Supporting Information

An Expeditious and High-Yield Formal Synthesis of Hirsutene Using Rh(I)-Catalyzed [(5+2)+1] Cycloaddition

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Contents

1. General

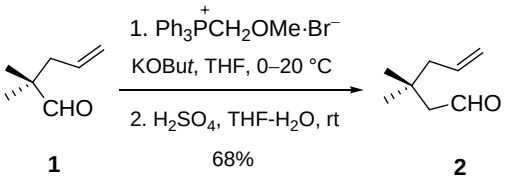
Air and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon. Similarly sensitive liquids and solutions were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using Thermostat-controlled silicone oil baths. Organic solutions were concentrated using a Büchi rotary evaporator with a desktop vacuum pump. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium and benzophenone prior to use. Dichloromethane was distilled from CaH_2 prior to use. Dioxane (extra dry, water < 50 ppm) was commercially available and used as received. Synthetic reagents were purchased from Acros, Aldrich, and Alfa Aesar and used without further purification, unless otherwise indicated. Analytical TLC was performed with 0.25 mm silica gel G plates with a 254 nm fluorescent indicator. The TLC plates were visualized by ultraviolet light and treatment with phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel and the purified compounds show a single spot by analytical TLC.

NMR spectra were measured on Varian Mercury 200 (^{1}H at 200 MHz, ^{13}C at 50 MHz) or Varian Mercury Plus 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) nuclear magnetic resonance spectrometers. Data for ^{1}H-NMR spectra are reported as follows: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, tdd = triplet of doublet of doublets, m = multiplet), coupling constant (Hz), and integration. Data for ^{13}C-NMR are reported in terms of chemical shift (ppm) relative to residual solvent peak ($CDCl_3$: 77.0 ppm). Infrared spectra were recorded on an AVATAR 330 Fourier transform spectrometer (FT-IR) with an OMNI sampler and are reported in wavenumbers (cm^{-1}). Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a VG-ZAB-HS mass spectrometer (EI, 70 eV).

Abbreviations:
THF = tetrehydrofuran
PE = petroleum ether
EA = ethyl acetate
DEAD = diethyl azodicarboxylate
mCPBA = 3-chloroperoxybenzoic acid
PCC = pyridinium chlorochromate
PTSA =4-methylbenzenesulfonic acid

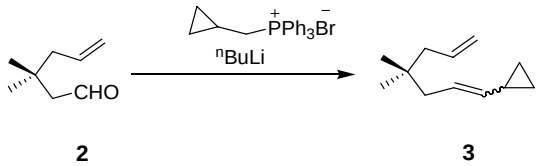
2. Experimental Procedures and Characterization Data

3,3-Dimethylhex-5-enal (2)



To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (76.34 g, 223 mmol) in 350 mL of anhydrous THF was slowly added a solution of KOBu^t (26.09 g, 233 mmol) in THF (300 mL) at 0 °C via cannula under argon. The resulting cherry-red solution was stirred at 0 °C for another 1 h. A solution of 2,2-dimethylpent-4-enal (**1**, 14.01 g, 125 mmol) in THF (100 mL) was added dropwise within 20 min, and the resulting mixture was stirred at 20 °C for 2 h. The reaction was quenched by addition of water (10 mL) and the reaction mixture turned from light cherry-red to yellow. The reaction mixture was evaporated under reduced pressure in a water bath (35 °C) to a volume of ca. 300 mL, then aqueous 30% H_2SO_4 (60 mL) was added at room temperature under stirring. When GC indicated the disappearance of the enol ether, saturated $NaHCO_3$ (200 mL) was added. The reaction mixture was extracted with ether and the combined organic extract was washed with water, dried over $MgSO_4$, and concentrated to give a light yellow oil. Flash column chromatography on silica gel (eluted with pentane/ether 30:1) gave aldehyde **2** (10.66 g, 68%) as a colorless oil. Spectroscopic data of **2** was identical to that reported.[1]

(E)-(4,4-dimethylhepta-1,6-dienyl)cyclopropane (3)

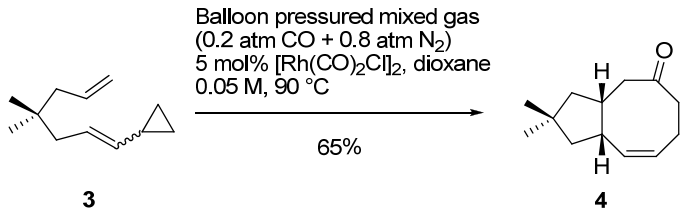


To a stirred suspension of (cyclopropylmethyl)triphenylphosphonium bromide (3.58 g, 9 mmol) in 40 mL of anhydrous THF was slowly added a solution of ^{n}BuLi (3.8 mL, 2.5 M，9.5mmol) at 0°C via cannula under argon. The resulting cherry-red solution was stirred at 0 °C for another 30 min. A solution of 3,3-Dimethylhex-5-enal (**2**, 990 mg, 6 mmol) in THF (10 mL) was added dropwise within 10 min, and the resulting mixture was stirred at 0 °C for 4 h. The reaction was quenched by addition of saturated aqueous solution of ammonium chloride (6 mL) and the reaction mixture turned from light cherry-red to light yellow. The reaction mixture was evaporated under reduced pressure in a water bath (15 °C) to a volume of ca. 10 ml. The mixture was diluted with ether, washed successively with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with pure petroleum ether 30-60°C) to afford **3** (*Z/E* = 2:1, determined by GC) as a colorless oil (1.16 g, 90%).

cis-isomer: ^{1}H NMR (200 MHz, $CDCl_3$): 0.28-0.34 (m, 2H), 0.67-0.76 (m, 2H), 0.90 (s, 6H), 1.47-1.68 (m, 1H), 1.99 (d, J = 6.8 Hz, 2H), 2.07 (d, J = 7.6 Hz, 2H), 4.83 (t, J = 10.2 Hz, 1H), 4.98-5.06 (m ,2H), 5.37 (dt, J = 10.5 and 8.0 Hz, 1H), 5.86 (ddt, J = 7.5, 18.8 and 7.6 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): 135.9, 135.8, 124.5, 116.8, 46.3, 39.4, 34.2, 26.7, 9.7, 6.8. IR (FT-IR): ν = 3078, 2959, 2927, 1639, 1468, 1384, 1045, 936, 912 cm^{-1}. MS (EI): m/z (%) = 164 (M^+, 5), 149 (10), 123 (10), 108 (12), 83 (65), 81 (70), 67(42), 55 (100), 41 (35). HRMS calcd for $C_{12}H_{20}$: 164.1565. Found: 164.1566.

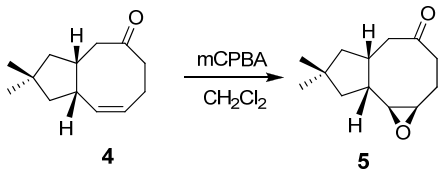
10,10-dimethyl-6-oxobicyclo[6.3.0]undec-2-en (4)



$[Rh(CO)_2Cl]_2$ (47 mg, 0.12 mmol) was charged in a base-washed, oven-dried Schlenk flask under an atmosphere of nitrogen, and then a solution of the cis/trans mixture of ene-VCP substrate **3** (400 mg, 2.4 mmol) in degassed dioxane (50 mL) was added. The solution was bubbled with the mixed CO gas (0.2 atm CO + 0.8 atm N_2) for 5 min. The reaction mixture was then stirred at 90 °C under the balloon pressured mixed gas of 0.2 atm CO and 0.8 atm N_2 for 120 h. After being cooled to room temperature, the mixture was concentrated and the residue was purified by flash column chromatography with silica gel (eluted with petroleum ether/ ethyl acetate 80:1) to afford the cycloaddition product **4** (304 mg, 65%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 1.0 (s, 3H), 1.12 (s, 3H), 1.16-1.20 (m, 1H), 1.48-1.53 (m, 2H), 1.81 (dd, J = 7.9 and 13.6, 1H), 2.17-2.34 (m, 4H), 2.42-2.55 (m, 3H), 2.74-2.82 (m, 1H), 5.47 (t, J = 9.5, 1H), 5.82-5.91 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 214.2, 135.4, 128.2, 47.5, 47.4, 46.2, 43.9, 40.3, 39.6, 37.6, 31.6, 31.4, 23.5. IR (FT-IR): ν = 2951, 2930, 2865, 1701, 1383, 1365 cm^{-1}. MS (EI): m/z (%) = 192 (M^+, 50), 177 (50), 151 (40), 135 (30), 107 (40), 93 (50), 83(100), 55 (65). HRMS calcd for $C_{13}H_{20}O$: 192.1514. Found: 192.1516.

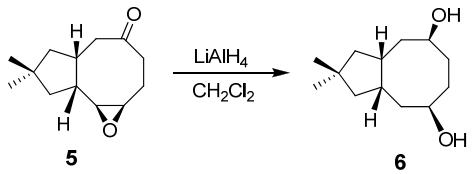
10,10-dimethyl-2,3-epoxy-6-oxobicyclo[6.3.0]undecane (5)



To a stirred solution of **4** (493 mg, 2.6 mmol) in 25 mL of CH_2Cl_2 was added $NaHCO_3$ (259 mg, 3.1 mmol) and mCPBA (760 mg, 70% wt, 3.1 mmol). The resulting mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with CH_2Cl_2, washed with saturated aqueous of K_2CO_3, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/ ethyl acetate 10:1) to afford **5** as a white solid (456 mg, 85%). The stereochemistry of **5** was determined by X-ray diffraction. Crystallographic data (excluding structure factors) for the structure of **5** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-702088. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

^{1}H NMR (200 MHz, $CDCl_3$): 1.03 (s, 3H), 1.17 (s, 3H), 1.32-1.46 (m, 2H), 1.61-1.72 (m, 1H), 1.73-1.89 (m, 3H), 2.37-2.48 (m, 3H), 2.60-2.75 (m, 3H), 2.94 (dd, J = 4.1 and 9.1 Hz, 1H), 3.23 (dt, J = 10.2 and 4.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 214.2, 58.7, 55.4, 47.8, 44.9, 44.2, 41.5, 41.2, 40.1, 37.7, 31.5, 31.2, 25.1. IR (FT-IR): ν = 2951, 2866, 1698, 1384, 1365, 1306, 929 cm^{-1}. MS (EI): m/z (%) = 208 (M^+, 5), 190 (10), 165 (30), 137 (30), 107 (65), 95(100), 81 (90). HRMS calcd for $C_{13}H_{20}O_2$: 208.1463. Found: 208.1466. m.p. 73-76 ℃.

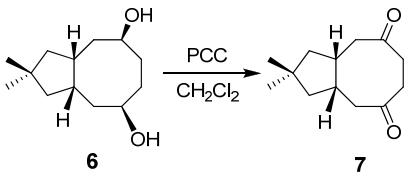
***cis*-10,10-dimethylbicyclo[6.3.0]undecane-3,6-diol (6)**



To a stirred solution of **5** (509 mg, 2.45 mmol) in dry THF (12 mL) under argon was added $LiAlH_4$ (232 mg, 6.1 mmol) slowly at 0 °C. After stirred at 0 °C for 10 min, the resulting mixture was refluxed for 4.5 h under argon.[3] Then the reaction mixture was cooled to 0 °C again, additional portion of Et_2O (25 mL) was added and then quenched by addition of 5% aqueous solution of HCl very slowly. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed successively with 5% HCl and water and brine, dried over $MgSO_4$ and concentrated. Purification of the residue via silica column chromatography (petroleum/ethyl acetate = 2:1) provided 477 mg (92%) of diol **6** as a white solid. The crude products of diol **6** can be directly used in the next reaction without further purification. The stereochemistry of **6** was determined by X-ray diffraction. Crystallographic data (excluding structure factors) for the structure of **6** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-702087. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

^{1}H NMR (200 MHz, $CDCl_3$): 0.97 (s, 3H), 1.00 (s, 3H), 1.03-1.14 (m, 2H), 1.38-1.48 (m, 2H), 1.50 (br s, 2H), 1.58-1.68 (m, 4H), 1.74-1.95 (m, 4H), 2.48-2.65 (m, 2H), 3.91-3.99 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 69.8, 51.5, 36.5, 31.7, 29.6, 28.0, 27.1. IR (FT-IR): ν = 3244, 2954, 2942, 2930, 2900, 1315, 1084, 1066, 1055 cm^{-1}. MS (EI): m/z (%) = 212 (M^+, 4), 194 (8), 176 (30), 161 (50), 135 (25), 110 (30), 95(100). HRMS calcd for $C_{13}H_{24}O_2$: 212.1776. Found: 212.1773. m.p. 173-175 ℃.

***cis*-10,10-dimethylbicyclo[6.3.0]undecane-3,6-dione (7)**



A solution of 40 mL CH_2Cl_2 containing the diol **6** (503 mg, 2.4 mmol) and PCC (2.11 g, 9.8 mmol) was stirred at room temperature for 6 h and quenched with 20 mL Et_2O. The suspension was filtered through an Al_2O_3 column. The filtered was neutralized by addition of K_2CO_3 solid and concentrated *in vacuum* to give the product **7** (478 mg, 97%). The residue can be used in next reaction without further purification. Spectroscopic data of **7** was identical to that reported.[2] When **7** was purified by flash column chromatography on silica gel (eluted with petroleum ether/ ethyl acetate 5:1), part of the product **7** can transfer to products **8** and **9**. The transformation of **7** to **8** and **9** can also be done directly with acidic catalyst: to a solution of diketone **7** in $CHCl_3$ was added catalytic amount of PTSA (0.2 eq.), the diketone **7** can transfer to products **8** and **9** (3:2) quantitatively. Spectroscopic data of **8** and **9** were identical to those reported. [1]

^{1}H NMR (300 MHz, $CDCl_3$): 0.97 (s, 3H), 1.08 (s, 3H), 1.31 (dd, J = 6.3, 13.0 Hz, 2H), 1.70 (dd, J = 6.3, 13.0 Hz, 2H), 2.25-2.36 (m, 2H), 2.48-2.71 (m, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 212.8, 46.9, 45.4, 40.1, 39.9, 36.4, 31.8, 31.5. m.p. 43-45 ℃.

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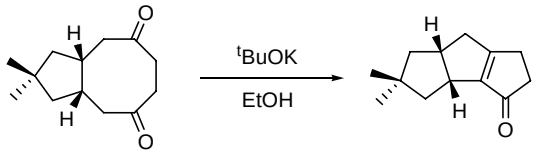
(3a*S*,3b*R*,6a*R*,7a*S*)-7a-Hydroxy-5,5-dimethyl-decahydro-cyclopenta[*a*]pentalen-3-one (9)



7 **9**

To a stirred solution of dione **7** (580 mg, 2.8 mmol) in absolute EtOH (25 mL) was added ^{t}BuOK (329 mg, 2.9 mmol) under argon. After stirred at room temperature for 3 h, the reaction mixture was concentrated and diluted with Et_2O.The resulting solution was washed successively with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with petroleum ether/ ethyl acetate 5:1) to afford **9** as a light yellow oil (525 mg, 99%). Spectroscopic data of **9** was identical to that reported. [1], [2]

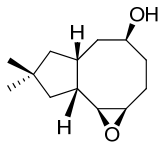
^{1}H NMR (300 MHz, $CDCl_3$): 0.93 (s, 3H), 1.02 (s,3H), 1.08-1.25 (m, 2H), 1.74-1.94 (m, 2H), 2.22 (dm, J = 19.0 Hz, 1H), 2.43-2.52 (m, 2H), 2.67-2.81 (m, 3H), 3.17-3.37 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 204.2, 184.7, 151.6, 49.1, 47.2, 44.8, 42.7, 41.3, 41.0, 38.5, 28.6, 26.8, 25.6.

References:

[1] Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421.

[2] Chandler, C. L.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737.

[3] Reduction at room temperature could produce a small amount of monoreduced intermediate **10** (see scheme below).



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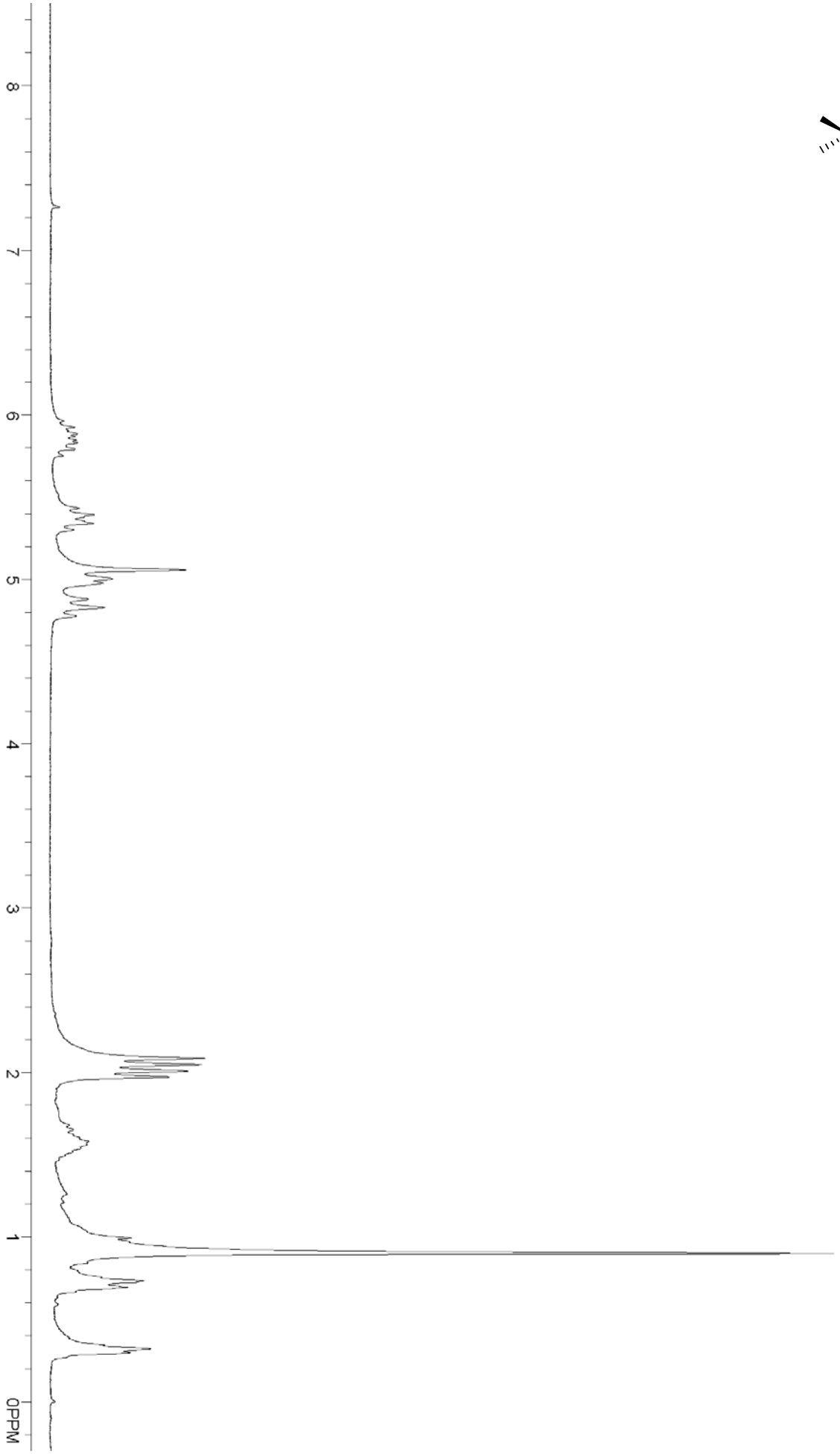
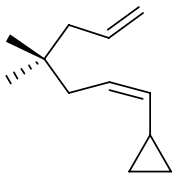
NMR spectra for compound **10**: ^{1}H NMR (200 MHz, $CDCl_3$): 1.05 (s, 3H), 1.15 (s, 3H), 1.39-1.77 (m, 7H), 1.86-2.17 (m, 5H), 2.40-2.60 (m, 1H), 2.82 (dd, J = 4.4 and 9.3 Hz, 1H), 2.95-3.04 (m, 1H), 4.20-4.28 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 21.7, 31.2, 31.6, 33.0, 34.8, 36.5, 37.1, 40.6, 46.0, 49.0, 56.9, 59.9, 67.7. IR (FT-IR): ν = 2928， 1594， 1025， 964， 876 cm^{-1}. MS (EI): m/z (%) = 210 (M^+, 15), 192 (40), 149 (45), 109 (87), 95 (100), 81 (79). HRMS calcd for $C_{13}H_{22}O_2$: 210.1620. Found: 210.1623.

3. ^{1}H and ^{13}C-NMR Spectra for New Compounds





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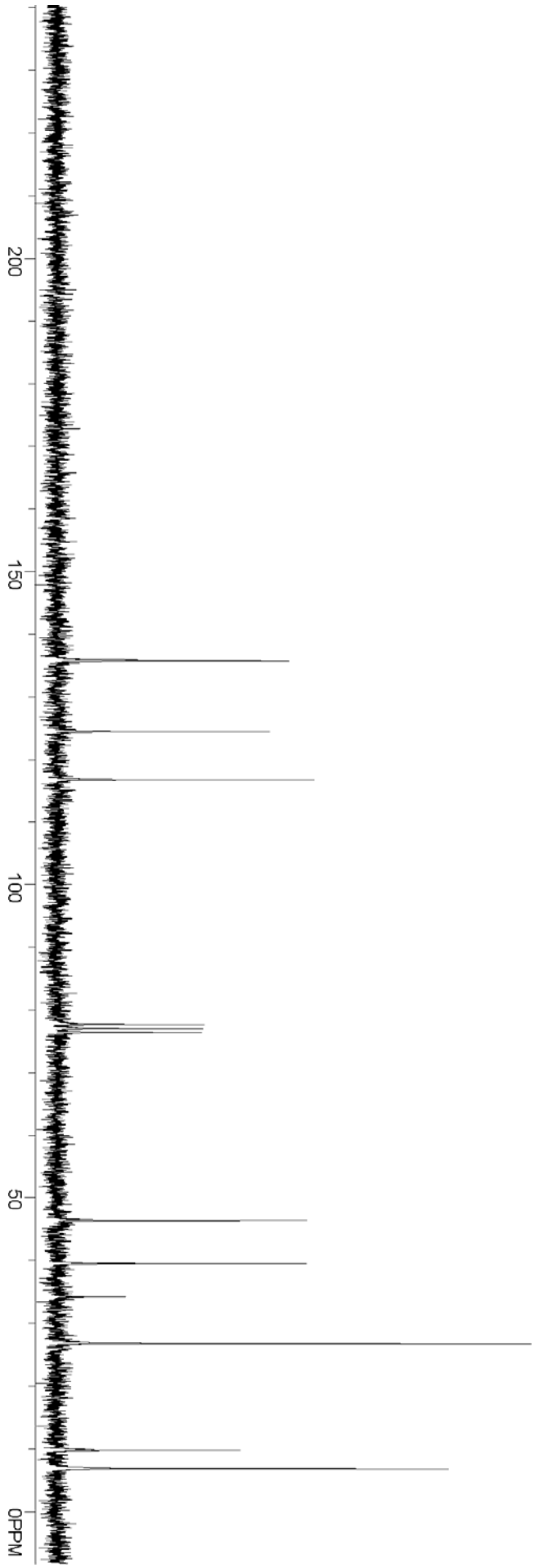

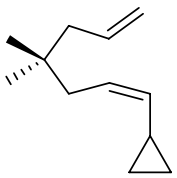

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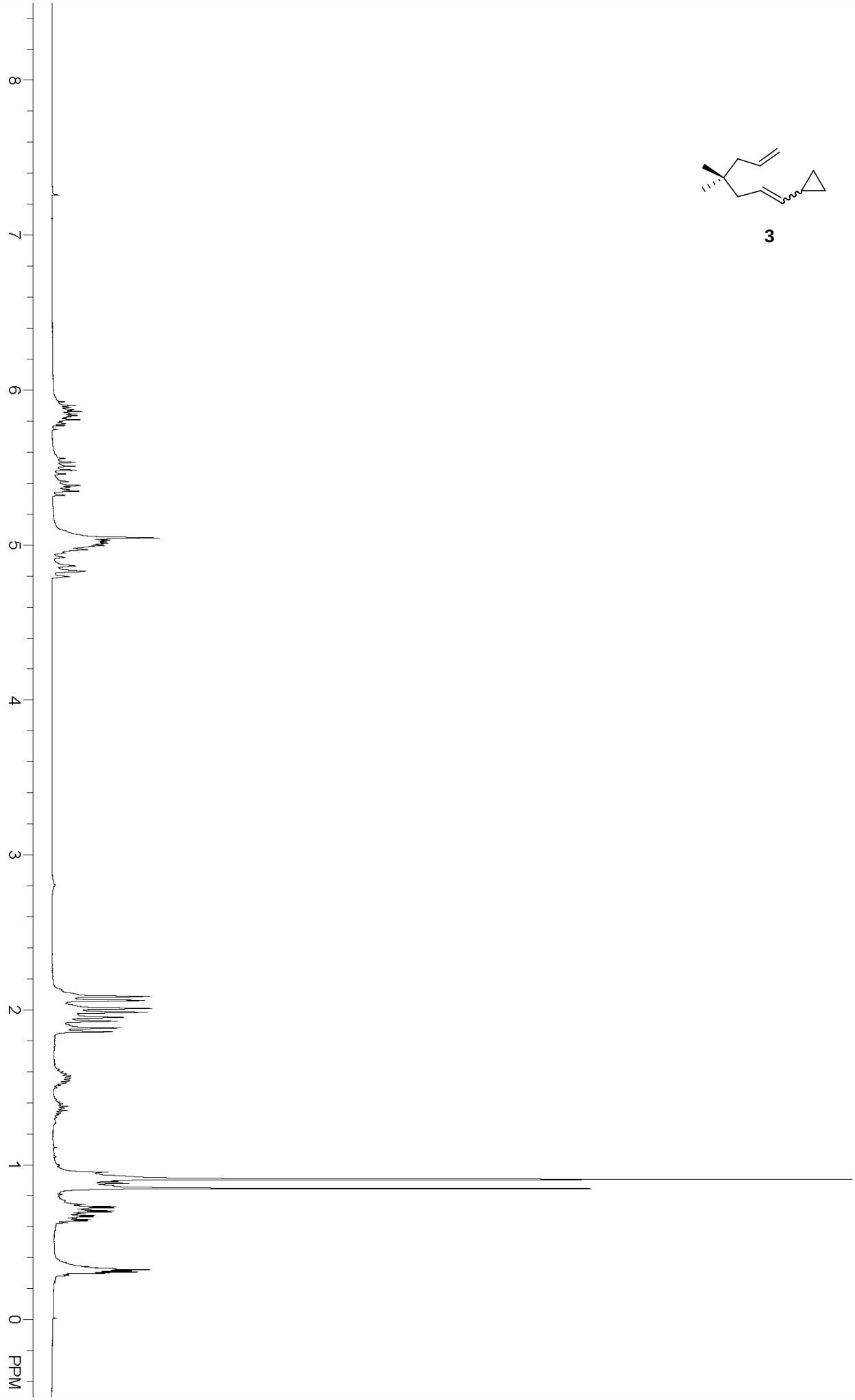

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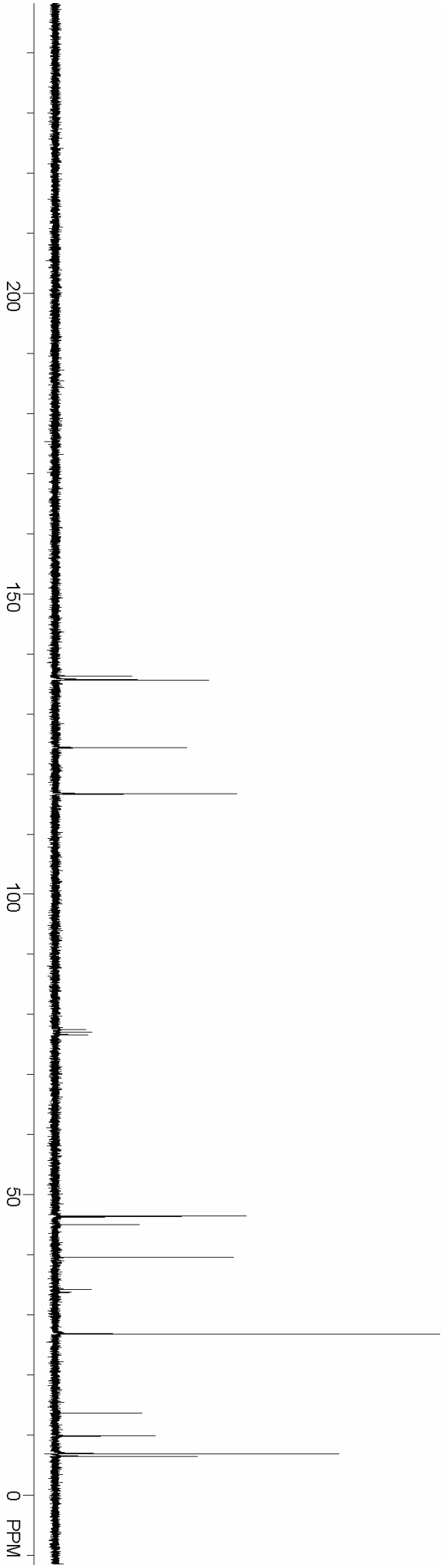

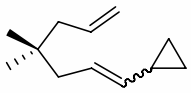

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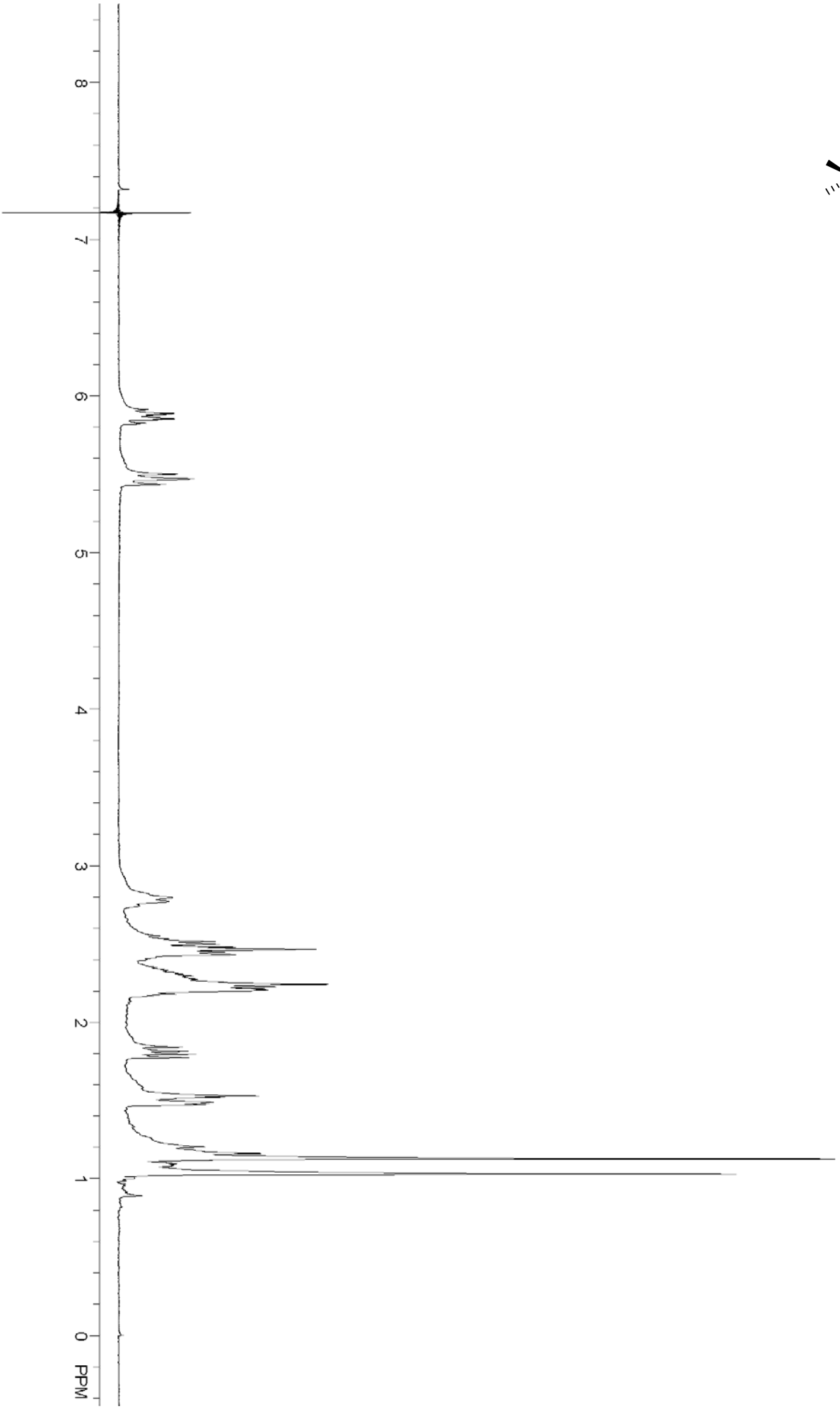

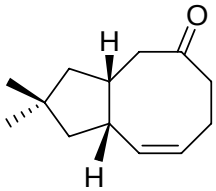

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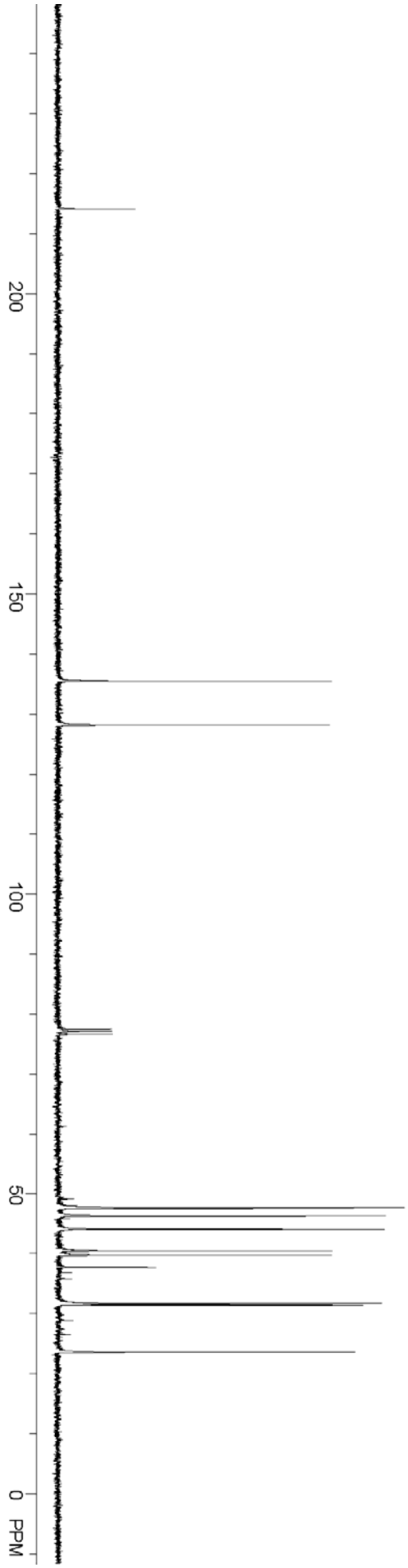

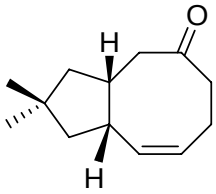

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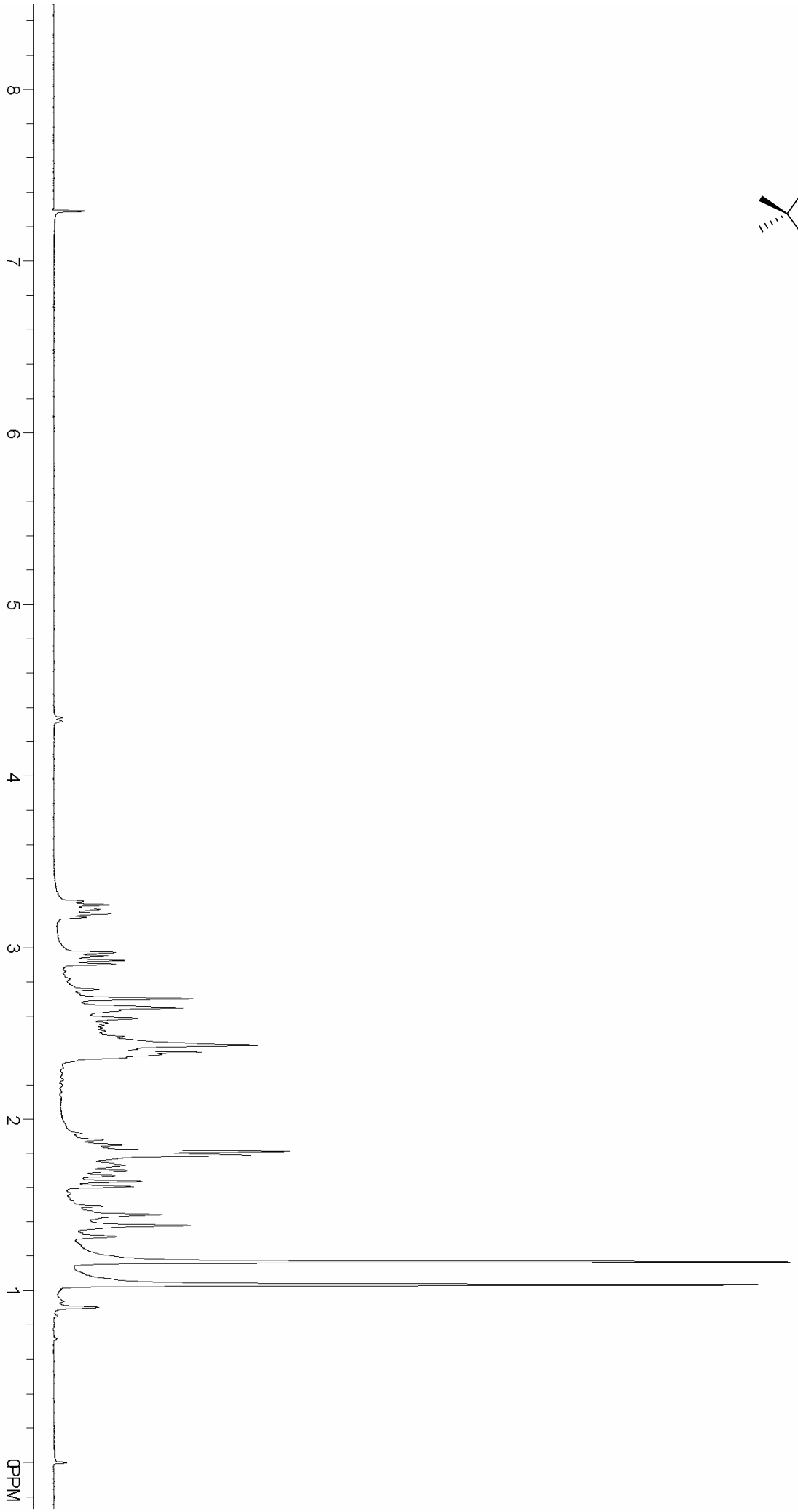

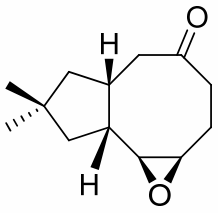

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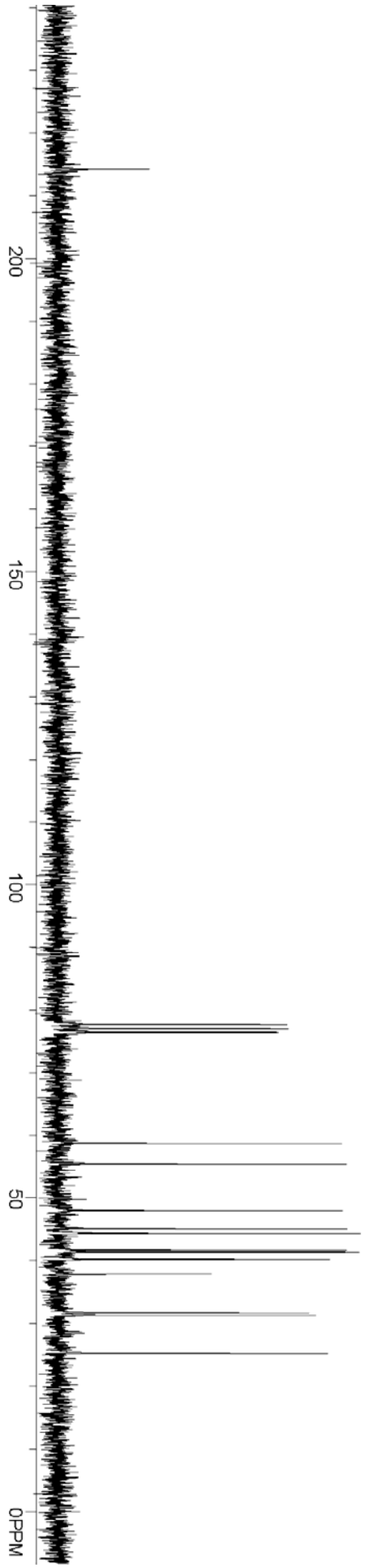

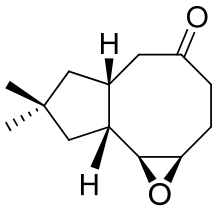

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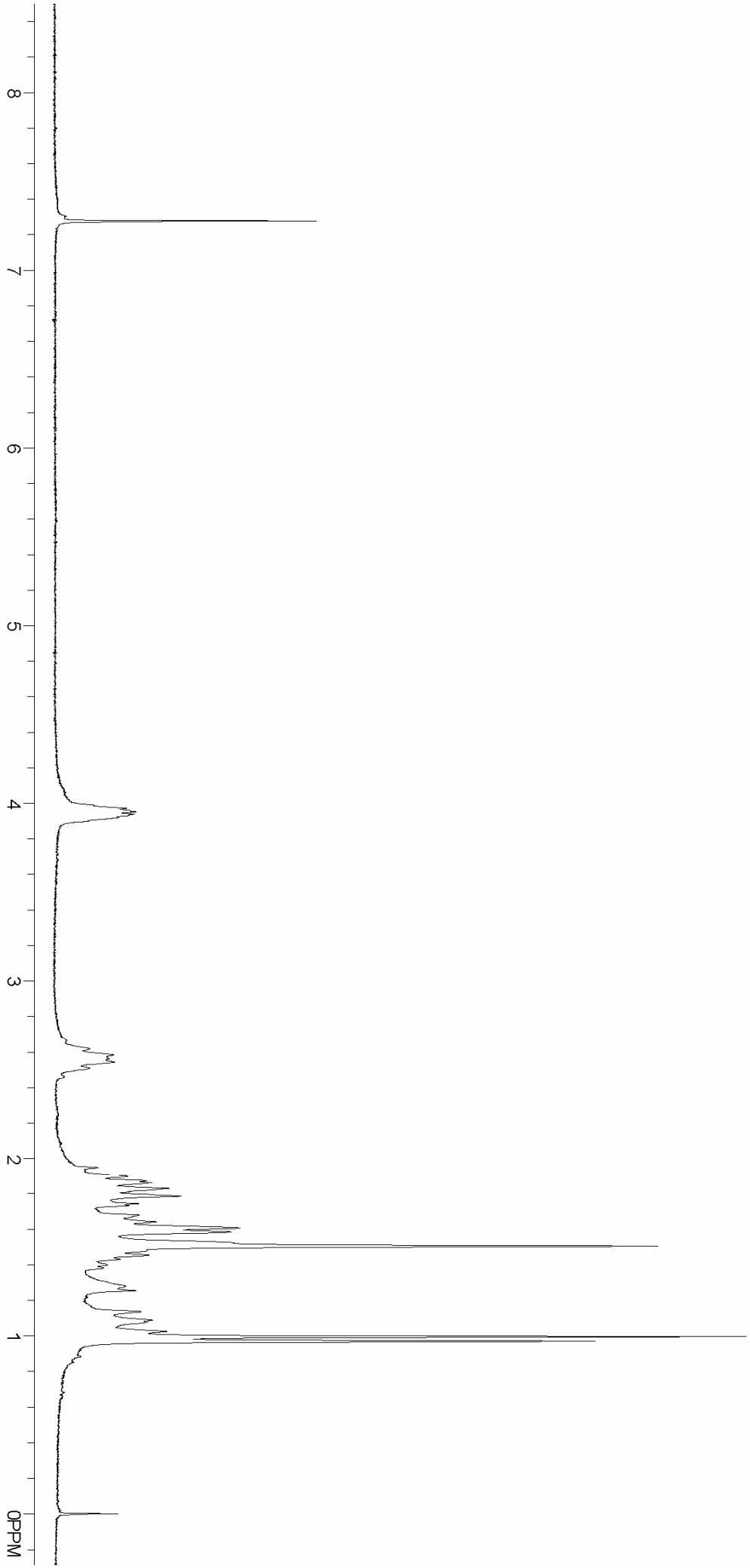

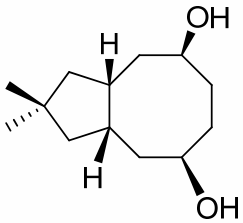

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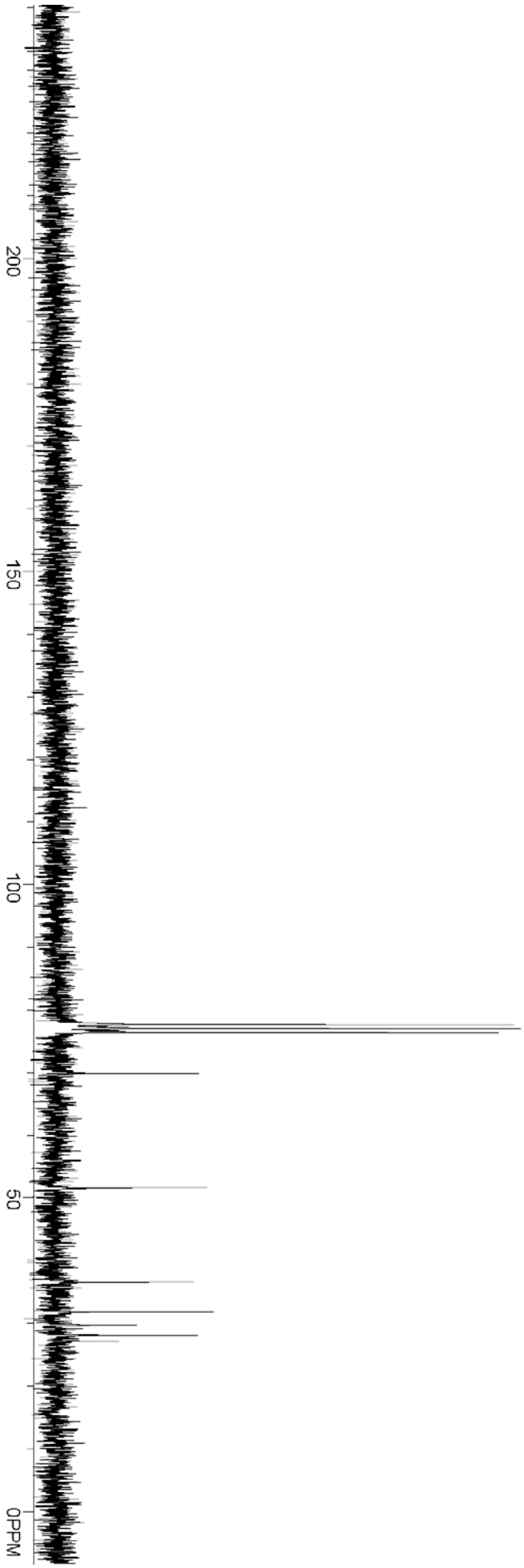

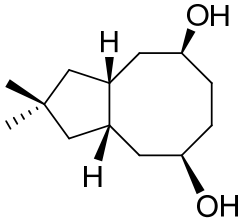

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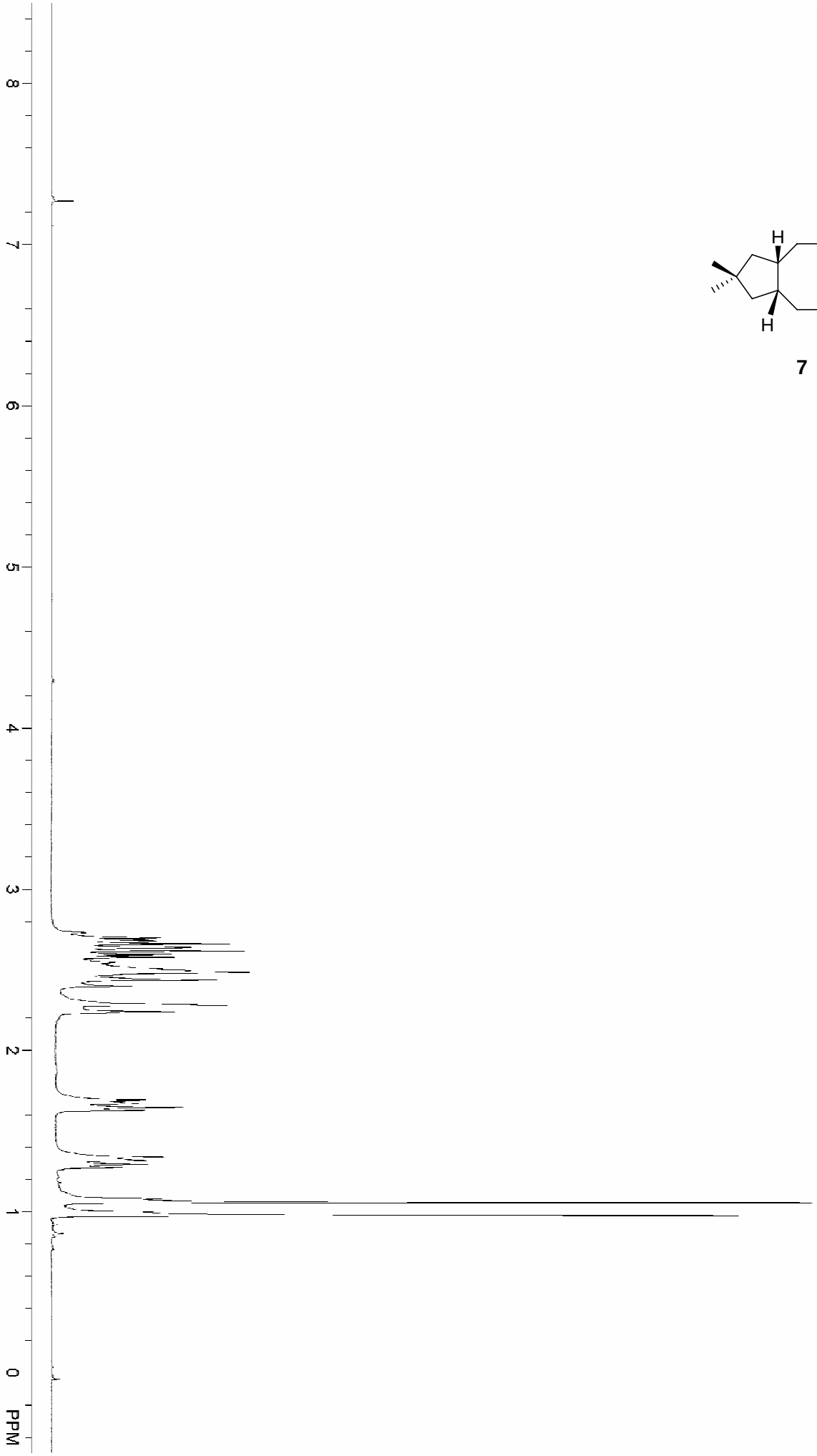

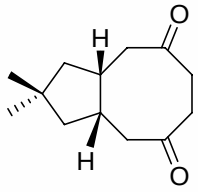

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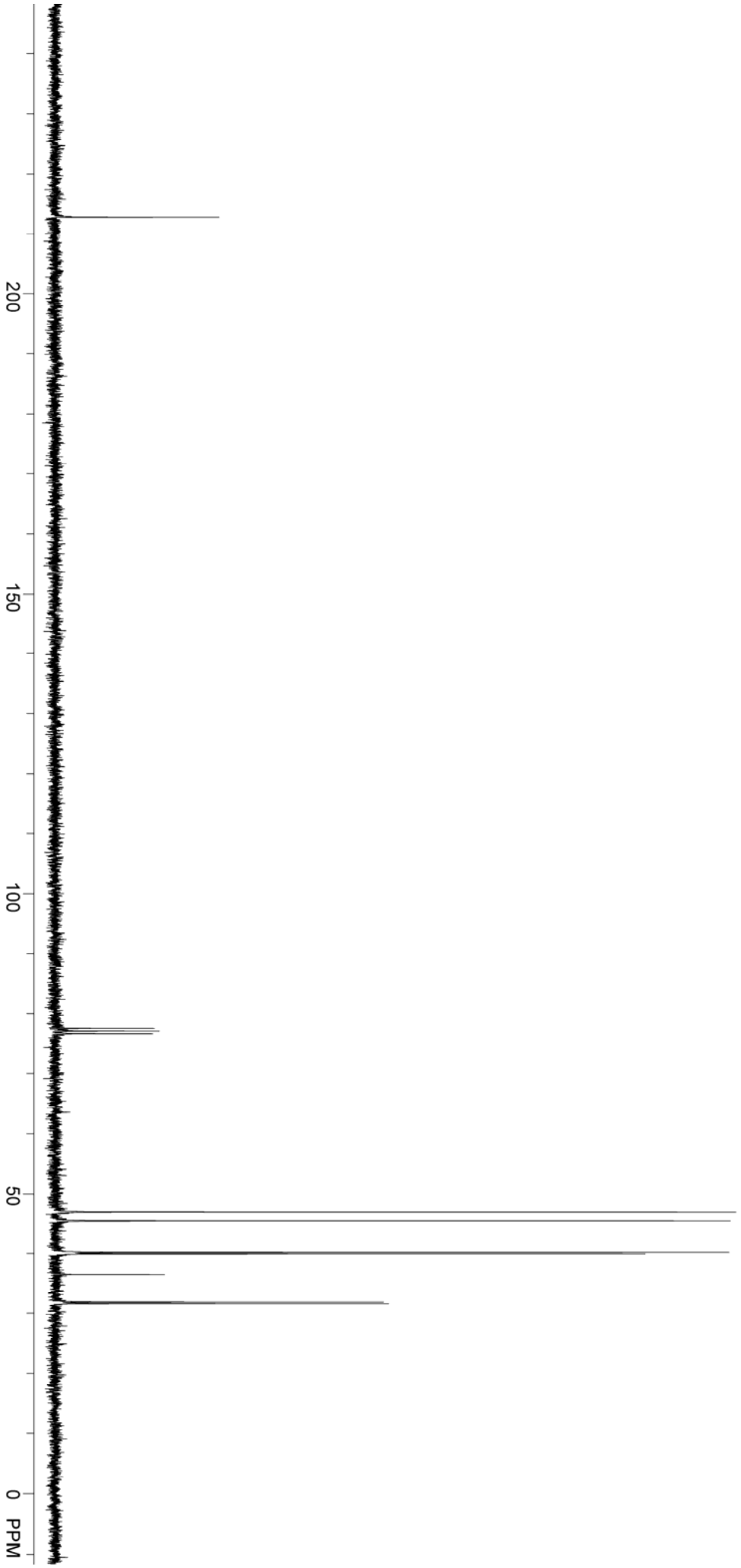

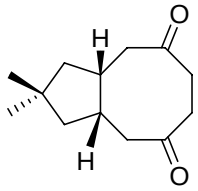

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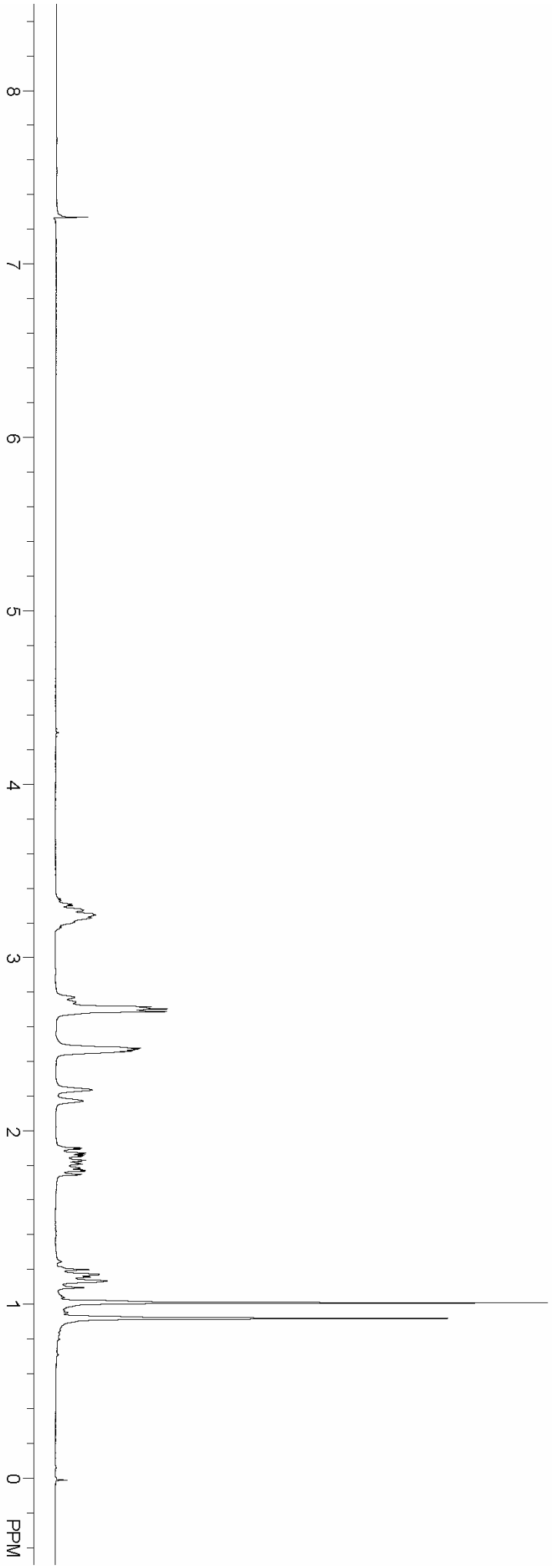

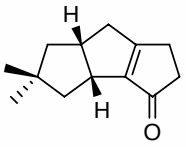

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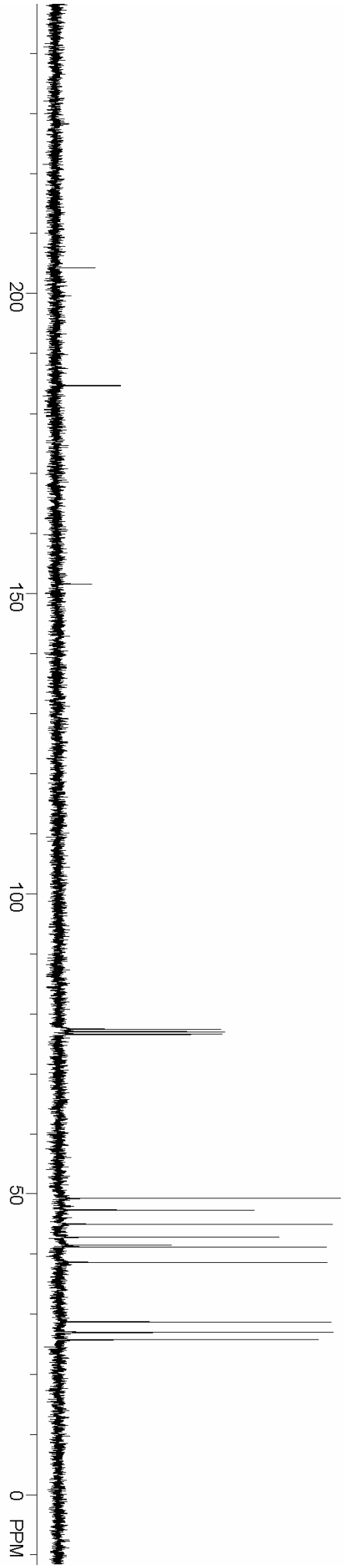

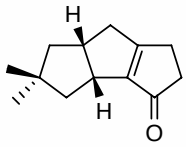

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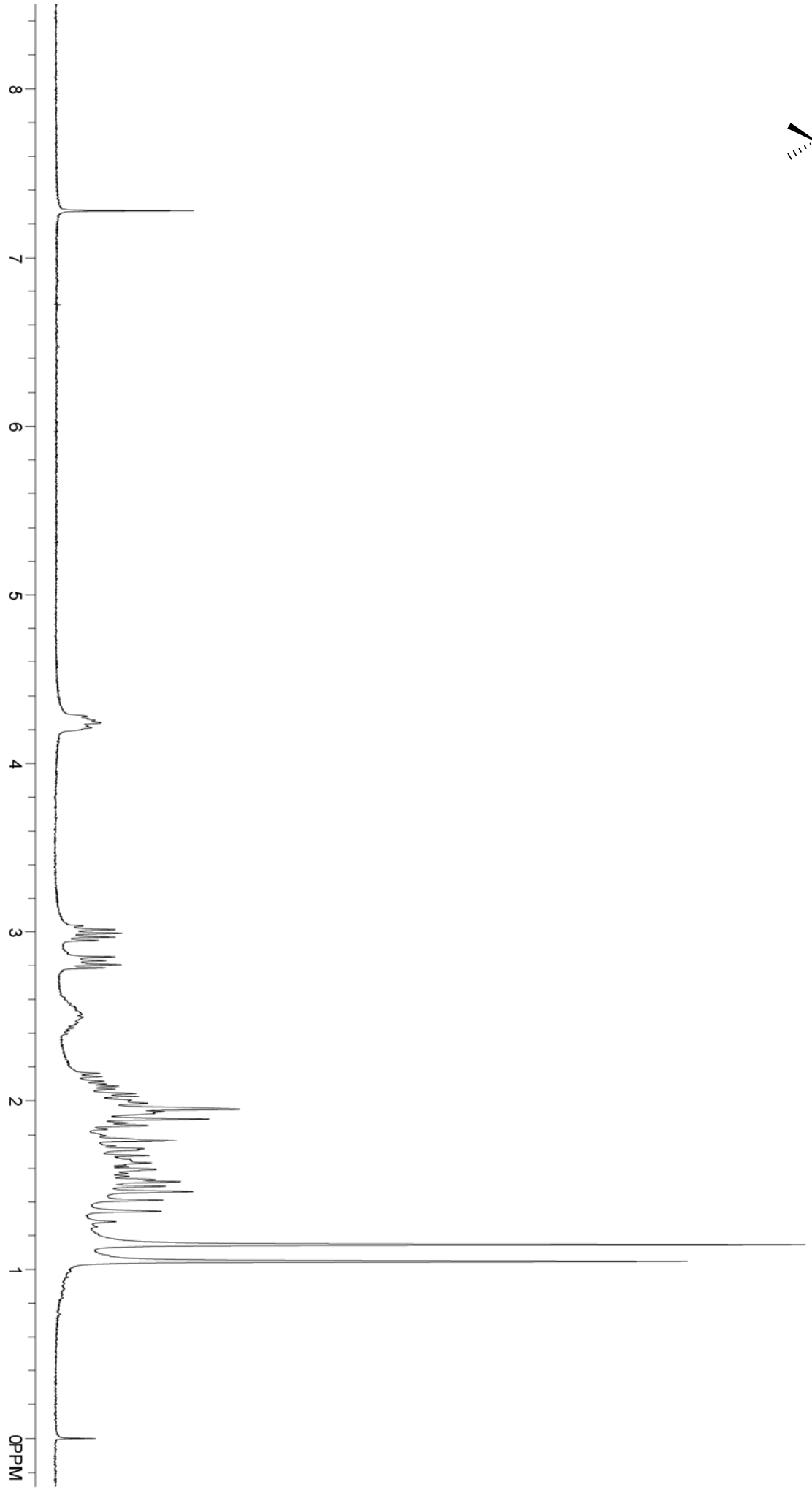

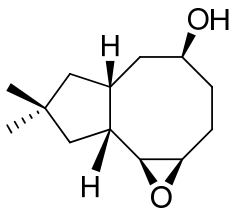

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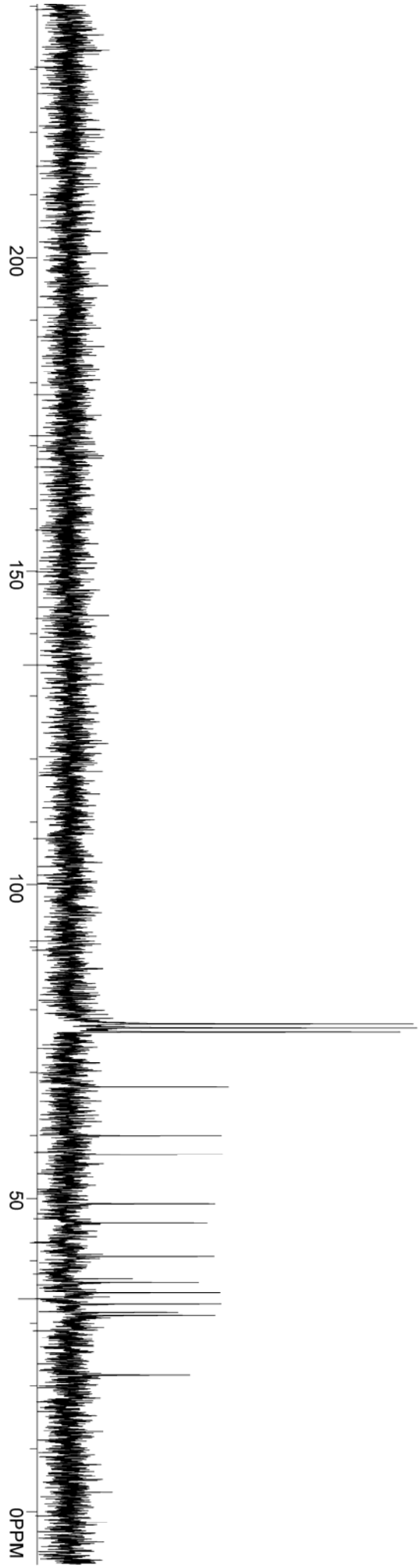

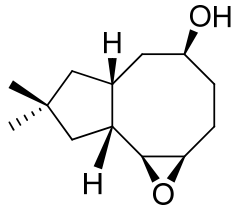

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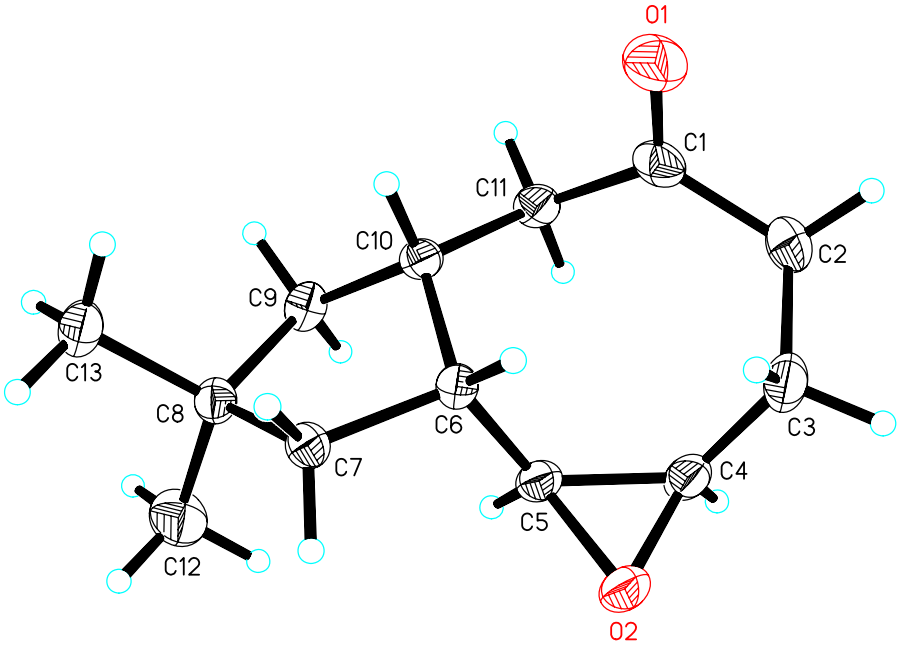
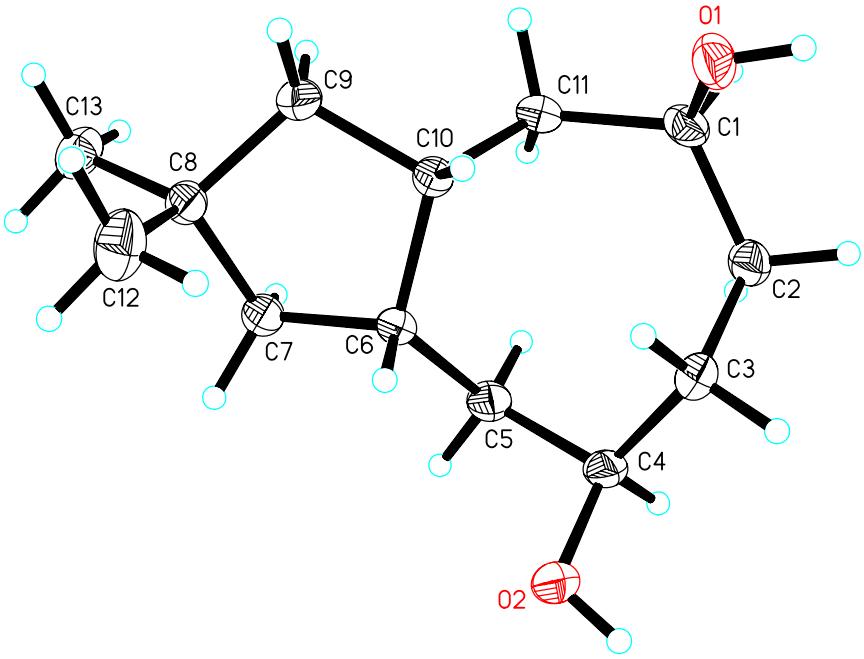
4. Crystal Structures of Compounds 5 and 6



Compound **5** (CCDC-702088)



Compound **6** (CCDC-702087)