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. $Ti(O\textit{i}Pr)_4$ was used after distillation of the commercially available reagent. $ClTi(O\textit{i}Pr)_3$ 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}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}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}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}C chemical shifts are reported relative to the central line of $CDCl_3$ (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:

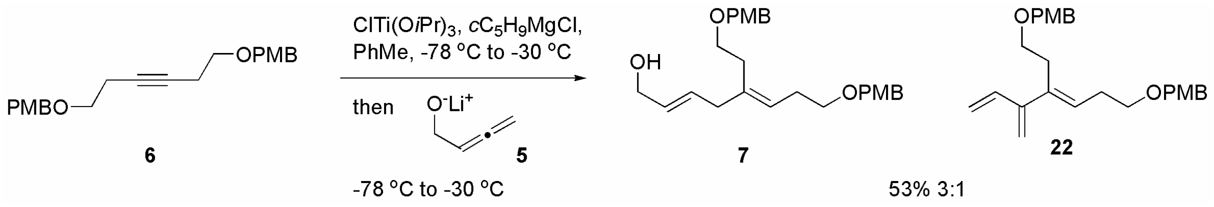
Allene 5. Molander, G. A.; Cormier, E. P.; *J. Org. Chem.* **2005**, *7*, 2622 - 2626.

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.

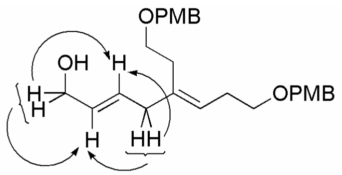


Synthesis of 1,4-Diene 7 and Triene 22. To a –78 °C solution of alkyne **6**[1] (266 mg, 0.75 mmol) in 5.0 mL of PhMe was added 1.50 mL of ClTi(O*i*Pr)$_3$ (1.0M in hexanes, 1.50 mmol) and 1.53 mL of *c*C$_5$H$_9$MgCl (1.96M in Et$_2$O, 3.00 mmol) dropwise via a gas-tight syringe. The resulting clear, 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 **5** (105 mg, 1.50 mmol) in 1.0 mL PhMe was added 610 µL of *n*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 °C titanium solution dropwise via cannula. After warming slowly to –30 °C over 1.5 hr, the reaction was quenched with 5 mL of sat. NH$_4$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$_3$ solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na$_2$SO$_4$. Flash column chromatography (10 % EtOAc/hexanes, then 50

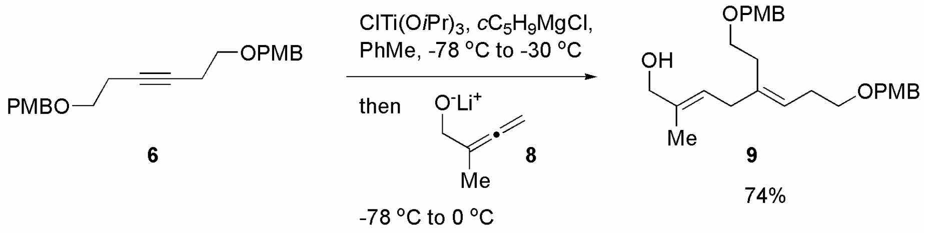
% EtOAc/hexanes) of the crude material (**7**:**22** = 3:1 by ^{1}H NMR) provided 128 mg (40 %) of diene **7** and 40 mg (13%) of triene **22** as clear, colorless oils.

(2E,5Z)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)octa-2,5-dien-1-ol, 7. ^{1}H NMR (500 MHz, CDCl$_3$) δ 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}C NMR (126 MHz, CDCl$_3$) δ 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 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{34}O_5Na$, 449.24 *m/z* (M + Na); observed, 449.4 (M + Na)$^+$ *m/z*.

Observed nOe enhancements for structure determination:



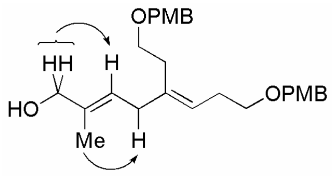
(3E)-1-(4-methoxybenzyloxy)-4-(2-(4-methoxybenzyloxy)ethyl)-5-vinyl-3,5-hexadiene, 22. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26-7.23 (m, 4H), 6.88-6.85 (m, 4H), 6.37 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.51 (t, *J* = 6.9 Hz, 1H), 5.24 (d, *J* = 17.3 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, H), 5.06 (s, 1H), 4.97 (s, 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}C NMR (126 MHz, CDCl$_3$) δ 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 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{32}O_4Na$, 431.23 *m/z* (M + Na); observed, 431.3 (M + Na)$^+$ *m/z*.

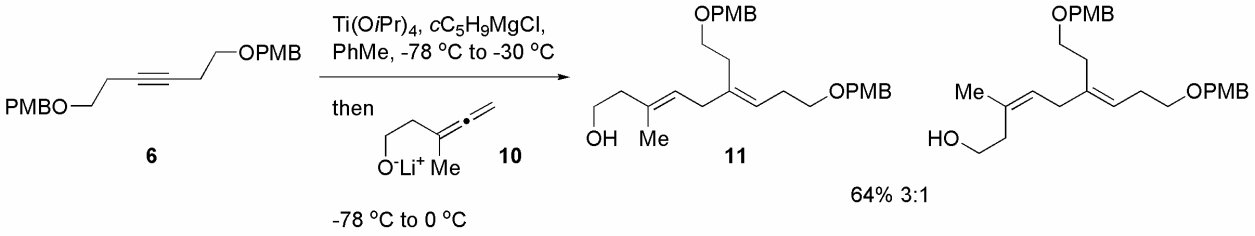


Synthesis of 1,4-Diene 9. To a –78 °C solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 850 µL of ClTi(O*i*Pr)$_3$ (1.0M in hexanes, 0.85 mmol) and 860 µL of *c*C$_5$H$_9$MgCl (1.96M in Et$_2$O, 1.69 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned 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 **8**^{2} (69 mg, 0.39 mmol) in 1.0 mL PhMe was added 160 µL 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 °C titanium solution dropwise via cannula. After warming slowly to 0 °C over 2 hr, the reaction was quenched with 5 mL of sat. NH$_4$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$_3$ solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na$_2$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}H NMR (400 MHz, CDCl$_3$) δ 7.26-7.23 (m, 4H), 6.89-6.85 (m, 4H), 5.42-5.37 (m, 1H), 5.24 (t, *J* = 7.1 Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 4.00 (d, *J* = 5.8 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; LRMS (EI, Na) calcd for $C_{27}H_{36}O_5Na$, 463.26 *m/z* (M + Na); observed, 463.3 $(M + Na)^+$ *m/z*.

Observed nOe enhancements for structure determination:

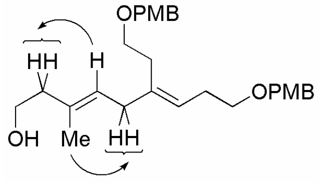


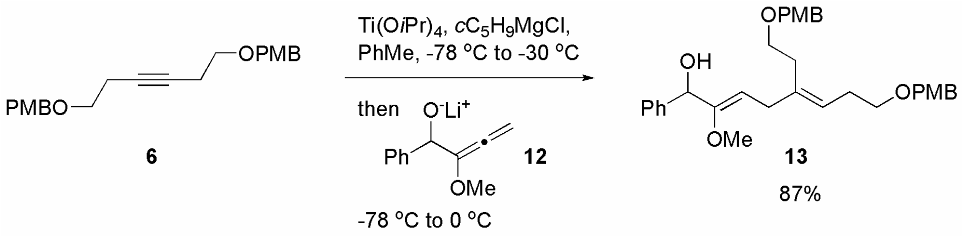


Synthesis of 1,4-Diene 11. To a –78 °C solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 250 μL of Ti(O*i*Pr)$_4$ (0.85 mmol) and 860 μL of *c*C_5H_9MgCl (1.96M in Et_2O, 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown 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 μL 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 °C titanium solution dropwise via cannula. After warming slowly to 0 °C over 2 hr, the reaction was quenched with 5 mL of sat. NH_4Cl solution. The mixture was warmed to room temperature before extracting with EtOAc (3 x 15 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na_2SO_4. 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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^{-1}; LRMS (EI, Na) calcd for $C_{28}H_{38}O_5Na$, 477.27 *m/z* (M + Na); observed, 477.4 $(M + Na)^+$ *m/z*.

Observed nOe enhancements for structure determination:

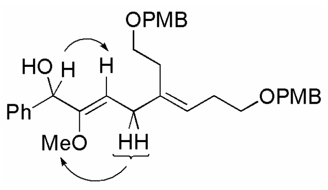


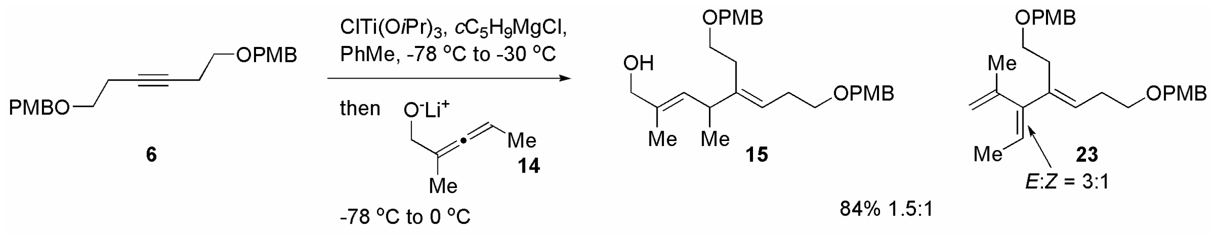


Synthesis of 1,4-Diene 13. To a –78 ^{o}C solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 250 μL of Ti(O*i*Pr)$_4$ (0.84 mmol) and 860 μL of *c*C$_5$H$_9$MgCl (1.96M in Et$_2$O, 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to –30 ^{o}C over 1 hr. The reaction mixture was stirred at –30 ^{o}C for 1 hr and then cooled to –78 ^{o}C. To a separate –78 ^{o}C solution of allene **12** (33 mg, 0.39 mmol) in 1.0 mL PhMe was added 160 μL 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 ^{o}C titanium solution dropwise via cannula. After warming slowly from –78 ^{o}C to –30 ^{o}C over 1 hr, then from –30 ^{o}C to 0 ^{o}C over 1 hr, then at 0 ^{o}C for 1 hr, the reaction was quenched with 5 mL of sat. NH$_4$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$_3$ solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na$_2$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}H NMR (500 MHz, CDCl$_3$) δ 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 Hz, 1H), 5.20 (d, *J* = 4.7 Hz, 1H), 4.93 (t, *J* = 7.6 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 Hz, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.85 (d, *J* = 7.3 Hz, 2H), 2.38-2.32 (m, 4H), 2.27 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 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 cm^{-1}; HRMS (EI, Na) calcd for $C_{33}H_{40}O_6Na$, 555.2825 *m/z* (M + Na); observed, 555.2717 $(M + Na)^+$ *m/z*.

Observed nOe enhancements for structure determination:



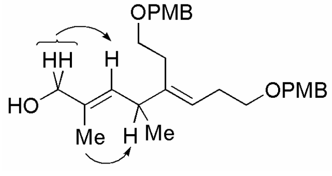


Synthesis of 1,4-Diene 15 and Triene 23. To a –78 °C solution of alkyne **6** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 850 μL of ClTi(O*i*Pr)$_3$ (1.0M in hexanes, 0.85 mmol) and 860 μL of *c*C$_5$H$_9$MgCl (1.96M in Et$_2$O, 1.69 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow 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 **14** (39 mg, 0.39 mmol) in 1.0 mL PhMe was added 160 μL 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 °C titanium solution dropwise via cannula. After warming slowly to –30 °C over 1 hr, then at –30 °C for 1 hr, then from –30 °C to 0 °C over 1 hr, the reaction was quenched with 5 mL of sat. NH$_4$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.

$NaHCO_3$ solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na_2SO_4. Flash column chromatography (5 % EtOAc/hexanes, then 10 % EtOAc/hexanes, then 50 % EtOAc/hexanes) of the crude material (**15**:**23** = 1.5:1 by ^{1}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. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; LRMS (EI, Na) calcd for $C_{28}H_{38}O_5Na$, 477.27 *m/z* (M + Na); observed, 477.4 $(M + Na)^+$ *m/z*.

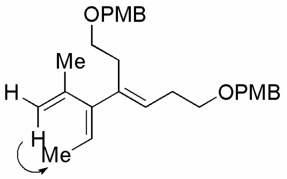
Observed nOe enhancements for structure determination:



(3E,5E)-1-(4-methoxybenzyloxy)-4-(2-(4-methoxybenzyloxy)ethyl)-5-(2-propenyl)-3,5-heptadiene, 23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86

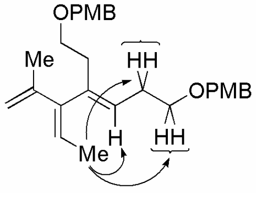
(m, 4H), 5.53 (t, *J* = 6.8 Hz, 1H), 5.51 (t, *J* = 7.1 Hz, 1H), 5.13-5.11 (m, 1H), 4.66-4.65 (m, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.44 (t, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 8.1 Hz, 2H), 2.57 (t, *J* = 8.1 Hz, 2H), 2.43 (dt, *J* = 14.1, 7.1 Hz, 2H), 1.72 (s, 3H), 1.68 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; LRMS (EI, Na) calcd for $C_{28}H_{36}O_4Na$, 459.26 *m/z* (M + Na); observed, 459.3 $(M + Na)^+$ *m/z*.

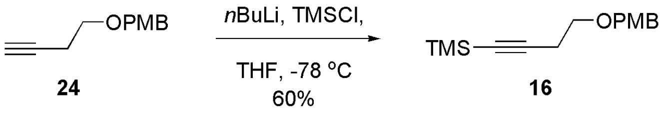
Observed nOe enhancements for structure determination:



(3E,5Z)-1-(4-methoxybenzyloxy)-4-(2-(4-methoxybenzyloxy)ethyl)-5-(2-propenyl)-3,5-heptadiene, 23a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 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 cm^{-1}; LRMS (EI, Na) calcd for $C_{28}H_{36}O_4Na$, 459.26 *m/z* (M + Na); observed, 459.3 $(M + Na)^+$ *m/z*.

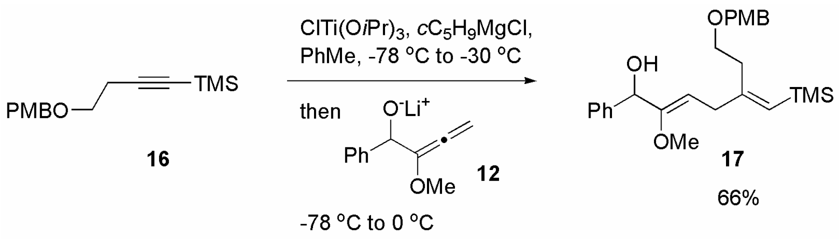
Observed nOe enhancements for structure determination:





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 °C. The reaction was stirred for 30 min at –78 °C, then 435 μL 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_2O (3 x 5 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution (1 x 10 mL) and brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. Purification of the crude material by flash column chromatography (5 % EtOAc/hexanes) provided 270 mg (60 %) of **16** as a clear, pale yellow oil.

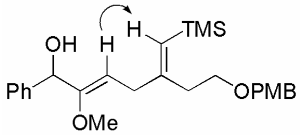
(4-(4-methoxybenzyloxy)but-1-ynyl)trimethylsilane, 16. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.49, (s, 2H), 3.81 (s, 2H), 3.57 (t, *J* = 7.3 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 0.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 130.3, 129.2, 113.8, 103.8, 85.7, 72.6, 68.1, 55.3, 21.3, 0.1; IR (thin film, NaCl) 2958, 2178, 1616, 1457, 1249, 1100, 1037, 842, 760 cm^{-1}; LRMS (EI, Na) calcd for $C_{15}H_{22}O_2SiNa$, 285.14 *m/z* (M + Na); observed, 285.2 $(M + Na)^+$ *m/z*.

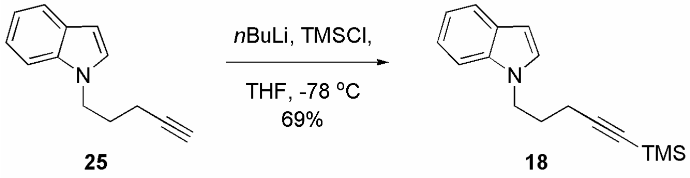


Synthesis of 1,4-Diene 17. To a –78 °C solution of alkyne **16** (116 mg, 0.44 mmol) in 2.9 mL of PhMe was added 660 μL of $ClTi(O\textit{i}Pr)_3$ (1.0M in hexanes, 0.84 mmol) and 680 μL of *c*C_5H_9MgCl (1.96M in Et_2O, 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black 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 **12** (54 mg, 0.31 mmol) in 1.0 mL PhMe was added 130 μL of *n*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 °C titanium solution dropwise via cannula. After warming slowly to 0 °C over 2 hr, the reaction was quenched with 5 mL of sat. NH_4Cl solution. The mixture was warmed to room temperature before extracting with EtOAc (3 x 15 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution (1 x 30 mL), brine (1 x 30 mL) and dried over anhydrous Na_2SO_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}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 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 cm^{-1}; LRMS (EI, Na) calcd for $C_{26}H_{36}O_4SiNa$, 463.24 *m/z* (M + Na); observed, 463.2 $(M + Na)^+$ *m/z*.

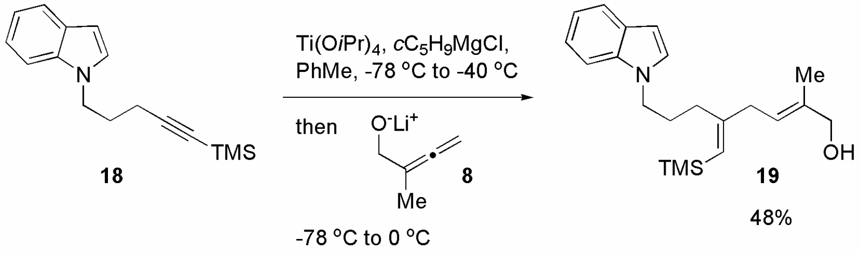
Observed nOe enhancements for structure determination:





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

1-(5-(trimethylsilyl)pent-4-ynyl)-1H-indole, 18. ^1H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (126 MHz, $CDCl_3$) δ 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 cm^{-1}; LRMS (EI, H) calcd for $C_{16}H_{22}NSi$, 256.14 *m/z* (M + H); observed, 256.0 $(M + H)^+$ *m/z*.

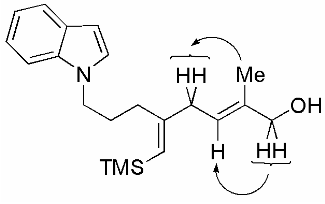


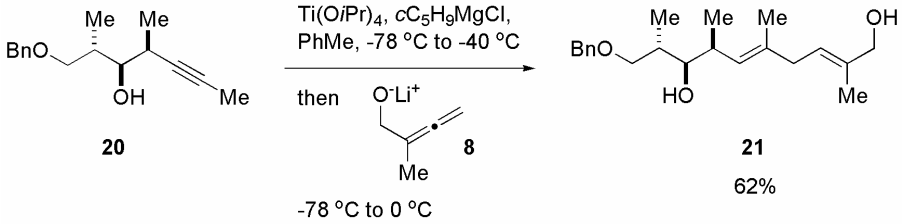
Synthesis of 1,4-Diene 19. To a solution of alkyne **18** (60 mg, 0.23 mmol) in 1.6 mL of PhMe was added 105 µL of Ti(O*i*Pr)$_4$. After cooling to –78 °C, 390 µL of *c*C$_5$H$_9$MgCl (1.85M in Et$_2$O, 0.72 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black while warming slowly to –40 °C over 1 hr. The reaction mixture was stirred at –40 °C for 1 hr and then cooled to –78 °C. To a separate –78 °C solution of allene **8** (14 mg, 0.16 mmol) in 0.5 mL PhMe was added 68 µL of *n*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 °C titanium solution dropwise via cannula. After warming slowly to 0 °C over 2 hr, the reaction was quenched with 5 mL of sat. NH$_4$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$_3$ solution (1 x 20 mL), brine (1 x 20 mL) and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent in vacuo gave a crude oil as a 4:1 mixture of regioisomers by ^{1}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}H NMR (500 MHz, CDCl$_3$) δ 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}C NMR (126 MHz, CDCl$_3$) δ 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 cm^{-1}.

Observed nOe enhancements for structure determination:

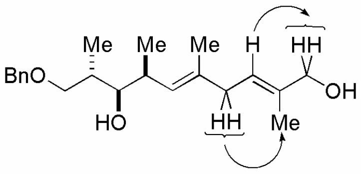




Synthesis of 1,4-Diene 21. To a –78 °C solution of alkyne **20**[4] (40 mg, 0.23 mmol) in 1.2 mL of PhMe was added 64 μL of *n*Buli (2.5M in hexanes, 0.16 mmol). After stirring for 10 min at –78 °C, 70 μL of Ti(O*i*Pr)$_4$ and 260 μL of *c*C$_5$H$_9$MgCl (1.85M in Et$_2$O, 0.48 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned black while warming slowly to –40 °C over 1 hr. The reaction mixture was stirred at –40 °C for 1 hr and then cooled to –78 °C. To a separate –78 °C solution of allene **8** (9 mg, 0.11 mmol) in 0.5 mL PhMe was added 44 μL of *n*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 °C titanium solution dropwise via cannula. After warming slowly to 0 °C over 2 hr, the reaction was quenched with 5 mL of sat. NH$_4$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. $NaHCO_3$ solution (1 x 20 mL), brine (1 x 20 mL) and dried over anhydrous Na_2SO_4. 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.

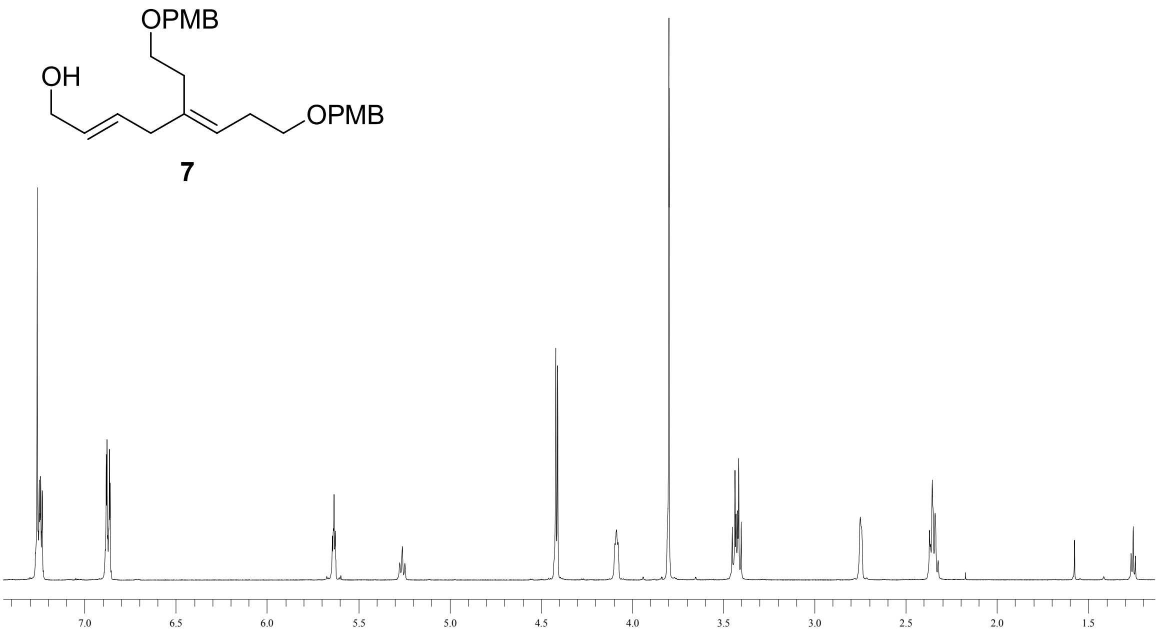
(2E,5E,7S,8R,9S)-10-(benzyloxy)-2,5,7,9-tetramethyldeca-2,5-diene-1,8-diol, 21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 5.40 (dt, J = 7.2, 1.3 Hz, 1H), 5.10 (dd, J = 9.5, 1.3 Hz, 1H), 4.52 (A of AB, J = 12.0 Hz, 1H), 4.48 (B of AB, J = 12.0 Hz, 1H), 4.02 (d, J = 5.7 Hz, 2H), 3.60 (dd, J = 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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^{-1}; LRMS (EI, Na) calcd for $C_{21}H_{31}NOSiNa$, 364.22 m/z (M + Na); observed, 364.4 $(M + Na)^+$ m/z.

Observed nOe enhancements for structure determination:

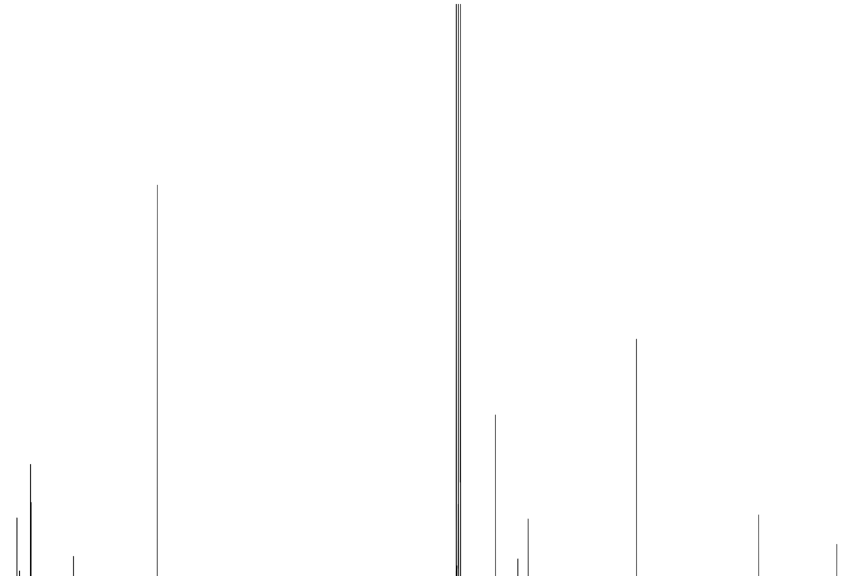


References:

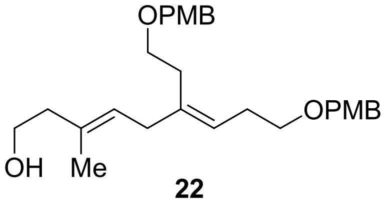
[1] Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764-2765.
[2] Allene 8 was used as a 3:1 mixture (minor component: 2-pentyn-1-ol). Reaction yield was based on the calculated amount of allene 8 present.
[3] Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*,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



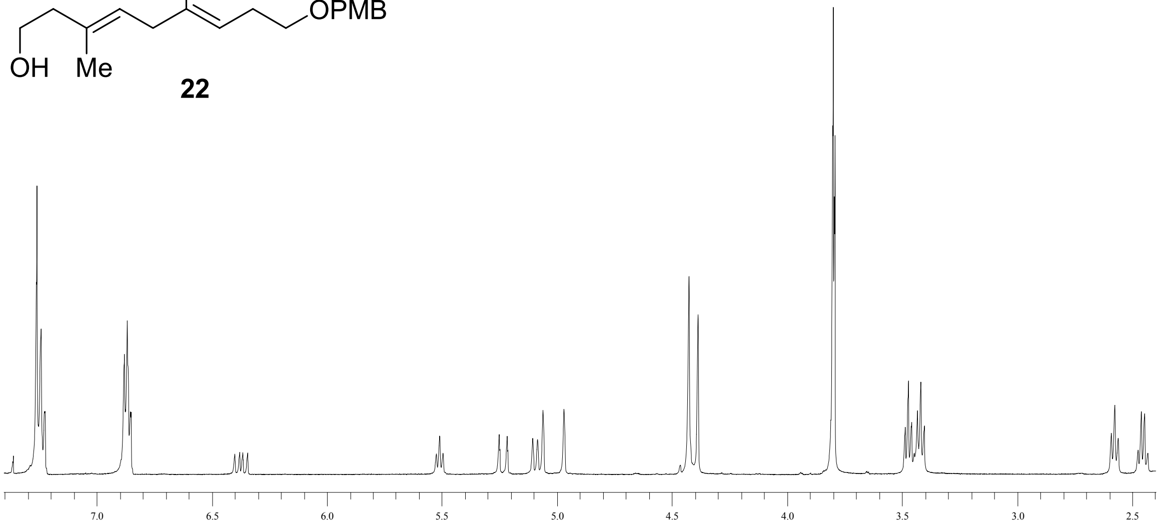
7

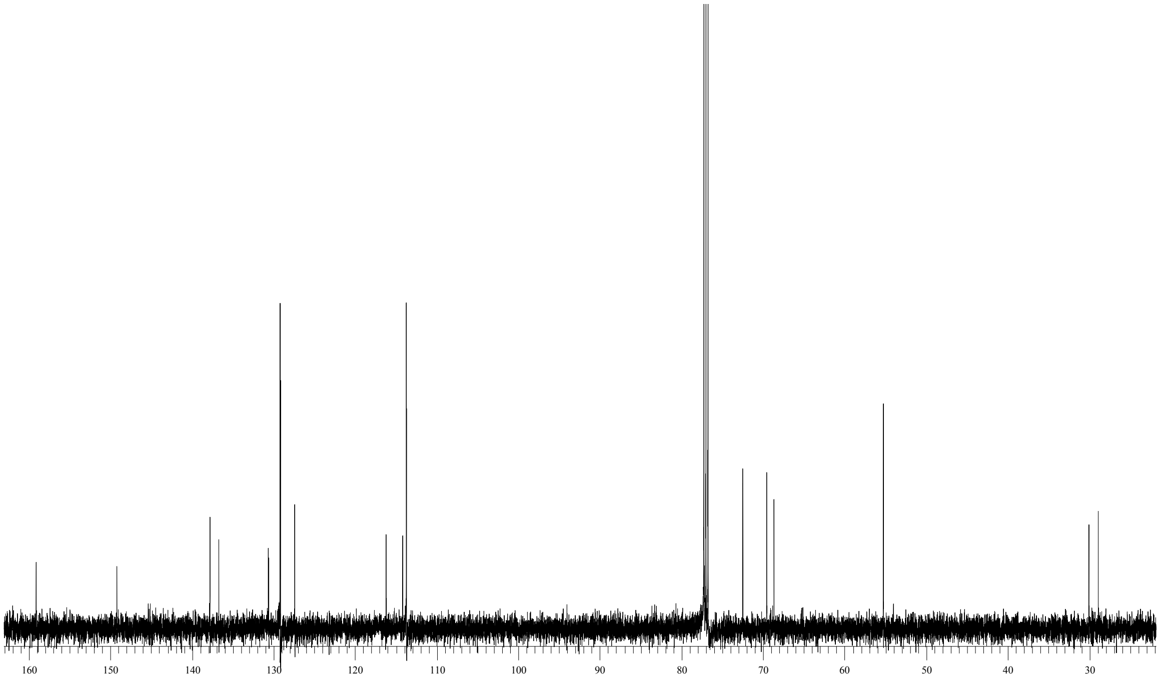


^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **7** ($CDCl_3$)

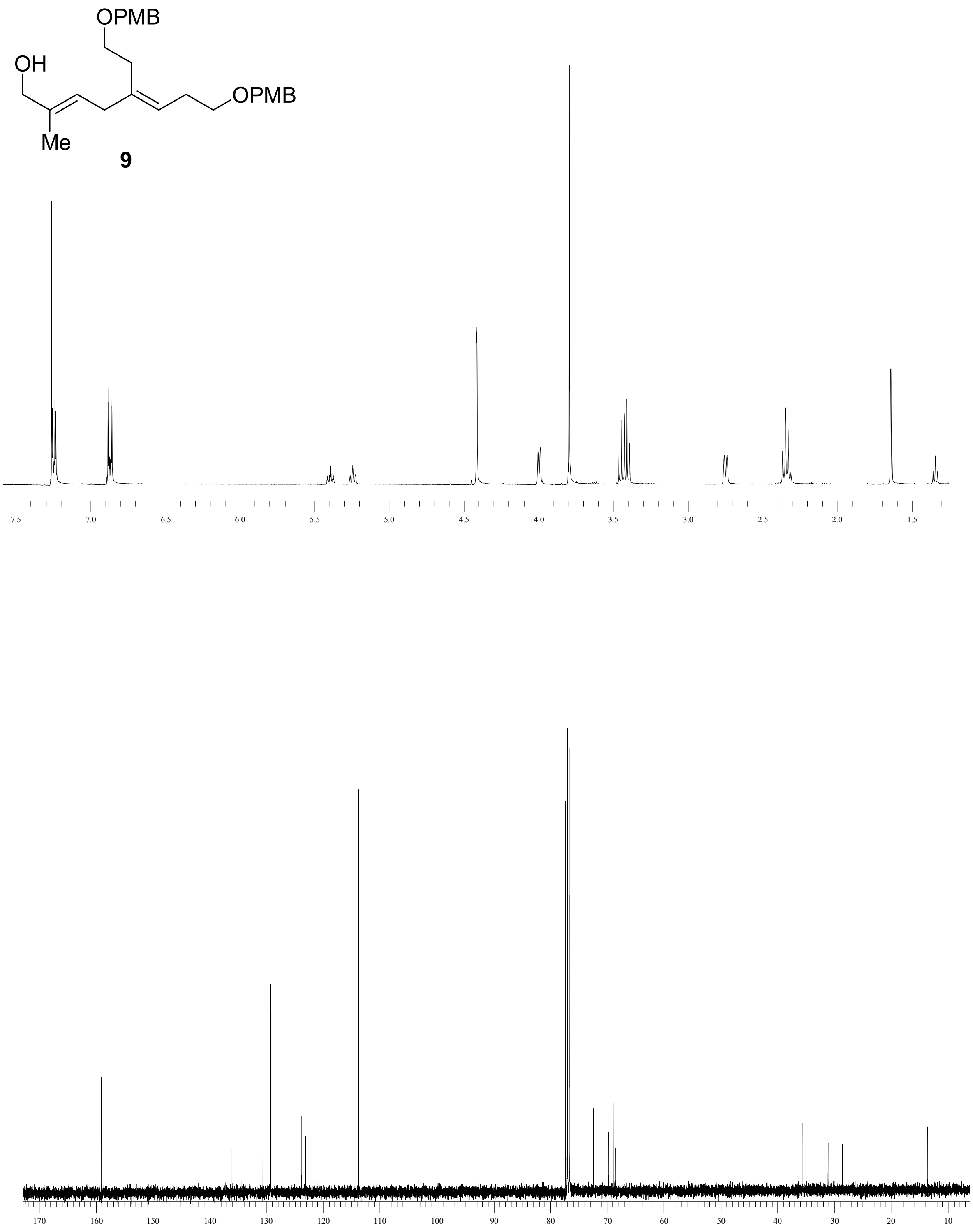


22

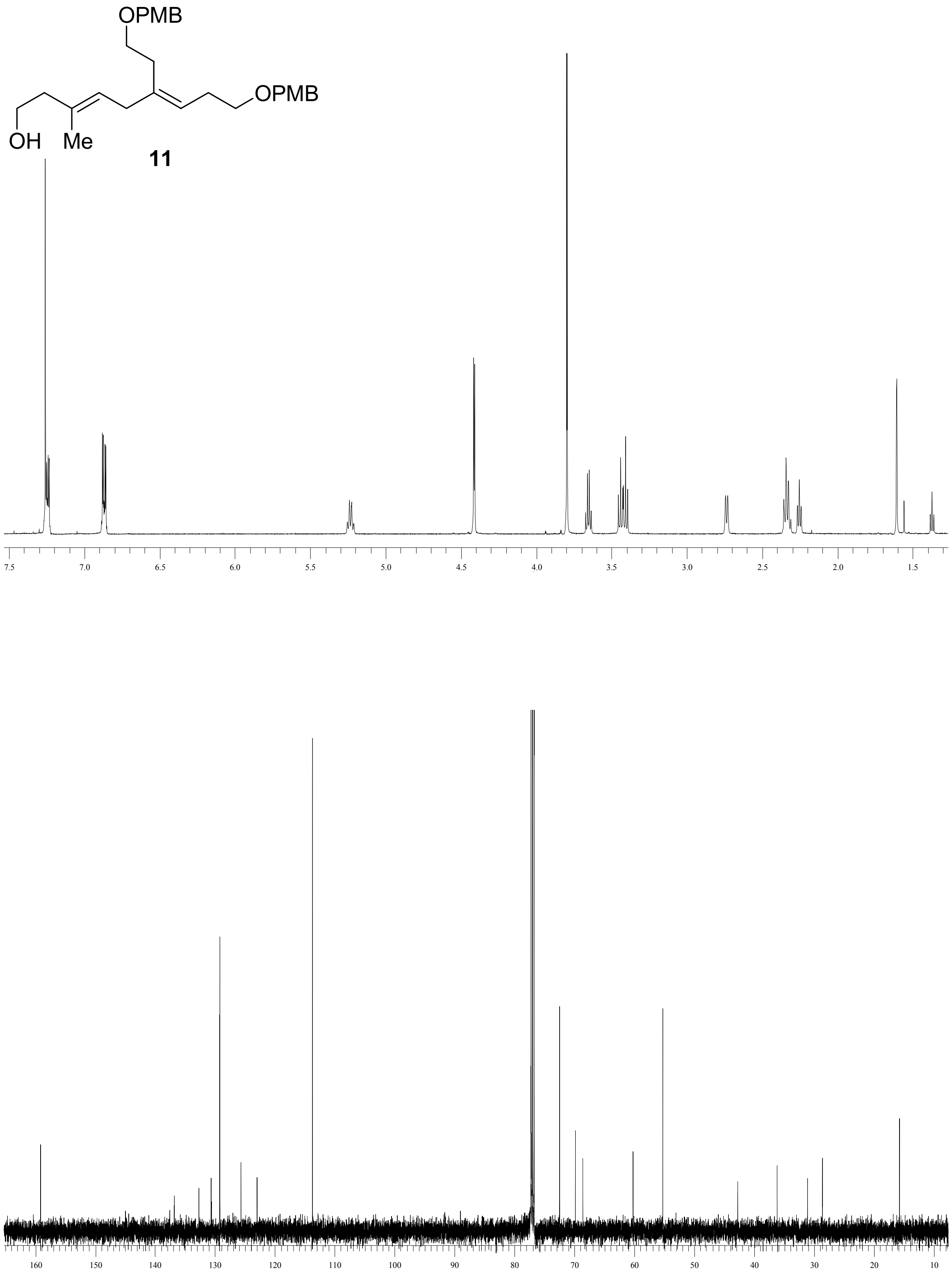




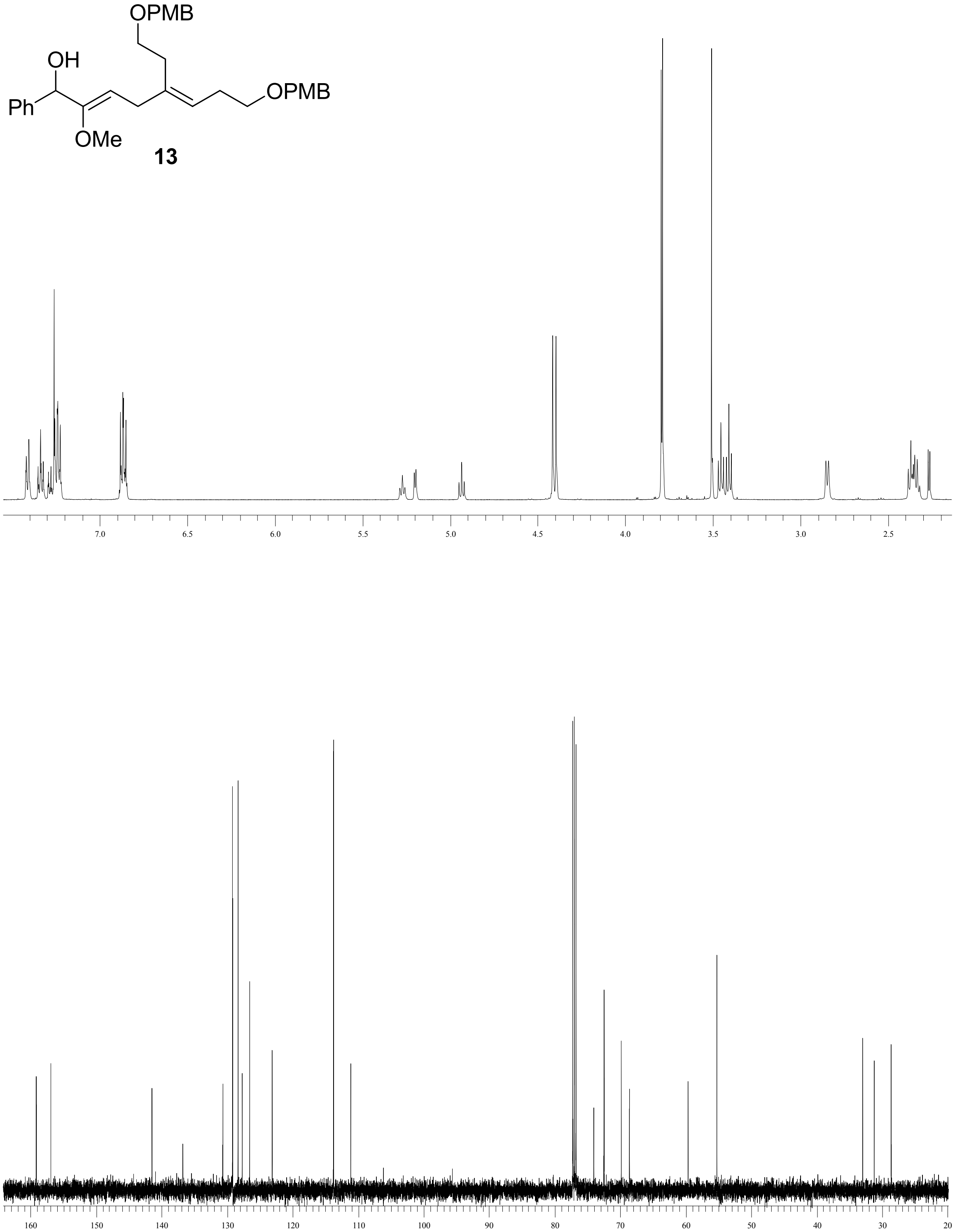
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **22** ($CDCl_3$)



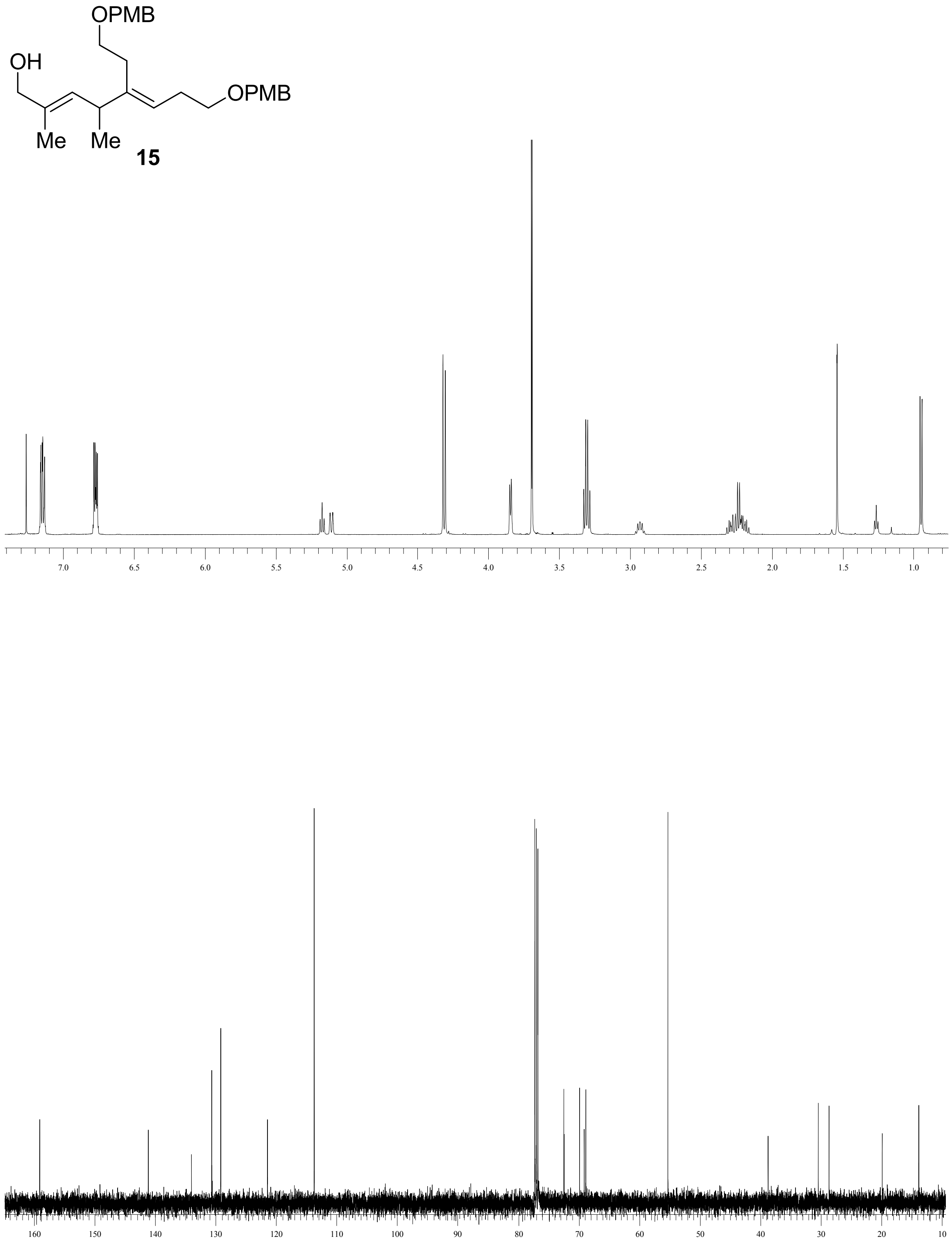
^{1}H (400 MHz) and ^{13}C (100 MHz) of compound **9** ($CDCl_3$)



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

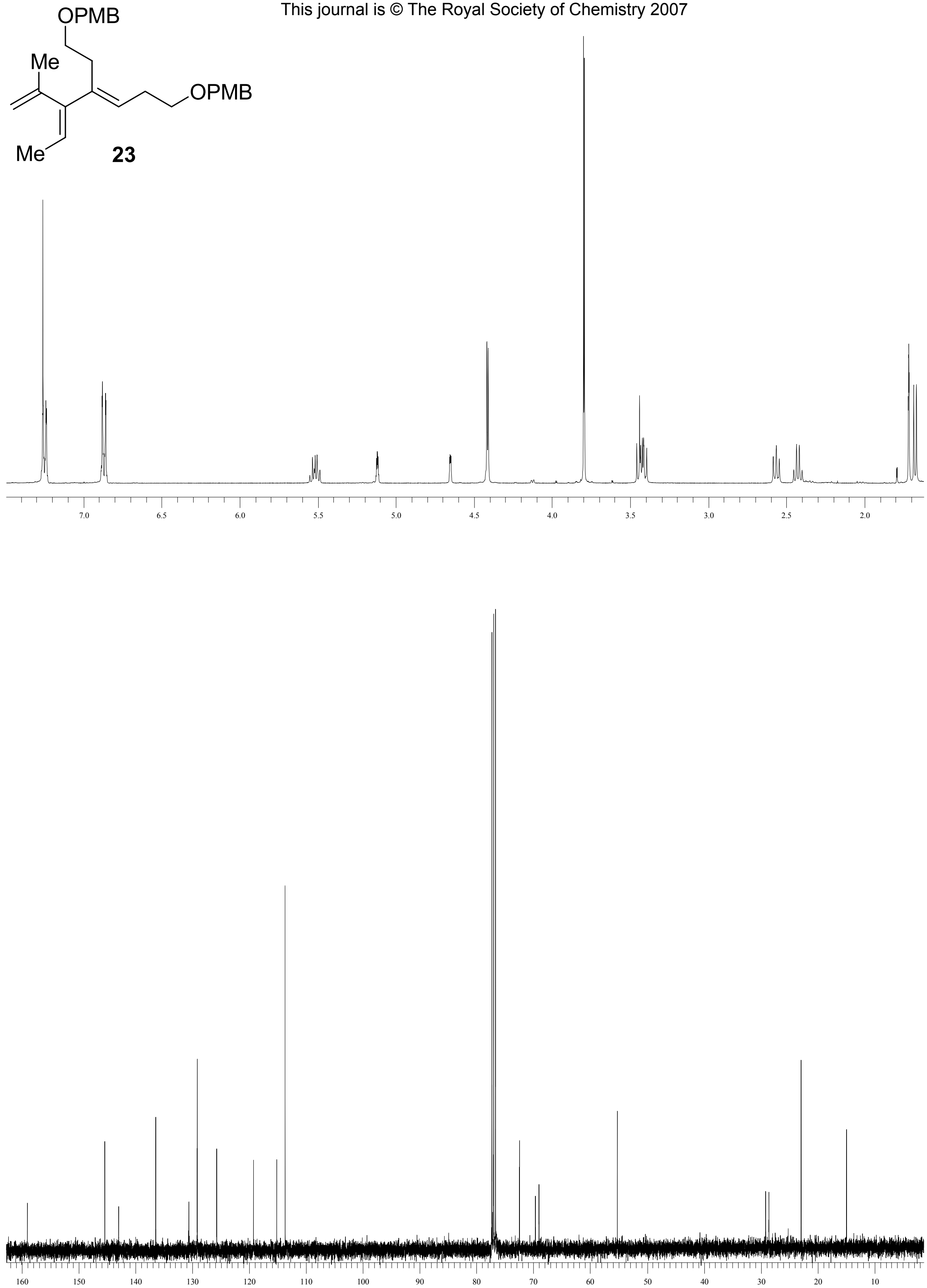


^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **13** ($CDCl_3$)



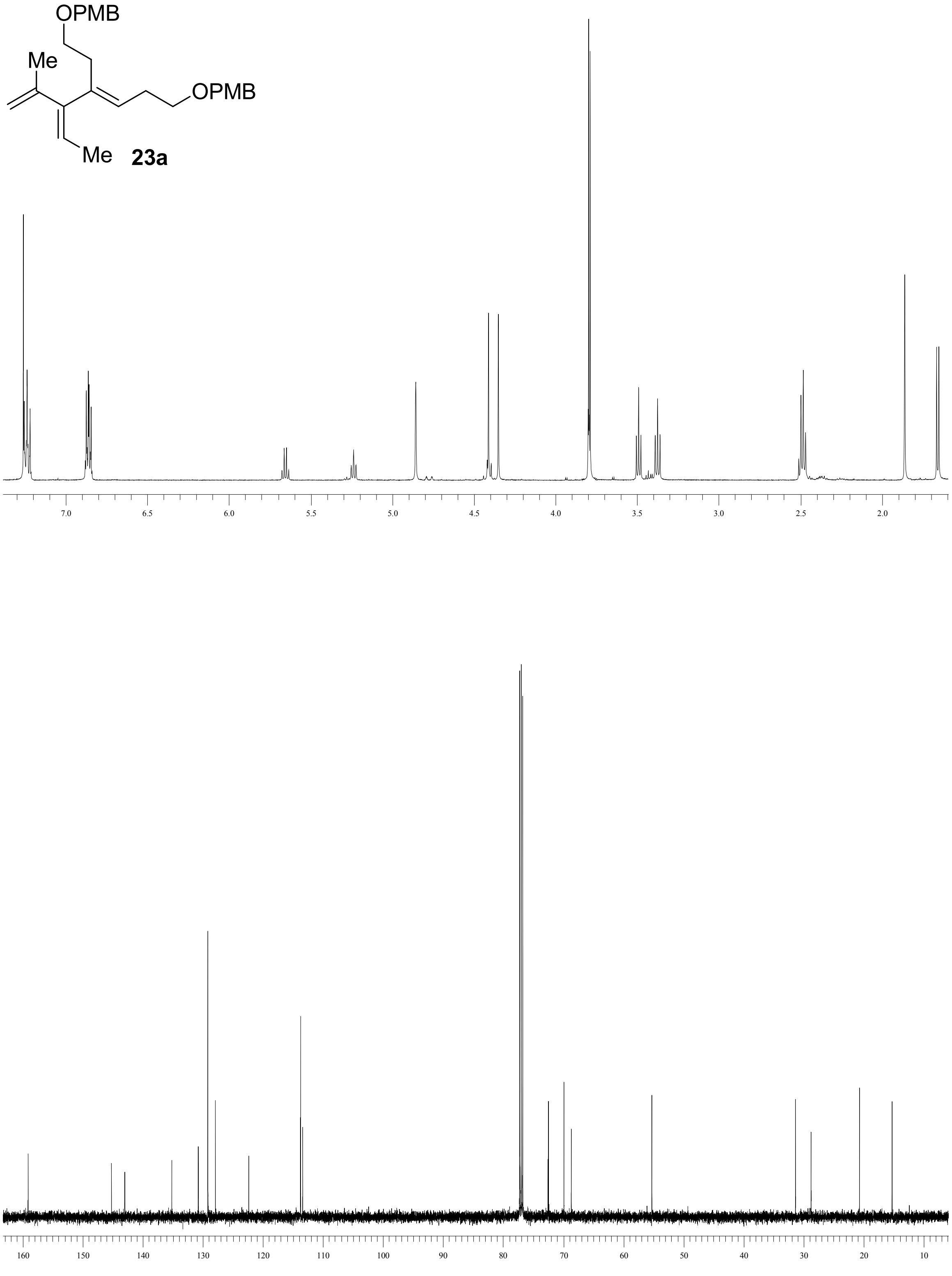
15

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

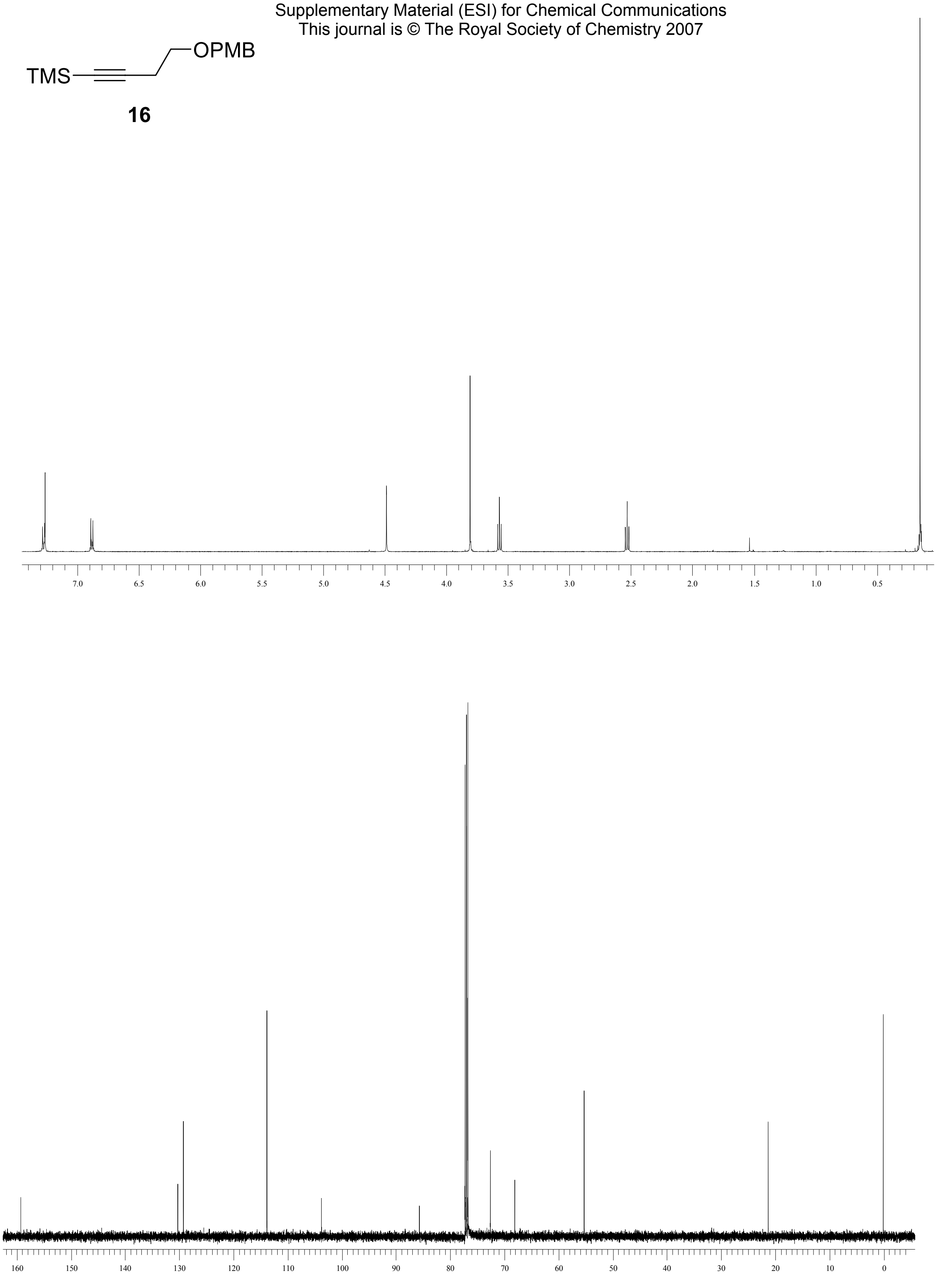


23

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

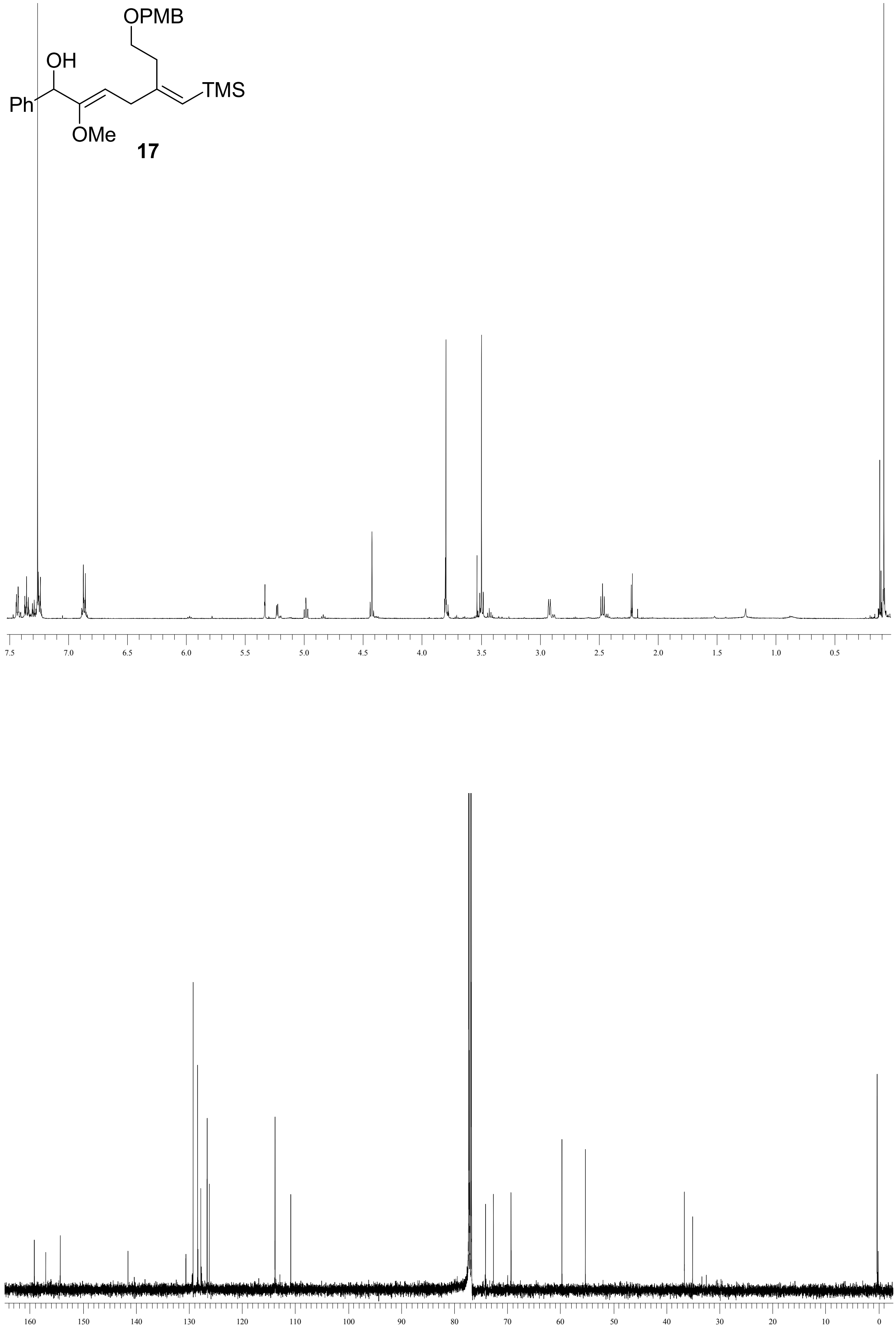


^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **23a** (CDCl$_3$)

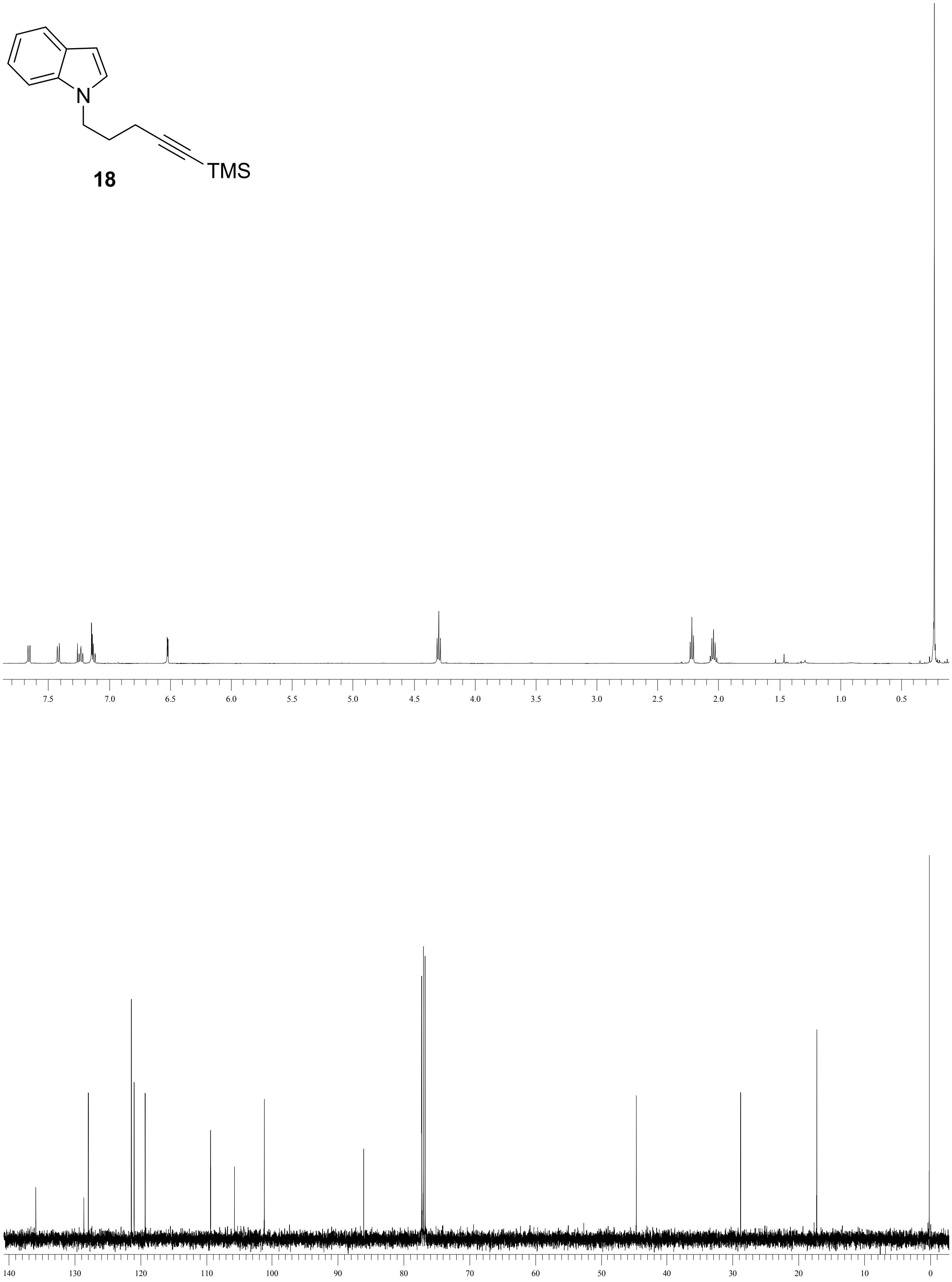


16

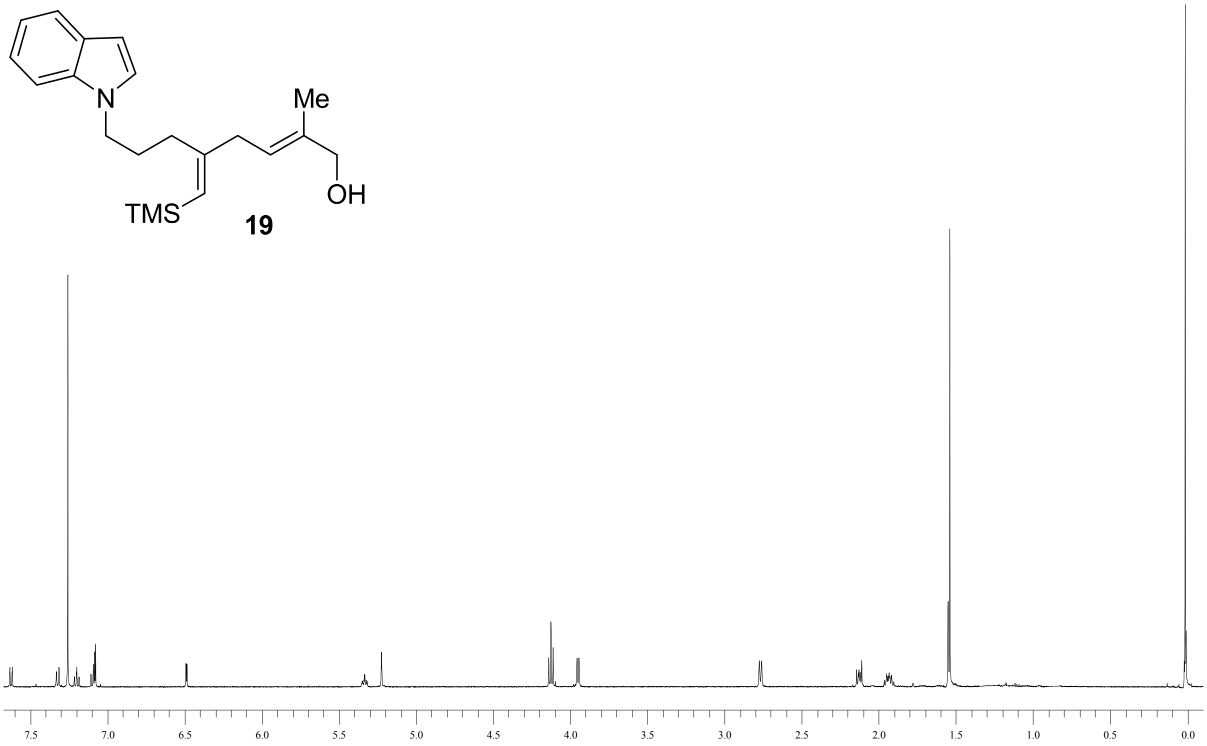
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **16** ($CDCl_3$)



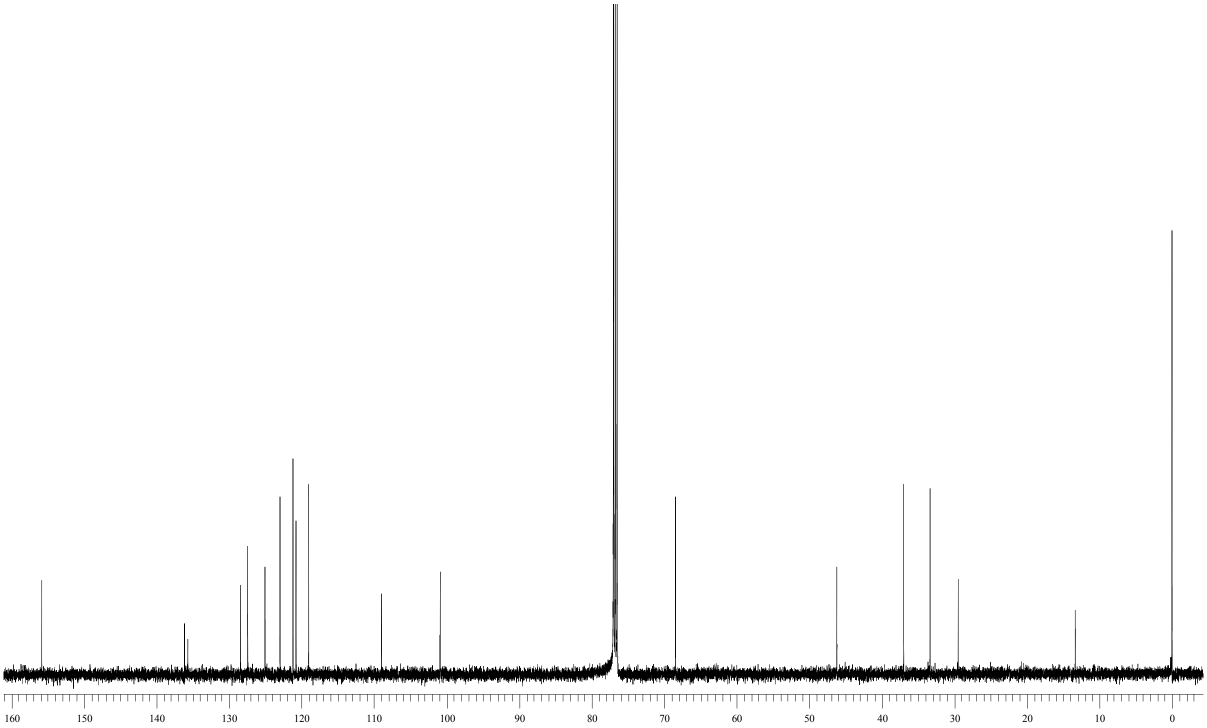
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **17** ($CDCl_3$)



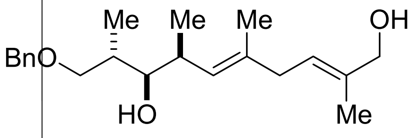
^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **18** ($CDCl_3$)



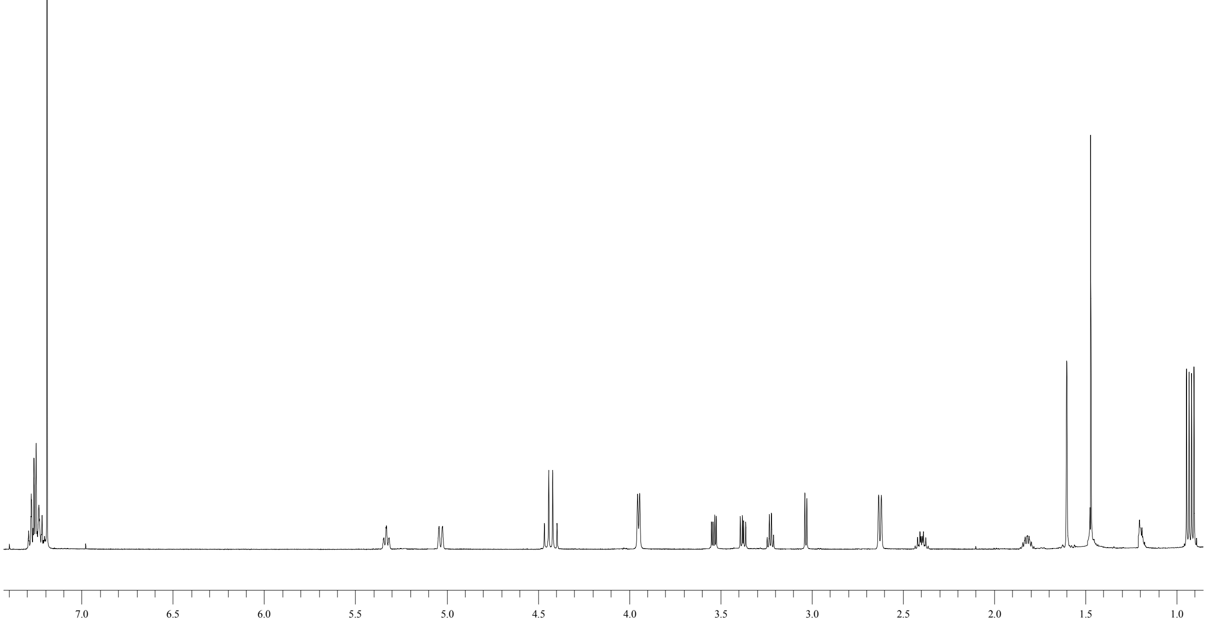
19

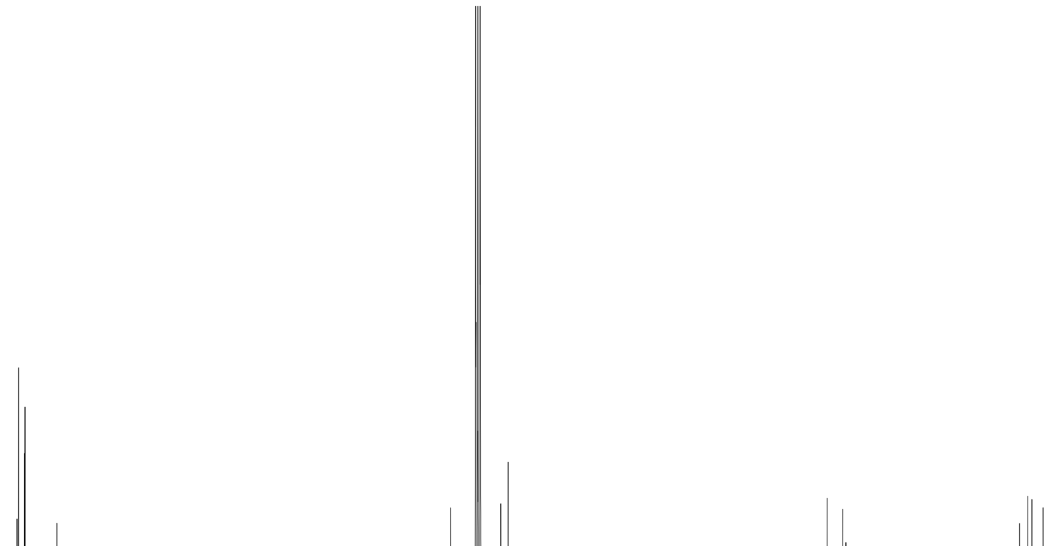


^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **19** ($CDCl_3$)



21





^{1}H (500 MHz) and ^{13}C (126 MHz) of compound **21** ($CDCl_3$)