (CH_2), 33.5 (CH_3), 33.4 (C), 24.4 (CH_3), 23.8 (CH_3), 21.7 (CH_3), 19.4 (CH_2), 19.1 (CH_2), 18.7 (CH_2), 15.2 (CH_3). IR (film) 1705, 1461, 1376, 1206, 1143, 1060, 855, 755, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{36}O_3Na$ ($M+Na^+$) 359.2562, found: 359.2574.

19: $[\alpha]_D^{25}$ = +49.8 (*c* 13.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (s, 1H), 4.01 – 3.81 (m, 4H), 3.55 (s, 3H), 2.92 (ddd, *J* = 13.0, 4.1, 2.4 Hz, 1H), 1.82 (ddd, *J* = 13.7, 11.5, 3.6 Hz, 1H), 1.75 (br d, *J*= 12.8 Hz, 1H), 1.70 – 1.03 (m, 10H), 1.31 (s, 3H), 1.01 (dd, *J* = 12.7, 2.6 Hz, 1H), 0.92 – 0.80 (m, 2H), 0.85 (s, 3H), 0.79 (s, 3H), 0.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5 (CH), 117.5 (C), 110.6 (C), 64.8 (CH_2), 64.8 (CH_2), 59.6 (CH), 55.9 (CH), 54.7 (CH_3), 42.4 (CH_2), 39.7 (C), 39.1 (CH_2), 38.1 (CH_2), 33.8 (CH_3), 33.7 (C), 27.3 (CH_2), 23.9 (CH_3), 23.3 (CH_2), 21.9 (CH_3), 19.6 (CH_2), 17.3

(CH_2), 14.5 (CH_3). IR (film) 1674, 1459, 1378, 1218, 1129, 1062, 867, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{36}O_3Na$ ($M+Na^+$) 359.2562, found: 359.2551.

1-((3aR,5aS,9aS,9bS)-3a,6,6,9a-tetramethyl-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-1H-cyclopenta[a]naphthalen-2-yl)ethanone (20).



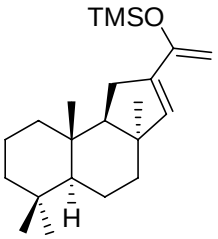
20

HCl (3 mL, 1M) was added to a stirred solution of **18** (100 mg, 0.30 mmol) in THF (15 mL). The reaction mixture was heated under reflux for 3 h, at which time TLC showed no **18.** The reaction was allowed to cool to room temperature and the solvent was evaporated in vacuo. Then, the residue was dissolved in ether (30 mL) and washed with water (2 x 10 mL) and brine (2 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (10% ether/hexanes) to give 69 mg (85%) of methyl ketone **20** as a colourless syrup.

$[\alpha]_D^{25}$ = +27.5 (*c* 3.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (s, 1H), 2.60 (ddd, *J* = 17.1, 8.2, 2.3 Hz, 1H), 2.46 (br d, *J* = 17.1 Hz, 1H), 2.28 (s, 3H), 1.87 (dt, *J* = 13.7, 6.6 Hz, 1H), 1.70 – 1.21 (m, 8H), 1.15 (ddd, *J* = 13.0, 13.0, 3.7 Hz, 1H), 1.08 (s, 3H), 0.92 (dd, *J* = 11.1, 5.3 Hz, 1H), 0.87 (m, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4 (C), 154.8 (CH), 143.0 (C), 59.7 (CH), 50.5 (CH), 48.8 (C), 42.4 (CH_2), 41.8 (CH_2), 36.8 (C), 33.5 (C), 33.5 (CH_2), 33.2 (CH_3), 31.4

(CH_2), 30.5 (CH_3), 26.7 (CH_3), 21.8 (CH_3), 19.5 (CH_2), 18.6 (CH_2), 15.8 (CH_3). IR (film) 1669, 1460, 1366, 1260, 1098, 1019, 803, 610 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{30}ONa$ ($M+Na^+$) 297.2194, found: 297.2183.

Trimethyl(1-((3aR,5aS,9aS,9bS)-3a,6,6,9a-tetramethyl-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-1H-cyclopenta[a]naphthalen-2-yl)vinyloxy)silane (9).



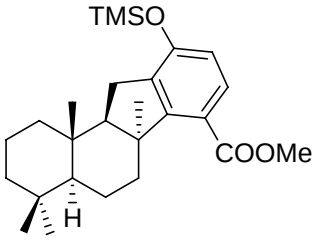
9

To a stirred solution of methyl ketone **20** (160 mg, 0.58 mmol) in dry dichloromethane (15 ml) cooled at 0 ºC, were added successively dropwise under argon atmosphere, *N,N*-diisopropylethylamine (0.30 ml, 1.74 mmol) and trimethylsilyl trifluoromethanesulfonate (0.11 mL, 0.64 mmol). After 30 min, sat. aqueous $NaHCO_3$ solution (5 ml) was added and the aqueous phase was extracted with dichloromethane (2 x 15 ml) and the combined organic phases were dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a crude product, which was purified by flash chromatography on aluminum oxide neutral (3% ether/hexanes), affording 194 mg of **9** (96%), as a white solid.

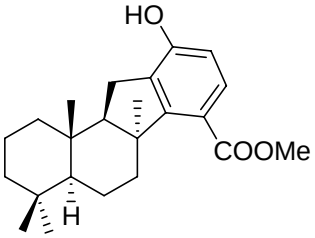
Mp 63.7ºC; $[\alpha]_D^{25}$ = +30.7 (*c* 19.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (s, 1H), 4.32 (s, 1H), 4.28 (s, 1H), 2.57 (ddd, *J* = 16.2, 8.4, 2.2 Hz, 1H), 2.22 (dd, *J* = 16.2, 1.3 Hz, 1H), 1.80 (dt, *J* = 13.2, 6.7 Hz, 1H), 1.62 -1.50 (m, 4H), 1.45 – 1.28 (m, 4H), 1.15 (m, 1H), 1.03 (s, 3H), 0.94 (dd, *J* = 10.7, 5.7 Hz, 1H), 0.87 (m, 1H), 0.86 (s, 3H), 0.76

(s, 3H), 0.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 140.0 (CH), 137.9 (C), 93.4 (CH_2), 60.5 (CH), 50.6 (CH), 47.5 (C), 42.5 (CH_2), 42.2 (CH_2), 36.9 (C), 33.9 (CH_2), 33.6 (C), 33.2 (CH_3), 33.0 (CH_2), 31.2 (CH_3), 21.8 (CH_3), 19.5 (CH_2), 18.7 (CH_2), 15.6 (CH_3), 0.3 ($3CH_3$). IR (film) 1637, 1589, 1459, 1356, 1251, 1009, 841 cm^{-1}.

(6aS,11bS)-methyl 4,4,6a,11b-tetramethyl-10-(trimethylsilyloxy)-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-carboxylate (21) and (4aS,6aS,11aR,11bS)-methyl 10-hydroxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-carboxylate (8).



21



8

Methyl propiolate (145 mg, 1.72 mmol) was added to a solution of diene **9** (300 mg, 0.86 mmol) in xylene (10 mL), and the mixture was heated at 150 °C for 3 days. At this time, TLC showed no remaining starting material. The reaction was allowed to cool to room temperature and then concentrated in vacuo to give an unresolvable mixture of adducts. To a solution of this crude product (400 mg) in 1,4-dioxane (15 mL) was added 2,3-dichloro-5,6- dicyano-1,4-benzoquinone (DDQ; 312 mg, 1.37 mmol), and the reaction mixture was stirred at 100 ºC for 3 h. Then the solvent was evaporated in vacuo, and the residue was dissolved in ether (50 mL), washed with water (5 x 15 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was chromatographed on silica gel (3% ether/hexanes) and

(35 %ether/hexanes) to give 225 mg of pure **21** (61%) and 83 mg of pure phenol **8** (27%).

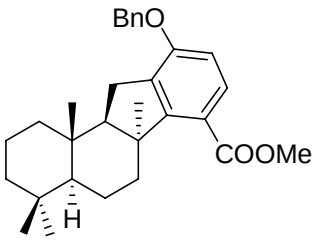
21: Colourless syrup $[\alpha]_D^{25}$ = +50.6 (*c* 8.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 3.86 (s, 3H), 2.81 (dd, *J* = 16.6, 7.1 Hz, 1H), 2.69 (d, *J* = 16.6 Hz, 1H), 2.43 (ddd, *J* = 14.7, 4.5, 4.5 Hz, 1H), 1.78 – 1.35 (m, 7H), 1.36 (s, 3H), 1.22 – 1.05 (m, 2H), 0.97 – 0.88 (m, 2H), 0.86 (s, 3H), 0.73 (s, 3H), 0.29 (s, 3H), 0.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (C), 153.7 (C), 152.7 (C), 136.1 (C), 129.3 (CH), 121.5 (C), 116.8 (CH), 63.3 (CH), 53.2 (CH), 51.9 (CH_3), 49.6 (C), 42.2 (CH_2), 41.0 (CH_2), 37.4 (C), 33.9 (C), 33.7 (CH_2), 33.2 (CH_3), 31.7 (CH_3), 28.6 (CH_2), 22.1 (CH_3), 19.9 (CH_2), 18.7 (CH_2), 15.4 (CH_3), 1.2 ($3CH_3$); IR (film) 1720, 1595, 1484, 1434, 1260, 1018, 848, 667cm^{-1}.

8: White solid Mp 142.3ºC. $[\alpha]_D^{25}$ = +89.2 (*c* 1.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 4.84 (s, 1H), 3.86 (s, 3H), 2.86 (dd, *J* = 16.0, 7.4 Hz, 1H), 2.66 (d, *J* = 16.0 Hz, 1H), 2.45 (ddd, *J* = 14.7, 4.6, 4.6 Hz, 1H), 1.76 (d, *J* = 7.3 Hz, 1H), 1.71 (br d, *J* = 13.1 Hz, 1H), 1.55 - 1.35 (m, 5H), 1.38 (s, 3H), 1.30 - 1.07 (m, 2H), 0.98 – 0.89 (m, 2H), 0.87 (s, 3H), 0.74 (s, 3H), 0.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5 (C), 153.8 (C), 153.2 (C), 130.5 (C), 130.2 (CH), 120.9 (C), 112.8 (CH), 63.5 (CH), 53.1 (CH), 51.9 (CH_3), 49.7 (C), 42.2 (CH_2), 41.0 (CH_2), 37.4 (C), 33.7 (CH_2), 33.6 (CH_3), 33.2 (C), 31.5 (CH_3), 27.4 (CH_2), 22.1 (CH_3), 19.9 (CH_2), 18.6 (CH_2), 15.4 (CH_3). IR (KBr) 3395, 1719, 1693, 1581, 1434, 1279, 1205, 1129, 761, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{32}O_3Na$ ($M+Na^+$) 379.2249, found: 379.2238.

Synthesis of hydroxy ester 8 from 21

To a solution of **21** (150 mg, 0.35 mmol) in methanol (7 mL) was added 1N HCl solution (0.2 mL), and the reaction was stirred at room temperature for 5 min, at which time TLC showed no **21**. Then, the solvent was evaporated in vacuo, ether (25 mL) was added and the mixture was washed with water and brine (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product, which was purified by flash chromatography on silica gel (40% ether/hexanes), affording 112 mg of phenol **8** (90 %), as white solid.

(4aS,6aS,11aR,11bS)-methyl 10-(benzyloxy)-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-carboxylate (22).

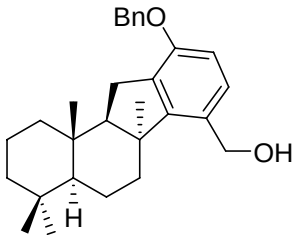


22

Benzyl bromide (73 mg, 0.43 mmol) was added to a stirred suspension of **8** (140 mg, 0.39 mmol) and K_2CO_3 (81 mg, 0.58 mmol) in dry acetone (10 mL) under argon atmosphere. The mixture was heated under reflux overnight. Then, the solvent was evaporated in vacuo, ether (40 mL) was added and the mixture was washed with water (2 x 10 mL) and brine (1 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was purified by flash chromatography (10% ether/hexanes) to give 167 mg (96%) of **22** as white solid.

Mp 82.1ºC. $[\alpha]_D^{25}$ = +44.6 (*c* 9.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.39 (dd, *J* = 7.4, 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 5.13 (s, 2H), 3.86 (s, 3H), 2.90 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.81 (d, *J* = 16.7 Hz, 1H), 2.43 (ddd, *J* = 14.6, 4.8, 4.8 Hz, 1H), 1.78 – 1.60 (m, 2H), 1.58 – 1.35 (m, 5H), 1.39 (s, 3H), 1.30 – 1.04 (m, 2H), 0.98 – 0.88 (m, 2H), 0.87 (s, 3H), 0.75 (s, 3H), 0.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (C), 156.8 (C), 152.6 (C), 137.2 (C), 133.6 (C), 129.9 (CH), 128.7 (2CH), 128.0 (CH), 127.2 (2CH), 120.9 (C), 109.2 (CH), 69.9 (CH_2), 63.4 (CH), 53.0 (CH), 51.9 (CH_3), 49.6 (C), 42.3 (CH_2), 41.0 (CH_2), 37.4 (C), 33.7 (CH_2), 33.6 (CH_3), 33.3 (C), 31.5 (CH_3), 28.3 (CH_2), 22.1 (CH_3), 19.9 (CH_2), 18.6 (CH_2), 15.4 (CH_3). IR (KBr) 1719, 1602, 1387, 1260, 1136, 778, 736, 695, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{30}H_{38}O_3Na$ ($M+Na^+$) 469.2719, found: 469.2728.

((4aS,6aS,11aR,11bS)-10-(benzyloxy)-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluoren-7-yl)methanol (23).



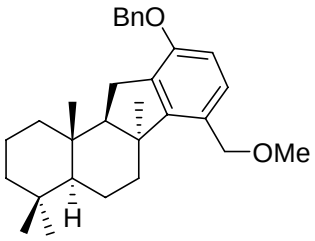
23

$LiAlH_4$ (44 mg, 1.17 mmol) was added to a stirred solution of **22** (175 g, 0.39 mmol) in dry THF (10 mL) cooled to 0ºC and the reaction mixture was kept stirred under an argon atmosphere for 2 h, at which time TLC showed no remaining starting material. Then 2 N HCl (0.5 mL) was added slowly at 0ºC, and the mixture was extracted with

ether (2 x 20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 152 mg of pure **23** (93%) as a white solid.

Mp 98.2ºC. $[\alpha]_D^{25}$ = -29.5 (*c* 10.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (dd, *J* = 7.2, 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 2H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.70 (d, *J* = 12.1 Hz, 1H), 2.90 (dd, *J* = 17.0, 7.5 Hz, 1H), 2.81 (d, *J* = 17.0 Hz, 1H), 2.61 (ddd, *J* = 14.3, 5.1, 5.1 Hz, 1H), 1.80 – 1.45 (m, 4H), 1.44 – 1.25 (m, 4H), 1.26 (s, 3H), 1.23 (m, 1H), 1.01 (dd, *J* = 11.2, 3.9 Hz, 1H), 0.89 (m, 1H), 0.90 (s, 3H), 0.79 (s, 3H), 0.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C), 151.3 (C), 137.7 (C), 132.8 (C), 129.2 (CH), 128.6 (2CH), 128.2 (C), 127.9 (CH), 127.2 (2CH), 109.7 (CH), 69.9 (CH_2), 63.1 (CH_2), 62.6 (CH), 53.0 (CH), 49.8 (C), 42.3 (CH_2), 41.0 (CH_2), 37.5 (C), 35.2 (CH_2), 33.6 (CH_3), 33.4 (C), 32.7 (CH_3), 28.5 (CH_2), 22.1 (CH_3), 20.0 (CH_2), 18.7 (CH_2), 15.6 (CH_3). IR (film) 3372, 1605, 1581, 1491, 1457, 1266, 1249, 1050, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{38}O_2Na$ ($M+Na^+$) 441.2770, found: 441.2759.

(4aS,6aS,11aR,11bS)-10-(benzyloxy)-7-(methoxymethyl)-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorine (24).

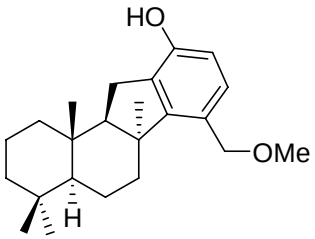


24

Sodium hydride 60% dispersion in mineral oil (100 mg, 2.5 mmol) was added to a stirred solution of **23** (157 mg, 0.38 mmol) in dry THF (12 mL) cooled to 0 ºC under an argon atmosphere. After 5 min, methyl iodide (0.2 mL, 3.21 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction was poured over ice (4g) and concentrated in vacuo to give a crude product, which was dissolved in ether (40 mL) and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (10% ether/hexanes) affording 159 mg of pure **24** (98%) as a white solid.

Mp 74.4ºC. $[\alpha]_D^{25}$ = -19.0 (*c* 7.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 7.5, 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 2H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 3.35 (s, 3H), 2.89 (dd, *J* = 16.9, 7.3 Hz, 1H), 2.79 (d, *J* = 16.9 Hz, 1H), 2.57 (m, 1H), 1.76 (br d, *J* = 11.8 Hz, 1H), 1.68 – 1.25 (m, 7H), 1.23 (s, 3H), 1.17 (ddd, *J* = 13.2, 13.2, 3.5 Hz, 1H), 0.99 (dd, *J* = 11.4, 3.3 Hz, 1H), 0.90 (s, 3H), 0.89 (m, 1H), 0.78 (s, 3H), 0.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6 (C), 151.6 (C), 137.8 (C), 132.7 (C), 129.9 (CH), 128.6 (2CH), 127.8 (CH), 127.2 (2CH), 125.3 (C), 109.3 (CH), 72.7 (CH_2), 69.8 (CH_2), 62.6 (CH), 57.6 (CH), 53.3 (CH_3), 49.9 (C), 42.3 (CH_2), 40.9 (CH_2), 37.5 (C), 35.0 (CH_2), 33.7 (CH_3), 33.3 (C), 32.5 (CH_3), 28.4 (CH_2), 22.1 (CH_3), 20.0 (CH_2), 18.7 (CH_2), 15.5 (CH_3). IR (film) 1606, 1581, 1492, 1459, 1380, 1267, 1247, 1094, 1051, 802, 733, 696 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{30}H_{40}O_2Na$ ($M+Na^+$) 455.2926, found: 455.2937.

(4aS,6aS,11aR,11bS)-7-(methoxymethyl)-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluoren-10-ol (25).

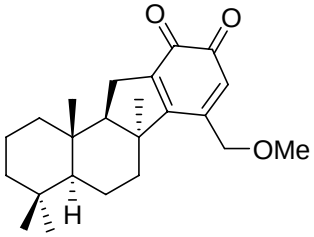


25

To a solution of **24** (200 mg, 0.46 mmol) in dry methanol (8 mL) was added 10 % Pd/C (30 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (2 atm) for 2 h. Filtration and concentration gave 150 mg of pure **25** (95 %) as a colourless syrup.

$[\alpha]_D^{25}$ = -4.32 (*c* 14.8, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 5.18 (br s, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 3.34 (s, 3H), 2.83 (dd, *J* = 16.1, 7.4 Hz, 1H), 2.64 (d, *J* = 16.1 Hz, 1H), 2.59 (m, 1H), 1.72 (m, 1H), 1.68 – 1.56 (m, 3H), 1.48 (m, 1H), 1.42 – 1.31 (m, 2H), 1.27 (m, 1H), 1.20 (s, 3H), 1.16 (m, 1H), 0.98 (dd, *J* = 11.5, 3.4 Hz, 1H), 0.91 (ddd, *J* = 12.8, 3.5, 3.5 Hz, 1H), 0.89 (s, 3H), 0.77 (s, 3H), 0.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.9 (C), 151.5 (C), 130.4 (CH), 129.7 (C), 124.8 (C), 112.5 (CH), 72.6 (CH_2), 62.6 (CH), 57.5 (CH), 53.3 (CH_3), 49.9 (C), 42.2 (CH_2), 40.9 (CH_2), 37.5 (C), 35.0 (CH_2), 33.7 (CH_3), 33.3 (C), 32.5 (CH_3), 27.5 (CH_2), 22.1 (CH_3), 20.0 (CH_2), 18.6 (CH_2), 15.5 (CH_3). IR (film) 3358, 1588, 1493, 1461, 1092, 812, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{34}O_2Na$ ($M+Na^+$) 365.2457, found: 365.2468.

(4aS,6aS,11aR,11bS)-7-(methoxymethyl)-4,4,6a,11b-tetramethyl-1,2,3,4,4a,5,6,6a,11,11a-decahydro-11bH-benzo[a]fluorene-9,10-dione (26).

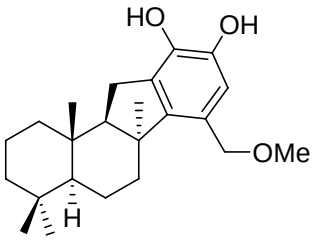


26

Benzeneseleninic anhydride (0.72 g, 2 mmol) was added to a stirred solution of **25** (122 mg, 0.35 mmol) in dry THF (10 mL) and the reaction mixture was refluxed (oil bath) under an argon atmosphere for 2 h, at which time TLC showed no **25**. The reaction mixture was allowed to cool to room temperature and then concentrated in vacuum to give a crude product, which was purified by flash chromatography on florisil (100-200 Mesh; H/E, 3:2), affording 104 mg of **26** (82%) as a red syrup.

$[\alpha]_D^{25}$ = -23.8 (*c* 2.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1H), 4.32 (s, 2H), 3.46 (s, 3H), 2.67 (dd, *J* = 18.8, 8.2 Hz, 1H), 2.56 (d, *J* = 18.8 Hz, 1H), 2.12 (dt, *J* = 14.1, 6.6 Hz, 1H), 1.71 (dq, *J* = 13.3, 6.4 Hz, 1H), 1.67 – 1.34 (m, 7H), 1.29 (s, 3H), 1.14 (dd, *J* = 13.4, 13.4, 3.5 Hz, 1H), 1.01 (dd, *J* = 10.9, 5.8 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H),0.84 (m, 1H), 0.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9 (C), 179.2 (C), 159.7 (C), 150.1 (C), 140.7 (C), 125.4 (CH), 71.0 (CH_2), 61.1 (CH), 59.0 (CH), 51.6 (C), 51.3 (CH_3), 42.1 (CH_2), 40.7 (CH_2), 37.4 (C), 33.5 (C), 33.1 (CH_2), 33.1 (CH_2), 30.7 (CH_3), 28.6 (CH_2), 21.6 (CH_3), 19.5 (CH_2), 18.5 (CH_2), 15.9 (CH_3). IR (film) 1736, 1674, 1601, 1490, 1463, 1216, 1096, 761, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{32}O_3Na$ ($M+Na^+$) 379.2249, found: 379.2261.

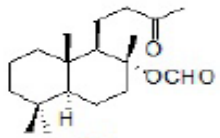
Akaol A (3).



3

Ni Raney 60-70% dispersion in water (0.5 mL) was added to a stirred solution of **26** (50 mg, 0.14 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 15 min, at which time TLC showed no remaining starting material. Then, the resulting mixture was filtered through a silica gel- anhydrous Na_2SO_4 pad and washed with acetone (50 mL). The solvent was evaporated to yield 50 mg of pure **3** (98%) as a white solid.

Mp 136.3ºC. $[\alpha]_D^{25}$ = -13.7 (*c* 8.0, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 6.58 (s, 1H),4.87 (s, 2H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 3.37 (s, 3H), 2.83 (dd, *J* = 16.4, 7.1 Hz, 1H), 2.75 (d, *J* = 16.4 Hz, 1H), 2.67 (m, 1H), 1.82 (br d, *J* = 12.6 Hz, 1H), 1.71 – 1.55 (m, 4H), 1.49 – 1.22 (m, 4H), 1.21 (s, 3H), 1.04 (dd, *J* = 11.5, 2.4 Hz, 1H), 0.98 (ddd, *J* = 13.1, 13.1, 3.4 Hz, 1H), 0.95 (s, 3H), 0.84 (s, 3H), 0.45 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 144.0 (C), 142.9 (C), 141.9 (C), 132.2 (C), 124.1 (C), 117.4 (CH), 73.7 (CH_2), 64.5 (CH), 57.5 (CH_3), 54.9 (CH), 50.1 (C), 43.3 (CH_2), 42.1 (CH_2), 38.6 (C), 36.6 (CH_2), 34.1(CH_3), 34.0 (C), 33.3 (CH_3), 28.8(CH_2), 22.5 (CH_3), 21.0(CH_2), 19.6(CH_2), 15.8 (CH_3). IR (KBr) 3377, 1601, 1461, 1387, 1366, 1291, 1095, 758 cm^{-1}. HRMS (ESI/TOF) *m/z*: calcd for $C_{23}H_{33}O_3$ $(M-H)^-$ 357.2430, found: 357.2425.



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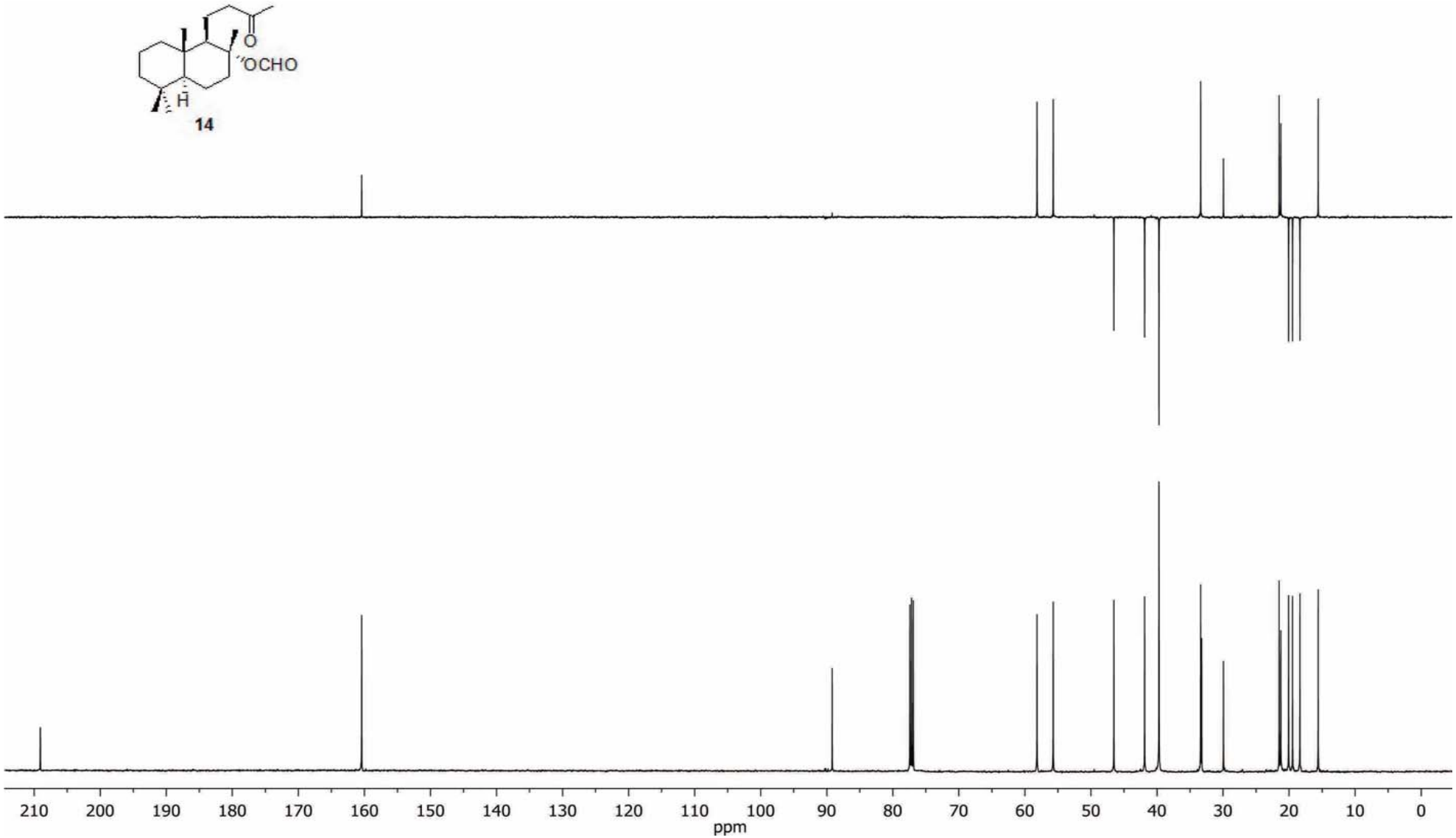

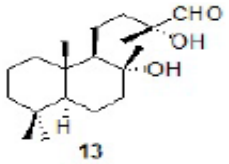

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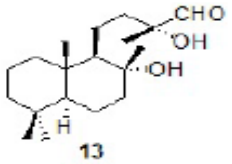

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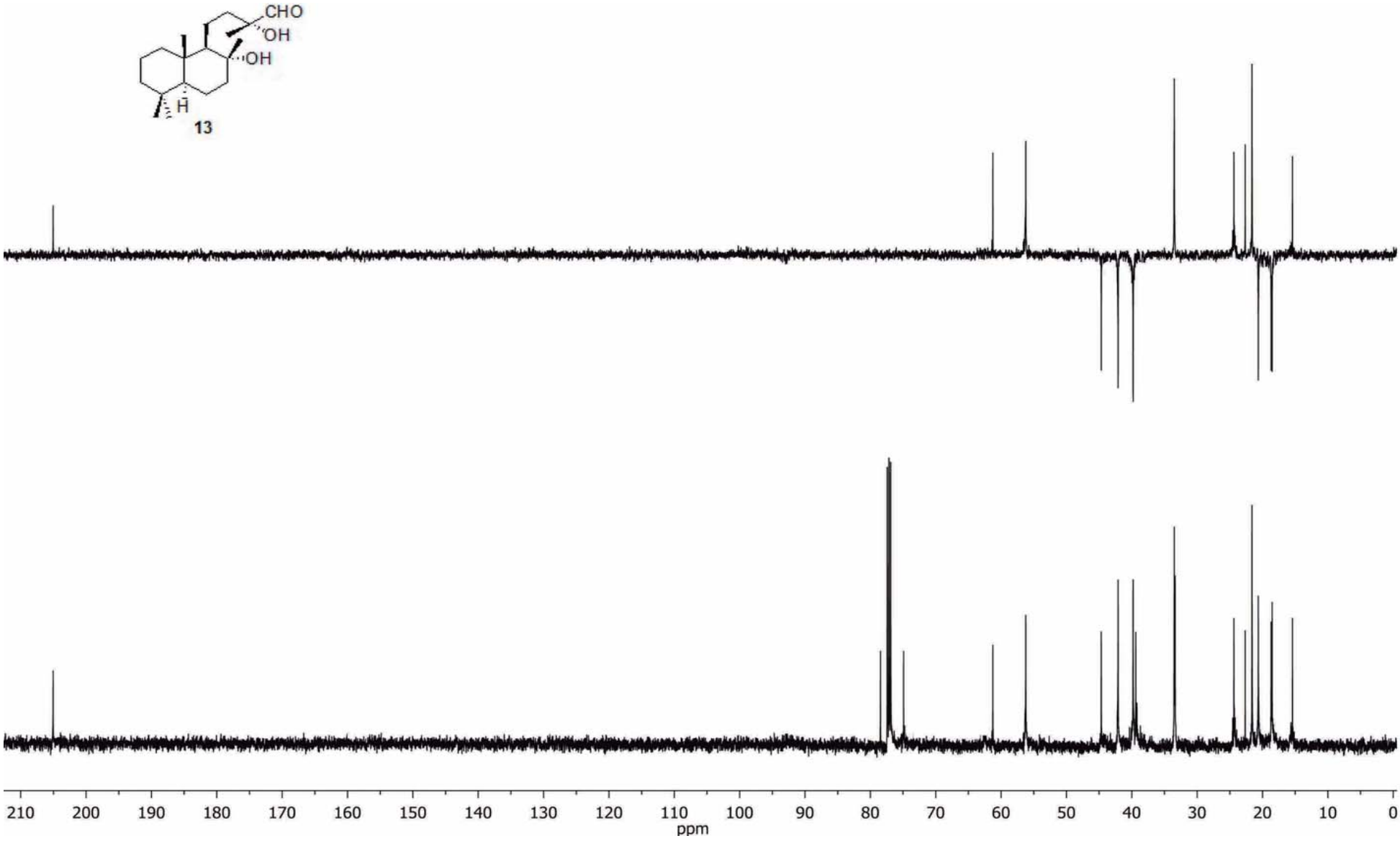

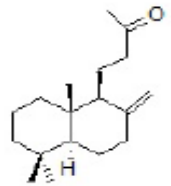

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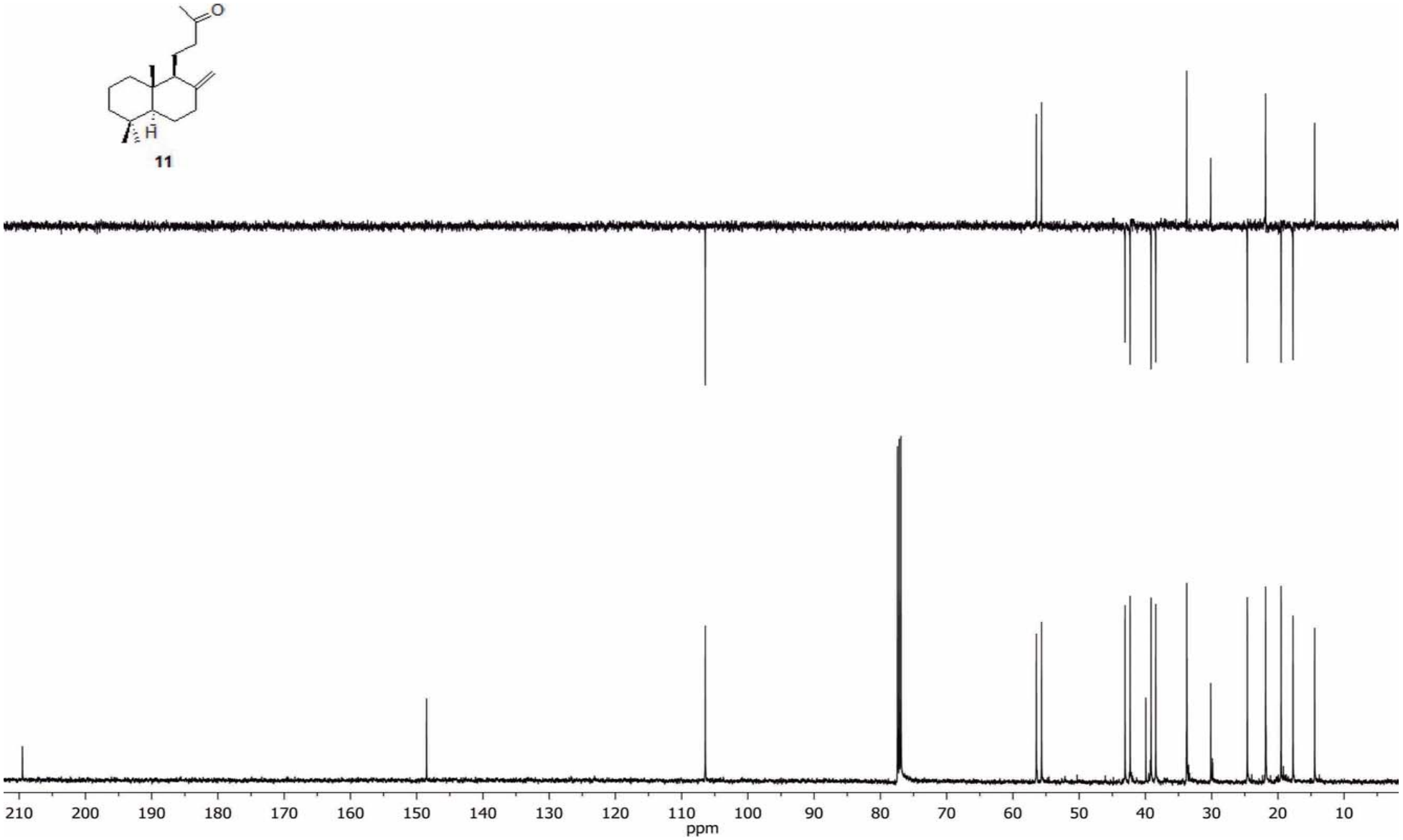

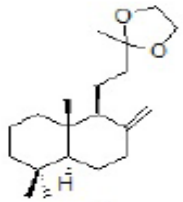

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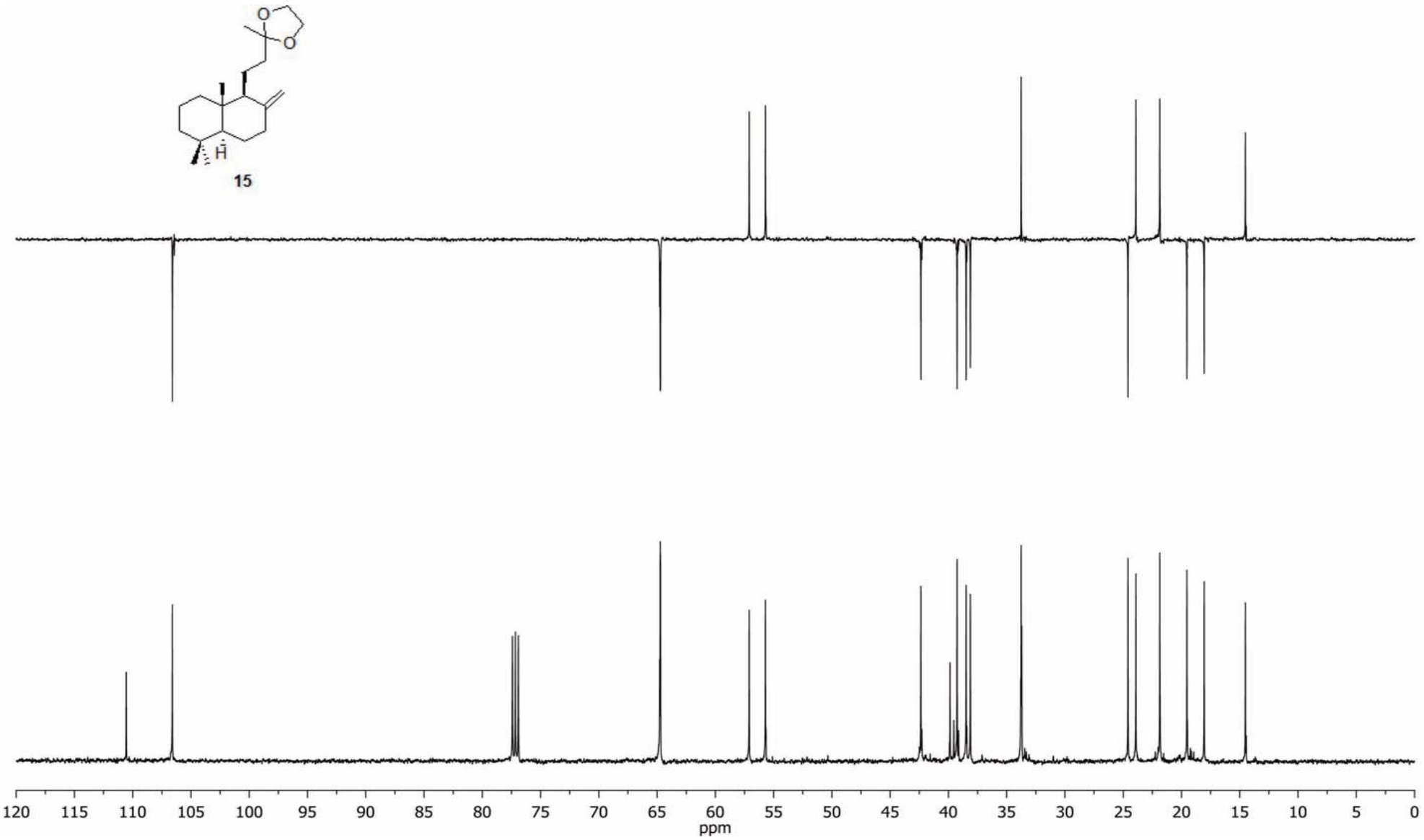

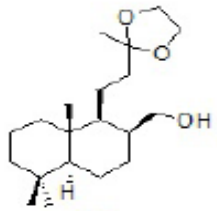

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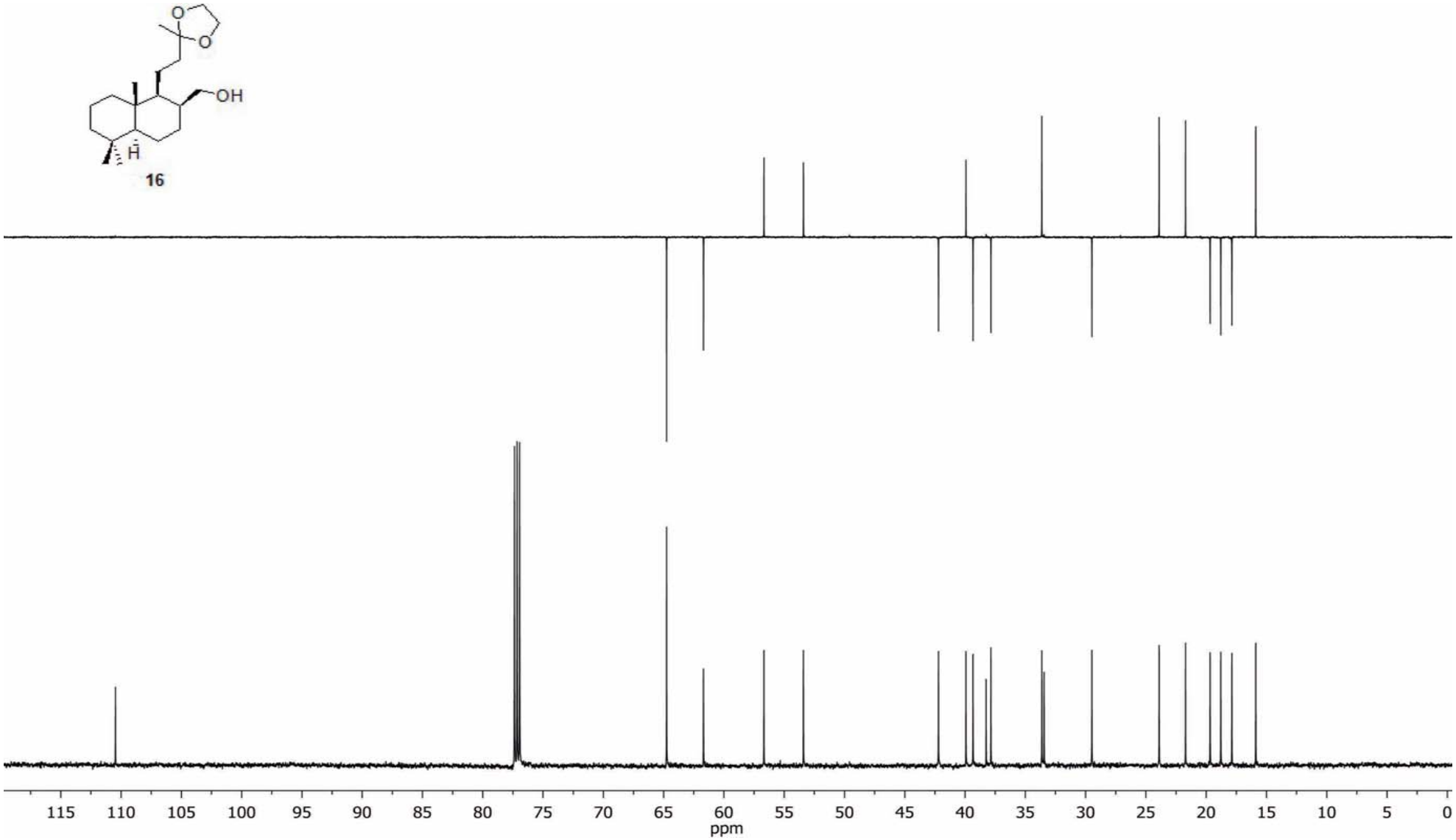

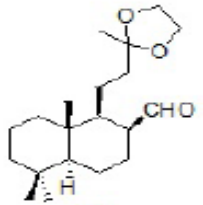

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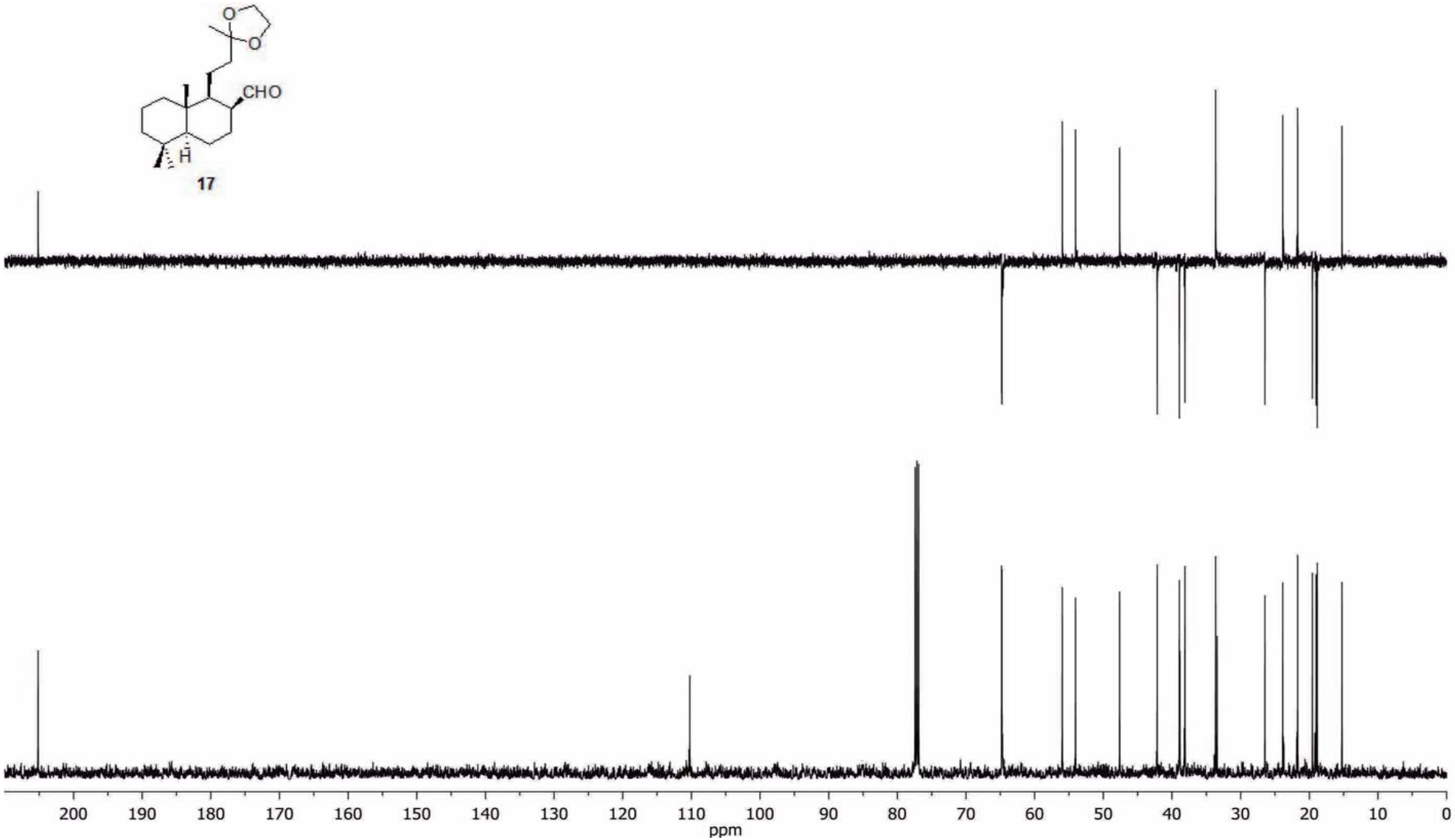

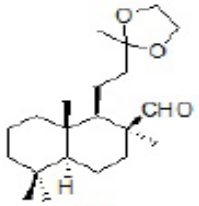

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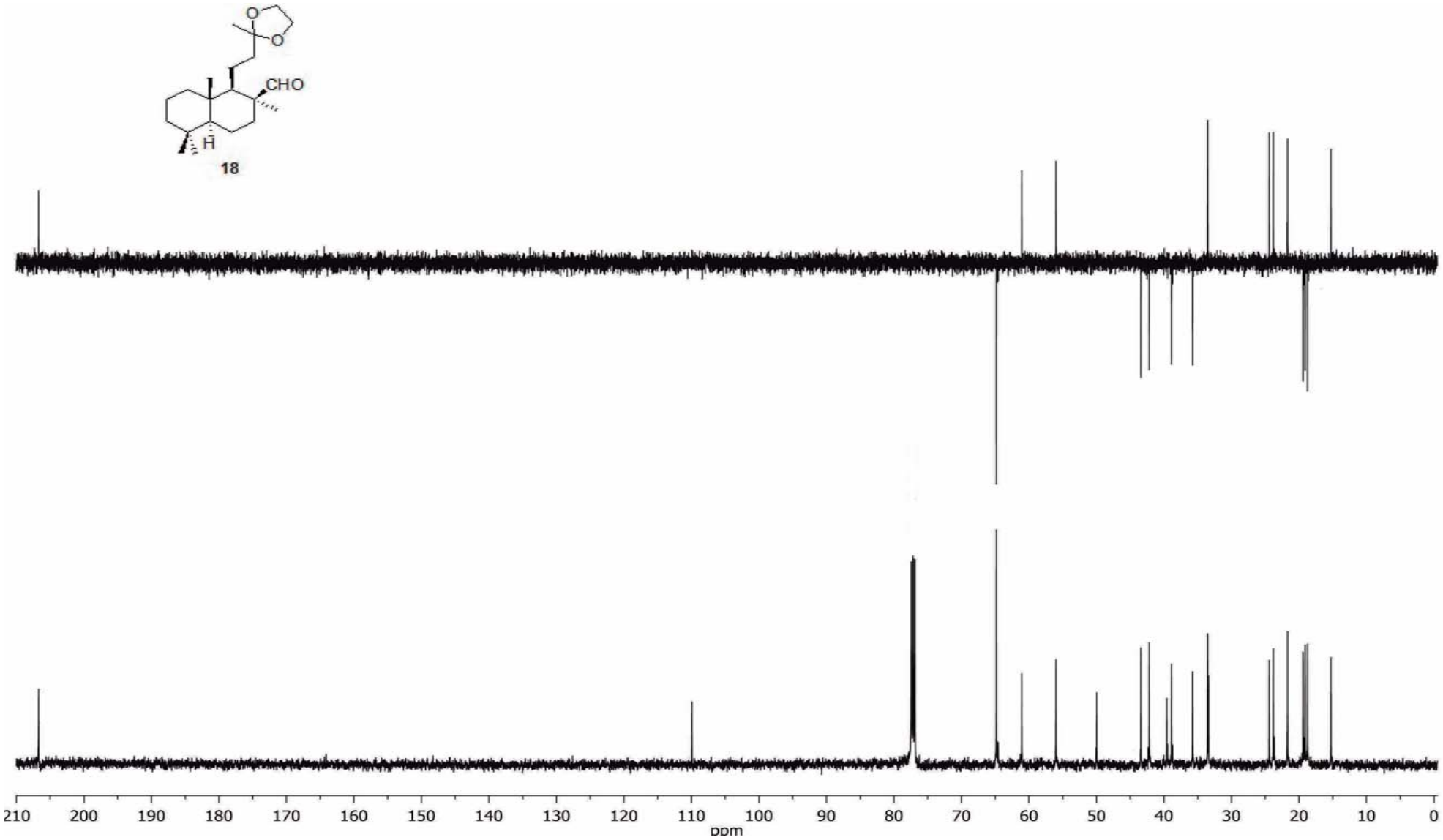

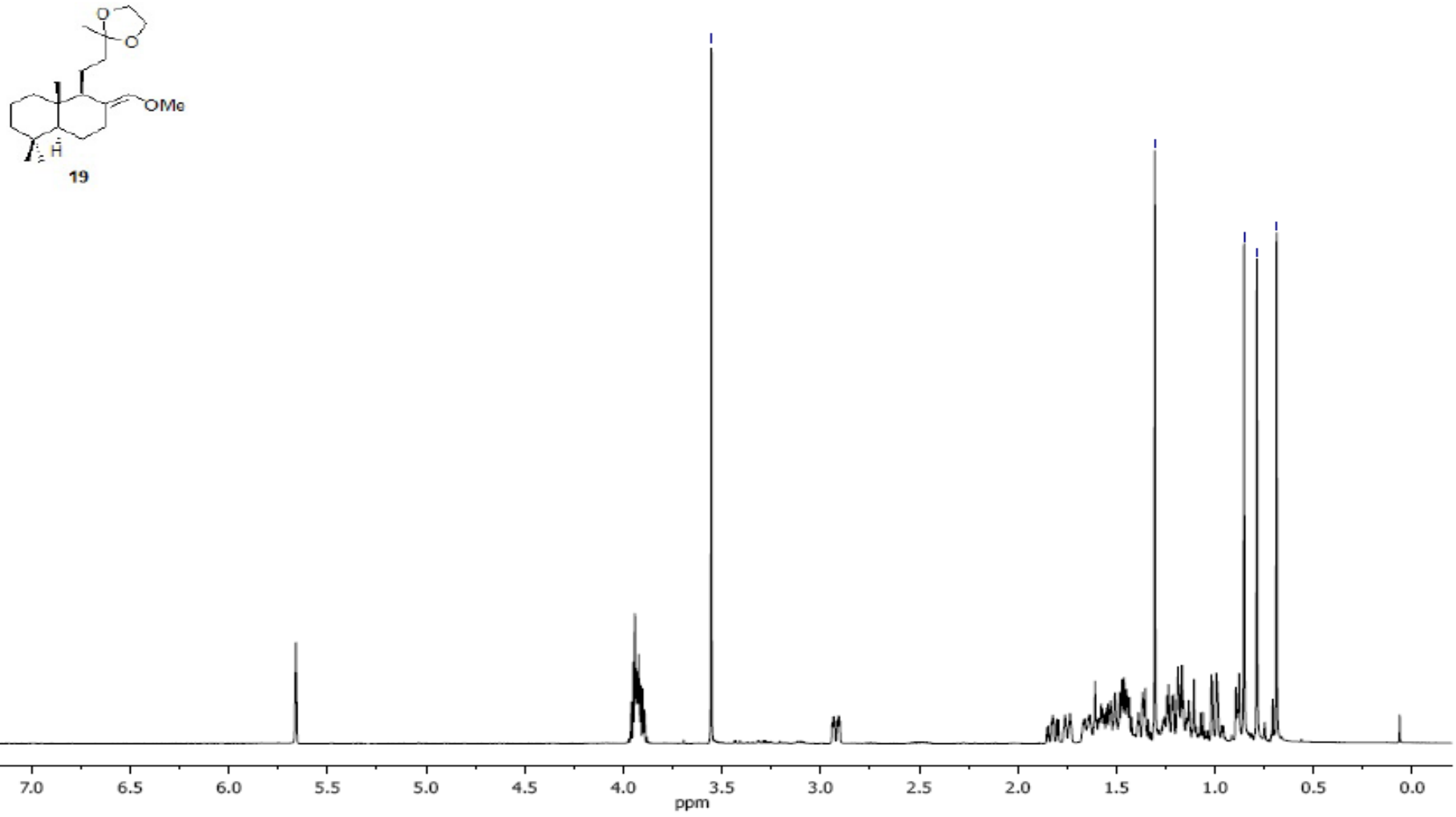

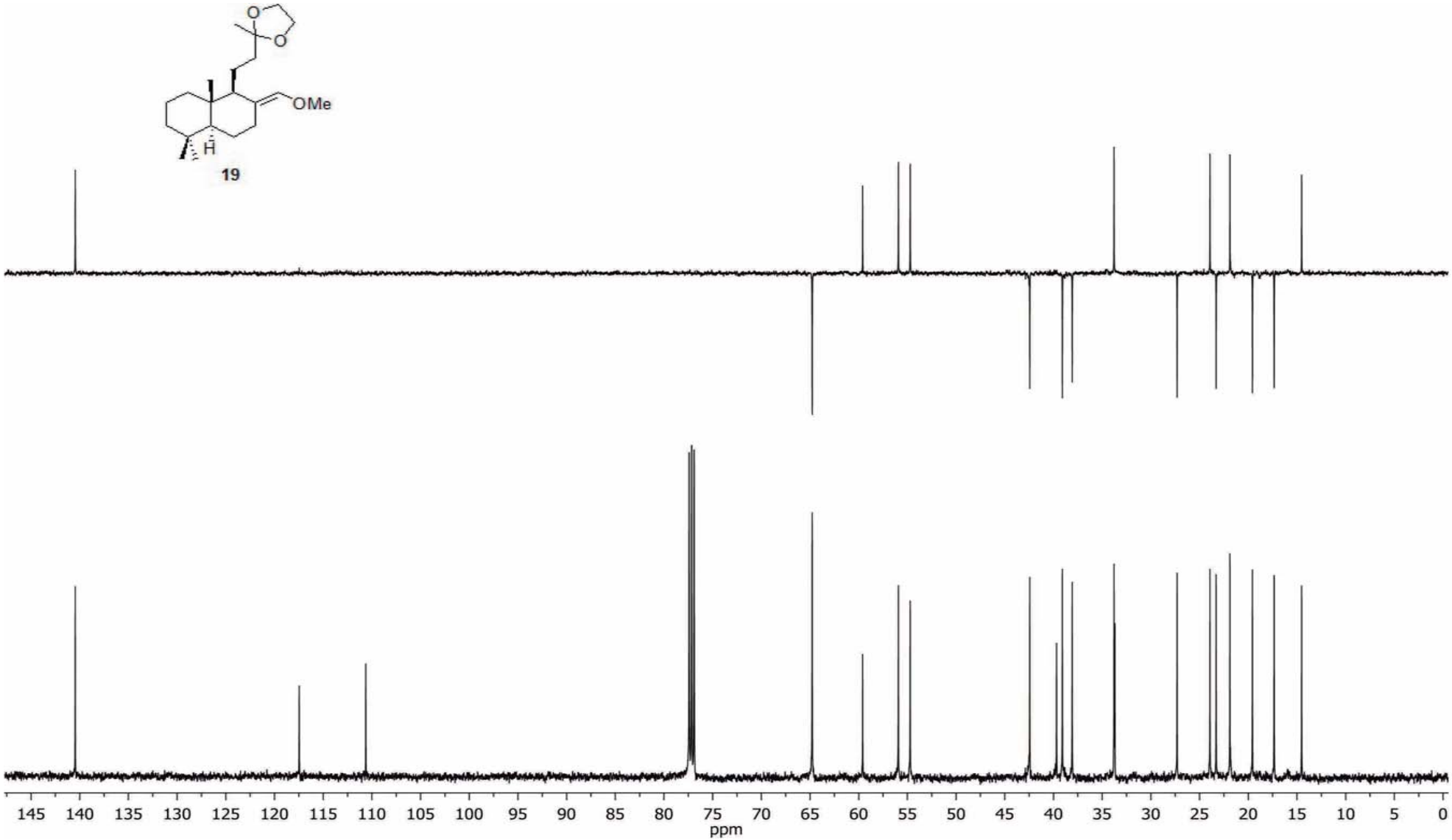

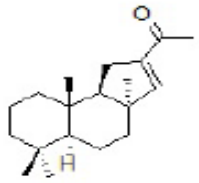

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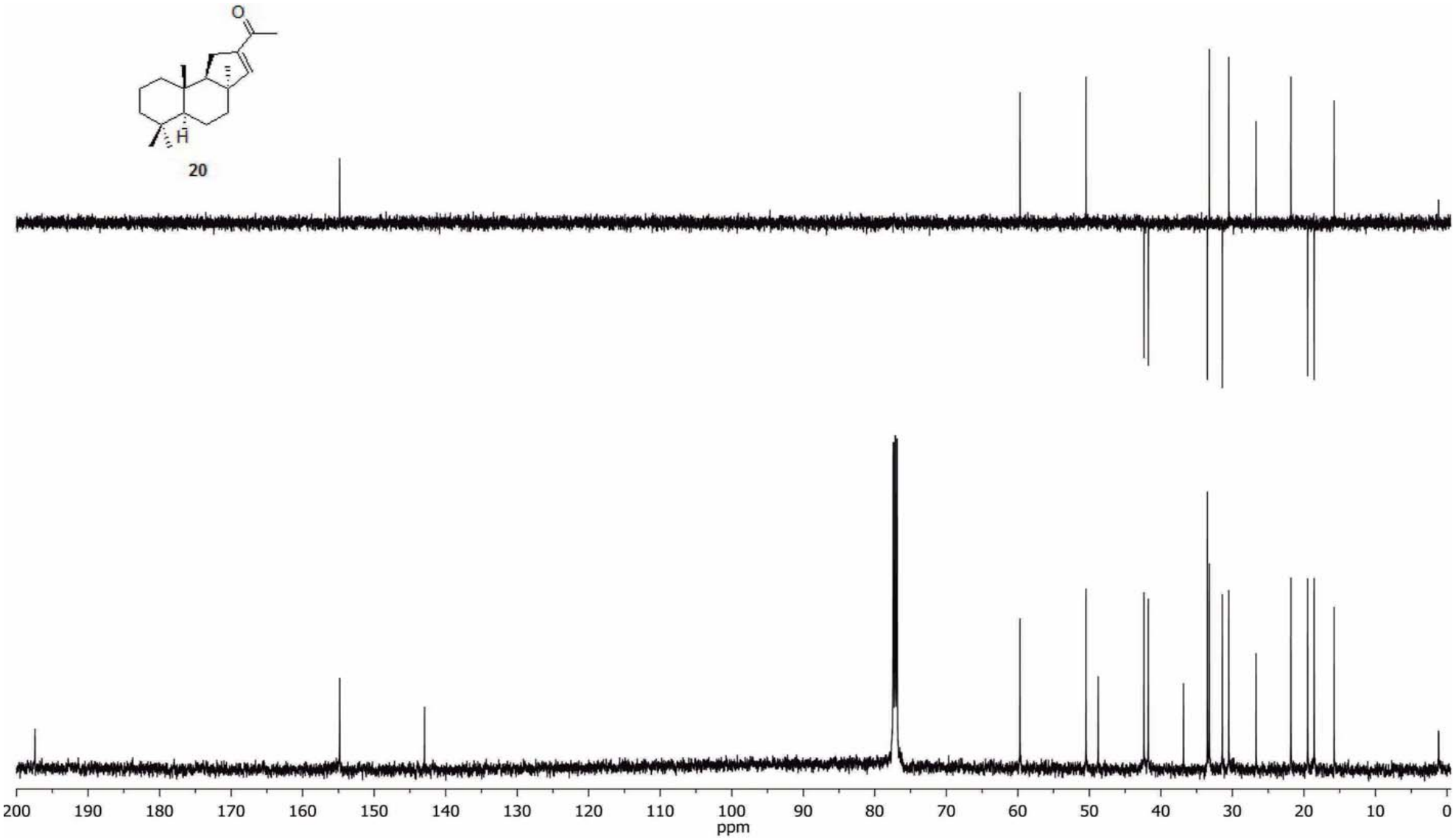

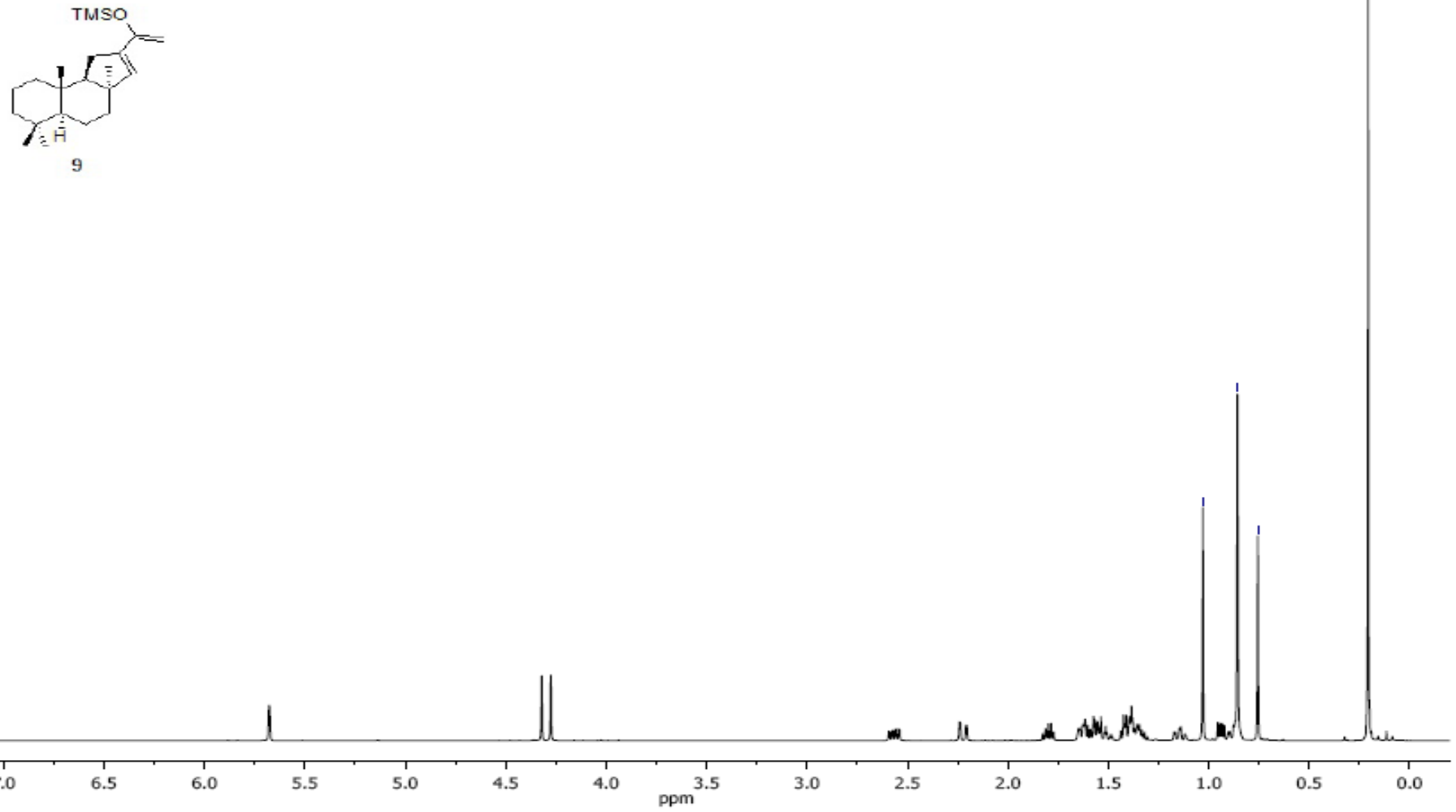

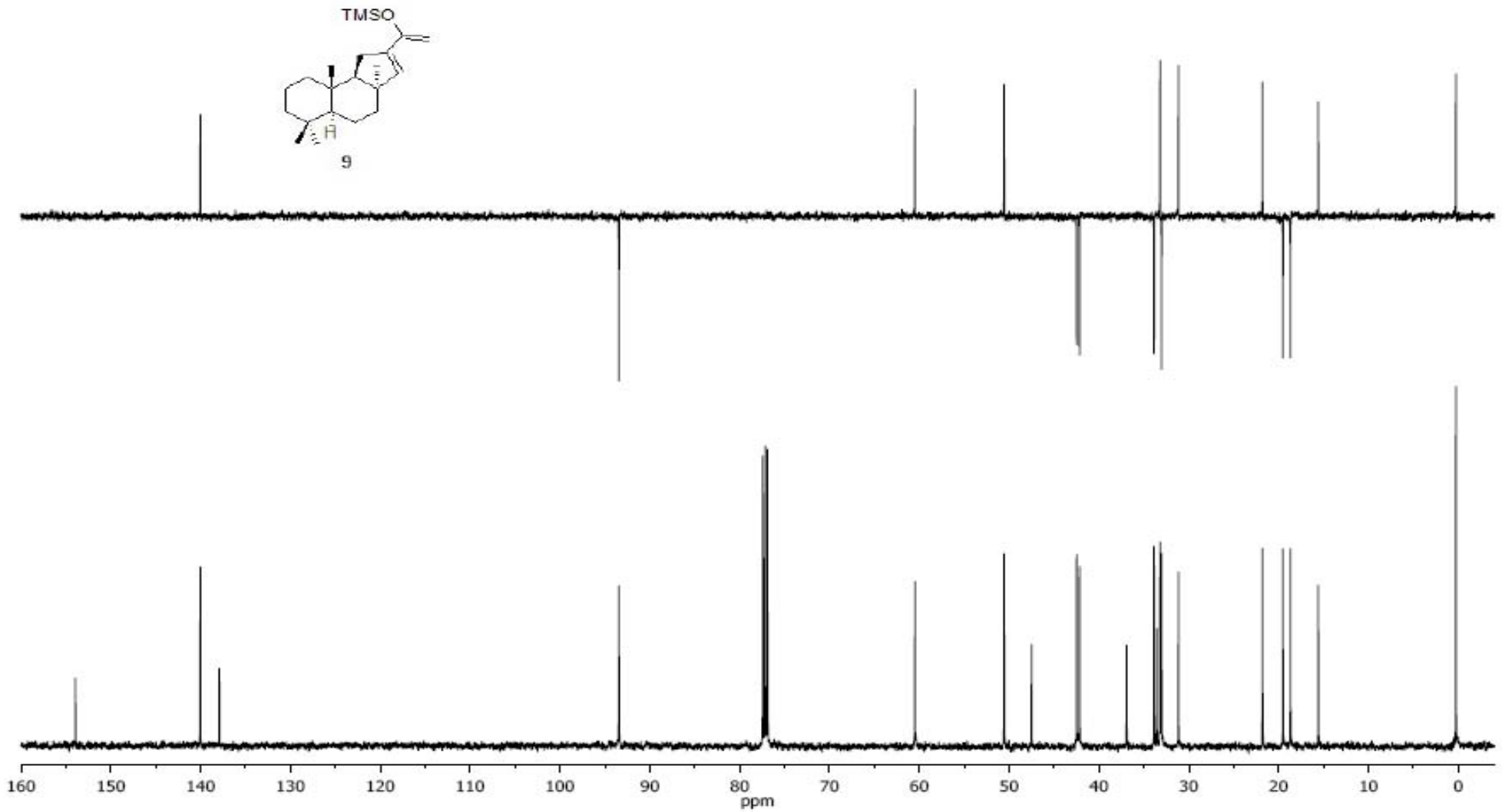

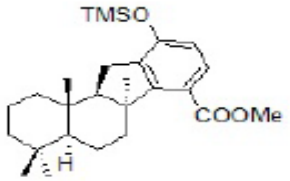

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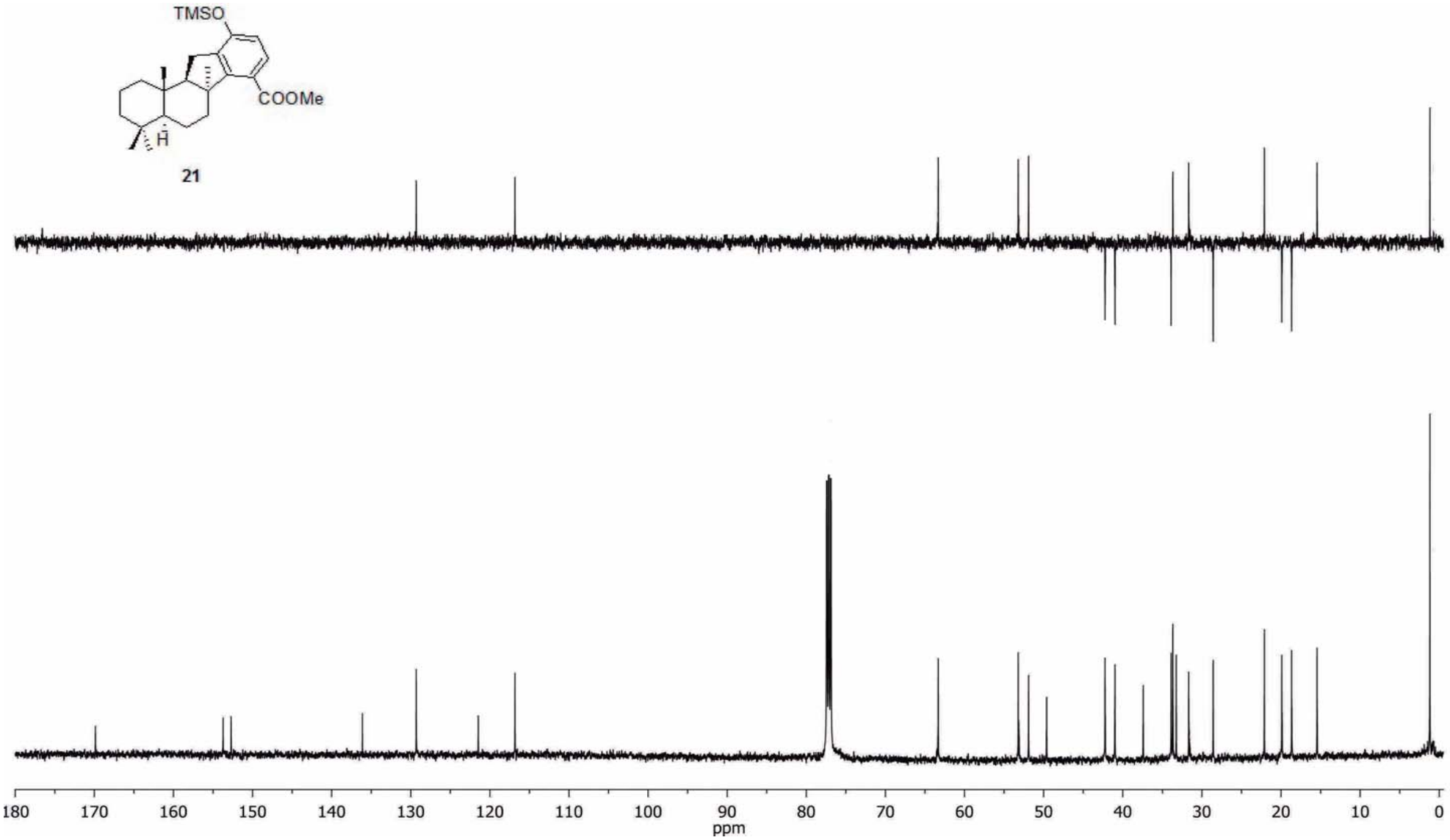

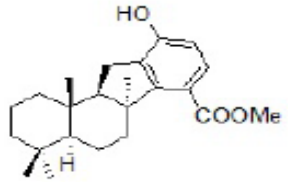

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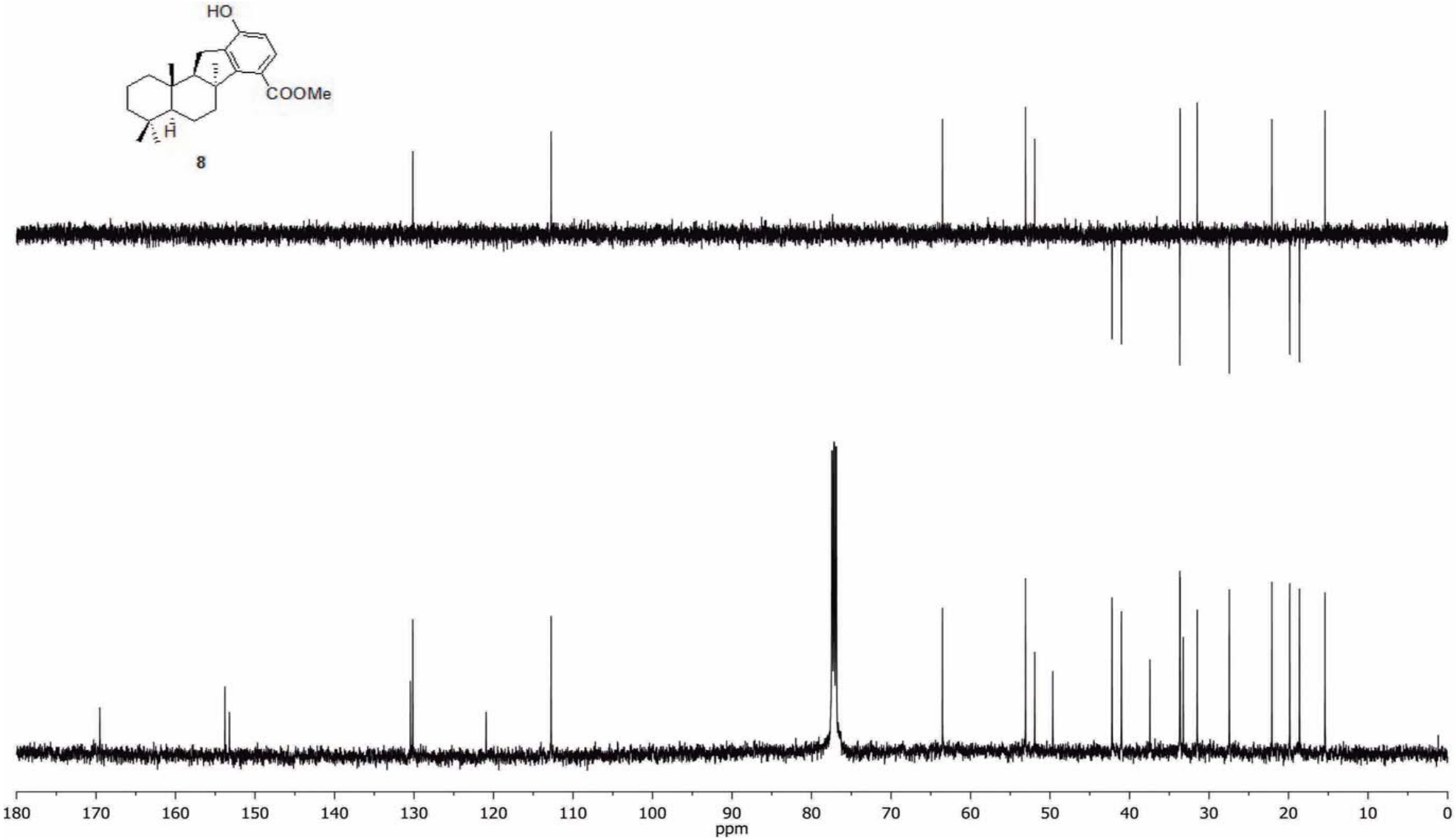

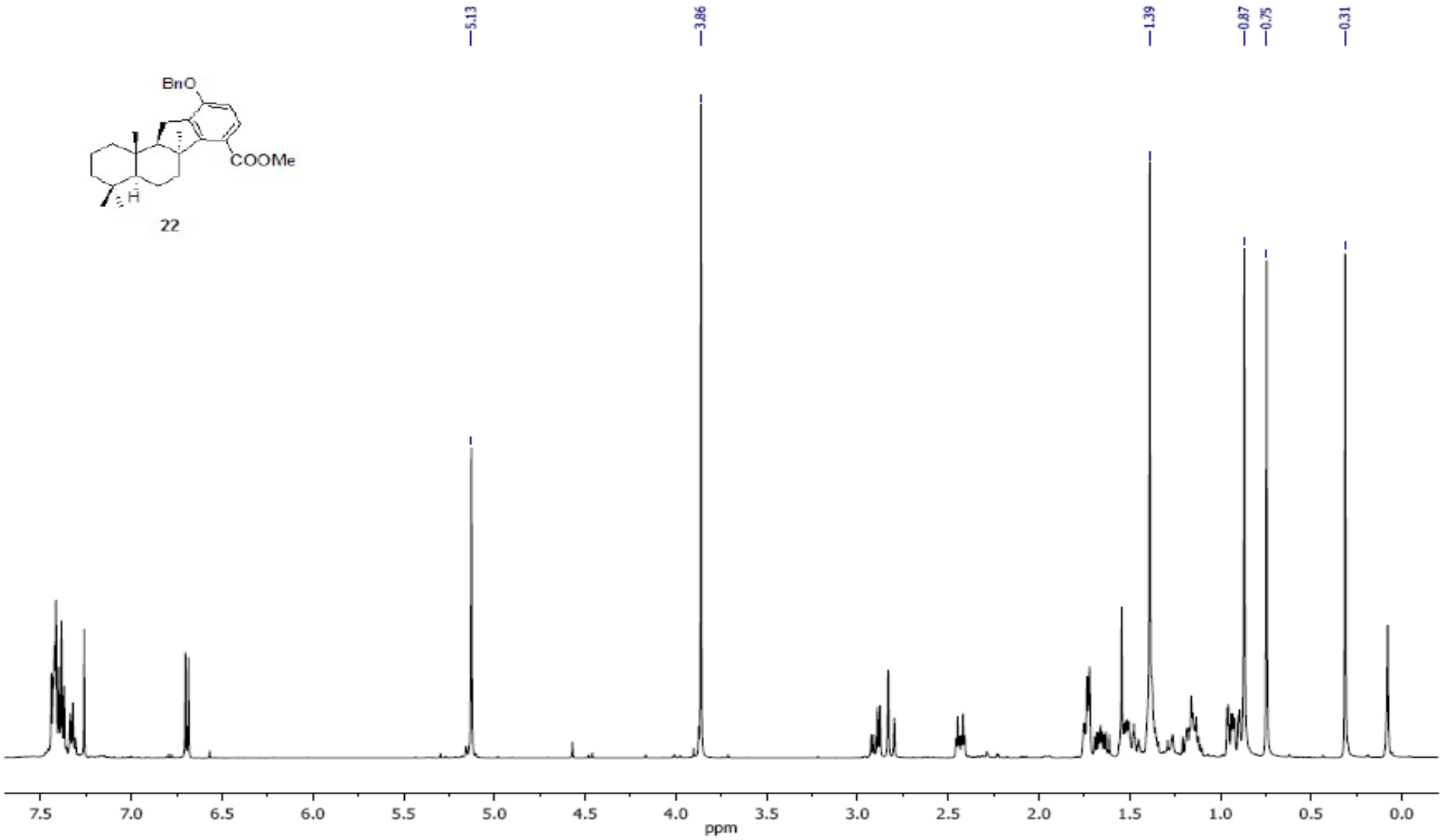

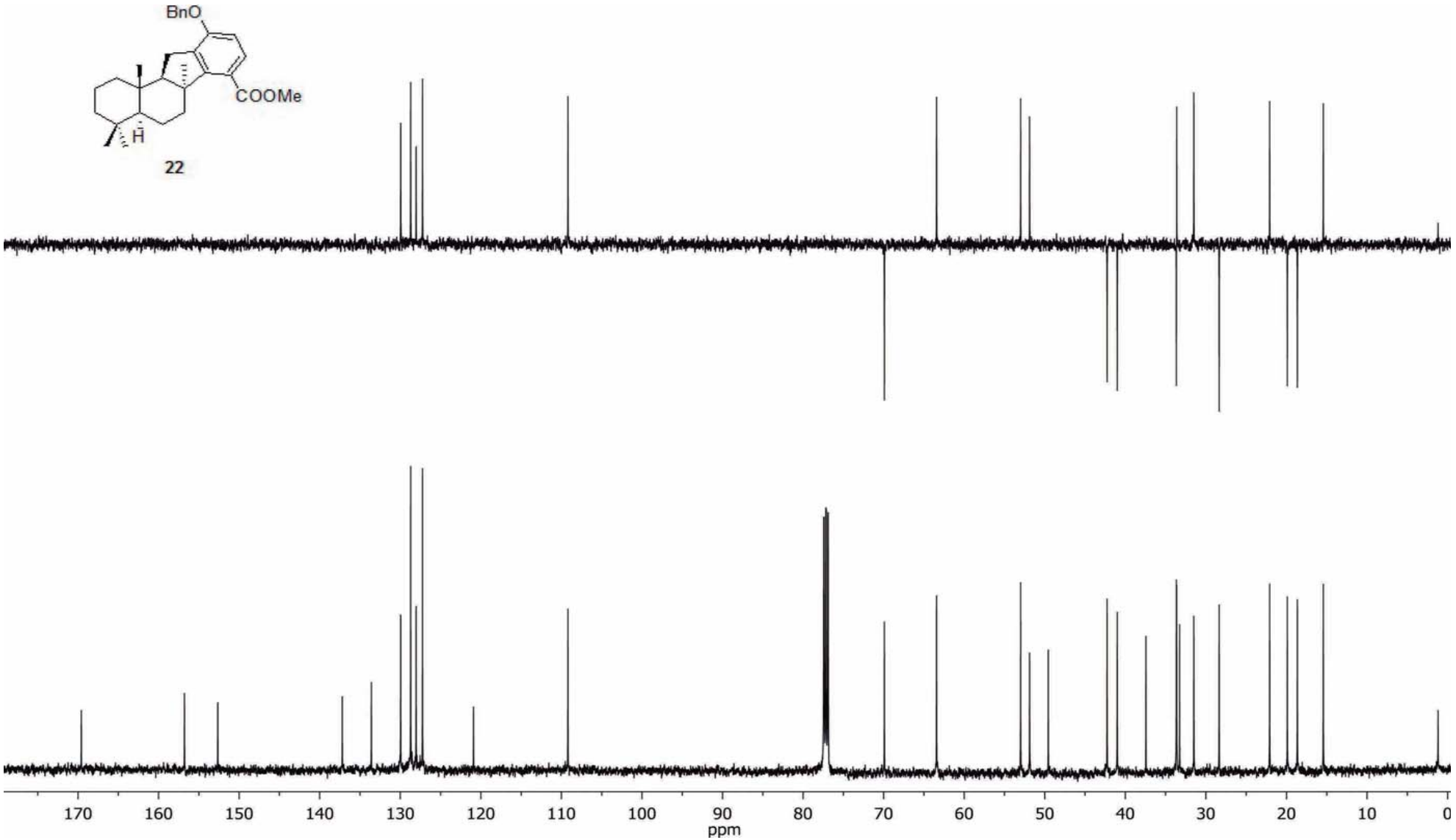

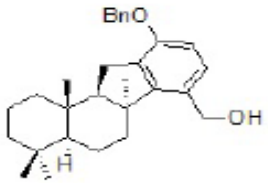

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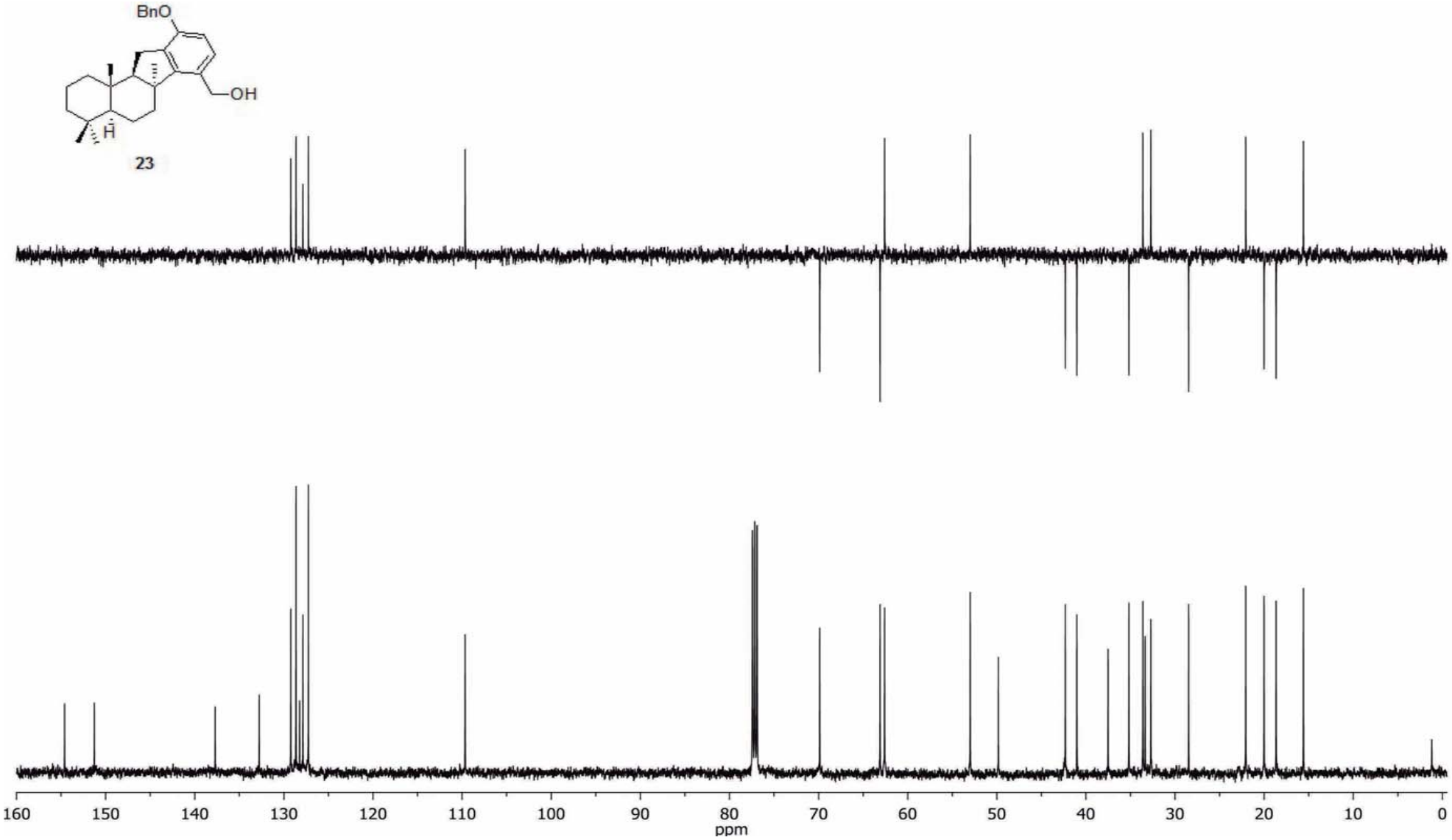

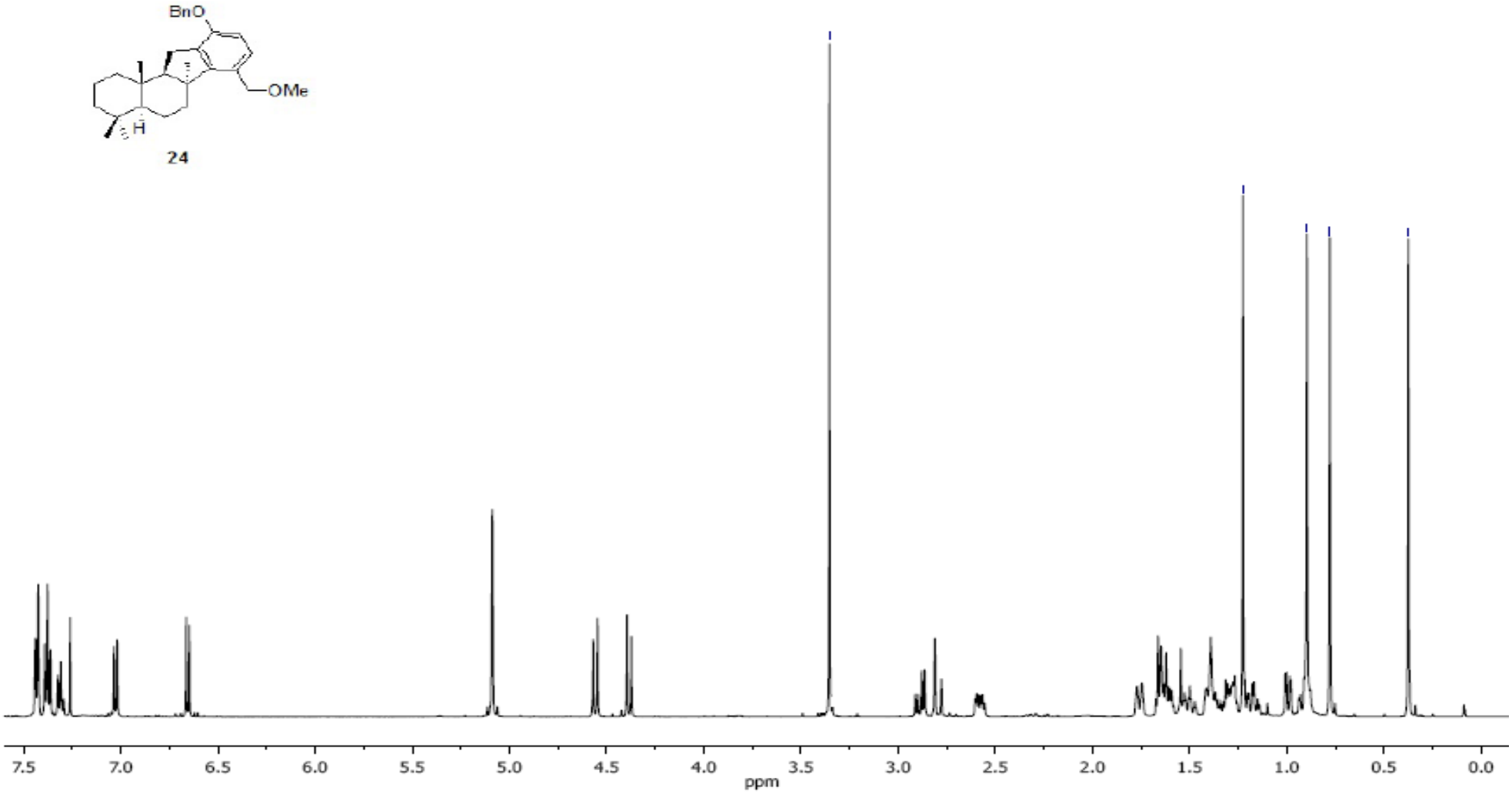

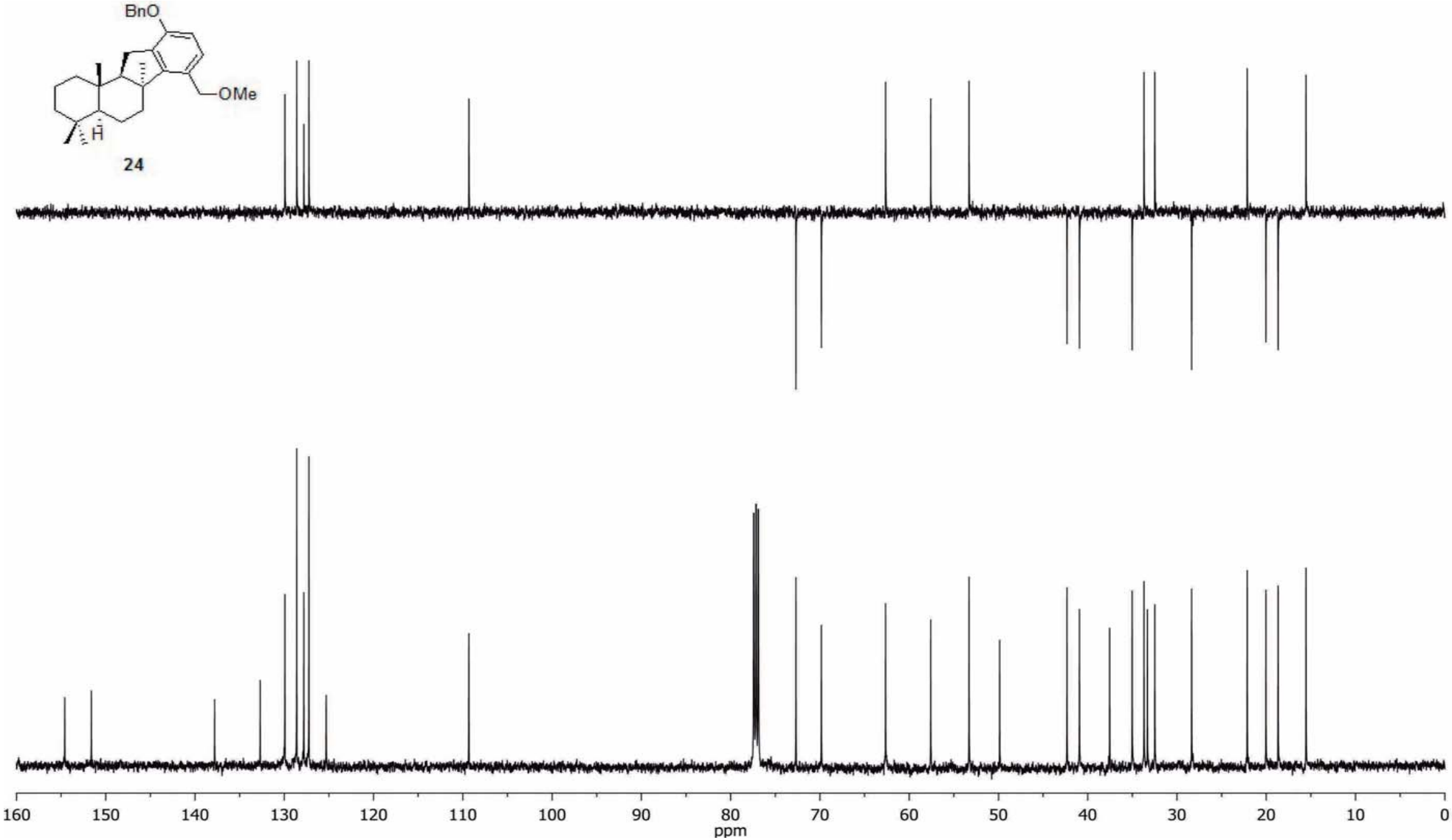

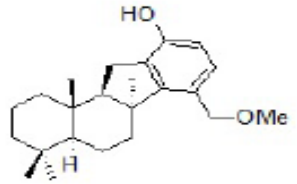

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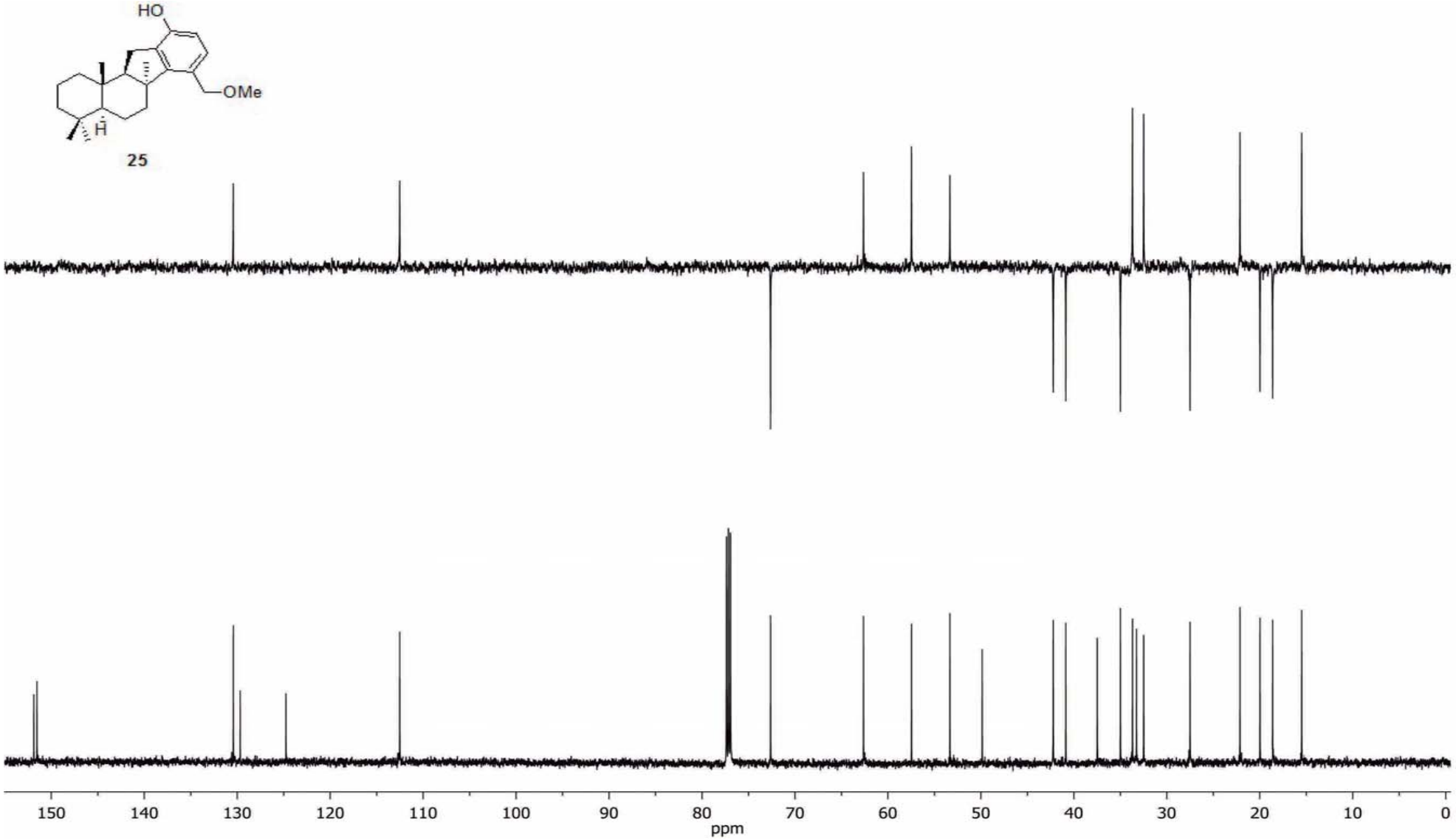

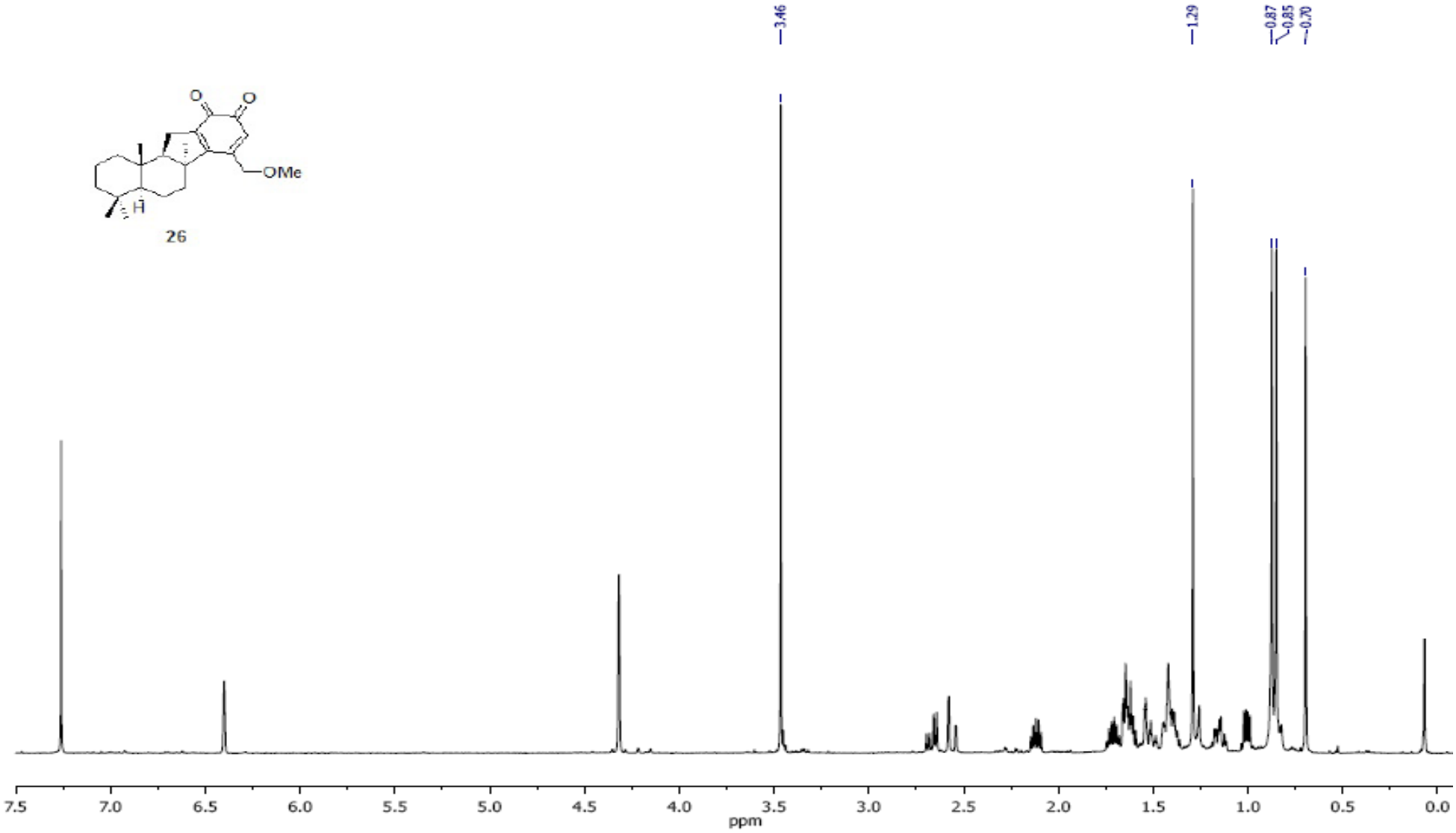

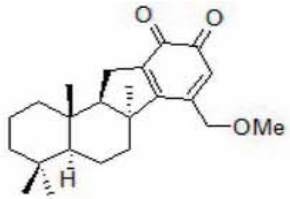

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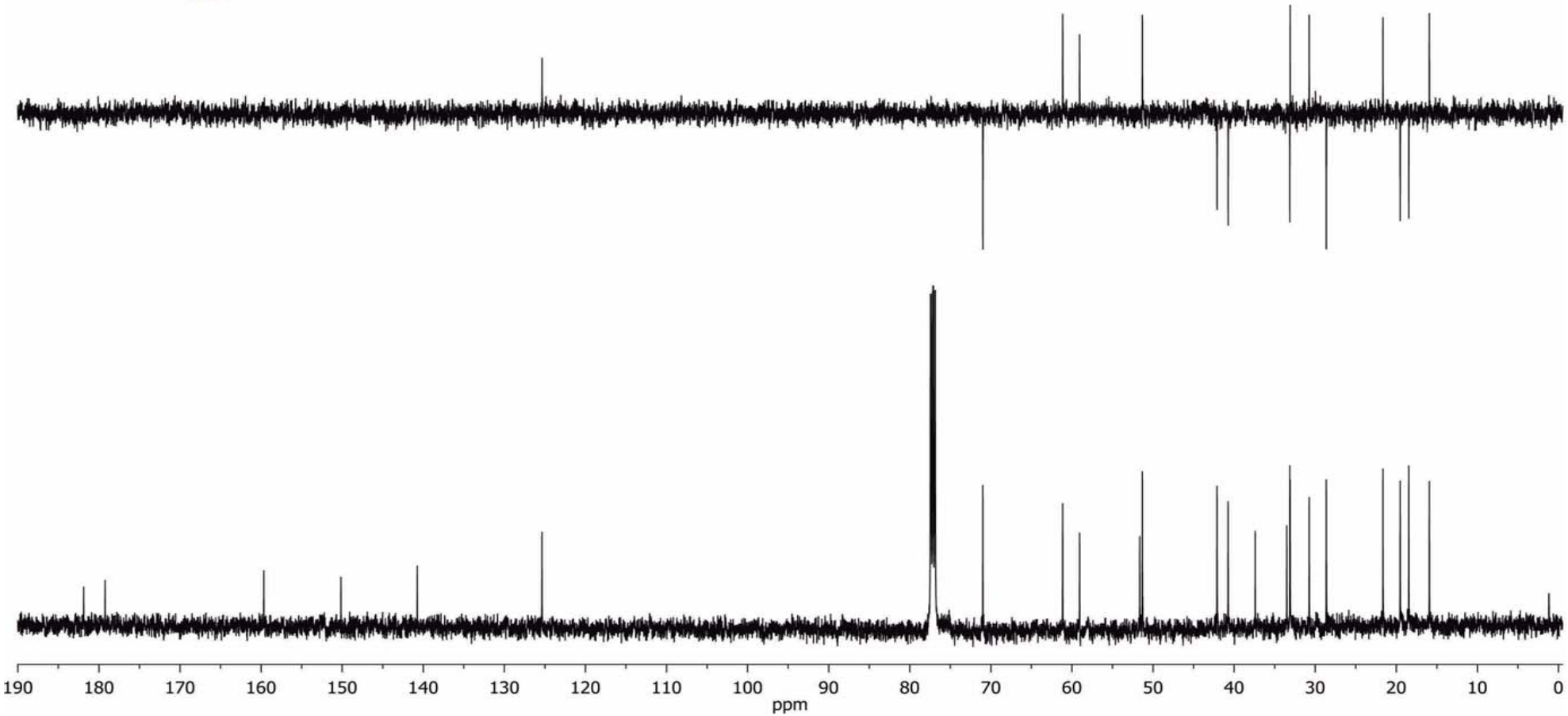

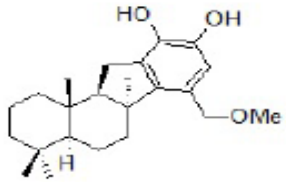

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