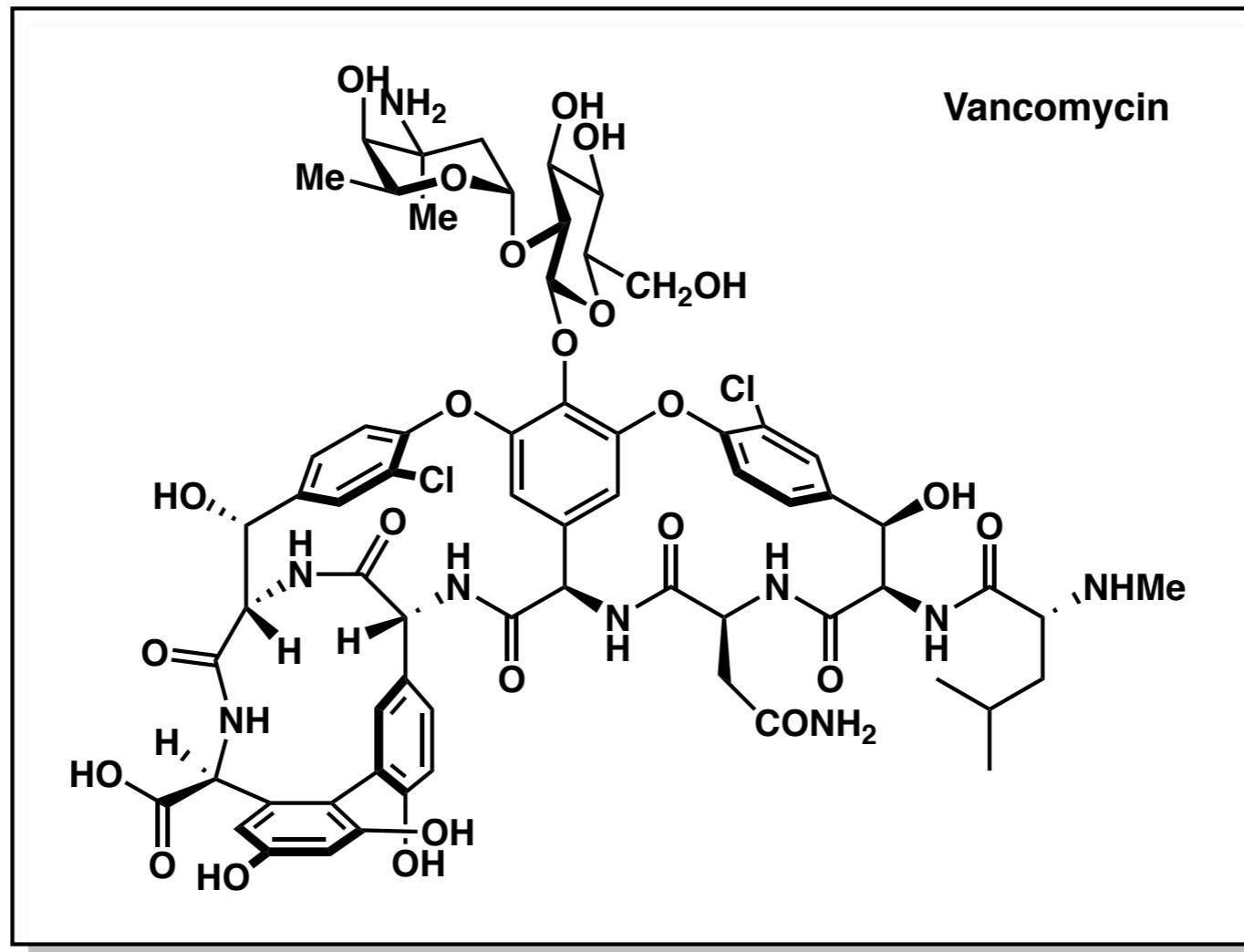


Total Synthesis of Vancomycin in the late 1990s

Ximing Li



Recent important publications:

- Chem. Rev.* **2017**, 117, 11952–11993; *J. Med. Chem.* **2019**, 62, 3184–3205; *J. Org. Chem.* **2017**, 82, 11961–11980;
ACS Infect. Dis. **2018**, 4, 1468–1474; *Chem. Eur. J.* **2017**, 23, 79–83; *Front. Microbiol.* **2018**, 9:1175;
Chem. Med. Chem. **2018**, 13, 1644–1657; *J. Med. Chem.* **2015**, 58, 2367–2377; *Org. Biomol. Chem.* **2015**, 13, 7477–7486;
Proc. Natl. Acad. Sci. **2017**, 114, 5052–5061; *Bioorg. Med. Chem. Lett.* **2016**, 26, 1025–1028;
Angew. Chem. Int. Ed. **2015**, 54, 13644–13649; *Angew. Chem. Int. Ed.* **2016**, 55, 7836–7840;
Bioorg. Med. Chem. Lett. **2015**, 25, 5477–5480

Total Synthesis of Vancomycin in the late 1990s

■ Isolated & disclosed: Eli Lilly, 1950; 1956

Approved for clinical use: 1958

Full structure assignment: 1982 (+25 years!)

■ A member of glycopeptide antibiotics, which...

- a) are among leading members of the clinically important natural products discovered through the isolation of bacterial metabolites;
- b) possess a broad spectrum of antibacterial activity against Gram-positive pathogens with manageable side effects;
- c) are recommended for use with patients allergic to β -lactam antibiotics and those undergoing cancer chemotherapy/dialysis therapy.

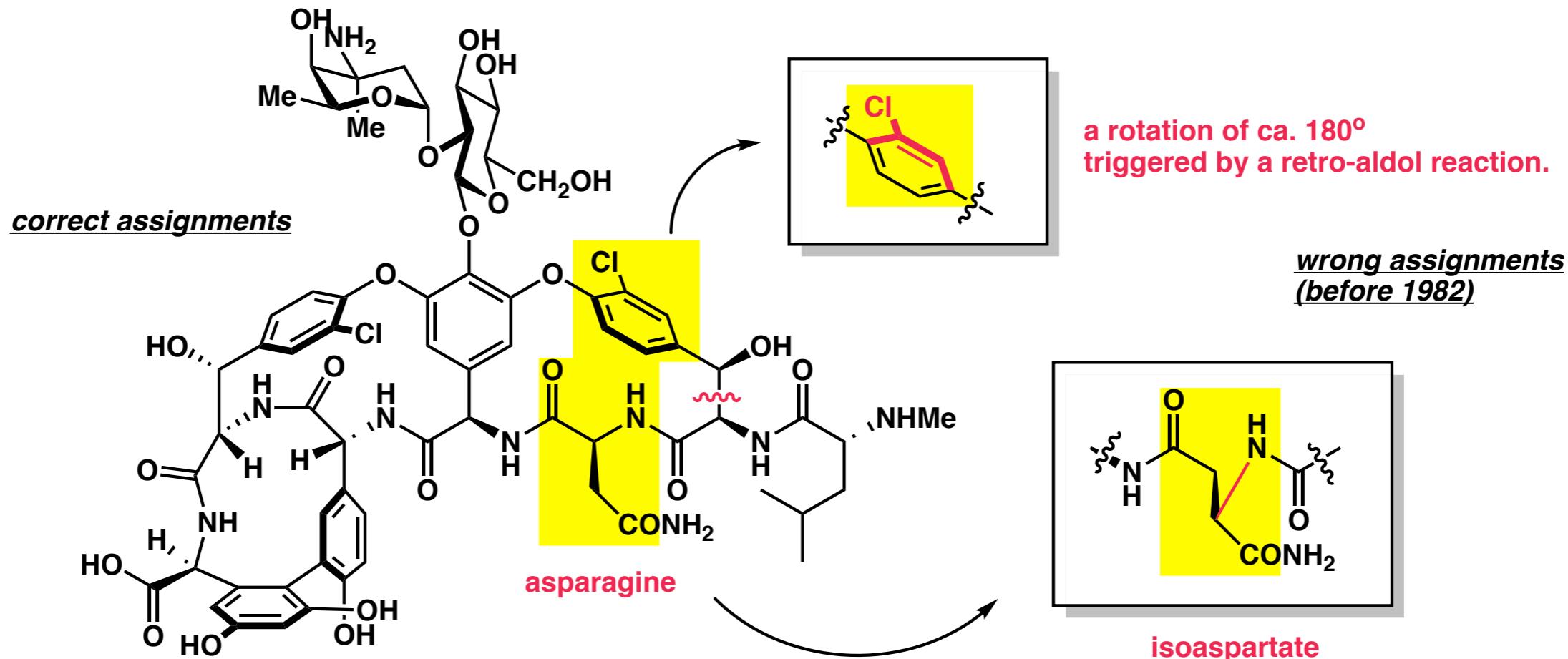
■ Structure corrections from...

...an unrecognized atropisomer isomerization:

Williamson & Williams, *J. Am. Chem. Soc.* **1981**, 103, 6580–6585

...an aspartagine to isoaspartate rearrangement

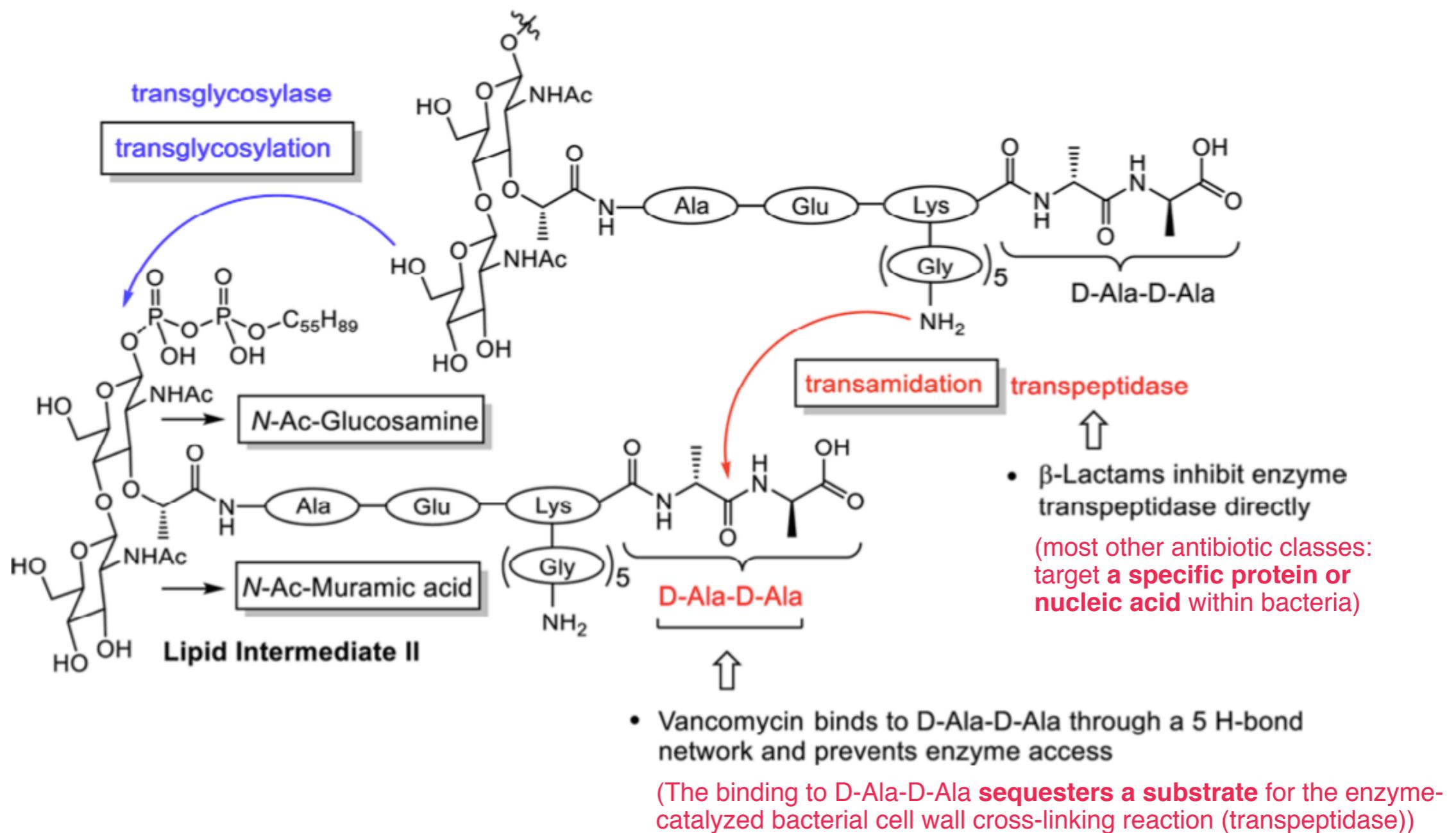
Harris & Harris, *J. Am. Chem. Soc.* **1982**, 104, 4293–4295



Total Synthesis of Vancomycin in the late 1990s

■ Mechanism:

Uniquely, the glycopeptides antibiotics directly bind the peptidoglycan precursors necessary for construction of the cell wall, thus make it difficult for bacteria to make single genetic alterations that result in resistant conferring changes.

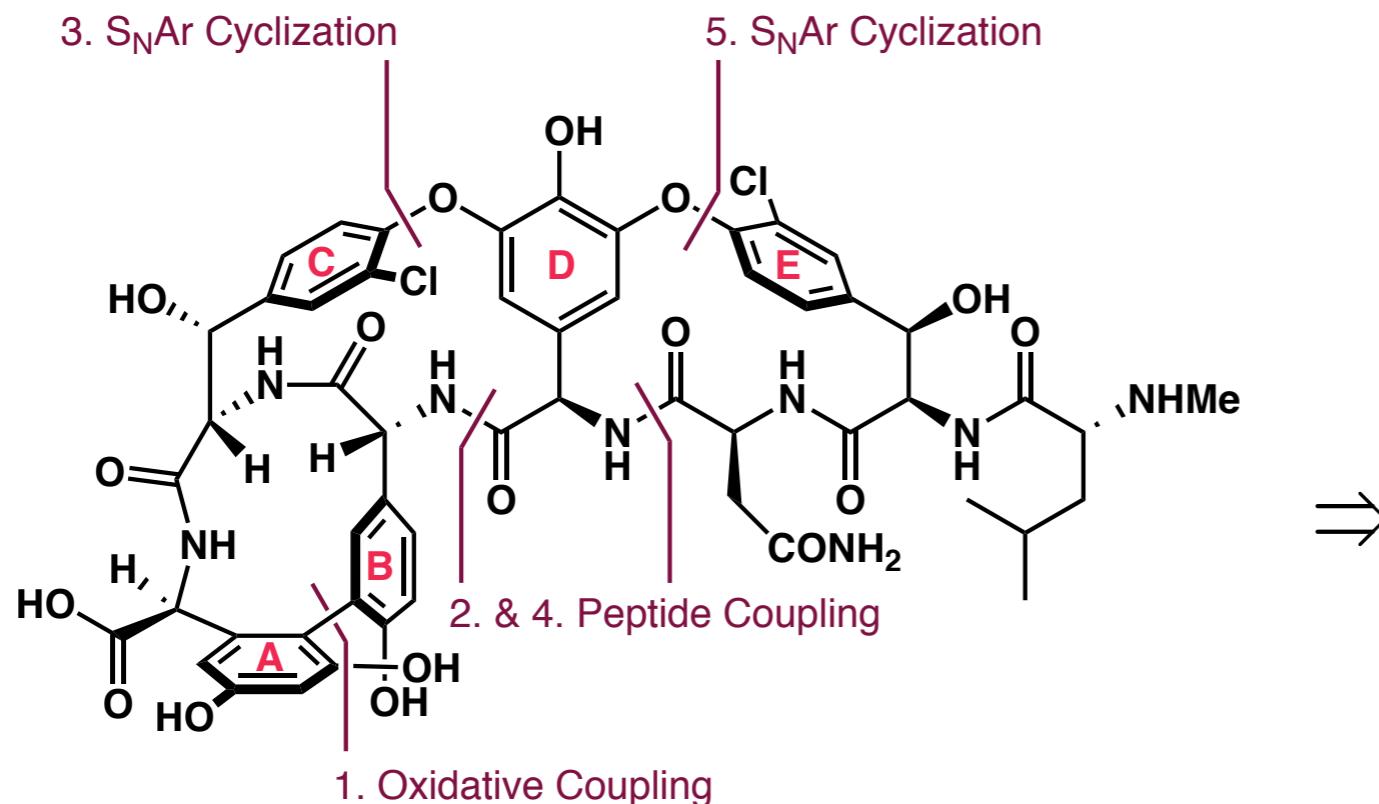


Total Synthesis of Vancomycin in the late 1990s

- 3 reported total synthesis of Vancomycin in 1998-1999: David A. Evans, K. C. Nicolaou, Dale L. Boger.
- Major difficulty: 3 centers of axial or planar (atropisomer) chirality in Vancomycin

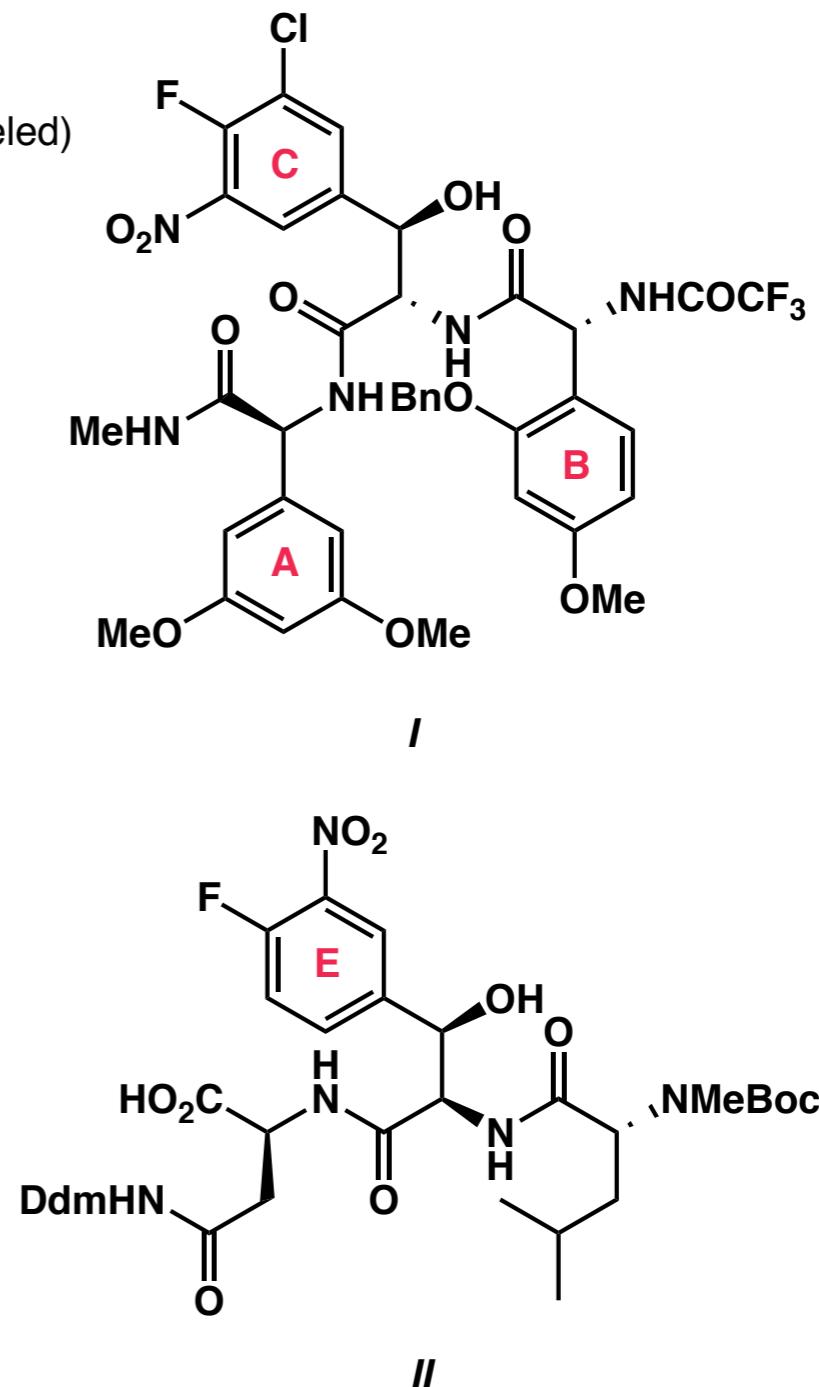
- Evans - retrosynthesis:

(based largely on their previous work with orienticin C: 2 chiral center canceled)



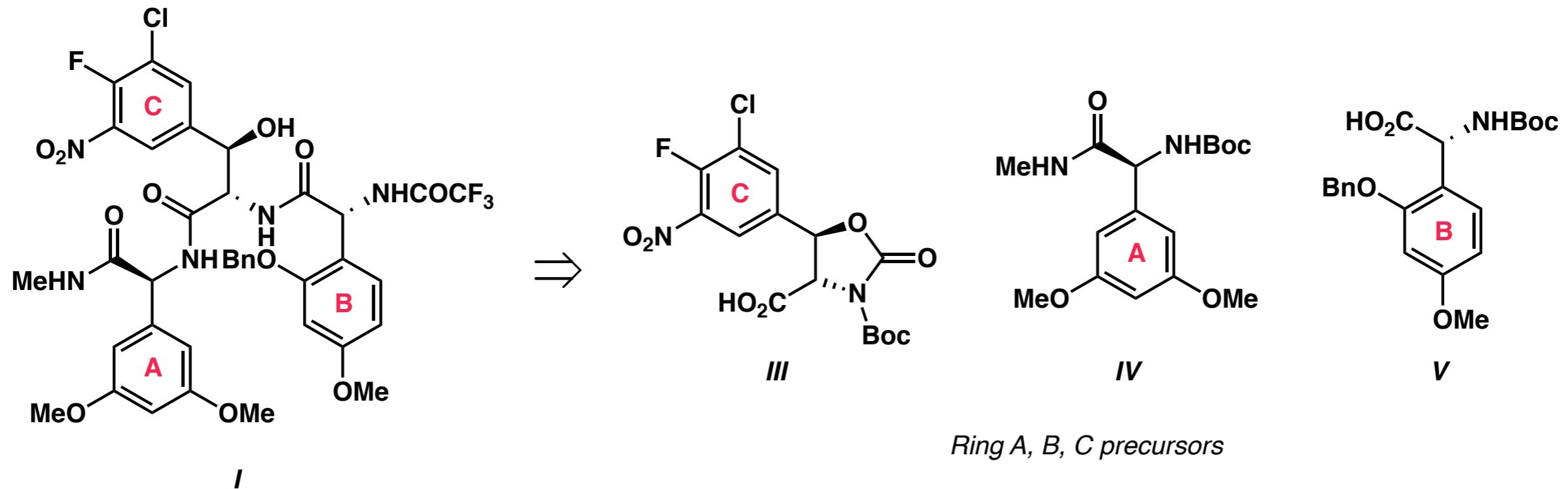
The ABCD acyclic tetrapeptide was prepared before sequentially closing the macrocycles in the reverse order, forming the CD ring macrocycle prior to formation of the AB ring system.

The AB, CD, and DE ring systems are sequentially introduced and relied on empirically defined substrate control of the kinetic atropodiastereoselectivity of the three key macrocyclization reactions.

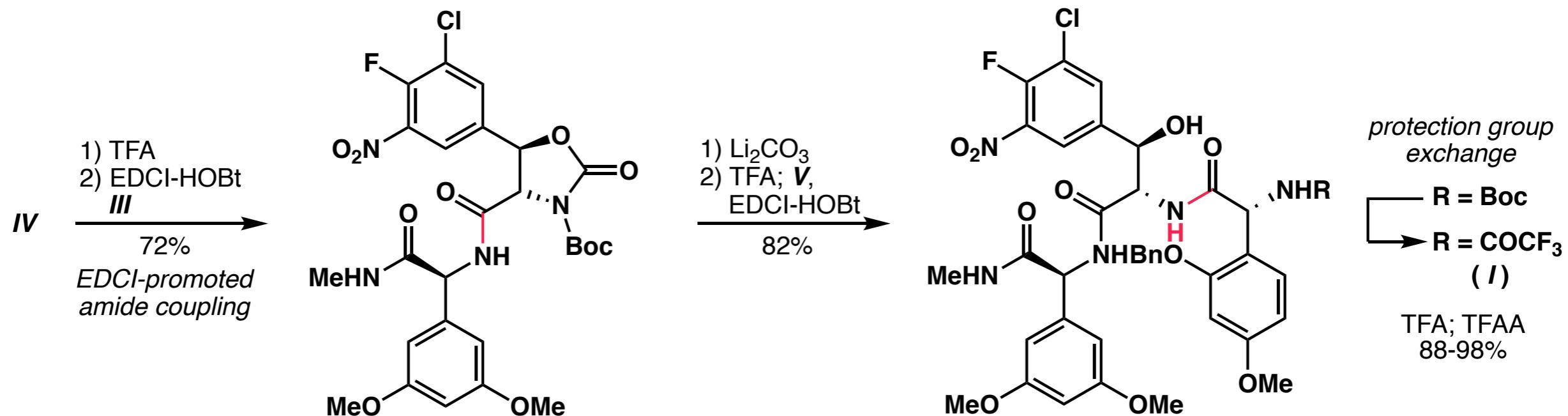


Total Synthesis of Vancomycin in the late 1990s

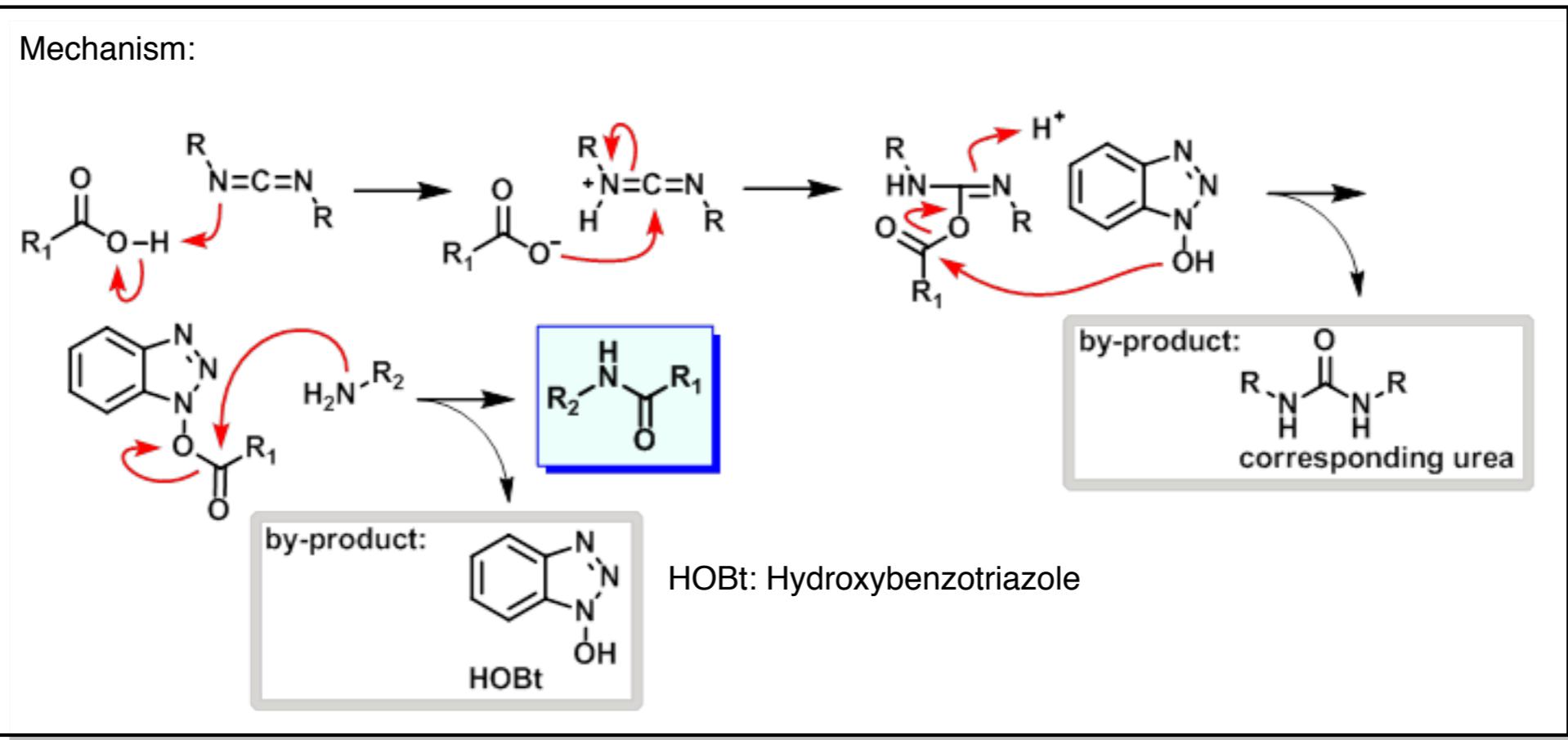
■ Evans - retrosynthesis:



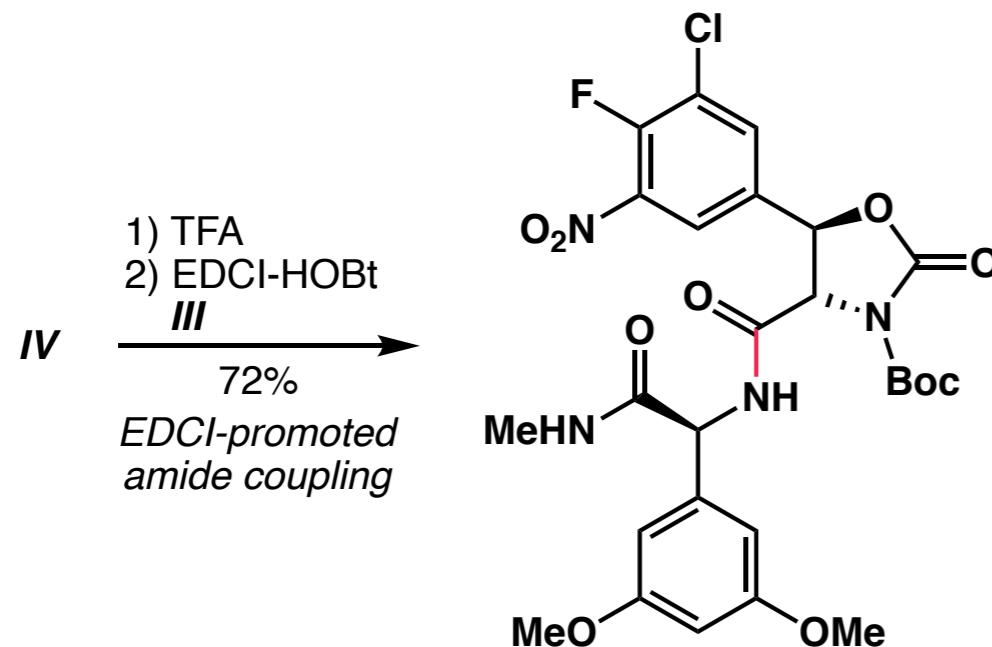
■ Evans synthesis



Total Synthesis of Vancomycin in the late 1990s

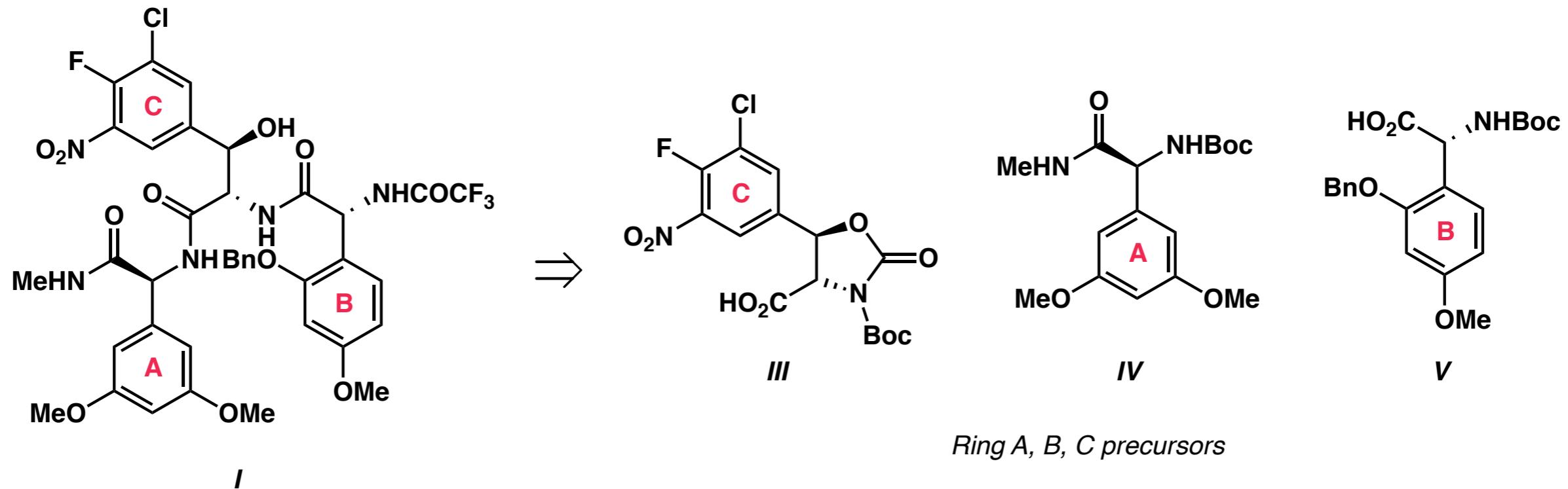


■ Evans synthesis

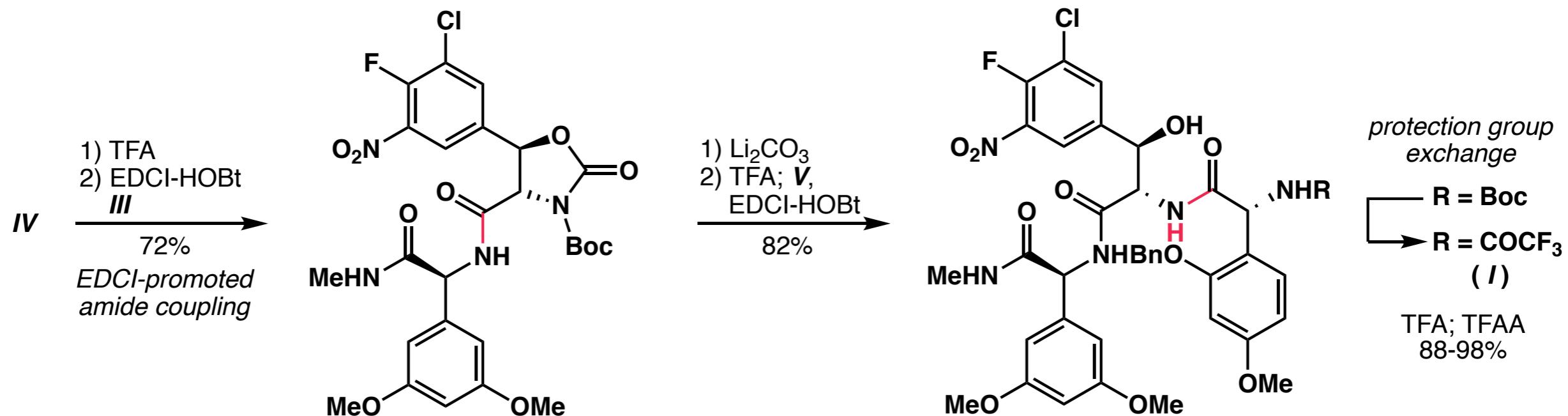


Total Synthesis of Vancomycin in the late 1990s

■ Evans - retrosynthesis:

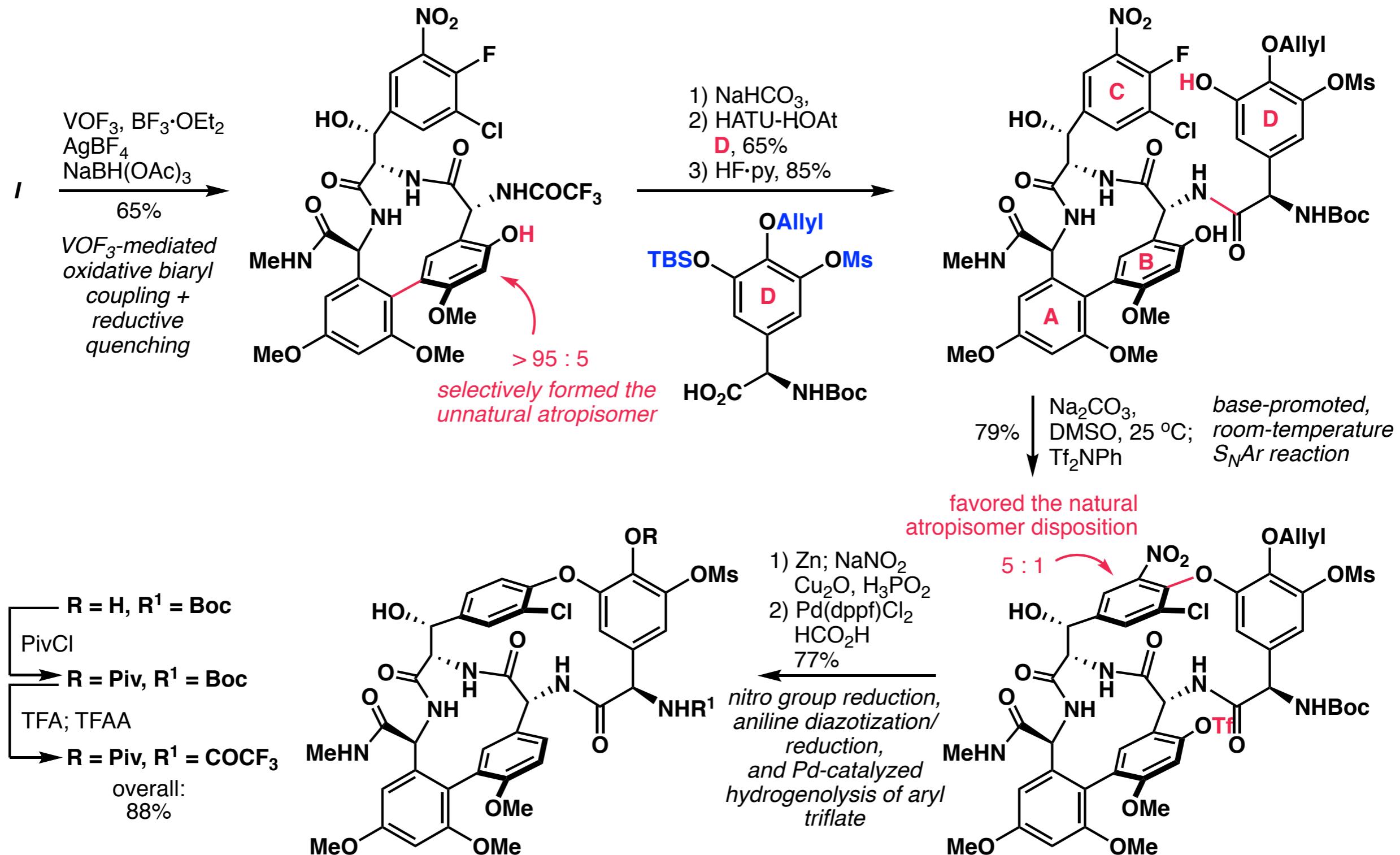


■ Evans synthesis



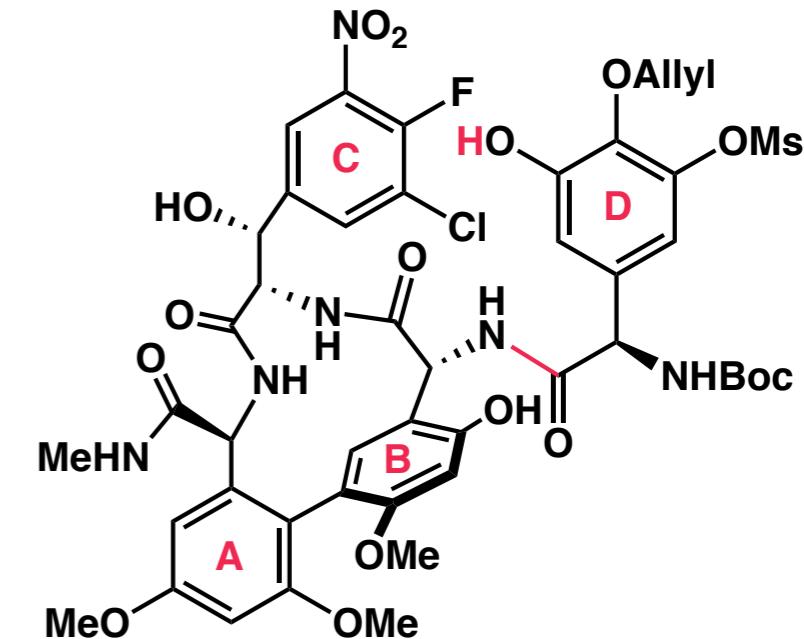
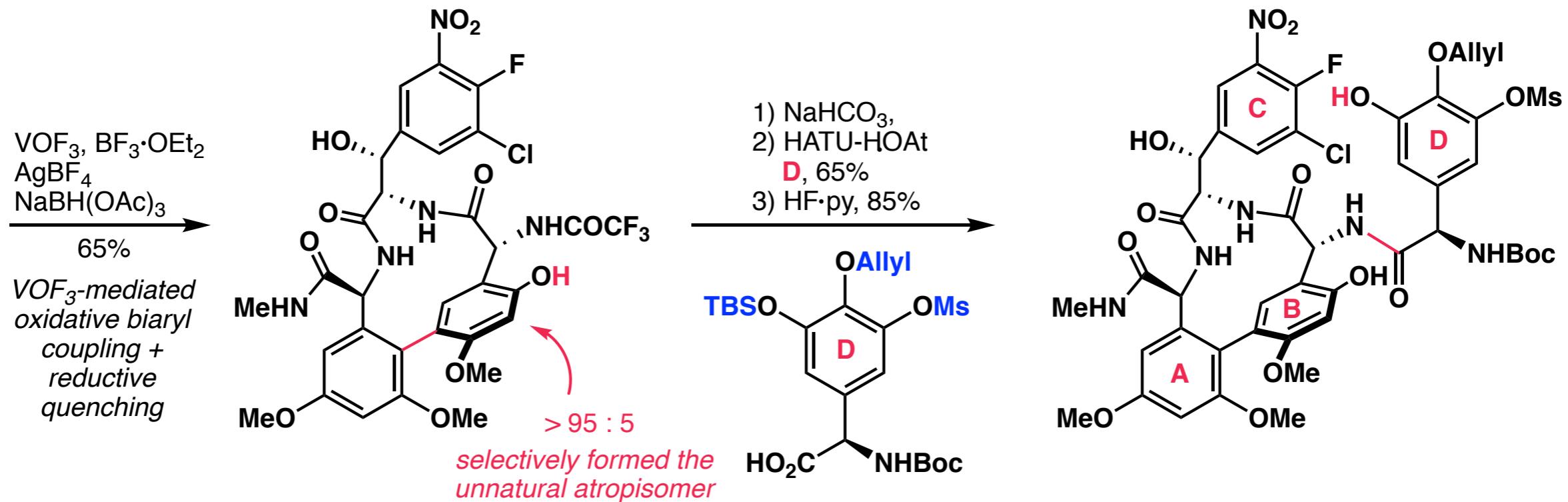
Total Synthesis of Vancomycin in the late 1990s

■ Evans synthesis

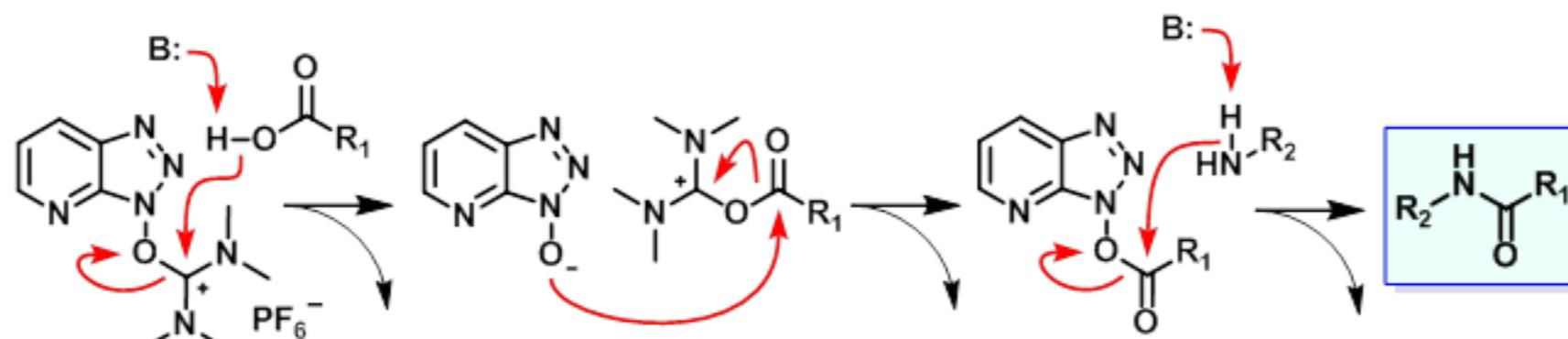


Total Synthesis of Vancomycin in the late 1990s

■ Evans synthesis



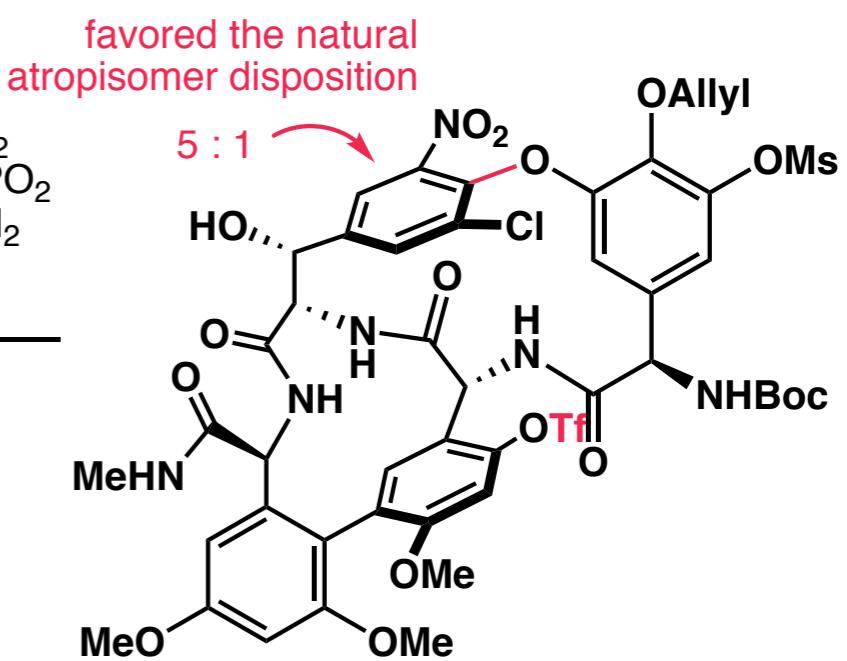
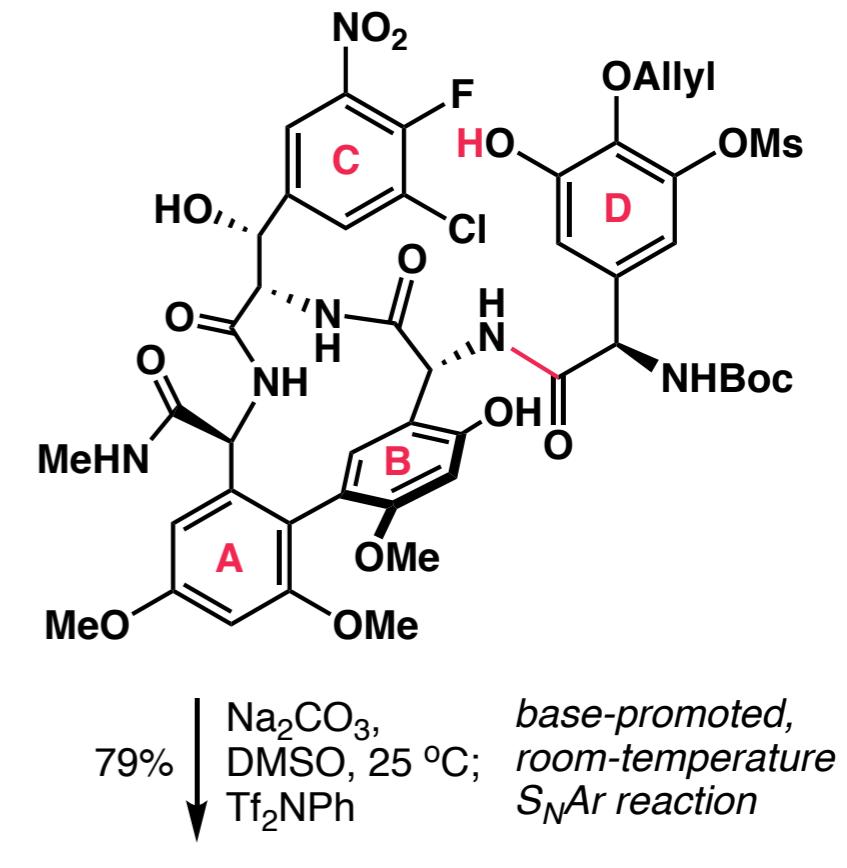
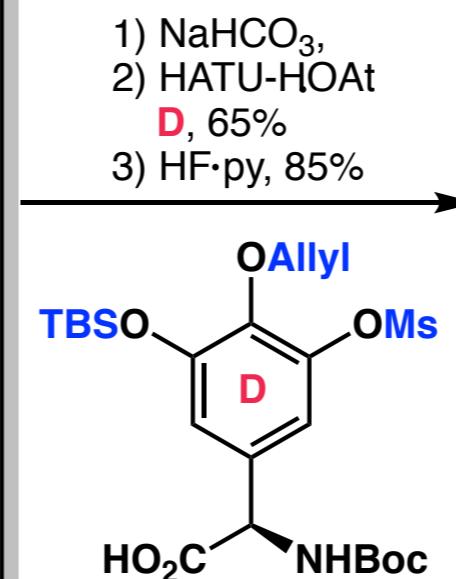
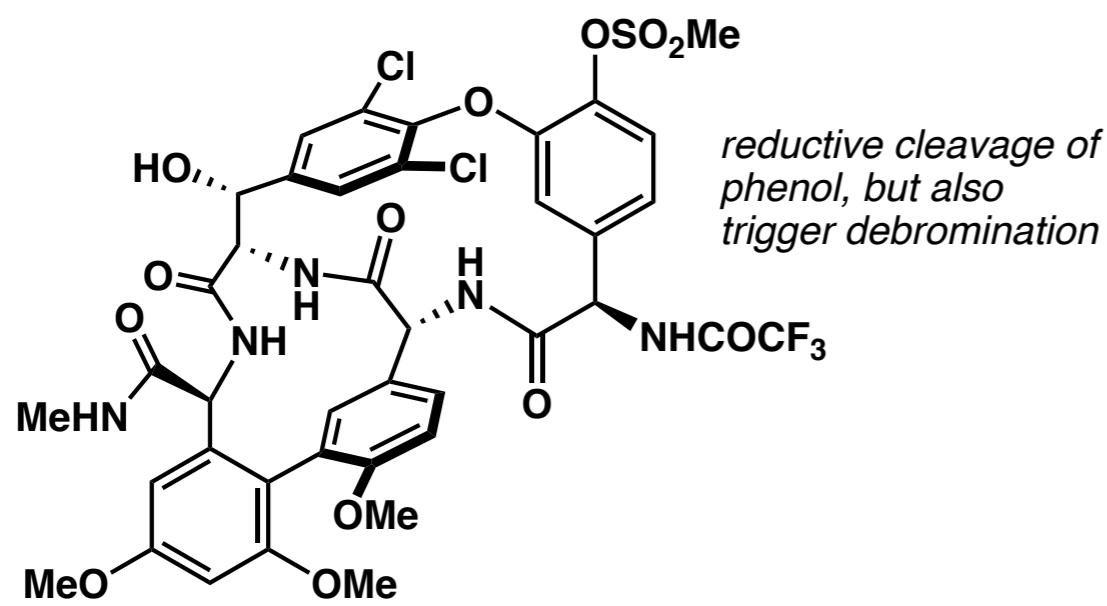
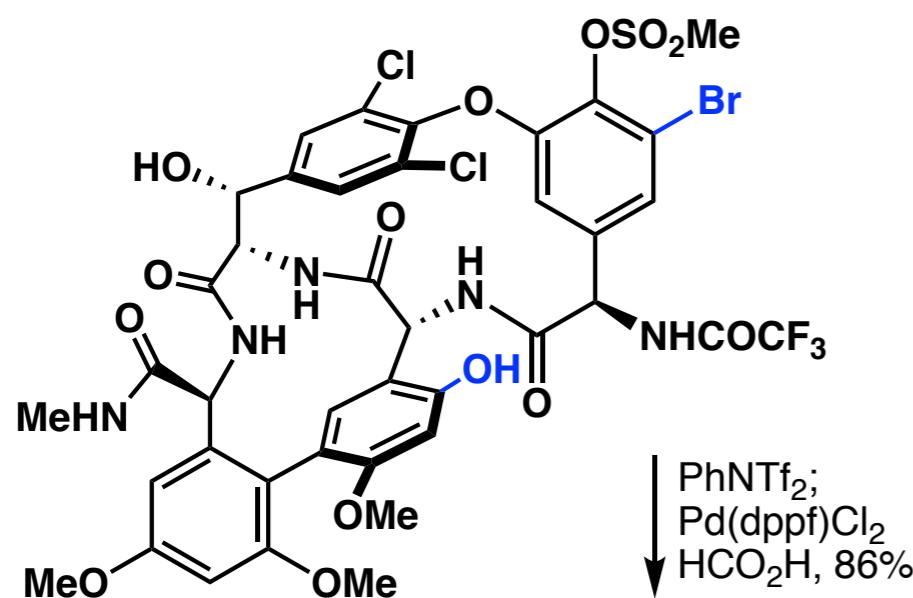
Mechanism:



Total Synthesis of Vancomycin in the late 1990s

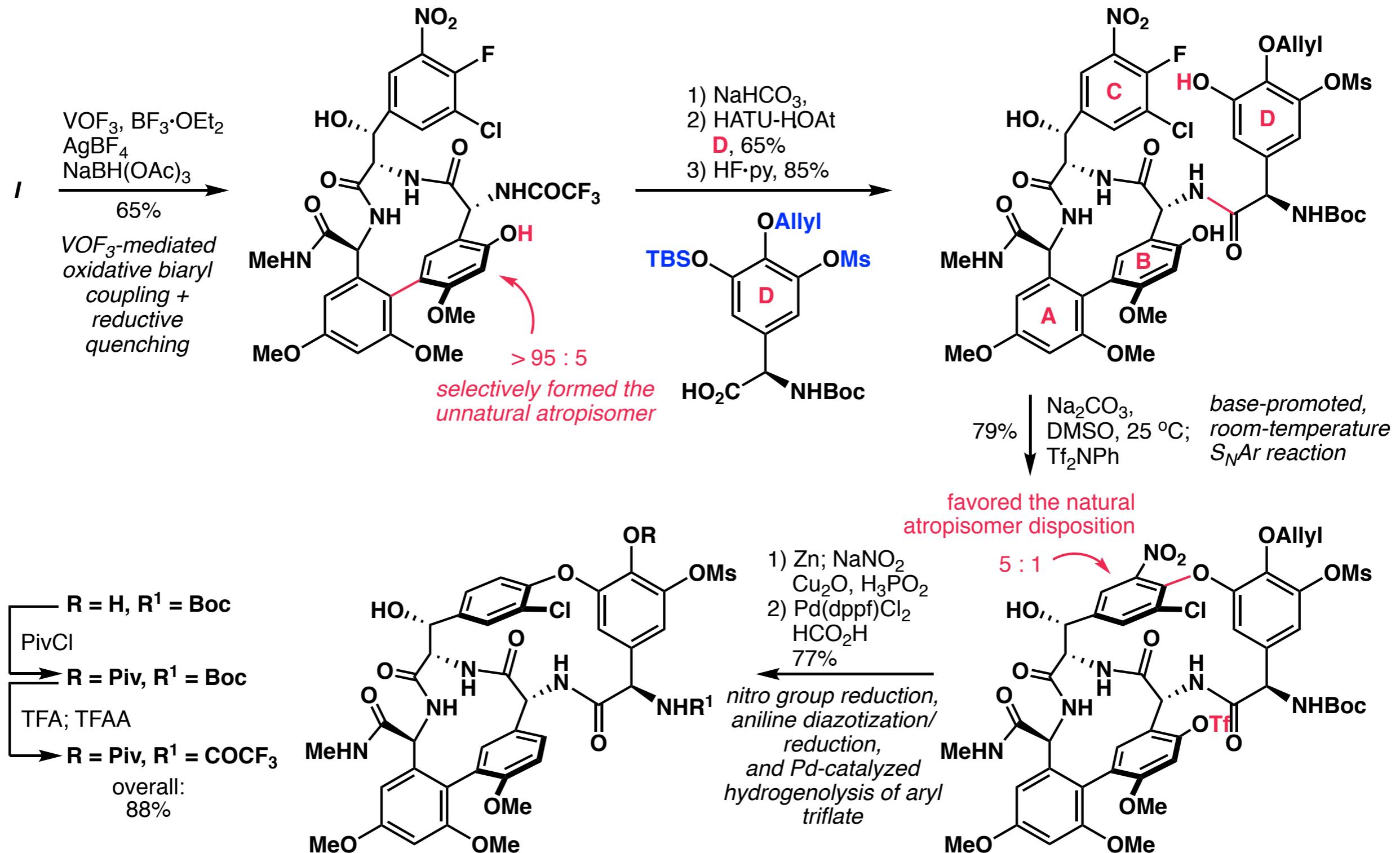
■ Evans synthesis

The triphenolic D ring was orthogonally protected as the *O*-allyl, *O*-TBS, and *O*-Ms derivatives, avoiding problematic debromination experienced in the total synthesis of orienticin C:



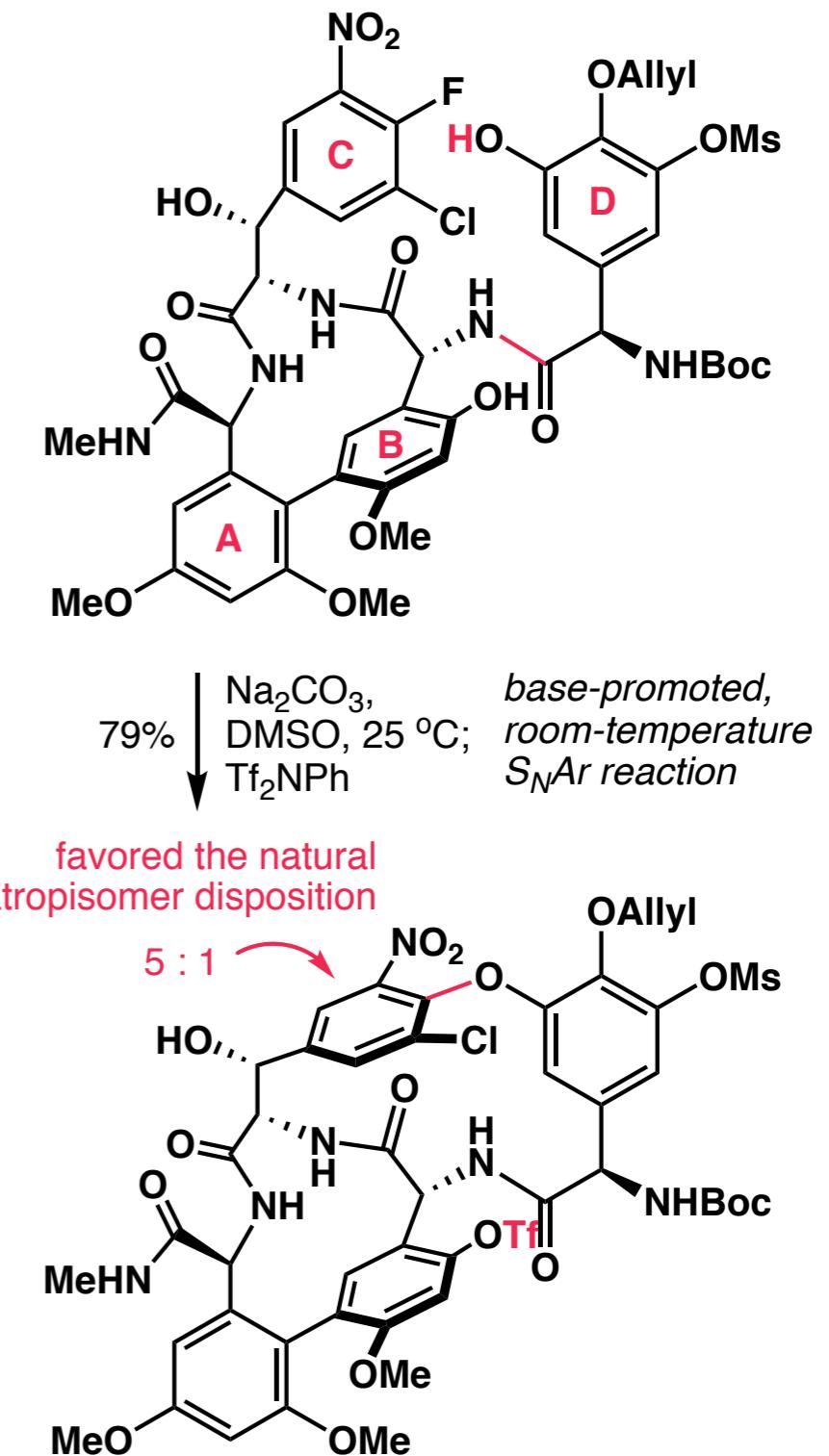
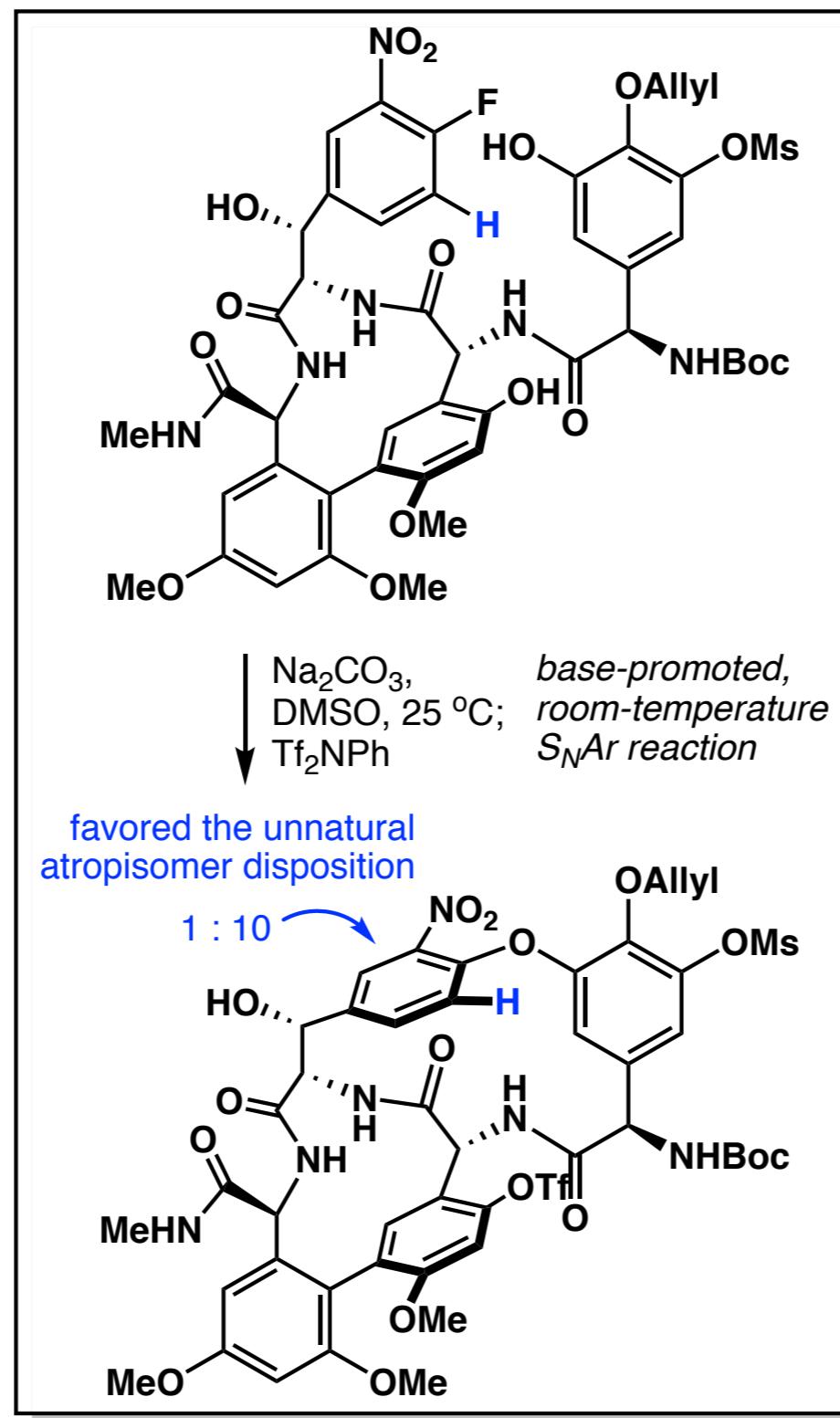
Total Synthesis of Vancomycin in the late 1990s

■ Evans synthesis



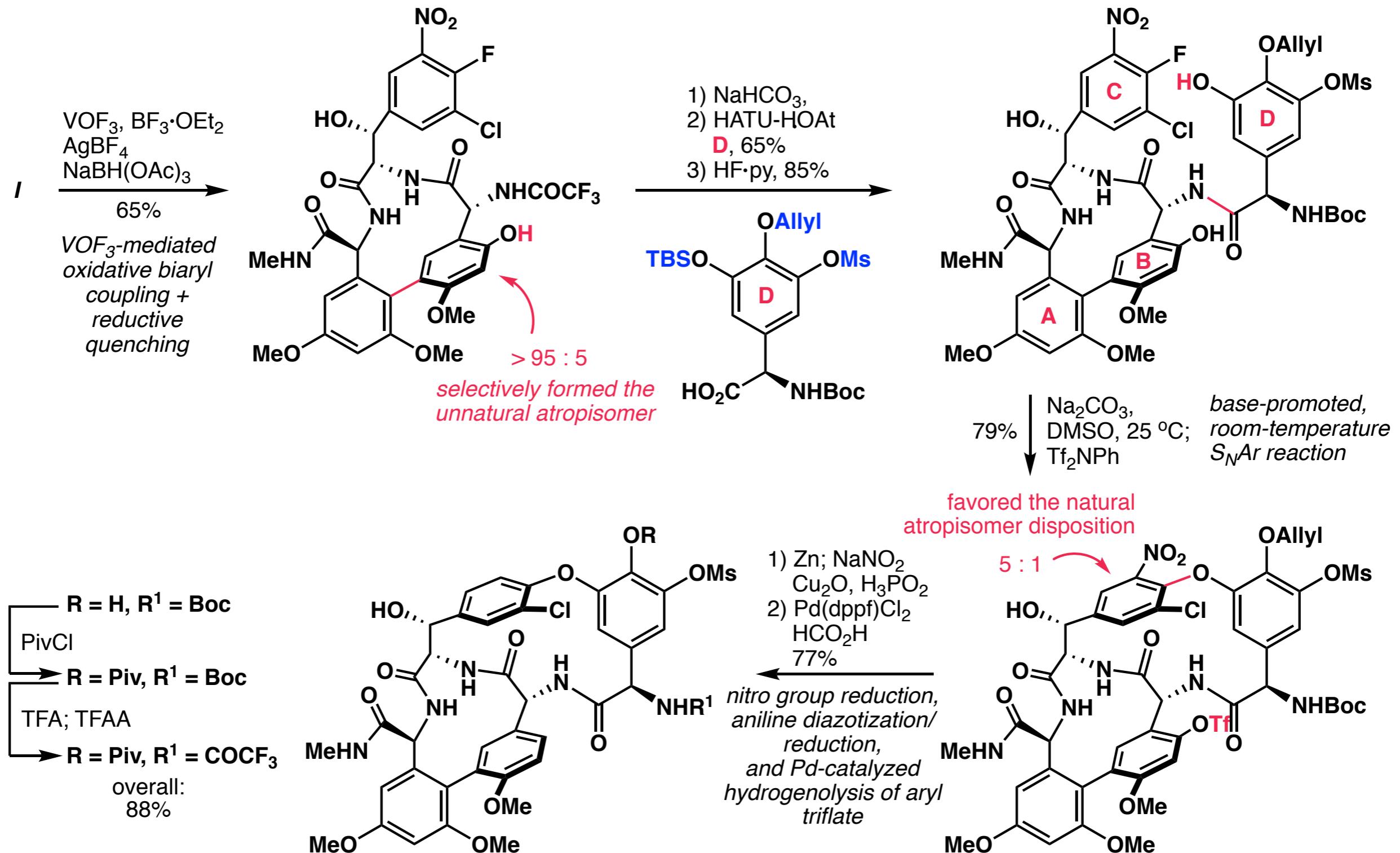
Total Synthesis of Vancomycin in the late 1990s

■ Evans synthesis



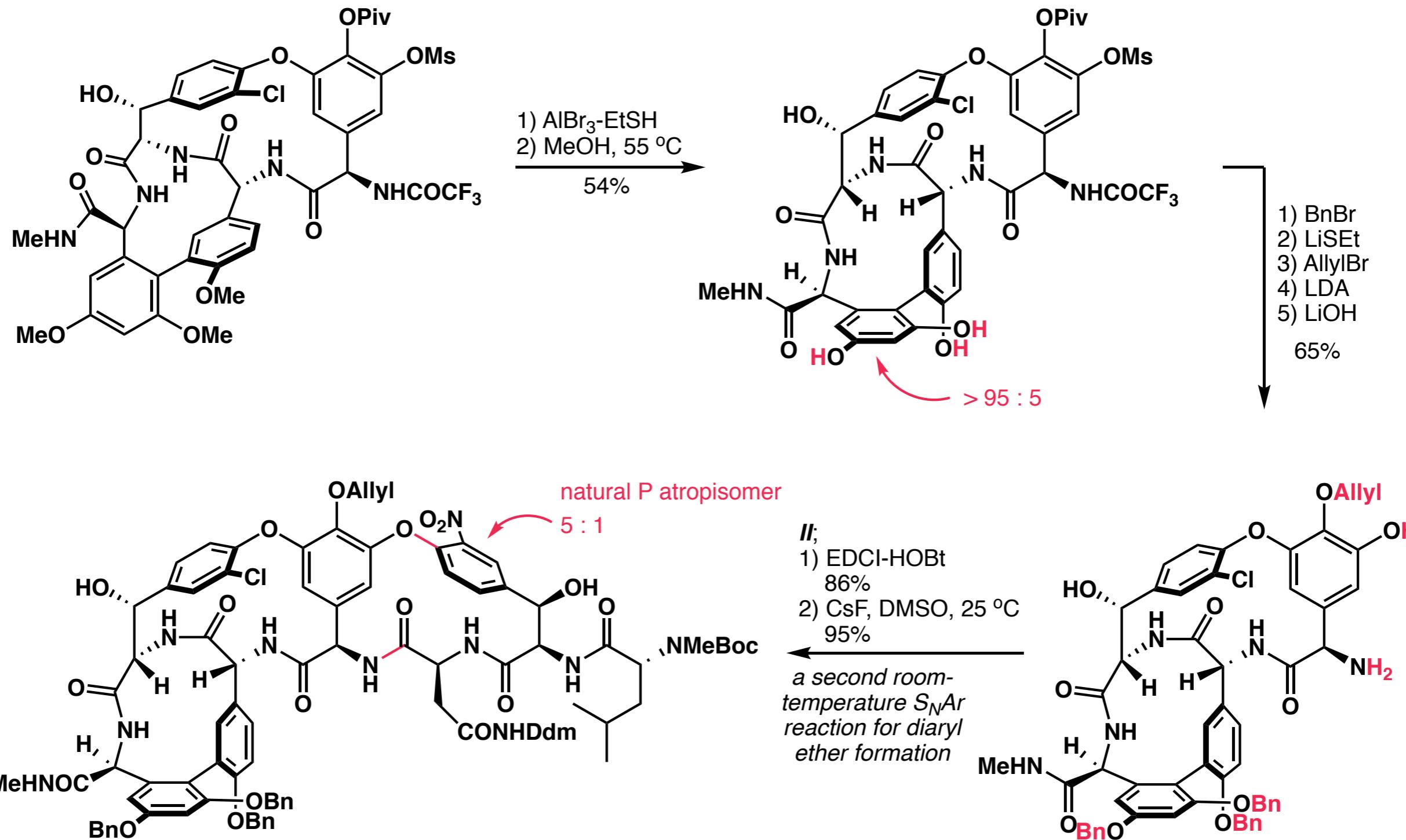
Total Synthesis of Vancomycin in the late 1990s

■ Evans synthesis



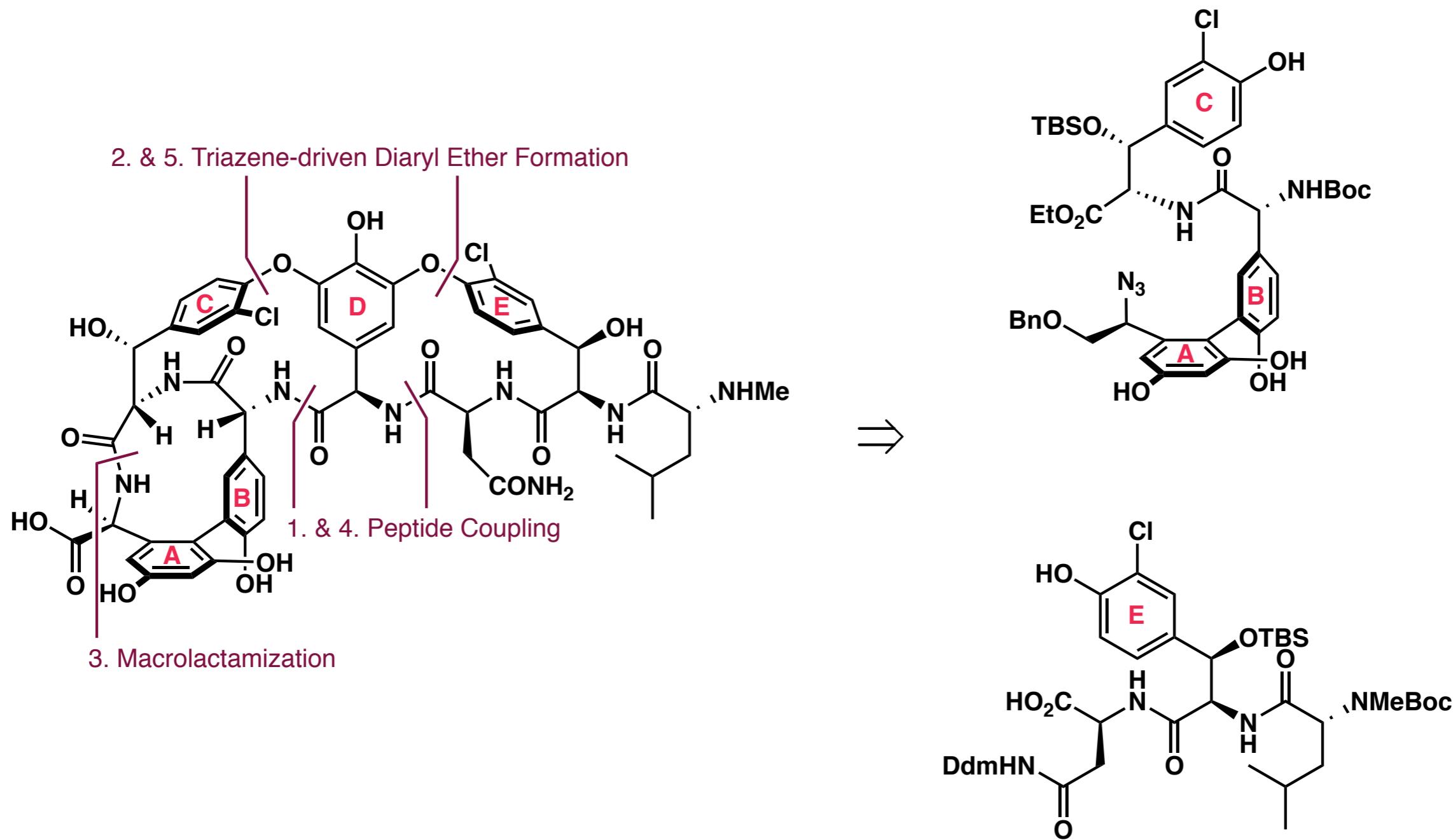
Total Synthesis of Vancomycin in the late 1990s

■ Evans synthesis



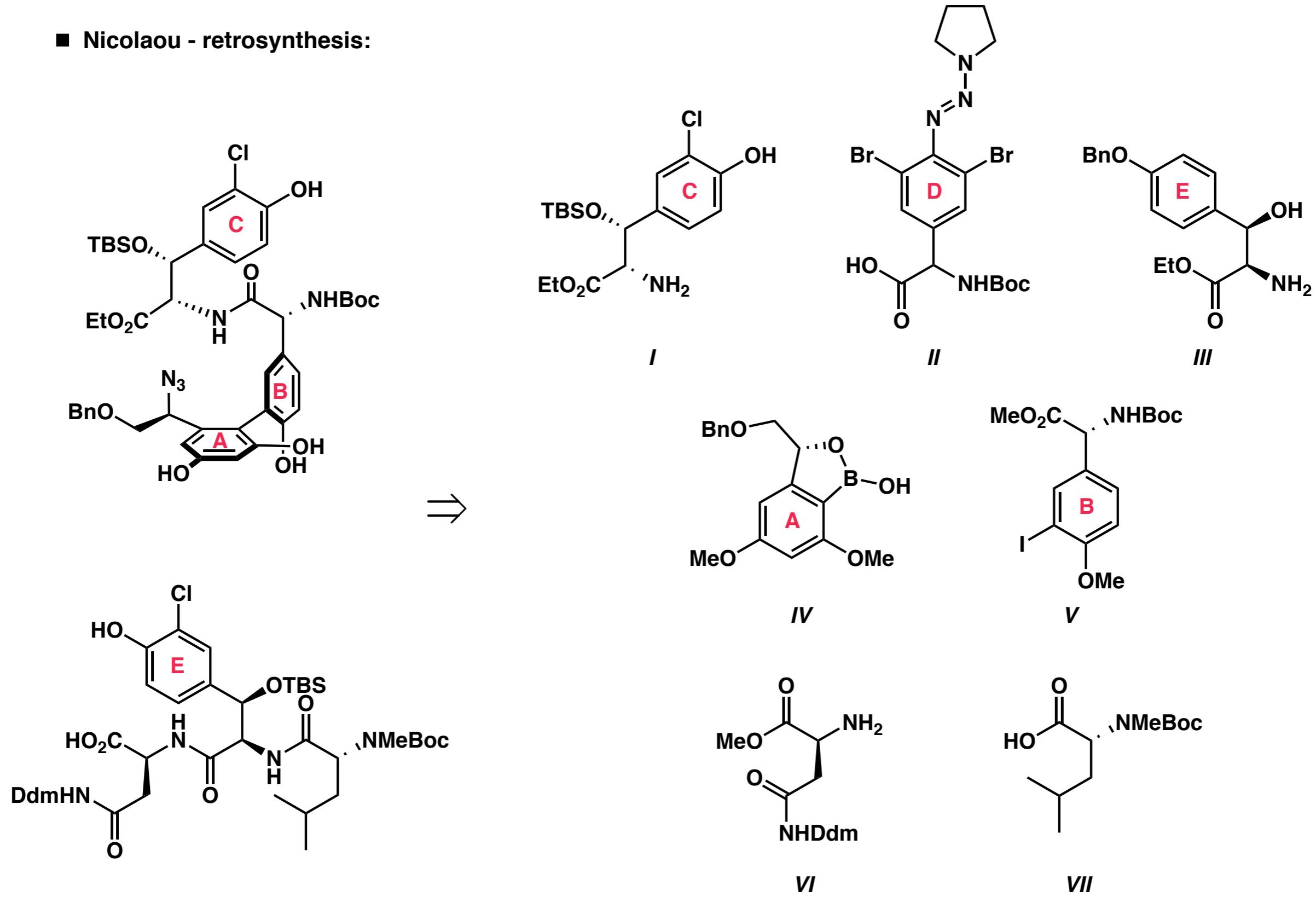
Total Synthesis of Vancomycin in the late 1990s

■ Nicolaou - retrosynthesis:



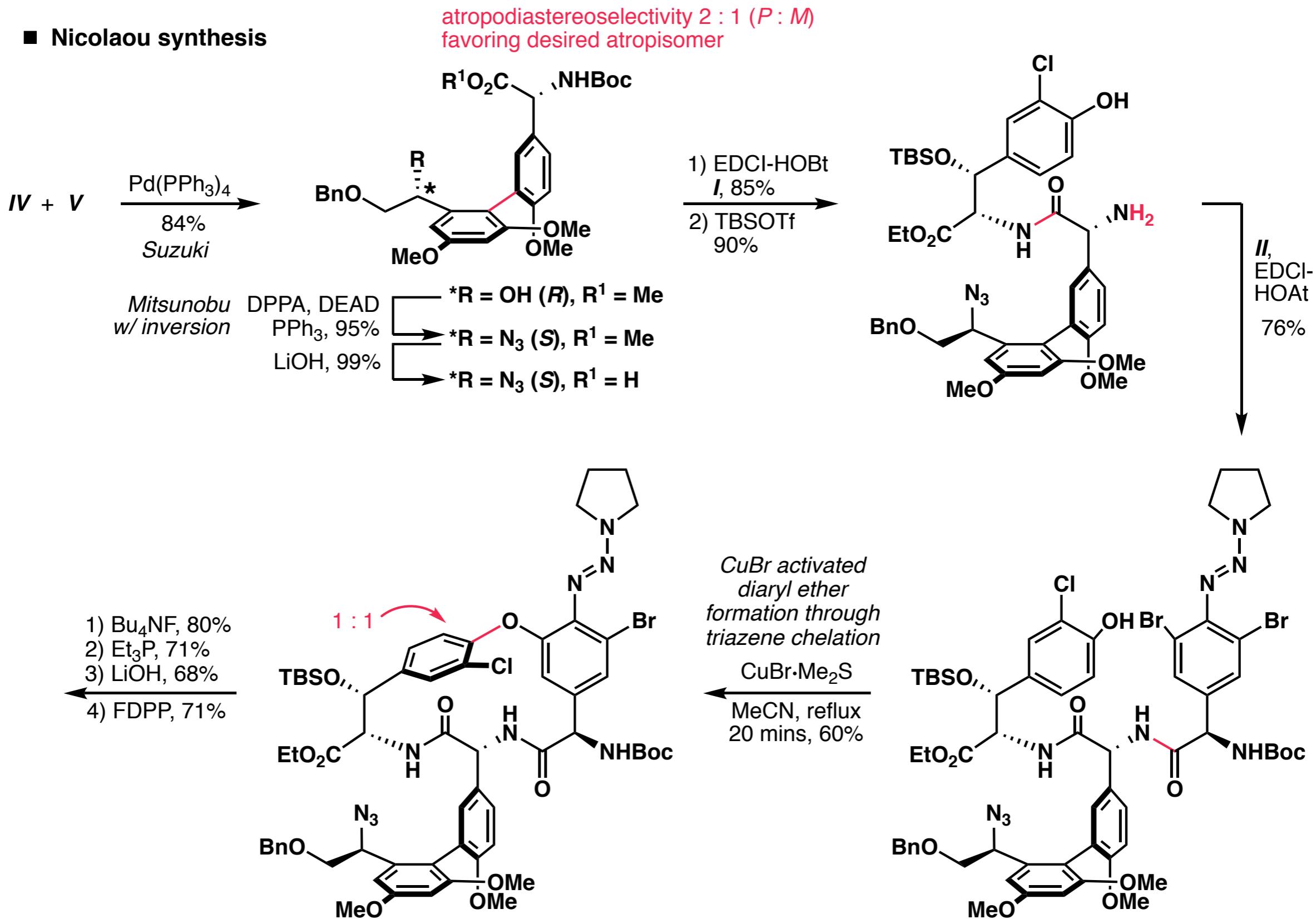
Total Synthesis of Vancomycin in the late 1990s

■ Nicolaou - retrosynthesis:



Total Synthesis of Vancomycin in the late 1990s

■ Nicolaou synthesis

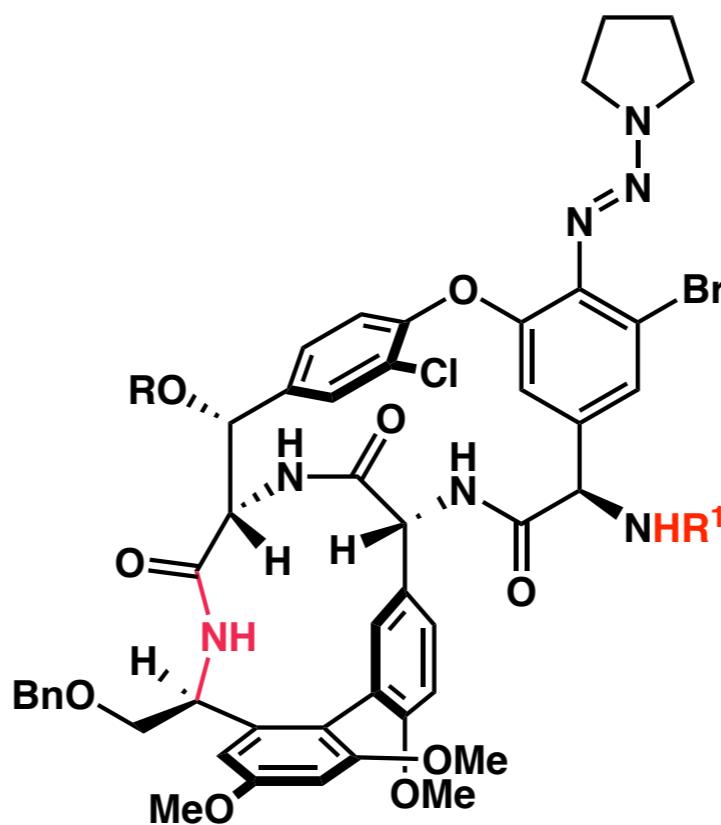


Total Synthesis of Vancomycin in the late 1990s

■ Nicolaou synthesis

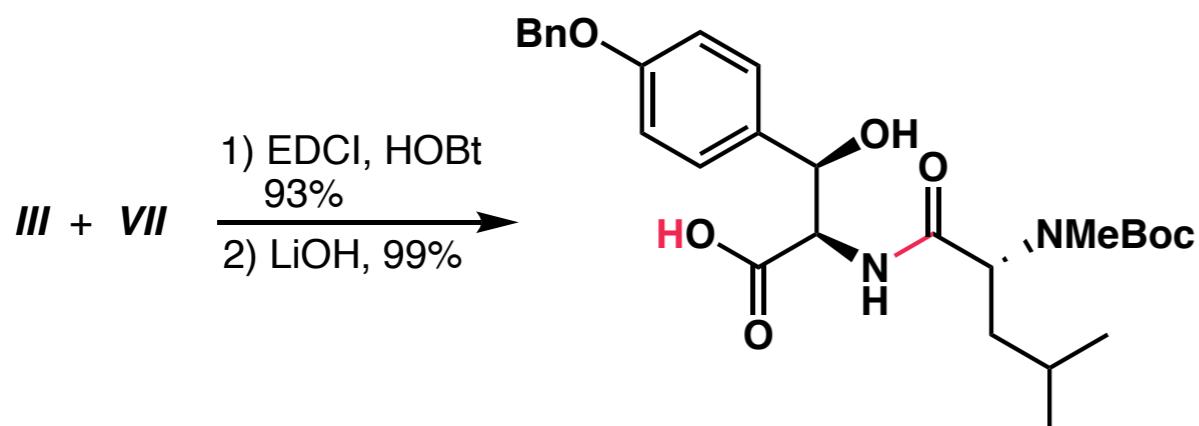
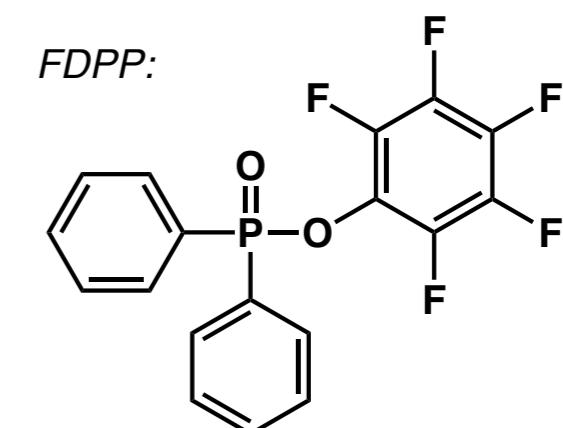
TBSOTf, 83%
 TMSOTf, 84%

$\xrightarrow{\quad}$ R = H, R¹ = Boc
 $\xrightarrow{\quad}$ R = TBS, R¹ = Boc
 $\xrightarrow{\quad}$ R = TBS, R¹ = H

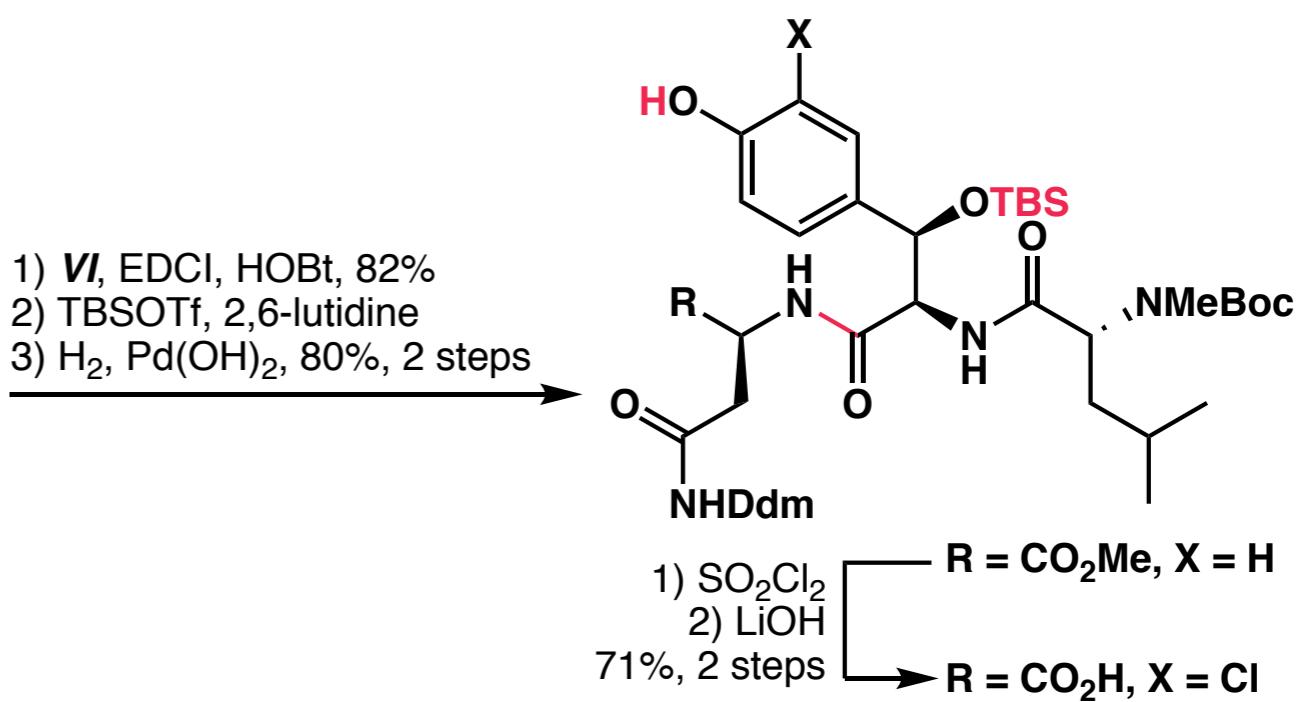


1) Bu₄NF, 80%
 2) Et₃P, 71%
 3) LiOH, 68%
 4) FDPP, 71%

TBS ether cleavage;
 azido group reduction;
 ethyl ester hydrolysis;
 FDPP-mediated
 macrolactamization.

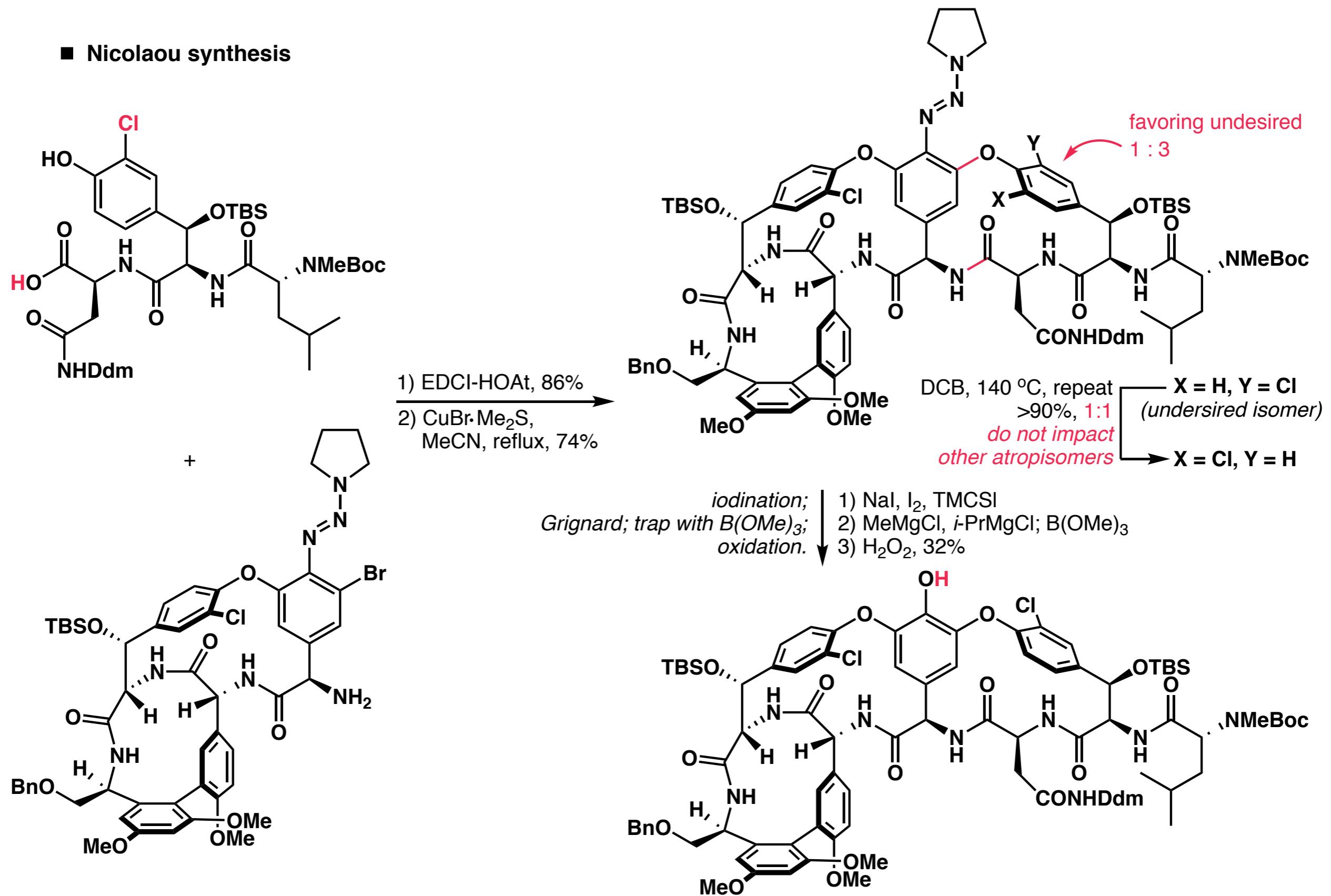


1) VI, EDCI, HOEt, 82%
 2) TBSOTf, 2,6-lutidine
 3) H₂, Pd(OH)₂, 80%, 2 steps



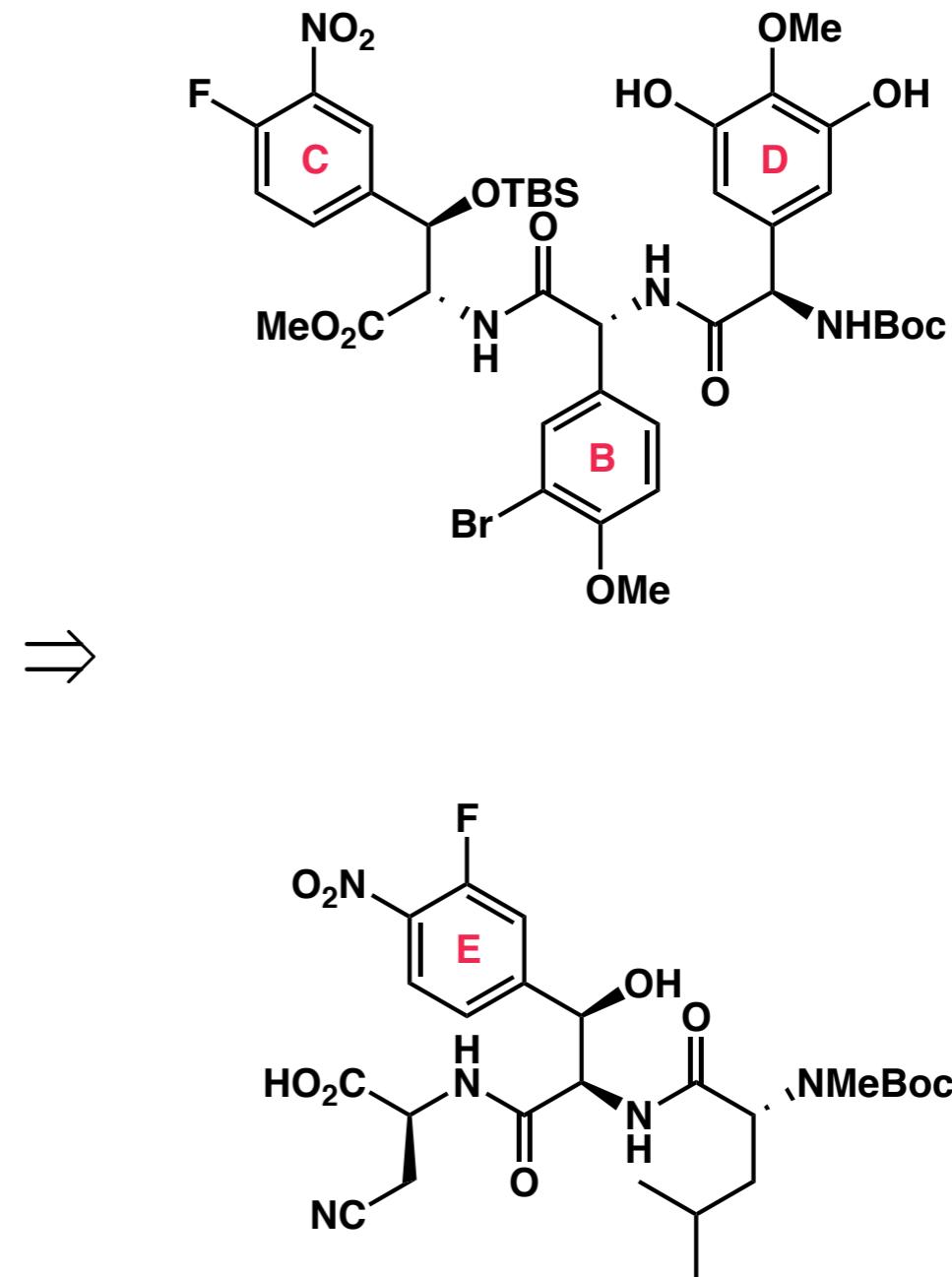
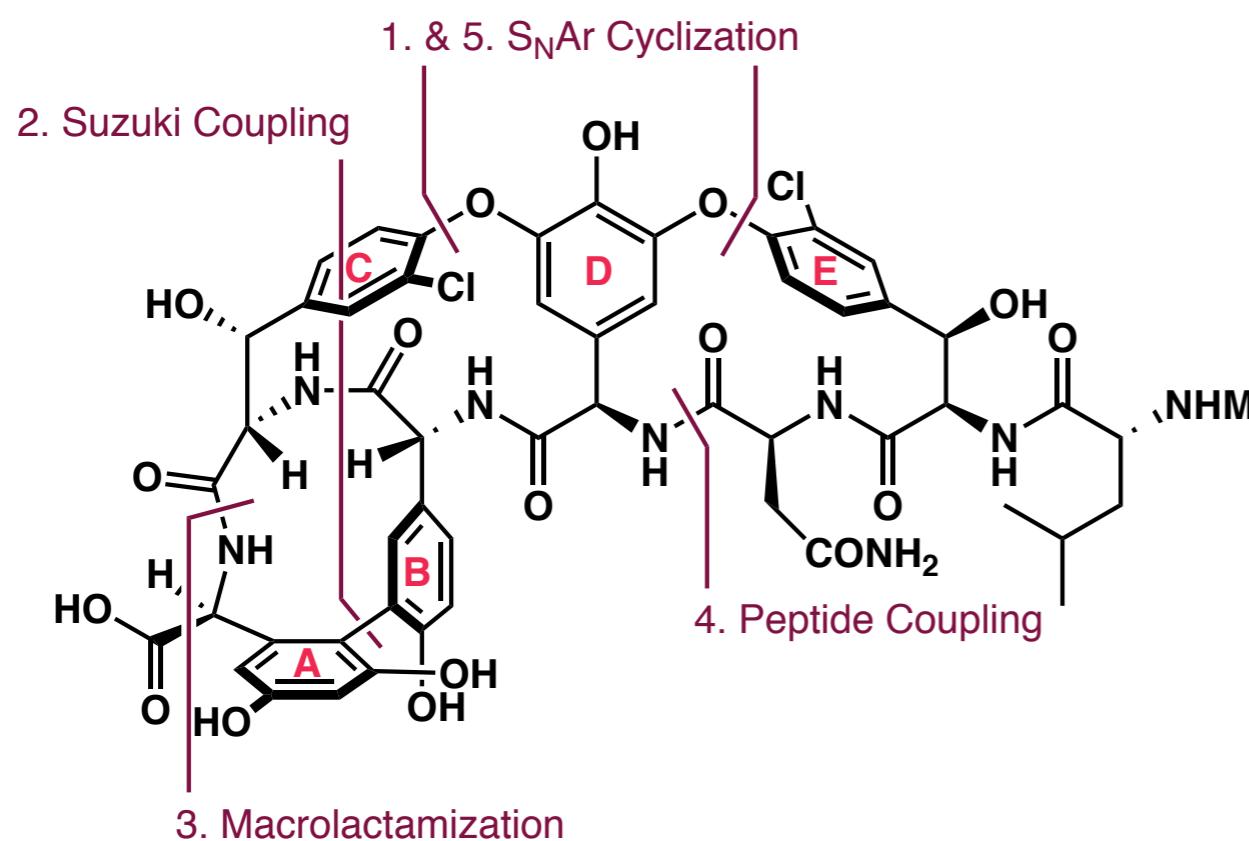
Total Synthesis of Vancomycin in the late 1990s

■ Nicolaou synthesis



Total Synthesis of Vancomycin in the late 1990s

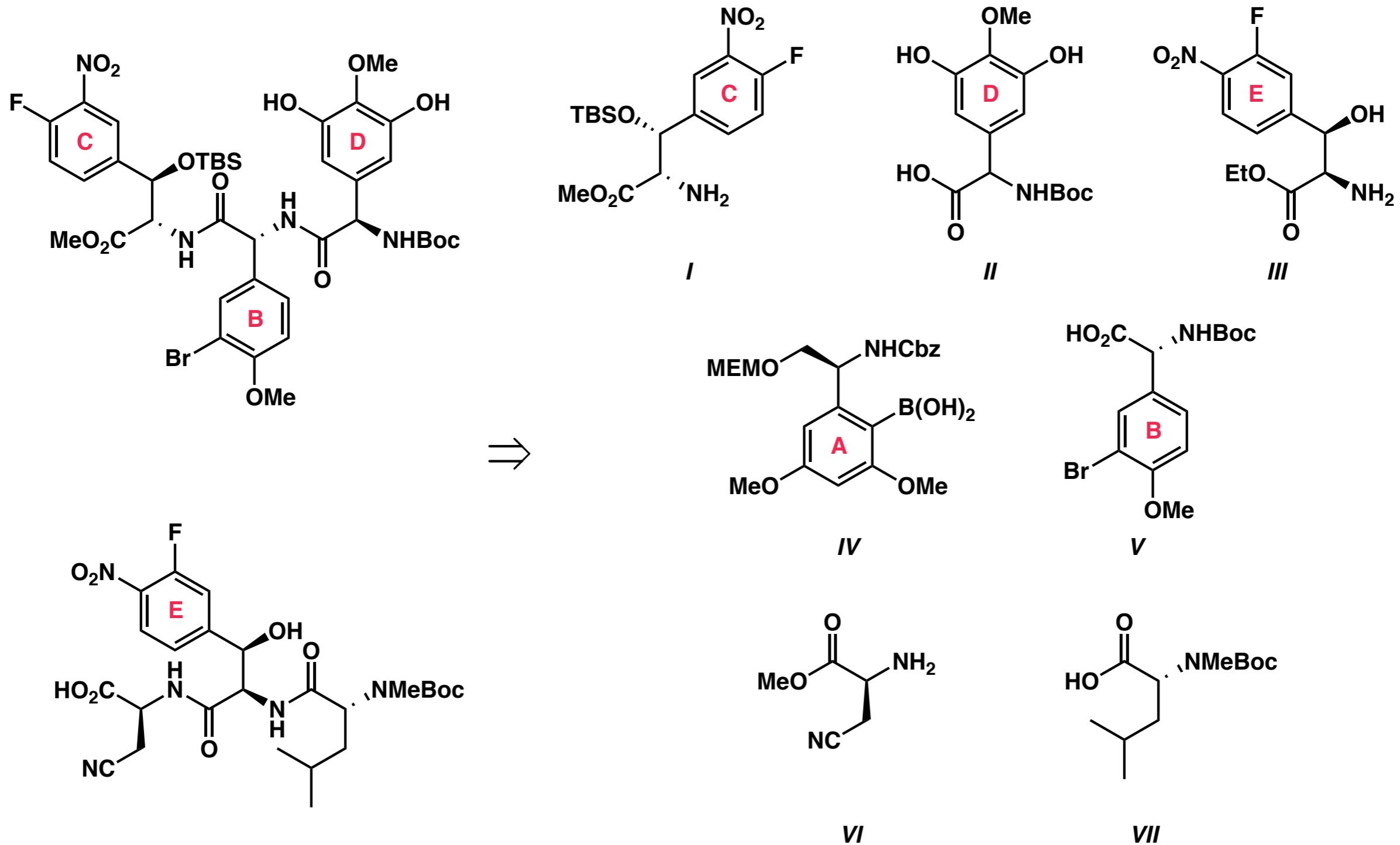
■ Boger - retrosynthesis:



The order permitted the recycling of any undesired atropisomer for each ring system and provided predictable control of the stereochemistry, dependably funneling all synthetic material into one of the eight atropodiastereomers found in the natural product.

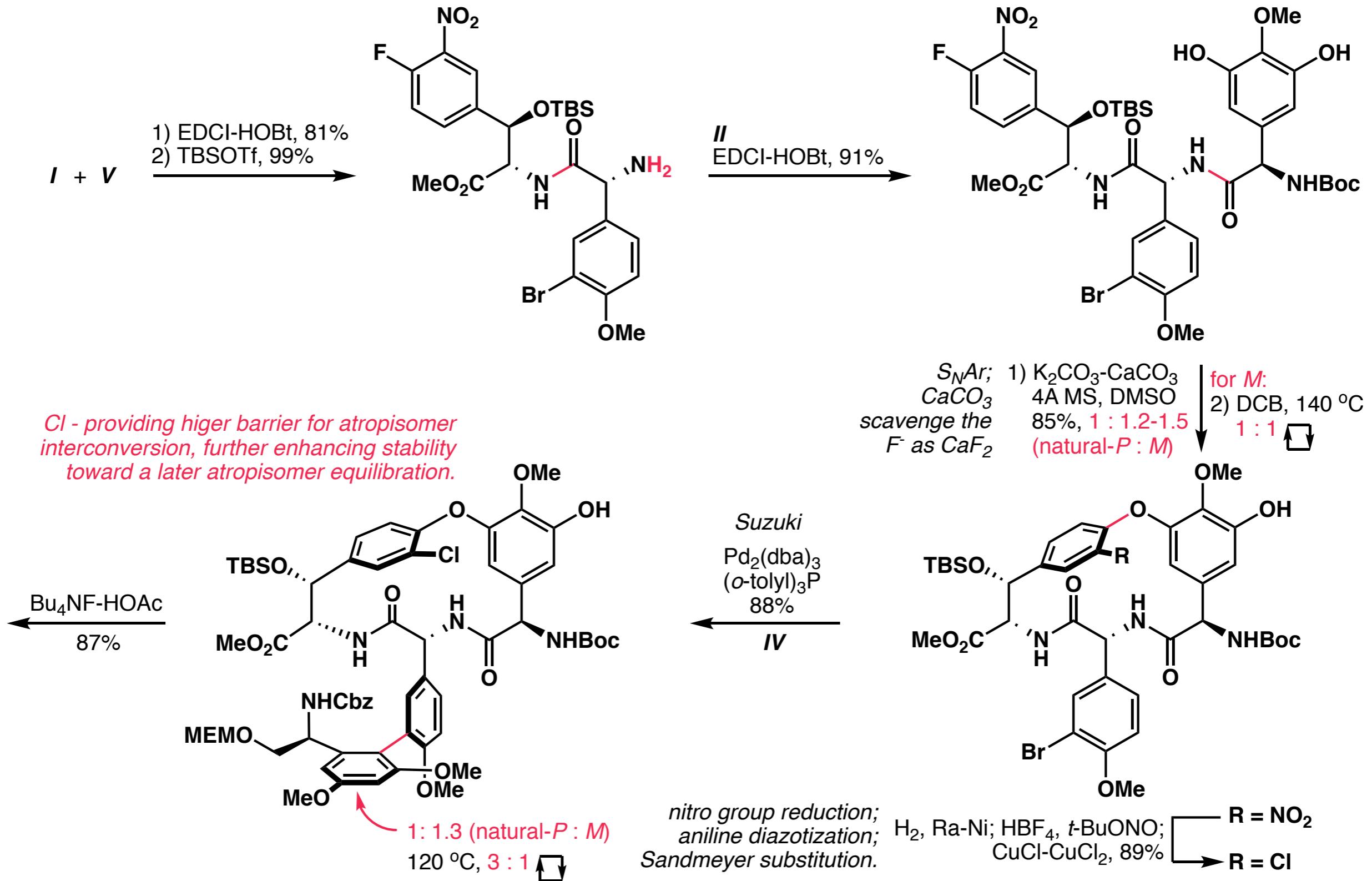
Total Synthesis of Vancomycin in the late 1990s

■ Boger - retrosynthesis:



Total Synthesis of Vancomycin in the late 1990s

■ Boger synthesis



Total Synthesis of Vancomycin in the late 1990s

■ Boger synthesis

