SUPPORTING INFORMATION

Enantioselective H-Atom Transfer Reaction: A Strategy to Synthesize Formaldehyde Aldol Products

Mukund P. Sibi* and Kalyani Patil
Department of Chemistry, North Dakota State University
Fargo, North Dakota 58105
Mukund.Sibi@ndsu.edu

Experimental Procedures. Methylene chloride and THF were dried using Solv-tek solvent purification system prior to use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh). Melting points were determined using the Fisher-Johns melting point apparatus. All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

¹H NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), or a Varian Unity/Inova-400 NB (400 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual CDCl₃ (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, b = broad), coupling constant(s) and integration. ¹³C NMR were recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian Unity/Inova-400 (100 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of CDCl₃ (77.0 ppm) as an internal standard. HPLC analyses were carried out on a Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Millennium³² workstation. Optical rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (HRMS) [ENa⁺] were obtained at the Mass spectrometry Laboratory, Ohio State University, Columbus, OH.

Compounds **5** and **6** were prepared according to the literature procedure.¹

Compound **7** was been prepared according to the literature procedure.²

Compound **15** was prepared by acetylating compound **6** under standard conditions.³

General procedure for enantioselective hydrogen atom transfer reactions using chiral Lewis acid: A suspension of MgI_2 (56 mg/0.2 mmol) and chiral ligand **11** (71 mg/0.2 mmol) in dichloromethane (1 mL) was stirred at room temperature for 45 minutes. This mixture was then cooled in a dry ice/acetone bath. The corresponding acrylate (0.2 mmol) solution in 1.5 mL dichloromethane was added to the suspension and stirred for 30 minutes. To this solution was added the radical precursor (10 mmol), Bu_3SnH (0.2 mL/3.6 mmol), and Et_3B /hexane solution (1.0M, 0.8 mL/3.6 mmol). At once, 5.0 mL O_2 was added via syringe. After complete consumption of starting material (TLC, ~3 h), the reaction was diluted with ether (20 mL). Silica gel (~2.5 g) was added and the mixture was concentrated. The resulting powder was washed with hexanes (100 mL) and the product was eluted with ether (60 mL). Evaporation of the ether fraction yielded the crude product as a colorless oil or solid. Silica gel chromatography furnished the desired compound in good yield.

HPLC analysis of the products:

Some of the products did not separate on HPLC. So we converted the product alcohols to the corresponding benzoates, which then allowed us to assess the enantiomeric purity. The following procedure was used for the conversion.

The products were converted to the corresponding benzoyl derivatives by adding excess benzoyl chloride and pyridine. The reaction mixture was stirred at room temperature for a few hours and after acidic work up, the benzoyl derivatives were obtained in quantitative yields. The enantiomeric purity of the benzoates was determined by HPLC.

2-Hydroxymethyl-pentanoic acid methyl ester 8a (Table 3,

Entry 1): This is a known compound.⁴ R_f = 0.6 (40:60-ethyl acetate:hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.93 (t, J = 7.1 Hz, 3H), 1.34-1.38 (m, 2H), 1.56-1.66 (m, 2H), 2.38 (s, 1H), 2.48-2.66 (m, 1H), 3.72 (s, 3H), 3.78 (bs, 2H); $[\alpha]_D$ 1.3 (c 0.15, CH_2Cl_2).

Benzoic acid 2-methoxycarbonyl-pentyl ester 8aa:

R_f = 0.9 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.36-1.44 (m, 2H), 1.54-1.62 (m, 1H), 1.68-1.77 (m, 1H), 2.86-2.93 (m, 1H), 3.72 (s, 3H), 4.42-4.49 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.52-7.58 (m, 1H), 8.01 (d, *J* = 7.1 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 14.1, 20.5, 31.1, 44.9, 52.1, 65.3, 128.6, 129.8, 130.8, 133.3, 162.5, 172.1; HPLC t_r 12.1 min; t_r 13.1 min [Chiralpak ODH (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 75 %ee.

2-Hydroxymethyl-4-methyl-pentanoic acid methyl ester 8b

(Table 3, Entry 2): Compound **8b** is a known compound.⁵ R_f = 0.6 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.92 (t, *J* = 5.8 Hz, 6H), 1.32-1.38 (m, 1H), 1.41-1.76 (m, 2H), 2.34 (s, 1H), 2.45-2.86 (m, 1H), 3.01-3.07 (m, 2H), 3.70 (s, 3H).

Benzoic acid 2-methoxycarbonyl-4-methyl-pentyl ester 8bb:

R_f = 0.9 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.94 (dd, *J* = 6.5, 3.7 Hz, 6H), 1.38-1.42 (m, 1H), 1.62-1.71 (m, 2H), 2.92-2.99 (m, 1H), 3.72 (s, 3H), 4.37-4.48 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.54-7.56 (m, 1H), 7.99 (d, *J* = 7.7 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.4, 22.9, 26.2, 38.0, 43.4, 52.1, 65.7, 128.6, 129.1, 130.8, 133.3, 166.4, 174.6; HPLC t_r 19.2 min; t_r 22.0 min [Chiralpak OJ (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99.5/0.5, 0.5 mL/min], 88 %ee.

3-Cyclohexyl-2-hydroxymethyl-propionic acid methyl ester 8c

(Table 3, Entry 4): This is a known compound.⁶ R_f = 0.6 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.83-0.92 (m, 2H), 1.13-1.37 (m, 5H), 1.49-1.76 (m, 6H), 2.16 (s, 1H), 2.67-2.72 (m, 1H), 3.71 (s, 3H), 3.72 (s, 2H); [α]_D -15.8 (*c* 1.21, CH₂Cl₂).

Benzoic acid 3-cyclohexyl-2-methoxycarbonyl-propyl ester 8cc: Rf= 0.9 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.86-0.98 (m, 2H), 1.12-1.32 (m, 4H), 1.38-1.46 (m, 1H), 1.62-1.74 (m, 5H), 1.76-1.82 (bd, 1H), 2.95-3.11 (m, 1H), 3.72 (s, 3H), 4.37-4.48 (m, 2H), 7.43 (t, J = 8.1 Hz, 2H), 7.54-7.58 (m, 1H), 7.99 (d, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 26.3, 26.6, 33.2, 33.6, 35.6, 36.6, 42.6, 52.1, 65.8, 128.6, 129.8, 130.2, 133.3, 162.6, 174.7; HPLC t_r 11.8 min; t_r 13.5 min [Chiralpak OJ (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 78 %ee.

2-Hydroxymethyl-4, 4-dimethyl-pentanoic acid methyl ester 8d (Table 3, Entry 5): Rf= 0.6 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.89 (s, 9H), 1.25 (dd, J = 14.1, 3.4 Hz, 1H), 1.71 (dd, J = 14.1, 8.3 Hz, 1H), 2.02 (bs, 1H), 2.63-2.68 (m, 1H), 3.66-3.69 (m, 2H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 29.5, 30.8, 42.3, 44.6, 52.1, 65.5, 176.9; HRMS m/z calcd for $\text{C}_9\text{H}_{18}\text{O}_3\text{Na}^+$: 197.1148, found: 197.1151; $[\alpha]_D$ 2.8 (*c* 1.65, CH_2Cl_2).

Benzoic acid 2-methoxycarbonyl-4, 4-dimethyl-pentyl ester 8dd: Rf= 0.9 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.93 (s, 9H), 1.34 (dd, J = 14.1, 2.9 Hz, 1H), 1.83 (dd, J = 14.1, 9.1 Hz, 1H), 2.91-2.98 (m, 1H), 3.70 (s, 3H), 4.29-4.42 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 8.01 (d, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.2, 29.5, 41.8, 42.4, 52.1, 66.9, 128.6, 129.8, 130.8, 133.3, 166.3, 175.4; HPLC t_r 10.6 min; t_r 12.2 min [Chiralpak OJ (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 92 %ee.

3-Cyclopentyl-2-hydroxymethyl-propionic acid methyl ester 8e (Table 3, Entry 3): Rf= 0.6 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.92 (t, J = 7.3 Hz, 2H), 1.04-1.11 (m, 2H), 1.33-1.38 (m, 2H), 1.48-1.52 (m, 3H), 1.65-1.70 (m, 1H), 1.77-1.81 (m, 1H), 2.15 (bs, 1H), 2.60-2.66 (m, 1H), 3.71 (s, 3H), 3.74 (d, J = 5.5 Hz, 2H); ^{13}C NMR (125

MHz, CDCl₃) δ 13.8, 25.3, 32.8, 32.9, 34.9, 38.1, 47.1, 51.9, 63.6, 176.4; HRMS m/z calcd for C₁₀H₁₈O₃Na⁺: 209.1148, found: 209.1148; [α]_D -10.0 (*c* 1.03, CH₂Cl₂).

Benzoic acid 3-cyclopentyl-2-methoxycarbonylpropyl ester 8ee: R_f= 0.9 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 1.06-1.13 (m, 2H), 1.50-1.58 (m, 3H), 1.59-1.64 (m, 2H), 1.75-1.86 (m, 4H), 2.88-2.96 (m, 1H),

3.72 (s, 3H), 4.39-4.49 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.53-7.56 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 25.2, 25.3, 32.8, 32.9, 35.3, 38.1, 44.7, 52.1, 65.6, 128.6, 129.8, 130.8, 133.3; HPLC *t*_r 20.5 min; *t*_r 24.3 min [Chiralpak OJ (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99.5/0.5, 0.5 mL/min], 90 %ee.

2-Hydroxymethyl-pentanoic acid *tert*-butyl ester 9a (Table 3, Entry 6): R_f= 0.7 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.34-1.39 (m, 2H), 1.47 (s,

9H), 1.58-1.62 (m, 2H), 2.25 (t, *J* = 6.3 Hz, 1H), 2.45-2.48 (m, 1H), 3.68-3.71 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 14.2, 16.6, 20.6, 26.8, 28.3, 30.9, 48.1, 63.5, 81.2, 175.2. HRMS m/z calcd for C₁₀H₂₀O₃Na⁺: 211.1304, found: 211.1306; [α]_D -4.5 (*c* 0.35, CH₃OH).

Benzoic acid 2-*tert*-butoxycarbonyl-pentyl ester 9aa: R_f= 0.9 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.95 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 1.49-1.59 (m, 2H), 1.64-1.72 (m, 2H), 2.73-2.78 (m, 1H), 4.36-

4.44 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.53-7.56 (m, 1H), 8.02 (d, *J* = 7.1 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 14.2, 20.5, 22.2, 28.3, 31.2, 45.9, 65.7, 80.9, 128.6, 129.8, 130.8, 133.2, 166.4, 173.1; HPLC *t*_r 12.6 min; *t*_r 15.6 min [Chiralpak AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 62 %ee.

2-Hydroxymethyl-4-methyl-pentanoic acid *tert*-butyl ester

9b (Table 3, Entry 7): Rf= 0.7 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.91 (dd, *J* = 10.3, 6.5 Hz, 6H), 1.25-1.31 (m, 1H), 1.34-1.41 (m, 1H), 1.46 (s, 9H), 1.51-1.56 (m, 1H), 2.22 (t, *J* = 6.1 Hz, 1H), 2.51-2.56 (m, 1H), 3.68 (t, *J* = 5.75 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 13.8, 16.6, 22.6, 22.9, 26.1, 28.3, 37.9, 46.5, 63.9, 81.1, 175.6; HRMS *m/z* calcd for C₁₁H₂₂O₃Na⁺: 225.1461, found: 225.1456; [α]_D 1.7 (*c* 0.45, CH₃OH).

Benzoic acid 2-*tert*-butoxycarbonyl-4-methyl-

pentyl ester 9bb: Rf= 0.9 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.95 (t, *J* = 5.5 Hz, 6H), 1.30-1.36 (m, 1H), 1.43 (s, 9H), 1.61-1.70 (m, 2H), 2.81-2.88 (m, 1H), 4.32-4.44 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.53-7.55 (m, 1H), 8.02 (d, *J* = 7.1 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.3, 23.1, 26.2, 28.2, 38.1, 44.4, 66.1, 80.9, 128.6, 129.8, 130.2, 133.2, 162.6, 173.4; HPLC *t*_r 16.6 min; *t*_r 20.9 min [Chiralpak AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 55 %ee.

3-Cyclohexyl-2-hydroxymethyl-propionic acid *tert*-butyl

ester 9c (Table 3, Entry 9): Rf= 0.7 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 1.12-1.30 (m, 5H), 1.32-1.41 (m, 1H), 1.46 (s, 9H), 1.49-1.53 (m, 1H), 1.58-1.80 (m, 6H), 2.28 (t, *J* = 6.3 Hz, 1H), 2.52-2.59 (m, 1H), 3.66 (t, *J* = 5.9 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 26.4, 26.7, 28.3, 33.3, 33.6, 35.6, 36.3, 45.8, 63.9, 81.1, 175.5; HRMS *m/z* calcd for C₁₄H₂₆O₃Na⁺: 265.1774, found: 265.1781; [α]_D 0.57 (*c* 0.50, CH₃OH).

Benzoic acid 2-*tert*-butoxycarbonyl-3-cyclohexyl-

propyl ester 9cc: Rf= 0.9 (40:60-ethyl acetate: hexane); ¹H NMR (500 MHz, CDCl₃) δ 0.85-0.93 (m, 2H), 1.13-1.24 (m, 3H), 1.43 (s, 9H), 1.57-1.66 (m, 3H), 1.68-1.74 (m, 4H), 1.79-1.84 (m, 1H), 2.82-2.88 (m, 1H), 4.32-4.43 (m, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.52-

7.56 (m, 1H), 8.01-8.04 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.2, 26.3, 26.4, 26.7, 28.3, 33.1, 33.7, 35.6, 36.5, 43.6, 66.2, 80.9, 128.4, 129.7, 130.3, 133.2, 166.4, 173.4; HPLC t_r 12.8 min; t_r 14.8 min [Chiralpak AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 71 %ee.

2-Hydroxymethyl-4, 4-dimethyl-pentanoic acid *tert*-butyl ester 9d (Table 3, Entry 10): R_f = 0.7 (40:60-ethyl acetate: hexane);

^1H NMR (500 MHz, CDCl_3) δ 0.91 (s, 9H), 1.19 (dd, J = 14.3, 3.2 Hz, 1H), 1.46 (s, 9H), 1.67 (dd, J = 14.1, 7.9 Hz, 1H), 2.1 (bs, 1H), 2.47-2.52 (m, 1H), 3.64 (t, J = 3.9 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.2, 29.6, 30.9, 42.3, 45.4, 65.7, 81.0, 175.8; HRMS m/z calcd for $\text{C}_{12}\text{H}_{24}\text{O}_3\text{Na}^+$: 239.1617, found: 239.1609; $[\alpha]_D$ -3.7 (c 0.30, CH_2Cl_2).

Benzoic acid 2-*tert*-butoxycarbonyl-4, 4-dimethyl-pentyl ester 9dd: R_f = 0.9 (40:60-ethyl acetate: hexane); ^1H

NMR (500 MHz, CDCl_3) δ 0.95 (s, 9H), 1.26 (dd, J = 14.1, 2.6 Hz, 1H), 1.42 (s, 9H), 1.81 (dd, J = 14.1, 8.9 Hz, 1H), 2.80-2.85 (m, 1H), 4.27-4.39 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.53-7.57 (m, 1H), 8.03 (d, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.1, 29.6, 30.9, 42.4, 42.9, 67.3, 80.9, 128.6, 129.8, 130.8, 133.2, 174.2, 176.9; HPLC t_r 10.3 min; t_r 12.0 min [Chiralpak AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 53 %ee.

3-Cyclopentyl-2-hydroxymethyl-propionic acid *tert*-butyl ester 9e (Table 3, Entry 8): R_f = 0.7 (40:60-ethyl acetate: hexane);

^1H NMR (500 MHz, CDCl_3) δ 1.07-1.10 (m, 2H), 1.36-1.43 (m, 1H), 1.46 (s, 9H), 1.49-1.53 (m, 1H), 1.59-1.67 (m, 4H), 1.78-1.83 (m, 3H), 2.25 (t, J = 6.1 Hz, 1H), 2.48-2.50 (m, 1H), 3.69 (t, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.2, 25.3, 28.3, 32.9, 35.1, 38.2, 47.8, 63.8, 81.1, 175.4; HRMS m/z calcd for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{Na}^+$: 251.1617, found: 251.1625; $[\alpha]_D$ 8.1 (c 0.95, CH_2Cl_2).

Benzoic acid 2-tert-butoxycarbonyl-3-cyclopentyl-propyl ester 9ee: $R_f = 0.9$ (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 1.08-1.14 (m, 2H), 1.25 (s, 1H), 1.43 (s, 9H), 1.45-1.52 (m, 2H), 1.59-1.64 (m, 2H), 1.72-1.88 (m, 4H), 2.76-2.81 (m, 1H), 4.33-4.46 (m, 2H), 7.43 (t, $J = 7.9$ Hz, 2H), 7.56 (t, $J = 7.3$ Hz, 1H), 8.01 (d, $J = 7.1$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.2, 25.2, 25.3, 28.3, 32.8, 33.1, 35.2, 38.2, 45.7, 66.1, 80.9, 128.5, 129.1, 130.8, 134.7, 166.4, 173.4; HPLC t_r 13.4 min; t_r 16.4 min [Chiralpak AD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 0.5 mL/min], 69 %ee.

2-Hydroxymethyl-pentanoic acid benzyl ester 10a (Table 3, Entry 11): $R_f = 0.7$ (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.91 (t, $J = 7.3$ Hz, 3H), 1.32-1.42 (m, 2H), 1.49-1.56 (m, 1H), 1.61-1.68 (m, 1H), 2.16 (bs, 1H), 2.63-2.68 (m, 1H), 3.72-3.79 (m, 2H), 5.17 (s, 2H), 7.32-7.39 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.2, 20.6, 30.8, 47.6, 63.3, 66.5, 128.3, 128.5, 128.8, 136.1, 175.5; HRMS m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{Na}^+$: 245.1148, found: 245.1148; $[\alpha]_D$ 1.0 (c 1.42, CH_2Cl_2); HPLC t_r 13.2 min; t_r 14.6 min [Chiralpak OD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 0.5 mL/min], 40 %ee.

2-Hydroxymethyl-4-methyl-pentanoic acid benzyl ester 10b (Table 3, Entry 12): $R_f = 0.7$ (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.89 (dd, $J = 12.5, 6.2$ Hz, 6H), 1.31-1.39 (m, 1H), 1.54-1.62 (m, 2H), 2.08 (bs, 1H), 2.69-2.72 (m, 1H), 3.74 (bs, 2H), 5.16 (s, 2H), 7.34-7.37 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.6, 22.7, 26.1, 37.7, 45.9, 63.7, 66.6, 128.3, 128.5, 128.8, 135.1, 175.7; HRMS m/z calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3\text{Na}^+$: 259.1304, found: 259.1286; $[\alpha]_D$ -1.8 (c 1.43, CH_2Cl_2); HPLC t_r 22.7 min; t_r 25.3 min [Chiralpak OD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 96/4, 0.5 mL/min], 44 %ee.

3-Cyclohexyl-2-hydroxymethyl-propionic acid

benzyl ester 10c (Table 3, Entry 14): Rf= 0.7 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.82-0.88 (m, 1H), 1.12-1.16 (m, 3H), 1.18-1.26 (m, 1H), 1.31-1.38 (m, 1H), 1.54-1.58 (m, 1H), 1.61-1.68 (m, 5H), 1.72-1.76 (m, 1H), 2.08 (bs, 1H), 2.72-2.78 (m, 1H), 3.71-3.76 (m, 2H), 5.11-5.23 (m, 2H), 7.34-7.39 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 26.3, 26.4, 26.6, 33.3, 33.5, 35.5, 36.2, 45.2, 63.9, 66.6, 128.4, 128.5, 128.8, 136.1, 175.8; HRMS m/z calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3\text{Na}^+$: 299.1617, found: 299.1617; $[\alpha]_D$ -1.85 (c 1.45, CH_2Cl_2); HPLC t_r 15.9 min; t_r 17.6 min [Chiralpak OD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 0.5 mL/min], 41 %ee.

2-Hydroxymethyl-4,4-dimethyl-pentanoic acid

benzyl ester 10d: Rf= 0.7 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.89 (s, 9H), 1.26 (dd, J = 14.3, 3.4 Hz, 1H), 1.74 (dd, J = 14.1, 8.1 Hz, 1H), 1.97 (bs, 1H), 2.68-2.70 (m, 1H), 3.69-3.73 (m, 2H), 5.15 (s, 2H), 7.31-7.37 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 29.5, 30.9, 42.2, 44.8, 65.5, 66.7, 128.4, 128.5, 128.8, 135.9, 176.2; HRMS m/z calcd for $\text{C}_{15}\text{H}_{22}\text{O}_3\text{Na}^+$: 273.1461, found: 273.1473.

3-Cyclopentyl-2-hydroxymethyl-propionic acid

benzyl ester 10e (Table 3, Entry 13): Rf= 0.7 (40:60-ethyl acetate: hexane); ^1H NMR (500 MHz, CDCl_3) δ 1.02-1.11 (m, 2H), 1.33-1.41 (m, 1H), 1.46-1.52 (m, 3H), 1.58-1.62 (m, 2H), 1.68-1.82 (m, 3H), 2.05 (t, J = 6.3 Hz, 1H), 2.64-2.72 (m, 1H), 3.74-3.79 (m, 2H), 5.16 (d, J = 3.2 Hz, 2H), 7.26-7.39 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.2, 26.8, 29.3, 32.9, 34.9, 38.1, 47.3, 63.7, 66.6, 128.3, 128.5, 128.8, 136.1, 175.7; HRMS m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{Na}^+$: 285.1461, found: 285.1448; $[\alpha]_D$ -3.03 (c 1.15, CH_2Cl_2); HPLC t_r 13.6 min; t_r 14.8 min [Chiralpak OD (0.46 cm x 50 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 0.5 mL/min], 48 %ee.

3-Acetoxy-2-cyclohexylmethyl-propionic acid *tert*-butyl ester 16 (Table 4, Entry 1): R_f = 0.7 (40:60-ethyl acetate:hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.86-0.92 (m, 2H), 1.10-1.28 (m, 5H), 1.45 (s, 9H), 1.47-1.51 (m, 1H), 1.62-1.72 (m, 4H), 1.76-1.81 (m, 1H), 2.03 (s, 3H), 2.65-2.72 (m, 1H), 4.06-4.18 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.0, 26.3, 26.4, 26.6, 28.2, 28.3, 30.1, 33.7, 35.6, 36.6, 43.5, 65.7, 80.8, 170.9, 173.5; HRMS m/z calcd for $\text{C}_{16}\text{H}_{28}\text{O}_4\text{Na}^+$: 307.1879, found: 307.1899. The ee for the product was determined by hydrolysis to the alcohol followed by benzoate formation (see compound **9cc**). ee = 34%.

2-Acetoxymethyl-4-methyl-pentanoic acid *tert*-butyl ester 17 (Table 4, Entry 3): R_f = 0.7 (40:60-ethyl acetate:hexane); ^1H NMR (500 MHz, CDCl_3) δ 0.91 (t, J = 5.9 Hz, 6H), 1.18-1.26 (m, 1H), 1.44 (s, 9H), 1.48-1.56 (m, 2H), 2.03 (s, 3H), 2.60-2.69 (m, 1H), 4.06-4.17 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.0, 22.3, 23.1, 26.2, 28.2, 28.3, 31.1, 38.0, 44.2, 65.6, 80.9, 170.9, 173.3; HRMS m/z calcd for $\text{C}_{13}\text{H}_{24}\text{O}_4\text{Na}^+$: 267.1566, found: 267.1572. The ee for the product was determined by hydrolysis to the alcohol followed by benzoate formation (see compound **9bb**). ee = 36%.

Determination of absolute stereochemistry of **8c**, **9c**, **10c**, and **16**:

Note: These sequences have not been optimized for yields.

Compound **8c** is known.⁶ The absolute stereochemistry of **8c** was determined to be (*S*) by comparing the sign of rotation with that of the known sample, $[\alpha]_D -15.8$ (c 1.215, CH_2Cl_2), lit $[\alpha]_D -19.0$ (c 2.3, CH_2Cl_2).⁶ Compound **9c** was hydrolyzed and was converted to the known methyl ester **8c**. The absolute stereochemistry of **9c** was determined to be (*R*) by comparing the sign of rotation with that of the known sample, $[\alpha]_D 13.1$ (c 0.55, CH_2Cl_2), lit $[\alpha]_D -19.0$ (c 2.3, CH_2Cl_2).⁶

General procedure for hydrolysis of *t*-butyl ester: To a solution of **9c** (0.2 mmol) in dichloromethane (10 mL), was added trifluoroacetic acid (0.5 mL) and the solution was stirred for 2-3 hours. After complete consumption of the starting material, the reaction mixture was concentrated in vacuum and was purified by flash chromatography to furnish the desired compound in 75-80% yield.

General procedure for the preparation of methyl ester: To a solution of **18** (0.11 mmol) in methanol (2 mL) at 0 °C was added trimethylsilyldiazomethane (0.09 mL/ 0.16 mmol) till yellow color persisted. The resulting solution was stirred at 0 °C for 1 hour and the reaction mixture was concentrated in vacuum and was purified by flash chromatography to furnish the desired compound in 78% yield.

Compound **10c** was subjected to standard hydrogenation condition, and then converted to the known methyl ester. The absolute stereochemistry of **10c** was determined to be (*S*) by comparing the sign of rotation with that of the known sample, $[\alpha]_D -7.4$ (c 0.78, CH_2Cl_2), lit $[\alpha]_D -19.0$ (c 2.3, CH_2Cl_2).⁶

Deprotection of the acetate group by $\text{K}_2\text{CO}_3/\text{MeOH}$ in compound **16** provided **9c** which was then hydrolyzed and converted to the methyl ester using above procedures. The absolute stereochemistry of **16** was determined to be (*S*) by comparing the sign of

rotation with that of the known sample, $[\alpha]_D -6.1$ (c 0.75, CH_2Cl_2), lit $[\alpha]_D -19.0$ (c 2.3, CH_2Cl_2).⁶

References

- (1) Basavaiah, D.; Krishnamacharyulu, M.; Rao, J. *Synth. Commun.* **2000**, *30*, 2061.
- (2) O'Leary, B. M.; Szabo, T.; Svenstrup, N.; Schalley, C. A.; Lutzen, A.; Schafer, M.; Rebek Jr. J. *J. Am. Chem. Soc.* **2001**, *123*, 11519.
- (3) Avci, D.; Kusefoglu, S. H.; Thompson, R. D.; Mathias, L. J. *J. Poly. Sci. Part A: Poly. Chem.* **1994**, *32*, 2937.
- (4) Hermann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *26*, 2429.
- (5) Park, J. D.; Kim, D. H. *J. Med. Chem.* **2002**, *45*, 911.
- (6) Imorgai, H.; Larcheveque, M. *Tetrahedron: Asymmetry* **1997**, *8*, 965.