Summer Scholar Report

Asymmetric Mannich Reactions via Pseudoephenamine Glycinamide Enolization

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Since the discovery of penicillin G (**1**, Fig. 1) nearly 75 years ago, β-lactams are some of the most widely prescribed antibiotics in the United States and around the world. Rapidly increasing resistance to β-lactams is threatening the limited arsenal of antibiotics available to physicians, and the lack of innovation and momentum in the field of antibiotic development has caused the drug pipeline to virtually dry out. Significant research in the practical and variable synthesis of antibiotics playing a central role in the battle against resistant bacteria.[1a,b]

The β-lactam's characteristic four-membered ring exerts its antibacterial effect by interfering with bacterial cell wall synthesis. In binding to the bacteria's β-lactambinding enzymes called PBPs (penicillin-binding proteins), the drug inhibits cell wall synthesis, eventually leading to cell death. Resistance mechanisms include: changes in one or more of the PBPs, which decreases the drug's ability to bind to the target bacteria; changes in cell wall porins, which prevent penetration of the antibiotic;i and finally, bacterial production of β-lactamases, which deactivates the antibiotic before it can reach its target.[ii]

The discovery of nocardicins (**2**, Fig. 1) in 1976, as well as others, prompted new interest in the pharmaceutical potential of monocyclic β-lactams, which has motivated chemists to develop a variety of routes to these compounds.[ii] Most notable among these is Aztreonam (**3**, Fig. 1), which represents the only fully synthetic monobactam to be developed as a commercial drug in the United States.[i] Developments in the synthesis of monocyclic β-lactams have included cyclization of amino acids,[v] [2+2] cycloaddition of ketenes and imines,[v] ester enolate-imine condensations,[vi] and others.[vi] Asymmetric enolate-imine condensations have been reported using *(S,S)*-pseudoephedrine[i] and chiral oxazolidinones; [x] however, these syntheses lack amino functionality at the C-3 position important to monocylic β-lactams activity. Using chemistry developed by the Myers group with pseudoephenamine glycinamide, this project aims to synthesize αβ-diamino acids, which are precursors to monocyclic β-lactam candidates.

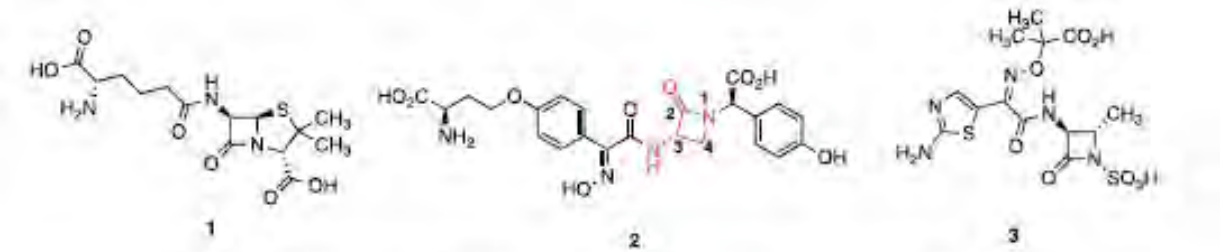
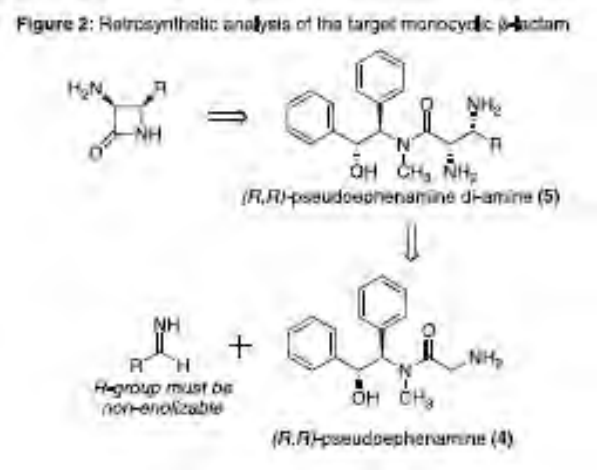
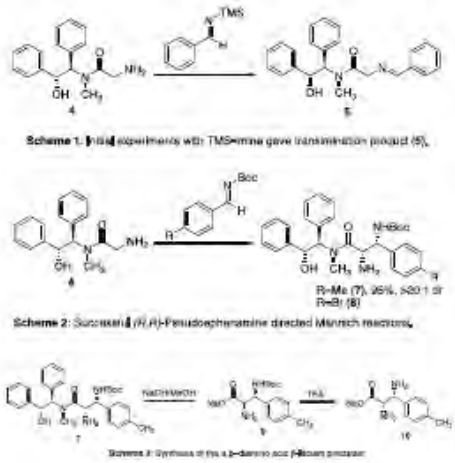


Figure 1: β-lactam antibiotics. Structures of (1) penicillin G, (2) nocardicin A, and (3) aztreonam.

The Myers group has shown that stereocontrolled synthesis of *syn*-β-hydroxy-α-amino acids can be achieved via direct aldolization of pseudoephenamine glycinamide.[xi] Analoguous enolization of pseudoephenamine glycinamide **(4)** followed by the trapping an imine electrophile was expected to deliver a diastereoselective Mannich reaction and produce the desired diamine **(5)** β-lactam precursor (Fig. 2).



Initial challenges in the project involved the choice of electrophile. Trimethylsilyl-benzaldimine was at first selected for its lability and consequent potential for simultaneous cyclization the β-lactam and cleavage of the auxiliary upon formation of the Mannich adduct. Several attempts to effect a Mannich coupling with TMS-imine were unsuccessful, leading instead to the transimination product (**6**, Scheme 1). By switching to Boc-imines, successful Mannich coupling was achieved. Boc-*p*-toluelbenzaldimine yielded a 95% yield of major diastereomer showing promise for a highly diastereoselective reaction (**6**, Scheme 2). Absolute determination of the product's stereochemistry remains to be determined via X-ray crystollography. The success of the Boc-imine electrophile indicates potential for the synthesis of a variety of other Mannich adducts from a variety of Bocimines. To date, Boc-*p*-bromobenzaldiminexii has also been successfully used as a Mannich substrate (**8**, Scheme 2).



Completing the β-lactam synthesis required removal of the auxiliary and deprotection of the Boc group to yield the corresponding alpha,β-diamino acid. Auxiliary cleavage in basic conditions gave the water-soluble carboxylate diamine (**9**, Scheme 3). Boc deprotection in TFA proceeded cleanly (**10**); however, subsequent cyclization attempts using Mukaiyama's reagent have yielded inconsistent results. Difficulty purifying the water-soluble cyclization substrate as well as the water sensitive nature of the cyclization may explain the unsuccessful results. Recent success in cleavage of the Boc group with the substrate still attached to the auxiliary offers the possibility of a cleaner cyclization route. Continued work on this project will involve further exploration of cleavage methods and cyclization pathways as well as diversification of possible Mannich adducts with a variety of imine electrophiles.

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