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An approach towards the total synthesis of (+)-epiquinamide and (+)-*α*-conhydrine from Garner aldehyde

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Abstract— A short and stereoselective route for the synthesis of 1-hydroxyquinolizidine, an advanced synthetic intermediate for the total synthesis of (+)-epiquinamide is presented. The key synthetic steps involve diastereoselective nucleophilic addition on L-serine derived Garner aldehyde and acid mediated (PTSA) ring closing metathesis. The methodology is also elaborated successfully for the total synthesis of (+)-α-conhydrine an important piperidine alkaloid.

1. Introduction

Exploiting natural products to ascertain a lead has always been an important technique in drug discovery. [1,2] As the major class of biologically active molecules contain nitrogen, substituted quinolizidine, indolizidine and piperidine containing natural products have been the major synthetic target.[3,4] Hence the efforts to find a short and high yielding synthetic route for this class of natural products are always of current interest. (+)-Epiquinamide **1**, isolated from the skin of the poisonous Ecuadorian frog *Epipedobates tricolor*,[5] represents a new class of nicotinic agonists and highly selective for α2 nicotinic acetyl-choline esterase. Some of the quinolizidine alkaloids have been identified as lead compounds for the development of anticancer, antiinflammatory, and cardiovascular drugs. quinolizidine 207I **2**, homopumiliotoxin 223G **3**, and (-)-indolizidine 209B **4** also continue to be of interest as synthetic targets due to their intriguing biological activities. In the similar way the piperidine containing alkaloids (+)-α-conhydrine **5** and (-)-β-conhydrine **6** (Figure 1), isolated from the seeds and leaves of plant *Conium maculatum*[6a] were employed externally to treat herpes, erysipelas and breast tumours.[6b] Unripe Conium seeds were also used as an antispasmodic, a sedative or an analgesic.[6]

There are five asymmetric syntheses[7-11] reported for (+)-epiquinamide **1** alongwith racemic[12] and formal[13] synthesis by Kanakubo and Voituriez *et. al.* respectively. Most of the groups have used ring closing metathesis[7-9,11] as the key step for cyclization but all the methods[7,8,11] suffer from exhaustive amide carbonyl reduction at the final step after RCM, except Gervick *et. al.*[9] Similarly, enantioselective synthesis of (+)-*α*-conhydrine **5** and its stereoisomers have also been targeted by several groups.[14-21] The RCM approach by Sutherland *et. al.* to synthesise **5** also encounters the same problem of reducing amide at the final stage after RCM.

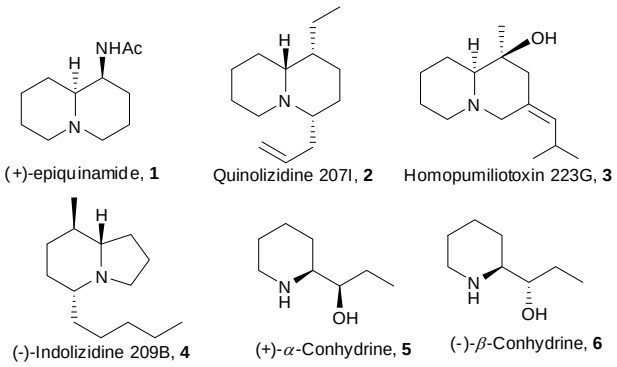


Fig. 1: Some important quinolizidine, indolizidine and piperidine alkaloids.

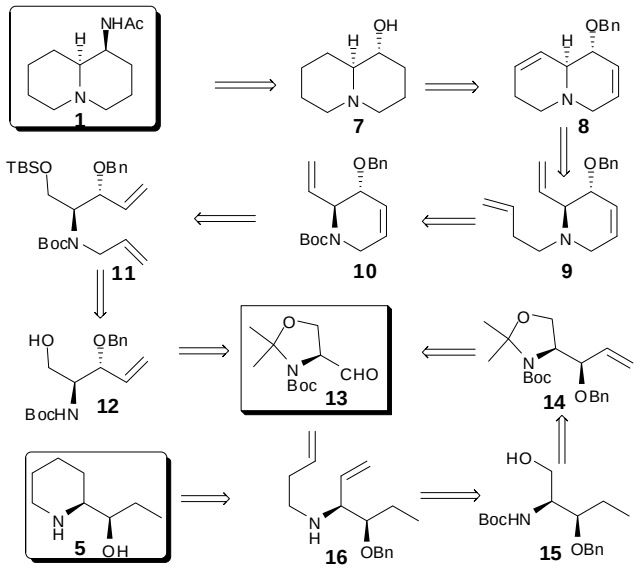
To the best of our knowledge no synthetic method is known for the synthesis of these natural products using amino acids as the starting material.

Recently, total synthesis of azepine containing natural product (-)-balanol and its analogues have been reported from our group.[22] To explore the scope of our reported methodology, we undertook the total synthesis of piperidine and quinolizidine containing natural products. Herein we wish to report a simple but reliable route for the synthesis of 1-hydroxyquinolizidine,[23-25] an advanced synthetic intermediate for the total synthesis of (+)-epiquinamide **1** along with the total synthesis of (+)-α-conhydrine from Garner aldehyde.[26] Diastereoselective Grignard reaction and acid mediated ring closing metathesis[27,28] have been successfully employed to accomplish the synthesis.

2. Results and discussions

2.1. Retrosynthetic analysis

The retrosynthetic analysis for the natural products has been illustrated in Scheme 1.

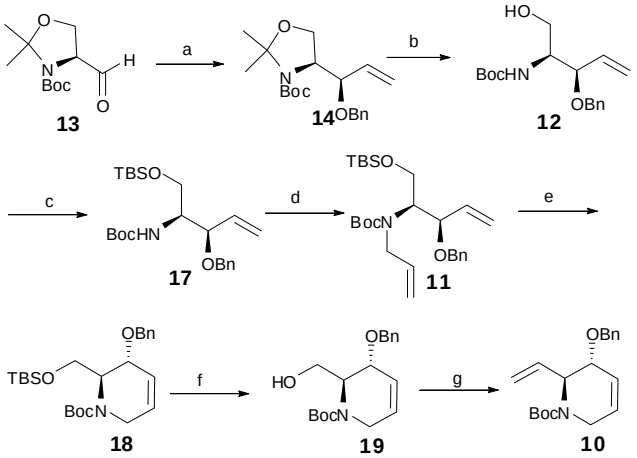


Scheme 1: Retrosynthetic analysis.

The quinolizidine ring of **1** can be accessed through ring closing metathesis of **9** followed by acid mediated debenzylation and double bond reduction through hydrogenolysis. Similarly, RCM precursor **9** can be synthesized from **11** through ring closing metathesis followed by desilylation, oxidation, Wittig reaction, Boc deprotection and homoallylation on amine. Compound **11** can easily be synthesized in pure diastereomeric form from Garner aldehyde. Similarly tetrahydropyridine precursor of (+)-*α*-conhydrine can be easily accessed through acid mediated ring closing metathesis of diene **16** which can easily be obtained from the Garner aldehyde derived alcohol **15.**

2.2. Synthesis of 1-hydroxyquinolizidine 7

First to achieve the synthesis of 1-hydroxyquinolizidine **7** compound **14** was synthesized from Garner aldehyde **13** using diastereoselective nucleophilic addition of vinylmagnesium bromide at -78°C followed by separation of major *anti* product through column chromatography and protecting the resulting alcohol as its benzyl ether.[22] Acetonide ring opening of **14** using PTSA/methanol resulted alcohol **12** which was further protected as silyl ether using TBDMSCl/imidazole in 97% yield. To obtain compound **11**, allylation of carbamate **17** was done using allylbromide and NaH in DMF with 87% yield to give diene **11,** which was converted to dihydropyridine **18** by ring closing metathesis using Grubbs 1st generation catalyst in 74% yield. Desilylation of compound **18** by TBAF in THF yielded alcohol **19**. Structure of compound **19** was established through 2D NMR correlations (Figure 2). Alcohol **19** was oxidized to the corresponding aldehyde followed by Wittig olefination using methyltriphosphonium bromide and KHMDS in THF to furnish **10** in 67% yields after two steps (Scheme 2). To avoid the epimerization of amino aldehyde, it was directly used for Wittig olefination after PCC oxidation.



Scheme 2: *Reagents and Conditions :* a) i) Vinyl magnesium bromide, THF, -78 °C; ii) BnBr, NaH, THF, 67% after two steps; b) PTSA, Methanol, 87%; c) TBSCl, imidazole, DCM, 30min, 97 %; d) NaH, Allylbromide, DMF, 0°C-rt, 87%; e) Grubb's cat **20** (8 mol %) DCM, 24 hrs, 74 %; f) TBAF, THF, 0°C, 10 min, 95%; g) i) PCC, DCM; ii) $BrCH_3PPh_3$, KHMDS, THF, 67%(over two steps).

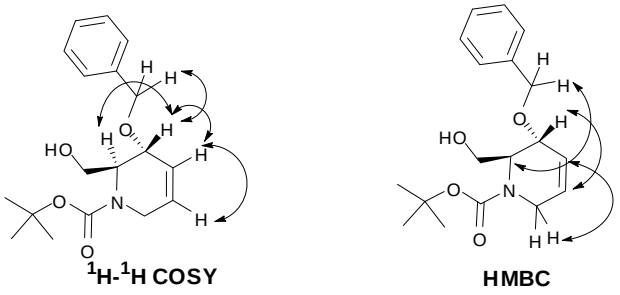
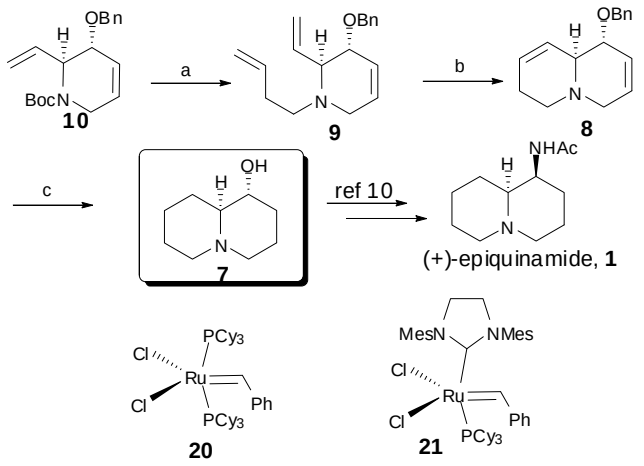


Figure 2: ^{1}H-^{1}H COSY and HMBC correlations of compound **19**.

Boc deprotection using TFA followed by homoallylation in DMF using homoallyl bromide and K_2CO_3 gave diene **9**. Several attempts of metathesis reaction on diene **9** using Grubbs 1st generation catalyst failed probably due to the presence of free amine. Metathesis reaction using Grubbs 2nd generation catalyst (15 mol %) gave moderate yield. Protonation of free amine by *p*-toluene sulphonic acid in stoichiometric amount gave encouraging result with reduction of reaction time and lowering (10 mol %) of catalyst loading. Hydrogenation of **8** using H_2/10% Pd-C gave only double bond reduced product due to the presence of free tertiary amine. Addition of HCl and hydrogenation using 20% $Pd(OH)_2$ in methanol furnished the advanced synthetic intermediate 1-hydroxyquinolizidine **7** (with overall yield 10%) which can be converted to (+)-

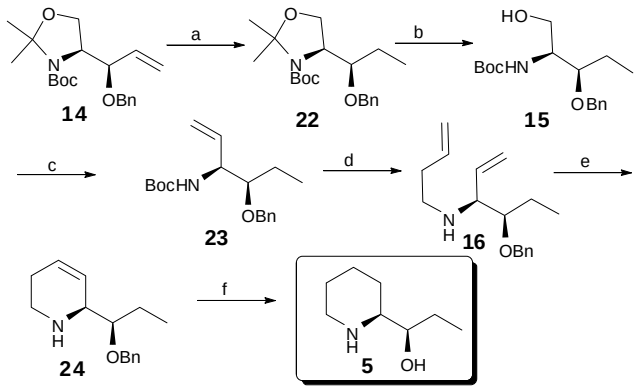
epiquinamide **1** using the reported methodology by Tong *et al*[10] (Scheme 3).



Scheme 3: *Reagents and Conditions:* a) i) TFA, DCM(1:1); ii) homoallylbromide, K_2CO_3, DMF, 76% after two steps; b) PTSA, DCM, **21** (10 mol%), 69%; c) HCl, H_2, 20% $Pd(OH)_2$, Methanol, 82%.

2.3. Total synthesis of (+)-α-conhydrine

To accomplish the total synthesis of (+)-α-conhydrine, we used **14** as the starting material which is easily accessible from Garner aldehyde **13**. The double bond was reduced selectively through hydrogenation using H_2/10% Pd-C/triethyl amine. Opening of acetonide in alcohol **15** using PTSA followed by oxidation and methyl Wittig furnished compound **23**. Several attempts of N-alkylation using homoallylbromide in DMF and NaH as base failed. Thus the Boc group was deprotected and mono N-alkylation was carried out using homoallylbromide and K_2CO_3 as base to obtain 16 (Scheme4).



Scheme 4: *Reagents and Conditions:* a) i) H_2, 10% Pd-C, TEA, MeOH, 96%; b) PTSA, MeOH, 81%; c) i) PCC, DCM; ii) ICH_3PPh_3, *n*-BuLi, THF/-78°C,49% over two steps; d) i)TFA/DCM; ii) Homoallyl bromide, K_2CO_3, 56%(over two steps); e) PTSA, DCM, **21** (8 mol %) 24 hrs, 70%; f) H_2, 20% $Pd(OH)_2$, Methanol, 74%.

Acid mediated ring closing metathesis of **16** using Grubb's second generation catalyst delivered the cyclized product **24** in 70% yield. Reduction of double bond along with debenzylation of **24.HCl** by hydrogenation using 20% $Pd(OH)_2$ provided (+)-α-conhydrine **5** in 11 % overall yield from **14** (Scheme 4). The spectral and analytical data of the synthesized (+)-α-conhydrine **5** were in accordance with the reported one.[19b]

3. Conclusions

In conclusion, we have reported a concise and highly diastereoselective approach to synthesize 1-hydroxyquinolizidine, an advance intermediate which is poised for the total synthesis of (+)-epiquinamide. Total synthesis of (+)-α-conhydrine has also been accomplished in highly stereoselective manner from Garner aldehyde. The intermediate **7** can further be explored to synthesize all other stereoisomers of (+)-epiquinamide and various quinolizidine analogues.

4. Experimental

4.1. General Methods

Organic solvents were dried by standard methods. All the products were characterized by ^1H, ^{13}C, two-dimensional homonuclear COSY (correlation spectroscopy), heteronuclear multiple bond correlation spectroscopy (HMBC), IR, ESI-MS, HRMS and elemental analysis (C, H, N). Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254),visualization was accomplished with iodine and under UV lamp. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). NMR spectra were recorded on Bruker Avance DPX 200FT, Bruker Robotics, Bruker DRX 300 and 400 Spectrometers at 200, 300, 400 MHz (1H) and 50, 75, 100 MHz (^{13}C). Experiments were recorded in $CDCl_3$ or $CDCl_3$+CCl_4 mixture and Acetone-d_6 at 25^0C. Chemical shifts are given on the δ scale and are referenced to the TMS at 0.00 ppm for proton and 0.00 ppm for carbon. For ^{13}C NMR reference $CDCl_3$ appeared at 77.16 ppm. IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell at 28^0C in chloroform and methanol as the solvents; concentrations mentioned are in g/100 mL.

4.1.1.*tert*-butyl-(*2S,3R*)-3-(benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pent-4-en-2-ylcarbamate 17: To a ice cooled solution of alcohol **12** (3.5 gm, 11.4 mmol) in dry DCM (25 mL), imidazole (1.16 gm, 17.1 mmol) was added followed by *tert*-butyldimethylchlorosilane (2.0 gm, 13.7 mmol). The reaction mixture was stirred at the same temperature for 30 minutes. After completion of the reaction, it was diluted with dichloromethane and washed with water followed by brine. The organic layer was dried over sodium sulphate. The solvent was evaporated and the residue was chromatographed over silica gel to furnish **17** (4.65 gm, 97%) as colorless oil, eluent for column

chromatography: EtOAc/Hexane (1/49, v/v), $[\alpha]_D^{30}$= -6.34 (*c* 1.42 Methanol) ; R_f 0.6 (5% ethylacetate/ hexane) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.33 (m, 5H, ArH), 5.93-5.81 (m, 1H), 5.35-5.30 (m, 2H), 4.81-4.77 (m, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* =11.7 Hz, 1H), 3.97-3.92 (m, 1H), 3.70-3.65 (m, 3H), 1.46(s, 9H), 0.92 (s, 9H), 0.08(s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 137.1, 134.8, 134.6, 127.0, 126.4, 126.3, 126.2, 117.8, 117.0, 78.7, 77.8, 69.3, 60.3, 53.4, 27.1, 24.6, 16.9, -6.75; IR (neat, cm^{-1}) 3780, 3695, 3021, 2926, 2359,1715, 1595, 1216, 1055, 930, 761, 671; mass (ESI-MS) m/z; 421.8 (100, $[M]^+$), 365.9 (45, $[M\text{-}^tBu]^+$), 322.1 (43, $[M\text{-}^tBoc]^+$); Elemental Analysis calcd for $C_{23}H_{39}NO_4Si$: C, 65.52; H, 9.32; N, 3.32; found: C, 65.45; H, 9.23; N, 3.02.

4.1.2.*tert*-butylallyl((*2S,3R*)-3-(benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pent-4-en-2-yl)carbamate 11: To an ice cooled solution of compound **17** (4.0 gm, 9.5 mmol) in dry DMF (30 mL), NaH (350 mg, 14.5 mmol) was added followed by freshly distilled allyl bromide (1.65 mL, 19.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction excess NaH was quenched with drop by drop addition of methanol and excess DMF was distilled under reduced pressure. The residue was diluted with ethyl acetate and the organic layer was washed with water followed by brine. The organic layer was dried over sodium sulphate and the solvent was evaporated. The residue was further chromatographed over silica gel coloumn to furnish the allylated product **11** (3.82 gm, 87 %) as colourless oil. $[\alpha]_D^{29}$= -13.2 (*c* 0.26 CH_3OH); R_f 0.55 (4%, EtOAc/Hexane); ^{1}HNMR (300 MHz, $CDCl_3$+CCl_4) δ 7.32-7.27 (m, 5H, ArH), 5.87-5.73 (m, 2H), 5.35-5.27 (m, 2H) 5.16-5.02 (m, 2H), 4.57 (t, *J* = 9.0 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.16-3.66 (m, 6H), 1.45 (s, 9H), 0.9 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 135.2, 134.9, 127.0, 126.9, 126.6, 126.3, 126.2, 126.1, 117.5, 114.1, 78.7, 77.9, 69.3, 69.1, 59.9, 27.2, 24.6, 16.9, -6.76; IR (Neat, cm^{-1});3781, 3697, 3633, 3019, 2932, 2361, 1682, 1216, 1104, 763, 670; mass (ESI-MS) m/z; 461.8 (100, $[M]^+$), 404.9 (47, $[M\text{-}^tBu]^+$), 361.8 (43, $[M\text{-}^tBoc]^+$), Elemental Analysis calcd for $C_{26}H_{43}NO_4Si$: C, 67.64; H, 9.39; N, 3.03; found: C, 67.43; H, 9.19; N, 3.01.

4.1.3.(*5R,6S*)-*tert*-butyl-5-(benzyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-5,6-dihydropyridine-1(*2H*)-carboxylate 18: To a solution of diene **11** (3.5 gm, 7.59 mmol) in dry DCM (45 mL) was added 5 mol% Grubb's catalyst Ist Generation **20** (312 mg, 0.38 mmol) at 45 °C. The reaction mixture was refluxed for 12 h and 3 mol % catalyst (187mg, 0.23mmol) was added further to complete the reaction. After clear formation of the cyclised product, solvent was evaporated and the residue was chromatographed to furnish **18** (2.45 gm, 74%) as yellowish syrup. $[\alpha]_D^{30}$= +23.7 (*c* 41.0 CH_3OH); R_f 0.4 (10% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H, ArH), 6.00-5.85 (m, 2H), 4.76-4.37 (m, 4H), 4.04 (s, 1H), 3.59-3.46 (m, 3H), 1.50 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4) δ 155.1, 138.5, 128.9, 128.3, 128.1, 127.7, 127.5, 122.8, 122.4, 79.7, 69.9, 61.5, 54.5, 40.3, 28.5, 25.9, 18.2,-5.4; IR (neat, cm^{-1});3781, 3694, 3021, 2359, 1713, 1597, 1216, 762, 671; mass (ESI-MS) m/z; 433.8 (100, $[M]^+$), 376.9 (54, $[M\text{-}^tBu]^+$), 333.1 (43, $[M\text{-}^tBoc]^+$); Elemental Analysis calc for $C_{24}H_{39}NO_4Si$: C, 66.47; H, 9.06; N, 3.23; found; C, 66.36; H, 9.01; N, 3.12.

4.1.4.(*5R,6S*)-*tert*-butyl-5-(benzyloxy)-6-(hydroxymethyl)-5,6-dihydropyridine-1(*2H*)-carboxylate 19: To a cooled solution of compound **18** (2.0 gm, 4.61 mmol) in dry THF (15 mL) solution of TBAF (1.0 M in THF, 5.0 mL) was added and the reaction mixture was stirred for 15 mins. After completion of the reaction, mixture was concentrated and the residue was diluted with ethyl acetate. The organic layer was washed with water followed by brine. The organic layer was dried over sodium sulphate and solvent was evaporated. The residue was chromatographed over silica gel to furnish alcohol **19** (1.4 gm, 95 %) as colorless oil. $[\alpha]_D^{29}$= +13.8 (*c* 0.11 CH_3OH); R_f 0.2 (30% EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.32 (m, 5H, ArH), 5.93-5.88 (m, 2H), 4.67(d, 2H, *J* = 11.7Hz), 4.52(d, 1H, *J* = 11.7Hz), 4.35(brs, 1H), 3.90(s, 1H), 3.56-3.53 (m, 3H), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 138.2, 128.3, 128.3, 127.8, 127.8, 127.6, 127.6, 122.6, 80.2, 70.2, 69.5, 60.3, 53.3. 29.6, 28.4; IR (neat, cm^{-1}) 3782, 3694, 3020, 2361, 1691, 1416, 1216, 760, 670; mass (ESI-MS) m/z; 343.4 (100, $[M+Na]^+$), Elemental Analysis calc for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39; found: C, 67.25; H, 7.35; N, 4.31.

4.1.5.(*5R,6S*)-*tert*-butyl-5-(benzyloxy)-6-vinyl-5,6-dihydropyridine-1(*2H*)-carboxylate 10: To a cooled solution of alcohol **19** (1.2 gm, 3.76 mmol) in dry DCM(15 mL) was added PCC (970 mg, 4.51 mmol) at 0 °C. The reaction mixture was warmed upto room temperature and stirred at the same temperature for 3 hrs. After completion of the reaction, solid was filtered through celite and filtrate was concentrated. The crude aldehyde was used in the next step without further purification. To a cooled solution of methyltriphenylphosphonium bromide (2.7 gm, 7.52 mmol) in dry THF at -78 °C, KHMDS (0.5 M in THF, 10 mL) was added and the mixture was stirred for 10 mins to generate the ylide. Solution of aldehyde in THF was added dropwise and the reaction mixture was warmed upto room temperature. The stirring continued for 5 hrs at the same temp. After complete consumption of aldehyde, reaction mixture was quenched by NH_4Cl and extracted by ethyl acetate. Organic layer was concentrated in vacuo and chromatographed over silica gel to obtain the desired olefine **10** (800 mg, 67.7 % over two steps) as colorless oil. $[\alpha]_D^{29}$= -55.4 (*c* 0.27 CH_3OH); R_f 0.56 (10%, EtOAc/Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.20 (m, 5H, Ar<u>H</u>), 5.84 (s, 2H), 5.62-5.51 (m, 1H), 5.11-5.05 (m, 3H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.46 (d, *J* = 10.8 Hz, 1H), 4.26 (d, *J* = 18.7 Hz, 1H), 3.81 (s, 1H), 3.54-3.41 (m, 1H), 1.41 (s, 9H. $C(C\underline{H}_3)_3$. IR (neat, cm^{-1}) 3782, 3698, 3018, 2361, 1685, 1411, 1217, 762, 669 ; mass (ESI-MS) m/z; 315.8 (64, $[M]^+$), 259.8 (100, $[M\text{-}^tBu]^+$), 216 (82, $[M\text{-}^tBoc]^+$); Elemental Analysis calc for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44; found: C, 72.32; H, 7.81; N, 4.34.

4.1.6.(*2S,3R*)-3-(benzyloxy)-1-(but-3-enyl)-2-vinyl-1,2,3,6-tetrahydropyridine 9: To a solution of compound **10** (500 mg, 1.59 mmol) in dry DCM (5 mL), 50% TFA in DCM was added. After completion of the reaction solvent was evaporated and the residue was co-evaporated twice with dry DCM to remove the excess TFA. The crude was redissolved in dry DMF and homoallylbromide (0.3 mL, 3.18 mmol) was added followed by K_2CO_3 (548 mg, 3.98 mmol). The reaction mixture was stirred at 45 °C for two hrs. The DMF was distilled under reduced pressure and the residue was diluted with ethyl acetate. The solution was washed with water followed by brine. The organic layer was dried over sodium sulphate, filtered and the solvent was evaporated under reduced pressure.The residue was chromatographed through a small silica column to furnish the homoallylated product **9**(324 mg, 76%) which was used for metathesis reaction. R_f 0.42(1:1, EtOAc/ Hexane); mass (ESI-MS) m/z; 270.2 (100, $[M+H]^+$).

4.1.7.(*1R,9aS*)-1-(benzyloxy)-4,6,7,9a-tetrahydro-*1H*-quinolizine 8: To a solution of compound **9** (450 mg, 1.67 mmol) in dry DCM, PTSA (316 mg, 1.80 mmol) was added and the mixture was heated up to 45 °C. To this refluxing solution, Grubb's second generation catalyst **21**(99 mg, 7 mol %) was added and the reaction mixture was stirred at the same temperature for 10 h. Afterwards, some additional amounts of the catalyst (42.5 mg, 3 mol %) was again added and the refluxing was continued for further 12 h. After completion of the reaction, solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with $NaHCO_3$ solution followed by brine. The extract was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was chromatographed through silica gel column to furnish tetrahydroquinolizine **8**(278.2 mg, 69%) as brown syrup. $[\alpha]_D^{28}$= +10.4 (*c* 0.48, $CHCl_3$); R_f 0.5 (2:3 EtOAc/Hexane) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5H, ArH), 5.89-5.71 (m, 2H), 5.22 (s, 2H), 4.63-4.45 (m, 2H), 3.82-3.73(m, 1H), 3.28-3.07 (m, 1H), 2.85-2.69(m, 2H), 2.42-2.13(m, 2H), 1.99-1.87(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.3, 127.8, 127.6, 127.2, 126.8, 126.3, 125.4, 71.1, 61.2, 54.5, 53.3, 50.6, 25.4; IR (neat, cm^{-1});3773, 3685, 3020, 2359, 1216, 760, 671; mass (ESI-MS) m/z; 242.2 (100, $[M+H]^+$), Elemental Analysis calc for : $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; found: C, 79.53; H, 7.76; N, 5.79.

4.1.8.(*1R,9aS*)-octahydro-1H-quinolizin-1-ol 7: To a solution of perhydroquinazoline **8** (150 mg, 0.54 mmol) in methanol 20% $Pd(OH)_2/C$ (30 mg, 10% w/w) and one drop of conc.HCl was added and stirred under the hydrogen atmosphere in balloon. After completion of the reaction, the catalyst was removed by filtration through celite and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution 2-3 times.The organic layer was concentrated and chromatographed over silica gel coloumn to furnish the pure **7** (68.7 mg, 82%) as oil. $[\alpha]_D^{28}$= -21.7 (*c* 0.85 $CHCl_3$); R_f 0.6 (pure CH_3OH) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55-3.48(m, 1H), 2.37-2.17(m, 5H), 1.38-1.25(m, 10H); mass (ESI-MS) m/z; 156.6 (100, $[M+H]^+$); Elemental Analysis calc for : $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; found: C, 69.31; H, 10.84; N,8.91.

4.1.9.*tert*-butyl-4-(*S*)-[(*R*)-1-(benzyloxy)propyl]-2,2-dimethyloxazolidine-3-carboxylate 22: To a solution of compound **14** (4.0g, 11.5 mmol) in methanol, catalytic amount of tryethylamine (0.22g, 2.3 mmol) and 10% Pd/C(0.2 g) was added and the solution was stirred under the pressure of H_2 atmosphere in balloon at room temperature for overnight. After completion of the reaction it was filtered through celite and the solvent was evaporated and the residue was chromatographed over silica gel coloumn to furnish **22** (3.85 g, 96%) as colourless oil. $[\alpha]_D^{29}$= -56.5 (*c* 0.26, CH_3OH) ; R_f 0.7 (10% ethylacetate/ hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.18(m, 5H, ArH), 4.50 (s, 2H), 4.06-3.99 (m, 1H), 3.86-3.80(m, 2H), 3.59(br,1H), 1.43(s, 17H), 0.87(t, *J* = 11Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4) δ 153.4, 138.9, 128.4, 127.9, 127.6, 127.4, 127.1, 94.6, 80.0, 73.3, 72.7, 64.1, 63.5, 28.7, 26.5, 25.1, 10.6; IR (neat, cm^{-1}) 3782, 3687, 3020, 2360, 1681, 1423, 1216, 1044, 760, 671; mass (ESI-MS) m/z; 349.9 (52, $[M]^+$), 293.9 (100, $[M-^tBu]^+$), 250.1 (42, $[M-^tBoc]^+$); Elemental Analysis calc for: $C_{20}H_{31}NO_4$; C, 68.74; H, 8.94; N, 4.01; found; C, 68.45; H, 8.38; N, 3.97.

4.1.10.*tert*-butyl (*2S,3R*)-3-(benzyloxy)1-hydroxypentan-2-ylcarbamate 15: To a solution of the compound **22** (3.0 g, 8.58 mmol) in methanol, catalytic amount of PTSA was added at 0^0C and stirred at the same temperature for 1 h when the reaction was completed. The reaction mixture was neutralized by saturated $NaHCO_3$ solution and was extracted with EtOAc.The organic layer was washed with brine and dried over anhydrous Na_2SO_4.The solvent was evaporated and the residue was chromatographed over silica gel column to furnish **15** (2.15 g, 81%) as colourless oil. $[\alpha]_D^{29}$= +35.3 (c 0.37, CH_3OH) ; R_f 0.4 (20% ethylacetate/ hexane) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.18 (m, 5H, ArH), 5.20-5.16 (br,1H, -NH), 4.58-4.37 (m, 2H), 3.86-3.81(m, 1H), 3.56-3.51 (m, *3H*), 2.90 (br, 1H, -OH), 1.68-1.36 (m, 11H), 0.91(t, *J* = 11.1Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4) δ 156.2, 138.0, 133.6, 130.1, 129.9, 128.7, 128.4, 128.0, 127.9, 79.9, 75.4, 72.8, 61.8, 54.2, 28.5, 24.0, 10.0; IR (neat, cm^{-1}); 3687, 3020, 2975, 2361, 1704, 1501, 1216, 761, 670; mass (ESI-MS) m/z; 309.9 (100, $[M]^+$), 253.9 (83, $[M-^tBu]^+$), 210.1 (94, $[M-^tBoc]^+$); Elemental Analysis calc. for $C_{17}H_{27}NO_4$ C, 65.99; H, 8.80; N, 4.53; found; C, 65.52; H, 8.51; N, 4.23.

4.1.11.*tert*-butyl (*3S,4R*)-4-(benzyloxy)hex-1-en-3-ylcarbamate 23: To a cooled solution of alcohol **15** (2.0 gm, 6.4 mmol) in dry DCM (25 mL) was added PCC (1.65 gm, 7.68 mmol). The reaction mixture was warmed upto room temperature and stirred for 2 h at the same temperature. After completion of the reaction solid was filtered through celite bed and the crude aldehyde was used in the next step without further purification. To the cooled solution of methyl tryphenylphosphonium iodide (8.67 g, 21.4 mmol) in dry THF at -78^{0}C under N_2 atmosphere, nBuLi (8.87 mL) of 1.6 M in THF was added drop wise. After 15 minutes the solution of the above crude aldehyde

(2.2 g, 7.1 mmol) in dry THF was added and the reaction was allowed to come at room temperature and stirring was continued for overnight. After completion of the reaction EtOAc was added and the organic layer was washed with water followed by brine. The organic layer was concentrated and the residue was chromatographed over silica gel coloumn to furnish colourless oil **23** (0.96 g, 49% over two steps). $[\alpha]_D^{29}$= -13.6 (c 0.139, CH_3OH); R_f 0.6 (15% ethylacetate/ hexane) ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.18 (m, 5H, ArH), 5.85-5.70 (m, 1H), 5.19-5.07 (m, 2H), 4.80-4.77(br, 1H), 4.57-4.43 (m, *2H*), 4.22 (s, 1H), 3.35-3.32 (m, 1H), 1.61-1.50 (m, 2H), 1.36 (s, 9H), 0.88(t, *J* = 7.4Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 137.9, 134.8, 128.7, 128.6, 128.1, 128.1, 128.0, 115.3, 82.8, 79.6, 72.3, 55.1, 28.7, 23.6, 10.5 ; IR (neat, cm^{-1}); 3780, 3690, 3021,2928, 2357, 1708, 1425, 1216, 928, 764, 672; mass (ESI-MS) m/z; 305.9 (63, $[M]^+$), 250.0 (100, $[M-{}^tBu]^+$), 206.1 (35, $[M-{}^tBoc]^+$); EI-HRMS: calcd for $C_{18}H_{28}NO_3$: 306.2069, measured 306.2060.

4.1.12.(*3S,4R*)-4-(benzyloxy)-N-(but-3-enyl)hex-1-en-3-amine 16: To a solution of compound **23** (0.8 g, 2.6 mmol) in DCM(8.0 mL), 50% TFA in DCM (1.0 mL) was added at 0^0C and stirred for 1 h. After completion of the reaction solvent was evaporated and the residue was co evaporated twice with dry DCM to remove excess TFA. The crude (0.7 g, 3.39 mmol) was redissolved in dry DMF(5.0 mL) and homoallylbromide(0.54 g, 4.06 mmol) was added followed by K_2CO_3 (1.87 g, 13.5 mmol). The reaction mixture was stirred at 45 °C for 2 h. The DMF was distilled under reduced pressure and the residue was diluted with ethyl acetate. The solution was washed with water followed by brine. The organic layer was dried over sodium sulphate, filtered, concentrated under reduced pressure and the crude was chromatographed over silica gel coloumn to furnish pure colourless oil **16** (0.38 g, 56% over two steps). $[\alpha]_D^{30}$= =+16.7 (*c* 0.127 CH_3OH); R_f 0.7 (40%, EtOAc/ Hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.15 (m, 5H, ArH), 5.68-5.61 (m, 2H), 5.12-4.94(m, 4H), 4.50 (s, 2H), 3.31-3.29 (m, 1H), 3.12-3.08 (m, 1H), 2.63-2.59 (m, 1H), 2.39-2.37 (m, 1H), 2.14 (t, *J* = 6.8Hz, 2H), 1.60-1.55(m, 2H), 0.84 (t, *J* = 7.4Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 137.6, 136.5, 128.3, 127.9, 127.7, 117.3, 116.2, 84.1, 72.2, 63.7, 46.5, 34.4, 23.3, 10.5; IR (neat, cm^{-1}); 3782, 3697, 3020, 2360, 1594, 1429, 1216, 761, 670; mass (ESI-MS) m/z; 260.1 (100, $[M]^+$; Elemental Analysis calc for $C_{17}H_{25}NO$; C, 78.72; H, 9.71; N, 5.40; found C, 78.56; H, 9.58; N, 5.23.

4.1.13.(*S*)-6-((*R*)-1-(benzyloxy)propyl)-1,2,3,6-tetrahydropyridine 24: To a solution of compound **16** (0.10 g, 0.38 mmol) in dry DCM (5.0 mL), equimoler amount of PTSA (0.073 g, 0.38 mmol) was added under N_2 atmosphere and the reaction mixture was warmed up to 45 °C. To this refluxing solution, Grubb's second generation catalyst 21 (0.016 g, 5 mol%) was added and the reaction mixture was stirred at the same temperature for 3 h. Afterwards, some additional amounts of the catalyst (0.01 g, 3 mol%) was added and refluxing was continued for next 1 h. After completion of the reaction, solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate. The organic layer was washed with $NaHCO_3$ solution followed by brine. The extract was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed through silica gel column to furnish tetrahydropyridine **24** as brown syrup (0.06 g, 70%). $[\alpha]_D^{30}$= -0.8 (*c* 0.12, CH_3OH); R_f 0.7 (5% $CH_3OH/CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.10 (m, 5H, ArH), 5.79-5.75 (m, 1H), 5.62-5.58 (m, 1H), 4.50 (s, 2H), 3.51 (s, 1H), 3.27-3.25 (m, 1H), 3.09-3.05 (m, 1H), 2.82-2.79 (m, 1H), 2.31 (s, 1H), 1.92 (s, 1H), 1.65-1.51(m, 2H), 0.88(t, *J* = 7.4Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 138.4, 129.0, 128.3, 127.9, 127.6, 127.2, 124.7, 82.4, 72.2, 54.9, 41.6, 24.1, 23.2, 10.2; IR (neat, cm^{-1}) 3782, 3696, 3020, 2361, 1594, 1427, 1216, 761, 670; mass (ESI-MS) m/z; 232.1 (100, $[M+H]^+$). EI-HRMS: calcd for: $C_{15}H_{21}NO$: 231.1623, measured 231.1606.

4.1.14. (+)-*α*-conhydrine 5: To a solution of **24.HCl** (0.02 g, 0.085 mmol) in CH_3OH, 20% $Pd(OH)_2/C$ (0.001 g) was added and stirred the reaction mixture under hydrogen atmosphere for 8 h. After completion of the reaction the catalyst was removed by filtration through celite and the filtrate was evaporated. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution 2-3 times.The organic layer was concentrated under reduced pressure and chromatographed over silica gel coloumn to furnish the pure **5** (0.008 g, 74%) as colourless oil. Spectral data was in accordance with the reported one. $[\alpha]_D^{28}$= +8.8 (*c* 0.85 MeOH); {Lit[19b] $[\alpha]_D^{27}$= +8.9 (*c* 0.85 EtOH)} R_f 0.6 (5% $CH_3OH/CHCl_3$). Elemental Analysis calc for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78; found C, 66.89; H, 11.43; N, 9.27.

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