

# Supporting Information

## Total Synthesis of Hirsutellone B via Ullmann-Type Direct 13-membered Macrocyclization

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## General Procedures

All non-aqueous reactions were carried out under an atmosphere of argon in flame- or oven-dried glassware with magnetic stirring, unless otherwise indicated. Dry diethyl ether ( $\text{Et}_2\text{O}$ ) and tetrahydrofuran (THF) were purchased from Wako Pure Chemical Industries, Ltd. in anhydrous grade. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) was distilled from phosphorous pentoxide and then from calcium hydride before use. *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexane, toluene, and xylenes were distilled from calcium hydride and stored over MS4A. Methanol (MeOH) was distilled from  $\text{Mg}(\text{OMe})_2$  and stored over MS3A. Benzene was distilled from sodium/benzophenone and stored over MS4A. Triethylamine ( $\text{Et}_3\text{N}$ ), hexamethylphosphoric triamide (HMPA), diisopropylamine (*i*- $\text{Pr}_2\text{NH}$ ) and diisopropylethylamine (DIPEA) were distilled from calcium hydride and stored over potassium hydroxide. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

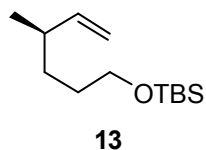
Reactions were monitored by thin-layer chromatography (TLC) analysis on 0.25 mm silica gel plates (E. Merck, Silica Gel 60 F<sub>254</sub>). TLC plates were visualized by exposure to ultraviolet (UV) light (254 nm), and/or by staining with an acidic ethanol solution of *p*-anisaldehyde or basic aqueous potassium permanganate ( $\text{KMnO}_4$ ) and then heating. Silica gel 60N (KANTO CHEMICAL CO., INC., spherical, neutral, 63–210  $\mu\text{m}$ ) was used for column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on Wakogel<sup>®</sup> B–5F (Wako Pure Chemical Industries, Ltd.).

NMR spectra were recorded on a JEOL JNM–LD400 spectrometer operating at 400 MHz for  $^1\text{H}$  NMR and 100 MHz for  $^{13}\text{C}$  NMR. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to residual  $\text{CHCl}_3$  ( $\delta = 7.26$  ppm for  $^1\text{H}$  NMR and  $\delta = 77.0$  ppm for  $^{13}\text{C}$  NMR) as an internal reference. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J*) are reported in Herz (Hz).

Melting points (mp) are uncorrected and were recorded on a Yanaco MP-J3 micro melting point apparatus. Optical rotations were measured using a JASCO P-1030 digital polarimeter using 50 mm cells and the sodium D line (589 nm) at room temperature in the solvent and concentration indicated. Infrared (IR) spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer using an attenuated total reflectance (ATR) attachment. Absorbance frequencies are reported in reciprocal centimeters ( $\text{cm}^{-1}$ ).

Electrospray ionization mass spectra (ESI-MS) were recorded on a SHIMADZU LCMS-2010EV system. High-resolution mass spectra (HRMS) were recorded on a Varian 910-MS Fourier transform mass spectrometer using electrospray ionization (ESI) or a JEOL JMS-SX102A mass spectrometer using fast atom bombardment (FAB).

**(*R*)-*tert*-butyldimethyl((4-methylhex-5-en-1-yl)oxy)silane (13)**



(*R*)-(-)-Citronellene **12** (23.0 g, 166 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (332 mL) and cooled to -78 °C. Ozone was bubbled through the solution and the reaction progress was closely monitored by TLC. Upon completion (disappearance of starting material, by TLC), the ozone flow was discontinued and the reaction mixture was purged with argon for 10 min. A solution of sodium borohydride (13.8 g, 365 mmol, 2.2 equiv) in MeOH (33 mL) was added dropwise to the reaction mixture and the resulting solution was allowed to warm to room temperature over 1 h with stirring. The reaction mixture was quenched by 1N aqueous HCl (300 mL) at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was used in the next step without further purification.

To a stirred solution of crude alcohol and imidazole (12.4 g, 183 mmol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (166 mL, 1.0 M) at 0 °C was added *tert*-butyldimethylsilyl chloride (27.5 g, 183 mmol, 1.1 equiv) portionwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched by saturate aqueous NaHCO<sub>3</sub> at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 1:0 → 10:1) to give the desired silyl ether **3** (29.3 g, 128 mmol, 77% yield for 2 steps) as a colorless oil.

$[\alpha]_{\text{D}}^{22} = -5.7$  ( $c = 1.21$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\text{max}} = 3078, 2955, 2929, 2857, 1641, 1472, 1387, 1254, 1097, 994, 937, 910, 833, 772, 660, 394 \text{ cm}^{-1}$ ;

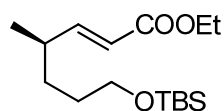
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 5.69$  (1H, ddd,  $J = 17.6, 10.3, 7.4$  Hz), 4.98 – 4.89 (2H, m), 3.59 (2H, t, 6.6 Hz), 2.15–2.08 (1H, m), 1.55–1.47 (2H, m), 1.34–1.28 (2H, m), 0.99 (3H, d,  $J = 6.8$  Hz), 0.89

(9H, s), 0.04 (6H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 144.7, 112.5, 63.4, 37.5, 32.7, 30.5, 26.0, 20.2, 18.4,  $-5.3$  ppm;

HRMS (ESI) calcd for  $\text{C}_{13}\text{H}_{29}\text{OSi}$   $[\text{M}+\text{H}]^+$  229.1982, found 229.1983.

**(*R,E*)-ethyl 7-((*tert*-butyldimethylsilyl)oxy)-4-methylhept-2-enoate (**14**)**



**14**

Silyl ether **13** (21.4 g, 93.7 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (160 mL) and MeOH (160 mL), and then cooled to  $-78$  °C. Ozone was bubbled through the solution and the reaction progress was closely monitored by TLC. Upon completion (disappearance of starting material, by TLC), the ozone flow was discontinued and the reaction mixture was purged with argon for 15 min. Triphenylphosphine (49.0 g, 187 mmol, 2.0 equiv) was added to the reaction mixture and the resulting suspension was allowed to warm to room temperature over 1 h with stirring. The reaction mixture was quenched by water (300 mL) at 0 °C. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was used in the next step without further purification.

Crude aldehyde and  $\text{Ph}_3\text{P}=\text{COOEt}$  (42.5 g, 122 mmol, 1.3 equiv) were dissolved in toluene (290 mL, 0.3 M). The reaction mixture was stirred and refluxed for 3 hr, and then cooled to room temperature. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 100:1) to give the desired  $\alpha,\beta$ -unsaturated ester **14** (26.3 g, 87.5 mmol, 93% yield for 2 steps) as a colorless oil.

$[\alpha]_{\text{D}}^{22} = -19.2$  ( $c = 1.40$ ,  $\text{CHCl}_3$ );

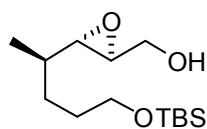
IR (ATR)  $\nu_{\text{max}}$  = 2955, 2930, 2857, 1720, 1651, 1463, 1367, 1256, 1204, 1176, 1095, 1038, 832, 773  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.84 (1H, dd,  $J$  = 15.6, 7.8 Hz), 5.76 (1H, dd,  $J$  = 15.6, 1.0 Hz), 4.16 (2H, q,  $J$  = 7.1 Hz), 3.57 (2H, t,  $J$  = 6.1 Hz), 2.34–2.24 (1H, m), 1.51–1.47 (2H, m), 1.45–1.36 (2H, m), 1.27 (3H, t,  $J$  = 7.1 Hz), 1.04 (3H, d,  $J$  = 6.8 Hz), 0.87 (9H, s), 0.02 (6H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 166.8, 154.3, 119.7, 63.0, 60.1, 36.3, 32.1, 30.3, 25.9, 19.4, 18.3, 14.2, –5.4 ppm;

HRMS (ESI) calcd. for  $\text{C}_{16}\text{H}_{33}\text{O}_3\text{Si}$   $[\text{M}+\text{H}]^+$  301.2194, found 301.2190.

**((2*S*,3*S*)-3-((*R*)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxiran-2-yl)methanol (**15**)**



**15**

To a stirred solution of  $\alpha,\beta$ -unsaturated ester **14** (18.6 g, 61.8 mmol) in THF (206 mL) at  $-78^\circ\text{C}$  was added diisobutylaluminum hydride (125 mL, 130 mmol, 1.04 M in hexane, 2.1 equiv) dropwise. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 2 h. The reaction mixture was quenched by MeOH, then diluted with  $\text{Et}_2\text{O}$  (168 mL) and added saturated aqueous Rochelle salt (168 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The crude residue was filtered through a short pad of silica gel and used in the next step without further purification.

A mixture of activated MS4A (6.39 g, 20 wt % based on starting material) and  $\text{CH}_2\text{Cl}_2$  (372 mL) was cooled to  $-23^\circ\text{C}$ . L-(-)-Diisopropyl tartrate (6.21 mL, 29.7 mmol, 0.24 equiv), titanium(IV) tetraisopropoxide (7.29 mL, 24.7 mmol, 0.2 equiv), and *tert*-butylhydroperoxide (50.0 mL, 272 mmol, 2.2 equiv, 5.4 M in  $\text{CH}_2\text{Cl}_2$ ) were added sequentially. After 10 min of stirring, the crude allyl alcohol was added dropwise over 15 min. After 35 min of stirring at  $-23^\circ\text{C}$ , the mixture was quenched sequentially with  $\text{P}(\text{OMe})_3$  (17.5 mL) and 400 mL of 10% aqueous L-(+)-tartrate. After 10 min of vigorous stirring at room temperature, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined

organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 8:1 →5:1) to give the desired epoxy alcohol **15** (28.8 g, 105 mmol, 85% yield for 2 steps) as a colorless oil.

$[\alpha]_D^{23} = -15.4$  ( $c = 0.21$ , CHCl<sub>3</sub>);

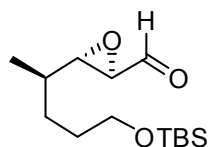
IR (ATR)  $\nu_{\max} = 3431, 2933, 2860, 1639, 1466, 1387, 1254 \text{ cm}^{-1}$ ;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 3.93\text{--}3.88$  (1H, m), 3.66–3.58 (3H, m), 2.99–2.97 (1H, m), 2.73 (1H, dd,  $J = 7.4, 2.5$  Hz), 1.72–1.66 (1H, m), 1.56–1.51 (1H, m), 1.46–1.29 (3H, m), 1.03 (3H, d,  $J = 6.1$  Hz), 0.89 (9H, s), 0.05 (6H, s) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 63.0, 61.8, 60.5, 58.5, 35.2, 30.2, 29.7, 25.8, 18.2, 17.0, -5.4$  ppm;

HRMS (FAB) calcd. for C<sub>14</sub>H<sub>31</sub>O<sub>3</sub>Si [M+H]<sup>+</sup> 275.2042, found 275.2043.

**(2R,3S)-3-((R)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxirane-2-carbaldehyde (S1)**



**S1**

To a solution of oxalyl chloride (7.63 mL, 87.4 mmol, 2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (437 mL) cooled at -78 °C was added dropwise DMSO (13.5 mL, 175 mmol, 4.0 equiv). After 20 min, a solution of epoxy alcohol **15** (12.0 g, 43.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (37.0 mL) was added dropwise. The reaction mixture was then stirred for 10 min at -78 °C and triethylamine (48.8 mL, 350 mmol, 8.0 equiv) was added dropwise. After 15 min at -78 °C, the mixture was allowed to warm to 0 °C for 40 min. The reaction mixture was quenched by water (300 mL) at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 12:1) to give the desired epoxy aldehyde **S1** (8.14 g, 29.9 mmol, 67% yield) as a colorless oil.

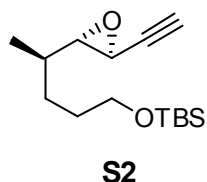
$[\alpha]_{\text{D}}^{23} = +72.4$  ( $c = 0.21$ ,  $\text{CHCl}_3$ );

IR (ATR)  $\nu_{\text{max}} = 2954, 2930, 2886, 2857, 1729, 1463, 1388, 1361, 1253, 1213, 1095, 1055, 1006, 939, 832, 773, 714, 661 \text{ cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 9.03$  (1H, d,  $J = 6.1$  Hz), 3.62-3.58 (2H, m), 3.20 (1H, dd,  $J = 6.4, 2.0$  Hz), 3.04 (1H, dd,  $J = 6.8, 2.0$  Hz), 1.64-1.42 (4H, m), 1.40-1.31 (1H, m), 1.07 (3H, d,  $J = 6.6$  Hz), 0.89 (9H, s), 0.04 (6H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 198.4, 62.9, 61.1, 58.9, 35.0, 30.1, 29.6, 25.9, 18.3, 16.9, -5.3$  ppm.

***tert*-butyl(((*R*)-4-((2*S*,3*S*)-3-ethynyloxiran-2-yl)pentyl)oxy)dimethylsilane (**S2**)**



To a stirred solution of potassium carbonate (4.95 g, 35.8 mmol, 1.5 equiv) in MeOH (60 mL) at 0 °C was added a solution of Ohira-Bestmann reagent (6.88 g, 35.8 mmol, 1.5 equiv) in MeOH (10 mL) dropwise. After 10 min, a solution of epoxy aldehyde **S2** (6.50 g, 23.9 mmol) in MeOH (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched by saturated aqueous  $\text{NH}_4\text{Cl}$  at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 30:1) to give the desired acetylene **S2** (5.40 g, 20.1 mmol, 84% yield) as a colorless oil.

$[\alpha]_{\text{D}}^{23} = -6.9$  ( $c = 0.22$ ,  $\text{CHCl}_3$ );

IR (ATR)  $\nu_{\text{max}} = 3313, 2955, 2929, 2886, 2857, 1471, 1463, 1388, 1361, 1253, 1093, 1006, 980, 938, 885, 832, 773, 712, 659, 628, 565 \text{ cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 3.65$ -3.56 (2H, m), 3.14 (1H, dd,  $J = 1.9, 1.9$  Hz), 2.89 (1H, dd,  $J = 6.8, 2.2$  Hz), 2.30 (1H, d,  $J = 1.4$  Hz), 1.60-1.30 (5H, m), 1.03 (3H, d,  $J = 6.4$  Hz), 0.89 (9H, s), 0.05



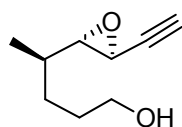
(6H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 80.6, 71.8, 64.8, 63.1, 44.7, 35.6, 30.3, 29.6, 26.0, 18.3, 16.8, -5.3

ppm;

ESI-MS(positive): 268.19  $[\text{M}+\text{Na}]^+$ .

**(R)-4-((2S,3S)-3-ethynyloxiran-2-yl)pentan-1-ol (16)**



**16**

To a stirred solution of acetylene **S2** (2.68 g, 10.0 mmol) in THF (33 mL) at 0 °C was added tetrabutylammonium fluoride (15.0 mL, 15.0 mmol, 1.5 equiv, 1.0 M in THF) dropwise over 10 min. The resulting mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (15 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:3) to give the desired alcohol **16** (1.54 g, 10.0 mmol, quantitative yield) as a colorless oil.

$[\alpha]_{\text{D}}^{23} = -8.9$  ( $c = 0.20$ ,  $\text{CHCl}_3$ );

IR (ATR)  $\nu_{\text{max}}$  = 3290, 2936, 2872, 2123, 1461, 1432, 1379, 1344, 1235, 1120, 1055, 979, 880, 786, 651, 566  $\text{cm}^{-1}$ ;

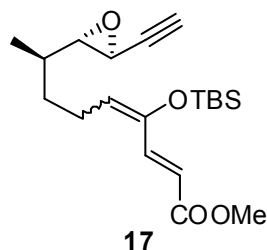
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.66 (2H, br), 3.17 (1H, dd,  $J = 2.0, 2.0$  Hz), 2.91 (1H, dd,  $J = 6.8, 2.2$  Hz), 2.31 (1H, d,  $J = 1.7$  Hz), 1.63-1.32 (6H, m), 1.04 (3H, d,  $J = 6.4$  Hz) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 80.5, 71.9, 64.6, 62.9, 44.7, 35.6, 30.2, 29.5, 16.7 ppm;

ESI-MS(positive): 176.90  $[\text{M}+\text{Na}]^+$ .

**(R,2E)-methyl 4-((tert-butyldimethylsilyl)oxy)-8-((2S,3S)-3-ethynyloxiran-2-yl)nona-2,4-dienoate**

(17)



To a solution of oxalyl chloride (0.523 mL, 6.00 mmol, 2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) cooled at -78 °C was added dropwise DMSO (0.927 mL, 12.0 mmol, 4.0 equiv). After 15 min, a solution of alcohol **16** (462 g, 3.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added dropwise. The reaction mixture was then stirred for 5 min at -78 °C and triethylamine (2.51 mL, 183.0 mmol, 6.0 equiv) was added dropwise. After 15 min at -78 °C, the mixture was allowed to warm to 0 °C for 30 min. The reaction mixture was quenched by water (30 mL) at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was used in the next step without further purification.

To a stirred solution of diisopropylethylamine (0.509 mL, 3.60 mmol, 1.2 equiv) in THF (20 mL) at 0 °C was added a solution of *n*-butyl lithium (2.17 mL, 3.45 mmol, 1.15 equiv, 1.59 M in hexane) dropwise. After 30 min, a solution of phosphonate **20** (1.22 g, 3.60 mmol, 1.2 equiv) in THF (5.0 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 30 min. The resulting mixture was re-cooled to 0 °C and added a solution of the crude aldehyde in THF (5.0 mL) dropwise and stirred for 5.5 h. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 8:1) to give the silyl enol ether **17** (689 mg, 1.89 mmol, 63% yield for 2 steps) as a pale yellow oil.

$[\alpha]_D^{23} = -33.8$  ( $c = 0.22$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\max}$  = 3266, 2955, 2931, 2858, 1716, 1630, 1606, 1471, 1462, 1434, 1390, 1362, 1298,

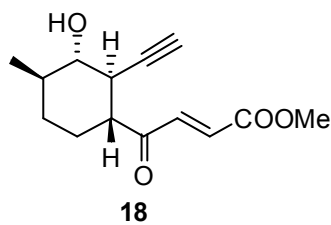
1259, 1225, 1190, 1164, 1129, 1041, 1014, 970, 940, 884, 869, 836, 825, 810, 779, 662, 550  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , *E* isomer)  $\delta$  = 7.47 (1H, d,  $J$  = 15.2 Hz), 6.16 (1H, d,  $J$  = 15.2 Hz), 5.13 (1H, t,  $J$  = 8.0 Hz), 3.76 (3H, s), 3.15 (1H, t,  $J$  = 2.1 Hz), 2.91 (1H, dd,  $J$  = 6.8, 2.2 Hz), 2.33-2.05 (3H, m), 1.78-1.30 (3H, m), 1.03 (3H, d,  $J$  = 6.4 Hz), 0.97 (9H, s), 0.14 (6H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , *E* isomer)  $\delta$  = 167.5, 146.9, 136.6, 119.6, 118.6, 80.3, 72.0, 64.4, 51.6, 44.6, 35.0, 33.8, 25.8, 24.4, 18.2, 16.4, -4.4 ppm;

ESI-MS(positive): 387.00  $[\text{M}+\text{Na}]^+$ .

**(*E*)-methyl 4-((1*R*,2*R*,3*S*,4*R*)-2-ethynyl-3-hydroxy-4-methylcyclohexyl)-4-oxobut-2-enoate (**18**)**



To a stirred solution of trimethylsilyl trifluoromethane sulfonate (0.952 mL, 10.0 mmol) in toluene (80 mL) at  $-78\text{ }^{\circ}\text{C}$  was added a solution of silyl enol ether **17** (1.83 g, 5.01 mmol) in toluene (20 mL) dropwise over 10 min. The resulting mixture was stirred for 6 h at the same temperature. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (50 mL) at  $-78\text{ }^{\circ}\text{C}$ . The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:2) to give the desired cyclization product **18** (976 mg, 3.90 mmol, 78% yield,  $>99\%\text{ee}$ ) as a pale yellow oil.

$[\alpha]_{\text{D}}^{23} = -16.0$  ( $c$  = 0.23,  $\text{CHCl}_3$ );

HPLC:  $t_{\text{R}} = 30.12$  min (CHIRAL CEL AD<sup>®</sup>, hexane:*i*-PrOH = 10:1);

IR (ATR)  $\nu_{\text{max}} = 3358, 3270, 2956, 2937, 2879, 2868, 1717, 1689, 1632, 1450, 1434, 1368, 1312, 1294, 1201, 1177, 1126, 1109, 1081, 1058, 995, 977, 690, 674\text{ cm}^{-1}$ ;

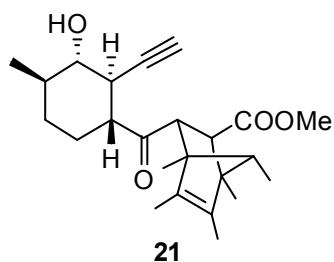
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.18 (1H, d,  $J$  = 15.9 Hz), 6.76 (1H, d,  $J$  = 15.9 Hz), 3.82 (3H, s), 3.18 (1H, t,  $J$  = 9.8 Hz), 2.89 (1H, ddd,  $J$  = 14.7, 12.0, 3.2 Hz), 2.58-2.64 (1H, m), 2.15 (1H, d,  $J$  = 2.2 Hz), 1.81-1.87 (2H, m), 1.13-1.50 (3H, m), 1.08 (3H, d,  $J$  = 6.6 Hz) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 199.3, 165.9, 138.6, 131.1, 83.3, 77.8, 72.0, 53.0, 52.4, 39.3, 37.8, 32.2, 28.1, 18.4 ppm;

ESI-MS(positive): 279.90  $[\text{M}+\text{Na}]^+$ .

**(1*S*,2*S*,3*S*,7*S*)-methyl**

**3-((1*R*,2*R*,3*S*,4*R*)-2-ethynyl-3-hydroxy-4-methylcyclohexanecarbonyl)-1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**21**)**



To a stirred solution of cyclization product **18** (511 mg, 2.04 mmol) in benzene (20 mL) at room temperature was added 1,2,3,4,5-pentamethylcyclopentadiene (556 mg, 4.08 mmol, 2.0 equiv) dropwise. The resulting mixture was stirred overnight at the same temperature. The organic solvent was removed by evaporation. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:3) to give the desired norbornene-type compound **21** (777 mg, 2.01 mmol, 99% yield) as a pale yellow oil.

IR (ATR)  $\nu_{\text{max}}$  = 3309, 2954, 2930, 1704, 1436, 1380, 1314, 1238, 1169, 1126, 1050, 912, 730, 646, 556  $\text{cm}^{-1}$ ;

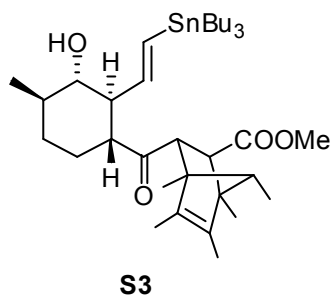
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 6.21-6.05 (1H, m), 5.69-5.49 (1H, m), 3.71-3.61 (3H, m), 3.29 (1H, dd,  $J$  = 5.7, 2.3 Hz), 2.87 (2H, m), 2.54 (1H, dd,  $J$  = 23.7, 12.5 Hz), 2.15 (4H, m), 1.75 (2H, m), 1.61-0.73 (16H, m), 0.52 (3H, m) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 212.7, 211.6, 21.7, 175.2, 175.1, 173.8, 136.0, 135.6, 135.4, 134.4, 134.0, 84.8, 84.4, 82.9, 77.9, 77.8, 77.8, 77.3, 72.7, 72.0, 71.6, 71.5, 65.2, 61.9, 59.8, 59.6, 59.0, 58.7, 58.3, 58.2, 58.1, 58.0, 57.8, 57.7, 57.6, 57.1, 56.8, 56.6, 56.6, 56.2, 56.0, 55.8, 54.2, 53.2, 52.1, 51.4, 51.3, 51.2, 40.9, 40.0, 40.0, 38.6, 38.4, 37.8, 37.8, 37.7, 32.5, 32.1, 32.0, 28.3, 27.8, 26.9, 18.4, 18.4, 15.0, 14.9, 14.3, 13.1, 12.7, 12.5, 11.8, 11.6, 11.1, 11.1, 9.5, 9.5, 9.4, 7.7, 7.6, 7.6 ppm;

HRMS (ESI) calcd. for  $\text{C}_{24}\text{H}_{35}\text{O}_4$   $[\text{M}+\text{H}]^+$  387.2530, found 387.2527.

**(1*S*,2*S*,3*S*,7*S*)-methyl**

**3-((1*R*,2*R*,3*S*,4*R*)-3-hydroxy-4-methyl-2-((*E*)-2-(tributylstannyl)vinyl)cyclohexanecarbonyl)-1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**S3**)**



To a stirred suspension of norbornene-type compound **21** (1.92 g, 4.96 mmol) and bis(triphenylphosphine)palladium(II) chloride (348 mg, 0.496 mmol, 0.1 equiv) in hexane (70 mL) and THF (10mL) at room temperature was added a solution of *n*-butyltin hydride (1.60 mL, 5.95 mmol, 1.2 equiv) in dropwise over 6 h. The resulting mixture was stirred overnight at the same temperature. The reaction mixture was filtered through a pad of Celite and rinsed with hexane, and concentrated *in vacuo*. The residue was purified by column chromatography (5%  $\text{Et}_3\text{N}$  silica gel, hexane/ $\text{EtOAc}$  = 100:1  $\rightarrow$  20:1) to give the desired vinyl stannane **S3** (2.50 g, 3.69 mmol, 74% yield) as a pale yellow oil.

IR (ATR)  $\nu_{\text{max}}$  = 3569, 2954, 2925, 2872, 2852, 1730, 1707, 1595, 1454, 1377, 1359, 1311, 1236, 1166,

1067, 1046, 998, 875, 659, 596  $\text{cm}^{-1}$ ;

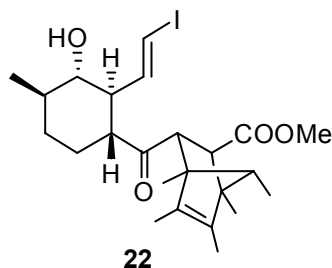
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 6.21-6.05 (1H, m), 5.69-5.49 (1H, m), 3.71-3.61 (3H, m), 3.29 (1H, dd,  $J$  = 5.7, 2.3 Hz), 2.87 (2H, m), 2.54 (1H, dd,  $J$  = 23.7, 12.5 Hz), 2.15 (4H, m), 1.75 (2H, m), 1.61-0.73 (44H, m), 0.52 (3H, m) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 211.6, 175.1, 175.1, 173.9, 163.5, 148.6, 148.3, 147.7, 135.9, 135.2, 135.1, 134.9, 134.4, 76.1, 76.0, 64.1, 62.9, 59.2, 58.7, 58.1, 57.9, 57.9, 57.8, 57.6, 56.8, 56.7, 56.6, 56.6, 55.5, 55.4, 54.9, 54.6, 54.5, 53.7, 53.1, 51.6, 51.5, 51.2, 37.7, 37.6, 32.6, 32.6, 29.1, 28.5, 28.4, 28.1, 27.6, 27.3, 27.3, 18.8, 17.0, 15.1, 14.5, 14.3, 13.6, 13.6, 12.8, 12.7, 12.3, 12.0, 11.1, 9.7, 9.5, 9.4, 9.4, 9.3, 7.7, 7.6, 7.5 ppm;

ESI-MS(positive): 701.10  $[\text{M}+\text{Na}]^+$  .

#### (1*S*,2*S*,3*S*,7*S*)-methyl

#### 3-((1*R*,2*R*,3*S*,4*R*)-3-hydroxy-2-((*E*)-2-iodovinyl)-4-methylcyclohexanecarbonyl)-1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**22**)



To a stirred solution of vinyl stannane **S3** (4.82 g, 7.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (70 mL) at 0 °C was added iodine (1.99 g, 7.82 mmol, 1.1 equiv) portionwise. The resulting mixture was stirred for 30 min at the same temperature. The reaction was quenched with saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (50 mL) at 0 °C and added a 8 M aqueous KF (200 mL) and stirred overnight at room temperature. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (5%  $\text{Et}_3\text{N}$  silica gel, hexane/EtOAc = 8:1) to give the vinyl iodide **22** (3.33 g, 6.47 mmol, 91% yield)

as a white amorphous solid.

IR (ATR)  $\nu_{\max}$  = 3497, 2955, 2929, 2872, 2254, 1702, 1607, 1435, 1379, 1314, 1236, 1193, 1170, 1123, 1096, 1044, 983, 947, 907, 850, 675, 647, 532, 492, 424, 401, 388  $\text{cm}^{-1}$ ;

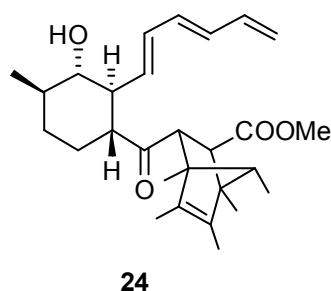
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 6.27-6.05 (2H, m), 3.68 (3H, m), 3.25 (1H, m), 2.91 (1H, m), 2.78 (1H, d,  $J$  = 4.9 Hz), 2.57-2.34 (2H, m), 2.15 (1H, d,  $J$  = 11.0 Hz), 2.04-1.89 (1H, m), 1.81-1.54 (6H, m), 1.47-1.35 (4H, m), 1.27-0.96 (10H, m), 0.54 (3H, m) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 214.8, 213.3, 211.3, 175.0, 174.8, 173.7, 146.5, 146.1, 145.8, 145.2, 136.0, 135.5, 135.2, 134.6, 134.4, 134.2, 80.1, 79.8, 78.9, 77.6, 77.5, 76.6, 76.5, 65.2, 62.6, 59.2, 59.1, 58.2, 58.1, 58.0, 57.8, 57.4, 57.1, 56.8, 56.7, 56.2, 56.0, 55.5, 55.3, 54.5, 54.1, 53.5, 52.6, 52.5, 52.0, 51.9, 51.7, 51.5, 51.3, 38.5, 38.3, 32.6, 32.3, 28.3, 27.9, 27.7, 27.1, 18.7, 15.1, 14.8, 14.4, 14.3, 13.2, 12.8, 12.7, 12.3, 11.7, 11.1, 9.6, 9.6, 9.5, 7.8, 7.7, 7.6 ppm;

ESI-MS(positive): 537.10  $[\text{M}+\text{Na}]^+$ .

**(1*S*,2*S*,3*S*,7*S*)-methyl**

**3-((1*R*,2*S*,3*S*,4*R*)-2-((1*E*,3*E*)-hexa-1,3,5-trien-1-yl)-3-hydroxy-4-methylcyclohexanecarbonyl)-1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**24**)**



To a stirred suspension of lithium chloride (2.32 g, 54.7 mmol, 6.0 equiv), copper chloride (4.51 g, 45.6 mmol, 5.0 equiv), and tetrakis(triphenyl)phosphine palladium (1.05 g, 0.912 mmol, 0.1 equiv) in THF (140 mL) at room temperature was added a solution of vinyl iodide **22** (4.69 g, 9.12 mmol) and dienyl stannane **23** (3.76 g, 10.9 mmol, 1.2 equiv) in THF (40 mL) dropwise. The resulting mixture

was stirred for 2 h at the same temperature. The reaction was quenched with 5% aqueous  $\text{NH}_4\text{OH}$  (30 mL) and brine (150 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (5%  $\text{Et}_3\text{N}$  silica gel, hexane/EtOAc = 8:1  $\rightarrow$  6:1) to give the desired triene-type compound **24** (3.31 g, 7.51 mmol, 82% yield) as a pale yellow oil.

IR (ATR)  $\nu_{\text{max}}$  = 3504, 2952, 2948, 2872, 1725, 1702, 1624, 1435, 1379, 1315, 1282, 1237, 1192, 1169, 1135, 1099, 1045, 1006, 974, 908, 850, 730, 647, 542, 518  $\text{cm}^{-1}$ ;

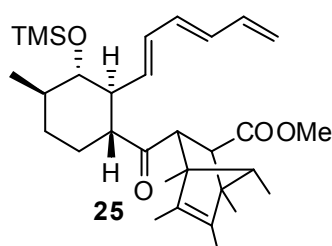
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 6.38-5.97 (3H, m), 5.43-5.08 (2H, m), 3.70-3.45 (3H, m), 3.24 (1H, m), 2.92 (1H, m), 2.73 (1H, dd,  $J$  = 16.0, 4.8 Hz), 2.48 (2H, m), 2.08-1.86 (1H, m), 1.81-1.66 (2H, m), 1.58-0.88 (21H, m), 0.52 (3H, m) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of four diastereomers)  $\delta$  = 213.6, 212.3, 211.3, 174.8, 174.6, 173.5, 136.5, 135.8, 135.4, 134.9, 134.7, 134.5, 134.4, 134.2, 134.1, 133.8, 133.7, 133.2, 132.9, 132.7, 132.5, 132.3, 132.1, 132.0, 131.9, 117.4, 117.1, 117.1, 76.8, 76.5, 65.3, 62.6, 60.0, 58.9, 58.8, 58.6, 58.0, 57.8, 57.7, 57.7, 57.6, 57.1, 56.7, 56.6, 56.5, 56.2, 56.0, 55.8, 55.4, 54.9, 53.5, 53.2, 53.1, 51.3, 51.2, 51.0, 50.9, 49.5, 49.4, 37.9, 37.7, 32.4, 32.4, 31.9, 28.2, 27.8, 26.8, 26.3, 18.4, 14.7, 14.0, 13.9, 13.1, 12.7, 12.4, 11.4, 11.2, 10.8, 9.2, 9.1, 7.4, 7.4, 7.3 ppm;

ESI-MS(positive): 463.15  $[\text{M}+\text{Na}]^+$ .

#### **(1*S*,2*S*,3*S*,7*S*)-methyl**

**3-((1*R*,2*S*,3*S*,4*R*)-2-((1*E*,3*E*)-hexa-1,3,5-trien-1-yl)-4-methyl-3-((trimethylsilyl)oxy)cyclohexanecarbonyl)-1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-ene-2-carboxylate (**25**)**





To a stirred solution of imidazole (1.54 g, 22.6 mmol, 3.0 equiv) and triene-type compound **24** (3.31 g, 7.51 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL) at 0 °C was added trimethylsilyl chloride (1.92 mL, 15.0 mmol, 2.0 equiv) dropwise. The resulting mixture was stirred for 30 min at the same temperature. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (75 mL) at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (5% Et<sub>3</sub>N silica gel, hexane/EtOAc = 20:1) to give the desired cyclization precursor **25** (2.65 g, 5.17 mmol, 69% yield) as a pale yellow amorphous solid.

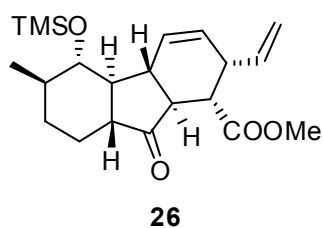
IR (ATR)  $\nu_{\text{max}}$  = 2954, 2929, 2873, 1728, 1704, 1435, 1379, 1315, 1249, 1168, 1137, 1093, 1006, 909, 868, 838, 750 cm<sup>-1</sup>;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, mixture of four diastereomers)  $\delta$  = 6.37-6.24 (1H, m), 6.17-5.95 (2H, m), 5.88-5.76 (1H, m), 5.35-5.25 (1H, m), 5.14 (1H, ddd,  $J$  = 18.8, 10.5, 8.8 Hz), 5.09-4.98 (1H, m), 3.71-3.45 (3H, m), 3.21 (1H, tt,  $J$  = 23.5, 7.5 Hz), 3.03 (1H, ddt,  $J$  = 27.2, 17.7, 7.5 Hz), 2.88 (1H, dd,  $J$  = 27.4, 22.3 Hz), 2.77-2.68 (1H, m), 2.64-2.28 (2H, m), 2.20-1.61 (3H, m), 1.57-0.85 (20H, m), 0.54-0.35 (3H, m), 0.08--0.01 (6H, m) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, mixture of four diastereomers)  $\delta$  = 212.6, 211.6, 175.3, 175.0, 173.9, 137.2, 137.2, 136.5, 136.2, 136.1, 135.7, 135.0, 134.5, 134.0, 133.9, 133.8, 133.6, 133.5, 133.4, 133.1, 133.0, 132.9, 132.3, 132.2, 132.2, 131.9, 128.7, 128.5, 128.4, 116.9, 116.6, 80.4, 80.3, 65.8, 63.2, 60.4, 59.3, 58.9, 58.8, 58.1, 58.1, 58.0, 57.4, 57.3, 57.1, 57.0, 56.9, 56.5, 55.6, 54.1, 53.6, 51.2, 51.2, 49.9, 49.8, 39.6, 39.5, 39.3, 32.9, 32.8, 32.4, 28.5, 28.1, 27.1, 26.7, 19.5, 15.1, 15.0, 14.3, 14.2, 13.0, 12.8, 11.8, 11.4, 11.1, 9.4, 9.4, 7.7, 7.5, 1.3, 1.1, 1.0 ppm.

**(1S,2S,4aS,4bS,5S,6R,8aR,9aS)-methyl**

**6-methyl-9-oxo-5-((trimethylsilyl)oxy)-2-vinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1H-fluorene-1-carboxylate (26)**



A solution of cyclization precursor **25** (2.65 g, 5.17 mmol) and BHT (114 mg, 0.517 mmol, 0.1 equiv) in xylenes (1.00 L) was refluxed for 24 h. The reaction mixture was cooled to room temperature. Then, organic solvent was removed by evaporation. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1) to give the IMDA adduct **26** (1.01 g, 2.68 mmol, 52% yield) as a pale yellow oil.

$[\alpha]_D^{23} = +64.6$  ( $c = 1.10$ ,  $\text{CHCl}_3$ );

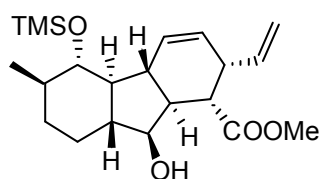
IR (ATR)  $\nu_{\text{max}} = 2951, 2875, 1737, 1455, 1435, 1350, 1250, 1193, 1161, 1117, 1073, 1013, 898, 836, 679 \text{ cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 6.36$  (1H, ddd,  $J = 10.0, 2.0, 2.0$  Hz), 5.68 (1H, ddd,  $J = 16.8, 10.2, 8.8$  Hz), 5.50 (1H, ddd,  $J = 6.4, 3.2, 3.2$  Hz), 5.06–5.01 (2H, m), 3.69 (3H, s), 3.24 (1H, dd,  $J = 9.0, 9.0$  Hz), 3.24–3.17 (1H, m), 2.94 (1H, dd,  $J = 11.4, 7.6$  Hz), 2.38 (1H, dd,  $J = 12.2, 12.2$  Hz), 2.13–2.00 (2H, m), 1.90–1.83 (1H, m), 1.72–1.45 (3H, m), 1.33–1.22 (1H, m), 1.16–1.05 (1H, m), 0.98 (3H, d,  $J = 6.6$  Hz), 0.20 (9H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 212.0, 171.8, 137.0, 129.7, 116.5, 81.3, 56.0, 52.0, 51.6, 51.3, 44.3, 42.8, 42.4, 41.1, 34.5, 25.2, 18.9, 1.0$  ppm.

**(1*S*,2*S*,4*aR*,4*bS*,5*S*,6*R*,8*aR*,9*S*,9*aS*)-methyl**

**9-hydroxy-6-methyl-5-((trimethylsilyl)oxy)-2-vinyl-2,4*a*,4*b*,5,6,7,8,8*a*,9,9*a*-decahydro-1*H*-fluorene-1-carboxylate (**28**)**



**28**

To a stirred solution of IMDA adduct **26** (422 mg, 1.12 mmol) in MeOH (22 mL) at 0 °C was added sodium borohydride (84.7 mg, 2.24 mmol, 2.0 equiv). The resulting mixture was stirred for 1.5 h at the same temperature. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1 → 5:1) to give the desired alcohol **28** (159 mg, 0.419 mmol, 38% yield) as a colorless oil.

$[\alpha]_D^{23} = +146.2$  ( $c = 0.94$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\max} = 3459, 2950, 2919, 2851, 1734, 1436, 1325, 1250, 1197, 1178, 1116, 1094, 1074, 1056, 1014, 903, 880, 836, 726, 679 \text{ cm}^{-1}$ ;

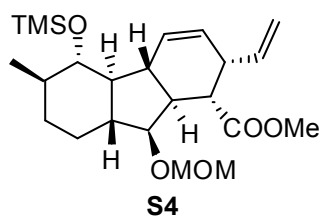
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 6.27$  (1H, d,  $J = 9.8$  Hz), 5.70 – 5.61 (1H, m), 5.40 (1H, ddd,  $J = 10.2, 3.4, 3.4$  Hz), 5.08–5.04 (2H, m), 4.22–4.17 (1H, m), 3.68 (3H, s), 3.36–3.29 (1H, m), 3.22 (1H, dd,  $J = 9.3, 9.3$  Hz), 3.03 (1H, dd,  $J = 11.7, 6.6$  Hz), 2.15–2.05 (1H, m), 1.97–1.90 (1H, m), 1.85–1.68 (3H, m), 1.50–1.00 (5H, m), 0.95 (3H, d,  $J = 8.4$  Hz), 0.17 (9H, s) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 174.6, 137.3, 131.3, 128.3, 117.4, 81.9, 74.3, 56.0, 54.5, 51.4, 45.3, 45.1, 44.6, 43.2, 41.0, 35.1, 29.1, 19.2, 1.1$  ppm.

**(1S,2S,4aR,4bS,5S,6R,8aR,9S,9aS)-methyl**

**9-(methoxymethoxy)-6-methyl-5-((trimethylsilyl)oxy)-2-vinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1**

**H-fluorene-1-carboxylate (S4)**



To a stirred solution of alcohol **28** (71.7 mg, 0.189 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9.5 mL) at 0 °C was added diisopropylethylamine (0.625 mL, 3.78 mmol, 20.0 equiv) and chloromethyl methyl ether (0.144 mL, 1.89 mmol, 10.0 equiv) successively. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to give the desired MOM ether **S4** (78.0 mg, 0.185 mmol, 98% yield) as a colorless oil.

$[\alpha]_D^{23} = +128.4$  ( $c = 1.17$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\max} = 2949, 2925, 2888, 1737, 1435, 1374, 1324, 1250, 1197, 1177, 1149, 1116, 1094, 1075, 1036, 917, 882, 836, 749, 729, 680, 607 \text{ cm}^{-1}$ ;

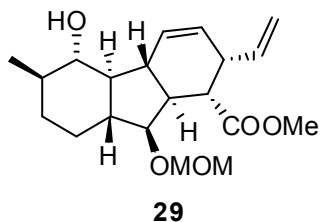
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 6.25$  (1H, d,  $J = 10.0$  Hz), 5.69 – 5.60 (1H, m), 5.41 (1H, ddd,  $J = 10.0, 3.2, 3.2$  Hz), 5.06–5.00 (2H, m), 4.52 (1H, d,  $J = 6.6$  Hz), 4.47 (1H, d,  $J = 6.6$  Hz), 3.87 (1H, dd,  $J = 7.3, 4.2$  Hz), 3.62 (3H, s), 3.28 (3H, s), 3.25–3.20 (2H, m), 3.03 (1H, dd,  $J = 12.0, 7.1$  Hz), 2.14–2.05 (1H, m), 1.98–1.77 (3H, m), 1.50–1.36 (2H, m), 1.31–1.09 (3H, m), 0.95 (3H, d,  $J = 6.6$  Hz), 0.17 (9H, s) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 173.7, 137.5, 131.1, 128.6, 116.7, 96.2, 81.9, 80.2, 55.4, 55.3, 55.2, 51.0, 45.0, 44.9, 44.2, 43.2, 41.1, 35.2, 29.4, 19.2, 1.1$  ppm.

**(1S,2S,4aS,4bS,5S,6R,8aR,9S,9aS)-methyl**

**5-hydroxy-9-(methoxymethoxy)-6-methyl-2-vinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1H-fluorene-**

### 1-carboxylate (**29**)



To a stirred solution of MOM ether **S4** (78.0 mg, 0.185 mmol) in THF (9.2 mL) at 0 °C was added a solution of tetra-*n*-butylammonium fluoride (0.370 mL, 0.370 mmol, 2.0 equiv, 1.0 M in THF) dropwise. The resulting mixture was stirred overnight at the same temperature. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1) to give the desired alcohol **29** (60.9 mg, 0.174 mmol, 94% yield) as a white solid.

mp = 75 – 76 °C

$[\alpha]_D^{23} = +170.6$  ( $c = 1.06$ , CHCl<sub>3</sub>);

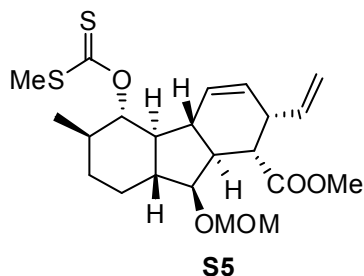
IR (ATR)  $\nu_{\max} = 3345, 2948, 2921, 2885, 1729, 1451, 1376, 1324, 1251, 1201, 1147, 1110, 1038, 1007, 916, 727, 620 \text{ cm}^{-1}$ ;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 6.32$  (1H, d,  $J = 10.0$  Hz), 5.70–5.61 (1H, m), 5.44–5.40 (1H, m), 5.06–5.02 (2H, m), 4.52 (1H, d,  $J = 6.6$  Hz), 4.47 (1H, d,  $J = 6.6$  Hz), 3.90 (1H, dd,  $J = 7.6, 4.6$  Hz), 3.62 (3H, s), 3.28 (3H, s), 3.28–3.20 (1H, m), 3.18 (1H, dd,  $J = 9.5, 9.5$  Hz), 3.02 (1H, dd,  $J = 12.0, 6.8$  Hz), 2.18–2.10 (1H, m), 1.99–1.80 (3H, m), 1.48–1.40 (1H, m), 1.37–1.22 (4H, m), 1.15–1.03 (1H, m), 1.02 (3H, d,  $J = 6.3$  Hz) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 173.7, 137.5, 130.9, 128.4, 116.6, 96.1, 80.6, 80.1, 55.2, 54.9, 54.6, 51.0, 45.0, 45.0, 44.4, 43.2, 40.9, 34.9, 28.9, 17.8$  ppm.

(1*S*,2*S*,4*aS*,4*bS*,5*S*,6*R*,8*aR*,9*S*,9*aS*)-methyl

9-(methoxymethoxy)-6-methyl-5-(((methylthio)carbonothioyl)oxy)-2-vinyl-2,4*a*,4*b*,5,6,7,8,8*a*,9,9*a*-decahydro-1*H*-fluorene-1-carboxylate (**S5**)



To a stirred solution of alcohol **29** (82.5 mg, 0.235 mmol) in THF (12 mL) at -78 °C was added CS<sub>2</sub> (0.056 mL, 0.940 mmol, 4.0 equiv) and sodium hexamethyldisilazide (0.43 mL, 0.470 mmol, 2.0 equiv) dropwise. The resulting mixture was stirred for 20 min at the same temperature, and then added methyl iodide (0.12 mL, 1.88 mmol, 8.0 equiv) dropwise. After 30 min stirring, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) at -78 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20:1 → 15:1) to give the desired xanthate **S5** (111 mg, 0.252 mmol, quantitative yield) as a colorless oil.

$[\alpha]_{\text{D}}^{23} = +76.6$  ( $c = 1.12$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\text{max}} = 2928, 1735, 1435, 1377, 1324, 1259, 1221, 1198, 1149, 1098, 1035, 918, 755, 729$  cm<sup>-1</sup>;

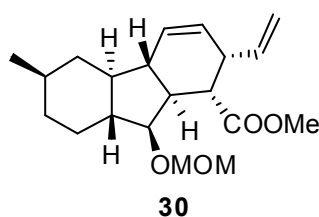
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 5.79$  (1H, d,  $J = 10.0$  Hz),  $5.73$  (1H, d,  $J = 10.0$  Hz),  $5.67$ – $5.59$  (1H, m),  $5.42$ – $5.38$  (1H, m),  $5.05$ – $5.01$  (2H, m),  $4.53$  (1H, d,  $J = 6.6$  Hz),  $4.47$  (1H, d,  $J = 6.6$  Hz),  $3.92$  (1H, dd,  $J = 7.3, 4.4$  Hz),  $3.61$  (3H, s),  $3.29$  (3H, s),  $3.25$ – $3.19$  (1H, m),  $3.00$  (1H, dd,  $J = 12.0, 6.8$  Hz),  $2.60$  (3H, s),  $2.26$ – $2.20$  (1H, m),  $2.05$ – $2.01$  (1H, m),  $1.93$ – $1.85$  (2H, m),  $1.80$ – $1.72$  (1H, m),  $1.64$ – $1.57$  (2H, m),  $1.44$ – $1.19$  (2H, m),  $0.93$  (3H, d,  $J = 6.4$  Hz) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 216.3, 173.5, 137.3, 129.5, 129.0, 116.8, 96.3, 90.5, 80.0, 55.4, 54.9,$

52.8, 51.0, 44.8, 44.7, 44.0, 43.2, 38.8, 34.8, 28.6, 19.0, 17.6 ppm.

(1*S*,2*S*,4*aS*,4*bS*,6*R*,8*aR*,9*S*,9*aS*)-methyl

9-(methoxymethoxy)-6-methyl-2-vinyl-2,4*a*,4*b*,5,6,7,8,8*a*,9,9*a*-decahydro-1*H*-fluorene-1-carboxylate (**30**)



A stirred solution of xanthate **S5** (105 mg, 0.238 mmol), tri-*n*-butylstannane (0.13 mL, 0.476 mmol, 2.0 equiv), and azobisisobutyronitrile (7.8 mg, 0.0476 mmol, 0.2 equiv) was refluxed for 30 min. The reaction mixture was cooled to room temperature. Then, organic solvent was removed by evaporation. The residue was purified by column chromatography (5% Et<sub>3</sub>N silica gel, hexane/EtOAc = 100:1 → 30:1) to give the desired deoxygenated compound **30** (74.7 mg, 0.224 mmol, 94% yield) as a colorless oil.

$[\alpha]_D^{23} = +159.2$  ( $c = 1.41$ , CHCl<sub>3</sub>);

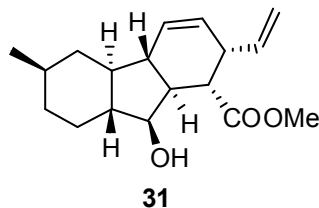
IR (ATR)  $\nu_{\max}$  = 3017, 2947, 2913, 1738, 1436, 1373, 1325, 1196, 1177, 1151, 1110, 1039, 918, 728 cm<sup>-1</sup>;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.93 (1H, d,  $J = 9.8$  Hz), 5.70–5.61 (1H, m), 5.46–5.42 (1H, m), 5.05–5.00 (2H, m), 4.54 (1H, d,  $J = 6.4$  Hz), 4.59 (1H, d,  $J = 6.4$  Hz), 3.85 (1H, dd,  $J = 7.1, 4.2$  Hz), 3.62 (3H, s), 3.29 (3H, s), 3.29–3.23 (1H, m), 3.01 (1H, dd,  $J = 11.5, 6.8$  Hz), 2.05–1.76 (5H, m), 1.43–1.22 (3H, m), 1.05–0.75 (3H, m), 0.93 (3H, d,  $J = 6.6$  Hz) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.7, 137.6, 128.8, 128.5, 116.5, 96.0, 79.9, 56.8, 55.2, 50.9, 48.7, 45.1, 44.9, 44.8, 43.7, 38.1, 36.2, 32.7, 29.5, 22.4 ppm.

(1*S*,2*S*,4*aS*,4*bS*,6*R*,8*aR*,9*S*,9*aS*)-methyl

9-hydroxy-6-methyl-2-vinyl-2,4*a*,4*b*,5,6,7,8,8*a*,9,9*a*-decahydro-1*H*-fluorene-1-carboxylate (**31**)



A stirred solution of deoxygenated compound **30** (74.7 mg, 0.223 mmol) and catalytic amounts of p-toluenesulfonic acid in MeOH (11 mL) was refluxed overnight. The resulting mixture was cooled to room temperature. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (10 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1) to give the desired hydroxy ester **31** (61.9 mg, 0.213 mmol, 95% yield) as a white solid.

mp = 79 – 81 °C;

$[\alpha]_{\text{D}}^{23} = +195.7$  ( $c = 1.01$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\text{max}} = 3533, 3011, 2947, 2921, 2844, 1719, 1438, 1257, 1203, 1144, 1112, 1064, 998, 961, 913, 780, 727, 680 \text{ cm}^{-1}$ ;

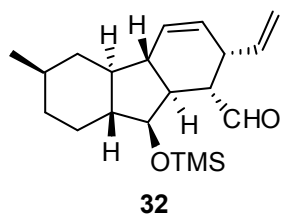
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 5.94$  (1H, d,  $J = 9.8$  Hz), 5.67 (1H, ddd,  $J = 16.6, 10.3, 8.3$  Hz), 5.43 (1H, ddd,  $J = 9.8, 4.0, 3.0$  Hz), 5.10–5.00 (2H, m), 4.17 (1H, dt,  $J = 7.0, 4.7$  Hz), 3.68 (3H, s), 3.37–3.31 (1H, m), 3.01 (1H, dd,  $J = 11.7, 6.6$  Hz), 2.60–1.88 (3H, m), 1.79–1.67 (3H, m), 1.45–1.17 (3H, m), 1.05–0.77 (3H, m), 0.93 (3H, d,  $J = 6.6$  Hz) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 175.0, 137.8, 129.2, 128.9, 117.4, 74.4, 58.0, 51.7, 48.1, 45.7, 45.5, 45.4, 44.1, 38.3, 36.3, 32.9, 29.5, 22.8$  ppm.

(1*S*,2*S*,4*aS*,4*bS*,6*R*,8*aR*,9*S*,9*aS*)-6-methyl-9-((trimethylsilyl)oxy)-2-vinyl-2,4*a*,4*b*,5,6,7,8,8*a*,9,9*a*-de



**cahydro-1H-fluorene-1-carbaldehyde (32)**



To a stirred solution of hydroxy ester **31** (136 mg, 0.467 mmol) in THF (41 mL) at 0 °C was added a LiAlH<sub>4</sub> (35.4 mg, 0.934 mmol, 2.0 equiv) in one portion. The resulting mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and quenched with 1N aqueous HCl (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was used in the next step without further purification.

To a stirred solution of crude residue in CH<sub>2</sub>Cl<sub>2</sub> (16 mL) was added TEMPO (14.6 mg, 0.0934 mmol, 0.2 equiv) and PhI(OAc)<sub>2</sub> (301 mg, 0.934 mmol, 2.0 equiv). After stirred overnight at room temperature, the resulting mixture was cooled to 0 °C and added imidazole (636 mg, 9.34 mmol, 20 equiv) and TMSCl (0.58 mL, 4.57 mmol, 10 equiv) successively. The resulting mixture was stirred at the same temperature for 30 min. The reaction was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) at 0 °C. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50:1) to give the desired siloxy aldehyde **32** (83.0 mg, 0.250 mmol, 53% yield for three steps) as a white amorphous solid.

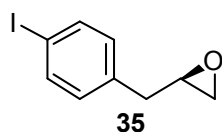
$[\alpha]_D^{23} = +185.7$  ( $c = 1.07$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\max} = 2956, 2912, 177, 1455, 1372, 1247, 1091, 1068, 1033, 988, 967, 955, 917, 893, 867, 836, 748, 714, 676, 515, 465, 412 \text{ cm}^{-1}$ ;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 9.68$  (1H, d,  $J = 2.2$  Hz), 5.95 (1H, d,  $J = 9.8$  Hz), 5.67 (1H, ddd,  $J = 16.6, 10.3, 8.3$  Hz), 5.43 (1H, ddd,  $J = 9.8, 4.0, 3.0$  Hz), 5.08-5.02 (2H, m), 4.11 (1H, dd,  $J = 6.8, 3.9$

Hz), 3.41 (1H, br), 2.99 (1H, ddd,  $J = 8.8, 6.6, 2.2$  Hz), 1.99-1.96 (3H, m), 1.82-1.76 (2H, m), 1.45-1.33 (1H, m), 1.31-1.22 (2H, m), 1.05–0.90 (5H, m), 0.83-0.75 (1H, m), 0.03 (9H, s) ppm;  
 $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 204.1, 137.5, 129.1, 128.7, 117.2, 73.8, 59.1, 51.3, 48.9, 45.1, 44.7, 42.1, 38.1, 36.3, 32.7, 29.4, 22.5, 0.3$  ppm.

**(*R*)-2-(4-iodobenzyl)oxirane (35)**



To a stirred solution of (*R*)-Glycidyl tosylate (2.28 g, 10.0 mmol) in THF (100 mL) at  $-78\text{ }^{\circ}\text{C}$  was added a solution of *tert*-butyl lithium (15.0 mL, 24.0 mmol, 2.4 equiv, 1.59M in hexane) dropwise. The resulting mixture was stirred for 20 min at the same temperature. The reaction mixture was added a solution of copper iodide (2.28 g, 12.0 mmol, 1.2 equiv) and lithium iodide (1.60 g, 12.0 mmol, 1.2 equiv) in THF (15 mL) and then warmed to  $-20\text{ }^{\circ}\text{C}$  over 4 h. Then, the resulting mixture was added a solution of 1,4-diiodobenzene (2.28 g, 10.0 mmol) in THF (10 mL) dropwise at  $-20\text{ }^{\circ}\text{C}$  and stirred for another 1 h at the same temperature. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (100 mL) at  $-20\text{ }^{\circ}\text{C}$ . The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1) to give the desired epoxide **35** (1.73 g, 7.20 mmol, 72% yield) as a pale yellow oil.

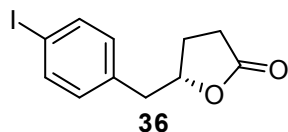
$[\alpha]_{\text{D}}^{23} = +5.0$  ( $c = 0.34$ ,  $\text{CHCl}_3$ );

IR (ATR)  $\nu_{\text{max}} = 2990, 2927, 2901, 1483, 1419, 1397, 1255, 1200, 1104, 1057, 1005, 928, 905, 860, 811, 791, 744, 621, 508, 438\text{ cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.63$  (2H, d,  $J = 8.0$  Hz),  $7.01$  (2H, d,  $J = 8.0$  Hz),  $3.14$ - $3.10$  (1H, m),  $2.82$ - $2.78$  (3H, m),  $2.52$  (1H, dd,  $J = 4.9, 2.7$  Hz) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 137.5, 136.7, 131.0, 91.9, 52.0, 46.6, 38.1$  ppm.

**(S)-5-(4-iodobenzyl)dihydrofuran-2(3H)-one (36)**



To a stirred solution of sodium (7.78 g, 33.8 mmol, 5.0 equiv) in EtOH (25 mL) was added a solution of diethylmalonate (6.1 mL, 40.6 mmol, 6.0 equiv) in THF (6.7 mL). The resulting mixture was stirred for 5 min at room temperature, then cooled to 0 °C and added a solution of epoxide **35** (1.67 g, 6.76 mmol) in THF (6.0 mL) dropwise. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with 1N aqueous HCl (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was used in the next step without further purification. To a stirred suspension of crude adduct in DMSO (14 mL) and water (1.3 mL) was added NaCl (6.00 g, 101 mmol, 15 equiv) in one portion. The reaction mixture was refluxed overnight. The reaction mixture was quenched by water (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1) to give the desired lactone **36** (1.55 g, 5.14 mmol, 76% yield for 2 steps) as a white solid.

mp = 61 – 64 °C (CHCl<sub>3</sub>/MeOH);

$[\alpha]_D^{23} = +22.0$  ( $c = 0.724$ , CHCl<sub>3</sub>);

HPLC:  $t_R = 23.97$  min (CHIRAL CEL OD<sup>®</sup>, hexane:*i*-PrOH = 5:1);

IR (ATR)  $\nu_{\max} = 3519, 2938, 1763, 1484, 1457, 1417, 1401, 1351, 1286, 1170, 1139, 1105, 1060, 1023, 1005, 917, 850, 791, 713, 650, 496$  cm<sup>-1</sup>;

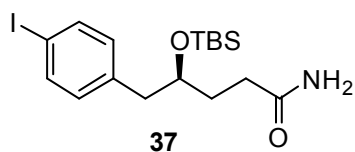
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 7.67$ - $7.63$  (2H, t,  $J = 6.3$  Hz),  $6.99$ - $6.97$  (2H, m),  $4.72$ - $4.65$  (1H, m),  $4.65$ - $4.72$  (1H, m),  $2.97$  (1H, dd,  $J = 14.1, 6.6$  Hz),  $2.91$  (1H, dd,  $J = 14.1, 5.6$  Hz),  $2.49$  (1H, ddd,  $J =$

17.8, 9.5, 8.3 Hz), 2.40 (1H, ddd,  $J = 17.8, 9.3, 4.6$  Hz), 2.32-2.24 (1H, m), 1.97-1.87 (1H, m) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 176.7, 137.5, 135.7, 131.4, 92.2, 80.2, 40.6, 28.5, 27.0$  ppm;

ESI-MS(positive): 319.00  $[\text{M}+\text{NH}_3]^+$ .

**(S)-4-((tert-butyldimethylsilyl)oxy)-5-(4-iodophenyl)pentanamide (37)**



To a stirred solution of lactone **36** (1.02 g, 3.38 mmol) in MeOH (6.8 mL) was added an aqueous ammonia solution (6.8 mL, 38% in  $\text{H}_2\text{O}$ ). The resulting mixture was stirred for 6 h at room temperature. The reaction mixture was evaporated directly and water was removed by azeotrope with benzene. The residue was used in the next step without further purification.

To a stirred suspension of crude amide and imidazole (690 mg, 10.1 mmol, 3.0 equiv) in DMF (17 mL) was added *tert*-butyldimethylsilyl chloride (764 mg, 5.07 mmol, 1.5 equiv) portionwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched by water (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 1:1) to give the desired siloxy amide **37** (1.17 g, 2.70 mmol, 80% yield for 2 steps) as a white solid.

mp = 88 – 90 °C;

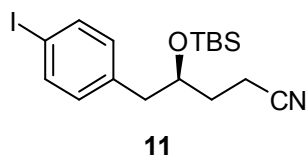
$[\alpha]_{\text{D}}^{24} = +8.4$  ( $c = 0.142$ ,  $\text{CHCl}_3$ );

IR (ATR)  $\nu_{\text{max}} = 3454, 3301, 3182, 2929, 2856, 1651, 1463, 1409, 1358, 1256, 1151, 1072, 1035, 1007, 973, 859, 836, 804, 772, 710, 665, 503$   $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.60$ - $7.52$  (2H, m),  $6.94$ - $6.91$  (2H, m),  $5.33$  (2H, br d),  $3.93$ - $3.87$  (1H, m),  $2.68$  (2H, m),  $2.37$ - $2.21$  (2H, m),  $1.84$ - $1.65$  (2H, m),  $0.87$  (9H, s),  $0.00$  (3H, s),  $-0.15$  (3H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 175.4, 138.2, 137.2, 131.7, 91.3, 72.3, 42.3, 31.9, 31.3, 25.8, 18.0, -4.7, -4.8 ppm.

**(S)-4-((tert-butyldimethylsilyl)oxy)-5-(4-iodophenyl)pentanenitrile (11)**



To a stirred solution of siloxy amide **37** (113 mg, 0.261 mmol) in DMF (5.2 mL) at 0 °C was added cyanuric chloride (31.7 mg, 0.172 mmol) in one portion. The resulting mixture was stirred for 1 h at the same temperature. The reaction was quenched with water (5.0 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20:1) to give the desired siloxy nitrile **11** (95.0 mg, 0.229 mmol, 88% yield) as a pale yellow oil.

$[\alpha]_{\text{D}}^{22} = -3.0$  ( $c = 1.42$ ,  $\text{CHCl}_3$ );

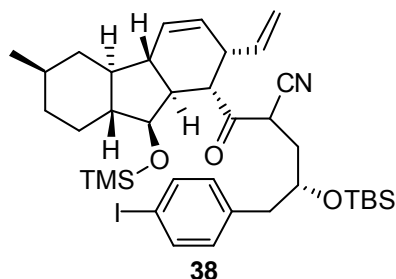
IR (ATR)  $\nu_{\text{max}}$  = 2953, 2929, 2885, 2856, 1485, 1472, 1401, 1361, 1256, 1083, 1007, 986, 835, 776, 517  $\text{cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.63-7.59 (2H, m), 6.92-6.90 (2H, m), 3.98-3.91 (1H, m), 2.78 (1H, dd,  $J = 13.5, 5.7$  Hz), 2.64 (1H, dd,  $J = 13.5, 6.6$  Hz), 2.39 (2H, t,  $J = 7.5$  Hz), 1.80-1.63 (2H, m), 0.88 (9H, s), 0.06 (3H, s), -0.06 (3H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 137.4, 131.5, 128.3, 119.7, 91.7, 71.1, 43.0, 31.9, 25.7, 17.9, 13.0, -4.7, -4.9 ppm.

**(4S)-4-((tert-butyldimethylsilyl)oxy)-5-(4-iodophenyl)-2-((1S,2S,4aS,4bS,6R,8aR,9S,9aS)-6-methy**

**1-9-((trimethylsilyl)oxy)-2-vinyl-2,4a,4b,5,6,7,8,8a,9,9a-decahydro-1H-fluorene-1-carbonyl)penta  
nenitrile (**38**)**



To a stirred solution of diisopropylethylamine (0.035 mL, 0.248 mmol, 1.8 equiv) in THF (14 mL) at 0 °C was added a solution of *n*-butyl lithium (0.140 mL, 0.228 mmol, 1.65 equiv, 1.62 M in hexane) dropwise. After 30 min, a solution of siloxy nitrile **11** (86.0 mg, 0.207 mmol, 1.5 equiv) in THF (3.0 mL) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 15 min, then added a solution of siloxy aldehyde (45.8 mg, 0.138 mmol) in THF (3.0 mL) dropwise and stirred for 15 min. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL) at -78 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was used in the next step without further purification.

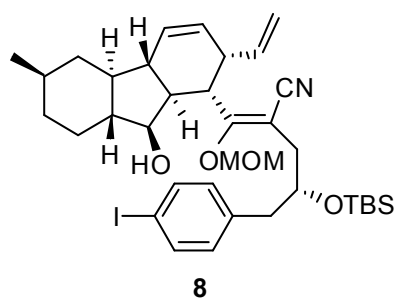
To a stirred solution of crude residue in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) at 0 °C was added NaHCO<sub>3</sub> (348 mg, 4.14 mmol, 30 equiv) and Dess-Martin periodinane (176 mg, 0.414 mmol, 3.0 equiv) successively. The resulting mixture was stirred overnight at the same temperature. The reaction was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5.0 mL) and saturated aqueous NaHCO<sub>3</sub> (5.0 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50:1) to give the desired keto nitrile **38** (78.2 mg, 0.105 mmol, 76% yield for 2 steps) as a pale yellow oil.

IR (ATR)  $\nu_{\text{max}}$  = 2951, 2926, 2856, 1725, 1485, 1456, 1372, 1249, 1064, 1025, 1007, 949, 922, 835, 775, 748, 513 cm<sup>-1</sup>;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 3:1 mixture of two diastereomers)  $\delta$  = 7.64-7.52 (2H, m), 6.92 (2H, m), 5.90 (1H, d,  $J$  = 9.8 Hz), 5.54-5.33 (2H, m), 5.07-4.90 (2H, m), 4.09-4.01 (1H, m), 3.99 (1H, dt,  $J$  = 11.5, 4.5 Hz), 3.65-3.58 (1H, m), 3.53-3.47 (1H, m), 3.47-3.28 (1H, m), 2.90 (1H, m), 2.76 (1H, m), 2.62 (1H, td,  $J$  = 13.4, 7.8 Hz), 1.93 (4H, m), 1.86-1.69 (2H, m), 1.60 (1H, m), 1.47-1.10 (4H, m), 1.01-0.67 (14H, m), 0.18 (2H, m), 0.08 (2H, m), 0.00 (2H, s), -0.07 (3H, s), -0.14 (3H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 3:1 mixture of two diastereomer)  $\delta$  = 200.5, 137.3, 137.1, 137.0, 136.6, 131.5, 131.1, 128.7, 128.5, 128.3, 117.6, 116.1, 91.5, 73.3, 69.8, 58.2, 49.4, 48.8, 46.1, 45.9, 43.7, 43.6, 43.4, 39.4, 37.8, 35.9, 33.7, 32.4, 32.4, 29.2, 25.5, 22.1, 17.6, 0.2, 0.0, -4.6, -5.0 ppm.

**(*R,Z*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(((1*S*,2*S*,4*aS*,4*bS*,6*R*,8*aR*,9*S*,9*aS*)-9-hydroxy-6-methyl-2-vinyl-2,4*a*,4*b*,5,6,7,8,8*a*,9,9*a*-decahydro-1*H*-fluoren-1-yl)(methoxymethoxy)methylene)-5-(4-iodophenyl)pentanenitrile (8)**



To a stirred solution of keto nitrile **38** (47.8 mg, 0.0641 mmol) in DMF (3.2 mL) was added  $\text{Cs}_2\text{CO}_3$  (418 mg, 1.28 mmol, 20 equiv) in one portion. After stirred for 15 min at room temperature, methoxymethyl chloride (0.024 mL, 0.321 mmol, 5.0 equiv) was added dropwise. Then, the resulting mixture was cooled to 0 °C and MeOH (2.0 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with water (5.0 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1→5:1) to give the desired cyclization precursor **8**.

(39.1 mg, 0.0545 mmol, 85% yield) as a white amorphous solid.

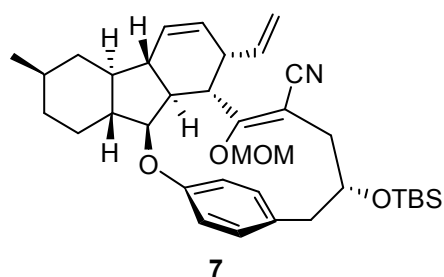
$[\alpha]_D^{23} = +88.1$  ( $c = 0.89$ ,  $\text{CHCl}_3$ );

IR (ATR)  $\nu_{\text{max}} = 3494, 2926, 2856, 2205, 1616, 1485, 1255, 1155, 1062, 1007, 924, 833, 776 \text{ cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , mixture of rotamers)  $\delta = 7.58$  (2H, d,  $J = 8.1$  Hz), 6.94 (2H, d,  $J = 7.8$  Hz), 5.93 (1H, d,  $J = 9.3$  Hz), 5.44 (1H, d,  $J = 9.5$  Hz), 5.13-5.01 (3H, m), 4.89 (1H, s), 4.24 (1H, d,  $J = 5.6$  Hz), 3.92 (1H, d,  $J = 14.6$  Hz), 3.48 (4H, m), 3.19 (1H, d,  $J = 11.0$  Hz), 2.84 (1H, t,  $J = 6.7$  Hz), 2.57 (1H, d,  $J = 9.5$  Hz), 2.43 (2H, m), 1.99 (4H, m), 1.74 (2H, m), 1.42-1.18 (4H, m), 1.07-0.74 (15H, m), -0.02 (1H, s), -0.06 (2H, d,  $J = 11.0$  Hz), -0.20 (1H, s), -0.37 (2H, s) ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , mixture of rotamers)  $\delta = 173.6, 170.4, 139.4, 138.6, 138.5, 137.9, 137.5, 137.3, 132.3, 129.6, 129.5, 128.8, 128.6, 120.7, 120.1, 117.5, 116.7, 115.1, 109.4, 98.8, 93.9, 93.7, 92.8, 91.7, 91.4, 75.3, 74.8, 72.9, 72.7, 70.3, 67.6, 60.7, 59.4, 59.3, 57.4, 57.3, 48.2, 47.8, 47.4, 47.1, 46.7, 46.6, 46.2, 46.1, 42.8, 42.6, 41.9, 38.4, 37.1, 36.4, 36.3, 35.6, 33.0, 32.9, 30.0, 29.7, 29.5, 29.3, 26.1, 22.8, 21.3, 18.2, 14.5, -4.4, -4.6, -4.8, -5.0$  ppm.

### Macrocycle (7)



A screw capped test tube was charged with CuI (19.0 mg, 0.100 mmol, 6.0 equiv), 1,10-phenanthroline (36.0 mg, 0.20 mmol, 12.0 equiv),  $\text{Cs}_2\text{CO}_3$  (652 mg, 2.00 mmol, 120 equiv), cyclization precursor **8** (12.0 mg, 0.0167 mmol) and toluene (3.3 mL). The test tube was sealed and the reaction mixture was stirred at 160 °C for 5 h. The resulting suspension was cooled to room temperature and filtered through a short pad of silica gel, eluting with diethyl ether. The filtrate was



concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10:1) to give the desired cyclization product **7** (4.1 mg, 0.0070 mmol, 42% yield) as a pale yellow oil.

$[\alpha]_D^{23} = +186$  ( $c = 0.08$ ,  $\text{CHCl}_3$ );

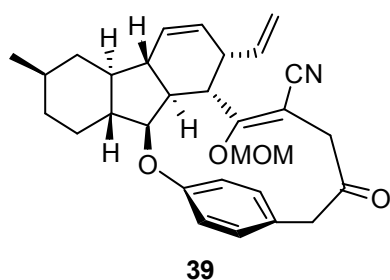
IR (ATR)  $\nu_{\text{max}} = 2951, 2926, 2856, 1725, 1485, 1456, 1372, 1249, 1064, 1025, 1007, 949, 922, 835, 775, 748, 513 \text{ cm}^{-1}$ ;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.07$  (1H, d,  $J = 8.8$  Hz), 6.92 (2H, s), 6.87 (1H, d,  $J = 8.8$  Hz), 5.83 (1H, d,  $J = 9.8$  Hz), 5.46 (1H, s), 4.89 (2H, dt,  $J = 20.0, 9.1$  Hz), 4.78 (1H, d,  $J = 5.6$  Hz), 4.63 (1H, d,  $J = 5.6$  Hz), 3.57 (2H, s), 3.28 (1H, s), 2.88 (1H, d,  $J = 5.4$  Hz), 2.39 (3H, dt,  $J = 24.2, 8.1$  Hz), 2.13-1.92 (2H, m), 1.69-1.46 (9H, m), 0.98-0.83 (17H, m), 0.17 (3H, s), 0.14 (3H, s). ppm;

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 167.1, 158.0, 138.2, 130.1, 129.7, 129.5, 128.9, 127.2, 120.9, 119.3, 115.9, 98.0, 83.6, 73.5, 57.4, 55.3, 49.5, 46.4, 46.2, 45.3, 44.3, 43.5, 37.9, 36.4, 36.0, 33.1, 29.7, 29.5, 25.9, 25.8, 22.5, 18.1, -4.6, -4.7$  ppm;

HRMS (FAB) calcd. for  $\text{C}_{36}\text{H}_{52}\text{NO}_4\text{Si}$   $[\text{M}+\text{H}]^+$  590.3666, found 590.3665.

### Keto nitrile (**39**)



To a stirred solution of cyclization product **7** (2.0 mg, 0.0034 mmol) in THF (0.5 mL) was added tetrabutylammonium fluoride (0.068 mL, 0.068 mmol, 20 equiv, 1.0 M in THF) dropwise. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (1.5 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and

concentrated *in vacuo*. The residue was used in the next step without further purification.

To a stirred solution of crude residue in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at 0 °C was added Dess-Martin periodinane (7.6 mg, 0.018 mmol, 5.0 equiv). The resulting mixture was stirred for 1 h at room temperature. The reaction was diluted with EtOAc (2.0 mL) and quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2.0 mL) and saturated aqueous NaHCO<sub>3</sub> (2.0 mL) at 0 °C. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by PTLC (silica gel, hexane/EtOAc = 1:1) to give the desired keto nitrile **39** (1.4 mg, 0.0031 mmol, 90% yield for 2 steps) as a pale yellow oil.

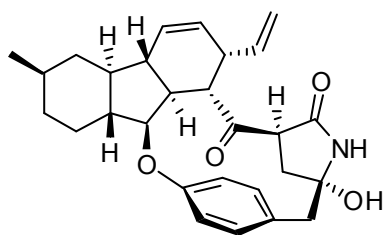
$[\alpha]_D^{23} = +169$  ( $c = 0.08$ , CHCl<sub>3</sub>);

IR (ATR)  $\nu_{\max} = 2928, 2854, 2205, 1616, 1485, 1255, 1249, 1064, 1025, 1007, 949, 922, 835, 775, 748, 513 \text{ cm}^{-1}$ ;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 7.15\text{--}7.11$  (1H, m), 7.10 (1H, t,  $J = 5.2$  Hz), 7.05 (1H, t,  $J = 5.4$  Hz), 6.98 (1H, dd,  $J = 8.1, 2.4$  Hz), 5.83 (1H, d,  $J = 9.8$  Hz), 5.42 (1H, d,  $J = 17.1$  Hz), 5.34 (1H, s), 4.88 (2H, dt,  $J = 19.7, 9.1$  Hz), 4.67–4.62 (2H, m), 4.56 (1H, d,  $J = 6.6$  Hz), 3.76 (1H, d,  $J = 15.4$  Hz), 3.69 (1H, d,  $J = 12.7$  Hz), 3.63 (3H, d,  $J = 12.0$  Hz), 3.50 (1H, d,  $J = 15.4$  Hz), 2.94 (1H, t,  $J = 8.9$  Hz), 2.67 (1H, d,  $J = 12.5$  Hz), 2.15 (2H, s), 1.99 (1H, s), 1.60–1.39 (7H, m), 0.99–0.85 (5H, m) ppm;

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 204.1, 169.3, 159.1, 137.7, 132.0, 130.1, 128.7, 127.2, 125.8, 122.2, 120.2, 118.1, 116.4, 98.3, 85.6, 83.9, 57.6, 55.4, 50.9, 49.7, 46.4, 45.9, 45.0, 43.2, 41.7, 37.9, 36.4, 33.1, 29.5, 22.5$  ppm.

### Hirsutellone B (1)



**Hirsutellone B (1)**

To a stirred solution of keto nitrile **39** (4.3 mg, 0.0091 mmol) in *t*-BuOH (2.0 mL) was added two pellets of KOH. The resulting mixture was refluxed for 30 min. The resulting suspension was cooled to room temperature and quenched with 1N aqueous HCl (2.0 mL). The aqueous layer was extracted with CHCl<sub>3</sub>. The combined organic layers were washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was used in the next step without further purification.

To a stirred solution of crude residue in *i*-PrOH (1.0 mL) was added 1N aqueous HCl (1.0 mL). The resulting mixture was stirred overnight at 60 °C. The resulting suspension was cooled to room temperature and quenched with saturated aqueous NaHCO<sub>3</sub> (2.0 mL). The aqueous layer was extracted with CHCl<sub>3</sub>. The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by PTLC (silica gel, EtOAc) to give the desired hirsutellone B **1** (3.5 mg, 0.0077 mmol, 85% yield for 2 steps) as a pale yellow oil.

$[\alpha]_D^{23} = +247$  ( $c = 0.07$ , MeOH);

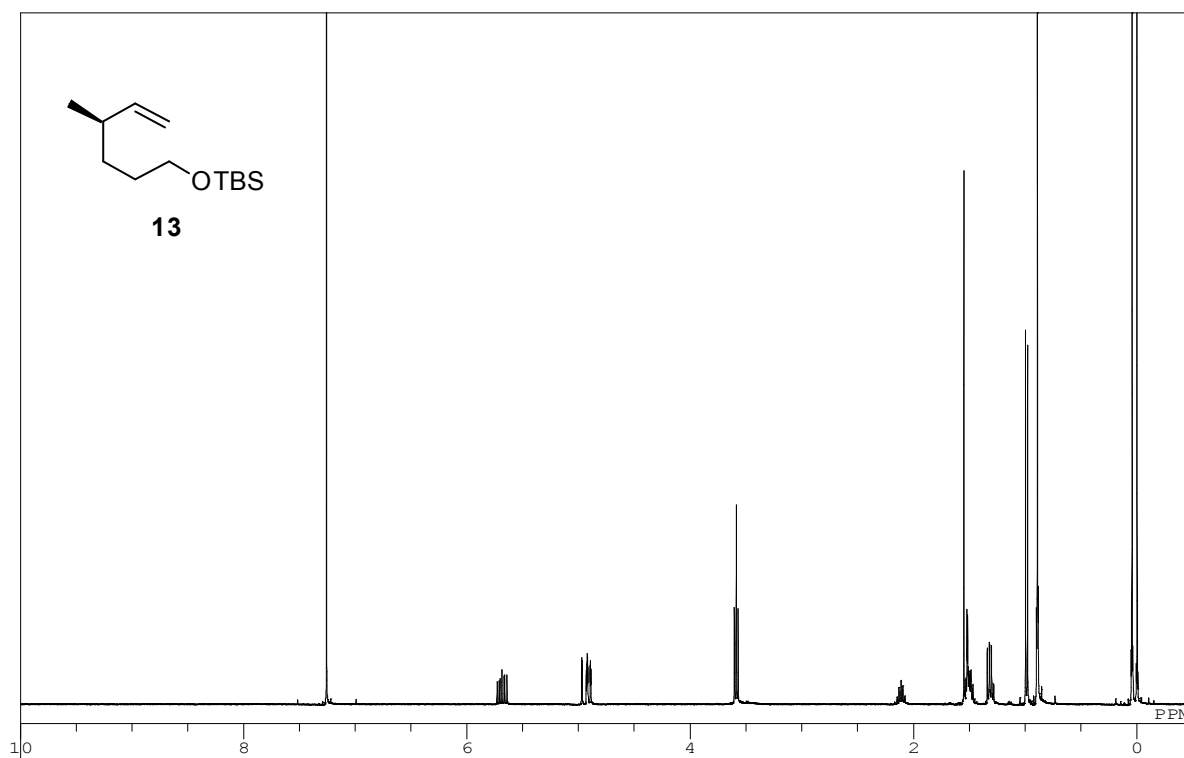
IR (ATR)  $\nu_{\max} = 3407, 3256, 2948, 2912, 1705, 1667, 1608, 1509, 1301, 1240, 1091, 1055, 997, 926, 728, 775, 748, 513 \text{ cm}^{-1}$ ;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 7.10$  (1H, dd,  $J = 8.4, 1.7$  Hz),  $7.05$  (1H, dd,  $J = 8.4, 2.2$  Hz),  $6.89$  (1H, dd,  $J = 8.4, 1.7$  Hz),  $6.86$  (1H, dd,  $J = 8.3, 2.2$  Hz),  $5.91$  (1H, br),  $5.81$  (1H, d,  $J = 9.8$  Hz),  $5.34$  (1H, ddd,  $J = 9.8, 4.9, 2.1$  Hz),  $5.22$  (1H, dt,  $J = 17.1, 9.6$  Hz),  $4.88$  (1H, dd,  $J = 16.9, 1.2$  Hz),  $4.86$  (1H, m),  $4.84$  (1H, m),  $3.50$  (1H, m),  $3.45$  (1H, dd,  $J = 11.0, 5.9$  Hz),  $3.00$  (1H, d,  $J = 13.0$  Hz),  $2.94$  (1H, dd,  $J = 12.3, 3.7$  Hz),  $2.86$  (1H, d,  $J = 13.0$  Hz),  $2.71$  (1H, dd,  $J = 15.0, 3.7$  Hz),  $2.47$  (1H, br),  $2.15$  (2H, m),  $1.97$  (1H, m),  $1.94$  (1H, dd,  $J = 14.8, 12.6$  Hz),  $1.85$  (1H, m),  $1.64$  (1H, m),  $1.48$  (1H, dt,  $J = 4.6, 11.5$  Hz),  $1.43$  (1H, m),  $1.40$  (1H, dq,  $J = 3.5, 12.5$  Hz),  $1.12$  (1H, dq,  $J = 3.8, 12.5$  Hz),  $0.95$  (3H, d,  $J = 6.6$  Hz),  $0.90$  (1H, m),  $0.82$  (1H, dq,  $J = 2.4, 11.1$  Hz) ppm;

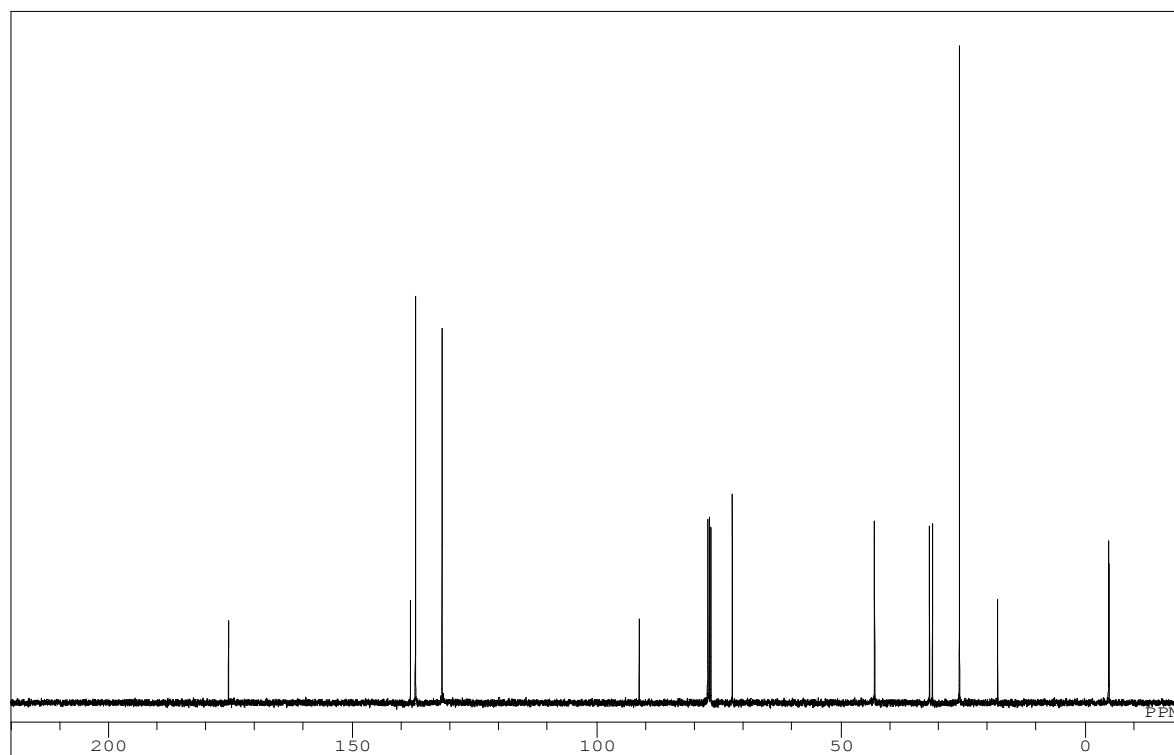
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta = 200.9, 171.9, 158.3, 137.3, 131.7, 131.4, 128.7, 127.4, 127.2, 121.8, 121.6, 116.4, 89.0, 84.6, 55.7, 53.9, 49.9, 48.9, 47.2, 46.7, 44.0, 42.4, 38.0, 36.5, 34.6, 33.1, 29.4, 22.5$  ppm;

HRMS (FAB) calcd. for  $\text{C}_{28}\text{H}_{34}\text{NO}_4$   $[\text{M}+\text{H}]^+$  448.2488, found 448.2489.

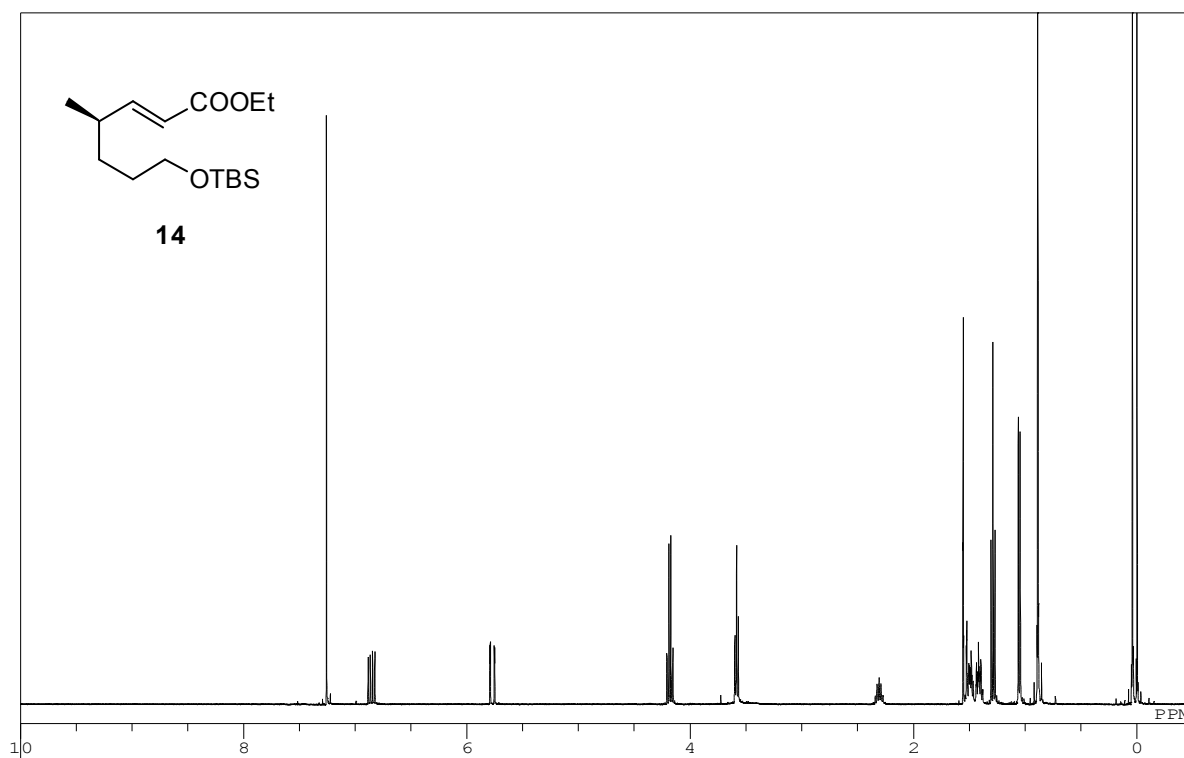
$^1\text{H}$  NMR spectrum of compound **13** (400 MHz,  $\text{CDCl}_3$ ).



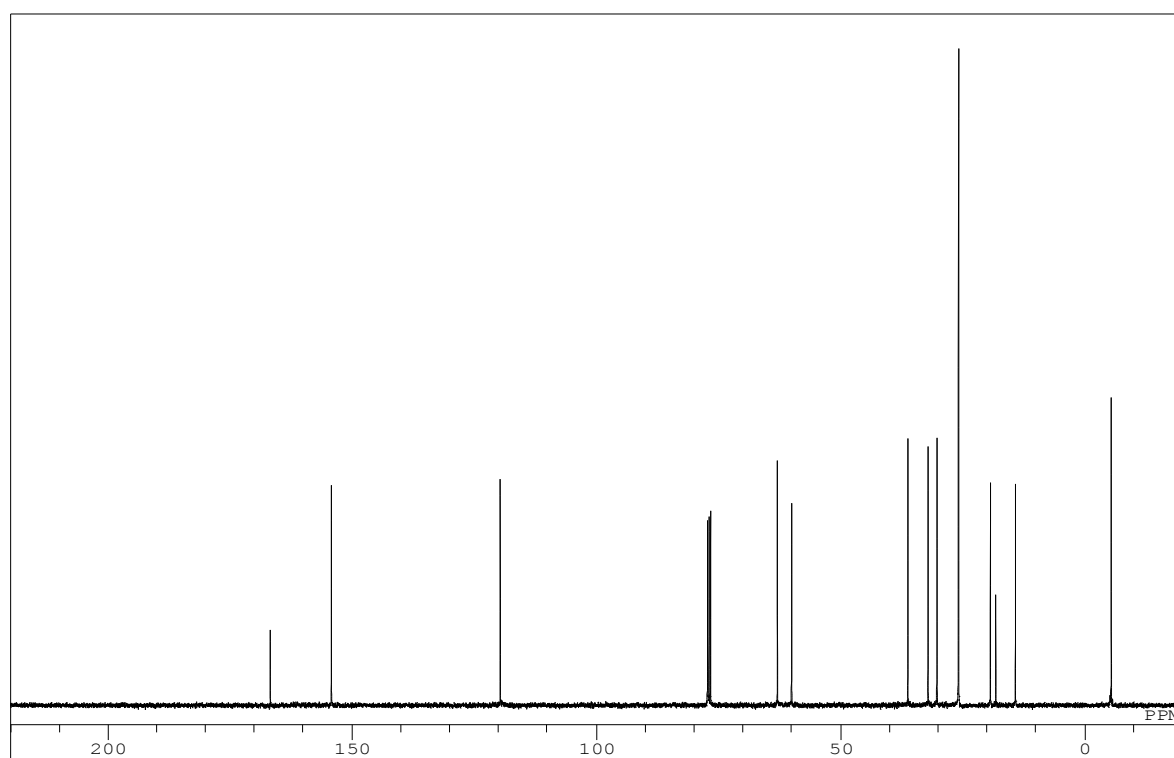
$^{13}\text{C}$  NMR spectrum of compound **13** (100 MHz,  $\text{CDCl}_3$ ).



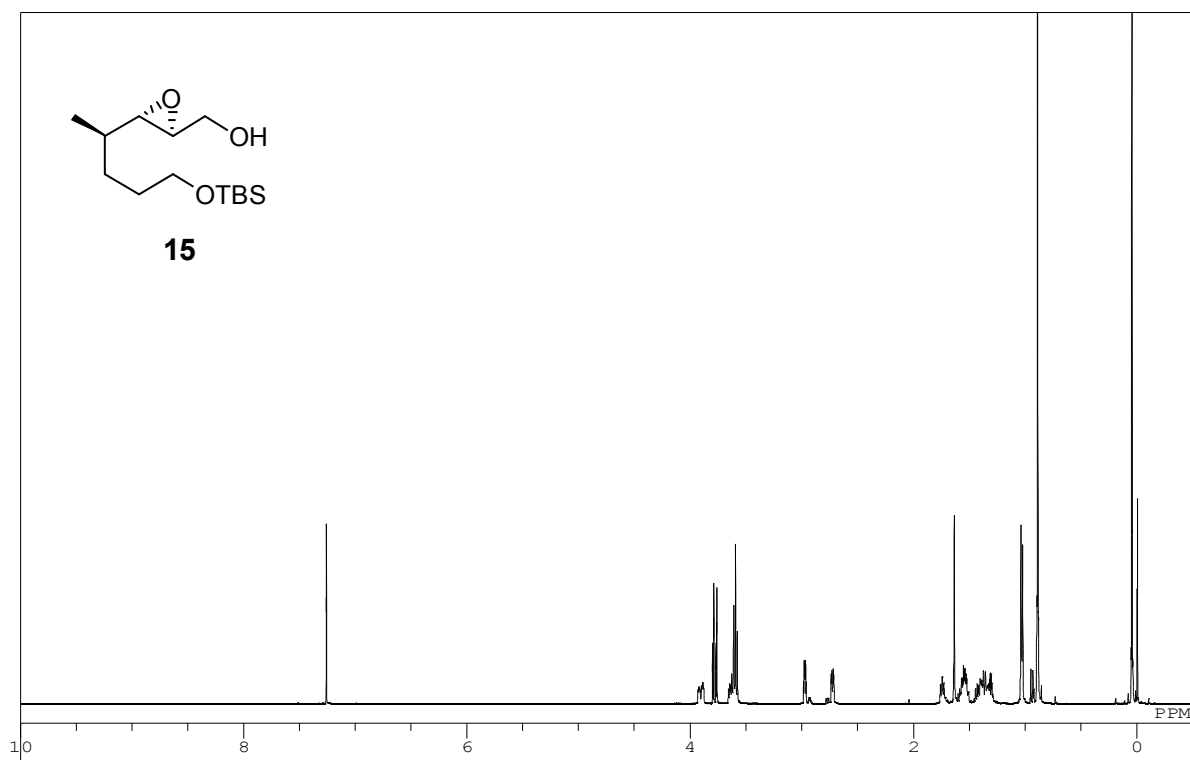
$^1\text{H}$  NMR spectrum of compound **14** (400 MHz,  $\text{CDCl}_3$ ).



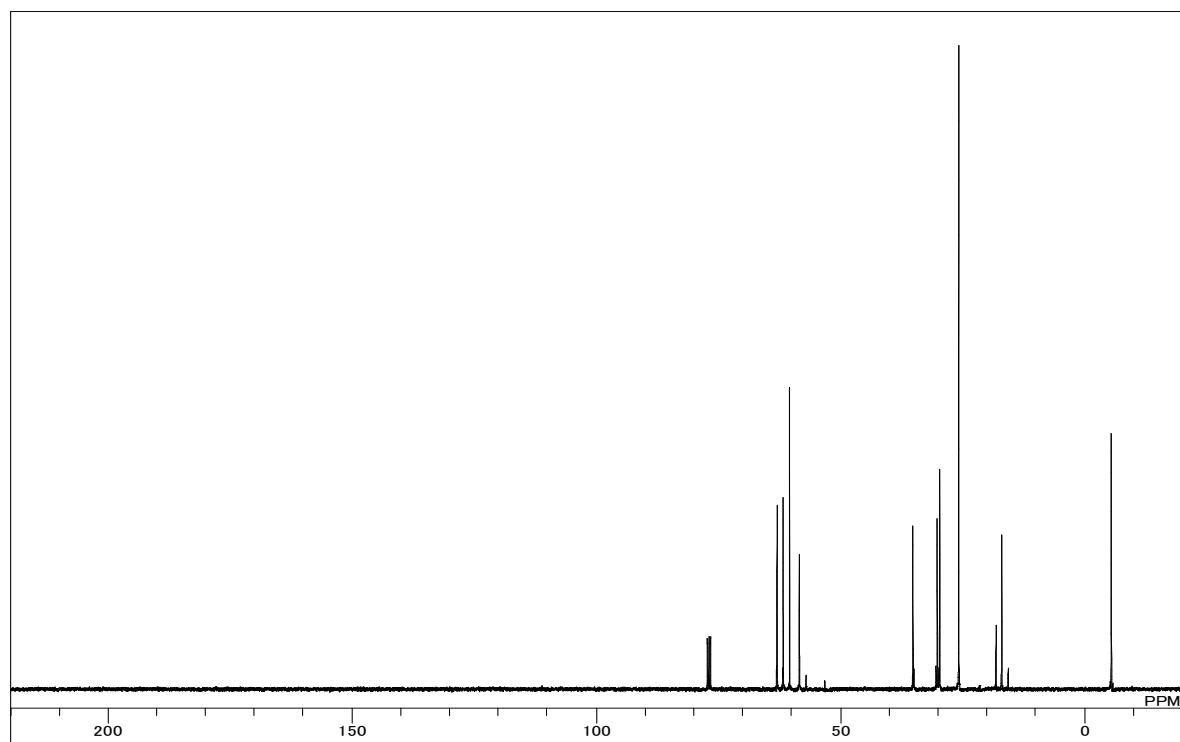
$^{13}\text{C}$  NMR spectrum of compound **14** (100 MHz,  $\text{CDCl}_3$ ).



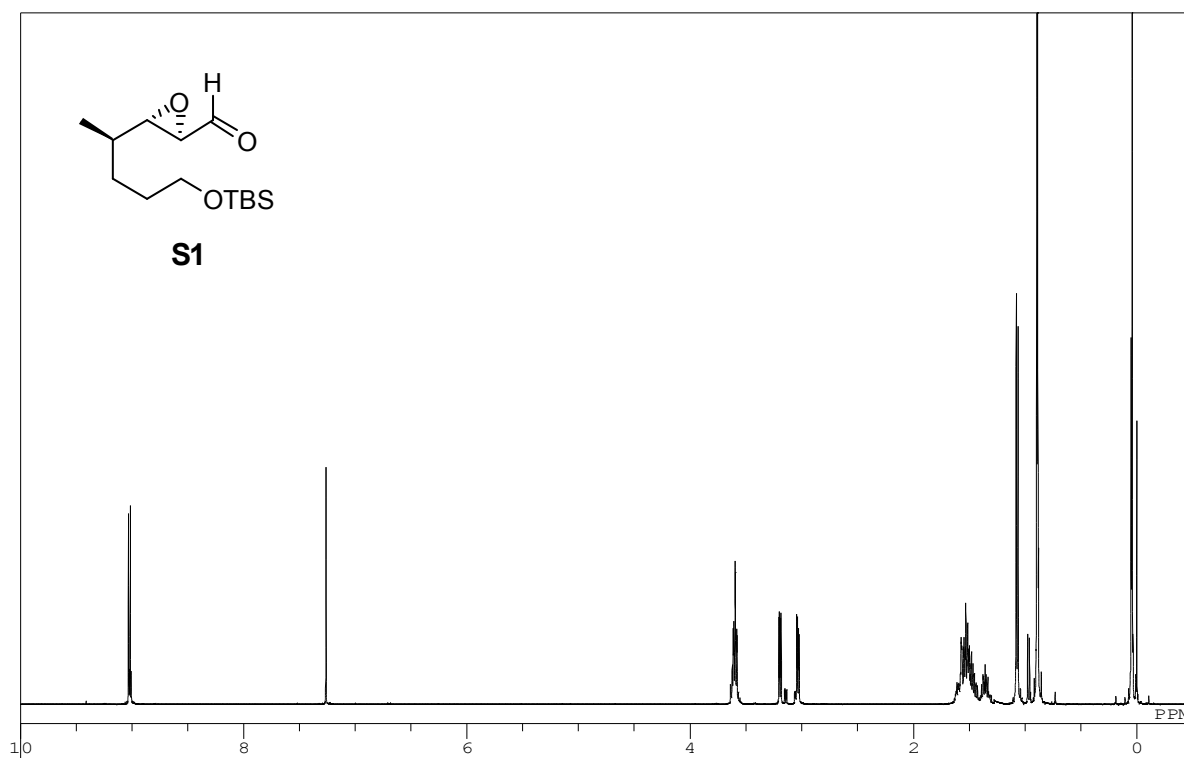
$^1\text{H}$  NMR spectrum of compound **15** (400 MHz,  $\text{CDCl}_3$ ).



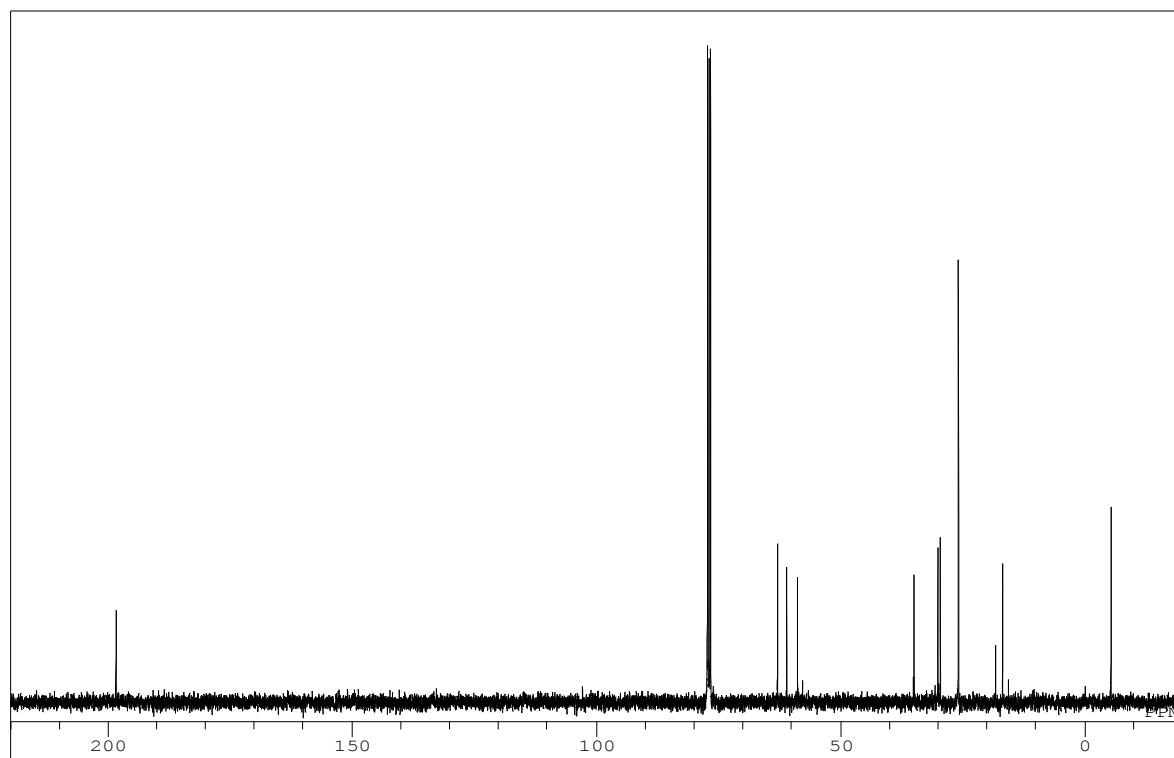
$^{13}\text{C}$  NMR spectrum of compound **15** (100 MHz,  $\text{CDCl}_3$ ).



$^1\text{H}$  NMR spectrum of compound **S1** (400 MHz,  $\text{CDCl}_3$ ).

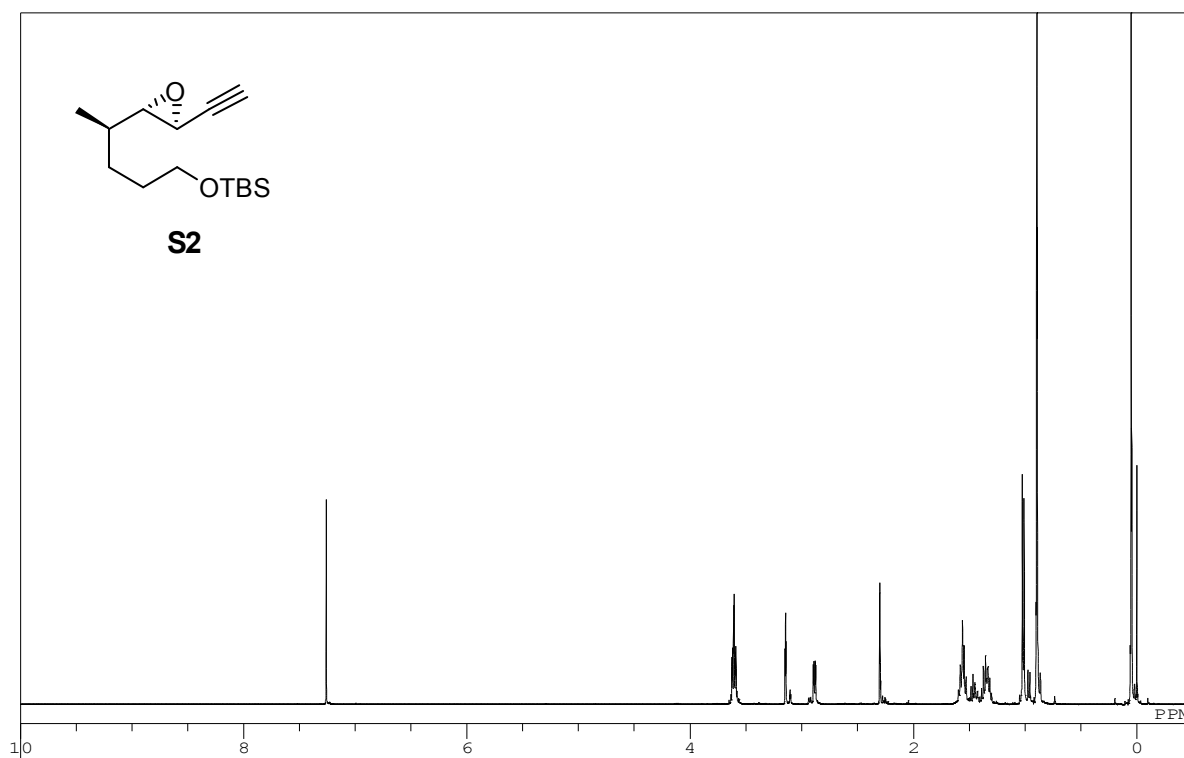


$^{13}\text{C}$  NMR spectrum of compound **S1** (100 MHz,  $\text{CDCl}_3$ ).

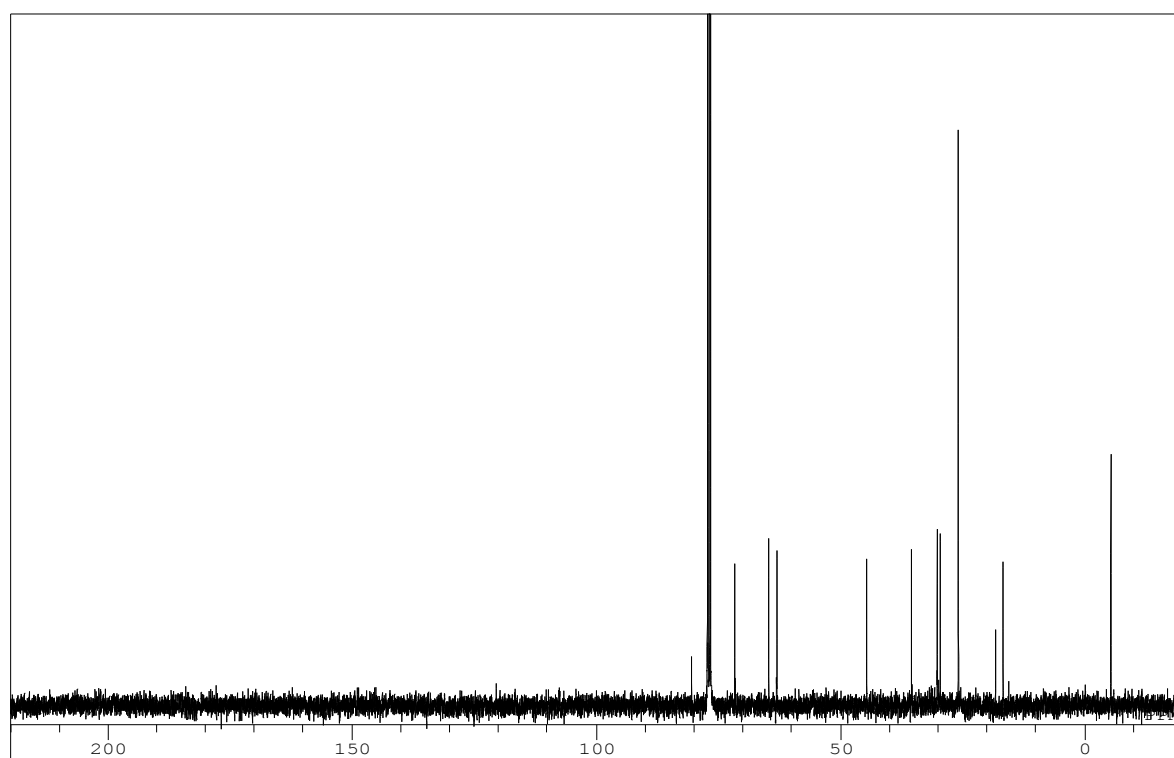




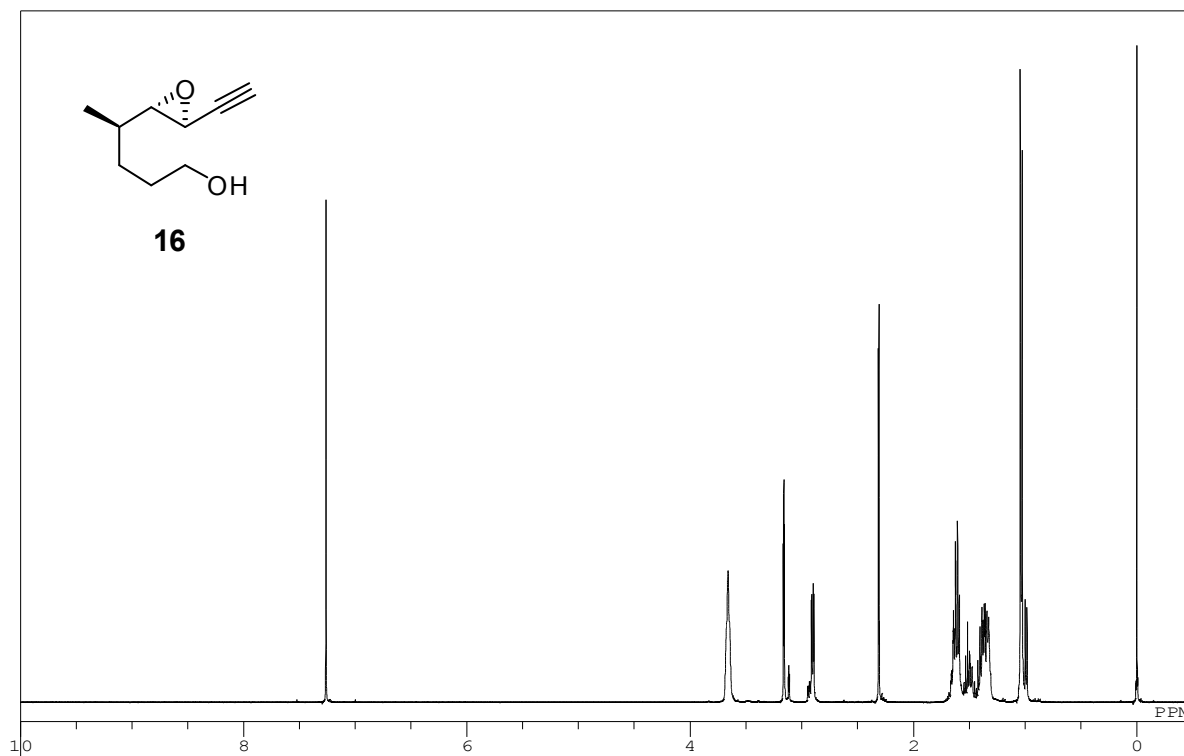
$^1\text{H}$  NMR spectrum of compound **S2** (400 MHz,  $\text{CDCl}_3$ ).



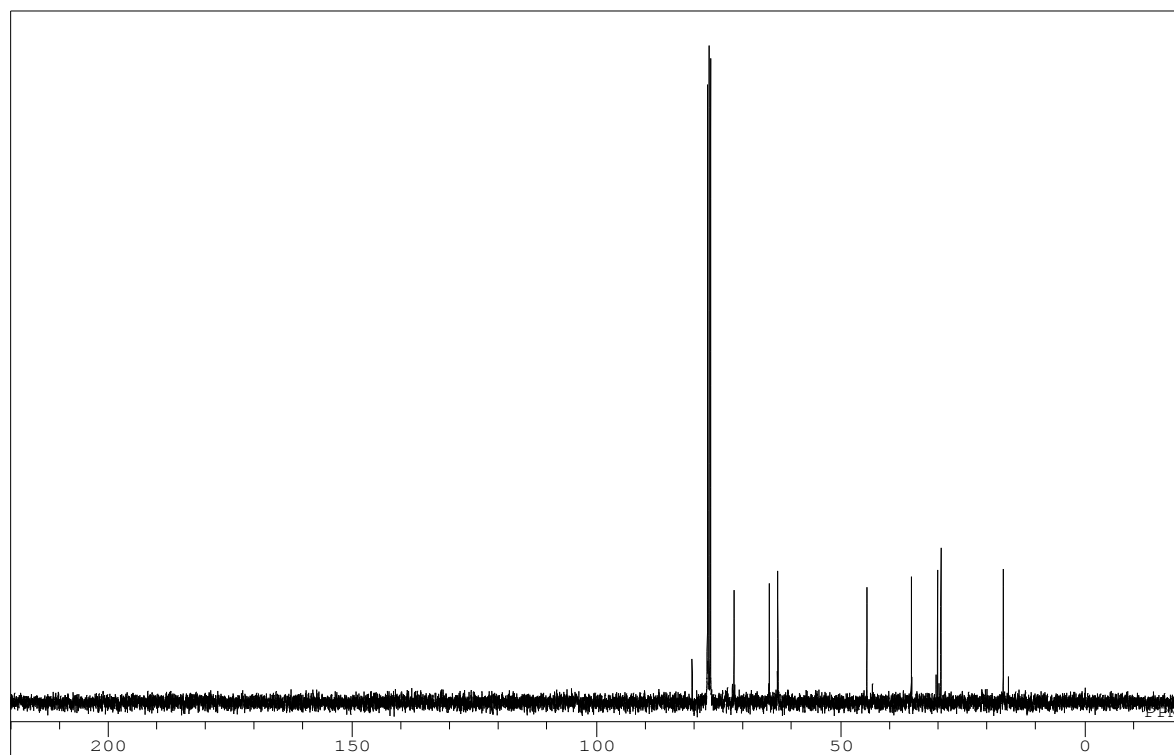
$^{13}\text{C}$  NMR spectrum of compound **S2** (100 MHz,  $\text{CDCl}_3$ ).



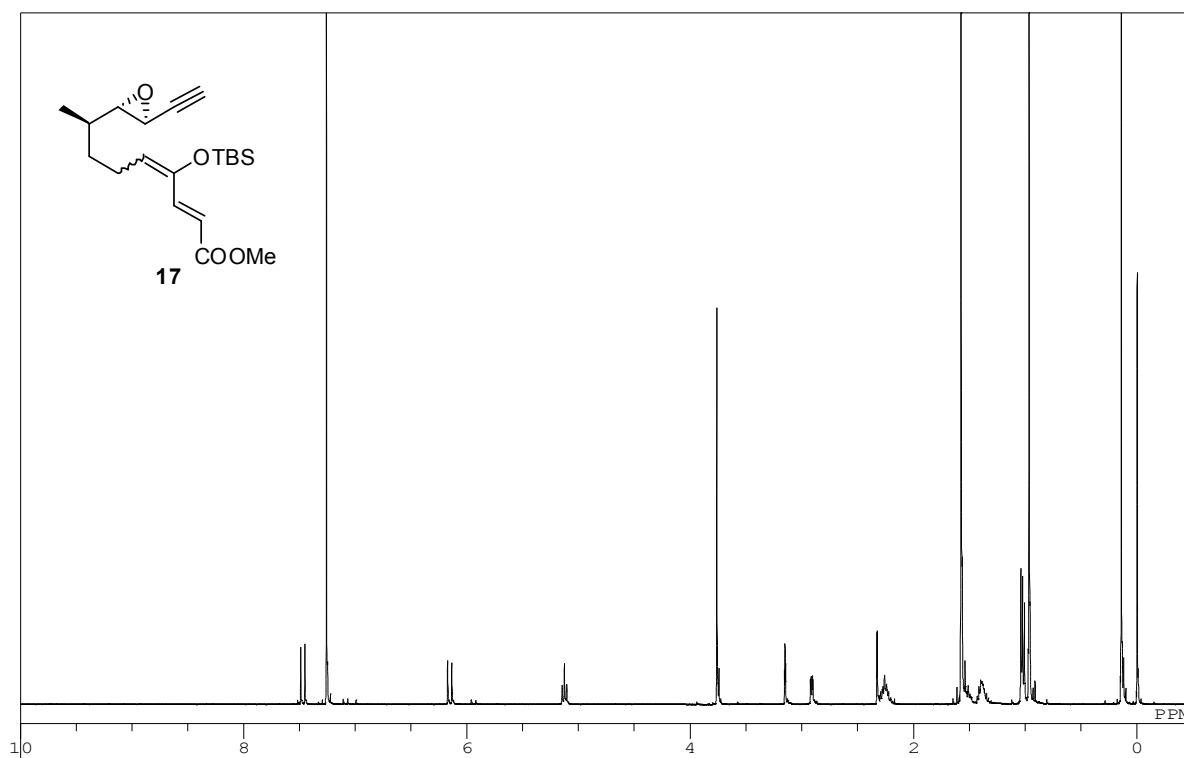
$^1\text{H}$  NMR spectrum of compound **16** (400 MHz,  $\text{CDCl}_3$ ).



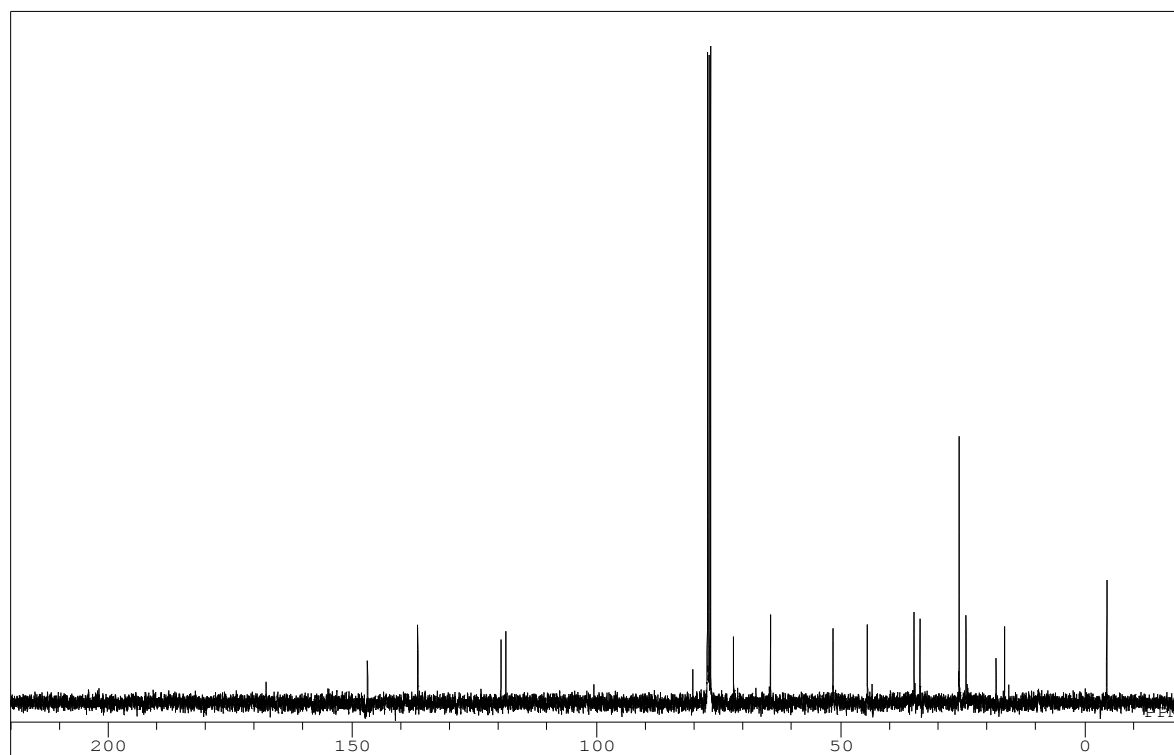
$^{13}\text{C}$  NMR spectrum of compound **16** (100 MHz,  $\text{CDCl}_3$ ).



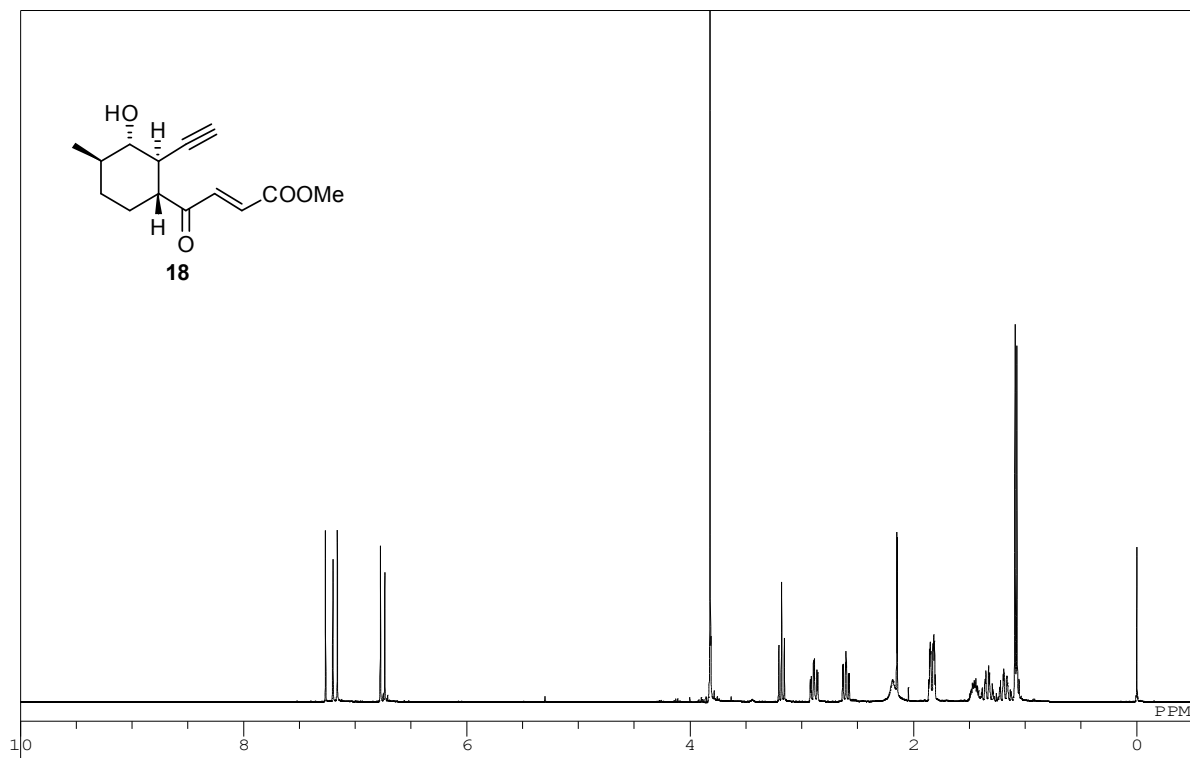
$^1\text{H}$  NMR spectrum of compound **17** (400 MHz,  $\text{CDCl}_3$ ).



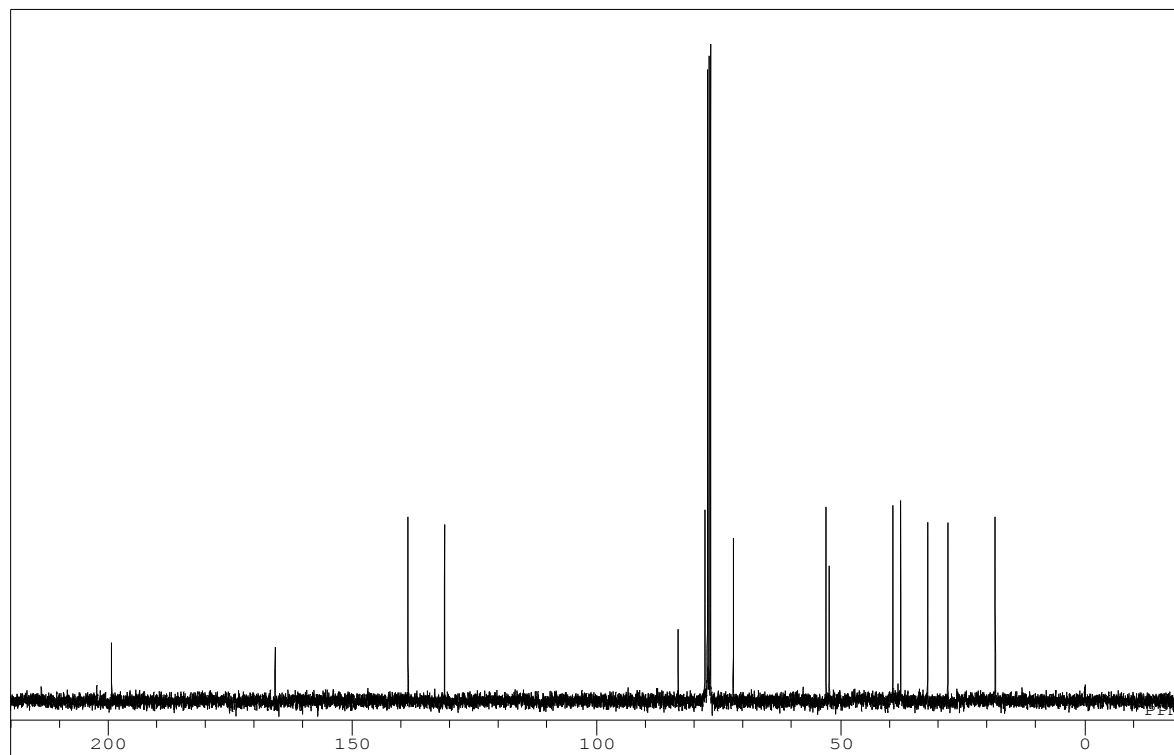
$^{13}\text{C}$  NMR spectrum of compound **17** (100 MHz,  $\text{CDCl}_3$ ).



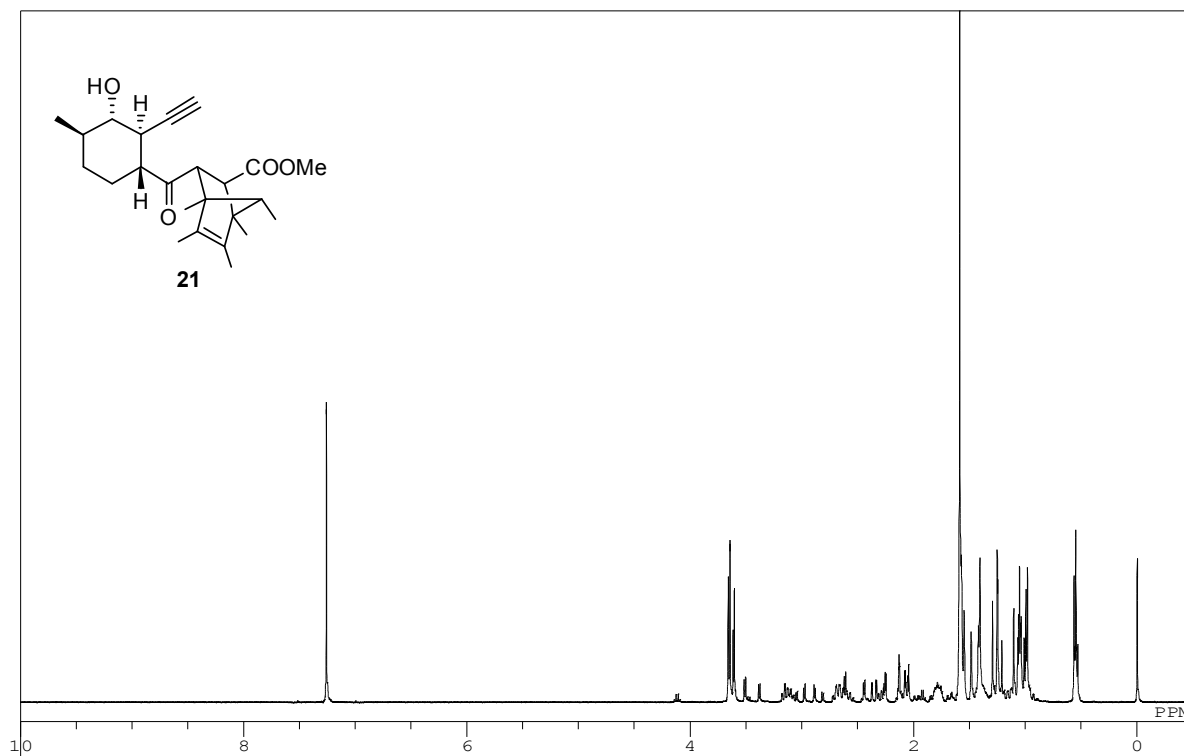
$^1\text{H}$  NMR spectrum of compound **18** (400 MHz,  $\text{CDCl}_3$ ).



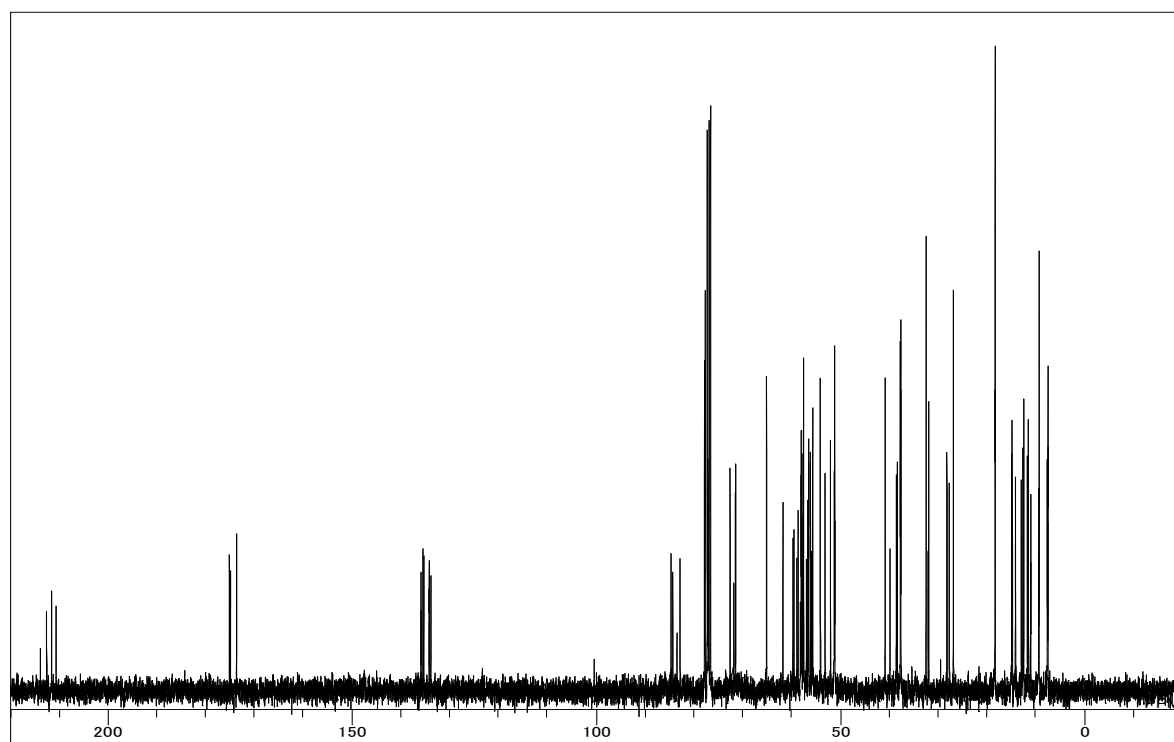
$^{13}\text{C}$  NMR spectrum of compound **18** (100 MHz,  $\text{CDCl}_3$ ).



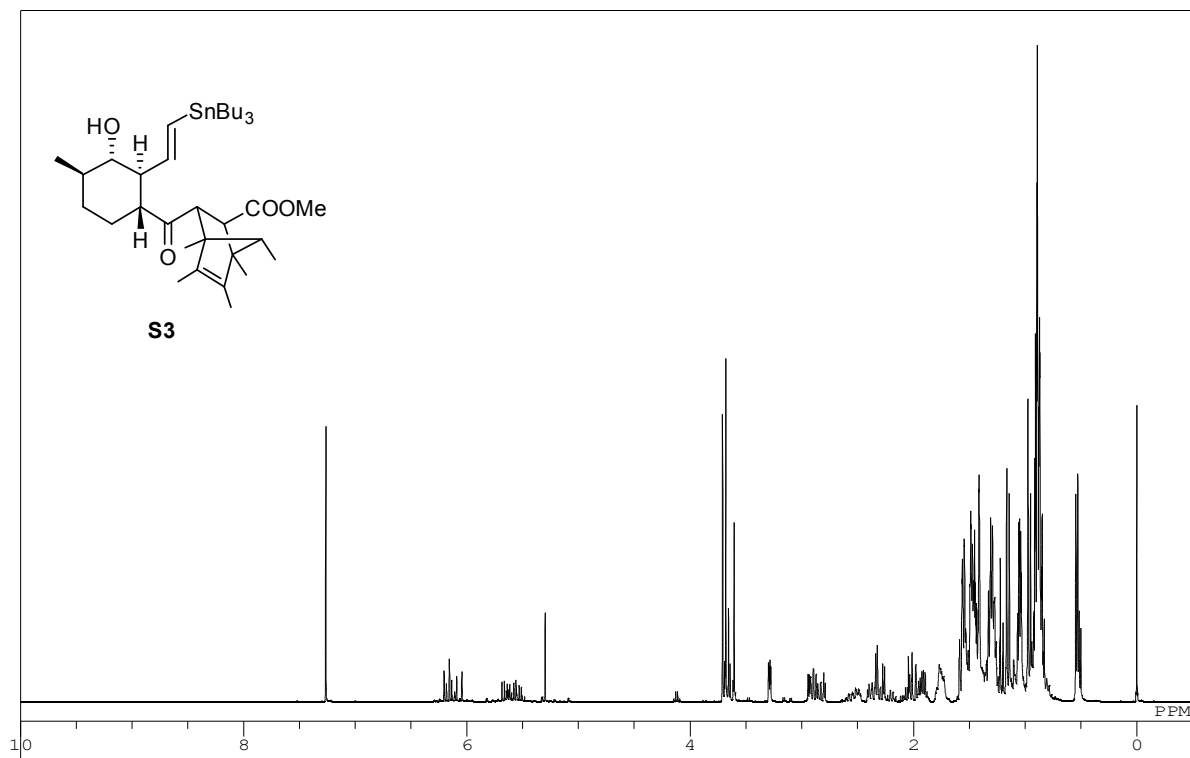
$^1\text{H}$  NMR spectrum of compound **21** (400 MHz,  $\text{CDCl}_3$ ).



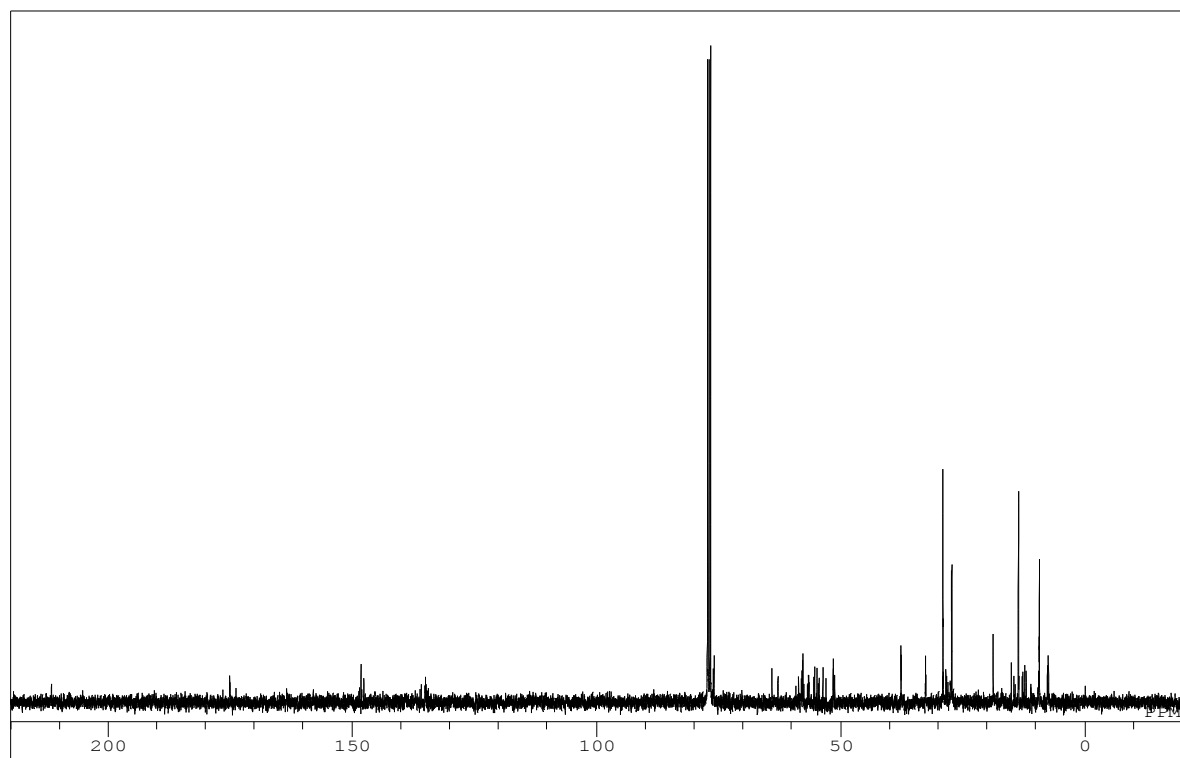
$^{13}\text{C}$  NMR spectrum of compound **21** (100 MHz,  $\text{CDCl}_3$ ).



$^1\text{H}$  NMR spectrum of compound **S3** (400 MHz,  $\text{CDCl}_3$ ).



$^{13}\text{C}$  NMR spectrum of compound **S3** (100 MHz,  $\text{CDCl}_3$ ).

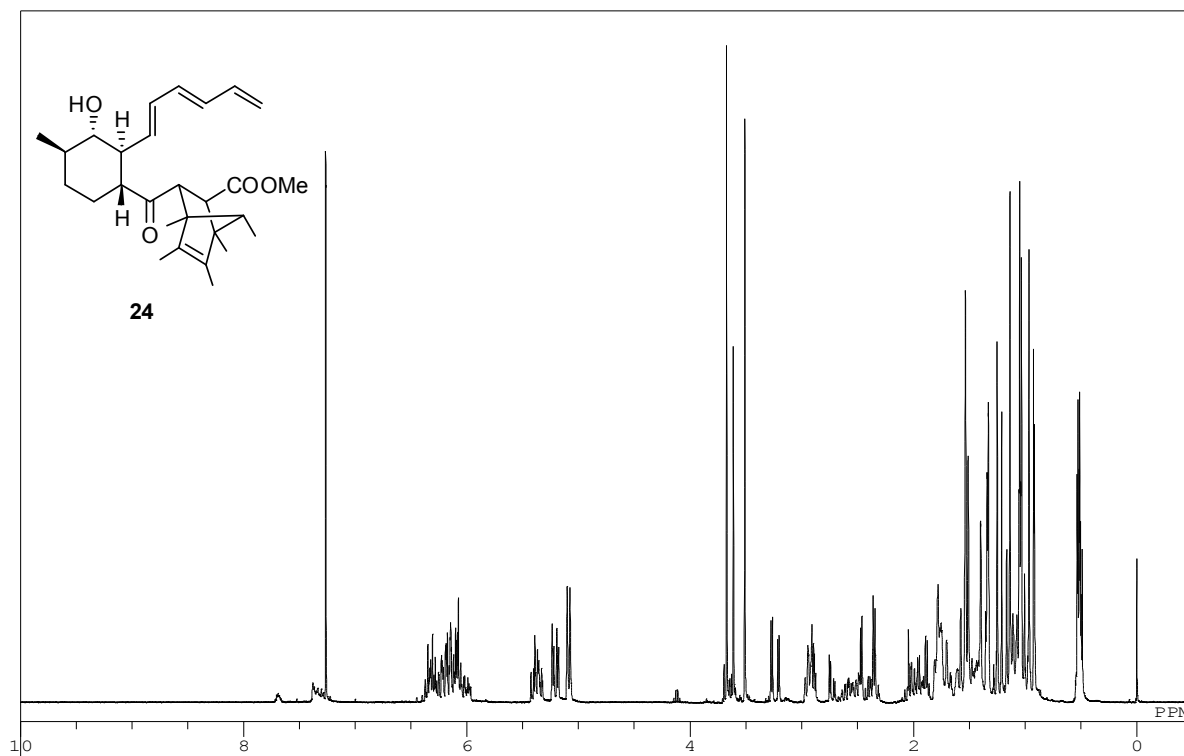


**22**

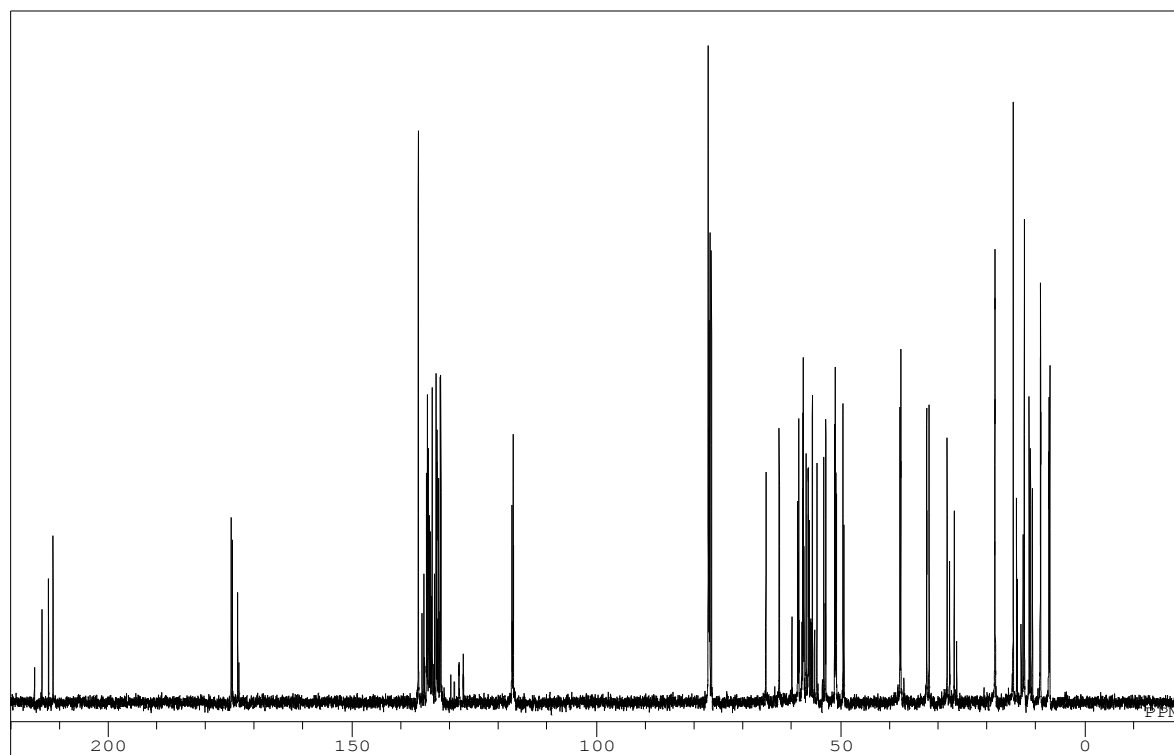
CCOC(=O)C1=C(C)C2=C(C1)C(=C(C)C2)C(=O)C3C(C)C(C)C(C3)O

10 8 6 4 2 0 PPM

$^1\text{H}$  NMR spectrum of compound **24** (400 MHz,  $\text{CDCl}_3$ ).

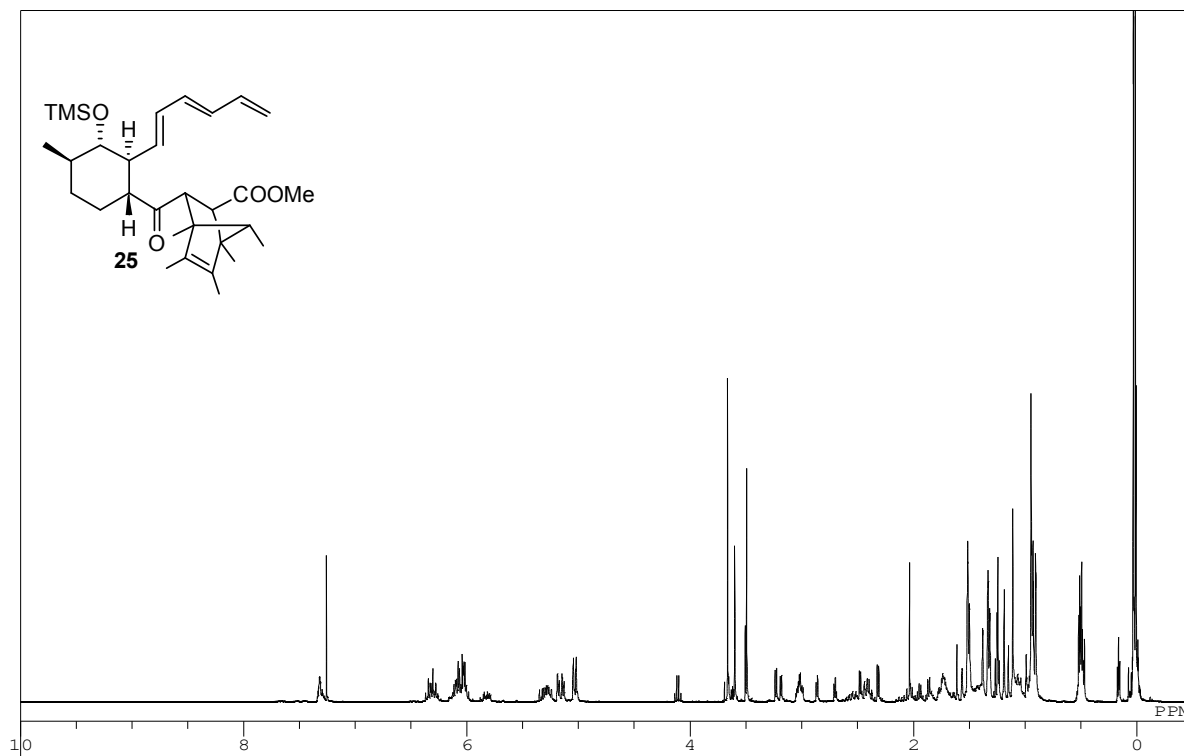


$^{13}\text{C}$  NMR spectrum of compound **24** (100 MHz,  $\text{CDCl}_3$ ).

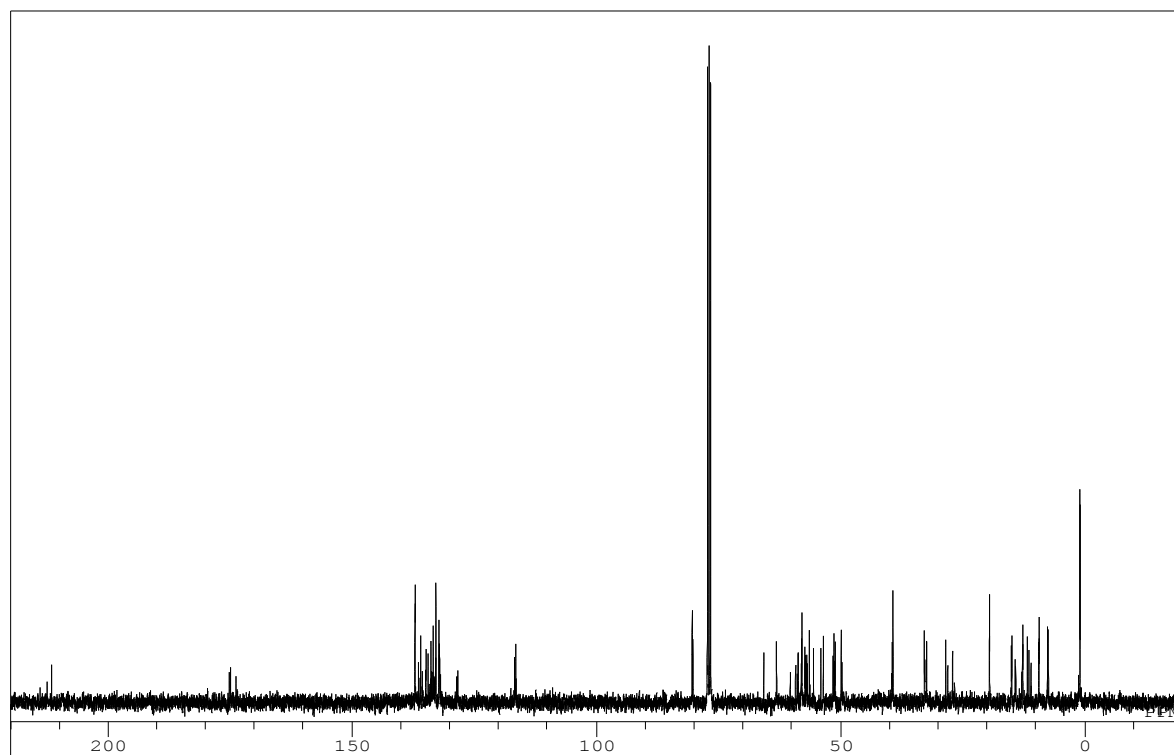




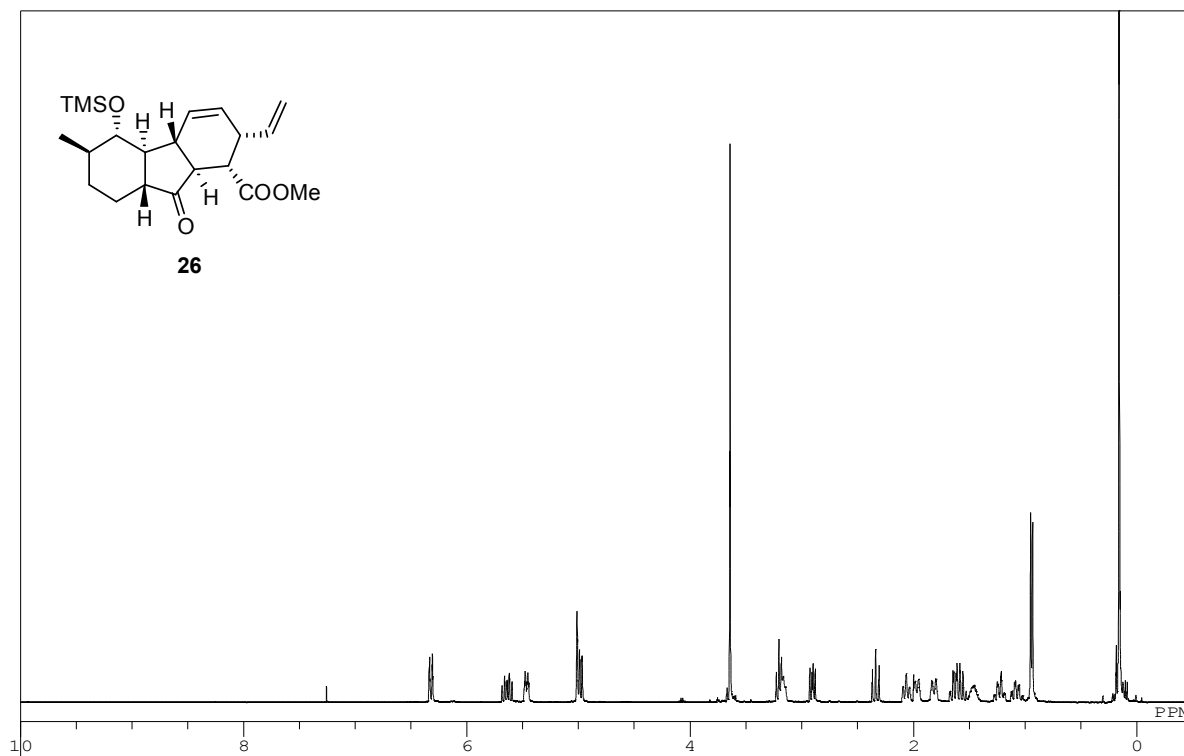
$^1\text{H}$  NMR spectrum of compound **25** (400 MHz,  $\text{CDCl}_3$ ).



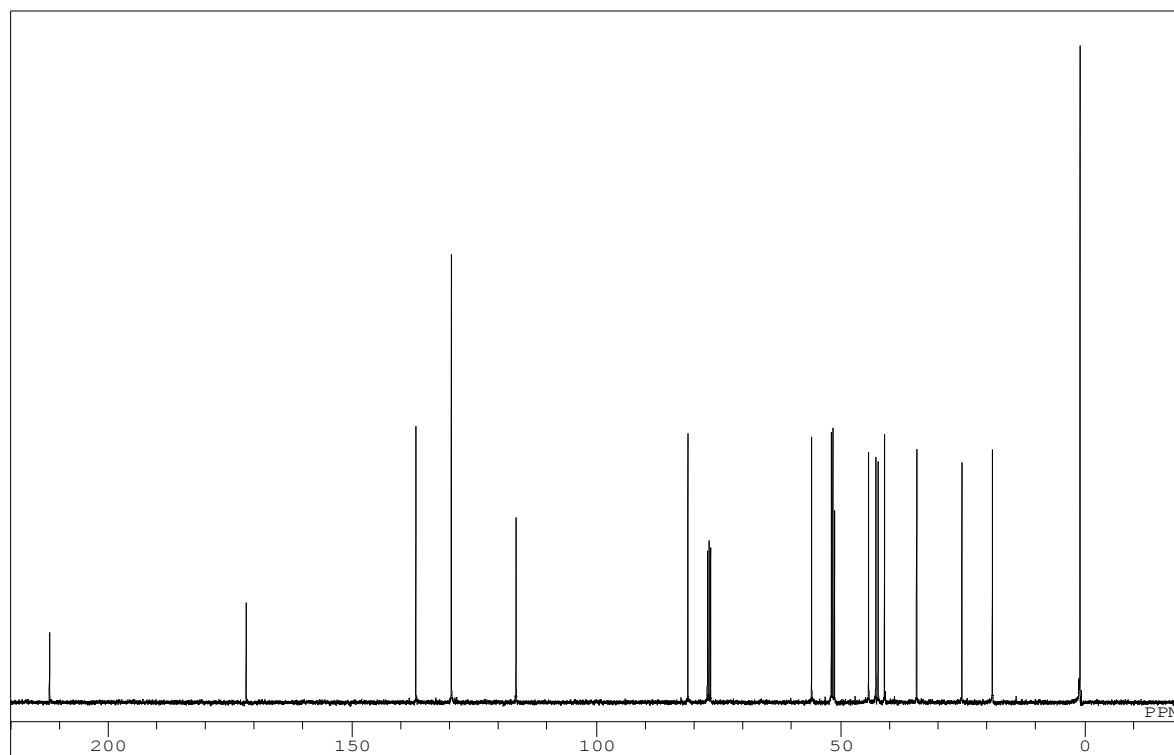
$^{13}\text{C}$  NMR spectrum of compound **25** (100 MHz,  $\text{CDCl}_3$ ).



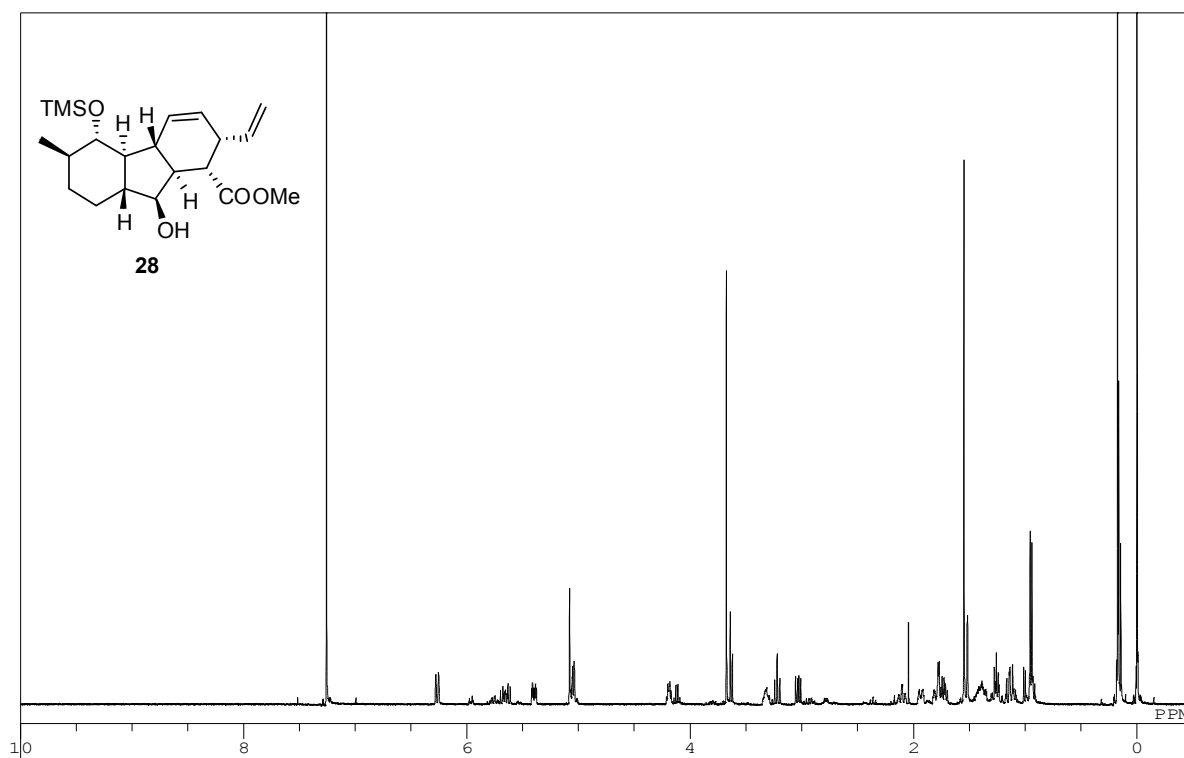
$^1\text{H}$  NMR spectrum of compound **26** (400 MHz,  $\text{CDCl}_3$ ).



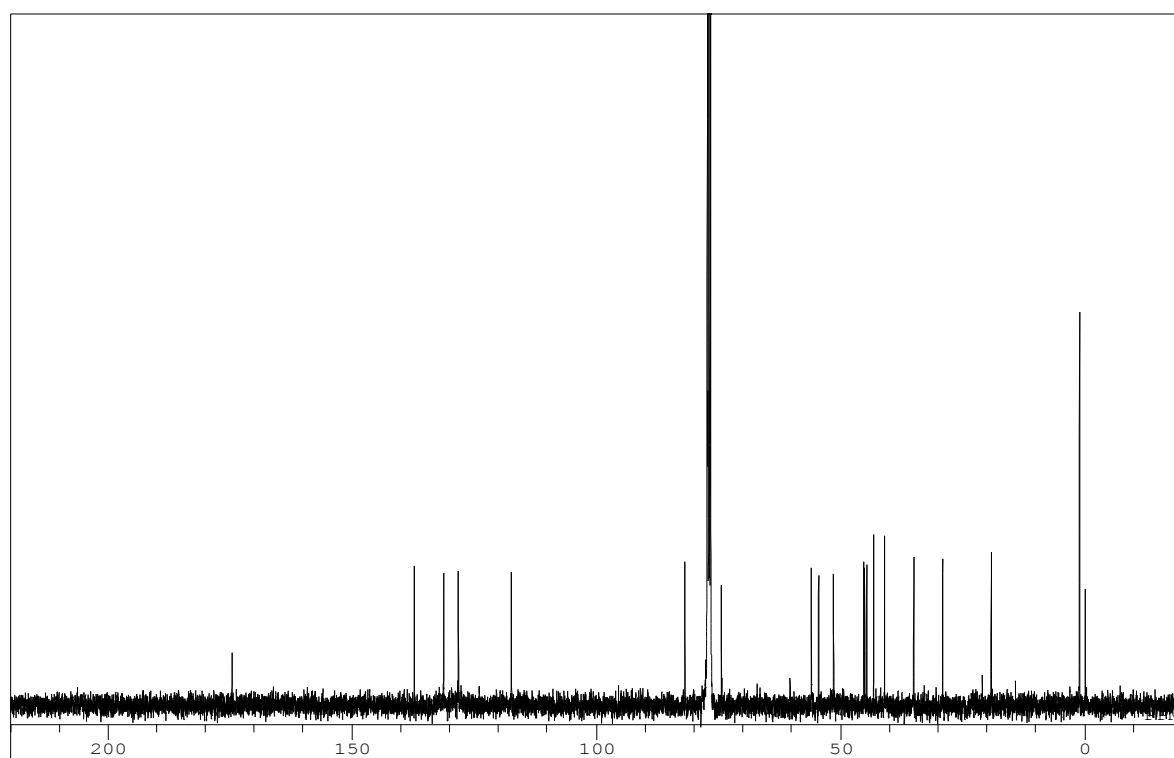
$^{13}\text{C}$  NMR spectrum of compound **26** (100 MHz,  $\text{CDCl}_3$ ).



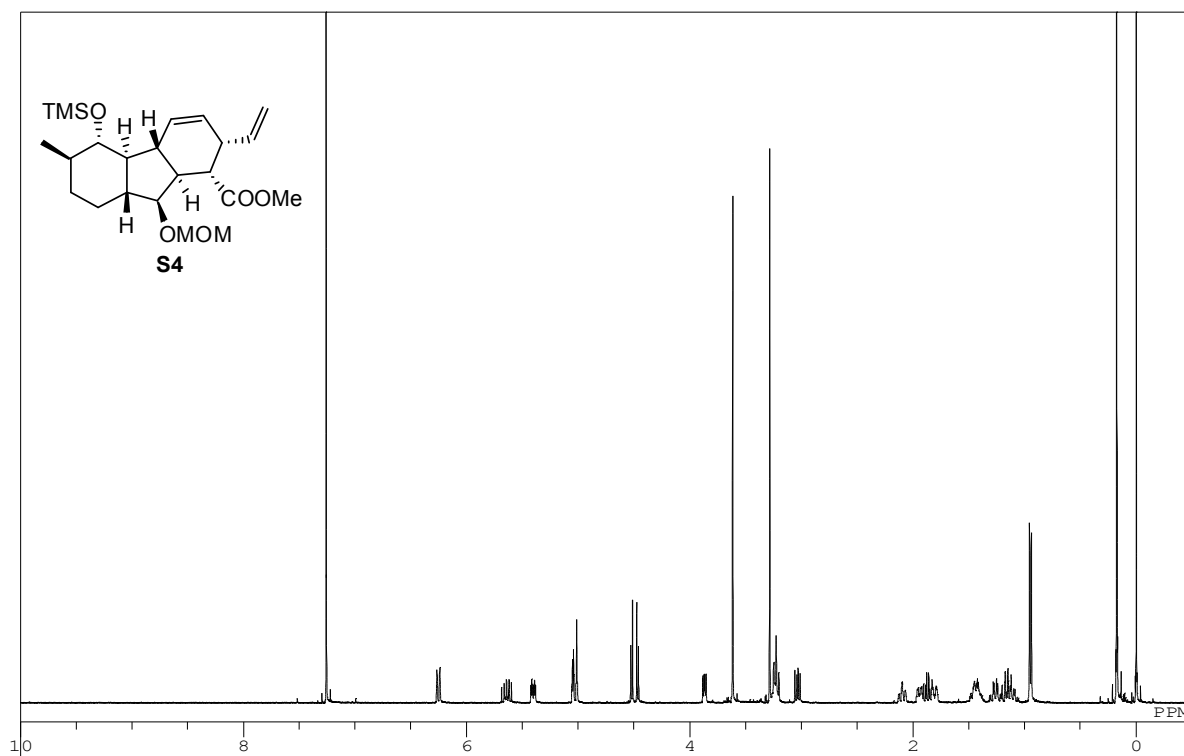
$^1\text{H}$  NMR spectrum of compound **28** (400 MHz,  $\text{CDCl}_3$ ).



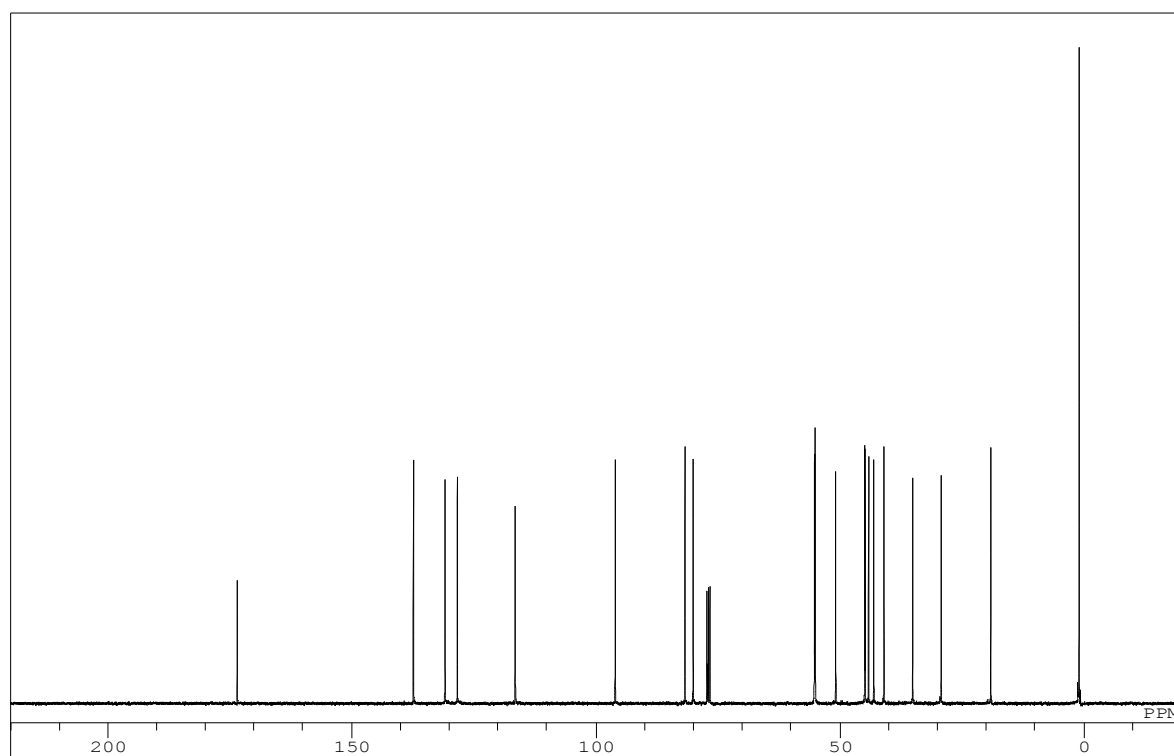
$^{13}\text{C}$  NMR spectrum of compound **28** (100 MHz,  $\text{CDCl}_3$ ).



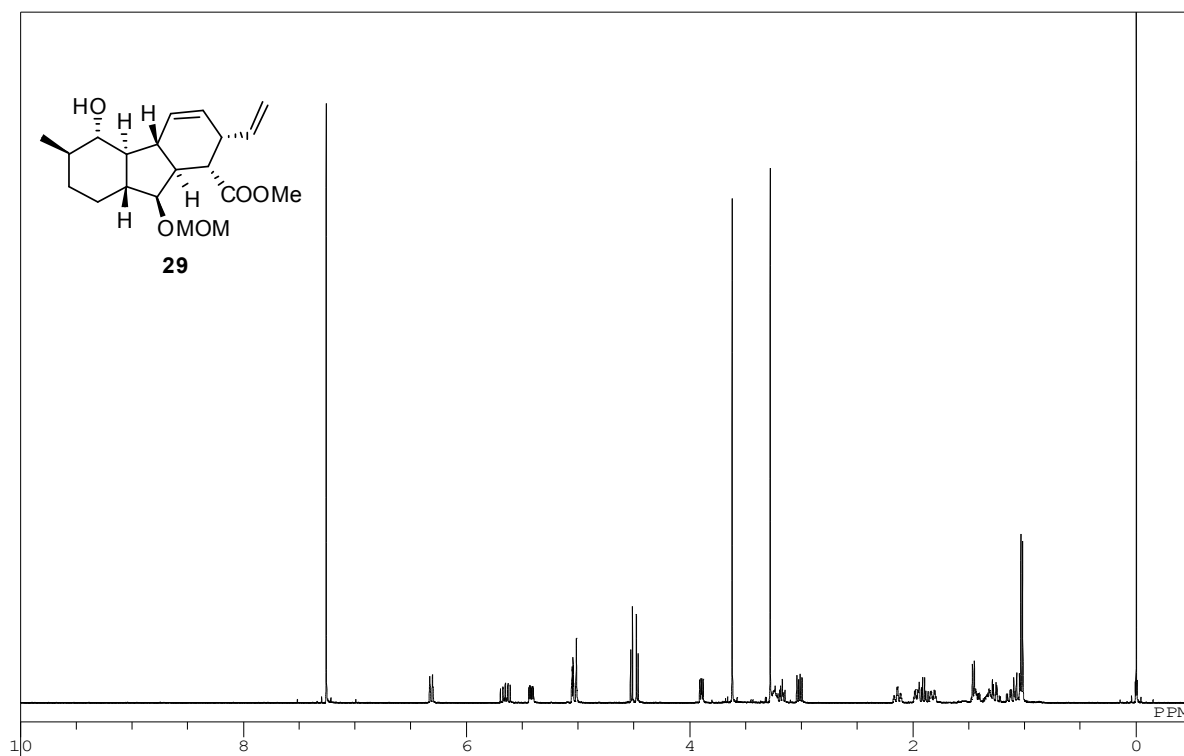
$^1\text{H}$  NMR spectrum of compound **S4** (400 MHz,  $\text{CDCl}_3$ ).



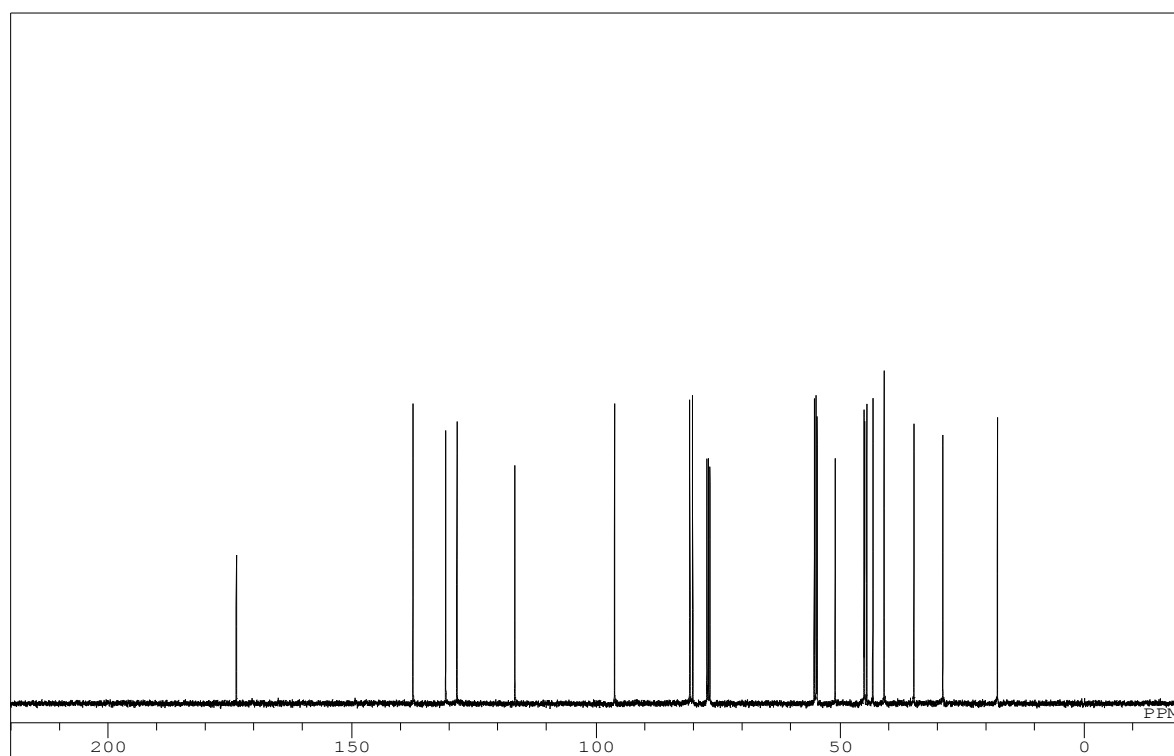
$^{13}\text{C}$  NMR spectrum of compound **S4** (100 MHz,  $\text{CDCl}_3$ ).



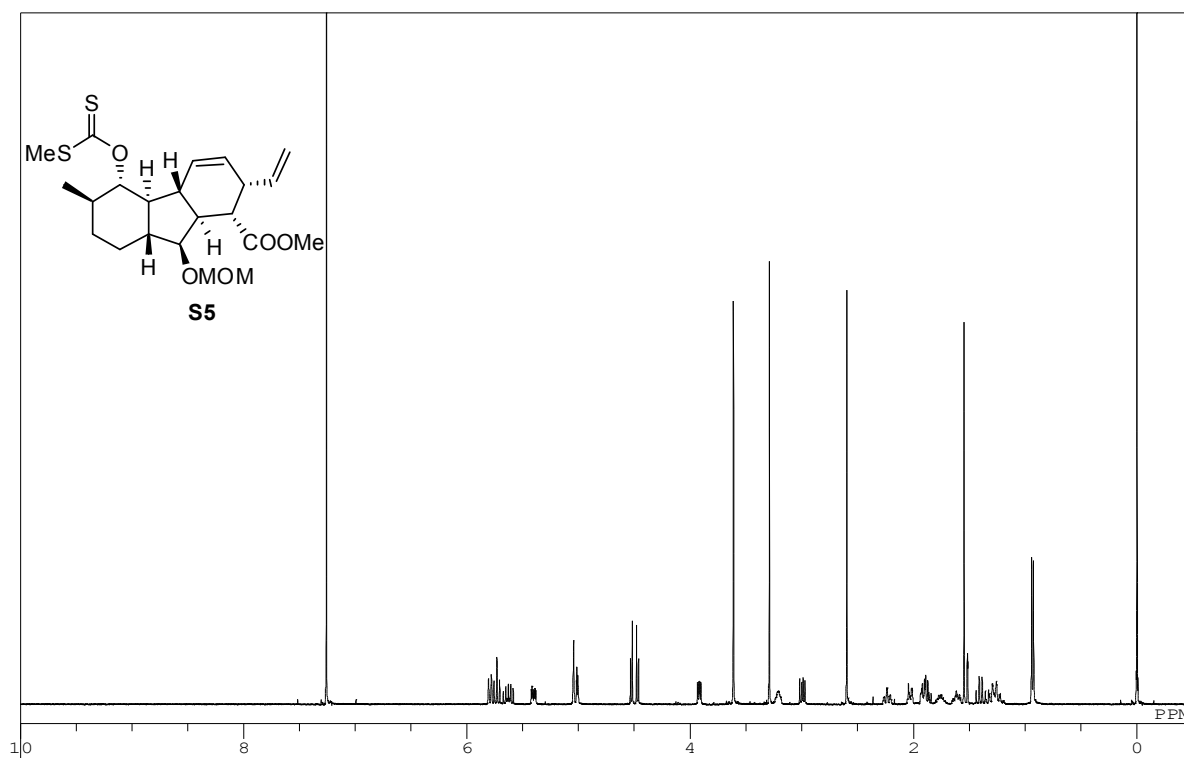
$^1\text{H}$  NMR spectrum of compound **29** (400 MHz,  $\text{CDCl}_3$ ).



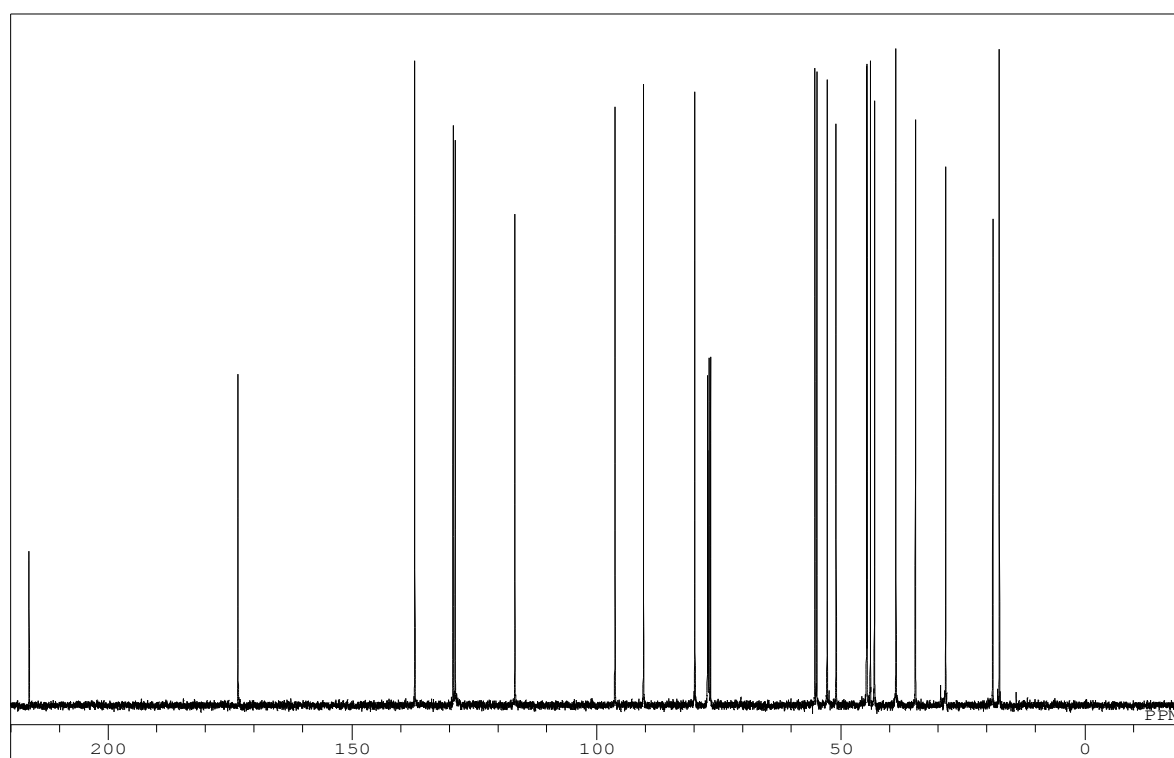
$^{13}\text{C}$  NMR spectrum of compound **29** (100 MHz,  $\text{CDCl}_3$ ).



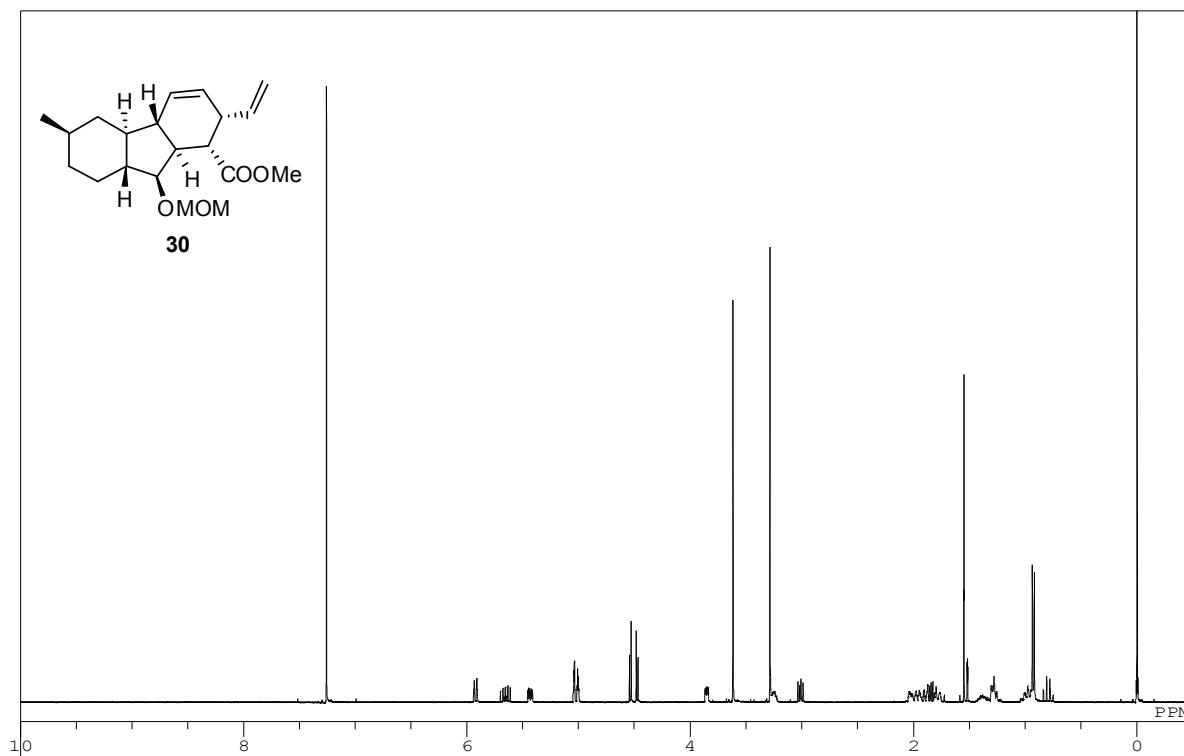
$^1\text{H}$  NMR spectrum of compound **S5** (400 MHz,  $\text{CDCl}_3$ ).



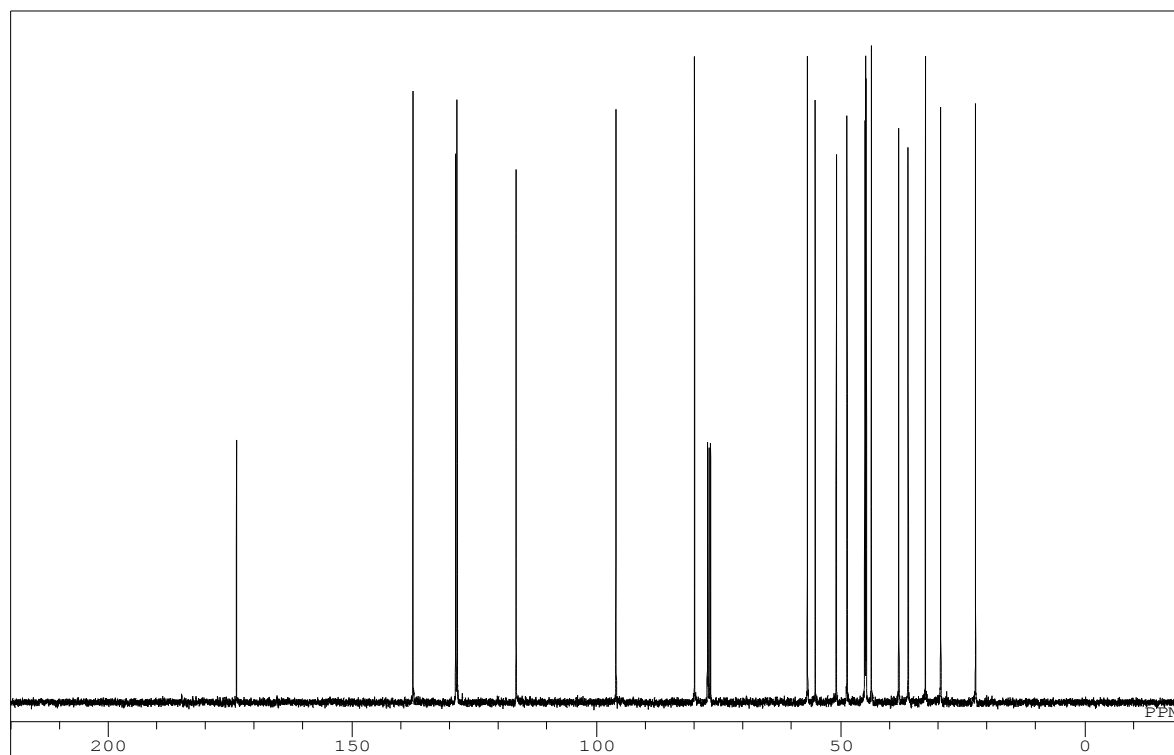
$^{13}\text{C}$  NMR spectrum of compound **S5** (100 MHz,  $\text{CDCl}_3$ ).



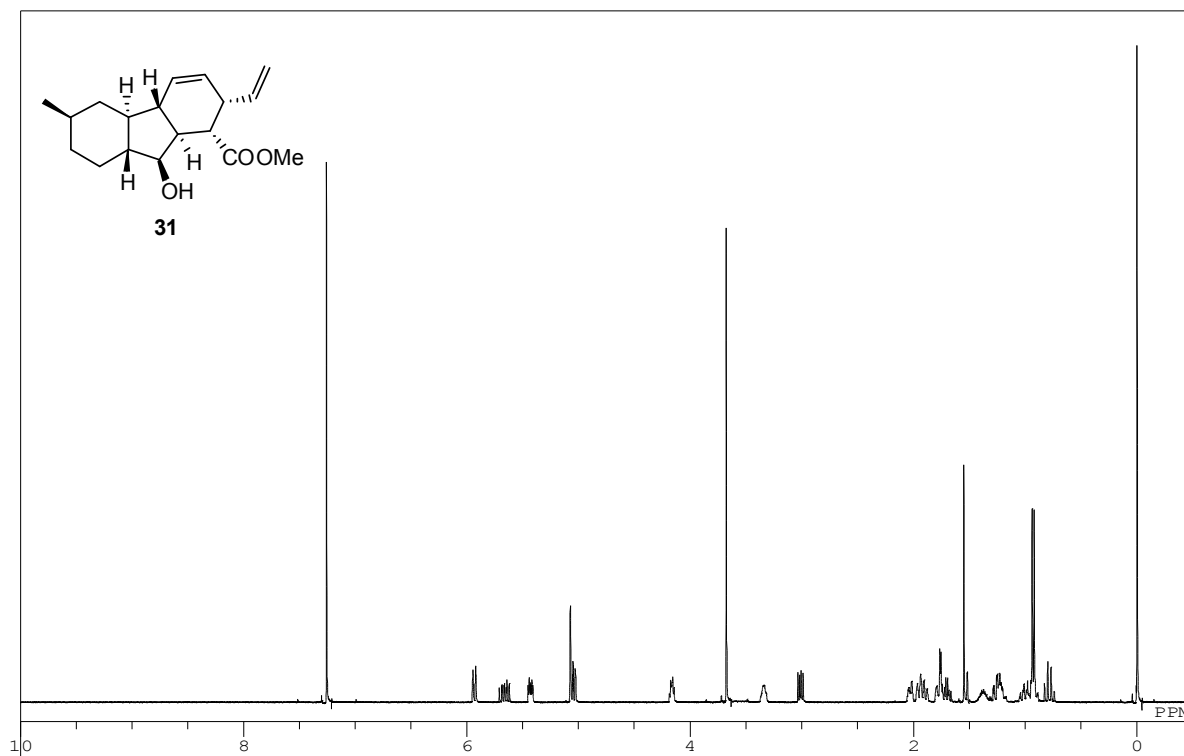
$^1\text{H}$  NMR spectrum of compound **30** (400 MHz,  $\text{CDCl}_3$ ).



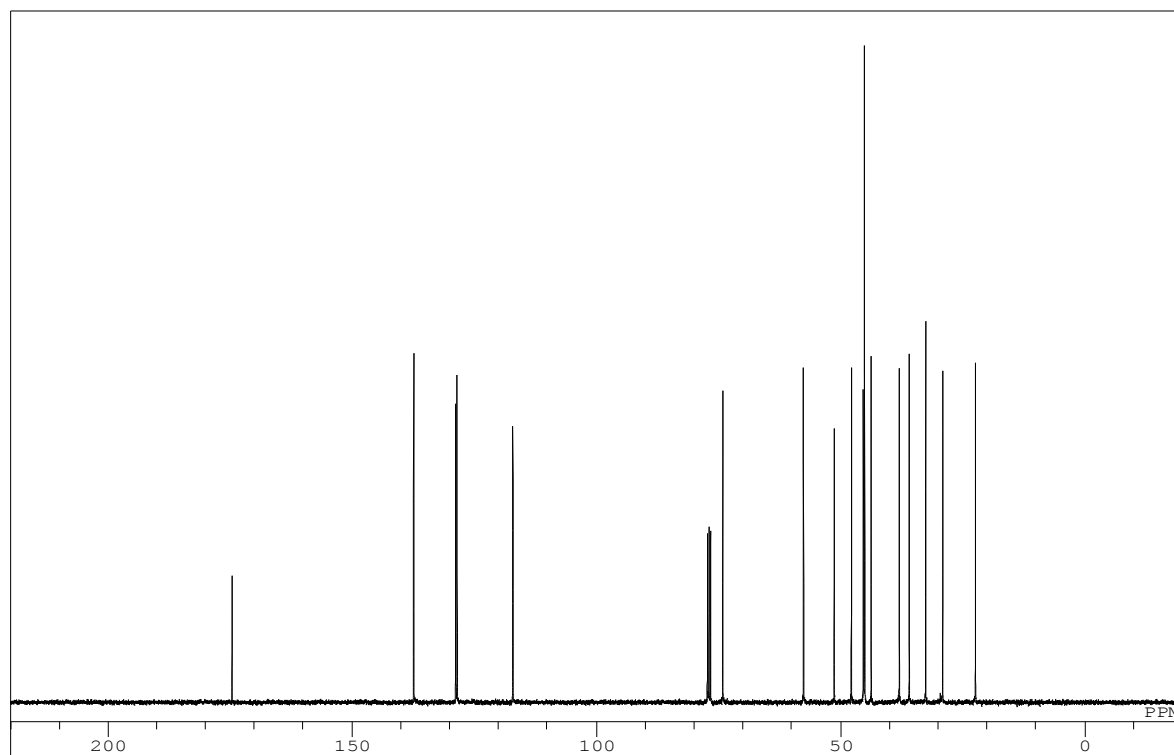
$^{13}\text{C}$  NMR spectrum of compound **30** (100 MHz,  $\text{CDCl}_3$ ).



$^1\text{H}$  NMR spectrum of compound **31** (400 MHz,  $\text{CDCl}_3$ ).

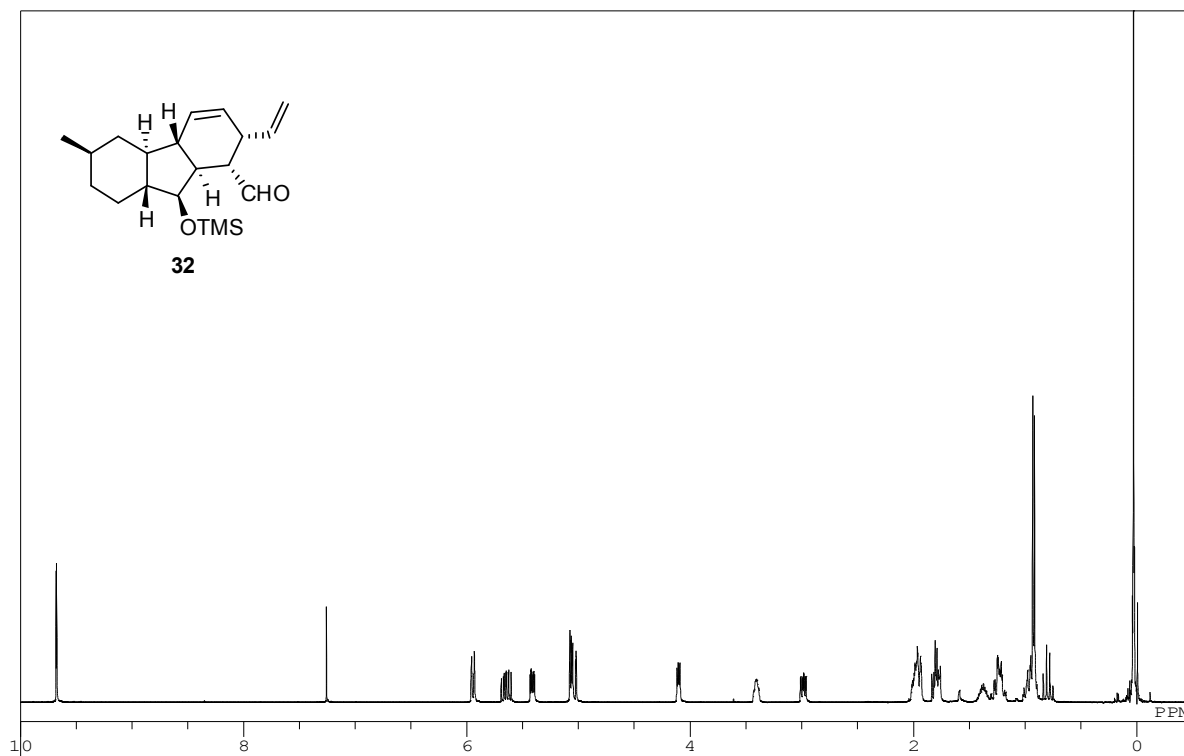


$^{13}\text{C}$  NMR spectrum of compound **31** (100 MHz,  $\text{CDCl}_3$ ).

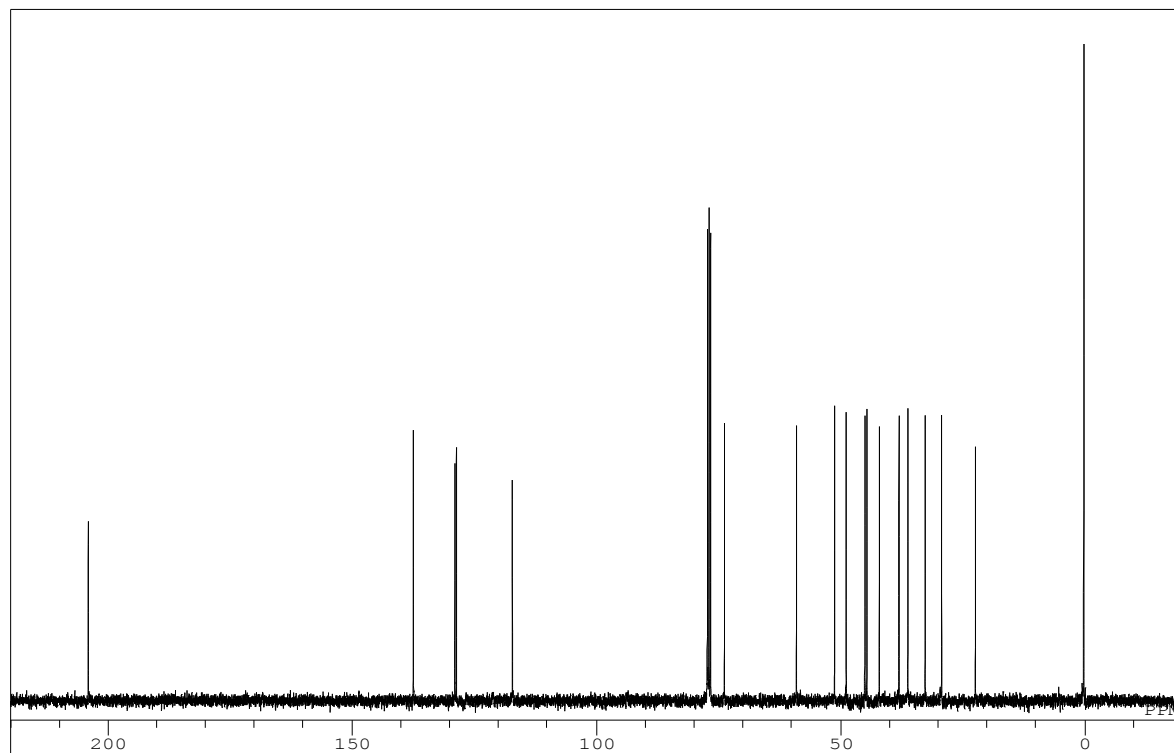




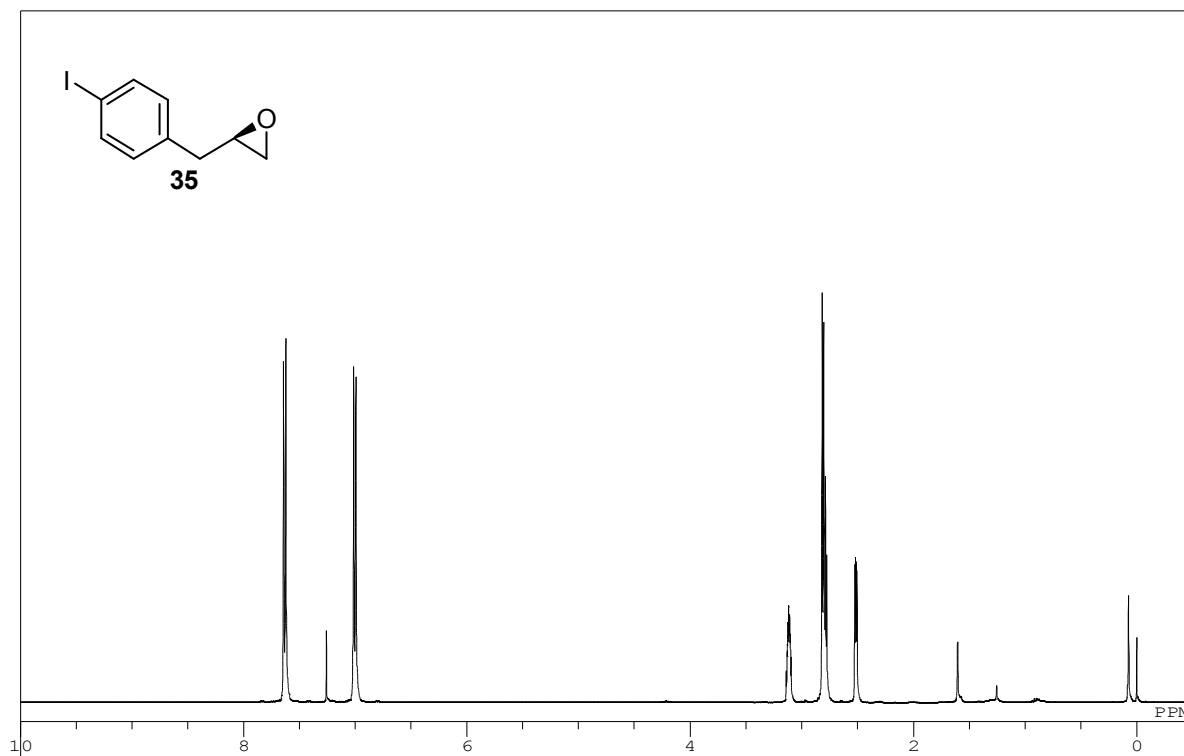
$^1\text{H}$  NMR spectrum of compound **32** (400 MHz,  $\text{CDCl}_3$ ).



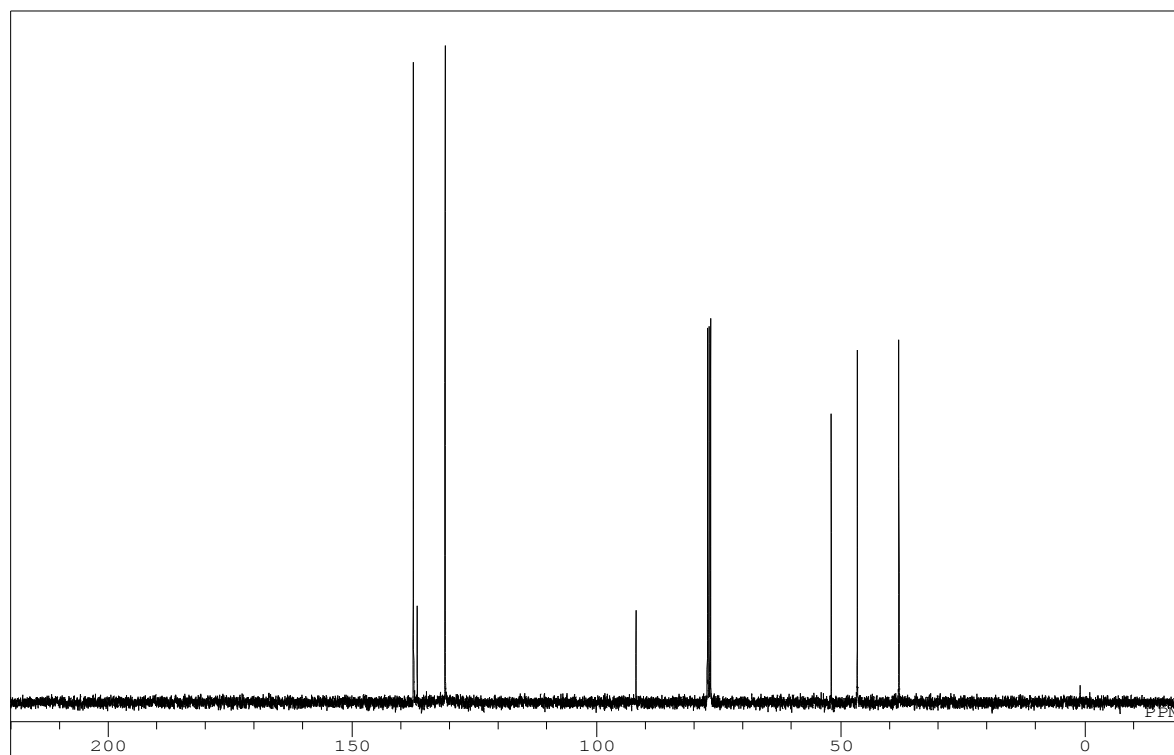
$^{13}\text{C}$  NMR spectrum of compound **32** (100 MHz,  $\text{CDCl}_3$ ).



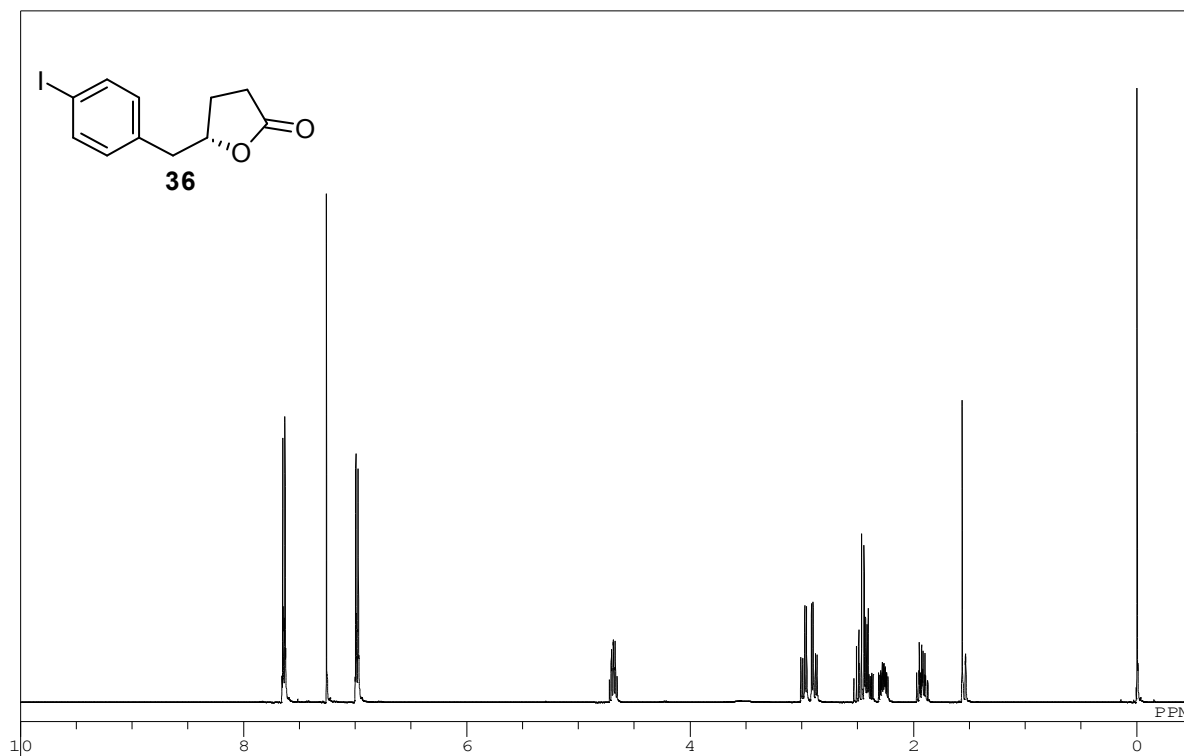
$^1\text{H}$  NMR spectrum of compound **35** (400 MHz,  $\text{CDCl}_3$ ).



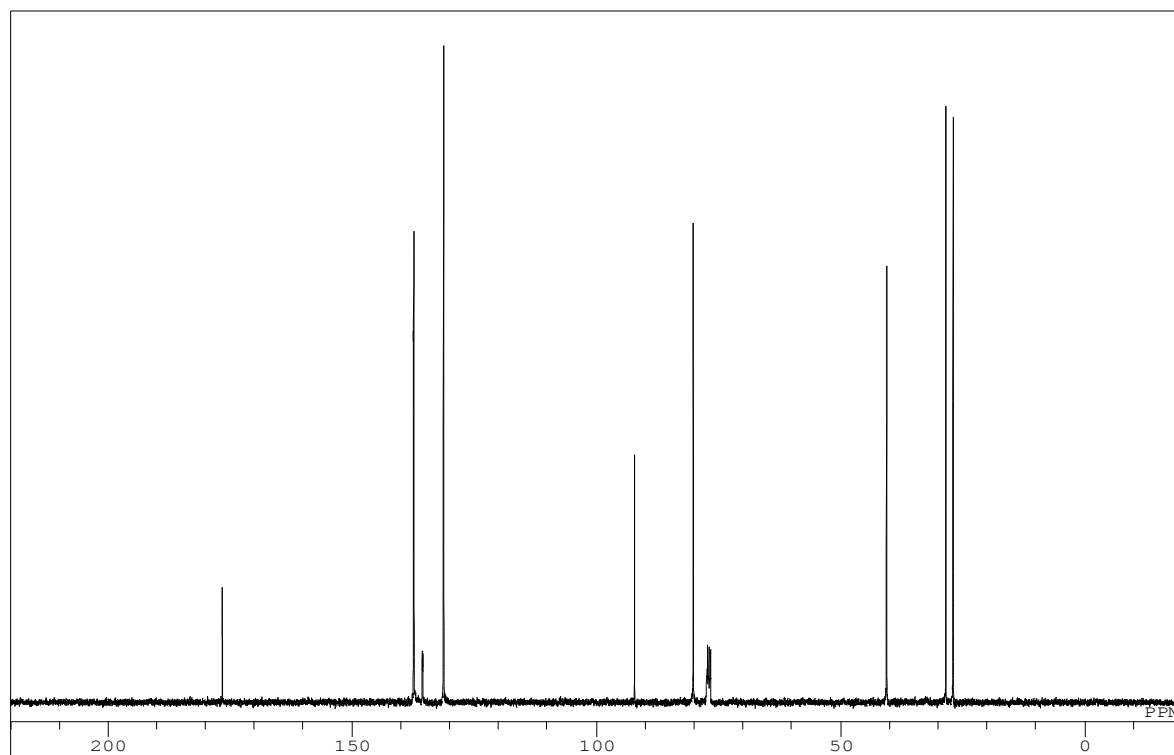
$^{13}\text{C}$  NMR spectrum of compound **35** (100 MHz,  $\text{CDCl}_3$ ).



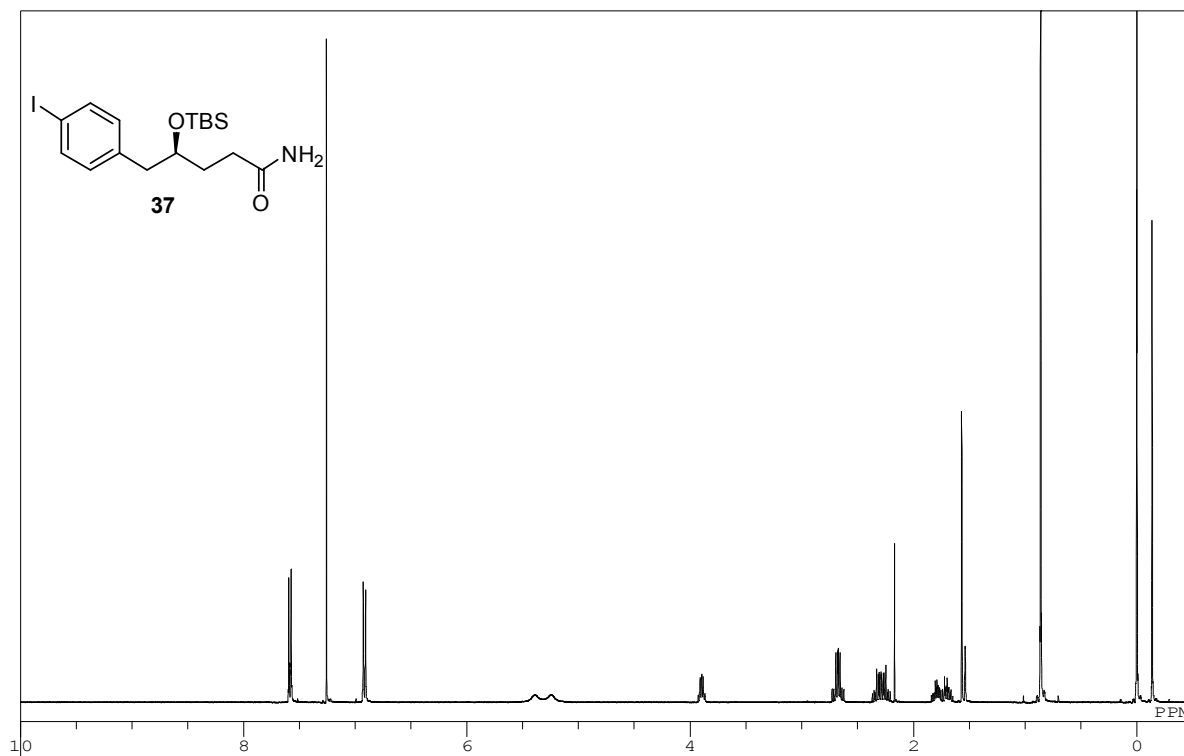
$^1\text{H}$  NMR spectrum of compound **36** (400 MHz,  $\text{CDCl}_3$ ).



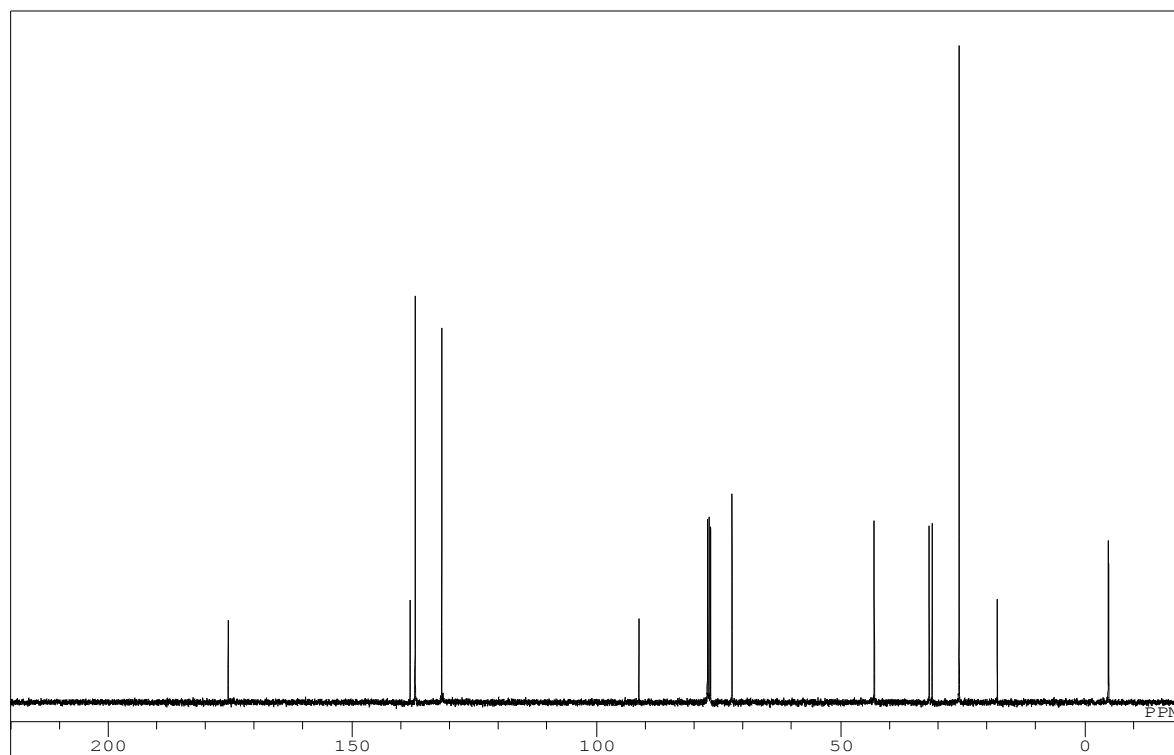
$^{13}\text{C}$  NMR spectrum of compound **36** (100 MHz,  $\text{CDCl}_3$ ).



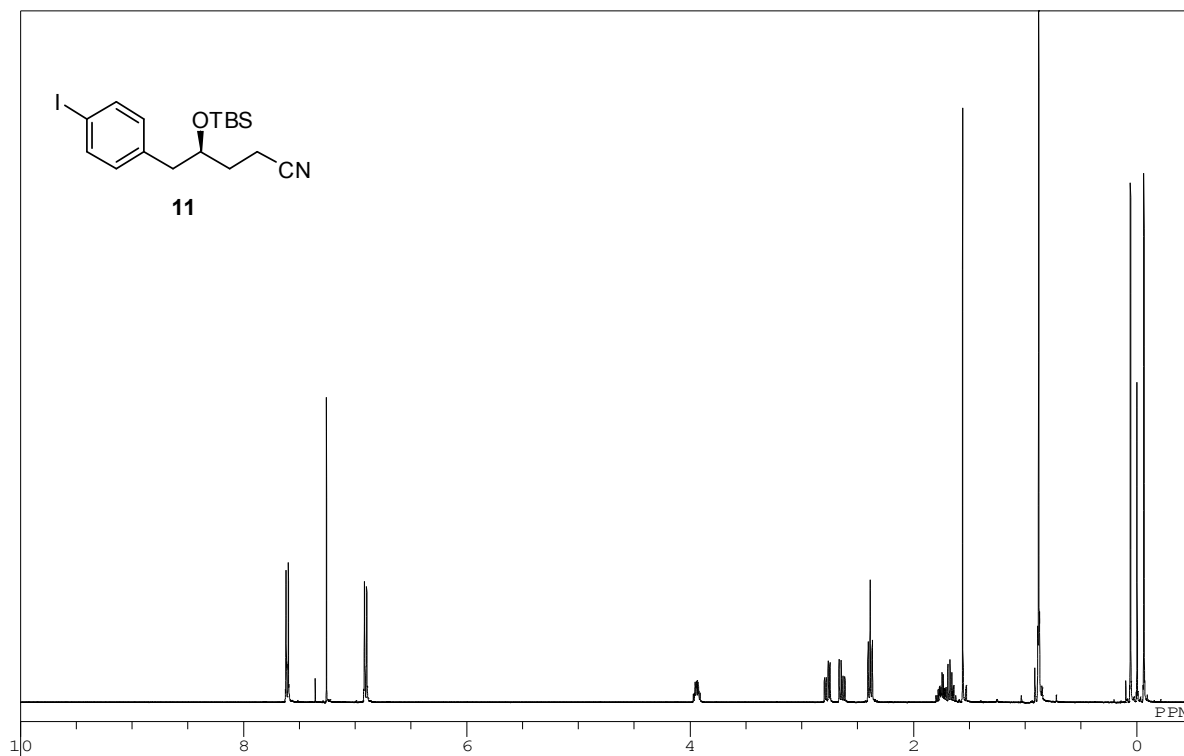
$^1\text{H}$  NMR spectrum of compound **37** (400 MHz,  $\text{CDCl}_3$ ).



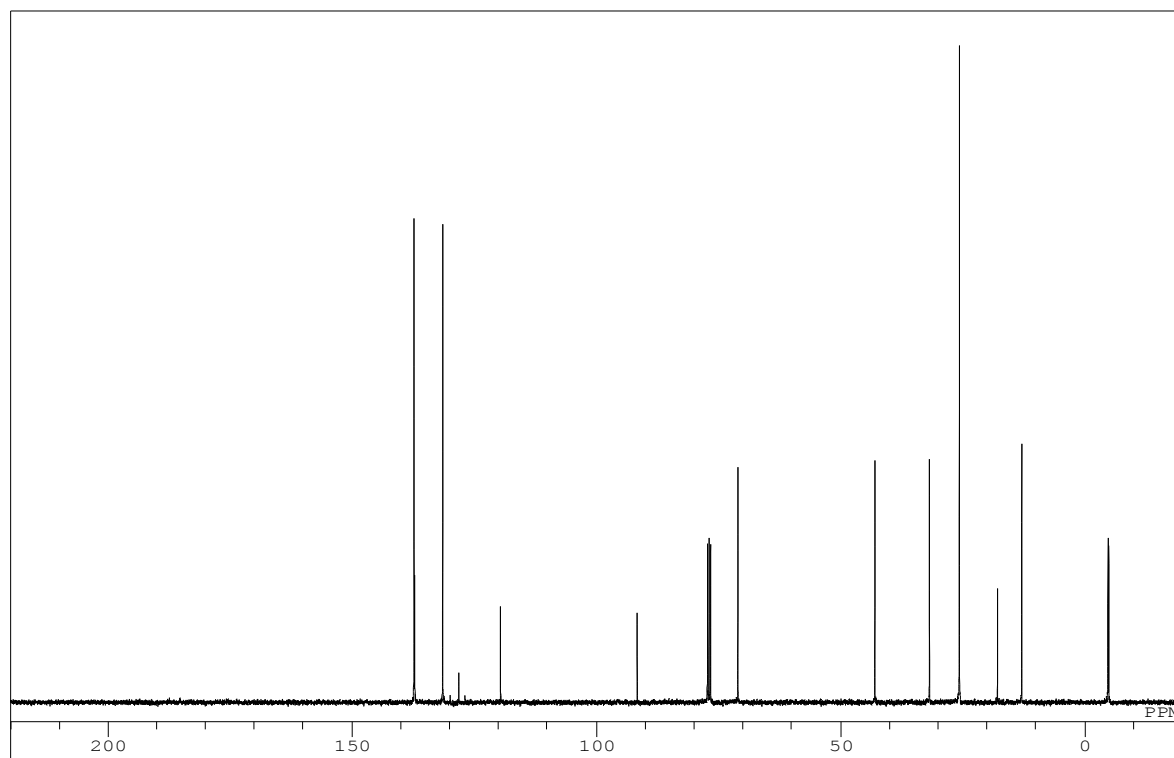
$^{13}\text{C}$  NMR spectrum of compound **37** (100 MHz,  $\text{CDCl}_3$ ).



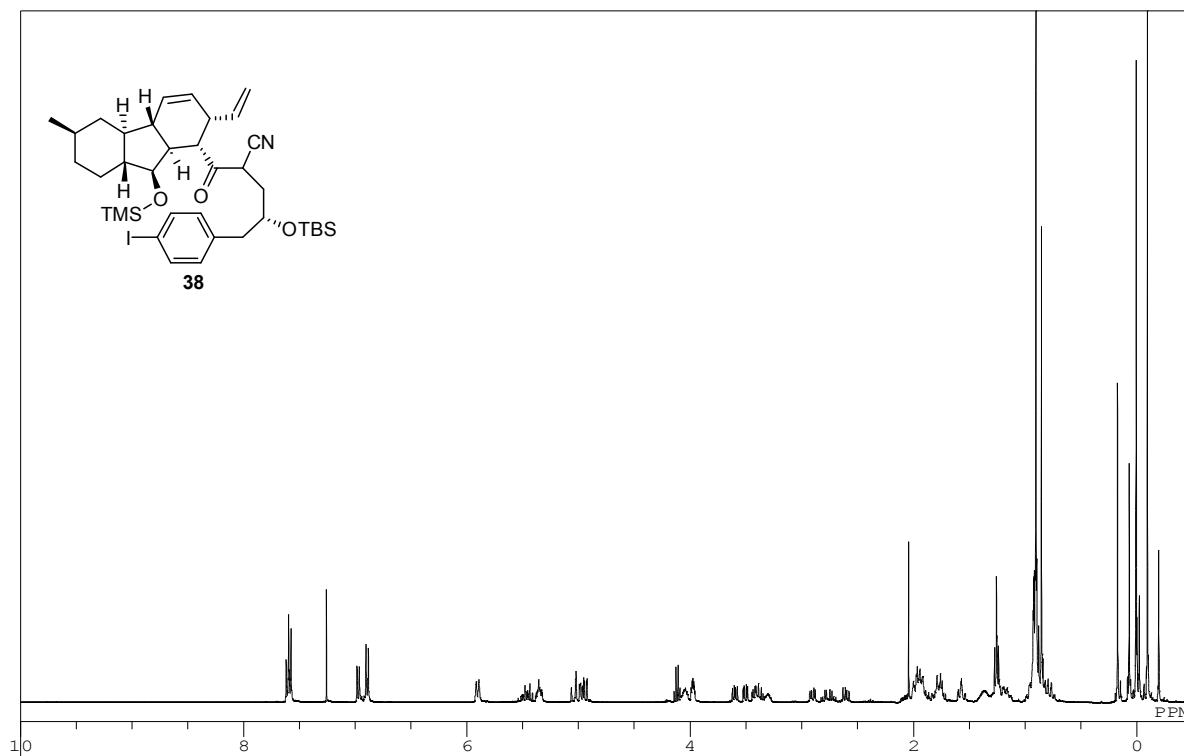
$^1\text{H}$  NMR spectrum of compound **11** (400 MHz,  $\text{CDCl}_3$ ).



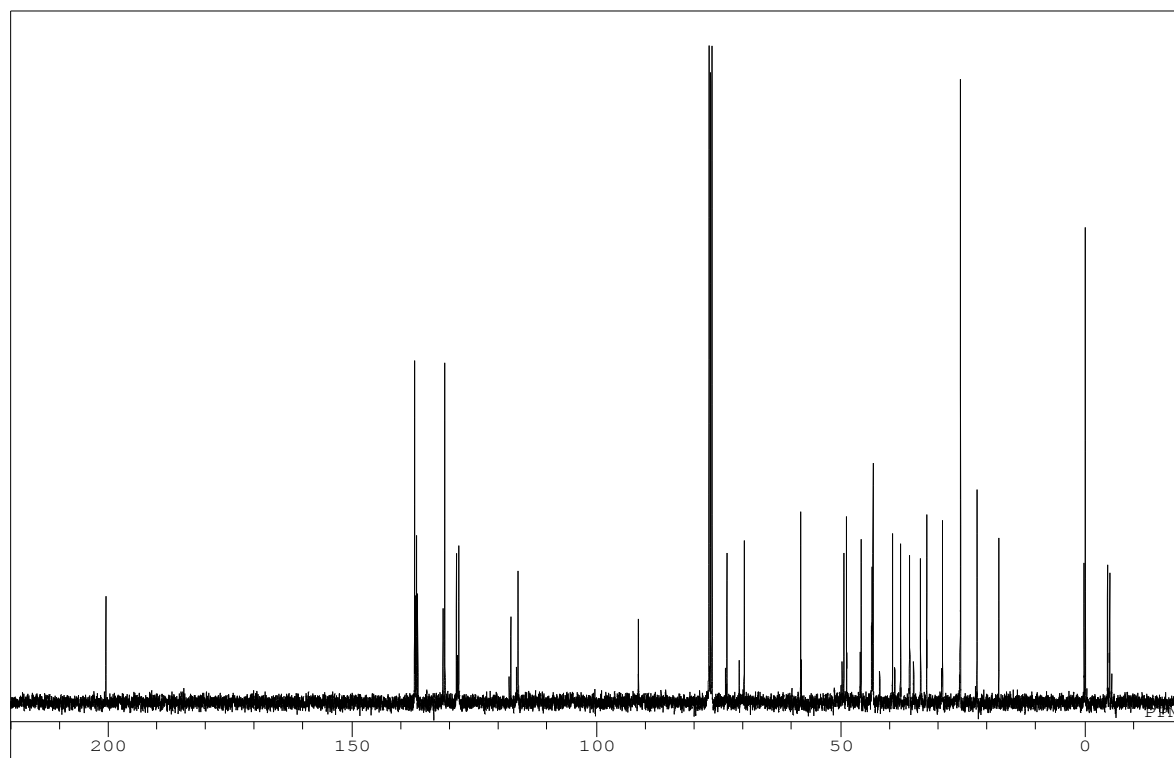
$^{13}\text{C}$  NMR spectrum of compound **11** (100 MHz,  $\text{CDCl}_3$ ).



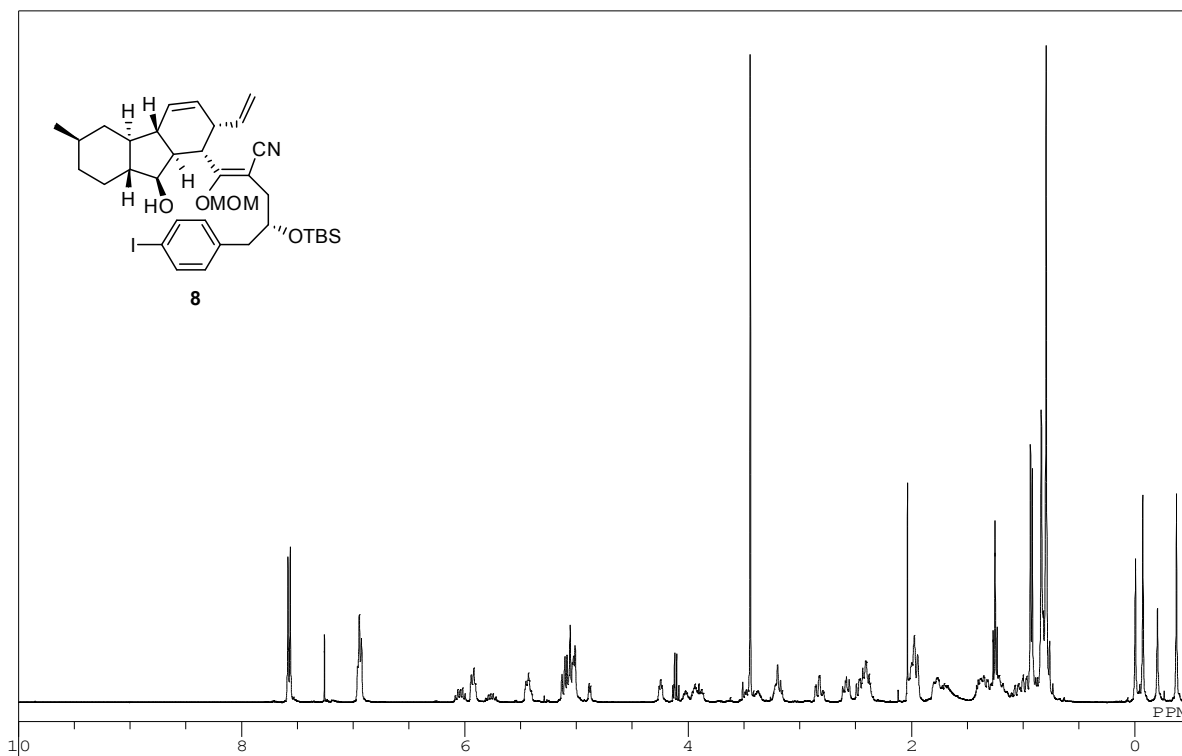
$^1\text{H}$  NMR spectrum of compound **38** (400 MHz,  $\text{CDCl}_3$ ).



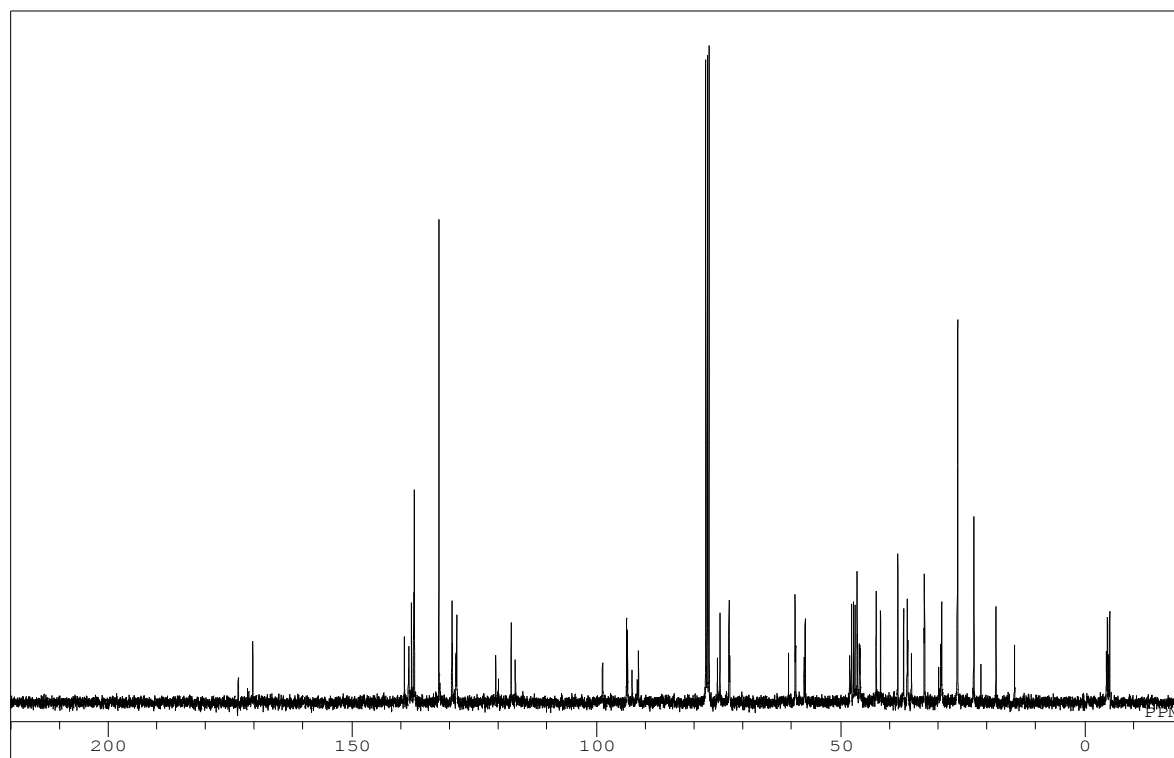
$^{13}\text{C}$  NMR spectrum of compound **38** (100 MHz,  $\text{CDCl}_3$ ).



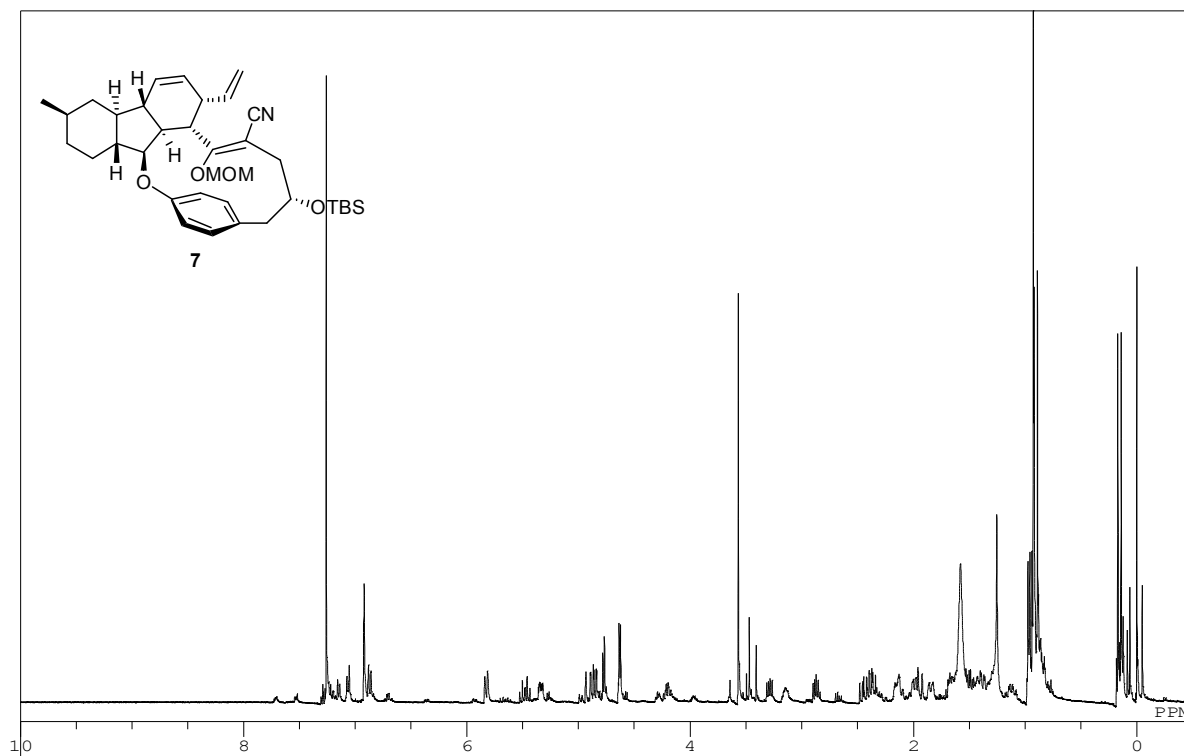
$^1\text{H}$  NMR spectrum of compound **8** (400 MHz,  $\text{CDCl}_3$ ).



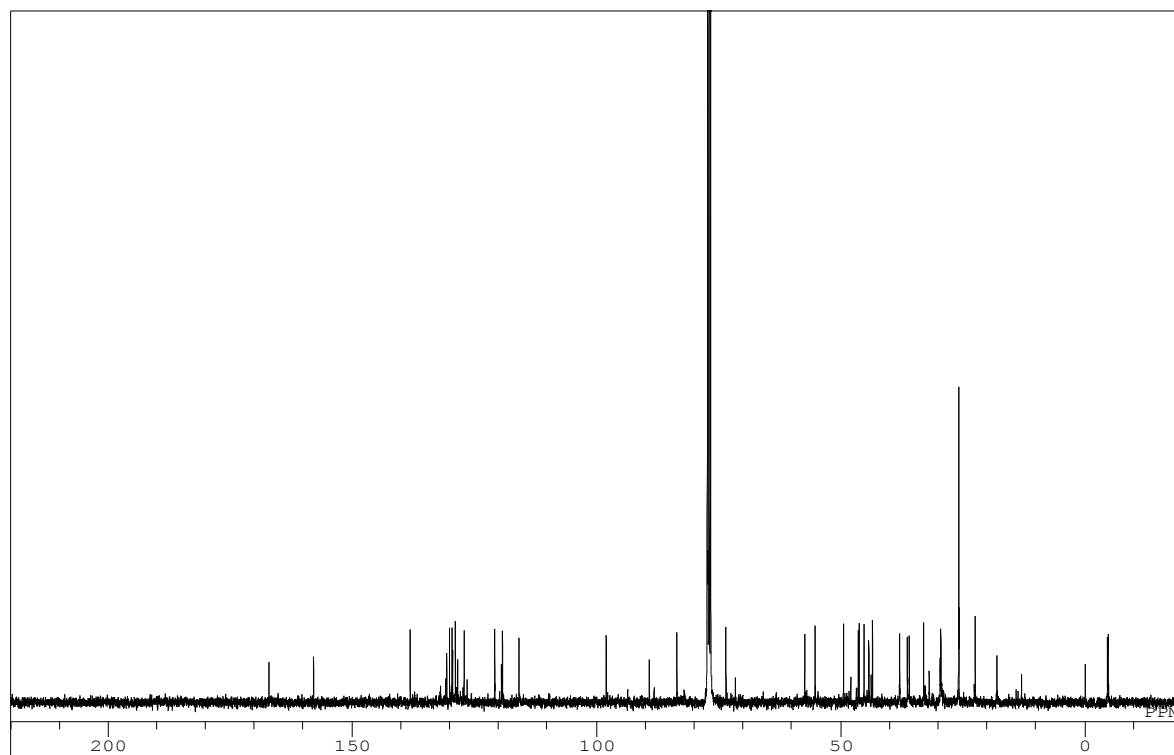
$^{13}\text{C}$  NMR spectrum of compound **8** (100 MHz,  $\text{CDCl}_3$ ).



$^1\text{H}$  NMR spectrum of compound **7** (400 MHz,  $\text{CDCl}_3$ ).

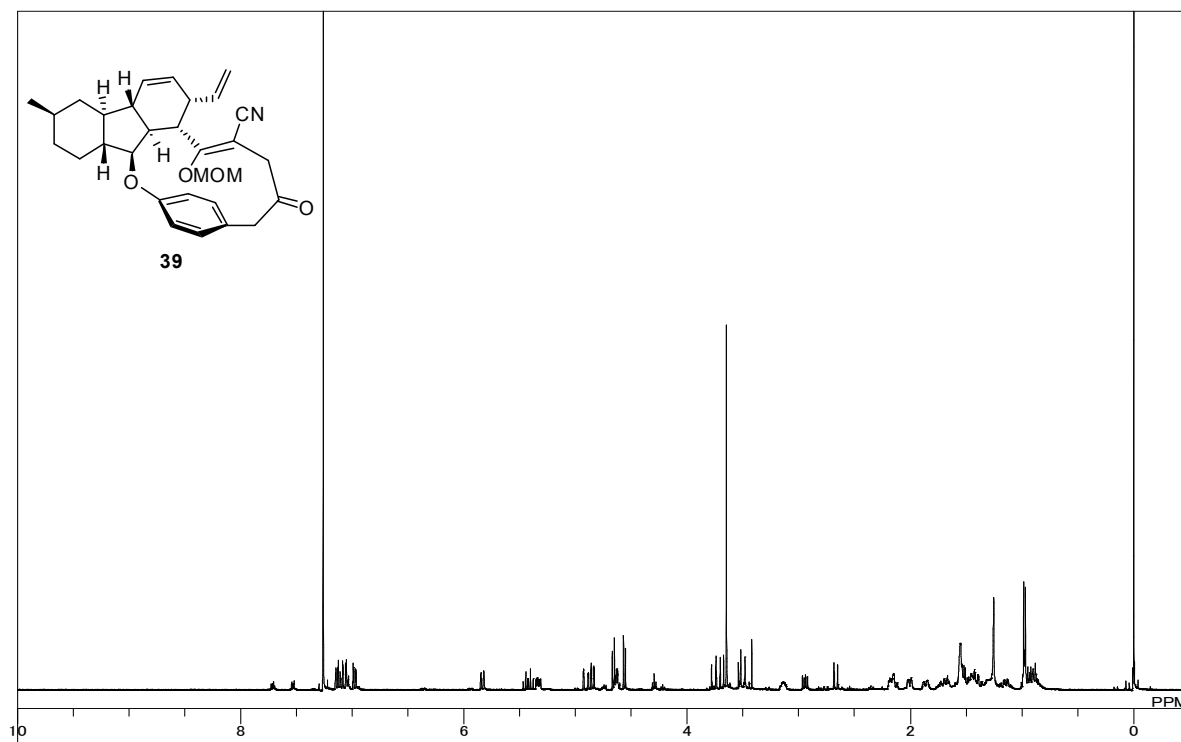


$^{13}\text{C}$  NMR spectrum of compound **7** (100 MHz,  $\text{CDCl}_3$ ).

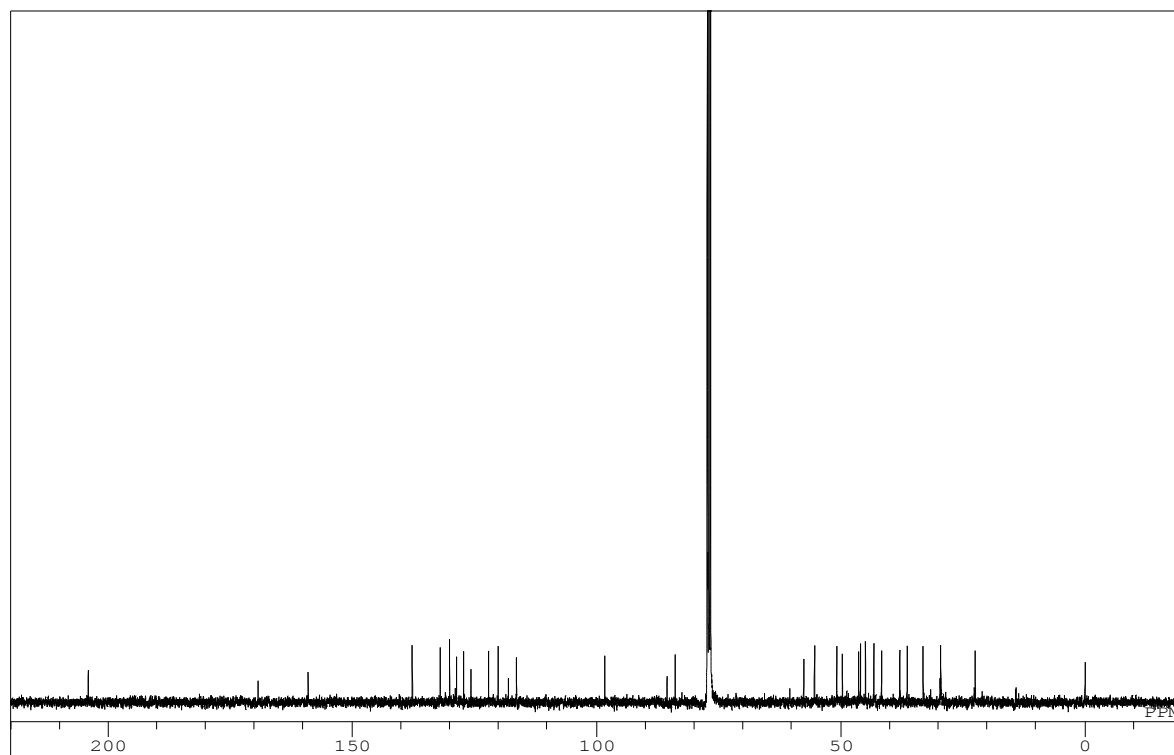




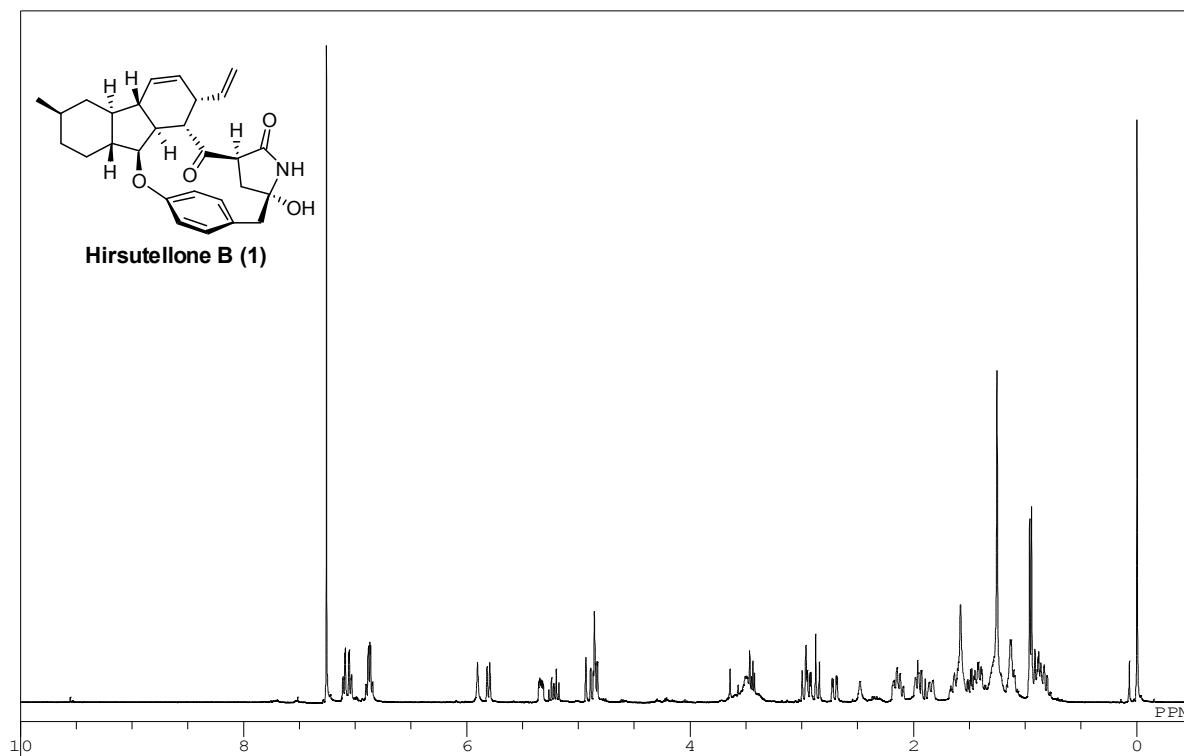
$^1\text{H}$  NMR spectrum of compound **39** (400 MHz,  $\text{CDCl}_3$ ).



$^{13}\text{C}$  NMR spectrum of compound **39** (100 MHz,  $\text{CDCl}_3$ ).



$^1\text{H}$  NMR spectrum of compound **1** (400 MHz,  $\text{CDCl}_3$ ).



$^{13}\text{C}$  NMR spectrum of compound **1** (100 MHz,  $\text{CDCl}_3$ ).

