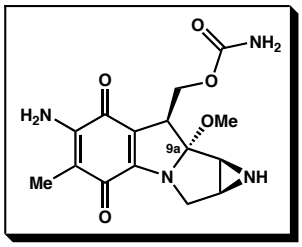
# Synthetic Enchantment with Mitomycinoids

**Jeremy May, Dan Caspi, Neil Garg,
Jenny Roizen and G. Sekar**




*Mitomycin C*

**Synthetic Challenges:**

- **Complex stereochemistry**
- **Avoiding aromatization to pyrrole, indole, or hydroquinone**
- **Sensitive aziridine and quinone**
- **Hemiaminal ether linkage at C(9a)**

**Monday, August 16th, 2004**

## History of the Mitomycins

- **Originally isolated and characterized by Japanese and American pharmaceutical companies as a consequence of antibiotic screens.**
- **Mitomycins A and B were isolated in 1956, followed by Mitomycin C in 1958.**
- **Mapping the structures engaged the interests of chemists and crystallographers for 20 years.**
- **Early on it was discovered that mitomycins are potent antibiotics (gram positive and gram negative bacteria, and mycobateria) and cytotoxic agents.**
- **Mitomycin C (Mutamycin®) is the most potent of the family, and is also a widely prescribed antitumor agent marketed by Bristol-Myers Squibb Oncology.**
- **Elucidation of the detailed biological mechanism was very challenging, and the original proposal in 1963 by Iyer and Szybalski has been experimentally verified with few changes.**
- **Mitomycin C is also among the first bioreductively activated drugs, and it is selective for hypoxic ($O_2$-deficient cells).**

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

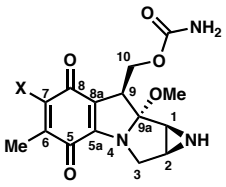
**Biosynthesis and mechanisms of action:**

Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.
Herbert, R. B. *Nat. Prod. Rep.* **2003**, *20*, 494.

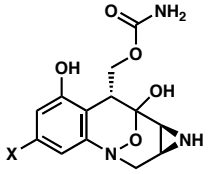
**Synthetic studies:**

Danishefsky, S. J. *Synlett* **1995**, 475.
Kono, M. *Synlett* **1992**, 778.

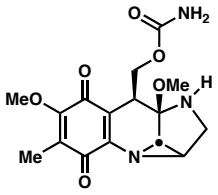
## The Mitomycinoid Family
### Key Structural Types



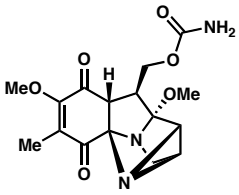
| | X |
|---|---|
| Mitomycin A | OMe |
| Mitomycin C | $NH_2$ |



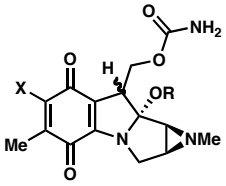
| | X |
|---|---|
| FR-900482 | CHO |
| FR-66979 | $CH_2OH$ |



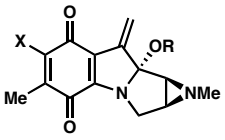
Isomitomycin A



Albomitomycin A



| | X | R | H |
|---|---|---|---|
| Mitomycin B | OMe | H | β |
| Mitomycin D | $NH_2$ | H | β |
| Mitomycin F | OMe | Me | α |
| Porifiromycin | $NH_2$ | Me | α |



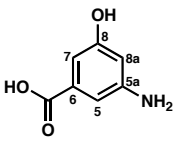
| | X | R |
|---|---|---|
| Mitomycin G | $NH_2$ | Me |
| Mitomycin H | OMe | H |
| Mitomycin K | OMe | Me |

## Biosynthesis of Mitomycin

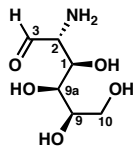
- Studies in the 1970's and 1980's revealed that 3-amino-5-hydroxy-benzoic acid (AHBA), D-glucosamine, carbamoyl phosphate and S-adenosyl methionine are involved in the convergent assembly of these natural products.

- The basic building blocks have been known for some time, but the specific order of assembly has remained undefined.

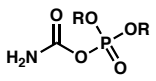
- Mutant strains of *S. lavendulae* allow for the isolation of biosynthetic intermediates (complete set of genes for mitomycin biosynthesis has been identified and characterized).



AHBA

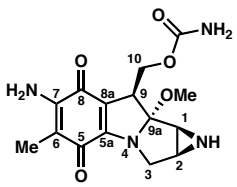


D-glucosamine



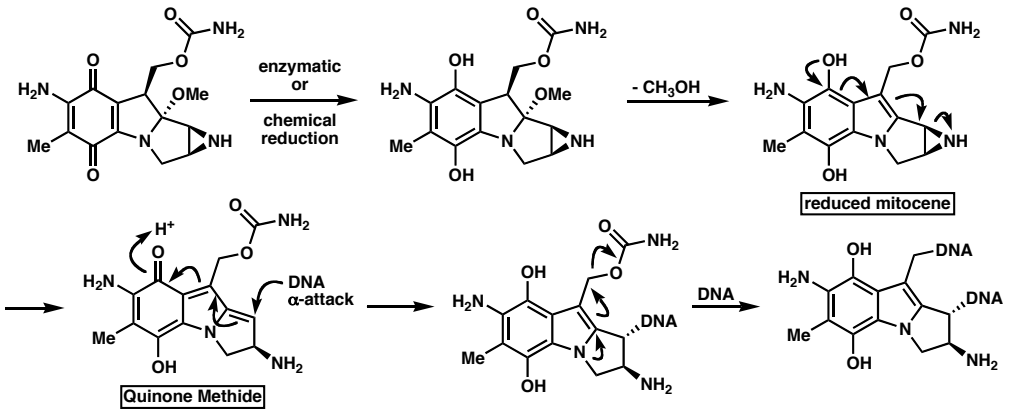
carbamoyl phosphate

(from L-citrulline or L-arginine)

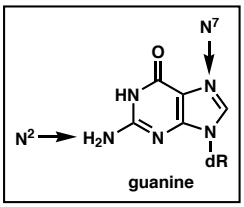



Sherman, D. H. *J. Am. Chem. Soc.* **2001**, *123*, 6712.
Sherman, D. H. *Chem. Biol.* **1999**, *6*, 251.
Sherman, D. H. *J. Bacteriol.* **1999**, *181*, 2199.

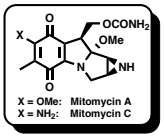
## Reductive Activation of Mitomycin C

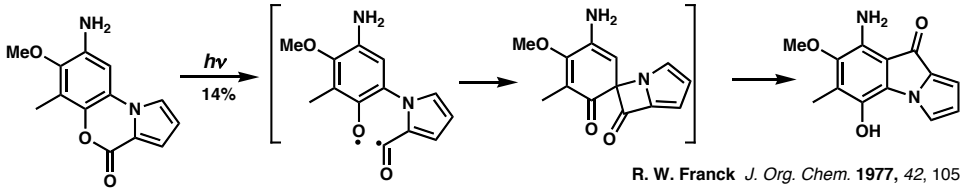



- $N^2$ and $N^7$ atoms of guanines in the minor groove of DNA are primary alkylation sites.
- Alkylation always proceeds in the order shown.
- α-attack is also observed with the unnatural enantiomer of MC, potentially accounting for the lower cytotoxicity (50%).
- Completely unreactive with DNA at pH 7-8, but in the presence of reductants, cross-linking occurs in < 1 min.



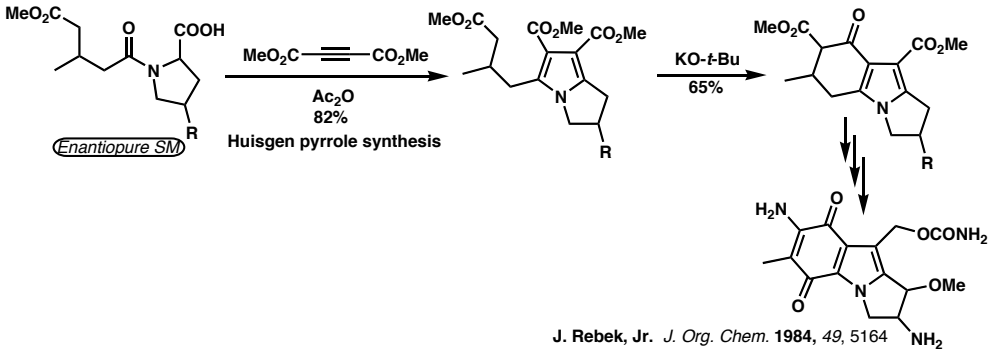

## *Franck's meta Photo-Fries Rearrangement Approach*



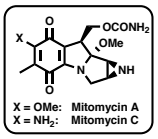

R. W. Franck *J. Org. Chem.* **1977,** *42*, 105

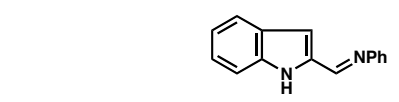
## *Rebek's Stepwise Approach*

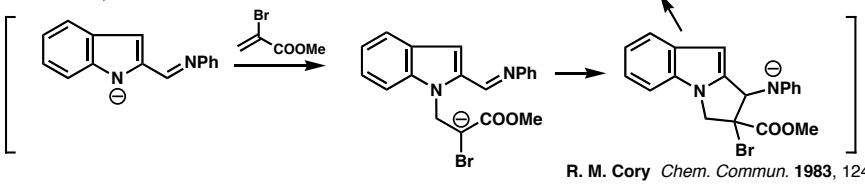



J. Rebek, Jr. *J. Org. Chem.* **1984,** *49*, 5164

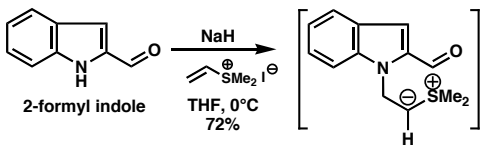
## *One-step Bicycloannulation Approach*



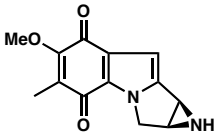



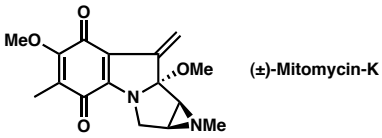
**R. M. Cory** *Chem. Commun.* **1983**, 1244




**L. S. Jimenez** *J. Am. Chem. Soc.* **1994**, *116*, 4977



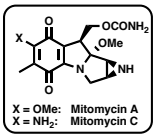
J. *Org. Chem.* **1996,** 6*1,* 818

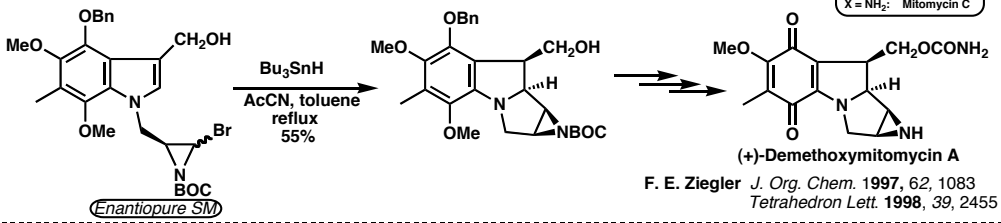


**(±)-Mitomycin-K**

*Tetrahedron Lett.* **1996**, *37*, 6049

## *Intramolecular Radical Cyclization*

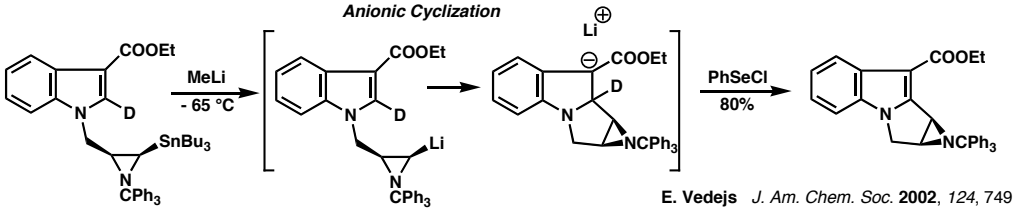


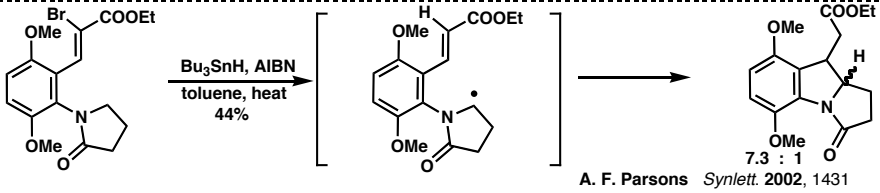

**(+)-Demethoxymitomycin A**

**F. E. Ziegler** *J. Org. Chem.* **1997,** 6*2,* 1083
*Tetrahedron Lett.* **1998**, *39*, 2455

***Anionic Cyclization***

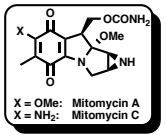


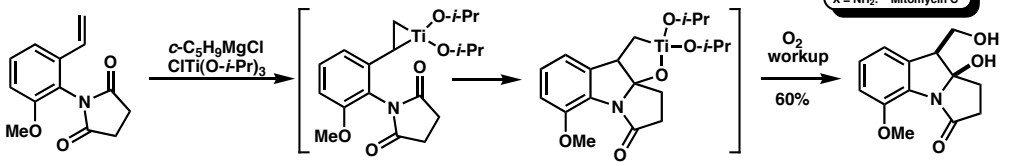

**E. Vedejs** *J. Am. Chem. Soc.* **2002**, *124*, 749




**A. F. Parsons** *Synlett.* **2002**, 1431

## *Cyclization Through Titanacyclopropane*




**Jin Kun Cha** *J. Am. Chem. Soc.* **1997**, *119*, 8127

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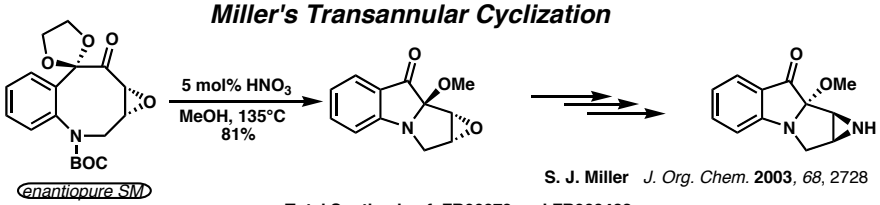
## *Miller's Transannular Cyclization*




*enantiopure SM*

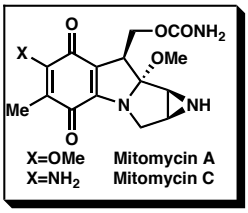
**S. J. Miller** *J. Org. Chem.* **2003**, *68*, 2728

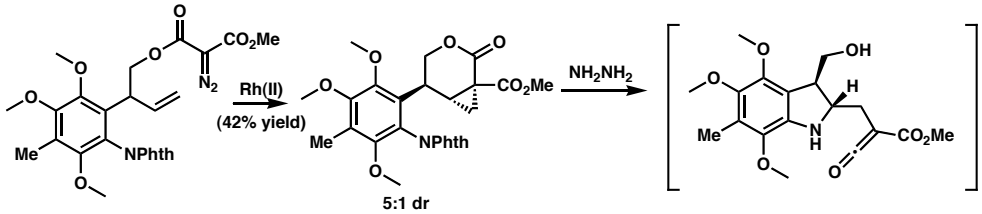
**Total Synthesis of FR66979 and FR900482**

**S. F. Martin** *J. Am. Chem. Soc.* **2000**, *122*, 10781
**R. M. Williams** *Angew. Chem. Int. Ed.* **2002**, *41*, 4883
**M. A. Ciufolini** *Angew. Chem. Int. Ed.* **2002**, *41*, 4888

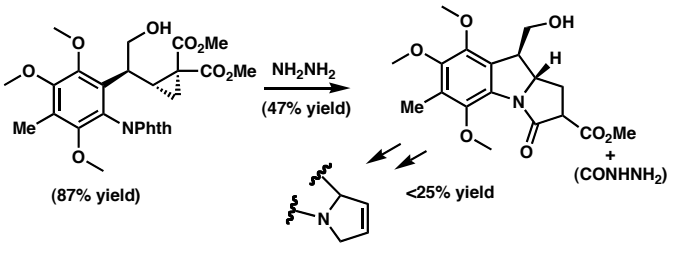
**Synthetic efforts before 1977**
**Y. Kishi** *J. Am. Chem. Soc.* **1977**, *99*, 4835 (references cited therein)

## Danishefsky's Attempts
### Activated Cyclopropanes

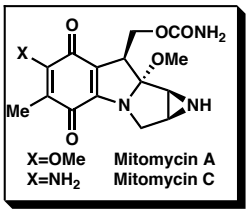


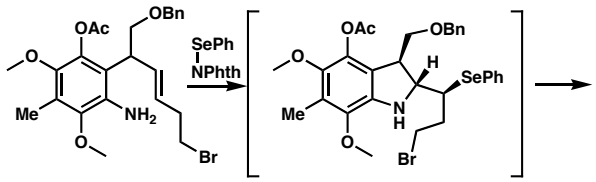

*From Claisen and Diazomalonate formation.*

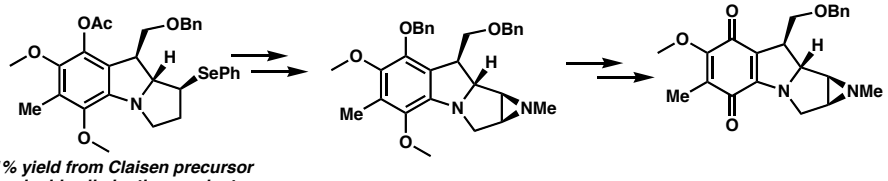


## Tandem Ring Formation



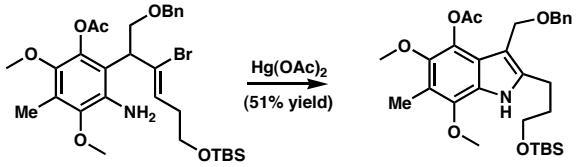

*From a Claisen rearrangement:*





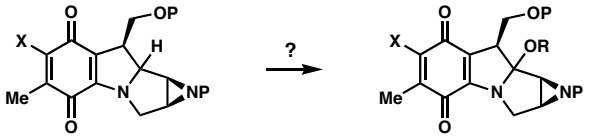
*31% yield from Claisen precursor to selenide elimination product.*

*Oxidation at C9a Needed!*

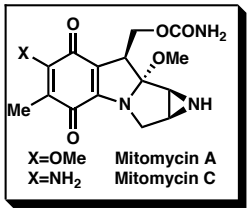


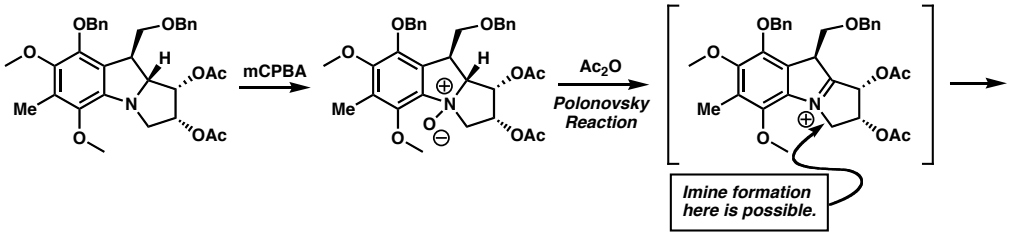
*Indole formation a continual problem.*

## Oxidation at C9a

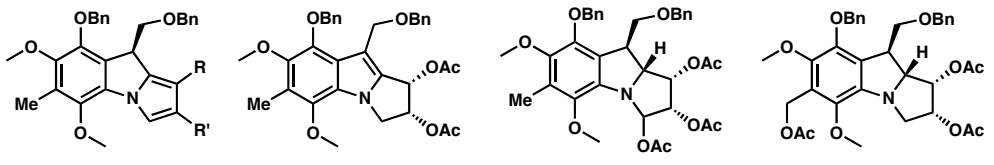


Looking at these sorts of compounds led to bioactivity studies.



*Imine formation here is possible.*



11% *either R or R' is OAc*

25%

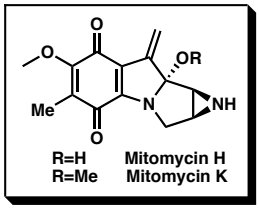
26%

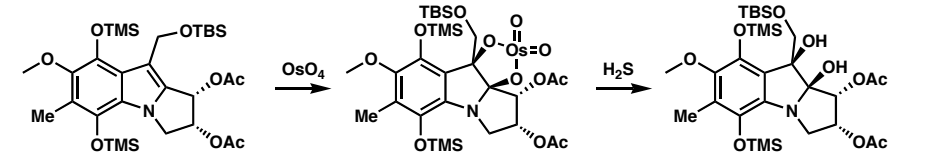
18%

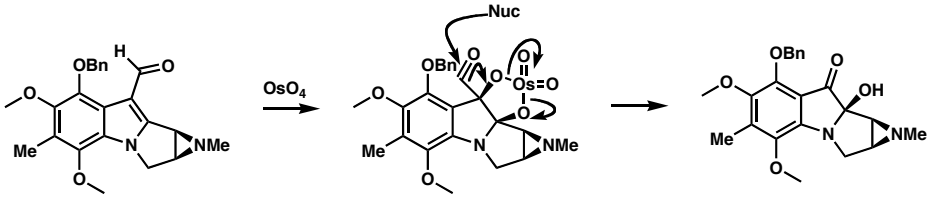
*Oxidation of C9a is not straightforward.*

## Mitomycin H and K

### Oxidation at C9-C9a



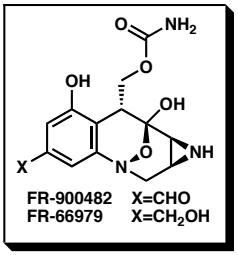



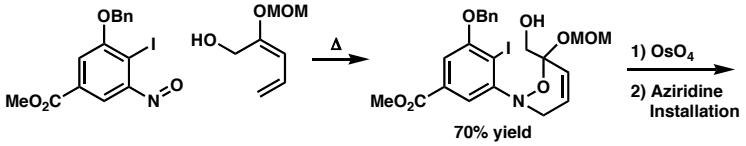

*Peterson Olefination*

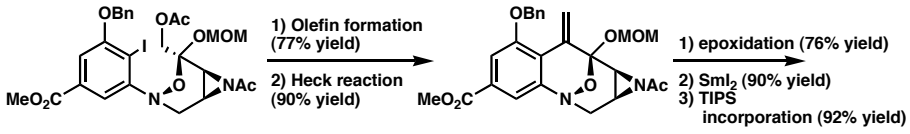
*Amazingly, this intermediate could not be equilibrated to Mitomycin H or K.*

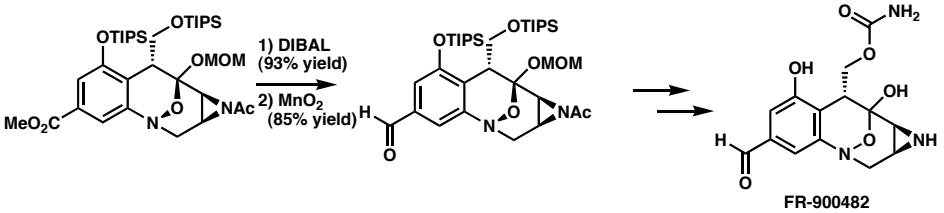
## The FR Series of Mitomycinoids

### Hetero Diels-Alder Reactions

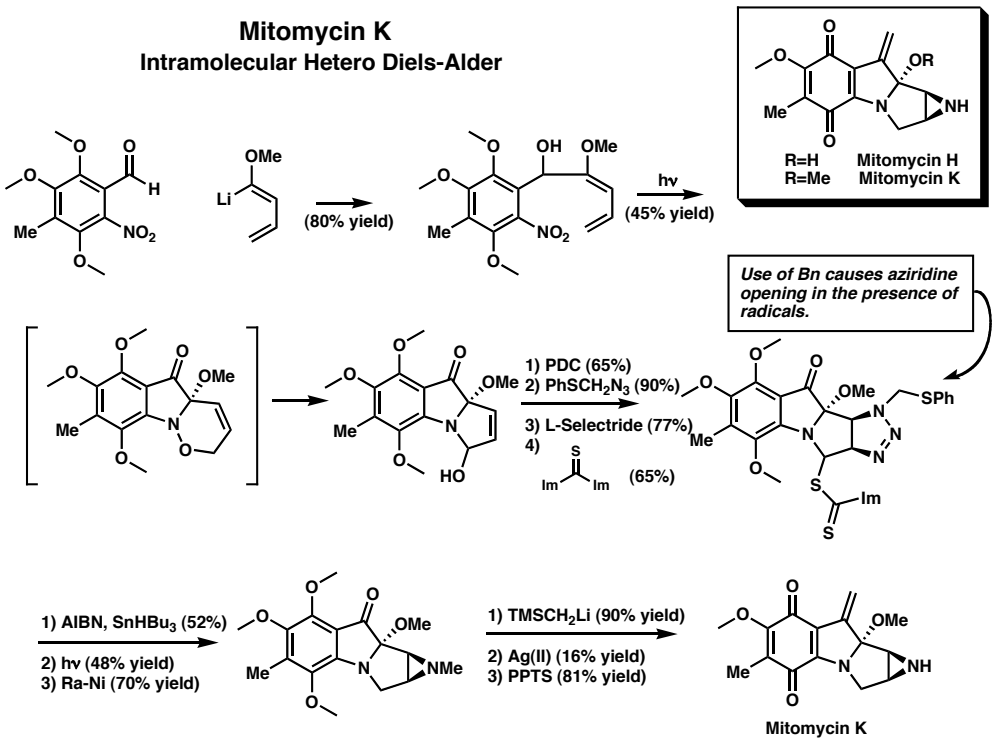


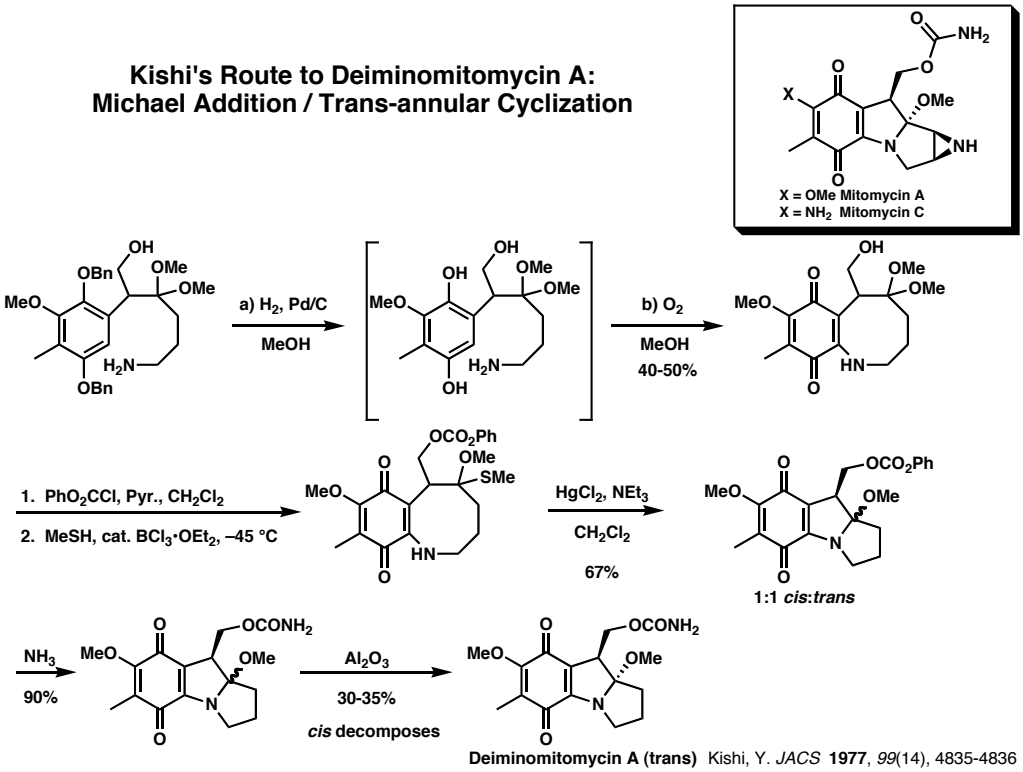



## Mitomycin K
### Intramolecular Hetero Diels-Alder

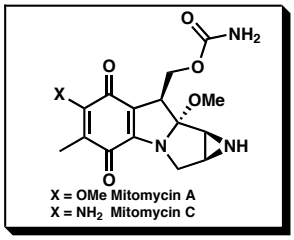


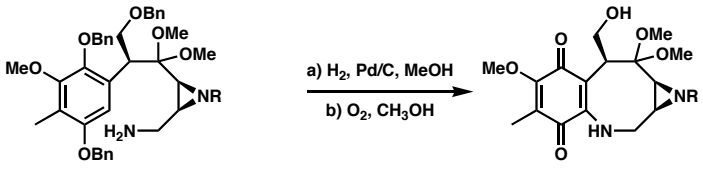

## Kishi's Route to Deiminomitomycin A:
## Michael Addition / Trans-annular Cyclization

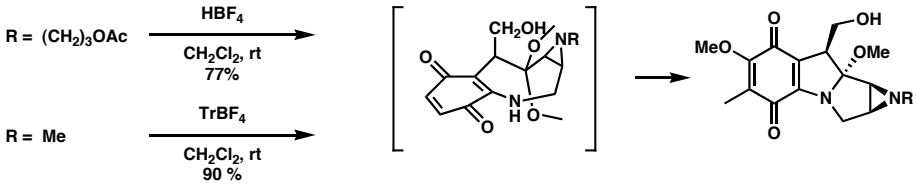



Kishi, Y. *JACS* **1977**, *99*(14), 4835-4836

## Kishi's Route to Mitomycin A: Michael Addition / Trans-annular Cyclization

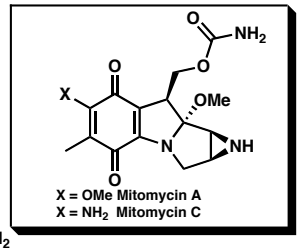


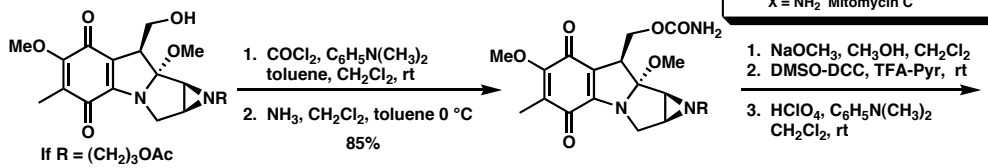



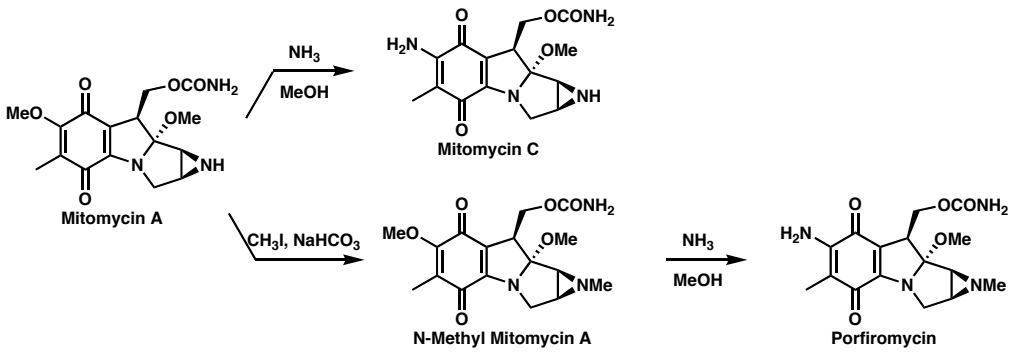




Kishi, Y. *TL* **1977**, *49*, 4295-4298
Kishi, Y. *JACS* **1977**, *99*(14), 8115-8116

## Kishi's Route to Mitomycins A and C, and Porfiromycin: End Game

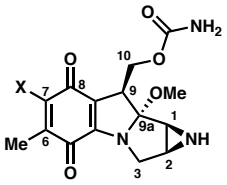


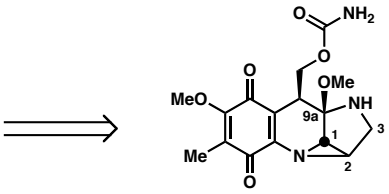




Lancaster, J. *JACS* **1962**, 3185-3187

## The Fukuyama Approach





| | X |
|---|---|
| Mitomycin A | OMe |
| Mitomycin C | $NH_2$ |

Isomitomycin A

**Problems to consider:**

reactive quinone
reactive aziridine
methanol elimination

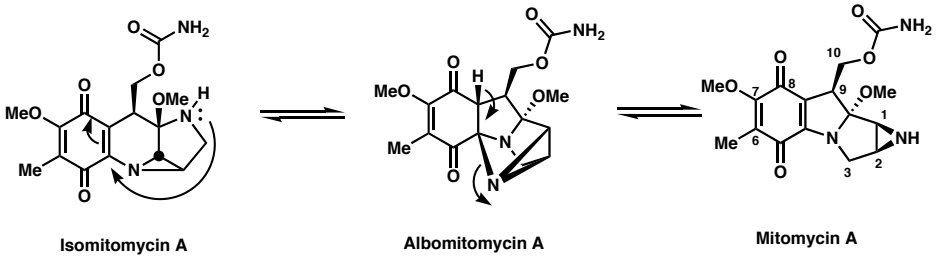
**Fukuyama's Solution:**

Prepare Isomitomycin A and perform 'Mitomycin Rearrangement'

**Fukuyama Total Synthesis Efforts:**

*JACS* 1987, *109*, 7881-7882; 1st generation synthesis
*JACS* 1987, *111*, 8303-8304; 2nd generation synthesis

## The Mitomycin Rearrangement

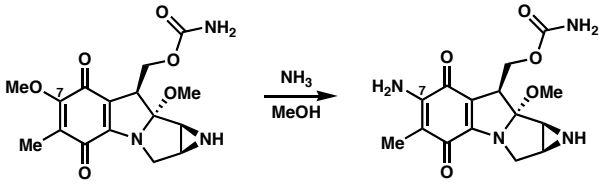


Isomitomycin A — Albomitomycin A — Mitomycin A

- Mixture isolated from fermentation broth of *streptomyces caespitosus*
- Mitomycin A is heavily favored

*JACS* 1987, *109*, 7224-7225

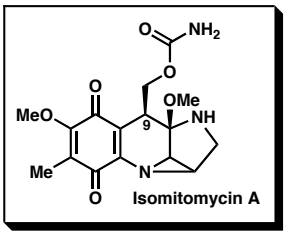
## Access to Both Mitomycins A & C

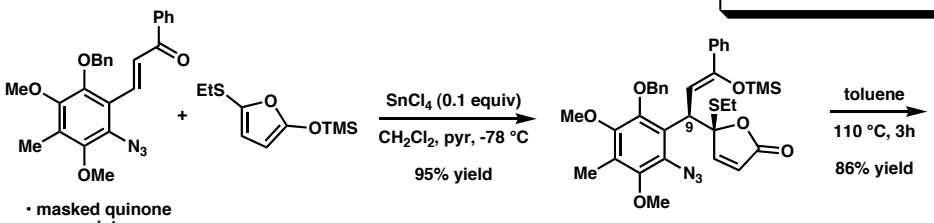


Mitomycin A — Mitomycin C

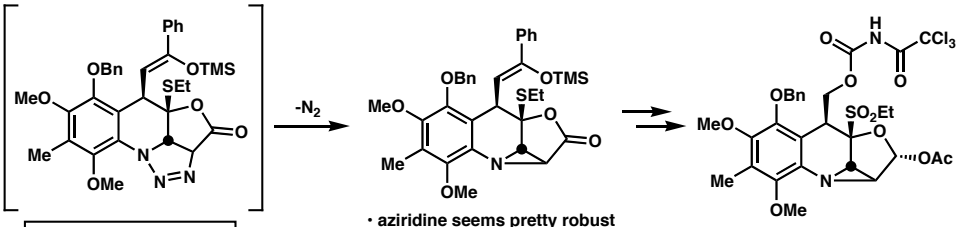
*JACS* 1962, *84*, 3185

## Fukuyama's Route to Isomitomycin A: Assembling the Carbon Framework



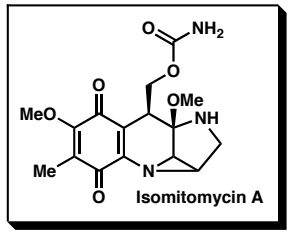

- masked quinone moiety
- High diastereoselectivity? Possibly endo Diels-Alder reaction, then retro aldol.

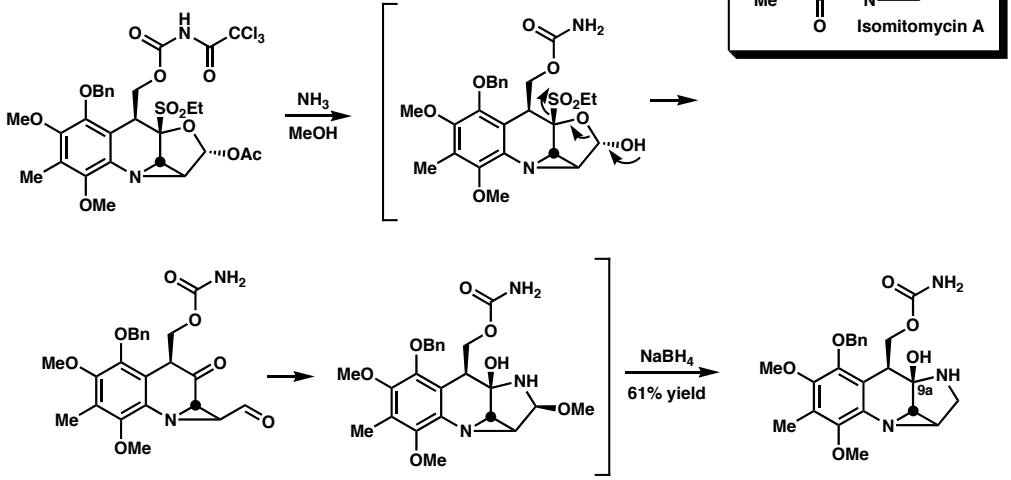



*JOC* 1981, 46, 3970-3977

- aziridine seems pretty robust

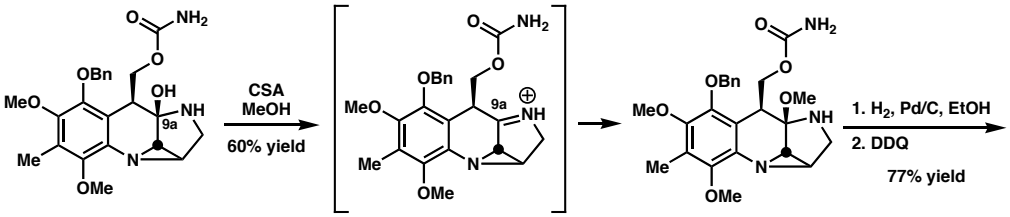
## Fukuyama's Route to Isomitomycin A: Late-Stage Manipulations



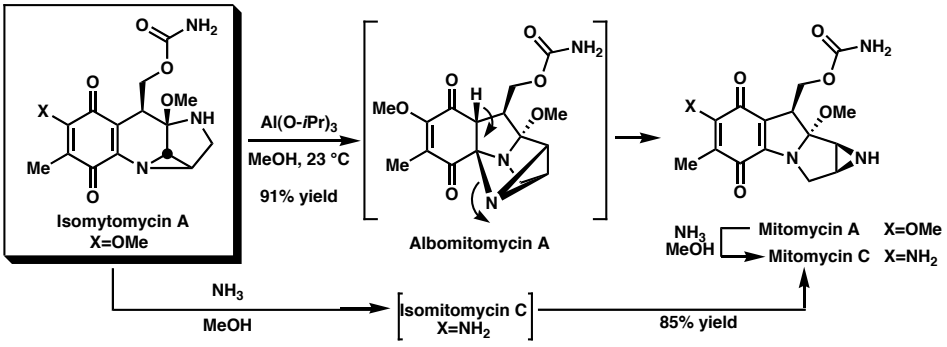




- bridgehead hemiaminal (9a) stable to reaction conditions!

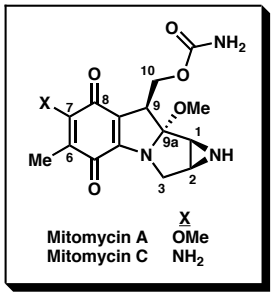
## The Total Synthesis of Isomitomycin A, Isomitomycin C, Mitomycin A, and Mitomycin C




- highly strained iminium ion formed under carefully controlled acidic conditions




## Mytomycin Synthetic Challenges and Solutions - Summary




| Problems | Solutions to date | New Solutions? |
|---|---|---|
| • quinone reactivity<br>-aromatization<br>-Michael acceptor | • install at late stage<br>• carry as aromatic derivative | Team 1 |
| • C(9a) reactivity<br>-loss of OMe | • install functionality at C(9a) early<br>• install C(9a) OMe at late stage | Team 2 |
| • reactive aziridine | • install at late stage | Team 3 |
| • stereocontrol<br>-no asymmetric synthesis to date | • make more rigid system to enhance diastereoselectivity | Team 4 |