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Building Polyfunctional Piperidines: A Stereoselective Strategy of Three-Component Mannich Reaction Inspired by Biosynthesis and Applications in the Synthesis of Natural Alkaloids (+)-241D; (-)-241D; Isosolenopsin A and (-)-Epimyrtine

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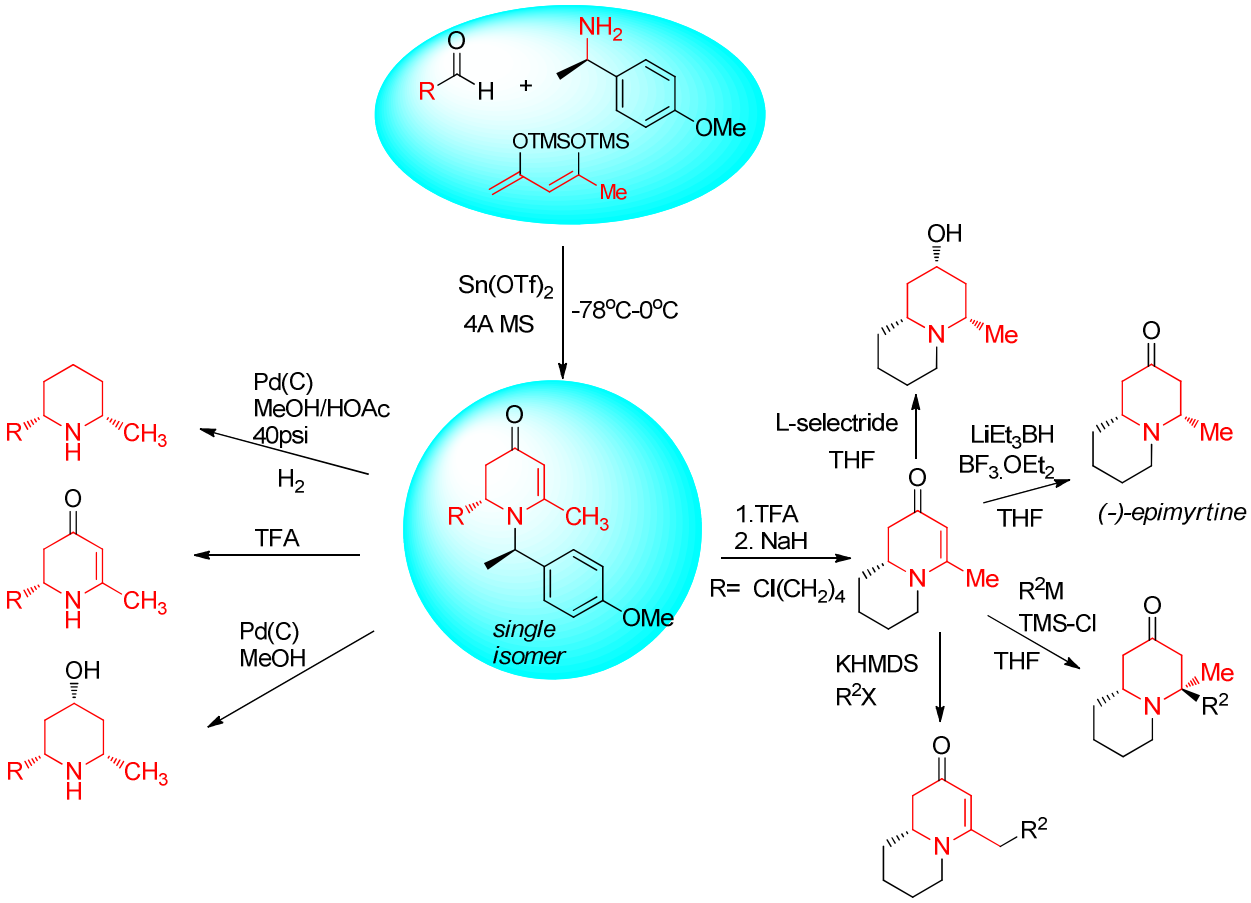


Abstract

A general method to assemble multi-substituted chiral piperidines was developed, inspired by the biosynthesis of piperidine natural products. In biosynthesis, Δ^1-piperideine **4** plays a key role as a common intermediate giving rise to a variety of piperidine-based natural alkaloids. Nature uses L-Lysine as building block, enzymatically transforming it into a δ-amino carbonyl intermediate **3** as the precursor to cyclize into Δ^1-piperideine **4**. We envisioned that such a process could be accomplished by a vinylogous type Mannich reaction if a functionalized dienolate was employed. A stereoselective three-component vinylogous Mannich-type reaction (VMR) of 1,3-bis-trimethylsily enol ether **7** was therefore investigated and was found to give cyclized chiral dihydropyridinone compounds **9** as adducts. Like Δ^1-piperideine in biosynthesis, the chiral 2,3-dihydropyridinone compounds **9** from VMR are versatile intermediates for building a variety of new chiral piperidine compounds. The method was showcased by concise two-step approaches in synthesis of the bioactive natural alkaloids (+)-241D; (-)-241D and Isosolenopsin A. Furthermore, when properly functionalized substrate aldehyde **24** was employed, corresponding dihydropyridinone adduct **25** cyclized to form a second piperidine ring, leading to a chiral polyfunctional quinolizidine enaminone **27**. This versatile intermediate was used to prepare a variety of new chiral quinolizidine compounds, including natural alkaloid (-)-epimyrtine.

Introduction:

Functionalized piperidine rings are common moieties incorporated in a variety of natural alkaloids and pharmaceutical molecules.[1] In fact, piperidine is the most frequently used non-aromatic ring in small molecule drugs listed in the FDA orange book.[2] Developing synthetic approaches for the stereoselective construction of these ring systems has been an area of intense research in synthetic organic chemistry for decades.[3] Among various piperidine derivatives, 2 and/or 6 substituted piperidines are particularly common and interesting[4] since such substitution patterns block metabolism of the piperidine ring and potentially have a significant impact on the ring's 3D conformation. For such reasons, installations α substitutions adjacent to the piperidine nitrogen are commonly employed as a strategy in medicinal chemistry research to tune either biological activities or pharmacological properties. In practice, the methyl group is one of the most common and simplest substituents serving this purpose. Interestingly, α-methyl multi-substituted piperidines are also commonly found in naturally occurring piperidine alkaloids such as (-)-Pindinol, (+)-241D and Isosolenopsine A *etc*. (Figure 1). Some of these natural alkaloids have demonstrated interesting pharmacological properties and served as valuable starting points for new drug discovery.[5]

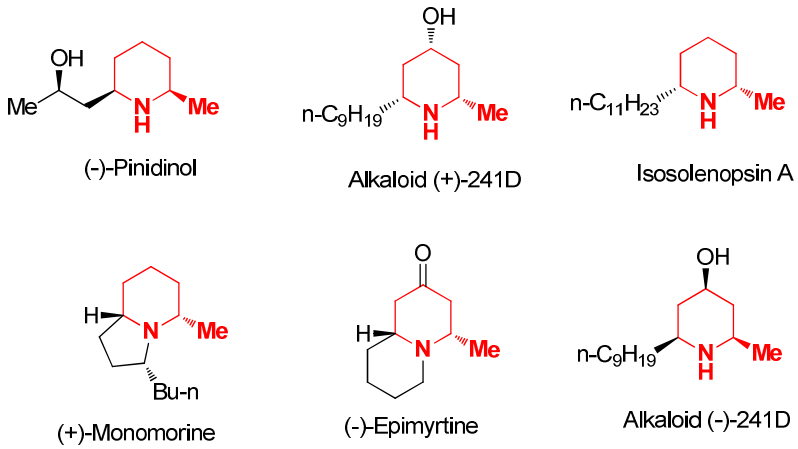


Figure 1: *Examples of natural alkaloids incorporating α-methyl substituted piperidines*

The biosynthetic pathway of many piperidine-based natural alkaloids has been studied. Δ^1-Piperideine **4,** which forms from an intramolecular imine cyclization of a δ-amino pentanal precursor **3,** was believed to be a key common intermediate in the pathway. Studies have shown that further transformations on this prototype piperidine ring lead to a variety of structurally diversified piperidine, quinolizidine and indolizidine alkaloids in nature.[6] The basic starting building block in this pathway is L-lysine, which undergoes several enzymatically catalyzed transformations, including decarboxylation by LDC (lysine decarboxylase) and oxidative deamination by CuAO (copper amine oxidase). The resulting δ-amino pentanal **3** then gives rise to the key Δ^1-piperideine ring. (Figure **2**) However, without nature's powerful enzyme tools, chemical synthesis of Δ1-piperideine is tedious[7] due to its instability and such intermediate is not practical to be widely applied in synthesis lab like its role in biosynthesis.[8] We envisioned however that similar δ-amino carbonyl precursor for Δ^1-piperideine can be assembled conveniently via a vinylogous Mannich-type reaction (VMR) with an aldimine if a properly functionalized dienolate was employed. As shown in Figure **2**, cyclization of the initial δ-amino carbonyl adduct would lead to a 2,3-dihydropyridinone, which could also be viewed as a tautomeric form of cyclic imine, but more stable and easier to handle (Figure **2**). In fact, the synthetic utility of dihydropyridinones has been extensively investigated by the Comins group, but to date the methodology for preparation of these intermediates has been limited.[9] Here we report the successful implementation of the VMR strategy to generate useful chiral dihydropyridone intermediates, and their subsequent transformation to a variety of interesting piperidine-containing natural products and compounds of medicinal interest.

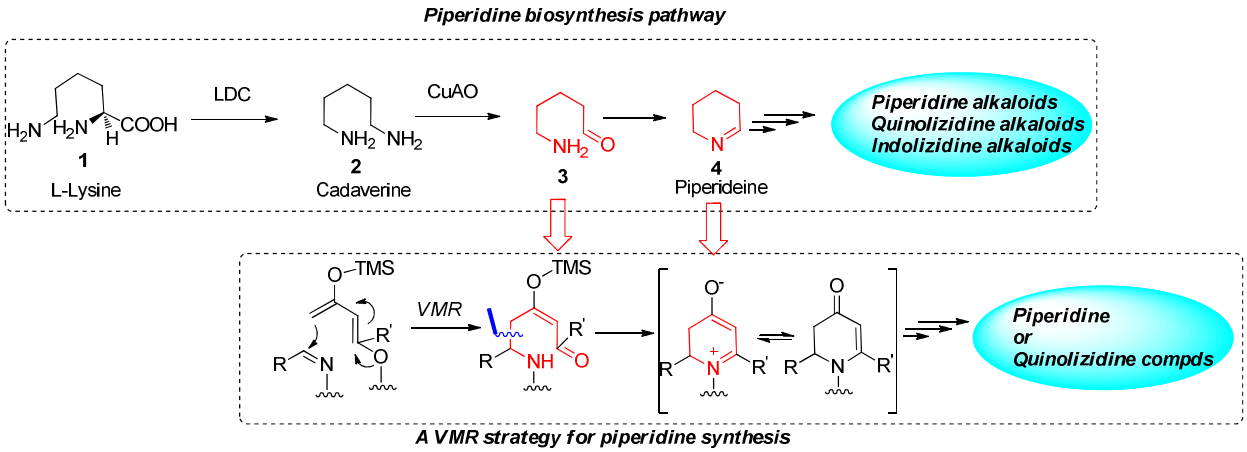
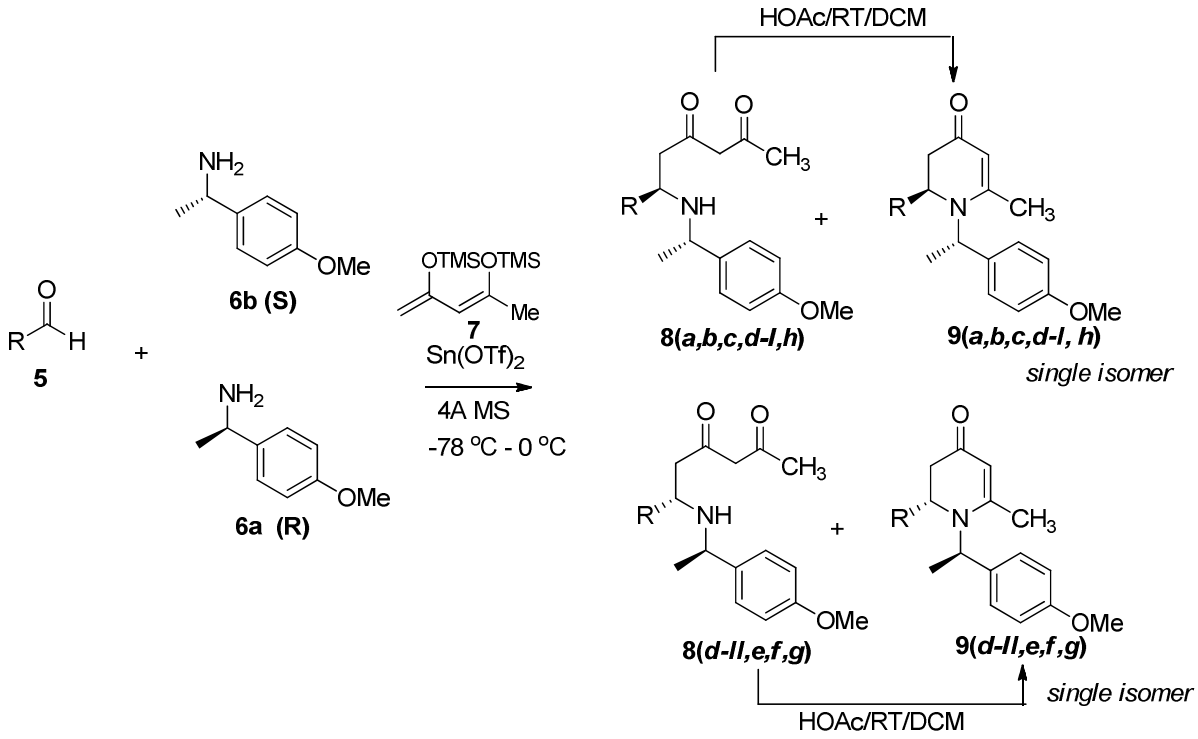


Figure 2: VMR strategy for piperidine synthesis inspired by biosynthesis

Results and Discussion

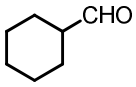
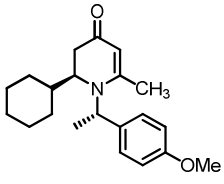
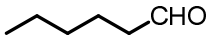
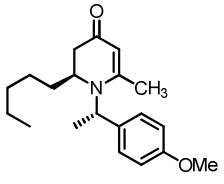
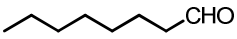
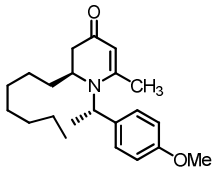
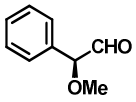
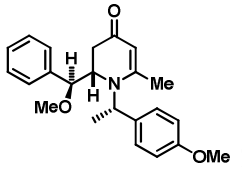
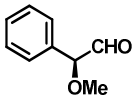
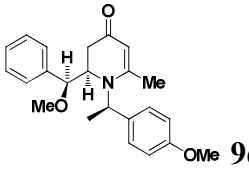
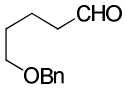
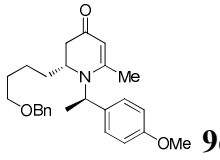
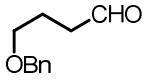
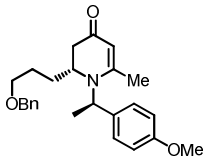
The simple 1,3-bis-trimethylsily enol ether **7** has been employed as a vinylogous nucleophilic reagent in several organic transformations such as cyclization with 1,2-dielectrophiles, bromination, and vinylogous aldol reaction.[10] Surprisingly, the use of **7** as dienolate in a Mannich-type reaction has never been reported.[11] To ensure stereoselective control in VMR, inexpensive commercially available chiral α-methyl benzylamine **6** was employed to form chiral aldimines *in situ*. The three-component VMR reaction of **6** and **7** with various aldehydes **5** was carried out in the presence of $Sn(OTf)_2$ in DCM at -78 ^{o}C to 0 ^{o}C. Corresponding adducts **8** were observed from reaction LC-MS analysis, however in a mixture with cyclized 2,3-dihydropyridinone products **9**. Treatment of the crude mixture with a catalytic amount of acetic acid in DCM led to complete conversion of acylic adducts **8** into **9**. (Scheme 1)

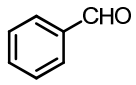
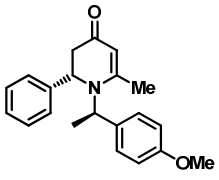
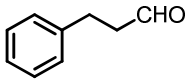
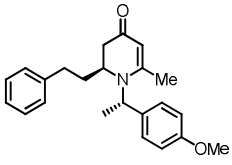


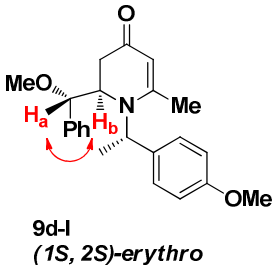
Scheme 1

The results of the VMR reaction of **7** with various aldehydes are summarized in Table **1**. Most of the reactions showed moderate to good yields. A variety of functional groups were well tolerated. The reactions showed excellent diastereoselectivities since in all cases only single isomers were observed and isolated from the reaction mixtures. In order to confirm that the stereoselectivities of the reaction were auxiliary directed, compounds **9d-I** and **9d-II** were prepared from the same chiral substrate aldehyde **5d**, in the presence of chiral amine auxiliary **6a** and its enantiomer **6b**. The proton NMR spectra of these compounds showed that the $J_{Ha/Hb}$ value for **9d-I** was 8.80 Hz while the corresponding value for **9d-II** was 9.2 Hz, suggesting that **9d-I** and **9d-II** were the *erythro* and *threo* isomers respectively, based on literature precedent.[12] These results confirmed auxiliary directed stereoselectivities and further supported the established sense of stereochemical induction in such VMR[13] (Figure **3**).

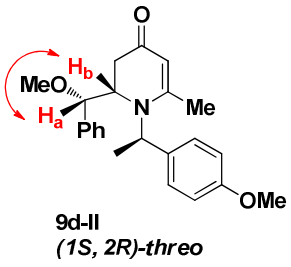
Table 1. Asymmetric three-component vinylogous Mannich reactions of 1,3-bis-trimethylsily enol ether 7

Entry	Substrate 5	6	9 (Yield)
1	 **5a**	**6b**	 **9a** (71%)
2	 **5b**	**6b**	 **9b** (65%)
3	 **5c**	**6b**	 **9c** (68%)
4	 **5d**	**6b**	 **9d-I** (59%)
5	 **5d**	**6a**	 **9d-II** (64%)
6	 **5e**	**6a**	 **9e** (66%)
7	 **5f**	**6a**	 **9f** (75%)

8	 **5g**	**6a**	 **9g** (75%)
9	 **5h**	**6b**	 **9h** (53%)



9d-I
(1S, 2S)-erythro

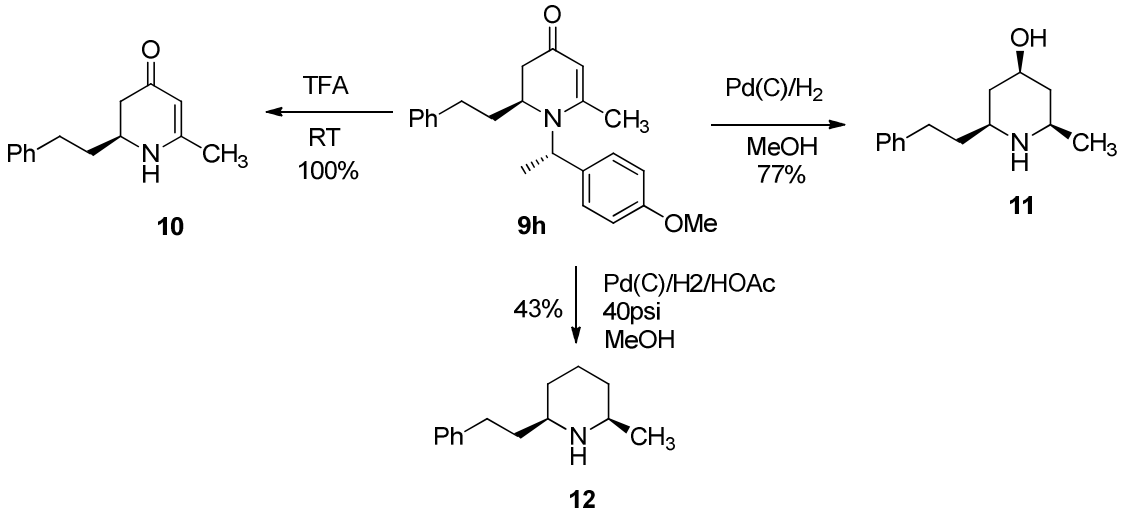


9d-II
(1S, 2R)-threo

Figure 3 NMR Analysis of **9**d-I and **9**d-II

To examine the synthetic utility of 2,3-dihydropyridinones obtained from the VMR, adduct compound **9**h was selected to probe further transformations. When the compound **9**h was treated with TFA at room temperature, the chiral benzyl directing group was cleaved to give cyclic enaminone **10** in quantitative yield. (Scheme **2**). We also found that the corresponding chiral substituted piperidine could be obtained from **9h** via palladium catalyzed hydrogenation. Interestingly, under different hydrogenation conditions, the reduction of **9h** yielded different major piperidine products. When hydrogenation was performed in MeOH in presence of palladium on carbon at room temperature, the reaction cleaved the chiral benzyl group and saturated the 2,3-dihydro-4-pyridinone simultaneously to give cis-3-hydroxy 2,6-disubstituted piperidine compound **11** stereospecifically as the major product, accompanied by deoxygenated piperidine compound **12** as the minor product (**11**/**12**, ratio 10:1)[14] (Scheme **2**). However, when

the hydrogenation was performed in a Parr hydrogenator under 40 psi hydrogen pressure in a mixture of methanol and acetic acid (1/1), the major product was deoxygented *cis*-2,6-dialkylated piperidine **12** accompanied by **11** as the minor product (**12**/**11**, 5:1). (Scheme **2**) The results could be explained by a shift in the equilibrium between 2,3-dihydropridinone and 2,3-dihydropridinium under different conditions.[15] Presumably, 2,3-dihydropridinone is the major species present under neutral conditions and hydrogenation led to 4-hydroxy piperidine product **11**. However, under acidic conditions, to the protonated 2,3-dihydropridinium species is the major (or more reactive) species present, and hydrogenation gives the corresponding deoxygenated piperidine **12** as the major product[16] (Figure **4**). Similar hydrogenations of 2,3-dihydropyridinones have been reported to yield 4-hydroxy piperidine compounds stereospecifically.[14] However, to our knowledge the direct deoxygenative reduction of 2,3-dihydropridinones is very rare. The results allowed accessing different substitution type piperidine compounds from 2,3-dihydropyridinones **9** by simply switching different reduction conditions.



Scheme 2

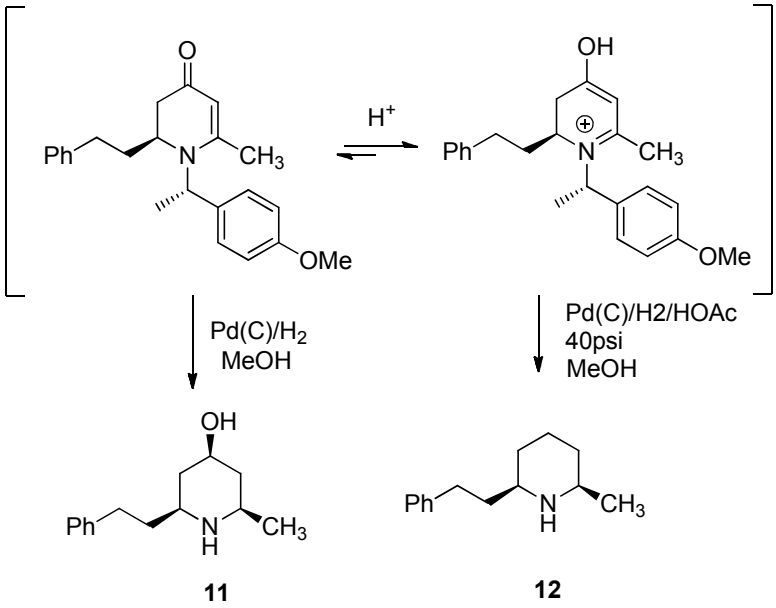
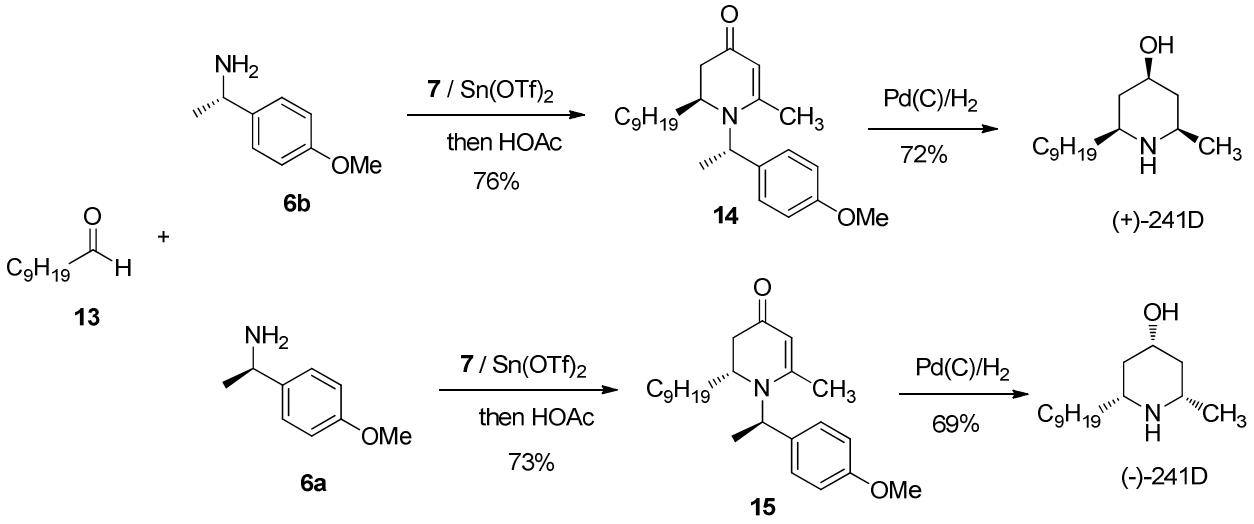


Figure 4.

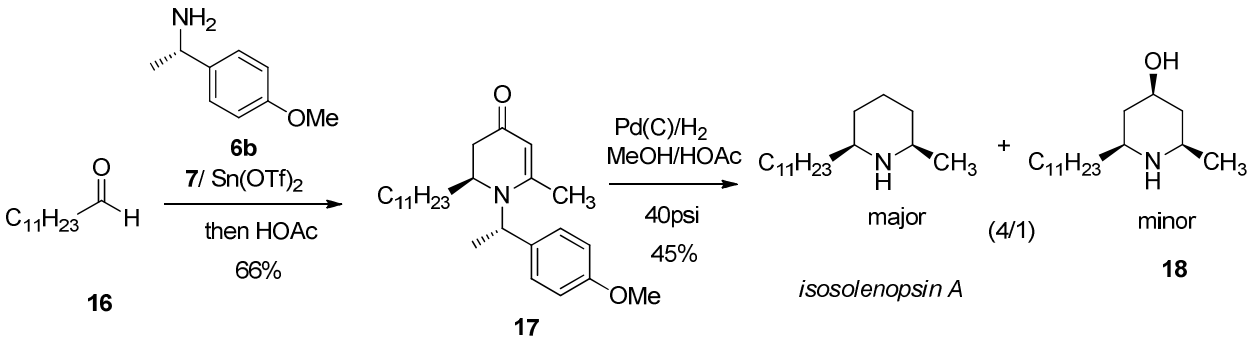
We further probed the utility of our chiral piperidine intermediates by applying the VMR methodology to the asymmetric synthesis of natural piperidine-containing alkaloids. Dendrobate alkaloid (+)-241D and its enantiomer (-)-241D were among our first targets. Dendrobate alkaloid (+)-241D was isolated from the methanolic skin extracts of the Panamanian poison frog *Dendrobates speciosus*.[17] The alkaloid shows interesting bioactivity as a potent non-competitive blocker of acetylcholine and ganglionic nicotinic receptor channels.[18] The structure of (+)-241D features an all-*cis* 2,4,6-trisubstituted piperidine core bearing three chiral centers. The asymmetric synthesis of (+)-241D has been reported by multiple research groups via a variety of synthesis routes employing between eight and eighteen steps.[19] We were delighted to find that using the newly developed VMR strategy, the asymmetric synthesis of (+)-241D and its enantiomer could be accomplished simply in two steps from inexpensive commercial materials. Using chiral α-methyl benzylamines **6a** & **6b** to control stereochemistry, the reaction of bis-trimethylsily enol ether **7** with decanal **13** yielded chiral adducts **14** & **15** respectively.

Subsequent reduction of 2,3-dihydro-4-pyridones **14** & **15** by palladium-catalyzed hydrogenation in methanol gave (+) 241D and (-) 241D in good yield (Scheme **3**).



Scheme 3 Enantioselective synthesis of (+)-241D and (-)-241D

The versatile utility of such VMR approach in assembling piperidine was further exampled in asymmetric synthesis of another natural alkaloid Isosolenopsin A which incorporate *cis*-2,6-dialkylpiperidine as a core. Isosolenopsin A was isolated from the venom of the fire ant *solenopsis* and was found to have a variety of interesting bioactivities including antibiotic, antifungal, anti-HIV, blockade of neuromuscular transmission and potent and selective inhibition of the neuronal nitric oxide synthase. [20] By the similar strategy, corresponding VMR adduct 2,3-dihydro-4-pyridones **17** was obtained when dodecanal **16** and chiral amine **6b** were employed. The palladium-catalyzed reduction on 2,3-dihydro-4-pyridone **17** was carried out in methanol in presence of acetic acid (50%) under 40psi hydrogen pressure in a Parr hydrogenator. Corresponding deoxygenated product Isosolenopsin A was obtained as the major product in moderate yield (45%). (Scheme **4**) The current approach presented the shortest route for asymmetric synthesis of Isosolenopsine A than any other reported methods. [21]



Scheme 4 Enantioselective synthesis of natural alkaloid Isosolenopsin A

Beyond applying to building simple multi-substituted piperidine compounds, current VMR strategy also provides potentials in synthesizing chiral quinolizidine compounds. Quinolizidine compounds structurally incorporate two fused piperidine rings sharing common nitrogen. Like piperidine, quinolizidine represent both a class compound of pharmaceutical interest and an important family of natural alkaloids. In nature, several hundred structurally related quinolizidine compounds have been identified from a variety of natural sources, predominately from plants and amphibian skin.[22] Some natural quinolizidine alkaloids exhibit interesting pharmacological properties [23] and serve as important starting points for the drugs discovery. [24] Interestingly, the biosynthesis of some quinolizidine alkaloids shares the same pathway of the natural piperidine alkaloids that undergo the same Δ^1-piperideine intermediate **4**, enzymatically starting from L-lysine.[25] As an example, in the biosynthesis of quinolizidine alkaloids Lupinine, Δ^1-piperideine is also the key intermediate to assemble the first piperidine ring for the quinolizidine core. To build the second piperidine ring, two Δ^1-piperideine intermediates undergo a cross Aldol-type coupling and one of the imine systems gets hydrolyzed after coupling and undergoes oxidation resulting in primary amine function **20**. Ultimately the formation of the quinolizidine nucleus in biosynthesis is accomplished by another intramolecular imine formation. (Figure **5**) We however envisioned

that in the VMR we developed, if the aldimine substrate has been properly functionalized, piperidine-like adducts arising from the asymmetric VMR may further conveniently cyclize to form second piperidine ring to give the desired quinolizidine product. As shown in Figure **5**, if a δ- leaving group is incorporated in the aldimine substrate and can be tolerated in the asymmetric VMR for the first piperidine ring construction, the quinolizidine structure **22** should be readily formed by a subsequent intramolecular SN2 cyclization. (Figure **5**)

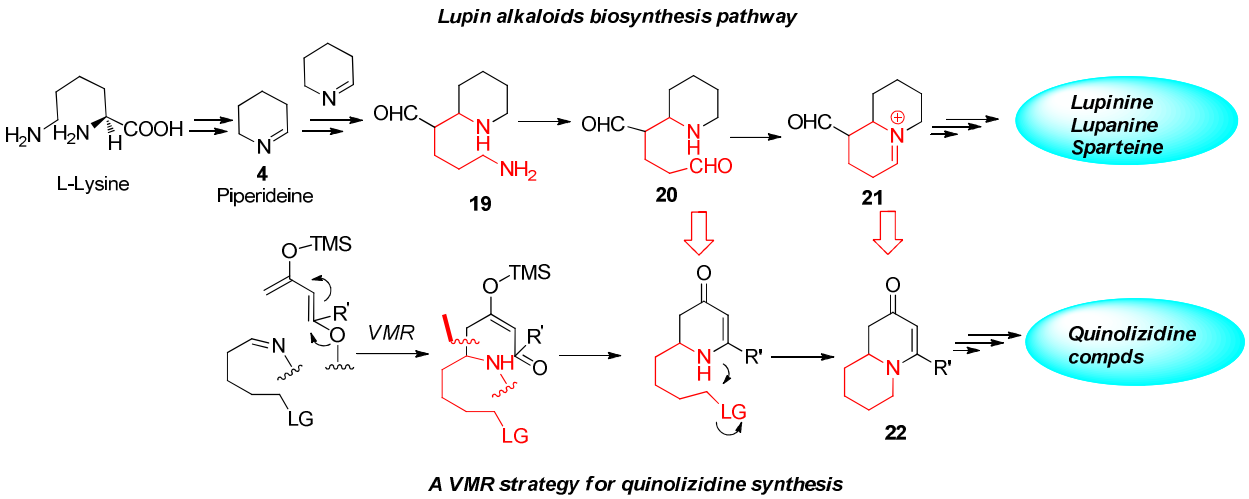
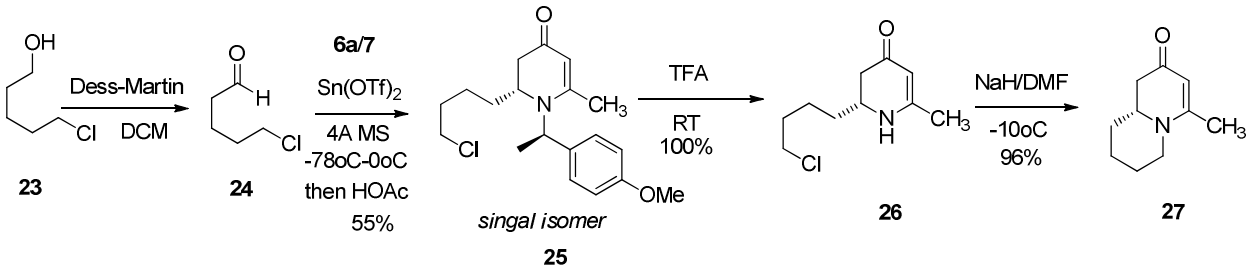


Figure 5. VMR strategy for quinolizidine synthesis

To test this idea 5-chloropentanal **24** was prepared from the oxidation of 5-chloropentan-1-ol **23** and the corresponding three-component VMR reaction was carried out. The reaction gave adduct **25** in expected excellent diastereoselectivity as a single stereoisomer. The δ chloride which serve as a future leaving group on the substrate, was well tolerated. (Scheme **5**) With dihydropyridinone **25** in hand we set out to construct the second ring for a quinolizidine core. The α-methyl benzyl group was cleaved cleanly upon the treatment with TFA at room temperature overnight to give compound **26** in quantitative yield. In presence of sodium hydride in DMF, intramolecular SN2 cyclization by **26** led to a quinolizidine intermediate **27** as a cyclic

enaminone. (Scheme **5**) We envisaged that such cyclic enaminone **27** could be a valuable polyfunctional quinolizidine intermediate since different organic transformations can be carried out at different positions on this molecule. It provides convenient entries to access different types chiral quinolizidine compounds. (Figure **6**)



Scheme 5

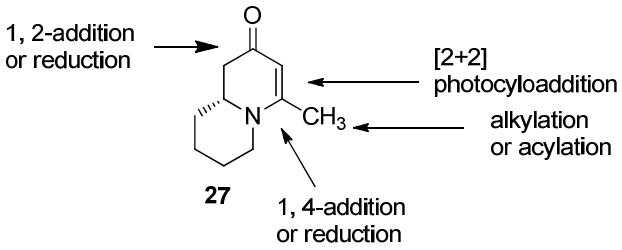
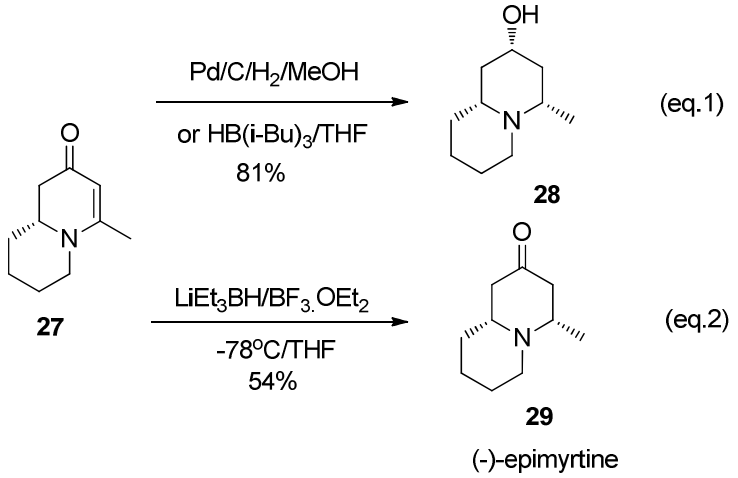


Figure 6. Synthesis Versatility of Quinolizidine Enaminone **27**

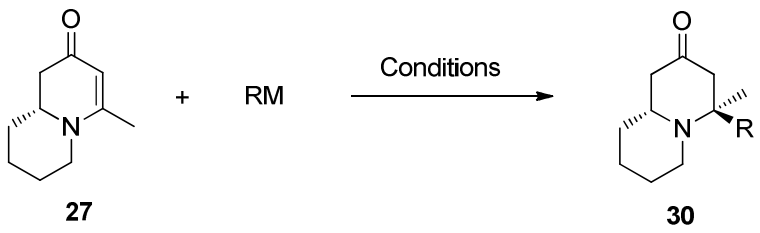
The reduction of cyclic enanminone **27** was first explored. It was found that under the conditions of either palladium-catalyzed hydrogenation in methanol or treating L-selectride ($LiBu^{i}_{3}BH$) in THF, both alkene and carbonyl were reduced affording *cis*-2-hydroxyl-4-methly quinolizidine **28** as product. (Scheme **6,** eq.1) Similarly as in the reduction of 2,3-dihydropyridinone, the reduction on quinolizidine enanminone also proceeded in stereoselective manner which is in agree with literature precedents.[26] When the reduction was carried out with "super hydride" ($LiEt_3BH$) in presence of $BF_3.Et_2O$ in THF, the alkene functionality was selectively reduced, giving **29** as natural quinolizidine alkaloid (-)-epimyrtine as the product in

good yield.[27] (Scheme **6**, eq.2) The results provided a concise approach for the enanotioselective synthesis of such natural alkaloid.[28]



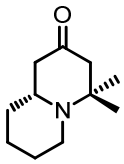
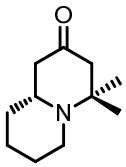
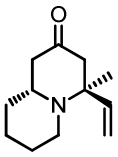
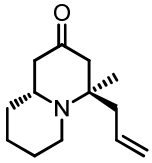
Scheme 6. Reduction of quinolizidine enaminone 27.

Conjugate additions to quinolizidine enaminone **27** were also explored. Although direct conjugate addition of Grignard reagents to cyclic enaminones has been previously reported, [29] in our hands, treatment of **27** with methyl magnesium bromide did not yield expected product (Table **1**, entry 1). Similarly, when methyl cuprate was employed, only a trace amount of product **30a** was observed (Table **1**, entry 2). However, when methyl Grignard addition was carried out in the presence of TMS-Cl, 1,4-conjugate addition went smoothly giving adduct **30** in good yield.[30] (Table **2**, entry 3) Under similar conditions, conjugate additions by vinyl and allyl Grignard reagents were also performed (Table **2**, entry 4&5). As the similar examples reported in literature, such conjugate addition on quinolizidine enaminone proceeded in stereoselective manner by generating a quaternary chiral carbon in the product.[31]



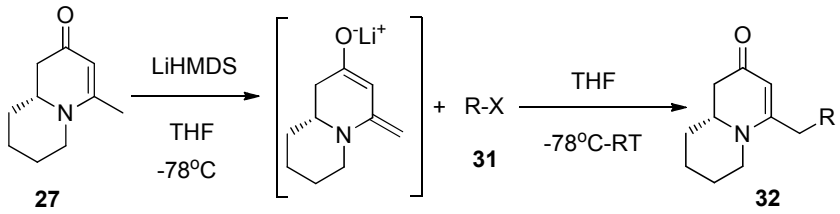
Scheme 7

Table 2 Conjugate addition reactions of quinolizidine enaminone 27

Entry	RM	Conditions	Products (Yield)
1	MeMgBr	THF (0-RT)	No reaction
2	MeMgBr/CuI (Me_2CuLi)	THF (0-RT)	 **30a** (<5%)
3	MeMgBr	THF/TMS-Cl(3eq) (0-RT)	 **30a** (65%)
4	VinylMgBr	THF/TMS-Cl(3eq) (0-RT)	 **30b** (57%)
5	AllylMgBr	THF/TMS-Cl(3eq) (0-RT)	 **30c** (51%)

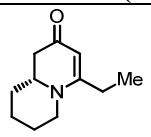
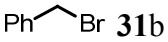
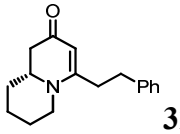
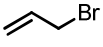
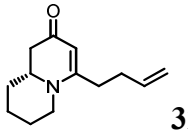
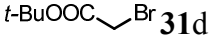
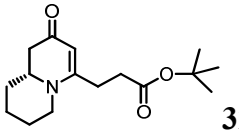
Finally, to further probe structural diversification, alkylation reaction on the methyl side chain of **27** was investigated. It was found that a corresponding enolate can be generated by

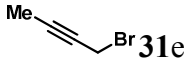
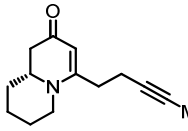
treating **27** with $LiN(SiMe_3)_2$ (LiHMDS) in THF at low temperature. By subsequently treating such enolate with alkylating agents **31,** corresponding alkylation products **32** could be obtained smoothly. The results of such reaction were summarized in Table 3. The reactions gave moderate to good yields by showing the tolerance toward different functional groups. No epimerization was observed in such enolate alkylation. Such alkylation reaction led to the side chain extension and provided opportunities to synthesize more structural diversified quinolizidine-based compound beyond α methyl substituted type.



Scheme 8

Table 3 Alkylation of Quinolizidine Enaminone 27

Entry	RX	32 (Yield)
1	 **31**a	 **32**a (82%)
2	 **31**b	 **32**b (78%)
3	 **31**c	 **32**c (55%)
4	 **31**d	 **32**d (79%)

5	 **31**e	 **32**e (61%)

Conclusion

In summary, inspired by the biosynthesis pathway of natural piperidine-based alkaloids, a general and practical approach to synthesize multi-substituted chiral piperidine was developed via a stereoselective three-component vinylogous Mannich-type reaction (VMR) by using 1,3-bis-trimethylsily enol ether **7** as a dienolate**.** The corresponding VMR adduct was chiral 2,3-dihydropyridinones **9** which played the role of cornerstone in building new targeted chiral piperidine compounds. The efficiency of such stereoselective synthesis approach was exampled in developing novel synthesis of bioactive natural alkaloids: dendrobate alkaloids (+)-241D; (-)-241D, and Isosolenopsin A in highly concise manners. Beyond simple piperidine compound synthesis, the method also provided rapid route for chiral quinolizidine construction. When pre-functionalized substrate aldehyde **24** was employed, the corresponding VMR adduct could cyclize to give versatile quinolizidine cyclic enaminone **27**. The different types transformations carried out on such polyfunctional intermediate gave rise a variety of new chiral quinolizidine compounds, including natural alkaloid (-)-Epimyrtine. We believe the presented VMR approach offers a general; stereoselective and efficient way to assemble multi-substituted chiral piperidine-based compound in organic synthesis.

Experimental Section

General Methods: All commercial reagents and solvents were used without purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer using TMS as the internal

standard (0 ppm). TLC analyses were carried out on aluminum sheets precoated with silica gel 60 F254, and UV radiation was used for detection. Flash column chromatography was performed on silica gel (SiliaFlash F60, 230-400 mesh). LC/MS analysis was performed on an Agilent 1100 series system equipped with an Agilent 1100 series binary pump, Agilent 1100 series autosampler, Agilent 1100 series DAD UV detector, Agilent 1100 series single quadrupole mass spectrometer with ESI source, and a SEDEX 75 ELSD. The mass spectrometer was set to scan from 100 to 1000 AMU. Mass spectrometric data were acquired in the positive ionization mode. The mobile-phase solvents used were (A) 0.05% aq TFA; and (B) 0.035% TFA in MeCN. The total mobile phase flow rate was 1.0 mL/min. The gradient was 10-90% in 3 min with an isocratic hold of 100% mobile-phase B for 0.49 min at the end of the gradient. A Waters *Atlantis* T3 (5 μm, 2.1 × 50 mm) column was used. ^{1}H and ^{13}C NMR spectra were recorded using 400MHz/100MHz Bruker spectrometer. Chemical shifts are reported in ppm, multiplicities are indicated by *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), and *m* (multiplet). All vinylogous Mannich reactions were carried out in oven-dried glassware under air atmosphere. 1,3-bis-trimethylsily enol ether 7 was prepared freshly following the procedure from literature.[10d] Diastereo-selectivities of VMR described in the manuscript were determined both by HPLC and NMR.

(S)-2-cyclohexyl-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (9a) To a round-bottom flask contains (R)-1-(4-methoxyphenyl)ethanamine (6b) (151mg, 1mmol, 1eq.) in dried DCM (0.1M) solution added 4AMS (500mg/mmol) followed by cyclohexane-carbaldehyde (5a) (112mg, 1mmol, 1eq). After stirring at room temperature for 10mins, 1,3-bis-trimethylsily enol ether 3 (292mg, 1.2mmol, 1.5eq) was added and the mixture solution was cooled to -78^{o}C. Tin (II) triflate (412mg, 1mmol, 1eq.) was then added and the

reaction was stirred at this temperature for 8hrs. The reaction temperature was raised to 0°C and kept the same temperature overnight. LC-MS analysis showed the mixture of **8**a and **9**a as new products (~2/1). The reaction was quenched with saturated aqueous solution of sodium bicarbonate and removed solid via filtration. The reaction mixture was then extracted with DCM (15mlx5). The combined organic phase was treated with acetic acid (0.1ml) and the resulting solution was stirred at room temperature for 1hr until **8**a disappeared from LC-MS analysis. The solution was then basified by treating with saturated aqueous solution of sodium bicarbonate and washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (ethyl acetate/hexane) to afford the product as colorless oil (232mg, 71% yield). ^{1}H-NMR (400MHz, $CDCl_3$, 25°C): δ=0.87 (m, 1H); 1.30(m, 4H); 1.41(m, 1H);1.55(d, 3H, J=6.8Hz, CH_3-); 1.70 (m, 5H); 2.02(m, 2H); 2.07(s, 3H, CH_3-); 2.97(m, 1H); 3.70(s, 3H, OCH_3); 4.87(s, 1H, CH=); 4.94(q, 1H, J=6.8Hz); 6.80(m, 2H); 7.13(d, 2H, J=8.4Hz). ^{13}C-NMR (100MHz, $CDCl_3$, 25°C): δ= 18.8; 21.8; 26.2; 26.5; 26.6; 29.7; 30.6; 36.6; 40.9; 55.3; 558; 57.3; 102.5; 114.1; 127.5; 133.8; 159.1; 161.6; 191.9. LC-MS: 100% (purity), m/e: 328 (M+1) Cal. For $C_{21}H_{30}NO_2$ (M+H): 328.22765; Found: 328.2272

Similar procedure was applied to synthesize compound **9a-h; 14; 15; 17**

(R)-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-pentyl-2,3-dihydropyridin-4(1H)-one (9b)

Colorless oil (Yield, 65%). 1H-NMR (400MHz, CDCl3, 25°C): δ=0.78 (t, 3H, J=6.8Hz, CH_3); 1.05(m, 1H); 1.18(m, 5H); 1.25(m, 2H); 1.56(d, 3H, J=6.8Hz, CH3-); 2.01 (d, 1H, J=16.58Hz); 2.20(dd, 1H, J_1=6Hz, J_2=16.51Hz); 2.07(s, 3H, CH3-); 3.16(m, 1H); 3.75(s, 3H, OCH3); 4.87(s, 1H, CH=); 4.98(q, 1H, J=6.8Hz); 6.83(m, 2H); 7.16(d, 2H, J=8.4Hz). 13C-NMR (100MHz, CDCl3, 25°C): δ= 14.0; 17.5; 21.5; 22.6; 25.7; 30.1; 31.7; 38.0; 52.9; 55.3; 55.4; 99.9; 100.0;

114.1; 127.6; 133.4; 159.1; 159.9; 190.6. LC-MS: 100% (purity), m/e: 316 (M+1). Cal. For C20H30NO (M+H): 316.2276 ; Found: 316.2271

(R)-2-heptyl-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (9c) Colorless oil (Yield, 68%). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ= 0.79 (t, 3H, J=6.88Hz, CH3); 1.16(m, 12H); 1.56(d, 3H, J=7.06 Hz, CH3-); 1.98(d, 1H, J=16.52Hz); 2.19(dd, 1H, J1=5.94Hz, J2=16.49Hz); 2.08(s, 3H, CH3-); 3.16(m, 1H); 3.74(s, 3H, OCH3); 4.86(s, 1H, CH=); 4.97(q, 1H, J=6.8Hz); 6.83(m, 2H); 7.16(d, 2H, J=8.69Hz). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ= 14.1; 17.5; 21.5; 22.6; 25.9; 29.2; 29.5; 30.1; 31.7; 38.0; 52.9; 55.3; 55.4; 99.9; 114.1; 127.7; 133.3; 159.1; 159.9; 190.6. LC-MS: 100% (purity), m/e: 344 (M+1). Cal. For C22H34NO2 (M+H): 344.2589; Found: 344.2584.

(S)-2-((S)-methoxy(phenyl)methyl)-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (9d-I) Colorless oil (Yield, 59%). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ= 0.45(d, J=7.14Hz, 3H); 1.33(dd, J=5.53Hz, J_2=16.92Hz, 1H); 2.04(s, 3H); 2.41(d, J=16.89Hz, 1H); 3.11(s, 3H); 3.26(ddd, J_1=1.62Hz; J_2=5.52Hz; J_3=8.80Hz, 1H); 3.70(s, 3H, OCH_3); 4.50(d, J=8.80Hz, 1H); 4.54(q, J=7.14Hz, 1H); 5.09(s, 1H); 6.74(m, 2H); 6.98(m, 2H); 7.18(dd, J_1=7.25, J_2=8.83Hz; 2H); 7.26(m, 1H); 7.30(m, 2H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ= 16.1; 21.7; 36.9; 55.3; 56.1; 57.8; 79.2; 104.4; 114.0; 127.5; 127.6; 128.1; 128.3; 133.5; 140.2; 159.1; 161.5; 192.6. LC-MS: 100% (purity), m/e: 366 (M+1). Cal. For C23H28NO3 (M+H): 366.2069; Found: 366.2065

(R)-2-((S)-methoxy(phenyl)methyl)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (9d-II) Colorless oil (Yield, 64%). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ= 1.47(dd, J_1=12.13Hz; J_2=29.37Hz, 1H); 1.69(d, J=7.21Hz, 3H); 1.97(m, 1H); 2.08(s,

3H); 3.08(s, 3H); 3.44(dd, J_1=6.88Hz; J_2=8.23Hz, 1H); 3.71(s, 3H); 4.49(d, J=9.19Hz, 1H); 4.95(s, 1H); 5.01(q, J=7.21Hz, 1H); 6.78(m, 2H); 7.20(m, 7H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=19.3; 21.7; 36.5; 55.3; 56.9; 57.1; 58.4; 79.6; 102.0; 114.1; 127.6; 127.8; 128.2; 128.6; 134.3; 139.1; 159.0; 161.0; 190.5. LC-MS: 100% (purity), m/e: 366 (M+1). Cal. For C23H28NO3 (M+H): 366.20692; Found: 366.2065

(R)-2-(4-(benzyloxy)butyl)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (9e) Colorless oil (Yield, 66%). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ= 1.19-1.41(m, 4H); 1.48(m, 2H); 1.52(d, J=7.04Hz, 3H); 1.95(d, J=5.09Hz, 1H); 1.99(m, 1H); 2.08(s, 3H); 2.18(dd, J_1=5.94Hz; J_2=16.54Hz); 3.17(m, 1H); 3.34(m, 2H); 3.71(s, 3H, OCH3); 4.39(s, 2H); 4.86(s, 1H); 4.95(q, J=7.04Hz, 1H); 6.81(m, 2H); 7.13(m, 2H); 7.23(m, 5H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=14.2; 17.5; 21.5; 22.7; 29.6; 29.8; 37.9; 52.8; 55.3; 55.5; 70.1; 73.0; 100.0; 114.1; 127.5; 127.64; 127.67; 127.70; 127.74; 128.4; 133.3; 138.5; 159.1; 159.9; 190.5. LC-MS: 100% (purity), m/e: 408 (M+1). Cal. For C26H34NO3 (M+H): 408.2538; Found: 408.2533

(R)-2-(3-(benzyloxy)propyl)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (9f) Colorless oil (Yield, 75%). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ=1.39-1.24(m, 1H); 1.47-1.40(m, 1H);1.55(d, J=7.20Hz, 3H); 1.98-1.94(m, 2H); 2.09(s, 3H); 2.26-2.13(m, 1H); 3.29-3.08(m, 1H); 3.50-3.29(m, 2H); 3.72(s, 3H, OCH3); 4.38(s, 2H); 4.87(s, 1H); 4.94(q, J=7.20Hz, 1H); 6.79(m, 2H); 7.10(m, 2H); 7.21(m, 5H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=190.4; 160.0; 159.1; 138.4; 133.3; 128.4; 127.7; 127.6; 127.5; 114.1; 100.0; 72.9; 69.8; 55.5; 55.3; 52.5 38.0; 26.7; 25.9; 21.5; 17.4. LC-MS: 100% (purity), m/e: 394(M+H). Cal. For C25H32NO3 (M+H): 394.2382 Found: 394.2377.

(R)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-phenyl-2,3-dihydropyridin-4(1H)-one

(9g) Colorless oil (Yield, 75%). 1H-NMR (400MHz, CDCl3, 25°C): δ= 1.24(d, J=7.2Hz, 3H), 2.18(d, J=16.3Hz, 1H); 2.23(s, 3H); 2.71(dd, J_1=7.53Hz; J_2=16.35Hz, 1H); 3.739(s, 3H); 4.42(m, 1H); 4.96(s, 1H); 5.12(q, J=6.97Hz, 1H); 6.85(m, 2H); 7.11(m, 3H); 7.18(m, 4H). 13C-NMR (100MHz, CDCl3, 25°C): δ=17.7; 21.6; 42.6; 55.4; 56.0; 56.1; 101.5; 114.2; 126.0; 127.3; 127.6; 128.6; 133.3; 140.6; 159.2; 161.6; 188.9. LC-MS: 100% (purity), m/e: 322(M+1). Cal. For C21H24NO2 (M+H): 322.1807; Found: 322.1802

(S)-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one

(9h) Colorless oil (Yield, 53%). 1H-NMR (400MHz, CDCl3, 25°C): δ=7.19(m, 2H); 7.13(m, 1H); 7.04(d, J=7.16Hz, 2H); 6.98(d, J=8.65Hz, 2H); 6.76(d, J=8.71Hz, 2H); 4.90(q, J=7.01Hz, 1H); 4.87(s, 1H); 3.73(s, 1H, OCH_3); 3.19(m, 1H); 2.61(m, 1H); 2.44(m, 1H); 2.30(m, 1H); 2.19(m, 1H); 2.08(s, 3H); 1.58(m, 1H); 1.38(d, J=7.07Hz, 3H, -CH_3). 13C-NMR (100MHz, CDCl3, 25°C): δ=190.3; 160.0; 159.1; 140.9; 132.9; 128.5; 127.7; 126.1; 114.0; 99.9; 55.6; 55.3; 51.5; 37.7; 31.9; 31.7; 21.5; 17.2. LC-MS: 100% (purity), m/e: 335(M+1). Cal. For C23H28NO2 (M+H): 350.2120; Found: 350.2115

(S)-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-nonyl-2,3-dihydropyridin-4(1H)-one (14) Colorless oil (Yield, 76%). 1H-NMR (400MHz, CDCl3, 25°C): δ=7.16(d, J=8.57Hz, 2H); 6.82(d, J=8.79Hz, 2H); 4.97(q, J=6.98Hz, 1H); 4.86(s, 1H); 3.73(s, 3H); 3.16(m, 1H); 2.19(dd, Ja=5.74Hz, Jb=16.53Hz 1H); 2.08(s, 3H); 1.97(m, 1H); 1.55(d, J=6.98Hz, 3H); 1.31-1.03(m, 14H); 0.79(t, J=6.90Hz, 3H). 13C-NMR (100MHz, CDCl3, 25°C): δ=190.6; 159.9; 159.1; 133.3; 127.6; 114.0; 99.8; 55.4; 55.3; 52.8; 38.0; 31.8; 30.1; 29.6; 29.5; 29.2; 25.9; 22.6; 21.5; 17.5; 14.1. LC-MS: 100% (purity), m/e: 372(M+1). Cal. For C24H38NO2 (M+H): 372.2902; Found: 372.2897

(R)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-nonyl-2,3-dihydropyridin-4(1H)-one (15) Colorless oil (Yield, 69%). 1H-NMR (400MHz, CDCl3, 25°C): δ=7.13(d, J=8.66Hz, 2H); 6.80(d, J=8.78Hz, 2H); 4.95(q, J=6.98Hz, 1H); 4.84(s, 1H); 3.71(s, 3H); 3.14(m, 1H); 2.17(dd, Ja=6.02Hz, Jb=16.62Hz 1H); 2.06(s, 3H); 1.95(m, 1H); 1.53(d, J=6.98Hz, 3H); 1.35-0.94(m, 14H); 0.77(t, J=6.89Hz, 3H). 13C-NMR (100MHz, CDCl3, 25°C): δ=190.6; 159.9; 159.1; 133.3; 127.6; 114.0; 99.8; 55.4; 55.3; 52.9; 38.0; 31.8; 30.1; 29.6; 26.5; 29.4; 29.2; 25.9; 22.6; 21.5; 17.5; 14.1. LC-MS: 100% (purity), m/e: 372(M+1). Cal. For C24H38NO2 (M+H): 372.2902; Found: 372.2897

(R)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-undecyl-2,3-dihydropyridin-4(1H)-one (17) Colorless oil (Yield, 66%). 1H-NMR (400MHz, CDCl3, 25°C): δ=7.21(d, J=8.62Hz, 2H); 6.88(d, J=8.62Hz, 2H); 5.03(q, J=6.99Hz, 1H); 4.92(s, 1H); 3.97(s, 3H, OMe); 3.22(m, 1H); 2.25(dd, J1=5.88Hz, J2=16.49Hz 1H); 2.14(s, 3H); 2.04(m, 2H); 1.61(d, J=6.99Hz, 3H); 1.35-1.10(m, 20H); 0.86(t, J=6.86Hz, 3H). 13C-NMR (100MHz, CDCl3, 25°C): δ=190.6; 159.9; 159.1; 133.3; 127.6; 114.0; 99.9; 55.4; 55.3; 52.9; 38.0; 31.9; 30.1; 29.6; 29.5; 29.4; 29.3; 25.9; 22.7; 21.5; 17.5; 14.1. LC-MS: 100% (purity), m/e: 400(M+1). Cal. For C15H42NO2 (M+H): 400.32155; Found: 400.3210

(S)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (10) To a flask contains (S)-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (9h) (75mg, 0.21mmol) added TFA (1.5ml) and the solution was stirred at room temperature overnight. TFA was removed by vacuum and the residue was re-dissolved in DCM (10ml). The solution was washed with saturated aqueous solution of sodium bicarbonate and brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (DCM/Methanol) to afford the product as colorless oil (46mg, 100% yield). 1H-NMR (400MHz,

CDCl3, 25°C): δ=7.22(m, 2H); 7.14(m, 3H); 4.59(s, 1H); 4.84(s, 1H); 3.57(sex, J=6.18Hz, 1H); 2.67(m, 1H); 2.61(m, 1H); 2.34(m, 1H); 2.22(dd, Ja=12.5Hz, Jb=16.08Hz, 1H); 1.93(m, 1H); 1.85(m, 1H); 1.81(s, 3H). 13C-NMR (100MHz, CDCl3, 25°C): δ=192.3; 161.8; 140.8; 128.7; 128.3; 126.4; 99.1; 53.0; 41.1; 35.7; 31.9; 21.2.. LC-MS: 100% (purity), m/e: 216(M+1). Cal. For C14H18NO (M+H): 216.1388; Found: 216.1383

(2R,4S,6S)-2-methyl-6-phenethylpiperidin-4-ol (11) To a flask contains methanol solution (0.1M) of 1(S)-1-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (9h) (120mg, 0.34mmol) added powder of palladium on carbon (12mg) cautiously under nitrogen stream. The flask was then washed and filled with hydrogen gas. The reaction was stirred at room temperature for 4hrs under hydrogen atmosphere and checked by LC-MS until starting material disappeared. After filtration to remove catalyst, the solvent was removed by vacuum and the crude product was purified by ISCO silica gel chromatography (DCM/Methanol) to afford the product as gray powder. (35mg, 77% yield).NMR (400MHz, CD3OD, 25°C): δ=7.10(m, 2H); 7.14(m, 2H); 7.05((t, J=7.13Hz, 1H); 3.46(ddd, Ja=4.54Hz, Jb=7.83Hz, Jc=11.08Hz); 2.56(m, 3H); 2.44(m, 1H); 1.93(m, 1H); 1.79(m, 1H); 1.68(m, 1H); 1.58(m, 1H); 1.01(d, J=6.37Hz, 3H, -Me); 0.91(m, 2H). 13C-NMR (100MHz, CD3OD, 25°C): δ=143.3; 129.5; 129.4; 126.9; 69.6; 55.6; 51.4; 43.9; 41.5; 39.3; 33.3; 22.1. LC-MS: 100% (purity), m/e: 220(M+1). Cal. For C14H22NO (M+H): 220.1701; Found: 220.1696

(2R,6R)-2-methyl-6-phenethylpiperidine (12) To Parr Shaker reaction vessel contains (0.1M) of 1(S)-1-((S)-1-(4-methoxyphenyl) ethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (5h) (120mg, 0.34mmol) in mixed solvent of methanol (5ml) and acetic acid 5ml)added powder of palladium on carbon (36mg) cautiously under nitrogen stream. The reaction was then carried out by Parr Shaker hydrogenation apparatus under 40psi overnight. After filtration to remove

catalyst, the solvent was removed by vacuum and the crude product was re-dissolved in mixture of chloroform and 2-propanol (3/1, 15ml). The solution was washed with saturated aqueous solution of sodium bicarbonate and brine and dried over sodium sulfate. After removing the solvent, the crude product was purified by ISCO silica gel chromatography (DCM/Methanol) to afford the product as colorless oil (Yield, 61%). (29mg, 43% yield).1H-NMR (400MHz, CD_3OD, 25°C): δ=7.26-6.21(m, 5H); 3.03(m, 1H); 2.93(m, 1H); 2.72-2.42(m, 2H); 2.01(m, 1H); 1.89(m, 1H); 1.81(m, 3H); 1.63(m, 1H); 1.46(m, 1H); 1.28(m, 1H); 1.21(d, J=6.41Hz, 3H, Me). 13C-NMR (100MHz, CD3OD, 25°C): δ=141.9; 129.7; 129.4; 129.3; 127.4; 58.3; 54.8; 36.9; 32.3; 31.8; 29.2; 23.6; 19.8. LC-MS: 100% (purity), m/e: 204 (M+1). Cal. For C14H22N (M+H): 204.1752; Found: 204.1747

(2S,4R,6R)-2-methyl-6-nonylpiperidin-4-ol [(-)-241D] Starting from 15 simillar hydrogenation procedure as in preparing 11 was applied to give (-)-241D as gray solid (Yield, 69%). (1H-NMR (400MHz, CD3OD, 25°C): δ=3.66(tt, J1=4.51Hz, J2=11.09Hz); 3.02(m, 1H); 2.90(m, 1H); 2.06(m, 1H); 1.98(m, 1H); 1.58(m, 1H); 1.43(m, 1H); 1.36-1.14(m, 17H); 1.09(dd, J1=12.35Hz, J2=24.34Hz, 2H); 0.80(t, J=6.85Hz, 3H, Me). 13C-NMR (100MHz, CD3OD, 25°C): δ=65.8; 55.2; 51.1; 40.1; 37.6; 33.7; 31.7; 29.2; 29.1; 29.0; 25.0; 22.4; 18.5; 13.1. LC-MS: 100% (purity), m/e: 242(M+1). Cal. For C15H32NO2 (M+H): 242.2483; Found: 242.2478. $[\alpha]_{D=}$-5.5° (c 0.62, MeOH)

(2R,4S,6S)-2-methyl-6-nonylpiperidin-4-ol [(+)-241D] Starting from 14 similar hydrogenation procedure as in preparing 11 was applied to give (+)-241D as gray solid (Yield, 72%). 1H-NMR (400MHz, CD3OD, 25°C): δ=3.72(tt, J1=4.42Hz, J2=11.06Hz); 3.16(m, 1H); 3.05(m, 1H); 2.13(m, 1H); 2.05(m, 1H); 1.62(m, 1H); 1.47(m, 1H); 1.41-1.18(m, 17H); 1.14(m, 2H); 0.80(t, J=6.84Hz, 3H, Me). 13C-NMR (100MHz, CD3OD, 25°C): δ=66.5; 56.8; 52.9; 40.6; 38.1; 34.4;

33.1; 30.6; 30.52; 30.55; 30.4; 26.2; 23.8; 19.2; 14.5. LC-MS: 100% (purity), m/e: 242(M+1). Cal. For C15H32NO2 (M+H): 242.2483; Found: 242.2478. $[\alpha]_D$=+5.8^o (c 0.69, MeOH)

(2S,6R)-2-methyl-6-undecylpiperidine (Isosolenopsin A) Starting from 17 similar hydrogenation procedure as in preparing 12 was applied to give Isosolenopsin A as colorless oil (Yield, 45%). 1H-NMR (400MHz, CD3OD, 25^{o}C): δ=3.07(m, 1H); 2.94(m, 1H); 1.92(m, 1H); 1.83(m, 2H); 1.75-1.52(m, 1H); 1.52-1.37(m, 2H); 1.37-1.09(m, 23H); 0.80(t, J=6.73Hz, 3H, Me). 13C-NMR (100MHz, CD3OD, 25^{o}C): δ=57.4; 53.4; 33.5; 31.7; 30.3; 29.3; 29.2; 29.0; 27.7; 24.7; 22.3; 22.1; 18.1; 13.0. LC-MS: 100% (purity), m/e: 254 (M+1). Cal. For C17H36N (M+H): 254.2847; Found: 254.2842. $[\alpha]_D$=+9.7^o (c 0.71, $CHCl_3$)

(R)-2-(4-chlorobutyl)-1-((R)-1-(4-methoxyphenyl)ethyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (25) To a round-bottom flask containing (R)-1-(4-methoxyphenyl)ethanamine (6a) (151mg, 1mmol, 1eq.) in dried DCM (0.1M) solution was added 4AMS (500mg/mmol) followed by 5-chloropentanal (24) (120mg, 1mmol, 1eq). After stirring at room temperature for 10mins, (1-Methoxy-buta-1,3-dienyloxy)-trimethyl-silane (7) (292mg, 1.2mmol, 1.2eq) was added and the solution was cooled to -78^{o}C. Tin (II) triflate (412mg, 1mmol, 1eq.) was then added and the reaction was stirred at this temperature for 8hrs. The reaction temperature was raised to 0^{o}C and kept at the same temperature overnight. LC-MS analysis of the reaction showed the disappearance of the starting materials. The reaction was quenched with saturated aqueous solution of sodium bicarbonate and solids were removed via filtration. The reaction mixture was then extracted with DCM (5X15ml). The combined organic phase was treated with acetic acid and the resulting solution was stirred at room temperature for 1hr until only compound 25 was observed from LC-MS analysis. The solution was then basified by treating with saturated aqueous solution of sodium bicarbonate, washed with brine and dried over sodium

sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (ethyl acetate/hexane) to afford the product 25 (ethyl acetate/hexane=5/1) as colorless oil (184mg, 55% yield). ^{1}HNMR (400MHz, CDCl3, 25^{o}C): δ=7.23(d, J=8.45Hz, 2H); 6.90(d, J=8.80Hz, 2H); 5.06(q, J=7.01Hz, 1H); 4.95(s, 1H); 3.82(s, 3H); 3.50(m, 2H); 3.25(m, 1H); 2.28(dd, Ja=5.94Hz, Jb=16.58Hz 1H); 2.17(s, 3H); 2.04(m, 1H); 1.72(m, 2H) 1.63(d, J=7.07Hz, 3H); 1.38 (m, 3H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ= 190.4; 160.0; 159.2; 133.1; 127.6; 114.1; 100.1; 55.4; 55.3; 52.7; 44.7; 38.0; 32.3; 29.4; 23.4; 21.5; 17.5. LC-MS: 100% (purity), m/e: 336 (M+1). Cal. For C19H27ClNO2 (M+H): 336.1730; Found: 336.1725.

(R)-2-(4-chlorobutyl)-6-methyl-2,3-dihydropyridin-4(1H)-one (26) To the flask containing compound 25 (120mg, 0.36mol) was added TFA (2ml, 99%) at room temperature and the resulting solution was stirred at room temperature overnight. TFA was removed by vacuum and the residue was re-dissolved in DCM (10ml). The solution was washed with saturated aqueous solution of sodium bicarbonate and brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (DCM/Methanol) to afford the product as colorless oil (72mg, 100% yield). ^{1}H-NMR (400MHz, CDCl3, 25^{o}C): δ=4.59(s, 1H); 4.85(s, 1H); 3.56(m, 1H); 2.32(dd, Ja=5.07Hz, Jb=16.10Hz); 2.19(dd, Ja=5.07Hz, Jb=16.10Hz); 1.91(s, 3H); 1.74(m, 2H); 1.63(m, 2H); 1.53(m, 1H); 1.47(m, 2H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ= 190.4; 162.5; 98.8; 53.0; 44.7; 40.9; 33.3; 32.2; 22.7; 21.2. LC-MS: 100% (purity), m/e: 202 (M+1). Cal. For C10H17ClNO (M+H): 202.0998; Found: 202.0993

(R)-4-methyl-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (27) To the DMF (5ml) solution contained 26 (95mg, 0.47mmol) added sodium hydride (56mg, 60% , 3eq.) at 0^{o}C. The reaction was stirred at this temperature for 2hrs before quenched with saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (10mlx3) and the combined

organic phase was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (ethyl acetate/hexane) to afford the product as colorless oil (74mg, 96% yield). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ=4.93(s, 1H); 3.72(m, 1H); 3.29(m, 1H); 2.75(td, J1=2.91Hz, J2=12.76Hz, 1H); 1.92(s, 3H); 1.80(m, 1H); 1.68(m, 1H); 1.58(m, 2H); 1.43(m, 2H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=191.5; 163.0; 101.8; 58.6; 48.1; 42.9; 31.4; 25.8; 23.7; 21.2. LC-MS: 100% (purity), m/e: 166 (M+1) Cal. For C10H16NO (M+H): 166.1231; Found: 166.1226.

(2R,4S,9aR)-4-methyloctahydro-1H-quinolizin-2-ol (28) To flask contained 27 (85mg, 0.51mmol) in THF (3ml) added L-Selectride (1M in THF, 2,5ml , 5eq.) at 0^{o}C. The reaction was stirred at this temperature for 2hrs before quenching with saturated aqueous solution of sodium bicarbonate. The mixture was extracted with mixed solvent (chloroform/isopropanol 3/1, 10mlx3) and the combined organic phase was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (chloroform/methanol) to afford the product as colorless oil (70mg, 81% yield). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ=4.13(s, 1H, OH); 3.70(m, 1H); 3.63(m, 1H); 3.40(m, 1H); 3.31(m, 1H); 2.45(m, 1H); 2.25(t, J=13.21Hz, 1H); 2.15(t, J=12.77Hz, 2H); 1.94(m, 3H); 1.83(m, 2H); 1.69(m, 1H); 1.44(m, 1H); 1.42(d, J=6.30Hz, 3H, Me). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=61.8; 59.2; 56.1; 50.9; 38.6; 37.4; 30.1; 23.3; 22.6; 17.2. LC-MS: 100% (purity), m/e: 170 (M+1). Cal. For C10H20NO (M+H): 170.1544; Found: 170.1539

(4S,9aR)-4-methylhexahydro-1H-quinolizin-2(6H)-one (29) To flask contained 27 (68mg, 0.41mmol) in THF (2ml) added $BF_3.OEt_2$ (57µl, 1.1eq.) at -78^{o}C. The reaction was stirred at this temperature for 10mins before adding lithium triethylborohydride "super hydride" (1M in THF, 0.49ml, 1.2eq). After stirring at -78^{o}C for 2hrs, the reaction was quenched with saturated

aqueous solution of sodium bicarbonate. The mixture was extracted with mixed solvent (chloroform/isopropanol 3/1, 10mlx3) and the combined organic phase was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (chloroform/methanol) to afford the product as colorless oil (37mg, 54% yield). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ=3.27(m, 1H); 2.33(m, 3H): 2.22(m, 2H): 2.12(t, J=10.95Hz, 1H); 1.78(m, 1H); 1.68(m, 2H); 1.58(m, 2H); 1.36(m, 1H); 1.20(m, 1H); 1.14(d, J=5.72Hz, 3H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=207.9; 61.6; 58.8; 50.5; 49.2; 48.1; 33.6; 25.4; 23.4; 20.2. LC-MS: 100% (purity), m/e: 168 (M+1). Cal. For C10H18NO (M+H): 168.1388; Found: 168.1383. $[\alpha]_D$=-16.9^{o} (c, 0.28, $CHCl_3$)

(R)-4,4-dimethylhexahydro-1H-quinolizin-2(6H)-one (30a) To the flask contained 27 (42mg, 0.25mmol) in dried THF (2ml) added TMS-Cl (80µl, 3eq.) at 0^{o}C. The reaction was stirred at this temperature for 10mins before adding methyl magnesium bromide (2M in ethyl ether, 0.18ml, 1.5eq). After stirring at 0^{o}C for 2hrs, the reaction temperature was allowed to raise to room temperature overnight. Quenched by saturated aqueous solution of sodium bicarbonate the reaction mixture was extracted with mixed solvent (chloroform/isopropanol 3/1, 10mlx3) and the combined organic phase was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (chloroform/methanol) to afford the product as colorless oil (28mg, 65% yield). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ=3.0(m, 1H); 2.48(m, 2H); 2.15(m, 2H); 1.99(m, 2H); 1.60(m, 3H); 1.45(m, 1H); 1.27(m, 1H); 1.10(m, 1H); 1.13(s, 3H); 0.81(s, 3H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=209.1; 58.0; 55.8; 55.4; 48.2; 45.4; 34.6; 29.6; 25.8; 23.8; 15.8. LC-MS: 100% (purity), m/e: 182 (M+1). Cal. For C11H20NO (M+H): 182.1544; Found: 182.1539.

(4S,9aR)-4-methyl-4-vinylhexahydro-1H-quinolizin-2(6H)-one (30b) Starting from 27 similar addition procedure as in preparing 30a was applied to give 30b as colorless oil (Yield, 57%). 1H-NMR (400MHz, CDCl3, 25^{o}C): δ= 5.82 (dd, J = 17.6, 11.1 Hz, 1H), 5.16 (d, J = 11.0 Hz, 1H), 5.01 (d, J = 17.5 Hz, 1H), 3.07 (m,1H), 2.84 – 2.42 (m, 2H), 2.37 (m, 1H), 2.21 (m, 3H), 1.93 – 1.72 (m, 1H), 1.63 (m, 3H), 1.57 – 1.41 (m, 1H), 1.27 (s, 3H), 1.18 (m, 2H). 13C-NMR (100MHz, CDCl3, 25^{o}C): δ=209.1; 137.1; 116.6; 61.2; 55.1; 51.9; 47.5; 44.9; 34.3; 26.5; 25.8; 23.3. LC-MS: 100% (purity), m/e: 194 (M+1). Cal. For C12H19NO (M+H): 194.1544; Found: 194.1540

(4R,9aR)-4-allyl-4-methylhexahydro-1H-quinolizin-2(6H)-one (30c) Starting from 27 similar addition procedure as in preparing 30a was applied to give 14 as colorless oil (Yield, 57%). 1H NMR (400 MHz, CDCl3, 25^{o}C) δ 5.81 – 5.44 (m, 1H), 5.15 – 4.86 (m, 2H), 3.22 – 2.97 (m, 1H), 2.80 – 2.59 (m, 1H), 2.31 (s, 2H), 2.27 – 2.11 (m, 3H), 2.08 – 1.97 (m, 2H), 1.66 (d, J = 9.9 Hz, 2H), 1.31 (m,2H), 1.18 (s, 2H), 1.15 (s, 3H). 13C NMR (101 MHz, CDCl3, 25^{o}C) δ 209.33, 133.84, 118.66, 61.04, 55.72, 51.76, 48.41, 45.38, 35.28, 34.28, 26.91, 26.43, 24.13. LC-MS: 100% (purity), m/e: 208 (M+1). Cal. For C13H22NO (M+H): 208.1701; Found: 208.1696

(1R,9aR)-1-benzyl-4-methyl-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (32b) To the flask contained 27 (42mg, 0.25mmol) in dried THF (2ml) added LiHMDS (0.3ml, 1M in THF) at -78^{o}C. The reaction was stirred at this temperature for 1hrs before adding benzyl bromide (88µl, 3eq). After stirring at 0^{o}C for 2hrs, the reaction temperature was allowed to raise to room temperature overnight. Quenched by saturated aqueous solution of sodium bicarbonate the reaction mixture was extracted with mixed solvent (Ethyl acetate, 10mlx3) and the combined organic phase was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISCO silica gel chromatography (Hexane/ethyl acetate) to afford

the product as colorless oil (49mg, 78% yield).1H NMR (400 MHz, CDCl3, 25°C) δ: 7.27 – 7.19 (m, 2H), 7.19 – 7.08 (m, 3H), 5.00 (s, 1H), 3.91 – 3.57 (m, 1H), 3.29 (dd, J = 5.9, 4.2 Hz, 1H), 2.97 – 2.62 (m, 3H), 2.62 – 2.38 (m, 3H), 2.23 (dd, J = 16.5, 10.7 Hz, 1H), 1.86 – 1.73 (m, 1H), 1.73 – 1.49 (m, 3H), 1.49 – 1.31 (m, 2H). 13C NMR (101 MHz, CDCl3, 25°C) δ= 191.2, 165.2, 139.7, 128.1, 127.8, 126.1, 100.5, 76.9, 58.2, 47.6, 42.2, 35.1, 33.9, 31.0, 25.5, 23.3. LC-MS: 100% (purity), m/e: 256 (M+1). Cal. For C17H22NO (M+H): 256.1701; Found: 256.1696

Starting from 27 similar alkylation procedure as in preparing 32b was applied to give **32a; 32c; 32d** and **32e**

(R)-4-ethyl-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (32a) Colorless oil (Yield, 82%). 1H NMR (400 MHz, CDCl3, 25°C) δ 4.99 (s, 1H), 3.81 – 3.63 (m, 1H), 3.39 – 3.19 (m, 1H), 2.74 (td, J = 12.7, 2.9 Hz, 1H), 2.47 (dd, J = 16.6, 5.9 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.17 (m, 1H), 1.79 (m 1H), 1.74 – 1.66 (m, 1H), 1.66 – 1.54 (m, 2H), 1.54 – 1.32 (m, 2H), 1.09 (t, J = 7.5 Hz, 3H). 13C NMR (101 MHz, CDCl3, 25°C) δ 191.2, 167.6, 99.4, 58.2, 47.3, 42.0, 31.0, 26.4, 25.5, 23.3, 11.9. LC-MS: 100% (purity), m/e: 180 (M+1). Cal. For C11H18NO (M+H): 180.1388; Found: 180.1383.

(R)-4-(but-3-en-1-yl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (32c) Colorless oil (Yield, 55%). 1H NMR (400 MHz, CDCl3, 25°C) δ 5.96 – 5.72 (m, 1H), 5.21 – 4.93 (m, 3H), 3.94 – 3.64 (m, 1H), 3.49 – 3.18 (m, 1H), 2.82 (td, *J* = 12.7, 2.8 Hz, 1H), 2.53 (dd, *J* = 16.4, 5.8 Hz, 1H), 2.45 – 2.19 (m, 3H), 1.92 – 1.83 (m, 1H), 1.83 – 1.74 (m, 3H), 1.69 (dd, J = 6.8, 3.6 Hz, 2H), 1.61 – 1.41 (m, 2H). 13C NMR (101 MHz, CDCl3, 25°C) δ 191.8, 165.7, 136.5, 115.9, 101.1, 58.6, 48.1, 42.8, 33.2, 32.1, 31.5, 26.0, 23.8. LC-MS: 100% (purity), m/e: 205 (M+1). Cal. For C13H20NO (M+H): 206.1545; Found: 206.1540.

(R)-tert-butyl3-(2-oxo-2,6,7,8,9,9a-hexahydro-1H-quinolizin-4-yl)propanoate (32d) Colorless oil (Yield, 79%). 1H NMR (400 MHz, CDCl3, 25^{o}C) δ 4.92 (s, 1H), 3.89 – 3.63 (m, 1H), 3.47 – 3.17 (m, 1H), 2.88 – 2.63 (m, 1H), 2.56 – 2.41 (m, 3H), 2.41 – 2.34 (m, 2H), 2.21 (dd, J = 16.4, 10.4 Hz, 1H), 1.86 – 1.75 (m, 1H), 1.75 – 1.65 (m, 1H), 1.65 – 1.52 (m, 2H), 1.52 – 1.39 (m, 2H), 1.38 (s, 9H, t-Bu). 13C NMR (101 MHz, CDCl3, 25^{o}C) δ 190.7, 170.2, 163.5, 99.6, 80.2, 57.7, 47.0, 41.7, 32.4, 30.3, 27.6, 27.1, 27.1, 24.9, 22.7. LC-MS: 100% (purity), m/e: 280 (M+1). Cal. For C16H26NO3 (M+H): 280.1913; Found: 280.1908.

(R)-4-(pent-3-yn-1-yl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (32e) Colorless oil (Yield, 61%). 1H NMR (400 MHz, CDCl3, 25^{o}C) δ 4.95 (s, 1H), 3.91 – 3.57 (m, 1H), 3.39 – 3.17 (m, 1H), 2.74 (td, J = 12.8, 2.8 Hz, 1H), 2.50 – 2.33 (m, 3H), 2.33 – 2.27 (m, 2H), 2.23 (dd, J = 16.5, 10.7 Hz, 1H), 1.89 – 1.74 (m, 1H), 1.71 (s, 3H), 1.69 – 1.65 (m, 1H), 1.65 – 1.51 (m, 2H), 1.51 – 1.33 (m, 2H). 13C NMR (101 MHz, 25^{o}C) δ 191.9, 164.5, 101.0, 77.2, 76.9, 58.6, 48.1, 42.8, 33.2, 31.4, 25.9, 23.8, 17.9, 3.5. LC-MS: 100% (purity), m/e: 218 (M+1). Cal. For C14H20NO (M+H): 218.1545; Found: 218.1541.

Acknowledgements

Dedicated to Emeritus Professor of ICCAS Prof. Dong Wang on the occasion of his 74th birthday. The author thanks Dr. Perry Gordon and Mr. Kevin Johnson for providing high resolution mass spectrometry data (HRMS) of all reported compounds. The author sincerely appreciates the management supports from Dr. John Tellew; Dr. Shifeng Pan; Dr. Dean P. Phillips and Dr. Valentina Molteni. The author is also grateful to Dr. John Tellew and Dr. Yahu A. Liu for helpful discussions and proof reading.

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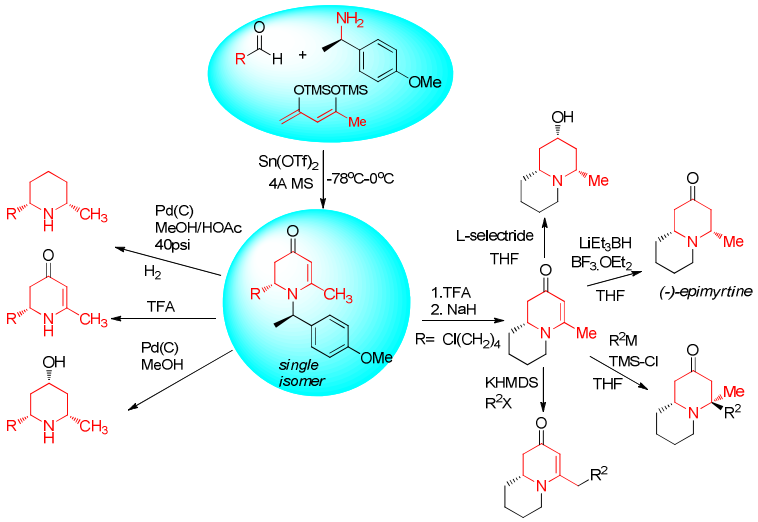

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