

Traceless Stereinduction in the One-Pot Assembly of all Three Rings of the  
Hexahydrodibenzopyrans.

Keith A. Korthals and William D. Wulff\*

Department of Chemistry, Michigan State University, East Lansing, MI 48824

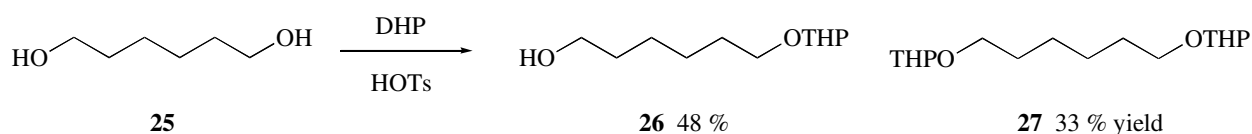
**SUPPORTING INFORMATION**

**Table of Contents**

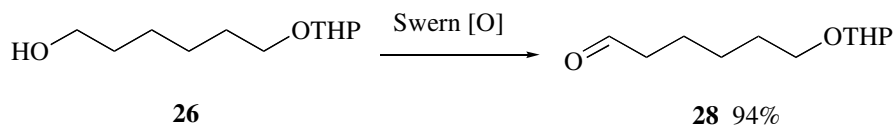
Preparation of Diol ( <i>S</i> )- <b>34</b> – Precursor to the Enynes <b>10</b> .	S2
Preparation of the Enyne ( <i>S</i> )- <b>10a</b> .	S7
Preparation of the Enyne ( <i>S</i> )- <b>10b</b> .	S9
Preparation of the Enyne ( <i>S</i> )- <b>10c</b> .	S11
Preparation of Racemic Enynes ( $\pm$ )- <b>10a</b> and ( $\pm$ )- <b>10b</b> .	S13
Preparation of Carbene Complex <b>11c</b> .	S15
General Procedure for the One-Pot Construction of Hexahydrodibenzo- pyrans – Illustrated for ( <i>6aR</i> , <i>10aR</i> )- <b>12a</b> .	S19
One-Pot Construction of the Hexahydrodibenzopyran ( <i>6aR</i> , <i>10aR</i> )- <b>12b</b> .	S27
One-Pot Construction of the Hexahydrodibenzopyran ( <i>6aR</i> , <i>10aR</i> )- <b>12c</b> .	S29
Synthesis of Enyne <b>13</b> .	S32
Preparation of racemic ( $\pm$ )- <b>13</b> .	S37
One-Pot Construction of the Hexahydrocyclopentabenzopyran ( <i>3aR</i> , <i>4R</i> )- <b>14</b> .	S38

Preparation of Enyne (3 <i>R</i> ,5 <i>S</i> )- <b>15</b> .	S40
Preparation of Enyne (5 <i>S</i> ,7 <i>S</i> )- <b>18</b> .	S45
Reaction of Enyne (3 <i>R</i> ,5 <i>S</i> )- <b>15</b> with Carbene Complex <b>11a</b> . Matched Case.	S48
Reaction of Enyne (3 <i>R</i> ,5 <i>S</i> )- <b>15</b> with Carbene Complex <b>11c</b> . Matched Case.	S52
Reaction of Enyne (3 <i>S</i> ,5 <i>S</i> )- <b>18</b> with Carbene Complex <b>11a</b> . Mismatched Case.	S56
Reaction of Enyne (3 <i>S</i> ,5 <i>S</i> )- <b>18</b> with Carbene Complex <b>11c</b> . Mismatched Case.	S58
References.	S60

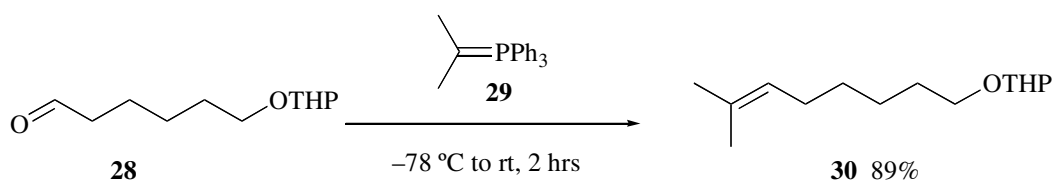
### Preparation of Diol (*S*)-**34** – Precursor to the Enynes **10**.



*Mono-protection of 1,6-hexanediol.* In a 500 mL round bottom flask was added 240 mL of dichloromethane, 1,6-hexanediol **25** (4.14 g, 35 mmol), THP (3.17 mL, 34 mmol), and tosylic acid (0.70 g, 3.7 mmol). The reaction was monitored by TLC, and the reaction was complete in 1.5 hours. Column chromatography (24 cm x 4 cm, silica gel) with 20 % ethyl acetate / 2 % triethyl amine / hexane gave 3.28 g (33 %, 11.6 mmol) of **27** and 3.37 g (48 %, 16.8 mmol) of **26**. Spectral data for **27**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.2 - 1.9 (m, 20 H), 3.3 - 3.6 (m, 4 H), 3.15 - 3.9 (m, 4 H), 4.52 (t, 2 H,  $J = 4.0$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 19.43, 25.31, 25.91, 29.49, 30.56, 62.00, 67.28, 98.55; Yellow oil,  $R_f = 0.65$  (50 % ethyl acetate / hexane). Spectral data for **26** was consistent with that reported for this compound:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.2 - 1.9 (m, 15 H), 3.2 - 3.8 (m, 6 H), 4.54 (t, 1 H,  $J = 2.7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 19.41, 25.24, 25.39, 25.81, 29.44, 30.50, 32.41, 62.08, 62.28, 67.31, 98.62; Yellow oil,  $R_f = 0.29$  (50 % ethyl acetate / hexane).

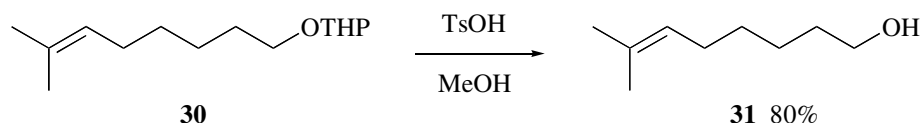


**Preparation of aldehyde **28**:** A 250 mL round bottom flask was charged with 64 mL of CH<sub>2</sub>Cl<sub>2</sub> and DMSO (1.05 mL, 14.7 mmol). The contents of the flask were cooled to –78 °C. To this solution was added oxalyl chloride (0.45 mL, 5.2 mmol) dropwise. Bubbling was noted. The contents of the flask were stirred for 15 minutes then alcohol **26** (1.03 g, 5.1 mmol) was added in a dropwise manner at –78 °C. The solution was cloudy when the addition was completed. The solution was stirred for 20 minutes at –78 °C then 5 mL (36 mmol) of triethyl amine was added. The solution was allowed to warm to room temperature for one hour. The contents of the flask were poured into 100 mL of water (no acid was used in workup). The organic phase was washed with 100 mL of saturated bicarbonate. Each aqueous phase was back extracted with 3 x 15 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined and dried over magnesium sulfate and filtered. The organic solvent was removed under reduced pressure. Column chromatography (21 x 2.8 cm, silica gel) with 20 % ethyl acetate / hexane then 30 % ethyl acetate / hexane gave 0.95 g (4.79 mmol) of **28** (94 % yield). On a 9.8 g (49 mmol) scale the yield was 87 %. The spectroscopic characterization of this compound was consistent with that previously reported.<sup>1</sup>

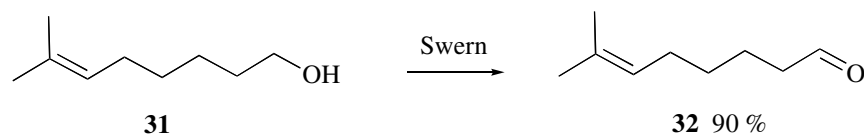


**Wittig olefination of aldehyde **28**.** A 500 mL round bottom flask was charged with isopropyltriphenylphosphonium iodide (12.5 g, 28.8 mmol) and 250 mL of THF. The contents of the flask were cooled to 0 °C and *n*-butyllithium (1.6 M) in hexanes (16.1 mL, 25.8 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for three hours. The contents of the 500 mL round bottom flask were cooled to –78 °C and the aldehyde **28** (4.73 g, 23.6 mmol) was added dropwise quickly. The reaction mixture was warmed to rt and stirred for 24 h. The contents of the flask were poured into an equal volume

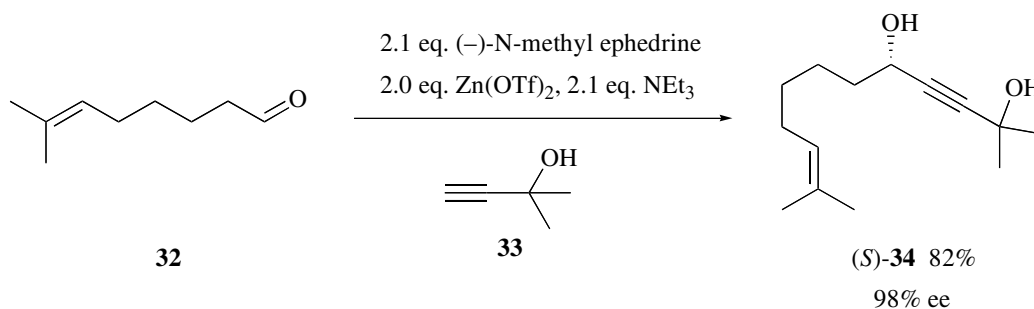
of hexane and the organic portion filtered through Celite-503. Column chromatography (25 cm x 5.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 4.78 g (89 % yield, 23.0 mmol) of the THP ether **30**. Spectral data for **30**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.27 (qt, 5 H,  $J = 3.8$  Hz), 1.39 - 1.54 (m, 6 H), 1.51 (s, 3 H), 1.56 - 1.63 (m, 1 H), 1.60 (d, 3 H,  $J = 0.9$  Hz), 1.65 - 1.79 (m, 2 H), 1.89 (dd, 2 H,  $J = 13.6, 6.6$  Hz), 3.24 - 3.34 (m, 1 H), 3.41 (dt, 1 H,  $J = 11.0, 5.1$  Hz), 3.60 - 3.70 (m, 1 H), 3.74 - 3.84 (m, 1 H), 4.49 (t, 1 H,  $J = 3.0$  Hz), 5.03 (tt, 1 H,  $J = 7.2, 1.4$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 17.54, 19.58, 25.45, 25.61, 25.83, 27.89, 29.60, 29.64, 30.69, 62.14, 67.51, 98.69, 124.63, 131.11. Clear oil (hexane),  $R_f = 0.62$  (30 % ethyl acetate / hexane). Spectroscopic properties were consistent with those previously reported.<sup>1</sup>



*Preparation of the alcohol **31**.* A 500 mL flask was charged with methanol (200 mL), compound **30** (4.78 g, 21.1 mmol), and TsOH (2.05 g, 10.8 mmol). The contents of the flask were stirred for 6 hours at room temperature. The reaction mixture was extracted with 500 mL x 3 ethyl acetate and dried over magnesium sulfate. The resulting alcohol **31** was used without further purification. The yield of **31** was 80 % (2.40 g, 16.9 mmol). The yield varied from 40 - 80 %. High vacuum was avoided because the compound was slightly volatile. Spectral data for **31**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.25 - 1.36 (m, 4 H), 1.44 - 1.53 (m, 1 H), 1.55 (s, 3 H), 1.63 (d, 3 H,  $J = 1.0$  Hz), 1.81 - 2.04 (m, 3 H), 3.57 (t, 2 H,  $J = 6.7$  Hz), 5.06 (br t, 1 H,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 17.58, 25.35, 25.64, 27.91, 29.61, 32.63, 62.74, 124.53, 131.31; Yellow oil (hexane),  $R_f = 0.28$  (30 % ethyl acetate / hexane). The spectroscopic properties were consistent with those previously reported.<sup>1</sup>

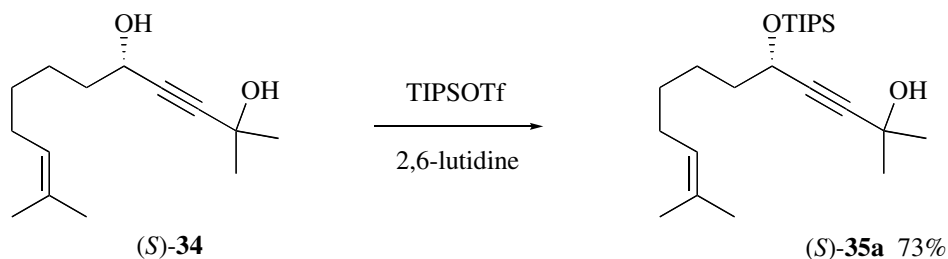


**Preparation of the aldehyde 32.** A flask was charged with dichloromethane (500 mL) and DMSO (11.6 g, 10.5 mL, 147 mmol). The contents of the flask were cooled to  $-78\text{ }^{\circ}\text{C}$ . To this solution was added oxalyl chloride (6.7 g, 4.6 mL, 53 mmol) in a dropwise manner. The release of bubbles was noted. The solution was stirred for 15 minutes. The alcohol **31** (6.83 g, 48 mmol) was added in a dropwise manner. The solution was stirred for 30 minutes and it was noted that the solution turned cloudy upon completion of the addition of the alcohol. Triethyl amine (47 mL, 336 mmol) was added quickly. The solution was allowed to warm to room temperature for an hour. The contents of the flask were poured into an extraction funnel and washed with 250 mL of saturated ammonium chloride solution. The organic layer was collected and the ammonium chloride solution was extracted with DCM (50 mL x 2). The organic layers were combined and washed with brine and the brine solution was extracted with DCM (30 mL x 2). The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate. The organic solvent was removed under reduced pressure. The exposure of **32** to high vacuum was limited due to the fact that it was volatile. Column chromatography with 5 % ethyl acetate / hexane gave 6 g (43.2 mmol) of **32** (90 % yield,) as an oil. This compound had spectroscopic properties consistent with those previously reported.<sup>1</sup>

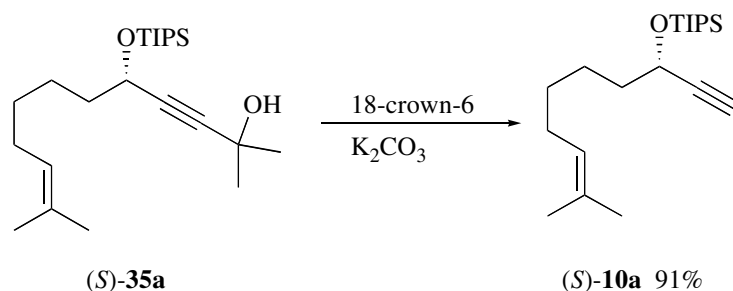


*Preparation of the diol (S)-34.*<sup>2</sup> A flask was charged with Zn(OTf)<sub>2</sub> (4.54 g, 12.5 mmol), (–)-N-methyl ephedrine (2.35 g, 13.1 mmol), triethyl amine (1.8 mL, 12.9 mmol), and 13 mL of toluene. This produced a cloudy suspension. The suspension was stirred rapidly for two hours at room temperature. The compound 2-methylbut-3-yn-2-ol (1.26 mL, 13.0 mmol) was added by rapid dropwise addition. The solution was stirred for 15 minutes then a 0.4 M solution of the aldehyde **32** (0.86 g, 6.2 mmol) was added dropwise via syringe pump over 4 hours. The solution was stirred 30 to 60 minutes after the addition of the aldehyde **32**. The reaction mixture was poured into 50 mL of saturated NH<sub>4</sub>Cl. This was back extracted with 50 mL, 2 x 20 mL of ethyl acetate. The organics were combined and extracted with 20 mL of brine solution. The aqueous layer was back extracted with 3 x 20 mL of ethyl acetate. The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate. Column chromatography (25 x 3.8 cm, silica gel) with 30 % ethyl acetate / hexane then 50 % ethyl acetate / hexane gave 1.15 g (82 % yield, 5.08 mmol) of (S)-**34**. On a 12.5 mmole scale the yield was 74 % following an identical procedure. The ee was determined to be 98 % after conversion to alcohol (S)-**36** as described below in the preparation of enyne **10c**. Spectral data for **34**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.34 (q, 2 H, *J* = 7.3 Hz), 1.37 - 1.45 (m, 2 H), 1.49 (s, 6 H), 1.57 (s, 3 H), 1.60 - 1.72 (m, 2 H), 1.66 (s, 3 H), 1.96 (q, 2 H, *J* = 7.1 Hz), 2.37 (br s, 2 H), 4.35 (t, 1 H, *J* = 6.64 Hz), 5.08 (t, 1 H, *J* = 7.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 17.66, 24.82, 25.67, 27.86, 29.44, 31.35, 37.69, 62.36, 65.10, 83.16, 89.55, 124.45, 131.49; IR (thin film): 3341 br s, 2931 s, 2932 s, 2859 s, 1456 m, 1377 m, 1237 m, 1167 m, 1026 w, 953 w cm<sup>-1</sup>; mass spectrum *m/z* (% rel intensity) 224 M<sup>+</sup> (10), 207 (38), 193 (14), 191 (19), 189 (21), 173 (35), 163 (17), 149 (17), 145 (39), 131 (32), 121 (22), 117 (25), 105 (78), 95 (100), 81 (96), 65 (41); Clear oil (hexane), R<sub>f</sub> = 0.1 (30 % ethyl acetate / hexane). [ $\alpha$ ]<sub>D</sub><sup>22</sup> +3.5° (c 1.33, CH<sub>2</sub>Cl<sub>2</sub>).

## Preparation of the Enyne (*S*)-10a.



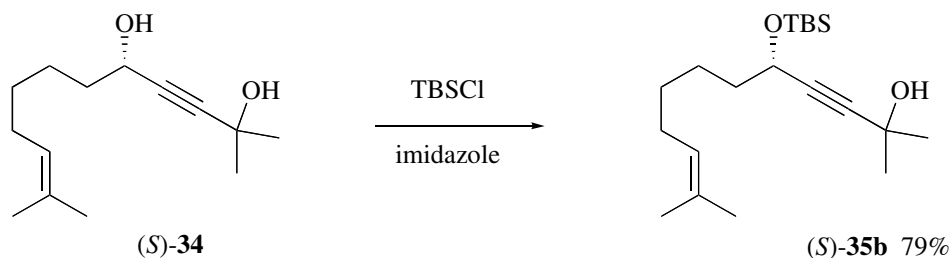
*Installation of the TIPS group.* A 100 mL flask was charged with compound (*S*)-**34** (1.68 g, 7.5 mmol, 98 % ee), DCM, and 2,6-lutidine (1.3 mL, 11.2 mmol, must be added before the triflate). The reaction mixture was cooled to 0 °C. The TIPSOTf (2.0 mL, 7.5 mmol) was added dropwise and the solution was allowed to warm to room temperature over 1 hour. The reaction mixture was poured into 50 mL of saturated ammonium chloride and the organic layers separated from the aqueous. The aqueous layer was back extracted with 3 x 50 mL of DCM. The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate and the solution was filtered through filter paper. The organic solvent was removed under reduced pressure. Column chromatography (25 cm x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 2.08 g (73 %, 5.48 mmol) of (*S*)-**35a**. Spectral data for (*S*)-**35a**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.00 - 1.10 (m, 21 H), 1.32 (p, 2 H,  $J = 7.2$  Hz), 1.42 (p, 2 H,  $J = 7.4$  Hz), 1.47 (s, 6 H), 1.58 (s, 3 H), 1.62 - 1.72 (m, 2 H), 1.66 (s, 3 H), 1.96 (q, 2 H,  $J = 7.2$  Hz), 4.45 (t, 1 H,  $J = 6.4$  Hz), 5.09 (t, 1 H,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 12.27, 17.67, 18.04, 24.74, 25.69, 27.93, 29.55, 31.30, 38.79, 62.95, 65.16, 84.12, 88.41, 124.66, 131.33; IR (thin film): 3360 br m, 2944 s, 2867 s, 1464 m, 1377 w, 1100 w, 884 w, 679 w  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 337  $\text{M}^+ - 43$  (1), 321 (1), 279 (3), 267 (1), 253 (6), 215 (1), 189 (7), 169 (5), 147 (16), 131 (58), 123 (11), 119 (14), 111 (11), 103 (84), 95 (71), 75 (100), 69 (55), 61 (45); Clear thick oil (hexane),  $R_f = 0.46$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -15.3^\circ$  (c 0.935,  $\text{CH}_2\text{Cl}_2$ ) at 98 % ee.



**Alkyne deprotection to give enyne (S)-10a.** A 100 mL round bottom flask was charged with alkyne (S)-35a (2.08 g, 5.5 mmol, 98 % ee), K<sub>2</sub>CO<sub>3</sub> (0.76 g, 5.5 mmol), 18-crown-6 (1.47 g, 5.5 mmol), and 55 mL of toluene. The contents of the flask were brought to reflux with a rapid nitrogen flow across the top of the straight condenser (a coiled condenser did not work). The contents of the flask were refluxed for 48 hours. The solvent was removed under reduced pressure. Column chromatography (20 x 5.8 cm, silica gel) with hexane then 5 % ethyl acetate / hexane gave 1.60 g (91 % yield, 5.0 mmol) of (S)-10a. Spectral data for (S)-10a: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.04 - 1.12 (m, 3 H), 1.06 (d, 18 H), 1.26 - 1.40 (m, 2 H), 1.41 - 1.53 (m, 2 H), 1.57 (s, 3 H), 1.65 - 1.72 (m, 2 H), 1.66 (s, 3 H), 1.97 (q, 2 H, *J* = 7.1 Hz), 2.35 (d, 1 H, *J* = 2.0 Hz), 4.44 (dt, 1 H, *J* = 2.1, 6.3 Hz), 5.09 (bt, 1 H, *J* = 7.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 12.24, 17.66, 18.01, 24.57, 25.70, 27.95, 29.58, 38.74, 62.89, 71.91, 85.78, 124.61, 131.35; IR (thin film): 3312 m, 2944 m, 2867 s, 1462 w, 1101 m cm<sup>-1</sup>; mass spectrum *m/z* (% rel intensity) 323 M<sup>+</sup> +1 (6), 322 M<sup>+</sup> (8), 321 (12), 279 (100), 237 (19), 209 (10), 195 (25), 169 (30), 157 (10), 147 (38), 131 (61), 103 (54), 95 (82); Anal calcd for C<sub>20</sub>H<sub>38</sub>OSi: C, 74.46; H, 11.87. Found; C, 74.14; H, 11.81. Clear oil (hexane), R<sub>f</sub> = 0.75 (30 % ethyl acetate / hexane). For optically active material [ $\alpha$ ]<sub>D</sub><sup>22</sup> -17.8° (c 1.62, CH<sub>2</sub>Cl<sub>2</sub>) at 98 % ee.

#### Preparation of the Enyne (S)-10b.

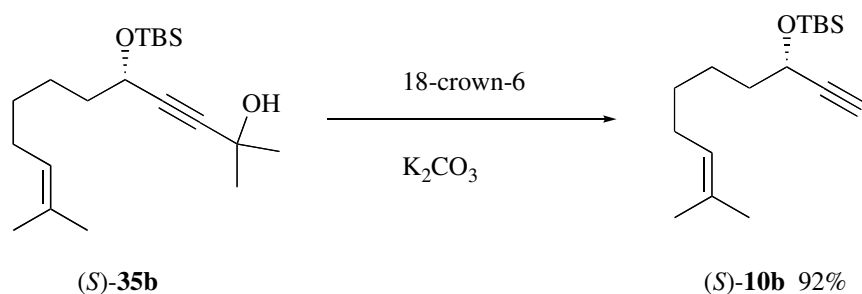




*Installation of the TBS group via TBSCl.* A 100 mL round bottom flask was charged with diol **(S)-34** (0.87 g, 3.9 mmol, 98 % ee), imidazole (0.31 g, 4.5 mmol), TBSCl (0.59 g, 3.9 mmol), and 50 mL of DMF. The reaction mixture was stirred for 12 to 24 hours at room temperature. The contents of the flask were poured into 30 mL of saturated  $\text{NH}_4\text{Cl}$  and back extracted with 3 x 30 mL of  $\text{CH}_2\text{Cl}_2$ . The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate and filtered. The organic solvent was removed under reduced pressure. Column chromatography (25 x 3.0 cm, silica gel) with hexane then 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane gave 1.03 g (3.08 mmol) of **(S)-35b** (79 % yield, 3.08 mmol).

*Installation of the TBS group via TBSOTf.* Compound **(S)-34** (0.14 g, 0.63 mmol, 98 % ee) was added to a 25 mL flask along with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The contents of the flask were cooled to 0 °C, and 2,6-lutidine (0.15 mL, 1.3 mmol) was added; lutidine must be added before the triflate or decomposition occurred. To this flask at 0 °C was added TBSOTf (0.15 mL, 0.65 mmol) and the reaction was stirred for 15 minutes at 0 °C and the reaction was allowed to warm to room temperature over 45 minutes. The reaction was quenched by pouring it into 10 mL of saturated  $\text{NH}_4\text{Cl}$ . The aqueous layer was extracted with 3 x 10 mL of  $\text{CH}_2\text{Cl}_2$ . The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate. The liquid was filtered through filter paper, and the solvent was removed under reduced pressure. Column chromatography (26 x 1.8 cm, silica gel) with hexane then 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane gave 0.16 g (67 %, 0.42 mmol) of **(S)-35b**. Spectral data for **(S)-35b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.07 (s, 3 H), 0.10 (s, 3 H), 0.87 (s, 9 H), 1.24 -

1.43 (m, 5 H), 1.47 (s, 6 H), 1.52 - 1.65 (m, 1 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.91 - 2.04 (m, 3 H), 4.31 (t, 1 H,  $J = 6.25$  Hz), 5.07 (t, 1 H,  $J = 7.12$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -4.99, -4.48, 17.64, 18.22, 24.93, 25.69, 25.77, 27.88, 29.88, 31.29, 31.36, 38.49, 62.81, 65.06, 83.94, 88.44, 124.57, 131.32; IR (thin film): 3372 br s, 2932 s, 2859 m, 1474 w, 1364 w, 1254 w, 1165 w, 839  $\text{m cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity)  $\text{M}^+$  (Not found), 281  $\text{M}^+ - 58$  (1, loss of acetone), 223 (4), 181 (10), 167 (7), 149 (21), 147 (31), 139 (20), 133 (46), 120 (13), 105 (29), 95 (45), 75 (100), 67 (31), 55 (15); Clear thick oil (hexane),  $R_f = 0.45$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -35.5^\circ$  (c 1.17,  $\text{CH}_2\text{Cl}_2$ ) at 98 % ee.

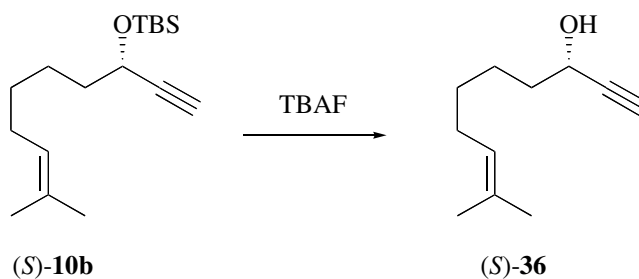


**Alkyne deprotection to give enyne (S)-10b.** A 50 ml round bottom flask was charged with alkyne (S)-35b (0.48 g, 1.4 mmol, 98 % ee), 18-crown-6 (0.45 g, 1.7 mmol),  $\text{K}_2\text{CO}_3$  (0.20 g, 1.4 mmol), and 20 mL of toluene. The contents of the flask were brought to reflux under a rapidly flowing stream of nitrogen. A straight condenser was used (a coiled condenser does not work). Additional  $\text{K}_2\text{CO}_3$  (0.11 g, 0.8 mmol) was added after one day of reflux. The reaction was refluxed an additional day. The toluene was removed under reduced pressure. Column chromatography (15 cm x 3.8 cm, silica gel) with hexanes then with 5 % ethyl acetate / hexane and finally with 10 % ethyl acetate / hexane gave 0.37 g of (S)-10b (92 % yield, 1.29 mmol). Spectral data for (S)-10b:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.09 (s, 3 H), 0.11 (s, 3 H), 0.89 (s, 9 H), 1.21 - 1.51 (m, 4 H), 1.58 (s, 3 H), 1.61 - 1.70 (m, 2 H), 1.66 (s, 3 H), 1.95 (q, 2 H,  $J = 7.1$  Hz), 2.34 (d, 1 H,  $J = 2.2$  Hz), 4.30 (dt, 1 H,  $J = 2.0$  Hz,  $J = 6.5$  Hz), 5.09 (bt, 1 H,  $J = 7.3$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -5.23, -4.70, 17.56, 18.17, 24.74, 25.71, 25.77, 27.79, 29.32, 38.51,

S10

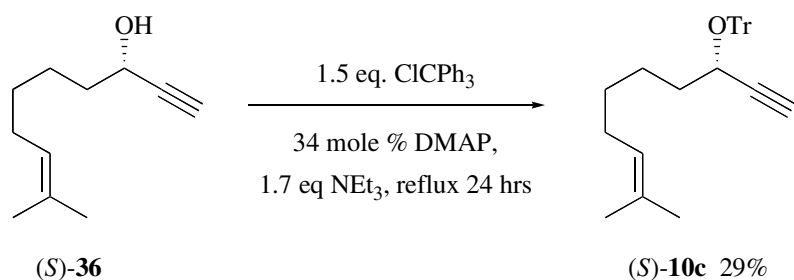
62.56, 71.84, 85.65, 124.57, 131.32; IR (thin film): 3312 m, 2930 s, 2054 s, 1472 w, 1404 w, 1252 m, 1098 m, 837 s, 777 s  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 280  $\text{M}^+$  (1), 224 (1), 203 (1), 181 (3), 169 (3), 167 (3); Anal calcd for  $\text{C}_{17}\text{H}_{32}\text{OSi}$ : C, 72.79; H, 11.50. Found; C, 72.61; H, 11.68. Clear oil (hexane),  $R_f = 0.69$  (10 % ethyl acetate / hexane). For optically active material,  $[\alpha]_D^{20} -34.6^\circ$  (c 0.49,  $\text{CH}_2\text{Cl}_2$ ) at 98 % ee.

### Preparation of the Enyne (*S*)-10c.



*Preparation of propargyl alcohol (S)-36.* Compound (*S*)-10b (0.045 g, 0.16 mmol, 98 % ee) and THF (2 mL) was placed into a 10 mL round bottom flask. The contents of the flask were cooled to 0 °C and TBAF (0.17 mL, 0.17 mmol) was added dropwise. The reaction was stirred until it was complete by TLC, which was about 30 minutes. The contents of the flask were poured into 5 mL of water, which was extracted, with 3 x 20 mL of  $\text{CH}_2\text{Cl}_2$ . The solution was dried over magnesium sulfate and sodium bicarbonate. The solution was filtered and the solvent removed under reduced pressure. This gave 0.025 g of (*S*)-36 (93 % yield, 0.15 mmol). This compound was analyzed by chiral GC with a Chiraldex B-MB, 30 m x 0.25 m column. The column was at 110 °C with no split and 1 mL/min flow rate. The non-racemic compound was compared to the racemate (98 % ee). The retention times were 43.64 minutes (major) and 45.30 minutes (minor). Spectral data for (*S*)-36:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.28 - 1.51 (m, 4 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.68 - 1.75 (m, 2 H), 1.81 (br s, 1 H), 1.97 (q, 2 H,  $J = 7.2$  Hz), 2.44 (d, 1 H,  $J = 2.1$  Hz), 4.34 (qd, 1 H,  $J = 6.1$  Hz, 2.0 Hz), 5.09 (t, 1 H,  $J = 7.2$  Hz);  $^{13}\text{C}$

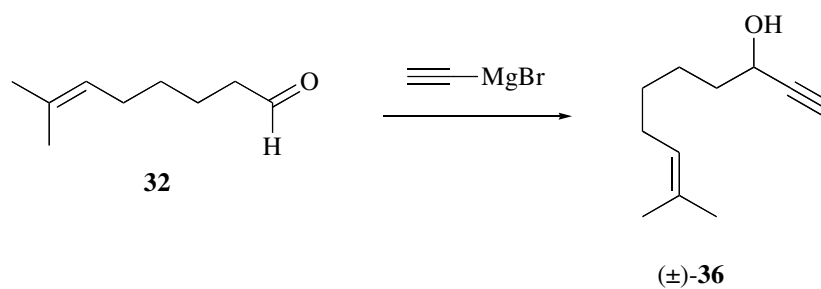
NMR (CDCl<sub>3</sub>)  $\delta$ : 17.60, 24.66, 25.63, 27.82, 29.40, 37.48, 62.14, 72.73, 85.00, 124.38, 131.42; IR (thin film): 3353 bm, 3306 s, 2930 s, 2859 s, 1455 w, 1377 w, 1078 w, 1019 w cm<sup>-1</sup>; mass spectrum  $m/z$  (% rel intensity) 166 M<sup>+</sup> (4), 165 (24), 151 (15), 147 (17), 137 (22), 133 (19), 123 (31), 111 (100), 97 (52), 95 (58), 81 (37), 67 (34), 55 (28); Anal calcd for C<sub>11</sub>H<sub>18</sub>O: C, 79.46; H, 10.91. Found; C, 79.51; H, 10.96. Clear oil (hexane), R<sub>f</sub> = 0.43 (30 % ethyl acetate / hexane).  $[\alpha]_D^{22}$  -2.0° (c 1.27, CH<sub>2</sub>Cl<sub>2</sub>) at 98 % ee.  $[\alpha]_D^{22}$  -1.0° (c 0.61, CH<sub>2</sub>Cl<sub>2</sub>) at 98 % ee.



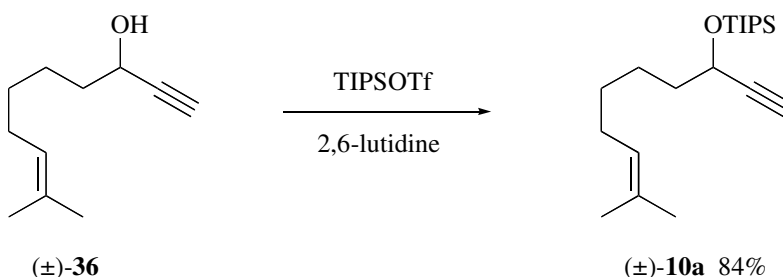
*Enyne (S)-10c via trityl protection of alcohol (S)-36.* A flask was charged with compound (S)-36 (0.35 g, 2.1 mmol, 98 % ee), trityl chloride (0.89 g, 3.2 mmol), triethyl amine (0.3 mL, 2.2 mmol), DMAP (0.09 g, 0.7 mmol), and DCM (25 mL). The contents of the flask were refluxed for 72 hours and the reaction was followed by TLC (KMnO<sub>4</sub> stain). When the TLC did not indicate further conversion the solution was concentrated under reduced pressure, and the residue was subjected to column chromatography (5 % ethyl acetate / hexane and then with 10 % ethyl acetate / hexane on 25 x 3.1 cm of silica gel). This gave 0.25 g (0.61 mmol) of product of (S)-10c (29 % yield) and 0.21 g of starting material (58 % recovery). Spectral data of (S)-10c: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.10 - 1.23 (m, 2 H), 1.24 - 1.38 (m, 2 H), 1.38 - 1.50 (m, 2 H), 1.56 (s, 3 H), 1.67 (d, 3 H,  $J$  = 1.0 Hz), 1.88 (q, 2 H,  $J$  = 7.2 Hz), 2.11 (d, 1 H,  $J$  = 2.1 Hz), 3.99 (m, 1 H), 5.05 (br t, 1 H,  $J$  = 7.1 Hz), 7.20 - 7.32 (m, 9 H), 7.51 - 7.55 (m, 6 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ : 17.66, 24.44, 25.68, 27.85, 29.48, 36.24, 64.46, 72.86, 84.22, 87.82, 124.63, 127.04, 127.65, 129.05, 131.24, 144.45; IR (thin film): 3303 m, 3059 w, 2961 s, 2926

s, 2853 m, 1449 m, 1262 s, 1127 s, 1026 s  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 408  $\text{M}^+$  (<1), 243 (100,  $\text{CPh}_3$ ), 184 (5), 165 (12), 91 (1), 77 (6); Clear thick oil (hexane),  $R_f = 0.69$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -45.8^\circ$  (c 0.85,  $\text{CH}_2\text{CH}_2$ ) at 98 % ee.

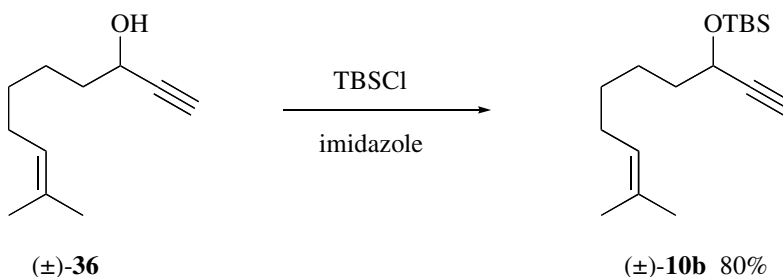
### Preparation of Racemic Enynes ( $\pm$ )-10a and ( $\pm$ )-10b.



*Addition of alkynyl Grignard to aldehyde 32.* In a 500 mL round bottom flask charged with aldehyde **32** (3.32 g, 23.7 mmol) (see preparation above) at 0 °C was added ethynylmagnesium bromide (0.5 M) in THF (95 mL, 47.5 mmol). The reaction was warmed to room temperature and the contents of the flask were stirred for 3 hours. The contents of the flask were poured into 200 mL of water. The water layer was back extracted with 50 mL x 3 of ethyl acetate. The organic layer was washed with brine 20 mL and the brine layer was extracted with 20 mL x 2 ethyl acetate. The organic layers were combined and dried with magnesium sulfate. The organic layer was removed under reduced pressure. Column chromatography (25 x 5.8 cm, silica gel) with 10 % ethyl acetate / hexane, 20 % ethyl acetate / hexane, and 30 % ethyl acetate / hexane which resulted in 2.41 g (61 % yield, 14.5 mmol) of ( $\pm$ )-**36**.

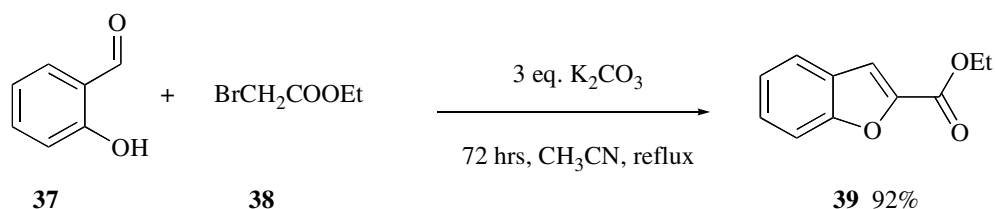


*Enyne (±)-10a via TIPS protection of (±)-36.* A 50 mL flask was charged with compound (±)-**36** (0.36 g, 2.2 mmol), dichloromethane (20 mL), and 2,6-lutidine (0.28 mL, 2.4 mmol). The contents of the flask were cooled to 0 °C and TIPSOTf (0.65 mL, 2.4 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes. The layers separated. Saturated ammonium chloride (15 mL) was added to the stirring solution. The organic layer was back extracted with dichloromethane (20 mL x 3). The organic layers were combined and solid sodium bicarbonate was added until no bubbles were noted and the solution dried over magnesium sulfate. The solution was then gravity filtered. Column chromatography (20 x 3.2 cm, silica gel) with 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane gave 0.59 g (84 %, 1.84 mmol) of (±)-**10a**. The spectroscopic data matched those given above for (S)-**10a**.



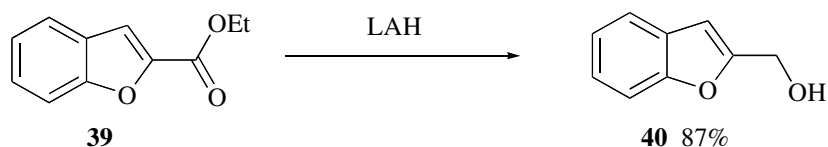
*Enyne (±)-10b via TBS protection of (±)-36.* The alcohol **36** (2.32 g, 13.9 mmol) was treated with TBSCl (2.4 g, 15.9 mmol) and imidazole (1.08 g, 15.9 mmol) in DMF (150 mL). The reaction was stirred for 18 to 24 hours at room temperature. The contents of the flask were poured onto 400 mL of water and the water layer was back extracted with ether 4 x 200 mL. The ether layers were combined and dried with magnesium sulfate. Column chromatography (25 x 3.8 cm, silica gel) with hexane, 10 % ethyl acetate / hexane, and 20 % ethyl acetate / hexane gave 3.11 g (80 % yield, 11.1 mmol) of racemic **10b** after the removal of the solvent under reduced pressure. The spectroscopic data matched those given above for (S)-**10b**.

### Preparation of Carbene Complex 11c.



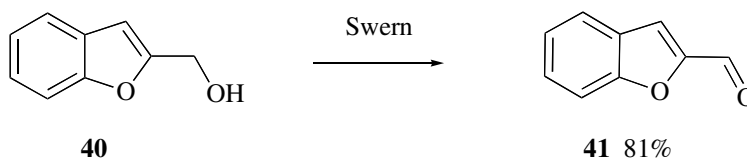
*Synthesis of Benzofuran 39.* The following is a modified procedure from the literature.<sup>3</sup>

A flask was charged with salicylaldehyde **37** (3.67 g, 30 mmol), ethyl bromoacetate **38** (4.0 mL, 36.2 mmol), potassium carbonate (12.3 g, 89.0 mmol), and acetonitrile (250 mL). The contents of the flask were refluxed for 72 hours. The contents of the flask were poured into 200 mL of water and back extracted with 100 mL x 3 of ethyl acetate. Column chromatography (23 x 3.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 5.27 g (92 % yield, 27.6 mmol) of compound **39** as a yellow oil. This solidified upon standing into a beige solid. Spectral data for **39**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.46 (t, 3 H, *J* = 7.1 Hz), 4.48 (q, 2 H, *J* = 7.1 Hz), 7.32 (t, 1 H, 7.3 Hz), 7.47 (t, 1 H, 7.2 Hz), 7.55 (s, 1 H), 7.62 (d, 1 H, 8.2 Hz), 7.70 (d, 1 H, 7.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.12, 61.28, 112.11, 113.55, 122.58, 123.54, 126.62, 127.34, 145.50, 155.47, 159.35; Yellow oil (hexane), beige crystalline solid after standing overnight, *R*<sub>f</sub> = 0.45 (30 % ethyl acetate / hexane). The above spectral data matched that previously reported for this compound.<sup>3</sup>

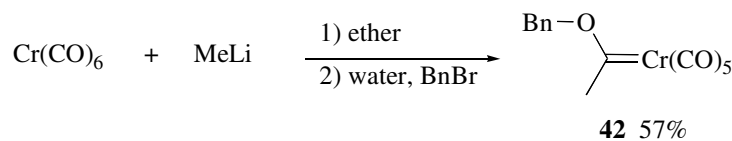


*Reduction of ester 39 to the alcohol 40.* Compound **40** was prepared by a modified procedure from the literature.<sup>3,4</sup> A flask was charged with LAH (0.78 g, 20.6 mmol) and THF (175 mL). The ester **39** (3.84 g, 20.2 mmol) was added in 50 mL of THF dropwise at room temperature. The contents of the flask were brought to reflux and heated for 3 hours. To this

flask was added 300 mL of saturated potassium carbonate and the contents of the flask were stirred for 15 minutes. The contents of the flask were poured into 200 mL of ethyl acetate and stirred for 15 minutes. The aqueous layer was separated and it was extracted with 200 mL, 100 mL, and 50 mL of ethyl acetate. Column chromatography (25 x 3.5 cm, silica gel) with 30 % ethyl acetate / hexane gave 2.60 g (87 % yield, 17.6 mmol) of compound **40**. The spectroscopic properties of **40** were consistent with those previously reported.<sup>3,4</sup>



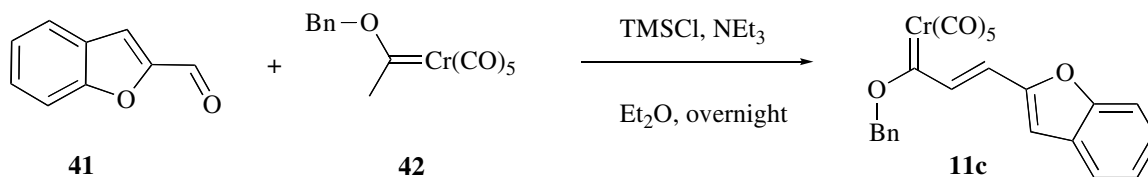
*Oxidation of **40** to aldehyde **41**:* A 250 mL round bottom flask was charged with DMSO (4.5 mL, 63.4 mmol) and dichloromethane (125 mL) and the contents of the flask were cooled to  $-78\text{ }^{\circ}\text{C}$ . Oxalyl chloride (6.1 mL, 70.0 mmol) was added dropwise. The solution was stirred for 10 minutes then compound **40** (3.00 g, 20.5 mmol) was added dropwise and the solution was stirred for 15 minutes. Triethyl amine (20 mL) was added. The solution was warmed at room temperature for 1 hour. Extraction with 100 mL of 1 M HCl, saturated bicarbonate solution, and brine was done. Each aqueous layer was back extracted with 100 mL of ethyl acetate x 3. Column chromatography (24 x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane was done giving 2.44 g (81 %, 16.61 mmol) of aldehyde **41**. The spectroscopic properties of **41** were consistent with those previously reported.<sup>5</sup>



*Preparation of carbene complex **42**.* This experiment was performed following a procedure adapted from the literature by Hoye and coworkers.<sup>6</sup> Chromium hexacarbonyl (3.07



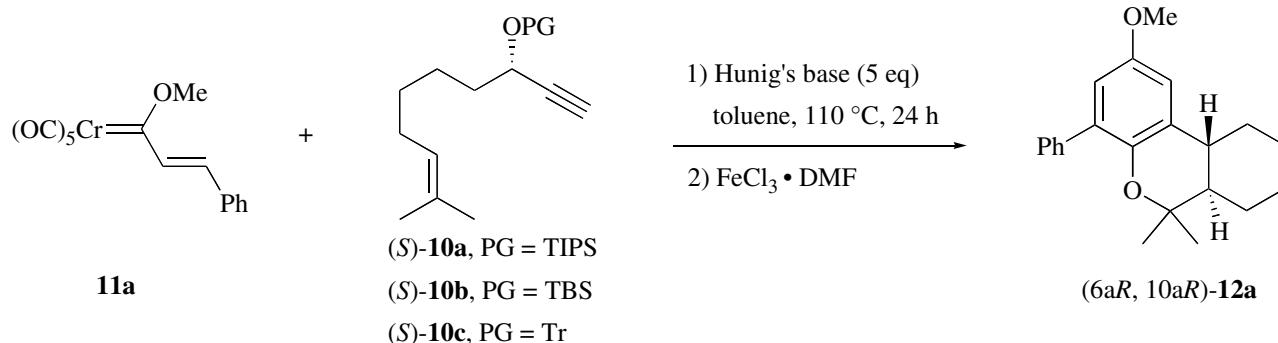
g, 13.9 mmol), methyllithium (10 mL, 1.4 mol/L in hexanes, 14 mmol), and ether (150 mL) were added to a 250 mL round bottom flask. This was stirred at reflux for 1.5 hours. The solvent was removed under reduced pressure. A flask was charged with this residue along with 150 mL of water, (*n*-Bu)<sub>4</sub>NBr (1 g, 3.1 mmol), and benzyl bromide (3.3 mL, 27.8 mmol). The solution was heated at 70 °C for three hours. The flask was cooled to room temperature. It was extracted with 3 x 200 mL of pentane. The organic layers were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure. Column chromatography (15 x 5.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.76 g (17 % yield, 2.36 mmol) of carbene complex **42**. A reaction that was setup side by side with the above reaction except using (*n*-Bu)<sub>4</sub>NI gave a 57 % yield. The spectroscopic properties of **42** were consistent with those reported in the literature.<sup>6</sup>



*Preparation of carbene complex 11c.* A magnetic stirring bar was placed into a flame-dried single neck flask (50 mL) that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. The flask was charged with aldehyde **41** (0.11 g, 0.8 mmol), carbene complex **42** (0.23 g, 0.7 mmol), ether (10 mL), TMSCl (0.4 mL, 3.2 mmol), and triethyl amine (0.3 mL, 2.2 mmol). Three freeze thaw cycles were done. The solution turned red in color in 10 minutes after the triethyl amine was added. The reaction was stirred overnight and was blood red the next day. The contents of the flask were poured onto 5 cc of silica gel and the solvent was removed under reduced pressure. Column chromatography (25 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave a red oil. A second column (10 cm x 2.8 cm, silica gel) was done with hexane until the yellow band came off the column then 5 % ethyl acetate / hexane was used to isolate the red band by elution. This gave 0.11 g of a red

oil which solidified upon standing. The resulting solid was triturated with hexanes and the hexanes were decanted. The remaining solid was used without further purification. The yield was 20 % (0.064 g, 0.14 mmol) after the trituration of carbene complex **11c**. Spectral data for **11c**:  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ )  $\delta$ : 6.11 (s, 2 H), 6.83 (d, 1 H,  $J = 15.1$  Hz), 7.14 - 7.64 (m, 10 H), 8.11 (d, 1 H,  $J = 15.0$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 82.30, 111.87, 115.98, 116.56, 122.13, 123.90, 127.62, 128.81, 129.06, 129.28, 129.37, 135.37, 138.80, 152.94, 156.50, 217.10, 225.16, 330.34; IR (thin film): 2921 w, 2858 w, 2056 m, 1931 s  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 454  $\text{M}^+$  (5), 370 (20), 307 (51), 289 (22), 136 (74); HRMS calcd for  $\text{C}_{23}\text{H}_{14}\text{CrO}_7$   $m/z$  454.0145, meas 454.0142. Dark solid (hexane), mp 114 - 120  $^\circ\text{C}$ ,  $R_f = 0.55$  (30 % ethyl acetate / hexane).

### General Procedure for the One-Pot Construction of Hexahydrodibenzopyrans – Illustrated for (6a*R*,10a*R*)-12a.



*Benzannulation/Heteroatom Diels-Alder Reaction with Oxidative Workup*. To a 50 mL flask which had the standard 14/20 tapered joint replaced with a threaded high vacuum Teflon valve was added toluene (8 mL), styryl carbene complex **11a** (82 mg, 0.24 mmol), alkyne **10** (0.28 mmol), and Hunig's base (0.21 mL, 5 equiv). The flask was deoxygenated by the freeze-thaw method (3 cycles) and then the flask was back-filled with argon. The flask was sealed at room temperature by closing the valve and then the flask was heated for 24 hours at 110  $^\circ\text{C}$ .

The solvent was removed by reduced pressure. The contents of the flask were taken up in 2 to 3 aliquots of 2 - 3 mL of DMF and transferred to a 20 mL vial. To this vial was added a solution of DMF•FeCl<sub>3</sub> complex (freshly made by adding 250 mg of FeCl<sub>3</sub>•6H<sub>2</sub>O to 4 mL of DMF and stirred for 30 minutes) and the solution stirred until the TLC indicated that the yellow chromium tricarbonyl arene complex was gone; note that the TLC streaked from the FeCl<sub>3</sub> which could be substantially reduced by quenching the aliquot with water prior to running the TLC. The oxidation with DMF•FeCl<sub>3</sub> general took about 30 minutes. To this solution was then added 10 to 15 mL of water and the solution was stirred 30 minutes. The solution was then extracted with CH<sub>2</sub>Cl<sub>2</sub>. Filtration through a 12 x 4.5 cm column of silica gel with 20 % ethyl acetate / hexane was followed by the solvent removal under reduced pressure. Preparative TLC on 1000 μm silica gel with fluorescent indicator was done with 20 % chloroform / hexane. The TLC plate was developed three times. The band that contained the product was scraped from the TLC plate and stirred with 15 mL of methanol. The solution was filtered through a glass-fritted funnel with Celite eluting with methanol and then CH<sub>2</sub>Cl<sub>2</sub>. The solvent was removed under reduced pressure. The remaining residual was taken up in CH<sub>2</sub>Cl<sub>2</sub> and filtered through a glass-fritted funnel with Celite and the resulting solvent was again removed under reduced pressure. This gave 0.045 g (58 %, 0.14 mmol) of the product (6aR,10aR)-**12a**. Also found by scraping the remainder of the TLC plate and washing the silica with methanol as above was 0.045 g of a complex mixture.

To make the system "one-pot" the DMF•FeCl<sub>3</sub> solution could be added directly to the reaction flask either with the toluene present or after it was removed under reduced pressure. With the toluene present, the reaction took 3 to 4 hours.

The enantiomeric excess was measured by HPLC analysis of phenol **43** obtained by demethylation or debenzoylation of **16** as described below. The absolute stereochemistry was

assigned by a mechanistic argument based on the stereochemistry previously obtained for similar systems in the literature.<sup>7</sup>

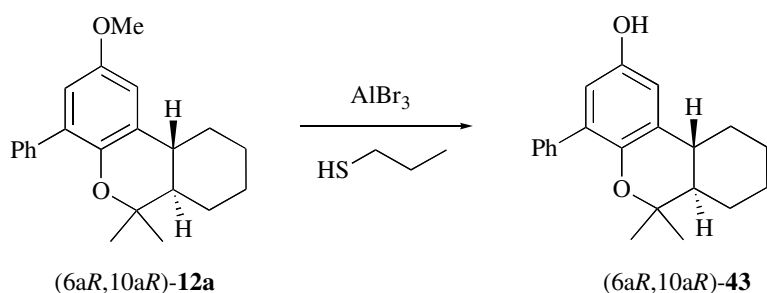
Other results of PG = TBS were preformed. At 90 °C with PG = TBS for 24 hours, the yield was 39 % with an ee of 94 %. At 100 °C with PG = TBS for 24 hours, the yield was 39 % with an ee of 94 %. At 100 °C for 48 hours, the yield was 51 % with 92 % ee. At 110 °C with PG = TBS for 24 hours, the yield was 58 % with 88 % ee.

A similar procedure was followed for the TIPS and Tr versions under identical conditions. At 90 °C with PG = TIPS for 24 hours, the yield was 42 % with an ee of 94 %. At 100 °C with PG = TIPS for 48 hours, the yield was 60 (average of two runs) with an ee of 90 %. At 110 °C with PG = TIPS for 24 hours, the yield was 48 % with an ee of 92 %. At 100 °C with PG = Tr for 48 hours, the yield was 45 % (average of two runs) with 86 % ee (average of two runs).

The stereochemistry of the ring junction was determined to be trans based on the coupling constants measured for the benzylic hydrogen on the corresponding chromium tricarbonyl complex **44b** which is described below. The benzylic proton in **12a** appears as a multiplet. The diastereomeric ratio for **12a** could be determined using GC/FID. With a reaction temperature of 110 °C or below the amount of the cis diastereomer was < 5%. The retention time was 7.0 minutes for the minor and 8.8 minutes for the major isomer. The temperature program was 80 °C for 1 minute then ramped to 230 °C at 10 °C / minute using an Alltech Econo-Cap SE54 column (30 m x 0.32 mm x 1.2 µm) with a 5 mL/min flow rate (no split).

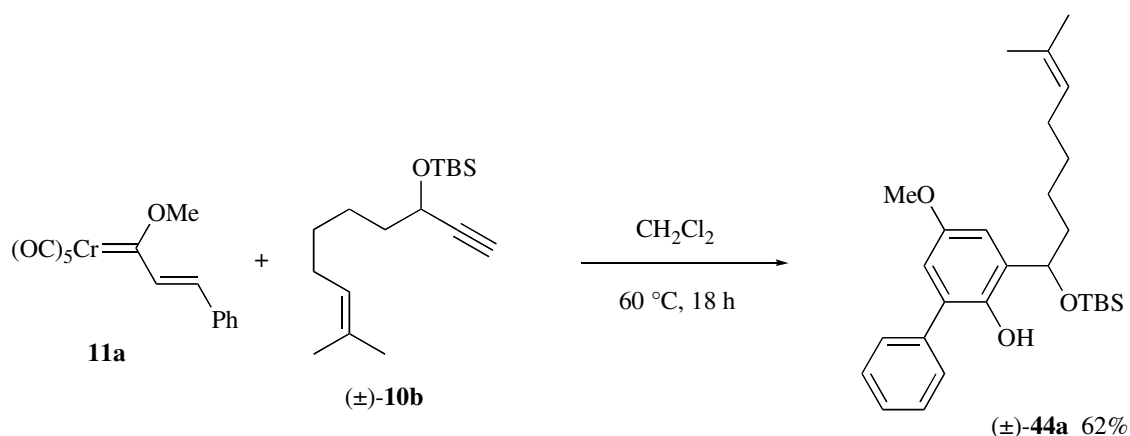
The retention time for GC/MS was 21.6 minutes (minor) and 22.7 minutes. The temperature program was 60 °C for 2 minutes then ramped to 260 °C at 10 °C / minute using a CP-SIL 8 low bleed column (30 m x 0.25 mm) with a 5 mL/min flow rate (1/20 split ratio). The integration between the MS and FID were consistent.

Spectral data for (6a*R*,10a*R*)-**12a**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.00 – 1.11 (m, 1 H), 1.15 (s, 3 H), 1.20 – 1.72 (m, 4 H), 1.30 (s, 3 H), 1.87 (m, 3 H), 2.37 – 2.47 (m, 2 H), 3.82 (s, 3 H), 6.75 (d, 1 H,  $J = 3$  Hz), 6.80 (d, 1 H,  $J = 3.0$  Hz), 7.20 – 7.60 (m, 5 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 20.06, 26.19, 26.36, 27.69, 27.76, 31.44, 36.79, 47.27, 55.79, 76.81, 111.00, 114.25, 126.43, 126.87, 127.69, 129.78, 130.33, 139.0, 144.25, 152.60; IR (thin film): 2926 s, 2853 m, 1464 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 323  $[\text{M}+1]^+$  (26), 322  $\text{M}^+$  (100), 280 (47), 238 (4), 215 (s); Anal calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_2$ : C, 81.95; H, 8.13. Found; C, 81.61; H, 8.34. Yellow solid (hexane), mp 92 - 95  $^\circ\text{C}$ ,  $R_f = 0.66$  (30 % ethyl acetate / hexane). For optically active material,  $[\alpha]_D^{22} +12.0^\circ$  (c 0.11,  $\text{CH}_2\text{Cl}_2$ ) at 94 % ee.



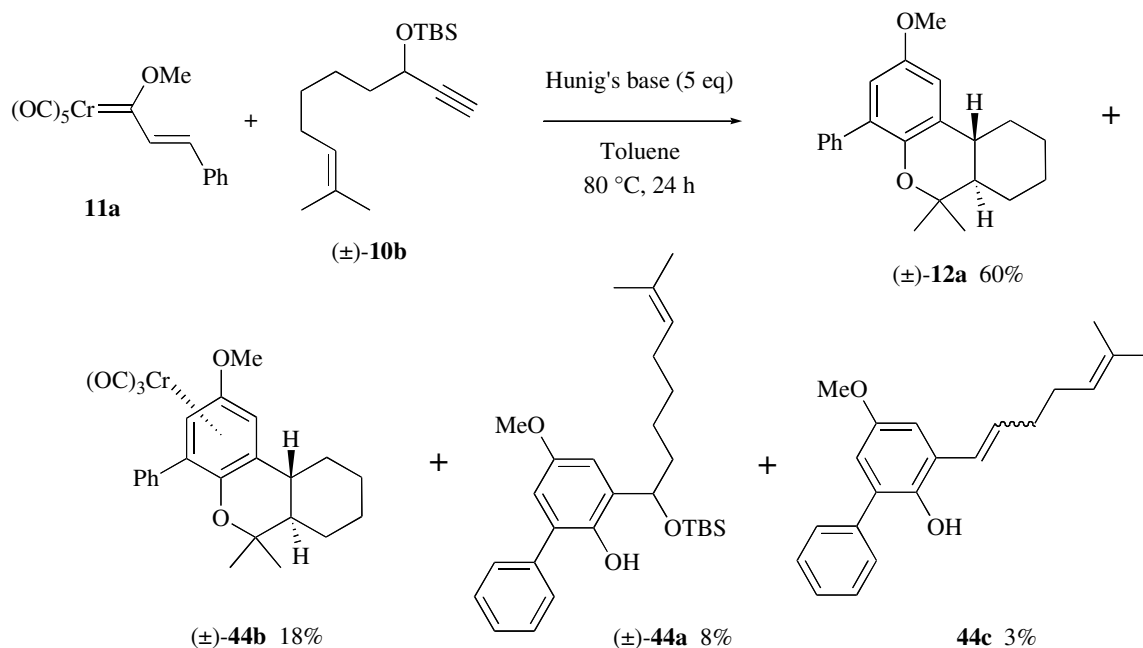
**Demethylation of (6a*R*,10a*R*)-**12a**.** A 20 mL vial was charged with 0.056 g (0.17 mmol) of compound (6a*R*,10a*R*)-**12a** and 4 mL of propane thiol. To this solution was added  $\text{AlBr}_3$  until the starting material was gone by TLC; a spatula at a time was added and reaction was stirred for 15 minutes in between. Column chromatography (15 x 1.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.022 g (70 %, 0.119 mmol) of (6a*R*,10a*R*)-**43**. The enantiomeric excess was determined to be 94 % ee for compound (6a*R*,10a*R*)-**43**. The enantiomeric excess could be determined by HPLC with Chiralpac AD column with 98 : 2 (hexane to isopropanol) with retention times of 42.3 minutes for the minor and 48.01 minutes for the major. Spectral data for (6a*R*,10a*R*)-**43**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.94 - 1.11 (m, 1 H), 1.11 (s, 3 H), 1.14 - 1.20 (m, 1 H), 1.21 - 1.47 (m, 3 H), 1.26 (s, 3 H), 1.73 - 1.93 (m, 3 H), 2.30 - 2.44 (m,

2 H), 4.70 (br s, 1 H), 6.65 (d, 1 H,  $J = 2.8$  Hz), 6.69 (d, 1 H,  $J = 2.8$  Hz), 7.20 - 7.28 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.49 - 7.54 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 19.97, 26.12, 26.28, 27.67, 27.76, 31.30, 36.59, 47.08, 76.80, 111.92, 115.70, 126.56, 127.06, 127.66, 129.60, 130.55, 138.66, 144.19, 148.18; IR (thin film): 3362 m, 2930 s, 2857 m, 1456 m, 1429 m, 1262 m, 1144 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 308  $[\text{M}+1]^+$  (84), 265 (100), 237 (21), 223 (24), 212 (14), 199 (60), 183 (24), 165 (13), 153 (14), 109 (67), 77 (60), 42 (95); Beige solid (hexane), mp 46 - 48 °C,  $R_f = 0.48$  (30 % ethyl acetate / hexane).  $[\alpha]_{20}^D -28.5^\circ$  (c 0.745,  $\text{CH}_2\text{Cl}_2$ ) at 88 % ee.



*Benzannulation/Heteroatom Diels-Alder Reaction without an Oxidative Workup and without a Base.* In a 50 mL single necked flask which had its standard 14/20 tapered joint replaced with a threaded high vacuum Teflon valve was added styryl carbene complex **11a** (104.3 mg, 0.31 mmol), alkyne (±)-**10b** (84.2 mg, 0.30 mmol), and  $\text{CH}_2\text{Cl}_2$  (5 mL). The contents of the flask were deoxygenated by the freeze-thaw method (3 cycles) and then opened to an argon atmosphere on the last cycle. The flask was heated at 60 °C for 18 hours. The contents of the reaction flask were stirred open to the air for 24 hours. Column chromatography (25 cm x 1.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 87.1 mg of compound (±)-**44a** (62 % yield, 0.186 mmol). Alternatively, the chromium tricarbonyl arene complex could first be isolated in 48 % yield without doing the air oxidation (chromium arene

was too unstable to fully characterize) and then the chromium arene complex could be air oxidized to the free phenol in 14 % yield by stirring in air for 2 days in acetonitrile. Spectral data for **44a**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.01 (s, 3 H), 0.12 (s, 3 H), 0.88 (s, 9 H), 1.10-1.48 (m, 4 H), 1.56 (s, 3 H), 1.65 (s, 3 H), 1.66-2.00 (m, 4 H), 3.76 (s, 3 H), 4.68 (t, 1 H,  $J = 6.0$  Hz), 5.06 (t, 1 H,  $J = 7.1$  Hz), 6.46 (d, 1 H,  $J = 3.0$  Hz), 6.75 (d, 1 H,  $J = 3.0$  Hz), 7.27-7.28 (m, 1 H), 7.29-7.40 (m, 2 H), 7.54-7.57 (m, 2 H), 7.86 (s, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -5.06, 17.65, 18.15, 25.52, 25.71, 27.87, 29.58, 38.17, 55.74, 77.71, 112.35, 114.22, 124.51, 126.96, 128.09, 129.37, 129.44, 130.10, 131.43, 138.46, 146.41, 152.31; IR (thin film) 3359 m, 2932 s, 2857 s, 1601 w, 1466 m, 1424 m, 1256 w, 1049 w, 837 w  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 455  $[\text{M}+1]^+$  (0.08), 454  $\text{M}^+$  (0.3), 379 (0.6), 322 (20), 314 (2), 279 (21), 251 (5), 237 (9), 226 (10), 213 (30), 109 (15), 75 (100); Yellow oil (hexane),  $R_f = 0.63$  (30 % ethyl acetate/ hexane).



### *Benzannulation/Heteroatom Diels-Alder Reaction without an Oxidative Workup.*

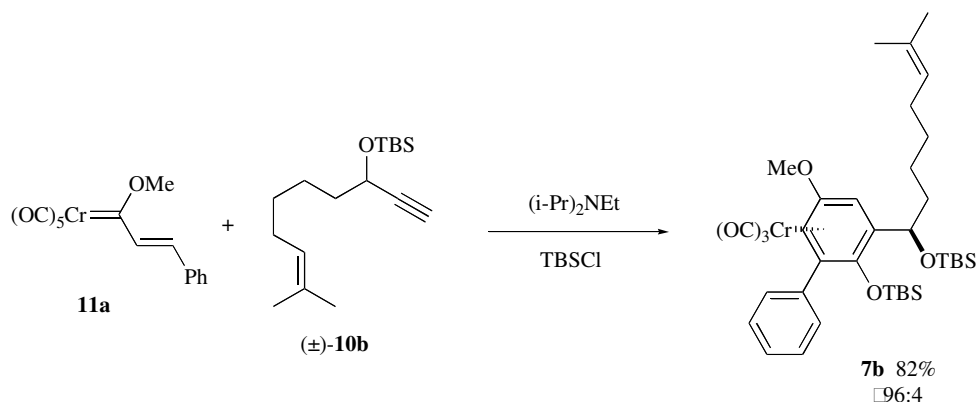
To a 50 mL round bottom single-necked flask which had the 14/20 standard tapered joint replaced with a threaded high vacuum Teflon valve was added styryl carbene complex **11a** (0.105 g, 0.31 mmol), alkyne **(±)-10b** (0.092 g, 0.33 mmol), Hunig's base (0.26 mL, 1.5 mmol), and toluene (10 mL). The contents of the flask were deoxygenated by the freeze-thaw method

(3 cycles) and then opened to an argon atmosphere on the last cycle. The reaction was heated at 80 °C for 24 hours. To the contents of the flask was added 20 mL of dichloromethane and the reaction was stirred for 4 days open to air. The contents of the flask were poured onto 2 - 4 cc of silica gel and the solvent removed under reduced pressure. The silica gel was dry loaded onto the top of a column. Column chromatography (30 cm x 1.8 cm, silica gel) with hexane as eluent and then with 5 % ethyl acetate / hexane as eluent gave two bands. The first band (0.079 g) was an inseparable 20:2.6:1 mixture of three compounds. The second yellow band was isolated to give 0.026 g (18% yield) of one pure compound identified as the chromium tricarbonyl complex ( $\pm$ )-**44b** which was obtained as a yellow-orange paste and as a single diastereomer. Spectral data for **44b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.15-1.37 (m, 3 H), 1.24 (s, 3 H), 1.34 (s, 3 H), 1.40-1.56 (m, 2 H), 1.73-1.97 (m, 3 H), 2.36 (br d, 1 H,  $J = 12.0$  Hz), 2.58 (td, 1 H,  $J = 11.5, 3.7$  Hz), 3.68 (s, 3 H), 5.30 (d, 1 H,  $J = 2.5$  Hz), 5.45 (d, 1 H,  $J = 2.5$  Hz), 7.32-7.42 (m, 3 H), 7.62 (dd, 2 H,  $J = 8.1, 1.5$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.18, 26.09, 26.23, 27.68, 27.77, 31.27, 36.40, 46.93, 55.78, 75.64, 80.17, 84.42, 94.49, 120.09, 127.70, 128.24, 129.54, 130.25, 134.35, 135.51, 233.07; IR (thin film) 2985m, 2936m, 2859m, 1952vs, 1869vs, 1456m, 1420m, 1200m, 1140m, 1038m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity,  $\text{FAB}^+$ ) 458  $\text{M}^+$  (64), 374 (100); HRMS calcd for  $\text{C}_{25}\text{H}_{26}\text{CrO}_5$   $m/z$  458.1185, meas 458.1187.  $R_f = 0.47$  (30 % ethyl acetate / hexane).

Two of the compounds in the first band were identified as **12a** and **44a** from the  $^1\text{H}$  NMR spectrum of the mixture with the aid of pure samples of **12a** and **44a** obtained as described above. The major component in the mixture was **12a** and the minor component was tentatively identified as the elimination product **44c** based upon the  $^1\text{H}$  NMR spectrum of a partially enriched sample. The yields of compounds ( $\pm$ )-**12a**, ( $\pm$ )-**44a**, and **44c** were calculated by integration of the  $^1\text{H}$  NMR. The calculated yield for compound ( $\pm$ )-**12a** was 60 % (0.20



mmol, 0.064 g) by integrating the region at 6.75 ppm (1 H) and subtracting the region at 5.06 ppm due to overlap of peaks at 6.75 ppm. The calculated yield of compound ( $\pm$ )-**44a** was 8 % (0.026 mmol, 0.012 g) by integrating the region at 5.06 ppm (1 H). The calculated yield of compound **44c** was 3 % (0.0099 mmol, 0.003 g) by integrating the region from 6.20 to 6.31 ppm (1 H). The mixture could be partially enhanced in **44c** by preparative TLC on 1000  $\mu$ m silica gel with fluorescent indicator with 10 % chloroform/hexane. The TLC plate was developed five times with this eluent and the second band from the top was taken. The  $^1\text{H}$  NMR spectra data of **44c** could be extracted from the spectra of the two mixtures of ( $\pm$ )-**12a**, ( $\pm$ )-**44a**, and **44c** in different ratios. Compound **44c** appeared to be a mixture of E and Z isomers but after the preparative TLC it appears to be the E-isomer. Spectral data for **44c**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.77-1.6 (m, 2 H, overlapped with other peaks), 1.60 (s, 3 H), 1.68 (s, 3 H), 2.03 (q, 2 H,  $J = 7.8$  Hz), 2.18-2.30 (m, 2 H), 3.78 (s, 3 H), 4.96 (s, 1 H), 5.13 (br t, 1 H,  $J = 7.2$  Hz), 6.25 (dt, 1 H,  $J = 17, 7$  Hz), 6.59-6.81 (m, 1 H), 6.67 (d, 1 H,  $J = 3.1$  Hz), 6.93 (d, 1 H,  $J = 3.0$  Hz), 7.20-7.60 (m, 5 H);  $R_f = 0.65$  (30 % ethyl acetate / hexanes).

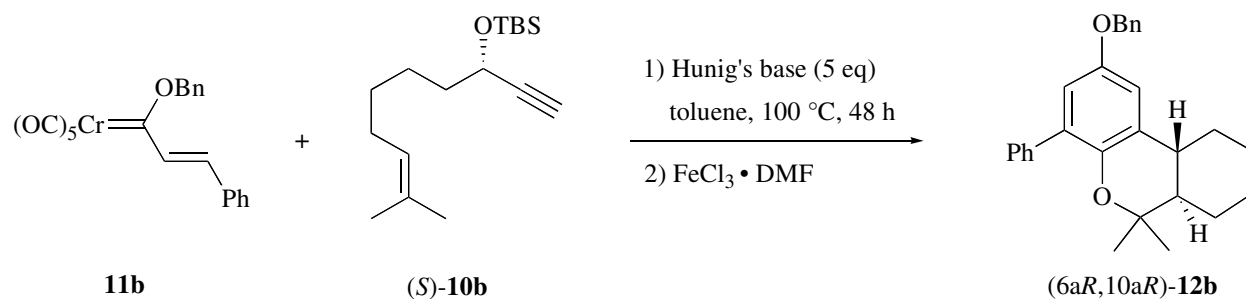


*Benzannulation/Heteroatom Diels-Alder Reaction in the Presence of a Trapping Agent.*

In a 50 mL round bottom flask which had its standard tapered joint replaced with a threaded high vacuum Teflon valve was added styryl carbene complex **11a** (97 mg, 0.34 mmol),  $\text{CH}_2\text{Cl}_2$  (5 mL), racemic alkyne ( $\pm$ )-**10b** (97 mg, 0.34 mmol), Hunig's base (0.3 mL), and TBSCl (154 mg, 1.0 mmol). The flask was deoxygenated by the freeze-thaw method (3 cycles). The flask

was opened to argon and sealed at room temperature by closing the valve. The flask was heated at 60 °C for 17 hours. The contents of the flask were poured onto silica (2 cc) and the solvent removed under reduced pressure. Column chromatography (26 cm x 1.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 187 mg of compound **7b** as a yellow-orange oil (82 % yield, 0.28 mmol). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra indicated the presence of a single diastereomer (dr  $\geq 96:4$ ). Spectral data for **7b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -0.41 (s, 3 H), -0.14 (s, 3 H), -0.07 (s, 3 H), 0.07 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 1.2 – 1.44 (m, 4 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 1.8 – 2.1 (m, 4 H), 3.65 (s, 3 H), 4.76 (d, 1 H,  $J = 9.8$  Hz), 5.13 (m, 1 H), 5.49 (d, 1 H,  $J = 2.4$  Hz), 5.77 (d, 1 H,  $J = 2.4$  Hz), 7.24 – 7.54 (m, 5 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -4.65, -4.35, -4.23, -4.01, 17.64, 18.01, 18.64, 25.68, 26.00, 26.76, 27.87, 29.52, 41.30, 56.33, 68.07, 81.41, 86.96, 103.75, 110.21, 124.60, 128.25, 128.53, 128.60, 128.78, 130.13, 130.98, 131.38, 132.66, 132.81, 133.39, 135.40, 233.99; Yellow-orange oil (hexane),  $R_f = 0.59$  (30 % ethyl acetate / hexane).

### One-Pot Construction of the Hexahydrodibenzopyran (**6aR,10aR**)-**12b**.

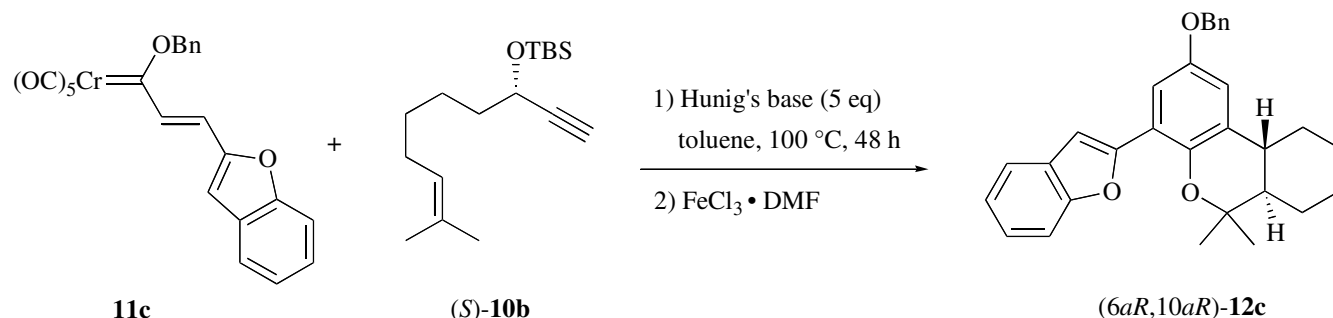


*Benzannulation/Heteroatom Diels-Alder with Oxidative Workup.* Following procedure described above for the reaction of complex **11a** with enyne **10**, the reaction of carbene **11b** (0.075 g, 0.18 mmol) and alkyne (**S**)-**10b** (0.066 g, 0.206 mmol) was carried at 100 °C and 48 hours and gave a 48% yield (0.034g, 0.085 mmol) of (**6aR,10aR**)-**12b** with 93 % ee. The



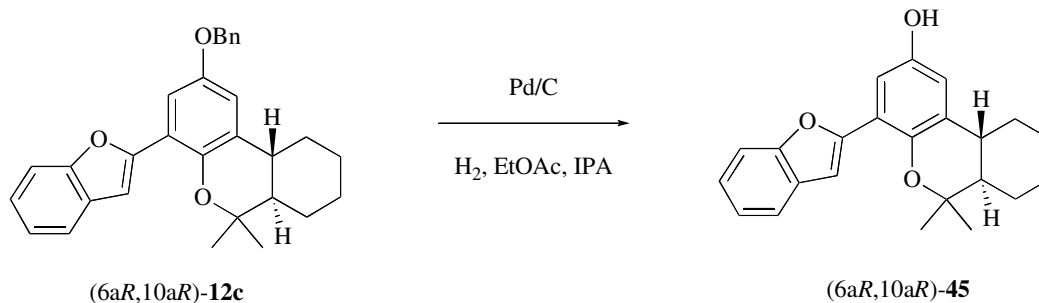
enantiomeric excess was determined by using a Chiralpac AD column with a flow rate of 0.7 mL / minute and 97:3 hexane / isopropanol. The retention times were 26.5 minutes and 29.5 with the major peak at 29.5 minutes (97:3 hexane / isopropanol).

### One-Pot Construction of the Hexahydrodibenzopyran (*6aR,10aR*)-**12c**.



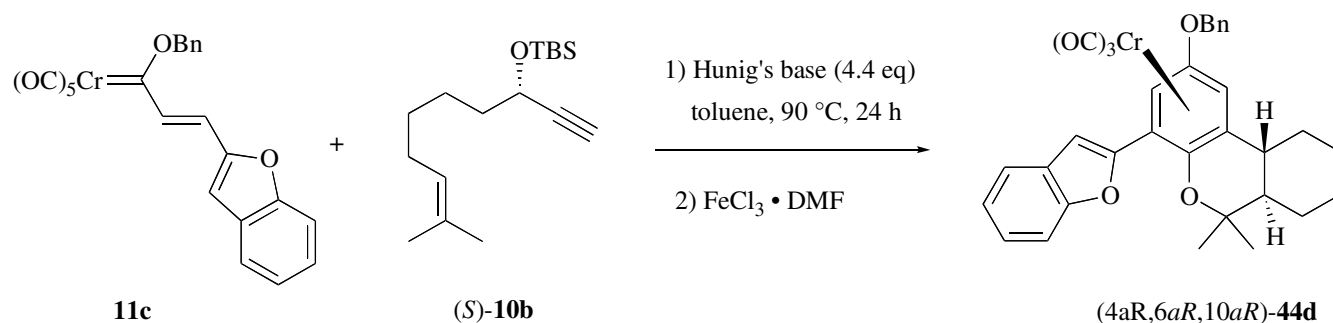
*Benzannulation/Heteroatom Diels-Alder Reaction with Oxidative Workup.* Following the procedure described above for the reaction of carbene complex **11a** and enyne **10**, the alkyne (*S*)-**10b** (0.066 g, 0.205 mmol, 98 % ee) was reacted with complex **11c** at 100 °C for 48 hours to give a 48% yield (0.0375 g, 0.098 mmol) of (*6aR,10aR*)-**12c** with 93 % ee. The % ee was obtained after debenzylation to the phenol **45**. Spectral data for (*6aR,10aR*)-**12c**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.96 - 1.16 (m, 1 H), 1.15 - 1.37 (m, 2 H), 1.20 (s, 3 H), 1.42 - 1.54 (m, 3 H), 1.55 (s, 3 H), 1.86 - 1.94 (m, 2 H), 2.35 - 2.52 (m, 2 H), 5.09 (s, 2 H), 6.89 (d, 1 H), 7.14 - 7.30 (m, 2 H), 7.31 - 7.44 (m, 4 H), 7.45 - 7.55 (m, 3 H), 7.56 - 7.77 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 20.48, 26.09, 26.21, 27.67, 28.01, 31.22, 36.43, 46.92, 70.83, 77.89, 106.28, 110.54, 110.74, 113.77, 119.00, 120.99, 122.54, 123.92, 127.01, 127.71, 127.88, 128.52, 129.93, 137.43, 145.14, 151.89, 152.65, 153.74; IR (thin film): 2973 w, 2930 s, 2857 m, 1684 w, 1653 w, 1566 w, 1458 s, 1262 m, 1144 m, 1042 m, 739 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity,  $\text{ESI}^-$ ) 438  $\text{M}^+$  (62), 293 (72), 265 (100), 194 (54); Yellow solid (hexane), mp 62 - 64 °C,  $R_f$  = 0.62 (30 %

ethyl acetate / hexane). For chiral material,  $[\alpha]_D^{22} -33.8^\circ$  (c 1.405, CH<sub>2</sub>Cl<sub>2</sub>),  $[\alpha]_D^{22} -28.5^\circ$  (c 1.24, CH<sub>2</sub>Cl<sub>2</sub>).



**Debenzylation of (6aR,10aR)-12c.** A 10 mL flask was charged with (6aR,10aR)-12c (12.3 mg, 0.026 mmol), 2 mL of ethyl acetate, 2 mL of isopropanol, and 40 mg of 10 % Pd on carbon. The atmosphere was removed and replaced with hydrogen by first pulling a vacuum for less than a second and then introducing a hydrogen filled balloon. The reaction was stirred for two hours until the reaction mixture was complete by TLC. The reaction mixture was filtered through Celite and the organic solvent was removed under reduced pressure. Preparative TLC with 5 % ethyl acetate / hexane developed three times gave 9.7 mg of compound (6aR,10aR)-45 (99 % yield, 12.2 mmol, 91 % ee) as a beige solid. The enantiomeric excess was determined with 97 : 3 (hexane / isopropanol) with a Chiralpak AD. The retention times were 59 minutes (minor) and 70 minutes (major). Spectral data for (6aR,10aR)-45: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.00 - 1.59 (m, 5 H), 1.19 (s, 3 H), 1.54 (s, 3 H), 1.81 - 1.95 (m, 3 H), 2.32 - 2.48 (m, 2 H), 4.46 (br s, 1 H), 6.74 (d, 1 H, *J* = 2.6 Hz), 7.13 - 7.28 (m, 2 H), 7.37 - 7.42 (m, 2 H), 7.43 - 7.49 (m, 1 H), 7.56 - 7.61 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 20.42, 26.07, 26.19, 27.65, 27.99, 31.21, 36.37, 46.89, 77.85, 106.38, 110.69, 111.34, 113.10, 119.18, 121.02, 122.55, 123.98, 127.20, 129.86, 144.85, 148.22, 152.38, 153.72; IR (thin film): 3364 br m, 2928 s, 2857 m, 1456 s, 1262 m, 1142 m, 939 m cm<sup>-1</sup>; mass spectrum *m/z* (% rel intensity) 348 M<sup>+</sup> (11), 305 (7), 263 (2), 252 (1), 239 (4), 223 (2), 211 (1), 205 (2), 193 (2), 181 (2), 170 (6), 164 (2), 153 (2), 149 (5), 141 (8), 131 (6), 97 (10), 84 (12), 71 (17), 56 (52), 44

(100). Beige solid (hexane), mp 58 - 62 °C,  $R_f$  = 0.41 (hexane).  $[\alpha]_D^{22}$  -57.1° (c 0.40, CH<sub>2</sub>Cl<sub>2</sub>) at 91 % ee.

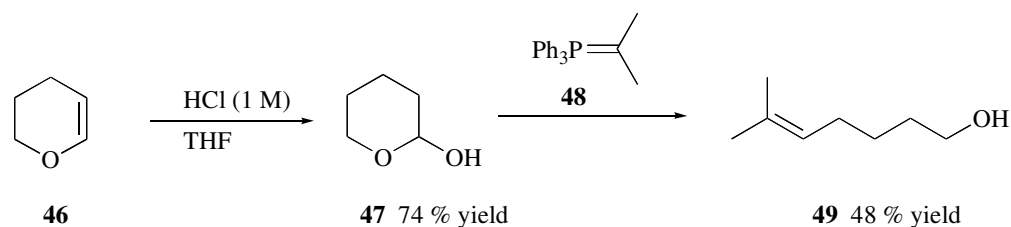


*Benzannulation/Heteroatom Diels-Alder Reaction without Oxidative Workup.* A

magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the 14/20 joint with a threaded high vacuum Teflon valve. The flask was charged with alkyne (*S*)-**10b** (0.070 g, 0.25 mmol, 98 % ee), carbene complex **11c** (0.105 g, 0.23 mmol), Hunig's base (0.2 mL, 1.1 mmol), and toluene (6 mL). The contents of the flask were deoxygenated by the freeze-thaw method (3 cycles) and opened to argon at room temperature on the last cycle. The Teflon valve was sealed and the flask was heated for 24 hours at 90 °C and then stirred two days at room temperature. The contents of the flask were taken up on silica gel and the solvent removed under reduced pressure. Column chromatography (20 x 2.2 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.046 g (35 % yield, 0.088 mmol) of compound **44d** which was a bright yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.01-1.20 (m, 2 H), 1.21-1.61 (m, 3 H), 1.45 (s, 3 H), 1.49 (s, 3 H), 1.78-1.89 (m, 3 H), 2.32 (br d, 1 H, *J* = 12.1 Hz), 2.62 (td, 1 H, *J* = 11.5, 3.8 Hz), 4.91 (d, 1 H, *J* = 10.6 Hz), 4.96 (d, 1 H, *J* = 10.6 Hz), 5.37 (d, 1 H, *J* = 2.4 Hz), 6.27 (d, 1 H, *J* = 2.5 Hz), 7.18-7.34 (m, 2 H), 7.35-7.53 (m, 7 H), 7.56-7.63 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 19.65, 25.59, 25.64, 27.34, 28.38, 30.76, 34.87, 46.71, 71.54, 76.22, 79.21, 81.17, 88.66, 94.95, 108.70, 111.07, 121.54, 123.07, 125.12, 126.78, 128.21, 128.62, 128.73, 129.00, 134.95, 135.23, 149.09, 154.01, 234.56; IR (thin film)

2973m, 2930s, 2857m, 1950vs, 1871vs, 1458s, 1144m, 739w  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity, +FAB) 574  $\text{M}^+$  (23), 438  $\text{M}^+ - \text{Cr}(\text{CO})_3$  (9), 399 (11), 347 (3), 329 (3), 303 (2); HRMS calcd for  $\text{C}_{33}\text{H}_{30}\text{CrO}_6$   $m/z$  574.1445, meas 574.1444. Orange solid (hexane), mp 55 - 60 (dec.)  $^{\circ}\text{C}$ ,  $R_f$  = 0.62 (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -477^{\circ}$  (c 0.055,  $\text{CH}_2\text{Cl}_2$ ) at 91 % ee.

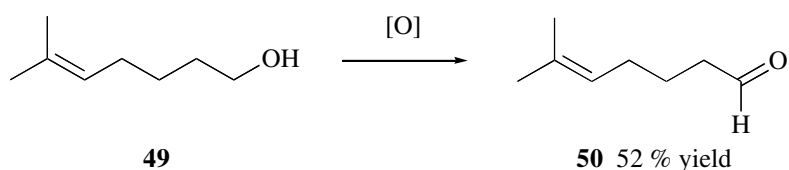
### Synthesis of Enyne 13.



*Preparation of alcohol 49.* Following a known literature preparation,<sup>8</sup> a 500 mL round bottom flask was charged with 3,4-dihydro-2H-pyran (20 mL, 21.9 mmol), THF (200 mL), and 1 M HCl (40 mL) at 0  $^{\circ}\text{C}$ . The contents of the flask were allowed to warm to room temperature and stirred for 4 hours. The solution was neutralized to pH ~7 with 3 M NaOH and extracted with 100 mL x 3 of ether. The ether layers were combined and extracted with 150 mL of brine, and the brine was back extracted with 50 mL of ether. The organic layers were combined. The solvent was dried with magnesium sulfate and filtered through Celite. The solvent was removed under reduced pressure. Kugelrohr distillation at 10 mm Hg and 120 - 160  $^{\circ}\text{C}$  gave 16.7 g (16.3 mmol, 74 % yield) of tetrahydro-2-hydroxy-2H-pyran as a clear oil. This compound was used without further purification. The spectroscopic properties were identical to that previously reported.<sup>8</sup>

A 2 L three neck round bottom was charged with isopropyltriphenylphosphonium iodide (95 g, 22.0 mmol), THF (1 L), potassium hydride (30 g, 22.4 mmol), and lastly tetrahydro-2-hydroxy-2H-pyran (22.3 g, 21 mmol) was added dropwise. The flask was equipped with a

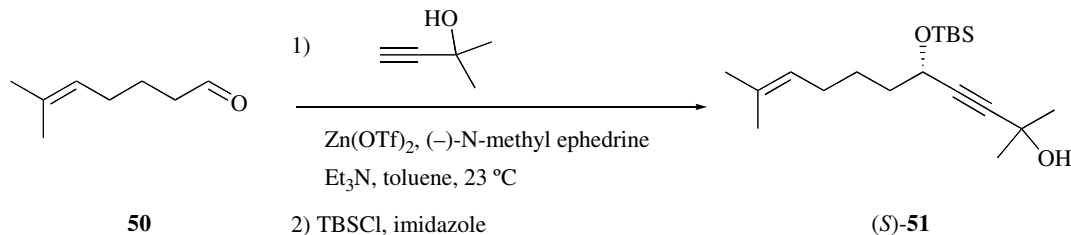
water-cooled reflux condenser. The unused necks of the flask were sealed with rubber septa. The contents of the flask were brought to reflux for three hours. The reaction mixture was cooled and poured into 100 mL of water and extracted with ether (50 mL x 3). The ether layers were combined and extracted with brine. The brine was extracted with 50 mL x 2 of ether. The ether layers were combined and dried with magnesium sulfate and filtered through Celite. The solvent was removed under reduced pressure. Column chromatography (30 cm x 4 cm, silica gel) with 30 % ethyl acetate / hexane gave 1.26 g (0.98 mmol, 48 % yield) of 6-methylhept-5-en-1-ol **49**. This compound was used without further purification and the spectroscopic properties were consistent with those previously reported.<sup>8</sup>



*Oxidation of **49** to aldehyde **50**.* A 500 mL round bottom flask was charged with DMSO (3.5 mL, 49.3 mmol) and dichloromethane. The contents of the flask were cooled to  $-78\text{ }^{\circ}\text{C}$  and oxalyl chloride (1.6 mL, 18.2 mmol) was added dropwise. The solution was stirred for 10 minutes while a gas was observed to evolve. The compound 6-methylhept-5-en-1-ol (2.1 g, 16.5 mmol) **49** was added dropwise to the flask. The contents of the flask were allowed to stir at  $-78\text{ }^{\circ}\text{C}$  for 20 minutes. Triethyl amine (11.6 g, 115 mmol) was then added. The reaction was stirred and warmed to room temperature over an hour. The contents of the reaction were poured into 300 mL of 1 M HCl and extracted. The layers were separated and the aqueous layer was extracted with 50 mL x 3 of dichloromethane. The organic layers were combined and extracted with brine. The brine layer was back extracted with 50 mL x 2 of dichloromethane. The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate. The solution was filtered through Celite. Column chromatography (23 x 4.3 cm, silica gel) of the residue with 10 % ethyl acetate / hexane gave 1.09 g (52 % yield, 8.7



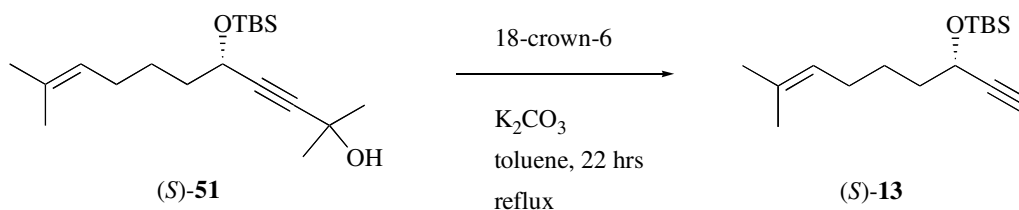
mmol) of **50** as a yellow oil. The spectroscopic properties were consistent with those previously reported.<sup>8</sup>



*Alkyynylation of aldehyde 50.*<sup>2</sup> A flask was charged with zinc triflate (5.45 g, 15.0 mmol), (–)-*N*-methyl ephedrine (2.846 g, 15.8 mmol), toluene (41 mL), and triethyl amine (2.2 mL, 15.8 mmol). This suspension was stirred for 2 hours at room temperature and 3-methyl-1-butyne-3-ol (1.5 mL, 15.5 mmol) was added. The reaction mixture was stirred for 15 minutes. The compound 2-methyl-2-hepten-7-al **50** (0.95 g, 7.5 mmol) was added as a 0.4 M solution in toluene over 4 hours via a syringe pump. After the addition, the solution was stirred an additional 30 to 45 minutes. The TLC was checked for completion of the reaction. The contents of the flask were poured into 100 mL of saturated ammonium chloride solution. The layers were separated and the organic layer collected. The aqueous layer was back extracted with 3 x 100 mL of DCM (ethyl acetate gave higher yields). The organic layers were combined and dried over solid sodium bicarbonate and magnesium sulfate. The solvent was filtered and removed under reduced pressure. Column chromatography (15 cm x 3.8 cm, silica gel) with 30 % ethyl acetate / hexane then 50 % ethyl acetate / hexane gave 1.04 g (66 % yield, 4.95 mmol) of the intermediate diol. This was not elementally pure and significant impurities were noted in the NMR. The compound was used without further purification to be cleaned-up in the next synthetic transformation.

A flask was charged with the diol, DMF (50 mL), imidazole (0.43 g, 6.2 mmol), and TBSCl (0.76 g, 5.03 mmol). The reaction mixture was stirred overnight at room temperature. The contents of the flask were poured into 100 mL of saturated ammonium chloride and back extracted with 3 x 50 mL DCM. The organic layers were combined and dried over sodium

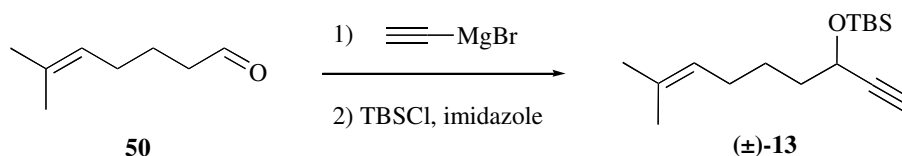
bicarbonate and magnesium sulfate. Column chromatography (25 cm x 4.3 cm, silica gel) with 5 % ethyl acetate / hexane gave 1.055 g (45 % yield over two steps, 3.38 mmol) of (*S*)-**51**. The enantiomeric excess was 98 % as determined after conversion to non-8-en-1-yn-3-ol. Spectral data for (*S*)-**51**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.08 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 1.32 - 1.45 (m, 2 H), 1.47 (s, 6 H), 1.55 - 1.68 (m, 2 H), 1.57 (s, 3 H), 1.66 (d, 3 H,  $J = 1.0$  Hz), 1.86 (br s, 1 H), 1.96 (q, 2 H,  $J = 7.2$  Hz), 4.32 (t, 1 H,  $J = 6.3$  Hz), 5.08 (br t, 1 H,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -4.95, -4.45, 17.67, 18.23, 25.52, 25.68, 25.80, 27.57, 31.33, 31.39, 38.22, 62.83, 65.10, 83.97, 88.50, 124.42, 131.59; IR (thin film): 3355 m, 2930 s, 2859 s, 1473 m, 1362 m, 1256 m, 1167 m, 1096 m, 837 m, 777 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 227  $\text{M}^+$ -97 (5), 224 (7), 210 (4), 207 (6), 185 (86), 167 (30), 157 (10), 149 (8), 143 (3), 123 (42), 99 (74), 75 (100), 67 (12), 59 (15); HRMS (Q-Tof) calcd for  $\text{C}_{19}\text{H}_{40}\text{NO}_2\text{Si}$  (+ $\text{NH}_4$ )  $m/z$  342.2828, meas 342.2818. Clear oil (hexane),  $R_f = 0.51$  (30 % ethyl acetate / hexane).  $[\alpha]_{\text{D}}^{20} -2.0^\circ$  (c 0.505,  $\text{CH}_2\text{Cl}_2$ ).



**Enyne (*S*)-13.** For the optically active material, a flask was charged with (*S*)-5-(*tert*-butyldimethylsilyloxy)-2,10-dimethylundec-9-en-3-yn-2-ol (*S*)-**51** (0.85 g, 2.6 mmol), toluene (30 mL), 18-crown-6 (0.81 g, 3.1 mmol), and potassium carbonate (0.41 g, 2.9 mmol). The reaction mixture was refluxed for 2 days under a constant and healthy stream of nitrogen gas. The reaction mixture was cooled and filtered through Celite. Column chromatography (25 x

4.4 cm, silica gel) with hexanes then 5 % ethyl acetate / hexane gave 0.68 g (97 %, 2.52 mmol) of (*S*)-**13**. The enantiomeric excess was determined to be 98 % ee after conversion to non-8-en-1-yn-3-ol. Spectral data for (*S*)-**13**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.09 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9H), 1.35 - 1.49 (m, 2 H), 1.58 (s, 3 H), 1.60 - 1.71 (m, 2 H), 1.67 (s, 3 H), 1.98 (q, 2 H,  $J = 7.2$  Hz), 2.35 (d, 1 H,  $J = 2.1$  Hz), 4.31 (td, 1 H,  $J = 6.5, 2.1$  Hz), 5.09 (t, 1 H,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -5.07, -4.58, 17.69, 18.22, 25.36, 25.70, 25.78, 27.58, 38.17, 62.71, 71.88, 85.74, 124.37, 131.66; IR (thin film): 3312 m, 2932 s, 2859 s, 1474 m, 1252 m, 1098 s, 839  $\text{m cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 266  $\text{M}^+$  (5), 265  $\text{M}^+ - 1$  (12), 251 (15), 209 (46), 173 (22), 167 (17), 135 (100), 107 (15), 93 (15); Clear oil (hexane),  $R_f = 0.25$  (100 % hexane),  $R_f = 0.75$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -34.7^\circ$  (c 0.825,  $\text{CH}_2\text{Cl}_2$ ) at 98 % ee.

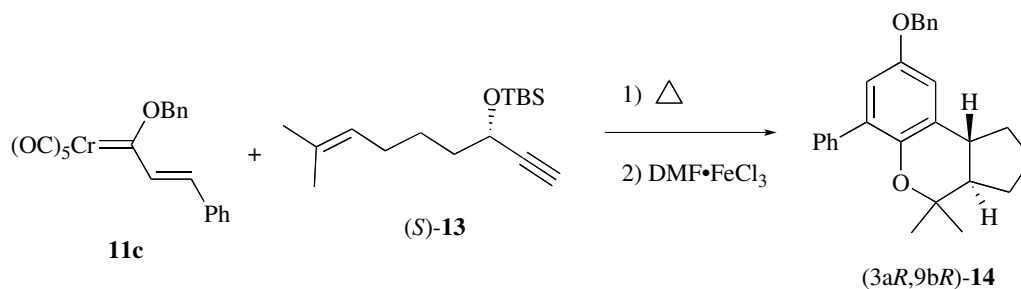
### Preparation of racemic ( $\pm$ )-**13**.



Aldehyde **50** (0.45 g, 3.6 mmol) (see preparation above) in THF (25 mL) was treated with ethynylmagnesium bromide (14 mL, 7.0 mmol) at  $-78\text{ }^{\circ}\text{C}$  and allowed to warm to  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $0\text{ }^{\circ}\text{C}$  for 1 hour. The reaction mixture was poured into 50 mL of saturated ammonium chloride and back extracted with ether (2 x 50 mL), brine (100 mL), ether (3 x 50 mL), and the organic layers were combined. The solvent was dried over solid sodium bicarbonate and magnesium sulfate. The solvent was removed under reduced pressure and the resulting propargyl alcohol was used without further purification. The spectroscopic properties of 8-methylnon-7-en-1-yn-3-ol were consistent with those previously reported.<sup>9</sup>

A 100 mL flask was charged with the residue from the above reaction (3.6 mmol) along with DMF (40 mL), imidazole (0.27 g, 4.0 mmol), and TBSCl (0.55 g, 3.6 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into 20 mL of water and back extracted with ethyl acetate (10 mL x 3). The organic layers were combined and dried over solid sodium bicarbonate and magnesium sulfate. The solution was then filtered through fluted filter paper and the remaining solvent was removed under reduced pressure. Column chromatography (20 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.69 g (72 %, 2.6 mmol) of ( $\pm$ )-**13**. The spectroscopic data matched those given above for (*S*)-**13**.

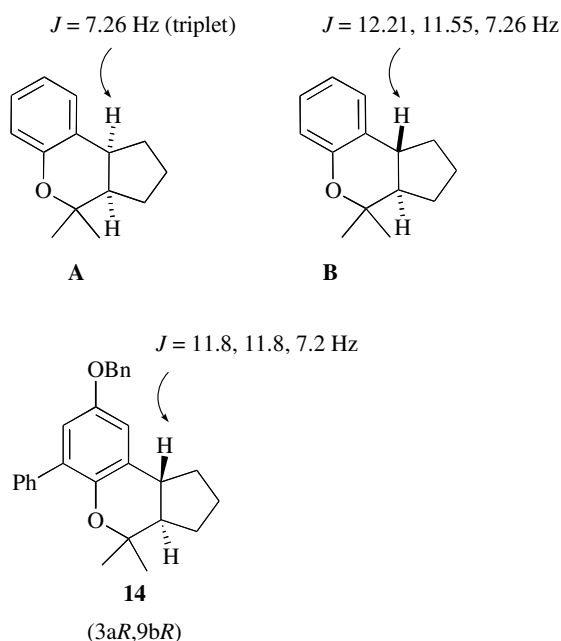
## One-Pot Construction of the Hexahydrocyclopentabenzopyran (**3a*R*,4*R***)-**14**.



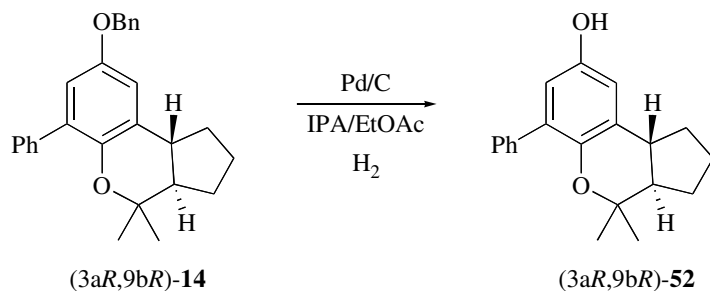
*Benzannulation/Heteroatom Diels-Alder.* Following the procedure reported above for the reaction of carbene complex **11a** and enyne **10**, the reaction of carbene complex **11c** (0.079 g, 0.192 mmol) with alkyne (**S**)-**13** (0.060 g, 0.225 mmol) was carried out at 100 °C and 48 hours to give (**3a*R*,9b*R***)-**14** in 43% yield (0.0315 g, 0.0819 mmol) with an ee of 94%. The trans to cis ratio was 93 : 7. The % ee and trans ratio were determined after debenzoylation to give (**3a*R*,9a*R***)-**52** as described below. Spectral data for (**3a*R*,9b*R***)-**14**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.22 (s, 3 H), 1.25 - 1.31 (m, 1 H), 1.39 (s, 3 H), 1.48 - 1.60 (m, 1 H), 1.64 - 1.75 (m, 1 H), 1.76 - 1.84 (m, 1 H), 1.85 - 1.96 (m, 1 H), 2.32 (dddd, 1 H,  $J = 11.3, 7.3, 7.3, 3.5$  Hz), 2.63 (ddd, 1 H,  $J = 11.8, 11.8, 7.2$ ), 5.02 (s, 3 H), 6.73 (d, 1 H,  $J = 3.6$  Hz), 6.85 (d, 1 H,  $J = 3.1$  Hz), 7.25 - 7.34 (m, 2 H), 7.35 - 7.41 (m, 4 H), 7.42 - 7.47 (m, 2 H), 7.54 - 7.60 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 20.81, 22.95, 25.91, 28.67, 29.16, 39.62, 51.35, 70.80, 78.89, 112.90, 115.16, 126.47, 127.58, 127.63, 127.80, 128.11, 128.49, 129.58, 137.51, 139.17, 145.05, 151.65 (one carbon missing); IR (thin film): 3032 w, 2965 s, 2872 s, 1601 m, 1456 s, 1422 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 385  $[\text{M}+1]^+$  (40), 293 (81), 275 (5), 251 (9), 237 (13), 199 (23), 181 (4), 152 (5), 91 (100); Beige solid (hexane), mp 108 - 112 °C,  $R_f = 0.60$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -21.5^\circ$  (c 1.39,  $\text{CH}_2\text{Cl}_2$ ) at 94 % ee.

For the hexahydrocyclopentabenzopyran ring system,<sup>10</sup> the *cis* compound **A** shows a triplet with  $J = 7.26$  Hz coupling constant at 3.26 ppm. For the *trans* compound **B**, a double of

doublets of doublets is observed with coupling constants of  $J = 12.21, 11.55,$  and  $7.26$  Hz. The coupling constants found in the current work are shown for compound (3a*R*,9b*R*)-**14** and are  $J = 11.8, 11.8,$  and  $7.2$  Hz.



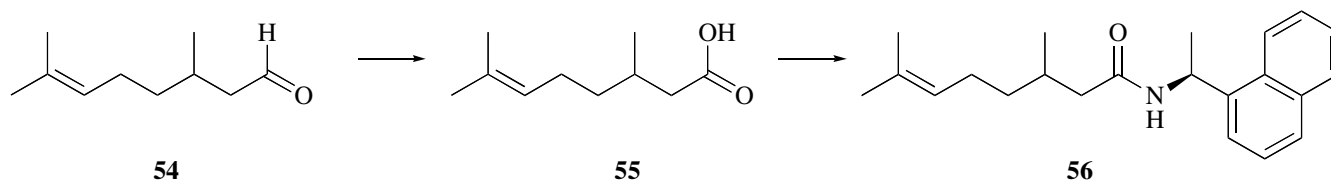
**Figure 1.** Coupling Constants for the cis and trans ring junctions.



**Debenzylation of 14.** A 10 mL flask was charged with 29 mg of compound (3a*R*,9b*R*)-**14** (0.08 mmol), 50 mg of 10 % Pd on carbon, 2 mL of isopropanol, and 2 mL of ethyl acetate. The atmosphere was replaced with hydrogen and the reaction mixture was stirred for 2 hours at room temperature. The carbon was removed by filtering through a Celite. This gave 0.016 g (0.053 mmol, 70 % yield) of compound (3a*R*,9b*R*)-**52**. This compound contained 7 % of the cis isomer (93 : 7 dr) as determined by integrating the peak at 6.7 ppm and 6.6 ppm in the <sup>1</sup>H

NMR. The enantiomeric excess was 94 % which was determined using HPLC with a Chiralpak AD column with retention times of 43 (major) and 51 minutes (minor) with a 98 : 2 hexane / isopropanol solvent mixture. With 99 : 1 hexane / isopropanol solvent mixture, the retention times were 100 minutes for the major peak and 122 minutes for minor peak. Spectral data for (3a*R*,9b*R*)-**52**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.20 (s, 3 H), 1.23 - 1.30 (m, 1 H, overlapping), 1.32 (s, 3 H), 1.49 (sex, 1 H,  $J = 10.7$  Hz), 1.69 (sex, 1 H,  $J = 5.9$  Hz), 1.83 - 1.94 (m, 2 H), 2.25 - 2.33 (m, 2 H), 2.59 (ddd, 1 H,  $J = 11.8, 11.8, 7.1$  Hz), 4.35 (s, 1 H), 6.56 (d, 1 H,  $J = 3.1$  Hz, sometimes appeared as a broad singlet), 6.66 (d, 1 H,  $J = 3.1$  Hz, sometimes appeared as a broad singlet), 7.23 - 7.30 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.51 - 7.57 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 20.79, 22.94, 25.90, 28.64, 29.15, 39.52, 51.31, 78.87, 112.68, 115.58, 126.57, 127.67, 128.32, 129.56, 129.82, 138.87, 144.79, 147.95; IR (thin film): 3343 m, 2959 s, 2926 s, 2872 s, 1603 w, 1454 m, 1417 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 294  $\text{M}^+$  (98), 279 (18), 251 (40), 225 (21), 212 (13), 209 (11), 199 (27), 181 (11), 177 (26), 165 (18); Beige oily solid (hexane),  $R_f = 0.1$  (10 % ethyl acetate / hexane),  $R_f = 0.35$  (30 % ethyl acetate / hexane).  $[\alpha]_{\text{D}}^{22} -15^\circ$  (c 0.095,  $\text{CH}_2\text{Cl}_2$ ) at 94 % ee.

### Preparation of Enyne (3*R*,5*S*)-15.



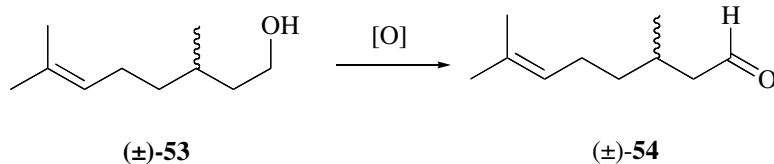
*Determination of the optical purity of commercial citronellal.* The analysis of optical purity of citronellal was conducted using known literature methods.<sup>11</sup> A 25 mL round bottom flask open to the air was charged with (*S*)-**54** (citronellal, 0.1 mL, 0.55 mmol) obtained from Aldrich, water (6 mL),  $\text{Ag}_2\text{O}$  (0.13 g, 0.556 mmol), and NaOH (0.10 g, 2.51 mmol). The

reaction mixture was heated at 70 °C for 30 to 45 minutes. The solution was then cooled to room temperature and acidified with concentrated HCl the saturated sodium bicarbonate was added until no further gas generation was noted. No further purification was done. This yielded 0.068 g (72 % yield, 0.40 mmol) of (*S*)-3,7-dimethyloct-6-enoic acid **55**.

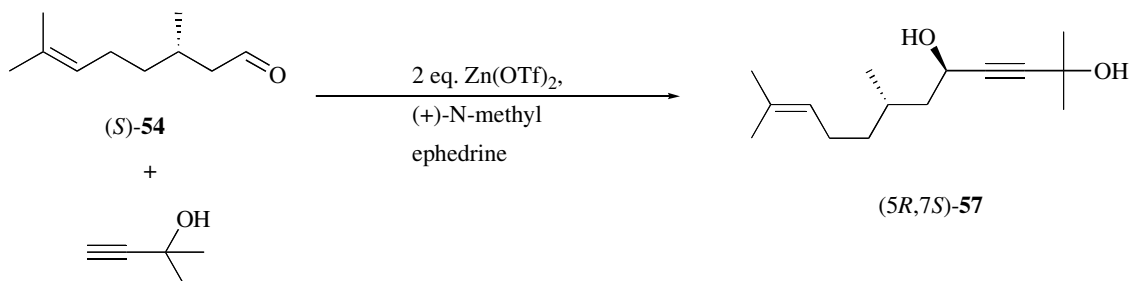
The (*S*)-3,7-dimethyloct-6-enoic acid (0.068 g, 0.40 mmol) in 5 mL of benzene was treated with 0.088 mL (0.144 g, 1.2 mmol) of thionyl chloride in a 10 mL round bottom flask. The reaction mixture was stirred for 30 minutes and then the solvent was removed under reduced pressure. Then 5 mL of ether was added to the residue and cooled to 0 °C. Then (*R*)-naphthyl ethyl amine (99.9 % ee, 0.13 mL, 0.81 mmol) was added. The mixture was stirred for one hour at 0 °C. The mixture was diluted with 100 mL of ether and washed successively with 1 M HCl (50 mL), saturated sodium bicarbonate (20 mL), water (10 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure. The resulting product was analyzed without further purification according to a literature procedure.<sup>12</sup> This gave a 62% yield (0.24 g, 0.74 mmol) of (*S*)-**56**. The enantiomeric excess was determined to be 96.4 % using HPLC with a Microsorb-MV 100 Å column. The solvent system was 97 % hexane and 3 % isopropanol. The retention times were 14.02 minute for the minor compound and 15.36 minutes for the major compound. The retention times were assigned by comparison to a sample of a mixture of diastereomers prepared from racemic citronellal whose preparation is shown below.

An identical procedure was followed for (*R*)-citronellal obtained from Aldrich which gave an ee of 86.5 % as determined from the de of the amide **56**. The yield of (*R*)-**55** was 61 % and the yield of **56** prepared from racemic citronellal was 50 %. The yield of racemic ( $\pm$ )-**55** was 68 % and the yield of **56** from racemic **55** was 56 %. On the basis of this analysis, all subsequent reactions were carried out on (*S*)-citronellal obtained from Aldrich which was 96.5% ee.



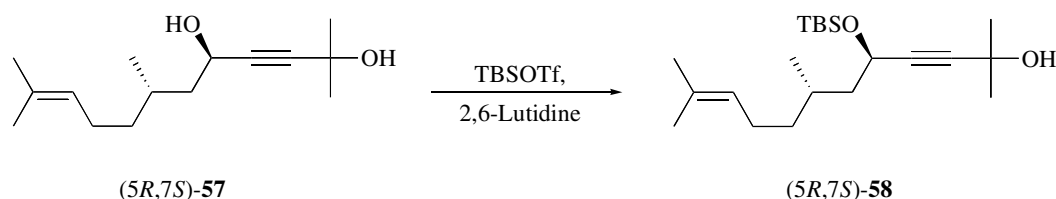


**Preparation of racemic citronellal ( $\pm$ )-54.** To a solution of DMSO (1.4 mL, 19.7 mmol) and dichloromethane (50 mL) at  $-78\text{ }^{\circ}\text{C}$  was added oxalyl chloride (0.6 mL, 6.87 mmol) in a 250 mL round bottom flask. This was stirred for 15 minutes and then 1.00 g (6.4 mmol) of racemic 3,7-dimethyloct-6-en-1-ol ( $[\alpha]_{\text{D}}^{22}$  0.00 (neat)) was added dropwise and the solution was stirred for 20 minutes at  $-78\text{ }^{\circ}\text{C}$ . Triethyl amine (6.24 mL, 44.8 mmol) was added. The reaction mixture was warmed to room temperature for 1 hour. Column chromatography (20 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.82 g (83 % yield, 5.33 mmol) of ( $\pm$ )-54. The spectroscopic properties were consistent with those of sample obtained from Aldrich.



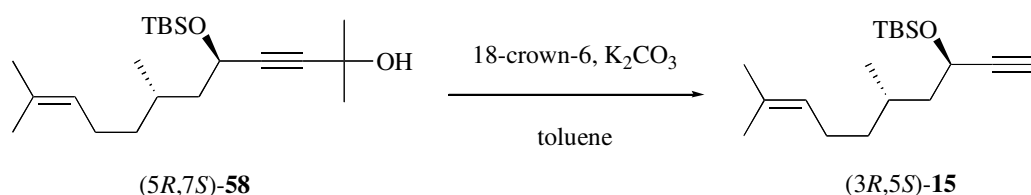
**Si-face alkynylation of (*S*)-citronellal 54.<sup>2</sup>** A 100 mL round bottom flask was charged with  $\text{Zn(OTf)}_2$  (6.57 g, 18.1 mmol), N-methyl ephedrine (3.58 g, 20.0 mmol), toluene (50 mL), and triethyl amine (2.51 mL, 18.0 mmol). The reaction mixture was stirred for 2 hours at room temperature and 2-methyl-3-butyn-2-ol (1.8 mL, 18.6 mmol) that had been previously distilled over calcium hydride was added. The solution was stirred for 20 minutes. Citronellal (*S*)-54 (1.6 mL, 8.8 mmol, 96.4 % ee) was added via syringe pump over 4 hours in 5 mL of toluene and the reaction mixture was stirred overnight. Column chromatography (30 x 3.5 cm, silica gel) with 30 % ethyl acetate / hexane to 50 % ethyl acetate / hexane gave 1.99 g (95 % yield, 8.36 mmol) of compound (*5R,7S*)-57. The ratio of diastereomers was  $\geq 20 : 1$  as determined by  $^1\text{H}$  NMR with the aid of a sample of the diastereomer (*5S,7S*)-59. Spectral data for

(5*R*,7*S*)-**57**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (d, 3 H,  $J$  = 6.7 Hz), 1.10 - 1.18 (m, 1 H), 1.27 - 1.37 (m, 1 H), 1.40 - 1.48 (m, 1 H), 1.48 (s, 6 H), 1.56 (s, 3 H), 1.63 - 1.76 (m, 2 H), 1.64 (s, 3 H), 1.88 - 2.01 (m, 2 H), 2.97 (br s, 2 H), 4.41 (dd, 1 H,  $J$  = 5.8 Hz, 7.8 Hz), 5.06 (br t, 1 H,  $J$  = 7.1 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 17.59, 19.22, 25.30, 26.64, 28.91, 31.29, 37.00, 45.04, 60.33, 64.93, 83.58, 89.32, 124.55, 131.18; IR (thin film): 3330 br s, 2969 s, 2926 s, 1456 m, 1377 m, 1237 w, 1165 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 223 (0.1), 220  $\text{M}^+ - 18$  (1), 205 (9), 187 (9), 177 (12), 163 (9), 145 (15), 135 (34), 121 (25), 107 (59), 95 (73), 82 (27), 67 (57), 56 (36), 42 (100); Thick clear oil (hexane),  $R_f$  = 0.13 (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} +10.3^\circ$  (c 1.13,  $\text{CH}_2\text{Cl}_2$ ) with > 20 : 1 dr.



*TBS protection of the diol (5*R*,7*S*)-57.* A 100 mL round bottom was charged with dichloromethane (30 mL), compound (5*R*,7*S*)-**57** (1.0 g, 4.2 mmol), and 2,6-lutidine (0.58 mL, 5 mmol). The reaction mixture was cooled to 0 °C and TBSOTf (0.95 mL, 4.1 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at 0 °C and 20 mL of saturated ammonium chloride was added. The reaction was extracted with dichloromethane, 10 mL of saturated bicarbonate with back extraction of 10 mL x 3, and the organic layers were dried over magnesium sulfate. Column chromatography (22 x 4.1 cm, silica gel) with hexane then 5 % ethyl acetate / hexane and then 10 % ethyl acetate / hexane gave 1.05 g (72 % yield, 3.00 mmol) of (5*R*,7*S*)-**58**. The diastereomeric ratio was  $\geq 96 : 4$  as determined by  $^1\text{H}$  NMR. Spectral data for (5*R*,7*S*)-**58**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.08 (s, 3 H), 0.11 (s, 3 H), 0.84 (d, 3 H, peak overlap), 0.87 (s, 9 H), 1.06 - 1.39 (m, 4 H), 1.47 (s, 6 H), 1.56 (s, 3 H), 1.65 (s, 3 H),

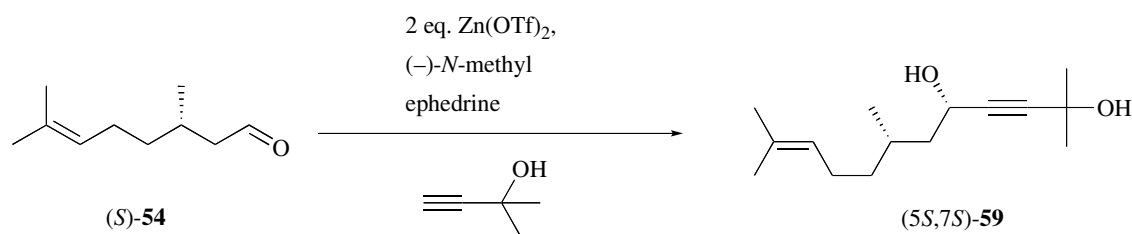
1.66 - 1.77 (m, 1 H), 1.95 (q, 2 H,  $J = 5.2$  Hz), 2.18 (br s, 1 H), 4.40 (dd, 1 H,  $J = 8.4, 5.0$  Hz), 5.06 (t, 1 H,  $J = 7.0$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -5.07, -4.31, 17.64, 18.17, 19.11, 25.34, 25.69, 25.76, 28.47, 31.29, 31.35, 37.27, 45.83, 60.85, 65.07, 84.30, 88.33, 124.69, 131.15; IR (thin film): 3353 bm, 2957 s, 2930 m, 2857 s, 1472 w, 1464 w, 1377 w, 1362 w, 1252 m, 1167 s, 1088 s  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 337 (1), 293 (1), 267 (5), 227 (5), 177 (8), 147 (12), 119 (16), 109 (30), 75 (100), 73 (42), 68 (36); Anal calcd for  $\text{C}_{21}\text{H}_{40}\text{O}_2\text{Si}$ : C, 71.53; H, 11.43. Found; C, 71.35; H, 11.51. Clear oil (hexane),  $R_f = 0.52$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} +48.3^\circ$  (c 0.553,  $\text{CH}_2\text{Cl}_2$ ) with  $> 20 : 1$  dr.



**Synthesis of enyne (3R,5S)-15.** A 50 mL flask was charged with alkyne (5R,7S)-58 (0.99 g, 2.8 mmol), 18-crown-6 (0.77 g, 2.9 mmol), potassium carbonate (0.40 g, 2.9 mmol), and toluene (30 mL). The contents of the flask were refluxed for 18 to 24 hours under a stream of nitrogen gas. The nitrogen gas was allowed to pass out of the flask to remove any volatiles formed during the reaction. The solvent was removed under reduced pressure and directly taken on to column chromatography. Column chromatography (35 x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.78 g (95 %, 2.66 mmol) of (3R,5S)-15. The diastereomeric ratio was  $\geq 96 : 4$  as determined by  $^1\text{H}$  NMR. Spectral data for (3R,5S)-15:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.09 (s, 3 H), 0.13 (s, 3 H), 0.88 (m, 12 H), 1.05 - 1.80 (m, 4 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.66 - 1.80 (m, 1 H), 1.96 (q, 2 H,  $J = 7.5$  Hz), 2.35 (d, 1 H,  $J = 2.0$  Hz), 4.38 (ddd, 1 H,  $J = 13.5, 4.8, 2.0$  Hz), 5.07 (t, 1 H,  $J = 7.1$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -5.18, -4.45, 17.64, 18.16, 19.14, 25.33, 25.69, 25.74, 28.46, 37.18, 45.78, 60.78, 71.78, 86.12, 124.68, 131.19; IR (thin film): 3312 m, 2957 s, 2930 s, 2859 s, 1464 m, 1379 w, 1252 m, 1090 m  $\text{cm}^{-1}$ ;

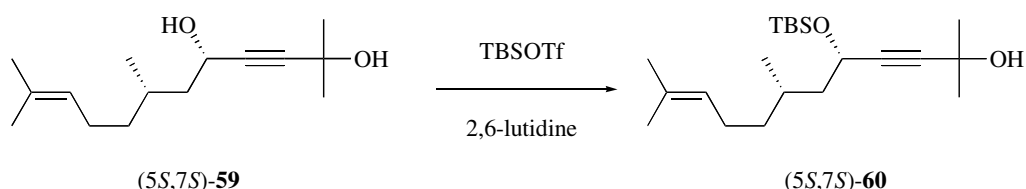
mass spectrum  $m/z$  (% rel intensity) 293  $M^+ - 1$  (2), 194 (35), 193 (42), 169 (8), 149 (12), 127 (25), 109 (100), 83 (95); Clear oil (hexane),  $R_f = 0.74$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} +27.0^\circ$  (c 0.414,  $CH_2Cl_2$ ).

### Preparation of Enyne (5S,7S)-18.

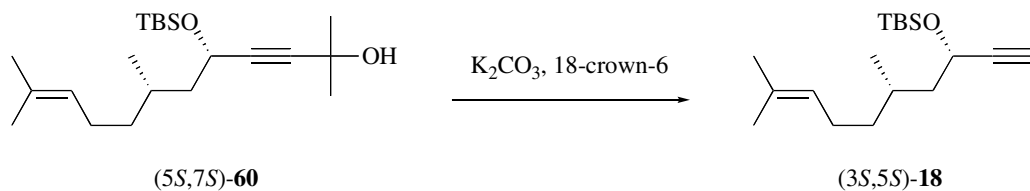


*Re-face alkynylation of (S)-citronellal 54.*<sup>2</sup> A 100 mL round bottom flask was charged with zinc triflate (4.20 g, 11.6 mmol), (-)-methyl ephedrine (2.21 g, 12.3 mmol), toluene (31 mL), and triethyl amine (1.6 mL, 11.5 mmol). This mixture was stirred for two hours at room temperature. To this solution was added 2-methylbut-3-yl-2-ol (1.1 mL, 11.4 mmol) and the reaction was stirred for 15 minutes. Over four hours, (-)-citronellal (S)-54 (1 mL, 5.5 mmol, 96.4 % ee) was added by syringe pump. The reaction mixture was allowed to stir overnight. The contents of the flask were poured into 40 mL of saturated ammonium hydroxide. The aqueous layer was back extracted with 20 mL x 3 of ethyl acetate. The organic layers were combined and neutralized with solid sodium bicarbonate. To this solution was added magnesium sulfate as a drying agent. The organic fraction was filtered through fluted filter paper, and the solvent was removed under reduced pressure. Column chromatography (25 x 4 cm, silica gel) with 30 % ethyl acetate / hexane gave 0.92 g (70 % yield, 3.85 mmol) of (5S,7S)-59. Spectral data for (5S,7S)-59:  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 0.90 (d, 3 H,  $J = 6.5$  Hz), 1.14 - 1.25 (m, 1 H), 1.31 - 1.40 (m, 1 H), 1.49 (s, 6 H), 1.51 - 1.56 (m, 1 H), 1.59 (s, 3 H), 1.62 - 1.67 (m, 2 H), 1.66 (s, 3 H), 1.93 - 2.03 (m, 4 H), 4.43 (t, 1 H,  $J = 6.7$  Hz), 5.08 (br t, 1 H,  $J = 7.1$  Hz);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$ : 17.65, 19.67, 25.28, 25.69, 29.35, 31.34, 36.88, 45.05, 60.99, 65.08,

83.21, 89.63, 124.56, 131.36; IR (thin film): 3339 s, 2967 s, 2926 s, 1456 w, 1377 m, 1165 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 220  $\text{M}^+$ -18 (1), 205 (4), 187 (9), 177 (12), 163 (9), 145 (16), 135 (29), 121 (25), 107 (54), 93 (25), 81 (33), 69 (91), 41 (100); Yellow oil (hexane),  $R_f = 0.11$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -15^\circ$  (c 0.025,  $\text{CH}_2\text{Cl}_2$ ) with  $> 20 : 1$  dr

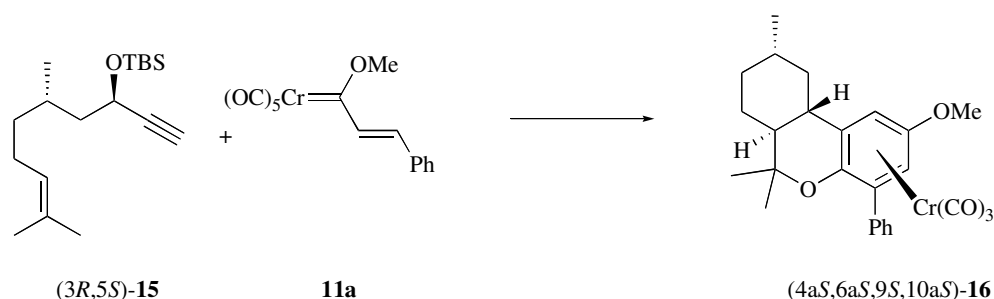


**TBS protection of diol (5S,7S)-59.** A 100 mL round bottom flask was charged with compound (5S,7S)-59 (0.92 g, 3.9 mmol), dichloromethane (50 mL), 2,6-lutidine (0.45 mL, 3.9 mmol), and the flask was cooled to 0 °C. To the pre-cooled flask was added TBSOTf (0.9 mL, 3.9 mmol) in a dropwise manor. The solution was stirred for 30 minutes at 0 °C. Column chromatography (30 x 4 cm, silica gel) with 10 % ethyl acetate / hexane gave 1.12 g (82 % yield, 3.20 mmol) of (5S,7S)-60. Spectral data for (5S,7S)-60:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.087 (s, 3 H), 0.11 (s, 3 H), 0.83 - 0.91 (m, 12 H, overlapped s and d), 1.05 - 1.15 (m, 1 H), 1.31 - 1.38 (m, 1 H), 1.47 (s, 6 H), 1.474 - 1.54 (m, 1 H), 1.57 - 1.68 (m, 2 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.85 (br s, 1 H), 1.90 - 2.02 (m, 2 H), 4.41 (t, 1 H,  $J = 6.9$  Hz), 5.07 (br t, 1 H,  $J = 6.6$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : -4.92, -4.43, 17.63, 18.19, 19.93, 25.29, 25.71, 25.80, 28.91, 31.29, 31.34, 36.63, 45.84, 61.30, 65.12, 83.98, 88.58, 124.68, 131.14; IR (thin film): 3418 br m, 2959 s, 2936 m, 2190 w, 1653 m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 335  $\text{M}^+$ -17 (3), 295 (5), 266 (6), 239 (6), 211 (8), 197 (4), 187 (23), 177 (19), 169 (9), 161 (26), 159 (22), 135 (14), 133 (26), 119 (35), 109 (58), 105 (38), 75 (100), 69 (40); Clear oil,  $R_f = 0.5$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} -6.0^\circ$  (c 0.17,  $\text{CH}_2\text{Cl}_2$ ).



**Synthesis of enyne (3S,5S)-18.** A 100 mL round bottom flask was charged with compound (5S,7S)-**60** (1.10 g, 3.1 mmol), 18-crown-6 (0.96, 3.6 mmol), potassium carbonate (0.48 g, 3.5 mmol), and toluene (30 mL). The contents of the flask were heated at 120 °C overnight under a moderate stream of nitrogen. The solvent was removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane (30 cm x 4 cm, silica gel) gave 0.92 g (94 % yield, 2.91 mmol) of (5S,7S)-**18**. This compound is known in the literature.<sup>13</sup> Spectral data for (5S,7S)-**18**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.10 (s, 3 H), 0.12 (s, 3 H), 0.89 (s, 9H), 0.88 - 0.90 (d, 3 H, doublet obscured), 1.09 - 1.30 (m, 1 H), 1.31 - 1.40 (m, 1 H), 1.48 - 1.55 (m, 1 H), 1.58 (s, 3 H), 1.64 - 1.71 (m, 2 H), 1.66 (s, 3 H), 1.88 - 2.05 (m, 2 H), 2.35 (d, 1 H, *J* = 2.2), 4.39 (td, 1 H, *J* = 7.1, 2.02 Hz), 5.08 (br t, 1 H, *J* = 7.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: -5.01, -4.51, 17.62, 18.19, 19.79, 25.34, 25.69, 25.79, 28.97, 36.83, 45.84, 61.35, 72.00, 85.79, 124.74, 131.12; IR (thin film): 3312 s, 2930 s, 2857 s, 1474 w, 1258 w, 1082 w cm<sup>-1</sup>; mass spectrum *m/z* (% rel intensity) 293 M<sup>+</sup>-1 (0.25), 185 (1), 169 (5), 109 (32), 105 (15), 75 (100); Clear oil (hexane), *R*<sub>f</sub> = 0.74 (30 % ethyl acetate / hexane). [ $\alpha$ ]<sub>D</sub><sup>22</sup> -23.3° (c 0.434, CH<sub>2</sub>Cl<sub>2</sub>) with > 20 : 1 dr.

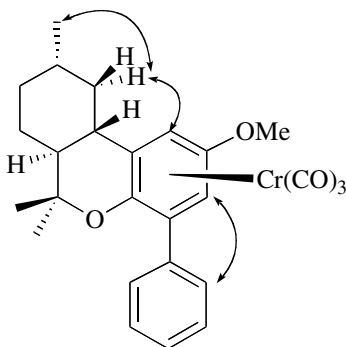
## Reaction of the Enyne (3*R*,5*S*)-**15** with the Carbene Complex **11a**. Matched Case.



*Benzannulation of Enyne (3*R*,5*S*)-**15** and **11a**.* In a 50 mL round bottom flask that had the standard tapered joint replaced with a threaded high vacuum Teflon valve was added styryl carbene complex **11a** (0.108 g, 0.32 mmol), alkyne (3*R*,5*S*)-**15** (0.108 g, 0.32 mmol), Hunig's base (0.30 mL, 1.7 mmol), and toluene (10 mL). The order of addition was carbene complex, toluene (5 mL), alkyne in toluene (5 mL), and Hunig's base. The mixture was deoxygenated by the freeze-thaw method and then the flask was back filled with argon at room temperature. The flask was sealed by closing the Teflon valve and then the flask heated at 80 °C for 24 hours. The reaction mixture was poured onto about 2 - 5 cc of silica gel and the solvent removed under reduced pressure and the silica gel loaded onto the top of a silica gel column. (30 cm x 1.8 cm). Elution with hexane and then 5 % ethyl acetate / hexane gave 0.0846 g (56 % yield, 0.179 mmol) of **16**. The diastereomeric ratio was found to be 98:2 which was determined after demetallation to give compound **61** (vide infra). Spectral data for (4*aS*,6*aS*,9*S*,10*aS*)-**16**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 0.84-1.00 (m, 2 H), 1.02 (d, 3 H, *J* = 6.6 Hz), 1.06 - 1.14 (m, 1 H), 1.25 (s, 3 H), 1.27 - 1.30 (m, 1 H), 1.34 (s, 3 H), 1.60 - 1.69 (m, 1 H), 1.78 (ddd, 1 H, *J* = 12.6, 6.3, 3.1 Hz), 1.84 (br d, 1 H, *J* = 13.0 Hz), 2.31 (br d, 1 H, *J* = 12.5 Hz), 2.63 (td, 1 H, *J* = 11.7, 3.8 Hz), 3.69 (s, 3 H), 5.32 (d, 1 H, *J* = 2.5 Hz), 5.45 (d, 1 H, *J* = 2.5 Hz), 7.32 - 7.42 (m, 3 H), 7.60 - 7.65 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 19.24, 22.36, 27.25, 28.18, 32.15, 34.17, 34.74, 39.20, 46.62, 56.08, 75.63, 80.33, 84.49, 94.49, 102.19, 127.77, 128.18, 128.31, 130.31, 134.47, 135.66, 234.66; IR (thin film): 2924 w, 2853 w, 1952 s, 1867 s, 1541 w, 1459

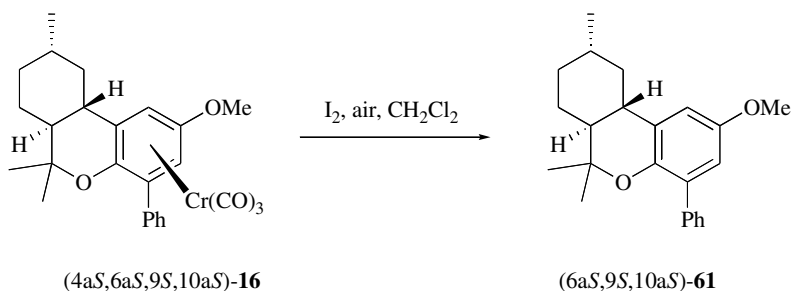
w, 1420  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity,  $\text{FAD}^+$ ) 472  $\text{M}^+$  (52), 388 (100), 336.2 (24); HRMS calcd for  $\text{C}_{26}\text{H}_{28}\text{CrO}_5$   $m/z$  472.1342, meas 472.1343. Yellow needle (hexane), mp 178 - 180  $^\circ\text{C}$  (dec.),  $R_f = 0.56$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} +21.5^\circ$  (c 0.27,  $\text{CH}_2\text{Cl}_2$ ) with > 20 : 1 dr.

**Compound 16** Homonuclear nOe  $^1\text{H}$ - $^1\text{H}$



**Table 3.** Yields of **16**

entry	solvent (M, carbene)	base	time	temp	% yield <b>16</b>
1	toluene (0.015)	$\text{N}(\text{iPr})_2\text{Et}$ 5 eq.	24 hrs	80	39
2	toluene (0.032)	$\text{N}(\text{iPr})_2\text{Et}$ 5 eq.	24 hrs	80	56
3	toluene (0.042)	none	24 hrs	80	34
4	toluene (0.046)	$\text{N}(\text{iPr})_2\text{Et}$ 5 eq.	13 hrs 11 hrs	60 80	27
5	toluene (0.073)	$\text{N}(\text{iPr})_2\text{Et}$ 5 eq.	13 hrs 11 hrs	60 80	26

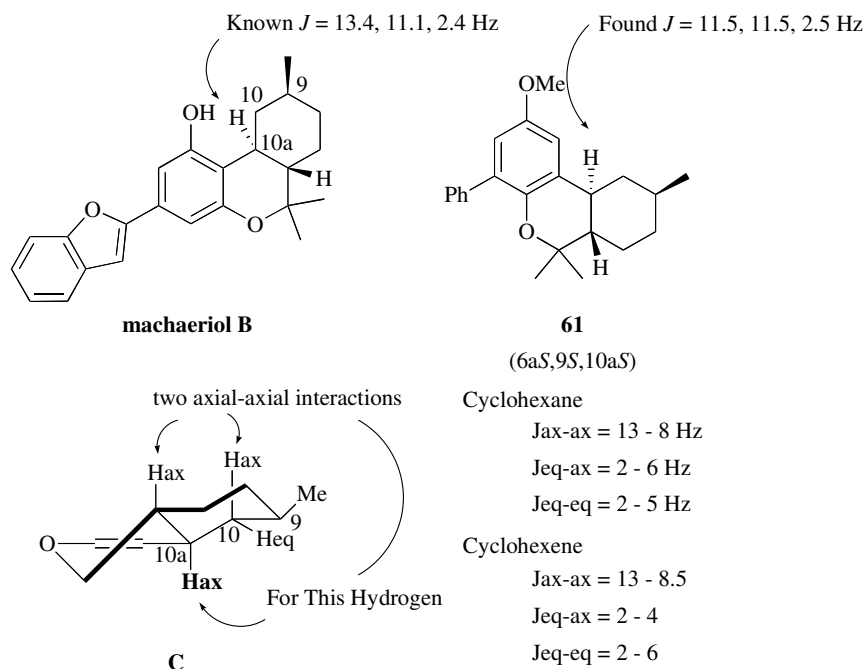




*Demetallation of chromium tricarbonyl complex 16.* Compound **16** (0.023 g, 0.05 mmol) was added to a solution of dichloromethane (5 mL) and one piece of iodine. The solution was stirred for 15 minutes. The solution was treated with saturated sodium sulfite and stirred for 15 minutes. The organic and aqueous layers were separated. The aqueous layer was extracted with 5 mL x 3 of dichloromethane. The organic layers were combined and extracted with saturated brine and the aqueous layer was back extracted with 5 mL x 3 of dichloromethane. The organic layers were combined and dried over magnesium sulfate. The solvent was filtered through fluted filter paper and the solvent removed under reduced pressure. Column chromatography on silica gel with 5 % ethyl acetate / hexane gave 0.01 g (54 % yield, 0.027 mmol) of (6a*S*,9*S*,10a*S*)-**61**. The isomer ratio was 98 : 2 which was determined by GC/FID on a Alltech Econo-Cap SE-54 (30 m x 0.32 mm x 1.2  $\mu$ m) with a temperature program of 80  $^{\circ}$ C hold for 1 minute and 10  $^{\circ}$ C / minute until 230  $^{\circ}$ C. The flow rate was 5 cc / minute directly determined with a flow meter with a splitless injector. The retention times were 12.1 minutes for the minor and 16.7 minutes for the major. The retention time for GC/MS was 21.6 minutes (minor) and 22.7 minutes (major). The temperature program was 60  $^{\circ}$ C for 2 minutes then ramped to 260  $^{\circ}$ C at 10  $^{\circ}$ C / minute using a CP-SIL 8 low bleed column (30 m x 0.25 mm) with a 5 mL/min flow rate (1/20 split ratio). The integration between the MS and FID were identical. The minor component was shown to be an isomer by GC/MS and was assumed to be the isomer with a cis-ring fusion. Spectral data for **61**: Major Isomer;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.77-0.92 (m, 1 H), 0.94-1.11 (m, 2 H), 1.00 (d, 3 H,  $J$  = 6.5 Hz), 1.14 (s, 3 H), 1.20-1.28 (m, 1 H), 1.31 (s, 3 H), 1.53-1.70 (m, 1 H), 1.77-1.89 (m, 2 H), 2.40 (d, 1 H,  $J$  = 12.6 Hz), 2.47 (td, 1 H,  $J$  = 11.5, 2.5 Hz), 3.79 (s, 3 H), 6.75 (d, 1 H,  $J$  = 3.0 Hz), 6.81 (d, 1 H,  $J$  = 3.0 Hz), 7.27 -7.32 (m, 1 H), 7.34-7.41 (m, 2 H), 7.53-7.59 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.02, 22.62, 27.54, 27.92, 32.62, 34.75, 36.34, 39.89, 46.81, 55.75, 76.87, 110.89, 114.17, 126.50, 126.77, 127.65, 129.64, 130.32, 139.00, 144.18, 152.52; IR (thin film) 2927s, 2860m, 1464s,

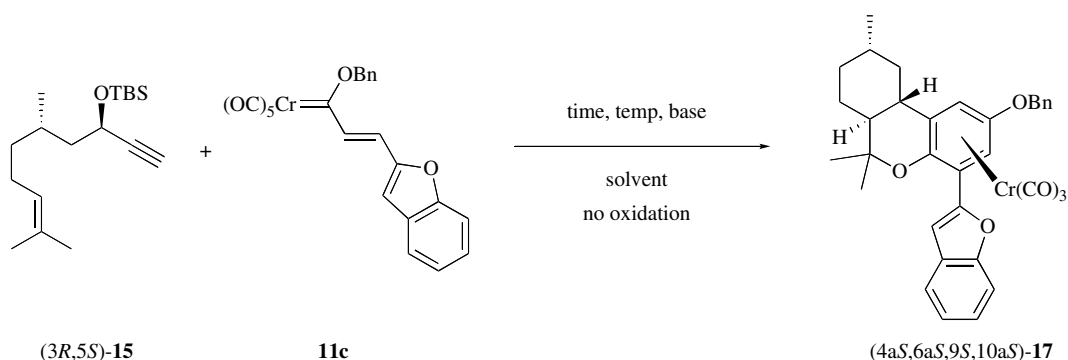
1200m, 1055m, 698m  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 336  $\text{M}^+$  (100), 293 (61), 251 (11), 213 (13); Clear oil (hexane),  $R_f = 0.58$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{22} +14.9^\circ$  (c 1.17,  $\text{CH}_2\text{Cl}_2$ ) with  $> 20 : 1$  dr. Minor Isomer; mass spectrum  $m/z$  (% rel intensity) 336  $\text{M}^+$  (100), 293 (23), 254 (6), 251 (3), 213 (11).

Figure 2 shows the coupling constants from the natural product machaeriol B<sup>14</sup> for the C10a proton and these are compared with those of compound **61**. The coupling constants in machaeriol B are  $J = 13.4, 11.1, \text{ and } 2.4 \text{ Hz}$ . In compound **61**, a similar set of coupling constants are observed of  $J = 11.5, 11.5, \text{ and } 2.5 \text{ Hz}$ . These coupling constant patterns are consistent with two axial-axial interactions and one axial-equatorial interaction as illustrated in structure **C**. The typical coupling constants of cyclohexanes and cyclohexenes<sup>15</sup> are also presented in Figure 2, and they are consistent with proposed structure **61**.



**Figure 2.** Coupling Constants of Hexahydrodibenzopyrans (6-6-6 Ring Systems)

## Reaction of the Enyne (3*R*,5*S*)-15 with the Carbene Complex 11c. Matched Case.

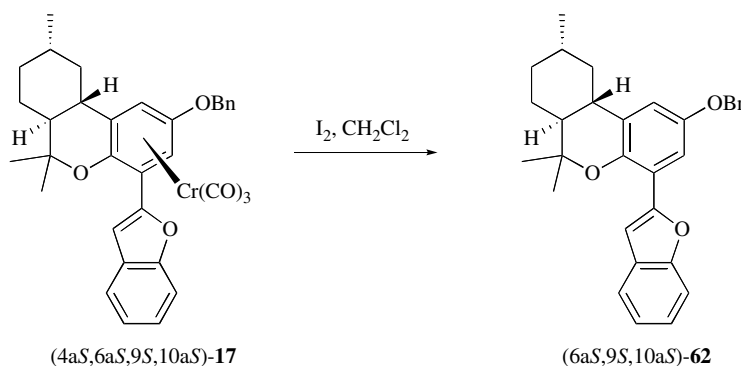


**Benzannulation of Enyne (3*R*,5*S*)-15 and 11a.** Following procedure for the reaction of (3*R*,5*S*)-15 with 11a given above, the following results were obtained with carbene complex 11c (0.104 g, 0.23 mmol), alkyne (3*R*,5*S*)-15 (0.078 g, 0.27 mmol), and 5 mL of toluene. The reaction mixture was heated 24 hours at 80 °C. The yield of (4a*S*,6a*S*,9*S*,10a*S*)-17 was 47%. The yields from other reaction conditions are shown below in Table 4. The trans to cis ratio was found to be  $\geq 96 : 4$  by integrating the protons at  $\delta = 6.23$  (minor) and  $\delta = 6.19$  ppm (major). Typically also recovered was 49% of the mass as a mixture of unidentified and inseparable products ( $R_f = 0.64$ , 30 % ethyl acetate / hexane) under all conditions examined. Spectral data for 17:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.77 - 0.86 (m, 2 H), 0.93 (d, 3 H,  $J = 6.5$  Hz), 1.02 - 1.12 (m, 1 H), 1.23 - 1.32 (td, 1 H,  $J = 11.7, 2.3$  Hz), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.49 - 1.62 (m, 1 H), 1.77 (t, 2 H,  $J = 12.3$ ), 2.18 (d, 1 H,  $J = 12.9$ ), 2.59 (td, 1 H,  $J = 11.6, 3.6$  Hz), 4.86 (d, 1 H,  $J = 10.6$  Hz), 4.90 (d, 1 H,  $J = 10.5$  Hz), 5.32 (d, 1 H,  $J = 2.3$  Hz), 6.19 (d, 1 H,  $J = 2.3$  Hz), 7.13 - 7.19 (m, 1 H), 7.23 (t, 1 H,  $J = 7.8$  Hz), 7.27 - 7.35 (m, 4 H), 7.37 - 7.44 (m, 3 H), 7.53 (d, 1 H,  $J = 7.7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 19.62, 22.39, 27.22, 28.51, 32.05, 34.13, 34.58, 39.18, 46.45, 71.58, 76.28, 79.17, 81.25, 88.59, 95.02, 108.69, 111.03, 121.52, 123.07, 125.10, 126.83, 128.21, 128.60, 128.72, 128.99, 134.92, 135.24, 149.06, 153.98, 234.54; IR (thin film): 2922 w, 2851 w, 1950 s, 1869 s, 1535 w, 1455 w, 1157 w, 1145 w  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity, FAB+) 588.4  $\text{M}^+$  (24), 504.4 (100), 452.4 (6), 413.2 (9), 91 (54);

HRMS calcd for  $C_{34}H_{32}CrO_6$   $m/z$  588.1604, meas 588.1610. Yellow-orange solid (hexane), mp 72 - 75 °C (dec.),  $R_f$  = 0.56 (30 % ethyl acetate / hexane).  $[\alpha]_D^{22}$   $-237.3^\circ$  (c 0.566,  $CH_2Cl_2$ ).

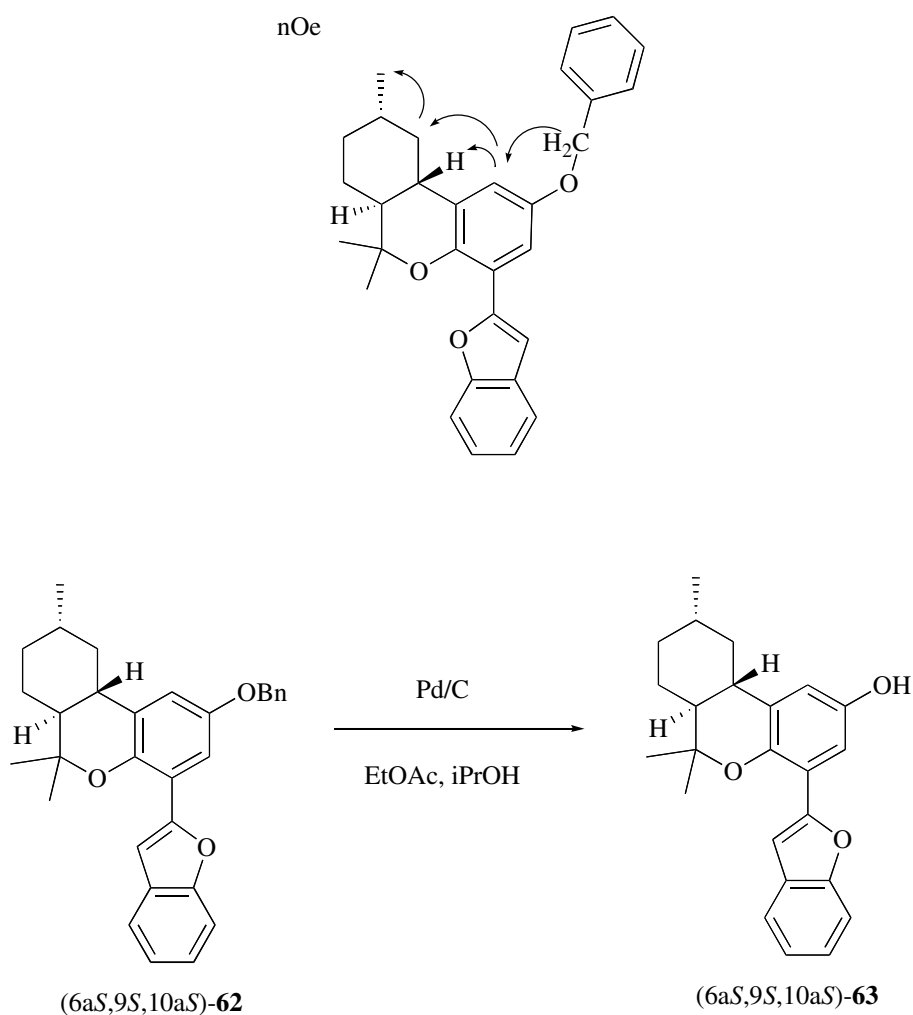
**Table 4.** Additional Results

entry	solvent (M, carbene)	base (M)	time	temp	% yield 17
1	toluene (0.01)	$N(iPr)_2Et$ (0.43)	24 hrs	80	38
2	toluene (0.028)	$N(iPr)_2Et$ (0.14)	24 hrs	80	44
3	toluene (0.04)	$N(iPr)_2Et$ (0.22)	24 hrs	80	47
4	toluene (0.11)	$N(iPr)_2Et$ (0.52)	24 hrs	80	43



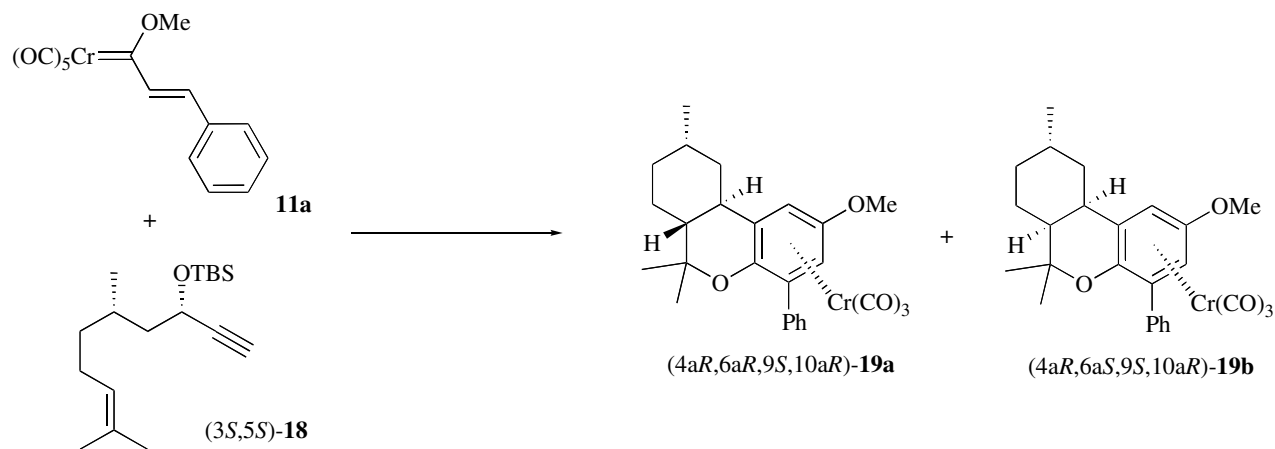
*Demetallation of chromium tricarbonyl complex 17.* A 10 mL round bottom was charged with compound (4aS,6aS,9S,10aS)-17 (0.049 g, 0.081 mmol), dichloromethane (2 mL), and one piece of iodine. The contents of the flask were stirred in air for 30 minutes and then treated with 8 mL of saturated sodium sulfate for 15 minutes and extracted with brine. Each aqueous layer was extracted with 3 mL x 3 of dichloromethane. Column chromatography (35 cm x 2 cm, silica gel) with 5 % ethyl acetate / hexane gave an oily solid (0.026 g, 0.057 mmol, 70 %) of (6aS,9S,10aS)-62. Spectral data for **62**:  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 0.84 - 0.97 (m, 2 H), 0.99 (d, 3 H,  $J$  = 6.6 Hz), 1.04 - 1.16 (m, 2 H), 1.20 (s, 3 H), 1.25 - 1.65 (m, 2 H), 1.48 (td, 1 H,  $J$  = 11.6, 2.7 Hz), 1.57 (s, 3 H), 1.86 (br t, 2 H,  $J$  = 10.5 Hz), 2.36 (br d,

1 H,  $J = 12.7$  Hz), 2.48 (td, 1 H,  $J = 11.3, 3.3$  Hz), 5.10 (s, 2 H), 6.91 (d, 1 H), 7.17 - 7.29 (m, 2 H), 7.30 - 7.36 (m, 1 H), 7.37 - 7.42 (m, 2 H), 7.47 - 7.53 (m, 2 H), 7.57 - 7.63 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 20.49, 22.56, 27.50, 28.09, 32.49, 34.66, 36.04, 39.75, 46.50, 70.80, 77.99, 106.25, 110.44, 110.74, 113.73, 118.92, 120.96, 122.51, 123.90, 126.95, 127.67, 127.84, 128.48, 129.90, 137.38, 145.13, 151.86, 152.63, 153.70; IR (thin film): 2924 m, 2867 m, 1566 m, 1456 m, 1262 w, 1157 w, 1144 m, 1044 w, 938 w, 739 w  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 452.3  $\text{M}^+$  (1), 361 (35), 343 (12), 319 (3), 315 (5), 305 (9), 287 (3), 263 (7), 239 (25), 129 (11), 91 (100), 69 (39); HRMS (Q-ToF) calcd for  $\text{C}_{31}\text{H}_{33}\text{O}_3$   $[\text{M}+1]^+$   $m/z$  453.2424, meas 453.2430. Beige solid (hexane), mp 134 - 137  $^\circ\text{C}$  (one isomer),  $R_f = 0.61$  (30 % ethyl acetate / hexane).  $[\alpha]_D^{20} +18^\circ$  (c 0.16,  $\text{CH}_2\text{Cl}_2$ ).



**Debenzylation of (6a*S*,9*S*,10a*S*)-**62**.** A 10 mL round bottom flask was charged with compound (6a*S*,9*S*,10a*S*)-**62** (0.0080 g, 0.018 mmol), 10 % Pd on carbon (0.0025 g), ethyl acetate (1 mL), isopropanol (1 mL). The contents of the flask were briefly exposed to vacuum and the atmosphere was replaced with hydrogen. The mixture was stirred for 10 hours at room temperature. The mixture was filtered through Celite giving 6 mg (0.017 mmol) or 92 % yield of phenol (6a*S*,9*S*,10a*S*)-**63**. Spectral data for **63**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.82 - 0.99 (m, 2 H), 1.00 (d, 3 H,  $J = 6.6$  Hz), 1.05 - 1.17 (m, 2 H), 1.20 (s, 3 H), 1.21 - 1.36 (m, 1 H), 1.48 (td, 2 H,  $J = 11.5, 2.7$  Hz), 1.57 (s, 3 H), 1.81 - 1.95 (m, 2 H), 2.27 (br d, 1 H,  $J = 12.5$  Hz), 2.48 (td, 1 H,  $J = 11.5, 3.5$  Hz), 4.45 (br s, 1 H), 6.78 (dd, 1 H,  $J = 3.0, 1.0$  Hz), 7.15 - 7.31 (m, 1 H), 7.38 - 7.66 (m, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 20.72, 22.83, 27.72, 28.37, 32.81, 34.88, 36.21, 39.98, 46.81, 78.22, 106.58, 110.93, 111.56, 113.27, 119.40, 121.33, 122.81, 124.24, 127.40, 130.11, 145.08, 148.48, 152.72, 154.01.

**Reaction of the Enyne (3*S*,5*S*)-**18** with the Carbene Complex **11a**. Mismatched Case.**



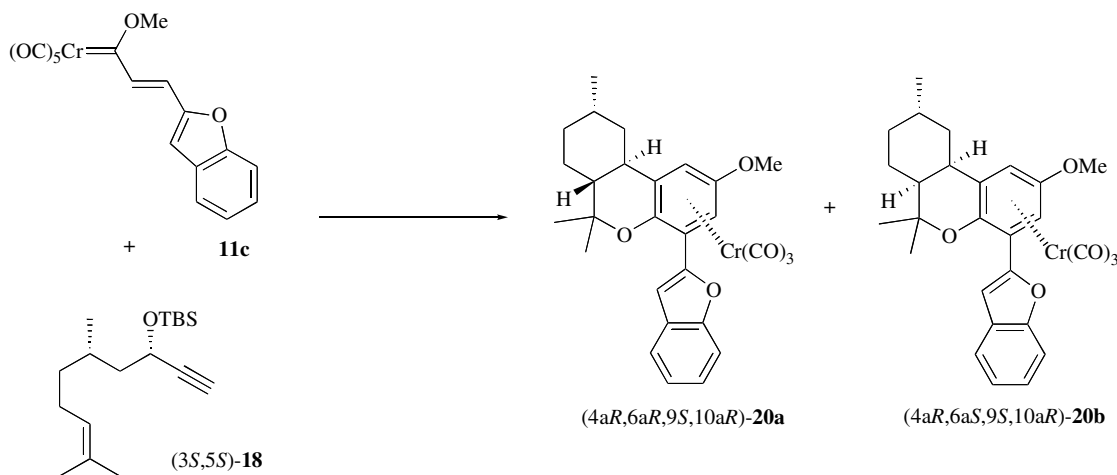
This reaction was carried out with the procedure described above for carbene complex **11a** and enyne (3*R*,5*S*)-**15**. Carbene complex **11a** (0.1039 g, 0.31 mmol) and alkyne (3*S*,5*S*)-**18** (0.107 g, 0.37 mmol) were heated in 10 mL of toluene at 80 °C for 24 hours. The product **19** was isolated as a mixture of diastereomers in a ratio of 100 : 65 : 5 (**19a** : **19b** : **19c**) in a

total of 34% yield (0.0498 g, 0.105 mmol). These isomers could not be separated. In a separate run, the reaction of the carbene complex **11a** (0.1011 g, 0.30 mmol) and alkyne (3*S*,5*S*)-**18** (0.093 g, 0.32 mmol) was carried out in 10 mL of toluene at 90 °C for 24 hours. The product **19** in this case was isolated as a mixture in a ratio of 100 : 36 : 15 (**19a** : **19b** : **19c**) in 65% total yield (0.092 g, 0.193 mmol). These two samples containing different proportions of the diastereomers of **19** were used to extract the <sup>1</sup>H NMR data for each isomer from the <sup>1</sup>H NMR spectrum of the mixture. The stereochemical assignment of **19a** was made as described above for **16**. A structural assignment for the minor component **19c** was not made. The stereochemical assignment for **19b** was made assuming it had the same structure as **20b** (see discussion below). Diastereomer **19a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.81-0.98 (m, 2 H), 1.13 (d, 3 H, *J* = 7.2 Hz), 1.24 (s, 3 H), 1.36 (s, 3 H), 1.00 - 1.77 (m, 3 H), 2.09-2.31 (m, 3 H), 2.85 (td, 1 H, *J* = 11.5, *J* = 3.1 Hz), 3.69 (s, 3 H), 5.26 (d, 1 H, *J* = 1.8 Hz), 5.44 (d, 1 H, *J* = 1.8 Hz), 7.30 - 7.45 (m, 3 H), 7.57 - 7.69 (m, 2 H). Diastereomer **19b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.81-0.98 (m, 2 H), 0.93 (d, 3 H, *J* = 6.0 Hz), 1.23 (s, 3 H), 1.00-1.77 (m, 3 H), 1.48 (s, 3 H), 2.09-2.31 (m, 2 H), 2.56 - 2.65 (m, 1 H), 3.47 (br s, 1 H), 3.70 (s, 3 H), 5.34 (d, 1 H, *J* = 1.7 Hz), 5.46 (d, 1 H, *J* = 1.9 Hz), 7.30 - 7.45 (m, 3 H), 7.57 - 7.69 (m, 2 H). Diastereomer **19c** (partial data): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.64 (br t, 1 H, *J* = 12.2 Hz), 5.15 (br s, 1 H), 5.23 (br s, 1 H). The following spectral data was collected on a mixture of the diastereomers: <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.10, 18.01, 19.29, 21.68, 22.63, 24.93, 26.23, 26.46, 27.42, 28.01, 29.10, 30.92, 31.26, 31.57, 34.27, 34.64, 36.47, 37.04, 40.26, 47.28, 56.06, 56.09, 75.50, 76.86, 79.16, 80.20, 84.32, 84.34, 91.84, 92.08, 94.64, 102.02, 102.27, 127.77, 127.79, 128.31, 128.33, 130.26, 130.33, 134.48, 134.50, 135.75, 234.72, 234.61; IR (thin film): 2936s, 2855m, 1950vs, 1867vs, 1543m, 1458m, 1420s, 1199m, 1144m cm<sup>-1</sup>; mass spectrum *m/z* (% rel intensity,

FAB+) 472 M<sup>+</sup> (56), 388 M<sup>+</sup>–3CO (100), 336 (38); HRMS calcd for C<sub>26</sub>H<sub>28</sub>CrO<sub>5</sub> *m/z* 472.1342, meas 472.1340.



## Reaction of the Enyne (3*S*,5*S*)-**18** with the Carbene Complex **11c**. Mismatched Case.

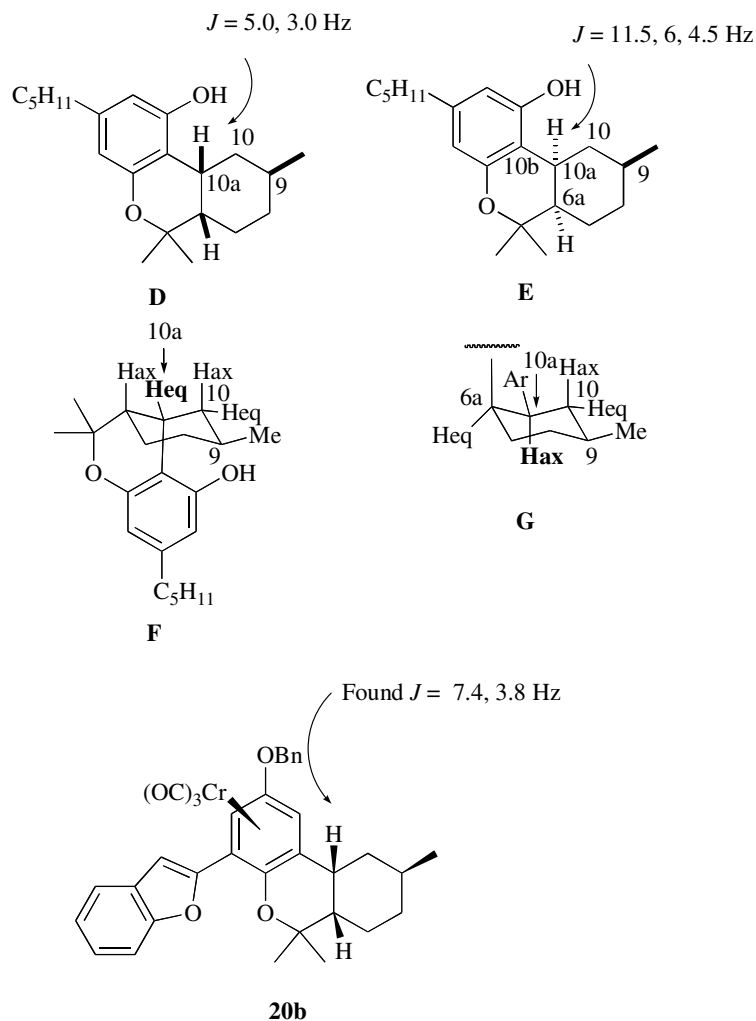


This reaction was carried out with the procedure described above for carbene complex **11a** and enyne (3*R*,5*S*)-**15**. Alkyne (3*S*,5*S*)-**18** (0.070 g, 0.24 mmol), carbene complex **11c** (0.097 g, 0.21 mmol), and 4.5 mL of toluene were heated at 80 °C for 30 hours. Purification gave a 39 % yield (0.049 g, 0.083 mmol) of **20** as a 100 : 44 : 10 mixture of **20a**, **20b**, and **20c** respectively, which could not be separated and were collected together. The ratio was determined by <sup>1</sup>H NMR by integrating the multiplets at δ = 2.35, 2.90, and 3.49 ppm. The following <sup>1</sup>H NMR data for each diastereomer was extracted from the spectrum of the mixture.

Diastereomer **20a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.92-1.08 (m, 1 H), 1.14 (d, 3 H, *J* = 7.26 Hz), 1.22-1.41 (m, 2 H), 1.484 (s, 3 H), 1.51 (s, 3 H), 1.54-1.76 (m, 3 H), 2.06-2.29 (m, 2 H), 2.90 (td, 1 H, *J* = 11.8, 3.7 Hz), 4.92 (d, 1 H, *J* = 12.0 Hz), 4.97 (d, 1 H, *J* = 12.0 Hz), 5.35 (d, 1 H, *J* = 2.54 Hz), 6.26 (d, 1 H, *J* = 2.57 Hz), 7.20-7.26 (m, 1 H), 7.29-7.33 (m, 1 H), 7.35-7.43 (m, 4 H), 7.43-7.52 (m, 3 H), 7.60 (d, 1 H, *J* = 7.8 Hz); Diastereomer **20b**: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.84 (d, 3 H, *J* = 6.0 Hz), 0.92-1.08 (m, 1 H), 1.22-1.41 (m, 2 H), 1.475 (s, 3 H), 1.54-1.76 (m, 3 H), 1.58 (s, 3 H), 2.06-2.29 (m, 1 H), 2.61-2.73 (m, 1 H), 3.49 (br dd, 1 H, *J* = 7.4, 3.8 Hz), 4.97 (d, 1 H, *J* = 11.0 Hz), 5.01 (d, 1 H, *J* = 11.0 Hz), 5.36 (d, 1 H, *J* = 2.54 Hz), 6.31 (d, 1 H, *J* = 2.57 Hz), 7.20-7.26 (m, 1 H), 7.29-7.33 (m, 1 H), 7.35-7.43 (m, 4 H), 7.43-7.52 (m, 3 H), 7.60 (d, 1 H, *J* = 7.8

Hz); Diastereomer **20c** (partial data):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.35 (br t, 1 H,  $J = 13.0$  Hz), 5.09 (d, 1 H,  $J = 10.0$  Hz, distorted), 5.12 (d, 1 H,  $J = 10.0$  Hz, distorted), 5.39 (d, 1 H,  $J = 2.55$  Hz), 6.27 (d, 1 H,  $J = 2.57$  Hz). The following spectral data was taken from the mixture of diastereomers:  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.10, 17.98, 19.72, 21.64, 22.22, 22.29, 22.63, 25.27, 26.10, 26.80, 27.35, 28.35, 29.10, 29.68, 30.85, 31.25, 31.57, 34.19, 36.38, 36.94, 40.36, 47.12, 71.55, 71.64, 76.06, 77.32, 79.00, 79.47, 80.02, 81.15, 88.54, 88.75, 92.35, 95.18, 108.74, 108.87, 111.07, 121.54, 123.08, 125.12, 125.15, 126.98, 127.34, 127.71, 127.89, 128.25, 128.51, 128.61, 128.72, 128.82, 129.02, 135.06, 135.17, 135.24, 135.46, 149.04, 149.14, 154.04, 234.52, 234.63;  $R_f = 0.35$  (30 % ethyl acetate / hexane).

The diastereomer **20a** was assigned as described above for **16**. The minor component **20c** was not given a structural assignment. The diastereomer **20b** was assigned as shown in Figure 3. The relative stereochemistry of *cis* and *trans* hexahydrodibenzopyrans has been determined from the cannabinol family.<sup>16</sup> In compound **D**, the hydrogens on carbon 10a and 6a are *cis* with the methyl on carbon 9. The coupling constants for the all *cis* compound is  $J = 5.0$  and 3.0 Hz. This can be rationalized by two equatorial-axial couplings and one equatorial-equatorial coupling both  $< 8$  Hz as shown in illustration **F**. In compound **E**, the hydrogens on carbons 10a and 6a are *cis* to each other but *trans* to the methyl on carbon 9. The coupling constants for compound **E** are  $J = 11.6$ , 6, and 4.5 Hz. This can be rationalized by one axial-axial coupling between hydrogen 10a and hydrogen 10 and two axial-equatorial couplings as shown in illustration **4-231**. For the compounds in the present work where the coupling constant could be determined such as compound **20b**, the couplings were  $< 8$  Hz with the all *cis* compound **20b** being consistent with the coupling reported for compound **D**.<sup>16</sup>



**Figure 3.** Coupling Constants of Hexahydrodibenzopyrans

#### References:

- 1) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42 (8), 2203 – 2209.
- 2) (a) Diez, R. S.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, 58 (41), 8341 - 8344. (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Organic Letters* **2002**, 4 (15), 2605 - 2606. (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, 123 (39), 9687 - 9688. (d) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Organic Letters* **2002**, 4 (15), 2605 - 2606. (e) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, 123 (39), 9687 - 9688

- 3) A) Jaouhari, R.; Dixneuf, P. H.; Lecolier, S. *Tetrahedron Lett.* **1986**, 27, 6315-6318. B) Bogdal, D.; Bednarz, S.; Lukasiewicz, M.; *Tetrahedron* **2006**, 61, 4381-4393.
- 4) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, 61 (18), 4381-4393.
- 5) Morrill, C.; Beutner, G.; Grubbs, R. *J. Org. Chem.* **2006**, 71 (20), 7813 – 7825.
- 6) Hoye, T.; Chen, K.; Vyvyan, J. *Organometallics* **1993**, 12 (7), 2806 – 2809.
- 7) See discussion in the manuscript.
- 8) Banwell, M.; Hockless, D.; McLeod, M. *New J. Chem.* **2003**, 27, 50 – 59.
- 9) Yadav, J.; Deshpande, P.; Sharma, G. *Tetrahedron* **1990**, 46 (20), 7033-46.
- 10) Shrestka, K.; Honda, K.; Asami, M.; Inoue, S. *Bull. Chem. Soc. Jap.* **1999**, 72, 73-83.
- 11) (a) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, 106 (18), 5208 - 5217. (b) Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, 112 (12), 4897 - 4905. (c) Hoye, T.; Koltun, D. *J. Am. Chem. Soc.* **1998**, 120 (19), 4638-4643. (d) Mori, K.; Kuwahara, S.; Levinson, H. Z.; Levinson, A. R. *Tetrahedron* **1982**, 38 (15), 2291 - 2297. (e) Mori, K.; Masuda, S.; Suguro, T. *Tetrahedron* **1981**, 37 (7), 1329 - 1340.
- 12) Valentine, D.; Chan, K.; Scott, C.; Johnson, K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, 41 (1), 62-65.
- 13) Onodera, A.; Kobashi, Y.; Kimura, Y.; Ohta, K.; Yokoo, C. *PCT Int. Appl.* **2004**. Sato, F.; Amano, T.; Kameo, K.; Tanami, T.; Mutoh, M.; Ono, N.; Goto, J. *PCT Int. Appl.* **1992**.
- 14) Muhammad, I.; Li, X.-C.; Jacob, M.; Tekwani, B.; Dunbar, D.; Ferreira, D. *J. Nat. Prod.* **2003**, 66, 804-809.
- 15) Aycard, J.-P.; Bodot, H. *Org. Mag. Res.* **1975**, 7, 226-236.
- 16) a) Arnone, A.; Merlini, L.; Servi, S. *Tetrahedron* **1975**, 31, 3093-3096. b) Uliss, D.; Handrick, G.; Dalzell, H.; Razdan, R. *Tetrahedron* **1978**, 34, 1885-1888.