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Diastereoselective total synthesis of piperidine alkaloids: (2*R*,5*R*)-5-hydroxyhomopipecolic acid and (2*R*,5*R*,8*R*)-5-hydroxysedamine

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ABSTRACT

Total synthesis of 2,5-disubstituted piperidine alkaloids, 5-hydroxyhomopipecolic acid (**1**) and 5-hydroxysedamine (**2**) was accomplished in overall high yields with a high level of 1,4-asymmetric induction. The ring opening of α-aminobutyrolactone, subsequent 1,3-diketone synthesis and heteroannulation via cascade reaction involving debenzylation, intramolecular cyclization and imine reduction under hydrogenation condition are the key steps involved in the synthesis.

The 2-substituted 5-piperidinol framework has attracted the attention of organic chemists in recent past because of its presence in natural and unnatural bioactive products.[1,2] Many efforts have been dedicated to the isolation and characterization of piperidine based natural products, and several elegantly designed methodologies have been innovated for their synthesis.[3] 3-Hydroxypiperidine based alkaloids are commonly found in *Conium*, *Prosopis*, *Azima*, *Carica* and *Cassia* species.[2c,4] Many of these alkaloids display significant pharmacological activities.[5] Some of the 2,5-*cis* substituted piperidinol natural products are 5-hydroxysedamine (**1**), cassine (**3**),[6] spectaline (**4**),[7] azimic acid (**5**), carpamic acid (**6**), prosopinine (**7**) and 5-hydroxypipecolic acid (**8**) (Fig. 1). *cis*-2-Carboxymethyl-5-hydroxypiperidine (**2**)[8] is one of the key intermediates used for the synthesis of antibiotic 593A, a natural product having strong antiviral and antitumor activity.[9] Most of these piperidine alkaloids possess stereochemically unfavorable *cis* relationship between the substituents at 2- and 5- position.[10] As a result of this, the synthesis of thermodynamically disfavored *cis*-2,5-disubstituted piperidine alkaloids is rarely reported in the literature.

The 5-hydroxysedamine (**1**) is first isolated by Ibebeke-Bomangwa and Hootele[11] from *Sedum acre* along with few other piperidine alkaloids such as 3-hydroxynorallosedamine and 3-hydroxyallosedamine. Plehiers and Hootele[12] reported the total

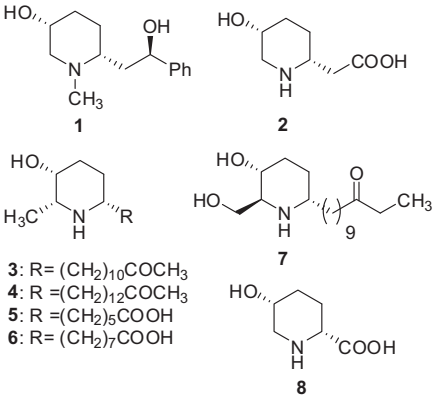

Figure 1. Structure of few naturally occurring piperidine alkaloids with 2,5-*cis* configuration.

synthesis of (−)-5-hydroxysedamine (**1**) by hydroboration of enecarbamates; however the hydroboration of enecarbamates resulted in the formation of a mixture of *cis* and *trans* isomer in a 1:3 ratio. This stereoisomeric mixture was then converted to the desired natural product by oxidation, and stereoselective reduction approach. The diastereoselective synthesis of 5-hydroxysedamine (**1**) reported by Liu involves α-amidoalkylation[13] with moderate 1,4-asymmetric induction. The synthesis of 5-hydroxysedamine

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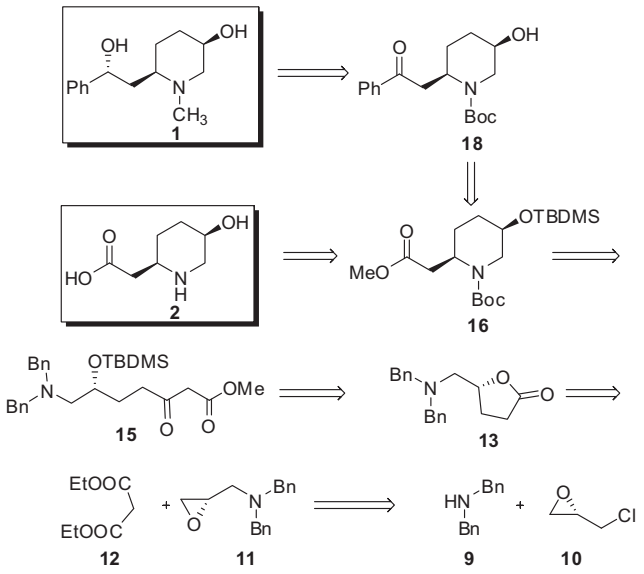


Scheme 1. Retrosynthetic approach.

(**1**) via hydroformylation approach is also reported in the literature.[14] Herdeis et al. reported the first diastereoselective total synthesis of *cis* and *trans*-5-hydroxyhomopipecolic acid (**2**) starting from the (2*RS*,5*S*) 5-(*t*-butyldimetahylsilyloxy)-2-(2′-propenyl)-piperidine-carboxylate.[15]

Most of these elegant syntheses though resulted in the required 2,5-disubstituted piperidine natural products in high yields, the use of complex reagents, reaction conditions and multistep synthetic sequences involved in these syntheses invites new and convergent approaches for their synthesis. Also some of these syntheses though began with chirally pure starting materials; the final products were isolated as a mixture of diastereomers or with moderate stereoselectivity. As a continuation of our effort to develop novel methodologies for the synthesis of biologically active natural products,[16] herein we describe our successful attempt towards the diastereoselective total synthesis of (2*R*,5*R*)-hydroxyhomopipecolic acid (**2**) and (3*R*,6*R*,8*R*)-5-hydroxysedamine (**1**) starting from enantiomerically pure (*S*)-epichlorohydrin.

The retrosynthetic strategy designed for the synthesis of (2*R*,5*R*)-hydroxyhomopipecolic acid (**2**) and (2*R*,5*R*,8*R*)-5-hydroxysedamine (**1**) is described in Scheme 1. The 5-hydroxysedamine (**1**) could be obtained from (2*R*,5*R*)-*t*-butyl 5-hydroxy-2-(2-oxo-2-phenylethyl)-piperidine-1-carboxylate (**18**) by diastereoselective reduction of ketone, and introduction of the *N*-methyl group via *N*-Boc reduction. The *N*-Boc hydroxyketone **18** could be obtained from TBDMS protected hydroxy ester **16** via Grignard reaction on Weinrub amide **17a**. The hydroxy ester **16** is anticipated to synthesize from γ-hydroxy-β-ketoester **15** by a cascade debenzylation and heteroannulation reaction under stereocontrolled reductive amination condition. The ring opening of chiral α-aminobutyrolactone **13** with lithium hydroxide followed by in situ TBDMS protection would provide a direct access to TBDMS protected γ-hydroxy-β-ketoester **15**. Chiral α-aminobutyrolactone **13** in turn could be obtained by the reaction of α-amino epoxide **11** with diethyl malonate **12** under basic conditions. The chiral α-amino epoxide **11** would be expected to obtain by the enantioselective ring opening of (*S*)-epichlorohydrin with dibenzyl amine. The hydroxyhomopipecolic acid (**2**) could be obtained from TBDMS protected *N*-Boc hydroxy ester **16** by the global deprotection of TBDMS, *N*-Boc and methyl ester under acidic conditions in a single pot procedure.

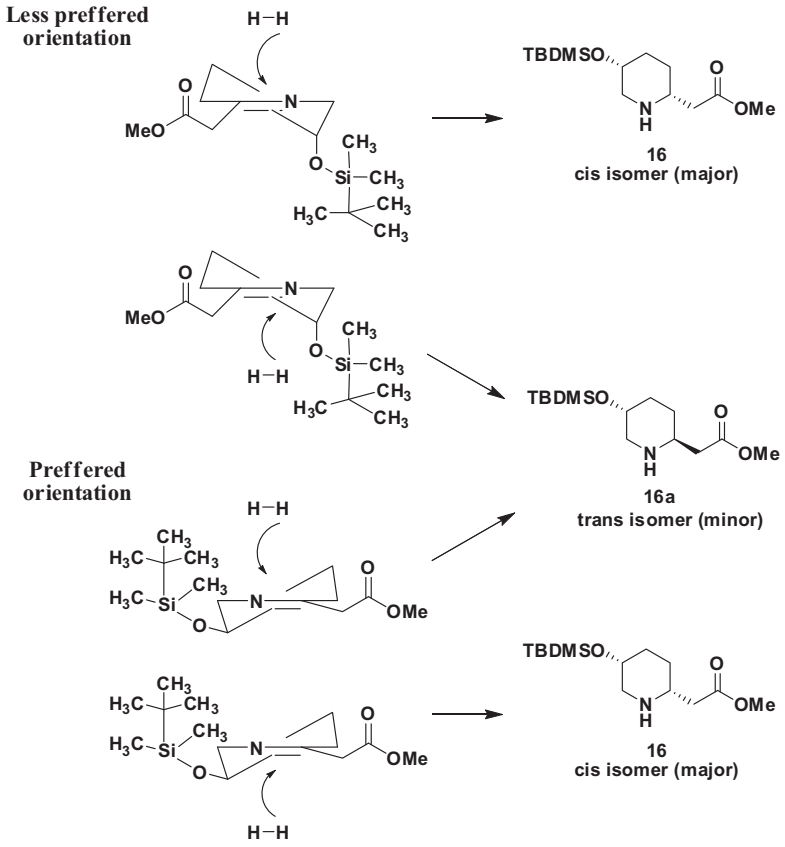
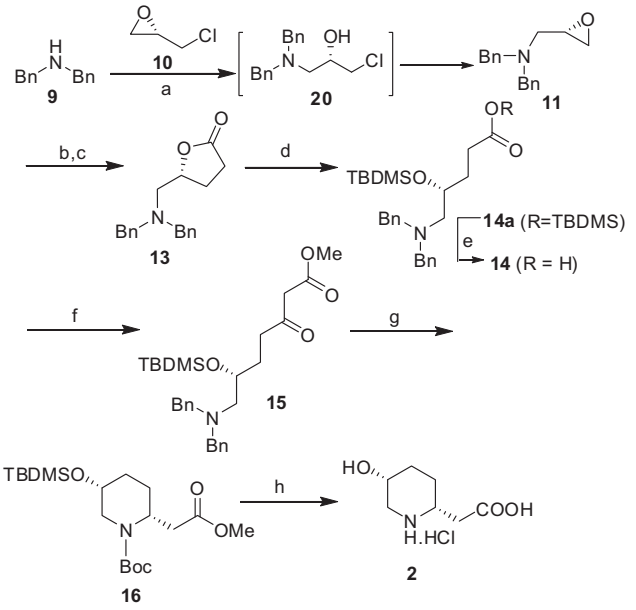


Figure 2. Plausible mechanism for cis stereoselectivity.

Results and discussion

The synthesis of 5-hydroxyhomopipecolic acid (**2**) and 5-hydroxysedamine (**1**) commenced with enantiomerically pure commercially available (*S*)-epichlorohydrin **10** and dibenzylamine **9**. Thus dibenzylamine **9** was reacted with (*S*)-epichlorohydrin **10** at ambient temperature to form the chlorohydrin **20** which was then, converted to α-amino epoxide **11** in the presence of potassium hydroxide in excellent yield. The α-amino epoxide **11** was converted to aminobutyrolactone **13** in moderate yield by the ring opening of oxirane with enolate of diethyl malonate **12** followed by in situ decarboxylation under Krapcho conditions.[17] The α-aminobutyrolactone **13** was converted to silyl protected γ-hydroxy acid[18] **14** in excellent yield via lithium hydroxide assisted ring opening of α-aminobutyrolactone and in situ protection of the hydroxyl group with *t*-butyldimethylsilyl chloride. The activation of the acid functionality in **14** with *N*,*N*′-carbonyldiimidazole (CDI) followed by in situ carbon acylation using the magnesium enolate of hydrogen methyl malonate afforded the corresponding β-ketoester **15** in 78% yield.[19]

After the synthesis of β-ketoester **15** in overall good yield we focused our attention towards the construction of 2,5-disubstituted *cis*-piperidine framework. Thus the β-ketoester **15** was subjected to hydrogenation under Pd/C condition. The cascade debenzylation and stereocontrolled reductive aminative heteroannulation of **15** was carried out using 10% Pd/C. The *cis*-diastereomer **16** was the sole product obtained under this reaction conditon.[16c] The steric hindrance provided by the bulky TBDMS group as shown in Figure 2 is probably the responsible factor for this high stereochemical 2,5-*cis* induction. The crude product was then in situ subjected to *N*-Boc protection and *N*-Boc *cis* piperidinol derivative **16** was isolated by column chromatography in 77% of overall yield over two steps. The global deprotection of TBDMS, *N*-Boc and ester group was attempted under acidic conditions in a single pot process. Thus **16** was treated with a solution of HCl in ethyl acetate at ambient temperature for 12–15 h followed by reflux in 6 N aqueous HCl, afforded 5-hydroxyhomopipecolic acid



Scheme 2. Reagents and conditions: (a) (i) *S*-epichlorohydrin (**10**), rt, 24 h (ii) KOH, 0 °C, 94% (b) Na, EtOH, Diethyl malonate (**12**) (c) LiCl, DMSO, 120–130 °C, 51% (d) LiOH, TBDMCl, imidazole, rt (e) K_2CO_3, MeOH, 92% (f) CDI, $MgCl_2$, potassium salt of methyl malonate, rt, 80% (g) (i)10% Pd/C, methanol, H_2, rt (ii) $(Boc)_2O$, sodium bicarbonate, DCM–water, 77.2% (h) (i) ethyl acetate·HCl (ii) 6 M HCl reflux, 79%.

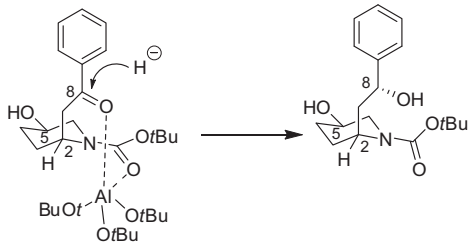
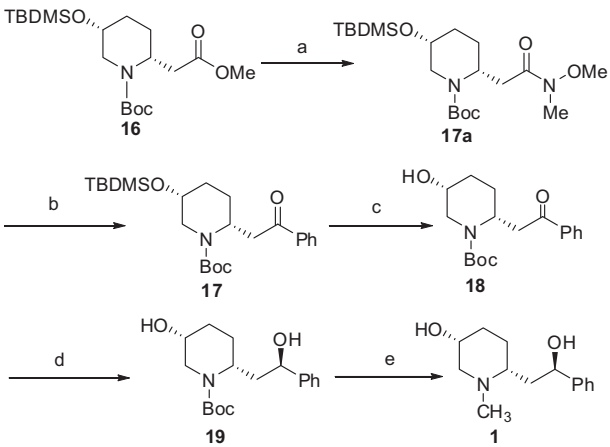


Figure 3. Plausible mechanism for stereoselective carbonyl reduction.

(**2**) as its hydrochloride salt in good yield. The spectral data[21] of synthetic 5-hydroxyhomopipecolic acid **2** (Scheme 2) were found to be in accordance with the reported literature values.[15]

After the successful completion of 5-hydroxyhomopipecolic acid synthesis, we focused our attention towards the synthesis of 5-hydroxysedamine (**1**). Thus TBDMS protected hydroxy ester **16** was converted to Weinrub amide **17a** under Bourdox conditions in excellent yield.[20] The Weinrub amide **17a** was converted to phenyl ketone **17** by reacting it with the excess phenyl magnesium bromide which was then purified by column chromatography in 72% yield. The deprotection of the bulky TBDMS group using tetrabutyl ammonium fluoride afforded *N*-Boc hydroxyketone **18** as a crystalline solid in excellent yield. In order to achieve the desired stereochemistry at C8 position in *N*-Boc ketone **18,** the reduction of the keto group was attempted with various reducing reagents such as $NaBH_4$, Vitride, etc., however these reactions afforded the required product **19** with very low diastereoselectivity. High diastereoselectivity was obtained when the reduction was carried out with $Li(t\text{OBu})_3AlH$ in THF at ambient temperature. The high stereoselectivity obtained under this reduction condition is probably due to the approach of the hydride ion from the less hindered side of the carbonyl group because of the selective complexation of amide and keto carbonyl oxygen with aluminium ion as shown in Figure 3.[22] The *N*-Boc-dihydroxy piperidine derivative **19** was then converted to the alkaloid, (+)-5-hydroxysedamine **1** by selective reduction of *N*-Boc to the *N*-methyl group using LAH at 50–60 °C. The SOR of our synthetic (+)-5-hydroxysedamine **1** {$[\alpha]_D^{25}$ +41.1° (*c* 0.83, MeOH)} is in agreement with the reported literature values {$[\alpha]_D^{25}$ +41° (*c* 0.9, MeOH)}.[11] The structure of (+)-5-hydroxysedamine **1** is further confirmed by spectral and analytical data,[23] and found to be in agreement with literature values[11] (Scheme 3).

In summary, a highly diastereoselective synthesis of (2*R*,5*R*)-5-hydroxyhomopipecolic acid **2** and (2*R*,5*R*,8*R*)-5-hydroxysedamine



Scheme 3. Reagents and conditions: (a) *i*-PrMgCl, NH(OMe)Me·HCl, THF, quantitative (b) PhMgBr, THF, 72% (c) 1 M-TBAF solution, 93% (d) lithium tri-*t*-butoxyaluminium hydride, THF, 25–30 °C, 90% (e) LAH, THF, 50–60 °C, 82%.

1 is developed, with good yields and diastereoselectivity in minimum number of synthetic transformations. In the synthesis, during the cascade reductive heteroannulation process, stereochemical outcome of the hydrogenation reaction is controlled by the steric bulkiness of the TBDMS group; whereas chelation controlled hydride transfer provided the stereospecificity in keto reduction. The developed route for these alkaloids utilizes fairly inexpensive reagents, and operational friendly reaction conditions. The current strategy can be utilized for the asymmetric synthesis of disubstituted and polysubstituted piperidine alkaloids. The application of this methodology for the synthesis of other biologically active complex piperidine alkaloids is currently underway and will be published in due course of time.

Note

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The authors declare no competing financial interest.

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Supplementary data

Supplementary data (detailed experimental analysis and spectral analysis including ^{1}H, ^{13}C, and HRMS) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.042.

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23. $[\alpha]_D^{25}$ +41.1° (*c* 0.83, MeOH) [lit.[12] $[\alpha]_D^{25}$ +41° (*c* 0.9, MeOH)]; IR (KBr) ν (cm^{-1}) = 3360 (broad), 2956, 1566, 1409, 1085,703; ^{1}H NMR (400 MHz, CD_3OD): δ 1.6–1.9 (m, 5H), 2.0–2.12 (m, 1H), 2.42 (s, 3H), 2.6–2.79 (m, 3H), 3.8 (m, 1H), 4.7 (dd, *J* = 10.2, 3.4 Hz, 1H), 7.20–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 128.4, 127.4, 125.5, 73.0, 63.6, 60.1, 58.0, 42.3, 39.7, 30.1, 29.9; MS (ESI) *m*/*z* 236 (M+H+); HRMS (ESI) calcd for $[C_{14}H_{21}NO_2+H]+$ 236.1651, found 236.1655.