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Total synthesis of 2-(2-hydroxyalkyl)-piperidine alkaloids (−)-halosaline and (−)-8-*epi*-halosaline via iterative asymmetric allylation/RCM strategy

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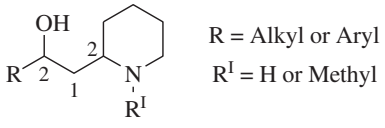
ABSTRACT

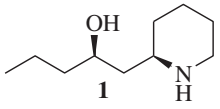
Total synthesis of 2-(2-hydroxyalkyl)-piperidine alkaloids, (−)-halosaline and (−)-8-*epi*-halosaline is reported from *n*-butyraldehyde using iterative asymmetric allylation, nucleophilic substitution with an azide and ring-closing metathesis as the key reactions.

1. Introduction

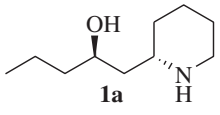
A wide range of piperidine alkaloid natural products shows excellent biological activities.[1] Many pharmaceutically active compounds possess piperidine derivatives as part structures and more are under clinical and preclinical studies.[2] Due to their important biological activities, substituted piperidine ring containing alkaloids have been the target of considerable synthetic efforts.[3] Thus, construction of the 2-(2-hydroxy substituted)-piperidine moiety is always a challenging task for synthetic chemists, more so if the piperidine ring is decorated with substituents (Fig. 1).



2-(2-hydroxy substituted)-piperidine moiety



(-)-Halosaline



(-)-8-*epi*-Halosaline

Fig. 1. 2-(2-Hydroxy substituted)-piperidine alkaloids.

Andrachne aspera spreng is a small perennial under shrub commonly found in Karachi and is used in the local system of medicine for the treatment of eye sores and eye sight improvement. The crude alkaloidal mixture was found to be biologically potent with predominantly antibacterial activity. *A. aspera spreng* was shown to contain piperidine alkaloids and the one 2-(2-hydroxyalkyl)-piperidine alkaloid (−)-8-*epi*-halosaline was isolated from this species,[4] another alkaloid (−)-halosaline, a diastereomer of (−)-8-*epi*-halosaline, was isolated from *Haloxylon salicornicum* (Fig. 1).[5]

As part of research program on the synthesis of natural products, we embarked on the synthesis of piperidine alkaloids that have interesting biological properties. Earlier, we reported total synthesis of some piperidine alkaloids.[6] In continuation, herein we describe the total synthesis of piperidine alkaloids (−)-halosaline **1** and (−)-8-*epi*-halosaline **1a**. Although syntheses for **1** and **1a** were reported,[7] the one described herein is strategically different, general and amenable for accessing other 2-(2-hydroxyalkyl)-piperidine natural products as well.[8]

Amongst all the reported syntheses, the most important ones are: Posner et al. have used a cylcopentanone ring-expansion based functionalized strategy,[7f] while Vincent et al.[7g] more recently have used a nitroso Diels–Alder cycloaddition/ring-rearrangement metathesis sequence while yet another impressive synthesis reported by Lesma et al.[7e] using a ruthenium catalyzed ring-opening/ring-closing metathesis reaction set as the key step in the stereoselective synthesis of targets is worth mentioning. Keeping these strategies in mind, herein we used an iterative Keck asymmetric allylation to garner both the stereogenic centers of (−)-halosaline **1** and (−)-8-*epi*-halosaline **1a**.[9] The nitrogen functionality was

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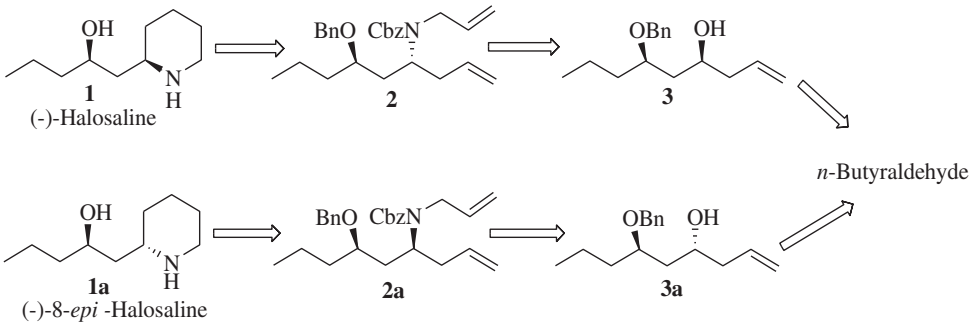
introduced by an S_N2 displacement of the appropriate hydroxyl functionality with an azide group followed by its reduction, allylation, and ring-closing metathesis to afford the piperidine ring-skeleton, which upon further transformations led to the target compounds. Thus the envisaged strategy is general, efficient and applicable to the synthesis of many such 2-(2-hydroxyalkyl)-piperidine ring containing alkaloids viz. (−)-halosaline, (−)-8-*epi*-halosaline, (+)-*N*-methylallosedridine,[10a] (+)-8-ethylnorlebolol,[10b] (+)-sedridine,[10c] (+)-allosedridine,[10d] (−)-allosedridine,[10e] and (+)-*N*-methylsedridine.[10f]

2. Results and discussion

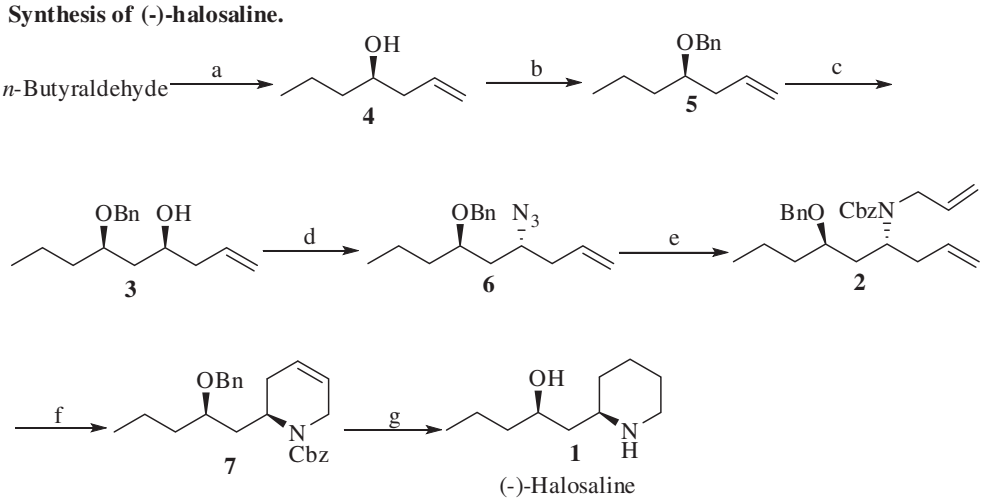
Scheme 1 depicts the retrosynthetic analysis of (−)-halosaline **1** and (−)-8-*epi*-halosaline **1a** from *n*-butyraldehyde using an iterative asymmetric Keck allylation to garner the two stereogenic centers to afford **3**/**3a** followed by functional group transformation of one of the hydroxyl groups into amine derivative through the S_N2 displacement of the corresponding mesylate with an azide. Subsequent conversions led to bis olefin **2**/**2a**. Finally, the piperidine ring formation was effected by the Grubbs' I catalyst assisted ring-closing metathesis protocol[11] and further conversions gave the target molecules.



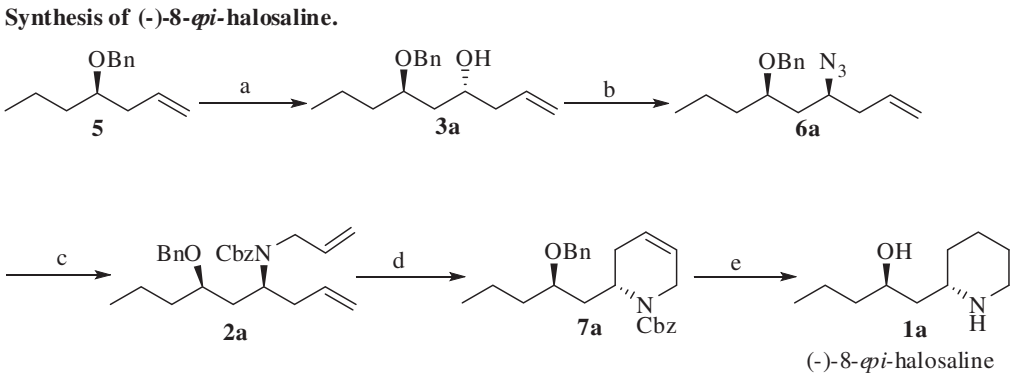
Scheme 1. Retrosynthetic analysis.

Accordingly, the synthesis (Schemes 2 and 3) began with *n*-butyraldehyde being subjected to the first asymmetric Keck allylation reaction {(*S*,*S*)-BINOL/Ti(O^iPr)$_4$/allyltri-*n*-butyltin/CH_2Cl_2/−78 °C to −20 °C} to afford the known homoallyl alcohol **4** in good yield (82%, >95% ee).[12] Data of alcohol **4** matched with the reported values.[12] Later, alcohol **4** was protected as its benzyl ether **5** (BnBr/NaH/THF/0 °C to room temperature, 86%).[13] Benzyl ether **5** was identified as the common intermediate for accessing both (−)-halosaline **1** and (−)-8-*epi*-halosaline **1a**. Consequently, compound **5** was subjected to one pot dihydroxylation, oxidative cleavage of diol (OsO_4/$NaIO_4$/2,6-lutidine/1,4-dioxane/H_2O) to furnish the corresponding aldehyde, which on second asymmetric Keck allylation gave the homoallyl alcohols **3** and **3a**[6c,13b] {for **3** (*S*,*S*)-BINOL; for **3a** (*R*,*R*)-BINOL are the chiral ligands used} in 76% (**3**), 80% (**3a**) with high diastereoselectivities (>94%). The diastereomeric ratio of **3** and **3a** was measured using ^{1}H NMR.

After having **3** and **3a** in hand, these were protected as mesylates under conventional conditions. The corresponding mesylates were subjected to azidation (NaN_3/DMF/50 °C) to afford homoallyl azides **6** (78% over two steps) and **6a** (83% over two steps). These azides were converted to the corresponding *N*-allyl benzylcarbamates **2** (68%) and **2a** (65%) via a two-step process; firstly to their amines using TPP in MeOH followed by allylation (allylbromide/K_2CO_3/MeOH) and later the second derivatization {Cbz−Cl/EtOAc/H_2O(1:1)} to afford **2** and **2a** that were subsequently cyclized via ring-closing metathesis using Grubbs I catalyst (10 mol %) in CH_2Cl_2 to furnish unsaturated piperidine carbamates **7** (92%) and **7a** (87%), respectively. Finally, natural products (−)-halosaline and (−)-8-*epi*-halosaline were obtained by global deprotection of the protecting groups like benzyl ether and benzylcarbamate with simultaneous saturation of the double bond, all three



Scheme 2. Reagents and conditions. (a) (*S*,*S*)-BINOL, 4 Å MS, Ti(O^iPr)$_4$, allyltri-*n*-butyltin, CH_2Cl_2, −78 to −20 °C, 24 h, 82%; (b) BnBr, NaH, THF, 0 °C to rt, 4 h, 86%; (c) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane:H_2O (3:1), rt, 4.5 h; (ii) (*S*,*S*)-BINOL, 4 Å MS, Ti(O^iPr)$_4$, allyltri-*n*-butyltin, CH_2Cl_2, −78 to −20 °C, 36 h, 76%; (d) (i) Mesyl chloride, Et_3N, 0 °C, 1.5 h; (ii) NaN_3, DMF, 50 °C, 3 h, (78% over two steps); (e) (i) TPP, MeOH, rt, 4 h; (ii) allylbromide, K_2CO_3, MeOH, 2 h; (iii) Cbz−Cl, EtOAc/H_2O (1:1), rt, 5 h (68% over three steps); (f) G-I catalyst, CH_2Cl_2, rt, 1.5 h, 92%; (g) H_2/Pd/C, MeOH, rt, 12 h, 81%.



Scheme 3. Reagents and conditions. (a) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1), rt, 4.5 h; (ii) (*R*,*R*)-BINOL, 4 Å MS, Ti(O^iPr)$_4$, allyltri-*n*-butyltin, CH_2Cl_2, −78 to −20 °C, 24 h, 80%; (b) Mesyl chloride, Et_3N, 0 °C, 1.5 h; (ii) NaN_3, DMF, 50 °C, 3 h (83% over two steps); (c) (i) TPP, MeOH, rt, 5 h; (ii) allylbromide, K_2CO_3, MeOH, 3 h (iii) Cbz−Cl, EtOAc/H_2O (1:1), rt, 4 h (65% over three steps); (d) G-I catalyst, CH_2Cl_2, rt, 2 h, 87%; (e) H_2/Pd/C, MeOH, rt, 8 h, 84%.

transformations were carried out under standard conditions (H_2/Pd/C/MeOH/room temperature/6 h) to afford **1** (81%) and **1a** (84%), respectively. The analytical data of synthetic compounds matched with reported data in literature {(−)-halosaline: solid. Mp 82 °C, $[\alpha]_D^{25}$ −24.5 (*c* 0.86, EtOH), reported[7b] $[\alpha]_D^{25}$ −19.5 (*c* 0.6, EtOH); (−)-8-*epi*-halosaline: thick syrup, $[\alpha]_D^{25}$ −12.1 (*c* 0.45, MeOH), reported[7c] $[\alpha]_D^{22}$ −8.0 (*c* 3.7, MeOH)}.

3. Conclusions

In conclusion we report a general strategy for the synthesis of 2-(2-hydroxyalkyl)-piperidines, whereby (−)-halosaline and (−)-8-*epi*-halosaline were accomplished in an overall yield of 21.2% (**1**), 22.2% (**1a**), respectively, using iterative Keck's asymmetric allylation, nucleophilic substitution with an azide and ring-closing metathesis. This strategy may be adopted for the synthesis of similar 2-(2-hydroxy substituted)-piperidine moiety containing alkaloids.

4. Experimental section

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 60−120 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, charred with α-napthol or ninhydrin charring solutions, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenoneketyl. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded either on a bruker 300 or Varian VXR 400 or Varian VXR 500 in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, HRMS spectra were recorded on a QTOF analyser (QSTAR XL, Applied Biosystems/MDS Sciex) at NCMS-IICT, Hyderabad. Unless stated otherwise, Elemental Analysis was carried on a Vario Micro Cube Elementar at Analytical Chemistry Division IICT, Hyderabad. Unless stated otherwise, all the reactions were performed under inert atmosphere.

*4.1.1. (R)-Hept-1-en-4-ol (**4**).* A mixture of (*S*,*S*)-BINOL (0.21 g, 0.69 mmol) and Ti(O^iPr)$_4$ (0.21 mL, 0.69 mmol) in CH_2Cl_2 (8.0 mL) in the presence of 4 Å molecular sieves (1.0 g) was stirred under reflux. After 1 h, the reaction mixture was cooled to room temperature and the commercially available butyaldehyde (0.5 g, 6.9 mmol), in CH_2Cl_2 (4.0 mL) was added and further stirred for 10 min. The reaction mixture was then cooled to −78 °C and allyltri-*n*-butyltin (2.37 mL, 7.64 mmol) was added to it and the stirring continued at −20 °C for 24 h. Later saturated aq $NaHCO_3$ solution (15.0 mL) was added to quench the reaction mixture, stirred for an additional 30 min and was then extracted with CH_2Cl_2 (2×40.0 mL). The organic phase was washed with water (10.0 mL), dried (Na_2SO_4), the solvent was evaporated and the residue purified by column chromatography (Silica gel, 60−120 mesh, R_f 0.75, EtOAc/*n*-hexane 1:9) gave **4** (0.65 g, 82%) as a clear oil. $[\alpha]_D^{25}$ −22.5 (*c* 0.65, $CHCl_3$); IR (Neat) ν_{max} 3330, 3055, 1620, 1497, 1208, 769, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.87−5.72 (1H, m, Olefinic−H), 5.14−5.08 (2H, m, Olefinic−H), 3.66−3.58 (1H, m, OCH), 2.32−2.23 (1H, m, Allylic−H), 2.16−2.06 (1H, m, Allylic−H), 1.51−1.33 (4H, m, $-CH_2$), 0.94 (3H, t, *J*=6.8 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 134.9, 118.1, 70.4, 42.2, 38.9, 18.7 14.1; EIMS (*m*/*z*): $[M]^+$ 114.

*4.1.2. (R)-((Hept-1-en-4-yloxy)methyl)benzene (**5**).* To a cooled (0 °C) suspension of NaH (0.17 g, 6.94 mmol, 60% w/w dispersion in paraffin oil) in THF (10 mL), a solution of (*R*)-hept-1-en-4-ol **4** (0.65 g, 5.7 mmol) in THF (8.0 mL) was added drop wise. After 15 min. BnBr (0.75 mL, 6.27 mmol) was added drop wise at 0 °C and stirred for 4 h at room temperature. The reaction mixture was quenched with saturated aq NH_4Cl solution (30.0 mL) and extracted with EtOAc (2×100.0 mL). The combined organic layers were washed with water (50.0 mL), brine (25.0 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography (Silica gel 60−120 mesh, EtOAc/*n*-hexane, 1:19) to afford **5** (1.00 g, 86%) as colorless liquid. $[\alpha]_D^{25}$ +12.8 (*c* 0.89, $CHCl_3$); IR (Neat) ν_{max} 3060, 2890, 1610, 1475, 1160, 810, 735 cm^{-1} ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32−7.31 (5H, m, Ar−H), 5.88−5.74 (1H, m, Olefinic−H), 5.09−5.00 (2H, m, Olefinic), 4.50 (2H, dd, *J*=11.5 Hz, OCH_2Ar), 3.44−3.37 (1H, m, −OCH), 2.30 (2H, br s, Allylic−H), 1.54−1.24 (4H, m, $-CH_2$), 0.90 (3H, t, *J*=6.9 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 139.0, 135.1, 128.3, 127.7, 127.3, 116.8, 78.4, 70.9, 38.3, 36.1, 18.7, 14.2.

*4.1.3. (4S,6R)-6-(Benzyloxy)non-1-en-4-ol (**3**).* To a cool (0 °C) stirred solution of **5** (0.4 g, 1.96 mmol) in 1,4-dioxane/H_2O (3:1, 5.0 mL), added OsO_4 (0.4 mL, 0.5 M in toluene) drop wise. After 5 min. 2,6-lutidine (0.27 mL, 2.35 mmol) and $NaIO_4$ (0.5 g, 2.35 mmol) was added at 0 °C and stirred for 4.5 h at room temperature. The reaction mixture was quenched with Na_2SO_3 (1.5 g) and extracted with EtOAc (2×50.0 mL). The combined organic layers were washed with water (40.0 mL), brine (30.0 mL), dried (Na_2SO_4), and evaporated. The obtained crude aldehyde was directly used for the next reaction.

A mixture of (*S*,*S*)-BINOL (0.06 g, 0.2 mmol) and Ti(O^iPr)$_4$ (0.06 mL, 0.2 mmol) in CH_2Cl_2 (6.0 mL) in the presence of 4 Å

molecular sieves (0.6 g) was stirred under reflux. After 1 h, the reaction mixture was cooled to room temperature and the obtained aldehyde in above in CH_2Cl_2 (4.0 mL) was added and further stirred for 10 min. The reaction mixture was then cooled to −78 °C and allyltri-*n*-butyltin (0.7 mL, 2.35 mmol) was added to it and the stirring continued at −20 °C for 16 h. Later saturated aq $NaHCO_3$ solution (10.0 mL) was added to quench the reaction mixture, stirred for an additional 30 min and was then extracted with CH_2Cl_2 (2×30.0 mL). The organic phase was washed with water (10.0 mL), dried (Na_2SO_4), the solvent was evaporated and the residue purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.80, EtOAc/*n*-hexane 1:15) to give **3** (0.37 g, 76%) as a yellow colorless oil; [Found: C, 74.95; H, 9.40. $C_{16}H_{24}O_2$ requires C, 77.38; H, 9.74%]; $[\alpha]_D^{25}$ −80.7 (*c* 0.22, $CHCl_3$); IR (Neat) ν_{max} 3470, 3051, 2950, 1635, 1590, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.23 (5H, m, Ar–H), 5.86–5.71 (1H, m, Olefinic–H), 5.08–5.02 (2H, m, Olefinic–H), 4.62 (1H, d, AB pattern, *J*=11.2 Hz, OCH_2Ar), 4.42 (1H, d, AB pattern, *J*=11.2 Hz, OCH_2Ar), 3.80–3.60 (2H, m, OCH), 2.17 (2H, qt, *J*=6.4 Hz, Allylic–H), 1.64–1.24 (6H, m, $-CH_2$), 0.94 (3H, t, *J*=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.0, 135.0, 128.5, 127.9, 127.7, 117.3, 79.7, 70.8, 70.6, 42.1, 40.3, 35.7, 17.9, 14.3; ESIMS (*m*/*z*): $[M+Na]^+$ 271.

*4.1.4. {(4R,6R)-6-(Azido)non-8-en-4-yloxymethyl}benzene (**6**).* To a stirred solution of alcohol **3** (0.33 g, 1.33 mmol) in CH_2Cl_2 (4.0 mL), Et_3N (0.37 mL, 2.66 mmol), and methanesulphonyl chloride (0.12 mL, 1.46 mmol) was added at 0 °C and allowed to stir at 0 °C for 1 h. After completion of reaction compound was diluted with CH_2Cl_2 (8.0 mL), washed with sat $NaHCO_3$ (1×5.0 mL), 1 N HCl (1×5.0 mL), and water (2×5.0 mL), and brine solution (1×6.0 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The reaction mixture was concentrated under reduced pressure and the crude mesylate used as such without further purification.

To a stirred solution of above yielded mesylate in dry DMF (4.0 mL), added NaN_3 (0.11 g, 1.73 mmol) and heated to 50 °C and stirring continued for 3 h. After completion of the reaction, reaction mixture was extracted with EtOAc/*n*-hexane (6:4) (2×15.0 mL), organic phase was washed with brine (10.0 mL), dried (Na_2SO_4), the solvent was evaporated and the residue purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.90 EtOAc/*n*-hexane 1:19) afforded **6** (0.28 g, 78% over two steps) as a yellow liquid; [Found: C, 70.17; H, 8.18; N, 14.93. $C_{16}H_{23}N_3O$ requires C, 70.30; H, 8.48; N, 15.37%]; $[\alpha]_D^{25}$ −183.5 (*c* 0.17, $CHCl_3$); IR (Neat) ν_{max} 3080, 2985, 2190, 1595, 785, 580 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.22 (5H, m, Ar–H), 5.85–5.72 (1H, m, Olefinic–H), 5.15–5.09 (2H, m, Olefinic–H), 4.49 (2H, dd, *J*=11.3 Hz, OCH_2Ar), 3.65–3.54 (2H, m, OCH, N_3CH), 2.29 (2H, t, *J*=6.4 Hz, Allylic–H), 1.65–1.35 (6H, m, $-CH_2$), 0.94 (3H, t, *J*=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.6, 133.8, 128.4, 127.9, 118.2, 75.7, 71.3, 59.7, 39.6, 39.4, 36.1, 18.2, 14.3; ESIMS (*m*/*z*): $[M+H]^+$ 274.

*4.1.5. Benzyl allyl((4R,6R)-6-(benzyloxy)non-1-en-4-yl)carbamate (**2**).* To a stirred solution of homoallyl azide **6** (0.23 g, 0.84 mmol) in methanol added TPP (0.44 g, 1.68 mmol) at 0 °C and stirred for 4 h at room temperature. After consuming azide into amine added K_2CO_3 (0.23 g, 1.68 mmol) and allylbromide (0.09 mL, 1.01 mmol) at 0 °C and stirred for 2 h. After completion of the reaction evaporated the methanol under reduced pressure. To this crude mixture added EtOAc/water (1:1, 3.0 mL), then added Cbz–Cl (0.14 mL, 1.01 mmol), at 0 °C and stirred for 5 h at room temperature. After completion of the reaction, diluted the reaction mixture with ethyl acetate and the combined organic layers were washed with brine (5.0 mL), dried (Na_2SO_4), organic solvent was evaporated under reduced pressure and the residue purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.95, EtOAc/*n*-hexane 1:30) afforded **2** (0.26 g, 68% over three steps) as a thick liquid. $[\alpha]_D^{25}$ −83.7 (*c* 0.23, $CHCl_3$); IR (Neat) ν_{max} 3060, 1650, 1610, 1280, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.15 (10H, m, Ar–H), 5.94–5.52 (2H, m, Olefinic–H), 5.21–4.90 (6H, m, Olefinic–H, OCH_2Ar), 4.45–4.23 (3H, m, OCH_2Ar, OH), 3.83 (1H, d, *J*=19.5 Hz, CHNH), 3.64–3.57 (1H, m, CHaHbNH), 3.32 (1H, br s, CHaHbNH), 2.40–2.12 (2H, m, Allylic–H), 1.74–1.25 (6H, m, $-CH_2$), 0.89 (3H, t, *J*=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 163.9, 135.7, 135.5, 135.2, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.4, 117.0, 116.6, 116.4, 76.2, 71.3, 67.1, 66.8, 38.8, 38.3, 37.9, 37.4, 36.2, 35.9, 29.7, 18.2, 14.4; HRESIMS (*m*/*z*): calcd for $[M+Na]^+$ 444.2514, found 444.2521.

*4.1.6. (R)-Benzyl 6-((R)-2-(benzyloxy)pentyl)-5,6-dihydropyridine-1(2H)-carboxylate (**7**).* Compound **2** (0.22 g, 0.5 mmol) was taken in an oven dried round bottom flask, added CH_2Cl_2 (40.0 mL) under nitrogen atmosphere, then added Grubbs I-generation catalyst (0.04 g, 10 mol %) and stirred for 1.5 h. After completion of the reaction CH_2Cl_2 was evaporated, the crude residue was purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.82 EtOAc/*n*-hexane 1:25) afforded **7** (0.19 g, 92%) as a colorless syrup. $[\alpha]_D^{25}$ −45.9 (*c* 0.15, $CHCl_3$); IR (Neat) ν_{max} 3060, 1655, 1620, 1405, 1280, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.12 (10H, m, Ar–H), 5.79–5.52 (2H, m, Olefinic–H), 5.19–4.90 (2H, m, OCH_2Ar), 4.76–4.59 (1H, m, OCHAr), 4.48–4.21 (3H, m, OCHAr, CHOH, CHNH), 3.49 (1H, tt, *J*=3.8, 7.2, 17.7 Hz, CHaHbNH), 3.34–3.18 (1H, m, CHaHbNH), 2.55–2.40 (1H, m, Allylic–H), 2.00–1.68 (2H, m, Allylic–H), 1.54–1.25 (5H, m, $-CH_2$), 0.90 (3H, t, *J*=6.8 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 140.9, 138.9, 128.5, 128.4, 128.2, 127.9, 127.6, 127.4, 126.9, 123.3 (m), 76.7, 71.5, 71.0, 67.0, 65.3, 46.0, 39.9, 36.3, 29.6, 29.3, 22.7, 18.3, 14.3; HRESIMS (*m*/*z*): calcd for $[M+Na]^+$ 416.2201, found 416.2204.

*4.1.7. (−)-Halosaline (**1**).* To a stirred solution of **7** (0.15 g, 0.35 mmol) in methanol (1 mL), 40 mg of 10% Pd/C was added and stirred under H_2 atmosphere for 12 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure adsorbed on silica to do the column chromatography (Silica gel 60–120 mesh, R_f 0.40, MeOH/$CHCl_3$ 5:95, 5% NH_4OH) to obtain **1** (0.049 g, 81%) as solid, mp 82 °C $[\alpha]_D^{25}$ −24.5 (*c* 0.86, EtOH); IR (Neat) ν_{max} 3450, 2950, 2860, 1570, 1320, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.91–3.82 (1H, m, OCH), 3.12 (1H, d, *J*=12.1 Hz, −CHNH), 2.97–2.87 (1H, m, CHaHbNH), 2.66–2.55 (1H, m, CHaHbNH), 1.88–1.80 (1H, m, −CHaCHbCH), 1.67–1.16 (11H, m, −CHaCHbCH, $-CH_2$), 0.92 (3H, t, *J*=6.9 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 68.9, 54.8, 47.0, 42.2, 40.1, 31.7, 26.3, 24.9, 18.9, 14.2; HRESIMS: calcd for $[M+H]^+$ 172.1701, found 172.1701.

*4.1.8. (4R,6R)-6-(Benzyloxy)non-1-en-4-ol (**3a**).* It was prepared using the same condition as described for compound **3**, purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.80 EtOAc/*n*-hexane 1:25) as a colorless liquid; [Found: C, 74.95; H, 9.40. $C_{16}H_{24}O_2$ requires C, 77.38; H, 9.74%]; $[\alpha]_D^{25}$ −48.7 (*c* 0.54, $CHCl_3$); IR (Neat) ν_{max} 3450, 3050, 2890, 1605, 1490, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.23 (5H, m, Ar–H), 5.85–5.71 (1H, m, Olefinic–H), 5.10–5.04 (2H, m, Olefinic–H), 4.53 (2H, 2×d, AB pattern, *J*=11.7 Hz, OCH_2Ar), 3.95–3.87 (1H, m, OCH), 3.72–3.64 (1H, m, OCH), 2.54 (1H, br s, OH), 2.18 (2H, t, *J*=6.4 Hz, Allylic–H), 1.73–1.26 (6H, m, $-CH_2$), 0.93 (3H, t, *J*=7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 138.4, 134.9, 128.4, 127.9, 127.7, 117.5, 76.9, 71.2, 67.7, 42.2, 39.3, 35.7, 18.7, 14.2; ESIMS (*m*/*z*): $[M+Na]^+$ 271.

*4.1.9. {(4R,6S)-6-(Azido)non-8-en-4-yloxymethyl}benzene (**6a**).* It was prepared using the same condition as described for compound **6**, purified by column chromatography (Silica gel,

60–120 mesh, R_f 0.91, EtOAc/*n*-hexane 1:20) as a yellow oily liquid; [Found: C, 70.04; H, 8.27; N, 14.91. $C_{16}H_{23}N_3O$ requires C, 70.30; H, 8.48; N, 15.37%]; $[\alpha]_D^{25}$ +11.4 (*c* 0.63, $CHCl_3$); IR (Neat) ν_{max} 3045, 2210, 1610, 745, 590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.23 (5H, m, Ar–H), 5.80–5.72 (1H, m, Olefinic–H), 5.14–5.09 (2H, m, Olefinic–H), 4.48 (2H, dd, *J*=11.3 Hz, OCH_2Ar), 3.46 (2H, sept, *J*=5.9 Hz, OCH, N_3CH), 2.31–2.19 (2H, m, Allylic–H), 1.82 (1H, qt, *J*=6.9 Hz, –CHaHbCH), 1.64–1.35 (5H, m, –CHaHbCH, $-CH_2$), 0.93 (3H, t, *J*=7.4 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 133.6, 130.2, 128.4, 127.8, 118.3, 75.7, 70.7, 58.9, 38.6, 37.9, 35.9, 18.3, 14.2; ESIMS (*m*/*z*): $[M+H]^+$ 274.

*4.1.10. Benzyl allyl((4S,6R)-6-(benzyloxy)non-1-en-4-yl)carbamate (**2a**).* It was prepared using the same condition as described for compound **2**, purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.95, EtOAc/*n*-hexane 1:30) as a colorless liquid. $[\alpha]_D^{25}$ –10.7 (*c* 0.78, $CHCl_3$); IR (Neat) ν_{max} 3050, 1640, 1620, 1580, 1250, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.17 (10H, m, Ar–H), 5.91–5.52 (2H, m, Olefinic–H), 5.16–4.94 (6H, m, Olefinic–H, OCH_2–Ar), 4.49–4.32 (2H, m, OCH_2–Ar), 4.14–3.98 (1H, m, OCH), 3.77–3.67 (2H, m, CH_2NH), 3.31 (1H, q, *J*=7.9 Hz, CHNH), 2.36–2.08 (2H, m, Allylic–H), 1.90–1.78 (1H, m, $CHaCHbCH_2$), 1.66–1.26 (6H, m, $CHaCHbCH_2$, CH_2), 0.90 (3H, t, *J*=6.4 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 135.7, 135.2, 128.5, 128.3, 127.7, 127.4, 126.9, 117.0, 116.4, 70.6, 67.2, 66.9, 37.9, 37.1, 29.7, 18.2, 14.2; HRESIMS (*m*/*z*): calcd for $[M+Na]^+$ 444.2514, found 444.2521.

*4.1.11. (S)-Benzyl 6-((R)-2-(benzyloxy)pentyl)-5,6-dihydropyridine-1(2H)-carboxylate (**7a**).* It was prepared using the same condition as described for compound **7**, purified by column chromatography (Silica gel, 60–120 mesh, R_f 0.80, EtOAc/*n*-hexane 1:20) as a colorless syrup. $[\alpha]_D^{25}$ +79.4 (*c* 0.11, $CHCl_3$); IR (Neat) ν_{max} 3065, 2950, 1650, 1400, 1615, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.16 (10H, m, Ar–H), 5.75–5.54 (2H, m, Olefinic–H), 5.15–4.97 (2H, m, CH_2OAr), 4.66–4.17 (4H, m, OCH_2–Ar, CHNH, OCH), 3.54 (1H, t, *J*=17.7 Hz, CHaHbNH), 3.41–3.32 (1H, m, CHaHbNH), 2.39 (1H, t, *J*=14.3 Hz, Allylic–H), 2.03–1.78 (2H, m, Allylic–H, CHaHb), 1.62–1.25 (5H, m, $-CH_2$), 0.89 (3H, t, *J*=6.8 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 136.8, 128.4, 128.3, 127.9, 127.7, 127.4, 70.5, 67.0, 46.1, 40.0, 36.0, 35.6, 29.7, 28.8, 22.6, 18.3, 14.2; HRESIMS (*m*/*z*): calcd for $[M+Na]^+$ 416.2201, found 416.2190.

*4.1.12. (–)-8-epi-Halosaline (**1a**).* It was prepared using the same condition as described for compound **1**, purified by column chromatography (Silica gel 60–120 mesh, R_f 0.40, MeOH/$CHCl_3$ 5:95, 5% NH_4OH) as a colorless oil. $[\alpha]_D^{25}$ –12.1 (*c* 0.45, MeOH); IR (Neat) ν_{max} 3052, 2938, 1712, 1441, 1359, 1275, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.85–3.71 (1H, m, CHOH), 3.18–3.05 (1H, m, CHNH), 2.75 (1H, t, *J*=10.6 Hz, CHaHbNH), 2.63 (1H, dt, *J*=2.6, 13.9 Hz, CHaHbNH), 1.84 (1H, m, CHaHbCH), 1.68–1.28 (12H, m, CH_2), 0.91 (3H, t, *J*=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 72.6, 58.3, 45.8, 42.4, 40.5, 33.9, 27.1, 24.4, 18.7, 14.1; HRESIMS (*m*/*z*): calcd for $[M+H]^+$ 172.1701, found 172.1693.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.11.045.

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