Enantioselective Michael additions to α,β -unsaturated imides catalyzed by a Salen-Al complex

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Supporting Information

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen, unless otherwise noted. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.

Materials. Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or Lancaster, and used as received with the following exceptions: toluene and tetrahydrofuran were distilled from sodium at 760 Torr, and acetonitrile and dichloromethane were distilled from calcium hydride at 760 Torr.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (400 MHz), Inova-500 (500 MHz), or an Inova-600 (600 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl_3 : δ 7.25). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and assignment. Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Melting points were measured on a Mel-Temp apparatus, and are uncorrected. The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility. Chiral GC analysis was performed on a Hewlett-Packard 5890 gas chromatograph. Chiral HPLC analysis was performed on either a Hewlett-Packard 1050, or a Shimadzu VP-series instrument.

Representative Experimental Procedures:

(A) Preparation of catalyst **1**:¹

In a flame-dried round-bottomed flask equipped with a stir bar and reflux condenser, (*S,S*)-*N,N'*-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamine (1.79 g, 3.28 mmol) was suspended in acetonitrile (10 mL) and toluene (3.3 mL). Trimethylaluminum (1.64 mL, 2.0 M solution in toluene, 3.28 mmol, 1.00 equiv.) was added dropwise by syringe at 23°C. The mixture was stirred at 23°C for 30 minutes, then heated to reflux and stirred for 5 hours. After cooling to 23°C, water (59 μL , 3.28 mmol, 1.00 equiv.) was added by syringe. The resulting mixture was heated to reflux and stirred for 15 hours. After cooling to 23°C, acetonitrile (25 mL) was added and the mixture filtered through Celite and washed with acetonitrile (total volume 200 mL). The filtrate was discarded, and the Celite washed with dichloromethane (total volume 125 mL). The filtrate was concentrated *in vacuo*, yielding the aluminum complex **1** as a pale yellow solid in 85% yield (1.61 g, 1.40 mmol).

Product: FTIR (CHCl_3 film, cm^{-1}): 3054 (m), 2961 (s), 2867 (m), 1626 (s), 1555 (m), 1416 (m), 1265 (s), 1177 (m), 1015 (w), 601 (w). mp > 300°C. ^1H NMR (500 MHz, d_{12} -cyclohexane): δ 7.99 (2H, s, $\text{HC}=\text{N}$), 7.55 (2H, s, $\text{HC}=\text{N}$), 7.45 (2H, s, ArH), 7.21 (2H, s, ArH), 6.98 (2H, s, ArH), 6.75 (2H, s, ArH), 3.34–3.29 (2H, m, $\text{CHN}=\text{C}$), 2.68–2.64 (2H, m, $\text{CHN}=\text{C}$), 2.27–2.26 (2H, m, $(\text{CH}_2)_4$), 1.85–1.82 (2H, m, $(\text{CH}_2)_4$), 1.56–1.12 (8H, m, $(\text{CH}_2)_4$), 1.50 (8H, s, $\text{C}(\text{CH}_3)_3$), 1.31 (8H, s, $\text{C}(\text{CH}_3)_3$), 1.24 (8H, s, $\text{C}(\text{CH}_3)_3$), 1.12 (8H, s, $\text{C}(\text{CH}_3)_3$), 0.99–0.96 (2H, m, $(\text{CH}_2)_4$), 0.80–0.78 (2H, m, $(\text{CH}_2)_4$). ^{13}C NMR (100 MHz, d_{12} -cyclohexane): δ 166.7, 166.0, 163.9, 160.1, 141.8, 141.5, 137.2, 136.3, 129.8, 129.1, 127.5, 126.7, 119.1, 119.1, 66.1, 62.5, 36.3, 35.9, 34.5, 34.3, 32.0, 30.3, 29.9, 29.0, 27.4, 27.0, 25.1, 24.3.

(B) General procedure for the preparation of α,β -unsaturated imides.

N-[3-(4-Fluoro-phenyl)-acryloyl]-benzamide (**2b**):²

¹ Procedure developed by Qinghao Chen. Compound **1** has been prepared by hydrolysis of the corresponding aluminum amide: Rutherford, D.; Atwood, D.A. *Organometallics* **1996**, *15*, 4417–4422.

² With the exception of **2b** and **2c**, the α,β -unsaturated imides used in this study have been reported previously. See: a) Myers, J.K.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960; b) Sammis, G.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443.

An oven-dried round-bottomed flask was capped with a septum and allowed to cool under nitrogen, then charged with (2-benzoylamino-2-oxo-ethyl)-phosphonic acid diethyl ester³ (14.97 g, 50.0 mmol) and undistilled THF (150 mL). DBU (8.23 mL, 55.0 mmol, 1.10 equiv.), then *p*-fluorobenzaldehyde (5.64 mL, 51.5 mmol, 1.03 equiv.) were added via syringe and the resulting mixture stirred at 23°C for 6 hours. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane, then washed twice with 1M aqueous hydrochloric acid, twice with saturated aqueous sodium bicarbonate solution, then once with brine. Drying over anhydrous sodium sulfate and removal of the solvent *in vacuo* yielded the crude product as a white solid. Recrystallization from hot ethyl acetate provided **2b** as white needles (two crops, 11.43 g total, 85% yield).

Product: mp 151-168°C. FTIR (cm⁻¹): 3055 (w), 1680 (s), 1599 (s), 1508 (s), 1235 (s), 831 (m), 704 (s). ¹H NMR (500 MHz, CDCl₃): δ 9.19 (1 $\square$, br s, NH), 7.95 (2H, d, J = 7.5 Hz, ArH), 7.86 (1H, d, J = 16.0 Hz, CH=CH), 7.79 (1H, d, J = 16.0 Hz, CH=CH), 7.64-7.61 (3H, m, ArH), 7.52 (2H, t, J = 8.0 Hz, ArH), 7.09 (2H, t, J = 9.0 Hz, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 166.3, 164.4 (d, J_{C-F} = 250 Hz), 145.5, 133.5, 133.2, 131.1 (d, J_{C-F} = 3.0 Hz), 130.8 (d, J_{C-F} = 8.3 Hz), 129.2, 128.1, 119.4, 116.3 (d, J_{C-F} = 21.3 Hz). MS (CI) m/z: 269.9 (100%) [M+H]⁺, 269.0 (80%) [M]⁻, 268.0 (50%) [M-H]⁻.

***N*-[3-(4-Chloro-phenyl)-acryloyl]-benzamide (2c):** Obtained in 73% yield (10 mmol scale) as a white solid after recrystallization from ethyl acetate.

Product: mp 180-182°C. FTIR (cm⁻¹): 3055 (m), 2988 (m), 1685 (m), 1458 (m), 1266 (s), 896 (m). ¹H NMR (500 MHz, CDCl₃): δ 9.02 (1 $\square$, br s, NH), 7.94 (2H, d, J = 7.0 Hz, ArH), 7.84 (2H, s, CH=CH), 7.63 (1H, t, J = 8.0 Hz, ArH), 7.57 (2H, d, J = 8.0 Hz, ArH), 7.53 (2H, t, J = 8.0 Hz, ArH), 7.38 (2H, d, J = 8.5 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 167.9, 166.2, 145.4, 136.9, 133.6, 133.3, 133.1, 130.0, 129.4, 129.3, 128.1, 120.2.

(C) General procedure for the conjugate addition of malononitrile to **2**.

(*R*)-*N*-(4,4-Dicyano-3-(phenylbutyryl)benzamide (3a):

An oven-dried round-bottomed flask was capped with a septum and charged with **2a** (126 mg, 0.50 mmol), catalyst (*S,S*)-**1** (28.8 mg, 0.025 mmol, 5 mol%), and cyclohexane (2.5 mL). To the resulting suspension was added malononitrile (40 mg, 0.60 mmol, 1.2 equiv.), then *t*-butanol (57 $\square$ L, 0.60 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 28 hours, then diluted with ethyl acetate and purified by flash column chromatography on silica (elution gradient 20% $\square$ 33% ethyl acetate in hexanes). The product **3a** was obtained as a white solid in 87% yield (138 mg) and 90% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 14% ethanol/hexanes,

³ For the preparation of (2-benzoylamino-2-oxo-ethyl)-phosphonic acid diethyl ester and its use in the Horner-Wadsworth-Emmons reaction, see: Goodman, S.N.; Jacobsen, E.N. *Adv. Synth. Catal.* **2002**, *344*, 935-956.

1.4 mL/min, 235 nm, r_{minor} 29.5 min, r_{major} 39.2 min). $[\alpha]_{\text{D}}^{25} -20^{\circ}$ ($c = 1.0$, CH_3CN). mp 105-112°C. FTIR (cm^{-1}): 3391 (w), 3055 (m), 2988 (w), 2307 (w), 1699 (m), 1464 (m), 1265 (s), 706 (s). ^1H NMR (500 MHz, CDCl_3): δ 8.72 (1H, br s, NH), 7.83 (2H, d, $J = 7.0$ Hz, ArH), 7.65 (1H, d, $J = 7.5$ Hz, ArH), 7.53 (2H, t, $J = 7.5$ Hz, ArH), 7.46-7.26 (5H, m, ArH), 4.58 (1H, d, $J = 5.5$ Hz, CH(CN)₂), 3.92-3.79 (1H, m, CHPh), 3.77-3.71 (2H, m, COCH₂). ^{13}C NMR (100 MHz, CDCl_3): δ 173.1, 165.7, 136.3, 134.0, 132.2, 129.6, 129.5, 129.4, 128.3, 127.9, 112.0, 111.7, 41.7, 39.9, 29.1. MS (CI) m/z : 317.6 (20%) $[\text{M}+\text{H}]^+$, 251.9 (100%) $[\text{M}-\text{C}_3\text{HN}_2]^+$, 315.8 (100%) $[\text{M}-\text{H}]^-$.

(D) General procedure for the conjugate addition of methyl cyanoacetate to **2**.

(R)-5-Benzoylamino-2-cyano-3-phenyl-5-oxo-pentanoic acid methyl ester (**4a**):

An oven-dried round-bottomed flask was capped with a septum and charged with **2a** (126 mg, 0.50 mmol), catalyst (*S,S*)-**1** (28.8 mg, 0.025 mmol, 5 mol%), and cyclohexane (2.5 mL). To the resulting suspension was added methyl cyanoacetate (110 μL , 1.25 mmol, 2.5 equiv.), then *t*-butanol (57 μL , 0.60 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 54 hours, then diluted with ethyl acetate and purified by flash column chromatography on silica (elution gradient 20%–33% ethyl acetate in hexanes). Residual methyl cyanoacetate after chromatography was removed *in vacuo*. After trituration with *n*-pentane, the product **4a** was obtained as a white solid in 98% yield and 88% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 235 nm, r_{minor} 41.6 min, r_{major} 48.7 min). $[\alpha]_{\text{D}}^{25} -26^{\circ}$ ($c = 1.0$, CH_3CN). mp 129-132°C. FTIR (cm^{-1}): 3395 (w), 3289 (w), 3055 (m), 2988 (m), 2307 (w), 1751 (s), 1697 (s), 1466 (s), 1265 (s), 910 (m), 731 (s). ^1H NMR (600 MHz, CDCl_3 , 2.35:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 8.50 (1H, br s, NH*), 8.43 (1H, br s, NH), 7.78 (4H, t $J = 7.2$ Hz, ArH*, ArH), 7.62-7.59 (2H, m, ArH*, ArH), 7.50 (4H, d, $J = 7.2$ Hz, ArH*, ArH), 7.38-7.24 (10H, m, ArH*, ArH) 4.83 (1H, d, $J = 6.0$ Hz, CH*(CN)(CO₂CH₃)), 4.07-4.02 (2H, m, CH*Ar, CHAr), 3.91 (1H, d, $J = 5.4$ Hz, CH(CN)(CO₂CH₃)), 3.71-3.59 (4H, m, COCH₂*, COCH₂), 3.71 (3H, s, CO₂CH₃), 3.64 (3H, s, CO₂CH₃*). ^{13}C NMR (100 MHz, CDCl_3): δ 174.2, 173.8, 166.0, 165.7, 138.9, 138.1, 133.7, 133.7, 132.6, 132.5, 129.3, 129.2, 129.2, 129.1, 128.6, 128.4, 128.3, 128.1, 128.0, 115.7, 115.5, 53.7, 53.6, 43.7, 43.6, 31.3, 31.1, 40.7, 40.3. MS (CI) m/z : 351.0 (100%) $[\text{M}+\text{H}]^+$, 348.9 (80%) $[\text{M}-\text{H}]^-$.

Analytical data, products **3b-3g**:

(R)-N-(4,4-Dicyano-3-(4-fluorophenyl)-butyryl)benzamide (**3b**): 5 mol% (*S,S*)-**1** (28.8 mg), 1.2 equiv. malononitrile (40 mg) and 1.2 equiv. *t*-butanol (57 μL) were used. After a reaction time of 36 hours, the product was obtained as a white solid in 88% yield (147 mg) and 93% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 235 nm, r_{minor} 27.4 min, r_{major} 37.4 min). $[\alpha]_{\text{D}}^{25}$

–19° (c = 1.0, CH₃CN). mp 211-214°C (decomp.) FTIR (cm⁻¹): 3393 (w), 3055 (m), 2988 (m), 2307 (w), 1700 (m), 1514 (m), 1265 (s), 737 (s). ¹H NMR (600 MHz, CDCl₃): δ 8.74 (1H, br s, NH), 7.81 (2H, d, J = 7.8 Hz, ArH), 7.63 (1H, t, J = 7.2 Hz, ArH), 7.51 (2H, t, J = 7.8 Hz, ArH), 7.42-7.40 (2H, m, ArH), 7.10 (2H, t, J = 8.4 Hz, ArH), 4.54 (1H, d, J = 5.4 Hz, CH(CN)₂), 3.88-3.85 (1H, m, CHAr), 3.73-3.66 (2H, m, COCH₂). ¹³C NMR (100 MHz, CDCl₃): δ 173.0, 165.8, 163.3 (d, J_{C-F} = 248 Hz), 134.1, 132.1, 130.2, 130.1, 129.5, 127.9, 116.6 (d, J_{C-F} = 22 Hz), 111.9, 111.5, 41.0, 39.9, 29.2. MS (CI) m/z: 269.9 (100%) [M-C₃HN₂]⁺, 333.9 (100%) [M-H]⁻.

(R)-N-(4,4-Dicyano-3-(4-chlorophenyl)-butyryl)benzamide (3c): 5 mol% (*S,S*)-1 (28.8 mg), 1.2 equiv. malononitrile (40 mg) and 2.5 equiv. *t*-butanol (119 μ L) were used. After a reaction time of 38 hours, the product was obtained as a white solid in 99% yield (176 mg) and 92% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 235 nm, rt_{minor} 30.5 min, rt_{major} 46.0 min). $[\alpha]_D^{25}$ –21° (c = 1.0, CH₃CN). mp 115-119°C. FTIR (cm⁻¹): 3055 (m), 2988 (w), 2307 (w), 1699 (m), 1265 (s), 735 (s). ¹H NMR (500 MHz, CDCl₃): δ 8.80 (1H, br s, NH), 7.84 (2H, d, J = 7.0 Hz, ArH), 7.66 (1H, t, J = 7.5 Hz, ArH), 7.54 (2H, t, J = 8.0 Hz, ArH), 7.42-7.39 (4H, m, ArH), 4.56 (1H, d, J = 5.0 Hz, CH(CN)₂), 3.90-3.86 (1H, m, CHAr), 3.74-3.68 (2H, m, COCH₂). ¹³C NMR (100 MHz, CDCl₃): δ 172.9, 165.8, 125.6, 134.7, 134.1, 132.0, 129.8, 129.7, 129.5, 127.9, 111.8, 111.5, 41.2, 39.8, 29.0. MS (CI) m/z: 351.0 (20%), [M-H]⁻, 349.6 (100%), [M-H]⁻.

(S)-N-(4,4-Dicyano-3-methyl-butyryl)benzamide (3d): 2.5 mol% (*R,R*)-1 (14.4 mg), 1.2 equiv. malononitrile (40 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 24 hours, the product was obtained as a white solid in 89% yield (113 mg) and 96% enantiomeric excess, as determined by chiral HPLC (Chiralpak OD, 5% isopropanol/hexanes, 1.0 mL/min, 235 nm, rt_{minor} 119 min, rt_{major} 133 min). $[\alpha]_D^{25}$ +5° (c = 1.0, CH₃CN). mp 120-123°C. FTIR (cm⁻¹): 3055 (m), 2988 (w), 2307 (w), 1699 (s), 1464 (m), 1265 (s), 739 (s). ¹H NMR (600 MHz, CDCl₃): δ 8.61 (1H, br s, NH), 7.81 (2H, d, J = 7.2 Hz, ArH), 7.63 (1H, t, J = 7.2 Hz, ArH), 7.51 (2H, t, J = 7.2 Hz, ArH), 4.40 (1H, d, J = 4.8 Hz, CH(CN)₂), 3.30 (1H, dd, J = 4.8, 18.6 Hz, COCH₂), 3.21 (1H, dd, J = 8.4, 18.6 Hz, COCH₂), 2.80-2.76 (1H, m, CHCH₃) 1.39 (3H, d, J = 6.6 Hz, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 174.0, 166.0, 134.0, 132.2, 129.4, 128.0, 112.6, 111.6, 40.8, 31.9, 28.1, 17.4. MS (CI) m/z: 255.9 (10%) [M+H]⁺, 253.9 (100%) [M-H]⁻.

(R)-N-(3-Dicyanomethyl-hexanoyl)benzamide (3e): 2.5 mol% (*S,S*)-1 (14.4 mg), 1.2 equiv. malononitrile (40 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 26 hours, the product was obtained as a white solid in 95% yield (134 mg) and 97% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 4% ethanol/hexanes, 1.0 mL/min, 235 nm, rt_{minor} 96.0 min, rt_{major} 100.1 min). $[\alpha]_D^{25}$ –19° (c = 1.0, CH₃CN). mp 110-111°C. FTIR (cm⁻¹): 3387 (w), 3277 (w), 3055 (m), 2967 (m), 2307 (w), 1696 (s), 1466 (m), 1265 (s), 737 (s). ¹H NMR (600 MHz, CDCl₃): δ 8.55 (1H, br s, NH), 7.81 (2H, d, J = 7.2 Hz, ArH), 7.63 (1H, t, J = 7.2 Hz, ArH), 7.51 (2H, d, J = 7.2 Hz, ArH), 4.44 (1H, d, J = 4.8 Hz, CH(CN)₂), 3.42 (1H, dd, J = 4.2, 18.6 Hz, COCH₂), 3.14 (1H, dd, J = 9.6, 18.6 Hz, COCH₂), 2.64-2.60 (1H, m, CH(C₃H₇)),

1.79-1.74 (1H, m, CH₂CH₂CH₃), 1.68-1.62 (1H, m, CH₂CH₂CH₃), 1.57-1.53 (1H, m, CH₂CH₂CH₃), 1.44-1.39 (1H, m, CH₂CH₂CH₃), 0.99 (3H, t, J = 7.2 Hz, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 174.4, 166.0, 134.0, 132.2, 129.4, 128.0, 112.7, 111.9, 38.4, 36.2, 33.6, 27.2, 20.1, 14.0. MS (CI) m/z: 283.9 (100%) [M+H]⁺, 282.0 (100%) [M-H]⁻.

(S)-N-(3-Dicyanomethyl-4-methyl-pentanoyl)benzamide (3f): 5 mol% (S,S)-1 (28.8 mg), 1.2 equiv. malononitrile (40 mg) and 2.5 equiv. *t*-butanol (119 μ L) were used. After a reaction time of 26 hours, the product was obtained as a white solid in 91% yield (129 mg) and 96% enantiomeric excess, as determined by chiral HPLC (L-leucine (Pirkle), 3% ethanol/hexanes, 1.0 mL/min, 235 nm, rt_{minor} 84.2 min, rt_{major} 86.0 min). $[\alpha]_D^{25}$ -17° (c = 1.0, CH₃CN). mp 107-109°C. FTIR (cm⁻¹): 3393 (w), 3055 (m), 2986 (m), 2307 (w), 1699 (m), 1466 (m), 1265 (s), 733 (s). ¹H NMR (600 MHz, CDCl₃): δ 8.64 (1 μ , br s, NH), 7.83 (2H, d, J = 7.2 Hz, ArH), 7.63 (1H, t, J = 7.8 Hz, ArH), 7.51 (2H, t, J = 7.8 Hz), 4.37 (1H, d, J = 5.4 Hz, CH(CN)₂), 3.40 (1H, dd, J = 3.0, 19.2 Hz, COCH₂), 3.16 (1H, dd, J = 9.0, 19.2 Hz, COCH₂), 2.64-2.61 (1H, m, CH(C₃H₇)), 2.23-2.20 (1H, m, CH(CH₃)₂), 1.11 (3H, d, J = 7.2 Hz, CH(CH₃)₂), 1.08 (3H, d, J = 6.6 Hz, CH(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃): δ 174.1, 165.9, 134.0, 132.3, 129.4, 127.9, 112.6, 112.4, 41.0, 35.7, 30.2, 25.8, 21.3, 18.2. MS (CI) m/z: 284.0 (100%) [M+H]⁺, 282.0 (100%) [M-H]⁻.

(R)-N-(3-Dicyanomethyl-4,4-dimethyl-pentanoyl)benzamide (3g): 5 mol% (S,S)-1 (28.8 mg), 1.2 equiv. malononitrile (40 mg) and 2.5 equiv. *t*-butanol (119 μ L) were used. After a reaction time of 48 hours, the product was obtained as a colorless oil in 88% yield (130 mg) and 97% enantiomeric excess, as determined by chiral HPLC (L-leucine (Pirkle), 7% ethanol/hexanes, 1.0 mL/min, 235 nm, rt_{minor} 45.7 min, rt_{major} 51.9 min). $[\alpha]_D^{25}$ -7° (c = 1.0, CH₃CN). mp 130-133°C. FTIR (cm⁻¹): 3400 (m), 3057 (m), 2971 (m), 2307 (w), 1690 (s), 1472 (s), 1265 (s), 731 (s). ¹H NMR (600 MHz, CDCl₃): δ 9.27 (1 μ , br s, NH), 7.88 (2H, d, J = 8.4 Hz, ArH), 7.60 (1H, t, J = 7.2 Hz, ArH), 7.50 (2H, t, J = 7.8 Hz, ArH), 4.09 (1H, br s, CH(CN)₂), 3.51 (1H, dd, J = 3.6, 18.6 Hz, COCH₂), 3.19 (1H, dd, J = 9.0, 18.6 Hz, COCH₂), 2.71-2.69 (1H, m, CH(C₄H₉)), 1.09 (9H, s, CHC(CH₃)₃). ¹³C NMR (100 MHz, CDCl₃): δ 174.7, 166.3, 133.8, 132.4, 129.3, 128.1, 113.5, 113.1, 45.3, 37.0, 34.6, 27.8, 23.7. MS (CI) m/z: 354.1 (100%) [M+H]⁺, 352.1 (100%) [M-H]⁻.

Analytical data, products **4b-4f**:

(R)-5-Benzoylamino-2-cyano-3-(4-fluorophenyl)-5-oxo-pentanoic acid methyl ester (4b): The reaction was performed on a 25 mmol scale, using 5 mol% (S,S)-1 (1.44 g), 2.5 equiv. methyl cyanoacetate (5.52 mL) and 1.2 equiv. *t*-butanol (2.85 mL). After a reaction time of 54 hours, the product was obtained as a white solid in 94% yield (8.34 g) and 89% enantiomeric excess as determined by chiral HPLC ((R,R)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 235 nm, rt_{minor} 40.7 min, rt_{major} 48.3 min). $[\alpha]_D^{25}$ -26° (c = 1.0, CH₃CN). mp 125-127°C. FTIR (cm⁻¹): 3393 (w), 3055 (m), 2988 (w), 2307 (w), 1751 (m), 1513 (m), 1265 (s), 735 (s). ¹H NMR (600 MHz, CDCl₃, 1.76:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 8.51 (1H, br s, NH*), 8.44 (1H, br s, NH), 7.79 (4H, t, J = 7.2 Hz, ArH*, ArH), 7.62-7.60 (2H, m, ArH* ArH), 7.51-7.48 (4H, m, ArH*, ArH), 7.37-7.24 (4H, m, ArH*, ArH), 7.02 (4H, t, J =

7.8 Hz, ArH*, ArH), 4.30 (1H, d, J = 5.4 Hz, CH*(CN)(CO₂CH₃)), 4.06-4.02 (2H, m, CH*Ar, CHAr), 3.89 (1H, d, J = 6.0 Hz, CH(CN)(CO₂CH₃)), 3.72-3.57 (4H, m, COCH*₂, COCH₂), 3.72 (3H, s, CO₂CH₃), 3.66 (3H, s, CO₂CH*₃). ¹³C NMR (100 MHz, CDCl₃): δ 173.9, 173.5, 166.0, 165.5, 162.8 (d, J_{C-F} = 246 Hz), 162.5 (d, J_{C-F} = 246 Hz), 134.6, 133.8, 133.8, 132.5, 132.4, 130.1, 130.0, 129.8, 129.7, 129.3, 129.3, 128.0, 128.0, 116.1 (d, J_{C-F} = 22 Hz), 116.1 (d, J_{C-F} = 21 Hz) 115.6, 115.3, 53.8, 53.6, 43.8, 43.6, 41.1, 40.6, 40.6, 39.9. MS (CI) m/z: 368.9 (100%) [M+H]⁺, 366.9 (100%) [M-H]⁻.

(R)-5-Benzoylamino-2-cyano-3-(4-chlorophenyl)-5-oxo-pentanoic acid methyl ester (4c): 5 mol% (S,S)-**1** (28.8 mg), 2.5 equiv. methyl cyanoacetate (110 μ L) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 48 hours, the product was obtained as a white solid in 99% yield (192 mg) and 89% enantiomeric excess as determined by chiral HPLC ((R,R)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 235 nm, rt_{minor} 43.3 min, rt_{major} 52.7 min). δ _D²⁵ -26° (c = 1.0, CH₃CN). mp 58-61°C. FTIR (cm⁻¹): 3393 (w), 3055 (m), 2988 (m), 2307 (w), 1751 (w), 1466 (m), 1263 (s), 750 (s). ¹H NMR (500 MHz, CDCl₃, 1.59:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 9.24 (1H, br s, NH*), 9.14 (1H, br s, NH), 7.86 (4H, t, J = 7.5 Hz, ArH*, ArH), 7.64-7.60 (2H, m, ArH* ArH), 7.53-7.49 (4H, m, ArH*, ArH), 7.29-7.25 (8H, m, ArH*, ArH), 4.28 (1H, d, J = 6.0 Hz, CH*(CN)(CO₂CH₃)), 4.05-4.02 (2H, m, CH*Ar, CHAr), 3.90 (1H, d, J = 5.5 Hz, CH(CN)(CO₂CH₃)), 3.73-3.63 (4H, m, COCH*₂, COCH₂), 3.71 (3H, s, CO₂CH₃), 3.66 (3H, s, CO₂CH*₃). ¹³C NMR (100 MHz, CDCl₃): δ 173.9, 173.6, 166.0, 165.5, 137.3, 136.6, 134.5, 134.3, 133.8, 133.8, 132.4, 132.4, 129.7, 129.4, 129.4, 129.3, 129.3, 128.1, 128.1, 115.5, 115.3, 53.9, 53.7, 43.6, 43.4, 40.9, 40.7, 40.2, 40.0. MS (CI) m/z: 384.3 (20%) [M+H]⁺, 382.6 (100%) [M-H]⁻, 384.1 (20%) [M+H]⁻.

(R)-5-Benzoylamino-2-cyano-3-methyl-5-oxo-pentanoic acid methyl ester (4d): 5 mol% (S,S)-**1** (28.8 mg), 2.5 equiv. methyl cyanoacetate (110 μ L) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 48 hours, the product was obtained as a colorless oil which gradually solidified in 96% yield (138 mg) and 86% enantiomeric excess as determined by hydrogenation to the corresponding β -lactam (1.2:1 mixture of diastereomers, Raney Ni, 650 PSI H₂; see preparation of **12** for procedure); analysis by chiral GC (β -TA, 141°C isotherm, , rt_{minor enantiomer, major diastereomer} 26.7 min, rt_{major enantiomer, major diastereomer} 27.6 min, rt_{minor enantiomer, minor diastereomer} 31.8 min, rt_{major enantiomer, minor diastereomer} 40.1 min)). δ _D²⁵ +1° (c = 1.0, CH₃CN). mp 114-117°C. FTIR (cm⁻¹): 3293 (w), 3057 (m), 2959 (m), 2307 (w), 1750 (s), 1468 (s), 1265 (s), 733 (s). ¹H NMR (600 MHz, CDCl₃, 3.65:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 9.23 (1H, br s, NH*), 9.19 (1H, br s, NH), 7.87-7.86 (4H, m, ArH*, ArH), 7.60-7.57 (2H, m, ArH*, ArH), 7.49-7.47 (4H, m, ArH, ArH*), 4.04 (1H, d, J = 4.2 Hz, CH*(CN)(CO₂CH₃)), 3.80 (3H, s, CO₂CH*₃), 3.78 (3H, s, CO₂CH₃), 3.76 (1H, d, J = 4.8 Hz, CH(CN)(CO₂CH₃)), 3.28 (1H, dd, J = 6.6, 18.0 Hz, COCH₂), 3.17-3.15 (2H, m, COCH*₂), 3.09 (1H, dd J = 7.2, 18.0 Hz, COCH₂) 1.21 (3H, d, J = 6.6 Hz, CHCH₃), 1.16 (3H, d, J = 7.2 Hz, CHCH*₃). ¹³C NMR (100 MHz, CDCl₃): δ 174.7, 174.5, 133.7, 133.7, 132.6, 132.5, 129.2, 129.2, 128.1, 115.9, 115.3, 53.7, 53.7, 42.8, 42.8, 41.9, 41.2, 31.1, 30.4, 18.4, 17.1. MS (CI) m/z: 298.0 (100%) [M+H]⁺, 287.0 (40%) [M-H]⁻.

(R)-3-(2-Benzoylamino-2-oxo-ethyl)-2-cyanohexanoic acid methyl ester (4e): 5 mol% (*S,S*)-**1** (28.8 mg), 2.5 equiv. methyl cyanoacetate (110 μ L) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 40 hours, the product was obtained as a colorless oil which gradually solidified in 93% yield (147 mg) and 90% enantiomeric excess as determined by chiral HPLC (Chiralpak OD, 33% isopropanol/hexanes, 1.5 mL/min, 235 nm, $r_{t\text{minor}}$ 6.0 min, $r_{t\text{major}}$ 11.2 min). $[\alpha]_{\text{D}}^{25} -10^{\circ}$ ($c = 1.0$, CH_3CN). FTIR (cm^{-1}): 3295 (w), 3057 (m), 2961 (m), 2307 (w), 2251 (w), 1795 (s), 1688 (s), 1468 (s), 1240 (s), 708 (s). ^1H NMR (600 MHz, CDCl_3 , 1.24:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 8.95 (1H, br s, NH^*), 8.89 (1H, br s, NH), 7.86-7.84 (4H, m, ArH^* , ArH), 7.61-7.58 (2H, m, ArH^* , ArH), 7.51-7.48 (4H, m, ArH , ArH^*), 4.11 (1H, d, $J = 4.2$ Hz, $\text{CH}^*(\text{CN})(\text{CO}_2\text{CH}_3)$), 3.84 (1H, d, $J = 4.8$ Hz, $\text{CH}(\text{CN})(\text{CO}_2\text{CH}_3)$), 3.81 (3H, s, CO_2CH_3), 3.78 (3H, s, CO_2CH_3), 3.34 (1H, dd, $J = 3.6, 18.6$ Hz, COCH_2^*), 3.24 (1H, dd, $J = 7.2, 18.0$ Hz, COCH_2), 3.17 (1H, dd, $J = 6.0, 18.0$ Hz, COCH_2), 3.06 (1H, dd, $J = 9.6, 18.6$ Hz, COCH_2^*) 2.79-2.75 (2H, m, $\text{CH}^*(\text{C}_3\text{H}_7)$, $\text{CH}(\text{C}_3\text{H}_7)$), 1.64-1.50 (2H, m, $\text{CH}_2^*\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.48-1.42 (2H, m, $\text{CH}_2^*\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.41-1.37 (2H, m, $\text{CH}_2\text{CH}_2^*\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.33-1.30 (2H, m, $\text{CH}_2\text{CH}_2^*\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.94-0.91 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 174.8, 174.4, 166.5, 166.5, 165.8, 165.7, 133.7, 133.7, 132.6, 132.5, 129.3, 129.3, 128.0, 115.7, 115.6, 53.7, 42.0, 41.3, 39.5, 39.2, 35.4, 34.8, 34.7, 33.8, 20.3, 20.2, 14.1, 14.0. MS (CI) m/z : 318.2 (70%) $[\text{M}+\text{H}]^+$, 315.0 (40%) $[\text{M}-\text{H}]^-$.

(S)-3-(2-Benzoylamino-2-oxo-ethyl)-2-cyano-4-methyl-pentanoic acid methyl ester (4f): 5 mol% (*S,S*)-**1** (28.8 mg), 5 equiv. methyl cyanoacetate (221 μ L) and 2.5 equiv. *t*-butanol (119 μ L) were used. After a 6 day reaction time, the product was obtained as a colorless oil in 89% yield (140 mg) and 95% enantiomeric excess as determined by chiral HPLC (Chiralpak OD, 25% isopropanol/hexanes, 1.5 mL/min, 235 nm, $r_{t\text{minor}}$ 8.4 min, $r_{t\text{major}}$ 22.5 min). $[\alpha]_{\text{D}}^{25} -11^{\circ}$ ($c = 1.0$, CH_3CN). FTIR (cm^{-1}): 3300 (m), 2965 (m), 2251 (w), 1748 (s), 1472 (s), 1242 (s), 737 (s). ^1H NMR (500 MHz, CDCl_3 , 1.2:1 mixture of diastereomers, with signals corresponding to the major indicated by): δ 9.46 (1H, br s, NH), 9.35 (1H, br s, NH^*), 7.92-7.90 (4H, m, ArH^* , ArH), 7.60-7.58 (2H, m, ArH^* , ArH), 7.52-7.50 (4H, m, ArH^* , ArH), 3.99 (1H, d, $J = 6.0$ Hz, $\text{CH}(\text{CN})(\text{CO}_2\text{CH}_3)$), 3.77 (3H, s, CO_2CH_3), 3.74 (3H, s, CO_2CH_3), 3.77-3.74 (1H, m, $\text{CH}^*(\text{CN})(\text{CO}_2\text{CH}_3)$), 3.32 (1H, dd, $J = 3.0, 18.5$ Hz, COCH_2^*), 3.27-3.25 (2H, m, COCH_2), 3.09 (1H, dd, $J = 10.0, 18.5$ Hz, COCH_2^*), 2.75-2.73 (2H, m, $\text{CH}^*\text{C}_3\text{H}_7$, CHC_3H_7), 1.97-1.91 (2H, m, $\text{CH}^*(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)_2$), 1.02 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.98 (3H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, CDCl_3): δ 175.7, 175.2, 167.1, 166.9, 166.2, 166.1, 133.7, 133.6, 132.7, 132.6, 129.2, 128.2, 116.1, 53.7, 53.7, 41.0, 40.7, 39.9, 37.7, 36.4, 31.3, 30.1, 21.4, 20.1, 19.8, 18.3. MS (CI) m/z : 316.9 (100%) $[\text{M}+\text{H}]^+$, 314.9 (100%) $[\text{M}-\text{H}]^-$.

(E) General procedure for preparation of methyl arylcyanoacetates.⁴

Methyl phenylcyanoacetate:

⁴ The method of Wallingford *et al* was used, with slight modifications: Wallingford, V.H; Jones, D.M; Homeyer, A.H. *J. Am. Chem. Soc.* **1942**, 64, 576-578.

To a solution of benzyl cyanide (3.80 mL, 33 mmol) and dimethyl carbonate (13.9 mL, 264 mmol, 8.0 equiv.) in toluene at 0°C was added sodium methoxide (15.1 mL, 25 wt% in methanol, 66 mmol, 2.0 equiv.) slowly by syringe. The resulting solution was stirred at 0°C for 10 minutes, then heated to 75–80°C and stirred for 12 hours. After quenching with 1M aqueous hydrochloric acid (75 mL), the mixture was extracted twice with diethyl ether (total volume 200 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated. The residue was purified by chromatography on silica (10% → 25% ethyl acetate in hexanes), to yield the product, methyl phenylcyanoacetate, as a colorless oil (4.19g, 73% yield). Characterization data were in agreement with literature values.⁵

Methyl (3-trifluoromethylphenyl)cyanoacetate: Obtained in 83% yield as a colorless oil. FTIR (cm⁻¹): 3016 (m), 2962 (s), 2255 (m), 1754 (s), 1618 (m), 1204 (s), 1020 (s), 914 (s), 768 (s), 701 (s). ¹H NMR (500 MHz, CDCl₃): δ 7.72 (1H, s, ArH), 7.70–7.68 (2H, m, ArH), 7.58 (2H, t, J = 7.5 Hz, ArH), 4.84 (1H, s, CH(CN)CO₂CH₃), 3.83 (3H, s, CO₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 165.0, 132.0 (q, J_{C-F} = 33 Hz), 131.6, 131.0, 130.3, 126.5 (q, J_{C-F} = 3.3 Hz), 125.2 (q, J_{C-F} = 3.3 Hz), 123.8 (q, J_{C-F} = 271 Hz), 54.5, 43.4. GC/MS (ES) m/z: 224 (10%) [M–F]⁺, 199 (50%) [M–CH₃CO]⁺, 184 (100%) [M–CO₂CH₃]⁺.

Methyl (4-methoxyphenyl)cyanoacetate: Obtained as a pale yellow oil in 42% yield. Characterization data were in agreement with literature values⁶.

3-(Cyano-methoxycarbonyl-methyl)-indole-1-carboxylic acid methyl ester: Obtained as a pale orange solid in 18% yield. Characterization data were in agreement with literature values⁷.

Cyano-thiophen-2-yl-acetic acid methyl ester: Obtained as an orange oil in 29% yield. FTIR: 3112 (w), 2958 (m), 2217 (w) (1755 (s), 1436 (m), 1244 (s), 1045 (m), 710 (m). ¹H NMR (500 MHz, CDCl₃): δ 7.37 (1H, dd, J = 5.5, 1.0 Hz, ArH), 7.23 (1H, d, J = 3.5 Hz, ArH), 7.03 (1H, dd, J = 5.5, 3.5 Hz, ArH), 5.00 (1H, s, CH(CN)CO₂CH₃), 3.83 (3H, s, CO₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 164.8, 130.5, 128.5, 127.7, 127.5, 115.0, 54.4, 38.9. GC/MS (ES) m/z: 181 (20%) [M]⁺, 122 (100%) [M–CO₂CH₃]⁺.

(F) General procedure for the conjugate addition of methyl arylcyanoacetates to **2**.

⁵ de Jongh, H.A.P; de Jonge, C.R.H.I; Mijs, W.J. *J. Org. Chem.* **1971**, 36 (21),3160-3167.

⁶ Chatterjee, S; Ghosal, P.K. *Tetrahedron Lett.* **1977**, 17, 1451-1452.

⁷ Morales-Rios, M.S; Joseph-Nathan, P. *Magn. Reson. Chem.* **1987**, 25, 911-918.

(2*S*,3*S*)- 3-(2-Benzoylamino-2-oxo-ethyl)-2-cyano-2-phenyl-hexanoic acid methyl ester (5a):

An oven-dried round-bottomed flask was capped with a septum and charged with **2e** (108 mg, 0.50 mmol), catalyst (*R,R*)-**1** (14.4 mg, 0.025 mmol, 2.5 mol%), and cyclohexane (2.5 mL). To the resulting suspension was added methyl phenylcyanoacetate (105 mg, 0.60 mmol, 1.2 equiv.), then *t*-butanol (57 μ L, 0.60 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 19 hours, then diluted with ethyl acetate and purified by flash column chromatography on silica (elution gradient 20% $\rightarrow$ 33% ethyl acetate in hexanes). The product was obtained as a white solid in 98% yield (192 mg): 14:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{minor}} = 3.79$ ppm, $\delta_{\text{major}} = 3.69$ ppm; $\delta_{\text{major}} = 3.17\text{--}3.12$ ppm, $\delta_{\text{minor}} = 3.02\text{--}2.96$ ppm); 97% enantiomeric excess, as determined by chiral HPLC (Chiralpak AD, 10% ethanol/hexanes, 1.2 mL/min, 220 nm, $r_{\text{minor diastereomers}} = 14.4, 16.6$ min, $r_{\text{minor enantiomer}} = 20.6$ min, $r_{\text{major enantiomer}} = 24.6$ min). $[\alpha]_{\text{D}}^{25} +58^\circ$ ($c = 0.99$, CHCl_3). mp 100–103°C. FTIR (cm^{-1}): 3055 (m), 2988 (m), 2305 (w), 1745 (w), 1699 (w), 1435 (m), 1269 (s), 896 (m), 721 (s). ^1H NMR (600 MHz, CDCl_3): δ 9.09 (1H, br s, NH), 7.92 (2H, d, $J = 7.2$ Hz, ArH), 7.61–7.57 (3H, m, ArH), 7.51 (2H, t, $J = 7.8$ Hz, ArH), 7.40–7.36 (3H, m, ArH), 3.69 (3H, s, CO_2CH_3), 3.36–3.31 (2H, m, $\text{CH}(\text{C}_3\text{H}_7)$, COCH_2), 3.17–3.12 (2H, m, COCH_2), 1.31–1.24 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.17–1.07 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.70 (3H, t, $J = 7.8$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 174.7, 168.4, 165.9, 133.7, 133.5, 133.8, 129.4, 129.3, 129.2, 128.2, 126.8, 117.4, 59.7, 54.2, 41.0, 40.9, 33.7, 20.3, 14.3. MS (CI) m/z : 272.0 (100%) $[\text{M}-\text{PhCONH}]^+$, 392.9 (20%) $[\text{M}+\text{H}]^+$, 174.1 (100%), $[\text{M}-(\text{C}_{14}\text{H}_{16}\text{NO}_2)]^-$, 391.0 (10%) $[\text{M}-\text{H}]^-$.

Analytical data, products **5b–5g**:

(2*S*,3*S*)-3-(2-Benzoylamino-2-oxo-ethyl)-2-cyano-2-(3-trifluoromethyl-phenyl)-hexanoic acid methyl ester (5b): 2.5 mol% (*R,R*)-**1** (14.4 mg), 1.2 equiv. methyl (3-trifluoromethylphenyl)cyanoacetate (146 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 15 hours, the product was obtained as a white solid in 96% yield (220 mg): 35:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 9.57$ ppm, $\delta_{\text{minor}} = 9.45$ ppm; $\delta_{\text{major}} = 3.26\text{--}3.21$ ppm, $\delta_{\text{minor}} = 2.86\text{--}2.92$ ppm); 98% enantiomeric excess, as determined by chiral HPLC (Chiralpak AD, 10% ethanol/hexanes, 1.2 ml/min, 220 nm, $r_{\text{minor}} = 10.9$ min, $r_{\text{major}} = 15.6$ min). $[\alpha]_{\text{D}}^{25} +46^\circ$ ($c = 1.0$, CHCl_3). mp 146–149°C. FTIR (cm^{-1}): 3283 (m), 3059 (m), 2962 (m), 2307 (w), 1748 (s), 1688 (s), 1468 (s), 1329 (s), 1244 (s), 1134 (s), 704 (s). ^1H NMR (500 MHz, CDCl_3): δ 9.57 (1H, br s, NH), 8.00 (2H, d, $J = 8.5$ Hz, ArH), 7.88 (1H, s, ArH), 7.84 (1H, d, $J = 8.0$ Hz, ArH), 7.68–7.62 (2H, m, ArH), 7.58–7.53 (3H, m, ArH), 3.72 (3H, s, CO_2CH_3), 3.45–3.41 (2H, m, $\text{CH}(\text{C}_3\text{H}_7)$, COCH_2), 3.26–3.21 (2H, m, COCH_2), 1.33–1.30 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.13–1.08 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.72 (3H, t, $J = 6.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$).

^{13}C NMR (100 MHz, CDCl_3): δ 174.8, 167.8, 166.1, 134.9, 133.7, 132.7, 131.9 (q, $J_{\text{C-F}} = 32.6$ Hz), 130.5, 130.0, 129.2, 128.2, 126.3 (q, $J_{\text{C-F}} = 3.8$ Hz), 123.8 (q, $J_{\text{C-F}} = 271$ Hz), 123.8 (q, $J_{\text{C-F}} = 3.8$ Hz), 116.8, 59.6, 54.4, 41.0, 40.7, 33.6, 20.2, 14.1. MS (CI) m/z : 460.9 (100%), $[\text{M}+\text{H}]^+$, 458.7 (100%), $[\text{M}-\text{H}]^-$.

5b was recrystallized from hot ethyl acetate/hexanes to provide crystals of suitable quality for X-ray crystallography.

(2S,3S)-3-(2-Benzoylamino-2-oxo-ethyl)-2-cyano-2-(4-methoxy-phenyl)-hexanoic acid methyl ester (5c): 2.5 mol% (*R,R*)-**1** (14.4 mg), 1.2 equiv. methyl (4-methoxyphenyl)cyanoacetate (123 mg) and 1.2 equiv. *t*-butanol (57 μL) were used. After a reaction time of 38 hours, the product was obtained as a white solid in 94% yield (198 mg): 6:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 7.96$ ppm, $\delta_{\text{minor}} = 7.80$ ppm; $\delta_{\text{major}} = 6.91$ ppm, $\delta_{\text{minor}} = 6.79$ ppm); 94% enantiomeric excess, as determined by chiral HPLC (Chiralpak OD, 15% isopropanol/hexanes, 1.2 mL/min, 235 nm, $\text{rt}_{\text{minor diastereomers}} = 10.9$ min, $\text{rt}_{\text{minor enantiomer}} = 12.5$ min, $\text{rt}_{\text{major enantiomer}} = 18.6$ min). $[\alpha]_{\text{D}}^{25} +52^\circ$ ($c = 1.03$, CHCl_3). mp 65–68°C. FTIR (cm^{-1}): 3055 (m), 2963 (w), 2307 (w), 1746 (m), 1512 (m), 1265 (s), 748 (s). ^1H NMR (500 MHz, CDCl_3): δ 9.23 (1H, br s, NH), 7.96 (2H, d, $J = 7.5$ Hz, ArH), 7.63 (1H, t, $J = 8.0$ Hz, ArH), 7.55–7.50 (4H, m, ArH), 6.90 (2H, d, $J = 8.5$ Hz, ArH), 3.82 (3H, s, ArOCH_3), 3.69 (3H, s, CO_2CH_3), 3.36–3.32 (2H, m, $\text{CH}(\text{C}_3\text{H}_7)$, COCH_2), 3.17–3.13 (1H, m, COCH_2), 1.35–1.20 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.14–1.11 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.74 (3H, t, $J = 7.0$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 174.5, 168.6, 165.8, 160.2, 133.5, 132.9, 129.2, 129.1, 128.1, 125.6, 117.6, 114.7, 59.0, 55.6, 54.1, 41.0, 40.8, 33.7, 20.3, 14.3. MS (CI) m/z : 422.7 (100%) $[\text{M}+\text{H}]^+$, 458.7 (100%) $[\text{M}+\text{Cl}]^-$.

(2R,3R)-3-[2-(2-Benzoylamino-2-oxo-ethyl)-1-cyano-1-methoxycarbonyl-pentyl]-indole-1-carboxylic acid methyl ester (5d): 5 mol% (*S,S*)-**1** (28.8 mg), 1.2 equiv. 3-(cyano-methoxycarbonyl-methyl)-indole-1-carboxylic acid methyl ester (163 mg) and 1.2 equiv. *t*-butanol (57 μL) were used. After a reaction time of 51 hours, the product was obtained as a white solid in 79% yield (192 mg): 14:1 d.r., as determined by ^1H NMR integration ($\delta_{\text{major}} = 0.74$ ppm, $\delta_{\text{minor}} = 1.00$ ppm); 97% enantiomeric excess, as determined by chiral HPLC (Chiralpak AS, 14% ethanol/hexanes, 1.4 mL/min, 220 nm, $\text{rt}_{\text{minor enantiomer}} = 10.8$ min, $\text{rt}_{\text{major enantiomer}} = 13.6$ min). $[\alpha]_{\text{D}}^{25} -49^\circ$ ($c = 1.08$, CHCl_3). mp 204–206°C. FTIR (cm^{-1}): 3057 (m), 2961 (m), 2305 (w), 1746 (s), 1456 (s), 1373 (s), 1238 (s), 768 (m), 692 (m). ^1H NMR (500 MHz, CDCl_3): δ 8.86 (1H, br s, NH), 8.27 (1H, d, $J = 8.0$ Hz, ArH), 7.92 (2H, d, $J = 8.0$ Hz, ArH), 7.89 (1H, d, $J = 8.0$ Hz, ArH), 7.63 (1H, t, $J = 8.0$ Hz, ArH), 7.53 (2H, t, $J = 8.5$ Hz, ArH), 7.39 (1H, t, $J = 8.5$ Hz, ArH), 7.28 (1H, t, $J = 8.0$ Hz, ArH), 4.05 (3H, s, $\text{ArNCO}_2\text{CH}_3$), 3.74 (3H, s, CO_2CH_3), 3.73–3.69 (1H, m, $\text{CH}(\text{C}_3\text{H}_7)$), 3.36 (1H, dd, $J = 17.5, 6.0$ Hz, COCH_2), 3.31 (1H, dd, $J = 17.5, 5.5$ Hz, COCH_2), 1.41–1.35 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.20–1.16 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.74 (3H, t, $J = 7.0$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 174.2, 167.4, 165.7, 151.0, 136.5, 133.6, 132.8, 129.3, 128.0, 126.6, 125.8, 123.9, 121.2, 117.3, 115.7, 114.9, 54.3, 54.2, 40.3, 38.1, 34.0, 20.3, 14.2. MS (CI) m/z : 489.5 (100%) $[\text{M}+\text{H}]^+$, 487.7 (100%) $[\text{M}-\text{H}]^-$.

(2*S*,3*S*)-3-(2-Benzoylamino-2-oxo-ethyl)-2-cyano-2-thiophen-2-yl-hexanoic acid methyl ester (5e): 5 mol% (*R,R*)-**1** (28.8 mg), 1.3 equiv. cyano-thiophen-2-yl-acetic acid methyl ester (120 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 4 days, the product was obtained as a red oil which gradually solidified in 76% yield (151 mg): 14:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 7.01$ ppm, $\delta_{\text{minor}} = 6.95$ ppm; ($\delta_{\text{major}} = 3.07$ ppm, $\delta_{\text{minor}} = 3.20$ ppm); 97% enantiomeric excess, as determined by chiral HPLC (Chiralpak OD, 15% ethanol/hexanes, 1.2 mL/min, 220 nm, $\text{rt}_{\text{minor diastereomers}} = 8.8$ min, $\text{rt}_{\text{minor enantiomer}} = 9.8$ min, $\text{rt}_{\text{major enantiomer}} = 14.3$ min). $[\alpha]_{\text{D}}^{25} +43^\circ$ ($c = 1.01$, CHCl_3). mp 99-103°C. FTIR (cm^{-1}): 3277 (m), 2961 (m), 2874 (w), 2247 (w), 1748 (w), 1686 (s), 1468 (m), 1240 (s), 710 (s). ^1H NMR (500 MHz, CDCl_3): δ 8.61 (1H, br s, NH), 7.87 (2H, d, $J = 7.5$ Hz, ArH), 7.63 (1H, t, $J = 7.5$ Hz, ArH), 7.53 (2H, t, $J = 8.0$ Hz, ArH), 7.37 (1H, dd, $J = 5.5, 1.5$ Hz, ArH), 7.33 (1H, dd, $J = 4.0, 1.5$ Hz, ArH), 3.81 (3H, s, CO_2CH_3), 3.34 (1H, dd, $J = 17.5, 5.5$ Hz, COCH_2), 3.26-3.24 (1H, m, $\text{CH}(\text{C}_3\text{H}_7)$), 3.18 (1H, dd, $J = 17.5, 4.5$ Hz, COCH_2), 1.41-1.36 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.21-1.19 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.82 (3H, t, $J = 6.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 174.4, 167.9, 165.9, 136.8, 133.6, 132.7, 129.3, 128.1, 127.5, 127.0, 116.9, 56.7, 54.4, 42.9, 40.4, 33.8, 20.4, 14.2. MS (CI) m/z : 277.9 (100%) $[\text{M}-\text{PhCONH}]^+$, 398.7 (30%) $[\text{M}+\text{H}]^+$, 180.1 (100%) $[\text{M}-(\text{C}_{13}\text{H}_{16}\text{NO}_2)]^-$, 396.7 (10%) $[\text{M}-\text{H}]^-$.

(2*R*,3*R*)-5-Benzoylamino-2-cyano-3-methyl-5-oxo-2-phenyl-pentanoic acid methyl ester (5f): 2.5 mol% (*S,S*)-**1** (14.4 mg), 1.2 equiv. methyl phenylcyanoacetate (105 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 24 hours, the product was obtained as a white solid in 95% yield (173 mg): 6:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 3.17$ ppm, $\delta_{\text{minor}} = 2.68$ ppm; ($\delta_{\text{minor}} = 1.33$ ppm, $\delta_{\text{major}} = 0.91$ ppm); 86% enantiomeric excess, as determined by hydrogenation to the corresponding β -lactam (Raney Ni, 720 PSI H_2 ; see preparation of **12** for procedure); analysis by chiral HPLC (Chiralpak AD, 10% ethanol/hexanes, 1.2 mL/min, 220 nm, $\text{rt}_{\text{minor diastereomers}} = 21.2, 26.5$ min, $\text{rt}_{\text{minor enantiomer}} = 23.8$ min, $\text{rt}_{\text{major enantiomer}} = 38.9$ min). $[\alpha]_{\text{D}}^{25} -43^\circ$ ($c = 1.01$, CHCl_3). mp 127-135°C. FTIR (cm^{-1}): 3285 (w), 3055 (m), 2963 (m), 2307 (w), 1746 (s), 1699 (s), 1468 (s), 1240 (s), 731 (s). ^1H NMR (500 MHz, CDCl_3): δ 8.90 (1H, br s, NH), 7.90 (2H, d, $J = 7.0$ Hz, ArH), 7.62 (3H, d, $J = 7.5$ Hz, ArH), 7.52 (2H, t, $J = 7.8$ Hz, ArH), 7.40-7.36 (3H, m, ArH), 3.78 (3H, s, CO_2CH_3), 3.39-3.36 (1H, m, $\text{CH}(\text{CH}_3)$), 3.32 (1H, dd, $J = 17.0, 7.0$ Hz, COCH_2), 3.17 (1H, dd, $J = 17.0, 2.0$ Hz, COCH_2), 0.91 (3H, d, $J = 6.5$ Hz, CHCH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 173.7, 168.2, 165.6, 133.6, 133.5, 132.8, 129.5, 129.3, 129.3, 128.0, 126.7, 116.8, 59.6, 54.3, 42.2, 37.0, 15.7. MS (CI) m/z : 243.9 (100%) $[\text{M}-\text{PhCONH}]^+$, 364.8 (20%) $[\text{M}+\text{H}]^+$, 174.1 (100%) $[\text{M}-(\text{C}_{11}\text{H}_{12}\text{NO}_2)]^-$, 362.8 (10%) $[\text{M}-\text{H}]^-$.

(2*S*,3*S*)-3-(2-Benzoylamino-2-oxo-ethyl)-2-cyano-5-methyl-2-phenyl-hexanoic acid methyl ester (5g): 5 mol% (*R,R*)-**1** (28.8 mg), 1.2 equiv. methyl phenylcyanoacetate (105 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 24 hours, the product was obtained as a white solid in 96% yield (195 mg): 16:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{minor}} = 3.79$ ppm, $\delta_{\text{major}} = 3.74$ ppm; ($\delta_{\text{major}} = 3.25$ ppm (2H), $\delta_{\text{minor}} = 3.02$ ppm (1H)); 96% enantiomeric excess, as determined by

chiral HPLC (Chiralpak AD, 10% ethanol/hexanes, 1.2 mL/min, 235 nm, $r_{\text{minor diastereomers}}$ 10.6 min, $r_{\text{minor enantiomer}}$ 19.1 min, $r_{\text{major enantiomer}}$ 22.3 min). $[\alpha]_{\text{D}}^{25} +61^\circ$ ($c = 1.0$, CHCl_3). mp 145-148°C. FTIR (cm^{-1}): 3285 (m), 2958 (m), 2870 (m), 2247 (w), 1746 (s), 1682 (s), 1471 (m), 1241 (s), 696 (m). ^1H NMR (500 MHz, CDCl_3): δ 8.63 (1H, br s, NH), 7.88 (2H, dd, $J = 8.5, 1.0$ Hz, ArH), 7.63 (3H, d, $J = 7.5$ Hz, ArH), 7.53 (2H, t, $J = 7.5$ Hz, ArH), 7.44-7.39 (3H, m, ArH) 3.74 (3H, s, CO_2CH_3), 3.45-3.43 (1H, m, $\text{CH}(\text{C}_4\text{H}_9)$), 3.25 (2H, m, COCH_2), 1.56-1.46 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.39-1.34 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.95-0.87 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$) 0.79 (3H, d, $J = 7.0$ Hz, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.76 (3H, d, $J = 7.0$ Hz, $\text{CH}_2\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, CDCl_3): δ 174.6, 168.4, 165.9, 133.7, 133.5, 132.8, 129.3, 129.3, 129.2, 128.2, 126.9, 117.3, 56.0, 54.1, 41.1, 41.0, 39.4, 25.2, 24.1, 21.4. MS (CI) m/z : 406.9 (100%) $[\text{M}+\text{H}]^+$, 405.0 (100%), $[\text{M}-\text{H}]^-$.

(G) Benzylamino-cyanoacetic acid ethyl ester⁸:

Benzaldehyde (1.12 mL, 11 mmol, 1.10 equiv.) was added to a suspension of cyanoglycine p-toluenesulfonic acid salt⁹ (3.00g, 10 mmol) in dichloromethane (40 mL). The resulting yellow solution was heated to 50°C and stirred 7 hours, then cooled to 0°C. Sodium triacetoxyborohydride was prepared by the addition of acetic acid (3.25 mL) to sodium borohydride (718 mg, 19 mmol, 1.9 equiv.) in dichloromethane (40 mL) and stirring the heterogeneous mixture for 1.5 hours at 23°C, then cooling to 0°C. The imine solution was added by cannula, and the resulting mixture was stirred at 0°C for 1.5 hours. After quenching with water (50 mL) and stirring 30 minutes, the organic portion was separated. The aqueous phase was extracted once with dichloromethane (100 mL). The combined organic extracts were washed with water, then with saturated sodium chloride solution, dried (sodium sulfate) and concentrated. The residue was purified by chromatography on silica (10% ethyl acetate in hexanes), yielding the product as a yellow oil (1.03 g, 47%).

Product: FTIR (cm^{-1}): 3338 (m), 2984 (m), 2858 (m), 2234 (w), 1752 (s), 1454 (m), 1195 (m), 1022 (m), 700 (m). ^1H NMR (500 MHz, CDCl_3): δ 7.38-7.34 (4H, m, ArH), 7.32-7.31 (1H, m, ArH), 4.31 (2H, q, $J = 7.5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.27 (1H, s, $\text{BnNHCH}(\text{CN})\text{CO}_2\text{Et}$), 4.06 (1H, d, $J = 13.0$ Hz, PhCH_2NH), 3.90 (1H, d, $J = 13.0$ Hz, PhCH_2NH), 2.60 (1H, br s, BnNH), 1.34 (3H, t, $J = 7.5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 165.1, 137.4, 129.0, 128.8, 128.3, 115.3, 63.6, 51.7, 51.2, 14.2. MS (CI) m/z : 192.1 (100%) $[\text{M}-\text{CN}]^+$, 217.1 (10%) $[\text{M}-\text{H}]^-$.

(H) General procedure for the conjugate addition of benzylamino-cyanoacetic acid ethyl ester to **2.**

⁸ Based upon a procedure reported by: Heitsch, H; Wagner, A; Yadov-Bhatnagar, N; Griffoul-Martreau, C. *Synthesis*, **1996**, 1325-1330.

⁹ Logemann, F.I; Shaw, G. *Chem. Ind.* **1980**, 541-542.

(2R,3R)-1-Benzyl-2-cyano-3-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (6a):

An oven-dried round-bottomed flask was capped with a septum and charged with **2d** (95 mg, 0.50 mmol), catalyst (*S,S*)-**1** (14.4 mg, 0.025 mmol, 2.5 mol%), and cyclohexane (2.5 mL). To the resulting suspension was added of benzylamino-cyanoacetic acid ethyl ester (131 mg, 0.60 mmol, 1.2 equiv.), then *t*-butanol (57 μ L, 0.60 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 26 hours, then diluted with ethyl acetate and purified by flash column chromatography on silica (elution gradient 10%–20% ethyl acetate in hexanes). The product was obtained as a pale yellow oil in 74% yield (106 mg): 10:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 5.05$ ppm, $\delta_{\text{minor}} = 4.56$ ppm; $\delta_{\text{minor}} = 4.48$ ppm, $\delta_{\text{major}} = 4.22$ ppm); 92% enantiomeric excess, as determined by chiral HPLC (Chiralpak OD, 5% ethanol/hexanes, 1.2 mL/min, 208 nm, $r_{\text{minor diastereomers}} = 12.3$ min, $r_{\text{minor enantiomer}} = 15.3$ min, $r_{\text{major enantiomer}} = 16.7$ min). $[\alpha]_{\text{D}}^{25} -41^\circ$ ($c = 1.02$, CHCl_3). FTIR (cm^{-1}): 3066 (m), 2980 (s), 2248 (w), 1747 (s), 1379 (w), 1241 (s), 703 (s). ^1H NMR (500 MHz, CDCl_3): δ 7.37–7.26 (5H, m, ArH), 5.05 (1H, d, $J = 15.0$ Hz, PhCH_2N), 4.22 (1H, d, $J = 15.0$ Hz, PhCH_2N), 3.90–3.82 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.74–3.68 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.00–2.95 (1H, m, $\text{CH}(\text{CH}_3)$), 2.61 (1H, dd, $J = 16.5, 8.5$ Hz, COCH_2CH), 2.34 (1H, dd, $J = 16.5, 12.0$ Hz, COCH_2CH), 1.15 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)$), 1.10 (3H, t, $J = 7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 173.5, 165.1, 134.4, 130.1, 128.8, 128.6, 115.7, 67.6, 64.6, 46.1, 39.6, 36.1, 14.1, 14.0. MS (CI) m/z : 260.0 (30%) $[\text{M}-\text{CN}]^+$, 262.0 (40%) $[\text{M}-(\text{C}_2\text{H}_5\text{O})+\text{NH}_3]^+$, 286.9 (40%) $[\text{M}+\text{H}]^+$, 241.0 (30%) $[\text{M}-\text{C}_2\text{H}_5\text{O}]^-$, 285.0 (5%) $[\text{M}-\text{H}]^-$.

Analytical data, products **6b–6d**:

(2R,3R)-1-Benzyl-2-cyano-5-oxo-3-propyl-pyrrolidine-2-carboxylic acid ethyl ester (6b): 5 mol% (*S,S*)-**1** (14.4 mg), 1.2 equiv. benzylamino-cyanoacetic acid ethyl ester (131 mg) and 1.2 equiv. *t*-butanol (57 μ L) were used. After a reaction time of 23 hours, the product was obtained as a pale yellow oil in 92% yield (106 mg): 14:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 5.05$ ppm, $\delta_{\text{minor}} = 4.82$ ppm; $\delta_{\text{minor}} = 4.36$ ppm, $\delta_{\text{major}} = 4.19$ ppm); 91% enantiomeric excess, as determined by chiral HPLC (Chiralpak OD, 5% ethanol/hexanes, 1.0 mL/min, 208 nm, $r_{\text{minor enantiomer}} = 14.7$ min, $r_{\text{major enantiomer}} = 19.4$ min). $[\alpha]_{\text{D}}^{25} -36^\circ$ ($c = 1.02$, CHCl_3). FTIR (cm^{-1}): 2962 (s), 2875 (m), 2249 (w), 1738 (s), 1456 (s), 1242 (s), 703 (s). ^1H NMR (500 MHz, CDCl_3): δ 7.36 (2H, d, $J = 7.0$ Hz, ArH), 7.32–7.26 (3H, m, ArH), 5.05 (1H, d, $J = 15.0$ Hz, PhCH_2N), 4.19 (1H, d, $J = 15.0$ Hz, PhCH_2N), 3.86–3.81 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.71–3.64 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.89–2.82 (1H, m, $\text{CH}(\text{C}_3\text{H}_7)$), 2.59 (1H, dd, $J = 16.0, 8.0$ Hz, COCH_2CH), 2.31 (1H, dd, $J = 16.0, 11.5$ Hz, COCH_2CH), 1.59–1.52 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.46–1.39 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.24–1.18 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.08 (3H, t, $J = 7.5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$),

0.93 (3H, d, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 173.4, 165.3, 134.4, 130.2, 128.7, 128.5, 115.9, 67.0, 63.6, 45.9, 44.5, 34.7, 31.7, 20.9, 14.1, 14.0. MS (CI) m/z : 314.9 (40%) $[\text{M}+\text{H}]^+$, 269.0 (60%) $[\text{M}-(\text{OC}_2\text{H}_5)]^-$, 313.0 (5%) $[\text{M}-\text{H}]^-$.

(2*R*,3*R*)-1-Benzyl-2-cyano-3-isobutyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (6c): 5.0 mol% (*S,S*)-**1** (28.8 mg), 1.2 equiv. benzylamino-cyanoacetic acid ethyl ester (131 mg) and 1.2 equiv. *t*-butanol (57 μL) were used. After a reaction time of 60 hours, the product was obtained as a pale yellow oil in 89% yield (146 mg, contaminated with 5% benzylamino-cyanoacetic acid ethyl ester): 13:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 5.06$ ppm, $\delta_{\text{minor}} = 4.83$ ppm; $\delta_{\text{minor}} = 4.36$ ppm, $\delta_{\text{major}} = 4.19$ ppm); 97% enantiomeric excess, as determined by chiral HPLC (Chiralpak OD, 5% ethanol/hexanes, 1.0 mL/min, 208 nm, $\text{rt}_{\text{minor enantiomer}} = 11.3$ min, $\text{rt}_{\text{major enantiomer}} = 16.5$ min). $[\alpha]_{\text{D}}^{25} -33^\circ$ ($c = 1.02$, CHCl_3). FTIR (cm^{-1}): 2961 (s), 2872 (m), 2249 (w), 1754 (s), 1456 (m), 1231 (s), 1019 (m), 704 (s). ^1H NMR (600 MHz, CDCl_3): δ 7.37-7.35 (2H, m, ArH), 7.32-7.26 (3H, m, ArH), 5.06 (1H, d, $J = 15.6$ Hz, PhCH_2N), 4.19 (1H, d, $J = 15.6$ Hz, PhCH_2N), 3.83-3.79 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.70-3.64 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.94-2.90 (1H, m, $\text{CH}(\text{C}_4\text{H}_9)$), 2.58 (1H, dd, $J = 16.2, 8.4$ Hz, COCH_2CH), 2.31 (1H, dd, $J = 16.2, 11.4$ Hz, COCH_2CH), 1.67-1.64 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.42-1.39 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.16-1.13 (1H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.09 (3H, t, $J = 12.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 0.95 (3H, d, $J = 6.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.90 (3H, d, $J = 6.6$ Hz, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, CDCl_3): δ 173.5, 165.3, 134.4, 130.2, 128.7, 128.5, 115.8, 67.1, 63.6, 46.0, 42.7, 38.4, 34.9, 26.1, 23.2, 22.1, 14.0. MS (CI) m/z : 329.0 (100%) $[\text{M}+\text{H}]^+$, 327.0 (80%) $[\text{M}-\text{H}]^-$.

(2*R*,3*S*)-1-Benzyl-2-cyano-5-oxo-3-phenyl-pyrrolidine-2-carboxylic acid ethyl ester (6d): 10 mol% (*S,S*)-**1** (57.7 mg), 1.2 equiv. benzylamino-cyanoacetic acid ethyl ester (131 mg) and 2.5 equiv. *t*-butanol (119 μL) were used. After a reaction time of 52 hours, the product was obtained as a white solid in 68% yield (118 mg): 20:1 d.r., as determined by integration of two sets of ^1H NMR signals ($\delta_{\text{major}} = 5.08$ ppm, $\delta_{\text{minor}} = 5.02$ ppm; $\delta_{\text{minor}} = 2.90$ ppm, $\delta_{\text{major}} = 2.78$ ppm); 96% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.2 mL/min, 208 nm, $\text{rt}_{\text{minor enantiomer}} = 25.3$ min, $\text{rt}_{\text{major enantiomer}} = 28.2$ min). $[\alpha]_{\text{D}}^{25} +30^\circ$ ($c = 13.2$, CHCl_3). mp 101-103°C. FTIR (cm^{-1}): 3063 (m), 2986 (m), 2251 (w), 1750 (s), 1717 (s), 1383 (m), 1234 (m), 1019 (m), 737 (s), 710 (s). ^1H NMR (500 MHz, CDCl_3): δ 7.38-7.26 (10H, m, ArH), 5.08 (1H, d, $J = 14.5$ Hz, PhCH_2N), 4.30 (1H, d, $J = 14.5$ Hz, PhCH_2N), 4.18 (1H, dd, $J = 12.0, 8.5$ Hz, CHPh), 3.47-3.42 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.34-3.29 (1H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.18 (1H, dd, $J = 17.0, 12.5$ Hz, COCH_2CH), 2.78 (1H, dd, $J = 17.0, 8.5$ Hz, COCH_2CH), 0.68 (3H, t, $J = 7.5$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3): δ 173.1, 164.3, 134.3, 132.4, 130.1, 129.3, 129.1, 128.7, 128.6, 128.3, 115.9, 68.4, 63.4, 49.2, 46.2, 32.6, 13.5. MS (CI) m/z : 349.0 (100%) $[\text{M}+\text{H}]^+$, 348.0 (100%) $[\text{M}]^-$.

Slow evaporation of solvent from a solution of **6d** in absolute ethanol/acetonitrile provided crystals of suitable quality for X-ray crystallography.

(I) Methanolysis of 3b to ester 9a:

3b (335 mg, 1.0 mmol, 92% e.e) was suspended in methanol (3.0 mL, excess) and acetonitrile (2.0 mL), then cooled to 4°C. Erbium trifluoromethanesulfonate (31 mg, 0.05 mmol, 5 mol%) was added, and the mixture stirred at 4°C for 20 hours. After removal of the solvent *in vacuo*, the residue was purified by chromatography on silica (elution gradient 10%–25% ethanol in hexanes). The product **9a** was obtained as a colorless oil in 76% yield (186 mg, 0.76 mmol) and 92% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.0 mL/min, 208 nm, $r_{t\text{minor}}$ 14.9 min, $r_{t\text{major}}$ 16.7 min). $[\alpha]_D^{25} +19^\circ$ ($c = 1.0$, CH_3CN). FTIR (neat, cm^{-1}): 3009 (m), 2913 (m), 2257 (w), 1738 (s), 1607 (s), 1439 (s), 1209 (s), 839 (s). ^1H NMR (600 MHz, CDCl_3): δ 7.33 (2H, dd, $J = 7.8, 5.4$ Hz, ArH), 7.09 (2H, t, $J = 9.0$ Hz, ArH), 4.46 (1H, d, $J = 5.4$ Hz, $\text{CH}(\text{CN})_2$), 3.72–3.68 (1H, m, CHAr), 3.02 (1H, dd, $J = 17.4, 8.4$ Hz, COCH_2), 2.90 (1H, dd, $J = 17.4, 6.0$ Hz, COCH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 170.9, 163.3 (d, $J_{\text{C-F}} = 248$ Hz), 131.7, 129.9, 116.7 (d, $J_{\text{C-F}} = 21$ Hz), 111.7, 111.4, 52.7, 41.7, 36.2, 29.1. MS (CI) m/z : 244.9 (100%) [M-H] $^-$.

(J) Alcoholysis of 3b to allyl ester 9b:

3b (168 mg, 0.50 mmol, 92% e.e) was suspended in allyl alcohol (1.5 mL, excess) and acetonitrile (1.0 mL), then cooled to 4°C. Erbium trifluoromethanesulfonate (15 mg, 0.025 mmol, 5 mol%) was added, and the mixture stirred at 4°C for 24.5 hours. The resulting solution was concentrated *in vacuo*, and the residue purified by chromatography on silica (elution gradient 10%–25% ethyl acetate in hexanes). The product **9b** was obtained as a colorless oil in 76% yield (104 mg) and 92% enantiomeric excess, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 6% ethanol/hexanes, 1.0 mL/min, 208 nm, $r_{t\text{minor}}$ 19.1 min, $r_{t\text{major}}$ 20.5 min). $[\alpha]_D^{25} +15^\circ$ ($c = 1.1$, CH_3CN). FTIR (cm^{-1}): 3084 (m), 2912 (m), 2257 (w), 1728 (s), 1608 (s), 1512 (s), 1231 (s), 990 (s). ^1H NMR (500 MHz, CDCl_3): δ 7.37–7.35 (2H, m, ArH), 7.12 (2H, t, $J = 9.0$ Hz, ArH), 5.89–5.81 (1H, m, $\text{CH}=\text{CH}_2$), 5.27 (2H, dd, $J = 11.5, 10.0$ Hz, $\text{CH}=\text{CH}_2$), 4.59 (2H, d, $J = 6.0$ Hz, OCH_2CH), 4.48 (1H, d, $J = 5.0$ Hz, $\text{CH}(\text{CN})_2$), 3.76–3.72 (1H, m, CHAr), 3.07 (1H, dd, $J = 17.5, 8.5$ Hz, COCH_2), 2.96 (1H, dd, $J = 17.4, 6.0$ Hz, COCH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 170.1, 163.3 (d, $J_{\text{C-F}} = 248$ Hz), 131.7, 131.4, 129.9 (d, $J_{\text{C-F}} = 9.1$ Hz), 119.5, 116.7 (d, $J_{\text{C-F}} = 22$ Hz), 111.7, 111.4, 66.4, 41.7, 36.4, 29.1. MS (CI) m/z : 317.6 (20%) [M+H] $^+$, 251.9 (100%) [$\text{M-C}_3\text{HN}_2$] $^+$, 315.8 (100%) [M-H] $^-$.

(K) Decarboxylation of 4b to 7:

The procedure described above for the methanolysis of **3b** was followed, using 368 mg (1.00 mmol, 89% e.e.) of **4b**. The product was obtained as a colorless oil (221 mg, 0.79 mmol, 79%) in 89% enantiomeric excess, as determined by chiral HPLC ((R,R)-Whelk-01 (Pirkle), 5% ethanol/hexanes, 1.2 mL/min, 208 nm, $r_{t\text{minor}}$ 20.6 min, $r_{t\text{major}}$ 22.9 min). $[\alpha]_D^{25} +8.6^\circ$ ($c = 1.2$, CH_3CN). FTIR (neat, cm^{-1}): 2959 (s), 2251 (w), 1744 (s), 1512 (s), 1439 (s), 1229 (s), 841 (s). ^1H NMR (600 MHz, CDCl_3 , 1:1:1 mixture of diastereomers, with signals corresponding to the major indicated by *): δ 7.27-7.23 (4H, m, ArH^* , ArH), 7.01-6.97 (4H, m, ArH^* , ArH), 4.17 (1H, d, $J = 5.4$ Hz, $\text{CH}^*(\text{CN})(\text{CO}_2\text{CH}_3)$), 3.88-3.84 (2H, m, CH^*Ar , CHAr), 3.80 (1H, d, $J = 5.4$ Hz, $\text{CH}^*(\text{CN})(\text{CO}_2\text{CH}_3)$), 3.77 (3H, s, CO_2CH_3), 3.74 (3H, s, CO_2CH_3), 3.62 (3H, s, CO_2CH_3), 3.56 (3H, s, CO_2CH_3), 2.99-2.86 (3H, m, COCH_2^* , COCH_2), 2.81 (1H, dd, $J = 16.8, 6.6$ Hz, COCH_2^*). ^{13}C NMR (100 MHz, CDCl_3): δ 171.4, 171.1, 165.4, 165.4, 162.8 (d, $J_{\text{C-F}} = 246$ Hz), 162.7 (d, $J_{\text{C-F}} = 246$ Hz), 134.3, 133.5, 129.8 (d, $J_{\text{C-F}} = 8.3$ Hz), 129.5 (d, $J_{\text{C-F}} = 8.3$ Hz), 116.2 (d, $J_{\text{C-F}} = 21$ Hz), 116.1 (111.7 d, $J_{\text{C-F}} = 21$ Hz), 115.3, 115.1, 53.9, 53.6, 52.3, 52.2, 43.9, 43.5, 41.2, 40.6, 37.4, 36.8. GCMS (EI) m/z : 279 (10%) $[\text{M}]^+$, 248 (10%) $[\text{M}-\text{OCH}_3]^+$, 219 (70%) $[\text{M}-\text{CO}_2\text{CH}_4]^+$, 139 (100%) $[\text{M}]^{2+}$.

Sodium chloride (29 mg, 0.50 mmol, 0.33 equiv.) was added to a solution of the methyl ester (423 mg, 1.52 mmol, 89% e.e) in dimethyl sulfoxide (6.4 mL) and water (1.1 mL). The mixture was heated to 130°C and stirred for 24 hours. After cooling to 23°C , 30 mL of saturated aqueous lithium chloride solution was added, and the mixture extracted four times with dichloromethane (total volume 200 mL). The combined organic extracts were washed with saturated aqueous lithium chloride solution, dried (sodium sulfate) and concentrated *in vacuo*. The crude product was passed through a short silica plug (eluent 50% ethyl acetate in hexanes) to yield the product as a pale yellow oil in 78% yield (263 mg) in 89% enantiomeric excess, as determined by chiral HPLC ((R,R)-Whelk-01 (Pirkle), 10% ethanol/hexanes, 1.0 mL/min, 208 nm, $r_{t\text{minor}}$ 18.1 min, $r_{t\text{major}}$ 20.7 min). $[\alpha]_D^{25} +11^\circ$ ($c = 1.1$, CH_3CN). FTIR (neat, cm^{-1}): 2957 (m), 2249 (w), 1728 (s), 1607 (s), 1512 (s). ^1H NMR (600 MHz, CDCl_3): δ 7.23-7.20 (2H, m, ArH), 7.02 (2H, t, $J = 7.2$ Hz, ArH), 3.62 (3H, s, CO_2CH_3), 3.51-3.46 (1H, m, CHAr), 2.82 (1H, dd, $J = 16.2, 7.8$ Hz, COCH_2), 2.73 (1H, dd, $J = 16.2, 7.2$ Hz, COCH_2), 2.70 (2H, d, $J = 6.0$ Hz, CH_2CN). ^{13}C NMR (100 MHz, CDCl_3): δ 171.5, 162.3 (d, $J_{\text{C-F}} = 245$ Hz), 136.5, 128.9 (d, $J_{\text{C-F}} = 8.3$ Hz), 118.1, 115.1 (d, $J_{\text{C-F}} = 21$ Hz), 52.1, 39.1, 37.6, 24.6. MS (CI) m/z : 190.0 (100%) $[\text{M}-\text{CH}_3\text{O}]^+$, 205.9 (80%) $[\text{M}-\text{CH}_3]^-$.

(L) Hydrolysis of **3b** to carboxylic acid **8**:^{2b}

A solution of **3b** (335 mg, 1.0 mmol) in tetrahydrofuran (10.0 mL) was cooled to 0°C. Freshly prepared 1M aqueous sodium hydroxide (2.05 mL, 2.05 mmol, 2.05 equiv.) was added dropwise by syringe. The mixture was stirred for 26 hours at 0°C. Saturated aqueous sodium bicarbonate (40 mL) was added, and the mixture was washed four times with dichloromethane (total volume of 150 mL), then acidified with concentrated hydrochloric acid, then extracted four times with dichloromethane (total volume of 150 mL). The combined organic extracts were dried (sodium sulfate) and concentrated *in vacuo* to yield the product (contaminated with approximately 15% benzoic acid) as an oil, which gradually solidified (159 mg, 0.69 mmol, 69% yield). The enantiomeric excess of the product was determined to be 90% by conversion to the methyl ester **9a** (oxalyl chloride, CH₂Cl₂, DMF (cat), 0°C $\rightarrow$ 23°C; methanol, pyridine, Et₂O, 0°C $\rightarrow$ 23°C) and analysis by HPLC as described for **9a**.

Product **5**: $[\alpha]_{\text{D}}^{25} +19^{\circ}$ ($c = 0.95$, CH₃CN). FTIR (CH₂Cl₂ film, cm⁻¹): 3476 (w), 3057 (m), 2988 (m), 2307 (w), 1713 (s), 1514 (s), 1265 (s), 731 (s). ¹H NMR (600 MHz, CDCl₃): δ 7.34 (2H, dd, $J = 8.4, 4.8$ Hz, ArH), 7.11 (2H, t, $J = 9.0$ Hz, ArH), 4.38 (1H, d, $J = 6.0$ Hz, CH(CN)₂), 3.73-3.70 (1H, m, CHAr), 3.10 (1H, dd, $J = 17.4, 8.4$ Hz, COCH₂), 2.99 (1H, dd, $J = 17.4, 6.6$ Hz, COCH₂). ¹³C NMR (100 MHz, CDCl₃): δ 176.0, 163.3 (d, $J_{\text{C-F}} = 248$ Hz), 131.4, 129.9 (d, $J_{\text{C-F}} = 8.4$ Hz), 116.8 (d, $J_{\text{C-F}} = 21$ Hz), 111.5, 111.3, 41.5, 36.3, 29.3. MS (CI) m/z : 317.6 (20%) [M+H]⁺, 251.9 (100%) [M-C₃HN₂]⁺, 315.8 (100%) [M-H]⁻.

(M) Aminolysis of **3b** with *N,O*-Dimethylhydroxylamine:

In a flame-dried round-bottomed flask under a nitrogen atmosphere, trimethylaluminum (525 μ L, 2.0 M in toluene, 1.05 mmol, 2.1 equiv.) was added dropwise to a suspension of *N,O*-dimethylhydroxylamine hydrochloride (102 mg, 1.05 mmol, 2.1 equiv.) in dichloromethane (2.0 mL) at 0°C. The mixture was stirred at 0°C for 10 minutes, then transferred by cannula (rinsed with an additional 1.0 mL of dichloromethane) to a suspension of **3b** (168 mg, 0.50 mmol, 92% e.e.) in dichloromethane (2.0 mL) at 0°C. After stirring at 0°C for 10 minutes, the mixture was allowed to warm to 23°C and stirred for 5 hours, then quenched with 1M aqueous tartaric acid (3.2 mL). The solution was extracted three times with dichloromethane, and the combined organic extracts washed once with saturated sodium chloride solution, dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified by chromatography on silica (elution

gradient 2:1 $\square$ 1:1 hexanes : ethyl acetate) to yield the product as a colorless oil in 85% yield (117 mg) and 92% e.e, as determined by chiral HPLC ((*R,R*)-Whelk-01 (Pirkle), 14% ethanol/hexanes, 1.4 mL/min, 210 nm, rt_{minor} 15.5 min, rt_{major} 22.3 min). $[\alpha]_{\text{D}}^{25} -23^\circ$ ($c = 1.0$, CH_3CN). FTIR (neat, cm^{-1}): 2974 (m), 2909 (s), 2266 (w), 1900 (w), 1659 (s), 1512 (s), 1229 (s), 997 (s), 841 (s). ^1H NMR (600 MHz, CDCl_3): $\square$ 7.37 (2H, dd, $J = 8.4, 5.4$ Hz, ArH), 7.09 (2H, t, $J = 8.4$ Hz, ArH), 4.76 (1H, d, $J = 4.8$ Hz, $\text{CH}(\text{CN})_2$), 3.75-3.72 (1H, m, CHAr), 3.68 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 3.11 (1H, dd, $J = 17.4, 10.2$ Hz, COCH_2), 2.98 (1H, dd, $J = 17.4, 4.8$ Hz, COCH_2). ^{13}C NMR (100 MHz, CDCl_3): $\square$ 170.4, 163.2. (d, $J_{\text{C-F}} = 251$ Hz), 132.5, 130.0, 116.5 (d, $J_{\text{C-F}} = 22$ Hz), 112.1, 111.9, 61.4, 41.2, 34.0, 32.4, 28.9. MS (CI) m/z : 243.9 (100%) [$\text{M}-\text{OCH}_3$] $^-$.

(N) Aminolysis of **3b with benzylamine:**

Benzylamine (273 mL, 2.5 mmol) was added dropwise by syringe to a solution of **3b** (335 mg, 1.0 mmol, 92% e.e.). The mixture was stirred at 23°C for 6 hours, then concentrated in vacuo. The residue was purified by chromatography on silica (33% ethyl acetate in hexanes) to yield the product as a white foamy solid in 89% yield (287 mg) and 90% e.e, as determined by chiral HPLC (Chiralcel OD, 25% isopropanol/hexanes, 1.2 mL/min, 208 nm, rt_{major} 9.1 min, rt_{minor} 17.0 min). $[\alpha]_{\text{D}}^{25} -13^\circ$ ($c = 1.04$, CH_3CN). FTIR (CH_2Cl_2 film, cm^{-1}): 3434 (m), 3055 (m), 2988 (m), 2307 (w), 1672 (s), 1514 (s), 1265 (s), 727 (s). ^1H NMR (500 MHz, CDCl_3): $\square$ 7.34-7.30 (5H, m, ArH), 7.13-7.06 (m, 4H, ArH), 6.13 (s, 1H, NH), 4.71 (1H, d, $J = 5.5$ Hz, $\text{CH}(\text{CN})_2$), 4.41 (dd, $J = 6.0, 14.5$ Hz, NHCH_2Ar), 4.31 (dd, $J = 5.0, 14.5$ Hz, NHCH_2Ar), 3.79-3.75 (1H, m, CHAr), 2.88 (1H, dd, $J = 8.5, 15.5$ Hz, COCH_2), 2.73 (1H, dd, $J = 6.0, 15.5$ Hz, COCH_2). ^{13}C NMR (100 MHz, CDCl_3): $\square$ 169.0, 163.2. (d, $J_{\text{C-F}} = 247$ Hz), 137.5, 137.5, 132.1 (d, $J_{\text{C-F}} = 3$ Hz), 129.9 (d, $J_{\text{C-F}} = 8$ Hz), 129.0, 128.1, 127.8, 116.6 (d, $J_{\text{C-F}} = 22$ Hz), 112.2, 111.9, 44.0, 42.0, 38.0, 29.0. MS (CI) m/z : 337.8 (70%) [$\text{M}+\text{NH}_3$] $^+$, 321.8 (60%) [$\text{M}+\text{H}$] $^+$, 319.8 (100%) [$\text{M}-\text{H}$] $^-$.

(O) Reductive decyanation of **9a.¹⁰ Determination of absolute configuration.**

A 0.10 M solution of SmI_2 in THF was prepared according to the following procedure: in a 25 mL Schlenk flask, samarium (150 mg, 1.0 mmol, 2.0 equiv.) was suspended in THF

¹⁰ Kang, H-Y; Hong, W.S. *Tetrahedron Lett.* **1995**, 36, 7661-7664.

(5.0 mL) under an atmosphere of nitrogen. Diiodomethane (40 μ L, 0.5 mmol, 1.0 equiv.) was added slowly by syringe. The mixture was stirred at 23°C for 4 hours.

A solution of **9a** (25 mg, 0.10 mmol, 92% e.e) in THF (3.0 mL) and HMPA (0.30 mL) in a flame-dried Schlenk tube was degassed by freezing at -78°C , removal of volatiles *in vacuo*, and thawing at 0°C (5 cycles). At 0°C , SmI_2 (3.0 mL, 0.10 M in THF, 0.30 mmol, 3.0 equiv.) was added by syringe. The purple mixture was allowed to warm to 23°C and stirred for 3 hours, then quenched with saturated aqueous ammonium chloride solution (5.0 mL), and extracted three times with ethyl acetate (total volume 60 mL). The combined organic extracts were washed five times with water, once with brine, then dried (sodium sulfate) and concentrated *in vacuo*. The resulting crude product was purified by passing through a short silica plug (eluent 20% ethyl acetate in hexanes), yielding the product **7** as a colorless oil, in 92% e.e. as determined by chiral HPLC (see characterization data of **7** for details). The absolute configuration of this sample was the same as that of **7** obtained from (*R*)-**4b**, demonstrating that additions of malononitrile and methyl cyanoacetate catalyzed by (*S,S*)-**1** result in products with the same absolute configuration. (For determination of the absolute configuration of **4b** by derivitization to (–)-paroxetine hydrochloride, see below.)

(P) Synthesis of paroxetine hydrochloride (Paxil[®]) from **4b**:¹¹

Recrystallization of **4b**:

4b (4.5g, 89% e.e.) and absolute ethanol (90 mL) were heated to 77°C until a homogeneous solution resulted. This solution was allowed to slowly cool to 23°C and aged 24 hours, then further cooled to 5°C and aged 5 days. The resulting white crystals were isolated by filtration and washed with ethanol (3.47g, 77% recovery). The enantiomeric excess of this material was determined to be 96% (see analytical data of **4d** for details).

Hydrogenation of **4b** to **12**:

A stainless steel autoclave was charged with **4b** (2.54 g, 7.0 mmol) and toluene (28 mL). Raney nickel (2800 mesh, 280 mg), then methanol (7 mL), were added, and the resulting suspension subjected to 650 PSI hydrogen pressure and heated to 75°C . After stirring for 14 hours, the solution was filtered through Celite, which was washed sequentially with methanol and dichloromethane. Solvents were removed *in vacuo* and the residue purified by flash chromatography on silica (33% hexanes in ethyl acetate to elute benzamide,

¹¹ This sequence of reactions was performed, with slight modifications as needed, as described by Sugi et al. (*Chem. Pharm. Bull.* **48** (4) 529-536 (2000)). Characterization data for all compounds were in excellent agreement with those provided in the above reference.

followed by 10% methanol in dichloromethane to elute product), providing the product as a white crystalline solid (1.94:1 diastereomeric ratio, 1.51g, 86% yield).

Steps 1-3:

Step 1: The mixture of diastereomeric β -lactams **12** (1.51g, 5.40 mmol, 1.94:1 diastereomeric ratio) was suspended in toluene (8.6 mL). Freshly prepared sodium methoxide (28 wt% in methanol, 123 μ L, 0.540 mmol, 10 mol%) was added by syringe, and the mixture heated to 75°C and stirred for 1 hour, then slowly cooled to 5°C for crystallization. After quenching with 1M aqueous hydrochloric acid, the mixture was diluted with dichloromethane and washed once with 1M aqueous hydrochloric acid, and once with brine, then dried over aqueous sodium sulfate and concentrated *in vacuo*. The crude product, obtained as a white solid (4.5:1 diastereomeric ratio), was used in step 2 without further purification.

Step 2: The crude product from step 1 (376 mg, 1.50 mmol) was added portionwise to a solution of lithium aluminum hydride (99.6 mg, 1.75 equiv.) in 1:1 THF/toluene (3.0 mL) (CAUTION: vigorous gas evolution and exotherm). The resulting mixture was heated to 75°C for 5 hours, then cooled to 23°C. Water (0.100 mL), then 25% aqueous sodium hydroxide solution (0.100 mL), then water (0.100 mL), were added sequentially. This heterogeneous mixture was dried over sodium sulfate and filtered (solids washed with diethyl ether), then concentrated *in vacuo* to yield the product as a colorless oil. This product was used in step 3 without further purification.

Step 3: To a solution of the crude product from step 2 (1.50 mmol) in THF (4.5 mL) were added sequentially Boc_2O (0.586 mL, 2.55 mmol, 1.7 equiv.), then 1M aqueous sodium hydroxide solution (1.88 mL, 1.88 mmol, 1.25 equiv.). The mixture was stirred at RT for 14 hours, then diluted with diethyl ether. The organic portion was washed twice with water, twice with 1M aqueous hydrochloric acid, then once with saturated aqueous sodium chloride solution. The resulting solution was dried (sodium sulfate) and concentrated, then the residue purified by chromatography on silica (elution gradient 4:1 $\square$ 2:1 hexanes:ethyl acetate) to yield the product as a single diastereomer (359 mg, 1.16 mmol, 77% overall, steps 1-3).

Steps 4-6:

Step 4: 4-(4-Fluoro-phenyl)-3-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.07 g, 3.47 mmol) and triethylamine (0.692 mL, 4.51 mmol, 1.3 equiv.) were dissolved in toluene (7.0 mL) and cooled to 0°C. Methanesulfonyl chloride (0.332 mL, 4.16 mmol, 1.2 equiv.) was added dropwise by syringe. After 5 minutes at 0°C, the mixture was allowed to warm to 23°C and stirred for 2 hours, then diluted with diethyl ether. The solution was washed once with water, once with 1M aqueous sodium hydroxide solution, dried (sodium sulfate) and concentrated. The resulting oil was used directly in step 5.

Step 5: The product obtained in step 4 (3.47 mmol) was dissolved in toluene (3.5 mL) and transferred via cannula (a further 1.5 mL toluene was used to rinse the flask) to a solution of sesamol (527 mg, 3.82 mmol, 1.1 equiv.) and 28% sodium methoxide in methanol (0.740 mL, 3.64 mmol, 1.05 equiv.) in toluene (4.0 mL). The mixture was heated to 80°C for 2 hours, then to 110°C for 12 hours. After cooling to 23°C, the mixture was diluted with diethyl ether, and washed twice with 1M aqueous sodium hydroxide solution, then once with saturated aqueous sodium chloride solution, then dried (sodium sulfate) and concentrated, to yield the product as a white foam (1.28g, 2.98 mmol, 86% yield). $[\alpha]_D^{25} -25.5^\circ$ (c = 0.50, 95% ethanol; lit⁶. -27.9°)

Step 6: N-Boc paroxetine (1.04 g, 2.42 mmol) was dissolved in isopropanol (12 mL). Concentrated hydrochloric acid (298 μ L, 1.5 equiv.) was added, and the solution heated to 75°C and stirred 5 hours. The resulting mixture was cooled to 23°C, pH adjusted to 2.0 with concentrated hydrochloric acid, and concentrated *in vacuo*, then dried by azeotroping twice with absolute ethanol, yielding (–)-paroxetine hydrochloride (0.92 g, 99%) as a white foamy solid. Recrystallization from toluene/water yielded the product as a white solid (80% recovery), $[\alpha]_D^{25} -89^\circ$ (c = 1.1, methanol; lit¹². -86.5°).

¹² Kreidl, J. et al. PCT INT. Appl. WO9801424 a1 980115.

(3a)

Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
14% ethanol/hexanes,
1.4 mL/min, 235 nm
90% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.485	MM	2.2737	2104.10205	15.42349	4.8746
2	39.189	MM	2.7106	4.10609e4	252.46822	95.1254

Totals : 4.31650e4 267.89171

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.253	MM	2.1150	5234.06982	41.24524	50.3753
2	41.541	MM	2.7636	5156.07617	31.09554	49.6247

Totals : 1.03901e4 72.34077

(3b)
 Chiral HPLC
 (R,R)-Whelk-01 (Pirkle)
 14% ethanol/hexanes
 1.4 mL/min, 235 nm
 93% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 B, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.411	MM	1.9109	615.20361	5.36564	3.1664
2	37.376	MM	2.4086	1.88140e4	130.18350	96.8336

Totals : 1.94292e4 135.54914

Racemic

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.019	MM	1.6422	5429.04004	55.10078	47.9865
2	38.596	MM	2.4115	5884.65234	40.67057	52.0135

Totals : 1.13137e4 95.77135

(3c)

Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
14% ethanol/hexanes
1.4 mL/min, 235 nm
92% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.481	MM	2.2136	1496.35779	11.26649	3.9573
2	46.019	MM	3.1852	3.63167e4	190.02582	96.0427

Totals : 3.78130e4 201.29231

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.485	MM	1.8463	2.07393e4	187.21422	49.8762
2	45.420	MM	2.8710	2.08423e4	120.99303	50.1238

Totals : 4.15815e4 308.20724

(3d)

Chiral HPLC
Chiralpak OD
5% isopropanol/hexanes
1.0 mL/min, 235 nm
96% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	118.899	MM	6.5153	1053.81262	2.69575	1.7942
2	133.281	MM	9.2118	5.76798e4	104.35854	98.2058

Totals : 5.87336e4 107.05428

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	131.404	MF	9.1935	5059.94238	9.17302	49.6621
2	150.060	FM	9.7608	5128.79102	8.75746	50.3379

Totals : 1.01887e4 17.93048

(3e)
Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
 4% ethanol/hexanes
 1.0 mL/min, 235 nm
96% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	82.590	MF	2.6328	1031.98877	6.53288	1.6090
2	86.016	FM	5.2207	6.31052e4	201.45741	98.3910

Totals : 6.41372e4 207.99029

Racemic

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	76.693	MF	3.8324	2.81000e4	122.20454	45.5307
2	83.917	FM	4.8635	3.36166e4	115.19930	54.4693

Totals : 6.17166e4 237.40384

(3f)
Chiral HPLC
L-Leucine (Pirkle)
3% ethanol/hexanes
1.0 mL/min, 235 nm
97% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	83.059	MF	1.0166	559.16730	9.16752	1.3377
2	84.765	FM	3.3754	4.12423e4	203.64000	98.6623

Totals : 4.18015e4 212.80752

Racemic

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	88.375	MF	2.4149	1.61410e4	111.39702	47.5641
2	93.380	FM	2.9793	1.77943e4	99.54436	52.4359

Totals : 3.39353e4 210.94138

(3g)
Chiral HPLC
L-Leucine (Pirkle)
7% ethanol/hexanes
1.0 mL/min, 235 nm
98% e.e.

Area Percent Report			
Sorted By	:	Signal	
Multiplier	:	1.0000	
Dilution	:	1.0000	

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.688	MM	1.6354	532.17047	5.42351	1.0204
2	49.139	MM	1.8196	5.16196e4	472.80963	98.9796

Totals : 5.21518e4 478.23314

Racemic

Area Percent Report			
Sorted By	:	Signal	
Multiplier	:	1.0000	
Dilution	:	1.0000	

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.469	MM	1.2682	8570.69434	112.63866	48.9805
2	50.448	MM	1.5594	8927.49121	95.41512	51.0195

Totals : 1.74982e4 208.05379

(4a)

Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
14% ethanol/hexanes,
1.4 mL/min, 235 nm
88% e.e.

=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.628	MM	3.0082	1985.94019	11.00300	6.1325
2	48.752	MM	3.1300	3.03980e4	161.86555	93.8675

Totals : 3.23840e4 172.86855

Racemic

=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.539	MM	2.8510	2.67827e4	156.56607	49.6410
2	49.304	MM	3.1931	2.71700e4	141.81516	50.3590

Totals : 5.39527e4 298.38123

(4b)
 Chiral HPLC
 (R,R)-Whelk-01 (Pirkle)
 14% ethanol/hexanes,
 1.4 mL/min, 235 nm
 89% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.686	MM	2.8927	1312.40552	7.56167	5.3985
2	48.343	MM	3.4180	2.29982e4	112.14249	94.6015

Totals : 2.43106e4 119.70416

Racemic

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.846	MM	2.7188	1.26013e4	77.24898	49.8821
2	50.006	MM	3.3490	1.26608e4	63.00800	50.1179

Totals : 2.52621e4 140.25698

(4c)
 Chiral HPLC
 (R,R)-Whelk-01 (Pirkle)
 14% ethanol/hexanes,
 1.4 mL/min, 235 nm
 89% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.290	MM	2.7052	3300.58276	20.33451	5.4516
2	52.703	MM	3.7228	5.72428e4	256.27008	94.5484

Totals : 6.05433e4 276.60459

Racemic

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 B, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.680	MM	2.7539	3.01206e4	182.28793	50.7235
2	54.604	MM	3.6474	2.92613e4	133.70869	49.2765

Totals : 5.93819e4 315.99663

(4d)

analysis as

Chiral GC

TA

141°C isothermal

86% e.e.

Area Percent Report

Sig. 1 in C:\PEAK\EXPORT2\SIGNAL.D

pk#	Ret Time	Area	Height	Type	Width	Area %
1	26.680	7643	270	NF	0.472	4.0017
2	27.641	97021	2083	FM	0.776	50.7975
3	31.767	6396	146	NM	0.729	3.3489
4	40.060	79935	925	NM	1.440	41.8518

Total area = 190995

User Modified

Racemic

Area Percent Report

\PEAK\EXPORT2\SIGNAL.D

Time	Area	Height	Type	Width	Area %
29.878	10400	2751	NF	0.630	27.5236
31.713	105400	2532	FM	0.694	27.8836
35.471	85906	1753	NM	0.817	22.7263
45.397	82656	1064	NM	1.295	21.8665

(4e)

Chiral HPLC
Chiralpak OD
33%
isopropanol/hexanes
1.5 mL/min, 235 nm
90% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.985	MM	0.5602	5745.38477	170.92149	4.9518
2	11.186	MM	2.9424	1.10281e5	624.66357	95.0482

Totals : 1.16026e5 795.58507

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 C, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.977	BB	0.4976	3.63768e4	1078.25476	48.8491
2	12.366	PB	2.7087	3.80909e4	210.74141	51.1509

Totals : 7.44677e4 1288.99617

(4f)
 Chiral HPLC
 Chiralpak OD
 25%
 isopropanol/hexanes
 1.5 mL/min, 235 nm
 95% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 D, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.353	MM	0.8046	1093.91760	22.66040	2.6820
2	22.525	MM	4.6674	3.96936e4	141.73944	97.3180

Totals : 4.07875e4 164.39984

Racemic

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 B, Sig=235,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.373	MM	0.6801	1.13036e4	277.00491	51.2732
2	25.072	MM	4.2870	1.07422e4	41.76241	48.7268

Totals : 2.20458e4 318.76732

(5a)

Chiral HPLC : CHIRALPAK AD, 10% ethanol/hexanes, 1.2 ml/min, 220 nm
Racemic

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
20.77	29366283	52.84
25.50	25206781	47.16
Totals	55573064	100.00

14:1 d.r., 97 %ee

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
20.57	299553	1.53
24.56	19341954	98.47
Totals	19641507	100.00

(5b)

Chiral HPLC : CHIRALPAK AD, 10% ethanol/hexanes, 1.2 ml/min, 220 nm
Racemic

SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
11.23	10296920	51.09
16.61	9858746	48.91
Totals	20155666	100.00

40:1 d.r., 98 %ee

SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
10.87	187054	1.14
15.60	16186830	98.86
Totals	16373884	100.00

(5c)

Chiral HPLC: Chiralpak OD, 15% isopropanol/hexanes, 1.2 mL/min, 220 nm
6:1 d.r., 95% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=220,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.911	MF	0.9187	4476.01660	81.20245	15.1037
2	12.541	FM	0.9989	680.26404	11.35005	2.2955
3	18.572	MM	1.3722	2.44789e4	297.30902	82.6008

Totals : 2.96352e4 389.86152

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=220,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.707	MF	0.9893	2159.91431	36.38787	6.5784
2	12.054	FM	0.9814	1.66594e4	282.92734	50.7394
3	18.058	MM	1.3571	1.40140e4	172.10689	42.6822

Totals : 3.28333e4 491.42209

(5d)

Chiral HPLC : CHIRALPAK AS, 14% ethanol/hexanes, 1.4 ml/min, 220 nm
Racemic

SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
11.69	4106423	46.65
15.70	4696912	53.35
Totals	8803335	100.00

14:1 d.r., 95 %ee

SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
11.50	163976	1.00
15.17	16248260	99.00
Totals	16412236	100.00

(5e)

Chiral HPLC : CHIRALPAK OD, 15% isopropanol/hexanes, 1.2 ml/min, 220 nm
Racemic

SPD-10Avp Ch1-220nm
 Results

Retention Time	Area	Area Percent
8.89	1077937	5.54
10.12	10099502	51.89
14.46	8287545	42.58

Totals:	19464984	100.00
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14:1 d.r., 91 %ee

SPD-10Avp Ch1-220nm
 Results

Retention Time	Area	Area Percent
8.80	722332	3.74
9.78	814671	4.22
14.32	17780129	92.04

Totals	19317132	100.00
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analysis as

(5)

Chiral HPLC : CHIRALPAK AD, 10% ethanol/hexanes, 1.2 ml/min, 220 nm
Racemic

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
23.63	1489978	50.47
39.60	1462464	49.53
Totals	2952442	100.00

5:1 d.r., 86 %ee

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
23.78	739055	7.07
38.88	9708581	92.93
Totals	10447636	100.00

(5g)

Chiral HPLC : CHIRALPAK AD, 10% ethanol/hexanes, 1.2 ml/min, 220 nm
Racemic

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
18.68	19838809	49.97
21.41	19865050	50.03
Totals	39703859	100.00

16:1 d.r., 96 %ee

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
19.06	126004	2.08
22.28	5926537	97.92
Totals	6052541	100.00

(6a)

Chiral HPLC : CHIRALPAK OD, 5% ethanol/hexanes, 1.2 ml/min, 220 nm

Racemic

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
15.41	7890760	52.33
16.84	7188436	47.67

Totals	15079196	100.00
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10:1 d.r., 92 %ee

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
15.34	730724	3.96
16.70	17744523	96.04

Totals	18475247	100.00
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(6b)

Chiral HPLC : CHIRALPAK OD, 5% ethanol/hexanes, 1.0 ml/min, 220 nm

Racemic

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
14.49	8014757	49.28
19.57	8248007	50.72

Totals	16262764	100.00
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14:1 d.r., 92 %ee

SPD-10Avp Ch1-220nm
Results

Retention Time	Area	Area Percent
14.69	823562	4.72
19.44	16610119	95.28

Totals	17433681	100.00
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(6c)

Chiral HPLC : CHIRALPAK OD, 5% ethanol/hexanes, 1.0 ml/min, 220 nm

Racemic

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
11.29	2233478	32.33
16.60	4674435	67.67
Totals	6907913	100.00

13:1 d.r., 97 %ee

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
10.32	107130	1.34
16.51	7907080	98.66
Totals	8014210	100.00

(6d)

Chiral HPLC : (R,R)-Whelk-01 (Pirkle), 5% ethanol/hexanes, 1.2 ml/min, 220 nm

Racemic

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
24.77	11956986	57.92
28.53	8687489	42.08

Totals	20644475	100.00
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20:1 d.r., 96 %ee

SPD-10Avp Ch1-220nm

Results

Retention Time	Area	Area Percent
25.35	152052	2.13
28.25	6975717	97.87

Totals	7127769	100.00
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Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
5% ethanol/hexanes
1.0 mL/min, 208 nm
88% e.e.

=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.588	MM	0.7740	4520.10400	97.32648	5.2376
2	22.880	MM	1.1504	8.17811e4	1184.85718	94.7624

Totals : 8.63012e4 1282.18365

Racemic

=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.525	MM	1.1387	3.19037e4	466.95016	49.6010
2	30.974	MM	1.9274	3.24170e4	280.31848	50.3990

Totals : 6.43207e4 747.26865

(7)
 Chiral HPLC
 (R,R)-Whelk-01 (Pirkle)
 10% ethanol/hexanes
 1.0 mL/min, 208 nm
 89% e.e.

Area Percent Report

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 A, Sig=210,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.085	MM	0.6443	1036.54834	26.81454	4.6378
2	20.711	VBA	0.7878	2.13136e4	396.08456	95.3622

Totals : 2.23502e4 422.89910

Racemic

Area Percent Report

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 A, Sig=210,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.904	VV	0.5647	1.08766e4	290.57669	49.8597
2	21.070	VV	0.7883	1.09378e4	205.72621	50.1403

Totals : 2.18144e4 496.30290

(9a)

Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
10% ethanol/hexanes
1.0 mL/min, 208 nm
91% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.489	MM	0.6804	3427.42578	83.96067	4.5080
2	17.565	MM	0.9998	7.26028e4	1210.30066	95.4920

Totals : 7.60302e4 1294.26133

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.770	MF	0.5982	1.83305e4	510.73788	49.2152
2	16.842	FM	0.7259	1.89150e4	434.28360	50.7848

Totals : 3.72455e4 945.02148

(9b)
Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
6% ethanol/hexanes
1.0 mL/min, 208 nm
91% e.e.

```

=====
                        Area Percent Report
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
  
```

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.745	VV	0.6866	2637.13623	58.42499	4.2924
2	22.017	VB	1.0182	5.88006e4	830.30988	95.7076

Totals : 6.14378e4 888.73487

Racemic

```

=====
                        Area Percent Report
=====
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
  
```

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.104	MF	0.6673	1.35177e4	337.63858	45.5599
2	20.536	FM	0.8622	1.61524e4	312.22852	54.4401

Totals : 2.96701e4 649.86710

(10)

Chiral HPLC
(R,R)-Whelk-01 (Pirkle)
14% ethanol/hexanes
1.4 mL/min, 208 nm
92% e.e.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 A, Sig=210,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.481	MM	0.8694	1322.66028	25.35586	4.1235
2	22.294	MM	1.3116	3.07537e4	390.78961	95.8765

Totals : 3.20764e4 416.14547

Racemic

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 B, Sig=220,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.044	MM	0.8179	8410.99121	171.39766	48.5059
2	22.297	MM	1.2984	8929.14844	114.62038	51.4941

Totals : 1.73401e4 286.01804

(11)
 Chiral HPLC
 Chiralpak OD
 25%
 isopropanol/hexanes
 1.2 mL/min, 208 nm
 89% e.e.

=====
 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.072	MM	0.9582	4.97651e4	865.55603	94.4379
2	16.959	MM	1.4904	2930.98218	32.77702	5.5621

Totals : 5.26960e4 898.33305

Racemic

**SPD-10Avp
 Ch1-220nm
 Results**

Retention Time	Area	Area %	Height	Height %
7.617	4154190	50.18	104999	65.41
14.283	4125207	49.82	55530	34.59
Totals	8279397	100.00	160529	100.00