Supplementary Content

Dehydrative annulation strategy for the construction of octahydroindolizine framework: A diastereoselective synthesis of (6*R*, 8*aS*)-octahydroindolizin-6-ol

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General method: All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent $\{(\text{NH}_4)_6\text{MoO}_4, \text{Ce}(\text{SO}_4)_2, \text{H}_2\text{SO}_4, \text{H}_2\text{O}\}$. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60-120 mesh). Melting points were determined using an electro thermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were recorded in CDCl_3 or $\text{DMSO}-d_6$ (all with TMS as internal standard) on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on an HP-5989A quadrupole mass spectrometer.

Preparation of (S)-N,N-dibenzyl-1-(oxiran-2-yl)-methanamine (3):

Epichlorohydrin (105.5 g, 1.1405 mmol) was added to dibenzylamine (75 g, 0.3801 mmol) and the reaction mass was stirred at 25-30 °C over a period of 16-18 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the excess of epichlorohydrin was distilled out at 50 °C under a reduced pressure. The crude was dissolved in isopropyl alcohol (150 ml) and cooled to 0-5 °C. To this was added potassium hydroxide (42.65 g, 0.7602 mmol) slowly and the mixture was stirred at 0-5 °C over a period of 1 h under nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was diluted with ethyl acetate (750 mL), washed with DM water (2 x 500 mL) followed by brine solution (750 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford 92 g of the compound 3.

Spectral data: Colorless oil; Yield: 95%; $[\alpha]_D^{25} = +10.41^\circ$ (c 1.0, CHCl_3); IR: 3027, 2796, 1631, 1474, 1453, 1131, 743, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.22-7.39 (m, 10H), 3.78 (d, $J = 13.7$ Hz, 2H), 3.55 (d, $J = 13.7$ Hz, 2H), 3.06-3.08 (m, 1H), 2.75 (dd, $J = 10.3, 3.4$ Hz, 1H), 2.66 (t, $J = 4.41$ Hz, 1H), 2.40-2.41 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 139.3, 128.9, 128.5, 128.4, 128.3, 128.2, 126.9, 58.8, 55.8, 51.0, 44.9; HRMS calcd for $\text{C}_{17}\text{H}_{19}\text{NO} + \text{H}$: 254.1545, found: 254.1549.

Preparation of (R)-5-((dibenzylamino)-methyl)-dihydrofuran-2(3H)-one (5):

To a prepared solution of sodium ethoxide in ethanol [sodium metal (11.37 g, 0.474 mmol) in 200.0 ml of ethanol] was added a solution of diethyl malonate (75.92.0 g, 0.474 mmol) in anhydrous THF at 25-30 °C over a period of one hour under nitrogen atmosphere. The reaction mass was cooled to 10-20 °C and then (S)-N,N-dibenzyl-1-(oxiran-2-yl)methanamine (40.0 g, 0.158 mmol) was added in portion wise over a period of 30-40 minutes. The temp of reaction mass was slowly brought to 25-30 °C and the mixture was stirred for 16-18 h (progress of reaction was monitored by TLC). The pH of the reaction mixture was carefully adjusted to 5 using 5N HCl and solvents were evaporated under reduced pressure. The white suspension thus obtained was treated with DMSO (120.0 mL), water (20 mL) and lithium chloride (7.5 g) and heated at 120-130 °C for 22-24 h (progress of reaction was monitored by TLC). The reaction mass was then cooled to 25-30°C and poured into ice water. The mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with DM water (2 x 200 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product (50 gm). The crude product was purified by column chromatography over silica gel using 10% EtOAc / n-hexane to obtain 32 g of the compound **5**.

Spectral data: Colorless oil; Yield: 68.6%; $[\alpha]_D^{25} = +11.85^\circ$ (c 1.0, CHCl_3); IR: 3061, 3027, 2937, 2803, 1774, 1453, 1183, 749, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.2-7.36 (m, 10H), 4.54-4.56 (m, 1H), 3.72 (d, $J = 13.7$ Hz, 2H), 3.58 (d, $J = 13.2$ Hz, 2H), 2.72 (dd, $J = 7.8, 6.4$ Hz, 1H), 2.64 (dd, $J = 5.4, 8.3$ Hz, 1H), 2.35-2.38 (m, 2H), 2.15-2.18 (m, 1H), 1.77-1.79 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 177.1, 138.9, 128.8, 128.5, 128.4, 128.3, 128.2, 127.5, 127.5, 127.0, 79.0, 59.2, 56.7, 28.0, 25.8; HRMS Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2 + \text{H}$: 296.1651, found: 296.1645.

Preparation of (R)-5-(dibenzylamino)-4-hydroxy-N-methoxy-N-methyl pentanamide (6):

To a slurry of $\text{Me}(\text{MeO})\text{NH}.\text{HCl}$ (6.60 g, 0.068 mmol) and (R)-5-((dibenzylamino) methyl) dihydrofuran-2(3H)-one (10.0 g, 0.0338 mmol) in THF (100 mL) was added isopropyl magnesium chloride in THF (136 mL, 1.0 M, 0.135 mol) at -5 to -10 $^\circ\text{C}$ over a period of 1 h under nitrogen. The reaction mass was stirred for 30 min at -10 $^\circ\text{C}$ and quenched with 20 wt % aqueous NH_4Cl . The mixture was extracted using ethyl acetate (2 x 100 mL). The combined organic layer was collected, washed with cold water, dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue obtained was dried under high vacuum to afford the 7.4 g of amide **6**.

Spectral data: Colorless oil; Yield: 92.9%; $[\alpha]_D^{25} = -30.98^\circ$ (c 1.0, CHCl_3); IR: 3445, 2937, 2808, 1652, 1452, 751, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.23-7.34 (m, 10H), 3.81 (d, $J = 13.7$ Hz, 2H), 3.74-3.76 (m, 1H), 3.64 (s, 3H), 3.41 (d, $J = 13.2$ Hz, 2H), 3.15 (s, 3H), 2.54-2.57 (m, 2H), 2.46 (d, $J = 6.9$ Hz, 2H), 1.78-1.82 (m, 1H), 1.72 (bs, 1H), 1.52-1.54 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 174.43, 138.4, 129.0, 128.8, 128.3, 128.2, 127.3, 127.2, 66.5, 61.1, 59.4, 59.3, 58.7, 32.1, 29.1, 27.9; HRMS Calcd m/z for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_3 + \text{H}$: 357.2178, found: 357.2180.

Preparation of (R)-1-(benzyloxy)-7-((tert-butyldimethylsilyl) oxy)-8-(dibenzylamino) octan-4-one (7):

To a solution of (R)-5-(dibenzylamino)-4-hydroxy-N-methoxy-N-methyl pentanamide (5.0 g, 0.0140 mmol) in dry THF (25 mL) was added (3-(benzyloxy) propyl) magnesium chloride (45 mL, 1.0 M, 0.0418 mmol) at 0-5 °C over a period of 30 minutes under argon atmosphere. The reaction mass was aged for 28-30 h at 25-30 °C and quenched with 20 wt % aqueous NH_4Cl (50 mL). The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was collected, washed with DM water (2 x 50 mL) followed by saturated sodium chloride solution, dried over anhydrous Na_2SO_4 , filtered and concentrated to afford the 5.5 g of crude compound as a liquid. To the above crude product was added anhydrous DMF (27.5 mL), imidazole (1.67 g, 0.0245 mmol), DMAP (catalytic) and TBDMS-Cl (2.22 g, 0.0147 mmol) at 0-5 °C. The reaction mixture was allowed to warm at room temperature and stirred for 20-24 h. After completion of the reaction, the mixture was diluted with water (150 mL) and extracted with ethyl acetate (2 x 55 mL). The combined organic layer was collected, washed with water (3 x 50 mL) followed by brine, dried over anhydrous NaSO_4 , filtered and evaporated under vacuum to give the crude product, which was purified by silica gel column chromatography (10:3; hexanes/EtOAc) to afford the 3.9 g of compound **7** in as a colorless viscous liquid.

Spectral data: Colorless viscous liquid; Yield: 49.6 %, IR: 3432, 3027, 2962, 1709, 1214, 745, 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 7.18-7.34 (m, 15H), 4.49 (s, 2H), 3.77-3.78 (m, 1H), 3.63 (d, J = 13.2 Hz, 2H), 3.46 (d, J = 6.4 Hz, 2H), 3.44 (d, J = 12.8 Hz, 2H), 2.32-2.46 (m, 4H), 2.16-2.18 (m, 1H), 1.82-1.98 (m, 4H), 1.55-1.67 (m, 1H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 210.8, 139.6, 129.0, 128.3, 128.1, 127.6, 127.6, 127.5, 126.9, 77.2, 72.8, 69.4, 59.8, 58.8, 39.2, 37.1, 28.2, 25.8, 23.8, 1.0, -4.4, -4.7; HRMS Calcd m/z for $\text{C}_{35}\text{H}_{49}\text{NO}_3\text{Si}$ +H: 560.3560, found: 560.3542.

Preparation of (3R, 6S)-6-(3-hydroxypropyl) piperidin-3-ol (B):

To the solution of (R)-1-(benzyloxy)-7-((tert-butyldimethylsilyl)oxy)-8-(dibenzylamino)octan-4-one (2.5 g, 0.0044 mol) in ethanol (25 mL) was added Pd/C (0.5 g, 20 mol%) and the mixture was stirred under a hydrogen atmosphere (using a balloon filled with H₂ gas) for 10-12 h at room temp. After completion of the reaction, the mixture was filtered through Celite bed. The filtrate was collected, and evaporated to give the title compound. The free amine was converted to HCl salt by treating it with 2N HCl for 10 min, and impurities were removed by washing the solution with DCM. The aqueous layer was collected, and concentrated completely under vacuum to afford the crystalline (3S,6R)-6-(3-hydroxypropyl) piperidin-3-ol hydrochloride salt which was further recrystallized from MeOH–ether (1:10) to give a mixture of diastereomers of the title compound as a crystalline solid (0.52g, 70.8%). Treatment of the salt with 2M NaOH (1 ml) and extraction with ether (3*15 ml) followed by evaporation of ether layer afforded the free base as a liquid, which was used for the separation of two diastereomers. The two diastereomers were separated by semi preparative HPLC method by using phenomenex (Lux amylose 21.2* 250mm) 10_u column and mobile phase A being n-Hexane (0.1%, DEA) and B being IPA (0.1%, DEA), Isocrate (80:20), (A:B), flow 4 ml/min to give **B1** (yield: 220 mg, 30.98%) and **B2** (yield: 24 mg, 3.38%).

Spectral data of compound B1: Colorless oil; $[\alpha]_D^{25} = -3.11^\circ$ (c 1.0, CHCl₃); Yield: 30.98%; IR (Neat): 3698, 3584, 2935, 1559, 1216, 1053, 756 cm⁻¹; ¹H NMR (400 MHz, D₂O) δ : 4.23 (s, 1H), 3.64 (t, *J* = 6 Hz, 2H), 3.30 (d, *J* = 13.2 Hz, 1H), 3.17 (d, *J* = 13.2 Hz, 2H), 1.95-1.82 (m, 2H), 1.79-1.64 (m, 6H); ¹³C NMR (100 MHz, D₂O) δ : 64.2, 63.8, 59.4, 52.0, 32.4, 30.4, 29.8, 25.4; HRMS Calcd *m/z* for C₈H₁₇NO₂ +H: 160.1338, found: 160.1336.

Spectral data of compound B2: ¹H NMR (400 MHz, D₂O) δ : 3.89 (s, 1H), 3.43 (t, *J* = 6.0 Hz, 2H), 3.04-2.98 (m, 3H), 1.74-1.48 (m, 8H).

Preparation of (6R, 8aS)-Octahydroindolizin-6-ol (A):

To a solution of (3R, 6S)-6-(3-hydroxypropyl) piperidin-3-ol (**B-1**, 150 mg, 0.0009 mmol) in dry THF (4 mL) was added triphenyl phosphine (472 mg, 0.0018 mmol, 2 eq) and diethyl azodicarboxylate (313 mg, 0.0018 mmol, 2 eq) under argon at 0-5 °C. The reaction mass was aged for 4 h at 0-5°C and quenched with (5 mL) 20 wt % aqueous NaHCO₃. The reaction mixture was diluted with DCM (15 mL), washed with DM water (2x5 mL) followed by brine solution and dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography using (10:2) DCM/MeOH to afford 96 mg of title compound (**A**) as a viscous liquid.

Spectral data: Viscous liquid, $[\alpha]_D^{25} = -27.94^\circ$ (c 1.0, CHCl₃); Yield: 72%; IR (Neat): 3019.3, 1217.6, 1020.1, 928.6, 775.3, 669.3, 627.0; ¹H NMR (400 MHz, D₂O) δ : 4.03 (s, br, 1H), 3.63-3.50 (m, 2H), 3.40-3.18 (m, 2H), 2.85 (s, br, 1H), 2.23-2.06 (m, 5H), 1.74-1.53 (m, 3H); ¹H NMR (400 MHz, DMSO-*d*₆) δ : 4.06 (s, 1H), 3.39-3.42 (m, 3H), 2.96-3.14 (m, 3H), 1.58-2.18 (m, 8H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 65.9, 62.0, 56.4, 52.4, 26.9, 26.4, 22.9, 20.0; HRMS Calcd m/z for C₈H₁₄NO+H: 142.1232 found: 142.1236.

Table 1. NMR data of optically pure **A** and that reported^[11] for (±)-**A**.

Data generated for optically pure A	Data reported for (±)- A ^{2h[11]}
¹ HNMR (400 MHz, D ₂ O) δ: 4.03 (s, br, 1H), 3.63-3.50 (m, 2H), 3.40-3.18 (m, 2H), 2.85 (s, br, 1H), 2.23-2.06 (m, 5H), 1.74-1.53 (m, 3H); ¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ: 4.06 (s, 1H), 3.39-3.42 (m, 3H), 2.96-3.14 (m, 3H), 1.58-2.18 (m, 8H);	¹ HNMR (δ, CDCl ₃ , 300 MHz) 1.30-1.91 (overlapping, 9H, H-1, H-1, H-2, H-2, H-7, H-7, H-8, H-8, H-8a), 2.09 (dt, <i>J</i> = 9.1, 9.1 Hz, H-3), 2.15 (dd, <i>J</i> = 2.4, 11.2 Hz, 1H, H-5ax), 2.40 (br s, 1H, OH, missing after deuteration), 2.97 (dt, <i>J</i> = 2.4, 9.1 Hz, 1H, H-3), 3.07 (ddd, <i>J</i> = 2.3, 2.4, 11.2 Hz, H-5eq), 3.88 (br quintet, <i>J</i> = 2.4 Hz, 1H, H-6);
¹³ CNMR (100 MHz, DMSO- <i>d</i> ₆) δ: 65.9 (C-6), 62.0 (C-8a), 56.4 (C-5), 52.4 (C-3), 26.9 (C-7), 26.4 (C-8), 22.9 (C-1), 20.0 (C-2);	¹³ CNMR (δ, CDCl ₃ , 75 MHz) 21.4 (t, C-2), 26.4 (t, C-1 or C-8), 31.1 (t, C-1 or C-8), 31.6 (t, C-7), 54.6 (t, C-3), 59.4 (t, C-5), 64.8 (d, C-8a), 66.0 (d, C-6).