The Development of the Enantioselective Addition of Ethyl Diazoacetate to Aldehydes: Asymmetric Synthesis of 1,2-Diols.

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SUPPORTING INFORMATION

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Experimental Section:

Materials and Methods

All magnesium-ProPhenol-catalyzed asymmetric additions of ethyl diazoacetate to aldehydes were performed in flame-dried glassware with magnetic stirring under an atmosphere of nitrogen in a -20 ºC cryostat. All indium-mediated reactions were performed using "open-flask" conditions. All organozinc-mediated couplings were performed under an atmosphere of nitrogen.

Anhydrous DMF, dichloromethane, chloroform, tetrahydrofuran, acetone, acetonitrile, and toluene were obtained from a Seca solvent purification system by Glass Contour. Solvents and reagents were transferred via a syringe, which had been oven dried and cooled in a dessicator. Microliter syringes were dried under high vacuum for 1 h prior to use. Aldehydes for the asymmetric addition were freshly distilled prior to use. All other reagents were purchased from Aldrich Chemical Company and were used without further purification.

Analytical thin-layer chromatography was preformed on precoated 250 μm layer thickness silica gel 60 F_{254} plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light and staining with ceric ammonium molybdate, potassium permanganate, or *p*-anisaldehyde. Organic solutions were concentrated by rotary evaporation at ambient temperature (essential for all diazo compounds). Flash column chromatography was performed using 40-63 μm silica gel (Silicycle silica gel) using compressed air. The eluents employed for flash chromatography are reported as volume: volume percentages.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired using Varian Inova 400 MHz, 500 MHz, 600 MHz, and Mercury 400 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to residual solvent peaks: proton ($CDCl_3$ 7.26 ppm). Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; m = multiplet. ^{13}C NMR spectra were recorded using a Varian Unity INOVA spectrometer at 125 MHz or a Varian Mercury at 100 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to residual solvent peaks: carbon ($CDCl_3$ 77.0 ppm).

Infrared spectroscopic data was recorded on NaCl plates as thin films on a Thermo Scientific Nicolet IR100 FT-IR spectrometer. The absorbance frequencies are recorded in

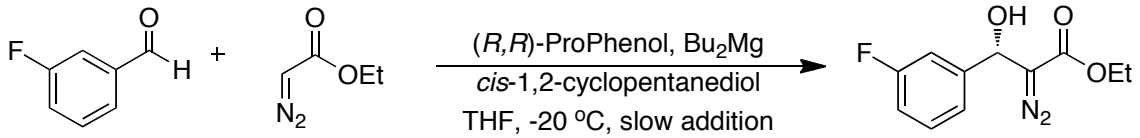
wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were acquired by the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University Mass Spectrometry (http://mass-spec.stanford.edu) on a Micromass Q-Tof API-US mass spectrometer (Waters Corporation, Milford, MA). Chiral HPLC analysis was performed on Daicel Chiralpack columns (AD, AS, OB-H, OC, OD, or OJ) using heptane/2-propanol mixtures. The respective ratio of the eluent mixture, flow rate, detection wavelength, and column are indicated within the experimental details. Retention times (T_r) are reported in minutes (min). Optical rotations were measured using a JASCO DIP-1000 digital polarimeter in 50-mm cells and the sodium D line (589 nm) at the temperature, solvent, and concentration indicated.

DBU-catalyzed addition of ethyl diazoacetate to aldehydes: preparation of racemates

Racemates were prepared for all compounds to develop conditions for the separation of enantiomers by chiral HPLC. These compounds were prepared by the addition of DBU (10 mol%) to a solution of ethyl diazoacetate and respective aldehyde in acetonitrile using a procedure described previously.[1]

Magnesium-catalyzed asymmetric direct aldol addition of ethyl diazoacetate to aldehydes:

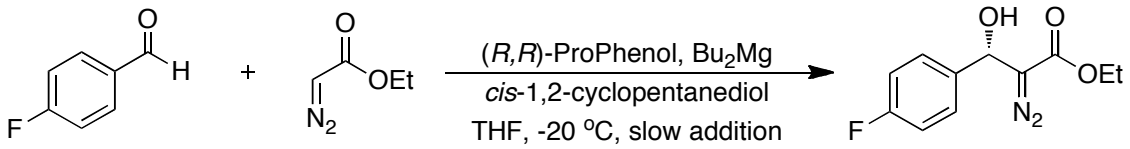
(*S*)-ethyl 2-diazo-3-(3-fluorophenyl)-3-hydroxypropanoate



To a solution of (*R*,*R*)-ProPhenol (28 mg, 0.044 mmol, 0.05 equiv) in anhydrous THF (0.82 mL) was added a solution of di-*n*-butylmagnesium (88 µl of a 1 M solution in heptane, 0.10 equiv). After stirring for 30 minutes, *cis*-1,2-cyclopentanediol (4.5 µL, 0.044 mmol, 0.05 equiv) was added and the reaction was stirred for an additional 45 minutes. To the reaction was added 3-fluorobenzaldehyde (93 µL, 0.88 mmol, 1.0 equiv). After stirring for 5 minutes at room temperature, the reaction was cooled to -20 °C and ethyl diazoacetate (100 mg, 0.88 mmol, 1.0 equiv) was added over 4 hours (~25 µL /hr). After stirring for 24h the reaction was quenched with pH 7 buffer and extracted with diethyl ether (5 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using a gradient of 15%-30% EtOAc/hexanes afforded 185 mg (78%, 91% ee) of the desired product as a yellow oil. R_f = 0.34 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ -20.89 (c. 13.7 mg/mL, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.32 (m, 1H), 7.40-7.32 (m, 1H), 7.22-7.16 (m, 2H), 7.06-6.98 (m, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 4.27 (d, *J* = 7.2, 2H), 2.90 (br s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1 (d, *J* = 202.6 Hz), 161.7, 141.5, 130.3 (d, *J* = 8.2 Hz), 121.3 (d, *J* = 3.0 Hz), 115.1 (d, *J* = 21.1 Hz), 112.9 (d, *J* = 22.8 Hz), 68.1, 61.3, 60.4, 14.4; IR (neat): ν_{max}

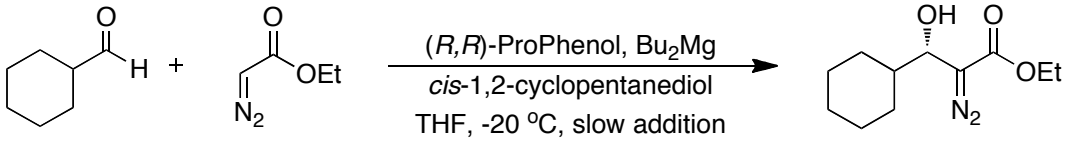
3436, 2985, 2100, 1871, 1592, 1292, 1111, 1031 cm^{-1}; HPLC T_r = 18.3 (major) and 20.6 (minor) (Chiracel® AD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 97:3, 0.8 mL/min).

(*S*)-ethyl 2-diazo-3-(4-fluorophenyl)-3-hydroxypropanoate



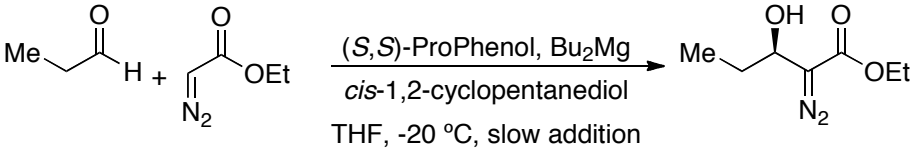
To a solution of (*R*,*R*)-ProPhenol (28 mg, 0.044 mmol, 0.05 equiv) in anhydrous THF (0.82 mL) was added a solution of di-*n*-butylmagnesium (88 µl of a 1 M solution in heptane, 0.10 equiv). After stirring for 30 minutes, *cis*-1,2-cyclopentanediol (4.5 µL, 0.044 mmol, 0.05 equiv) was added and the reaction was stirred for an additional 45 minutes. To the reaction was added 4-fluorobenzaldehyde (95 µL, 0.88 mmol, 1.0 equiv). After stirring for 5 minutes at room temperature, the reaction was cooled to -20 °C and ethyl diazoacetate (100 mg, 0.88 mmol, 1.0 equiv) was added over 8 hours (~12.5 µL/hr). After stirring for 24h the reaction was quenched with pH 7 buffer and extracted with diethyl ether (5 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using a gradient of 15%-30% EtOAc/hexanes afforded 208 mg (87%, 94% ee) of the desired product as a yellow oil. R_f = 0.29 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ -30.35 (83% ee, c. 20.6 mg/mL, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 - 7.37 (m, 2H), 7.12 - 7.03 (m, 2H), 5.90 (d, *J* = 3.2 Hz, 1H), 4.28 (q, *J* = 7.4 Hz, 2H), 2.96 (br s, 1H), 1.30 (t, *J* = 7.4 Hz, 3H) ppm matches literature values[2]; IR (neat): ν_{max} 3434, 2990, 2099, 1374, 1296, 1111, 1031 cm^{-1}; HPLC T_r = 18.8 (major) and 21.1 (minor) (Chiracel® AD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 97:3, 0.8 mL/min).

(*R*)-ethyl 3-cyclohexyl-2-diazo-3-hydroxypropanoate



To a solution of (*R*,*R*)-ProPhenol (56 mg, 0.088 mmol, 0.05 equiv) in anhydrous THF (0.82 mL) was added a solution of di-*n*-butylmagnesium (176 µl of a 1 M solution in heptane, 0.10 equiv). After stirring for 30 minutes, *cis*-1,2-cyclopentanediol (9.0 µL, 0.088 mmol, 0.05 equiv) was added and the reaction was stirred for an additional 45 minutes. To the reaction was added cyclohexanecarboxaldehyde (106 µL, 0.88 mmol, 1.0 equiv). After stirring for 5 minutes at room temperature, the reaction was cooled to -20 °C and ethyl diazoacetate (200 mg, 1.76 mmol, 2.0 equiv) was added over 10 hours (20 µL/hr). Upon completion, the reaction was quenched with pH 7 buffer and extracted with diethyl ether (5 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using a gradient of 10%-20% EtOAc/hexanes afforded 110 mg (49%, 91% ee) of the desired product as a yellow oil. R_f = 0.38 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ -1.96 (c. 23.5 mg/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.42 (br s, 1H), 1.81 - 1.50 (m, 5H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26 - 0.95 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.7, 71.4, 60.9, 42.1, 30.9, 29.1, 26.2, 25.8, 25.6, 14.4; IR (neat): ν_{max} 3449, 2928, 2854, 2093, 1692, 1671, 1373, 1291, 1106 cm^{-1}; HPLC T_r = 7.1 min (major) and 7.7 min (Chiracel® OB Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 97:3, 0.8 mL/min). This compound has previously been reported.[3]

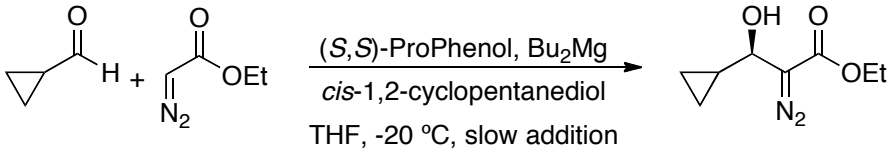
(*R*)-ethyl 2-diazo-3-hydroxypentanoate



To a solution of (*S,S*)-ProPhenol (28 mg, 0.044 mmol, 0.05 equiv) in anhydrous THF (0.82 mL) was added a solution of di-*n*-butylmagnesium (88 µl of a 1 M solution in heptane, 0.10 equiv). After stirring for 30 minutes, *cis*-1,2-cyclopentanediol (4.5 µL, 0.044 mmol, 0.05 equiv) was added and the reaction was stirred for an additional 45 minutes. The reaction was cooled to -20 °C and propionaldehyde (100 µL, 1.76 mmol, 2.0 equiv) was added. After stirring for 10 minutes ethyl diazoacetate (100 mg, 0.88 mmol, 1.0 equiv) was added over 4 hours (~25 µL/h) and the mixture was stirred at -20 °C overnight. The reaction was quenched with pH 7 buffer and extracted with Et_2O (4 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using 10% EtOAc/hexanes afforded 89 mg (52%, 96%

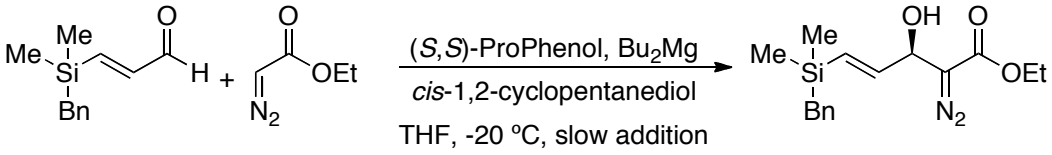
ee) of the desired product as a yellow oil. R_f = 0.15 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +29.7 (96% ee using (*S*,*S*)-ProPhenol, c. 31.5 mg/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 - 4.56 (m, 1H), 4.25 (q, *J* = 8.0 Hz, 2H), 2.55 (br s, 1H), 1.83 - 1.71 (m, 1H), 1.69-1.56 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.1, 61.0, 27.8, 27.2, 14.5, 10.0 ppm; IR (neat): ν_{max} 3429, 2970, 2937, 2095, 1692, 1374, 1297, 1134, 1085 cm^{-1}; HPLC T_r = 31.5 and 34.5 min (major) (Chiracel® AD, λ = 220 nm, isocratic elution: heptane:*i*-PrOH = 99:1, flow rate = 0.8 mL/min).

(*R*)-ethyl 3-cyclopropyl-2-diazo-3-hydroxypropanoate



To a solution of (*S*,*S*)-ProPhenol (28 mg, 0.044 mmol, 0.05 equiv) in anhydrous THF (0.82 mL) was added a solution of di-*n*-butylmagnesium (88 µl of a 1 M solution in heptane, 0.10 equiv). After stirring for 30 minutes, *cis*-1,2-cyclopentanediol (4.5 µL, 0.044 mmol, 0.05 equiv) was added and the reaction was stirred for an additional 45 minutes. The reaction was cooled to -20 °C and cyclopropanecarboxaldehyde (132 µL, 1.76 mmol, 2.0 equiv) was added. After stirring for 10 minutes ethyl diazoacetate (100 mg, 0.88 mmol, 1.0 equiv) was added over 4 hours (~25 µL/h) and the mixture was stirred at -20 °C overnight. The reaction was quenched with pH 7 buffer and extracted with Et_2O (4 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using 20% EtOAc/petroleum ether afforded 125 mg (77%, >99% ee) of the desired product as a yellow oil. R_f = 0.36 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +19.2 (>99% ee, c. 9.9 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (q, *J* = 7.1 Hz, 2H), 4.18 (dd, *J* = 7.8, 3.2 Hz, 1H), 2.67 (br s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.13-1.05 (m, 1H), 0.70 - 0.64 (m, 1H), 0.62 - 0.49 (m, 2H), 0.41 - 0.34 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 69.7, 61.0, 14.5, 14.1, 3.1, 1.7 ppm; IR (neat): ν_{max} 3441, 2984, 2097, 1690, 1373, 1340, 1294, 1101, 1026 cm^{-1}; HPLC T_r = 29.7 (major) and 35.9 (minor) (Chiracel® AS Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 99.5:0.5, 1.0 mL/min); HRMS (ES+) calcd for $C_8H_{12}N_2NaO_3$ $[M+Na]^+$ 207.0748 found 207.0746.

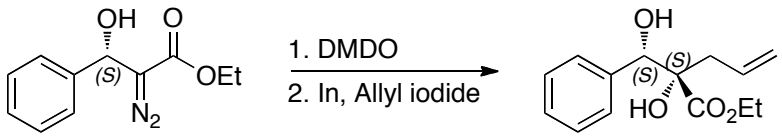
(*R*,*E*)-ethyl 5-(benzyldimethylsilyl)-2-diazo-3-hydroxypent-4-enoate



To a solution of (*S,S*)-ProPhenol (28 mg, 0.044 mmol, 0.05 equiv) in anhydrous THF (0.82 mL) was added a solution of di-*n*-butylmagnesium (88 µl of a 1 M solution in heptane, 0.10 equiv). After stirring for 30 minutes, *cis*-1,2-cyclopentanediol (4.5 µL, 0.044 mmol, 0.05 equiv) was added and the reaction was stirred for an additional 45 minutes. The reaction was cooled to -20 °C and (*E*)-3-(benzyldimethylsilyl)-acrylaldehyde (180 mg, 0.88 mmol, 1.0 equiv) was added. After stirring for 10 minutes ethyl diazoacetate (100 mg, 0.88 mmol, 1.0 equiv) was added over 4 hours (~25 µL/hr) and the mixture was stirred at -20 °C overnight. The reaction was quenched with pH 7 buffer and extracted with diethyl ether (4 x 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using a gradient of 10%-20% EtOAc/petroleum ether afforded 240 mg (86%, 90% ee) of the desired product as a yellow oil. R_f = 0.15 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +9.08 (90% ee, c. 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 - 7.19 (m, 2H), 7.09-7.04 (m, 1H), 6.99 - 6.97 (m, 2H), 6.10 (dd, *J* = 18.8, 1.2 Hz, 1H), 6.02 (dd, *J* = 18.8, 3.8 Hz, 1H), 5.26 (ddd, *J* = 3.8, 3.8, 1.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.51 (br s, 1H), 2.15 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.07 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 142.5, 139.4, 130.6, 128.2, 128.1, 124.1, 68.3, 61.1, 25.8, 14.5, -3.5, -3.5 ppm; IR (neat): ν_{max} 3435, 3024, 2983, 2958, 2097, 1672, 1373, 1340, 1287, 1250, 1108, 833 cm^{-1}; HPLC T_r = 17.1 (major) and 24.9 (minor) (Chiracel® IB Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 99:1, 1.0 mL/min).

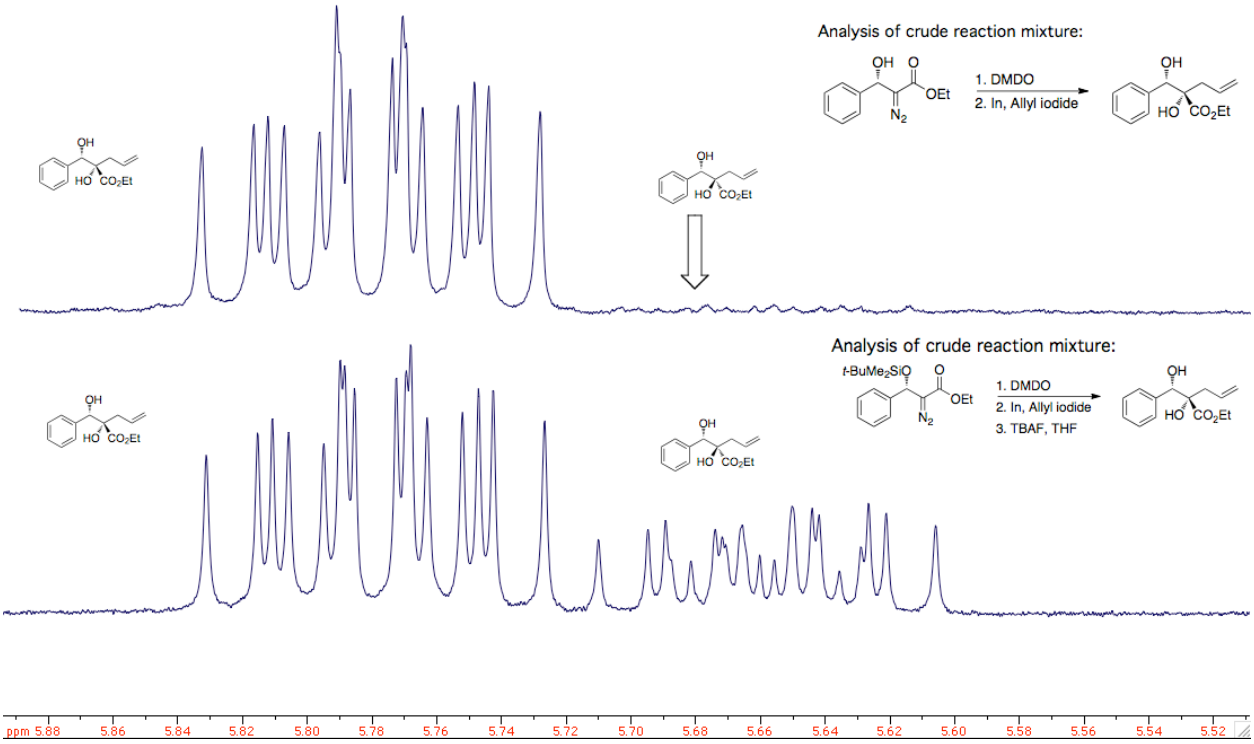
Diastereoselective organoindium-mediated alkyl transfer

(*S*)-ethyl 2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)pent-4-enoate



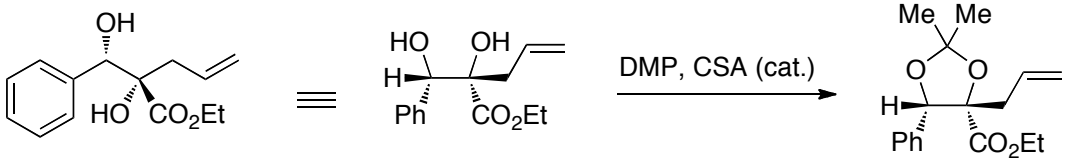
To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (40 mg, 0.18 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 3.7 mL, 0.37 mmol, 1.7 eq) at -35 °C. Upon completion of the reaction (determined by TLC, ~ 1h) the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Methylene chloride was added, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (1.6 mL) and indium powder (23 mg, 0.2 mmol, 1.1 eq.) and allyl iodide (33 µL, 0.36 mmol, 2.0 eq) were added sequentially. The reaction mixture was stirred 12h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel chromatography using a 20%-33% EtOAc/petroleum ether gradient afforded 45 mg (>99%, 91% ee) of the desired product as a white solid. R_f = 0.25 (20% EtOAc/Petroleum ether – $KMnO_4$ stain); mp = 49-51 °C; $[\alpha]_D^{25}$ -34.2 (91% ee, c. 9.3 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 5H), 5.78 (dddd, *J* = 17.0, 10.3, 8.2, 6.5 Hz, 1H), 5.13 (m, 1H), 4.77 (d, *J* = 8.0 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.99 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.36 (s, 1H), 3.06 (d, *J* = 8.0 Hz, 1H), 2.86 (ddt, *J* = 14.0, 6.9, 1.2, 0.6 Hz, 1H), 2.63 (ddd, *J* = 14.0, 7.4, 0.6 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 139.4, 132.5, 128.5, 128.3, 127.4, 119.4, 80.7, 77.7, 62.3, 40.7, 14.3 ppm; IR (neat): ν_{max} 3649, 3503, 1733, 1717, 1699, 1558, 1541, 1507, 1456 1223, 1150 cm^{-1}; HPLC T_r = 13.1 (minor) and 14.6 (major) (Chiracel® AD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 1.0 mL/min); HRMS (ES+) calcd for $C_{14}H_{18}NaO_4$ $[M+Na]^+$ 273.1103 found 273.1100.

Determination of diastereoselectivity



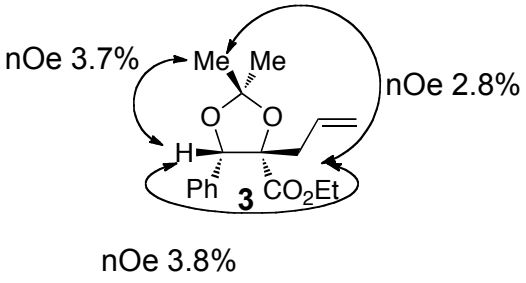
Determination of relative stereochemistry

(*4SR,5SR*)-ethyl 4-allyl-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate

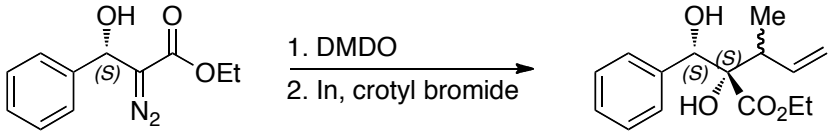


To a solution of (*SR*)-ethyl 2-hydroxy-2-((*SR*)-hydroxy(phenyl)methyl)pent-4-enoate (30 mg, 0.12 mmol, 1.0 eq) in acetone (5 mL) was added 2,2-dimethoxy propane (147.2 µL, 1.2 mmol, 10.0 eq) and 10-CSA (15 mg, 0.06 mmol, 0.5 eq). After stirring for 3h, the reaction quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (4 x 8 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford 33 mg (95%) of the desired product as a as a yellow oil. R_f = 0.37 (10% Et_2O/Hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H),

5.78 (dddd, J = 17.0, 10.3, 8.2, 6.5 Hz, 1H), 5.13 (m, 2H), 5.07 (s, 1H), 3.76 (dq, J = 10.7, 7.2 Hz, 1H), 3.51 (dq, J = 10.7, 7.2 Hz, 1H), 2.87 (ddt, J = 14.2, 6.5, 1.3 Hz, 1H), 2.57 (dd, J = 14.2, 7.8 Hz, 1H), 1.79 (s, 3H), 1.52 (s, 3H), 0.84 (dd, J = 7.2, 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 135.3, 132.4, 128.4, 128.2, 126.1, 119.4, 110.3, 88.0, 83.9, 60.7, 39.5, 26.7, 26.6, 13.5 ppm; IR (neat): ν_{max} 2984, 2937, 1747, 1378, 1247, 1218, 1135, 1060 cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{22}NaO_4$ $[M+Na]^+$ 313.1416 found 313.1403.

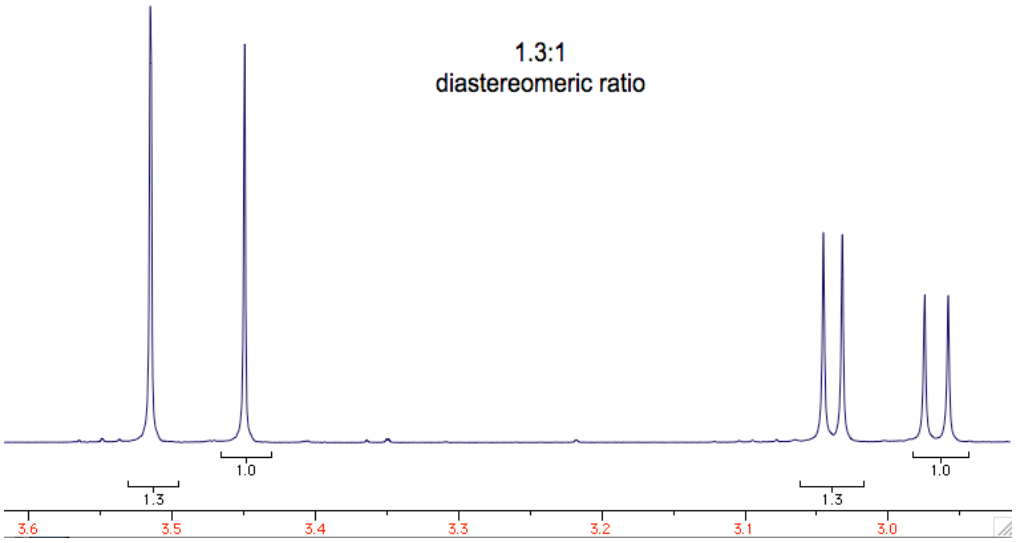


(*S*)-ethyl 2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)-3-methylpent-4-enoate



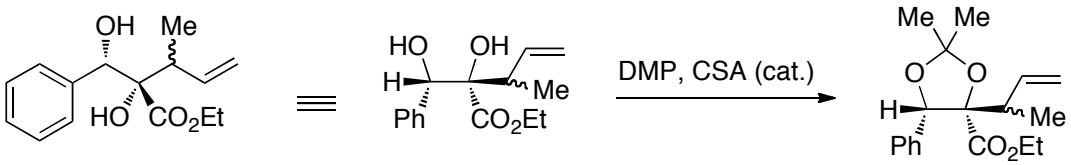
To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (50 mg, 0.22 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 3.7 mL, 0.37 mmol, 1.7 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (2 mL) and indium powder (28 mg, 0.24 mmol, 1.1 eq) and crotyl bromide (85% pure, 53.4 μL, 0.44 mmol, 2.0 eq) were added. After 16 h additional crotyl bromide (85% pure, 53.4 μL, 0.44 mmol, 2.0 eq) was added and the reaction mixture stirred for 2 h at 35 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (20% EtOAc/petroleum ether) and afforded 41 mg (72%, 94% ee (major), 90% ee (minor)) of the desired compound as 1.3:1 mixture of diastereomers (determined

by NMR) as a light yellow solid. R_f = 0.30 (20% EtOAc/petroleum ether – KMnO4 stain); mp = 62-64 °C; $[\alpha]_D^{25}$ -29.4 (94% ee, c. 8.3 mg/mL, $CHCl_3$); ^{1}H NMR mixture of two diastereomers (500 MHz, $CDCl_3$): δ 7.35-7.26 (m, 10H), 6.03-5.93 (m, 2H), 5.24-5.10 (m, 4H), 4.95 (t, *J* = 7.7 Hz, 2H), 4.10-4.03 (m, 2H), 3.96-3.89 (m, 2H), 3.52 (s, 1H), 3.45 (s, 1H), 3.04 (d, *J* = 6.7 Hz, 1H), 2.97 (d, *J* = 8.2 Hz, 1H), 2.89-2.83 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H) 1.13 (d, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 173.1, 139.6, 139.2, 139.0, 128.5, 128.0, 127.9, 127.8, 127.3, 127.2, 116.6, 82.2, 82.2, 75.8, 75.1, 61.9, 61.8, 44.1, 43.4, 15.6, 15.0, 13.9, 13.8 ppm; IR (neat): ν_{max} 3492, 2980, 1727, 1232, 1139, 1022, 701 cm^{-1}; HPLC T_r = 25.2 (minor diastereomer 1), 27.5 (major diastereomer 2), 30.9 (major diastereomer 1), 34.1 (minor diastereomer 2) (Chiracel® OD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 99:1, 0.8 mL/min); ee = 94% (major), 90% (minor); HRMS (ES+) calcd for $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1259 found 287.1263.



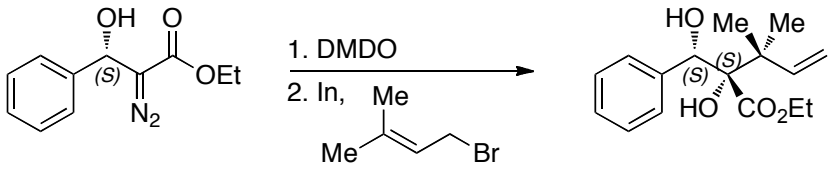
Determination of relative stereochemistry

(*4SR,5SR*)-ethyl 4-allyl-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate



To a solution of (*SR*)-ethyl 2-hydroxy-2-((*SR*)-hydroxy(phenyl)-methyl)pent-4-enoate (30 mg, 0.12 mmol, 1.0 eq) in acetone (5 mL) was added 2,2-dimethoxy propane (147.2 μL, 1.2 mmol, 10.0 eq) and 10-CSA (15 mg, 0.06 mmol, 0.5 eq). After stirring for 3h, the reaction quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (4 x 8 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford 33 mg (95%) of the desired product as a yellow oil. $R_f = 0.37$ (10% Et_2O/Hexanes); ^1H NMR (600 MHz, $CDCl_3$) mixture of diastereoisomers: δ 7.34-7.27 (m, 9H), 5.99-5.93 (m, 1H), 5.80 (ddd, *J* = 17.2, 10.2, 9.0 Hz, 1H), 5.34 (dd, *J* = 8.3, 1.8 Hz, 1H), 5.23 (s, 1H), 5.22 (s, 1H), 5.04 (ddd, *J* = 17.2, 1.8, 0.7 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.82 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.75 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.49-3.40 (m, 2H), 2.90-2.82 (m, 2H), 1.81 (s, 3H), 1.80 (s, 3H), 1.52 (s, 3H), 1.48 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 170.9, 139.4, 135.9, 135.9, 128.2, 128.1, 128.1, 126.3, 125.9, 117.6, 116.3, 109.8, 109.6, 90.8, 90.8, 81.8, 81.5, 60.6, 60.4, 42, 41.1, 26.8, 26.7, 26.6, 17.3, 15.1, 13.5, 13.4 ppm; IR (neat): ν_{max} 2982, 1747, 1249, 1220, 1141 cm^{-1}; HRMS (ES+) calcd for $C_{18}H_{24}NaO_4$ $[M+Na]^+$ 327.1572 found 327.1566. The acetonide diastereoisomers were inseparable by silica gel chromatography, complicating nOe analysis. Relative configuration determined by analogy.

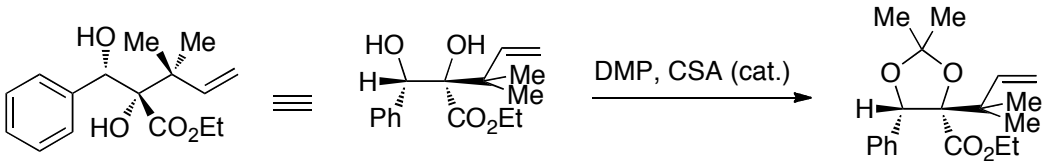
(*S*)-ethyl 2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)-3,3-dimethylpent-4-enoate



To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (40 mg, 0.18 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 6 mL, 0.6 mmol, 3.3 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (1.6 mL) and indium powder (23 mg, 0.2 mmol, 1.1 eq) and 3,3-dimethylallyl bromide (90% pure, 46.6 µL, 0.36 mmol, 2.0 eq) were added. After 16 h additional 3,3-dimethylallyl bromide (90% pure, 53.4 µL, 0.44 mmol, 2.0 eq) was added and the reaction mixture stirred for 2 h at 35 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After extraction with Et_2O (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (gradient 20%-33% EtOAc/petroleum ether) and afforded the title compound (20.7 mg, 62%, 95% ee) as a white solid. R_f = 0.40 (20% EtOAc/petroleum ether); mp = 97-99 °C; $[\alpha]_D^{25}$ +24.0 (95% ee, c. 3.3 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.24 (m, 5H), 6.29 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.19-5.09 (m, 3H), 4.00 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.81 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.55 (s, 1H), 2.90 (d, *J* = 8.2 Hz, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 144.7, 140.2, 128.1, 127.9, 127.6, 113.1, 83.1, 74.9, 62.0, 43.7, 23.5, 23.2, 13.8 ppm; IR (neat): ν_{max} 3465, 2979, 1715, 1261, 1105 cm^{-1}; HPLC T_r = 7.3 (minor) and 9.1 (major) (Chiracel® IA Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 1.0 mL/min); ee = 95%; HRMS (ES+) calcd for $C_{16}H_{22}NaO_4$ $[M+Na]^+$ 301.1416 found 301.1408.

Determination of relative stereochemistry

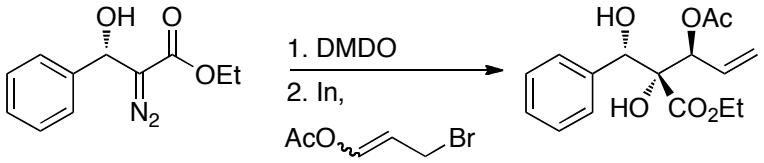
(*4SR,5SR*)-ethyl 2,2-dimethyl-4-(2-methylbut-3-en-2-yl)-5-phenyl-1,3-dioxolane-4-carboxylate



Prepared according to representative procedure above. (*SR*)-ethyl 2-hydroxy-2-((*SR*)-hydroxy(phenyl)methyl)-3,3-dimethylpent-4-enoate used: 30 mg. The reaction mixture was

stirred over night. The title compound (28 mg, 80%) was isolated as a yellow oil. R_f = 0.61 (20% Et_2O/Hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 6.21 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.18-5.11 (m, 3H), 4.00 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.70 (dq, *J* = 10.8, 7.2 Hz, 1H), 2.17 (s, 1H), 1.75 (s, 3H), 1.50 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H), 0.96 (dd, *J* = 7.2, 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 144.7, 136.9, 128.2, 128.2, 127.7, 113.4, 109.7, 92.5, 82.1, 60.7, 42.4, 27.3, 26.9, 23.8, 23.6, 13.6 ppm; IR (neat): ν_{max} 2983, 1740, 1246, 1093 cm^{-1}; HRMS (ES+) calcd for $C_{19}H_{26}NaO_4$ $[M+Na]^+$ 341.1729 found 341.1716.

(2*R*,3*S*)-ethyl 3-acetoxy-2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)pent-4-enoate



To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (50 mg, 0.22 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1M solution in acetone, 6 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (2 mL) and indium powder (28 mg, 0.24 mmol, 1.1 eq) and (*EZ*)-3-bromoprop-1-enyl acetate[4] (80 µL, 0.44 mmol, 2.0 eq) were added. The reaction mixture was stirred for 15 h and then quenched with saturated aqueous $NaHCO_3$ solution. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography using a gradient of 10%-33% EtOAc/petroleum ether to afford 52.4 mg (85%, 92% ee (major), 90% ee (minor)) of the product as a light yellow oil. R_f = 0.36 (33% EtOAc/petroleum ether); $[\alpha]_D^{25}$ -48.9 (92% ee, c. 10.5 mg/mL, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (m, 5H), 6.04 (ddd, *J* = 17.2, 10.8, 6.8 Hz, 1H), 5.68 (ddd, *J* = 6.6, 1.1, 1.1 Hz, 1H), 5.45 (ddd, *J* = 17.2, 1.3, 1.1 Hz, 1H), 5.39 (ddd, *J* = 10.8, 1.3, 1.1 Hz, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.12-3.91 (m, 2H), 3.62 (s, 1H), 3.09 (d, *J* = 6.8 Hz, 1H), 2.08 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 169.5, 138.3, 131.4, 128.4, 128.1, 128.0, 127.3, 127.0, 120.3, 81.4, 75.4, 74.3, 62.2, 20.9, 13.8 ppm; IR (neat): ν_{max} 3475,

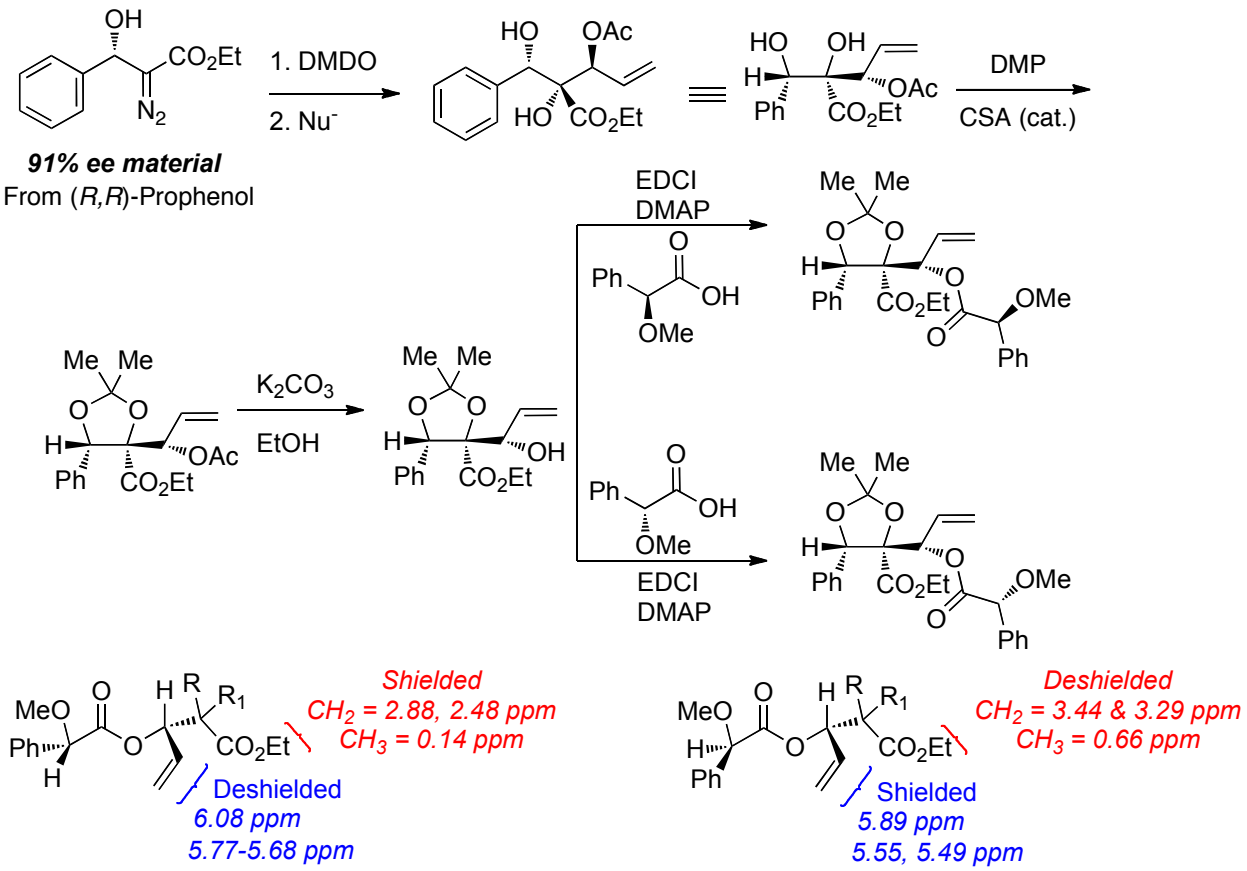
1742, 1232, 1024 cm^{-1}; HPLC T_r = 22.2 (minor diastereomer 1), 24.6 (major diastereomer 2), 26.4 (major diastereomer 1), and 32.1 (minor diastereomer 2) (Chiracel® IA Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 0.8 mL/min); ee = 92% (major), 90% (minor); HRMS (ES+) calcd for $C_{16}H_{20}NaO_6$ $[M+Na]^+$ 331.1158 found 331.1150.

Z:E = 5.24 ppm (*J* = 8.1, 6.3 Hz, 1H): 5.70 ppm (*J* = 12.3, 8.1, 1H)

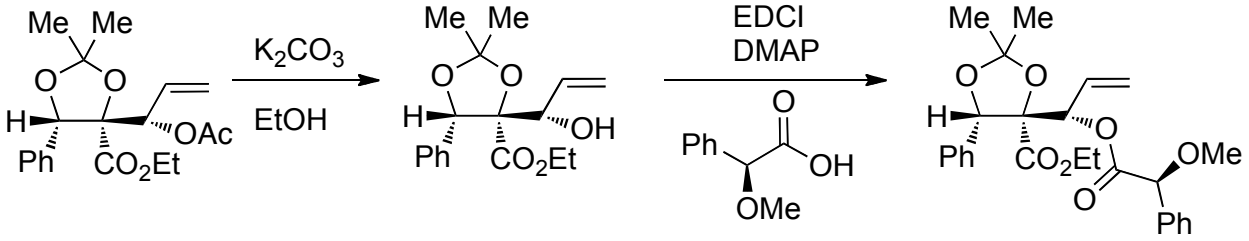
Allylating agent	Diastereoselectivity
(*Z*:*E*) = 1.3: 1.0	>20:1, 5:1
(*Z*:*E*) = 1.0:5.5	>20:1, 5:1

Determination of absolute and relative stereochemistry:

Protection of the diol as an acetonide, hydrolysis of the acetate, and acylation of the allylic alcohol with both enantiomers of *O*-methoxy-mandelic acid gave the ester as a mixture of diastereoisomers reflective of the chirality of the starting material. Based on the analysis the absolute stereochemistry of the carbon was assigned as (*S*). Relative stereochemistry was further verified by nOe analysis.



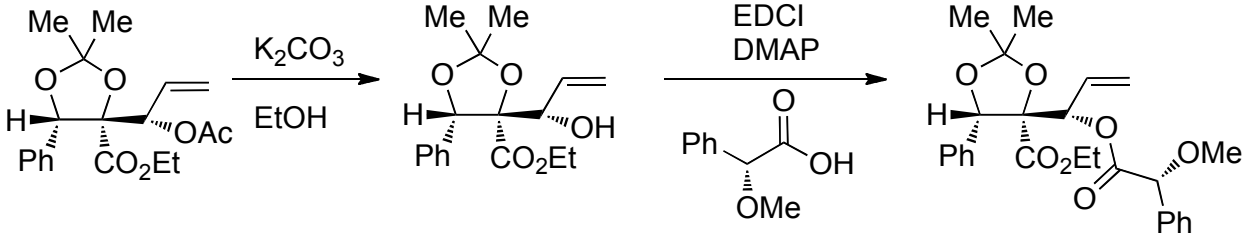
(4*S*,5*S*)-ethyl 4-((*S*)-1-((*S*)-2-methoxy-2-phenylacetoxy)allyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate



Potassium carbonate (100 mg, 0.72 mmol, 2.1 equiv) was added to a solution of (*4S,5S*)-ethyl 4-(1-acetoxyallyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (110 mg, 0.34 mmol) in ethanol (3 mL). The reaction was stirred at room temperature for 24h, diluted with CH_2Cl_2 (20 mL) and filtered. The compound was taken forward directly as is without further manipulation. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.26 (m, 5H), 6.07 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H), 5.42

(ddd, *J* = 17.3, 1.5, 1.5 Hz, 1H), 5.36 (s, 1H), 5.33 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.43-4.41 (m, 1H), 3.82 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.68 (dq, *J* = 10.7, 7.2 Hz, 1H), 2.95 (bs, 1H), 1.77 (s, 3H), 1.52 (s, 3H), 0.97 (dd, *J* = 7.2, 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.0, 135.6, 128.5, 128.1, 126.9, 117.9, 110.9, 88.9, 84.1, 76.9, 61.2, 26.7, 265, 13.6 ppm; IR (neat): ν_{max} 3480, 2938, 1747, 1376, 1250, 1220, 1058 cm^{-1}. To a solution of (4*S*,5*S*)-ethyl 4-((*S*)-1-hydroxyallyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (10 mg, 0.032 mmol) in CH_2Cl_2 was successively added (*S*)-*O*-methoxy-phenylacetic acid (10.9 mg, 0.065 mmol, 2 equiv), EDCI (19.0 mg, 0.097 mmol, 3 equiv), and DMAP (0.4 mg, 0.0032 mmol, 0.1 equiv). The mixture was stirred at room temperature for 24h, loaded directly onto a preparative thin layer chromatography and developed using 20% EtOAc /hexanes to afford 9.4 mg (64%) of the desired product as a colorless oil. R_f = 0.34 (20% EtOAc/hexanes – cerric ammonium molybdate); $[\alpha]_D^{25}$ +49.7 (c. 9.4 mg/mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.20 (m, 10H), 6.08 (ddd, *J* = 17.4, 10.2, 8.9 Hz, 10H), 5.77 (ddd, *J* = 17.4, 1.3, 0.6 Hz, 1H), 5.70-5.68 (m, 1H), 5.66 (d, *J* = 8.9 Hz, 1H), 5.03 (s, 1H), 4.74 (s, 1H), 3.32 (s, 3H), 2.88 (dq, *J* = 10.4, 7.2 Hz, 1H), 2.48 (dq, *J* = 10.4, 7.2 Hz, 1H), 1.84 (s, 3H), 1.51 (s, 3H), 0.14 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 168.2, 135.8, 134.6, 130.9, 128.7, 128.6, 128.6, 128.5, 128.4, 127.1, 126.0, 124.6, 111.3, 89.2, 81.9, 81.3, 76.2, 60.6, 57.1, 26.7, 26.5, 12.7 ppm; IR (neat): ν_{max} 2985, 2936, 1751, 1250, 1188, 1167 cm^{-1}; HRMS (ES+) calcd for $C_{26}H_{30}NaO_7$ $[M+Na]^+$ 477.1890 found 477.1884.

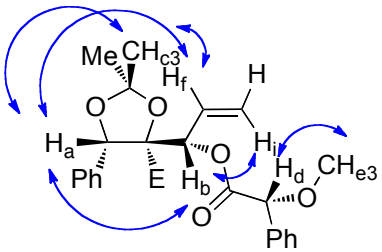
(4*S*,5*S*)-ethyl 4-((*S*)-1-((*R*)-2-methoxy-2-phenylacetoxy)allyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate.



Potassium carbonate (100 mg, 0.72 mmol, 2.1 equiv) was added to a solution of (*4S,5S*)-ethyl 4-(1-acetoxyallyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (110 mg, 0.34 mmol) in

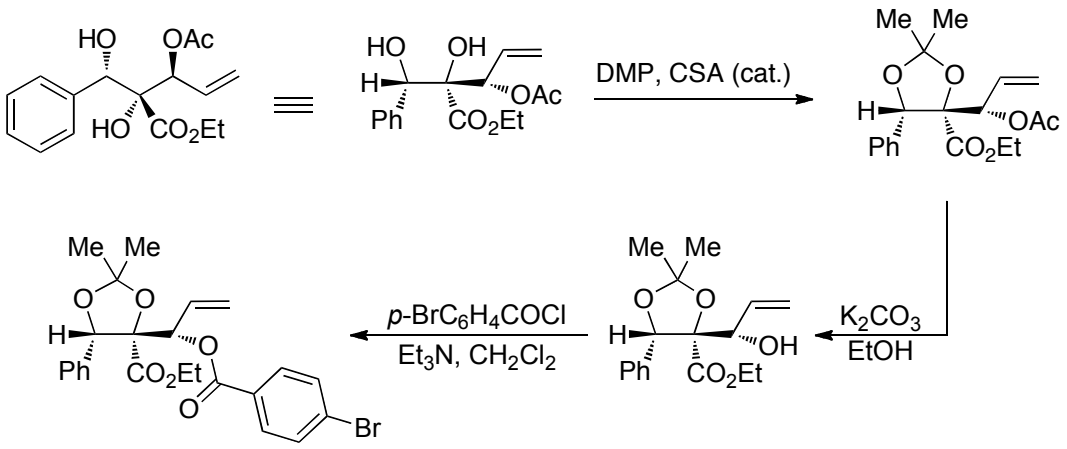
ethanol (3 mL). The reaction was stirred at room temperature for 24h, diluted with CH_2Cl_2 (20 mL) and filtered. The compound was taken forward directly as is without further manipulation. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.26 (m, 5H), 6.07 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H), 5.42 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.36 (s, 1H), 5.33 (dt, *J* = 10.6, 1.4 Hz, 1H), 4.43-4.41 (m, 1H), 3.82 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.68 (dq, *J* = 10.7, 7.2 Hz, 1H), 2.95 (bs, 1H), 1.77 (s, 3H), 1.52 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.0, 135.6, 128.5, 128.1, 126.9, 117.9, 110.9, 88.9, 84.1, 76.9, 61.2, 26.7, 265, 13.6 ppm; IR (neat): ν_{max} 3480, 2938, 1747, 1376, 1250, 1220, 1058 cm^{-1}. To a solution of (4*S*,5*S*)-ethyl 4-((*S*)-1-hydroxyallyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate (10 mg, 0.032 mmol) in CH_2Cl_2 was successively added (*R*)-*O*-methoxy-phenylacetic acid (10.9 mg, 0.065 mmol, 2 equiv), EDCI (19.0 mg, 0.097 mmol, 3 equiv), and DMAP (0.4 mg, 0.0032 mmol, 0.1 equiv). The mixture was stirred at room temperature for 24h, loaded directly onto a preparative thin layer chromatography and developed using 20% EtOAc/hexanes to afford 10.2 mg (70%) of the desired product as a colorless oil. R_f = 0.30 (20% EtOAc/hexanes – cerric ammonium molybdate); $[\alpha]_D^{25}$ -23.0 (c. 10.2 mg/mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.27 (m, 11H), 5.89 (ddd, *J* = 17.0, 10.0, 8.6 Hz, 1H), 5.81 (d, *J* = 8.6 Hz, 1H), 5.55 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.49 (dd, *J* = 10.0, 1.4 Hz, 1H), 5.05 (s, 1H), 4.71 (s, 1H), 3.44-3.36 (m, 1H), 3.32 (s, 3H), 3.29-3.25 (m, 1H), 1.84 (s, 3H), 1.47 (s, 3H), 0.56 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 168.9, 135.7, 134.7, 130.7, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 127.2, 127.1, 126.1, 126.0, 123.8, 111.3, 89.4, 82.4, 81.5, 75.8, 61.0, 57.2, 26.7, 26.5, 13.1 ppm; IR (neat): ν_{max} 2985, 1751, 1249, 1188 cm^{-1}; HRMS (ES+) calcd for $C_{26}H_{30}NaO_7$ $[M+Na]^+$ 477.1890 found 477.1884.

nOe correlations to reinforce relative stereochemical assignment:



List of nOe's
Hb - Hi 2.7%
Hb - Ha 3.2%
Ha - Hb 4.4%
Ha - Hf 2.9%
Ha - Hc 3.4%
Hc - Ha 3.0%
Hd - He 4.0% (assignment of singlet @ 4.71)
Hc - Hf 1.8%

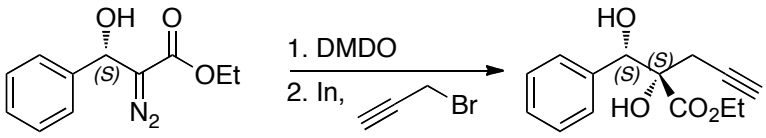
(4*S*,5*S*)-ethyl 4-((*S*)-1-acetoxyallyl)-2,2-dimethyl-5-phenyl-1,3-dioxolane-4-carboxylate



Prepared according to representative procedure above. (2*R*,3*S*)-ethyl 3-acetoxy-2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)pent-4-enoate used: 132 mg. The reaction mixture was stirred over night. The crude product was purified by silica gel chromatography using a gradient of 10% - 20% EtOAc/ petroleum ether to 129 mg (88%) of the desired compound as a white solid. R_f = 0.43 (20% EtOAc/petroleum ether); mp = 92-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 6.03 (ddd, *J* = 17.6, 10.2, 8.8 Hz, 1H), 5.75-5.67 (m, 2H), 5.63 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.09 (s, 1H), 3.79 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.36 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.98 (s, 3H), 1.85 (s, 3H), 1.51 (s, 3H), 0.75 (dd, *J* = 7.1, 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 169.1, 134.7, 131.4, 128.7, 128.4, 126.1, 123.7, 111.3, 89.7, 81.4, 75.4, 60.9, 26.7, 26.4, 20.9, 13.5 ppm; IR (neat): ν_{max} 2986, 2939, 1750, 1373, 1224, 1187, 1145, 1032 cm^{-1}; HRMS (ES+) calcd for $C_{19}H_{24}NaO_6$ $[M+Na]^+$ 371.1471 found 371.1474. Potassium carbonate (100 mg, 0.72 mmol) was added to a solution of the resulting acetonide (129 mg, 0.37 mmol) in ethanol (2 mL). The reaction was stirred at room temperature for 24h and concentrated under reduced pressure. The crude product was directly carried onto the next step. To a solution of the resulting alcohol (10 mg, 0.032 mmol) in CH_2Cl_2 (250 uL) was sequentially added Et_3N (9.9 mg, 0.097 mmol), DMAP (0.4 mg, 0.003 mmol), and *para*-bromobenzoyl chloride (8.6 mg, 0.039 mmol). The reaction was stirred 24 h, directly applied onto a preparative TLC plate and developed with 10% EtOAc/hexanes to afford 12.9 mg (80% over two steps) of the desired product as a white solid. Recrystallization of the resulting solid in heptane afforded X-ray

quality crystals. $[\alpha]_D^{25}$ -4.3 (c. 12.0 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 2H), 7.52 (m, 2H), 7.37-7.30 (m, 5H), 6.16-6.07 (m, 1H), 5.90 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 17.2 Hz, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 5.14 (s, 1H), 3.62-3.60 (m, 1H), 3.31-3.24 (m, 1H), 1.88 (s, 3H), 1.54 (s, 3H), 0.59-0.54 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 164.4, 134.7, 132.3, 131.9, 131.7, 131.3, 131.2, 128.8, 128.5, 128.4, 126.2, 123.7, 111.4, 89.7, 76.5, 60.9, 26.8, 26.5, 13.4 ppm; IR (neat): ν_{max} 2983, 2929, 1742, 1721, 1250, 1186, 1145, 1059, 757 cm^{-1}; HRMS (ES+) calcd for $C_{26}H_{30}NaO_7$ $[M+Na]^+$ 477.1890 found 477.1884.

(*S*)-ethyl 2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)pent-4-ynoate

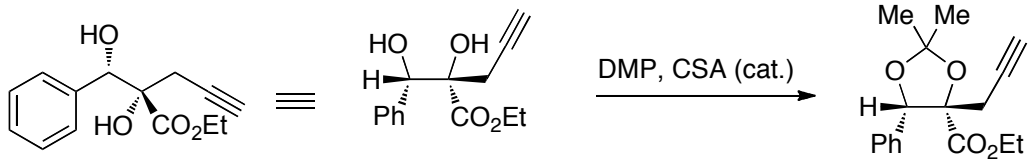


To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (50 mg, 0.22 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1M solution in acetone, 6 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (2 mL) and Indium powder (28 mg, 0.24 mmol, 1.1 eq) and propargyl bromide (80% pure, 49.2 µL, 0.44 mmol, 2.0 eq) were added. After 16 h additional propargyl bromide (80% pure, 49.2 µL, 0.44 mmol, 2.0 eq) was added and the reaction mixture stirred for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography using a gradient of 15%-33% EtOAc/petroleum ether to afford 32 mg (60%, 95% ee) of the desired compound as a light yellow oil along with the corresponding allene product (5:1 ratio). R_f = 0.60 (50% EtOAc/PE); $[\alpha]_D^{25}$ +16.2 (95% ee, c. 8.3 mg/mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H), 4.80 (s, 1H), 4.17 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.07 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.62 (br s, 1H), 2.97 (dd, *J* = 16.8, 2.6 Hz, 1H), 2.82 (dd, *J* = 16.8, 2.6 Hz, 1H), 2.04 (dd, *J* = 2.6, 2.6 Hz, 1H), 1.20 (dd, *J* = 7.1, 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 138.5, 128.5, 128.1, 128.0, 127.5, 127.0, 79.4, 78.9, 76.8, 71.3,

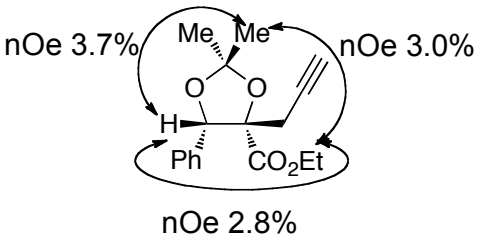
62.5, 27.0, 14.0 ppm; IR (neat): ν_{max} 3492, 3293, 1733, 1217, 1118, 1023, 702 cm^{-1}; T_r = 26.0 (minor) and 36.4 (major) (Chiracel® OJ Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 0.8 mL/min); HRMS (ES+) calcd for $C_{14}H_{16}NaO_4$ $[M+Na]^+$ 271.0946 found 271.0937.

Determination of relative stereochemistry

(*4SR,5SR*)-ethyl 2,2-dimethyl-5-phenyl-4-(prop-2-ynyl)-1,3-dioxolane-4-carboxylate

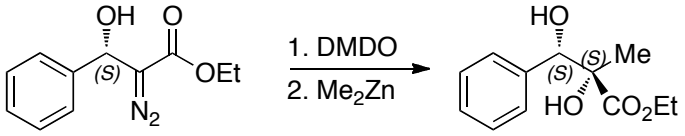


Prepared according to representative procedure above. (*SR*)-ethyl 2-hydroxy-2-((*SR*)-hydroxy(phenyl)methyl)pent-4-ynoate used: 10 mg. The reaction mixture was stirred over night. The crude product was purified by silica gel chromatography using a gradient of 5%-10% Et_2O/Hexanes and afforded 9 mg (78%) of the desired compound as a yellow oil. R_f = 0.65 (20% EtOAc/petroleum ether); ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 5.37 (s, 1H), 3.78 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.60 (dq, *J* = 10.7, 7.2 Hz, 1H), 2.94 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.90 (dd, *J* = 17.4, 2.7 Hz, 1H), 2.15 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.82 (s, 3H), 1.62 (s, 3H), 0.89 (dd, *J* = 7.2, 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 134.7, 128.6, 128.3, 126.0, 110.9, 88.6, 83.0, 79.3, 71.5, 61.2, 26.8, 26.5, 24.8, 13.5 ppm; IR (neat): ν_{max} 3277, 2985, 2937, 1748, 1454, 1378, 1247, 1219, 1175, 1147, 1081, 1065, 1027, 915 cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{20}NaO_4$ $[M+Na]^+$ 311.1259 found 311.1246.



Addition of alkylzinc and vinylzinc compounds

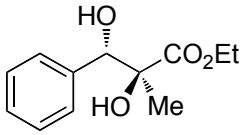
(*2S,3S*)-ethyl 2,3-dihydroxy-2-methyl-3-phenylpropanoate

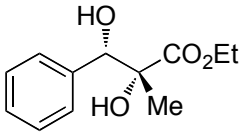


To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (50 mg, 0.22 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1M solution in acetone, 6 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (1 mL) and cooled to -78 °C. Dimethylzinc (1.2M solution in toluene, 0.6 mL, 0.66 mmol, 3.0 eq) was added dropwise and the reaction was allowed to warm gently to room temperature. After 40 h the reaction was quenched with pH 7 buffer and extracted with diethyl ether (4 x 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography using a gradient of 15%-33% EtOAc/petroleum ether to afford 35 mg (71%, 94% ee) of the desired product as a light yellow oil. R_f = 0.15 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +10.0 (94% ee, c. 10.0 mg/mL, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 4.74 (d, *J* = 7.4 Hz, 1H), 4.11 (dq, *J* = 10.4, 7.0 Hz, 1H), 4.03 (dq, *J* = 10.4, 7.0 Hz, 1H), 3.34 (s, 1H), 3.01 (d, *J* = 7.4 Hz, 1H), 1.56 (s, 3H), 1.18 (dd, *J* = 7.0, 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 139.1, 128.2, 128.0, 127.0, 77.9, 775, 62.0, 22.6, 13.9 ppm; IR (neat): ν_{max} 3473, 2984, 2939, 1730, 1453, 1243, 1160, 1049, 1026, 702 cm^{-1}; HPLC T_r = 16.5 (minor) and 18.0 (major) (Chiracel® AD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 0.8 mL/min). Submitted for MS.

Determination of Diastereoselectivity

Diastereoselectivity was assigned based on comparison to literature assigned structure for diastereomer.

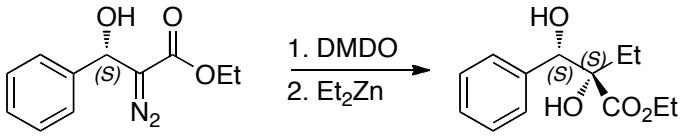




^{1}H NMR (400 MHz, $CDCl_3$): δ
7.36-7.27 (m, 5H)
4.74 (d, *J* = 7.4 Hz, 1H)
4.11 (dq, *J* = 10.4, 7.0 Hz, 1H)
4.03 (dq, *J* = 10.4, 7.0 Hz, 1H)
3.34 (s, 1H)
3.01 (d, *J* = 7.4 Hz, 1H)
1.56 (s, 3H)
1.18 (dd, *J* = 7.0, 7.0 Hz, 3H)

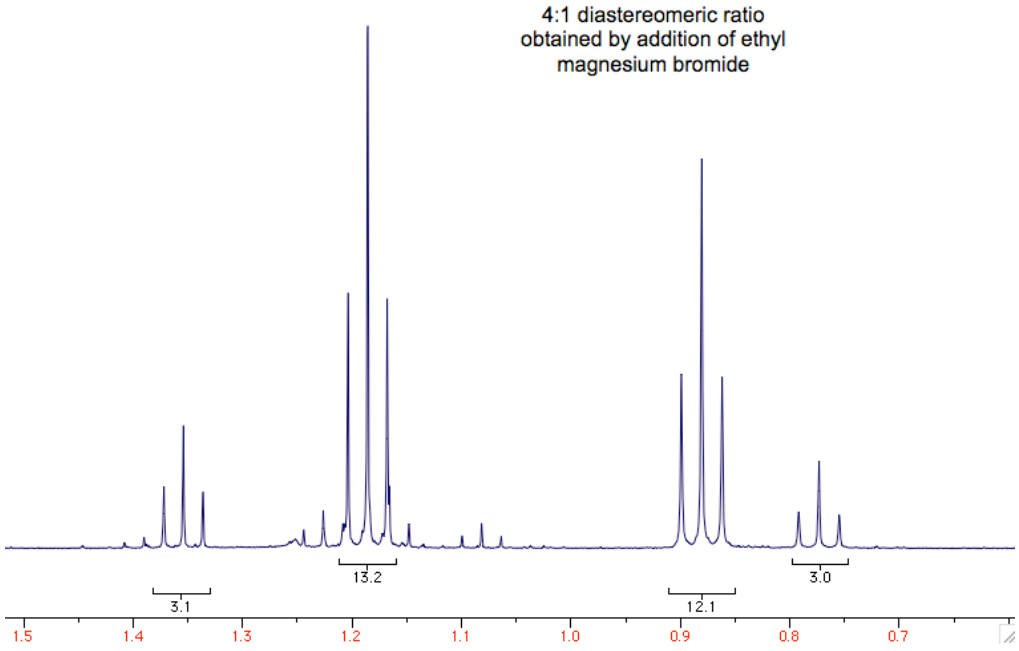
^{1}H-NMR (400 MHz, $CDCl_3$): δ
7.46-7.35 (m, 5H)
4.87 (d, 1H, *J* = 6.6 Hz)
4.34 (m, 2H)
3.55 (s, 1H)
2.71 (d, 1H, *J* = 6.6 Hz)
1.37 (t, 3H, *J* = 7.0 Hz)
1.23 (s, 3H)

(*S*)-ethyl 2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)butanoate

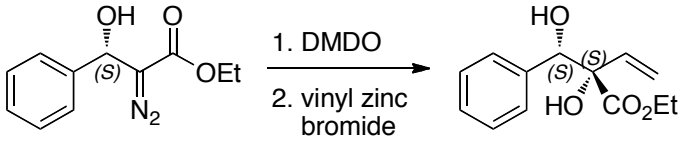


To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (50 mg, 0.22 mmol, 1.0 eq) in acetone (2 mL) was added DMDO (~0.1M solution in acetone, 6 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (1 mL) and cooled to -78 °C. Diethylzinc (1M solution in hexanes, 0.7 mL, 0.66 mmol, 3.0 eq) was added dropwise and the reaction was allowed to warm to RT over night. After 20 h the reaction was quenched with pH 7 buffer and extracted with Et_2O (4 x 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography using a gradient of 15%-33% EtOAc/petroleum ether to afford 42 mg (80%, 95% ee) of the desired product as a white solid. R_f = 0.45 (33% EtOAc/PE); mp = 52 °C; $[\alpha]_D^{25}$ +3.4 (95% ee, c. 9.0 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 5H), 4.73 (d, *J* = 7.8 Hz, 1H), 4.11 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.00 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.34 (s, 1H), 2.96 (d, *J* = 8.1 Hz, 1H), 2.1 (dq, *J* = 14.3, 7.3 Hz, 1H), 1.93 (dq, *J* = 14.3, 7.3 Hz, 1H), 1.19 (dd, *J* = 7.1, 7.1 Hz, 3H), 0.88

(dd, J = 7.3, 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 139.4, 128.1, 128.0, 127.0, 81.1, 77.8, 62.0, 28.8, 14.0, 7.9 ppm; IR (neat): ν_{max} 3479, 2979, 1730, 1235, 1148, 1026 cm^{-1}; HPLC T_r = 12.6 (minor) and 14.0 (major) (Chiracel® AD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 1.0 mL/min). HRMS (ES+) calcd for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ 261.1103 found 261.1097.



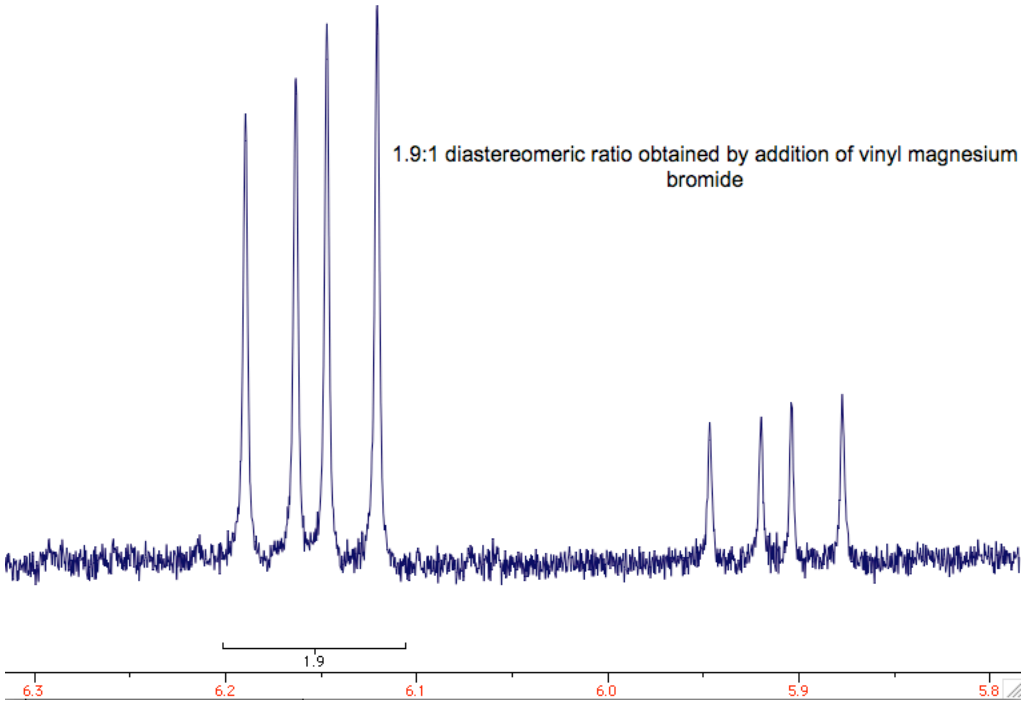
(*S*)-ethyl 2-hydroxy-2-((*S*)-hydroxy(phenyl)methyl)but-3-enoate



To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (25 mg, 0.11 mmol, 1.0 eq) in acetone (1 mL) was added DMDO (~0.1M solution in acetone, 3 mL, 0.3 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to room temperature and concentrated. CH_2Cl_2 was added, the solution was dried over

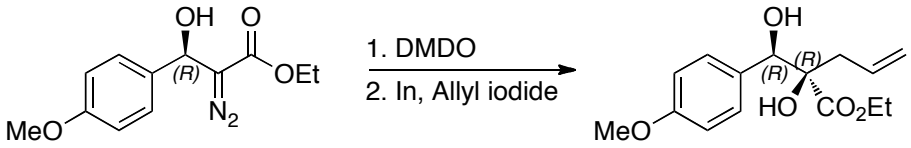
Na_2SO_4, filtered, and concentrated. The residue was dissolved in THF (0.6 mL) and cooled to -78 °C. Vinylzinc bromide (0.33 M solution*, 1 mL, 0.33 mmol, 3.0 eq) was added dropwise and the reaction was allowed to warm to RT over night. After 40 h the reaction was quenched with pH 7 buffer and extracted with Et_2O (4 x 5 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography using a gradient of 15%-33% EtOAc/petroleum ether afforded 18 mg (69%, 84% ee) of the desired product as a yellow oil. R_f = 0.24 (20% EtOAc/PE); $[\alpha]_D^{25}$ +26.6 (84% ee, c. 7.9 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 6.15 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.70 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.40 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.91-4.86 (m, 1H), 4.16-4.06 (m, 2H), 3.36 (s, 1H), 2.83-2.80 (m, 1H), 1.22 (dd, *J* = 7.2, 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 138.1, 135.7, 128.3, 128.0, 127.3, 117.7, 80.5, 77.2, 62.4, 13.9 ppm; IR (neat): ν_{max} 3484, 2984, 1731, 1238, 1157, 1024, 701 cm^{-1}; HPLC T_r = 17.2 (minor) and 22.4 (major) (Chiracel® AD Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 0.8 mL/min); HRMS (ES+) calcd for $C_{13}H_{16}NaO_4$ $[M+Na]^+$ 259.0946 found 259.0955.

*Previously prepared by addition of vinylmagnesium bromide (1 M solution in THF, 2 mL, 2.0 mmol, 1.0 eq) to $ZnCl_2$ (0.66 M solution in Et_2O, 3 mL, 2.0 mmol, 1.0 eq). After stirring for 3 h 1,4-dioxane (1.2 mL) was added and the reaction mixture stirred for an additional hour. The stirring was stopped and after 1 h the supernatant of the mixture was used for the reaction.


1.9:1 diastereomeric ratio obtained by addition of vinyl magnesium bromide
1.9
6.3
6.2
6.1
6.0
5.9
5.8

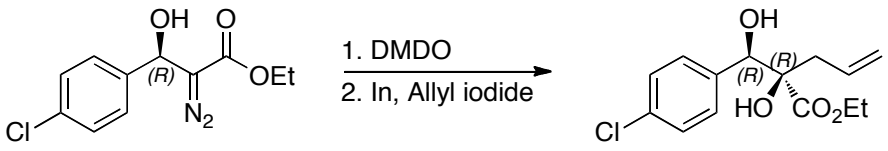
Expanding the scope of the carbonyl acceptors

(*R*)-ethyl 2-hydroxy-2-((*R*)-hydroxy(4-methoxyphenyl)methyl)pent-4-enoate



To a solution of (*R*)-ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)-propanoate (55 mg, 0.22 mmol, 1.0 eq, 87% ee) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 6.0 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (determined by TLC, ~ 1h) the reaction mixture was warmed to room temperature and concentrated under reduced pressure. CH_2Cl_2 was added, the solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in DMF (2.0 mL) and indium powder (28 mg, 0.24 mmol, 1.1 eq) and allyl iodide (40 μL, 0.44 mmol, 2.0 eq) were added sequentially. The reaction mixture was stirred 12h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel chromatography using 20% EtOAc/petroleum ether afforded 56 mg (91%, 85% ee) of the desired product as a white solid. R_f = 0.17 (20% EtOAc/petroleum ether); mp = 65-67°C; $[\alpha]_D^{25}$ +30.7 (85% ee, c. 6.6 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.82-5.72 (m, 1H), 5.16-5.08 (m, 2H), 4.72 (d, *J* = 7.9 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.00 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.35 (s, 1H), 2.98 (d, *J* = 7.9 Hz, 1H), 2.83 (dddd, *J* = 14.0, 6.4, 1.3, 1.3 Hz, 1H), 2.60 (dddd, *J* = 14.0, 8.1, 0.8, 0.8 Hz, 1H), 1.19 (dd, *J* = 7.2, 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 159.4, 132.2, 131.2, 128.2, 119.0, 113.3, 80.4, 76.9, 61.9, 55.1, 40.4, 14.0 ppm; IR (neat): ν_{max} 3485, 3076, 2981, 1730, 1613, 1514, 1250, 1178, 1151, 1032 cm^{-1}; HPLC T_r = 21.6 (minor) and 31.8 (major) (Chiracel® IC Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 90:10, 1.0 mL/min); ee = 85%; HRMS (ES+) calcd for $C_{15}H_{20}NaO_5$ $[M+Na]^+$ 303.1208 found 303.1207.

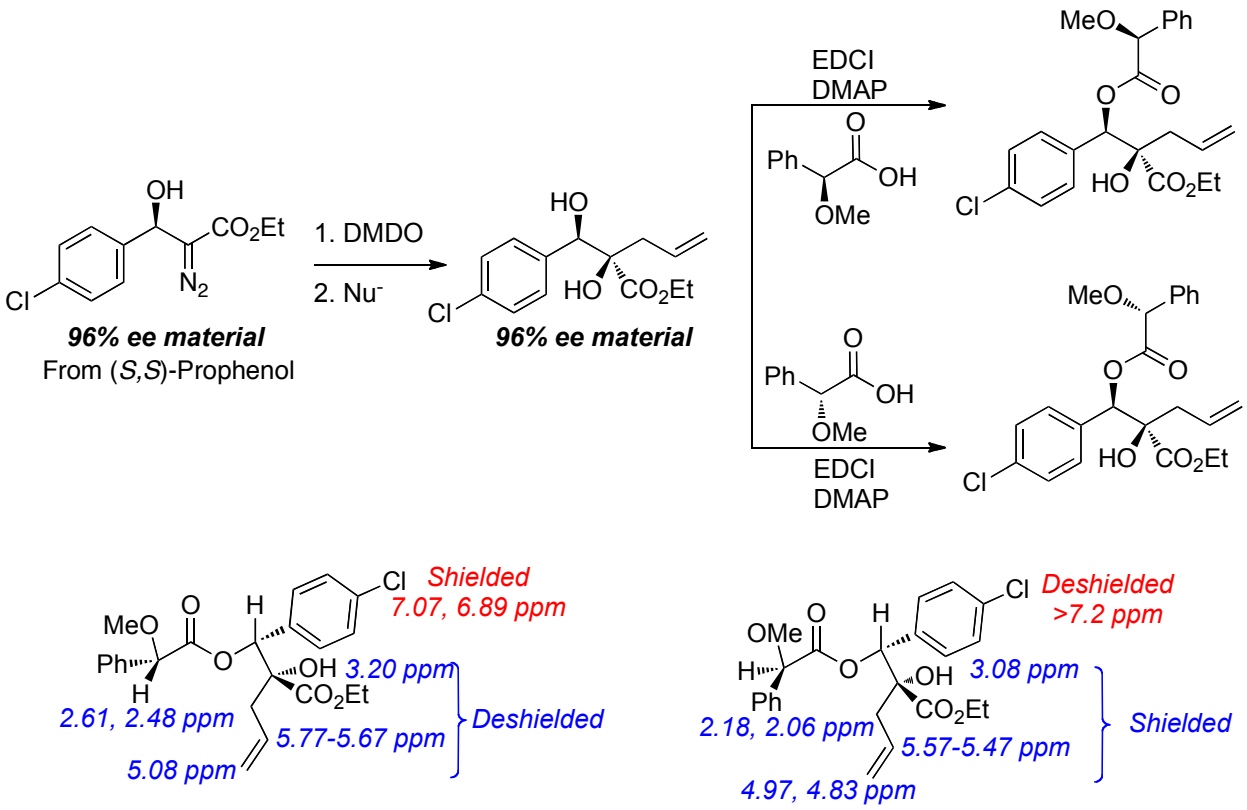
(*R*)-ethyl 2-((*R*)-(4-chlorophenyl)(hydroxy)methyl)-2-hydroxypent-4-enoate



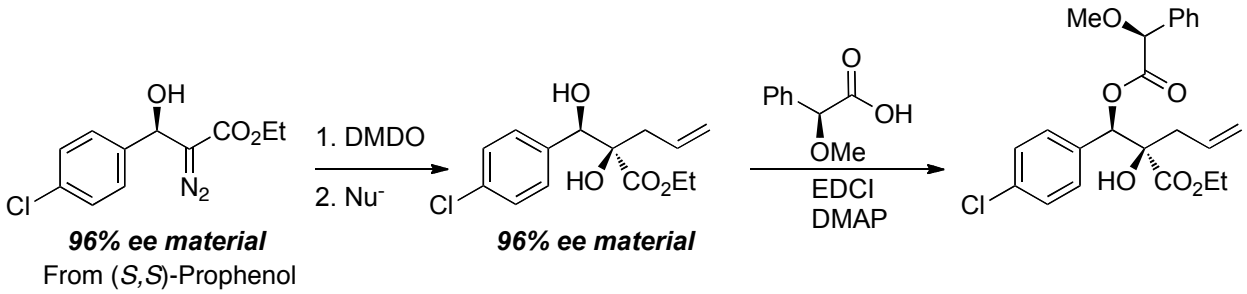
To a solution of (*R*)-ethyl 3-(4-chlorophenyl)-2-diazo-3-hydroxypropanoate (56 mg, 0.22 mmol, 1.0 eq, 96% ee) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 6.0 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (determined by TLC, ~ 1h) the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Methylene chloride was added, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (2.0 mL) and indium powder (28 mg, 0.24 mmol, 1.1 eq) and allyl iodide (40 μL, 0.44 mmol, 2.0 eq) were added sequentially. The reaction mixture was stirred 12h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel chromatography using 20% EtOAc/petroleum ether afforded 59 mg (94%, 96% ee) of the desired product as a white solid. R_f = 0.30 (20% EtOAc/petroleum ether); mp = 72 °C; $[\alpha]_D^{25}$ +42.4 (96% ee, c. 4.9 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 4H), 5.80-5.65 (m, 1H), 5.16-5.07 (m, 2H), 4.75 (d, *J* = 4.8 Hz, 1H), 4.16-4.08 (m, 1H), 4.07-3.97 (m, 1H), 3.41 (s, 1H), 3.14 (d, *J* = 7. Hz, 1H), 2.80 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.59 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.19 (td, *J* = 7.2, 0.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 137.6, 134.0, 131.9, 129.3, 128.5, 128.3, 128.1, 119.4, 80.2, 76.8, 62.2, 40.4, 14.0 ppm; IR (neat): ν_{max} 3473, 3078, 2982, 1731, 1491, 1224, 1151, 1091, 1015 cm^{-1}; HPLC T_r = 13.3 (minor) and 16.0 (major) (Chiracel® IC Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 95:5, 1.0 mL/min); ee = 96%; HRMS (ES+) calcd for $C_{14}H_{17}ClNaO_4$ $[M+Na]^+$ 307.0713 found 307.0709.

Determination of Absolute Stereochemistry

The absolute stereochemistry was determined via the conversion of the alcohol to both enantiomers of the mandelate ester.



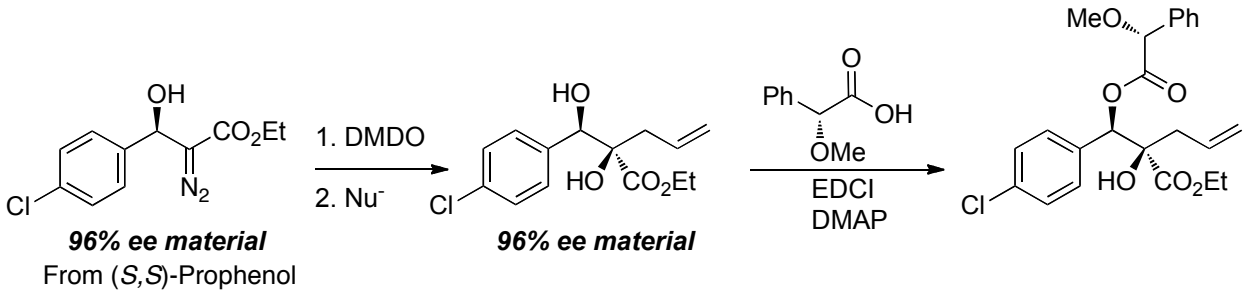
(*R*)-ethyl 2-((*R*)-(4-chlorophenyl)((*S*)-2-methoxy-2-phenylacetoxy)methyl)-2-hydroxypent-4-enoate.



To a solution of (*R*)-ethyl 2-((*R*)-(4-chlorophenyl)(hydroxy)methyl)-2-hydroxypent-4-enoate (7 mg, 0.025 mmol) in CH_2Cl_2 was successively added (*S*)-*O*-methoxy-phenylacetic acid (8.3 mg, 0.050 mmol, 2 equiv), EDCI (14.4 mg, 0.075 mmol, 3 equiv), and DMAP (0.3 mg, 0.0025 mmol, 0.1 equiv). The mixture was stirred at room temperature for 24h, loaded directly onto a preparative thin layer chromatography and developed using 20% EtOAc/hexanes to afford 8 mg (74%) of the desired product as a colorless oil. $R_f = 0.26$ (20% EtOAc/hexanes – cerric

ammonium nitrate); $[\alpha]_D^{25}$ +80.7 (96 % ee, c. 7.0 mg/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.31 (m, 5H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 2H), 5.95 (s, 1H), 5.77-5.67 (m, 1H), 5.08 (dd, *J* = 9.4, 9.1 Hz, 2H), 4.89 (s, 1H), 4.20-4.06 (m, 3H), 3.40 (s, 3H), 3.20 (bs, 1H), 2.61 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.48 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 169.6, 135.7, 134.7, 133.5, 131.7, 129.2, 129.1, 128.9, 128.3, 127.6, 119.7, 82.6, 79.5, 78.0, 62.9, 57.6, 40.4, 14.4 ppm; IR (neat): ν_{max} 3504, 2981, 2929, 1756, 1736, 1491, 1225, 1165, 1113, 1013 cm^{-1}; HRMS (ES+) calcd for $C_{23}H_{25}ClNaO_6$ $[M+Na]^+$ 455.1238 found 455.1232.

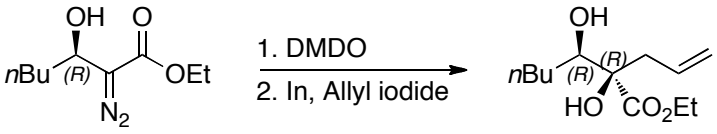
(*R*)-ethyl 2-((*R*)-(4-chlorophenyl)((*R*)-2-methoxy-2-phenylacetoxy)methyl)-2-hydroxypent-4-enoate.



To a solution of (*R*)-ethyl 2-((*R*)-(4-chlorophenyl)(hydroxy)methyl)-2-hydroxypent-4-enoate (7 mg, 0.025 mmol) in CH_2Cl_2 was successively added (*R*)-*O*-methoxy-phenylacetic acid (8.3 mg, 0.050 mmol, 2 equiv), EDCI (14.4 mg, 0.075 mmol, 3 equiv), and DMAP (0.3 mg, 0.0025 mmol, 0.1 equiv). The mixture was stirred at room temperature for 24h, loaded directly onto a preparative thin layer chromatography and developed using 20% EtOAc/hexanes to afford 8 mg (74%) of the desired product as a colorless oil. R_f = 0.33 (20% EtOAc/hexanes – cerric ammonium nitrate stain); $[\alpha]_D^{25}$ -30.0 (96 % ee, c. 7.0 mg/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.23 (m, 9H), 5.89 (s, 1H), 5.57-5.47 (m, 1H), 4.97 (d, *J* = 9.2 Hz, 1H), 4.85 (s, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.15-4.03 (m, 2H), 3.37 (s, 3H), 3.08 (bs, 1H), 2.18 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.06 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 169.6, 135.9, 134.7, 133.8, 131.3, 129.3, 129.0, 128.7, 128.3, 127.3, 119.4, 82.4, 79.4, 77.6, 62.5, 57.3, 39.8, 14.1 ppm; IR (neat): ν_{max} 3503, 3074, 2981, 2930, 1753, 1736,

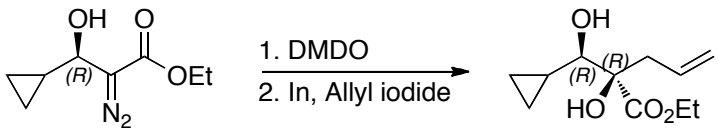
1491, 1225, 1198, 1166, 1111, 1012 cm^{-1}; HRMS (ES+) calcd for $C_{23}H_{25}ClNaO_6$ $[M+Na]^+$ 455.1238 found 455.1232.

(*2R,3R*)-ethyl 2-allyl-2,3-dihydroxyheptanoate



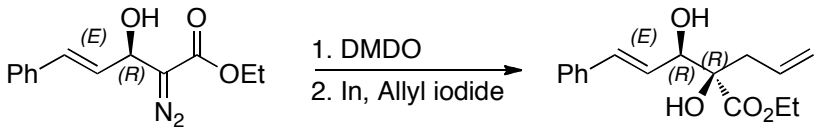
To a solution of (*R*)-ethyl 2-diazo-3-hydroxyheptanoate (25 mg, 0.13 mmol, 1.0 eq, 97% ee) in acetone (1.1 mL) was added DMDO (~0.1 M solution in acetone, 3.5 mL, 0.35 mmol, 2.8 eq) at -35 °C. Upon completion of the reaction (determined by TLC, ~ 1h) the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Methylene chloride was added, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (1.1 mL) and indium powder (16 mg, 0.14 mmol, 1.1 eq) and allyl iodide (23 μL, 0.25 mmol, 2.0 eq) were added sequentially. The reaction mixture was stirred 12h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel chromatography using 15% EtOAc/petroleum ether afforded 24 mg (91%, 97% ee) of the desired product as a yellow oil. R_f = 0.32 (15% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +31.2 (97% ee, c. 4.8 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79-5.69 (m, 1H), 5.13-5.08 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.62 (td, *J* = 9.6, 1.9 Hz, 1H), 3.62 (td, *J* = 9.6, 1.9 Hz, 1H), 3.37 (s, 1H), 2.69 (dddd, *J* = 14.0, 6.7, 1.3, 1.3 Hz, 1H), 2.48 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.09 (d, *J* = 9.0 Hz, 1H), 1.50-1.24 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 5H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 132.2, 119.0, 79.9, 75.2, 62.0, 40.2, 31.4, 28.1, 22.4, 14.2, 13.9 ppm; IR (neat): ν_{max} 3481, 2956, 2934, 2861, 1730, 1266, 1221, 1156, 1081, 1034 cm^{-1}; HPLC T_r = 9.3 (major) and 10.1 (minor) (Chiracel® AD Chiral HPLC, λ = 208 nm, heptane:*i*-PrOH = 90:10, 0.8 mL/min); HRMS (ES+) calcd for $C_{12}H_{22}NaO_4$ $[M+Na]^+$ 253.1416 found 253.1405.

(*R*)-ethyl 2-((*R*)-cyclopropyl(hydroxy)methyl)-2-hydroxypent-4-enoate



To a solution of (*R*)-ethyl 3-cyclopropyl-2-diazo-3-hydroxypropanoate (41 mg, 0.22 mmol, 1.0 eq, 99% ee) in acetone (2.0 mL) was added DMDO (~0.1 M solution in acetone, 6.0 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (determined by TLC, ~ 1h) the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Methylene chloride was added, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (2.0 mL) and indium powder (28 mg, 0.24 mmol, 1.1 eq) and allyl iodide (40 µL, 0.44 mmol, 2.0 eq) were added sequentially. The reaction mixture was stirred 12h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel chromatography using 20% EtOAc/petroleum ether afforded 41 mg (86%, >99% ee) of the desired product as a yellow oil. R_f = 0.32 (15% EtOAc/petroleum ether – $KMnO_4$); $[\alpha]_D^{25}$ +14.6 (>99% ee, c. 7.6 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (dddd, *J* = 16.9, 10.4, 8.1, 6.5 Hz, 1H), 5.15-5.10 (m, 2H), 4.30 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.49 (s, 1H), 2.93 (t, *J* = 8.4 Hz, 1H), 2.72 (ddt, *J* = 14.0, 6.5, 1.3 Hz, 1H), 2.54 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.20 (d, *J* = 8.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.05 (dtt, *J* = 9.1, 8.2, 5.0 Hz, 1H), 0.53 (m, 2H), 0.39 (m, 1H), 0.23 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 132.2, 119.0, 80.1, 79.8, 62.0, 40.2, 14.2, 12.8, 3.8, 2.2 ppm; IR (neat): ν_{max} 3454, 2981, 2924, 1730, 1221, 1149, 1030 cm^{-1}; HPLC T_r = 28.7 (major) and 31.2 (minor) (Chiracel® IA Chiral HPLC, λ = 208 nm, heptane:*i*-PrOH = 98:2, 1.0 mL/min); 97% ee; HRMS (ES+) calcd for $C_{11}H_{18}NaO_4$ $[M+Na]^+$ 237.1103 found 237.1095.

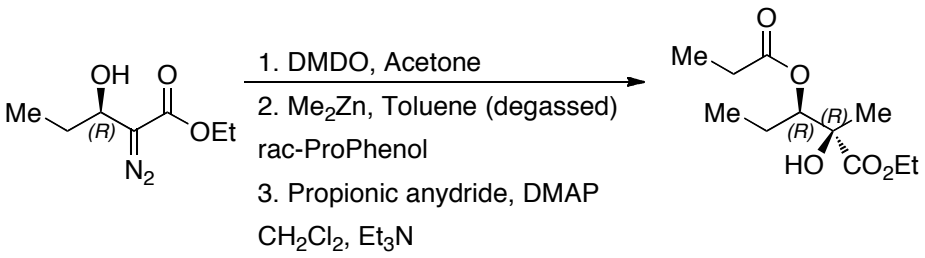
(*2R,3R,E*)-ethyl 2-allyl-2,3-dihydroxy-5-phenylpent-4-enoate



To a solution of (*R,E*)-ethyl 2-diazo-3-hydroxy-5-phenylpent-4-enoate (54 mg, 0.22 mmol, 1.0 eq, 87% ee) in acetone (2.0 mL) was added DMDO (~0.1 M solution in acetone, 6.0 mL, 0.6 mmol, 2.7 eq) at -35 °C. Upon completion of the reaction (determined by TLC, ~ 1h) the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Methylene chloride was added, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (2.0 mL) and indium powder (28 mg, 0.24 mmol, 1.1 eq) and allyl iodide (40 μL, 0.44 mmol, 2.0 eq) were added sequentially. The reaction mixture was stirred 12h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 x 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel chromatography using 20% EtOAc/petroleum ether afforded 20 mg (33%, 82% ee) of the desired product as a yellow oil. R_f = 0.23 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +32.2 (82% ee, c. 7.9 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.83-5.75 (m, 1H), 5.17-5.09 (m, 2H), 4.35-4.31 (m, 1H), 4.24 (dd, *J* = 7.1, 1.9 Hz, 2H), 3.48 (s, 1H), 2.70 (dddd, *J* = 14.1, 6.6, 1.3, 1.3 Hz, 1H), 2.57 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.49 (d, *J* = 7.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 136.3, 133.5, 131.8, 128.6, 128.0, 126.6, 126.1, 119.3, 79.9, 62.3, 39.9, 14.3 ppm; IR (neat): ν_{max} 3474, 2980, 2925, 1729, 1221, 1151 cm^{-1}; HPLC T_r = 26.4 (minor) and 29.3 (major) (Chiracel® IC Chiral HPLC, λ = 220 nm, heptane:*i*-PrOH = 95:5, 1.0 mL/min); HRMS (ES+) calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1259 found 299.1263.

Synthetic utility: Synthesis of a fragment for several natural products

(2*R*,3*R*)-ethyl 2-hydroxy-2-methyl-3-(propionyloxy)pentanoate

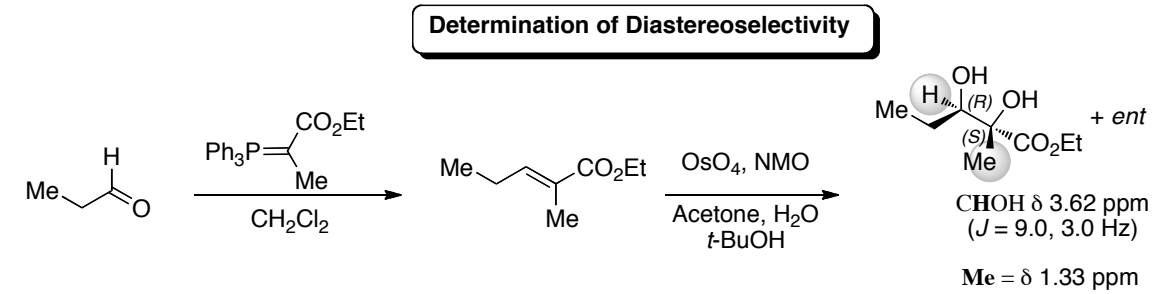


Oxidation and methyl addition: To a solution of *(R)*-ethyl 2-diazo-3-hydroxypentanoate (33 mg, 0.19 mmol, 1.0 eq) in acetone (1.2 mL) was added DMDO (~0.1 M solution in acetone, 4.0 mL, 0.4 mmol, 2.0 eq) at -35 °C. Upon completion of the reaction (checked by TLC, approx. 1 h) the reaction mixture was warmed to RT and concentrated. CH_2Cl_2 was added, the solution dried over Na_2SO_4 and concentrated. To the residue was added racemic ProPhenol (31.8 mg, 0.05 mmol, 0.25 eq) and the mixture was dissolved in degassed toluene (1 mL) and cooled to -78 °C. Dimethylzinc (1.0M solution in heptane, 0.6 mL, 0.6 mmol, 3.0 eq) was added dropwise and the reaction was allowed to warm gently to room temperature. After 18 h the reaction was quenched with pH 7 buffer and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was carried forward. *Analysis of crude reaction mixture demonstrated a 10:1 diastereoselectivity based upon comparison to literature data*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (q, *J* = 6.8 Hz, 2H), 3.47 (dd, *J* = 8.8, 4.0 Hz, 1H), 1.43 (s, 3H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 78.0, 77.0, 25.1, 22.7, 14.4, 14.2, 11.1 ppm.

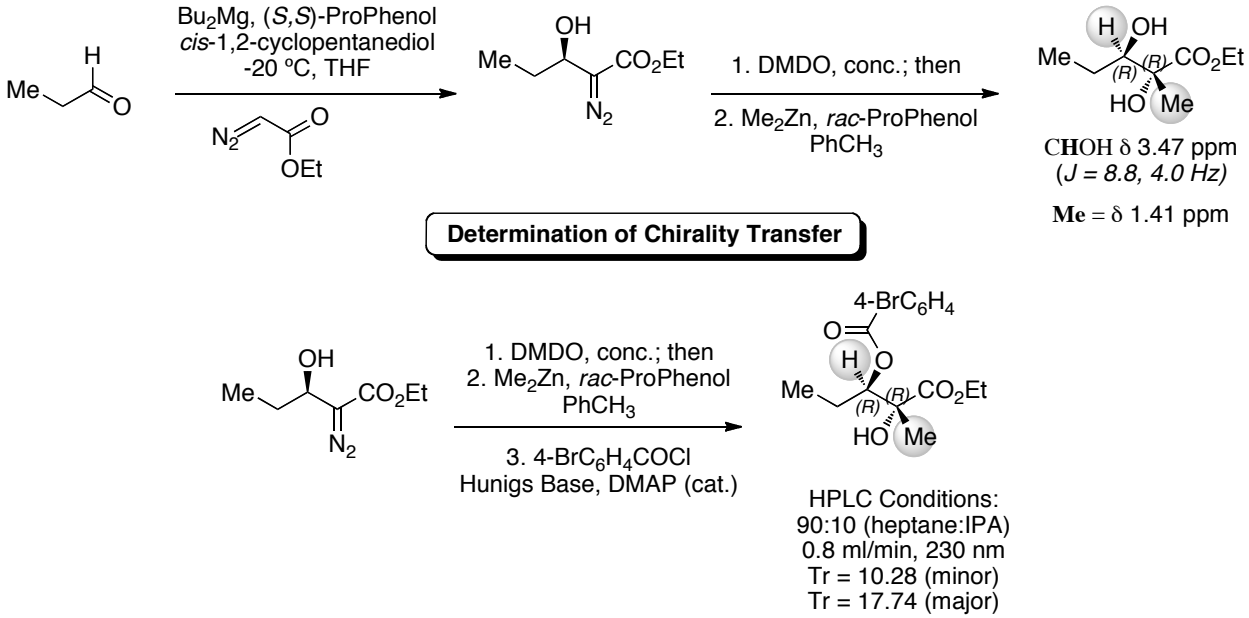
Chemoselective acylation with propionic anhydride: To a solution of the crude diol in CH_2Cl_2 (2.0 mL) was added DMAP (2.3 mg, 0.02 mmol, 0.1 equiv), Et_3N (26 uL, 0.19 mmol, 1 equiv), and propionic anhydride (25 uL, 0.19 mmol, 1 equiv). The reaction was stirred for 2h at room temperature, quenched with saturated aqueous $NaHCO_3$, and stirred for an additional 30 minutes. The reaction mixture was extracted with CH_2Cl_2 (4 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. Silica gel chromatography using a gradient of 10-20% EtOAc/petroleum ether afforded 20 mg (45%) of the desired product as a colorless oil. R_f = 0.4 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ -1.0 (using (*S*,*S*)-ProPhenol, c. 6.0 mg/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (dd, *J* = 10.4, 3.0 Hz, 1H), 4.26 (qd, *J* = 7.3, 1.8 Hz, 2H), 3.33 (s, 1H), 2.41 (q, *J* = 7.6 Hz, 2H), 1.70 (ddq, *J* = 14.4, 10.4, 7.3 Hz, 1H), 1.53-1.44 (m, 1H), 1.35 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR

(100 MHz, $CDCl_3$): δ 77.6, 62.4, 27.6, 22.5, 22.3, 14.1, 10.3, 9.3 ppm; IR (neat): ν_{max} 3506, 2979, 2942, 1740, 1257, 1184, 1085 cm^{-1}; HRMS (ES+) calcd for $C_{11}H_{20}NaO_5$ $[M+Na]^+$ 255.1208 found 255.1199.

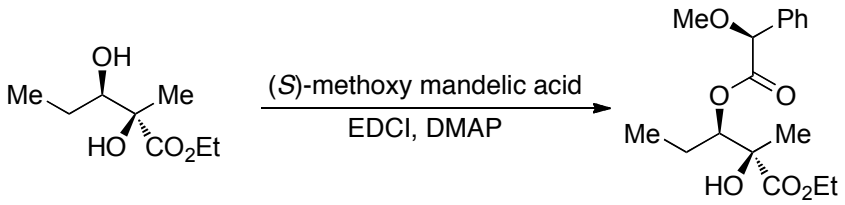
Chemoselective acylation with p-bromobenzoyl chloride: To a solution of the crude diol in CH_2Cl_2 (2.0 mL) was added DMAP (2.3 mg, 0.02 mmol, 0.1 equiv), Et_3N (26 uL, 0.19 mmol, 1 equiv), and 4-bromobenzoyl chloride (50 mg 0.23 mmol, 1.2 equiv – assuming quantitative yield in methyl addition). The reaction was stirred for 8h at room temperature, quenched with saturated aqueous $NaHCO_3$, and stirred for an additional 30 minutes. The reaction mixture was extracted with CH_2Cl_2 (4 x 2 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. Silica gel chromatography using a gradient of 10-20% EtOAc/petroleum followed by preparative thin layer chromatography using 5% ether/benzene ether afforded 22 mg (32% over 3 steps) of the desired product as a colorless oil. R_f = 0.4 (25% EtOAc/hexanes); $[\alpha]_D^{25}$ -5.1 (using (*S*,*S*)-ProPhenol, c. 16.0 mg/mL, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 5.29 (dd, *J* = 10.3, 2.9 Hz, 2H), 4.30-4.22 (m, 2H), 3.42 (s, 1H), 1.89-1.77 (m, 1H), 1.69-1.59 (m, 1H), 1.42 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 165.7, 131.8, 131.3, 128.7, 128.3, 78.9, 75.9, 62.6, 22.6, 22.1, 14.1, 10.4 ppm; IR (neat): ν_{max} 3505, 2976, 1726, 1589, 1269, 1173, 1099, 1011, 755 cm^{-1}; HPLC HPLC R_t = 10.28 (minor) and 17.7 min (major) (Chiracel® AD, λ = 220 nm, isocratic elution: heptane:*i*-PrOH = 90:10, flow rate = 0.8 mL/min); HRMS (ES+) calcd for $C_{15}H_{19}BrNaO_5$ $[M+Na]^+$ 381.0314 (100.0%), 383.0293 (97.3%) found 381.0308 and 383.0287.



Forbes, J. E.; Pattenden, G. J. *Chem. Soc., Perkin Trans. 1* **1991,** 1959.



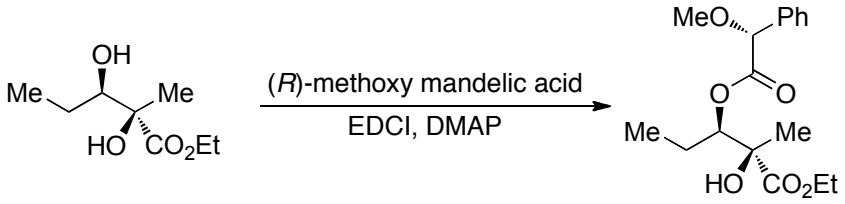
(2*R*,3*R*)-ethyl 2-hydroxy-3-((*S*)-2-methoxy-2-phenylacetoxy)-2-methylpentanoate.



To a solution of (2*R*,3*R*)-ethyl 2,3-dihydroxy-2-methylpentanoate (10 mg, 0.056 mmol) in CH_2Cl_2 was successively added (*S*)-*O*-methoxy-phenylacetic acid (14.4 mg, 0.085 mmol, 1.5 equiv), EDCI (17.4 mg, 0.112 mmol, 2.0 equiv), and DMAP (0.68 mg, 0.0056 mmol, 0.1 equiv). The mixture was stirred at room temperature for 24h, loaded directly onto a preparative thin layer chromatography and developed using 20% EtOAc/hexanes to afford 11 mg (60%) of the desired product as a colorless oil. $R_f = 0.19$ (20% EtOAc/hexanes – cerric ammonium

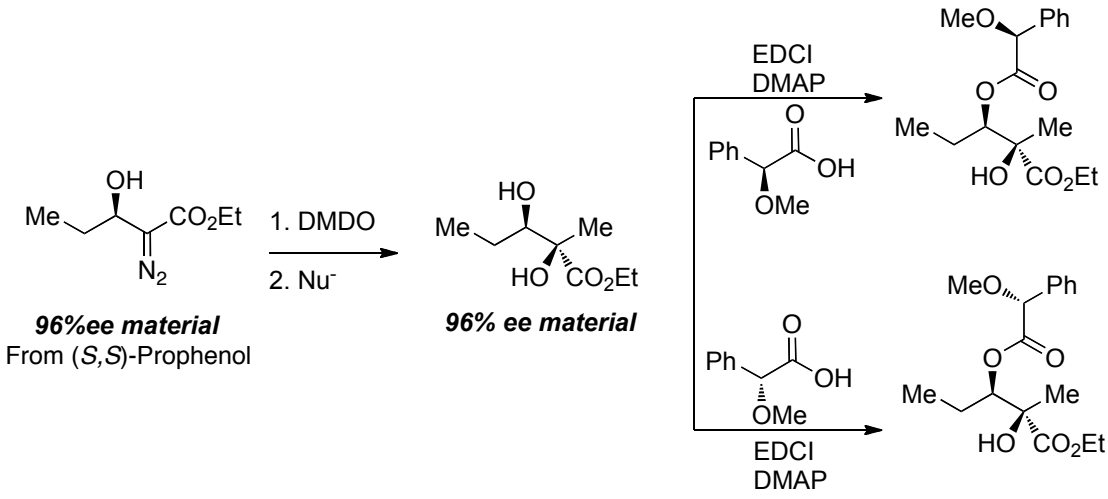
molybdate); $[\alpha]_D^{25}$ +41.4 (c. 6.7 mg/mL, CH_2Cl_2 using (*S*,*S*)-ProPhenol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.38-7.32 (m, 3H), 5.08 (dd, *J* = 10.6, 2.8 Hz, 1H), 4.83 (s, 1H), 4.27-4.21 (m, 2H), 3.42 (s, 3H), 3.30 (s, 1H), 1.57-1.51 (m, 1H), 1.34 (s, 3H), 1.37-1.29 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.43 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 170.7, 136.2, 128.8, 128.6, 127.3, 82.4, 78.7, 75.8, 62.5, 57.2, 29.7, 22.4, 14.1, 9.6 ppm; IR (neat): ν_{max} 3494, 2977, 2935, 1747, 1257, 1174, 1101, 1000 cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{24}NaO_6$ $[M+Na]^+$ 347.1471 found 347.1465.

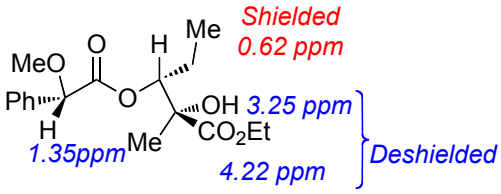
(2*R*,3*R*)-ethyl 2-hydroxy-3-((*R*)-2-methoxy-2-phenylacetoxy)-2-methylpentanoate.

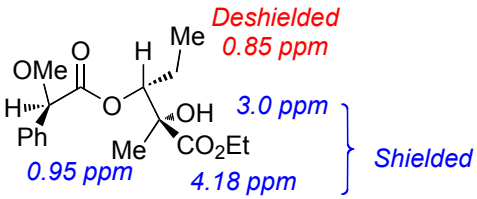


To a solution of (2*R*,3*R*)-ethyl 2,3-dihydroxy-2-methylpentanoate (10 mg, 0.056 mmol) in CH_2Cl_2 was successively added (*R*)-*O*-methoxy-phenylacetic acid (14.4 mg, 0.085 mmol, 1.5 equiv), EDCI (17.4 mg, 0.112 mmol, 2.0 equiv), and DMAP (0.68 mg, 0.0056 mmol, 0.1 equiv). The mixture was stirred at room temperature for 24h, loaded directly onto a preparative thin layer chromatography and developed using 20% EtOAc/hexanes to afford 12 mg (66%) of the desired product as a colorless oil. R_f = 0.23 (20% EtOAc/hexanes – cerric ammonium molybdate); $[\alpha]_D^{25}$ -44.3 (c. 6.0 mg/mL, CH_2Cl_2 using (*S*,*S*)-ProPhenol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.49 (m, 2H), 7.40-7.32 (m, 3H), 5.08 (dd, *J* = 10.8, 2.8 Hz, 2H), 4.83 (s, 1H), 4.19-4.14 (m, 2H), 3.43 (s, 3H), 3.00 (s, 1H), 1.74-1.64 (m, 1H), 1.54-1.42 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 170.6, 136.2, 128.9, 128.7, 127.3, 82.5, 78.9, 75.9, 62.3, 57.3, 29.7, 22.7, 22.1, 14.1, 10.3 ppm; IR (neat): ν_{max} 3505, 2976, 2936, 1737, 1174, 1102 cm^{-1}; HRMS (ES+) calcd for $C_{17}H_{24}NaO_6$ $[M+Na]^+$ 347.1471 found 347.1465.

Determination of Absolute Stereochemistry







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