ENZYMATIC ALDOL CONDENSATION AS A ROUTE TO HETEROCYCLES: SYNTHESIS OF 1,4-DIDEOXY-1,4-IMINO-D-ARABINITOL, FAGOMINE, 1-DEOXYNOJIRIMYCIN AND 1-DEOXYMANNOJIRIMYCIN[1]

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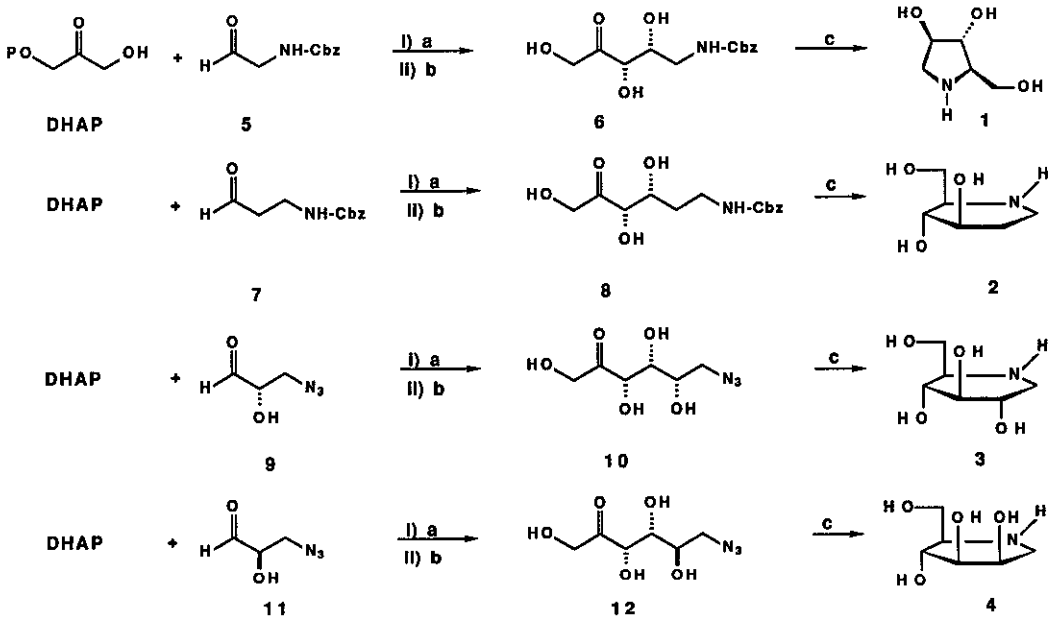
Abstract-1,4-Dideoxy-1,4-imino-D-arabinitol, fagomine (1, 2, 5-trideoxy-1, 5-imino-D-arabinohexitol), 1-deoxynojirimycin (1,5-dideoxy-1,5-imino-D-glucitol) and 1-deoxymannojirimycin (1,5-dideoxy-1,5-imino-D-mannitol) have been prepared via fructose-1,6-diphosphate aldolase catalyzed condensation followed by catalytic intramolecular reductive amination.

Naturally occurring polyhydroxylated alkaloids 1,4-dideoxy-1,4-imino-D-arabinitol (**1**), fagomine (**2**), 1-deoxynojirimycin (**3**) and 1-deoxymannojirimycin (**4**) are of considerable interest as specific inhibitors of glycosidases.[2,3] These four alkaloids are natural products. **1** was isolated from *Angylocalyx boutiqueanus.*[4] **2** was isolated from Japanese buckwheat (*Fagopyrum esculentum* Moench).[5] **3** was isolated from plants of genus *Morus*[6] and from strains of *Bacillus*[7] and **4** was isolated from the legume of *Lonchocarpus.*[8] Syntheses of these alkaloids from natural sugars and tartaric acid have been reported.[6,7,13-22] Of these procedures, the combined microbial oxidation/intramolecular reductive amination[17] for **3** and intramolecular aminomercuration[19] for both **3** and **4** are considered to be the most efficient.

We have recently reported the synthesis of **3** and **4**, in 60-70% isolated yields from the corresponding chiral aldehyde, via fructose-1,6-diphosphate (FDP) aldolase-catalyzed condensation and reductive amination[11,12] (see Scheme 1). The aldehydes **9** and **11** used as acceptors in the aldol reaction were prepared via a lipase-catalyzed kinetic resolution of the racemic acetal precursors[12] (see Scheme 2). When the racemic aldehyde (**9** and **11**) was used as a substrate, a kinetic diastereoselectivity was observed in the aldol reaction giving **12** as the major product (~80%). The donor, dihydroxyacetone phosphate (DHAP) can be replaced with dihydroxyacetone and catalytic amount of inorganic arsenate, and the enzyme can be obtained from rabbit muscle (from Sigma) or *E. coli.*[12,23-24] We report here the extension of this synthetic methodology to the preparation of **1** and **2**.

The condensation of **5** or **7** (Scheme 1) and DHAP, catalyzed by FDP aldolase, followed by removal of the phosphate, catalyzed by acid phosphatase, gave the corresponding Cbz-pentulose and Cbz-hexuloses. Hydrogenation of the mixture over Pd/C at 50 psi H_2 gave **1** and **2** respectively. All of the enzymes used



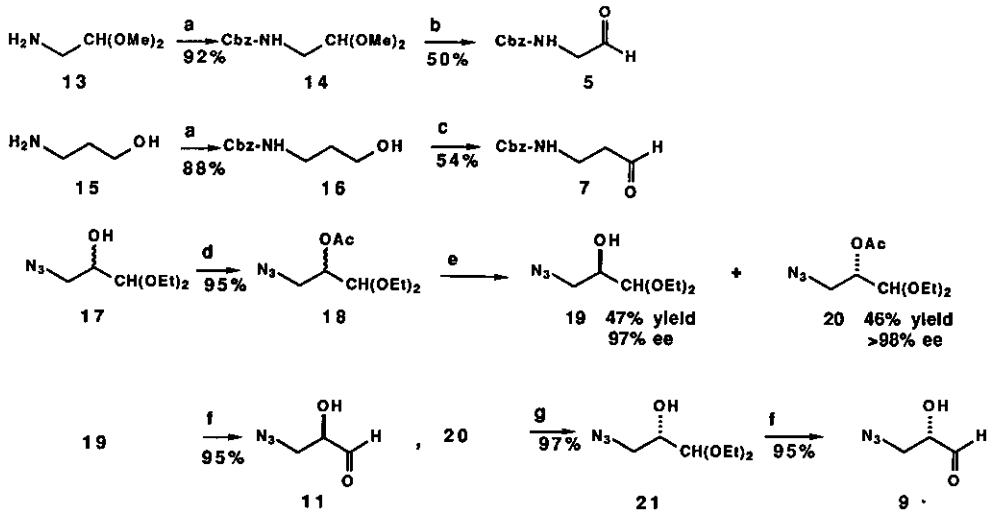
Scheme 1. A combined enzymatic aldol condensation and reductive amination as an efficient route to 1,4-dideoxy-1,4-imino-D-arabinitol (1), fagomine (2), 1-deoxynojirimycin (3), and 1-deoxymannojirimycin (4). a) FDP aldolase; b) acid phosphatase; c) H_2/Pd.

were purchased from Sigma Chemical Company and used without further purification.

EXPERIMENTAL

1,4-Dideoxy-1,4-imino-D-arabinitol **1** (Scheme 1)

To a 100 ml round-bottomed flask containing a magnetic stirbar and 56 ml of a 86 mM solution of DHAP[25] (4.8 mmol) at pH 7.0, was added 2.04 g (10.5 mmol) of **5** in 11.5 ml of DMSO. Upon addition of **5** in DMSO, the solution turned milky white and remained white during the entire reaction. FDP aldolase (200 U) was added and the solution was stirred for 18 h. Barium chloride 4.40 g (18.0 mmol) was added and the pH adjusted to 8.0 with 2 N NaOH. Two equivalent volumes of acetone (~200 ml) were added and the solution was stored at 0° C for 6 h. The precipitate was isolated and washed twice with cold acetone by centrifuging (15 min at 3000 RPM). The precipitate was suspended in 200 ml of water and treated with Dowex 50 (H^+) until the pH remained at 1.5. The solution was filtered, the pH adjusted to 4.8 with 2 N NaOH, acid phosphatase (200 U) was added and the mixture was incubated at 37° C, with stirring, for 18 h. Ames test[26] for phosphates indicated 100 % hydrolysis of the phosphate ester. The pH was readjusted to 7.0 and lyophilized. The semi-solid residue was treated with methanol (3 x 50 ml) and filtered to remove insoluble material. The methanol was removed under reduced pressure until ~10 ml remained, 20 ml of water and 1.0 g of 10% Pd/C was added. The solution was hydrogenated over 50 psi H_2 for 24 h. The Pd/C was removed by filtration and the solvent removed under reduced pressure. **1** was purified by recrystallizing the hydrochloride salt from methanol : ether (11 : 1) and was the only compound seen by nmr, to obtain 241 mg, 28 % yield (based on DHAP). The ^1H and ^{13}C nmr, the optical rotation and the melting point are consistent



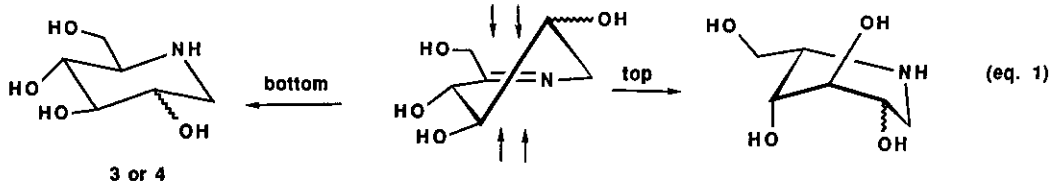
Scheme 2. Synthesis of the aldehydes used in aldol reactions. 9 has S stereochemistry and 11 has R stereochemistry. a) Cbz-Cl, aq. acetone, $NaHCO_3$; b) THF/H_2O, $(COOH)_2$, reflux 4 days; c) PCC; d) Ac_2O, pyridine; e) Pseudomonas lipoprotein lipase, 51% conversion; f) HCl, H_2O, 65° C, 12 h; g) CH_3OH/NaH (cat.), 2 h, 25° C.

with reported values.[4,9] The low yield is attributed to the poor water solubility of **5**. It is worth noting that the free base is a hygroscopic oil, the corresponding hydrochloride is crystalline and relatively easy to handle.

Fagomine **2** (Scheme 1)

Fagomine was prepared by the same procedure above, from aldehyde **7**. The product was purified by silica gel column chromatography to yield 350 mg of **2**, 34% yield (based on DHAP). The ^1H nmr, the optical rotation and the melting point are consistent with reported values.[5,20] The ^{13}C nmr of **2** is reported here.[10] It is interesting that under the reductive amination condition, only one diastereomer is produced. The reason for such diastereofacial selectivity is not clear, from the results obtained; however, we propose that the stereocontrol is originated from the hydrogenation of the imine intermediate (eq 1). During the reaction, palladium must first coordinate with the double bond, and hydrogen must approach from the same side as palladium. The C-OH group adjacent to the carbon-nitrogen double bond may play an important role in the facial selectivity. Attack of hydrogen from the bottom face seems to be more favorable as it would avoid the torsional strain developed via attack from the top face. This bottom approach will result in a chair form product with C4-C5 in a trans relation. The same argument can be applied to the reduction of **6** to **1** and that of **8** to **2**, both resulting in the same trans relationship.

In summary, enzymatic aldol condensation combined with reductive amination appears to be an efficient



(eq. 1)

approach to the synthesis of piperidines and pyrrolidines. The chiral centers are obtained with remarkably high diastereoselectivity in the combined catalytic processes. Minimal protection and deprotection steps are used in the overall process. We are currently investigating the use of other aldolases on the synthesis of related polyhydroxylated alkaloids.

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