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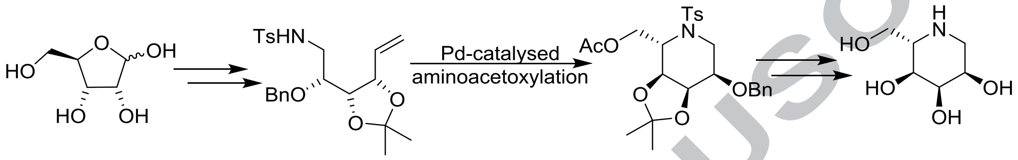

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Pintu Das, Sama Ajay and Arun K. Shaw∗

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute (CSIR-CDRI), Sector 10, Jankipuram Extension, Sitapur road, Lucknow-226031, U. P., India.

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ABSTRACT

Palladium catalysed intramolecular aminoacetoxylation of D-ribose derived alkenyl tosylsulfonamide to deliver L-deoxyallonojirimycin in an overall yield of 19%. The preliminary screening of L-deoxyallonojirimycin against carbohydrate processing enzymes showed moderate inhibitory activity against α-glucosidase (yeast) and α-mannosidases.

Introduction

Palladium (II)-catalyzed stereoselective vicinal difunctionalization of alkene is among the most important and powerful methodology in modern organic chemistry for the formation of C-N bond.[1] Palladium-catalyzed aminoacetoxylation[2] and diamination[3] of alkenes with hypervalent iodine [PhI(O$_2$CR)$_2$] as the stoichiometric oxidant has also gained much pace in the recent years. A wide variety of nitrogen nucleophiles are known to attack the palladium (II)-activated alkene to give an alkyl palladium (II) intermediate followed by PhI(O$_2$CR)$_2$ induced oxidative cleavage of the Pd-C bond, presumably via Pd$^{\text{III}}$ or Pd$^{\text{IV}}$ intermediates. This intermolecular difunctionalization process involves the tandem X-N and C-X (X= N, O, C, halides, etc.) bond formation.[4]

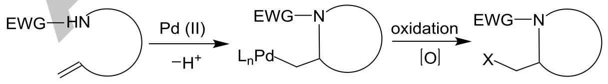


Figure 1. General palladium catalyzed difunctionalization.

In 2005, Sorensen[5] and Muñiz[6] reported the intramolecular Pd-catalyzed aminoacetoxylation and diamination of alkenes by trapping the Pd-C intermediate in presence of an oxidant PhI(OAc)$_2$.[2b] Later Sanford and co-workers demonstrated that PhI(OAc)$_2$ could serve as an oxidizing agent to facilitate C-X bond formation by converting Pd$^{\text{II}}$ to Pd$^{\text{IV}}$.[7] In 2006, Liu and Stahl reported highly regio- and diastereoselective intermolecular aminoacetoxylation of terminal alkenes using an excess of alkene with respect to the nitrogen nucleophile.[2b] Recently, Martıñez and Muñiz modified the Stahl conditions with complete chemo-, regio-, and diastereoselectivity of intermolecular diamination[8] of internal alkenes with the alkene as the limiting reagent. In 2010, Wolfe and co-workers developed the enantioselective synthesis of pyrrolidine derivatives via Pd-catalyzed alkene carboamination reactions with aryl bromides. Michael and co-workers reported a novel method for Pd(II) catalyzed carboamination of alkenes using *N*-fluorobenzenesulfonimide (NFBS) as an oxidant for the synthesis of five-, six- and seven-membered-ring nitrogen heterocycles.[9] These reports thus led to understand that the intramolecular aminoacetoxylation of alkene (tandem C-N and C-O bond formation) could be a method of choice for the stereoselective construction of nitrogen heterocycles, which are common building blocks existing in various natural products.

As a part of our on-going programme towards synthesis of iminosugars and azacycles using newly developed synthetic strategies,[10] we decided to investigate the synthesis of piperidine iminosugars from sugar derived alkenyl sulphonamide by Pd(II)-catalyzed oxidative tandem cyclization reaction. L-(+)-1-deoxynojirimycin (**2**), isolated from the roots of *mulberry* trees[11] has been shown to be inhibitor for α-glucosidases I and II[12] while 1-deoxymannojirimycin (**3**), isolated from *Lonshocarpus sericeus* by L.E. Fellows in 1979,[13] exhibited a potent inhibition against α-L-fucosidase, α-D-mannnosidase and α-D-glucosidase.[14] Due to the interesting biological activities of compounds **2** and **3**, as well as their derivatives, several stereoselective synthetic routes[15] of these types of piperidine iminosugars have been developed. Encouraged by above literature reports, herein we disclosed palladium catalyzed intramolecular aminoacetoxylation of sugar derived alkene to obtain optically active L-1-deoxyallonojirimycin **1**.

∗ Corresponding author. Tel.: +91-9415403775, 91-7754097788; e-mail: akshaw55@yahoo.com

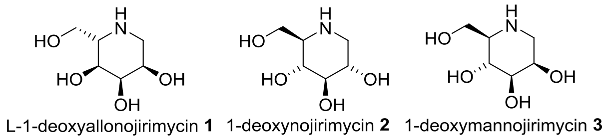
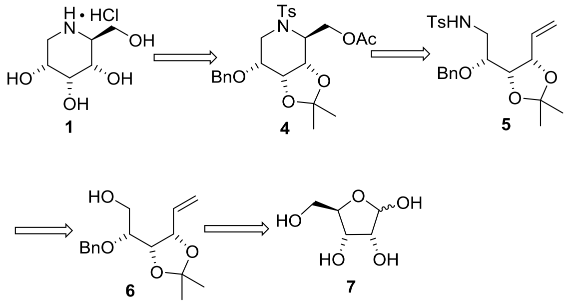


Figure 2. Some piperidine iminosugars.

Results and discussion

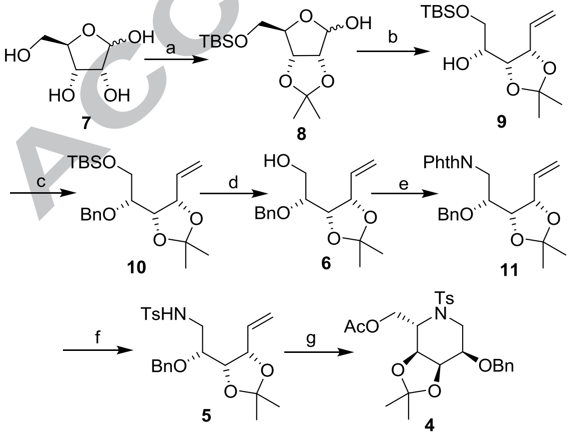
Retrosynthetic strategy for target piperidine iminosugar **1** is delineated in Scheme 1. We envisioned that **1** could be elaborated from N-tosylated compound **4** which could be obtained from alkenyl tosylsulfonamide **5** using palladium-catalyzed ring forming aminoacetoxylation. Its synthesis could be possible from alkenyl alcohol **6** which in turn could be accessed from commercially available D-ribose **7** via Wittig olefination and protecting group manipulations.



Scheme 1. Retrosynthetic analysis of L-1-deoxyallonojirimycin **1**.

Synthesis of L-1-deoxyallonojirimycin 1

Synthesis of piperidine **1**, commenced from commercially available D-ribose **7** was first converted to 2,3-*O*-isopropylidine-D-ribose by treating it with 2,2-dimethoxypropane in acetone in presence of catalytic amount of *p*-toluenesulfonic acid. The primary hydroxyl group of 2,3-*O*-isopropylidine-D-ribose was protected as silyl ether by using TBDMSCl and imidazole to give the known hemiacetal **8**[16] in 90% yield. Its Wittig methylenation with methyltriphenylphosphonium bromide in presence of potassium *tert*-butoxide in THF at 0 °C furnished alkenol **9**. The benzylation of its free hydroxyl group in DMF with BnBr and NaH yielded compound **10**. Its deprotection using tetrabutylammonium fluoride at 0 °C afforded compound **6**.



Scheme 2. *Reagents and conditions:* (a) (i) 2,2-dimethoxypropane, PTSA, acetone, 0 °C, 2 h, 90%; (ii) TBDMSCl, imidazole, DCM, 0 °C, 2 h, 90%; (b) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C to 25 °C, 3 h, 82%; (c) BnBr, NaH, THF, 0 °C, 3 h, 88%; (d) TBAF, THF, 0 °C, 92%; (e) PPh_3, DIAD, phthalimide, THF, 0 °C to 20 °C to rt, overnight, 94%; (f) (i) 40% aq. $MeNH_2$, 60 °C, 3 h, rt.; (ii) TsCl, Et_3N, DCM, 3 h, 72% over two steps; (g) $Pd(OAc)_2$, $PhI(OAc)_2$, Bu_4NOAc, DCM, 0 °C to 25 °C, 3 h, 72%.

Single step conversion of hydroxyl functionality in **6** into its corresponding amine was performed by Mitsunobu reaction in presence of PPh_3, phthalimide and DIAD in THF at 0 °C to room temperature. The desired phthalimido compound **11** was obtained in 94% yield. Its conversion to the amine was done smoothly by treating it with 40% aqueous $MeNH_2$ at 60 °C for 3 h. The reaction mixture was concentrated and tosyl protection of the crude primary amine was achieved by treating it with triethylamine and *p*-toluenesulfonyl chloride at 0 °C in DCM to obtain amine **5** in overall 72% yield from **11**. Its treatment with 10 mol % $Pd(OAc)_2$ in presence of 2.0 equiv of $PhI(OAc)_2$ and 1.0 equiv of Bu_4NOAc in CH_2Cl_2 at 0 °C to 25 °C for 3 hours resulted in the formation of aminoacetoxylation product **4** as an exclusive product in 72% yield (Scheme 2).[2a]

The 1D and 2D NMR experiments of compound **4** showed the formation of piperidine skeleton but its stereochemical outcome could not be analysed due to the appearance of overlapping signals for H-5 (1H) and H-6 (2H) at 4.08-4.02 (3H) ppm in ^1H spectra. Therefore, in order to establish its stereochemistry completely, we choose its benzyl analogue **12**. In its ^1H NMR spectra the signals for H-5 (1H) and H-6 (2H) got separated and appeared at 3.99-3.97 H-5 (1H) ppm and 3.57-3.53 H-6 (1H), 3.48-3.44 H-6 (1H) ppm respectively.

The structure of the product **12** was finally confirmed by detailed analysis of its NMR spectral data. The ^1H NMR spectral data, combined with extensive decoupling experiments and 2D ^1H-^1H COSY spectra data, defined the complete connectivity of the hydrogen atoms. NOESY correlation between H-3 and H-1, H-3 and H-2, H-3 and H-4, H-3 and H-6 and no correlation between H-3 and H-5 indicated that H-5 must be in equatorial position (Figure 3). In addition, very small (1.4 Hz) coupling constant value also supported the 1,2-di equatorial position of proton H-4 and H-5.

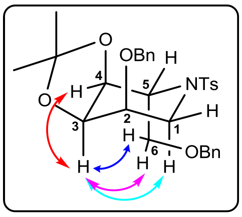
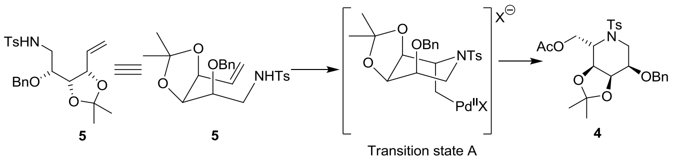


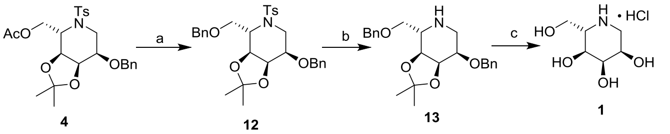
Figure 3. NOESY correlations of compound **12**.

Thus, the above NMR studies established the structure of compound **12**. The stereoselective formation of **4** could be explained by assuming that the cyclization proceeded *via* transition state A in which palladium made complex with the alkene on the α-face opposite to that of all the substituents leading to the exclusive formation of compound **6** (Scheme 3).



Scheme 3. Transition state for the formation of **4**.

The conversion of the *N*-tosylated piperidine **4** to iminosugar **1** was completed in three-step sequence. *N*-detosylation of compound **4** using several methods (Na/naphthalene, SmI_2 and Mg in methanol) turned out to be futile. Therefore, we slightly changed our strategy at this step and thought that replacement of more labile acetate functionality with more stable benzyl group may work well as well as this modification could prevent the need for deacetylation step at the final stage. Thus deacetylation of compound **4** with sodium methoxide in methanol followed by benzylation using BnBr in DMF gave compound **12** (Scheme 4). Its *N*-tosyl group was deprotected by Na-napthalenide at -78 °C within 10 min. in THF to afford compound **13** in 92% yield.[17] Removal of the benzyl group and acetonide group in **13** was done in single step by treating it with $Pd(OH)_2/C$ in the presence of H_2 in methanolic HCl to obtain the target piperidine iminosugar (2R,3R,4S,5S)-5-(hydroxymethyl)piperidine-2,3,4,-triol (**1**) as its HCl salt.[18]



Scheme 4. *Synthesis of L-1-deoxyallonojirimycin* ***1****:* (a) (i) NaOMe, MeOH 0 °C; (ii) BnBr, NaH, THF, 0 °C, 3 h, 88%; (b) Na-Napthalene, THF, -78 °C, 92%; (c) H_2, $Pd(OH)_2/C$, MeOH-HCl, 12 h, 98%.

Glycosidase Inhibition

L-1-deoxyallonojirimycin **1** was subjected to a preliminary screening against carbohydrate processing enzymes and its inhibition results are summarised in Table 1. It showed moderate inhibitory activity against α-glucosidase (yeast) and α-mannosidase. Further efforts to obtain selective inhibitors and their relevance to anti-cancer activity are currently underway.

Table 1. Concentration of piperidine **1** giving 50% inhibition[a] (IC_{50}) of various glycosidases.

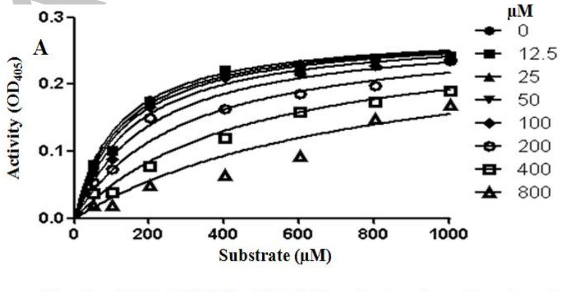
α-glucosidase			β-glucosidase	α-galactosidase	β-galactosidase	α-mannosidase	α-L-Fucosidase
Yeast	Rice	*Asp. niger*	NI	NI	NI	234.76 **131**	NI
529.7 **137.3**[b]	NI[c]	NI					

[a]Inhibition was competitive in all cases

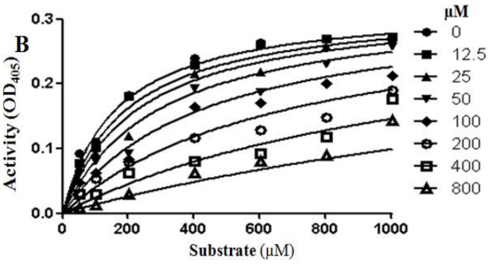
[b]K_i values are given in bold

[c]NI: No inhibition at 800 μM

Graphs A and B (Figure 4) represent Michaelis-Menten plot of Activity *versus* substrate concentration for inhibition of various enzymes by compound **1**. The K_i values were determined by nonlinear regression using Graph Pad Prism. Activity is represented as absorbance of liberated *p*-nitrophenol measured at 405 nm. Competitive inhibition is indicated in each case.



Ki value 137.3 μM, IC50 ~ 529.7μM against α-glucosidase (yeast)



Ki value 61.85 μM, IC50 ~ 234.76μM against Manosidase (Jack beans)

Figure 4. Michaelis-Menten plot of Activity *vs* Substrate concentration for inhibition of various enzymes by piperidine **1**. The K_i were determined by non-linear regression using Graph Pad Prism (version 6.01 for Windows, Graph Pad Software, San Diego California USA).

Conclusions

In conclusion, we have described the stereoselective synthesis of L-1-deoxyallonojirimycin **1**, started from D-ribose, with an overall yield of 19%. The key step in the sequence is palladium(II)-catalyzed intramolecular ring forming aminoacetoxylation of the alkenyl sulphonamide. The title compound was subjected to preliminary screening against carbohydrate processing enzymes and it showed moderate inhibitory activity against α-glucosidase (yeast) and α-mannosidases.

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18. **(2S,3S,4R,5R)-2-(hydroxymethyl)piperidine-3,4,5-triol (1):** Catalytic amount of 10% Pd$(OH)_2$/C (20 mg) was added to a solution of **13** (40 mg, 0.104 mmol) in methanolic HCl (5 mL). A vacuum was created in a round bottom flask containing the above reaction mixture with the help of pump for few seconds and then the reaction mixture was left for stirring under a positive pressure of H_2 in a balloon. After the completion of the reaction (TLC control, 48 h) catalyst was removed by filtration, washed with methanol twice and the combined filtrate was concentrated to afford a crude mixture which was purified by flash column chromatography to give HCl salt of compound **1** as a colorless oil (17 mg, 0.102 mmol, 98%). Eluent for column chromatography: Et_2O/MeOH/ 25% aq. NH_3 = (100/1/0, v/v) to Et_2O/MeOH/ 25% aq. NH_3 = (90/10/2, v/v); $[\alpha]_D^{28}$ -25 (*c* 0.800, H_2O)[15d]; R_f = 0.21 (2/8, MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, D_2O) δ 4.20 (s, 1H), 4.04-3.85 (m, 4H), 3.37-3.28 (m, 2H), 3.15 (t, *J* = 11.82 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 69.9, 65.3, 64.5, 57.6, 54.7, 41.5; IR (neat, cm^{-1}) 3412, 3019, 1643, 1384; DART–HRMS: m/z $[M+H]^+$ Calcd for $C_6H_{14}NO_4$ 164.0922, found 164.0913.

Highlights

- Completed the synthesis of L-1-deoxyallonojirimycin, with an overall yield of 19%.
- Palladium-catalyzed intramolecular ring forming aminoacetoxylation is the key step.
- The L-1-deoxyallonojirimycin showed moderate inhibitory activity.
- Mechanistic explanation has been given for the key step.