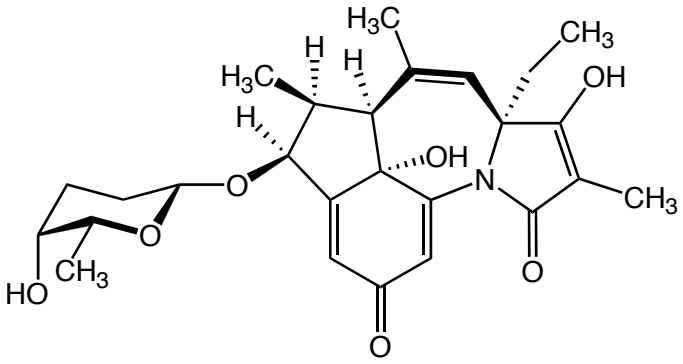
Quinones in Organic Chemistry:
Synthesis of and Applications Towards Natural Products



Tetrapetalone A (revised structure)
TL, **2003**, *44*, 7417

Literature Presentation
Ryan Zeidan
Stoltz Group Meeting 2/16/04

<u>Outline of Quinones</u>

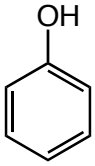
I. Introduction to Quinones
   A. Nomenclature
   B. Biochemistry
   C. Biosynthesis

II. Synthesis of Quinones via Oxidation
   A. Fremy's Salt
   B. CAN
   C. LTA
   D. DDQ
   E. Air

III. Other Syntheses of Quinones/Uses
   A. Boronic Esters
   B. Indoles
   C. DMP oxidation of anilides
   D. Cyclobutenediones
   E. Benzoin reaction

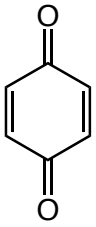
IV. Applications to Natural Products
   A. Aflatoxin B
   B. Elisabethin A
   C. Lemonomycin

Quinone Background - Nomenclature

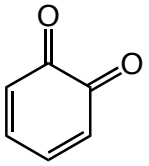


Phenol

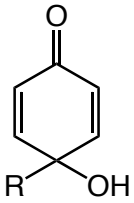
Hydroquinone



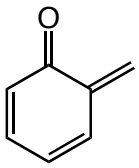
p-Quinone



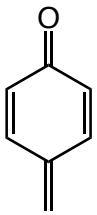
o-Quinone



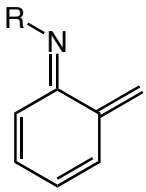
Quinol



o-Quinone methide

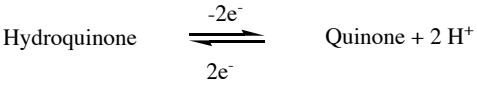


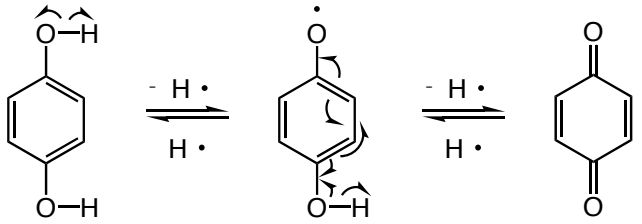
p-Quinone methide



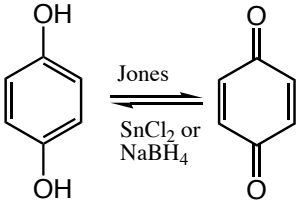
o-Quinone methide imine

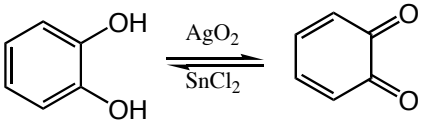
<u>Redox Process</u>





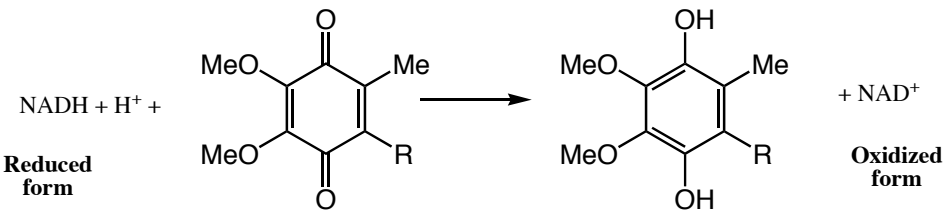
hydroquinone semiquinone quinone

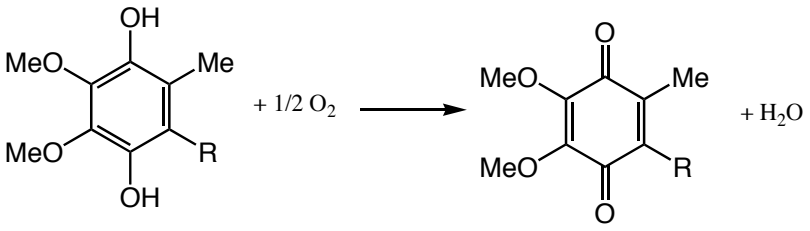




Quinones in Nature

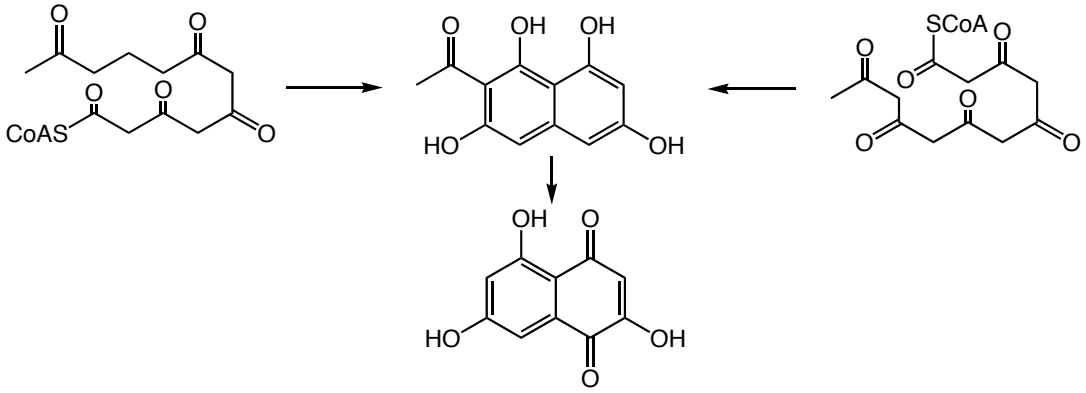
- Ubiquinones mediate electron transfer processes involved in energy production through their redox reactions:

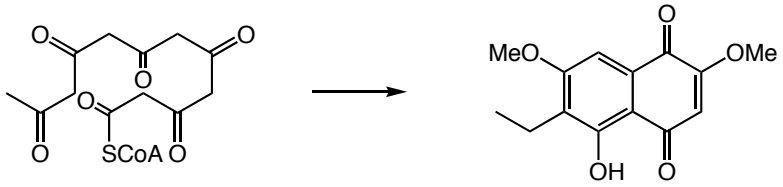




Net Change: $NADH + 1/2\ O_2 + H^+ \longrightarrow NAD^+ + H_2O$

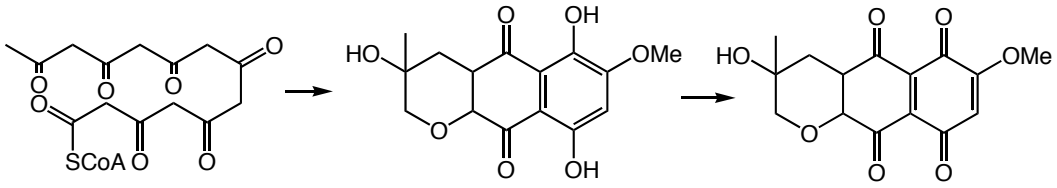
Biosynthesis of Quinones: Pentaketides



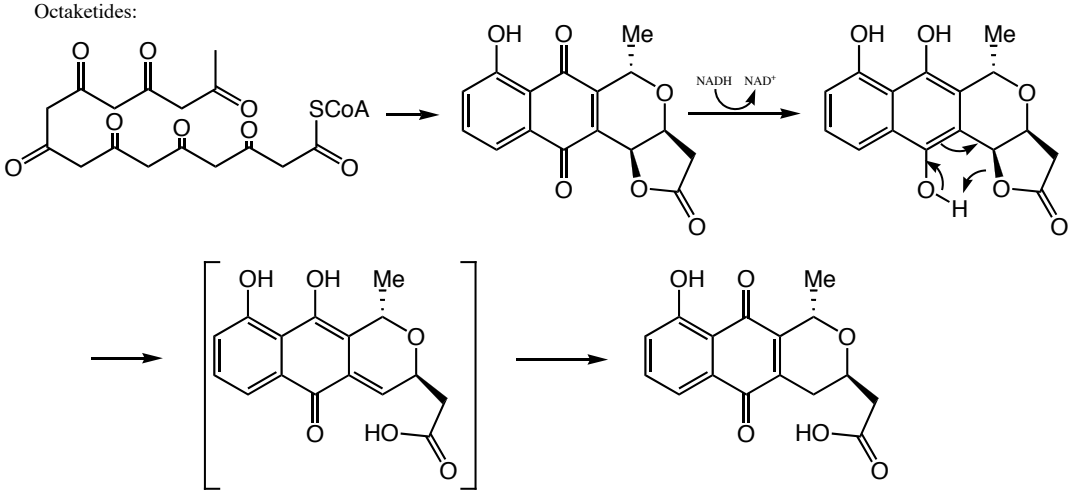


Biosynthesis Continued

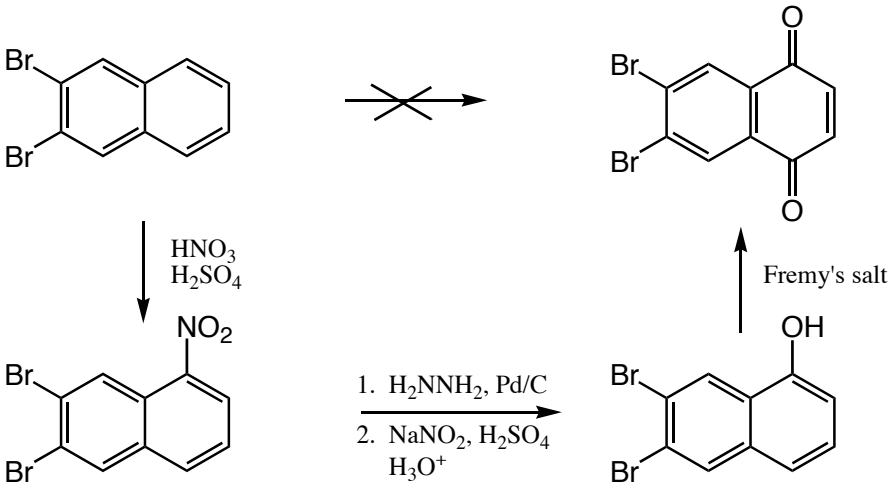
Heptaketides:



Octaketides:



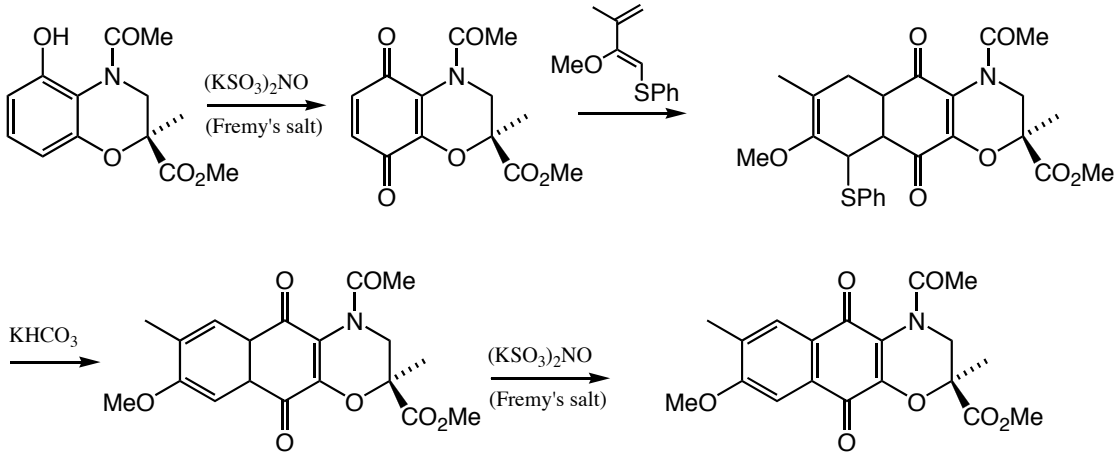
A Representative Difficulty in Direct Oxidation of Arenes



- Direct oxidation of the unactivated arene was not achievable
- A round about sequence of nitration, reduction, diazotization, displacement by hydroxide and finally oxidation of the phenol was necessary to form the quinone
- Unactivated arenes present a difficulty in quinone synthesis

Fremy's Salt

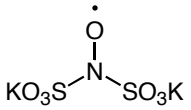
A Typical Example:



JOC, **1981**, *46*, 2426.

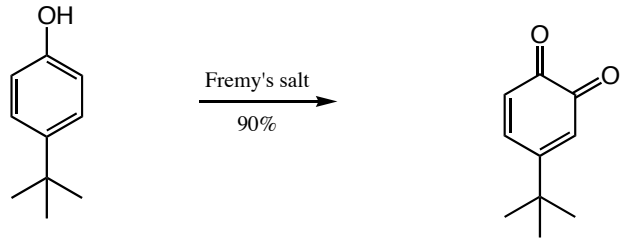
- Fremy's salt oxidizes most phenols to p-quinones when there is no para substituent on the phenol
- Salt is a stable free radical that oxidizes via a free radical mechanism
- Oxygen incorporation occurs exclusively from the oxygen of Fremy's salt

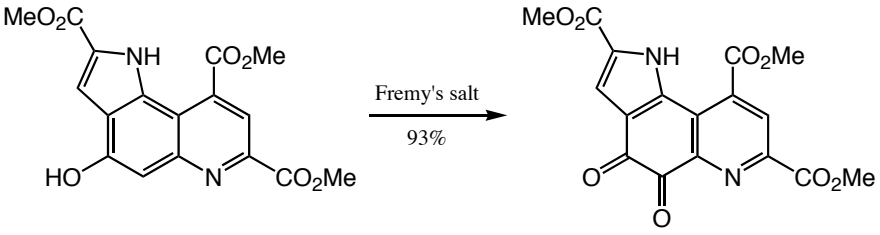
Fremy's salt =



Fremy's Salt (cont'd)

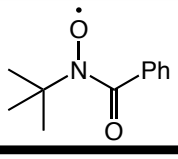
Gives o-quinones when para position is substituted:



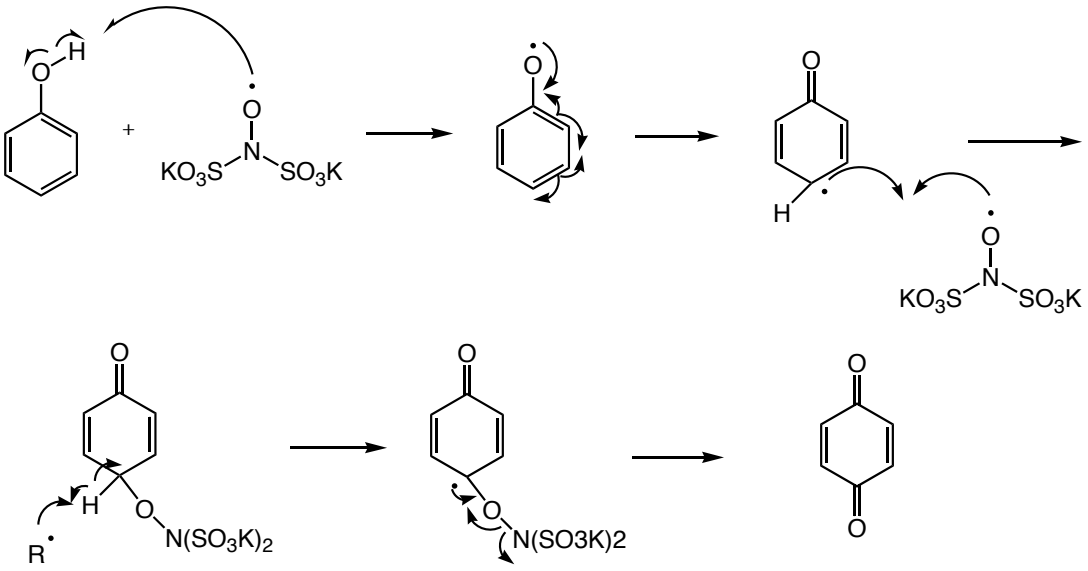


MacKenzie, A. R. *Tetrahedron*, **1986**, *42*, 3259

A more oganic soluble form of Fremy's catalyst =

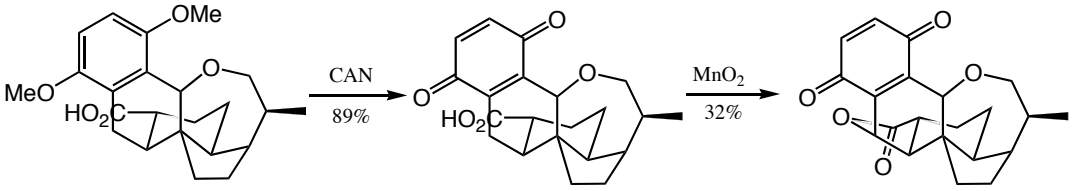


Fremy's Salt Mechanism



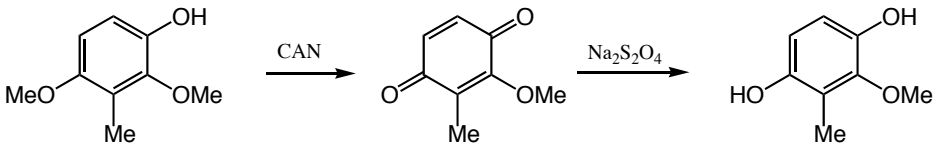
-O^{18} isotope experiments showed that oxygen incorporation was exclusively from Fremy's salt oxygen

CAN Oxidations



pleurotin

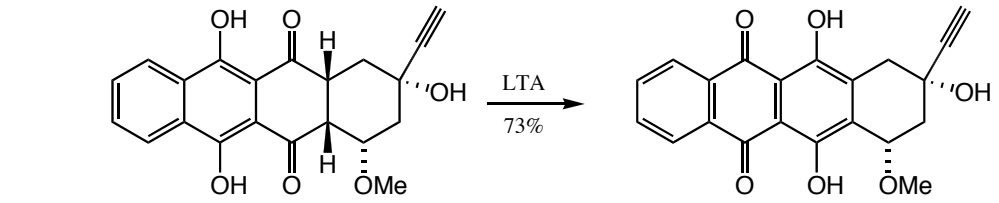
JACS, **1988**, *11*, 1634



JACS, **2003**, *125*, 4680

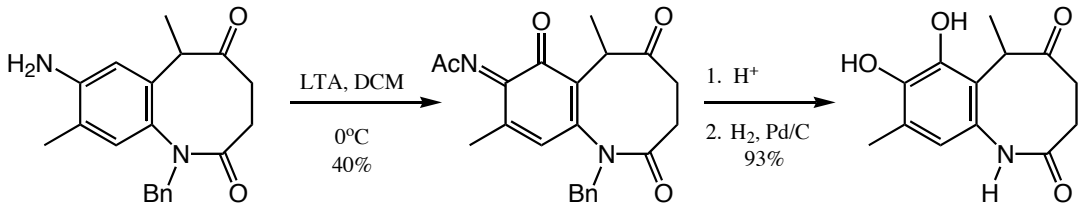
- CAN is the reagent of choice for oxidative demethylation of methoxyarenes
- CAN/$Na_2S_2O_4$ sequence provides an overall net demethylation of methoxyarenes
- CAN is $(NH_4)_2Ce(NO_3)_6$

LTA Oxidations



J. Chem. Soc., P.T. 1, **1985**, 525

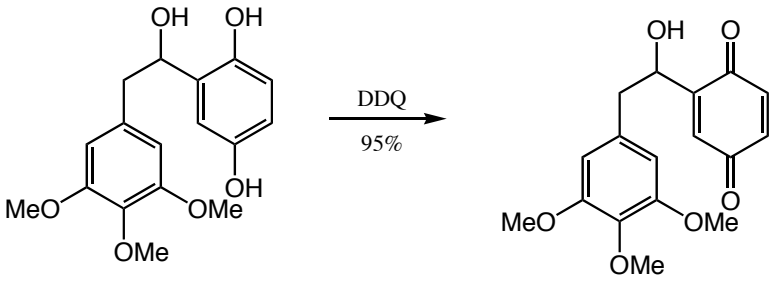
- LTA can cause an oxidative isomerization



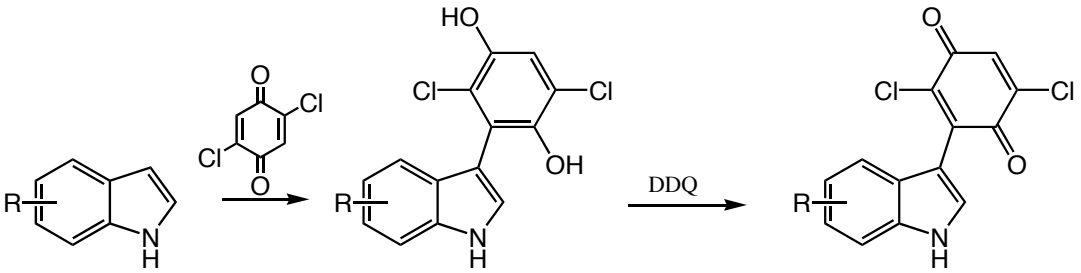
JOC, **1988**, *53*, 5355

- Oxidation of the aniline to the o-quinoneimide occurs in modest yield

DDQ Oxidations



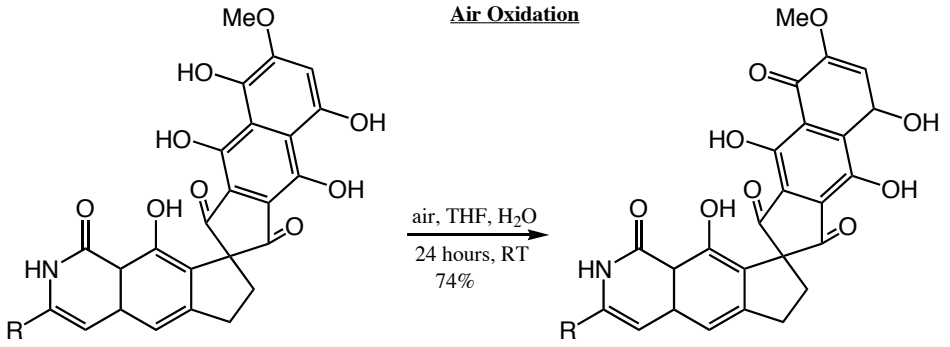
JOC, **1999,** *64*, 1720



Org. Lett., **2001**, *3*, 365

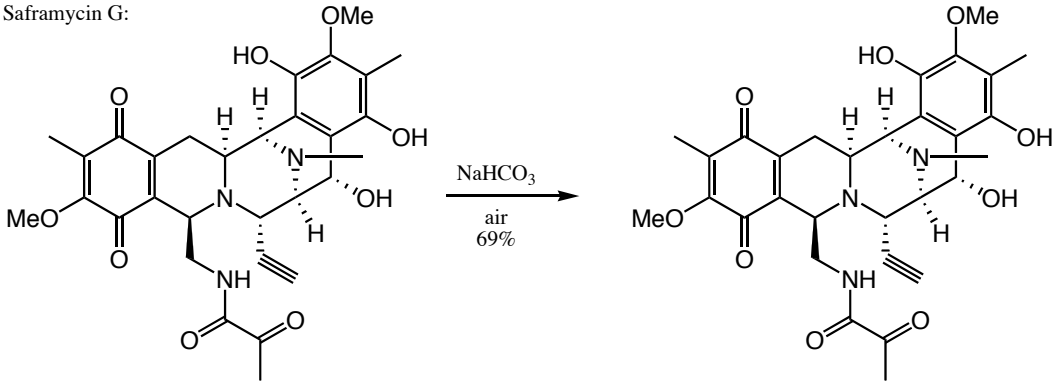
- DDQ is a competant oxidant for quinone formation, although CAN is more robust and typically higher yielding

Air Oxidation



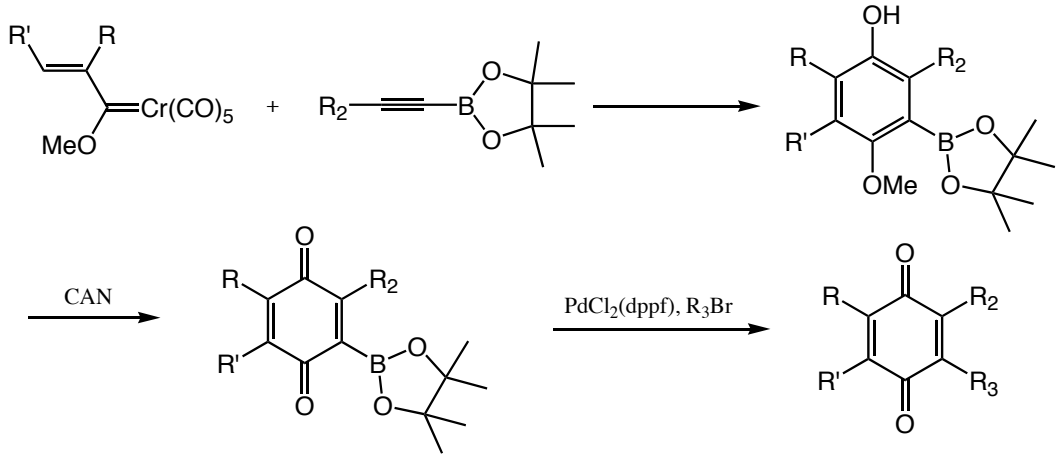
Kita, Y. *JACS*, **2001**, *123*, 3214

Saframycin G:



Chem. Pharm. Bull., **1995**, *43*, 777.

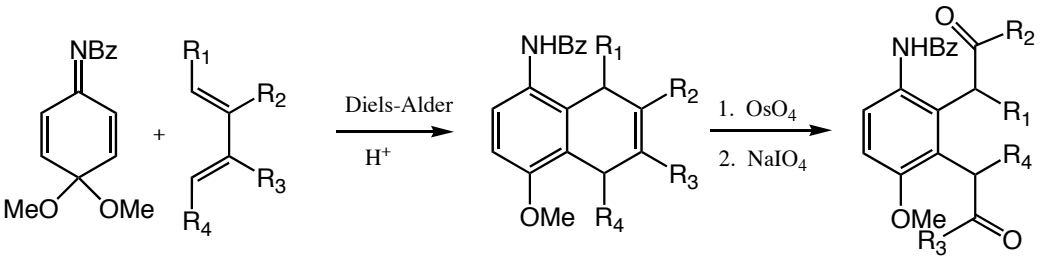
Quinone Boronic Esters

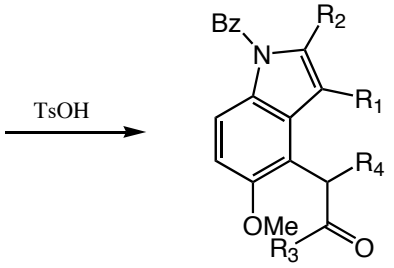


- Allows for regioselective hydroquione formation
- Cerium oxidation of crude reaction mixture afforded quinones in good yields
- Quinone boronic esters were reactive in Suzuki couplings to give unsymmetrical quinone products as single regioisomers

Harrity, J. P. A., et. al. *J. Org. Chem.*, **2001**, *66*, 3525

Synthesis of Indoles from Quinones

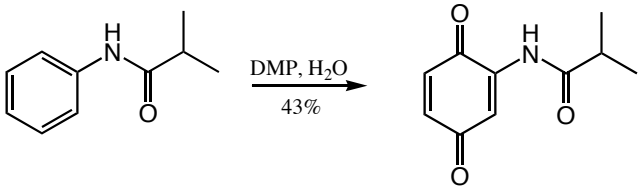




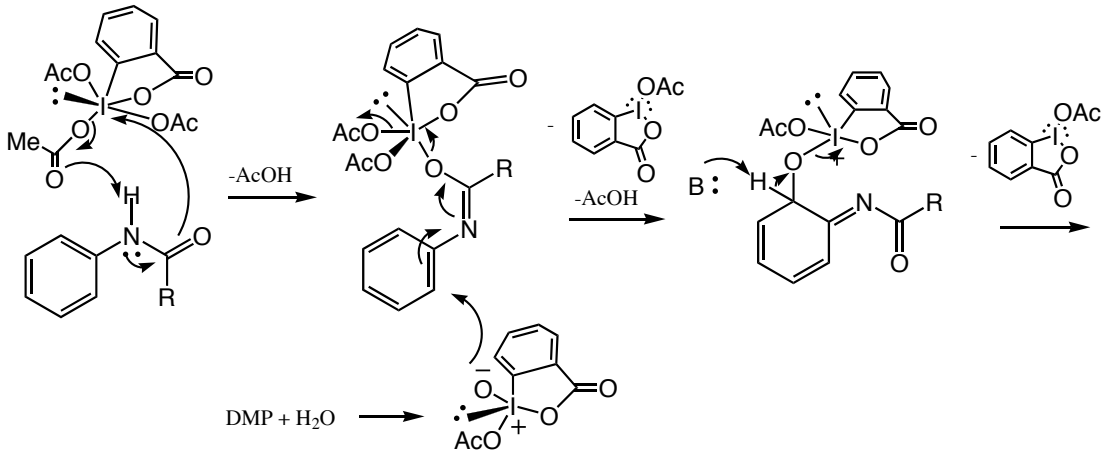
Indoles made in 32-70% overall yields with wide range of substitution tolerated

Kerr, M. A., et. al. Org. Lett, **2001**, *3*, 3325.

DMP Oxidations

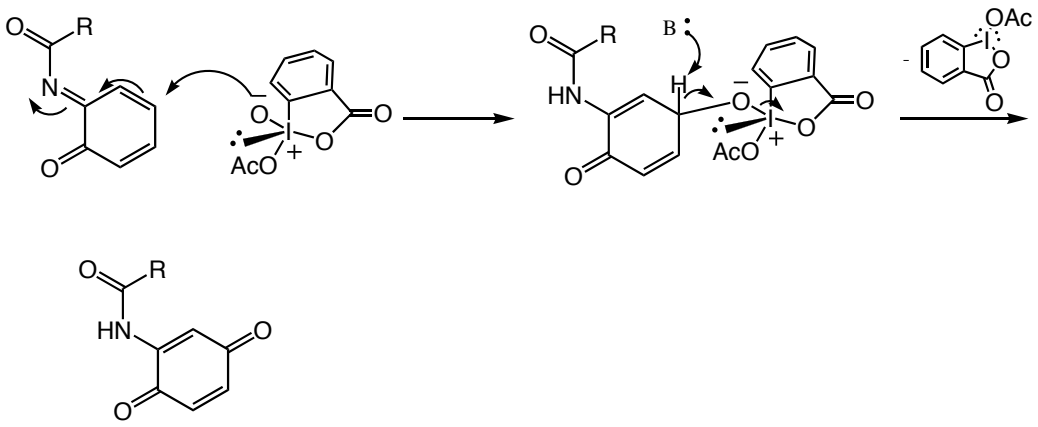


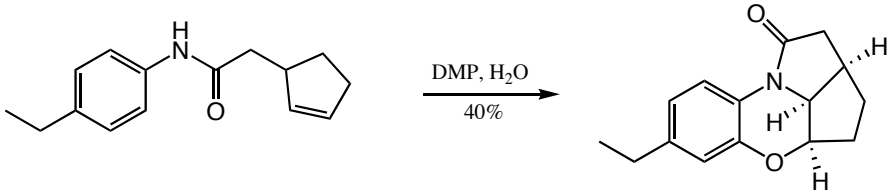
Mechanism:



Nicolau, K.C. *JACS*, **2002**, *124*, 2212.

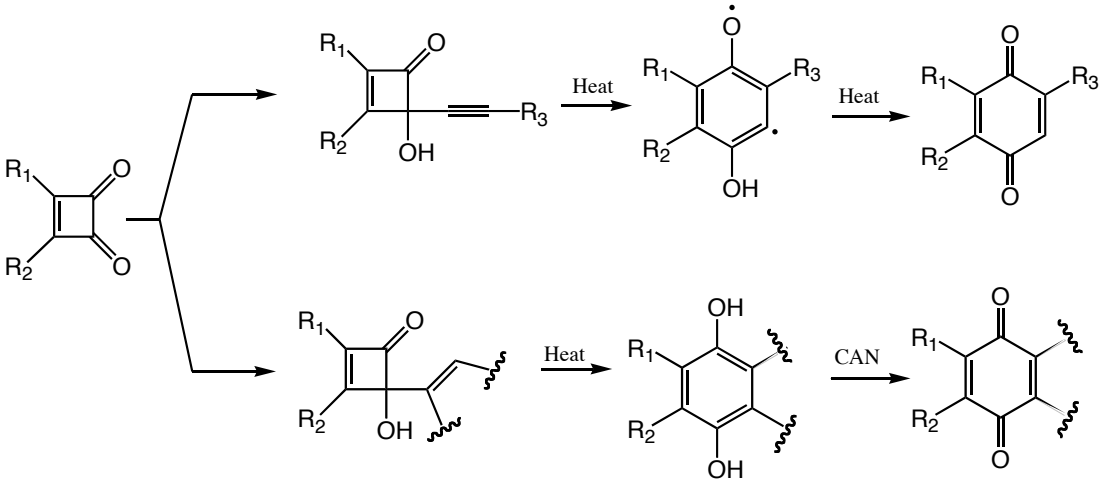
DMP Oxidation (cont'd)





Nicolau, K.C. *JACS*, **2002**, *124*, 2212.

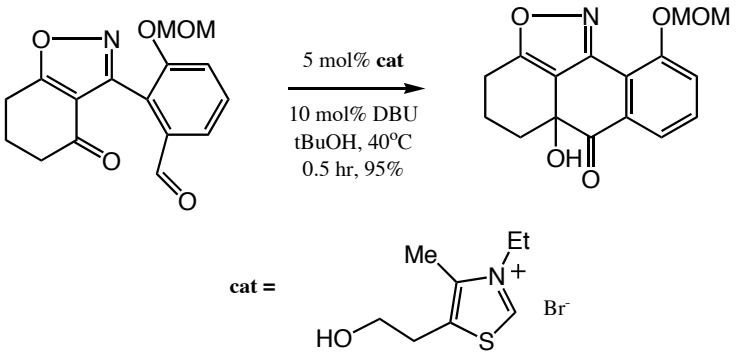
Regiospecific Synthesis of Quinones from Cyclobutenediones

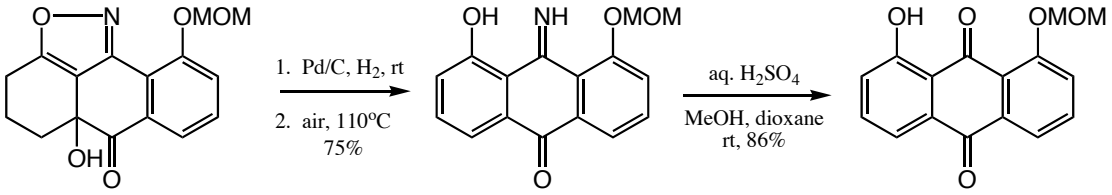


- For synthesis of cyclobutenediones see JOC, 1988, *53*, 2477.

Liebeskind, L. S., et. al. *J. Org. Chem.*, **1992**, *57*, 4345

Benzoin Reaction Approach to Quinones

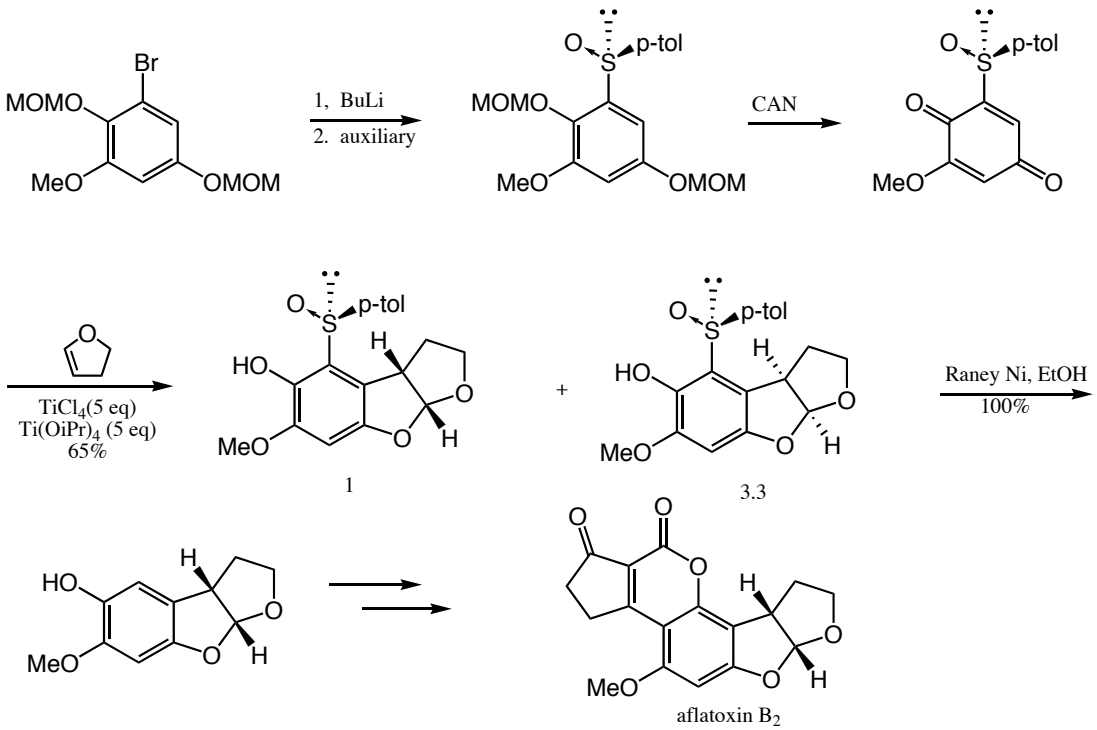




- Crossed aldehyde-ketone benzoin reaction worked well for a variety of substrates
- Substitution allows access to functionalized anthraquinones

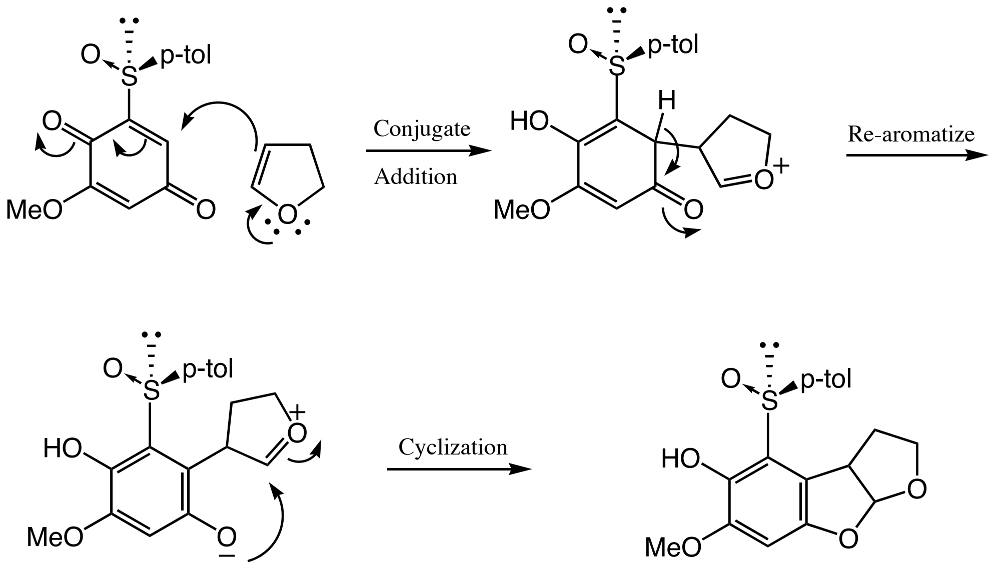
Suzuki, K. *JACS*,, **2003**, *125*, 8432

Quinone Approach to Aflatoxin B_2



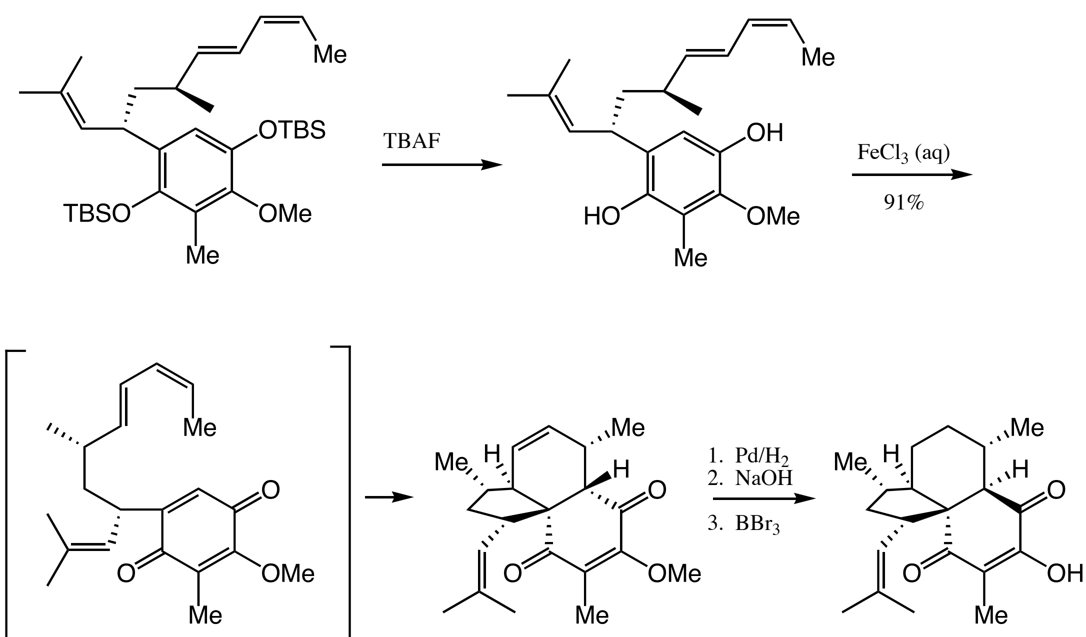
Noland, W. E. *Org. Lett.*, **2000**, *2*, 2109

Mechanism of Furan Addition



Chem. Lett., **1987**, 2169

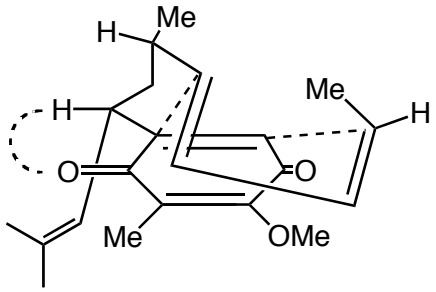
Total Synthesis of Elisabethin A: IMDA Using a Quinone



elisabethin A

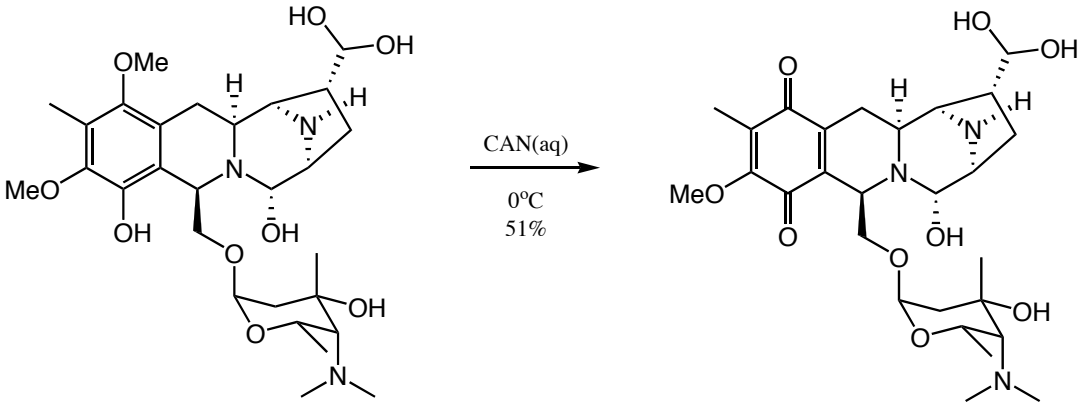
Mulzer, J. *JACS*, **2003**, *125*, 4680.

IMDA Transition State



Minimizing allylic strain controls facial selectivity
in the DA transition state, taken into account
with an endo approach gives rise to the observed selectivity

Stoltz Lab Quinone Work: Lemonomycin



Ashley, E.R.; Cruz, E. G.; Stoltz, B.M. *JACS*, **2003**, *125*, 15000.