

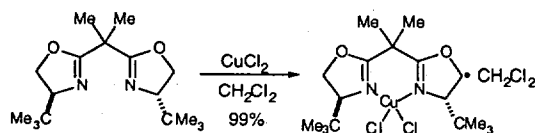
C₂-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Carbonyl-Ene Reactions with Glyoxylate and Pyruvate Esters

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Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego.¹ CuCl₂ and AgSbF₆, from Cerac Chemical, and Cu(OTf)₂, from Aldrich, were stored in an inert atmosphere dry box and used without further purification. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Melting points were measured with a Büchi SMP-20 melting point apparatus equipped with an Omega Model 450 AET thermocouple and are uncorrected. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: [α]_D²⁵ (c g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H NMR spectra were recorded on a Bruker AM-400 (400 MHz) and AM-500 (500 MHz) spectrometers and are reported in ppm from internal tetramethylsilane. Data are reported as: (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration; proton assignments). Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker AM-400 (100 MHz) and AM-500 (125 MHz) spectrometers and are reported in ppm using solvent as the internal standard (CDCl₃ at 77.0 ppm). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Gas chromatography was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split-mode capillary injection system and flame ionization detector using the following chiral columns: J&W Scientific CYCLODEX-B (30 m x 0.25 mm) and J&W Scientific DB-1701 (30 m x 0.25 mm). Medium pressure liquid chromatography (MPLC) was performed using a high capacity pump (Fluid Metering, Inc. Model RPD-OSSY) and Merck LiChroprep Si 60 (column size B) silica gel columns. Preparative HPLC was performed on a Ramin Dynamax system equipped with a SD-200 Solvent Delivery System and a variable wavelength detector (Model UV-C) using a Zorbax Sil (21.2 mm x 25 cm) column. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1050 Series HPLC equipped with a variable wavelength detector using a Chiralcel OD-H column (0.46 cm x 25 cm) from Daicel or a Zorbax Sil column (0.46 x 25 cm). X-ray crystallographic data was collected using a Siemens SMART CCD (charge coupled device) based diffractometer equipped with an LT-2 low-temperature apparatus operating at 213 K.



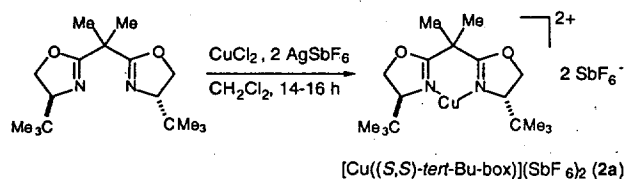
[Cu((*S,S*)-*tert*-Bu-box)]Cl₂•CH₂Cl₂. A round-bottom flask with a magnetic stirrer was charged with (*S,S*)-*tert*-butyl-bis(oxazoline)² (1.472 g, 5.0 mmol, 1.0 equiv) and CuCl₂ (0.672 g, 5.0 mmol, 1.0 equiv). Methylene chloride (20 mL) was added *via* syringe and the reaction stirred 3.5 h, until the insoluble CuCl₂ had solubilized. The

green solution was transferred *via* cannula under nitrogen to a syringe fitted with a 0.45 μ filter, and into a Schlenk flask. The solvent was removed *in vacuo* to deliver 2.52 g (99%) of a light green powder: mp > 180 °C; [α]_D²⁵ -251° (c 1.06, CH₂Cl₂); IR (CH₂Cl₂) 2968, 1655, 1484, 1371, 1239, 1135, 947 cm⁻¹.

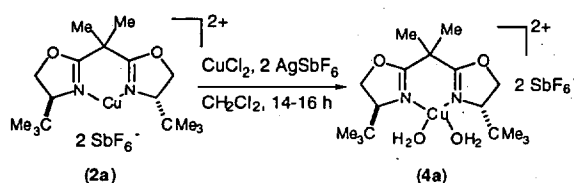
Anal. Calcd for C₁₈H₃₂Cl₄CuN₂O₂: C, 42.08; H, 6.28; N, 5.45. Found: C, 42.21; H, 6.24; N, 5.51.

Supporting Information

S-2



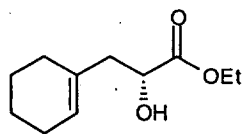
mL). The mixture was stirred 2-3 h in the absence of light to produce a green solution with a white AgCl precipitate. The mixture was filtered through a plug of oven-dried Celite to provide a solution of **2a** as a clear dark green solution. The development of a blue color in room temperature solutions of this catalyst is indicative of the formation of the bis(aquo) complex **4a**.



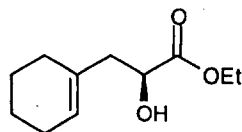
[Cu((S,S)-*tert*-butyl-box)(H₂O)₂](SbF₆)₂ (**4a**). The CH₂Cl₂ solution of **2a** obtained after the Celite filtration step in the preceding experiment was washed through with 4 x 15 mL CH₂Cl₂ (sat. with H₂O) into a flask. The blue solution containing the aquated complex was concentrated slowly *in vacuo* to afford 344 mg (99% yield) of **4a** as an air-stable light blue solid.²

Method A : General Procedure for the Addition of Olefins to Ethyl Glyoxylate Catalyzed by 1 and 2. To an oven-dried, 10-mL round-bottom flask containing a magnetic stirring bar was added, the olefin (0.50 mmol), and ethyl glyoxylate (3-10 equiv). To this mixture was added the catalyst solution **1** or **2** (0.05-0.005 mmol in 1.5 mL CH₂Cl₂) in one portion. After the reaction was complete (1-48 h) the mixture was directed loaded onto a 2 x 6 cm silica gel flash column and eluted with the indicated solvent to provide the title compounds.

Method B: General Procedure for the Addition of Olefins to Ethyl Glyoxylate Catalyzed by 4. To an oven-dried, 10-mL round-bottom flask containing a magnetic stirring bar was added, the olefin (0.50 mmol), ethyl glyoxylate (3-10 equiv) and CH₂Cl₂ (1.5 mL). To this solution was added solid **4** (0.05-0.005 mmol) in one portion. After the reaction was complete (1-48 h) the mixture was directed loaded onto a 2 x 6 cm silica gel flash column and eluted with the indicated solvent to provide the title compounds.



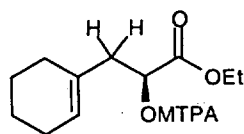
Preparation of (R)-Ethyl 3-(1'-Cyclohexenyl)-2-hydroxypropionate (6). Prepared according to **Method A** (0 °C, 12 h) using methylene cyclohexane (60 µL, 0.50 mmol), ethyl glyoxylate (200 µL, 1.5 mmol) and catalyst **1c** (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 99% yield (98 mg, 0.49 mmol, 87% ee) after flash chromatography with 30% Et₂O/hexanes.



Preparation of (S)-Ethyl 3-(1'-Cyclohexenyl)-2-hydroxypropionate (6). Prepared according to **Method B** (1.5 mL CH₂Cl₂, 0 °C, 1 h) using methylene cyclohexane (60 µL, 0.50 mmol), ethyl glyoxylate (200 µL, 1.5 mmol) and catalyst **4** (0.005 mmol) to provide the pure product as a clear oil in 96% yield (95 mg, 0.48 mmol, 97% ee) after flash chromatography with 30% Et₂O/hexanes. [α]_D²⁵ -5.8° (c 5.3, C₆H₆); IR (film) 3476, 3046,

2930, 2856, 1736, 1666, 1439, 1270, 1207, 1098, 1031 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.48 (br s, 1H, C=CH), 4.32 (dd, *J* = 8.0, 4.6 Hz, 1H, CH(OH)), 4.19 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 2.85 (br s, 1H, OH), 2.39 (dd, *J* = 14.6, 4.6 Hz, 1H, CH₂CH(OH)), 2.24 (dd, *J* = 14.0, 8.2 Hz, 1H, CH₂CH(OH)), 1.98-1.88 (m, 4H, -CH₂-), 1.51-1.48 (m, 4H, -CH₂-), 1.25 (t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 132.9, 125.2, 69.1, 61.3, 43.1, 28.3, 25.1, 22.7, 22.0, 14.1; LRMS (Cl/NH₃) *m/z* 199 (MH)⁺, 216 (M+NH₄)⁺; HRMS (Cl/NH₃) exact mass calcd for (C₁₁H₁₈O₃NH₄)⁺ requires *m/z* 216.1600, found *m/z* 216.1600 Enantiomeric excess was determined by GC with a CYCLODEX-B column (14.0 psi, 120 °C, at *t* = 26.8 min, rate 5 °C/min, final *T* = 130 °C); (*R*) enantiomer *t*_r = 25.0 min; (*S*) enantiomer *t*_r = 26.8 min; 97% ee.

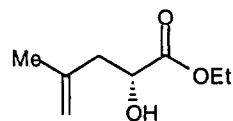
General Procedure for preparation of Mosher MTPA Esters: To a solution of substrate (0.1 mmol) in 2 mL CH₂Cl₂, triethylamine (28 µL, 0.2 mmol), MTPA-Cl (28 µL, 0.14 mmol), and DMAP (catalytic) were added. After stirring overnight at RT, the resulting suspension was filtered through a plug of SiO₂ and concentrated *in vacuo* to afford the product.



(R) MTPA δ 2.56, 2.53
(S) MTPA δ 2.50, 2.47

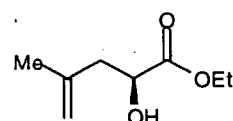
Determination of Absolute Configuration by Mosher MTPA analysis: (R) MTPA Ester: ^1H NMR (500 MHz, CDCl_3) δ 7.58–7.38 (m, 5H, ArH), 5.52 (br s, 1H, C=CH), 5.29 (dd, $J=4.6, 4.5$ Hz, 1H, CH(OMTPA)), 4.21 (q, $J=7.2$ Hz, 2H, OCH_2CH_3), 3.56 (s, 3H, OCH_3), 2.56 (m, 1H, $\text{CH}_2\text{CH(OMTPA)}$), 2.53 (m, 1H,

$\text{CH}_2\text{CH(OMTPA)}$), 1.96 (m, 4H, $-\text{CH}_2-$), 1.62–1.51 (m, 4H, $-\text{CH}_2-$), 1.25 (t, $J=7.2$ Hz, CH_2CH_3); LRMS (CI/NH_3) m/z 415 (MH^+), 432 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{21}\text{H}_{26}\text{O}_5\text{F}_3)^+$ requires m/z 415.1732 found m/z 415.1728. (S) MTPA Ester: ^1H NMR (500 MHz, CDCl_3) δ 7.64–7.34 (m, 5H, ArH), 5.38 (br s, 1H, C=CH), 5.25 (dd, $J=4.6, 4.1$ Hz, 1H, CH(OMTPA)), 4.24 (m, 2H, OCH_2CH_3), 3.64 (s, 3H, OCH_3), 2.50 (m, 1H, $\text{CH}_2\text{CH(OMTPA)}$), 2.47 (m, 1H, $\text{CH}_2\text{CH(OMTPA)}$), 1.89 (m, 4H, $-\text{CH}_2-$), 1.52–1.33 (m, 2H, $-\text{CH}_2-$), 1.25 (t, $J=7.2$ Hz, CH_2CH_3); LRMS (FAB, NaI) m/z 415 (MH^+), 437 ($\text{M}+\text{Na}^+$); HRMS (FAB, NaI) exact mass calcd for $(\text{C}_{21}\text{H}_{26}\text{O}_5\text{F}_3\text{Na})^+$ requires m/z 437.1552, found m/z 437.1541.



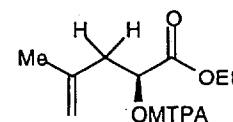
chromatography with 30% Et_2O /hexanes.

Preparation of (R)-Ethyl 2-Hydroxy-5-methyl-5-pentenoate (7): Prepared according to Method A (0 °C, 12 h) using a 1-M solution of isobutylene in dichloroethane (500 μL , 0.50 mmol), ethyl glyoxylate (200 μL , 1.5 mmol) and catalyst 1c (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 92% yield (73 mg, 0.46 mmol, 92% ee) after flash



Preparation of (S)-Ethyl 2-Hydroxy-5-methyl-5-pentenoate (7): Prepared according to Method B (1.5 mL CH_2Cl_2 , 0 °C, 1 h) using a 1-M solution of isobutylene in dichloroethane (500 μL , 0.50 mmol), ethyl glyoxylate (200 μL , 1.5 mmol) and catalyst 4 (0.005 mmol) to provide the pure product as a clear oil in 97% yield (77 mg, 0.48 mmol,

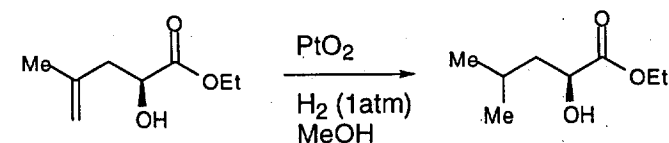
96% ee) after flash chromatography with 30% Et_2O /hexanes. $[\alpha]_D^{25}$ -9.5° (c 5.3, Et_2O); IR (film) 3473, 3077, 2982, 1731, 1649, 1446, 1347, 1202, 1100 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.84 (d, $J=1.4$ Hz, 1H, C=CHH), 4.78 (d, $J=0.8$ Hz, 1H, C=CHH), 4.29 (dd, $J=8.2, 4.3$ Hz, 1H, CH(OH)), 4.21 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 2.80 (br s, 1H, OH), 2.49 (dd, $J=14.1, 4.2$ Hz, 1H, $\text{CH}_2\text{CH(OH)}$), 2.33 (dd, $J=14.1, 8.3$ Hz, 1H, $\text{CH}_2\text{CH(OH)}$), 1.76 (s, 3H, C=CCH₃), 1.27 (t, $J=7.1$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 141.0, 113.9, 69.1, 61.6, 42.7, 22.4, 14.2; LRMS (CI/NH_3) m/z 159 (MH^+), 176 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for $(\text{C}_8\text{H}_{14}\text{O}_3+\text{NH}_4)^+$ requires m/z 176.1287, found m/z 176.1291. Enantiomeric excess was determined by GC with a CYCLODEX-B column (13.5 psi, 100 °C); (R) enantiomer $t_r = 21.3$ min; (S) enantiomer $t_r = 21.5$ min; 96% ee.



(R) MTPA δ 2.64
(S) MTPA δ 2.58

Determination of Absolute Configuration by Mosher MTPA analysis:

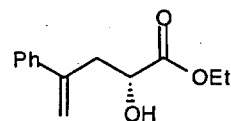
(R) MTPA Ester: ^1H NMR (500 MHz, CDCl_3) δ 7.58 (m, 2H, ArH), 7.40 (m, 3H, ArH), 5.35 (dd, $J=5.0, 3.4$ Hz, 1H, CH(OMTPA)), 4.87 (s, 1H, C=CHH), 4.80 (s, 1H, C=CHH), 4.21 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 3.55 (s, 3H, OCH_3), 2.64 (m, 2H, $\text{CH}_2\text{CH(OMTPA)}$), 1.76 (s, 3H, C=CCH₃), 1.26 (t, $J=7.1$ Hz, CH_2CH_3); LRMS (CI/NH_3) 392 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{23}\text{H}_{23}\text{O}_5\text{F}_3+\text{NH}_4)^+$ requires m/z 392.1685, found m/z 392.1697. (R) MTPA Ester: ^1H NMR (500 MHz, CDCl_3) δ 7.62 (m, 2H, ArH), 7.40 (m, 3H, ArH), 5.33 (dd, $J=5.5, 2.8$ Hz, 1H, CH(OMTPA)), 4.73 (s, 1H, C=CHH), 4.66 (s, 1H, C=CHH), 4.25 (m, 2H, OCH_2CH_3), 3.64 (s, 3H, OCH_3), 2.58 (m, 2H, $\text{CH}_2\text{CH(OMTPA)}$), 1.64 (s, 3H, C=CCH₃), 1.29 (t, $J=7.1$ Hz, CH_2CH_3); LRMS (CI/NH_3) 392 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{23}\text{H}_{23}\text{O}_5\text{F}_3+\text{NH}_4)^+$ requires m/z 392.1685, found m/z 392.1697.



Determination of Absolute Configuration (S)-Ethyl 2-Hydroxy-4-methyl-4-pentenoate (6) by Correlation with (S)-Leucinic Acid Ethyl Ester: To a solution of (S)-ethyl 2-hydroxy-4-methyl-4-pentenoate (150 mg, 0.95 mmol, 97% ee) in 4 mL EtOH at RT, Adam's catalyst

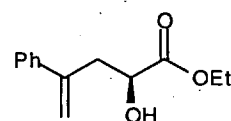
(PtO_2) (22 mg, 0.095 mmol) was added. The flask was purged with H_2 and allowed stir under 1 atm H_2 for 16 h. The reaction was then diluted with Et_2O and eluted through a short plug of SiO_2 . The eluent was concentrated *in vacuo* and purified by flash chromatography with 30% Et_2O /hexanes to afford (S)-leucinic acid ethyl ester as a volatile liquid (115 mg, 72% yield). The spectral data for this material was identical to that in the literature and the material exhibited the identical optical rotation of the reported (S) enantiomer.³ $[\alpha]_D^{25}$ -17.5° (c 1.2, Et_2O); $[\alpha]_D^{25}$ (Lit.) -18.1° (c 1.2, Et_2O); IR (film) 3480, 2958, 2871, 1733, 1470, 1369, 1268,

1210, 1143 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.84 (d, $J = 1.4$ Hz, 1H, C=CHH), 4.78 (d, $J = 0.8$ Hz, 1H, C=CHH), 4.29 (dd, $J = 8.2, 4.3$ Hz, 1H, CH(OH)), 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 2.80 (br s, 1H, OH), 2.49 (dd, $J = 14.1, 4.2$ Hz, 1H, $\text{CH}_2\text{CH}(\text{OH})$), 2.33 (dd, $J = 14.1, 8.3$ Hz, 1H, $\text{CH}_2\text{CH}(\text{OH})$), 1.76 (s, 3H, C=CCH₃), 1.27 (t, $J = 7.1$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.7, 141.0, 113.9, 69.1, 61.6, 42.7, 22.4, 14.2; LRMS (CI/NH_3) m/z 178 ($\text{M}+\text{NH}_4$)⁺; HRMS (CI/NH_3) exact mass calcd for ($\text{C}_8\text{H}_{16}\text{O}_3+\text{NH}_4$)⁺ requires m/z 178.1443, found m/z 178.1448.

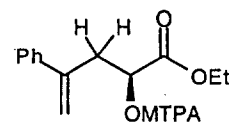


$\text{Et}_2\text{O}/\text{hexanes}$.

Preparation of (S)-Ethyl 2-Hydroxy-5-phenyl-5-pentenoate (8): Prepared according to Method A (0 °C, 12 h) using α -methyl styrene (65 μL , 0.50 mmol), ethyl glyoxylate (200 μL , 1.5 mmol) and catalyst 1c (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 99% yield (109 mg, 0.49 mmol, 89% ee) after flash chromatography with 30%



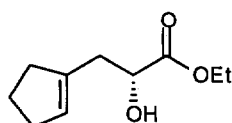
Preparation of (S)-Ethyl 2-Hydroxy-5-phenyl-5-pentenoate (8). Prepared according to Method B (1.5 mL CH_2Cl_2 , 0 °C, 1 h) using α -methyl styrene (65 μL , 0.50 mmol), ethyl glyoxylate (200 μL , 1.5 mmol) and catalyst 4 (0.05 mmol) to provide the pure product as a clear oil in 97% yield (107 mg, 0.48 mmol, 93% ee) after flash chromatography with 30% $\text{Et}_2\text{O}/\text{hexanes}$. $[\alpha]_D^{25}$ -1.8° (c 7.5, C_6H_6); IR (film) 3476, 3083, 2982, 2906, 1736, 1445, 1210, 1094, 1029, 905 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.31 (m, 5H, ArH), 5.40 (s, 1H, C=CHH), 5.22 (s, 1H, C=CHH), 4.28 (dd, $J = 7.6, 4.7$ Hz, 1H, CH(OH)), 4.06 (m, 2H, OCH_2CH_3), 3.07 (dd, $J = 14.5, 4.5$ Hz, 1H, $-\text{CH}_2-$), 3.01 (br s, 1H, OH), 2.86 (dd, $J = 14.5, 7.6$ Hz, 1H, $-\text{CH}_2-$), 1.22 (t, $J = 7.1$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 143.5, 140.2, 128.1, 127.6, 126.3, 116.02, 69.1, 61.4, 40.4, 13.96; LRMS (CI/NH_3) m/z 221 (MH)⁺, 238 ($\text{M}+\text{NH}_4$)⁺; HRMS (CI/NH_3) exact mass calcd for ($\text{C}_{13}\text{H}_{16}\text{O}_3\text{NH}_4$)⁺ requires m/z 238.1443, found m/z 238.1443. Enantiomeric excess was determined by GC with a CYCLODEX-B column (12.0 psi, at $t=80$ min rate = 4.0 psi/min, final 22 psi, 120 °C); (R) enantiomer $t_r = 84.7$ min; (S) enantiomer $t_r = 85.2$ min; 93% ee.



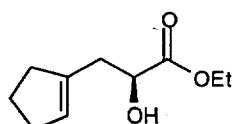
(R) MTPA δ 3.25, 3.01
(S) MTPA δ 3.20, 2.96

Determination of Absolute Configuration by Mosher MTPA analysis:

(R) MTPA Ester : ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.25 (m, 10 H, ArH), 5.40 (s, 1H, C=CHH), 5.23 (dd, $J = 7.1, 3.7$ Hz, 1H, CH(OMTPA)), 5.22 (s, 1H, C=CHH), 4.16 (m, 2H, OCH_2CH_3), 3.49 (s, 3H, OCH_3), 3.25 (dd, $J = 11.4, 3.5$ Hz, 1H, $-\text{CH}_2-$), 3.01 (dd, $J = 9.8, 5.2$ Hz, 1H, $-\text{CH}_2-$), 1.22 (t, $J = 7.1$ Hz, CH_2CH_3); LRMS (CI/NH_3) 436 ($\text{M}+\text{NH}_4$)⁺; HRMS (CI/NH_3) exact mass calcd for ($\text{C}_{23}\text{H}_{23}\text{O}_5\text{F}_3\text{NH}_4$)⁺ requires m/z 436.1498, found m/z 436.1511 (S) MTPA Ester : ^1H NMR (500 MHz, CDCl_3) δ 7.43–7.25 (m, 10 H, ArH), 5.23 (s, 1H, C=CHH), 5.20 (dd, $J = 5.4, 3.9$ Hz, 1H, CH(OMTPA)), 5.02 (s, 1H, C=CHH), 4.16 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.59 (s, 3H, OCH_3), 3.20 (dd, $J = 11.0, 3.8$ Hz, 1H, $-\text{CH}_2-$), 2.96 (dd, $J = 9.4, 5.6$ Hz, 1H, $-\text{CH}_2-$), 1.26 (t, $J = 7.1$ Hz, CH_2CH_3); LRMS (FAB, NaI) 437 (MH)⁺, 459 ($\text{M}+\text{Na}$)⁺; HRMS (FAB, NaI) exact mass calcd for ($\text{C}_{23}\text{H}_{23}\text{O}_5\text{F}_3\text{Na}$)⁺ requires m/z 459.1395, found m/z 459.1413.



Preparation of (R)-Ethyl 3-(1' Cyclopentenyl)-2-hydroxypropionate (9). Prepared according to Method A (0 °C, 12 h) using methylene cyclopentane (52 μL , 0.50 mmol), ethyl glyoxylate (200 μL , 1.5 mmol) and catalyst 1c (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 97% yield (89 mg, 0.48 mmol, 76% ee) after flash chromatography with 30% $\text{Et}_2\text{O}/\text{hexanes}$.



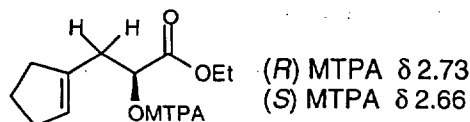
Preparation of (S)-Ethyl 3-(1' Cyclopentenyl)-2-hydroxypropionate (9). Prepared according to Method B (1.5 mL CH_2Cl_2 , 0 °C, 1 h) using methylenecyclopentane (52 μL , 0.50 mmol), ethyl glyoxylate (200 μL , 1.5 mmol) and catalyst 4 (0.05 mmol) to provide the pure product as a clear oil in 95% yield (87 mg, 0.47 mmol, 96% ee) after flash chromatography with 30% $\text{Et}_2\text{O}/\text{hexanes}$. $[\alpha]_D^{25}$ -6.9° (c 6.1, C_6H_6); IR (film) 3470, 3044, 29.49,

2847, 1732, 1444, 1209, 1096, 1030 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.48 (br t, $J = 1.1$, 1H, C=CH), 4.28 (dd, $J = 7.5, 4.4$ Hz, 1H, CH(OH)), 4.21 (q, $J = 5.2$ Hz, 2H, OCH_2CH_3), 2.70 (br s, 1H, OH), 2.58 (dd, $J = 15.7, 3.1$ Hz, 1H, $\text{CH}_2\text{CH}(\text{OH})$), 2.47 (dd, $J = 15.4, 7.5$ Hz, 1H, $\text{CH}_2\text{CH}(\text{OH})$), 2.31–2.21 (br m, 4H, $-\text{CH}_2-$), 1.85 (m, 2H, $-\text{CH}_2-$), 1.27 (t, $J = 7.2$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 139.3, 127.8, 69.4, 36.2, 35.2, 23.5, 14.2; LRMS (CI/NH_3) m/z 185 (MH)⁺, 202 ($\text{M}+\text{NH}_4$)⁺; HRMS (CI/NH_3) exact mass calcd for

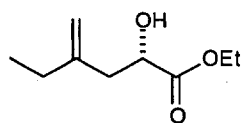
Supporting Information

S-5

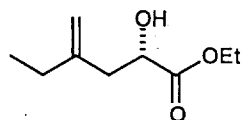
(C₁₀H₁₆O₃NH₄)⁺ requires m/z 202.1443, found m/z 202.1438. Enantiomeric excess was determined by GC with a CYCLODEX-B column (13.5 psi, 110 °C) (*R*) enantiomer t_r = 21.3 min; (*S*) enantiomer t_r = 21.5 min; 96% ee.

**Determination of Absolute Configuration by Mosher MTPA analysis:**

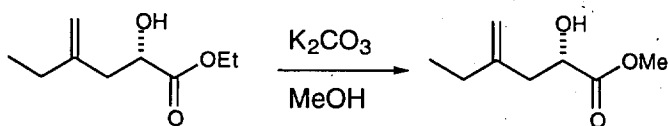
(*R*) MTPA Ester: ¹H NMR (500 MHz, CDCl₃) δ 7.57 (m, 2H, ArH), 7.41 (m, 2H, ArH), 5.48 (br s, 1H, C=CH), 5.35 (dd, J = 4.7, 4.2 Hz, 1H, CH(OMTPA)), 4.20 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.54 (s, 3H, OCH₃), 2.73 (m, 2H, -CH₂-), 2.29-2.22 (br m, 4H, -CH₂-), 1.86 (m, 2H, -CH₂-), 1.27 (t, J = 7.2 Hz, CH₂CH₃); LRMS (CI/NH₃) m/z 418 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₂₀H₂₃O₅F₃NH₄)⁺ requires m/z 418.1841, found m/z 418.1838. (*R*) MTPA Ester: ¹H NMR (500 MHz, CDCl₃) δ 7.63 (m, 2H, ArH), 7.39 (m, 2H, ArH), 5.32 (br s, 1H, C=CH), 5.29 (dd, J = 4.4, 4.2 Hz, 1H, CH(OMTPA)), 4.23 (m, 2H, OCH₂CH₃), 3.65 (s, 3H, OCH₃), 2.66 (m, 2H, -CH₂-), 2.17-2.09 (br m, 4H, -CH₂-), 1.77-1.72 (m, 2H, -CH₂-), 1.28 (t, J = 7.2 Hz, CH₂CH₃); LRMS (FAB, NaI) m/z 401 (MH)⁺, 423 (M+Na)⁺; HRMS (FAB, NaI) exact mass calcd for (C₂₀H₂₃O₅F₃Na)⁺ requires m/z 423.1395, found m/z 423.1400.

**Preparation of (2S)-Ethyl 5-ethyl-2-hydroxy-5-pentenoate (10).**

Prepared according to Method B (1.5 mL CH₂Cl₂, 25 °C, 12 h) using 2-methyl-2-butene (87 μ L, 0.50 mmol), ethyl glyoxylate (200 μ L, 1.5 mmol) and catalyst 4 (0.005 mmol) to provide the product as a clear oil in 78% yield (67 mg, 0.39 mmol, 84% ee, 55:45 regioselectivity, 15:85 *E/Z* ratio.) after flash chromatography with 10-20% EtOAc/hexanes.

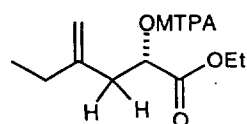
**Preparation of (2S)-Ethyl 5-ethyl-2-hydroxy-5-pentenoate (10) and (E)/(Z) Ethyl 5-methyl-2-hydroxy-5-pentenoate:**

Prepared according to Method A (25 °C, 12 h) using 2-methyl-2-butene (87 μ L, 0.50 mmol), ethyl glyoxylate (200 μ L, 1.5 mmol) and catalyst *ent*-1c (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 91% yield (77 mg, 0.45 mmol, 90% ee, 67:33 regioselectivity) after flash chromatography with 10-20% EtOAc/hexanes. $[\alpha]_D^{25}$ -12.1° (c 1.7, CH₂Cl₂); IR (film) 3482, 2968, 1734, 1647, 1204, 1100 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.89 (s, 1H, C=CHH), 4.85 (s, 1H, C=CHH), 4.30 (m, 1H, CHOH), 4.23 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 2.70 (d, J = 5.8, 1H, CHOH), 2.57 (dd, J = 4.0, 14.3 Hz, 1H, CHH(CHOH)), 2.37 (dd, J = 8.3, 14.3 Hz, 1H, CHH(CHOH)), 2.08 (m, 2H, CH₂CH₃), 1.30 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.05 (t, J = 7.4 Hz, 3H, CH₂CH₃); Additional resonances for (*E*) / (*Z*) ethyl 4-methyl-2-hydroxy-4-pentenoate: 5.34 (m, 1H, C=CH), 1.66 (s, 3H, CH₃), 1.60 (d, J = 6.6 Hz, CHCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 146.5, 111.6, 69.3, 61.7, 41.4, 28.7, 14.3, 12.2; Additional resonances for (*E*) / (*Z*) ethyl 4-methyl-2-hydroxy-4-pentenoate: 170.7, 175.2, 130.8, 123.2, 52.4, 46.5, 44.7, 25.1, 15.7, 13.6; LRMS (CI/NH₃) 173 (M+H)⁺, 190 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₉H₁₆O₃+NH₄)⁺ requires m/z 190.1443 found m/z 190.1438. Regioisomers can be separated by Preparative HPLC using a Zorbax Sil (21.2 mm x 25 cm) column (1% iPrOH:Hexanes, 10 ml/min): T_r (*Z*) ethyl 4-methyl-2-hydroxy-4-pentenoate = 19.0 min (shoulder), T_r (Ethyl 4-ethyl-2-hydroxy-4-pentenoate = 20.0 min), T_r (*E*) Ethyl 4-methyl-2-hydroxy-4-pentenoate = 23.0 min. Regiomer and diastereomeric excess was determined by GC with a DB-1701 column (10 psi, 100 °C); T_r (Ethyl 4-ethyl-2-hydroxy-4-pentenoate = 10.9 min), T_r (*Z*) Ethyl 4-methyl-2-hydroxy-4-pentenoate = 11.6 min, T_r (*E*) Ethyl 4-methyl-2-hydroxy-4-pentenoate = 12.1 min; 67 : 33 regioselectivity, 18 : 82 *E/Z* ratio. Enantiomeric excess of pure ethyl 4-ethyl-2-hydroxy-4-pentenoate was determined by GC with a CYCLODEX-B column (10 psi, 80 °C, at t = 25 min, rate 2.5 °C, final T = 100 °C); (*R*) enantiomer t_r = 34.2 min; (*S*) enantiomer t_r = 34.5 min; 90% ee.

**Determination of Olefin Isomers by Conversion to the Methyl Ester:**

To a solution of (2S)-Ethyl 4-ethyl-2-hydroxy-4-pentenoate and (*E*) / (*Z*) ethyl 4-methyl-2-hydroxy-4-pentenoate (50 mg, 0.29 mmol) in MeOH (4 mL) at RT, K₂CO₃ (59 mg, 0.44 mmol) was added.

After 2 h the reaction was diluted with EtOAc and poured into pH 7 buffer and extracted. The organics were washed with brine and dried with Na₂CO₃. Concentration *in vacuo* followed by purification by flash chromatography with 30% Et₂O/hexanes afforded 30 mg (65% yield) of (2S)-methyl 4-ethyl-2-hydroxy-4-pentenoate and (*E*) / (*Z*) methyl 4-methyl-2-hydroxy-4-pentenoate as a colorless oil. The spectral data for this material were identical to that in the literature.

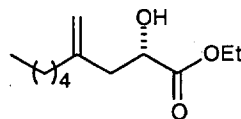


(*R*) MTPA δ 2.69, 2.60
(*S*) MTPA δ 2.62, 2.54

Determination of Absolute Configuration by Mosher MTPA

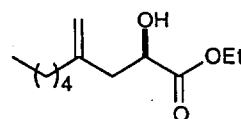
analysis: (*R*) MTPA Ester: ^1H NMR (500 MHz, CDCl_3) δ 7.58 (m, 2H, PhH), 7.39 (m, 3H, PhH), 5.33 (dd, J = 4.0, 9.5 Hz, 1H, CHOMTPA), 4.88 (s, 1H, C=CHH), 4.84 (s, 1H, C=CHH), 4.21

(q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.54 (s, 3H, OCH_3), 2.69 (dd, J = 3.7, 14.8 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 2.60 (dd, J = 9.6, 14.9 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 2.05 (m, 2H, CH_2CH_3), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.02 (t, J = 7.4 Hz, 3H, CH_2CH_3); LRMS (CI) 406 ($\text{M}+\text{NH}_3$) $^+$ (*S*) MTPA Ester: ^1H NMR (500 MHz, CDCl_3) δ 7.61 (m, 2H, PhH), 7.39 (m, 3H, PhH), 5.31 (dd, J = 4.2, 9.1 Hz, 1H, CHOMTPA), 4.71 (s, 1H, C=CHH), 4.67 (s, 1H, C=CHH), 4.23 (m, 2H, OCH_2CH_3), 3.64 (s, 3H, OCH_3), 2.62 (dd, J = 4.1, 14.8 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 2.54 (dd, J = 9.1, 14.7 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 1.94 (m, 2H, CH_2CH_3), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.93 (t, J = 7.4 Hz, 3H, CH_2CH_3); LRMS (CI) 406 ($\text{M}+\text{NH}_3$) $^+$



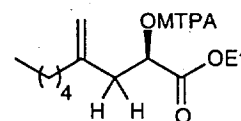
Preparation of (2*S*)-Ethyl 5-pentyl-2-hydroxy-5-penteneoate (11). Prepared according to Method B (1.5 mL CH_2Cl_2 , 25 $^\circ\text{C}$, 12 h) using 2-methyl-1-heptene (78 μL , 0.50 mmol), ethyl glyoxylate (250 μL , 1.9 mmol) and catalyst 4 (0.005 mmol) to provide the pure product as a clear oil in 89% yield (95 mg, 0.45 mmol, 96% ee, 74:26 regioselectivity)

after flash chromatography with 10-20% EtOAc/hexanes.



Preparation of (2*R*)-Ethyl 5-pentyl-2-hydroxy-5-penteneoate (11). Prepared according to Method A (25 $^\circ\text{C}$, 12 h) using 2-methyl-1-heptene (78 μL , 0.50 mmol), ethyl glyoxylate (250 μL , 1.9 mmol) and catalyst 1c (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 81% yield (87 mg, 0.40 mmol, 91% ee, 90:10 regioselectivity) af-

ter flash chromatography with 10-20% EtOAc/hexanes. $[\alpha]_D^{25} +7.1^\circ$ (c 0.7, CHCl_3); IR (film) 3474, 3080, 2935, 2873, 1731, 1648, 1447, 1378, 1201, 1106, 1033, 895, 728 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.88 (s, 1H, C=CHH), 4.85 (s, 1H, C=CHH), 4.30 (dd, J = 4.2, 8.4 Hz, 1H, CHOH), 4.24 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.72 (br s, 1H, CHOH), 2.54 (dd, J = 4.1, 14.3 Hz, 1H, $\text{CH}_2(\text{CHOH})$), 2.34 (dd, J = 8.4, 14.3 Hz, 1H, $\text{CH}_2(\text{CHOH})$), 2.05 (t, J = 7.7 Hz, 2H, $\text{CH}_2\text{C}=\text{CH}_2$), 1.48-1.25 (m, 9H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, OCH_2CH_3), 0.89 (t, J = 6.9 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 145.1, 112.7, 69.3, 61.7, 41.1, 35.9, 31.6, 27.4, 22.6, 14.3, 14.1; LRMS (CI/ NH_3) 215 (MH) $^+$, 232 ($\text{M}+\text{NH}_4$) $^+$; HRMS (CI/ NH_3) exact mass calcd for ($\text{C}_{12}\text{H}_{22}\text{O}_3+\text{NH}_4$) $^+$ requires m/z 232.1913, found m/z 232.1915. Enantiomeric excess and regioisomer ratios were determined by GC analysis of the (*S*) MTPA esters with a DB-1701 column (170 $^\circ\text{C}$, 20 psi); (*R*) enantiomer t_r = 34.4 min; (*S*) enantiomer t_r = 38.8 min; other regioisomers: t_r = 30.5, 35.0, 37.4, 41.9 min.

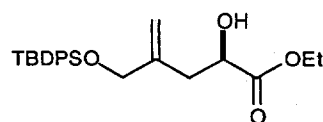


(*R*) MTPA δ 2.60, 2.52
(*S*) MTPA δ 2.67, 2.58

Determination of Absolute Configuration by Mosher MTPA

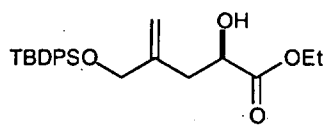
analysis: (*R*) MTPA Ester: ^1H NMR (400 MHz, CDCl_3) δ 7.63-7.37 (m, 5H, ArH), 5.30 (dd, J = 4.3, 9.0 Hz, 1H, CHOMTPA), 4.72 (s, 1H, C=CHH), 4.68 (s, 1H, C=CHH), 4.24 (q, J = 7.1 Hz, 2H,

OCH_2CH_3), 3.64 (s, 3H, OCH_3), 2.60 (dd, J = 4.0, 14.9 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 2.52 (dd, J = 9.0, 14.8 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 1.91 (t, J = 7.8 Hz, 2H, $\text{CH}_2\text{C}=\text{CH}_2$), 1.44-1.15 (m, 9H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, OCH_2CH_3), 0.87 (t, J = 7.2 Hz, 3H, CH_2CH_3); LRMS (FAB) 431 (MH) $^+$, 453 ($\text{M}+\text{Na}$) $^+$. (*S*) MTPA Ester: ^1H NMR (400 MHz, CDCl_3) δ 7.59-7.34 (m, 5H, ArH), 5.33 (dd, J = 4.0, 9.5 Hz, 1H, CHOMTPA), 4.88 (s, 1H, C=CHH), 4.83 (s, 1H, C=CHH), 4.20 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.55 (s, 1H, OCH_3), 2.67 (dd, J = 3.9, 15.0 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 2.58 (dd, J = 9.4, 14.9 Hz, 1H, $\text{CH}_2(\text{CHOMTPA})$), 2.02 (t, J = 7.6 Hz, 2H, $\text{CH}_2\text{C}=\text{CH}_2$), 1.44-1.21 (m, 9H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, OCH_2CH_3), 0.89 (t, J = 7.2 Hz, 3H, CH_2CH_3); LRMS (FAB) 431 (MH) $^+$, 453 ($\text{M}+\text{Na}$) $^+$.

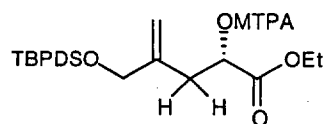


Preparation of (2*R*)-Ethyl 5-*t*-butyldiphenylsilyloxymethyl-2-hydroxy-5-pentenoate (12). Prepared according to Method A (25 $^\circ\text{C}$, 12 h) using 2-*t*-butyldiphenylsilyloxymethyl-1-propene (157 μL , 0.50 mmol), ethyl glyoxylate (250 μL , 1.9 mmol) and catalyst 1c (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure

product as a clear oil in 85% yield (175 mg, 0.42 mmol, 91% ee) after flash chromatography with 10-20% EtOAc/hexanes.



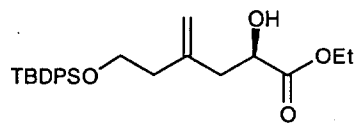
Preparation of (2S)-Ethyl 5-t-butyldiphenylsiloxyethyl-2-hydroxy-5-pentenoate (12). Prepared according to **Method B** (1.5 mL CH₂Cl₂, 25 °C, 12 h) using 2-t-butyldiphenylsiloxyethyl-1-propene (157 μ L, 0.50 mmol), ethyl glyoxylate (250 μ L, 1.9 mmol) and catalyst **4** (0.005 mmol) to provide the pure product as a clear oil in 72% yield (148 mg, 0.36 mmol, 96% ee) after flash chromatography with 10-20% EtOAc/hexanes. $[\alpha]_D^{25} +1.4^\circ$ (c 4.6, CHCl₃); IR (film) 3501, 3060, 2925, 2862, 1731, 1477, 1431, 1270, 1202, 1104, 1031, 905, 823, 741, 702, 615 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.26 (m, 10H, ArH), 5.26 (s, 1H, C=CHH), 5.03 (s, 1H, C=CHH), 4.32 (br ddd, J = 3.8, 5.8, 7.9 Hz, 1H, CHOH), 4.22 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 4.18 (s, 2H, TBDPSOCH₂), 3.09 (br d, J = 5.9, 1H, CHOH), 2.63 (dd, J = 3.7, 14.4 Hz, 1H, CH₂(CHOH)), 2.42 (dd, J = 7.9, 14.4 Hz, 1H, CH₂(CHOH)), 1.28 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.09 (s, 9H, (CH₃)₃C); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 143.4, 135.6, 133.3, 129.8, 127.7, 113.5, 69.8, 66.8, 61.6, 38.3, 26.8, 19.2, 14.2; LRMS (FAB) 413 (MH)⁺, 435 (M+Na)⁺; HRMS (FAB) exact mass calcd for (C₂₄H₃₂O₄Si+Na)⁺ requires m/z 435.1968, found m/z 435.1978. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (1.5% ¹PrOH:Hexanes, 1.0 ml/min); (S) enantiomer t_r = 7.38 min; (R) enantiomer t_r = 9.12 min; 94% ee.



(R) MTPA δ 2.76, 2.60
(S) MTPA δ 2.70, 2.57

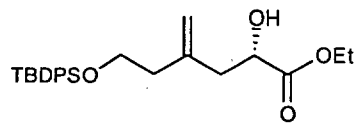
Determination of Absolute Configuration by Mosher

MTPA analysis: (R) MTPA Ester : ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.35 (m, 15H, ArH), 5.36 (dd, J = 3.8, 9.7 Hz, 1H, CHOMTPA), 5.23 (s, 1H, C=CH₂), 4.97 (s, 1H, C=CH₂), 4.20 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 4.12 (s, 2H, TBDPSOCH₂), 3.50 (s, 3H, OCH₃), 2.76 (dd, J = 3.5, 14.9 Hz, 1H, CH₂CHOMTPA), 2.60 (dd, J = 9.7, 5.2 Hz, 1H, CH₂CHOMTPA), 1.24 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.05 (s, 9H, (CH₃)₃C); LRMS (FAB) 629 (MH)⁺, 651 (M+Na)⁺. (S) MTPA Ester : ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.26 (m, 15H, ArH), 5.35 (dd, J = 4.0, 9.2 Hz, 1H, CHOMTPA), 5.04 (s, 1H, C=CH₂), 4.79 (s, 1H, C=CH₂), 4.23 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 4.02 (q, J = 13.8, 2H, TBDPSOCH₂), 3.61 (s, 3H, OCH₃), 2.70 (dd, J = 3.8, 14.8 Hz, 1H, CH₂CHOMTPA), 2.57 (dd, J = 9.2, 14.8 Hz, 1H, CH₂CHOMTPA), 1.27 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.07 (s, 9H, (CH₃)₃C); LRMS (FAB) 629, (MH)⁺, 651 (M+Na)⁺.



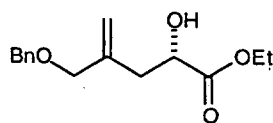
Preparation of (2R)-Ethyl 5-t-butyldiphenylsiloxyethyl-2-hydroxy-5-pentenoate (13). Prepared according to **Method A** (25 °C, 12 h) using 3-t-butyldiphenylsiloxyethyl-1-butene (157 μ L, 0.50 mmol), ethyl glyoxylate (200 μ L, 1.5 mmol) and catalyst **1c** (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure

product as a clear oil in 75% yield (145 mg, 0.37 mmol, 48% ee) after flash chromatography with 10-20% EtOAc/hexanes.

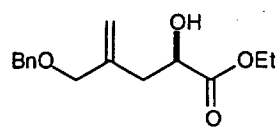


Preparation of (2S)-Ethyl 5-t-butyldiphenylsiloxyethyl-2-hydroxy-5-pentenoate (13). Prepared according to **Method B** (25 °C, 12 h) using 4-t-butyldiphenylsiloxy-2-methyl-1-butene (157 μ L, 0.50 mmol), ethyl glyoxylate (200 μ L, 1.5 mmol) and catalyst **2** (0.005 mmol) to provide the pure product as a

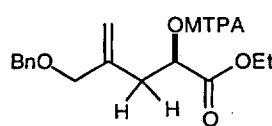
clear oil in 71% yield (138 mg, 0.35 mmol, 55% ee) after flash chromatography with 10-20% EtOAc/hexanes. $[\alpha]_D^{25} -1.6^\circ$ (c 2.1, CH₂Cl₂); IR (film) 3475, 3071, 3050, 2958, 2932, 2857, 1732, 1646, 1428, 1263, 1208, 1111 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.37 (m, 10H, ArH), 4.92 (s, 1H, C=CHH), 4.90 (s, 1H, C=CHH), 4.23 (m, 3H, OCH₂CH₃, CHOH), 3.78 (t, J = 6.7 Hz, 2H, TBDPSOCH₂), 2.75 (br s, 1H, CHOH), 2.63 (dd, J = 3.9, 14.4 Hz, 1H, CH₂(CHOH)), 2.34 (m, 2H, CH₂(CHOH), CHOH), 1.29 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.05 (s, 9H, (CH₃)₃C); ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 148.7, 142.1, 138.9, 135.6, 133.8, 129.7, 127.7, 69.4, 61.6, 41.3, 38.9, 26.9, 19.2, 14.2; LRMS (FAB) 427 (MH)⁺, 444 (M+Na)⁺; HRMS (FAB) exact mass calcd for (C₂₅H₃₄O₄Si+Na)⁺ requires m/z 444.2552 found m/z 444.2570. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (1.5% ¹PrOH:Hexanes, 1 ml/min); (R) enantiomer t_r = 8.0 min; (S) enantiomer t_r = 9.7 min; 55% ee). Absolute stereochemistry determined by analogy.



Preparation of (2S)-Ethyl 5-benzoyloxymethyl-2-hydroxy-5-pentenoate (14). Prepared according to **Method B** (1.5 mL CH₂Cl₂, 25 °C, 12 h) using 2-benzoyloxymethyl-1-propene (87 μ L, 0.50 mmol), ethyl glyoxylate (250 μ L, 1.9 mmol) and catalyst **4** (0.01 mmol) to provide the pure product as a clear oil in 62% yield (82 mg, 0.31 mmol, 98% ee) after flash chromatography with 10-20% EtOAc/hexanes.

**Preparation of (2R)-Ethyl 5-benzyloxymethyl-2-hydroxy-5-pentenoate (14).**

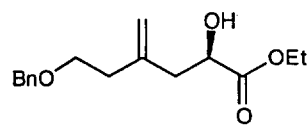
Prepared according to **Method A** (25 °C, 12 h) using 2-benzyloxymethyl-1-propene (87 μ L, 0.50 mmol), ethyl glyoxylate (250 μ L, 1.9 mmol) and catalyst **1c** (0.01 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 88% yield (116 mg, 0.44 mmol, 92% ee) after flash chromatography with 10-20% EtOAc/hexanes. $[\alpha]_D^{25}$ -3.4° (c 3.9, CHCl_3); IR (film) 3448, 3000-2857, 1734, 1204, 1098, 1028, 908, 738, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.26 (m, 5H, ArH), 5.19 (s, 1H, C=CHH), 5.09 (s, 1H, C=CHH), 4.53 (m, 2H, ArCH₂), 4.35 (br ddd, J = 3.7, 5.3, 7.9 Hz, 1H, CHOH), 4.23 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.01 (s, 2H, BnOCH_2), 3.34 (br d, J = 5.3, 1H, CHOH), 2.66 (dd, J = 3.7, 14.3 Hz, 1H, $\text{CH}_2(\text{CHOH})$), 2.49 (dd, J = 7.9, 14.3 Hz, 1H, $\text{CH}_2(\text{CHOH})$), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 141.4, 137.9, 128.4, 128.0, 127.7, 93.3, 72.2, 69.9, 61.5, 38.9, 14.2; LRMS (CI/ NH_3) 282 ($\text{M}+\text{NH}_4$)⁺; HRMS (CI/ NH_3) exact mass calcd for ($\text{C}_{15}\text{H}_{20}\text{O}_4+\text{NH}_4$)⁺ requires m/z 282.1705, found m/z 282.1716. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (5% $^i\text{PrOH}$:Hexanes, 1 mL/min); (S) enantiomer t_r = 11.32 min; (R) enantiomer t_r = 12.72 min; 92% ee.



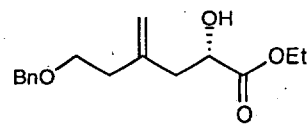
(R) MTPA δ 2.72, 2.62
(S) MTPA δ 2.79, 2.67

Determination of Absolute Configuration by Mosher MTPA

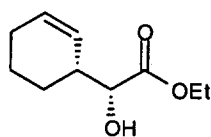
analysis: (R) MTPA Ester : ^1H NMR (400 MHz, CDCl_3) δ 7.62-7.26 (m, 10H, ArH), 5.36 (dd, J = 4.1, 9.1 Hz, 1H, CHOMTPA), 5.03 (s, 1H, C=CH₂), 4.89 (s, 1H, C=CH₂), 4.38 (m, 2H, ArCH₂), 4.24 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.84 (s, 2H, BnOCH_2), 3.64 (s, 3H, OCH_3), 2.72 (dd, J = 3.9, 15.1 Hz, 1H, $\text{CH}_2\text{CHOMTPA}$), 2.62 (dd, J = 9.1, 15.1 Hz, 1H, $\text{CH}_2\text{CHOMTPA}$), 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3); LRMS (FAB) 481 (MH)⁺, 503 ($\text{M}+\text{Na}$)⁺; HRMS (FAB) exact mass calcd for ($\text{C}_{25}\text{H}_{27}\text{F}_3\text{O}_6+\text{Na}$)⁺ requires m/z 503.1657, found m/z 503.1656. (S) MTPA Ester : ^1H NMR (400 MHz, CDCl_3) δ 7.59-7.26 (m, 10H, ArH), 5.39 (dd, J = 4.0, 9.2 Hz, 1H, CHOMTPA), 5.19 (s, 1H, C=CH₂), 5.04 (s, 1H, C=CH₂), 4.45 (m, 2H, ArCH₂), 4.21 (q, J = 6.1 Hz, 2H, OCH_2CH_3), 3.96 (s, 2H, BnOCH_2), 3.53 (s, 3H, OCH_3), 2.79 (dd, J = 4.0, 15.0 Hz, 1H, $\text{CH}_2\text{CHOMTPA}$), 2.67 (dd, J = 9.3, 15.0 Hz, 1H, $\text{CH}_2\text{CHOMTPA}$), 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3); LRMS (FAB) 481 (MH)⁺, 503 ($\text{M}+\text{Na}$)⁺; HRMS (FAB) exact mass calcd for ($\text{C}_{25}\text{H}_{27}\text{F}_3\text{O}_6+\text{Na}$)⁺ requires m/z 503.1657, found m/z 503.1659.

**Preparation of (2R)-Ethyl 5-benzyloxy-2-hydroxy-5-pentenoate (15).**

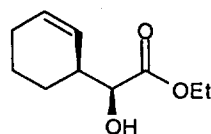
Prepared according to **Method A** (25 °C, 12 h) using 3-benzyloxy-2-methyl-1-butene (102 μ L, 0.50 mmol), ethyl glyoxylate (200 μ L, 1.5 mmol) and catalyst **1c** (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 98% yield (137 mg, 0.49 mmol, 89% ee) after flash chromatography with 10-20% EtOAc/hexanes.

**Preparation of (2S)-Ethyl 5-benzyloxy-2-hydroxy-5-pentenoate (15).**

Prepared according to **Method B** (25 °C, 12 h) using 3-benzyloxy-2-methyl-1-butene (102 μ L, 0.50 mmol), ethyl glyoxylate (200 μ L, 1.5 mmol) and catalyst **4** (0.005 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 98% yield (137 mg, 0.49 mmol, 82% ee) after flash chromatography with 10-20% EtOAc/hexanes. $[\alpha]_D^{25}$ -2.4° (c 0.5, CH_2Cl_2); IR (film) 3442, 3066, 3025, 2956, 2925, 1750, 1734, 1646, 1456, 1100, 1070 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.27 (m, 5H, ArH), 4.95 (s, 2H, C=CHH), 4.32 (m, 1H, CHOH), 4.23 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.62 (t, J = 6.6 Hz, 2H, BnOCH_2), 2.94 (br s, 1H, CHOH), 2.58 (dd, J = 3.9, 14.4 Hz, 1H, $\text{CH}_2(\text{CHOH})$), 2.41 (m, 3H, $\text{CH}_2(\text{CHOH})$, $\text{BnOCH}_2\text{CH}_2$), 1.27 (t, J = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 142.2, 138.3, 128.4, 127.7, 127.6, 114.7, 73.0, 69.5, 68.9, 61.6, 41.4, 36.0, 14.2; LRMS (CI) 279 (MH)⁺, 296 ($\text{M}+\text{NH}_4$)⁺; HRMS (CI) exact mass calcd for ($\text{C}_{16}\text{H}_{22}\text{O}_4+\text{NH}_4$)⁺ requires m/z 296.1862 found m/z 296.1869. Regioisomers ratios were determined by HPLC with a Zobax column (5% $^i\text{PrOH}$:Hexanes, 0.5 ml/min): t_r (major) 15.0 min, t_r (minor) 17.4 min. Regioisomers must be separated by Preparative HPLC using a Zorbax Sil (21.2 mm x 25 cm) column (5% $^i\text{PrOH}$:Hexanes, 10 ml/min) before determination of enantiomeric excess. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (5% $^i\text{PrOH}$:Hexanes, 0.5 ml/min); (R) enantiomer t_r = 22.1 min; (S) enantiomer t_r = 25.6 min; 82% ee). Absolute stereochemistry determined by analogy.

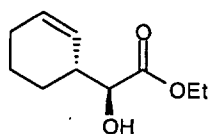


(1'R, 2R)-Ethyl 2-(2'-cyclohexenyl)-2-hydroxyacetate (16). Prepared according to **Method A** (0 °C, 12 h) using cyclohexene (52 μ L, 0.50 mmol), ethyl glyoxylate (667 μ L, 5.0 mmol) and catalyst **1c** (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 70% yield (64 mg, 0.35 mmol, 94% ee, (1'S,2S):(1'R, 2S) = 95:5) after flash chromatography with 30% Et₂O/hexanes.

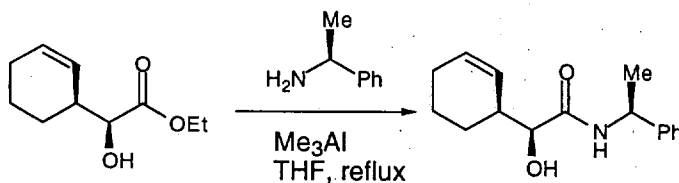


(1'S, 2S)-Ethyl 2-(2'-cyclohexenyl)-2-hydroxyacetate (16). Prepared according to **Method A** (0 °C, 12 h) using cyclohexene (52 μ L, 0.50 mmol), ethyl glyoxylate (667 μ L, 5.0 mmol) and catalyst **2a** (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 95% yield (87 mg, 0.47 mmol, 98% ee, (1'S, 2S):(1'R, 2S) = 86:14) after flash chromatography with 30% Et₂O/hexanes. Diastereoisomers can be separated using Merck LiChroprep Si 60

(column size B) using 15% Et₂O/hexanes as eluent (150-200 mg sample size). Enantiomeric excess of major (1'S, 2S) was determined by GC with a CYCLODEX-B column (12.5 psi, 90 °C, at t = 20 min, rate 0.2 °C/min, final T = 110 °C) (2R) enantiomer t_r = 60.6 min; (2S) enantiomer t_r = 60.9 min; 98% ee. Enantiomeric excess of minor (1'R, 2S) was determined by GC with a CYCLODEX-B column (20.0 psi, 90 °C, at t = 20 min, rate 0.2 °C/min, final T = 110 °C) (2R) enantiomer t_r = 35.7 min; (2S) enantiomer t_r = 36.3 min; 98% ee. (1'S,2S):(1'R,2S) = 86:14. [α]_D²⁵ -38.7° (c 1.37, CH₂Cl₂); IR (film) 3489, 3021, 2981, 2934, 1731, 1448, 1205, 1111, 1024 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.87 (m, 1 H, CH=CH), 5.42 (d, J = 10.2, CH=CH), 4.26 (m, 2H, OCH₂CH₃), 4.06 (br s, 1 H, CHOH), 2.60 (br s, 1H, OH), 1.99 (br s, 2H, -CH₂-), 1.81 (m, 2H, -CH₂-), 1.57 (m, 2H, -CH₂-), 1.29 (m, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 131.2, 125.1, 73.8, 61.6, 40.1, 25.8, 24.9, 21.7, 14.3; LRMS (CI/NH₃) m/z 185 (MH)⁺, 202 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₀H₁₆O₃NH₄)⁺ requires m/z 202.1443, found m/z 202.1440.

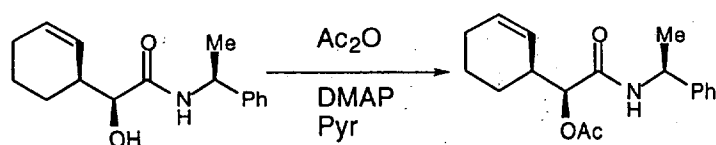


(1'R,2S)-Ethyl 2-(2'-cyclohexenyl)-2-hydroxyacetate (16): [α]_D²⁵ +15.5° (c 1.5, CH₂Cl₂); IR (film) 3494, 3021, 2981, 2932, 2862, 1729, 1447, 1368, 1205, 1116, 1025 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.87 (m, 1 H, CH=CH), 5.60 (dd J = 8.0, 2.1, CH=CH), 4.26 (m, 2H, OCH₂CH₃), 4.20 (br d, 2.1 Hz, 1 H, CHOH), 2.60 (br m, 1H, OH), 1.99 (br s, 2H, -CH₂-), 1.81 (m, 2H, -CH₂-), 1.54 (m, 2H, -CH₂-), 1.31 (m, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 130.2, 127.2, 73.4, 61.8, 40.0, 24.8, 22.6, 21.5, 14.3; LRMS (CI/NH₃) m/z 185 (MH)⁺, 202 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₀H₁₆O₃NH₄)⁺ requires m/z 202.1443, found m/z 202.1440.



(1'S,2S)-[(S)- α -Methylbenzyl]-2-(2'-cyclohexenyl)-2-hydroxyacetamide. To a solution of (S)- α -methylbenzyl amine (612 μ L, 4.75 mmol) in 10 mL of THF at 0 °C was added dropwise 2.4 mL (4.75 mmol, 2.0 M in toluene) of trimethylaluminum solution with the concomitant evolution of gas. The solution was stirred for

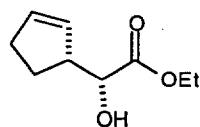
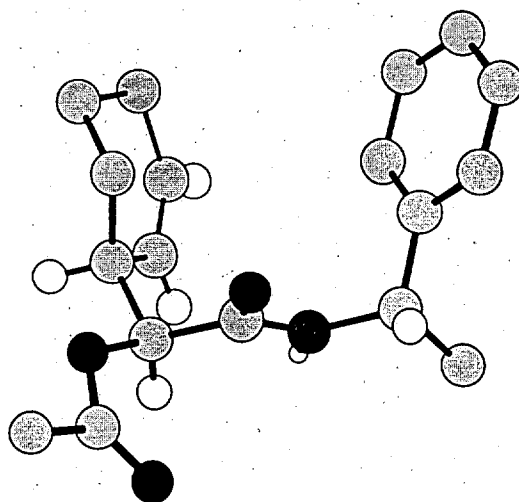
30 min at 25 °C. A solution of 175 mg (0.95 mmol) of (1'S,2S)-ethyl 2-(2'-cyclohexenyl)-2-hydroxyacetate in 5 mL THF was added dropwise. The resulting solution was refluxed for 2 h. Upon cooling, the solution was cannulated rapidly into an ice cooled beaker containing 100 mL of aqueous 2% HCl (CAUTION: Gas evolution). The aqueous layer was then basified to pH 8 with NaHCO₃. The layers were separated and the aqueous layer was extracted with two 50 mL portions of EtOAc. The combined organics were washed with 50 mL brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography with 40% EtOAc/hexanes afforded 208 mg (85% yield) of the title compound as a white solid. m.p. 88-89 °C [α]_D²⁵ +15.5° (c 1.5, CH₂Cl₂); IR (film) 3413, 3013, 2933, 2864, 2838, 1665, 1515, 1218, cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.25 (m, 5 H, ArH), 6.69 (d, 1H, 6.7 Hz, NH), 5.95 (m, 1 H, CH=CH), 5.48 (d, J = 10.0 Hz, 1 H, CH=CH), 5.16 (m, 1H, -CHPh), 4.00 (m, 1 H, CHOH), 2.85 (m, 1H, -CH-), 2.60 (d, J = 6.1 Hz, 1H, OH), 2.01-1.53 (m, 4H, -CH₂-), 1.51 (d, 6.9 Hz, 3 H, -CH₃), 1.47-1.40 (m, 2H, -CH₂-); ¹³C NMR (125 MHz, CDCl₃) δ 171.9, 142.9, 132.9, 128.7, 127.5, 126.3, 125.0, 74.7, 48.8, 39.7, 25.6, 25.0, 22.0, 21.5; LRMS (CI/NH₃) m/z 260 (MH)⁺, 277 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₆H₂₁O₃N₁NH₄)⁺ requires m/z 277.1916, found m/z 277.1906.



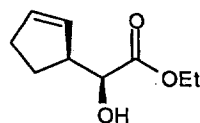
Determination of Absolute Configuration by X-Ray of (1'S, 2S)-[(S)-α-Methylbenzyl]-2-(2'-cyclohexenyl)-2-acetoxyacetamide. To a solution of (1'S, 2S)-[(S)-α-methylbenzyl amide]-2-(2'-cyclohexenyl)-2-hydroxyacetate (50 mg, 0.19 mmol) in 2 mL pyridine

was added 20 μ L acetic anhydride (0.21 mmol) followed by DMAP (catalytic). After 12 h the reaction was diluted with 50 mL EtOAc and poured into pH 7 buffer. The layers were separated and the aqueous layer was extracted with two 50 mL portions of EtOAc. The combined organics were washed with 50 mL brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography with 40% EtOAc/hexanes afforded 53 mg (92% yield) of the title compound as a white solid. m.p. 114–115 $^\circ\text{C}$ $[\alpha]_D^{25}$ -74.4 $^\circ$ (c 1.0, CHCl_3); IR (film) 3420, 3030, 3020, 2932, 2865, 2840, 1743, 1674, 1514, 1230, 1211 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.25 (m, 5 H, ArH), 6.16 (d, 1H, 7.6 Hz, NH), 5.83 (m, 1 H, CH=CH), 5.48 (d, J =10.2 Hz, 1 H, CH=CH), 5.16 (m, 1H, -CHPh), 5.00 (d, J =5.4 Hz, 1 H, CHOAc), 2.80 (m, 1H, -CH-), 2.12 (s, 3H, C=OCH₃), 2.01–1.53 (m, 4H, -CH₂-), 1.52 (d, 6.9 Hz, 3 H, -CH₃), 1.47–1.40 (m, 2H, -CH₂-); ^{13}C NMR (125 MHz, CDCl_3) δ 170.2, 168.0, 142.6, 130.3, 128.8, 127.6, 126.2, 76.9, 48.6, 37.8, 25.4, 24.9, 21.6, 21.4, 20.1; LRMS (CI/NH_3) m/z 302 (MH^+), 319 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for ($\text{C}_{18}\text{H}_{23}\text{O}_3\text{N}_1\text{NH}_4$)⁺ requires m/z 277.2022, found m/z 319.2017.

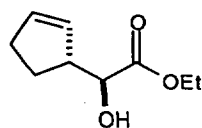
X-Ray Crystal Structure of (1'S,2S)-[(S)-α-Methylbenzyl amide]-2-(2'-cyclohexenyl)-2-acetoxyacetamide.



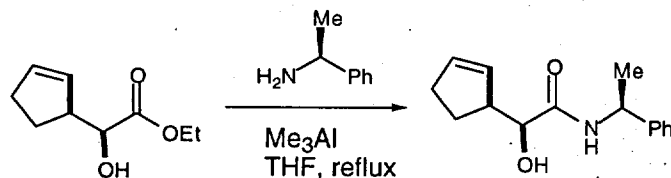
(1'R, 2R)-Ethyl 2-(2'-cyclopentenyl)-2-hydroxyacetate (17). Prepared according to Method A (0 $^\circ\text{C}$, 12 h) using cyclopentene (44 μ L, 0.50 mmol), ethyl glyoxylate (667 μ L, 5.0 mmol) and catalyst 2c (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 72% yield (60 mg, 0.36 mmol, 78% ee, (1'R, 2R) : (1'S, 2R) = 73 : 27 after flash chromatography with 30% Et_2O /hexanes.



(1'S, 2S)-Ethyl 2-(2'-cyclopentenyl)-2-hydroxyacetate (17). Prepared according to Method A (0 $^\circ\text{C}$, 12 h) using cyclohexene (44 μ L, 0.50 mmol), ethyl glyoxylate (667 μ L, 5.0 mmol) and catalyst 1 (0.05 mmol, 1.5 mL CH_2Cl_2) to provide the pure product as a clear oil in 83% yield (70 mg, 0.42 mmol, 96% ee, (1'S,2S) : (1'R,2S) = 66:33) after flash chromatography with 30% Et_2O /hexanes. Diastereoisomers can be separated using Merck LiChroprep Si 60 (column size B) using 15% Et_2O /hexanes as eluent (150–200 mg sample size). Enantiomeric excess of major (1'S, 2S) was determined by GC with a CYCLODEX-B column (12.5 psi, 90 $^\circ\text{C}$, at t = 15 min, rate 0.5 $^\circ\text{C}$, final T = 110 $^\circ\text{C}$) major (1'S, 2S) : (2R) enantiomer t_r = 26.4 min; (2S) enantiomer t_r = 26.7 min, 96% ee; minor (1'R, 2S) : (2R) enantiomer t_r = 28.8 min; (2S) enantiomer t_r = 29.5 min; 96% ee. (1'S, 2S) : (1'R, 2S) = 66 : 33. $[\alpha]_D^{25}$ +63.4 $^\circ$ (c 1.1, CHCl_3); IR (film) 3490, 3052, 2979, 2939, 2852, 1732, 1462, 1368, 1196 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.93 (m, 1 H, CH=CH), 5.51 (m, 1H, CH=CH), 4.26 (m, 2H, OCH₂CH₃), 4.11 (m, 1 H, CHOH), 3.13 (br s, 1H, -CH), 2.51 (d, 8.0 Hz, 1H, -OH), 2.44 (m, 1H, -CH₂-), 2.39 (m, 1H, -CH₂-), 2.08 (m, 1H, -CH₂-), 1.86 (m, 1H, -CH₂-), 1.30 (m, 3H, OCH₂CH₃); ^{13}C NMR (125 MHz, CDCl_3) δ 174.5, 135.1, 128.2, 73.2, 61.5, 50.0, 32.6, 25.9, 14.3; LRMS (CI/NH_3) m/z 171 (MH^+), 188 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for ($\text{C}_9\text{H}_{14}\text{O}_3\text{NH}_4$)⁺ requires m/z 188.1287, found m/z 188.1282.



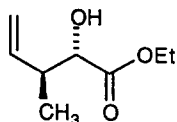
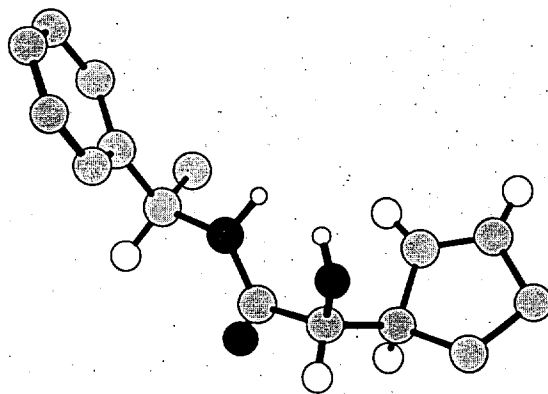
(1'R, 2S)-Ethyl 2-(2'-cyclopentenyl)-2-hydroxyacetate (17). $[\alpha]_D^{25}$ -110° (c 0.8, CHCl_3); IR (film) 3491, 3052, 2979, 2939, 2852, 1728, 1202, 1096 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.89 (m, 1 H, $\text{CH}=\text{CH}$), 5.66 (m, 1 H, $\text{CH}=\text{CH}$), 4.26 (m, 2H, OCH_2CH_3), 4.22 (m, 1 H, CHOH), 3.16 (br s, 1H, $-\text{CH}$), 2.72 (br s, 1H, $-\text{OH}$), 2.39 (m, 1H, $-\text{CH}_2-$), 2.29 (m, 1H, $-\text{CH}_2-$), 1.88 (m, 1H, $-\text{CH}_2-$), 1.75 (m, 1H, $-\text{CH}_2-$), 1.31 (m, 3H, OCH_2CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ 174.6, 133.7, 130.3, 72.5, 61.7, 50.0, 32.4, 23.5, 14.3; LRMS (CI/NH_3) m/z 171 (MH^+), 188 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for $(\text{C}_9\text{H}_{14}\text{O}_3\text{NH}_4)^+$ requires m/z 188.1287, found m/z 188.1290.



(1'S, 2S)-[(S)- α -Methylbenzyl]-2-(2'-cyclopentenyl)-2-hydroxyacetamide. To a solution of (*S*)- α -methylbenzyl amine (306 μL , 2.38 mmol) in 10 mL of THF at 0°C was added dropwise 1.2 mL (2.38 mmol, 2.0 M in toluene) of trimethylaluminum solution with the concomitant evolution of gas. The solution was stirred for 30 min at 25°C .

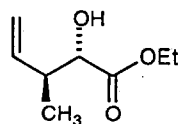
A solution of 175 mg (0.47 mmol) of (*1'S, 2S*)-ethyl 2-(2'-cyclopentenyl)-2-hydroxyacetate (**17**) in 5 mL THF was added dropwise. The resulting solution was heated at reflux for 2 h. Upon cooling, the solution was cannulated rapidly into an ice cooled beaker containing 100 mL of aqueous 2% HCl (CAUTION: Gas evolution). The aqueous layer was then basified to pH 8 with NaHCO_3 . The layers were separated and the aqueous layer was extracted with two 50 mL portions of EtOAc. The combined organics were washed with 50 mL brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography with 40% EtOAc/hexanes afforded 84 mg (73% yield) of the title compound as a white solid. m.p. $79-81^\circ\text{C}$ $[\alpha]_D^{25}$ $+196^\circ$ (c 1.0, CHCl_3); IR (cell, CHCl_3) 3412, 3057, 3028, 3019, 3011, 2959, 2929, 2360, 1662, 1517, 1456 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.25 (m, 5 H, ArH), 6.69 (br s, 1H, NH), 5.98 (m, 1 H, $\text{CH}=\text{CH}$), 5.53 (m, 1H, $\text{CH}=\text{CH}$), 5.16 (m, 1H, $-\text{CHPh}$), 4.04 (m, 1 H, CHOH), 3.43 (br s, 1H, $-\text{CH}$), 2.39 (d, 6.7 Hz, 1H, $-\text{OH}$), 2.35 (m, 2H, $-\text{CH}_2-$), 2.12 (m, 1H, $-\text{CH}_2-$), 1.74 (m, 1H, $-\text{CH}_2-$), 1.51 (d, 6.8 Hz, 3 H, $-\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 172.0, 142.9, 136.1, 128.7, 128.1, 127.5, 126.2, 74.2, 57.5, 49.6, 48.6, 46.4, 32.5, 25.8, 21.9; LRMS (CI/NH_3) m/z 246 (MH^+), 263 ($\text{M}+\text{NH}_4^+$); HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{15}\text{H}_{19}\text{O}_2\text{N}_1\text{NH}_4)^+$ requires m/z 263.1760 found m/z 263.1750.

X-ray Crystal Structure of (*1'S, 2S*)-[(*S*)- α -Methylbenzyl]-2-(2'-cyclopentenyl)-2-hydroxyacetamide. (Note structure shown is the enantiomer, absolute assignment based on (*S*)- α -methylbenzyl amine starting material)

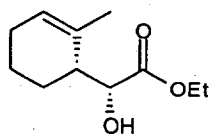


Preparation of (2S, 3S)-Ethyl 3-methyl-2-hydroxy-5-pentenoate (19). To an oven-dried, round-bottom flask containing a magnetic stirring bar was added, in an inert atmosphere box, $\text{Cu}((R,R)\text{-Ph-box})\text{Cl}_2$ (23.4 mg, 0.05 mmol) and AgSbF_6 (34.3 mg, 0.10 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box and charged with CH_2Cl_2 (1.0 mL). The mixture was stirred 2–3 h in the absence of light to produce a green solution with a white AgCl precipitate. The mixture was transferred *via* cannula under nitrogen to a syringe fitted with a $0.45\ \mu$ filter, and into an oven dried sealed tube with 14/20 side arm joint attached containing ethyl glyoxylate (67 μL , 0.5 mmol) and 0.5 mL CH_2Cl_2 . The flask was cooled to -78°C and *cis*-butene was condensed into the flask using a dry-ice condenser (large excess). The flask was then sealed and allowed to warm to 25°C for 48 h to provide the prod-

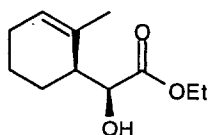
uct as a clear oil in 60% yield (48 mg, 0.30 mmol, 90% ee, 88:12 diastereoselectivity) after flash chromatography with 20% Et₂O/hexanes. Major diastereoisomer can be purified to > 95:5 using Merck LiChroprep Si 60 (column size B) using 15% Et₂O/hexanes as eluent (150-200 mg sample size). $[\alpha]_D^{25}$ 3.3° (c 0.8, Et₂O); IR (film) 3525, 2981, 2935, 1734, 1214, 1132 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.74 (m, 1H, HC=CHH), 5.08 (s, 1H, HC=CHH), 5.04 (d, 3.7 Hz, 1H, HC=CHH), 4.23 (m, 2H, OCH₂CH₃), 4.10 (br s, 1H, CHOH), 2.71 (d, *J* = 5.2, 1H, CHOH), 2.65 (m, 1H, CHCH₃), 1.29 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.15 (d, *J* = 7.0 Hz, 3H, CHCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 174.3, 137.7, 116.5, 74.4, 61.7, 42.0, 16.4, 14.3; LRMS (CI/NH₃) 176 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₈H₁₄O₃+NH₄)⁺ requires *m/z* 176.1293, found *m/z* 176.1287. Diastereomer ratios were determined by GC with a DB-1701 column (10 psi, 70 °C); (2*S*, 3*S*) diastereomer *t_r* = 6.7 min; (2*S*, 3*R*) diastereomer *t_r* = 7.1 min; 88:12 ratio. Enantiomeric excess was determined by GC with a CYCLODEX-B column (8 psi, 60 °C, at *t* = 30 min, rate 2.5 °C, final *T* = 110 °C); (*R*) enantiomer *t_r* = 40.3 min; (*S*) enantiomer *t_r* = 40.4 min; 90% ee. The spectral data for this diastereomer was identical to that in the literature.⁵ Absolute stereochemistry based on analogy.



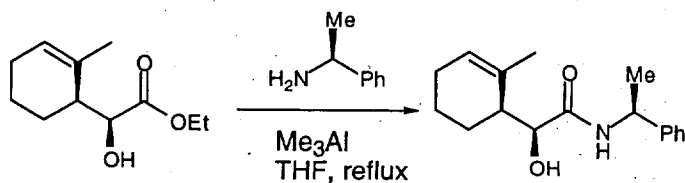
Preparation of (2*S*, 3*S*)-Ethyl 3-methyl-2-hydroxy-5-pentenoate (19). To an oven-dried, round-bottom flask containing a magnetic stirring bar was added, in an inert atmosphere box, Cu((*S,S*)-*t*-Bu-box)Cl₂ (21.4 mg, 0.05 mmol) and AgSbF₆ (34.3 mg, 0.10 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box and charged with CH₂Cl₂ (1.0 mL). The mixture was stirred 2-3 h in the absence of light to produce a green solution with a white AgCl precipitate. The mixture was transferred *via* cannula under nitrogen to a syringe fitted with a 0.45 μ filter, and into an oven dried sealed tube with 14/20 side arm joint attached containing ethyl glyoxylate (67 μL, 0.5 mmol) and 0.5 mL CH₂Cl₂. The flask was cooled to -78 °C and *cis*-butene was condensed into the flask using a dry-ice condenser (large excess). The flask was then sealed and allowed to warm to 25 °C for 48 h to provide the product as a clear oil in 54% yield (43 mg, 0.27 mmol, 98% ee (2*S*, 3*S* diastereomer), (% ee for 2*S*, 3*R* diastereomer not determined), 40:60 (2*S*, 3*S*): (2*S*, 3*R*) after flash chromatography with 20% Et₂O/hexanes.



(1'*R*, 2*R*)-Ethyl 2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetate (20). Prepared according to Method A (0 °C, 18 h) using 1-methyl cyclohexene (59 μL, 0.50 mmol), ethyl glyoxylate (200 μL, 1.5 mmol) and catalyst 1c (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 86% yield (85 mg, 0.43 mmol, 92% ee, (1'*R*, 2*R*): (1'*S*, 2*R*) = 89:11) after flash chromatography with 30% Et₂O/hexanes.



(1'*S*, 2*S*)-Ethyl 2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetate (20). Prepared according to Method B (0 °C, 18 h) using 1-methyl cyclohexene (59 μL, 0.50 mmol), ethyl glyoxylate (200 μL, 1.5 mmol) and catalyst 4 (0.005 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 86% yield (85 mg, 0.43 mmol, >98% ee, (1'*S*, 2*S*): (1'*R*, 2*S*) = 78:22) after flash chromatography with 30% Et₂O/hexanes. Diastereomers cannot be separated. $[\alpha]_D^{25}$ +18.7° (c 0.7, CHCl₃); IR (film) 3512, 2933, 2861, 1729, 1446, 1378, 1219, 1095 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.65 (br s, 1 H, CH=C, minor), 5.55 (m, 1 H, CH=C, major), 4.51 (d, 2.5 Hz, 1 H, CHOH, minor), 4.20 (d, 1.2 Hz, 1 H, CHOH, major), 4.26 (m, 2H, OCH₂CH₃), 2.86 (br s, 1H, OH, major), 2.75 (br s, 1H, OH, minor), 2.61 (br m, 1 H, -CH-, major), 2.51 (br m, 1 H, -CH-, minor), 1.94 (br m, 2H, -CH₂-), 1.78 (m, 2H, -CH₂-), 1.67 (s, 3H, -CH₃), 1.52 (m, 2H, -CH₂-), 1.28 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 132.1, 126.5, 126.3, 77.2, 72.6, 70.6, 61.8, 61.6, 43.3, 42.4, 26.3, 25.3, 25.2, 22.7, 22.4, 21.5, 21.3, 20.7, 14.3, 14.2; LRMS (CI/NH₃) *m/z* 199 (MH)⁺, 216 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₁H₁₈O₃NH₄)⁺ requires *m/z* 216.1600, found *m/z* 216.1605. Enantiomeric excess of major (1'*S*, 2*S*) was determined by GC with a CYCLODEX-B column (15.0 psi, 80 °C, at *t* = 20 min, rate 0.5 °C, final *T* = 120 °C) major (1'*S*, 2*S*): (2*S*) enantiomer *t_r* = 69.8 min, (2*R*) enantiomer *t_r* = 71.2 min; >98% ee; minor (1'*R*, 2*S*): (2*S*) enantiomer *t_r* = 75.8 min, (2*R*) enantiomer *t_r* = 79.0 min; 69% ee. (1'*S*, 2*S*): (1'*R*, 2*S*) = 78:22.

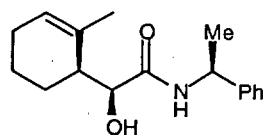


(1'*S*, 2*S*)-[(*S*)-α-Methylbenzyl]-2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetamide. To a solution of (*S*)-α-methylbenzyl amine (612 μL, 4.75 mmol) in 10 ml of THF at 0 °C was added dropwise 2.4 mL (4.75 mmol, 2.0 M in toluene) of trimethylaluminum solution with the concomitant evolution of gas. The solution was

Supporting Information

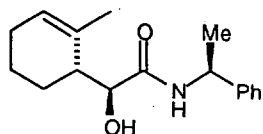
S-13

stirred for 30 min at 25 °C. A solution of 190 mg (0.95 mmol) of (*I'S*, 2*S*)-ethyl 2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetate in 5 mL THF was added dropwise. The resulting solution was refluxed for 2 h. Upon cooling, the solution was cannulated rapidly into an ice cooled beaker containing 100 mL of aqueous 2% HCl (CAUTION: Gas evolution). The aqueous layer was then basified to pH 8 with NaHCO₃. The layers were separated and the aqueous layer was extracted with two 50 mL portions of EtOAc. The combined organics were washed with 50 mL brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography with 40% EtOAc/hexanes afforded 220 mg (85% yield) of the title compound as a white solid. Diastereomers can be separated by Preparative HPLC using a Zorbax Sil (21.2 mm x 25 cm) column (2% *i*PrOH:Hexanes, 15 ml/min) : T_R (major) = 24.3 min, T_R (minor) = 29.0 min.



(*I'S*, 2*S*)-[(*S*)-α-Methylbenzyl]-2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetamide.

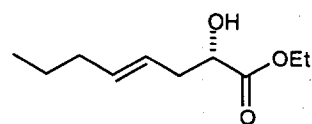
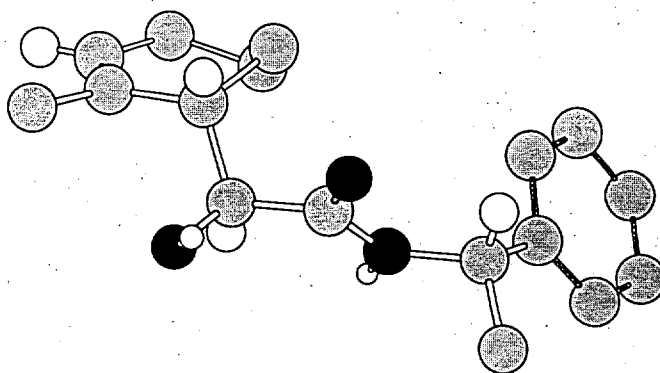
m.p. 97-98 °C [α]_D²⁵ -106° (c 1.6, CHCl₃); IR (cell, CHCl₃): 3413, 3155, 2978, 2936, 2864, 2254, 1664, 1514, 1451, 1382, 1095 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.25 (m, 5 H, ArH), 6.71 (d, 1H, 7.3 Hz, NH), 5.71 (m, 1 H, CH=CH), 5.13 (m, 1H, -CHPh), 4.12 (m, 1 H, CHOH), 2.86 (m, 1H, -CH-), 2.78 (d, 6.1 Hz, 1H, OH), 1.81-1.74 (m, 4H, -CH₂-), 1.72 (d, 0.5 Hz, 3 H, -CH₃), 1.48 (d, 6.9 Hz, 3 H, -CHCH₃), 1.47-1.40 (m, 2H, -CH₂-); ¹³C NMR (125 MHz, CDCl₃) δ 172.5, 142.8, 131.4, 129.7, 128.7, 127.5, 126.3, 73.5, 48.8, 42.1, 27.1, 25.15, 22.7, 21.7, 19.9; LRMS (CI/NH₃) *m/z* 274 (MH)⁺, 291 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₇H₂₄O₂N₁NH₄)⁺ requires *m/z* 291.2073 found *m/z* 291.2063.



(*I'R*, 2*S*)-[(*S*)-α-Methylbenzyl]-2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetamide.

m.p. 130-131 °C [α]_D²⁵ -72.7° (c 0.6, CHCl₃, 69% ee); IR (cell, CHCl₃): 3414, 3155, 2972, 2936, 2863, 2254, 1663, 1521, 1456, 1381, 1090 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.25 (m, 5 H, ArH), 6.95 (d, 1H, 7.2 Hz, NH), 5.78 (m, 1 H, CH=CH), 5.20 (m, 1H, -CHPh), 4.42 (m, 1 H, CHOH), 2.86 (m, 1H, -CH-), 2.73 (br s, 1H, OH), 1.81-1.74 (m, 4H, -CH₂-), 1.73 (s, 3 H, -CH₃), 1.52 (d, 6.9 Hz, 3 H, -CHCH₃), 1.47-1.40 (m, 2H, -CH₂-); ¹³C NMR (125 MHz, CDCl₃) δ 177.8, 131.9, 129.1, 128.7, 126.3, 77.3, 71.9, 48.3, 42.3, 27.1, 25.3, 22.5, 21.9, 21.5; LRMS (CI/NH₃) *m/z* 274 (MH)⁺, 291 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₇H₂₄O₂N₁+H)⁺ requires *m/z* 274.1807 found *m/z* 274.1809.

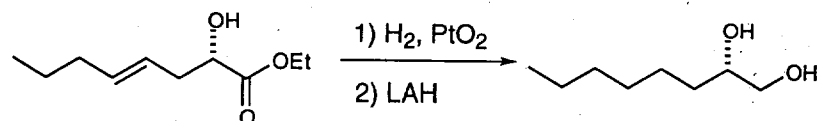
Xray Structure of (*I'S*,2*S*)-[(*S*)-α-Methylbenzyl]-2-(2'-methyl-2'-cyclohexenyl)-2-hydroxyacetamide.



Preparation of (2*S*)-Ethyl 2-hydroxy-5-octenoate (21). Prepared according to Method A (25 °C, 48 h) using 1-hexene (63 μL, 0.50 mmol), ethyl glyoxylate (667 μL, 5.0 mmol) and catalyst 2c (0.05 mmol, 1.5 mL CH₂Cl₂) to provide the pure product as a clear oil in 96% yield (89 mg, 0.48 mmol) after flash chromatography with 10-20% EtOAc/hexanes. [α]_D²⁵ -2.1° (c 3.5, CHCl₃); IR (neat) 3486, 2960, 2930,

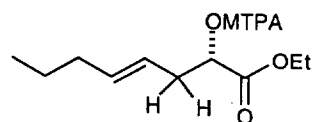
2872, 1734, 1458, 1368, 1264, 1200, 1136, 1090, 1026, 970, 863 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.53 (ddd, *J* = 7.2, 7.2, 14.6 Hz, 1H, CH=CH), 5.37 (m, 1H, CH=CH), 4.20 (m, 3H, CHOH, CO₂CH₂CH₃), 2.80 (br s, 1H, OH), 2.46 (m, 1H, CHCH₂CHOH), 2.36 (ddd, *J* = 6.9, 6.9, 13.8 Hz, 1H, CHCH₂CHOH), 1.96 (dd, *J* =

7.3, 14.3 Hz, 2H, CHCH₂CH₂), 1.35 (dd, $J = 7.4, 14.7$ Hz, 2H, CH₃CH₂CH₂), 1.27 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃), 0.86 (t, $J = 7.4$ Hz, 3H, CH₃CH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 134.9, 123.5, 70.3, 61.5, 37.6, 34.6, 22.4, 14.2, 13.5; LRMS (CI/NH₃) m/z 187 (MH)⁺, 204 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₁₀H₁₈O₃+NH₄)⁺ requires m/z 204.1600, found m/z 204.1603. Enantiomeric excess was determined by GC with a CYCLODEX-B column (100 °C, 25 psi); (E-*S*) enantiomer $t_r = 12.7$ min; (E-*R*) enantiomer $t_r = 12.3$ min; (Z-*S*/*R*) enantiomer $t_r = 13.6$ min; (Z-*S*/*R*) enantiomer $t_r = 14.5$ min; 98% ee, 95:5 *E*:*Z*.



Determination of the Absolute Configuration of (2*S*)-Ethyl 2-hydroxy-4-octenoate by Correlation with (2*S*)-octane-1,2-diol.

The absolute stereochemistry was determined by conversion to the diol via sequential hydrogenation and reduction. (2*S*)-Ethyl 2-hydroxy-4-octenoate (49 mg, 0.26 mmol, 98% ee) was dissolved in EtOAc (20 mL) and PtO₂ (~20 mg) was added. This mixture was fitted with a H₂ balloon and stirred for 18 h, filtered through Celite with EtOAc and the resultant solution was concentrated to yield an oil (43 mg, 0.23 mmol). To a 0 °C solution of the oil in THF (5 mL) was added LiAlH₄ (0.69 mL of 1.0M THF solution, 0.69 mmol) dropwise. After 15 min the reaction was quenched by careful addition of 1N HCl until gas evolution had ceased. The mixture was diluted with EtOAc (10 mL) and brine (5 mL), the layers separated, and the aqueous layer was backwashed with EtOAc (10 mL). The combined organic extracts were subsequently washed with sat. aq. NaHCO₃ (5 mL) and sat. aq. Na/K tartrate (5 mL), dried, and concentrated. The resultant oil was chromatographed with 50% EtOAc to yield the pure (2*S*)-octane-1,2-diol (22 mg, 0.15 mmol). The spectral data and optical rotation for this material were identical to that in the literature.⁶ [α]_D²⁰ -16.1° (c 1.1, EtOH); [α]_D²⁰ (Lit.) -16.3° (c 2.0, EtOH).



(*R*) MTPA δ 2.64
(*S*) MTPA δ 2.55

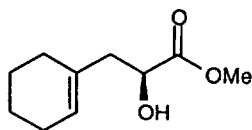
Determination of Absolute Configuration by Mosher MTPA analysis:

(*R*) MTPA Ester: ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.42 (m, 5H, ArH), 5.57 (ddd, $J = 6.8, 6.8, 14.5$ Hz, 1H, CH=CH), 5.36 (m, 1H, CH=CH), 5.21 (dd, $J = 4.6, 7.8$ Hz, 1H, CHOMTPA), 4.21 (m, 2H, CO₂CH₂CH₃), 3.57 (s, 3H, OCH₃), 2.64 (m, 2H, CHCH₂CHOMTPA), 1.95 (dd, $J = 7.2, 14.2$ Hz, 2H, CHCH₂CH₂), 1.30 (m, 2H, CH₃CH₂CH₂), 1.27 (t, 3H, OCH₂CH₃), 0.88 (t, $J = 7.2$ Hz, 3H, CH₃CH₂CH₂); LRMS (FAB) 403 (MH)⁺, 425 (M+Na)⁺. (*S*) MTPA Ester: ¹H NMR (400 MHz, CDCl₃) δ 7.65–7.41 (m, 5H, ArH), 5.48 (ddd, $J = 7.0, 7.0, 15.0$ Hz, 1H, CH=CH), 5.19 (m, 2H, CH=CH, CHOMTPA), 4.24 (m, 2H, CO₂CH₂CH₃), 3.65 (s, 3H, OCH₃), 2.55 (m, 2H, CHCH₂CHOMTPA), 1.88 (dd, $J = 6.9, 13.9$ Hz, 2H, CHCH₂CH₂), 1.29 (m, 5H, CH₃CH₂CH₂, OCH₂CH₃), 0.84 (t, $J = 7.4$ Hz, 3H, CH₃CH₂CH₂); LRMS (FAB) 403 (MH)⁺, 425 (M+Na)⁺.

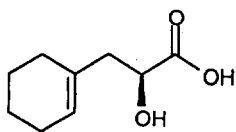
Large Scale Preparation of (S)-Ethyl 3-(1'-Cyclohexenyl)-2-hydroxypropionate (6). To a -78 °C solution of methylene cyclohexane (3.0 mL, 25 mmol), ethyl glyoxylate (10.5 mL, 75 mmol) in CH₂Cl₂ (25 mL), catalyst **4** (43 mg, 0.05 mmol) was added and the solution allowed to warm to 0 °C and stirred for 18 h. The reaction volume was reduced in half *in vacuo* and directly loaded onto a 4 x 14 cm silica gel flash column and eluted with 10 % EtOAc/hexanes to provide the pure product as a clear oil in 86% yield (4.3 g, 21.5 mmol, 97% ee).

General Procedure for the Addition of Olefins to Undistilled Ethyl Glyoxylate Catalyzed by **4.** To an oven-dried, 10 mL round-bottom flask containing a magnetic stirring bar was added, the olefin (0.50 mmol), ethyl glyoxylate (50% in toluene, 352 μL, 1.5 mmol) and CH₂Cl₂ (1.5 mL). To this solution was added solid **4** (0.005 mmol) in one portion. After the reaction was complete (24 h) the mixture was directed loaded onto a 2 x 6 cm silica gel flash column and eluted with 30% Et₂O/hexanes to provide the title compounds.

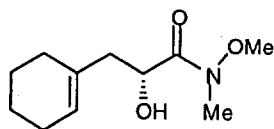
General Procedure for the Addition of Olefins to Undistilled Ethyl Glyoxylate Catalyzed by **1c.** To an oven-dried, 10 mL round-bottom flask containing a magnetic stirring bar was added, the olefin (0.50 mmol), and ethyl glyoxylate (50% in toluene, 352 μL, 1.5 mmol) and CH₂Cl₂ (1.5 mL). To this mixture was added the catalyst solution **1c** (0.05 mmol in 1.5 mL CH₂Cl₂) in one portion. After the reaction was complete (24h) the mixture was directed loaded onto a 2 x 6 cm silica gel flash column and eluted with 30% Et₂O/hexanes to provide the title compounds.



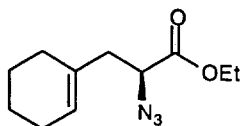
Preparation of (S)-Methyl 3-(1'-Cyclohexenyl)-2-hydroxypropionate (22). To a solution of (S)-methyl 3-(1'-cyclohexenyl)-2-hydroxypropionate (88 mg, 0.44 mmol, 97% ee) in MeOH (4 mL) at 25 °C, K_2CO_3 (59 mg, 0.44 mmol) was added. After 2 h the reaction was diluted with EtOAc and poured into pH 7 buffer and extracted. The organics were washed with brine and dried with Na_2CO_3 . Concentration *in vacuo* followed by purification by flash chromatography with 30% Et₂O/hexanes afforded 69 mg (85% yield, 97% ee) of the title compound as a colorless oil. $[\alpha]_D^{25}$ -11.0° (c 0.7, $CHCl_3$); IR (film) 3540, 3026, 2931, 2860, 2838, 1737, 1440, 1268, 1220, 1096 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 5.53 (br s, 1H, C=CH), 4.29 (m, 1H, CH(OH)), 3.77 (s, 3H, OCH_3), 2.59 (d, 7.0 Hz, 1H, OH), 2.44 (dd, J =14.1, 3.2 Hz, 1H, $CH_2CH(OH)$), 2.29 (dd, J =14.0, 8.2 Hz, 1H, $CH_2CH(OH)$), 2.00-1.92 (m, 2H, $-CH_2-$), 1.65-1.24 (m, 4H, $-CH_2-$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 133.0, 125.6, 69.2, 52.4, 43.3, 28.4, 25.4, 22.8, 22.2; LRMS (CI/ NH_3) m/z 185 (MH)⁺, 202 (M+ NH_4)⁺; HRMS (CI/ NH_3) exact mass calcd for $(C_{10}H_{16}O_3NH_4)^+$ requires m/z 202.1443, found m/z 202.1448. Enantiomeric excess was determined by GC with a CYCLODEX-B column (14.0 psi, 120 °C); (R) enantiomer t_R = 18.6 min; (S) enantiomer t_R = 19.2 min; 97% ee.



Preparation of (S)-3-(1'-Cyclohexenyl)-2-hydroxypropionic acid (23). To a solution of (S)-ethyl 3-(1' cyclohexenyl)-2-hydroxypropionate (6) (185 mg, 0.93 mmol, 95% ee) in 10 mL MeOH was added 10 mL aqueous 10% KOH. After 2 h, the solution was acidified to pH 2 with 1 N HCl and extracted 3 x 50 mL ethyl acetate. The combined organics were washed with brine (1 x 50 mL) and dried over Na_2SO_4 and concentrated *in vacuo* to afford a white powder (135 mg, 0.79 mmol, 85% yield). m.p. 45-47 °C $[\alpha]_D^{25}$ -14.6° (c 0.5, MeOH); IR (cell, $CHCl_3$) 3518, 3407, 2929, 2858, 1766, 1717, 1438, 1334, 1094 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 5.58 (br s, 1 H, CH=C), 4.34 (dd, J = 4.0, 8.8 Hz, 1H, CHOH), 2.71 (d, J =4.0 Hz, 1H, $-CH_2-$), 2.53 (d, J =4.0 Hz, 1H, $-CH_2COH$), 2.29 (dd, J = 8.8, 14.0 Hz, 1H, $-CH_2COH$), 1.63 (m, 4H, $-CH_2-$), 1.56 (m, 4H, $-CH_2-$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 132.6, 126.5, 68.6, 42.9, 28.2, 25.4, 22.8, 22.2; LRMS (CI/ NH_3) m/z 188 (M+ NH_4)⁺; HRMS (CI/ NH_3) exact mass calcd for $(C_9H_{14}O_3+NH_4)^+$ requires m/z 170.0943, found m/z 170.0943. The title compound was converted to the methyl ester using CH_2N_2 and enantiomeric excess was determined by GC with a CYCLODEX-B column (14.0 psi, 120 °C); (R) enantiomer t_R = 16.9 min; (S) enantiomer t_R = 17.4 min; 95% ee.

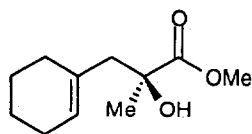


(S)-N-methoxy-N-methyl-3-(1'-cyclohexenyl)-2-hydroxypropionamide (24). To a solution of N,O-dimethylhydroxylamine hydrochloride (202 μ L, 2.5 mmol) in 10 mL of THF at 0 °C was added dropwise 1.25 mL (2.5 mmol, 2.0 M in toluene) of trimethylaluminum solution with the concomitant evolution of gas. The solution was stirred for 30 min at 25 °C. A solution of 99 mg (0.50 mmol) of (S)-methyl 3-(1' cyclohexenyl)-2-hydroxypropionate in 5 mL THF was added dropwise. The resulting solution was refluxed for 18 h. Upon cooling, the solution was added rapidly via cannula into an ice cooled beaker containing 100 mL of aqueous 2% HCl (CAUTION: Gas evolution). The aqueous layer was then brought to pH 8 with $NaHCO_3$. The layers were separated and the aqueous layer was extracted with two 50 mL portions of EtOAc. The combined organics were washed with 50 mL brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography with 40% EtOAc/hexanes afforded 86 mg (82% yield) of the title compound as a white solid. m.p. 47-48 °C $[\alpha]_D^{25}$ +55.7° (c 1.0, CH_2Cl_2); IR (cell, $CHCl_3$) 3493, 2938, 2859, 1658, 1440, 1370, 1195 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 5.51 (br s, 1 H, CH=C), 4.51 (br m, 1 H, CHOH), 3.71 (s, 3H, OCH_3), 3.23 (s, 3H, NCH_3), 3.14 (d, J = 8.1 Hz, 1H, -OH), 2.35 (br d, J = 14.3, 1H, -CHH-), 2.35 (dd, J = 8.5, 13.9, 1H, -CHH-), 2.00 (m, 4H, $-CH_2-$), 1.56 (m, 4H, $-CH_2-$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 133.5, 124.6, 67.6, 61.3, 43.4, 32.4, 28.6, 25.3, 22.8, 22.2; LRMS (EI) m/z 213 (M)⁺; HRMS (EI) exact mass calcd for $(C_{11}H_{19}O_3N)^+$ requires m/z 213.1365 found m/z 213.1375. Enantiomeric excess was determined by NMR of the R and S Mosher esters (>95% ee).



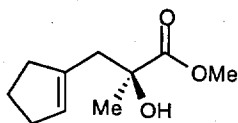
Preparation of (R)-Ethyl 3-(1' Cyclohexenyl)-2-azidopropionate (25). To a solution of 350 mg (1.76 mmol) of (S)-methyl 3-(1' cyclohexenyl)-2-hydroxypropionate (6) in 10 mL DMF at RT was added 774 mg (2.11 mmol) of bis(*para*-nitrophenyl) phosphorazidate forming a heterogeneous solution. Upon addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (250 μ L, 1.67 mmol) the solution became homogeneous and turned yellow. After 12 h at 50 °C, the solution was poured into 2% HCl and extracted with EtOAc (50 mL). The organics were washed with water (3x50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography with 10% EtOAc/hexanes afforded 265 mg (72% yield) of the title compound as a oil.

$[\alpha]_D^{25} +3.3^\circ$ (c 3.0, CH_2Cl_2); IR (film) 2983, 2930, 2106, 1743, 1592, 1524, 1439, 1343, 1285, 1184 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.57 (br s, 1 H, $\text{CH}=\text{C}$), 4.34 (dd, $J=1.2, 7.2$ Hz, 1H, CHOH), 2.71 (d, $J=4.0$ Hz, 1H, $-\text{CH}_2-$), 2.49 (dd, $J=5.8, 14.1$ Hz, 1H, $-\text{CH}_2\text{COH}$), 2.43 (dd, $J=8.89, 14.0$ Hz, 1H, $-\text{CH}_2\text{COH}-$), 1.99 (br m, 4H, $-\text{CH}_2-$), 1.56 (m, 4H, $-\text{CH}_2-$); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 132.1, 126.0, 61.7, 40.1, 27.9, 25.4, 22.1, 14.2; LRMS (CI/NH_3) m/z 188 ($\text{M}+\text{NH}_4$) $^+$; HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{11}\text{H}_{17}\text{O}_2\text{N}+\text{NH}_4)^+$ requires m/z 241.1665 found m/z 241.1658. Enantiomeric excess was determined by GC with a CYCLODEX-B column (15 psi, 100 $^\circ\text{C}$, at $t=60$ min, rate 2.5 $^\circ\text{C}$, final $T=150$ $^\circ\text{C}$); (R) enantiomer $t_r=72.6$ min; (S) enantiomer $t_r=73.0$ min; $\geq 95\%$ ee.



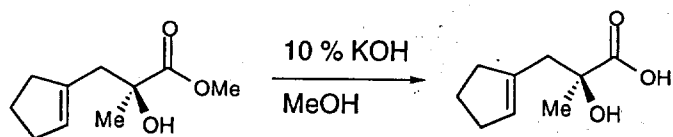
Preparation of (S)-Methyl 3-(1'Cyclohexenyl)-2-hydroxy-2-methylpropionate (26).

Prepared according to Method A (1.5 mL CH_2Cl_2 , reflux, 48 h) using methylenecyclohexane (600 μL , 5.0 mmol), methyl pyruvate (45 μL , 0.5 mmol) and catalyst **2a** (0.10 mmol) to provide the pure product as a clear oil in 84% yield (84 mg, 0.42 mmol, 98% ee) after flash chromatography with 15% EtOAc/hexanes. $[\alpha]_D^{25} +8.5^\circ$ (c 0.6, CH_2Cl_2); IR (film) 3523, 2929, 2858, 1732, 1437, 1216, 1111, 917 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.48 (br s, 1H, $\text{C}=\text{CH}$), 3.74 (s, 3H, OCH_3), 3.04 (br s, 1H, OH), 2.42 (d, $J=13.6$, 1H, $\text{CH}_2\text{CCH}_3(\text{OH})$), 2.26 (d, $J=13.6$ Hz, 1H, $\text{CH}_2\text{CCH}_3(\text{OH})$), 1.94-1.84 (m, 4H, $-\text{CH}_2-$), 1.58-1.46 (m, 4H, $-\text{CH}_2-$), 1.41 (s, 3H, $\text{C}(\text{OH})\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 177.3, 133.3, 162.6, 74.7, 52.5, 48.9, 40.1, 26.1, 25.5, 23.0, 22.1; LRMS (CI/NH_3) m/z 216 ($\text{M}+\text{NH}_4$) $^+$; HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{11}\text{H}_{18}\text{O}_3\text{NH}_4)^+$ requires m/z 216.1600, found m/z 216.1594. Enantiomeric excess was determined by GC with a CYCLODEX-B column (20.0 psi, 110 $^\circ\text{C}$); (R) enantiomer $t_r=13.1$ min; (S) enantiomer $t_r=13.7$ min; 98% ee. Absolute configuration determined by analogy.



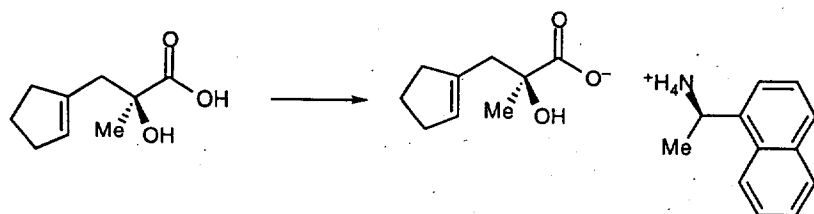
Preparation of (S)-Methyl 3-(1'Cyclopentenyl)-2-hydroxy-2-methylpropionate (27).

Prepared according to Method A (1.5 mL CH_2Cl_2 , reflux, 48 h) using methylenecyclopentane (520 μL , 5.0 mmol), methyl pyruvate (45 μL , 0.5 mmol) and catalyst **2a** (0.025 mmol) to provide the pure product as a clear oil in 95% yield (88 mg, 0.47 mmol, 98% ee) after flash chromatography with 15% EtOAc/hexanes. $[\alpha]_D^{25} +6.1^\circ$ (c 2.0, CH_2Cl_2); IR (film) 3499, 3046, 2952, 2848, 1734, 1455, 1372, 1260, 1205, 1155, 1105, 1038, 983 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.47 (br s, 1H, $\text{C}=\text{CH}$), 3.75 (s, 3H, OCH_3), 3.08 (br s, 1H, OH), 2.60 (d, $J=14.0$ Hz, 1H, $-\text{CH}_2-$), 2.48 (d, $J=14.0$ Hz, 1H, $-\text{CH}_2-$), 2.31-2.14 (br m, 4H, $-\text{CH}_2-$), 1.85 (m, 2H, $-\text{CH}_2-$), 1.42 (s, 3H, $\text{C}(\text{OH})\text{CH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 177.3, 139.3, 129.1, 74.5, 52.6, 42.0, 36.0, 32.5, 26.2, 23.7; LRMS (CI/NH_3) m/z 185 (MH) $^+$, 202 ($\text{M}+\text{NH}_4$) $^+$; HRMS (CI/NH_3) exact mass calcd for $(\text{C}_{10}\text{H}_{16}\text{O}_3\text{NH}_4)^+$ requires m/z 202.1443 found m/z 202.1435. Enantiomeric excess was determined by GC with a CYCLODEX-B column (15.0 psi, 100 $^\circ\text{C}$) (R) enantiomer $t_r=14.3$ min; (S) enantiomer $t_r=15.2$ min; 98% ee.



Preparation of (S)-3-(1'Cyclopentenyl)-2-hydroxy-2-methylpropionic acid.

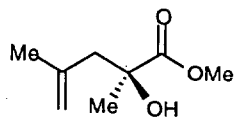
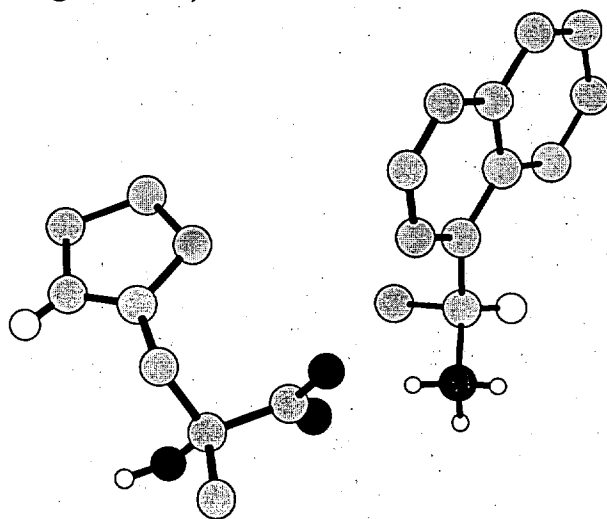
To a solution of (S)-methyl 3-(1'Cyclopentenyl)-2-hydroxy-2-methylpropionate (688 mg, 3.73 mmol) in 20 mL MeOH was added 20 mL aqueous 10% KOH. After 2 h, the solution was acidified to pH 2 with 1 N HCl and extracted 3 x 50 mL ethyl acetate. The combined organics were washed with brine (1 x 50 mL) and dried over Na_2SO_4 and concentrated *in vacuo* to afford a white powder (570 mg, 3.35 mmol, 90% yield). m.p. 82-83 $^\circ\text{C}$ $[\alpha]_D^{25} +14.5^\circ$ (c 0.8, MeOH); IR (cell, CHCl_3) 3541, 3400, 3043, 2928, 2851, 1776, 1745, 1711, 1343, 1290, 1217, 1157 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.54 (br s, 1 H, $\text{CH}=\text{C}$), 2.71 (d, $J=13.9$ Hz, 1H, $-\text{CH}_2-$), 2.50 (s, 1H, OH), 2.53 (d, $J=13.9$ Hz, 1H, $-\text{CH}_2-$), 2.29 (m, 5H, $-\text{CH}_2-$, OH), 1.85 (m, 2H, $-\text{CH}_2-$), 1.49 (s, 3H, $\text{C}(\text{OH})\text{CH}_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 181.4, 138.8, 129.9, 74.3, 41.7, 36.1, 32.5, 26.1, 23.7; LRMS (CI/NH_3) m/z 188 ($\text{M}+\text{NH}_4$) $^+$; HRMS (CI/NH_3) exact mass calcd for $(\text{C}_9\text{H}_{14}\text{O}_3+\text{NH}_4)^+$ requires m/z 188.1287 found m/z 188.1289.



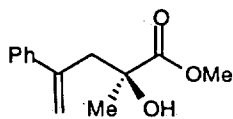
Preparation of (S)-3-(1' Cyclopentenyl)-2-hydroxy-2-methylpropionic acid, (R)-1-(1-naphthyl) ethylammonium salt. To a solution of (S)-methyl 3-(1' cyclopentenyl)-2-hydroxy-2-methylpropionic acid (150 mg, 0.88 mmol) in 5 mL CH₂Cl₂ was added (R)-1-(1-naphthyl)ethylamine (149 μ L, 0.92

mmol). After stirring at RT for 1 hr, solvent was removed *in vacuo* to afford a white powder which was washed 2 x 1 mL hexanes to afford the title compound as a pure compound (300 mg, 0.87 mmol, 99% yield). m.p. 148-149 °C [α]_D²⁵ +1.8° (c 1.0, MeOH); IR (cell, CHCl₃) 3469, 3052, 2930, 2849, 1576, 1335, 1264, 1103 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.91-7.43 (m, 7H, ArH), 6.50 (br s, 3H, NH₄), 5.23 (br s, 1 H, CH=C), 5.12 (q, *J*=6.6 Hz, 1H, -CH(CH₃)), 2.13 (m, 6 H, -CH₂-), 1.70 (m 5H, -CH(CH₃), -CH₂-), 1.01 (s, 3H, C(OH)CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 183.0, 140.6, 136.5, 133.9, 130.1, 129.8, 127.3, 126.9, 126.1, 125.5, 122.5, 122.0, 74.7, 46.7, 41.5, 36.4, 32.5, 26.1, 23.6, 22.0; LRMS (FAB, neg. ion) *m/z* 169 (M)⁻; Anal Calcd for C₂₁H₂₇N₁O₃: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.12; H, 7.90; N 4.01.

X-ray Crystal Structure for (S)-3-(1' Cyclopentenyl)-2-hydroxy-2-methylpropionic acid, (R)-1-(1-naphthyl) ethylammonium salt. (Note structure shown is the enantiomer, absolute assignment based on (R)-1-(1-naphthyl) ethylamine starting material)



Preparation of (S)-Methyl 2-Hydroxy-2-methyl-5-methyl-5-pentenoate (28). To an oven-dried, round-bottom flask containing a magnetic stirring bar was added, in an inert atmosphere box, Cu((S)-*t*-Bu-box)Cl₂ (21.4 mg, 0.05 mmol) and AgSbF₆ (34.3 mg, 0.10 mmol). The flask was fitted with a serum cap, removed from the inert atmosphere box and charged with CH₂Cl₂ (1.0 mL). The mixture was stirred 2-3 h in the absence of light to produce a green solution with a white AgCl precipitate. The mixture was transferred *via* cannula under nitrogen to a syringe fitted with a 0.45 μ filter, and into an oven dried sealed tube with 14/20 side arm joint attached containing methyl pyruvate (45 μ L, 0.5 mmol) and 0.5 mL CH₂Cl₂. The flask was cooled to -78 °C and 2-methylpropene was condensed into the flask using a dry-ice condenser (large excess). The flask was then sealed and allowed to warm to 45 °C for 48 h to provide the product as a clear oil in 76% yield (60 mg, 0.38 mmol, 98% ee) after flash chromatography with 15% EtOAc /hexanes. [α]_D²⁵ +10.5° (c 1.0, CH₂Cl₂); IR (film) 3522, 3077, 2981, 2954, 1733, 1645, 1456, 1427, 1267, 1212, 1115, 981 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.87 (d, *J* = 0.6 Hz, 1H, C=CHH), 4.73 (d, *J* = 0.6 Hz, 1H, C=CHH), 3.76 (s, 3H, OCH₃), 3.13 (br s, 1H, OH), 2.52 (d, *J* = 13.6, 1H, -CH₂-), 2.36 (d, *J* = 13.6, 1H, -CH₂-), 1.74 (s, 3H, C=C-CH₃), 1.43 (s, 3H, C(OH)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 177.2, 141.3, 115.1, 52.6, 48.0, 26.4, 23.9; LRMS (CI/NH₃) *m/z* 159 (MH)⁺, 176 (M+NH₄)⁺; HRMS (CI/NH₃) exact mass calcd for (C₈H₁₄O₃+NH₄)⁺ requires *m/z* 176.1287 found *m/z* 176.1283. Enantiomeric excess was determined by GC with a CYCLODEX-B column (10.0 psi, 80 °C); (R) enantiomer *t*_R = 10.4 min; (S) enantiomer *t*_R = 11.0 min; 98% ee.



Preparation of (S)-Methyl 2-Hydroxy-2-methyl-5-phenyl-5-pentenoate (29). Prepared according to Method A (1.5 mL CH₂Cl₂, reflux, 48 h) using α -methyl styrene (650 μ L, 5.0 mmol), methyl pyruvate (45 μ L, 0.5 mmol) and catalyst **2a** (0.025 mmol) to provide the pure product as a clear oil in 94% yield (103 mg, 0.47 mmol, 98% ee) after flash chromatography with 15% EtOAc/hexanes. [α]_D²⁵ -4.5° (c 2.2, CH₂Cl₂); IR (film) 3519, 3082, 3023, 2952, 1736, 1626, 1448, 1270, 1129, 980 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.24 (m, 5H, ArH), 5.35 (s, 1H, C=CHH), 5.19 (s, 1H, C=CHH), 3.29 (s, 3H, OCH₃), 3.11 (d, J =13.7, 1H, -CH₂-), 3.08 (s, 1H, OH), 2.86 (dd, J =10.9, 1H, -CH₂-), 1.47 (s, 3H, C(OH)CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 176.2, 143.9, 141.2, 128.2, 127.5, 126.8, 74.2, 52.1, 46.2, 25.9; LRMS (EI) m/z 220 (M)⁺, HRMS (EI) exact mass calcd for (C₁₃H₁₆O₃)⁺ requires m/z 220.1100, found m/z 220.1094. Enantiomeric excess was determined by GC with a CYCLODEX-B column (20.0 psi, 110 °C); (R) enantiomer t_r = 38.3 min; (S) enantiomer t_r = 39.4 min; 98% ee.

References and Notes

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