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Stereoselective strategy for the synthesis of (+)-polyoxamic acid and some polyhydroxylated pyrrolidines

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ABSTRACT

An efficient strategy for the synthesis of dihydroxy chiral amino moiety which can be utilized for the synthesis of polyoxamic acid, 1,4-dideoxy-1,4-imino-D-xylitol, and dihydroxy pyrrolidine by using highly diastereoselective nucleophilic addition on chiral imine has been reported.

Dihydroxy chiral amino moiety which is shown in Fig. 1 is an important unit of many biologically active natural compounds such as polyoxin J **1a**, polyoxin L **1b**, polyoxin B **1c**, polyoxin D **1d**, 1,4-dideoxy-1,4-imino-D-xylitol **2**, and also dihydroxy alkylated pyrrolidine **3**. Polyoxamic acid **4**, a well known acyclic 3,4-dihydroxy amino acid moiety, is a structural component of the above polyoxins.[1] These polyoxins are the peptidyl nucleoside antibiotics and they act against serinepalmitoyl transferase[2] to block the biosynthesis of sphingolipids, phytopathogenic fungus, and chitin synthetase[3] of *candida albicans* and human fungi pathogen.[4] 1,4-Dideoxy-1,4-imino-D-xylitol **2** belongs to an important class of iminosugars (polyhydroxylated pyrrolidines) isolated from the pteridophyte *Arachniodes standishii*,[5] which is a known glycosidase inhibitor[6] and also a weak inhibitor of glycogen phosphorylase b.[7] It has also been observed that alkyl substituent iminosugars are showing strong glycosidase inhibitor activity.[8] Generally, glycosidases are involved in several important metabolic processes such as digestion, biosynthesis of glycoproteins, and the lysosomal catabolism of glycoconjugation, therefore glycosidase inhibitors have therapeutic applications for cancer, diabetes, bacterial, viral infections, and lysosomal storage disorders.[9] Despite the numerous clinical applications, many reports have been developed for the synthesis of **2** and **4** compounds.[10,11] Compound

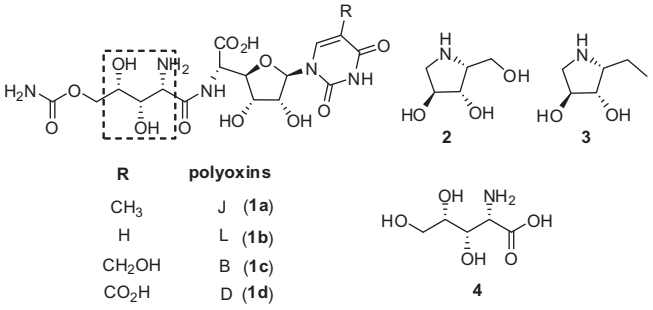

Figure 1. Some of the representative biologically active compounds.

3 comes under the class of alkylated dihydroxy pyrrolidine, whose structural analogues are known for their glycosidase inhibitor activity.[8] So far one synthesis has been reported for **3** in the form of its enantiomer.[12]

In continuation our efforts in developing a synthetic approach toward iminosugars and phytosphingosines using a highly stereoselective nucleophilic addition on N-glycosylamine derivatives,[13] herein we report an efficient strategy for the generation of dihydroxy chiral amino moiety **5** which can be utilized for the synthesis of (+)-polyoxamic acid **4**,[11] 1,4-dideoxy-1,4-imino-D-xylitol **2**,[10] and alkyl substituted dihydroxy pyrrolidine **3**[12] using a highly stereoselective Grignard addition of chiral imine as shown in Scheme 1.

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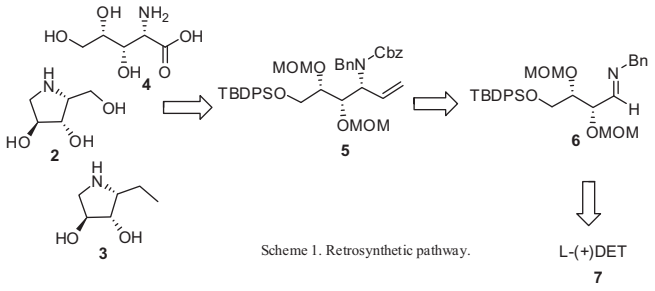
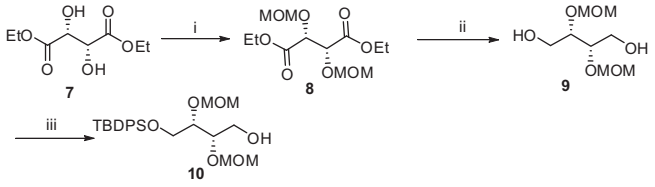


Scheme 1. Retrosynthetic pathway.



Scheme 2. Synthesis of key intermediate **10**. Reagents and conditions: (i) MOMCl, DIPEA, DMAP, DCM, 0 °C to rt, 12 h, 99%; (ii) LAH, THF, 0 °C to rt, 2h, 98%; (iii) TBDPSCl, *n*-BULi, THF, 0 °C, 1 h, 99%.

Our synthesis commenced from the commercially available diethyl L-tartarate **7**. Treatment of **7** with MOMCl and DIPEA in DCM gave compound **8** in 99% yield Scheme 2.[14a]

Reduction of ester functionality in **8** with $LiAlH_4$ in THF afforded the diol **9** in 98% yield.[14a] Selective protection of diol **9** in THF using TBDPSCl and *n*-BuLi gave alcohol **10** in 99% yield.[15] Swern oxidation of primary alcohol **10** gave the desired aldehyde, which on treatment with $BnNH_2$ in DCM at −4 °C gave the corresponding imine **6**. Grignard addition on crude imine **6** with vinylmagnesium bromide at 0 °C gave *threo* isomer **11** diasteroselectively as the sole product in 85% (from **10**). The highly diasteroselective addition was expected on the basis of the Chelation–Cram model, in which the nucleophile (vinyl) approaches from the less hindered face of the conformationally locked imine (Fig. 2).[16] Treatment of the secondary amine in **11** with CbzCl and $NaHCO_3$ in MeOH gave compound **5** in good yield. For the synthesis of polyoxamic acid, ozonolysis of the terminal olefin in compound **5** at −78 °C afforded the aldehyde, which underwent Pinnick oxidation to give acid **12** in 80% (over two steps). The compound **12** was subjected to hydrogenolysis over catalytic Pd/C in MeOH followed by acid treatment with 6 M HCl afforded the desired final product (+)-polyoxamic acid **4**. The analytical and spectral data were in good agreement with the reported values.[11n]

This approach helps in synthesizing polyoxin J **1a,** polyoxin L **1b,** polyoxin B **1c**, and polyoxin D **1d**. Removal of the silyl group in **5** with TBAF followed by known carbamoylation[17] and oxidation of the olefin will give carbamoyl polyoxamic acid. Coupling of this acid with appropriately protected thymine polyoxin C, will yield the above polyoxins based on the reported procedures Scheme 3.[17]

For the synthesis of 1,4-dideoxy-1,4-imino-D-xylitol **2**, compound **5** in DCM was subjected to ozonolysis at −78 °C to afford the aldehyde, which on reduction with $NaBH_4$ in MeOH gave primary alcohol **13** in 85% yield (for 2 steps). Protection of primary alcohol in **13** as MOM ether using MOMCl and DIPEA in DCM gave compound **14** in 90% yield. Cleavage of the silylether group in **14** using TBAF in THF afforded alcohol **15** in good yield. Treatment of primary alcohol **15** with MsCl and Et_3N in DCM gave the mesylated product, which on hydrogenolysis in the presence of catalytic Pd/C in MeOH and treatment of the crude mixture with 6 M HCl gave the desired final compound 1,4-dideoxy-1,4-imino-D-xylitol **2** in 80% yield (over 2 steps), whose spectral and analytical data were in good accordance with the literature values Scheme 4.[10a]

Then, we turned our attention to synthesize dihydroxy pyrrolidine **3**. Treatment of compound **5** with TBAF gave alcohol **16** in 90% yield. For the construction of the pyrrolidine ring, compound **16** was mesylated and the mesylated mixture was subjected to hydrogenolysis followed by acid treatment with 6 M HCl to afford

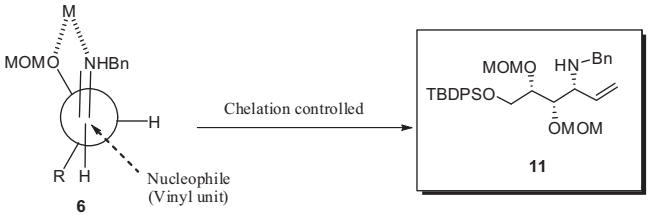
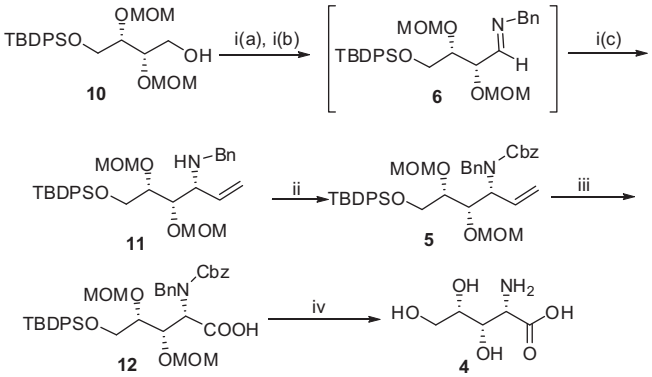
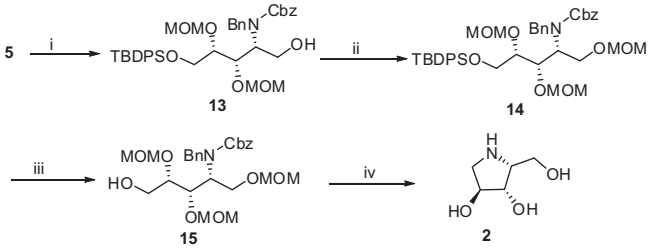


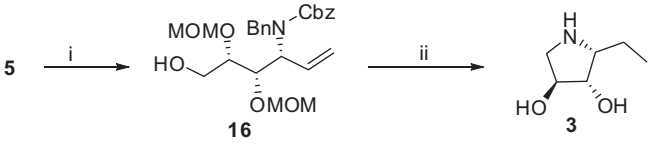
Figure 2. Chelation-controlled addition of imine **6**.



Scheme 3. Synthesis of (+)-polyoxamic acid **4**. Reagents and conditions: (i) (a) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 2 h; (b) $BnNH_2$, DCM, 4 Å molecular sieves, Na_2SO_4, −4 °C,4 h; (c) vinylmagnesium bromide, THF, 0 °C to rt, 30 min, 85% (over 3 steps); (ii) CbzCl, $NaHCO_3$, MeOH, 0 °C to rt, 2 h, 90%; (iii) (a) O_3, DCM, −78 °C, then Me_2S; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, 0 °C to rt, 2 h, 80% (over 2 steps); (iv) 10% Pd/C, H_2, MeOH, rt, 12 h, then 6 M HCl, rt, 6 h, 85%.



Scheme 4. Synthesis of 1,4-dideoxy-1,4-imino-D-xylitol **2**. Reagents and conditions: (i) (a) O_3, DCM, 30 min, then Me_2S, −78 °C; (b) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 85% (over 2 steps); (ii) MOMCl, DIPEA, DCM, DMAP, 0 °C to rt, 12 h, 90%; (iii) TBAF, THF, rt, 1 h, 87%; (iv) (a) MsCl, Et_3N, DCM, DMAP, 30 min; (b) 10% Pd/C, H_2, MeOH, rt, 12 h, then 6 M HCL, rt, 12 h, 80%.



Scheme 5. Synthesis of dihydroxy pyrrolidine **3**. Reagents and conditions: (i) TBAF, THF, rt, 1 h, 90%; (ii) (a) MsCl, Et_3N, DCM, DMAP, 30 min; (b) 10% Pd/C, H_2, MeOH, rt, 12 h, then 6 M HCL, rt, 6 h, 80%.

the final compound pyrrolidine **3** in good yield, whose spectral and analytical data were in good accordance with the reported *ent*-**3** values Scheme 5.[12]

In conclusion, we have achieved the synthesis of dihydroxy chiral amino moiety **5** a versatile intermediate for the synthesis of (+)-polyoxamic acid **4**, 1,4-dideoxy-1,4-imino-D-xylitol **2**, and dihydroxy pyrrolidine **3** using a highly diastereoselctive Grignard addition on imine **6** as the key step from the commercially available diethyl L-tartarate as a starting material. Future applications of this strategy for the synthesis of some molecules containing polyhydroxy chiral amino units are under progress.

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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.2013.08.126.

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