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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.

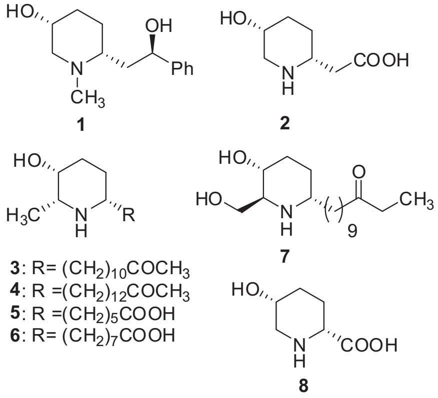

Figure 1. Structure of few naturally occurring piperidine alkaloids with 2,5-*cis* configuration.

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 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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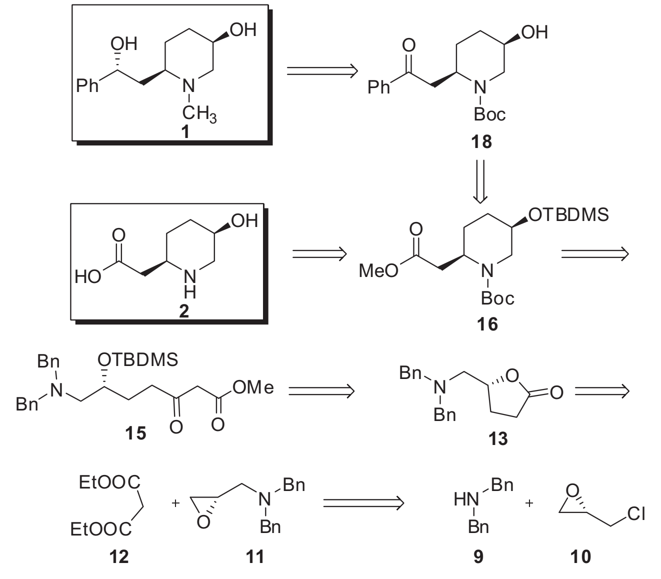

Scheme 1. Retrosynthetic approach.

(**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.

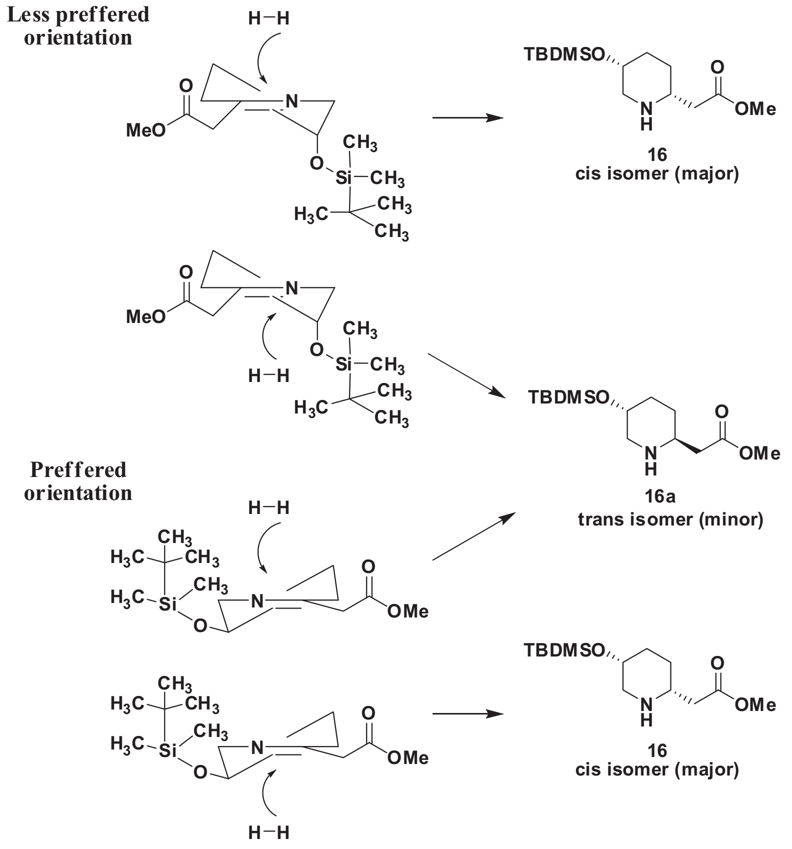

Figure 2. Plausible mechanism for cis stereoselectivity.