

## Memory of Chirality in the Transannular Cyclization of Cyclodecenyl Radicals

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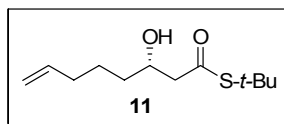
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### Experimental Procedures and Compound Characterization

#### General Experiment Details

All moisture- and air-sensitive reactions were carried out in flame- or oven-dried glassware using magnetic stirring under a positive pressure of argon gas. Standard syringe/septa techniques were employed. Reaction solvents were distilled or obtained from an alumina filtration system when necessary. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV plates. Concentration of organic solutions was performed using a Büchi rotary evaporator. Flash chromatography was performed on EM Science 230-400 mesh silica gel. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR. NMR spectra were recorded on Bruker GN 500, Bruker Omega 500, and Bruker DRX 400 MHz FTNMR instruments. Proton NMR spectra were obtained using CDCl<sub>3</sub> as solvent and referenced to residual protiated solvent ( $\delta$  7.26 ppm) or C<sub>6</sub>D<sub>6</sub> and referenced to  $\delta$  7.16 ppm. Carbon NMR spectra were recorded in ppm relative to the residual solvent signal: CDCl<sub>3</sub> ( $\delta$  77.0 ppm) or C<sub>6</sub>D<sub>6</sub> ( $\delta$  128.4 ppm). Mass spectra were determined on an AE2-MS 30, a PG 7070E-HF, a CG Analytical 7070E, or a Fisons autospec spectrometer. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. Tetrahydrofuran, ethyl ether and methylene chloride were dried by

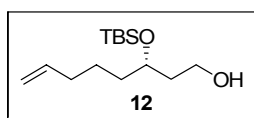
filtration through alumina according to the procedure by Grubbs.<sup>1</sup> Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument equipped with a FID detector. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).



**$\beta$ -Hydroxy thioester 11.** A mixture of *R*-(+)-1,1'-Bi-2-naphthol (793 mg, 2.77 mmol, 0.2 equiv),  $\text{Ti}(\text{O-}i\text{-Pr})_4$  (0.82 mL, 2.77 mmol, 0.2 equiv) and oven dried powdered 4 Å molecular sieves (5.7 g) in anhydrous ether (57 mL) was heated at reflux for 1 h. The blood-red mixture was cooled to room temperature and 5-hexenal (1.4 g, 14.3 mmol, 1.0 equiv) was added. After 5 min of stirring, the resultant solution was cooled to  $-78^\circ\text{C}$  and 1-*tert*-butylthio-1-(trimethylsilyl)oxy ethene (4.6 mL, 20.0 mmol, 1.4 equiv) was added. The mixture was warmed to  $-25^\circ\text{C}$  and stirred 20 h then pH 7 phosphate buffer was added and the contents were stirred for 15 min. The resultant solution was filtered through a pad of Celite and the filtrate was extracted with ethyl ether ( $2 \times 30$  mL), the combined extracts washed with brine and dried ( $\text{MgSO}_4$ ). The ethereal layers were concentrated *in vacuo* to give the unpurified product as the free alcohol and silylated alcohol, which was treated with 10%  $\text{HCl}/\text{MeOH}$  (100 mL). After 3 h, the solution was concentrated *in vacuo* and the resultant oil was purified by column chromatography

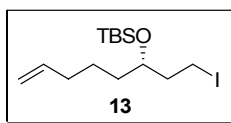
<sup>1</sup> Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(SiO<sub>2</sub>, 30% ether/hexanes, collected R<sub>f</sub> 0.42) to give 3.29 g (89%, 89% ee, determined by Mosher ester analysis) of **11** as a colorless oil:  $[\alpha]_D^{22} +20.1^\circ$  (*c* 0.66, CHCl<sub>3</sub>); IR (neat) 3434, 3077, 1681, 1364, 1163 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.79 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1 H), 5.00 (dd, *J* = 17.1, 1.9 Hz, 1 H), 4.95 (dd, *J* = 10.2, 2.0 Hz, 1 H), 4.06–3.99 (m, 1 H), 2.76 (d, *J* = 3.8 Hz, 1 H), 2.54 (dd, *J* = 15.7, 3.1 Hz, 1 H), 2.56 (dd, *J* = 15.7, 8.7 Hz, 1 H), 2.08–2.06 (m, 2 H), 1.54–1.43 (m, 4 H), 1.47 (s, 9 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  200.6, 138.5, 114.7, 68.6, 50.9, 48.5, 35.9, 33.5, 29.8, 24.6; HRMS (FAB) calcd for [C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>S+NH<sub>4</sub>]<sup>+</sup> 231.1419, found 231.1422.

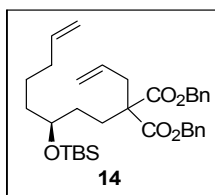


**Alcohol 12.** A flame-dried 100 mL round bottom flask was charged with  $\beta$ -hydroxy thioester **11** (3.24 g, 14.1 mmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (51 mL). The solution was cooled to 0 °C and 2,6-lutidine (2.1 mL, 18.3 mmol, 1.3 equiv) was added *via* syringe. The ice–H<sub>2</sub>O bath was removed and the reaction mixture was allowed to stir for 50 min, after which an additional 0.3 equiv of 2,6-lutidine (0.5 mL, 4.36 mmol) and *tert*-butyldimethylsilyltriflate (4.2 mL, 18.3 mmol) were added *via* syringe. The resultant solution was stirred an additional 1 h, after which the reaction mixture was diluted with an equal volume of ether and washed with satd. aq. NaHCO<sub>3</sub> (1  $\times$  30 mL), brine (1  $\times$  30 mL), dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo* to give 4.45 g (quantitative yield) of the silyl ether as a colorless oil:  $[\alpha]_D^{22} +28.6^\circ$  (*c* 1.02, CHCl<sub>3</sub>); IR (neat) 3078, 1682, 1364, 1255, 1078, 836, 775 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.78 (ddt, *J* =

17.1, 10.3, 6.6 Hz, 1 H), 5.00 (dd,  $J = 17.1, 1.8$  Hz, 1 H), 4.95 (dd,  $J = 10.2, 1.8$  Hz, 1 H), 4.16–4.12 (m, 1 H), 2.62 (dd,  $J = 14.5, 7.0$  Hz, 1 H), 2.51 (dd,  $J = 14.5, 5.6$  Hz, 1 H), 2.04 (ddd,  $J = 7.0, 7.0, 7.0$  Hz, 2 H), 1.51–1.38 (m, 4 H), 1.45 (s, 9 H), 0.86 (s, 9 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  198.4, 138.6, 144.6, 69.1, 52.2, 48.0, 36.8, 33.6, 29.8, 25.8, 24.1, 18.0,  $-4.5, -4.7$ ; HRMS (FAB) calcd for  $[\text{C}_{19}\text{H}_{36}\text{O}_2\text{SSi}+\text{H}]^+$  345.2284, found 345.2283. Anal. calcd for  $\text{C}_{19}\text{H}_{36}\text{O}_2\text{SSi}$ : C, 62.73; H, 10.53. Found: C, 62.88; H, 10.28. To a cooled ( $-25\text{ }^\circ\text{C}$ ) solution of the above silyl ether (1.96 g, 5.69 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (81 mL) was added DIBALH (17.1 mL, 1.0 M in toluene, 17.1 mmol, 3.0 equiv) slowly *via* syringe. The solution was stirred at  $-30\text{ }^\circ\text{C}$  for 2 h. After quenching with Rochelle's salt (70 mL) and satd. aq.  $\text{NH}_4\text{Cl}$  (7 mL), the aqueous layer was extracted with EtOAc ( $3 \times 100$  mL), washed with brine ( $1 \times 100$  mL), dried ( $\text{MgSO}_4$ ) and concentrated. Purification by column chromatography ( $\text{SiO}_2$ , 40% EtOAc/hexanes,  $R_f$  0.33) provided 1.37 g of a colorless oil (93%):  $[\alpha]_D^{22} +26.3^\circ$  ( $c$  0.67,  $\text{CHCl}_3$ ); IR (neat) 3364, 3078, 1642, 1255, 1062, 836, 775  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.79 (ddt,  $J = 17.1, 10.3, 6.6$  Hz, 1 H), 5.03 (dd,  $J = 17.1, 1.7$  Hz, 1 H), 4.96 (dd,  $J = 10.2, 1.7$  Hz, 1 H), 3.95–3.91 (m, 1 H), 3.86–3.83 (m, 1 H), 3.73–3.69 (m, 1 H), 2.45 (br s, 1 H), 2.08–2.03 (m, 2 H), 1.86–1.78 (m, 1 H), 1.69–1.51 (m, 3 H), 1.43–1.37 (m, 2 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  138.6, 114.6, 71.7, 60.2, 37.7, 36.2, 33.7, 36.2, 33.7, 25.8, 24.6, 18.0,  $-4.4, -4.7$ ; HRMS (FAB) calcd for  $[\text{C}_{14}\text{H}_{30}\text{O}_2\text{Si}+\text{H}]^+$  259.2094, found 259.2093. Anal. calcd for  $\text{C}_{14}\text{H}_{30}\text{O}_2\text{Si}$ : C, 65.06; H, 11.70. Found: C, 65.24; H, 11.53.

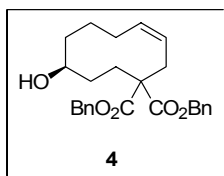


**Iodide 13.** To a cooled (0 °C) solution of alcohol **12** (332 mg, 1.28 mmol, 1.0 equiv), triphenylphosphine (442 mg, 1.67 mmol, 1.3 equiv) and imidazole (139 mg, 2.05 mmol, 1.6 equiv) in 18 mL CH<sub>2</sub>Cl<sub>2</sub> was added I<sub>2</sub> (424 mg, 1.67 mmol, 1.3 equiv). The clear solution immediately turned yellow and the solution was stirred at 0 °C for 2 h. Purified without workup (SiO<sub>2</sub>, 10% diethyl ether/hexanes, R<sub>f</sub> 0.78). Obtained 408 mg (94%) of **13** as a faint yellow oil:  $[\alpha]_D^{22} +27.7^\circ$  (*c* 0.70, CHCl<sub>3</sub>); IR (neat) 3077, 1641, 1255, 1069, 836, 775 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.79 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1 H), 5.03 (dd, *J* = 17.1, 1.7 Hz, 1 H), 4.96 (dd, *J* = 10.2, 1.7 Hz, 1 H), 3.75–3.72 (m, 1 H), 3.24–3.19 (m, 1 H), 2.05–2.04 (m, 2 H), 1.98–1.95 (m, 2 H), 1.48–1.39 (m, 5 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  138.6, 114.7, 72.0, 40.9, 36.2, 33.8, 25.9, 24.1, 18.1, 3.3, –4.3, –4.4; HRMS (FAB) calcd for [C<sub>14</sub>H<sub>29</sub>IOSi–CH<sub>3</sub>]<sup>+</sup> 353.0789, found 353.0799. Anal. calcd for C<sub>14</sub>H<sub>29</sub>IOSi: C, 45.65; H, 7.93. Found: C, 45.78; H, 7.87.



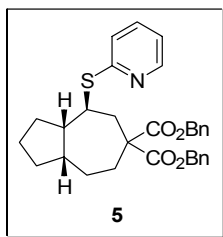
**Diene 14.** NaH (130 mg, 3.25 mmol, 1.2 equiv), washed 3 × with hexanes, was suspended in 0.5 mL of THF. The suspension was cooled to 0 °C and allyl

dibenzylmalonate (881 mg, 2.71 mmol, 1.0 equiv), dissolved in 1.0 mL THF, was added *via* cannula, washing with 1.0 mL of THF. After 2 h of stirring at 0 °C, iodide **13** was added *via* syringe and the solution was stirred, with warming to room temperature, for 13 h. The reagents were quenched with 5.0 mL satd. aq. NH<sub>4</sub>Cl and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated to provide an orange oil. Purification by silica gel chromatography (10% ether/hexanes, R<sub>f</sub> 0.38 in 30% EtOAc/hexanes) provided 982 mg (94%) of **14** as a colorless oil:  $[\alpha]_D^{22} -4.3^\circ$  (*c* 1.17, CHCl<sub>3</sub>); IR (neat) 3070, 3034, 1734, 1641, 1457, 1255, 1209, 835 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.32–7.28 (m, 5 H), 7.27–7.24 (m, 5 H), 5.76 (ddd, *J* = 16.9, 10.2, 6.8, 6.8 Hz, 1 H), 5.63–5.54 (m, 1 H), 5.18–4.92 (m, 8 H), 3.59–3.53 (m, 1 H), 2.67 (d, *J* = 7.3 Hz, 2 H), 2.05–1.96 (m, 3 H), 1.88–1.82 (m, 1 H), 1.39–1.21 (m, 6 H), 0.86 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.9, 156.1, 138.8, 135.5, 132.2, 128.5, 128.2, 128.2, 119.0, 114.4, 97.3, 72.0, 66.9, 57.6, 37.0, 36.4, 33.8, 31.1, 28.4, 25.9, 24.4, 18.1, –4.5; HRMS (CI<sup>+</sup>) calcd for [C<sub>34</sub>H<sub>48</sub>O<sub>5</sub>Si+Na]<sup>+</sup> 587.3169, found 587.3152. Anal. calcd for C<sub>34</sub>H<sub>48</sub>O<sub>5</sub>Si: C, 72.30; H, 8.57. Found: C, 72.10; H, 8.36.

**Cyclodecenol 4.**

To a solution of diene **14** (822 mg, 1.46 mmol, 1.0 equiv) in 1.6 L of degassed CH<sub>2</sub>Cl<sub>2</sub> (0.001 M in substrate) was added 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium catalyst (186 mg, 0.22 mmol, 0.15 equiv). The faint pink solution was heated at reflux for 18 h. Additional catalyst (62 mg, 73 μmol, 0.5 equiv) was added and the reaction mixture was heated for 6 h. After cooling to room temperature, the reaction mixture was concentrated and poured through a plug of silica gel (10% EtOAc/hexanes eluent) and purified by column chromatography (10% EtOAc/hexanes, R<sub>f</sub> 0.29). Obtained 690 mg (88%) of the macrocycle as a colorless oil: [α]<sub>D</sub><sup>22</sup> −4.9° (*c* 1.17, CHCl<sub>3</sub>); IR 3414, 2929, 1732, 1455, 1258, 1083, 697 cm<sup>−1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.38–7.13 (m, 10 H), 5.55–5.45 (m, 1 H), 5.26–5.00 (m, 5 H), 3.82–3.69 (m, 1 H), 3.16–3.00 (m, 1 H), 2.71–2.40 (m, 2 H), 2.15–1.20 (m, 10 H), 0.89 (s, 3 H), 0.86 (s, 6 H), 0.00 (s, 3 H), −0.02 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.4, 171.1, 170.9, 170.8, 135.7, 135.5, 134.8, 133.5, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 126.5, 126.2, 125.9, 124.0, 123.7, 77.3, 76.8, 72.0, 71.9, 70.8, 66.9, 57.1, 56.4, 30.9, 30.2, 29.7, 29.5, 29.3, 28.6, 27.9, 26.8, 26.4, 25.8, 25.1, 24.3, 23.8, 20.5, 18.1, 18.0, −4.5, −4.9, −4.9. HRMS (CI<sup>+</sup>) calcd for [C<sub>32</sub>H<sub>44</sub>O<sub>5</sub>Si+H]<sup>+</sup> 536.3036, found 537.3032. Anal. calcd for C<sub>32</sub>H<sub>44</sub>O<sub>5</sub>Si: C, 71.60; H, 8.26. Found: C, 71.51; H, 8.39. The above silyl ether (197 mg, 0.37 mmol, 1.0 equiv) in 1.2 mL THF at 0 °C was treated with TBAF (0.44 mL, 1.0 M in THF, 0.44 mmol, 1.2 equiv). The reaction was warmed to room temperature and stirred 16 h. The reagents were quenched with satd. aq. NaHCO<sub>3</sub> (1 mL) and extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated. Purification by silica gel chromatography (30% EtOAc/hexanes, R<sub>f</sub> 0.24) provided 147 mg (95%) of **4** as a colorless oil: IR (neat) 3416,

1726, 1498, 1478, 1471, 1453, 1263, 1200, 1163, 1081  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33–7.28 (m, 6 H), 7.27–7.23 (m, 4 H), 5.59–5.45 (m, 1 H), 3.85–3.74 (m, 1 H), 3.14–2.98 (m, 1 H), 2.63–2.37 (m, 2 H), 2.10–1.90 (m, 3 H), 1.85–1.32 (m, 7 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 135.4, 134.4, 133.5, 128.5, 128.3, 128.1, 124.1, 123.9, 71.5, 70.4, 67.0, 56.9, 56.4, 29.9, 29.7, 29.2, 28.9, 28.5, 27.6, 26.7, 26.7, 26.5, 25.0, 23.9, 23.8, 20.3; HRMS ( $\text{CI}^+$ ) calcd for  $[\text{C}_{26}\text{H}_{30}\text{O}_5]^+$  422.2093, found 422.2097.



### Thioether **5**.

Representative procedure for radical deoxygenation: Oxalyl chloride (62  $\mu\text{L}$ , 0.71 mmol, 20 equiv) was added *via* syringe to a solution of cyclodecenol **4** (15 mg, 36  $\mu\text{mol}$ , 1.0 equiv) in 0.4 mL of  $\text{CH}_2\text{Cl}_2$  at room temperature. After 3 h, the solution was concentrated and the residue was redissolved in 3.6 mL of toluene. The reaction mixture was then cooled to  $-15\text{ }^\circ\text{C}$  and *N*-hydroxyl pyridine thione (6 mg, 43  $\mu\text{mol}$ , 1.2 equiv) and DMAP (0.4 mg, 4  $\mu\text{mol}$ , 0.1 equiv) were added and the resultant solution was photolyzed for 1 h. After an additional 1 h of stirring in the absence of light, the mixture was concentrated. Purification by column chromatography ( $\text{SiO}_2$ , 20→30% EtOAc/hexanes,  $R_f$  0.53) provided 9.3 mg (51%, 84:16 er, determined by chiral HPLC, OD-H column, 90:10 hexanes/IPA, 0.9 mL/min) of thioether **5** as a colorless oil:  $[\alpha]_D^{22}$



+32.6° (*c* 0.135, CHCl<sub>3</sub>); IR 3414, 2925, 1729, 1452, 1261, 1112 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.38 (d, *J* = 4.0 Hz, 1 H), 7.43 (t, *J* = 7.3 Hz, 1 H), 7.33–7.18 (m, 8 H), 7.16–7.09 (m, 4 H), 6.90 (t, *J* = 5.3 Hz, 1 H), 5.22 (d, *J* = 12.4 Hz, 1 H), 4.86 (d, *J* = 12.5 Hz, 1 H), 3.96 (t, *J* = 11.0 Hz, 1 H), 2.86 (d, *J* = 14.8 Hz, 1 H), 2.55 (dd, *J* = 14.2, 7.2 Hz, 1 H), 2.49 (dd, *J* = 14.8, 10.6 Hz, 1 H), 2.31–2.21 (m, 1 H), 2.17–2.05 (m, 1 H), 2.02–1.90 (m, 2 H), 1.90–1.78 (m, 1 H), 1.68–1.50 (m, 4 H), 1.44–1.22 (m, 2 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.5, 171.0, 135.5, 135.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 67.0, 66.9, 58.0, 49.4, 42.5, 41.8, 35.8, 34.9, 33.6, 28.4, 25.1; HRMS (Cl<sup>+</sup>) calcd for [C<sub>31</sub>H<sub>33</sub>NO<sub>4</sub>S+H]<sup>+</sup> 516.2209, found 516.2185.