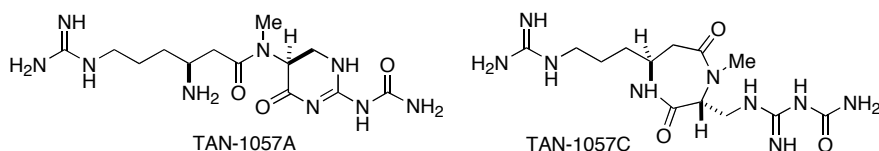


## IV. DEVELOPMENT OF NEW STRATEGIES TO TREAT DRUG-RESISTANT BACTERIA

### (a) TAN-1057A-D

Takeda Pharmaceutical Co., Japan, recently isolated four new compounds identified as TAN-1057 A-D from a *Flexibacter* sp. PK-74 and PK-176. These compounds were found to be dipeptide antibiotics with potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA). The development of drug resistance to many commonly used antibiotics has become an alarmingly acute problem in hospitals and the search for new antibiotics that have good activity against drug-resistant pathogens has become an extremely important endeavor. The search for new biochemical targets in bacteria appears to be the most promising avenue of exploration. We have chosen the TAN-1057 agents due to their unique chemical structure and excellent activity against MRSA *in vivo*.



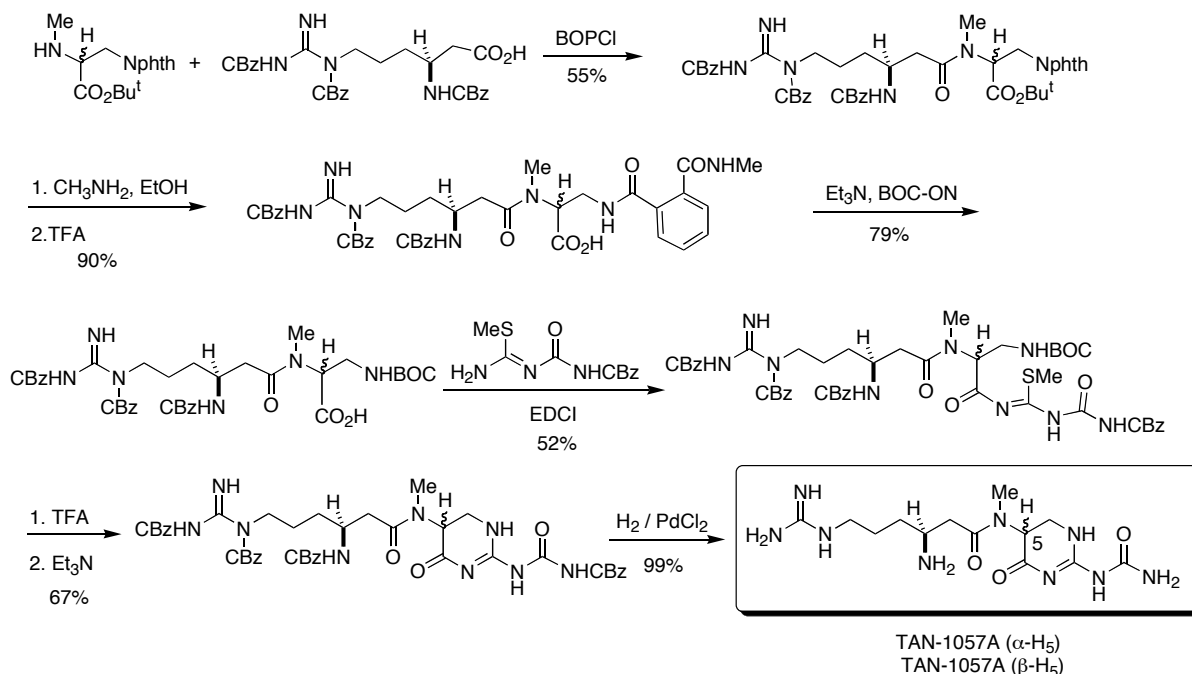
Our objectives are to develop a general method to synthesize the TAN-1057 structural class and several analogs to probe the mechanism of antibacterial activity in this unique class of antibiotics. The mechanism of how these substances inhibit the growth of Gram-(+) microorganisms is currently unknown and is under study.

#### Major accomplishments:

1. The first total synthesis of TAN-1057A,B has been achieved. (see: *J. Am. Chem. Soc.* **1997**, *119*, 11,777~11,784). In addition, the synthesis of the seven-membered ring congeners, TAN-1057C,D has also been completed.
2. The synthesis of biologically active analogs of TAN-1057 (active against MRSA) has been completed and patents have been filed on this technology. (see: *J. Antibiotics*, **1998**, *51*, 189~201).

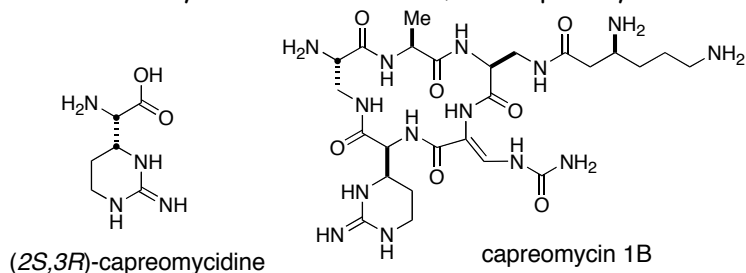
The total synthesis of TAN-1057A,B is shown below. The synthesis developed employed a new synthetic method to make amidinoureas, which is a unique functionality found in the natural antibiotics.

#### The Total Synthesis of TAN-1057A/B



## (b) Capreomycin IB

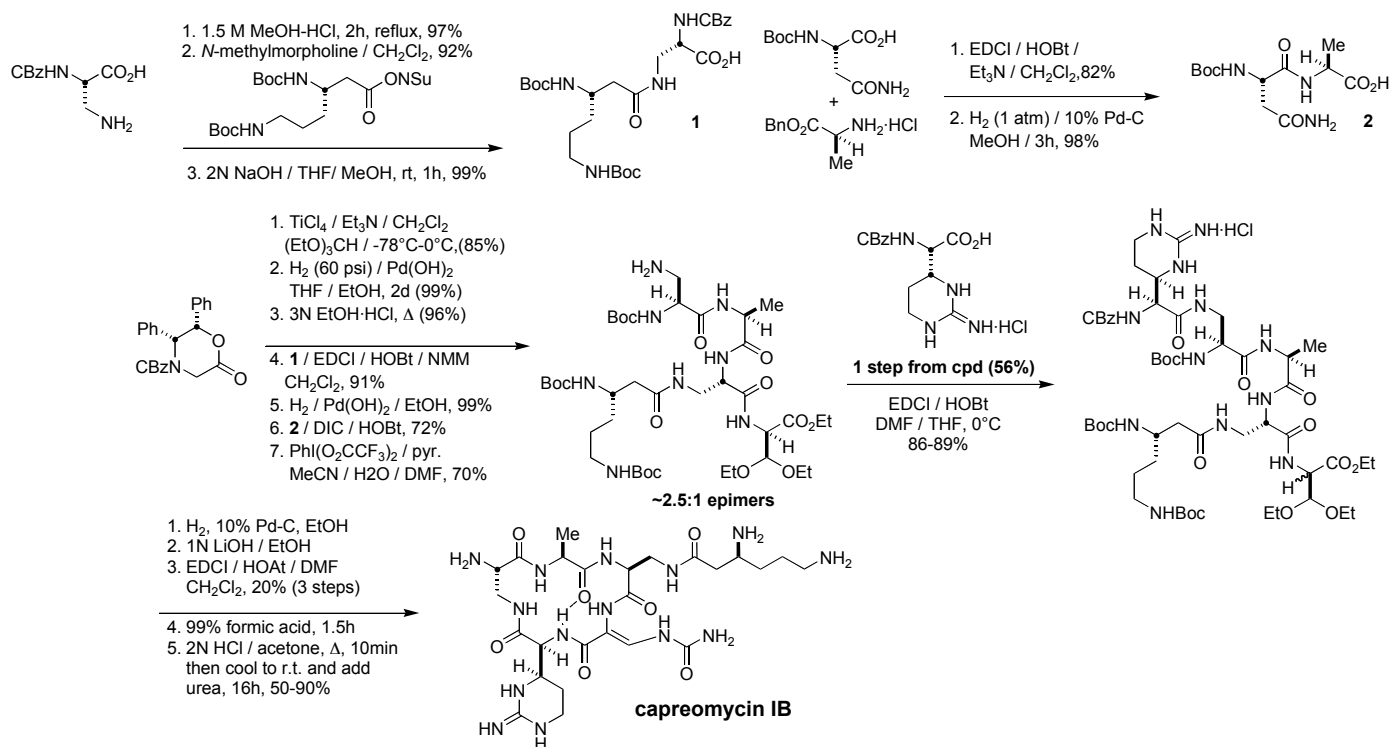
Capreomycin is a non-proteinogenic amino acid that is a constituent of the capreomycins and the tuberactinomycins. These cyclic pentapeptides are known for their unique tuberculostatic properties. First discovered by Herr *et al.* in 1960, the capreomycins have recently attracted attention due to their demonstrated effectiveness against resistant strains of *Mycobacterium tuberculosis*. Our goals are to develop a general synthetic approach to this class of antibacterial agents and to utilize this chemistry to further probe the mechanism of action of these agents and to explore their utility against INH-resistant strains of *Mycobacterium tuberculosis*.



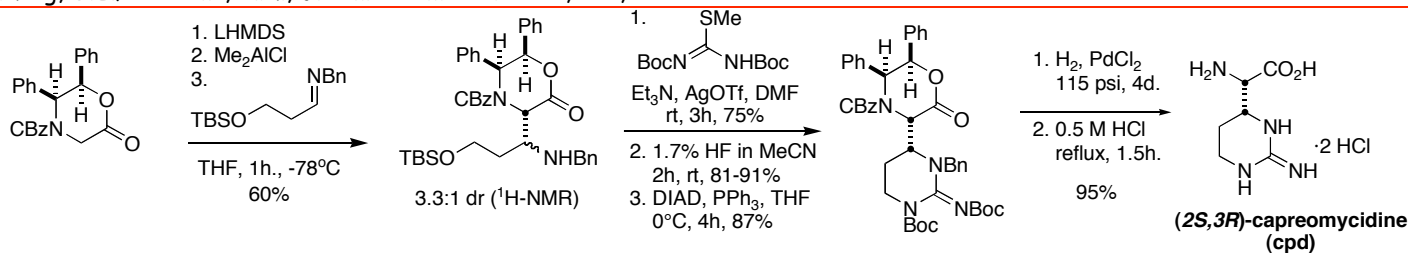
### Major accomplishments:

1. The first asymmetric synthesis of capreomycin has been accomplished and has been utilized to complete a concise asymmetric total synthesis of capreomycin IB. (see: DeMong, D.E.; Williams, R.M., *J. Am. Chem. Soc.* **2003**, *125*, 8561 and DeMong, D.E.; Williams, R.M., *Tetrahedron Lett.* **2001**, *42*, 3529~3532).
2. The first asymmetric synthesis of  $\alpha$ -formylglycine, a precursor to the unsaturated amino acid constituent in the capreomycins, has been accomplished. (see: DeMong, D.E.; Williams, R.M., *Tetrahedron Lett.* **2002**, *43*, 2355~2357).

### The Asymmetric Synthesis of Capreomycin IB



DeMong, D.E.; Williams, R.M., *J. Am. Chem. Soc.* **2003**, *125*, 8561



DeMong, D.E.; Williams, R.M., *Tetrahedron Lett.* **2001**, *42*, 3529-3532.