RSC Advances

This article can be cited before page numbers have been issued, to do this please use: S. Chavan, L. B. Khairnar, K. P. Pawar, P. N. Chavan and S. A. Kawale, *RSC Adv.*, 2015, DOI: 10.1039/C5RA06429E.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA06429E

Journal Name

RSCPublishing

ARTICLE

Enantioselective syntheses of (*R*)-pipecolic, (2*R*,3*R*)-3-hydroxypipecolic acid, *β*-(+)-conhydrine and (-)-swainsonine using aziridine derived common chiral synthon

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Subhash P. Chavan,* Lalit B. Khairnar, Kailash P. Pawar, Prakash N. Chavan and Sanket A. Kawale

Concise total syntheses of (*R*)-pipecolic acid, (*R*)-ethyl-6-oxopipecolate, (2*R*,3*R*)-3-hydroxypipecolic acid and formal syntheses of *β*-(+)-conhydrine, (-)-lentiginosine, (-)-swainsonine and -1,2-*di*-epi-swainsonine have been accomplished starting from the common chiral synthon. Present strategy employs regioselective aziridine ring opening, Wittig olefination and RCM as the key chemical transformations.

Introduction

(*S*)-Pipecolic acid **1**, is a cyclic non-proteinogenic amino acid[1] and its natural, non natural derivatives have found widespread applications in therapeutic chemistry (Figure 1). Pipecolic acid acts as an integral framework of many pharmaceutically important molecules such as immunosuppressors rapamycin,[2] FK506, immunomycin,[3] the antitumor antibiotic sandramycin,[4] local anaesthetics like bupivacaine and ropivacaine.[5] Similarly (*R*)-pipecolic acid *ent*-**1** is a key constituent of the histone deacetylase (HDAC) inhibitors recognized as the potential anticancer drugs.[6] (*R*)-Piperidin-2-ylmethanol **2**, a reduced analogue of *ent*-**1** has been used as a precursor in the synthesis of (–)-lentiginosine **6**, a naturally occurring alkaloid having amylo-glucosidase enzyme inhibition properties.[7] 3-Hydroxypipecolic acids are important scaffolds with piperidine skeleton and found in many biologically significant molecules.[8] *Trans*-(–)-(2*R*,3*R*)-3-hydroxypipecolic acid **3** is a cyclic *β*-hydroxy-*α*-amino acid that has been used as a precursor in the synthesis of (–)-swainsonine **4**,[9] a potent anti-cancer drug and specific inhibitor of α-D-mannosidase.[10] The stereochemistry of enantiomer of **3** is found in (+)-febrifugine, a potent antimalarial agent,[11] and its reduced analogues were found as important structure motif's of (+)-prosopinine and (+)-prosophylline which exhibit analgesic, anaesthetic and antibiotic activities.[12] *cis* Stereoisomer of 3-hydroxypipecolic acid is main constituent of (+)-isofebrifugine

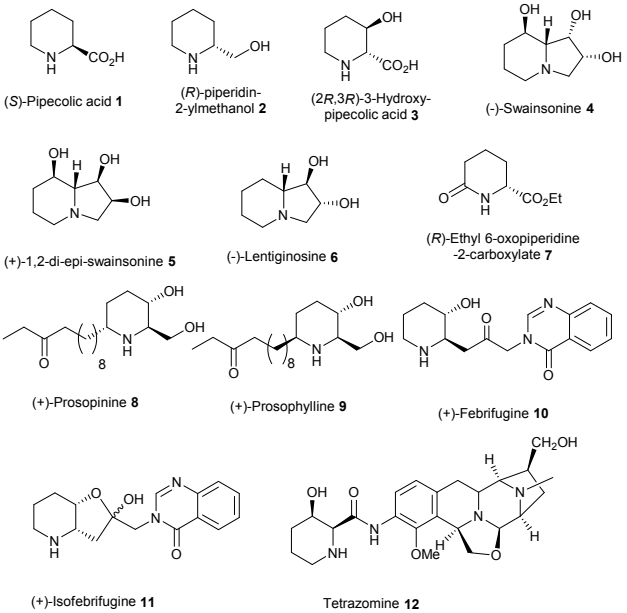


Fig 1: Pipecolic acid and its derivatives.

View Article Online
DOI: 10.1039/C5RA06429E
Journal Name

which also shows antimalarial activity and of tetrazomine **12** which shows antitumor antibiotic activities.[13] Oxopipecolate **7** has been utilized in medicinal chemistry and to prepare an important class of antitumor agents and is useful for the synthesis of pipecolic acid derivatives (Figure 1).[14] Pipecolic acid and its 3-hydroxy derivatives have also been incorporated in peptides which can induce a *β*-turn with resultant therapeutic significance[15] and are also useful as organocatalysts.[16] In general, pipecolic acid and its diverse functionalities are useful chiral building blocks for the synthesis of a variety of pharmaceutically important molecules.

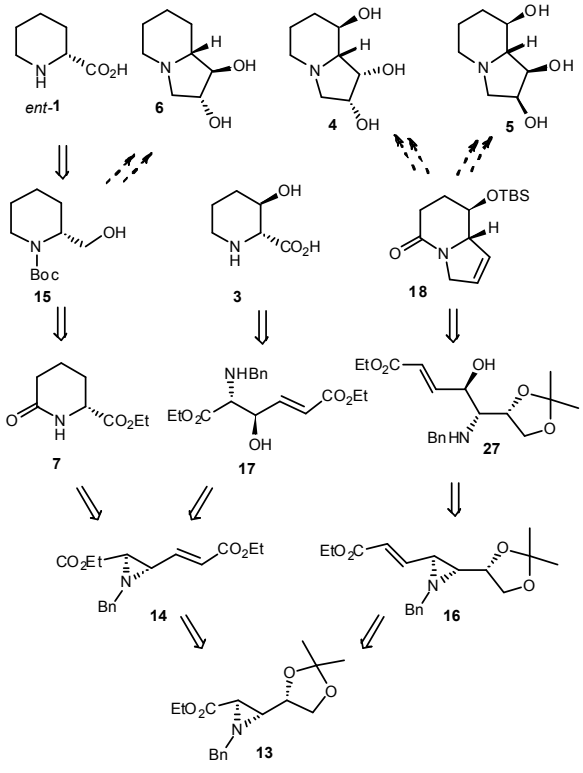
Owing to their importance, enantiomerically pure syntheses of pipecolic acid and its derivatives has gained wide attention and have been extensively reviewed.[17,18,19] As part of our continued interest toward development of efficient and practical synthetic routes to piperidine alkaloids.[20] Herein we report an alternate practical and efficient syntheses of (*R*)-pipecolic acid *ent*-**1**, (*R*)-ethyl-6-oxopipeclate **7**, (2*R*,3*R*)-3-hydroxypipecolic acid **3** and formal synthesis of (−)-swainsonine **4**, (+)-1,2-di-*epi*-swainsonine **5** and (–)-lentiginosine **6** from *trans* aziridine-2-carboxylate **13** as the common synthetic precursor derived from commercially available and cheap starting material *viz.* D-mannitol diacetonide. We have earlier described syntheses of *R* and *S* pipecolic acids 3-hydroxy pipecolic acid from *cis* aziridine.[20]

Results and Discussions

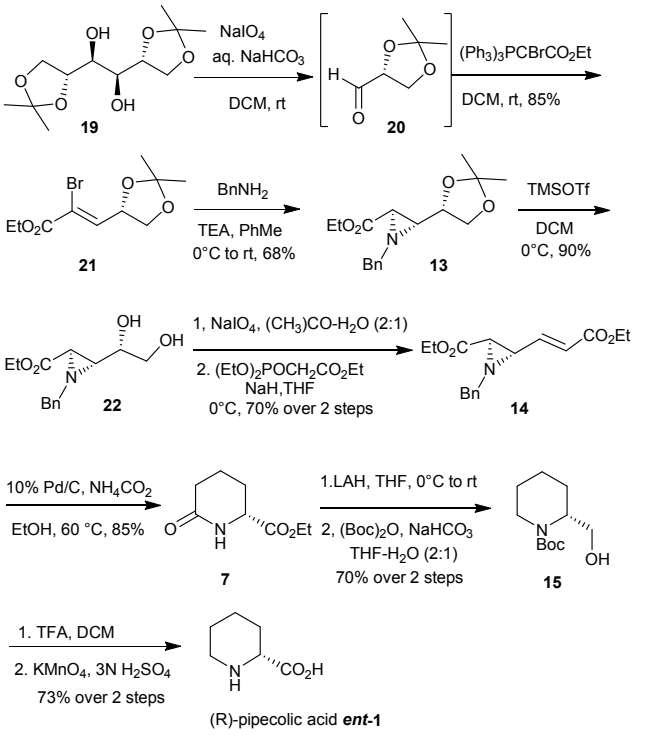
Enantiomerically pure aziridines have been considered to be prominent precursors in the synthesis of natural and unnatural amino compounds due to their inherent ability to undergo regio and chemoselective nucleophilic ring opening reactions.[21] Inspite of that, aziridines are relatively less explored compared to their three membered analog oxiranes due to less reactivity and selectivity towards ring opening reactions. However these drawbacks can be overcome by proper manipulations of functional groups attached to aziridine ring.

Thus as shown in the retrosynthetic plan (Scheme 1), it was envisioned that all of the six piperidine alkaloids could be derived from aziridine carboxylic acid **13** as the common precursor. For the synthesis of pipecolic acid as well as 3-hydroxypipecolic acid, it was surmised that vinyl aziridine ester **14** would serve as ideal substrate. The vinyl aziridine ester **14** could be readily derived from aziridine ester **13** by chain propagation from the acetonide side. Ester **14** by proper choice of reaction conditions could be converted to (*R*)-ethyl-6-oxo-pipecolate **7**, which serves as an important intermediate for pipecolic acid derivatives.[14] Compound **7** in turn can be further converted to the intermediate **15**, a precursor for the synthesis of (−)-lentiginosine[22] and (*R*)-pipecolic acid *ent*-**1**. Aziridine ester **14** on regio and stereoselective ring opening under acidic condition by hydroxyl group could be converted to amino-alcohol **27** which could be further transformed to *trans* 3-hydroxypipecolic acid **3**. Similarly, aziridine ester **13** on propagation from ester side would furnish *α*,*β*-unsaturated ester aziridine **17** which on regio and stereoselective ring opening by hydroxy group followed by cyclization, *N*-allylation and RCM would give intermediate **18**, enantiomer of which is well explored towards the synthesis of (+)-swainsonine *ent*-**4** and (–)-8,8a-di-*epi*-swainsonine *ent*-**5**.[23]

The synthetic endeavor for pipecolic acid and derivatives started with readily available and cheap starting material D-mannitol diacetonide **19** (Scheme 2). Accordingly, D-mannitol diacetonide **19**



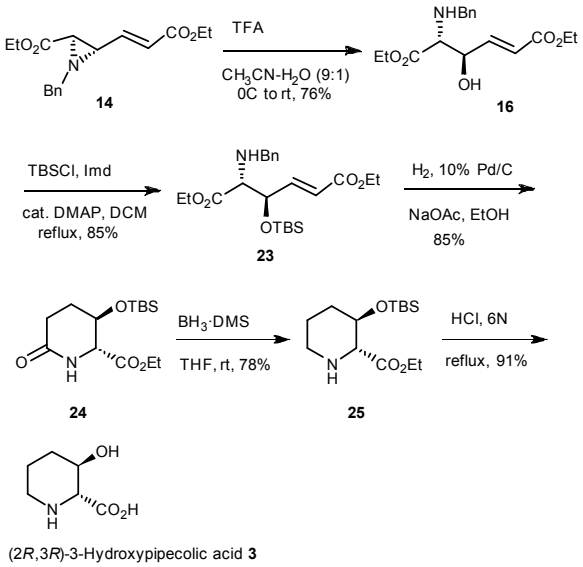
Scheme 1: Retrosynthetic analysis for target compounds.



Scheme 2: Synthesis of (*R*)-pipecolic acid *ent*-**1**.

View Article Online
DOI: 10.1039/C5RA06429E

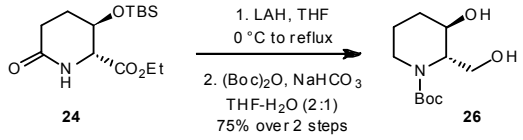
on diol cleavage using $NaIO_4$ yielded acetonide protected (*R*)-glyceraldehyde **20** which on Wittig olefination using bromophosphorane[24] in dichloromethane afforded bromoester **21.** The Gabriel-Cromwell reaction of 2-acrylic carboxylate derivative **21** with benzyl amine in toluene as solvent furnished *trans* aziridine-2-carboxylate **13** as the major isomer *via* conjugate addition, proton transfer and S_N2 ring closure in 68% yield.[25] The *trans* aziridine **13** was readily obtained by column chromatography. Acetonide *trans* aziridine **13** was deprotected using $TMSOTf/CH_2Cl_2$ at 0 °C,[26] to furnish diol **22** in excellent yield (90%). Diol **22** was then subjected to sodium metaperiodate mediated oxidative cleavage to yield crude aldehyde which was subjected to Horner-Wadsworth-Emmons olefination to afford *α,β*-unsaturated aziridine-ester **14** in 70% yield over two steps. This *α,β*-unsaturated aziridine carboxylate **14** (Scheme 2) when subjected to palladium mediated transfer hydrogenation conditions,[25b,27] underwent one pot efficient regioselective aziridine ring cleavage with concomitant olefin reduction, *N*-debenzylation and cyclisation of resultant amine as the key step to give access to (*R*)-ethyl-6-oxopipecolate **7** in 85% yield. Pipecolate **7** was further converted to (*R*)-*N*-Boc-2-piperidinemethanol **15** over two steps using LAH induced lactam/ester reduction followed by protection of resulting crude amino-alcohol as *N*-Boc derivative in 97% ee by HPLC analysis. (*R*)-*N*-Boc-2-piperidinemethanol **15** can be utilized as a precursor towards synthesis of (−)-lentiginosine **6**.[22] Finally compound **15** was converted to (*R*)-pipecolic acid *ent*-**1** by Boc deprotection using TFA followed by oxidation using $KMnO_4$ in aqueous 3 N H_2SO_4. The synthesis of (*R*)-pipecolic acid has been achieved in 27% overall yields while (*R*)-ethyl-6-oxo-pipecolate was achieved in 54% overall yield from *trans* aziridine-2-carboxylate **13** respectively**.**



Scheme 3: Synthesis of (2*R*,3*R*)-3-hydroxy pipecolic acid **3**.

After achieving the site selective functional group transformation at the acetonide group of aziridine-2-carboxylate **13**, attention was diverted to regioselective ring opening of aziridine ring in compound **13** by water as the nucleophile. In the next step, when compound **14** was treated with TFA (2 equiv.) in $CH_3CN–H_2O$ (9:1), it underwent regio and stereoselective nucleophilic ring opening reaction using water as nucleophile to afford *γ*-hydroxy-*δ*-amino-*α,β*-conjugated ester **16** as the only isomer in 76% yield (Scheme 2). Selective protection of hydroxyl group of amino-alcohol **16** was achieved using TBSCl, imidazole and cat. DMAP in refluxing dichloromethane to furnish TBS ether **23** in 85% yield. The crucial step *viz.* reductive cyclization of **23** was carried out under hydrogenation conditions using hydrogen gas and palladium hydroxide over carbon in ethanol to provide amide **24** in 85% yield (Scheme 3). In next step amido ester **24** was subjected to selective reduction of amide functionality using borane dimethyl sulfide complex in anhydrous THF to furnish the amino ester **25** in 78% yield. Finally the global deprotection involving ester hydrolysis as well as TBS group deprotection of **25** was carried out in a single step using 6N HCl to provide (2*R*,3*R*)-3-hydroxypipecolic acid **3** in 91% yield. The spectral data and optical rotation values of **3** thus obtained were in good agreement with the reported one.[28]

In order to ascertain the chiral purity, the lactam **25** was subjected to reduction using lithium aluminum hydride in anhydrous THF followed by *N*-Boc protection to provide *N*-Boc derivative **26**. The chiral HPLC analysis of the **26** revealed that the chiral purity was ~97% *ee* (Scheme 4). Thus the total synthesis of *trans* (2*R*,3*R*)-3-hydroxypipecolic acid **3** was accomplished in 24.6% overall yield in 8 steps from *trans* aziridine **13**.

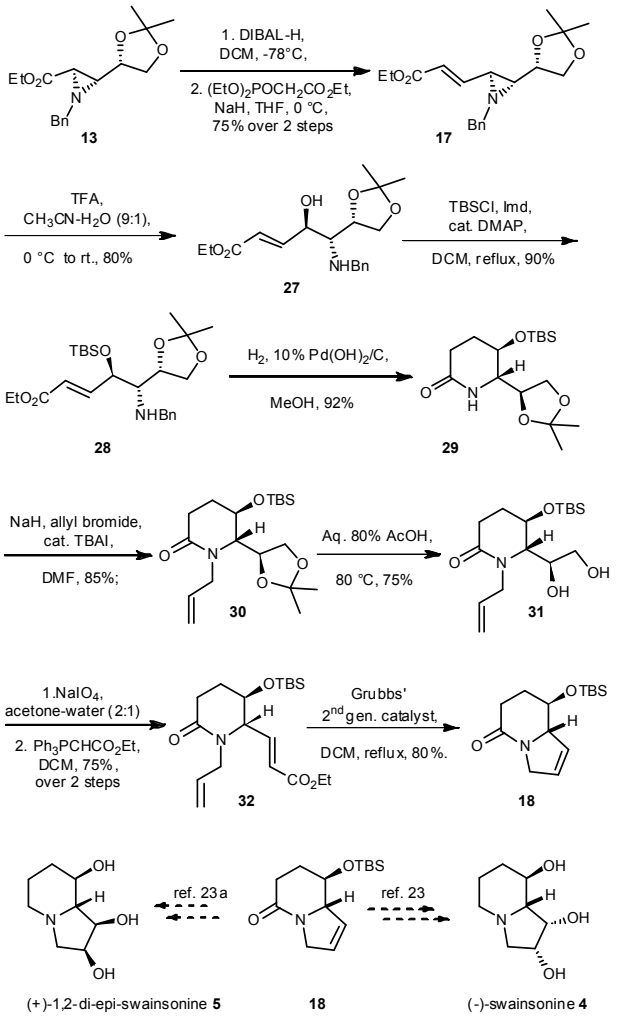


Scheme 4: Synthesis of diol **26**.

Our endeavor towards formal synthesis of (–)-swainsonine **4** and (+)-1,2-di-*epi*-swainsonine **5** started with aziridine-2-carboxylate **13** whose acetonide moiety was kept intact as a masked aldehyde while ester group was propagated to give *trans*-aziridine-*α,β*-unsaturated ester **17**. Thus *trans* aziridne-2-carboxylate **13** on reaction with DIBAL-H (1.2 eq.) yielded aldehyde which was used as such for the next step, Horner-Wadsworth-Emmons reaction on the resultant aldehyde furnished *α,β*-unsaturated *trans* aziridine ester **17** in 75% yield over two steps. Following the aziridine ring opening reaction under acidic conditions, compound 17 gave amino alcohol **27** (Scheme 5). Hydroxyl functionality of this amino-alcohol **27** was protected as its TBS ether **28** in 90% yield. Compound **28** on Palladium mediated hydrogenation/hydrogenolysis afforded lactam **29** in 92% yield. Allylation of lactam **29** was carried out using allyl bromide and NaH in DMF as the solvent to give *N*-allylated lactam **30** in 85% yields. Lactam **30** was exposed to 80% aqueous acetic acid at 80 °C to furnish diol **31** by selective deprotection of terminal acetonide functionality in presence of secondary –OTBS group in 75% yield.[29] After failing to convert 1,2-diol functionality of the

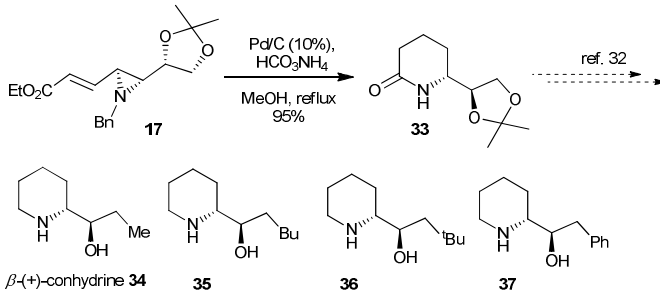
View Article Online
DOI: 10.1039/C5RA06429E Journal Name

compound **31** into corresponding alkene in one step using PPh_3/I_2/imidazole,[30] it was cleaved using $NaIO_4$ in acetone-water to



Scheme 5: Synthesis of (-)-swainsonine **4** and (+)-1,2-di-*epi*-swainsonine **5**.

furnish the crude aldehyde which, without purification, was subjected to 2-carbon Wittig homologation in dichloromethane to yield *α,β*-unsaturated ester **32** in 75% yield over two steps. Finally performing the ring closing metathesis reaction on



Scheme 6: Synthesis of key intermediate **33**

compound **32** using Grubbs' 2nd generation catalyst[31] in refluxing anhydrous dichloromethane gave access to key intermediate *viz.* bicyclic lactam **18** having requisite indolizidine skeleton of swainsonine. Enantiomer of **18** and its convertion to *ent*-**4** and *ent*-**5** is well documented in the literature. The spectral data of **18** were in good agreement with the reported one except for the sign of optical rotation (Scheme 5).

Additionally, aziridine ester **17** when subjected to transfer hydrogenation conditions yielded lactam **33** in excellent yield. Lactam **33** is key intermediate towards the syntheses of *β*-(+)-conhydrine and its analogues (Scheme 6).[32]

Conclusions

In conclusion, an efficient enantioselective total synthesis (*R*)-pipecolic acid *ent*-1, (*R*)-ethyl-6-oxopipecolate **7** and *trans* (2*R*,3*R*)-3-hydroxypipecolic acid **3**. A concise formal synthesis of (−)-swainsonine **4**, (+)-1,2-di-*epi*-swainsonine **5** and (−)-lentiginosine **6** have also been achieved from *trans* aziridine-2-carboxylate **13** as the common chiral synthon. The notable features of these syntheses are regio and stereoselective Wittig olefination, ring closing metathesis, reductive cyclisation and regio and stereoselective aziridine ring opening as key chemical transformations.

Syntheses are operationally simple and practical in terms of overall yield. The *trans* aziridine ester synthon was found to be a versatile highly efficient for the synthesis of various piperidine skeletons.

Experimental

General information:

All reagents and solvents were used as received from the manufacturer. HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 68B or on a Perkin-Elmer 1615 FT Infrared spectrophotometer. Melting points of solids were measured in Buchi melting point apparatus and are uncorrected. Optical rotation values were recorded on P-2000 polarimeter at 589 nm. ^{1}H (200 and 400 MHz) and ^{13}C (50 and 100 MHz) NMR spectra were recorded on Bruker and Bruker Advance 400 spectrometers, using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to chloroform, δ 7.27 (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra. The following abbreviations were used to explain the multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet. The reaction progress was monitored by the TLC analysis using thin layer plates precoated with silica gel 60 F_{254} (Merck) and visualized by fluorescence quenching or iodine or by charring after treatment with ethanolic solution of ninhydrin or anisaldehyde. Merck's flash silica gel (230-400 mesh) was used for column chromatography.

Experimental:

(*S*)-Ethyl 2-bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (21):[33] Freshly prepared (*R*)-glyceraldehyde

View Article Online
DOI: 10.1039/C5RA06429E ARTICLE

acetonide **20** (5.24 g, 0.020 mol) from di-*O*-isopropylidene (D)-mannitol **19** was taken in CH_2Cl_2 (75 mL). To this was added a solution of ethyl 2-bromo-2-(triphenylphosphoranylidene) acetate[34] **(**18.8 g, 0.044 mol) in CH_2Cl_2 (150 mL) and stirred for 2 h at room temperature. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2. Combined organic layer was dried over anhydrous Na_2SO_4, filtered and solvent was evaporated under reduced pressure. Residue was purified by column chromatography using pet. ether: ethyl acetate (95:5) to give bromoester **21** (*E/Z* = 7:93). R_f: 0.5 (pet. ether-ethyl acetate, 9:1); Yield: 10.5 g, 84% over two steps; IR ($CHCl_3$, cm^{-1}): νmax 2980, 1720, 1620; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.36 (t, J = 8.0 Hz, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 3.70 (dd, J = 6.6 & 8.3 Hz, 1H), 4.27 (q, J = 8.0 Hz, 3H), 4.95 (dd, J = 6.7 & 13.3 Hz, 1H), 7.36 (d, J = 6.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): δ 14.1, 25.5, 26.4, 62.6, 68.0, 75.5, 110.2, 116.7, 144.0, 161.4. MS (ESI): *m/z*: 279 $(M+H)^+$.

(2*R*,3*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (13): 8.37 g (0.030 mol) of bromoacrylate **3** was dissolved in dry toluene (100 mL) and the solution was stirred. To this stirred solution was added 3.21 g (0.030 mol) of benzylamine and 3.03 g (0.030 mol) of triethylamine at −5 °C. The reaction mixture was stirred for 24 h at room temperature. Solvent was filtered on simple filter paper, residue was again washed with toluene (20 mL) and concentrated under reduced pressure to yield yellow oil of *trans* aziridine **13** as major isomer and *cis* aziridine **33** as minor isomer in ratio of 9:1 which were separated using flash chromatography (pet. ether-ethyl acetate, 9:1). Yield: 75%; For **13**- Yield: 68%; For **33**- Yield: 7%

(2*R*,3*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (13): R_f: 0.5 (pet. ether-ethyl acetate, 8:2); IR ($CHCl_3$, cm^{-1}): νmax 2984, 1728, 1599, 1107. $[\alpha]_D^{25}$ +52.41 (*c* 1, $CHCl_3$), {Lit.[1] $[\alpha]_D^{25}$ +52.8 (*c* 1, $CHCl_3$)}.^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.19 (t, J = 8 Hz, 3H), 1.34 (s, 3 H), 1.42 (s, 3 H), 2.48 (t, J = 2.4 Hz, 1H), 2.63 (d, J = 2.4 Hz, 1H), 3.63-3.68 (m, 1H), 3.86-3.97 (m, 3H), 4.07-4.17 (m, 3H), 7.27-7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.0, 25.5, 26.6, 37.2, 47.4, 54.8, 60.1, 66.4, 75.9, 109.5, 126.9, 128.1, 138.8, 168.5; MS (ESI): *m/z*: 306.71 $[M+H]^+$; HRMS: Calculated for $C_{17}H_{24}NO_4$-306.1700, found-306.1694.

(2*S*,3*R*)-Ethyl 1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate (33): R_f: 0.4 (pet. ether-ethyl acetate, 8:2); IR ($CHCl_3$, cm^{-1}): νmax 2986, 1728, 1600, 1107; $[\alpha]_D^{25}$ −9.7 (*c* 1, $CHCl_3$), {Lit.[1] $[\alpha]_D^{25}$ −9.9 (*c* 1, $CHCl_3$)}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.18 (t, 3H), 1.27 (s, 3 H), 1.37 (s, 3H), 2.08 (t, J = 6.7 Hz, 1H), 2.23 (d, J = 6.7 Hz, 1H), 3.42 (d, J = 13.0 Hz, 1H), 3.66 (dd, J = 6.0 & 8.0 Hz, 1H), 3.89-3.97 (m, 2H), 4.11-4.22 (m, 3H), 7.27-7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.1, 25.3, 26.8, 40.4, 47.8, 61.0, 63.2, 66.9, 75.2, 109.6, 127.2, 127.9, 128.2, 137.2 , 168.9; MS (ESI): *m/z*: 306.18 $[M+H]^+$; HRMS: Calculated for $C_{17}H_{24}NO_4$-306.1700, found-306.1698.

(2*R*,3*R*)-Ethyl -1-benzyl-3-((*S*)-1,2-dihydroxyethyl)aziridine-2-carboxylate (22): To a stirred, ice-cold solution of the aziridine acetonide **13** (0.163 g, 0.53 mmol) in anhydrous CH_2Cl_2 (2 mL) under an inert atmosphere, was added TMSOTf (0.24 mL, 1.3 mmol) through a syringe. The resulting reaction mixture was stirred at the same temperature for 1 h, followed by quenching the reaction by addition of a saturated aqueous $NaHCO_3$ solution. After stirring the mixture for 5 min, the organic layer was separated and the aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. Concentration of the solvent under reduced pressure and column chromatographic purification (pet. ether-ethyl acetate, 7:3) of the residue provided the pure acetonide-cleaved product **22** as a thick liquid (0.127 g). R_f: 0.4 (pet. ether-ethyl acetate, 1:1); Yield: 90%; $[\alpha]_D^{25}$ +20.22 (*c* 2.1, $CHCl_3$), {Lit[35] $[\alpha]_D^{25}$ +19.6 (*c* 0.56, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): νmax 3588, 3369, 2927, 1727, 1603, 1454, 1371, 1193; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.23 (t, J = 7.2 Hz, 3H), 2.52 (t, J = 2.9 Hz, 1H), 2.75 (d, J = 2.9 Hz, 1H), 3.26-3.32 (m, 1H), 3.44-3.50 (m, 1H), 3.61 (br s, 1H), 3.96 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 7.27-7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.1, 37.4, 46.4, 54.4, 61.3, 65.2, 69.1, 127.5, 128.5, 128.6, 138.4, 168.5; MS (ESI): *m/z*: 266.13 $(M+H)^+$, 288.10 $(M+Na)^+$; HRMS: Calculated for $C_{14}H_{20}O_4N$-266.1387, found-266.1385.

(2*R*,3*S*)-Ethyl 1-benzyl-3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)aziridine-2-carboxylate (14): Diol **22** (0.21 g, 0.79 mmol) was dissolved in acetone–water (3 mL, 2:1) at 0 ℃, treated with sodium metaperiodate (0.203 g, 0.95 mmol) and stirred at 15 ℃ for 15 min. The reaction was quenched using ethylene glycol (0.01 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford crude aldehyde which was used as such for next reaction. To a stirred solution of NaH (0.038 g, 1.58 mmol, prewashed with *n*-hexane) dissolved in THF (2 mL), was added triethyl phosphonoacetate (0.31 mL, 1.58 mmol) slowly at 0 °C and stirred for 10 minutes. The aldehyde from above reaction dissolved in dry THF (3 mL) was added and stirring continued for another 2 h at same temperature until completion of reaction. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification on flash column chromatography (pet. ether-ethyl acetate, 9:1) furnished compound **14** (0.168 g) as thick colorless oil. R_f: 0.5 (pet. ether-ethyl acetate, 4:1); Yield: 0.168 g, 70%; $[\alpha]_D^{25}$ −36 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): νmax 2926, 2850, 1720, 1651, 1456, 1368, 1265, 1180, 1030; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.22-1.32 (m, 6H), 2.55-2.73 (m, 1H), 2.46-3.17 (m, 1H), 3.84-4.20 (m, 8H), 6.05-6.25 (m,1H), 6.60-6.89 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 14.0, 14.1, 42.9, 45.9, 54.4, 60.2, 61.1, 123.3, 127.6, 127.9, 128,2, 138.4, 145.3, 165.4, 167.8;

View Article Online
DOI: 10.1039/C5RA06429E
Journal Name

doubling of peaks in ^{1}H and ^{13}C is attributed to invertomerism; MS (ESI): *m/z*: 303.28 $(M)^{+}$, 326.21 $(M+Na)^{+}$; HRMS: Calculated for $C_{17}H_{21}NO_4Na$-326.1363, found-326.1358.

(*R*)-Ethyl 6-oxopiperidine-2-carboxylate (7): To a stirred solution of compound **14** (0.15 g, 0.49 mmol) in ethanol (5 mL) was added ammonium formate (0.27 g, 4.9 mmol) and 10% Pd/C (0.05 g) and refluxed for 1 h under nitrogen atmosphere. Reaction mass was filtered through celite, dried and column purified (pet. ether: ethyl acetate, 10:90) to yield 0.071 g of amide-ester **7** as colourless liquid. R_f: 0.3 (ethyl acetate); Yield: 85%; $[\alpha]_D^{25}$ +13.4 (*c* 1.4, $CHCl_3$) {Lit.[36] for *ent*-**7**, $[\alpha]_D^{25}$ −13.7 (*c* 0.3, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): νmax 2958, 1739, 1666, 1468, 1198; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.3 Hz, 3H), 1.78-1.98 (m, 3H), 2.20-2.22 (m, 1H), 2.36-2.47 (m, 2H), 4.1 (dd, *J* = 5.5 & 7.0 Hz, 1H), 4.24 (qd, *J* = 1.2 & 7.3 Hz, 2H), 6.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.1, 19.2, 25.2, 30.7, 54.7, 61.9, 170.7, 171.9; MS (ESI): *m/z*: 194.08 $(M+Na)^{+}$; HRMS: Calculated for $C_8H_{14}O_3N$-172.0968, found-172.0966.

(*R*)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (15): To a stirred suspension of LAH (0.22g, 5.85 mmol) in dry THF (5 mL) was added amide **7** (0.2 g, 1.17 mmol) dissolved in dry THF (5 mL) slowly at 0 °C *via* syringe under inert atmosphere (N_2 gas). After stirring for 24 h at room temperature, the reaction mixture was cooled to 0 °C, quenched carefully with minimum amount of water followed by 15% NaOH (0.25 mL). Again water (1 mL) was added and stirred for 0.5 h at room temperature. Anhydrous Na_2SO_4 was added and stirring continued for another 0.5 h. Filtration through Celite and concentration under vacuum gave crude amine which was used as such for next reaction. To a solution of amine in THF: water (5 mL, 1:1) was added solid $NaHCO_3$ (0.2 g, 2.34 mmol) and $(Boc)_2O$ (0.536 mL, 2.34 mmol) and then the mixture was vigorously stirred at room temperature for 6 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography (pet. ether–ethyl acetate, 8:2) to afford **15** as a white solid. R_f: 0.5 (pet. ether-ethyl acetate, 8:2); Yield: 0.176 g, 70% over two steps; MP: 81-84 °C, lit[37] 81-84 °C; $[\alpha]_D^{25}$ +38.5 (*c* 1, $CHCl_3$) {For *ent*-**15** Lit[5] $[\alpha]_D^{25}$ −40.5 (*c* 1, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): νmax 3443, 2940, 2890, 1655, 1280; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.46 (s, 9H), 1.60-1.65 (m, 6H), 2.11 (br s, 1H), 2.87 (t, *J* = 13.0 Hz, 1H), 3.59 (dd, *J* = 5.9 & 11.0 Hz, 1H), 3.79 (dd, *J* = 9.0 & 11.0 Hz, 1H), 3.93 (br d, *J* = 13.5 Hz, 1H), 4.25-4.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 19.3, 24.8, 25.1, 28.3, 39.7, 52.0, 60.6, 79.4, 155.8; MS (ESI): *m/z*: 238 $(M+Na)^{+}$; HRMS: Calculated for $C_{11}H_{22}O_3N$-216.1954, found-216.1600; HPLC detail for racemic hydroxy compound (**15**): HPLC Kromacil 5-Amycoat column (250×4.6 mm). Isopropanol/n-Hexane = 4:96; flow rate 0.5 ml/min, λ = 210 nm) retention time (min): rt1 = 22.18; rt2 = 24.05 (1:1). Enantiomerically pure hydroxy compound (**15**) HPLC Kromacil 5-Amycoat column (250 × 4.6 mm) isopropanol/n-hexane = 4:96; flow rate 0.5 ml/min, λ = 210 nm) retention time (min): rt1 = 22.07 (major); rt2 = 24.02 (>97% *ee*).

(*R*)-Piperidine-2-carboxylic acid (*ent*-1): To a solution of alcohol **15** (0.1 g, 0.465 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was slowly added TFA (0.1 mL, 1.3 mmol) and the reaction mixture was stirred at same temperature for 0.5 h, concentrated and resulting salt was used as such for next step. To a solution of salt from above step in 3N H_2SO_4 (4.5 mL) at 10 °C, was slowly added $KMnO_4$ (0.12 g, 0.744 mmol) and the reaction mixture was stirred at room temperature for 3 h, filtered through a pad of Celite and concentrated. (*R*)-Pipecolic acid *ent*-**1** was isolated after elution on Dowex 50W-X4 ion-exchange column (NH_4OH, 1 N). Yield: 0.044 g, 73%; R_f: 0.4 (CH_2Cl_2-MeOH-NH_4OH, 9:1:1%); MP: 271-273 °C; lit.[38] 271-274 °C; $[\alpha]_D^{25}$ +24.9 (*c* 1.15, H_2O) {Lit.[5] $[\alpha]_D^{25}$ +25.8 (*c* 1, H_2O)}; ^{1}H NMR (400 MHz, D_2O): δ 1.46-1.64 (m, 3H), 1.73-1.80 (m, 2H), 2.14-2.18 (m, 1H), 2.87-2.94 (m, 1H), 3.31-3.54 (m, 1H), 3.78 (dd, *J* = 8.0 Hz & 10.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O): δ 21.5, 21.6, 26.0, 44.0, 57.2, 172.2; MS (ESI): *m/z*: 152.28 $(M+Na)^{+}$.

(4*R*,5*R*,*E*)-Diethyl 5-(benzylamino)-4-hydroxyhex-2-enedioate (16): To a stirred solution of ester **14** (1.18 g, 3.89 mmol) in CH_3CN:water (9:1, 20 mL) was added TFA (0.45 mL, 7.79 mmol) drop wise at 0 ºC. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 5-6 h). Reaction was quenched by excess $NaHCO_3$, water (10 mL) was added and organic mass was extracted with ethyl acetate (3 × 15 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure followed by column chromatographic purification using ethyl acetate:pet ether (15:85) to yield 0.95 g of amino-alcohol **16** as thick liquid. R_f: 0.5 (pet ether-ethyl acetate, 7:3); Yield: 76% over two steps; $[\alpha]_D^{25}$ +20 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): νmax 3554, 3359, 2980, 1720, 1620; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 1.26-1.34 (m, 6H), 3.53 (d, *J* = 5Hz, 1H), 3.68 (d, *J* = 13 Hz, 1H), 3.94 (d, *J* = 13 Hz, 1H), 4.13-4.28 (m, 4H), 4.52-4.56 (m, 1H), 6.08 (dd, *J* = 2 & 15.5 Hz, 1H), 6.75 (dd, *J* = 4.0 & 15.5 Hz, 1H), 7.27-7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 14.2, 52.6, 60.3, 61.3, 64.1, 70.1, 122.7, 127.5, 128.2, 128.4, 138.9, 145.2, 165.7, 171.6; MS (ESI):*m/z*: 344.18 $(M+Na)^{+}$; HRMS: Calculated for $C_{17}H_{24}O_5N$-322.1649, found-322.1640.

(4*R*,5*R*,*E*)-Diethyl 5-(benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (23): To a stirred solution of hydroxyl amino ester **16** (0.7 g, 2.18 mmol), imidazole (0.3 g, 4.36 mmol) and DMAP (0.027 g, 0.22 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (0.6 g, 4.36 mmol) dissolved in CH_2Cl_2 (5 mL) slowly at 0 ºC after which reaction was heated to reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed by column chromatography using ethyl acetate-pet ether (5:95) to yield 0.8 g of hydroxy amino TBS ether **23** as

View Article Online
DOI: 10.1039/C5RA06429E ARTICLE

thick colorless liquid. R_f: 0.5 (pet. ether-ethyl acetate, 8:2); Yield: 85% over two steps. $[\alpha]_D^{25}$ −7.69 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): νmax 2980, 1720, 1620; ^1H NMR (500 MHz, $CDCl_3$+CCl_4): 0.01 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.24-1.31 (m, 6H), 2.17 (br s, 1H), 3.28 (d, *J* = 5.5 Hz, 1H), 3.65 (d, *J* = 13 Hz, 1H), 3.84 (d, *J* = 13.0 Hz, 1H), 4.12-4.20 (m, 5H), 4.47-4.48 (m, 1H), 5.95 (dd, *J* = 1.5 & 15.5 Hz, 1H), 6.95 (dd, *J* = 5.2 & 15.5 Hz, 1H), 7.21-7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$+CCl_4): −4.6, −4.4, 14.3, 18.1, 25.7, 52.2, 60.3, 60.7, 65.7, 73.7, 121.7, 127.1, 128.2, 128.3, 139.4, 147.5, 166.0, 172.0; MS (ESI): *m/z*: 436.68 $(M+H)^+$; HRMS: Calculated for $C_{23}H_{38}ON_5Si$-436.2514, found-436.2505.

(2*R*,3*R*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-6-oxopiperidine-2-carboxylate (24): The amino ester **23** (0.8 g, 2.2 mmol) was dissolved in ethanol (10 mL) and to that was added catalytic amount of palladium hydroxide over carbon (10%, 20 mg). The resulting reaction mixture was stirred under hydrogen atmosphere using balloon for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography using silica gel (pet ether-ethyl acetate, 7:3) to provide amide **24** (0.52 g) as a colorless thick oil. R_f: 0.4 (pet. ether-ethyl acetate, 8:2); Yield: 85%; $[\alpha]_D^{25}$ −26 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): νmax 3399, 2955, 2857, 1732, 1643, 1215; ^1H NMR (200 MHz, $CDCl_3$): *δ* 0.12 (s, 6H), 0.90 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.68 (br s, 1H), 1.79-1.88 (m, 2H), 2.26-2.40 (m, 1H), 2.54-2.72 (m, 1H), 3.99-4.02 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.35-4.39 (m, 1H), 5.96 (br s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): *δ* –5.1, –4.9, 14.1, 17.9, 25.6, 26.4, 26.5, 61.8, 62.3, 65.4, 170.1, 171.4. MS (ESI): *m/z*: 302.2 $(M+H)^+$; HRMS: Calculated for $C_{14}H_{28}O_4NSi$-302.1782, found-302.1777.

(2*R*,3*R*)-Ethyl 3-((*tert*-butyldimethylsilyl)oxy)piperidine-2-carboxylate (25): To the amide **24** (0.2 g, 0.7 mmol) in anhydrous THF (5 mL) was added BH_3·DMS (0.2 mL, 2 mmol) dropwise at 0 ºC. The resulting reaction mixture was further stirred at 5 ºC for 20 h. Methanol (excess) was added to the reaction mixture, stirred for 4 h and concentrated under reduced pressure. Water (10 mL) was added and the reaction mixture was extracted using dichloromethane (3 × 10 mL). The collected organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified using flash chromatography over silica gel (70:30, EtOAc: pet ether) to furnish amine **25** (0.147 g, 78%) as a colorless dense liquid. R_f: 0.5 (pet. ether-ethyl acetate, 2:8); Yield: 78%; $[\alpha]_D^{25}$ –27 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): νmax 3436, 3020, 2931, 2400, 1731, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.00 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.36 (t, *J* = 7.3 Hz, 3H), 1.41-1.51 (m, 2H), 1.58-1.68 (m, 2H), 1.84-1.87 (m, 1H), 2.01-2.05 (m, 1H), 2.53-2.64 (m, 1H), 3.11 (dd, *J* = 1.1 & 10.1 Hz, 1H), 3.32 (d, *J* = 13.5 Hz, 1H), 3.78 (dt, *J* = 5.4 & 10.5 Hz, 1H), 3.98 (m, 1H), 4.10-4.18 (m, 1H), 4.31-4.39 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$+CCl_4): δ –5.3, –4.2, 13.9, 17.8, 23.1, 25.5, 32.2, 52.2, 61.8, 70.2, 70.5, 170.8; MS (ESI): *m/z*: 288.23 $(M+H)^+$, 310.14 $(M+Na)^+$; HRMS: Calculated for $C_{14}H_{30}O_3NSi$- 288.1989, found- 288.1979.

(2*R*,3*R*)-3-Hydroxypiperidine-2-carboxylic acid (3): A mixture of amine **25** (100 mg, 0.35 mmol) and 6 N HCl (10 mL) was kept at 120 ºC for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (50 mL). The mixture was loaded on an ion-exchange column (DOWEX 50W X8) and eluted with H_2O and then with aq. NH_3 solution. The eluate of aq. NH_3 was concentrated to dryness under reduced pressure to give **3** (46 mg, 91%) as a crystalline solid. R_f: 0.3 (CH_2Cl_2-MeOH-NH_4OH, 9:1:1%); Yield: 91%; MP: 238–243 ºC (dec.), lit.[39] 230-238 °C; $[\alpha]_D^{25}$–13.8 (*c* 1.0, aq. HCl 10%), {lit.[7] $[\alpha]_D^{20}$ –14 (*c* 0.5, aq. HC1 10%)}; IR ($CHCl_3$, cm^{-1}): νmax 3287, 2920, 1625, 1405 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 1.64-1.80 (m, 2H), 2.02-2.08 (m, 2H), 2.22 (s, 1H), 3.07-3.12 (m, 1H), 3.40-3.36 (m, 1H), 3.83 (d, *J* = 7.8 Hz, 1H), 4.17-4.13 (m, 1H); ^{13}C-NMR (100 MHz, D_2O): δ 18.5, 28.7, 42.5, 60.8, 65.5, 170.0; MS (ESI): *m/z*: 146 $(M+H)^+$.

(2*S*,3*R*)-*tert*-Butyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (26): To stirred suspension of LAH (0.152 g, 4 mmol) in anhydrous THF (3 mL) was added the lactam **24** (240 mg, 0.8 mmol) dissolved in anhydrous THF (3 mL) and the reaction mixture was stirred for 8 h at room temperature. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue thus obtained was purified by flash chromatography (pet ether–ethyl acetate 10:90) to afford diol **26** (138 mg) as a white crystalline solid. R_f: 0.5 (pet. ether-ethyl acetate, 2:8); Yield: 75%; MP: 126-128 ºC, lit.[8] 124-126 °C; $[\alpha]_D^{25}$+27 (c 1.0, MeOH), {lit.[40] $[\alpha]_D^{25}$ +29.8 (*c* 0.99, MeOH)}; IR ($CHCl_3$, cm^{-1}) : υmax 3448, 3025, 2945, 1674, 1215, 1120, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 1.15-1.29 (m, 1H), 1.39 (s, 9H), 1.61-1.82 (m, 3H), 2.69-2.82 (m, 1H), 3.45-3.61 (m, 2H), 3.89-3.92 (m, 2H), 4.08-4.16 (m, 1H); ^{13}C (125 MHz, $CDCl_3$+CCl_4+DMSO-d_6): δ 18.8, 26.3, 28.0, 39.6, 59.1, 59.8, 63.8, 79.1, 155.9; MS(ESI): *m/z*: 232 $(M+H)^+$, 254 $(M+Na)^+$; HRMS: Calculated for $C_{11}H_{21}NNaO_4$-254.1368, found-254.1369. HPLC detail for racemic dihydroxy compound (**26**) HPLC chiracel OJ-H column (250×4.6 mm). Isopropanol/pet ether = 5:95 flow rate 0.5 ml/min, λ = 210 nm) retention time (min): rt1 = 13.39; rt2 = 14.98 (1:1). Enantiomerically pure dihydroxy compound (**26**) HPLC chiracel OJ-H column (250 × 4.6 mm) isopropanol/pet ether = 5:95 flow rate 0.5 ml/min, λ = 210 nm) retention time (min): rt1 = 13.18 (major); rt2 = 15.05 (>97% *ee*).

(*E*)-Ethyl 3-((2*S*,3*R*)-1-benzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridin-2-yl)acrylate (17): To a stirred solution of *trans* aziridine-2-carboxylate **13** (1 g, 3.27 mmol) in dry CH_2Cl_2 (30 mL) was added DIBAL-H (3.6 mL, 3.6 mmol, 1 M solution in toluene) at −78 °C slowly over period of 15 min and

View Article Online
DOI: 10.1039/C5RA06429E Journal Name

stirred for another 15 min. TLC showed complete convertion of ester to aldehyde. Reaction was quenched by addition of MeOH (0.3 mL) and allowed to warm to 0 °C. Saturated aqueous NH_4Cl (10 mL) was added and stirred for 0.25 h after which organic layer was separated and aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and used as such for next reaction. To a stirred solution NaH (0.09 g, 3.6 mmol, prewashed with dry *n*-hexane) dissolved in THF (10 mL) was added triethyl phosphonoacetate (0.71 mL, 3.6 mmol) slowly at 0 °C and stirred for 10 minutes. The aldehyde from above reaction dissolved in 5 ml of dry THF was added and stirring continued for another 2 h at same temperature until completion of reaction. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification on flash column chromatography (pet. ether: ethyl acetate, 1:9) furnished compound **17** (0.75 g) as thick colorless oil. R_f: 0.5 (pet ether-ethyl acetate, 8:2); Yield: 75%, over two steps; IR ($CHCl_3$, cm^{-1}): νmax 2984, 2932, 1716, 1644, 1370, 1265; $[\alpha]_D^{25}$ −34 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.30 (t, *J* = 7.0 Hz, 3H), 1.33 (s, 3H), 1.40 (s, 3H), 2.12 (dd, *J* = 2.6 & 4.9 Hz, 1H), 2.72 (dd, *J* = 2.4 & 9.9 Hz, 1H), 3.61 (dd, *J* = 5.5 & 7.9 Hz, 1H), 3.72-3.85 (m, 2H), 3.91-4.09 (m, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 6.13 (d, *J* = 15.2 Hz, 1H), 6.89 (dd, *J* = 9.9 & 15.2 Hz, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 14.2, 25.5, 26.7, 40.1, 49.6, 57.0, 60.3, 66.24, 76.1, 109.5, 125.1, 127.1, 127.9, 128.2, 138.6, 142.9, 165.3; MS (ESI): *m/z*: 354.15 $[M+Na]^+$; HRMS: Calculated for $C_{19}H_{26}O_4N$-332.1856, found-332.1858.

(4*R*,5*R*,*E*)-Ethyl 5-(benzylamino)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxypent-2-enoate (27): To a stirred solution of ester **17** (1.4 g, 4.2 mmol) in CH_3CN: water (9:1, 25 mL) was added TFA (0.64 mL, 8.4 mmol) dropwise at 0 ºC. The reaction mixture was slowly warmed to room temperature and stirred until complete disappearance of starting material (~ 5-6 h). Reaction was quenched by addition of excess $NaHCO_3$, water (10 mL) was added and organic mass was extracted with ethyl acetate (3 × 20 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure followed by column chromatographic purification using ethyl acetate-pet. ether (15:85) to yield 1.11 g of amino-alcohol **27** as thick liquid. R_f: 0.5 (pet. ether-ethyl acetate, 7:3); Yield: 80%; IR ($CHCl_3$, cm^{-1}): νmax 3453, 2985, 1717, 1656, 1455, 1370, 1263, 1175; $[\alpha]_D^{25}$ −50 (*c* 1.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.32 (s, 3H), 1.39 (s,3H), 2.74 (dd, *J* = 3.6 & 5.4 Hz, 1H), 3.77-4.03 (m, 4H), 4.1-4.26 (m, 3H), 4.55 (dd, *J* = 3.6 & 5.4Hz, 1H), 6.2 (dd, *J* = 2 & 15.6 Hz, 1H), 6.9 (dd, *J* = 3.7 & 15.6 Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 25.1, 26.3, 51.0, 60.3, 61.3, 67.3, 69.0, 74.9, 109.0, 121.3, 127.1, 128.1, 128.4, 139.5, 147.0, 166.1; MS (ESI):*m/z*: 372.14 $[M+Na]^+$. HRMS: Calculated for $C_{19}H_{28}O_5N$-350.1962, found 350.1967.

(4*R*,5*S*,*E*)-Ethyl 5-(benzylamino)-4-((tert-butyldimethylsilyl)oxy)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-enoate (28): To a stirred solution of hydroxyl amino ester **27** (1 g, 2.86 mmol), imidazole (0.4 g, 6 mmol) and DMAP (0.0.24 g, 0.2 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (1.27 g, 8.44 mmol) dissolved in CH_2Cl_2 (5 mL) slowly at ^{o}C after which reaction was heated to reflux for 6 h until completion of reaction. Reaction mass was concentrated under reduced pressure followed by column chromatography using ethyl acetate: pet ether (5:95) to yield 1.18 g of -OTBS protected amino-alcohol **28** as thick colourless liquid. R_f: 0.5 (pet. ether-ethyl acetate, 8:2); Yield: 90%; IR ($CHCl_3$, cm^{-1}): νmax 2984, 2931, 1721, 1657, 1472, 1369, 1260, 1160, 1059. $[\alpha]_D^{25}$ +11.11 (*c* 2.7, $CHCl_3$); ^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.04 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.31 (t, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 2.72 (br s, 1H), 3.70 (t, *J* = 7.7 Hz, 1H), 3.84-4.04 (m, 1H), 4.22 (q, 2H), 4.29-4.46 (m, 2H), 6.08 (dd, *J* = 1.4 & 15.6 Hz, 1H), 7.1 (dd, *J* = 5.2 & 15.6 Hz, 1H), 7.25-7.36 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ −4.9, −4.5, 14.1, 18.1, 25.2, 25.8, 26.8, 53.1, 60.3, 63.7, 66.9, 73.3, 75.5, 108.8, 121.4, 126.9, 128.2, 149.0, 166.2; MS (ESI): *m/z*: 486.27 $[M+Na]^+$; HRMS: Calculated for $C_{25}H_{42}O_5NSi$-464.2827, found-464.2847.

(5*R*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (29): A suspension of **28** (0.9 g, 1.94 mmol) and 10% $Pd(OH)_2$/C (60 mg) in MeOH (20 mL) was stirred under a H_2 atmosphere at room temperature for 2.5 h, filtered through Celite and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/pet. ether = 1:3) to afford amide **29** (0.59 g) as a colorless thick liquid. R_f: 0.5 (pet. ether-ethyl acetate, 1:1); Yield: 92%; IR ($CHCl_3$, cm^{-1}): νmax 3408, 2927, 1670, 1457, 1380, 1216; $[\alpha]_D^{25}$ –22.9 (*c* 1.15, $CHCl_3$). ^{1}HNMR (400 MHz, $CDCl_3$+CCl_4): δ 0.1 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.34 (s, 3H), 1.41 (s, 3H), 1.78-1.87 (m, 1H), 1.94-2.01 (m, 1H), 2.29-2.38 (m, 1H), 2.47-2.85 (m, 1H), 3.20 (t, *J* = 7 Hz, 1H), 3.72-3.77 (m, 1H), 3.84 (dd, *J* = 5 & 8 Hz, 1H), 4.00-4.1 (m, 2H), 6.02 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ –4.5, –4.1, 17.9, 25.2, 25.8, 26.6, 28.5, 29.1, 61.7, 67.2, 68.1, 76.3, 109.3, 170.6; MS (ESI): *m/z*: 352.18 $[M+Na]^+$; HRMS: Calculated for $C_{16}H_{32}O_4NSi$-330.2101, found-330.2095.

(5*R*,6*S*)-1-Allyl-5-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (30): To the NaH (0.044 g, 1.8 mmol, prewashed with dry *n*-hexane) in DMF (2 mL) was added amide **29** (0.4 gm, 1.21 mmol) in DMF (2 mL) dropwise at 0 ºC and stirred for 1 h at room temperature. Allyl bromide (0.154 mL, 1.8 mmol) was added dropwise at 0 ºC. The resulting reaction mixture stirred for 3-4 h at room temperature. Reaction mixture was then quenched using water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organics washed with brine, dried over anhydrous

View Article Online
DOI: 10.1039/C5RA06429E ARTICLE

Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was column purified on flash chromatography (pet. ether-ethyl acetate, 7:3) to afford the allylated product **30** as colorless liquid. R_f: 0.5 (pet. ether-ethyl acetate, 2:1); Yield: 0.357 g, 85%; IR ($CHCl_3$, cm^{-1}): νmax 2986, 1630, 1420, 1107. $[\alpha]_D^{25}$ – 83.4 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.35 (s, 3H), 1.43 (s, 3H), 1.88-1.92 (m, 4H), 2.33-2.44 (m, 1H),), 2.53-2.67 (m, 1H), 3.33-3.37 (m, 1H), 3.54-3.75 (m, 3H), 4.03-4.05 (m, 2H), 4.9 (m, 1H), 5.11-5.24 (m, 2H), 5.61-5.81 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4):δ –4.9, 17.8, 25.4, 25.5, 25.6, 26.3, 26.5, 48.4, 64.4, 65.4, 66.7, 78.5, 109.6, 117.1, 133.4, 168.8; MS (ESI): *m/z*: 356.41 $[M+H]^+$.

((5*R*,6*S*)-1-Allyl-5-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-1,2-dihydroxyethyl)piperidin-2-one (31): Protected lactam **30** (0.2 g, 0.56 mmol) was treated with 80% aqueous acetic acid (2 mL), and the resulting mixture was allowed to react at 80 °C. The reaction was monitored by TLC and was judged to be complete after 3 h. The solution was then diluted with H_2O (8 mL) and extracted with EtOAc (3 × 10 mL). The extracts were treated with saturated $NaHCO_3$ solution, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude residue that was purified by flash chromatography (pet. ether-ethyl acetate, 1:9). Pure terminal diol **31** (0.14 g) was obtained as a thick gummy liquid. R_f: 0.4 (ethyl acetate); Yield: 75%; IR ($CHCl_3$, cm^{-1}): νmax 3554, 3340, 2986, 1627, 1423, 1107; $[\alpha]_D^{25}$ –34.9 (*c* 1, $CHCl_3$); ^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.99-2.11 (m, 2H), 2.14-2.33 (m, 1H), 2.53-2.63 (m, 1H), 3.35-3.37 (m, 1H), 3.54-3.69 (m, 4H), 3.94 (s, 1H), 4.71-4.77 (m, 2H), 5.26-5.58 (m, 2H), 5.72-5.88 (m, 1H); ^{13}C NMR(100 MHz, $CDCl_3$+CCl_4): –4.8, –4.7, 18.0, 25.3, 25.8, 26.9, 50.3, 64.1, 64.7, 66.1, 73.6, 117.5, 132.8, 171.0; MS (ESI): *m/z*: 352.23 $[M+Na]^+$.

(*E*)-Ethyl 3-((2*S*,3*R*)-1-allyl-3-((tert-butyldimethylsilyl)oxy)-6-oxopiperidin-2-yl)acrylate (32): Diol **31** (0.2 g, 0.607 mmol) was dissolved in acetone–water (3 mL, 2:1) at 0 ºC, treated with sodium metaperiodate (0.2 g, 0.9 mmol) and stirred at 15 ºC for 15 min. The reaction was quenched using ethylene glycol (0.01 mL), extracted with CH_2Cl_2 (3 ×10 mL), washed with brine, dried over anhydrous Na_2SO_4 and filtered. The combined organics were concentrated under reduced pressure to afford crude aldehyde which was used as such for next reaction.

To a solution of aldehyde from above reaction in CH_2Cl_2 (15 mL) was added (carboethoxymethylene) triphenylphosphorane (0.4 g, 1.2 mmol) and the reaction mixture was stirred for 6 h. Solvent was evaporated and the reaction mixture was adsorbed on silica. Purification by column chromatography (pet. ether–ethyl acetate, 8:2) gave **32** as a thick liquid (0.167 g). R_f: 0.5 (pet. ether-ethyl acetate, 1:1); Yield: 75%; IR ($CHCl_3$, cm^{-1}): νmax 2986, 1723, 1656, 1630, 1107; $[\alpha]_D^{25}$ –45 (*c* 1, $CHCl_3$) ^{1}HNMR (200 MHz, $CDCl_3$+CCl_4): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.30 (t, *J* = 7 Hz, 3H), 1.73-1.75 (m, 1H), 1.86-1.93 (m, 1H),), 2.35 (m, 1H), 2.59-2.68 (m, 1H), 2.99 (dd, *J* = 7 & 16 Hz, 1H), 3.99 (m, 1H), 4.19 (q, *J* = 7 Hz, 2H), 5.84 (dt, *J* = 2 & 16 Hz, 1H), 5.11-5.18 (m, 1H), 5.62-5.72 (m, 1H), 5.88 (dd, *J* = 1 & 16 Hz, 1H), 6.73 (dd, *J* = 6 & 16 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ -4.8, 14.2, 24.8, 25.6, 26.7, 47.3, 60.7, 64.3, 67.0, 117.3, 123.9, 132.3, 144.5, 165.4, 169.1; MS (ESI) *m/z*: 390.12 $[M+Na]^+$; HRMS: Calculated for $C_{19}H_{34}O_4NSi$-368.2252, found-368.2247.

(8*R*,8a*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-6,7,8,8a-tetrahydroindolizin-5(3H)-one (18): The olefinic compound **32** (0.075 g, 0.2 mmol) and Grubbs' 2nd generation catalyst (5 mg, 2 mol%) in anhydrous CH_2Cl_2 (50 mL) was refluxed for 5 h. The reaction mixture was filtered through Celite and concentrated *in vacuo* to provide crude **3**. The crude product was purified using column chromatography (pet. ether-ethyl acetate, 1:1) to provide the ring closed product **18** (0.044 g, 80%) as a colorless sticky liquid. R_f: 0.3 (pet. ether-ethyl acetate, 1:1); Yield: 80%; IR ($CHCl_3$, cm^{-1}): νmax 1640, 1620; $[\alpha]_D^{25}$ +53 (*c* 1, $CHCl_3$); lit[41] {for *ent*-$[\alpha]_D^{25}$ –53.73 (*c* 1.10, $CHCl_3$)}; ^{1}HNMR (400 MHz, $CDCl_3$+CCl_4): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.79-1.81 (m, 1H), 2.02-2.03 (m, 1H), 2.39-2.46 (m, 1H), 2.60-2.62 (m, 1H), 3.53-3.55 (m, 1H), 4.02-4.06 (m, 1H), 4.15-4.16 (m, 1H), 4.45-4.50 (m, 1H), 5.92-5.94 (m, 2H); ^{13}C NMR(100 MHz, $CDCl_3$+CCl_4): δ −4.6, −4.1, 18.0, 25.7, 29.7,30.2, 53.3, 69.1, 71.1, 126.8, 128.5, 168.2. MS (ESI): *m/z*: 268.02 $[M+H]^+$. HRMS: Calculated for $C_{14}H_{26}NO_2Si$-268.1733; found-268.1741.

***R*)-6-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)piperidin-2-one (33):** To a stirred solution of aziridine ester 1**7** (0.66 g, 1.99 mmol) in methanol (10 mL) was added ammonium formate (1.24 g, 19.9 mmol) and 10% Pd/C (100 mg), and the mixture was refluxed for 3 h. The reaction mixture was filtered through Celite, concentrated and purified by column chromatography (pet ether-ethyl acetate, 2:8) to afford **33** as a thick yellowish liquid. R_f: 0.4 (ethyl acetate); Yield: 0.37 g, 95%; $[\alpha]_D^{25}$ −17.5 (*c* 1.1, $CHCl_3$); {lit.[42] $[\alpha]_D^{25}$ –14.4, (*c* 0.5, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): νmax 3402, 2985, 2936, 1664, 1457, 1371, 1072; ^{1}H NMR (400 MHz, $CDCl_3$+CCl_4): δ 1.20-1.28 (m, 1H), 1.33 (s, 3H), 1.40 (s, 3H), 1.63-1.83 (m, 2H), 1.85-2.01 (m, 1H), 2.17-2.49 (m, 2H), 3.31 (td, *J* = 5.4 & 8.7 Hz, 1H), 3.66 (dd, *J* = 5.4 & 8.2 Hz, 1H), 3.86-3.88 (m, 1H), 4.03 (dd, *J* = 6.0 & 8.2 Hz, 1H), 6.21 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 19.7, 24.8, 25.3, 26.8, 31.3, 56.2, 66.2, 79.1, 109.79, 171.2; MS (ESI): *m/z*: 200.11 $(M+H)^+$, 222.10 $(M+Na)^+$; HRMS: Calculated for $C_7H_{18}NO_3$-200.1281, found-200.1277.

Aknowledgement

LBK, KPP, PNC and SK thank CSIR, New Delhi, India for fellowship. We also thank Dr. U R Kalkote, Dr. H B Borate, Dr. N. B. Dumare and D. B. Kalbhor for helpful discussion. The authors thank CSIR, New Delhi for financial support as of XII year plan programme under title ORIGIN (CSC-0108) and ACT (CSC-0301).

View Article Online
DOI: 10.1039/C5RA06429E Journal Name

Notes and references

[a] CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008, Maharashtra, India.
Email: sp.chavan@ncl.res.in

† Electronic Supplementary Information (ESI) is available at DOI: 10.1039/b000000x/

1. Review articles: (*a*) M. He, *J. Ind. Microbiol. Biotechnol.,* 2006, **33**, 401;(*b*) H. P. Broquist, *Annu. Rev. Nutr.,* 1991, **11**, 435; (*c*) V. Vranova, L. Lojkova, K. Rejsek, and P. Formanek, *Chirality,* 2013, **25**, 823.
2. (*a*) D. C. N. Swindells, P. S. White and J. A. Findlay, *Can. J. Chem.,* 1978, **56**, 2491; (*b*) A. B. Smith III, K. J. Hale, L. M. Laakso, K. Chen and A. Riéra, *Tetrahedron Lett.*, 1989, **30**, 6963; (*c*) A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer Jr., J. W. Leahy and R. E. Maleczka Jr., *J. Am. Chem. Soc.,* 1997, **119**, 962l; (*d*) A. B. Smith III, C. M. Adams, *Acc. Chem. Res.,* 2004, **37**, 365.
3. (*a*) H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto and T. Taga, *J. Am. Chem. Soc.,* 1987, **109**, 5031; (*b*) D. Romo, S. D. Meyer, D. D. Johnson and S. L. Schreiber, *J. Am. Chem. Soc.,* 1993, **115**, 7906; (*c*) R. E. Ireland, J. L. Gleason, L. D. Gregnas and T. K. A. Highsmith, *J. Org. Chem.*, 1996, **61**, 6856.
4. D. L. Boger, J.-H. Chen and K. W. Saionz, *J. Am. Chem. Soc.*, 1996, **118**, 1629.
5. J. B. Rangisetty, M. R. Pullagurla, R. J. J. Muthiah and C. N. Jobdevairakkam, *US patent 7683175*, 2008.
6. (*a*) T. Fujii, M. Mukaihara, H. Agematu and H. Tsunekawa, *Biosci. Biotechnol. Biochem.,* 2002, **66**, 622; (*b*) S. B. Singh, D. L. Zink, J. M. Liesch, R. T. Mosley, A. W. Dombrowski, G. F. Bills, S. J. Darkin-Rattray, D. M. Schmatz and M. A. Goetz, *J. Org. Chem.,* 2002, **67**, 815; (*c*) A. V. Bieliauskas and M. K. H. Pflum, *Chem. Soc. Rev.,* 2008, **37**, 1402.
7. I. Pastuszak, R. J. Molyneux, L. F. James and A. D. Elbein, *Biochemistry,* 1990, **29**, 1886.
8. M. A. Wijdeven, J. Willemsen and F. P. J. T. Rutjes, *Eur. J. Org. Chem.,* 2010, 2831.
9. F. Ferreira, C. Greck and J. P. Genet, *Bull. Soc. Chim. Fr.*, 1997, **134**, 615.
10. (*a*) M. J. Humphries, K. Matsumoto, S. L. White, R. J. Molyneux and K. Olden, *Cancer Res.* 1988, **48**, 1410; (*b*) J. W. Dennis, *Cancer Res.,* 1986, **46**, 5131; (*c*) C. Galustian, S. Foulds, J. F. Dye and P. J. Guillou, *Immunopharmacology*, 1994, **27**, 165; (*d*) P. C. Das, J. D. Roberts, S. L. White and K. Olden, *Oncol. Res.* 1995, **7**, 425; (e) H. Motohiro, N. Kunio, T. Hiroshi, H. Junji, K. Masanobu, A. Hatsuo and I. Hiroshi, Patent *EP 104826*; *Chem. Abstr.,* 1984, **101**, 28283x.
11. (*a*) F. A., Jr., Kuehl, C. F. Spencer and K. Folkers, *J. Am. Chem. Soc.,* 1948, **70**, 2091; (*b*) Sh. Kobayashi, M. Ueno and R. Suzuki, *Tetrahedron Lett.,* 1999, **40**, 2175.
12. (*a*) G. Ratle, X. Monseur, B. C. Das, J. Yassi, Q. Khuong-Huu and R. Goutarel, *Bull. Soc. Chim. Fr.,* 1966, 2945; (*b*) Q. Khuong-Huu, G. Ratle, X. Monseur and R. Goutarel, *Bull. Soc. Chim. Belg.,* 1972, **81**, 425; (*c*) Q. Khuong-Huu, G. Ratle, X. Monseur and R. Goutarel, *Bull. Soc. Chim. Belg.,* 1972, **81**, 443; (*d*) P. Bourinet and A. Quevauviller, *Compt. Rend. Soc. Biol.,* 1968, **162**, 1138 [CA 70: 95233k]; (*e*) P. Bourinet and A. Quevauviller, *Ann. Phar. Fr.,* 1968, **26**, 787 [CA 71: 29012g].
13. J. D. Scott, T. N. Tippie and R. M. Williams, *Tetrahedron Lett.,* 1998, **39**,3659.
14. (*a*) S.-B. Huang, J. S. Nelson and D. D. Weller, *Synth. Commun.,* 1989, **19**, 3485; (*b*) A. Sadiq and N. Sewald, *ARKIVOC,* 2012, **5**, 28; (*c*) S. A. Hermitage and M. G. Moloney, *Tetrahedron:Asymmetry,* 1994, **5**, 1463; (*d*) T. J. Hodgkinson and M. Shipman, *Synthesis,* 1998, 1141; (*e*) P. K. Upadhyay and P. Kumar, *Synthesis*, 2010, **15**, 2512.
15. For reviews, see: (*a*) S. Hanessian, G. McNaughton-Smith, H.-G.; Lombart and W. D. Lubell, Tetrahedron, 1997, **53**, 12789; (*b*) S. M. Cowell, Y. S. Lee, J. P. Cain and V. J. Hruby, *Curr. Med. Chem.,* 2004, **11**, 2785; (*c*) T. D. Copeland, E. M. Wondrak, J. Toszer, M. M. Roberts and S. Oraszan, *Biochem. Biophys. Res. Commun.,* 1990**,** **169**, 310; (*d*) M. Quibell, A. Benn, N. Flinn, T. Monk, M. Ramjee, Y. Wang and J. Watts, *Bio-org. Med. Chem.,* 2004, **12**, 5689.
16. (*a*) P. H.-Y. Cheoug, H. Zhang, R. Thayumanavan, F. Tanaka, K. N. Houk and C. F. Barbas III, *Org. Lett.,* 2006, **8**, 811; (*b*) C. E.; Aroyan, M. M. Vasbinder and S. Miller, *Org. Lett.,* 2005, **7**, 3849; (*c*) X. Liu, L. Lin and X. Feng, *Acc. Chem. Res.,* 2011, **44**, 574 and references cited therein.
17. For recent syntheses of pipeclic acid: (a) A. Sadiq and N. Sewald, *J. Amino Acids*, 2013, 8; (b) R. A. Fernandes and J. L. Nallasivam, *Org. Biomol. Chem.*, 2012, **10**, 7789; (c) T. K. Beng and R. E. Gawley, *J. Am. Chem. Soc*., 2010, **132**, 12216; (d) B. V. S. Reddy, D. N. Chaya, J. S. Yadav and R. Gree, *Synthesis*, 2012, 297. For reviews on syntheses of pipecolic acid and derivatives, see: (e) C. Agami, F. Couty and C. Puchot-Kadouri, *Synlett*, 1998, 449; (f) F. Couty, *Amino Acids*, 1999, **16**, 297; (g) F. P. J. T. Rutjes, L. B. Wolf and H. E. J. Schoemaker, *Chem. Soc., Perkin Trans. 1*, 2000, 4197; (h) K.-H. Park and M. J. Kurth, *Tetrahedron*, 2002, **58**, 8629; (i) C. Kadouri-Puchot, S. Comesse, *Amino Acids*, 2005, **29**, 101; (j) A. A. Cant and A. Sutheland, *Synthesis*, 2012, 1935; (k) S. Mohapatra, S. Bhakta, N. Baral and S. Nayak, *Res. Chem. Intermed*., 2014, 1-9. For some recent synthesis of 3-hydroxypipecolic acid: (l) O. K. Karjalainen and A. M. P. Koskinen, *Tetrahedron*, 2014, **70**, 2444; (m) S. V. Pansare and E. K. Paul, *Org. Biomol. Chem*., 2012, **10**, 2119; (n) S. Begliomini, L. Sernissi, D. Scarpi and E. G. Occhiato, *Eur. J. Org. Chem*., 2014, ASAP. For review on synthesis of 3-hydroxypipecolic acid: (o) A. Cochi, D. Gomez Pardo and J. Cossy, *Eur. J. Org. Chem*., 2013, 809.
18. For recent syntheses of lentiginosine, see: (*a*) S. Du-a-man, D. Soorukram, C. Kuhakarn, P. Tuchinda, V. Reutrakul, M. Pohmakotr, *Eur. J. Org. Chem.,* 2014, 1708; (*b*) S. V. Kauloorkar, V. Jha, G. Jogdand and P. Kumar, *Org. Bio. Chem.,* 2014, **12**, 4454; (*c*) G.-W. Kim, T. Jin, J.-S. Kim, S.-H. Park, K.-H. Lee, S.-S. Kim, I.-S. Myeong and W.-H. Ham, *Tetrahedron: Asymmetry,* 2014, **25**, 87; (*d*) M. Lingamurthy, A. Rajender and B. V. Rao, *Tetrahedron:*

View Article Online
DOI: 10.1039/C5RA06429E

Asymmetry, 2014, **25**, 860; (*e*) H. Yoon, K. S. Cho and T. Sim, *Tetrahedron: Asymmetry,* 2014, **25**, 497; (*f*) J. Zeng, Q. Zhang, H.-K. Zhang and A. Chen, *RSC Adv.,* 2013, **3**, 20298; (*g*) J. Shao and J.-S. Yang, *J. Org. Chem.,* 2012, **77**, 7891; (*h*) S.-W. Liu, H.-C. Hsu, C.-H. Chang, H.-H. G. Tsai and D.-R. Hou, *Eur. J. Org. Chem.,* 2010, 4771; (*i*) R. Lahiri, H. P. Kokatla and Y. D. Vankar, *Tetrahedron Lett.,* 2011, **52**, 781; (*j*) I. S. Kim, Q. R. Li, G. R. Dong, Y. C. Kim, Y. J. Hong, M. Lee, K.-W. Chi, J. S. Oh and Y. H. Jung, *Eur. J. Org. Chem.,* 2010, 1569; (*k*) M.-J. Chen and Y.-M. Tsai, *Tetrahedron Lett.,* 2007, **48**, 6271; (*l*) S. R. Angle, D. Bensa and D. S. Belanger, *J. Org. Chem.,* 2007, **72**, 5592; and references cited therein. For a review on lentiginosine, see: (*m*) F. Cardona, A. Goti and A.Brandi, *Eur. J. Org. Chem.,* 2007, 1551; (n) F. M. Cordero, D. Giomi and A. Brandi, *Curr. Top. Med. Chem.,* 2014, **14**, 1294.

19. For recent syntheses of swainsonine, see: (*a*) P. Singh, S. K. Manna and G. Panda, *Tetrahedron,* 2014, **70**, 1363; (b) X.-G. Wang, A.-E. Wang and P.-Q. Huang, *Chin. Chem. Lett.* 2014, **25**, 193; (*c*) Q. R. Li, G. R. Dong, S. J. Park, Y. R. Hong, I. S. Kim and Y. H. Jung, *Eur. J. Org. Chem.,* 2013, 4427; (*d*) V. Dhand, J. A. Draper, J. Moore and R. Britton, *Org. Lett.,* 2013, **15**, 1914; (*e*) G. Archibald, C. Lin, P. Boyd, D. Barker and V. J. Caprio, *J. Org. Chem.,* 2012, **77**, 7968; (*f*) M.-J. Chen and Y.-M. Tsai, *Tetrahedron,* 2011, **67**, 1564; (*g*) H. G. Choi, J. H. Kwon, J. C. Kim, W. K. Lee, H. Eum and H.-J. Ha, *Tetrahedron Lett.,* 2010, **51**, 3284; (*h*) D. J. Wardrop and E. G. Bowen, *Org. Lett.,* 2011, **13**, 2376; (*i*) Y.-S. Tian, J.-E. Joo, B.-S. Kong, V.-T. Pham, K.-Y. Lee and W.-H. Ham, *J. Org. Chem.,* 2009, **74**, 3962; (*j*) J. Louvel, F. Chemla, E. Demont, F. Ferreira, A. Perez-Luna, *Org. Lett.,* 2011, **13**, 6452; (*k*) H. K. Zhang, S. Q. Xu, J. Zhuang, J. Ye and P. Q. Huang, *Tetrahedron,* 2012, **68**, 6656; (*l*) R. W. Bates and M. R. Dewey, *Org. Lett.,* 2009, **11**, 3706; (*m*) S. J. Oxenford, S. P. Moore, G. Carbone, G. Barker, P. O'Brien, M. R. Shipton, J. Gilday and K. R. Campos, *Tetrahedron: Asymmetry,* 2010, **21**, 1563; (*n*) S. N. Murthy and Y. V. D. Nageswar, *Synthesis,* 2011, 755. For a review of swainsonine syntheses, see: (*o*) L. Nin, H. Ba and A. Haji, *Chin. J. Org. Chem.,* 2009, **29**, 1354; (*p*) S. G. Pyne, *Curr. Org. Synth.,* 2005, **2**, 39; (*q*) A. E. Nemr, *Tetrahedron,* 2000, **56**, 8579; (q) B. K. Lee, H. G. Choi, E. J. Roh, W. K. Lee and T. Sim, *Tetrahedron Lett*. 2013, **54**, 553.

20. (*a*) S. P. Chavan, K. R. Harale, N. B. Dumare and U. R. Kalkote, *Tetrahedron: Asymmetry,* 2011, **22**, 587; (*b*) S. P. Chavan, N. B. Dumare and K. R. Harale and U. R. Kalkote, *Tetrahedron Lett.,* 2011, **52**, 404; (*c*) S. P. Chavan, K. R. Harale and K. P. Pawar, *Tetrahedron Lett.,* 2013, **54**, 4851; (*d*) S. P. Chavan and C. Praveen, *Tetrahedron Lett.,* 2004, **45**, 421; (*e*) S.P. Chavan, N. B. Dumare and K. P. Pawar, *RSC Adv.*, 2014, **4**, 32594; (*f*) S. P. Chavan, L. B. Khairnar, P. C. Chavan and D. B. Kalbhor, *Tetrahedron: Asymmetry*, 2014, **25**, 1246; (g) S. P. Chavan, L. B. Khairnar, P. C. Chavan, N. B. Dumare and D. B. Kalbhor *Tetrahedron Lett.* 2014, **55**, 6423.

21. For reviews, see: (*a*) U. M. Lindström, P. Somfai, *Synthesis,* 1998, 109; (*b*) B. Zwanenburg and P. ten Holte, *Top. Curr. Chem.,* 2001, **216**, 93; (*c*) J. B. Sweeney, *Chem. Soc. Rev.,* 2002, **31**, 247; (*d*) X. E. Hu, *Tetrahedron,* 2004, **60**, 2701; (*e*) D. Tanner, *Angew. Chem., Int. Ed. Engl.,* 1994, **33**, 599; (*f*) H. M. I. Osborn and J. Sweeney, *Tetrahedron: Asymmetry,* 1997, **8**, 1693; (*g*) W. M. McCoull, F. A. Davis, *Synthesis,* 2000, 1347; (*h*) I. D. G. Watson, L. Yu and A. K. Yudin, *Acc. Chem. Res.,* 2006, **39**, 194; (*i*) A. Padwa, S. S. Murphree, *ARKIVOC,* 2006, **3**, 6; (*j*) D. S. Tsang, S. Yang, F. A. Alphonse and A. K. Yudin, *Chem. Eur. J.,* 2008, **14**, 886; (*k*) G. S. Singh, S. M. D'hooghe and N. De Kimpe, *Chem. Rev.,* 2007, **107**, 2080; (*l*) C. Schneider, *Angew. Chem. Int. Ed.,* 2009, **48**, 2082; (*m*) S. Stanković, S. D'hooghe, M. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe and H.-J. Ha, *Chem. Soc. Rev.,* 2012, **41**, 643; (*n*) P. Lu, *Tetrahedron,* 2010, **66**, 2549; (o) T. Ishikawa, *Heterocycles,* 2012, **85**, 2837. p) H. Ohno, *Chem. Rev.* 2014, *ASAP*.

22. (*a*) T. M. Shaikh and A. Sudalai, *Tetrahedron: Asymmetry,* 2009, **20**, 2287; (*b*) A. S. Kamal and R. Vangala, *Tetrahedron,* 2011, **67**, 1341; (*c*) M. K. Gurjar, L. Ghosh, M. Syamala and V. Jayasree, *Tetrahedron Lett.,* 1994, **35**, 8871.

23. (*a*) T. Oishi, T. Iwakuma, M. Hirama and S. Itô, *Synlett*, 1995, 404; (*b*) S. Chooprayoon, C. Kuhakarn, P. Tuchinda, V. Reutrakul and M. Pohmakotr, *Org. Biomol. Chem.,* 2011, **9**, 531.

24. D. B. Denny and S. T. Ross, *J. Org. Chem.,* 1961, **27**, 998.

25. (*a*) H.-D. Ambrosi, W. Duczek, E. Gründemann, M. Ramm and K. Jähnisch, *Liebigs Ann. Chem.,* 1994, 1013; (*b*) K. S. Ajish Kumar, V. D. Chaudhari and D. D. Dhavale, *Org. Biomol. Chem.,* 2008, **6**, 703.

26. K. W. C. Poon, K. M. Lovell, K. N. Dresner and A. Datta, *J. Org. Chem.,* 2008, **73**, 752.

27. a) T. Bieg and W. Szeja, *Synthesis* 1985, 76; For Pd catalyzed regioselective cleavage of vinyl aziridines please see: b) Ref. 25b; c) G. W. Spears, K. Nakanishi and Y Ohfune. *Synlett,* **1991.** 91; d) K. Fugami. K. Miura. **Y.** Morizawa, K. Oshima, K. Utimoto and H. Nozaki, *Tetrahedron*, 1989, **45***,* 3089; For hydrogenation of ester aziridines and C(2)-N, C(3)-N bond cleavage, Please see: e) Y. Lim and W. K. Lee *Tetrahedron Lett.*, 1995, **36**, 8431.

28. C. Greck, F. Ferreira and J. P. Genêt, *Tetrahedron Lett.,* 1996, **37**, 2031.

29. G. Rassu, L. Auzzas, V. Zambrano, P. Burreddu, L. Pinna, L. Battistini, F. Zanardi and G. Casiraghi, *J. Org. Chem.,* 2004, **69**, 1625.

30. (*a*) P. J. Garegg and B. Samulesson, *Synthesis,* 1979, 469; (*b*) H. B. Mereyala, P. M. Goud, R. R. Gadikota and K. R. Reddy, *J. Carbohydr. Chem.,* 2000, **19**, 1211.

31. (*a*) R. H. Grubbs, *Handbook of Metathesis. In Applications in Organic Synthesis*; WILEY-VCH, 2003; **Vol. 2**; (*b*) G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.,* 1992, **114**, 7324.

32. S. C. Deshmukh, A. Roy and P. Talukdar, *Org. Biomol. Chem*., 2012, **10**, 7536.

33. H.-D. Ambrosi, W. Duczek, E. Gründemann. M. Ramm and K. Jähnisch, *Liebigs Ann. Chem.,* 1994, 1013.

34. D. B. Denny and S. T. Ross, *J. Org. Chem.*, 1961, **27**, 998.

35. K. Jähnisch, *Liebigs Ann./Recueil*, 1997, 757.

36. S.-B. Huang, J. S. Nelson and D. D. Weller, *Synth. Commun.,* 1989, **19**, 3485.

37. F. Sánchez-Sancho and B. Herradón, *Tetrahedron: Asymmetry*, 1998, **9**, 1951.

View Article Online
DOI: 10.1039/C5RA06429E
Journal Name

38. (a) D-R. Hou, S-Y. Hung and C-C. Hu, *Tetrahedton: Asymmetry*, 2005, **16**, 3858, (b) L.-A. Watanabe, S. Haranaka, B. Jose, M. Yoshida, T. Kato, M. Moriguchi, K. Soda and N. Nishino, *Tetrahedron: Asymmetry*, 2005, **16**, 903.
39. L. Battistini, F. Zanardi, G. Rassu, P. Spanu, G. Pelosi, G. G. Fava, M. B. Ferrari and G. Casiraghi, *Tetrahedron: Asymmetry* **1997**, *8*, 2975.
40. W. H. Chiou, G. H.; Lin and C. W. Liang, *J. Org. Chem*., 2010, **75**, 174.
41. (a) T. Oishi, T. Iwakuma, M. Hirama and S. Itô, *Synlett*, 1995**,** 404; (b) S. Chooprayoon, C. Kuhakarn, P. Tuchinda, V. Reutrakul and M. Pohmakotr, *Org. Biomol. Chem.*, 2011**, 9**, 531.
42. Deshmukh, S. C.; Roy, A.; Talukdar, P. *Org. Biomol. Chem.* **2012**, *10*, 7536.