Enantioselective Total Synthesis of (+)-Cassiol

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Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. Liquids and solutions were transferred via syringe or cannula. All the starting materials were purchased from Sigma-Aldrich or Alfa Aesar, and used as received, unless otherwise stated. Previously reported methods were used to prepare (R)-t-BuPHOX (8),1 Pd2(pmdba)3,2 and PdCl2(CH3CN)2.3 Osmium tetroxide and Pb(OAc)4 were purchased from Sigma-Aldrich, and the Pb(OAc)4 was stored under a glovebox atmosphere prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or KMnO4 staining. SiliCycle® SiliaFlash® P60 Academic Silica Gel (particle size 40–63 µm; pore diameter 60 Å), or Florisil® (100–200 mesh) were used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. 1H and 13C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to Me4Si (δ 0.0 ppm). Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm⁻¹). Melting points are uncorrected. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.
Vinylogous Thioester 4. To a solution of diketone SI1 (5.00 g, 39.82 mmol, 1.00 equiv) in CH$_3$CN (44 mL) was added Et$_3$N (6.2 mL, 44.40 mmol, 1.12 equiv), and the solution was allowed to stir for 5 min, then cooled to 0 °C. Methanesulfonyl chloride (3.26 mL, 42.00 mmol, 1.06 equiv) was added, and the reaction was warmed to 23 °C over 2 h. Stirring was continued for 5 h, and the reaction was cooled to 0 °C. Triethylamine (6.2 mL, 44.40 mmol, 1.12 equiv) was added, followed by benzethiol (4.2 mL, 40.80 mmol, 1.03 equiv). The reaction was allowed to warm to 23 °C over 2 h and stirring was continued for 9 h. Saturated aq Na$_2$CO$_3$ (70 mL) was added, the phases were separated, and the aq phase was extracted with Et$_2$O (3 x 120 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded vinylogous thioester \( \text{4 (7.15 g, 82% yield)} \) as a white crystalline solid. \( R_f = 0.33 \) (20% EtOAc in hexanes); mp 85 °C; \(^1\)H NMR (500 MHz, CDCl$_3$) \( \delta \) 7.51-7.49 (m, 2H), 7.44-7.37 (comp m, 3H), 2.38 (t, \( J = 6.5 \) Hz, 2H), 2.18 (tq, \( J = 6.5, 2.0 \) Hz, 2H), 1.97 (t, \( J = 2.0 \) Hz, 3H), 1.87 (app pentuplet, \( J = 6.0 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl$_3$) \( \delta \) 195.6, 157.9, 130.3(2C), 129.6, 129.5, 37.3, 30.5, 22.9, 12.4; IR (Neat Film NaCl) 2944, 1655, 1578, 1339, 1296 cm$^{-1}$; HRMS (FAB+) m/z: calc’d for C$_{13}$H$_{14}$OS [M + H]$^+$: 219.0844, found 219.0843.

\( \beta \)-Ketoester 7. To a –78 °C solution of diisopropylamine (2.63 mL, 18.78 mmol, 2.00 equiv) in toluene (70 mL) was added dropwise n-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to 0 °C, allowed to stir for 10 min, and cooled to –78 °C. A solution of thioester 4 (2.00 g, 9.16 mmol, 1.00 equiv) in toluene (15 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (1.02 mL, 9.62 mmol, 1.05 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. Stirring was continued for 4 h, then aq KHSO$_4$ (1 N, 70 ml) was added, and the resulting solution was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et$_2$O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

To a solution of the crude yellow oil (3.32 g) in CH$_3$CN (40 mL) was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv), and iodomethane (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at 80 °C for 5 h, and then MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at 80 °C for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na$_2$SO$_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded \( \beta \)-ketoester \( (+)-7 \) (2.26 g, 78% yield over two steps) as white solid. \( R_f = 0.35 \) (30% EtOAc in hexanes); mp 34 °C; \(^1\)H NMR (300 MHz, CDCl$_3$) \( \delta \) 7.51-7.35 (comp m, 5H), 5.87 (app ddt, \( J = 10.5, 17.1, 5.4 \) Hz, 1H), 5.27 (app ddt, \( J = 17.1, 1.7, 1.8 \) Hz, 1H), 5.22 (app ddt, \( J = 9.9, 1.7, 1.2 \) Hz, 1H), 4.65 (dddd, \( J = 1.5, 1.8, 5.7, 13.5 \) Hz, 1H), 4.55 (ddddd, \( J = 1.5, 1.8, 5.7, 13.5, 13.5 \) Hz, 1H), 2.41-
2.32 (m, 1H), 2.30-2.21 (m, 1H), 2.16-2.06 (1H), 2.00 (t, J = 1.8 Hz, 3H), 1.78 (ddd, J = 4.5, 8.1, 13.2 Hz, 1H), 1.38 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 193.0, 172.6, 156.7, 135.6, 131.9, 129.7, 129.5, 128.9, 118.1, 65.7, 52.3, 33.1, 27.4, 20.7, 12.9; IR (Neat Film NaCl) 2936, 1733, 1656, 1580, 1314, 1254, 1238, 1174, 985, 752, 693 cm$^{-1}$; HRMS (FAB+) m/z: calc’d for C$_{18}$H$_{20}$O$_3$S [M + H]$^+$: 317.1211, found 317.1211.

**Allyl Ketone (−)-9.** A solution of Pd$_2$(pmdba)$_3$ (0.1306 g, 0.1185 mmol, 0.025 equiv) and (R)-t-BuPHOX (8) (0.1148 g, 0.2964 mmol, 0.0625 equiv) in toluene (30 mL) was prepared in a glovebox under N$_2$ atmosphere, and allowed to stir at 23 °C for 30 min. A solution of β-ketoester (±)-7 (1.50 g, 4.741 mmol, 1.00 equiv) in toluene (10 mL) was transferred to the reaction vessel dropwise via glass pipette, washing with toluene (7.5 mL) for quantitative transfer. The reaction vessel was sealed with a rubber septum, removed from the glove box, heated in a 60 °C oil bath, and the solution was allowed to stir for 24 h. The reaction vessel was cooled to room temperature, and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford allyl ketone (−)-9 (0.92 g, 71% yield, 92% ee as determined by chiral HPLC using a Chiralpak AD column with 4% EtOH in hexanes as the eluent, see graphical HPLC data on page SI 9) as a colorless oil. $R_f$ = 0.45 (30% EtOAc in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.52-7.48 (m, 2H), 7.43-7.35 (comp m, 3H), 5.68 (app ddt, J = 10.8, 16.8, 7.5 Hz, 1H), 5.03 (dddt, J = 9.9, 2.4, 0.9, 0.6 Hz, 1H), 5.01 (dddt, J = 17.4, 2.4, 1.5, 1.2 Hz, 1H), 2.32 (app ddt, J = 13.8, 7.2, 1.2 Hz), 2.19-2.10 (comp m, 3H), 1.96 (t, J = 1.8 Hz, 3H), 1.86-1.75 (m, 1H), 1.66-1.56 (m, 1H), 1.04 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 199.5, 155.6, 135.6, 134.4 130.3, 129.6, 129.5, 128.8, 43.1, 41.7, 33.1, 26.9, 22.3, 12.9; IR (Neat Film NaCl) 3074, 2964, 1997, 1932, 1733, 1652, 1584, 1339, 1287, 1228 cm$^{-1}$; HRMS (FAB+) m/z: calc’d for C$_{17}$H$_{20}$OS [M + H]$^+$: 273.1313, found 273.1317; [α]$_D$$^{25.4}$ = −57.4 (c 1.00, CH$_2$Cl$_2$).

**Isomerized alkene (−)-10.** A solution of allyl ketone (−)-9 (0.80 g, 2.94 mmol, 1.00 equiv) and PdCl$_2$(CH$_3$CN)$_2$ (76.3 mg, 0.29 mmol, 0.10 equiv) in benzene (5.8 mL) was sparged with Ar for 10 min. The flask was sealed, and heated to 60 °C for 12 h. The reaction was cooled to room temperature, the solvent was evaporated in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford an inseparable mixtures of isomerized alkene (−)-10 and starting material (−)-9 (0.7951 g, 99% overall yield, ratio of 13:1 of 10:9 by NMR). $R_f$ = 0.45 (30% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ (additional peaks correspond to compound 9) 7.52-7.47 (m, 2H), 7.36-7.42 (comp m, 3H), 5.45 (dq, J = 1.5, 15.5 Hz, 1H), 5.33 (dq, J = 6.0, 15.5 Hz, 1H), 2.26-2.04 (m, 2H), 1.98 (t, J = 1.5 Hz, 3H), 1.83-1.72 (m, 2H), 1.66 (dd, J = 2.0, 6.5 Hz, 3H), 1.14 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 198.1, 155.9, 135.5, 133.7, 130.4, 129.5, 129.4, 129.3, 124.9, 46.2, 35.3, 27.4, 24.3, 18.5, 12.9;
IR (Neat Film NaCl) 2923, 1651, 1588, 1440, 1339, 1025 cm⁻¹; HRMS (FAB+) m/z: calc’d for C₁₇H₂₀OS [M + H]⁺: 273.1313, found 273.1314; [α]D₂⁰⁻34.8 (c 1.00, CH₂Cl₂).

To a solution of the crude white solid (0.64 g) in benzene (17 mL) was added Pb(OAc)₄ (1.02 g, 2.31 mmol, 1.10 equiv), and the solution was allowed to stir at 30 °C for 1 h. The solution was concentrated in vacuo, and the resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford aldehyde (−)-11 (0.40 g, 70% yield over two steps) as a white solid. Rf = 0.60 (30% EtOAc in hexanes); mp 41 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.57 (s, 1H), 7.52-7.36 (comp m, 5H), 2.35-2.10 (m, 3H), 1.98 (t, J = 1.5 Hz, 3H), 1.76-1.67 (m, 1H), 1.27 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.1, 193.7, 159.2, 135.9, 130.0, 129.7, 129.4, 128.9, 56.4, 29.0, 26.7, 18.9, 12.5; IR (Neat Film NaCl) 2931, 1725, 1642, 1578, 1440, 1319, 1239, 1025 cm⁻¹; HRMS (FAB+) m/z: calc’d for C₁₅H₁₆O₂S [M + H]⁺: 261.0949, found 261.0944; [α]D²⁰⁻30.4 (c 1.00, CH₂Cl₂).

Alcohol (−)-3. A solution of lithium tri-tert-butoxy aluminium hydride (1.34 mL, 1.00 M solution in THF, 1.41 mmol, 1.05 equiv) in THF (7 mL) was cooled to 0 °C. This solution was then added to a 0 °C solution of aldehyde (−)-11 (0.35 g, 1.35 mmol, 1.00 equiv) in THF (20 mL) in seven equal portions over 2 h. The reaction was allowed to stir for an additional 30 min, then H₂O (0.3 mL) was added, followed by 15% aq NaOH (0.3 mL), and then H₂O (0.9 mL). The reaction was warmed to 23 °C, and allowed to stir for 30 min. The solution was filtered through Celite (washing with EtOAc), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford alcohol (−)-3 (0.30 g, 85% yield) as a white solid (90.3% ee as determined by chiral HPLC using a Chiralpak AD column with 80% EtOH in hexanes as the eluent, see graphical HPLC data on page S1 11). Rf = 0.22 (30% EtOAc in hexanes); mp 49 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.54-7.49 (m, 2H), 7.46-7.40 (comp m, 3H), 3.51 (dd, J =11.1, 8.1 Hz, 2H), 2.88 (dd, J = 5.1, 7.8 Hz, 1H), 2.38-2.10 (comp m, 2H), 1.98-1.88 (comp m, 4H), 1.46 (ddd, J = 3.3, 4.8, 13.2 Hz, 1H), 1.11 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 202.2, 157.8, 135.8, 129.8, 129.6, 128.4, 69.5, 44.5, 31.1, 26.7, 18.8, 12.5; IR (Neat Film NaCl) 3433 (br), 2927, 1642, 1578, 1440, 1339, 1025, 750 cm⁻¹; HRMS (FAB+) m/z: calc’d for C₁₅H₁₆O₈S [M + H]⁺: 263.1106, found 263.1115; [α]D²⁰⁻13.3 (c 1.00, CH₂Cl₂).
Vinyl iodide 5. 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 0.0424 g, 0.27 mmol, 0.10 equiv) was added to a solution of alcohol 6 (0.40 g, 2.74 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (8 mL), and the reaction was allowed to stir for 5 min. To the reaction vessel was added saturated aq NaHCO$_3$ via cannula, washing with ether (2.5 mL) 2.5 mmol, 1 equiv) in diethyl ether (2.5 mL) was cooled to 0 °C, and added to the reaction vessel dropwise. The solution was allowed to stir for 1 h, and then warmed to 0 °C. A solution of alcohol (trans isomer) 6.02 (dd, $J = 8.5, 12.0$ Hz, 2H), 3.25 (dd, $J = 9.0, 12.0$ Hz, 2H), 2.04 (dtt, $J = 9.0, 8.5, 5.0$ Hz, 1H), 1.38 (s, 3H), 1.20 (s, 3H); (cis isomer): 5.79 (dd, $J = 7.5$ Hz, 1H), 5.79 (dd, $J = 7.5, 8.5$ Hz, 1H), 3.67 (dd, $J = 4.0, 11.5$ Hz, 2H), 3.41 (dd, $J = 7.0, 11.5$ Hz, 2H), 3.25 (dd, $J = 9.0, 11.5$ Hz, 2H), 2.66 (dtt, $J = 7.0, 8.5, 4.0$ Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); $^1$C NMR (75 MHz, C$_6$D$_6$) δ (trans isomer) 143.6, 98.0, 78.5, 63.2, 42.2, 27.6, 21.2; IR (Neat Film NaCl) 2992, 2940, 2863, 1604, 1478, 1453, 1386, 1371, 1262, 78.5, 63.2, 42.2; 1H NMR) as a thick yellow oil. Purification by column chromatography (gradient elution of 3% to 10% EtOAc in hexanes) yielded vinyl iodide 5 (0.42 g, 58% yield, 5:1 E/Z mixture) by $^1$H NMR as a thick yellow oil. $R_f = 0.29$ (10% EtOAc in hexanes); $^1$H NMR (500 MHz, C$_6$D$_6$) δ (trans isomer) 6.02 (dd, $J = 8.5, 15.0$ Hz, 1H), 5.62 (d, $J = 15.0$ Hz, 1H), 3.45 (dd, $J = 5.0, 12.0$ Hz, 2H), 3.25 (dd, $J = 9.0, 12.0$ Hz, 2H), 2.04 (dtt, $J = 9.0, 8.5, 5.0$ Hz, 1H), 1.38 (s, 3H), 1.20 (s, 3H); (cis isomer): 5.89 (d, $J = 7.5$ Hz, 1H), 5.79 (dd, $J = 7.5, 8.5$ Hz, 1H), 3.67 (dd, $J = 4.0, 11.5$ Hz, 2H), 3.41 (dd, $J = 7.0, 11.5$ Hz, 2H), 3.25 (dd, $J = 9.0, 11.5$ Hz, 2H), 2.66 (dtt, $J = 7.0, 8.5, 4.0$ Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); $^1$C NMR (75 MHz, C$_6$D$_6$) δ (trans isomer) 143.6, 98.0, 78.5, 63.2, 42.2, 27.6, 21.2; IR (Neat Film NaCl) 2992, 2940, 2863, 1604, 1478, 1453, 1386, 1371, 1262, 1205, 1153, 1131, 1076, 1036, 949, 830 cm$^{-1}$; HRMS (FAB+) $m/z$: calc’d for C$_8$H$_{12}$O$_2$I [M + H]$^+$: 269.0039, found 269.0040.

(+)-Cassiol (1). To a solution of vinyl iodide 5 (0.204 g, 0.76 mmol, 2.00 equiv) in diethyl ether (5 mL) at −78 °C was added dropwise $t$-BuLi (1.37 M soln in pentane, 1.18 mL, 1.62 mmol, 4.25 equiv). The solution was allowed to stir for 1 h, and then warmed to 0 °C. A solution of alcohol (−)-3 (0.10 g, 0.38 mmol, 1 equiv) in diethyl ether (2.5 mL) was cooled to 0 °C, and added to the reaction vessel dropwise via cannula, washing with ether (2.5 mL) for quantitative transfer. The resulting solution was warmed to 24 °C, and allowed to stir for 72 h. To the reaction vessel was added saturated aq NaHCO$_3$ buffered to pH 8 with saturated aq NH$_4$Cl (7 mL). The phases were separated, the aq phase was extracted with
EtOAc (3 x 10 mL), and the combined organic extracts were concentrated in vacuo. The residue was dissolved in t-butyl methyl ether (8 mL), and 10% aq HCl solution (10 mL) was added to the reaction vessel. The solution was allowed to stir for 2 h, and solid NaHCO$_3$ (4.0 g) was added in small portions. The phases were separated, and the aq phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (10% MeOH in EtOAc), followed by purification by column chromatography on Florisil (100% EtOAc) afforded (+)-cassiol (1, 35.0 mg, 36%) as a thick colorless oil. $R_f=0.10$ (10% MeOH in CH$_2$Cl$_2$); $^1$H NMR (500 MHz, D$_2$O) $\delta$ 6.27 (d, $J = 16.5$ Hz, 1H), 5.66 (dd, $J = 8.5$, 16.5 Hz, 1H), 3.77 (d, $J = 11.5$, 1H), 3.74 (ddd, $J = 3.0$, 6.0, 11.0 Hz, 2H), 3.66 (ddd, $J = 2.0$, 7.0, 11.0 Hz, 1H), 1.80 (s, 3H), 1.75 (app dt, $J = 13.5$, 6.0 Hz, 1H), 1.11 (s, 3H); $^{13}$C NMR (125 MHz, D$_2$O, uncorrected) $\delta$ 204.8, 162.4, 136.7, 132.0, 129.6, 69.7, 64.139, 64.131, 47.7, 41.0, 34.0, 32.1, 21.1, 13.7. HRMS (FAB+) $m/z$: calc'd for C$_{14}$H$_{22}$O$_4$ [M + H]$^+$: 255.1596, found 255.1604; $\left[\alpha\right]_D^{26.8} +8.2$ (c 1.00, MeOH).

NMR data for (+)-cassiol was also collected in CDCl$_3$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.23 (d, $J = 16.5$ Hz, 1H), 5.59 (dd, $J = 8.0$, 16.5 Hz, 1H), 3.73-3.86 (comp m, 4H), 3.67 (d, $J = 11.5$ Hz, 1H), 2.78-2.58 (comp. m, 3H), 2.58-2.51 (comp m, 2H), 2.41 (br. s, 1H), 2.21 (ddd, $J = 6.5$, 10.5, 14.0 Hz, 1H), 1.82 (s, 3H), 1.64 (dt, $J = 13.5$, 5.5 Hz, 1H), 1.13 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 199.6, 158.4, 135.4, 132.1, 129.6, 69.7, 64.139, 64.131, 47.7, 41.0, 34.0, 32.1, 21.1, 13.7.

### Comparison Tables for Properties of Synthetic and Natural Cassiol:

**Table SII.** Comparison of $^1$H NMR data for synthetic, literature, and natural (+)-cassiol.

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$^a$ $^1$H NMR data measured at 500 MHz in D$_2$O (this work).

$^b$ $^1$H NMR data measured at 250 MHz in D$_2$O.$^8$

$^c$ $^1$H NMR data measured at 250 MHz in D$_2$O.$^9$
**Table SI2.** Comparison of $^{13}$C NMR data for synthetic, literature, and natural (+)-cassiol.

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</tr>
<tr>
<td>48.0</td>
<td>50.30</td>
<td>50.1</td>
<td></td>
</tr>
<tr>
<td>40.8</td>
<td>43.18</td>
<td>43.1</td>
<td></td>
</tr>
<tr>
<td>33.5</td>
<td>35.89</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>30.8</td>
<td>33.28</td>
<td>33.2</td>
<td></td>
</tr>
<tr>
<td>20.5</td>
<td>23.02</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>13.2</td>
<td>15.63</td>
<td>15.5</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ $^{13}$C NMR data measure at 125 MHz in D$_2$O (this work).

$^b$ $^{13}$C NMR data measure at 50 MHz in D$_2$O.

$^c$ $^{13}$C NMR data measure at 50.3 MHz in 1:1 CDCl$_3$/methanol-$d_4$.

**Table SI3.** Comparison of IR data for synthetic, literature, and natural (+)-cassiol.

<table>
<thead>
<tr>
<th></th>
<th>Synthetic$^a$</th>
<th>Literature$^b$</th>
<th>Natural sample$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3369</td>
<td>3368</td>
<td>3400</td>
<td></td>
</tr>
<tr>
<td>2930</td>
<td>2930</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2868</td>
<td>2876</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1643</td>
<td>1644</td>
<td>1650</td>
<td></td>
</tr>
<tr>
<td>1591</td>
<td>1594</td>
<td>1600</td>
<td></td>
</tr>
<tr>
<td>1455</td>
<td>1456</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1358</td>
<td></td>
<td>1340</td>
<td></td>
</tr>
<tr>
<td>1038</td>
<td>1044</td>
<td>1040</td>
<td></td>
</tr>
<tr>
<td>975</td>
<td></td>
<td>980</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Thin film (this work).

$^b$ Neat.

$^c$ Thin film.
**Table SI4.** Comparison of HRMS data for synthetic, literature, and natural (+)-cassiol.

<table>
<thead>
<tr>
<th>Synthetic calculated</th>
<th>Synthetic found&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Literature calculated</th>
<th>Literature found&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Natural sample found&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>255.1596</td>
<td>255.1604</td>
<td>254.1518</td>
<td>254.1519</td>
<td>254</td>
</tr>
</tbody>
</table>

<sup>a</sup> FAB+, measured [M + H]<sup>+</sup> (this work).

<sup>b</sup> EI-MS, measured [M]<sup>+</sup>.<sup>10</sup>

<sup>c</sup> EI-MS, measured [M]<sup>+</sup>.<sup>9</sup>

**Table SI5.** Comparison of optical rotation data for synthetic, literature, and natural (+)-cassiol.

<table>
<thead>
<tr>
<th>Synthetic&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Literature&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Natural sample&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>[α]&lt;sup&gt;D&lt;/sup&gt;&lt;sub&gt;26.8&lt;/sub&gt; +8.2</td>
<td>[α]&lt;sup&gt;D&lt;/sup&gt;&lt;sub&gt;30&lt;/sub&gt; +8.3</td>
<td>[α]&lt;sup&gt;D&lt;/sup&gt;&lt;sub&gt;28.5&lt;/sub&gt; +8.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> c = 1.00 in MeOH (this work).

<sup>b</sup> c = 0.35 in MeOH.<sup>8</sup>

<sup>c</sup> c = 0.25 in MeOH.<sup>9</sup>
Graphical HPLC Data for Compounds 9 and 3:

Data File C:\HPCHM\3\DATA\KVP\AYH179W.D  Sample Name: AYH-I-79U

KV-199, racemic, inst. 3, pos. 2

Inj Volume : 5 µl

Graphical HPLC Data for Compounds 9 and 3:

Area Percent Report

Signal 1: Wavelength=254 nm

Results obtained with standard integrator!

*** End of Report ***
Supporting Information for Petrova, Mohr, and Stoltz: Enantioselective Total Synthesis of (+)-Cassiol

SI

Enantioenriched (R-tBu-PhOX)

Injection Date: 4/10/2008 10:04:27 PM  
Sample Name: KVP265E  
Acq. Operator: KVP  
Inj Volume: 5 μl

Sample Name: KVP265E  
Location: Vial 11

Analysis Method: C:\HPCHEM\METHODS\A-E0120.M
Last changed: 9/22/2002 11:43:36 PM by jeff

Modified after loading

POSITION #2 METHOD: Valve to Position # 2 (Column #1).

-9, 91.6% ee  
Chiralpak AD
4% EtOH in hexane  
Isocratic, 1 mL/min

Signal 1: VWD λ, Wavelength=254 nm

Signal: [ ]

Sorted Ev: Signal
Multiplier: 1.0000
Dilution: 1.0000

Peak RetTime Type Width Area Height Area %
# [min] [min] [μAU] [μAU] %
---------|--------|--------|--------|--------|
1 6.724 MM 0.1550 14.26756 1.44141 4.1762
2 6.346 MM 0.2123 327.36058 25.70616 95.6239

Totals: 341.64854 27.14757

Results obtained with stander integrator!

*** End of Report ***
Supporting Information for Petrova, Mohr, and Stoltz: Enantioselective Total Synthesis of (+)- Cassiol

racemic alcohol, inst. 3, pos. 2, 80% EtOH

Injection Date : 7/14/2008 6:11:42 AM   Seq. Line : 3
Sample Name : KVP-rac13   Location : Vial 12
Acq. Operator : KVP   Inj Volume : 5 μl
Acq. Method : C:\HPCHEM\METHODS\00-EOH30.N
Last changed : 9/20/2005 10:52:31 AM by dave
Analysis Method : C:\HPCHEM\METHODS\PO52.N
Last changed : 7/14/2008 7:22:15 AM by KVP (modified after loading)

POSITION #2 METHOD : Valve to Position # 2 (Column # 1).

-------------------------------------

Aces Percent Report

-------------------------------------

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: WVDl Å, Wavelength=254 nm, TT

Peak RetTime Type Width Area Height Area
# [min] [min] mAU [s] mAU [s]

1 9.995 MM 0.2557 8985.10547 563.58981 49.3911
2 12.088 MM 0.3360 9206.64258 456.72882 50.6089

Totals : 1.61917e4 1020.28864

Results obtained with standard integrator!

*** End of Report ***
Enantioselective Total Synthesis of (+)-Cassiol

**Supporting Information for Petrova, Mohr, and Stoltz:**

KVP alcohols, inst 3, pos 2, 80% EOH30

Injection Date: 7/14/2008 6:21:00 PM  Seq. Line: 5
Sample Name: KVP-calc  Location: Vial 12
Acq. Operator: KVP  Inj: 1
Acq. Method: C:\HPCHER\METHODS\00-EOH30.M
Last changed: 9/20/2005 10:52:31 AM by dave
Analysis Method: C:\HPCHER\METHODS\POL.jpg
Last changed: 7/14/2008 7:18:39 AM by KVP
(modified after loading)

POSITION #2 METHOD: Valve to Position # 2 (Column # 1).

---

**Area Percent Report**
---

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000

Signal 1: WVD1 A, Wavelength=254 nm, TT
Peak RetTime Type Width Area Height Area
# [min] [min] nAU s nAU %
---|-------|--------|--------|--------|--------|
1 10.011 MM 0.2556 4251.78027 265.76372 4.8197
2 11.915 MM 0.4543 8.3964e4 3080.27637 95.1803

Totals: 3347.04459

Results obtained with standard integrator!
---

*** End of Report ***
$^{1}H$ and $^{13}C$ NMR Spectra:
Supporting Information for Petrova, Mohr, and Stoltz: Enantioselective Total Synthesis of (+)-Cassiol

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\(-\)-9
Supporting Information for Petrova, Mohr, and Stoltz: Enantioselective Total Synthesis of (+)-Cassiol
References:


