One-Pot Asymmetric Synthesis of β -Cyanohydroxymethyl α -Amino Acid Derivatives: Formation of Three Contiguous Stereogenic Centers

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Supporting Information

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. 5-(*tert*-Butyldimethylsiloxy)-1-pentanal was prepared from 5-hexen-1-ol according to Brosius *et al.*¹ For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25g), Ce(SO₄)₂•H₂O (10g), conc. H₂SO₄ (60 mL), and H₂O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H₂SO₄ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). ¹H NMR and ¹³C NMR spectra were recorded on Bruker DRX 600, DRX 500 and AMX 400 instruments. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in CDCl₃ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ¹H NMR, and CDCl₃ was used as internal standard (δ = 77.0) for ¹³C NMR. High-resolution mass spectra were recorded on an Ion Spec Fourier Transform Mass Spectrometer using dihydrobenzoic acid (DHB) as the matrix. HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-Detector, and a L-6200A Intelligent Pump. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter (λ = 589 nm, 1dm cell).

General procedure for the tandem asymmetric Mannich-cyanization reaction between *N*-PMP-protected α -imino ethyl glyoxylate, aldehyde donors and diethylaluminum cyanide: In a typical experiment, *N*-PMP-protected α -imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous THF (5 mL) and the corresponding aldehyde donor (1.0 mmol) was added, followed by L-proline (0.15 mmol). After stirring for overnight (16-20 h) at room temperature, diethylaluminum cyanide (1 M in toluene) (2 mmol) was added at -78 °C and the solution was stirred as shown in Table 1, 2 and 3. The mixture was worked with saturated NaHCO₃ solution and extracted with ethyl acetate. The organic layers were combined, dried over MgSO₄, filtered, and concentrated. Column chromatography (silica gel, hexanes/ethyl acetate mixtures) afforded the corresponding cyanohydrin product. The ee was determined by chiral phase HPLC analysis.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyanohydroxymethyl]-2-(*p*-methoxyphenylamino)-hexanoate (**1a**):

¹H NMR (600 MHz): δ = 0.96 (t, 3H, CH₂CH₃), 1.26 (t, 3H, OCH₂CH₃), 1.42-1.55 (m, 2H), 1.55-1.64 (m, 1H), 1.66-1.75 (m, 1H), 2.38 (bs, 1H), 3.74 (s, 3H, OCH₃), 4.10-4.25 (m, 4H), 4.80 (bs, 1H, CHCN), 6.71 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.78 (d, 2H, *J* = 8.8 Hz, Ar*H*); ¹³C NMR (150 MHz): δ = 172.6, 153.5, 139.8, 118.8, 116.8, 114.6, 62.7, 61.6, 59.5, 55.3, 44.0, 27.3, 20.6, 13.9, 13.7;

HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm); *t_R* (major) = 11.15 min; *t_R* (minor) = 13.71 min; 93% ee; [α]_D = -14.0 (*c* = 2.0, CHCl₃); HRMS (MALDI): Calcd for C₁₇H₂₄N₂O₄ (M+H⁺): 321.1809, found: 321.1802.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyanohydroxymethyl]-2-(*p*-methoxyphenylamino)-4-methyl-pentanoate (**1b**):

¹H NMR (500 MHz): δ = 1.10 (d, 3H, *J* = 5.5 Hz, CHCH₃), 1.16 (d, 3H, *J* = 5.1 Hz, CHCH₃), 1.28 (t, 3H, OCH₂CH₃), 2.18 (bs, 2H), 3.74 (s, 3H, OCH₃), 4.22 (q, 2H, OCH₂CH₃), 4.39 (bs, 1H, CHNHPMP), 4.87 (bs, 1H,

(1) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am Chem. Soc.* **1999**, *121*, 700-709.

CHCN), 6.70 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.79 (d, 2H, $J = 8.8$ Hz, *ArH*); ^{13}C NMR (125 MHz): $\delta = 173.4, 153.4, 139.9, 119.2, 116.4, 114.8, 61.6, 61.2, 57.8, 55.6, 50.7, 26.3, 21.4, 20.7, 13.9$;
HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm); t_{R} (major) = 8.32 min; t_{R} (minor) = 12.59 min; 94% ee; $[\alpha]_{\text{D}} = -13.3$ ($c = 2.5$, CHCl_3); HRMS (MALDI): Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 321.1809, found: 321.1811.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyano-hydroxymethyl]-2-(*p*-methoxyphenylamino)-heptanoate (1c):

^1H NMR (400 MHz): $\delta = 0.93$ (t, 3H, CH_2CH_3), 1.27 (t, 3H, OCH_2CH_3), 1.30-1.50 (m, 4H), 1.55-1.70 (m, 2H), 2.35-2.42 (m, 1H), 3.74 (s, 3H, OCH_3), 4.10-4.25 (m, 4H), 4.83 (d, 1H, *CHCN*), 6.72 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.79 (d, 2H, $J = 8.8$ Hz, *ArH*); ^{13}C NMR (100 MHz): $\delta = 172.7, 153.9, 139.9, 118.8, 117.2, 114.8, 63.2, 61.8, 59.9, 55.6, 44.4, 29.7, 25.5, 22.7, 14.0, 13.7$;
HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm); t_{R} (major) = 10.35 min; t_{R} (minor) = 13.11 min; 93% ee; HRMS (MALDI): Calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 335.1965, found: 335.1963.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyano-hydroxymethyl]-2-(*p*-methoxyphenylamino)-octanoate (1d):

^1H NMR (500 MHz): $\delta = 0.91$ (t, 3H, CH_2CH_3), 1.27 (t, 3H, OCH_2CH_3), 1.30-1.40 (m, 4H), 1.40-1.52 (m, 2H), 1.55-1.68 (m, 1H), 1.70-1.82 (m, 1H), 2.37-2.42 (m, 1H), 3.75 (s, 3H, OCH_3), 4.10-4.25 (m, 4H), 4.85 (d, 1H, *CHCN*), 6.73 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.79 (d, 2H, $J = 8.8$ Hz, *ArH*); ^{13}C NMR (125 MHz): $\delta = 172.7, 153.9, 139.9, 118.9, 117.3, 114.8, 63.2, 61.8, 60.1, 55.6, 44.4, 31.8, 27.3, 25.7, 22.3, 14.0, 13.9$;
HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm); t_{R} (major) = 10.15 min; t_{R} (minor) = 13.14 min; 98% ee; $[\alpha]_{\text{D}} = -12.5$ ($c = 1.3$, CHCl_3); HRMS (MALDI): Calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 349.2122, found: 349.2111.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyano-hydroxymethyl]-2-(*p*-methoxyphenylamino)-nonanoate (1e):

^1H NMR (500 MHz): $\delta = 0.90$ (t, 3H, CH_2CH_3), 1.22-1.38 (m, 9H), 1.39-1.50 (m, 2H), 1.55-1.68 (m, 1H), 1.70-1.80 (m, 1H), 2.37-2.42 (m, 1H), 3.45 (s, 3H, OCH_3), 4.10-4.25 (m, 4H), 4.85 (d, 1H, *CHCN*), 6.73 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.79 (d, 2H, $J = 8.8$ Hz, *ArH*); ^{13}C NMR (125 MHz): $\delta = 173.0, 154.5, 140.2, 119.2, 117.9, 115.3, 63.9, 62.4, 60.8, 56.1, 44.8, 31.9, 29.8, 28.1, 26.2, 23.0, 14.49, 14.47$;
HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm); t_{R} (major) = 10.96 min; t_{R} (minor) = 14.12 min; 98% ee; $[\alpha]_{\text{D}} = -19.8$ ($c = 0.8$, CHCl_3); HRMS (MALDI): Calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 363.2278, found: 363.2264.

Ethyl (2*S*,3*S*,4*R*)-4-cyano-4-hydroxy-2-(*p*-methoxyphenylamino)-3-phenylmethyl-butanoate (1f):

^1H NMR (400 MHz) $\delta = 1.25$ (t, 3H, OCH_2CH_3), 2.62-2.69 (m, 1H), 3.02 (d, 2H, PhCH_2), 3.70 (s, 3H, OCH_3), 4.01-4.17 (m, 3H), 4.78 (bd, 1H, *CHCN*), 6.47 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.69 (d, 2H, $J = 8.8$ Hz, *ArH*), 7.23-7.40 (m, 5H, *ArH*); ^{13}C NMR (125 MHz): $\delta = 172.8, 153.9, 139.9, 138.2, 129.6, 129.0, 127.3, 119.0, 116.9, 115.1, 62.8, 62.3, 58.4, 55.9, 47.3, 32.5, 14.3$;
HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm); t_{R} (major) = 16.54 min; t_{R} (minor) = 19.06 min; >99% ee; $[\alpha]_{\text{D}} = -0.6$ ($c = 3.0$, CHCl_3); HRMS (MALDI): Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 369.1809, found: 369.1805.

E t h y l (2*S*,3*S*)-6-*tert*-butyldimethylsilyloxy-3-[(*R*)-cyano-hydroxymethyl]-2-(*p*-methoxyphenylamino)-hexanoate (1g):

^1H NMR (600 MHz): $\delta = 0.08$ (s, 6H, $\text{Si}(\text{CH}_3)_2$), 0.91 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 1.26 (t, 3H, OCH_2CH_3), 1.68-1.82 (m, 4H), 2.48 (bs, 1H), 3.60-3.70 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 4.15-4.25 (m, 3H), 4.81 (bd, 1H, *CHCN*), 6.72 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.78 (d, 2H, $J = 8.8$ Hz, *ArH*); ^{13}C NMR (150 MHz): $\delta = 173.5, 154.8, 140.9, 119.9, 118.1, 115.7, 64.3, 63.9, 62.7, 61.1, 56.5, 45.3, 31.3, 26.8, 23.7, 19.2, 15.0, -4.5$;
HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, $\lambda = 254$ nm); t_{R} (major) = 8.85 min; t_{R} (minor) = 10.51 min; >99% ee; $[\alpha]_{\text{D}} = -1.4$ ($c = 1.65$, CHCl_3); HRMS (MALDI): Calcd for $\text{C}_{23}\text{H}_{38}\text{N}_2\text{O}_5\text{Si}$ ($\text{M}+\text{H}^+$): 451.2623, found: 451.2631.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyanohydroxymethyl]-2-(*p*-methoxyphenylamino)-undec-5-enoate (1h**):**

¹H NMR (500 MHz) δ = 0.89 (t, 3H, CH₂CH₃), 1.22-1.42 (m, 9H), 1.95-2.07 (m, 2H), 2.42 (bs, 3H), 3.74 (s, 3H, OCH₃), 4.10-4.25 (m, 4H), 4.81 (bd, 1H, CHCN), 5.40-5.48 (m, 1H), 5.62-5.70 (m, 1H), 6.69 (d, 2H, *J* = 8.8 Hz, *ArH*), 6.78 (d, 2H, *J* = 8.8 Hz, *ArH*); ¹³C NMR (125 MHz): δ = 172.6, 153.7, 139.9, 135.3, 125.4, 118.8, 116.9, 114.8, 62.7, 61.8, 59.2, 55.6, 44.8, 32.5, 31.4, 29.5, 28.9, 22.5, 14.0;

HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 98:2, flow rate 1.0 mL/min, λ = 254 nm); *t_R* (major) = 8.80 min; *t_R* (minor) = 12.00 min; >99% ee; [α]_D = -19.8 (*c* = 2.5, CHCl₂); HRMS (MALDI): Calcd for C₂₂H₃₂N₂O₄ (M+H⁺): 389.2435278, found: 389.2429.

(2*S*,3*S*,4*R*)-4-Cyano-2-(*p*-methoxyphenylamino)-3-propyl-4-butanolide (2a**):**

¹H NMR (500 MHz) δ 1.05 (t, 3 H, CH₂CH₃), 1.40-1.60 (m, 2 H), 1.80-1.90 (m, 1 H), 1.97-2.07 (m, 1 H), 2.65-2.75 (m, 1 H), 3.83 (s, 3 H, OCH₃), 4.11 (d, 1 H, *J* = 11.8 Hz, NHCH), 5.27 (d, 1 H, *J* = 7.7 Hz, NCCH), 6.76 (d, 2H, *J* = 8.8 Hz, *ArH*), 6.87 (d, 2H, *J* = 8.8 Hz, *ArH*); ¹³C NMR (125 MHz): δ = 173.9, 153.6, 139.5, 115.9, 114.9, 114.0, 67.0, 57.9, 55.6, 45.0, 31.4, 20.2, 13.9;

HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm); *t_R* (major) = 15.24 min; *t_R* (minor) = 20.19 min; HRMS (MALDI): Calcd for C₁₅H₁₈N₂O₃ (M⁺): 274.1312, found: 274.1311.

(2*S*,3*S*,4*R*)-4-Cyano-2-(*p*-methoxyphenylamino)-3-(1-methylethyl)-4-butanolide (2b**):**

¹H NMR (500 MHz) δ 1.02 (t, 3 H, CHCH₃), 1.10 (t, 3 H, CHCH₃), 2.10-2.20 (m, 1 H), 2.27-2.37 (m, 1 H), 3.68 (bd, 1 H), 3.75 (s, 3 H, OCH₃), 4.11 (m, 1 H, NHCH), 5.15 (d, 1 H, *J* = 8.1 Hz, NCCH), 6.66 (d, 2H, *J* = 8.8 Hz, *ArH*), 6.80 (d, 2H, *J* = 8.8 Hz, *ArH*); ¹³C NMR (125 MHz): δ = 174.5, 153.4, 139.2, 115.6, 114.9, 114.5, 66.8, 57.4, 55.6, 50.2, 30.3, 20.9, 20.5;

HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm); *t_R* (major) = 37.02 min; *t_R* (minor) = 49.87 min; HRMS (MALDI): Calcd for C₁₅H₁₈N₂O₃ (M⁺): 274.1312, found: 274.1313.

(2*S*,3*S*,4*R*)-3-Butyl-4-cyano-2-(*p*-methoxyphenylamino)-4-butanolide (2c**):**

¹H NMR (600 MHz) δ 0.90 (t, 3 H, CH₂CH₃), 1.35-1.40 (m, 5 H), 1.72-1.82 (m, 1 H), 1.90-1.98 (m, 1 H), 2.55-2.65 (m, 1 H), 3.74 (s, 3 H, OCH₃), 3.78 (bs, 1 H), 4.02 (d, 1 H, *J* = 11.8 Hz, NHCH), 5.16 (d, 1 H, *J* = 7.9 Hz, NCCH), 6.67 (d, 2H, *J* = 8.8 Hz, *ArH*), 6.79 (d, 2H, *J* = 8.8 Hz, *ArH*); ¹³C NMR (150 MHz): δ = 174.0, 153.6, 139.5, 115.9, 114.9, 114.1, 67.0, 57.9, 55.6, 45.0, 29.1, 28.9, 22.5, 13.6;

HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm); *t_R* (major) = 13.74 min; *t_R* (minor) = 19.96 min; HRMS (MALDI): Calcd for C₁₆H₂₀N₂O₃ (M⁺): 288.1468, found: 288.1468.

Transformation of **1b to **2b**:** To a solution of **1b** (46.0 mg, 0.14 mmol) in THF (2 mL), diethylaluminium cyanide (1 M in toluene, 0.43 mL) was added at 0 °C and the mixture was stirred at the same temperature for 1 h and at room temperature for 3 h. The mixture was added to saturated NaHCO₃ solution and extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered, concentrated. Purification by column chromatography (silica gel, hexanes/ethyl acetate = 3:1) afforded **2b** (29.0 mg, 75%).

1f

1f

350 mS ROESY spectrum