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Novel chemoenzymatic synthesis of an enantiopure *allo*-inosamine hexaacetate from benzyl azide

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ABSTRACT

A facile and short chemoenzymatic synthesis of (−) 1L-5-amino-5-deoxy-*allo*-inositol hexaacetate is described using benzyl azide as starting material. The key transformations consist of an enzymatic dioxygenation using the toluene dioxygenase enzymatic complex, followed by an allylic azide double sigmatropic [3,3] shift to introduce the nitrogen functionality in the ring in a stereoselective manner. Azide reduction and further regioselective oxidation of the diene moiety afforded the desired inosamine in only eight steps from benzyl azide.

Aminocyclitols (or aminocarbasugars) are a group of aminocycloalkane polyols that have gained great importance because of their remarkable biological activities.[1] Functioning as mimics of natural carbohydrates they present a wide range of biological activities such as alpha-glucosidase inhibitors,[2] antibiotics,[3] antifungals,[4] and potential therapeutics for diseases of carbohydrate metabolism.[5] In addition, some aminocyclitols are advanced key structural motifs in the total synthesis of several *Amaryllidaceae* alkaloids.[6] Figure 1 shows some structural examples: amino-inositols **1**–**3** are part of antibiotic KA-3093,[7] methoxyhygromycin,[8] and minosaminomycin[9] respectively. Also compounds **4**–**5** present interesting biological activities for Gaucher disease.[5,10]

Due to these interesting biological properties, the enantioselective preparation of aminocyclitols has attracted the attention of the synthetic community in the last decades.[1a] In particular, *cis*-cyclohexadienediols prepared by biotransformation of arenes using bacterial dioxygenases have been widely used as starting materials for aminocyclitol synthesis (Fig. 2A).[11] These substrates already possess two hydroxyl groups and the additional ones may be introduced by further stereoselective oxidations. Regarding the nitrogen functionality, several different methodologies have been used for its strereocontrolled introduction into the ring as reviewed recently by Lewis and co-workers[11b] Acyl nitroso cycloaddition to the diene moiety;[12] alkene regio- and stereoselective epoxidation followed by ring-opening with a nitrogen nucleophile[6b,12b,13] and also alkene aziridination[13b,e,l,14] are the three main strategies that have been used for this aim (Fig. 2A).

Recently we described the structures of novel interesting azido dienediols obtained from the biotransformation of benzyl azide by the toluene dioxygenase (TDO) enzymatic complex expressed in *Escherichia coli* JM109 (pDTG601).[15] In addition to the expected diol **11**, the exocyclic diene **12** was found; its formation was explained by an spontaneous stereoselective double sigmatropic

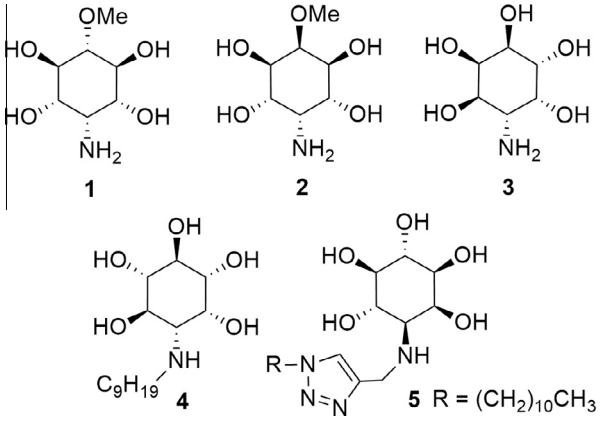

Figure 1. Representative aminocyclitol units present in important biologically active products.

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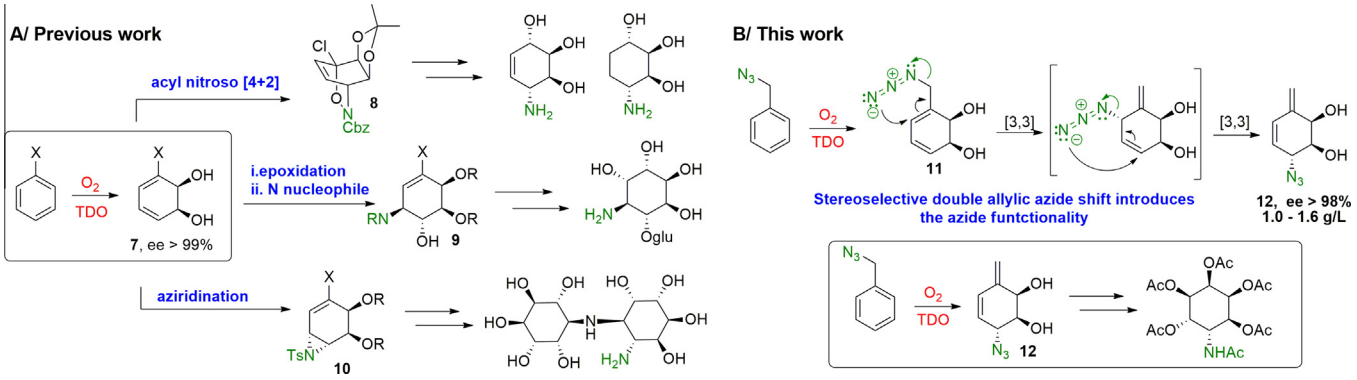

Figure 2. (A) Previous strategies for introducing nitrogen functionality in *cis*-cyclohexadienediols for aminocyclitol synthesis. (B) Stereoselective azide functionalization via double allylic azide sigmatropic shift used in this work.

[3,3] shift from **11** (Fig. 2B). This type of rearrangement was previously reported by Boyd et al. on cyclic dienediols from microbial origin.[16] Production of **12** was optimized in a bioreactor scale to render a yield of 1.0–1.6 g/L.[15]

In this work we use the azido dienediol **12** as starting material for the enantioselective preparation of (−) 1L-5-amino-5-deoxy-*allo*-inositol hexaacetate. The proposed synthetic design allows for a facile and straightforward inosamine preparation since the nitrogen containing functionality is already present and with the right configuration in the starting material. The same inosamine skeleton with the proper stereochemistry has led to the synthesis of interesting derivatives such as a methylenedioxoacetal related to hygromycin A,[17] and the corresponding azido analog.[18] However, to the best of our knowledge, the target aminocyclitol has only one previous enantioselective synthesis in the literature[19] and other racemic approaches.[20]

As a first approach we studied oxidative conditions to selectively oxidize the *exo*- or *endo*-cyclic olefins in diol **12**. Standard dihydroxylation procedures using $RuCl_3$ or OsO_4, as well as epoxidation using *m*-CPBA, afforded mixtures of products with poor regio-selectivities. Ozonolysis in DCM/Py afforded the best results to oxidize the *exo*-olefin to give the corresponding ketone, which was reduced under Luche conditions,[21] and acetylated to give **13** as a chromatographically inseparable 7:3 mixture of diastereomers in an overall yield of 40% (Fig. 3).

In order to be able to separate the diastereomeric mixture for further spectroscopic characterization, we decided to change the protecting groups of the triol moiety. To our disappointment, transesterification of **13** with K_2CO_3/MeOH followed by diol protection with the isopropylidene group afforded products **14a** and **14b** where the azide group underwent an allylic [3,3] rearrangement. According to our previous findings, we reasoned that this sigmatropic shift is favored by hydrogen bonding between the azide and the vicinal free hydroxyl group.[15a] At this stage, we became concerned that this rearrangement could also take place

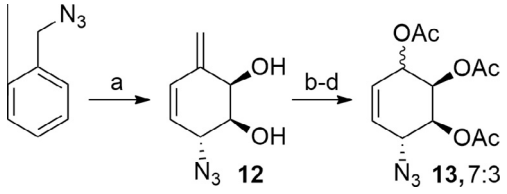

Figure 3. First approach toward aminocyclitol synthesis using diol **12**. (a) *E. coli* JM109 (pDTG601) then 1 week at rt, 1.0–1.6 g/L; (b) O_3, DCM: Py −78 °C; (c) $NaBH_4$ $CeCl_3{\cdot}7H_2O$, MeOH; (d) Ac_2O, Et_3N, DMAP, DCM, 0 °C, overall b-d 40%.

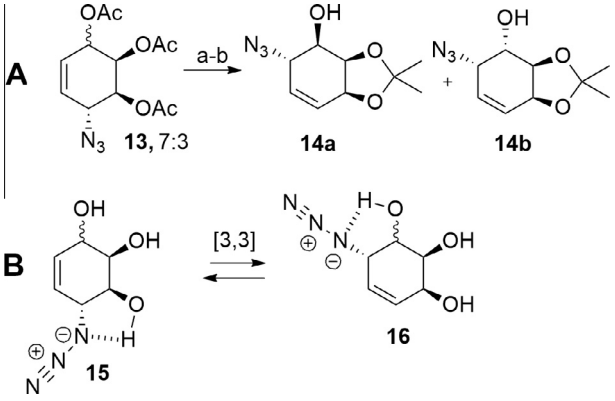

Figure 4. (A) (a) K_2CO_3, MeOH; (b) 2,2-dimethoxypropane, acetone, *p*-TsOH. (B) The [3,3] sigmatropic shift is promoted by the hydrogen bond generated in the alpha hydroxy azide moiety and can jeopardize the stereochemical integrity of the product.

immediately after the ozonolysis/reduction of **12**, in which case the allylic azide in triol **15** (Fig. 4B) would be shifted to give **16**. Since in both structures there is a vicinal hydroxyazide, an equilibrium could take place and jeopardize the enantiomeric integrity of the product (**15** and **16** are enantiomers when the three hydroxyl groups are *syn*). In view of these results we decided to change our synthetic design reducing first the azide group in **12**, in order to avoid the above mentioned sigmatropic shifts.

Figure 5 shows our second approach. Staudinger conditions on **12** smoothly produced the desired amine in 98% yield, which was fully protected to give triacetate **17**.

Unexpectedly, oxidation of **17** using previous ozonolysis conditions gave a complex mixture of products affording the desired ketone only in traces. However, we were delighted to find that, epoxidation conditions in **17** using *m*-CPBA in the presence of fluoride salts (NaF/KHF_2)[22] as additives afforded epoxide **18** in a 63% yield, whose stereochemistry (epoxide *syn* to the acetamido group) was proposed according to *J* coupling analysis. Trace amounts of another diastereomer with the same regiochemistry were also found in the reaction mixture (probably with the epoxide *anti* to the acetamido group). The obtained regio- and stereoselectivity of **18** could be explained by coordination of the epoxidation agent with the acetamide function acting as a directing group. Then acidic hydrolysis of **18** followed by acetylation, gave tetraol **19** with complete regiocontrol.