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A New Route to Platencin via Decarboxylative Radical Cyclization

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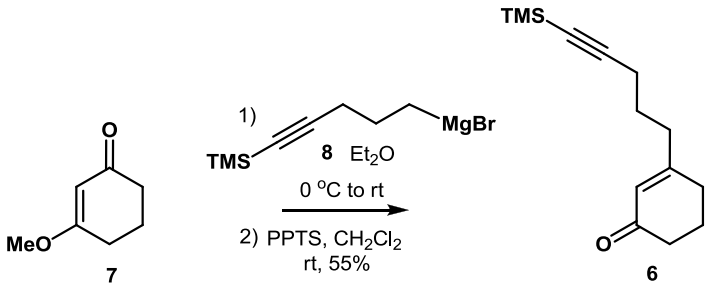
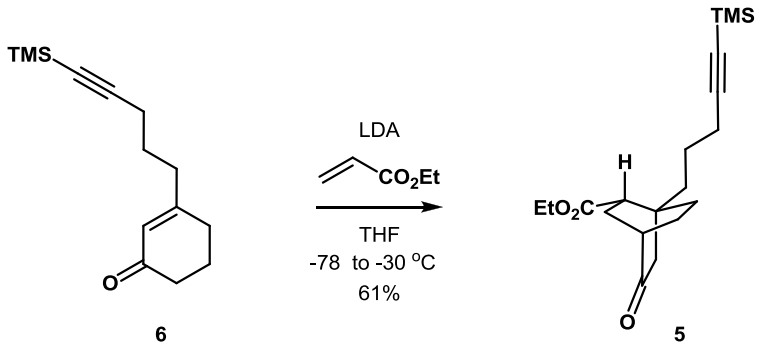
General. All reagents were used as received from commercial suppliers unless otherwise noted. ^{1}H NMR spectra (500 or 300 MHz) and ^{13}C NMR spectra (125 MHz) were measured in the specified solvents. Chemical shifts are reported in ppm relative to the residual solvent signal [chloroform-*d*: 7.26 ppm (^{1}H NMR), 77.0 ppm (^{13}C NMR) or Benzene-d_6: 7.15 ppm (^{1}H NMR), 128.0 ppm (^{13}C NMR)]. FT-IR spectra were recorded for samples loaded as neat films on NaCl plates. Mass spectra were obtained according to the specified technique. Analytical thin layer chromatography (TLC) was performed using Kieselgel 60 F_{254}, and compounds were visualized with UV light and stained with anisaldehyde solution or phosphomolybdic acid solution.

Experimental Section



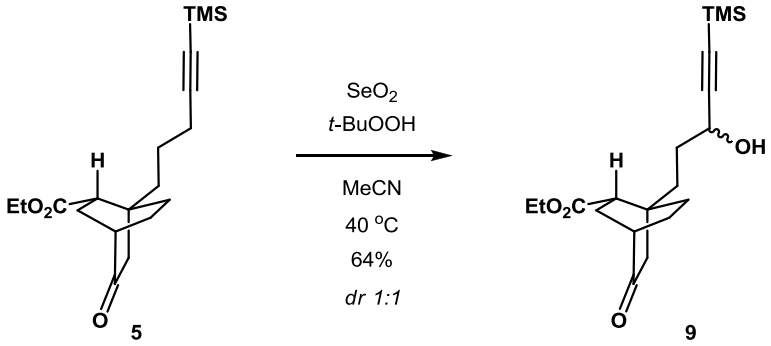
Enone 6: To a stirred solution of 5-(trimethylsilyl)-4-pentynylmagnesium bromide **8**,[1] which was freshly prepared from 5-bromo-l-(trimethylsily1)pentyne (6.0 g, 27.4 mmol) and Mg (1.33 g, 54.8 mmol) in Et_2O (20 mL), at 0 ^{o}C was slowly added a solution of enone **7** (4.15 g, 32.9 mmol) in Et_2O (20 mL). The mixture was allowed to warm to room temperature and stirring was continued for 2 h. Upon quenching at 0 ^{o}C with sat. NH_4Cl, the mixture was transferred to a separatory funnel where it was extracted with Et_2O. The phases were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated. (*The TLC analysis showed that the crude mixture contained enone **6** as a major product along with a small amount of unidentified less polar material, which, upon treatment with PPTS as described below, gave desired enone **6**.) Then the residue was dissolved in CH_2Cl_2 (30 mL), and PPTS (50 mg) was added at room temperature. After 1 h of stirring at the same temperature, the mixture was quenched with sat. $NaHCO_3$ and transferred to a separatory funnel where it was extracted with CH_2Cl_2. The phases were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The

residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:5 v/v) to afford enone **6** (3.51 g, 55% in 2 steps) as a pale yellow oil. **Enone 6:** IR (neat) ν 2174, 1670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (s, 1 H), 2.33-2.23 (m, 6H), 2.21 (t, *J* = 6.9 Hz, 2H), 1.95 (quintet, 2H, *J* = 6.9 Hz), 1.67 (quintet, 2H, *J* = 6.9 Hz), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 165.2, 125.9, 106.0, 85.4, 37.2, 36.7, 29.6, 25.8, 22.6, 19.3, 0.0; HRMS (MALDI) calcd for $C_{14}H_{23}OSi$ $(M+H)^+$: 235.1513, found: 235.1518.

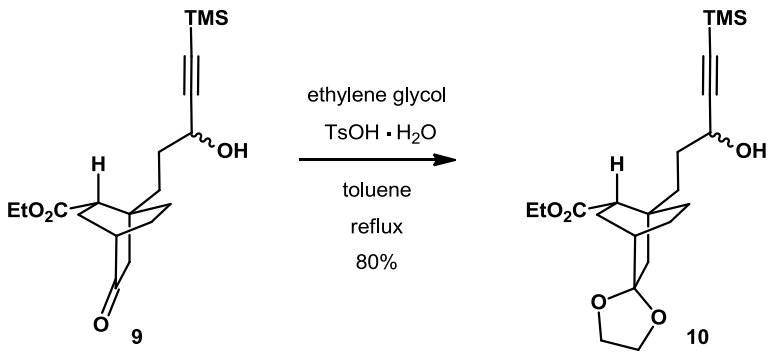


Bicyclic ester 5: To a stirred solution of freshly prepared LDA (1.0 M in THF; 2.22 mL, 2.22 mmol) was slowly added a solution of enone **6** (400 mg, 1.71 mmol) in THF (10 mL) at -78 °C, and the mixture was stirred for 30 min at the same temperature. Following slow addition of ethyl acrylate (200 µL, 1.88 mmol), the mixture was warmed to -30 °C and stirring was continued for an additional 1.5 h. Then the mixture was cooled to -78 °C and an additional amount of ethyl acrylate (10 µL, 0.094 mmol) was added before warming to -30 °C. After 1 h of stirring, again the mixture was cooled to -78 °C and an additional amount of ethyl acrylate (10 µL, 0.094 mmol) was added. After being warmed to -30 °C, the mixture was stirred for an additional 30 min. Upon quenching with sat. NH_4Cl, the mixture was transferred to a separatory funnel where it was extracted with Et_2O. The phases were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:10 v/v) to remove less polar impurity. Further elution with EtOAc/*n*-hexane (1:6 v/v) gave bicyclic ester **5** (350 mg, 61%) as a pale yellow oil. **Bicyclic ester 5:** IR (neat) ν 2174, 1730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19-4.08 (m, 2H), 2.70-2.63 (m, 2H), 2.35-2.32 (m, 1H), 2.21-2.15 (m, 2H), 2.07-2.02 (m, 2H), 1.97 (dd, *J* =

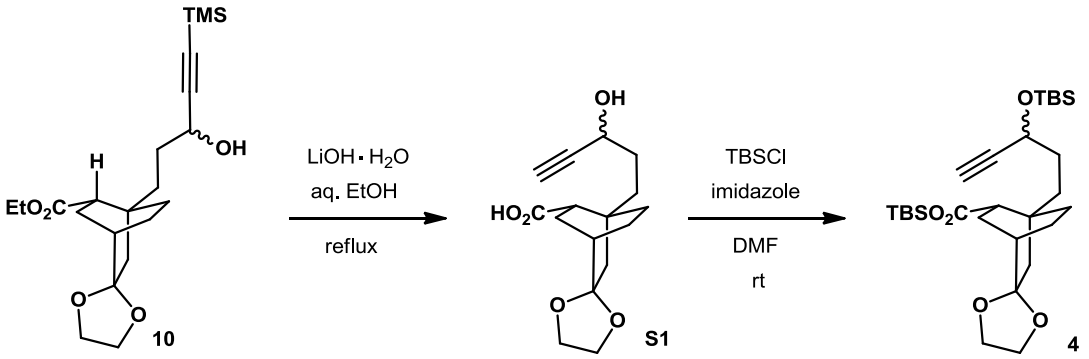
18.9, 1.7 Hz, 1H), 1.89-1.76 (m, 2H), 1.66-1.54 (m, 2H), 1.48-1.38 (m, 3H), 1.32 (dd, *J* = 12.3, 9.5 Hz,1H), 1.26 (t, *J* = 6.9 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 174.7, 106.6, 84.8, 60.4, 44.8, 43.9, 41.7, 38.3, 36.9, 29.8, 27.8, 22.9, 22.6, 20.3, 14.2, 0.0; HRMS (MALDI) calcd for $C_{19}H_{30}O_3SiNa$ $(M+Na)^+$: 357.1856, found: 357.1857.



Alcohol 9: To a stirred solution of enone **5** (340 mg, 1.01 mmol) in MeCN (15 mL) at room temperature were added SeO_2 (112 mg, 1.01 mmol) and TBHP (5.5 M in nonane, 367 µL, 2.02 mmol). Then the mixture was warmed to 40 °C and stirred at the same temperature for 3.5 h. Upon quenching with sat. $NaHCO_3$ and sat. $Na_2S_2O_3$, the whole mixture was transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:4 v/v) to give unreacted starting material (74 mg, 22% recovered). Further elution with EtOAc/*n*-hexane (2:5 v/v) gave alcohol **9** (229 mg, 64%) as a pale yellow oil. **Alcohol 9** (1:1 diastereomeric mixture by ^{1}H NMR analysis)**:** IR (neat) ν 3422, 2172 (weak), 1728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33-4.24 (m, 1H), 4.16-4.10 (m, 2H), 2.71-2.63 (m, 2H), 2.35-2.31 (m, 1H), 2.08-2.02 (m, 3H), 1.97 (dd, *J* = 18.9, 3.4 Hz, 0.5H), 1.96 (dd, *J* = 18.9, 3.4 Hz, 0.5H), 1.88-1.73 (m, 3H), 1.67-1.32 (m, 5H), 1.253 (t, *J* = 6.9 Hz, 1.5H), 1.249 (t, *J* = 6.9 Hz, 1.5H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.26, 215.24, 174.88, 174.86, 106.53, 106.48, 89.9, 63.05, 62.99, 60.8, 45.3, 45.2, 44.14, 44.12, 42.0, 38.39, 38.37, 33.2, 33.1, 31.9, 31.7, 30.1, 28.1, 23.2, 14.4, 0.0; HRMS (MALDI) calcd for $C_{19}H_{30}O_4SiNa$ $(M+Na)^+$: 373.1806, found: 373.1802.

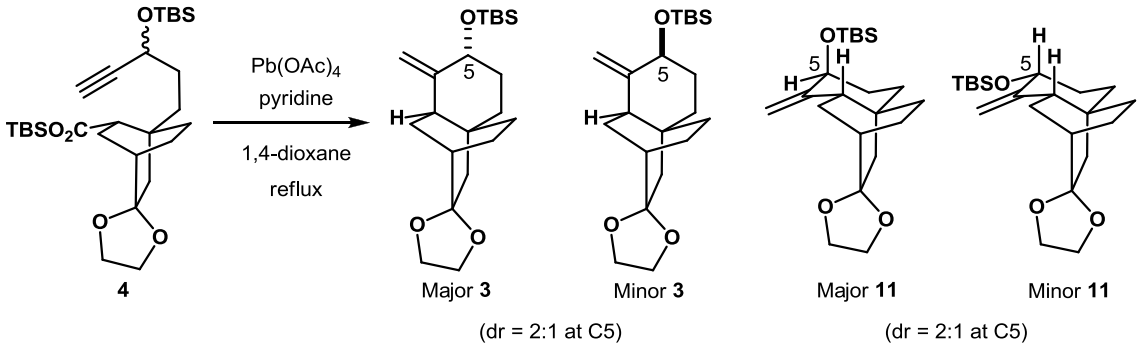


Ketal 10: In a flame-dried flask connected to a Dean–Stark apparatus were placed alcohol **9** (1.45 g, 4.14 mmol) and toluene (80 mL). To this solution at room temperature were added ethylene glycol (2.78 mL, 49.68 mmol) and TsOH·H_2O (236 mg, 1.24 mmol). Then the mixture was heated under reflux for 2 h, cooled, and quenched slowly with sat. $NaHCO_3$. The whole mixture was transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:3 v/v) to give ketal **10** (1.30 g, 80%) as a pale yellow oil. Further elution with EtOAc/*n*-hexane (1:1 v/v) gave unreacted starting material (149 mg, 10% recovered). **Ketal 10** (1:1 diastereomeric mixture by ^{1}H NMR analysis)**:** IR (neat) ν 3452, 2170 (weak), 1728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27-4.19 (m, 1H), 4.14-4.08 (m, 2H), 3.98-3.80 (m, 4H), 2.41-2.35 (m, 1H), 2.32 (d, *J* = 14.3 Hz, 1H), 2.07-2.00 (m, 1H), 1.99-1.95 (m, 1H), 1.91-1.83 (m, 2H), 1.81-1.74 (m, 1H), 1.73-1.53 (m, 3H), 1.48-1.26 (m, 5H), 1.242 (t, *J* = 6.9 Hz, 1.5H), 1.237 (t, *J* = 6.9 Hz, 1.5H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 110.6, 106.8, 106.7, 89.5, 64.1, 64.0, 63.34, 63.30, 60.29, 60.27, 44.14, 44.12, 41.1, 36.05, 36.03, 33.4, 33.3, 32.8, 32.0, 31.8, 29.6, 27.08, 27.06, 21.4, 14.5, 0.0; HRMS (MALDI) calcd for $C_{21}H_{34}O_5SiNa$ $(M+Na)^+$: 417.2068, found: 417.2066.



Disilylated ketal 4: To a solution of ketal **10** (87 mg, 0.22 mmol) in EtOH-H_2O (5 mL; 1:1 v/v) at room temperature was added LiOH·H_2O (138 mg, 3.3 mmol). After being stirred under reflux for 1.5 h, the mixture was cooled, concentrated, and acidified with acetic acid. The mixture was diluted with EtOAc and then transferred to a separatory funnel where it was partitioned between EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give the crude but sufficiently pure hydroxy acid **S1** (75 mg) as a pale yellow oil. **Hydroxy acid S1** (crude): IR (neat) ν 3412, 3288, 2114 (weak), 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (brs, 1H), 4.34-4.25 (m, 1H), 4.01-3.82 (m, 4H), 2.50-2.41 (m, 2H), 2.28 (d, *J* = 14.3 Hz, 1H), 2.10-2.02 (m, 1H), 1.92-1.79 (m, 2H), 1.78-1.60 (m, 3H), 1.59-1.25 (m, 6H).

The above-mentioned crude hydroxy acid **S1** was dissolved in DMF (4 mL) and imidazole (68 mg, 1.0 mmol) and TBSCl (151 mg, 1.0 mmol) were added at room temperature. After being stirred at the same temperature for 1 h, the mixture was cooled to 0 ^oC, diluted with water, and transferred to a separatory funnel where it was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to give the crude disilylated ketal **4** (120 mg) that was sufficiently pure and somewhat unstable on silica gel column chromatography. Therefore, the crude disilylated ketal **4** was used for the next step without purification. **Disilylated ketal 4** (crude; 1:1 diastereomeric mixture by ^1H NMR analysis): Pale yellow oil; IR (neat) ν 3312, 2114 (weak), 1709 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.35-4.27 (m, 1H), 3.55-3.45 (m, 2H), 3.42-3.35 (m, 2H), 2.71-2.63 (m, 1H), 2.37-2.26 (m, 2H), 2.06-2.03 (m, 1H), 1.96-1.87 (m, 1H), 1.83-1.45 (m, 7H), 1.16-1.10 (m, 2H), 1.012 (s, 4.5H), 1.008 (s, 4.5H), 0.996 (s, 4.5H), 0.987 (s, 4.5H), 0.354 (s, 1.5H), 0.347 (s, 3H), 0.344 (s, 1.5H), 0.20 (s, 3H), 0.14 (s, 1.5H), 0.13 (s, 1.5H).



Cyclized compounds 3 and 11: To a stirred solution of the above-mentioned crude disilylated ketal **4** (120 mg, 0.23 mmol) in 1,4-dioxane (8 mL) were added pyridine (186 µL, 2.30 mmol) and lead tetraacetate (>80%, 510 mg, 0.92 mmol) at room temperature. The mixture was heated under reflux for 10 min and cooled to room temperature at which temperature an additional amount of lead tetraacetate (255 mg, 0.46 mmol) was added. After being stirred under reflux for 5 min, the mixture was again cooled to room temperature, and additional amounts of lead tetraacetate (255 mg, 0.46 mmol) and pyridine (93 µL, 1.15 mmol) were added. Stirring was continued for further 5 min under reflux, and the mixture was again cooled to room temperature. To this was added lead tetraacetate (127.5 mg, 0.23 mmol), and the mixture was heated for further 5 min under reflux. The reaction mixture was then cooled to room temperature and quenched with ethylene glycol and water. The whole mixture was diluted with Et_2O and transferred to a separatory funnel where the organic layer was washed 5 times with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by passing it through a short column of silica gel eluting with EtOAc/*n*-hexane (1:12 v/v) to afford the cyclized compounds **3** (dr = 2:1) and **11** (dr = 2:1) (48 mg, 60% in 3 steps from ketal **10**) as a colorless oil consisting of four diastereomers whose ratio was determined by ^{1}H NMR analysis. The spectrum is provided in page S28.

N.B.: Flash silica gel column chromatography (Et_2O/*n*-hexane 1:35 v/v) of the products obtained from a large scale reaction, in which ketal **4** (1.20 g, 2.30 mmol), lead tetraacetate (>80%, 11.48 g, 20.7 mmol) and pyridine (2.6 mL, 32.2 mmol) were reacted in refluxing 1,4-dioxane (80 mL) in the same manner as described above, allowed us to separate and characterize all the four diastereomers as described below:

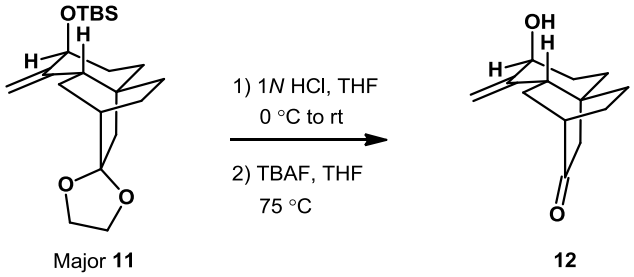
Major 3: Colorless oil; IR (neat) ν 2951, 2928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.79 (s, 1H), 4.27-4.23 (m, 1H), 3.99-3.84 (m, 4H), 2.58-2.51 (m, 1H), 1.88-1.55 (m, 11H), 1.43-1.35 (m, 1H), 1.05 (dt, *J* = 13.2, 2.9 Hz, 1H), 0.86 (s, 9H), 0.02 (s, 3H) -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 111.2, 107.7, 74.0, 63.9, 63.8, 49.5, 36.9, 35.7, 33.1, 31.5, 31.1, 25.8, 23.7, 23.6, 21.9, 18.1, -4.6, -5.1; HRMS (MALDI) calcd for $C_{21}H_{37}O_3Si$ $(M+H)^+$: 365.2506, found: 365.2506.

Major 11: Colorless waxy solid; IR (neat) ν 2951, 2928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.82 (s, 1H), 4.28-4.24 (m, 1H), 3.95-3.80 (m, 4H), 2.47-2.41 (m, 1H), 1.97-1.90 (m, 2H), 1.89-1.77 (m, 2H), 1.73-1.68 (m, 1H), 1.62-1.48 (m, 4H), 1.47-1.40 (m, 1H), 1.34-1.27 (m, 1H), 1.14 (dd, *J* = 14.3, 1.7 Hz, 1H), 1.08 (dt, *J* = 13.2, 2.9 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 111.4, 108.9, 74.0, 63.9, 63.7, 40.4, 36.3, 35.2, 33.7, 33.1, 31.6, 31.0, 25.8, 24.0, 21.8, 18.1, -4.7, -5.1; HRMS (MALDI) calcd for $C_{21}H_{37}O_3Si$ $(M+H)^+$: 365.2506, found: 365.2498.

Minor 3: Colorless oil; IR (neat) ν 2953, 2928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.90 (s, 1H), 4.00-3.80 (m, 5H), 2.06-1.97 (m, 1H), 1.93-1.81 (m, 1H), 1.79-1.31 (m, 10H), 0.95-0.80 (m, 2H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 111.0, 104.0, 74.3, 63.9, 63.8, 49.2, 41.4, 35.8, 35.7, 33.2, 33.0, 25.9, 24.3, 24.0, 21.7, 18.4, -4.96, -4.98; HRMS (MALDI) calcd for $C_{21}H_{37}O_3Si$ $(M+H)^+$: 365.2506, found: 365.2492.

Minor 11: Colorless oil; IR (neat) ν 2951, 2928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.93 (s, 1H), 3.92-3.79 (m, 5H), 2.12-2.05 (m, 1H), 1.99-1.92 (m, 2H), 1.89-1.81 (m, 1H), 1.75-1.69 (m, 2H), 1.58 (ddd, *J* = 13.7, 10.3, 3.4 Hz, 1H), 1.51-1.30 (m, 5H), 1.27-1.20 (m, 1H), 1.13 (dd, *J* = 14.3, 1.7 Hz, 1H), 0.91 (s, 9H), 0.06 (s, 3H) 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 111.2, 105.1, 74.3, 63.8, 63.7, 40.9, 40.6, 36.1, 35.5, 33.5, 33.3, 33.2, 25.9, 24.6, 21.6, 18.4, -4.9, -5.0; HRMS (MALDI) calcd for $C_{21}H_{37}O_3Si$ $(M+H)^+$: 365.2506, found: 365.2501.

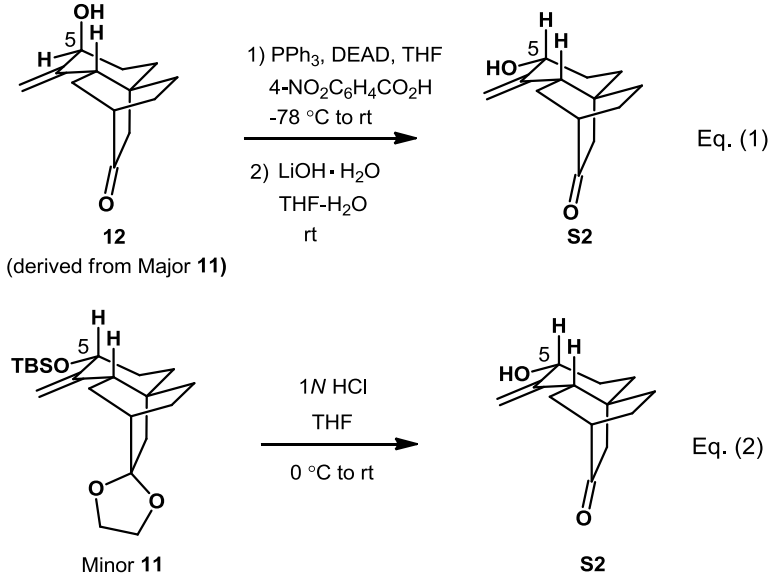
Determination of stereochemistry of major 11:



Major **11** **12**

To a stirred solution of major **11** (13.2 mg, 0.036 mmol) in THF (2 mL) at 0 ^{o}C was added 1*N* HCl (165 µL, 0.165 mmol). The mixture was warmed to room temperature and stirred for 3.5 h. Then the mixture was cooled to 0 ^{o}C, quenched with sat. $NaHCO_3$, and transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in THF (1.5 mL) and TBAF (1.0 M in THF, 53 µL, 0.053 mmol) was added at room temperature. The mixture was warmed to 75 ^{o}C and stirring was continued for 75 min. Then the mixture was cooled to room temperature, quenched with sat. NH_4Cl, and transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:2 v/v) to give alcohol **12** (6.9 mg, 93% in 2 steps) as a colorless solid. The stereochemistry of this material was determined by X-ray crystallographic analysis. The details are given in page S15-S16. **Alcohol 12:** Colorless cubic crystals of mp 110-111 ºC (*n*-hexane); IR (neat) ν 3420, 1705 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (d, *J* = 2.3 Hz, 1H), 4.79 (d, *J* = 2.3 Hz, 1H), 4.40 (dd, *J* = 2.9, 2.3 Hz, 1H), 2.79 (dddd, *J* = 8.0, 8.0, 4.0, 2.3 Hz,1H), 2.36 (dd, *J* = 18.6, 2.9 Hz, 1H), 2.33 (quintet, *J* = 2.9 Hz, 1H), 1.99-1.80 (m, 6H), 1.71-1.60 (m, 3H), 1.53 (ddd, *J* = 13.2, 10.9, 5.7 Hz, 1H), 1.45 (bsr, 1H), 1.27 (ddd, *J* = 13.7, 4.0, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 150.0, 110.9, 73.3, 43.2, 42.7, 37.6, 36.6, 33.5, 30.4, 29.4, 25.1, 23.4; HRMS (MALDI) calcd for $C_{13}H_{19}O_2$ $(M+H)^+$: 207.1380, found: 207.1378.

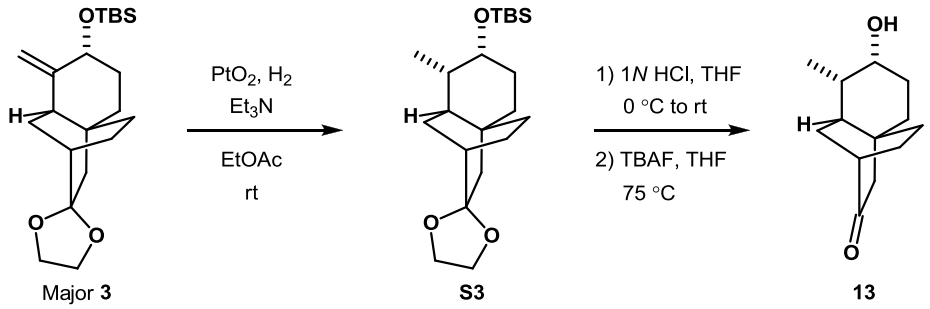
Chemical correlations of major 11 with minor 11:



To a stirred solution of alcohol **12** (1.8 mg, 0.0087 mmol) in THF (0.75 mL) at -78 °C (a dry ice-acetone bath) were sequentially added Ph_3P (13.6 mg, 0.052 mmol), DEAD (40% w/v in toluene; 28 μL, 0.072 mmol) and 4-nitrobenzoic acid (12.2 mg, 0.072 mmol). The dry ice-acetone bath was removed and the mixture was stirred at room temperature for 3.5 h. Then, sat. $NaHCO_3$ was added and the mixture was transferred to a separatory funnel where it was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by passing it through a short column of silica gel eluting with EtOAc/*n*-hexane (1:3 v/v) to afford benzoate. The benzoate was dissolved in THF-H_2O (2 mL; 1:1 v/v) and $LiOH{\cdot}H_2O$ (9 mg, 0.22 mmol) was added at room temperature. After being stirred at the same temperature for 1 h, the mixture was diluted with Et_2O and transferred to a separatory funnel where it was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (Et_2O/*n*-hexane 3:2 v/v) to give alcohol **S2** (1.3 mg, 72% in 2 steps) as a colorless solid whose spectral data were identical to those of the product obtained in equation (2) by deketalization/desilylation of minor **11** (The spectra are provided in page S39).

Procedure for transformation of minor 11 to alcohol S2 (equation 2): To a stirred solution of minor **11** (8.5 mg, 0.023 mmol) in THF (2 mL) at 0 °C was added 1*N* HCl

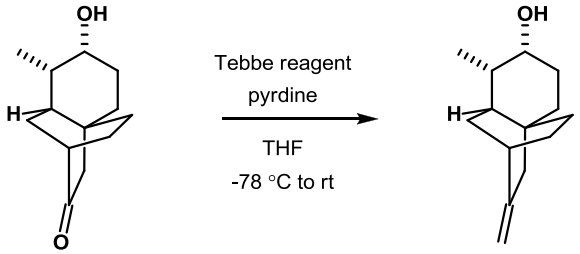
(115 µL, 0.115 mmol). The mixture was warmed to room temperature and stirred for 3.5 h. Then the mixture was cooled to 0 ^{o}C, quenched with sat. $NaHCO_3$, and transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:2 v/v) to give alcohol **S2** (4.2 mg, 88%) as a colorless solid The mentioned transformations in equations (1) and (2) allowed us to confirm that major **11** and minor **11** produced by the radical cyclization of disilylated ketal **4** (page S7) shared the same molecular architecture except the stereochemistry at C5.



To a stirred solution of major **3** (71.5 mg, 0.20 mmol) in EtOAc (5 mL) at room temperature were added Et_3N (140 µL, 1.0 mmol) and PtO_2 (7.2 mg, 10% w/w). The mixture was stirred at the same temperature under hydrogen atmosphere for 1 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give sufficiently pure ketal **S3** that was used for the next step without purification. **Ketal S3** (crude)**:** Colorless oil; IR (neat) ν 2951, 2928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00-3.82 (m, 4H), 3.71-3.67 (m, 1H), 2.02-1.94 (m, 1H), 1.89-1.74 (m, 2H), 1.70-1.62 (m, 2H), 1.61-1.39 (m, 6H), 1.34-1.26 (m, 1H), 1.01-0.90 (m, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.5, 71.4, 64.0, 63.6, 50.1, 39.7, 36.1, 33.08, 33.06, 31.2, 29.34, 29.28, 25.9, 24.1, 22.7, 18.2, 15.9, -4.5, -4.9; HRMS (MALDI) calcd for $C_{21}H_{39}O_3Si$ $(M+H)^+$: 367.2663, found: 367.2663.

To a stirred solution of the crude ketal **S3** (72 mg) in THF (5 mL) at 0 ^{o}C was added 1*N* HCl (1.0 mL, 1.0 mmol). The mixture was warmed to room temperature and stirred for 3 h. Then the mixture was cooled to 0 ^{o}C, quenched with sat. $NaHCO_3$, and then transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue (65 mg) was

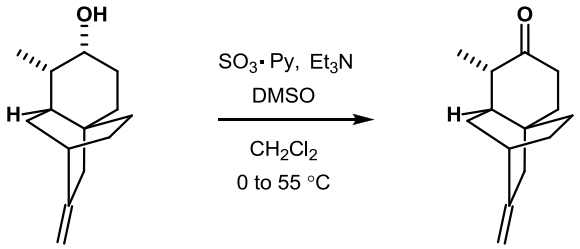
dissolved in THF (3.5 mL) and TBAF (1.0 M in THF, 0.80 mL, 0.80 mmol) was added at room temperature. The mixture was warmed to 75 ^{o}C, stirred for 4 h, and then cooled to room temperature. The reaction was quenched with sat. NH_4Cl, and transferred to a separatory funnel where it was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:1 v/v) to give hydroxyketone **13** (40 mg, 98% in 3 steps) as a colorless oil. **Hydroxyketone 13:** IR (neat) ν 3412, 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80-3.77 (m, 1H), 2.28-2.22 (m, 1H), 2.14-2.06 (m, 1H), 2.13 (d, *J* = 18.9 Hz, 1H), 2.06-1.99 (m, 1H), 1.92 (dd, *J* = 18.9, 2.9 Hz, 1H), 1.82-1.73 (m, 2H), 1.71-1.60 (m, 4H), 1.54-1.45 (m, 2H), 1.29-1.17 (m, 2H), 1.16-1.09 (m, 1H), 0.98 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 70.4, 52.5, 42.9, 38.9, 37.2, 35.2, 30.8, 30.3, 28.7, 23.9, 23.7, 15.3; HRMS (MALDI) calcd for $C_{13}H_{21}O_2$ $(M+H)^+$: 209.1536, found: 209.1536.



13 **S4**

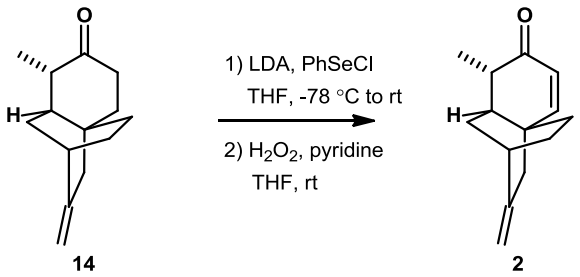
Alcohol S4: To a stirred solution of hydroxyketone **13** (27 mg, 0.13 mmol) in THF (4 mL) at -78 ^{o}C were added pyridine (84 μL, 1.04 mmol) and Tebbe reagent (0.5 M in toluene, 0.572 mL, 0.268 mmol). After being stirred for 10 min at the same temperature, the mixture was warmed to room temperature and stirring was continued for an additional 20 min. The mixture was then cooled to 0 ^{o}C, quenched with sat. $NaHCO_3$, and transferred to a separatory funnel where it was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:12 v/v) to give alcohol **S4** (25 mg, 94%) as a colorless solid. **Alcohol S4:** Colorless solid of mp 78-79 ºC, IR (neat) ν 3404, 2928 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72-4.69 (m, 1H), 4.58-4.55 (m, 1H), 3.77-3.73 (m, 1H), 2.20-2.12 (m, 2H), 1.99-1.91 (m, 2H), 1.87-1.80 (m, 1H), 1.70-1.62

(m, 2H), 1.61-1.56 (m, 2H), 1.55-1.28 (m, 4H), 1.13-1.04 (m, 2H), 1.02-0.96 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 104.5, 71.0, 44.5, 39.0, 37.5, 36.1, 34.2, 32.7, 30.9, 28.7, 26.9, 24.8, 15.3; HRMS (MALDI) calcd for $C_{14}H_{23}O$ $(M+H)^+$: 207.1743, found: 207.1732.



S4 **14**

Ketone 14: To a stirred solution of alcohol **S4** (25 mg, 0.12 mmol) in CH_2Cl_2 (3.5 mL) at 0 ^oC were added Et_3N (169 µL, 1.20 mmol) and DMSO (256 µL, 3.60 mmol). Then, SO_3·Py (95 mg, 0.60 mmol) was added, and the mixture was allowed to warm to room temperature. After stirring for 1.5 h at the same temperature, additional amounts of Et_3N (100 µL, 0.71 mmol), DMSO (200 µL, 2.82 mmol) and SO_3·Py (47.5 mg, 0.30 mmol) were added. After 30 min, the mixture was heated to 55 ^oC and stirred at this temperature for further 75 min. Then, SO_3·Py (19 mg, 0.12 mmol) was added and stirring at 55 ^oC was continued for an additional 15 min. The mixture was then diluted with Et_2O and transferred to a separatory funnel where it was sequentially washed with sat. $NaHCO_3$ and water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:20 v/v) to give ketone **14** (18.2 mg, 74%) as a pale yellow oil. Further elution gave unreacted alcohol **S4** (2.7 mg, 11% recovered). **Ketone 14:** IR (neat) ν 2932, 1711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78-4.75 (m, 1H), 4.62-4.59 (m, 1H), 2.47 (dddd, J = 14.3, 14.3, 5.7, 1.1 Hz, 1H), 2.30-2.18 (m, 5H), 1.98-1.91 (m, 2H), 1.75-1.66 (m, 3H), 1.55 (ddd, J = 14.0, 14.0, 4.6 Hz, 1H), 1.46-1.39 (m, 1H), 1.30-1.23 (m, 2H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 150.8, 105.4, 47.9, 46.5, 43.4, 37.8, 37.6, 35.6, 35.3, 33.0, 26.7, 24.9, 11.2; HRMS (MALDI) calcd for $C_{14}H_{21}O$ $(M+H)^+$: 205.1587, found: 205.1584.



14 2

Enone 2: To a stirred solution of freshly prepared LDA (1.0 M in THF; 63 μL, 0.063 mmol) in THF (0.2 mL) at -78 ^{o}C was slowly added a solution of ketone **14** (9.8 mg, 0.048 mmol) in THF (1.2 mL). After 30 min, a solution of PhSeCl (11.1 mg, 0.058 mmol) in THF (1.2 mL) was slowly added, and the whole mixture was stirred for an additional 30 min. Then, the mixture was warmed to room temperature and stirring was continued for further 30 min before being quenched with sat. NH_4Cl. The whole mixture was transferred to a separatory funnel where it was extracted with Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by passing it through a short column of silica gel eluting with EtOAc/*n*-hexane (1:40 v/v) to give a selenide. The resultant selenide was dissolved in THF (1.8 mL), and pyridine (84 μL, 1.04 mmol) and H_2O_2 (30 % in H_2O, 34 μL, 0.3 mmol) were added at room temperature. After being stirred at the same temperature for 2.5 h, the mixture was quenched with sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ and transferred to a separatory funnel where it was extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:60 v/v) to give enone **2** (6.5 mg, 67% in two steps) as a colorless oil. **Enone 2:** IR (neat) ν 2934, 2864, 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, *J* = 10.0 Hz, 1H), 5.87 (d, *J* = 10.0 Hz, 1H), 4.83-4.81 (m, 1H), 4.68-4.66 (m, 1H), 2.39 (dt, *J* = 16.0, 2.9 Hz, 1H), 2.36-2.32 (m, 1H), 2.27 (sextet, *J* = 6.9 Hz, 1H), 2.16-2.11 (m, 1H), 2.03-1.96 (m, 1H), 1.83-1.68 (m, 4H), 1.53-1.47 (m, 1H), 1.29 (ddd, *J* = 13.2, 8.6, 1.7 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 155.5, 148.9, 127.2, 106.7, 43.7, 42.6, 41.1, 36.0, 35.6, 34.3, 26.3, 24.9, 11.3; HRMS (MALDI) calcd for $C_{14}H_{19}O$ $(M+H)^+$: 203.1430, found: 203.1429. The above-mentioned spectroscopic and analytical data were in good agreement with those reported in the literature.[2]

X-ray crystallographic analysis of compound 12:

A Suitable single crystal of compounds **12** were carefully selected under an optical microscope and glued to thin glass fibers. Single-crystal X-ray diffraction data were collected on a Rigaku AFC-7R diffractometer and Mercury CCD detector equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 103K, installed at the institute of scientific and industrial research, Osaka University. The intensity data sets were reduced by *CrystalClear* software.[3] The structures were solved by direct methods using *SIR2004* program[4] and refined by full-matrix least squares on F^2 using *SHELXL-97* program[5], implemented in program package WinGX.[6] The final models include anisotropic refinement for the non-hydrogen atoms and an isotropic riding model for H atoms. Further details of the refinements are given table 1.

Crystallographic data for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC-1022475).

Table 1. Crystallographic data for compounds **12**

Compound	**12**
Empirical formula	$C_{13}H_{18}O_2$
Formula weight	206.27
Temperature (K)	103
Crystal system	monoclinic
Space group	*c*2/c
a (Å)	9.001 (11)
b (Å)	11.207(13)
c (Å)	20.96 (2)
β (°)	90.919 (14)
V (Å^3)	2,114 (4)
Z	8
D_{calcd} (g/cm^3)	1.296
R_1 [a]	0.1327
wR_2 [b]	0.4116
Goodness-of-fit [c]	1.594

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a $$\mathbf{R1} = \frac{\Sigma\big||\mathbf{Fo}| - |\mathbf{Fc}|\big|}{\Sigma|\mathbf{Fo}|}$$

b $$\mathbf{wR2} = \left\{\frac{\Sigma[\mathbf{w}(\mathbf{Fo}^2 - \mathbf{Fc}^2)^2]}{\Sigma[\mathbf{w}(\mathbf{Fo}^2)^2]}\right\}^{\frac{1}{2}}$$

c $$\mathbf{GOF} = \left\{\frac{\Sigma[\mathbf{w}(\mathbf{Fo}^2 - \mathbf{Fc}^2)^2]}{\mathbf{n} - \mathbf{p}}\right\}^{\frac{1}{2}}$$,where n = number of measured data and p = number of parameters.

References

1. (a) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876. (b) Mao, B.; Fananas-Mastral, M.; Lutz, M.; Feringa, B. L. *Chem. Eur. J.* **2013**, *19*, 761.
2. (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed*. **2008**, *47*, 1780. (b) Hayashida, J.; Rawal, V. H. *Angew. Chem., Int. Ed*. **2008**, *47*, 4373. (c) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909. (d) Tiefenbacher, K.; Mulzer, J. *J. Org. Chem.* **2009**, *74*, 2937.
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4. Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidor, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381.

5. Sheldrick, G. M. *Acta Cryst*. **2008**, *A64*, 112.
6. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.

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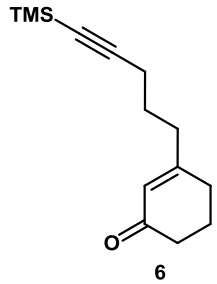
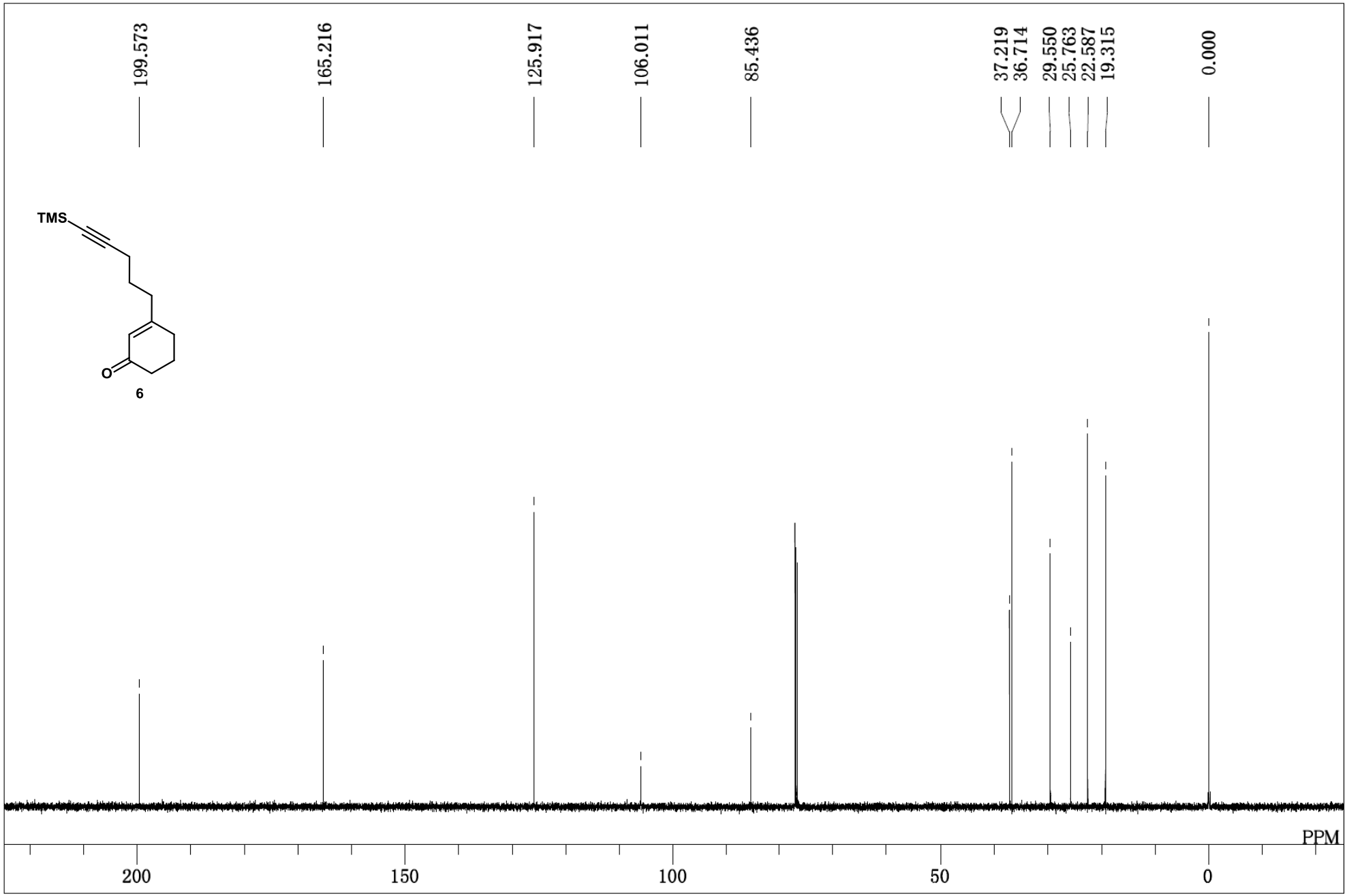
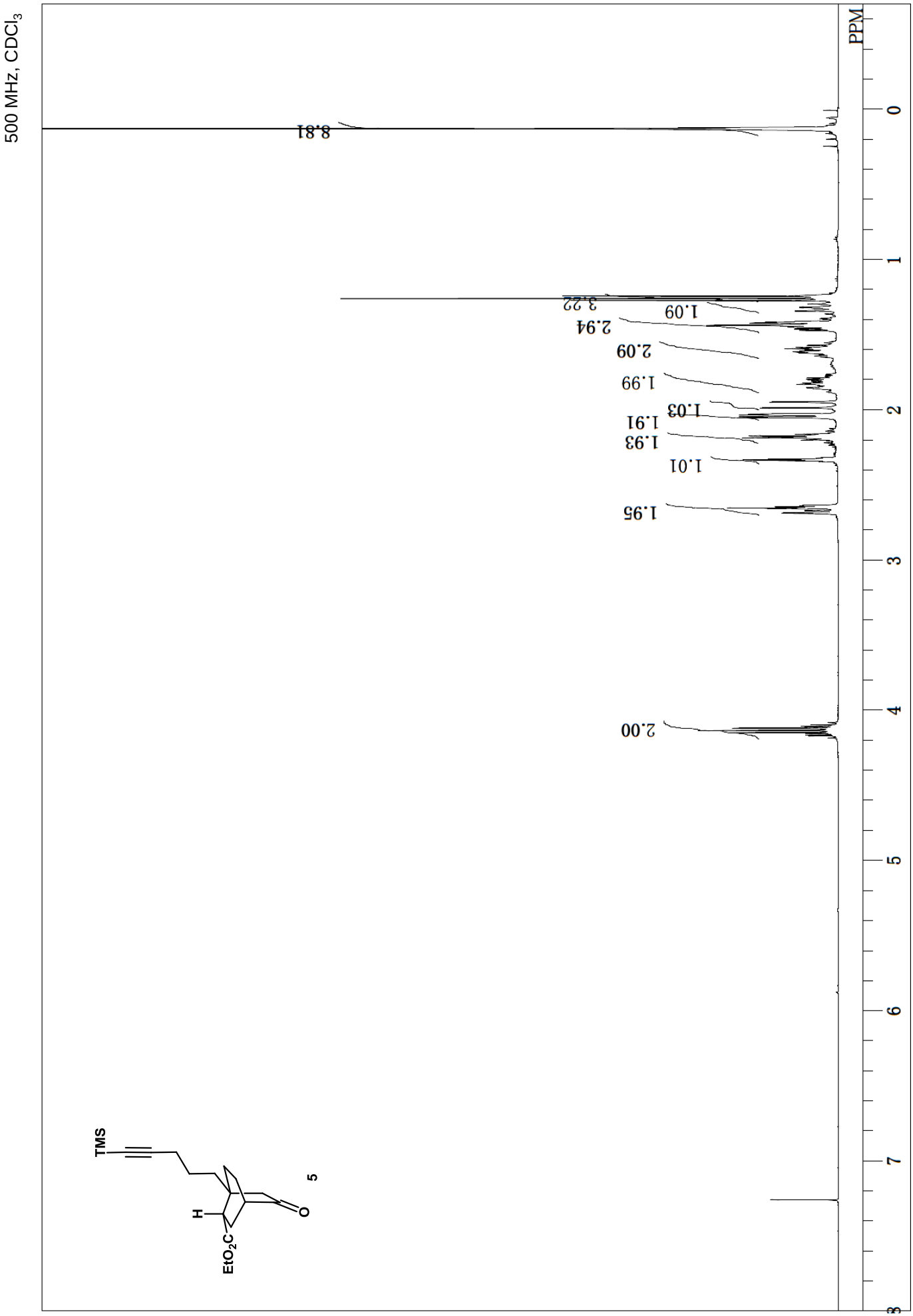


6

125 MHz, $CDCl_3$

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2.09
1.99
1.03
1.91
1.93
1.01
1.95
2.00
PPM
0
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2
3
4
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6
7
8
TMS
H
EtO_2C
O
5

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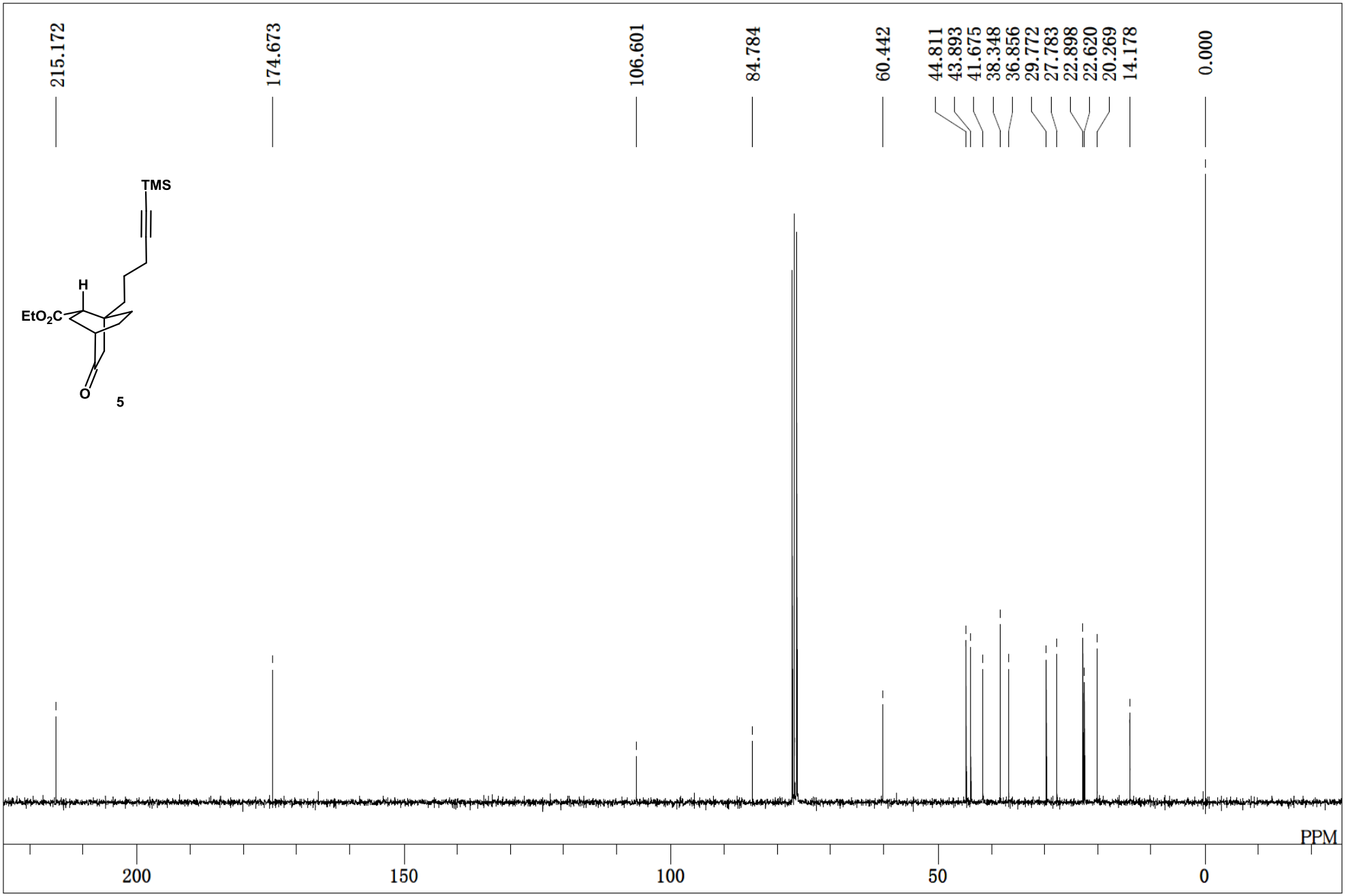

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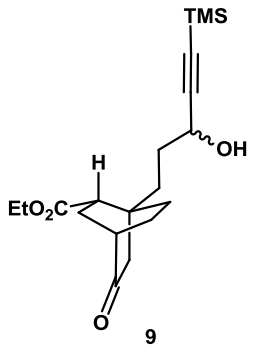
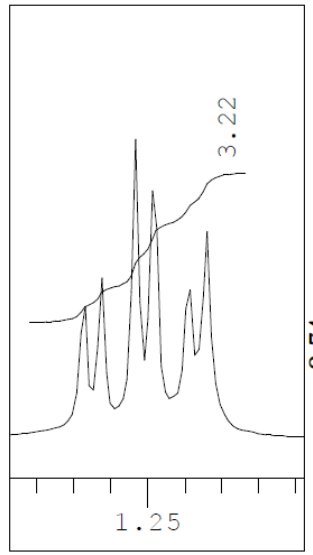


9

(dr ca. 1:1)

S22



dr ca. 1:1

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PPM

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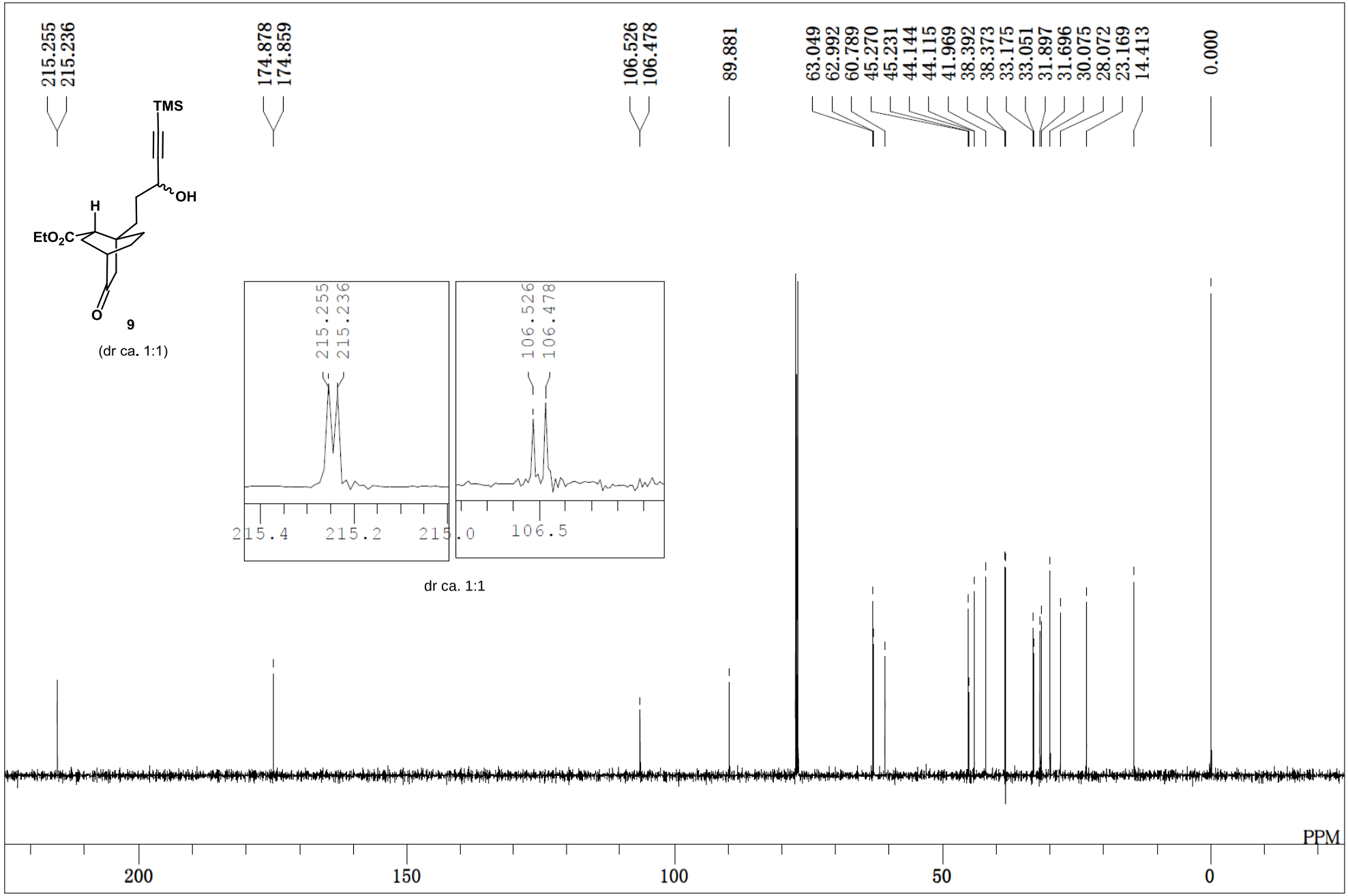
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30.075
28.072
23.169
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OH
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O
9
(dr ca. 1:1)
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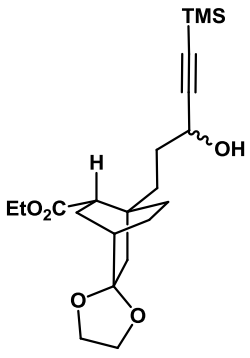
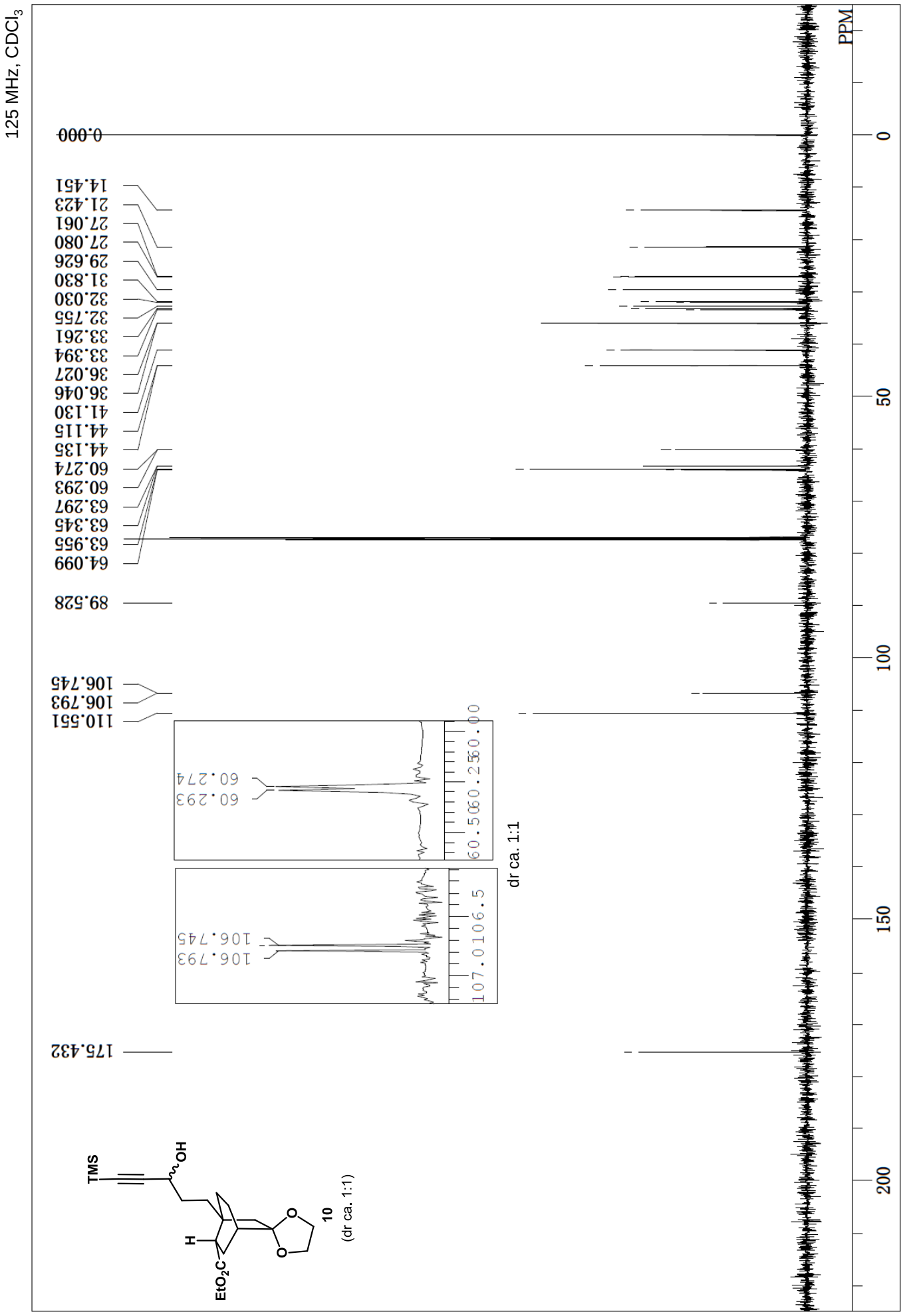
215.0
106.5
dr ca. 1:1
PPM
200
150
100
50
0

500 MHz, $CDCl_3$



10
(dr ca. 1:1)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100
150
200
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27.080
29.626
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32.755
33.261
33.394
36.027
36.046
41.130
44.115
44.135
60.274
60.293
63.297
63.345
63.955
64.099
89.528
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106.793
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175.432
60.293
60.274
60.50
60.25
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106.745
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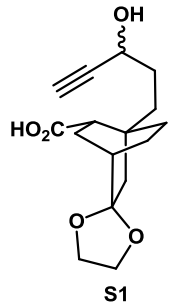
H
EtO2C
10
(dr ca. 1:1)

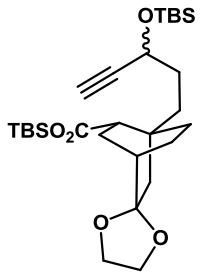
500 MHz, $CDCl_3$



S1

(crude material)

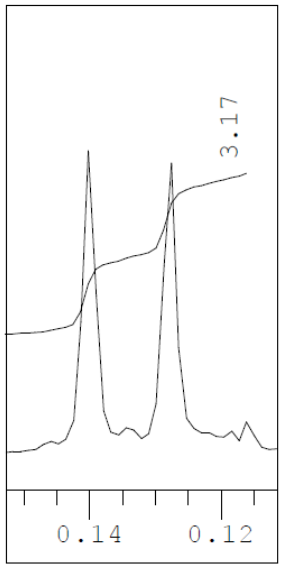
500 MHz, C_6D_6



4

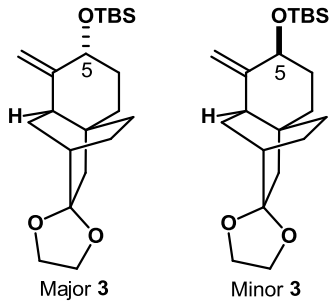
(dr ca. 1:1)

(crude material)



dr ca. 1:1

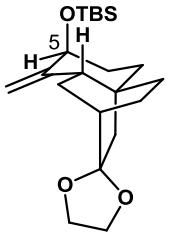
500 MHz, $CDCl_3$



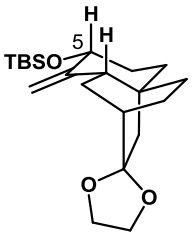
Major **3**

Minor **3**

(dr = 2:1 at C5)



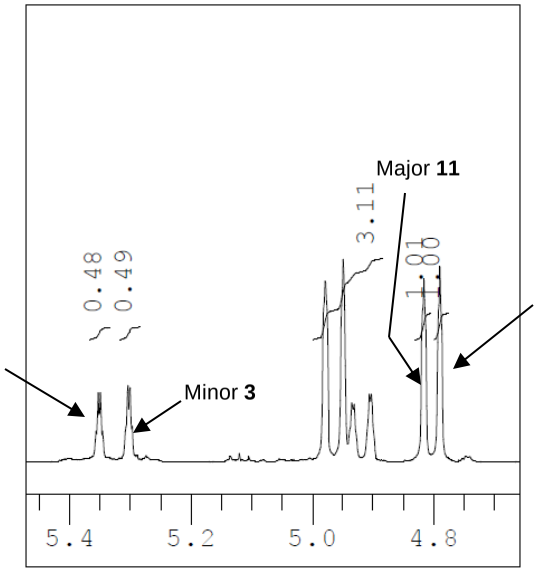
Major **11**

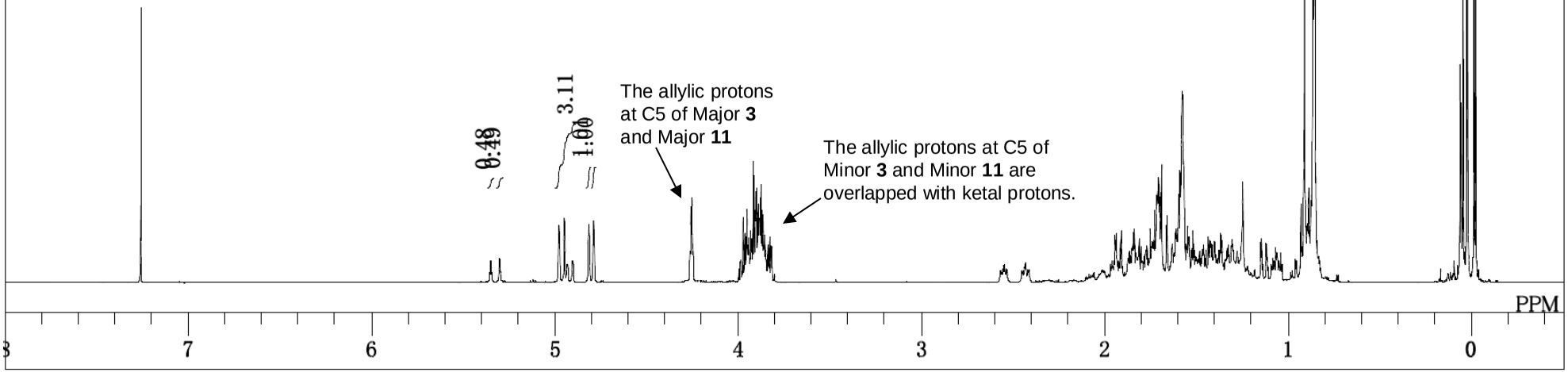


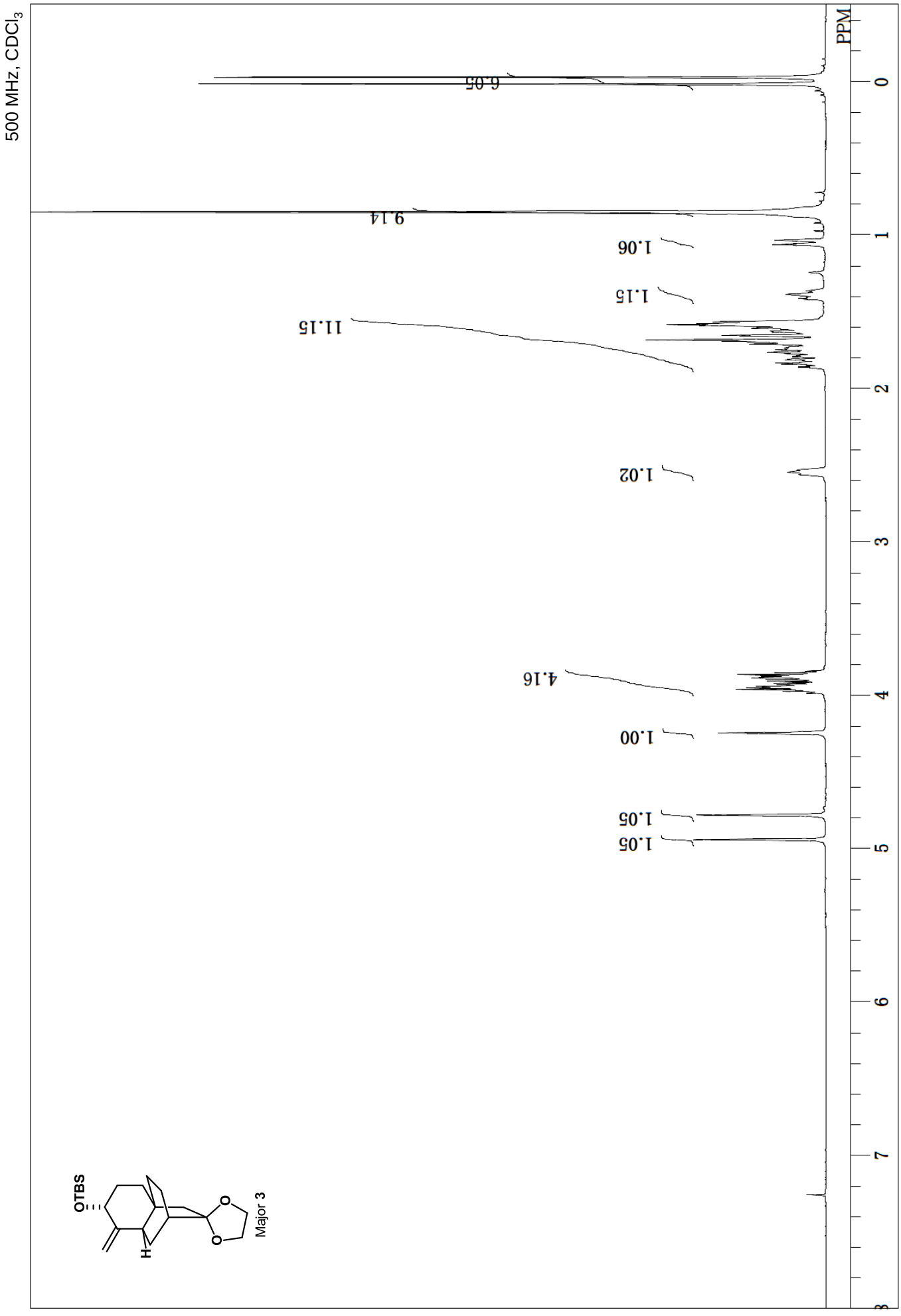
Minor **11**

(dr = 2:1 at C5)

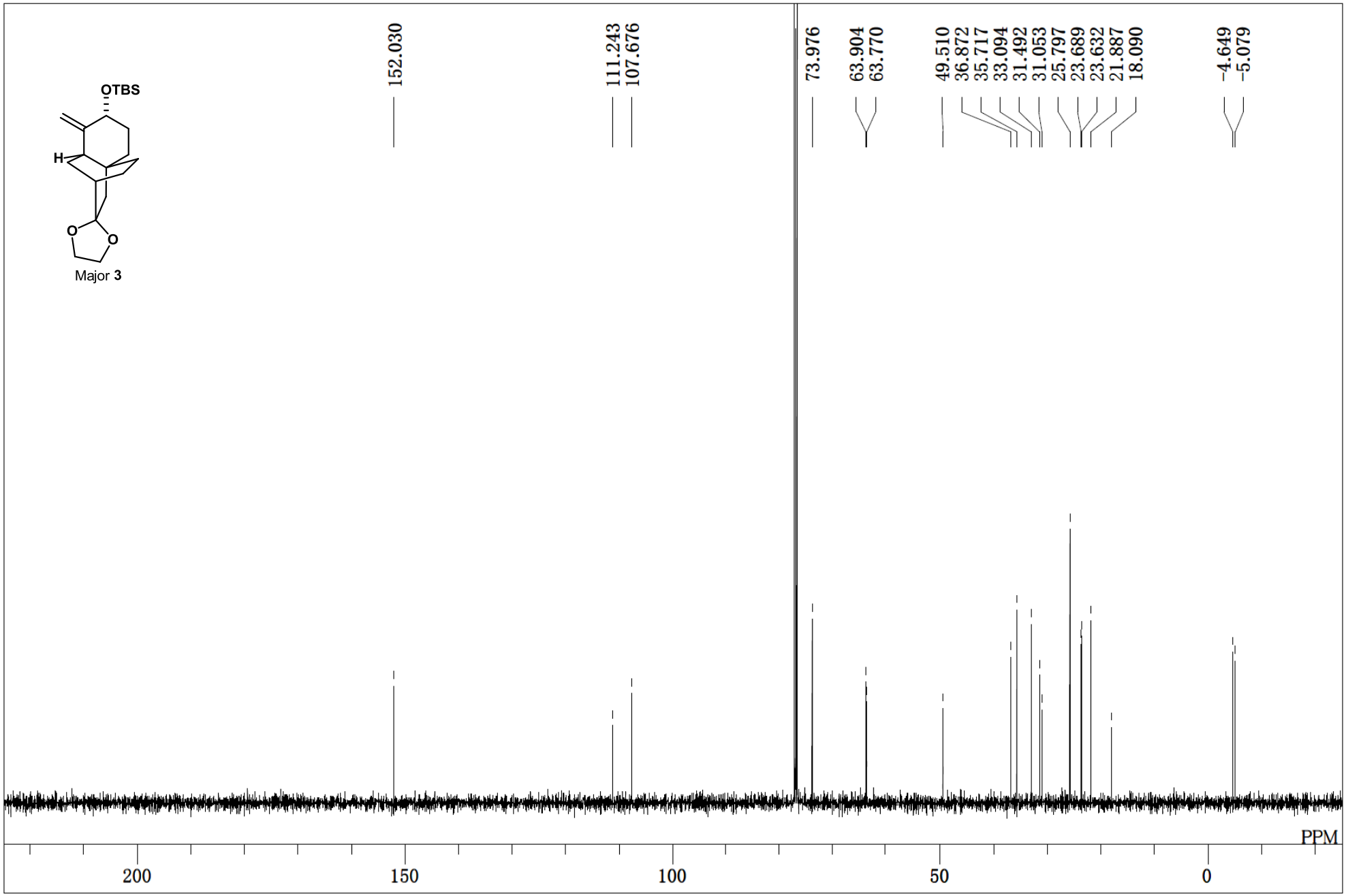
This spectrum shows the mixture of four diastereomers obtained by a short path silica gel filtration as described in page S7. The ratios of Major **3**:Minor **3**: Major **11**: Minor **11** were determined to be 2:1:2:1.



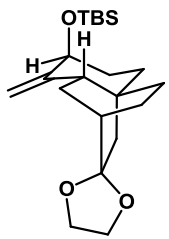



500 MHz, CDCl3
PPM
6.05
9.14
1.06
1.15
11.15
1.02
4.16
1.00
1.05
1.05
OTBS
H
Major 3

125 MHz, $CDCl_3$

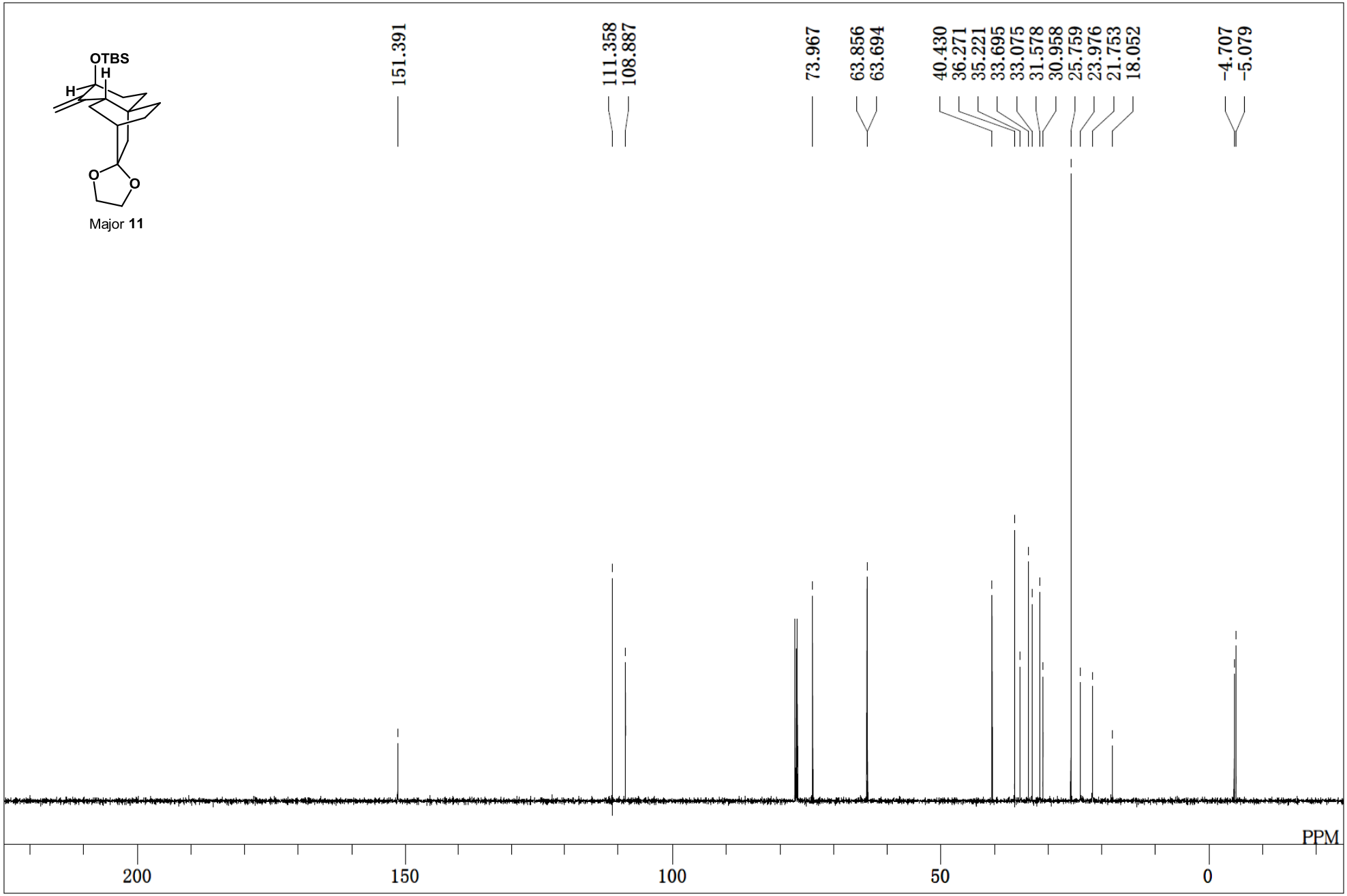


500 MHz, $CDCl_3$

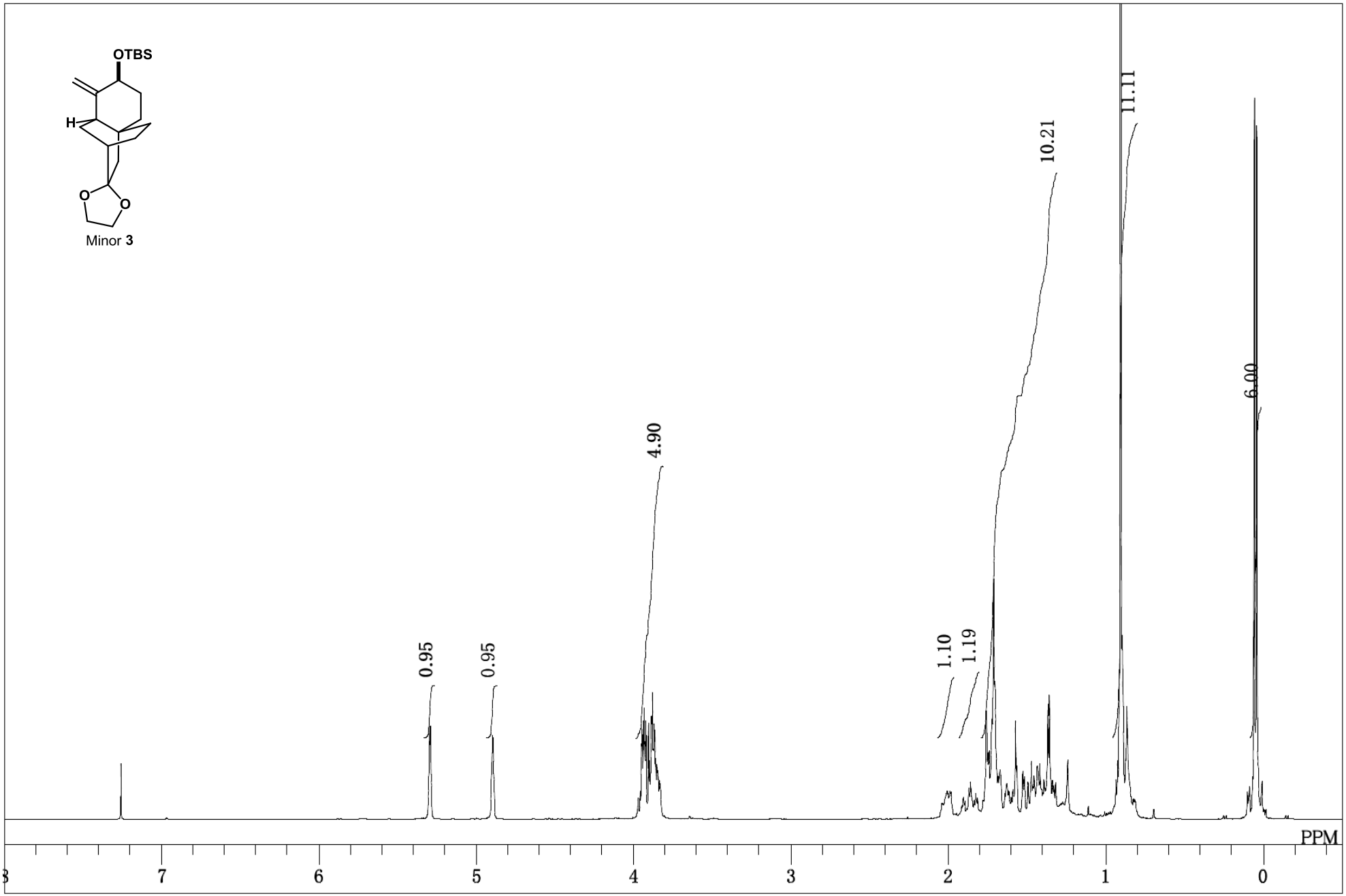


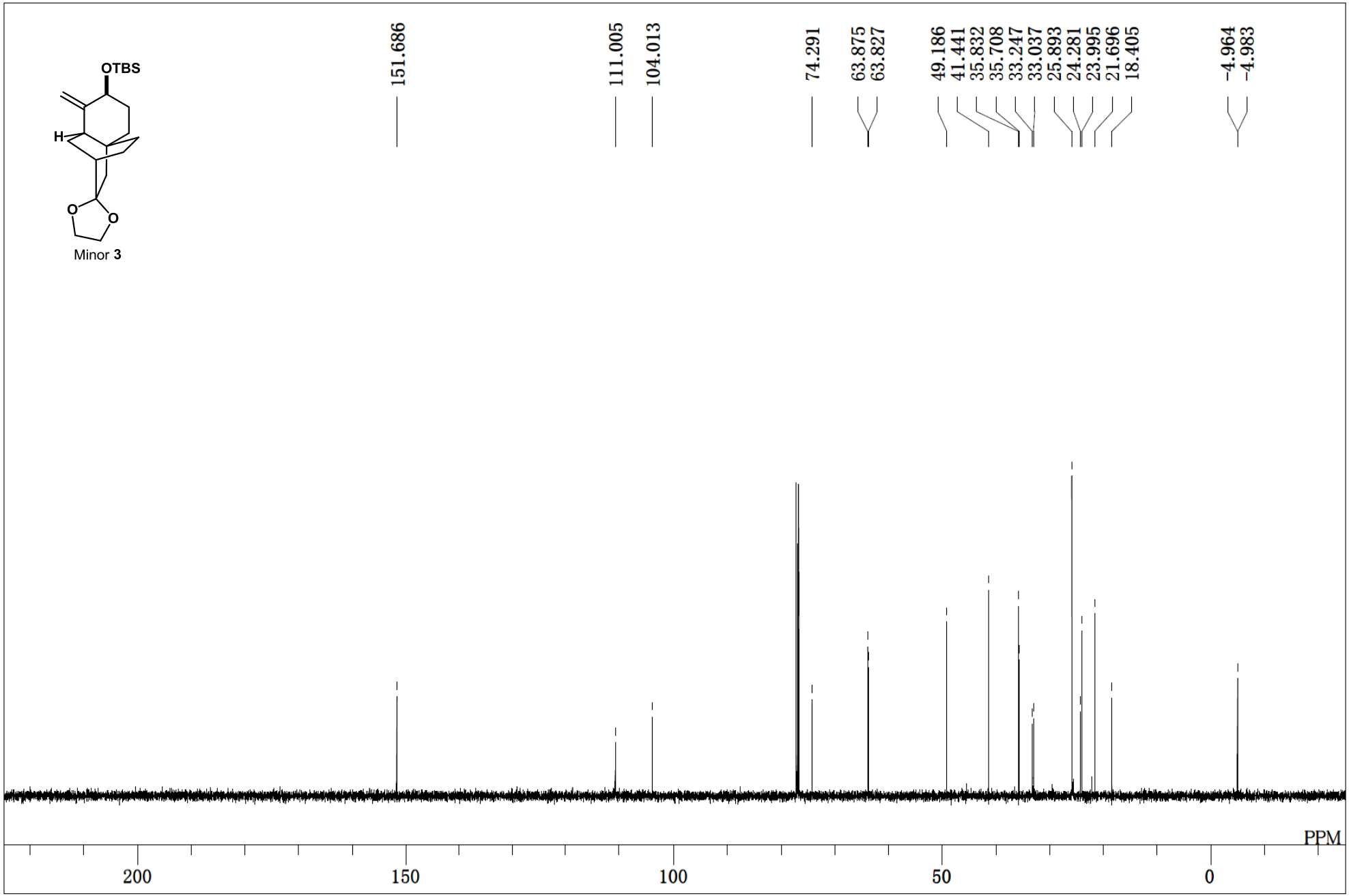
Major **11**

125 MHz, $CDCl_3$

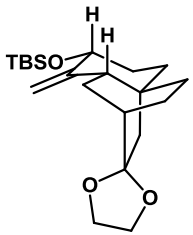


500 MHz, $CDCl_3$

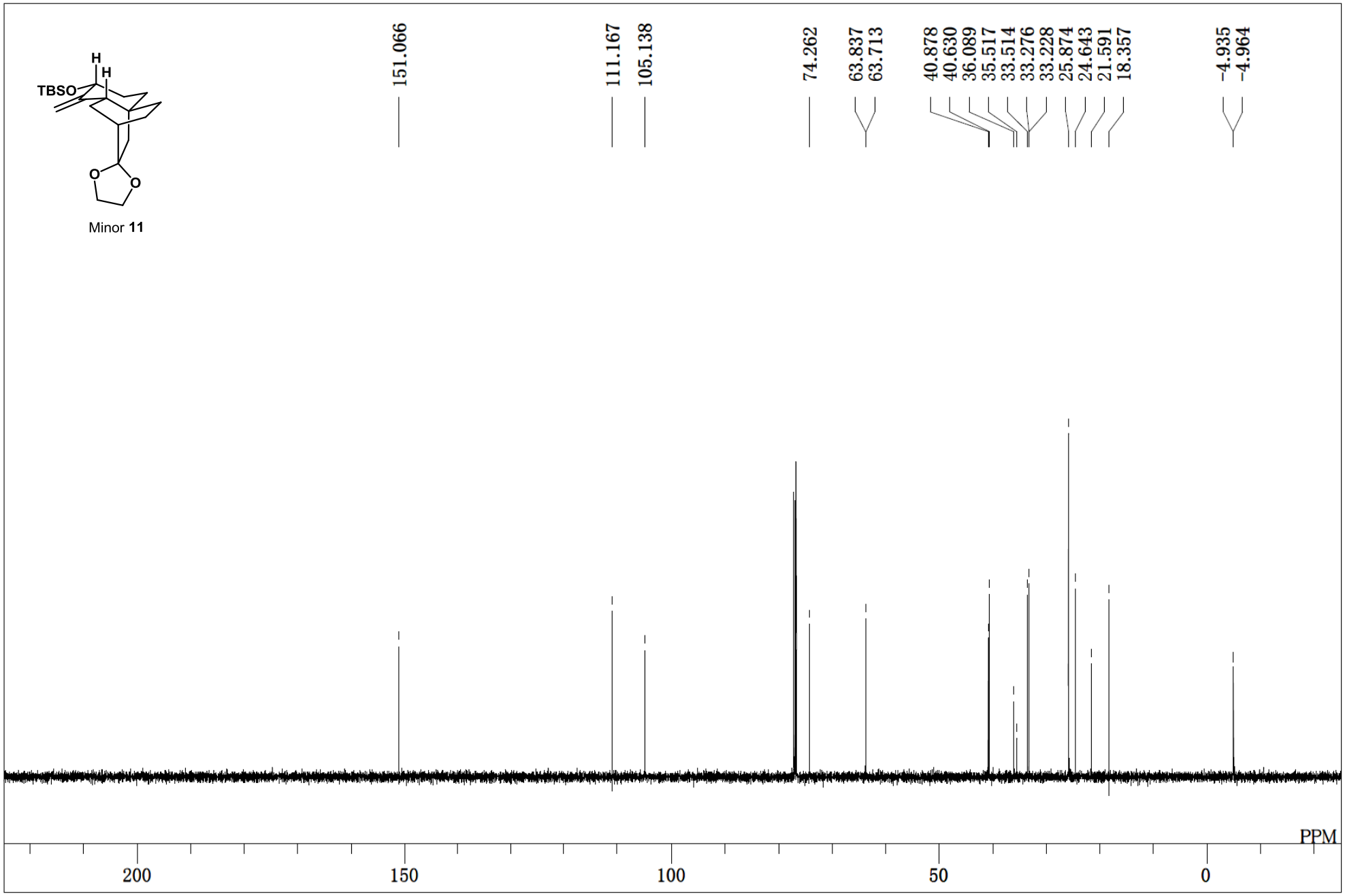



OTBS
H
O
O
Minor 3
151.686
111.005
104.013
74.291
63.875
63.827
49.186
41.441
35.832
35.708
33.247
33.037
25.893
24.281
23.995
21.696
18.405
−4.964
−4.983
PPM
200
150
100
50
0

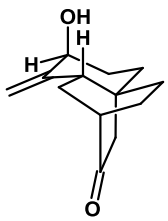
500 MHz, $CDCl_3$



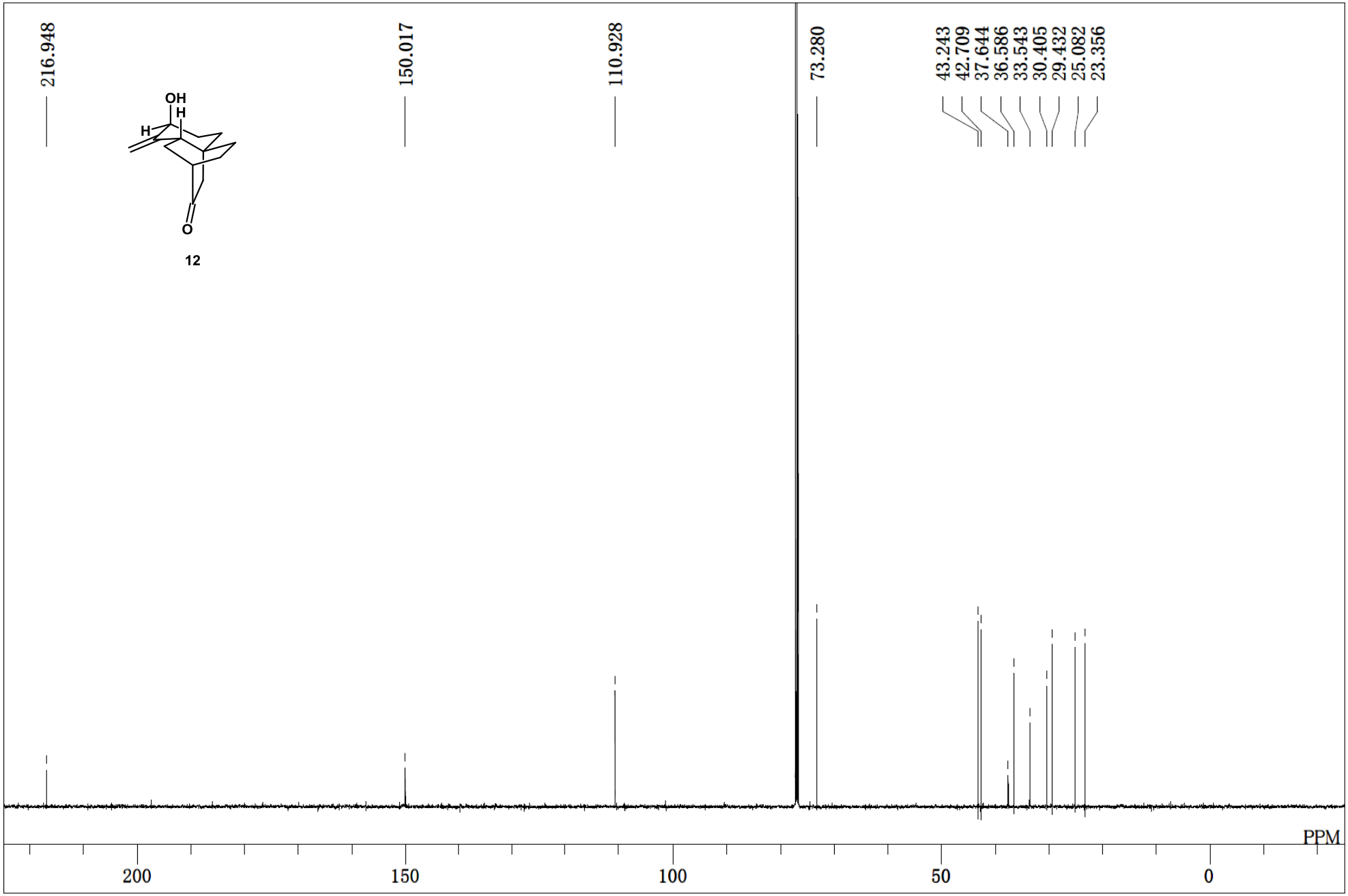
Minor **11**


H
H
TBSO
O
O
Minor 11
151.066
111.167
105.138
74.262
63.837
63.713
40.878
40.630
36.089
35.517
33.514
33.276
33.228
25.874
24.643
21.591
18.357
-4.935
-4.964
PPM
200
150
100
50
0

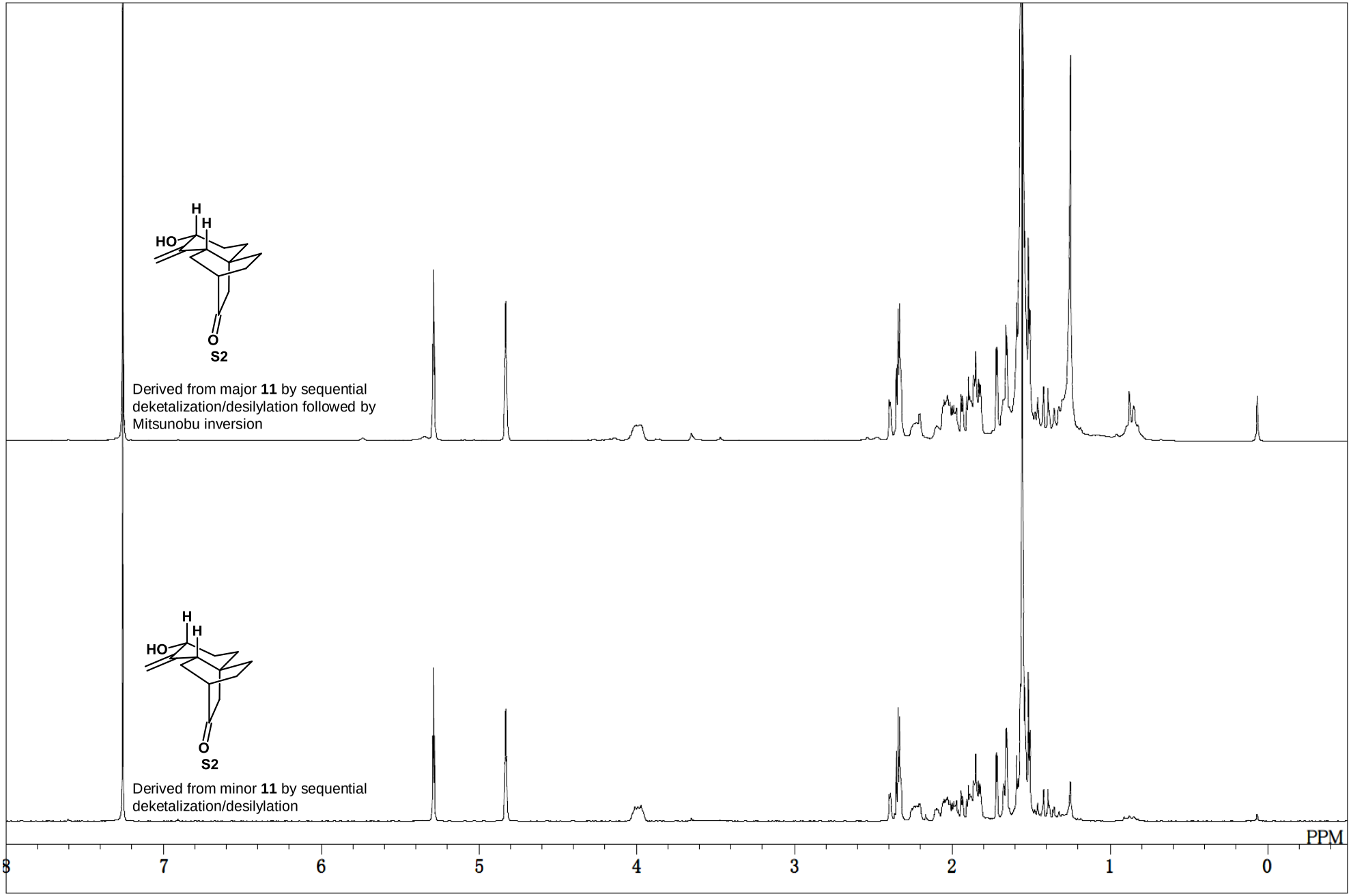
500 MHz, $CDCl_3$



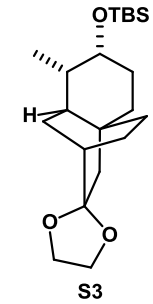
12


216.948
150.017
110.928
73.280
43.243
42.709
37.644
36.586
33.543
30.405
29.432
25.082
23.356
OH
H
H
O
12
PPM
200
150
100
50
0

300 MHz, $CDCl_3$



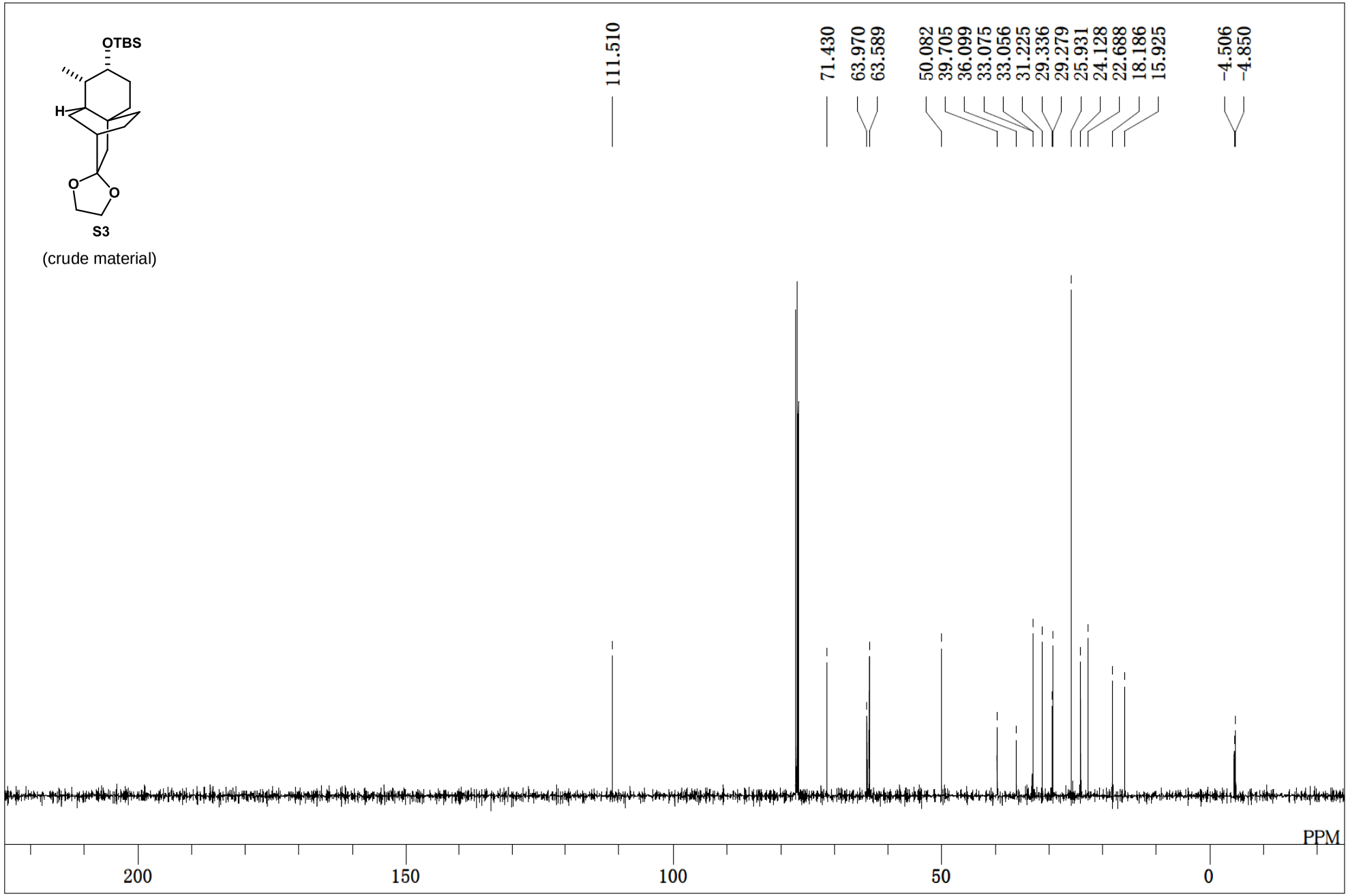
500 MHz, $CDCl_3$



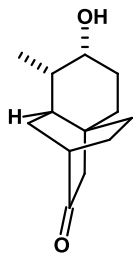
S3

(crude material)

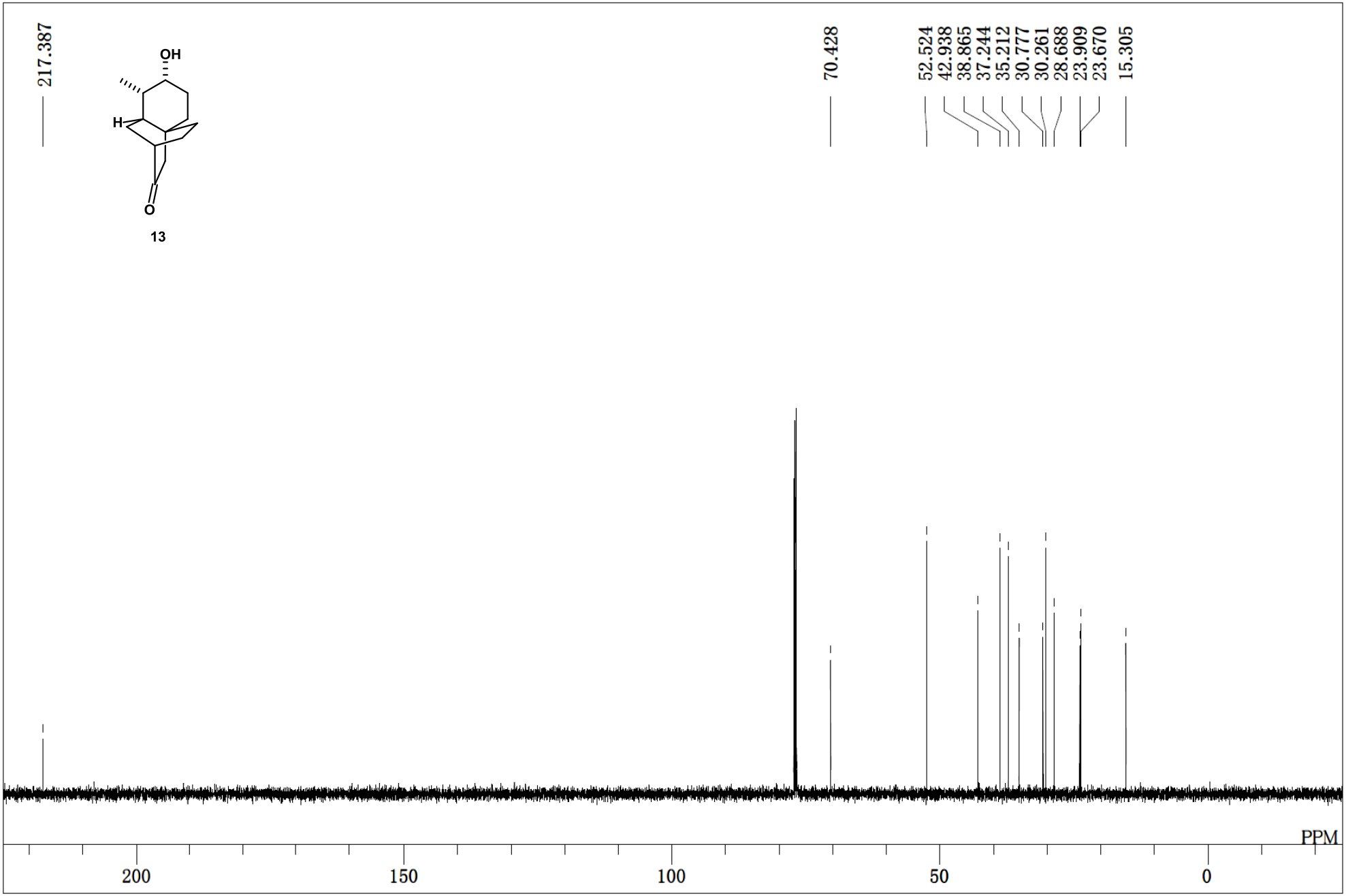
125 MHz, $CDCl_3$



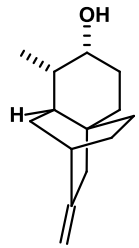
500 MHz, $CDCl_3$



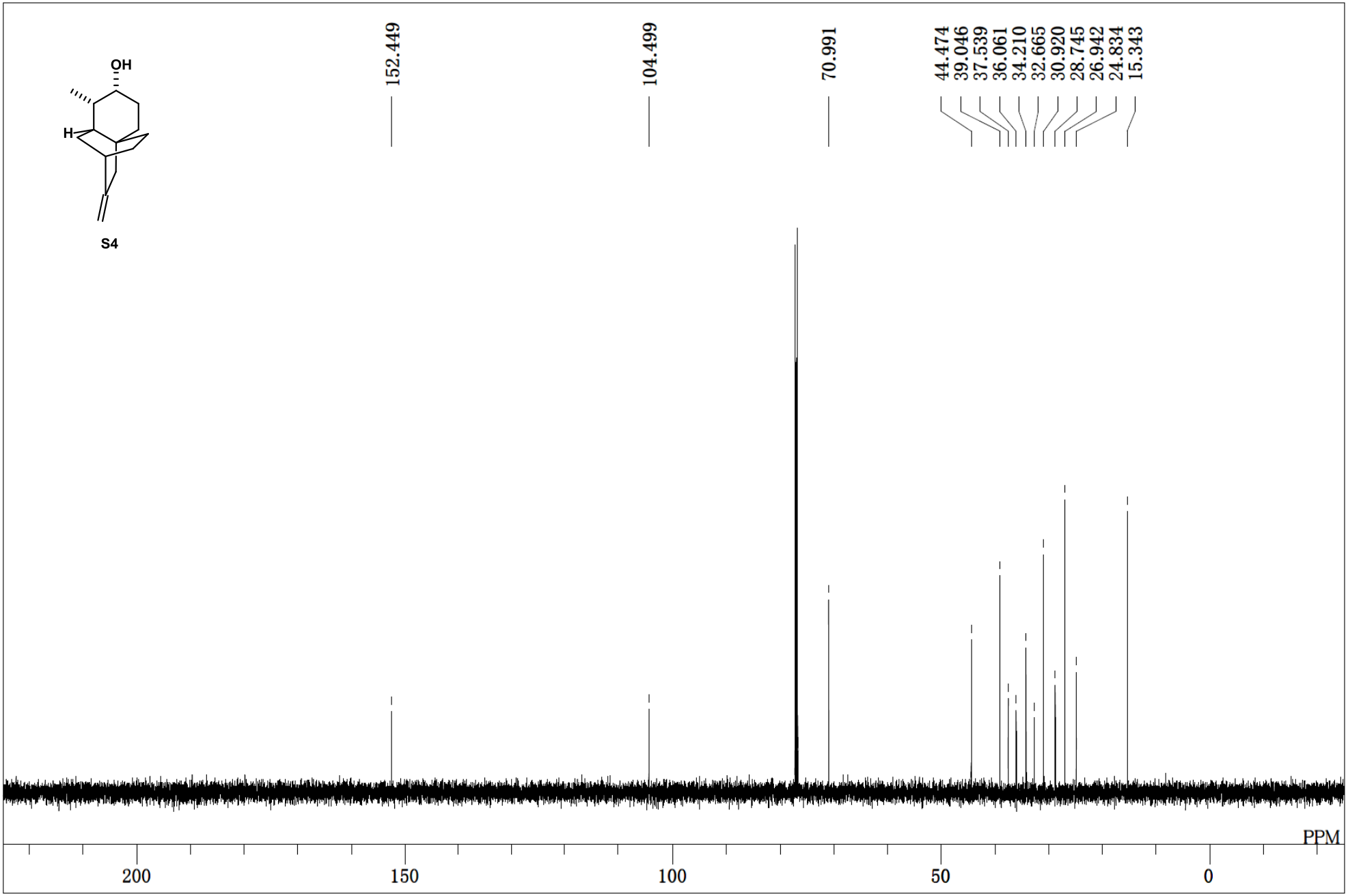
13


217.387
70.428
52.524
42.938
38.865
37.244
35.212
30.777
30.261
28.688
23.909
23.670
15.305
OH
H
O
13
PPM
200
150
100
50
0

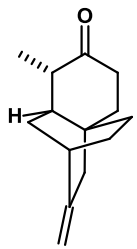
500 MHz, $CDCl_3$



S4

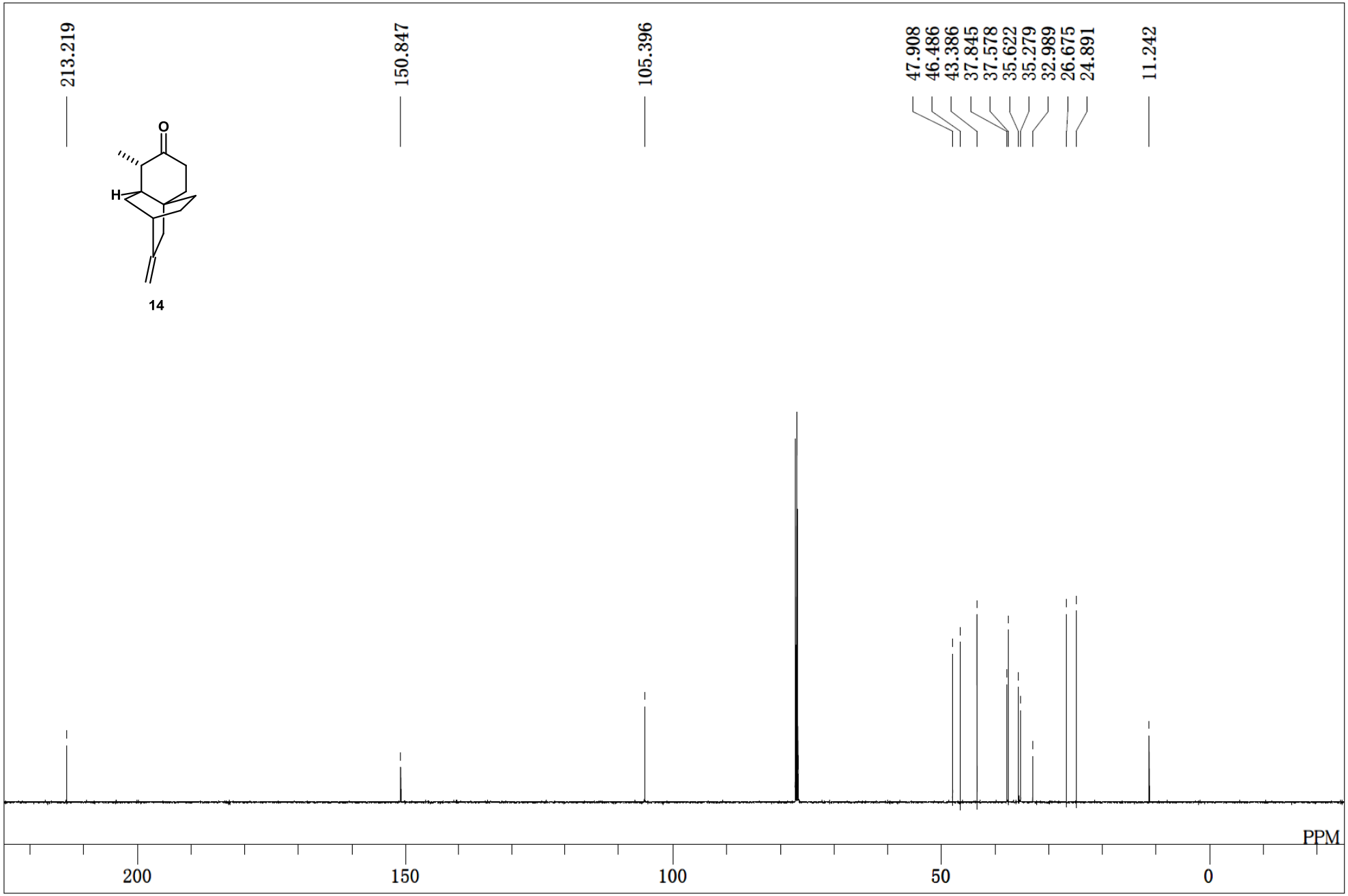

OH
H
S4
152.449
104.499
70.991
44.474
39.046
37.539
36.061
34.210
32.665
30.920
28.745
26.942
24.834
15.343
PPM
200
150
100
50
0

500 MHz, $CDCl_3$

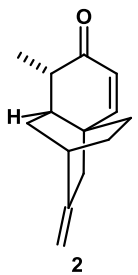


14

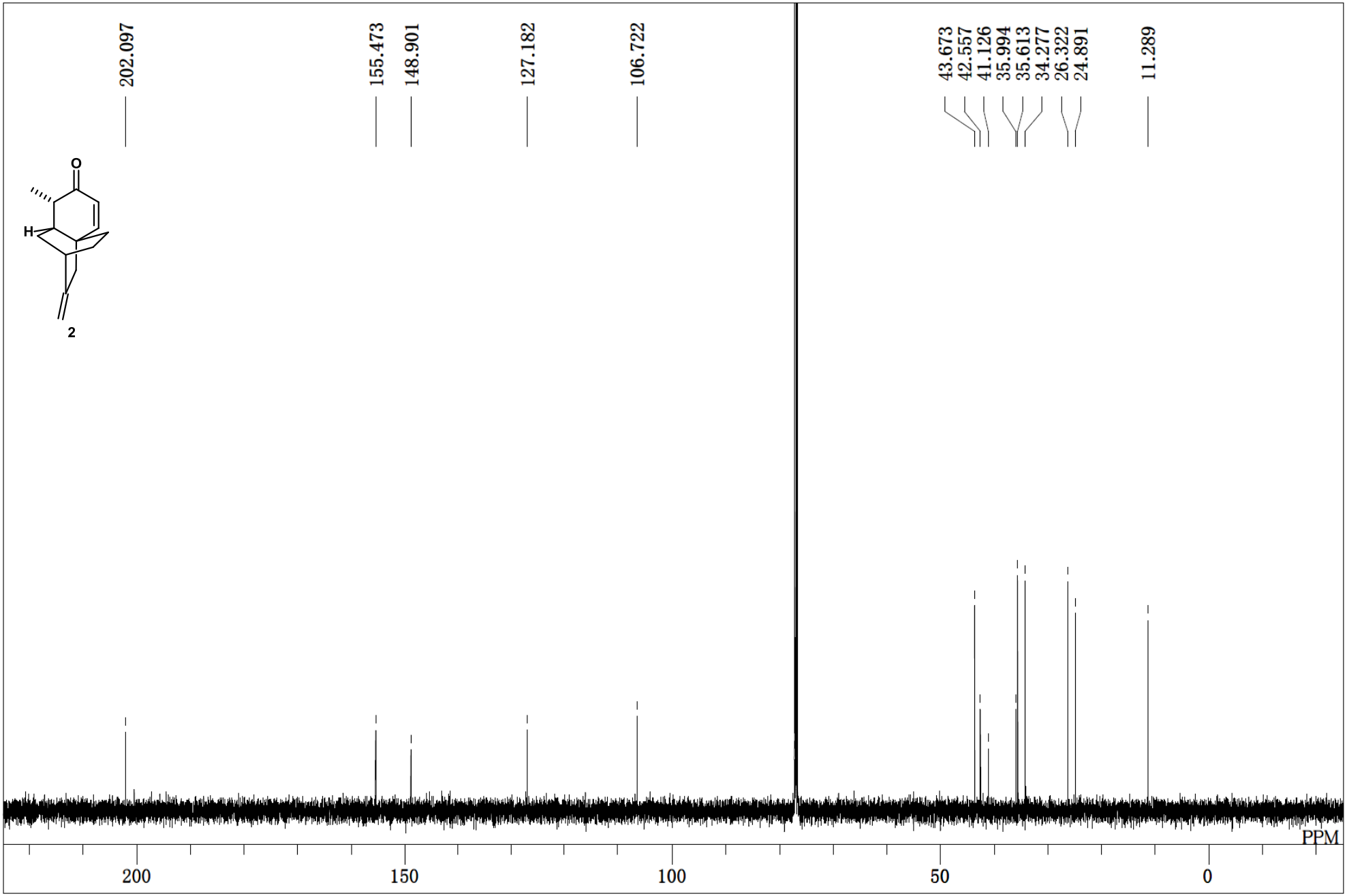
125 MHz, $CDCl_3$



500 MHz, $CDCl_3$



2


202.097
155.473
148.901
127.182
106.722
43.673
42.557
41.126
35.994
35.613
34.277
26.322
24.891
11.289
O
H
2
PPM
200
150
100
50
0