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Halogenated D-xylono-δ-lactams: synthesis and enzyme inhibition study

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ABSTRACT

A concise synthesis of four C-3 fluoro/chloro-D-xylono-δ-lactams **3/4** has been reported. The methodology involves Corey–Link approach with suitably protected 3-oxo-D-gluco-furanose to introduce F/Cl as well as ester/amide functionalities at C-3 of glucose. In next steps, 5,6-*O*-isopropylidene group was converted to the 5-azido xylosugars that on opening of 1,2-acetonide group, and intramolecular Schmidt–Boyer reaction with TFA/H_2O, in one pot, afforded lactams **3/4**. Conformational aspect of δ-lactams was studied by the ^{1}H NMR spectroscopy. The halogenated δ-lactams **3/4** showed no inhibition against different glycosidase enzymes.

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1. Introduction

Iminosugars are sugar mimics with the nitrogen atom instead of the oxygen atom in a ring. Analogues of iminosugars are potent therapeutics in the treatment of diabetes, obesity, Gaucher disease, and viral infection including AIDS due to their inhibition, and/or modulatory action toward a wide range of enzymes that act as carbohydrate recognizing proteins.[1–5] Nojirimycin (NJ) **1a** (Fig. 1) is the first molecule of iminosugar family that was found to be an inhibitor of several glycosidases. The presence of aminal moiety in **1a** was found to be susceptible to enzyme hydrolysis, and therefore aminal moiety was reduced to give 1-deoxynojirimycin (DNJ) **1b** which showed better glycosidase inhibitory activity than parent molecule.[4–7] On the contrary, the microbial oxidation of aminal group in **1a** led to the discovery of D-glucono-δ-lactam **2** which, although nonbasic, was found to be a selective glycosidase inhibitor.[8] This activity of **2** was attributed to the geometric resemblance with the flat 'oxonium' ion transition state of the glycosidase processes due to the involvement of sp^2 hybridized carbonyl group, and the tautomeric form of amide which is able to act as both imine as well as 2-hydroxyl group suitable for the hydrogen bonding.[9–11]

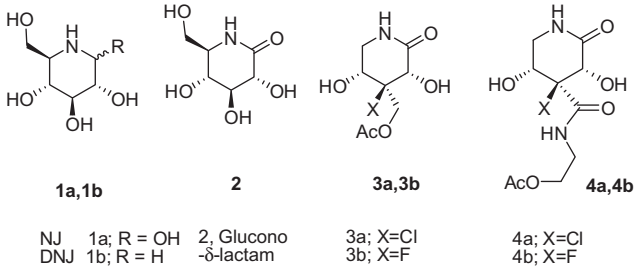

Figure 1. Iminosugars and glycono-δ-lactams.

In view of this, a number of polyhydroxylated-γ-and-δ-lactams were synthesized. For example Lillelund et al. have reported the synthesis of D-gluco-/D-manno-/D-galacto-fagomine lactams, and showed the D-galacto-δ-lactam to be more potent against β-galactosidase (*Aspergillus oryzae*).[12] Wang et al. have reported the synthesis of *N*-substituted δ- and ε-hexanolactams which showed weak inhibition of wild type β-glucocerebrosidase however, were found to be highly potent pharmacological chaperones for treatment of N370S mutant Gaucher disease.[10,13] Fleet et al. have synthesized L-fuconic-δ-lactams which showed weak but specific α-L-fucosidase inhibitory activity.[14] Takeuchi and co-workers have synthesized eight stereoisomers of the D-glucono-δ-lactams, studied their conformations by X-ray crystallography, and correlated with the glycosidase inhibitory activity.[15] All these glycono-δ-lactams were synthesized either from azido sugar lactones by internal

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azide reduction–cyclization or by one pot oxidation of sugar derived δ-amino-alcohols/aldehydes.[12–19] In addition, intramolecular Schmidt–Boyer reaction of δ-azido aldehydes/ketones, under acidic conditions, also afforded corresponding glycono-δ-lactams.[20,21] Although a variety of sugar-δ-lactams are known, the xylono-δ-lactams with halogen (F/Cl) substitution, to the best of our knowledge, are not known. In medicinal chemistry, the introduction of lighter halogen groups such as fluorine or chlorine is known to enhance the potency of a molecule as a drug candidate due to the presence of strong C—F/C—Cl bond that increases the lipophilicity, and gives more resistance power to metabolic degradation.[22,23] Iminosugars with Cl/F atom were investigated to get potent drug candidates.[24–26] Inspired by this observation and as part of our continuous efforts in the area of iminosugars,[27,28] we report here synthesis of D-xylono-δ-lactams **3a**/**3b**, and **4a**/**4b** (Fig. 1) with highly functionalized C-3 quaternary center having Cl/F, and hydroxymethyl/amide functionalities, and study of their glycosidase inhibitory activity.

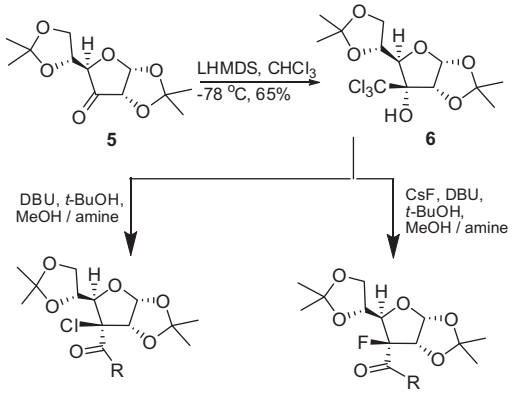
An obvious way to introduce chlorine/fluorine atom in the iminosugar framework is by S_Ni/S_N2 displacement of hydroxyl group (by converting into good leaving group) using Cl^-/F^- as nucleophiles with retention/inversion of configuration at different positions in the iminosugar.[29,30] Other method involves chlorocyclization of sugar derived aminoalkenitols using $Pd(II)/CuCl_2$.[31] Alternatively, gem-difluorinated iminosugars have been synthesized by using Percy's method via the [2,3] Wittig rearrangement of difluoroallylic alcohols.[32,33] Our approach to the halogenated-xylono-δ-lactams involves introduction of the halogen functionality by the modified Corey–Link[34–36] reaction with C-3 trichloro-carbinol-D-glucofuranose while; the δ-lactam skeleton was visualized by intramolecular Schmidt–Boyer[37–39] reaction with subsequently obtained 5-azido-1,2-*O*-isopropylidene-α-D-xylofuranose. Our results in the successful application of the above methodology are described herein.

2. Results and discussion

2.1. Synthesis of δ-lactams

Recently, we have utilized the Corey–Link[34–36] approach with suitably protected D-gluco, D-allo, and D-manno-5-oxo-furanoses for the synthesis of iminosugars,[40] and D-gluco-3-oxofuranose for the synthesis of C-3 azido C3/C4 trans vicinal diacid which was found to be γ-turn mimetic.[41] Inspired with this observation, we applied this approach to get halo-substituted sugar framework. Thus, as shown in Scheme 1, the reaction of 1,2:5,6-di-*O*-isopropylidene-3-oxo-α-D-glucofuranose **5** with $CHCl_3$ in the presence of LHMDS in THF at −78 °C afforded exclusive formation of 3(*R*)-trichloromethyl carbinol **6**.[42,43] The observed high stereoselectivity at C-3 is due to the presence of-α-oriented 1,2 acetonide group that hinders attack of nucleophile to the C-3 carbonyl group from the *Re*-face'.[21,23] Treatment of **6** with DBU in methanol afforded 3(*S*)-chloro methyl ester **7** in 85% yield.[44] This Corey–Link reaction of **6** with DBU is known to proceed via in situ formation of α-oriented dichloroepoxide followed by nucleophilic attack of the chloride ion (as internal nucleophile) at C-3 from the opposite side of the dichloroepoxide to give 3β-chloro-3α-acid chloride that on methanolysis affords **7**. At this stage, we thought of using fluoride ion as an external nucleophile in the Corey–Link reaction as reported for the synthesis of α-fluoro carboxylic acids.[45] Thus, reaction of **6** with CsF (4 equiv) and DBU in methanol at 35 °C afforded a mixture of 3β-chloro/fluoro-3α-methylester in the 1:4 ratio. This could be due to the competitive pathways between the internal (Cl^-) and external (F^-) nucleophiles. To overcome this problem, we attempted the reaction by using 5, 7, and 10 equivalents of CsF, and the best result was obtained with CsF (10 equiv) that led to the exclusive formation of 3β-fluoro-3α-methylester **8** in 80% yield as the only isolable product.

As this reaction involves in situ formation of acid chloride (on opening of dichloroepoxide), it occurred to our mind to trap the acid chloride with different nucleophilic amines in a synergetic way (weaker nucleophiles as compared to Cl/F) to get halogen substituted amide sugars. Robert Stick, and co-workers reported the reaction of 6 with DBU using benzylamine in DCM, and isolated 3β-chloro 3α-benzylamide in 37% yield. However, the reaction in the presence of external nucleophile like CsF, and benzylamine to get 3β-fluoro 3α-amide is not reported. At our hand, the reaction of **6** with DBU, and benzylamine in *t*-BuOH (instead of DCM) at room temperature gave 3β-chloro-3α-benzylamide **9a** in 88% yield. The better yield obtained for **9a** by changing solvent from DCM (37%) to *t*-BuOH (88%) is attributed to the high solvation ability of chloro benzylamide as a product in *t*-BuOH as compared to DCM that lowers the activation energy for its formation through solvation in *t*-BuOH. This fact is supported by using more polar protic solvent like dioxane/H_2O (1:1.5) in the presence of NaOH (2 equiv) that afforded **9a** in 76% yield (Table 1, entries 1 and 2). With this success, the above reaction was generalized by using a combination of either NaOH-dioxane/H_2O or DBU-*t*-BuOH with different nucleophilic amines (3 equiv) like morpholine, propargylamine, 2-amino pyridine, and ethanolamine that afforded corresponding 3β-chloro-3α-amides (**9b**–**9e**) in high yield (Table 1, entries 3–10). The reaction of 2-amino pyridine in DBU/*t*-BuOH led to the formation of a complex mixture however, the same reaction in NaOH (2 equiv) in dioxane/H_2O gave **9d** in 71% yield (Table 1, entries 7 and 8). This observation could be attributed to the high solubility of 2-aminopyridine in dioxane/H_2O as compared to *t*-BuOH. Encouraged with this observation, we used CsF as an external nucleophile in the reaction. Thus, reaction of **6** with CsF (10 equiv) in benzylamine, morpholine, propargylamine, and ethanolamine (3 equiv) gave corresponding 3β-fluoro-3α-amides (**10a**–**10d**) in good yields (Table 1, entries 11–14). The formation of fluoro amides (**10a**–**10d**) in high yields is striking as the nucleophilicity of fluoride ion in polar protic solvent is known to be low due to the tight solvation through intermolecular hydrogen bonding. However, our results are in accordance with the recent report of Kim et al.,[46,47] who has given a mechanistic study on enhancement of nucleophilic fluorination of alkali metal fluorides in polar protic solvent like *t*-BuOH. According to this report, the CsF forms intermolecular H-bonding with the *t*-BuOH, which generate a solvated 'flexible' fluoride ion species by weakening ionic bonding of the alkali metal fluoride thus making CsF as a good nucleophile.[48,49] In addition, more efficient solvation of product namely halogenated amide **9**/**10** is another favorable factor that facilitates reaction in polar protic solvent to give high yield.[44]



Scheme 1. Synthesis of chloro/fluoro methyl ester/amides.

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