Supplementary material

A CONCISE ENANTIOSELECTIVE SYNTHESIS OF NATURALLY ACTIVE (*S*)-3-HYDROXYPIPERIDINE

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Contents	S1
General methods	S2
Experimental Section	S3-S9
¹ H & ¹³ C NMR SPECTRA	S10-S17

General Methods:

Unless otherwise stated, all the chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical Thin Layer Chromatography was done on pre-coated silica gel plates (Kieselgel 60F₂₅₄, Merck). Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. IR spectra were recorded on a Thermo Scientific– Nicolet 380 FT-IR and absorption is expressed in cm⁻¹. ¹H NMR and ¹³C NMR spectra were recorded on Bruker AC-200 spectrometer unless mentioned otherwise. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer. Purification was carried out using column chromatography (60–120 mesh). Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a suitable chiral column. All chemical shifts were reported in ppm downfield to TMS and peak multiplicities were referred to as singlet (s), doublet (d), quartet (q) and multiplet (m).

Experimental Section

Pent-4-enoic acid (7)

A mixture of allylic alcohol 6 (10 g, 58.13 mmol), triethyl orthoacetate (29 mL, 58.13 mmol) and hexanoic acid (0.363 mL, 1.85 mmol) was placed in a round-bottomed flask equipped with thermometer, Claisen head and condenser. The solution was heated simultaneously with distillation of ethanol (upto 70-150 °C). After 3 h, distillation of ethanol slowed and another 0.1 mL portion of hexanoic acid was added. Additional portions (0.1 mL) of hexanoic acid were added again after 3 and 4 h, followed by continued heating for the next 6 h. It was allowed to cool to RT and aq. solution of KOH (6.5 g, 116.32 mmol, 20 mL) in MeOH (80 mL) was added. The resulting mixture was refluxed for 4 h and then allowed to cool to room temperature. The resulting solution was then washed with diethyl ether and acidified with aq. dil. HCl. The acidic solution was extracted with diethyl ether and the organic layer dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude product 7 (13.79 g, 80%). The crude material can be used as such for the next reaction without any further purification.

Yield: 13.7g; 80%; colorless liquid; IR (CHCl₃, cm⁻¹): $\nu_{\max}$ 1291, 1711, 2932, 2967, 3083; ¹H NMR (200 MHz, CDCl₃): δ 2.34-2.51 (m, 4H), 4.99-5.12 (m, 2H), 5.73-5.93 (m, 1H), 10.84 (br s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 28.4, 33.3, 115.1, 136.2, 179.9; Anal. Calcd for C₅H₈O₂ requires C, 59.98; H, 8.05; found: C, 59.95; H, 8.03%.

5-(iodomethyl)dihydrofuran-2(3H)-one (8)

To a solution of olefinic acid 7 (13 g, 130 mmol) in acetonitrile (20 mL), solid I₂ (22 g, 416 mmol) was added at 0 °C under N₂ atmosphere. The reaction mixture was protected from light and stirred for 24 h. After the completion of the reaction (monitored by TLC), it was quenched with the addition of saturated solution of aq. NaHCO₃ followed by extraction with diethyl ether. Organic layer was separated and washed with 20% aq. Na₂S₂O₃ until colorless, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude product, which on column chromatographic purification with silica gel using petroleum ether:ethyl acetate (8:2) as eluent gave 8 in pure form.

Yield: 24.97g; 85%; gum; ^1H NMR (200 MHz, MeOH-d_4): δ 1.29 (m, 1H), 1.64 (m, 2H), 2.27 (d, $J = 13.4$ Hz, 1H), 2.45 (m, 2H), 2.61 (dd, $J = 7.0$ and 13.1 Hz, 1H), 2.94-3.01 (m, 2H), 3.53 (s, 1H); ^{13}C NMR (50 MHz, MeOH-d_4): δ 7.7, 27.8, 28.5, 78.0, 175.7; Anal. Calcd for $\text{C}_5\text{H}_7\text{IO}_2$ requires C, 26.57; H, 3.12; found: C, 26.56; H, 3.10%.

Methyl -3-(oxiran-2-yl)propanoate (9)

To a solution of iodolactone 62 (23 g, 110.6 mmol) in MeOH (50 mL), finely powdered anhydrous Na_2CO_3 (11.86 g, 111.8 mmol) was added and the reaction mixture refluxed for 8 h under N_2 atmosphere. After the completion of the reaction (monitored by TLC), the resulting reaction mixture was concentrated under reduced pressure and partitioned between 50 mL water and 50 mL diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the corresponding crude product, which on column chromatographic purification with silica gel using petroleum ether:ethyl acetate (9:1) as eluent gave 9 in pure form.

Yield: 9.26g; 70%; colorless liquid; IR (CHCl_3 , cm^{-1}): ν_{max} 920, 1290, 1737, 1963; ^1H NMR (200 MHz, CDCl_3): δ 1.69-1.86 (m, 1H), 1.91-2.08 (m, 1H), 2.44-2.53 (m, 3H), 2.75-2.79 (t, $J = 4.2$ Hz, 1H), 2.95-3.03 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 27.5, 30.1, 46.9, 51.1, 51.6, 173.2; Anal. Calcd for $\text{C}_6\text{H}_{10}\text{O}_3$ requires C, 55.37; H, 7.75; found: C, 55.35; H, 7.71%.

Hydrolytic Kinetic Resolution of 3-substituted epoxy ester (9)

To a solution of (*R, R*)-(salen)Co(II)complex (0.024 mmol, 0.5 mol %) in toluene (1 mL), AcOH (0.014 g, 0.24 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min during which time the color changed from orange-red to a dark brown. It was then concentrated under reduced pressure to get the (*S, S*)-(salen)Co(III)-salen complex as brown colored solid. To this, racemic epoxy ester ($\pm$)-9 (7 g, 60.3 mmol) and H_2O (0.543 g, 30.2 mmol) were added at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. After completion of reaction (monitored by TLC), the crude product was extracted purified by column chromatography over silica gel to give chiral epoxy ester 10 [solvent system; petroleum ether:ethyl acetate (9:1)] and chiral γ -butyrolactone 11 [solvent system; petroleum ether:ethyl acetate (1:1)] in pure form.

(R)-methyl-3-(oxiran-2-yl)propanoate (10)

Yield: 50%; colorless liquid; $[\alpha]_{\text{D}}^{25} +17.5$ (*c* 1, CHCl₃); {lit.^{14c} $[\alpha]_{\text{D}}^{25} +17.9$ (*c* 7.4, CHCl₃)};

Optical purity: The optical purity of epoxide 10 was found to 98%, based on comparison of its specific rotation with the reported value.

(S)-5-(hydroxymethyl)dihydrofuran-2-(3H)-one (11)

Yield: 48%; colorless liquid; $[\alpha]_{\text{D}}^{25} +51.8$ (*c* 1, CHCl₃) {lit.^{14d} $[\alpha]_{\text{D}}^{25} +53.5$ (*c* 3.17, CHCl₃)};

Optical purity: The optical purity of lactone 11 was found to 97%, based on comparison of its specific rotation with the reported value; IR (CHCl₃, cm⁻¹): ν_{max} 1045, 1620, 2934, 2109, 3438; ¹H NMR (200 MHz, CDCl₃): δ 2.13-2.36 (m, 1H), 2.43-2.64 (m, 2H), 2.79-2.85 (t, *J* = 5.8 Hz, 1H), 3.58-3.68 (m, 1H), 3.87-3.94 (m, 1H) 4.57-4.68 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 23.0, 28.5, 63.7, 177.9; Anal. Calcd for C₅H₈O₃ requires C, 51.72; H, 6.94; found: C, 51.75; H, 6.93%.

(S)-(5-oxotetrahydrofuran-2-yl)methyl methanesulfonate (12)

To a stirred solution of lactone 11 (3 g, 25.86 mmol) and triethylamine (5.4 mL, 38.79 mmol) in CH₂Cl₂ (20 mL), mesyl chloride (2.4 mL, 31.03 mmol) was added at 0 °C under N₂ atmosphere. The resulting solution was stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude mesylate 12. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (7:3) as eluent gave 12 in pure form.

Yield: 4.7g; 92%; colorless liquid; $[\alpha]_{\text{D}}^{25} +33.5$ (*c* 1, CHCl₃); IR (CHCl₃, cm⁻¹): ν_{max} 938, 1035, 1090, 1150, 1789; ¹H NMR (200 MHz, CDCl₃): δ 2.10-2.21 (m, 1H), 2.31-2.49 (m, 1H), 2.56-2.66 (m, 2H), 3.08 (s, 3H), 4.26-4.47 (m, 2H) 4.73-4.84 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 23.1, 27.8, 37.4, 70.0, 77.6, 176.1; Anal. Calcd for C₆H₁₀O₅S requires C, 37.11; H, 5.19; found: C, 37.10; H, 5.13%.

(S)-5-(azidomethyl)dihydrofuran-2-(3H)-one (13)

To a stirred mixture of mesylate 12 (3 g, 15.44 mmol) in DMF (15 mL) was added sodium azide (1.25 g, 18.52 mmol). The reaction mixture was stirred for 8 h at 80 °C. After completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na₂SO₄. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone, which was purified by column chromatography with silica gel using petroleum ether:ethyl acetate (8:2) as eluent to give pure azide 13.

Yield: 2g; 95%; pale yellow oil; $[\alpha]_D^{25} +91.7$ (*c* 1, CHCl₃); IR (CHCl₃, cm⁻¹): $\nu_{\max}$ 930, 1040, 1291, 1789, 2105; ¹H NMR (200 MHz, CDCl₃): δ 2.03-2.11 (m, 1H), 2.31-2.37 (m, 1H), 2.55-2.63 (m, 2H), 3.45-3.49 (dd, *J* = 4.8 and 12.9 Hz, 1H), 3.59-3.63 (dd, *J* = 3.9 and 13.1 Hz, 1H), 4.63-4.69 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 24.5, 28.1, 54.0, 77.8, 175.9; Anal. Calcd for C₅H₇N₃O requires C, 42.55; H, 5.00; found: C, 42.53; H, 5.03%.

3-azidopropan-1-ol (17)

To a stirred solution of 1,3-propanediol 15 (5 g, 65.71 mmol) and triethylamine (13.8 mL, 98.56 mmol) in CH₂Cl₂ (100 mL), mesyl chloride (6.1 mL, 31.03 mmol) was added at 0 °C under N₂ atmosphere. The resulting solution was stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude mesylate 16, which was without further purification kept for next reaction.

To a stirred solution of crude mesylate 16 in DMF (100 mL) was added sodium azide (25.6 mL, 394.26 mmol). The reaction mixture was stirred for 8 h at 80 °C. After completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na₂SO₄. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone, which was purified by column chromatography with silica gel using petroleum ether:ethyl acetate (8:2) as eluent to give pure azido alcohol 17.

Yield: 7.6 g; 70%; colourless oil; ^1H NMR (200 MHz, CDCl_3): δ 1.68(bris, 1H), 1.79-1.87 (m, 2H), 3.45 (t, 2H, $J = 6.6$ Hz), 3.76 (t, 2H, $J = 6.0$ Hz); ^{13}C NMR (50 MHz, CDCl_3): 31.3, 48.2, 59.4; Anal. Calcd for $\text{C}_3\text{H}_7\text{N}_3\text{O}$ requires C 35.64; H 6.98; N 41.56%; found C 35.68; H 6.92; N 41.66%.

3-azidopropanal (18)

To a stirred solution of 3-azidopropanol 17 (4 g, 39.56 mmol) in CH_2Cl_2 (100 mL) was added pyridium chloroformate (PCC) (17 g, 79.12 mmol). The reaction was stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered over Celite (CH_2Cl_2 elute) and the filtrate was concentrated under reduced pressure, which was then purified by column chromatography using petroleum ether:ethyl acetate (9:1) as eluent to obtain pure aldehyde 18 (3.8 g, 98%).

Yield: 3.8 g; 98%; colourless liquid; ^1H NMR (200 MHz, CDCl_3): δ 1.79-1.87 (m, 2H), 3.42 (t, 2H, $J = 6.6$ Hz), 3.52 (t, 2H, $J = 6.0$ Hz); ^{13}C NMR (50 MHz, CDCl_3): 31.3, 46.5, 49.4; Anal. Calcd for $\text{C}_3\text{H}_5\text{N}_3\text{O}$ requires C 36.36; H 5.09; N 42.41%; found C 36.29; H 5.14; N 42.46%.

(S)-5-Hydroxypiperidin-2-one (14)

From HKR route:

To a solution of azide 13 (1.5 g, 10.62 mmol) in dry MeOH was added 20% $\text{Pd}(\text{OH})_2$ (0.037 g, 0.53 mmol) and the reaction mixture was stirred under an atmosphere of H_2 (1 atm) for 24 h at 25 °C. After completion of the reaction (monitored by TLC), the catalyst was filtered over Celite and the filtrate concentrated under reduced pressure to provide crude hydroxylactam, which was purified by column chromatography using ethyl acetate:methanol (9:1) as eluent to obtain pure hydroxylactam 14 (1.19 g, 98%).

From Organocatalytic route:

To a pre-cooled solution of aldehyde 18 (3 g, 30.27 mmol) in CH_3CN (100 mL) at -20 °C, nitrosobenzene (3.4 g, 30.27 mmol) and L-proline (0.64 g, 6.0 mmol) were added. The reaction was then stirred at -20 °C for 24 h, followed by the addition triethyl phosphono

acetate (10.1 g, 45.4 mmol), DBU (6.9 g, 45.4 mmol) and LiCl (1.4 g, 33.29 mmol) at 0 °C for 2 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of ammonium chloride. Then solvent was evaporated and organic layer was extracted with EtOAc (3x50 mL). The combined EtOAc layers were dried over anhyd. Na₂SO₄, concentrated to give the crude γ -aminooxy- α,β -unsaturated ester A, which was directly used for the next step without purification.

To a stirred solution of crude γ -aminooxy- α,β -unsaturated ester A in MeOH (50 mL) was added 10% Pd/C (0.16 g, 1.51 mmol) under H₂ (1 atm) at 25 °C. The reaction mixture was stirred for 2 h at the same temperature. After completion of reaction (monitored by TLC), it was filtered through Celite (EtOAc eluent) and the solvent was evaporated under reduced pressure to afford the crude compound, which purified by column chromatography using ethyl acetate:methanol (9:1) as eluent to obtain pure hydroxylactam 14 (2.2 g, 65%).

Yield: 2.2 g, 65%; $[\alpha]_D^{25}$ -13.3 (*c* 1, MeOH) {lit.^{4a} $[\alpha]_D^{25}$ -12.4 (*c* 0.5, MeOH)}; IR (CHCl₃, cm⁻¹): $\nu_{\max}$ 1636, 1652, 3439; ¹H NMR (200 MHz, MeOH-d₄): δ 1.72-1.87 (m, 2H), 2.12-2.27 (m, 1H), 2.32-2.49 (m, 1H), 3.03-3.12 (dd, *J* = 4.8 and 12.7 Hz, 1H), 3.20-3.22 (m, 1H), 3.27-3.35 (dd, *J* = 3.9 and 12.7 Hz, 1H), 3.92-4.01 (m, 1H); ¹³C NMR (50 MHz, MeOH-d₄): δ 28.1, 28.8, 49.4, 63.8, 174.5; Anal. Calcd for C₅H₉NO₂ requires C, 52.16; H, 7.88; found: C, 52.15; H, 7.85%.

(S)-Piperidin-3-ol (1)

To a solution of lactam 14 (1.2 g, 10.43 mmol) in dry THF (20 mL), BH₃.SMe₂ (0.95 mL, 8.68 mmol) was added dropwise at 0 °C under N₂ atmosphere and the mixture was then refluxed for 6 h. After the reduction was complete (monitored by TLC). THF was removed under reduced pressure to give the crude product, which was purified by column chromatography with silica gel using petroleum ether:ethyl acetate (6:4) as eluent to give pure 1.

Yield: 0.91g; 85%; viscous liquid; $[\alpha]_D^{25}$ -7.3 (*c* 1.3, MeOH); {lit.^{4a} $[\alpha]_D^{25}$ -7.5 (*c* 2, MeOH)}; IR (CHCl₃, cm⁻¹): $\nu_{\max}$ 1636, 1652, 3439; ¹H NMR (200 MHz, MeOH-d₄): δ 1.55-1.64 (m, 2H), 1.67-1.77 (m, 2H), 2.60-2.62 (m, 1H), 3.04-3.12 (m, 2H), 3.19-3.23 (m, 1H),

3.65-3.74(m, 1H); ^{13}C NMR (50 MHz, MeOH- d_4): δ 23.5, 32.8, 45.9, 53.3, 66.2; Anal. Calcd for $\text{C}_5\text{H}_{10}\text{NO}$ requires C, 59.37; H, 10.96; found: C, 59.33; H, 10.91%.

¹H & ¹³C NMR of 7

^1H & ^{13}C NMR of 8

^1H & ^{13}C NMR of 9

^1H & ^{13}C NMR of 11

^1H & ^{13}C NMR of 12

^1H & ^{13}C NMR of 13

^1H & ^{13}C NMR of 14

^1H & ^{13}C NMR of 1