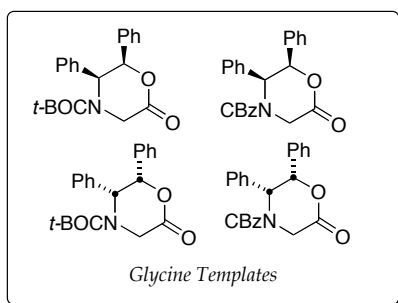


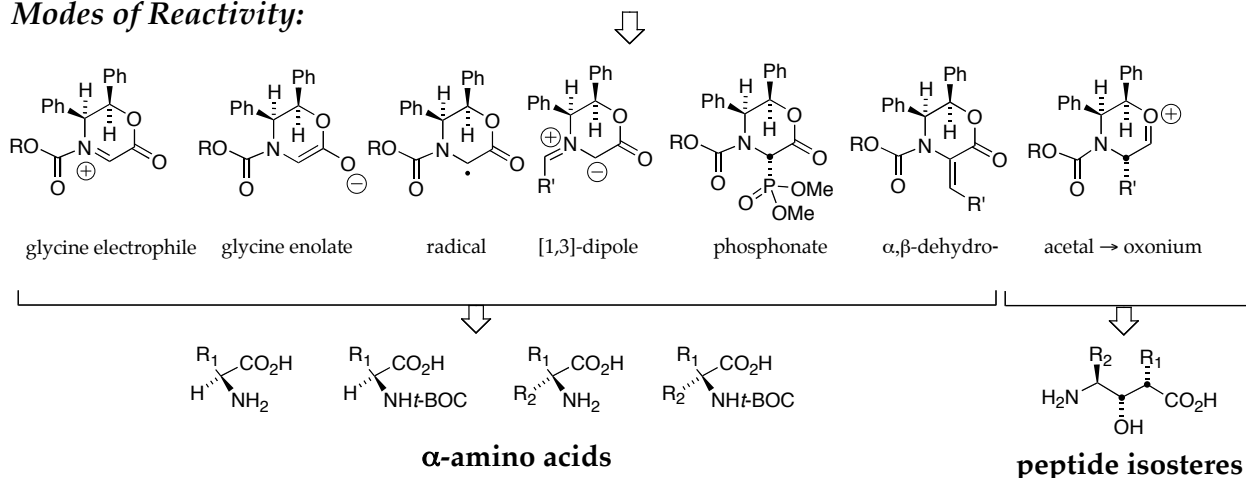
III. DEVELOPMENT OF SYNTHETIC METHODOLOGY

The Asymmetric Synthesis of α -Amino Acids and Peptide Isoesters

We have developed a general, asymmetric synthesis of α -amino acids based on a variety of C-C bond-forming strategies to optically active glycinate. We are studying the construction of difficult classes of amino acids including the vancomycins, diaminopimelic acids, 1-aminocyclopropane carboxylic acids, vinyl glycines, and α,α -disubstituted amino acids. The optically active glycinate are now commercially available from Aldrich. This methodology is being applied to the total synthesis of various natural products containing or derived from unusual amino acids and numerous mechanism-based inhibitors of amino acid biosynthesis (ie., diaminopimelic acid) are being synthesized via the glycinate methodology. We are also engaged in utilizing this technology to provide unusual amino acids that will be useful for creating large combinatorial libraries of compounds for a wide range of biological screening projects.



Modes of Reactivity:



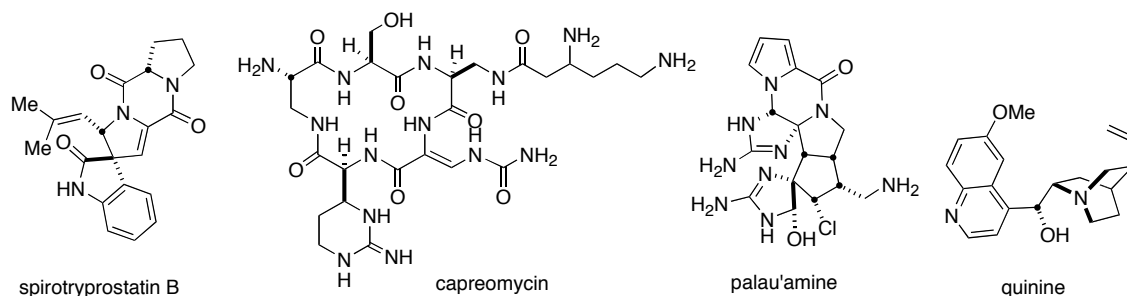
A very recent area of investigation in this project has been devoted to a direct asymmetric synthesis of hydroxymethylene- and hydroxyethylene peptide isoesters.

Major accomplishments:

1. The design, synthesis and commercialization (Aldrich) of one of the most versatile templates for asymmetric amino acid synthesis has been developed. Numerous natural products have been synthesized with this methodology. (see: Williams, R.M., *Aldrichimica Acta*, **1992**, *25*, 11).
2. Exploitation of enolate, cation, radical, [1,3]dipolar cycloaddition, phosphonate and α,β -dehydro reactivity has been investigated for accessing a wide structural array of optically pure α -amino acids.
3. The N-t-BOC glycinate provide the *only* direct asymmetric synthesis of non-proteinogenic N-t-BOC- α -amino acids. While many methods exist for the synthesis of amino acids, and other chiral glycine templates have been developed, the strength of these glycine systems are their demonstrated versatility, ease of cleavage, and most significantly, the direct access to the t-BOC-protected non-proteinogenic amino acids. This work was a direct outgrowth of the total synthesis of bicyclomycin.

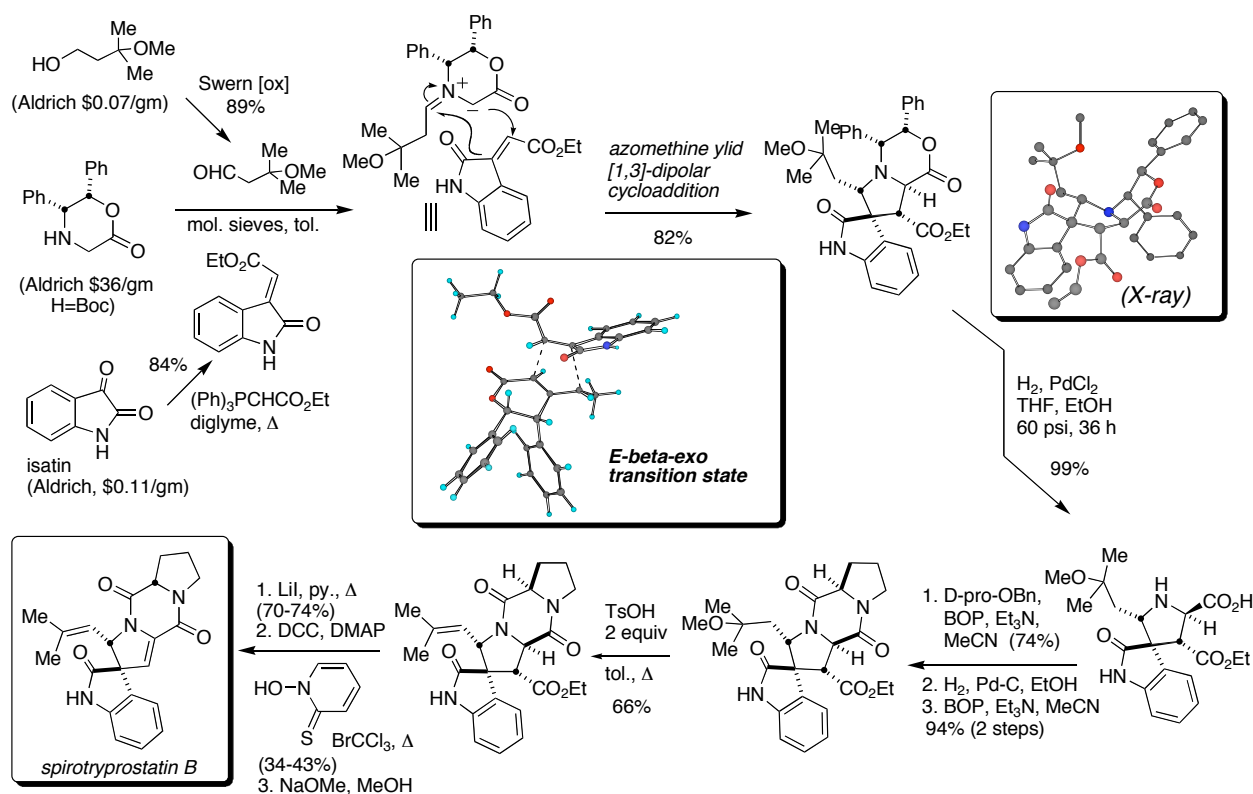
Application of the Williams' Glycinates to Natural Products Synthesis

Ongoing methodology development is directed toward the total synthesis of natural products with structurally challenging functional group arrays such as spirotryprostatin, capreomycin and hapalasin, shown below.



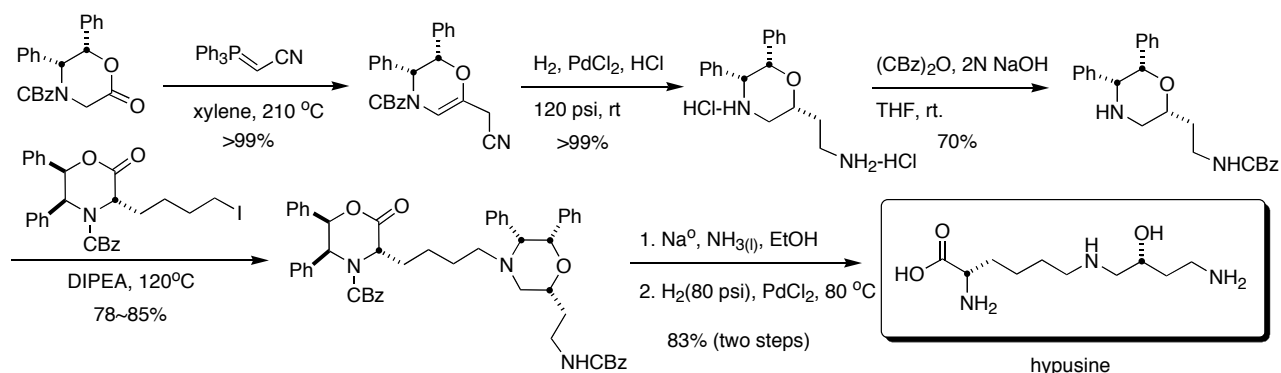
A recently completed asymmetric total synthesis of spirotryprostatin B shown below, illustrates the power and versatility of these simple amino acid templates.

The Asymmetric, Stereocontrolled Total Synthesis of Spirotryprostatin B



Sebahar, P.; Williams, R.M., *J. Am. Chem. Soc.* **2000**, *122*, 5666~5667.

The Asymmetric Stereocontrolled Total Synthesis of Hypusine



Jain, R.P.; Albrecht, B.K.; DeMong, D.E.; Williams, R.M., *Org. Lett.* **2001**, *24*, 4287~4289.