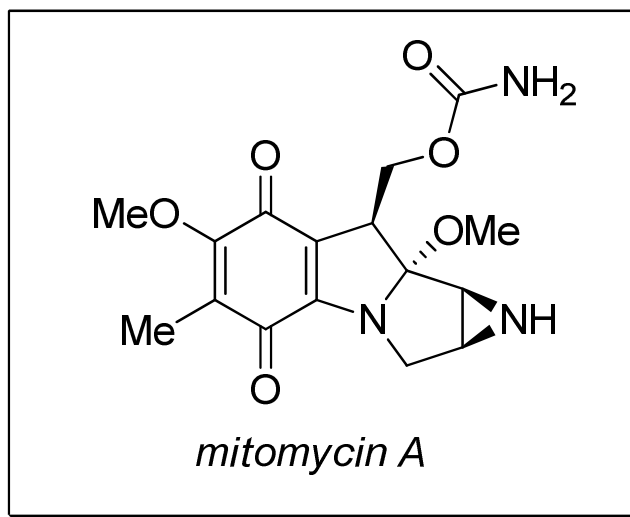


Mitomycin



Molecule in Review

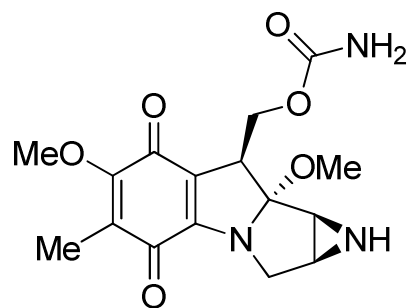
Rockford Coscia (Lambert)
September 4, 2009

Synthesis Literacy Group
Columbia University Chemistry

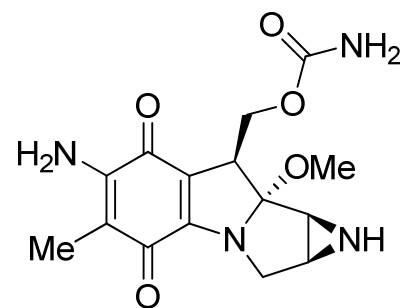
Mitomycins – A Brief History

- Mitomycin A isolated from *streptomyces caespitosus* in 1956 – structure elucidated in 1962
- Currently 17 mitomycins known
- Sixteen of the known mitomycins exhibit biological activity – mostly antibiotic and antitumor
- Mitomycin C, aka *Mutamycin*, marketed by Bristol-Myers Squibb for the treatment of stomach and pancreatic cancer
- No commercial synthesis (isolated from the bacteria) and enantioselective route has never been completed

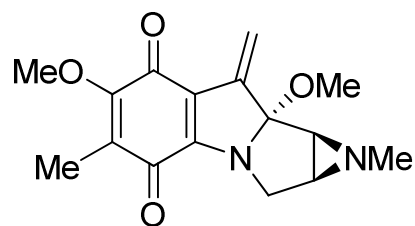
The Mitomycin Family



mitomycin A

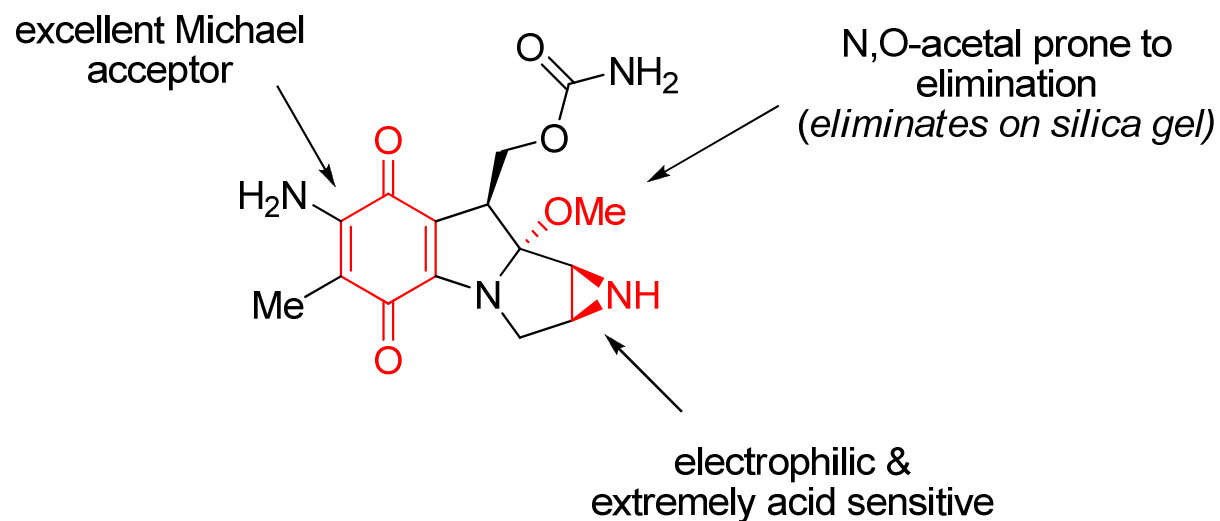


mitomycin C



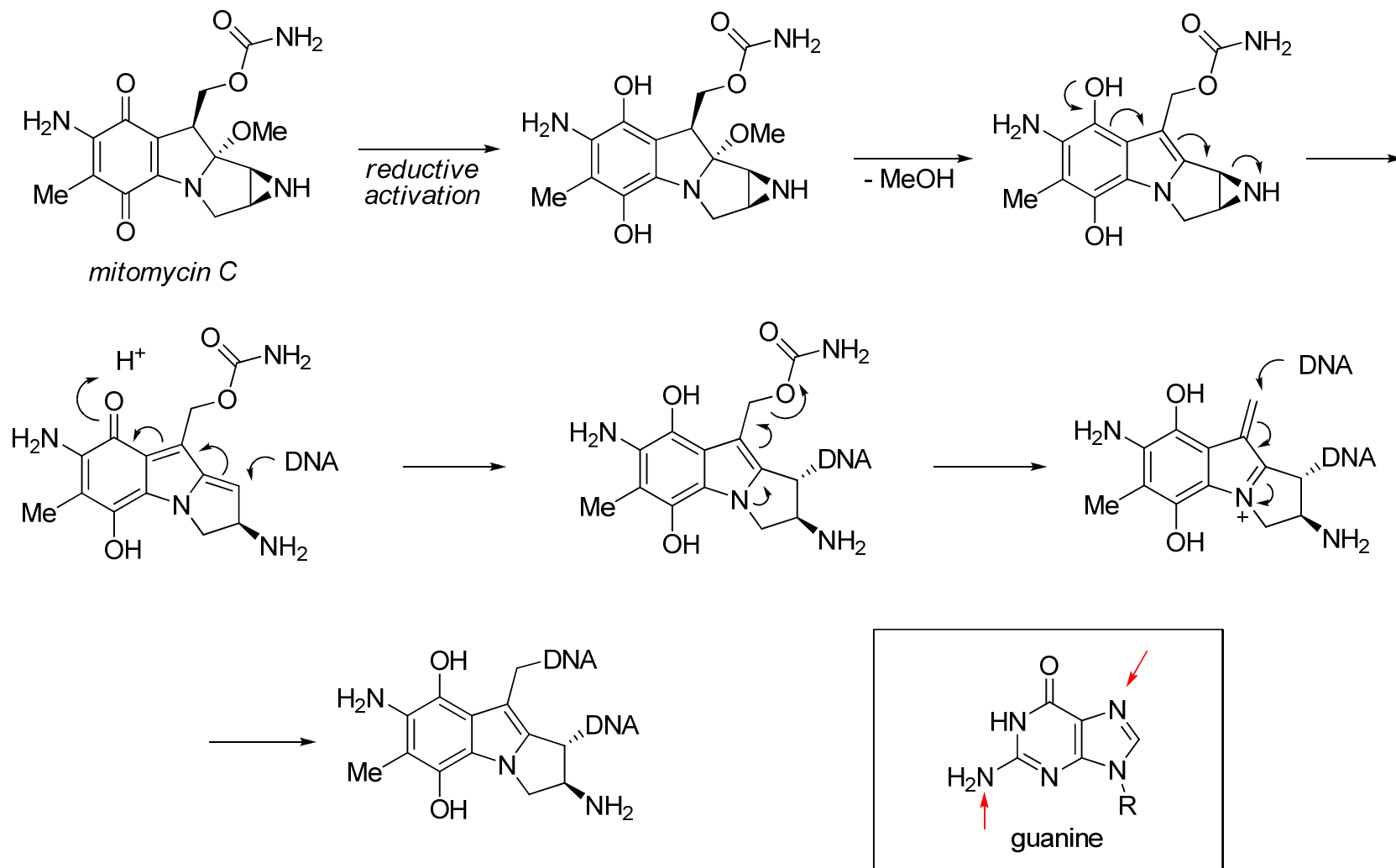
mitomycin K

Synthetic Difficulties



"The synthesis of a mitomycin is the chemical equivalent of walking on egg shells"
-S. J. Danishefsky

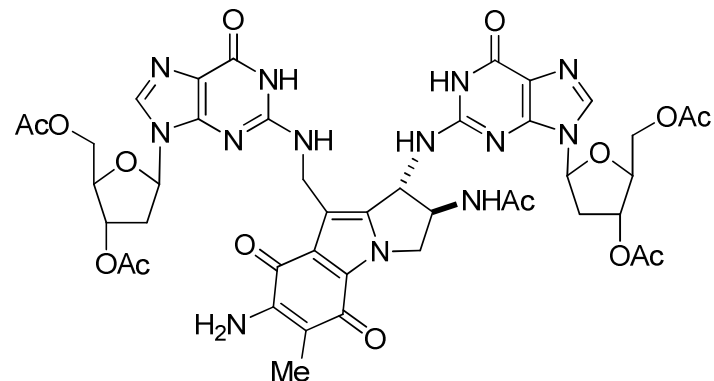
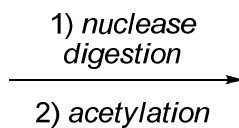
Mode of Action



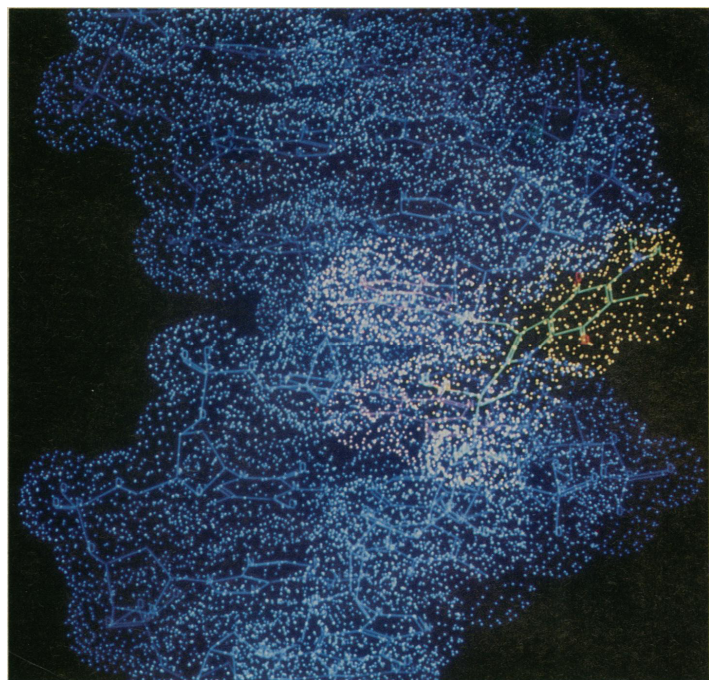
Coscia 5 - CU Synthesis Lit Group - Mitomycin

Mode of Action – A Koji Contribution

Mitomycin C + DNA adduct



isolated and characterized



Nakanishi et al, *Science*, **1987**, 235, 1204

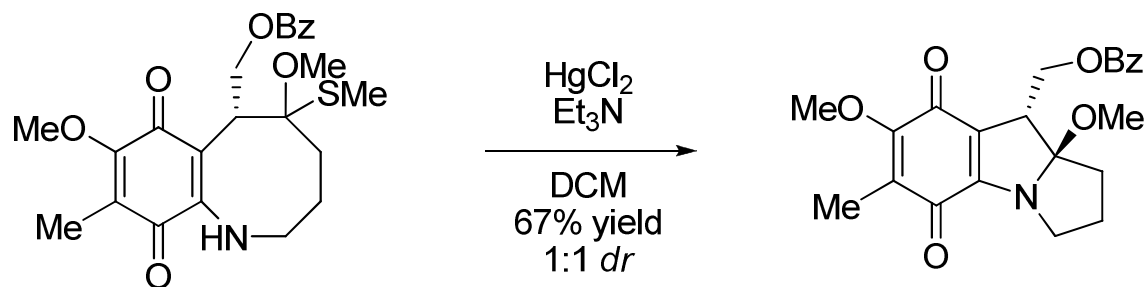
Coscia 6 - CU Synthesis Lit Group - Mitomycin

Total Syntheses

- Kishi – Mitomycins A & C, 1977
 - 45 & 46 steps, respectively
 - 0.05% overall yield (but 84% average yield!)
- Fukuyama – Mitomycins A & C, 1987
 - 29 & 30 steps, respectively
 - 7% overall yield
- Danishefsky – Mitomycin K, 1992
 - 12 steps
 - 0.3% overall yield
- Jimenez – Mitomycin K, 1996
 - 13 steps
 - 1.4% overall yield

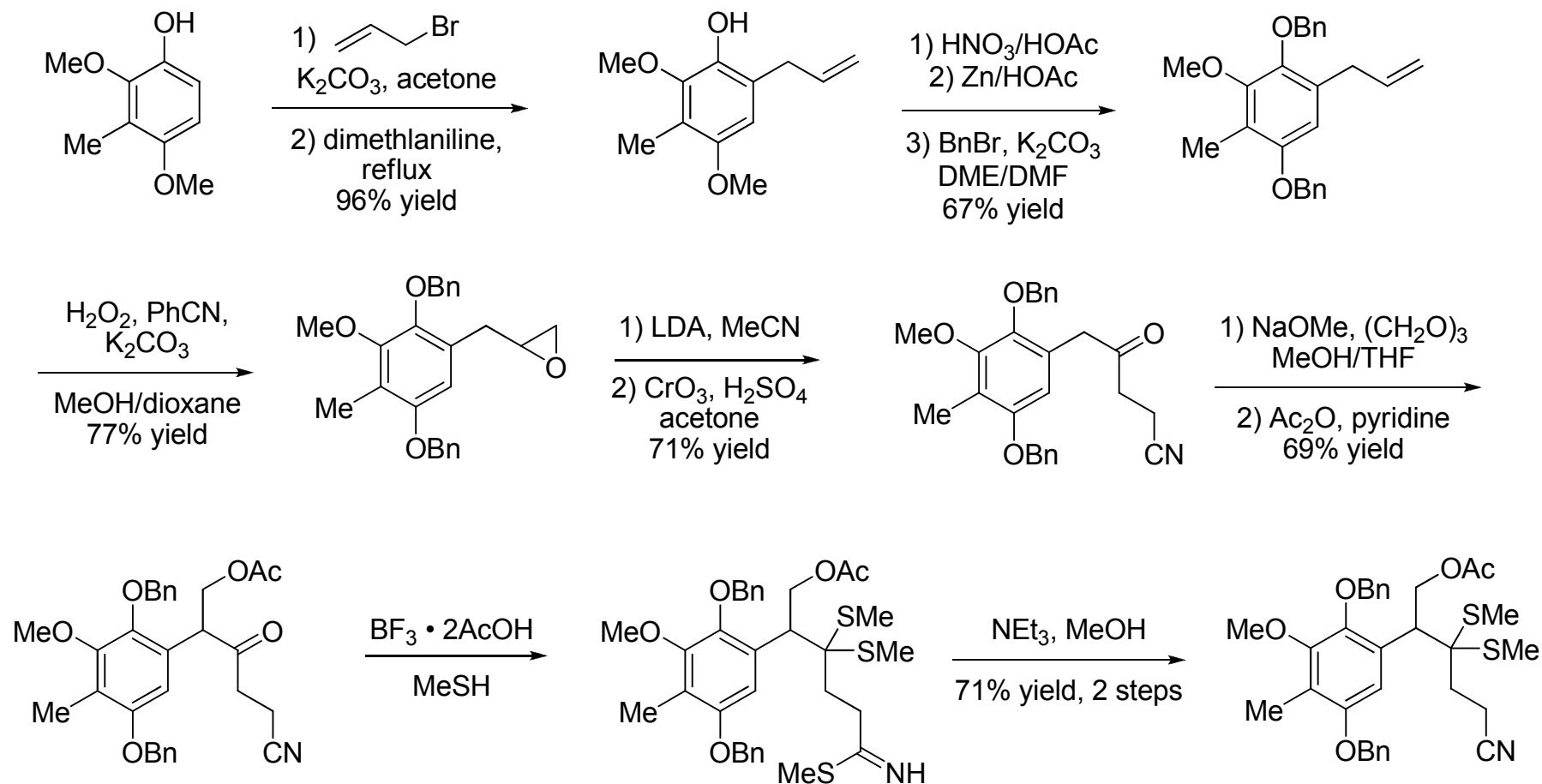
Kishi Synthesis – Early Investigations

- Trans-annular cyclization approach



Kishi et al, *JACS*, **1977**, 99, 4835

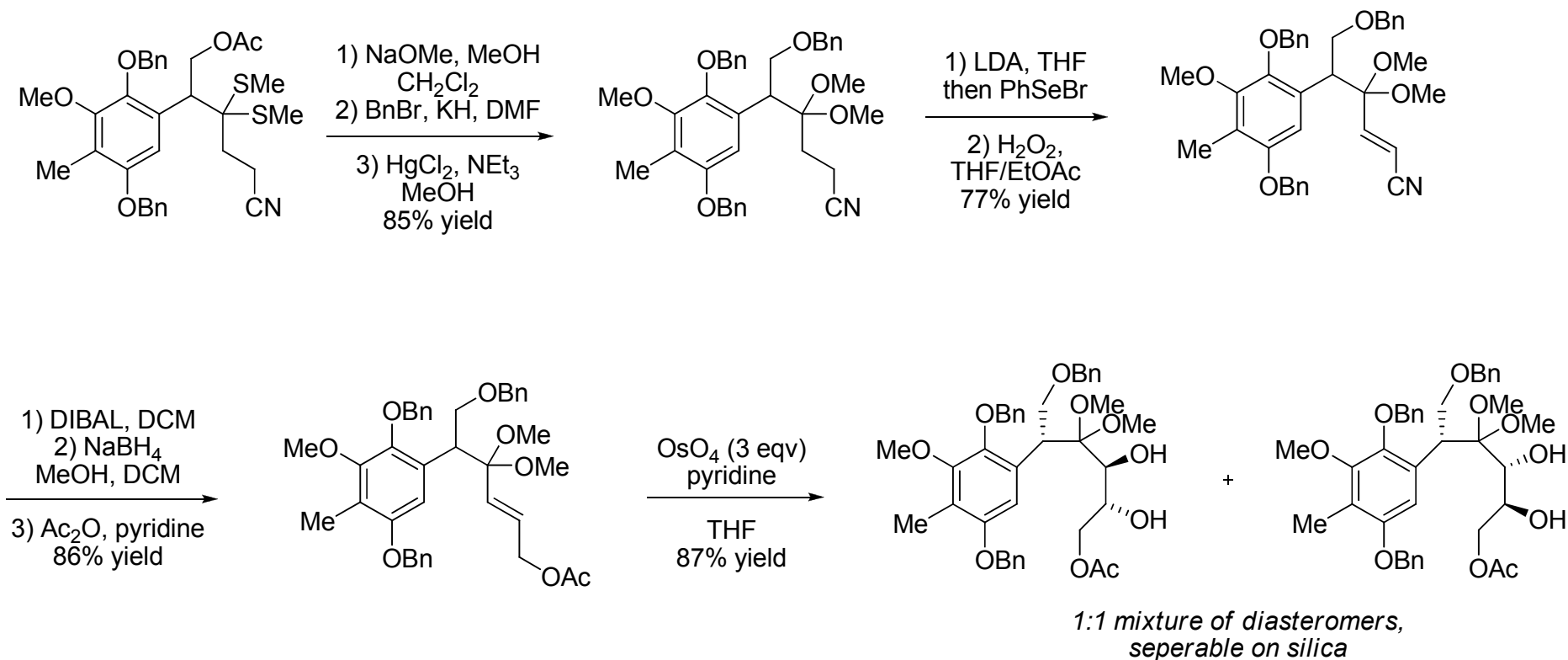
Kishi Synthesis



attempts to form simple acetals caused elimination of the acetoxy (or hydroxy) group

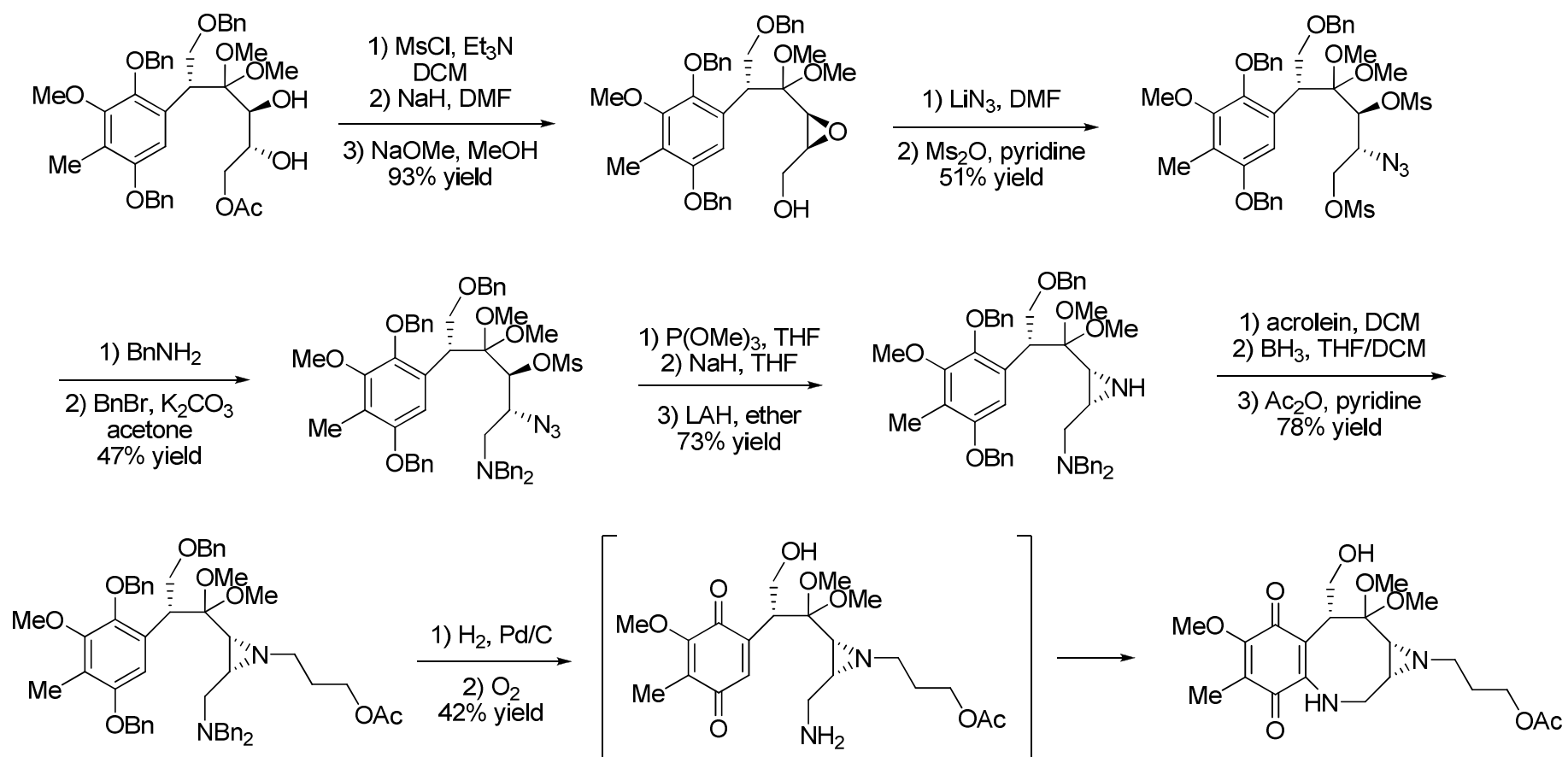
Coscia 9 - CU Synthesis Lit Group - Mitomycin

Kishi Synthesis – Getting Closer



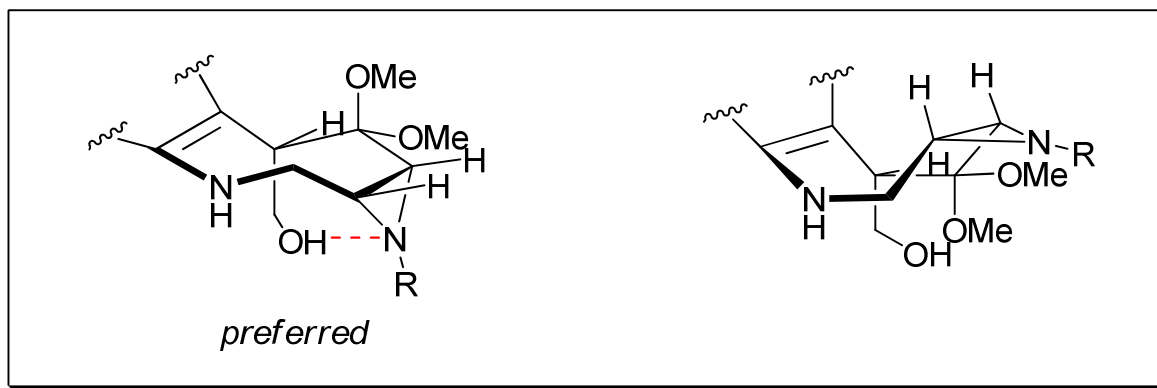
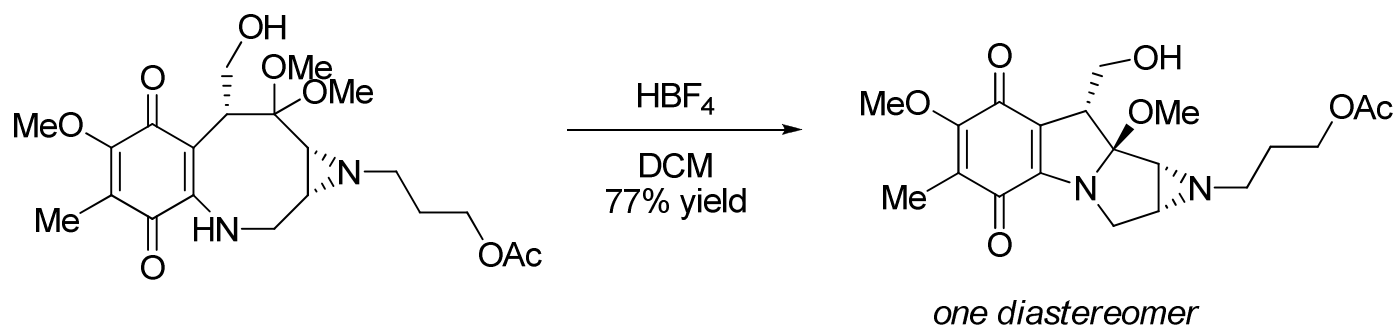
Coscia 10 - CU Synthesis Lit Group - Mitomycin

Kishi Synthesis - Macrocyclization

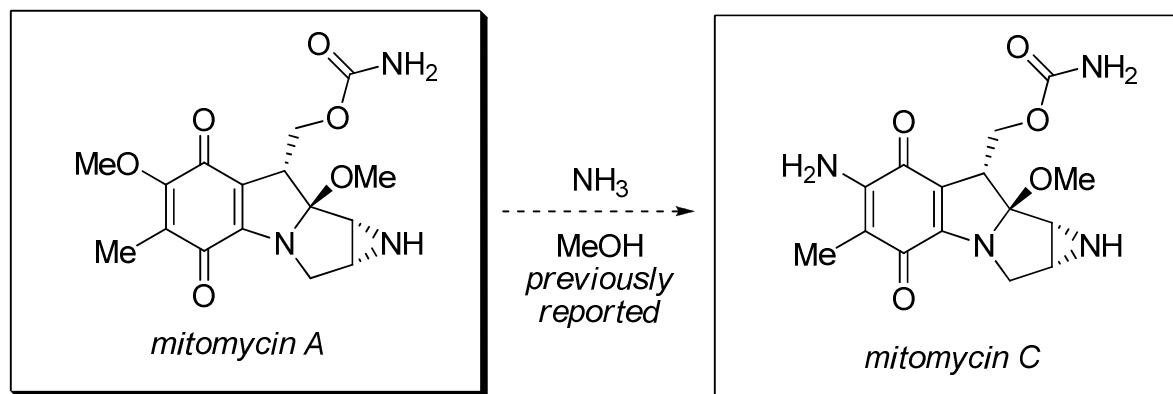
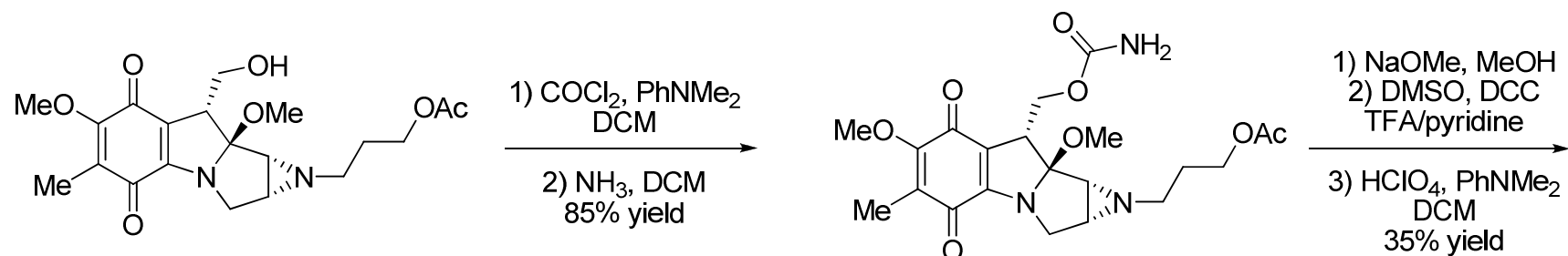


Coscia 11 - CU Synthesis Lit Group - Mitomycin

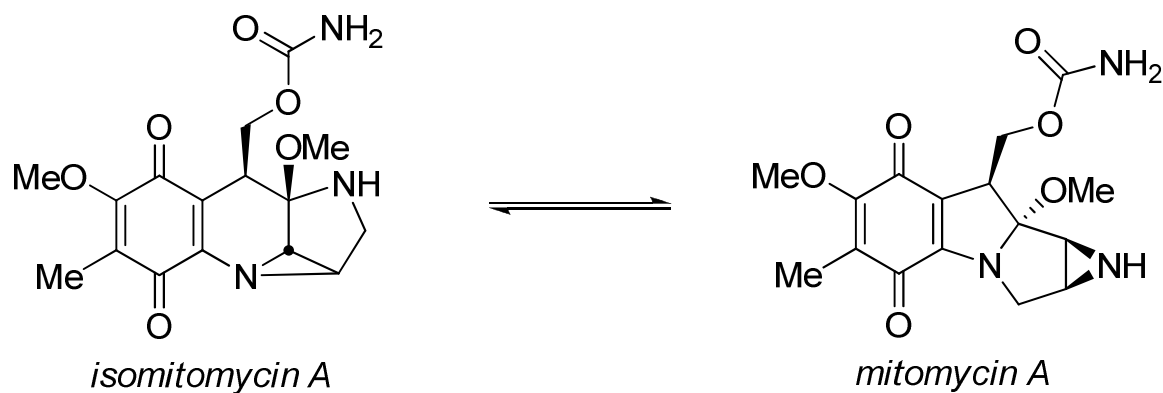
Kishi Synthesis – Key Step!



Kishi Synthesis – End Game



An Interesting Equilibrium

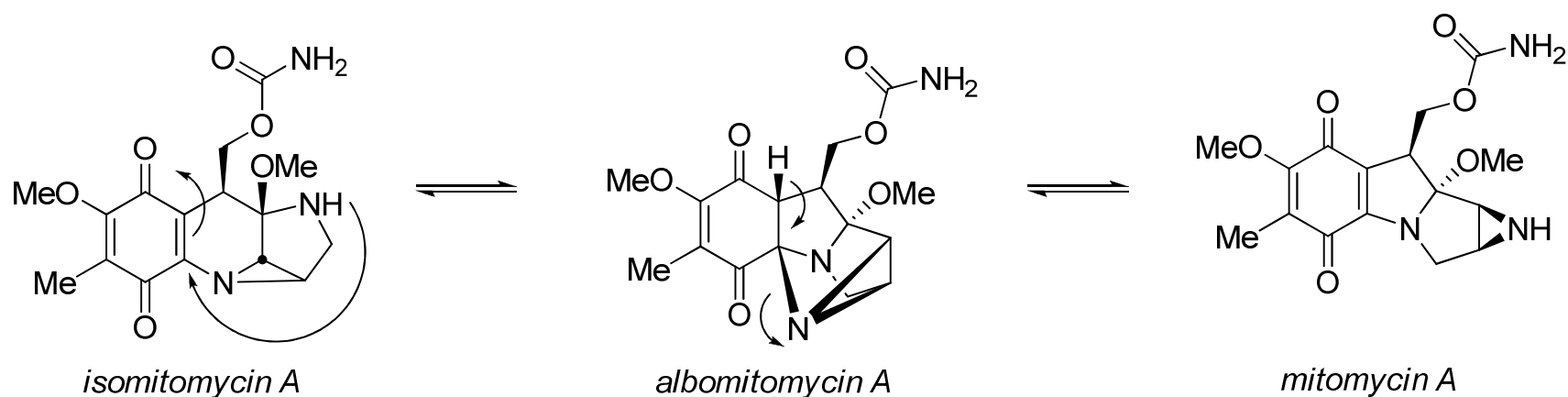


Mechanism?

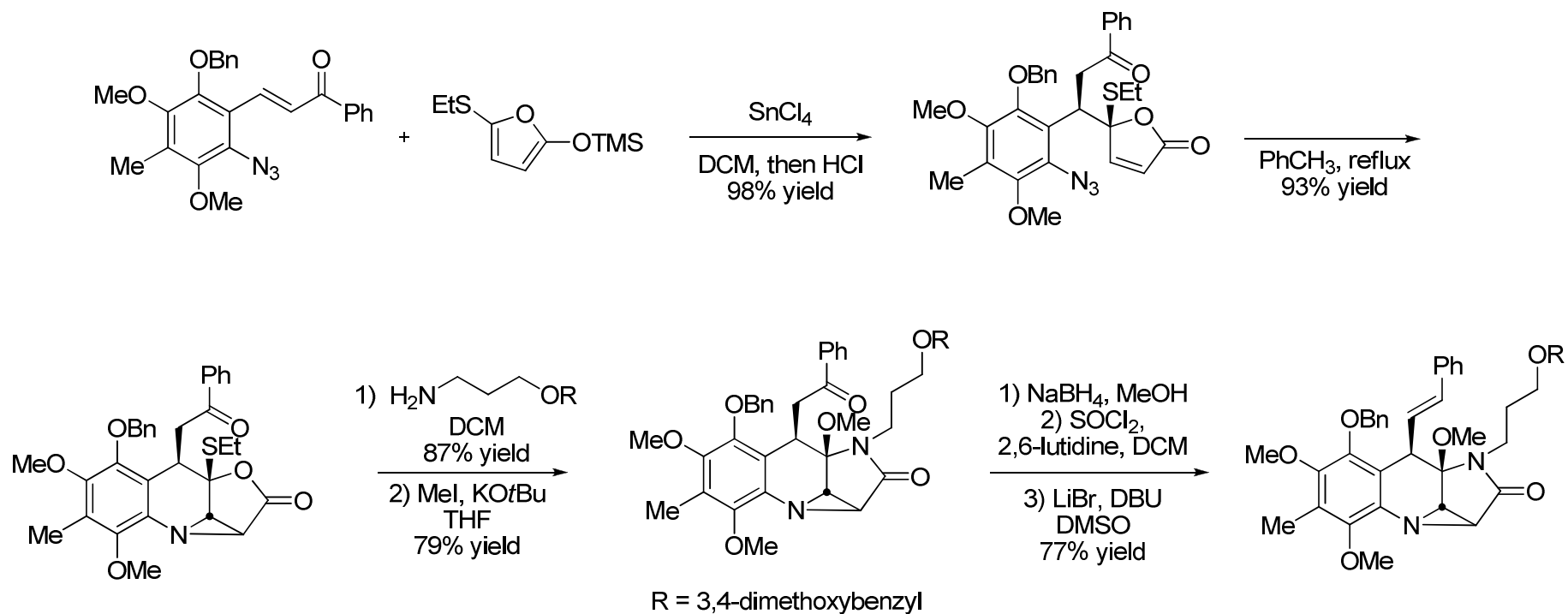
Kono et al, *JACS*, **1987**, *109*, 7224

Coscia 14 - CU Synthesis Lit Group - Mitomycin

Mechanism: Answer

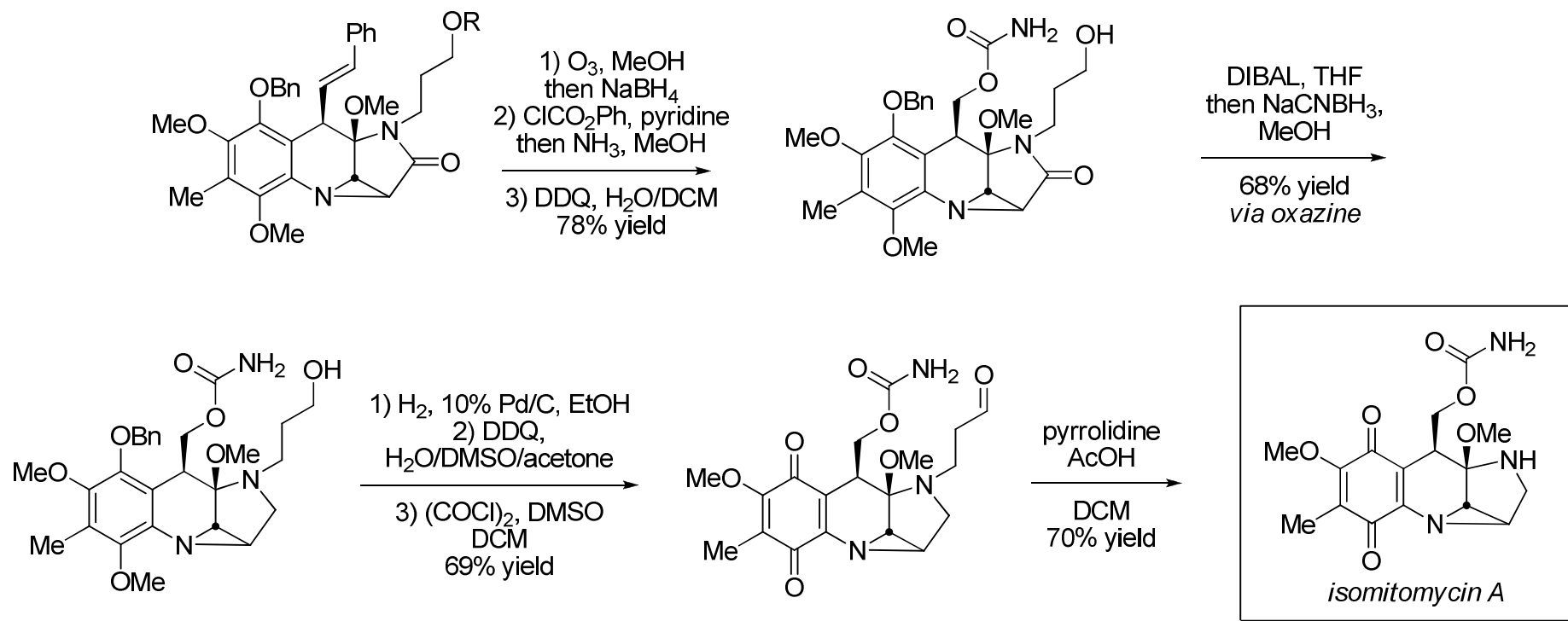


Fukuyama Synthesis



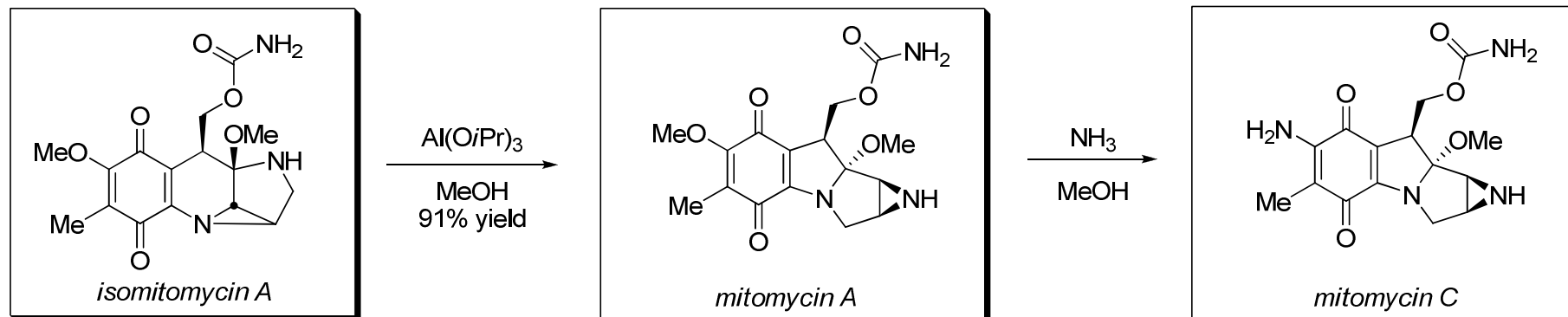
Coscia 16 - CU Synthesis Lit Group - Mitomycin

Fukuyama Synthesis



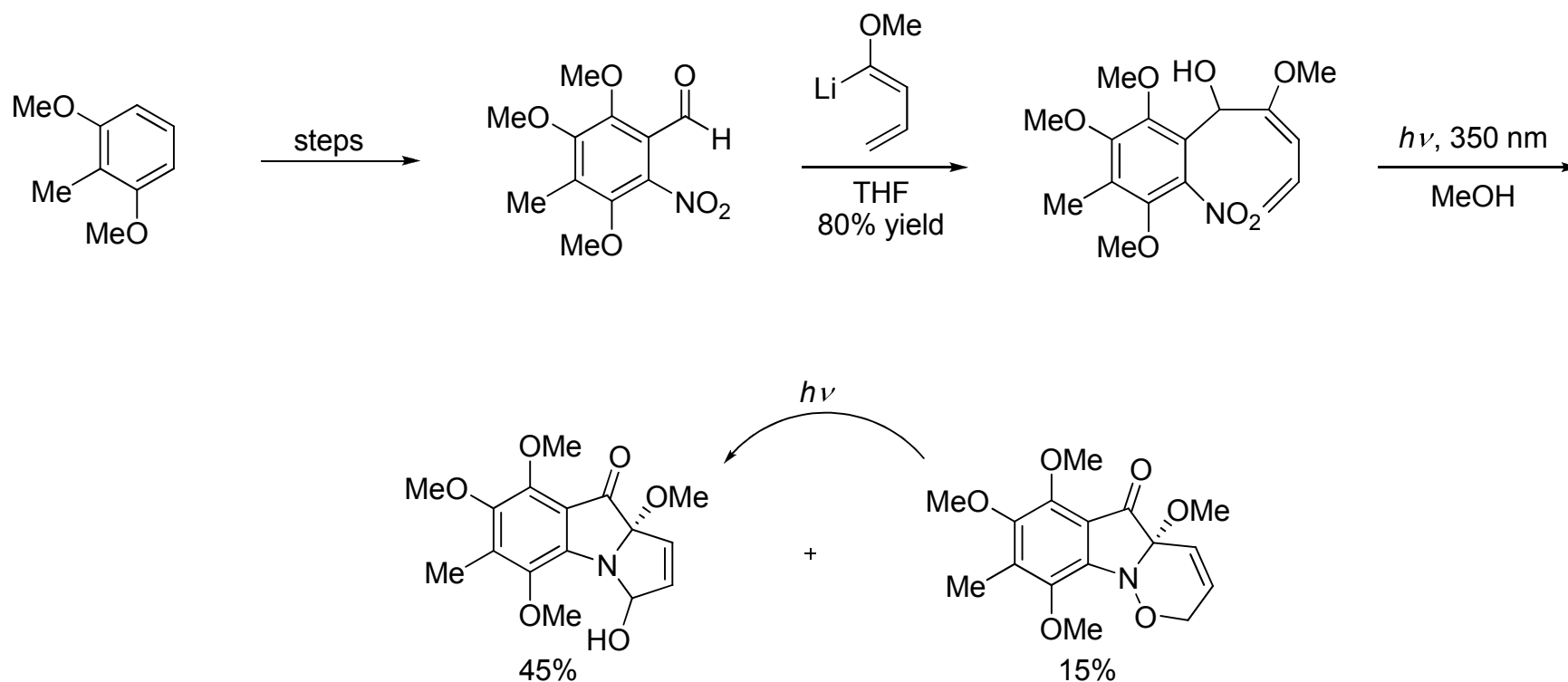
Last Name 17 - CU Synthesis Lit Group - Mitomycin

Fukuyama End Game



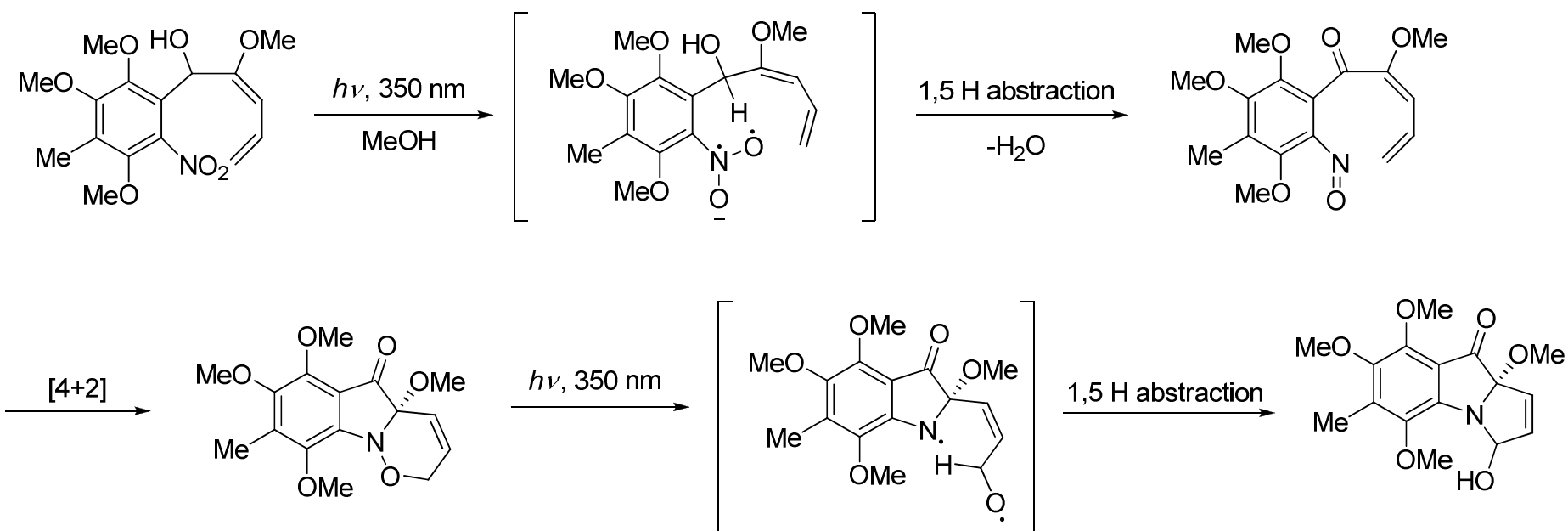
Coscia 18 - CU Synthesis Lit Group - Mitomycin

Danishefsky Synthesis



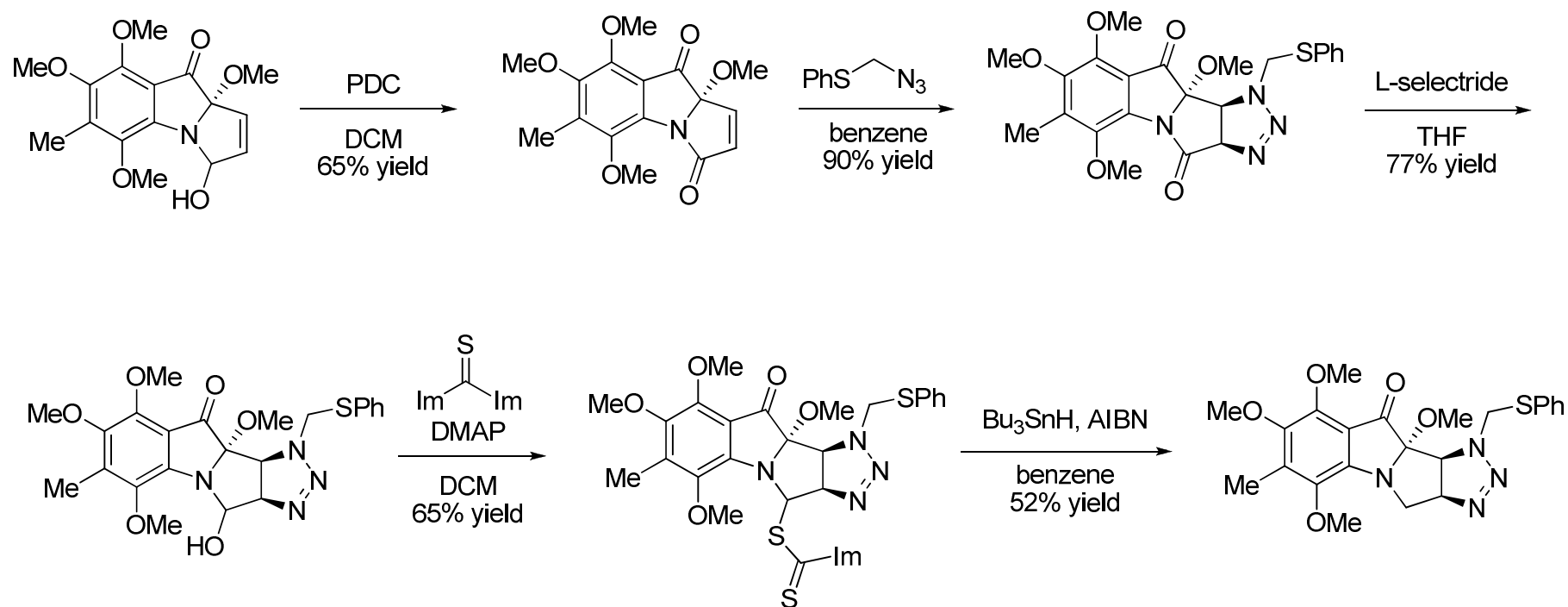
Last Name 19 - CU Synthesis Lit Group - Mitomycin

Radical Cyclization Mechanism



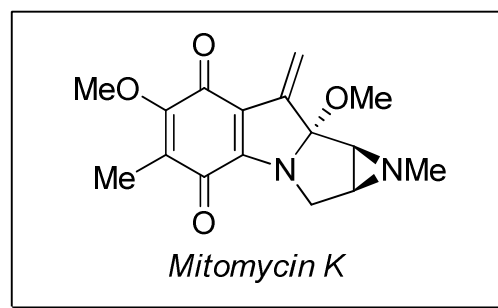
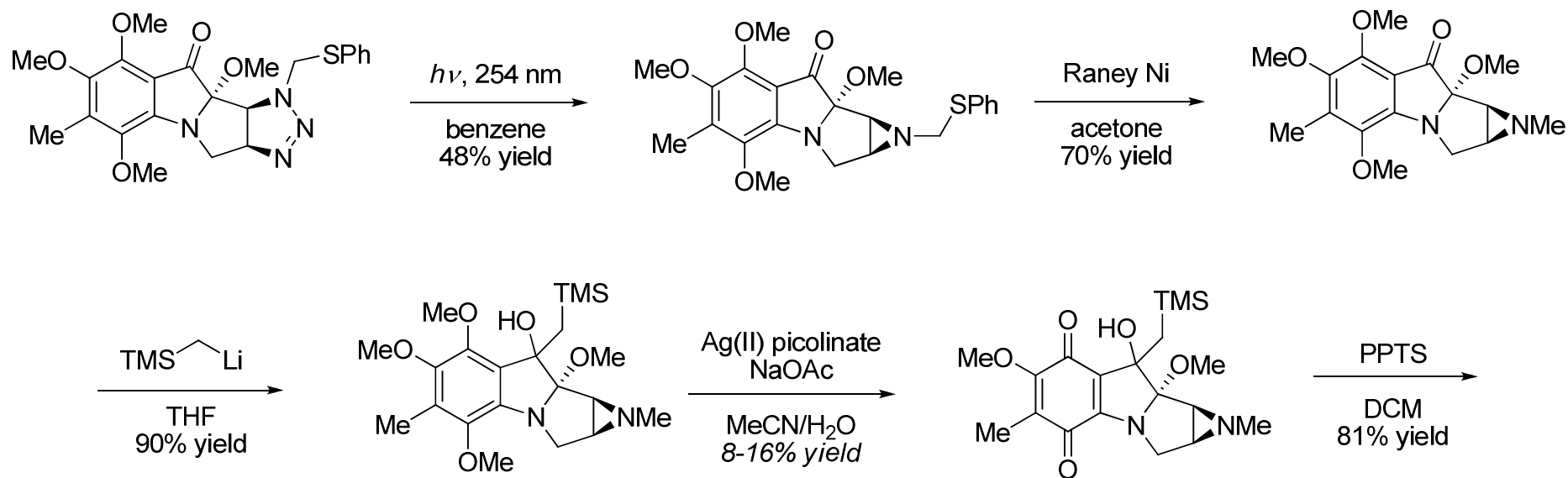
Coscia 20 - CU Synthesis Lit Group - Mitomycin

Danishefsky Synthesis



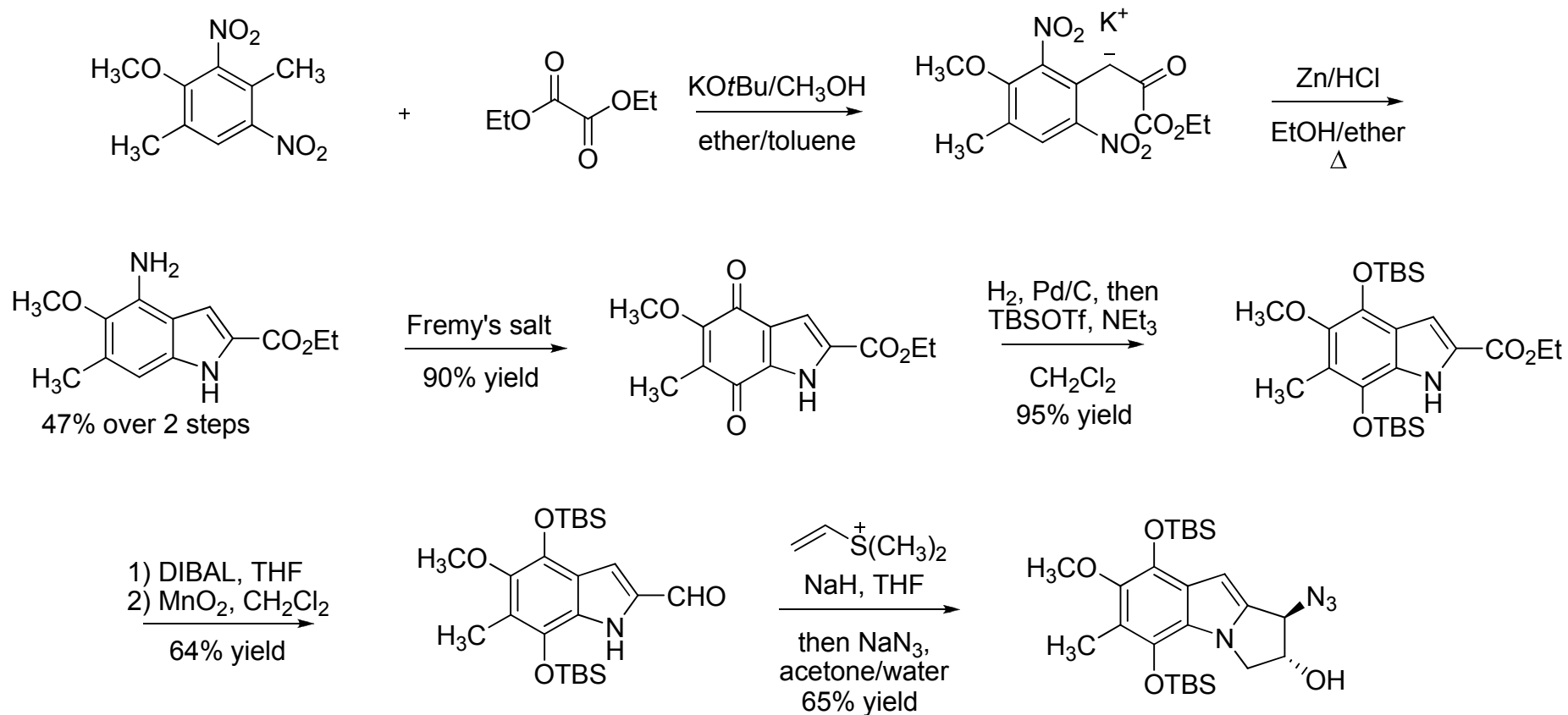
thio compound rearranges to thioester which undergoes acyl exchange

Danishefsky End Game



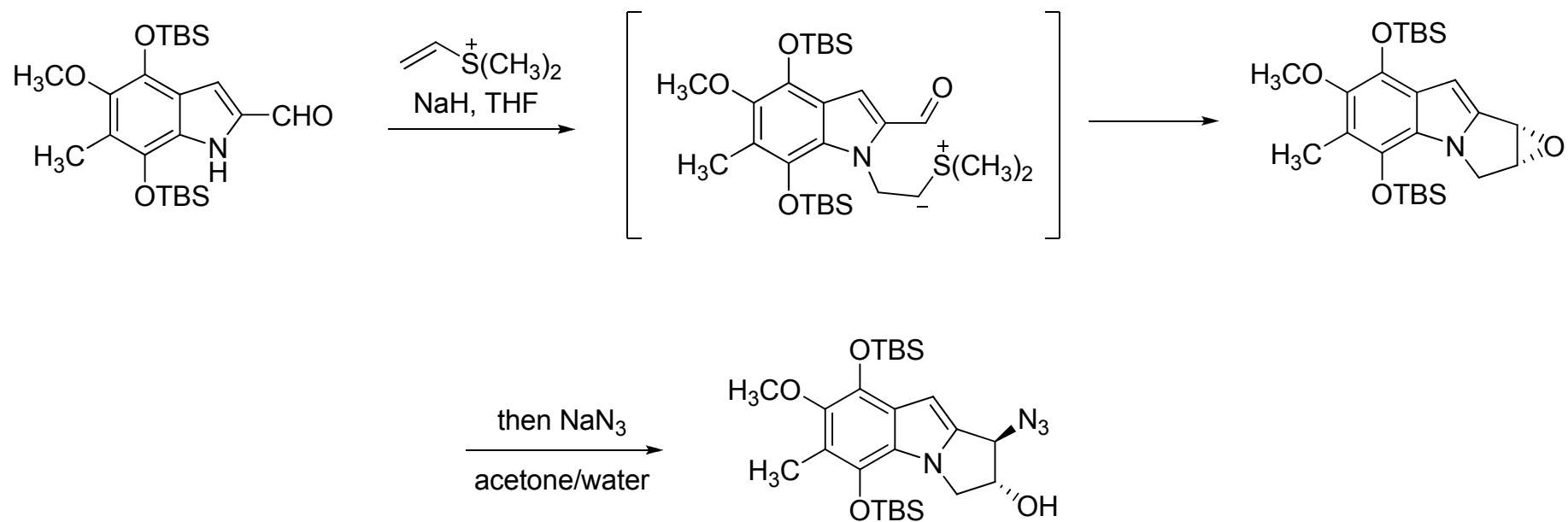
Coscia 22 - CU Synthesis Lit Group - Mitomycin

Jimenez Approach



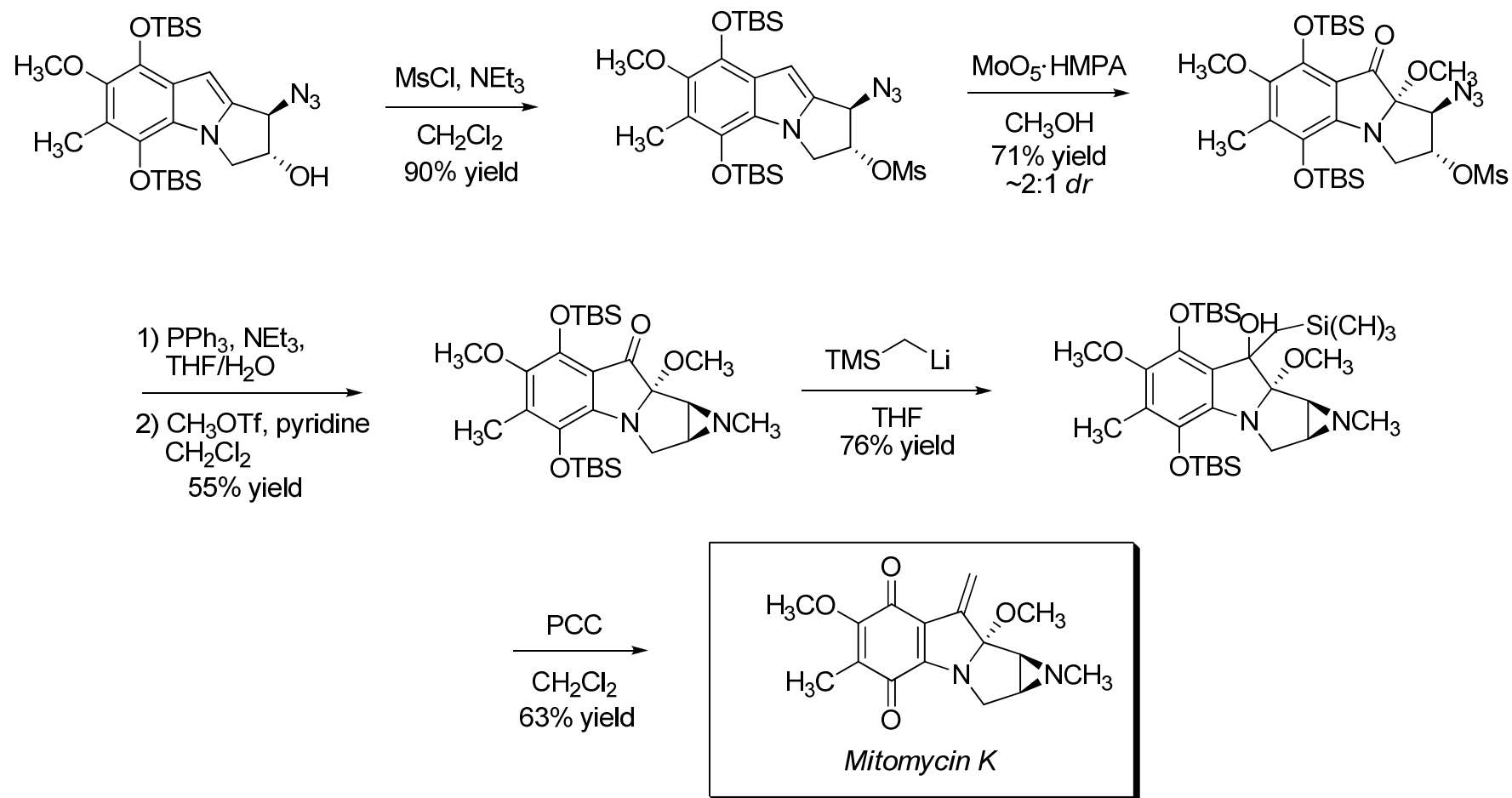
Coscia 23 - CU Synthesis Lit Group - Mitomycin

Sulfonium Ylide Cyclization



Coscia 24 - CU Synthesis Lit Group - Mitomycin

Jimenez Synthesis



Coscia 25 - CU Synthesis Lit Group - Mitomycin

Summary of Syntheses

- Kishi – Mitomycins A & C (1977)
 - OMG steps! But first synthesis by over 10 years!
 - Trans-annular cyclization key step
- Fukuyama – Mitomycins A & C (1987)
 - Reasonably efficient
 - Isomitomycin A / Mitomycin isomerization
- Danishefsky – Mitomycin K (1992)
 - Photolysis – cycloaddition – fragmentation – recombination sequence
- Jimenez – Mitomycin K (1996)
 - Novel sulfonium ylide cyclization

References

- Kishi – Mitomycins A & C (1977)
 - *JACS*, **1977**, *99*, 4835-4836
 - *JACS*, **1977**, *99*, 8115-8116
 - *TL*, **1977**, *49*, 4295-4298
- Fukuyama – Mitomycins A & C (1987)
 - *JACS*, **1987**, *109*, 7881-7882
- Danshefsky – Mitomycin K (1992)
 - *ACIEE*, **1992**, *31*, 915-917
 - *JACS*, **1993**, *115*, 12305-12314
- Jimenez – Mitomycin K (1996)
 - *JOC*, **1996**, *61*, 816-818
 - *TL*, **1996**, *37*, 6049-6052