

## A Catalytic Enantioselective Total Synthesis of (-)-Wodeshiol

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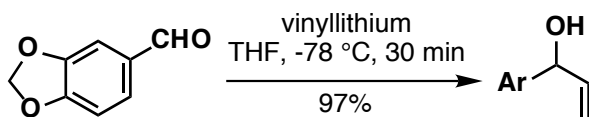
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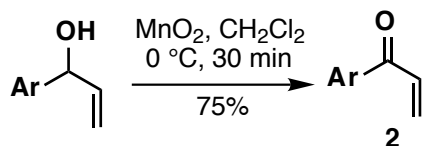
**Supporting Information:** Full experimental procedures for the synthesis of (-)-wodeshiol.

**Material and Methods.** Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. Azotropic drying of starting materials was performed by the addition of dry toluene or benzene followed by slow application of full vacuum at room temperature in order to prevent bumping. Molecular sieves were dried by heating them at 110 °C at 50 torr for at least 24 h. CuCl was recrystallized from concentrated HCl, and dried under high vacuum for 15 h. Benzene (PhH) was distilled from calcium hydride under nitrogen. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) was distilled from P<sub>2</sub>O<sub>5</sub> (essential for removing alcohol stabilizers) under nitrogen. Diethyl ether (Et<sub>2</sub>O), tetrahydrofuran (THF), and toluene (PhCH<sub>3</sub>) were distilled from sodium benzophenone ketyl under nitrogen, utilizing sodium dispersion in paraffin. Dimethyl sulfoxide (DMSO) was stirred over flame dried CaSO<sub>4</sub> powder overnight and vacuum distilled with bath temperature not higher than 80 °C. All other commercially obtained reagents were used as received. Reaction temperature was controlled by a Scientific Instruments temperature modulator model 2230. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are reported relative to Me<sub>4</sub>Si (δ 0.0). High resolution mass spectra were performed at The Harvard

University Mass Spectrometry Center. Chiralcel HPLC columns were obtained from Daicel Chemical Industries, Ltd. Specific optical rotations  $[\alpha]$ , were measured using a Perkin-Elmer 241 polarimeter at the indicated temperature with a sodium lamp (D line, 589 nm), unless otherwise noted, and are reported in degrees per unit of concentration,  $c$  (10 mg/mL), per unit of length (10 cm).  $\text{Pd}(\text{PPh}_3)_4^1$  was prepared as previously described.

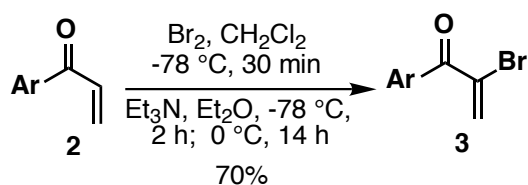


**1-(3,4-Methylenedioxyphenyl)-1-propenol.** To a cooled (-78 °C) solution of vinyl lithium (2.2 M in THF, 38.0 mL, 83.6 mmol) and THF (80 mL) was added piperonal (10.5 g, 70 mmol) in THF (20 mL) dropwise. The reaction mixture was stirred at -78 °C for 30 min, then quenched by the addition of water (10 mL) and PH = 7 buffer solution (20 mL). After separation, the aqueous layer was extracted with ether (2 X 40 mL). The combined organic layers were washed with 10% KOH (2 X 60 mL) and brine (2 X 70 mL), then dried over  $\text{Na}_2\text{SO}_4$ . The combined organic layers were concentrated to a residue that was subjected to column chromatography (1:3 EtOAc/hexanes) to give the title compound (12.1 g, 97% yield) as a light yellow oil spectroscopically identical with literature values.<sup>2</sup>



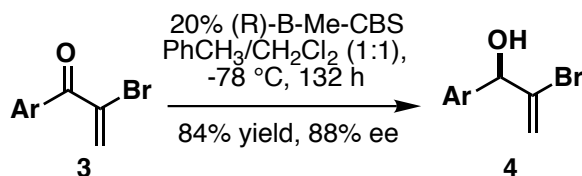
**1-(3,4-Methylenedioxyphenyl)-1-propenone (2).**  $\text{MnO}_2$  (58 g, azotropically dried with benzene (PhH) [2 X 50 mL]) was added to a flame dried flask, then  $\text{CH}_2\text{Cl}_2$  (100 mL) was introduced at room temperature. A solution of

the alcohol (5.76 g, 32.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added dropwise at 0 °C to the above mixture. The mixture was stirred at 0°C for 30 min, and filtered through a pad of Celite. The solid residue in the funnel was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 X 60 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> solutions were concentrated to afford ketone **2** (4.28 g, 75% yield) as a light yellow liquid spectroscopically identical with reported literature values.<sup>3</sup>



**2-Bromo-(3,4-methylenedioxyphenyl)-1-propenone (3).** Into a flame-dried 250 mL of one-neck round bottom flask equipped with a magnetic stir bar was placed ketone **2** (4.76 g, 27.0 mmol, aprotically dried with PhH [2 X 10 mL]) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL). Bromine (1.39 mL, 27.0 mmol) was added at -78 °C to the above mixture over 10 min. The mixture was stirred at -78 °C for 30 min, then 1-hexene (0.9 mL) was added to quench excess of Br<sub>2</sub>. The mixture was warmed up to room temperature, stirred at this temperature for 30 min, and recooled to -78 °C. A solution of Et<sub>3</sub>N (4.52 mL, 32.4 mmol) in freshly distilled, peroxide-free Et<sub>2</sub>O (35 mL) was added dropwise at -78 °C to the above mixture in 10 min. The mixture was stirred at -78 °C for 2 h, then warmed up to 4 °C and stirred at this temperature for 14 h. The mixture was diluted with freshly distilled, peroxide-free ether (120 mL), and washed with sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 mL). After the aqueous layer was extracted with freshly distilled ether (3 X 25 mL), the combined organic layers were washed with brine (2 X 80 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The combined organic layers were concentrated to a residue that was subjected to column chromatography (1:7 EtOAc/hexanes) to give bromo

ketone **3** (4.82 g, 70 % yield) as a light yellow solid; FTIR (film) 1659  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (dd,  $J = 8.2, 1.7$  Hz, 1H), 7.35 (d,  $J = 1.7$  Hz, 1H), 6.86 (d,  $J = 8.1$  Hz, 1H), 6.40 (d,  $J = 2.4$  Hz, 1H), 6.37 (d,  $J = 2.4$  Hz, 1H), 6.07 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.6, 152.3, 148.1, 129.0, 128.4, 128.0, 126.8, 109.5, 107.9, 102.1; HRMS (EI) for  $[\text{C}_{10}\text{H}_7\text{BrO}_3]^+$ ,  $m/z$  calcd 253.9579, found 253.9586.



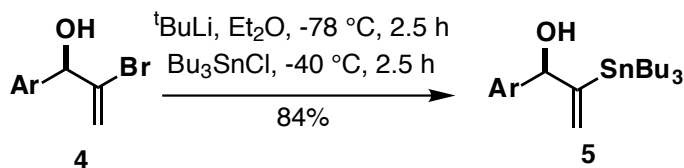
**(R)-2-Bromo-1-(3,4-Methylenedioxyphenyl)-1-propenol (4).**

Bromoketone **3** (2.04 g, 8.0 mmol) was added to a flame-dried 100 mL one-neck round bottom flask, and azeotropically dried with  $\text{PhCH}_3$  (2 X 7 mL) at room temperature.  $\text{PhCH}_3$  (22 mL) and  $\text{CH}_2\text{Cl}_2$  (35 mL) were added to the above flask, and the resulting mixture was cooled to  $-78^\circ\text{C}$ . The above mixture was treated with (R)-B-Me catalyst (8.0 mL, 1.6 mmol, 0.20 M in  $\text{PhCH}_3$ ).

Catecholborane (1.71 mL, 16.0 mmol) in  $\text{PhCH}_3$  (5 mL) was added dropwise in 40 min at  $-78^\circ\text{C}$ . The resulting clear mixture was stirred at  $-78^\circ\text{C}$  for 132 h.

$\text{MeOH}$  (8.0 mL) was added down the side of the flask and the mixture was stirred at  $-78^\circ\text{C}$  for 15 min. The mixture was warmed up to room temperature, diluted with ether (330 mL) and washed with pH = 13 buffer solution until the aqueous washings were clear (11 X 30 mL). The dark aqueous washes were extracted with ether (2 X 40 mL), then these two ether washes were combined and washed with pH = 13 buffer solution (2 X 10 mL). The combined all ether layers were washed with brine (150 mL), and concentrated to a residue that was subjected to column chromatography (1:5 EtOAc/hexanes) to give alcohol

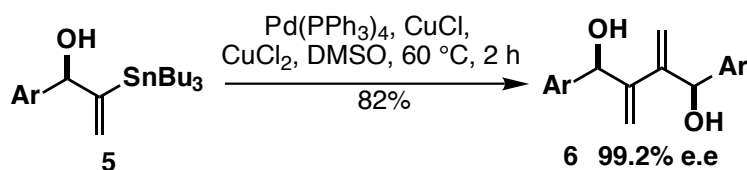
**4** (1.725 g, 84% yield) as a colorless oil of 88% ee (determined by chiral HPLC), which became an off-white solid upon storing at -20 °C;  $[\alpha]_D^{23}$  -20.4 (c 1.2, CHCl<sub>3</sub>); FTIR (film) 3403 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.90 (d, J = 0.50 Hz, 1H), 6.89 (dd, J = 7.9, 0.52 Hz, 1H), 6.80 (dd, J = 7.9, 0.50 Hz, 1H), 6.06 (dd, J = 1.8, 1.2 Hz, 1H), 5.97 (s, 2H), 5.67 (dd, J = 2.0, 0.55 Hz, 1H), 5.19 (d, J = 4.8 Hz, 1H), 2.34 (d, J = 5.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 147.8, 147.6, 135.5, 133.7, 120.6, 117.3, 108.1, 107.1, 101.2, 77.6; HRMS (EI) for [C<sub>10</sub>H<sub>9</sub>BrO<sub>3</sub>]<sup>+</sup>, m/z calcd 255.9735, found 255.9736; HPLC (chiral) Chiralcel OD at 23 °C, n = 254 nm (90:10 hexane/2-propanol eluent) retention times 11.9 (S) and 16.3 (R) min at 1 mL/min flow rate.



**(R)-1-(3,4-Methylenedioxyphenyl)-2-(tri-n-butylstannyl)-1-propenol**

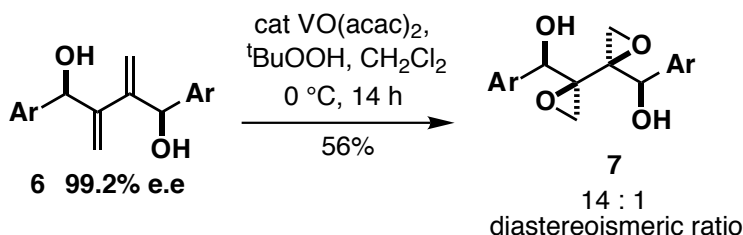
**(5).** To a cooled (-78°C) solution of bromo alcohol **4** (0.257 g, 1.0 mmol, azotropically dried with PhH [2 x 2 mL]) in Et<sub>2</sub>O (3 mL) was added <sup>t</sup>BuLi (1.7 M in pentane, 1.88 mL, 3.2 mmol) dropwise over 6 min. The reaction mixture was stirred at -78 °C for 2.5 h. Freshly distilled Bu<sub>3</sub>SnCl (0.38 mL, 1.4 mmol) was added over 3 min. The reaction mixture was stirred at -78 °C for 10 min, warmed to -40 °C and stirred at -40°C for 2.5 h. The reaction mixture was quenched by the addition of a mixture of pH = 7.0 buffer solution (10 mL) and water (10 mL) at -40 °C, and allowed to warm up to room temperature. The mixture was extracted with Et<sub>2</sub>O (3 x 40 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to a residue that was subjected to column chromatography (1:19 EtOAc/hexanes containing 1% Et<sub>3</sub>N as eluent) to

give vinyltin **5** (0.40 g, 84% yield) as a colorless liquid;  $[\alpha]^{23}_{\text{D}} +6.3$  (c 0.52,  $\text{CHCl}_3$ ); FTIR (film)  $3421\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.81 - 6.77 (m, 3H), 5.94 (s, 2H), 5.92 (app t,  $J = 1.8\text{ Hz}$ ,  $J_{\text{SnH}} = 61.2\text{ Hz}$ , 1H), 5.32 (app t,  $J = 1.7\text{ Hz}$ ,  $J_{\text{SnH}} = 30.8\text{ Hz}$ , 1H), 5.24 - 5.23 (m,  $J_{\text{SnH}} = 18.0\text{ Hz}$ , 1H), 1.89 (d,  $J = 3.3\text{ Hz}$ , 1H), 1.38 - 1.31 (m, 6H), 1.28 - 1.21 (m, 6H), 0.85 (t  $J = 7.2\text{ Hz}$ , 9H), 0.78 - 0.73 (m, 6H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.9, 147.7, 146.8, 137.1, 124.0, 119.9, 107.9, 107.2, 100.9, 80.1, 28.9, 27.3, 13.6, 9.9; HRMS (EI) for  $\text{C}_{18}\text{H}_{27}\text{O}_3\text{Sn}$  [ $\text{M} - \text{C}_4\text{H}_9$ ] $^+$ ,  $m/z$  calcd 411.0982, found 4110970.

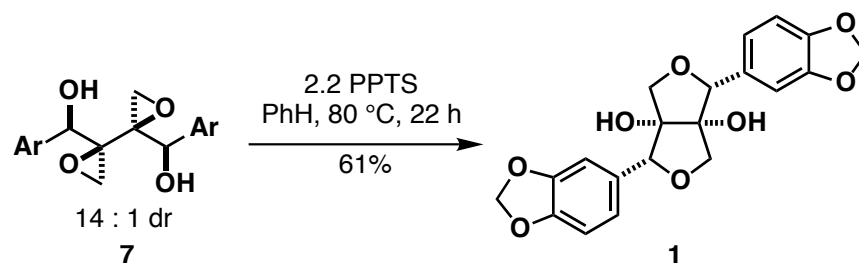


**Diene 6.** A flame-dried Schlenk tube, was charged with  $\text{Pd}(\text{PPh}_3)_4$  (71.6 mg, 0.062 mmol),  $\text{CuCl}$  (307 mg, 3.1 mmol), and  $\text{CuCl}_2$  (167 mg, 1.24 mmol) and vacuum purged (4 x) with Ar. Vinyltin **5** (0.29 g, 0.62 mmol) in DMSO (5 mL) was added to the above mixture with concomitant stirring, then the flask was rinsed with additional DMSO (1.2 mL) and the rinse was added to the above reaction mixture. The resulting mixture was vacuum purged (3 x) with Ar. The reaction mixture was stirred at room temperature for 10 min, then was heated at  $60\text{ }^\circ\text{C}$  for 2.0 h. The reaction mixture was cooled, diluted with  $\text{Et}_2\text{O}$  (80 mL), and washed with a mixture of brine (80 mL) and 5% aqueous  $\text{NH}_4\text{OH}$  (10 mL). The aqueous layers were back-extracted with  $\text{Et}_2\text{O}$  (2 x 15 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (2 x 50 mL), then concentrated to a residue that was subjected to column chromatography (45:55  $\text{EtOAc}$ /hexanes eluent) to afford diene **6** and meso **6** (8:1 mixture, 90.0 mg, 82% yield) as a light yellow solid; m. p. ( $\text{EtOAc}$ /hexanes)  $119 - 121\text{ }^\circ\text{C}$ ;  $[\alpha]^{23}_{\text{D}} -$

70.0 (c 0.74, CHCl<sub>3</sub>); FTIR (film) 3369 cm<sup>-1</sup>; HRMS (EI) calcd for [C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>]<sup>+</sup>, m/z calcd 354.1104, found 354.1114. Spectra data for diene **6**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.69 (d, J = 0.95 Hz, 2H), 6.64 (d, J = 0.91 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 5.35 (s, 1H), 5.30 (s, 1H), 5.17 (s, 1H), 2.30 (d, J = 3.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 147.8, 147.5, 147.0, 135.5, 120.4, 114.5, 107.8, 107.2, 101.0, 75.2.



**Diepoxide 7.** The diene (30 mg, 0.085 mmol) was weighed into a Schlenk tube and azotropically dried with PhH (2 x 2 mL). CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and <sup>t</sup>BuOOH (0.25 mmol, 26.4 μL, neat) were added. After the mixture was cooled to 0 °C, a CH<sub>2</sub>Cl<sub>2</sub> solution of VO(acac)<sub>2</sub> was added in four portions (0 h, 2 h, 4 h, 6 h) to keep the reaction brownish red (each time 30 μL, totally about 15 mol% of the catalyst in 150 μL of CH<sub>2</sub>Cl<sub>2</sub>, 0.085 M in CH<sub>2</sub>Cl<sub>2</sub>). After all of the necessary VO(acac)<sub>2</sub> was added, the mixture was stirred at 0 °C for an additional 12 h. After the mixture was filtered through a pad of silica gel, the filtrate was concentrated to a residue that was subjected to column chromatography (50:50 EtOAc/hexanes) to give diepoxide **7** (18.3 mg, 56% yield) as an off-white foam; [α]<sub>D</sub><sup>23</sup> -14.2 (c 0.27, CHCl<sub>3</sub>); FTIR (film) 3386 cm<sup>-1</sup>; HRMS (FAB) calcd for [C<sub>20</sub>H<sub>18</sub>O<sub>8</sub> + Na]<sup>+</sup>, m/z calcd 409.0899, found 409.0907. Spectra data for the major isomer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.89 (d, J = 1.7 Hz, 1H), 6.80 (dd, J = 8.1, 1.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.96 (s, 2H), 4.94 (s, 1H), 3.21 (br s, 1H), 2.66 (d, J = 5.2 Hz, 1H), 2.41 (d, J = 5.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 147.5, 147.4, 132.3, 120.6, 107.8, 107.6, 101.1, 73.9, 59.2, 50.1.



**(-)-Wodeshiol (1).** Diepoxide **7** (36.3 mg, 0.094 mmol) was added to a 25 mL of round bottom flask, and azeotropically dried with PhH (2 x 2 mL). PhH (20 mL) and pyridinium p-toluenesulfonate (52.0 mg, 0.21 mmol) were added. The resulting mixture was refluxed for 22h. After it was cooled to room temperature, the mixture was filtered through a plug of silica gel. The filtrate was concentrated to a residue that was subjected to column chromatography (40:60 EtOAc/hexanes) to give (-)-wodeshiol (22.2 mg, 61% yield) as a colorless solid: m.p. (EtOAc/hexanes) 152 - 153 °C;  $[\alpha]_D^{23}$  -11.7 (c 0.71, CHCl<sub>3</sub>); FTIR (CHCl<sub>3</sub>) 3460 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.90 (s, 1H), 6.84 (s, 2H), 5.98 (s, 2H), 5.00 (s, 1H), 4.12 (s, 2H), 2.41 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 148.0, 147.7, 129.6, 120.3, 108.4, 107.6, 101.2, 87.5, 86.9, 76.4; HRMS (FAB) calcd for [C<sub>20</sub>H<sub>18</sub>O<sub>3</sub> + Na]<sup>+</sup>, m/z calcd 409.0899, found 409.0879.

## References

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