Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

A Site- and Stereoselective Intermolecular Alkene-Alkyne Coupling Process

Holly A. Reichard and Glenn C. Micalizio*

Department of Chemistry, Yale University, New Haven, CT 06520

E-mail: glenn.micalizio@yale.edu

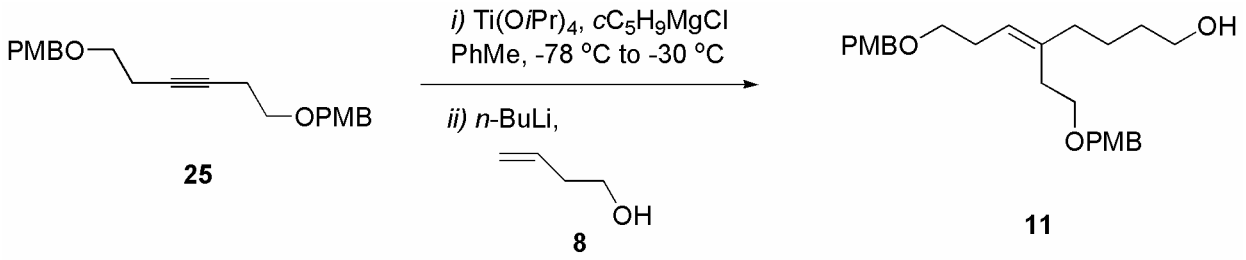
SUPPORTING INFORMATION:

General. All reactions were conducted in flame-dried glassware under nitrogen. Toluene was dried by distillation over sodium and benzophenone. Titanium tetraisopropoxide was purifed by distillation at 50 millitorr. All other commercially available reagents were used as received.

^{1}H NMR data were recorded at 400 MHz or 500 MHz using a Bruker AM-400 or BrukerAM-500 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 or BrukerAM-400 instrument. ^{13}C NMR chemical shifts were reported relative to the central line of $CDCl_3$ (77.23 ppm). Infrared spectra were recorded using a Thermo Electron Nicolet 6700 FT-IR Spectrometer. Low resolution mass spectrometry was performed on a Waters Micromass ® ZQ_{TM} instrument using electrospray ionization (EI). Mass spectra were acquired with an Applied Biosystems Voyager-DE Pro MALDI-TOF mass spectrometer. Optical rotations were measured on Perkin Elmer Model 341 polarimeter using a 1 mL capacity micro cell with a 10 cm path length.

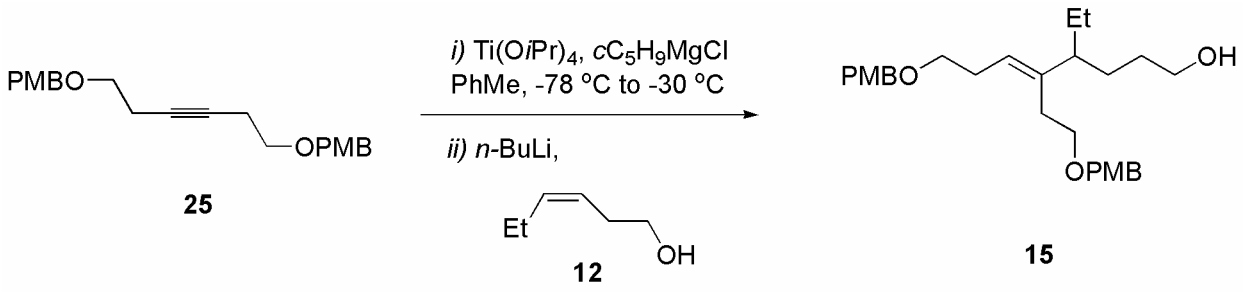
Chromatographic purifications were performed using 60Å, 35-75 μm particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Preparative HPLC normal phase separations were performed using an HPLC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

Synthesis of Substituted Olefins via Titanium-mediated Reductive Coupling:



Synthesis of (*Z*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)oct-5-en-1-ol (11). To a solution of alkyne **25**[1] (52 mg, 0.151 mmol) in 1.5 mL toluene was added $Ti(O\textit{i}Pr)_4$ (68 μL, 0.226 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added $c C_5H_9MgCl$ (1.74 M in diethyl ether, 0.452 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of commercially available olefin **8** (6 μL, 0.075 mmol) in 1.0 mL toluene was added *n*-BuLi (2.17 M in hexanes, 0.090 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −30 °C, stirred for 4 h, and quenched at −30 °C with 2 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 25 % EtOAc-hexanes, to provide 20 mg (68%) of olefin **11**.

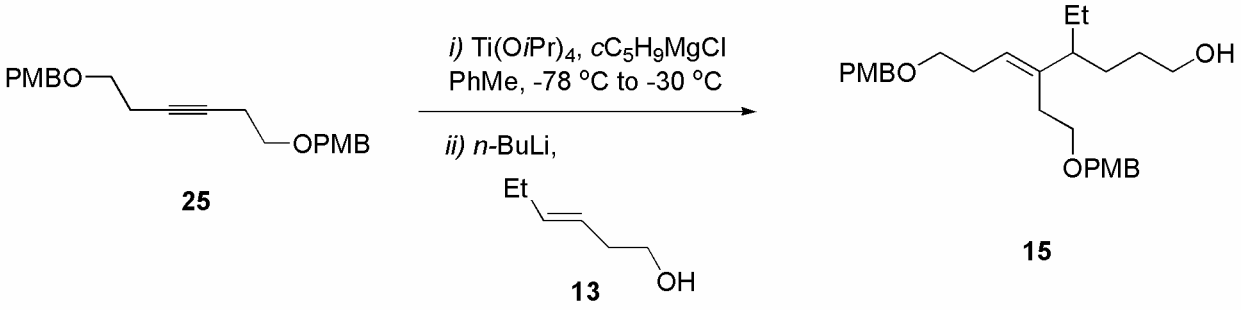
Data for (*Z*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)oct-5-en-1-ol (11).: ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-7.23 (m, 4H), 6.88-6.86 (m, 4H), 5.23 (t, J = 7.1 Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.62 (dt, J = 6.3 Hz, 6.3 Hz, 2H), 3.44 (t, J = 7.6 Hz, 2H), 3.41 (t, J = 7.3 Hz, 2H), 2.37-2.30 (m, 4H), 2.02 (t, J = 7.4 Hz, 2H), 1.54-1.50 (m, 2H), 1.48-1.43 (m, 2H), 1.21 (t, J = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 137.8, 130.8, 129.4, 123.0, 114.0, 72.7, 70.2, 69.0, 63.1, 55.5, 37.3, 32.6, 31.0, 28.8, 24.4; IR (thin film, NaCl) 3392, 2926, 2853, 1612, 1512, 1246, 1091, 1034 cm^{-1}; LRMS (MALDI-TOF, Na) calcd for $C_{26}H_{36}NaO_5$, 451.3 *m/z* (M + Na); observed, 451.8 $(M + Na)^+$ *m/z*.



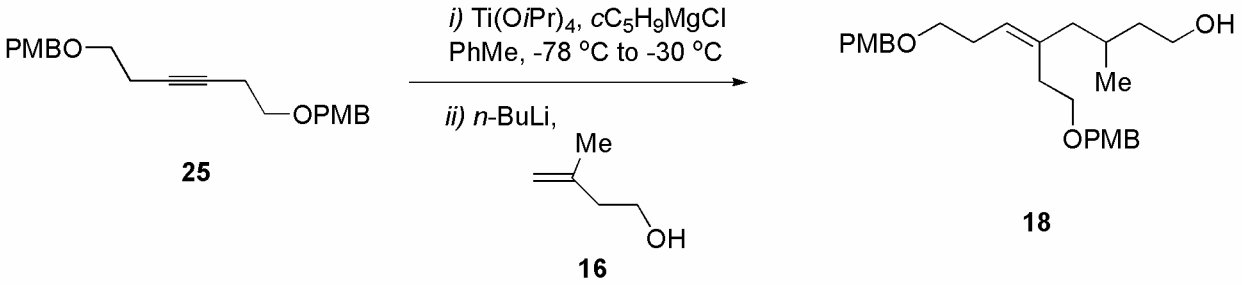
Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-ethyloct-5-en-1-ol (15) from alkyne 25 and olefin 12. To a solution of alkyne **25**[1] (52 mg, 0.151 mmol) in 1.5 mL toluene was added $Ti(OiPr)_4$ (68 μL, 0.226 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added cC_5H_9MgCl (1.80 M in diethyl ether, 0.452 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of commercially available olefin **12** (8 μL, 0.075 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.090 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −30 °C, stirred for 4 h, and quenched at −30 °C with 2 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 25 % EtOAc-hexanes, to provide 19 mg (55%) of olefin **15**.

Data for (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-ethyloct-5-en-1-ol (15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.20 (t, J = 7.2 Hz, 1H), 4.42 (s, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.58-3.52 (m, 2H), 3.42 (t, J = 7.1 Hz,

2H), 3.41 (t, J = 7.1 Hz, 2H), 2.38-2.28 (m, 4H), 1.86-1.80 (m, 1H), 1.44-1.30 (m, 6H), 1.17 (t, J = 5.4, 1H), 0.77 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 139.4, 130.9, 130.8, 129.5, 129.4, 124.3, 114.0, 72.7, 70.3, 69.4, 63.4, 55.5, 49.3, 31.1, 30.0, 29.7, 28.9, 27.1, 12.2; IR (thin film, NaCl) 3447, 2917, 2857, 1617, 1512, 1246, 1035 cm^{-1}; LRMS (EI, Na) calcd for $C_{28}H_{40}NaO_5$, 479.3 *m/z* (M + Na); observed, 479.2 (M + Na)$^+$ *m/z*.



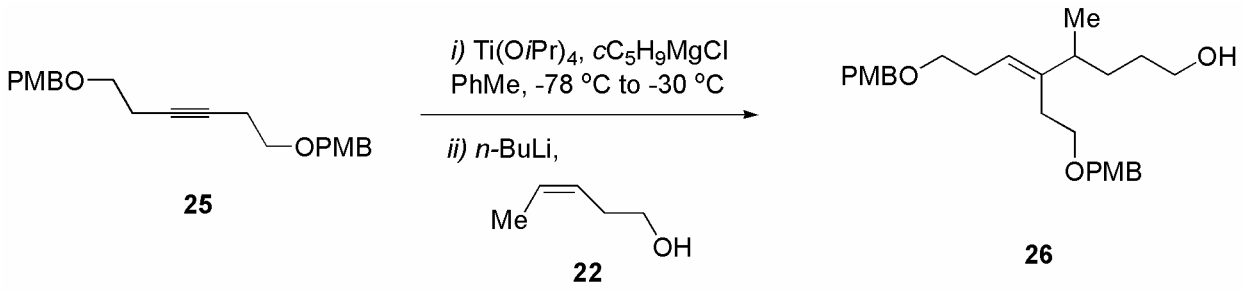
Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-ethyloct-5-en-1-ol (15) from alkyne 25 and olefin 13. Procedure and spectral characteristics are identical to those above.



Synthesis of ((*Z*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-3-methyloct-5-en-1-ol (18). To a solution of alkyne **25**[1] (52 mg, 0.151 mmol) in 1.5 mL toluene was added Ti(O*i*Pr)$_4$ (68 μL, 0.226 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added *c*C_5H_9MgCl (1.80 M in diethyl ether, 0.452 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to

afford a black solution. To a separate −78 °C solution of commercially available olefin **16** (7 μL, 0.075 mmol) in 1.0 mL toluene was added *n*-BuLi (2.44 M in hexanes, 0.090 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −30 °C, stirred for 3 h, and quenched at −30 °C with 2 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 25 % EtOAc-hexanes. The olefin was further purified by HPLC [EtOAc/hexanes: 35-55% (0-20 min, 7 mL/min), 65% (20-30 min, 7 mL/min) and a Microsorb (Si 80-120-C5 H410119) column] to afford 20 mg (64%) of olefin **18**.

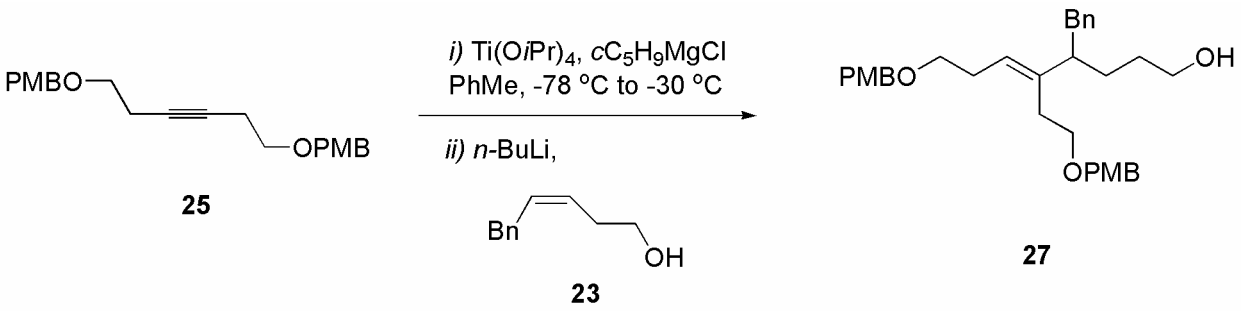
Data for ((*Z*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-3-methyloct-5-en-1-ol (18): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.23 (m, 4H), 6.88-6.86 (m, 4H), 5.22 (t, *J* = 7.4 Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70-3.58 (m, 2H), 3.45-3.41 (m, 4H), 2.39-2.28 (m, 4H), 2.02 (dd, *J* = 6.0 Hz, 13.6 Hz, 1H), 1.80 (dd, *J* = 7.7 Hz, 13.4 Hz, 1H), 1.76-1.69 (m, 1H), 1.59-1.53 (m, 1H), 1.35-1.29 (m, 1H), 1.18 (t, *J* = 5.5, 1H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4,136.6, 130.8, 129.4, 124.7, 114.0, 72.7, 70.2, 68.9,61.3, 55.5, 45.7, 39.9, 30.7, 28.8, 27.8, 19.9; IR (thin film, NaCl) 3309, 2923, 1653, 1513, 1248, 972 cm^{-1}; LRMS (EI, Na) calcd for $C_{27}H_{38}NaO_5$, 465.3 *m/z* (M + Na); observed, 465.6 (M + Na)$^+$ *m/z*.



Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-methyloct-5-en-1-ol (26). To a solution of alkyne **25**[1] (35 mg, 0.101 mmol) in 1.0 mL toluene was added $Ti(OiPr)_4$ (44 μL, 0.152 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added cC_5H_9MgCl (1.73 M in diethyl ether, 0.303 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of commercially available olefin **22** (5 μL, 0.051 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.061 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −30 °C, stirred for 2 h, and quenched at −30 °C with 2 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 25 % EtOAc-hexanes, to provide 13 mg (56%) of olefin **26**.

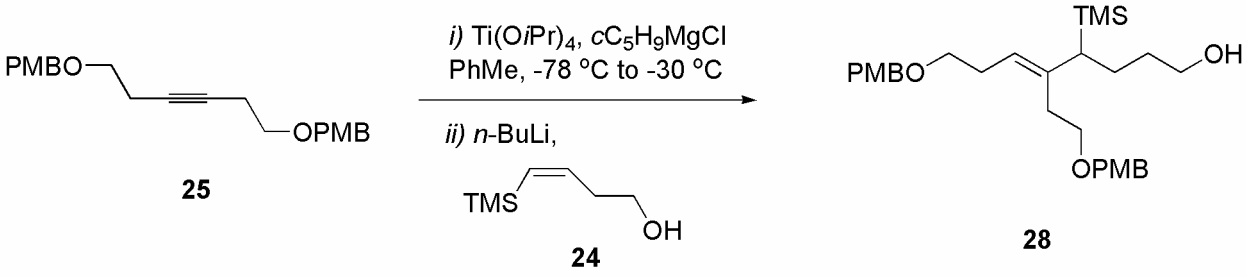
Data for (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-methyloct-5-en-1-ol (26): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.22 (t, J = 7.1 Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.60-3.55 (m, 2H), 3.43-3.40 (m, 4H), 2.36-2.31 (m, 4H), 2.10-2.06 (m, 1H), 1.61 (s, 1H), 1.50-1.39 (m, 2H), 1.34-1.27 (m, 2H), 0.98

(d, J = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.0, 130.8, 129.4, 122.4, 114.0, 72.7, 70.2, 69.5, 63.4, 55.5, 41.1, 31.9, 31.0, 30.0, 28.8, 20.6; IR (thin film, NaCl) 3420, 2934, 2860, 1613, 1513, 1248, 1094, 1035 cm^{-1}; LRMS (EI, Na) calcd for $C_{27}H_{38}NaO_5$, 465.3 *m/z* (M + Na); observed, 465.5 $(M + Na)^+$ *m/z*.



Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-benzyloct-5-en-1-ol (27). To a solution of alkyne **25**[1] (207 mg, 0.600 mmol) in 6.0 mL toluene was added Ti(O*i*Pr)$_4$ (265 μL, 0.900 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added *c*C_5H_9MgCl (1.80 M in diethyl ether, 1.800 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of olefin **23**[2] (49 mg, 0.300 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.360 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to 0 °C, stirred for 1 h, and quenched at 0 °C with 5 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 15 mL), brine (1 x 15 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 25 % EtOAc-hexanes, to provide 77 mg (50%) of olefin **27**.

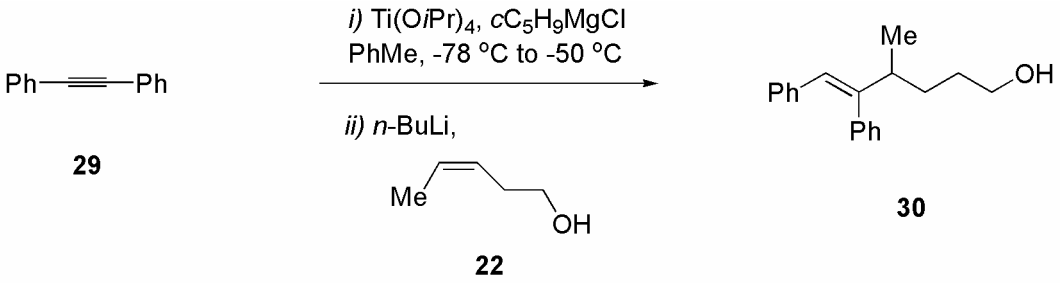
Data for (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-benzyloct-5-en-1-ol (27): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.06 (m, 9H), 6.89-6.86 (m, 4H), 5.21 (t, *J* = 7.3 Hz, 1H), 4.39 (s, 2H), 4.37 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.53-3.50 (m, 2H), 3.36-3.31 (m, 4H), 2.66 (dd, *J* = 7.3, 13.6 Hz, 1H), 2.58 (dd, *J* = 7.3, 13.2 Hz, 1H), 2.34-2.23 (m, 5H), 1.51-1.37 (m, 4H), 1.19 (t, *J* = 5.5, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 141.1, 139.5, 130.9, 130.7, 129.4, 128.2, 125.9, 124.4, 114.0, 72.7, 70.1, 69.1, 63.2, 55.5, 49.0, 41.7, 30.9, 30.7, 29.5, 28.8; IR (thin film, NaCl) 3442, 2934, 2858, 1612, 1513, 1248, 1092, 1035, 821 cm^{-1}; LRMS (EI, Na) calcd for $C_{33}H_{43}O_5$, 519.7 *m/z* (M + H); observed, 519.3 $(M + H)^+$ *m/z*.



Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-(trimethylsilyl)oct-5-en-1-ol (28). To a solution of alkyne **25**[1] (52 mg, 0.151 mmol) in 1.5 mL toluene was added $Ti(OiPr)_4$ (68 μL, 0.226 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added cC_5H_9MgCl (1.80 M in diethyl ether, 0.452 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of olefin **24**[3] (10 mg, 0.075 mmol) in 1.0 mL toluene was added *n*-BuLi (2.44 M in hexanes, 0.090 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to room temperature, stirred for 12 h, and quenched with 2 mL of 1 N HCl. The resulting

aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on deactivated silica gel eluting with 30 % EtOAc-hexanes, to provide 22 mg (63%) of olefin **28**.

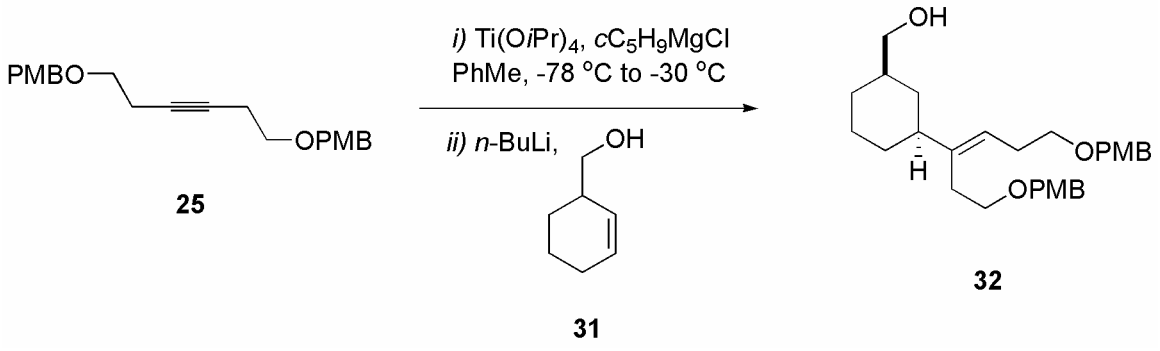
Data for (*E*)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-4-(trimethylsilyl)oct-5-en-1-ol (28): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.89-6.86 (m, 4H), 5.02 (t, *J* = 7.3 Hz, 1H), 4.40 (s, 4H), 3.80 (s, 3H), 3.79 (s, 3H), 3.57-3.53 (m, 2H), 3.43-3.39 (m, 4H), 2.62-2.56 (m, 1H), 2.41-2.30 (m, 4H), 1.99-1.93 (m, 1H), 1.54-1.48 (m, 1H), 1.37-1.34 (m, 2H), 1.18 (t, *J* = 5.7, 1H), 0.00 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 138.6, 130.9, 130.8, 129.5, 129.4, 128.9, 120.3, 114.0, 72.8, 70.6, 68.8, 63.3, 55.5, 37.0, 34.2, 32.7, 29.0, 25.6, -2.4; IR (thin film, NaCl) 3443, 2951, 2857, 1613, 1513, 1247, 1093, 1036, 833 cm^{-1}; LRMS (EI, Na) calcd for $C_{29}H_{44}O_5SiNa$, 523.3 *m/z* (M + Na); observed, 523.4 $(M + Na)^+$ *m/z*.



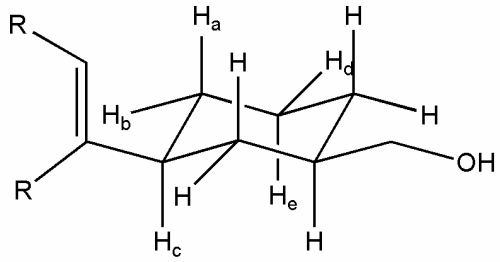
Synthesis of (*Z*)-4-methyl-5,6-diphenylhex-5-en-1-ol (30). To a solution of commercially available alkyne **29** (89 mg, 0.500 mmol) in 5.0 mL toluene was added $Ti(OiPr)_4$ (482 μL, 0.750 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added cC_5H_9MgCl (2.0 M in diethyl ether, 1.500 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −50 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution.

To a separate −78 °C solution of commercially available olefin **22** (22 mg, 0.250 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.300 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −30 °C, stirred for 2 h, and quenched at −30 °C with 2 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 10 % EtOAc-hexanes, to provide 38 mg (58%) of olefin **30**.

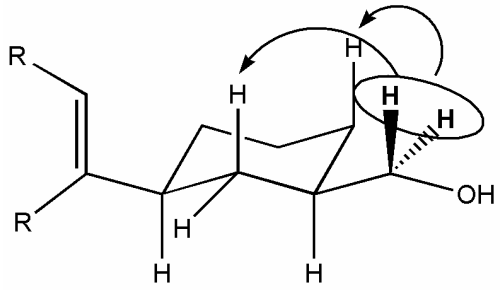
Data for (*Z*)-4-methyl-5,6-diphenylhex-5-en-1-ol (30): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 3H), 7.12-7.03 (m, 5H), 6.86-6.84 (m, 2H), 6.40 (s. 1H), 3.65 (dt, *J* = 6.5, 6.5 Hz, 2H), 2.60-2.54 (m, 1H), 1.71-1.64 (m, 2H), 1.60-1.53 (m, 1H), 1.43-1.34 (m, 1H), 1.20 (t, J =Hz, 1H) 1.14 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ147.8, 141.0, 137.6, 129.2, 128.6, 128.0, 127.0, 126.3,63.4,43.3, 31.5, 31.0, 20.2; IR (thin film, NaCl) 3327, 2930 cm^{-1}; LRMS (EI, Na) calcd for $C_{19}H_{23}O$, 266.2 *m/z* (M + H); observed, 266.5 $(M + H)^+$ *m/z*.

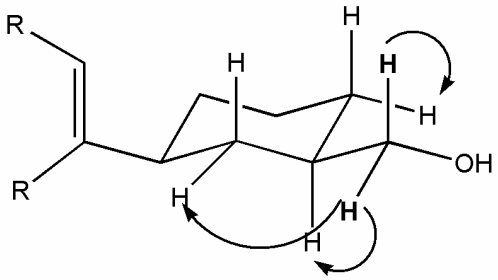


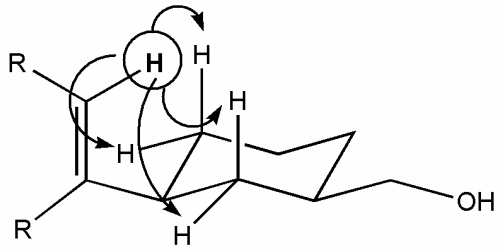
Structure Proof and Observed nOe's of 32:

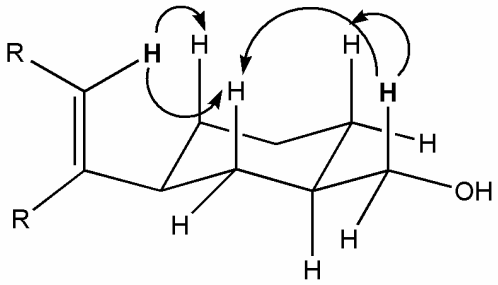


H_a = dddd
$J_{a,b}$ = 12.6 Hz $J_{a,c}$ =12.6 Hz
$J_{a,d}$ = 3.3 Hz $J_{a,e}$ = 12.6 Hz





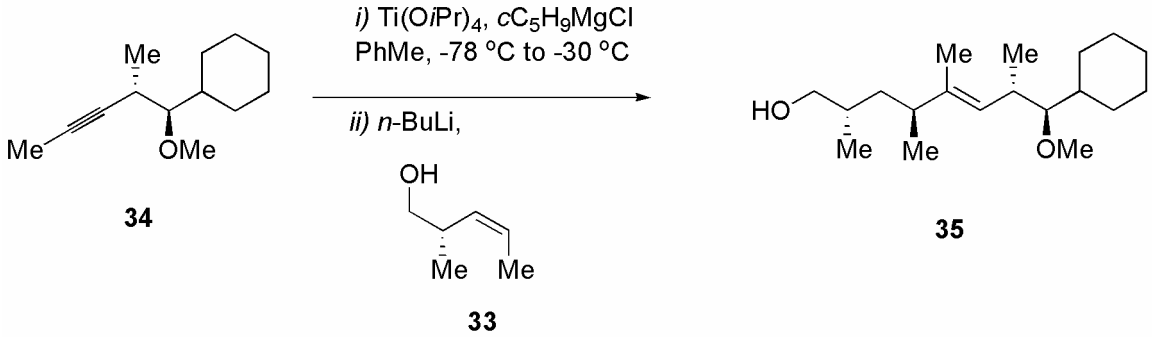




Synthesis of (*cis*)-1-((*E*)-1,6-bis(4-methoxybenzyloxy)hex-3-en-3-yl)-3-(hydroxymethyl)cyclohexane (32). To a solution of alkyne **25**[1] (207 mg, 0.600 mmol) in 6.0 mL toluene was added $Ti(OiPr)_4$ (265 μL, 0.900 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added cC_5H_9MgCl (1.80 M in diethyl ether, 1.800 mmol), in a dropwise manner via gas-tight syringe. The resulting

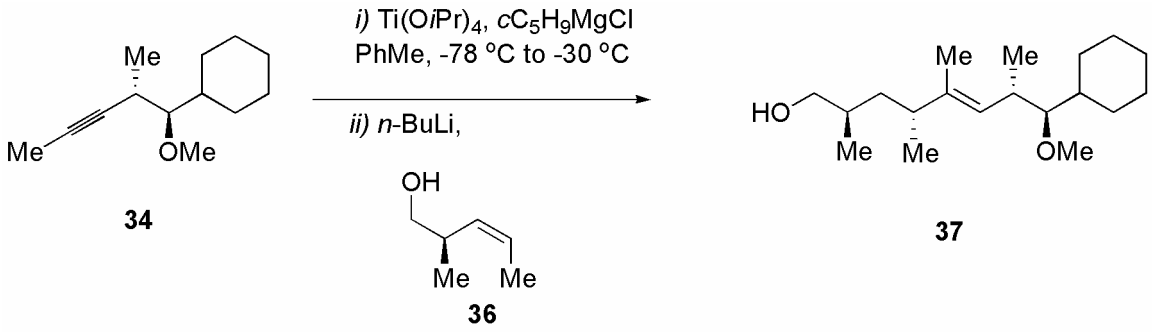
yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of olefin **31**[4] (49 mg, 0.300 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.360 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to 0 °C, stirred for 1 h, and quenched at 0 °C with 5 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 15 mL), brine (1 x 15 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 20 % EtOAc-hexanes, to provide 81 mg (58%) of olefin **32**.

Data for (*cis*)-1-((*E*)-1,6-bis(4-methoxybenzyloxy)hex-3-en-3-yl)-3-(hydroxymethyl)cyclohexane (32): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.21 (t, *J* = 7.1 Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.46-3.38 (m, 6H), 2.39-2.30 (m, 4H), 1.90-1.69 (m, 4H), 1.55-1.47 (m, 1H), 1.31-1.24 (m, 3H), 1.06 (app.qd, *J* = 3.3, 12.6, 12.6 Hz, 1H), 0.91-0.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 142.8, 130.9, 129.4, 121.3, 114.0, 72.7, 70.2, 69.5, 68.9, 55.5, 45.0, 41.1, 35.6, 32.7, 30.8, 29.4, 28.8, 26.2; IR (thin film, NaCl) 3450, 2922, 2854, 1613, 1513, 1248, 1093, 1036, 820 cm^{-1}; LRMS (EI, Na) calcd for $C_{29}H_{40}O_5Na$, 491.3 *m/z* (M + Na); observed, 491.4 $(M + Na)^+$ *m/z*.



Synthesis of (2*S*,4*S*,7*S*,8*R*,*E*)-8-cyclohexyl-8-methoxy-2,4,5,7-tetramethyloct-5-en-1-ol (35). To a solution of alkyne **34**[1] (232 mg, 1.2 mmol) in 12.0 mL toluene was added $Ti(O\textit{i}Pr)_4$ (530 μL, 1.8 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added $\textit{c}C_5H_9MgCl$ (1.80 M in diethyl ether, 3.6 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of olefin **33**[5] (60 mg, 0.60 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.72 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −20 °C, stirred for 12 h, and quenched at −20 °C with 10 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 25 mL), brine (1 x 25 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 20 % EtOAc-hexanes, to provide 96 mg (54%) of olefin **35**.

Data for (2*S*,4*S*,7*S*,8*R*,*E*)-8-cyclohexyl-8-methoxy-2,4,5,7-tetramethyloct-5-en-1-ol (35): $[\alpha]_{589}^{20}$ +1.35 ° (*c* 0.38, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.18 (d, *J* = 9.5 Hz, 1H), 3.52 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.43-3.38 (m, 4H), 2.66 (dd, *J* = 6.9, 4.4 Hz, 1H), 2.62-2.58 (m, 1H), 2.26-2.19 (m, 1H), 1.92-1.85 (m, 1H), 1.75-1.47 (m, 5H), 1.39-1.23 (m, 5H), 1.21-1.11 (m, 5H), 0.98-0.90 (m, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ138.8, 126.6, 91.2, 68.3, 61.8, 41.8, 40.5, 38.7, 34.8, 33.8, 30.3, 29.0, 26.9, 26.7, 26.5, 20.0, 18.6, 17.4, 12.5; IR (thin film, NaCl) 3371, 2925, 2852, 1457, 1099, 1044 cm^{-1}; LRMS (EI, Na) calcd for $C_{19}H_{36}O_2Na$, 319.3 *m/z* (M + Na); observed, 319.6 $(M + Na)^+$ *m/z*.



Synthesis of (2*R*,4*R*,7*S*,8*R*,*E*)-8-cyclohexyl-8-methoxy-2,4,5,7-tetramethyloct-5-en-1-ol (37). To a solution of alkyne **34**[1] (116 mg, 0.600 mmol) in 6.0 mL toluene was added $Ti(OiPr)_4$ (265 μL, 0.900 mmol) in a dropwise manner via a dry gas-tight syringe, followed by cooling to −78 °C. To the clear, colorless solution was added cC_5H_9MgCl (1.80 M in diethyl ether, 1.800 mmol), in a dropwise manner via gas-tight syringe. The resulting yellow-brown solution was then slowly warmed to −30 °C, stirred for 1 h, then cooled to −78 °C to afford a black solution. To a separate −78 °C solution of olefin **36**[5] (30 mg, 0.300 mmol) in 1.0 mL toluene was added *n*-BuLi (2.5 M in hexanes, 0.360 mmol) in a dropwise manner via gas-tight syringe. The resulting solution was warmed to 0 °C, followed by dropwise transfer via cannula into the original −78 °C black titanium solution. The solution was then slowly warmed to −20 °C, stirred for 12 h, and quenched at −20 °C with 5 mL of 1 N HCl. The resulting aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (1 x 15 mL), brine (1 x 15 mL), and dried over anhydrous Na_2SO_4. The resulting crude material was purified by flash column chromatography on silica gel eluting with 20 % EtOAc-hexanes, to provide 45 mg (51%) of olefin **37**.

Data for (2*R*,4*R*,7*S*,8*R*,*E*)-8-cyclohexyl-8-methoxy-2,4,5,7-tetramethyloct-5-en-1-ol (37): $[\alpha]_{589}^{20}$ −7.37 ° (*c* 0.37, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.198 (d, *J* = 9.9 Hz, 1H), 3.54 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.45-3.37 (m, 4H), 2.66 (dd, *J* = 7.6, 3.8 Hz, 1H), 2.62-2.57 (m, 1H),

2.27-2.18 (m, 1H), 1.93-1.87 (m, 1H), 1.75-1.49 (m, 5H), 1.38-1.25 (m, 5H), 1.21-1.09 (m, 5H), 0.98-0.88 (m, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ138.7, 126.5, 91.3, 68.0, 61.9, 41.9, 40.6, 38.6, 34.7, 33.8, 30.2, 29.3, 28.9, 26.8, 26.5, 20.2, 18.7, 17.7, 12.2; IR (thin film, NaCl) 3389, 2925, 2852, 1450, 1099, 1042 cm^{-1}; LRMS (EI, Na) calcd for $C_{19}H_{36}O_2Na$, 319.3 *m/z* (M + Na); observed, 319.5 $(M + Na)^+$ *m/z.*

---

[1]Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764-2765.

[2]Larock, R. C.; Stolz-Dunn, S. K. *Synlett* **1990**, 341-343.

[3]Flann, C. J.; Malone, T. C.; Overman, L. E. *Org. Synth.* **1990**, *68*, 182.

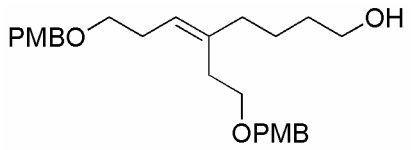
[4]Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1992**, *57*, 1713-1718.

[5]Ehrlich, G.; Kalesse, M. *Synlett* **2005,** 655-657.

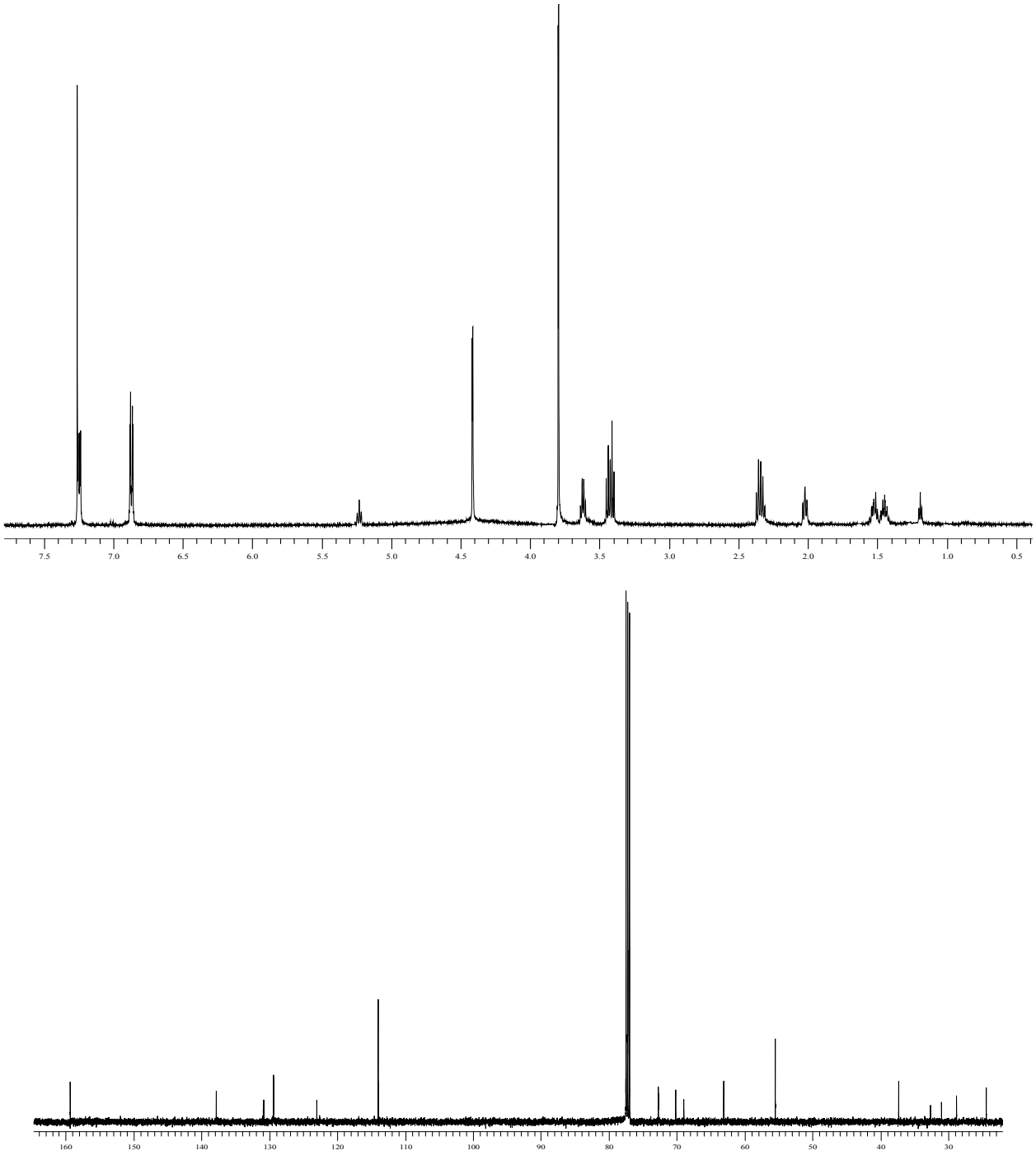
A Site- and Stereoselective Intermolecular Alkene-Alkyne Coupling Process

SUPPORTING INFORMATION-2

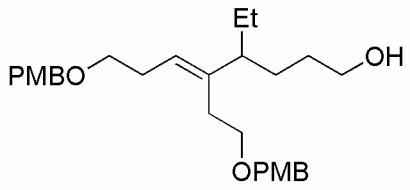
Spectral Data for Olefins 11-37



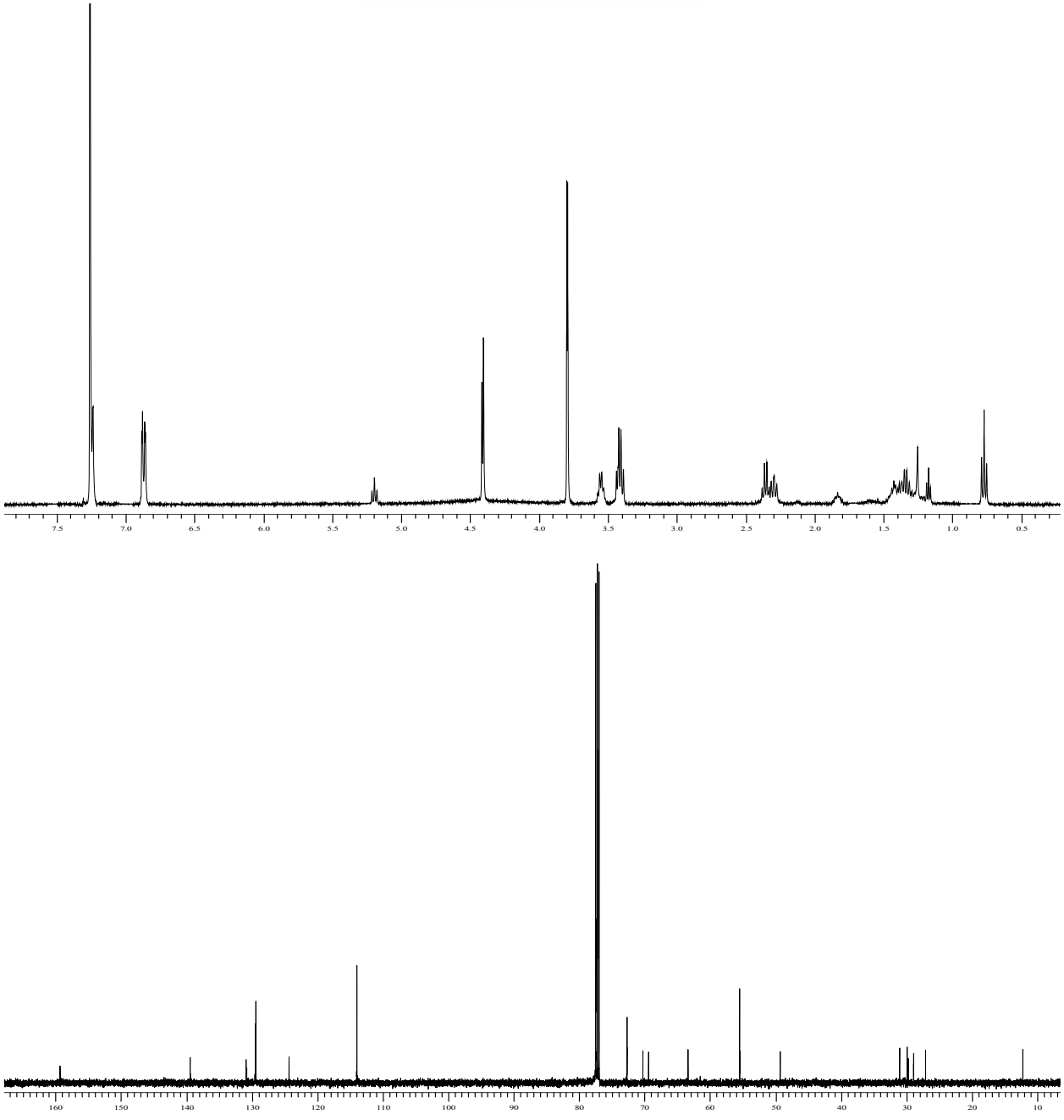
11



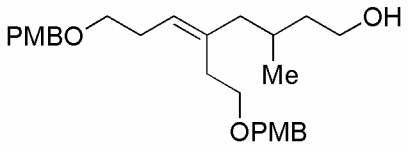
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **11** ($CDCl_3$)



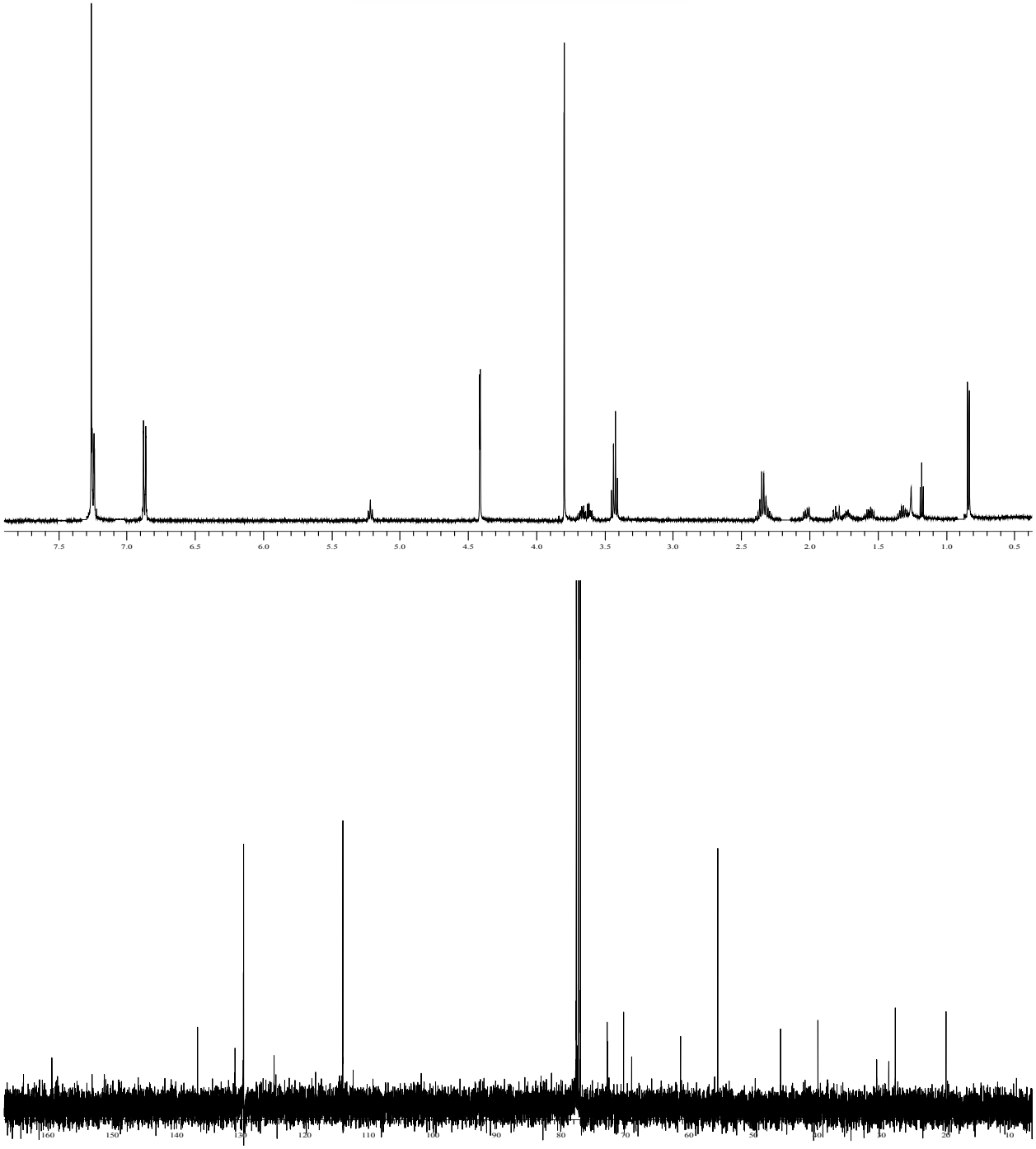
15



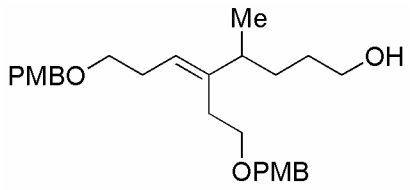
^{1}H NMR (400 MHz) and ^{13}C NMR (126 MHz) of compound **15** ($CDCl_3$)



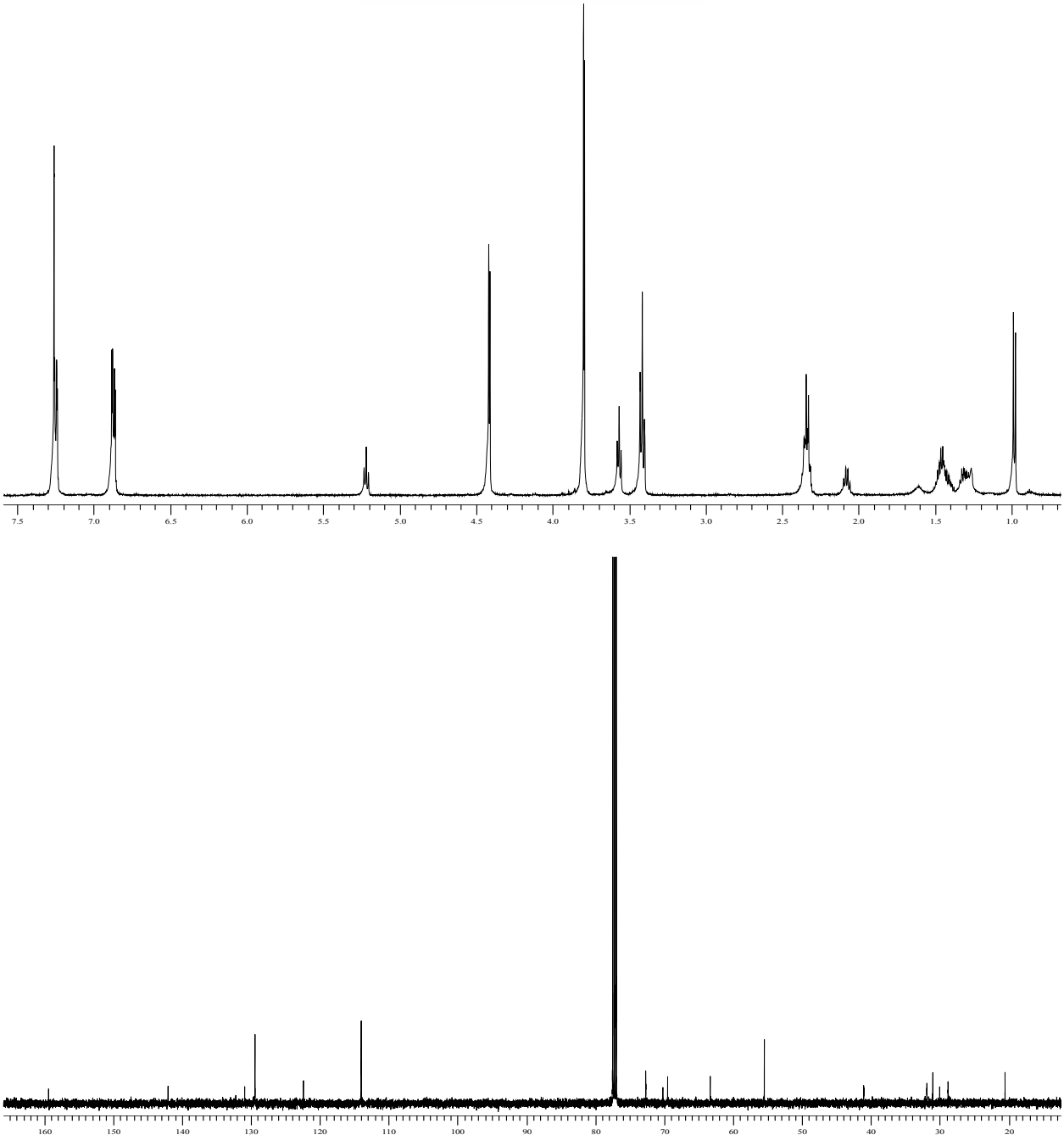
18



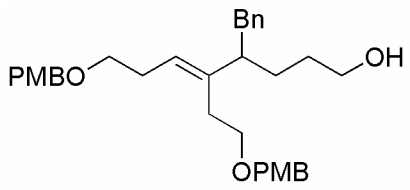
^{1}H NMR (500 MHz) and ^{13}C NMR (100 MHz) of compound **18** ($CDCl_3$)



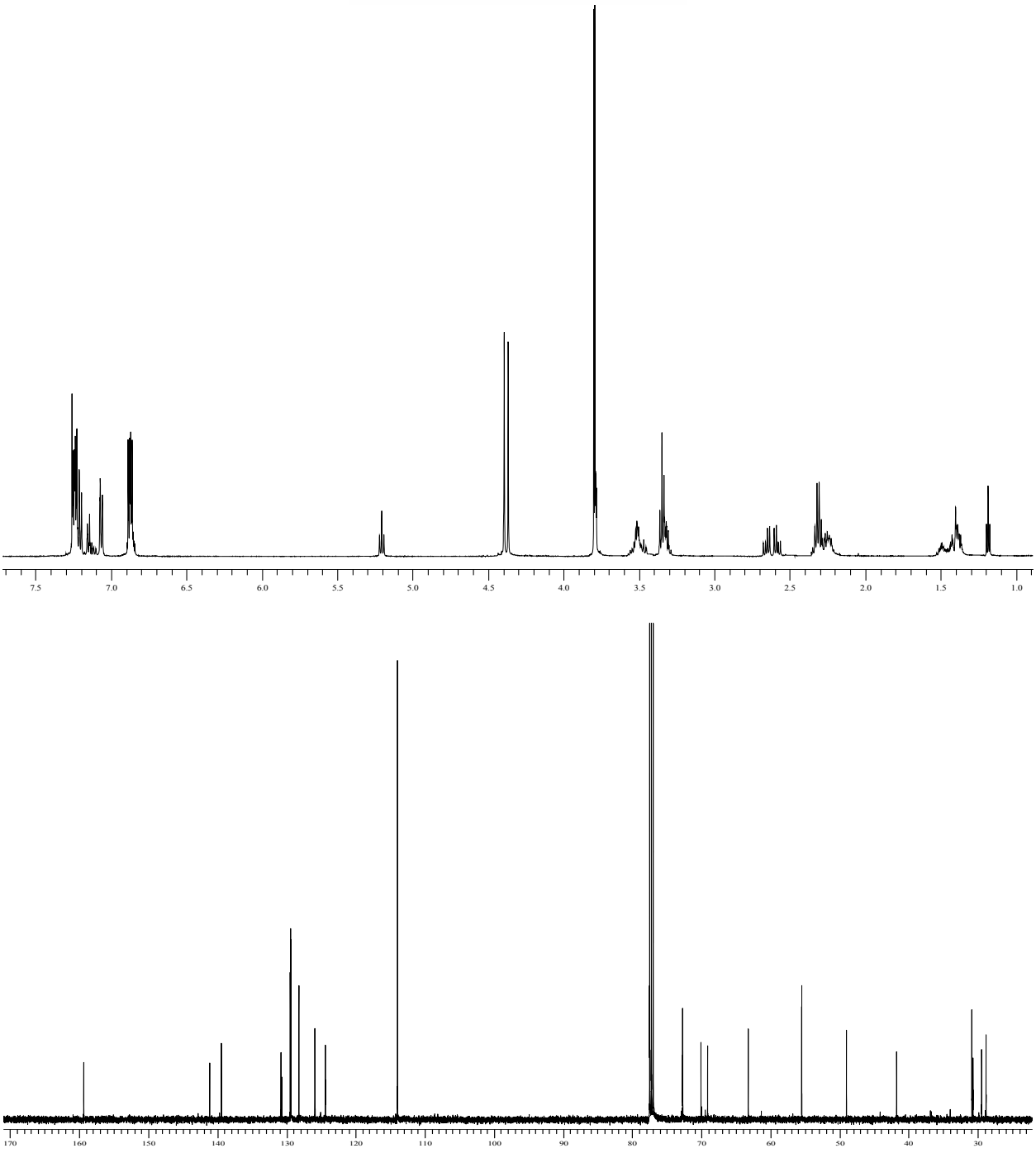
26



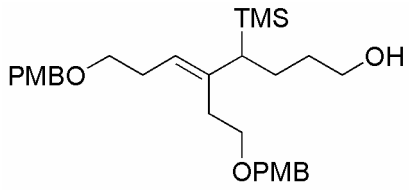
^{1}H NMR (500 MHz) and ^{13}C NMR (100 MHz) of compound **26** ($CDCl_3$)



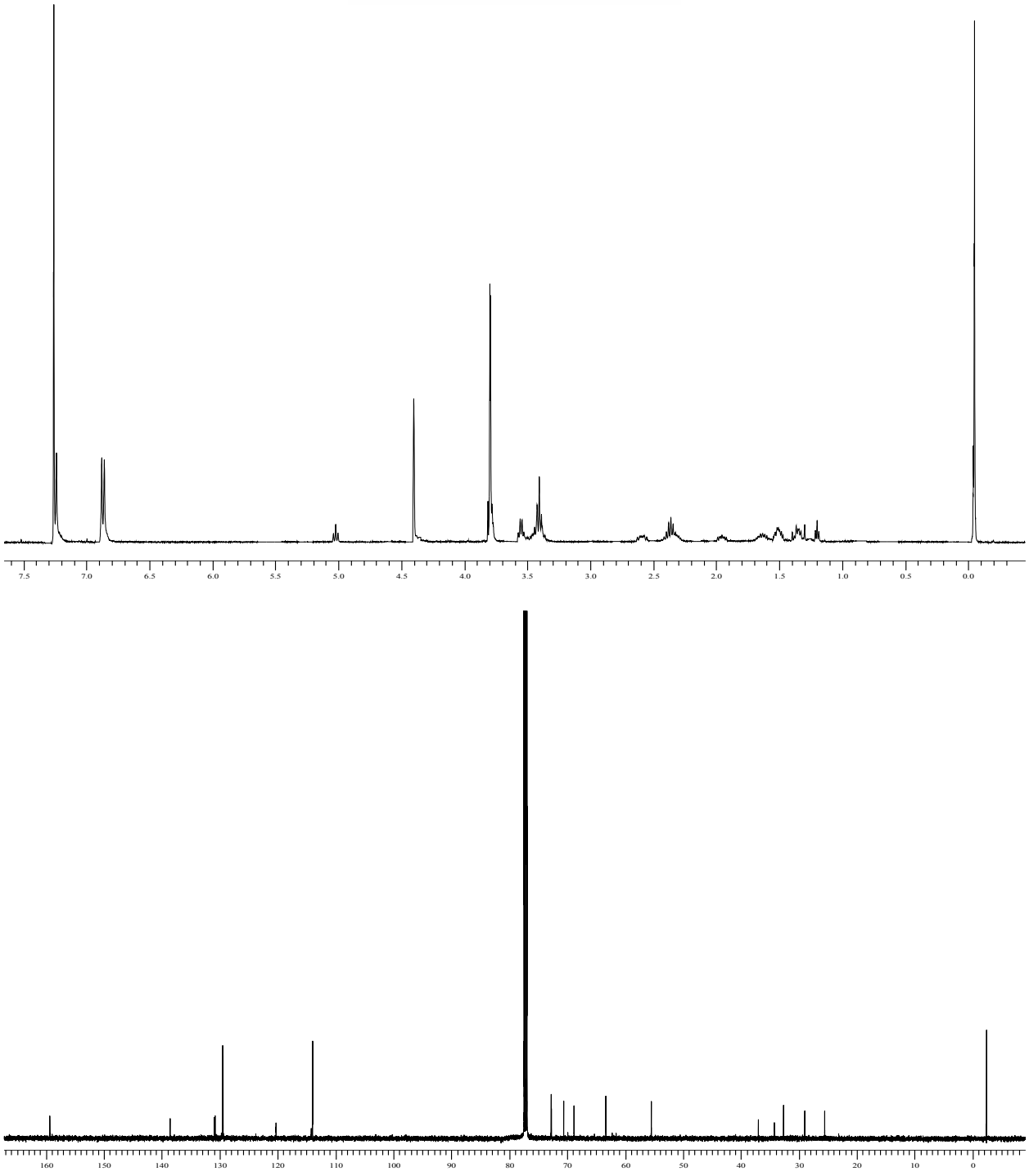
27



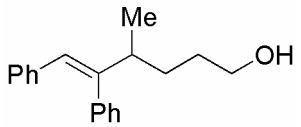
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **27** ($CDCl_3$)



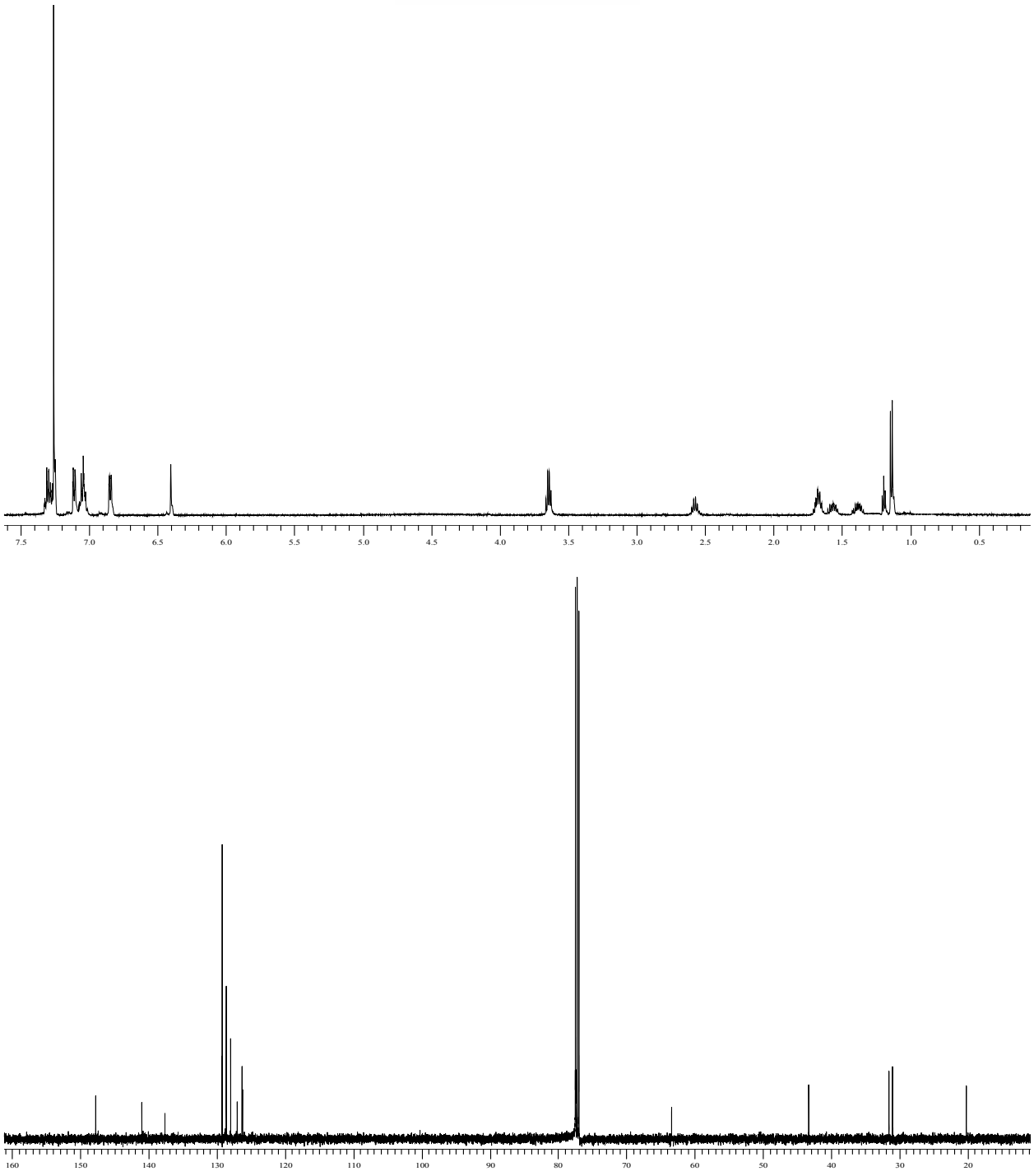
28



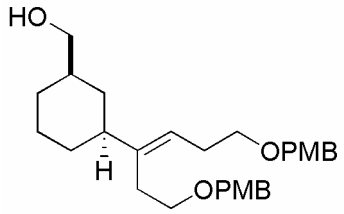
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **28** ($CDCl_3$)



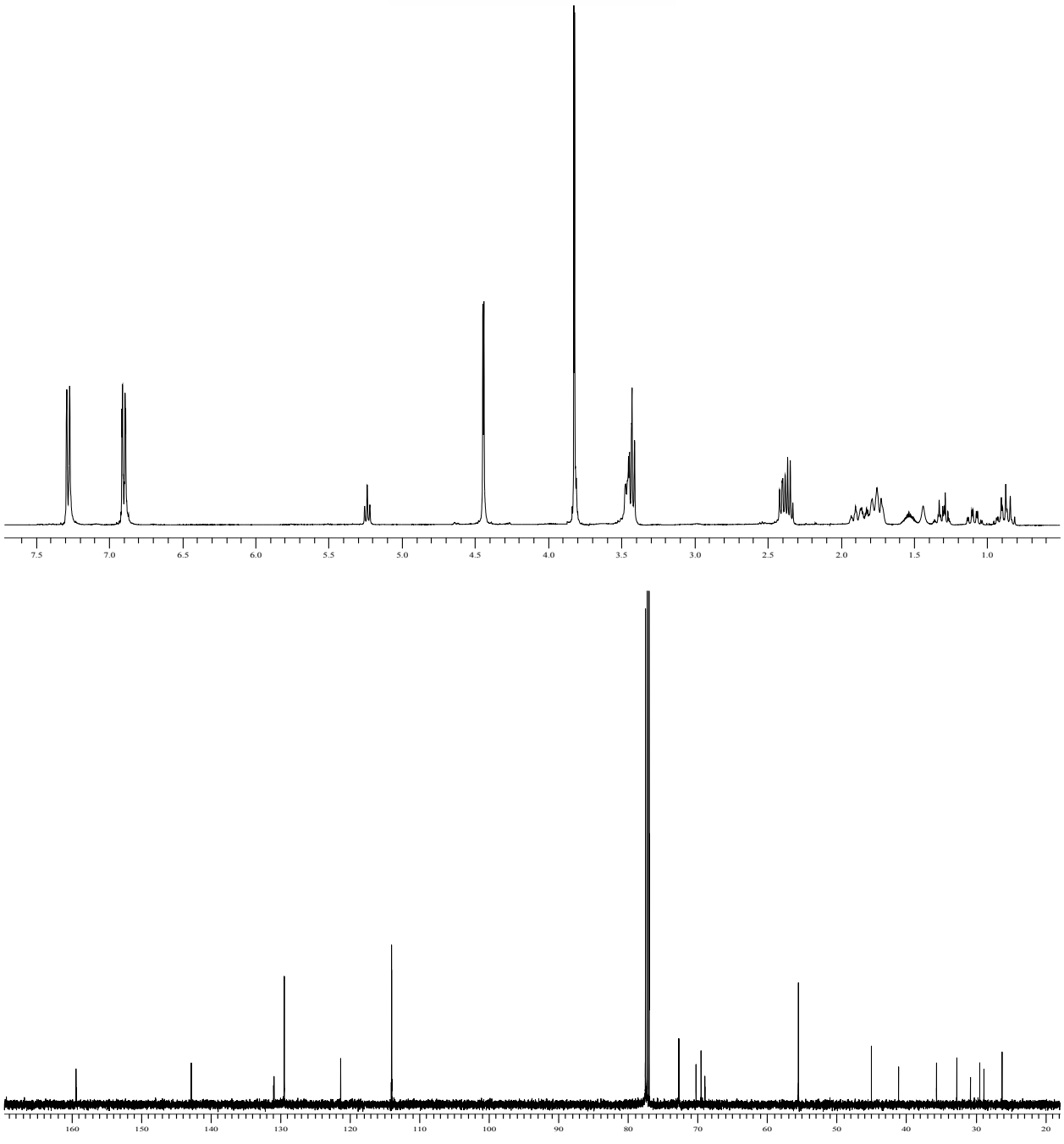
30



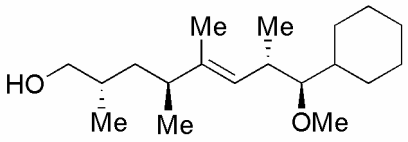
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **30** ($CDCl_3$)



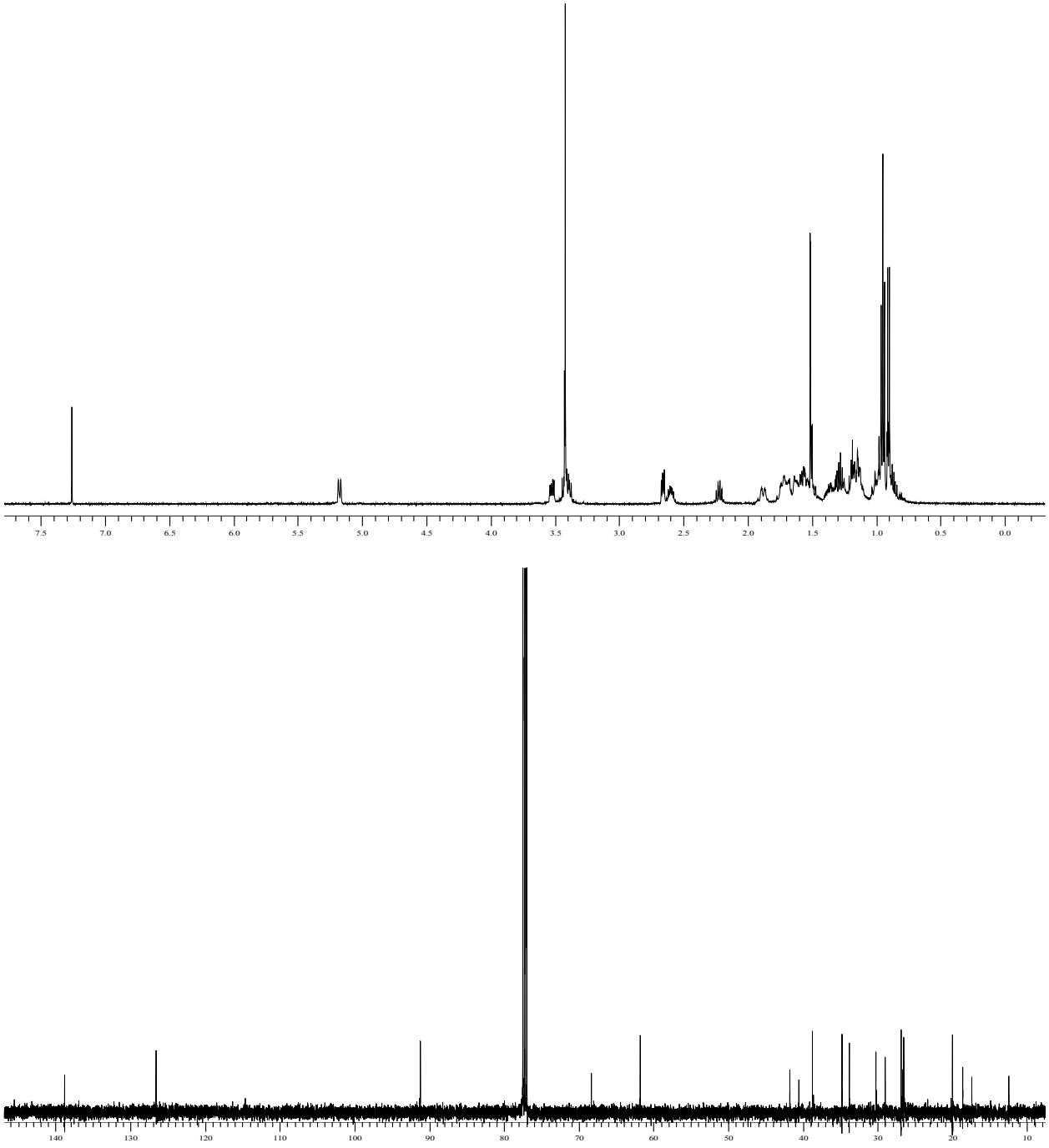
32



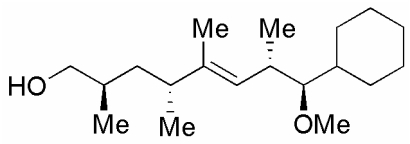
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **32** ($CDCl_3$)



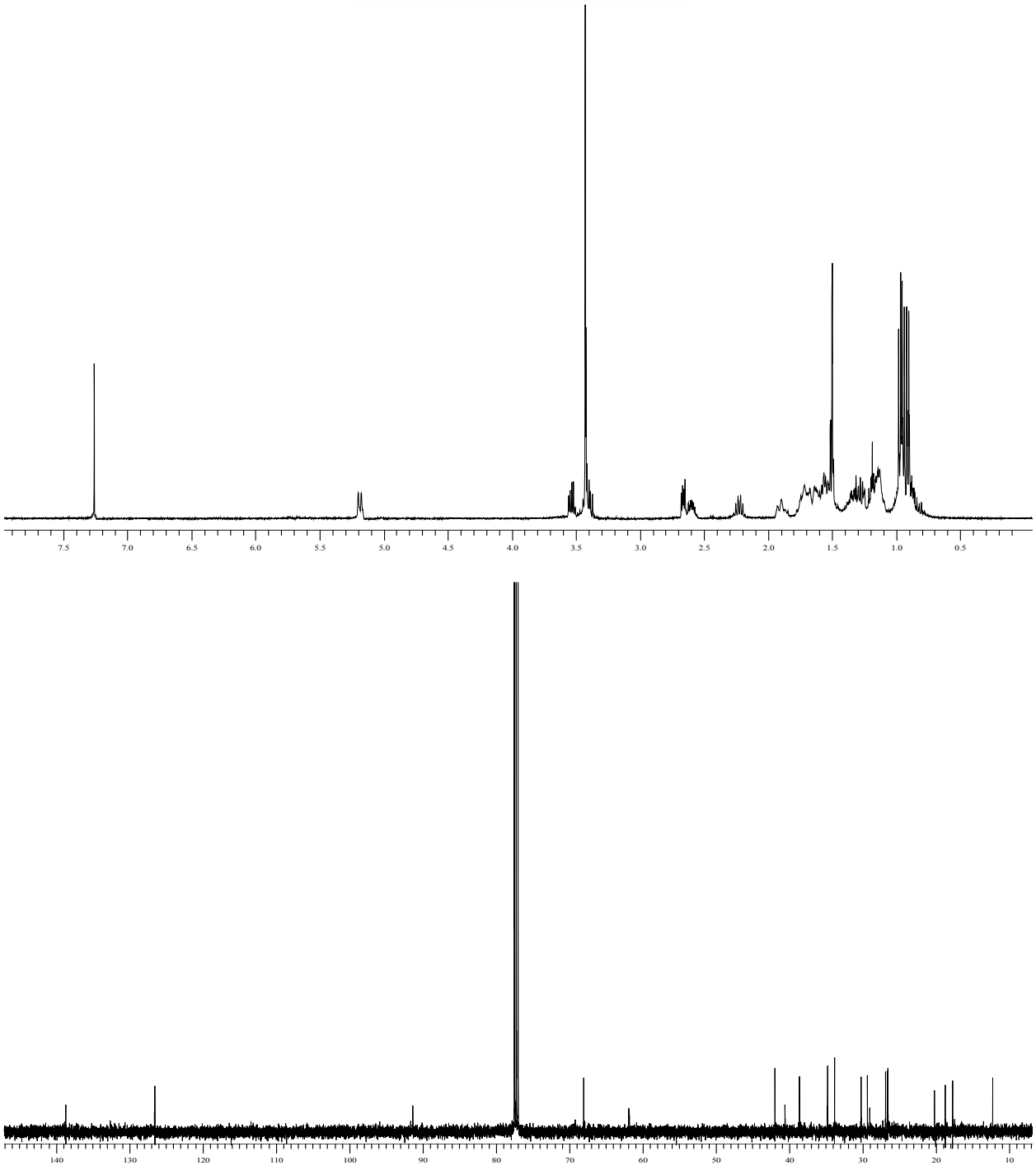
35



^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **35** ($CDCl_3$)



37



^{1}H NMR (400 MHz) and ^{13}C NMR (126 MHz) of compound **37** ($CDCl_3$)