

**An Alkoxide-Directed Alkyne-Allene Cross-  
Coupling for Stereoselective Synthesis of 1,4-Dienes**

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**SUPPORTING INFORMATION:**

**General.** All reactions were conducted in flame-dried glassware under nitrogen using anhydrous solvents. Toluene and tetrahydrofuran were distilled from sodium/benzophenone ketyl before using. Diethyl ether was used after passing through an activated alumina column.  $\text{Ti}(\text{O}i\text{Pr})_4$  was used after distillation of the commercially available reagent.  $\text{ClTi}(\text{O}i\text{Pr})_3$  was purchased as a 1M solution in hexanes from Aldrich® and was used without further analysis or purification. All other commercially available reagents were used as received.

$^1\text{H}$  NMR data were recorded at 500 MHz or 400 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument.  $^1\text{H}$  NMR chemical shifts are reported relative to residual  $\text{CHCl}_3$  (7.26 ppm).  $^{13}\text{C}$  NMR data were recorded at 126 MHz or 100 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument.  $^{13}\text{C}$  chemical shifts are reported relative to the central line of  $\text{CDCl}_3$  (77.00 ppm). Infrared spectra were recorded using a Midac Spectrometer M-series. Low resolution mass spectrometry (LRMS) was performed on a Waters Micromass® ZQ™ instrument using electrospray ionization (EI). High resolution mass spectrometry (HRMS) was performed on a 9.4T Bruker Qe FT-ICR instrument using EI. Optical rotations were measured on Perkin Elmer Model 341 polarimeter using a 1 mL capacity micro cell with a 10 cm path length.

Chromatographic purifications were performed using 60Å, 35-75µm particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Semi-preparative and analytical HPLC normal phase separations were performed using an HPLC system composed of two Dynamax SD-1 pumps, a Rheodyne injector and a Dynamax UV-1 absorbance detector.

All allenes are known compounds prepared according to the published procedures:

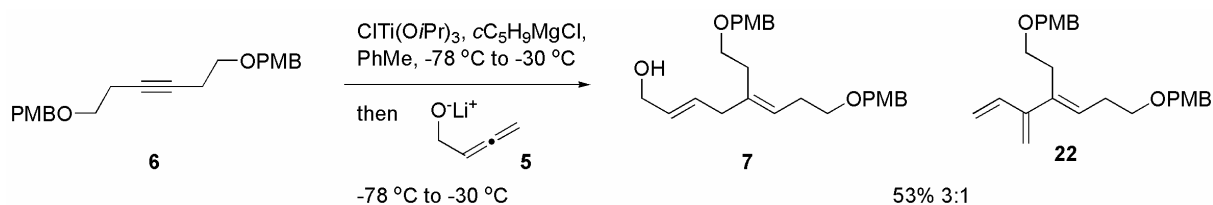
**Allene 5.** Molander, G. A.; Cormier, E. P.; *J. Org. Chem.* **2005**, *7*, 2622 - 2626.

**Allene 8.** Djahanbini, D.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3441-3452.

**Allene 10.** Xu, D.; Lu, Z.; Li, Z.; Ma, S.; *Tetrahedron*, **2004**, *60*, 11879-11887.

**Allene 12.** Hormuth, S.; Reissig, H. *J. Org. Chem.* **1994**, *59*, 67-73.

**Allene 14.** Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837-2847.

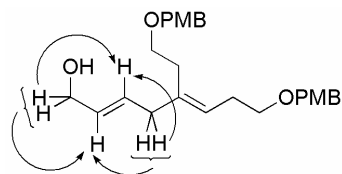


**Synthesis of 1,4-Diene 7 and Triene 22.** To a  $-78\text{ }^\circ\text{C}$  solution of alkyne **6**<sup>1</sup> (266 mg, 0.75 mmol) in 5.0 mL of PhMe was added 1.50 mL of  $\text{ClTi}(\text{O}i\text{Pr})_3$  (1.0M in hexanes, 1.50 mmol) and 1.53 mL of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.96M in  $\text{Et}_2\text{O}$ , 3.00 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to  $-30\text{ }^\circ\text{C}$  over 1 hr. The reaction mixture was stirred at  $-30\text{ }^\circ\text{C}$  for 1 hr and then cooled to  $-78\text{ }^\circ\text{C}$ . To a separate  $-78\text{ }^\circ\text{C}$  solution of allene **5** (105 mg, 1.50 mmol) in 1.0 mL PhMe was added 610  $\mu\text{L}$  of  $n\text{BuLi}$  (2.45M in hexanes, 1.50 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78\text{ }^\circ\text{C}$  titanium solution dropwise via cannula. After warming slowly to  $-30\text{ }^\circ\text{C}$  over 1.5 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before extracting with  $\text{EtOAc}$  (3 x 15 mL). The combined organic layer was washed with sat.  $\text{NaHCO}_3$  solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Flash column chromatography (10 %  $\text{EtOAc}$ /hexanes, then 50

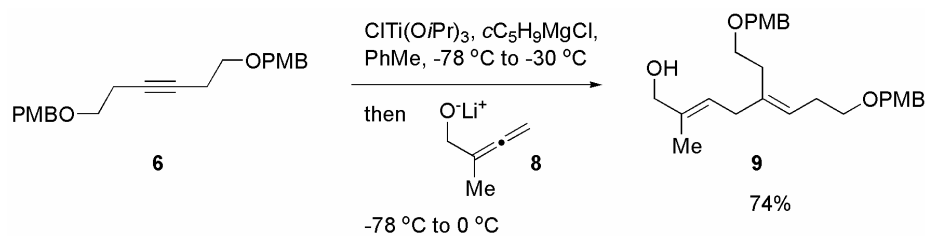
% EtOAc/hexanes) of the crude material (7:22 = 3:1 by  $^1\text{H}$  NMR) provided 128 mg (40 %) of diene **7** and 40 mg (13%) of triene **22** as clear, colorless oils.

**(2E,5Z)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)octa-2,5-dien-1-ol, 7.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.23 (m, 4H), 6.88-6.86 (m, 4H), 5.64-5.63 (m, 2H), 5.26 (t,  $J = 7.3$  Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 4.09 (br s, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.44 (t,  $J = 7.3$ , 2H), 3.42 (t,  $J = 6.9$  Hz, 2H), 2.75 (br s, 2H), 2.37-2.32 (m, 4H), 1.25 (t,  $J = 6.0$ , 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 136.2, 130.9, 130.6, 130.5, 129.2, 129.1, 123.9, 113.7, 72.4, 69.7, 68.4, 63.6, 55.2, 40.3, 30.8, 28.6; IR (thin film, NaCl) 3426, 2934, 2858, 1613, 1513, 1464, 1361, 1248, 1173, 1093, 1035, 820  $\text{cm}^{-1}$ ; LRMS (EI, Na) calcd for  $\text{C}_{26}\text{H}_{34}\text{O}_5\text{Na}$ , 449.24  $m/z$  (M + Na); observed, 449.4 (M + Na) $^+$   $m/z$ .

**Observed nOe enhancements for structure determination:**



**(3E)-1-(4-methoxybenzyloxy)-4-(2-(4-methoxybenzyloxy)ethyl)-5-vinyl-3,5-hexadiene, 22.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.23 (m, 4H), 6.88-6.85 (m, 4H), 6.37 (dd,  $J = 17.3, 10.7$  Hz, 1H), 5.51 (t,  $J = 6.9$  Hz, 1H), 5.24 (d,  $J = 17.3$  Hz, 1H), 5.10 (d,  $J = 10.4$  Hz, H), 5.06 (s, 1H), 4.97 (s, 1H), 4.43 (s, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.47 (t,  $J = 7.3$  Hz, 2H), 3.42 (t,  $J = 7.3$  Hz, 2H), 2.58 (t,  $J = 7.3$  Hz, 2H), 2.46 (dt,  $J = 13.9, 7.3$  Hz, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.09, 159.05, 149.2, 137.8, 136.7, 130.63, 130.57, 129.2, 129.1, 127.4, 116.2, 114.2, 113.72, 113.69, 72.50, 72.48, 69.5, 68.7, 55.2, 30.1, 28.9; IR (thin film, NaCl) 2935, 2857, 1613, 1586, 1513, 1464, 1361, 1302, 1249, 1173, 1097, 1035, 821  $\text{cm}^{-1}$ ; LRMS (EI, Na) calcd for  $\text{C}_{26}\text{H}_{32}\text{O}_4\text{Na}$ , 431.23  $m/z$  (M + Na); observed, 431.3 (M + Na) $^+$   $m/z$ .

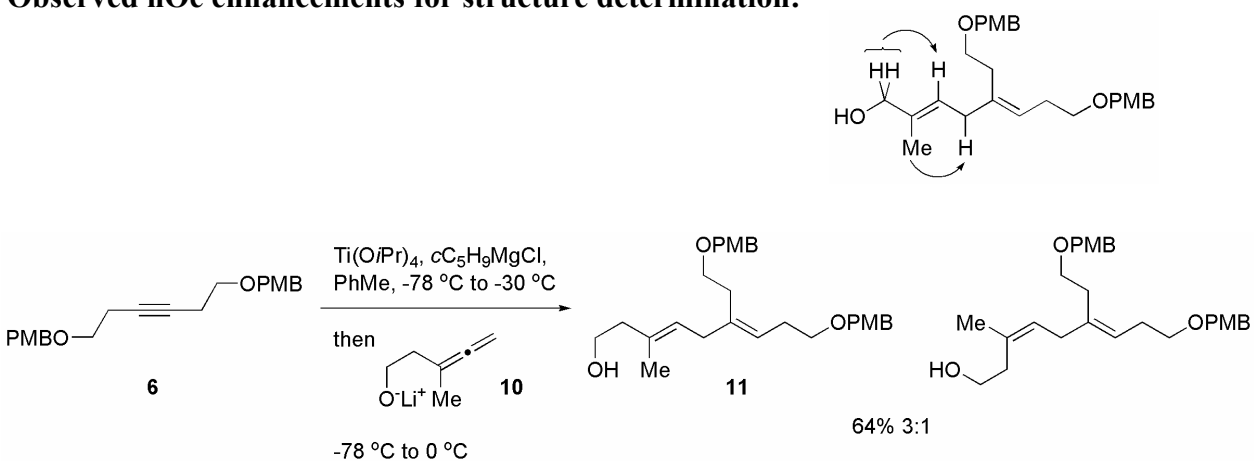


**Synthesis of 1,4-Diene 9.** To a  $-78\text{ }^\circ\text{C}$  solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 850  $\mu\text{L}$  of  $\text{ClTi(OiPr)}_3$  (1.0M in hexanes, 0.85 mmol) and 860  $\mu\text{L}$  of  $\text{cC}_5\text{H}_9\text{MgCl}$  (1.96M in  $\text{Et}_2\text{O}$ , 1.69 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to  $-30\text{ }^\circ\text{C}$  over 1 hr. The reaction mixture was stirred at  $-30\text{ }^\circ\text{C}$  for 1 hr and then cooled to  $-78\text{ }^\circ\text{C}$ . To a separate  $-78\text{ }^\circ\text{C}$  solution of allene **8**<sup>2</sup> (69 mg, 0.39 mmol) in 1.0 mL PhMe was added 160  $\mu\text{L}$  of *n*BuLi (2.45M in hexanes, 0.39 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78\text{ }^\circ\text{C}$  titanium solution dropwise via cannula. After warming slowly to  $0\text{ }^\circ\text{C}$  over 2 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before extracting with EtOAc (3 x 15 mL). The combined organic layer was washed with sat.  $\text{NaHCO}_3$  solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Flash column chromatography of the crude material (20 % EtOAc/hexanes, then 50 % EtOAc/hexanes) provided 127 mg (74 %) of diene **9** as a clear, colorless oil. A small portion was further purified by HPLC [EtOAc/hexanes: gradient from 35 % to 55 % (0-20 min, 25 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] to obtain a sample for analytical characterization.

**(2E,5Z)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-2-methylocta-2,5-dien-1-ol, 9.**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.23 (m, 4H), 6.89-6.85 (m, 4H), 5.42-5.37 (m, 1H), 5.24 (t,  $J = 7.1\text{ Hz}$ , 1H), 4.42 (s, 2H), 4.41 (s, 2H), 4.00 (d,  $J = 5.8\text{ Hz}$ , 2H),

3.80 (s, 3H), 3.80 (s, 3H), 3.46-3.39 (m, 4H), 2.75 (d,  $J = 7.3$  Hz, 2H), 2.34 (dt,  $J = 14.7, 7.6$  Hz, 2H), 2.33 (t,  $J = 7.3$  Hz, 2H), 1.64 (s, 3H), 1.34 (t,  $J = 6.1$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 136.6, 136.0, 130.6, 130.5, 129.21, 129.16, 123.8, 123.1, 113.7, 77.2, 72.5, 69.8, 68.8, 68.6, 55.2, 35.7, 31.1, 28.6, 13.6; IR (thin film, NaCl) 3433, 2907, 2857, 1613, 1513, 1464, 1360, 1302, 1173, 1093, 1035, 802  $\text{cm}^{-1}$ ; LRMS (EI, Na) calcd for  $\text{C}_{27}\text{H}_{36}\text{O}_5\text{Na}$ , 463.26  $m/z$  ( $\text{M} + \text{Na}$ ); observed, 463.3 ( $\text{M} + \text{Na}$ ) $^+$   $m/z$ .

**Observed nOe enhancements for structure determination:**

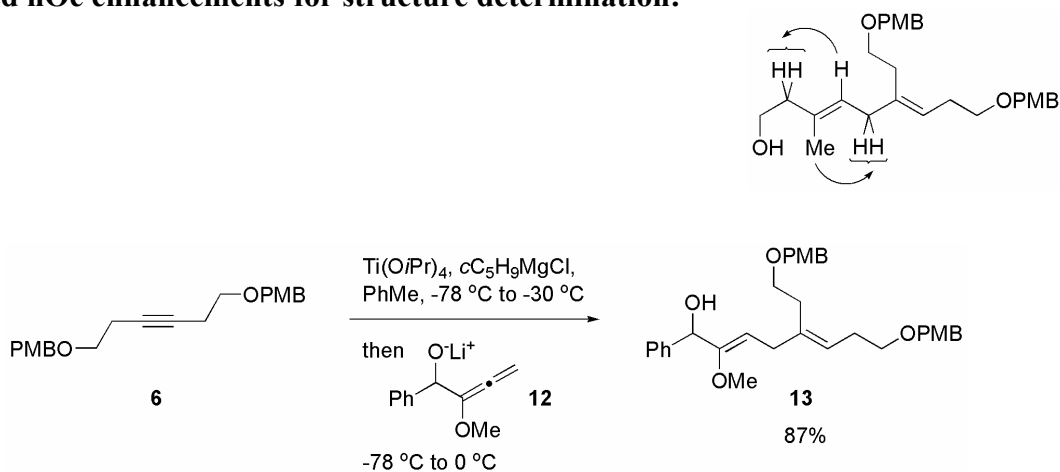


**Synthesis of 1,4-Diene 11.** To a  $-78$  °C solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 250  $\mu\text{L}$  of  $\text{Ti}(\text{O}i\text{Pr})_4$  (0.85 mmol) and 860  $\mu\text{L}$  of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.96M in  $\text{Et}_2\text{O}$ , 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to  $-30$  °C over 1 hr. The reaction mixture was stirred at  $-30$  °C for 1 hr and then cooled to  $-78$  °C. To a separate  $-78$  °C solution of allene **10** (38 mg, 0.39 mmol) in 1.0 mL PhMe was added 160  $\mu\text{L}$  of  $n\text{BuLi}$  (2.45M in hexanes, 0.39 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78$  °C titanium solution dropwise via cannula. After warming slowly to  $0$  °C over 2 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before

extracting with EtOAc (3 x 15 mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Flash column chromatography (15 % EtOAc/hexanes, then 40 % EtOAc/hexanes) of the crude material provided 113 mg (64 %) of diene **11** as a clear, colorless oil in a 3:1 (E:Z) mixture of olefin isomers. Separation of the isomers by HPLC [EtOAc/hexanes: gradient from 35 % to 50 % (0-15 min, 25 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] provided an analytically pure sample of **11**.

**(3E,6Z)-9-(4-methoxybenzyloxy)-6-(2-(4-methoxybenzyloxy)ethyl)-3-methylnona-3,6-dien-1-ol, 11.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.27-7.23 (m, 4H), 6.89-6.85 (m, 4H), 5.25-5.21 (m, 2H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.65 (dt, *J* = 12.3, 6.3 Hz, 2H), 3.44 (t, *J* = 7.6 Hz, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.74 (d, *J* = 7.3 Hz, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.33 (dt, *J* = 15.4, 7.6 Hz, 2H), 2.25 (t, *J* = 6.0 Hz, 2H), 1.61 (s, 3H), 1.37 (t, *J* = 6.0 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 159.1, 136.8, 132.6, 130.64, 130.56, 129.19, 129.16, 125.7, 123.0, 113.7, 72.5, 69.8, 68.6, 60.2, 55.2, 42.7, 36.2, 31.1, 28.6, 15.7; IR (thin film, NaCl) 3439, 2857, 1613, 1513, 1464, 1302, 1248, 1173, 1093, 1036, 820 cm<sup>-1</sup>; LRMS (EI, Na) calcd for C<sub>28</sub>H<sub>38</sub>O<sub>5</sub>Na, 477.27 *m/z* (M + Na); observed, 477.4 (M + Na)<sup>+</sup> *m/z*.

**Observed nOe enhancements for structure determination:**



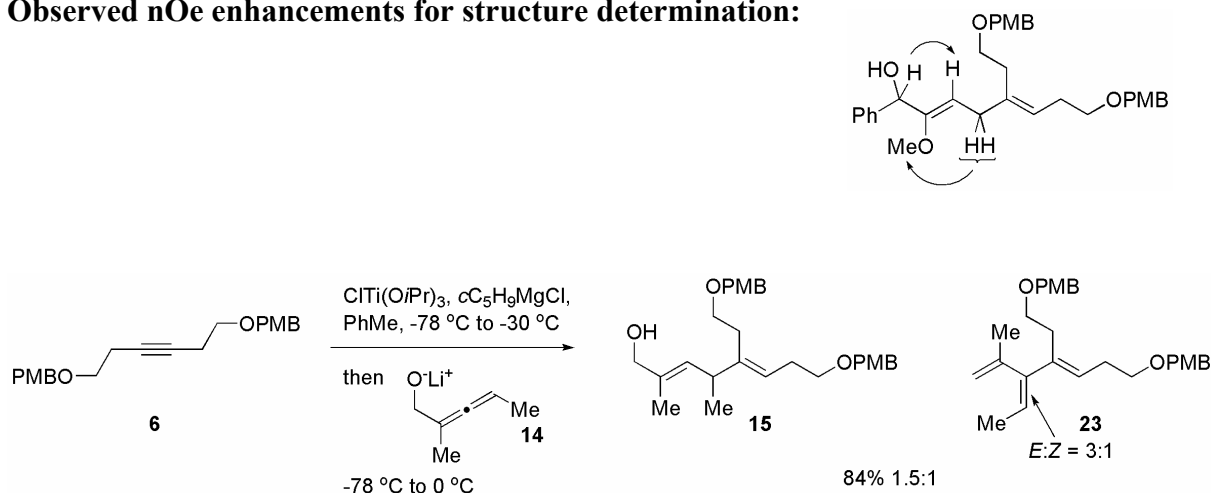
**Synthesis of 1,4-Diene 13.** To a  $-78\text{ }^{\circ}\text{C}$  solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 250  $\mu\text{L}$  of  $\text{Ti}(\text{O}i\text{Pr})_4$  (0.84 mmol) and 860  $\mu\text{L}$  of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.96M in  $\text{Et}_2\text{O}$ , 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to  $-30\text{ }^{\circ}\text{C}$  over 1 hr. The reaction mixture was stirred at  $-30\text{ }^{\circ}\text{C}$  for 1 hr and then cooled to  $-78\text{ }^{\circ}\text{C}$ . To a separate  $-78\text{ }^{\circ}\text{C}$  solution of allene **12** (33 mg, 0.39 mmol) in 1.0 mL PhMe was added 160  $\mu\text{L}$  of  $n\text{BuLi}$  (2.45M in hexanes, 0.39 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78\text{ }^{\circ}\text{C}$  titanium solution dropwise via cannula. After warming slowly from  $-78\text{ }^{\circ}\text{C}$  to  $-30\text{ }^{\circ}\text{C}$  over 1 hr, then from  $-30\text{ }^{\circ}\text{C}$  to  $0\text{ }^{\circ}\text{C}$  over 1 hr, then at  $0\text{ }^{\circ}\text{C}$  for 1 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before extracting with EtOAc (3 x 15 mL). The combined organic layer was washed with sat.  $\text{NaHCO}_3$  solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Flash column chromatography (20 % EtOAc/hexanes, then 50 % EtOAc/hexanes) of the crude material provided 180 mg (87 %) of diene **13** as a clear, colorless oil. A small portion was further purified by HPLC [EtOAc/hexanes: gradient from 30 % to 45 % (0-10 min, 25 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] to obtain a sample for analytical characterization.

**(2Z,5Z)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-2-methoxy-1-phenylocta-2,5-dien-1-ol, 13.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.40 (m, 2H), 7.35-7.32 (m, 2H), 7.30-7.22 (m, 5H), 6.89-6.84 (m, 4H), 5.27 (t,  $J = 7.3\text{ Hz}$ , 1H), 5.20 (d,  $J = 4.7\text{ Hz}$ , 1H), 4.93 (t,  $J = 7.6\text{ Hz}$ , 1H), 4.42 (s, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.51 (s, 3H), 3.46 (t,  $J = 7.3\text{ Hz}$ , 2H), 3.41 (t,  $J = 6.9\text{ Hz}$ , 2H), 2.85 (d,  $J = 7.3\text{ Hz}$ , 2H), 2.38-2.32 (m, 4H), 2.27 (d,  $J = 4.7\text{ Hz}$ , 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.14, 159.12, 156.9, 141.5,



136.8, 130.7, 130.6, 129.2, 129.1, 128.3, 127.7, 126.6, 123.1, 113.8, 113.7, 111.1, 77.2, 74.0, 72.49, 72.46, 69.8, 68.6, 59.7, 55.3, 33.0, 31.2, 28.6; IR (thin film, NaCl) 3423, 2936, 2847, 1613, 1513, 1454, 1360, 1302, 1248, 1174, 1091, 1035, 820, 703  $\text{cm}^{-1}$ ; HRMS (EI, Na) calcd for  $\text{C}_{33}\text{H}_{40}\text{O}_6\text{Na}$ , 555.2825  $m/z$  ( $\text{M} + \text{Na}$ ); observed, 555.2717 ( $\text{M} + \text{Na}$ )<sup>+</sup>  $m/z$ .

**Observed nOe enhancements for structure determination:**

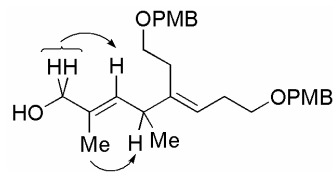


**Synthesis of 1,4-Diene **15** and Triene **23**.** To a  $-78\text{ }^\circ\text{C}$  solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of  $\text{PhMe}$  was added 850  $\mu\text{L}$  of  $\text{ClTi}(\text{O}i\text{Pr})_3$  (1.0M in hexanes, 0.85 mmol) and 860  $\mu\text{L}$  of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.96M in  $\text{Et}_2\text{O}$ , 1.69 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to  $-30\text{ }^\circ\text{C}$  over 1 hr. The reaction mixture was stirred at  $-30\text{ }^\circ\text{C}$  for 1 hr and then cooled to  $-78\text{ }^\circ\text{C}$ . To a separate  $-78\text{ }^\circ\text{C}$  solution of allene **14** (39 mg, 0.39 mmol) in 1.0 mL  $\text{PhMe}$  was added 160  $\mu\text{L}$  of  $n\text{BuLi}$  (2.45M in hexanes, 0.39 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78\text{ }^\circ\text{C}$  titanium solution dropwise via cannula. After warming slowly to  $-30\text{ }^\circ\text{C}$  over 1 hr, then at  $-30\text{ }^\circ\text{C}$  for 1 hr, then from  $-30\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$  over 1 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before extracting with  $\text{EtOAc}$  (3 x 15 mL). The combined organic layer was washed with sat.

NaHCO<sub>3</sub> solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Flash column chromatography (5 % EtOAc/hexanes, then 10 % EtOAc/hexanes, then 50 % EtOAc/hexanes) of the crude material (**15:23** = 1.5:1 by <sup>1</sup>H NMR) provided 91 mg (51 %) of diene **15** and 57 mg (33 %) of triene **23** as clear, colorless oils. Triene **23** was isolated as a 3:1 mixture of olefin isomers, favoring *E*-isomer **23** (shown) over *Z*-isomer **23a**. Separation of the triene olefin isomers using HPLC [EtOAc/hexanes: gradient from 10 % to 15 % (0-10 min, 29 mL/min); then 15 % to 30 % (10-15 min, 29 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] provided analytically pure samples of **22** and **22a**.

**(2E,5E)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-2,4-dimethylocta-2,5-dien-1-ol, 15.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26-7.23 (m, 4H), 6.88-6.86 (m, 4H), 5.28 (t, *J* = 6.9 Hz, 1H), 5.21 (d, *J* = 9.5 Hz, 1H), 4.42 (s, 2H), 4.40 (s, 2H), 3.95 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.41 (dt, *J* = 14.8, 7.3 Hz, 4H), 3.03 (dq, *J* = 8.8, 6.9 Hz, 1H), 2.42-2.26 (m, 4H), 1.64 (s, 3H), 1.36 (t, *J* = 6.0 Hz, 1H), 0.95 (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.1, 141.1, 134.0, 130.7, 130.63, 130.57, 129.18, 129.15, 121.4, 113.7, 72.45, 72.41, 69.9, 69.1, 68.8, 55.2, 38.7, 30.4, 28.6, 19.8, 13.8; IR (thin film, NaCl) 3429, 2958, 2859, 1613, 1513, 1463, 1361, 1302, 1248, 1173, 1093, 1035, 820 cm<sup>-1</sup>; LRMS (EI, Na) calcd for C<sub>28</sub>H<sub>38</sub>O<sub>5</sub>Na, 477.27 *m/z* (M + Na); observed, 477.4 (M + Na)<sup>+</sup> *m/z*.

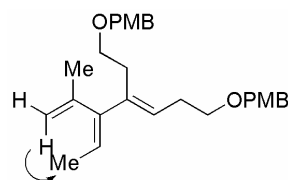
**Observed nOe enhancements for structure determination:**



**(3E,5E)-1-(4-methoxybenzyloxy)-4-(2-(4-methoxybenzyloxy)ethyl)-5-(2-propenyl)-3,5-heptadiene, 23.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26-7.24 (m, 4H), 6.88-6.86

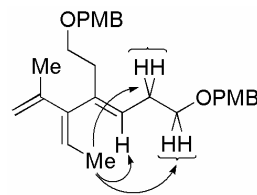
(m, 4H), 5.53 (t,  $J = 6.8$  Hz, 1H), 5.51 (t,  $J = 7.1$  Hz, 1H), 5.13-5.11 (m, 1H), 4.66-4.65 (m, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.44 (t,  $J = 7.1$  Hz, 2H), 3.42 (t,  $J = 8.1$  Hz, 2H), 2.57 (t,  $J = 8.1$  Hz, 2H), 2.43 (dt,  $J = 14.1, 7.1$  Hz, 2H), 1.72 (s, 3H), 1.68 (d,  $J = 6.8$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 159.0, 145.4, 143.0, 136.5, 130.7, 130.6, 129.2, 129.1, 125.7, 119.2, 115.2, 113.7, 77.0, 72.4, 69.7, 69.0, 55.2, 29.1, 28.6, 22.9, 14.9; IR (thin film, NaCl) 2935, 2854, 1613, 1513, 1257, 1361, 1302, 1248, 1173, 1093, 1036, 820  $\text{cm}^{-1}$ ; LRMS (EI, Na) calcd for  $\text{C}_{28}\text{H}_{36}\text{O}_4\text{Na}$ , 459.26  $m/z$  (M + Na); observed, 459.3 (M + Na) $^+$   $m/z$ .

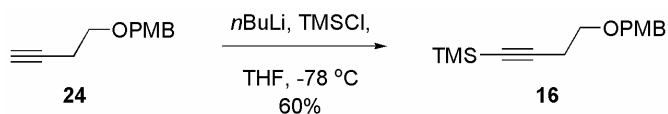
**Observed nOe enhancements for structure determination:**



**(3E,5Z)-1-(4-methoxybenzyloxy)-4-(2-(4-methoxybenzyloxy)ethyl)-5-(2-propenyl)-3,5-heptadiene, 23a.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26-7.21 (m, 4H), 6.88-6.84 (m, 4H), 5.65 (q,  $J = 6.9$  Hz, 1H), 5.24 (t,  $J = 7.3$  Hz, 1H), 4.86 (s, 2H), 4.41 (s, 2H), 4.35 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.49 (t,  $J = 3.5$  Hz, 2H), 3.38 (t,  $J = 7.3$  Hz, 2H), 2.49 (dt,  $J = 14.2, 6.9$  Hz, 2H), 1.86 (s, 3H), 1.66 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.11, 159.07, 145.2, 143.0, 135.2, 130.78, 130.75, 129.2, 127.9, 122.3, 113.75, 113.71, 77.2, 72.52, 72.46, 69.9, 68.7, 55.3, 31.3, 28.8, 20.7, 15.3; IR (thin film, NaCl) 2954, 2854, 1614, 1514, 1457, 1302, 1248, 1173, 1098, 1036, 821  $\text{cm}^{-1}$ ; LRMS (EI, Na) calcd for  $\text{C}_{28}\text{H}_{36}\text{O}_4\text{Na}$ , 459.26  $m/z$  (M + Na); observed, 459.3 (M + Na) $^+$   $m/z$ .

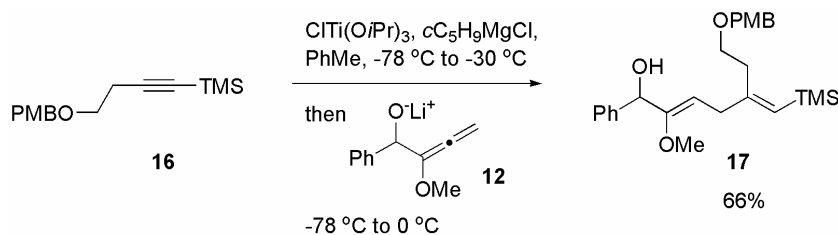
**Observed nOe enhancements for structure determination:**





**Synthesis of Alkyne 16.** To alkyne **24** (328 mg, 1.72 mmol) in 14 mL of THF was added 1.1 mL of *n*BuLi (2.45M in hexanes, 2.58 mmol) dropwise at  $-78\text{ }^\circ\text{C}$ . The reaction was stirred for 30 min at  $-78\text{ }^\circ\text{C}$ , then 435  $\mu\text{L}$  of TMSCl was added and the reaction was stirred overnight warming to room temperature. The resulting mixture was quenched with water and extracted with Et<sub>2</sub>O (3 x 5 mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> solution (1 x 10 mL) and brine (1 x 10 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Purification of the crude material by flash column chromatography (5 % EtOAc/hexanes) provided 270 mg (60 %) of **16** as a clear, pale yellow oil.

**(4-(4-methoxybenzyloxy)but-1-ynyl)trimethylsilane, 16.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.49, (s, 2H), 3.81 (s, 2H), 3.57 (t, *J* = 7.3 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 0.15 (s, 9H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  159.3, 130.3, 129.2, 113.8, 103.8, 85.7, 72.6, 68.1, 55.3, 21.3, 0.1; IR (thin film, NaCl) 2958, 2178, 1616, 1457, 1249, 1100, 1037, 842, 760 cm<sup>-1</sup>; LRMS (EI, Na) calcd for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>SiNa, 285.14 *m/z* (M + Na); observed, 285.2 (M + Na)<sup>+</sup> *m/z*.



**Synthesis of 1,4-Diene 17.** To a  $-78\text{ }^\circ\text{C}$  solution of alkyne **16** (116 mg, 0.44 mmol) in 2.9 mL of PhMe was added 660  $\mu\text{L}$  of ClTi(OiPr)<sub>3</sub> (1.0M in hexanes, 0.84 mmol) and 680  $\mu\text{L}$

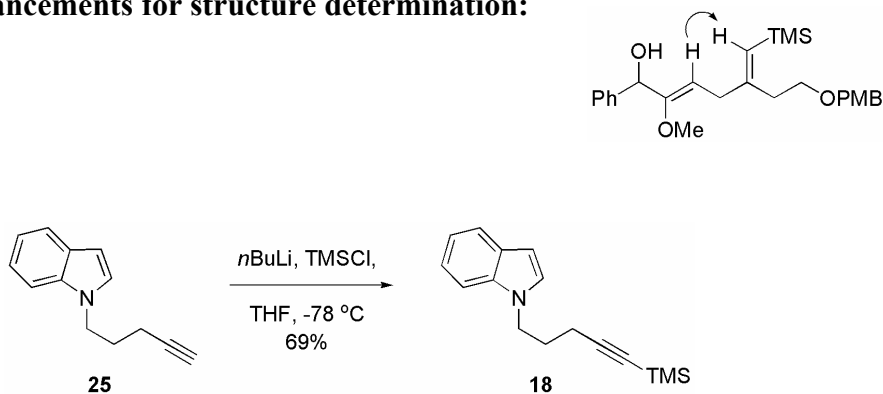
of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.96M in  $\text{Et}_2\text{O}$ , 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black while warming slowly to  $-30\text{ }^\circ\text{C}$  over 1 hr. The reaction mixture was stirred at  $-30\text{ }^\circ\text{C}$  for 1 hr and then cooled to  $-78\text{ }^\circ\text{C}$ . To a separate  $-78\text{ }^\circ\text{C}$  solution of allene **12** (54 mg, 0.31 mmol) in 1.0 mL PhMe was added 130  $\mu\text{L}$  of  $n\text{BuLi}$  (2.45M in hexanes, 0.31 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78\text{ }^\circ\text{C}$  titanium solution dropwise via cannula. After warming slowly to  $0\text{ }^\circ\text{C}$  over 2 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before extracting with EtOAc (3 x 15 mL). The combined organic layer was washed with sat.  $\text{NaHCO}_3$  solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Flash column chromatography of the crude material (10 % EtOAc/hexanes, then 20 % EtOAc/hexanes) provided 90 mg (66 %) of diene **17** as a clear, colorless oil in a 4:1 mixture of regioisomers. Attempts at further purification using HPLC [EtOAc/hexanes: gradient from 16 % to 35 % (0-10 min, 25 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] were unsuccessful; analytical characterization of **17** was carried out on a 5:1 mixture of regioisomers.

**(2Z,5Z)-7-(4-methoxybenzyloxy)-2-methoxy-1-phenyl-5-**

**((trimethylsilyl)methylene)hept-2-en-1-ol, 17.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44-7.22 (m, 6H), 6.88-6.85 (m, 3H), 5.33 (s, 1H), 5.23 (d,  $J = 5.0$  Hz, 1H), 4.98 (t,  $J = 8.2$  Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.50 (t,  $J = 7.6$  Hz, 2H), 3.50 (s, 3H), 2.92 (d,  $J = 7.6$  Hz, 2H), 2.47 (t,  $J = 7.6$  Hz, 2H), 2.22 (d,  $J = 4.7$  Hz, 1H), 0.08 (s, 9H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 157.0, 154.3, 141.5, 130.6, 129.2, 128.4, 127.8, 126.6, 126.2, 113.7, 110.8, 74.1, 72.6, 69.3, 59.7, 55.3, 36.6, 35.1, 0.3; IR (thin film, NaCl) 3433, 2952, 2835, 1616, 1513, 1457, 1248,

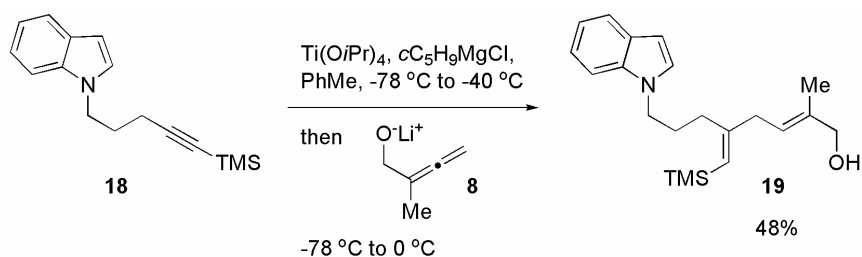
1088, 1036, 838  $\text{cm}^{-1}$ ; LRMS (EI, Na) calcd for  $\text{C}_{26}\text{H}_{36}\text{O}_4\text{SiNa}$ , 463.24  $m/z$  ( $\text{M} + \text{Na}$ ); observed, 463.2 ( $\text{M} + \text{Na}$ )<sup>+</sup>  $m/z$ .

**Observed nOe enhancements for structure determination:**



**Synthesis of Alkyne 18.** To alkyne **25**<sup>3</sup> (74 mg, 0.4 mmol) in 2.0 mL of THF was added 240  $\mu\text{L}$  of  $n\text{BuLi}$  (2.5M in hexanes, 0.6 mmol) dropwise at  $-78\text{ }^\circ\text{C}$ . The reaction was warmed to  $0\text{ }^\circ\text{C}$  over 2 hr, then 91  $\mu\text{L}$  of  $\text{TMSCl}$  was added and the reaction was stirred at  $0\text{ }^\circ\text{C}$  for 1 hr. Removal of the solvent in vacuo and purification of the crude material by flash column chromatography (5 %  $\text{EtOAc}$ /hexanes) provided 70 mg (69 %) of **18** as a clear, colorless oil.

**1-(5-(trimethylsilyl)pent-4-ynyl)-1H-indole, 18.**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 7.9$  Hz, 1H), 7.41 (d,  $J = 8.2$  Hz, 1H), 7.23 (t,  $J = 7.9$  Hz, 1H), 7.14-7.11 (m, 2H), 6.52 (d,  $J = 3.2$  Hz, 1H), 4.29 (t,  $J = 6.9$  Hz, 2H), 2.22 (t,  $J = 6.6$  Hz, 2H), 2.04 (dt,  $J = 13.6, 6.9$  Hz, 2H), 0.20 (s, 9H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  135.9, 128.6, 127.9, 121.4, 120.9, 119.3, 109.3, 105.7, 101.2, 86.1, 44.6, 28.8, 17.2, 0.1; IR (thin film, NaCl) 3056, 2959, 2175, 1512, 1464, 1316, 1249, 1169, 1025, 842, 761, 740, 639  $\text{cm}^{-1}$ ; LRMS (EI, H) calcd for  $\text{C}_{16}\text{H}_{22}\text{NSi}$ , 256.14  $m/z$  ( $\text{M} + \text{H}$ ); observed, 256.0 ( $\text{M} + \text{H}$ )<sup>+</sup>  $m/z$ .



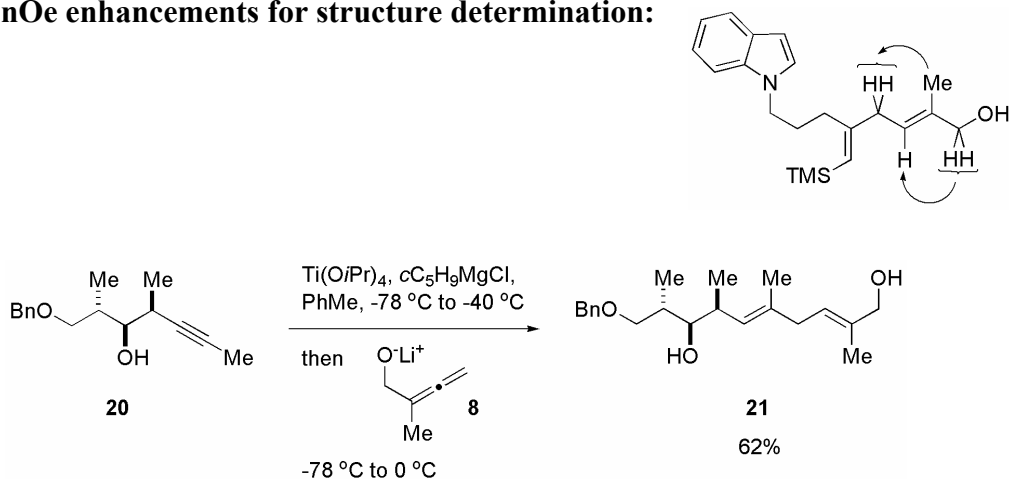
**Synthesis of 1,4-Diene 19.** To a solution of alkyne **18** (60 mg, 0.23 mmol) in 1.6 mL of PhMe was added 105  $\mu$ L of  $\text{Ti}(\text{O}i\text{Pr})_4$ . After cooling to  $-78$   $^\circ\text{C}$ , 390  $\mu$ L of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.85M in  $\text{Et}_2\text{O}$ , 0.72 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black while warming slowly to  $-40$   $^\circ\text{C}$  over 1 hr. The reaction mixture was stirred at  $-40$   $^\circ\text{C}$  for 1 hr and then cooled to  $-78$   $^\circ\text{C}$ . To a separate  $-78$   $^\circ\text{C}$  solution of allene **8** (14 mg, 0.16 mmol) in 0.5 mL PhMe was added 68  $\mu$ L of  $n\text{BuLi}$  (2.5M in hexanes, 0.17 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78$   $^\circ\text{C}$  titanium solution dropwise via cannula. After warming slowly to  $0$   $^\circ\text{C}$  over 2 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to room temperature before extracting with EtOAc (3 x 10 mL). The combined organic layer was washed with sat.  $\text{NaHCO}_3$  solution (1 x 20 mL), brine (1 x 20 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Removal of the solvent in vacuo gave a crude oil as a 4:1 mixture of regioisomers by  $^1\text{H}$  NMR. Flash column chromatography (10 % EtOAc/hexanes, then 20 % EtOAc/hexanes) provided 26 mg (48 %) of diene **19** as a clear, colorless oil. Further purification of a small sample using HPLC [EtOAc/hexanes: gradient from 13 % to 28 % (0-10 min, 25 mL/min), 28 % to 40 % (10-15 min, 25 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] provided an analytically pure sample for characterization.

**(2E,5E)-8-(1H-indol-1-yl)-2-methyl-5-((trimethylsilyl)methylene)oct-2-en-1-ol, 19.**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (d,  $J = 7.9$  Hz, 1H), 7.32 (d,  $J = 7.9$  Hz, 1H), 7.20 (dt,  $J =$

6.9, 1.3 Hz, 1H), 7.11-7.08 (m, 2H), 6.49 (dd,  $J = 3.2, 0.6$  Hz, 1H), 5.33 (tq,  $J = 7.3, 1.3$  Hz, 1H), 5.22 (app t,  $J = 1.3$  Hz, 1H), 4.13 (t,  $J = 6.9$  Hz, 2H), 3.95 (d,  $J = 6.9$  Hz, 2H), 2.76 (d,  $J = 6.9$  Hz, 2H), 2.14-2.11 (m, 2H), 1.96-1.90 (m, 2H), 1.55 (s, 1H), 1.54 (s, 3H), 0.01 (s, 9H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.8, 136.1, 135.7, 128.4, 127.4, 125.1, 123.0, 121.2, 120.8, 119.0, 109.0, 100.9, 68.5, 46.2, 37.0, 33.3, 29.5, 13.3, 0.0; IR (thin film, NaCl) 3374, 2951, 1612, 1512, 1464, 1316, 1247, 1174, 1014, 838, 739  $\text{cm}^{-1}$ .

**Observed nOe enhancements for structure determination:**



**Synthesis of 1,4-Diene 21.** To a  $-78\text{ }^\circ\text{C}$  solution of alkyne **20**<sup>4</sup> (40 mg, 0.23 mmol) in 1.2 mL of PhMe was added 64  $\mu\text{L}$  of  $n\text{Buli}$  (2.5M in hexanes, 0.16 mmol). After stirring for 10 min at  $-78\text{ }^\circ\text{C}$ , 70  $\mu\text{L}$  of  $\text{Ti}(\text{O}i\text{Pr})_4$  and 260  $\mu\text{L}$  of  $c\text{C}_5\text{H}_9\text{MgCl}$  (1.85M in  $\text{Et}_2\text{O}$ , 0.48 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black while warming slowly to  $-40\text{ }^\circ\text{C}$  over 1 hr. The reaction mixture was stirred at  $-40\text{ }^\circ\text{C}$  for 1 hr and then cooled to  $-78\text{ }^\circ\text{C}$ . To a separate  $-78\text{ }^\circ\text{C}$  solution of allene **8** (9 mg, 0.11 mmol) in 0.5 mL PhMe was added 44  $\mu\text{L}$  of  $n\text{BuLi}$  (2.5M in hexanes, 0.11 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath and added to the  $-78\text{ }^\circ\text{C}$  titanium solution dropwise via cannula. After warming slowly to  $0\text{ }^\circ\text{C}$  over 2 hr, the reaction was quenched with 5 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The mixture was warmed to

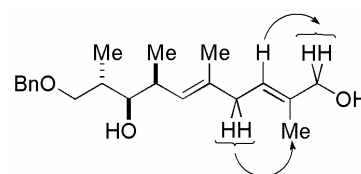


room temperature before extracting with EtOAc (3 x 10 mL). The combined organic layer was washed with sat. NaHCO<sub>3</sub> solution (1 x 20 mL), brine (1 x 20 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Flash column chromatography (20 % EtOAc/hexanes) provided 23 mg (62 %) of diene **21** as a clear, colorless oil. A small sample was further purified using HPLC [EtOAc/hexanes: gradient from 16 % to 35 % (0-10 min, 25 mL/min) on a Microsorb (Si 80-199-C5 F310195) column] to obtain an analytically pure sample for characterization.

**(2E,5E,7S,8R,9S)-10-(benzyloxy)-2,5,7,9-tetramethyldeca-2,5-diene-1,8-diol, 21.**

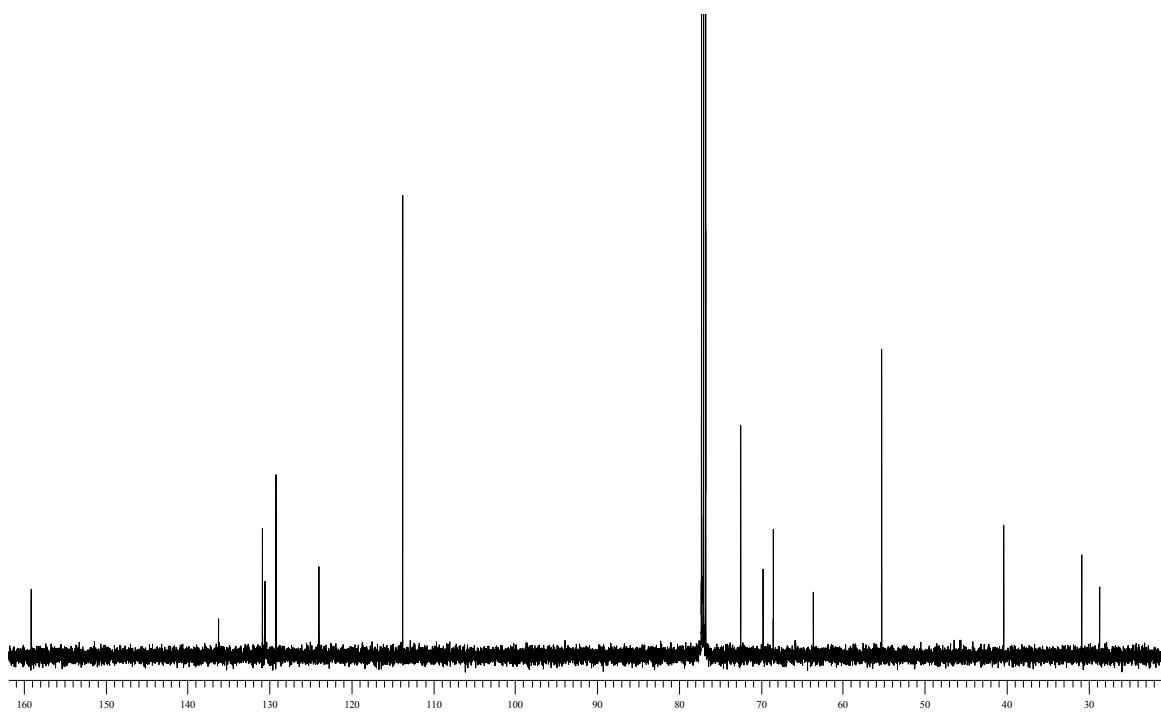
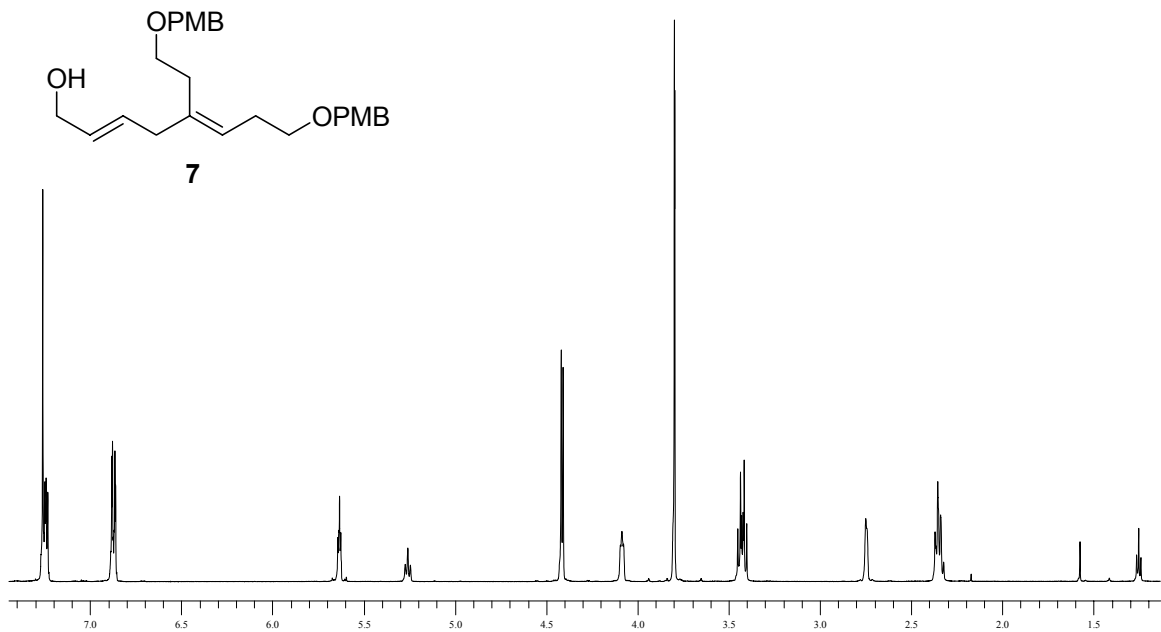
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36-7.27 (m, 5H), 5.40 (dt, *J* = 7.2, 1.3 Hz, 1H), 5.10 (dd, *J* = 9.5, 1.3 Hz, 1H), 4.52 (A of AB, *J* = 12.0 Hz, 1H), 4.48 (B of AB, *J* = 12.0 Hz, 1H), 4.02 (d, *J* = 5.7 Hz, 2H), 3.60 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.45 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.30 (dd, *J* = 11.7, 5.7 Hz, 1H), 3.10 (d, *J* = 5.7 Hz, 1H), 2.69 (d, *J* = 7.3 Hz, 2H), 2.50-2.43 (m, 1H), 1.93-1.85 (m, 1H), 1.67 (s, 3H), 1.54 (s, 3H), 1.27 (br s, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 137.8, 135.9, 132.9, 128.6, 128.4, 127.8, 127.7, 124.2, 80.1, 74.4, 73.6, 37.9, 36.1, 35.8, 16.3, 15.4, 14.9, 13.7; IR (thin film, NaCl) 3415, 2963, 2915, 2864, 1653, 1455, 1357, 1076, 1013, 736, 698 cm<sup>-1</sup>; LRMS (EI, Na) calcd for C<sub>21</sub>H<sub>31</sub>NOSiNa, 364.22 *m/z* (M + Na); observed, 364.4 (M + Na)<sup>+</sup> *m/z*.

**Observed nOe enhancements for structure determination:**

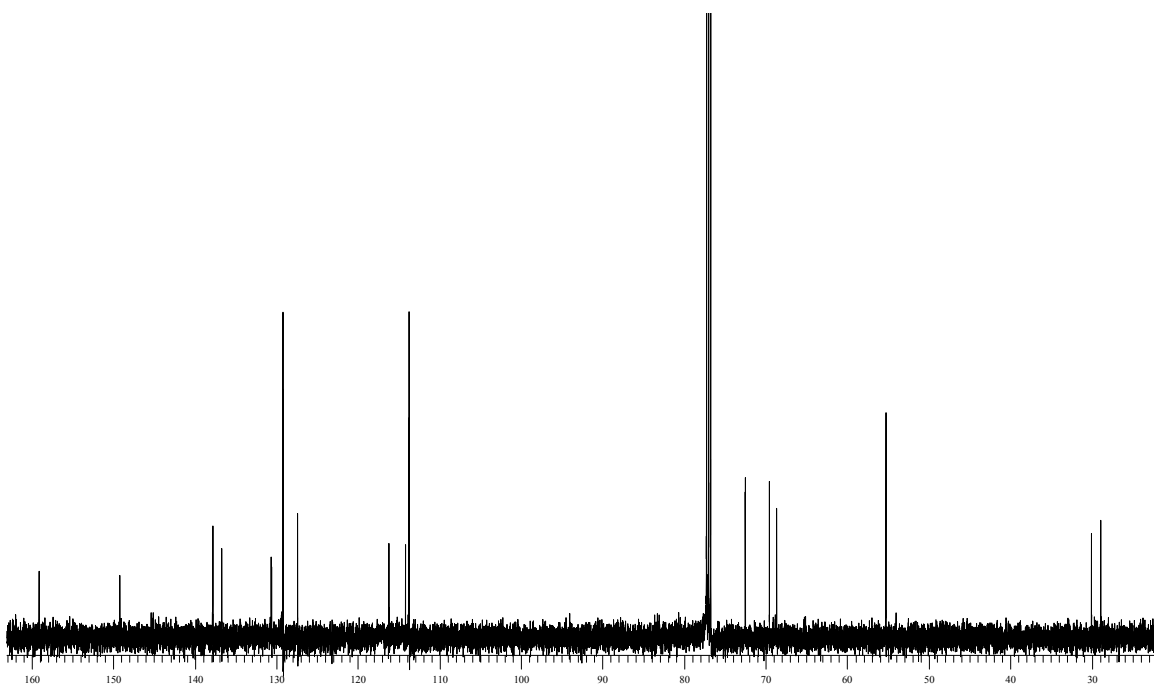
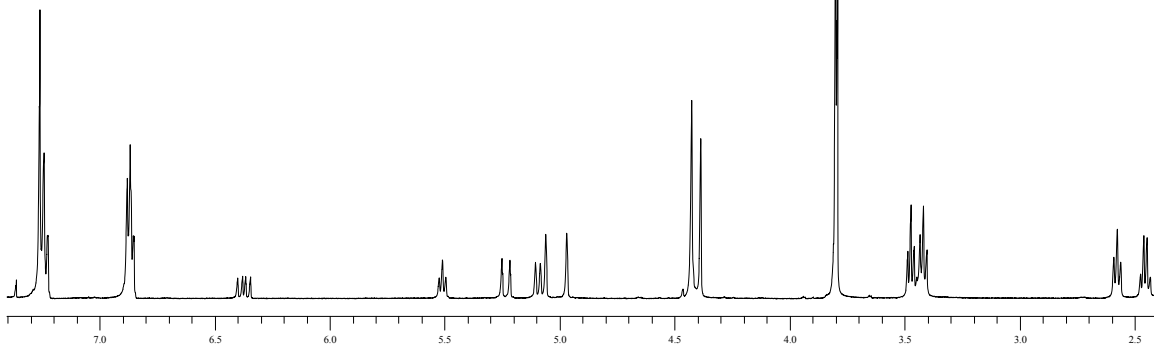
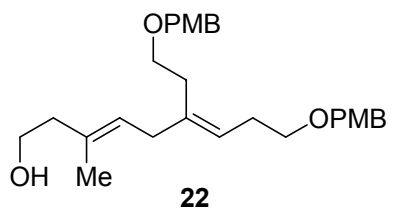


**References:**

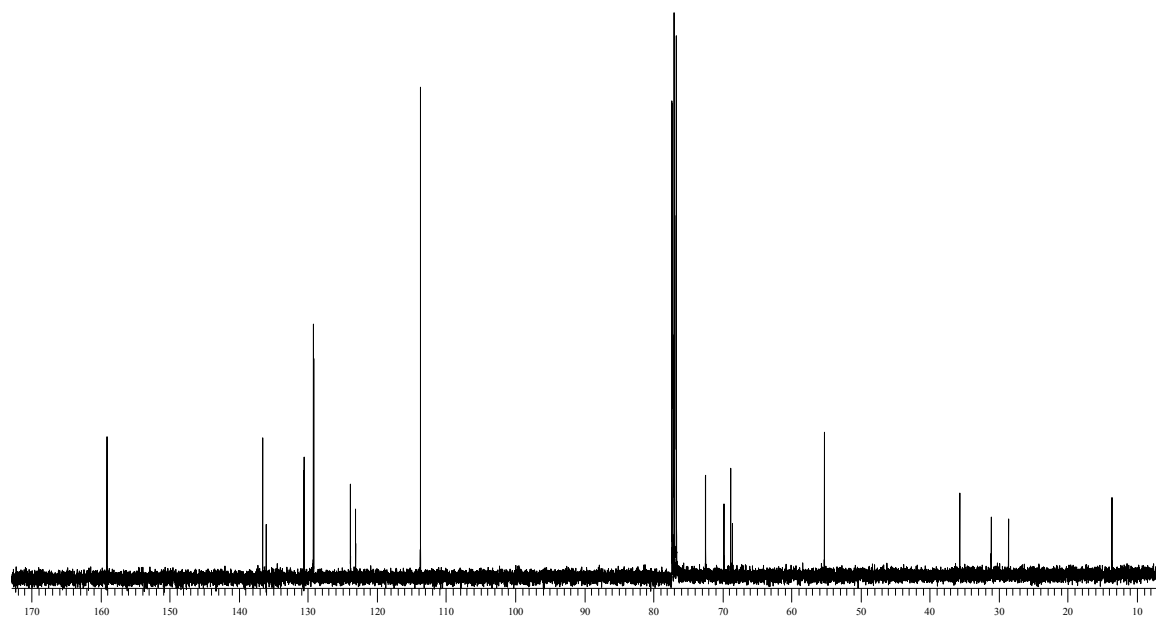
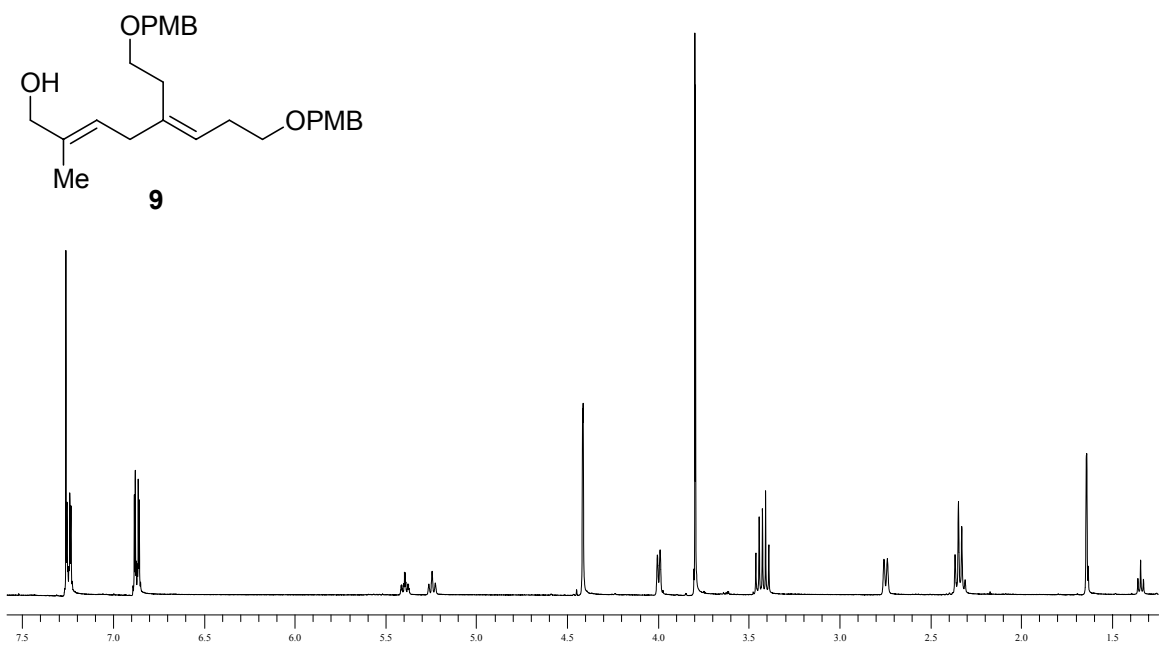
- <sup>1</sup> Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764-2765.
- <sup>2</sup> Allene **8** was used as a 3:1 mixture (minor component: 2-pentyn-1-ol). Reaction yield was based on the calculated amount of allene **8** present.
- <sup>3</sup> Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2091-2093.
- <sup>4</sup> Bahadoor, A. B.; Micalizio, G. C. *J. Am. Chem. Soc.*, **2005**, *127*, 3694-3695.



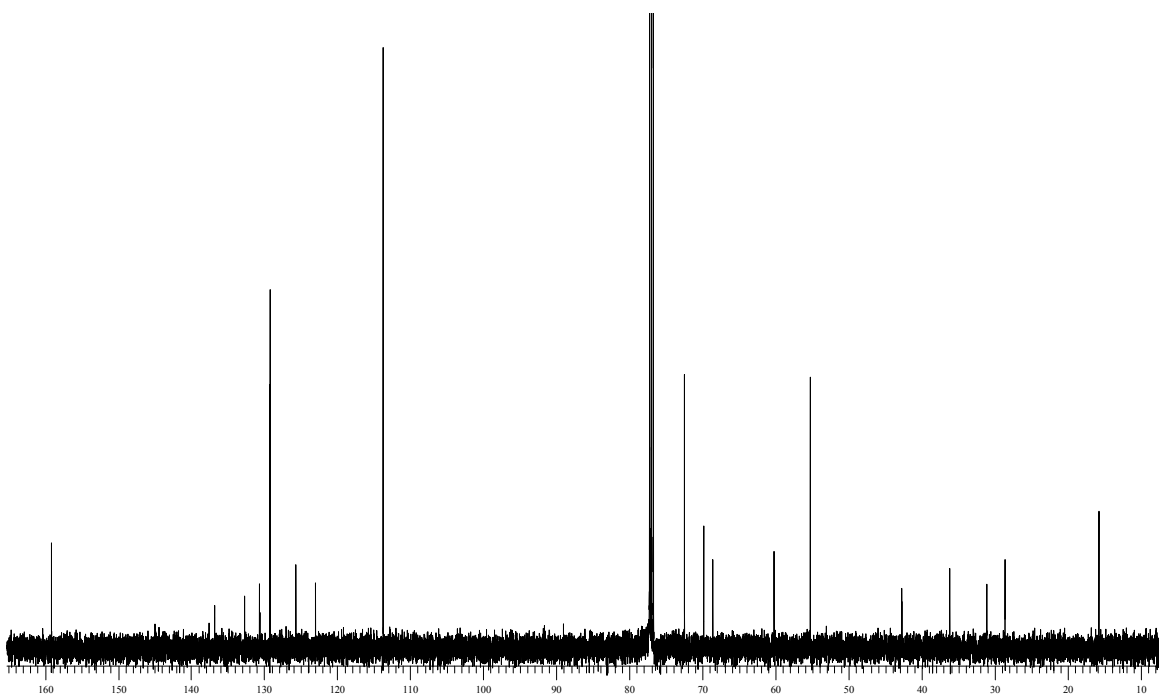
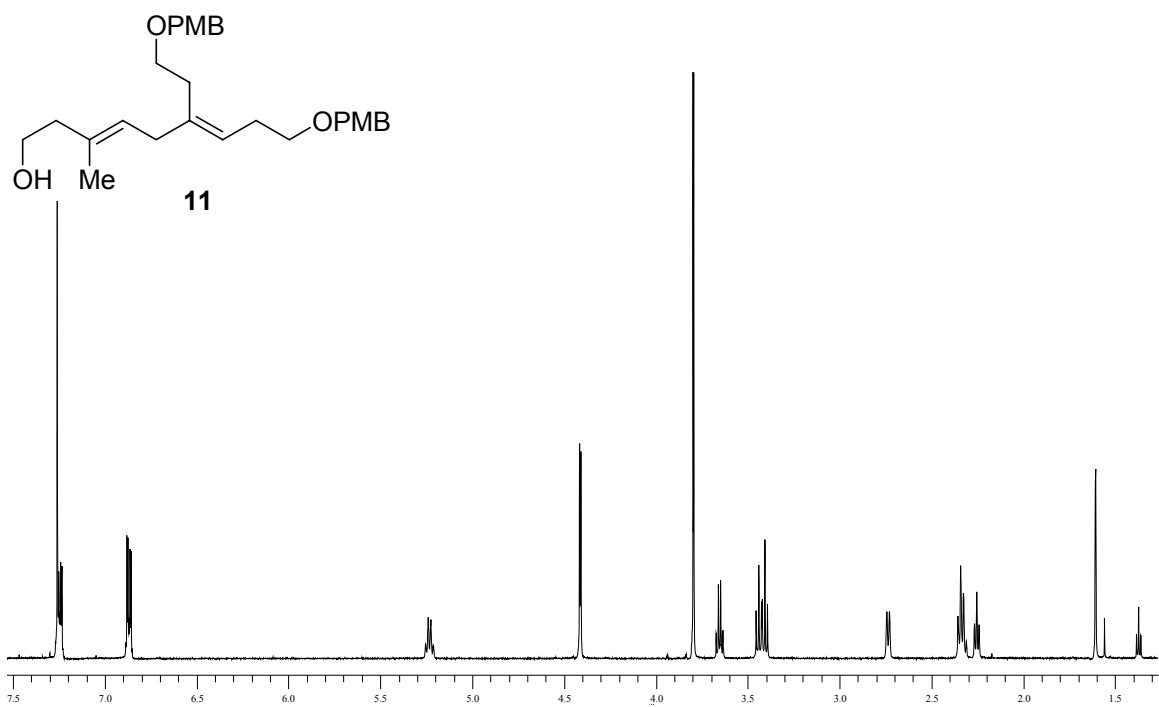
$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **7** ( $\text{CDCl}_3$ )



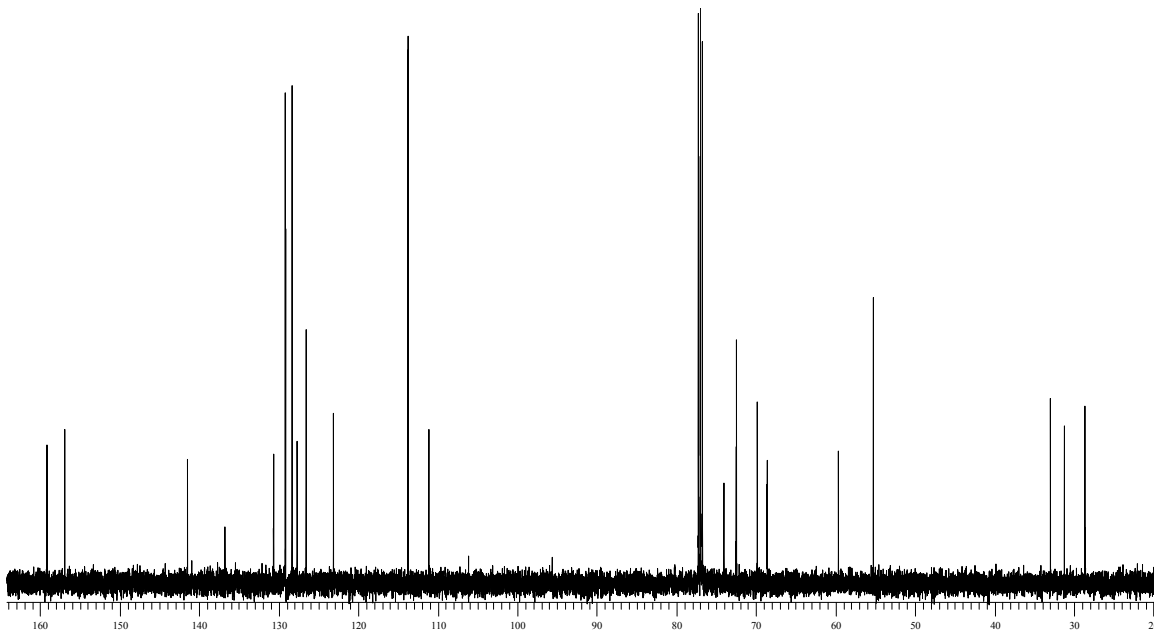
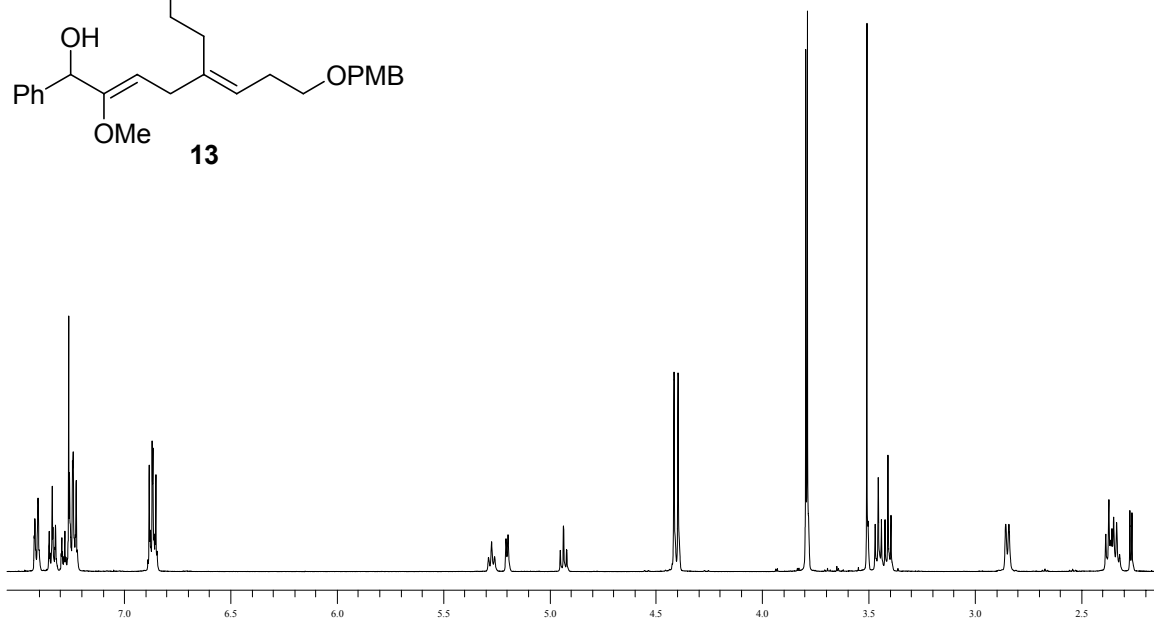
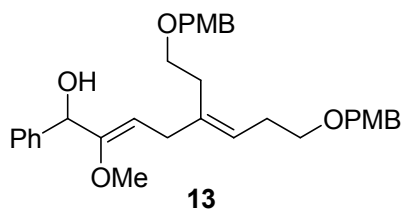
$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **22** ( $\text{CDCl}_3$ )



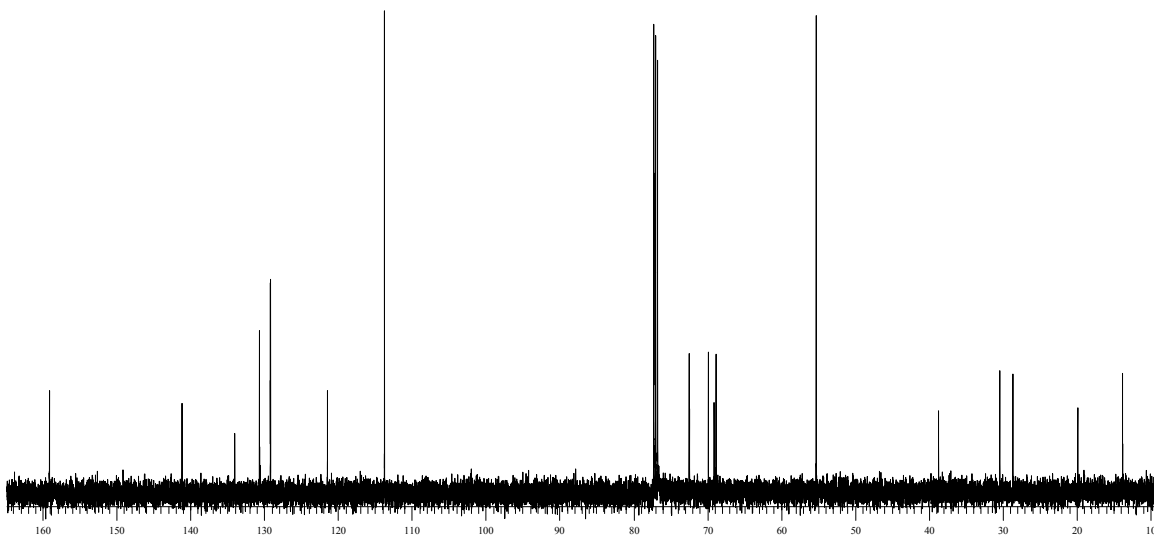
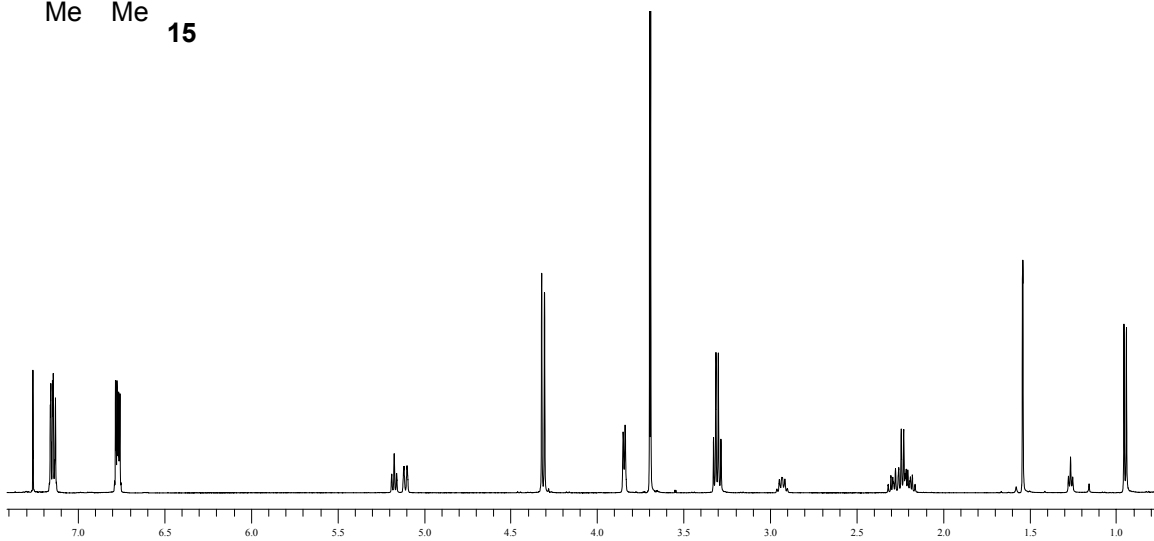
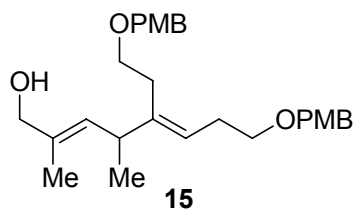
<sup>1</sup>H (400 MHz) and <sup>13</sup>C (100 MHz) of compound **9** (CDCl<sub>3</sub>)



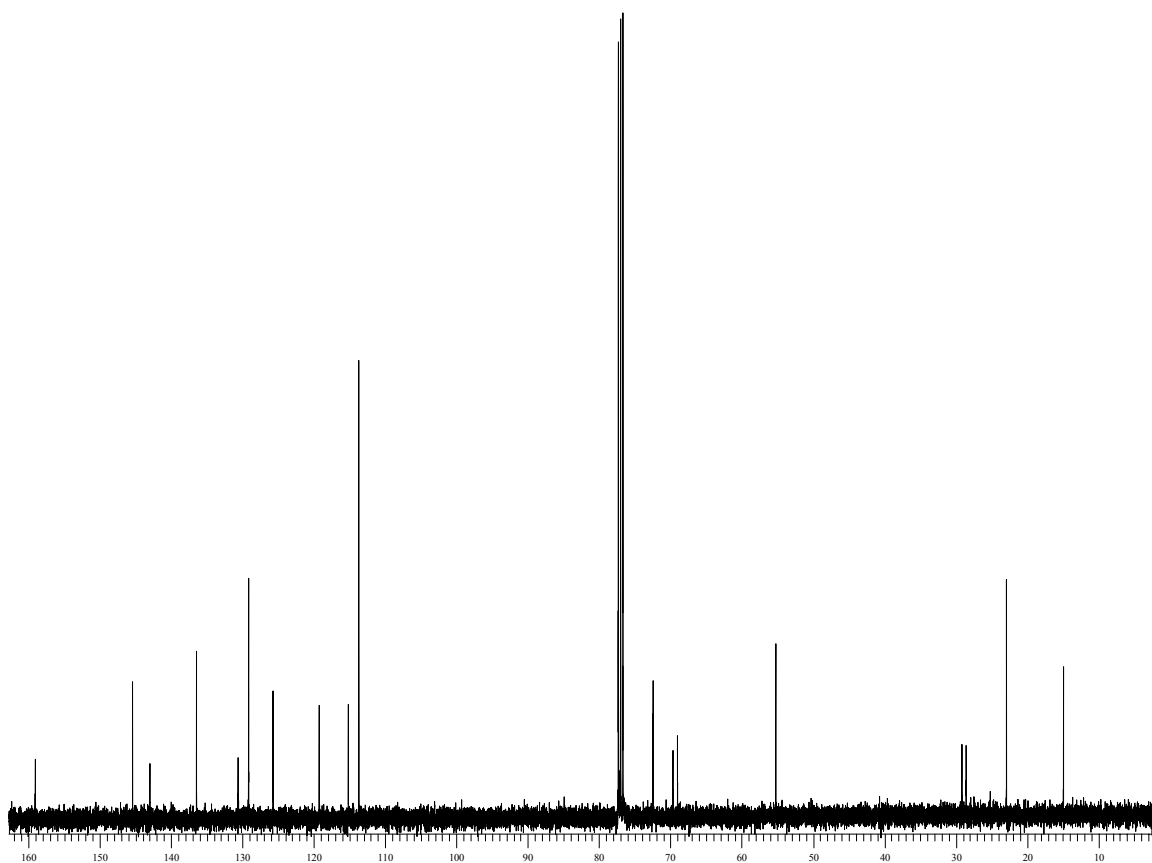
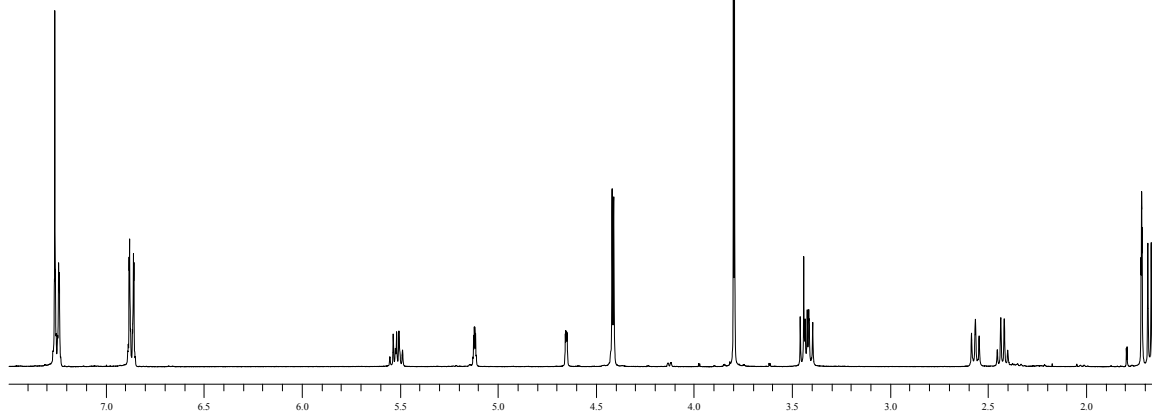
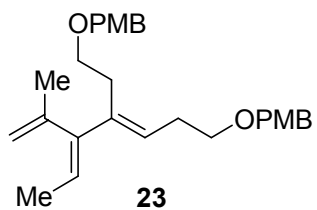
$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **11** ( $\text{CDCl}_3$ )



$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **13** ( $\text{CDCl}_3$ )

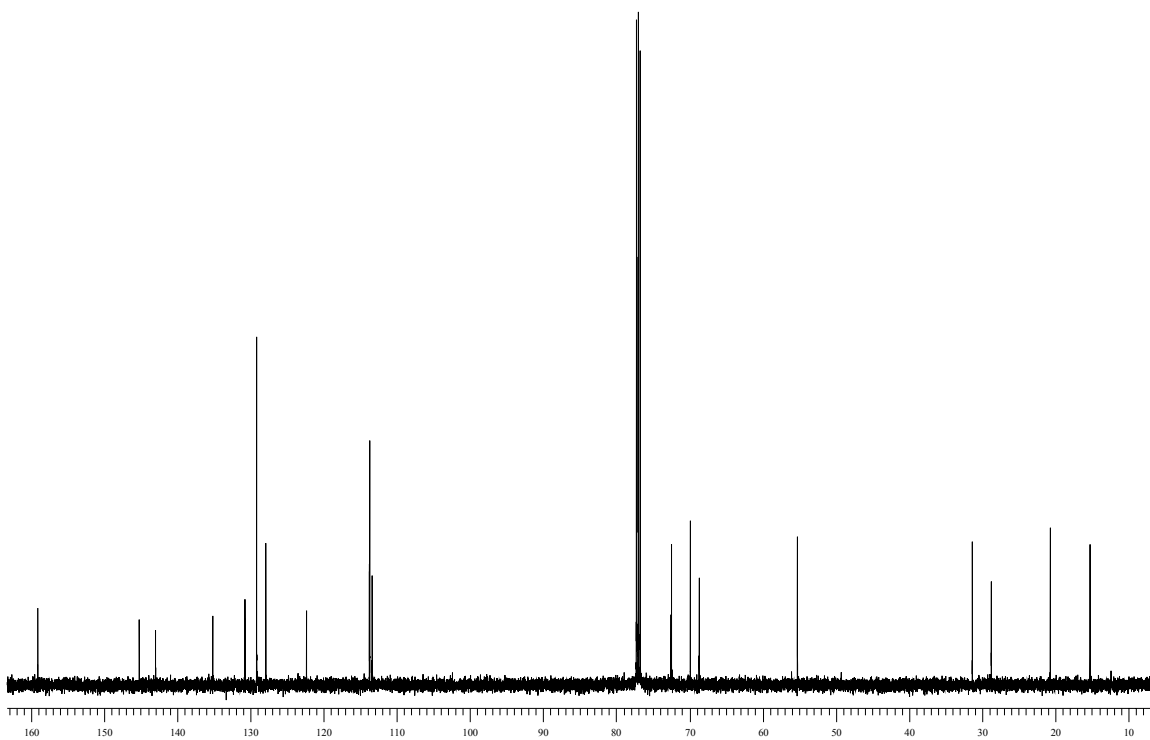
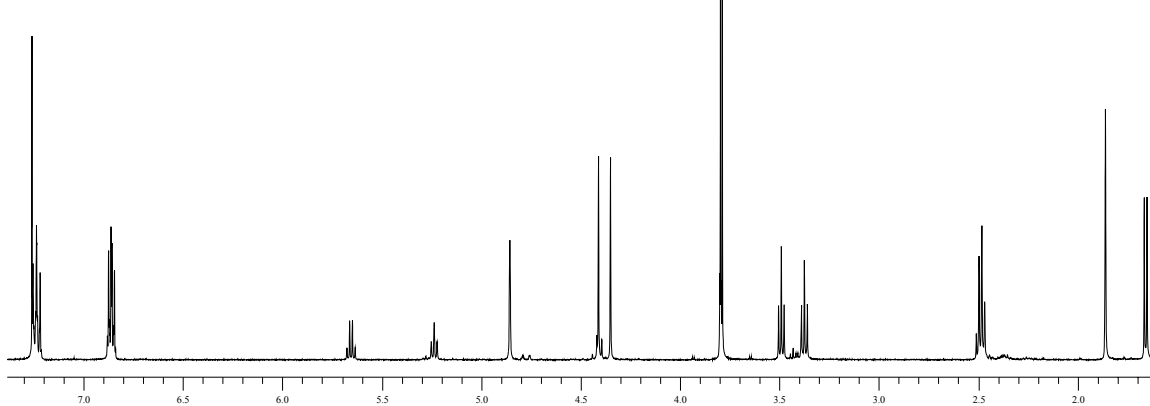
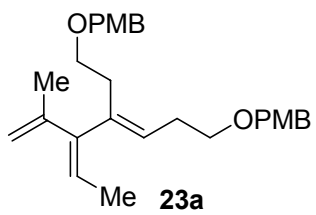


$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (100 MHz) of compound **15** ( $\text{CDCl}_3$ )

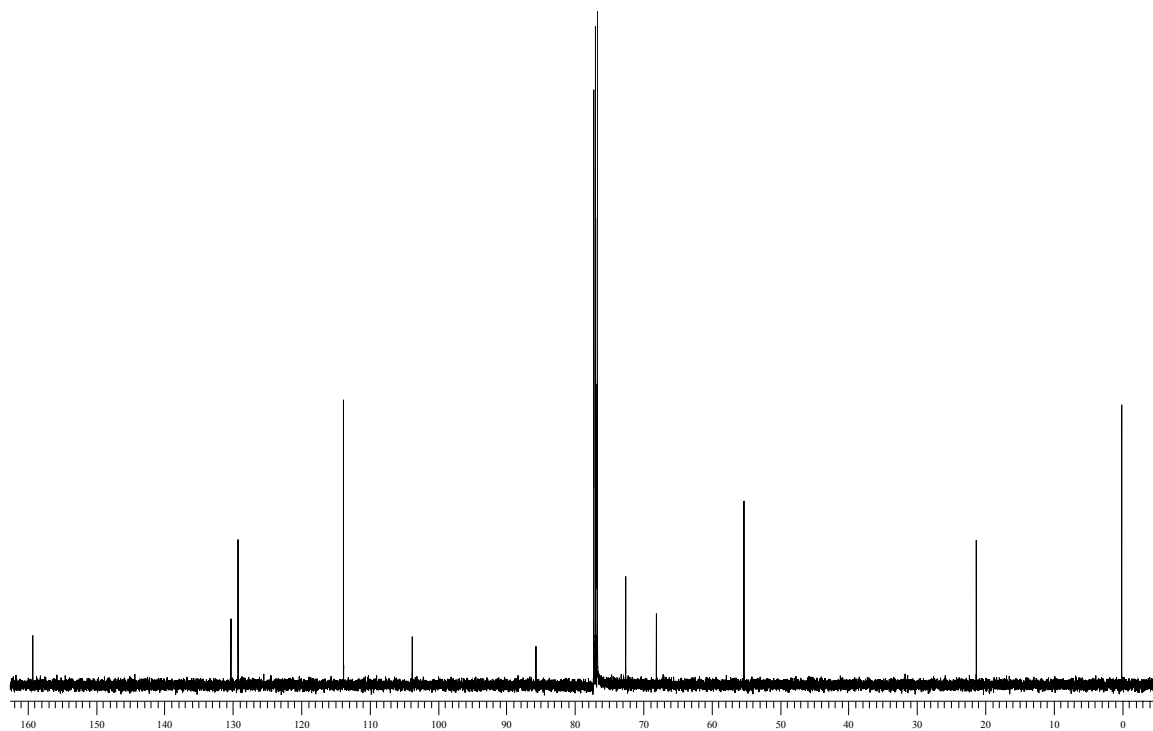
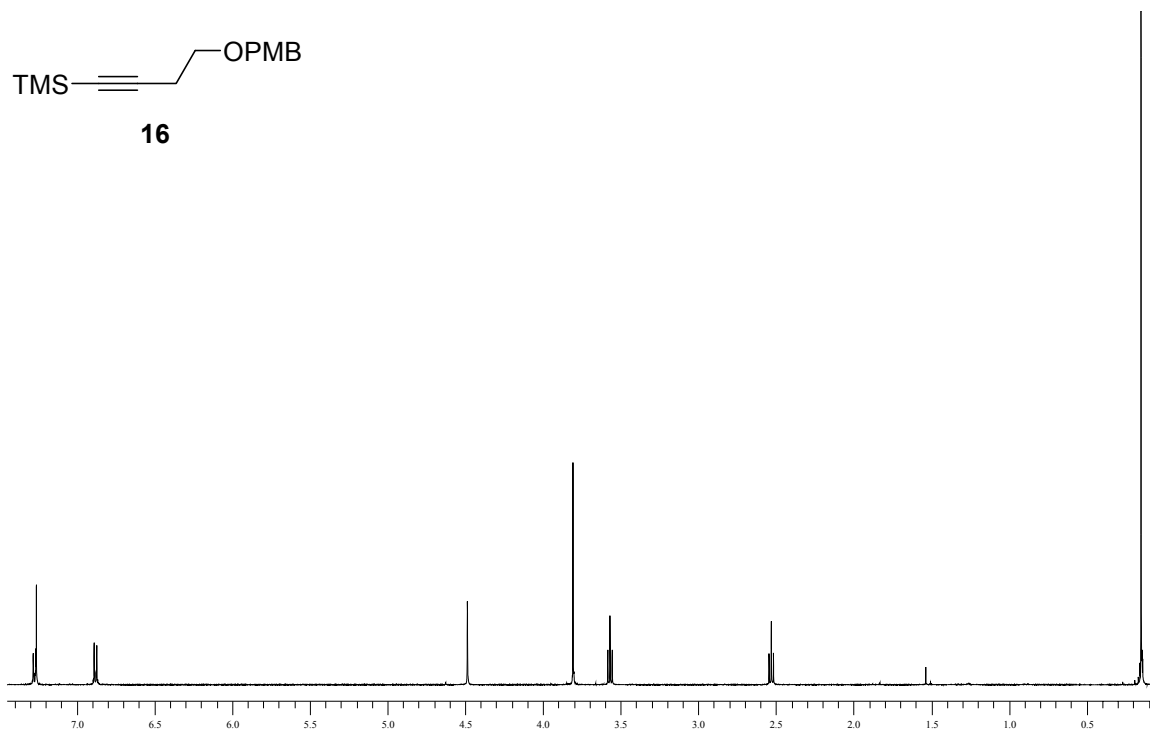
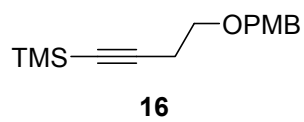


$^1\text{H}$  (400 MHz) and  $^{13}\text{C}$  (100 MHz) of compound **23** ( $\text{CDCl}_3$ )

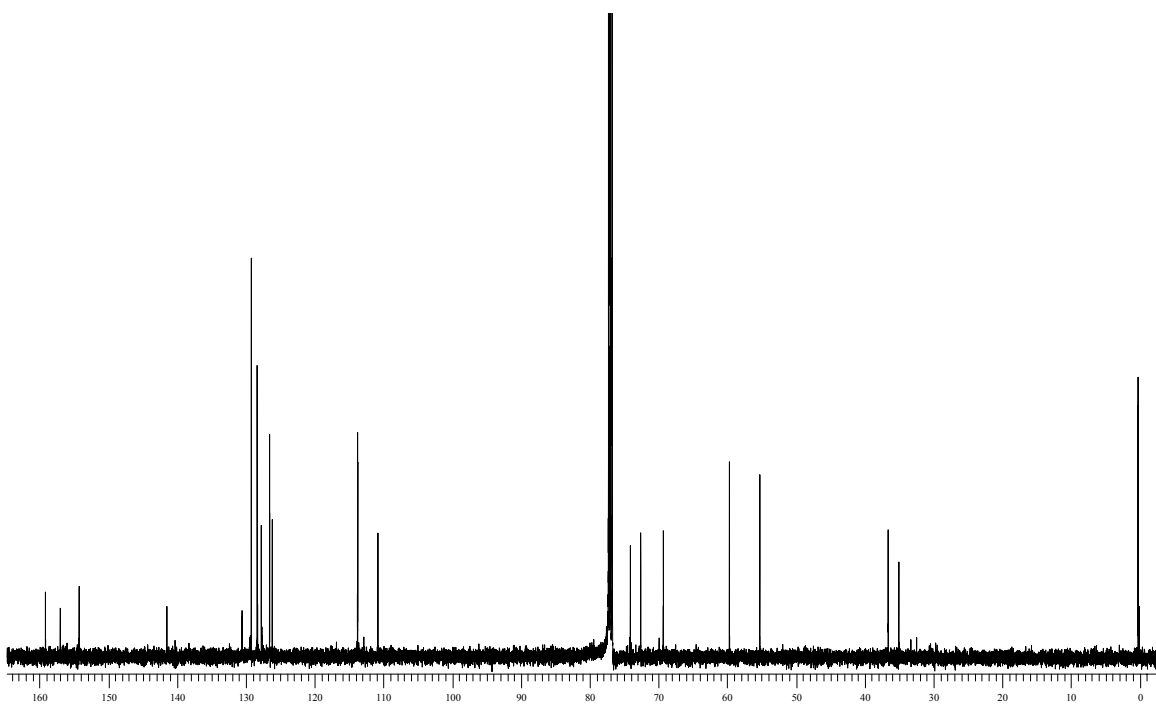
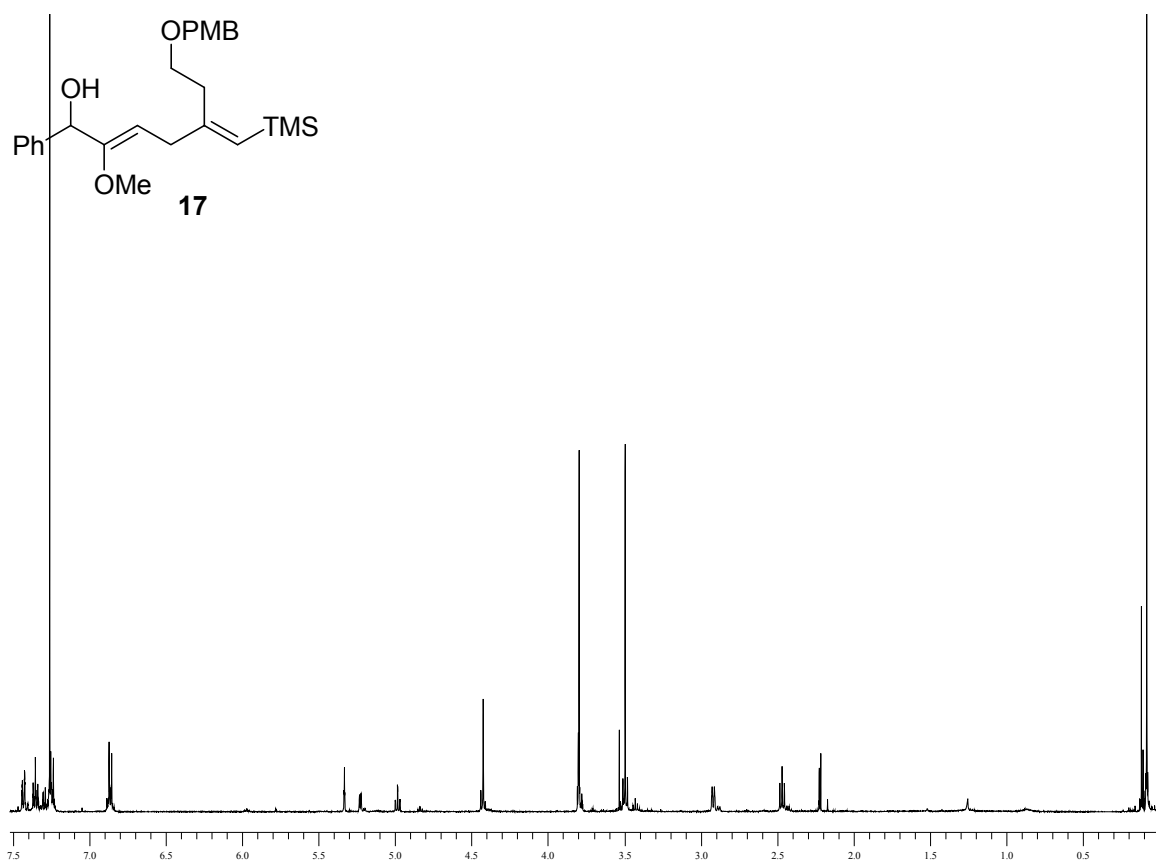




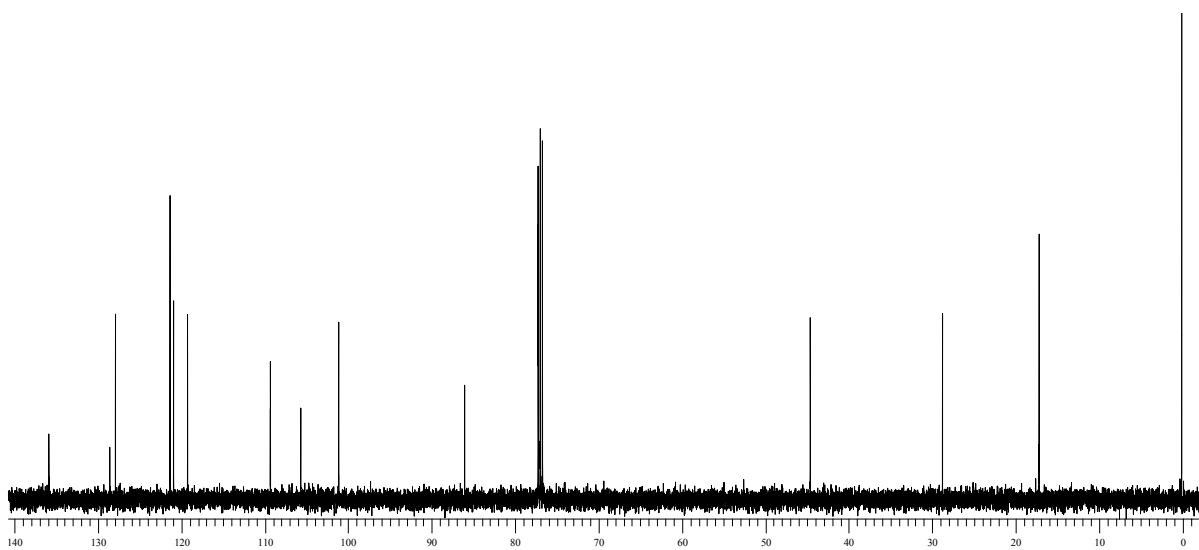
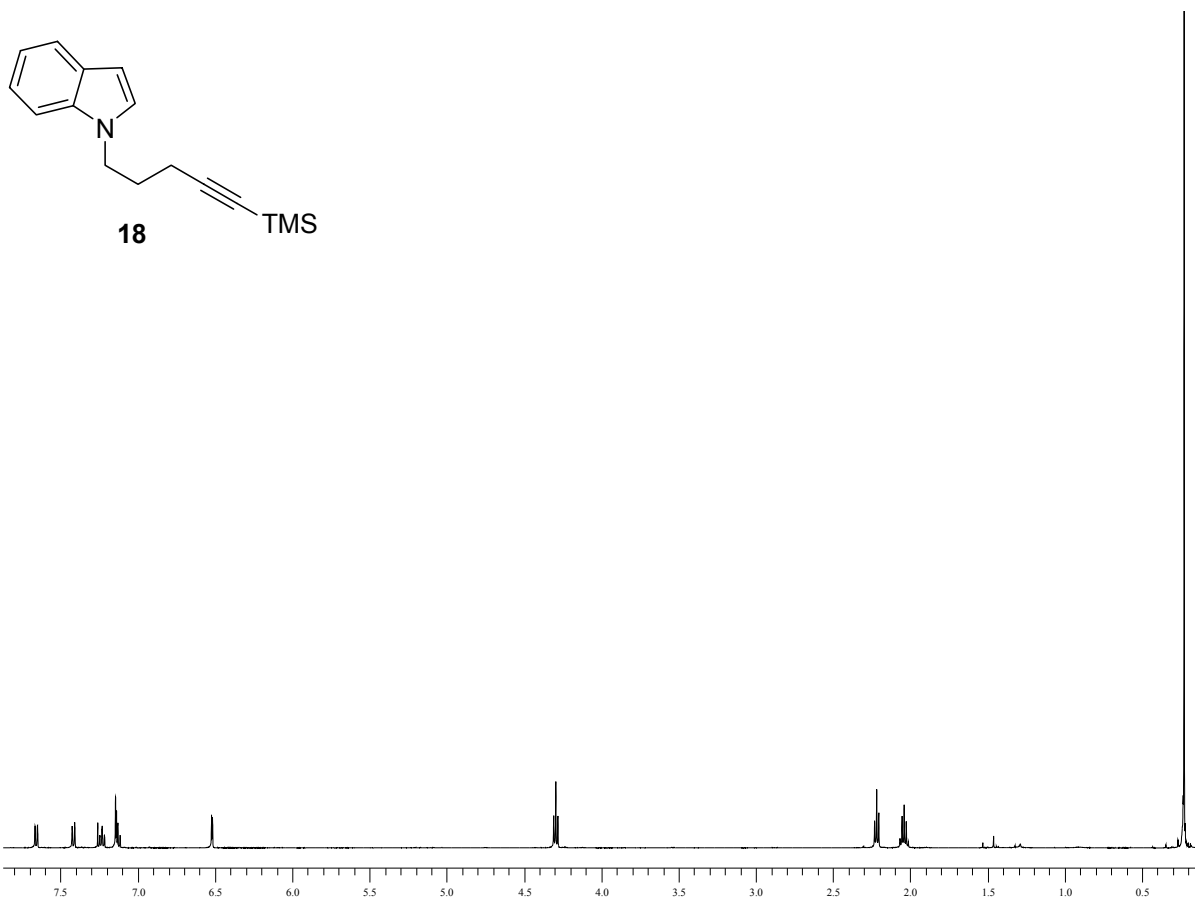
$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **23a** ( $\text{CDCl}_3$ )



$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **16** ( $\text{CDCl}_3$ )

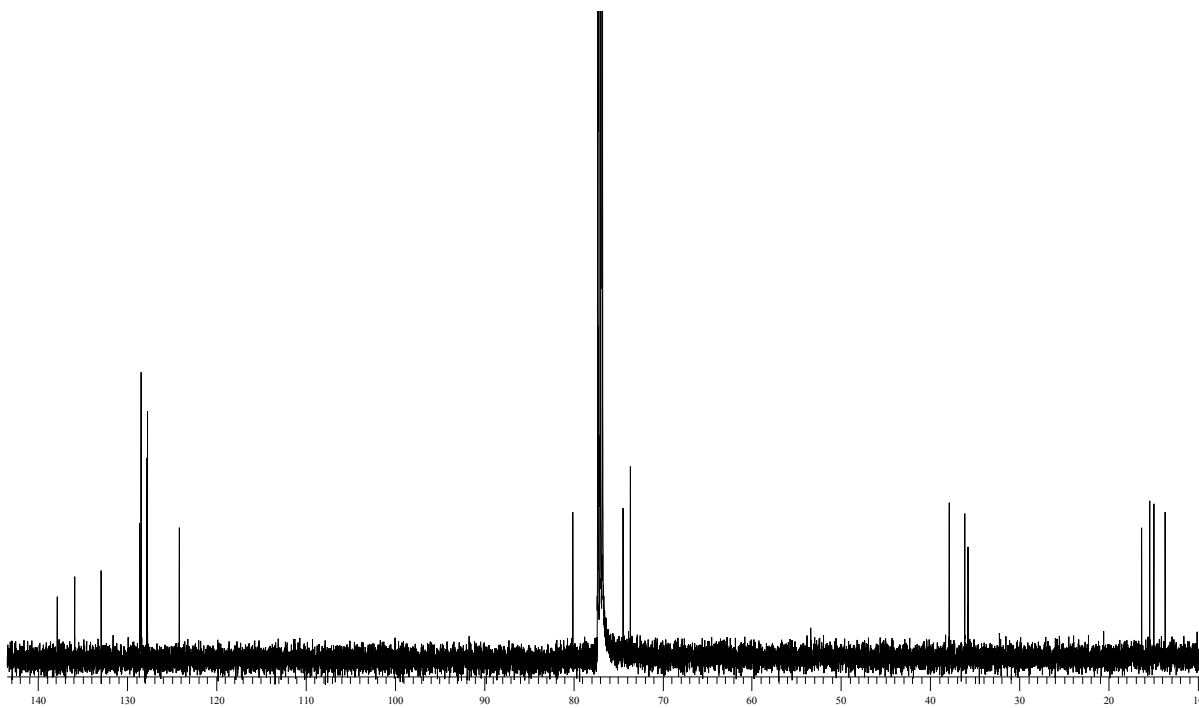
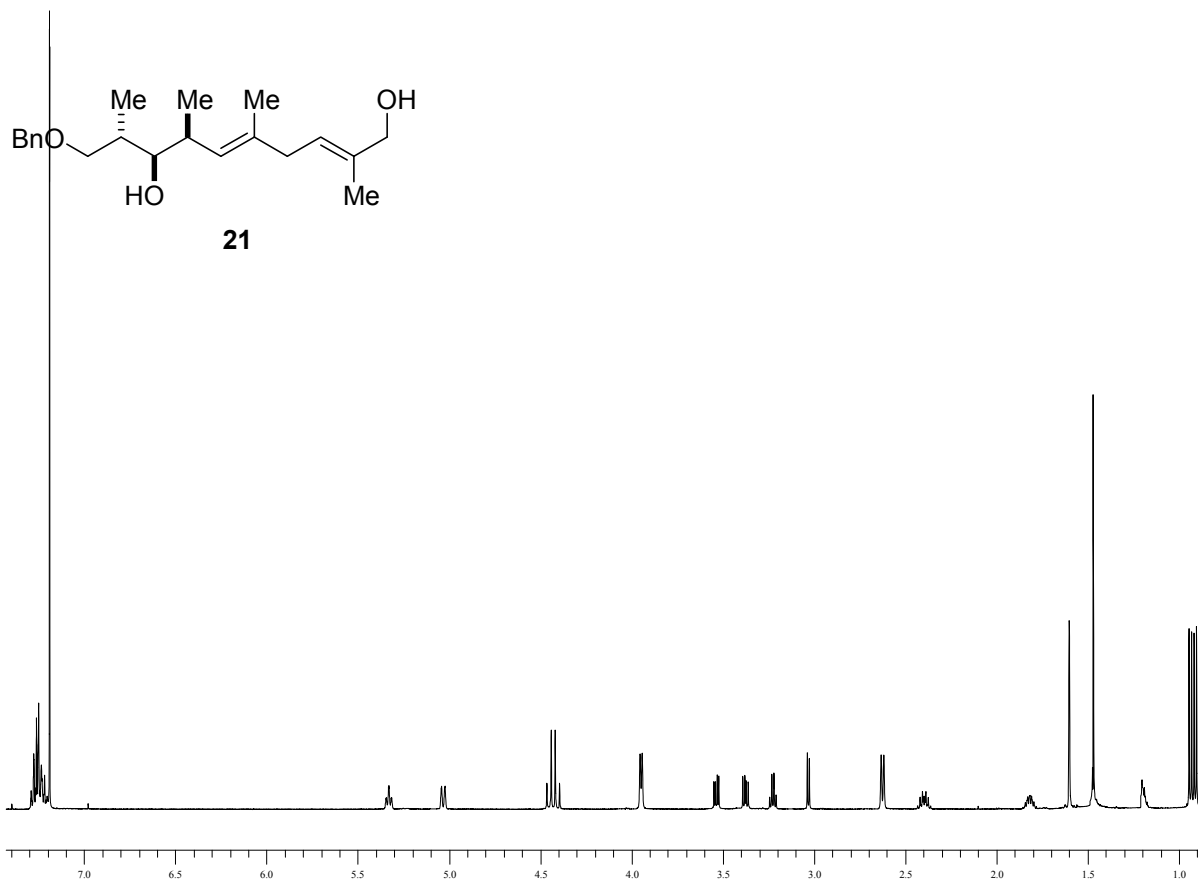


<sup>1</sup>H (500 MHz) and <sup>13</sup>C (126 MHz) of compound **17** (CDCl<sub>3</sub>)



$^1\text{H}$  (500 MHz) and  $^{13}\text{C}$  (126 MHz) of compound **18** ( $\text{CDCl}_3$ )





<sup>1</sup>H (500 MHz) and <sup>13</sup>C (126 MHz) of compound **21** (CDCl<sub>3</sub>)