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A divergent, short, and stereoselective approach to pyrrolidine iminosugars: synthesis of 1,4-dideoxy-1,4-imino-derivatives of D-allitol, D-ribitol, ethyl-erythritol, and (−)-2,3-*trans*-3-4-*cis*-dihydroxyproline

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ABSTRACT

A highly stereoselective addition of Grignard reagent on lactamine for the synthesis of 1,4-dideoxy-1,4-imino-derivatives of D-allitol, D-ribitol, ethyl-erythritol, and (−)-2,3-*trans*-3-4-*cis*-dihydroxyproline has been described from commercially available D-ribose as a starting material.

Introduction

Polyhydroxylated pyrrolidine and piperidine alkaloids, also known as iminosugars or azasugars, show structural resemblance to monosaccharides but would appear to be fairly widespread as secondary metabolites in nature since they have been isolated from species of both tropical and temperate plants from quite unrelated families having enormous therapeutic potential for many diseases such as viral,[1] bacterial, and fungal infections,[2] diabetes,[3] hyperglycemic,[4] Gaucher's disease[5] etc. Most of the azasugars show powerful glycosidase inhibitory activity.[6] Some of these compounds are available in the market as drugs. The structural features and biological activity of these molecules have led to increasing interest among biologists and chemists.[7]

Naturally occurring iminosugars having 1,4-didexoy-1,4-imino-hexitol core, in specific, molecules containing 3,4-dihydroxy pyrrolidine moiety show interesting biological activity. For example homo DMDP (2,5-dideoxy-2,5-imino-D-mannitol) **1** is a specific intestinal α-glucosidase inhibitor (IC_{50} = 0.92 μM) (Fig. 1).[8] The compound 1,4-dideoxy-1,4-imino-D-allitol **2** is a strong inhibitor of β-glucosidase and β-galactosidase.[9] 1,4-Dideoxy-1,4-imino-D-ribitol **3**, a natural compound, is a mimic of furanoside and was isolated from roots of the mulberry tree of the species *Morus alba*. Because of the strong specific inhibitiory activity of eukaryotic polymerases, compound **3** is a potential anti-HIV agent[10] and also acts as an anti-proliferative and anti-neoplastic agent.

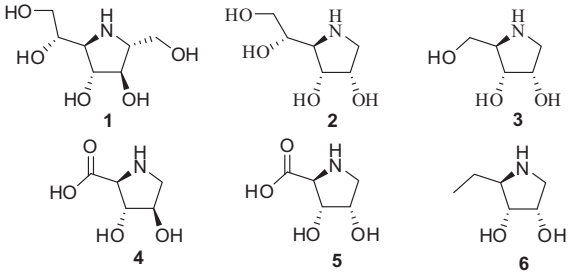

Figure 1. Structures of some biologically active iminosugars.

Extensive studies elicited that the 2-methylamino[11a,b] and 5-*O*-alkyl and 5-*O*-aryl derivatives[12] of **3** have shown anti cancer activity. Also Guanidino-alkyl-ribitol derivatives and *N*-aryl-methyl-iminoribitol derivatives of **3** exhibits nucleoside hydrolyzing inhibition.[13]

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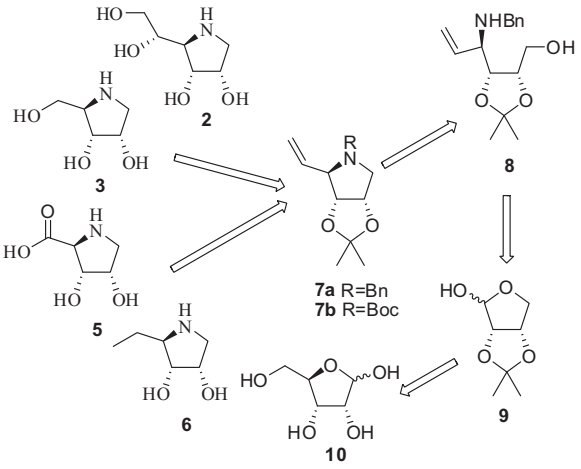


Scheme 1. Retrosynthetic pathway for iminosugars.

(−)-2,3-*trans*-3,4-*trans*-Dihydroxyproline **4** was isolated in 1980 by Buku et al. from the acid hydrolysis of the toxic mushroom *Amanita virosa* and is identified as a constituent of virotoxin cyclic heptapeptides.[14]

(−)-2,3-*trans*-3-4-*cis*-Dihydroxyproline **5**, a C-4 epimer of **4** was isolated from the marine mussel *Mythilus edulis* and found as a constituent of the sixth residue in the repeating decapeptide sequence of the adhesive protein Mefp1.[15a] Before the isolation of (−)-2,3-*trans*-3-4-*cis*-dihydroxyproline **5** by Taylor et al., Fleet and coworkers had reported its synthesis from D-gluconolactone.[15b] Ethyl-1,4-dideoxy-1,4-iminoerythritol **6**, a synthetic compound is a potent inhibitor of α-D-galactosidase and α-L-fucosidase and a moderate inhibitor of β-D-glucosidase.[16]

The important biological activity of these compounds obviously attracted the attention of many synthetic chemists. There are some reports in the literature for the synthesis of **2**,[17a,b] **3**,[12,17c] **5**,[15b,17d] and **6**[16] using different strategies from different starting materials. In continuation of our efforts in the stereoselective synthesis of azasugars[18] by using nucleophilic Grignard addition reaction on sugar imines, herein we report the application of above strategy for the synthesis of **2**, **3**, **5,** and **6** (Fig. 1).

Results and discussion

All the target compounds can be obtained from vinylpyrrolidine derivatives **7a** and **7b** which in turn can be obtained from the vinyl amino derivative **8**. Compound **8** can be prepared from isopropylidene erythrose **9**. Preparation of compound **9** from D-ribose **10** is already reported in the literature (Scheme 1).[19] Treatment of **9** with $BnNH_2$ in MeOH under reflux condition afforded lactamine **11**. Without further purification, lactamine **11** underwent a nucleophilic addition with vinylmagnesium bromide in THF to give *anti* amino alcohol **8** in 85% yield (over two steps). The newly generated stereocentre in **8** was *anti* in relation to an adjacent chiral center as per our earlier observations (Scheme 2). The highly diasteroselective addition was expected on the basis of Felkin–Anh model, in which the nucleophile approaches from the least hindered face of the conformationally locked imine **11** (Fig. 2).[18a–f] Further the

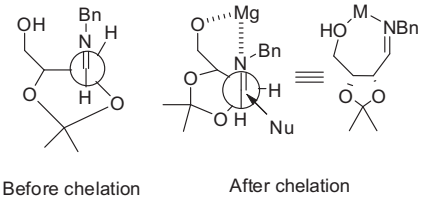
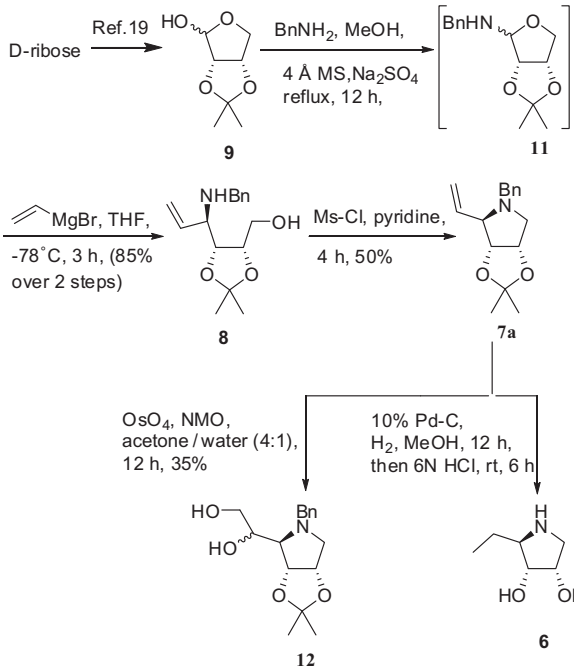
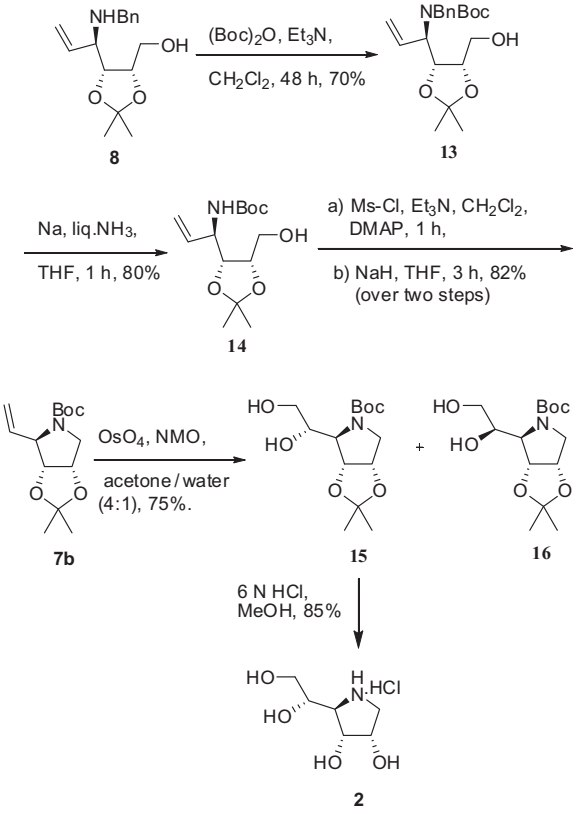


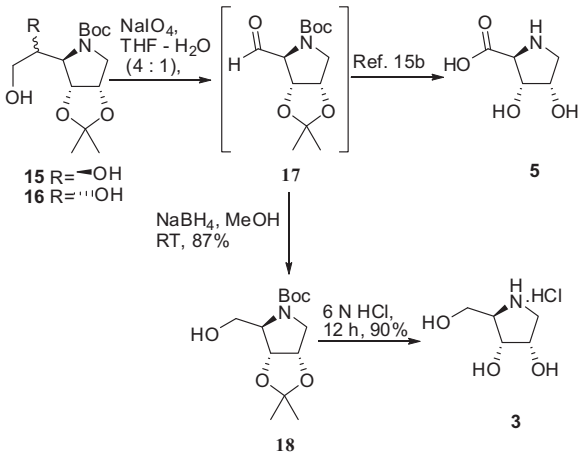
Figure 2. Seven membered transition state of the Felkin–Anh model.



Scheme 2. Synthesis of ethyl-1,4-dideoxy-1,4-iminoerythritol.



Scheme 3. Synthesis of 1,4-dideoxy-1,4-imino-D-allitol.



Scheme 4. Synthesis of 1,4-dideoxy-1,4-imino-D-ribitol and (−)-2,3-*trans*-3-4-*cis*-dihydroxyproline.

newly generated stereocentre of the compound **8** was confirmed by 2D NOE in cyclized form **7a** (Scheme 2).[18h]

The key intermediate **8** was treated with pyridine and Ms-Cl at room temperature to give the amino pyrrolidine **7a** in 50% yield. Hydrogenolysis of **7a** for 12 h followed by deprotection of acetonide with 6 N HCl gave the ethyl-imino erythritol **6** whose spectral and physical data were in good agreement with the reported values.[16] Dihydroxylation of **7a** with OsO_4 and NMO in the mixture of acetone/water (4:1) afforded the inseparable diastereomeric mixture **12** in 35% yield in almost 1:1 ratio (Scheme 2).

In an attempt to improve the yield and diastereomeric excess, it was planned to carry out the OsO_4 dihydroxylation on *N*-Boc derivative **7b**. For this, the compound **8** was subjected to $(Boc)_2O$, Et_3N in DCM to give **13**. Deprotection of *N*-benzyl group in **13** using Na and liq. NH_3 at −78 °C gave the desired amino alcohol **14** in 80% yield. The primary alcohol **14** was treated with Ms-Cl, Et_3N, and DMAP in CH_2Cl_2 gave mesylate derivative which upon without purification was treated with NaH in THF yielded the required vinylpyrrolidine **7b** in 82% yield (over two steps) (Scheme 3).

The *N*-Boc vinyl pyrrolidine **7b** was subjected to dihydroxylation with OsO_4 and NMO in acetone/water (4:1) and afforded separable diastereomers **15**[15b] and **16** in 9:1 ratio in 75% yield. The global deprotection of **15** with 6 N HCl in MeOH gave the final product 1,4-dideoxy-1,4-imino-D-allitol **2** in 85% yield as a hydrochloride salt, whose spectral and physical data were in good agreement with the reported values.[17a]

Oxidative cleavage of diols **15** and **16** by sodium periodate in combination with THF/H_2O (4:1) gave aldehyde **17** which was reduced to alcohol **18** in the presence of $NaBH_4$ in MeOH. The spectral data of **18** were in good agreement with the reported values (Scheme 4).[20] Global deprotection of *N*-Boc and acetonide with 6 N HCl gave the required salt **3**, whose spectral data were in good accordance with the reported values.[12] Compound **17** has already been converted to (2*S*,3*R*,4*S*)-3,4-dihydroxyproline **5** in two steps by Fleet et al.[15b]

Conclusion

We have developed a short and stereoselective synthesis of D-allitol **2**, 1,4-dideoxy-1,4-imino-D-ribitol **3**, (−)-2,3-*trans*-3-4-*cis*-dihydroxyproline **5,** and ethyl-erythritol **6**. The key intermediates vinyl pyrrolidines **7** could be easily accessible from erythrolactol **9**, which could be a useful chiral precursor for the important bioactive iminosugars such as swansonine, lentiginosine, fagomine, australine etc.

Acknowledgments

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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.2015.01.115.

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Spectral data of compound (**2**.**HCl**): mp: 109–111 °C; $[\alpha]_D^{26}$: +26.9 (*c* 1.1, H_2O), [lit.[17a] $[\alpha]_D^{26}$ +25.6 (*c* 0.9, H_2O)]; IR (neat) ν_{max} (KBr)/cm^{-1}: 3420, 1443; **^{1}H NMR** (D_2O, 500 MHz): δ 4.33 (m, 1H), 4.24 (dd, 1H, *J* = 8.9 and 4.4 Hz), 3.98 (q, 1H, *J* = 8.9 and 4.4 Hz), 3.75 (dd, 1H, *J* = 12.0 and 3.8 Hz), 3.64 (dd, 1H, *J* = 12.0 and 5.1 Hz), 3.52 (dd, 1H, *J* = 8.9 and 3.8 Hz), 3.44 (dd, 1H, *J* = 13.3 and 3.8 Hz), 3.33 (dd, 1H, *J* = 12.7 and 1.2 Hz); **^{13}C NMR** (D_2O, 75 MHz): δ 73.1, 70.2, 68.8, 64.3, 62.6, 50.9; HRMS (ESI, Orbitrap): calcd for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0922 found 164.0919.

Spectral data of compound (**3**.**HCl**): mp 125–127 °C; $[\alpha]_D^{26}$: +50.4 (*c* 1.1, H_2O) {lit.,[12] $[\alpha]_D^{25}$ +53.3 (*c* 0.75, H_2O)}; IR (neat) ν_{max} (KBr)/cm^{-1}: 3448, 2926, 1259, 1154; **^{1}H NMR** (D_2O, 500 MHz): δ 4.45 (m, 1H), 4.25 (dd, 1H, *J* = 7.9 and 3.9 Hz), 4.02 (dd, 1H, *J* = 11.9 and 2.4 Hz), 3.87 (dd, 1H, *J* = 12.4 and 5.4 Hz), 3.68 (m, 1H), 3.55 (dd, 1H, *J* = 12.9 and 2.9 Hz), 3.47 (d, 1H, *J* = 12.9 Hz); **^{13}C NMR** (D_2O, 75 MHz): δ 72.0, 70.2, 62.6, 58.9. 50.5; HRMS (ESI, Orbitrap): calcd for $C_5H_{12}O_3N$ $[M+H]^+$ 134.08117 found 134.08110.

Spectral data of compound (**6**): $[\alpha]_D^{26}$: +17.3 (*c* 1.0, MeOH), IR (neat) ν_{max} (KBr)/cm^{-1}: 3421, 1381, 1211, 1217, 1086; **^{1}H NMR** (400 MHz, D_2O): δ 4.42 (m, 1H), 4.11 (m, 1H), 3.67 (m, 1H), 3.21 (m, 1H), 2.81 (m, 1H), 1.30–1.79 (2 m, 2H), 0.95 (t, 3H); **^{13}C NMR** (100 MHz, D_2O): δ 76.2, 70.9, 62.5, 49.6, 25.39, 10.4; HRMS (ESI, Orbitrap): calcd for $C_6H_{14}O_2N$ $[M+H]^+$ 132.10191 found 132.10166.