Direct Enantioselective Conjugate Addition of Carboxylic Acids with Chiral Lithium Amides as Traceless Auxiliaries

Ping Lu, Jeffrey J. Jackson, John A. Eickhoff, Armen Zakarian*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106

Supplementary Information 1

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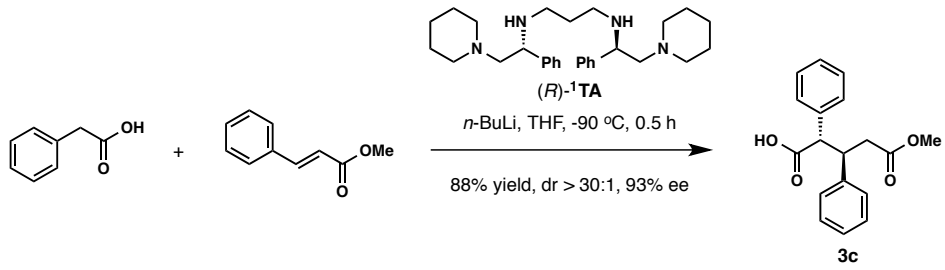
Synthesis

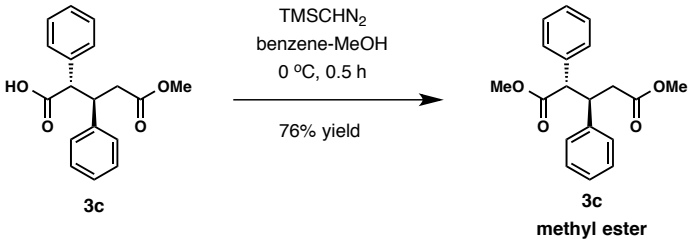
General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether (diethyl ether) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine and triethylamine were distilled from calcium hydride in a continuous still under and atmosphere of argon. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (EMD, Geduran, no. 1.11567.9026) as the stationary phase. Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova. Carbon nuclear magnetic resonance spectra were recorded at 100 MHz, 125 MHz, and 150 MHz on Varian Unity Inova, and Varian Unity Inova spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical Rotations were measured on a Rudolph Autopol III polarimeter. High resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.



General Procedure I:

(2*S*,3*R*)-5-Methoxy-5-oxo-2,3-diphenylpentanoic acid (3c). A solution of *n*-BuLi (0.81 mL, 2.46 M in hexanes, 1.99 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (68.1 mg, 0.500 mmol) and (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (5.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was then cooled to -90 °C and stirred for an additional 5 min. A solution of (*E*)-methyl cinnamate (81.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.30 mL + 2×0.10 mL rinses) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 20 min before a quench with a mixture of THF-MeOH (3:1, 0.64 mL) at -90 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (2-4% methanol in dichloromethane) to afford the pure product **3c** (0.132 g, 0.442 mmol, 88% yield). $[\alpha]_D^{23}$ +25.8 (*c* 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43-7.39 (m, 2H), 7.37-7.29 (m, 3H), 7.27-7.21 (m, 4H), 7.20-7.16 (m, 1H), 3.87-3.78 (m, 2H), 3.37 (s, 3H), 2.42 -2.33 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 177.1, 171.9, 140.8, 135.9, 128.9, 128.7, 128.4, 128.2, 127.9, 127.2, 57.4, 51.4, 44.7, 38.5. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{18}O_4Na$, 321.1103; found, 321.1091.

In most cases, ee values for the product were measured using the corresponding methyl ester due to low solubility of the free carboxylic acid in the HPLC eluent system (e.g. 1% *i*-PrOH in hexanes, 0.1% TFA).



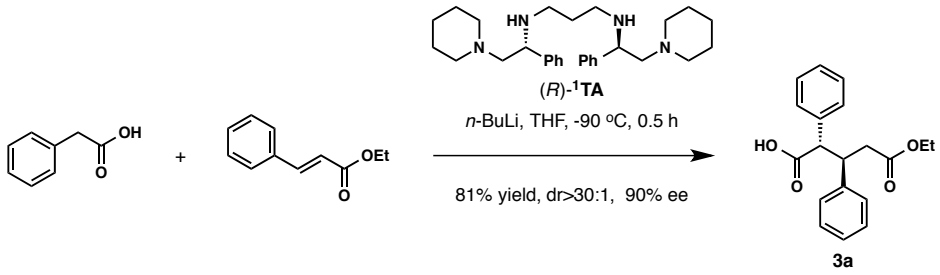
(2*S*,3*R*)-Dimethyl 2,3-diphenylpentanedioate (3c methyl ester). A solution of $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) was added dropwise to a solution of carboxylic acid **3c** (9.3 mg, 31.2 μmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford the product **3c methyl ester** (7.4 mg, 23.7 μmol, 76% yield). Ee: 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=15.0 min; t_2=18.5 min). $[\alpha]_D^{23}$ +15.9 (*c* 0.57, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.47 (d, *J*=7.4 Hz, 2H), 7.37 (t, *J*=7.4 Hz, 2H), 7.34-7.27 (m, 5H), 7.25-7.19 (m, 1H), 3.91-3.83 (m, 2H), 3.39 (s, 3 H), 3.37 (s, 3 H), 2.47-2.35 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 172.6, 172.0, 141.2, 136.5, 128.9, 128.7, 128.4, 128.0, 127.9, 127.1, 57.7, 51.8, 51.4, 45.2, 38.6. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{20}O_4Na$, 335, found 335.

Practical preparation of 3c at gram scale with recovery of the tetramine (*R*)-^{1}**TA.**

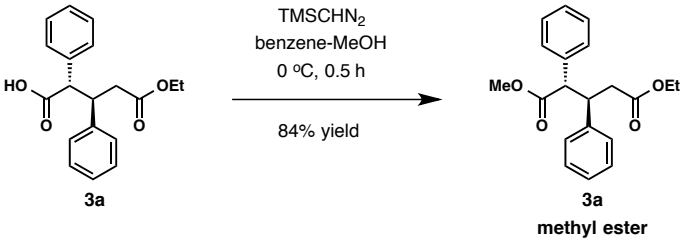
To a 3-neck round-bottom flask was attached a gas-inlet adapter, glass-stopper, and thermometer adapter fitted with a low-temperature thermometer. After flame drying under vacuum and back filling with argon, the flask was charged with phenylacetic acid (3.50 g, 25.7 mmol), (*R*)-^{1}**TA** (11.8 g, 26.4 mmol, 1.03 equiv), and THF (220 mL) under a positive pressure of argon gas. The reaction mixture was cooled in an ice-water bath to 0 °C and a solution of *n*-BuLi (39.0 mL, 2.65 M in hexanes, 103 mmol, 4.0 equiv) was added dropwise, keeping the internal reaction temperature below 15 °C. The mixture was stirred at 0 °C for additional 15 min. The reaction mixture was then cooled to -78 °C and stirred for an additional 10 min. A solution of (*E*)-methyl cinnamate (4.59 g, 28.3 mmol, 1.1 equiv) in THF (50 mL + 15 mL rinse) was added to the reaction mixture dropwise over 30 min, maintaining the internal reaction temperature below -70 °C. The resultant mixture was stirred for additional 30 min before a quench with a mixture of THF-MeOH (3:1, 32 mL) at -78 °C. After 5 min, the reaction mixture was acidified to pH = 1 with a 1 M aqueous solution of HCl and extracted with ethyl acetate (400 mL X 3). The combined organic phase was sequentially washed with 1 M aqueous solution of HCl (300 mL) and brine, dried over Na_2SO_4, concentrated. Crude product **3c** was obtained as a light yellow solid (8.09 g, 89% ee). The crude product was dissolved in a minimal amount of EtOAc (~30 mL) using heat and sonication to aid dissolution. The solution was cooled to room temperature and then to 0 °C in an ice-water bath. The formed precipitate was filtered through a medium-porosity sintered glass funnel and washed with ice-cold EtOAc to yield pure product **3c** as a white solid (4.02 g, 13.5 mmol, 52% yield, 95% ee). A second recrystallization of the material recovered from the mother liquor of the first crystallization provided a second batch of

pure product **3c** (1.95 g, 6.54 mmol, 25% yield, 80% ee). The two batches provided a total of 5.97 g of **3c** (20.0 mmol, 78% yield, 90% ee).

Recovery of (*R*)-^{1}TA: The combined acidic aqueous layers were washed with diethyl ether then basified with sodium hydroxide to pH >12 at room temperature, and extracted with diethyl ether (400 mL X 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to recover pure (^{1}H NMR analysis) (*R*)-**^{1}TA** (11.8 g, 26.3 mmol, 99%).

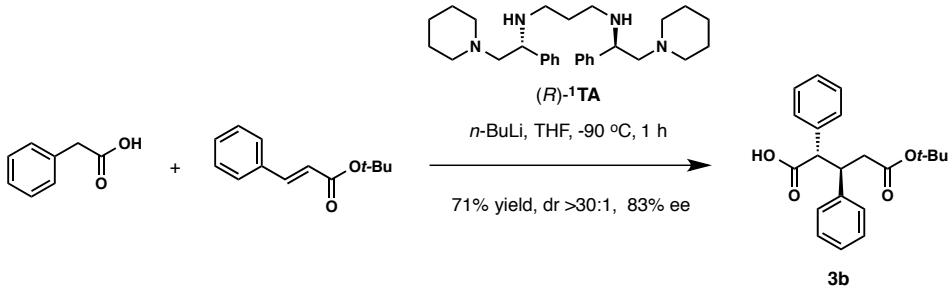


(2*S*,3*R*)-5-Ethoxy-5-oxo-2,3-diphenylpentanoic acid (3a). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.46 M in hexanes, 1.99 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-ethyl cinnamate (85 μL, 89.2 mg, 0.506 mmol, 1.0 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **3a** (0.126 g, 0.403 mmol, 81%) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23}$ +28.2 (*c* 0.54, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.45–7.39 (m, 2H), 7.39–7.28 (m, 3H), 7.28–7.20 (m, 4H), 7.20–7.15 (m, 1H), 3.86–3.76 (m, 4H), 2.42–2.31 (m, 2H), 0.97 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 177.0, 171.5, 140.8, 136.0, 128.9, 128.7, 128.6, 128.4, 128.1, 128.0, 127.1, 60.2, 57.5, 44.7, 38.7, 13.9. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{20}O_4Na$, 335.1259; found, 335.1248.

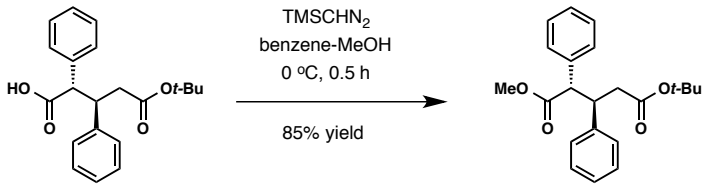


(2*S*,3*R*)-5-Ethyl-1-methyl 2,3-diphenylpentanedioate (3a methyl ester). The title compound was prepared using carboxylic acid **3a** (14.2 mg, 45.5 μmol), $TMSCHN_2$ in hexane (0.12 mL, 1.76 M, 0.211 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **3a methyl ester** (12.4 mg, 38.0 μmol, 84% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=13.3 min; t_2=16.6 min). $[\alpha]_D^{23}$ +22.6 (*c* 0.62, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.50–7.45 (m, 2H), 7.39–7.34 (m, 2H), 7.34–7.27 (m, 5H), 7.24–7.19 (m, 1H), 3.93–3.78 (m, 4H), 3.37 (s, 3H), 2.46–2.33 (m, 2H), 0.99 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 172.6, 171.5, 141.2, 136.5, 128.9, 128.7, 128.4, 128.01, 127.95, 127.0,

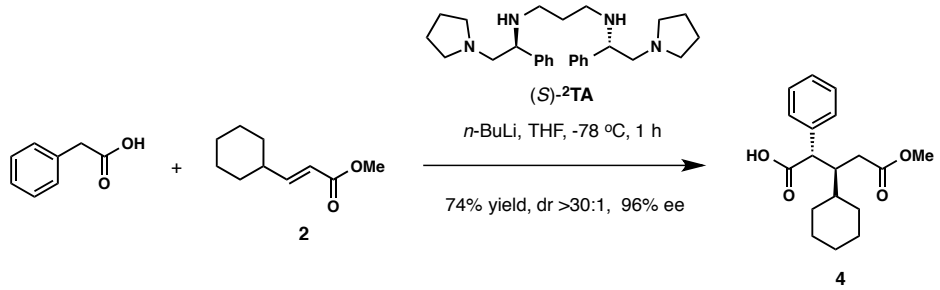
60.2, 57.9, 51.8, 45.2, 38.8, 13.9. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{20}H_{22}O_4Na$, 349, found 349.



(2*S*,3*R*)-5-*tert*-Butoxy-5-oxo-2,3-diphenylpentanoic acid (3b). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.46 M in hexanes, 1.99 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl cinnamate (102 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product **3b** (0.121 g, 0.355 mmol, 71%) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23}$ +24.6 (*c* 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J*=6.7 Hz, 2H), 7.35 (t, *J*=7.2 Hz, 2H), 7.34-7.27 (m, 1H), 7.27 (d, *J*=7.2 Hz, 2H), 7.22 (d, *J*=7.9 Hz, 2H), 7.18 (t, *J*=6.8 Hz, 1H), 3.81-3.70 (m, 2H), 2.27 (d, *J* = 6.8 Hz, 2H), 1.12 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 177.2, 170.8, 140.7, 136.1, 128.9, 128.7, 128.22, 128.18, 128.0, 127.0, 80.3, 57.8, 45.0, 39.8, 27.7. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{21}H_{24}O_4Na$, 363.1572; found, 363.1562.

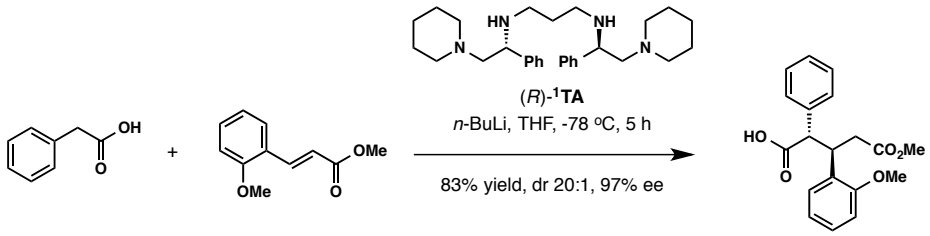


(2*S*,3*R*)-5-*tert*-Butyl-1-methyl 2,3-diphenylpentanedioate (3b methyl ester). The title compound was prepared using carboxylic acid **3b** (10.3 mg, 30.3 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **3b methyl ester** (9.1 mg, 25.7 μmol, 85% yield). Ee: 83% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=6.0 min; t_2=7.2 min). $[\alpha]_D^{23}$ +17.1 (*c* 0.48, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.50-7.44 (m, 2H), 7.40-7.33 (m, 2H), 7.35-7.24 (m, 5H), 7.24-7.17 (m, 1H), 3.84-3.76 (m, 2H), 3.37 (s, 3H), 2.36-2.23 (m, 2H), 1.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 172.7, 170.8, 141.1, 136.6, 128.9, 128.6, 128.2, 127.9, 126.9, 80.3, 58.2, 51.7, 45.6, 39.9, 27.7. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{22}H_{26}O_4Na$, 377, found 377.



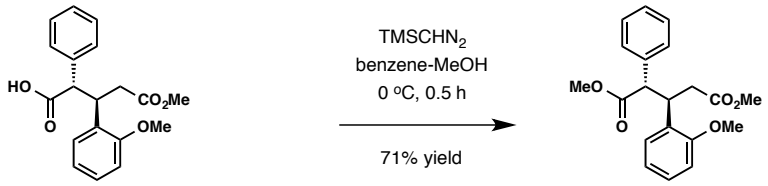
(2*R*,3*R*)-3-Cyclohexyl-5-methoxy-5-oxo-2-phenylpentanoic acid (4). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-**²TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl 3-cyclohexylacrylate **2** (84.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 1 h and product **4** (0.113 g, 0.370 mmol, 74%) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23}$ +5.6 (*c* 1.4, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37 (d, *J*=6.7 Hz, 2H), 7.33-7.21 (m, 3H), 3.60 (d, *J*=11.7 Hz, 1H), 3.38 (s, 3H), 2.81 (*virt.* dtd, *J*=11.7, 6.0, 2.9 Hz, 1H), 2.16 (dd, *J*=16.0, 6.2 Hz, 1H), 1.92 (dd, *J*=16.0, 5.7 Hz, 1H), 1.80-1.71 (m, 3H), 1.70-1.62 (m, 2H), 1.58-1.48 (m, 1H), 1.32-1.05 (m, 4H), 1.02-0.92 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.1, 173.6, 136.4, 129.3, 128.6, 127.9, 54.7, 51.4, 42.8, 40.8, 33.0, 31.6, 27.1, 26.8, 26.6, 26.5. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{24}O_4Na$, 327.1572; found, 327.1556.

(2*R*,3*R*)-Dimethyl 3-cyclohexyl-2,3-diphenylpentanedioate (4 methyl ester). The title compound was prepared using carboxylic acid **4** (28.7 mg, 94.3 μmol), $TMSCHN_2$ in hexane (0.20 mL, 1.76 M, 0.352 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **4 methyl ester** (27.9 mg, 87.6 μmol, 93% yield). Ee: 96% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=6.7 min; t_2=7.5 min). $[\alpha]_D^{23}$ +9.9 (*c* 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39-7.33 (m, 2H), 7.31-7.27 (m, 2H), 7.6-7.20 (m, 1H), 3.65 (s, 3H), 3.60 (d, *J*=11.6 Hz, 1H), 3.38 (s, 3H), 2.82 (*virt.* dtd, *J*=11.6, 6.0, 3.0 Hz, 1H), 2.15 (dd, *J*=16.0, 6.4 Hz, 1H), 1.93 (dd, *J*=16.0, 5.7 Hz, 1H), 1.81-1.71 (m, 3H), 1.70-1.63 (m, 2H), 1.44 (*virt.* td, *J*=12.0, 3.0 Hz, 1H), 1.32-1.04 (m, 4H), 1.01-0.91 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.0, 173.6, 137.0, 129.2, 128.5, 127.6, 54.7, 51.9, 51.3, 43.1, 40.9, 33.1, 31.5, 27.2, 26.8, 26.7, 26.5. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{26}O_4Na$, 341, found 341.



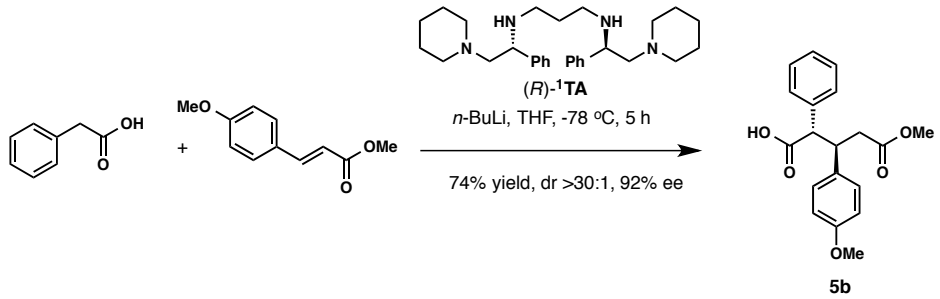
5a

(2*S*,3*R*)-5-Methoxy-3-(2-methoxyphenyl)-5-oxo-2-phenylpentanoic acid (5a). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl-3-(2-methoxyphenyl)acrylate (101 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product **5a** (0.136 g, 0.413 mmol, 83%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +34.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43-7.37 (m, 2H), 7.36-7.26 (m, 3H), 7.16 (d, *J*=7.4 Hz, 2H), 6.81 (d, *J*=7.4 Hz, 2H), 4.21 (d, *J*=11.2 Hz, 1H), 4.01 (ddd, *J*=11.2, 9.5, 4.6 Hz, 1H), 3.80 (s, 3H), 3.36 (s, 3H), 2.59 (dd, *J*=15.6, 9.5 Hz, 1H), 2.36 (dd, *J*=15.5, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 178.2, 172.5, 157.4, 136.4, 130.2, 128.9, 128.6, 128.3, 128.2, 127.8, 120.4, 111.0, 55.3, 54.6, 51.2, 41.3, 36.1. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{20}O_5Na$, 351.1208; found, 351.1196.

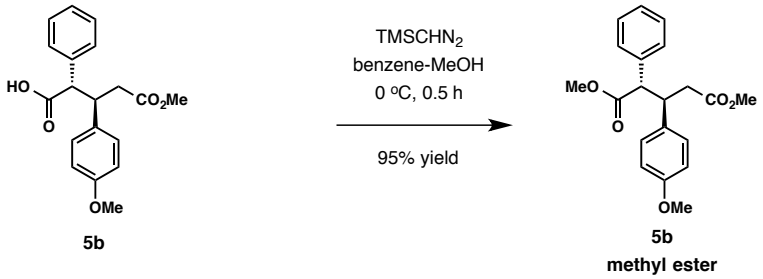


5a **5a methyl ester**

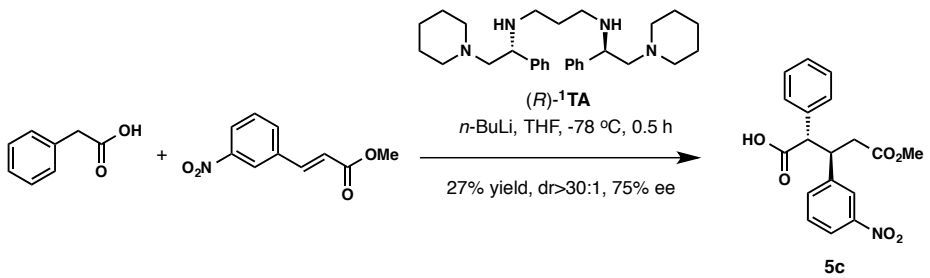
(2*R*,3*R*)-Dimethyl 3-(2-methoxyphenyl)-2-phenylpentanedioate (5a methyl ester). The title compound was prepared using carboxylic acid **5a** (16.4 mg, 49.9 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5a methyl ester** (12.1 mg, 35.3 μmol, 71% yield). Ee: 97% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=12.3 min; t_2=30.9 min). $[\alpha]_D^{23}$ +32.2 (*c* 0.61, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49-7.44 (m, 2H), 7.39-7.33 (m, 2H), 7.31-7.27 (m, 1H), 7.23 (dd, *J*=7.9, 1.7 Hz, 1H), 7.22-7.17 (m, 1H), 6.91-6.84 (m, 2H), 4.29 (d, *J*=11.4 Hz, 1H), 4.10-4.01 (m, 1H), 3.89 (s, 3H), 3.37 (s, 3H), 3.37 (s, 3H), 2.64 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.37 (dd, *J* = 15.5, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 178.2, 172.5, 157.4, 136.4, 128.9, 128.7, 128.2, 127.8, 120.4, 111.0, 55.3, 54.6, 51.2, 36.1. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{20}H_{22}O_5Na$, 365; found, 365.



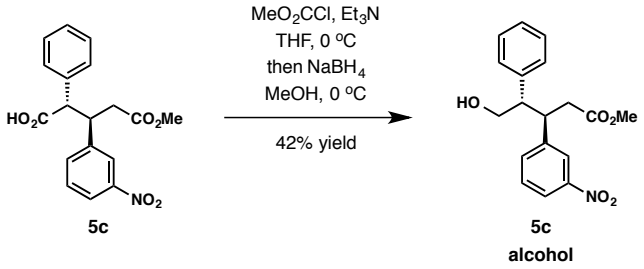
(2*S*,3*R*)-5-Methoxy-3-(4-methoxyphenyl)-5-oxo-2-phenylpentanoic acid (5b). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(4-methoxyphenyl)acrylate (101 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product **5b** (0.121 g, 0.369 mmol, 74%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +24.4 (*c* 0.30, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.47 (d, *J*=7.3 Hz, 2H), 7.39 (t, *J*=7.3 Hz, 2H), 7.31 (t, *J*=7.3 Hz, 1H), 7.28 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 3.89 (d, *J*=11.7 Hz, 1H), 3.73 (s, 3H), 3.59 (*virt.* td, *J* = 11.3, 4.0 Hz, 1H), 3.30 (s, 3H), 2.41 (dd, *J* = 15.5, 10.9 Hz, 1H), 2.13 (dd, *J* = 15.5, 4.0 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 173.2, 171.6, 157.9, 137.6, 133.8, 129.2, 128.7, 128.4, 127.6, 113.4, 56.7, 54.9, 51.1, 44.2, 38.4. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{20}O_5Na$, 351.1208; found, 351.1198.



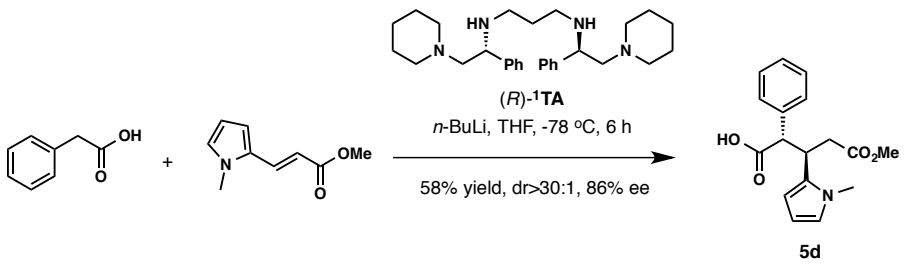
(2*R*,3*R*)-Dimethyl 3-(4-methoxyphenyl)-2-phenylpentanedioate (5b methyl ester). The title compound was prepared using carboxylic acid **5b** (7.2 mg, 21.9 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5b methyl ester** (7.1 mg, 20.7 μmol, 95% yield). Ee: 97% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=59.8 min; t_2=74.5 min). $[\alpha]_D^{23}$ +27.2 (*c* 0.34, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49-7.44 (m, 2H), 7.39-7.34 (m, 2H), 7.33-7.28 (m, 0H), 7.23 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 3.89-3.78 (m, 2H), 3.79 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 2.43-2.31 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.7, 172.1, 158.5, 136.6, 133.1, 128.9, 128.9, 128.7, 127.9, 113.8, 58.0, 55.1, 51.8, 51.4, 44.4, 38.8. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{20}H_{22}O_5Na$, 365; found, 365.



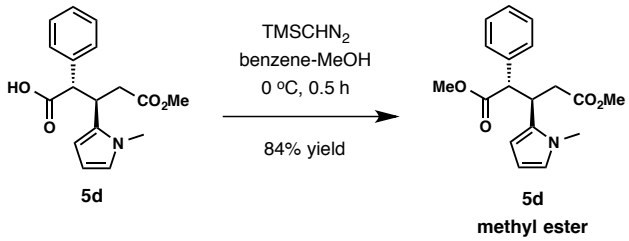
(2*S*,3*R*)-5-Methoxy-3-(3-nitrophenyl)-5-oxo-2-phenylpentanoic acid (5c). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(3-nitrophenyl)acrylate (0.114 g, 0.552 mmol, 1.1 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 0.5 h and product **5c** (46.1 mg, 0.114 mmol, 27%) was obtained after purification by column chromatography on silica gel (35% diethyl ether in hexanes with 0.5% AcOH). $[\alpha]_D^{23}$ +35.0 (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (t, *J*=1.8 Hz, 1H), 8.08-8.05 (m, 1H), 7.65-7.62 (m, 1H), 7.42-7.33 (m, 6H), 3.93 (dt, *J*=11.8, 7.2 Hz, 1H), 3.85 (d, *J*=11.8 Hz, 1H), 3.41 (s, 3H), 2.42 (d, *J*=7.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 176.4, 171.6, 148.5, 143.6, 135.5, 135.0, 129.6, 129.4, 128.8, 128.7, 123.0, 122.6, 57.2, 51.9, 44.5, 38.3. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{17}NO_6Na$, 366.0954; found, 366.0941.



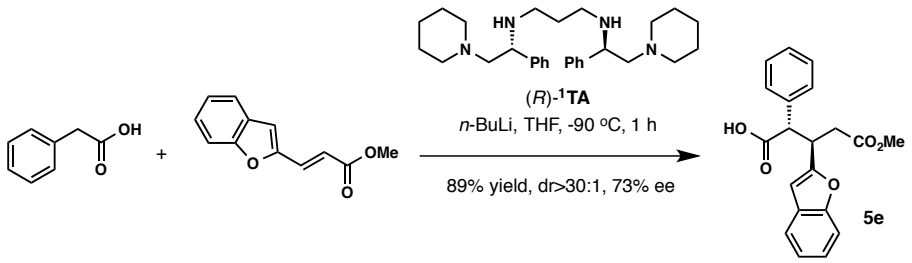
(3*R*, 4*S*)-Methyl 5-hydroxy-3-(3-nitrophenyl)-4-phenylpentanoate (5c alcohol). Methyl chloroformate (9 μL, 0.114 mol, 1.4 equiv) was added dropwise to a solution of carboxylic acid **5c** (28.0 mg, 0.0816 mmol) in THF (0.82 mL) and Et_3N (34 μL, 0.244 mmol, 3.0 equiv) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. $NaBH_4$ (15.0 mg, 0.408 mmol, 5.0 equiv) was added to the crude reaction followed by MeOH (1.0 mL) at 0 °C. The reaction was stirred at the same temperature for 20 min. The solvent was removed by rotary evaporation and the crude reaction mixture was quenched with saturate aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (70% diethyl ether in hexanes) to afford the product **5c alcohol** (8.0 mg, 24.3 μmol, 42% yield). Ee: 75% (Chiralcel® OD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=25.1 min; t_2=32.9 min). $[\alpha]_D^{19}$ -0.59 (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H), 8.13 (d, *J*=8.2Hz, 1H), 7.66 (d, *J*=7.8 Hz, 1H), 7.52 (t, *J*=7.9 Hz, 1H), 7.44-7.38 (m, 2H), 7.36-7.30 (m, 3H), 3.66 (*virt.* dt, *J*=11.0, 7.5 Hz, 1H), 3.57 (dd, *J*=11.1, 7.8 Hz, 1H), 3.47 (dd, *J*=11.1, 4.1 Hz, 1H), 3.42 (s, 3H), 3.04 (ddd, *J*=11.5, 7.8, 4.1 Hz, 1H), 2.54-2.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 171.9, 144.5, 139.5, 134.6, 129.6, 129.2, 128.6, 127.8, 122.6, 122.2, 64.9, 53.5, 51.6, 43.6, 39.2. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{19}NO_5Na$, 352; found, 352.



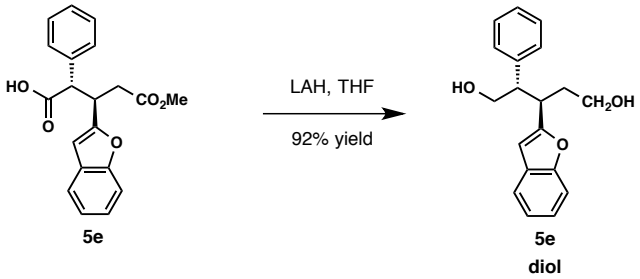
(2*S*,3*R*)-5-Methoxy-3-(1-methyl-1*H*-pyrrol-2-yl)-5-oxo-2-phenylpentanoic acid (5d). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(1-methyl-1*H*-pyrrol-2-yl)acrylate (86.7 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 6 h and product **5d** (86.9 mg, 0.288 mmol, 58%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +48.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.46–7.26 (m, 5H), 6.41 (dd, *J*=2.7, 1.6 Hz, 1H), 6.03 (dd, *J*=3.6, 2.7 Hz, 1H), 5.99 (dd, *J*=3.6, 1.6 Hz, 1H), 3.86 (ddd, *J*=11.2, 7.8, 5.9 Hz, 1H), 3.80 (d, *J*=11.2 Hz, 1H), 3.63 (s, 3H), 3.43 (s, 3H), 2.41–2.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 177.8, 172.2, 136.2, 133.0, 128.9, 128.5, 128.0, 121.4, 106.7, 104.9, 57.8, 51.5, 39.0, 35.2, 33.6. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{17}H_{19}NO_4Na$, 324.1212; found, 324.1198.



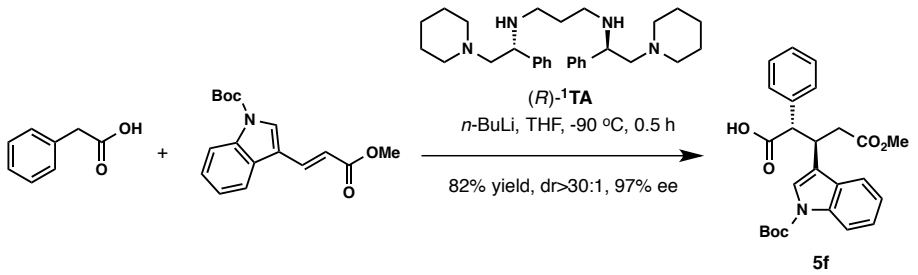
(2*S*,3*R*)-Dimethyl 3-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylpentanedioate (5d methyl ester). The title compound was prepared using carboxylic acid **5d** (18.0 mg, 59.7 μmol), $TMSCHN_2$ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5d methyl ester** (15.9 mg, 50.4 μmol, 95% yield). Ee: 86% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=13.9 min; t_2=16.1 min). $[\alpha]_D^{23}$ +53.0 (*c* 0.76, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J* = 6.9 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.46 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.04 (*virt.* t, *J* = 3.1 Hz, 1H), 6.00 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.91 (ddd, *J* = 11.5, 8.5, 5.6 Hz, 1H), 3.81 (d, *J* = 11.5 Hz, 1H), 3.74 (s, 3H), 3.44 (s, 3H), 3.44 (s, 3H), 2.42–2.32 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.0, 172.2, 136.7, 133.3, 128.9, 128.5, 128.0, 121.3, 106.7, 104.8, 57.9, 52.0, 51.5, 39.0, 35.7, 33.8. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{21}NO_4Na$, 338; found, 338.



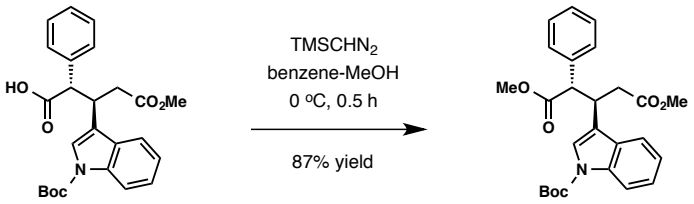
(2*S*,3*R*)-3-(Benzofuran-2-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid (5e). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(benzofuran-2-yl)acrylate (0.106 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product **5e** (0.150 g, 0.443 mmol, 89%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +54.9 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.70 (brs, 1 H), 7.42 (d, *J*=7.3 Hz, 1H), 7.38-7.09 (m, 8H), 6.50 (s, 1H), 4.20-4.00 (m, 2H), 3.45 (s, 3H), 2.56-2.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 177.7, 171.9, 157.2, 154.6, 135.3, 128.9, 128.8, 128.3, 128.1, 123.7, 122.6, 120.8, 111.0, 103.9, 54.6, 51.7, 38.4, 35.5. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{20}H_{18}O_5Na$, 361.1044; found, 361.1043.



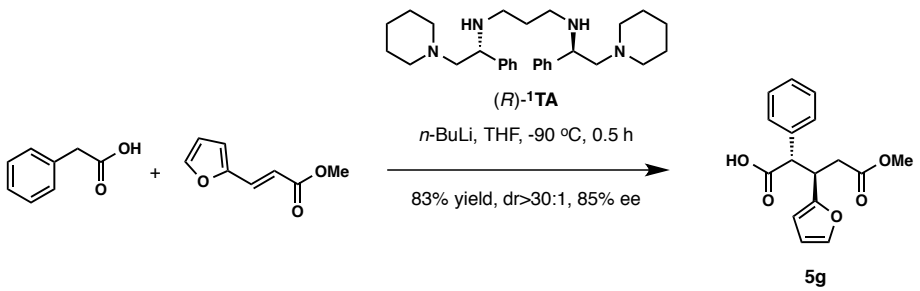
(2*S*,3*R*)-3-(Benzofuran-2-yl)-2-phenylpentane-1,5-diol (5e diol). To a solution of acid **5e** (13.9 mg, 39.4 μmol) in THF (2 mL) was added lithium aluminum hydride (LAH, 20.1 mg, 0.529 mmol) at 0 °C. After stirring for 1 h at the same temperature, the reaction was carefully quenched by adding 20 μL of water. After stirring for 5 min, 20 μL of aqueous NaOH (15% w/w) solution was added and the mixture was stirred for 5 min. Water (60 μL) was added and the mixture was stirred for additional 5 min. The white solid was filtered off, the filtrate was concentrated and the residue was purified by column chromatography on silica gel (50% of ethyl acetate in hexanes) to afford **5e diol** (10.7 mg, 36.1 μmol, 92%). Ee: 73% (Chiralcel® OD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=19.0 min; t_2=34.0 min). $[\alpha]_D^{23}$ +15.7° (*c* 0.51, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.55-7.49 (m, 1H), 7.49-7.43 (m, 1H), 7.42-7.34 (m, 2H), 7.34-7.27 (m, 3H), 7.30-7.18 (m, 2H), 6.57 (d, *J*=0.9 Hz, 1H), 3.68 (dd, *J*=11.2, 7.7 Hz, 1H), 3.63 (dd, *J*=11.2, 4.3 Hz, 1H), 3.49 (ddd, *J*=10.8, 6.6, 4.2 Hz, 1H), 3.45-3.31 (m, 2H), 3.23 (ddd, *J*=10.7, 7.7, 4.3 Hz, 1H), 1.85 (dddd, *J*=13.9, 11.3, 5.6, 4.3 Hz, 1H), 1.70 (dddd, *J*=13.9, 8.9, 6.6, 3.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 158.7, 154.8, 140.6, 129.0, 128.6, 128.3, 127.3, 123.6, 122.8, 120.5, 111.0, 104.4, 65.6, 60.6, 52.1, 38.2, 34.7. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{20}O_3Na$, 319; found, 319.



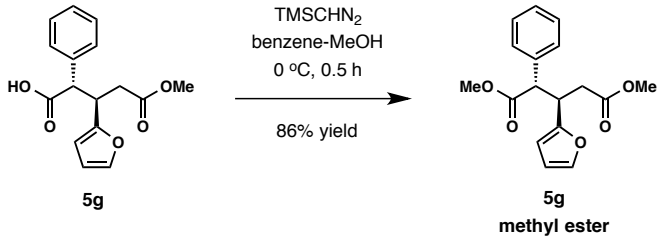
(2*S*,3*R*)-3-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid (5f). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-*tert*-butyl 3-(3-methoxy-3-oxoprop-1-enyl)-1*H*-indole-1-carboxylate (0.158 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **5f** (0.180 g, 0.411 mmol, 82%) was obtained after purification by column chromatography on silica gel (25% ethyl acetate in hexanes then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +41.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.10 (brs, 1H), 7.65 (d, *J*=7.8 Hz, 1H), 7.46 (s, 1H), 7.42-7.36 (m, 2H), 7.38-7.25 (m, 4H), 7.25-7.18 (m, 1H), 4.16 (ddd, *J*=10.9, 8.7, 4.8 Hz, 1H), 4.06 (d, *J*=10.9 Hz, 1H), 3.36 (s, 3H), 2.50 (dd, *J*=15.7, 4.8 Hz, 1H), 2.43 (dd, *J*=15.7, 8.7 Hz, 1H), 1.65 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 177.5, 171.9, 149.5, 135.8, 129.4, 128.9, 128.8, 128.1, 124.4, 123.1, 122.4, 121.0, 119.3, 115.2, 83.6, 56.1, 51.4, 37.8, 35.3, 28.2. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{25}H_{27}NO_6Na$, 460.1736; found, 460.1718.



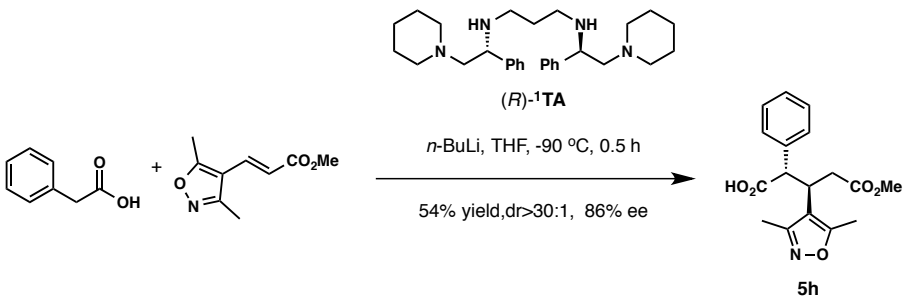
(2*S*,3*R*)-Dimethyl 3-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-phenylpentanedioate (5f methyl ester). The title compound was prepared using carboxylic acid **5f** (15.9 mg, 36.3 μmol), $TMSCHN_2$ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5f methyl ester** (14.2 mg, 31.5 μmol, 87% yield). Ee: 97% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=24.4 min; t_2=28.6 min). $[\alpha]_D^{23}$ +41.3 (*c* 0.71, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.11 (brs, 1H), 7.71 (d, *J*=7.8 Hz, 1H), 7.53-7.45 (m, 3H), 7.40-7.35 (m, 2H), 7.35-7.29 (m, 2H), 7.28-7.25 (m, 1H), 4.21 (ddd, *J*=11.4, 8.1, 5.5 Hz, 1H), 4.09 (d, *J*=11.4 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.51 (dd, *J*=15.9, 5.5 Hz, 1H), 2.47 (dd, *J*=15.9, 8.1 Hz, 1H), 1.68 (s, 9H). LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{26}H_{29}NO_6Na$, 474; found, 474.



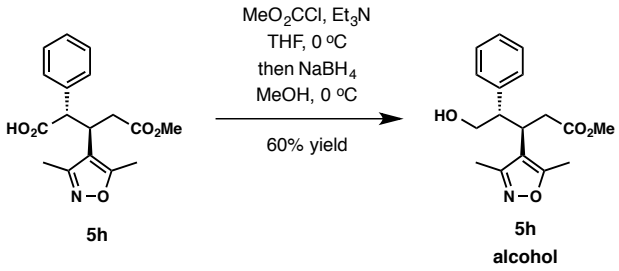
(2*S*,3*R*)-3-(Furan-2-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid (5g). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.81 mL, 2.47 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(furan-2-yl)acrylate (79.9 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **5g** (0.120 g, 0.415 mmol, 83%) was obtained after purification by column chromatography on silica gel (2-5% methanol in dichloromethane). $[\alpha]_D^{23}$ +41.4 (*c* 0.96, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38-7.28 (m, 6H), 6.23 (dd, *J*=3.2, 1.8 Hz, 1H), 6.13 (d, *J*=3.2 Hz, 1H), 4.01 (ddd, *J*=11.1, 9.2, 4.3 Hz, 1H), 3.95 (d, *J*=11.1 Hz, 1H), 3.49 (s, 3H), 2.44 (dd, *J*=15.8, 9.2 Hz, 1H), 2.37 (dd, *J*=15.8, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 178.0, 171.8, 153.9, 141.7, 135.3, 128.9, 128.7, 128.2, 110.2, 106.9, 55.0, 51.6, 38.2, 35.9. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{16}H_{16}O_5Na$, 311.0895; found, 311.0881.



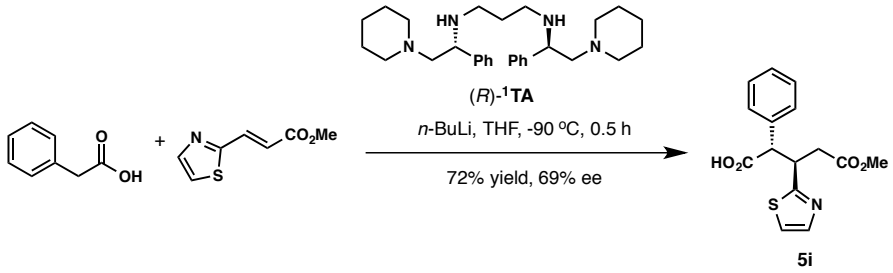
(2*S*,3*R*)-Dimethyl 3-(furan-2-yl)-2-phenylpentanedioate (5g methyl ester). The title compound was prepared using carboxylic acid **5g** (26.7 mg, 92.7 μmol), $TMSCHN_2$ in hexane (0.2 mL, 1.76 M, 0.352 mmol) in a mixture of benzene-MeOH (4:1, 2.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5g methyl ester** (24.2 mg, 80.0 μmol, 86% yield). Ee: 85% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=22.9 min; t_2=30.0 min). $[\alpha]_D^{23}$ +41.7 (*c* 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40-7.37 (m, 2H), 7.37-7.32 (m, 3H), 7.32-7.27 (m, 1H), 6.27 (dd, *J*=3.2, 1.8 Hz, 1H), 6.15 (d, *J*=3.2 Hz, 1H), 4.04 (ddd, *J*=11.3, 9.6, 4.4 Hz, 1H), 3.96 (d, *J*=11.3 Hz, 1H), 3.54 (s, 3H), 3.49 (s, 3H), 2.46 (dd, *J*=15.7, 9.6 Hz, 1H), 2.37 (dd, *J*=15.7, 4.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.7, 171.8, 154.3, 141.7, 135.9, 128.9, 128.7, 128.0, 110.2, 106.7, 55.2, 52.0, 51.5, 38.6, 36.0. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{17}H_{18}O_5Na$, 325; found, 325.



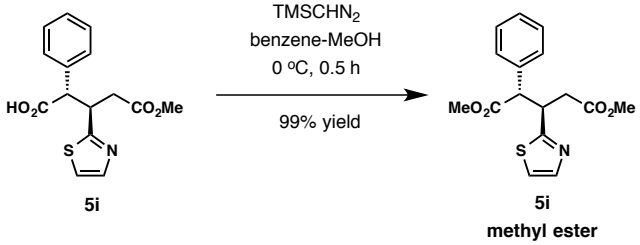
(2*S*,3*R*)-3-(3,5-Dimethylisoxazol-4-yl)-5-methoxy-5-oxo-2-phenylpentanoic acid (5h). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(3,5-dimethylisoxazol-4-yl)acrylate (0.100 g, 0.552 mmol, 1.1 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **5h** (86.0 mg, 0.271 mmol, 54%) was obtained after purification by column chromatography on silica gel (50% diethyl ether in hexanes with 0.5% AcOH). $[\alpha]_D^{23}$ +2.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (m, 5H), 3.78 (d, *J*=11.8 Hz, 1H), 3.71 (dt, *J*=11.8, 3.7 Hz, 1H), 3.46 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.42-2.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.0, 171.8, 171.7, 171.6, 135.5, 129.2, 128.5, 128.4, 112.8, 55.2, 51.7, 36.0, 33.9, 11.6, 10.9. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{19}NO_5Na$, 340.1161; found, 340.1153.



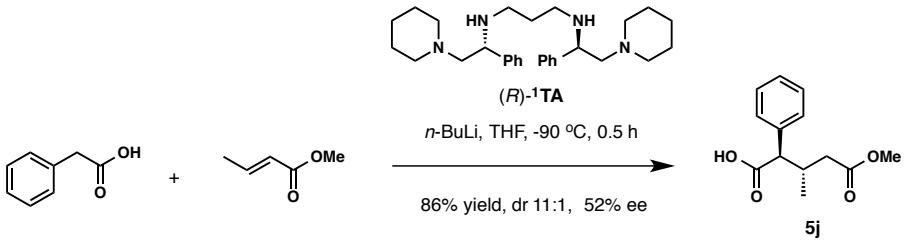
(2*S*,3*R*)-Methyl 3-(3,5-dimethylisoxazol-4-yl)-5-hydoxy-4-phenylpentanoate (5h alcohol). Methyl chloroformate (15 μL, 0.176 mmol, 1.4 equiv) was added dropwise to a solution of carboxylic acid **5h** (40.0 mg, 0.126 mmol) in THF (0.42 mL) and Et_3N (53 μL, 0.378 mmol, 3.0 equiv) at 0 °C. The resultant mixture was stirred at the same temperature for 0.5 h. Then $NaBH_4$ (24.0 mg, 0.630 mmol, 5.0 equiv) was added followed by MeOH (1.0 mL) at 0 °C. The reaction was stirred at the same temperature for 20 min. The reaction mixture was quenched with saturate aqueous NH_4Cl and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (70% diethyl ether in hexanes) to afford the product **5h alcohol** (23.0 mg, 75.6 μmol, 60% yield). Ee: 86% (Chiralcel® OD-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=21.2 min; t_2=27.1 min). $[\alpha]_D^{24}$ +30.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO) δ (ppm): 7.39-7.27 (m, 5H), 3.52-3.46 (m, 2H), 3.43 (s, 3H), 3.35-3.32 (m, 1H), 2.98-2.93 (m, 1H), 2.47 (dd, *J* = 15.6, 11.8 Hz, 1H), 2.31 (s, 3H), 2.30-2.26 (m, 1H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ (ppm): 172.8, 165.9, 159.6, 142.8, 129.6, 129.1, 127.5, 113.8, 63.8, 52.1, 51.3, 37.3, 33.6, 12.0, 11.4. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{21}NO_4Na$, 326.14; found, 326.14.



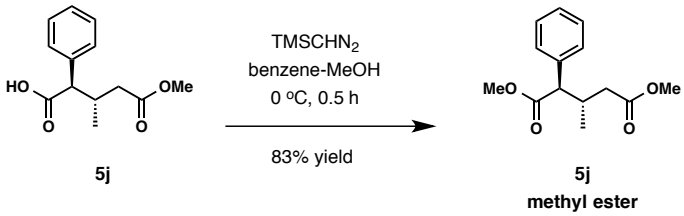
(2*S*,3*R*)-5-Methoxy-5-oxo-2-phenyl-3-(thiazol-2-yl)pentanoic acid (5i). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of methyl (*E*)-methyl 3-(thiazol-2-yl)acrylate (93.0 mg, 0.552 mmol, 1.1 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **5i** (0.111 g, 0.361 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (50% ethyl acetate in hexanes with 0.5% AcOH). $[\alpha]_D^{21}$ +33.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.66 (d, *J*=3.3 Hz, 1H), 7.37-7.30 (m, 5H), 7.16 (d, *J*=3.3 Hz, 1H), 4.32 (*virt.* dt, *J*=10.9, 3.8 Hz, 1H), 4.20 (d, *J*=11.0 Hz, 1H), 3.48 (s, 3H), 2.63 (dd, *J*=16.5, 10.1 Hz, 1H), 2.43 (dd, *J*=16.5, 3.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 176.0, 171.7, 171.0, 142.1, 135.8, 129.3, 128.9, 128.5, 119.2, 56.2, 51.9, 42.0, 37.9. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{15}NO_4SNa$, 328.0619; found, 328.0609.



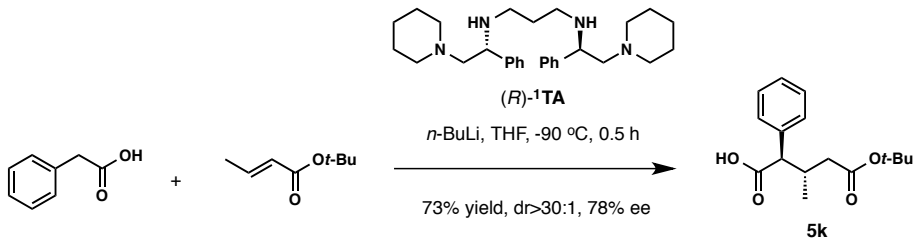
(2*S*,3*R*)-Dimethyl 2-phenyl-3-(thiazol-2-yl)pentanedioate (5i methyl ester). The title compound was prepared using carboxylic acid **5i** (10.0 mg, 32.7 μmol), $TMSCHN_2$ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (30-40% diethyl ether in hexanes) to afford product **5i methyl ester** (10.3 mg, 32.4 μmol, 99% yield). Ee: 69% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=24.6 min; t_2=28.3 min). $[\alpha]_D^{22}$ +63.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.72 (d, *J*=2.8 Hz, 1H), 7.44-7.30 (M, 5H), 7.23 (d, *J*=2.8 Hz, 1H), 4.38 (*virt.* dt, *J*=10.9, 3.6 Hz, 1H), 4.20 (d, *J*=11.5 Hz, 1H), 3.52 (s, 3H), 3.50 (s, 3H), 2.67 (dd, *J* = 16.4, 10.2 Hz, 1H), 2.44 (dd, *J*=16.4, 3.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 172.8, 171.8, 170.5, 142.4, 136.2, 129.3, 128.8, 128.4, 119.0, 56.3, 52.4, 51.9, 42.3, 37.9. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{17}NO_4SNa$, 342; found, 342.



(2*R*,3*S*)-5-Methoxy-3-methyl-5-oxo-2-phenylpentanoic acid (5j). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**[1]TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl crotonate (53 μL, 50.0 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **5j** (0.101 g, 0.429 mmol, 86% yield) was obtained after purification by column chromatography on silica gel (5% methanol in dichloromethane). $[\alpha]_D^{23}$ -23.1 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36-7.27 (m, 5H), 3.58 (s, 3H), 3.39 (d, *J*=10.7 Hz, 1H), 2.79-2.66 (m, 1H), 2.17 (dd, *J*=15.5, 4.0 Hz, 1H), 1.92 (dd, *J*=15.5, 9.3 Hz, 1H), 1.13 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.1, 172.8, 136.6, 128.8, 128.7, 127.9, 57.7, 51.4, 38.3, 33.4, 18.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{16}O_4Na$, 259.0946; found, 259.0939.



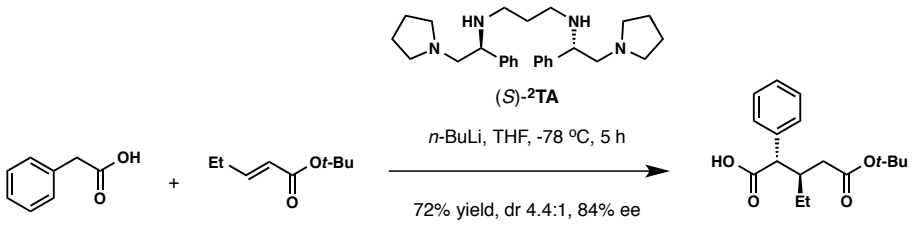
(2*R*,3*S*)-Dimethyl 3-methyl-2-phenylpentanedioate (5j methyl ester). The title compound was prepared using carboxylic acid **5j** (9.1 mg, 38.6 μmol), $TMSCHN_2$ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5j methyl ester** (8.0 mg, 32.0 μmol, 83% yield). Ee: 52% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; *anti*: t_1=18.9 min; t_2=22.7 min; *syn*: t_1=29.4 min; t_2=61.1 min). $[\alpha]_D^{23}$ -26.9 (*c* 0.24, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38-7.30 (m, 4H), 7.28-7.23 (m, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.39 (d, *J*=10.8 Hz, 1H), 2.77-2.68 (m, 1H), 2.17 (dd, *J*=15.5, 4.0 Hz, 1H), 1.91 (dd, *J*=15.5, 9.4 Hz, 1H), 1.08 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.7, 172.8, 137.2, 128.7, 128.6, 127.7, 57.7, 51.9, 51.4, 38.4, 33.8, 18.6. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{18}O_4Na$, 273; found, 273.



(2*R*,3*S*)-5-*tert*-Butoxy-3-methyl-5-oxo-2-phenylpentanoic acid (5k). The title compound was prepared according to general procedure I using phenylacetic acid (0.136 g, 0.999 mmol), (*R*)-**[1]TA** (0.462 g, 1.03 mmol, 1.03 equiv), *n*-BuLi (1.64 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (10 mL) followed by addition of a solution of (*E*)-*tert*-butyl crotonate (0.171 g, 1.20 mmol, 1.2 equiv) in THF (1.0 mL) at -90 °C. The reaction was quenched after 0.5 h and product **5k** (0.203 g, 0.730 mmol, 73% yield) was obtained after recrystallization from ethyl acetate and hexanes. $[\alpha]_D^{23}$ -31.7 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38-7.24 (m, 5H), 3.38 (d, *J*=10.8 Hz, 1H), 2.72-2.61 (m, 1H), 2.09 (dd, *J*=15.1, 3.4 Hz, 1H), 1.80 (dd, *J*=15.1, 9.7 Hz, 1H), 1.40 (s, 3H), 1.13 (d, *J*=6.4 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.4, 171.8, 136.7, 128.7, 128.6, 127.7, 80.4, 57.7, 39.7, 33.5, 28.0, 18.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$, 301.1416; found, 301.1392.

5k **5k methyl ester**

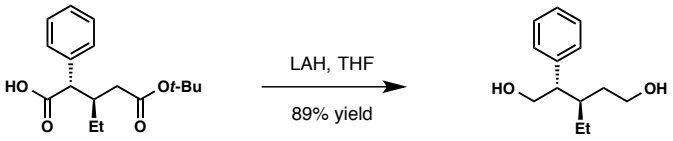
(2*R*,3*S*)-5-*tert*-Butyl 1-methyl-3-methyl-2-phenylpentanedioate (5k methyl ester). The title compound was prepared using carboxylic acid **5k** (23.5 mg, 84.4 μmol), $TMSCHN_2$ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5k methyl ester** (22.8 mg, 78.0 μmol, 92% yield). Ee: 78% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; t_1=9.8 min; t_2=10.4 min). $[\alpha]_D^{23}$ -41.8 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35-7.29 (m, 4H), 7.28-7.24 (m, 1H), 3.65 (s, 3H), 3.39 (d, *J*=10.7 Hz, 1H), 2.72-2.62 (m, 1H), 2.08 (dd, *J*=15.1, 3.8 Hz, 1H), 1.79 (dd, *J*=15.1, 9.6 Hz, 1H), 1.40 (s, 9H), 1.08 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.8, 171.8, 137.4, 128.7, 128.6, 127.5, 80.3, 57.6, 51.9, 39.8, 33.9, 28.1, 18.2. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_4Na$, 315; found, 315.



5l

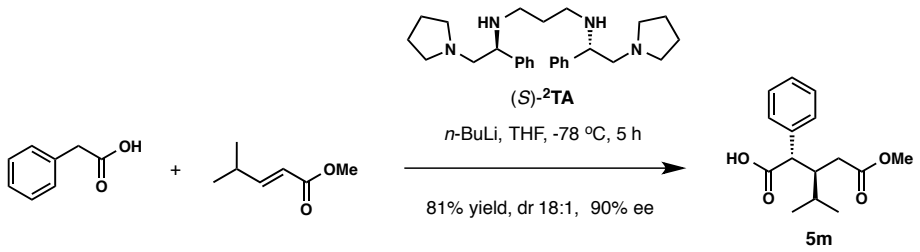
(2*S*,3*R*)-5-*tert*-Butoxy-3-ethyl-5-oxo-2-phenylpentanoic acid (5l). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-**[2]TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl pent-2-enoate (82.0 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product **5l** (0.105 g, 0.359 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (20% ethyl acetate in hexanes, then

5% methanol in dichloromethane). $[\alpha]_D^{23}$ +29.1 (*c* 1.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.22 (m, 5H), 3.59 (d, *J*=10.7 Hz, 1H), 2.61–2.50 (m, 1H), 2.10 (dd, *J*=15.6, 4.2 Hz, 1H), 1.90 (dd, *J*=15.6, 7.9 Hz, 1H), 1.64–1.54 (m, 1H), 1.53–1.46 (m, 1H), 1.38 (s, 9H), 0.95 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.6, 171.9, 137.0, 128.9, 128.7, 127.6, 80.3, 55.4, 39.2, 35.8, 28.0, 24.7, 10.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}O_4Na$, 315.1572; found, 315.1561.



5l **5l diol**

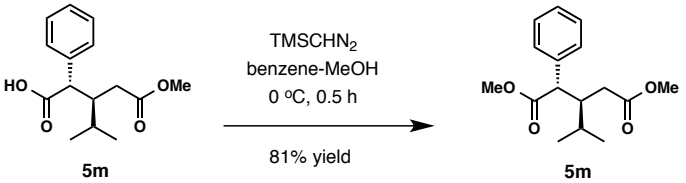
(2*S*,3*R*)-3-Ethyl-2-phenylpentane-1,5-diol (5l diol). The title compound was prepared using carboxylic acid **5l** (11.2 mg, 36.6 μmol), and lithium aluminum hydride (20.0 mg, 0.526 mmol) in THF (2.0 mL) at 0 °C. The reaction was quenched after 1 h, and product **5l diol** (6.8 mg, 32.6 μmol, 89% yield) was obtained after purification by column chromatography on silica gel (66% ethyl acetate in hexanes). Ee: 84% (Chiralcel® OJ-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=11.7 min; t_2=14.0 min). $[\alpha]_D^{23}$ +9.9 (*c* 0.28, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.36–7.29 (m, 2H), 7.28–7.18 (m, 3H), 3.94 (dd, *J*=11.0, 5.9 Hz, 1H), 3.83 (dd, *J*=11.0, 8.4 Hz, 1H), 3.62 (ddd, *J*=10.3, 7.4, 5.0 Hz, 1H), 3.51 (ddd, *J*=10.3, 7.8, 6.7 Hz, 1H), 2.87 (*virt.* td, *J*=8.2, 5.8 Hz, 1H), 1.92–1.80 (m, 1H), 1.61–1.28 (m, 6H), 0.95 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 141.1, 128.8, 128.6, 126.8, 64.7, 61.3, 50.6, 37.3, 33.3, 23.5, 10.4. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{20}O_2Na$, 231; found, 231.



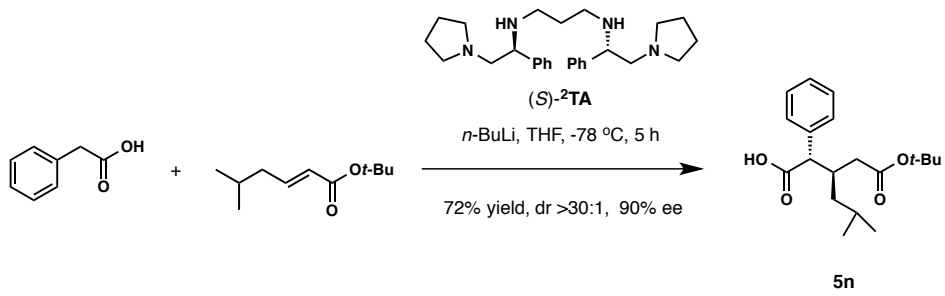
5m

(2*R*,3*R*)-3-Isopropyl-5-methoxy-5-oxo-2-phenylpentanoic acid (5m). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl-4-methylpent-2-enoate (67.3 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product **5m** (0.107 g, 0.400 mmol, 81% yield) was obtained after purification by column chromatography on silica gel (10% ethyl acetate in hexanes, then 5% methanol in dichloromethane). $[\alpha]_D^{23}$ +8.2° (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40–7.35 (m, 2H), 7.32–7.23 (m, 3H), 3.52 (d, *J*=11.7 Hz, 1H), 3.36 (s, 3H), 2.91–2.77 (m, 1H), 2.13 (dd, *J*=15.9, 5.8 Hz, 1H), 2.00– 1.93 (m, 1H), 1.89 (dd, *J* = 15.9, 6.0 Hz, 1H), 0.98 (d, *J*=6.8 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm):

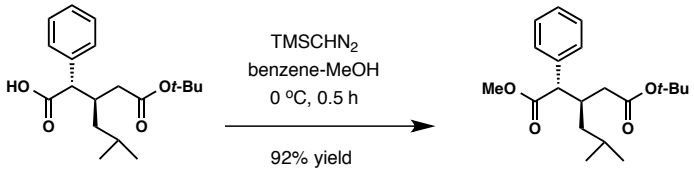
178.9, 173.6, 136.3, 129.3, 128.6, 127.9, 55.5, 51.4, 43.1, 31.9, 29.7, 21.2, 16.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{20}O_4Na$, 287.1259; found, 287.1250.



(2*R*,3*R*)-Dimethyl 3-isopropyl-2-phenylpentanedioate (5m methyl ester). The title compound was prepared using carboxylic acid **5m** (14.3 mg, 54.1 μmol), $TMSCHN_2$ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5m methyl ester** (12.2 mg, 43.8 μmol, 81% yield). Ee: 90% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=10.3 min; t_2=13.2 min). $[\alpha]_D^{23}$ +7.9 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40-7.34 (m, 2H), 7.33-7.25 (m, 2H), 7.28-7.21 (m, 1H), 3.65 (s, 3H), 3.53 (d, *J*=11.6 Hz, 1H), 3.37 (s, 3H), 2.90-2.82 (m, 1H), 2.12 (dd, *J*=15.9, 6.0 Hz, 1H), 1.90 (dd, *J*=15.9, 5.9 Hz, 1H), 1.88-1.83 (m, 1H), 0.98 (d, *J*=6.9 Hz, 3H), 0.89 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.9, 173.6, 136.9, 129.2, 128.5, 127.7, 55.4, 52.0, 51.4, 43.4, 32.2, 29.8, 21.1, 16.3. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{22}O_4Na$, 301; found, 301.

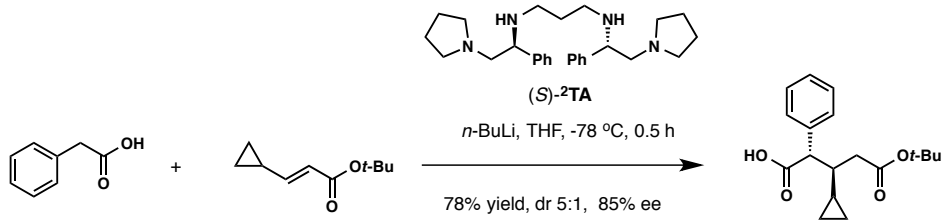


(2*S*,3*R*)-3-(2-*tert*-Butoxy-2-oxoethyl)-5-methyl-2-phenylhexanoic acid (5n). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl 5-methylhex-2-enoate (96.7 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product **5n** (0.116 g, 0.362 mmol, 72% yield) was obtained after purification by column chromatography on silica gel (10% ethyl acetate in hexanes, then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +26.8 (*c* 1.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37-7.34 (m, 2H), 7.33-7.29 (m, 2H), 7.30-7.23 (m, 1H), 3.69 (d, *J*=10.1 Hz, 1H), 2.67-2.56 (m, 1H), 2.21 (dd, *J*=15.7, 4.6 Hz, 1H), 1.89 (dd, *J*=15.7, 5.8 Hz, 1H), 1.75-1.65 (m, 1H), 1.45-1.36 (m, 1 H), 1.39 (s, 9H), 1.28-1.17 (m, 1H), 0.92 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.6, 171.7, 136.8, 129.1, 128.6, 127.6, 80.3, 55.8, 41.8, 36.3, 36.1, 28.0, 25.4, 23.7, 21.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{28}O_4Na$, 343.1885; found, 343.1871.



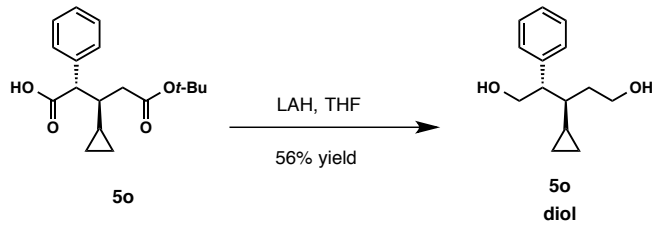
5n **5n methyl ester**

(2*S*,3*R*)-5-*tert*-Butyl 1-methyl-3-isobutyl-2-phenylpentanedioate (5n methyl ester). The title compound was prepared using carboxylic acid **5n** (14.7 mg, 45.9 μmol), $TMSCHN_2$ in hexane (0.14 mL, 1.76 M, 0.246 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5n methyl ester** (14.1 mg, 42.2 μmol, 92% yield). Ee: 90% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 210 nm; t_1=7.6 min; t_2=8.8 min). $[\alpha]_D^{23}$ +7.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.34 (m, 2H), 7.34–7.27 (m, 2H), 7.28–7.23 (m, 1H), 3.69 (d, *J*=10.2 Hz, 1H), 3.65 (s, 3H), 2.67–2.54 (m, 1H), 2.19 (dd, *J*=15.6, 4.7 Hz, 1H), 1.88 (dd, *J*=15.6, 5.8 Hz, 1H), 1.72–1.63 (m, 1H), 1.43–1.35 (m, 1 H), 1.39 (s, 9H), 1.15 (ddd, *J*=13.6, 9.4, 4.1 Hz, 1H), 0.91 (d, *J*=6.3 Hz, 3H), 0.90 (d, *J*=6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.2, 171.7, 137.4, 128.9, 128.5, 127.4, 80.2, 55.8, 51.8, 41.9, 36.4, 36.4, 28.1, 25.4, 23.8, 21.6. LRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{30}O_4Na$, 357; found, 357.

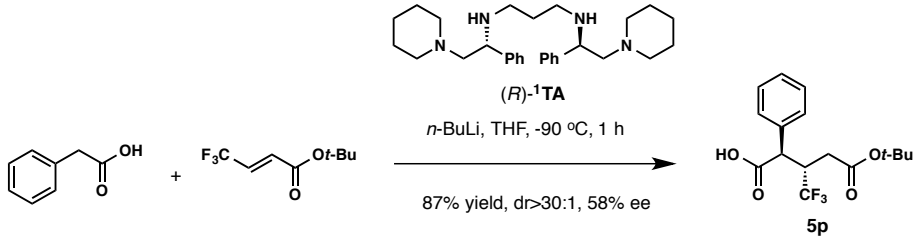


5o

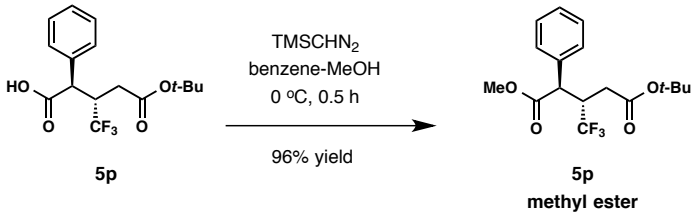
(2*S*,3*S*)-5-*tert*-Butoxy-3-cyclopropyl-5-oxo-2-phenylpentanoic acid (5o). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl-3-cyclopropylacrylate (84.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 0.5 h and product **5o** (0.119 g, 0.391 mmol, 78% yield) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23}$ +4.1 (*c* 0.60, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39–7.31 (m, 2H), 7.34–7.22 (m, 3H), 3.73 (d, *J*=10.1 Hz, 1H), 2.22 (dd, *J*=15.0, 3.9 Hz, 1H), 2.01 (dd, *J*=15.0, 8.1 Hz, 1H), 1.96–1.82 (m, 1H), 1.40 (s, 9H), 0.87–0.77 (m, 1H), 0.53–0.44 (m, 2H), 0.37–0.32 (m, 1H), 0.31–0.22 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.7, 171.9, 136.7, 128.9, 128.5, 127.6, 80.3, 56.6, 43.4, 38.9, 28.0, 15.2, 5.1, 3.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_4Na$, 327.1572; found, 327.1560.



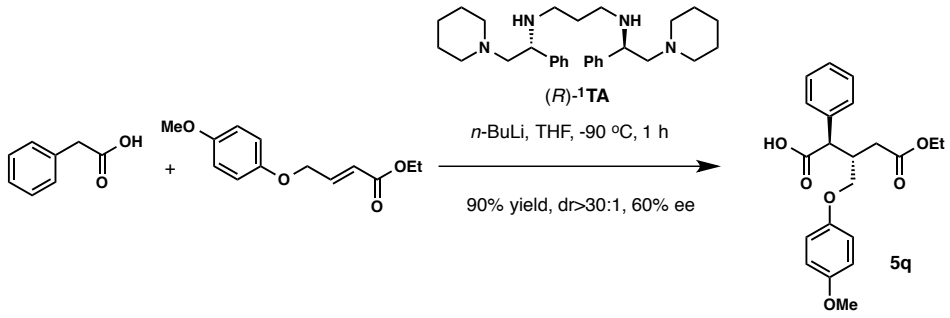
(2*S*,3*S*)-3-Cyclopropyl-2-phenylpentane diol (5o diol). The title compound was prepared using carboxylic acid **5o** (29.1 mg, 95.7 μmol), and lithium aluminum hydride (36.4 mg, 0.957 mmol) in THF (3.0 mL) at 0 °C. The reaction was quenched after 1 h, and product **5o diol** (11.9 mg, 54.0 μmol, 56% yield) was obtained after purification by column chromatography on silica gel (55% ethyl acetate in hexanes). Ee: 85% (Chiralcel® OJ-H; 5% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=15.8 min; t_2=22.4 min). $[\alpha]_D^{23}$ +7.7 (*c* 0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35–7.28 (m, 2H), 7.27–7.20 (m, 3H), 4.11 (dd, *J*=11.0, 6.0 Hz, 1H), 3.91 (dd, *J*=11.0, 8.3 Hz, 1H), 3.78–3.58 (m, 2H), 2.96 (td, *J*=8.0, 6.0 Hz, 1H), 1.72–1.65 (m, 1H), 1.60–1.40 (m, 3H), 1.19–1.10 (m, 1H), 0.60–0.48 (m, 3H), 0.28–0.16 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 141.0, 128.8, 128.5, 126.8, 65.0, 61.2, 53.7, 42.5, 35.8, 14.9, 4.9, 4.7. LRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{20}O_2Na$, 243; found, 243.



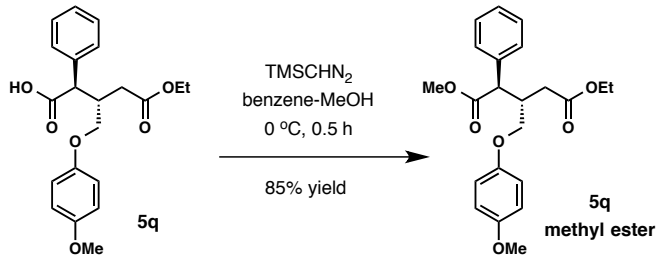
(2*R*,3*S*)-5-*tert*-Butoxy-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoic acid (5p). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.82 mL, 2.44 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-*tert*-butyl-3-trifluoromethylacrylate (0.103 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product **5p** (0.144 g, 0.433 mmol, 87% yield) was obtained after purification by column chromatography on silica gel (4–6% methanol in dichloromethane). $[\alpha]_D^{23}$ +12.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.29 (m, 5H), 3.82–3.69 (m, 2H), 2.25 (dd, *J*=17.0, 6.9 Hz, 1H), 2.09 (dd, *J*=17.0, 3.7 Hz, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 176.8, 169.4, 133.75, 129.2, 129.1, 128.6, 127.1 (q, *J* = 280.8 Hz), 81.4, 50.2, 42.0 (q, *J*=26.0 Hz), 32.5 (q, *J* = 2.2 Hz), 27.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -69.9 (d, *J*=7.2 Hz). HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{19}F_3O_4Na$, 355.1133; found, 355.1130.



(2*R*,3*S*)-5-*tert*-Butyl 1-methyl-2-phenyl-3-(trifluoromethyl)pentanedioate (5p methyl ester). The title compound was prepared using carboxylic acid **5p** (15.4 mg, 46.3 μmol), $TMSCHN_2$ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5p methyl ester** (15.4 mg, 44.5 μmol, 96% yield). Ee: 58% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 0.5 mL/min; detection at 215 nm; t_1=8.7 min; t_2=9.5 min). $[\alpha]_D^{23}$ +7.4 (*c* 0.52, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37–7.28 (m, 5H), 3.80–3.73 (m, 2H), 3.68 (s, 3H), 2.29–2.20 (m, 1H), 2.13–2.01 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.2, 169.4, 134.4, 129.1, 129.0, 127.2 (q, *J*=281.0 Hz), 81.3, 52.5, 50.3 (q, *J*=2.2 Hz), 42.2 (q, *J*=25.8 Hz), 32.7 (q, *J*=2.2 Hz), 27.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): –70.0 (d, *J*=7.0 Hz). LRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{21}F_3O_4Na$, 369; found, 369.

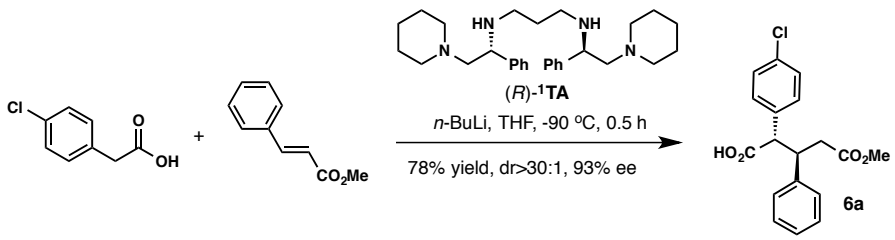


(2*R*,3*S*)-5-Ethoxy-3-((4-methoxyphenoxy)methyl)-5-oxo-2-phenylpentanoic acid (5q). The title compound was prepared according to general procedure I using phenylacetic acid (68.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-ethyl 4-(4-methoxyphenyloxy)but-2-enoate (0.124 g, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at –90 °C. The reaction was quenched after 1 h and product **5q** (0.168 g, 0.452 mmol, 90% yield) was obtained after purification by column chromatography on silica gel (20% ethyl acetate in hexanes, then 4% methanol in dichloromethane). $[\alpha]_D^{23}$ +29.8 (*c* 1.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41–7.28 (m, 5H), 6.83 (d, *J*=9.1 Hz, 2H), 6.78 (d, *J*=9.1 Hz, 2H), 4.10 (dd, *J*=9.6, 4.9 Hz, 1H), 4.06–3.96 (m, 3H), 3.90 (d, *J*=10.4 Hz, 1H), 3.75 (s, 3H), 3.20–3.08 (m, 1H), 2.28 (d, *J*=6.4 Hz, 2H), 1.15 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 178.6, 172.2, 153.9, 152.7, 135.9, 128.9, 128.8, 127.9, 115.4, 114.6, 68.9, 60.4, 55.6, 52.3, 37.8, 33.3, 14.0. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{24}O_6Na$, 395.1471; found, 395.1454.

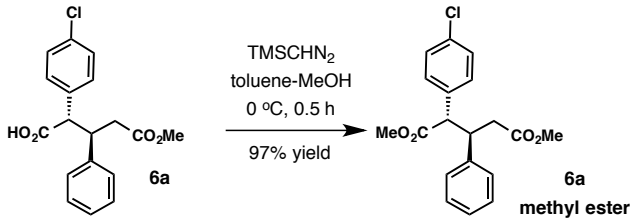


(2*R*,3*S*)-5-Ethyl 1-methyl-3-((4-methoxyphenoxy)methyl)-2-phenylpentanedioate (5q methyl ester). The title compound was prepared using carboxylic acid **5q** (14.9 mg, 40.1 μmol), $TMSCHN_2$ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL)

at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **5q methyl ester** (13.1 mg, 33.9 μmol, 85% yield). Ee: 60% (Chiralcel® OJ-H; 1% *i*-PrOH in hexanes; flow rate = 1 mL/min; detection at 215 nm; t_1=77.7 min; t_2=95.4 min). $[\alpha]_D^{23}$ +36.4 (*c* 0.62, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39–7.30 (m, 4H), 7.32–7.26 (m, 1H), 6.88–6.79 (m, 4H), 4.08–3.95 (m, 4H), 3.89 (d, *J*=10.4 Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 3.17–3.06 (m, 1H), 2.34–2.20 (m, 2H), 1.15 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.5, 172.2, 154.0, 152.9, 136.5, 128.8, 128.8, 127.8, 115.5, 114.6, 68.9, 60.4, 55.7, 52.1, 52.1, 38.2, 33.4, 14.1. LRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{26}O_6Na$, 409; found, 409.

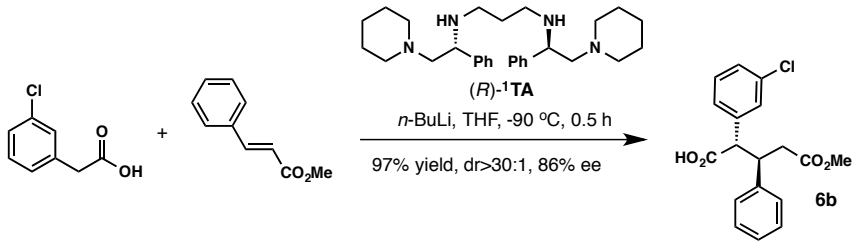


(2*S*,3*R*)-2-(4-Chlorophenyl)-5-methoxy-5-oxo-3-phenylpentanoic acid (6a). The title compound was prepared according to general procedure I using 4-chlorophenylacetic acid (85.3 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product **6a** (0.130 g, 0.392 mmol, 78% yield) was obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane with 0.5% HOAc). $[\alpha]_D^{23}$ +39.3° (*c* 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.37 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.26–7.23 (m, 4H), 7.22–7.17 (m, 1H), 3.84 (d, *J*=11.4 Hz, 1H), 3.77 (ddd, *J*=11.4, 8.8, 5.3 Hz, 1H), 3.39 (s, 3H), 2.41 (dd, *J*=15.6, 8.8 Hz, 1H), 2.41 (dd, *J*=15.6, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 177.1, 171.7, 140.6, 134.5, 134.2, 130.1, 129.1, 128.5, 127.9, 127.3, 56.7, 51.5, 44.8, 38.4. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{17}ClO_4Na$, 355.0713; found, 355.0704.

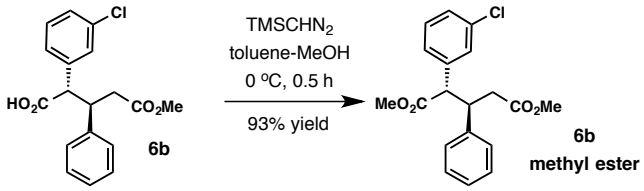


(2*S*,3*R*)-Dimethyl 2-(4-chlorophenyl)-3-phenylpentanedioate (6a methyl ester). The title compound was prepared using carboxylic acid **6a** (14.7 mg, 44.1 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford product **6a methyl ester** (14.7 mg, 42.5 μmol, 97% yield). Ee: 93% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=11.6 min; t_2=14.8 min). $[\alpha]_D^{23}$ +25.5 (*c* 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.44–7.40 (m, 2H), 7.36–7.32 (m, 2H), 7.32–7.27 (m, 2H), 7.25–7.20 (m, 1H), 3.89–3.80 (m, 2H), 3.41 (s, 3H), 3.37 (s, 3H), 2.46–2.41 (m, 1H), 2.38 (dd, *J*=15.6, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.3, 171.8, 140.8, 135.0, 134.0,

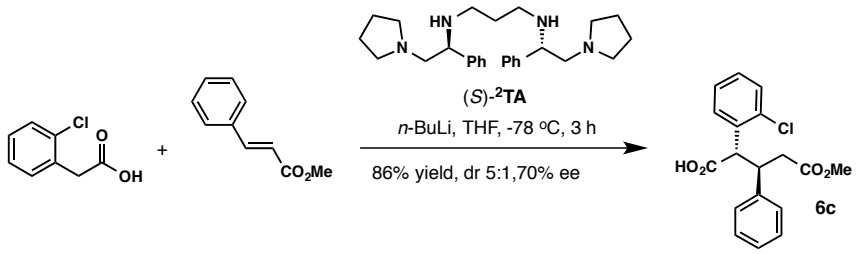
130.1, 129.0, 128.5, 127.9, 127.2, 57.0, 51.9, 51.4, 45.2, 38.5. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{19}ClO_4Na$, 369; found, 369.



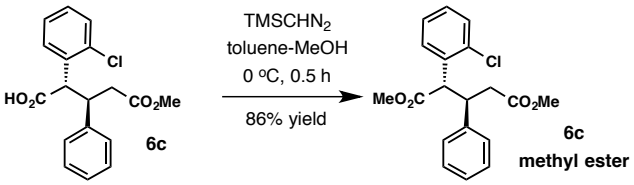
(2*S*,3*R*)-2-(3-Chlorophenyl)-5-methoxy-5-oxo-3-phenylpentanoic acid (6b). The title compound was prepared according to general procedure I using 3-chlorophenylacetic acid (85.3 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **6b** (0.160 g, 0.487 mmol, 97% yield) was obtained after purification by column chromatography on silica gel (5% methanol in dichloromethane with 0.5% HOAc). $[\alpha]_D^{23}$ +26.9 (*c* 0.47, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.48-7.45 (m, 1H), 7.37-7.27 (m, 7H), 7.24-7.19 (m, 1H), 3.87 (d, *J*=11.6 Hz, 1H), 3.86-3.75 (m, 1H), 3.41 (s, 3H), 2.43 (dd, *J*=15.0, 8.1 Hz, 1H), 2.38 (dd, *J*=15.0, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 176.7, 171.7, 140.4, 137.9, 134.8, 130.2, 128.9, 128.5, 128.5, 127.9, 127.4, 127.0, 57.0, 51.5, 44.8, 38.5. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{17}ClO_4Na$, 355.0713; found, 355.0697.



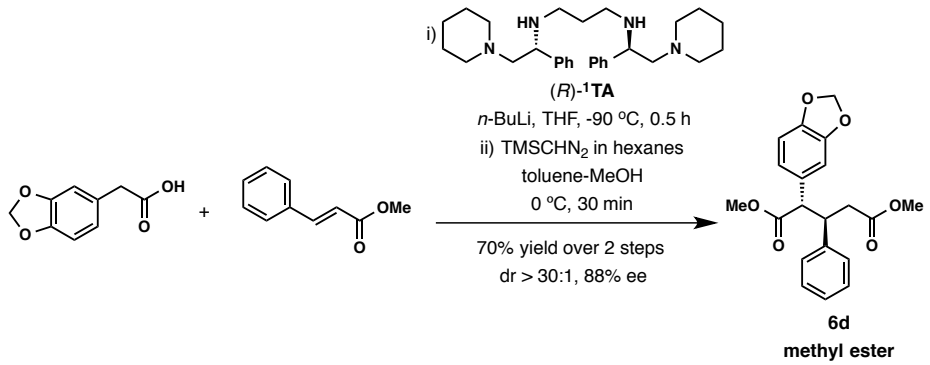
(2*S*,3*R*)-Dimethyl 2-(3-chlorophenyl)-3-phenylpentanedioate (6b methyl ester). The title compound was prepared using carboxylic acid **6b** (14.0 mg, 42.1 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford product **6b methyl ester** (13.5 mg, 39.0 μmol, 93% yield). Ee: 86% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes flow rate = 1.0 mL/min; detection at 215 nm; t_1=12.3 min; t_2=16.8 min). $[\alpha]_D^{23}$ +13.6° (*c* 0.50, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.50-7.47 (m, 1H), 7.39-7.35 (m, 1H), 7.33-7.28 (m, 6H), 7.23 (d, *J*=6.1 Hz, 1H), 3.88-3.81 (m, 2H), 3.41 (s, 3H), 3.38 (s, 3H), 2.48-2.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.2, 171.8, 140.9, 138.6, 134.8, 130.2, 128.9, 128.6, 128.4, 128.0, 127.4, 127.0, 57.4, 52.0, 51.6, 45.3, 38.6. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{19}ClO_4Na$, 369; found, 369.



(2*S*,3*R*)-2-(2-Chlorophenyl)-5-methoxy-5-oxo-3-phenylpentanoic acid (6c). The title compound was prepared according to general procedure I using 3-chlorophenylacetic acid (85.3 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 3 h and products **6c** (0.143 g, 0.431 mmol, dr 5:1, 86% yield) together with inseparable 3-chlorophenylacetic acid (11.0 mg, 64.5 μmol, 13% yield) were obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.64 (dd, *J*=7.8, 1.8 Hz, 1H), 7.43 (dd, *J*=7.9, 1.5 Hz, 1H), 7.34-7.14 (m, 7H), 4.61 (d, *J*=11.5 Hz, 1H), 3.82 (*virt.* td, *J*=11.2, 4.4 Hz, 1H), 3.37 (s, 3H), 2.53 (dd, *J*=15.6, 10.9 Hz, 1H), 2.31 (dd, *J*=15.6, 4.4 Hz, 1H). LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{18}H_{17}ClO_4Na$, 355; found, 355.

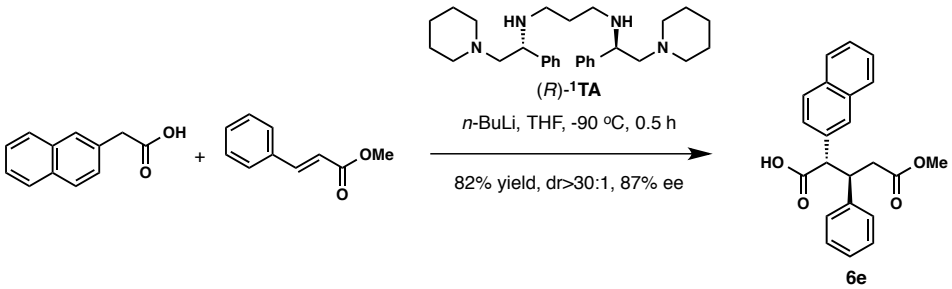


(2*S*,3*R*)-Dimethyl 2-(2-chlorophenyl)-3-phenylpentanedioate (6c methyl ester). The title compound was prepared using carboxylic acid **6c** (10.0 mg, 30.0 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **6c methyl ester** (9.0 mg, 26.0 μmol, 86% yield). Ee: 70% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=9.6 min; t_2=12.8 min). $[\alpha]_D^{23}$ +44.3 (*c* 0.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (dd, *J*=7.8, 1.7 Hz, 1H), 7.42 (dd, *J*=8.0, 1.4 Hz, 1H), 7.39-7.28 (m, 5H), 7.25-7.19 (m, 2H), 4.61 (d, *J*=11.6 Hz, 1H), 3.86 (*virt.* td, *J*=11.3, 4.4 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.56 (dd, *J*=15.6, 11.0 Hz, 1H), 2.32 (dd, *J*=15.6, 4.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.2, 172.0, 141.2, 135.0, 134.4, 129.9, 129.14, 129.09, 128.6, 128.2, 127.7, 127.3, 52.3, 52.0, 51.5, 45.9, 38.1. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{19}ClO_4Na$, 369.0870; found, 369.0860.



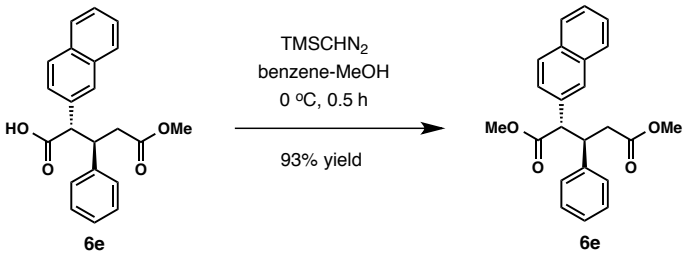
(2*S*,3*R*)-2-(1,3-Benzodioxol-5-yl)-5-methoxy-5-oxo-3-phenylpentanoic acid (6d). The title compound was prepared according to general procedure I using 2-(1,3-benzodioxol-5-yl)-acetic acid (90.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (83.5 mg, 0.515 mmol, 1.03 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and the crude product **6d** (0.168 g) was obtained after work up. Due to its extremely low solubility, no effort was attempted to purify by column chromatography, and the crude product was directly submitted to the next step.

(2*S*,3*R*)-Dimethyl 2-(1,3-benzodioxol-5-yl)-3-phenylpentanedioate (6d methyl ester). The title compound was prepared using above crude acid **6d** (0.168 g), $TMSCHN_2$ in hexane (1.30 mL, 1.13 M, 1.47 mmol) in a mixture of toluene-MeOH (3:1, 16 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **6d methyl ester** (0.124 mg, 0.348 mmol, 70% yield over steps). Ee: 88 % (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=30.1 min; t_2=37.9 min). $[\alpha]_D^{23}$ +21.6 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.32-7.27 (m, 4H), 7.24-7.18 (m, 1H), 7.03 (d, *J*= 1.8Hz, 1H), 6.88 (dd, *J*=7.9, 1.8 Hz, 1H), 6.78 (d, *J*=7.9 Hz, 1H), 5.97 (d, *J*=1.5 Hz, 1H), 5.96 (d, *J*=1.5 Hz, 1H), 3.83-3.75 (m, 2H), 3.42 (s, 3H), 3.37 (s, 3H), 2.48-2.39 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.6, 172.0, 148.1, 147.4, 141.1, 130.2, 128.4, 127.9, 127.1, 122.4, 108.5, 108.4, 101.2, 57.3, 51.8, 51.4, 45.4, 38.6. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{20}H_{20}O_6Na$, 379.1158; found, 379.1146.

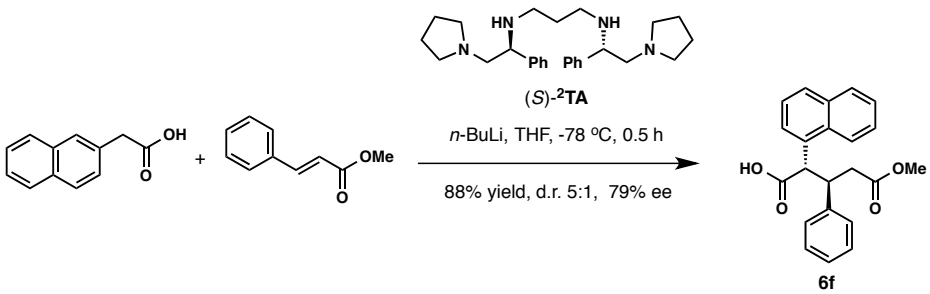


(2*S*,3*R*)-5-Methoxy-2-(naphthalen-2-yl)-5-oxo-3-phenylpentanoic acid (6e). The title compound was prepared according to general procedure I using 2-naphthaleneacetic acid (93.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **6e** (0.143 g, 0.410 mmol, 82% yield) was

obtained after purification by column chromatography on silica gel (4% methanol in dichloromethane). $[\alpha]_D^{23}$ +33.9 (*c* 0.38, $CHCl_3$). ^1H NMR (500 MHz $CDCl_3$) δ (ppm): ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.87 (d, *J*=1.8 Hz, 1H), 7.86-7.76 (m, 3H), 7.56 (dd, *J*=8.6, 1.8 Hz, 1H), 7.53-7.44 (m, 2H), 7.34-7.27 (m, 2H), 7.24 (t, *J*=7.5 Hz, 2H), 7.20-7.11 (m, 1H), 4.02 (d, *J*=11.6 Hz, 1H), 3.94 (ddd, *J*=11.6, 9.5, 5.0 Hz, 1H), 3.32 (s, 3H), 2.41 (dd, *J*=15.5, 9.5 Hz, 1H), 2.38 (dd, *J*=15.5, 5.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 176.6, 171.9, 140.8, 133.36, 133.35, 133.0, 128.8, 128.5, 128.2, 127.9, 127.6, 127.2, 126.4, 126.3, 125.9, 57.4, 51.4, 44.7, 38.6, 29.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{20}O_4Na$, 371.1259; found, 371.1249.

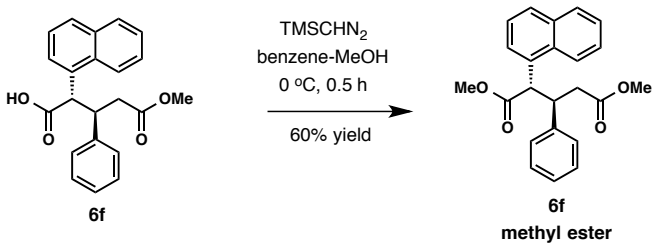


(2*S*,3*R*)-Dimethyl 2-(naphthalen-2-yl)-3-phenylpentanedioate (6e methyl ester). The title compound was prepared using carboxylic acid **6e** (18.6 mg, 53.4 μmol), $TMSCHN_2$ in hexane (0.15 mL, 1.76 M, 0.264 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **6e methyl ester** (18.0 mg, 49.7 μmol, 93% yield). Ee: 87% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=19.3 min; t_2=24.6 min). $[\alpha]_D^{23}$ +33.7 (*c* 0.86, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.92 (d, *J*=1.7 Hz, 1H), 7.90-7.82 (m, 3H), 7.65 (dd, *J*=8.5, 1.8 Hz, 1H), 7.53-7.46 (m, 2H), 7.40-7.36 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.22 (m, 1H), 4.06 (d, *J*=11.6 Hz, 1H), 4.01 (ddd, *J*=11.6, 9.4, 4.3 Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 2.47 (dd, *J*=15.6, 9.4 Hz, 1H), 2.41 (dd, *J*=15.6, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.6, 171.9, 141.2, 134.0, 133.4, 133.0, 128.7, 128.5, 128.1, 128.0, 127.9, 127.6, 127.1, 126.4, 126.2, 126.0, 57.8, 51.8, 51.3, 45.1, 38.7. LRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{22}O_4Na$, 385; found, 385.



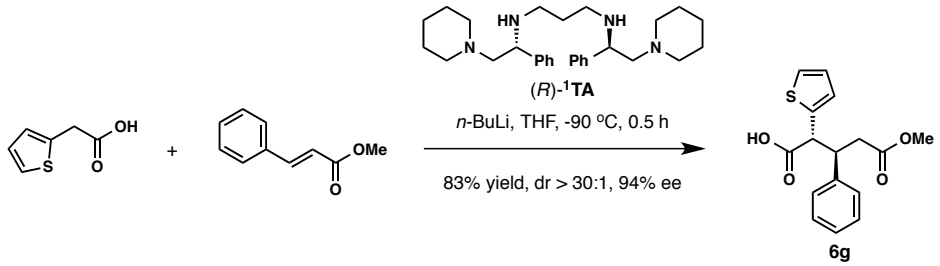
(2*S*,3*R*)-5-Methoxy-2-(naphthalen-1-yl)-5-oxo-3-phenylpentanoic acid (6f). The title compound was prepared according to general procedure I using 1-naphthaleneacetic acid (93.1 mg, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 0.5 h and product **6f** (0.167 g, 0.478 mmol, dr 5:1, 88% yield)

was obtained after purification by column chromatography on silica gel (6% methanol in dichloromethane). Pure major diastereomer could be separated partially by column chromatography on silica gel (6% methanol in dichloromethane). $[\alpha]_D^{23}$ +71.4 (*c* 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.24 (d, *J*=8.5 Hz, 1H), 7.89 (d, *J*=8.1 Hz, 1H), 7.81 (d, *J*=8.0 Hz, 1H), 7.76 (d, *J*=7.4 Hz, 1H), 7.58 (t, *J*=7.4 Hz, 1H), 7.56-7.49 (m, 1H), 7.48 (t, *J*=7.7 Hz, 1H), 7.35 (d, *J*=7.3 Hz, 2H), 7.23 (t, *J*=7.5 Hz, 2H), 7.16 (t, *J*=7.3 Hz, 1H), 4.77 (d, *J*=9.9 Hz, 1H), 4.10-3.98 (m, 1H), 3.32 (s, 3H), 2.41 (dd, *J*=15.6, 10.7 Hz, 1H), 2.30 (dd, *J*=15.6, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 177.1, 172.0, 141.0, 134.0, 132.2, 129.1, 128.5, 128.4, 128.1, 127.2, 126.7, 125.8, 125.7, 122.8, 51.3, 45.0, 38.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{20}O_4Na$, 371.1259; found, 371.1244.



6f **6f methyl ester**

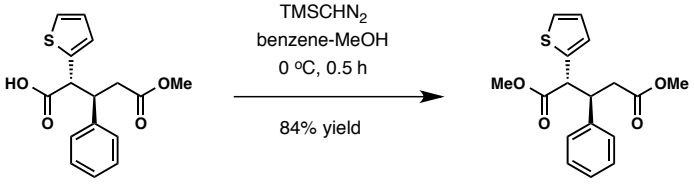
(2*S*,3*R*)-Dimethyl 2-(naphthalen-1-yl)-3-phenylpentanedioate (6f methyl ester). The title compound was prepared using the **6f** (18.2 mg, 52.3 μmol, dr 5:1), $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford pure diastereomer product **6f methyl ester** (11.4 mg, 31.5 mol, 60% yield). Ee: 79% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=18.7 min; t_2=27.3 min). $[\alpha]_D^{23}$ +89.3 (*c* 1.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.34 (d, *J*=8.5 Hz, 1H), 7.94-7.87 (m, 2H), 7.85 (d, *J*=8.1 Hz, 1H), 7.63 (ddd, *J*=8.4, 6.8, 1.4 Hz, 1H), 7.58-7.51 (m, 2H), 7.51-7.45 (m, 2H), 7.41-7.33 (m, 2H), 7.31-7.24 (m, 1H), 5.00-4.69 (m, 1H), 4.22-4.13 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.49 (dd, *J*=15.6, 10.8 Hz, 1H), 2.36 (dd, *J*=15.6, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.6, 171.9, 141.4, 134.0, 132.7, 132.2, 129.1, 128.4, 128.3, 128.1, 127.1, 126.7, 125.74, 125.71, 122.8, 51.8, 51.3, 45.5, 38.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{22}O_4Na$, 385.1416; found, 385.1400.



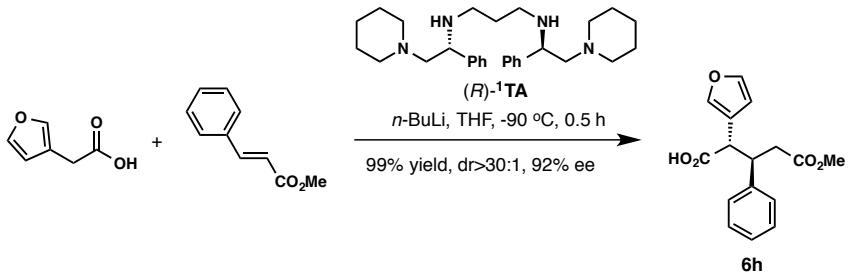
6g

(2*R*,3*R*)-5-Methoxy-5-oxo-3-phenyl-2-(thiophen-2-yl)pentanoic acid (6g). The title compound was prepared according to general procedure I using 2-thiopheneacetic acid (71.1 mg, 0.500 mmol), (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 1 h and product **6g** (0.126 g, 0.414 mmol, 93% yield) was obtained after purification by column chromatography on silica gel (16% ethyl acetate in

hexanes, then 4-6% methanol in dichloromethane). $[\alpha]_D^{23}$ +14.9 (*c* 0.35, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.23 (d, *J*=5.1 Hz, 1H), 7.22-7.14 (m, 5H), 7.01 (d, *J*=3.5 Hz, 1H), 6.95 (dd, *J*=5.1, 3.5 Hz, 1H), 4.10 (d, *J*=11.0 Hz, 1H), 3.74 (*virt.* td, *J*=10.4, 4.4 Hz, 1H), 3.42 (s, 3H), 2.54 (dd, *J*=15.6, 4.4 Hz, 1H), 2.46 (dd, *J*=15.6, 10.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 176.9, 172.1, 140.5, 138.2, 128.4, 127.9, 127.20, 127.17, 126.8, 125.5, 52.9, 51.5, 46.1, 38.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{16}O_4NaS$, 327.0667; found, 327.0653.

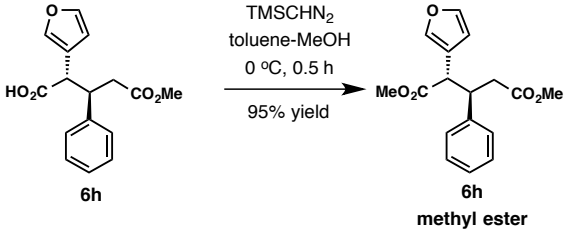


(2*R*,3*R*)-Dimethyl 3-phenyl-2-(thiophen-2-yl)pentanedioate (6g methyl ester). The title compound was prepared using carboxylic acid **6g** (10.3 mg, 33.8 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **6g methyl ester** (9.1 mg, 28.6 μmol, 84% yield). Ee: 94% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1 mL/min; detection at 215 nm; t_1=22.2 min; t_2=23.1 min). $[\alpha]_D^{23}$ +6.3 (*c* 0.43, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.33-7.25 (m, 5H), 7.26-7.18 (m, 1H), 7.09 (dd, *J*=3.5, 1.2 Hz, 1H), 6.99 (dd, *J*=5.2, 3.5 Hz, 1H), 4.17 (d, *J*=11.3 Hz, 1H), 3.80 (ddd, *J*=11.3, 10.0, 4.6 Hz, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 2.57 (dd, *J*=15.7, 4.6 Hz, 1H), 2.51 (dd, *J*=15.7, 10.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 171.9, 171.9, 140.6, 138.6, 128.5, 127.9, 127.3, 127.0, 126.8, 125.6, 52.9, 52.0, 51.5, 46.7, 38.5. LRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{18}O_4NaS$, 341; found, 341.

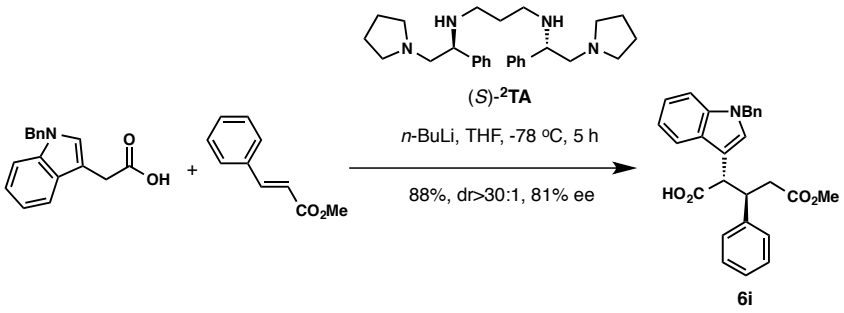


(2*S*,3*R*)-2-(Furan-3-yl)-5-Methoxy-5-oxo-3-phenylpentanoic acid (6h). The title compound was prepared according to general procedure I using 3-furanacetic acid (63.1 mg, 0.500 mmol), (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -90 °C. The reaction was quenched after 0.5 h and product **6h** (0.113 g, 0.442 mmol, 99% yield) was obtained after purification by column chromatography on silica gel (20% ethylacetate in hexanes with 1% AcOH). $[\alpha]_D^{23}$ +31.1 (*c* 0.25, MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.44-7.39 (m, 2H), 7.25-7.18 (m, 5H), 6.51-6.43 (m, 1H), 3.81 (d, *J* = 10.0 Hz, 1H), 3.69 (*virt.* td, *J* = 10.0, 5.0

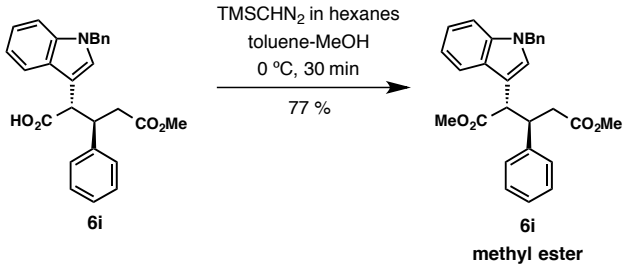
Hz, 1H), 3.45 (s, 3H), 2.62 (dd, *J*=15.7, 5.0 Hz, 1H), 2.49 (dd, *J*=15.7, 9.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 176.9, 172.0, 143.5, 141.2, 140.5, 128.5, 127.8, 127.3, 120.2, 110.2, 51.5, 48.0, 44.4, 38.3. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{16}H_{16}O_5Na$, 311.0895; found, 311.0881.



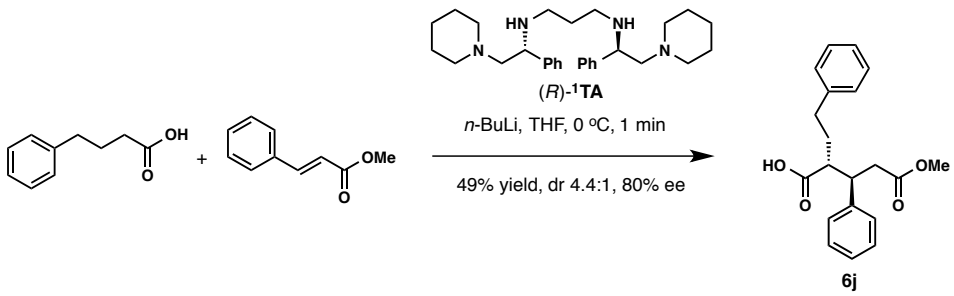
(2*S*,3*R*)-Dimethyl 2-(furan-3-yl)-3-phenylpentanedioate (6h methyl ester). The title compound was prepared using carboxylic acid **6h** (18.6 mg, 64.6 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexanes) to afford product **6h methyl ester** (18.5 mg, 61.2 μmol, 95% yield). Ee: 92 % (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=17.0 min; t_2=21.7 min). $[\alpha]_D^{23}$ +9.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44-7.38 (m, 2H), 7.30-7.15 (m, 5H), 6.50 (m, 1H), 3.83 (d, *J*=10.9 Hz, 1H), 3.69 (*virt.* td, *J*=10.4, 4.5 Hz, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.61 (dd, *J*=15.6, 4.5 Hz, 1H), 2.48 (dd, *J*=15.6, 9.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 172.5, 172.1, 143.5, 141.0, 141,0, 128.5, 127.9, 127.3, 120.9, 110.3, 51.9, 51.6, 48.5, 45.0, 38.5. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{17}H_{18}O_5Na$, 325; found, 325.



(2*S*,3*R*)-2-(1-benzyl-1*H*-indol-3-yl)-5-methoxy-5-oxo-3-phenylpentanoic acid (6i). The title compound was prepared according to general procedure I using N-benzyl-3-indolylacetic acid (0.133 g, 0.500 mmol), (*S*)-**^{2}TA** (0.217 g, 0.515 mmol, 1.03 equiv), *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.00 mmol, 4.0 equiv) in THF (5.0 mL) followed by addition of a solution of (*E*)-methyl cinnamate (85.1 mg, 0.525 mmol, 1.05 equiv) in THF (0.50 mL) at -78 °C. The reaction was quenched after 5 h and product **6i** (0.189 g, 0.442 mmol, 88% yield) was obtained after purification by column chromatography on silica gel (8% methanol in dichloromethane with 1% AcOH). $[\alpha]_D^{23}$ +5.7 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.81-7.77 (m, 1H), 7.35-7.14 (m, 12H), 7.14-7.09 (m, 2H), 5.29 (s, 2H), 4.18 (d, *J*=11.2 Hz, 1H), 3.97 (*virt.* td, *J*=10.5, 4.4 Hz, 1H), 3.33 (s, 2H), 2.62 (dd, *J*=15.7, 4.5 Hz, 1H), 2.52 (dd, *J*=15.6, 10.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 177.5, 172.3, 141.3, 137.1, 136.6, 128.8, 128.4, 127.9, 127.7, 127.7, 127.1, 126.8, 122.2, 119.9, 119.6, 110.0, 109.9, 51.3, 50.2, 48.8, 44.9, 38.8. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{27}H_{25}NO_4Na$, 450.1681; found, 450.1664.

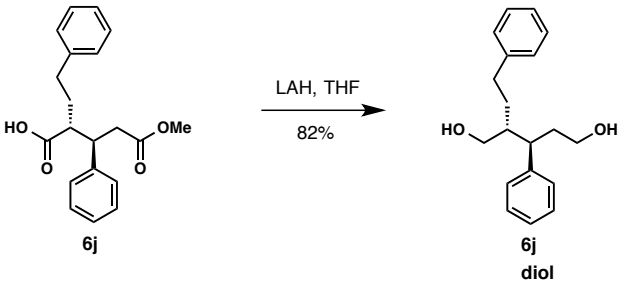


(2*S*,3*R*)-Diemthyl 2-(1-benzyl-1*H*-indol-3yl)-3-phenylpentanedioate (6i methyl ester). The title compound was prepared using carboxylic acid **6i** (10.0 mg, 23.4 μmol), $TMSCHN_2$ in hexane (0.10 mL, 1.31 M, 0.131 mmol) in a mixture of toluene-MeOH (3:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (6% ethyl acetate in hexanes) to afford product **6i methyl ester** (7.9 mg, 17.9 μmol, 77% yield). Ee: 81% (Chiralcel® OD-H; 2% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=37.6 min; t_2=68.9 min). $[\alpha]_D^{23}$ +12.2 (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84-7.77 (m, 1H), 7.36-7.25 (m, 9H), 7.24-7.16 (m, 3H), 7.15-7.11 (m, 2H), 5.30 (s, 2H), 4.18 (d, *J*=11.3 Hz, 1H), 3.99 (ddd, *J*=11.3, 10.1, 4.6 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 2.61 (dd, *J*=15.7, 4.6 Hz, 1H), 2.52 (dd, *J*=15.6, 10.1 Hz, 1H). ^{13}C NMR(126 MHz, $CDCl_3$) δ (ppm): 173.2, 172.3, 141.6, 137.2, 136.5, 128.8, 128.4, 127.9, 127.7, 127.5, 127.0, 126.8, 122.1, 119.8, 119.5, 110.5, 110.0, 51.7, 51.3, 50.2, 49.1, 45.4, 38.9. LRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{28}H_{27}NO_4Na$, 464; found, 464.

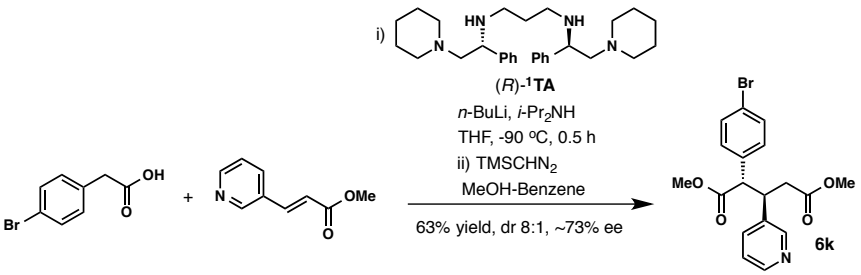


(2*R*,3*R*)-5-Methoxy-5-oxo-2-phenylethyl-3-phenylpentanoic acid (6j). A solution of *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) was added dropwise to a solution of *i*-Pr_2NH (0.14 mL, 0.101 g, 1.00 mmol) and (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Then 4-phenylbutyric acid (82.1 mg, 0.500 mmol) in THF (1.0 mL + (0.2 + 0.3) mL rinses) was added dropwise. After additional 30 min, a solution of methyl cinnamate (81.1 mg, 0.500 mmol, 1.0 equiv) in THF (0.30 mL + 2×0.10 mL rinses) was added to the reaction mixture dropwise over 1 min, immediately followed by a mixture of THF-MeOH (3:1, 0.64 mL). After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (20-66% ethyl acetate in hexanes then 6% methanol in dichloromethane) to afford the pure major diastereomer product **6j** (65.3 mg, 0.200 mmol, 40% yield) together with minor diastereomer (15.1 mg, 46.3 mmol, 9% yield). $[\alpha]_D^{23}$ +9.9 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.30-7.23 (m, 4H), 7.22-7.11 (m, 6H), 3.53 (s, 3H), 3.49 (ddd, *J* = 9.4, 7.4, 5.8 Hz, 1H), 2.86 (dd, *J*=15.8, 5.6 Hz, 1H), 2.78-

2.64 (m, 3H), 2.58-2.48 (m, 1H), 2.03-1.91 (m, 1H), 1.90 – 1.78 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 179.4, 172.2, 141.1, 140.6, 128.40, 128.37, 128.35, 128.0, 127.1, 126.0, 51.6, 50.3, 43.7, 37.4, 33.7, 31.2. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{20}H_{22}O_4Na$, 349.1416; found, 349.1406. Absolute configuration of this compound remained undetermined.

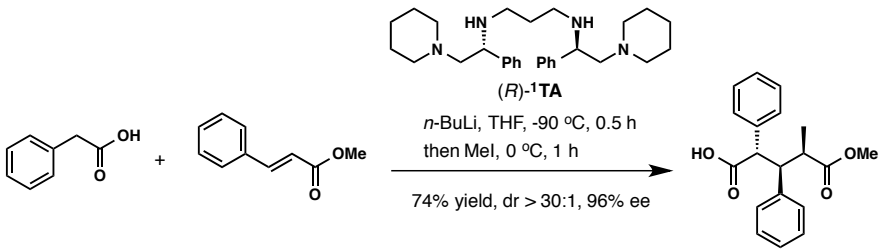


(2*R*,3*R*)-2-phenylethyl-3-phenylpentane diol (6j diol). The title compound was prepared using carboxylic acid **6j** (31.4 mg, 96.3 μmol), and lithium aluminum hydride (40.1 mg, 1.06 mmol) in THF (2.0 mL) at 23 °C. The reaction was quenched after 2 h, and product **6j diol** (22.5 mg, 79.1 μmol, 82% yield) was obtained after purification by column chromatography on silica gel (50% ethyl acetate in hexanes). Ee: 80% (Chiralcel® OJ-H; 10% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; t_1=20.0 min; t_2=30.7 min). $[\alpha]_D^{23}$ +17.8 (*c* 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.34-7.24 (m, 4H), 7.25-7.15 (m, 6H), 3.58 (dd, *J*=11.1, 4.9 Hz, 1H), 3.55-3.46 (m, 1H), 3.46-3.33 (m, 2H), 2.91 (ddd, *J*=11.0, 7.0, 3.9 Hz, 1H), 2.73 (ddd, *J*=13.8, 10.1, 5.5 Hz, 1H), 2.60 (ddd, *J*=13.8, 9.9, 5.6 Hz, 1H), 2.08 (dddd, *J*=14.3, 8.8, 7.0, 4.0 Hz, 1H), 1.92-1.62 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 143.0, 142.4, 128.5, 128.3, 128.3, 126.4, 125.7, 62.9, 61.2, 45.6, 42.9, 34.9, 33.5, 30.2. HRMS-ESI (*m*/z): $[M+Na]^+$ calcd for $C_{19}H_{24}O_2Na$, 307.1674; found, 307.1670. Absolute configuration of this compound remained undetermined.



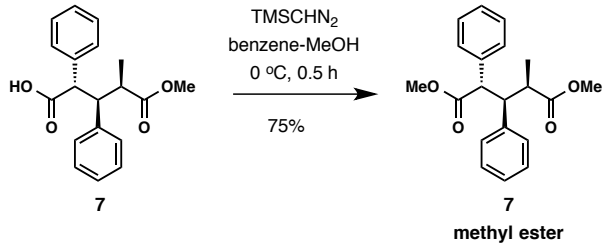
(2*S*,3*R*)-Dimethyl 2-(4-bromophenyl)-3-(pyridin-3-yl)pentanedioate (6k). A solution of *n*-BuLi (0.80 mL, 2.50 M in hexanes, 2.00 mmol, 4.0 equiv) was added dropwise to a solution of *i*-Pr_2NH (0.14 mL, 0.101 g, 1.00 mmol) and (*R*)-**1TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (3.5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Then 4-bromophenylacetic acid (0.108 g, 0.502 mmol) in THF (1.0 mL + (0.2 + 0.3) mL rinses) was added dropwise. After additional 30 min, the reaction mixture was cooled to -78 °C. After 5 min, a solution of (*E*)-methyl 3-(pyridin-3-yl)acrylate (85.7 mg, 0.525 mmol, 1.05 equiv) in THF (0.30 mL + 2×0.10 mL rinses) was added to the reaction mixture dropwise over 10 min. After stirring for further 20 min, the reaction mixture was quenched with a mixture of THF-MeOH (3:1, 0.64 mL). After 5 min, the reaction mixture was brought to pH of about 5 with 1.0 M aqueous solution of HCl (4.0 mL, 4.0 mmol), diluted with H_2O, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was used directly in the next methyl ester formation without purification.

The title compound **6k** was prepared using above crude acid, $TMSCHN_2$ in hexane (1.40 mL, 1.13 M, 1.58 mmol) in a mixture of benzene-MeOH (3:1, 5 mL) at 0 °C for 2 h. The solvent was removed and the residue was purified by column chromatography on silica gel (40-50% ethyl acetate in hexanes) to afford product **6k** (0.124 g, 0.316 mmol, 63% yield over two steps). Ee: ~73% (Chiralcel® OJ-H; 5% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 210 nm; t_1=28.8 min; t_2=34.8 min). $[\alpha]_D^{23}$ +1.3° (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.56 (s, 1H), 8.48 (s, 1H), 7.62 (d, *J*=7.8 Hz, 1H), 7.48 (d, *J*=8.0 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.27-7.18 (m, 1H), 3.89-3.76 (m, 2H), 3.40 (s, 3H), 3.37 (s, 3H), 2.46-2.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 171.7, 171.2, 149.6, 148.6, 136.4, 135.4, 134.9, 132.1, 130.2, 123.3, 122.3, 56.3, 52.0, 51.5, 42.7, 37.9. LRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{19}BrNO_4$, 392.05; found,.

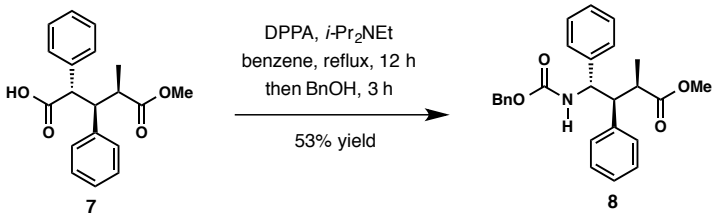


7

(2*S*,3*R*,4*R*)-5-Methoxy-4-methyl-5-oxo-2,3-diphenylpentanoic acid (7). A solution of *n*-BuLi (1.6 mL, 2.51 M in hexanes, 4.02 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (136 mg, 1.00 mmol) and (*R*)-**^{1}TA** (0.462 g, 1.03 mmol, 1.03 equiv) in THF (10 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was then cooled to -90 °C and stirred for an additional 5 min. A solution of methyl cinnamate (162 mg, 1.00 mmol, 1.0 equiv) in THF (0.60 mL + 2×0.20 mL rinses) was added to the reaction mixture dropwise over 10 min. The resultant mixture was stirred for additional 20 min before a quench with a mixture of THF-MeOH (3:1, 1.3 mL) at -90 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes with 0.5% HOAc) to afford the pure product **7** (0.230 g, 0.736 mmol, 74% yield). $[\alpha]_D^{23}$ +31.7 (*c* 1.2, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.54 (d, *J*=6.7 Hz, 2H), 7.41 (t, *J*=7.6 Hz, 2H), 7.36-7.27 (m, 3H), 7.28-7.21 (m, 3H), 4.21 (d, *J*=12.3 Hz, 1H), 3.92 (dd, *J*=12.3, 4.3 Hz, 1H), 3.41 (s, 3H), 2.33 (qd, *J*=7.0, 4.3 Hz, 1H), 0.78 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 174.4, 173.3, 138.9, 137.3, 128.8, 128.7, 128.5, 127.9, 127.7, 126.8, 53.4, 51.2, 49.1, 40.2, 10.7. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{20}O_4Na$, 335.1259; found, 335.1246.



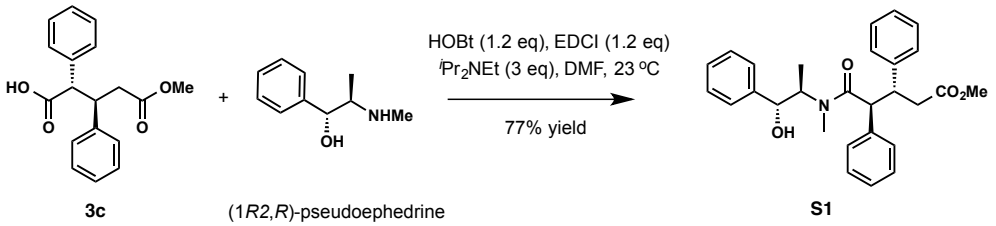
(2*R*,3*R*,4*S*)-Dimethyl-2-methyl-3,4-diphenylpentanedioate (7 methyl ester). The title compound was prepared using carboxylic acid **7** (12.7 mg, 40.7 μmol), $TMSCHN_2$ in hexane (0.1 mL, 1.76 M, 0.176 mmol) in a mixture of benzene-MeOH (4:1, 1.0 mL) at 0 °C for 0.5 h. The solvent was removed and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford product **7 methyl ester** (10.0 mg, 30.6 μmol, 75% yield). Ee: 96% (Chiralcel® AD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 ml/min; detection at 215 nm; t_1=20.5 min; t_2=26.8 min). $[\alpha]_D^{23}$ +40.9 (*c* 0.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51 (d, *J*=6.9 Hz, 2H), 7.37 (t, *J*=7.4 Hz, 2H), 7.34-7.26 (m, 3H), 7.25-7.19 (m, 3H), 4.10 (d, *J*=12.1 Hz, 1H), 4.04 (dd, *J*=12.1, 4.9 Hz, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 2.52 (qd, *J*=7.0, 4.9 Hz, 1H), 0.89 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 175.1, 172.7, 138.6, 136.3, 128.9, 128.8, 128.7, 128.2, 128.0, 127.2, 55.1, 51.8, 51.4, 49.6, 41.3, 11.9. LRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{22}O_4Na$, 349; found, 349.



(2*R*,3*S*,4*S*)-Methyl 4-(benzyloxycarbonylamino)-2-methyl-3,4-diphenylbutanoate (8). A solution of acid **7** (78.1 mg, 0.250 mmol), diphenylphosphoryl azide (DPPA, 80 μL, 0.102 g, 0.372 mmol) and *i*-Pr_2NEt (90 μL, 66.8 mg, 0.517 mmol) in benzene was heated to reflux for 12 h. Then benzyl alcohol (80 μL, 83.2 mg, 0.769 mmol) was added, and the reaction mixture was stirred at reflux for additional 5 h. After cooling, the reaction mixture was diluted with CH_2Cl_2, washed with 1 M aqueous solution of NaOH, extracted with CH_2Cl_2. The combined organic phase was washed with 10% aqueous solution of H_2SO_4 and brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford product **8** (55.5 mg, 0.133 mmol, 53% yield). $[\alpha]_D^{23}$ -0.67 (*c* 1.4, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.71 (d, *J*=9.4 Hz, 1H), 7.50-7.45 (m, 2H), 7.41-7.33 (m, 2H), 7.32-7.22 (m, 7H), 7.20-7.16 (m, 2H), 7.08-7.02 (m, 2H), 5.03 (dd, *J*=11.4, 9.4 Hz, 1H), 4.92 (d, *J*=12.8 Hz, 1H), 4.76 (d, *J*=12.8 Hz, 1H), 3.66 (dd, *J*=11.4, 5.0 Hz, 1H), 3.39 (s, 3H), 2.35 (qd, *J*=7.0, 5.0 Hz, 1H), 0.82 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.3, 155.2, 141.7, 138.1, 137.1, 129.0, 128.3, 128.2, 127.8, 127.5, 127.1, 126.6, 64.8, 56.3, 51.7, 51.2, 40.6, 11.5. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{27}NO_4Na$, 440.1838; found, 440.1817.

Determination of Absolute and Relative Configuration for Compounds 3c, 5k, 6j, 7

1) Determination of the absolute configuration of 3c.

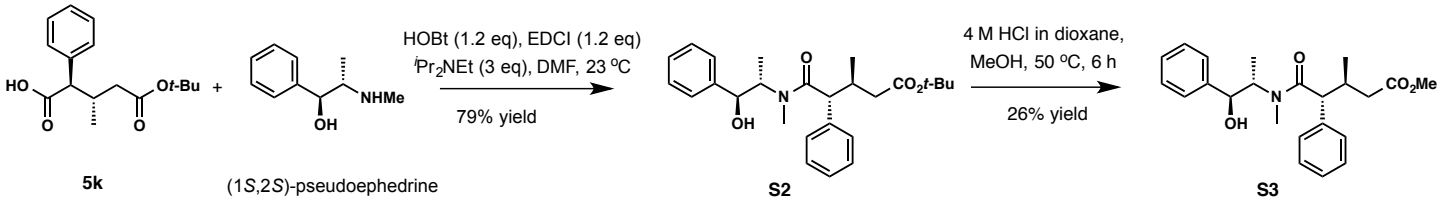


(3*R*,4*S*)-Methyl 5-(((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)methyl)amino)-5-oxo-3,4-diphenylpentanoate (S1).

A solution of **3c** (11.8 mg, 40.0 μmol, 93% ee), (1*R*,2*R*)-(-)-pseudoephedrine (9.8 mg, 59.3 μmol), hydroxybenzotriazole (HOBt, 6.4 mg, 47.5 μmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI, 9.1 mg, 47.5 μmol), and *i*-Pr_2NEt (20 μL, 0.119 mmol) in DMF (0.80 mL) was stirred at 23 °C for 21 h. The reaction mixture was quenched with 1 M aqueous solution of HCl, extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (40% ethyl acetate in hexanes) to afford product **S1** (13.5 mg, 30.3 μmol, 77% yield). ^1H NMR (600 MHz, Acetonitrile-d_3, 2:1 rotamer ratio) δ (ppm): 7.50 (d, *J*=7.1 Hz, 2H), 7.43-7.29 (m, 7H), 7.26-7.20 (m, 2H), 7.17-7.04 (m, 2H), 6.96 (d, *J*=6.7 Hz, 2H), 4.39-4.29 (m, 2H), 4.20 (d, *J*=11.0 Hz, 1H), 3.93-3.83 (m, 2H), 3.33 (s, 3H), 2.53 (s, 3H), 2.39 (dd, *J*=15.4, 10.7 Hz, 1H), 2.26 (dd, *J*=15.4, 4.3 Hz, 1H), 0.67 (d, *J*=7.0 Hz, 3H). The ^1H NMR data for the major rotamer data matched the literature precedent[1].

The diastereomer of **S1** was also prepared from **3c** and (1*S*,2*S*)-(+)-pseudoephedrine using an analogous procedure. Its NMR data were different from **S1**.

2) Determination of the absolute configuration of 5k.



(3*S*,4*R*)-Methyl 5-(((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)methyl)amino)-3-methyl-5-oxo-4-phenylpentanoate (S3).

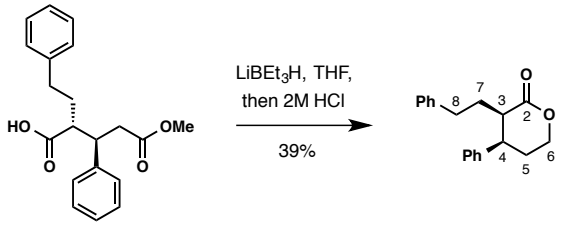
A solution of **5k** (22.7 mg, 81.6 μmol, 78% ee), (1*S*,2*S*)-(+)-pseudoephedrine (20.2 mg, 0.122 mmol), hydroxybenzotriazole (HOBt, 13.2 mg, 97.9 μmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI, 18.8 mg, 97.9 μmol), and *i*-Pr_2NEt (40 μL, 0.230 mmol) in DMF (2.0 mL) was stirred at 23 °C for 21 h. The reaction mixture was quenched with 1 M aqueous solution of HCl, extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (33% ethyl acetate in hexanes) to afford product **S2** (27.5 mg, 64.7 μmol, 79% yield). ^1H NMR (500 MHz, $CDCl_3$, 2:1 rotamer ratio) δ (ppm): 7.31-7.24 (m, 7H), 7.22 -7.18 (m, 1H), 7.16-7.10 (m, 2H), 4.60 (d, *J*=7.1 Hz, 1H), 4.31 (brs, 1H), 3.62 (d, *J*=10.0 Hz, 1H), 2.80-2.64 (m, 1 H), 2.74 (s, 3H), 2.07 (dd, *J*=15.0, 4.3 Hz, 1H), 1.78 (dd, *J*=15.0, 8.6 Hz, 1H), 1.11 (d, *J*=7.0 Hz, 3H), 1.03 (d, *J*=6.5 Hz, 3H). **S2** was directly used to the next step without further characterization.

[1] Smitrovich, J. H.; DiMichele, L,; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903-1908.

A solution of **S2** (14.3 mg, 33.6 μmol) and 4 M HCl in dioxane (80 μL) in MeOH was heated at 50 °C for 6 h. After cooling, the solvent was removed and the residue was purified by column chromatography on silica gel (33-40% ethyl acetate in hexanes) to afford product **S3** (3.4 mg, 8.87 μmol, 26% yield). ^{1}H NMR (500 MHz, Acetonitrile-d_3, 3:1 rotamer ratio) δ (ppm): 7.40-7.16 (m, 10H), 4.64-4.57 (m, 1H), 4.54 (brs, 1H), 4.35-4.20 (m, 1H), 3.61 (d, *J*=10.1 Hz, 1H), 3.50 (s, 3H), 2.78 (s, 3H), 2.67-2.57 (m, 1H), 2.00 (dd, *J*=15.3, 4.3 Hz, 1H), 1.86 (dd, *J*=15.3, 9.6 Hz, 1H), 0.92 (d, *J*=6.6 Hz, 3H), 0.89 (d, *J*=6.5 Hz, 3H). The ^{1}H NMR data for the major rotamer were consistent with the literature precedent.[1]

The diastereomer of **S3** was also prepared from **3c** and (1*R*,2*R*)-(-)-pseudoephedrine using an analogous procedure. Its NMR data were different from **S3**.

3) Determination of relative configuration of 6j.

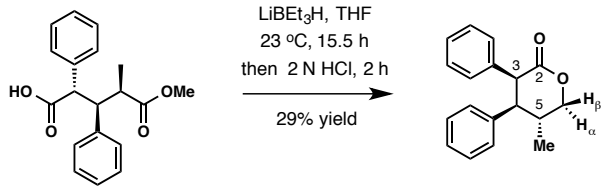


6j **S4**

(3*R, 4*R**)-3-Phenethyl-4-phenyltetrahydro-2*H*-pyran-2-one (S4).** $LiBEt_3H$ (1.0 M, 1.7 mL, 1.70 mmol) was added to a solution of acid **6j** (68.8 mg, 0.211 mmol) in THF (5 mL) at 0 °C. After stirring at 23 °C for 14 h, the reaction mixture was quenched with 2 M aqueous solution of HCl (1.7 mL, 3.40 mmol) at 0 °C. The resultant mixture was stirred at 23 °C for further 24 h and extracted with CH_2Cl_2. The combined organic phase was washed brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford the pure product **S4** (22.8 mg, 81.3 μmol, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35-7.29 (m, 2H), 7.27-7.20 (m, 3H), 7.18-7.11 (m, 3H), 7.10-7.03 (m, 2H), 4.40 (ddd, *J*=11.5, 5.6, 3.6 Hz, 1H, H-6β), 4.31 (*virt.* td, *J* = 11.2, 3.9 Hz, 1H, H-6α), 3.47 (dt, *J*=8.5, 7.2 Hz, 1H, H-4), 2.75 (td, *J*=7.5, 6.1 Hz, 1H, H-3), 2.69 (ddd, *J*=13.7, 9.1, 6.2 Hz, 1H, H-8), 2.60 (ddd, *J*=13.8, 9.0, 6.6 Hz, 1H, H-8), 2.39 (ddt, *J*=14.7, 8.6, 3.7 Hz, 1H, H-5α), 2.06 (dddd, *J*=14.7, 10.8, 6.9, 5.6 Hz, 1H, H-5β), 1.94 (dddd, *J*=13.8, 9.0, 7.4, 6.2 Hz, 1H, H-7), 1.43 (ddt, *J*=14.1, 9.1, 6.4 Hz, 1H, H-7). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.5, 141.5, 141.3, 128.8, 128.4, 128.4, 128.0, 127.1, 126.0, 65.8, 42.1, 40.6, 33.2, 31.0, 29.1. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{20}O_2Na$, 303.1361; found, 303.1349.

4) Determination of absolute configuration of 7.

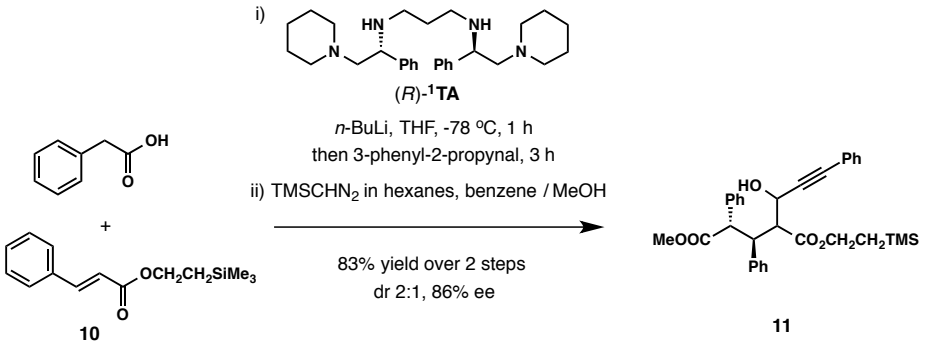
[1] Smitrovich, J. H.; DiMichele, L,; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903-1908.



7 **S5**

(3*S*,4*R*,5*R*)-5-Methyl-3,4-diphenyltetrahydro-2*H*-pyran-2-one (S5). $LiBEt_3H$ (1.0 M, 0.79 mL, 0.790 mmol) was added to a solution of acid **7** (30.8 mg, 98.6 μmol) in THF (2 mL) at 0 °C. After stirring at 23 °C for 15.5 h, the reaction mixture was quenched with 2 M aqueous solution of HCl (0.79 mL, 1.58 mmol) at 0 °C. The resultant mixture was stirred at 23 °C for further 2 h and extracted with ethyl acetate. The combined organic phase was washed brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (9% ethyl acetate in hexanes) to afford the pure product **S5** (7.6 mg, 28.5 μmol, 29% yield). $[\alpha]_D^{23}$ -31.6 (*c* 0.36, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.20–7.13 (m, 4H), 7.12–7.07 (m, 2H), 6.79–6.71 (m, 4H), 4.60 (dd, *J*=11.6, 5.7 Hz, 1H, H-6β), 4.19 (*virt.* t, *J*=11.6 Hz, 1H, H-6α), 4.08 (d, *J*=6.7 Hz, 1H, H-3), 3.11 (dd, *J*=9.2, 6.7 Hz, 1H, H-4), 2.74–2.61 (m, 1H, H-5), 0.94 (d, *J*=6.6 Hz, 3H, H-Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 172.1, 139.2, 135.1, 129.8, 128.9, 128.2, 127.7, 127.2, 127.1, 73.6, 51.9, 51.4, 31.1, 15.5. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{18}O_2Na$, 289.1204; found, 289.1195.

Synthesis of Proposed Structure of Pulveraven B (9).



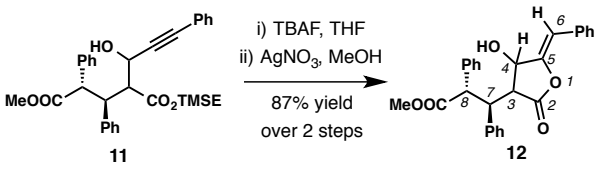
10 **11**

Alcohol 11. A solution of *n*-BuLi (0.80 mL, 2.51 M in hexanes, 2.01 mmol, 4.0 equiv) was added dropwise to a solution of phenylacetic acid (68.1 mg, 0.500 mmol) and (*R*)-**^{1}TA** (0.231 g, 0.515 mmol, 1.03 equiv) in THF (5.0 mL) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. The reaction mixture was then cooled to -78 °C and stirred for an additional 5 min. A solution of (*E*)-2-(trimethylsilyl)ethyl 3-phenyl-2-butenoate **10** (0.149 g, 0.600 mmol, 1.2 equiv) in THF (0.30 mL + 2×0.10 mL rinses) was added to the reaction mixture dropwise over 10 min. After stirring for additional 50 min, a solution of 3-phenyl-2-propynal (0.325 g, 2.50 mmol) was added. The reaction mixture was stirred for additional 3 h before a quench with a mixture of THF–MeOH (3:1, 0.64 mL) at -78 °C. After 5 min, the reaction mixture was acidified with 1 M aqueous solution of HCl and extracted with ethyl acetate. The combined organic phase was sequentially washed with 1 M aqueous solution of HCl and brine, dried over Na_2SO_4, concentrated, and the residue was directly used for the next step.

The above crude acid was dissolved in a mixture of benzene-MeOH (4:1, 5.0 mL) and $TMSCHN_2$ in hexane (2.6 mL, 0.57 M in hexanes, 1.48 mmol) was added at 0 °C. The resultant mixture was stirred at the same temperature for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (9–11% ethyl acetate in hexanes) to afford the product **11** (0.221 g, 0.418 mol, dr 2:1, 83% yield).

Major diastereomer. Ee: 87% (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; major diasteremoer t_1=18.0 min; t_2=54.5 min). $[\alpha]_D^{23}$ -5.2 (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.52–7.46 (m, 2H), 7.43–7.37 (m, 2H), 7.38–7.28 (m, 6H), 7.29—7.23 (m, 5H), 4.21 (d, *J*=11.2 Hz, 1H), 4.15–4.05 (m, 1H), 3.78–3.66 (m, 1H), 3.51 (d, *J*=10.5 Hz, 1H), 3.44–3.33 (m, 1H), 3.28 (s, 3H), 2.97 (dd, *J*=9.8, 3.9 Hz, 1H), 0.88–0.75 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.6, 172.4, 139.0, 135.6, 131.6, 129.8, 128.9, 128.54, 128.46, 128.3, 128.2, 128.0, 127.5, 122.3, 88.1, 85.4, 63.3, 61.6, 57.2, 55.3, 51.7, 47.1, 17.2, -1.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{36}O_5NaSi$, 551.2230; found, 551.2217.

Minor diastereomer. Ee: 86% ee. (Chiralcel® OD-H; 1% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 215 nm; minor diasteremoer t_1=21.9 min; t_2=29.8 min).



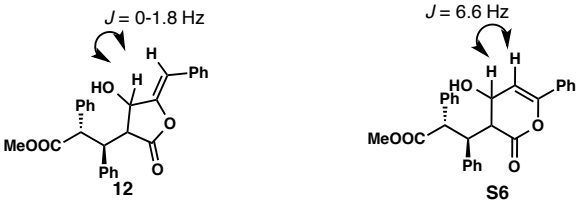
Lactone (12). To a solution of ester **11** (51.8 mg, 98.0 μmol) in THF (2 mL) was added TBAF (1.0 M in THF, 0.25 mL, 0.250 mmol) at 23 °C. After stirring for 2 h, the reaction mixture was diluted with ethyl ether, quenched with water, and extracted with ethyl ether. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated, and the crude acid was directly used for the next step.

To a solution of above crude acid in MeOH (2 mL) was added $AgNO_3$ (16.6 mg, 97.7 μmol) at 23 °C. Additional $AgNO_3$ (16.6 mg, 97.7 μmol) was added after 14 h, followed by third portion of $AgNO_3$ (33.2 mg, 0.195 mmol) after 10 h. The resultant mixture was stirred for further 14 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (25% ethyl acetate in hexanes) to afford the product **12** (36.6 mg, 85.4 mmol, dr 2:1, 87% yield over two steps.). The two diastereomers could be partially separated by column chromatography.

Major diastereomer: $[\alpha]_D^{23}$ +56.1 (*c* 0.71, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49–7.44 (m, 2H), 7.34–7.27 (m, 4H), 7.27–7.18 (m, 9H), 5.62 (s, 1H, H-6), 4.99 (d, *J*=7.9 Hz, 1H, H-8), 4.66 (*virt.* t, *J*=5.7 Hz, 1H, H-4), 3.87 (*virt.* t, *J*=8.1 Hz, 1H, H-7), 3.55 (s, 3H), 3.54 (dd, *J*=8.0, 6.5 Hz, 1 H, H-3), 1.88 (d, *J*=5.3 Hz, 1H, H-O*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 174.1, 172.8, 149.1, 138.0, 136.8, 132.9, 129.6, 129.2, 128.8, 128.6, 128.4, 128.2, 127.7, 127.6, 127.5, 106.8, 52.6, 51.9, 46.6, 46.1. LRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{27}H_{24}O_5Na$, 451; found, 451.

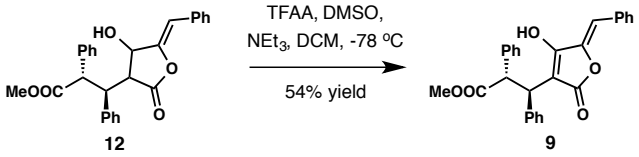
Minor diastereomer: $[\alpha]_D^{23}$ -89.7 (*c* 0.75, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71–7.65 (m, 2H), 7.48–7.38 (m, 4H), 7.39–7.32 (m, 1H), 7.29–7.12 (m, 7H), 7.11–7.03 (m, 1H), 5.40 (d, *J*=1.8 Hz, 1H, H-6), 4.87 (*virt.* td, *J*=9.0, 1.8 Hz, 1H, H-4), 4.63 (d, *J*=12.2 Hz, 1H,

H-8), 4.06 (dd, *J*=12.2, 3.6 Hz, 1H, H-7), 3.33 (s, 3H), 2.82 (dd, *J*=8.9, 3.5 Hz, 1H, H-3), 2.06 (d, *J*=9.1 Hz, 1H, H-O*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.0, 172.5, 149.9, 138.1, 136.6, 132.9, 129.1, 129.0, 128.9, 128.8, 128.4, 128.19, 128.15, 128.10, 127.0, 104.5, 70.3, 54.4, 51.8, 46.1, 44.9. LRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{24}O_5Na$, 451; found, 451.

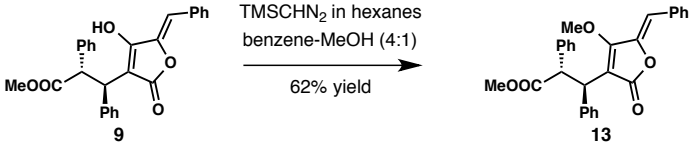


Scheme 1. Comparison of *J*-coupling constants

The regioselectivity of the Ag-mediated cyclization reaction was confirmed by *J*-coulping constants as shown in Scheme 1. Dihydro-2-pyrone **S6** was prepared using $Hg(OAc)_2$ as catalyst instead of $AgNO_3$ (63% yield).[1]



(2*S*,3*R*)-methyl 3-((*Z*)-5-benzylidene-4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-2,3-diphenylpropanoate (9).[2] Trifluoroacetic anhydride (TFAA, 40 μL, 0.283 mmol) was added to a solution of DMSO (40 μL, 0.563 mmol) in CH_2Cl_2 (1.5 mL) at -78 °C. After stirring for 0.5 h, alcohol **12** (2:1 mixture of diastereomers, 36.6 mg, , 85.5 μmol) in CH_2Cl_2 (1.5 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 2.5 h before NEt_3 (0.15 mL, 1.08 mmol) was added. After stirring for 2 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic phase was washed brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes then 5% methanol in dichloromethane) to afford the pure product **9** (19.7 mg, 46.2 μmol, 54% yield). $[\alpha]_D^{23}$ +51.2 (*c* 0.14, $CHCl_3$). ^{1}H NMR (500 MHz, Acetone-d_6) δ (ppm): 7.67-7.60 (m, 4H), 7.52-7.46 (m, 2H), 7.39-7.26 (m, 7H), 7.28-7.18 (m, 2H), 6.22 (s, 1H), 4.94 (d, *J*=12.2 Hz, 1H), 4.88 (d, *J*=12.2 Hz, 1H), 3.41 (s, 3H). ^{13}C NMR (126 MHz, Acetone-d_6) δ (ppm): 206.2, 173.4, 169.2, 164.0, 143.3, 142.0, 138.4, 133.7, 131.0, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.6, 127.9, 107.1, 104.5, 53.9, 52.1, 43.7, 30.2, 30.0, 29.8, 29.7, 29.5. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{22}O_5Na$, 449.1365; found, 449.1346.

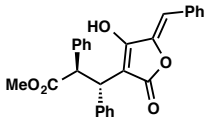


(2*S*,3*R*)-methyl 3-((*Z*)-5-benzylidene-4-methoxy-2-oxo-2,5-dihydrofuran-3-yl)-2,3-diphenylpropanoate (13). A solution of $TMSCHN_2$ in hexane (0.29 mL, 0.57 M in hexanes, 0.165 mmol)

[1] Jong, T. T.; Williard, P. G.; Porwoll, J. P. *J. Org. Chem.* **1984**, *49*, 735.
2 Matsuo, K.; Sakaguchi, Y. *Chem. Pharm. Bull.* **1997**, *45*, 1620.

was added dropwise to a solution of tetronic acid **9** (14.0 mg, 32.9 μmol) in a mixture of benzene–MeOH (4:1, 1.0 mL) at 0 °C. The resultant mixture was stirred at the same temperature for 2 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford the product **13** (9.0 mg, 20.4 μmol, 62% yield). $[\alpha]_D^{23}$ +87.9 (*c* 0.44, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.64–7.56 (m, 4H), 7.51–7.46 (m, 2H), 7.35–7.28 (m, 6H), 7.26–7.20 (m, 3H), 5.97 (s, 1H), 5.09 (d, *J*=12.0 Hz, 1H), 4.88 (d, *J*=12.0 Hz, 1H), 4.11 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.2, 168.9, 164.2, 142.1, 140.5, 137.0, 132.5, 130.3, 128.81, 128.79, 128.76, 128.65, 128.31, 128.26, 127.9, 127.3, 107.7, 60.9, 52.8, 52.0, 44.6. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{24}O_5Na$, 463.1521; found, 463.1504.

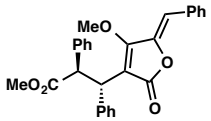
Table 1. Comparison of ^{1}H NMR Data of Synthetic **9** and Reported for Pulveraven B (d_6-Acetone)



pulveraven B (9)
proposed structure

synthetic **9** (500 MHz)	reported for natural pulveraven B (500 MHz)[2]
7.67-7.60 (m, 4H)	7.70 (d, *J*=7.2 Hz, 2H)
7.52-7.46 (m, 2H)	7.45-7.30 (m, 6H)
7.39-7.26 (m, 7H)	7.13-7.04 (m, 4H)
7.28-7.18 (m, 2H)	6.95-6.85 (m, 3H)
6.22 (s, 1H)	5.95 (s, 1H)
4.94 (d, *J*=12.2 Hz, 1H)	5.20 (d, *J*=12.2 Hz, 1H)
4.88 (d, *J*=12.2 Hz, 1H)	4.46 (d, *J*=12.2 Hz, 1H)
3.41 (s, 3H).	3.50 (s, 3H)

Table 2. Comparison of ^{1}H NMR Data of Synthetic **13** and Reported for Pulveraven B Methyl Ester ($CDCl_3$)



pulveraven B methyl ester (13)
proposed structure

synthetic **13** (500 MHz)	reported for natural pulveraven B (500 MHz)[3]
7.64-7.56 (m, 4H)	7.72 (d, *J*=11.8 Hz, 2H)
7.51-7.46 (m, 2H)	7.37-7.30 (m, 3H)
7.35-7.28 (m, 6H)	7.22-7.14 (m, 5H)
7.26-7.20 (m, 3H)	7.11-7.07 (m, 5H)
5.97 (s, 1H)	6.19 (s, 1H)
5.09 (d, *J*=12.0 Hz, 1H)	5.09 (d, *J*=12.0 Hz, 1H)
4.88 (d, *J*=12.0 Hz, 1H)	4.88 (d, *J*=12.0 Hz, 1H)
4.11 (s, 3H),	4.42 (s, 3H)
3.45 (s, 3H)	3.63 (s, 3H)

[2] Duncan, C. J. G.; Cuendet, M.; Fronczek, F. R.; Pezzuto, J. M.; Mehta, R. G.; Hamann, M. T.; Ross, S. A. *J. Nat. Prod.* **2003**, *66*, 103-107.
[3] Quang, D. N.; Hashimoto, T,; Nukada, M.; Yamamoto, I.; Tanaka, M.; Takaoka, S.; Asakawa, Y. *Chem. Phar. Bull.* **2003**, *66*, 330-332.