Building polyfunctional piperidines: a stereoselective strategy of a 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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A general method to assemble multi-substituted chiral piperidines was developed, inspired by the biosynthesis of piperidine natural products. In biosynthesis, Δ1-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 a building block, enzymatically transforming it into a Δ1-amino carbonyl intermediate 3 as the precursor to cyclize into Δ1-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-trimethylsilyl enol ether 7 was therefore investigated and was found to give cyclized chiral dihydropyridinone compound 9 as an adduct. Like Δ1-piperideine in biosynthesis, the chiral 2,3-dihydropyridinone compound 9 from VMR is a versatile intermediate for building a variety of new chiral piperidine compounds. The method was showcased by concise two-step approaches in the synthesis of the bioactive natural alkaloids (+)-241D; (−)-241D and isosolenopsin A. Furthermore, when properly functionalized substrate aldehyde 24 was employed, the corresponding dihydropyridinone adduct 25 cyclized to form a second piperidine ring, leading to a chiral polyfunctional quinolizidine enamimone 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 the various piperidine derivatives, 2 and/or 6 substituted piperidines are particularly common and interesting4 since such substitution patterns block the metabolism of the piperidine ring and potentially have a significant impact on the ring’s 3D conformation. For such reasons, installation of 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 (−)-pinidinol, (+)-241D and isosolenopsin A etc. (Fig. 1). Some of these natural alkaloids have demonstrated interesting pharmacological properties and served as valuable starting points for new drug discovery.5

The biosynthetic pathway of many piperidine-based natural alkaloids has been studied. Δ1-Piperideine 4, which forms from an intramolecular imine cyclization of a Δ1-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 Δ1-amino pentanal 3 then gives rise to the key Δ1-piperideine ring (Fig. 2). However, without nature’s
powerful enzyme tools, chemical synthesis of \( \Delta^1 \)-piperideine is tedious\(^7\) due to its instability and such intermediate is therefore not practical to be widely applied in synthesis lab like its role in biosynthesis.\(^8\) We envisioned however that similar \( \delta \)-amino carbonyl precursor for \( \Delta^1 \)-piperideine can be assembled conveniently via a vinylogous Mannich-type reaction (VMR) with an aldmine if a properly functionalized dienolate was employed. As shown in Fig. 2, cyclization of the initial \( \delta \)-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 (Fig. 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.

Results and discussion

The simple 1,3-bis-trimethylsilyl 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 \( \alpha \)-methyl benzylamine 6 was employed to form chiral aldmines \( \text{in situ} \). 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 \(-78^\circ\text{C}\) to \(0^\circ\text{C}\). 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 acyclic adducts 8 into 9 (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 \( J_{\text{Ha/Hb}} \) 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\(^{13}\) (Fig. 3).

To examine the synthetic utility of 2,3-dihydropyridinones obtained from the VMR, adduct compound 9h was selected to probe further transformations. When the compound 9h 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 \( \text{via} \) palladium catalyzed hydrogenation. Interestingly, under different hydrogenation conditions, the reduction of 9h yielded

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**Fig. 1** Examples of natural alkaloids incorporating \( \alpha \)-methyl substituted piperidines.

**Fig. 2** VMR strategy for piperidine synthesis inspired by biosynthesis.
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)\(^\text{14}\) (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 deoxygenated 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-dihydropiridinone and 2,3-dihydropridinium under different conditions.\(^\text{15}\) Presumably, 2,3-dihydropiridinone is the major species present under neutral conditions and hydrogenation led to 4-hydroxy piperidine product 11. However, under acidic conditions, the protonated 2,3-dihydropiridinium species is the major (or more reactive) species present, and hydrogenation gives the corresponding deoxygenated piperidine 12 as the major product\(^\text{16}\) (Fig. 4). Similar hydrogenations of 2,3-dihydropiridinones have been reported to yield 4-hydroxy piperidine compounds stereospecifically.  

However, to our knowledge the direct deoxygenative reduction of 2,3-dihydropiridinones is rarely reported. The results allowed accessing different substitution type piperidine compounds from 2,3-dihydropiridinones 9 by simply switching different reduction conditions.

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*.\(^\text{17}\) The alkaloid shows interesting bioactivity as a potent non-competitive blocker of acetylcholine and ganglionic nicotinic receptor channels.\(^\text{18}\) 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.\(^\text{19}\) 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-trimethylsilyl 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).

The versatile utility of such VMR approach in assembling piperidine was further exemplified 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 *solenosia* 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.\(^\text{20}\) By the similar strategy, corresponding VMR adduct 2,3-dihydro-4-pyridones 17 was obtained when dodecan 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 40 psi 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 isosolenopsin A than any other reported methods.\(^\text{21}\)
Table 1  Asymmetric three-component vinylogous Mannich reactions of 1,3-bis-trimethylsilyl 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%)                  |
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. Some natural quinolizidine alkaloids exhibit interesting pharmacological properties and serve as important starting points for the drugs discovery. Interestingly, the biosynthesis of some quinolizidine alkaloids shares the same pathway of the natural piperidine alkaloids that undergo the same \( \Delta^1 \)-piperideine intermediate \( 4 \), enzymatically starting from \( L \)-lysine. As an example, in the biosynthesis of quinolizidine alkaloids lupine, \( \Delta^1 \)-piperideine is also the key intermediate to assemble the first piperidine ring for the quinolizidine core. To build the second piperidine ring, two \( \Delta^1 \)-piperideine intermediates undergo a cross aldol-type coupling and one of the imine systems gets hydrolyzed a \( \Rightarrow \) 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 (Fig. 5). We however envisioned that in the VMR we developed, if the aldmine 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 Fig. 5, if a \( \delta \)-leaving group is incorporated in the aldmine 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 (Fig. 5).

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 \( \delta \) chloride group 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 \( \alpha \)-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 enamine (Scheme 5). We envisaged that such cyclic enamnine \( 27 \) 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 (Fig. 6).

The reduction of cyclic enamnine \( 27 \) was first explored. It was found that under the conditions of either palladium-catalyzed hydrogenation in methanol or treating \( l \)-selectride (LiBu\(_4\)BH) in THF, both alkene and carbonyl were reduced affording \( cis \)-2-hydroxyl-4-methly quinolizidine \( 28 \) as product (Scheme 6, eqn (1)). Similarly as in the reduction of \( 2,3 \)-dihydropyridinone, the reduction on quinolizidine enamnine also proceeded in stereoselective manner which is in agree with literature precedents. When the reduction was carried out with “super hydride” (LiEt\(_3\)BH) in presence of BF\(_3\)-Et\(_2\)O in THF, the alkene functionality was selectively reduced, giving \( 29 \) as natural quinolizidine alkaid (-)-epimyrtine as the product in good yield \( 27 \) (Scheme 6, eqn (2)). The results provided a concise approach for the enantioselective synthesis of such natural alkaid.

Conjugate additions to quinolizidine enamnine \( 27 \) were also explored. Although direct conjugate addition of Grignard reagents to cyclic enamnines has been previously reported, 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 (Table 2, entry 3). Under similar conditions, conjugate additions by vinyl and allyl Grignard reagents were also performed (Table 2, entries 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 (Scheme 7).

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(SiMe3)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 a methyl substituted type (Scheme 8).

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-trimethylsilyl 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 exemplified in developing novel synthesis of bioactive natural alkaloids: dendrobate alkaloids (+)-241D; (-)-241D, and iso-solenopsin 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. 1H and 13C 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⁻¹. 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 x 50 mm) column was used. Chemical shifts of NMR spectra are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). All vinyllogous Mannich reactions were carried out in oven-dried glassware under air atmosphere. 1,3-Bis-trimethylsilyl enol ether was prepared freshly following the procedure from literature.

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) (151 mg, 1 mmol, 1 eq.) in dried DCM (0.1 M) solution added 4-AMS (500 mg mmol⁻¹) followed by cyclohexane-carbaldehyde (5a) (112 mg, 1 mmol, 1 eq.). After stirring at room temperature for 10 min, 1,3-bis-trimethylsilyl enol ether 3 (292 mg, 1.2 mmol, 1.5 eq.) was added and the mixture solution was cooled to −78 °C. Tin(II) triflate (412 mg, 1 mmol, 1 eq.) was then added and the reaction was stirred at this temperature for 8 h. The reaction temperature was raised to 0 °C and kept the same temperature overnight. LC-MS analysis showed the mixture of 8a and 9a 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 (15 mL x 5). The combined organic phase was treated with acetic acid (0.1 mL) and the resulting solution was stirred at room temperature for 1 h until 8a 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 byISCO silica gel chromatography (ethyl acetate/hexane) to afford the product as colorless oil (232 mg, 71% yield). 1H-NMR (400 MHz, CDCl₃, δ 25 °C): δ = 0.87 (m, 1H); 1.30 (m, 4H); 1.41 (m, 1H); 1.55 (d, 3H, J = 6.8 Hz, CH₃–); 1.70 (m, 5H); 2.02 (m, 2H); 2.07 (s, 3H, CH₃–); 2.97 (m, 1H); 3.70 (s, 3H, OCH₃); 4.87 (s, 1H, CH); 4.94 (q, 1H, J = 6.8 Hz); 6.80 (m, 2H); 7.13 (d, 2H, J = 8.4 Hz). 13C-NMR (100 MHz, CDCl₃, δ 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/z: 328 (M + 1). Calcd for C₂₁H₃₂NO₂ (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%). ^1^H-NMR (400 MHz, CDCl₃, 25 °C): δ = 0.78 (t, 3H, J = 6.8 Hz, CH₃); 1.05 (m, 5H); 1.18 (m, 5H); 1.56 (d, 6H, J = 6.8 Hz, CH₃); 2.01 (d, 1H, J = 16.58 Hz); 2.20 (dd, 1H, J₁ = 6 Hz, J₂ = 16.51 Hz); 2.07 (s, 3H, CH₃); 3.16 (m, 1H); 3.75 (s, 3H, OCH₃); 4.87 (s, 1H, CH = ): 4.98 (q, 1H, J = 6.8 Hz); 6.83 (m, 2H); 7.16 (d, 2H, J = 8.4 Hz). ^1^C-NMR (100 MHz, CDCl₃, 25 °C): δ = 14.0; 17.5; 25.1; 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/z: 366 (M + 1). Calcd for C₂₃H₂₈NO₃ (M + H): 366.2069; found: 366.2065.

(R)-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%). ^1^H-NMR (400 MHz, CDCl₃, 25 °C): δ = 0.45 (d, J = 7.14 Hz, 3H); 1.33 (dd, J = 5.53 Hz, J₁ = 16.92 Hz, 1H); 2.04 (s, 3H); 2.41 (d, J = 16.89 Hz, 1H); 3.11 (s, 3H); 3.26 (dd, J₁ = 1.62 Hz, J₂ = 5.52 Hz); 3.70 (s, 3H, OCH₃); 4.50 (d, J = 8.80 Hz, 1H); 4.54 (q, J = 7.14 Hz, 1H); 5.09 (s, 1H); 6.74 (m, 2H); 6.98 (m, 2H); 7.18 (dd, J₁ = 7.25, J₂ = 8.83 Hz); 7.26 (m, 1H); 7.30 (m, 2H). ^1^C-NMR (100 MHz, CDCl₃, 25 °C): δ = 16.1; 21.7; 36.9; 55.3; 56.3; 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/z: 366 (M + 1). Calcd 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%). ^1^H-NMR (400 MHz, CDCl₃, 25 °C): δ = 0.47 (dd, J₁ = 12.13 Hz, J₂ = 29.37 Hz, 1H); 1.69 (d, J = 7.21 Hz, 3H); 1.97 (m, 1H); 2.08 (s, 3H); 3.08 (s, 3H); 3.44 (dd, J₁ = 6.88 Hz, J₂ = 8.23 Hz, 1H); 3.71 (s, 3H); 4.49 (d, J = 9.19 Hz, 1H); 4.95 (s, 1H); 5.01 (q, J = 7.21 Hz, 1H); 6.78 (m, 2H); 7.20 (m, 7H). ^1^C-NMR (100 MHz, CDCl₃, 25 °C): δ = 19.3; 21.7; 36.5; 55.3; 56.9; 57.1; 58.4; 79.6; 102.0; 114.1; 127.6; 128.2; 128.6; 134.3; 139.1; 159.0; 161.0; 190.5. LC-MS: 100% (purity), m/z: 366 (M + 1). Calcd for C₂₃H₂₈NO₃ (M + H): 366.2069; found: 366.2065.
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 = 7.20 Hz, 1H); 6.79 (m, 2H); 7.10 (m, 2H); 7.21 (m, 5H).

13C-NMR (100 MHz, CDCl3, 25°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; 55.3; 55.2 38.0; 26.7; 25.9; 21.5; 17.4. LC-MS: 100% (purity), m/z: 394 (M + 1). Calcd 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 (400 MHz, CDCl3, 25°C): δ = 1.24 (d, J = 7.2 Hz, 3H); 2.18 (d, J = 16.3 Hz, 1H); 2.23 (s, 3H); 2.71 (dd, J1 = 7.53 Hz, J2 = 16.35 Hz, 1H); 3.739 (s, 3H); 4.42 (m, 1H); 4.96 (s, 1H); 5.12 (q, J = 6.97 Hz, 1H); 6.85 (m, 2H); 7.11 (m, 3H); 7.18 (m, 4H).

13C-NMR (100 MHz, CDCl3, 25°C): δ = 17.7; 21.6; 42.6; 55.4; 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/z: 322 (M + 1). Calcd for C21H24NO2 (M + H): 322.1807; found: 322.1802.

(S)-1-((S)-1-(4-Methoxyphenyl)ethyl)-6-methyl-2-nonyl-2,3-dihydropyridin-4(1H)-one (14). Colorless oil (yield, 76%). 1H-NMR (400 MHz, CDCl3, 25°C): δ = 1.19 (m, 2H); 1.73 (m, 1H); 2.19 (m, 1H); 2.19 (m, 1H); 2.08 (s, 3H); 1.58 (m, 1H); 1.38 (d, J = 7.07 Hz, 3H, -CH3). 13C-NMR (100 MHz, 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/z: 350 (M + 1). Calcd for C23H28NO2 (M + H): 350.2120; found: 350.2115.

Table 2 Conjugate addition reactions of quinolizidine enaminone 27

| Entry | RM         | Conditions                        | Products (yield) |
|-------|------------|-----------------------------------|------------------|
| 1     | MeMgBr     | THF (0-RT)                        | No reaction      |
| 2     | MeMgBr/CuI | THF (0-RT)                        |                  |
| 3     | MeMgBr     | THF/TMS-Cl (3 eq.) (0-RT)         |                  |
| 4     | VinylMgBr  | THF/TMS-Cl (3 eq.) (0-RT)         |                  |
| 5     | AllylMgBr  | THF/TMS-Cl (3 eq.) (0-RT)         |                  |
Table 3  Alkylation of quinolizidine enaminone 27

| Entry | RX | Yield (%) |
|-------|----|-----------|
| 1     |    | 32a (82%) |
| 2     |    | 32b (78%) |
| 3     |    | 32c (55%) |
| 4     |    | 32d (79%) |
| 5     |    | 32e (61%) |

99.8; 55.4; 55.3; 52.8; 38.0; 31.8; 30.1; 29.6; 29.2; 25.9; 22.6; 21.5; 17.5; 14.1. LC-MS: 100% (purity), m/z: 372 (M + 1). Calcd for C_{24}H_{38}NO_{2} (M + H): 372.2902; found: 372.2897.

(R)-1-[(R)-1-(4-Methoxyphenylethyl)-6-methyl-2-undecyl-2,3-dihydropyridin-4(1H)-one (17). Colorless oil (yield, 66%). 1H-NMR (400 MHz, CDCl_{3}, 25 °C): δ = 7.21 (d, J = 8.62 Hz, 2H); 6.88 (d, J = 8.62 Hz, 2H); 5.03 (q, J = 6.99 Hz, 1H); 4.92 (s, 1H); 3.97 (s, 3H, OMe); 3.22 (m, 1H); 2.25 (dd, J_{1} = 5.88 Hz, J_{2} = 16.49 Hz 1H); 2.14 (s, 3H); 2.04 (m, 2H); 1.61 (d, J_{1} = 6.99 Hz, 3H); 1.35–1.10 (m, 20H); 0.86 (t, J = 6.86 Hz, 3H). 13C-NMR (100 MHz, CDCl_{3}, 25 °C): δ = 190.6; 159.9; 159.1; 133.3; 127.6; 114.0; 99.9; 55.4; 55.3; 52.8; 38.0; 31.8; 30.1; 29.6; 29.2; 25.9; 22.6; 21.5; 17.5; 14.1. LC-MS: 100% (purity), m/z: 400 (M + 1). Calcd for C_{13}H_{24}NO_{2} (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-(6-(4-methoxyphenylethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (9h) (75 mg, 0.21 mmol) added TFA (1.5 mL) and the solution was stirred at room temperature overnight. TFA was removed by vacuum and the residue was re-dissolved in DCM (10 mL). 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 (46 mg, 100% yield). 1H-NMR (400 MHz, CDCl_{3}, 25 °C): δ = 7.22 (m, 2H); 7.14 (m, 3H); 4.59 (s, 1H); 4.84 (s, 1H); 3.57 (sex, J = 6.18 Hz, 1H); 2.67 (m, 1H); 2.61 (m, 1H); 2.34 (m, 1H); 2.22 (dd, J_{1} = 12.5 Hz, J_{2} = 6.98 Hz, 1H); 1.93 (m, 1H); 1.85 (m, 1H); 1.81 (s, 3H). 13C-NMR (100 MHz, CDCl_{3}, 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/z: 216 (M + 1). Calcd for C_{13}H_{24}NO (M + H): 216.1388; found: 216.1383.

(S)-6-Methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (11). To a flask contains methanol solution (0.1 M) of 1(S)-1-(6-(4-methoxyphenylethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (9h) (120 mg, 0.34 mmol) added powder of palladium on carbon (12 mg) cautiously under nitrogen stream. The reaction was stirred at room temperature for 4 h 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 (35 mg, 77% yield). NMR (400 MHz, CD_{2}OD, 25 °C): δ = 7.10 (m, 2H); 7.14 (m, 2H); 7.05 (t, J = 7.13 Hz, 1H); 3.46 (dd, J_{1} = 4.54 Hz, J_{2} = 7.83 Hz, J_{3} = 11.08 Hz); 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 (dd, J = 6.37 Hz, 3H), -Me); 0.91 (m, 2H). 13C-NMR (100 MHz, CD_{2}OD, 25 °C): δ = 143.3; 129.5; 124.9; 126.9; 69.6; 55.6; 51.4; 43.9; 41.5; 39.3; 33.3; 22.1. LC-MS: 100% (purity), m/z: 220 (M + 1). Calcd for C_{14}H_{26}NO (M + H): 220.1701; found: 220.1696.

(2R,4S,6S)-2-Methyl-6-phenethylpiperidin-4-ol (12). To Parr shaker reaction vessel contains (0.1 M) of 1(S)-1-(6-(4-methoxyphenylethyl)-6-methyl-2-phenethyl-2,3-dihydropyridin-4(1H)-one (5h) (120 mg, 0.34 mmol) in mixed solvent of methanol (5 mL) and acetic acid (5 mL) added powder of palladium on carbon (36 mg) cautiously under nitrogen stream. The reaction was then carried out by Parr shaker hydrogenation apparatus under 40 psi overnight. After filtration to remove catalyst, the solvent was removed by vacuum and the crude product was redissolved in mixture of chloroform and 2-propanol (3/1, 15 mL). 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...
ISOCO silica gel chromatography (DCM/methanol) to afford the product as colorless oil (yield, 61%) [29 mg, 43% yield]. 3H-NMR (400 MHz, CD3OD, 25 °C): δ = 7.26–6.21 (m, 29H), 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 = 6.41 Hz, 3H, Me). 13C-NMR (100 MHz, CD3OD, 25 °C): δ = 141.9; 129.7; 129.4; 127.4; 58.3; 54.8; 36.9; 32.3; 31.8; 29.2; 23.6; 19.8. LC-MS: 100% (purity), m/z: 204 (M + 1). Caled for C14H22N2 (M + H): 204.1752; found: 204.1747.

(25,4R,6R)-2-Methyl-6-nonylpiperidin-4-ol ([–]241D). Starting from 15 similar hydrogenation procedure as in preparing 11 was applied to give (–)241D as gray solid (yield, 69%). 3H-NMR (400 MHz, CD3OD, 25 °C): δ = 3.66 (t, J = 4.51 Hz, JZ = 11.09 Hz); 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 = 12.35 Hz, JZ = 24.34 Hz, 2H); 0.80 (t, J = 6.85 Hz, 3H, Me). 13C-NMR (100 MHz, CD3OD, 25 °C): δ = 66.5; 56.8; 55.2; 51.1; 40.1; 37.6; 33.7; 31.7; 29.2; 29.1; 29.0; 25.2; 18.5; 13.1. LC-MS: 100% (purity), m/z: 242 (M + 1). Caled for C15H32NO2 (M + H): 242.2483; found: 242.2478 [α]D = +5.5° (C, 0.62, MeOH).

(2R,4R,6S,8S)-2,3-Dihydropyridin-4(1H)-one (26). To the flask containing compound 25 (120 mg, 0.36 mol) was added TFA (2 mL, 99%) at room temperature and the resulting solution was stirred at room temperature overnight. TFA was removed by vacuum and the residue was redissolved in DCM (10 mL). 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 ISOCO silica gel chromatography (DCM/methanol) to afford the product as colorless oil (72 mg, 100% yield). 3H-NMR (400 MHz, CD3OD, 25 °C): δ = 4.59 (s, 1H); 4.85 (s, 1H); 3.56 (m, 1H), 2.32 (dd, J1 = 5.07 Hz, JZ = 16.10 Hz); 2.19 (dd, J1 = 5.07 Hz, JZ = 16.10 Hz); 1.91 (s, 3H); 1.74 (m, 2H); 1.63 (m, 2H); 1.53 (m, 1H); 1.47 (m, 2H). 13C-NMR (100 MHz, CD3OD, 25 °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/z: 202 (M + 1). Caled for C10H17CINO (M + H): 202.0998; found: 202.0993.

(1R)-1-Methyl-7,8,9,9e-tetrahydro-1H-quinolin-2(6H)-one (27). To the DMF (5 mL) solution contained 26 (95 mg, 0.47 mmol) added sodium hydride (56 mg, 60%, 3 eq.) at 0 °C. The reaction was stirred at this temperature for 2 h before quenched with saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (10 mL × 3) and the combined organic phase was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by ISOCO silica gel chromatography (ethyl acetate/hexane) to afford 27 (74 mg, 96% yield). 3H-NMR (400 MHz, CD3OD, 25 °C): δ = 4.93 (s, 1H); 3.72 (m, 1H); 3.29 (m, 1H); 2.75 (t, J = 6.01 Hz, 2H, 1H); 2.27 (td, J1 = 2.91 Hz, JZ = 12.76 Hz, 2H, 1H); 1.92 (s, 3H), 1.80 (m, 1H); 1.68 (m, 1H), 1.58 (m, 2H), 1.43 (m, 2H). 13C-NMR (100 MHz, CD3OD, 25 °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/z: 166 (M + 1). Caled for C10H17N4O (M + H): 166.1231; found: 166.1226.

(2R,4A,9eR)-4-Methyloctahydro-1H-quinolin-2-ol (28). To flask contained 27 (85 mg, 0.51 mmol) in THF (3 mL) added t-selectride (1 M in THF, 2.5 mL, 5 eq.) at 0 °C. The reaction was stirred at this temperature for 2 h before quenching with saturated aqueous solution of sodium bicarbonate. The mixture was extracted with mixed solvent (chloroform/isopropanol 3:1, 10 mL × 3) and the combined organic phase was washed with brine and dried over sodium sulfate. After concentration, the
To 3.07 (m, 1H), 2.84 (m, 1H), 2.84–2.42 (m, 2H), 2.37 (m, 1H), 2.13 (m, 1H), 1.93–1.72 (m, 1H), 1.63 (m, 3H), 1.57–1.41 (m, 1H), 1.27 (s, 3H), 1.10 (m, 2H). 13C-NMR (100 MHz, CDCl3, 25 °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/z: 170 (M + 1). Caled for C16H30NO (M + H): 232.1544; found: 232.1543.

(4R,9R)-4-Allyl-1-methylhexahydro-1H-quinolizin-2(6H)-one (30). Starting from 27 similar addition procedure as in preparing 30a was applied to give 30 as colorless oil (yield, 57%). 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, 3H); 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 = 191.2; 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/z: 205 (M + 1). Caled for C16H30NO (M + H): 232.1543; found: 232.1542.
(R)-tert-Butyl-3-(2-oxo-2,6,7,8,9,9a-hexahydro-1H-quinozin-4-yl)propanoate (32d). Colorless oil (yield, 79%). 1H NMR (400 MHz, CDCl3, 25 °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 °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/z: 280 (M + H): 280.1913; found: 280.1908.

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