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Iminoalditol-amino acid hybrids: synthesis and evaluation as glycosidase inhibitors

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Abstract—Cyclization by double reductive amination of D-*xylo*-hexos-5-ulose with the terminal amino group of α-*N*-Boc-lysine methyl ester gave a 4:1-mixture of (1′*R*)-*N*-methoxycarbonyl-(1-*N*-Boc-amino)pentyl-1-deoxynojirimycin and the corresponding L-*ido* epimer whereas D-*lyxo*-hexos-5-ulose furnished the desired N-alkylated 1-deoxymannojirimycin derivative without any observable epimer formation at C-5. By subsequent modification of the lysine moiety, additional chain-extended derivatives as well as fluorescent compounds were obtained. All fluorescent iminoalditol-amino acid hybrids prepared in this study exhibited glycosidase inhibitory activities better than or comparable to the parent compounds'.

Keywords: Iminoalditol; Amino acid conjugate; Glycosidase inhibitor; Glucosidase; Mannosidase

1. Introduction

Iminoalditols are well-known, (usually) competitive, glycosidase inhibitors.[1] Representatives of this class of compounds, for example, glucosidase inhibitor **1** and mannosidase inhibitor **2** have found important roles as biological probes such as in the investigation of glycoprotein trimming glycosidases[2] or as pharmaceutical substances such as in the treatment of diabetes type II symptoms (Miglitol by Bayer) and other metabolic disorders including Gaucher disease (Zavesca by Actelion) (Fig. 1). It was demonstrated that immobilized N-alkylated imino- alditols can be employed as affinity ligands in glycosidase isolation and purification protocols.[3]

We have been interested in derivatives of such compounds featuring 'added value' properties suitable for analytical purposes. Recently, we have found that some fluorescently labelled derivatives of the glucosidase inhibitor 2,5-dideoxy-2,5-imino-D-mannitol (or DMDP) are powerful inhibitors exceeding the activity of the parent compound by two orders of magnitude.[4]

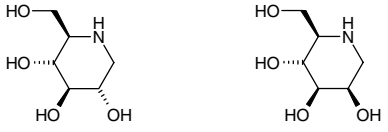

Figure 1.

In this context, we have reported syntheses and glycosidase inhibitory activities of various N-alkylated iminoalditols featuring fluorescent tags such as dansyl moieties attached to simple N-substituents.[5] Based on the encouraging inhibitory activities of these compounds, we envisaged more convenient properties with compounds providing a suitably positioned amine for tagging as well as an additional 'handle' for chain-extensions and with a view to the preparation of glycosidase-recognizing arrays by immobilization on surfaces.

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2. Results and discussion

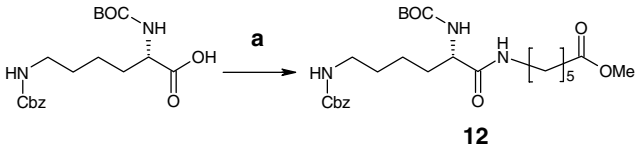
Partially protected L-lysine derivatives featuring a free terminal amino group were found to be useful reaction partners in ring-closing reactions with 5-ulohexoses by reductive amination[6] to provide lysine-iminoalditol hybrids (Scheme 1) ready for a wide range of useful follow-up modifications.

Again, the presence of a dansyl residue attached to the α-nitrogen in the L-lysine component was found to improve inhibitory potencies whereas the second functional 'handle', the terminal carboxylic moiety, can clearly be employed for the attachment, via linkers, to suitable surfaces.

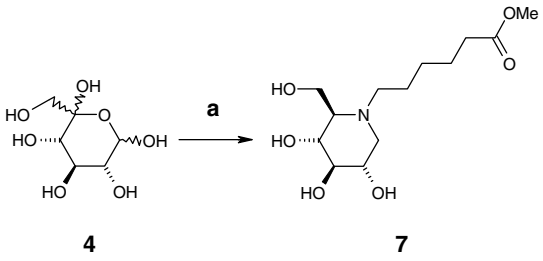
(5*R*)-Spiro-oxirane **3**,[7] readily available from methyl α-D-glucopyranoside via Garegg reaction, per-O-acetylation, AgF-mediated[8] 5,6-ene formation (78%), and *m*-CPBA oxidation (80%), gave by conventional Zemplén deprotection and acidic hydrolysis known[9] D-*xylo*-hexos-5-ulose (**4**). The latter was reacted with α-*N*-Boc-ε-*N*-benzyloxycarbonyl-L-lysine methyl ester (**5**) at ambient pressure under an atmosphere of hydrogen in the presence of $Pd(OH)_2$ (20%) on carbon. Hydrogenolytic deprotection at the terminal amine followed by double reductive amination was expected to proceed with high diastereoselectivity at the newly formed chiral centre at C-5 of desired inhibitor **6**. Contrary to previous results with methyl 6-aminohexanoate, which exclusively provided iminoglucitol **7** under the same conditions, with the amino acid, a 4:1 mixture of N-alkylated 1,5-dideoxy-1,5-imino-D-glucitol **6** and -L-iditol **8** was obtained. Separation was found to be difficult on a preparative scale. Deprotection of the secondary amine in compound **6** followed by reaction with dansyl chloride provided fluorescent iminoglucitol **9**. Chain-extended derivatives **10** and **11**, were readily available from **4** by reaction with **12**, which was prepared from commercially available α-*N*-Boc-ε-*N*-Cbz-L-lysine by standard coupling with methyl 6-aminohexanoate. Removal of the Boc group followed by N-dansylation gave compounds **13** and **14** (Schemes 2–6).

Compound **15**, featuring two fluorescent moieties of significantly different emission spectra in the same molecule was prepared by saponification of methyl ester **13** to the free acid followed by conventional coupling to the NBD fluorophor in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) (Scheme 7).

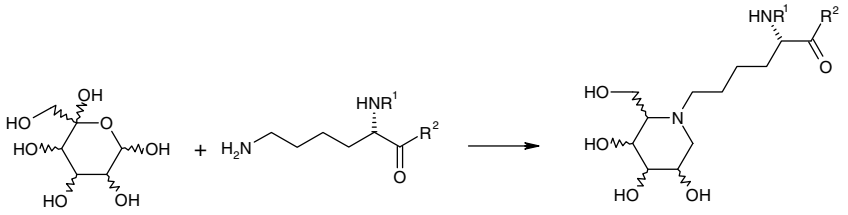
In the D-*manno* series, (5*R*)-oxirane **16**[7] (prepared in 44% overall yield from methyl α-D-mannopyranoside)



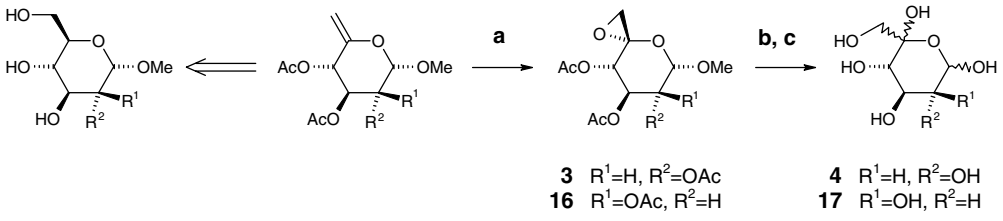
Scheme 3. Reagents and conditions: (a) methyl 6-aminohexanoate hydrochloride, NEt_3, DMF, TBTU.



Scheme 4. Reagents and conditions: (a) methyl 6-aminohexanoate hydrochloride, aq MeOH, NEt_3, $Pd(OH)_2/C$ (20%), H_2.



Scheme 1.



Scheme 2. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, aq $NaHCO_3$; (b) NaOMe, MeOH, −30°C; (c) H_2O, Amberlite IR-120.