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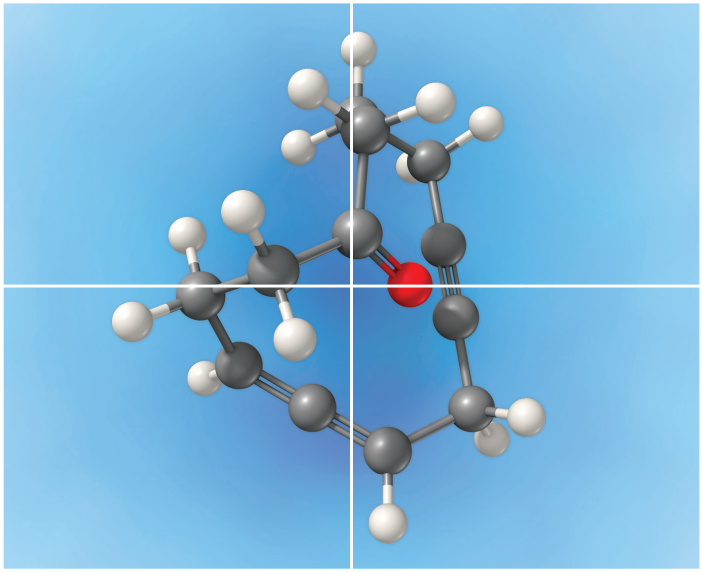

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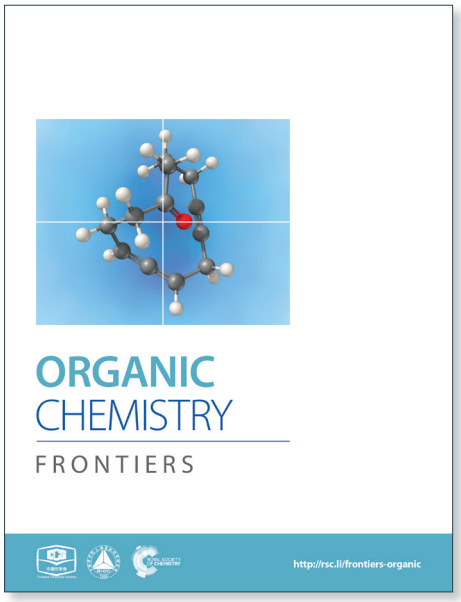

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COMMUNICATION

Stereoconvergent synthesis of 1-deoxynojirimycin isomers by using the 3 component 4 centred Ugi reaction

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Chandra S. Azad, Anil K. Saxena*

A new reductive cyclization/Ugi multicomponent reaction sequence for the synthesis of 1-deoxyallonojirimycin and 1-deoxyaltronojirimycin has been developed. The method was successfully applied to the azido-hemiacetal derived from commercially available D-Ribose. The very selective reagents were used for the synthesis of Ugi bis-amides which were sub sequentially hydrolysed to Iminosugars.

Iminosugars are the carbohydrate mimics which have the nitrogen atom instead of endocyclic oxygen. This simple substitution raises numerous synthetic challenges and opens the approach to get novel molecules with significant biological properties. Iminosugars definitely form the most eye-catching class of carbohydrate mimics described so far.[1] The real era of iminosugars was initiated by Paulsen in 1966 by the first synthesis of 1-deoxynojirimycin (**1**) (DNJ).[2] In the same year, Inouye *et al*. identified its antibiotic properties by isolating it from bacteria (Streptomyces).[3] Various iminosugars are currently in clinical trials and the first success was drug Glyset (**2**) in 1996 for the treatment of complications associated with type II diabetes. Recently, iminosugars based Zavesca (**3**) was also developed as the first oral treatment for Gaucher disease (a severe lysosomal storage disorder) in 2003 and several other molecules are under clinical trial (**Figure 1**).[4] The importance of DNJ is clearly reflected as its two derivatives are drug molecules. Although iminosugars are highly active molecules nevertheless they did not gain much attention as compared to other therapeutically important scaffolds. The main reason is the challenging chemical synthesis, because of the polar nature of the polyhydroxylated structures and their stereochemical complexity.[5] The D-and L-enantiomers of 1-DNJ were evaluated by the Kato *et al*, where L-DNJ isomer showed potential inhibition of α-glucosidase rice (IC_{50} 4.3 μM) while the L-allo-DNJ showed the inhibition of rat epididymis (IC_{50} 59 μM) and L-altro-DNJ showed inhibition of α-glucosidase (IC_{50} 450 μM) as compared to their inactive D-isomers.[6]

The selectivity of L-iminosugars may contribute to its effective medicinal use, as the beginning of adverse effects by their D enantiomers (due to their capacity to inhibit disaccharidases and/or their biosynthesis in intestinal brush border membrane) have often hindered in vivo clinical trials.[7] These results highlights the significance of the synthesis and screening of iminosugars with

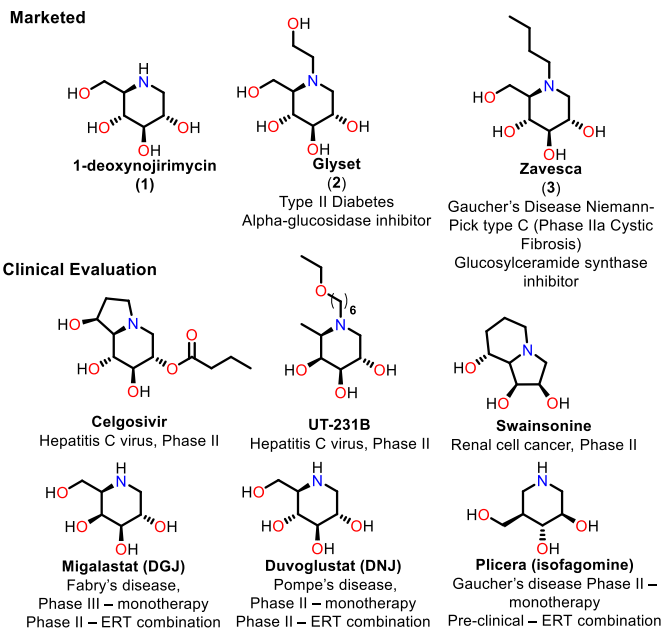
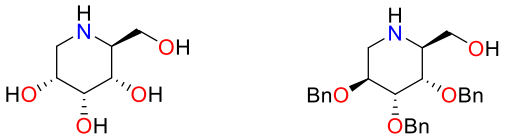


Figure1. Marketed drug molecules and current status of other iminosugars.

unnatural L-configurations having little stereo chemical resemblance to the enzyme's natural substrates. Still, few attempts have been made towards the syntheses of such isomers of 1-DNJ, viz. L-1-deoxyallonojirimycin (L-*allo*-DNJ) and L-1-deoxyaltronojirimycin (L-*altro*-DNJ). In continuation of our interest in the synthesis of nitrogen containing heterocycles, we envisaged the syntheses of L-1-deoxyallonojirimycin (L-allo-DNJ) and L-1-deoxyaltronojirimycin (L-altro-DNJ) by a chiral pool strategy using D-Ribose as the starting material and Ugi reaction as the core approach (**Figure 2**). The main synthetic challenges for the L-allo-DNJ and L-altro-DNJ syntheses were the development of one pot cost effective reductive Ugi cyclization for the construction of piperidine moiety, preservation of hydroxy groups with correct stereochemistry and mild hydrolysis of Ugi bis-amide.

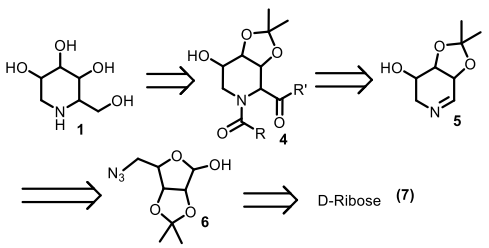


L-1-deoxyallonojirimycin (L-*allo*-DNJ)

L-1-deoxyaltrojirimycin (L-*altro*-DNJ)

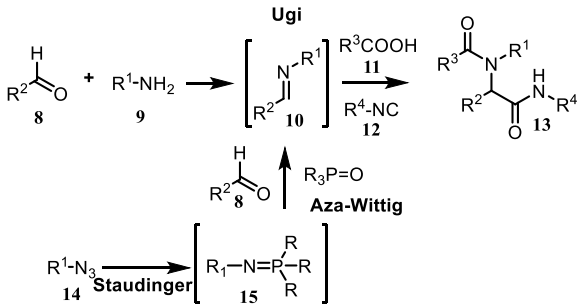
Figure 2. Structures of synthesised DNJ-isomers.

A careful examination of the DNJ structure **1** in figure **1** reveals that its six membered ring can be constructed by the Ugi reaction on the shiff"s base **5** through **4.**[8] The **5** can easily be constructed by the Staudinger aza-Wittig cyclization of azido hemi-acetal **6**. Finally DNJ **1** can be obtained by the hydrolysis of the bis-amide **4** (Scheme **1**).



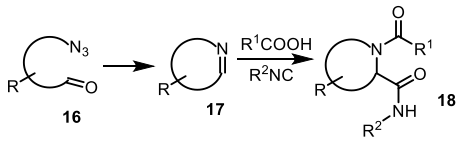
Scheme 1. Retro-synthetic pathway of 1-DNJ's isomers.

The generation of the bis-substituted imine **10**, which is a key component in the Ugi-4CR reaction, could be accomplished by performing a tandem Staudinger/aza-Wittig reaction.[9]



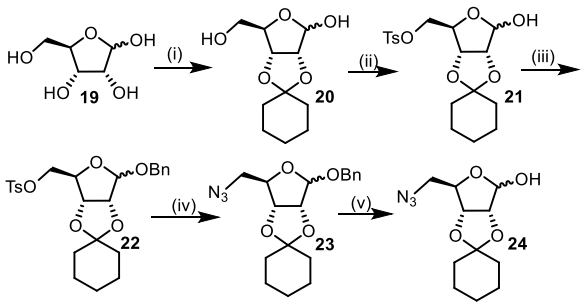
Scheme 2. Schematic presentation of Staudinger/aza-Wittig reaction coupled with Ugi reaction.

Therefore the reaction of the azide **14** with trialkyl(aryl)phosphine would lead to the formation of the intermediate phosphazene **15** which, in sequence, may go through an aza-Wittig reaction with the aldehyde **8** to yield the imine **10** and the inert trialkyl(aryl)phosphine oxide (Scheme **2).** The substrate having both an azide and an aldehyde, in addition to functional groups (R) may provide access to a substituted cyclic imine, thus opening a new dimension to the synthesis of cyclic dipeptides via reductive cyclization Ugi Reaction (Scheme **3**). Although this Staudinger/aza-Wittig reaction provides a good methodology nevertheless it has major drawback of removal of side products e.g. phosphine oxide which subsequently lower its yield.[10] So to perform this reductive cyclization step a novel, mild and cost effective method has been developed for the synthesis of 1-DNJ's isomers and is reported in this manuscript.



Scheme 3. Cyclic dipeptides via reductive cyclization Ugi reaction.

The required azido hemi-acetal **24** for the synthesis of DNJ isomers, was prepared by the commercially available D-ribose (**19**). Firstly C2-C3 cis-hydroxy of **19** were protected with the freshly distilled cyclohexanone using p-toluenesulphonic acid as catalyst. The primary hydroxyl in 2,3-O-cyclohexylidene-D-ribose (**20**) was selectively tosylated (**21**) and the anomeric hydroxy was subsequently benzylated to give the fully protected ribofuranoside (**22**). The **22** was treated with sodium azide in DMF at high temperature to give azide **23**, which on successive anomeric debenzoylation using a catalytic amount of sodium methoxide in methanol afforded the target azido hemi-acetal **24** in an overall good yield (Scheme **4**).[11]



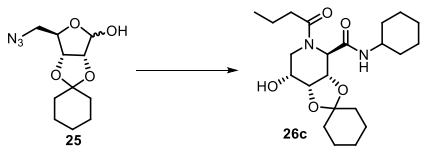
Reagents: (i) Cyclohexanone, pTSA (ii) TsCl, py (iii) BzCl, py (iv) NaN3, DMF, (v) NaOMe (cat.), MeOH.

Scheme 4. Synthesis of required azido hemi-acetal.

After getting required **24** we searched the literature for cost effective reductive cyclization method and we found a new methodology for the reduction of azide followed by cyclization reported by the Kamal *et al*., in which azide was reduced with the $FeSO_4.7H_2O/NH_3$ in DCM.[12] It has been thought that if azide is reduced in situ then it may probably react with aldehyde generated form hemi-acetal in mild acidic condition to form imine which further undergo Ugi reaction to give bisamide. To extend the scope of the reaction a

model reaction having butanoic acid and cyclohexylisocyanide as Ugi reactants has been performed at room temperature with different reductive cyclization methodologies. The results of this study are summarized in the table **1**.

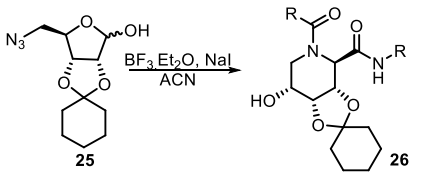
Table 1. Screening of various reductive methods.

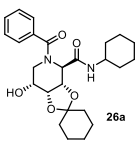
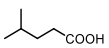
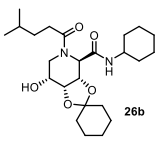
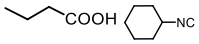
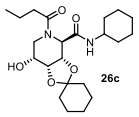
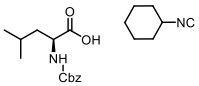
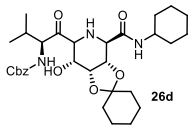
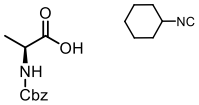
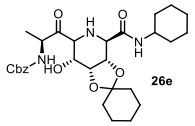
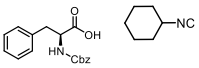
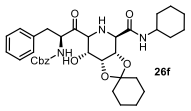
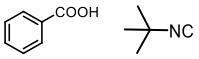
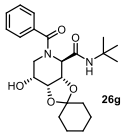
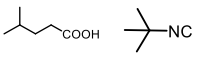
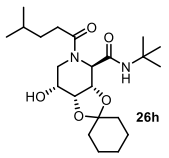
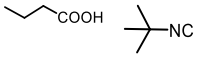
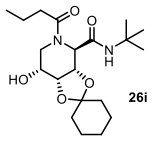
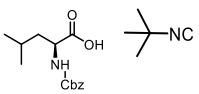
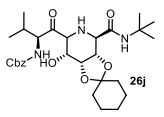
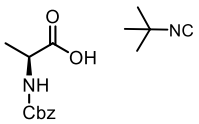
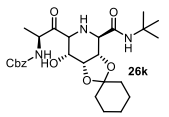
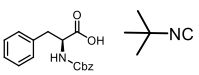
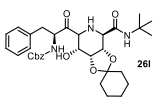


Entry	Reagent	Solvent	Time	Yield
1.	HMDST[13]	MeOH	10h	---
2.	Baker's Yeast[14]	EtOH:H_2O	16h	---
3.	TMSCl/NaI[15]	ACN	2h	35
4.	$FeSO_4/NH_3$[12]	DCM	6h	26
5.	$FeCl_3$/NaI[16]	ACN	2h	38
6.	HI[17]	H_2O	6h	---
7.	$Zn/HCOONH_4$[18]	MeOH	6h	Mixture
8.	$BF_3.Et_2O$/EtSH[19]	DCM	4h	42
9.	$AlCl_3$/NaI[20]	DCM	6h	40
10.	$BF_3.Et_2O$/NaI[21]	ACN	2h	66

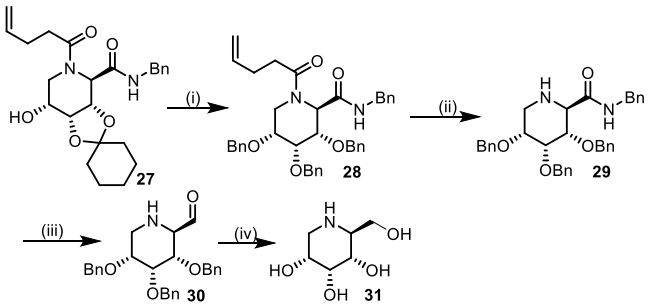
The promising result was obtained when reaction was performed with $BF_3.Et_2O$ in acetonitrile solvent. After getting results with $BF_3.Et_2O$/NaI we screened the solvents viz. DCM, DCE, $CHCl_3$, DMF and DMSO in which ACN was found to be best among all the solvents. This type of novel reductive cyclization method never been performed coupled with Ugi reaction. To explain the applicability of the reaction, reductive cyclization/Ugi reaction performed with the variety of acids and isocyanides (table **2**).

Table 2. Successful example of developed methodology.



Entry	Acid	Isocyanide	Product	Time (h)	Yield
1	Benzoic acid			3	43
2				4.5	66
3				2	56
4				3	55
5				3.5	52
6				4	50
7				3	47
8				3.5	44
9				3	52
10				4	60
11				4	48
12				3.5	46

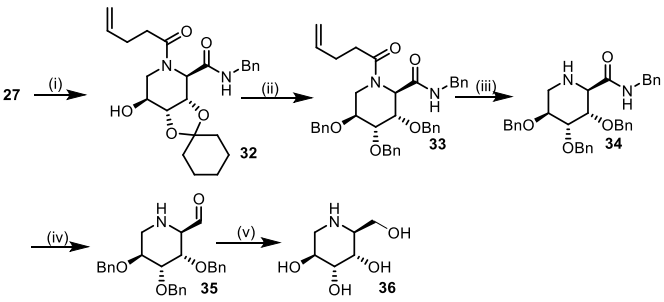
This Lewis acid mediated reductive cyclization followed by Ugi has been reported for the first time in this manuscript. After getting bisamides **26** several methods were applied for the amide bond hydrolysis but no satisfactory result was obtained. After visualizing the ease of hydrolysis of amide bond with proper substrate, the pent-4-enoic acid and benzyl isocyanide were chosen as the Ugi reagents. After reductive cyclization followed by Ugi the bis-amide **27** was formed. The cyclohexyl protection of cis hydroxy group of **27** was cleaved in mild conditions by using Hydrogen fluoride-pyridine.[22] The resulted triol was subsequently benzylated to give **28**, which was hydrolysed by the Iodine in THF:H_2O system to give amide **29**.[23] The other left amide bond was selectively reduced to aldehyde **30** by the treatment with triflic anhydride, 2-fluoro-pyridine and triethylsilylhydride in DCM.[24] The **30** was subsequently hydrogenated in Pd/C in MeOH to give L-1-deoxyallonojirimycin (**31**) via debenzylation coupled with aldehyde reduction (Scheme **5**).



Reagents: (i) (a) HF(py), $CHCl_3$ (b) BnBr, NaI, DMF (ii) I_2, THF:H_2O (iii) Tf_2O,2-FPyr, Et_3SiH, DCM (iv) H_2, Pd/C, MeOH

Scheme 5. Synthetic route for (L-*allo*-DNJ).

The other isomer L-1-deoxyaltronojirimycin (**36**) can easily be obtained by the inversion of configuration of the hydroxy of bisamide **27** by Mitsunobu reaction. The free hydroxy group was converted into picolinic ester which was subsequently hydrolysed under neutral condition to give bis-amide (**32**). After flipping sterocenter the same synthetic methodologies has been applied for achieving (**36) (**scheme **6**).



Reagents: (i) (a) PPh_3, DIAD, Picolinic acid, THF (b) $Cu(OAc)_2$, MeOH (ii) (a) HF(py), $CHCl_3$ (b) BnBr, NaI, DMF (iii) I_2, THF:H_2O (iv) Tf_2O,2-FPyr, Et_3SiH, DCM (v) H_2, Pd/C, MeOH

Scheme 6. Synthetic route for (L-*altro*-DNJ).

Conclusions

In conclusion, we synthesized L-1-deoxyallonojirimycin and L-1-deoxyaltronojirimycin by developing a cost effective mild and three component four centred Ugi reaction coupled with novel reductive cyclization as a key step from commercially available D-Ribose.

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Notes and references

[a] Division of Medicinal and Process Chemistry CSIR-Central Drug Research Institute, Lucknow- 226 031, U.P., India.

Electronic Supplementary Information (ESI) available: Preparation of substrates, characterization data, ^1H, ^{13}C NMR, CHN analysis and ESI. See DOI: 10.1039/c000000x/

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