Preparation of *Syn*- α,β -Dialkyl β -Amino Acids That Contain Polar Functionality

*Joseph M. Langenhan and Samuel H. Gellman**

Department of Chemistry, University of Wisconsin, Madison, WI 53706-1396

gellman@chem.wisc.edu

Table of Contents

Experimental Section	S2
General Procedures	S2
Preparation of 2-7	S4
Assignment of α,β -unsaturated ester stereochem.	S21
Preparation of Mosher Amides	S22
^1H and ^{13}C NMR spectra	S25-S86
References	S87

Experimental Section

General Procedures.

Melting points (mp) were obtained on a capillary melting point apparatus and are uncorrected. Optical rotations were measured on a digital polarimeter using sodium light (D line, 589.3 nm); concentrations (c) are reported in g / 100 mL. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in deuterated solvents on a 300 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (0.00) for *d*-chloroform, or the residual protic solvent peak for other solvents. ^1H NMR splitting patterns with observed first order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m), broad (br), or apparent (a). Minor isomer resonances are reported in brackets. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 300 MHz spectrometer. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra are referenced to TFA (-78.50 ppm). Mass spectra (MS) were obtained using electrospray ionization. THF and benzene were distilled from sodium benzophenone ketyl under nitrogen. Et_3N and CH_2Cl_2 were distilled from CaH_2 . Hexanes were distilled at atmospheric pressure. Commercially available reagents and solvents were used without further purification. Analytical thin layer chromatography (TLC) was carried out on TLC plates pre-coated with silica gel 60 (250 μm layer thickness). Visualization was accomplished using either a UV lamp, potassium permanganate stain (2 g KMnO_4 , 13.3 g K_2CO_3 , 2 mL 2M NaOH, 200 mL H_2O), or phosphomolybdic acid stain (10 % phosphomolybdic acid in ethanol). Flash

column chromatography was performed on silica gel 60 (230 – 400 mesh). Solvent mixtures used for TLC and flash column chromatography are reported in v/v ratios.

Procedure A (preparation of α,β -unsaturated esters). A flame-dried flask was charged with THF (5 mL/mmol *t*-butyl ester) and cooled to 0 °C. *i*-Pr₂NH (1.08 eq.) was added via syringe, followed by 2.5 M *n*-BuLi in hexane (1.04 eq.). The solution was allowed to warm to rm temp, and was then cooled to -78 °C via a dry ice acetone bath. *tert*-Butyl ester (1.0 eq.) was added to this solution dropwise via syringe pump over ~20 min, and the solution was stirred for 45 min. Aldehyde was added and the solution was stirred 15 min. Saturated aq. NH₄Cl was added, and the reaction was allowed to warm to rm temp. THF was removed via rotary evaporation, and the remaining solution was diluted with water. The aqueous layer was extracted three times with Et₂O. The combined organic extracts were dried over MgSO₄. The crude product was obtained by rotary evaporation of the solvent. The aldol product was dissolved in CH₂Cl₂ (5 mL/mmol *t*-butyl ester) and cooled to 0 °C. DMAP (1.1 eq.) was added followed by TsCl (1.1 eq.), and Et₃N (2.0 eq.). The solution was stirred overnight at rm temp, washed two times with 1 M HCl, dried over MgSO₄, and concentrated. The resulting tosyl esters were dissolved in Et₂O (5 mL/mmol tosyl ester) and cooled to -78 °C. KO*t*-Bu was added and the reaction was stirred for 2 h or until complete by TLC. The reaction mixture was concentrated; the residue was partitioned between Et₂O and 1 M HCl. The layers were separated, and the aq. layer was extracted one additional time with Et₂O. The combined organic layers were dried over MgSO₄ and concentrated to provide the crude α,β -unsaturated ester.

Procedure B (protecting group manipulation for hydrophobic residues). The tertiary amino ester was dissolved in *t*-BuOH (10 mL/mmol tertiary amino ester). Pd (10 % on carbon) was added (~ 80 % by weight) followed by HCOONH₄ (5.0 eq.). The reaction mixture was lightly refluxed overnight, then cooled, filtered through Celite, and concentrated. The residue was dissolved in 80 % TFA in CH₂Cl₂ (2 mL/mmol tertiary amino ester) and stirred for 2 h. The TFA solution was evaporated under a stream of nitrogen, and the remaining residue was dissolved in benzene and evaporated two times to remove residual TFA. The resulting crude amino acid was dissolved in acetone/water (2:1, 10 mL/mmol tertiary amino ester) and cooled to 0 °C. NaHCO₃ (5.0 eq.) was added, followed by FmocOSu (0.95 eq.), and the mixture was stirred overnight at room temp. The reaction mixture was acidified to pH 2 with 1 M HCl, and the acetone was removed via rotary evaporation. The aq. residue was extracted three times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, and concentrated to provide the crude Fmoc-protected amino acid.

Benzyl-(5-oxo-pentyl)-carbamic acid *tert*-butyl ester (2b). 5-(*tert*-butoxycarbonyl)amino valeric acid (50 g, 230 mmol) was dissolved in *t*-BuOH (1400 mL). Boc₂O (70.3 g, 322 mmol) and DMAP (8.43 g, 69.0 mmol) were added and the reaction mixture was stirred overnight at 40 °C. The solution was concentrated, and the residue was redissolved in Et₂O. The Et₂O solution was washed two times with 1 M HCl and two times with sat. aq. NaHCO₃. The organic layer was dried over MgSO₄. The crude material was partially purified by SiO₂ column chromatography eluting with 1:3

Et₂O/hexane (TLC R_f = 0.18 in 1:4 Et₂O/hexane) affording 44.64 g of *tert*-butyl ester. A significant amount of an unknown impurity was present. Product ¹³C resonances upfield of 40 ppm could not be distinguished from impurity resonances; therefore, all the observed resonances in this region are listed: ¹H NMR (CDCl₃, 300 MHz) δ 4.78 (m, 1H), 3.12 (aq, 2H), 2.24 (m, 2H), 1.66-1.21 (m, 4H), 1.44 (s, 18H); ¹³C NMR (CDCl₃, 75.4 MHz): δ 172.7, 155.6, 79.9, 78.7, 67.3, 40.0, 34.9, 34.0, 29.3, 28.2, 27.9, 27.7, 22.1, 21.7; Electrospray ionization-MS *m/z* (M + Na) calculated for C₁₄H₂₇O₄NNa 296.3, observed 296.1. To a solution of the impure Boc-protected ester (44.6 g, 163 mmol) in THF (163 mL) at 0 °C was added KO^t-Bu (19.2 g, 171 mmol). The solution was stirred 15 min, and then BnBr (23.3 mL, 196 mmol) was added dropwise. The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was suspended in 1 M HCl and extracted three times with Et₂O. The combined organic layers were dried over MgSO₄ and concentrated. The crude residue was partially purified by SiO₂ column chromatography eluting with 5:1 hexane/Et₂O (TLC R_f = 0.34 in 1:4 Et₂O/hexane). This protocol afforded 39.6 g of 5-(benzyl-*tert*-butoxycarbonyl-amino)-pentanoic acid *tert*-butyl ester. Line broadening in the ¹H spectrum and extra resonances observed in the ¹³C spectrum were attributed to tertiary carbamate rotamers: ¹H NMR (CDCl₃, 300 MHz) δ 7.25 (m, 5H), 4.43 (m, 2H), 3.17 (br d, 2H), 2.19 (m, 2H), 1.53-1.42 (m, 13H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 75.4 MHz): δ 172.5, 155.4, 138.3, 130.6, 128.6, 128.5, 128.2, 127.4, 126.9, 79.7, 79.3, 67.1, 63.8, 50.2, 49.5, 34.9, 34.0, 33.2, 28.2, 27.9, 27.7, 27.5, 27.2, 22.1, 21.6; Electrospray ionization-MS *m/z* (M + Na) calculated for C₂₁H₃₃O₄NNa 386.4, observed 386.1. The protected amino ester (25.6 g, 70.4 mmol) was dissolved in CH₂Cl₂ (700 mL) and cooled to -78 °C. DIBAL-H (88 mL, 88.0 mmol,

1 M solution in CH₂Cl₂) was added dropwise. After 40 min, MeOH was added to quench excess hydride, and the reaction mixture was warmed to rt temp and poured into a solution of sat. sodium potassium tartrate. The resulting mixture was stirred for 30 min, and then the layers were separated. The aqueous layer was extracted three times with CH₂Cl₂, and the combined organic layers were dried over MgSO₄ and concentrated. SiO₂ column chromatography of the residue, eluting with 1:1 hexane/Et₂O (TLC R_f=0.46), afforded aldehyde **2b** (10.86 g, 25 % yield over three steps): ¹H NMR (CDCl₃, 300 MHz) δ 9.66 (t, 1H, *J* = 1.6), 7.24 (m, 5H), 4.41 (s, 2H), 3.18 (m, 2H), 2.36 (br s, 2H), 1.47 (m, 13H); ¹³C NMR (CDCl₃, 75.4 MHz): δ 201.3, 155.1, 138.0, 128.0, 127.1, 126.6, 79.0, 49.9, 49.4, 45.6, 42.8, 27.9, 26.9, 18.7; Electrospray ionization-MS *m/z* (M + Na) calculated for C₁₇H₂₅O₃NNa 314.3, observed 314.1.

(1R,2S,αR)-6-(Benzyl-*tert*-butoxycarbonyl-amino)-2-{1-[N-benzyl-N-α-methylbenzylamino]-ethyl}-*tert*-butyl hexanoate (5a). To a solution of dioxane/water (2:1, 415 mL) was added 6-aminocaproic acid (20 g, 152 mmol), and 2 M NaOH (76 mL). The mixture was cooled to 0 °C, and Boc₂O (36.6 g, 168 mmol) was added. The reaction mixture was stirred overnight. Dioxane was removed under reduced pressure, and EtOAc was then added. The reaction solution was acidified to pH 2 with 1 M HCl, and extracted three times with EtOAc. The combined organic layers were dried over MgSO₄. A white crust was obtained in quantitative yield after the solvent was removed. The material (35.3 g, 152 mmol) was dissolved in *t*-BuOH (1525 mL). Boc₂O (46.6 g, 213 mmol) and DMAP (5.59 g, 45.7 mmol) were added and the reaction mixture was stirred overnight at 40 °C. The solution was concentrated, and the residue was redissolved in Et₂O; then the solution was washed two times with 1 M HCl. The organic

layer was dried over MgSO_4 and concentrated. The crude residue was partially purified by SiO_2 column chromatography eluting with 1:2 Et_2O /hexane (TLC R_f = 0.35) affording 34.84 g of 6-*tert*-butoxycarbonylamino-hexanoic acid *tert*-butyl ester. A significant amount of an unknown impurity was present. Product ^{13}C resonances upfield of 40 ppm could not be distinguished from impurity resonances; therefore, all the observed resonances in this region are listed: ^1H NMR (CDCl_3 , 300 MHz) δ 5.07 (m, 1H), 3.10 (q, 2H), 2.23 (m, 2H), 1.66-1.21 (m, 6H), 1.44 (s, 18H); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 172.6, 155.7, 79.5, 78.2, 66.9, 39.9, 35.0, 34.1, 29.4, 28.0, 27.7, 25.8, 24.3, 21.4; Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{15}\text{H}_{29}\text{O}_4\text{NNa}$ 310.3, observed 310.1. To a solution of the crude protected amino ester (34.8 g, 121 mmol) in THF (120 mL) at 0 °C was added KOt-Bu (15.0 g, 133 mmol). The solution was stirred 15 min, and then BnBr (17.3 mL, 145 mmol) was added dropwise. The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was suspended in 1 M HCl and extracted three times with Et_2O . The combined organic layers were dried over MgSO_4 and concentrated. The crude residue was partially purified by SiO_2 column chromatography eluting with 5:1 hexane/ Et_2O (TLC R_f = 0.26). This protocol afforded 35.0 g (61 % yield over three steps) of **1a** that was contaminated with an unknown impurity: ^1H NMR (CDCl_3 , 300 MHz) δ 7.25 (m, 5H), 4.43 (m, 2H), 3.16 (br d, 2H), 2.19 (m, 2H), 1.61-1.19 (m, 6H), 1.49 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 172.4, 155.5, 155.1, 138.3, 128.6, 128.3, 128.0, 127.9, 127.8, 127.3, 126.9, 126.7, 79.4, 79.0, 66.8, 50.1, 49.4, 46.1, 45.8, 35.0, 34.1, 28.0, 27.7, 27.3, 25.9, 24.4, 21.4; Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{22}\text{H}_{35}\text{O}_4\text{NNa}$ 400.4, observed 400.1. Via procedure A, *tert*-butyl ester **1a** (35.0 g, 92.7 mmol) underwent an

aldol reaction with **2a** (6.52 mL, 116 mmol), and was converted to the corresponding tosylate. The crude tosylates were purified by SiO₂ column chromatography eluting with hexane/Et₂O (3:1; v/v) affording two inseparable diastereomers (TLC R_f = 0.14, 0.17), 28.74 g as a light yellow oil: Electrospray ionization-MS *m/z* (M + Na) calculated for C₃₁H₄₅O₇NSNa 598.7, observed 598.1. Crude **3a** was partially purified by SiO₂ column chromatography eluting with Et₂O/hexanes (1:6; v/v). A 91:9 E/Z mixture was obtained as a clear oil (TLC R_f = 0.27, 0.21), 11.7 g. NMR resonance doubling was attributed to tertiary carbamate rotamers: ¹H NMR (CDCl₃, 300 MHz): 7.30 (m, 5H), 6.74 and 6.81 (q, atropisomeric, 1H, *J* = 7.2) [5.82 (q, 0.09H, *J* = 7.1)], 4.42 (br s, 2H), 3.18 (br d, 2H), 2.26 (m, 2H), 1.73 (d, 3H, *J* = 7.2) [1.90 (d, 0.46H, *J* = 7.1)], 1.49 (m, 16H); ¹³C NMR (CDCl₃, 75.4 MHz): δ 166.9, 155.7, 155.3, 138.4, 135.8, 134.3, 128.2, 127.4, 126.8, 79.5, 79.1, 50.1, 49.7, 46.2, 28.2, 28.0, 26.1, 25.9, 13.9; Electrospray ionization-MS *m/z* (M + Na) calculated for C₂₄H₃₇O₄NNa 426.4, observed 426.1. Conjugate addition of **4** to **3a** (11.7 g, 28.9 mmol) was carried out using the conditions described by Davies.¹ The first column was eluted with hexane/Et₂O (5:1; v/v) to remove 2,6-di-*tert*-butylphenol. The second column was eluted with 2.5 % Et₂O in benzene. Product **5a** (TLC R_f = 0.13 in 1:9 Et₂O/hexane) was obtained as an oil, 6.73 g (12 % yield over three steps), estimated > 90 % d.e. by ¹H NMR integration: ¹H NMR (CDCl₃, 300 MHz) δ 7.31-7.07 (m, 15H), 4.38 (br d, 2H), 3.91 (q, 1H, *J* = 6.9), 3.75 (A of AB, 1H, *J* = 14.1), 3.65 (B of AB, 1H, *J* = 14.1), 3.10-2.87 (m, 3H), 2.12 (m, 1H), 1.48-1.22 (m, 24H), 1.09 (d, 3H, *J* = 6.6); ¹³C NMR (CDCl₃, 75.4 MHz): δ 175.0, 144.2, 141.1, 128.8, 128.3, 128.2, 128.04, 127.99, 127.7, 126.9, 126.6, 126.5, 79.9, 79.3, 57.0, 53.6, 52.2, 50.1, 46.4, 30.3, 28.4, 27.9, 24.6,

15.0; Electrospray ionization-MS m/z ($M + H$) calculated for $C_{39}H_{55}O_4N_2$ 615.9, observed 615.4.

(1R,2S)-6-(Benzyl-*tert*-butoxycarbonyl-amino)-2-(1-benzyloxycarbonylamino-ethyl)-hexanoic acid (6a). Amino ester **5a** (6.73 g, 10.9 mmol) was dissolved in *t*-BuOH (110 mL) and ~5 g of 10 % Pd-C was added, followed by $HCOONH_4$ (3.45 g, 54.7 mmol). The reaction mixture was heated at a light reflux overnight, cooled, filtered through Celite, and concentrated. The residue was dissolved in 2:1 acetone/water (110 mL) and cooled to 0 °C. $NaHCO_3$ (9.19 g, 109 mmol) and Cbz-OSu (3.54 g, 14.2 mmol) were added, and the reaction mixture was stirred at room temperature overnight. The acetone was removed under reduced pressure, and the mixture was acidified to pH 2 with 1 M HCl, then extracted three times with CH_2Cl_2 , dried over $MgSO_4$, and concentrated. The crude residue was partially purified by SiO_2 column chromatography eluting with 1:1 Et_2O /hexane (TLC R_f = 0.38). The product was obtained as an oil, 3.39 g. This material was dissolved in 80 % TFA in CH_2Cl_2 (65 mL) and stirred for 2 h. The TFA/ CH_2Cl_2 solvent was evaporated using a stream of nitrogen, then dissolved in benzene and evaporated two times to remove residual TFA. The residue was dissolved in THF (85 mL) and cooled to 0 °C. Et_3N (19 mL, 137 mmol) and Boc_2O (2.81 g, 12.9 mmol) were added, and the reaction mixture was stirred at room temperature for two days. The reaction mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and 1 M HCl. The aqueous layer was extracted three times with CH_2Cl_2 , and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by SiO_2 column chromatography eluting with 2:1 Et_2O /hexane with 0.5 % acetic acid (TLC

$R_f = 0.22$). The product acid **6a** was obtained as an oil, 2.79 g (53 % yield over two steps). NMR resonance doubling was attributed to tertiary carbamate rotamers: ^1H NMR (CDCl_3 , 300 MHz) δ 10.29 (br s, 0.68H), 7.42-7.18 (m, 10H), 5.25 and 6.04 (m, 1H, atropisomeric), 5.08 (m, 2H), 4.39 (s, 2H), 3.90 (m, 1H), 3.13 (m, 2H), 2.48 (m, 1H), 1.70-1.10 (m, 15H), 1.14 (d, 3H, $J = 6.6$); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 178.1, 155.6, 138.4, 136.8, 128.4, 128.2, 128.0, 127.0, 79.7, 66.6, 50.3, 49.7, 48.0, 46.2, 28.3, 27.9, 27.6, 24.8, 17.3; Electrospray ionization-MS m/z ($M - H$) calculated for $\text{C}_{28}\text{H}_{37}\text{O}_6\text{N}_2$ 497.6, observed 497.2.

(1R,2S)-6-tert-Butoxycarbonylamino-2-[1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-hexanoic acid (7a). Ammonia (280 mL) was condensed in a three-neck round bottom flask at $-78\text{ }^\circ\text{C}$. Sodium (771 mg, 33.5 mmol) was added, and the resulting blue solution was stirred for 30 min. A solution of **6a** (2.79 g, 5.59 mmol) in THF (62 mL) was added dropwise to the reaction solution, and the reaction solution was stirred for 30 min at $-78\text{ }^\circ\text{C}$. The reaction was quenched by the addition of NH_4OAc (2.8 g, 36.3 mmol) and the ammonia was allowed to evaporate. Precautions were taken to ensure that water did not enter the reaction vessel during evaporation. Once evaporation was complete, the remaining THF was removed under reduced pressure. The residue was dissolved in water and lyophilized. The resulting white crust was dissolved in 2:1 acetone/water (60 mL). The pH was checked to ensure that it was neutral. NaHCO_3 (4.70 g, 55.9 mmol) and FmocOSu (5.66 g, 16.8 mmol) were added, and the mixture was stirred at rt overnight. The acetone was removed under reduced pressure, and the remaining mixture was acidified to pH 2 with 1 M HCl and then extracted three times

with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and concentrated. The crude material was purified by SiO_2 column chromatography eluting with 2:1 hexane/acetone. The product was recrystallized by dissolving the material in chloroform (rm temp), adding hexane until the solution became turbid, and refrigerating for 30 min. After filtration, the Fmoc-protected amino acid **7a** was obtained as a white solid, 1.92 g (69 % yield). (TLC $R_f=0.54$ in 1:1 acetone/hexanes): mp 161-164.5 °C; ^1H NMR (d_6 -acetone, 300 MHz) δ 7.85 (d, 2H, $J = 7.2$), 7.69 (d, 2H, $J = 7.3$), 7.43-7.30 (m, 4H), 6.44 (d, 0.67H, $J = 8.9$), 5.93 (bs, 0.89H), 4.44-4.20 (m, 3H), 3.89 (m, 1H), 3.04 (m, 2H), 2.49 (m, 1H), 1.63-1.20 (m, 6H), 1.39 (s, 9H), 1.19 (d, 3H, $J = 6.5$); ^{13}C NMR (d_6 -acetone, 75.4 MHz): δ 175.5, 156.6, 145.1, 142.1, 128.5, 127.9, 126.1, 126.0, 120.8, 78.3, 66.7, 52.0, 49.3, 49.2, 48.2, 40.9, 40.8, 30.8, 28.7, 25.4, 19.3; Electrospray ionization-MS m/z (M - H) calculated for $\text{C}_{28}\text{H}_{35}\text{O}_6\text{N}_2$ 495.6, observed 495.3; $[\alpha]_D = -10.5^\circ$ (c 3.33×10^{-1} , CH_3OH); The optical purity was determined as 91 % e.e. (> 97 % de) by integration of the trifluoromethyl groups in the corresponding (R) and (S) Mosher amides.

2,5-Dimethyl-hex-2-enoic acid *tert*-butyl ester (3c). Via procedure A, **1b** (7.0 mL, 46.5 mmol) underwent an aldol reaction with **2c** (5.03 mL, 46.9 mmol), and was converted to the corresponding tosylate. The crude tosylates were purified by SiO_2 column chromatography eluting with hexane/ Et_2O (5:1; v/v) affording two inseparable diastereomers (TLC $R_f=0.28$ and 0.34), 14.24 g as a light yellow oil: Electrospray ionization-MS m/z (M + Na) calculated for $\text{C}_{19}\text{H}_{30}\text{O}_5\text{SNa}$ 393.4, observed 393.1. Crude **3c** was purified by SiO_2 column chromatography eluting with 2.5 % Et_2O in hexanes. A 95:5 E/Z mixture, contaminated with 2 % of a non-conjugated isomer, was obtained as a

clear oil (TLC R_f =0.51), 5.83 g (63 % yield): ^1H NMR (CDCl_3 , 300 MHz) δ 6.69 (tq, 1H, J = 7.5, 1.4) [5.83 (tq, 0.05H, J = 7.6, 1.6)], 2.04 (tq, 2H, J = 7.3, 0.7) [2.30 (tq, 0.16H, J = 7.0, 1.2)], 1.78 (s, 3H), 1.74 (m, 1H), 1.49 (s, 9H), 1.29 (m, 2H), 0.93 (d, 6H, J = 6.6); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 167.5, 140.0, 129.5, 79.7, 37.7, 31.5, 28.3, 22.4, 14.0, 12.4; Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{12}\text{H}_{22}\text{O}_2\text{Na}$ 221.2, observed 221.1.

4-Cyclohexyl-2-methyl-but-2-enoic acid *tert*-butyl ester (3d). Via procedure A, **1b** (5.0 mL, 33.2 mmol) underwent an aldol reaction with 2-cyclohexyl ethanal² (5.05 mL, 36.0 mmol), and was converted to the corresponding tosylate. The crude tosylates were purified by SiO_2 column chromatography eluting with hexane/ Et_2O (9:1; v/v) affording two inseparable diastereomers (TLC R_f =0.45 and 0.38 in 1:4 Et_2O /hexane), 3.34 g as a light yellow oil: Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{22}\text{H}_{34}\text{O}_5\text{SNa}$ 433.5, observed 433.2. Crude **3d** was purified by SiO_2 column chromatography eluting with 5 % Et_2O in hexanes. A 93:7 E/Z mixture was obtained as a clear oil (TLC R_f =0.50 in 1:9 Et_2O /hexane), 1.62 g (20 % yield): ^1H NMR (CDCl_3 , 300 MHz) δ 6.69 (tq, 7.9, 1.4) [5.83 (tq, 0.07H, J = 7.6, 1.4)], 2.03 (t, 2H, J = 7.1) [2.31 (t, 0.16H, J = 7.5)], 1.77 (s, 3H) 1.73-1.63 (m, 6H), 1.48 (s, 9H), 1.29-1.15 (m, 3H), 1.00-0.86 (m, 2H); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 167.1, 139.6, 129.3, 79.3, 37.6 36.3, 34.4, 27.8, 26.2, 26.1, 12.2; Electron impact ionization-MS m/z (M^+) calculated for $\text{C}_{15}\text{H}_{26}\text{O}_2$ 238.4, observed 238.2.

2-Benzyl-but-2-enoic acid *tert*-butyl ester (3f). Via procedure A, **1c** (10.9 g, 53.7 mmol) underwent an aldol reaction with **2a** (3.88 mL, 0.66 mmol), and was converted to

the corresponding tosylate. The crude tosylates were purified by SiO₂ column chromatography eluting with hexane/Et₂O (4:1; v/v) affording two inseparable diastereomers (TLC R_f=0.21 and 0.28), 18.23 g as a light yellow oil: Electrospray ionization-MS *m/z* (M + Na) calculated for C₂₂H₂₈O₅SNa 427.4, observed 427.1. Crude **3f** was purified by SiO₂ column chromatography eluting with Et₂O/hexanes (1:20; v/v). An 87:13 E/Z mixture was obtained as a clear oil (TLC R_f=0.30 and 0.23), 10.03 g (82 % yield): ¹H NMR (CDCl₃, 300 MHz) δ 7.20-7.04 (m, 5H), 6.90 (q, 1H, *J* = 7.2) [5.87 (q, 0.15H, *J* = 7.2)], 3.61 (s, 2H) [3.50 (s, 0.31H)], 1.74 (d, 3H, *J* = 7.2) [1.95 (d, 0.47H, *J* = 7.1)], 1.36 (s, 9H) [1.32 (s, 1.61H)]; ¹³C NMR (CDCl₃, 75.4 MHz): δ 166.5, 139.8 [139.6], 136.9 [136.0], 133.4 [133.5], 128.0 [128.5], 125.6 [125.8], 79.7 [80.0], 31.9 [31.4], 27.7 [22.5], 14.2 [13.9]; Electrospray ionization-MS *m/z* (M + Na) calculated for C₁₅H₂₀O₂Na 255.2, observed 255.1.

2-(4-Methoxy-benzyl)-but-2-enoic acid *tert*-butyl ester (3g). Via procedure A, **1d** (5.0 g, 27.7 mmol) underwent an aldol reaction with **2a** (1.61 mL, 28.6 mmol), and was converted to the corresponding tosylate. The crude tosylates were purified by SiO₂ column chromatography eluting with hexane/Et₂O (4:1; v/v) affording two inseparable diastereomers (TLC R_f= 0.20), 5.75 g (58 % yield) as a light yellow oil: Electrospray ionization-MS *m/z* (M + Na) calculated for C₂₃H₃₀O₆SNa 457.5, observed 457.1. Crude **3g** was purified by SiO₂ column chromatography eluting with Et₂O/hexanes (1:20; v/v). A 94:6 E/Z mixture was obtained as a clear oil (TLC R_f=0.33 and 0.37), 2.86 g (48 % yield): ¹H NMR (CDCl₃, 300 MHz): δ 7.07 (d, 2H, *J* = 8.6), 6.89 (q, 1H, *J* = 7.0) [5.87 (qt, 0.06H, *J* = 7.2, 1.1)], 6.76 (d, 2H, *J* = 8.7), 3.69 (s, 3H), 3.56 (s, 2H), 1.81 (d, 3H, *J* =

7.1) [1.95 (dt, 0.19H, $J = 7.2$, 1.1)], 1.39 (s, 9H); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 166.5, 157.5 [157.7], 136.5 [135.3], 133.7 [133.9], 131.8 [131.5], 128.8 [129.4], 113.3, 79.6 [79.9], 54.7, 30.9 [31.3], 27.7 [27.3], 14.1 [13.8]; Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{Na}$ 285.2, observed 285.1.

2-(3,4,5-Trimethoxy-benzyl)-but-2-enoic acid *tert*-butyl ester (3h). Via procedure A, **1e** (4.92 g, 16.6 mmol) underwent an aldol reaction with **2a** (1.17 mL, 20.8 mmol), and was converted to the corresponding tosylate. The crude tosylates were purified by SiO_2 column chromatography eluting with hexane/ Et_2O (1:1; v/v) affording two inseparable diastereomers (TLC R_f = 0.23, 0.27), 5.23 g as a light yellow oil: Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{25}\text{H}_{34}\text{O}_8\text{SNa}$ 517.5, observed 517.1. Crude **3h** was purified by SiO_2 column chromatography eluting with Et_2O /hexanes (1:20; v/v). A 91:9 E/Z mixture was obtained as a clear oil (TLC R_f = 0.34), 2.88 g (84 % yield): ^1H NMR (CDCl_3 , 300 MHz): 6.94 (q, 0.89H, $J = 7.0$) [5.94 (q, 0.09H, $J = 7.2$, 1.0)], 6.42 (s, 2H) [6.41], 3.83-3.81 (m, 9H) [3.61 (s, 1.89H)], 1.87 (d, 2.69H, $J = 7.1$) [1.98 (dt, 0.28H, $J = 7.2$, 1.2)], 1.43 (s, 9H); ^{13}C NMR (CDCl_3 , 75.4 MHz): δ 166.6, 152.7, 137.1, 135.5, 133.1, 104.9 [105.5], 79.8 [80.1], 60.4, 55.7, 31.9, 27.7, 14.2 [15.2]; Electrospray ionization-MS m/z ($\text{M} + \text{Na}$) calculated for $\text{C}_{16}\text{H}_{22}\text{O}_3\text{Na}$ 345.3, observed 345.1.

(2S,3R, α R)-3-(N-benzyl-N- α -methylbenzylamino)-2,5-dimethyl-*tert*-butyl hexanoate (5c). Conjugate addition of **4** to **3c** (5.83 g, 29.4 mmol) was carried out using the conditions described by Davies.¹ The crude material was purified by SiO_2 column chromatography eluting with hexane/ Et_2O (40:1; v/v). A light yellow oil was obtained

(TLC R_f =0.41 in 1:9 Et₂O/hexanes), estimated > 98 % d.e. by ¹H NMR integration, 7.94 g (66 % yield): ¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.16 (m, 10H), 4.04 (q, 1H, J = 7.0), 3.99 (A of AB, 1H, J = 15.7), 3.80 (B of AB, 1H, J = 15.7), 2.83 (m, 1H), 2.46 (m, 1H), 1.81 (m, 1H), 1.45-1.39 (m, 1H), 1.39 (s, 9H), 1.24 (d, 3H, J = 1.69), 1.15-1.10 (m, 1H), 0.94 (d, 3H, J = 7.1), 0.85 (d, 3H, J = 6.8), 0.60 (d, 3H, J = 6.5); ¹³C NMR (CDCl₃, 75.4 MHz): δ 175.6, 145.2, 143.3, 128.10, 128.06, 127.85, 127.76, 126.8, 126.2, 79.8, 60.4, 59.1, 51.0, 43.7, 40.3, 28.0, 24.8, 23.6, 22.0, 21.2, 17.0; Electrospray ionization-MS m/z (M + H) calculated for C₂₇H₃₉O₂N 432.5, observed 432.3.

(2S,3R, α R)-3-(N-benzyl-N- α -methylbenzylamino)-4-cyclohexyl-2-methyl-*tert*-butyl butyrate (5d). Conjugate addition of **4** to **3d** (1.62 g, 6.80 mmol) was carried out using the conditions described by Davies.¹ The crude material was purified by SiO₂ column chromatography eluting with hexane/Et₂O (40:1; v/v). A light yellow oil was obtained (TLC R_f =0.46 in 1:9 Et₂O/hexanes), estimated > 93 % d.e. by ¹H NMR integration, 1.62 g (53 % yield): ¹H NMR (CDCl₃, 300 MHz) δ 7.38-7.16 (m, 10H), 4.04 (q, 1H, J = 6.8), 4.00 (A of AB, 1H, J = 15.7), 3.79 (B of AB, 1H, J = 15.7), 2.86 (m, 1H) [2.97 (m, 0.04H)], 2.47 (m, 1H) [2.59 (m, 0.04H)], 1.69-1.00 (m, 10H), 1.40 (s, 9H), 1.24 (d, 3H, J = 6.8), 0.96 (d, 3H, J = 7.2), 0.88 (m, 2H), 0.56 (m, 1H); ¹³C NMR (CDCl₃, 75.4 MHz): δ 175.6, 145.3, 143.5, 128.1, 128.0, 127.8, 127.7, 126.7, 126.2, 79.7, 60.7, 58.3, 50.9, 43.7, 38.8, 34.3, 34.2, 32.9, 31.5, 27.9, 26.7, 26.2, 21.4, 17.0; Electrospray ionization-MS m/z (M + H) calculated for C₃₀H₄₃O₂N 472.6, observed 472.3.

(2S,3R, α R)-2-Benzyl-3-(N-benzyl-N- α -methylbenzylamino)-*tert*-butyl butyrate (5g**).**

Conjugate addition of **4** to **3g** (2.86 g, 10.9 mmol) was carried out using the conditions described by Davies.¹ The crude material was purified by SiO₂ column chromatography eluting with hexane/Et₂O (20:1; v/v). A light yellow oil was obtained (TLC R_f=0.39 in 1:9 Et₂O/hexanes), estimated 86 % d.e. by ¹H NMR integration, 3.49 g (67 % yield): ¹H NMR (CDCl₃, 300 MHz) δ 7.49-7.15 (m, 10H), 6.85 (d, 2H, *J* = 8.7), 6.69 (d, 2H, *J* = 8.7), 3.99 (q, 1H, *J* = 7), 3.86 (A of AB, 1H, *J* = 14.0), 3.71 (B of AB, 1H, *J* = 14), 3.00 (m, 2H) [3.20 (m, 0.06H)], 2.46 (m, 1H) [2.63 (m, 0.08H)], 1.94 (dd, 1H, *J* = 13.9, 12.0), 1.39 (d, 3H, *J* = 6.8), 1.18 (s, 9H), 1.15 (d, 3H, *J* = 6.8); ¹³C NMR (CDCl₃, 75.4 MHz): δ 174.2, 157.7 [157.8], 144.0, 141.0, 132.2, 129.6, 128.8, 128.2, 128.0, 127.8, 126.7, 126.6, 113.3 [113.5], 79.7 [79.8], 57.0, 55.0, 54.2, 53.8, 50.2, 35.9, 27.7 [27.9], 15.0, 14.8; Electrospray ionization-MS *m/z* (M + H) calculated for C₃₁H₃₉O₃N 474.7, observed 474.2.

(2S,3R)-3-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2,5-dimethyl-hexanoic acid

(7c). Via procedure B, amino ester **5c** (7.94 g, 19.4 mmol) was hydrogenated using ~5 g of 10 % Pd-C, deprotected, and Fmoc-protected. The crude Fmoc acid was purified by SiO₂ column chromatography eluting with a gradient of 2:1 hexane/acetone to 1:2 hexane/acetone with 0.5 % acetic acid. The product was recrystallized by dissolving the material in chloroform (rm temp), adding hexane until the solution became turbid, and refrigerating for 30 min. After filtration 4.63 g (63 % yield) of **7c** was obtained as a white solid (TLC R_f=0.13 in 1:2 acetone/hexanes): mp 137-138.5 °C; ¹H NMR (*d*₆-acetone, 300 MHz) δ 7.85 (d, 2H, *J* = 7.4), 7.70-7.67 (m, 2H), 7.43-7.29 (m, 4H), 6.28 (d,

0.80H, $J = 9.7$), 4.48-4.32 (m, 2H), 4.24-4.19 (m, 1H), 4.02-3.92 (m, 1H), 2.53 (p, 1H), 1.69 (m, 1H), 1.51 (m, 1H), 1.26 (m, 1H), 1.15 (d, 3H, $J = 6.8$), 0.90 (dd, 6H, $J = 6.6$, 2.2); ^{13}C NMR (d_6 -acetone, 75.4 MHz): δ 186.0, 166.8, 154.9, 154.7, 151.8, 138.1, 137.5, 135.8, 135.7, 130.4, 76.2, 62.0, 57.9, 55.3, 35.3, 33.7, 31.4, 24.0; Electrospray ionization-MS m/z (M - H) calculated for $\text{C}_{23}\text{H}_{26}\text{O}_4\text{N}$ 380.5, observed 380.1; $[\alpha]_{\text{D}} = 8.10^\circ$ (c 3.33 $\times 10^{-1}$, CH_3OH); The optical purity was determined as 96 % e.e. (> 92 % de) by integration of the trifluoromethyl groups in the corresponding (*R*) and (*S*) Mosher amides.

(2*S*,3*R*)-4-Cyclohexyl-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-methyl-butyric acid (7d). Via procedure B, amino ester **5d** (1.62 g, 3.60 mmol) was hydrogenated using ~1.5 g of 10 % Pd-C, deprotected, and Fmoc-protected. The product was recrystallized by dissolving the material in chloroform (rm temp), adding hexane until the solution became turbid, and refrigerating for 30 min. After filtration, the recrystallization was repeated. This treatment afforded 0.638 g (42 % yield) of **7d** as a white solid (TLC $R_{\text{f}}=0.18$ in 1:1 acetone/hexanes): mp 153.5-156.5 °C; ^1H NMR (d_6 -acetone, 300 MHz) δ 7.86 (d, 2H, $J = 7.5$), 7.70 (d, 2H, $J = 7.5$), 7.44-7.30 (m, 4H), 6.30 (d, 0.56H, $J = 9.8$), 4.43-4.34 (m, 3H), 4.00 (m, 1H), 2.53 (p, 1H, $J = 7.3$), 1.93 (br d, 1H, $J = 12.4$), 1.65 (m, 4H), 1.51-0.79 (m, 8H), 1.14 (d, 3H, $J = 7.2$); ^{13}C NMR (d_6 -acetone, 75.4 MHz): δ 176.4, 157.1, 145.1, 142.1, 128.5, 127.9, 126.0, 120.8, 66.7, 51.6, 48.1, 45.7, 41.4, 35.1, 34.9, 32.8, 27.2, 27.1, 26.8, 14.3; Electrospray ionization-MS m/z (M - H) calculated for $\text{C}_{26}\text{H}_{31}\text{O}_4\text{N}$ 420.5, observed 420.3; $[\alpha]_{\text{D}} = 10.8^\circ$ (c 3.33 $\times 10^{-1}$, CH_3OH); The optical purity was determined as 92 % e.e. (> 99 % de) by integration of the trifluoromethyl groups in the corresponding (*R*) and (*S*) Mosher amides.

(2S,3R)-2-Benzyl-3-(9H-fluoren-9-ylmethoxycarbonylamino)-butyric acid (7f).

Conjugate addition of **4** to **3f** (10.0 g, 43.2 mmol) was carried out using the conditions described by Davies.¹ The crude material was partially purified by SiO₂ column chromatography eluting with hexane/Et₂O (20:1; v/v). As much as 33 % of an unknown impurity co-eluted with the product. A light yellow oil was obtained (TLC R_f=0.37 in 1:9 Et₂O/hexanes), estimated 89 % d.e. by ¹H NMR integration, 12.46 g: ¹H NMR (CDCl₃, 300 MHz) δ 7.44-7.08 (m, 15H), 4.00 (q, 1H, *J* = 6.7), 3.88 (A of AB, 1H, *J* = 14.0), 3.73 (B of AB, 1H, *J* = 14.0), 3.05 (m, 2H) [3.22 (m, 0.06H)], 2.50 (m, 1H) [2.66 (m, 0.09H)], 1.94 (dd, 1H, *J* = 14.0, 12.1), 1.41 (d, 3H, *J* = 6.8), 1.16 (d, 3H, *J* = 6.6), 1.15 (s, 9H); ¹³C NMR (CDCl₃, 75.4 MHz): δ 174.2, 144.0, 141.0, 140.3, 128.92, 128.85, 128.3, 128.1, 128.0, 127.9, 126.8, 126.7, 125.7, 79.9 [80.0], 57.0 [58.3], 54.1 [54.4], 53.8, 50.3 [50.3], 37.0 [37.7], 27.7 [28.0], 15.2, 14.7 [14.4]; Electrospray ionization-MS *m/z* (M + H) calculated for C₂₉H₃₈O₂N 443.6, observed 444.2.* Via procedure B, amino ester **5f** (12.5 g, 28.1 mmol) was hydrogenated using ~10 g of 10 % Pd-C, deprotected, and Fmoc-protected. The crude product was recrystallized by dissolving the material in chloroform (rm temp), adding hexane until the solution became turbid, and refrigerating for 30 min. This treatment afforded 7.20 g (62 % yield) of **7f** as a white solid (TLC R_f=0.18 in 1:1 acetone/hexanes): mp 168-170 °C; ¹H NMR (*d*₆-DMSO, 300 MHz) δ 12.25 (br s, 0.3H), 7.89 (d, 2H), 7.72 (d, 2H), 7.43-7.14 (m, 9H), 4.46-4.22 (m, 3H), 3.73 and 3.61 (m, atropisomeric, 1H), 2.82-2.50 (m, 3H), 1.10 (d, 3H); ¹³C NMR (*d*₆-DMSO, 75.4 MHz): δ 174.5, 155.6, 143.91, 143.85, 140.8, 139.5, 128.6, 128.2, 127.6, 127.0, 126.1, 125.2, 125.1, 120.1, 65.1, 53.3, 48.2, 48.1, 46.9, 35.1, 19.1; Electrospray

ionization-MS m/z (M - H) calculated for C₂₆H₂₅O₄N 414.5, observed 414.1; $[\alpha]_D = -14.7^\circ$ (c 3.33 $\times 10^{-1}$, CH₃OH); The optical purity was determined as 91 % e.e. (> 99 % de) by integration of the trifluoromethyl groups in the corresponding (*R*) and (*S*) Mosher amides.

*Davies previously obtained **5f** and its *anti* diastereomer in a 1:1 ratio during efforts to generate *anti*- α,β -dialkyl β -amino acids.³ The NMR assignments of **5f** and its diastereomer in that paper appear to be reversed (i.e., what we show here to be the *syn* diastereomer was assigned as *anti*). Our assignment of a *syn* disposition of the α and β -groups for **5f** was confirmed by the crystal structure of an oligoamide containing a residue derived from **5f**.⁴

(2S,3R)-3-(9H-Fluoren-9-ylmethoxycarbonylamino)-2-(4-methoxy-benzyl)-butyric acid (7g). Via procedure B, amino ester **5g** (3.49 g, 7.4 mmol) was hydrogenated using ~3 g of 10 % Pd-C, deprotected, and Fmoc-protected. The product was recrystallized by dissolving the material in chloroform (rm temp), adding hexane until the solution became turbid, and refrigerating for 30 min. This treatment afforded 2.42 g (74 % yield) of **7g** as a white solid (TLC $R_f=0.18$ in 1:1 acetone/hexanes): mp 152.5-154 °C; ¹H NMR (d_6 -DMSO, 300 MHz) δ 12.30 (bs, 0.75H), 7.90 (d, 2H, $J = 7.3$), 7.77 (d, 2H, $J = 7.3$), 7.47-7.32 (m, 5H), 7.13 (d, 2H, $J = 8.4$), 6.88 (d, 2H, $J = 8.4$), 4.53-4.27 (m, 3H), 3.82 (m, 1H), 3.74 (s, 3H), 2.84-2.64 (m, 3H), 1.78 (d, 3H, $J = 6.7$); ¹³C NMR (d_6 -DMSO, 75.4 MHz): δ 174.7, 157.7, 155.8, 143.98, 143.93, 140.9, 131.4, 129.7, 127.6, 127.1, 125.24, 125.16, 120.1, 113.7, 65.2, 54.9, 53.7, 48.3, 47.0, 34.4, 19.2; Electrospray ionization-MS m/z (M - H) calculated for C₂₆H₂₅O₄NNa 468.4, observed 468.1; $[\alpha]_D = -12.9^\circ$ (c

3.33×10^{-1} , CH₃OH); The optical purity was determined as 89 % e.e. (> 99 % de) by integration of the trifluoromethyl groups in the corresponding (*R*) and (*S*) Mosher amides.

(2*S*,3*R*)-3-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-(3,4,5-trimethoxy-benzyl)-butyric acid (7*h*). Conjugate addition of **4** to **3h** (2.88 g, 8.94 mmol) was carried out using the conditions described by Davies.¹ The crude material was partially purified by SiO₂ column chromatography eluting with hexane/Et₂O (3:1; v/v). A light yellow oil was obtained (TLC R_f=0.20 in 1:3 Et₂O/hexanes), which was contaminated with starting material (63:37 **5h**/**3h**), and an additional unknown impurity. Amino ester **5h** was estimated to be 89 % d.e. by ¹H NMR integration (4.20 g): Electrospray ionization-MS *m/z* (M + H) calculated for C₃₁H₃₉O₃N 534.7, observed 534.2. Via general procedure B, crude amino ester **5h** (4.20 g) was hydrogenated using ~3 g of 10 % Pd-C, deprotected, and Fmoc-protected. The crude Fmoc acid was purified by SiO₂ column chromatography eluting with a gradient of acetone/hexane (1:1) to acetone/hexane (2:1) with 0.5 % acetic acid. The product was recrystallized by dissolving the material in chloroform (rm temp), adding hexane until the solution became turbid, and refrigerating for 30 min. This treatment afforded 0.554 g (14 % yield) of **7h** as a white solid (TLC R_f=0.13 in 1:1 acetone/hexanes): mp 166.5-170 °C; ¹H NMR (CDCl₃, 300 MHz) δ 7.75 (d, 2H, *J* = 7.3), 7.57 (m, 2H), 7.40-7.26 (m, 4H), 6.42 (s, 2H), 6.15 (d, 0.65H, *J* = 8.8), 4.46-4.35 (m, 2H), 4.20 (t, 1H, *J* = 6.8), 4.04 (m, 1H), 3.80 (s, 9H), 3.01 (m, 2H), 2.70 (m, 1H), 1.23 (d, 3H, *J* = 6.5); ¹³C NMR (CDCl₃, 75.4 MHz): δ 178.0, 155.6, 153.1, 143.8, 141.3, 136.6, 134.1, 127.7, 127.0, 124.9, 120.0, 105.8, 66.7, 60.8, 56.1, 51.9, 48.1, 47.2, 35.1, 17.4; Electrospray ionization-MS *m/z* (M - H) calculated for C₂₉H₃₀O₇N 504.6, observed 504.2;

Figure S1: ^{13}C Chemical shifts characteristic of an E and Z configuration, respectively.

$[\alpha]_{\text{D}} = -8.70^\circ$ (c 3.33×10^{-1} , CH_3OH); The optical purity was determined as 89 % e.e. (> 96 % de) by integration of the trifluoromethyl groups in the corresponding (R) and (S) Mosher amides.

Assignment of α,β -Unsaturated Ester Stereochemistry. The described aldol addition/elimination strategy is known to predominantly afford the desired E isomer,^{1a} but ^{13}C chemical shift analyses were carried out to confirm that the E isomer was the major isomer in the reactions disclosed above. In α,β -unsaturated esters, methylene carbons in position “a” are known to resonate downfield for Z isomers relative to the E isomer (a γ - or gauche-effect) (see Figure S1). Via SiO_2 column chromatography, small amounts of the two isomeric forms of **3f** were isolated, and a DEPT-135 experiment was carried out to identify the resonance corresponding to methylene carbon “a.” The compound corresponding to the major isomer (I) displayed a methylene carbon “a” resonance that was upfield relative to the minor isomer (II). This observation confirms the identity of the major isomer of **3f** as the E isomer. Vinyl proton “b” of isomer I was

Figure S2: Mosher amide strategy to assess optical purity.

found to resonate downfield of vinyl proton “b” of isomer II. These ^{13}C and ^1H chemical shift trends were used to confirm that products **3a-d** and **3f-h** were predominately the *E* isomer.

Preparation of Mosher Amides. In order to ascertain the ee of Fmoc-protected β -amino acids **7**, the corresponding Mosher amides were synthesized (Figure S2). A solid phase synthesis protocol was employed to synthesize these amides for several reasons. First, solid phase synthesis allowed the simultaneous synthesis of all the Mosher amides in a

convenient manner. Second, because the reaction of a homochiral Mosher acid with a mixture of enantiomers gives rise to diastereomeric transition states, a kinetic resolution is possible if the reaction is not driven to completion, leading to an inaccurate measurement of ee. The solid phase protocol allows excess reagents to be used, ensuring a complete reaction. Most importantly, the solid phase protocol allowed the isolation of pure Mosher amides without employing column chromatography to separate away unreacted starting materials and coupling reagent byproducts. Avoiding column chromatography is important when examining Mosher amides or esters so that diastereomeric products are not separated away from the isomeric product mixture.

In a 1.5 mL Alltech tube was placed 16.8 mg 2-chlorotrityl resin (1.49 mmol/g). The Fmoc acid (0.03 mmol) was dissolved in 0.2 mL of a 0.5 M DIEA solution in CH_2Cl_2 . These solutions were transferred to Alltech tubes, and the mixtures were rocked for 2 h. The resin in each tube was then filtered, washed with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{DIEA}$ (17:2:1) 3 times, transferred to a 4 mL Alltech tube, and then washed with CH_2Cl_2 3 times, and DMF 3 times. The resin in each tube was Fmoc-deprotected using 1.25 mL of 20 % piperidine in DMF (rocked for 15 min). The resin was filtered and washed with CH_2Cl_2 (3 times) and then DMF (3 times). The appropriate Mosher's acid (0.075 mmol, 17.6 mg) was dissolved in 1.25 mL DMF, and then HBTU was added (0.075 mmol, 28.5 mg). The solutions were vortexed and then added to the appropriate batch of resin. After 0.5 M HOBt in DMF (150 μL) and 0.5 M DIEA in DMF (300 μL) were added, the resin mixtures were rocked for 2 h. The resin in each tube was filtered and then washed with CH_2Cl_2 (3 times), DMF (3 times), and CH_2Cl_2 (1 time). The products were removed from resin using 0.5 % TFA in CH_2Cl_2 for 2 h. The deprotection solutions were drained

into vials. The beads were washed with CH_2Cl_2 ; this solution was also placed in the vials. The solutions were evaporated under reduced pressure and then placed under high vacuum overnight. A trace of TFA was added to each sample as an internal NMR reference, and ^{19}F spectra were obtained in CDCl_3 . The ^{19}F spectra for each compound 7 are included below with the rest of the NMR spectra. Enantiomeric excesses were calculated by integrating the trifluoromethyl resonances. Extra resonances observed adjacent to the major resonances in each spectrum were attributed to additional diastereomers. These peaks were integrated, and used to calculate the reaction de. In most cases both Mosher amides were synthesized and the reported ee value represents the average ee value obtained from the two spectra.

^1H spectrum of **2b**

¹H spectrum of **3b**

S36

CCCCC/C=C/C(=O)OC(C)(C)C

S45

S50

¹H spectrum of 3d

S51

¹³C spectrum of 3d

S52

¹H spectrum of 3f

¹H spectrum of **5c**

S60

S63

S68

¹H spectrum of 7c

S72

S77

S80

¹H spectrum of 7g

S81

References

- (1) a) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153-1155; b) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc. Perkin Trans. I* **1994**, 9, 1141-1147.
- (2) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, 48, 1853-1868.
- (3) Davies, S.G.; Walters, I.A.S. *J. Chem. Soc. Perkin Trans. I* **1994**, 9, 1129-1139.
- (4) Langenhan, J.M.; Guzei, I.A.; Gellman, S.H. *Angew. Chem. Int. Ed.*, in press.