Diastereoselective direct aldol reaction and subsequent cyclization of 2-azetidinone-tethered azides for the preparation of a 4-hydroxypipecolic acid analogue

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1. ABSTRACT

The reaction of enantiopure 3-azido-4-oxoazetidine-2-carbaldehyde with acetone was catalyzed by L-proline, to give the corresponding aldol adduct. This product was stereocontrolled cyclized by using intramolecular reductive amination achieving a new 4-hydroxypipecolic acid analogue with a bicyclic β-lactam structure.

2. INTRODUCTION

4-Hydroxypipecolic acids are naturally occurring non-proteinogenic amino acids which have been isolated from several plants,[1] and are present in many biologically active natural and synthetic products such as depsipeptide antibiotics,[2] NMDA receptor antagonists,[3] and HIV protease inhibitors such as palinavir (Figure 1).[4] Because of their biological importance and synthetic value, much effort has been devoted to their preparation, and different synthetic approaches have been reported.[5] On the other hand, an organocatalytic molecule that has been studied extensively is proline, which promotes the aldol reaction between carbonyl and unmodified ketones for obtaining a stereoselective carbon–carbon bond.[6]

In addition to the important antibiotic and nonantibiotic uses of 2-azetidinones,[7] the β-lactam skeleton is a versatile synthons for the preparation of α- and β-amino acids, alkaloids, heterocycles and taxoids.[8] Continuing with our project on the asymmetric synthesis of nitrogenated compounds of biological interest,[9] we wish to describe here a new stereocontrolled access to 4-hydroxypipecolic acid analogue with a bicyclic β-lactam skeleton, which rely on heterocyclization reactions in a 2-azetidinone-tethered azidoaldol (Figure 1).

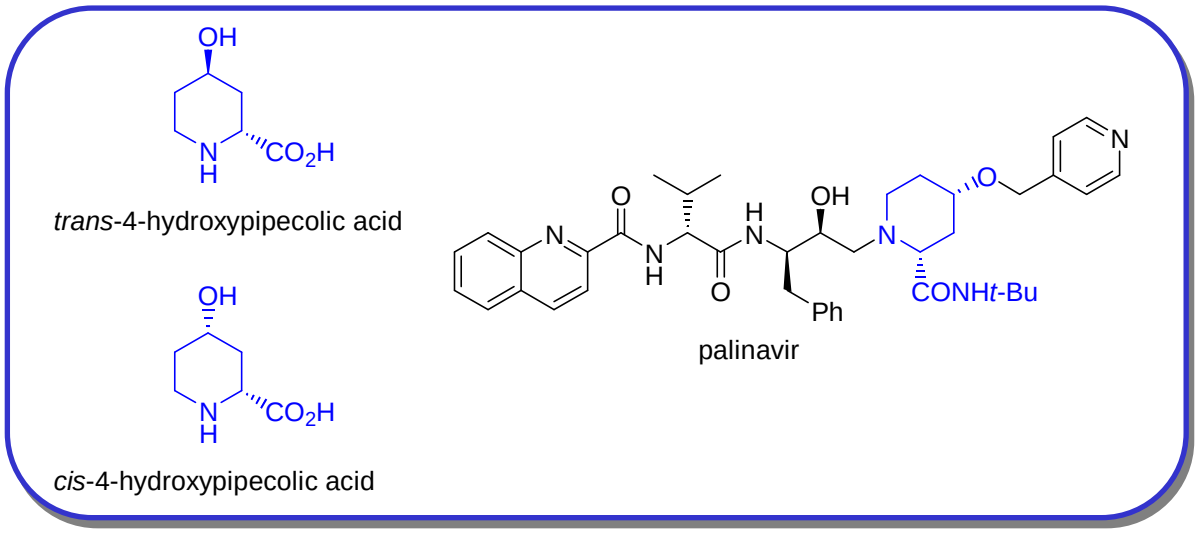
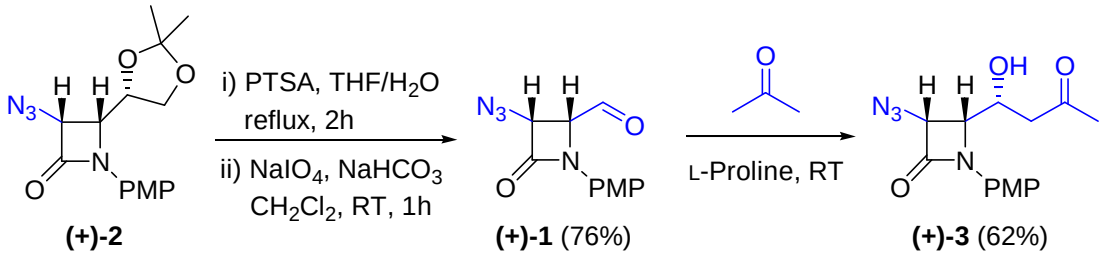


Figure 1. Representative biologically relevant 4-hydroxypipecolic acids.

3. RESULTS AND DISCUSSION

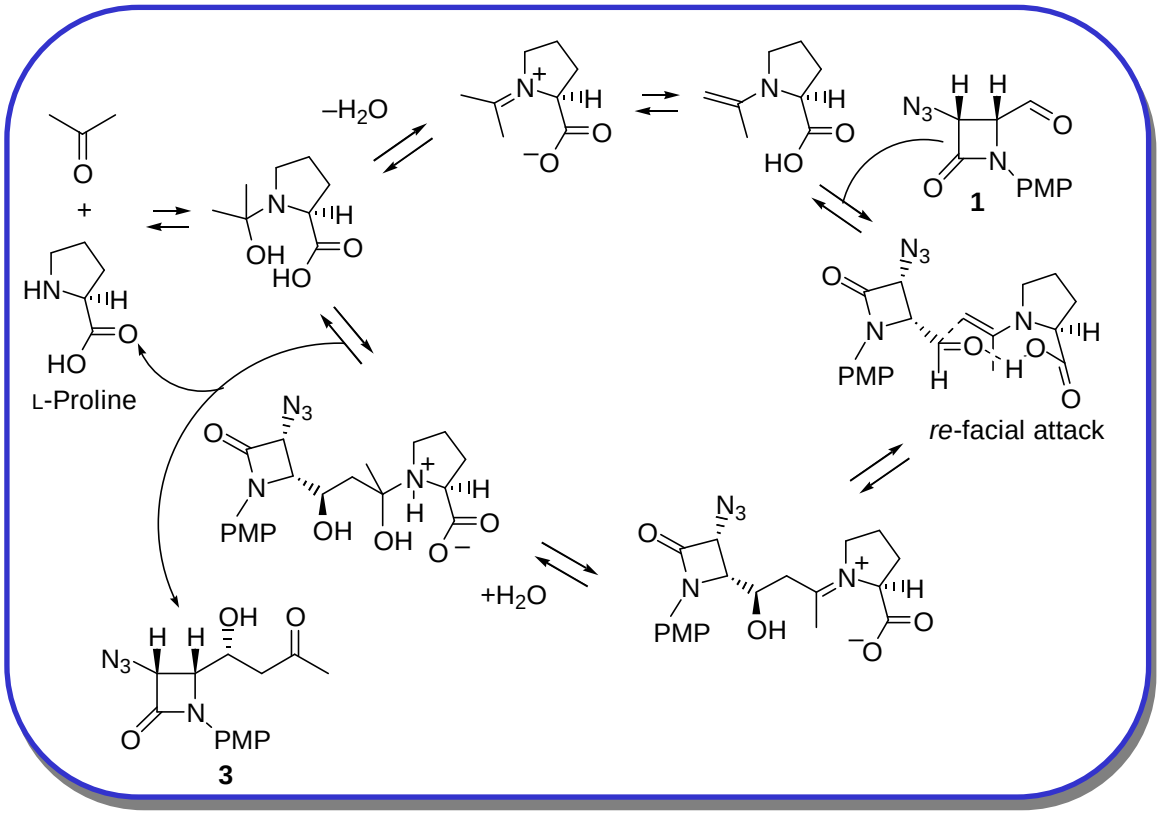
Starting substrate, 3-azido-4-oxoazetidine-2-carbaldehyde **1**, was prepared in optically pure form using standard methodology. Enantiopure 2-azetidinone **2** was obtained as a single *cis*-enantiomer[10] from the corresponding imine of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with azidoacetyl chloride in the presence of Et_3N. Selective acetonide hydrolysis provided the corresponding diol, which after oxidative cleavage smoothly formed the 3-azido-4-oxoazetidine-2-carbaldehyde **1** (Scheme 1). Having obtained the starting substrate, then next stage was set to carry out the aldol process. A model reaction of 4-oxoazetidine-2-carbaldehyde **1** was carried out by mixing acetone and 10 mol% of L-proline in the corresponding solvent at ambient temperature. Indeed, the desired adduct **3** was formed when the reaction was conducted in DMSO (yield 53%, de 40%), DMF (yield 48%, de 60%), or acetone (yield 62%, de 100%). Acetone was

selected as the solvent for further reactions since a higher yield and better diastereoselectivity was obtained for the corresponding aldol **2**. The effect of the amount of the organocatalyst on the conversion rate as well as on the product ratio was studied. Lower yields were obtained when the amount of catalyst was decreased (5 mol%). It was found that the efficiency of the process did not increase on increasing the amount of catalyst (20 mol%). The reaction was carried out by mixing acetone, 10 mol% L-proline, and the β-lactam aldehyde **1** in acetone at ambient temperature. The desired adduct **3** was formed in high yield and good diastereoselectivity (adduct **3** as the exclusive isomer) (Scheme 1).



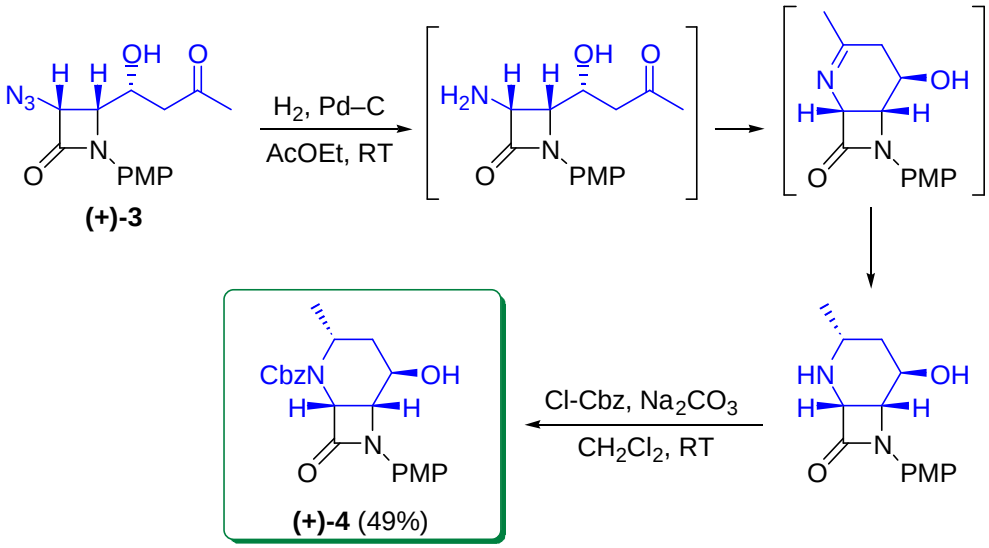
Scheme 1. Direct aldol reaction between azidoaldol **3** and ketone.

The absolute configuration of the aldol product was in good agreement with previously proposed models on proline-catalyzed aldol reactions (Scheme 2).[11] According to this proposal, proline functions as a microaldolase, with the secondary amine acting as a nucleophilic enamine catalyst and the carboxylic acid moiety as a general Brønsted co-catalyst. The observed stereochemistry can be explained by invoking a metal-free Zimmerman–Traxler-like transition state. An hydrogen bond involving the carboxylate, enamine, and aldehyde organizes the transition state. Steric interactions between the aldehyde and enamine substituents may be the most important, accounting for the enantiofacial selectivity exhibited by this reaction. The observed high selectivity for the L-proline-catalyzed reaction of **1** can be rationalized as the cumulative effect of steric inhibitions posed by the chiral aldehyde and the facial preference of the organocatalyst (favored, match).



Scheme 2. Mechanistic explanation for the obtention of azidoaldol **3**.

The conversion of azides to amines can be achieved by a large variety of reported methods.[12] For this reason, the exposure of **3** to chemoselective reductive conditions might serve as a straightforward procedure for the preparation of new bicyclic 4-hydroxypipecolic acid analogues, because under the reaction conditions the resulting amino group would attack the aldol functionality. Treatment of aldol adduct **3** with a reductive system (Ph_3P–H_2O) did not afford the aminocyclization product. When, the hydrogenation reaction was carried out in the presence of Boc_2O, small amount of the cyclization product was observed by ^1H NMR. Taking these results into account, the reduction of the azide, subsequent cyclization and protection of the resultant secondary amine as the benzylcarbamate was developed in situ. Catalytic hydrogenation of the compound **3** (H_2, 1 atm) in the presence of 10% of Pd/C in ethyl acetate at room temperature followed by the addition of benzyl chloroformate, provided the 4-hydroxypipecolic acid analogue **4** with a bicyclic β-lactam structure (Scheme 3).



Scheme 3. Preparation of enantiopure 4-hydroxypipecolic acid analogue **4**.

The *cis*-stereochemistry of the four-membered ring was transferred unaltered during the cyclization step. The stereochemistry at the carbinolic and *C*-methyl stereogenic centers for compound **4** was assigned by selective NOE experiments. The configuration of this carbinolic chiral center was consistent with a Zimmerman–Traxler six-membered ring chair-like model for the aldolization step,[13] as depicted in Scheme 2. In our case, the stereoselective formation of bicycle **4** can be understood on the basis of *cis* addition of hydrogen atoms to the less hindered face of the unsaturated centre; being the more accessible side of the intermediate imine the face which is no blocked by the β-lactam ring.

4. CONCLUSIONS

In conclusion, we have described here a different stereocontrolled route to new 4-hydroxypipecolic acid analogues with a bicyclic β-lactam structure. We have shown that combination of proline-catalyzed diastereoselective direct aldol reaction and subsequent intramolecular reductive amination reaction in 2-azetidinone-tethered azides may lead to a useful preparation of the piperidine fused β-lactam core. Applications to different heterocycles employing this aminocyclization is underway.

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