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Diastereoselective total synthesis of 3,6-disubstituted piperidine alkaloids, (3*R*,6*S*)-*epi*-pseudoconhydrine and (3*R*,6*R*)-pseudoconhydrine

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In memory of Dr. K. Anji Reddy, the founder of Dr. Reddy's Laboratories Ltd.

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ABSTRACT

Diastereoselective total synthesis of 3,6-disubstituted piperidine alkaloids, *epi*-pseudoconhydrine (**1**) and pseudoconhydrine (**2**) has been developed starting from enantiopure (*S*)-epichlorohydrin. The key steps in the synthesis of these alkaloids involved α-aminobutyrolactone ring opening with *N*,*O*-dimethyhydroxyl amine followed by a Grignard reaction and cascade debenzylation-reductive aminative cyclization under hydrogenation conditions. High de was obtained in the synthesis of *epi*-pseudoconhydrine (**1**).

Development of new synthetic methodologies for the enantioselective and diastereoselective synthesis of functionalized chiral piperidines has achieved significant importance in the recent past, because of their widespread presence in several biologically active natural and unnatural products.[1] Cassine (**3**),[2] spectaline (**4**),[3] deoxocassine (**5**), azimic acid (**6**), carpamic acid (**7**), 5-hydroxy sedamine (**8**), and prosopinine (**9**) are few of the biologically active piperidine based natural products (Fig. 1) with varied biological activities. These six membered nitrogen heterocyclic natural products exhibit antibiotic and anesthetic properties.[4] Pseudoconhydrine (**2**) is one of the difunctionalized piperidine based alkaloids, isolated from poison Hemlock, *Conium maculatum* L.,[5] along with coniine, *N*-methylconiine, γ-coniceine, and conhydrine. The (−) pseudoconhydrine (**2**) is (3*R*,6*R*)-6-propylpiperidin-3-ol with *trans* stereochemical relationship between the substituents on a piperidine frame work, whereas (+)-*epi*-pseudoconhydrine (**1**) has a *cis* (3*R*,6*S*) stereochemical relationship. Similar to *epi*-pseudoconhydrine (**1**), *cis* stereochemical relationship between 3,6-disubstitution on piperidine ring has also been found in a number of natural products such as 5-hydroxy sedamine (**8**), azimic acid (**6**), carpamic acid (**7**), and cassine (**3**).[6]

Though thermodynamically favored 3,6-*trans*-diastereoselective synthesis of pseudoconhydrine (**2**) is well reported,[7] the synthesis of challenging *cis* isomer, that is, *epi*-pseudoconhydrine (**1**) has limited precedence in the literature.[8] The racemic pseudoconhydrine synthesis is reported way back in 1949 by Leo Marion and W. F. Cockburn et al. starting from appropriately substituted pyridine derivative.[9] Diastereoselective synthesis of pseudoconhydrine is developed from homochiral *N*-alkenylurethane[7b] and also from *N*-Boc-2-acyloxazolidines.[7k] The ring expansion strategy of

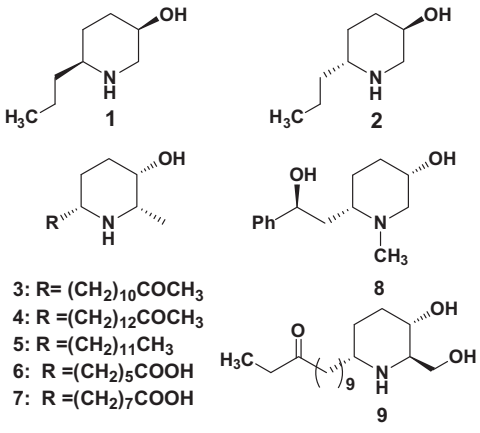

Figure 1. Natural products containing piperdin-3-ol framework.

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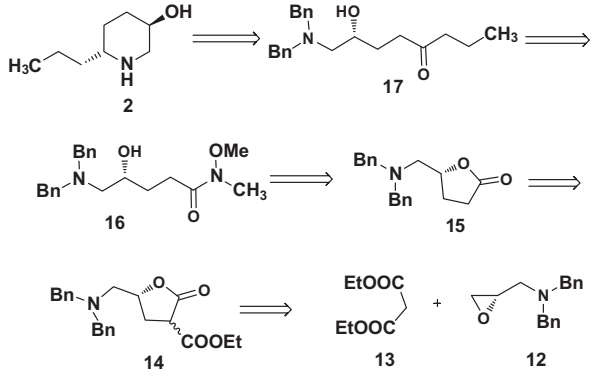
appropriately substituted dihydrofuranone derivatives has been utilized in the synthesis of pseudoconhydrine and *epi*-pseudoconhydrine.[8b] Harrity and co-workers reported the cycloaddition reaction of substituted aziridines with Pd–trimethylenemethane complexes for the synthesis of pseudoconhydrine.[10] Other noteworthy syntheses of pseudoconhydrine and *epi*-pseudoconhydrine includes tandem hydroformylation–condensation reaction,[7t] ring expansion of the substituted proline derivatives[7h], and also the metal-free regioselective aminotrifluoroacetoxylation of alkenes.[11]

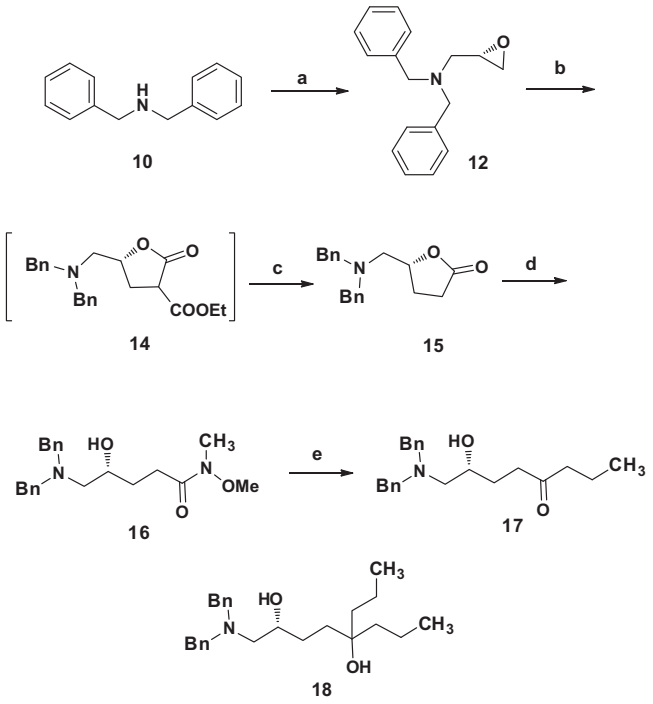
Most of these *epi*-pseudoconhydrine (**1**) and pseudoconhydrine (**2**) syntheses gave the product in high yields and *de* and in some cases with high *ee*, the use of complex reagents, and unstable intermediates makes some of these syntheses quite difficult to perform on higher scales. Some of these reported syntheses although began with chirally pure starting materials, the final products were isolated as diastereomeric mixtures.

As part of our continued efforts to develop new methodologies for the synthesis of biologically active natural and unnatural products,[12] herein we report our successful efforts toward the total synthesis of (+)-*epi*-pseudoconhydrine (**1**) and (−)-pseudoconhydrine (**2**) starting with enantiomerically pure (*S*)-epichlorohydrin. The retrosynthetic analysis of pseudoconhydrine (**2**) is provided in Scheme 1. Pseudoconhydrine (**2**) could be obtained from chiral γ-hydroxyketone **17** by a cascade debenzylation-stereocontrolled reductive amination process. The ring opening of chiral α-aminobutyrolactone **15** with *N*,*O*-dimethylhydroxylamine followed by Grignard reaction would provide a direct access to γ-hydroxyketone **17**. Chiral α-aminobutyrolactone **15** in turn could be obtained from dihydrofuranone-3-carboxylate (**14**) formed by the reaction of α-aminoepoxide (**12**) and diethyl malonate (**13**).

We initiated the synthesis of (−)-pseudoconhydrine (**2**) from enantiomerically pure (*S*)-epichlorohydrin **11**, and dibenzylamine **10**. Thus dibenzylamine **10** was reacted with (*S*)-epichlorohydrin **11** in the presence of sodium hydroxide at 65–70 °C under neat reaction conditions and the required product α-aminoepoxide **12** was isolated in 95% yield with SOR, +6.5°. The oxirane ring in **12** was opened with diethyl malonate **13** in THF, in the presence of freshly prepared sodium ethoxide to yield (5*R*)-ethyl 5-((dibenzylamino)methyl)-2-oxotetrahydrofuran-3-carboxylate **14**, which was then subjected to in situ hydrolysis and decarboxylation under Krapcho conditions.[13] The product (*R*)-5-((dibenzylamino)methyl)dihydrofuran-2(3*H*)-one **15** was isolated in 51% of overall yield. Though ring opening of α-aminobutyrolactone **15** with *n*-propyl magnesium bromide was attempted, the reaction did not yield the expected product (*R*)-8-(dibenzylamino)-7-hydroxyoctan-4-one (**17**), and unwanted tertiary alcohol **18** was isolated as the major product (Scheme 2). Thus to synthesis γ-hydroxyketone **17**, a stepwise approach was explored. The magnesium *N*,*O*-dimethylhydroxylamine was generated from Me(MeO)NH under Bodrouxs reaction conditions using isopropyl magnesium chloride, which was then used for the ring opening of **15** and the corresponding Weinreb amide **16** was isolated in 75% yield.[14] The Weinreb amide **16** was then reacted with excess *n*-propyl magnesium bromide and the product γ-hydroxyl ketone **17** was obtained in 70% yield after column chromatographic purifications.

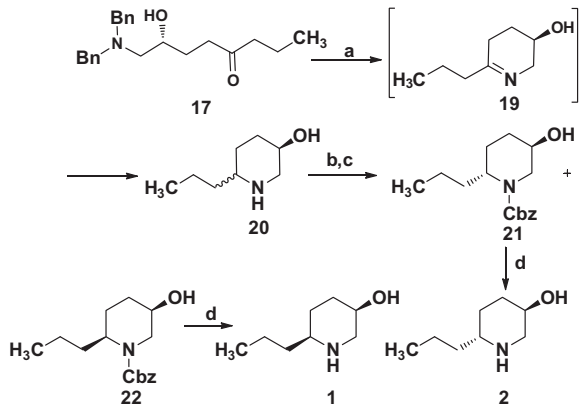


Scheme 1. Retrosynthesis.



Scheme 2. (a) *S*-Epichlorohydrin (**11**), NaOH, 65–70 °C, 95% (b) Na, EtOH, Diethyl malonate (**13**), RT (c) LiCl, DMSO, 120–130 °C (d) HCl.HN(OMe)Me, *i*-PrMgCl, THF, −5 °C (e) *n*-PrMgBr, THF, 0–10 °C.

A one pot three-step cascade reaction which involves debenzylation, cyclization, and reductive amination was then investigated on **17** to get the required natural product **2**.[15] Thus γ-hydroxy ketone **17** was subjected for hydrogenation reaction with 10% Pd/C in ethanol at room temperature under 30 psi hydrogen pressure (Scheme 3). The debenzylation, concomitant reductive amination reaction on **17** resulted the *epi*-pseudoconhydrine (**1**) and pseudoconhydrine (**2**), in 1.7:1 *cis*:*trans* diastereoselectivity. Our subsequent efforts to improve the diastereoselectivity during the reductive amination reaction under these conditions were not successful.

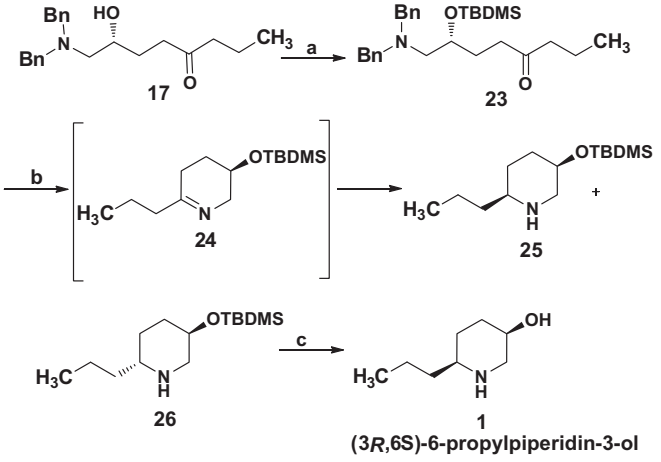


Scheme 3. (a) 10% Pd/C, EtOH, RT (b) CbzCl, Na_2CO_3, THF–H_2O, RT (c) Separation by column chromatography (d) 10% Pd/C, EtOH.

Our efforts toward the separation of the diastereomers (**20**) by crystallization or by column chromatography were not successful, and thus decided to separate these diastereomers by protection–deprotection protocols. The *N*-Cbz protection was performed on the diastereomeric pair (**20**)[7j] and individual *N*-Cbz protected piperidines **21** and **22** were separated by column chromatography. *N*-Cbz deprotection[16] was then carried on **21** and **22** to yield the pseudoconhydrine (**2**) and *epi*-pseudoconhydrine (**1**). The *epi*-pseudoconhydrine (**1**)[19], and (−)-pseudoconhydrine (**2**)[17], thus obtained were confirmed by spectral and analytical data and found to be identical with the reported literature values. [(−)-Pseudoconhydrine (**2**): mp 184.48 °C (water); lit.[7t] mp 185–185.5 °C], specific optical rotation, $[\alpha]_D^{25} = -5.5°$ {*c* 0.26, EtOH (free base)}; lit.[7h] $[\alpha]_D^{25} = -6°$ (*c* 1.05, MeOH, HCl salt), lit.,[10] $[\alpha]_D^{25} = -11.4°$ (*c* 0.99, CH_2Cl_2, free base). {*epi*-Pseudoconhydrine (**1**) $[\alpha]_D^{25} = +9.4°$ (*c* 1.0, MeOH, HCl salt)}; lit.[7b], $[\alpha]_D^{25} = +9.24°$, MeOH. {lit. data for the (−) enantiomer,[7r] $[\alpha]_D^{25} = -11.1°$ (*c* 1.0, EtOH)}.

To increase the diastereoselectivity during the hydrogenation reaction, which involves debenzylation and reductive aminative cyclization, we decided to protect the –OH group in γ-hydroxyketone **17** with a bulky protecting group (Scheme 4). The hydroxyl group in **17** was protected with TBDMS using TBDMSCl/imidazole in the presence of a catalytic amount of DMAP and the product **23** was isolated in 82% yield as viscous liquid. The cascade debenzylation-reductive aminative cyclization on **23** with 10% Pd/C under hydrogenation conditions yielded a mixture of TBDMS protected *epi*-pseudoconhydrine **25**, and TBDMS protected pseudoconhydrine **26** in 9:1 diastereomeric ratio in 91% yield. The deprotection of TBDMS group in **25** and **26**[18] and further purification by column chromatography afforded (+)-*epi*-pseudoconhydrine (**1**) as a single diastereomer in 76% yield. The spectral data[19] of our synthetic (+)-*epi*-pseudoconhydrine (**1**) are in accordance with the reported values.[7b]

The diastereoselectivity in the cascade debenzylation-reductive aminative cyclization is probably due to the increased steric bulkiness of O-TBDMS group, which directs the hydrogenation from its *anti* phase as shown in Fig. 2. The hydrogenation of imine in **24** will occur from less hindered β-face, and yields *cis* (**3*R*,6*S***) isomer **25** as the major distereomer,[20] whereas the hydrogenation from the same face of bulky O-TBDMS group results the *trans* (**3*R*,6*R***) isomer **26** as the minor isomer. The unprotected –OH group in **19** does not have the ability to direct the imine hydrogenation under these conditions, hence resulted in poor diastereoselectivity in pseudoconhydrine synthesis.



Scheme 4. (a) TBDMSCl, imidazole, DMAP, DCM (b) 10% Pd/C, EtOH (c) EtOH, IPA.HCl.

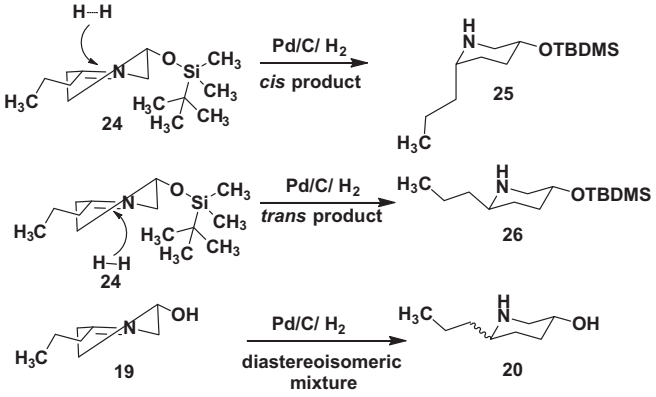


Figure 2. Plausible mechanism for stereoselectivity.

In summary, a highly diastereoselective synthesis of (3*R*,6*S*)-*epi*-pseudoconhydrine (**1**) and (3*R*,6*R*)-pseudoconhydrine (**2**) has been developed, with good yields. The three-step cascade reaction involving debenzylation, cyclization, and reductive amination was performed in a one pot process. The stereochemical outcome of the hydrogenation reaction can be rationalized by the steric bulkiness of the protecting groups. The developed routes for these alkaloids utilize fairly inexpensive reagents, and an operational friendly process. This strategy opens a new way for the enantioselective construction of disubstituted and polysubstituted piperidine alkaloids in good yield and highlights the usefulness of α-aminobutyrolactones in asymmetric synthesis. The application of this methodology for the synthesis of other biologically active complex piperidine alkaloids is currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.051.

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16. *(3R,6R)-6-Propylpiperidin-3-ol hydrochloride (−)-Pseudoconhydrine (**2**):* Palladium on charcoal (0.275 g, 20 mol%, 10% Pd on charcoal) was added to a solution of (3*R*,6*R*)-benzyl 5-hydroxy-2-propylpiperidine-1-carboxylate, (**21**) (1.1 g, 0.004 mol) in ethanol (11 mL), and the mixture was hydrogenated using H_2 balloon pressure for 1 h. The solution was filtered through Celite bed and the filtrate evaporated to give the title compound. The free amine was converted to HCl salt by treating with 2 N HCl for 10 min, (impurities were removed by extraction with DCM) the aqueous layer was concentrated completely under vacuum to afford crystalline pseudoconhydrine hydrochloride salt which was further recrystallized from MeOH–ether (1:10) to give a crystalline title compound (0.6 g, 85%). For determining the SOR, free base was generated as follows. Treatment of the salt with 2 M NaOH (1 ml) and extraction with ether (3 × 1.5 ml) followed by concentration of ether layer afforded the product as a solid, which was used for comparing the SOR.
17. *Spectral data of (**2**):*Yield: 0.6 g, 84.6%; mp: 184.48 °C, HCl salt, $[\alpha]_D^{20} = -5.5°$ (*c* 0.26, EtOH, free base) lit.[7h] $[\alpha]_D^{20} = -6°$ (*c* 1.05, MeOH, HCl salt), lit.[10] $[\alpha]_D^{20} = -11.4°$ (*c* 0.99, CH_2Cl_2, free base).; IR 3378, 2965, 2941, 2801, 1610, 1433, 1104, 1075; ^{1}HNMR (400 MHz, D_2O) δ 3.89 (m, 1H), 3.40 (dd, *J* = 3.4 & 12.2 Hz, 1H), 3.12 (m, 1H), 2.74 (t, *J* = 11.2 Hz, 1H), 2.08–2.1 (m, 2H) 1.3–1.63 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (400 MHz, D_2O) δ 66.531, 58.594, 50.9, 36.9, 32.9, 28.7, 20.9, 15.7; HRMS calcd *m*/*z* for $C_8H_{18}NO$+H: 144.1381, found: 144.1388.
18. *3R,6S)-6-Propylpiperidin-3-ol hydrochloride ((+)-epi-pseudoconhydrine) (**1**):* (3*R*,6*S*)-5-((*tert*-butyldimethylsilyl) oxy)-2-propylpiperidine (**24** and **25**, 9:1 ratio) (1.9 g, 0.0074 mol) was stirred for 20 h in 30 mL of ethanol: IPA·HCl (3:1) and then concentrated to obtain a crude hydrochloride salt. Crude salt was stirred with 19 mL, 1 N HCl for 15 min and washed with 3 × 19 mL dichloromethane and discarded the organic layer. pH of the aqueous layer was adjusted to **14** using NaOH and the aqueous layer was extracted with 19 mL dichloromethane (three times). Concentration of organic layer gave desired product with 9:1 *cis*:*trans* selectivity. This product was further purified by flash chromatography (SiO_2, DCM/methanol, 93:7) to afford only *cis* product (3*R*,6*S*-*epi*-pseudoconhydrine).Treatment of *epi*-pseudoconhydrine free amine with 1 N HCl for 10 min followed by extraction with dichloromethane, concentration of aqueous layer completely under vacuum afforded the *epi*-pseudoconhydrine hydrochloride salt (1.0 g, 76%).
19. *Spectral data of (**1**):* Yield: 0.9 g, 85.0% (free base); mp: 130.69 °C, $[\alpha]_D^{20} = +9.4°$ (*c* 1.0, MeOH). lit.,[7b] $[\alpha]_D^{20} = +9.24°$, MeOH.; IR 3397, 2960, 1623, 1445, 982; ^{1}H NMR (400 MHz, D_2O): δ 4.22 (s, 1H), 3.14–3.31 (m, 3H), 1.39–1.95 (m, 8H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (400 MHz, D_2O): δ 64.254, 59.335, 51.296, 37.818, 30.414, 25.505, 20.578, 15.727; HRMS calcd *m*/*z* for $C_8H_{18}NO$+H:144.1387, found: 144.1388.
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