

Synthesis of Several Members of the Antitumor Antibacterial Tetrahydroisoquinoline Family

ACS Literature Group Meeting
December 7, 2005

Biological Activity



Ecteinascidin 743

Isolated from the marine tunicate *Ecteinascidia turbinata* (1g / 1 ton tunicate)

Highly potent antitumor agent

Antiproliferative activity greater than that of taxol

Forms a covalent bond with exocyclic 2-amino group of guanine in DNA

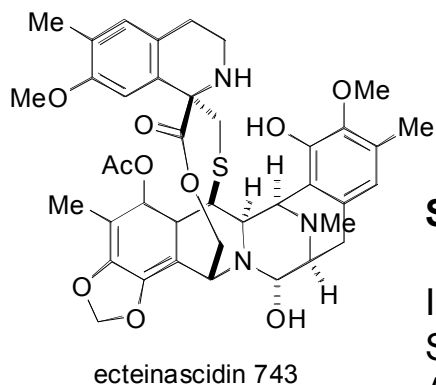
Presence of FG subunit very important to antitumor activity, analogues w/o 10-50 times less active

Currently in Phase II/III trials for ovarian, endometrial, breast cancer, and several types of sarcoma

Total synthesis by Corey in 1996, Fukuyama in 2002.

Synthesized by Pharma Mar in Spain from cyanosafracin B

Synthetic Approaches from Williams, Kubo, Danishefsky, Magnus, Liu



Saframycin A

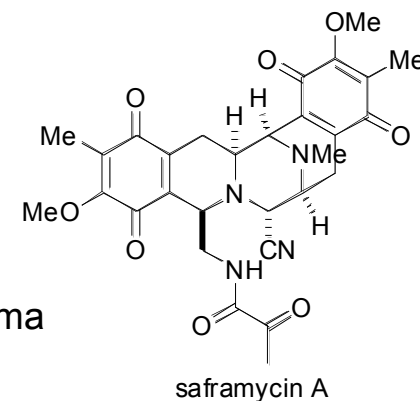
Isolated from *Streptomyces lavendulae* No. 314

Shows strong antitumor activity

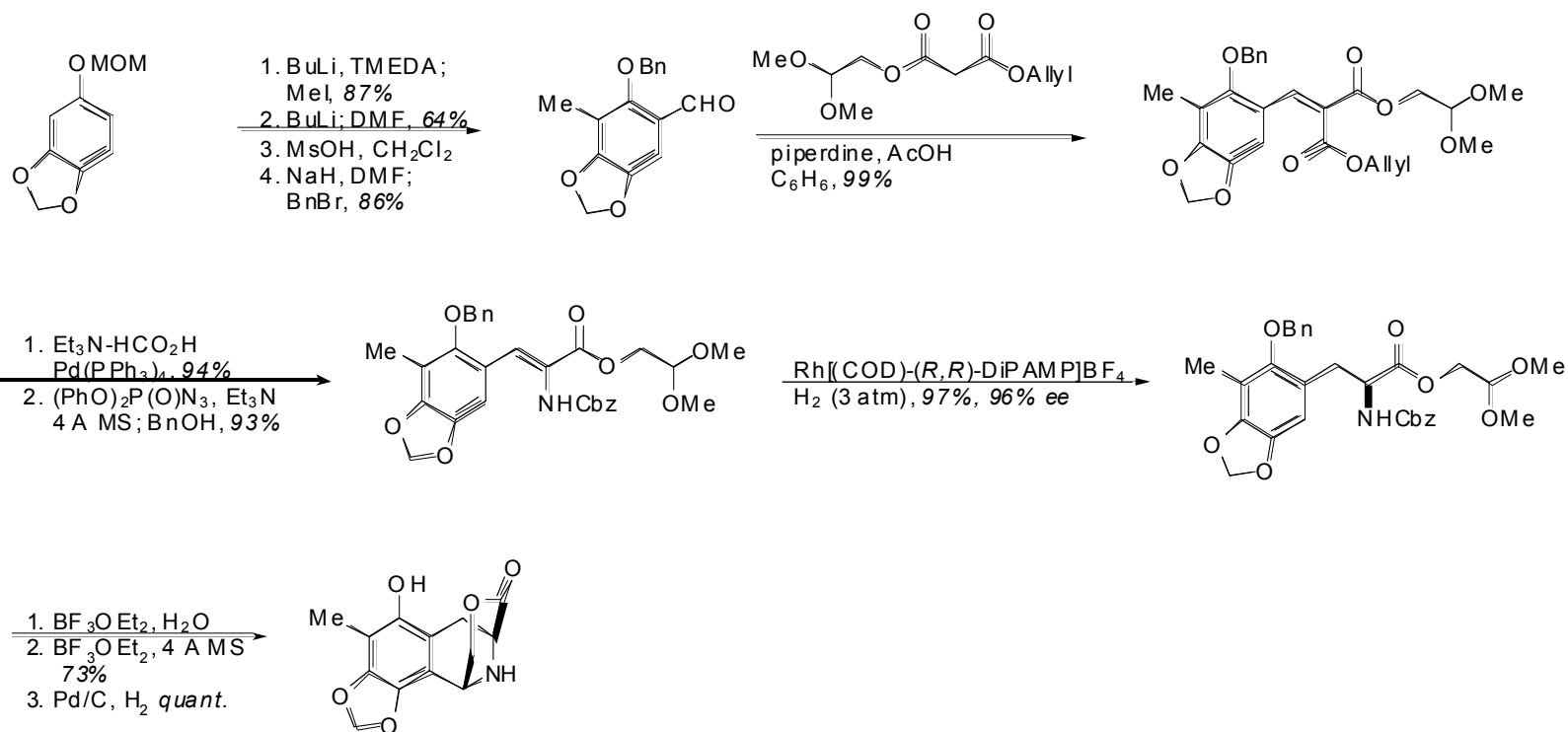
Active against Gram-positive bacteria

Synthesized by several groups, including Myers, Fukuyama

Saito, Corey, Danishefsky and several others

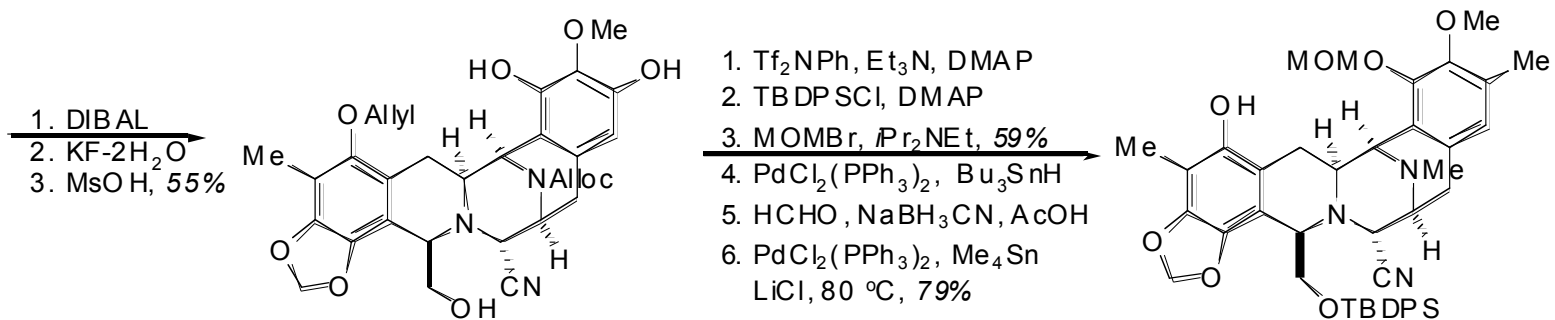
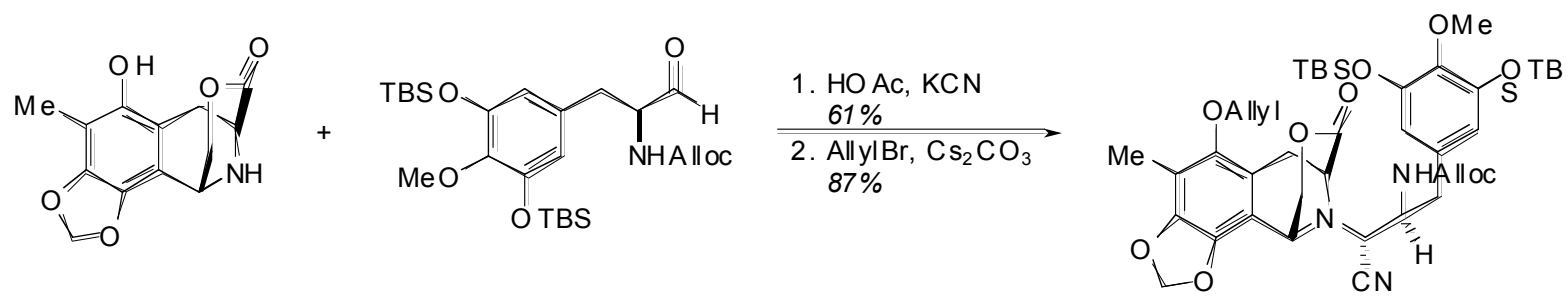


Synthesis of Ecteinascidin 743 Fragment

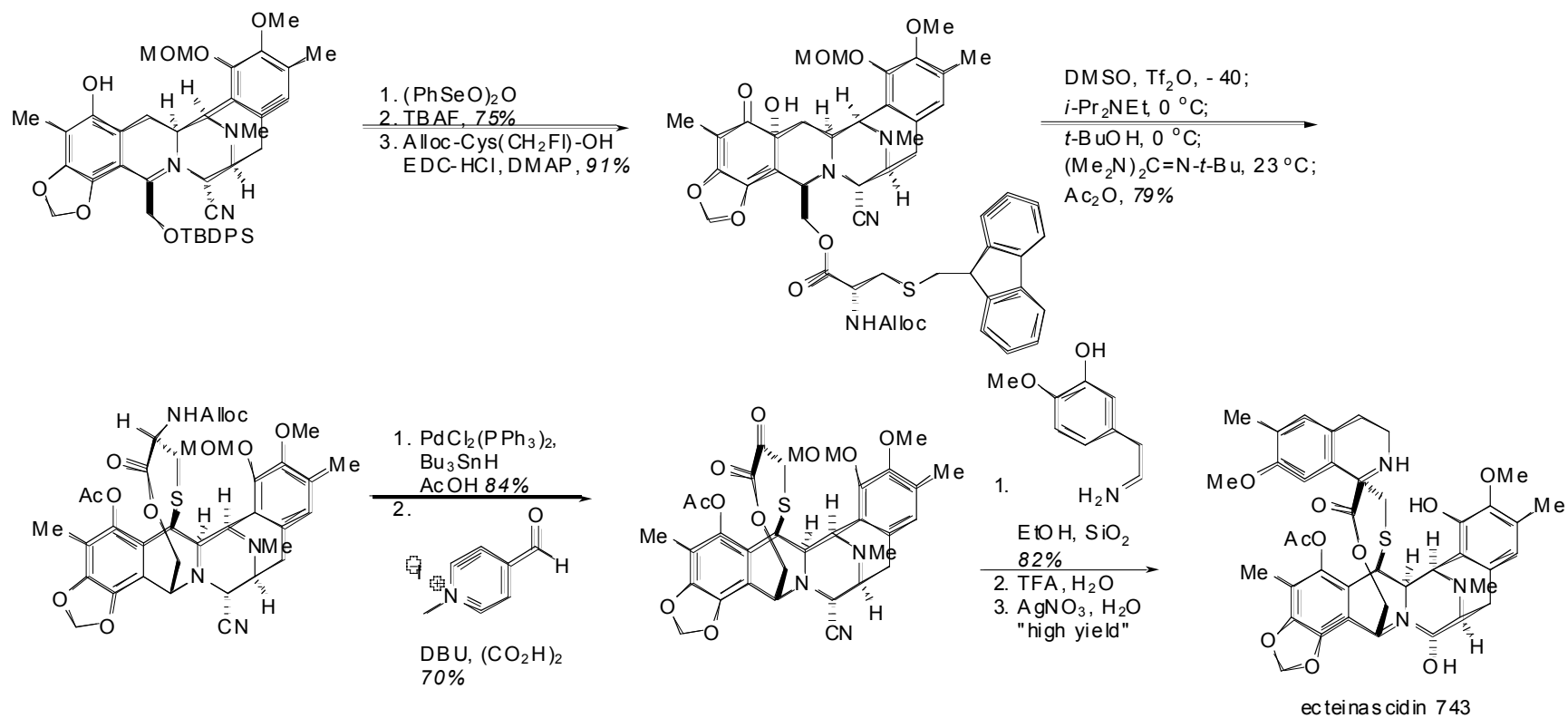


Corey, E. J., Gin, D., Kania, R. *JACS* **1996**, 9202.

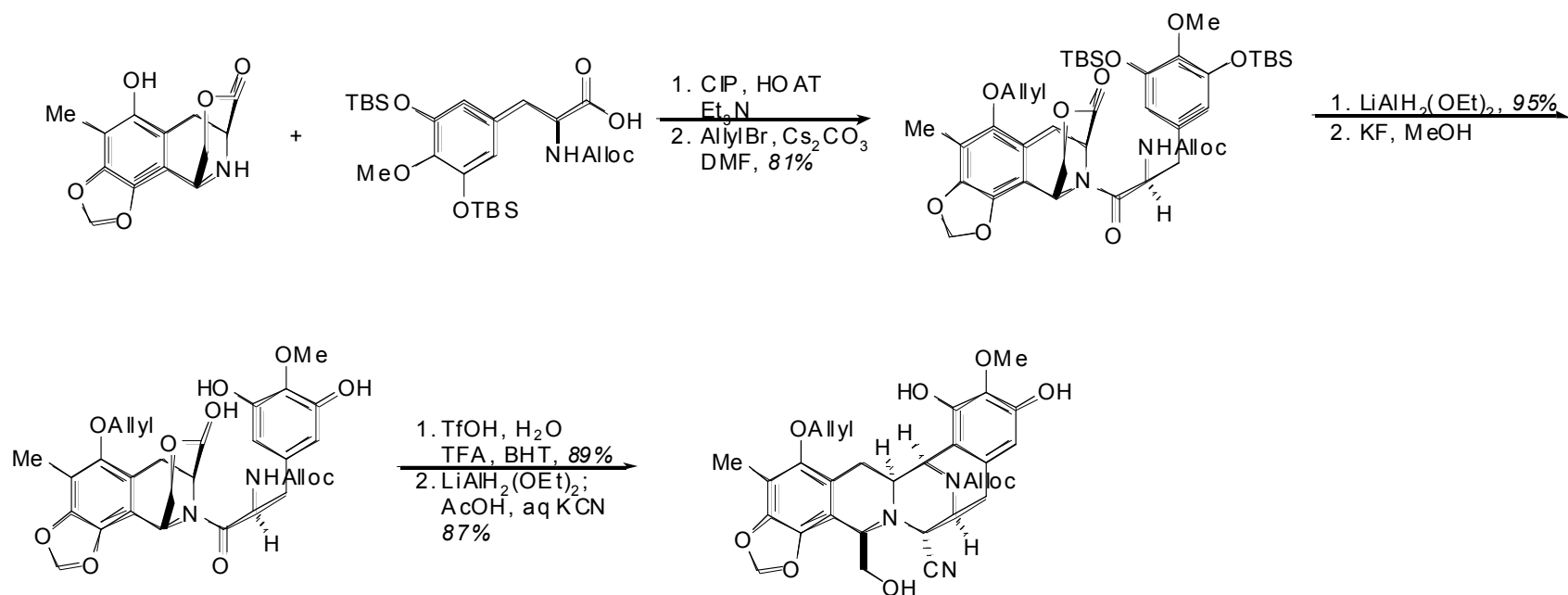
Coupling of Fragments



Completion of Ecteinascidin 743



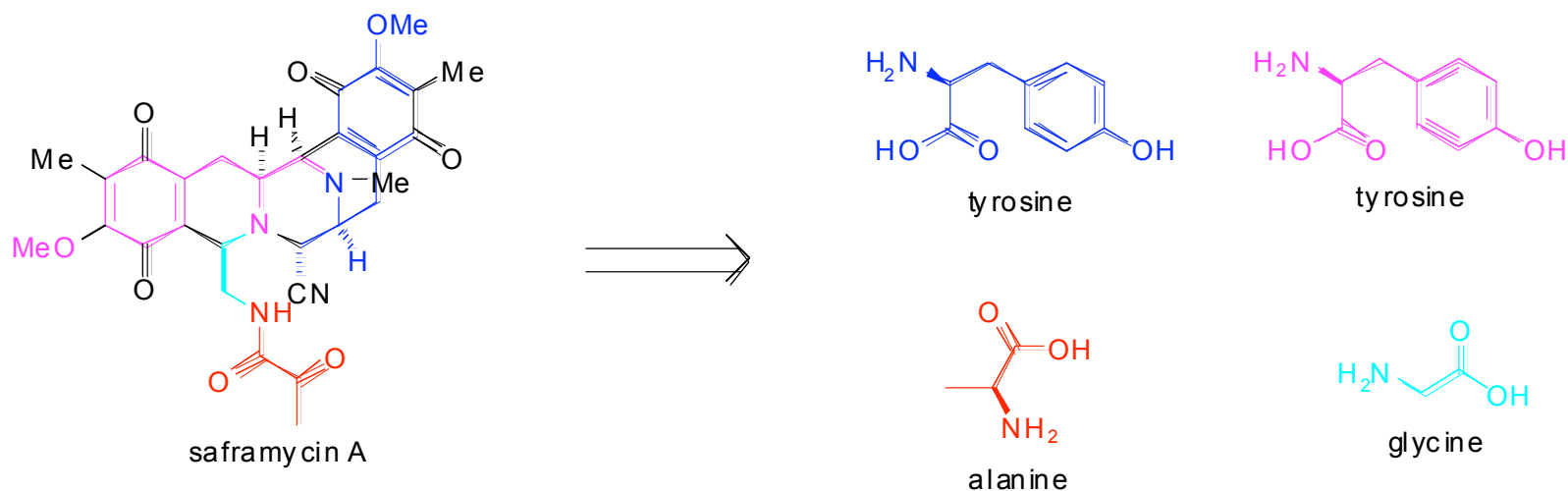
Corey's Improved Route



Corey, E. J., Martinez, E. *OL* **2000**, 993.

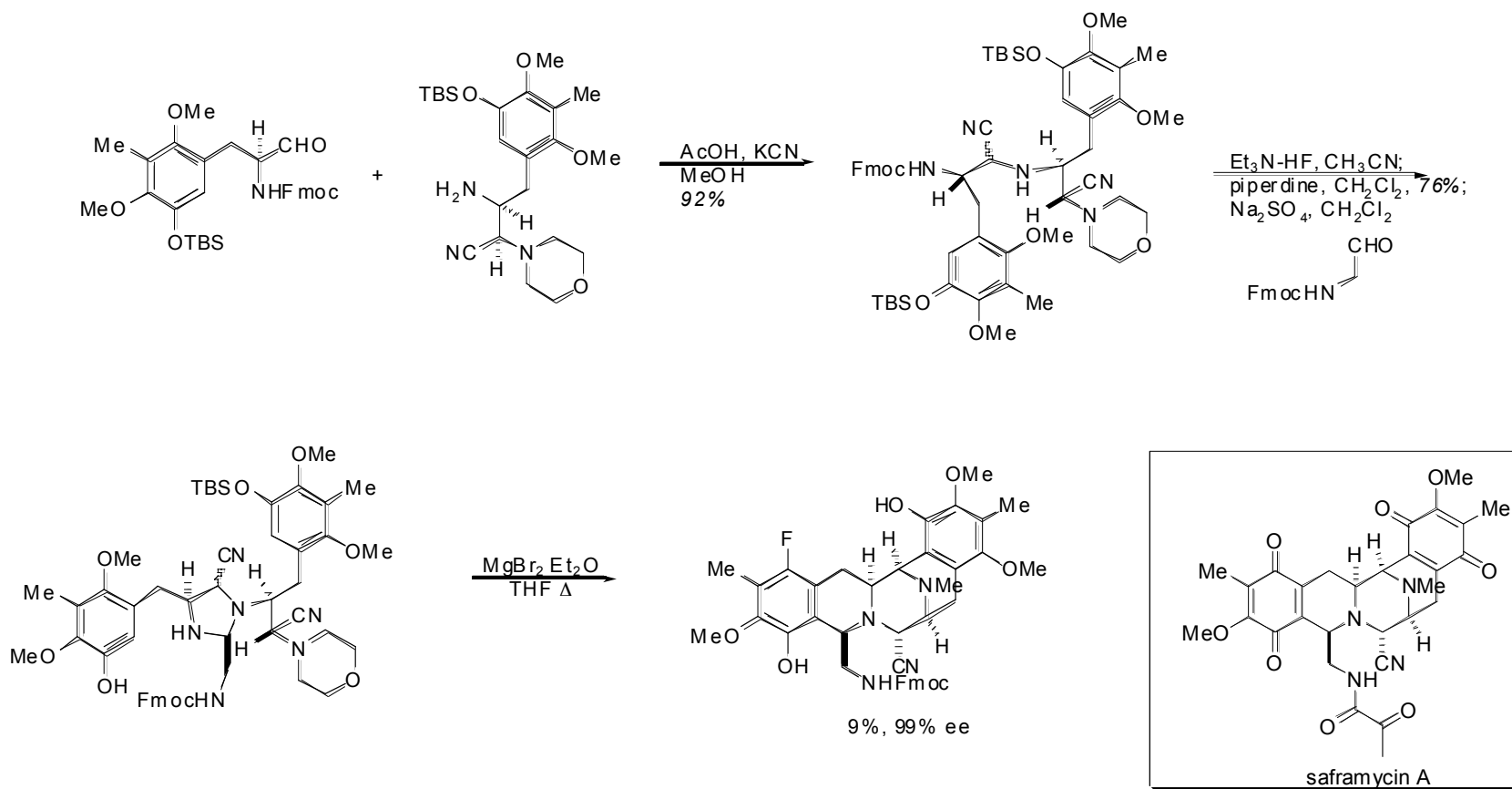
Proposed Biosynthetic Pathway to Saframycin

- Biosynthetic studies have shown that saframycin can be assembled from glycine, alanine, and two equivalents of tyrosine
- After mapping the amino acid precursors onto the structure below, it can be seen that the glycine and tyrosine residues have been reduced to the aldehyde oxidation state during biosynthesis

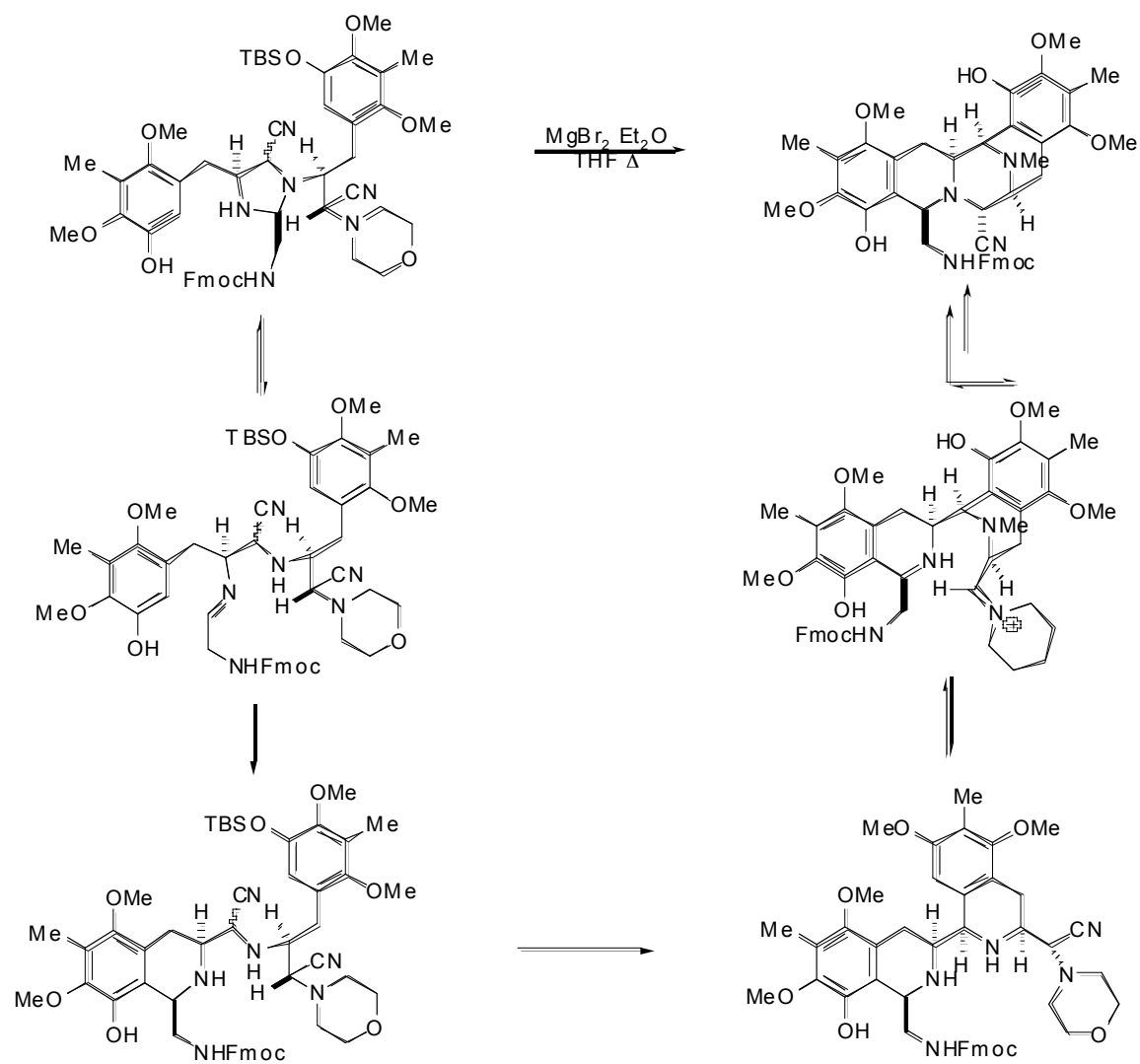


Myers, A. *OL* **2000**, 3019
Myers, A. *JACS* **1999**, 10828

Possible Biosynthetic Route to Saframycin



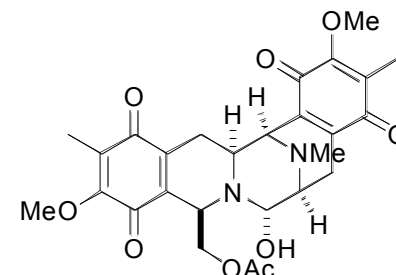
Proposed Pathway of “N-Linked Oligomer” to Saframycin Precursor



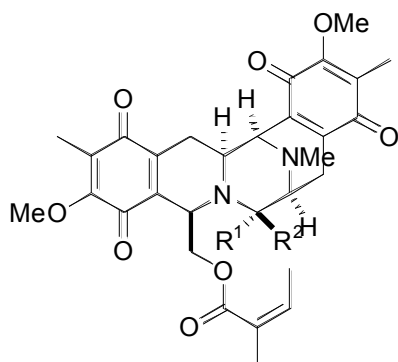
Biological Activity of Renieramycin and Jorumycin

Jorumycin

- Isolated from the mantle and mucus of the pacific nudibranch *Jorunna funebris*
- Activity against NIH 3T3 tumor cells (100% inhibition at 50 ng/mL)
- Cytotoxic (IC₅₀ 12.5 ng/mL) against other cell lines
- Inhibits growth of gram-positive bacteria at conc. < 50 ng/mL



(-)-jorumycin



renieramycin G, R¹ = R² = O
renieramycin E, R¹ = OH, R² = H
renieramycin M, R¹ = CN, R² = H

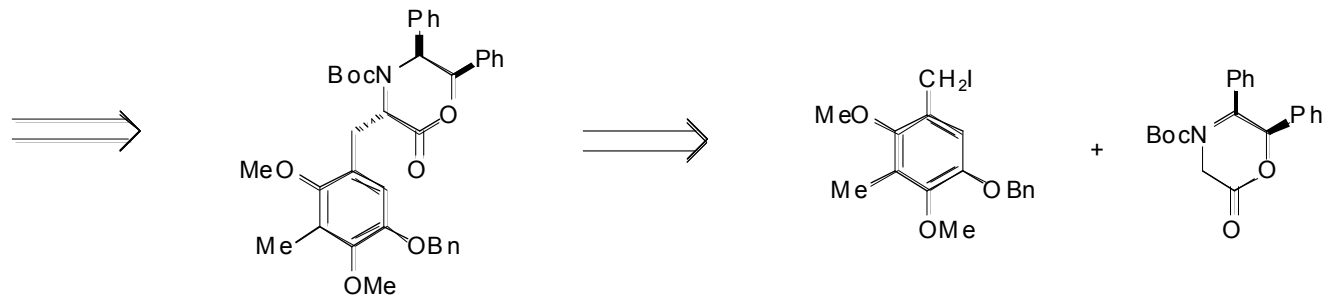
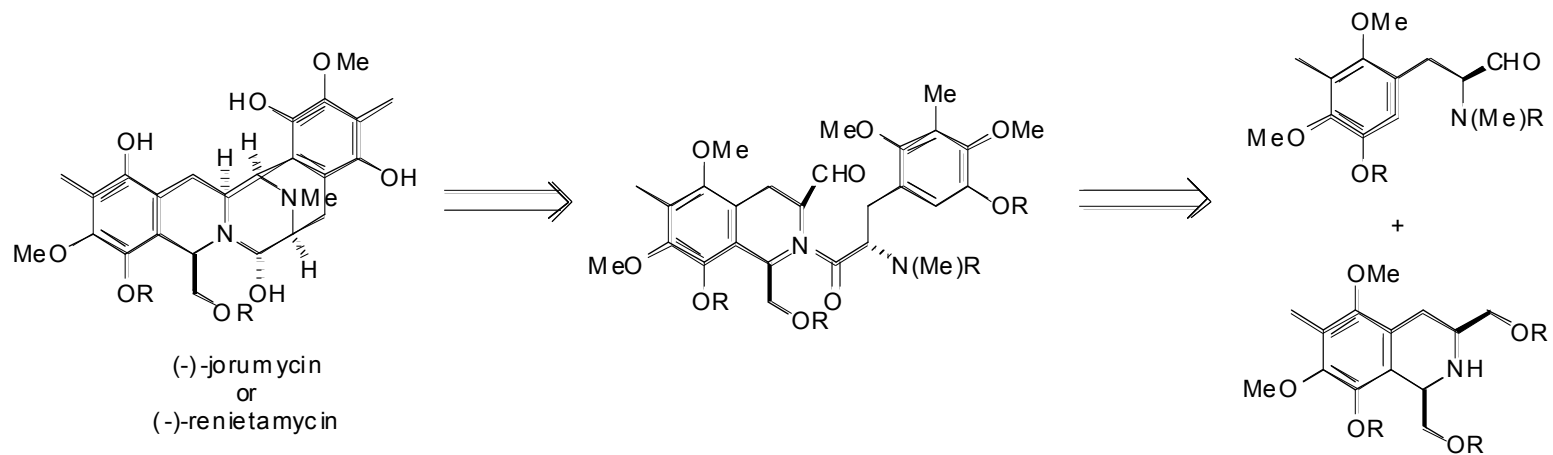
Renieramycin G

Isolated from the marine sponge *Xestospongia caycedoi*
Retains cytotoxicity against human cancer cell lines even though all other members of the family contain carbinolamine or cyano function at C-21 that has been implicated in the formation of covalent bonds to DNA.

Also synthesized by Magnus and Fukuyama

Williams, R. *JACS* **2005**, 12684

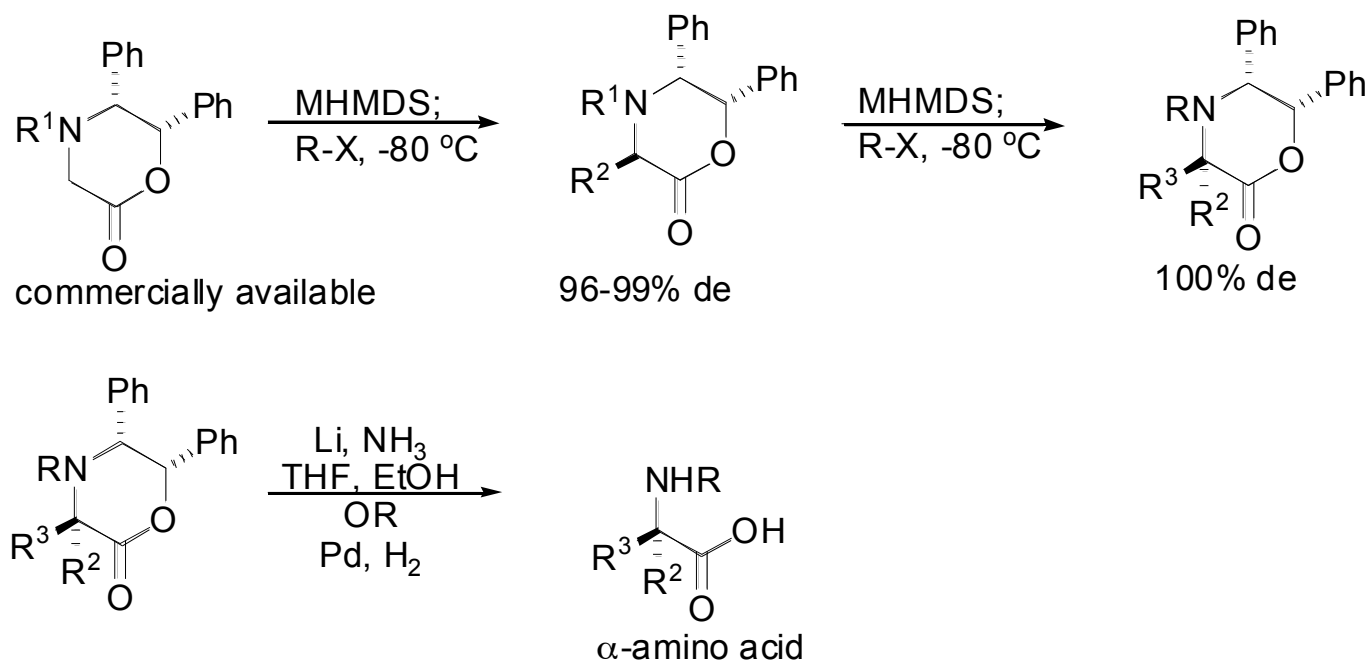
Retrosynthetic Analysis



Williams Methodology

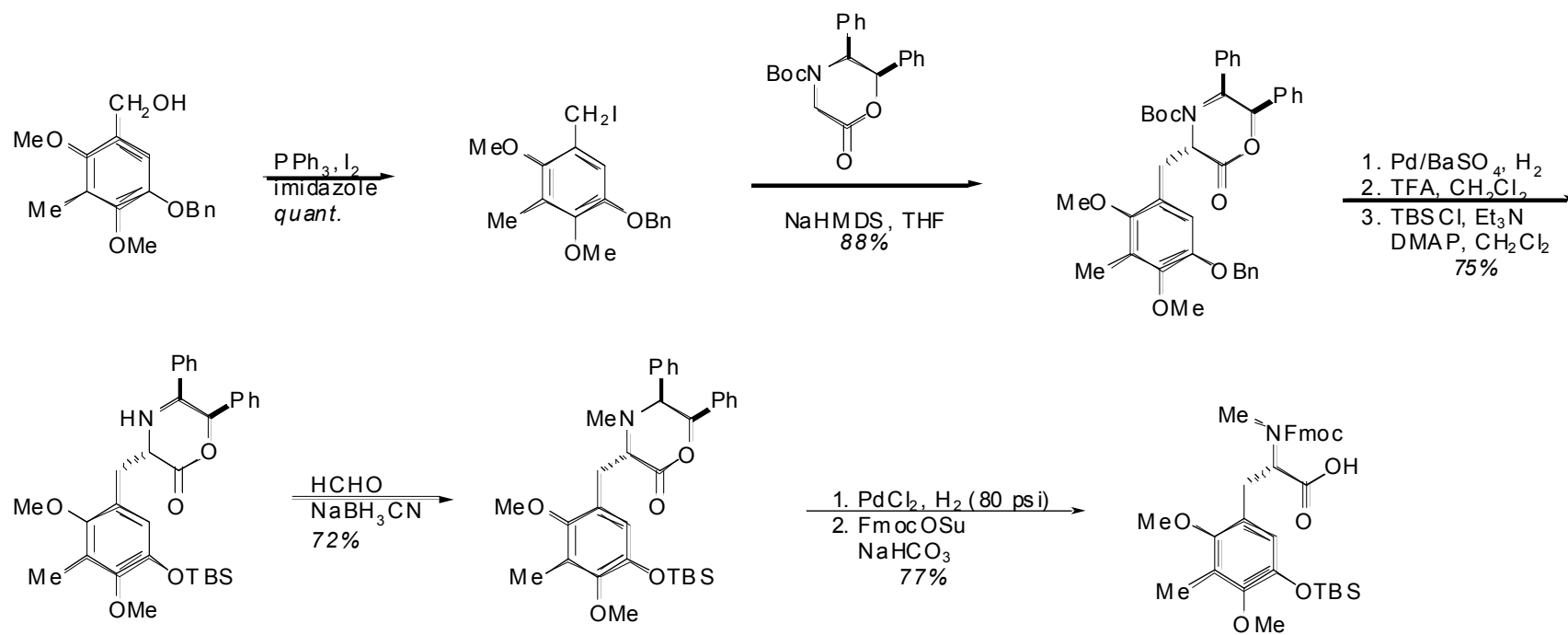
M = Li, Na, J

R = Allyl, Me, Bn, alkyl, etc

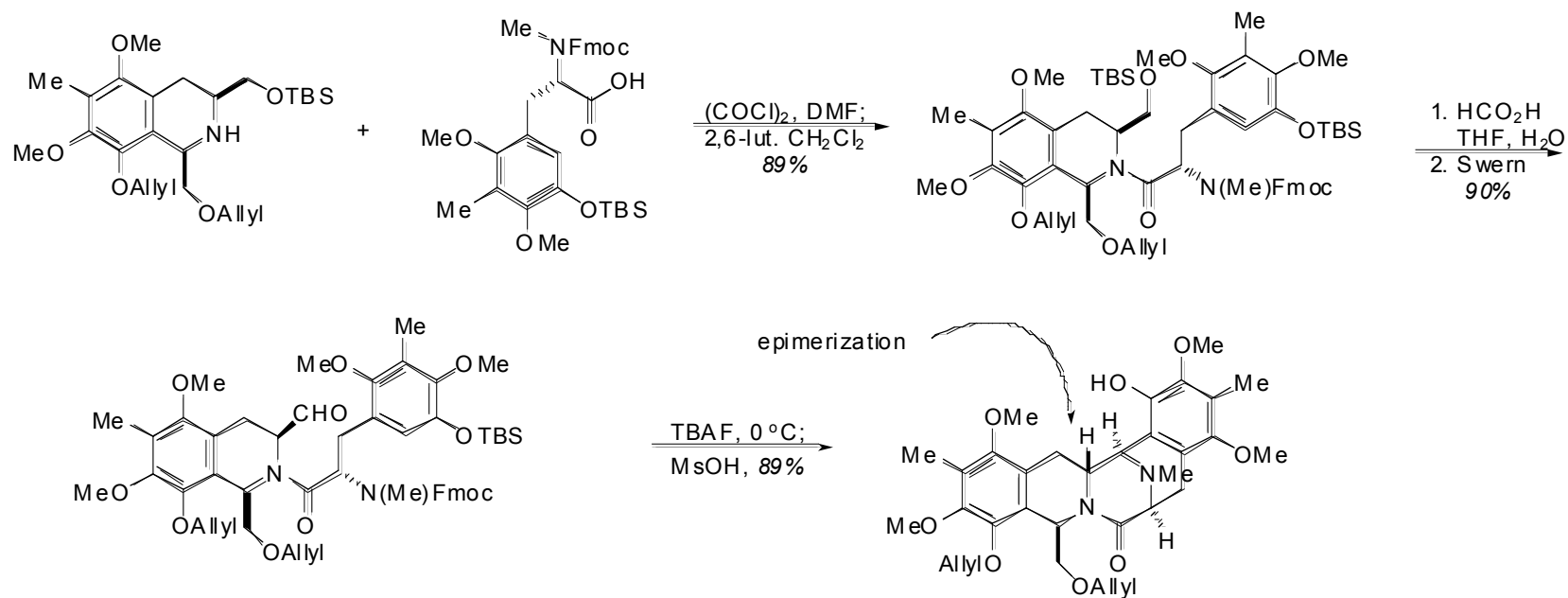


Williams, R. *JACS* **1991**, 9276.

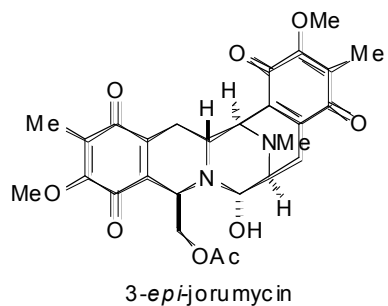
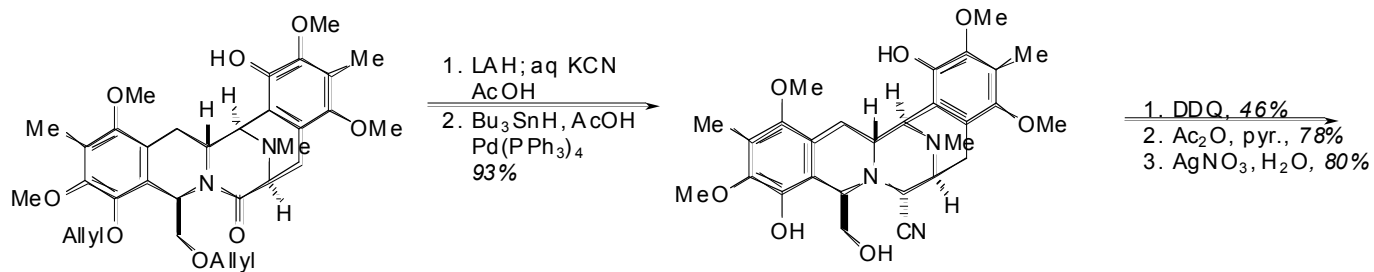
Synthesis of Acid Fragment



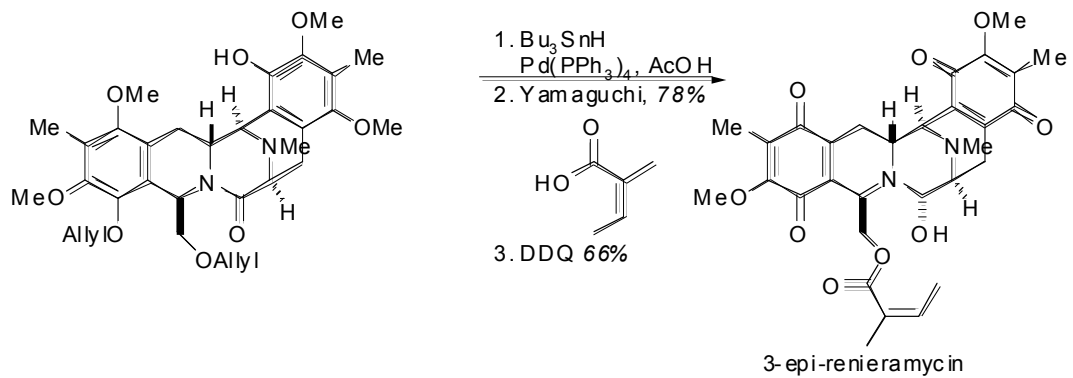
Coupling of Major Fragments



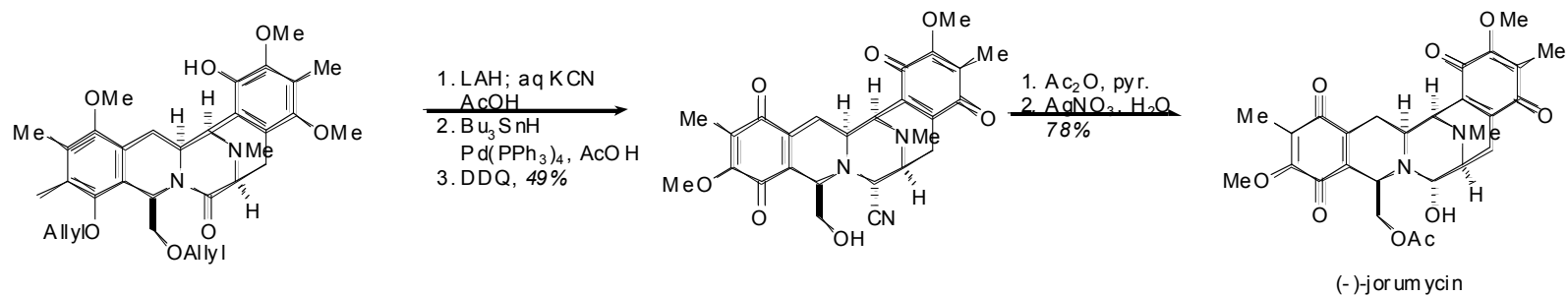
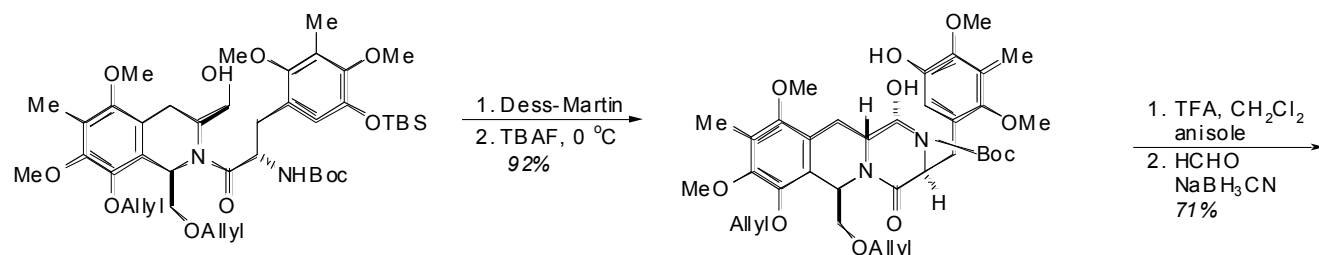
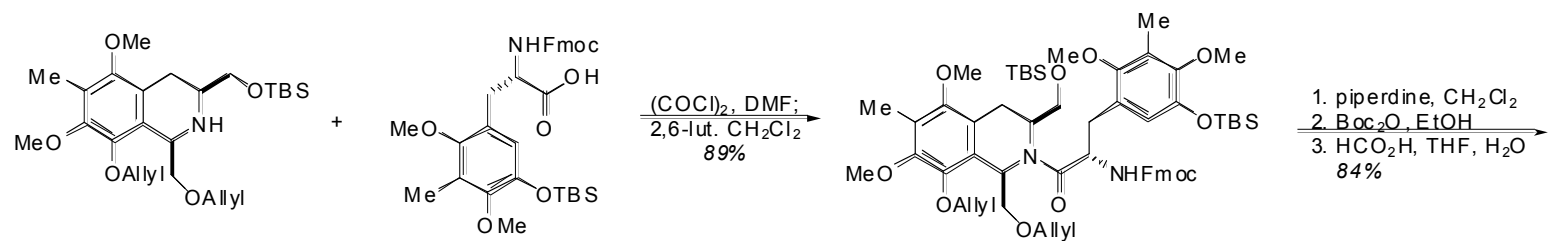
Synthesis of Epimers



these epi-intermediates all show significant cytotoxicity
modelling studies show that the active site for alkylation of guanine residues
is in the relative conformation of the natural products



Completion of Jorumycin



Completion of Renieramycin G

