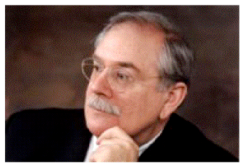
Comparative Syntheses of Vancomycin

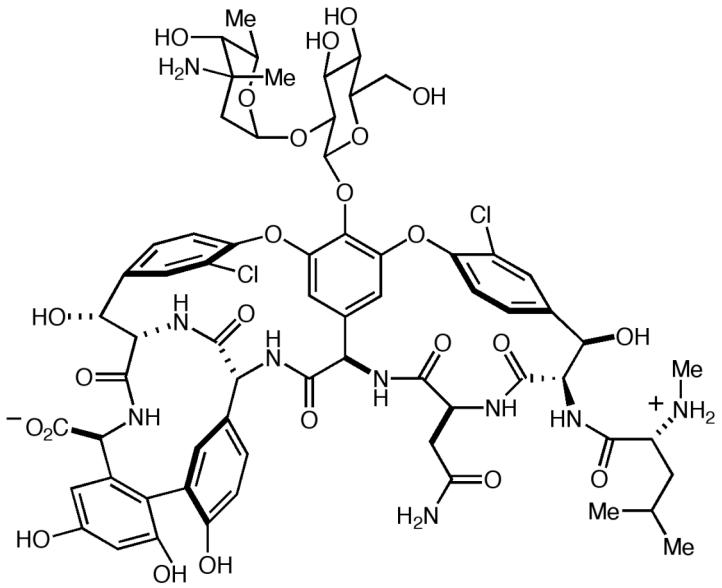
Ian Mangion
MacMillan Group Meeting
September 28, 2005



Dave Evans, Harvard
1998

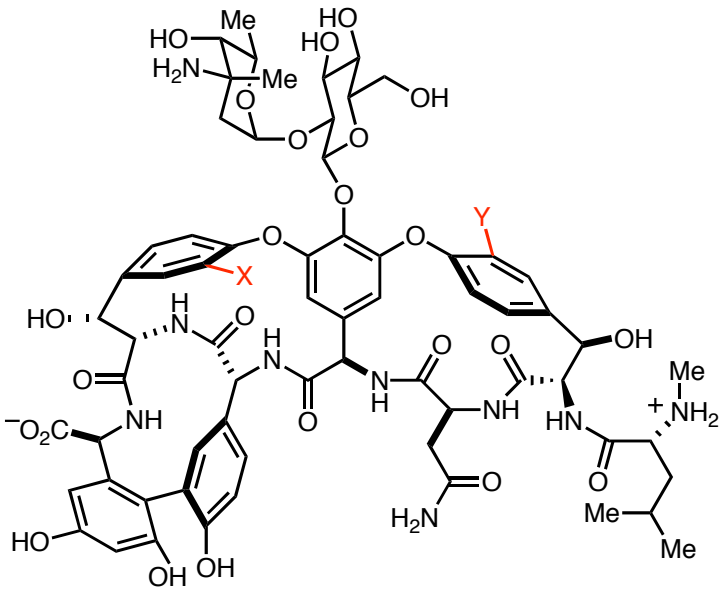
K.C. Nicolaou, Scripps
1998, 1999

Dale Boger, Scripps
1999

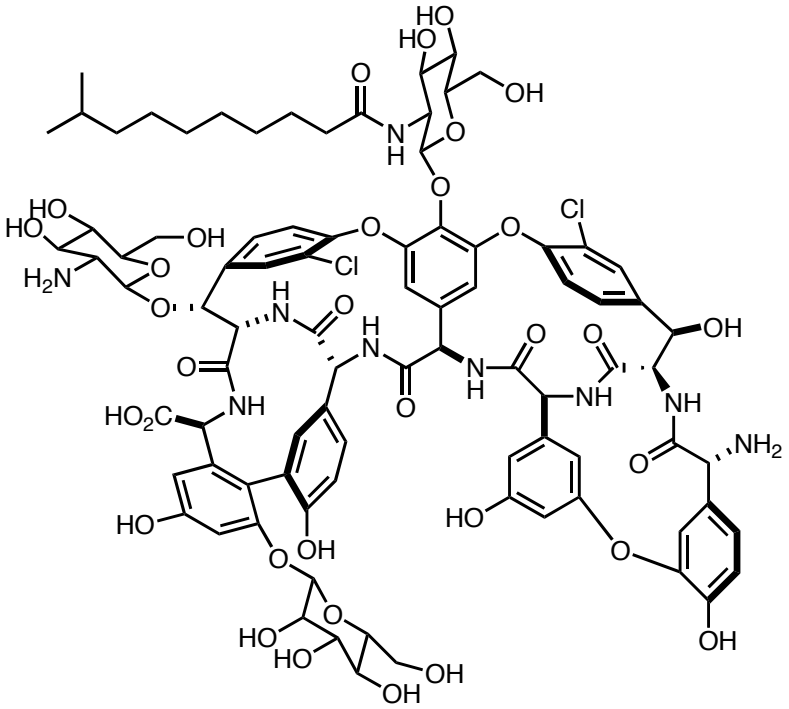


Structural Features of Vancomycin Type Glycopeptide Antibiotics

■ Generally characterized by an aryl-rich polypeptide backbone with varying crosslinking and glycosidation patterns



X = Y = Cl; Vancomycin
X = H, Y = Cl; Eremomycin
X = Y = H; Orienticin C



Teicoplanin

■ Useful references

Hubbard, B. K.; Walsh, C. T. *Angew. Chem. Int. Ed.,* **2003**, *42,* 730

Kahne, D.; Leimkuhler, C.; Lu, W.; Walsh, C. *Chem. Rev.,* **2005**, *105,* 425

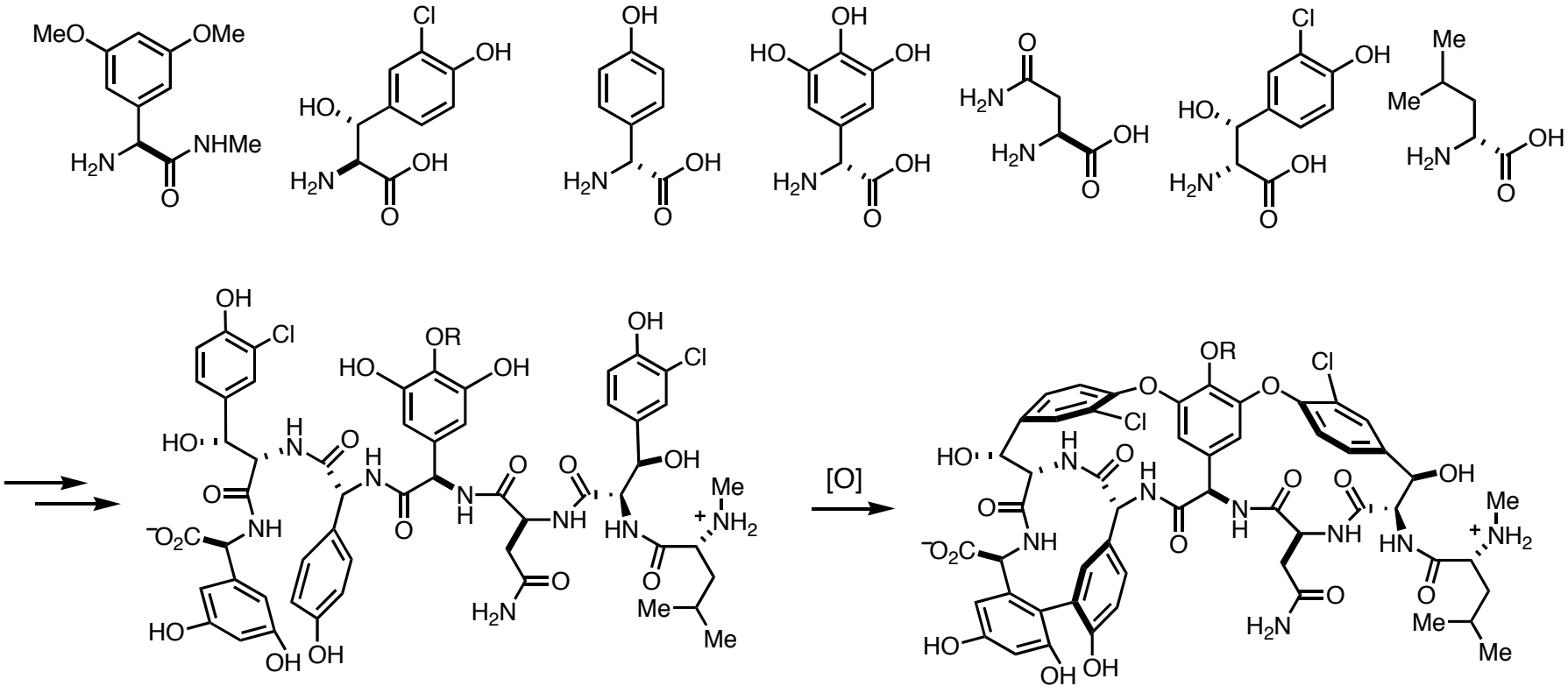
Evans, D.; Wood, M. R.; rotter, W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem. Int. Ed.,* **1998**, *37*, 2700

Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Winsigger, N.; Hughes, R.; Bando, T. *Angew. Chem. Int. Ed.,* **1999**, *38*, 240

Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.,* **1999**, *121*, 10004

Proposed Biosynthesis of Vancomycin-Type Glycopeptides

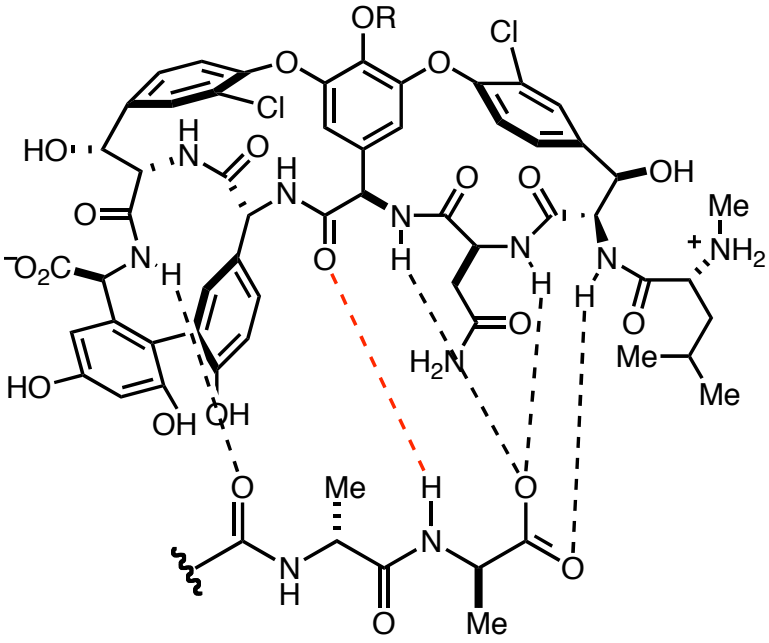
- Remarkably, genes and proteins responsible for the biosynthesis of these molecules have been characterized
- Biosynthesis can be reduced to peptide elongation and post-translational modification



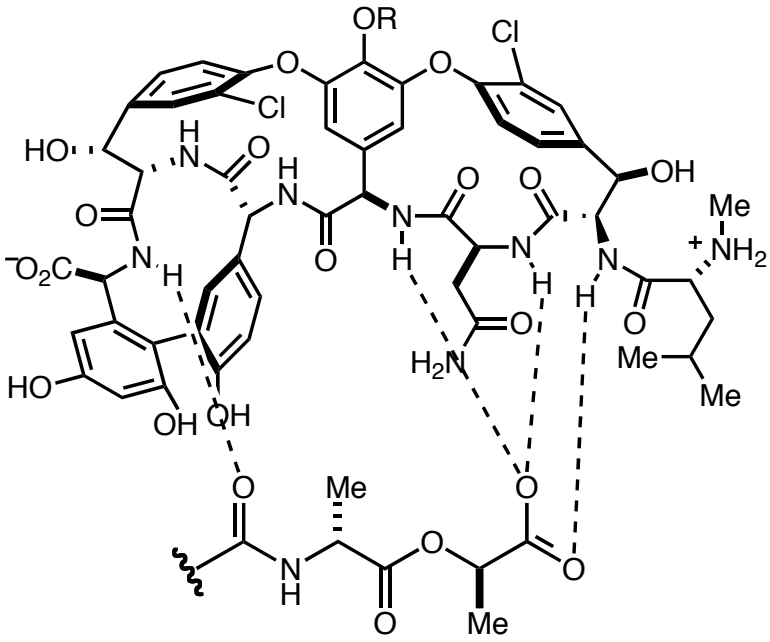
- The challenge to the synthetic chemist is immense: biosynthesis entails 35 total steps

Biological Activity (Gram-Positive Bacteria)

- Vancomycin inhibits cell wall cross-linking through tight binding, eventually leading to cell lysis



Alanine dimer - normally linked to glycan outer wall of cell

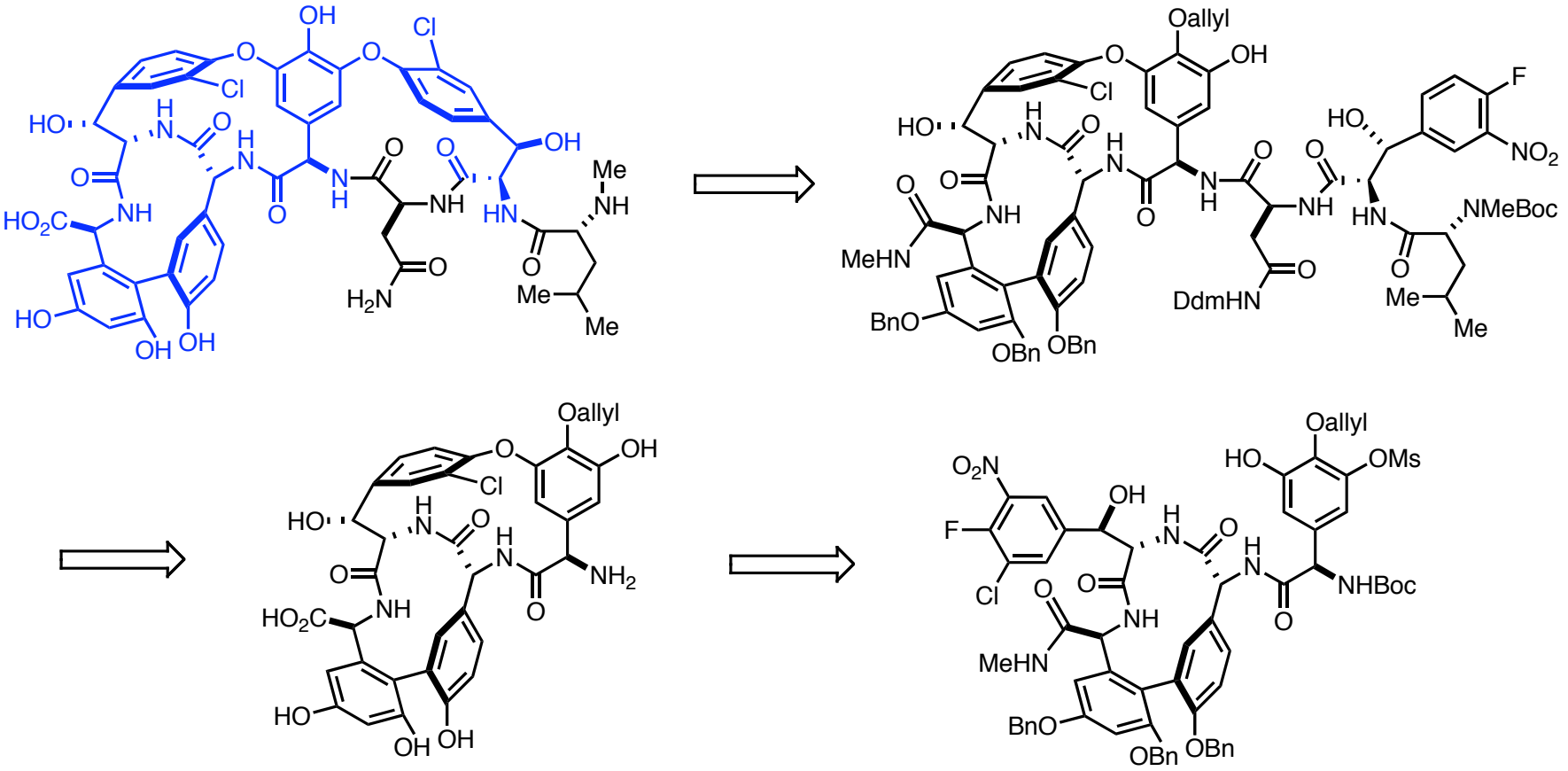


(resistance)

- Disruption of just one of the five hydrogen bonds leads to a 1000-fold loss in activity

The Evans Design

- Chiral auxiliary technology will be used to create most amino acid stereocenters

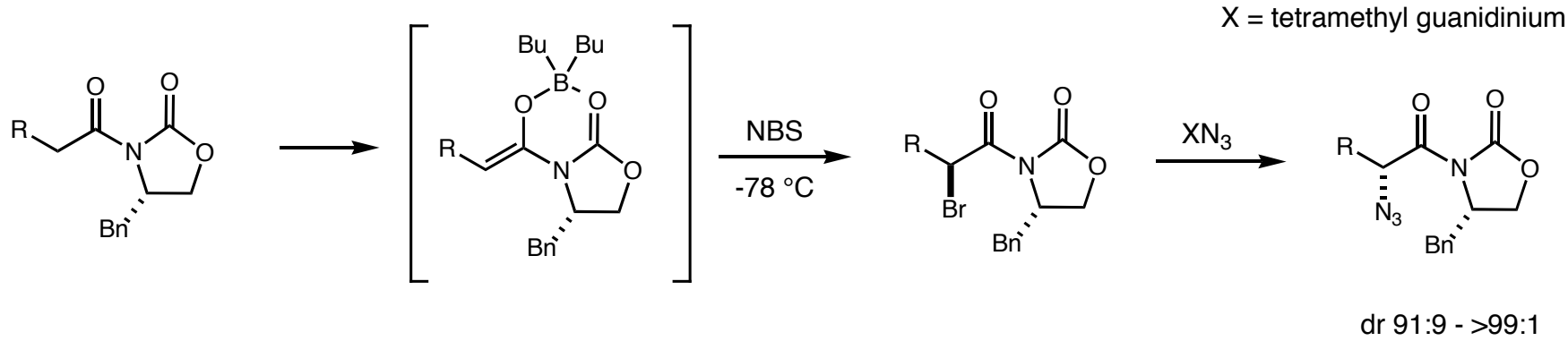


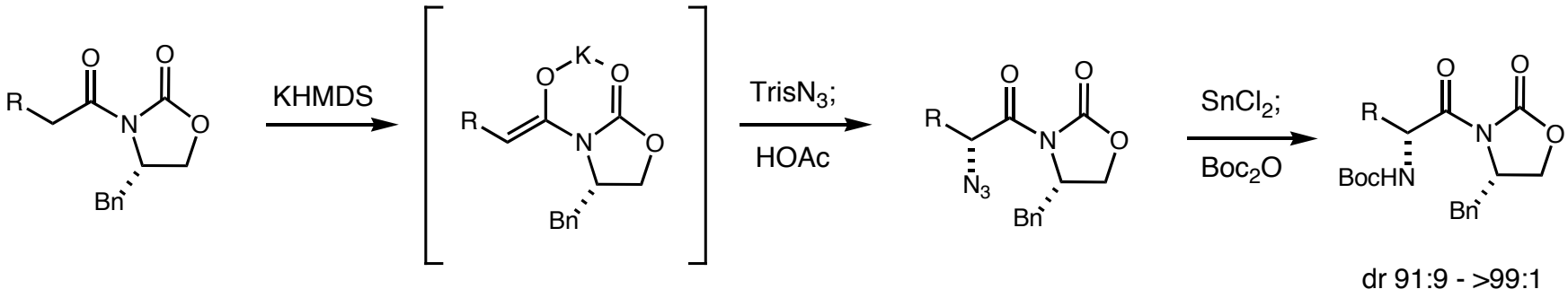
- This strategy relies on atropdiastereoselective macrocyclizations

Oxazolidinone-Based Amino Acid Synthesis

■ Chiral auxiliary approach creates labile arylglycine stereocenters in controlled fashion

X = tetramethyl guanidinium





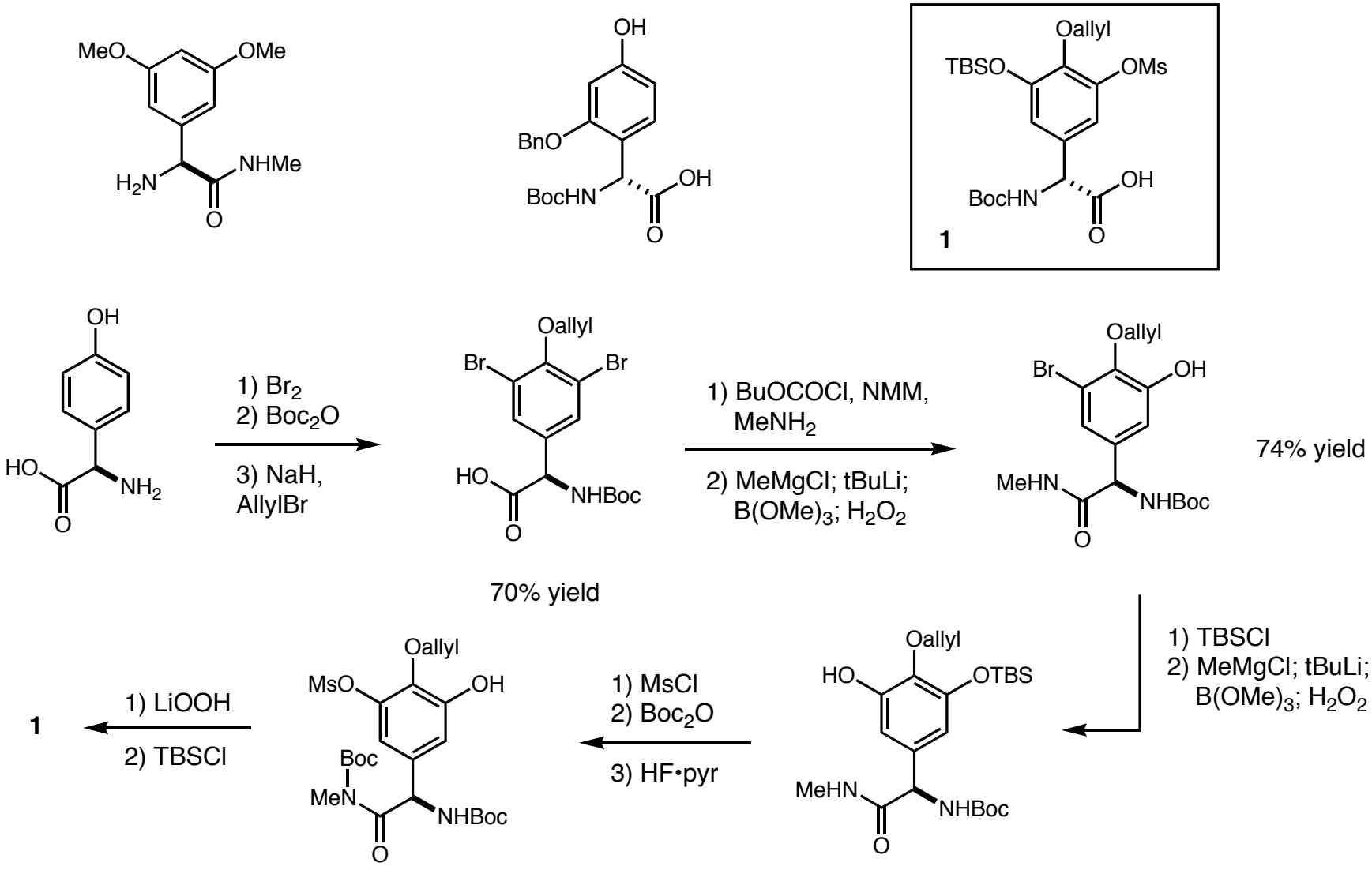
Tris = 2,4,6-triisopropyl phenyl

■ This strategy is applied to all arylglycines in the Evans synthesis

Evans, *JACS*, 4011, **1990**

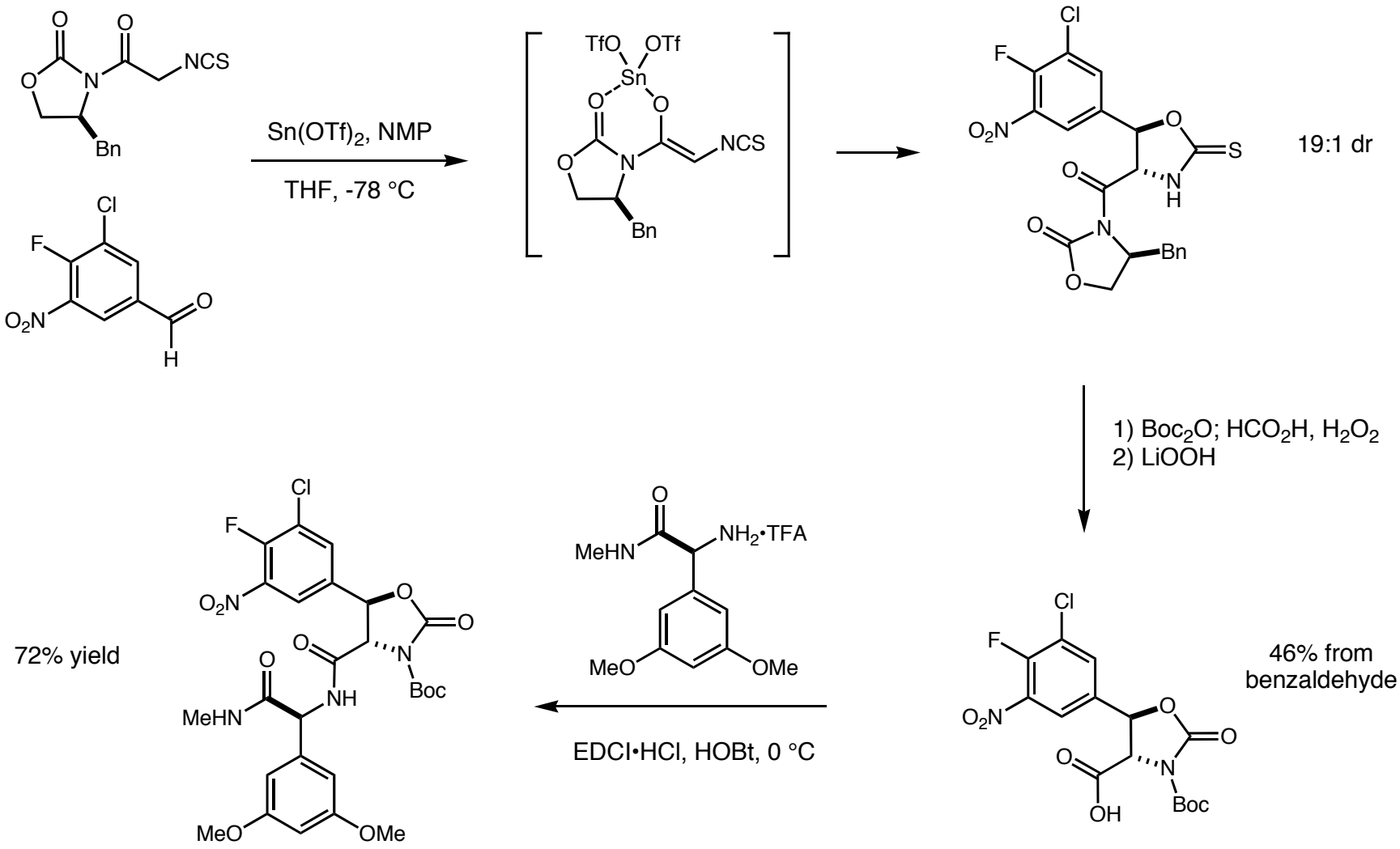
Oxazolidinone-Based Amino Acid Synthesis

■ The auxiliary approach proves unsuccessful for the central resorcinol-type arylglycine

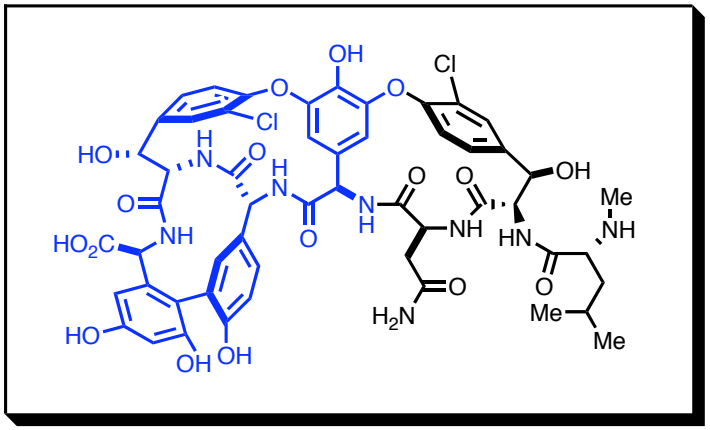


Synthesis of the Left Macrocycle

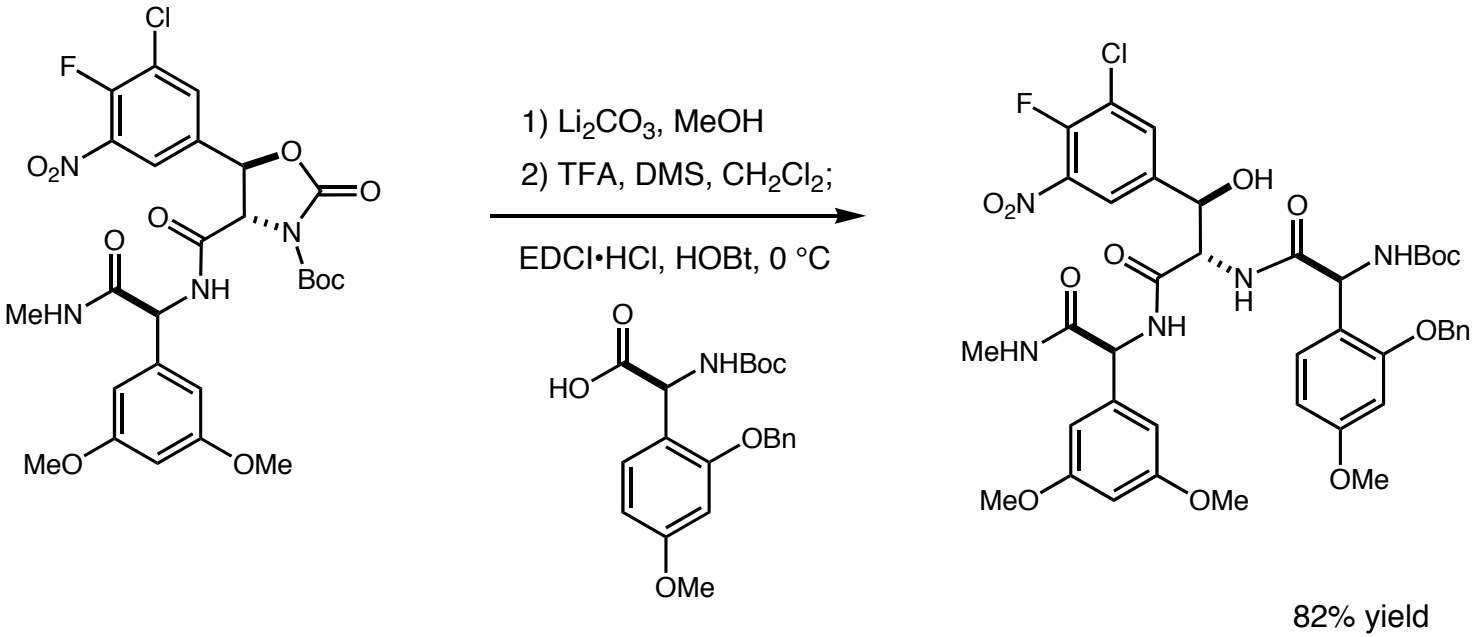
■ Oxazolidinone methodology is employed to stereoselectively access a protected amino alcohol



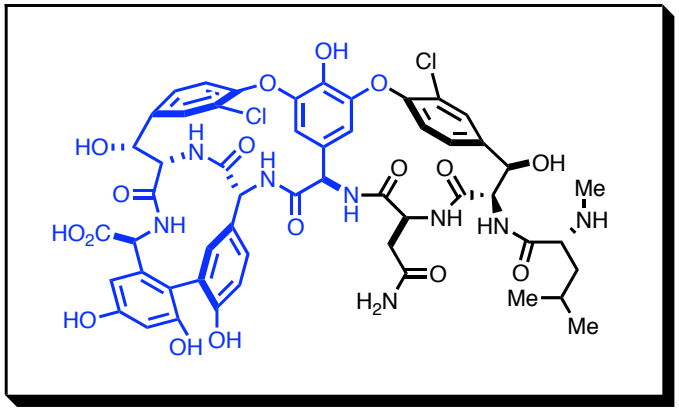
Synthesis of the Left Macrocycle



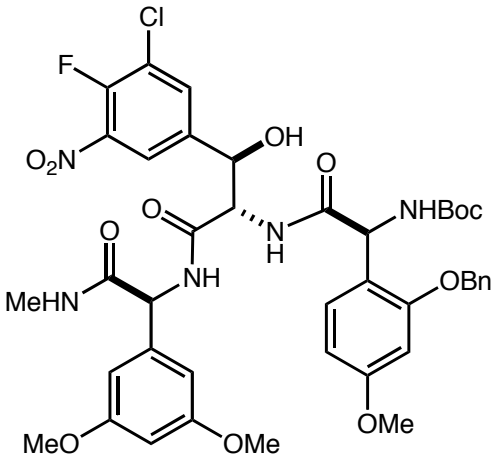
■ Functional group adjustment and amino acid coupling



Synthesis of the Left Macrocycle

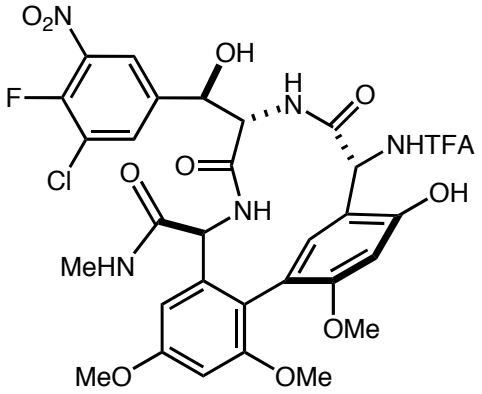


- Oxidative coupling provides undesired atropisomer



1) TFA, DMS; TFAA

2) VOF_3, $BF_3 \cdot Et_2O$, $AgBF_4$, TFA/CH_2Cl_2; $NaBH(OAc)_3$

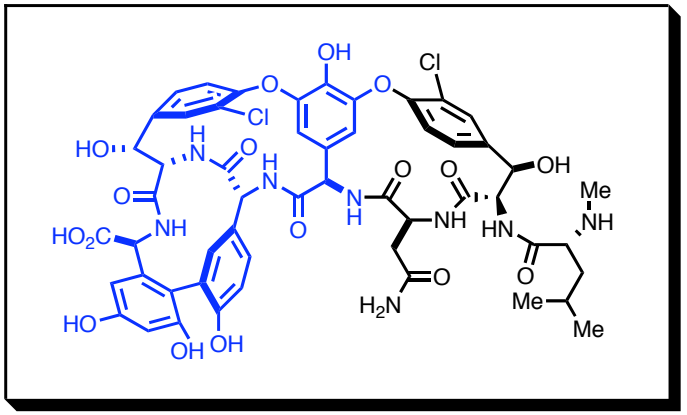


65% yield, 19:1 dr

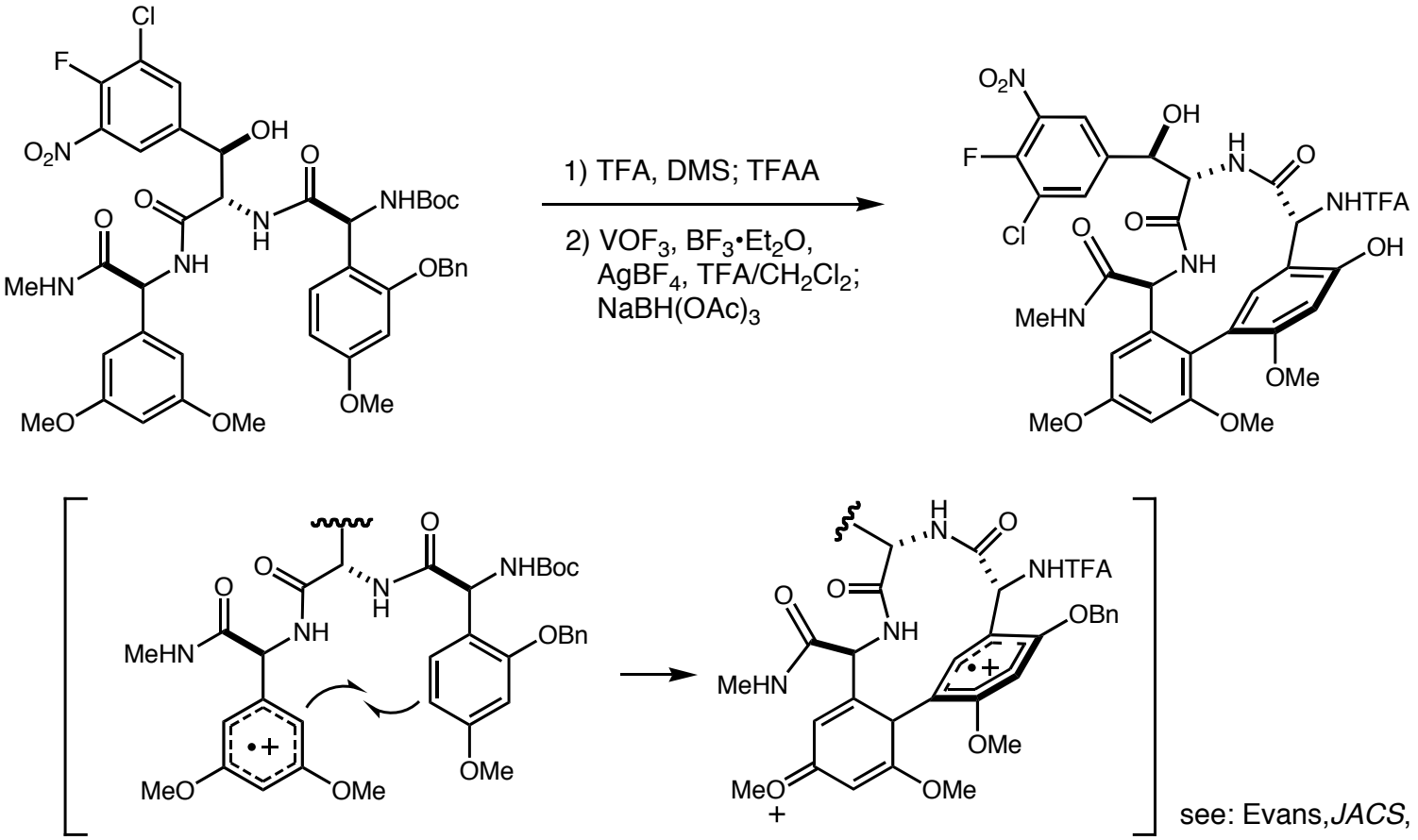
- Vanadium serves as oxidant, BF_3 as trap for oxygen nucleophiles, silver as trap for chloride ion impurities, TFA as part of solvent mixture, $NaBH(OAc)_3$ as reductive quench

see: Evans,*JACS*, 6426 **1993**

Synthesis of the Left Macrocycle

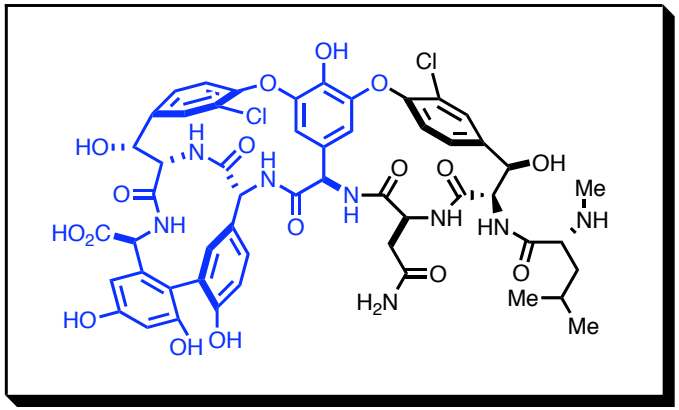


- Oxidative coupling proceeds via radical cation

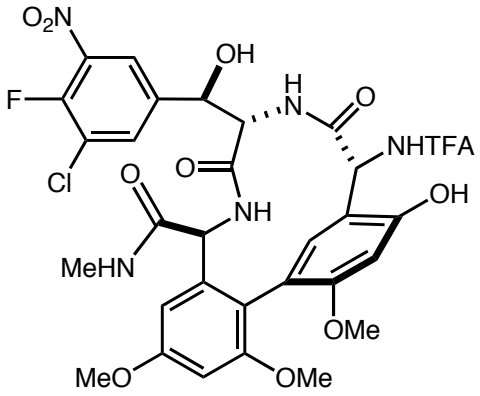


see: Evans, *JACS*, 6426 **1993**

Synthesis of the Left Macrocycle

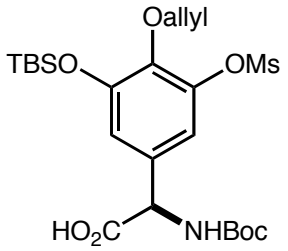


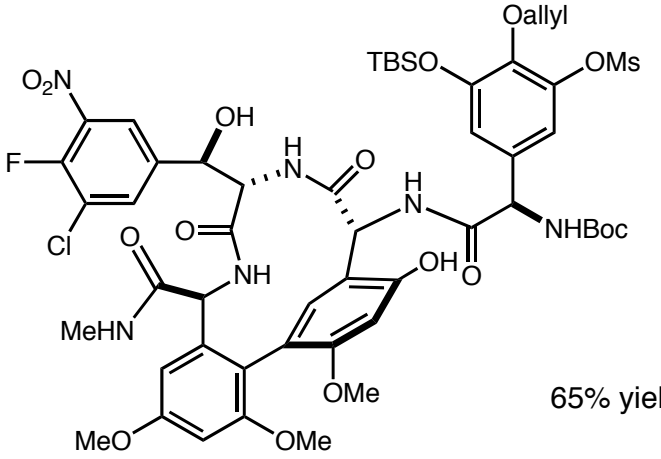
- Careful coupling introduces the central aryl fragment



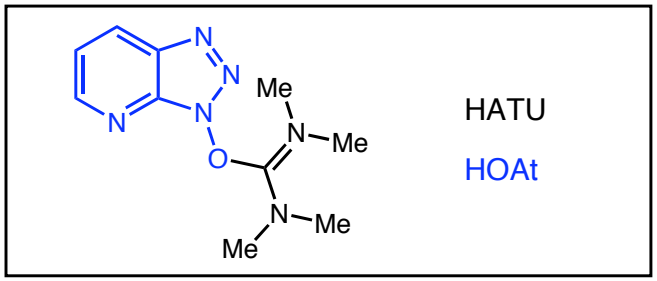
1) $NaHCO_3$, MeOH, 6 d

2) HATU, HOAt, collidine
CH_2Cl_2/DMF, -20 °C



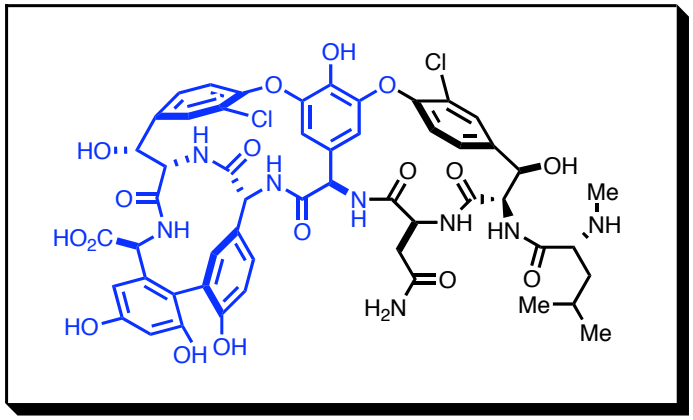


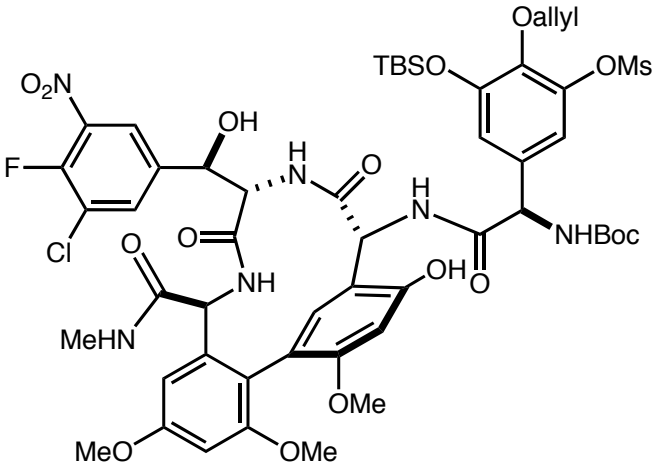
65% yield



Synthesis of the Left Macrocycle

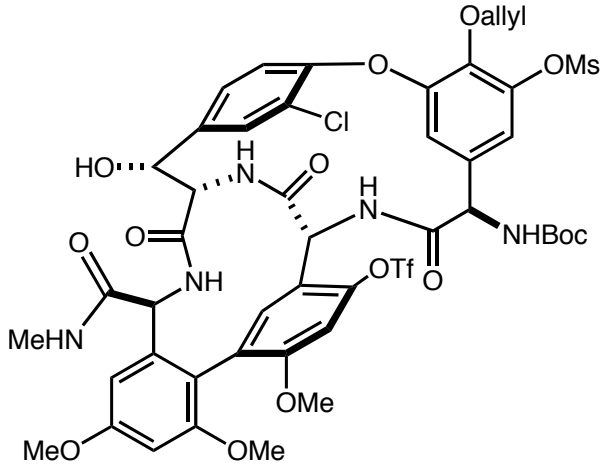
- Macrocyclization occurs with good selectivity





1) HF•pyridine
2) Na_2CO_3, DMSO; $PhNTf_2$

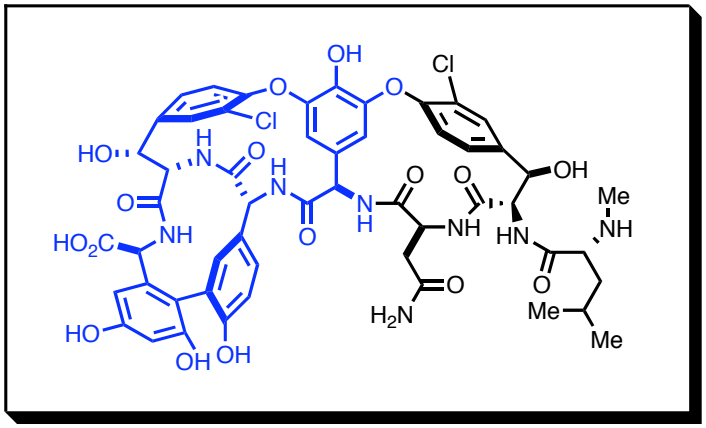
3) Zn^0, AcOH
4) $NaNO_2$, H_3PO_2, cat. Cu_2O



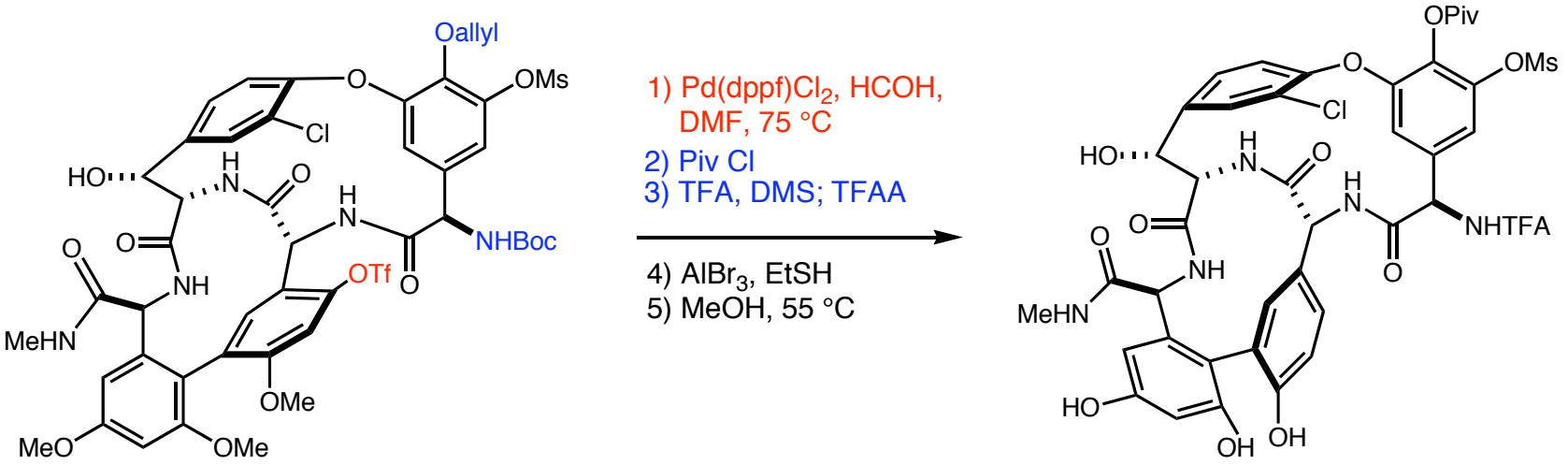
62% yield
5:1 dr

(10:1 dr w/o Cl)

Synthesis of the Left Macrocycle



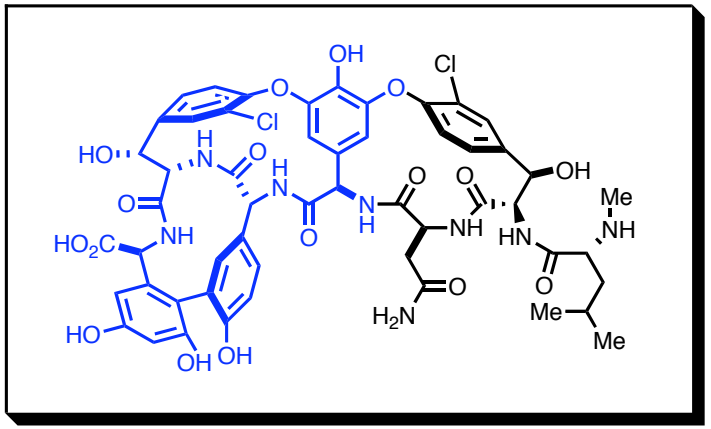
- Thermal equilibration provides the desired atropisomer



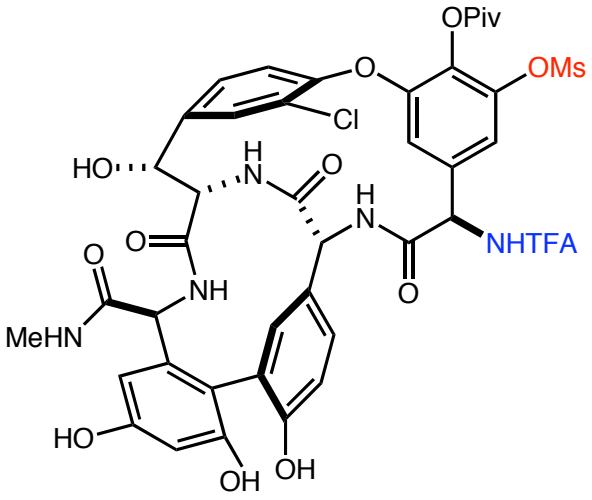
44% yield
19:1 dr

see: Evans,*JACS*, 6426 **1993**

Synthesis of the Left Macrocycle

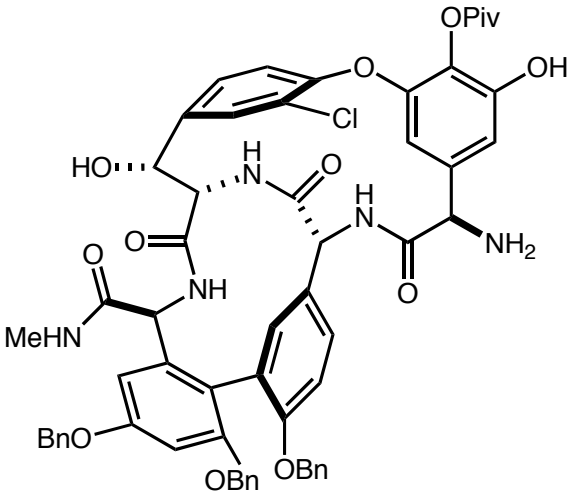


- Thermal equilibration provides the desired atropisomer



1) BnBr, Cs_2CO_3
2) LiSEt, THF, 0 °C

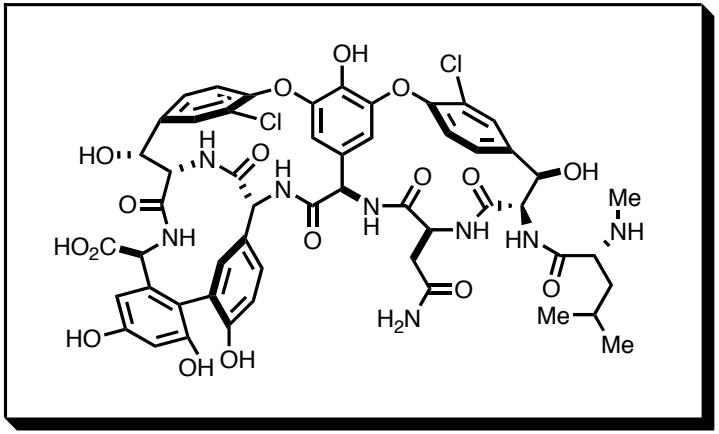
3) allyl-Br, Cs_2CO_3
4) LDA, -78 °C
5) LiOH, THF/MeOH

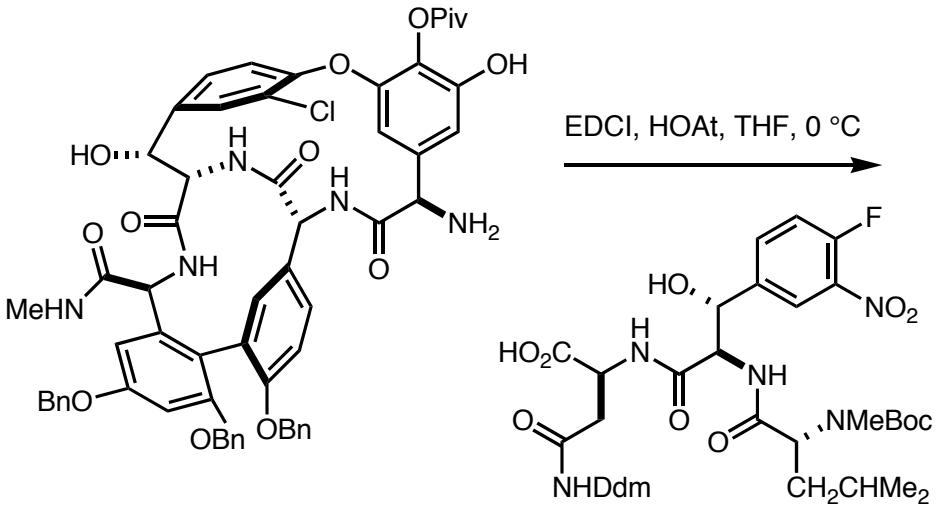


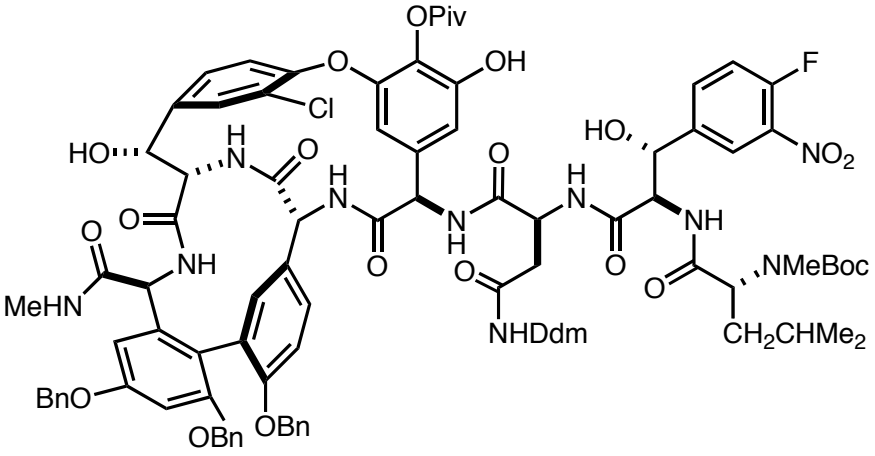
65% yield

Synthesis of the Right Macrocycle

- Fragment coupling completes the peptide chain

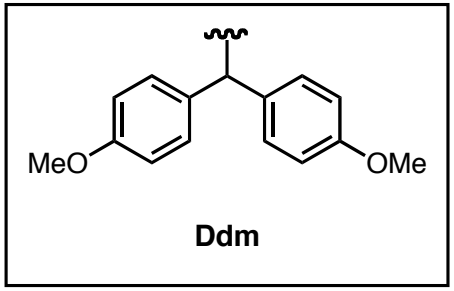






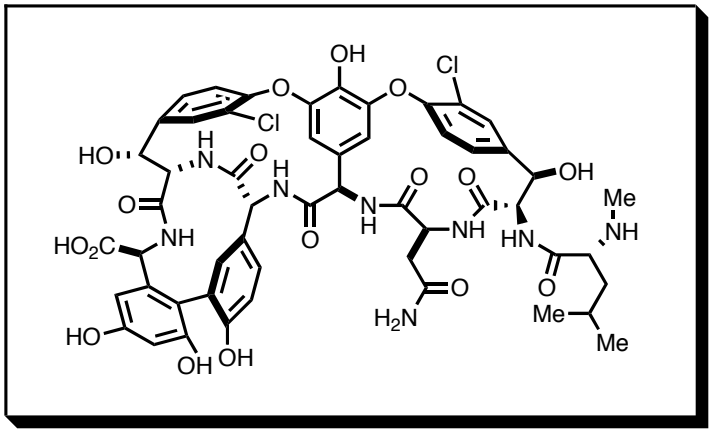
86% yield

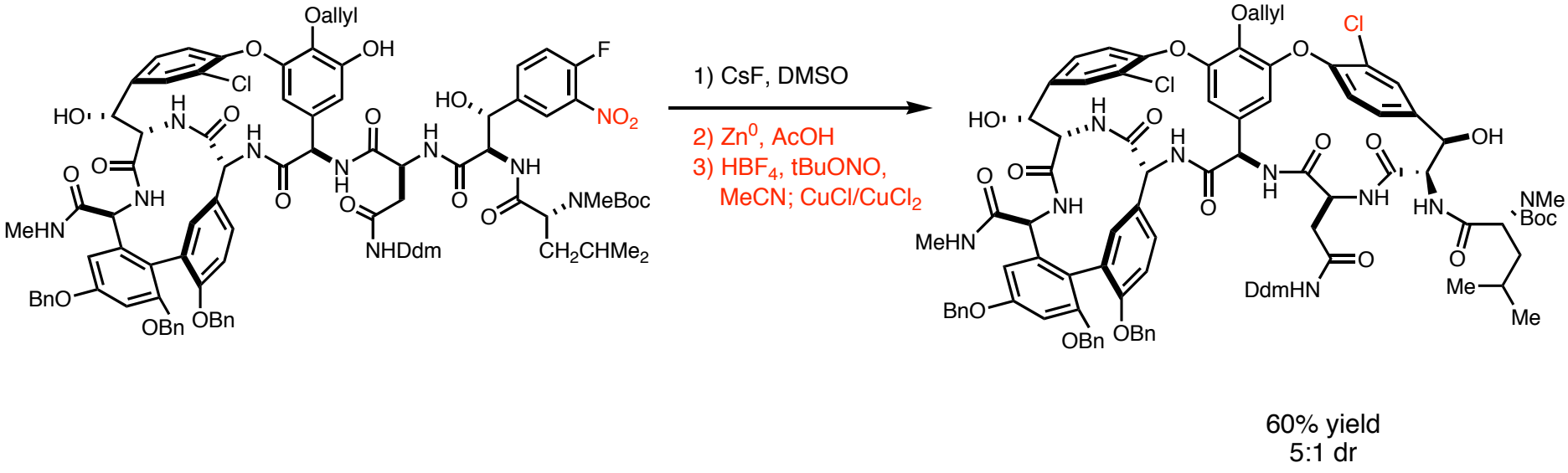
For synthesis of tripeptide, see Nicolaou *Classics II*, p. 290



Synthesis of the Right Macrocycle

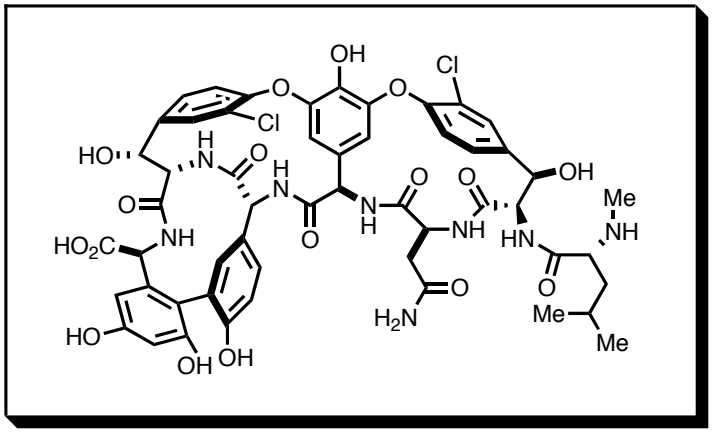
- Closure of the second macrocycle proceeds with the desired atropdiastereoselectivity

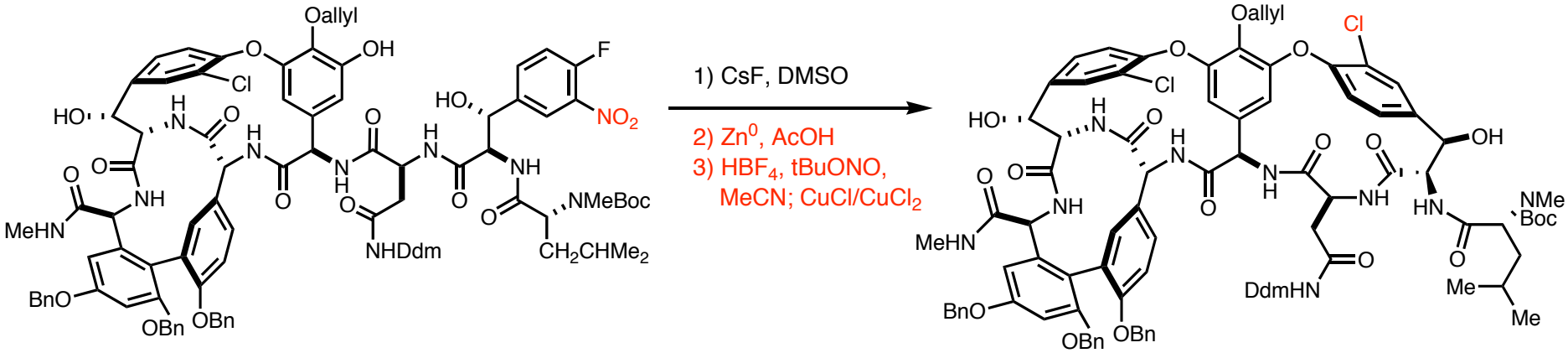




Synthesis of the Right Macrocycle

- Closure of the second macrocycle proceeds with the desired atropdiastereoselectivity





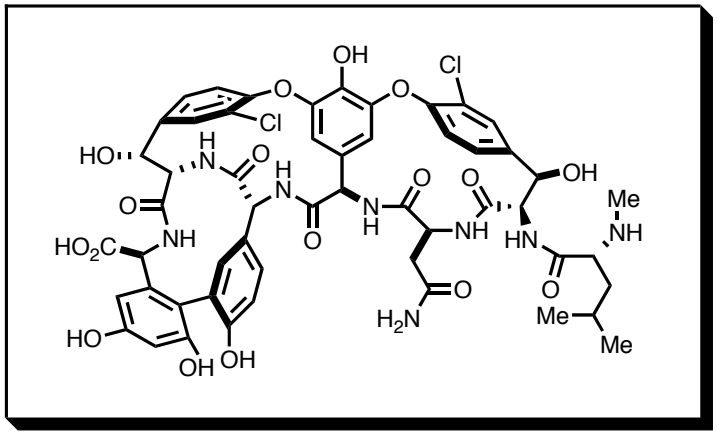
60% yield
5:1 dr

Mechanism for Sandmeyer reaction not fully known, but may be as follows:

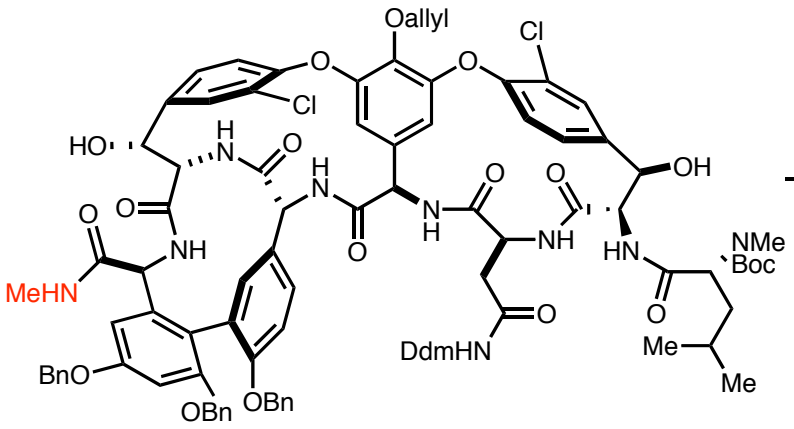
$ArN_2^+ X^- + CuX \longrightarrow Ar\bullet + N_2 + CuX_2$

$Ar\bullet + CuX_2 \longrightarrow ArX + CuX$

Completion of Vancomycin

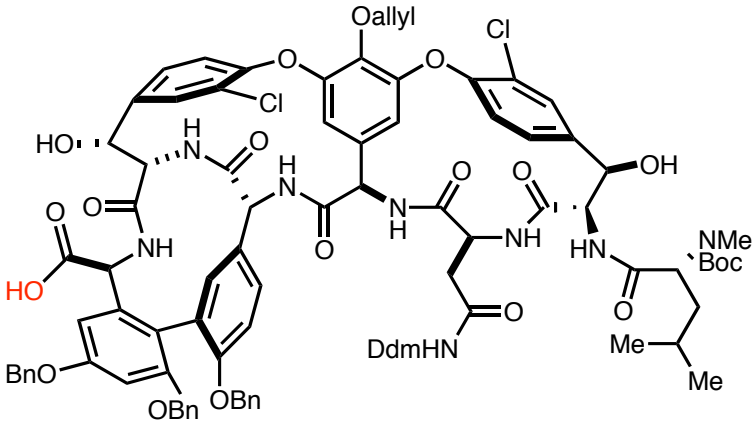


- An unusual mild deprotection reveals a carboxylic acid



1) N_2O_4, NaOAc

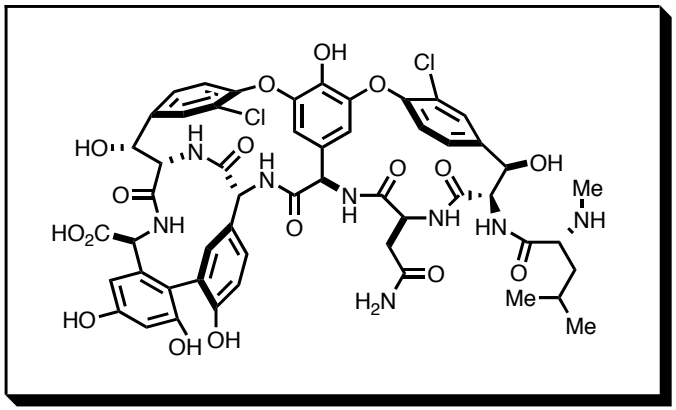
2) H_2O_2, LiOH



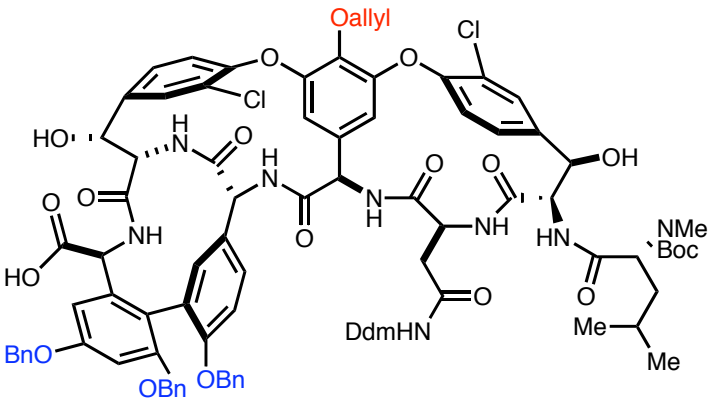
68% yield

- Nitrosation in the presence of seven amide functionalities

Completion of Vancomycin



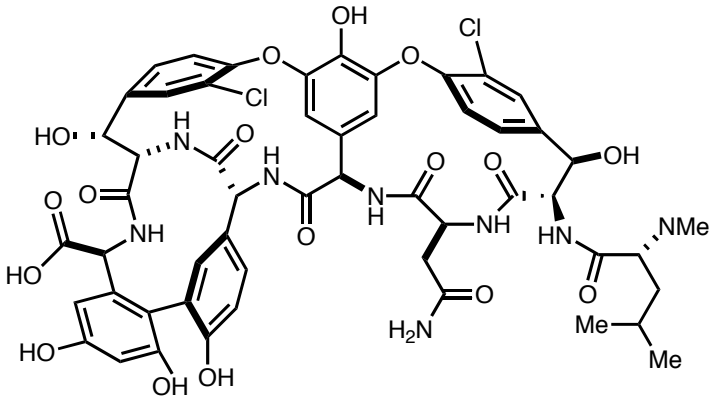
- Final deprotection proves uneventful



1) $Pd(PPh_3)_4$

2) Pd/C, EtOH, 1,4-cyclohexadiene

3) TFA, DMS, CH_2Cl_2



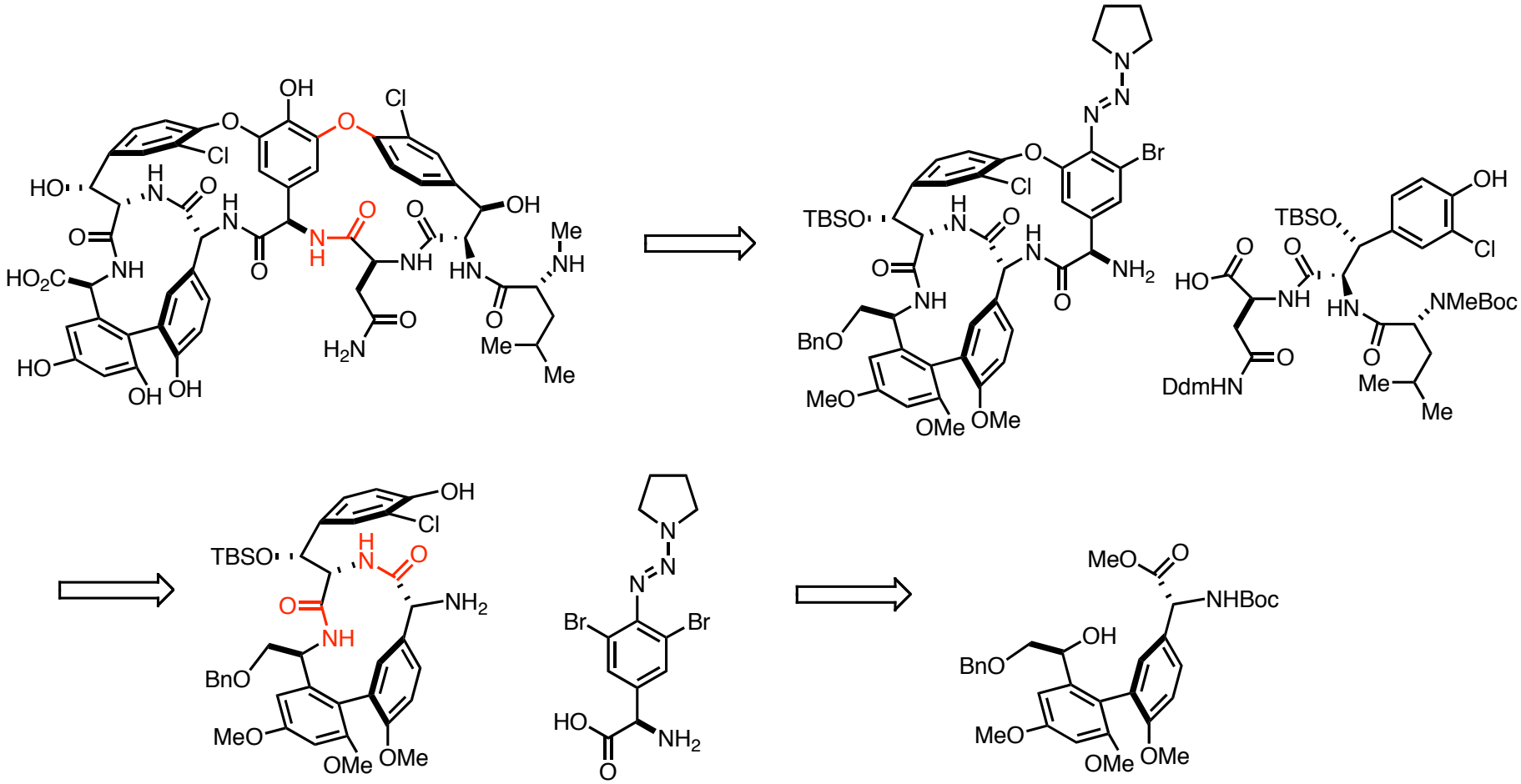
62% yield

- Completion of vancomycin aglycon in 40 linear steps

Evans, Wood, Trotter, Richardson, Barrow, Katz *ACIEE*, **1998**, 2700

The Nicolaou Design

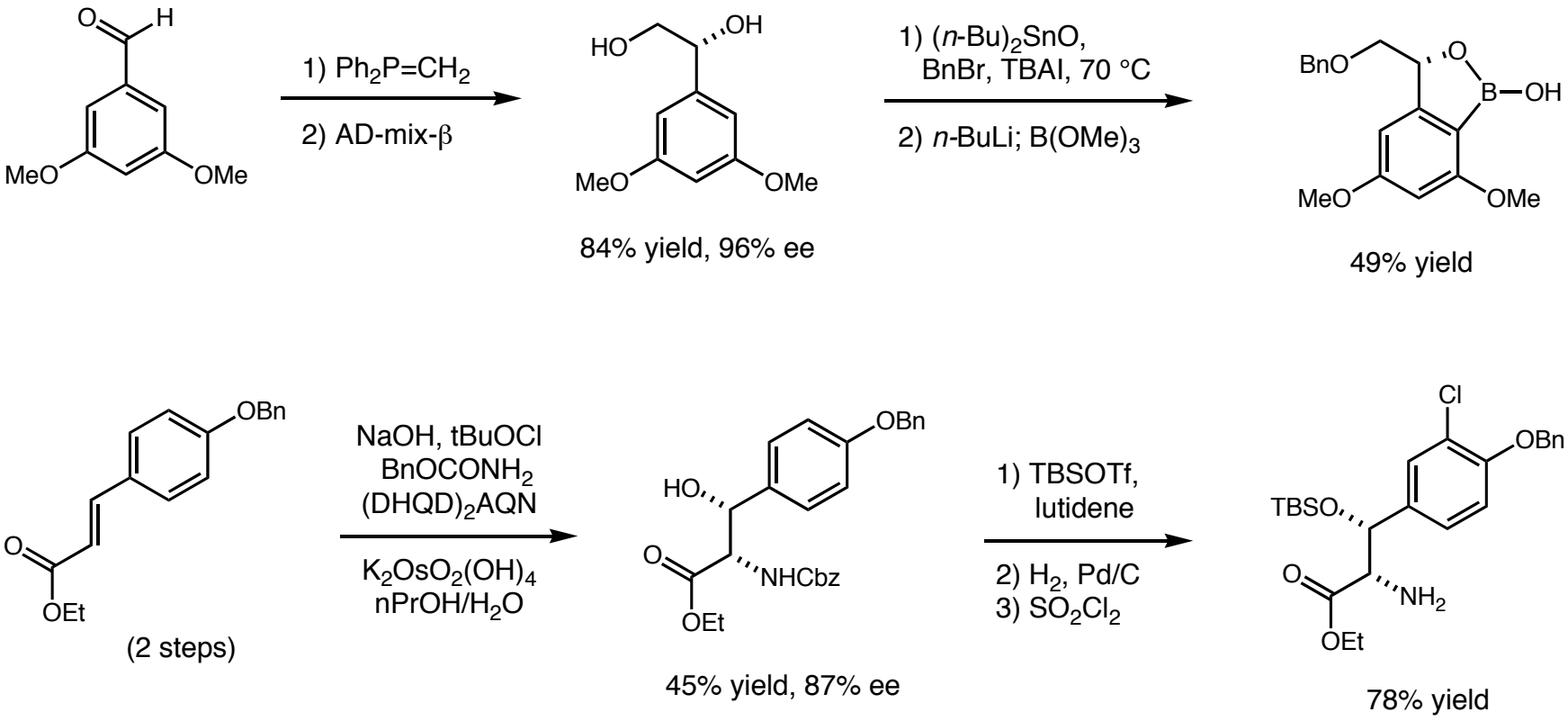
- Sharpless asymmetric catalysis will be used to create most amino acid stereocenters



- Atropdiastereoselctivity left unaddressed in the design

Dihydroxylation/Aminohydroxylation Based Approach

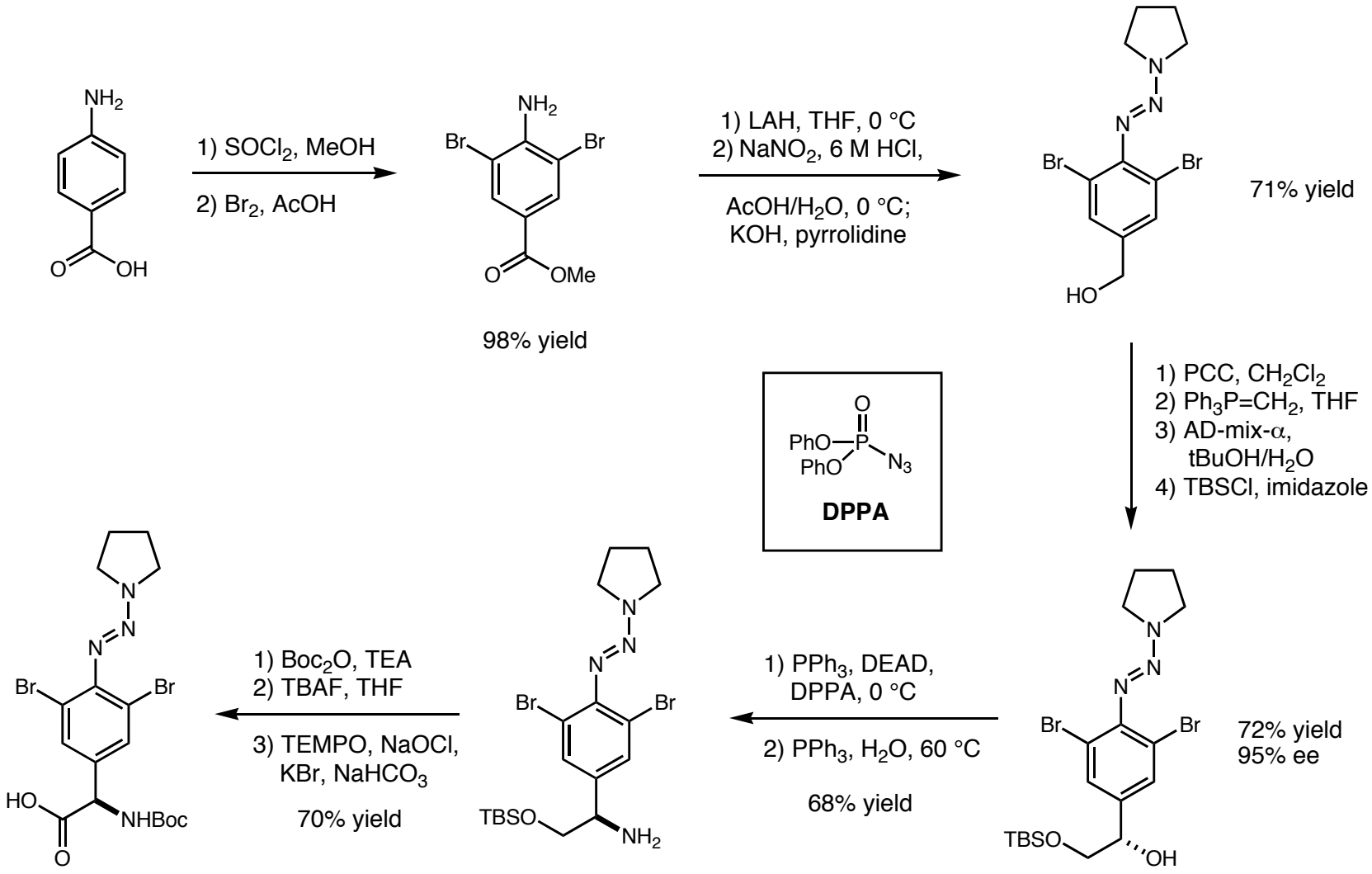
■ Sharpless methodology used to create aryl amino acid stereocenters



■ Enantioenrichment attained through amino acid coupling

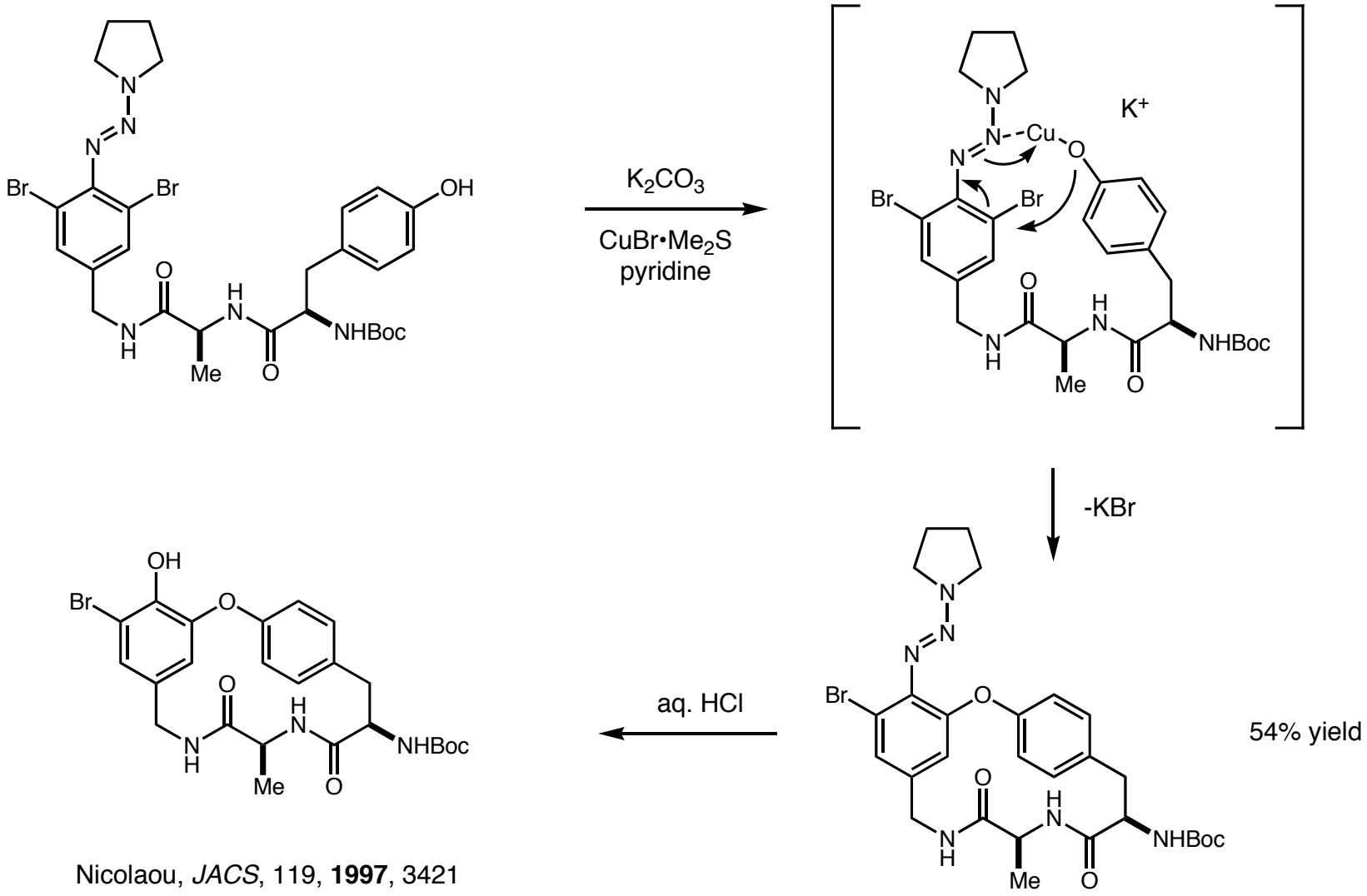
Dihydroxylation/Aminohydroxylation Based Approach

- As in the Evans synthesis, creating the central fragment is challenging



Nicolaou's Triazene-Driven Ether Synthesis

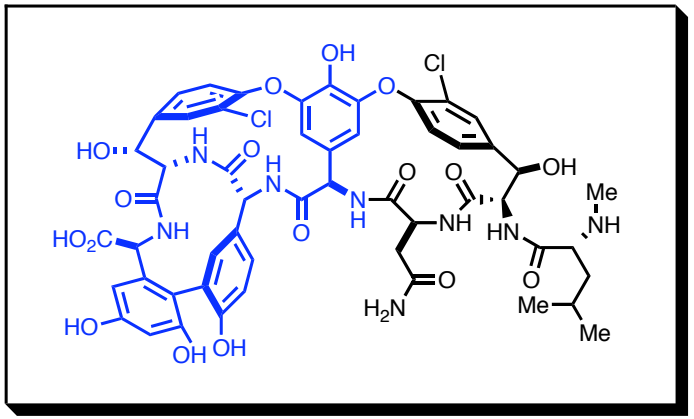
■ Triazene serves to activate aryl ring for S_NAr and acts as functional handle for phenol

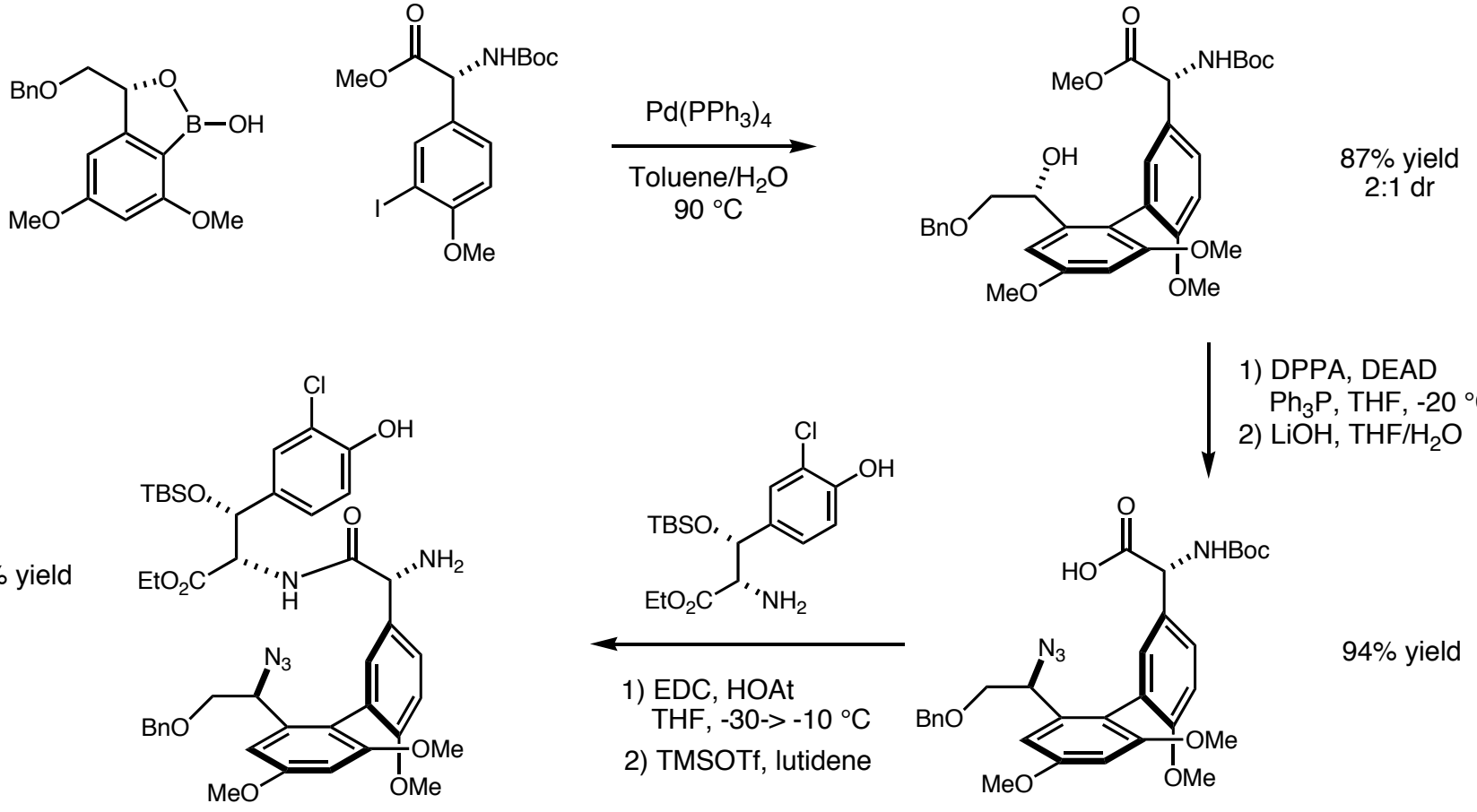


Nicolaou, *JACS*, 119, **1997**, 3421

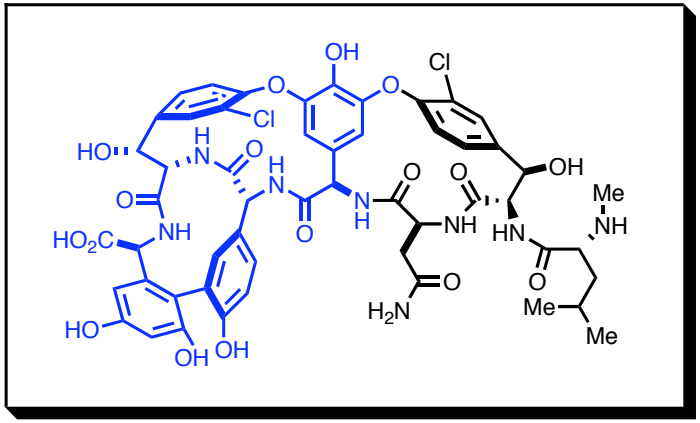
Approach to the Left Macrocycle

- A Suzuki coupling builds the biaryl bond

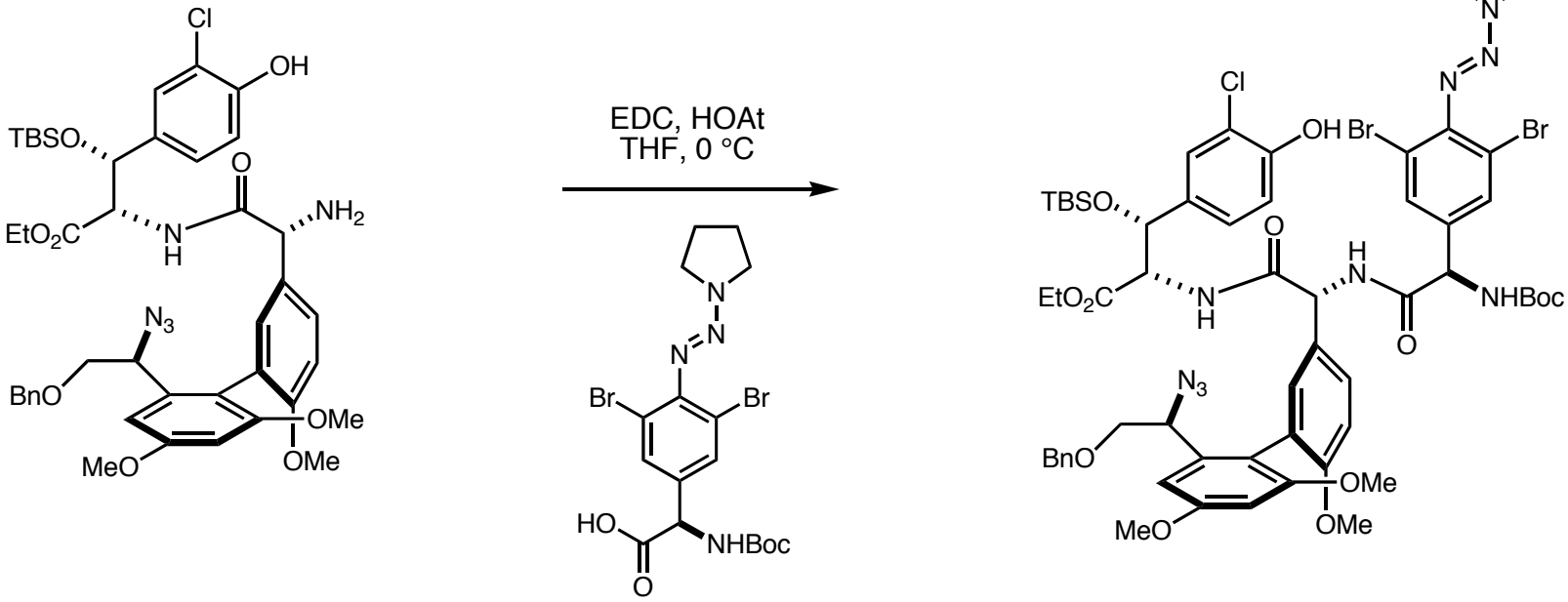




Approach to the Left Macrocycle

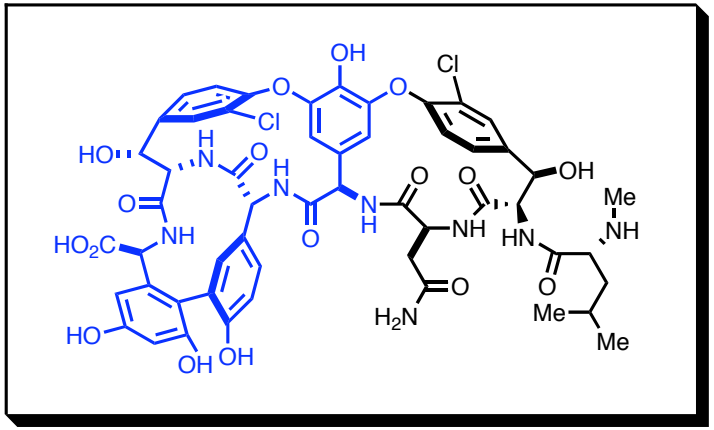


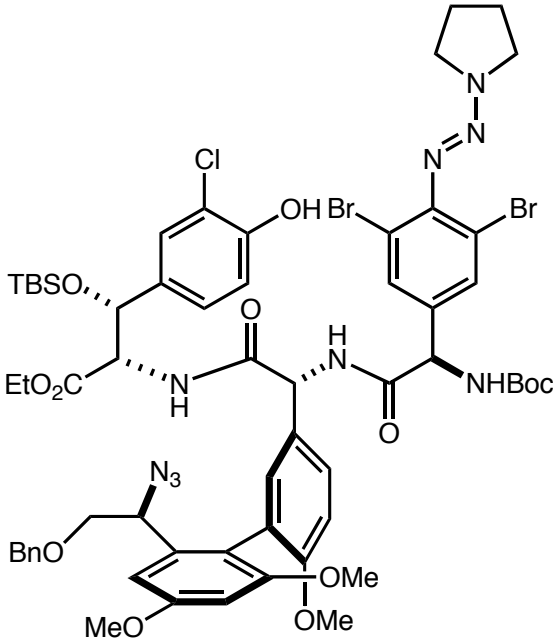
- Peptide coupling sets up biaryl ether synthesis



Closure of the Left Macrocycle

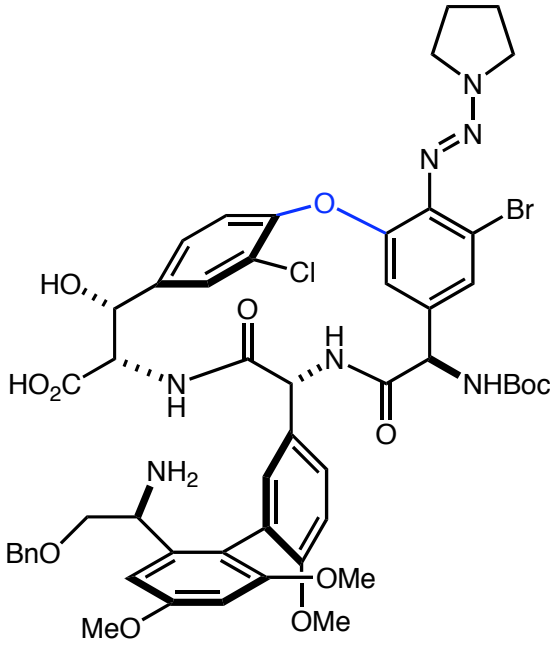
- Ether formation proceeds without atropdiastereoselectivity





1) CuBr, K_2CO_3
MeCN, 82 °C

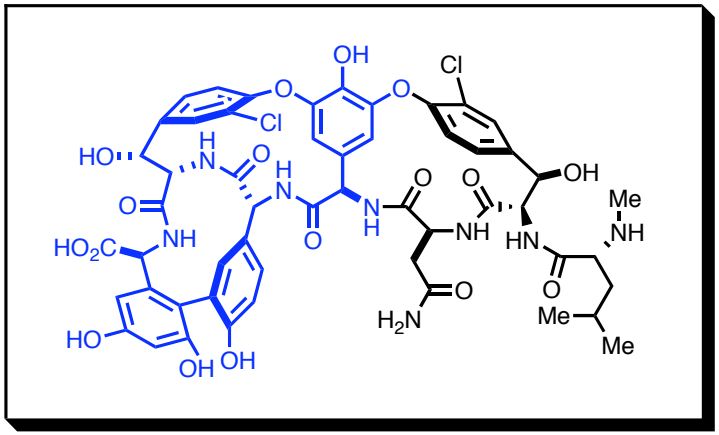
2) TBAF, -15 °C
3) Et_3P, $MeCN/H_2O$
4) LiOH, THF/H_2O

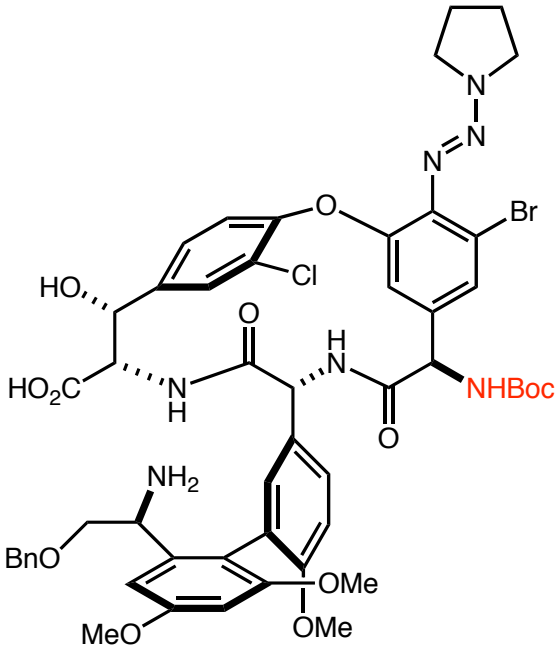


46% yield
1:1 dr

Amide Formation and Deprotection

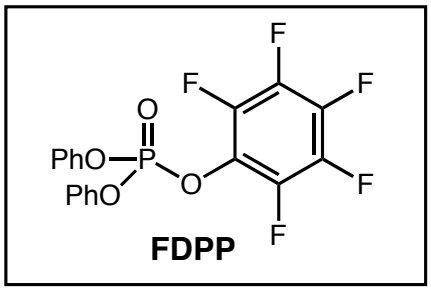
- Completion of the left half achieved via lactamization

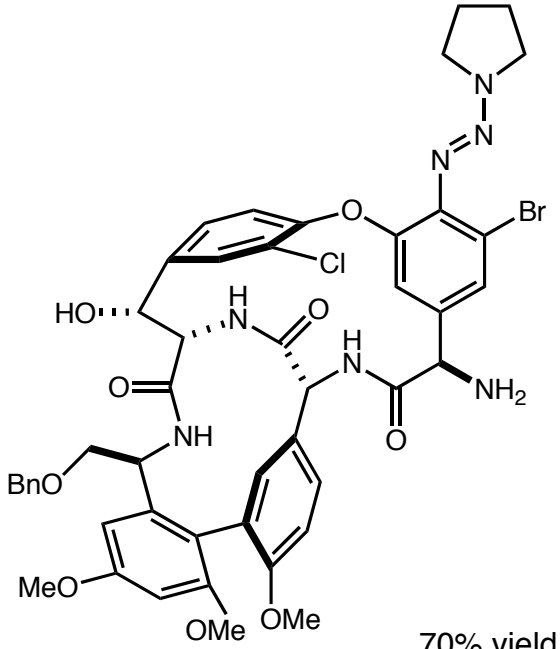




1) FDPP, DIPEA
DMF, 0-> 25 °C

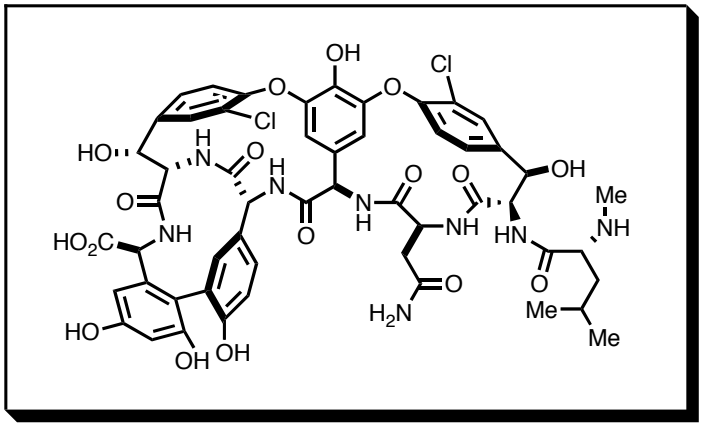
2) TBSOTf,
lutidene
3) TMSOTf,
lutidene



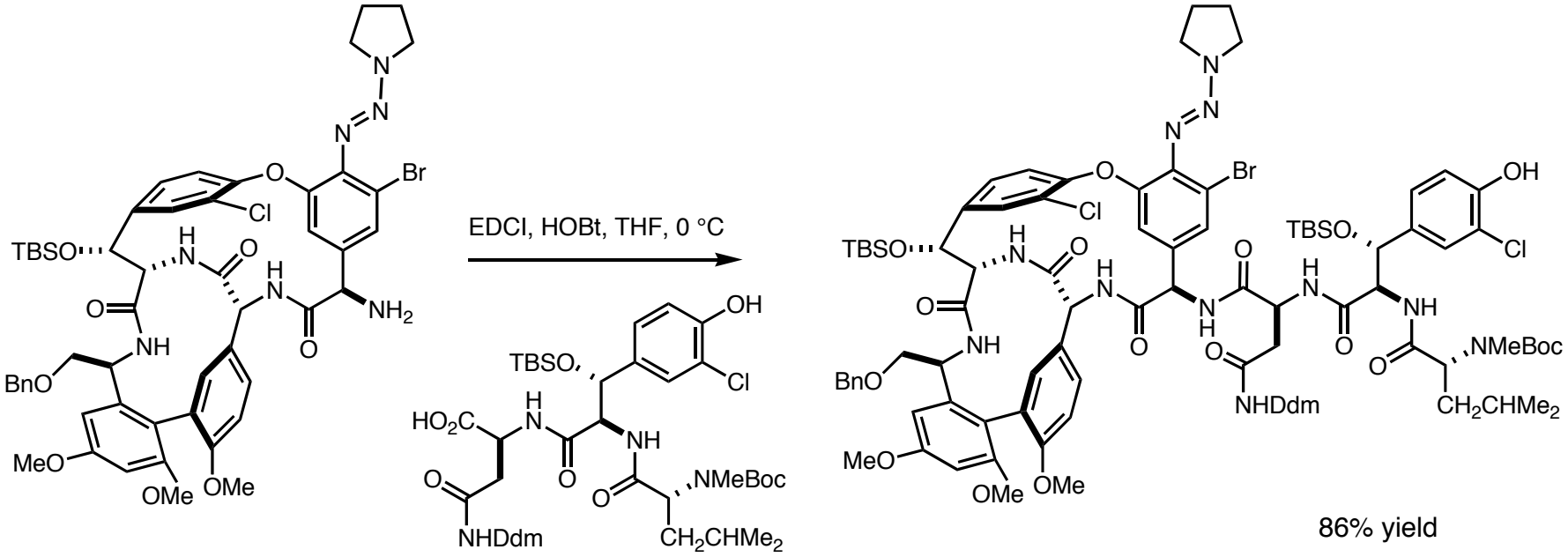


70% yield

Synthesis of the Right Macrocycle

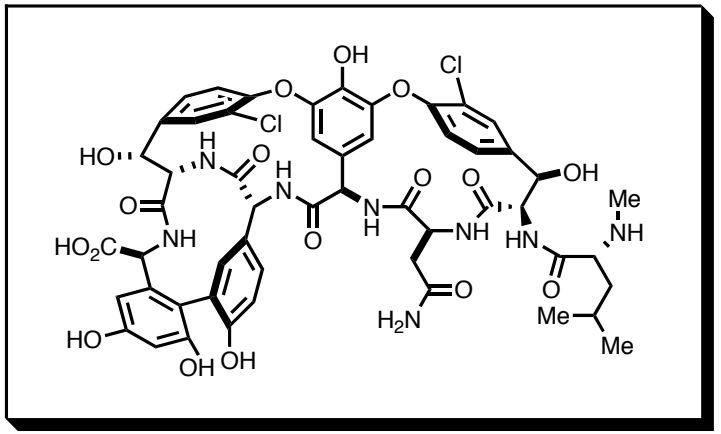


- Fragment coupling completes the peptide chain

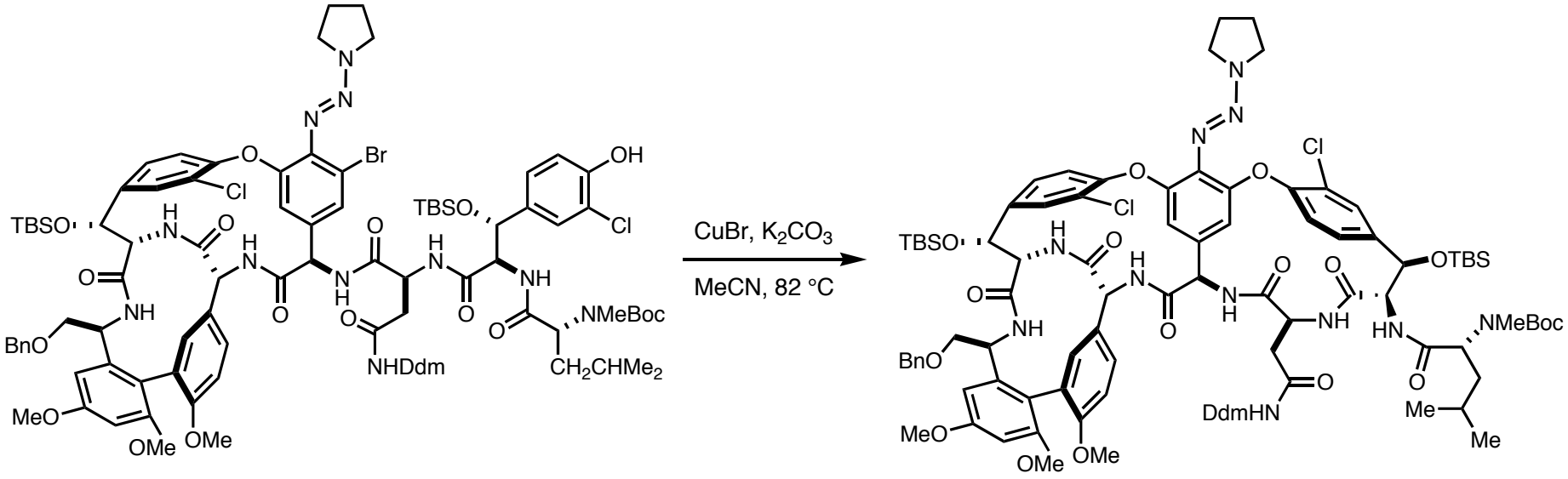


For synthesis of tripeptide, see Nicolaou *Classics II*, p. 268

Synthesis of the Right Macrocycle



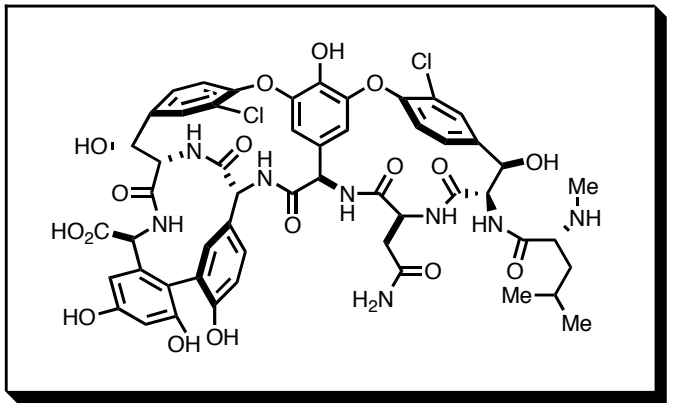
- Triazene-activated ether formation favors unnatural atropisomer; thermal equilibration is possible

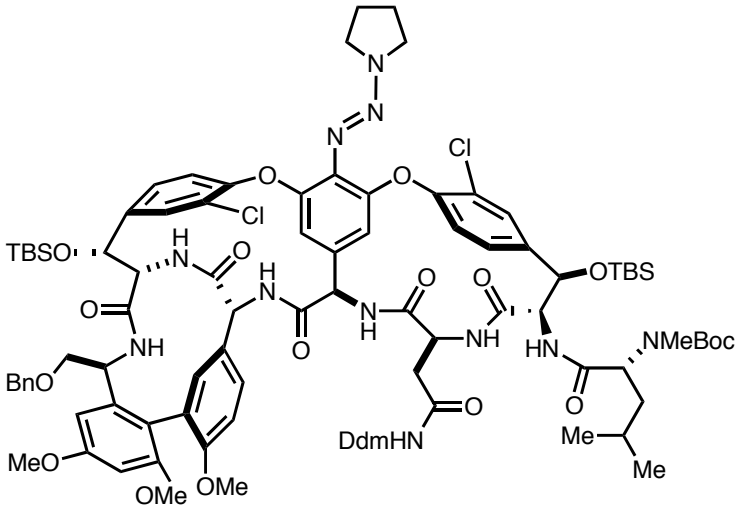


- Heating unnatural isomer at 140 °C provides 2:3 mix in 80-85% yield

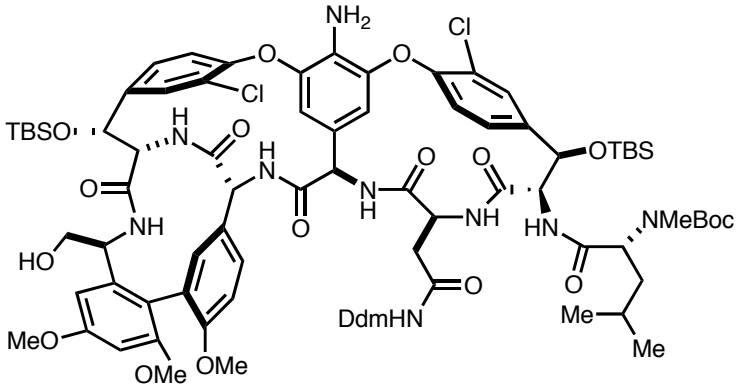
Final Functionalizations

- Triazene proves difficult to functionalize as phenol



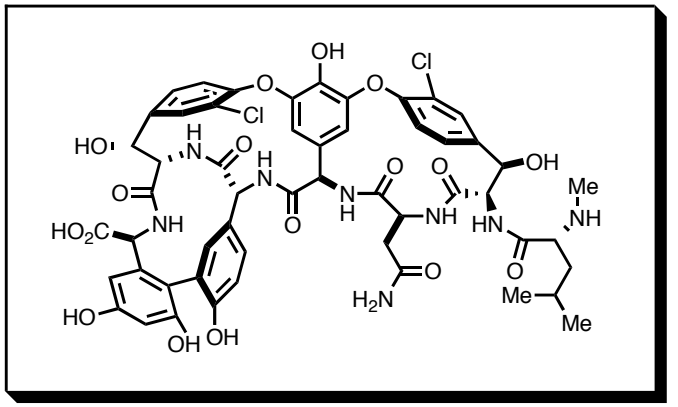


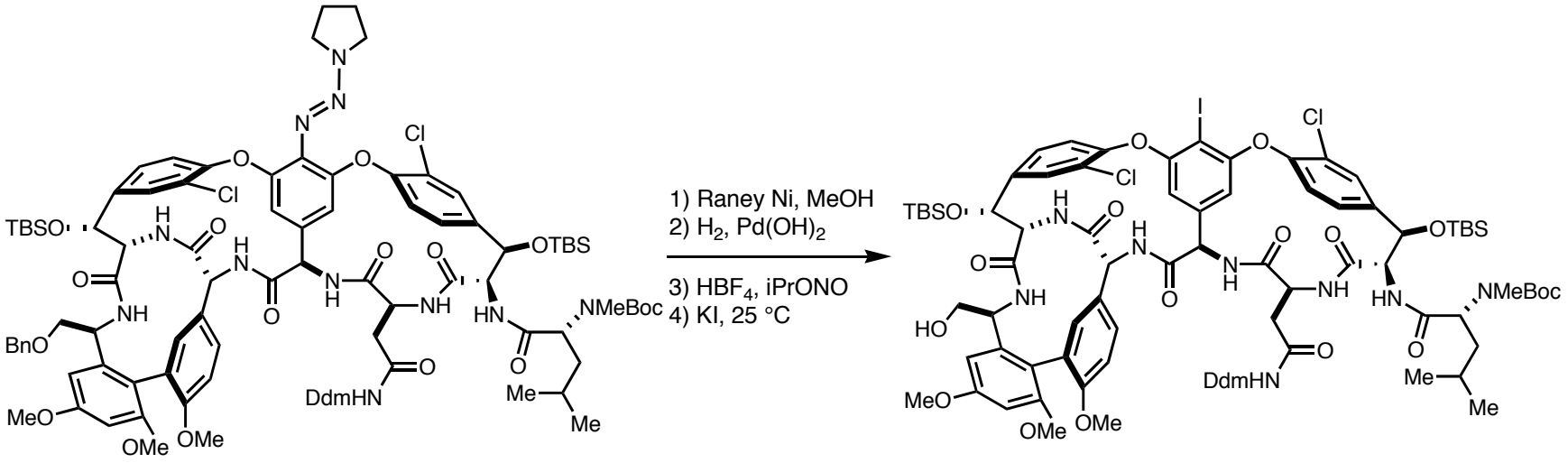
1) Raney Ni, MeOH
2) H_2, $Pd(OH)_2$



Final Functionalizations

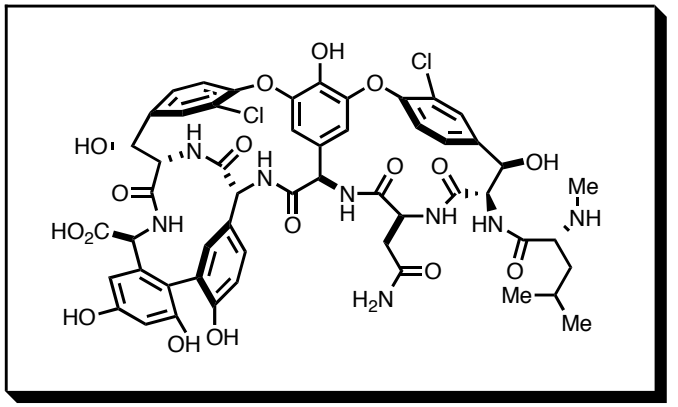
- Triazene proves difficult to functionalize as phenol

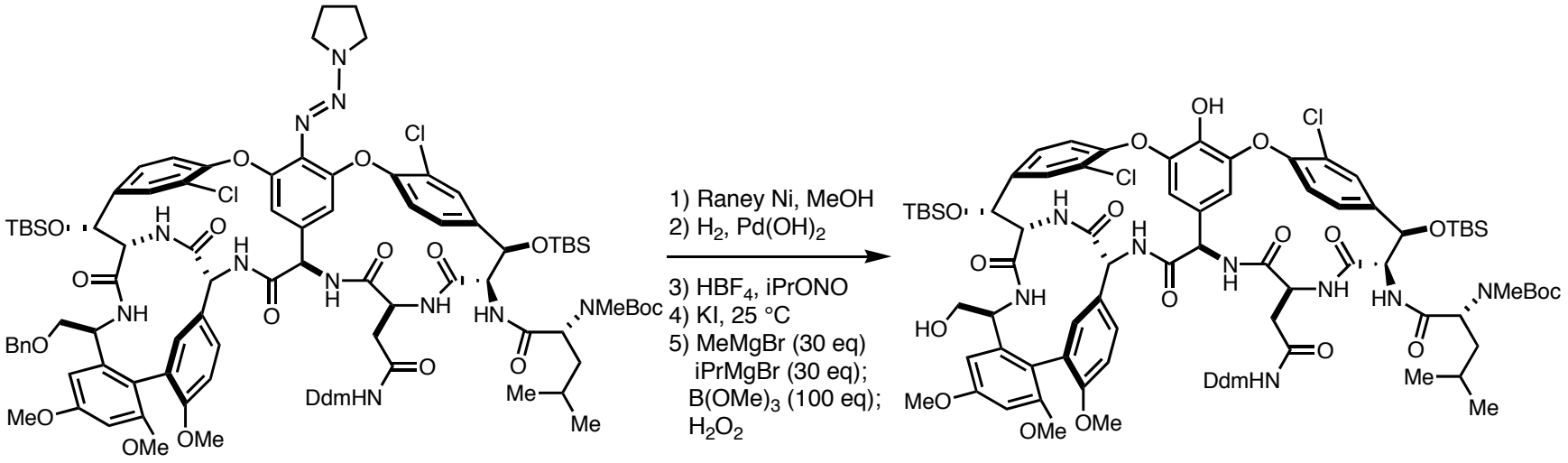




Final Functionalizations

- Triazene proves difficult to functionalize as phenol

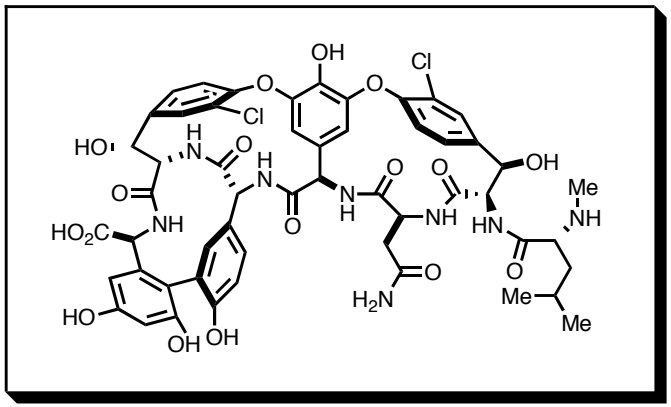


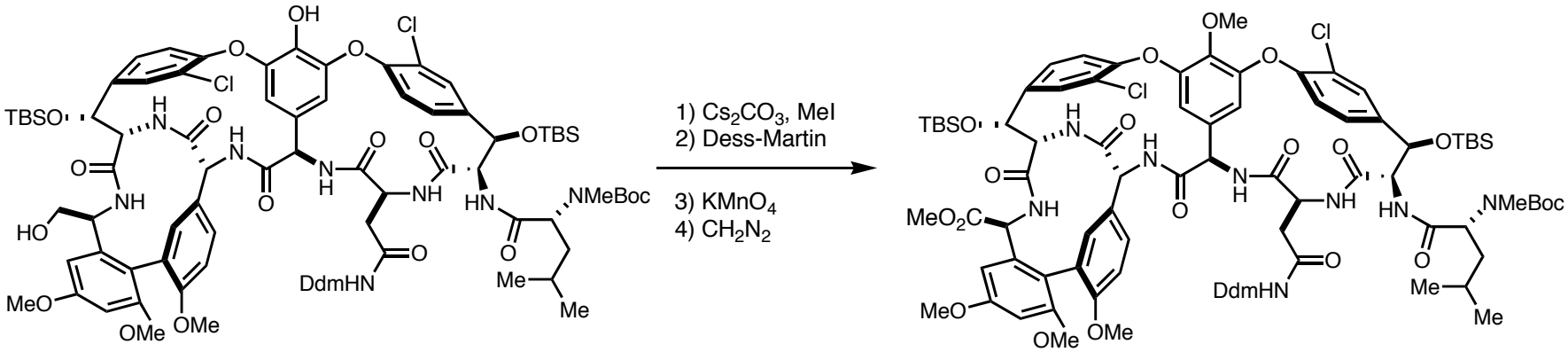


32% yield

Final Functionalizations

- Phenol protection and introduction of methyl ester

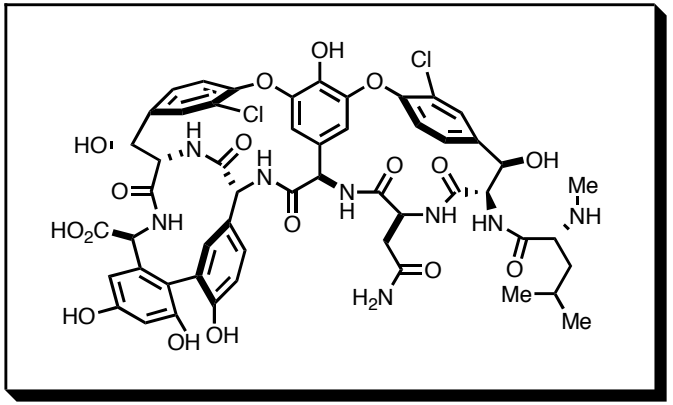


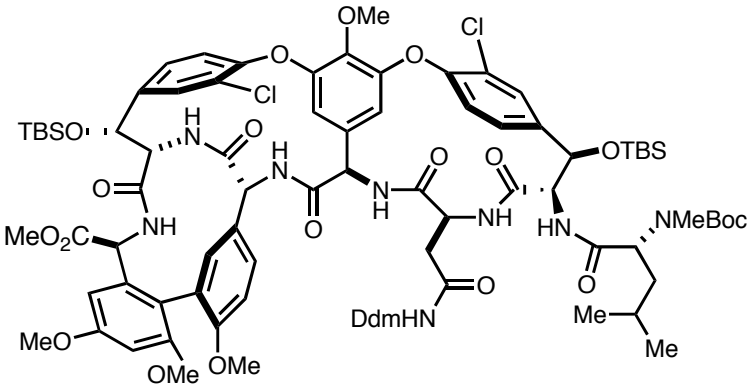


74% yield

Completion of the Natural Product

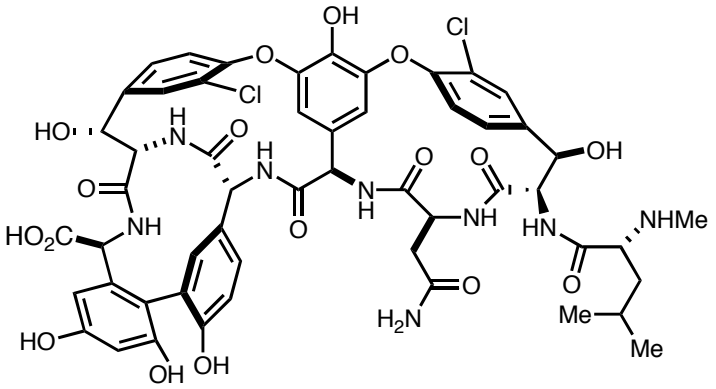
- Desilylation is followed by global deprotection





1) HF•pyr, pyridine

2) $AlBr_3$, EtSH

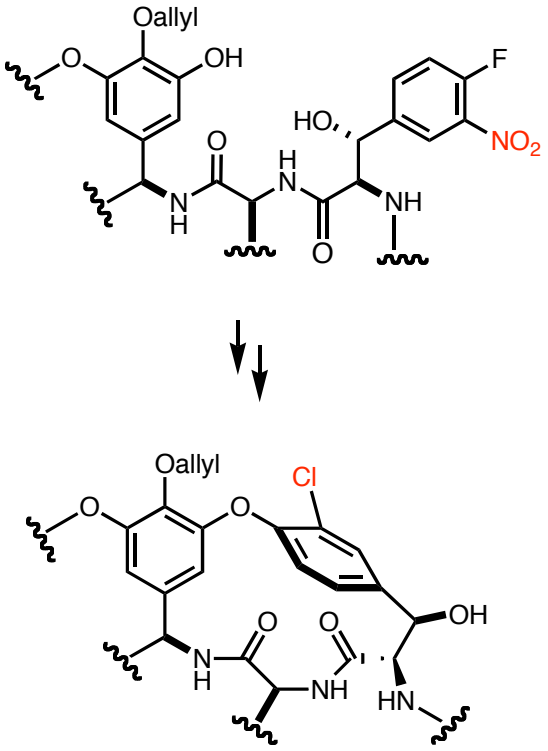


62% yield

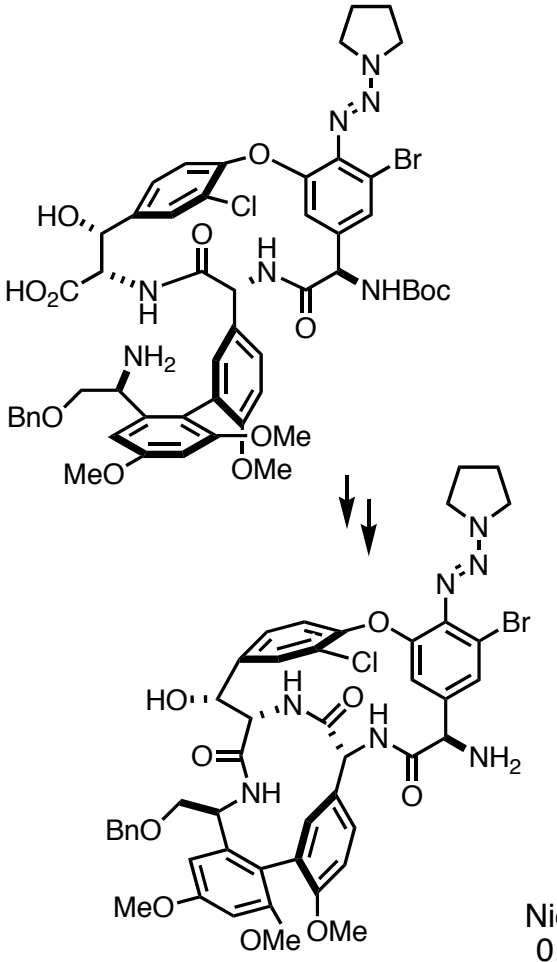
Nicolaou, Takayanagi, Jain, Natarajan, Koumbis, Bando, Ramanjulu, *ACIEE*, **1998**, 2717

Conclusions

- While synthesis is not an issue in the supply of Vancomycin, fascinating chemistry has been discovered in pursuit of an expedient synthesis



Evans - 36 steps
0.2% overall yield
84% average



Nicolaou - 36 steps
0.13% overall yield
82% average

- Control over the wide variety of stereocenters in the context of a complex synthesis is most notable