Supporting Information

Synthesis of β -Substituted α -Amino Acids via Lewis Acid Promoted Enantioselective Radical Conjugate Additions

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General Experimental Details

Diethyl ether, methylene chloride, and tetrahydrofuran were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina.¹ Flash chromatography was carried out using 60–230 mesh silica gel. ¹H NMR spectra were acquired on a 500 MHz spectrometer with chloroform (7.27 ppm) or DMSO (2.50 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ¹³C NMR spectra were acquired on a spectrometer operating at 125 MHz with chloroform (77.23 ppm) or DMSO (39.51 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using EI or FAB techniques.

***N*-Benzyl-2-nitroacetamide (5).** A solution of **4**² (10.0 g, 84 mmol) in MeOH (120 mL) was treated dropwise with benzylamine (46 mL, 45 g, 420 mmol) and stirred at rt for 3 d, during which time white solids precipitated. The mixture was concentrated in vacuo, and the residue was acidified with 1 N HCl (pH = 4) and extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄), and concentrated in vacuo. Trituration of the resultant solid with cold Et₂O (130 mL) afforded **5** (16.0 g, 82 mmol, 98%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.38–7.29 (m, 3H), 7.28–7.26 (m, 2H), 6.87 (br s, 1H), 5.09 (s, 2H), 4.47 (d, *J* = 5.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 160.2, 136.8, 129.1 (2C), 128.2, 128.0 (2C),

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 15, 1518.

² Zen, S.; Koyama, M.; Koto, S. *Org. Synth.* **1988**, Coll. Vol. VI, 797.

77.9, 44.3; IR (film) ν_{max} 2975, 1733, 1628, 1360 cm^{-1} ; HRMS (EI) m/z 195.0760 (MH^+ , $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3\text{H}$ requires 195.0769).

General procedure for Knoevenagel condensation of methyl nitroacetate or **5 with aldehydes.** To a stirred solution of methyl nitroacetate (**4**)³ or **5** (3.1 mmol) and aldehyde (4.6 mmol) in anhydrous THF (25 mL) at $-10\text{ }^{\circ}\text{C}$ was added TiCl_4 (1.0 M solution in CH_2Cl_2 , 5.2 mL, 5.2 mmol). The resultant yellow mixture was stirred for 10 min and treated with *N*-methyl morpholine (1.3 mL, 1.2 g, 12.4 mmol) dropwise over 20 min. The mixture was then allowed to warm to rt and stir for an additional 18 h. The reaction was quenched with H_2O (20 mL), and the organic layer was separated. The aqueous layer was extracted with THF ($2 \times 15\text{ mL}$), and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography ($5 \times 15\text{ cm}$, 5–20% EtOAc in hexanes gradient elution) afforded α,β -unsaturated α -nitro esters **1a–d** or α,β -unsaturated α -nitro amides **6a–c**. Amides **6a–c** were obtained as the *E* isomers.

Methyl 3-(4-methoxyphenyl)-2-nitroacrylate (1a): Data for this compound were identical to that previously reported by Montgomery and co-workers.⁴

³ Zen, S.; Koyama, M.; Koto, S. *Org. Synth.* **1988**, *Coll. Vol. VI*, 797.

⁴ Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528.

Figure S1. ORTEP Diagram of Z-1a.

Methyl 2-nitro-3-phenylacrylate (1b) (2:1 mixture of diastereomers): Pale yellow oil, 76% yield; ^1H NMR (CDCl_3 , 500 MHz) δ 8.11 and 7.56 (2s, 1H), 7.53–7.47 (m, 2H), 7.46–7.38 (m, 3H), 3.97 and 3.93 (2s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 161.9 and 159.9, 140.0 and 137.2, 133.5, 132.7 and 132.5 (2C), 130.6 and 130.0, 129.6 (2C), 129.0, 53.9 and 53.8; IR (film) ν_{max} 3016, 2892, 1732, 1643, 1601, 1229 cm^{-1} ; HRMS (EI) m/z 207.0534 (M^+ , $\text{C}_{10}\text{H}_9\text{NO}_4$ requires 207.0531).

Figure S2. ORTEP Diagram of Z-1b.

Methyl 3-(4-fluorophenyl)-2-nitroacrylate (1c) (2:1 mixture of diastereomers): White solid, 66% yield; ^1H NMR (CDCl_3 , 500 MHz) δ 8.06 and 7.51 (2s, 1H), 7.56–7.50 and 7.48–7.43 (2m, 2H), 7.19–7.10 (m, 2H), 3.97 and 3.92 (2s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.0 (d, $J = 254$ Hz), 161.8 and 159.8, 141.6, 136.0 and 135.9, 132.6 and 132.5 (2C), 132.3 and 132.0, 125.3, 117.0 (d, $J = 22$ Hz) and 116.9 (d, $J = 16$ Hz), 53.9 and 53.7; IR (film) ν_{max} 3023, 2959, 1732, 1644, 1603, 1229 cm^{-1} ; HRMS (EI) m/z 225.0439 (M^+ , $\text{C}_{10}\text{H}_8\text{FNO}_4$ requires 225.0438).

Methyl 4-methyl-2-nitropent-2-enoate (1d): Data for this compound were identical to that previously reported by Montgomery and co-workers.⁴

(E)-N-Benzyl-3-(4-methoxyphenyl)-2-nitroacrylamide (6a): Yellow solid, 0.68 g, 2.0 mmol, 66% yield; ^1H NMR (CDCl_3 , 500 MHz) δ 8.02 (s, 1H), 7.47 (d, $J = 9.0$ Hz, 2H), 7.39–7.25 (m, 5H), 6.83 (d, $J = 9.0$ Hz, 2H), 6.33 (br s, 1H), 4.62 (d, $J = 6.0$ Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 163.3, 161.0, 142.2, 136.8, 136.7 (2C), 133.4 (2C), 129.0 (2C), 128.4 (2C), 121.6, 115.0 (2C), 55.7, 44.5; IR (film) ν_{max} 3287, 2933, 1660, 1603, 1516, 1028 cm^{-1} ; HRMS (FAB) m/z 335.1001 (MNa^+ , $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4\text{Na}$ requires 335.1007).

Figure S3. ORTEP Diagram of 6a.

(*E*)-*N*-Benzyl-2-nitro-3-phenylacrylamide (6b): Pale yellow solid, 0.55 g, 1.8 mmol, 58% yield; ^1H NMR (CDCl_3 , 500 MHz) δ 8.01 (s, 1H), 7.51–7.45 (m, 3H), 7.41–7.33 (m, 7H), 6.32 (br s, 1H), 4.66 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 160.5, 144.4, 136.7, 136.4, 132.4, 130.9 (2C), 129.6, 129.5, 129.3, 129.0 (2C), 128.3 (2C), 128.1, 44.5; IR (film) ν_{max} 3280, 2946, 1658, 1601, 1516, 1078 cm^{-1} ; HRMS (FAB) m/z 305.0901 (MNa^+ , $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ requires 305.0902).

(*E*)-*N*-Benzyl-3-(4-fluorophenyl)-2-nitroacrylamide (6c): Pale yellow solid, 0.50 g, 1.5 mmol, 49% yield; ^1H NMR (CDCl_3 , 500 MHz) δ 8.01 (s, 1H), 7.52–7.45 (m, 2H), 7.36–7.26 (m, 5H), 7.04–7.01 (m, 2H), 6.52 (br s, 1H), 4.60 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.1 (d, $J = 255$ Hz), 160.3, 144.1, 136.6, 135.4 (2C), 133.4, 133.3, 129.1 (2C), 128.4, 128.2, 125.4, 116.8 (d, $J = 22$ Hz, 2C), 44.5; IR (film) ν_{max} 3023, 2959, 1732, 1644, 1603, 1229 cm^{-1} ; HRMS (FAB) m/z 323.0796 (MNa^+ , $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{O}_3\text{Na}$ requires 323.0808).

Methyl 3-(4-Fluorophenyl)-4-methyl-2-nitropentanoate (2c). Prepared according to the General Procedure listed in the Experimental Section and isolated as a 1:1 mixture of diastereomers: ^1H NMR (CDCl_3 , 500 MHz) δ 7.20–7.04 (m, 2H), 7.02–6.95 (m, 2H), 5.62 and 5.59 (2d, $J = 11.0$ and 10.5 Hz, 1H), 3.86 and 3.54 (2s, 3H), 3.65–3.59 (m, 1H), 2.06–2.02 (m, 1H), 0.90 and 0.86 (2d, $J = 11.0$ and 11.5 Hz, 6H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 165.7 (d, $J = 272$ Hz), 164.3 and 160.8, 132.5 and 132.4, 131.3 and 131.2, 131.0 and 130.9, 117.0 and 115.5 (2d, $J = 37$ and 35 Hz, 2C), 90.9 and 90.7, 53.9 and 53.8, 53.5 and 51.8, 29.6 and 29.4, 21.7 and 21.1, 18.1 and 17.9; IR (film) ν_{max} 3267, 1655, 1551 cm^{-1} ; HRMS (EI) m/z 269.1067 (M^+ , $\text{C}_{13}\text{H}_{16}\text{FNO}_4$ requires 269.1063).

Methyl 2-Deuterio-3-(4-fluorophenyl)-4-methyl-2-nitropentanoate (d-2c): ^1H NMR (CDCl_3 , 500 MHz) was identical to **2c** except for the absence of the two doublets at δ 5.62 and 5.59. Also the two doublet of doublets at δ 3.63 and 3.58 appeared as two doublets ($J = 9.0$ and 9.5 Hz).

Methyl 3-(4-Methoxyphenyl)-2-nitropropionate (3a): Data for this compound were identical to that previously reported by Ohwada and co-workers.⁵

Methyl 3-(4-Fluorophenyl)-2-nitropropionate (3c): ^1H NMR (CDCl_3 , 500 MHz) δ 7.20–7.17 (m, 2H), 7.03–7.05 (m, 2H), 5.31 (dd, $J = 5.0, 9.0$ Hz, 1H), 3.84 (s, 3H), 3.53 (dd, $J = 6.0, 14.5$ Hz, 1H), 3.44 (dd, $J = 5.5, 14.0$ Hz, 1H). This compound was obtained as a mixture with **2c** and hence was not fully characterized.

N-Benzyl-3-(4-fluorophenyl)-4-methyl-2-nitropentanamide (7c). Prepared according to the General Procedure listed in the Experimental Section and isolated as a 1:1 mixture of diastereomers: ^1H NMR (CDCl_3 , 500 MHz) δ 7.38–7.30 (m, 1H), 7.28–

⁵ Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 5282.

7.18 (m, 5H), 7.11–7.05 (m, 1H), 7.00–6.92 (m, 1H), 6.89–6.84 (m, 1H), 6.82 and 6.44 (2 br s, 1H), 5.62 and 5.58 (2d, $J = 9.0$ and 10.5 Hz, 1H), 4.47 and 4.23 (2dd, $J = 8.0$, 14.5 Hz, 1H), 4.45 and 4.21 (2dd, $J = 8.5$, 14.5 Hz, 1H), 3.58–3.48 (m, 1H), 2.10–1.99 (m, 1H), 0.92 and 0.86 (2d, $J = 6.5$ and 7.0 Hz, 3H), 0.83 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 163.1 (d, $J = 283$ Hz), 162.7 and 160.9, 136.9 and 136.8, 131.5 and 131.4, 130.9 and 130.8, 129.1 and 128.9 (2C), 128.2 (2C), 128.0 and 127.8 (2C), 115.6 and 115.4 (2d, $J = 26$ and 27 Hz, 2C), 92.8 and 92.6, 53.7 and 53.3, 44.3 and 44.0, 28.1 and 27.1, 21.7 and 21.3, 18.2 and 17.7; IR (film) ν_{max} 3261, 1650, 1561 cm^{-1} ; HRMS (FAB) m/z 367.1432 (MNa^+ , $\text{C}_{19}\text{H}_{21}\text{FN}_2\text{O}_3\text{Na}$ requires 367.1434).

***N*-Benzyl-3-(4-methoxyphenyl)-2-nitropropionamide (8a).** Contaminated with **7a** and unreacted starting material and thus not fully characterized: ^1H NMR (CDCl_3 , 500 MHz) δ 7.41–7.39, (m, 5H), 7.21–7.19 (m, 2H), 6.90–6.88 (m, 2H), 6.81 (br s, 1H), 5.28 (dd, $J = 8.5$, 11.5 Hz, 1H), 4.55–4.52 (m, 2H), 3.79 (s, 3H), 3.52 (m, 2H).

***N*-Benzyl-3-phenyl-2-nitropropionamide (8b).** Contaminated with **7b** and unreacted starting material and thus not fully characterized: ^1H NMR (CDCl_3 , 500 MHz) δ 7.37–7.22 (m, 10H), 6.73 (br s, 1H), 5.27 (dd, $J = 8.0$, 10.0 Hz, 1H), 4.56–4.54 (m, 2H), 3.58–3.54 (m, 2H).

***N*-Benzyl-3-(4-fluorophenyl)-2-nitropropionamide (8c).** Contaminated with **7c** and unreacted starting material and thus not fully characterized: ^1H NMR (CDCl_3 , 500 MHz) δ 7.38–7.29 (m, 5H), 6.84–6.78 (m, 4H), 6.50 (br s, 1H), 5.22 (dd, $J = 9.0$, 12 Hz, 1H), 4.57–4.54 (m, 2H), 3.57 (dd, $J = 9.5$, 14.5 Hz, 1H), 3.55–3.52 (m, 1H).

General procedure for nitro hydrogenation and *N*-Cbz protection (Note: this procedure is difficult to reproduce in the presence of tin byproducts and should only be

used on samples of pure **2** or **7**. If tin byproducts are present, the In-mediated procedure given in the Experimental Section should be employed). A solution of **2** (0.12 mmol) or **7** (0.080 mmol) in degassed MeOH (7 mL) was treated with 10% Pd/C (20 mg). The resulting mixture was stirred at rt under H₂ (1 atm) for 12 hr, then filtered through a pad of Celite and concentrated in vacuo. The crude amine was dissolved in dioxane–H₂O (10:1, 1 mL), treated with NaHCO₃ (20 mg, 0.20 mmol), and stirred at rt for 10 min. Benzyl chloroformate (15 μ l, 23 mg, 0.12 mmol) was added to the mixture, and it was stirred for 1 h then concentrated in vacuo. The residue was taken up in CH₂Cl₂ (10 mL) and H₂O (5 mL), the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (SiO₂, 2 $\times$ 12 cm, 5–15% EtOAc in hexanes gradient elution) afforded **9** or **10** as colorless oils.

Methyl 2-Benzyloxycarbonylamino-4-methyl-3-phenylpentanoate (9b) (1:1 mixture of diastereomers): ¹H NMR (CDCl₃, 500 MHz) δ 7.40–7.31 (m, 8H), 7.06–7.01 and 7.00–6.94 (2m, 2H), 5.14 and 5.12 (2s, 2H), 5.01–4.95 (m, 1H), 4.92–4.89 (m, 1H), 3.64 and 3.63 (2s, 3H), 2.88 and 2.66 (2dd, J = 3.5, 9.5 Hz and 6.0, 9.0 Hz, 1H), 2.34–2.27 and 2.18–2.10 (2m, 1H), 1.18 and 1.16, (2d, J = 5.0 and 6.0 Hz, 3H), 0.79 and 0.75 (2d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 172.6 and 171.6, 156.5 and 155.7, 138.7 and 138.6, 136.5 and 136.4 (2C), 129.2 (3C), 128.8 and 128.7 (2C), 128.5 and 128.4 (2C), 128.3, 127.5 and 127.4, 67.3 and 67.2, 57.1 and 56.0, 55.9 and 55.4, 52.3 and 52.1, 28.9 and 28.3, 21.5 and 21.4, 21.2; IR (film) ν_{max} 3337, 2941, 1718, 1603, 1034 cm^{–1}; HRMS (FAB) m/z 378.1691 (MNa⁺, C₂₁H₂₅NO₄Na requires 378.1701).

When **9b** was produced according to the chiral Lewis acid mediated procedure given in the Experimental Section, *syn*-**9b** was obtained in 9% ee, as analyzed by HPLC (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; R_T = 13.2 min (major), 21.8 min). *Anti*-**9b** was obtained in 17% ee, as analyzed by HPLC under identical conditions (R_T = 7.6 min (major), 23.1 min).

Methyl 2-Benzyloxycarbonylamino-2-deuterio-4-methyl-3-phenylpentanoate (*d*-9b**):** ^1H NMR (CDCl_3 , 500 MHz) was identical to **9b** except for the absence of the two signals at δ 5.01–4.97 and 4.92–4.89. Also the two doublet of doublets at δ 2.88 and 2.66 appeared as doublets (J = 10.5 Hz). HRMS (FAB) m/z 379.1744 (MNa^+ , $\text{C}_{21}\text{H}_{24}\text{DNO}_4\text{Na}$ requires 379.1744).

Methyl 2-Benzyloxycarbonylamino-3-(4-fluorophenyl)-4-methylpentanoate (9c**)** (1:1 mixture of diastereomers): ^1H NMR (CDCl_3 , 500 MHz) δ 7.40–7.33 (m, 4H), 7.32–7.22 (m, 4H), 7.06 and 7.01 (2d, J = 7.5 and 6.5 Hz, 1H), 5.14 and 5.12 (s, 2H), 5.00 and 4.88 (2d, J = 9.0 and 6.0 Hz, 1H), 4.94 and 4.87 (2dd, J = 4.0, 10 Hz and 6.0, 9.5 Hz, 1H), 3.67 and 3.65 (2s, 3H), 2.87–2.81 and 2.69–2.67 (2m, 1H), 2.27–2.24 and 2.09–2.03 (2m, 1H), 1.18 and 1.14 (2d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.5 and 171.6, 162.2 (d, J = 244 Hz), 156.5 and 155.7, 136.4 and 134.4, 130.6 and 130.2 (2C), 128.9, 128.6 (3C), 128.4, 128.2, 115.7 and 115.4 (2d, J = 21 Hz, 2C), 67.4 and 67.2, 56.2 and 56.1, 55.8 and 52.5, 52.3 and 52.1, 28.7 and 28.6, 21.5, 21.4 and 21.0; IR (film) ν_{max} 3340, 2949, 1728, 1603, 1048 cm^{-1} ; HRMS (FAB) m/z 396.1593 (MNa^+ , $\text{C}_{21}\text{H}_{24}\text{FNO}_4\text{Na}$ requires 396.1587).

When **9c** was produced according to the chiral Lewis acid mediated procedure given in the Experimental Section, *syn*-**9c** was obtained in 6% ee, as analyzed by HPLC

(Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; R_T = 15.6 min (major), 20.5 min). *Anti*-**9c** was obtained in 12% ee, as analyzed by HPLC under identical conditions (R_T = 8.4 min (major), 16.7 min).

Methyl 2-Benzyloxycarbonylamino-2-deuterio-3-(4-fluorophenyl)-4-methylpentanoate (*d*-9c): ^1H NMR (CDCl_3 , 500 MHz) was identical to **9c** except for the absence of the two signals at δ 4.94 and 4.87. Also, the two multiplets at δ 2.87–2.81 and 2.69–2.67 appeared as two doublets centered at δ 2.85 and 2.67 (J = 10.5 and 9.0 Hz). HRMS (FAB) m/z 375.1826 (MH^+ , $\text{C}_{21}\text{H}_{23}\text{DFNO}_4\text{H}$ requires 375.1831).

***N*-Benzyl 2-Benzyloxycarbonylamino-4-methyl-3-phenylpentanamide (10b)** (1:1 mixture of diastereomers): ^1H NMR (CDCl_3 , 500 MHz) δ 7.38–7.26 (m, 5H), 7.25–7.20 (m, 4H), 7.19–7.09 (m, 5H), 6.80 (d, J = 3.0 Hz, 1H), 6.21 and 5.96 (2br s, 1H), 5.34 and 4.97 (2d, J = 9.0 and 8.5 Hz, 1H), 5.09 and 5.08 (2s, 2H), 4.75 and 4.65 (2t, J = 5.5 and 9.5 Hz, 1H), 4.43 and 4.31 (2dd, J = 4.5, 11.5 and 6.5, 15 Hz, 1H), 4.06 (dd, J = 4.5, 15 Hz, 1H), 3.20–3.17 and 2.90–2.83 (2m, 1H), 2.37–2.29 and 2.08–2.01 (2m, 1H), 1.09 and 0.92 (2d, J = 5.5 and 6.0 Hz, 3H), 0.81 and 0.77 (2d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.9, 156.3, 138.4, 137.6 and 136.3, 129.8 and 129.3, 128.79, 128.72, 128.5, 128.4(2C), 128.36, 128.3(2C), 127.8, 127.7(3C), 127.6, 127.4, 127.3, 67.4, 57.2, 54.8 and 53.6, 43.5, 31.1 and 28.4, 21.8, 18.5; IR (film) ν_{max} 3280, 2933, 1645, 1526, 1251 cm^{-1} ; HRMS (FAB) m/z 453.2141 (MNa^+ , $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_3\text{Na}$ requires 453.2155).

When **10b** was produced according to the chiral Lewis acid mediated procedure given in the Experimental Section, *syn*-**10b** was obtained in 64% ee, as analyzed by HPLC of the corresponding acetate *syn*-**12b** (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1

mL/min; R_T = 5.7 min (major), 9.4 min). *Anti*-**10b** was obtained in 62% ee, as analyzed by HPLC under identical conditions (R_T = 15.2 min (major), 21.8 min).

***N*-Benzyl 2-Benzylloxycarbonylamino-2-deuterio-4-methyl-3-phenylpentanamide (*d*-10b):** ^1H NMR (CDCl_3 , 500 MHz) was identical to **10b** except for the absence of the two signals at δ 4.75 and 4.65. Also, the two multiplets at δ 3.20–3.17 and 2.90–2.83 appeared as two doublets centered at δ 3.19 and δ 2.88 (J = 9.0 Hz). HRMS (FAB) m/z 454.2184 (MNa^+ , $\text{C}_{27}\text{H}_{29}\text{DN}_2\text{O}_3\text{Na}$ requires 454.2193).

***N*-Benzyl 2-Benzylloxycarbonylamino-3-(4-fluorophenyl)-4-methylpentanamide (10c)** (1:1 mixture of diastereomers): ^1H NMR (CDCl_3 , 500 MHz) δ 7.38–7.32 (m, 4H), 7.30–7.26 (m, 3H), 7.25–7.20 (m, 2H), 7.12–7.06 (m, 2H), 6.98–6.93 (m, 2H), 6.83–6.82 (m, 1H), 6.20 and 5.91 (2br s, 1H), 5.25 and 4.90 (2d, J = 9.5 Hz, 1H), 5.12 and 5.08 (2s, 2H), 4.72 and 4.57 (2t, J = 6.5 and 10 Hz, 1H), 4.44–4.27 and 4.37 (m and dd, J = 6.5, 15.5 Hz, 1H), 4.07 (dd, J = 6.5, 15 Hz, 1H), 3.20–3.15 and 2.91–2.86 (2m, 1H), 2.32–2.26 and 2.06–1.98 (2m, 1H), 1.07 and 0.90 (2d, J = 6.5 Hz, 3H), 0.79 and 0.75 (2d, J = 6.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.6 and 170.4, 164.3 (d, J = 297 Hz), 156.3, 137.5 (2C), 136.2, 134.1 (3C), 131.3, 131.2, 129.8 and 128.6 (3C), 128.2 (2C), 127.7 (2C), 115.4 (d, J = 20 Hz, 2C), 67.5 and 67.4, 57.2 and 56.8, 53.6 and 53.0, 43.6 and 43.5, 31.8 and 28.4, 22.8 and 20.2, 21.7 and 18.3; IR (film) ν_{max} 3288, 2946, 1644, 1526, 1254, 1039 cm^{-1} ; HRMS (FAB) m/z 471.2076 (MNa^+ , $\text{C}_{27}\text{H}_{29}\text{FN}_2\text{O}_3\text{Na}$ requires 471.2050).

When **10c** was produced according to the chiral Lewis acid mediated procedure given in the Experimental Section, *syn*-**10c** was obtained in 72% ee, as analyzed by HPLC of the corresponding acetate *syn*-**12c** (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1

mL/min; R_T = 5.9 min (major), 9.0 min). *Anti-10c* was obtained in 50% ee, as analyzed by HPLC under identical conditions (R_T = 14.2 min (major), 20.6 min).

***N*-Benzyl 2-Benzoyloxycarbonylamino-2-deuterio-3-(4-fluorophenyl)-4-methylpentamide (*d*-10c):** ^1H NMR (CDCl_3 , 500 MHz) was identical to **10c** except the signals at δ 4.72 and 4.57 integrated as 0.11H. Also, the multiplet at δ 3.20–3.15 appeared as a doublet centered at δ 3.17 (J = 9.5 Hz), and the multiplet at δ 2.91–2.86 appeared as a broad singlet at δ 2.88. HRMS (FAB) m/z 472.2114 (MNa^+ , $\text{C}_{27}\text{H}_{28}\text{DFN}_2\text{O}_3\text{Na}$ requires 472.2123).

General procedure for the synthesis of acetamides 12 and 13. A solution of crude amine (0.20 mmol) in CH_2Cl_2 (3 mL) was treated with Ac_2O (20.7 μL , 22.4 mg, 0.22 mmol). The resulting mixture was stirred at rt for 12 h and concentrated in vacuo. Flash chromatography (SiO_2 , 50–75% EtOAc in hexanes gradient elution for amides **12** and 25–40% EtOAc in hexanes gradient elution for esters **13**) afforded the products as white solids. Analytical samples were prepared from diastereomerically pure amines.

***N*-Benzyl 2-Acetylamino-3-(4-methoxyphenyl)-4-methylpentanamide (*syn*-12a):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.17–7.10 (m, 5H), 6.78 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 7.5 Hz, 2H), 6.45 (br s, 1H), 6.35 (br s, 1H), 4.97 (t, J = 8.5 Hz, 1H), 4.35 (dd, J = 7.5, 15.0 Hz, 1H), 3.91 (dd, J = 3.0, 15.5 Hz, 1H), 3.79 (s, 3H), 2.95 (dd, J = 4.5, 11.5 Hz, 1H), 2.22–2.14 (m, 1H), 2.03 (s, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.1, 170.0, 158.6, 137.3, 130.8 (2C), 129.5, 128.3 (2C), 127.3 (2C), 127.1, 113.5 (2C), 55.12, 55.08, 52.7, 43.1, 27.9, 23.3, 21.6, 17.6; IR (film) ν_{max} 3276, 3089, 1642, 1556 cm^{-1} ; HRMS (FAB) m/z 369.2170 (MH^+ , $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3\text{H}$ requires 369.2178).

***N*-Benzyl 2-Acetylamino-2-deuterio-3-(4-methoxyphenyl)-4-methylpentanamide** (*syn-d*-**12a**): ^1H NMR (CDCl_3 , 300 MHz) was identical to *syn*-**12a** except for the absence of the triplet at δ 4.97. Also, the dd at δ 2.95 appeared as a doublet ($J = 4.2$ Hz).

***N*-Benzyl 2-Acetylamino-3-(4-methoxyphenyl)-4-methylpentanamide** (*anti*-**12a**): ^1H NMR (CDCl_3 , 500 MHz) δ 7.34–7.28 (m, 3H), 7.20 (d, $J = 7.0$ Hz, 2H), 7.02 (d, $J = 9.0$ Hz, 2H), 6.83 (d, $J = 8.5$ Hz, 2H), 6.51 (br s, 1H), 5.64 (d, $J = 8.0$ Hz, 1H), 4.89 (t, $J = 8.5$ Hz, 1H), 4.47–4.38 (m, 2H), 3.80 (s, 3H), 3.13 (t, $J = 7.5$ Hz, 1H), 2.01–1.93 (m, 1H), 1.85 (s, 3H), 0.97 (d, $J = 7.0$ Hz, 3H), 0.77 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.0, 170.1, 158.5, 137.8, 130.3 (2C), 129.4, 128.6 (2C), 127.7 (2C), 127.5, 113.6 (2C), 55.2, 54.7, 52.1, 43.5, 28.7, 23.1, 21.7, 18.9; IR (film) ν_{max} 3257, 1644, 1563 cm^{-1} ; HRMS (FAB) m/z 369.2169 (MH^+ , $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3\text{H}$ requires 369.2178).

***N*-Benzyl 2-Acetylamino-2-deuterio-3-(4-methoxyphenyl)-4-methylpentanamide** (*anti-d*-**12a**): ^1H NMR (CDCl_3 , 300 MHz) was identical to *anti*-**12a** except for the absence of the triplet at δ 4.89. Also, the triplet at δ 3.13 appeared as a doublet ($J = 6.0$ Hz).

***N*-Benzyl 2-Acetylamino-3-phenyl-4-methylpentanamide** (*syn*-**12b**): ^1H NMR (CDCl_3 , 500 MHz) δ 7.27–7.25 (m, 4H), 7.20 (dd, $J = 2.0, 5.0$ Hz, 2H), 7.16–7.11 (m, 2H), 6.66 (d, $J = 7.0$ Hz, 2H), 6.49 (d, $J = 9.0$ Hz, 1H), 6.38 (br s, 1H), 5.03 (dd, $J = 9.0, 10.5$ Hz, 1H), 4.29 (dd, $J = 7.0, 15.5$ Hz, 1H), 3.93 (dd, $J = 5.0, 15.0$ Hz, 1H), 3.01 (dd, $J = 5.0, 11.0$ Hz, 1H), 2.25–2.18 (m, 1H), 2.03 (s, 3H), 0.86 (d, $J = 7.0$ Hz, 3H), 0.84 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.0, 170.1, 137.7, 137.3, 129.9 (2C), 128.4 (2C), 128.1 (2C), 127.2 (2C), 127.1, 127.0, 55.0, 53.5, 43.2, 27.9, 23.3, 21.6, 17.7;

IR (film) $\nu_{\max}$ 3279, 1642, 1553 cm^{-1} ; HRMS (FAB) m/z 339.2069 (MH^+ , $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2\text{H}$ requires 339.2073).

***N*-Benzyl 2-Acetylamino-2-deuterio-3-phenyl-4-methylpentanamide (*syn-d*-**12b**):** ^1H NMR (CDCl_3 , 500 MHz) was identical to *syn*-**12b** except for the absence of the dd at δ 5.03. Also, the dd at δ 3.01 appeared as a doublet ($J = 4.0$ Hz).

***N*-Benzyl 2-Acetylamino-3-phenyl-4-methylpentanamide (*anti*-**12b**):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.34–7.27 (m, 5H), 7.26–7.21 (m, 1H), 7.19 (d, $J = 6.5$ Hz, 2H), 7.11 (d, $J = 7.0$ Hz, 2H), 6.44 (br s, 1H), 5.60 (d, $J = 8.5$ Hz, 1H), 4.93 (t, $J = 8.5$ Hz, 1H), 4.43 (dd, $J = 2.5, 5.5$ Hz, 2H), 3.19 (t, $J = 7.5$ Hz, 1H), 2.06–1.98 (m, 1H), 1.85 (s, 3H), 0.99 (d, $J = 6.5$ Hz, 3H), 0.78 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.8, 170.1, 137.7, 137.6, 129.4 (2C), 128.7 (2C), 128.3 (2C), 127.7 (2C), 127.5, 127.0, 54.6, 52.8, 43.6, 28.6, 23.1, 21.7, 19.0; IR (film) $\nu_{\max}$ 3250, 1647, 1552 cm^{-1} ; HRMS (FAB) m/z 339.2078 (MH^+ , $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2\text{H}$ requires 339.2073).

***N*-Benzyl 2-Acetylamino-2-deuterio-3-phenyl-4-methylpentanamide (*anti-d*-**12b**):** ^1H NMR (CDCl_3 , 500 MHz) was identical to *anti*-**12b** except for the absence of the triplet at δ 4.93. Also, the triplet at δ 3.19 appeared as a doublet ($J = 6.5$ Hz).

***N*-Benzyl 2-Acetylamino-3-(4-fluorophenyl)-4-methylpentanamide (*syn*-**12c**):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.17–7.13 (m, 5H), 6.90 (t, $J = 8.5$ Hz, 2H), 6.76 (br s, 1H), 6.66 (d, $J = 6.0$ Hz, 2H), 6.64 (br s, 1H), 5.04 (t, $J = 10.0$ Hz, 1H), 4.33 (dd, $J = 7.0, 14.5$ Hz, 1H), 3.87 (dd, $J = 4.5, 15.5$ Hz, 1H), 3.02 (dd, $J = 4.5, 11.5$ Hz, 1H), 2.22–2.14 (m, 1H), 2.01 (s, 3H), 0.84 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.9, 170.2, 161.9 (d, $J = 244$ Hz), 137.2, 133.2, 131.35, 131.28 (2C), 128.4 (2C), 127.2 (2C), 114.8 (d, $J = 21$ Hz, 2C), 54.9, 52.7, 43.1, 27.7, 23.2, 21.5,

17.4; IR (film) $\nu_{\max}$ 3279, 1639, 1552 cm^{-1} ; HRMS (FAB) m/z 357.1974 (MH^+ , $\text{C}_{21}\text{H}_{25}\text{FN}_2\text{O}_2\text{H}$ requires 357.1978).

***N*-Benzyl 2-Acetylamino-2-deuterio-3-(4-fluorophenyl)-4-methylpentanamide**
(*syn-d-12c*): ^1H NMR (CDCl_3 , 500 MHz) was identical to *syn-12c* except for the absence of the triplet at δ 5.04. Also, the dd at δ 3.02 appeared as a doublet ($J = 6.0$ Hz).

***N*-Benzyl 2-Acetylamino-3-(4-fluorophenyl)-4-methylpentanamide** (*anti-12c*):
 ^1H NMR ($\text{DMSO}-d_6$, 500 MHz) δ 8.60 (t, $J = 6.5$ Hz, 1H), 7.63 (d, $J = 9.0$ Hz, 1H), 7.30–7.22 (m, 3H), 7.15–7.05 (m, 6H), 4.86 (t, $J = 9.5$ Hz, 1H), 4.28 (dd, $J = 6.5$, 15.5 Hz, 1H), 4.20 (dd, $J = 5.5$, 13 Hz, 1H), 2.95 (dd, $J = 6.0$, 9.0 Hz, 1H), 1.87–1.79 (m, 1H), 1.70 (s, 3H), 0.80 (d, $J = 6.0$ Hz, 3H), 0.67 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 125 MHz) δ 170.9, 169.0, 160.9 (d, $J = 240$ Hz), 139.2, 134.4, 131.2, 131.1, 128.1 (2C), 127.2 (2C), 126.7, 114.3 (d, $J = 20$ Hz, 2C), 54.1, 52.5, 42.0, 28.0, 22.5, 21.7, 18.4; IR (film) $\nu_{\max}$ 3279, 1647, 1549 cm^{-1} ; HRMS (FAB) m/z 357.1981 (MH^+ , $\text{C}_{21}\text{H}_{25}\text{FN}_2\text{O}_2\text{H}$ requires 357.1978).

***N*-Benzyl 2-Acetylamino-2-deuterio-3-(4-fluorophenyl)-4-methylpentanamide**
(*anti-d-12c*): ^1H NMR ($\text{DMSO}-d_6$, 500 MHz) was identical to *anti-12c* except for the absence of the triplet at δ 4.86. Also, the dd at δ 2.95 appeared as a doublet ($J = 3.5$ Hz).

Methyl 2-Acetylamino-3-(4-methoxyphenyl)-4-methylpentanoate (*syn-13a*):
 ^1H NMR (CDCl_3 , 500 MHz) δ 6.93 (d, $J = 9.0$ Hz, 2H), 6.83 (d, $J = 8.5$ Hz, 2H), 5.78 (d, $J = 10.0$ Hz, 1H), 5.12 (dd, $J = 6.0$, 9.0 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.60 (dd, $J = 6.0$, 10.0 Hz, 1H), 2.25–2.18 (m, 1H), 1.99 (s, 3H), 1.19 (d, $J = 6.5$ Hz, 3H), 0.72 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.7, 169.1, 158.7, 130.5, 129.9 (2C),

113.6 (2C), 55.9, 55.1, 53.8, 52.0, 29.0, 23.3, 21.3, 21.1; IR (film) $\nu_{\max}$ 3288, 2958, 1743, 1656, 1513 cm^{-1} ; HRMS (FAB) m/z 294.1712 (MH^+ , $\text{C}_{16}\text{H}_{23}\text{NO}_4\text{H}$ requires 294.1705).

Methyl 2-Acetylamino-2-deuterio-3-(4-methoxyphenyl)-4-methylpentanoate (*syn-d-13a*): ^1H NMR (CDCl_3 , 300 MHz) was identical to *syn-13a* except for the absence of the dd at δ 5.12. Also, the dd at δ 2.60 appeared as a doublet ($J = 9.9$ Hz).

Methyl 2-Acetylamino-3-(4-methoxyphenyl)-4-methylpentanoate (*anti-13a*): ^1H NMR (CDCl_3 , 500 MHz) δ 6.98 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 5.56 (d, $J = 9.5$ Hz, 1H), 5.16 (dd, $J = 5.0, 10.0$ Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 2.85 (dd, $J = 4.5, 9.5$ Hz, 1H), 2.00 (s, 3H), 1.99–1.94 (m, 1H), 1.14 (d, $J = 6.5$ Hz, 3H), 0.75 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.6, 170.0, 158.7, 130.2, 129.5 (2C), 114.0 (2C), 55.2, 54.2, 53.6, 52.2, 28.3, 23.3, 21.4, 20.7; IR (film) $\nu_{\max}$ 3370, 2957, 1745, 1660, 1512 cm^{-1} ; HRMS (FAB) m/z 294.1703 (MH^+ , $\text{C}_{16}\text{H}_{23}\text{NO}_4\text{H}$ requires 294.1705).

Methyl 2-Acetylamino-2-deuterio-3-(4-methoxyphenyl)-4-methylpentanoate (*anti-d-13a*): ^1H NMR (CDCl_3 , 300 MHz) was identical to *anti-13a* except for the absence of the dd at δ 5.16. Also, the dd at δ 2.85 appeared as a doublet ($J = 9.9$ Hz).

Methyl 2-Acetylamino-3-phenyl-4-methylpentanoate (*syn-13b*): ^1H NMR (CDCl_3 , 500 MHz) δ 7.31–7.24 (m, 3H), 7.02 (d, $J = 6.5$ Hz, 2H), 5.79 (d, $J = 8.5$ Hz, 1H), 5.15 (dd, $J = 6.0, 9.0$ Hz, 1H), 3.67 (s, 3H), 2.66 (dd, $J = 6.0, 10.0$ Hz, 1H), 2.31–2.24 (m, 1H), 1.99 (s, 3H), 1.21 (d, $J = 6.5$ Hz, 3H), 0.73 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.5, 169.2, 138.7, 129.0 (2C), 128.3 (2C), 127.2, 56.7, 53.8, 52.0, 28.9, 23.3, 21.3, 21.1; IR (film) $\nu_{\max}$ 3283, 2959, 1744, 1656, 1538 cm^{-1} ; HRMS (FAB) m/z 264.1596 (MH^+ , $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{H}$ requires 264.1600).

Methyl 2-Acetylamino-2-deuterio-3-phenyl-4-methylpentanoate (*syn-d-13b*):

^1H NMR (CDCl_3 , 300 MHz) was identical to *syn-13b* except for the absence of the dd at δ 5.15. Also, the dd at δ 2.66 appeared as a doublet ($J = 9.9$ Hz).

Methyl 2-Acetylamino-3-phenyl-4-methylpentanoate (*anti-13b*): ^1H NMR (CDCl_3 , 500 MHz) δ 7.34–7.26 (m, 3H), 7.07 (d, $J = 8.5$ Hz, 2H), 5.59 (d, $J = 10.0$ Hz, 1H), 5.21 (dd, $J = 4.5, 10.0$ Hz, 1H), 3.68 (s, 3H), 2.90 (dd, $J = 4.5, 10.0$ Hz, 1H), 2.07–2.02 (m, 1H), 2.01 (s, 3H), 1.16 (d, $J = 6.5$ Hz, 3H), 0.75 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.5, 170.0, 138.4, 128.6 (4C), 127.3, 55.1, 53.5, 52.2, 28.2, 23.4, 21.4, 20.8; IR (film) ν_{max} 3283, 1745, 1659 cm^{-1} ; HRMS (FAB) m/z 264.1604 (MH^+ , $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{H}$ requires 264.1600).

Methyl 2-acetylamino-2-deuterio-3-phenyl-4-methylpentanoate (*anti-d-13b*):

^1H NMR (CDCl_3 , 300 MHz) was identical to *anti-13b* except for the absence of the dd at δ 5.21. Also, the dd at δ 2.90 appeared as a doublet ($J = 9.9$ Hz).

Methyl 2-Acetylamino-3-(4-fluorophenyl)-4-methylpentanoate (*syn-13c*): ^1H NMR (CDCl_3 , 500 MHz) δ 6.99 (d, $J = 7.0$ Hz, 4H), 5.79 (d, $J = 8.5$ Hz, 1H), 5.13 (dd, $J = 6.0, 8.5$ Hz, 1H), 3.66 (s, 3H), 2.68 (dd, $J = 6.0, 9.5$ Hz, 1H), 2.26–2.18 (m, 1H), 2.00 (s, 3H), 1.18 (d, $J = 7.0$ Hz, 3H), 0.72 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.5, 169.2, 162.0 (d, $J = 230$ Hz), 134.3, 130.4, 130.36, 115.1 (d, $J = 20$ Hz, 2C), 55.8, 53.8, 52.1, 28.9, 23.3, 21.2, 20.8; IR (film) ν_{max} 3287, 1744, 1657, 1510 cm^{-1} ; HRMS (FAB) m/z 282.1506 (MH^+ , $\text{C}_{15}\text{H}_{20}\text{FNO}_3\text{H}$ requires 282.1505).

Methyl 2-Acetylamino-2-deuterio-3-(4-fluorophenyl)-4-methylpentanoate

(*syn-d-13c*): ^1H NMR (CDCl_3 , 500 MHz) was identical to *syn-13c* except for the absence of the dd at δ 5.13. Also, the dd at δ 2.68 appeared as a doublet ($J = 9.5$ Hz).

Methyl 2-Acetylamino-3-(4-fluorophenyl)-4-methylpentanoate (*anti*-13c): ^1H NMR (CDCl_3 , 500 MHz) δ 7.04–7.00 (m, 4H), 5.54 (d, $J = 9.5$ Hz, 1H), 5.20 (dd, $J = 4.5$, 10.0 Hz, 1H), 3.69 (s, 3H), 2.88 (dd, $J = 4.5$, 9.5 Hz, 1H), 2.01 (s, 3H), 1.99–1.95 (m, 1H), 1.16 (d, $J = 6.0$ Hz, 3H), 0.74 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.4, 170.0, 162.0 (d, $J = 250$ Hz), 134.1, 130.1, 130.0, 115.5 (d, $J = 21$ Hz, 2C), 54.5, 53.4, 52.3, 28.4, 23.3, 21.4, 20.6; IR (film) ν_{max} 3296, 2960, 1745, 1659, 1509 cm^{-1} ; HRMS (FAB) m/z 282.1495 (MH^+ , $\text{C}_{15}\text{H}_{20}\text{FNO}_3\text{H}$ requires 282.1505).

Methyl 2-Acetylamino-2-deuterio-3-(4-fluorophenyl)-4-methylpentanoate (*anti-d*-13c): ^1H NMR (CDCl_3 , 500 MHz) was identical to *anti*-13c except for the absence of the dd at δ 5.20. Also, the dd at δ 2.88 appeared as a doublet ($J = 9.5$ Hz).

Determination of the absolute configuration of both diastereomers of 7b. A sample of **7b** was reduced to the corresponding amine with indium according to the General Procedure in the Experimental Section. The diastereomers were separated by flash chromatography (SiO_2 , 1–4% MeOH in CH_2Cl_2 gradient elution), and one diastereomer (15.2 mg, 0.0512 mmol) was treated with 6 N HBr (3 mL) and heated at 160 $^\circ\text{C}$ in a sealed tube for 5 h. The resulting mixture was cooled to rt and loaded on an ion-exchange column (Amberlite IR120 (H^+) resin, 20 g). The column was washed with distilled H_2O until the eluant was neutral, and the amino acid was eluted with 15% aq NH_4OH . Concentration and lyophilization afforded **15** (5.3 mg, 50%) as a white solid. Comparison of the data for this compound to that previously reported by Hruby and co-workers⁶ established its identity as the *anti* (2*R*,3*R*)-isomer. Similarly, amide hydrolysis of the other diastereomer established its identity as the *syn* (2*R*,3*S*)-isomer.

⁶ Liao, S.; Shenderovich, M. D.; Lin, J.; Hruby, V. J. *Tetrahedron* **1997**, 53, 16645.

***N*-Benzyl 2-Benzylloxycarbonylamino-3-(4-methoxyphenyl)-pentanamide**

(*syn*-**17a**): prepared according to the chiral Lewis acid mediated procedure given in the Experimental Section; ^1H NMR (CDCl_3 , 500 MHz) δ 7.39–7.33 (m, 5H), 7.25–7.18 (m, 3H), 7.10 (d, $J = 8.5$ Hz, 2H), 6.84–6.78 (m, 4H), 5.57 (br s, 1H), 5.50 (d, $J = 9.5$ Hz, 1H), 5.10 (AB system, $J_{\text{AB}} = 12.0$ Hz, 1H), 5.08 (AB system, $J_{\text{AB}} = 12.0$ Hz, 1H), 4.28 (dd, $J = 6.5, 15.0$ Hz, 1H), 4.23 (t, $J = 9.5$ Hz, 1H), 4.05 (dd, $J = 4.5, 14.5$ Hz, 1H), 3.80 (s, 3H), 2.78 (br t, $J = 10.0$ Hz, 1H), 1.99–1.90 (m, 1H), 1.66–1.58 (m, 1H), 0.72 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.6, 158.6, 156.3, 137.2, 136.1, 132.3, 129.3 (2C), 128.5 (2C), 128.4 (2C), 128.2, 128.0 (2C), 127.5 (2C), 127.4, 114.1 (2C), 67.1, 60.7, 55.1, 50.1, 43.4, 24.6, 11.9; IR (film) ν_{max} 3322, 1697, 1655, 1543, 1513 cm^{-1} ; HRMS (FAB) m/z 447.2292 (MH^+ , $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_4\text{H}$ requires 447.2284).

***N*-Benzyl 2-Acetylamino-3-(4-methoxyphenyl)-pentanamide** (*syn*-**18a**, the corresponding acetate of *syn*-**17a**): prepared according to the chiral Lewis acid mediated procedure given in the Experimental Section; ^1H NMR ($\text{DMSO}-d_6$, 500 MHz) δ 8.31 (t, $J = 5.5$ Hz, 1H), 8.15 (d, $J = 9.0$ Hz, 1H), 7.15–7.09 (m, 5H), 6.83 (d, $J = 9.0$ Hz, 2H), 6.69 (d, $J = 6.5$ Hz, 2H), 4.56 (t, $J = 9.5$ Hz, 1H), 4.21 (dd, $J = 7.0, 16.0$ Hz, 1H), 3.91 (dd, $J = 5.0, 15.5$ Hz, 1H), 3.74 (s, 3H), 2.78 (dt, $J_{\text{d}} = 3.5$ Hz, $J_{\text{t}} = 11.5$ Hz, 1H), 1.87 (s, 3H), 1.76–1.66 (m, 1H), 1.51–1.40 (m, 1H), 0.61 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 125 MHz) δ 170.6, 169.1, 157.8, 139.0, 132.7, 129.6 (2C), 127.9 (2C), 126.6 (2C), 126.3, 113.5 (2C), 57.3, 54.9, 48.6, 41.6, 24.2, 22.5, 11.8; IR (film) ν_{max} 3256, 1641, 1561 cm^{-1} ; HRMS (FAB) m/z 355.2022 (MH^+ , $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3\text{H}$ requires 355.2022).

***N*-Benzyl 2-Benzylloxycarbonylamino-3-(4-methoxyphenyl)-pentanamide**

(*anti*-**17a**): prepared according to the chiral Lewis acid mediated procedure given in the

Experimental Section; ^1H NMR (CDCl_3 , 500 MHz) δ 7.35–7.27 (m, 8H), 7.15 (d, $J = 6.0$ Hz, 2H), 7.06 (d, $J = 8.5$ Hz, 2H), 6.80 (d, $J = 8.5$ Hz, 2H), 6.10 (br s, 1H), 5.11–5.05 (m, 3H), 4.44–4.32 (m, 3H), 3.79 (s, 3H), 3.25 (dt, $J_{\text{d}} = 4.5$ Hz, $J_{\text{t}} = 9.5$ Hz, 1H), 1.82–1.72 (m, 1H), 1.70–1.62 (m, 1H), 0.83 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.5, 158.6, 156.1, 137.7, 136.0, 130.9, 129.4 (2C), 128.6 (2C), 128.5 (2C), 128.3, 128.0 (2C), 127.8 (2C), 127.5, 114.1 (2C), 67.1, 59.5, 55.2, 47.7, 43.5, 24.1, 12.0; IR (film) ν_{max} 3293, 1698, 1652, 1543, 1513 cm^{-1} ; HRMS (FAB) m/z 447.2272 (MH^+ , $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_4\text{H}$ requires 447.2284).

Syn-17a was obtained in 57% ee, as analyzed by HPLC of the corresponding acetate *syn-18a* (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; $R_{\text{T}} = 9.0$ min (major), 11.4 min). *Anti-17a* was obtained in 64% ee, as analyzed by HPLC under identical conditions ($R_{\text{T}} = 36.3$ min (major), 46.3 min).

***N*-Benzyl 2-Benzoyloxycarbonylamino-3-cyclohexyl-3-(4-methoxyphenyl)-propanamide (*syn-17b*):** prepared according to the chiral Lewis acid mediated procedure given in the Experimental Section; ^1H NMR (CDCl_3 , 500 MHz) δ 7.37–7.28 (m, 5H), 7.26–7.16 (m, 3H), 7.05 (d, $J = 8.5$ Hz, 2H), 6.87–6.80 (m, 2H), 6.77 (d, $J = 8.5$ Hz, 2H), 5.91 (br s, 1H), 5.27 (d, $J = 9.0$ Hz, 1H), 5.15 (AB system, $J_{\text{AB}} = 12.0$ Hz, 1H), 5.09 (AB system, $J_{\text{AB}} = 12.0$ Hz, 1H), 4.63 (t, $J = 9.5$ Hz, 1H), 4.38 (dd, $J = 6.5, 15.0$ Hz, 1H), 4.09 (dd, $J = 4.5, 14.5$ Hz, 1H), 3.79 (s, 3H), 2.82 (dd, $J = 6.5, 9.0$ Hz, 1H), 1.94–1.85 (m, 1H), 1.82–1.74 (m, 1H), 1.71–1.62 (m, 3H), 1.34–1.22 (m, 2H), 1.16–1.07 (m, 1H), 1.94–0.93 (m, 1H), 0.91–0.78 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.8, 158.6, 156.0, 137.4, 136.1, 130.5, 130.4 (2C), 128.6 (2C), 128.4 (2C), 128.3, 128.1 (2C), 127.5 (2C), 127.3, 113.7 (2C), 67.1, 56.3, 55.1, 53.5, 43.3 (2C), 38.4, 32.1, 29.1, 26.5, 26.3; IR

(film) $\nu_{\max}$ 3295, 2926, 1694, 1651, 1539, 1513 cm^{-1} ; HRMS (FAB) m/z 501.2759 (MH^+ , $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_4\text{H}$ requires 501.2753).

***N*-Benzyl 2-Acetylamino-3-cyclohexyl-3-(4-methoxyphenyl)-propanamide** (*syn*-**18b**, the corresponding acetate of *syn*-**17b**): prepared according to the chiral Lewis acid mediated procedure given in the Experimental Section; ^1H NMR (CDCl_3 , 500 MHz) δ 7.26–7.12 (m, 3H), 7.08 (d, $J = 9.0$ Hz, 2H), 6.80 (d, $J = 9.0$ Hz, 2H), 6.78–6.74 (m, 2H), 6.05 (d, $J = 9.0$ Hz, 1H), 5.95 (br s, 1H), 4.91 (t, $J = 10.0$ Hz, 1H), 4.39 (dd, $J = 7.5$, 15.0 Hz, 1H), 4.00 (dd, $J = 4.0$, 14.5 Hz, 1H), 3.81 (s, 3H), 2.90 (dd, $J = 5.5$, 11.0 Hz, 1H), 2.04 (s, 3H), 1.81–1.73 (m, 1H), 1.70–1.65 (m, 4H), 1.32–1.23 (m, 1H), 1.16–1.09 (m, 1H), 1.00–0.93 (m, 1H), 0.92–0.78 (m, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.9, 170.0, 158.6, 137.3, 130.6 (2C), 130.3, 128.4 (2C), 127.4 (2C), 127.3, 113.6 (2C), 55.1, 54.5, 52.8, 43.3, 38.6, 32.2, 28.5, 26.6, 26.5, 26.3, 23.4; IR (film) $\nu_{\max}$ 3255, 1640, 1560 cm^{-1} ; HRMS (FAB) m/z 409.2495 (MH^+ , $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_3\text{H}$ requires 409.2491).

***N*-Benzyl 2-Benzyloxycarbonylamino-3-cyclohexyl-3-(4-methoxyphenyl)-propanamide** (*anti*-**17b**): prepared according to the chiral Lewis acid mediated procedure given in the Experimental Section; ^1H NMR (CDCl_3 , 500 MHz) δ 7.37–7.25 (m, 8H), 7.08–7.03 (m, 2H), 7.02 (d, $J = 9.0$ Hz, 2H), 6.81 (d, $J = 8.5$ Hz, 2H), 6.21 (br s, 1H), 5.14–5.04 (m, 2H), 4.96 (d, $J = 8.5$ Hz, 1H), 4.73 (br s, 1H), 4.46–4.38 (m, 1H), 4.34–4.27 (m, 1H), 3.79 (s, 3H), 3.20 (br t, $J = 6.0$ Hz, 1H), 1.97–1.90 (m, 1H), 1.80–1.73 (m, 1H), 1.61–1.56 (m, 1H), 1.54–1.48 (m, 1H), 1.27–1.16 (m, 2H), 1.12–0.98 (m, 4H), 0.82–0.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 171.1, 158.5, 156.0, 137.8, 136.0, 130.0 (2C), 128.6 (2C), 128.5 (2C), 128.3, 128.1 (2C), 127.7 (2C), 127.4 (2C), 113.9 (2C), 67.2, 56.0, 55.2, 51.5, 43.3 (2C), 37.6, 31.3, 30.5, 26.3, 26.2; IR (film) $\nu_{\max}$

3294, 2925, 1697, 1653, 1542, 1513 cm^{-1} ; HRMS (FAB) m/z 501.2739 (MH^+ , $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_4\text{H}$ requires 501.2753).

Syn-**17b** was obtained in 80% ee, as analyzed by HPLC of the corresponding acetate *syn*-**18b** (Chiralcel OD-H, 98:2 hexane:*i*-PrOH, 1 mL/min; R_T = 7.9 min (major), 13.0 min). *Anti*-**17b** was obtained in 81% ee, as analyzed by HPLC under identical conditions (R_T = 22.5 min (major), 32.1 min).

13

Pulse Sequence: zgpg30

13

Pulse Sequence: szpul

pfloroknevestat

Pulse Sequence: zgpg30

pflorolatesknev

Pulse Sequence: szpul

6

Pulse Sequence: zgpg30

6

Pulse Sequence: szpul

5 1h

Pulse Sequence: szpul

5 1h

Pulse Sequence: s2pul

4 1h

Pulse Sequence: s2pul

4 13c

Pulse Sequence: szpul

1est:

Pulse Sequence: szpul

Last

Pulse Sequence: zgpg30

STANDARD PROTON PARAMETERS

Pulse Sequence: zgpg1 pmtwysunkw

pmethoxyamknev

Pulse Sequence: szpul

benzylamknevih

Pulse Sequence: zgpg30

6b (CDCl₃, 500 MHz)

benzylkneavam

Pulse Sequence: szpul

6b (CDCl₃, 125 MHz)

p1loranbneuv

Pulse Sequence: szpul

pFloramknev

Pulse Sequence: szpu1

pmethoxyamrca

Pulse Sequence: zgpg30

pmhancra

Pulse Sequence: szpul

benzylamrca

Pulse Sequence: szpul

7b (CDCl₃, 500 MHz)

benzylamca13c

Pulse Sequence: zgpg30

7b (CDCl₃, 125 MHz)

11h

Pulse Sequence: s2puls

p10romrcal3c

Pulse Sequence: szpul

12

Pulse Sequence: zgpg30

12

Pulse Sequence: szpul

STANDARD PROTON PARAMETERS
Pulse Sequence: zgpg30

11

Pulse Sequence: szpul

STANDARD PROTON PARAMETERS
Pulse Sequence: #2pul

10

Pulse Sequence: szpul

9

Pulse Sequence: szpul

9

Pulse Sequence: szpul

benzylamcbz

Pulse Sequence: szpu1

10b (CDCl₃, 500 MHz)

8

Pulse Sequence: szpul

10b (CDCl₃, 125 MHz)

Pulse Sequence: s2pul

7

Pulse Sequence: szpul

10c (CDCl₃, 125 MHz)

11wen-2-193syn-500MHz
Pulse Sequence: s2pul1

liven-2-191syn-carbon-125MHz

Pulse Sequence: szpul

14000-2-193ant1-500MHz

Pulse Sequence: szpul

liven-2-13anti-carbon-125MHz

Pulse Sequence: szpul

liven-2-194syn-500MHz

Pulse Sequence: szpul

125MHz-2-194syn-carbon-125MHz

Pulse Sequence: szpul

syn-12b (CDCl₃, 125MHz)

11wen-2-194ant1-500MHz

Pulse Sequence: szpul

liven-2-194antl-carbon-125MHz

Pulse Sequence: szpul

Iiven-2-195syn-500MHz

Pulse Sequence: s2pu1

11ven-2-195syn-carbon-125MHz

Pulse Sequence: szpu1

l1wen-2-195ant1-500MHz
Pulse Sequence: szpul

liven-2-195anti-carbon-125MHz

Pulse Sequence: szpul

11ven-2-196syn-500MHz
Pulse Sequence: szpu1

11ven-2-196syn-carbon-125MHz

Pulse Sequence: szpul

11wv2-196ant1-500MHz
Pulse Sequence: szpul

11wv-2-196ant1-carbon-125MHz

Pulse Sequence: szpul

11ven-2-197syn-500MHz
Pulse Sequence: zgpg30

liven-2-197syn-carbon-125MHz

Pulse Sequence: zgpg30

11ven-2-197anti-500MHz
Pulse Sequence: szpu1

11wen-2-19/anti-carbon-125mhz
Pulse Sequence: szpul

11wen-2-198eyn-500MHz

Pulse Sequence: szpul

syn-13c(CDCl₃, 500MHz)

11ven-2-198syn-carbon-125MHz

Pulse Sequence: s2pul

liven-2-19anti-b-500MHz

Pulse Sequence: szpul

11ven-2-198anti-b-carbon-125MHz

Pulse Sequence: szpul

liven-2-202syn-500MHz

Pulse Sequence: szpul

liven-2-202apn-carbon-125MHz

Pulse Sequence: szpul

11ven-2-174syn-Ac-500MHz

Pulse Sequence: szpul

liven-2-174syn-Ac-carbon-125MHz
Pulse Sequence: szpul

11ven-2-202ant1-500MHz

Pulse Sequence: szpul

liven-2-202anti-carbon-125MHz

Pulse Sequence: s2pul

11ven-2-203syn-500MHz

Pulse Sequence: szpul

liven-2-203syn-125MHz

Pulse Sequence: s2pul

syn-17b(CDCl₃, 125MHz)

liven-2-175sp-Ac-500MHz

Pulse Sequence: szpul

liven-2-175cp-Ac-carbon-125MHz

Pulse Sequence: szpul

syn-18b (CDCl₃, 125MHz)

11wen-2-20Jan11-500MHz

Pulse Sequence: szpul

11wen-2-203anti-carbon-125MHz
Pulse Sequence: szpul