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Supporting Information

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Highly Enantioselective Thiourea-catalyzed Nitro-Mannich Reactions

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General.

Unless otherwise indicated, all compounds were purchased from Aldrich and/or Alfa Aesar. Toluene was distilled from sodium, ether was distilled from sodium/benzophenone ketyl, and triethylamine (Et_3N) and diisopropylethylamine (DIPEA) were distilled from CaH_2 immediately prior to use. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane were fractionally distilled and stored under an atmosphere of N_2. *N*-Boc imines (**3a–j**)[1] and *t*-butyldimethyl-(2-nitroethoxy)-silane (**5**)[2] were prepared according to previously reported procedures. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other compounds obtained from commercial sources were used as recieved without further purification.

Instrumentation

Optical rotations were measured on a Jasco DIP 370 digital polarimeter using a 2-mL cell with a 1-dm path length (λ 589). Infrared (IR) spectra were recorded using a Mattson Galaxy Series FTIR 3000 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 (400 MHz), Inova-500 (500 MHz), or an Inova-600 (600 MHz) 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 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants in Hertz (Hz), and integration. Low-resolution electrospray mass spectra (LRMS) were obtained at the Harvard University Mass Spectrometry Facility using an LCT mass spectrometer (Micromass Inc., Beverley, MA). Chiral HPLC analysis was performed using a Shimadzu VP-series instrument. Preparatory HPLC was performed using a Rainin Dynamax SD-200 instrument.

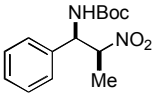
Experimental Procedures

I. Enantioselective Nitro-Mannich Reactions.

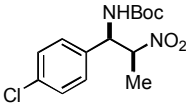
General Procedure A. Powdered 4Å molecular sieves (150 mg) were placed in a 25 mL Schlenk tube equipped with a stirbar and flame-dried under vacuum. After cooling to room temperature, the flask was flushed with N_2, and *N*-Boc imine (0.25 mmol), catalyst **2b** (8.9 mg,

25 μmol), and toluene (1 mL) were added. The reaction was cooled to 0 °C, and DIPEA (44 μL, 0.25 mmol) and the appropriate nitroalkane (0.625 mmol) were added sequentially. After 18 h, the reaction was quenched with aqueous1N HCl (3 mL) and extracted with EtOAc. The organics were dried (Na_2SO_4), concentrated by rotavap, and purified by flash chromatography on silica gel.

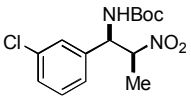
General Procedure B. Powdered 4Å molecular sieves (150 mg) were placed in a 25 mL Schlenk tube equipped with a stirbar and flame-dried under vacuum. After cooling to room temperature, the flask was flushed with N_2, and the *N*-Boc imine (0.25 mmol), catalyst **2b** (8.9 mg, 25 μmol), and toluene (1 mL) were added. The reaction was cooled to 0 °C, and DIPEA (87 μL, 0.50 mmol) and the appropriate nitroalkane (1.25 mmol) were added sequentially. After 18 h, the reaction was quenched with aqueous 1N HCl (3 mL) and extracted with EtOAc. The organics were dried (Na_2SO_4), concentrated by rotavap, and purified by flash chromatography on silica gel.



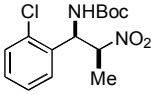
(1*R*,2*S*)-2-Nitro-1-phenylpropyl carbamic acid *t*-butyl ester (4a) . Prepared from benzaldehyde *N*-(*t*-butoxycarbonyl)imine **3a** (51.3 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to General Procedure A, affording 67.2 mg (0.24 mmol, 96% yield) white solid after chromatography (4:1 hexanes:EtOAc); *syn*:*anti* 15:1; *syn* 91% ee; $[\alpha]_D = -26.5$ (c = 1.0, acetone). The ^1H and ^{13}C NMR spectra are consistent with values previously reported in the literature. The enantiomeric purity was determined by HPLC with a Chiralcel OJ column (1% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 35.3 min, t_r(minor) = 58.4 min; *anti* isomer t_r = 27.5 and 30.3 min.



(1*R*,2*S*)-1-(*p*-Chlorophenyl)-2-nitropropyl carbamic acid *t*-butyl ester (4b) . Prepared from *p*-chlorobenzaldehyde *N*-(*t*-butoxycarbonyl)imine **3b** (59.9 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to General Procedure A, affording 77.5 mg (0.24 mmol, 98% yield) white solid after chromatography (4:1 hexanes:EtOAc); *syn*:*anti* 7:1; *syn* 95% ee; $[\alpha]_D = -28.3$ (c = 1.0, acetone). The ^1H and ^{13}C NMR spectra are consistent with values previously reported in the literature. The enantiomeric purity was determined by HPLC with a Chiralcel AD column (8% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 17.4 min, t_r(minor) = 11.0 min; *anti* isomer t_r = 15.8 and 16.6 min.

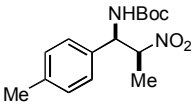


(1*R*,2*S*)-1-(*m*-Chlorophenyl)-2-nitropropyl carbamic acid *t*-butyl ester (4c) . Prepared from *m*-chlorobenzaldehyde *N*-(*t*-butoxycarbonyl)imine **3c** (59.9 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to General Procedure A, affording 67.1 mg (0.21 mmol, 85% yield) white solid after chromatography (4:1 hexanes:EtOAc); *syn*:*anti* 7:1; *syn* 96% ee; $[\alpha]_D = -23.7$ (c = 1.0, acetone). IR (thin film) 3332, 2980, 1703, 1554, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.31 (m, 3H), 7.13 (m, 1H), 5.4 (br s, 1H), 5.18 (dd, *J* = 5.9 Hz, 8.8 Hz, 1H), 4.9 (br s, 1H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz) δ 154.8, 138.5, 134.8, 130.2, 128.8, 127.1, 125.0, 85.4, 80.8, 56.8, 28.2, 15.1; LRMS (ESI) m/z: 300 $[M(^{35}Cl)+H-CH_3]^+$ (100%), 302 $[M(^{37}Cl)+H-CH_3]^+$ (30%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (3% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 20.8 min, t_r(minor) = 16.9 min; *anti* isomer t_r = 24.5 min.

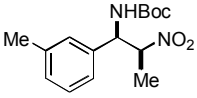


(1*R*,2*S*)-1-(*o*-Chlorophenyl)-2-nitropropyl carbamic acid *t*-butyl ester (4d) . Prepared from *o*-chlorobenzaldehyde *N*-(*t*-butoxycarbonyl)imine **3d** (59.9 mg, 0.25 mmol) and nitroethane (92 μL, 1.25 mmol) according to General Procedure B, affording 77.5 mg (0.24 mmol, 98% yield) colorless oil after chromatography (4:1 hexanes:EtOAc); *syn*:*anti* 2:1; *syn* 93% ee; IR (thin film) 3334, 2981, 1704, 1554, 1164 cm^{-1}; LRMS (ESI) m/z: 300 $[M(^{35}Cl)+H–CH_3]^+$ (100%), 302 $[M(^{37}Cl)+H–CH_3]^+$ (50%), 315 $[M(^{35}Cl)+H]^+$ (10%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (5% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 14.7 min, t_r(minor) = 16.5 min; *anti* isomer t_r = 12.3 and 21.7 min.

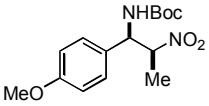
The diastereomers were separated for analysis by preparatory HPLC using a Zorbax RX-Sil column (15% ethyl acetate:hexanes, 20 mL/min flow). *Syn* isomer: $[\alpha]_D$ = +23.3 (c = 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.26 (m, 3H), 5.67 (m, 1H), 5.48 (br s , 1H), 5.15 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz) δ 154.7, 134.3, 133.0, 130.4, 129.8, 127.4, 83.9, 80.7, 55.1, 29.7, 28.2, 14.9. *Anti* isomer: $[\alpha]_D$ = +9.3 (c = 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.26 (m, 3H), 5.92 (m, 1H), 5.49 (br s, 1H), 5.16 (m, 1H), 1.64 (d, *J* = 6.3 Hz, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) δ 155.0, 135.0, 132.5, 130.1, 129.6, 128.0, 127.4, 85.0, 80.6, 54.5, 28.2, 17.1.



(1*R*,2*S*)-2-Nitro-1-*p*-tolylpropyl carbamic acid ester*t*-butyl ester (4e) . Prepared from *p*-tolualdehyde *N*-(*t*-butoxycarbonyl)imine **3e** (54.8 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to General Procedure A, affording 66.3 mg (0.21 mmol, 90% yield) white solid after chromatography (6:1 hexanes:EtOAc); *syn*:*anti* 12:1; 96% ee; $[\alpha]_D$ = –31.6 (c = 1.0, acetone). IR (thin film) 3377, 2973, 1687, 1548, 1529, 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.16 (m, 4H), 5.34 (br s, 1H), 5.16 (m, 1H), 4.91, (br s, 1H), 2.32 (s, 3H), 1.52 (d, *J* = 6.59, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz) δ 154.9, 138.4, 133.3, 129.6, 126.7, 85.8, 80.4, 57.2, 28.2, 21.0, 15.3; LRMS (ESI) m/z: 280 $[M+H–CH_3]^+$ (100%), 295 $[M+H]^+$ (20%), 312 $[M+NH_4]^+$ (30%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (1% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 46.6 min, t_r(minor) = 35.6 min; *anti* isomer t_r = 44.0 and 58.6 min.

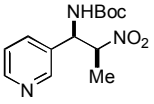


(1*R*,2*S*)-2-Nitro-1-*m*-tolylpropyl carbamic acid ester*t*-butyl ester (4f) . Prepared from *o*-tolualdehyde *N*-(*t*-butoxycarbonyl)imine **3f** (54.8 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to General Procedure A, affording 72.7 mg (0.25 mmol, 99% yield) white solid after chromatography (6:1 hexanes:EtOAc); *syn*:*anti* 9:1; *syn* 95% ee; $[\alpha]_D$ = –22.4 (c = 1.0, acetone). IR (thin film) 3336, 2980, 1703, 1553, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.26 (m, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 7.03 (m, 2H), 5.33 (br s, 1H), 5.17 (m, 1H), 4.9 (br s, 1H), 2.33 (s, 1H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.43 (s, 9H); ^{13}C NMR δ 154.9, 138.6, 136.3, 129.3, 128.8, 127.6, 123.7, 85.8, 80.4, 57.3, 28.2, 21.3, 15.2; LRMS (ESI) m/z: 280 $[M+H–CH_3]^+$ (100%), 295 $[M+H]^+$ (20%), 312 $[M+NH_4]^+$ (30%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (3% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 18.1 min, t_r(minor) = 17.0 min; *anti* isomer t_r = 22.2 and 29.5 min.

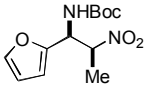


(1*R*,2*S*)-1-(*p*-Methoxyphenyl)-2-nitropropyl carbamic acid *t*-butyl ester (4g). Prepared from *p*-methoxybenzaldehyde *N*-(*t*-butoxycarbonyl)imine **3g** (58.8 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to

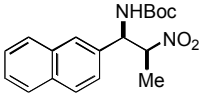
General Procedure A, affording 73.7 mg (0.24 mmol, 99% yield) white solid after chromatography (4:1 hexanes:EtOAc); *syn*:*anti* 16:1; *syn* 96% ee; $[\alpha]_D$ = –31.2 (c = 1.0, acetone); IR (thin film) 3377, 2977, 1687, 1549, 1517, 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.32 (br s, 1H), 5.10 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.9 (br s, 1H), 3.78 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR δ 159.6, 154.8, 128.0, 127.6, 114.3, 85.9, 80.4, 57.0, 55.2, 28.2, 15.4; LRMS (ESI) m/z: 296 $[M+H–CH_3]^+$ (100%), 311 $[M+H]^+$ (40%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (8% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 17.1 min, t_r(minor) = 15.3 min; *anti* isomer t_r = 19.0 and 23.0 min.



(1*R*,2*S*)-2-Nitro-1-(3-pyridyl)-propyl carbamic acid *t*-butyl ester (4h). Powdered 4Å molecular sieves (150 mg) were placed in a 25 mL Schlenk tube equipped with a stirbar and flame-dried under vacuum. After cooling to room temperature, the flask was flushed with N_2, and 3-pyridinecarboxaldehyde *N*-(*t*-butoxycarbonyl)imine **3h** (51.6 mg, 0.25 mmol), catalyst **2b** (8.9 mg, 25 μmol), and toluene (1 mL) were added. The reaction was cooled to 0 °C, and DIPEA (87 μL, 0.50 mmol) and the appropriate nitroalkane (1.25 mmol) were added sequentially. After 18 h, the reaction was quenched with aqueous 1N HCl (3 mL), neutralized with saturated aqueous $NaHCO_3$ (6 mL) and extracted with EtOAc. The organics were dried (Na_2SO_4), concentrated by rotavap, and purified by flash chromatography on silica gel (1:2 hexanes:EtOAc), affording 55.4 mg (0.20 mmol, 79% yield) white solid; *syn*:*anti* 7:1; *syn* 97% ee; $[\alpha]_D$ = –29.9 (c = 1.0, acetone). IR (thin film) 3227, 2981, 1712, 1553, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54–8.57 (m, 2H), 7.58 (m, 1H), 7.26–7.30 (m, 1H), 5.69 (br s, 1H), 5.19 (m, 1H), 4.95 (br s, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.7, 149.9, 148.6, 134.5, 134.1, 123.7, 85.3, 81.0, 55.4, 28.1, 15.4; LRMS (ESI) m/z: 282 $[M+H]^+$ (100%), 323 $[M+H+CH_3CN]^+$ (90%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (10% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 13.8 min, t_r(minor) = 13.1 min; *anti* isomer t_r = 18.9 and 20.8 min.

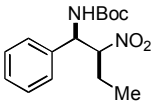


(1*R*,2*S*)-1-2-Furyl)-2-nitropropyl carbamic acid *t*-butyl ester (4i). Prepared from furfural *N*-(*t*-butoxycarbonyl)imine **3i** (48.8 mg, 0.25 mmol) and nitroethane (46 μL, 0.625 mmol) according to General Procedure A, affording 64.0 mg (0.24 mmol, 95% yield) white solid after chromatography (6:1 hexanes:EtOAc); *syn*:*anti* 6:1; *syn* 93% ee; $[\alpha]_D$ = –51.2 (c = 1.0, acetone). IR (thin film) 3362, 2981, 1683, 1546, 1526, 1175 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.36 (s, 1H), 6.31 (s, 1H), 5.35–5.40 (m, 2H), 4.93 (m, 1H),1.60 (d, *J* = 6.4 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.7, 149.0, 142.8, 110.5, 108.3, 84.3, 80.7, 51.6, 28.2, 15.2; LRMS (ESI) m/z: 256 $[M+H–CH_3]^+$ (100%), 271 $[M+H]^+$ (20%), 310 $[M–H+CH_3CN]^+$ (50%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (3% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 18.0 min, t_r(minor) = 15.2 min; *anti* isomer t_r = 16.7 and 21.9 min.

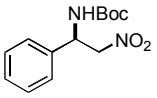


(1*R*,2*S*)-1-(2-Naphthyl)-2-nitropropyl carbamic acid *t*-butyl ester (4j) . Prepared from 2-naphthaldehyde *N*-(*t*-butoxycarbonyl)imine **3j** (63.8 mg, 0.25 mmol) and nitroethane (92 μL, 1.25 mmol) according to General Procedure B, affording 75.5 mg (0.23 mmol, 91% yield) white solid after chromatography (4:1 hexanes:EtOAc); *syn*:*anti* 5:1; *syn* 97% ee; $[\alpha]_D$ = –30.9 (c = 1.0, acetone); IR (thin film) 3371,

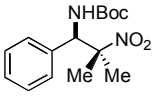
2979, 1687, 1550, 1524, 1170 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85–7.99 (m, 3H), 7.76 (m, 1H), 7.52–7.56 (m, 2H), 7.38–7.39 (m, 1H), 5.49 (br s, 1H), 5.44 (m, 1H), 5.07 (br s, 1H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.8, 133.1, 129.0, 129.0, 128.0, 127.6, 126.6, 126.6, 126.5, 126.3, 125.9, 85.7, 80.6, 57.5, 28.2, 17.1. LRMS (ESI) m/z: 316 $[M+H–CH_3]^+$ (100%), 331 $[M+H]^+$ (20%), 348 $[M+NH_4]^+$ (30%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (7% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 23.1 min, t_r(minor) = 20.5 min; *anti* isomer t_r = 26.4 and 29.1 min.



(1*R*,2*S*)-2-Nitro-1-phenylbutyl carbamic acid *t*-butyl ester (6a) . Prepared from benzaldhyde *N*-(*t*-butoxycarbonyl)imine **3a** (51.3 mg, 0.25 mmol) and 1-nitropropane (112 μL, 1.25 mmol) according to General Procedure B, affording 68.6 mg (0.23 mmol, 93% yield) white solid after chromatography (6:1 hexanes:EtOAc); *syn*:*anti* 7:1; *syn* 92% ee; $[\alpha]_D$ = –11.8 (c = 1.0, acetone). IR (thin film) 3386, 2977, 1686, 1546, 1525, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.35 (m, 3H), 7.23–7.26 (m, 2H), 5.21 (m, 1H), 5.16 (br s, 1H), 4.75 (br s, 1H), 2.04 (m, 1H), 1.89 (m, 1H),1.42 (s, 9H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.9, 136.6, 128.8, 128.6, 126.8, 93.0, 80.5, 56.8, 28.2, 23.4, 10.4. LRMS (ESI) m/z: 280 $[M+H–CH_3]^+$ (100%), 295 $[M+H]^+$ (10%), 312 $[M+NH_4]^+$ (10%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (7%EtOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 7.6 min, t_r(minor) = 8.4 min; *anti* isomer t_r = 9.2 and 9.8 min.

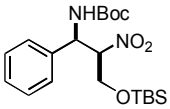


(*R*)-2-Nitro-1-phenylethyl carbamic acid *t*-butyl ester (6b) . Powdered 4 Å molecular sieves (150 mg) were placed in a 25 mL Schlenk tube equipped with a stirbar and flame-dried under vacuum. After cooling to room temperature, the flask was flushed with N_2, and benzaldehyde *N*-(*t*-butoxycarbonyl)imine **3a** (51.3 mg, 0.25 mmol), catalyst **2b** (8.9 mg, 25 μmol), and toluene (1 mL) were added. The reaction was cooled to 0 °C, and DIPEA (87 μL, 0.50 mmol) and nitromethane (68 μL, 1.25 mmol) were added sequentially. After 40 h, the reaction was quenched with aqueous 1N HCl (3 mL) and extracted with EtOAc. The organics were dried (Na_2SO_4), concentrated by rotavap, and purified by flash chromatography on silica gel (4:1 hexanes:EtOAc) to afford 57.9 mg (0.22 mmol, 87% yield) white solid; 92% ee; $[\alpha]_D$ = –26.5 (c = 1.0, acetone). The ^1H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[3] The enantiomeric purity was determined by HPLC with a Chiralcel AD column (5% EtOH:hexanes, 1 mL/min flow); t_r(major) = 18.1 min, t_r(minor) = 21.0 min.

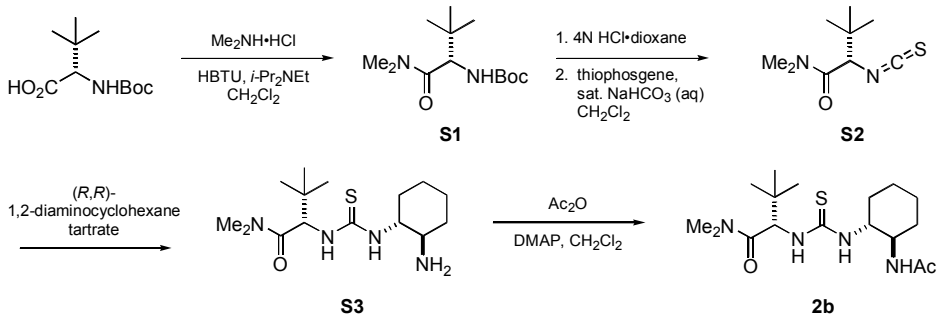


(*R*)-2-Methyl-2-nitro-1-phenylpropyl carbamic acid *t*-butyl ester (6c) . Powdered 4Å molecular sieves (150 mg) were placed in a 25 mL Schlenk tube equipped with a stirbar and flame-dried under vacuum. After cooling to room temperature, the flask was flushed with N_2, and benzaldehyde *N*-(*t*-butoxycarbonyl)imine **3a** (51.3 mg, 0.25 mmol), catalyst **2b** (8.9 mg, 25 μmol), and toluene (1 mL) were added. The reaction was cooled to 0 °C, and triethylamine (79 μL, 0.50 mmol) and 2-nitropropane (112 μL, 1.25 mmol) were added sequentially. After 48 h, the reaction was quenched with aqueous 1N HCl (3 mL) and extracted with EtOAc. The organics were dried (Na_2SO_4), concentrated by rotavap, and purified by flash chromatography on silica gel (4:1 hexanes:EtOAc) to afford 64.1 mg (0.22 mmol, 87% yield) white solid; 92% ee; $[\alpha]_D$ = –22.6 (c = 1.0, acetone). IR (thin film) 3332, 2981, 1700, 1544, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.34 (m, 3H), 7.16–7.17

(m, 2H), 5.86 (br d, J = 8.4 Hz, 1H), 5.05 (d, J = 10.2 Hz, 1H), 1.68 (s, 3H), 1.53 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.1, 136.6, 128.5, 128.4, 127.7, 90.5, 80.2, 60.8, 28.2, 25.0, 23.1. LRMS (ESI) m/z: 280 $[M+H–CH_3]^+$ (100%), 295 $[M+H]^+$ (20%), 312 $[M+NH_4]^+$ (20%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (1% *i*-PrOH:hexanes, 1 mL/min flow); t_r(major) = 20.4 min, t_r(minor) = 18.8 min.



(*1R*,2*R*)-3-(*t*-Butyldimethylsilyloxy)-2-nitro-1-phenylpropyl carbamic acid *t*-butyl ester (6d). Prepared from benzaldehyde *N*-(*t*-butoxycarbonyl)imine **3a** (51.3 mg, 0.25 mmol) and *t*-butyldimethyl-(2-nitroethoxy)-silane **5** (128 mg, 0.625 mmol) according to General Procedure B, affording 87.3 mg (0.21 mmol, 85% yield) colorless oil after chromatography (hexanes → 8:1 hexanes:EtOAc gradient); *syn*:*anti* 4:1; *syn* 95% ee; $[\alpha]_D$ = –22.4 (c = 1.0, acetone); IR (thin film) 3402, 3336, 2932, 1704, 1556, 1169 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.39 (m, 5H), 5.83 (br s, 1H), 5.45 (br s, 1H), 4.72–4.76 (m, 1H), 4.14 (dd, J = 11.7, 2.9 Hz, 1H), 4.00 (dd, J = 11.2, 5.9 Hz, 1H), 1.42 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 137.2, 129.0, 128.5, 126.6, 126.2, 92.7, 90.1, 61.2, 28.2, 25.6, 18.0, –5.9. LRMS (ESI) m/z: 411 $[M+H]^+$ (100%), 428 $[M+NH_4]^+$ (20%). The enantiomeric purity was determined by HPLC with a Chiralcel AD column (2% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer t_r(major) = 24.6 min, t_r(minor) = 11.2 min; *anti* isomer t_r = 13.1 and 18.7 min.



II. Catalyst Preparation.[4] A 100 mL round-bottomed flask equipped with a stirbar was charged with *N*-Boc-(D)-*t*-leucine (2.0 g, 8.65 mmol) in 25 mL CH_2Cl_2. HBTU (3.28 g, 8.65 mmol) was then added, followed by dimethylamine hydrochloride (584 mg, 8.65 mmol). After 2 minutes, DIPEA (4.5 mL, 25.9 mmol) was added, and the reaction was allowed to stir overnight at ambient temperature. After 18h, the reaction was quenched by addition of aqueous 1N HCl (25 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), concentrated on rotavap, and purified by flash chromatography on silica gel with ethyl acetate as eluant.

The resulting amide (**S1**) was placed in a 100 mL round-bottomed flask equipped with a stirbar. 4N HCl in dioxane was added (15 mL), and the reaction was stirred at ambient temperature. After 18h, the volatiles were removed on rotavap. The unpurified hydrochloride salt was diluted with 10 mL CH_2Cl_2, cooled to 0 °C, and treated with 10 mL saturated aqueous $NaHCO_3$. Thiophosgene (9.52 mmol) was added to this biphasic mixture, and after 1 h, the layers were separated. The organic layer was concentrated *in vacuo*, providing isothiocyanate **S2**. This residue was diluted with 50 mL CH_2Cl_2.

(*R*,*R*)-1,2-Diaminocyclohexane tartrate salt (4.6 g, 17.3 mmol) was added to a rapidly stirring solution of aqueous 5 M NaOH (100 mL). The reaction was let cool to ambient temperature and was then extracted with CH_2Cl_2. The organics were dried (Na_2SO_4) and added directly to the isocyanate solution from the previous step. After 1 h, the reaction was concentrated by rotavap, and the residue was purified by chromatography on silica gel, eluting with 5% MeOH in NH_3-saturated CH_2Cl_2.

The primary amine was taken up in CH_2Cl_2 and treated sequentially with pyridine (3.5 mL, 43.3 mmol) and acetic anhydride (4.1 mL, 43.3 mmol). After 12 h, aqueous 1N HCl was added (50 mL), and the reaction was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated by rotavap. The residue was dissolved in a minimal amount of ethyl acetate and precipitated with hexanes to afford 894 mg (2.51 mmol, 29% yield over 4 steps) of **2b** as white powder. $[\alpha]_D$ = +62.5 (c = 1.0, acetone); IR (thin film) 3293, 2936, 1634, 1644, 1538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 6.8 Hz, 1H), 5.55 (d, *J* = 9.3 Hz, 1H), 4.40 (m, 1H), 3.50 (m, 1H), 3.25 (s, 3H), 2.92 (s, 3H), 2.10 (m, 2H), 1.95 (s, 3H), 1.74 (m, 2H), 1.21–1.36 (m, 4H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 183.8, 172.2, 171.8, 59.8, 56.4, 56.3, 38.8, 36.2, 35.9, 32.8, 32.7, 26.8, 25.1, 24.9, 23.5. LRMS (ESI) m/z: 312 $[M–H–CH_3CO]^+$ (100%), 357 $[M+H]^+$ (50%), 713 $[2M+H]^+$ (50%).

References

[1] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

[2] C. W. Holzapfel, *Synth. Commun.* **1994**, *24*, 3197–3211.

[3] B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419.

[4] Compounds **S1–S3** have previously been prepared by this procedure, and full characterization data for them have been reported. See: P. Vachal, E. N.Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.

Effect of Additives

General Procedure for Table S1: A solution of *N*-Boc benzaldimine 3a (51.3 mg, 0.25 mmol) and urea catalyst **2a** (8.5 mg, 25 μmol) in toluene was placed in a flame-dried 25 mL Schlenk tube equipped with stirbar. The additive was added in the quantity described in Table S1. The reaction was then cooled to 0 °C and triethylamine (35 μL, 0.25 mmol) was added by syringe, followed by nitroethane (46 μL, 0.625 mmol). After 24 h, the reaction was quenched with aqueous 1N HCl (3 mL) and extracted with EtOAc. The organics were dried (Na_2SO_4), concentrated by rotavap.

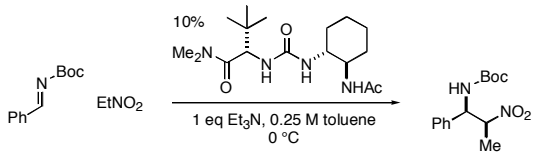
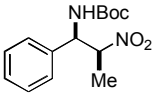


Table S1. Effect of additives on the nitro-Mannich reaction.

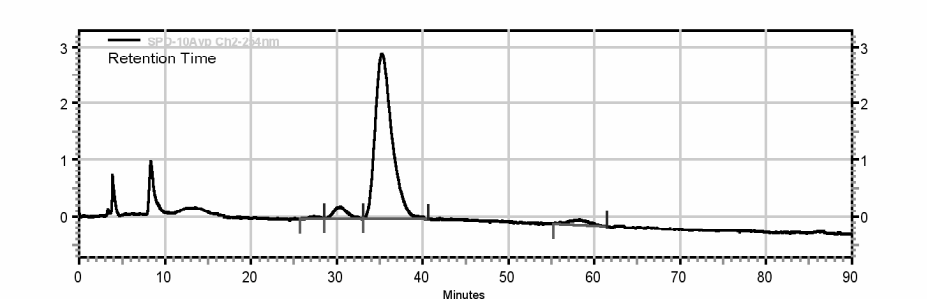
entry	additive	amount	conv. (%)	d.r. (syn:anti)	*syn* ee (%)	*anti* ee (%)
1	none	--	> 95	8.4 : 1	91	57
2	acetic acid	0.25 mmol	13	--	--	--
3	*t*-butanol	0.25 mmol	90	3.8 : 1	71	46
4	phenol	0.25 mmol	11	--	--	--
5	Na_2SO_4	50 mg	77	4.6 : 1	74	47
6	Na_2SO_4[a]	50 mg	39	2.9 : 1	55	37
7	$MgSO_4$[a]	50 mg	10	--	--	--
8	$CaCl_2$[a]	50 mg	29	2.3 : 1	57	35
9	3A sieves[a]	150 mg	87[b]	5.5 : 1	87	49
10	4A sieves	50 mg	>95	7.4 : 1	94	69
11	4A sieves[a]	150 mg	99[b]	10.0 : 1	92	64
12	5A sieves[a]	150 mg	37[b]	2.0 : 1	65	36

[a] Additive flame-dried under vacuum immediately before introduction to the reaction. [b] Isolated yield after silica gel chromatography using 4:1 hexanes:EtOAc as eluant.

HPLC Data



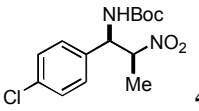
4a **Chiral HPLC: Chiralcel OJ, 1% isopropanol:hexanes, 1 mL/min**



SPD-10Avp Ch2-254nm
Results

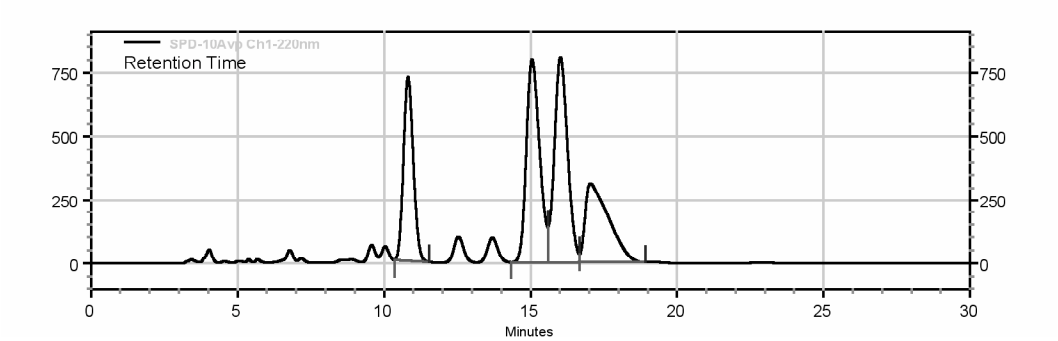
Retention Time	Area	Area Percent
27.333	3443	0.786
30.433	24410	5.572
35.300	394583	90.062
58.258	15686	3.580

Totals		
	438122	100.000



4b **Chiral HPLC: Chiralcel AD, 8% isopropanol:hexanes, 1 mL/min**

Racemate:

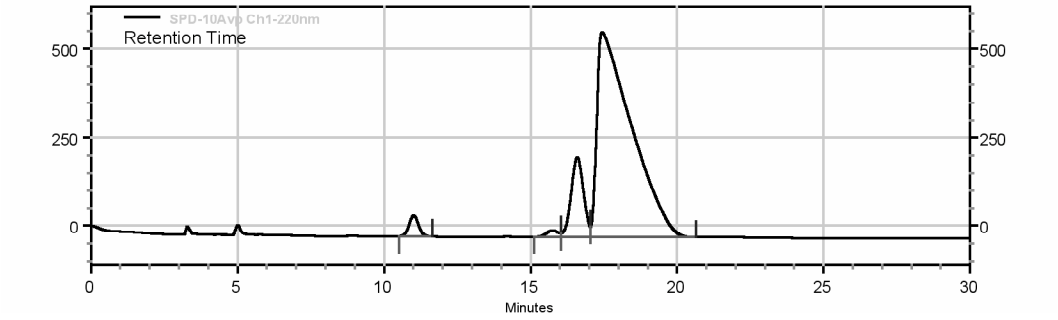


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
10.817	16938346	19.994
15.050	25042457	29.560
16.025	25501330	30.102
17.042	17235511	20.345

Totals		
	84717644	100.000

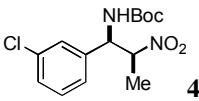
Enantioenriched:



SPD-10Avp Ch1-220nm Results

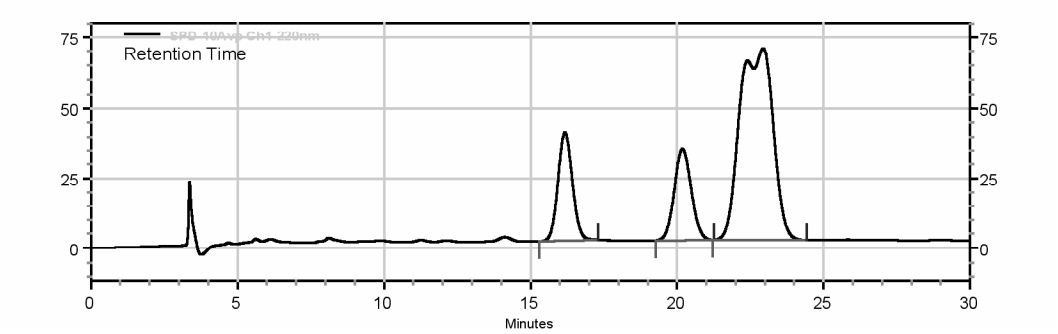
Retention Time	Area	Area Percent
11.017	1293406	2.309
15.750	515774	0.921
16.592	6660561	11.891
17.442	47542598	84.879

Totals		
	56012339	100.000



4c **Chiral HPLC: Chiralcel AD, 3% isopropanol:hexanes, 1 mL/min**

Racemate:

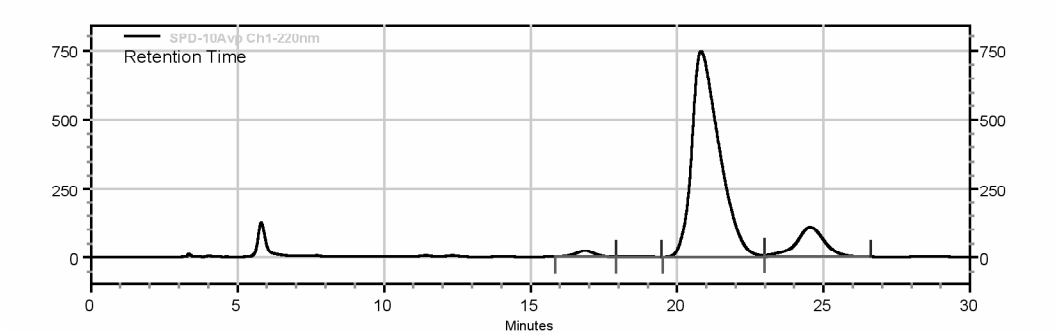


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
16.175	1328155	16.562
20.183	1323582	16.505
22.942	5367556	66.933

Totals		
	8019293	100.000

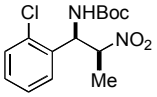
Enantioenriched:



SPD-10Avp Ch1-220nm Results

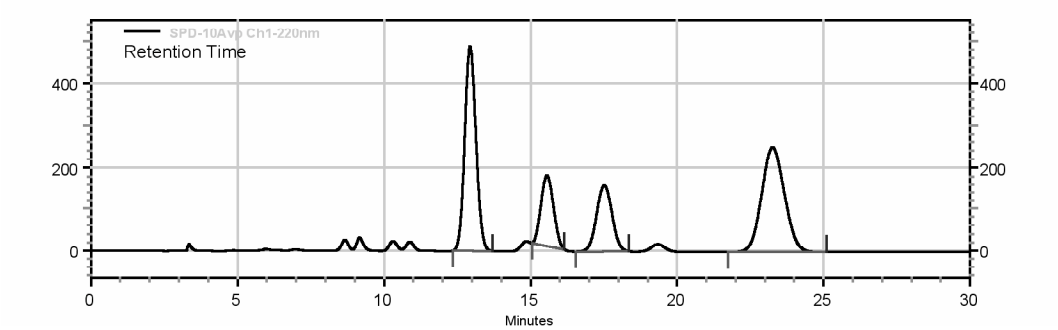
Retention Time	Area	Area Percent
16.858	985327	1.728
20.817	48677803	85.358
24.542	7309131	12.817

Totals		
	57028022	100.000



4d **Chiral HPLC: Chiralcel AD, 5% isopropanol:hexanes, 1 mL/min**

Racemate:

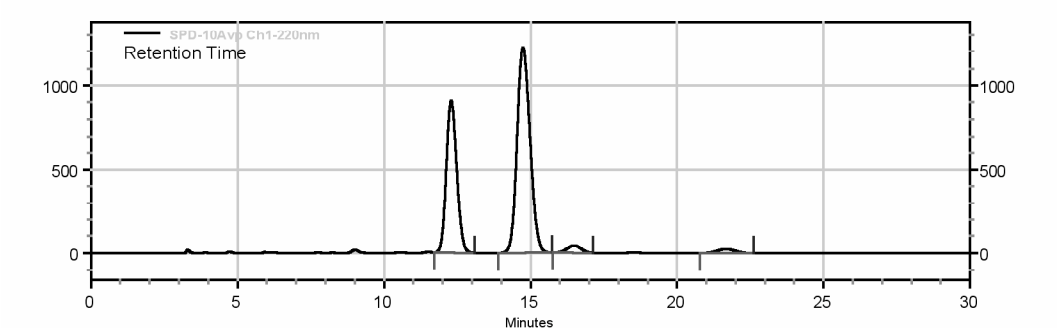


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
12.933	13076138	34.881
15.558	5003758	13.348
17.517	5821205	15.528
23.258	13586626	36.243

Totals		
	37487727	100.000

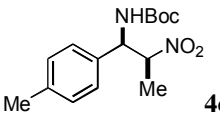
Enantioenriched:



SPD-10Avp Ch1-220nm Results

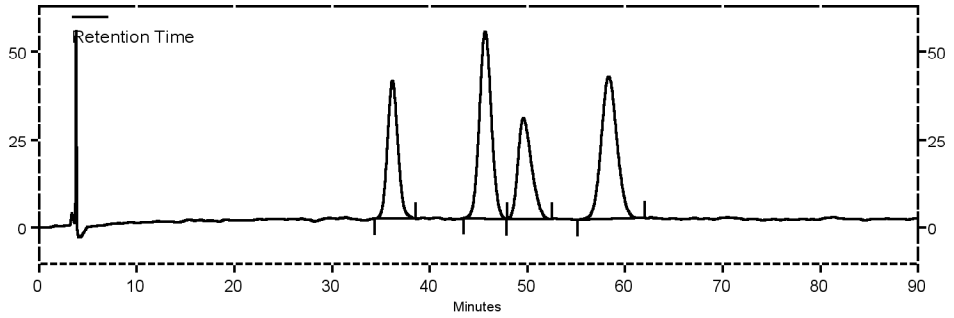
Retention Time	Area	Area Percent
12.292	22538273	35.857
14.742	37771869	60.093
16.483	1432915	2.280
21.667	1112559	1.770

Totals		
	62855616	100.000



4e **Chiral HPLC: Chiralcel AD, 1% isopropanol:hexanes, 1 mL/min**

Racemate:

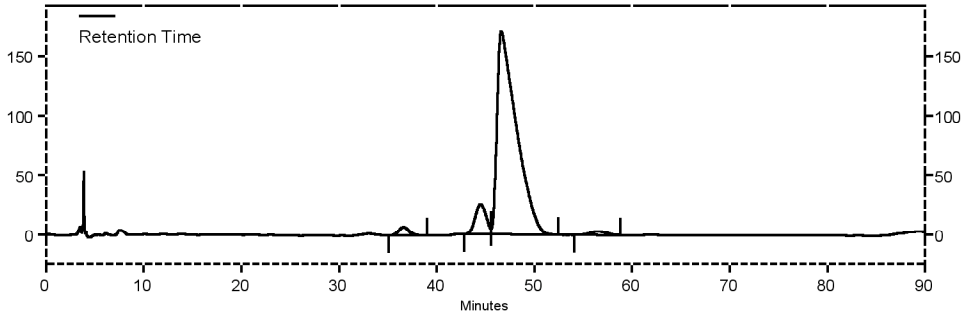


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
36.183	2922706	19.695
45.683	4546205	30.635
49.608	2782679	18.751
58.325	4588417	30.919

Totals		
	14840007	100.000

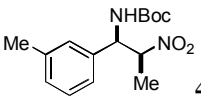
Enantioenriched:



SPD-10Avp Ch1-220nm Results

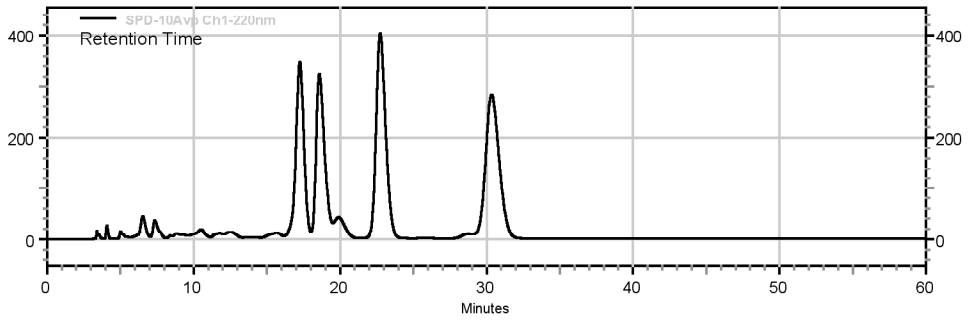
Retention Time	Area	Area Percent
36.608	514903	1.969
44.492	1911024	7.309
46.608	23348957	89.303
56.508	370929	1.419

Totals		
	26145813	100.000



4f **Chiral HPLC: Chiralcel AD, 3% isopropanol:hexanes, 1 mL/min**

Racemate:

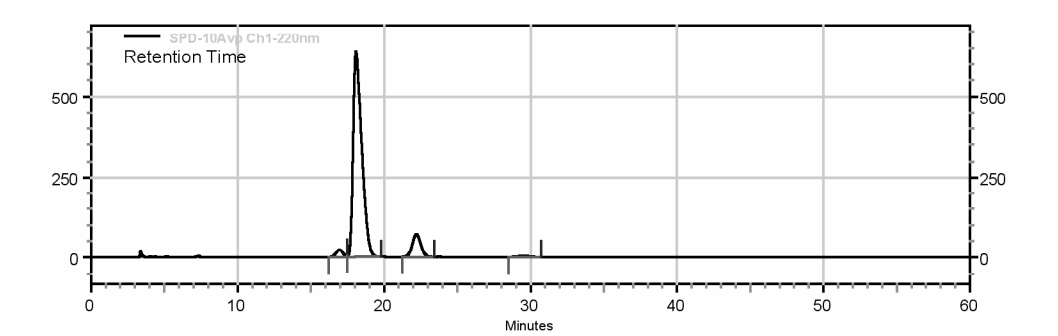


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
17.258	12379478	20.968
18.583	11134195	18.859
22.742	18068267	30.604
30.342	17457657	29.569

Totals		
	59039597	100.000

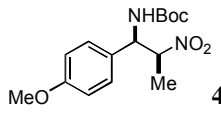
Enantioenriched:



SPD-10Avp Ch1-220nm Results

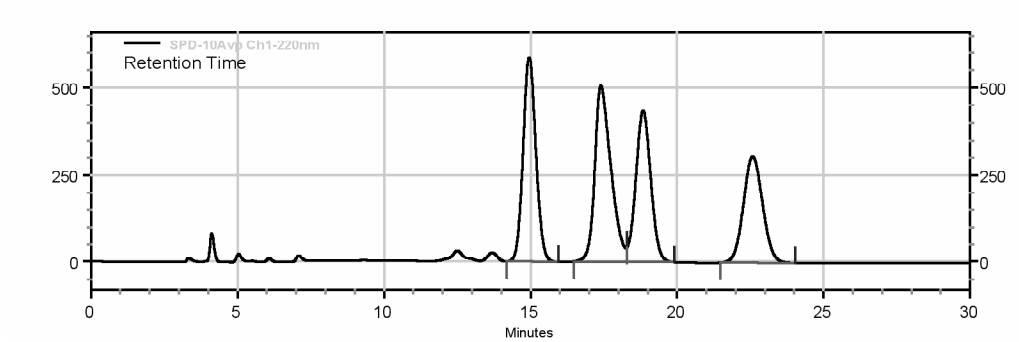
Retention Time	Area	Area Percent
16.958	735672	2.458
18.083	26199077	87.547
22.208	2802909	9.366
29.517	188063	0.628

Totals		
	29925721	100.000



4g **Chiral HPLC: Chiralcel AD, 8% isopropanol:hexanes, 1 mL/min**

Racmate:

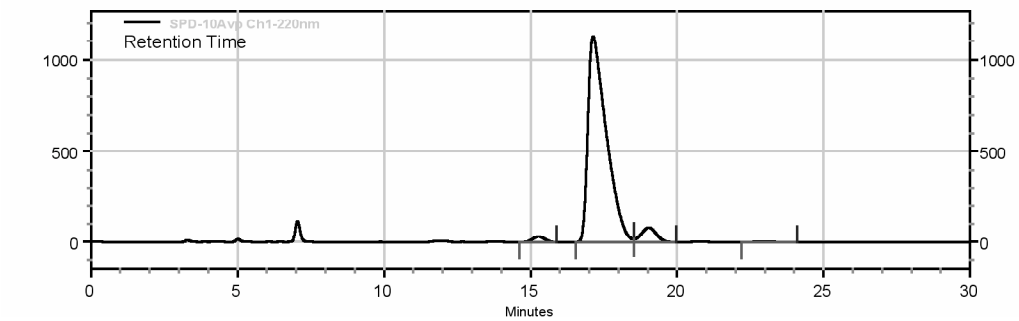


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
14.950	17942720	26.706
17.400	19574140	29.134
18.842	15582838	23.193
22.583	14087367	20.967

Totals	67187065	100.000

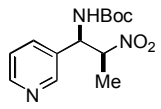
Enantioenriched:



SPD-10Avp Ch1-220nm Results

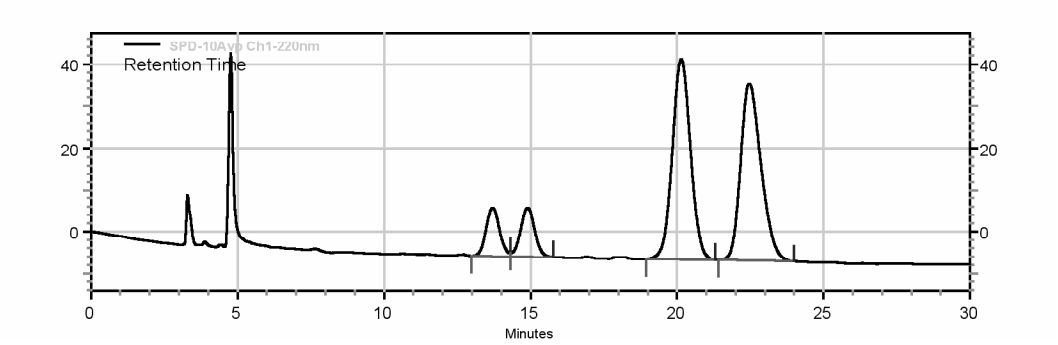
Retention Time	Area	Area Percent
15.275	940141	1.752
17.133	49544544	92.325
19.033	2939868	5.478
22.983	238529	0.444

Totals	53663082	100.000



4h **Chiral HPLC: Chiralcel AD, 10% isopropanol:hexanes, 1 mL/min**

Racemate:

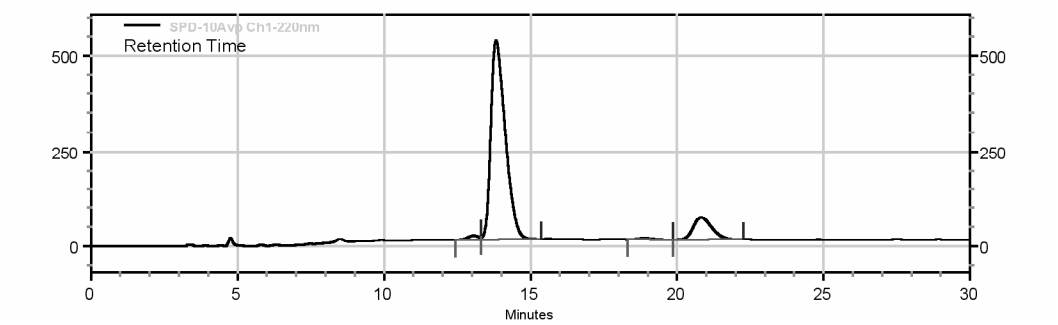


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
13.708	373716	7.618
14.900	395532	8.062
20.142	2074300	42.282
22.467	2062349	42.038

Totals		
	4905897	100.000

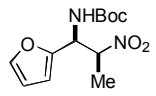
Enantioenriched:



SPD-10Avp Ch1-220nm Results

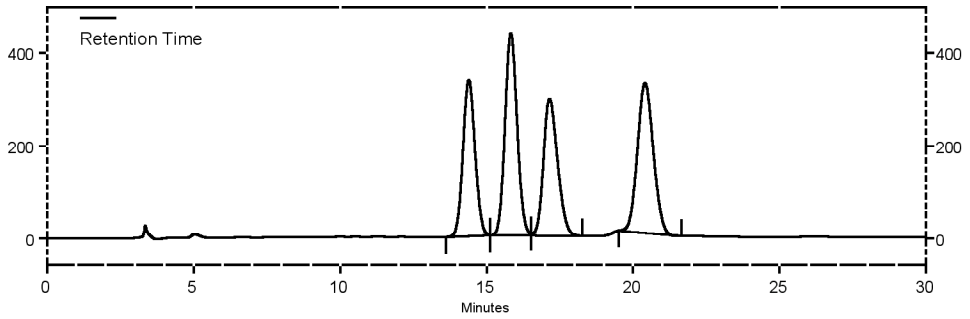
Retention Time	Area	Area Percent
13.058	284902	1.369
13.825	17853725	85.775
18.908	139439	0.670
20.825	2536535	12.186

Totals		
	20814601	100.000



4i **Chiral HPLC: Chiralcel AD, 3% isopropanol:hexanes, 1 mL/min**

Racemate:

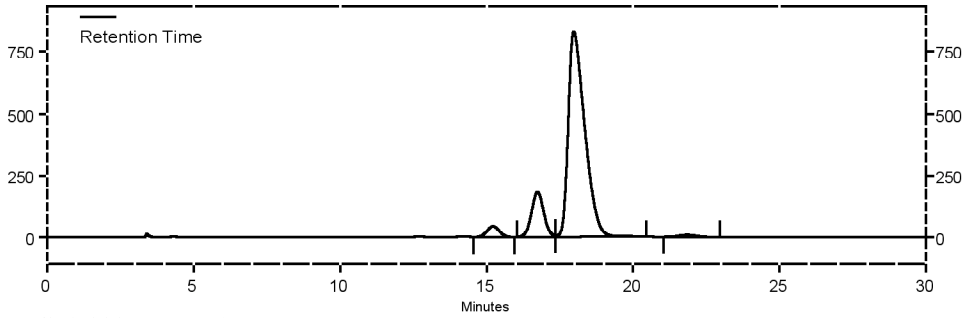


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
14.392	9626926	21.788
15.825	12557762	28.422
17.150	9862402	22.321
20.408	12136900	27.469

Totals		
	44183990	100.000

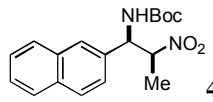
Enantioenriched:



SPD-10Avp Ch1-220nm Results

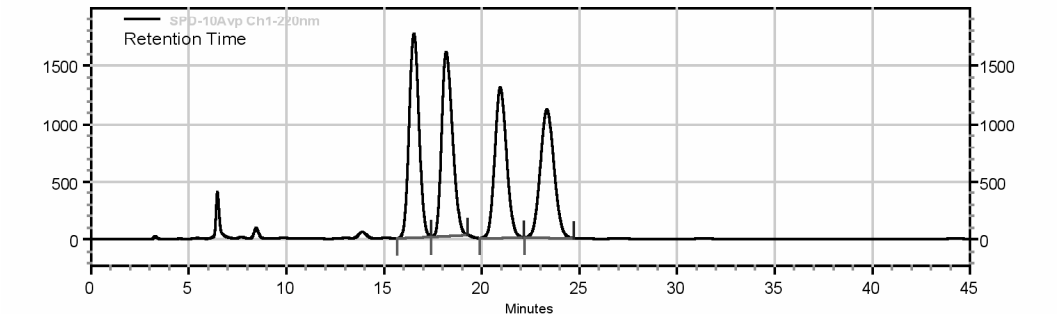
Retention Time	Area	Area Percent
15.225	1276807	3.180
16.742	5354696	13.336
17.975	33189194	82.657
21.850	332263	0.827

Totals		
	40152960	100.000



4j **Chiral HPLC: Chiralcel AD, 7% isopropanol:hexanes, 1 mL/min**

Racemate:

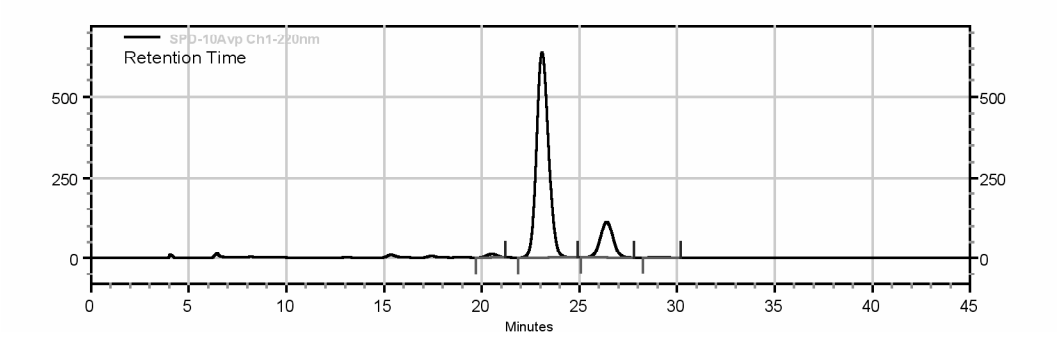


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
16.525	62165258	26.622
18.183	61795379	26.463
20.950	54652639	23.404
23.342	54901518	23.511

Totals		
	233514794	100.000

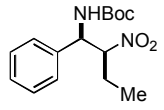
Enantioenriched:



SPD-10Avp Ch1-220nm Results

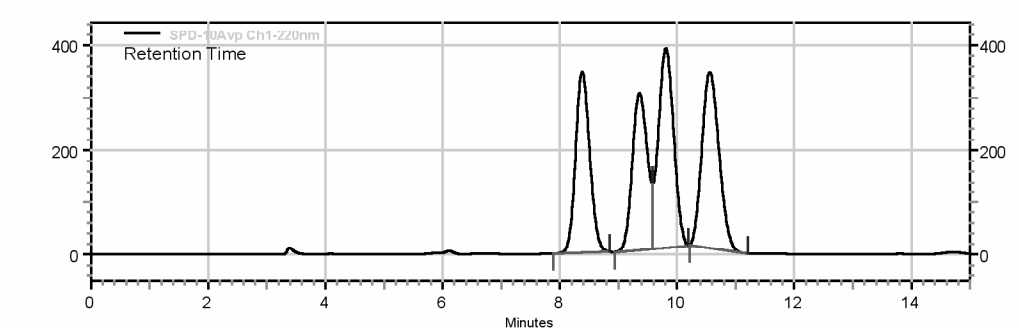
Retention Time	Area	Area Percent
20.525	405644	1.241
23.083	27129047	82.967
26.400	5067877	15.499
29.092	95977	0.294

Totals		
	32698545	100.000



6a **Chiral HPLC: Chiralcel AD, 7% ethanol:hexanes, 1 mL/min**

Racemate:

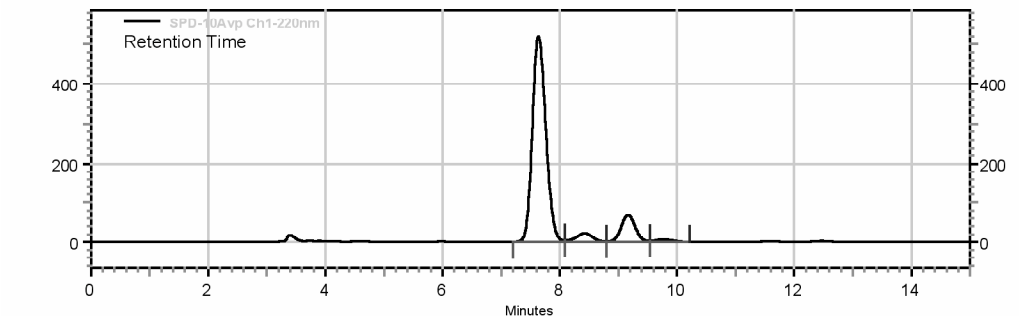


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
8.383	5816898	23.215
9.358	5397244	21.541
9.808	6989372	27.895
10.558	6852632	27.349

Totals		
	25056146	100.000

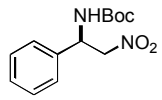
Enantioenriched:



SPD-10Avp Ch1-220nm Results

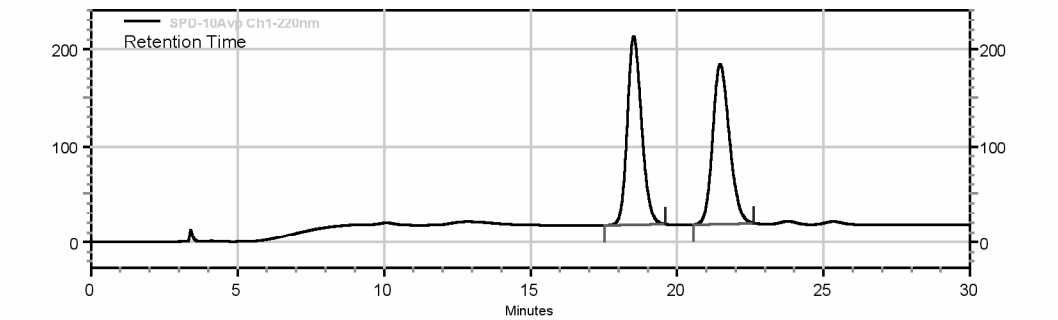
Retention Time	Area	Area Percent
7.633	8326097	83.130
8.425	429277	4.286
9.167	1124426	11.227
9.767	135996	1.358

Totals		
	10015796	100.000



6b Chiral HPLC: Chiralcel AD, 5% ethanol:hexanes, 1 mL/min

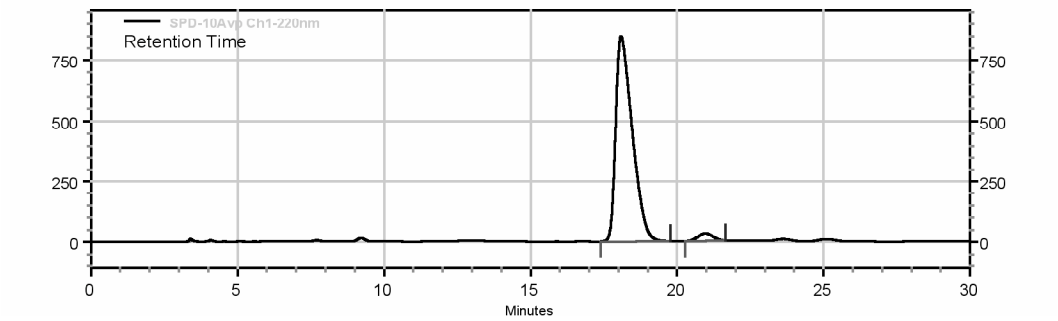
Racemate:



SPD-10Avp Ch1-220nm Results

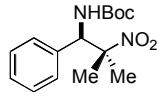
Retention Time	Area	Area Percent
18.517	6610964	50.100
21.467	6584459	49.900
Totals	13195423	100.000

Enantioenriched:



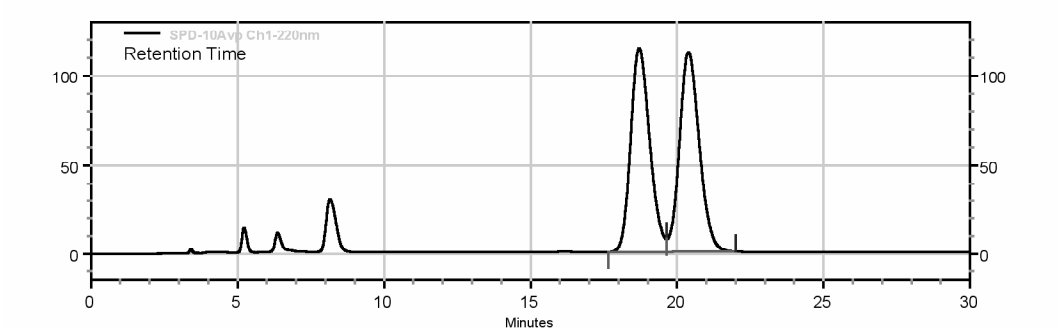
SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
18.092	33335953	96.574
20.967	1182590	3.426
Totals	34518543	100.000



6c **Chiral HPLC: Chiralcel AD, 1% isopropanol:hexanes, 1 mL/min**

Racemate:

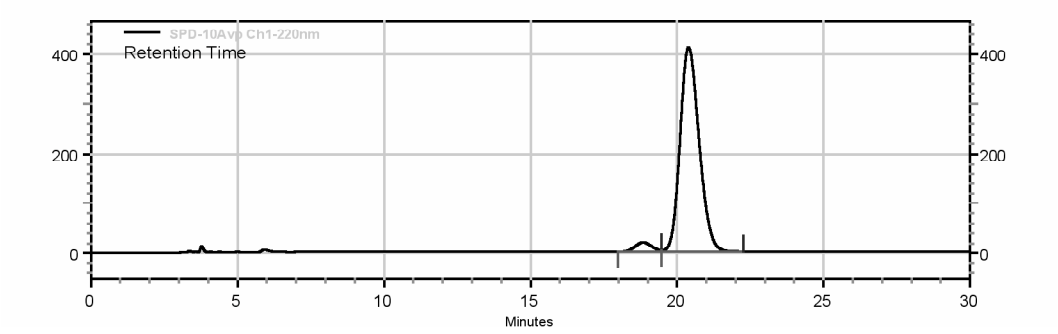


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
18.708	5175720	49.529
20.392	5274205	50.471

Totals	10449925	100.000

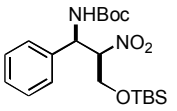
Eantioenriched:



SPD-10Avp Ch1-220nm Results

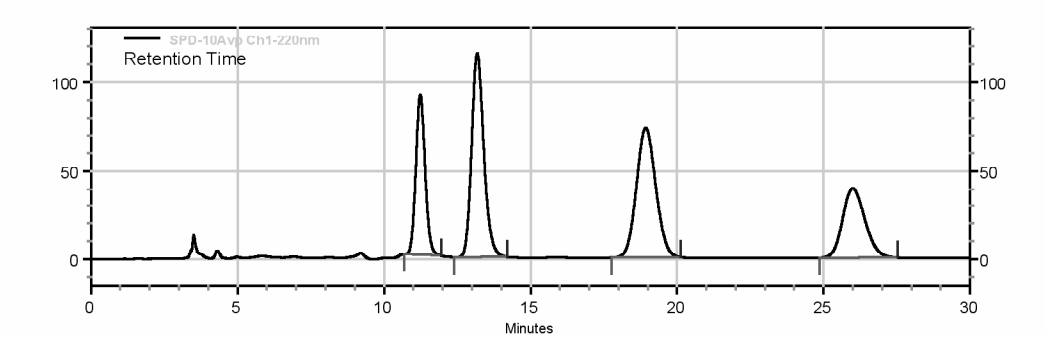
Retention Time	Area	Area Percent
18.842	765797	3.964
20.392	18554437	96.036

Totals	19320234	100.000



6d **Chiral HPLC: Chiralcel AD, 2% isopropanol:hexanes, 1 mL/min**

Racemate:

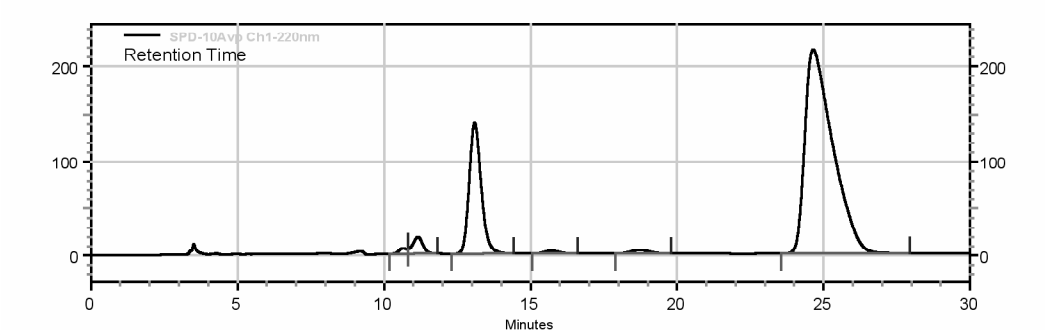


SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
11.233	1991005	18.499
13.183	3333326	30.971
18.933	3361033	31.228
26.000	2077384	19.302

Totals		
	10762748	100.000

Enantioenriched:



SPD-10Avp Ch1-220nm Results

Retention Time	Area	Area Percent
10.650	108562	0.567
11.158	441236	2.304
13.092	3980911	20.783
15.700	103704	0.541
18.717	166843	0.871
24.642	14353607	74.935

Totals		
	19154863	100.000