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Cite this: *RSC Adv.*, 2014, **4**, 3238

Organocatalytic stereoselective approach to the total synthesis of (−)-halosaline†

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Received 28th August 2013
Accepted 19th November 2013

DOI: 10.1039/c3ra44700f

www.rsc.org/advances

A practical and efficient organocatalytic approach to the synthesis of substituted piperidine alkaloids in high enantio- and diastereomeric excess was achieved using proline-catalyzed sequential α-aminoxylation/α-amination reaction and HWE olefination reaction of an aldehyde.

Introduction

Naturally occurring alkaloids containing multifunctionalized piperidine rings are found abundantly in nature and many of them exhibit a wide range of biological and pharmacological activity.[1,2] These include piperidine ring containing oxygenated side chains such as halosaline, epi-halosaline, *etc.* and fused piperidines with bicyclic rings such as elaeokanine A, elaeokanine C *etc.* or tricyclic ring such as tetraponerine T-4 (Fig 1). (−)-Halosaline **1**, a 2-(2-hydroxy substituted)-piperidine was isolated from *Haloxylon salicornicum*.[3] (−)-8-Epi-halosaline **2**, a diastereomer of (−)-halosaline, was isolated from *Andrachne aspera spreng*,[4] a small perennial under shrub commonly found in Karachi. Tetraponerine T-4 **3** was isolated from the venom of a New Guinean ant *Tetraponera* sp.[5] Elaeocarpus alkaloids elaeokanine A **4** and C **5** were isolated from *Ekaeocarous kaniensis Schltr.*,[6] a large rain-forest tree found in New Guinea.

There are several literature reports on the synthesis of (−)-halosaline.[7] The most recent publication by Yadav *et al.*[7a] describes its synthesis *via* Prins cyclization followed by reductive ring opening reaction. While Radha Krishna *et al.*[7b] used an iterative asymmetric allylation/RCM strategy, Posner *et al.*[7d] have utilized a cyclopentanone ring-expansion based functionalized strategy. In another report, Lesma *et al.*[7e] employed ruthenium catalyzed ring-opening/ring-closing metathesis strategy, whereas Takahata *et al.*[7g] used an iterative asymmetric dihydroxylation strategy to arrive at target molecule.

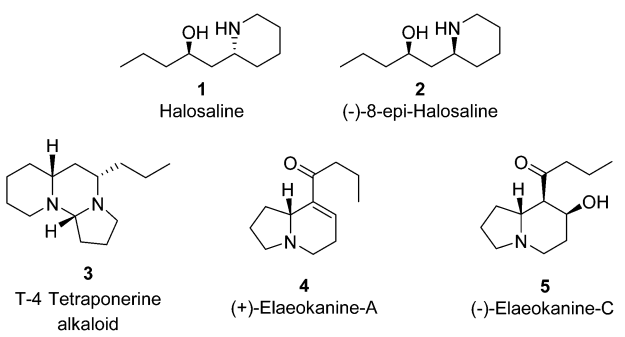

Fig. 1 Substituted piperidine alkaloids.

In recent years, there has been growing interest in the use of small organic molecules to catalyze organic reactions. As a result, the area of organocatalysis has emerged as a promising strategy and as an alternative to enzyme catalysis and metal catalysis,[8] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[9] Proline in the recent past has been defined as 'universal catalyst' because of its utility in different reactions providing rapid access to enantiomerically pure products.[10] Similarly organocatalytic tandem reactions are characterized by high efficiencies and are in a way biomimetic. They often proceed with excellent stereocontrol and are environmentally friendly.[11]

Recently, we have developed[12] an efficient approach to the asymmetric synthesis of 1,3-amino alcohols using sequential α-aminoxylation[13a,b]/α-amination[13c,d] and HWE olefination reaction catalyzed by proline. In continuation of our interest in organocatalysis[14] and asymmetric synthesis of substituted piperidine alkaloids,[15] we further became interested to extrapolate the above knowledge to develop a general flexible approach to chiral 2-substituted piperidines. Herein we report our successful endeavours to devise a simple route towards synthesis of (−)-halosaline, employing sequential α-aminoxylation/α-amination reaction and HWE olefination of an aldehyde catalyzed by proline.

Results and discussion

Our synthetic approach for (−)-halosaline was envisioned *via* the retrosynthetic route shown in the Scheme 1. (−)-Halosaline **1** was thought to be synthesized from cyclic aminoalcohol **6**. The piperidine ring in cyclic aminoalcohol **6** could be

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra44700f

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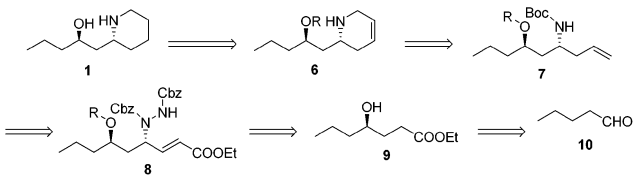


Scheme 1 Retrosynthetic route to (−)-halosaline.

constructed by the allylation and ring closing metathesis of homoallylic amine **7**, which could be synthesized from 1,3-aminoalcohol **8** using standard protocol. Compound **8** could be obtained from γ-hydroxy ester **9** by α-amination which in turn could be easily obtained by the sequential α-aminoxylation and HWE olefination of the corresponding aldehyde **10**.

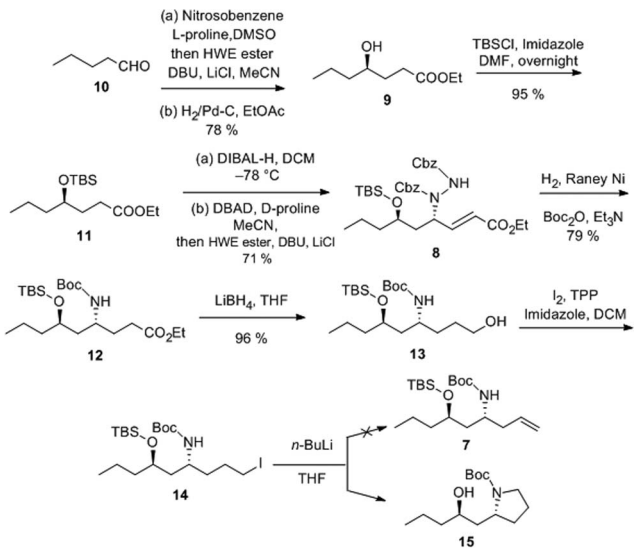
Thus as shown in Scheme 2, synthesis started from the commercially available valeraldehyde **10** which on sequential α-aminoxylation using nitroso benzene as oxygen source and L-proline as catalyst and subsequent Horner–Wadsworth–Emmons (HWE) olefination using ylide generated from triethyl phosphonoacetate followed by hydrogenation using catalytic amount of Pd/C furnished the γ-hydroxy esters **9**[16] in 78% yield and 94% ee.[17] The free hydroxy group of γ-hydroxy ester **9** was protected as TBS ether using TBSCl in DMF to furnish compound **11** in 95% yield. The DIBAL-H reduction of ester **11** at −78 °C furnished the corresponding aldehyde which was then subjected to α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as a nitrogen source and D-proline as a catalyst to furnish the α-amino aldehyde, which on *in situ* trapping by triethyl phosphonoacetate (HWE olefination) in presence of DBU furnished the *anti*-1,3-amino alcohol **8** in 71% yield and 98 : 2 diastereomeric ratio as determined from HPLC analysis.[17] The absolute and relative configuration of amino alcohol **8** is based on L- or D-proline used in the reaction and analogous to those as reported by us in our earlier studies.[12] The *N*–*N*-bond of diastereomerically pure 1,3-*anti*-aminoalcohol **8** was easily cleaved with concomitant reduction of double bond under hydrogenation conditions using freshly prepared RANEY®-Ni at 60 psi to give free amine, which was subsequently converted into its Boc derivative using Boc_2O to furnish ester **12** in 79% yield. Compound **12** was reduced using $LiBH_4$ to give alcohol **13** which was subsequently converted to its iodo derivative **14** using Appel reaction conditions. Dehydrohalogenation[18] of **14** was attempted using *n*-BuLi but to our disappointment we could get only the cyclic aminoalcohol **15** instead of the expected compound **7**. The formation of **15** was confirmed using ^1H NMR spectrum and HRMS.

By analyzing the result, we concluded that due to presence of NH proton, nucleophilic displacement was the predominant reaction instead of dehydrohalogenation leading to exclusive formation of **15**. Therefore, further attempts were made to functionalize the amine group of compound **12**. For this purpose, compound **12** was treated with Boc_2O in presence of catalytic DMAP, but to our disappointment once again we obtained cyclic amide **17** as the only product instead of di-boc compound **16** (Scheme 3).

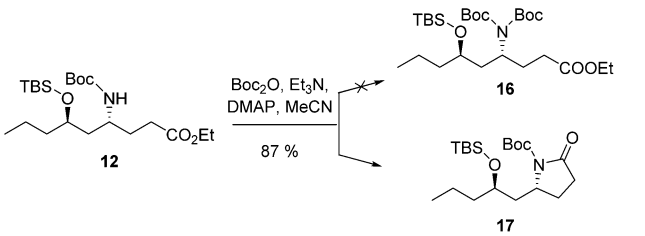
We then switched over to a different strategy to construct the piperidine ring, *via* one carbon homologation and further cyclization of alcohol **13**. Towards this end, the free hydroxy group of **13** was converted into its toluenesulfonate derivative which on subsequent treatment with NaCN in dry DMF at 100 °C furnished the cyano compound **18** in 85% yield. Compound **18** was subjected to reduction using DIBAL-H at −78 °C followed by acid hydrolysis to give the aldehyde which on subsequent treatment with $NaBH_3CN$ afforded the cyclized product **19**, along with small amount of open chain product **20** (Scheme 4). The formation of compound **19** was confirmed by ^1H NMR spectrum and HRMS. We have used both the products **19** and **20** for the synthesis of the target molecule (−)-halosaline.

Towards this end, compound **19** was subjected to the double bond reduction under hydrogenation conditions using 10% Pd–C in EtOAc to give piperidine **21** which on global deprotection of both the TBS and Boc groups with TFA afforded the target compound (−)-halosaline **1** (Scheme 4). The physical and spectroscopic data of compound **1** matched with reported data in literature {solid. Mp 80–82 °C [ref. 7b 82 °C], $[\alpha]_D^{25}$: −18.9 (*c* 0.9, EtOH) [ref. 3 $[\alpha]_D^{25}$: −19.5 (*c* 0.6, EtOH)]}.

Similarly, the open chain compound **20** obtained as the minor product, was also converted into (−)-halosaline **1** by two-step process. As shown in the Scheme 4, compound **20** was first converted into its *p*-toluene sulfonate derivative. Subsequent global deprotection of both the TBS and Boc groups with TFA



Scheme 2 Attempted synthesis of homoallylic amine.



Scheme 3 Attempted functionalization of amino ester compound.

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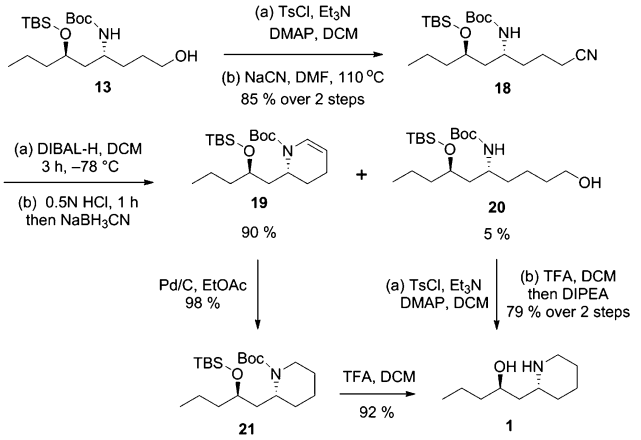

Scheme 4 Revised synthetic strategy and completion of synthesis of (−)-halosaline.

followed by nucleophilic displacement of tosylate with the resultant amine in the presence of diisopropylethyl amine afforded (−)-halosaline **1** in 79% yield.

Conclusions

In conclusion, a stereoselective synthesis of (−)-halosaline was accomplished using proline-catalyzed sequential α-aminoxylation/α-amination reaction and HWE olefination reaction of an aldehyde as the key step. The strategy used is amenable to both the *syn*- and *anti*-1,3-aminoalcohols with a high degree of enantio- and diastereoselectivities. The *syn*- and *anti*-configuration of the 1,3-amino-alcohol moiety can be manipulated simply by changing the proline in the α-aminoxylation/α-amination step. The synthetic strategy described here has significant potential for stereochemical variations and gives further access to other stereoisomers as well as various other substituted piperidine alkaloids.

Experimental section

Ethyl (*R*)-4-hydroxyheptanoate (9)

To a solution of valeraldehyde **10** (2.0 g, 23.2 mmol) and nitroso benzene (0.83 g, 7.74 mmol) in anhydrous CH_3CN (50 mL) was added L-proline (0.27 g, 2.32 mmol) at 0 °C. The mixture was vigorously stirred for 24 h under argon (the color of the reaction changed from green to orange red during this time) at 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (9.25 mL, 46.4 mmol), DBU (6.95 mL, 46.4 mmol) and LiCl (1.969 g, 46.4 mmol) in CH_3CN (40 mL) was added quickly (1–2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5 × 100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo* to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd–C (10%) under hydrogenation conditions at 4 atm and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated *in vacuo* to give γ-hydroxy ester **9**. The crude product was then purified by using silica gel flash column chromatography using pet ether : EtOAc (85 : 15) as eluent to give (*R*)-ethyl 4-hydroxyheptanoate **9** as a colorless liquid (1.05 g, Yield 78%, based on nitrosobenzene). $[\alpha]_D^{25}$: +11.66 (*c* 2.4, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2934, 1719, 1466, 1177. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91–0.96 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.38–1.49 (m, 3H), 1.61–2.05 (m, 4H), 2.46 (t, J = 7.2 Hz, 2H), 3.58–3.78 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 18.7, 30.7, 32.1, 39.6, 60.4, 70.8, 174.3 ppm. MS (ESI): *m*/*z* 197.1862 $(M + Na)^+$. HRMS: 197.1173 $(M + Na)^+$ calcd 197.1148.

Ethyl (*R*)-4-((*tert*-butyldimethylsilyl)oxy)heptanoate (11)

To an ice-cold stirred solution of **9** (1.0 g, 5.75 mmol) in DMF (12 mL) were added imidazole (0.452 g, 6.64 mmol) and TBSCl (1.00 g, 6.64 mmol) at room temperature. The resulting mixture was stirred for 6 h at 0 °C before H_2O (20 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether : ethyl acetate: 99 : 1) of the crude product gave ethyl (*R*)-4-((*tert*-butyldimethylsilyl)oxy)-heptanoate **11** as a colorless liquid (1.57 g, yield 95%). $[\alpha]_D^{25}$: −7.98 (*c* 1.34, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 2958, 1727, 1463, 1256, 908. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.87–0.93 (m, 3H), 0.89 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H), 1.29–1.46 (m, 4H), 1.63–1.83 (m, 2H), 2.36 (t, J = 7.8 Hz, 2H), 3.68–3.73 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.6, −4.5, 14.2, 18.0, 18.4, 25.8, 25.9, 31.7, 39.3, 60.2, 70.9, 173.9 ppm. MS (ESI): *m*/*z* 311.3840 $(M + Na)^+$. Analysis for $C_{15}H_{32}O_3Si$: calcd C, 62.45; H, 11.18; found: C, 62.64; H, 11.12%.

Dibenzyl 1-((4*S*,6*R*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate (8)

To a solution of ethyl ester **11** (1.0 g, 3.5 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (1.7 mL 2.25 M solution in toluene, 3.85 mmol) at −78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then solution of tartaric acid (5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a cooled solution of dibenzylazodicarboxylate (DBAD) (1.02 g, 2.9 mmol) and D-proline (0.038 g, 0.28 mmol) in CH_3CN (40 mL) at 0 °C was added above aldehyde (1.0 g, 3.5 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at

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10 °C. This was followed by addition of lithium chloride (0.22 g, 4.3 mmol), triethyl phosphonoacetate (1.02 mL, 4.3 mmol) and DBU (0.5 mL, 2.9 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product (diastereomeric ratio/ 98 : 2). Silica gel column chromatography (petroleum ether : ethyl acetate: 90 : 10) of the crude product gave dibenzyl 1-((4*S*,6*R*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate **8** as a colorless syrupy liquid (1.52 g, yield 71%, based on DBAD). $[\alpha]_D^{25}$: −1.56 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 3428, 2950, 1717, 1652, 1399, 1084. ^1H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.84 (m, 12H), 1.24–1.31 (m, 5H), 1.40–1.53 (m, 2H), 1.72–1.81 (m, 1H), 1.89–2.02 (m, 1H), 3.58–3.90 (m, 1H), 4.17 (q, J = 7.0 Hz, 2H), 4.84–5.25 (m, 5H), 5.92 (d, J = 17.5 Hz, 1H), 6.51 (m, 1H), 6.85 (dd, J = 6.4, 15.1 Hz, 1H), 7.31 (m, 10H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.9, −4.4, 14.0, 14.2, 17.9, 25.8, 39.4, 60.4, 67.5, 68.1, 121.9, 122.7, 127.9, 128.1, 128.3, 135.6, 146.0, 155.5, 156.3, 166.2 ppm. MS (ESI): *m*/*z* 635.5057 $(M + Na)^+$, 651.5379 $(M + K)^+$. HRMS: 635.3116 $(M + Na)^+$ calcd 635.3123.

Diastereomeric ratio was determined by HPLC analysis; 98 : 2 dr.

UV detector: Merck-HITACHI L-7400 series

Column: Grace Denali RP-18, Flow rate: 1.0 mL min^{-1}, MeOH : H_2O = 97 : 3; t_R for (*anti*)-isomer = 6.90 min and t_R for (*syn*)-isomer = 6.31 min.

Ethyl (4*R*,6*R*)-4-((*tert*-butoxycarbonyl)amino)-6-((*tert*-butyldimethylsilyl)oxy)nonanoate (12)

The solution of dibenzyl 1-((4*S*,6*R*,*E*)-6-((*tert*-butyldimethyl silyl)oxy)-1-ethoxy-1-oxonon-2-en-4-yl)hydrazine-1,2-dicarboxylate **8** (2.0 g, 3.3 mmol) in MeOH (12 mL) and acetic acid (8 drops) was treated with RANEY® nickel (4.0 g, excess) under H_2 (70 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude free amino alcohol which was further treated with triethylamine (0.93 mL, 6.7 mmol) and Boc anhydride (1.2 mL, 5.1 mmol) in dry DCM (4 mL) for 2 h. Ice pieces were added to the reaction mixture and organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give crude *N*-Boc derivative. Silica gel column chromatography (petroleum ether : ethyl acetate: 85 : 15) of the crude product gave ethyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-8-((*tert*-butyldimethylsilyl)oxy)octanoate **12** as a viscous liquid (1.11 g, 79%). $[\alpha]_D^{25}$: −10.37 (*c* 1.1, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 3382, 2956, 1722, 1703, 1173. ^1H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (m, 12H), 1.25 (t, J = 7.0 Hz, 3H), 1.31–1.35 (m, 2H), 1.43 (s, 9H), 1.47–1.60 (m, 4H), 1.76–1.86 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 3.59–3.87 (m, 2H), 4.12 (q, J = 7.0 Hz, 2H), 4.92–4.95 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): −4.7, −4.3, 14.2, 17.9, 18.2, 25.9, 28.3, 30.9, 39.4, 40.7, 47.8, 60.3, 69.7, 78.7, 155.6, 173.6 MS(ESI): *m*/*z* 454.21 $(M + Na)^+$. Analysis for $C_{22}H_{45}NO_5Si$: calcd C, 61.21; H, 10.51; N, 3.24; found: C, 61.29; H, 10.44; N, 3.29%.

tert-Butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxynonan-4-yl)carbamate (13)

To a stirred suspension of $LiBH_4$ (0.60 g, 2.2 mmol) in dry THF (1 mL) was added a solution of **12** (0.60 g, 1.4 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at room temperature for 3 h. After being cooled to ambient temperature, the mixture was quenched with ice pieces and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether : ethyl acetate: 65 : 35) of the crude product gave *tert*-butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxynonan-4-yl)carbamate **13** as a colorless liquid (0.51 g, 96%). $[\alpha]_D^{25}$: −8.29 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 3525, 3365, 2929, 1691, 1100. ^1H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (m, 12H), 1.20–1.38 (m, 4H), 1.43 (s, 9H), 1.54–1.66 (m, 6H), 3.60–3.91 (m, 4H), 5.12 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): −4.8, −4.4, 14.2, 17.9, 18.2, 25.9, 28.3, 28.6, 32.1, 39.9, 40.3, 47.6, 62.3, 69.7, 78.8, 155.9 ppm. MS(ESI): *m*/*z* 412.20 $(M + Na)^+$. HRMS: 390.3032 $(M + H)^+$ calcd 390.3034.

tert-Butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-cyanononan-4-yl)carbamate (18)

To an ice-cold stirred solution of **13** (0.50 g, 1.33 mmol) and triethylamine (0.27 mL, 1.99 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise toluenesulfonyl chloride (0.5 mL, 2.66 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 6 h. After diluting with 10 mL CH_2Cl_2, the solution was washed with (3 × 15 mL) brine, dried over Na_2SO_4 and concentrated to give the crude tosylated product which was subjected to next reaction without purification.

To a solution of tosyl ester in DMF was added NaCN (0.13 g, 2.66 mmol) and was stirred at 115 °C for 10 h. After the consumption of starting material the reaction mixture was poured into H_2O and extracted with ether (25 mL), The organic phase was washed with H_2O and brine (15 mL), dried ($NaSO_4$) and concentrated *in vacuo*. Silica gel column chromatography of the crude product using (petroleum ether : ethyl acetate 90 : 10) gave *tert*-butyl ((4*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-cyanononan-4-yl)carbamate **18** as yellow syrupy liquid. (0.44 g, 85%). $[\alpha]_D^{25}$: −18.34 (*c* 1.4, $CHCl_3$), IR ($CHCl_3$, cm^{-1}): ν^{max} 3369, 2957, 2931, 2247, 1704, 1505, 1253, 1056. ^1H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (m, 12H), 1.19–1.35 (m, 4H), 1.43 (s, 9H), 1.56–1.74 (m, 6H), 2.41 (t, J = 6.7 Hz, 2H), 3.59–3.89 (m, 2H), 5.04 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): −4.9, −4.4, 14.9, 16.8, 17.8, 18.0, 21.8, 25.7, 28.2, 29.5, 34.9, 39.3, 46.9, 69.4, 78.6, 119.5, 155.6 ppm. MS(ESI): *m*/*z* 421.20 $(M + Na)^+$ HRMS: 421.2856 $(M + Na)^+$, calcd 421.2857.

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tert-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (19)

To a solution of **18** (0.250 g, 0.65 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (0.715 mL 1 M solution in toluene, 0.71 mmol) at −78 °C under argon atmosphere. The reaction was stirred at this temperature for 2 h. Then saturated solution of ammonium chloride (0.8 mL) was added. The resulting mixture was warmed to ambient temperature and was then diluted with 0.2 M aqueous HCl (0.67 mL) followed by EtOAc and organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde, which was directly used in the next step without further purification.

To the cooled solution of anhydrous THF and a drop of MeOH was added $NaBH_3CN$ (0.098 g, 2.6 mmol) over 20 min followed by addition of aldehyde derived from **18**. The reaction mixture was allowed to warm to room temperature and was stirred for 8 h. After being cooled to ambient temperature, the mixture was quenched with ice pieces and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude product. The crude product was then purified by silica gel flash column chromatography using (pet ether : EtOAc: 19 : 1) to give **19** (0.216 g, 90%) as a yellow oil. Continued chromatography with pet ether : EtOAc/4 : 1 provided **20** (0.026 g, 5%) as a colorless liquid. $[\alpha]_D^{25}$: +42.97 (*c* 0.6, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν^{max} 2929, 2857, 1702, 1649, 1254 ^1H NMR (500 MHz, $CDCl_3$): spectra showed 1 : 1 mixture of amide rotamers δ 0.06 (s, 6H), 0.88 (m, 12H), 1.26–1.44 (m, 4H), 1.48 (s, 9H), 1.53–1.63 (m, 2H), 1.69–1.73 (m, 1H), 1.80–1.82 (m, 1H), 1.94–1.98 (m, 1H), 2.06–2.12 (m, 1H), 3.70–3.79 (m, 1H), 4.07–4.15 (m, 0.5H), 4.30–4.33 (m, 0.5H), 4.77–4.88 (m, 1H), 6.65 (d, J = 7.3 Hz, 0.5H), 6.79 (d, J = 7.4 Hz, 0.5H) ppm.^{13}C NMR (125 MHz, $CDCl_3$): −4.5, −4.4, 14.3, 18.0, 23.9, 24.5, 25.9, 28.3, 30.3, 38.3, 38.5, 39.0, 39.3, 47.6, 48.8, 69.9, 80.3, 80.5, 104.5, 104.8, 124.0, 124.4, 151.9, 152.3 ppm. MS(ESI): *m*/*z* 406.24 (M + Na)$^+$ HRMS: 384.2929 (M + H)$^+$ calcd 384.2928.

tert-Butyl ((5*R*,7*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-hydroxydecan-5-yl)carbamate (20)

$[\alpha]_D^{25}$: −18.47 (*c* 1.0, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν^{max} 3365, 2930, 1692, 1366, 1100. ^1H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (m, 12H), 1.29–1.35 (m, 4H), 1.43 (s, 9H), 1.47–1.57 (m, 4H), 1.58–1.68 (m, 2H), 1.76–1.88 (m, 2H), 3.58–3.73 (m, 3H), 3.78–3.91 (m, 1H), 5.02 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): −4.7, −4.3, 14.3, 17.9, 18.3, 21.8, 25.9, 28.4, 29.7, 32.5, 35.5, 39.5, 47.6, 62.7, 69.8, 78.7, 155.8 ppm. MS(ESI): *m*/*z* 426.26 (M + Na)$^+$

tert-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl) piperidine-1-carboxylate (21)

To the solution of **19** (0.1 g, 0.27 mmol) in ethyl acetate was added Pd–C (10%) under hydrogenation conditions. The reaction mixture was allowed to stir overnight. On completion of reaction, (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated *in vacuo* to give **21** as a colorless liquid (0.098 g, 98%). $[\alpha]_D^{25}$: +23.91 (*c* 1.05, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν^{max} 2931, 2858, 1693, 1416, 1253, 1167. ^1H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (m, 12H), 1.26–1.41 (m, 4H), 1.46 (s, 9H), 1.57–1.62 (m, 6H), 1.70–1.83 (m, 2H), 2.69–2.82 (m. 1H), 3.59–3.71 (m, 1H), 3.91–3.97 (m, 1H), 4.11–4.35 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): spectra showed amide rotamers −4.5, −4.4, 14.0, 14.3, 18.0, 18.3, 19.0, 19.2, 25.6, 25.9, 28.4, 28.5, 29.7, 30.3, 37.8, 39.3, 48.5, 70.8, 79.1, 154.9 ppm. MS(ESI): *m*/*z* 408.18 (M + Na)$^+$ HRMS: 386.3085 (M + H)$^+$ calcd 386.3085.

(−)-Halosaline (1)

To the solution of **21** (0.1 g, 0.27 mmol) in dry CH_2Cl_2 (1 mL) was added TFA (0.075 mL, 0.78 mmol) at 0 °C and reaction mixture was allowed to stir at rt for 2 h. Then solvent was evaporated and neutralized with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude product. Silica gel column chromatography of the crude product using ($MeOH/CH_2Cl_2/NH_4OH$: 8/95/2) gave (−)-halosaline **1** (0.042 g, 92%) as a solid compound. Mp 80–82 °C, [α]: −18.9 (*c* 0.9, EtOH) [lit.[3] $[\alpha]_D^{25}$: −19.5 (*c* 0.6, EtOH); IR ($CHCl_3$, cm^{-1}): ν^{max} 3445, 3373, 2928, 1399, 1125. ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, J = 7.1 Hz, 3H), 1.25–1.95 (m, 12H), 2.84 (dt, J = 4.5, 12.1 Hz, 1H), 3.19–3.34 (m, 1H), 3.41 (d, J = 12.7 Hz, 1H), 3.87–4.00 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): 13.8, 18.7, 22.1, 22.6, 28.6, 39.2, 39.4, 45.0, 55.0, 66.8 ppm. MS(ESI): *m*/*z* 194.06 (M + Na)$^+$ HRMS: 172.1696 (M + H)$^+$ calcd 172.1696.

tert-Butyl (*R*)-2-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)pentyl)-5-oxopyrrolidine-1-carboxylate (17)

To an ice-cold stirred solution of **12** (0.060 g, 0.15 mmol) and triethylamine (0.03 mL, 0.2 mmol) in anhydrous CH_3CN (2 mL) was added dropwise Boc anhydride (0.05 mL, 0.2 mmol) and DMAP (catalytic) at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred for 6 h. Ice pieces were added to the reaction mixture and organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude *N*-Boc derivative. Silica gel column chromatography (petroleum ether : ethyl acetate: 9 : 1) of the crude product gave **17** as a colorless liquid (0.075 g, 92%). $[\alpha]_D^{25}$: +17.34 (*c* 1.7, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 3019, 1777, 1728, 1215. ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.89 (m, 12H), 1.31–1.47 (m, 4H), 1.53 (s, 9H), 1.60–1.67 (m, 1H), 1.85–2.11 (m, 3H), 2.38–2.45 (m, 1H), 2.52–2.62 (m, 1H), 3.74–3.80 (m, 1H), 4.04–4.09 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5, 14.2, 18.1, 23.9, 25.8, 28.0, 31.1, 39.9, 40.7, 57.1, 70.9, 82.7, 149.7, 174.4 ppm. MS (ESI): *m*/*z* 408.20 (M + Na)$^+$. HRMS: 408.2541 (M + H)$^+$ calcd 408.2541.

tert-Butyl (*R*)-2-((*R*)-2-hydroxypentyl)pyrrolidine-1-carboxylate (15)

To a cooled (0 °C), stirred solution of Ph_3P (0.35 g, 1.46 mmol) in THF–MeCN (1 : 1, 5 mL) were added imidazole (0.10 g, 1.45

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mmol) and I_2 (0.34 g, 1.46 mmol). The mixture was stirred for 2 h and then a solution of alcohol **13** (0.50 g, 1.33 mmol) in THF (10 mL) was added at 0 °C. The mixture was stirred for 2 h, then diluted with 10% aq $Na_2S_2O_3$ (6 mL) and extracted with EtOAc (2 × 6 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure and then used without purification for the next step.

To the crude iodo compound dissolved in THF (5 mL) was added *n*-BuLi (0.4 mL, 2.66 mmol) and the mixture was stirred at r.t. for 1 h. Then, the mixture was poured into aq. NH_4Cl and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (2 × 10 mL), dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography (petroleum ether : ethyl acetate: 9 : 1) afforded **15** as a colorless liquid (0.26 g, 76%). $[\alpha]_D^{25}$: +21.56 (*c* 1.7, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν^{max} 3419, 2928, 1690, 1415, 1163. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.1$ Hz, 3H), 1.24–1.37 (m, 5H), 1.44 (s, 9H), 1.51–1.60 (m, 2H), 1.83–2.00 (m, 3H), 3.28–3.35 (m, 2H), 3.39–3.49 (m, 1H), 4.11–4.21 (m, 1H), 4.94 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 19.1, 23.5, 28.3, 31.1, 38.9, 43.9, 46.4, 53.6, 67.0, 79.7, 156.6 ppm. MS (ESI): *m*/*z* 280.20 $(M + Na)^+$. HRMS: 280.1878 $(M + Na)^+$ calcd 280.1883.

Acknowledgements

V. J. thanks UGC New Delhi for fellowship. We thank Ms. S. Kunte for HPLC analysis. The authors thank CSIR, New Delhi for financial support as part of XII Five Year Plan under title ORIGIN (CSC0108).

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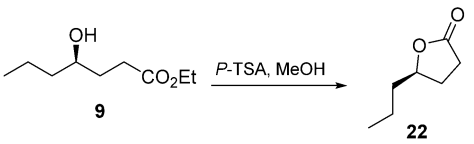

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