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A fast, efficient and stereoselective synthesis of hydroxy-pyrrolidines

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ABSTRACT

A five-step, protecting group free synthesis of 2,3-*cis* substituted hydroxy-pyrrolidines is presented. Key steps in the synthesis are the chemoselective formation of a primary amine via a Vasella reductive amination using ammonia as the nitrogen source, and the stereoselective formation of a cyclic carbamate from an alkenylamine. Improvement of the reductive amination, by way of the use of α-picoline borane as a more environmentally benign reducing agent, is also presented.

1. Introduction

The constant pressure to prepare compounds in a more efficient manner has placed the process by which traditional synthetic chemistry is conducted under scrutiny.[1] The 'ideal synthesis' has been described as one that uses readily available, inexpensive starting materials and proceeds in a simple, safe, environmentally acceptable and efficient manner.[2]

Key in improving the efficiency and atom economy of a synthesis is the omission of protecting groups in the synthetic plan.[1] Although the use of protecting groups has undoubtedly led to a surge in the successful completion of increasingly complex synthetic targets, and justifies the continual development of new and specialised protecting groups,[3] the incorporation and subsequent removal of a protecting group adds to the total number of steps in a synthetic sequence and leads to reductions in overall yield and atom economy.[4] In addition, the material that corresponds to the protecting group (and the reagents used for its introduction/removal) must be separated from the desired compound and discarded, leading to an increase in overall waste production.

There are a number of strategies that can be applied so as to achieve a total synthesis without the need for protecting groups, and a number of elegant reviews have been devoted to this topic.[1,4,5] Traditional methodologies have included the synthesis of compounds with few competing reactivities,[6] protection by protonation,[7] and biomimetic synthesis,[8] while more recent strategies have incorporated new chemistries involving the development of new chemoselective reagents and processes.[1,4,5] With an interest in developing efficient syntheses of iminosugars,[9] we turned our attention to the development of new synthetic methodologies that would enable pyrrolidines to be synthesised without the need for protecting groups. The initial focus of our work was the synthesis of 2,3-*cis*-substituted pyrrolidines (Fig. 1). Of these pyrrolidines, 1,4-dideoxy-1,4-imino-D-xylitol (**1**), isolated from the Pteridophyte *Arachniodes standishii*,[10] is a weak glycogen phosphorylase b inhibitor,[11] while its L-isomer, 1,4-dideoxy-1,4-imino-L-xylitol (**2**), and

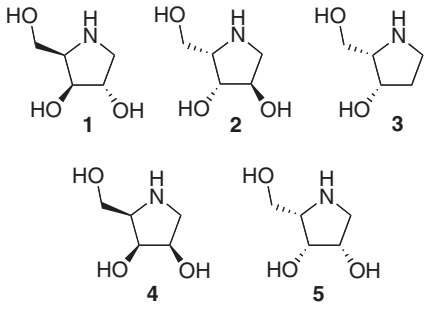

Figure 1. 2,3-*cis*-Substituted pyrrolidines.

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the trideoxy analogue, 1,2,4-trideoxy-1,4-imino-L-xylitol (**3**), are yet to be isolated or tested for biological activity. Of the lyxitol pyrrolidines, 1,4-dideoxy-1,4-imino-D-lyxitol (**4**), the structure tentatively assigned to a pyrrolidine found from *Raispalia* sp.,[12] is a potent α-galactosidase inhibitor,[13,14] while 1,4-dideoxy-1,4-imino-L-lyxitol (**5**) has not been isolated or assayed. A fast, efficient synthesis of pyrrolidines such as these will undoubtedly aid in a more thorough assessment of their therapeutic activities.

In the work presented herein, we report on the applicability of our novel protecting group free strategy[15,16] to the synthesis of L-xylitol **2** and D-lyxitol **4** and provide an explanation for the remarkable diastereoselectivity observed in our carbamate annulation methodology. Our efforts to improve the overall protecting group free strategy via the implementation of more environmentally favourable reductive amination protocols will also be presented. For a summary of other synthetic strategies that can be used to prepare pyrrolidines, there are a number of recent reviews published in this area.[17]

2. Results and discussion

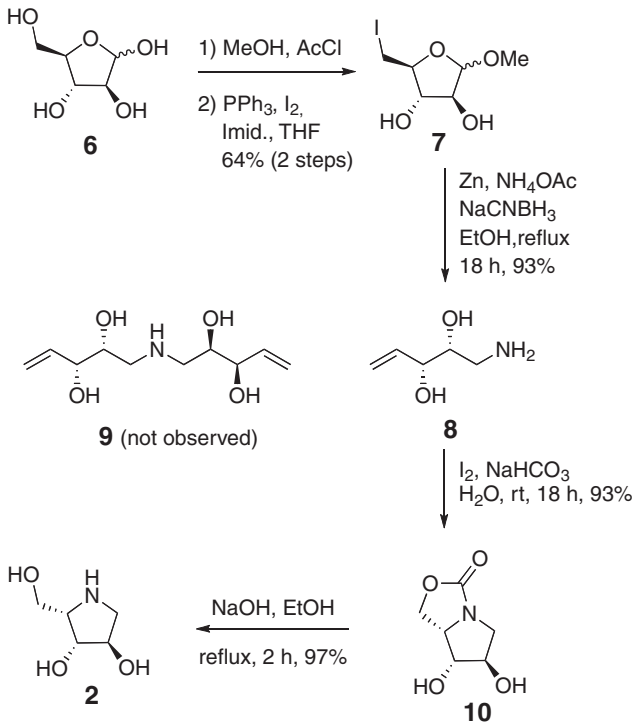
To achieve a protecting group free synthesis of 1,4-dideoxy-pyrrolidines, we envisioned a retrosynthetic analysis that involved three key synthetic transformations: carbamate hydrolysis (**A**→**B**), carbamate annulation (**B**→**C**) and Vasella reductive amination (**C**→**D**) (Scheme 1). Central to this work was the development of a novel tandem halo-cyclisation–carbonylation using sodium bicarbonate as the source of carbon dioxide (**B**→**C**).[15] An efficient reductive amination protocol that uses ammonia, instead of a protected amine, as the nitrogen source to directly yield a primary amine was also key in achieving this protecting group free strategy. Such a transformation has been difficult to effect in the past.[19]

The synthesis of 1,4-dideoxy-1,4-imino-L-xylitol (**2**) commenced with the uneventful transformation of D-arabinose (**6**) to the corresponding iodinated methyl glycoside **7**,[19] although, with iodine, triphenylphosphine and imidazole used in excess, this represents the least environmentally benign aspect of the sequence (Scheme 2). Glycoside **7** was then treated with activated zinc, $NaCNBH_3$, a saturated solution of NH_4OAc in ethanol and aqueous NH_3. Following 18 hours at reflux and purification via Dowex H^+ resin, the corresponding linear alkenylamine **8** was isolated in an excellent yield (93%). When ammonia is used as a nucleophile during reductive amination, typically over-alkylation occurs, resulting in the dimeric product[20] (e.g., **9**). Our modified conditions, however, lead to the exclusive formation of monomer **8** and no trace of dimer **9**. Alkenylamine **8** was then subjected to our iodine-mediated carbamate annulation methodology, which gave carbamate **10** in an excellent yield (93%) and as the major product (>20:1 d.s., as determined by ^1H NMR of the crude reaction mixture). Hydrolysis of the carbamate and comparison of the NMR spectral data and optical rotation values of the hydrolysed product with those in the literature[21,22] confirmed the identity of the resulting pyrrolidine to be that of 1,4-dideoxy-1,4-imino-L-xylitol (**2**). With an overall yield of 54%, this five-step synthesis is remarkably efficient.

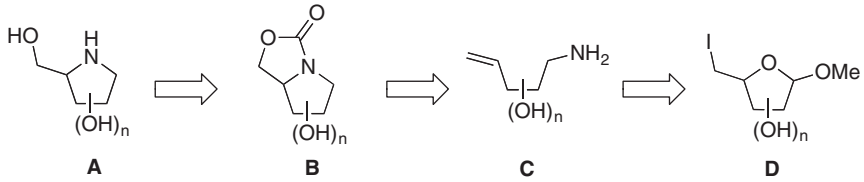
Given our success in preparing 1,4-dideoxy-1,4-imino-L-xylitol (**2**), we anticipated employing a similar synthetic strategy for the synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol (**4**) (Scheme 3). However, unlike most other iodo-pentofuranosides,[18] literature precedent for the formation of the iodinated methyl glycoside **13** involved either a six-step synthesis commencing with D-mannose[23] or a five-step synthesis from 1,2-*O*-cyclohexylidene-α-D-xylofuranose.[24] Being keen to develop a shorter, and potentially more efficient synthesis, we subjected D-lyxose (**11**) to a solution of AcCl in MeOH and stirred the reaction for 18 h at room temperature (Scheme 3). Though a sometimes fickle reaction,[25] with the major impediment being the formation of the undesired thermodynamically more stable methyl pyranoside, these conditions nevertheless lead to the formation of the desired methyl glycoside **12** in 87% yield (with 8% of the pyranose isomer). Next, glycoside **12** was subjected to a solution of triphenylphosphine, iodine and imidazole in THF to install the iodide at the primary position. This transformation proceeded smoothly, with the iodo precursor **13** being prepared in good yield (76%).

With the iodinated methyl glycoside **13** in hand, this was then subjected to our reductive amination conditions. Again, transformation to the linear alkenylamine proceeded smoothly with alkenylamine **14** being prepared in 90% yield. The alkenylamine **14** was then treated with iodine and $NaHCO_3$ to give carbamate **15** in 99% yield (>20:1 d.s.). Following hydrolysis, 1,4-dideoxy-1,4-imino-D-lyxitol (**4**) was then obtained and NMR spectral data and optical rotation values were used to confirm the stereochemistry of the final product.[14]

Having established a general procedure for the synthesis of iminopentitols, attempts were then made to improve the overall



Scheme 2. Protecting group free synthesis of 1,4-dideoxy-1,4-imino-L-xylitol.



Scheme 1. Retrosynthesis for the formation of 1,4-dideoxy-pyrrolidines.