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Dehydrative Annulation Strategy for the Construction of Octahydroindolizine Framework: A Diastereoselective Synthesis of (6*R*, 8a*S*)-Octahydroindolizin-6-ol

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Abstract

A dehydrative annulation strategy involving an intramolecular ring closure under a Mitsunobu type reaction condition has been used for the construction of octahydroindolizine framework successfully. This strategy that was reported to be unsuccessful when applied to a similar other system allowed us to perform a diastereoselective synthesis of (6*R*, 8a*S*)-octahydroindolizin-6-ol [a precursor of (-)-8a-epidesacetoxyslaframine] starting from commercially available chiral (*S*)-epichlorohydrin *via* a piperidine intermediate i.e. (3*R*, 6*S*)-6-(3-hydroxypropyl)piperidin-3-ol. The methodology has potential to afford a library of optically pure small molecules of pharmacological importance based on the related indolizine framework.

Graphical Abstract:

KEYWORDS: octahydroindolizine, (*S*)-epichlorohydrin, Mitsunobu reaction, diastereoselectivity

INTRODUCTION

The development of synthetic tools to construct optically pure heterocycles of biological importance is of great interest in both organic and medicinal chemistry as this effort provides quick access to the relevant natural and unnatural analogs for various studies including pharmacological activities.

The octahydroindolizine (or 1-azabicyclo[4.3.0]nonane) framework is widespread in many alkaloids[1],[2],[3] such as coniceine (isolated from the skin secretions of neotropical amphibians), slaframine (a mycotoxin that generally causes salivation in most animals and is usually produced by the fungus *Rhizoctonia leguminicola*), castanospermine (a potent glycosidase inhibitor) and a number of poisonous-frog alkaloids typified by pumiliotoxin B1. Thus construction of octahydroindolizine ring in a stereoselective fashion has attracted enormous attention.[4-11] Being a precursor of (-)-8a-epidesacetoxyslaframine, the (6-*R*)-octahydroindolizin-6-ol (**A**, Fig.1) attracted our particular attention as this compound could provide us access to a library of

indolizine based small molecules in addition to (-)-8a-epidesacetoxyslaframine. This and our interest in piperidine

derivatives[12] prompted us to report a new approach to the octahydroindolizine skeleton of compound **A** starting from enantiomerically pure (*S*)-epichlorohydrin using dehydrative annulation strategy as a key step. Notably, previous synthesis of (±)-**A** involved intramolecular nitrone cycloaddition strategy, using 2-pyrrolecarbaldehyde as starting material followed by hydrogenation.[11] However, formation of a mixture of isomeric cycloadducts during the intramolecular nitrone cycloaddition step could potentially be a major concern for this strategy to be used as a practical route to **A**. Moreover, this methodology do not provide an optically pure **A**. Additionally, the dehydrative annulation strategy (the Mitsunobu-like protocol) was not successful when applied to a similar system earlier by Casiraghi *et al*.[10]

RESULTS AND DISCUSSIONS

A retro-synthetic analysis of **A** (Fig. 1) suggested that this (6*R*)-octahydroindolizin-6-ol could be obtained from a chiral precursor i.e. (3*R*,6*S*)-6-(3-hydroxypropyl)piperidin-3-ol (**B**) *via* intra-molecular displacement of the activated primary hydoxy group by the piperidine nitrogen. The alcohol **B** could be obtained from the chiral γ-hydroxy-ketone (**C**) by de-benzylation followed by a stereo-controlled reductive amination process, a strategy similar to that used earlier.[13] Based on this retro-synthetic analysis we initiated the actual synthesis of compound **A**. Initially, the synthesis of its precursor i.e. the piperidine intermediate (**B**) was

undertaken (Scheme 1). Since the synthesis of amide **6** has been reported earlier[13] hence we followed the same method for its preparation. Thus, the reaction of (*S*)-epichlorohydrin and dibenzylamine (**1**) afforded (S)-*N*,*N*-dibenzyl-1-(oxiran-2-yl)methanamine (**3**) (via **2**) which on treatment with the *in situ* generated sodium salt of diethyl malonate afforded the lactone **4** via opening of the oxirane ring of **3**. Subsequent Krapcho[14] type decarboxylation of **4** in the same pot afforded (*R*)-5-[(dibenzylamino)-methyl]-dihydrofuran-2(3*H*)-one (**5**) with specific optical rotation (SOR) +11.85°. The Bodroux type reaction of **5** with *N*,*O*-dimethylhydroxylamine afforded Weinreb amide (**6**).[15] The amide **6** on reaction with excess of [(3-chloropropoxy)methyl]benzene in the presence of magnesium produced a γ-hydroxyketone, the hydroxyl group of which was further protected using TBDMS chloride to give the corresponding compound **7** in 50% yield. Next we performed a one-pot three step cascade reaction of **7** involving sequential (i) debenzylation, (ii) intramolecular cyclization and (iii) subsequent reduction of the imine bond formed *in situ* in the

same pot. This step was carried out using Pd/C catalyst under hydrogen atmosphere. The product obtained was treated with 2N HCl to remove the TBDMS group and to afford the HCl salt of a diastereomeric mixture (i.e. **B-1**.HCl and **B-2.**HCl, Scheme 1) of the piperidine derivative (**B**) *via* a 2,3,4,5-tetrahydropyridine intermediate (**8**) generated *in situ*. The HCl salts were washed with DCM to remove the minor impurities present. The crystalline (3*S*,6*R*)-6-(3-hydroxypropyl) piperidin-3-ol hydrochloride salt on treatment with base regenerated pure **B**. Notably, the

diastereomeric mixture of **B** was found to contain (3*R*,6*S*)-6-(3-hydroxypropyl)piperidin-3-ol (**B-1**) as a major isomer and (3*R*,6*R*)-6-(3-hydroxypropyl)piperidin-3-ol (**B-2**) as a minor isomer in a ratio of **B-1** / **B-2** ~ 10:1 (yield of pure **B-1** and **B-2** was 30.9% and 3.37% respectively with respect to **7**. While the HCl salt of **B-1**/**B-2** mixture was isolated as a crystalline solid in ~ 70% yield, the loss of material occurred during separation and purification of **B-1** and **B-2**). The observed diastereoselectivity during the one-pot conversion of **7** to **B** can be explained by using a transition state involving the intermediate **8** generated *in situ* as shown in Fig 2 and 3. While the hydrogentation of the imine bond formed *in situ* may takes place in two different pathways

depending on approach of hydrogen molecule towards the –C=N- of **8**, the steric bulk of the hydroxypropyl chain seemed to have played a key role in the observed diastereoselectivity. Thus the approach of hydrogen molecule towards the –C=N- from the side opposite to the bulky hydroxypropyl chain is expected to be more favorable (Fig. 2) over that involved the approach from the same side of the hydroxypropyl chain (Fig. 3). The former pathway affords the *cis* isomer whereas the other one affords the *trans* isomer. It is therefore not surprising that the *cis* isomer i.e. **B-1** was obtained as a major product in this step. Nevertheless, both the diasteromers **B-1** and **B-2** were separated *via* a semi preparative HPLC method by using phenomenex (Lux amylose 21.2* 250 mm) 10_u column {mobile phase I: II = 80: 20 where I is n-hexane (0.1%, DEA) and II is IPA (0.1%, DEA) with a flow rate of 4 mL/min}. The ^{1}HNMR spectra obtained for the cis isomer **B-1** showed a signal at δ

4.23 (s, 1H) due to the tertiary proton of –C*H*(OH) group. It is worthy to mention that the same proton of a structurally very similar compound reported in the literature[13],[16,17] appeared at δ 4.22 (s, 1H)[13] or 4.08 (s,1H)[16] for the cis isomer and at δ 3.89 (m, 1H)[13] or 3.83 (m, 1 H)[17] for the trans isomer. Indeed, the appearance of this proton at δ 3.89 (s, 1H) in case of **B-2** clearly suggests that **B-1** is a cis isomer.

Having prepared (3*R*, 6*S*)-6-(3-hydroxypropyl)piperidin-3-ol (**B-1**) as a precursor of **A** we then attempted to construct the final bicyclic skeleton of **A**. A literature search revealed that the construction of a similar bicyclic skeleton was performed earlier using a tetrahydroxypiperidine derivative.[10] While, the cyclization i.e. intramolecular displacement of the activated primary -OH group by the piperidine nitrogen was successful when carried out in the presence of PPh_3 / CCl_4 / Et_3N, the use of a Mitsunobu-like protocol in the presence of PPh_3 / DEAD (diethyl azodicarboxylate) was reported to be unsuccessful. Although the exact reason for this observation was not clear the interference caused by other hydroxyl groups present on the side chain could be a possible reason. Based on this we anticipated that the Mitsunobu-like protocol might work in our case as **B-1** contains less number of hydroxyl groups compared to that used earlier.[10] To our satisfaction, when **B-1** was treated with PPh_3 and DEAD,[18,19] the reaction proceeded well *via* an intramolecular dehydrative annulation process to give the target product i.e. (6*R*, 8a*S*)-octahydroindolizin-6-ol (**A**) in 72% yield (Scheme 2).

The compound **A** was isolated as a viscous liquid that showed optical rotation $[\alpha]_D^{25}$ = -27.94° (c 1.0, $CHCl_3$). This compound was characterized by NMR, IR and HRMS data and was compared with that reported earlier for (±)-**A**[2h] (see Table 1 in the supplementary content). It should be noted that the NMR data of optically pure **A** has not been reported in the literature. Moreover, the reported data of (±)-**A** was recorded using $CDCl_3$ as a solvent and a 300 MHz instrument whereas D_2O as well as DMSO-d_6 along with 400 MHz instrument was used in the present case. However, in spite of differences observed between the ^{1}HNMR data generated by us and that reported earlier, the ^{13}C NMR data of optically pure **A** and (±)-**A** showed good correlations. Since the two stereocenters of **B-1** did not participate in the reaction leading to **A** hence their configuration was expected to remain same in the product too. Indeed, the position and nature of ^{1}HNMR signal of tertiary proton of –C*H*(OH) group that appeared at δ 4.23 (s, 1H) in case of **B-1** was not changed significantly in case of product **A** and appeared at δ 4.03 (s, br, 1H) or 4.06 (s, 1H) when recorded in D_2O or DMSO-d_6, respectively (see Table 1 in the supplementary content).

CONCLUSIONS

In conclusion, a dehydrative annulation strategy was used for the construction of octahydroindolizine framework successfully. This strategy involved an intramolecular ring closure under a Mitsunobu type reaction conditions that was reported to be unsuccessful when applied to a similar system earlier. The strategy allowed us to perform a diastereoselective synthesis of (6*R*, 8a*S*)-octahydroindolizin-6-ol starting from commercially available chiral (*S*)-epichlorohydrin that afforded the piperidine

precursor i.e. (3*R*,6*S*)-6-(3-hydroxypropyl)piperidin-3-ol as a major product after several steps. The last step being a sequential combination of debenzylation, intramolecular cyclization, and subsequent reduction of the imine bond formed *in situ* was performed in a single pot. The diastereoselectivity of the imine bond reduction appeared to be governed by the steric bulk of the hydroxypropyl chain. Overall, the present synthesis of (6*R*,8a*S*)-octahydroindolizin-6-ol could provide a useful alternative to the previously reported method involving intramolecular nitrone cycloaddition strategy. The present method could also provide access to the indolizine based natural and unnatural products and may find wide usage in both organic and medicinal chemistry.

EXPERIMENTAL

Preparation Of (6R, 8as)-Octahydroindolizin-6-Ol (A)

To a solution of (3R, 6S)-6-(3-hydroxypropyl) piperidin-3-ol (**B-1**, 150 mg, 0.0009 mmol) in dry THF (4 mL) was added triphenyl phosphine (472 mg, 0.0018 mmol, 2 eq) and diethyl azodicarboxylate (313 mg, 0.0018 mmol, 2 eq) under argon at 0-5 °C. The reaction mass was aged for 4 h at 0-5°C and quenched with (5 mL) 20 wt % aqueous $NaHCO_3$. The reaction mixture was diluted with DCM (15 mL), washed with DM water (2x5 mL) followed by brine solution and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using (10:2) DCM/MeOH to afford 96 mg of title compound (**A**) as a viscous liquid; $[\alpha]_D^{25}$ = -27.94° (c 1.0, $CHCl_3$); Yield: 72%; IR (Neat): 3019.3, 1217.6, 1020.1, 928.6, 775.3, 669.3, 627.0; ^{1}H NMR (400 MHz, D_2O) δ: 4.03 (s, br,

1H), 3.63-3.50 (m, 2H), 3.40-3.18 (m, 2H), 2.85 (s, br, 1H), 2.23-2.06 (m, 5H), 1.74-1.53 (m, 3H);^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.06 (s, 1H), 3.39-3.42 (m, 3H), 2.96-3.14 (m, 3H), 1.58-2.18 (m, 8H); ^{13}C NMR (100 MHz, DMSO) δ: 65.9, 62.0, 56.4, 52.4, 26.9, 26.4, 22.9, 20.0; HRMS Calcd m/z for $C_8H_{14}NO$+H: 142.1232 found: 142.1236.

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SUPPLEMENTAL MATERIAL

Full experimental detail, spectral data, ^{1}H and ^{13}C NMR spectra, and HPLC traces for this article can be accessed on the publisher's website.

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Figure 1. Retro-synthetic analysis for the construction of octahydroindolizine framework of **A**

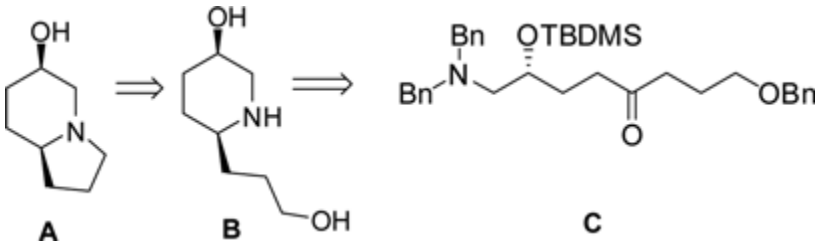


Figure 2. Approach of hydrogen molecule towards the –C=N- from the side opposite to the bulky hydroxypropyl chain.

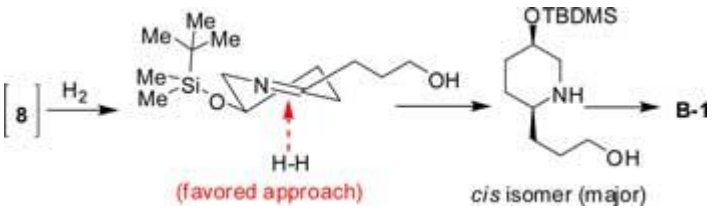
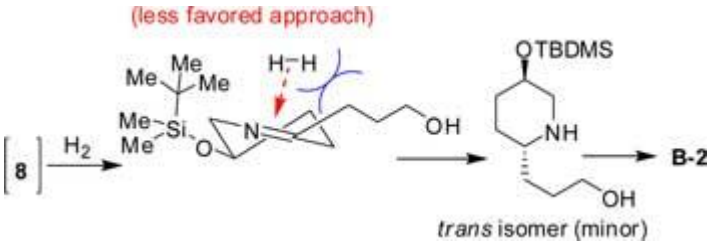
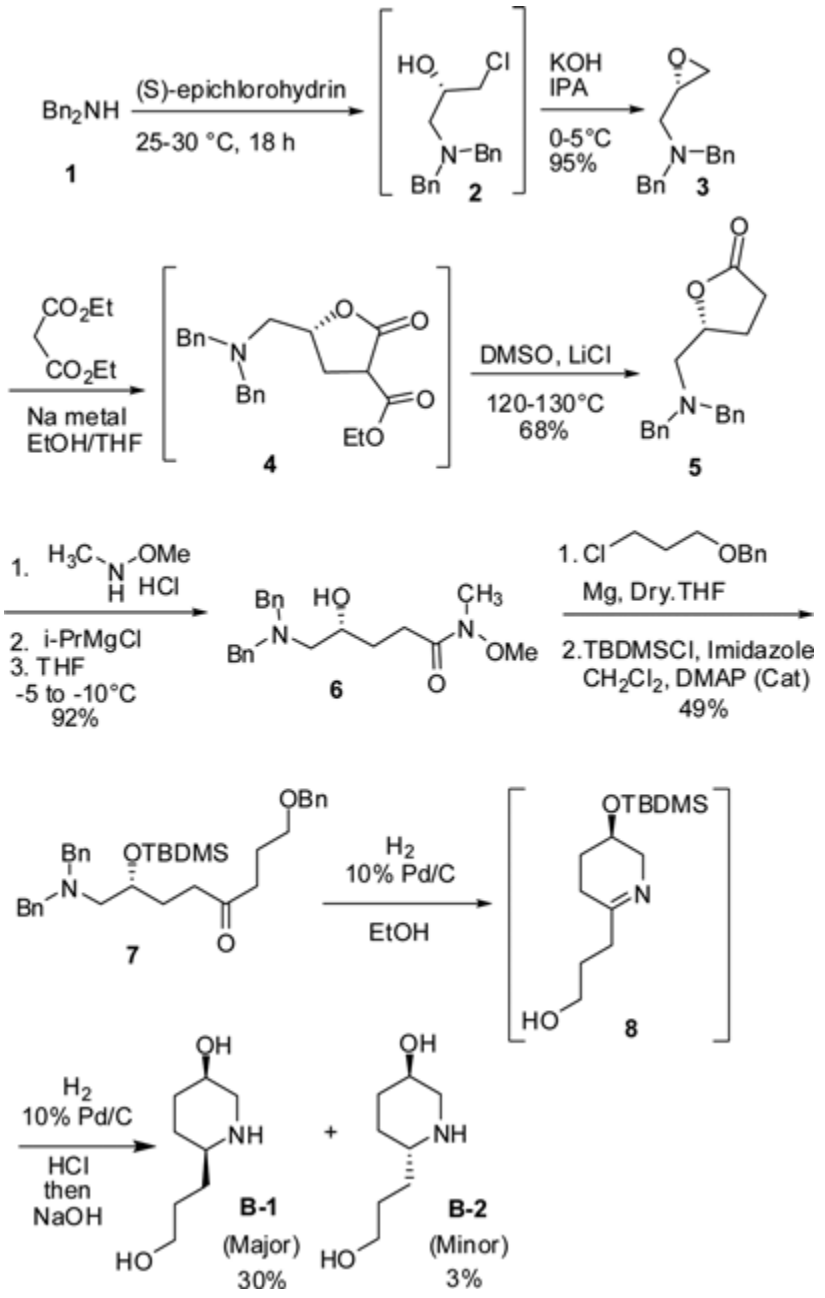


Figure 3. Approach of hydrogen molecule towards the –C=N- from the same side of the bulky hydroxypropyl chain.



Scheme 1. Synthesis of piperidine intermediate (**B**)



Scheme 2. Synthesis of (6*R*, 8a*S*)-octahydroindolizin-6-ol (**A**) *via* the dehydrative annulation strategy.