A common approach to the total synthesis of L-1-deoxyallonojirimycin, L-homo-1-deoxyazaallose and triacetyl derivative of 5-*epi* hyacinthacine A_5

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A common approach to the total synthesis of L-1-deoxyallonojirimycin, L-homo-1-deoxyazaallose and triacetyl derivative of 5-*epi* hyacinthacine A_5

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ABSTRACT

A common strategy for the synthesis of polyhydroxylated piperidines L-1-deoxyallonojirimycin, L-homo-1-deoxyazaallose and triacetyl derivative of 5-*epi* hyacinthacine A_5 from the readily available D-ribose as a starting material has been described.

Polyhydroxylated piperdines and pyrrolidines are well known in nature as mimics of monosaccharides. These are commonly known as azasugars or iminosugars, where in the ring oxygen of the sugar moiety is replaced by nitrogen atom. They are in general found to be potent inhibitors of many carbohydrate-processing enzymes [1] and could be very useful for the treatment of various diseases such as diabetes [2], cancer [3] and viral infections [4] including AIDS [5]. Natural or synthetically produced six membered iminosugars (polyhydroxylated piperidines) effectively inhibit the oligosaccharide processing

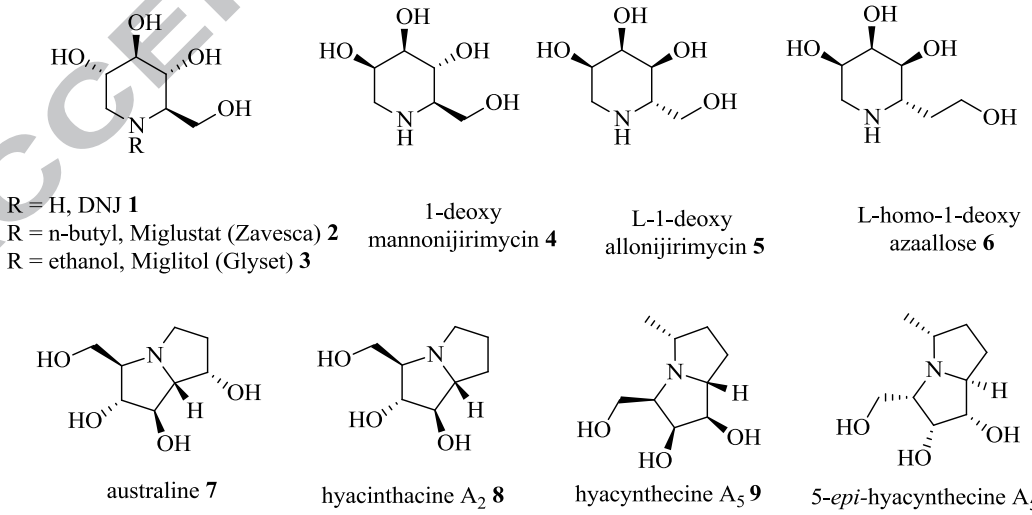

Figure 1. Some of polyhydroxylated piperidines and pyrrolidines

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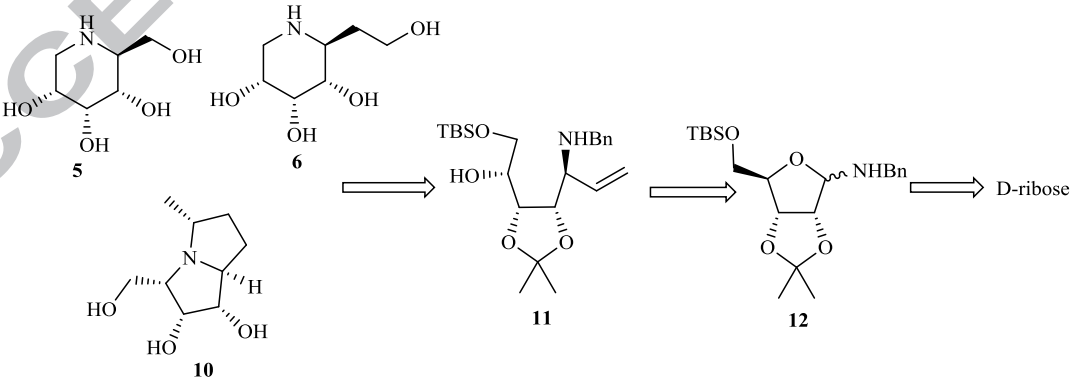
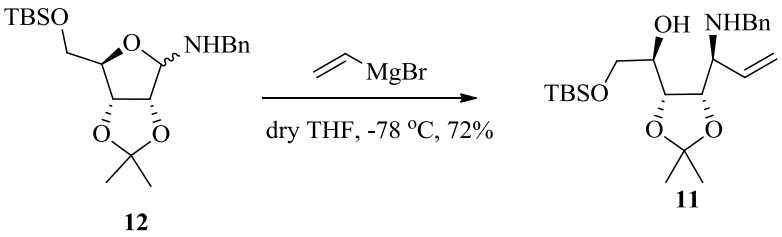
enzymes, especially glycosidases and glycosyltransferases which are involved in a whole range of the essential biological transformations.[6] Some of the polyhydroxylated piperidines are used as drugs for the treatment of various diseases.[7] Miglustat (Zavesca®, **2**) and Miglitol (Glyset®, **3**) are currently used in the market for the treatment of Gaucher's disease and type-II diabetes (**fig. 1**) [7, 8] and these are derivatives of 1-Deoxynojirimycin (DNJ, **1**), a natural compound. Some more derivatives have also been found to be Glucosylceramide synthase inhibitors, which are useful in the therapy of HIV and Hepatitis C infection.[8, 9] 1-Deoxymannonojirimycin **4** and L-1-deoxyallonojirimycin **5** have good inhibitory activity towards human lysosomal α-mannosidase [10], which plays a vital role in maintaining cellular homeostasis.[11] Polyhydroxylated pyrrolizidines such as hyacinthacine family having one carbon side chain at C(3) and/or C(5) have shown significant activity against viral infections, cancer and diabetes.[12,13] For example australine **7** and hyacinthacine A_2 **8** are good inhibitors of amyloglucosidase [14] and was found to display antiviral and anti-HIV activity.[15] Compounds hyacinthacine A_2 **8**, hyacinthacine A_5 **9** and 5-*epi* hyacynthecine A_5 **10** are also good inhibitors of amyloglucosidase. [16]

Due to their promising therapeutic profiles, many reports have been disclosed for the synthesis of DNJ **1**, its isomers, homoanalogues [17, 18] and also hyacinthacine A_5 [19]**9** using different strategies. Majority of the synthesis are based on the chiron approach but many of them are lacking stereo selectivity and general applicability.[20] Herein, we wish to report an efficient and highly stereoselective approach to polyhydroxylated piperidines such as L-1-deoxyallonijirimycin **5**[18,19,21] L-homo-1-deoxyazaallose **6** [22] and pyrrolidizine 5-*epi* hyacynthecine A_5 **10**. Over the past few years, our group has been involved in the synthesis of some iminosugars or azasugars and phytosphingosines starting from the readily available materials.[23, 24] Recently we reported a highly stereoselective nucleophilic addition on *N*-glycosylamine **12** to give exclusively *anti* amino hydroxyl unit **11** [24], and its application in the synthesis of some bicyclic iminosugars. [25] In this publication we are presenting the extension of our strategy for the synthesis of polyhdroxylated piperdines **5**, **6** and 5-*epi* hyacynthecine A_5 **10**. As per the retrosynthetic analysis (Scheme 1). The glycosylamine **12** was synthesized from the commercially available D-ribose in three step procedure [25]. Nucleophilic addition on glycosylamine **12** with vinylmagnesium bromide at -78 °C in dry tetrhydrofuran gave the *anti* adduct **11** exclusively in 72% yield (Scheme 2). [24, 25]The formation of anti product can be explained *via* seven membered chelation or felkin anh model.[24]



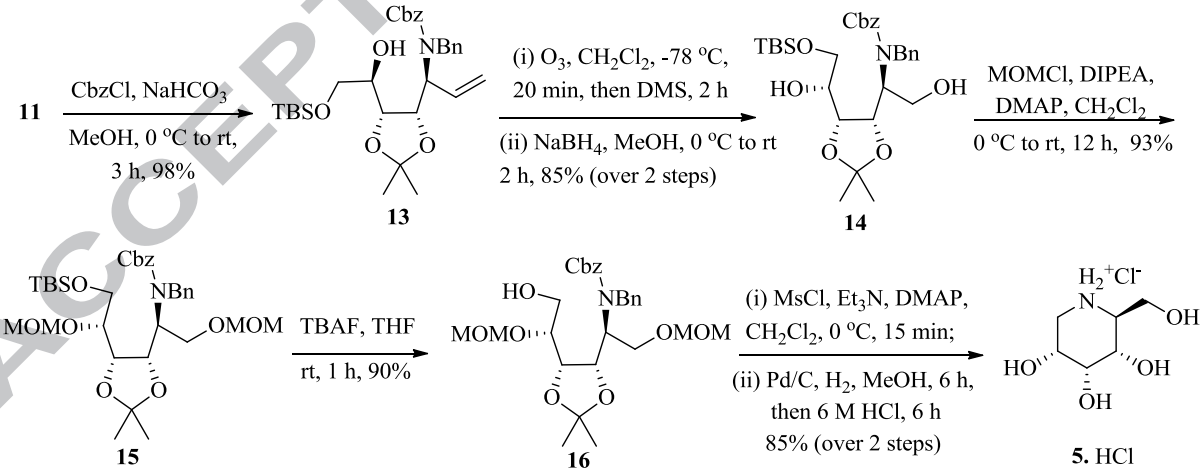
Scheme1. Retrosynthetic analysis



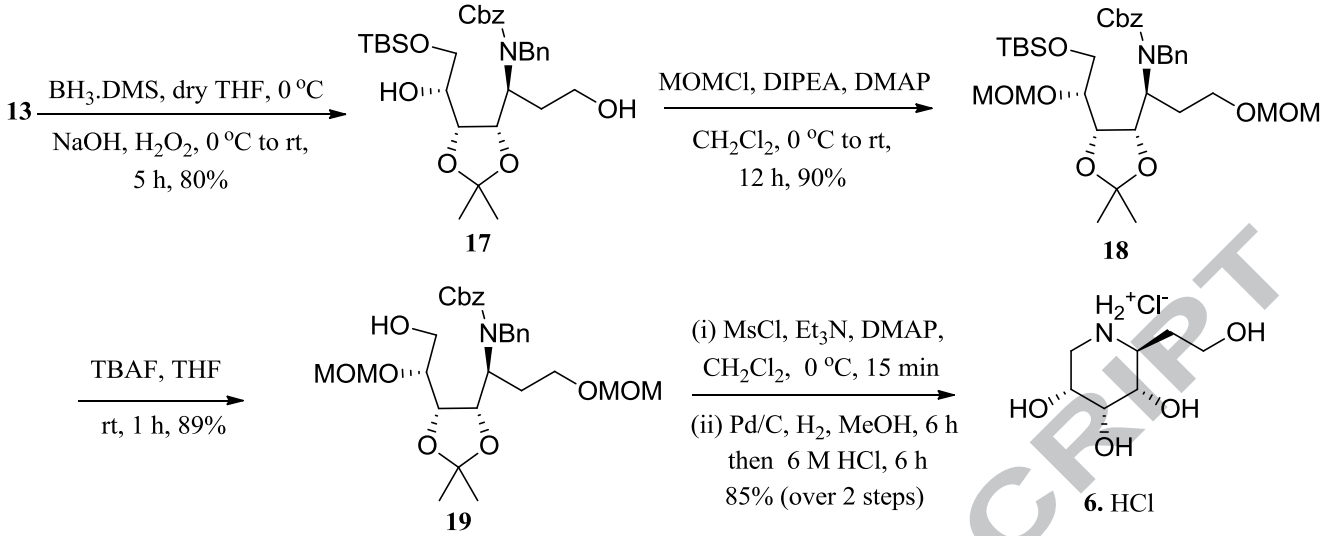
Scheme 2. Preparation of key intermediate *erythro* amino alcohol **11**

For the synthesis of L-1-deoxyallonojirimycin **5** (Scheme 3), compound **11** was treated with benzyloxycarbonyl chloride and sodium bicarbonate in methanol to give the *N*Cbz derivative **13** in 98% yield. Ozonolysis of the terminal olefin in **13** gave the corresponding aldehyde, which was reduced with sodium borohydride in methanol to afford the desired diol **14** in 85% yield. Masking of the diol functionality in **14** as methoxy methyl ethers with methoxy methyl chloride and diisopropylethylamine in dichlromethane furnished the required compound **15** in 93% yield. Deprotection of silyl-ether in **15** with tetrabutylammonium flouride in tetrahydrofuran gave the primary alcohol **16** in 90% yield. For the construction of the piperidne ring, compound **16** was subjected to mesylation using mesyl chloride, triethylamine and *N, N*-dimethylamino pyridine in dichloromethane at 0 ^{o}C, the crude mesylate derivative on hydrogenolysis in presence of palladium on carbon and then treatment of the crude with 6M hydrochloric acid afforded the required final product L-1-deoxyallonijirimycin **5** as hydrochloride salt. The spectral and analytical data of **5** were in accordance with the reported values. [21]The conversion of **16** to **5** has taken place in three steps without any isolation and purification of the intermediates. This transformation involves cyclisation to piperidine ring, deprotection of the benzyloxycarbonyl, benzyl, methoxymethyl and acetonide groups.

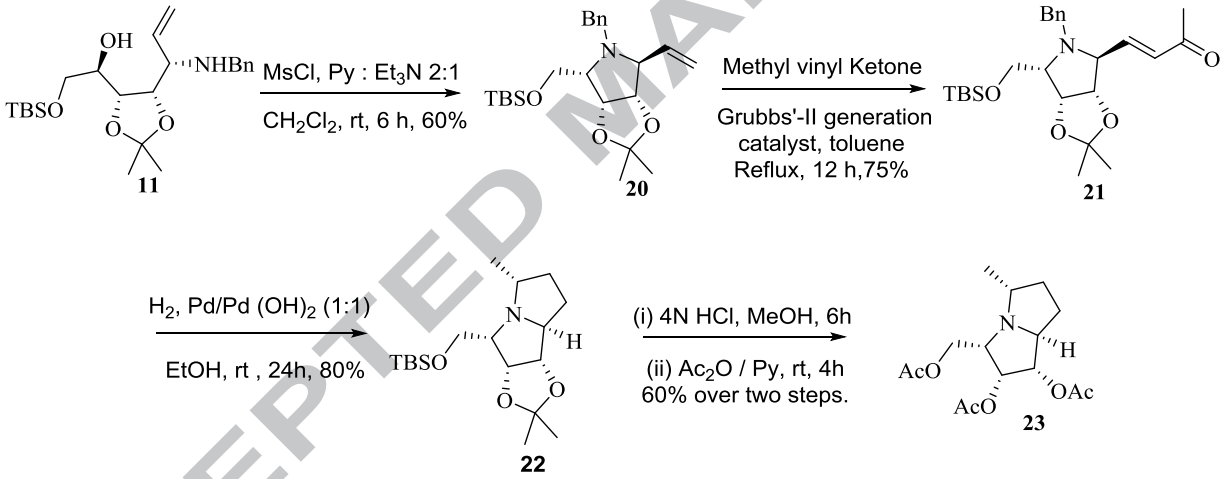
For the synthesis of L-homo-1-deoxyazaallose **6** (Scheme 4), the terminal olefin in **13** was subjected to hydroboration/oxidation using borane dimethylsulphide in dry tetrahydrofuran followed by treatment with sodiumhydroxide and hydrogen peroxide at 0 ^{o}C gave the diol **17** in 80% yield. The diol functionality in **17** was converted to methoxymethyl ethers to furnish **18** in 90% yield. Treatment of **18** in tetrahydrofuran with tetrabutylammonium flouride afforded the primary alcohol **19** in 89% yield. Alcohol **19** on mesylation using mesyl chloride and triethylamine in dichloromethane gave the mesylated product, which on hydrogenolysis in the presence of catalytic palladium on carbon and cleavage of the protecting groups under acidic condition, gave the desired final product L-homo-1-deoxyazaallose **6** as hydrochloride salt in 85% yield (over 2 steps), whose spectral and physical data were in good agreement with the reported values. [22]



Scheme 3. Synthesis of L-1-deoxyallonojirimycin **5**



Scheme 4. Synthesis of L-homo-1-deoxyazaallose **6**



Scheme 5: Synthesis of acetyl derivative of 5-*epi* hyacinthacine A_5

Our next task was to synthesise 5-*epi*-hyacinthacine A_5 **10** from compound **11** as shown in **Scheme 5**. The compound **11** underwent SN^2 cyclisation by treating with mesyl chloride in the presence of pyridine and triethylamine (2:1) to give 2, 5 disubstituted pyrrolidine compound **20** in 60% yield. This differentially disubstituted pyrrolidine compound **20** is a good template for the synthesis of polyhydroxy pyrrolidine skeletons. The compound **20** was subjected to cross metathesis with methyl vinyl ketone using Grubb's second generation catalyst to afford the desired α,β-unsaturated carbonyl compound **21** in 75% yield. Hydrogenation of **21** to **22** using Pd-C: $Pd(OH)_2$ (1:1) in ethanol gave **22** in 80 % yield. Conversion of **21** to **22** is a tandem process which involves debenzylation, reduction of double bond via cyclic enamine formation and then reduction of enamine from the less hindered side. Then global deprotection of the compound **22** with 4N HCl in methanol followed by treatement with acetic anhydride and pyridine gave the acetyl derivative of (-)-5-*epi*- hyacinthacine A_5 **23** in 60 % over two steps. The spectral and physical data of compound **23** were in good agreement with the literature values.[19]

In summary, a simple, efficient and divergent synthesis of imino sugars such as L-1-deoxyallonijirimycin, L-homo-1-deoxyazaallose and triacetyl derivative of 5-*epi* hyacinthacine A_5 has been achieved from the commercially available D-ribose. The key reactions are highly stereoselective nucleophilc addition, reductive amination and cross metathesis.

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Supplementary material

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Graphical Abstract

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A common approach to the total synthesis of L-1-deoxy allonijirimycin, L-homo-1-deoxyazaallose and triacetyl derivative of 5-*epi*-hyacinthacineA_5

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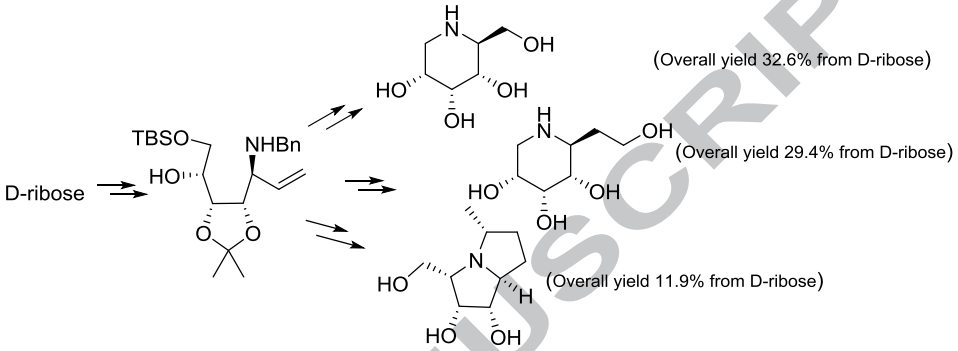

Highlights:

1. Explanation has been given for key steps in the manuscript.
2. All the abbreviations have been defined in schemes 3-5.
3. We have indicated the overall yield in Graphical abstract.
4. The hydrochloride salts of the compound 5 and 6 indicated as H_2^+ Cl^- in the manuscript.