Supporting information

Synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde

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# Table of contents

General Experimental 2-15

1. $^1$H and $^{13}$C spectra for compound 6a 16
2. $^1$H and $^{13}$C spectra for compound 6b 20
3. $^1$H and $^{13}$C spectra for compound 7a 24
4. $^1$H and $^{13}$C spectra for compound 7b 25
5. $^1$H and $^{13}$C spectra for compound 8a 26
6. $^1$H and $^{13}$C spectra for compound 8b 27
7. $^1$H and $^{13}$C spectra for compound 9a 28
8. $^1$H and $^{13}$C spectra for compound 9b 29
9. $^1$H and $^{13}$C spectra for compound 1 30
10. $^1$H and $^{13}$C spectra for compound 2 31
11. $^1$H and $^{13}$C spectra for compound 10 32
12. $^1$H and $^{13}$C spectra for compound 11 33
13. $^1$H and $^{13}$C spectra for compound 12 34
14. $^1$H and $^{13}$C spectra for compound 14 35
15. $^1$H and $^{13}$C spectra for compound 16 36
16. $^1$H and $^{13}$C spectra for compound 15 37
17. $^1$H and $^{13}$C spectra for compound 17 38
18. $^1$H and $^{13}$C spectra for compound 3 39
General Methods:

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Anhydrous solvents were used for reactions. Solvents used for chromatography were distilled at respective boiling points using known procedures.

All commercial reagents were obtained from Sigma-Aldrich Chemical Co. and Lancaster Chemical Co. (UK). Progress of the reactions was monitored by TLC using precoated aluminium plates (Merck kieselgel 60 F254). Column chromatographies were performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. Typical syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents.

IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FT-IR. $^1$H NMR spectra were recorded on Bruker AC-200, Bruker AV-400, Bruker DRX – 500 and Jeol-400 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (J) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, douplet; t, triplet; m, multiplet). $^{13}$C NMR spectra were recorded on Bruker AC-200, Bruker AV- 400, Bruker DRX-500 and Jeol-400 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. $^{13}$C NMR chemical shifts are reported in ppm relative to the central line of CDCl$_3$ ($\delta$ 77.0). HRMS was determined at CMC division of National Chemical Laboratory, Pune. All HPLC analyses used to determine enantiomeric purity were calibrated with sample of the racemate.
General Procedure for the preparation of aldehydes 5a,b:

To a solution of 1,5-pentanediol/1,5-hexanediol (8.5 mmol) in CH₂Cl₂ (17 mL) was added imidazole (0.58 g, 8.5 mmol) and TBSCI (1.278 g, 8.5 mmol) at 0 °C and reaction mixture was stirred at room temperature for 4h. It was quenched with saturated solution of NH₄Cl and extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated to give crude product. Silica gel column chromatography of the crude product using petroleum ether/Ethyl acetate (9:1) provided mono TBS protected alcohol as a pale yellow oil.

To a suspension of TBS protected alcohol (2.16 mmol) in ethyl acetate was added IBX (1.21 g, 4.32 mmol) and refluxed until complete consumption of alcohol. The mixture was cooled to room temperature then filtered through a pad of celite, washed with ethyl acetate. The filtrate was collected and concentrated under reduced pressure to give aldehyde 5a/5b which was subjected to further reaction without purification.

Full characterization of aldehydes 5a and 5b is documented in literature.¹,²
(R,E)-Dibenzyl 1-(7-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (6a):

**General procedure for sequential α-amination/ Horner-Wadsworth-Emmons olefination:**

To a cooled solution of dibenzylazodicarboxylate (DBAD) (0.54 g, 1.81 mmol) and L-proline (0.02 g, 8 mol%) in CH₃CN (34 mL) at 0 °C was added aldehyde 5a (0.5 g, 2.17 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. This was followed by addition of lithium chloride (0.11 g, 2.7 mmol), triethylphosphonoacetate (0.54 mL, 2.71 mmol) and DBU (0.27 mL, 1.81 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 85:15) of the crude product gave 6a as a colorless syrupy liquid (0.84 g, yield 68%).

[α]D₂⁵: + 4.73 (c 1.0, CHCl₃), IR (CHCl₃, cm⁻¹): νmax 3296, 2995, 2857, 1720, 1657, 1258, 1097. ¹H NMR (200 MHz, CDCl₃): δ 0.03 (s, 6H), 0.87 (s, 9H), 1.29 (t, J = 7Hz, 3H), 1.43-1.58 (m, 2H), 4.70-4.88 (m, 1H), 5.03-5.22 (m, 4H), 5.94 (d, J = 15.2 Hz, 1H), 6.57 (brs, 1H), 6.86 (dd, J = 15.2 Hz, 6.6 Hz, 1H), 7.27-7.39 (m, 10H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ -5.4, 14.1, 18.3, 25.9, 27.1, 28.9, 58.7, 60.5, 62.4, 67.7, 68.3, 122.9, 126.9, 127.4, 127.8, 128.1, 128.4, 135.6, 144.8, 155.6, 156.4, 166.1 ppm. MS(ESI) : m/z 607.29 (M+Na)+


HPLC: Kromasil 5 –Amycoat ( 250 X 4.6mm ) (2-propanol: Pet ether = 10:90, flow rate 0.5ml/min, λ = 254 nm). Retention time (min):13.458 (major) and 18.067 (minor). The racemic standard was prepared in the same way using dl-proline as a catalyst, ee 94%.
Dibenzyl (R,E)-1-(8-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-y1)hydrazine-1,2-dicarboxylate (6b):

Colorless oil; [α]D25 + 2.67 (c 1.0, CHCl3), IR (CHCl3, cm⁻¹): vmax 3297, 1716, 1044, 695. ¹H NMR (200 MHz, CDCl3): δ 0.03 (s , 6H), 0.88 (s , 9H), 1.28 (t, J = 7 Hz, 3H), 1.37-1.59 (m, 4H), 1.59-1.76 (m, 2H), 3.50-3.65 (m, 2H), 4.18 (q, J = 7 Hz, 2H) 4.64-4.89 (m, 1H) 5.02-5.14 (m, 1H), 5.92 (d, J =15.4 Hz, 1H), 6.62 (brs, 1H), 6.87 (dd, J = 7.2 Hz, 15.4 Hz, 1H), 7.27-7.32 (m, 10H) ppm. ¹³C NMR (50 MHz, CDCl3): -5.4, 14.1, 18.2, 22.0, 25.8, 30.4, 32.1, 58.8, 60.4, 62.6, 67.7, 68.2, 122.9, 127.8, 128.1, 128.2, 128.4, 135.6, 144.8, 155.5, 156.5, 166.1 ppm. MS(ESI) : m/z 621.24 (M+Na)⁺ HRMS : 621.2963 (M+Na)⁺ Calcd. 621.2966

HPLC: Kromasil 5–Amycoat ( 250 X 4.6mm ) (2-propanol : Petroleum ether = 10:90, flow rate 0.5ml/min, λ = 230 nm). Retention time (min): 13.300 (major) and 16.225 (minor). The racemic standard was prepared in the same way using dl-proline as a catalyst, ee 91%.

(R)-5-(3-((tert-butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (7a):

General procedure of N-N bond cleavage using Raney-Ni:

The solution of 6a (0.5 g, 0.83 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney nickel (1.0 g, excess) under H₂ (70 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude amino alcohol which was stirred in EtOH at 55 °C for 6 h. The reaction mixture was concentrated in vacuo to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 40:60) of the crude product gave lactam 7a as a colorless liquid. (0.16 g, yield 70%) (over two steps)

[α]D25 + 37.76 (c 1.0, CHCl3) IR (CHCl3, cm⁻¹): vmax 2857, 1694, 1651, 1255, 1099. ¹H NMR (200 MHz, CDCl3) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.46-1.62 (m, 4H), 1.67-1.76 (m, 1H), 2.17-
2.39 (m, 3H), 6.55 (brs, 1H) ppm. $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ -5.4, 18.2, 25.9, 27.2, 29.1, 30.2, 33.4, 54.5, 62.7, 178.5 ppm. MS(ESI) : m/z 280.12 (M+Na)$^+$ HRMS: 280.2639(M+Na)$^+$ Calcd. 280.1703

(R)-5-(4-((tert-Butyldimethylsilyl)oxy)butyl)pyrrolidin-2-one (7b):

![Chemical structure](attachment:structure.png)

Viscous liquid; $[^\alpha]D$$^2$ + 35.52 (c 1.0, CHCl$_3$), IR (CHCl$_3$, cm$^{-1}$): $\nu$ max 2858, 1712, 1255, 1099. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.05 (s, 6H), 0.89 (s, 9H), 1.33 - 1.42 (m, 2H), 1.46 - 1.60 (m, 4H), 1.68 - 1.74 (m, 1H), 2.20 - 2.38 (m, 3H), 3.58 - 3.67 (m, 3H), 6.14 (brs, 1H) ppm. $^{13}$C NMR (50 MHz, CDCl$_3$): -5.4, 18.3, 22.1, 25.9, 27.2, 30.2, 32.5, 36.4, 54.6, 62.8, 178.5 ppm. MS(ESI) : m/z 294.13 (M+Na)$^+$ HRMS: 272.20402 (M+Na)$^+$ Calcd. 272.20403

(R)-5-(3-Hydroxypropyl)pyrrolidin-2-one (8a):

![Chemical structure](attachment:structure.png)

General procedure for TBS deprotection:

The solution of 7a (0.25 g, 0.92 mmol) was treated with TBAF (0.5 mL, 1.8 mmol) in THF (3 mL) at 0°C. The reaction mixture was stirred for 2 h and quenched with H$_2$O (1 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure to give a crude product. Silica gel column chromatography (CH$_2$Cl$_2$: MeOH: 95:5) of the crude product afforded 8a as a syrupy liquid (0.13 g, 90%).

$[^\alpha]D$$^2$ - 27.50 (c 1.0, CHCl$_3$), IR (CHCl$_3$, cm$^{-1}$): $\nu$ max 3412, 2953, 2857, 1694, 1096. $^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ 1.59-1.65 (m, 3H), 1.66-1.76 (m, 1H), 2.18-2.25 (m, 3H), 2.28-2.39 (m, 2H), 3.59-3.79 (m, 3H), 6.94 (brs, 1H) ppm. $^{13}$C NMR (50 MHz, CDCl$_3$) : $\delta$ 27.3, 28.9, 30.4, 33.4, 54.7, 62.0, 178.7 ppm. MS(ESI) : m/z 144.09 (M+H)$^+$ HRMS: 144.1015 (M+H)$^+$ Calcd. 144.1019
(R)-5-(4-Hydroxybutyl)pyrrolidin-2-one (8b):

Viscous liquid; [α]_D^{25} : - 23.94 (c 1.0, CHCl_3) IR (CHCl_3, cm⁻¹): ν_{max} 3435, 2928, 1668, 1101. 

^1H NMR (200 MHz, CDCl_3): δ 1.42-1.49 (m, 2H), 1.50-1.60 (m, 2H), 1.70-1.84 (m, 4H), 2.21-2.41 (m, 3H), 3.61-3.69 (m, 3H), 6.55 (brs, 1H) ppm. 

^13C NMR (50 MHz, CDCl_3): 22.1, 27.2, 30.4, 32.1, 36.3, 54.7, 61.9, 179.15 ppm. MS(ESI): m/z 180 (M+Na)⁺ HRMS: 158.1176 (M+Na)⁺ Calcd.158.1176

Tetrahydro-1H-pyrrolizin-3(2H)-one (9a):

General procedure for cyclisation:

To an ice-cold stirred solution of 8a (0.05g, 0.31 mmol) and triethylamine (0.08 mL, 0.63 mmol) in anhydrous CH_2Cl_2 (2 mL) was added toluenesulfonyl chloride (0.07 g, 0.34 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 8 h. After diluting with 6 mL CH_2Cl_2, the solution was washed with water (3 x 15 mL), brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude tosylated product which was subjected to next step without further purification.

To a solution of tosylated compound in THF cooled to 0 °C was added NaH (0.019 g, 60% dispersion in oil). On completion of reaction as indicated by TLC (8h) the reaction mixture was cooled to 0 °C, quenched by addition of ice pieces, and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with water, brine, and dried (Na_2SO_4). Silica gel column chromatography in EtOAc furnished 9a as a colorless liquid (0.035 g, 80%).

[α]_D^{25} : - 18.68 (c 0.4, CHCl_3) IR (CHCl_3, cm⁻¹): ν_{max} 2972, 2876, 1645. 

^1H NMR (200 MHz, CDCl_3) : δ 1.25-1.37 (m, 1H), 1.66-1.79 (m, 1H), 1.97-2.14 (m, 3H), 2.25-2.34 (m, 3H), 2.39-
2.52 (m, 1H), 3.0-3.12 (m, 1H), 3.48-3.57 (m, 1H), 3.82-3.97 (m, 1H) ppm. $^{13}$C NMR (50 MHz, CDCl$_3$): 26.9, 27.1, 32.2, 35.4, 40.9, 62.1, 174.8 ppm. MS(ESI): m/z 126.13 (M+H)$^+$

HRMS: 126.0914 (M+H)$^+$ Calcd. 126.0914

(R)-Hexahydroindolizin-3(2H)-one (9b):

\[
\begin{align*}
\text{[\alpha]}_D^{25} & : -32.14 (c 0.4, \text{CHCl}_3) \\
\text{IR} (\text{CHCl}_3, \text{cm}^{-1}) & : \nu_{\text{max}} 2933, 1663, 1570. \ \ \text{H NMR} (200 MHz, \ \text{CDCl}_3): \delta 1.13 - 1.26 (m, 1H), 1.34-1.46 (m, 2H), 1.52-1.68 (m, 2H), 1.83-1.93 (m, 2H), 2.12-2.26 (m, 1H), 2.32-2.40 (m, 2H), 2.55-2.69 (m, 1H), 3.33-3.48 (m, 1H), 4.08-4.17 (m, 1H) ppm. \ \ \text{C NMR} (50 MHz, CDCl$_3$): 23.7, 24.4, 25.3, 30.3, 38.6, 40.2, 57.3, 178.7 ppm. \ \ \text{MS (ESI): m/z 140.12 (M+H)$^+$ HRMS: 140.1070 (M+H)$^+$ Calcd. 140.1070

Hexahydro-1H-pyrrolizine (1)

General procedure for amide reduction:

To a stirred suspension of LiAlH$_4$ (0.015 g, 0.39 mmol) in dry THF (1 mL) was added a solution of 9a (0.025 g, 0.39 mmol) in THF (1 mL), and the mixture was refluxed for 6 h. After being cooled to ambient temperature, the mixture was treated with a saturated aqueous solution of sodium sulfate (2 mL) and extracted with CH$_2$Cl$_2$ (3 X 5 mL). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated under reduced pressure. Silica gel column chromatography (MeOH: CH$_2$Cl$_2$: 2:8) of the crude product gave as a colorless liquid.
\(^1H\) NMR (200 MHz, CDCl\(_3\)): \(\delta\) 1.26-1.72 (m, 8H), 2.06-2.86 (m, 4H), 3.67-3.73 (m, 1H) ppm. \(^{13}C\) NMR (50 MHz, CDCl\(_3\)): 27.4, 33.5, 54.5, 62.4 ppm. (ESI): m/z 112.09 (M+H)\(^+\)

HRMS: 112.1123 (M+H)\(^+\) Calcd.112.1121

\((R)\)-Octahydroindolizine(2):

\([\alpha]_D^{25}\) : - 9.8 (c 1.1, EtOH), \{Lit\}[\(\alpha\)]\(_D\)^{25}: -10.2 (c 1.76, EtOH) \n
IR (CHCl\(_3\), cm\(^{-1}\)) : \(\nu_{\text{max}}\) 2952, 2920, 1461, 1454, 1320,1255, 1096. \(^1H\) NMR (200 MHz, CDCl\(_3\)): \(\delta\) 1.12-1.85 (m, 10 H), 2.27-2.50 (m, 3H), 3.48-3.61 (m, 2H) ppm. \(^{13}C\) NMR (50 MHz, CDCl\(_3\)): 23.0, 27.1, 29.6, 30.2, 32.2, 44.6, 54.5, 64.7 ppm. MS (ESI): m/z 126.19(M+H)\(^+\) HRMS: 126.1278 (M+H)\(^+\) Calcd.126.1277

Ethyl\((R)-4-((\text{tert}-\text{butoxycarbonyl})\text{amino})-8-((\text{tert}-\text{butyldimethylsilyl})\text{oxy})\text{octanoate (10):}

The solution of dibenzyl \((R,E)-1-((\text{tert}-\text{butyldimethylsilyl})\text{oxy})-1\text{-ethoxy-1-oxooct-2-en-4-yl})\text{hydratine-1,2-dicarboxylate 6b} (2.0 g, 3.3 mmol) in MeOH (12 mL) and acetic acid (8 drops) was treated with Raney nickel (4.0 g, excess) under \(H_2\) (70 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude free amino alcohol which was further treated with triethylamine (0.93 mL, 6.7 mmol), Boc anhydride (1.2 mL, 5.1 mmol) and cat. DMAP in dry DCM (4 ml) for 2 h. Ice pieces were added to the reaction mixture and organic layer was separated. The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated under reduced pressure to give crude \(N\)-Boc derivative. Silica gel
column chromatography (petroleum ether: ethyl acetate: 85:15) of the crude product gave 10 as a viscous liquid (0.98 g, 70%).

\[ \alpha \] \text{D}^25: + 0.23 (c 1.2, CHCl\textsubscript{3}) \text{ IR (CHCl\textsubscript{3}, cm}^{-1}): \nu^\text{max} 3366, 2862, 1699. \text{H NMR (200 MHz, CDCl\textsubscript{3})}: \delta 0.04 (s, 6H), 0.89 (s, 9H), 1.25 (t, \text{J} = 7.2\text{Hz}, 2H), 1.31-1.38 (m, 2H), 1.43 (s, 9H), 1.48-1.61 (m, 3H), 1.62-1.93 (m, 3H), 2.36 (t, \text{J} = 7.4\text{Hz}, 2H), 3.51-3.67 (m, 3H), 4.13 (q, \text{J} = 7.2\text{Hz}, 2H), 4.26-4.31 (m, 1H) ppm. \text{C NMR (50 MHz, CDCl\textsubscript{3})}: -5.3, 14.2, 18.3, 22.2, 25.9, 28.3, 30.5, 31.1, 32.6, 35.5, 50.3, 60.4, 62.9, 78.9, 155.6, 173.6 ppm. \text{MS (ESI)}: m/z 440.26 (M+Na)\textsuperscript{+} \text{ HRMS: 440.2812 (M+Na)\textsuperscript{+} Calcd.440.2803}

**tert-Butyl (R)-(8-((tert-butyl(dimethyl)silyl)oxy)-1-hydroxyoctan-4-yl)carbamate (11):**

\[
\begin{align*}
\text{TBSO} & \quad \text{NHBOc} \\
& \quad \text{OH}
\end{align*}
\]

To a stirred suspension of LiBH\textsubscript{4} (0.60 g, 2.2 mmol) in dry THF (1 mL) was added a solution of 11 (0.60 g, 1.4 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at room temperature for 3 h. After being cooled to ambient temperature, the mixture was quenched with ice pieces and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 X 5 mL). The combined organic layers were washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether: ethyl acetate: 65:35) of the crude product gave 11 as a colorless liquid (0.48 g, 90%).

\[ \alpha \] \text{D}^25: + 0.82 (c 1.0, CHCl\textsubscript{3}) \text{ IR (CHCl\textsubscript{3}, cm}^{-1}): \nu^\text{max} 3368, 2930, 1688, 1098 \text{H NMR (200 MHz, CDCl\textsubscript{3})}: \delta 0.04 (s, 6H), 0.89 (s, 9H), 1.26 - 1.38 (m, 4H), 1.44 (s, 9H), 1.49 - 1.58 (m, 3H), 1.61 - 1.64 (m, 3H), 3.52 - 3.69 (m, 5H), 4.33 (brs, 1H) ppm. \text{C NMR (50 MHz, CDCl\textsubscript{3})}: -5.3, 18.3, 22.2, 25.9, 28.4, 28.9, 32.1, 32.6, 35.4, 50.4, 62.6, 62.9, 78.9, 155.9 ppm. \text{MS (ESI)}: m/z 398.18 (M+Na)\textsuperscript{+} \text{ HRMS: 398.2703 Calcd. 398.2697 (M+Na)\textsuperscript{+}; 376.2882 Calcd. 376.2878(M+H)\textsuperscript{+}}
**tert-Butyl (S)-(8-((tert-butyldimethylsilyl)oxy)-1-cyanoctan-4-yl)carbamate (12):**

![Diagram](attachment:Diagram.png)

To an ice-cold stirred solution of **11** (0.50 g, 1.33 mmol) and triethylamine (0.27 mL, 1.99 mmol) in anhydrous CH$_2$Cl$_2$ (8 mL) was added toluenesulfonyl chloride (0.5 g, 2.66 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 6 h. After diluting with 10 mL CH$_2$Cl$_2$, the solution was washed with (3 x 15 mL) brine, dried over Na$_2$SO$_4$ and concentrated to give the crude tosylated product which was subjected to next reaction without purification.

To a solution of tosyl ester in DMF was added NaCN (0.13 g, 2.66 mmol) and was stirred at 115 °C for 10 h. After the consumption of starting material the reaction mixture was poured into H$_2$O and extracted with ether (25 mL), The organic phase was washed with H$_2$O and brine (15 mL) dried (Na$_2$SO$_4$) and concentrated in vacuo. Silica gel column chromatography of the crude product using (petroleum ether: ethyl acetate 90:10) gave **12** as yellow syrupy liquid. (0.41 g, 80%)

$[\alpha]_D^{25}$: -2.62 (c 1.0 , CHCl$_3$), IR (CHCl$_3$,cm$^{-1}$): $\nu_{max}$ 3360, 2936, 2247, 1688, 1170 ¹H NMR (200 MHz, CDCl$_3$): $\delta$ 0.05 (s, 6H), 0.90 (s, 9H), 1.26-1.38 (m, 2H), 1.44 (s, 9H), 1.49-1.58 (m, 4H), 1.61-1.76 (m, 4H), 2.40 (t, $J = 6.8$Hz, 2H), 3.52-3.67 (m, 3H), 4.27 (brs, 1H) ppm.

¹³C NMR (50 MHz, CDCl$_3$): -5.3, 16.9, 18.3, 22, 22.2, 25.9, 28.3, 32.5, 34.8, 35.5, 49.7, 62.9, 79.2, 119.5, 155.8 ppm. MS(ESI): m/z 407.21 (M+Na)$^+$ HRMS: 407.2700 (M+Na)$^+$ Calcd. 407.2700

**tert-Butyl 2-(4-((tert-butyldimethylsilyl)oxy)butyl)-3,4-dihydropyridine-1(2H) carboxylate (14):**

![Diagram](attachment:Diagram.png)
To a solution of 12 (0.25 g, 0.65 mmol) in CH₂Cl₂ (10 mL), was added DIBAL-H (0.715 mL 1M solution in toluene, 0.71 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 2 h. Then, saturated solution of ammonium chloride (0.8 mL) was added. The resulting mixture was warmed to ambient temperature and was then diluted with 0.2 M aqueous HCl (0.67 mL) followed by EtOAc and organic layer was separated. The aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers were dried (Na₂SO₄), filtered and evaporated under reduced pressure to give aldehyde 13 as a colorless liquid, which was directly used in the next step without further purification.

To the cooled solution of anhydrous THF was added a solution of NaBH₃CN (0.164 g, 2.6 mmol) in absolute methanol in one portion with stirring for 20 min followed by addition of aldehyde 13. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After being cooled to ambient temperature, the mixture was quenched with ice pieces and extracted with EtOAc (3 X 5 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated under reduced pressure to give pale yellow oil. The crude product was then purified by using silica gel flash column chromatography using (pet ether: EtOAc: 90:10) gave 14 as a pale yellow oil as major product. Continuation of the column chromatography by increasing the polarity (pet ether: EtOAc 75:25) eluted 15 as a colorless oil as minor product.

\[ \text{[a]D}^{25} : -56.17 \ (c \ 0.5, \text{CHCl}_3) \]  
\text{IR (CHCl}_3, \text{ cm}^{-1}) : \nu^\text{max} 2929, 2857, 1720, 1649, 1360  
\text{H NMR (200 MHz, CDCl}_3) : \delta 0.05 \ (s, \ 6H), 0.80 \ (s, \ 9H), 1.26-1.44 \ (m, \ 4H), 1.49 \ (s, \ 9H), 1.54-1.61 \ (m, \ 3H), 1.64-1.80 \ (m, \ 2H), 1.94-2.01 \ (m, \ 1H), 3.61 \ (t, \ J = 6.3Hz, \ 2H), 4.13-4.29 \ (m, \ 1H), 4.77-4.87 \ (m, \ 1H), 6.64-6.82 \ (m, \ 1H) \ \text{ppm.}  
\text{C NMR (50 MHz, CDCl}_3) : \text{as a rotameric mixture (2:1) -5.3, 17.5, 18.3, 25.9, 28.3, 30.2, 30.8, 32.7, 49.5, 50.6, 63.0, 80.2, 104.6, 105.1, 123.9, 124.2, 152.2, 152.6 \ \text{ppm.}  
\text{MS(ESI) : m/z 392.15 (M+Na)}^+ \  \text{HRMS : 370.2771 (M+H)}^+ \ \text{Calcd. 370.2772.}  

\text{tert-Butyl (S)-(1-((tert-butyldimethylsilyl)oxy)-9-hydroxynonan-5-yl)carbamate (15):}
[\alpha]_D^{25}: -2.10 (c 0.6 CHCl₃) IR (CHCl₃, cm⁻¹): 𝜈_{max} 3365, 2929, 2857, 1691. ¹H NMR (200 MHz, CDCl₃): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.25-1.40 (m, 4H), 1.44 (s, 9H), 1.48-1.61 (m, 5H), 2.68 - 2.82 (m, 1H), 3.65 (t, J = 6.5Hz, 2H), 3.90-4.02 (m, 1H), 4.16-4.28 (m, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): -5.3, 21.9, 22.2, 24.1, 25.9, 28.4, 29.7, 32.5, 32.6, 35.4, 50.4, 62.7, 63.0, 79.4, 155.8 ppm. MS(ESI): m/z 412.16 (M+Na)⁺ HRMS: 390.3032 (M+ H)⁺ Calcd. 390.3034

tert-Butyl (S)-2-(4-hydroxybutyl)piperidine-1-carboxylate (16)

To the solution of 14 (0.1 g, 0.27 mmol) in ethyl acetate was added Pd-C (10%) under hydrogenation conditions. The reaction mixture was allowed to stir overnight. On completion of reaction (until ¹H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give 16 as a colorless liquid. (0.062 g, 90%).

[\alpha]_D^{25}: -24.26 (c 0.8 CHCl₃) IR (CHCl₃, cm⁻¹): 𝜈_{max} 3436, 2933, 2862, 1688, 1668. ¹H NMR (200 MHz, CDCl₃): δ 1.26 - 1.42 (m, 5H), 1.45 (s, 9H), 1.49-1.59 (m, 6H), 1.69-1.76 (m, 1H), 2.68 - 2.82 (m, 1H), 3.65 (t, J = 6.5Hz, 2H), 3.90-4.02 (m, 1H), 4.16-4.28 (m, 1H) ppm. ¹³C NMR (50 MHz, CDCl₃): as a rotameric mixture (2:1): 18.9, 22.3, 25.6, 28.4, 29.3, 29.6, 32.4, 38.7, 50.5, 62.6, 79.1, 155.2 ppm. MS(ESI): m/z 280.09 (M+Na)⁺ HRMS: 280.1878 (M+ Na)⁺ Calcd. 280.1883

tert-Butyl (1,9-dihydroxynonan-5-yl)carbamate (17):

The solution of 15 (0.1g, 0.25 mmol) in THF (3mL) was treated with TBAF (0.15 mL, 0.51 mmol) at 0 °C. The reaction mixture was stirred for 2 h and quenched with H₂O (1 mL) and
extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude product. Silica gel column chromatography (Petether: EtOAc 35: 65) of the crude product afforded 18 as a syrupy liquid (0.63 g, 90 %).

**IR** (CHCl₃, cm⁻¹): νmax 3347, 2935, 2864, 1688, 1172. **¹H NMR** (200 MHz, CDCl₃): δ 1.25-1.40 (m, 4H), 1.44 (s, 9H), 1.51-1.62 (m, 4H), 1.83-2.10 (m, 4H), 2.49-3.72 (m, 5H), 4.38 (brs, 1H) ppm. **¹³C NMR** (50 MHz, CDCl₃): 21.9, 28.4, 32.4, 35.4, 50.3, 60.6, 79.1, 156.0 ppm.

**MS(ESI):** m/z 298.05 (M+Na)⁺ **HRMS:** 298.1985 (M+ Na)⁺ Calcd. 298.1989

**Octahydro-2H-quinolizine(3):**

To an ice-cold stirred solution of 16 (0.05g, 0.19 mmol) and triethylamine (0.08 mL, 0.58mmol) in anhydrous CH₂Cl₂ (2 mL) was added toluenesulfonyl chloride (0.08 g, 0.38mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 8 h. After diluting with 5 mL CH₂Cl₂, the solution was washed with water (3 x 10 mL), brine, dried over anhyd. Na₂SO₄ and concentrated to give the crude tosylated product which was subjected to next step without further purification.

To a solution of tosylated compound in THF cooled to 0 °C was added NaH (0.023 g, 60% dispersion in oil). On completion of reaction as indicated by TLC (8h) the reaction mixture was cooled to 0 °C, quenched by addition of ice pieces, and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with water, brine, and dried (Na₂SO₄). Silica gel column chromatography in EtOAc furnished 3 as a colorless liquid (0.016 g, 60%).

**IR** (CHCl₃, cm⁻¹): νmax 3367, 3020, 2400, 1215. **¹H NMR** (200 MHz, CDCl₃): δ 1.13-1.44 (m, 6H), 1.45 (s, 9H), 1.48-1.60 (m, 5H), 1.73-2.06 (m, 4H), 2.31 -2.65 (m, 2H) ppm **¹³C NMR** (50 MHz, CDCl₃): 22.8, 29.6, 30.0, 55.6, 64.9 ppm. **MS(ESI):** m/z 140.21 (M+H)⁺ **HRMS:** 140.1434 (M+H)⁺ Calcd.140.1434
(R,E)-Dibenzyl 1-[(7-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (6a):
Detector A - 1 (254nm)

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Totals
7564740 100.000

Project Leader: Dr. P.K. TRIPATHI
Column: Kromasil 5-AmyCoat (250x4.6 mm)
Mobile Phase: IPA. Pet Ether (10:90)
Wavelength: 254nm
Flow Rate: 0.5ml/min(29Kgf)
conc.: 1mg/1.0 mL
Inj vol: 5 ul

TBSO Cbz Cbz NH

COOEt
Comparison
(R,E)-Dibenzy11-(8-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxo-oct-2-en-4-yl)hydrazine-1,2-dicarboxylate (6b):
Detector A - I (230nm)

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Totals

8409925 100.000

Project Leader: Dr. Pradeep kumar
Column: Kromasil 5-AmyCoat(250x4.6 mm)
Mobile Phase: IPA: Pet ether (10:90)
Wavelength: 230nm
Flow Rate: 0.5ml/min(396psi)
conc.: 1mg/1.0 mL
Inj vol.: 5ul

TBSO-\text{CbzHN}_2\text{Ncbz}-\text{COOEt}
Detector A - I (254nm)

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Totals: 15744590

Project Leader: Dr. P.K. TRIPATHI
Column: Kromasil 5-AmyCoat (250x4.6 mm)
Mobile Phase: IPA: Pet Ether (10:90)
Wavelength: 254nm
Flow Rate: 0.5ml/min (29Kgf)
conc.: 1mg/1.0 mL
Inj vol: 5 ul

\[ \text{CbzHN} \quad \text{N\text{Cbz}} \]
\[ \text{COOEt} \]

TBSO
Comparison
(R)-5-(3-((tert-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (7a):
(R)-5-((tert-Butyldimethylsilyl)oxy)butyl)pyrrolidin-2-one (7b):

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(R)-5-(3-Hydroxypropyl)pyrrolidin-2-one (8a):
(R)-5-(4-Hydroxybutyl)pyrrolidin-2-one (8b):
(R)-Tetrahydro-1H-pyrrolizin-3(2H)-one (9a):
(R)-Hexahydroindolizin-3(2H)-one (9b):
Hexahydro-1H-pyrrolizine (1)
(R)-Octahydroindolizine (2):
(R)-Ethyl 4-((tert-butoxycarbonyl)amino)-8-((tert-butyldimethylsilyl)oxy)octanoate (10):
**tert-Butyl(R)-(8-((tert-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)carbamate (11):**

![NMR spectrum of tert-Butyl(R)-(8-((tert-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)carbamate (11) in chloroform-d.](image)
**tert-Butyl(S)-(8-((tert-butyldimethylsilyl)oxy)-1-cyanoctan-4-yl)carbamate (12):**

[Chemical structure and NMR spectra images are present in the document.]

S34
**tert-Butyl(R)-2-(4-((tert-butyldimethylsilyl)oxy)butyl)-3,4-dihydropyridine-1(2H)-carboxylate (14):**

![Chemical Structure Image]

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**tert-Butyl(S)-2-(4-hydroxybutyl)piperidine-1-carboxylate (16):**

![Chemical Structure and NMR Spectra](image-url)
**tert-Butyl(S)-(1-((tert-butyldimethylsilyl)oxy)-9-hydroxynonan-5-yl)carbamate (15):**
**t**ert-Butyl (1,9-dihydroxynonan-5-yl)carbamate (17):
Octahydro-2H-quinolizine (3):
References: