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Synthetic studies towards a new scaffold, spirobicycloimidazoline

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Abstract—A new scaffold consisting of a carbocycle and a substituted imidazoline in an orthogonal arrangement was synthesized as a potential specific inhibitor of glycosidases. The spirobicycloimidazoline, (5*R*,6*R*,7*R*,8*R*)-8-(hydroxymethyl)-2-phenyl-1,3-diaza-spiro[4.4]non-1-ene-6,7-diol, was synthesized from methyl 2-*O*-*p*-methoxybenzyl-3,4-di-*O*-benzyl-α/β-D-*gluco*-6-enopyranoside via (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4-bis(benzyloxy)-2-(4-methoxybenzyloxy)-5-vinyl-cyclopentanol. The ring contraction of the 6-enopyranoside in the presence of zirconocene equivalent ('Cp_2Zr') reagent gave exclusively the corresponding cyclopentanol without cleavage of the PMB protecting group. In the course of the study, a new α-mannosidase inhibitor, (1*R*,2*R*,3*R*,5*R*)-5-amino-3-hydroxy-methyl-cyclopentane-1,2-diol, was also discovered.

Keywords: Glycosidase inhibitors; Spiro compounds; Imidazoline; Carbocyclic compounds

1. Introduction

The glycosidases, which are related to the control of various biological phenomena, are one of the most important families of carbohydrate-related enzymes.[1,2] Inhibitors of glycosidases are useful tools when investigating biochemical processes,[3–5] in enzyme purification as affinity ligands,[6,7] and also as drug candidates.[8–11] Thus, many compounds, either isolated from natural sources or chemically synthesized, have been reported as inhibitors of glycosidases. Recent advances in three-dimensional analysis based on the crystal structures of glycosidases have also been used to design inhibitors of these enzymes. A majority of compounds in the class carry a cationic moiety in the structure that mimics the oxocarbenium ion species in the transition state.

One well-known family of glycosidase inhibitors with a five-membered ring is hydroxylated pyrrolidines, represented by DMDP and DAB-1 (Chart 1).[12,13] It is believed that the powerful inhibitory activities are the result of a strong charge interaction between the ammonium group and the carboxylate group in the active site of glycosidase. A combinatorial chemistry approach is expected to result in further improvement of activity.[14,15] Cyclopentitols having a sugar-like carbocycle are another class of inhibitors that deserve attention. Mannostatin A, isolated from *Streptoverticillium verticillus*, is a specific and potent inhibitor of Golgi α-mannosidase II.[16,17] The structure of Mannostatin A does not resemble the three-dimensional structure of a mannopyranoside, the substrate of the mannosidase, and the inhibitory mechanism is thus of great interest.

Bicyclic cyclopentitol-related compounds have also been studied as potential inhibitors of various glycosidases. Trehazoline and allosamidin are known to be good inhibitors of trehalase and chitinase, respectively.[18,19] Despite the accumulated information regarding inhibitory activities, the prediction of enzyme specificity in the inhibition by five-membered ring compounds is, in general, difficult because of the conformational freedom of these rings and the resulting unpredictable three-dimensional placement of functional groups.

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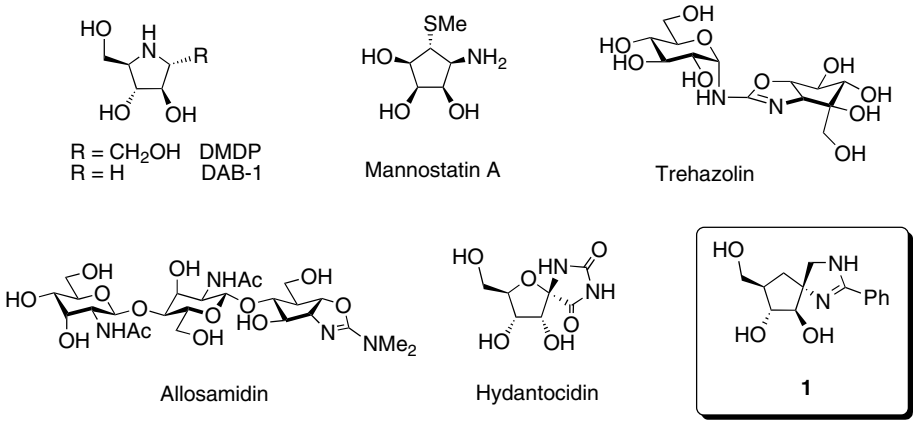

Chart 1.

Hydantocidin, a naturally occurring spiroribofuranose derivative, was reported to show strong herbicidal activity with no toxicity to microorganisms or animals.[20,21] An analogue of hydantocidin, in which the endocyclic oxygen of the sugar moiety has been replaced by a methylene group, is known.[22–24] This type of compound, having a fused ring system in an orthogonal arrangement, might provide valuable information and hopefully serve as a source of potent glycosidase inhibitors. This consideration was based on fact that the natural product salacinol with a 'semi-' spiro system as the result of intramolecular ion pairing, showed potent inhibitory activity against α-glucosidase.[25] However, cancellation of charge in the molecule is considered to be unfavourable for glycosidase inhibition. We thus designed a new scaffold consisting of a carbocycle and a substituted imidazoline, where the hydroxylated carbocycle ring mimics the glycon moiety, the imidazoline moiety provides hydrogen-bonding capability in the catalytic site of the enzyme, and an aglycon moiety can be incorporated at the amidino-group. We report here the synthesis of spirobicycloimidazoline (**1**), which is expected to become a compound in a novel class of compounds. In the course of these studies a new α-mannosidase inhibitor, (1*R*,2*R*,3*R*,5*R*)-5-amino-3-hydroxymethyl-cyclopentane-1,2-diol, was also discovered.

2. Results and discussion

2.1. Synthesis

Our target bicyclospiro compound, imidazoline (**1**), consists of a five-membered carbocycle and an imidazoline. In this study, we selected as a target backbone 5-amino-3-hydroxymethyl-cyclopentane-1,2-diol, which might provide new information when searching for and/or designing new inhibitors of glycosidases. In the construction of this scaffold we chose an approach in which the key steps were a ring contraction of an enopyranoside (**i**) to provide a cyclopentitol derivative (**ii**), subsequent conversion of **ii** into a ketone (**iii**) and finally introduction of a C–C bond into **iii** leading eventually to **iv**. Diamine **iv** is a precursor to imidazoline **1** (Scheme 1).

A suitably protected 6-enopyranoside (**3**), which was to be subjected to the ring contraction, was synthesized from D-glucose (Scheme 2). The 2-OH of compound **2**, which is transformed to the spiro-centre of **1**, should be distinct from other hydroxyl groups, so we chose *p*-methoxybenzyl (PMB) ether as the protecting group. Compound **2** was obtained in high yield by conventional protection of the hydroxyl groups, and the spectral data matched the reported data.[26,27] Oxidation of the hydroxymethyl group of **2** gave the corresponding aldehyde, which was converted into **3** by a Wittig reaction.

It had been reported that the ring contraction of 6-enopyranoside was promoted by a zirconocene equivalent ('Cp_2Zr') reagent.[28] Although the reaction generally required a Lewis acid to assist with elimination of the aglycone group when methyl glycosides were used as substrates, Ito et al. reported that this reaction sometimes proceeded in the absence of a Lewis acid.[29] However, the details of the reaction conditions were not revealed in the paper, and it was also anticipated that in our case that the use of Lewis acid could prove troublesome due to cleavage of the PMB group. After some experimentation, we found suitable reaction conditions. In the absence of a Lewis acid, the ring contraction of the olefin–Zr complex, which was generated in situ at −78 °C, proceeded smoothly by rapidly increasing the temperature. This suggests that multiple intermediates may exist, although it does not indicate that all of them become precursors of carbocyclic compound (**4**). Although we could not determine the structure of these species, compounds **3α** and **3β** were efficiently converted into compound **4** accompanied by small amounts of