Synthesis of Substituted 1,4-Dienes by Direct Alkylation of Allylic Alcohols

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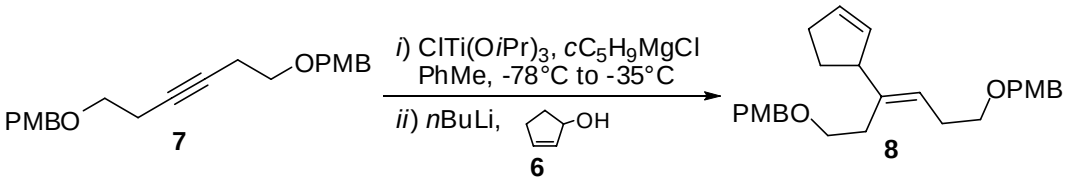
SUPPORTING INFORMATION:

General. All reactions were conducted in flame-dried glassware under nitrogen atmosphere using anhydrous solvents. Toluene and tetrahydrofuran were dried and deoxygenated by distillation over sodium metal and benzophenone. Titanium tetraisopropoxide was purified by distillation at 45 millitorr. Chlorotriisopropoxytitanium(IV) was purchased as a 1.0 M solution in hexanes (*Aldrich*) and was used as received. Commercially available allylic alcohols **9**, **23**, **25**, **27** and **36** were kept over 3Å molecular sieves prior to use. All other allylic alcohols and alkyne **42** were synthesized by known literature procedures and kept over 3Å molecular sieves. Other commercially available reagents were used as received.

^{1}H NMR data was recorded at 500 MHz or 400 MHz using a Bruker AM-500, a Bruker Avance DPX-500 and a Bruker AM-400 instrument. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). Proton decoupled ^{13}C NMR data was recorded at 126 MHz or 100 MHz using a Bruker AM-500, a Bruker Avance DPX-500 or a Bruker AM-400 instrument. ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.23 ppm). Infrared spectra of the neat samples were recorded using a Thermo Electron Nicolet 6700 FT-IR spectrometer. Low resolution mass spectra were recorded on a Waters Micromass® ZQTM instrument using electrospray ionization, and on the Agilent 5973 GC-MS system using electron impact ionization.

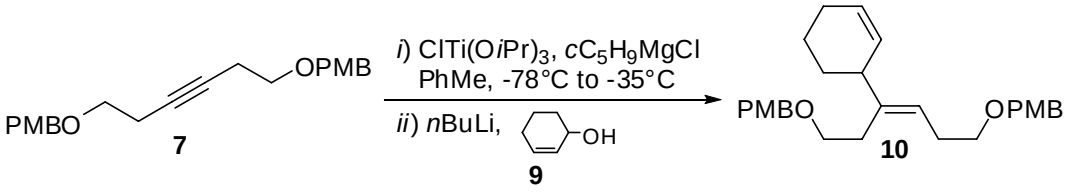
Chromatographic purifications were performed using 60Å, 35-75μm particle size silica gel from Silicycle. Semi-preparative HPLC normal phase separations were performed using an HPLC system composed of two Varian ProStar M210 pumps, a Dynamax-100Å column, and a Varian ProStar M320 absorbance detector. Chiral GC was preformed on HP 6890 CG system using Chiraldex BDM column. All yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise indicated.

Synthesis of Substituted 1,4-Dienes via Titanium-mediated Allylic Alkylation:



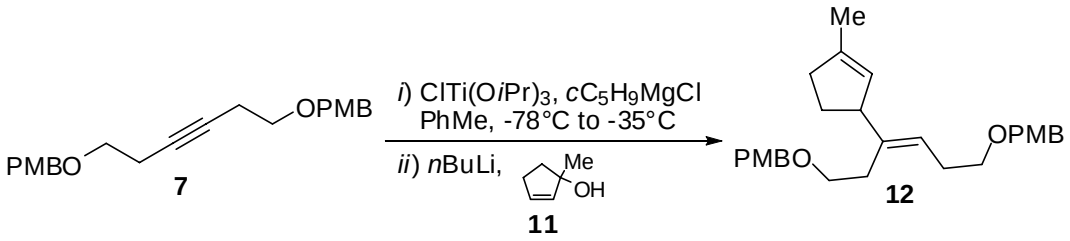
Synthesis of (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)-ethyl)but-1'-en-1'-yl)cyclopent-1-ene (8): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **6** (24 μL, 23.7 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **8** as a colorless oil (78 mg, 65%).

Data for (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)cyclopent-1-ene (8): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.80 (m, 1H), 5.57 (m, 1H), 5.23 (t, 1H, *J*=7.2 Hz), 4.42 (s, 4H), 3.80 (d, 6H, *J*=2.4 Hz), 3.42 (m, 4H), 3.3 (s, 1H), 2.35 (m, 6H), 2.10 (m, 1H), 1.52 (m, 1H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.2, 141.1, 133.7, 131.9, 130.8, 130.7, 129.4, 129.3, 121.9, 113.9, 72.6, 70.0, 69.3, 55.4, 52.8, 32.3, 30.7, 30.6, 28.8; **IR** (thin film, NaCl, cm^{-1}) 3046, 2998, 2936, 2853, 2790, 1613, 1513, 1360, 1248, 1095, 1036 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{27}H_{34}O_4Na$, 445.5 *m/z* $(M + Na)^+$; observed, 445.4 *m/z* $(M + Na)^+$.



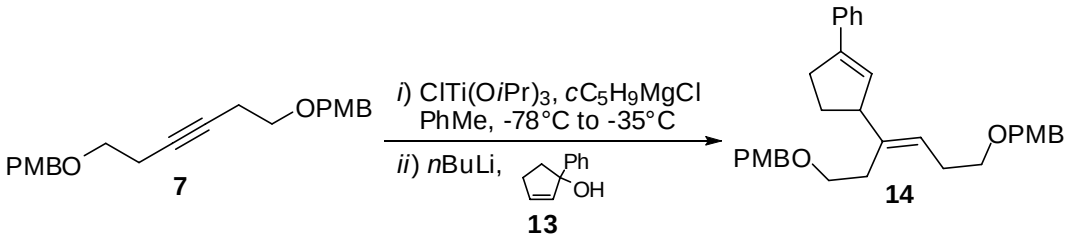
Synthesis of (1'-*E*)-)3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)cyclohex-1-ene (10): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **9** (28 μL, 27.6 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **10** as a colorless oil (83 mg, 68%).

Data for (1'-*E*)-)3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)cyclohex-1-ene (10): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.76 (m, 1H), 5.49 (app. d, 1H, *J*=10 Hz), 5.23 (t, 1H, *J*=7.25 Hz), 4.42 (d, 4H, *J*=3 Hz), 3.80 (d, 6H, *J*=2.5 Hz), 3.43 (m, 4H), 2.74 (s, 1H), 2.46 (m, 1H), 2.35 (quart, 2H, *J*=6 Hz), 2.28 (m, 1H), 1.97 (broad s, 2H), 1.74 (m, 1H), 1.64 (m, 1H), 1.49 (m, 1H), 1.41 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 141.3, 130.9, 130.8, 130.4, 129.4, 128.2, 123.7, 113.9, 72.6, 70.1, 69.4, 55.4, 42.7, 30.7, 29.0, 28.8, 25.4, 20.8; **IR** (thin film, NaCl, cm^{-1}) 3015, 2931, 2855, 2836, 1612, 1586, 1512, 1301, 1246, 1091, 1035 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{28}H_{36}O_4Na$, 459.6 *m/z* $(M + Na)^+$; observed, 459.4 *m/z* $(M + Na)^+$.



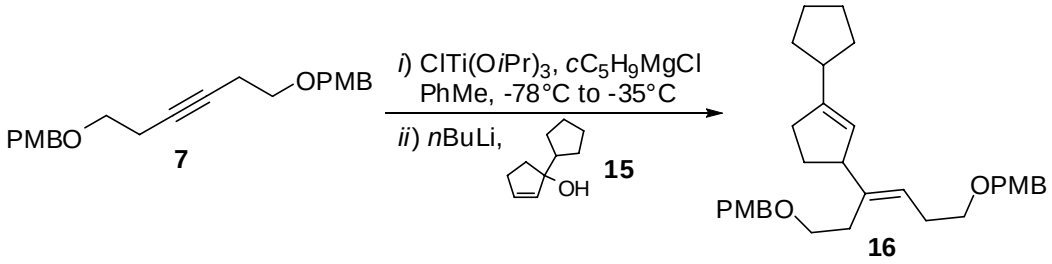
Synthesis of (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2'-(4-methoxybenzyloxy)-ethyl)but-1'-en-1'-yl)-1-methylcyclopent-1-ene (12): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **11**[3] (30 μL, 27.9 mg, 0.284 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **12** as a colorless oil (75 mg, 61%).

Data for (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)-1-methylcyclopent-1-ene (12): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.22 (t, 1H, *J*=7.5 Hz), 5.15 (broad s, 1H), 4.41 (d, 4H, *J*=3.5 Hz), 3.80 (d, 6H, *J*=3.5 Hz), 3.42 (m, 4H), 3.27 (broad s, 1H), 2.39-2.09 (m, 7H), 1.73 (s, 3H), 1.54 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 141.7, 130.9, 130.8, 129.3, 127.5, 121.5, 113.9, 72.6, 70.1, 69.4, 55.4, 53.1, 36.6, 31.4, 30.5, 28.8, 16.9; **IR** (thin film, NaCl, cm^{-1}) 2998, 2934, 2854, 1613, 1586, 1513, 1302, 1248, 1173, 1094, 1036, 820 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{28}H_{36}O_4Na$, 459.6 *m/z* $(M + Na)^+$; observed, 459.3 *m/z* $(M + Na)^+$.



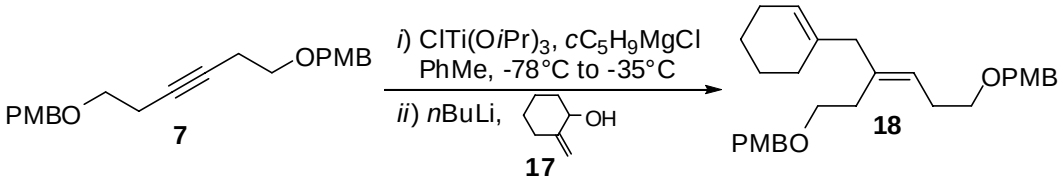
Synthesis of (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)-ethyl)but-1'-en-1'-yl)-1-phenylcyclopent-1-ene (14): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **13**[3] (42 μL, 45.6 mg, 0.284 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **14** as a colorless oil (111 mg, 79%).

Data for (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)-1-phenylcyclopent-1-ene (14): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.80 (m, 1H), 5.57 (m, 1H), 5.23 (t, 1H, *J*=7.2 Hz), 4.42 (s, 4H), 3.80 (d, 6H, *J*=2.4 Hz), 3.42 (m, 4H), 3.3 (s, 1H), 2.35 (m, 6H), 2.10 (m, 1H), 1.52 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.2, 141.1, 133.7, 131.9, 130.8, 130.7, 129.4, 129.3, 121.9, 113.9, 72.6, 70.0, 69.3, 55.4, 52.8, 32.3, 30.7, 30.6, 28.8; **IR** (thin film, NaCl, cm^{-1}) 3046, 2998, 2936, 2853, 2790, 1613, 1513, 1360, 1248, 1095, 1036 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{33}H_{38}O_4Na$, 521.6 *m/z* $(M + Na)^+$; observed, 521.4 *m/z* $(M + Na)^+$.



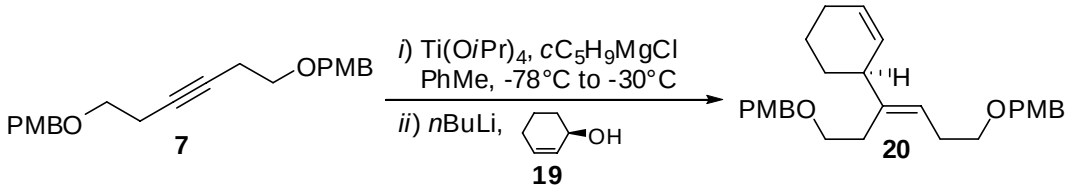
Synthesis of (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)-ethyl)but-1'-en-1'-yl)-1-cyclopentylcyclopent-1-ene (16): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **15**[7] (43 μL, 43 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **16** as a colorless oil (55 mg, 40%).

Data for (1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)-1-cyclopentylcyclopent-1-ene (16): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.22 (t, 1H, *J*=7.2 Hz), 5.16 (m, 1H), 4.41 (d, 4H, *J*=4.8 Hz), 3.79 (d, 6H, *J*=2.8 Hz), 3.44-3.39 (m, 4H), 3.26 (broad s, 1H), 2.52-2.06 (m, 7H), 1.79-1.31 (m, 10H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 149.7, 141.7, 130.9, 129.3, 124.7, 121.6, 113.9, 72.6, 70.2, 69.5, 55.4, 52.8, 41.9, 33.7, 31.7, 31.0, 30.5, 28.9, 25.3; **IR** (thin film, NaCl, cm^{-1}) 2951, 2863, 1613, 1513, 1464, 1360, 1302, 1248, 1172, 1094, 1037, 820 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{32}H_{42}O_4Na$ 513.6 *m/z* $(M + Na)^+$; observed, 513.5 *m/z* $(M + Na)^+$.



Synthesis of (2'-*E*)-2-(5'-(4-methoxybenzyloxy)-2'-(2''-(4-methoxybenzyloxy)-ethyl)pent-2'-en-1'-yl)cyclohex-1-ene (18): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **17**[2] (34 μL, 32.2 mg, 0.287 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **18** as a colorless oil (72 mg, 57%).

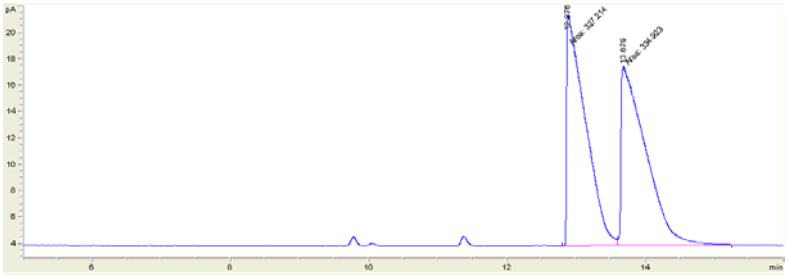
Data for (2'-*E*)-2-(5'-(4-methoxybenzyloxy)-2'-(2''-(4-methoxybenzyloxy)ethyl)pent-2'-en-1'-yl)cyclohex-1-ene (18): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.41 (app. s, 1H), 5.25 (t, 1H, *J*=7.25 Hz), 4.41 (d, 4H, *J*=6.5 Hz), 3.80 (d, 6H, *J*=2.5 Hz), 3.42 (m, 4H), 2.61 (s, 2H), 2.34 (m, 4H), 1.97 (app. s, 2H), 1.79 (app. s, 2H), 1.53 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 136.0, 130.8, 129.4, 129.3, 124.6, 123.3, 113.9, 72.7, 72.6, 70.2, 68.8, 55.4, 47.1, 30.4, 28.9, 27.9, 25.5, 23.1, 22.7; **IR** (thin film, NaCl, cm^{-1}) 3033, 2997, 2930, 2855, 2835, 1612, 1586, 1512, 1247, 1093, 1036 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{29}H_{38}O_4Na$, 473.6 *m/z* $(M + Na)^+$; observed, 473.3 *m/z* $(M + Na)^+$.



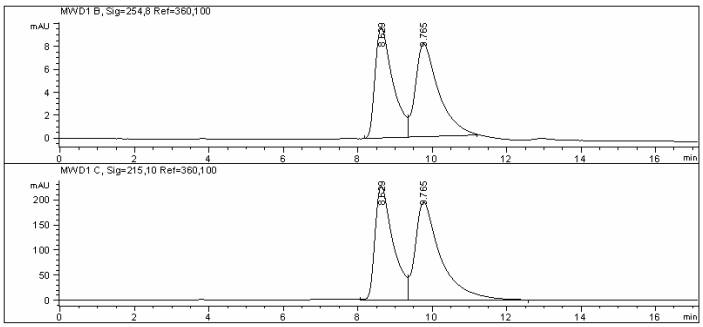
Synthesis of (*S*)-(1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxy-benzyloxy)ethyl)but-1'-en-1'-yl)cyclohex-1-ene (20): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added Ti(O*i*Pr)$_4$ (168μL, 160.4 mg, 0.565 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with *c*C$_5$H$_9$MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -30°C, stirred at -30°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **19**[4,5] (28 μL, 27.5 mg, 0.281 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous MgSO$_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **20** as a colorless oil (66 mg, 54%) with an optical purity of 92% ee. Absolute stereochemistry of **20** was assigned based on the proposed empirical model.

Data for (*S*)-(1'-*E*)-3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)-but-1'-en-1'-yl)cyclohex-1-ene (24): Data for (1'-*E*)-)3-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)ethyl)but-1'-en-1'-yl)cyclohex-1-ene (20): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.76 (m, 1H), 5.49 (app. d, 1H, *J*=10 Hz), 5.23 (t, 1H, *J*=7.25 Hz), 4.42 (d, 4H, *J*=3 Hz), 3.80 (d, 6H, *J*=2.5 Hz), 3.43 (m, 4H), 2.74 (s, 1H), 2.46 (m, 1H), 2.35 (quart, 2H, *J*=6 Hz), 2.28 (m, 1H), 1.97 (broad s, 2H), 1.74 (m, 1H), 1.64 (m, 1H), 1.49 (m, 1H), 1.41 (m, 1H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 159.3, 141.3, 130.9, 130.8, 130.4, 129.4, 128.2, 123.7, 113.9, 72.6, 70.1, 69.4, 55.4, 42.7, 30.7, 29.0, 28.8, 25.4, 20.8; **IR** (thin film, NaCl, cm^{-1}) 3015, 2931, 2855,

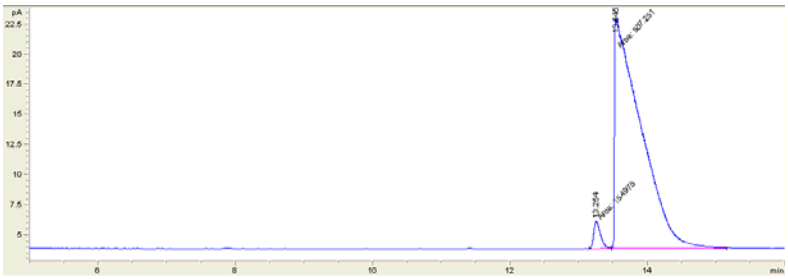
2836, 1612, 1586, 1512, 1301, 1246, 1091, 1035 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{28}H_{36}O_4Na$, 459.6 *m/z* $(M + Na)^+$; observed, 459.4 *m/z* $(M + Na)^+$; **HPLC** (Chiralpak AD, 98/2 hexanes/ethanol, 0.8 mL/min, monitor at 254 and 215 nm, 20 bar) 8.6 min (4.0%) and 9.7 min (96.0%), 92% ee.



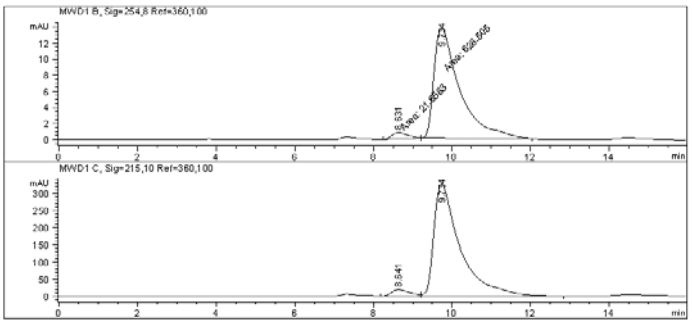
GC chromatogram of rac-**19** (HP 6890 GC system with Chiraldex BDM column, 1.5 mL/min, 100°C; retention times: 12.88 min (50.0%) and 13.68 min (50.0%)).



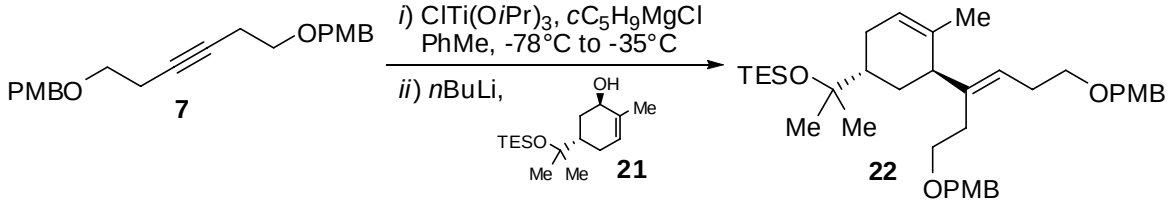
HPLC chromatogram of rac-**20** (Chiralpak AD, 0.8 mL/min, 98:2 hexanes/ethanol, 20 bar, retention rimes: 8.63 (47.6%) and 9.76 (52.4%)).



GC chromatogram of **19** (HP 6890 GC system with Chiraldex BDM column, 1.5 mL/min, 100°C; retention times: 13.26 min (2.9%) and 13.55 min (97.0%)).

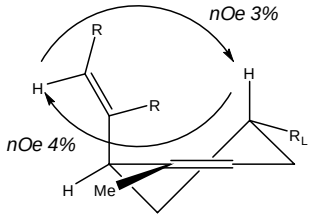


HPLC chromatogram of **20** (Chiralpak AD, 0.8 mL/min, 98:2 hexanes/ethanol, 20 bar, retention rimes: 8.63 (4.1%) and 9.73 (95.8%)).

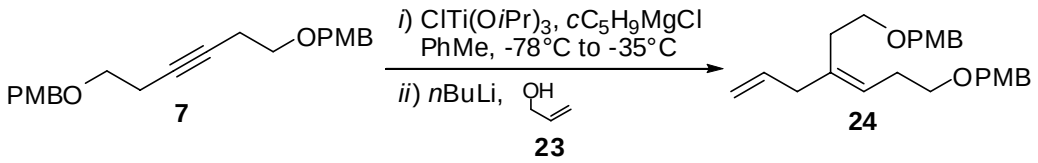


Synthesis of (4*R*,6*S*)-(1'-*E*)-6-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxy-benzyloxy)ethyl)but-1'-en-1'-yl)-4-(dimethyltriethylsilyloxymethyl)-1-methyl-cyclohex-1-ene (22): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **21** (85 μL, 80.2 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **22** as a colorless oil (88 mg, 50%). The syn diastereomer of **22** could not be

detected by ^{1}H NMR. Relative stereochemistry of **22** was determined by the indicated nOe contacts.



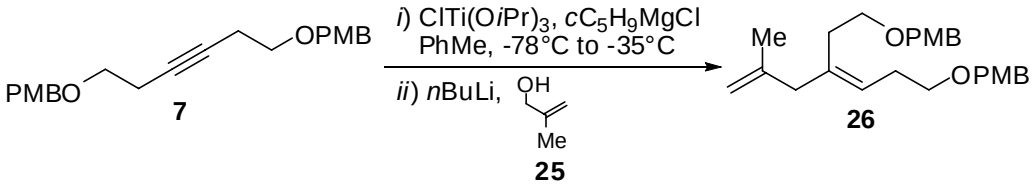
Data for (4*R*,6*S*)-(1'-*E*)-6-(4'-(4-methoxybenzyloxy)-1'-(2''-(4-methoxybenzyloxy)-ethyl)but-1'-en-1'-yl)-4-(dimethyltriethylsilyloxymethyl)-1-methyl-cyclohex-1-ene (22): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.53 (broad s, 1H), 5.06 (t, 1H, *J*=7.5 Hz), 4.41 (d, 4H, *J*=9 Hz), 3.80 (d, 6H, *J*=2 Hz), 3.48 (t, 2H, *J*=7 Hz), 3.40 (t, 2H, *J*=7.5 Hz), 2.62-2.56 (m, 2H), 2.36 (m, 2H), 2.19 (m, 1H), 1.99 (m, 1H), 1.78-1.72 (m, 2H), 1.54 (s, 3H), 1.47 (m, 1H), 1.32 (m, 1H), 1.11 (s, 3H), 1.09 (s, 3H), 0.92 (t, 9H, *J*=7.5 Hz), 0.53 (quart, 6H, *J*=8 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 138.5, 134.3, 130.9, 130.8, 129.4, 124.3, 124.0, 113.9, 75.1, 72.8, 72.7, 70.4, 69.5, 55.5, 46.4, 39.5, 31.4, 29.0, 28.2, 27.8, 27.5, 27.1, 22.4, 7.4, 7.0; **IR** (thin film, NaCl, cm^{-1}) 2954, 2911, 2874, 1613, 1513, 1463, 1248, 1096, 1039, 743 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{38}H_{58}O_5SiNa$, 645.9 *m/z* $(M + Na)^+$; observed, 645.6 *m/z* $(M + Na)^+$;



Synthesis of (*Z*)-7-(4-methoxybenzyloxy)-4-(2'-(4-methoxybenzyloxy)ethyl)-hepta-1,4-diene (24): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **23** (20 μL, 17 mg, 0.294 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to

0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **24** as a colorless oil (45 mg, 41%).

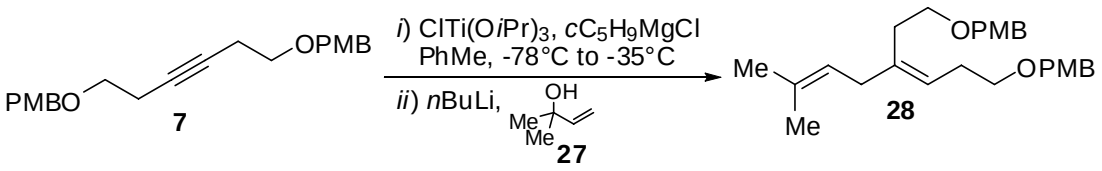
Data for (*Z*)-7-(4-methoxybenzyloxy)-4-(2'-(4-methoxybenzyloxy)ethyl)hepta-1,4-diene (24): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.76 (m, 1H), 5.26 (t, 1H, *J*=7.2 Hz), 5.03 (m, 1H), 4.99 (s, 1H), 4.42 (d, 4H, *J*=2.8 Hz), 3.80 (d, 6H, *J*=1.6 Hz), 3.43 (m, 4H), 2.75 (d, 2H, *J*=6 Hz), 2.36 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 137.0, 136.5, 130.8, 129.4, 129.3, 124.0, 116.2, 113.9, 72.7, 70.0, 68.7, 55.4, 42.2, 31.0, 28.9; **IR** (thin film, NaCl, cm^{-1}) 3073, 2999, 2906, 2854, 1613, 1512, 1464, 1247, 1094 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{25}H_{32}O_4Na$, 419.5 *m/z* $(M + Na)^+$; observed, 419.3 *m/z* $(M + Na)^+$.



Synthesis of (*Z*)-7-(4-methoxybenzyloxy)-4-(2'-(4-methoxybenzyloxy)ethyl)-2-methyl-hepta-1,4-diene (26): To a stirred solution of alkyne **7** [1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **25** (24 µL, 20.4 mg, 0.283 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color.

The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **26** as a colorless oil (76 mg, 66%).

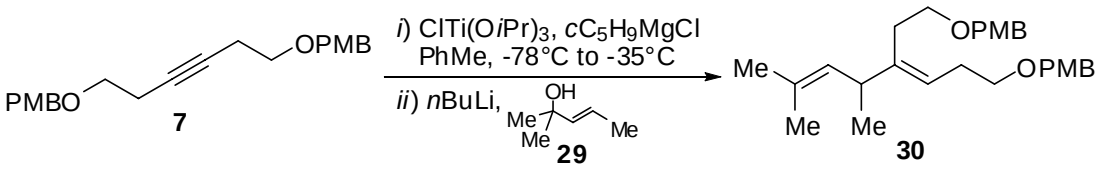
Data for (*Z*)-7-(4-methoxybenzyloxy)-4-(2'-(4-methoxybenzyloxy)ethyl)-2-methyl-hepta-1,4-diene (26): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.29 (t, 1H, *J*=7.5 Hz), 4.77 (s, 1H), 4.70 (s, 1H), 4.42 (d, 4H, *J*=5.5 Hz), 3.80 (d, 6H, *J*=2.5 Hz), 3.43 (dt, 4H, *J*=7 Hz, *J*=2.5 Hz), 2.70 (s, 2H), 2.35 (m, 4H), 1.63 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 144.1, 135.6, 130.8, 129.4, 129.3, 125.1, 113.9, 112.3, 72.7, 72.6, 70.1, 68.7, 55.5, 46.8, 30.4, 28.9, 22.0; **IR** (thin film, NaCl, cm^{-1}) 2935, 2907, 2854, 1613, 1513, 1464, 1457, 1360, 1247, 1093 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{26}H_{34}O_4Na$, 433.5 *m/z* $(M + Na)^+$; observed, 433.4 *m/z* $(M + Na)^+$.



Synthesis of (*Z*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2-methyl-octa-2,5-diene (28): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **27** (30 μL, 24.9 mg, 0.289 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The

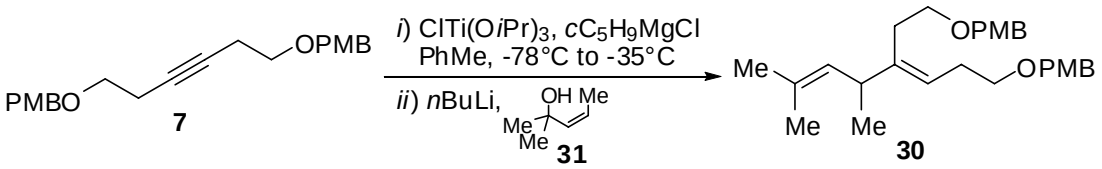
crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **28** as a colorless oil (63 mg, 53%).

Data for (*Z*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2-methyl-octa-2,5-diene (28): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.23 (t, 1H, *J*=7.25 Hz), 5.10 (t, 1H, *J*=7.25 Hz), 4.42 (d, 4H, *J*=2 Hz), 3.80 (d, 6H, *J*=2.5 Hz), 3.43 (m, 4H), 2.69 (d, 2H, *J*=7.5 Hz), 2.35 (m, 4H), 1.70 (s, 3H), 1.59 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 137.5, 132.9, 130.9, 129.4, 129.3, 122.8, 122.6, 113.9, 72.6, 70.1, 68.9, 55.4, 36.4, 31.8, 31.3, 28.8, 25.9, 25.0, 17.8; **IR** (thin film, NaCl, cm^{-1}) 2934, 2855, 1653, 1614, 1513, 1457, 1361, 1302, 1248, 1096, 1036 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{27}H_{36}O_4Na$, 447.6 *m/z* $(M + Na)^+$; observed, 447.3 *m/z* $(M + Na)^+$.



Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2,4-dimethyl-octa-2,5-diene (30): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **29**[6] (35 μL, 28.6 mg, 0.286 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **30** as a colorless oil (73 mg, 59%).

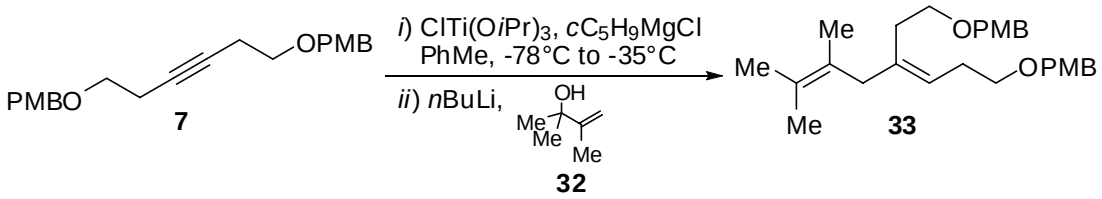
Data for (*E*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2,4-dimethyl-octa-2,5-diene (30): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.25 (t, 1H, *J*=7.25 Hz), 4.93 (d, 1H, *J*=9.5 Hz), 4.42 (d, 4H, *J*=7.5 Hz), 3.80 (d, 6H, *J*=2.5 Hz), 3.42 (quart, 4H, *J*=7 Hz), 2.98 (app. quin, 1H, *J*=7 Hz), 2.42-2.28 (m, 4H), 1.66 (s, 3H), 1.60 (s, 3H), 1.02 (d, 3H, *J*=6.5 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 142.0, 130.8, 129.8, 129.4, 121.1, 113.9, 72.6, 70.2, 69.4, 55.4, 39.4, 30.6, 28.9, 26.0, 20.3, 18.0, 14.3; **IR** (thin film, NaCl, cm^{-1}) 2959, 2929, 2855, 1613, 1513, 1457, 1361, 1302, 1248, 1095, 1037 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{28}H_{38}O_4Na$, 461.6 *m/z* $(M + Na)^+$; observed, 461.4 *m/z* $(M + Na)^+$.



Synthesis of (*E*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2,4-dimethyl-octa-2,5-diene (30): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **31** (36 μL, 28.1 mg, 0.281 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **30** as a colorless oil (83 mg, 67%).

Data for (*E*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2,4-dimethyl-octa-2,5-diene (30): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.25 (t, 1H, *J*=7.25 Hz), 4.93 (d, 1H, *J*=9.5 Hz), 4.42 (d, 4H, *J*=7.5 Hz), 3.80 (d,

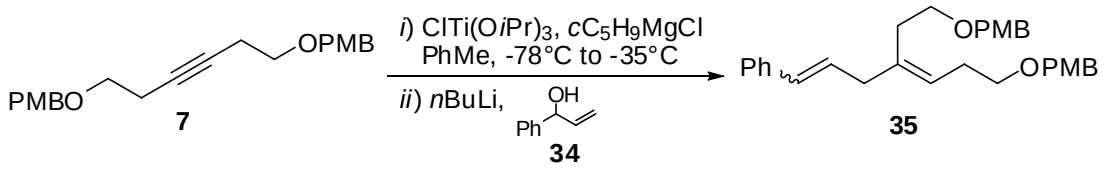
6H, *J*=2.5 Hz), 3.42 (quart, 4H, *J*=7 Hz), 2.98 (app. quin, 1H, *J*=7 Hz), 2.42-2.28 (m, 4H), 1.66 (s, 3H), 1.60 (s, 3H), 1.02 (d, 3H, *J*=6.5 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 142.0, 130.8, 129.8, 129.4, 121.1, 113.9, 72.6, 70.2, 69.4, 55.4, 39.4, 30.6, 28.9, 26.0, 20.3, 18.0, 14.3; **IR** (thin film, NaCl, cm^{-1}) 2959, 2929, 2855, 1613, 1513, 1457, 1361, 1302, 1248, 1095, 1037 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{28}H_{38}O_4Na$, 461.6 *m/z* $(M + Na)^+$; observed, 461.4 *m/z* $(M + Na)^+$.



Synthesis of (*Z*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2,3-dimethylocta-2,5-diene (33): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **32**[7] (33 μL, 28.2 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **33** as a colorless oil (70 mg, 57%).

Data for (*Z*)-8-(4-methoxybenzyloxy)-5-(2'-(4-methoxybenzyloxy)ethyl)-2,3-dimethylocta-2,5-diene (33): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.88-6.86 (m, 4H), 5.18 (t, 1H, *J*=7 Hz), 4.42 (d, 4H, *J*=3 Hz), 3.80 (d, 6H, *J*=3 Hz), 3.42 (app. quart, 4H, *J*=7 Hz), 2.73 (s, 2H), 2.38-2.28 (m, 4H), 1.66 (s, 3H), 1.63 (s, 3H), 1.54 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 136.0, 130.9, 129.4, 126.2, 125.5, 123.2,

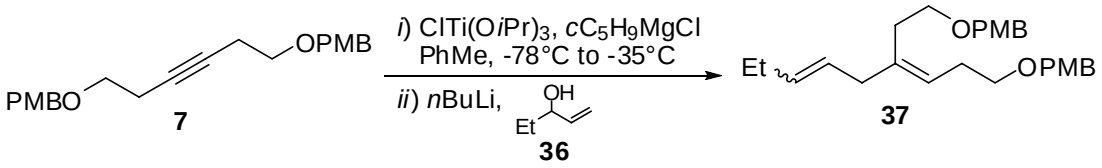
113.9, 72.7, 70.2, 69.0, 55.4, 42.5, 31.1, 28.9, 20.9, 20.6, 18.3; **IR** (thin film, NaCl, cm^{-1}) 2929, 2855, 1613, 1513, 1464, 1360, 1302, 1248, 1173, 1097, 1037, 820 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{28}H_{38}O_4Na$, 461.6 *m/z* $(M + Na)^+$; observed, 461.4 *m/z* $(M + Na)^+$.



Synthesis of (4*Z*)-7-(4-methoxybenzyloxy)-4-(2'-(4-methoxybenzyloxy)ethyl)-1-phenylhepta-1,4-diene (1:1 mixture of 1-*E/Z* isomers) (35): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added ClTi(O*i*Pr)$_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with *c*C$_5$H$_9$MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **34**[7] (37 μL, 37.8 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford pale yellow diene **35** as 1:1 mixture of *E/Z* isomers (104 mg, 78%).

Data for (4*Z*)-7-(4-methoxybenzyloxy)-4-(2'-(4-methoxybenzyloxy)ethyl)-1-phenyl-hepta-1,4-diene (1:1 mixture of 1-*E/Z* isomers) (35): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.20 (m, 18H), 6.88-6.83 (m, 8H), 6.53 (d, 1H, *J*=11.5 Hz), 6.37 (d, 1H, *J*=16 Hz), 6.16 (m, 1H), 5.69 (m, 1H), 5.35 (m, 2H), 4.42 (d, 8H, *J*=3 Hz), 3.78 (s, 12H), 3.50-3.41 (m, 8H), 3.02 (d, 2H, *J*=7.5 Hz), 2.91 (d, 2H, *J*=7.0 Hz), 2.42-2.36 (m, 8H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 137.8, 137.5, 136.8, 131.4, 130.8, 130.5, 130.4, 129.4, 129.3, 128.9, 128.8, 128.7, 128.3, 127.9, 127.1, 126.8, 126.2, 124.3, 123.6, 113.9, 72.7, 70.0,

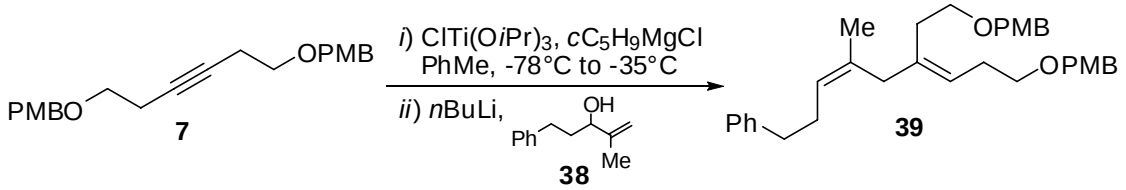
69.7, 68.6, 55.4, 41.4, 36.4, 31.6, 31.2, 28.9, 28.3; **IR** (thin film, NaCl, cm^{-1}) 3001, 2934, 2855, 1613, 1586, 1513, 1464, 1302, 1248, 1095, 820 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{31}H_{36}O_4Na$, 495.6 *m/z* $(M + Na)^+$; observed, 495.4 *m/z* $(M + Na)^+$.



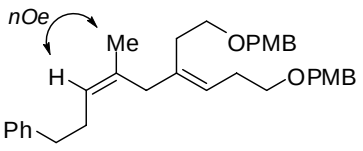
Synthesis of (6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)ethyl)-nona-3,6-diene (1:1 mixture of 3-*E/Z* isomers) (37): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **36** (29 μL, 24.3 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **37** as 1:1 mixture of *E/Z* isomers (80 mg, 67%).

Data for (6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)ethyl)nona-3,6-diene (1:1 mixture of 3-*E/Z* isomers) (37): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 8H), 6.88-6.86 (m, 8H), 5.45 (m, 2H), 5.34 (m, 2H), 5.26 (quart, 2H, *J*=7.2 Hz), 4.42 (m, 8H), 3.80 (d, 12H, *J*=1.5 Hz), 3.43 (m, 8H), 2.75 (d, 2H, *J*=7 Hz), 2.69 (d, 2H, *J*=7 Hz), 2.36 (m, 8H), 2.02 (m, 4H), 0.963 (quart, 6H, *J*=7.83 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 137.2, 137.0, 133.9, 133.1, 130.9, 129.4, 129.3, 127.2, 126.9, 123.4, 123.1, 113.9, 72.6, 70.1, 68.8, 55.4, 41.0, 35.4, 31.3, 31.0, 28.9, 28.8, 25.7, 20.6, 14.4, 14.0; **IR**

(thin film, NaCl, cm^{-1}) 3001, 2958, 2933, 2908, 2854, 1613, 1586, 1512, 1247, 1094 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{27}H_{36}O_4Na$, 447.6 *m/z* $(M + Na)^+$; observed, 447.3 *m/z* $(M + Na)^+$.

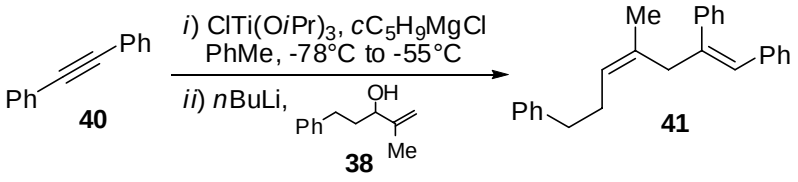


Synthesis of (3*Z*,6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)-ethyl)-1-phenyl-4-methylnona-3,6-diene (39): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **38**[7] (48 μL, 49.8 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **39** as a colorless oil (104 mg, 72%). No evidence for was found for the formation of the stereoisomer of **39** bearing (*E*)-trisubstituted olefin. Double bond geometry was determined by the indicated nOe.

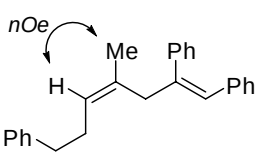


Data for (3*Z*,6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)ethyl)-1-phenyl-4-methylnona-3,6-diene (39): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.20 (m, 9H), 6.92-6.88 (m, 4H), 5.35 (t, 1H, *J*=7 Hz), 5.28 (t, 1H, *J*=7.5 Hz), 4.44 (d, 4H, *J*=6 Hz),

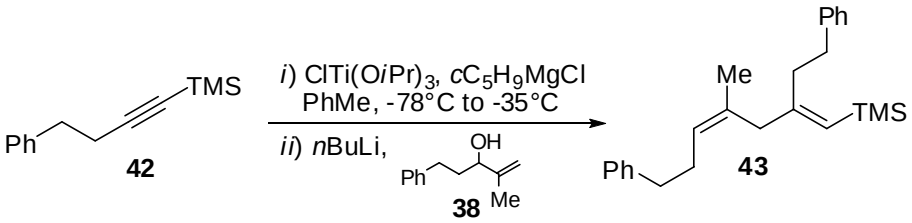
3.82 (d, 6H, *J*=5.5 Hz), 3.47 (m, 4H), 2.75 (s, 2H), 2.67 (t, 2H, *J*=7.5 Hz), 2.42-2.32 (m, 6H), 1.64 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 142.4, 135.3, 133.7, 130.8, 129.4, 129.3, 128.6, 128.4, 126.3, 125.8, 123.8, 113.8, 72.6, 70.1, 68.9, 55.4, 40.0, 36.4, 31.0, 30.2, 28.8, 23.5; **IR** (thin film, NaCl, cm^{-1}) 3061, 2999, 2933, 2854, 2789, 1613, 1586, 1513, 1248, 1094 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{34}H_{42}O_4Na$, 537.7 *m/z* $(M + Na)^+$; observed, 537.4 *m/z* $(M + Na)^+$.



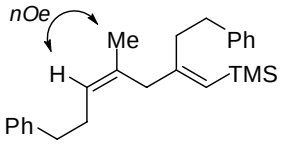
Synthesis of (3*Z*,6*Z*)-1,6,7-triphenyl-4-methylhepta-3,6-diene (41): To a stirred solution of alkyne **40** (50.3 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -55°C, stirred at -55°C for 90 min, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **38**[7] (48 μL, 49.8 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 5% ethyl acetete/hexanes to afford diene **41** as pale yellow oil (74 mg, 77%). No evidence for was found for the formation of the stereoisomer of **41** bearing (*E*)-trisubstituted olefin. Double bond geometry was determined by the indicated nOe.



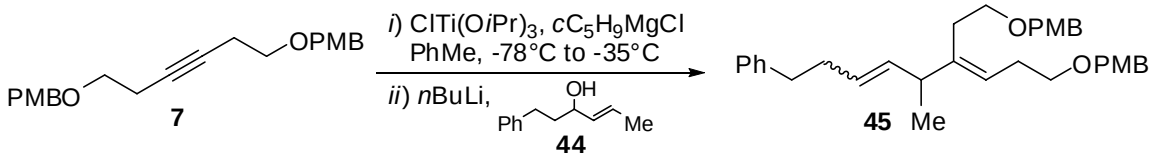
Data for (3*Z*,6*Z*)-1,6,7-triphenyl-4-methylhepta-3,6-diene (41): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-6.92 (m, 13H), 6.81-6.79 (m, 2H), 6.30 (s, 1H), 5.20 (t, 1H, *J*=7 Hz), 3.05 (s, 2H), 2.34 (t, 2H, *J*=8 Hz), 2.11-2.06 (quart, 2H, *J*=7 Hz), 1.64 (d, 3H, *J*=1.5 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.4, 141.7, 140.6, 137.6, 132.7, 129.2, 129.1, 128.6, 128.4, 128.0, 127.2, 127.1, 126.4, 125.9, 43.3, 36.2, 30.2, 23.7; **IR** (thin film, NaCl, cm^{-1}) 3080, 3057, 3025, 2963, 2928, 1600, 1495, 1443, 1075, 699 cm^{-1}; **LRMS** (GC-MS, EI) calcd for $C_{26}H_{26}$, 338.5 *m/z* $(M)^+$; observed, 339.0 *m/z* $(M)^+$.



Synthesis of (3*Z*,6*E*)-7-trimethylsilyl-6-(2'-phenylethyl)-1-phenyl-4-methyl hepta-3,6-diene (43): To a stirred solution of alkyne **42**[8] (64.1 μL, 57.1 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **38**[7] (48 μL, 49.8 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 5% ethyl acetete/hexanes to afford diene **43** (73 mg, 71%) with regiomeric ratio >20:1 (^{1}H NMR). No evidence for was found for the formation of the stereoisomer of **43** bearing (*E*)-trisubstituted olefin. Double bond geometry was determined by the indicated nOe.

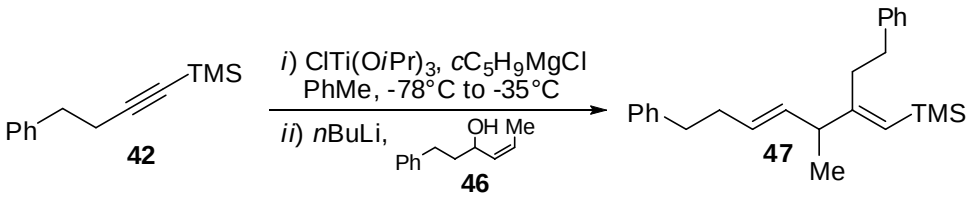


Data for (3*Z*,6*E*)-7-trimethylsilyl-6-(2'-phenylethyl)-1-phenyl-4-methylhepta-3,6-diene (43): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H), 7.23-7.20 (m, 6H), 5.39 (t, 1H, *J*=7 Hz), 5.30 (s, 1H), 2.87 (s, 2H), 2.76-2.67 (m, 4H), 2.42-2.34 (m, 4H), 1.67 (s, 3H), 0.13 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.7, 142.4, 142.3, 133.9, 128.6, 128.5, 126.6, 126.1, 125.9, 125.4, 42.0, 38.3, 36.5, 36.0, 30.4, 23.7, 0.6; **IR** (thin film, NaCl, cm^{-1}) 3085, 3062, 3027, 2952, 2857, 1606, 1496, 1454, 1247, 837 cm^{-1}; **LRMS** (GC-MS, EI) calcd for $C_{25}H_{34}Si$, 362.6 *m/z* $(M)^+$; observed, 363.0 *m/z* $(M)^+$.



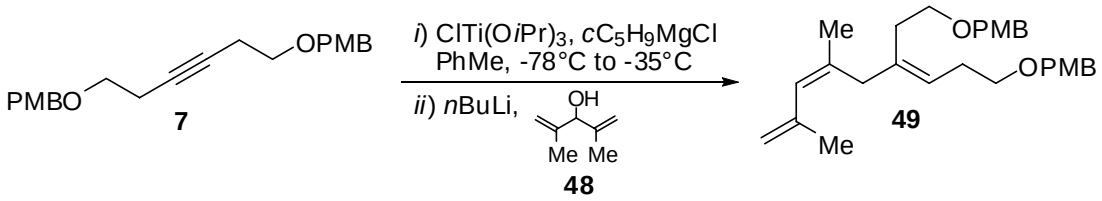
Synthesis of (6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)ethyl)-1-phenyl-5-methylnona-3,6-diene (1:1 mixture of 3-*E/Z* isomers) (45): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **44**[6] (52 μL, 50.0 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford diene **45** as a 1:1 mixture of *E/Z* isomers (98 mg, 67%).

Data for (6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)ethyl)-1-phenyl-5-methylnona-3,6-diene (1:1 mixture of 3-*E/Z* isomers) (45): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.19 (m, 18H), 6.92-6.88 (m, 8H), 5.47-5.27 (m, 4H), 5.23 (t, 1H, *J*=10.5 Hz), 4.47-4.43 (m, 8H), 3.83-3.82 (m, 12H), 3.46-3.43 (m, 8H), 3.10 (m, 1H), 2.77 (m, 1H), 2.68 (m, 4H), 2.45-2.31 (m, 12H), 1.01 (d, 6H, *J*=7.5 Hz); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 142.2, 141.5, 135.4, 135.3, 130.9, 129.4, 129.3, 128.6, 128.4, 128.2, 126.0, 122.0, 121.6, 113.9, 72.6, 70.1, 69.4, 60.5, 55.4, 43.6, 38.5, 36.1, 34.5, 30.5, 30.4, 29.5, 28.9, 21.2, 20.1, 19.5, 14.4; **IR** (thin film, NaCl, cm^{-1}) 3061, 2957, 2933, 2855, 1613, 1586, 1513, 1454, 1248, 1094, 820 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{34}H_{42}O_4Na$, 537.7 *m/z* $(M + Na)^+$; observed, 537.4 *m/z* $(M + Na)^+$.

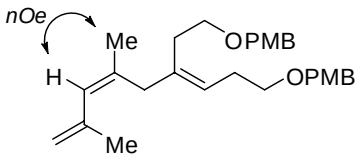


Synthesis of (3*E*,6*E*)-7-trimethylsilyl-6-(2'-phenylethyl)-1-phenyl-5-methyl-hepta-3,6-diene (47): To a stirred solution of alkyne **42**[8] (64.1 μL, 57.1 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **46** (52 μL, 50.0 mg, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 5% ethyl acetete/hexanes to afford diene **47** (60 mg, 59%) in >20:1 regioselectivity (^{1}H NMR). *E/Z* ratio = 8:1 (double bond geometry determined by ^{1}H NMR and nOe spectroscopy).

Data for (3*E*,6*E*)-7-trimethylsilyl-6-(2'-phenylethyl)-1-phenyl-5-methylhepta-3,6-diene (47): (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 10H), 5.50-5.32 (m, 2H), 5.27 (s, 1H), 2.87 (m, 1H), 2.71-2.63 (m, 4H), 2.41-2.31 (m, 4H), 1.11 (d, 3H), 0.11 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.3, 142.5, 142.2, 135.9, 128.7, 128.6, 128.5, 128.4, 126.0, 125.9, 122.4, 44.3, 37.9, 36.4, 36.3, 34.5, 29.6, 20.2, 0.7; **IR** (thin film, NaCl, cm^{-1}) 3085, 3063, 3027, 2954, 2858, 1605, 1496, 1454, 1247, 863 cm^{-1}; **LRMS** (GC-MS, EI) calcd for $C_{25}H_{34}Si$, 362.6 *m/z* $(M)^+$; observed, 363.0 *m/z* $(M)^+$.



Synthesis of (3*Z*,6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)-ethyl)-2,4-dimethylnona-1,3,6-triene (49): To a stirred solution of alkyne **7**[1] (100 mg, 0.282 mmol) in 2.8 mL of toluene was added $ClTi(OiPr)_3$ (1.0 M in hexanes, 0.564 mmol) via gas-tight syringe, followed by cooling to -78°C. The solution was then treated dropwise with cC_5H_9MgCl (2.07 M in diethyl ether, 1.128 mmol) via gas tight syringe. The resulting solution was slowly warmed to -35°C, stirred at -35°C for 1 h, and then cooled to -78°C. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **48**[9] (37 μL, 31.6, 0.282 mmol) in THF (0.2 mL) at −78 °C with *n*BuLi (2.60 M in hexanes, 0.310 mmol) followed by warming to 0 °C over 30 min, was added in a dropwise manner to the black solution of Ti–alkyne complex at −78°C via cannula. The mixture was then warmed to 0°C over 30 min and stirred at 0°C for 1 h. The reaction was quenched by the addition of 6 mL of water and rapid stirring until the precipitate became grey in color. The resulting aqueous layer was extracted three times with diethyl ether. Combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 15% ethyl acetete/hexanes to afford triene **49** as a colorless oil (79 mg, 63%). No evidence for was found for the formation of the stereoisomer of **49** bearing (*E*)-trisubstituted olefin. Double bond geometry was determined as described previously.



Data for (3*Z*,6*Z*)-9-(4-methoxybenzyloxy)-6-(2'-(4-methoxybenzyloxy)ethyl)-2,4-dimethylnona-1,3,6-triene (49): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.89-6.86 (m, 4H), 5.79 (s, 1H), 5.21 (t, 1H, *J*=7.2 Hz), 4.85 (s, 1H), 4.78 (s, 1H), 4.41 (d, 4H, *J*=2.8 Hz), 3.80 (d, 6H, *J*=1.6 Hz), 3.44 (m, 4H), 2.93 (s, 2H), 2.36 (m, 4H), 1.80 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 142.0, 135.7, 135.4, 130.9, 129.6, 129.4, 123.7, 113.9, 113.3, 72.7, 70.1, 68.8, 55.4, 40.7, 31.6, 28.9, 24.4, 23.8; **IR** (thin film, NaCl, cm^{-1}) 2998, 2934, 2854, 1613, 1586, 1513, 1464, 1248, 1173, 1095 cm^{-1}; **LRMS** (ESI, H) calcd for $C_{29}H_{38}O_4Na$, 473.6 *m/z* $(M + Na)^+$; observed, 473.4 *m/z* $(M + Na)^+$.

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