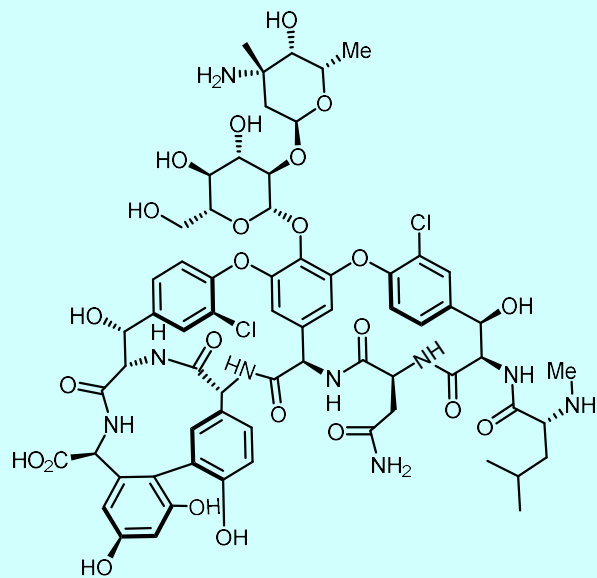




Vancomycin

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References:

Chem. Rev., **2017**, 117, 11952

Sussmuth, R. D. in *Medicinal Chemistry of Bioactive Natural Products*, pp 35-72



1-1. Background

- isolated in 1952 by Dr. E. C. Kornfield at Eli Lilly
- isolated from a soil sample containing *Amycolatopsis orientalis*, which produced a substance active against most gram-positive organisms
- approved for clinical use in 1958 but its structure wasn't fully established until 1982
- today's use:
 - antibiotic of last resort, especially against methicillin-resistance *Staphylococcus aureus* (MRSA) strains
 - for those with penicillin allergies

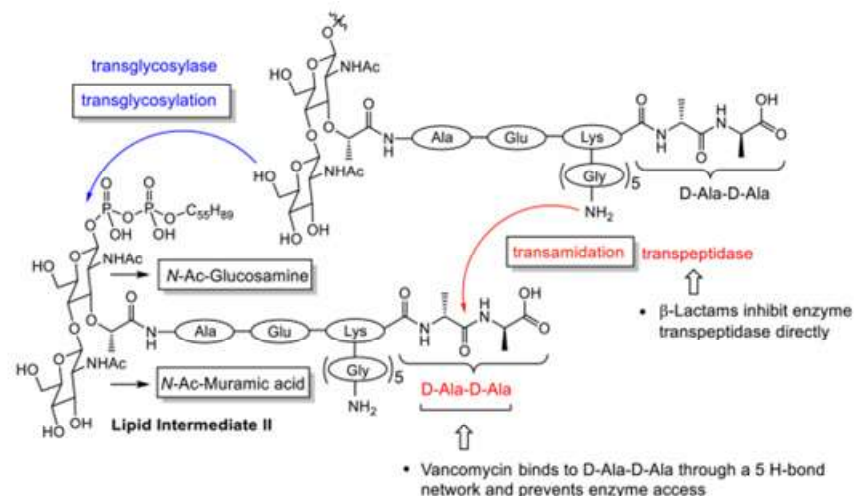


Fig. 1 Vancomycin's mechanism of action. (figure copied from *Chem. Rev.*, 2017, 117, 11954)

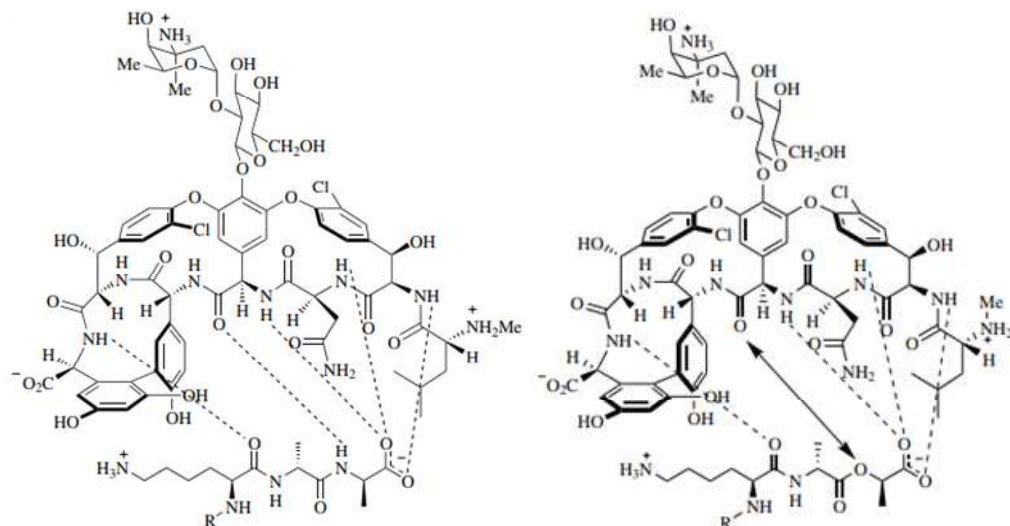
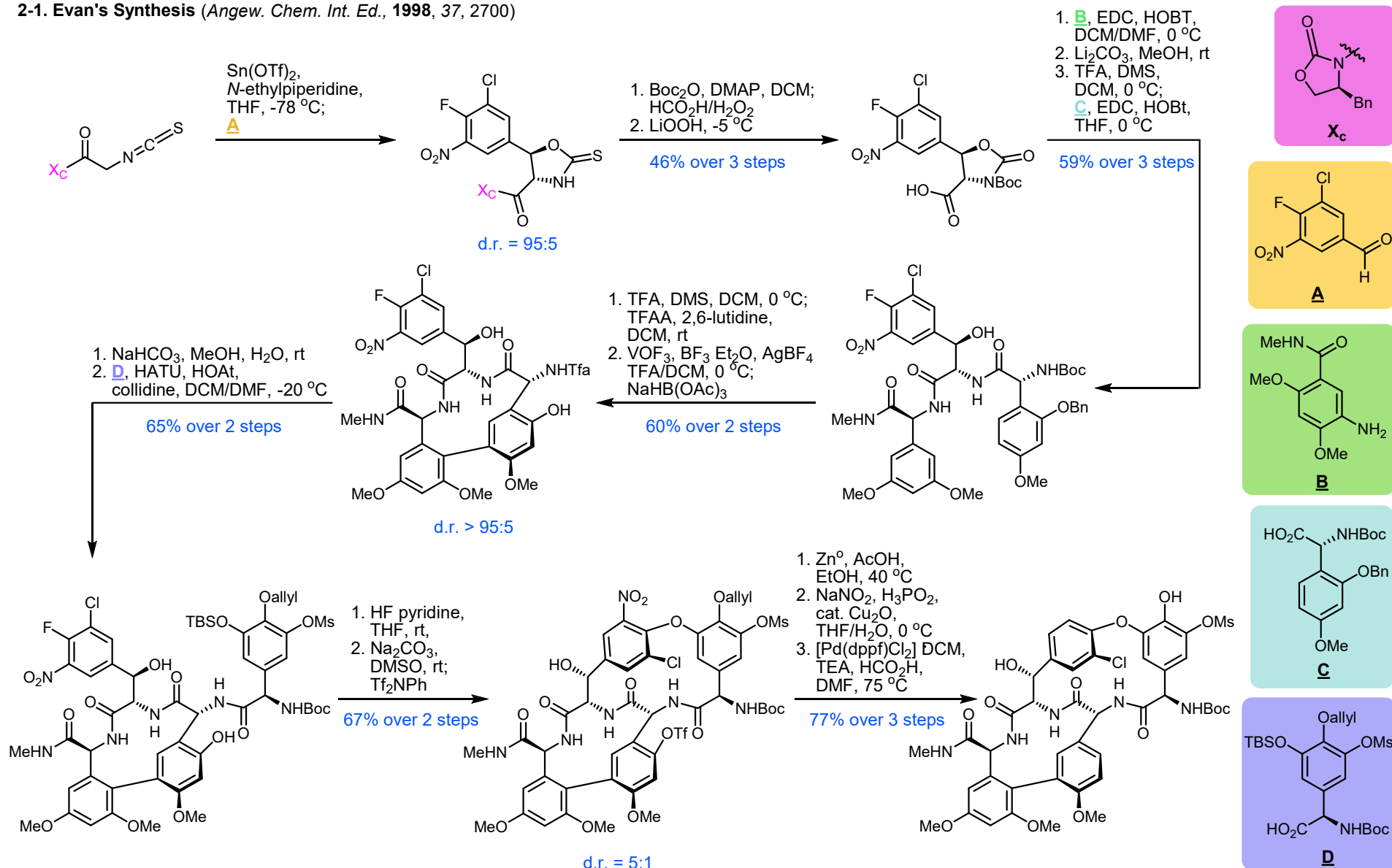
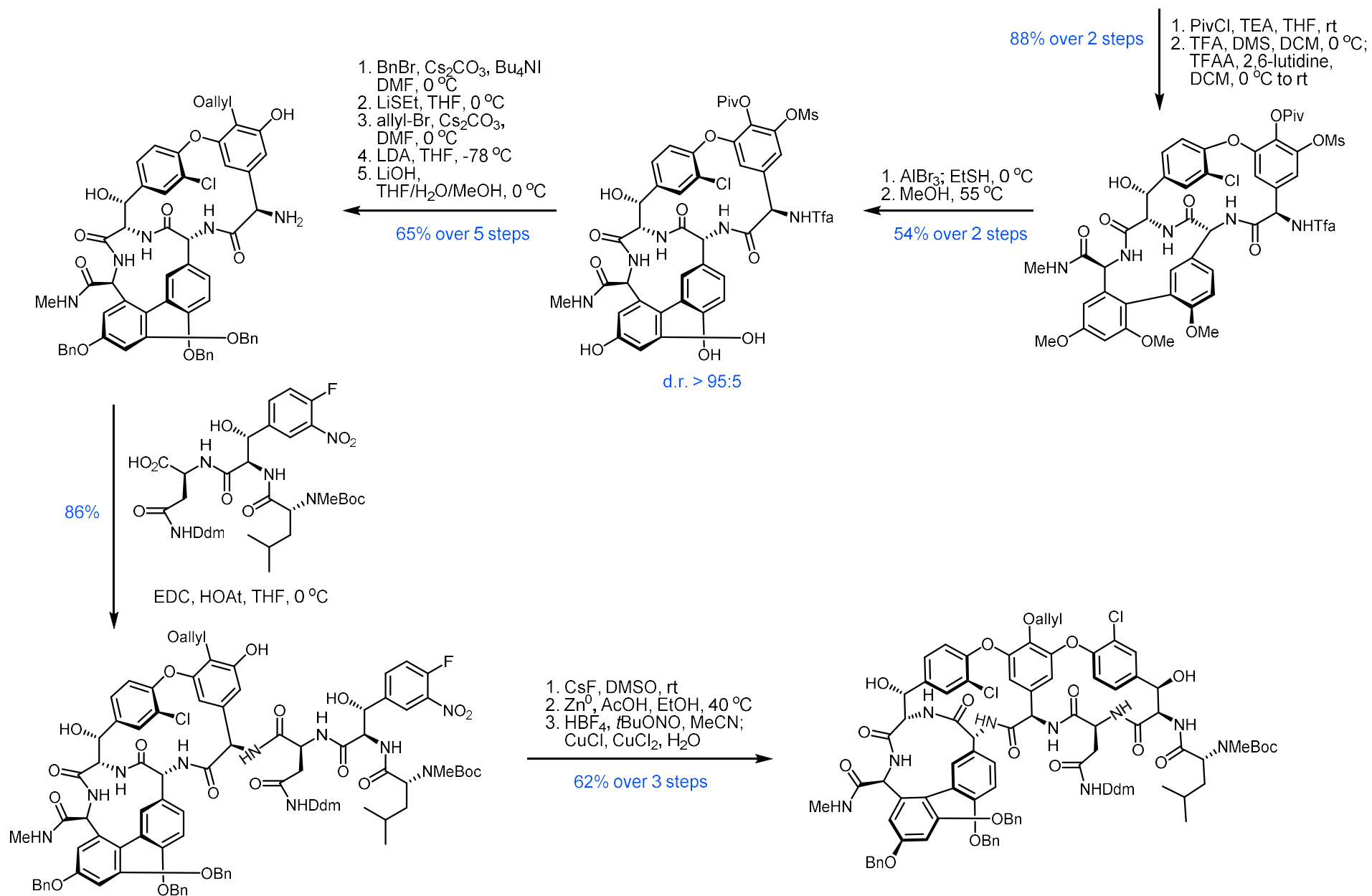


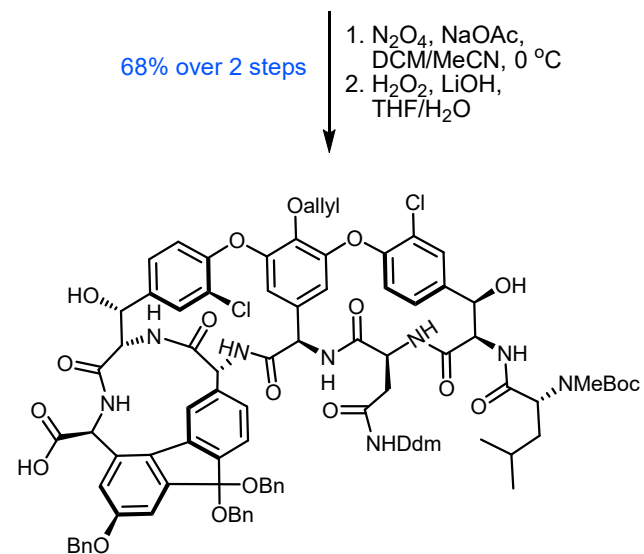
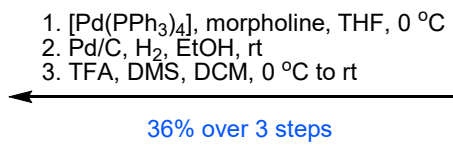
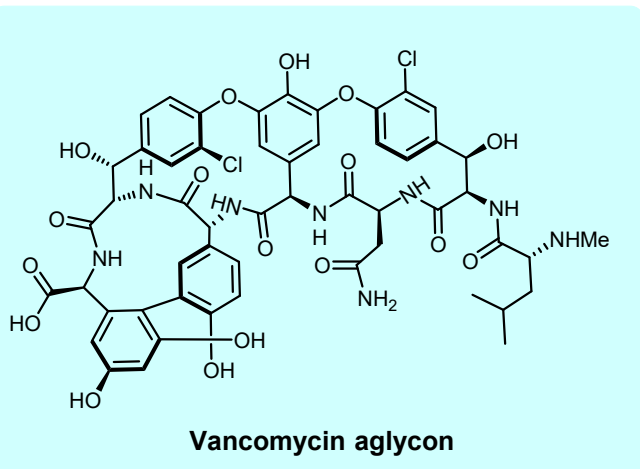
Fig. 2 Molecular basis for resistance to vancomycin.
(figures copied from *Medicinal Chemistry of Bioactive Natural Products*, 2006, 35)

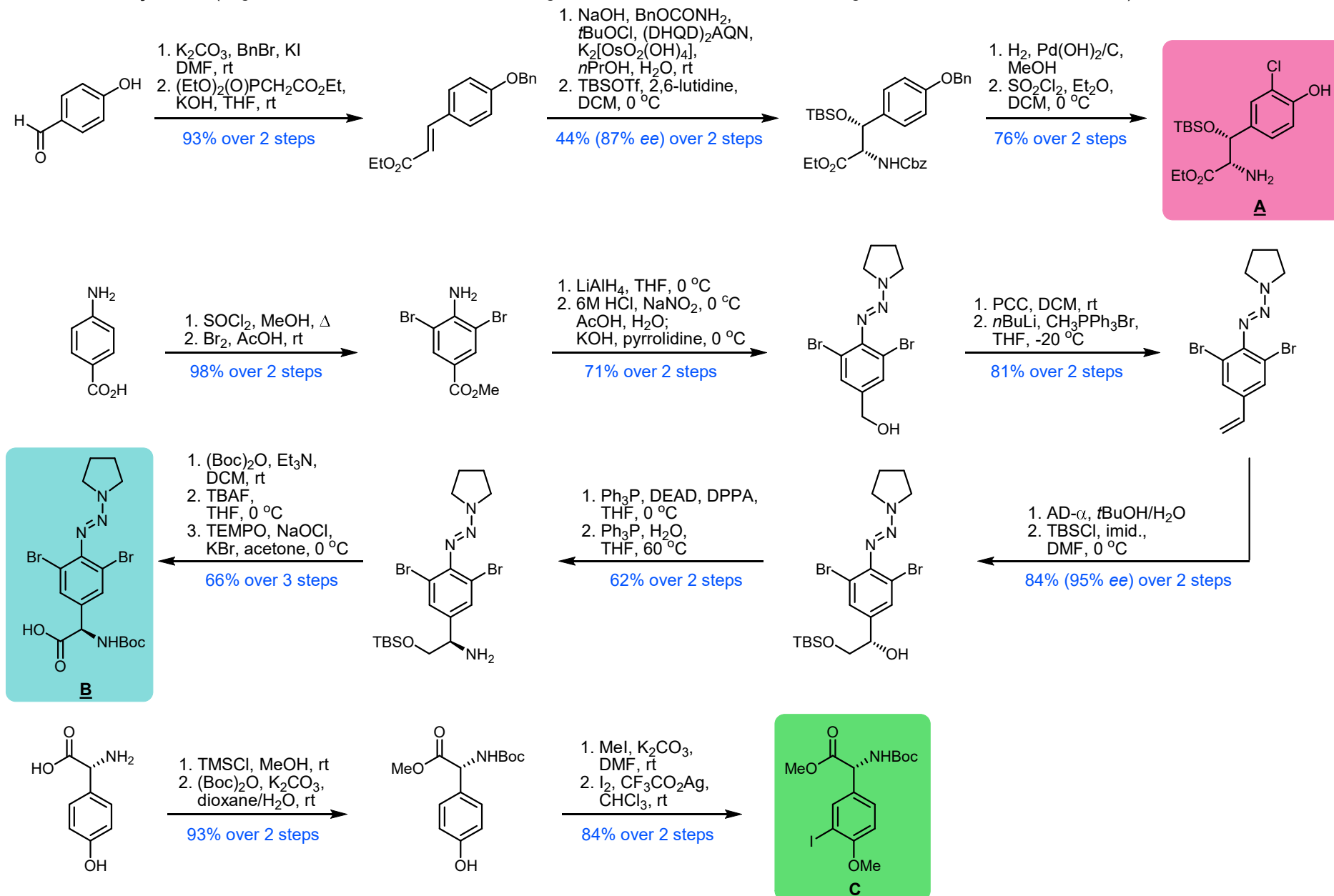
1-2. Mechanism of Action and Resistance

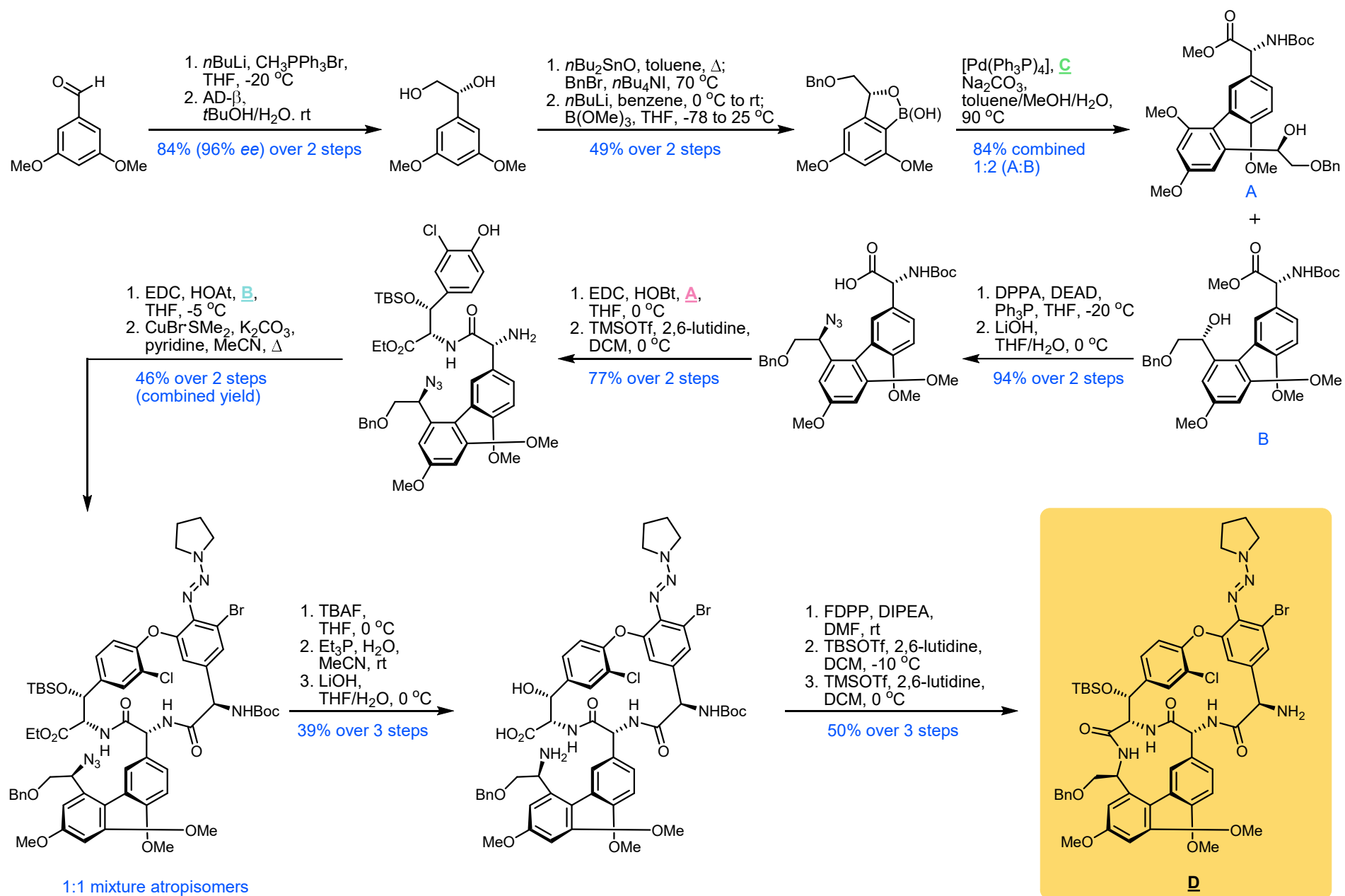
- peptidoglycan layer gives mechanical stability to the cell wall of the bacteria
 - an important intermediate of this layer is muramyl-pentapeptide
 - vancomycin binds to D-Ala-D-Ala thereby preventing transamidation and transglycosylation reactions
- Vancomycin resistant enterococci and *S. aureus* strains have emerged
 - molecular basis: peptidoglycan intermediates are altered
 - D-alanyl-D-lactate (VanA, VanB, VanD)
 - as seen on the left, the ester linkage causes the loss of a hydrogen bond, resulting in ~1000-fold decrease in binding affinity
 - D-alanyl-D-serine (VanC, VanE, VanG)

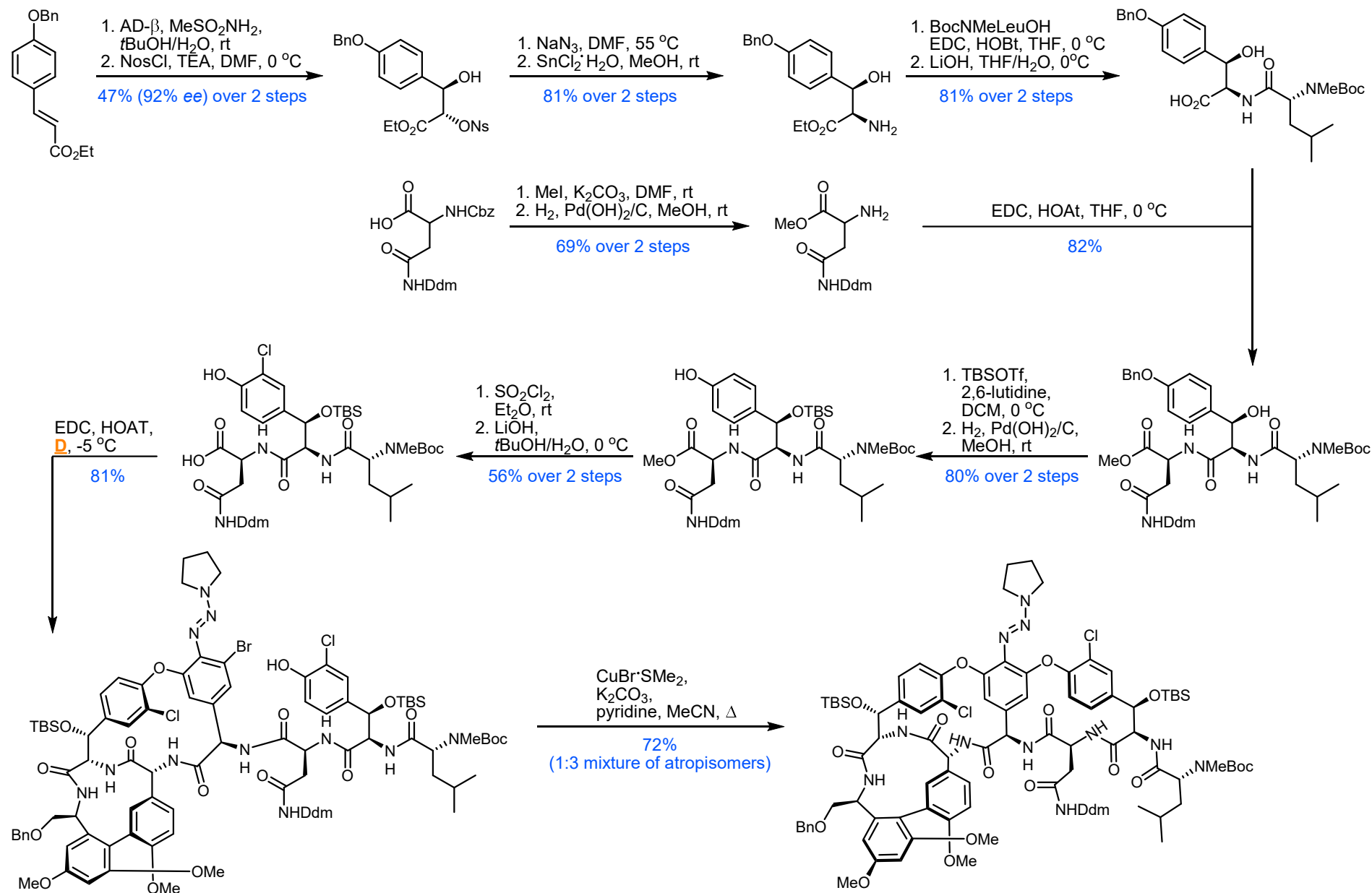
2-1. Evan's Synthesis (*Angew. Chem. Int. Ed.*, 1998, 37, 2700)

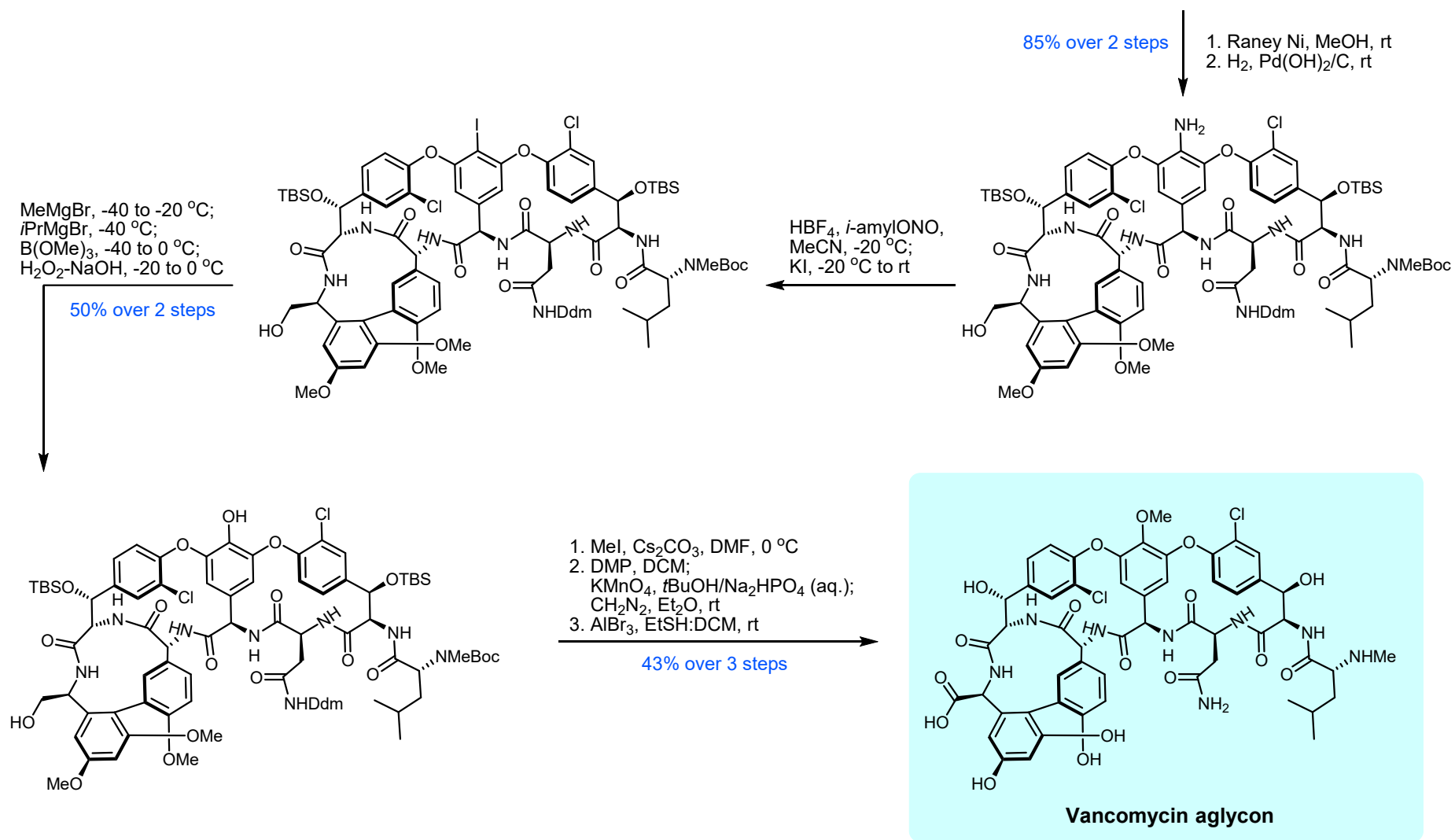




2-2. Nicolaou's Synthesis (*Angew. Chem. Int. Ed.*, **1998**, 37, 2708; *Angew. Chem. Int. Ed.*, **1998**, 37, 2714; *Angew. Chem. Int. Ed.*, **1998**, 37, 2717)







2-3. Boger's Synthesis (*J. Am. Chem. Soc.*, **1999**, 121, 10004; *J. Org. Chem.*, **1997**, 62, 4721)