Diastereoselective Reductions of α-chiral, α-alkoxy Tosyl Hydrazones

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of the requirements for Honors Studies in Biophysical Chemistry

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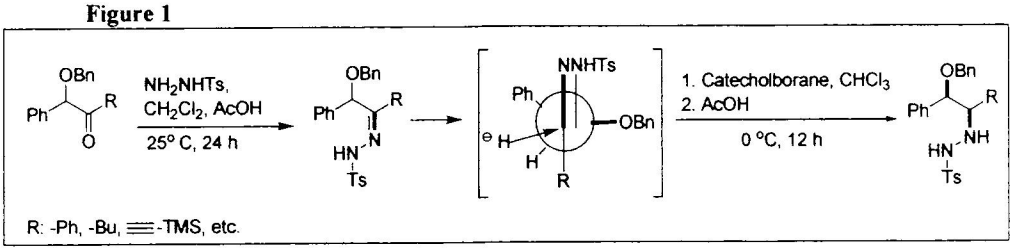
Natural products chemistry is an important field of research for the development of new chemotherapeutic agents. A number of natural products from biological sources display promising potential against various types of cancer. For example, paclitaxel, or taxol, stabilizes microtubules and thus suppresses cell division, halting the rapidly dividing cancer cells. However, the supply of natural products is often severely limited, as many come from rare sources that can be both difficult to locate and costly to retrieve. Synthetic organic chemistry offers ways to confront these problems through the development of laboratory methods for generating such natural products efficiently and economically. The discipline of synthetic organic chemistry includes both methods development and total synthesis of complex molecules.

Currently, I am developing methods for diastereoselective reductions of α-chiral, α-alkoxy tosyl hydrazones in the lab of principal investigator Matt McIntosh. The reductions are intended to lead to the diastereoselective synthesis of vicinal amino alcohols. These compounds are well-recognized in asymmetric synthesis, as many chiral auxiliaries and ligands, such as statine and sphingosine,[1] contain this substructure. Achieving proper stereochemistry of a molecule is of extreme importance in pharmaceutical development because usually only one particular stereoisomer will function in a biological sytem. The goal is to develop novel strategies and methods that will result in general and flexible approaches to diversified analogous compounds containing the vicinal amino alcohol substructure. Molecules such as vicinal aminols serve as important precursors to several anti-cancer agents.

A variety of methods for the diastereoselective reduction of α-hydroxy oximes and α-alkoxy oximes have been reported using $LiAlH_4$ and various borane reagents, including catecholborane and pinocholborane, to obtain vicinal aminols.[2] The stereoselectivities range from modest to high. By contrast, only a single report of diastereoselective hydride addition to α-chiral, α-alkoxy hydrazones exists in the patent literature.[3] Based on results for the

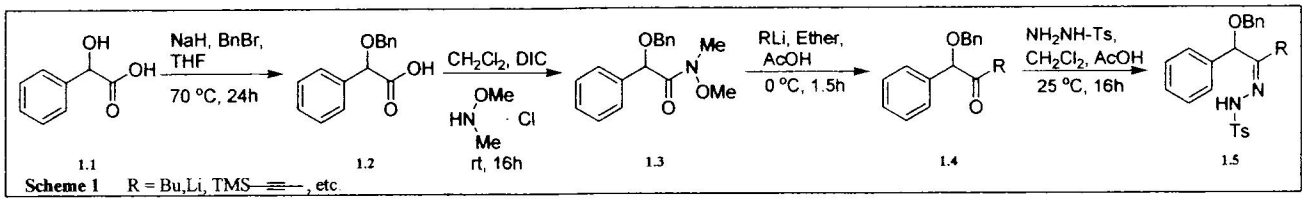
stereoselective reduction of oximes[2], we reason that reduction of chiral α-OBn sulfonyl hydrazones could occur in similar fashion (Fig. 1).

Figure 1



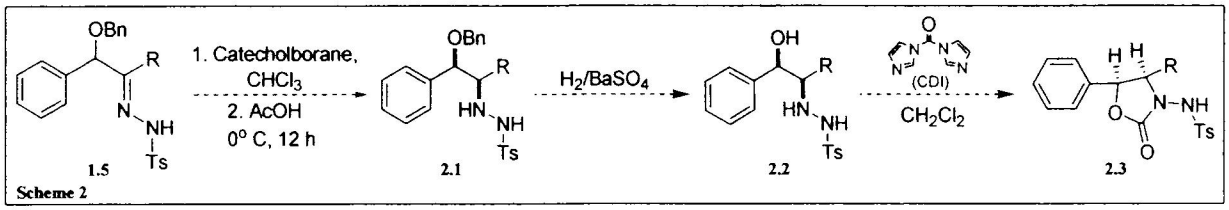
The key to the mechanism exhibited in Fig. 1 is molecular conformation. The most important conformations of a carbonyl compound with a stereogenic center adjacent to the carbonyl group are those that place the largest group perpendicular to the carbonyl group. This arrangement allows for external hydride addition to the transition state rotamer with bonded borane sterically and electronically shielding one C=N face.

I began the synthesis of requisite precursors in January of 2005. Mandelic acid (**1.1**) was chosen as a simple starting material, and hydrazone **1.5** (Scheme 1) was the initial synthetic target. It was necessary to first protect the hydroxyl group at C2, which was accomplished through drop-wise addition of benzyl bromide (BnBr). I chose one of the N-methoxy-N-methylamides developed by Nahm and Weinreb as a highly useful group for nucleophilic addition to the carbonyl group, affording the desired mono-alkylation product **1.4**.[4] All reactions and purification methods were optimized so that relatively high yields (76%-96%) were achieved in each step.



Scheme 1 R = Bu,Li, TMS—≡—, etc.

My current research efforts are directed toward the synthesis and stereochemical determination of hydrazine **2.1** (Scheme 2). An excess of catecholborane (10 eq.) will serve as the reducing agent to yield the *syn*-hydrazine. The proposed *syn*-isomer is expected to appear in a 10:1 ratio with the *anti*-isomer. Selective debenzylation of the primary benzyl group of ether **2.1** to alcohol **2.2** will be achieved via hydrogenation at high pressure. The mild debenzylation of **2.1** will allow for the subsequent conversion of amino alcohol **2.1** to oxazolidinone **2.3**. Carbonyl di-imidazole will serve to lock the compound into the form of a more readily characterizeable oxazolidinone. The aminols will be characterized as the five-membered oxazolidinone via ^{1}H-NMR. Further reactions of target **2.2** will be pursued to enhance its chemo-therapeutic potential as an integral substructure.



Scheme 2

The development of novel synthetic methods for the generation of *syn*-vicinal aminols is highly advantageous since chiral α-amino alcohols not only occur as natural products and drugs,[5,6] but also as components of amino sugars,[7] peptides and peptide analogs.[8] Examples include the carbohydrate component of the anti-cancer anthracycline antibiotics adriamycin, daunomycin, and carninomycin;[7] vancomycin and pepstatin. Pepstatin is an interesting transition-state analogue which inhibits cell proliferation.[8] New synthetic methods will lead to new promising anti-cancer agents with mechanisms similar to these. My novel, economic and efficient diastereoselective route to *syn*-vicinal aminols will provide a reliable, reasonably simple synthesis for an imperative substructure. We hope that the final procedure will be useful in the generation of a variety of diverse biologically active products.

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