Tetrahedron 72 (2016) 5479–5487

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Ketenimine mediated synthesis of lactam iminosugars: development of one-pot process *via* tandem hydrative amidation of amino-alkynes and intramolecular transamidation

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ARTICLE INFO

*Article history:*
Received 7 June 2016
Received in revised form 7 July 2016
Accepted 10 July 2016
Available online 12 July 2016

*Keywords:*
Amidation
Iminosugar
Ketenimine
Lactams
*N*-heterocycles

ABSTRACT

Cu-catalysed ketenimine mediated multicomponent reaction led to an efficient installation of *N*-allyl *N*-sulfonyl amide functionality onto a sugar derived terminal alkyne via intramolecular 3,3 sigmatropic rearrangement of an initially formed *N*-sulfonyl imidate. This strategy is further extended to the application of hydrative amide synthesis on chiral alkynyl amines followed by in situ intramolecular transamidation which led to the development of a novel one-pot reaction for the construction of a $\delta$-lactam iminosugar.



## 1. Introduction

Iminosugars are monosaccharide mimics with a nitrogen atom in place of ring oxygen atom.[1] Fig. 1 represents some biologically active polyhydroxylated piperidine iminosugars. Currently counted amongst the most promising classes of glycosidase inhibitors,[2] iminosugars are therapeutically relevant[3] largely because of their ability to act as transition state analogs of glycosidase catalysed pathway.[4] This analogy corresponds to the mimicry of the transition state of enzyme catalysed reaction by iminosugars either in terms of charge or shape or both.[5] Charge mimics are anticipated to replicate the positive charge distribution of the oxocarbenium ion-like transition state whereas compounds that mimic the planar geometry of the transition state are classified as Shape mimics. An important feature of the shape mimics is the presence of a trigonal centre at the anomeric position and/or the endocyclic oxygen of the corresponding substrate. Examples of non-iminosugar shape mimics include glyconohydroximolactam **8** and gluconolactam **9** (Fig. 2) which show low micromolar inhibition of glycosidases and iminosugar shape mimics **10** (Zanamivir or Relenza) and **11**

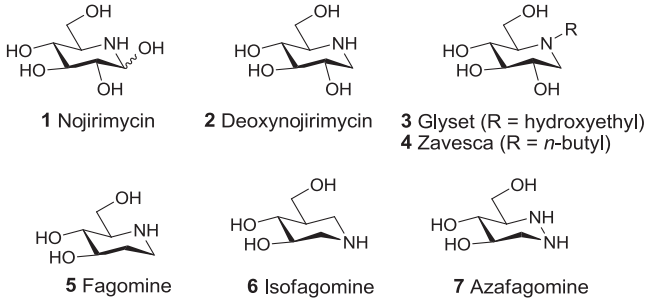


**Fig. 1.** Representative examples of polyhydroxylated piperidine iminosugars.

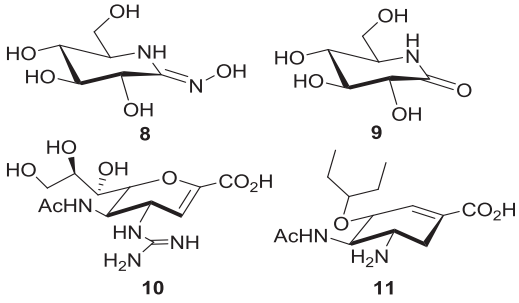


**Fig. 2.** Examples of shape mimics of transition state of glycosyl hydrolases.

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http://dx.doi.org/10.1016/j.tet.2016.07.036
0040-4020/

(Oseltamivir or Tamiflu) which are approved drugs and act against viral neuraminidases.

According to literature reports,[6] it is evident from the kinetic isotopic effect studies that during glycoside hydrolysis the transition state has various degrees of $sp^2$ hybridisation at the anomeric carbon. Lactone and lactam sugars have $sp^2$ carbon at the anomeric centre and thus inhibit glycosidases despite being uncharged which suggests that these molecules mimic the shape of the transition state very closely. Additionally the carbonyl group interacts with the catalytic acid residues thereby enhancing the binding affinity. Consequently, various lactam iminosugars have been synthesised and evaluated for glycosidase inhibition.[7] Some selected lactam iminosugars and their activity against glycosidases are represented in Fig. 3. For example, Isofagomine lactam **14** was found to be a xylanase inhibitor.[8a] The X-ray crystallographic studies revealed that this lactam bound to the enzyme as the amide tautomer.[8b]

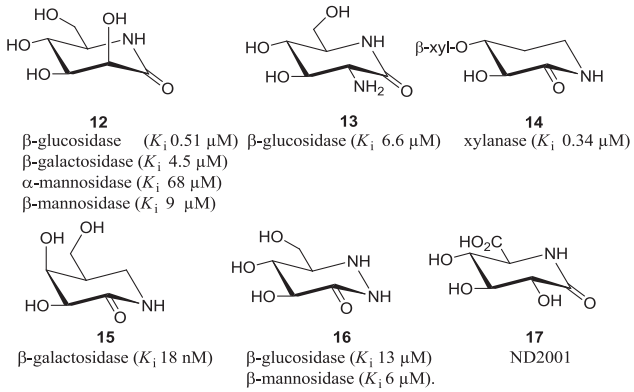



**Fig. 3.** Examples of iminosugar lactams as glycosidase inhibitors.

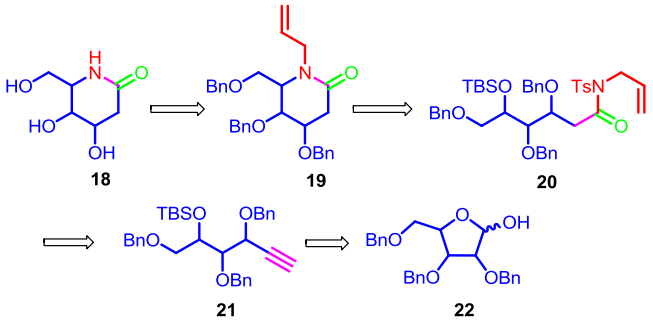
Lactam iminosugars are also known to act as anti-cancer agents. Inhibitors of both tumor metastasis and tumor angiogenesis are rapidly emerging as important drug candidates for cancer therapy. Iminosugars are found to interact with enzymes involved in metabolic pathway of glycans responsible for tumor cell invasion and migration. Sodium D-glucuro-*δ*-lactam (ND2001) **17** (Fig. 3) derived from Nojirimycin is known as a potent competitive β-D-glucoronidase inhibitor in vitro ($IC_{50}$ 0.18 μM, bovine liver) and in vivo[9] and also inhibits invasion and metastasis of tumor cells.[10] Thus, lactam iminosugars hold promise for new drug candidates for cancer chemotherapy. A recent report describes N-arylated lactam iminosugars as potent immunosuppressive agents.[11]

Ketenimines, the imine analogues of ketenes, are an important class of reactive species and useful synthetic intermediates. Except for a few isolable ketenimines, these species are exceptionally labile and mostly prepared in situ as reactive intermediates followed by their use in one-pot reactions. They have been reported to undergo nucleophilic additions, radical additions, cycloaddition reactions, electrocyclic ring closure reactions and sigmatropic rearrangements.[12] Various methodologies involving these intermediates have been utilised to construct complex organic compounds and biologically attractive heterocycles. One of the interesting applications of ketenimines demonstrated by Chang and co-workers is the synthesis of amides via a copper-catalysed MCR involving the intermediacy of *N*-sulfonyl imidates.[13]

Our recent efforts in the construction of conformationally restricted iminosugars as glycosidase inhibitors gained success.[14] Inspired by the activity of lactam iminosugars and reactivity of ketenimine intermediates to form amides, we intended to install the amide functionality onto sugar motifs employing carbohydrate derived alkynes and alkynyl amines as one of the components of a three-component MCR. This would involve generation of sugar ketenimines followed by their conversion to sugar amides by trapping them with appropriate nucleophiles. These sugar amides could then be intramolecularly cyclised for the construction of lactam iminosugars. To the best of our knowledge, the use of ketenimine intermediates in sugar chemistry has so far not been explored. Furthermore, from the synthetic point of view, these polyhydroxylated lactams can also be exploited for the construction of iminosugar aglycone mimics through reductive alkylation to create quaternary centered and C-alkylated iminosugars which may further be elaborated to bicyclic and spiro templates for the synthesis of novel second-generation iminosugars.

## 2. Results and discussion

The retrosynthetic strategy for the construction of fagomine based lactam iminosugar **18** is represented in Scheme 1. Enantiopure acetylenes of general structure **21** are easily accessible from pentoses of type **22** employing Bestmann-Ohira reagent. The protected acetylene **21** could be used as the alkyne component of *N*-sulfonyl ketenimine mediated MCR to yield amide **20**. Amide **20** on deprotection of silyl ether and desulfonylation followed by subsequent cyclisation would furnish N-allylated iminosugar lactam **19** which after required deprotections would yield the desired fagomine lactam iminosugar **18**.




**Scheme 1.** Retro-analysis for the synthesis of Fagomine lactam iminosugars.

The proposed lactam derivative **36** of L-4-*epi*-fagomine **35** (Scheme 2) should be accessible from D-Ribose according to the above described strategy. To begin with, D-(−)-ribose was converted to its *O*-benzyl protected hemiacetal **23** according to literature procedures.[15] The hemiacetal **23** on treating with freshly prepared Bestmann-Ohira reagent[16] and $K_2CO_3$ as a base in MeOH at room temperature for 8–12 h furnished enantiopure terminal alkyne **24**.[17] The free hydroxyl group of **24** was protected as silyl ether using TBDMSCl and imidazole in DCM to give fully protected alkyne **25** for examining the intramolecular imidate-amide rearrangement on carbohydrate derived substrate.[18] The key reaction comprised of the synthesis of *N*-sulfonylimidate **26** from acetylene **25** via copper-catalysed MCR. For this **25** was treated with *p*-toluenesulfonyl azide and allyl alcohol using catalytic amount of copper (I) iodide and $Et_3N$ as a base in anhydrous chloroform and $N_2$ atmosphere at room temperature to yield imidate **26** in 78% yield (Scheme 2).[13a]

The allylic imidate **26** was then subjected to a Pd-catalysed rearrangement to form tertiary amide **27** (Scheme 2) by treating it with 7–15 mol % of Pd (II) catalyst in DCE whereby it undergoes 3,3 sigmatropic rearrangement to yield *N*-allyl *N*-tosyl amide **27**.[19,20] This efficiency of this transformation was explored with two palladium catalysts *viz.* bis(acetonitrile)palladium (II) chloride,