Singlet Oxygen in Organic Synthesis

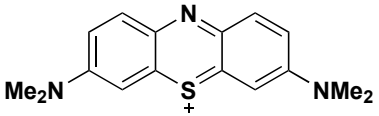
Reviews: *Acc. Chem. Res.* **2008**, 1001
Tetrahedron, **2006**, 5308
Tetrahedron, **2005**, 6665
Pure Appl. Chem., **1975**, 481
Chem. Rev., **1981**, 91

Characteristics of Singlet Oxygen

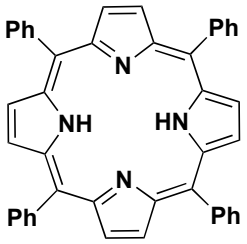
- 94.3 kJ/mol above Triplet State
- Singlet→Triplet transition is spin forbidden
- Lifetime of 74 minutes in gas phase
- Solution lifetime is highly solvent dependent
  - -CCl_4 : 59 ms
  - -Benzene : 30 μs
  - -H_2O : 3.5 μs

Generation and Reaction Conditions

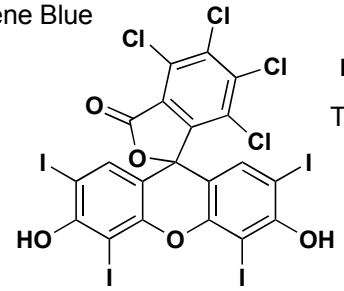
-Easily generated using light and a suitable photosensitizer
-Typically sensitized with Methylene Blue, Tetraphenylporphryin, or Rose Bengal



Methylene Blue



Tetraphenylporphryin

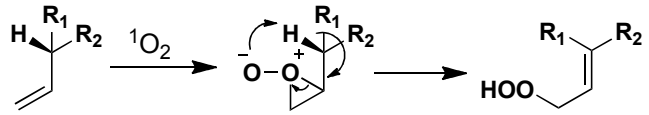


Rose Bengal

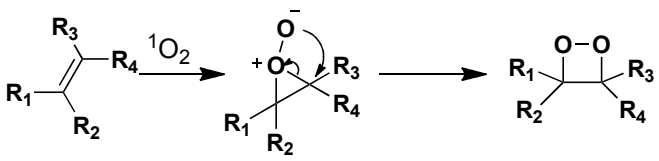
- Can also be generated by decomposition of hydrogen peroxide or organic peroxides
- Typical reaction conditions involve irradiation at low temperature because of the instability of many organic peroxides

Prototypical Singlet Oxygen Reactions

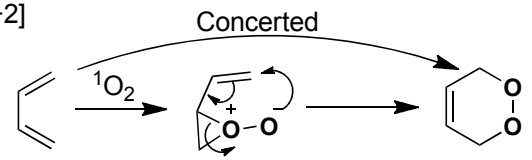
Ene:



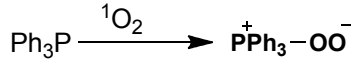
[2+2]



[4+2]

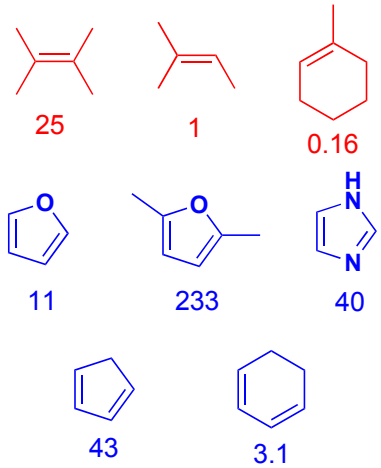


Heteroatom Oxidation



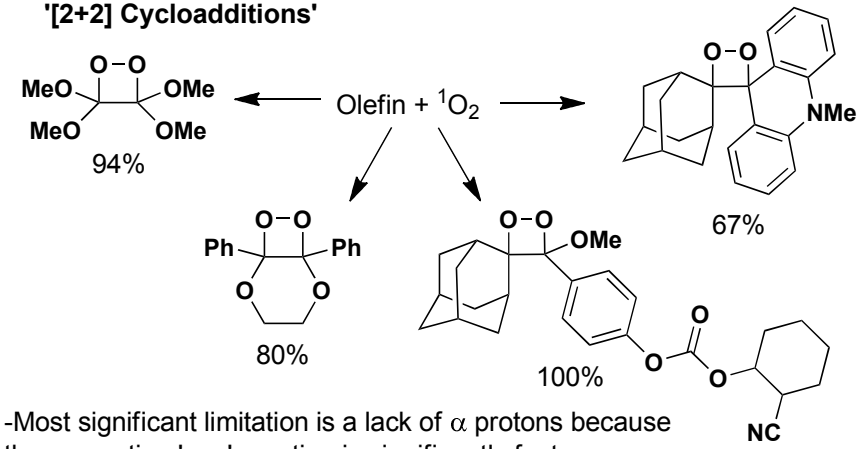
Chem. Rev., **2008**, 1052

Relative Rates of Reaction



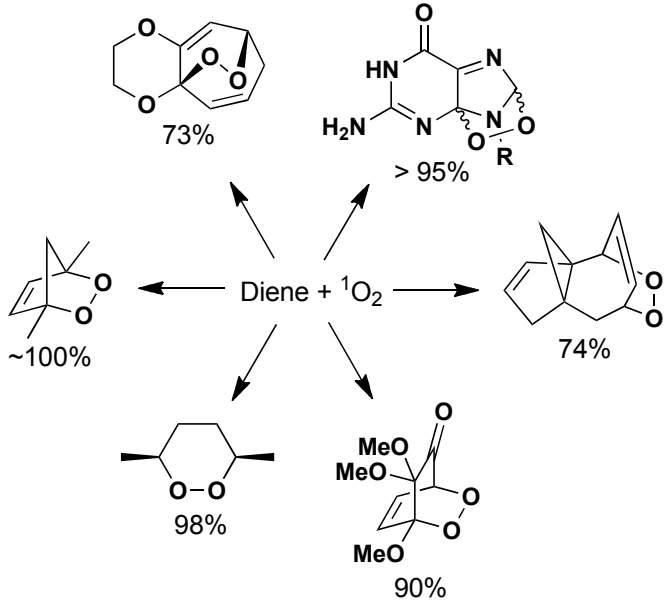
Frimer, A. A., *Singlet O_2,* ***1985***

'[2+2] Cycloadditions'



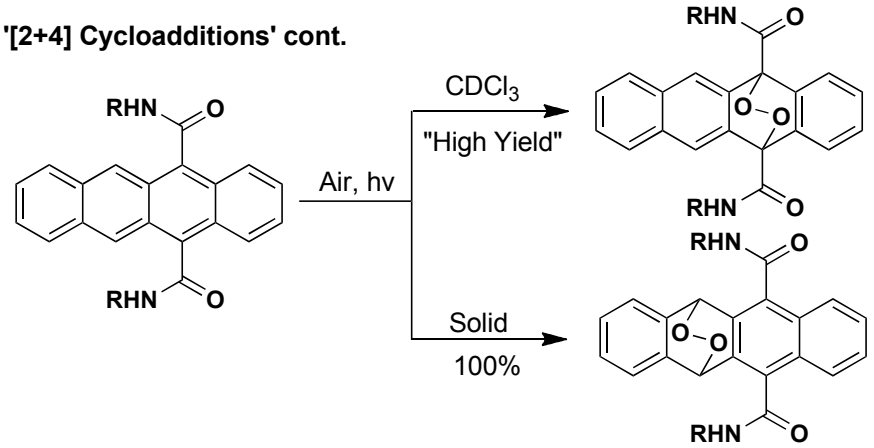
-Most significant limitation is a lack of α protons because the competing 'ene' reaction is significantly faster.

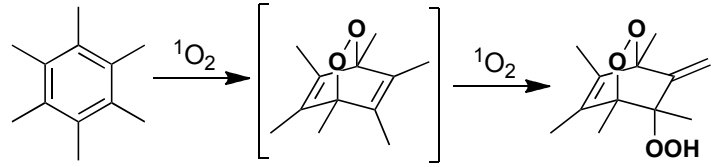
'[2+4] Cycloadditions'

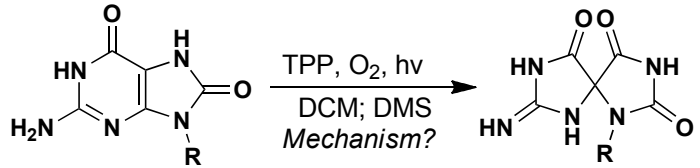


Handbook of Synthetic Photochemistry, 353

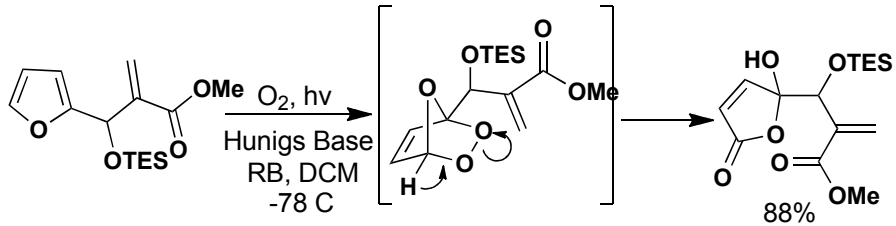
'[2+4] Cycloadditions' cont.





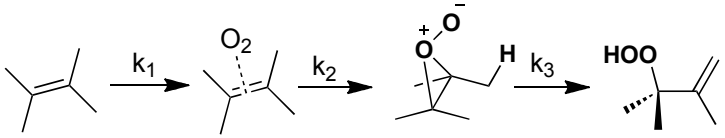


JACS, **2004**, 16777



Tet. Let., **2008**, 10831

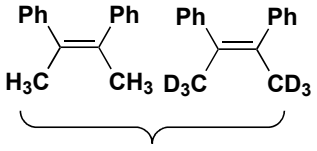
Ene Reactions



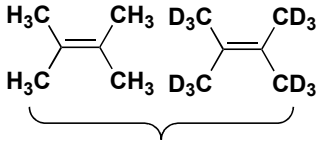
Mechanistic Details:

Exciplex Formation:
- Rate of reaction is > 10^3 less than diffusion control
- Reactions are characterized by low (or negative) activation enthalpies and high activation entropy

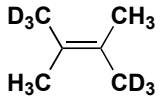
Periperoxide:
- Inter vs Intramolecular Isotope Effects



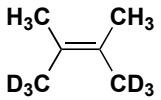
k_H/k_D = 1.08



k_H/k_D = 1.11

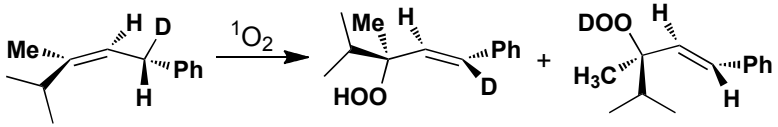


k_H/k_D = 1.40



k_H/k_D = 1

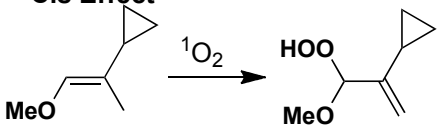
Ene Reaction is Suprafacial



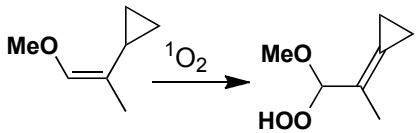
Tetrahedron, **2000**, 9151

Regioselectivity of the Ene Reaction

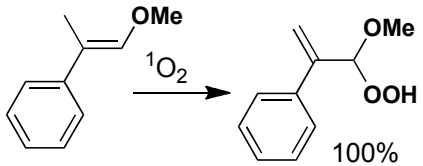
"Cis Effect"



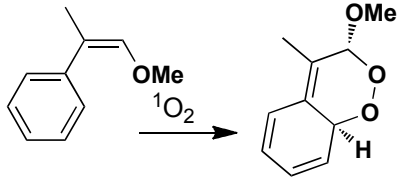
100%



72%



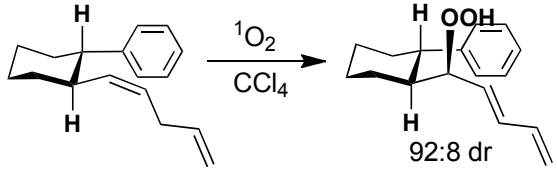
100%



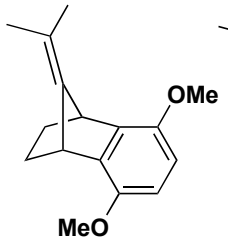
100%

Tet. Let. , **1977**, 2517
Tet. Let., **1978**, 3227

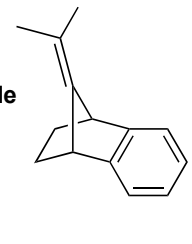
Steric and Electronic Effects



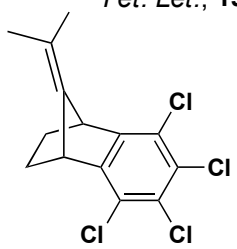
92:8 dr
Tet. Let., **1992**, 443



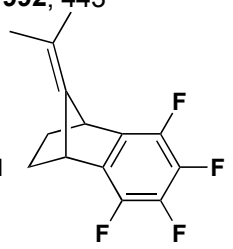
Trans/Cis 79:21



80:20



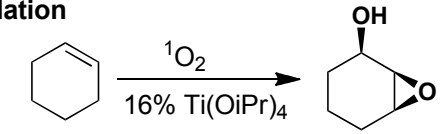
48:52



46:54

JACS, **1978**, 6510

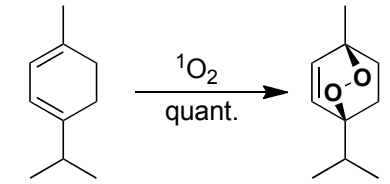
In-situ ene/epoxidation



91%
98:2 cis:trans

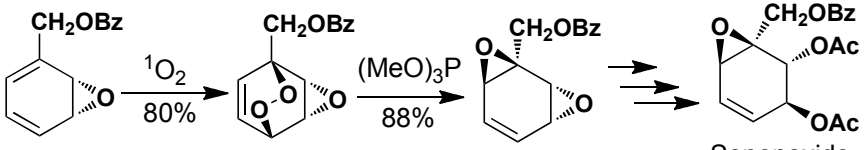
JACS, **1989**, 203

Synthetic applications of [4+2] and of resulting endoperoxides

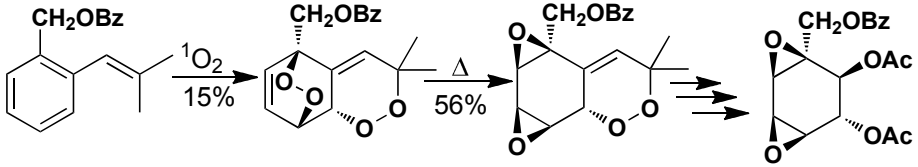


α-terpene ascaridole

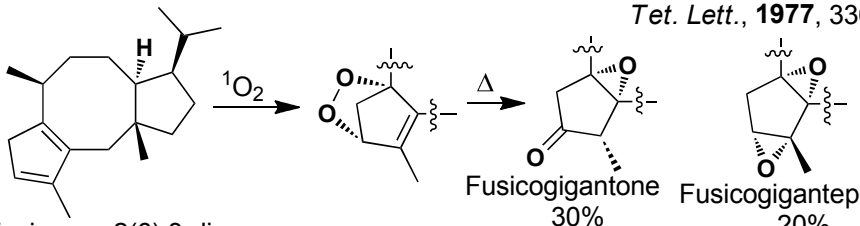
Naturwissenschafen, **1944**, 157



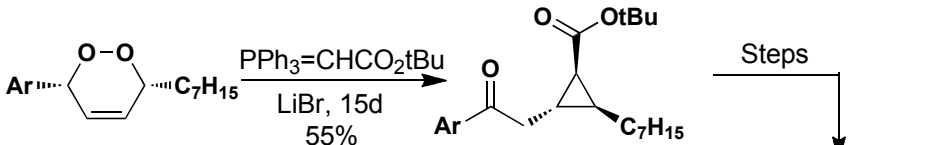
Senepoxide
JACS, **1978**, 352



Crotepoxide
Tet. Lett., **1977**, 3361



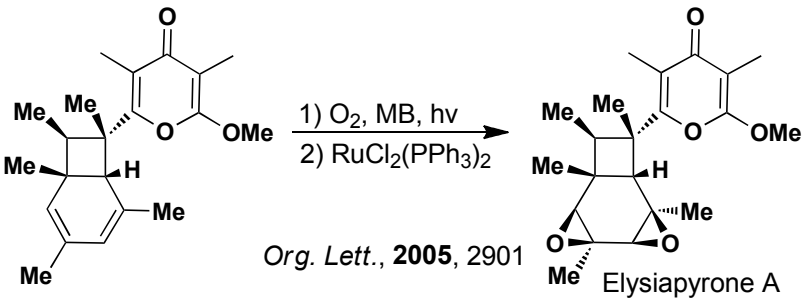
Fusicocca-2(6),3-diene
Fusicogigantone 30%
Fusicogigantepoxide 20%
Tet. Lett., **1994**, 8205



Mechanism?

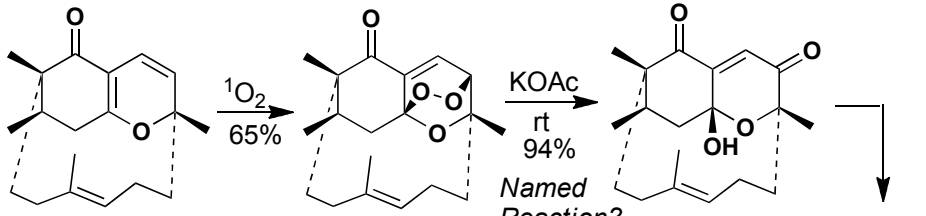
Org. Biomol. Chem., **2006**, 323

Grenadamide



Org. Lett., **2005**, 2901

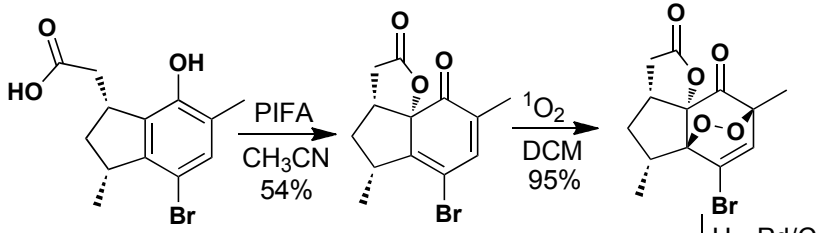
Elysiapyrone A



Named Reaction?

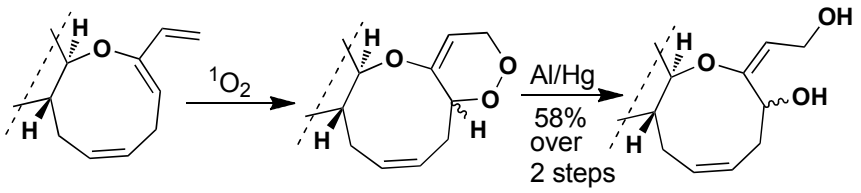
Org. Lett. **2009**, 1591

(+)-Phomactin

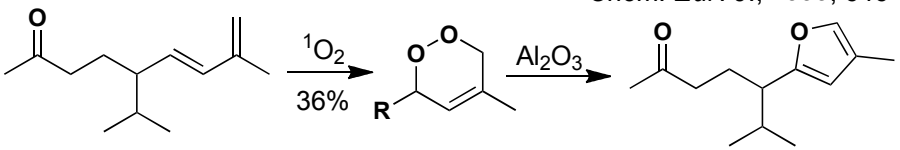


8 Step synthesis of Ryanodine BCE ring system
Tet., **2003**, 8855

Synthetic applications of [4+2] and of resulting endoperoxides (cont).



Chem. Eur. J., **1999**, 646

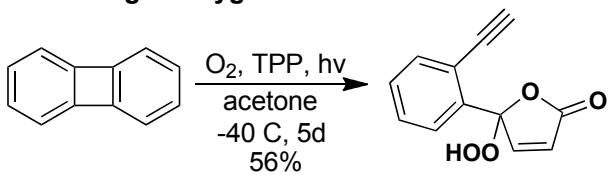


Solanone

Soloanofuran

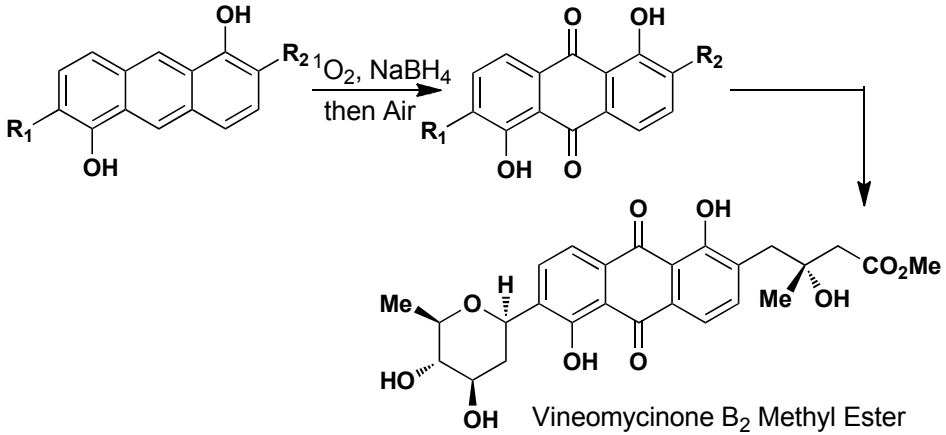
Helv. Chem. Act., **1972**, 265

Reactions of Singlet Oxygen with Arenes



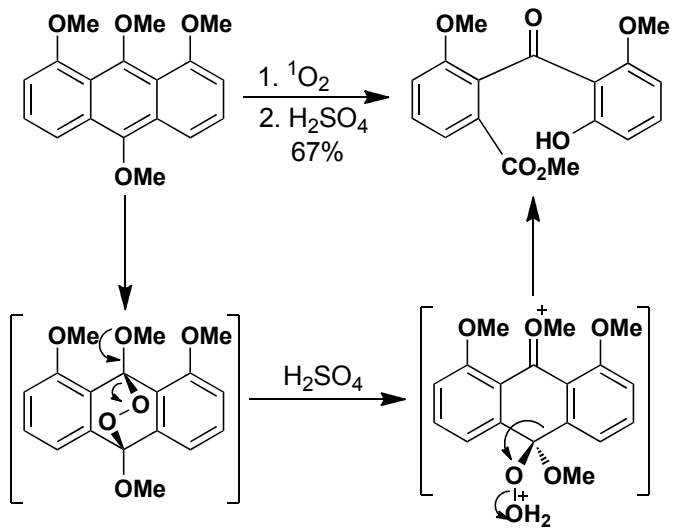
Mechanism?

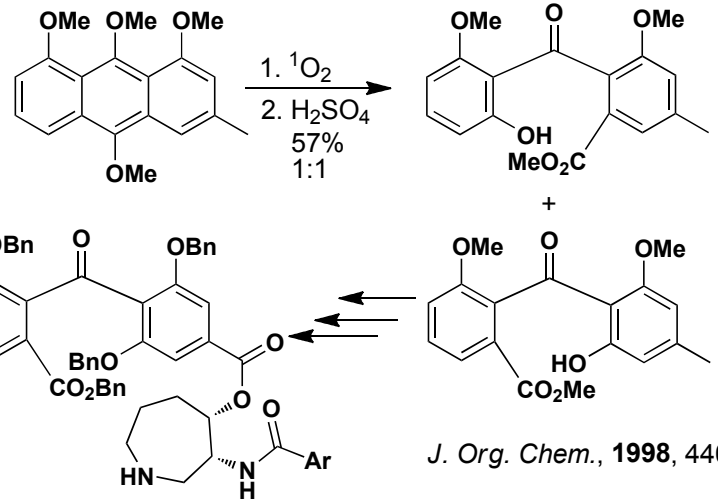
J. Org. Chem., **1998**, 8544



Vineomycinone B_2 Methyl Ester

JACS, **1991**, 6320

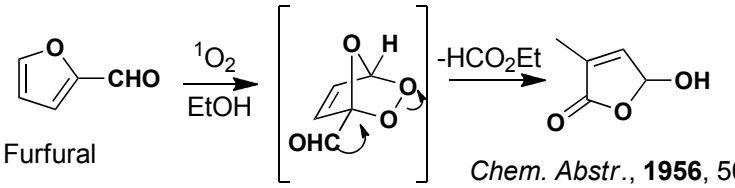




(-)-Balanol

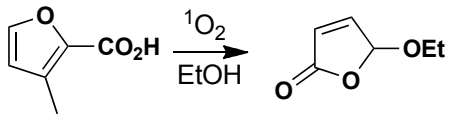
J. Org. Chem., **1998**, 4403

Reactions of Singlet Oxygen with Furans

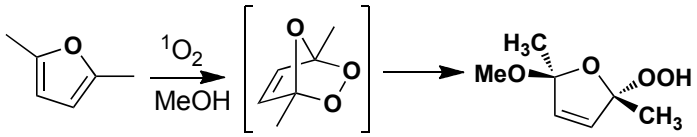


Furfural

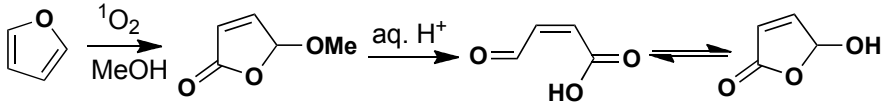
Chem. Abstr., **1956**, 5035



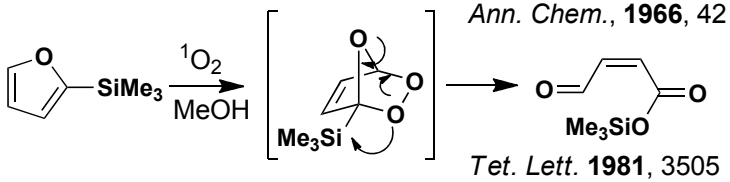
Ibid. **1977**, 3361



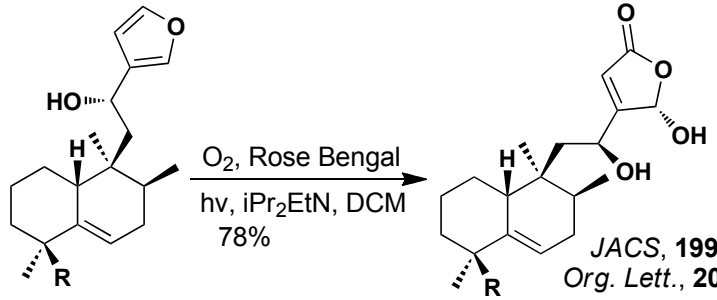
Tet., **1967**, 2583



Ann. Chem., **1953**, 156
Ann. Chem., **1966**, 42

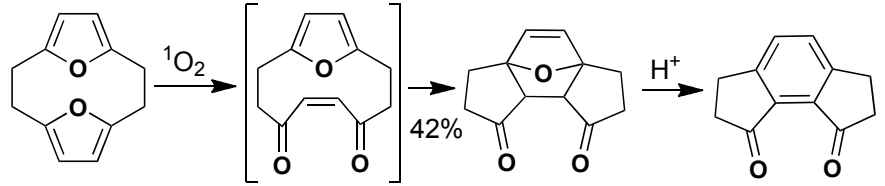


Tet. Lett. **1981**, 3505

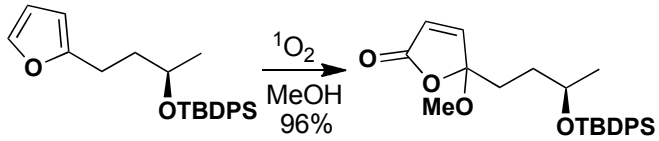


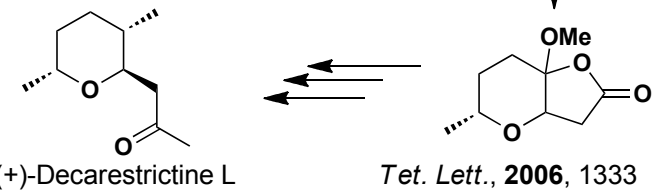
JACS, **1997**, 12425
Org. Lett., **2000**, 3177

Dysidiolide



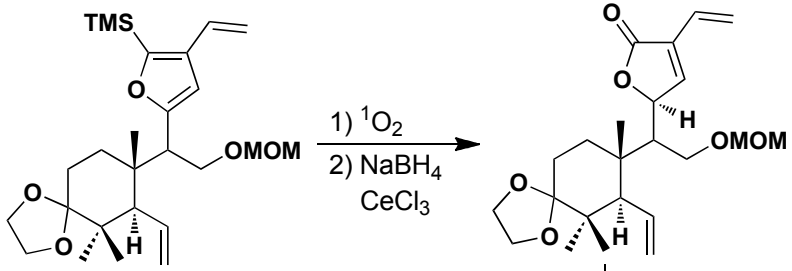
JACS, **1962**, 4611

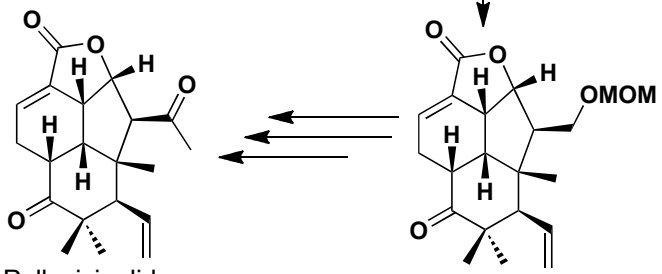




(+)-Decarestrictine L

Tet. Lett., **2006**, 1333

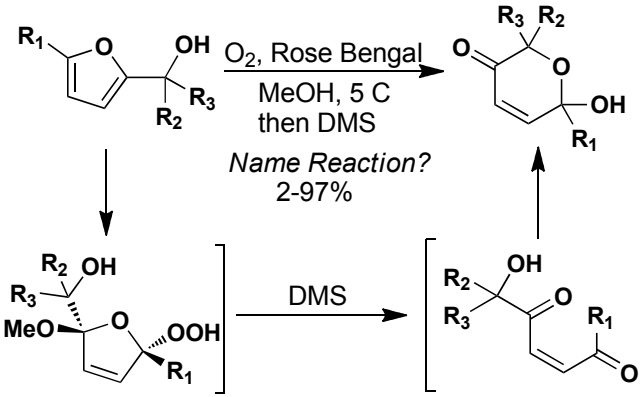




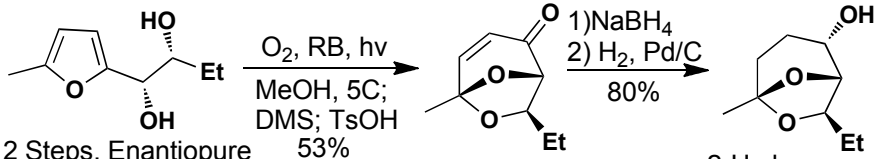
Pallavicinolide

Angew. Chem. Int. Ed., **2009**, 2351

Using Furan Endoperoxides in Cascade Reactions



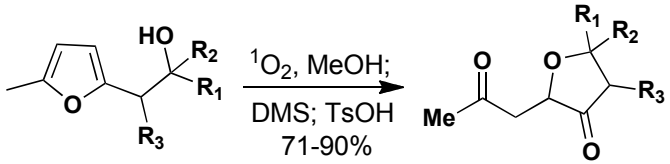
Name Reaction?
2-97%



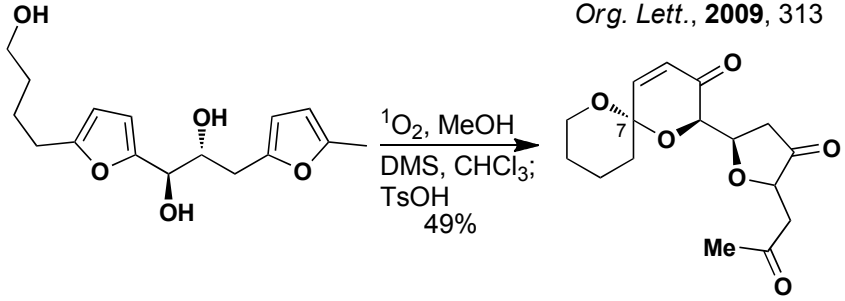
2 Steps, Enantiopure

Org. Lett., **2011**, 1166

2-Hydroxy-exo-brevicomin



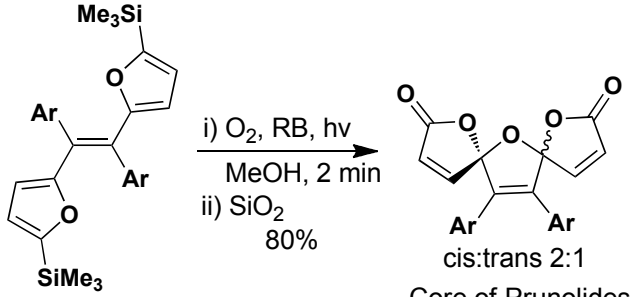
Org. Lett., **2009**, 313



Chem. Comm., **2010**, 259

7:3 dr at C-7
ABC ring system of the Pectenotoxins

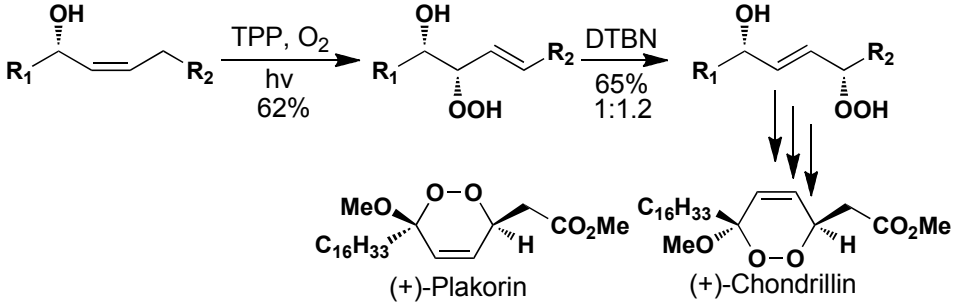
Using Furan Endoperoxides in Cascade Reactions (cont.)



E:Z = 3:1
Ar = p-anisyl

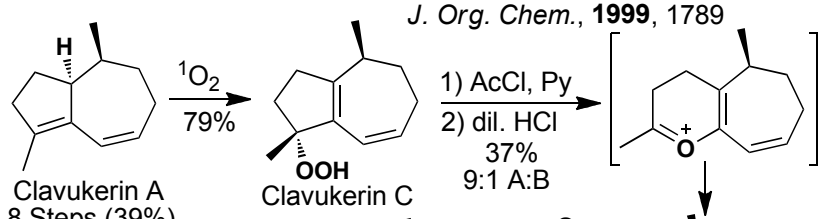
cis:trans 2:1
Core of Prunolides
Org. Lett. **2005**, 2357

Biomimetic Synthesis of Peroxide Containing Natural Products



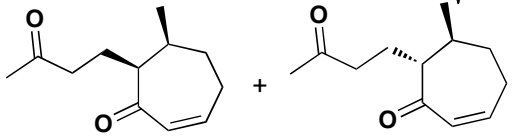
(+)-Plakorin
(+)-Chondrillin

J. Org. Chem., **1999**, 1789



Clavukerin A
8 Steps (39%)

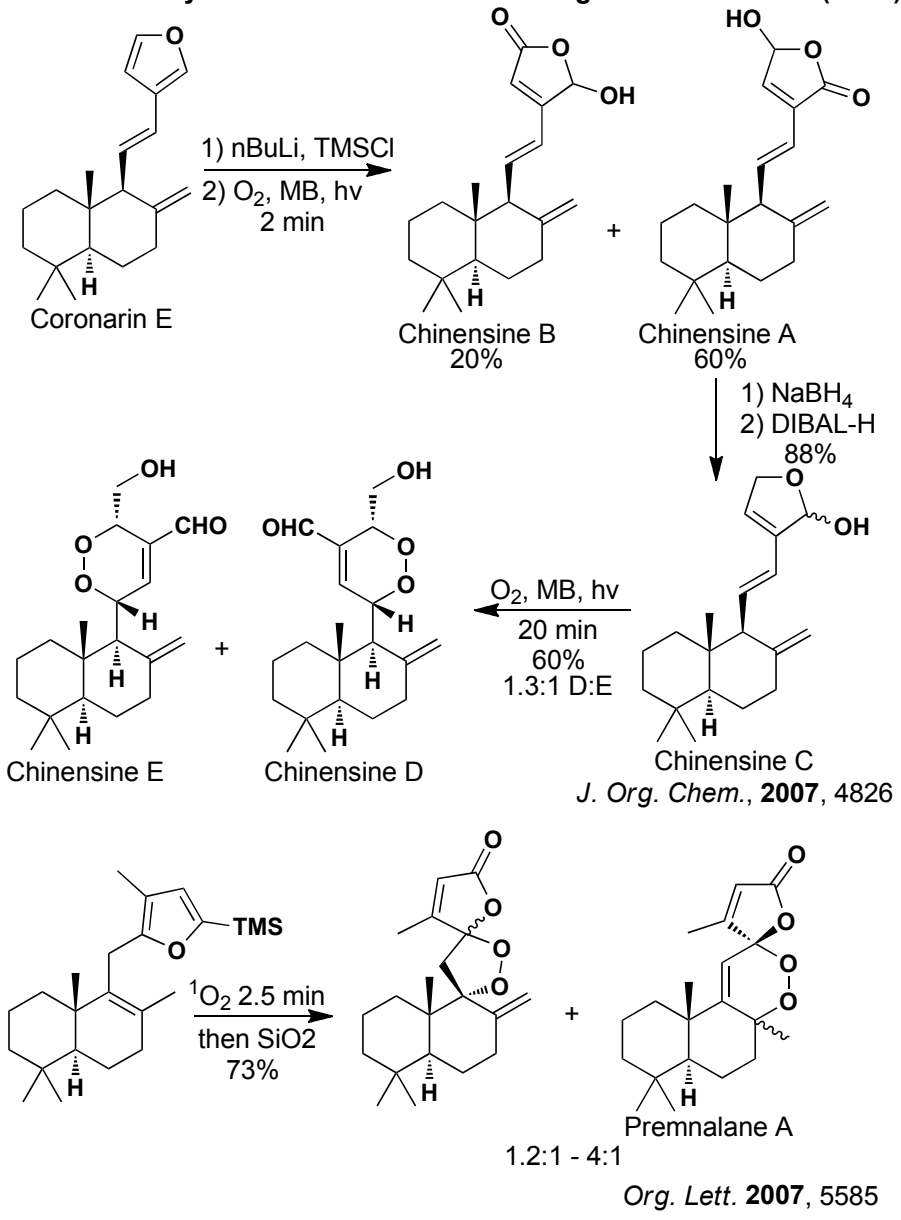
Clavukerin C

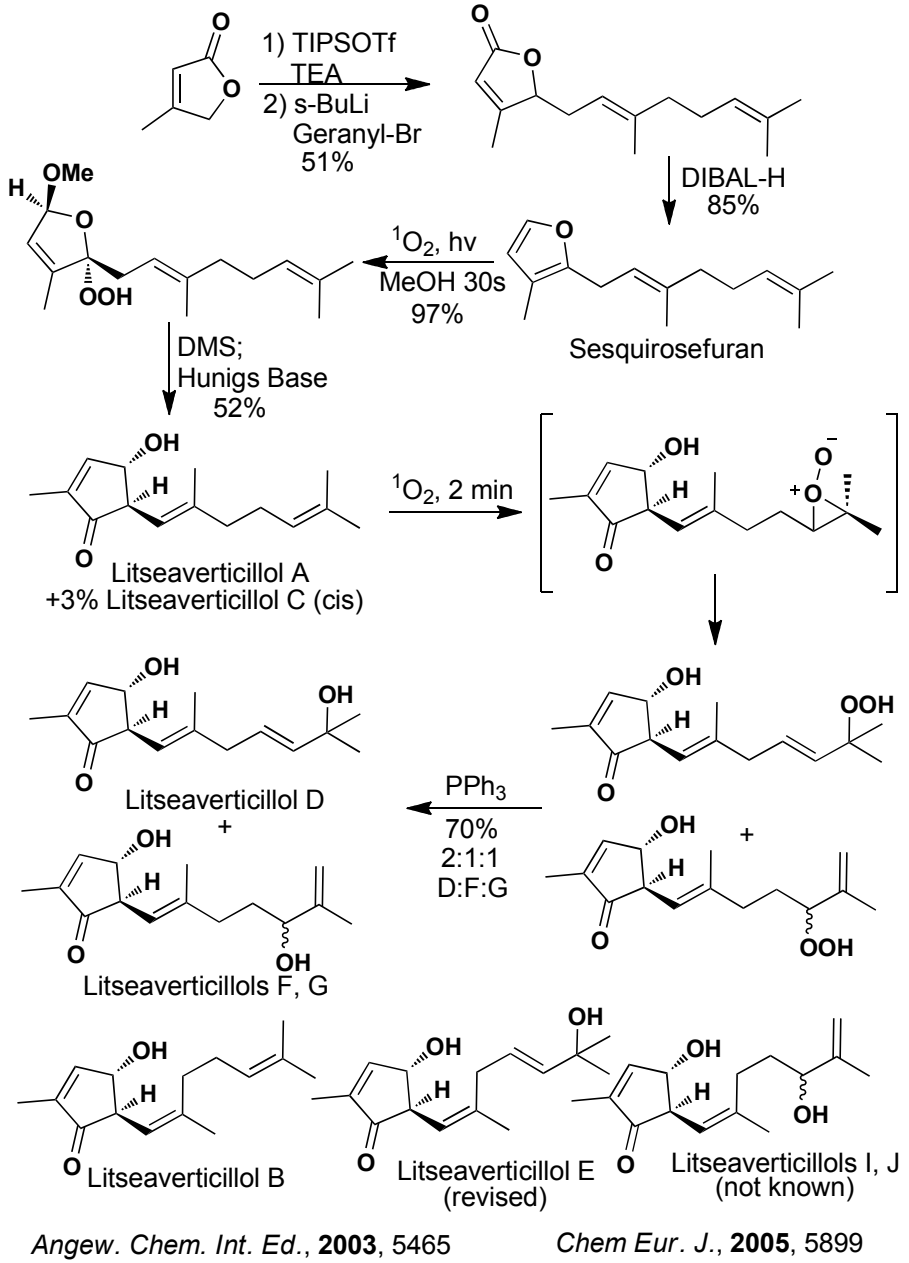


Clavulerin A + Clavulerin B

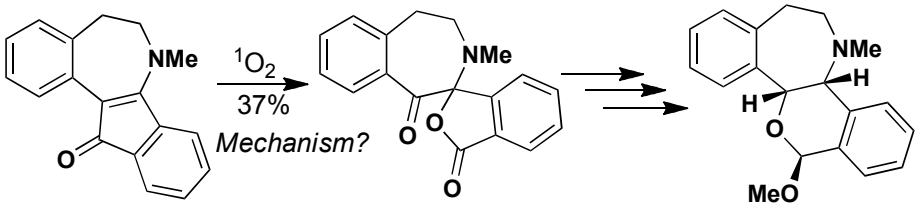
J. Org. Chem., **1991**, 6829

Biomimetic Synthesis of Peroxide Containing Natural Products (cont.)

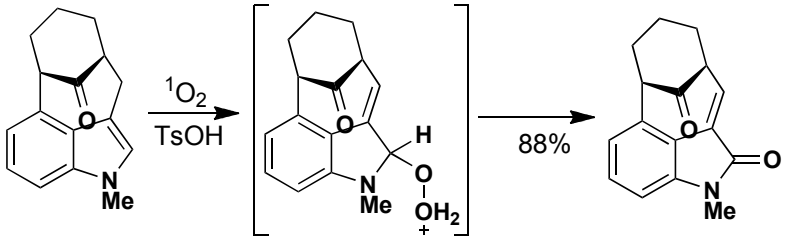




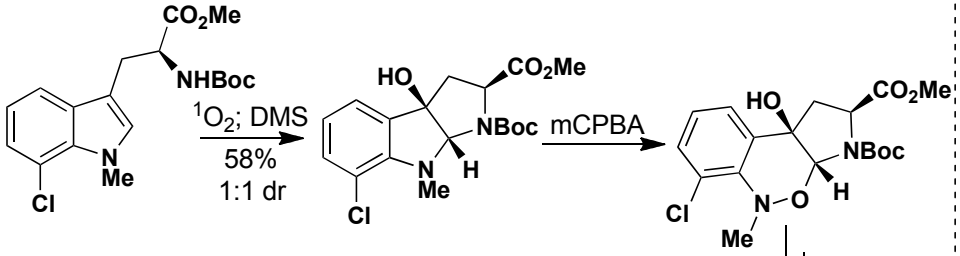
Reactions of other heterocycles with Singlet Oxygen



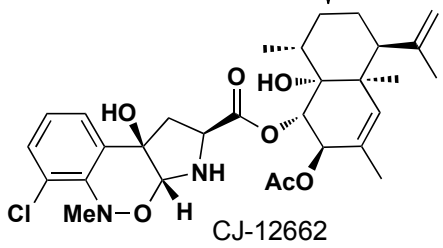
Alpinine
JACS, **1974**, 1944



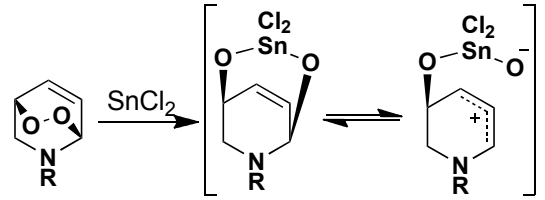
Tet. Lett., **2009**, 3283



J. Org. Chem., **2004**, 7875



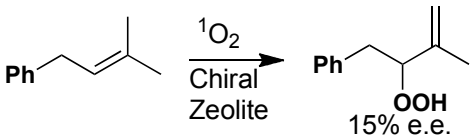
CJ-12662



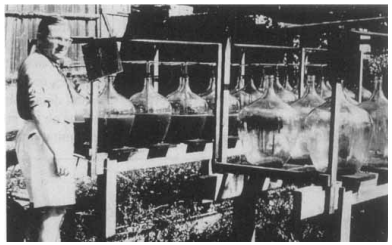
Nuc: heterocycles, Enol ethers, etc

Tet. Lett., **1979**, 3473

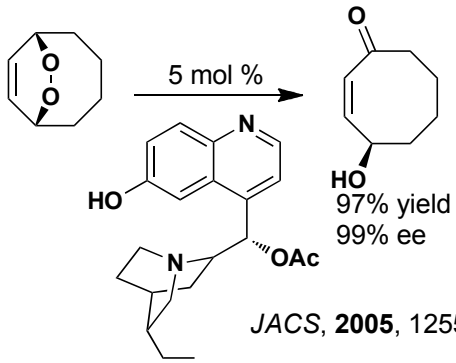
Misc. Singlet Oxygen Chemistry



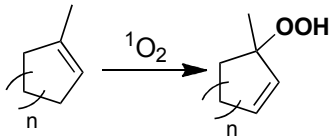
Tet. Lett., **1997**, 8825



Schenck at his ascaridol pilot plant in 1952
Solar Photochemistry: *Angew. Chem. Int. Ed.*, **1994**, 2009

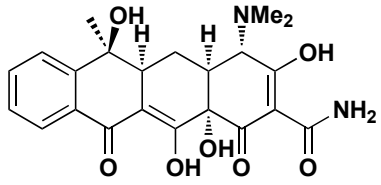


JACS, **2005**, 12556

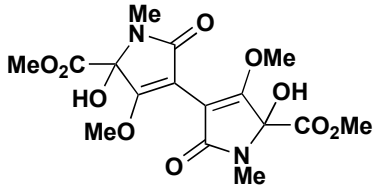


JACS, **2007**, 4132

Other Applications of Singlet Oxygen Not Covered



Tetracycline
Classics III



Isochrysohermidin
Classics II