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An expedient total synthesis of optically active piperidine and indolizidine alkaloids (−)-β-conhydrine and (−)-lentiginosine

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ABSTRACT

Attempts directed toward the stereocontroled total synthesis of piperidine and indolizidine alkaloids resulted in the synthesis of (−)-β-conhydrine **1** and (−)-lentiginosine **3**. The synthesis of **1** and **3** were developed from protected D-mannitol as the chiral precursor, which involved nucleophilic addition and azide nucleophilic substitution, Barbier allylation, ring closing metathesis, and Sharpless asymmetric dihydroxylation as the key steps.

1. Introduction

Exploiting natural products to ascertain a lead has always been an important technique in drug discovery.[1] The piperidine and indolizidine moieties are found as core structures in many structurally diverse and stereochemically interesting alkaloids. Many of these alkaloids also possess potent and therapeutically interesting biological activities. Particularly, those that are α-substituted by 1-hydroxy alkyl side chain constitutes a framework, that is, frequently encountered in natural alkaloids, such as conhydrine and lentiginosine (Fig. 1) and have attracted much attention due to their antiviral, antitumor, and anti-HIV properties.[2] (−)-β-Conhydrine **1** is one of the alkaloids of the hemlock, isolated from the seeds and leaves of the poisonous alkaloids plant *Conium maculatum* L., whose extracts were used in the Greece for the execution of criminals in 1856[3] and its structure was elucidated in 1933.[4] The polyhydroxylated indolizidine alkaloid (−)-lentiginosine **3** is the *trans*-dihydroxylated indolizidine alkaloid isolated from the leaves of *Astrayalus lentiginousus* in 1990.[5] Polyhydroxylated indolizidine alkaloids with glycosidase inhibitory properties have been the subject of an intense research effort during the last two decades. Such inhibitors are not only useful as potential drugs for the treatment of viral infections, cancer, autoimmune pathologies, diabetes, and other metabolic disorders but can also provide a new insight into the widespread and important glycoside cleavage/formation processes.[6] In view of their enormous biological importance of this class of compounds, a number of auxiliary supported or chiral pool approaches have been reported for (+)-β-conhydrine **2**[7] and (+)-lentiginosine **4**.[8] However not much attention has been given to the enantioselective syntheses for the preparation of (−)-β-conhydrine **1**[9] and (−)-lentiginosine **3**.[10, 17]

As part of our research program aimed at developing enantioselective syntheses of naturally occurring alkaloids and lactones,[7c,11] we became interested in developing a general route capable of providing not only the target molecules **1** and **3** but also their other stereoisomers. Herein, we would like to report an efficient total synthesis of (−)-β-conhydrine **1** and (−)-lentiginosine **3** employing an entirely different approach. This strategy involves

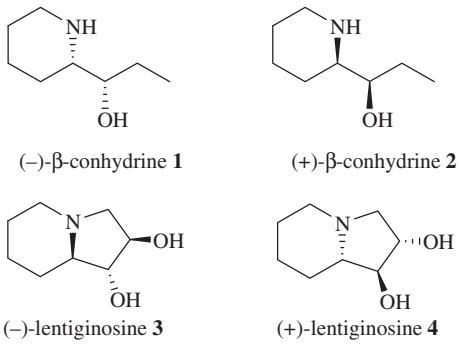

Fig. 1. 1-Hydroxy piperidine molecules.

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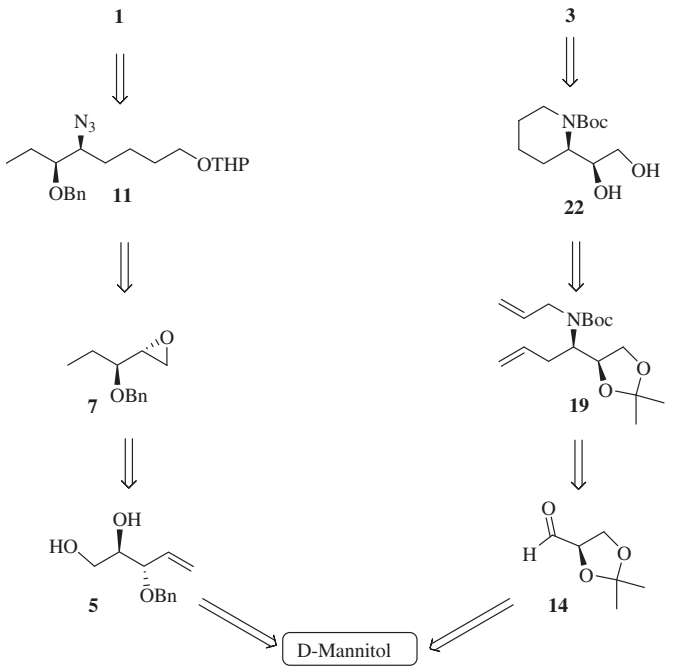
practically simple and high yielding reactions for the synthesis of both (−)-β-conhydrine **1** and (−)-lentiginosine **3** starting from D-mannitol.

2. Result and discussions

2.1. Retrosynthetic analysis

As per our retrosynthetic analysis (Scheme 1), the (−)-β-conhydrine **1** could be easily obtained from the precursor **11**, which inturn could be synthesized from intermediate **5** via epoxide (**7**) and also the (−)-lentiginosine **3** could be easily obtained from the precursor **22**. Compound **22** could be prepared from **19** involving ring closing metathesis and Pd−C/H_2 reduction for saturation of double bond and compound **19**[7c] is expected to be obtained from **14**. Whereas,



Scheme 1. Retrosynthetic approach for (−)-β-conhydrine **1** and (−)-lentiginosine **3**.

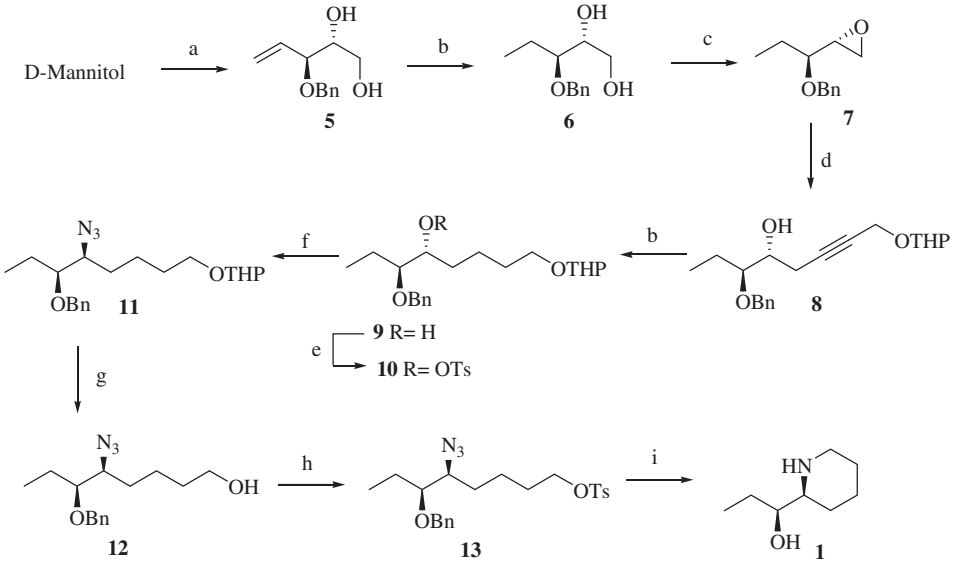
5[11a] and **14**[12] could be prepared from optically active D-mannitol by using known protocols. This could be an effective route for the preparation of (−)-β-conhydrine **1** and (−)-lentiginosine **3**.

2.2. Synthesis of (−)-β-conhydrine (Scheme 2)

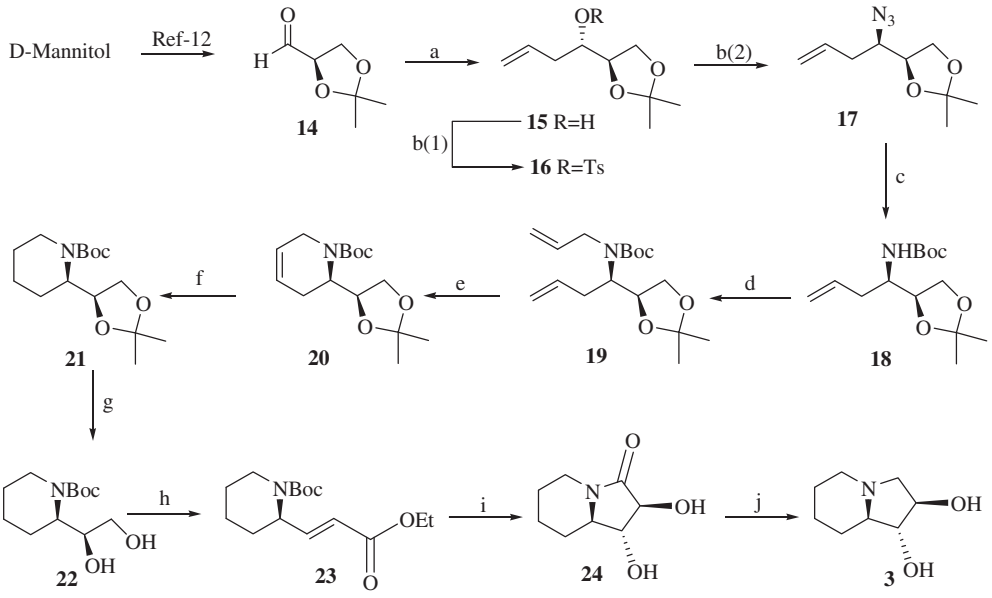
Our journey for the synthesis of (−)-β-conhydrine **1** began with (2*R*,3*S*)-3-(benzyloxy)-4-pentene-1,2-diol **5**, which was obtained by using a known protocol.[11a] Compound **5** was exposed to Lindlar's catalyst that results in the saturation of double bond in EtOAc to provide diol **6** in quantitative yield. The oxirane formation was achieved by the selective tosylation of the primary hydroxyl group in **6** using Martinelli standard conditions[13] employing *p*-toluenesulfonyl chloride, dibutyltin oxide, and trimethylamine in CH_2Cl_2 to afford the monoprotected tosylate of **6**. Then the crude tosylate was taken up for the cyclization step using K_2CO_3 in methanol to afford the epoxide **7**[16] in an excellent yield. This epoxide **7**, on treatment with 2-(2-propynyloxy)tetrahydro-2*H*-pyran (**25**) in the presence of *n*-BuLi and $BF_3\cdot Et_2O$ in THF at −78 °C for 3 h, afforded **8**. Compound **8** was exposed to Lindlar's catalyst that results in the saturation of triple bond in EtOAc to provide **9** in 95% yield. The secondary alcohol of the compound **9** was converted to the corresponding tosylated compound **10** by using *p*-toluenesulfonyl chloride and pyridine. The crude compound **10** was then subjected to nucleophilic displacement with NaN_3 in DMF at 60 °C to furnish the corresponding azide **11** in 72% yield (for two steps). Deprotection of the THP group in compound **11** was carried out by using PTSA to afford **12**. The primary alcohol in **12** was converted to tosylate using *p*-toluenesulfonyl chloride and TEA to give the corresponding tosylate compound **13**. Finally, the target molecule was achieved by the reduction of azide and deprotection of benzyl group using Pd−C/H_2 in EtOAc and added one drop 30% methanolic NaOH solution in the reaction mixture to give the desired (−)-β-conhydrine **1** in 82% yield. The physical and spectroscopic data of **1** were in agreement with those reported in the literature. However, this method has provided good overall yield with enhanced stereoselectivity of the target molecule, (−)-β-conhydrine **1**.

2.3. Synthesis of (−)-lentiginosine 3 (Scheme 3)

Synthesis of (−)-lentiginosine **3** began with the Barbier allylation reaction on *R*-2,3-*O*-isopropylidene glyceraldehyde **14**, using



Scheme 2. Reaction conditions: (a) Ref. 11a; (b) Lindlar's catalyst-H_2, ethanol, rt, 4 h, 95%; (c) *p*-toluenesulfonyl chloride, dibutyltin oxide, triethylamine, dry CH_2Cl_2, 0 °C to rt, 4 h, then K_2CO_3, MeOH, rt, 3 h, 92%; (d) **25**, *n*-BuLi, $BF_3\cdot Et_2O$, dry THF, −78 °C, 3 h, 78%; (e) *p*-toluenesulfonyl chloride, pyridine, 0 °C to rt, 16 h; (f) NaN_3, DMF, 60 °C, 14 h, 72% (for two steps); (g) PTSA, MeOH, rt, 5 h, 96%; (h) *p*-toluenesulfonyl chloride, TEA, dry CH_2Cl_2, rt, 92%; (i) 10% Pd−C/H_2, EtOAc, one drop 30% NaOH, rt, 6 h, 85%.



Scheme 3. Reaction conditions: (a) Zn, allyl bromide, THF, saturated aq NH_4Cl, 0 °C to rt, 8 h, 65%; (b) (1) *p*-toluenesulfonyl chloride, pyridine, 0 °C to rt, 91% (2) NaN_3, DMF, 60 °C, 14 h, 85%; (c) (1) $LiAlH_4$, THF, 0 °C to rt, 1 h (2) 15% NaOH, $(Boc)_2O$, 0 °C to rt, 4 h, 88%; (d) NaH, allyl bromide, THF, saturated aq NH_4Cl, 0 °C to rt, 18 h, 85%; (e) first generation Grubb's catalyst, dry CH_2Cl_2, reflux, 8 h, 91%; (f) 10% Pd–C/H_2, EtOAc, rt, 6 h, 96%; (g) PTSA, MeOH, rt, 5 h, 85%; (h) (1) $NaIO_4$, saturated aq $NaHCO_3$, CH_2Cl_2, rt; (2) $Ph_3P{=}CHCO_2Et$, dry C_6H_6, 50 °C; (i) (1) AD-mix-β, $CH_3SO_2NH_2$, H_2O:*t*-BuOH=1:1, 0 °C, 24 h; (2) TFA, rt, 10 h; (3) EtOH, reflux, 6 h, 62% (for three steps); (j) $LiAlH_4$, THF, reflux, 12 h, 84%.

Zn-allyl bromide at 0 °C to give the homoallylic alcohol **15**[7c] with good diastereoselectivity (*syn-anti*= 5:95). This alcohol was converted to the corresponding tosylate **16** in excellent yield (91%) by using *p*-toluenesulfonyl chloride and pyridine. This tosylated compound **16** was then subjected to nucleophilic displacement with NaN_3 in DMF at 60 °C to furnish the corresponding azide **17** in good yield (85%). Compound **17** was treated with $LiAlH_4$, which results in the reduction of the azide functionality to its corresponding amine. The reaction mixture was then quenched with 10% NaOH solution and $(Boc)_2O$ was added immediately to convert the amine to its *N*-Boc derivative **18**[7c] in 88% yield. This on allylation with allyl bromide and NaH in THF at 0 °C gave *N*-allyl compound **19**. The RCM of **19** in the presence of Grubb's first generation catalyst[10h–j,14] $Cl_2Ru(=CHPh)(Cy_3)_2$ (5 mol %) in dry CH_2Cl_2 at reflux condition proceeds to give compound **20**, which was exposed to Pd–C/H_2 that results in the saturation of double bond in EtOAc to provide compound **21** in quantitative yield. Deprotection of the primary acetonide in compound **21** with PTSA in MeOH furnished the diol **22**[15] in good yield. This was treated with $NaIO_4$ in the presence of saturated $NaHCO_3$ to give piperidine carboxaldehyde, which on in situ Wittig olefination by using stabilized ylide ($Ph_3P{=}CHCO_2Et$) gives α,β-unsaturated *N*-Boc piperidine **23** in good yield. The geometry of the newly formed double bond was assigned by the detection of the J_{trans} coupling constant (15.86 Hz between the protons at δ 5.73 and 6.81, respectively). This was then taken up for the stereoselective incorporation of hydroxyl groups via a Sharpless asymmetric dihydroxylation. The enantioselective Sharpless asymmetric dihydroxylation of α,β-unsaturated *N*-Boc piperidine **23** with ADmix β, in *t*-BuOH/H_2O (1:1) provided the diol. This was further treated with TFA without purification for deprotection of Boc group, followed by refluxing the crude compound in EtOH to furnish indolizidinone **24**[17] in 62% yield (for three steps). The reduction of the carbonyl group in indolizidinone **24** was carried out by using $LiAlH_4$ to give **3** in 84% yield. The physical and spectroscopic data of **3** were in agreement with those reported in the literature. However, this method has provided good overall yield with enhanced stereoselectivity of the target molecule, (−)-lentiginosine **3**.

3. Conclusion

In conclusion, we report the asymmetric total synthesis of (−)-β-conhydrine **1** and (−)-lentiginosine **3** from the commercially available starting material D-mannitol in good overall yields. The present method not only involves simple and high yielding reactions like reduction, nucleophilic addition, nucleophilic displacement but could also provide an easy practical access to the synthesis of a variety of structural analogues of (−)-β-conhydrine **1** and (−)-lentiginosine **3** for evaluating their biological properties.

4. Experimental

4.1. General experimental

All reagents were purchased from Aldrich (Sigma–Aldrich, St. Louis, MO, USA). Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254. Column chromatography was performed with Merck 60–120 mesh silica gel. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^1H NMR spectra were recorded on a Bruker UXNMR/XWIN-NMR-300 MHz spectrometer. ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million downfield from internal TMS standard. Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), doublet doublet (dd), doublet doublet doublet (ddd), triplet doublet (td), and multiplet (m). ESI spectra were recorded on Micro mass, Quattro LC using ESI^+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter.

*4.1.1. (2R,3S)-3-(Benzyloxy)pentane-1,2-diol (**6**).* A mixture of compound **5** (2 g, 9.62 mmol) and Lindlar's catalyst (50 mg) in dry ethanol (20 mL) was stirred under hydrogen atmosphere at room temperature for 4 h. The reaction mixture was filtered through Celite and the solvent evaporated in vacuo to give the crude product, which was purified by column chromatography (hexane/EtOAc, 7:3) to give compound **6** (1.92 g, 95%) as a syrup. $[\alpha]_D^{27}$ +21 (*c*

1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.25 (5H, m, Ar–*H*), 4.72–4.45 (2H, m, PhCH_2), 3.79–3.55 (3H, m, CH_2OH, and C*H*OH), 3.54–3.39 (1H, m, C*H*OBn), 2.74–2.04 (2H, br s, O*H*), 1.82–1.50 (2H, m, CH_2CH$_3$), 1.00 (3H, t, *J* 7.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.22, 128.45, 127.91, 127.72, 82.32, 72.65, 72.22, 63.63, 23.05, 9.62; IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2966, 2931, 2877, 1713, 1455, 1274, 1070, 1024, 701 cm^{-1}; ESI: *m*/*z* 233.2 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}O_3Na$: 233.1153; found: 233.1158.

*4.1.2. (R)-2-((S)-1-(benzyloxy)propyl)oxirane (**7**).* To a stirred solution of compound **6** (2 g, 9.52 mmol), dibutyltin oxide (35 mg, 0.05 mmol), and Et_3N (1.37 mL, 9.52 mmol) in dry CH_2Cl_2, *p*-toluenesulfonyl chloride (1.82 g, 9.52 mmol) was added at 0 °C under N_2 atmosphere. On completion of reaction after stirring for 4 h at room temperature, water was added and the reaction mixture was extracted with CH_2Cl_2. The organic extract was washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded a crude mass, which was used for next step without any purification. To the monotosylate derivative of **6** in dry MeOH (25 mL), anhydrous K_2CO_3 (3.94 g, 28.57 mmol) was added under N_2 atmosphere and stirred for 3 h. On completion of reaction, MeOH was evaporated under reduced pressure keeping the temperature below 30 °C. The residue was redissolved in CH_2Cl_2, washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded a residue, which on purification with silica gel column chromatography (hexane/EtOAc, 9:1) afforded epoxide **7** (1.68 g, 92%) as a colorless liquid. $[\alpha]_D^{35}$ +5.6 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.25 (5H, m, Ar–*H*), 4.66–4.48 (2H, m, PhCH_2), 3.22–3.18 (1H, m, C*H*OBn), 2.95–2.92 (1H, m, OC*H*), 2.79–2.77 (1H, m, OCH_2CH), 2.72–2.69 (1H, m, OCH_2CH), 1.81–1.54 (2H, m, CH_2CH$_3$), 1.1 (3H, t, *J* 7.2 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.81, 128.21, 127.77, 127.65, 82.23, 72.42, 70.21, 63.92, 23.45, 9.62; IR ($CHCl_3$, cm^{-1}): ν_{max} 2966, 2924, 2361, 1455, 1071, 1028, 847, 737, 698 cm^{-1}; MS (ESI) *m*/*z*: 215(M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{16}O_2Na$: 215.1047; found: 215.1047.

*4.1.3. (3S,4R)-3-(Benzyloxy)-8-(tetrahydro-2H-pyran-2-yloxy)oct-6-yn-4-ol (**8**).* To a stirred solution of **25** (1.28 g, 9.98 mmol) in dry THF (40 mL), *n*-BuLi (5.96 mL, 9.98 mmol, 1.6 N hexane solution) was added drop wise under N_2 atmosphere at −78 °C and stirred for 30 min. To this reaction mixture, $BF_3.OEt_2$ (1.17 mL, 8.33 mmol) was added, followed by a solution of compound **7** (1.6 g, 8.33 mmol) in dry THF (10 mL) after 10 min interval and the resulting solution stirred for an additional 3 h at −78 °C. After completion of reaction, the reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and saturated NH_4Cl solution (20 mL) at −78 °C and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3×50 mL), washed with water (2×20 mL), dried over Na_2SO_4, evaporated, and the residue obtained was purified by silica gel column chromatography (EtOAc/hexane, 1.5:8.5) to furnish **8** (2.1 g, 78%) as a yellow liquid. $[\alpha]_D^{35}$ +7.5 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.25 (5H, m, Ar–*H*), 4.86–4.76 (1H, m, THP-*H*), 4.72–4.51 (2H, m, PhCH_2), 4.32–4.18 (2H, m, OCH_2C), 3.94–3.72 (2H, m, THP-*H*), 3.59–3.39 (2H, m, C*H*OH, and C*H*OBn), 2.59–2.46 (1H, m, CCH_2CH), 2.46–2.41 (1H, m, CCH_2CH), 1.94–1.54 (8H, m, CH_2CH$_3$, and THP-*H*), 0.99–0.92 (3H, q, *J* 7.18 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.32, 127.82, 127.77, 127.62, 96.84, 81.86, 81.25, 78.35, 72.25, 70.49, 61.96, 54.51, 30.22, 25.25, 23.03, 22.16, 19.02, 9.45; IR ($CHCl_3$, cm^{-1}): ν_{max} 3423, 2941, 2875, 2203, 1454, 1116, 1074, 1023, 927, 902, 749, 698 cm^{-1}; MS (ESI) *m*/*z*: 355 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{28}O_4Na$: 355.1885; found: 355.1879.

*4.1.4. (3S,4R)-3-(Benzyloxy)-8-(tetrahydro-2H-pyran-2-yloxy)octan-4-ol (**9**).* A mixture of compound **8** (2 g, 6.02 mmol) and Lindlar's catalyst (50 mg) in dry ethanol (20 mL) was stirred under a hydrogen atmosphere at room temperature for 4 h. On completion of reaction, the reaction mixture was filtered through Celite and the solvent evaporated in vacuo to give the crude product, which was purified by column chromatography (hexane/EtOAc, 94:6) to afford compound **9** (1.93 g, 95%) as colorless oil. $[\alpha]_D^{35}$ +4.9 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.25 (5H, m, Ar–*H*), 4.72–4.46 (3H, m, PhCH_2, and THP-*H*), 3.92–3.73 (2H, m, OCH_2CH$_2$), 3.52–3.36 (2H, m, THP-*H*), 3.32–3.25 (1H, m, C*H*OH), 3.24–3.19 (1H, m, C*H*OBn), 1.96–1.33 (14H, m, OCH$_2$(CH_2)$_3$CH, CH_2CH$_3$, and THP-*H*), 1.05–0.93 (3H, q, *J* 7.38 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.31, 127.83, 127.77, 127.62, 98.82, 83.69, 72.03, 71.55, 67.45, 62.27, 31.74, 30.72, 29.71, 25.43, 22.89, 21.62, 19.63, 10.24; IR ($CHCl_3$, cm^{-1}): ν_{max} 3467, 2941, 2871, 1454, 1119, 1075, 1027, 904, 754, 698, 666 cm^{-1}; MS (ESI) *m*/*z*: 359 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{32}O_4Na$: 359.2198; found: 359.2192.

*4.1.5. 2-((5S,6S)-5-Azido-6-(benzyloxy)octyloxy)-tetrahydro-2H-pyran (**11**).* To a stirred solution of compound **9** (1 g, 2.97 mmol) in dry CH_2Cl_2 (10 mL), excess of pyridine (6 mL) was added at room temperature and the reaction mixture was cooled to 0 °C. *p*-Toluenesulfonyl chloride (0.57 g, 2.97 mmol) was added and the reaction mixture was stirred for 16 h at room temperature. After completion of the reaction, the solvent was removed under reduced pressure to obtain crude tosylate **10**. To the crude tosylate **10** (3 g, 9.2 mmol) in dry DMF (10 mL) was added NaN_3 (0.24 g, 3.57 mmol). This heterogeneous mixture was stirred at 60 °C for 14 h, and then it was cooled to room temperature followed by addition of water (20 mL), and extraction with ether (3×30 mL). The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4, evaporated, and the residue obtained was purified by silica gel column chromatography (hexane/EtOAc, 96:4) to afford azide **11** (0.80 g, 72%) as a colorless liquid. $[\alpha]_D^{35}$ −21.6 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.26 (5H, m, Ar–*H*), 4.68–4.53 (3H, m, PhCH_2, and THP-*H*), 3.89–3.83 (1H, m, C*H*OBn), 3.83–3.71 (1H, m, C*H*N$_3$), 3.56–3.26 (4H, m, OCH_2CH$_2$, and THP-*H*), 1.91–1.34 (14H, m, OCH$_2$(CH_2)$_3$CH, CH_2CH$_3$, and THP-*H*), 1.02–0.91 (3H, q, *J* 7.18 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.31, 127.79, 127.73, 127.58, 98.88, 82.44, 72.51, 67.21, 64.13, 62.32, 30.69, 30.07, 29.45, 25.3, 23.51, 23.22, 19.62, 9.57; IR ($CHCl_3$, cm^{-1}): ν_{max} 2941, 2869, 2101, 1454, 1262, 1120, 1077, 1033, 736, 697 cm^{-1}; MS (ESI) *m*/*z*: 384 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{20}H_{31}N_3O_3Na$: 384.2263; found: 384.2251.

*4.1.6. (5S,6S)-5-Azido-6-(benzyloxy)octan-1-ol (**12**).* A mixture of compound **11** (0.5 g, 1.38 mmol) and PTSA (12 mg, 5 mol %) in MeOH (10 mL) was stirred at room temperature for 5 h. After completion of reaction saturated $NaHCO_3$ solution was added and stirred for additional 15 min followed by removal of the solvent under reduced pressure. The residual compound was redissolved in CH_2Cl_2 and the organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by column chromatographic purification (hexane/EtOAc, 9:1) afforded a pure compound **12** (0.37 g, 96%) as a colorless thick liquid. $[\alpha]_D^{35}$ −22.1 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.25 (5H, m, Ar–*H*), 4.65–4.53 (2H, m, PhCH_2), 3.67–3.59 (2H, m, CH_2OH), 3.45–3.25 (2H, m, C*H*OBn, and C*H*N$_3$), 1.71–1.34 (8H, m, CH(CH_2)$_3$OH, and CH_2CH$_3$), 0.99–0.92 (3H, q, *J* 7.36 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.28, 127.80, 127.75, 127.59, 82.35, 72.47, 64.14, 62.45, 32.31, 29.96, 23.46, 22.65, 9.54; IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2931, 2103, 1216, 1069, 758 cm^{-1}; MS (ESI) *m*/*z*: 300 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}N_3O_2Na$: 300.1687; found: 300.1682.

*4.1.7. (5S,6S)-5-Azido-6-(benzyloxy)octyl 4-methylbenzenesulfonate (**13**).* To a stirred solution of compound **12** (0.250 g, 0.9 mmol) in dry CH_2Cl_2 (5 mL) was added TEA (2 mL) at room temperature and cooled to 0 °C. *p*-Toluenesulfonyl chloride (0.19 g, 1 mmol) was

added and reaction mixture was stirred for 4 h at room temperature. After removal of the solvent under reduced pressure a residue was obtained, which was purified by column chromatography (hexane/EtOAc, 94:6) to give the tosylate compound **13** (350 mg, 92%) as a colorless liquid. $[\alpha]_D^{35}$ −20.2 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.81–7.75 (2H, d, *J* 8.31 Hz, Ar–*H*), 7.33–7.21 (7H, m, Ar–*H*), 4.64–4.49 (2H, m, PhCH_2), 4.04–3.96 (2H, t, *J* 6.23 Hz, 00CH_2CH_2), 3.36–3.25 (1H, m, C*H*OBn), 3.21–3.12 (1H, m, C*H*N_3), 2.45 (3H, s, PhCH_3), 1.74–1.22 (8H, m, CH(CH_2)$_3$OH, and CH_2CH_3), 1.01–0.89 (3H, q, *J* 7.36 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.71, 138.14, 132.99, 129.81, 128.32, 127.81, 127.69, 127.52, 82.26, 72.46, 70.12, 63.93, 29.55, 28.57, 23.41, 22.42, 21.58, 9.52; IR ($CHCl_3$, cm^{-1}): ν_{max} 2941, 2133, 1217, 1069, 778, 698 cm^{-1}; MS (ESI) *m*/*z*: 454 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{29}N_3O_4SNa$: 454.1687; found: 454.1682.

*4.1.8. (S)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**15**).* To a stirred suspension of Zn (4.5 g, 69 mmol) in dry THF (30 mL), a solution of *R*-2,3-*O*-isopropylidene glyceraldehyde **14** (3 g, 23 mmol) in dry THF (15 mL) was added and cooled to 0 °C under nitrogen atmosphere. After stirring at 0 °C for 15 min, allyl bromide (6 mL, 69 mmol) was added and the reaction mixture was stirred for 8 h at room temperature. The reaction mass quenched with saturated aq NH_4Cl at 0 °C and resulting reaction mixture was filtered through a pad of Celite, followed by removal of the solvent under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 9:1) to give compound **15** (2.85 g, 72%) as a pale yellow liquid. $[\alpha]_D^{27}$ +10.8 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.09–5.75 (1H, m, C*H*=CH_2), 5.16–5.06 (2H, m, CH=CH_2), 3.99–3.83 (3H, m, OCH_2CH, and OC*H*), 3.73–3.66 (1H, m, C*H*OH), 2.35–2.31 (2H, m, CHCH_2CH), 1.93 (1H, br s, O*H*), 1.39 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$): δ 134.5, 118.6, 109.5, 78.6, 70.5, 65.7, 38.1, 27.0, 25.7; IR ($CHCl_3$, cm^{-1}): ν_{max} 3688, 2989, 2936, 2360, 1376, 1217, 1066, 920 cm^{-1}; MS (ESI) *m*/*z*: 172 (M^+).

*4.1.9. (S)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl 4-methylbenzenesulfonate (**16**).* To a solution of compound **15** (2 g, 11.6 mmol) taken in dry CH_2Cl_2 (10 mL), were added *p*-toluenesulfonyl chloride (2.47 g, 13 mmol) and excess of pyridine (6 mL) at room temperature. The reaction mixture then stirred for 16 h followed by removal of the solvent under reduced pressure to give a residue, which was purified by column chromatography (hexane/EtOAc, 94:6) to give compound **16** (3.448 g, 91% yield) as a thick yellow liquid. $[\alpha]_D^{27}$ +32.1 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.77–7.75 (2H, d, *J* 8.3 Hz, Ar–*H*), 7.33–7.28 (2H, d, *J* 8.3 Hz, Ar–*H*), 5.75–5.53 (1H, m, C*H*=CH_2), 5.15–4.96 (2H, m, CH=CH_2), 4.58–4.46 (1H, q, *J* 6.7 Hz, C*H*OTs), 4.14–4.01 (1H, m, OCH_2CH), 3.97–3.91 (1H, m, OC*H*CH), 3.77–3.71 (1H, m, OCH_2CH), 2.45 (3H, s, PhCH_3), 2.41(2H, t, *J* 6.1, CHCH_2CH), 1.30 (3H, s, CH_3), 1.27 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 131.7, 129.6, 127.8, 119.1, 109.6, 96.1, 81.2, 75.1, 66.4, 35.6, 26.6, 25.2, 21.6; IR ($CHCl_3$, cm^{-1}): ν_{max} 2986, 2934, 1642, 1598, 1453, 1367, 1256, 1215, 1178, 1069, 996, 902, 851, 814, 777, 668 cm^{-1}; MS (ESI) *m*/*z*: 349 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{22}O_5NaS$: 349.1085; found: 349.1076.

*4.1.10. (S)-4-((R)-1-Azidobut-3-enyl)-2,2-dimethyl-1,3-dioxolane (**17**).* To a stirred solution of tosylate **16** (3 g, 9.2 mmol) in dry DMF (15 mL) was added NaN_3 (0.72 g, 11 mmol). This heterogeneous mixture was stirred for 14 h at 60 °C, cooled to room temperature followed by addition of water (20 mL), and extraction with diethyl ether (3×30 mL). The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4, evaporated, and the residue obtained was purified by silica gel column chromatography (hexane/EtOAc, 96:4) to give the azide **17** (1.54 g, 85%) as a pale yellow liquid. $[\alpha]_D^{27}$ +5.6 (*c* 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.9–5.75 (1H, m, C*H*=CH_2), 5.23–5.13 (2H, m, CH=CH_2), 4.13–4.07 (1H, q, *J* 6.7 Hz, OCH_2CH), 4.00–3.95 (1H, t, *J* 6.1 Hz, OC*H*), 3.79–3.74 (1H, q, *J* 6.7 Hz, OCH_2CH), 3.22–3.16 (1H, q, *J* 6.7 Hz, C*H*N_3), 2.36–2.32 (2H, t, *J* 7.5 Hz, CHCH_2CH), 1.45 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.3, 118.5, 109.9, 77.7, 66.3, 62.5, 35.2, 26.4, 25.3; IR ($CHCl_3$, cm^{-1}): ν_{max} 2987, 2929, 2109, 1382, 1372, 1262, 1216, 1158, 1110, 1069, 995, 968, 923, 855, 814, 617 cm^{-1}; MS (ESI) *m*/*z*: 197 (M^+); HRMS (ESI): *m*/*z* calcd for $C_9H_{15}N_3O_2Na$: 220.1061; found: 220.1071.

*4.1.11. tert-Butyl (R)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl) but-3-enylcarbamate (**18**).* To a stirred solution of compound **17** (1.40 g, 7.1 mmol) in THF (10 mL) was cooled to 0 °C and added to $LiAlH_4$ (0.27 g, 7.1 mmol). The reaction mixture was stirred for 1 h at room temperature after which the reaction was quenched with 15% NaOH solution at 0 °C and $(Boc)_2O$ (1.55 g, 7.1 mmol) was immediately added, then the reaction mixture was stirred for 4 h to convert the amine into the *N*-Boc derivative 18. The resulting reaction mixture filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 9:1) to give compound **18** (1.69 g, 88%) as a thick brown liquid. $[\alpha]_D^{27}$ +29.7 (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.86–5.71 (1H, m, C*H*=CH_2), 5.12–5.05 (2H, m, CH=CH_2), 4.62–4.59 (1H, br s, N*H*), 4.16–4.08 (1H, t, *J* 9.4 Hz, OCH_2CH), 3.97–3.93 (1H, t, *J* 6.6 Hz, OC*H*), 3.71–3.61 (2H, m, OCH_2CH, and C*H*NH), 2.33–2.27 (2H, t, *J* 7.1 Hz, CHCH_2CH), 1.43 (9H, s, C(CH_3)$_3$), 1.41 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 134.7, 118.3, 109.2, 79.3, 76.4, 66.3, 50.2, 38.1, 28.4, 26.4, 25.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 3078, 2971, 2925, 1665, 1460, 1410, 1365, 1254, 1164, 1040 cm^{-1}; MS (ESI) *m*/*z*: 294 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{14}H_{25}NO_4Na$: 294.1681; found: 294.1687.

*4.1.12. tert-Butyl allyl((R)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl) but-3-enyl)carbamate (**19**).* To a stirred suspension of NaH (0.26 g, 11 mmol) in dry THF (10 mL), a solution of **18** (1.5 g, 5.5 mmol) in dry THF (5 mL) was added drop wise at 0 °C under a nitrogen atmosphere. The resulting solution was stirred for 15 min at room temperature, allyl bromide (1.38 g, 11 mmol) was added, and the reaction mixture was stirred for 18 h. After completion of reaction, the reaction mixture quenched with saturated aq NH_4Cl at 0 °C and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (hexane/EtOAc, 95:5) to afford pure **19** (1.56 g, 91%) as a thick yellow liquid. $[\alpha]_D^{27}$ +34.8 (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.98–5.68 (2H, m, C*H*=CH_2), 5.16–5.03 (4H, m, CH=CH_2), 4.26–4.08 (2H, m, C*H*N, and OCH_2CH), 4.01–3.96 (1H, q, *J* 6.7 Hz, OC*H*), 3.83 (2H, d, *J* 5.2 Hz, CH_2N), 3.63 (1H, t, *J* 8.3 Hz, OCH_2CH), 2.53–2.04 (2H, m, CHCH_2CH), 1.43 (9H, s, C(CH_3)$_3$), 1.40 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 136.4, 134.9, 117.3, 115.7, 115.3, 79.5, 76.7, 67.2, 66.6, 48.2, 34.0, 28.3, 26.4, 25.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 3079, 2981, 2930, 1693, 1642, 1453, 1403, 1367, 1251, 1154, 1067, 993 cm^{-1}; MS (ESI) *m*/*z*: 312(M^++H); HRMS (ESI): *m*/*z* calcd for $C_{17}H_{29}NO_4Na$: 334.1994; found: 334.2010.

*4.1.13. (R)-tert-Butyl 6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**20**).* To a stirred solution of diene **19** (0.8 g, 2.57 mmol) in dry CH_2Cl_2 (20 mL) was added Grubbs's first generation catalyst (90 mg, 0.11 mmol, 0.1 equiv), the resulting purple solution turned brown after 10 min. The reaction mixture stirred for 8 h at reflux temperature, and concentrated in vacuo obtained residue. The residue was purified by column chromatography (hexane/EtOAc, 94:6) afford a pure compound **20** (0.67 g, 93%) as a dark brown oil. $[\alpha]_D^{27}$ +5.9 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.85–5.68 (2H, m, C*H*=C*H*), 4.42–4.19 (3H, m, OC*H*, OCH_2CH, and CH_2N), 4.18–3.99 (1H, t, *J* 8.1 Hz, C*H*N),

3.79–3.48 (2H, br s, OCH_2CH, and CH_2N), 2.51–2.42 (1H, dd, *J* 10.9, 5.1 Hz, CHCH_2CH), 1.79–1.71 (1H, d, *J* 7..3 Hz, CHCH_2CH), 1.47 (9H, s, C(CH_3)$_3$), 1.43 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 124.4, 122.1, 109.2, 79.3, 74.4, 67.2, 51.6, 40.8, 28.2, 26.5, 25.8, 25.3; IR ($CHCl_3$, cm^{-1}): ν_{max} 2975, 1695, 1676, 1457, 1414, 1391, 1366, 1307, 1256, 1229, 1173, 1051, 1026, 977, 961 cm^{-1}; MS (ESI) *m*/*z*: 306 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{15}H_{25}NO_4Na$: 306.1681; found: 306.1672.

*4.1.14. (R)-tert-Butyl 2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidine-1-carboxylate (**21**).* A mixture of compound **20** (0.5 g, 1.76 mmol) and 10% palladium on charcoal (0.04 g) in dry EtOAc (5 mL) was stirred under a hydrogen atmosphere at room temperature for 6 h. The reaction mixture was filtered through Celite and the solvent evaporated in vacuo to give the crude product, which was purified by flash chromatography (hexane/EtOAc, 95:5) to afford compound **21** (0.48 g, 95%) as colorless oil. $[\alpha]_D^{27}$ +4.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.39–4.33 (1H, q, *J* 7.5 Hz, OC*H*), 4.19–3.95 (3H, m, OCH_2CH, and C*H*N), 3.58 (1H, t, *J* 7.7 Hz, CH_2N), 2.96 (1H, t, *J* 10.4 Hz, CH_2N), 1.79–1.48 (6H, m, piperidine-*H*), 1.44 (9H, s, C(CH_3)$_3$), 1.39 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 109.3, 79.2, 77.2, 74.9, 67.4, 39.9, 28.4, 26.6, 26.5, 25.6, 25.2, 19.8; IR ($CHCl_3$, cm^{-1}): ν_{max} 3009, 2977, 2937, 2869, 1667, 1424, 1366, 1275, 1166, 1063, 1040, 869, 756 cm^{-1}; MS (ESI) *m*/*z*: 308 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{15}H_{27}NO_4Na$: 308.1837; found: 308.1828.

*4.1.15. (R)-tert-Butyl 2-((S)-1,2-dihydroxyethyl)piperidine-1-carboxylate (**22**).* A mixture of compound **21** (1.0 g, 4.08 mmol) and PTSA (40 mg, 5 mol %) in MeOH (10 mL) was stirred at room temperature for 5 h. After completion of reaction saturated $NaHCO_3$ solution was added and stirred for additional 15 min followed by removal of the solvent under reduced pressure. The residual compound was redissolved in CH_2Cl_2 and the organic layer was washed with water, brine and, dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by column chromatographic purification (hexane/EtOAc, 8:2) afford a pure compound **22** (0.73 g, 85%) as a light brown viscous liquid. $[\alpha]_D^{27}$ +27.1 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23–4.05 (2H, br s, O*H*), 4.09–3.95 (1H, q, *J* 7.2 Hz, OC*H*), 3.91–3.78 (2H, br s, OCH_2CH, and C*H*N), 3.71–3.58 (1H, d, *J* 10.56 Hz, OCH_2CH), 3.56–3.40 (1H, m, CH_2N), 2.95–2.75 (1H, m, CH_2N), 1.78–1.51 (6H, m, piperidine-*H*), 1.41 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 79.7, 70.8, 63.9, 51.6, 40.5, 28.2, 25.7, 24.9, 19.4; IR ($CHCl_3$, cm^{-1}): ν_{max} 3387, 2931, 2868, 1667, 1423, 1366, 1275, 1167, 1039, 925, 870, 770 cm^{-1}; MS (ESI) *m*/*z*: 268 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{12}H_{23}NO_4Na$: 268.1524; found: 268.1529.

*4.1.16. (R,E)-tert-Butyl 2-(3-ethoxy-3-oxoprop-1-enyl)piperidine-1-carboxylate (**23**).* To a stirred solution of compound **22** (0.7 g, 2.85 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and sequentially added saturated aq $NaHCO_3$ (0.2 mL) and $NaIO_4$ (0.73 g, 3.42 mmol) portion wise. The reaction mixture stirred for 1 h at room temperature, after completion of reaction the reaction mass was filtered through anhydrous Na_2SO_4 bed. The filtrate was concentrated under reduced presser to afford the corresponding crude aldehyde, which was subjected to Witting olefination without purification. To a solution of aldehyde in dry benzene (20 mL) was added Ph_3P=$CHCO_2Et$ (1 g, 3.0 mmol) and the reaction mixture was stirred at 50 °C for 6 h. After completion of the reaction, reaction mixture was cooled to 25 °C, extracted with EtOAc (3×50 mL), washed with water, brine and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was then purified by column chromatography (hexane/EtOAc, 9:1) over to give the unsaturated ester **23** (0.72 g, 90% for two steps) as a gum. $[\alpha]_D^{27}$ +3.7 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84–6.77 (1H, dd, *J* 15.8, 3.9 Hz, olefin), 5.76–5.69 (1H, dd, *J* 15.8, 2.7 Hz, olefin), 4.80 (1H, s, C*H*N), 4.16–4.07 (2H, q, *J* 7.2 Hz, OCH_2CH$_3$), 3.99 (1H, d, *J* 10.8 Hz, CH_2N), 2.82–2.7 (1H, t, *J* 12.6 Hz, CH_2N), 1.85–1.56 (6H, m, piperidine-*H*), 1.44 (9H, s, C(CH_3)$_3$), 1.25–1.16 (3H, t, *J* 7.2 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2. 154.9, 147.4, 121.9, 79.7, 60.4, 51.6, 39.9, 28.8, 28.3, 25.2, 19.8, 14.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 2977, 2938, 1720, 1695, 15,882, 1408, 1306, 1266, 1163, 1043, 868, 771 cm^{-1}; MS (ESI) *m*/*z*: 306 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_{15}H_{25}NO_4Na$: 306.1681; found: 306.1669.

*4.1.17. (1R,2S,8aR)-1,2-Dihydroxy-hexahydroindolizin-3(5H)-one (**24**).* To a solution of AD-mix-β (3.5 g) and $CH_3SO_2NH_2$ (235 mg, 2.47 mmol) in *t*-BuOH/H_2O=1:1 (5 mL) was stirred for 10 min at room temperature then cooled to 0 °C and alkene **23** (0.7 g, 2.47 mmol) was added and stirred at 0 °C. After 24 h, the reaction mixture was quenched with sodiumsulfite, it was diluted with EtOAc (20 mL), filtered through Celite and the filtrate was concentrated under reduced pressure to give a diol. This crude diol was stirred in 10 mL of TFA for (Boc deprotection) 10 h and evaporated TFA in vacuo followed by refluxing this mixture in ethanol for 6 h gave indolizidinone, which was purified by flash column chromatography ($CHCl_3$/MeOH/Et_3N, 30:68:2) to give pure indolizidinone **24** (0.24 g, 62%). $[\alpha]_D^{27}$ −58.7 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.30 (2H, br s, O*H*), 4.41–4.17 (1H, m, C*H*C=O), 4.12–4.07 (1H, t, *J* 7.2 Hz, COC*H*OH), 3.63–3.29 (1H, m, C*H*N), 2.76–2.54 (1H, m, piperidine-*H*), 2.27–2.14 (1H, m, piperidine-*H*), 2.11–1.61 (4H, m, piperidine-*H*), 1.49–1.21(2H, m, piperidine-*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 80.1, 73.4, 58.8, 39.8, 25.6, 24.5, 22.9; IR ($CHCl_3$, cm^{-1}): ν_{max} 3352, 2987, 2950, 1682, 1474, 1457, 1203, 1182, 1132, 1035, 833, 801, 721 cm^{-1}; MS (ESI) *m*/*z*: 194 (M^++Na); HRMS (ESI): *m*/*z* calcd for $C_8H_{13}NO_3Na$: 194.0555; found: 194.0562.

*4.1.18. (−)-β-Conhydrine (**1**).* To a solution of **13** (0.2 g, 0.464 mmol) in ethanol (10 mL) was added 20 mg of 10% Pd/C and mixture was stirred under a hydrogen atmosphere for 6 h then added one drop 30% methanolic NaOH solution in the reaction mixture. After completion of reaction, the solution was filtered through Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$/MeOH, 97:3) to give the (−)-β-conhydrine **1** as a white solid (0.056 g, 85%). Mp: 67–68 °C {lit.[9b] mp 67 °C} $[\alpha]_D^{27}$ −34.5 (*c* 1, $CHCl_3$) {lit.[9b] $[\alpha]_D^{20}$ = −34.1(*c* 0.4, $CHCl_3$)}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.18 (1H, td, *J* 7.8, 3.5 Hz, C*H*OH), 3.0–3.08 (1H, m, C*H*NH), 2.52 (1H, td, *J* 11.5, 2.7 Hz, CH_2NH), 2.3 (1H, ddd, *J* 10.2, 7.5, 2.5 Hz, CH_2NH), 1.04–1.55 (8H, m, CH_2CH$_3$, and piperidine-*H*), 0.93 (3H, t, *J* 7.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 76.1, 61.3, 47, 29.7, 26.9. 25.0, 10.4; IR (Neat, cm^{-1}): ν_{max} 3285, 2928, 2855, 1726, 1635, 1455, 1269, 1114, 976 cm^{-1}; MS (ESI) *m*/*z*: 144(M^++1); HRMS (EI): *m*/*z* calcd for $C_8H_{18}NO$: 144.1025; found: 144.1022.

*4.1.19. (−)-Lentiginosine **3**.* To a stirred solution of (100 mg, 0.584 mmol) of indolizidinone **24** in THF (10 mL) at 0 °C was added $LiAlH_4$ (44 mg, 1.16 mmol). The suspended mixture was stirred at reflux temperature for 12 h, cooled to 0 °C, diluted with 2 mL of THF, and then carefully treated successively with water and 10% aq NaOH. The resulting mixture was stirred for 1 h and filtered through pad Celite; filtrate was dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was then purified by column chromatography on silica gel ($CHCl_3$/MeOH, 8:2) to give 76 mg of pure target molecule **3** as a colorless solid 84%. Mp 106–108 °C [lit.[10f] mp 106–107 °C]; $[\alpha]_D^{27}$ −3.1 (*c* 0. 5, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 4.07–4.03 (1H, ddd, *J* 7.1, 3.5, 2.4 Hz, CHC*H*CH), 3.63–3.57 (1H, dd, *J* 8.4, 3.5 Hz, OC*H*CH$_2$), 2.95–2.77 (2H, br d, *J* 10.5 Hz, CHCH_2N), 2.71–2.61 (1H, dd, *J* 7.1, 3.5 Hz, C*H*N), 2.07–1.96 (1H, m, piperidine-*H*), 1.94–1.76 (2H, m, piperidine-*H*), 1.71–1.53 (2H, m, piperidine-*H*), 1.47–1.25 (2H, m, piperidine-*H*), 1.22–1.09 (1H, m, piperidine-*H*); ^{13}C NMR (75 MHz, D_2O): δ 82.2, 75.0, 68.1, 59.7, 52.2, 27.1, 23.5, 26.6; IR ($CHCl_3$, cm^{-1}): ν_{max} 3351,

3113, 2930, 2852, 1557, 1442, 1141, 1115, 1042, 995 cm^{-1}; MS (ESI) *m*/*z*: 158 (M^++H); HRMS (ESI): *m*/*z* calcd for $C_8H_{16}NO_2$: 158.0942; found: 158.0944.

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