A Multi-Component Approach towards Functionalised Iminoalditols as Building Blocks for Glyco Probes

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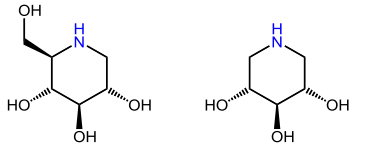
INTRODUCTION

1-Deoxynojirimycin (**1**), a typical representative of iminoalditols, is well known as excellent inhibitor of glucosidases. Recently, this compound class was recognised as pharmacological chaperones (PC) for the chaperone mediated treatment (CMT) of lysosomal storage disorders (LSD) [1]. In this respect, compound **1** shows a K_i value of 79 µM and iminoxylitol **2** shows a K_i value of 1.3 µM against human lysosomal β-glucocerebrosidase (*β*-Glu), the enzyme involved in Gaucher disease [2].



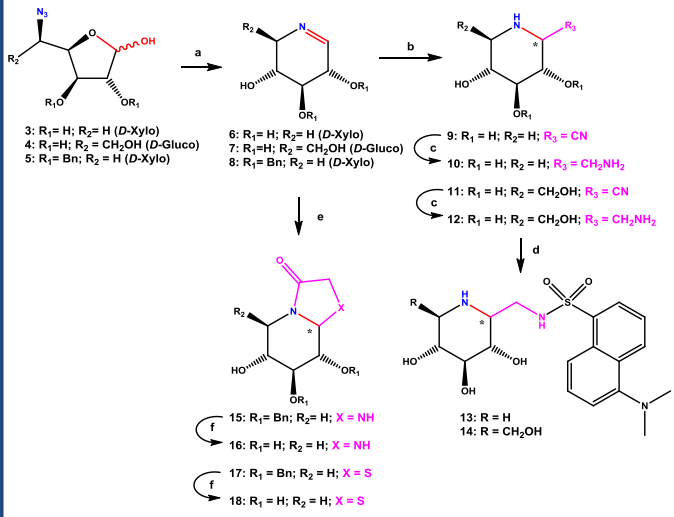
1 K_i = 79 µM **2** K_i = 1.3 µM

Figure 1: Structure and K_i values of compounds **1** and **2**.

Looking for an efficient synthetic approach towards such compounds we became aware of the Staudinger/aza-Wittig (SAW, [3]) reaction sequence. When applied to azidosugar substrates (**3-5**) the corresponding iminium ion intermediates (**6-8**) are obtained which can easily undergo stereoselective nucleophilic attack by different nucleophiles. By this approach, 1-*C*-iminoalditol building blocks can be generated in a straight forward manner (**Scheme 1**) which are ready for chemo- and regioselective functionalization [4].

RESULTS

Starting from 5-azido-5-deoxy-sugars **3-5**, the respective iminium intermediates **6-8** were formed under optimized SAW conditions. By employing cyanide as nucleophile, the corresponding 1-*C*-cyano iminoalditols **9** and **11** were formed and were found to show K_i values of 34 and 716 µM, respectively, against the human lysosomal *β*-Glu. Reduction of the nitrile to compounds **10** and **12** followed by chemo- and regioselective N-dansylation gave compounds **13** and **14**. Compound **13** shows an excellent K_i value of 7,5 nM, surpassing its parent compound **1** by four orders of magnitude. Using mercaptoacetic methyl ester and glycine methyl ester, respectively, as nucleophiles, the corresponding bicyclic compounds **16** and **18**, respectively, were obtained. Biological evaluation of compounds **14**, **16** and **18** is currently in progress.



Scheme 1: a) PMe_3, MeOH; b) NaCN, MeOH; c) H_2, $Pd(OH)_2/C$, MeOH, 5bar; d) dansyl chloride, Et_3N, MeOH; e) $HXCH_2COOMe$; MeOH; f) H_2, $Pd(OH)_2/C$, 1 atm.

Table 1: Configurations of newly formed chiral centers * determined from J_{H-H} coupling of H-NMR spectra as well as by x-ray analysis; K_i values against human lysosomal β-Glu; i.p. in progress.

Product	Yield	*	K_i (µM)
9	>99%	R	34
11	95%	R	716
13	30%	R	**0,0075**
14	20%	R	i.p.
16	55%	S	i.p.
18	64%	S	i.p

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Support by NAWI Graz