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Graphical Abstract

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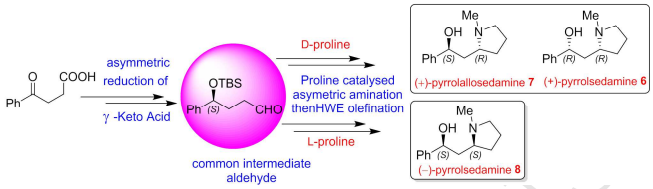

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ABSTRACT

A general approach for the synthesis of pyrolidine member of sedum alkaloids has been developed by employing proline catalysed sequential α-amination and Horner–Wadsworth–Emmons (HWE) olefination of an aldehyde as the key step. This method can be extended for the synthesis of various bioactive natural products containing pyrolidine skeleton.

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1. Introduction

The sedum alkaloids have been isolated from the genus *Sedum*.[1] The most commonly occurring members of this family often display the 2-substituted piperidine and pyrolidine core, with the different side chains featuring various relative stereochemistries of 1,3-amino alcohol moiety and a selected set of piperidine/pyrrolidine members are shown in Figure 1.[2] Sedamine **1**, sedridine **4** and allosedamine **2** have been isolated from *Sedum acre*[3,4] and Indian tobacco plant[5] *Lobelia inflate*, respectively. (-)-Halosaline **5** has been isolated from *Haloxylon salicornicum*.[6] The pyrrolidine alkaloids pyrrolsedamine **6** and pyrrolallosedamine **7** have subsequently been detected in *Sedum oryzi Johum*.[1] Hygroline **10** was isolated from the mother liquors of cocaine preparations obtained from *Erythroxylum coca* extracts in 1943.[7] The sedum alkaloids have been shown to exhibit a wide range of physiological activities which include therapeutic effects e.g., control of anxiety and also are effective in the treatment of cognitive disorders.[8]

As result of useful biological activities of sedum alkaloids, many researchers have been attracted towards the development of new strategies for the synthesis of sedum alkaloids. The synthetic strategies mostly based upon manipulation of chiral pool starting materials and asymmetric methods have been reported.[9] To our knowledge, only one asymmetric synthesis of the (*R*,*R*)-(+)-pyrrolsedamine **6** is reported in literature by Davies *et al.*[9j]. They have explored the scope of lithium amide conjugate addition method for the stereo controlled synthesis of (*R*)-(*R*)-(+)-pyrrolsedamine **6** in 18% overall yield.

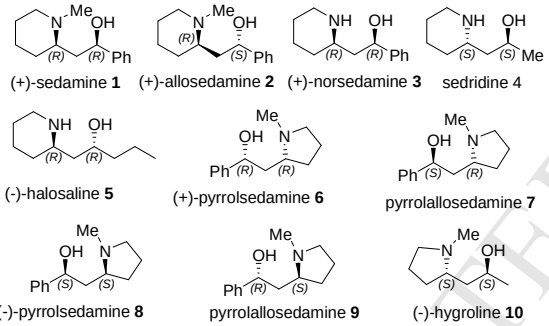
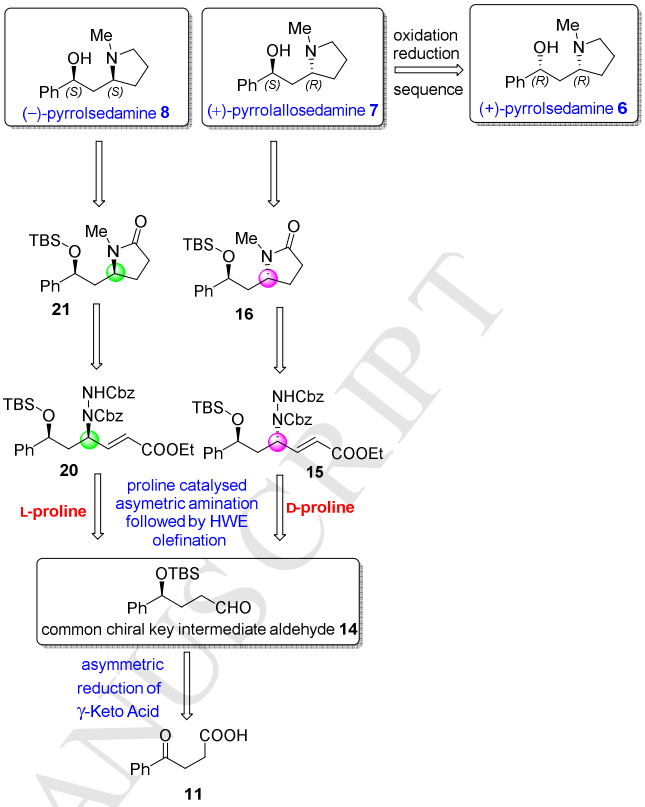


Figure 1 Selected examples of piperidine/pyrrolidine member of sedum alkaloids

As part of our research program into the stereocontrolled synthesis of biologically active molecules,[10] we became interested in the synthesis of sedum alkaloids. Herein we would like to describe the first enantioselective synthesis of pyrrolidine members of sedum alkaloids (*S*)-(*R*)-(+)-pyrrolallosedamine **7**, (*S*)-(*S*)-**(-)**-pyrrolsedamine **8** and second enantioselective synthesis of (*R*)-(*R*)-(+)-pyrrolsedamine **6** by using sequential organocatalytic proline catalysed asymmetric α-amination of aldehyde followed by HWE olefination reaction.[11]

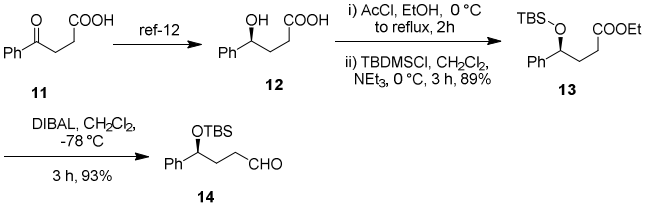
2. Result and discussion

The retrosynthetic analysis of Pyrrolsedamine alkaloids **6**, **7** and **8** is shown in the Scheme 1. The (*S*)-(*R*)-(+)-pyrrolallosedamine **7** and (*S*)-(*S*)-**(-)**-pyrrolsedamine **8** can be obtained by *N*-methylation, TBDMS ether deprotection and reduction of lactams **16** and **21**. (*R*)-(*R*)-(+)-Pyrrolsedamine **6** can be obtained from **7** by performing oxidation reduction-reduction sequence on **7**. The lactams **21** and **16** may be derived through cyclisation of amino esters **20** and **15**, which in turn can be obtained through sequential α-amination and HWE olefination of the common intermediate aldehyde **14**.[11] Aldehyde **14** could be accessible from **11** by asymmetric reduction of γ-keto acid **11** with diisopinocampheylborane.[12]



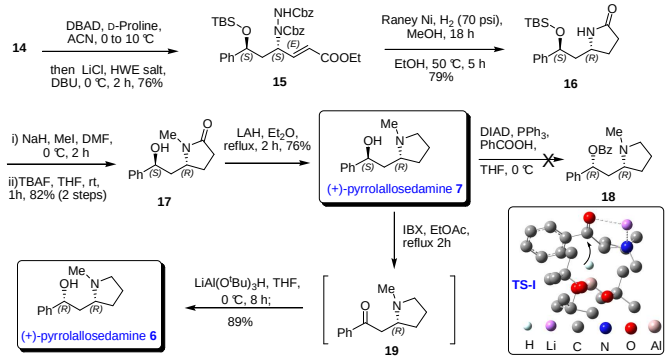
Scheme 1: Retrosynthetic analysis of pyrrolidine member of sedum alkaloids

The synthesis of the chiral key intermediate aldehyde **14** is shown in Scheme 2. Our synthetic endeavour began from the known 3-benzoylpropanoic acid **11**, which was subjected to asymmetric reduction by diisopinocampheylborane to afford chiral (*S*)-4-hydroxy-4-phenylbutanoic acid **12** in 90% yield.[12] The esterfication of acid **12** in EtOH was promoted by *in situ* generated HCl and further protection of free hydroxy group of γ-hydroxy ester with TBDMSCl in CH_2Cl_2 afforded ester **13** in 89% yield over two steps. The reduction of ethyl (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanoate **13** with DIBAL in CH_2Cl_2 at -78 °C gave the desired (*S*)-4-((*tert*-butyldimethylsilyl)oxy)-4-phenylbutanal **14** in 93% yield. Next, we envisioned the transformation of a chiral key intermediate aldehyde **14** into pyrrolidine member of sedum alkaloids (Scheme 3). The synthesis commenced with sequential α-amination of aldehyde **14** using D-proline and dibenzyl azodicarboxylate (DBAD) as amine source, subsequent Horner–Wadsworth–Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate afforded desired γ-amino-α,β unsaturated ester **15** in 76% overall yield. The absolute and relative configuration of amino alcohol **15** is based on L- or D-proline used in the reaction.[11]



Scheme 2 Synthesis of chiral key intermediate aldehyde **14** from 3-benzoylpropanoic acid **11**

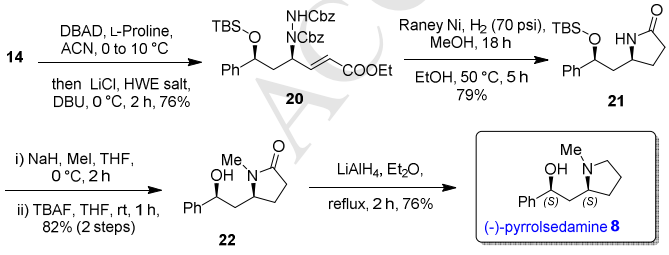
Further compound **15** was subjected for reductive hydrogenation using Raney nickel to furnish free amine, which on subsequent heating in EtOH at 50 °C gave lactam **16** as separable mixture of diastereomers (97:3, dr) in 79% overall yield. *N*-Methylation of lactam **16** is achieved by treatment with NaH and MeI, subsequent deprotection of TBDMS group with TBAF in THF afforded free hydroxyl compound **17** in 82% overall yield over two steps. The reduction of the **17** with $LiAlH_4$ provided desired synthetic isomer (*S*)-(*R*)-(+)-pyrrolallosedamine **7** $[\alpha]_D^{20}$ = +5.69 (*c* 0.5, EtOH)] in 76% yield.



Scheme 3 Synthesis of (*S*)-(*R*)-(+)-pyrrolallosedamine **7** and (*R*)-(*R*)-(+)-pyrrolsedamine **6**

After successful preparation of synthetic isomer (*S*)-(*R*)-(+)-pyrrolallosedamine **7,** we focused our attention towards the synthesis of natural isomer (*R*)-(*R*)-(+)-pyrrolsedamine **6**. Initially, we had planned inversion of benzylic stereocenter of **7** by Mitsunobu reaction under various conditions, but instead of expected compound **18** complex reaction mixture was observed. The IBX oxidation of (*S*)-(*R*)-(+)-pyrrolallosedamine **7** followed by reduction of ketone **19** with $LiAl(OtBu)_3H$ in THF at 0 °C gave desired (*R*)-(*R*)-**(+)**-pyrrolsedamine **6** as single *syn* diastereomer in 89% yield $[\alpha]_D^{20}$ = +72.1 (*c* 2.00, EtOH) [ref[9j] $[\alpha]_D^{25}$ = +73.7 (*c* 2.00, EtOH)]. The stereoselectivity obtained in the reduction reaction of ketone **19** can be explained by chelation of Li with carbonyl and amine functionality as shown in transition state **TS-I**. The chelation of the lithium directs hydride delivery from the least hindered face of the ketone, which resulted in exclusive formation of single syn isomer **8**.

The scheme 4 represents the synthesis of synthetic isomer (*S*)-(*S*)-(-)-pyrrolsedamine **8** from chiral key intermediate aldehyde **14**.



Scheme 4 Synthesis of (*S*)-(*S*)-(-)-pyrrolsedamine **8**

Sequential α-amination of aldehyde **14** using L-proline and dibenzyl azodicarboxylate (DBAD) followed by subsequent Horner–Wadsworth–Emmons (HWE) olefination afforded desired *γ*-amino-*α,β* unsaturated ester **20** in 76% yield. Further ester **20** was subjected for reductive hydrogenation using Raney nickel to furnish the free amine product, which on subsequent heating in EtOH at 50 °C furnished lactam **21** in 79% overall yield (98:2, dr). The diastereomers are separated by column chromatography. The *N*-Methylation was carried with NaH/MeI, followed by deprotection of TBDMS group with TBAF afforded hydroxyl compound **22** in 82% yield over two steps. The reduction of the lactam of **22** using $LiAlH_4$ gave the desired (*S*)-(*S*)-**(-)**-pyrrolsedamine **8** $[\alpha]_D^{20}$ = -13.3 (*c 0.19*, MeOH) in 76% yield.[13]

3. Conclusion

In conclusion, we have accomplished first enantioselective synthesis of (*S*)-(*R*)-(+)-pyrrolallosedamine **7** and (*S*)-(*S*)-(-)-pyrrolsedamine **8** as well as second enantioselective synthesis (*R*)-(*R*)-(+)-pyrrolsedamine **6** by using sequential proline catalysed α-amination and Horner Wadsworth–Emmons olefination reactions. This organocatalytic protocol is simple and efficient, which provided *R*)-(*R*)-(+)-pyrrolsedamine **6**, (*S*)-(*R*)-(+)-pyrrolallosedamine **7** and (*S*)-(*S*)-(-)-pyrrolsedamine **8** in 31, 28 and 31% yields, respectively. The present method can be easily applied for the synthesis of a variety of other alkaloids which encountered these ring systems.

4. Experimental section

General Experimental Details

All reagents were obtained from commercial suppliers unless otherwise stated and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. All moisture sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reactions were magnetically stirred and monitored by analytical thin-layer chromatography (TLC) E. Merck 0.25 mm silica gel 60 F_{254}. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of potassium permanganate ($KMnO_4$), an acidic solution of Ninhydrin or a solution of PMA followed by heating with a heat gun. Chromatography was performed using silica gel (100-200 mesh) with solvents distilled prior to use. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material. All spectra were recorded at 25 °C. ^{1}H NMR spectra were recorded on 500 MHz and 400 MHz spectrometers and ^{13}C NMR spectra were obtained at 500 NMR (126 MHz) and 400 (101 MHz) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Chemical shifts were recorded in ppm, and coupling constants (*J*) were in Hz. HRESIMS were taken on Bruker Impact HD quadrupole plus ion trap at CIF, S. P. Pune University. Infrared spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer. Optical rotations were measured on a digital polarimeter. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, m: multiplet, bs: broad singlet dd: doublet of doublet for proton spectra.

*4.1.Ethyl-(S)-4-((tert-butyldimethylsilyl)oxy)-4-phenylbutanoate (**13**):*

Acetyl chloride (1 mL) was added dropwise over period of 10 min to EtOH (10 mL) at 0 °C. The solution was stirred for extra 10 min and then acid **12** (1.0 g, 5.5 mmol) was added in one portion. The solution was heated to reflux for 2 h, after complete consumption of starting material (TLC check), the reaction mixture was concentrated in vacuo to give the crude product, which without any chromatographic purification subjected to next reaction. To a cooled solution of above crude ester and NEt_3

(1.55 mL, 11.10 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added TBDMSCl (1.0 g, 6.66 mmol) portion wise over the period of 15 min and after stir it for 3 h at same temperature. After completion of reaction (TLC check), residue was diluted with water and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using Hexane: EtOAc (95:5) gave ester **13** as yellowish liquid (1.59 g, 89%)

Yellow liquid, R_f = 0.66 (Hexane: EtOAc, 9:1);

$[\alpha]_D^{20}$= -8.71 (*c* 0.60, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (5H, m), 4.76 (1H, t, *J* = 6.0 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 2.47 – 2.27 (2H, m), 2.07 – 1.96 (2H, m), 1.27 (3H, t, *J* = 7.1 Hz), 0.92 (9H, s), 0.05 (3H, s), -0.12 (3H, s);

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 144.7, 128.1, 127.0, 125.8, 73.7, 60.2, 35.6, 30.1, 25.8, 18.1, 14.2, -4.7, -5.0;

HRMS (ESI^+)$[M+Na]^+$: found 345.1860.$C_{18}H_{30}NaO_3Si$ requires 345.1862

*4.2. (S)-4-((tert-butyldimethylsilyl)oxy)-4-phenylbutanal (**14**)*

A solution of ester **13** (1.0 g, 3.10 mmol) in 20 mL of CH_2Cl_2 at −78 °C under an N_2 atmosphere was treated with a 1 M solution of DIBAL in THF (3.10 mL, 3.10 mmol) and stirred for 3 h. The reaction mixture was quenched with saturated tartaric acid, diluted with Et_2O, and stirred vigorously for 2 h at room temperature. The organic layer was separated, and the aqueous layer was diluted with brine and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give crude aldehyde **14**. The crude product was purified by silica gel column chromatography using Hexane: EtOAc (95:5) to give the aldehyde **14** as a thick liquid (0.805 mg, 93% yield).

Thick liquid, R_f = 0.63 (Hexane/EtOAc, 9:1);

$[\alpha]_D^{20}$= -9.23 (*c* 0.27, MeOH);

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (1H, t, *J* = 1.6 Hz), 7.43 – 7.25 (5H, m), 4.79 (1H, dd, *J* = 6.6, 4.9 Hz), 2.56 – 2.33 (2H, m), 2.08 – 1.97 (2H, m), 0.91 (9H, s), 0.05 (3H, s), -0.13 (3H, s);

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 144.4, 128.1, 127.2, 125.8, 73.7, 39.7, 33.0, 25.8, 18.1, -4.7, -5.0;

HRMS (ESI+)[M+Na]+: found 301.1602. $C_{16}H_{26}NaO_2Si$ requires 301.1600

*4.3.Dibenzyl1-((1S,3S,E)-1-((tert-butyldimethylsilyl)oxy)6 ethoxy 6oxo-1-phenylhex-4-en-3-yl)hydrazine-1,2-dicarboxylate (**15**)*

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.445 g**,** 1.49 mmol) and D-proline (0.051 g, 0.446 mmol) in CH_3CN (30 mL) at 0 °C was added aldehyde **14** (0.5 g, 1.79 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 (0.098 g, 2.33 mmol), triethyl phosphonoacetate (0.44 mL, 2.33 mmol) and DBU (0.272 mL, 1.79 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. Silica gel column chromatography (Hexane: EtOAc; 85:15) of the crude product gave **15** as a colourless syrupy. (0.914 g, 76% yield based on aldehyde)

Colourless syrupy; R_f = 0.45 (Hexane/EtOAc, 7:3);

$[\alpha]_D^{20}$= -3.08 (*c* 0.50, MeOH);

^{1}H NMR (500 MHz, $CDCl_3$) (rotamers) δ 7.49 – 7.19 (15H, m), 6.83 (1H, bs), 6.54 (1H, bs), 5.91 (1H, bs), 5.17 (6H, bs), 4.16 (2H, q, 7.0 Hz), 1.89 – 1.80 (1H, m), 1.66 (1H, bs), 1.28 (3H, t, *J* = 7.1 Hz), 0.88 (9H, s), 0.03 (3H, s), -0.25 (3H, s);

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 156.1, 154.6, 145.3, 144.0, 136.0, 128.5, 128.3, 128.0, 127.4, 125.8, 122.9, 71.8, 68.5, 67.7, 60.3, 60.1, 56.5, 55.6, 41.6, 29.5, 28.9, 25.6, 14.2, -5.0, -5.2;

HRMS (ESI^+)$[M+Na]^+$: found 669.2972. $C_{36}H_{46}N_2NaO_7Si$ requires 669.2972

*4.4.(R)-5-((S)-2-((tert-butyldimethylsilyl)oxy)-2-phenylethyl) pyrrolidin-2-one (**16**)*

The solution of compound **15** (0.5 g) in MeOH (10 mL) and acetic acid (5 drops) was treated with RANEY® nickel (1 g, excess) under a H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to the give the crude free amine which was further subjected to cyclisation by stirring in EtOH at 50 °C for 5 h. The reaction mixture was concentrated in vacuo to give the crude product. Silica gel column chromatography (Hexane: EtOAc, 6:4) of the crude product gave **16** as a thick liquid (0.201 g, 79%).

Thick liquid, R_f = 0.40 (Hexane: EtOAc/ 1:1);

$[\alpha]_D^{20}$= -4.62 (*c* 0.24, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.20 (5H, m), 5.90 (1H, s), 4.80 (1H, dd, *J* = 8.4, 4.1 Hz), 3.85 – 3.74 (1H, m), 2.34 – 2.22 (2H, m), 1.94 – 1.73 (4H, m), 0.92 (9H, s), 0.04 (3H, s), -0.16 (3H, s);

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 144.2, 127.9, 127.5, 124.9, 73.8, 51.6, 47.1, 30.1, 27.8, 25.8, 17.8, -4.5, -4.9;

HRMS (ESI^+)$[M+Na]^+$: found 342.1862 $C_{18}H_{29}NNaO_2Si$ requires 342.1865.

*4.5.(R)-5-((S)-2-hydroxy-2-phenylethyl)-1-methylpyrrolidin-2-one (**17**)*

To a solution of NaH (28 mg, 1.13 mmol) in 2 mL of DMF was added solution of lactam **16** (0.300 g, 0.94 mmol) in DMF (1 mL) at 0 °C under an N_2 atmosphere and stirred for 2 h. The reaction mixture was quenched with water and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum gave crude N-methylated lactam, which as is subjected for next reaction. A solution of tetrabutylammonium fluoride (TBAF; 0.736 g, 1 M in THF, 2.81 mmol) was added to a stirred solution of crude N-methylated lactam in THF at 0 °C and the mixture stirred for another 1 h at room temperature. The reaction was quenched by the addition of water, and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried with Na_2SO_4, and concentrated under vacuum. The crude product purified by column chromatography on silica gel by using Hexane/EtOAc (9:1) to give alcohol **17** as a thick liquid (170 mg, 82%)

Thick liquid*;* R_f = 0.12 (EtOAc/ hexane, 8:2);

$[\alpha]_D^{20}$= +5.16 (*c* 0.22, MeOH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (5H, m), 4.80 (1H, t, *J* = 6.9 Hz), 3.49 – 3.38 (1H, m), 2.79 (3H, s), 2.41 (1H, ddd, *J* = 15.6, 9.6, 6.1 Hz,), 2.28 – 2.23 (1H, m), 2.23 – 2.08 (2H, m), 1.95 – 1.78 (2H, m);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 143.9, 128.8, 128.1, 125.8, 72.1, 58.0, 42.5, 29.9, 28.1, 25.0;

HRMS (ESI^+)$[M+Na]^+$: found 242.1154 $C_{18}H_{29}NNaO_2Si$ requires 242.1157

*4.6. (S)-2-((R)-1-methylpyrrolidin-2-yl)-1-phenylethan-1-ol/(S)-(R)-(+)-pyrrolallosedamine (**7**)*

To a suspension of $LiAlH_4$ (28 mg, 0.72 mmol) in anhydrous Et_2O (3 mL), a solution of **17** (80 mg, 0.36 mmol) in Et_2O (2 mL) was added and reaction mixture was heated to reflux for 2 h. After completion of reaction (TLC check), a 15% aqueous NaOH solution (0.3 mL) and water (1 mL) were successively added, and the resulting mixture was then extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and

concentrated in vacuo to give crude product **7**. The crude product was purified by silica gel column chromatography using CH_2Cl_2: MeOH (9:1) to give the **7** as white solid (57 mg, 76%).
White solid; Mp 88–92 °C;
R_f = 0.42 (CH_2Cl_2/MeOH, 9:1);
$[\alpha]_D^{20}$= +5.69 (*c* 0.50, MeOH);
IR (neat): cm^{-1} 3355, 3092, 2951 1510;
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 7.7 Hz,), 7.37–7.27 (3H, m), 4.97 (1H, dd, *J* = 9.9, 1.8 Hz), 3.76 – 3.67 (1H, m), 3.55 – 3.47 (2H, m), 3.31 (3H, s), 2.77 – 2.71 (1H, m), 2.49 – 2.41 (1H, m), 2.33 (1H, ddd, *J* = 16.2, 9.9, 2.6 Hz), 2.16 – 2.06 (2H, m), 2.03 – 1.98 (1H, m);
^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5, 128.5, 126.6, 124.9, 73.8, 65.0, 55.9, 43.0, 42.7, 29.5, 23.3;
HRMS (ESI^+)$[M+H]^+$: found 206.1541 $C_{13}H_{20}NO$ requires 206.1545.

*4.7.(R)-2-((R)-1-methylpyrrolidin-2-yl)-1-phenylethan-1-ol/ (R,R)-(+)-pyrrolsedamine (**6**)*
To the solution **7** (50 mg, 0.24 mmol) in EtOAc was added IBX (103 mg, 0.36 mmol), and the mixture was heated to reflux for 2h. After complete consumption of starting material (TLC check) reaction mixture was cooled to room temperature and diluted with EtOAc. The precipitate was removed by filtration and solid residue was washed with EtOAc (3 x 5 mL). The combined filtrates were again washed with 5% $NaHCO_3$ (2 x 3 mL), H_2O (3 x 3 mL), and dried (Na_2SO_4), followed by removal of solvent invacuo to give crude product, which without any further chromatographic purification subjected to next reaction. To a suspension of $LiAl(O^tBu)_3H$ (124 mg, 0.60 mmol) in THF (1.5 mL), was dropwise added solution of crude ketone in THF (1 mL) at 0 °C and stirred for 8 h. After complete consumption of starting material (TLC check) reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried with Na_2SO_4, and concentrated under vacuum. The crude product purified by silica gel column chromatography (eluent CH_2Cl_2: MeOH, 9:1) gave syn-6 as white solid (44.5 mg, 89%)
White solid, (25 mg, 89%); Mp 88–93 °C;
R_f = 0.43 (CH_2Cl_2/MeOH, 9:1);
$[\alpha]_D^{20}$ = +72.1 (*c* 2.00, EtOH) [ref[9j]$[\alpha]_D^{25}$ = +73.7 (*c 2.00*, EtOH)].
IR (neat): cm^{-1} 3350, 3085, 2955 1490;
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40– 7.28 (4H, m), 7.28 – 7.24 (1H, m), 4.88 (1H, d, *J* = 10.0 Hz), 4.11 (1H, bs), 3.15 (1H, dt, *J* = 10.7, 6.5 Hz), 2.95 – 2.87 (1H, m), 2.47 – 2.42 (4H, m), 2.09 – 2.04 (1H, m), 1.86 – 1.78 (3H, m), 1.66 (1H, ddd, *J* = 14.1, 5.7, 2.5 Hz), 1.49 – 1.40 (1H, m);
^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 128.2, 127.0, 125.5, 73.8, 66.1, 55.4, 43.0, 42.9, 30.4, 22.7;
HRMS (ESI^+)$[M+H]^+$: found 206.1541 $C_{13}H_{20}NO$ requires 206.1545

*4.8. Dibenzyl-1((1S,3R,E)-1-((tert-butyldimethylsilyl)oxy)-6-ethoxy6oxo-1phenylhex-4-en3yl)hydrazine-1,2dicarboxylate (**20**)*
To a cooled solution of dibenzyl azodicarboxylate (DBAD) (0.445 g**,** 1.49 mmol) and L-proline (0.051 g, 0.446 mmol) in CH_3CN (30 mL) at 0 °C was added aldehyde **14** (0.5 g, 1.79 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 (0.098 g, 2.33 mmol), triethyl phosphonoacetate (0.44 mL, 2.33 mmol) and DBU (0.272 mL, 1.79 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. Silica gel column chromatography (Hexane: EtOAc; 85:15) of the crude product gave **20** as a colourless syrupy (0.911 g, yield 76% based on aldehyde)
Colourless syrupy; R_f = 0.44 (Hexane: EtOAc, 3:7);
$[\alpha]_D^{20}$= -1.70 (*c* 0.67, MeOH);
^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 7.30 (15H, s), 6.92 (1H, dd, *J* = 7.5, 6.6 Hz), 6.74 (1H, bs), 5.98 (1H, s), 5.25 – 4.80 (6H, m), 4.18 (2H, q, *J* = 7.0 Hz), 2.36 (1H, bs), 1.95 – 1.90 (1H, m), 1.29 (3H, t, *J* = 7.0 Hz,), 0.91 (9H, s), 0.03 (3H, s), -0.21 (3H, s);
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 156.6, 155.2, 144.8, 144.2, 135.6, 128.5, 128.3, 128.0, 127.4, 126.0, 122.9, 72.1, 68.3, 67.7, 60.5, 60.3, 56.2, 41.6, 29.7, 29.0, 25.8, 14.2, 14.1, -4.5, -5.0;
HRMS (ESI^+)$[M+Na]^+$: found 669.2972. $C_{36}H_{46}N_2NaO_7Si$ requires 669.2972.

*4.9.(S)-5-((S)-2-((tert-butyldimethylsilyl)oxy)-2-phenylethyl) pyrrolidin-2-one (**21**)*
The solution of compound **20** (0.5 g) in MeOH (10 mL) and acetic acid (5 drops) was treated with RANEY® nickel (1 g, excess) under a H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to the give the crude free amine which was further subjected to cyclisation by stirring in EtOH at 50 °C for 5 h. The reaction mixture was concentrated in vacuo to give the crude product. Silica gel column chromatography (Hexane: EtOAc, 6:4) of the crude product gave **21** as a thick liquid (0.203 g, 79%).
Thick liquid, R_f = 0.40 (Hexane: EtOAc, 1:1);
$[\alpha]_D^{20}$= -2.74 (*c* 0.2, MeOH);
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.26 (5H, m), 5.92 (1H, s), 4.80 (1H, dd, *J* = 8.5, 3.9 Hz,), 3.81 – 3.71 (1H, m), 2.33 – 2.26 (2H, m), 1.95 – 1.90 (1H, m), 1.87 – 1.73 (3H, m), 0.91 (9H, s), 0.04 (3H, s), -0.16 (3H, s);
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 144.3, 128.4, 127.5, 125.7, 74.2, 52.3, 47.7, 29.9, 28.2, 25.8, 18.1, -4.5, -4.9;
HRMS (ESI^+)$[M+Na]^+$: found 342.1862 $C_{18}H_{29}NNaO_2Si$ requires 342.1865

*4.10. (S)-5-((S)-2-hydroxy-2-phenylethyl)-1-methylpyrrolidin-2-one (**22**)*
To a solution of NaH (14 mg, 0.56 mmol) in 2 mL of DMF was added solution of lactam **21** (0.150 g, 0.47 mmol) in DMF (1 mL) at 0 °C under an N_2 atmosphere and stirred for 2 h. The reaction mixture was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum gave crude *N*-methylated lactam, which as is subjected for next reaction. A solution of tetrabutylammonium fluoride (TBAF; 0.368 g, 1 M in THF, 1.40 mmol) was added to a stirred solution of crude N-methylated lactam in THF at 0 °C and the mixture stirred for another 1 h at room temperature. The reaction was quenched by the addition of water, and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried with Na_2SO_4, and concentrated under vacuum. The crude product purified by column chromatography on silica gel by using Hexane/EtOAc (9:1) to give alcohol **22** as a thick liquid (85 mg, 82% two steps)
Thick liquid*;* R_f = 0.13 (Hexane: EtOAc, 8:2);
$[\alpha]_D^{20}$= -1.35 (*c* 0.21, MeOH);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (5H, m), 5.31(1H, s) 4.80 (1H, dd, *J* = 13.0, 2.9 Hz), 3.88 – 3.78 (1H, m), 2.81 (3H, s), 2.48 – 2.37 (1H, m), 2.31 (1H, dd, *J* = 9.6, 6.6 Hz), 2.27 – 2.21 (2H, m), 1.89 – 1.79 (1H, m), 1.65 – 1.53 (1H, m);
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 144.3, 128.7, 127.9, 125.5, 71.0, 57.7, 42.3, 29.8, 27.8, 24.2;
HRMS (ESI^+)$[M+Na]^+$: found 242.1152 $C_{18}H_{29}NNaO_2Si$ requires 242.1157

*4.11. (S)-2-((S)-1-methylpyrrolidin-2-yl)-1-phenylethan-1-ol/ (S)-(S)-(-) pyrrolsedamine (**8**)*

To a suspension of $LiAlH_4$ (10 mg, 0.252 mmol) in anhydrous Et_2O (3 mL), a solution of **22** (28 mg, 0.126 mmol) in Et_2O (2 mL) was added and reaction mixture was heated to reflux for 2 h. After completion of reaction (TLC check), a 15% aqueous NaOH solution (0.3 mL) and water (1 mL) were successively added, and the resulting mixture was then extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to give crude product **7**. The crude product was purified by silica gel column chromatography using CH_2Cl_2: MeOH (9:1) to give the **8** as white solid (20 mg, 76%).

White solid, Mp 88–93 °C; R_f = 0.42 (CH_2Cl_2/MeOH, 9:1);

$[\alpha]_D^{20}$ = -13.3 (*c* 0.19, MeOH)

IR (neat): cm^{-1} 3354, 3085, 2955 1492;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (4H, m), 7.30 – 7.23 (1H, m), 4.87 (1H, dd, *J* = 10.0, 2.5 Hz,), 4.27 (1H, bs), 3.23 – 3.12 (1H, m), 2.98 –2.92 (1H, m), 2.49 – 2.42 (4H, m), 2.08 (1H, ddd, *J* = 16.0, 12.7, 8.0 Hz), 1.88 – 1.77 (3H, m), 1.68 (1H, ddd, *J* = 14.1, 5.8, 2.6 Hz), 1.47 – 1.42 (1H, m);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 128.2, 127.0, 125.5, 73.7, 66.1, 55.3, 42.8, 42.7, 30.4, 22.7

HRMS (ESI^+)$[M+H]^+$: found 206.1541 $C_{13}H_{20}NO$ requires 206.1545

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13. The detailed comparison NMR data of natural isomer (*R*)-(*R*)-(+)-pyrrolsedamine **6** and synthetic isomer (*S*)-(*S*)-(-)-pyrrolsedamine **8** is provided in supporting information (Table 1).

Supplementary Material

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Table 1. ^{1}H and ^{13}C NMR data comparison of 6 and 8

Sr. No.	(*R*)-(*R*)-(+)-pyrrolsedamine **6** (natural isomer)		(*S*)-(*S*)-(-)-pyrrolsedamine **8** (synthetic isomer)	
	δH (*J* in Hz)	δC	δH (*J* in Hz)	δC
1	4.88 (1H, d, *J* = 10.0 Hz)	73.8	4.87 (dd, *J* = 10.0, 2.5 Hz, 1H)	73.7
2	1.66 (1H, ddd, *J* = 14.1, 5.7, 2.5 Hz) H_a and 1.86 – 1.78 (1H, m) H_b	42.9	1.68 (ddd, *J* = 14.1, 5.8, 2.6 Hz, 1H) H_a and 1.88 – 1.77 (m, 1H) H_b	42.7
3	2.95 – 2.87 (1H, m)	66.1	2.98 –2.92 (m, 1H)	66.1
4	1.49 – 1.40 (1H, m) H_a and 2.09 – 2.04 (1H, m) H_b	30.4	1.47 – 1.42 (1H, m) H_a and 2.08 (ddd, *J* = 16.0, 12.7, 8.0 Hz, 1H) H_b	30.4
5	1.86 – 1.78 (2H, m),	22.7	1.88 – 1.77 (m, 2H)	22.7
6	2.47 – 2.42 (1H, m) H_a and 3.15 (1H, dt, *J* = 10.7, 6.5 Hz) H_b	55.4	2.49 – 2.42 (m, 1H) H_a and 3.23 – 3.12 (m, 1H) H_b	55.3
7	2.47 – 2.42 (3H, m) NMe	43.0	2.49 – 2.42 (m, 3H) Nme	42.8
8	-	145.4 i-Ph	-	145.3 i-Ph
9	7.40– 7.28 (4H, m)	128.2 o-Ph	7.42 – 7.32 (m, H)	128.2 o-Ph
10		125.5 m-Ph		125.5 m-Ph
11	7.28 – 7.24 (1H, m)	127.0 p-Ph	7.28 – 7.24 (1H, m)	127.0 p-Ph
12	OH 4.11 (1H, bs)		OH 4.27 (1H, bs)	