Tandem Staudinger–azaWittig mediated ring expansion: rapid access to new isofagomine-tetrahydroxyazepane hybrids†

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New seven-membered iminosugars with potent and selective inhibition towards glycosidases have been prepared as 1-*N*-iminosugar homologues *via* a tandem Staudinger–azaWittig mediated ring expansion.

Glycosidases, believed to increase the rate of glycosidic bond hydrolysis by a factor of 10^{17}, making them among the most proficient enzymes in nature,[1] are involved in many aspects of biochemistry and metabolism. The quest for strong and selective inhibitors of this class of enzymes has been the subject of extensive interest in the past three decades among chemists and biochemists[2] and some iminosugar-based structures have displayed great potential in the treatment of diabetes,[3] HIV infection,[4] viral infections[5] or cancer[6] leading in some cases to therapeutics.[7] To date, a huge number of five- and six-membered iminosugars, mimicking their parent sugar both in terms of hydroxyl pattern and ring size have been synthesized and evaluated.[8] Much less efforts have been put into higher ring analogs. Paulsen[9] was the first to report polyhydroxylated seven-membered iminosugars such as **1**. Later on Depezay[10] developed a straightforward synthesis of this iminoalditol and Wong[11] disclosed the strong inhibition activity of this class of compounds on glycosidases.

In a program devoted to the exploration of conformational flexibility in the field of glycosidase inhibitors, we have previously reported the synthesis of nojirimycin and deoxynojirimycin ring homologues,[12] some of these compounds displaying fairly potent and selective glycosidase inhibition. These results encouraged us to apply this ring expansion to other famous glycosidase inhibitors. In 1994, Bols *et al.* reported the synthesis of a new and very potent β-glucosidase inhibitor coined isofagomine **2**.[13] This 1-*N*-imino sugar, protonated at physiological pH, was designed to mimic the carbocationic form of the oxycarbenium-like transition state in which the positive charge would be located at the anomeric carbon. The potency of this compound was further improved by inserting a hydroxyl group at the C-2 position to afford noeuromycin **3**, a nanomolar β-glucosidase inhibitor.[14]

The potency of 1-*N*-iminosugars **2** and **3** and the conformational flexibility of azepane **1** prompted us to combine these structures into a new seven-membered hybrid molecule (Chart 1).

Such iminosugar can be seen as a stable (relative to its hemiaminal function) and flexible analogue of noeuromycin with a defined stereochemistry for the C-2 hydroxyl group.

The desired iminoalditol can be obtained by chemical manipulation of an aldopyranose and starts with a 6-azido-6-deoxy-sugar. Available methyl 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **4**[15] was converted to the corresponding lactol **5**. Direct transformation under acidic conditions using literature procedures was found sluggish and gave low yields in our hands.[16] A more convenient acetolysis–deacetylation sequence was thus applied to afford azidolactol **5** in good yield (90% yield over two steps). The ring expansion step was then examined. A cyclisation involving a Pd-mediated reductive amination of azidolactol **5** was first applied. Such strategy has been successfully used for the synthesis of tetrahydroxylated azepanes[11] and for the protein kinase C inhibitor balanol.[17] Treatment of azidolactol **5** under hydrogenation conditions (20% $Pd(OH)_2$/C in methanol) in the presence of triethylamine to minimize debenzylation followed by reduction of the transient imine with sodium cyanoborohydride led to the expected β-hydroxyazepane **6** (23%) along with more polar compounds. A more efficient route was needed and a tandem Staudinger/intramolecular aza-Wittig approach[18] was investigated. Azidolactol **5** was treated with triphenyl phosphine in dry THF to yield the iminophosphorane adduct which reacted with the aldehyde *via* an intramolecular azaWittig reaction to afford the corresponding imine **8**. This imine, as previously observed by Wong[11] and Fuentes,[19] probably exists in equilibrium with the hemiaminal **7** and the bicyclic anhydro derivative **9**. Subsequent reduction with sodium cyanoborohydride under acidic conditions afforded the expected β-hydroxy azepane **6** in high yield (Scheme 1).

We can notice that compound **6** is a very useful building block to desymmetrize the C-2 symmetric tetrahydroxyazepane **1** and introduce diversity in this class of compounds.

Completion of the synthesis consisted in the homologation of the free hydroxyl group in **6** *via* an oxidation–olefination–hydroboration–oxidation sequence. Preliminary protection of the

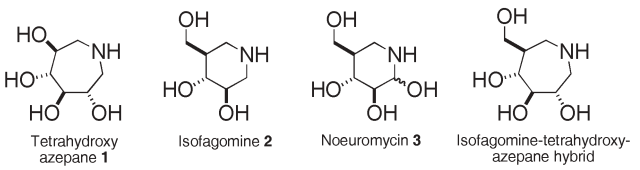

Chart 1

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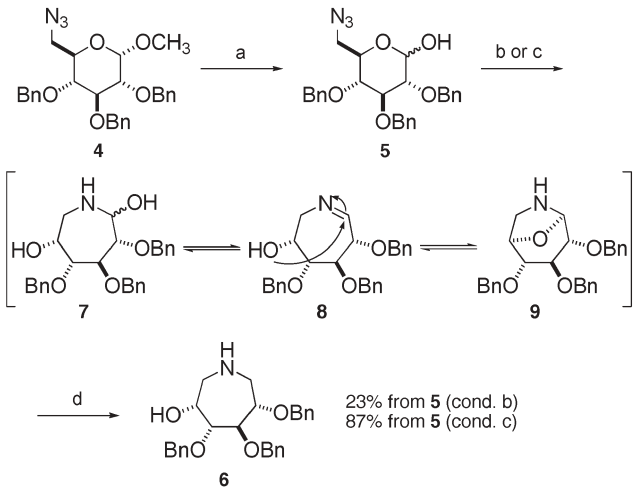
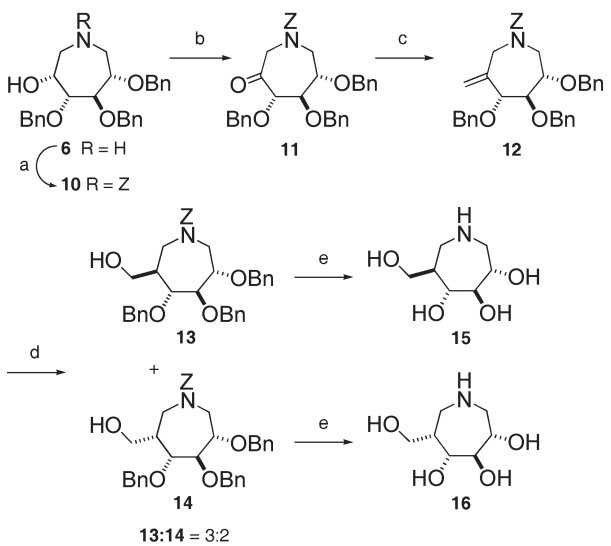


Scheme 1 *Reagents and conditions*: (a) Ac_2O, H_2SO_4, CH_2Cl_2, 0 °C then CH_3ONa, CH_3OH, 90% over two steps; (b) $Pd(OH)_2/C$, Et_3N, H_2, CH_3OH; (c) PPh_3, anhydrous THF; (d) $NaBH_3CN$, 1 M HCl in CH_3OH, 4Å MS, CH_3OH, 23–87% over two steps.

free NH group as its benzyloxycarbonyl derivative **10** (93% yield) to prevent nitrogen oxidation during the forthcoming step was accomplished and subsequent PCC oxidation of the β-hydroxyl group afforded the corresponding ketone **11** in 94% yield. Subsequent Wittig olefination gave the desired exoalkene **12** in a satisfactory 78% yield. Olefin **12** was then submitted to a hydroboration–oxidation sequence (BH_3, NaOH, H_2O_2) and afforded a separable mixture of two hydroxymethyl derivatives **13** and **14** in a 3 : 2 ratio. Final hydrogenolysis yielded the target iminosugar **15** along with its diastereoisomer **16** (Scheme 2).

Iminoalditols **15** and **16** have been assayed for their inhibitory activities towards fourteen commercially available glycosidases. Albeit weaker than the parent isofagomine **2** and noeuromycin **3**, isofagomine homologue **15** displays potent and selective inhibition on almonds β-glucosidase (Ki = 4 μM, uncompetitive). It is also a



Scheme 2 *Reagents and conditions*: (a) ZCl, $KHCO_3$, AcOEt/H_2O 1:1, 93%; (b) PCC, 4Å MS, CH_2Cl_2, 94%; (c) Ph_3P,CH_3Br, n-BuLi, THF, 78%; (d) BH_3, THF then H_2O_2, 3M NaOH, 77%; (e) H_2, 10% Pd/C MeOH/1 M HCl, quant.

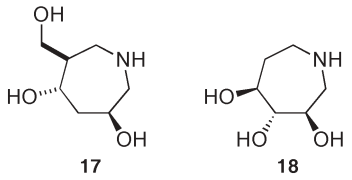


Chart 2

very weak inhibitor of amyloglucosidases from *Aspergillus niger* and *Rhizopus mold* and jack bean α-mannosidase (less than 50% of inhibition at 1 mM concentration) and did not inhibit α-L-fucosidase from bovine kidney, α-galactosidases from coffee beans and *E. coli*, β-galactosidases from *E. coli* and *Aspergillus oryzae*, α-glucosidases from yeast and rice, β-mannosidase from *Helix pomatia*, β-xylosidase from *Aspergillus niger*, β-*N*-acetylglucosaminidase from jack bean and bovine kidney. Its diastereoisomer **16** is a rather potent and selective inhibitor of jack bean α-mannosidase (Ki = 42 μM, uncompetitive). Interestingly, two azepane-based structures **17** and **18** designed to mimic isofagomine have been previously reported by Mehta[20] and Martin[21], respectively (Chart 2), and displayed only moderate inhibition on glycosidases, thus emphasizing the importance of a very accurate hydroxyl pattern to generate strong inhibition for this class of compounds.

Finally, iminocyclitol **15** and tetrahydroxyazepane **1** both display a similar activity toward almond β-glucosidase with Ki of 4 and 12 μM, respectively, but iminosugar **15** is much more selective than azepane **1**[11] towards this enzyme thus indicating that desymmetrisation and substituent tuning at β position to the nitrogen is of interest to obtain more potent and selective azepane-based glycosidase inhibitors.

In conclusion, new seven-membered iminosugars have been prepared as 1-*N*-iminosugar ring homologues *via* a short route including a tandem Staudinger–azaWittig mediated ring expansion as the key step. Albeit less potent than their piperidine counterparts, the inhibition data obtained with these flexible iminosugars clearly demonstrate that a fine tuning of the substituents in tetrahydroxylated azepanes can lead to improved selectivity and new profile of inhibition for this class of compounds.

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