

**Chemoselective Reductive Cross-Coupling of 1,5-Dienes with Alkynes: A Facile  
Entry to Stereodefined Skipped Trienes**

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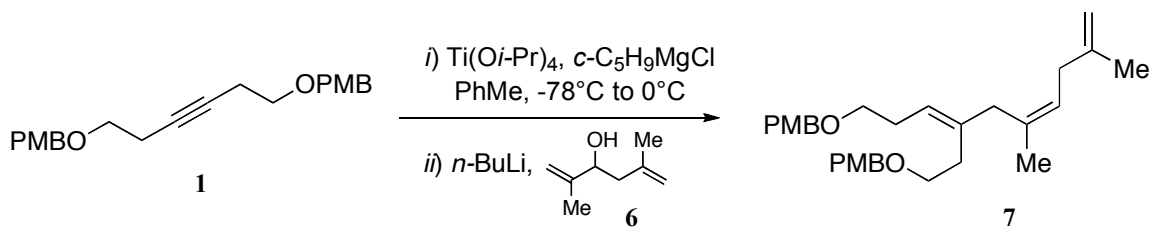
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**SUPPORTING INFORMATION:**

**General.** All reactions were conducted in flame-dried glassware under an argon atmosphere with dry solvents, unless otherwise noted. Anhydrous tetrahydrofuran

(THF), dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), and toluene (PhMe) were obtained by passing HPLC grade solvents through activated alumina columns. Anhydrous diethyl ether (Et<sub>2</sub>O) was obtained by distillation of HPLC grade diethyl ether over sodium and benzophenone. Anhydrous methanol (MeOH) was purchased from Aldrich. Titanium tetraisopropoxide was purified by distillation prior to use. *n*-, *s*-, and *t*-BuLi solutions were purchased from Aldrich and titrated monthly against *N*-benzylbenzamide. *c*-C<sub>5</sub>H<sub>9</sub>MgCl was purchased from Aldrich and titrated monthly using 1,10-phenanthroline and *s*-butanol. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR) homogeneous materials, unless otherwise stated. Flash column chromatography was performed using Silicycle SiliaFlash P60 silica gel, 40-63 μm particle size. <sup>1</sup>H NMR data were recorded in CDCl<sub>3</sub> at 400 MHz on a Bruker AM-400 with calibration of spectra to residual CHCl<sub>3</sub> (7.26 ppm). <sup>13</sup>C data were recorded at 100 MHz on a Bruker AM-400 with calibration to the central line of CDCl<sub>3</sub> (77.36 ppm). Infrared spectra were recorded on a PerkinElmer SpectrumOne FT-IR instrument. HRMS data for **7**, **9**, **11**, and **13** (DART-TOF ionization) was obtained by the University of Florida mass spectrometry lab. All other HRMS data was obtained from the University of Illinois Urbana-Champaign mass spectrometry lab. 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. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Relative stereochemistry was defined using the *R*\*/*S*\* convention proposed by IUPAC. Brine refers to a saturated aqueous solution of NaCl.

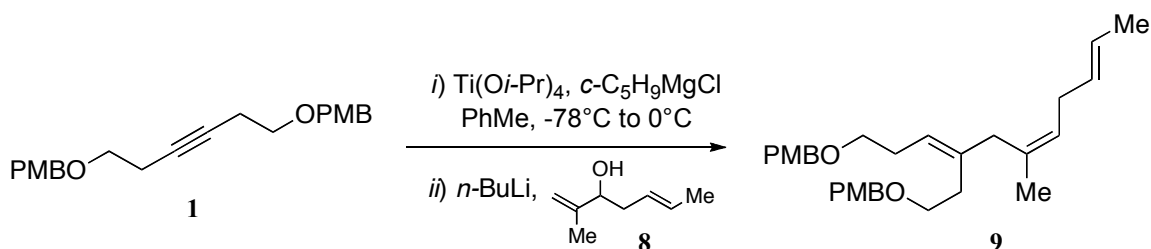
## **Experimental Data**



**Synthesis of (3Z,6Z)-O-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-6,9-dimethyldeca-3,6,9-trien-1-ol (7):** To a stirred solution of alkyne **1** (993 mg, 2.8 mmol) in 24 mL of PhMe was added Ti(Oi-Pr)<sub>4</sub> (1.70 ml, 1.59 g, 5.60 mmol) via gas-tight syringe. The solution was cooled to  $-78^\circ\text{C}$  and treated dropwise with *c*-C<sub>5</sub>H<sub>9</sub>MgCl (2.00 M in Et<sub>2</sub>O, 11.2 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^\circ\text{C}$  over 30 min, stirred at  $-35^\circ\text{C}$  for 1 h, and cooled to  $-78^\circ\text{C}$ . A solution of lithium alkoxide was prepared by adding *n*-BuLi (2.38 M in hexanes, 1.54 mmol) to alcohol **6** (176 mg, 1.40 mmol) in THF (4.6 mL) at  $-78^\circ\text{C}$  then warming to  $0^\circ\text{C}$  over 20 min. This solution was added in a dropwise manner to the black solution of Ti-alkyne complex via cannula. The mixture was then warmed to  $0^\circ\text{C}$  over 5 h and stirred for 1 h. The reaction was then poured into 50 mL of stirring, saturated aqueous NH<sub>4</sub>Cl at  $0^\circ\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 20 ml of Et<sub>2</sub>O to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with EtOAc and the filtered aqueous layer was extracted 3X with Et<sub>2</sub>O. Combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 5% then 10% EtOAc in hexanes to afford 612 mg of a mixture of **7** and the reduction product of alkyne **1** that was 61% **7** by mass (back-calculated 57% yield of **7**). The mixture was further purified by HPLC to obtain pure **7** as a colorless oil. The stereochemistry of the central olefin was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup>

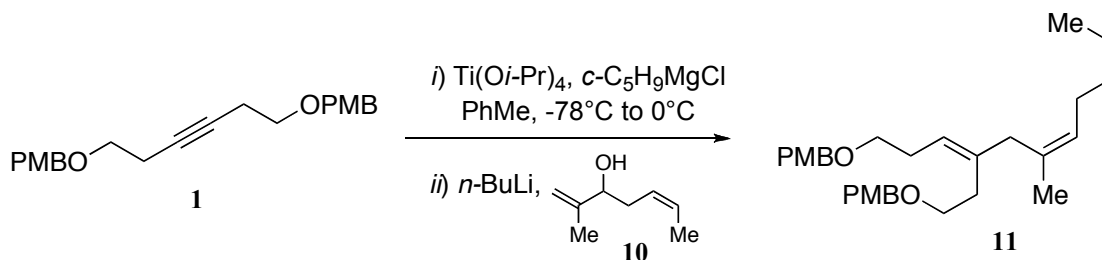
**Data for (3Z,6Z)-O-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-6,9-dimethyldeca-3,6,9-trien-1-ol (7):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (dd, 4H,  $J_1 = 9.0$  Hz,  $J_2 = 4.0$  Hz), 6.87 (dd, 4H,  $J_1 = 9.0$  Hz,  $J_2 = 4.0$  Hz), 5.30 (t, 1H,  $J = 6.0$  Hz), 5.28 (t, 1H,  $J = 7.2$  Hz), 4.71-4.67 (m, 2H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.44 (t, 2H,  $J = 7.2$  Hz), 3.42 (t, 2H,  $J = 7.2$  Hz), 2.74 (s, 2H), 2.66 (d, 2H,  $J = 8.0$  Hz),

2.36 (dt, 2H,  $J_1 = 7.2$  Hz,  $J_2 = 7.2$  Hz), 2.31 (t, 2H,  $J = 7.6$  Hz), 1.70 (s, 3H), 1.63 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.44, 159.43, 145.65, 135.55, 134.70, 134.04, 134.01, 129.53, 129.49, 124.62, 124.14, 114.07, 110.32, 72.84, 70.29, 69.08, 55.61, 55.59, 40.12, 36.75, 31.19, 29.05, 23.75, 23.00; IR (thin film, KBr) 2934, 2854, 1613, 1513, 1442, 1359, 1301, 1247, 1172, 1094, 1036, 820  $\text{cm}^{-1}$ ; HRMS (DART)  $m/z$  calc'd for  $\text{C}_{30}\text{H}_{40}\text{O}_4 + \text{H}^+$  465.2927, found 465.3005



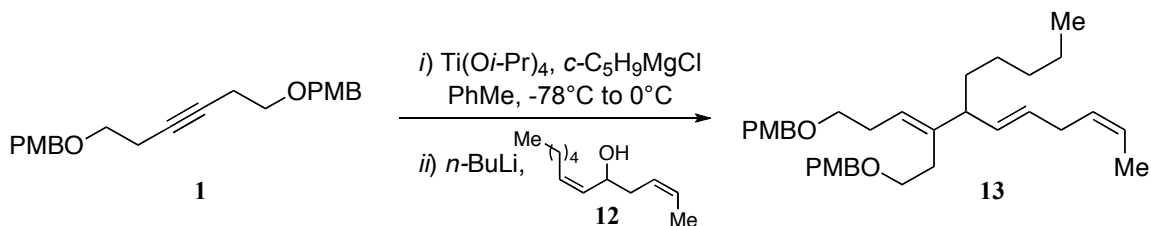
**Synthesis of (3Z,6Z,9E)-O-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-6-methylundeca-3,6,9-trien-1-ol (9):** To a stirred solution of alkyne **1** (993 mg, 2.8 mmol) in 24 mL of  $\text{PhMe}$  was added  $\text{Ti}(\text{O}i\text{-Pr})_4$  (1.59 g, 5.6 mmol) via gas-tight syringe. The solution was cooled to  $-78^\circ\text{C}$  and treated dropwise with  $c\text{-C}_5\text{H}_9\text{MgCl}$  (2.00 M in  $\text{Et}_2\text{O}$ , 11.2 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^\circ\text{C}$  over 30 min, stirred at  $-35^\circ\text{C}$  for 1 h, and cooled to  $-78^\circ\text{C}$ . A solution of lithium alkoxide was prepared by adding  $n\text{-BuLi}$  (2.38 M in hexanes, 1.54 mmol) to alcohol **8** (176 mg, 1.40 mmol) in THF (4.6 mL) at  $-78^\circ\text{C}$  then warming to  $0^\circ\text{C}$  over 20 min. This solution was added in a dropwise manner to the black solution of Ti-alkyne complex via cannula. The mixture was then warmed to  $0^\circ\text{C}$  over 5 h and stirred for 1 h. The reaction was quenched by pouring it into 50 mL of stirring, saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^\circ\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 20 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$  and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 5% then 10%  $\text{EtOAc}$  in hexanes to afford 659 mg of a mixture of **9** and the reduction product of alkyne **1** that was 57% **9** by mass

(back-calculated 57% yield of **9**). **9** was separated from the reduced alkyne via HPLC to obtain a clear oil. The stereochemistry of the central olefin was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for: (3*Z*,6*Z*,9*E*)-*O*-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-6-methylundeca-3,6,9-trien-1-ol (**9**):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.25 (dd, 4H, *J*<sub>1</sub> = 9.0 Hz, *J*<sub>2</sub> = 4.0 Hz), 6.87 (dd, 4H, *J*<sub>1</sub> = 9.0 Hz, *J*<sub>2</sub> = 4.0 Hz), 5.41-5.37 (m, 2H), 5.27-5.23 (m, 2H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.44 (t, 2H, *J* = 7.2 Hz), 3.42 (t, 2H, *J* = 7.2 Hz), 2.74 (s, 2H), 2.66 (dd, 2H, *J*<sub>1</sub> = 4.0 Hz, *J*<sub>2</sub> = 4.0 Hz), 2.36 (dt, 2H, *J*<sub>1</sub> = 7.2 Hz, *J*<sub>2</sub> = 7.2 Hz), 2.31 (t, 2H, *J* = 7.6 Hz), 1.64 (d, 3H, *J* = 4.8 Hz), 1.60 (d, 3H, *J* = 1.40 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 159.44, 159.43, 135.55, 133.76, 131.02, 131.04, 130.28, 129.52, 129.48, 125.36, 125.28, 124.05, 114.08, 114.06, 72.82, 70.30, 69.05, 55.60, 55.58, 40.15, 31.65, 31.16, 29.02, 23.67, 18.25; IR (thin film, KBr) 3400, 2935, 2865, 1710, 1611, 1513, 1249, 1171, 1097, 1033, 825 cm<sup>-1</sup>; HRMS (DART) *m/z* calc'd for C<sub>30</sub>H<sub>40</sub>O<sub>4</sub>+H<sup>+</sup> 465.2927, found 465.3008



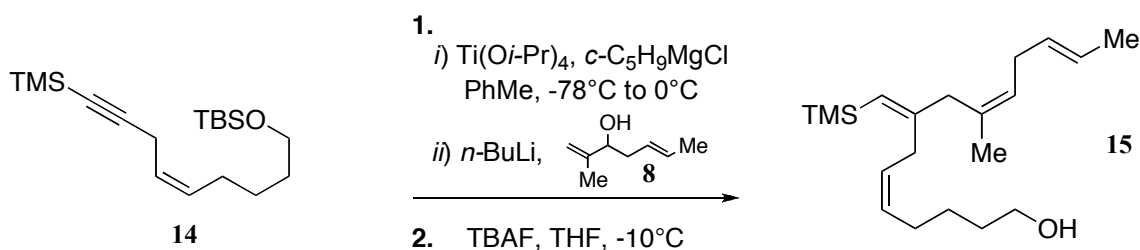
**Synthesis of (3*Z*,6*Z*,9*Z*)-*O*-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-6-methylundeca-3,6,9-trien-1-ol (**11**):** To a stirred solution of alkyne **1** (830 mg, 2.34 mmol) in 23 mL of PhMe was added Ti(Oi-Pr)<sub>4</sub> (753 mg, 2.65 mmol) via gas-tight syringe. The solution was cooled to -78°C and treated dropwise with *c*-C<sub>5</sub>H<sub>9</sub>MgCl (2.00 M in Et<sub>2</sub>O, 5.3 mmol) via gas-tight syringe. The resulting solution was warmed to -35°C over 30 min, stirred at -35°C for 1 h, and cooled to -78°C. A solution of lithium alkoxide was prepared by adding *n*-BuLi (2.39 M in hexanes, 0.858 mmol) to alcohol **10** (100 mg, 0.780 mmol) in THF (2.3 mL) at -78 °C then warming to 0°C over 20 min. This solution was added in a dropwise manner to the black solution of Ti-alkyne complex via cannula. The mixture was then warmed to 0°C over 5 h and stirred for 1 h.

The reaction was quenched by pouring it into 50 mL of stirring, saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^\circ\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 20 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$  and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 5% then 10%  $\text{EtOAc}$  in hexanes to afford 275 mg of **11** as a clear oil (76%). The stereochemistry of the central olefin was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for (3*Z*,6*Z*,9*Z*)-*O*-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-6-methylundeca-3,6,9-trien-1-ol (11):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (dd, 4H,  $J_1 = 9.0$  Hz,  $J_2 = 4.0$  Hz), 6.87 (dd, 4H,  $J_1 = 9.0$  Hz,  $J_2 = 4.0$  Hz), 5.48-5.39 (m, 1H), 5.38-5.30 (m, 1H), 5.28-5.20 (m, 2H), 4.42 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.45 (t, 2H,  $J = 7.2$  Hz), 3.42 (t, 2H,  $J = 7.2$  Hz), 2.74 (s, 2H), 2.73 (dd, 2H,  $J_1 = 6.8$  Hz,  $J_2 = 6.8$  Hz), 2.36 (dt, 2H,  $J_1 = 7.2$  Hz,  $J_2 = 7.2$  Hz), 2.32 (t, 2H,  $J = 7.2$  Hz), 1.62-1.59 (m, 6H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.42, 159.43, 135.48, 133.62, 131.03, 131.00, 129.53, 129.48, 125.45, 124.03, 124.02, 114.07, 72.84, 70.29, 69.07, 55.60, 55.59, 40.23, 31.26, 29.03, 26.37, 23.68, 13.12; IR (think film, KBr)  $\text{cm}^{-1}$ ; HRMS (DART)  $m/z$  calc'd for  $\text{C}_{30}\text{H}_{40}\text{O}_4 + \text{H}^+$  465.2927, found  $\text{C}_{30}\text{H}_{40}\text{O}_4 + \text{NH}_4^+$  482.3268



**Synthesis of (3*E*,6*E*,9*Z*)-*O*-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-5-pentylundeca-3,6,9-trien-1-ol (13):** To a stirred solution of alkyne **1** (642 mg, 1.81 mmol) in 23 mL of  $\text{PhMe}$  was added  $\text{Ti}(\text{O}i\text{-Pr})_4$  (582 mg, 2.05 mmol) via gas-tight syringe. The solution was cooled to  $-78^\circ\text{C}$  and treated dropwise with  $c\text{-C}_5\text{H}_9\text{MgCl}$  (2.00 M in  $\text{Et}_2\text{O}$ , 4.1 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^\circ\text{C}$

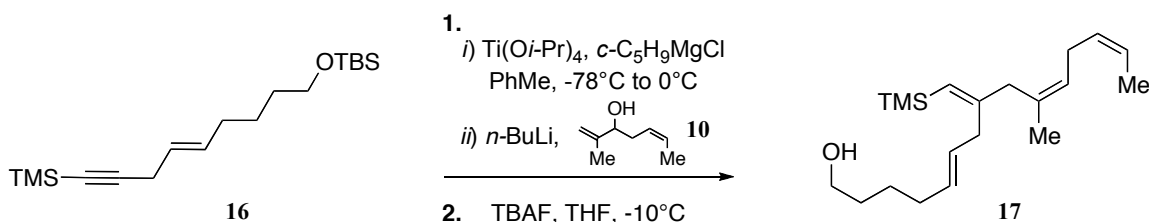
over 30 min, stirred at  $-35^{\circ}\text{C}$  for 1 h, and cooled to  $-78^{\circ}\text{C}$ . A solution of lithium alkoxide was prepared by adding *n*-BuLi (2.39 M in hexanes, 0.664 mmol) to alcohol **12** (110 mg, 0.604 mmol) in THF (2 mL) at  $-78^{\circ}\text{C}$  then warming to  $0^{\circ}\text{C}$  over 20 min. This solution was added in a dropwise manner to the black solution of Ti–alkyne complex via cannula. The mixture was then warmed to  $0^{\circ}\text{C}$  over 5 h and stirred for 1 h. The reaction was then poured into 50 mL of stirring, saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^{\circ}\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 20 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$  and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 5% then 10%  $\text{EtOAc}$  in hexanes to afford a mixture of reduced alkyne and coupled product. This mixture was separated via HPLC to afford 171 mg of **11** as a clear oil (53%). The stereochemistry of the central olefin was assigned *E* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for: (3*E*,6*E*,9*Z*)-*O*-4-Methoxybenzyl-4-(2-(4-methoxybenzyloxy)ethyl)-5-pentylundeca-3,6,9-trien-1-ol (13):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (dd, 4H,  $J_1 = 9.0$  Hz,  $J_2 = 4.0$  Hz), 6.87 (dd, 4H,  $J_1 = 9.0$  Hz,  $J_2 = 4.0$  Hz), 5.53-5.43 (m, 1H), 5.42-5.30 (m, 1H), 5.28-5.20 (m, 2H), 4.42 (s, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.47-3.45 (m, 4H), 2.72 (dd, 2H,  $J_1 = 6.5$  Hz,  $J_2 = 6.5$  Hz), 2.52 (dt, 1H,  $J_1 = 7.2$  Hz,  $J_2 = 7.2$  Hz), 2.40-2.27 (m, 4H), 1.60 (d, 3H,  $J = 6.8$  Hz), 1.46-1.12 (m, 8H), 0.87 (t, 3H,  $J = 7$  Hz);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.44, 140.50, 134.13, 131.05, 131.01, 129.52, 128.86, 128.40, 124.72, 122.83, 114.08, 72.81, 72.80, 70.34, 69.54, 55.60, 50.53, 33.61, 32.23, 30.58, 30.40, 29.07, 27.53, 22.96, 14.45, 13.06; IR (thin film, KBr) 3013, 2929, 2856, 1612, 1512, 1459, 1359, 1301, 1247, 1172, 1095, 1037, 820  $\text{cm}^{-1}$ ; HRMS (DART)  $m/z$  calc'd for  $\text{C}_{34}\text{H}_{48}\text{O}_4 + \text{H}^+$  521.3625, found  $\text{C}_{34}\text{H}_{48}\text{O}_4 + \text{NH}_4^+$  538.3891



**Synthesis of (5Z,8E,10Z,13E)-10-methyl-8-((trimethylsilyl)methylene)pentadeca-5,10,13-trien-1-ol (15):** To a stirred solution of eneyne **14** (482 mg, 1.49 mmol) in 15 mL of PhMe was added  $\text{Ti}(\text{O}i\text{-Pr})_4$  (466 mg, 1.64 mmol) via gas-tight syringe. The solution was cooled to  $-78^\circ\text{C}$  and treated dropwise with  $c\text{-C}_5\text{H}_9\text{MgCl}$  (2.00 M in  $\text{Et}_2\text{O}$ , 3.28 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^\circ\text{C}$  over 30 min, stirred at  $-35^\circ\text{C}$  for 1 h, and cooled to  $-78^\circ\text{C}$ . A solution of lithium alkoxide was prepared by adding  $n\text{-BuLi}$  (2.59 M in hexanes, 0.661 mmol) to alcohol **8** (76 mg, 0.601 mmol) in THF (1.5 mL) at  $-78^\circ\text{C}$  then warming to  $0^\circ\text{C}$  over 20 min. This solution was added in a dropwise manner to the brown solution of Ti-alkyne complex via cannula. The mixture was then warmed to  $0^\circ\text{C}$  over 5 h and stirred for 1 h. The reaction was then poured into 30 mL of stirring, saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^\circ\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 10 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$  and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 100% hexanes then 2%  $\text{Et}_2\text{O}$  in hexanes gave a mixture of coupled product and reduced eneyne. The concentrated mixture of products was dissolved in THF (4 ml), cooled to  $-10^\circ\text{C}$  and treated dropwise with TBAF (1.5 ml, 1M in THF). The reaction was complete by TLC within 1 h. It was diluted with saturated aqueous  $\text{NH}_4\text{Cl}$  dropwise (2 ml). The organic layer was separated and the aqueous layer extracted with  $\text{Et}_2\text{O}$  (3X). The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 5% to 15%  $\text{EtOAc}$  in hexanes gave a clear mixture of product **15** (back-calculated yield of 60%) and deprotected/reduced eneyne. The mixture was further purified to obtain **15** as a colorless oil. The stereochemistry of the olefin at the 10 position was assigned *Z* by analogy with our

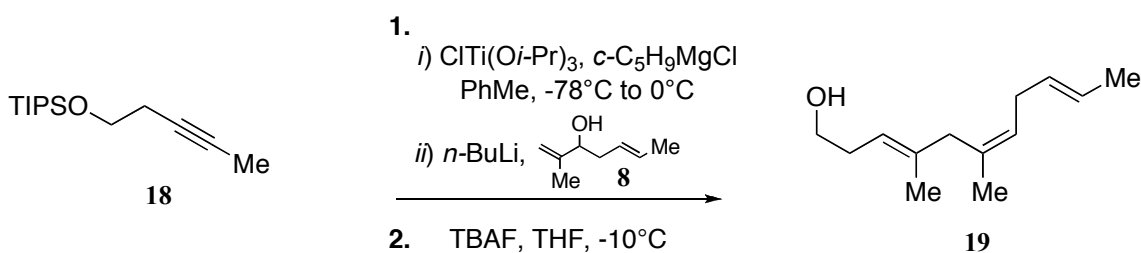


previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for (5Z,8E,10Z,13E)-10-methyl-8-((trimethylsilyl)methylene)pentadeca-5,10,13-trien-1-ol (15):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.48-5.21 (m, 6H), 3.66 (dt, 2H, *J*<sub>1</sub> = 6.4 Hz, *J*<sub>2</sub> = 6.3 Hz), 2.84 (d, 2H, *J* = 6.8 Hz), 2.74 (s, 2H), 2.61 (dd, 2H, *J*<sub>1</sub> = 4.8 Hz, *J*<sub>2</sub> = 4.8 Hz), 2.11 (dt, 2H, *J*<sub>1</sub> = 6.4 Hz, *J*<sub>2</sub> = 6.4 Hz), 1.65-1.56 (m, 8H), 1.49-1.42 (m, 2H), 1.21 (t, 1H, *J* = 7.2 Hz), 0.10 (s, 9H), 0.07 (s, silicon grease); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.08, 133.73, 131.09, 130.35, 128.81, 125.71, 125.24, 124.62, 63.27, 41.5, 34.63, 32.83, 31.72, 27.61, 26.08, 24.06, 18.25, 1.37; IR (thin film, KBr) 3435, 2094, 1645, 1247, 913, 743 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc'd for C<sub>20</sub>H<sub>36</sub>OSi+H<sup>+</sup> 321.2614 found 321.2619



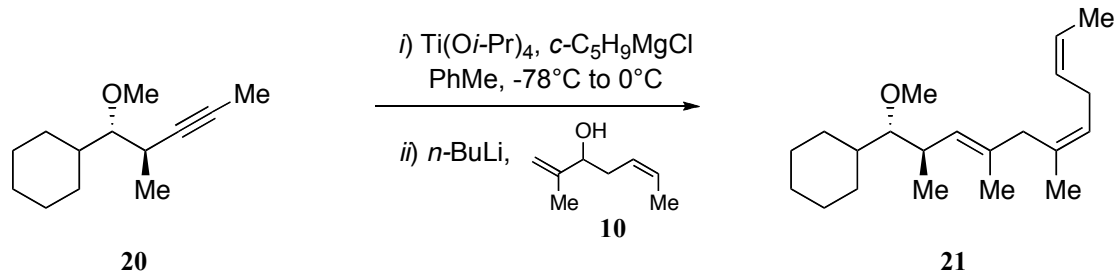
**Synthesis of (5E,8E,10Z,13Z)-10-methyl-8-((trimethylsilyl)methylene)pentadeca-5,10,13-trien-1-ol (17):** To a stirred solution of enyne **16** (482 mg, 1.49 mmol) in 15 mL of PhMe was added Ti(O*i*-Pr)<sub>4</sub> (466 mg, 1.64 mmol) via gas-tight syringe. The solution was cooled to -78°C and treated dropwise with *c*-C<sub>5</sub>H<sub>9</sub>MgCl (2.00 M in Et<sub>2</sub>O, 3.28 mmol) via gas-tight syringe. The resulting solution was warmed to -35°C over 30 min, stirred at -35°C for 1 h, and cooled to -78°C. A solution of lithium alkoxide was prepared by adding *n*-BuLi (2.59 M in hexanes, 0.661 mmol) to alcohol **10** (76 mg, 0.601 mmol) in THF (1.5 mL) at -78 °C then warming to 0°C over 20 min. This solution was added in a dropwise manner to the brown solution of Ti-alkyne complex via cannula. The mixture was then warmed to 0°C over 5 h and stirred for 1 h. The reaction was then poured into 30 mL of stirring, saturated aqueous NH<sub>4</sub>Cl at 0°C. The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 10 ml of Et<sub>2</sub>O to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with EtOAc and the filtered aqueous layer was extracted 3X with Et<sub>2</sub>O. Combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with

100% hexanes then 2% Et<sub>2</sub>O in hexanes gave a mixture of coupled product and reduced eneyne. The concentrated mixture of products was dissolved in 4 ml of THF, cooled to -10°C and treated dropwise with 1.5 ml of TBAF (1M in THF). The reaction was complete by TLC within 1 h. It was quenched by adding saturated aqueous NH<sub>4</sub>Cl dropwise (2 ml). The organic layer was separated and the aqueous layer extracted with Et<sub>2</sub>O 3X. The organic extracts were combined, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 5% to 15% EtOAc in hexanes gave a clear mixture of product **17** (back-calculated yield of 51%) and deprotected/reduced eneyne. **17** was separated via HPLC. The stereochemistry of the olefin at the 10 position was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for (5*E*,8*E*,10*Z*,13*Z*)-10-methyl-8-((trimethylsilyl)methylene)pentadeca-5,10,13-trien-1-ol (**17**):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.50-5.32 (m, 4H), 5.27-5.23 (m, 2H), 3.64 (dt, 2H, *J*<sub>1</sub> = 6.8 Hz, *J*<sub>2</sub> = 6.6 Hz), 2.80-2.75 (m, 4H), 2.69 (dd, 2H, *J*<sub>1</sub> = 4.8 Hz, *J*<sub>2</sub> = 4.8 Hz), 2.04 (dt, 2H, *J*<sub>1</sub> = 5.6 Hz, *J*<sub>2</sub> = 5.6 Hz), 1.65-1.57 (m, 8H), 1.48-1.39 (m, 2H), 1.19 (t, 1H, *J* = 7.2 Hz), 0.09 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 154.64, 133.71, 132.09, 129.64, 128.83, 125.64, 125.29, 124.03, 63.25, 41.68, 39.20, 32.69, 26.51, 25.98, 23.92, 13.15, 0.70; IR (thin film, KBr) 3338, 2933, 1612, 1438, 1247, 1070, 837 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc'd for C<sub>20</sub>H<sub>36</sub>OSi+H<sup>+</sup> 321.2614 found 321.2617



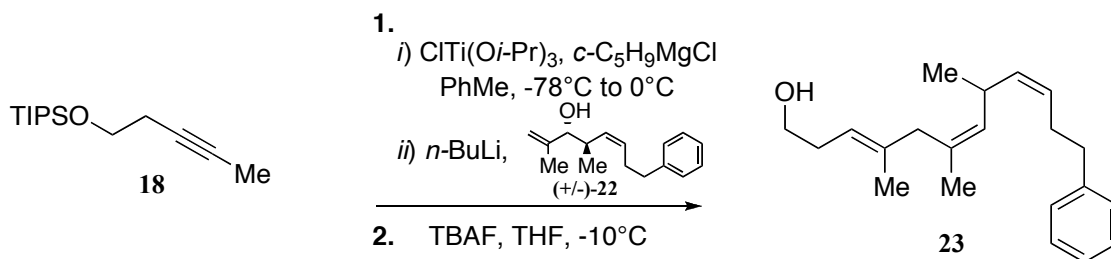
**Synthesis of (3*E*,6*Z*,9*E*)-4,6-dimethylundeca-3,6,9-trien-1-ol (**19**):** To a stirred solution of alkyne **18** (762 mg, 3.17 mmol) in 32 mL of PhMe was added ClTi(O*i*Pr)<sub>3</sub> (1M in hexanes, 4.76 mmol) via gas-tight syringe. The solution was cooled to -78°C and treated dropwise with *c*-C<sub>5</sub>H<sub>9</sub>MgCl (2.00 M in Et<sub>2</sub>O, 9.52 mmol) via gas-tight syringe. The

resulting solution was warmed to  $-35^{\circ}\text{C}$  over 30 min, stirred at  $-35^{\circ}\text{C}$  for 1 h, and cooled to  $-78^{\circ}\text{C}$ . A solution of lithium alkoxide was prepared by adding *n*-BuLi (2.38 M in hexanes, 0.920 mmol) to alcohol **10** (106 mg, 0.836 mmol) in THF (2.4 mL) at  $-78^{\circ}\text{C}$  then warming to  $0^{\circ}\text{C}$  over 20 min. This solution was added in a dropwise manner to the dark solution of Ti-alkyne complex via cannula. The mixture was warmed to  $-20^{\circ}\text{C}$  over the course of 8 h ( $7.25^{\circ}\text{C}$  per h) then stirred overnight at  $-20^{\circ}\text{C}$ . The solution was then warmed to  $0^{\circ}\text{C}$ , stirred for 1 h, then poured into 60 ml of stirring saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^{\circ}\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 10 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with EtOAc and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude oil was chromatographed over silica gel with 100% hexanes then 3%  $\text{Et}_2\text{O}$  in hexanes to give a mixture of the coupled product and reduced alkyne. This mixture was dissolved in 3.2 ml of THF, cooled to  $-10^{\circ}\text{C}$ , and treated dropwise with TBAF (1M in THF, 1.37 ml) that had been previously stirred with  $\text{Na}_2\text{SO}_4$  and molecular sieves for 30 minutes. The reaction was stirred at  $-10^{\circ}\text{C}$  until complete by TLC (2 h), quenched dropwise with saturated aqueous  $\text{NH}_4\text{Cl}$ , extracted 3X with  $\text{Et}_2\text{O}$ , dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude oil was chromatographed over silica gel with 7.5% to 20% EtOAc in hexanes to afford 88 mg of the desired regioisomer as a clear oil (54% yield of the desired regioisomer, 9:1 regioselectivity). The stereochemistry of the central olefin was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for (3*E*,6*Z*,9*E*)-4,6-dimethylundeca-3,6,9-trien-1-ol (19):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.47-5.37 (m, 2H), 5.27 (t, 1H,  $J = 8$  Hz), 5.16 (tq, 1H,  $J_1 = 8.0$  Hz,  $J_2 = 1.2$  Hz), 3.63 (dt, 2H,  $J_1 = 6.8$  Hz,  $J_2 = 6.8$  Hz), 2.74 (s, 2H), 2.70 (dd, 2H,  $J_1 = 4.0$  Hz,  $J_2 = 4.0$  Hz), 2.30 (dt, 2H,  $J_1 = 7.6$  Hz,  $J_2 = 7.5$  Hz), 1.65 (d, 3H,  $J = 4.8$  Hz), 1.62 (dt, 3H,  $J_1 = 1.6$  Hz,  $J_2 = 1.6$  Hz), 1.58 (s, 3H), 1.31 (t, 1H,  $J = 5.6$  Hz);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  136.89, 133.63, 130.24, 125.35, 125.26, 121.25, 62.87, 42.17, 31.96, 31.61, 23.63, 18.24, 16.41; IR (thin film, KBr) 3350, 2918, 1440, 1375, 1046, 964  $\text{cm}^{-1}$



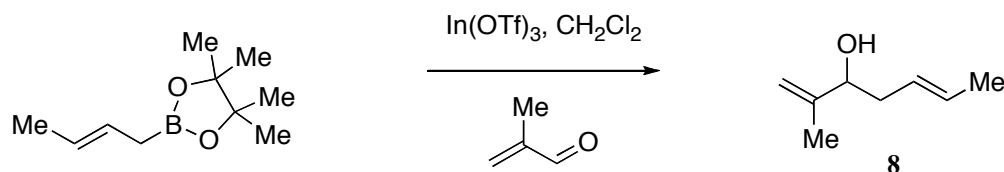
**Synthesis of ((1*S*\*,2*R*\*,3*E*,6*Z*,9*Z*)-1-methoxy-2,4,6-trimethylundeca-3,6,9-trienyl)cyclohexane (21):** To a stirred solution of racemic alkyne **20** (536 mg, 2.77 mmol) in 28 mL of PhMe was added  $\text{Ti(Oi-Pr)}_4$  (1.18 g, 4.16 mmol) via gas-tight syringe. The solution was cooled to  $-78^\circ\text{C}$  and treated dropwise with  $c\text{-C}_5\text{H}_9\text{MgCl}$  (2.01 M in  $\text{Et}_2\text{O}$ , 8.32 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^\circ\text{C}$  over 30 min, stirred at  $-35^\circ\text{C}$  for 1 h, and cooled to  $-78^\circ\text{C}$ . A solution of lithium alkoxide was prepared by adding  $n\text{-BuLi}$  (2.38 M in hexanes, 1.02 mmol) to alcohol **10** (117 mg, 0.927 mmol) in THF (2.6 mL) at  $-78^\circ\text{C}$  then warming to  $0^\circ\text{C}$  over 20 min. This solution was added in a dropwise manner to the black solution of Ti-alkyne complex via cannula. The mixture was then warmed to  $-20^\circ\text{C}$  over 5 h, then stirred at  $-20^\circ\text{C}$  for 10 h, then at  $0^\circ\text{C}$  for 1 h. The reaction was then poured into 50 mL of stirring saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^\circ\text{C}$ . The mixture was stirred rapidly until becoming white. The organic layer was separated. Titanium dioxide was removed by adding 10 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$  and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude oil was chromatographed over silica gel with 100% hexanes then 3%  $\text{Et}_2\text{O}$  in hexanes to give a clear mixture containing the product **21** (65%, back-calculated by  $^1\text{H NMR}$ ) and trace amounts of reduced alkyne and alkyne homodimer. **21** was further purified via HPLC to give a clear oil. The stereochemistry of the central olefin was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for ((1*S*\*,2*R*\*,3*E*,6*Z*,9*Z*)-1-methoxy-2,4,6-trimethylundeca-3,6,9-trienyl)cyclohexane (21):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.48-5.33 (m, 2H), 5.24-5.19 (m, 2H), 3.44 (s, 3H), 2.82-2.76 (m, 2H), 2.71-2.58 (m, 3H), 1.95

(d, 1H,  $J = 12.4$  Hz), 1.90-0.95 (m, 23H) contained within this multiplet: [1.63 (d, 3H,  $J = 6.8$  Hz), 1.59 (dt, 3H,  $J_1 = 1.2$  Hz,  $J_2 = 1.2$  Hz), 1.52 (d, 3H,  $J = 1.2$  Hz), 0.99 (d, 3H,  $J = 6.8$  Hz)];  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  134.12, 132.45, 129.74, 128.44, 124.83, 123.91, 91.31, 61.97, 42.45, 41.99, 35.36, 30.27, 29.42, 26.99, 26.75, 26.64, 26.31, 23.39, 18.79, 15.90, 13.14; IR (thin film, KBr) 2924, 2852, 1448, 1373, 1156, 1099  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{21}\text{H}_{36}\text{O}+\text{H}^+$  305.2844, found 305.2841



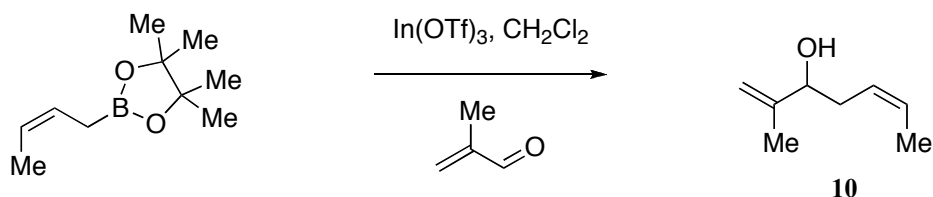
**Synthesis of (3*E*,6*Z*,9*Z*)-4,6,8-trimethyl-12-phenyldodeca-3,6,9-trien-1-ol (23):** To a stirred solution of alkyne **18** (183 mg, 0.760 mmol) in 6.6 mL of PhMe was added  $\text{ClTi}(\text{O}i\text{Pr})_3$  (1M in hexanes, 1.14 mmol) via gas-tight syringe. The solution was cooled to  $-78^\circ\text{C}$  and treated dropwise with  $c\text{-C}_5\text{H}_9\text{MgCl}$  (2.01 M in  $\text{Et}_2\text{O}$ , 2.28 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^\circ\text{C}$  over 20 min, stirred at  $-35^\circ\text{C}$  for 45 min, and cooled to  $-78^\circ\text{C}$ . A solution of lithium alkoxide was prepared by adding  $n\text{-BuLi}$  (2.38 M in hexanes, 0.272 mmol) to alcohol **22** (57 mg, 0.247 mmol) in THF (2.4 mL) at  $-78^\circ\text{C}$  then warming to  $0^\circ\text{C}$  over 15 min. This solution was added in a dropwise manner to the dark solution of Ti-alkyne complex via cannula. The mixture was warmed to  $-10^\circ\text{C}$  over 8 h, then poured into 10 ml of stirring, saturated aqueous  $\text{NH}_4\text{Cl}$  at  $0^\circ\text{C}$ . The mixture was stirred rapidly until the solution became white. The mixture was diluted with 5 ml of  $\text{Et}_2\text{O}$  and the organic layer separated. 5 ml of  $\text{Et}_2\text{O}$  was added to the aqueous layer and the mixture was filtered through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude oil was chromatographed over silica gel with 100% hexanes to give a mixture of the coupled product and reduced alkyne. This mixture was dissolved in 1 ml of THF, cooled to  $-10^\circ\text{C}$ , and treated dropwise with TBAF (1M in THF, 0.650 mmol) that had been previously stirred with  $\text{Na}_2\text{SO}_4$  and molecular sieves for

30 minutes. The reaction was stirred at  $-10^{\circ}\text{C}$  until complete by TLC (1 h), quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$ , extracted 3X with  $\text{Et}_2\text{O}$ , dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude oil was chromatographed over silica gel with 5% to 20%  $\text{EtOAc}$  in hexanes then subjected to high vacuum for 1 h to afford 42 mg of the desired regioisomer **23** (58%) as a clear oil. The stereochemistry of the central olefin was assigned *Z* by analogy with our previously described couplings of allylic alcohols and alkynes.<sup>1</sup> **Data for (3*E*,6*Z*,9*Z*)-4,6,8-trimethyl-12-phenyldodeca-3,6,9-trien-1-ol (23):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.32-5.23 (m, 2H), 5.18-5.10 (m, 2H), 3.61 (dt, 2H,  $J_1 = 6.4$  Hz,  $J_2 = 6.4$  Hz), 3.40-3.29 (m, 1H), 2.80-2.60 (m, 4H), 2.41-2.34 (m, 2H), 2.29 (dt, 2H,  $J_1 = 6.6$  Hz,  $J_2 = 6.4$  Hz), 1.58 (s, 3H), 1.57 (s, 3H), 1.32 (t, 1H,  $J = 5.6$  Hz), 0.91 (d, 3H,  $J = 6.4$  Hz);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  142.36, 136.70, 135.78, 132.04, 131.31, 128.75, 128.62, 126.61, 126.15, 121.35, 62.84, 42.48, 36.45, 31.95, 31.46, 29.87, 23.58, 22.47, 16.46; IR (thin film, KBr) 3338, 3026, 3001, 2963, 2924, 2866, 1495, 1453, 1375, 1046, 735, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{21}\text{H}_{30}\text{O}+\text{H}^+$  299.2375, found 299.2373



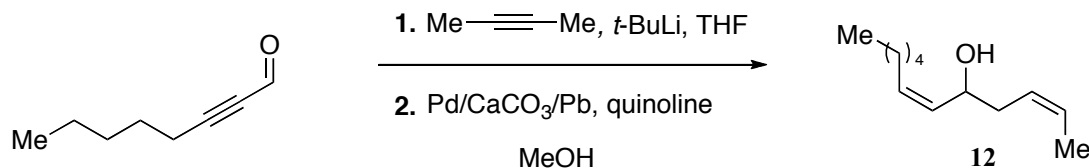
**Synthesis of (E)-2-methylhepta-1,5-dien-3-ol (8):** In a drybox, to a 500 ml round bottom flask with a reflux condenser and stirbar was added  $\text{In}(\text{OTf})_3$  (2.62 g, 4.66 mmol). The condenser was capped with a septum, removed from the dry box, and charged with 204 ml of  $\text{CH}_2\text{Cl}_2$ . The dioxaboralane (7.44 g, 40.87 mmol) was added to the flask via syringe and the mixture cooled to  $-78^{\circ}\text{C}$ . Freshly distilled methacrolein (3.44 g, 49.04 mmol) was then added dropwise and the reaction warmed to room temperature over 4 h. The reaction was heated to reflux, stirred for one h, then cooled back to room temperature. The reaction was then quenched with 200 ml of saturated aqueous  $\text{NH}_4\text{Cl}$  and the aqueous layer extracted 3X with  $\text{Et}_2\text{O}$ . The combined organic phases were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude oil was

chromatographed over silica gel with 2% to 15% Et<sub>2</sub>O in pentanes to give 1.03 g (34%, 11:1 *E/Z*) of **8** as a yellow oil.<sup>2</sup> **Data for (*E*)-2-methylhepta-1,5-dien-3-ol (**8**):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.64-5.63 (m, 1H), 5.44-5.36 (m, 1H), 4.97-4.96 (m, 1H), 4.86-4.84 (m, 1H), 4.05 (dt, 1H, *J*<sub>1</sub> = 3.6 Hz, *J*<sub>2</sub> = 3.6 Hz), 2.37-2.27 (m, 1H), 2.24-2.17 (m, 1H), 1.74-1.73 (m, 3H), 1.69 (d, 3H, *J* = 5.6 Hz), 1.56 (br, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 147.11, 128.51, 127.07, 110.93, 74.96, 38.80, 18.12, 18.05; IR (thin film, KBr) 3376, 2918, 1438, 1008, 964, 897, 733 cm<sup>-1</sup>; HRMS (EI) *m/z* calc'd for C<sub>8</sub>H<sub>14</sub>O 126.10447, found C<sub>8</sub>H<sub>14</sub>O<sup>+</sup> 126.10393



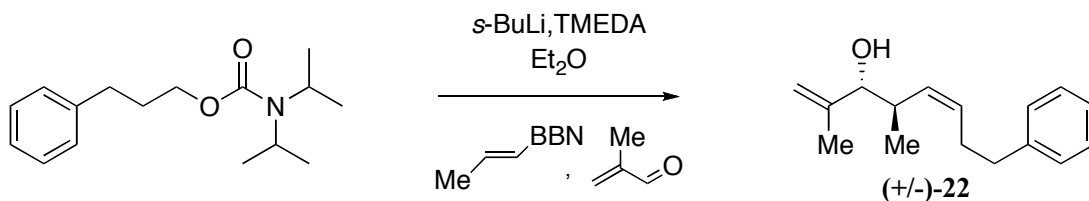
**Synthesis of (*Z*)-2-methylhepta-1,5-dien-3-ol (**10**):** In a drybox, to a 1000 ml round bottom flask with a reflux condenser and stirbar was added In(OTf)<sub>3</sub> (3.99 g, 7.1 mmol). The condenser was capped with a septum, removed from the dry box, and charged with 312 ml of CH<sub>2</sub>Cl<sub>2</sub>. The dioxaboralane (11.38 g, 62.55 mmol) was added to the flask via syringe and the mixture cooled to -78°C. Freshly distilled methacrolein (5.26 g, 75.06 mmol) was then added dropwise and the reaction warmed to room temperature over 4 h. The reaction was heated to reflux, stirred for one h, then cooled back to room temperature. The reaction was then quenched with 300 ml of saturated aqueous NH<sub>4</sub>Cl and the aqueous layer extracted 3X with Et<sub>2</sub>O. The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude oil was chromatographed over silica gel with 2% to 15% Et<sub>2</sub>O in pentanes to give 2.68 g (34%, 14:1 *Z/E*) of **10** as a yellow oil.<sup>2</sup> **Data for (*Z*)-2-methylhepta-1,5-dien-3-ol (**10**):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.68-5.61 (m, 1H), 5.43-5.36 (m, 1H), 4.98-4.97 (m, 1H), 4.86 (dq, 1H, *J*<sub>1</sub> = 2.0 Hz, *J*<sub>2</sub> = 2.0 Hz), 4.13-4.07 (m, 1H), 2.34 (dd, 2H, *J*<sub>1</sub> = 6.4 Hz, *J*<sub>2</sub> = 6.4 Hz), 1.76 (ddd, 3H, *J*<sub>1</sub> = 0.4 Hz, *J*<sub>2</sub> = 0.3 Hz, *J*<sub>3</sub> = 0.3 Hz), 1.65 (d, 3H, *J* = 6.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 147.21, 126.90, 126.12, 111.18, 75.30, 32.99, 18.00, 13.16; IR (thin film, KBr) 3360, 2918, 1651, 1442, 1371, 1024, 896, 690 cm<sup>-1</sup>; HRMS (EI) *m/z* calc'd

for C<sub>8</sub>H<sub>14</sub>O 126.10447, found C<sub>8</sub>H<sub>14</sub>O<sup>+</sup> 126.10376

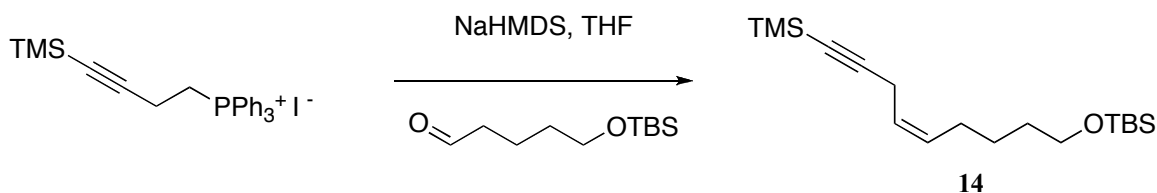


**Synthesis of (2Z,6Z)-dodeca-2,6-dien-5-ol (12):** 1.3 g (24.16 mmol) of 2-butyne was added to 60 ml of THF at  $-78^{\circ}\text{C}$ . *t*-BuLi was then added dropwise and the mixture warmed to  $0^{\circ}\text{C}$  over 1 h and stirred for an additional 1 h. The solution was then cooled to  $-78^{\circ}\text{C}$  and the aldehyde added via syringe. The reaction was stirred at  $-78^{\circ}\text{C}$  for 2.5 h then quenched by gradually adding 120 ml of 1M HCl at  $0^{\circ}\text{C}$ . The aqueous layer was separated, extracted 3X with Et<sub>2</sub>O, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 5% then 15% EtOAc in hexanes gave the desired alkyne (35%) and undesired allene (35%). 512 mg of the alkyne (2.87 mmol) was then dissolved in 5 ml of anhydrous MeOH. In a separate flask, quinoline (370mg, 2.87 mmol) and Pd/CaCO<sub>3</sub>/Pb (1.5 g) were added to 6 ml of anhydrous MeOH. H<sub>2</sub> was bubbled through the Pd/CaCO<sub>3</sub>/Pb solution for 30 min after which the solution of alkyne was added and the reaction stirred for 5 hrs under H<sub>2</sub>. The reaction was then filtered through a plug of Celite which was washed with CH<sub>2</sub>Cl<sub>2</sub>. Concentration *in vacuo* and column chromatography over silica gel with 10% to 15% EtOAc in hexanes gave 429 mg (82%) of **12** as a clear, brown oil. **Data for (2Z,6Z)-dodeca-2,6-dien-5-ol (12):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.67-5.60 (m, 1H), 5.53-5.46 (m, 1H), 5.46-5.38 (m, 2H), 4.51-5.44 (m, 1H), 2.41-2.34 (m, 1H), 2.25-2.18 (m, 1H), 2.14-2.03 (m, 2H), 1.65 (d, 3H, *J* = 6.8 Hz), 1.50 (d, 1H, *J* = 3.2 Hz), 1.23-1.42 (m, 6H), 0.89 (t, 3H, *J* = 7.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  132.87, 132.20, 127.49, 125.89, 67.73, 35.47, 31.81, 29.69, 28.05, 22.85, 14.35, 13.39; IR (thin film, KBr) 3342, 2957, 2926, 2872, 2858, 1457, 1030, 748, 704 cm<sup>-1</sup>; LRMS (EI) *m/z* calc'd for C<sub>12</sub>H<sub>22</sub>O<sup>+</sup> 182.1671, found C<sub>12</sub>H<sub>22</sub>O<sup>+</sup> 182.2 and [C<sub>12</sub>H<sub>22</sub>O - H<sub>2</sub>O]<sup>+</sup> 164.2



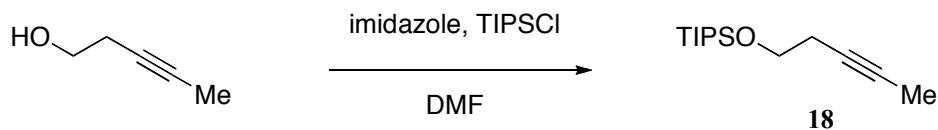


**Synthesis of (3*R*\*,4*R*\*,*Z*)-2,4-dimethyl-8-phenylocta-1,5-dien-3-ol (22):** 416 mg (3.58 mmol) of TMEDA was added to a flame dried round-bottom flask with 10 ml of Et<sub>2</sub>O. The solution was cooled to  $-78^\circ\text{C}$  and *s*-BuLi was added via syringe. After stirring for 5 minutes a 1M solution of the carbamate (674 mg, 2.56 mmol) was added dropwise via cannula. The light orange solution was stirred at  $-78^\circ\text{C}$  for 5 h after which a 1M solution of the borane (849 mg, 5.24 mmol) in Et<sub>2</sub>O was added dropwise via cannula and the solution turned clear. This was stirred for 40 min after which neat methacrolein was added via gas-tight syringe. The solution was warmed to room temperature over 1 h. The solution was cooled to  $0^\circ\text{C}$  then 15 ml of a 2:1 mixture of 2M NaOH/30% H<sub>2</sub>O<sub>2</sub> was added slowly. The solution was neutralized by the dropwise addition of 6M HCl, the organic layer separated, and the aqueous layer extracted 3X with Et<sub>2</sub>O. The combined organic extracts were dried with MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 2.5% to 5% EtOAc in hexanes afforded 295 mg (50%) of **23** as a clear liquid.<sup>3</sup> **Data for (3*R*\*,4*R*\*,*Z*)-2,4-dimethyl-8-phenylocta-1,5-dien-3-ol (22):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28-7.24 (m, 2H), 7.18-7.14 (m, 3H), 5.58-5.51 (m, 1H), 5.31-5.26 (m, 1H), 4.98-4.97 (m, 1H), 4.94-4.92 (m, 1H), 3.65 (dd, 1H,  $J_1 = 8.0$  Hz,  $J_2 = 2.4$  Hz), 2.68-2.56 (m, 3H), 2.45-2.36 (m, 2H), 1.77 (dd, 3H,  $J_1 = 1.6$  Hz,  $J_2 = 0.8$  Hz), 1.40 (d, 1H,  $J = 2.8$  Hz), 0.876 (d, 3H,  $J = 6.8$  Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  145.37, 141.96, 132.95, 131.71, 128.75, 128.58, 126.19, 113.91, 80.50, 36.21, 36.15, 29.87, 17.58, 17.07; IR (thin film, KBr) 3466, 2962, 2926, 1651, 1603, 1495, 1453, 1372, 1074, 1028, 899, 738, 698 cm<sup>-1</sup>; HRMS (EI) *m/z* calc'd for C<sub>16</sub>H<sub>22</sub>O 230.16707, found C<sub>16</sub>H<sub>22</sub>O<sup>+</sup> 230.16805



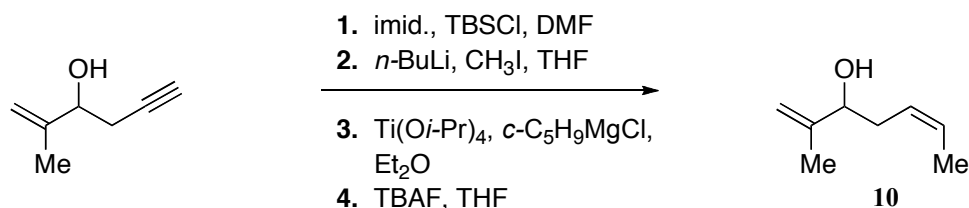
**Synthesis of (*Z*)-*tert*-butyldimethyl(9-(trimethylsilyl)non-5-en-8-ynoxy)silane (**14**):**

The phosphonium salt (16.7 g, 32.4 mmol) in THF (147 ml) was cooled to  $-10^{\circ}\text{C}$  and NaHMDS (35.6 mmol, 1M in THF) added dropwise over 5 minutes. The solution turned red and was stirred an additional 10 minutes, then cooled to  $-78^{\circ}\text{C}$ . The aldehyde (6.34 g, 29.5 mmol) was added dropwise via syringe and the reaction stirred for 2 h. The reaction was warmed to  $-20^{\circ}\text{C}$  and quenched by the addition of aqueous saturated  $\text{NH}_4\text{Cl}$  (150 ml). The organic phase was separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  (3X). The combined organic phases were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 2% to 5%  $\text{Et}_2\text{O}$  in hexanes afforded a yellow oil from which excess triphenylphosphine (from the preparation of the phosphonium salt) was removed by dissolving in 25 ml of  $\text{Et}_2\text{O}$ , cooling to  $0^{\circ}\text{C}$ , and adding 30% aqueous  $\text{H}_2\text{O}_2$  dropwise until the disappearance of the triphenylphosphine was observed by TLC. The solution was diluted with hexanes (50 ml) and concentrated *in vacuo* to a volume of 10 ml, this was then passed over a silica plug which was flushed with hexanes. Concentration gave **14** (3.53 g, 37%) as an off-white, transparent oil. **Data for (*Z*)-*tert*-butyldimethyl(9-(trimethylsilyl)non-5-en-8-ynoxy)silane (**14**)**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  with TMS)  $\delta$  5.50-5.39 (m, 2H), 3.61 (t, 2H,  $J = 6.4$  Hz), 2.98 (d, 2H,  $J = 5.2$  Hz), 2.05 (dt, 2H,  $J_1 = 7.2$  Hz,  $J_2 = 7.2$  Hz), 1.56-1.49 (m, 2H), 1.45-1.38 (m, 2H), 0.89 (s, 9H), 0.15 (s, 9H), 0.04 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  132.54, 124.38, 105.70, 84.35, 63.52, 32.75, 27.28, 26.32, 25.94, 18.70, 0.45,  $-4.94$ ; IR (thin film, KBr) 2956, 2930, 2897, 2858, 2177, 1472, 1463, 1250, 1101, 839, 775,  $760\text{ cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc'd for  $\text{C}_{18}\text{H}_{36}\text{OSi}_2+\text{H}^+$  325.2383, found 325.2384



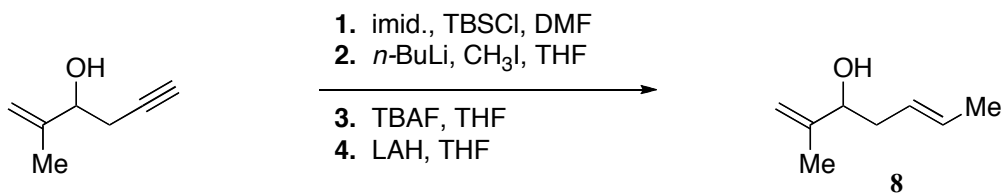
**Synthesis of triisopropyl(pent-3-yn-1-yloxy)silane (18):** To a stirred solution of imidazole (1.58 g, 23.2 mmol) in DMF (90 ml) was added pent-3-yn-1-ol (1.5 g, 17.9 mmol). TIPSCl was added and the reaction stirred 24 h. The reaction was diluted with water (450 ml) followed by 50 ml of Et<sub>2</sub>O. The Et<sub>2</sub>O layer was separated and the aqueous layer extracted with Et<sub>2</sub>O (3X). Combined organic extracts were dried with MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with hexanes afforded **18** as a clear oil (3.43 g, 80%). **Data for triisopropyl(pent-3-yn-1-yloxy)silane (18):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.77 (t, 2H, *J* = 7.2 Hz), 2.37 (tq, 2H, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 2.4 Hz), 1.77 (t, 3H, *J* = 2.4 Hz), 1.04-1.12 (m, 21H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 76.90, 76.34, 62.96, 23.54, 18.23, 12.35, 3.64; IR (thin film, KBr) 2943, 2867, 1463, 1109, 882, 681, 658 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc'd for C<sub>14</sub>H<sub>28</sub>ONaSi<sup>+</sup> 263.1807, found 263.1813

### Alternative pathways for the stereoselective synthesis of 8 and 10



**Synthesis of (Z)-2-methylhepta-1,5-dien-3-ol (10):** 2-methylhex-1-en-5-yn-3-ol (14.97 g, 136 mmol) was dissolved in DMF (300 ml). Imidazole (12.37 g, 181.7 mmol) and TBSCl (27.4 g, 182 mmol) were added. The reaction was stirred 15 h then diluted with 1.5 L of water. The solution was extracted with MTBE (3X). The combined extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with hexanes afforded a clear oil (64%) of which

9.84 g (43.9 mmol) were dissolved in THF (100 ml). The solution was cooled to  $-78^{\circ}\text{C}$  and *n*-BuLi (48.3 mmol, 2.53 M in hexanes) was added. The solution was stirred at  $-78^{\circ}\text{C}$  for 30 min, warmed to  $0^{\circ}\text{C}$  over 5 min, stirred 30 min, and re-cooled to  $-78^{\circ}\text{C}$ . MeI (12.5 g, 87.8 mmol) was added and the reaction stirred overnight. The reaction was quenched by the addition of aqueous saturated  $\text{NH}_4\text{Cl}$  (100 ml) and the organic phase separated. The aqueous phase was extracted 3X with MTBE. The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* (under a fume hood), to give 9.8 g (94%) of the methylated product as a clear oil. This was dissolved in  $\text{Et}_2\text{O}$  (275 ml) and 23.4 g (82.3 mmol)  $\text{Ti}(\text{O}i\text{-Pr})_4$  was added via gas-tight syringe. The solution was cooled to  $-78^{\circ}\text{C}$  and treated dropwise with *c*- $\text{C}_5\text{H}_9\text{MgCl}$  (2.00 M in  $\text{Et}_2\text{O}$ , 11.2 mmol) via gas-tight syringe. The resulting solution was warmed to  $-35^{\circ}\text{C}$  over 30 min, and stirred for 1 h. The black mixture was quenched with aqueous saturated  $\text{NH}_4\text{Cl}$  (100 ml) and the organic phase separated. The mixture was stirred rapidly until becoming colorless. The organic layer was separated. Titanium dioxide was removed by adding 50 ml of  $\text{Et}_2\text{O}$  to the aqueous layer and filtering the mixture through a frit with a thin layer of silica. The frit was rinsed with  $\text{EtOAc}$  and the filtered aqueous layer was extracted 3X with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude oil was dissolved in THF (90 ml) and treated with TBAF (75 mmol, 1M in THF). The reaction was stirred overnight, and quenched by the addition of a mixture of  $\text{CaCO}_3$  (5.00 g) suspended in 150 ml of water. The organic phase was separated. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3X). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography over silica gel with 5% to 20%  $\text{Et}_2\text{O}$  in hexanes followed by distillation ( $80\text{-}84^{\circ}\text{C}$ , 40 mbar) gave 5.3 g of a mixture of **10** and a *tert*-Butyldimethylsilyl deprotection product suspected to be TBSOH. **Data for (Z)-2-methylhepta-1,5-dien-3-ol (10):**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.68-5.61 (m, 1H), 5.43-5.36 (m, 1H), 4.98-4.97 (m, 1H), 4.86 (dq, 1H,  $J_1 = 2.0$  Hz,  $J_2 = 2.0$  Hz), 4.13-4.07 (m, 1H), 2.34 (dd, 2H,  $J_1 = 6.4$  Hz,  $J_2 = 6.4$  Hz), 1.76 (ddd, 3H,  $J_1 = 0.4$  Hz,  $J_2 = 0.3$  Hz,  $J_3 = 0.3$  Hz), 1.65 (d, 3H,  $J = 6.8$  Hz); see 1<sup>st</sup> generation synthesis for other relevant data



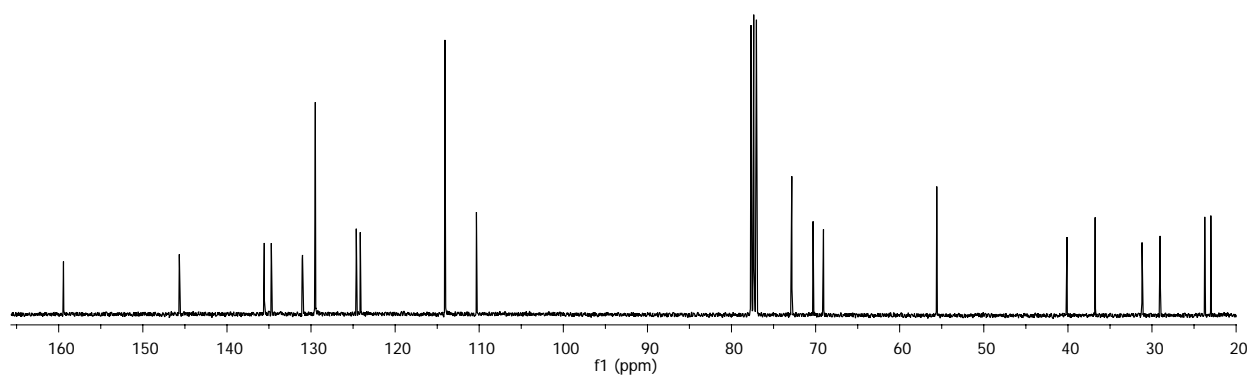
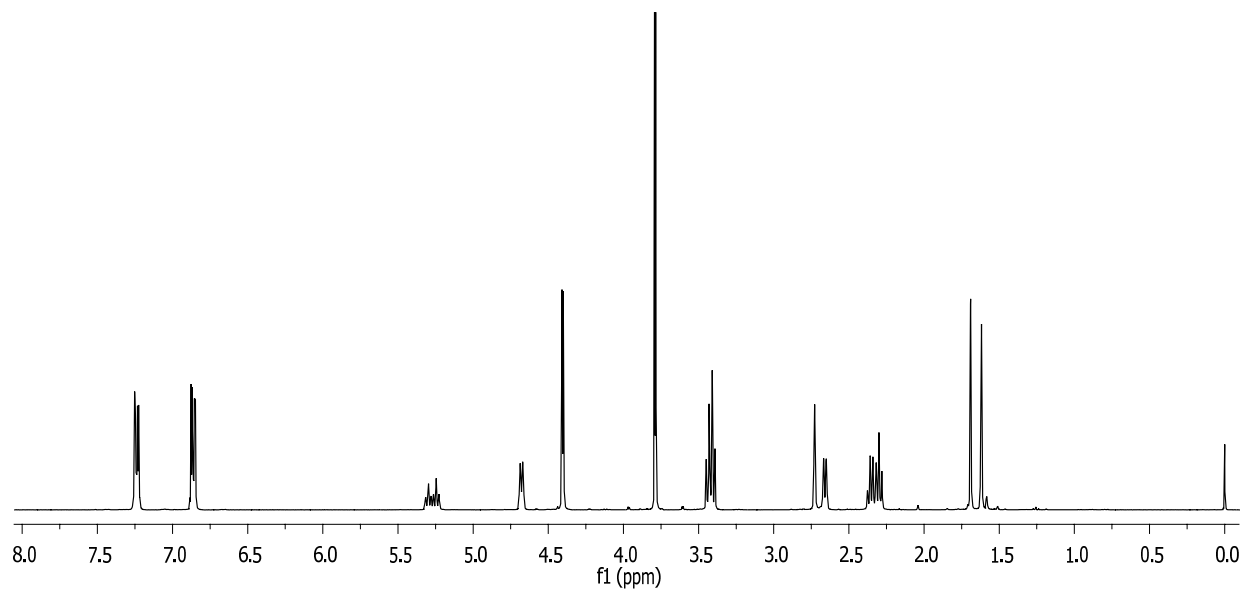
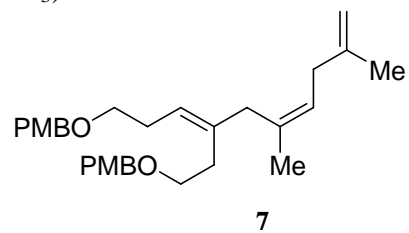
**Synthesis of (*E*)-2-methylhepta-1,5-dien-3-ol (**8**):** 2-methylhex-1-en-5-yn-3-ol (14.97 g, 136 mmol) was dissolved in DMF (300 ml). Imidazole (12.37 g, 181.7 mmol) and TBSCl (27.4 g, 182 mmol) were added. The reaction was stirred 15 h then diluted with 1.5 L of water. The solution was extracted MTBE (3X). These extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography over silica gel with hexanes afforded a clear oil (64%) of which 10.00 g (44.6 mmol) were dissolved in THF (100 ml). The solution was cooled to  $-78^{\circ}\text{C}$  and *n*-BuLi (53.5 mmol, 2.53 M in hexanes) was added. The solution was stirred at  $-78^{\circ}\text{C}$  for 30 min, warmed to  $0^{\circ}\text{C}$  over 5 min, stirred 30 min, and re-cooled to  $-78^{\circ}\text{C}$ . MeI was added (12.7 g, 89.2 mmol) and the reaction stirred overnight. The reaction was quenched by the addition of 100 ml of aqueous saturated NH<sub>4</sub>Cl and the organic phase separated. The aqueous phase was extracted MTBE (3X). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* (under a fume hood), to give 10.1 g (95%) of the methylated product as a clear oil. 4.06 g of this oil (17.1 mmol) was dissolved in THF (57 ml) and treated with TBAF (51.2 mmol, 1M in THF). The reaction was stirred overnight, and diluted with 50 ml of a mixture of CaCO<sub>3</sub> (2.00 g) suspended in water. The organic phase was separated. The aqueous phase was extracted with Et<sub>2</sub>O (3X). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered through a silica plug, and concentrated *in vacuo*. 1.5 g of this crude light brown oil was dissolved in THF (60 ml) in a round-bottom flask equipped with a reflux condenser. 2.78 g (73.2 mmol) of LAH was added to the solution. The reaction was heated to reflux and stirred for 48 h. The reaction was cooled to  $0^{\circ}\text{C}$  and 3 ml of water were added dropwise. 3 ml of saturated aqueous NaOH were added followed by 3 ml of water. The solution was then neutralized by the addition of saturated aqueous NaHCO<sub>3</sub>. The organic phase was separated and the aqueous layer extracted with Et<sub>2</sub>O (3X). Column chromatography over silica gel with 5% to 15% Et<sub>2</sub>O in pentanes followed by distillation ( $80\text{--}84^{\circ}\text{C}$ , 40 mbar) gave 1.3 g of a mixture of **8** and a *tert*-Butyldimethylsilyl deprotection product suspected

to be TBSOH. **Data for (*E*)-2-methylhepta-1,5-dien-3-ol (8):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.64-5.63 (m, 1H), 5.44-5.36 (m, 1H), 4.97-4.96 (m, 1H), 4.86-4.84 (m, 1H), 4.05 (dt, 1H,  $J_1 = 3.6$  Hz,  $J_2 = 3.6$  Hz), 2.37-2.27 (m, 1H), 2.24-2.17 (m, 1H), 1.74-1.73 (m, 3H), 1.69 (d, 3H,  $J = 5.6$  Hz), 1.56 (br, 1H); see 1<sup>st</sup> generation synthesis for other relevant data

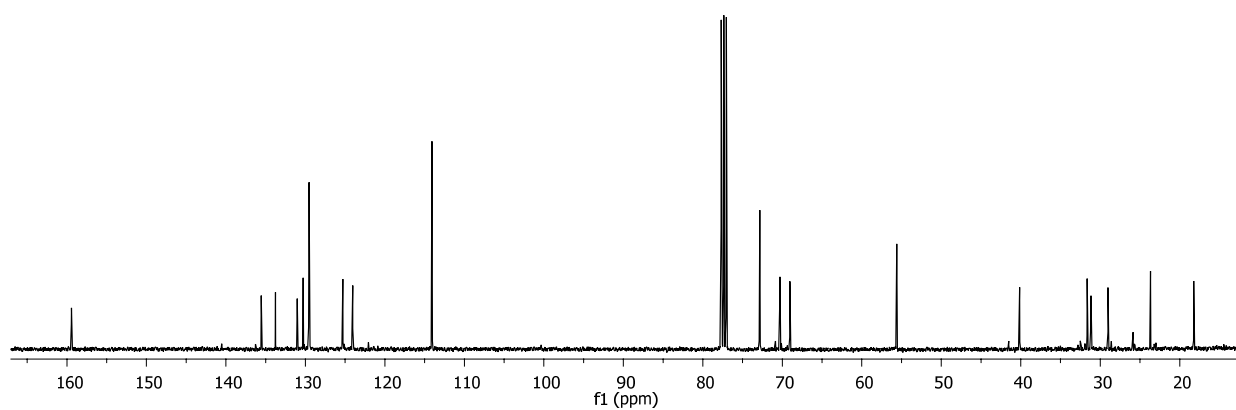
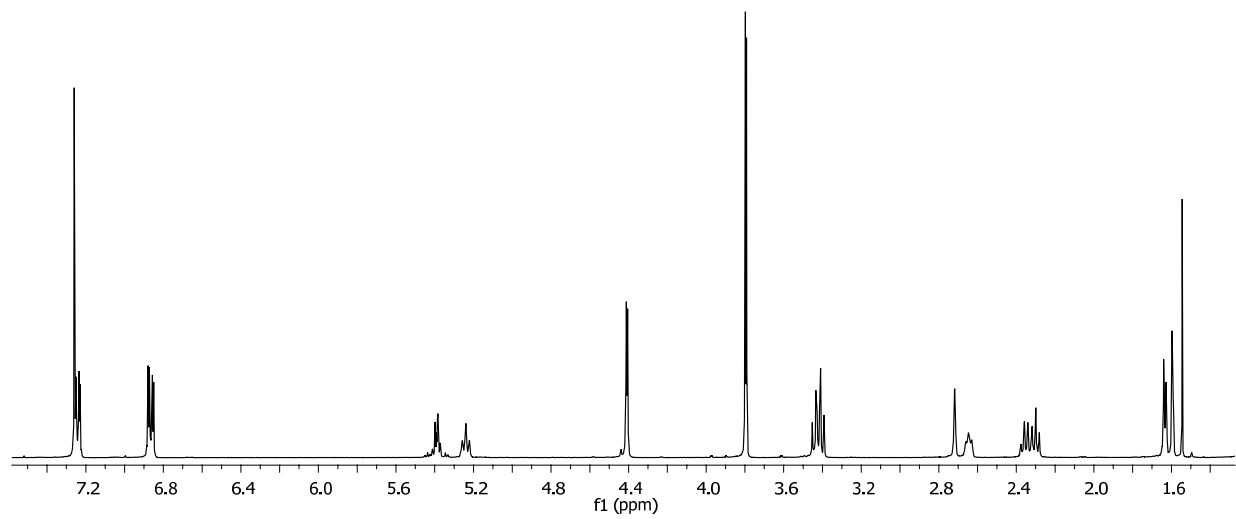
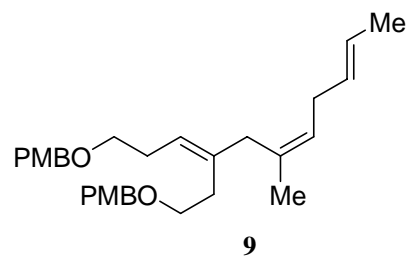
- (1) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112.
- (2) P. V. Ramachandran, D. P., D. Biswas *Chem. Commun.* **2005**, 1988.
- (3) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 5922.

## Spectral Data

Figure S1:  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$  with TMS) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **7**

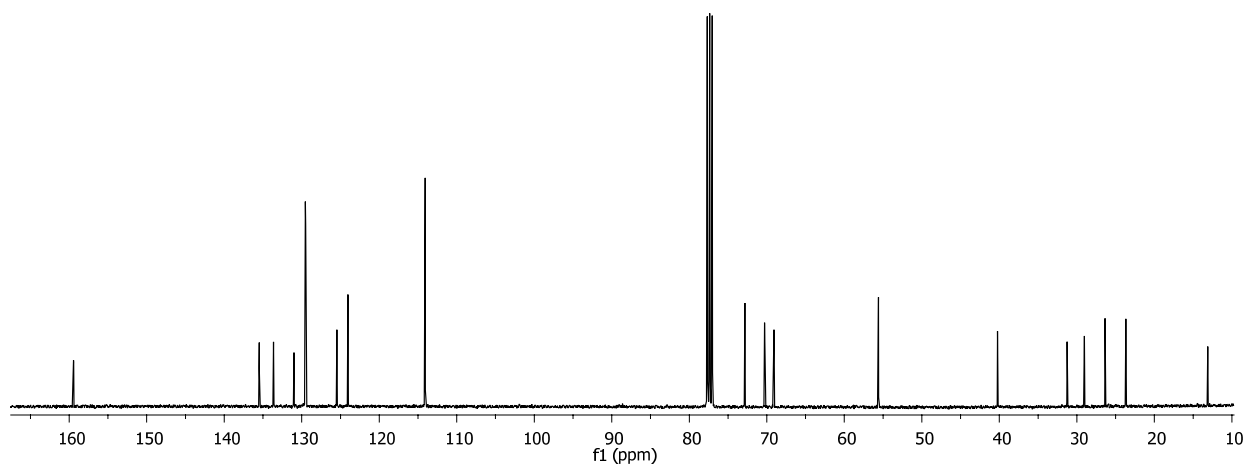
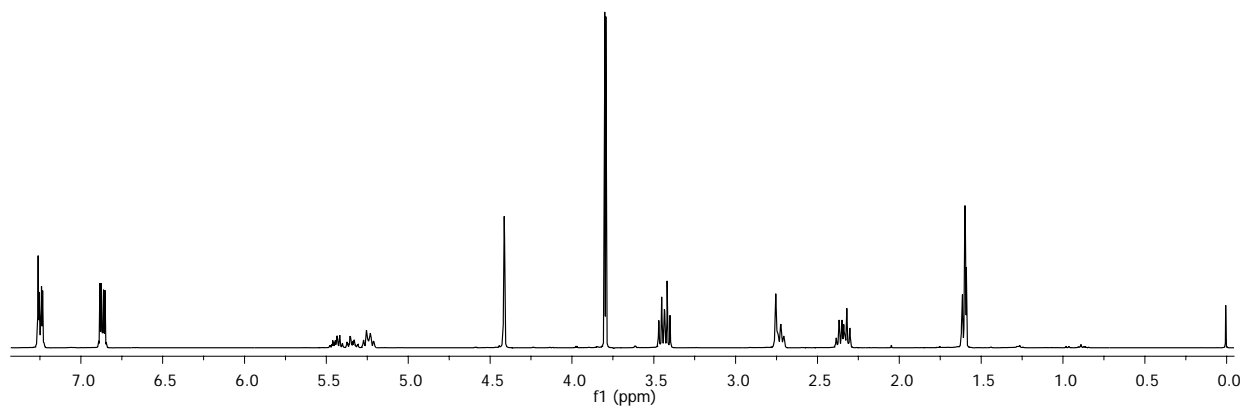
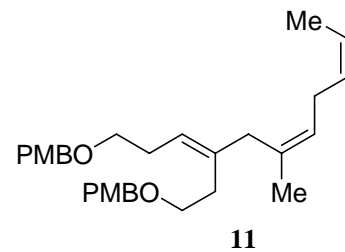


**Figure S2:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **9**

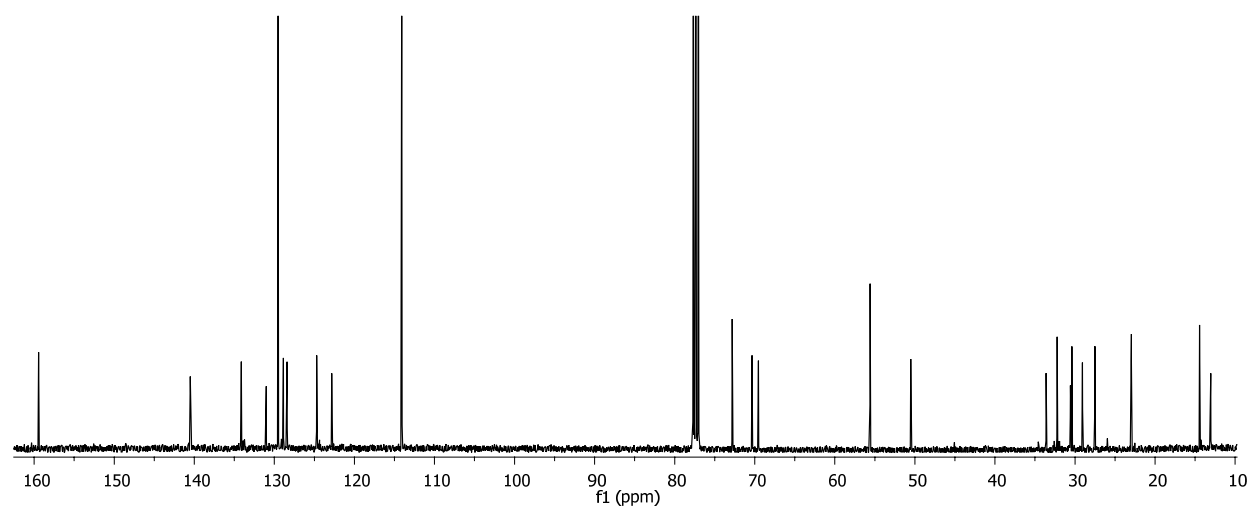
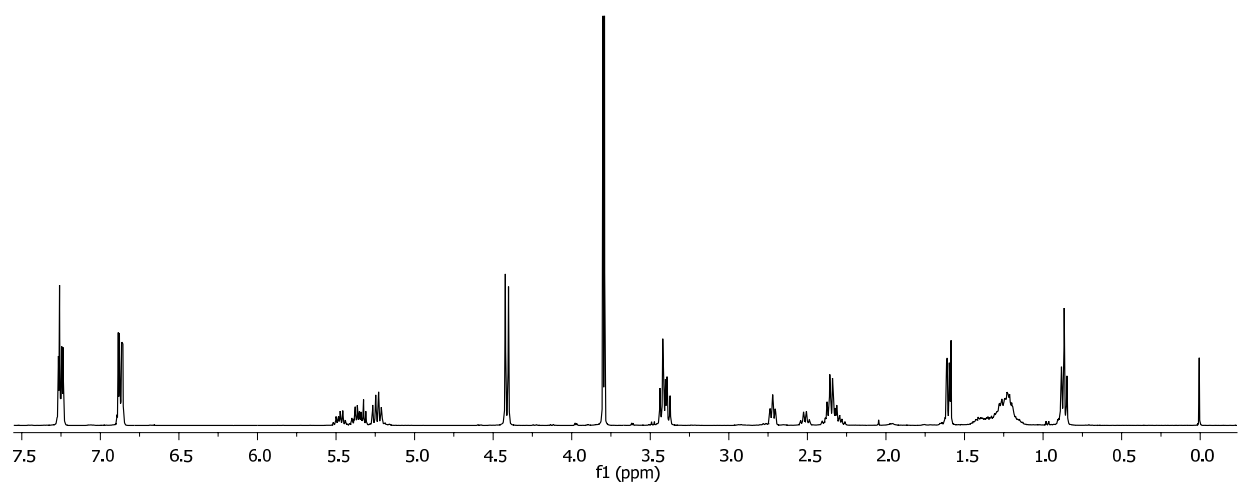
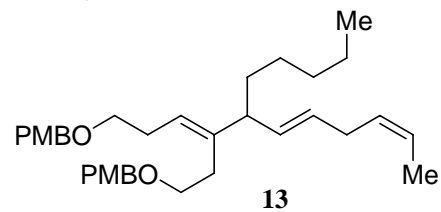




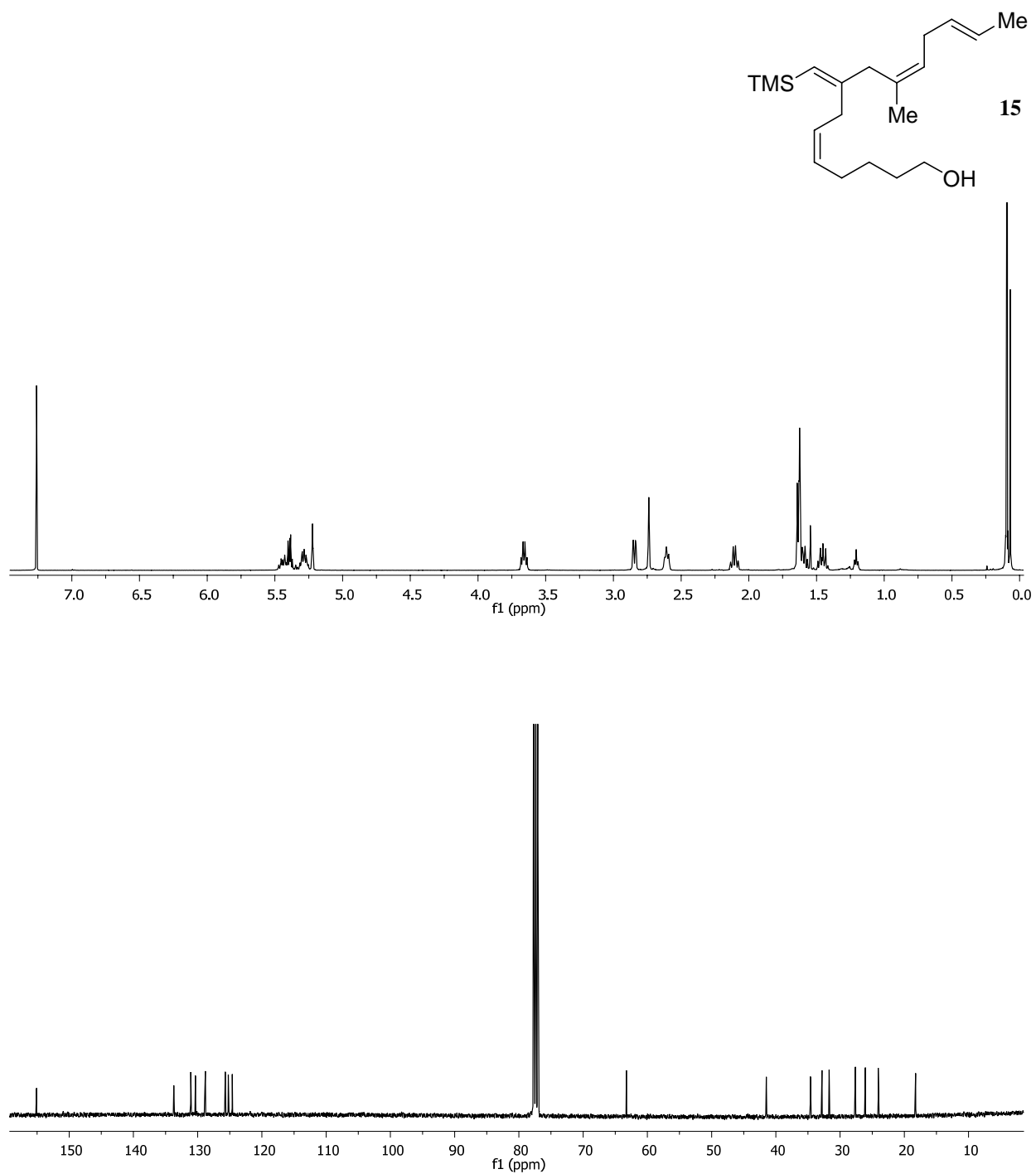
**Figure S3:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$  with TMS) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **11**



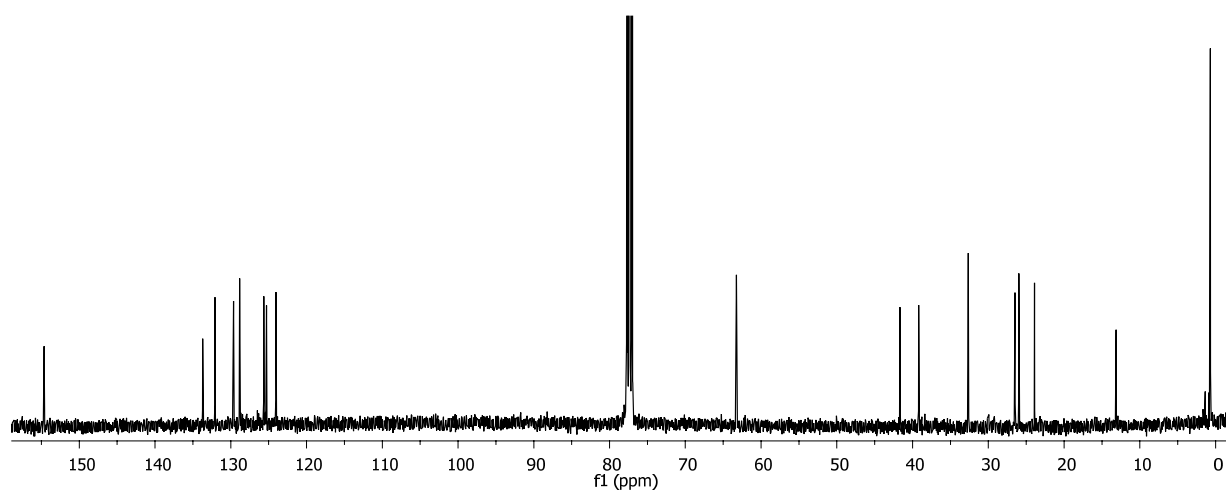
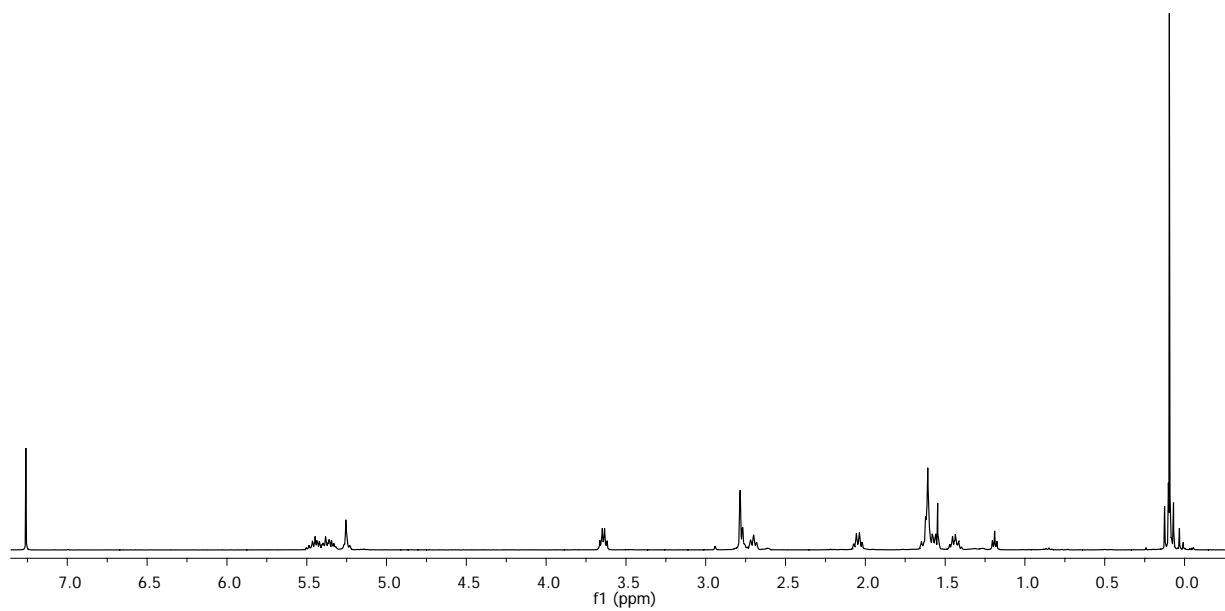
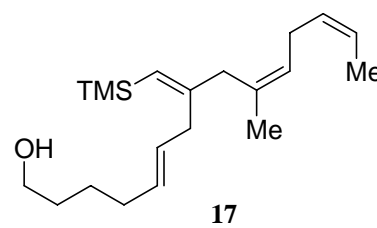
**Figure S4:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$  with TMS) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **13**



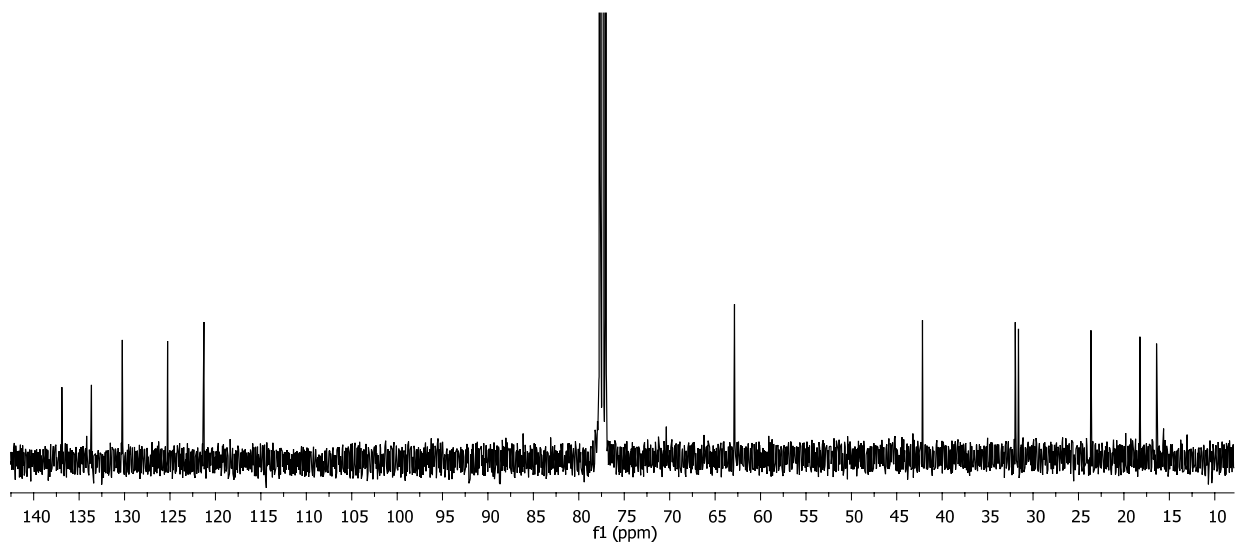
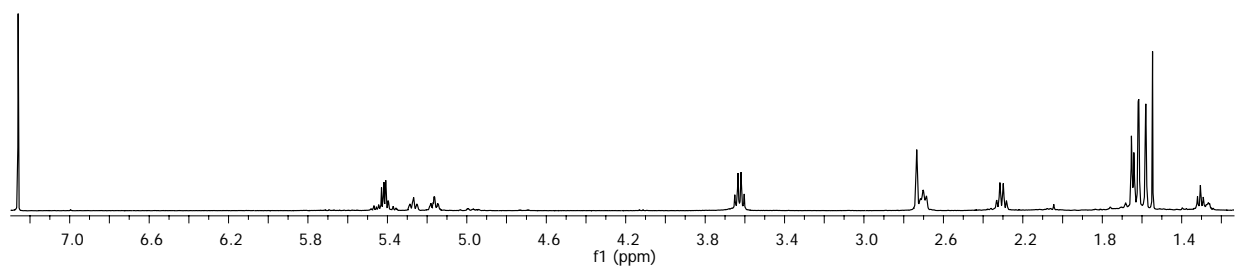
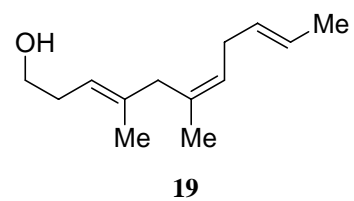
**Figure S5:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **15**  
(generated from a 11:1 *E:Z* mixture of **8**)



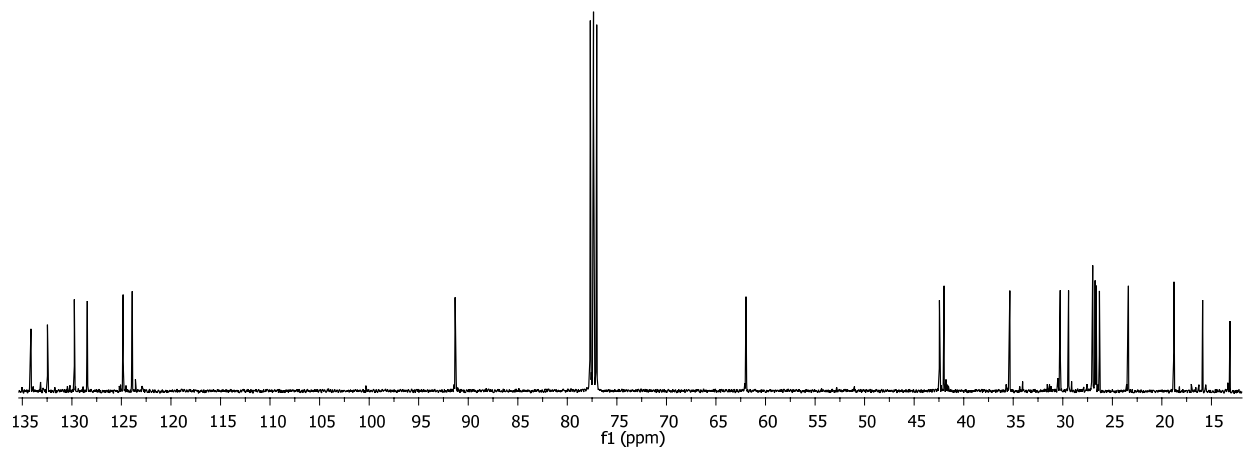
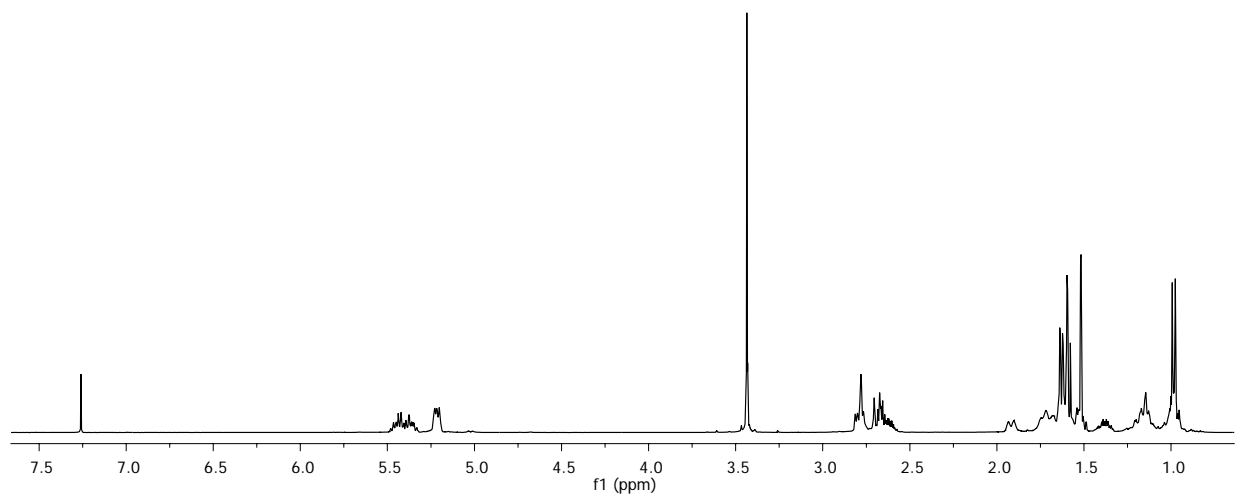
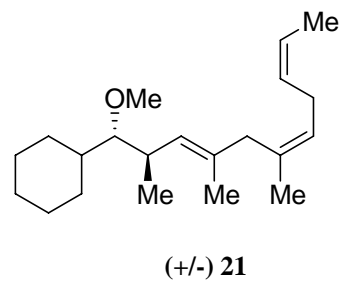
**Figure S6:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **17**  
(generated from a 14:1 *Z:E* mixture of **10**)



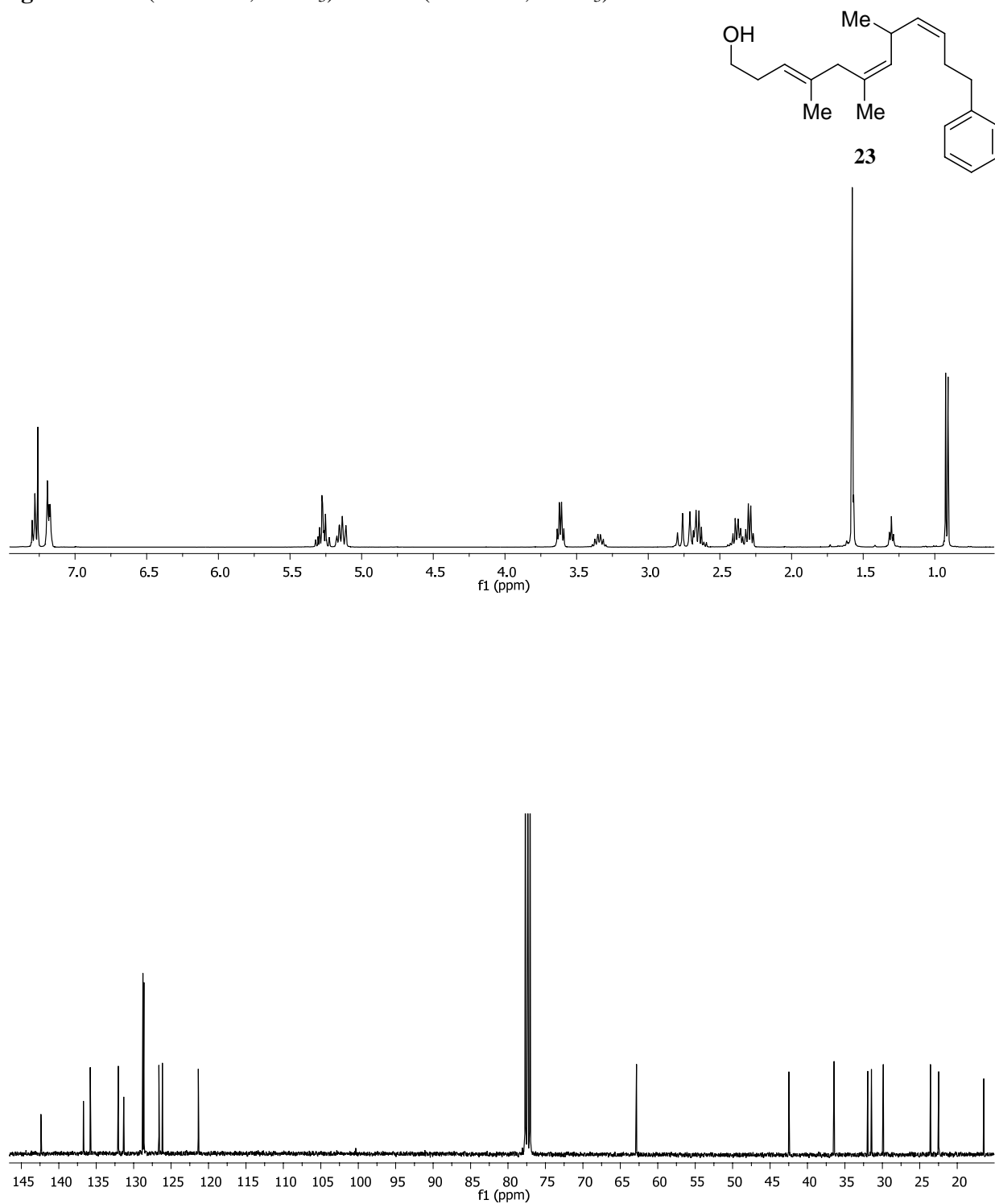
**Figure S7:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **19**  
(generated from a 11:1 *E:Z* mixture of **8**)



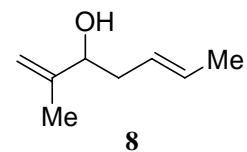
**Figure S8:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of (+/-) **21**  
(generated from a 14:1 *Z:E* mixture of **10**)



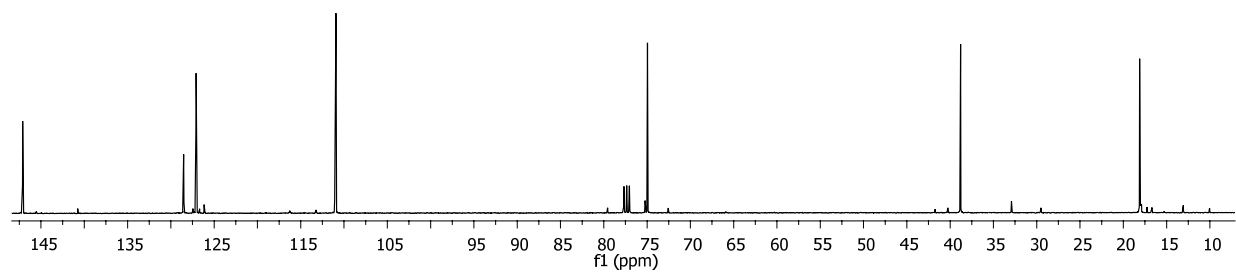
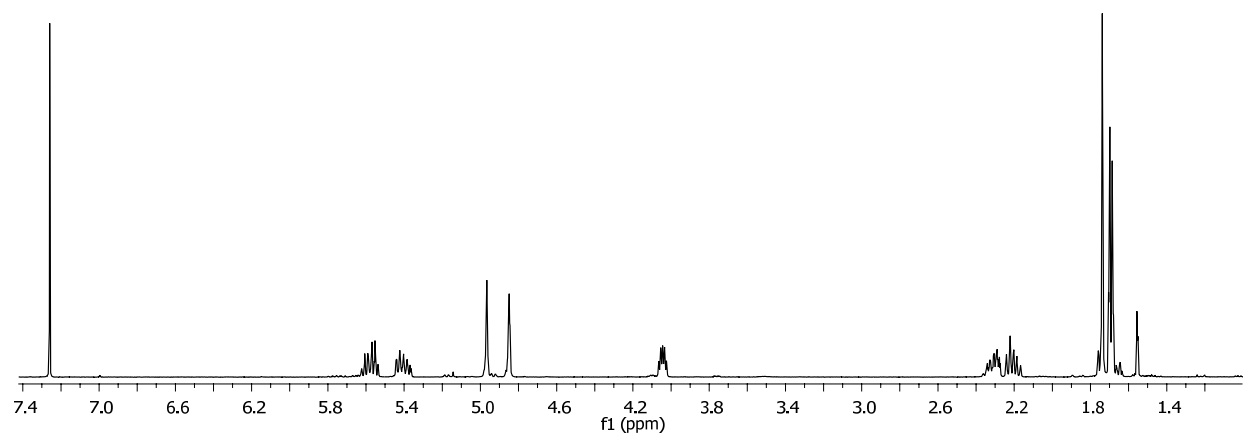
**Figure S9:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **23**



**Figure S10:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **8**

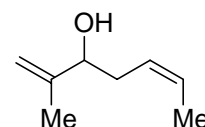


(1,2-disubstituted olefin 11:1 *E:Z*)

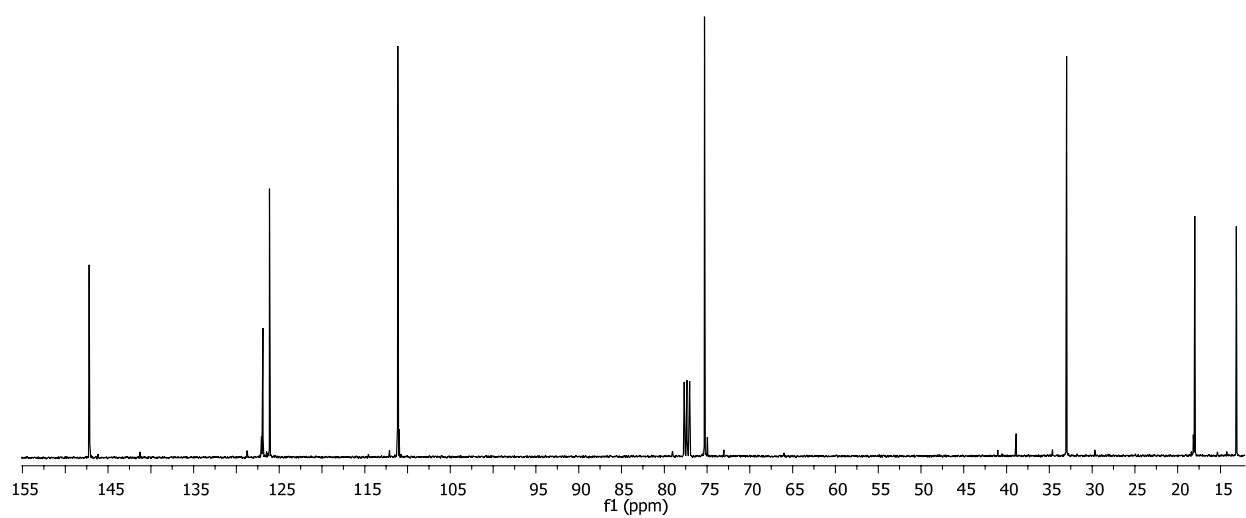
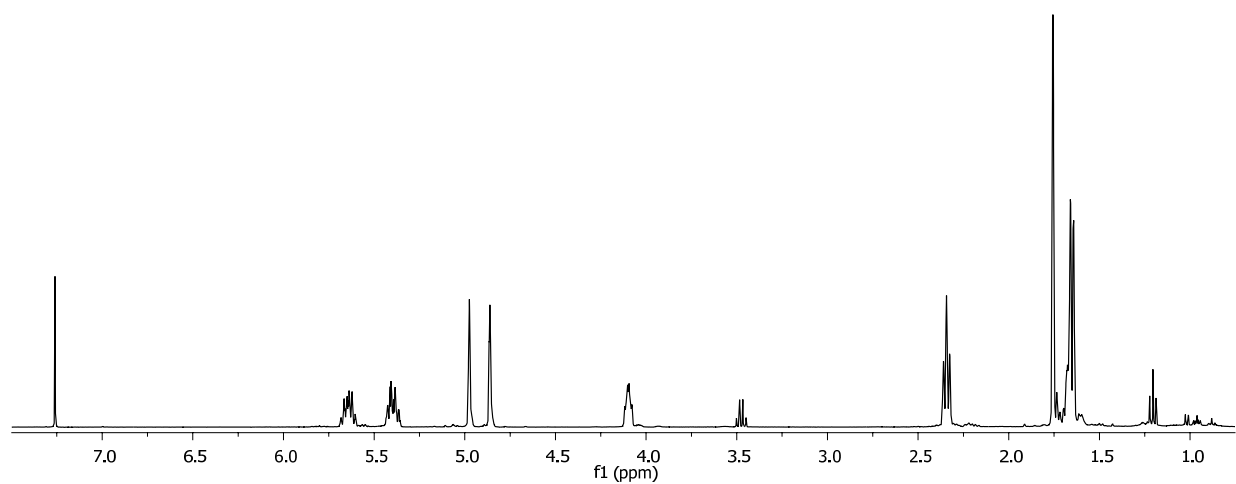




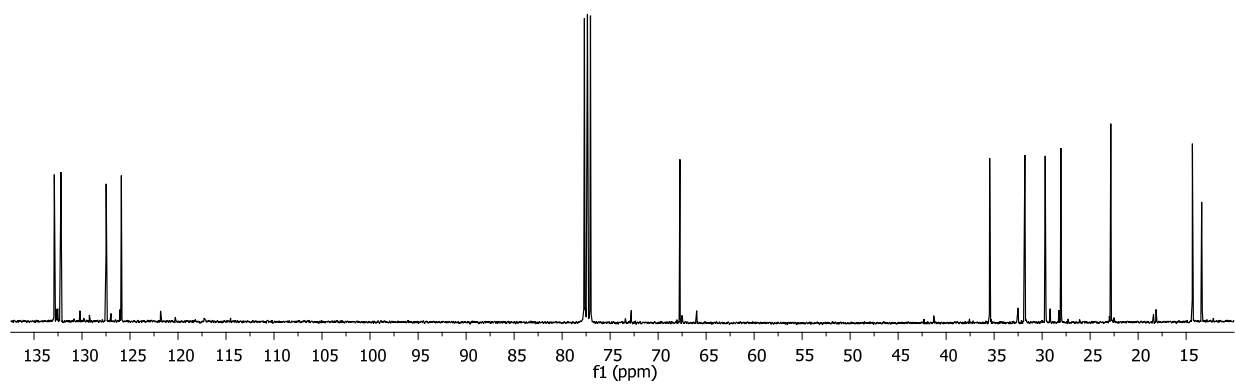
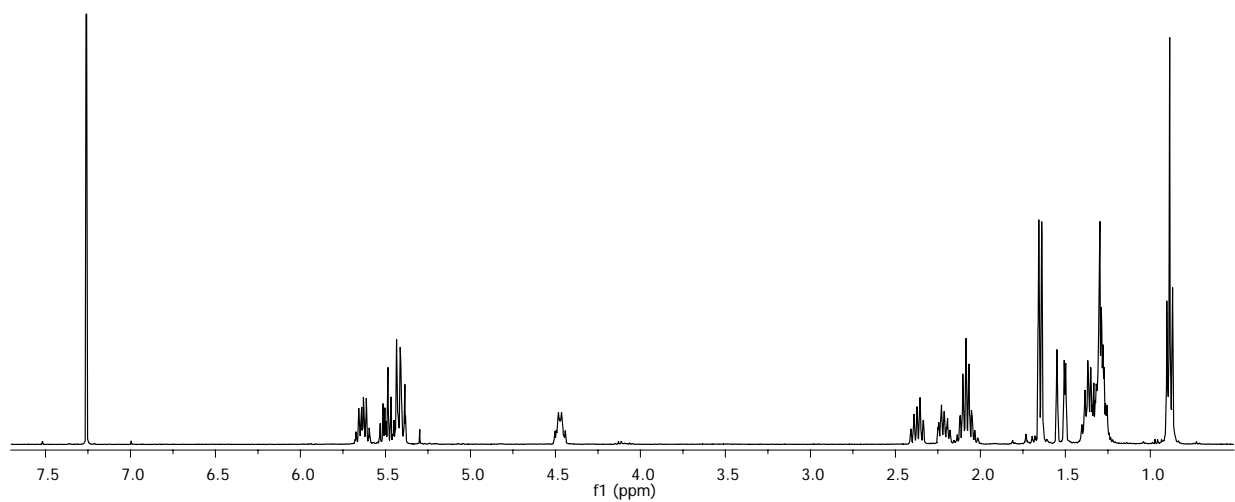
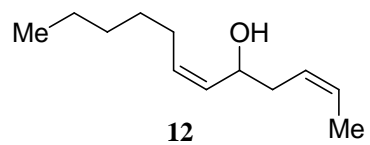
**Figure S11:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **10** (with trace amounts of  $\text{Et}_2\text{O}$  in  $^1\text{H}$  spectrum)



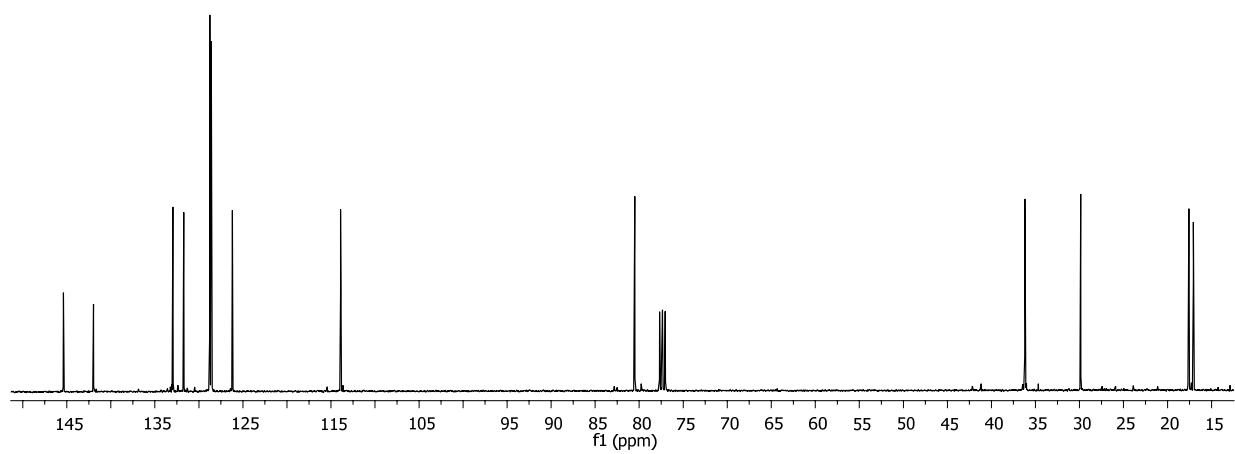
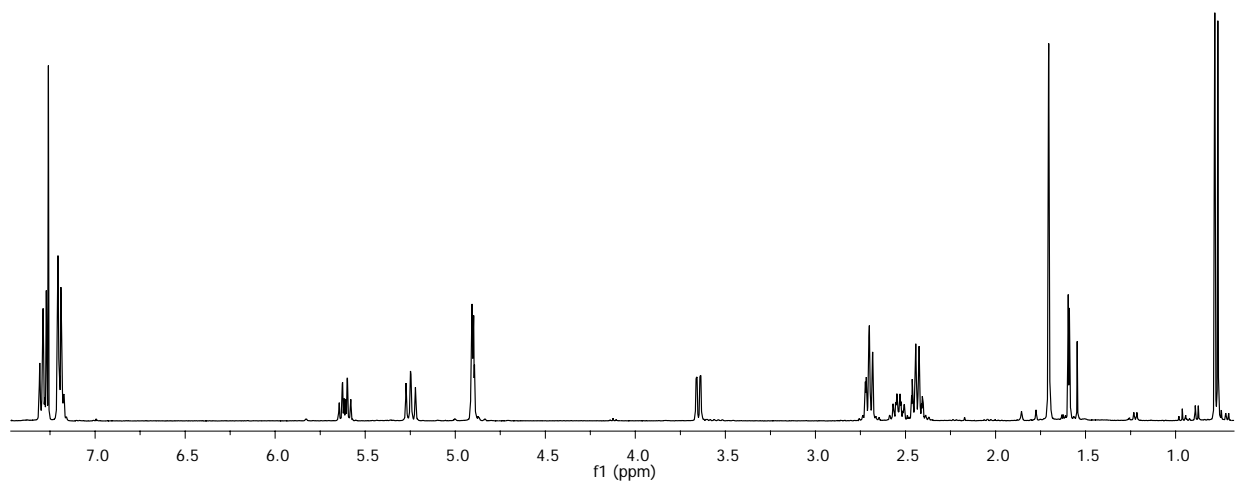
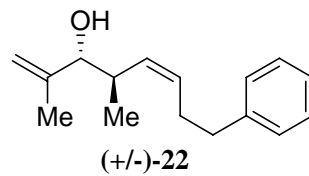
(1,2-disubstituted olefin 14:1 *Z:E*) **10**



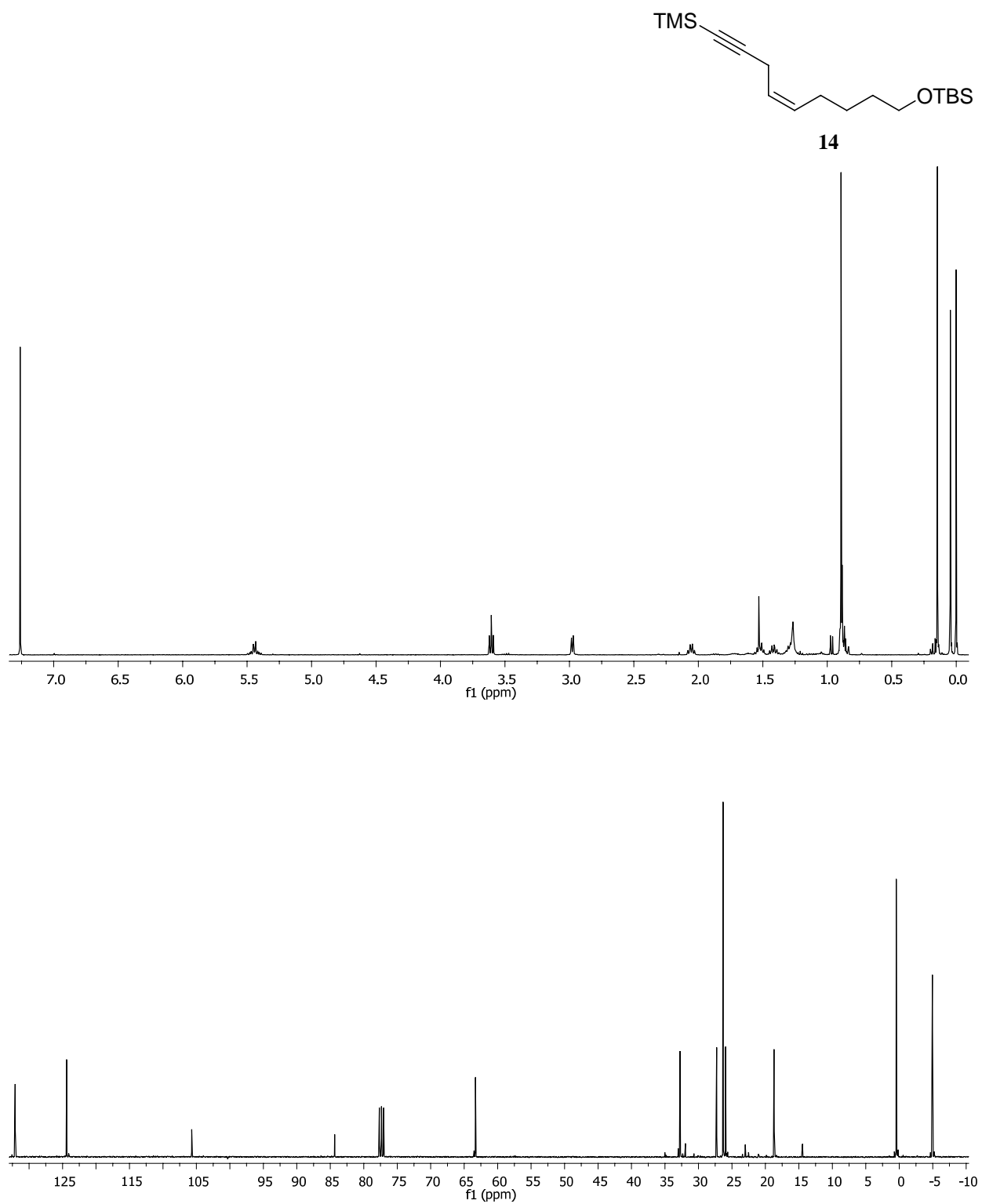
**Figure S12:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **12**



**Figure S13:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of (+/-) **22**



**Figure S14:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$  with TMS) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **14**



**Figure S15:**  $^1\text{H}$  (400 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ ) of **18**  
(contains trace amounts of a triisopropylsilyl impurity)

