Versatile Asymmetric Synthesis of the Kavalactones: The First Synthesis of (+)-Kavain

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Supporting Information

General Information. Oxygen- or moisture-sensitive reactions were carried out in flame-dried or oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen. Similarly sensitive liquids and solutions were transferred by gas-tight syringe or canula. Unless indicated otherwise, reagents and solvents were purchased and used without purification. Ether, THF, and CH₂Cl₂, were purified by passage through a bed of activated alumina.¹ Analytical TLC was performed with 0.25 mm silica gel 60 plates with 254 nm fluorescent indicator from SiliCycle. Plates were visualized under UV light and treatment with either acidic *p*-anisaldehyde stain or aqueous ceric ammonium molybdate solution followed by gentle heating. The term flash chromatography refers to preparative silica gel column chromatography as described by Still and co-workers.² Some chromatography was accomplished using an Isco Combiflash System Sg 100c. Silica gel 60, 230–240 mesh, was purchased from SiliCycle (R10030B). Analytical high performance liquid chromatography (HPLC) was carried out on an Agilent 1100 chromatograph equipped with a variable wavelength detector. ¹H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or Bruker DPX300 (300 MHz) spectrometer and are reported in ppm using tetramethylsilane (0.00 ppm) or solvent (CDCl₃: 7.24 ppm) as an internal standard. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C NMR spectra were recorded at 125 MHz or 75 MHz and are reported in ppm using solvent as an internal standard (CDCl₃: 77.00 ppm). Infrared spectra were recorded as thin films on NaCl plates on a Perkin-Elmer 710 Series Fourier transform spectrometer (FTIR). Melting points were determined with a Laboratory Devices Mel-Temp II apparatus equipped with an Fluke Model 51 K/J thermocouple and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter using the sodium (589, D line) lamp and are reported as follows: [α] _{λ} ^{T °C} (c = g/100 mL, solvent). Combustion analyses were performed by Atlantic Microlab, Norcross, Georgia. High Resolution mass spectra (HRMS) were recorded at the Nebraska Center for Mass Spectrometry.

General Procedure: TiCl₄-mediated aldol reaction of *N*-acetylthiazolidinethione with aldehydes.³

To a 25 mL round-bottom flask was added *N*-acetyl thiazolidinethione **7** (2.5 mmol, 1.0 equiv) in 12.6 mL CH₂Cl₂ (0.2 M in **7**). The bright yellow solution was cooled to –78 °C, TiCl₄ (2.75 mmol, 1.1 equiv) was added, and the suspension was warmed to –40 °C. After 10 min, the resulting homogeneous orange solution was recooled to –78 °C and *i*Pr₂NEt (2.75 mmol, 1.1 equiv) was added. The blood-red solution was warmed to –40 °C and stirred for 2 h. This titanium enolate solution was recooled to –78 °C and the aldehyde (2.75 mmol, 1.1 equiv) was added dropwise with rapid stirring. After 1 h, the reaction was quenched by pouring into 25 mL of rapidly stirring sat. aq. NH₄Cl. The layers were separated and the aqueous portion was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 1518.

(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem* **1978**, 43, 2923.

(3) Adapted from the general procedure of González, Á.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, 37, 8949.

Na₂SO₄ and concentrated *in vacuo*. The diastereomeric ratio of the crude product was determined by NMR and HPLC (Zorbax sil. Column, 20% EtOAc/hexanes, 2.5 mL/min, 305 nm). Flash chromatography (0–50% Et₂O/hexanes) afforded the pure major diastereomer.

(E)(R)-3-hydroxy-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-5-phenylpent-4-en-1-one (8a)⁴

The title compound was prepared according to General Procedure (thiazolidinethione **7**, 511 mg, 2.51 mmol; TiCl₄, 304 μ L, 2.76 mmol; ⁱPr₂NEt, 482 μ L, 2.76 mmol, cinnamaldehyde, 349 μ L, 2.76 mmol) and isolated as a bright yellow oil (710 mg, 84% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.41–7.19 (m, 5H), 6.67 (d, 1H, J = 16.0 Hz), 6.27 (dd, 1H, J = 15.9, 5.9 Hz), 5.15 (dd, 1H, J = 7.3, 6.8 Hz), 4.90–4.80 (m, 1H), 3.73 (dd, 1H, J = 17.5, 3.1 Hz), 3.49 (dd, 1H, J = 11.5, 7.9 Hz), 3.43 (dd, 1H, J = 17.5, 8.7 Hz), 3.06 (b s, 1H), 3.00 (d, 1H, J = 11.5 Hz), 2.42–2.30 (m, 1H), 1.05 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 7.0 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 203.0, 172.3, 136.4, 130.5, 130.0, 128.5, 127.7, 126.5, 71.3, 68.7, 45.2, 30.8, 30.6, 19.0, 17.1 ppm; IR (film) 3423, 2963, 1691, 1467, 1363, 1312, 1257, 1164, 1093, 1041, 968, 750, 693 cm⁻¹; [α]_D²⁵ = +310.5° (c = 1.41, CHCl₃); HRMS (CI): Exact mass calcd for C₁₇H₂₁NO₂S₂Li [M + Li]⁺: 342.1174; Found: 342.1174; Anal Calcd for C₁₇H₂₁NO₂S₂: C, 60.86%, H, 6.31%, N, 4.18%; Found: C, 60.61%, H, 6.49%, N, 4.11%.

(S)-3-hydroxy-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-5-phenylpentan-1-one (8b)

The title compound was prepared according to General Procedure (thiazolidinethione **7**, 279 mg, 1.37 mmol, 1.2 equiv; TiCl₄, 181 μ L, 1.65 mmol, 1.44 equiv; ⁱPr₂NEt, 288 μ L, 1.65 mmol, 1.44 equiv, dihydrocinnamaldehyde, 151 μ L, 1.14 mmol, 1 equiv) and isolated as bright yellow crystals (201 mg, 54% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.31–7.14 (m, 5H), 5.14 (dd, 1H, J = 7.3, 6.7 Hz), 4.19–4.08 (m, 1H), 3.63 (dd, 1H, J = 17.8, 2.5 Hz), 3.49 (dd, 1H, J = 11.5, 8.0 Hz), 3.17 (dd, 1H, J = 17.8, 9.2 Hz), 3.00 (d, 1H, J = 11.4 Hz), 2.98 (b s, 1H), 2.89–2.78 (m, 1H), 2.77–2.65 (m, 1H), 2.40–2.27 (m, 1H), 1.96–1.72 (m, 2H), 1.05 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 202.9, 173.0, 141.7, 128.4, 128.3, 125.7, 71.2, 67.1, 45.5, 37.8, 31.7, 30.7, 30.4, 19.0, 17.7 ppm; IR (KCl wafer) 3568, 3535, 2960, 1682, 1365, 1242, 1162, 1092, 1042, 702 cm⁻¹; m.p. = 96–98 °C; [α]_D²³ = +351° (c = 1.00, CH₂Cl₂); HRMS (EI): Exact mass calcd for C₁₇H₂₃NO₂S₂ [M]⁺: 337.1170; Found: 337.1158; Anal calcd for C₁₇H₂₃NO₂S₂: C, 60.50%, H, 6.87%, N, 4.15%; Found: C, 60.59%, H, 6.77%, N, 4.21%.

(4) Jeong, T. M.; Park, K. H. *J. Korean Chem. Soc.* **1989**, 33, 426. See also reference 3.

(E)(R)-5-(tributylstannyl)-3-hydroxy-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)pent-4-en-1-one (8c)

To a 25 mL round-bottom flask in a dry box was added $\text{Sn}(\text{OTf})_2$ (450 mg, 1.08 mmol, 2.3 equiv, Strem Chemicals). The flask was fitted with a rubber septum and was moved to the hood. After attaching an argon line, CH_2Cl_2 (3.0 mL) was added. The gray suspension was cooled to -50°C and *N*-ethylpiperidine (148 μL , 1.08 mmol, 2.3 equiv) was added. To the resulting light yellow solution was added thiazolidinethione **7** (143 mg, 0.704 mmol, 1.5 equiv) in CH_2Cl_2 (2.1 mL). After stirring for 4 h at -50°C , the tin enolate solution was cooled to -78°C and (*E*)-3-(tributylstannyl)-2-propenal⁵ (162 mg, 0.469 mmol, 1.0 equiv) was added in CH_2Cl_2 (2.5 mL) over 10 min. After 30 min, the reaction was quenched pouring into pH 7 buffer (7.0 mL) with rapid stirring. The subsequent emulsion was filtered through Celite, sat. aq. NH_4Cl (25 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4 . Filtration and concentrated *in vacuo* afforded a greenish-yellow oil. Flash chromatography on Silicycle *Si-Diol* functionalized silica gel (0–50% Et_2O /hexanes) provided the title compound as an orange oil (213 mg, 83%): ^1H NMR (300 MHz, CDCl_3) δ 6.26 (dd, 1H, $J = 19.2, 1.2$ Hz), 6.06 (dd, 1H, $J = 19.2, 4.8$), 5.15 (dd, 1H, $J = 7.4, 6.7$ Hz), 4.69–4.60 (m, 1H), 3.65 (dd, 1H, $J = 17.5, 3.0$ Hz), 3.52 (dd, 1H, $J = 11.5, 7.9$ Hz), 3.32 (dd, 1H, $J = 17.5, 8.9$ Hz), 3.04 (dd, 1H, $J = 11.5, 0.8$ Hz) 2.86 (b s, 1H), 2.45–2.31 (m, 1H), 1.56–1.43 (m, 6H), 1.38–1.22 (m, 6H), 1.07 (d, 3H, $J = 6.8$ Hz), 1.01 (d, 3H, $J = 7.6$ Hz), 0.94–0.84 (m, 15H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 202.9, 172.6, 148.1, 128.8, 71.4, 70.9, 45.1, 30.8, 30.7, 29.0, 27.2, 19.0, 17.8, 13.7, 9.4 ppm; IR (film) 3417, 2957, 2926, 1695, 1464, 1374, 1255, 1167, 1043, 989, 865, 662 cm^{-1} ; $[\alpha]_{\text{D}}^{21.5} = +219.9^\circ$ ($c = 1.00$, CH_2Cl_2); Anal. calcd for $\text{C}_{23}\text{H}_{43}\text{NO}_2\text{S}_2\text{Sn}$: C, 50.37%, H, 7.90%, N, 2.55%; Found: C, 50.64%, H, 8.02%, N, 2.59%.

General Procedure: Transacylation of thiazolidinethione aldol adducts. To a 10 mL concentration flask containing a solution of thiazolidinethione aldol adduct (0.346 mmol, 1 equiv) in THF (0.86 mL, 0.4 M) was added potassium ethyl malonate (0.692 mmol, 2.0 equiv, Aldrich) followed by MgCl_2 (0.346 mmol, 1.0 equiv, Aldrich #24,413-9). The flask was flushed with Ar and the suspension was stirred rapidly at rt. After 30 min, imidazole (0.346 mmol, 1.0 equiv) was added in one portion and the suspension stirred rapidly at rt overnight. During this time the bright yellow color slowly faded to a very light yellow. The reaction was diluted with EtOAc (10 mL), washed with 0.5 M HCl (5 mL), and the aqueous layer was back-extracted with EtOAc (3 x 2 mL). The combined organic layers were then washed with 0.5 M NaHCO_3 (5 mL) and back-extracted with EtOAc (3 x 2 mL). Finally, the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give a light yellow oil containing the desired product contaminated with free thiazolidinethione auxiliary. Flash chromatography (0→30% EtOAc/hexanes or 0→8% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) afforded the pure δ -hydroxy- β -ketoester.

(5) Oswald, R.; Chavant, P.; Stadtmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143.

Ethyl (*E*)(*R*)-5-hydroxy-3-oxo-7-phenylhept-6-enoate (9a)

The title compound was prepared according to General Procedure (thiazolidinethione **8a**, 116 mg, 0.346 mmol; potassium ethyl malonate, 118 mg, 0.692 mmol; MgCl_2 , 33 mg, 0.346 mmol; imidazole, 24 mg, 0.346 mmol; stirred for 7 h) and isolated as a pale yellow oil (80 mg, 88%): ^1H NMR (300 MHz, CDCl_3) δ 7.44-7.21 (m, 5H), 6.65 (d, 1H, $J = 15.9$ Hz), 6.21 (dd, 1H, $J = 15.9, 6.1$ Hz), 4.84-4.75 (m, 1H), 4.20 (q, 2H, $J = 7.1$ Hz), 3.51 (s, 2H), 2.87 (d, 2H, $J = 6.0$ Hz), 1.28 (t, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 202.2, 166.4, 135.9, 130.2, 129.3, 128.1, 127.3, 126.0, 67.9, 61.1, 49.5, 49.1, 13.6 ppm; IR (film) 3467, 2982, 1734, 1713, 1033, 972, 748, 693 cm^{-1} ; $[\alpha]_{\text{D}}^{19.2} = +14.0^\circ$ ($c = 1.00$, CH_2Cl_2); HRMS (CI): Exact mass calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Li}$ $[\text{M} + \text{Li}]^+$: 269.1365; Found: 269.1378; Anal calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4$: C, 68.68%, H, 6.92%; Found: C, 68.93%, H, 6.79%.

Ethyl (*S*)-5-hydroxy-3-oxo-7-phenylheptanoate (9b)

The title compound was prepared according to General Procedure (thiazolidinethione **8b**, 99 mg, 0.29 mmol; potassium ethyl malonate, 100 mg, 0.59 mmol; MgCl_2 , 28 mg, 0.29 mmol; imidazole, 20 mg, 0.29 mmol; stirred for 6 h) and isolated as a pale yellow oil (68 mg, 89%): ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.12 (m, 5H), 2.68 (q, 2H, $J = 7.1$ Hz), 4.11-4.03 (m, 1H), 3.44 (s, 2H), 2.96 (d, 1H, $J = 3.8$ Hz), 2.86-2.61 (m, 4H), 1.89-1.64 (m, 2H), 1.26 (t, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 203.5, 166.8, 141.6, 128.3 (2 peaks), 125.8, 66.7, 61.4, 49.8, 49.6, 38.0, 31.6, 14.0 ppm; IR (film) 3442, 3027, 2931, 1741, 1712, 1496, 1455, 1409, 1368, 1318, 1155, 1029, 750, 701 cm^{-1} ; $[\alpha]_{\text{D}}^{23} = +13^\circ$ ($c = 1.00$, CH_2Cl_2); HRMS (EI): Exact mass calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3$ $[\text{M} - \text{H}_2\text{O}]^+$: 246.1256; Found: 246.1265; Anal calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16%, H, 7.63%; Found: C, 67.88%, H, 7.72%.

Ethyl (*E*)(*R*)-7-(tributylstannyl)-5-hydroxy-3-oxohept-6-enoate (9c)

The title compound was prepared according to General Procedure (thiazolidinethione **8c**, 3.374 g, 6.14 mmol; potassium ethyl malonate, 2.091 g, 12.3 mmol; MgCl_2 , 585 mg, 6.14 mmol; imidazole, 418 mg, 6.14 mmol; stirred overnight) and isolated as a yellow oil (2.395 g, 82%): ^1H NMR (500 MHz, CDCl_3) δ 6.23 (dd, 1H, $J = 19.1, 1.3$ Hz), 6.00 (dd, 1H, $J = 19.1, 5.0$ Hz), 4.60-4.54 (m, 1H), 4.21 (q, 2H, $J = 7.2$

Hz), 3.49 (s, 2H), 2.82-2.72 (m, 2H), 2.68 (bs 1H), 1.57-1.40 (m, 6H), 1.37-1.23 (m, 9H), 0.95-0.84 (m, 15H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 202.8, 166.9, 148.1, 128.9, 70.7, 61.5, 50.0, 49.4, 29.0, 27.2, 14.1, 13.6, 9.4 ppm; IR (film) 3453, 2957, 2926, 2853, 1742, 1714, 1652, 1464, 1376, 1316, 1235, 1177, 1033, 874, 690, 666, 596, 507 cm^{-1} ; $[\alpha]_{\text{D}}^{21} = +13.8^\circ$ ($c = 1.00$, CH_2Cl_2).

Ethyl (*E*)(4*R*,5*S*)-5-hydroxy-4-methyl-3-oxo-7-phenylhept-6-enoate (23**)**

The title compound was prepared according to General Procedure (thiazolidinethione **19**, 226 mg, 0.569 mmol; potassium ethyl malonate, 194 mg, 1.137 mmol; MgCl_2 , 54 mg, 0.569 mmol; imidazole, 39 mg, 0.569 mmol; stirred overnight) and isolated as a pale yellow oil (94.0 mg, 60%): ^1H NMR (500 MHz, CDCl_3) δ 7.44-7.18 (m, 5H), 6.64 (d, 1H, $J = 15.9$ Hz), 6.16 (dd, 1H, $J = 15.9, 6.1$ Hz), 4.71-4.60 (m, 1H), 4.19 (q, 2H, $J = 7.1$ Hz), 3.63-3.53 (m, 2H), 3.00-2.90 (m, 1H), 2.61 (bs, 1H), 1.27 (t, 3H, $J = 7.1$ Hz), 1.20 (d, 3H, $J = 7.2$ Hz) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 206.5, 167.2, 136.4, 131.7, 128.6, 128.5, 127.8, 126.5, 72.5, 61.5, 51.3, 48.8, 14.1, 10.6 ppm; IR (film) 3500, 2981, 2926, 1739, 1709, 1646, 1450, 1369, 1313, 1258, 1157, 1022, 969, 753, 696 cm^{-1} ; $[\alpha]_{\text{D}}^{21.5} = -18.2^\circ$ ($c = 1.00$, CH_2Cl_2).

Ethyl (*E*)(4*S*,5*R*)-5-hydroxy-4-methyl-3-oxo-7-phenylhept-6-enoate (24**)**

The title compound was prepared according to General Procedure (thiazolidinethione **20**, 74 mg, 0.186 mmol; potassium ethyl malonate, 63 mg, 0.372 mmol; MgCl_2 , 18 mg, 0.186 mmol; imidazole, 13 mg, 0.186 mmol; stirred overnight) and isolated as a pale yellow oil (30.7 mg, 60%). All spectral data were identical to those reported for **23** above except for the optical rotation: $[\alpha]_{\text{D}}^{21.5} = +16.2^\circ$ ($c = 1.00$, CH_2Cl_2);

Ethyl (*E*)(4*S*,5*S*)-5-hydroxy-4-methyl-3-oxo-7-phenylhept-6-enoate (25**)**

The title compound was prepared according to General Procedure (thiazolidinethione **21**, 80.0 mg, 0.201 mmol; potassium ethyl malonate, 74.5 mg, 0.438 mmol; MgCl_2 , 21.2 mg, 0.223 mmol; imidazole, 13.6 mg, 0.200 mmol; stirred overnight) and isolated as a pale yellow oil (29.0 mg, 52% yield): ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.26 (m, 5H), 6.63 (d, 1H, $J = 16$ Hz), 6.18 (dd, 1H, $J = 7.3, 16$ Hz), 4.38 (ap t, 1H, $J = 7.8$ Hz), 4.20 (q, 2H, $J = 6.8$ Hz), 3.60 (ap d, 2H, $J = 7.8$ Hz), 2.93 (ap quintet, 1H, $J = 7.3$ Hz), 2.35 (bs, 1H), 1.28 (t, 3H, $J = 8.2$ Hz), 1.14 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 136.4, 132.9, 129.4, 128.9, 128.3, 126.8, 75.7, 51.9, 50.1, 14.3, 13.9; IR (film) 3504, 2980, 1741, 1709, 1458, 1368, 1311, 1260, 1156, 1020, 959, 751, 694 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +35.3^\circ$ ($c = 1.50$, CH_2Cl_2); HRMS (CI): Exact mass calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4 + \text{NH}_4$ $[\text{M} + \text{NH}_4]^+$, 294.1706. Found 294.1705.

Ethyl (*E*)(4*R*,5*S*)-5-hydroxy-4-methyl-3-oxo-7-phenylhept-6-enoate (23**)**

The title compound was prepared according to General Procedure (thiazolidinethione **22**, 89.8 mg, 0.292 mmol; potassium ethyl malonate, 98.8 mg, 0.580 mmol; MgCl_2 , 27.4 mg, 0.288 mmol; imidazole, 20.5 mg, 0.301 mmol; stirred overnight) and isolated as a pale yellow oil (49.6 mg, 61% yield). All spectral data were identical to those reported for **23** above.

General Procedure: Lactonization/Methylation. To a 25 mL round-bottom flask was added δ -hydroxy- β -ketoester (0.656 mmol, 1 equiv) in methanol (3.3 mL, 0.2 M in ester). Powdered anhydrous K_2CO_3 (1.311 mmol, 2 equiv) was added and the suspension was stirred at rt. After 2h, TLC indicated complete lactonization. The methanol solvent was removed *in vacuo* and was replaced with acetone (3.3 mL). Me_2SO_4 (1.311 mmol, 2 equiv) was added and the suspension was stirred overnight. The reaction was diluted with EtOAc (20 mL) and was washed with 0.5 M HCl (20 mL). The aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (0→50% EtOAc/hexanes) afforded the pure kavalactone.

(R)-5,6-dihydro-4-methoxy-6-styrylpyran-2-one, (+)-kavain (1)

The title compound was prepared according to General Procedure (δ -hydroxy- β -ketoester **9a**, 172 mg, 0.656 mmol; K_2CO_3 , 181 mg, 1.311 mmol; Me_2SO_4 , 124 μ L, 1.311 mmol; stirred overnight) and isolated as white crystals (131 mg, 87% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.24 (m, 5H), 6.74 (d, 1H, J = 16.0 Hz), 6.26 (dd, 1H, J = 16.0, 6.2 Hz), 5.20 (s 1H), 5.11-5.02 (m, 1H), 3.77 (s, 3H), 2.67 (dd, 1H, J = 17.1, 10.7 Hz), 2.55 (dd, 1H, J = 17.1, 4.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 167.2, 136.2, 133.6, 129.1, 128.8, 127.1, 125.9, 91.0, 76.3, 56.5, 33.7 ppm; IR (film) 1703, 1626, 1394, 1248, 1233, 1063, 1024, 971, 747, 693 cm^{-1} ; m.p. = 112.2-113.0 $^{\circ}C$; $[\alpha]_D^{20}$ = +124.3 $^{\circ}$ (c = 1.00, EtOH); HRMS (EI): Exact mass calcd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943; Found: 230.0941; Anal calcd for $C_{14}H_{14}O_3$: C, 73.03%, H, 6.13%; Found: C, 72.86%, H, 6.00%. HPLC comparison to a racemic sample indicated an enantiomeric purity of 97.4% ee (Chiralcel AD column, 7% i PrOH/hexanes, 0.7 mL/min, 254 nm).

(S)-5,6-dihydro-4-methoxy-6-phenethylpyran-2-one, (+)-7,8-dihydrokavian (2)

The title compound was prepared according to General Procedure (δ -hydroxy- β -ketoester **9b**, 288 mg, 1.09 mmol; K_2CO_3 , 301 mg, 2.18 mmol; Me_2SO_4 , 206 μ L, 2.18 mmol; stirred overnight) and isolated as off-white crystals (210 mg, 83% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 5.14 (s, 1H), 4.42-4.30 (m, 1H), 3.72 (s, 3H), 2.94-2.71 (m, 2H), 2.50 (dd, 1H, J = 17.0, 11.9 Hz), 2.30 (dd, 1H, J = 17.0, 3.9 Hz), 2.20-2.05 (m, 1H), 1.99-1.85 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 167.2, 140.8, 128.5, 128.4, 126.1, 90.3, 74.7, 56.0, 36.3, 33.0, 30.9 ppm; IR (KCl wafer) 3026, 2941, 2856, 1707, 1624, 1497, 1454, 1443, 1396, 1374, 1294, 1223, 1090, 1038, 997, 869, 823, 751, 701 cm^{-1} ; m.p. = 57.3-58.0 $^{\circ}C$; $[\alpha]_D^{25}$ = +31.1 $^{\circ}$ (c = 1.00, MeOH); HRMS (EI): Exact mass calcd for $C_{14}H_{16}O_3$ $[M]^+$: 232.1099; Found: 232.1107; Anal calcd for $C_{14}H_{16}O_3$: C, 72.39%, H, 6.94%; Found: C, 72.18%, H, 6.93%.

(R)-6-((E)-2-(tributylstannyl)vinyl)-5,6-dihydro-4-methoxypyran-2-one (11)

The title compound was prepared according to General Procedure (δ -hydroxy- β -ketoester **9c**, 64 mg, 0.135 mmol; K_2CO_3 , 37 mg, 0.268 mmol; Me_2SO_4 , 25 μ L, 0.268 mmol; stirred overnight) and isolated as an orange oil (47 mg, 79% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, 1H, J = 19.2 Hz), 6.06 (dd, 1H, J = 19.2, 5.1 Hz), 5.15 (s, 1H), 4.91-4.80 (m, 1H), 3.75 (s, 3H), 2.58 (dd, J = 17.1, 10.3 Hz), 2.48 (dd, J = 17.1, 5.0 Hz), 1.57-1.42 (m, 6H), 1.39-1.23 (m, 6H), 0.97-0.84 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.35, 166.95, 143.51, 132.95, 90.51, 77.91, 55.99, 32.81, 28.98, 27.20, 13.65, 9.47 ppm; IR (film) 2956, 2926, 2871, 2853, 1715, 1627, 1463, 1382, 1279, 1227, 1065, 1023, 995, 960, 873, 824, 691, 667 cm^{-1} ; $[\alpha]_D^{21.5} = +47.8^\circ$ (c = 1.00, CH_2Cl_2); Anal calcd for $C_{20}H_{36}O_3Sn$: C, 54.20%, H, 8.19%; Found: C, 54.29%, H, 8.28%.

5,6-dihydro-4-methoxy-6-styrylpyran-2-one, ($\pm$)-kavain (($\pm$)-**1**)

The title compound was prepared according to General Procedure (δ -hydroxyester (**±**)-**28a**, 157 mg, 0.572 mmol; K_2CO_3 , 158 mg, 1.145 mmol; Me_2SO_4 , 108 μ L, 1.145 mmol; stirred overnight) and isolated from as colorless crystals (94 mg, 71% yield): All spectral data were identical to those reported for **1** above except for the melting point (145.8–146.9 $^\circ C$) and absence of optical activity.

5,6-dihydro-4-methoxy-6-phenethylpyran-2-one, ($\pm$)-7,8-dihydrokavian (($\pm$)-**2**)

The title compound was prepared according to General Procedure (δ -hydroxyester (**±**)-**28b**, 206 mg, 0.746 mmol; K_2CO_3 , 206 mg, 1.491 mmol; Me_2SO_4 , 141 μ L, 1.491 mmol; stirred overnight) and isolated as colorless crystals (155 mg, 90% yield): All spectral data were identical to those reported for **2** above except for absence of optical activity.

General Procedure: Stille Coupling. To a 10 mL round-bottom flask was sequentially added the aryl iodide (0.236 mmol, 1.1 equiv), THF or toluene (1.0 mL), the phosphine ligand (0.0189 mmol, 0.088 equiv), and $Pd_2(dba)_3$ (0.0047, 0.022 equiv). After stirring at rt for 15 min, the solution was warmed to 50 $^\circ C$, stannane **11** (0.214 mmol, 1.0 equiv) was added in THF (0.5 mL), and the reaction was stirred overnight. The solvent was removed *in vacuo* and the brown residue was subjected to flash chromatography (0→50% EtOAc/hexanes). Stirring with triamine-functionalized silica gel (SiliCycle: Si-Triamine) removed the residual Bu_3SnI to afford the pure kavalactones.

(*R*)-5,6-dihydro-4-methoxy-6-styrylpyran-2-one, (+)-kavain (1**)**

The title compound was prepared according to General Procedure (iodobenzene, 26.3 μ L, 0.236 mmol; $P(2\text{-furyl})_3$, 4.4 mg, 0.0189 mmol; $\text{Pd}_2(\text{dba})_3$, 4.3 mg, 0.0047 mmol, stannane **11**, 95 mg, 0.214 mmol; stirred overnight) and isolated as white crystals (38 mg, 75% yield): All spectral data were identical to those reported for **1** above.

(*R*)-6-(4-methoxystyryl)-5,6-dihydro-4-methoxypyran-2-one, (+)-5,6-dihydroyangonin (12**)**

The title compound was prepared according to General Procedure (4-iodoanisole, 55 mg, 0.235 mmol; $P(o\text{-MeO-Ph})_3$, 3.6 mg, 0.0103 mmol; $\text{Pd}_2(\text{dba})_3$, 2.4 mg, 0.0026 mmol, stannane **11**, 52 mg, 0.117 mmol; stirred overnight) and isolated as colorless crystals (16 mg, 52% yield): ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, 2H, $J = 8.7$ Hz), 6.86 (d, 2H, $J = 8.7$ Hz), 6.67 (d, 1H, $J = 15.9$ Hz), 6.12 (dd, 1H, $J = 15.9, 6.5$ Hz), 5.19 (s, 1H), 5.06-4.99 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.65 (dd, 1H, $J = 17.1, 10.9$ Hz), 2.53 (dd, 1H, $J = 17.1, 4.3$ Hz) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 172.3, 166.8, 159.7, 132.8, 128.4, 127.9, 123.2, 114.0, 90.5, 76.1, 56.0, 55.3, 33.4 ppm; IR (film) 1705, 1623, 1512, 1389, 1249, 1224, 1177, 1016, 816 cm^{-1} ; $[\alpha]_D^{19} = +99.8^\circ$ ($c = 1.00$, CH_2Cl_2).

(*R*)-6-((*E*)-2-(benzo[*d*][1,3]dioxol-6-yl)vinyl)-5,6-dihydro-4-methoxypyran-2-one, (+)-methysticin (3**)**

The title compound was prepared according to General Procedure (1-iodo-3,4-methylenedioxybenzene 73 mg, 0.293 mmol; $P(o\text{-MeO-Ph})_3$, 4.5 mg, 0.0129 mmol; $\text{Pd}_2(\text{dba})_3$, 2.9 mg, 0.0032 mmol, stannane **11**, 65 mg, 0.147 mmol; stirred overnight) and isolated as off-white crystals (18 mg, 44% yield): ^1H NMR (500 MHz, CDCl_3) δ 6.92 (d, 1H, $J = 1.6$ Hz), 6.83 (dd, 1H, $J = 8.0, 1.6$ Hz), 6.76 (d, 1H, $J = 8.0$ Hz), 6.38 (d, 1H, $J = 15.9$ Hz), 6.09 (dd, 1H, $J = 15.9, 6.4$ Hz), 5.96 (s, 2H), 5.19 (s, 1H), 5.05-4.99 (m, 1H), 3.77 (s, 3H), 2.65 (dd, 1H, $J = 17.1, 10.9$ Hz), 2.53 (dd, 1H, $J = 17.1, 4.3$ Hz) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 172.3, 166.7, 148.1, 147.8, 132.9, 130.2, 123.6, 121.7, 108.3, 105.8, 101.2, 90.6, 76.0,

56.1, 33.4 ppm ; IR (film) 1705, 1623, 1505, 1490, 1446, 1392, 1250, 1223, 1096, 1036, 965, 930, 866, 798 cm^{-1} ; $[\alpha]_{\text{D}}^{19} = +119.5^{\circ}$ ($c = 1.00$, CH_2Cl_2).