The Stereoselective Synthesis of 2-(2-hydroxyalkyl)piperidine alkaloids through Prins-Ritter reaction

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SUPPLEMENTARY CONTENT:

Commercial reagents were used without further purification, all solvents were purified by standard techniques and Infrared spectra were recorded on Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. NMR spectra were recorded in CDCl₃ on Varian Gemini 200, Bruker 300 and Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60-120 mesh) and flash chromatographic separations were carried out using 230-400 mesh, silica gel. Mass spectra were recorded on Micromass VG-7070H for EI and VG Autospec M for FABMS.

(R)-2-Hydroxypent-4-enyl-4-methylbenzenesulfonate (4): Compound **4** was synthesized by using the procedures reported in ref. 8, 9 $[\alpha]_D^{25} = -7.2$ ($c = 1.0$, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.3$ Hz, 2H), 5.79-5.70 (m, 1H), 5.13-5.07 (m, 2H), 4.01 (dd, $J = 3.0, 9.8$ Hz, 1H), 3.93-3.83 (m, 2H), 2.47 (s, 3H), 2.30-2.20 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 144.9, 132.8, 129.8, 127.8, 118.6, 72.9, 68.4, 37.3, 21.5. IR (KBr): ν 3449, 3072, 2928, 1642, 1598, 1494, 1451, 1400, 1355, 1173, 1097, 983, 817, 669 cm^{-1} . HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{O}_4\text{NaS}$: 279.0661, found: 279.0659.

((2R,4S,6R)-4-Acrylamido-6-methyl-tetrahydro-2H-pyran-2-yl)methyl-4-

methylbenzenesulfonate (5a): To a mixture of acetaldehyde (0.66 mL, 11.7 mmol) and homoallyl alcohol **4a** (2.0 g, 7.8 mmol) in acrylonitrile (20.0 mL) was added boron trifluoride etherate (0.02 mL, 0.12 mmol) slowly at 0°C. The resulting mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with sat. NaHCO_3 solution and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 , concentrated under reduced pressure and purified by column chromatography to afford the compound **5a** (1.5 g, 54%). $R_f = 0.3$ (SiO_2 , 30% EtOAc in hexane) as brown solid m.p 82-84 °C. $[\alpha]_D^{25} = -9.9$ ($c = 1.8$, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 7.78 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 6.3-6.22 (m, 1H), 6.08-5.95 (m, 1H), 5.68-5.60 (m, 1H), 5.55 (d, $J = 7.9$ Hz, 1H), 4.15-3.9 (m, 3H), 3.67-3.43 (m, 2H), 2.47 (s, 3H), 2.0-1.88 (m, 2H), 1.32-1.21 (dd, $J = 7.1, 10.4$ Hz, 2H),

1.14 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 164.9, 144.8, 132.7, 130.6, 129.7, 127.9, 126.6, 73.1, 72.4, 71.9, 45.6, 39.2, 33.3, 21.5, 21.3; IR (KBr): ν 3389, 2924, 2854, 1660, 1541, 1456, 1360, 1175, 1096, 978, 812, 667 cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{23}\text{O}_5\text{NNaS}$: 376.11891, found: 376.11826.

***N*-((2*R*,4*S*,6*R*)-2-(Iodomethyl)-6-methyl-tetrahydro-2*H*-pyran-4-yl)acrylamide (**6a**):**

A mixture of **5a** (1.5 g, 4.25 mmol) and NaI (3.2 g, 21.25 mmol) in 30 mL of acetone was stirred under reflux for 24 h. After completion, the solvent was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate and dried over Na_2SO_4 . Removal of the solvent followed by purification on silica gel column chromatography gave the compound **6a** (1.17 g, 90%) as a white solid. m.p. 87-89 $^\circ\text{C}$; $R_f = 0.3$ (SiO_2 , 30% EtOAc in hexane). $[\alpha]_D^{25} = -25.5$ ($c = 1.5$, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 6.34-6.22 (m, 1H), 6.08-5.92 (m, 1H), 5.70-5.60 (m, 1H), 5.33 (d, $J = 6.8$ Hz, 1H), 4.21-4.04 (m, 1H), 3.67-3.57 (m, 1H), 3.44-3.34 (m, 1H), 3.18 (d, $J = 5.3$ Hz, 2H), 2.23-2.15 (m, 1H), 2.0-1.90 (m, 1H), 1.24 (d, $J = 6.0$ Hz, 3H), 1.07 (dd, $J = 2.6, 12.1$ Hz, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 164.7, 130.7, 126.7, 74.9, 72.6, 45.8, 39.4, 37.7, 21.5, 9.0; IR (KBr): ν 3352, 2925, 2855, 1642, 1598, 1494, 1451, 1355, 1240, 1173, 1097, 950, 817, 669 cm^{-1} ; HRMS calcd for $\text{C}_{10}\text{H}_{17}\text{O}_2\text{NI}$ 310.02894, found: 310.02985.

***N*-((4*R*,6*R*)-6-Hydroxyhept-1-en-4-yl)acrylamide (7a):** A mixture of iodide **6a** (1.5 g, 3.72 mmol) and zinc dust (3.65 g, 55.8 mmol) in ethanol (30 mL) was stirred under reflux for 8 h. After completion, it was quenched with solid ammonium chloride (6 g) and diluted with ether (90 mL). The resulting mixture was stirred for 15 min to form a gray suspension which was then filtered through Celite. The filtrate was concentrated in vacuo and then purified by flash chromatography to give the compound **7a** (612 mg, 90%) as a colorless liquid. $R_f = 0.4$ (SiO₂, 30% EtOAc in hexane). $[\alpha]_D^{25} = -12.9$ ($c = 1.1$, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 6.26-6.20 (m, 1H), 6.08-6.0 (m, 1H), 5.78-5.66 (m, 2H), 5.64-5.59 (m, 1H), 5.10-5.02 (m, 2H), 4.21 (brd, 1H), 3.70-3.63 (m, 1H), 3.54-3.44 (m, 1H), 2.30-2.18 (m, 2H), 1.56-1.50 (m, 1H), 1.39-1.32 (m, 1H), 1.11 (d, $J = 6.2$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 166.5, 133.9, 130.2, 127.3, 118.4, 63.4, 46.0, 45.0, 39.4, 22.6; IR (KBr): ν 3280, 2924, 2853, 1657, 1545, 1440, 1409, 1317, 1149, 1067, 987, 802, 707 cm⁻¹; HRMS calcd for C₁₀H₁₈O₂N: 184.13321, found: 184.13344.

***N*-((4*R*,6*R*)-6-(tert-Butyldimethylsilyloxy)hept-1-en-4-yl)acrylamide (8a):** To a stirred solution of **7a** (625 mg, 3.4 mmol) in DCM (15 mL) were added imidazole (0.65 g, 9.4 mmol), TBSCl (1.06 g, 7.0 mmol) and catalytic amount of DMAP at 0 °C. The resulting solution was stirred at room temperature for 1 h. After completion, the mixture was quenched with sat. NH₄Cl (10 mL) and the organic layer was extracted with DCM, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane:EtOAc 7:3) to afford the compound **8a** in 95% yield (960 mg) as a pale yellow oil; $R_f = 0.7$ (EtOAc:hexane, 30%). $[\alpha]_D^{25} = -8.5$ ($c = 1.1$, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 6.30-

6.19 (m, 1H), 6.09-5.92 (m, 2H), 5.83-5.67 (m, 2H), 5.62-5.54 (m, 1H), 5.11-5.01 (m, 2H), 4.18-3.98 (m, 2H), 2.46-2.21 (m, 2H), 1.72-1.53 (m, 2H), 1.16 (d, $J = 6.2$ Hz, 3H), 0.92 (s, 9H), 0.08 (d, $J = 3.7$ Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 164.8, 134.5, 131.2, 125.9, 117.5, 66.6, 46.8, 41.8, 38.7, 25.9, 23.6, 17.9, -4.7, -4.2; IR (KBr): ν 3275, 3078, 2955, 1625, 1549, 1460, 1247, 1061, 911, 842, 665 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{31}\text{O}_2\text{NNaSi}$: 320.18598, found: 320.18535.

(R)-6-((R)-2-(tert-Butyldimethylsilyloxy)propyl)-5,6-dihydropyridin-2(1H)-one (9a):

To a stirred solution of **8a** (0.950 g, 3.2 mmol) in degassed CH_2Cl_2 (500 mL) was added bis(tricyclohexylphosphine)benzylideneruthenium dichloride (250 mg, 0.3 mmol) at room temperature under argon atmosphere. The resulting mixture was stirred for 12 h at room temperature and then the solvent was evaporated under reduced pressure. Thus residue was purified by silica gel column chromatography ($\text{EtOAc/Hexane} = 3.5:6.5$) to afford the compound **9a** (0.775 g, 90%) as a colorless semi-solid. $[\alpha]_{\text{D}}^{25} = -19.8$ ($c = 0.97$, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 6.59- 6.50 (m, 1H), 6.34 (brs, 1H), 5.87 (d, $J = 9.6$ Hz, 1H), 4.13-4.06 (m, 1H), 3.90-3.80 (m, 1H), 2.31-2.10 (m, 2H), 1.83-1.71 (m, 1H), 1.56-1.49 (m, 1H), 1.21 (d, $J = 6.2$ Hz, 3H), 0.91 (s, 9H), 0.09 (d, $J = 3.4$ Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 165.9, 140.3, 124.6, 66.3, 47.5, 43.3, 30.8, 25.7, 22.7, 17.9, -5.0, -4.5; IR (KBr): ν 3338, 2965, 2928, 1669, 1604, 1456, 1372, 1304, 1140, 950, 810, 640 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{14}\text{H}_{28}\text{O}_2\text{NSi}$: 270.18838, found: 270.18781.

(*R*)-6-((*R*)-2-(tert-Butyldimethylsilyloxy)propyl) piperidin-2-one (10a): To a stirred solution of **9a** (0.8 g, 2.97 mmol) in MeOH (15 mL) at room temperature were added a catalytic amount of Pd/C and triethylamine (0.008 mL, 0.06 mmol). The resulting mixture was stirred under H₂ atmosphere. The progress of the reaction was monitored by TLC. After completion, the mixture was filtered through a pad of celite and the solvent was evaporated to give the product **10a** (0.76 g, 95%) as a pale yellow liquid. $R_f = 0.3$ (SiO₂, 40% EtOAc in hexane). $[\alpha]_D^{25} = -13.6$ ($c = 1.0$, CHCl₃); ¹H NMR (CDCl₃ 300 MHz): δ 6.58 (brd, 1H), 4.13-4.05 (m, H), 3.67-3.58 (m, 1H), 2.40-2.30 (m, 1H), 2.28-2.19 (m, 1H), 1.93-1.34 (m, 6H), 1.20 (d, $J = 5.9$ Hz, 3H), 0.9 (s, 9H), 0.09 (d, $J = 3.9$ Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ 172.0, 66.2, 49.5, 45.0, 30.9, 29.5, 25.7, 23.0, 19.9, -4.9, -4.5; IR (KBr): ν 3210, 2935, 1669, 1558, 1413, 1261, 1082, 841 cm⁻¹. HRMS (m/z) calcd for C₁₄H₂₀O₂NSi: 272.20403, found: 272.20339.

(*R*)-6-((*R*)-2-Hydroxypropyl)piperidin-2-one (11a): To a stirred solution of **10a** (0.75 g, 2.76 mmol) in anhydrous THF (25 mL) was added TBAF (4.15 mL, 1.0 M in THF) at 0 °C. After 15 min, the mixture was brought to room temperature and then stirred it for another 5 h. After completion of the reaction, it was quenched by addition of sat. NH₄Cl (6 mL) solution, extracted with ethyl acetate (2 x 40 mL), washed with brine and dried over anhydrous Na₂SO₄. After removing the solvent, the product was purified by column chromatography to afford the pure lactam **11a** (0.41 g, 95% yield) as a pale yellow liquid. $R_f = 0.7$ (SiO₂, 5% MeOH in DCM). $[\alpha]_D^{25} = -15.0$ ($c = 0.25$, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 4.14-4.04 (m, 1H), 3.75- 3.67 (m, 1H), 2.39-2.20 (m, 2H), 1.95-1.35 (m, 6H), 1.24 (d, $J = 5.9$ Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 172.7, 64.2, 49.2, 44.2, 31.0, 29.0, 23.9, 23.3; IR (KBr): ν 3450, 3385, 2952, 1657,

1456, 1304, 1093, 1025, 764 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_8\text{H}_{16}\text{NO}_2$: 158.11756, found: 158.11710.

(-)-Sedridine (1a): To a stirred solution of lactam **11a** (0.4 g, 2.54 mmol) in 15 mL of anhydrous ether was added lithium aluminum hydride (0.115 g, 3.0 mmol) slowly and the stirring was continued under reflux for 2 h. After completion, the reaction was quenched with 14 mL of 10% NaOH solution and then extracted with ethyl acetate (3 x 40 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated in vacuo. The crude product was purified by column chromatography (91% CH_2Cl_2 , 7.6% MeOH, 1.4% NH_4OH) to afford the (-)-Sedridine **1a** (0.27 g, 76%) as a white solid. m.p. 78-80 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{25}$: -24.2 ($c = 1.0$, EtOH); Lit $[\alpha]_{\text{D}}^{25} = -25.6$ ($c = 0.95$, EtOH); ^1H NMR (CDCl_3 , 300 MHz): δ 5.68 (brd, 1H), 4.2-4.07 (m, 1H), 3.38-3.06 (m, 2H), 2.70 (td, $J = 3.7, 12.8$ Hz, 1H), 1.80-1.55 (m, 6H), 1.53-1.40 (m, 2H), 1.2 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 63.4, 54.3, 44.9, 41.9, 29.6 (2C), 23.3 (2C); IR (KBr) ν 3270, 2926, 2854, 1569, 1458, 1406, 1378, 1053, 940, 770, 652 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_8\text{H}_{18}\text{ON}$: 144.13829, found: 144.13798.

((2R,4S,6R)-4-Acrylamido-6-propyltetrahydro-2H-pyran-2-yl)methyl-4-methylbenzenesulfonate (5b):

$[\alpha]_{\text{D}}^{27} = -10.1$ ($c = 0.6$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.79 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.3$ Hz, 2H), 6.24-6.33 (m, 1H), 5.98-6.10 (m, 1H), 5.63-5.70 (m, 1H), 5.41 (brd, $J = 7.5$ Hz, 1H), 3.92- 4.15 (m, 3H), 3.56- 3.67 (m, 1H), 3.28- 3.41 (m, 1H), 1.95 (dd, $J = 4.5, 12.0$ Hz, 3H),

1.54- 1.87 (m, 3H), 0.93-1.56 (m, 5H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.7, 144.6, 132.2, 130.6, 129.5, 127.5, 126.0, 75.8, 72.8, 71.5, 45.4, 37.5, 37.1, 33.1, 21.2, 18.1, 13.7; IR (KBr) ν 3584, 3272, 2954, 1654, 1629, 1543, 1405, 1354, 1189, 1175, 974 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{19}\text{H}_{27}\text{O}_5\text{NNaS}$: 404.1500, found: 404.1502.

***N*-((2*R*,4*S*,6*R*)-2-(Iodomethyl)-6-propyltetrahydro-2*H*-pyran-4-yl)acrylamide (6b):**

$[\alpha]_{\text{D}}^{27} = -26.8$ ($c = 0.5$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.21-6.31 (m, 1H), 5.95- 6.08 (m, 1H), 4.02- 4.20 (m, 1H), 3.32- 3.52 (m, 2H), 3.17 (d, $J = 6.0$ Hz, 2H), 2.14- 2.23 (m, 1H), 1.86- 1.96 (m, 1H), 1.24- 1.63 (m, 4H), 0.97- 1.13 (m, 2H), 0.93 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.7, 130.6, 126.7, 76.2, 75.0, 45.9, 37.9, 37.7, 18.6, 13.9, 8.9; IR (KBr) ν 3271, 3074, 2948, 2854, 1626, 1543, 1428, 1240, 1143, 1049, 950, 757 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2\text{NINa}$: 360.0430, found: 360.0430.

***N*-((4*R*,6*R*)-6-Hydroxynon-1-en-4-yl)acrylamide (7b):**

$[\alpha]_{\text{D}}^{27} = -12.9$ ($c = 0.55$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.25- 6.38 (m, 1H), 6.02- 6.17 (m, 1H), 5.66-5.85 (m, 2H), 5.60 (brd, $J = 9.0$ Hz, 1H), 5.07- 5.17 (m, 2H), 4.22- 4.38 (m, 1H), 4.19 (brs, 1H), 3.47- 3.57 (m, 1H), 2.22-2.41 (m, 2H), 1.23- 1.64 (m, 8H), 0.89 (t, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.5, 134.0, 130.2, 126.9, 117.9, 67.0, 46.0, 42.9, 39.1, 39.0, 18.9, 14.0; IR (KBr) ν 3435, 2957, 1651, 1626, 1435, 646 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{12}\text{H}_{21}\text{O}_2\text{NNa}$: 234.1464, found: 234.1465.

***N*-((4*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)non-1-en-4-yl)acrylamide (8b):**

$[\alpha]_D^{27} = -27.8$ ($c = 0.4$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.18- 6.29 (m, 1H), 6.05 (brd, $J = 6.6$ Hz, 1H), 5.92- 6.03 (m, 1H), 5.66- 5.84 (m, 1H), 5.55- 5.62 (m, 1H), 4.99- 5.10 (m, 2H), 4.01- 4.14 (m, 1H), 3.79- 3.92(m, 1H), 2.18- 2.46 (m, 2H), 1.57- 1.68 (m, 2H), 1.18- 1.50 (m, 4H), 0.85- 0.95 (m, 12H), 0.04-0.10 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.9, 134.4, 131.1, 125.7, 117.5, 70.2, 46.7, 39.0, 25.8, 18.3, 14.1, -4.4, -4.5; IR (KBr) ν 3210, 2955, 2857, 1659, 1628, 1549, 1442, 1247, 1061, 842 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{18}\text{H}_{35}\text{O}_2\text{NNaSi}$: 348.2329, found: 348.2329.

(R)-6-((R)-2-((tert-Butyldimethylsilyl)oxy)pentyl)-5,6-dihydropyridin-2(1H)-one (9b):

$[\alpha]_D^{27} = +50.0$ ($c = 0.25$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.50- 6.58 (m, 1H), 6.47 (brs, 1H), 5.86 (d, $J = 10.5$ Hz, 1H), 3.77- 3.96 (m, 2H), 2.07- 2.36 (m, 2H), 1.70- 1.83 (m, 1H), 1.40- 1.69 (m, 3H), 1.22- 1.39 (m, 2H), 0.83- 0.90 (m, 12H), 0.04- 0.16 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.8, 140.8, 124.7, 70.2, 47.7, 40.5, 38.2, 31.0, 25.7, 18.8, 17.9, 14.0, -4.7, -4.6; IR (KBr) ν 3211, 3062, 2953, 2929, 1681, 1651, 1615, 1416, 1256, 1037, 826 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{16}\text{H}_{32}\text{O}_2\text{NSi}$: 298.2192, found: 298.2196.

(R)-6-((R)-2-((tert-Butyldimethylsilyl)oxy)pentyl)piperidin-2-one (10b):

$[\alpha]_D^{27} = -5.0$ ($c = 0.15$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.93 (brs, 1H), 3.78- 3.89 (m, 1H), 3.41- 3.56 (m, 1H), 2.05- 2.33 (m, 2H), 1.01- 1.95 (m, 10H), 0.73-0.93 (m, 12H), -0.7- 0.01 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.6, 70.1, 49.4, 42.2, 38.6, 31.0, 29.7, 25.8, 20.0, 18.8,

14.1, -4.5, -4.6; IR (KBr) ν 3210, 2935, 1669, 1678, 1558, 1413, 1261, 1082, 841 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{16}\text{H}_{33}\text{O}_2\text{NNaSi}$: 322.2172, found: 322.2169.

(R)-6-((R)-2-Hydroxypentyl)piperidin-2-one (11b):

$[\alpha]_{\text{D}}^{27} = -15.0$ ($c = 0.25$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.52 (brs, 1H), 3.89 (brs, 1H), 3.80- 3.87 (m, 1H), 3.65- 3.74 (m, 1H), 2.18- 2.36 (m, 2H), 1.79- 1.92 (m, 2H), 1.56- 1.78 (m, 3H), 1.23- 1.55 (m, 5H), 0.93 (t, $J = 7.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.8, 67.0, 48.8, 42.7, 39.2, 30.8, 28.6, 18.99, 18.7, 13.8; IR (KBr) ν 3449, 3385, 2952, 1638, 1457, 1334, 1093, 1021, 764 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_2\text{Na}$: 208.1308, found: 208.1308.

(-)-Halosaline (1b):

$[\alpha]_{\text{D}}^{27} = -18.6$ ($c = 0.25$, CHCl_3); reported $[\alpha]_{\text{D}}^{27} = -18.2$ ($c = 0.30$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 3.89- 4.0 (m, 1H), 3.41 (d, $J = 12.8$ Hz, 1H), 3.20- 3.31 (m, 1H), 2.74- 2.88 (m, 1H), 1.60- 2.03 (m, 7H), 1.10- 1.59 (m, 7H), 0.90 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 66.6, 54.7, 44.7, 39.4, 28.8, 22.9, 22.7, 22.3, 18.9, 13.9; IR (KBr) ν 3270, 2928, 2864, 1560, 1408, 1263, 1013, 769 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{10}\text{H}_{22}\text{ON}$: 172.1695, found: 172.1696.

((2R,4R,6S)-4-(acrylamido)-6-ethyl-tetrahydro-2H-pyran-2-yl)methyl-4-methylbenzenesulfonate (5c):

$[\alpha]_{\text{D}}^{27} = +16.7$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 6.22-6.33 (m, 1H), 5.98-6.10 (m, 1H), 5.63-5.69 (m, 1H), 5.41 (br s, 1H), 3.92-

4.12 (m, 3H), 3.53–3.66 (m, 1H), 3.20–3.31 (m, 1H), 2.44 (s, 3H), 1.85–2.06 (m, 2H), 1.34–1.57 (m, 2H), 0.93–1.56 (m, 3H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 164.7, 144.6, 132.2, 130.6, 129.5, 127.5, 126.0, 75.8, 72.8, 71.5, 45.4, 37.5, 37.1, 33.1, 20.1, 10.7; IR (KBr) ν 3281, 3065, 2928, 1660, 1625, 1542, 1359, 1177, 982, 814, 668 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_5\text{S}$ 368.1531, found: 368.1540.

***N*-((4*S*,6*S*)-6-Hydroxyoct-1-en-4-yl)acrylamide (7c):**

$[\alpha]_{\text{D}}^{27} = +9.3$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 6.27–6.41 (m, 1H), 6.04–6.20 (m, 1H), 5.66–5.92 (m, 2H), 5.60 (d, $J = 8.3$ Hz, 1H), 5.09–5.20 (m, 2H), 4.29–4.44 (m, 1H), 3.49–3.61 (m, 1H), 2.22–2.41 (m, 2H), 1.23–1.64 (m, 5H), 0.89 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 166.5, 134.0, 130.2, 126.9, 117.9, 67.0, 46.0, 42.9, 39.1, 30.0, 20.9, 10.0; IR (KBr) ν 3319, 3077, 2967, 1655, 1540, 1439, 1321, 1147, 987, 764 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{11}\text{H}_{20}\text{NO}_2$ 198.1494, found: 198.1503.

***N*-((4*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-4-yl)acrylamide (8c):**

$[\alpha]_{\text{D}}^{27} = +20.6$ (c 0.4, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 6.17–6.30 (m, 1H), 5.94–6.13 (m, 2H), 5.66–5.87 (m, 1H), 5.55–5.61 (m, 1H), 4.99–5.13 (m, 2H), 4.01–4.14 (m, 1H), 3.76–3.88 (m, 1H), 2.21–2.47 (m, 2H), 1.56–1.73 (m, 2H), 1.45–1.50 (m, 3H), 0.93 (s, 9H), 0.86 (t, $J = 7.5$ Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 164.9, 134.4, 131.1, 125.7, 117.5, 70.2, 46.7, 39.0, 20.8, 10.1, -4.4, -4.5; IR (KBr) ν 3276, 3074, 2956, 1657, 1626, 1547, 1465, 1254, 1072, 911, 773, 665 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{17}\text{H}_{34}\text{NO}_2\text{Si}$ 312.2358, found: 312.2363.

(*R*)-6-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)butyl)-5,6-dihydropyridin-2-(1*H*)-one (9c):

$[\alpha]_D^{27} = +50.0$ (c 0.25, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 6.45–6.58 (m, 1H), 5.86(d, $J = 9.8$ Hz, 1H), 3.75–3.90 (m, 2H), 2.05–2.34 (m, 2H), 1.68–1.85 (m, 1H), 1.46–1.66 (m, 2H), 1.22–1.39 (m, 2H), 0.92 (s, 9H), 0.87 (t, $J = 7.5$ Hz, 3H), 0.04–0.11 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ 165.8, 140.8, 124.7, 70.2, 47.7, 40.5, 38.2, 31.0, 22.7, 10.0, -4.7, -4.6; IR (KBr) ν 3450, 3227, 2931, 2857, 1679, 1464, 1424, 1366, 1102, 829, 769 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{15}\text{H}_{30}\text{NO}_2\text{Si}$ 284.2045, found: 284.2046.

(+)-8-Ethylnorlobelol (1c):

$[\alpha]_D^{27} = +29.3$ (c 0.5, EtOH); ^1H NMR (300 MHz, CDCl_3): δ 3.76–3.90 (m, 1H), 2.85–3.07 (m, 4H), 2.43–2.60 (m, 1H), 1.79–1.81 (m, 1H), 1.32–1.65 (m, 9H), 0.91 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 70.5, 54.7, 41.7, 31.4, 30.7, 26.4, 25.2, 10.9; IR (KBr) ν 3270, 2928, 2864, 1560, 1408, 1263, 1013, 769 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_9\text{H}_{19}\text{NO}$ 157.1593, found: 157.1568.

((2*S*,4*R*,6*R*)-4-Acrylamido-6-phenyltetrahydro-2H-pyran-2-yl)methyl-4-methylbenzenesulfonate (5d):

$[\alpha]_D^{27} = +2.3$ (c = 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.21–7.37 (m, 7H), 6.29 (d, $J = 16.6$ Hz, 1H), 6.04 (dd, $J = 9.8, 16.6$ Hz, 1H), 5.67 (d, $J = 9.8$ Hz, 1H), 5.45 (brd, $J = 7.5$ Hz, 1H), 4.43 (dd, $J = 10.5, 2.2$ Hz, 1H), 4.19–4.38 (m, 1H), 4.05–4.17 (m, 2H), 3.78–3.88 (m, 1H), 2.42 (s, 3H), 2.16–2.26 (m, 1H), 2.01–2.09 (m, 1H), 1.23–1.42 (m, 2H);

^{13}C NMR (75 MHz, CDCl_3) δ 164.8, 144.8, 141.1, 132.7, 130.5, 129.7, 128.2, 127.9, 127.6, 126.9, 125.5, 78.0, 73.6, 71.7, 45.9, 39.7, 33.5, 21.6; IR (KBr) ν 3280, 2924, 1718, 1650, 1545, 1356, 1170, 876, 772 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{22}\text{H}_{26}\text{O}_5\text{NS}$: 416.1526, found: 416.1516.

***N*-((2*S*,4*R*,6*R*)-2-(Iodomethyl)-6-phenyltetrahydro-2*H*-pyran-4-yl)acrylamide (6d):**

$[\alpha]_{\text{D}}^{27} = -4.0$ ($c = 0.55$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.23-7.44 (m, 5H), 6.25-6.35 (m, 1H), 6.02-6.13 (m, 1H), 5.63-5.73 (m, 2H), 4.56 (dd, $J = 2.2, 11.3$ Hz, 1H), 4.27-4.44 (m, 1H), 3.46-3.57 (m, 1H), 3.25-3.40 (m, 2H), 2.23 (dd, $J = 2.2, 12.0$ Hz, 2H), 1.22-1.45 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.7, 141.4, 130.6, 128.3, 127.5, 125.5, 77.8, 74.7, 45.9, 39.7, 37.6, 9.5; IR (KBr) ν 3292, 3059, 2954, 2926, 1655, 1624, 1544, 1535, 1093, 756 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2\text{NI}$: 372.0455, found: 372.0449.

***N*-((1*R*,3*S*)-1-Hydroxy-1-phenylhex-5-en-3-yl)acrylamide (7d):**

$[\alpha]_{\text{D}}^{27} = -14.0$ ($c = 0.55$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.17-7.42 (m, 5H), 6.30-6.41 (m, 1H), 6.07-6.20 (m, 1H), 5.66- 5.88 (m, 3H), 5.08-5.15 (m, 2H), 4.60- 4.70 (m, 1H), 4.55(d, $J = 3.7$ Hz, 1H), 4.35- 4.49 (m, 1H), 2.26- 2.42 (m, 2H), 1.85-1.97 (m, 1H), 1.63-1.74 (m, 1H); ^{13}C NMR (75MHz, CDCl_3) δ 166.58, 143.91, 133.8, 130.2, 128.2, 127.4, 127.1, 125.5, 118.4, 69.8, 46.2, 45.2, 39.1; IR (KBr) ν 3286, 3270, 3066, 2954, 2920, 1656, 1623, 1546, 1413, 1248, 1064, 699 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2\text{NNa}$: 268.1308, found: 268.1303.

***N*-((1*R*,3*S*)-1-((tert-Butyldimethylsilyl)oxy)-1-phenylhex-5-en-3-yl)acrylamide (8d):**

$[\alpha]_D^{27} = +43.1$ ($c = 0.6$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.65 (m, 5H), 6.41-6.57 (m, 1H), 6.20- 6.31 (m, 2H), 5.93-6.12 (m, 1H), 5.85 (dd, $J = 1.3, 10.1$ Hz, 1H), 5.27-5.38 (m, 2H), 5.10 (dd, $J = 3.3, 8.8$ Hz, 1H), 4.30-4.46 (m, 1H), 2.53- 2.73 (m, 2H), 2.14-2.27 (m, 1H), 1.96-2.07 (m, 1H), 1.13 (s, 9H), 0.29 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.7, 144.6, 134.4, 131.1, 128.2, 127.3, 125.8, 117.5, 73.0, 46.8, 43.6, 38.8, 25.8, 18.0, -4.5, -5.0; IR (KBr) ν 3214, 2950, 2889, 1645, 1614, 1254, 1054, 771 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{21}\text{H}_{33}\text{O}_2\text{NNaSi}$: 382.2172, found: 382.2168.

(S)-6-((R)-2-((tert-Butyldimethylsilyl)oxy)-2-phenylethyl)-5,6-dihydropyridin-2(1H)-one (9d):

$[\alpha]_D^{27} = +59.3$ ($c = 0.5$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.21-7.37 (m, 5H), 6.45- 6.53 (m, 1H), 6.44 (brs, 1H), 5.85 (dd, $J = 2.2, 9.8$ Hz, 1H), 4.97- 5.03 (m, 1H), 3.54- 3.55 (m, 1H), 2.10- 2.18 (m, 2H), 1.98- 2.09 (m, 1H), 1.77- 1.88 (m, 1H), 0.94 (s, 9H), 0.09 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.8, 143.1, 140.0, 128.3, 127.3, 125.5, 124.6, 73.1, 47.5, 44.5, 30.7, 25.8, 18.1, -4.7, -5.1; IR (KBr) ν 3218, 2952, 2894, 1645, 1615, 1256, 1057, 772 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{19}\text{H}_{30}\text{NO}_2\text{Si}$: 332.2040, found: 332.2036

(S)-6-((R)-2-((tert-Butyldimethylsilyl)oxy)-2-phenylethyl)piperidin-2-one (10d):

$[\alpha]_D^{27} = +89.2$ ($c = 0.5$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.62 (m, 5H), 7.0 (brs, 1H), 5.19 (t, $J = 4.9$ Hz, 1H), 3.51- 3.63 (m, 2H), 1.95-2.15 (m, 3H), 1.70- 1.94 (m, 2H), 1.32-1.63 (m, 2H), 1.13 (s, 9H), 0.29 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.2, 143.3, 128.3, 127.3, 125.6, 72.9, 49.4, 46.0, 30.8, 29.4, 25.8, 19.7, 18.1, -4.7, -5.1.; IR (KBr) ν 3201, 3057, 2952, 2926, 1663, 1654, 1459, 1406, 1257, 1090, 839, 777 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{19}\text{H}_{32}\text{O}_2\text{NSi}$: 334.2196, found: 334.2192.

(S)-6-((R)-2-Hydroxy-2-phenylethyl)piperidin-2-one (11d):

$[\alpha]_D^{27} = +40.4$ ($c = 0.5$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.62 (brs, 1H), 7.13-7.35 (m, 5H), 4.91- 5.0 (m, 1H), 4.33- 4.63 (brs, 1H), 3.38- 3.52 (m, 1H), 2.01- 2.23 (m, 2H), 1.43- 1.93 (m, 5H), 1.18-1.40 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.7, 144.2, 128.0, 126.7, 125.3, 70.2, 49.0, 44.5, 30.0, 28.6, 19.0; IR (KBr) ν 3224, 2918, 2852, 1605, 1537, 1445, 1380, 1228, 995, 807 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2\text{N}$: 220.1332, found: 220.1327.

(+)-noralloxedamine (1d):

white solid, m.p 103-105 °C. $[\alpha]_D^{27} = +37.8$ ($c = 0.35$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.20- 7.39 (m, 5H), 5.09 (dd, $J = 3.7, 7.5$ Hz, 1H), 3.17 (d, $J = 12.8$ Hz, 1H), 2.84- 2.96 (m, 1H), 2.61 (dt, $J = 12.0, 2.2$ Hz, 1H), 1.98- 2.09 (m, 1H), 1.78- 1.89 (m, 1H), 1.31- 1.71 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.4, 128.2, 126.9, 125.4, 70.3, 54.3, 45.4, 42.7, 30.4, 24.1, 23.5; IR (KBr) ν 3367, 2935, 1560, 1415, 1332, 1054, 756 cm^{-1} ; HRMS (m/z) calcd for $\text{C}_{13}\text{H}_{20}\text{ON}$: 206.1539, found: 206.1537.

Energy minimized structure of compound **5b** along with the characteristic NOEs

Figure: Energy minimized structure of compound **5b**

The structure and stereochemistry of compound **5b** was derived by extensive NMR experiments including 2-D Nuclear Overhauser Effect spectroscopy (NOESY) and Double Quantum Filtered Correlation Spectroscopy (DQFCOSY). From the one dimensional ^1H NMR experiments, the coupling constants involving the six membered ring, $^3J_{\text{H2-H3}(\text{pro-S})} = 2.0$, $^3J_{\text{H2-H3}(\text{pro-R})} = 11.5$, $^3J_{\text{H3}(\text{pro-S})-\text{H4}} = 4.0$, $^3J_{\text{H3}(\text{pro-S})-\text{H3}(\text{pro-R})} = 12.0$, $^3J_{\text{H3}(\text{pro-R})-\text{H4}} = 12.0$, $^3J_{\text{H4-H5}(\text{pro-S})} = 12.0$, $^3J_{\text{H4-H5}(\text{pro-R})} = 4.0$, $^3J_{\text{H5}(\text{pro-S})-\text{H5}(\text{pro-R})} = 12.0$, $^3J_{\text{H5}(\text{pro-S})-\text{H6}} = 11.2$, $^3J_{\text{H5}(\text{pro-R})-\text{H6}} = 2.0\text{Hz}$ were obtained. The large values of $^3J_{\text{H2-H3}(\text{pro-R})}$, $^3J_{\text{H3}(\text{pro-R})-\text{H4}}$, $^3J_{\text{H4-H5}(\text{pro-S})}$ and $^3J_{\text{H5}(\text{pro-S})-\text{H6}}$ clearly

Figure: Energy minimized structure of **5b** along with the characteristic NOEs.

indicate their diaxial disposition. The characteristic NOE correlations H2/H4, H2/H6, H4/H6 and H3(*pro-R*)/H5(*pro-S*) strongly support the above findings and are consistent with 4c_1 chair conformation of the six-membered ring. In addition ${}^3J_{\text{H4-H7}} = 8.2\text{Hz}$ and NOE correlations, H3(*pro-R*)/H7 and H5(*pro-S*)/H7 support an *anti* conformation of H4 and H7. The energy minimized structure (Figure 2, Figure 3) adequately supports the proposed structure.

^1H -NMR and ^{13}C -NMR of compound **4a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **5a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **6a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **7a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **8a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **9a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **10a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound **11a** in CDCl_3

^1H -NMR and ^{13}C -NMR of compound (-)-sedridine (**1a**) in CDCl_3