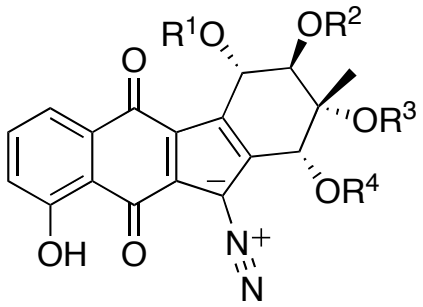
Total Synthesis of Kinamycins C, F, and J



Kinamycin scaffold

K.C. Nicolaou, Hongming Li, Andrea L. Nold, Doron Pappo, and Achim Lenzen

J. Am. Chem. Soc., **2007**, *ASAP*

John Maciejewski
Wipf Group Current Literature
August 18, 2007

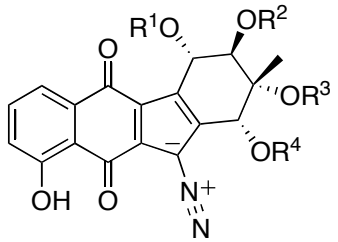
Isolation and Brief History

Kinamycins A, B, C, and D isolated from fermentation broth of *Streptomyces murayamaensis* (Ito, Hata)

Assignment of core structure subject of controversy

Installation of densely oxygenated cyclohexane D-ring and diazo functionality present synthetic challenges

Kinamycin family known to possess antibiotic and antitumor activities

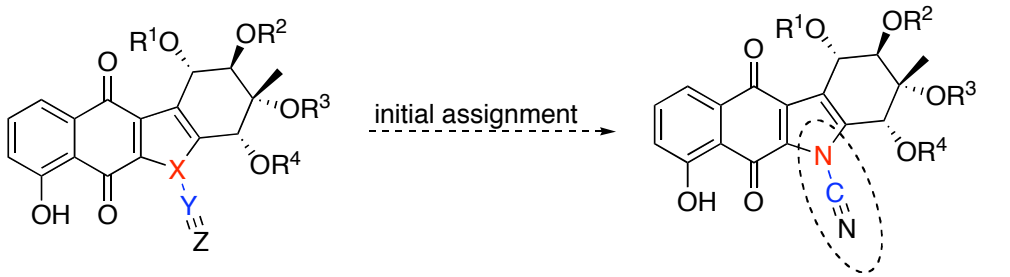


Kinamycin scaffold

Kinamycin **A**: R^1 = H, R^2 = Ac, R^3 = Ac, R^4 = Ac
Kinamycin **B**: R^1 = H, R^2 = H, R^3 = Ac, R^4 = H
Kinamycin **C**: R^1 = Ac, R^2 = Ac, R^3 = H, R^4 = Ac
Kinamycin **D**: R^1 = H, R^2 = Ac, R^3 = H, R^4 = Ac

Ito, S.; *J. Antibiot.* **1970**, *23*, 315
Hata, T; *J. Antibiot.* **1971**, *24*, 353
Gould, S. J.; *Chem. Rev.* **1997**, *97*, 2499

Initial Structural Assignment of Kinamycin Core



cyanobenzo[*b*]carbazole system

Used IR, ^{1}H, ^{13}C, and X-ray analysis to assign kinamycin core

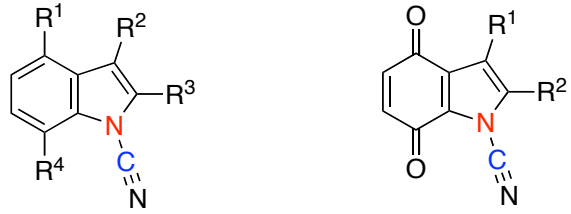
- Poor quality X-ray data of kinamycin C
- Could not unambiguously assign X-Y-Z connectivity
- Either cyanide or isocyanide (diazo connectivity not considered(?))

Hata, T.; *Isr. J. Chem.* **1972**, *10*, 173
Dmitrienko, G. I.; *J. Am. Chem. Soc.* **1994**, *116*, 2207 - 2208

Structural Revisions

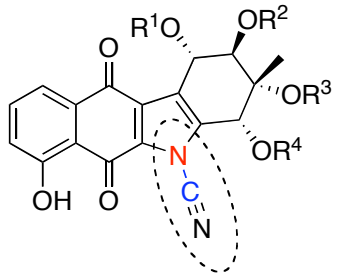
Gould and Dmitrienko independently revised structure based upon (original) X-ray structure, as well as indepth IR, NMR, and synthetic studies.

Scaffolds prepared by Dmitrienko



compared to…

Original assignment of kinamycin core



cyanobenzo[*b*]carbazole system

22 *N*-cyanoindole derivatives (Dmitrienko):

- IR range (2237 - 2245 cm^{-1})
- ^{13}C NMR (δ 105 - 108) for cyanamide carbon

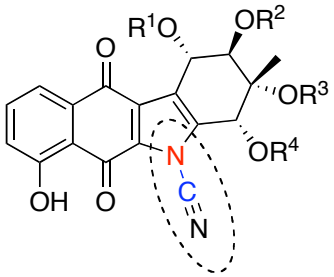
Kinamycin spectral data (Hata):

- IR range (2119 - 2170^{-1})
- ^{13}C NMR (δ 78.5 - 83.7) “cyanamide” carbon

Dmitrienko, G. I.; *Tet. Lett.* **1990**, *31*, 3681
Gould, S.; *J. Am. Chem. Soc.* **1994**, *116*, 2207 - 2210.
Dmitrienko, G. I.; *J. Am. Chem. Soc.* **1994**, *116*, 2207 - 2208

Structural Revisions

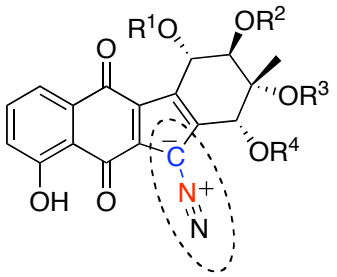
Original assignment of kinamycin core
(Hata)



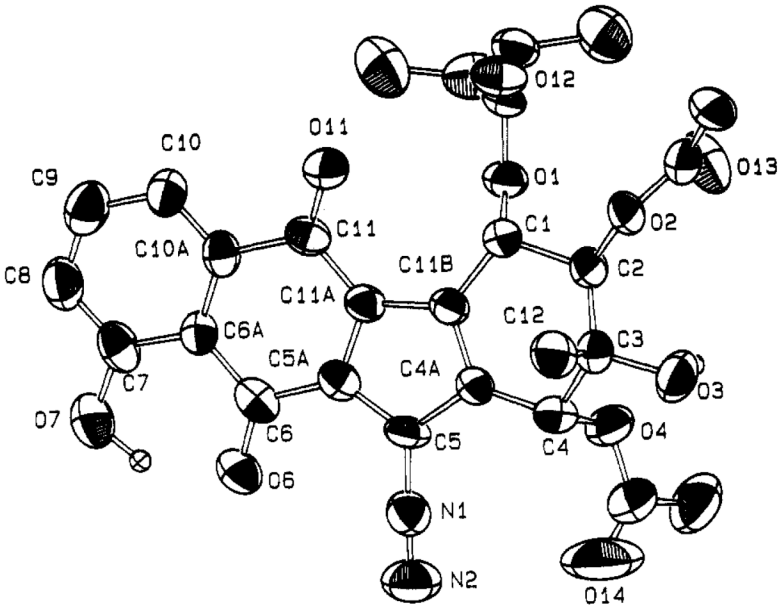
cyanobenzo[*b*]carbazole system

reassignment

Revised kinamycin core
(Gould & Dmitrienko)



diazobenzo[*b*]fluorene ring system



Crystal structure of kinamycin D (Gould)

Kinamycin spectral data:

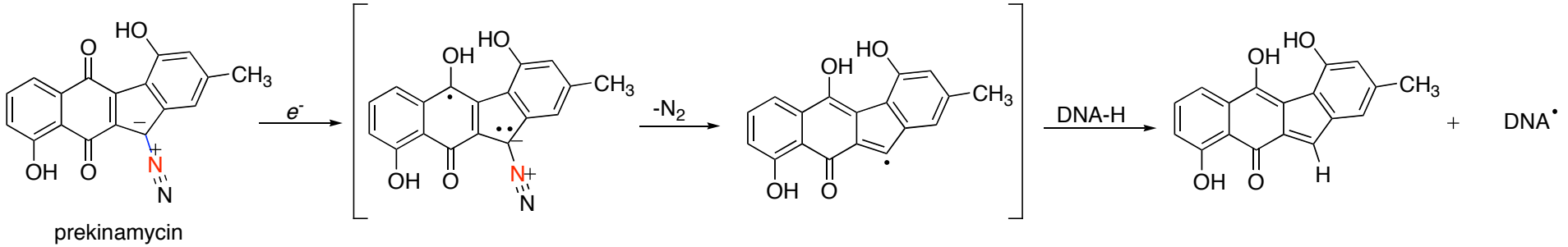
Diazo bands - IR (2119 - 2170^{-1}) -C=N=N

^{13}C NMR (δ 78.5 - 83.7) diazo carbon

Gould, S.; *J. Am. Chem. Soc.* **1994**, *116*, 2207 - 2210.
Dmitrienko, G. I.; *J. Am. Chem. Soc.* **1994**, *116*, 2207 - 2208

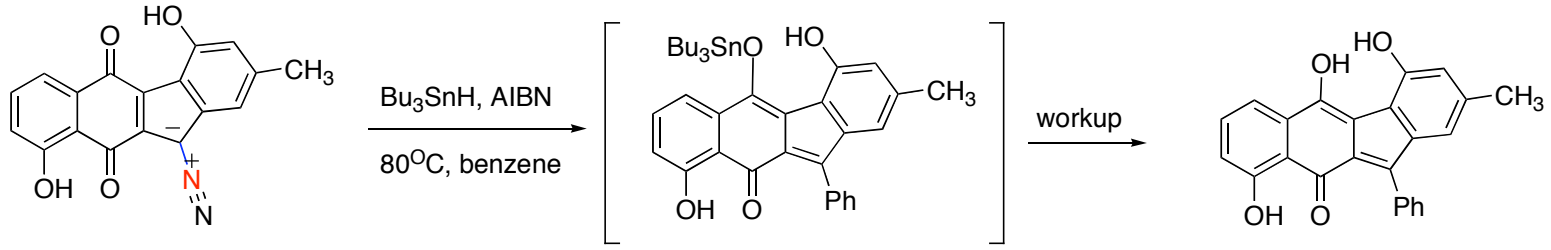
Proposed mechanism-of-action

Pathways to DNA cleavage



prekinamycin

Experimental observations

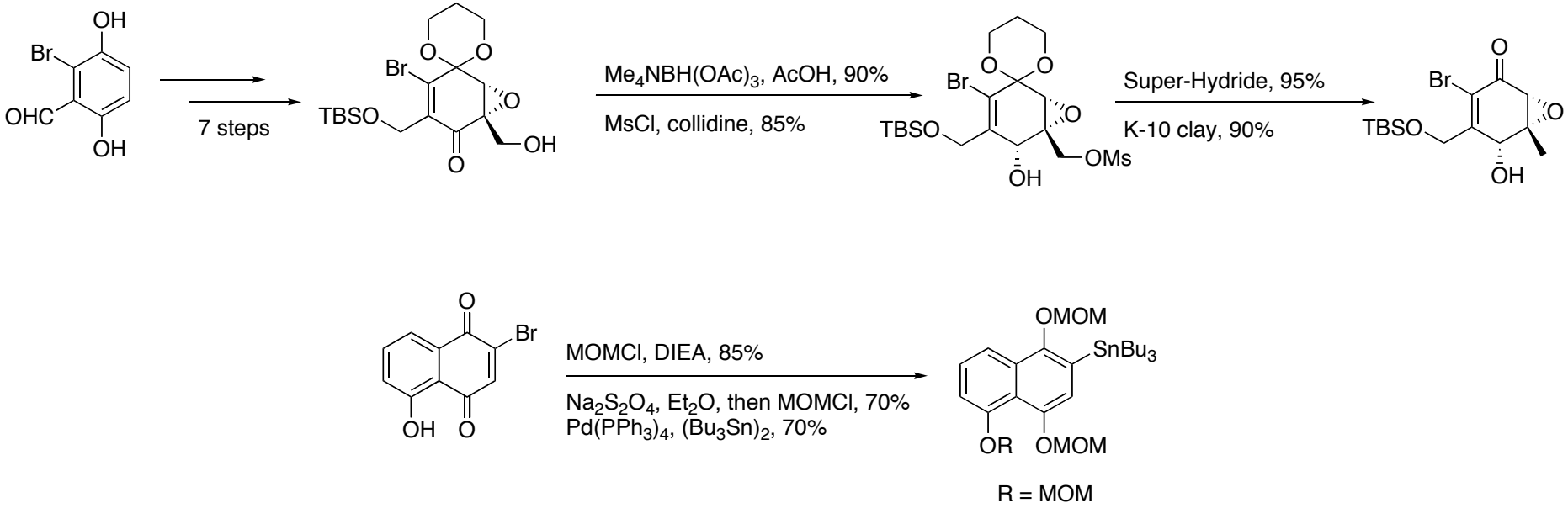


multiple aromatic solvents were screened

Feldman, K. S.; *J. Am. Chem. Soc.* **2005**, *127*, 15344
Melander, C.; *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5148
Arya, D. P.; *J. Org. Chem.* **1995**, 3268

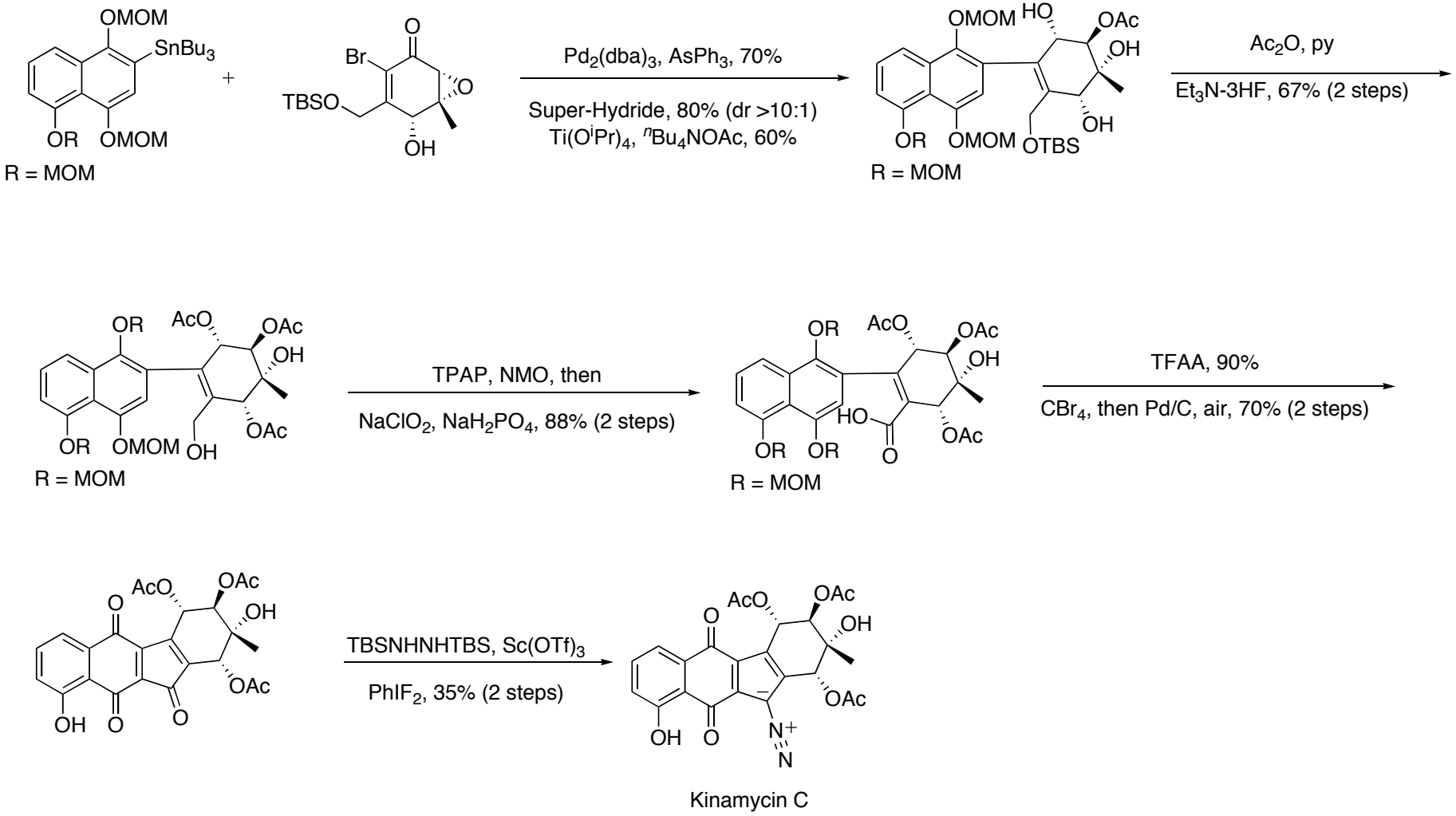
First Enantioselective Synthesis of Kinamycin C

Synthesis of two main fragments



Porco, J. A.; *J. Am. Chem. Soc.* **2006**, *128*, 14790

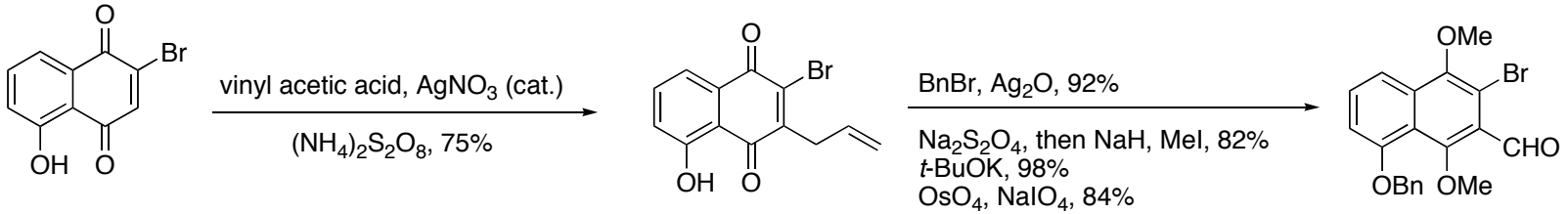
First Enantioselective Synthesis of Kinamycin C

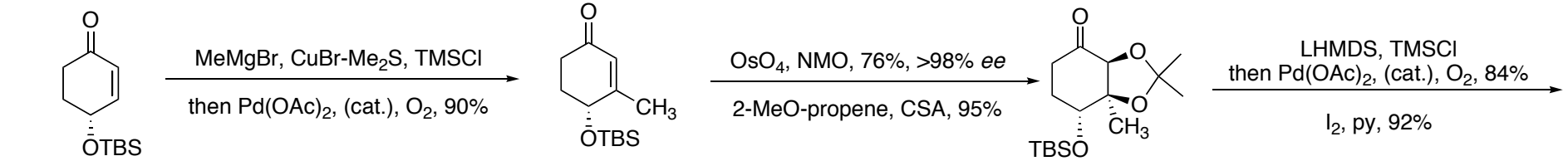


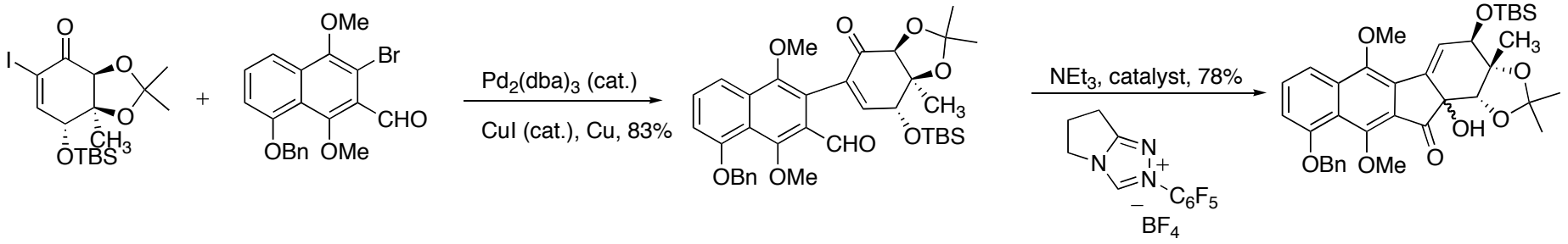
Porco, J. A.; *J. Am. Chem. Soc.* **2006**, *128*, 14790

Kinamycins C, F, and J

Assembling the kinamycin core

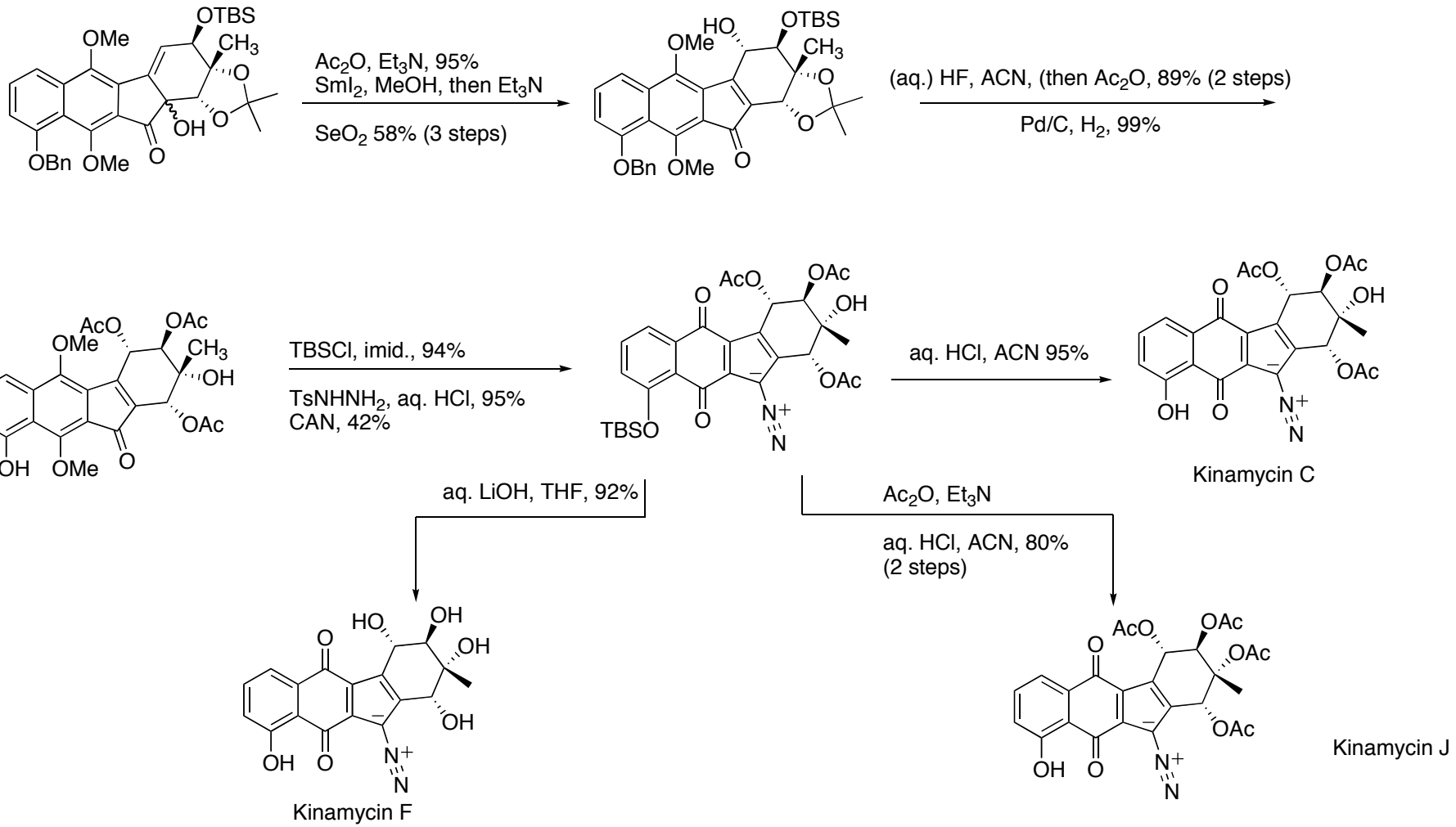






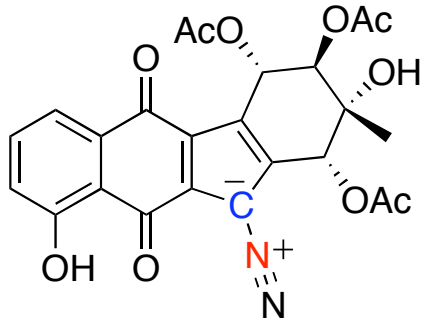
Nicolaou, K. C.; *J. Am. Chem. Soc.,* **2007**, *ASAP*

Kinamycins C, F, and J



Nicolaou, K. C.; *J. Am. Chem. Soc.,* **2007**, *ASAP*

Conclusions



Kinamycin C

Nicolaou synthesis summary:

- further manipulates kinamycin C to analogs F and J
- innovative benzoin-like addition to form C-ring
- used enantiomerically pure enone to control D-ring stereochemistry
- utilized CAN oxidation* to install quinone and diazo moiety

Porco synthesis summary:

- used proposed biomimetic approach to form C-ring
- uses asymmetric epoxidation to control stereochemistry of D-ring

*Kumamoto, T.; *Tetrahedron* **2007**, *63*, 5189