

# Mn(III) Promoted Radical Reactions

An Evans group afternoon seminar

by Victor Cee

April 27, 1999

- I. Mn(OAc)<sub>3</sub> Intermolecular Additions
- II. Mechanism
- III. Hexenyl Radical Cyclizations
- IV. Heptenyl Radical Cyclizations
- V. Mn(pic)<sub>3</sub>

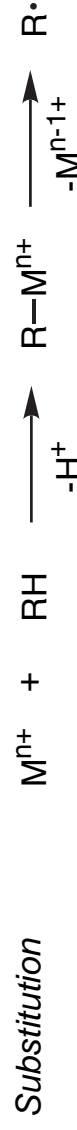
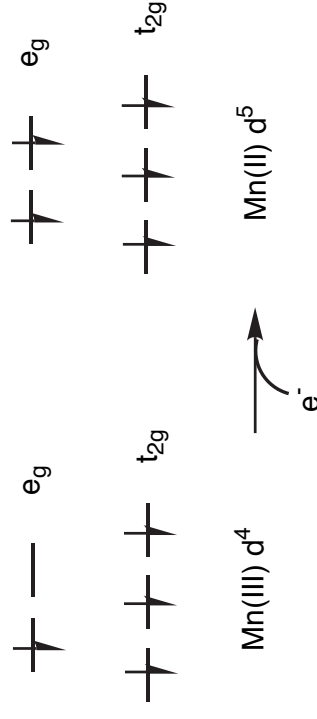
- Leading References:
- Melikyan, G. G. *Aldrichimica Acta* **1998**, 31, 50
- Melikyan, G. G. In *Organic Reactions*; Paquette, L. A. Ed; John Wiley: New York, NY, 1997; Vol. 49, 427.
- Snider, B. B. *Chem. Rev.* **1996**, 96, 339
- Iqbal, J. Bhatia, B. Nayyar, N. K. *Chem. Rev.* **1994**, 94, 519.
- Melikyan, G. G. *Synthesis*, **1993**, 833.

# Manganese (III): A One Electron Oxidant

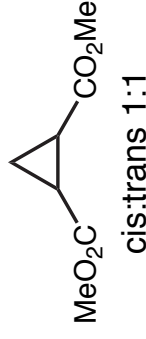
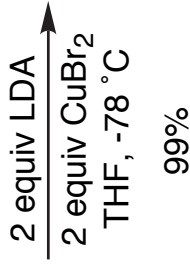
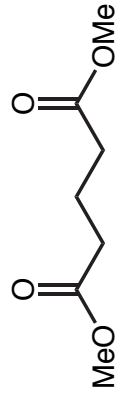
## One Electron Oxidants

Reaction	$E^\circ$ (V)
$\text{Co}^{3+} + 1e^- \rightarrow \text{Co}^{2+}$	1.92
$\text{Ce}^{4+} + 1e^- \rightarrow \text{Ce}^{3+}$	1.61
$\text{Mn}^{3+} + 1e^- \rightarrow \text{Mn}^{2+}$	1.51
$\text{Fe}^{3+} + 1e^- \rightarrow \text{Fe}^{2+}$	0.77
$\text{Cu}^{2+} + 1e^- \rightarrow \text{Cu}^{1+}$	0.16

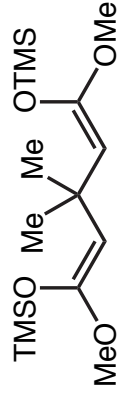
## Electronic Structure ( $O_h$ , high spin)



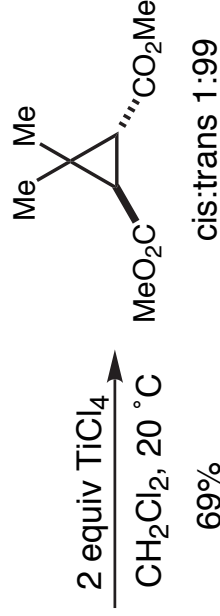
# Metal-Induced Carboxymethyl Radicals



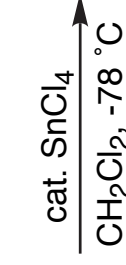
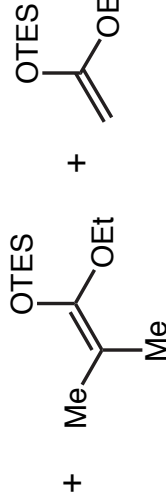
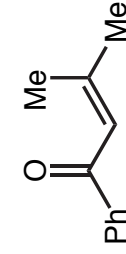
Chung *J. Org. Chem.* **1983**, 48, 1125



mixture of isomers



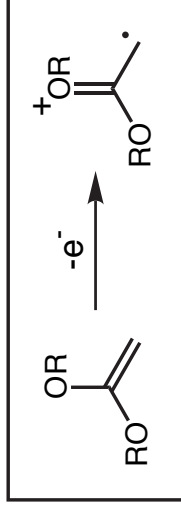
Chan *Tetrahedron* **1983**, 39, 847



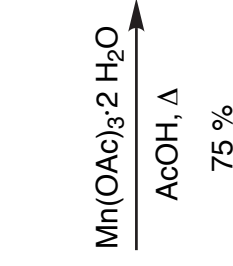
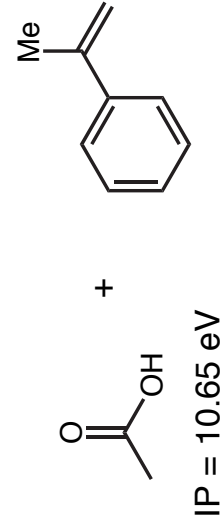
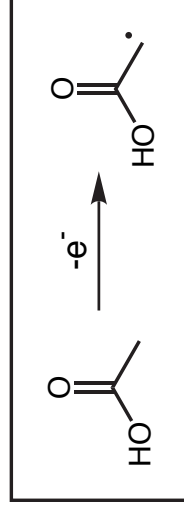
85%  
only product observed

IP = 7.25 eV      IP = 7.74 eV

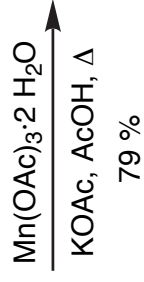
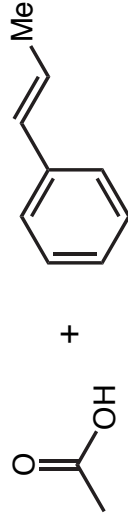
Fukuzumi *J. Org. Chem.* **1996**, 61, 2951  
*J. Am. Chem. Soc.* **1992**, 114, 10271



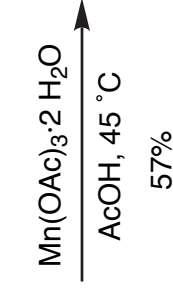
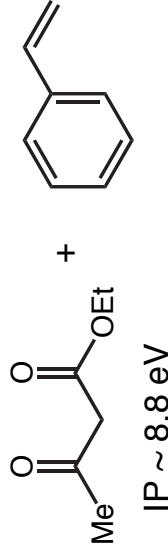
# Mn(III) Induced Carboxymethyl Radicals



Bush and Finkbeiner *J. Am. Chem. Soc.* **1968**, *90*, 5903



Heiba *J. Am. Chem. Soc.* **1968**, *90*, 5905

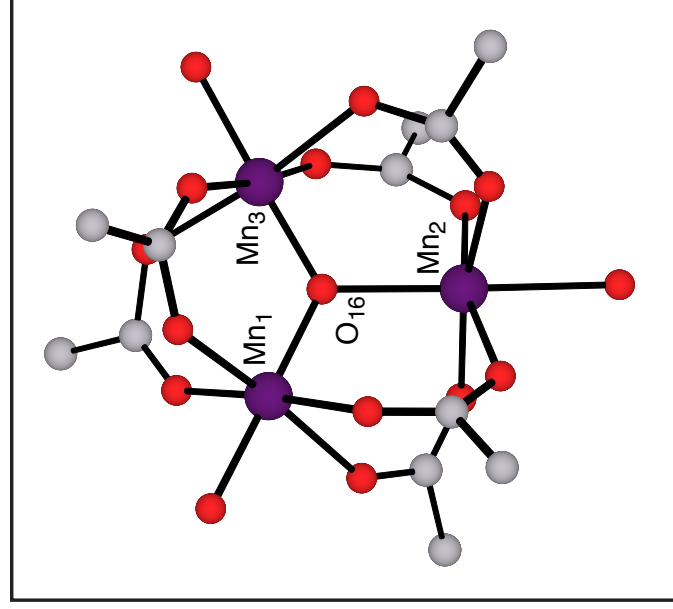


Heiba *J. Org. Chem.* **1974**, *34*, 3456

# Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O and Anhydrous "Mn(OAc)<sub>3</sub>"

- Anhydrous Mn(OAc)<sub>3</sub> and the dihydrate are indistinguishable in solution, and undergo metathesis with other acids readily. The commercially available dihydrate is the most popular.

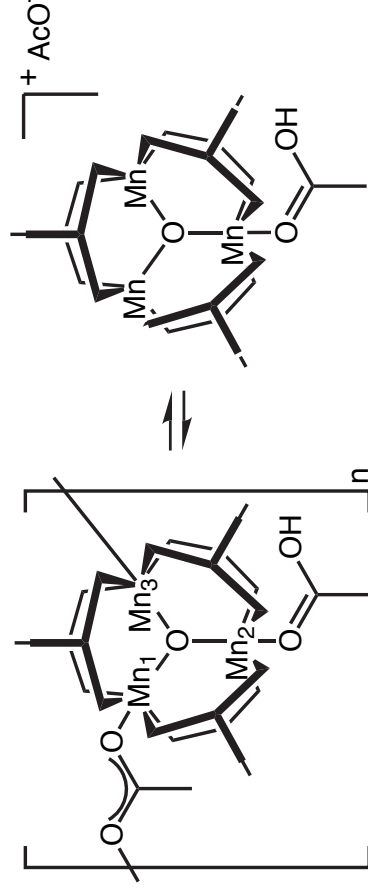
## Solid-State Structure of Anhydrous Mn(OAc)<sub>3</sub> [Mn<sub>3</sub>O(OAc)<sub>6</sub>·AcOH·OAc]<sub>n</sub>



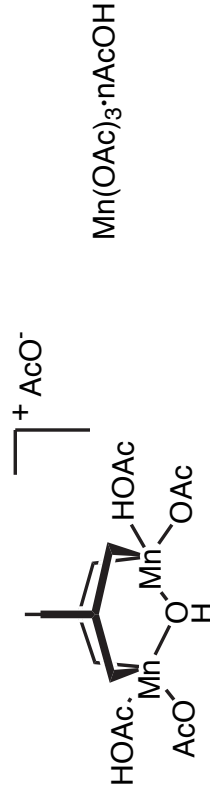
Bond	Distance (Å)
Mn <sub>1</sub> -O <sub>16</sub>	1.848
Mn <sub>3</sub> -O <sub>16</sub>	1.858
Mn <sub>2</sub> -O <sub>16</sub>	2.108

## Solution Structure (AcOH)

- A trimeric solution structure has been proposed



- Dimeric and monomeric species may also be present



Hessel C. *Rec. Trav. Chim.* **1969**, *88*, 545.

# Importance of Bridged Mn Centers: Catalases

## *T. thermophilus* Catalase

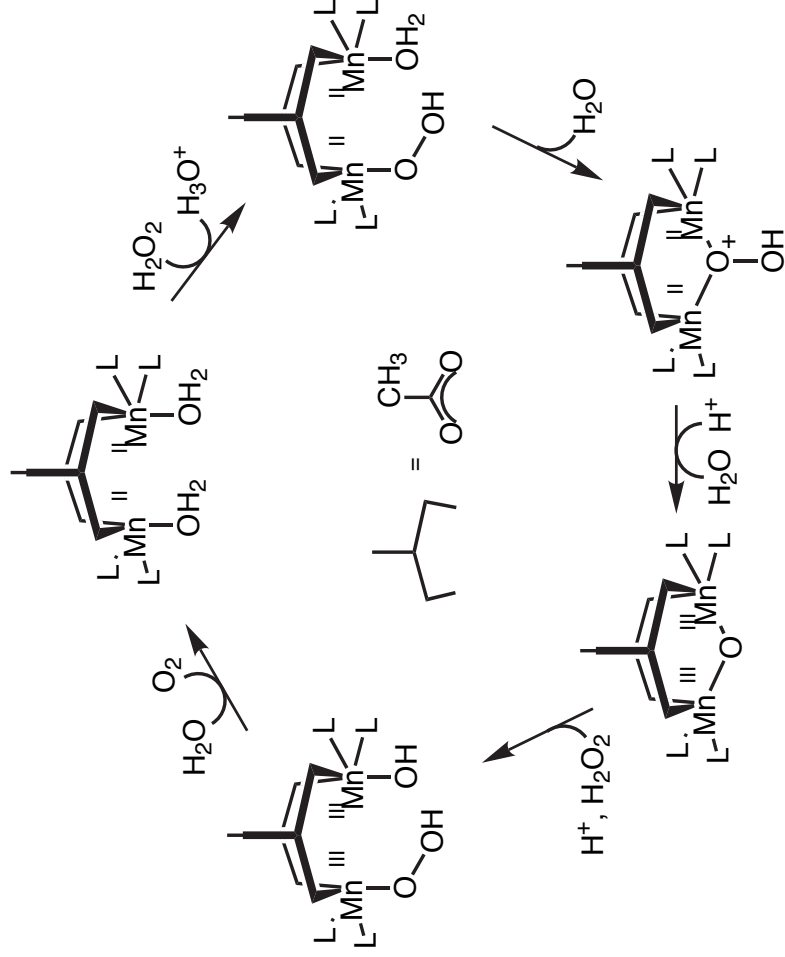
Catalyzes the disproportionation of  $\text{H}_2\text{O}_2$ :



## Standard Reduction Potentials

Reaction	$E^\circ$ (V)
$\text{H}_2\text{O}_2 + 2 \text{H}_3\text{O}^+ + 2 \text{e}^- \rightarrow 4 \text{H}_2\text{O}$	1.78
$\text{Mn}^{3+} + 1 \text{e}^- \rightarrow \text{Mn}^{2+}$	1.51
$\text{O}_2 + 2 \text{H}_3\text{O}^+ + 2 \text{e}^- \rightarrow \text{H}_2\text{O}_2 + 2 \text{H}_2\text{O}$	0.68

## Proposed Mechanism

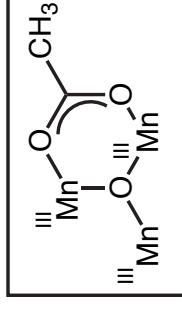


Close proximity of two manganese centers is established by bridging acetates

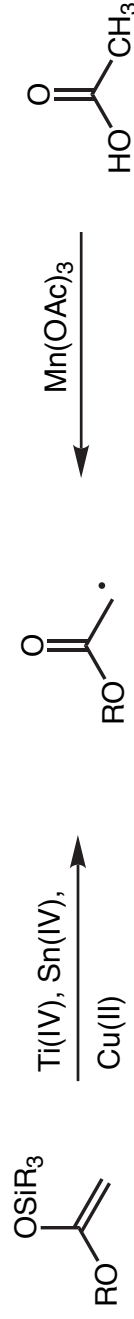
Net Result: Redox chemistry at the diffusion-controlled rate

Dismukes, G. C. *Chem. Rev.* **1996**, *96*, 2909.

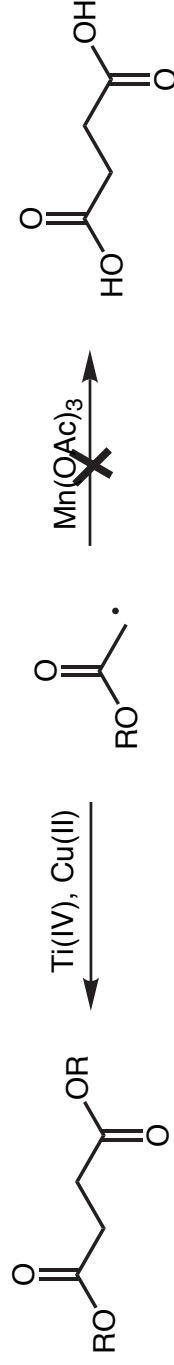
# Unique Features of Mn(III) Attributed to the Trimeric Nature of Mn(OAc)<sub>3</sub>



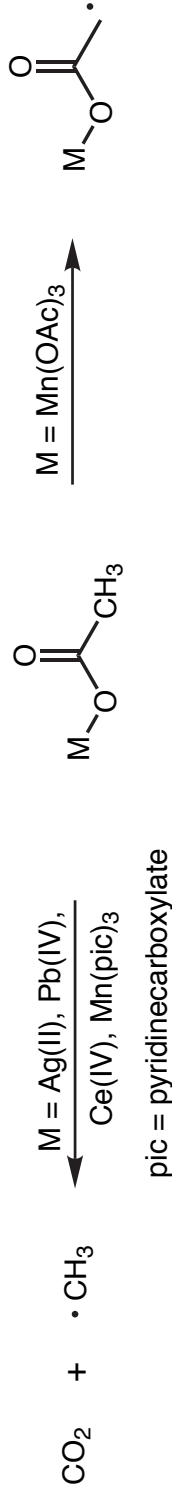
- Ability to oxidize free acids



- Dimerization is not a dominant pathway

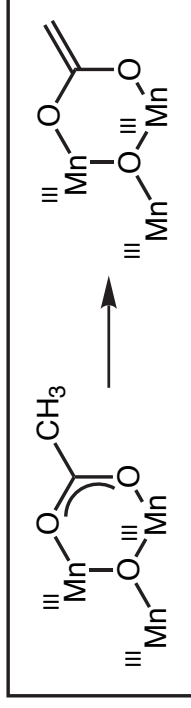
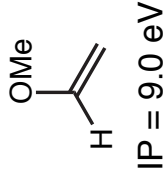
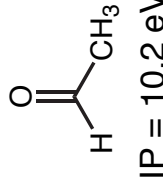


- Decarboxylation is not a dominant pathway

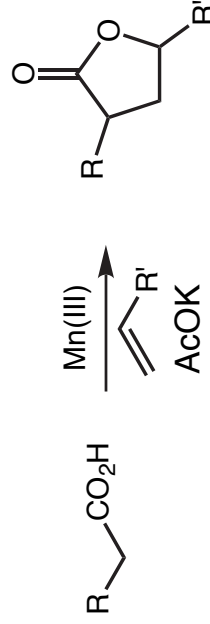


# Mechanism of Mn(III) Oxidative Lactonization: Enolization

- Ionization Potentials: Carbonyl vs. Enol Ether

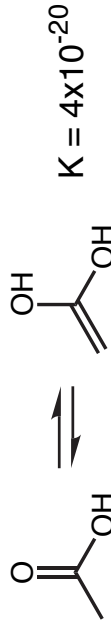


- Enolization Proposed as the Rate-Determining Step



Fristad *J. Org. Chem.* **1985**, 50, 10

- Enol Content - Small



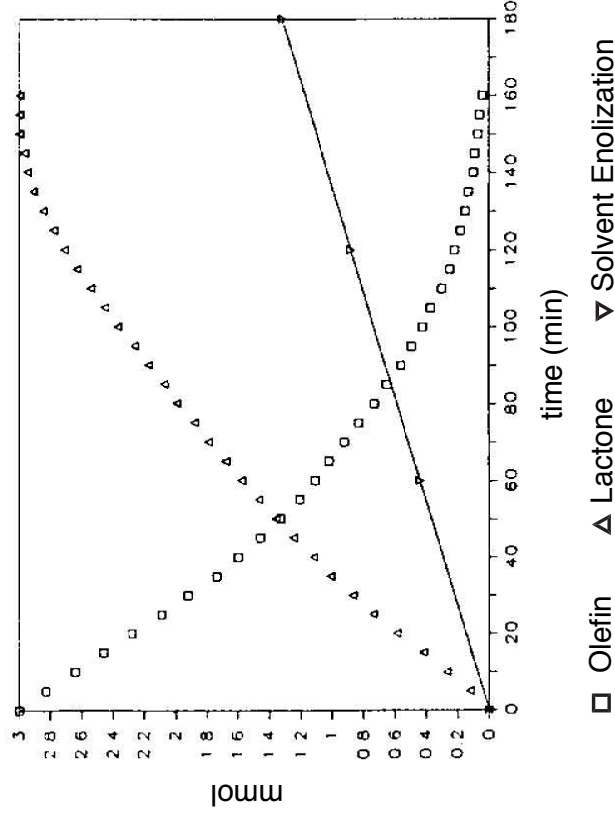
R	pK <sub>a</sub> α-H (ester)	relative rate
H	25	1
Cl	22	1.1 x 10 <sup>1</sup>
SO <sub>2</sub> Ph	14	3.8 x 10 <sup>3</sup>
CO <sub>2</sub> Me	13	1.1 x 10 <sup>4</sup>
CN	9	4.0 x 10 <sup>5</sup>

- Activation by Mn

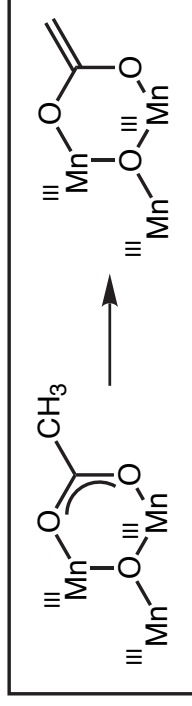


# Mechanism of Mn(III) Oxidative Lactonization: Enolization

Comparison of Enolization and Reaction Rates



Conclusion: Once enolization occurs, rapid electron transfer and reaction ensue. Enolization is irreversible



The reaction:

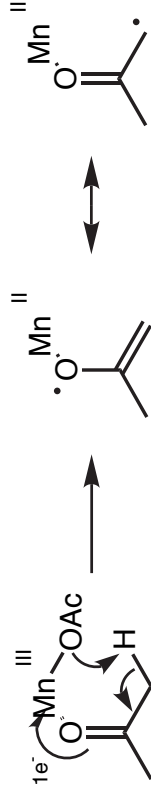


Rate of enolization  $\sim$  rate of deuterium incorporation:

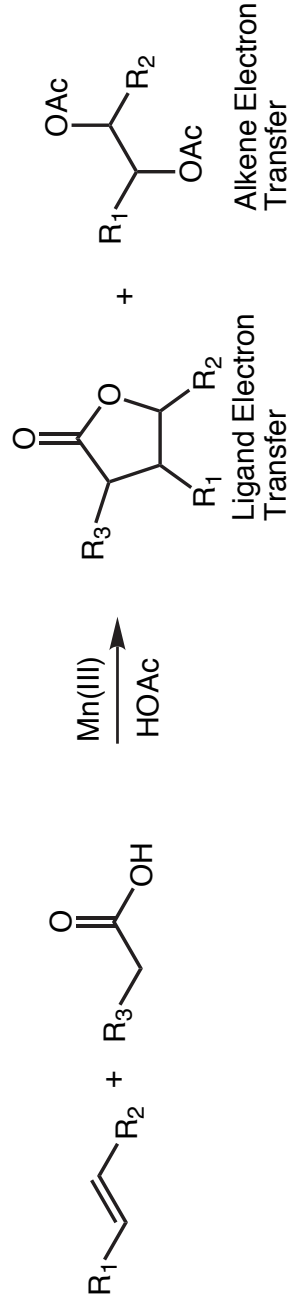
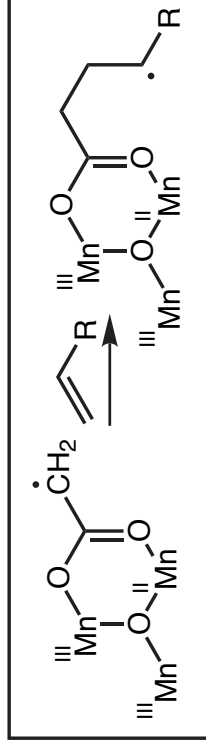


Presence of Mn(III) has no effect on D incorporation!

Alternative Conclusion: Enolization and electron transfer occur in a concerted step



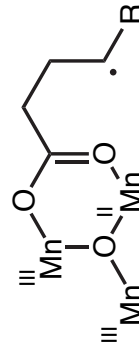
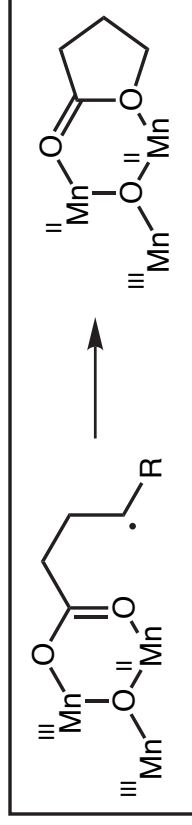
# Mechanism of Mn(III) Oxidative Lactonization: Radical Addition



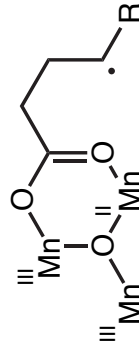
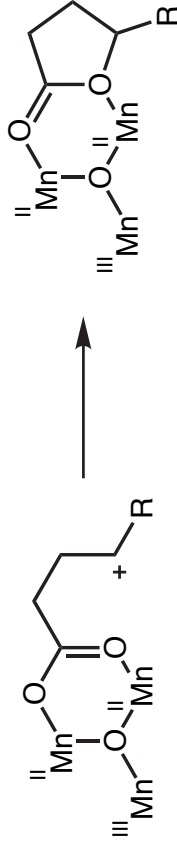
Alkene	IP (eV)	Alkene Electron Transfer (%)	
		R <sub>3</sub> = H	R <sub>3</sub> = CO <sub>2</sub> Me
1-hexene	9.65	0	0
4-methylstyrene	8.20	6	0
indene	8.14	54	0
<i>trans</i> -stilbene	8.00	96	0

Fristad *Tetrahedron*, 1986, 42, 3429

# Mechanism of Mn(III) Oxidative Lactonization: Oxidation and Cyclization



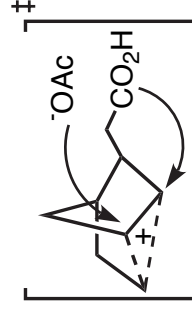
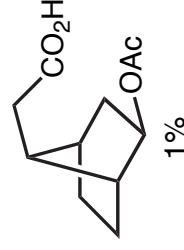
Heiba: Oxidation to a carbocation



Fristad: Radical Cyclization

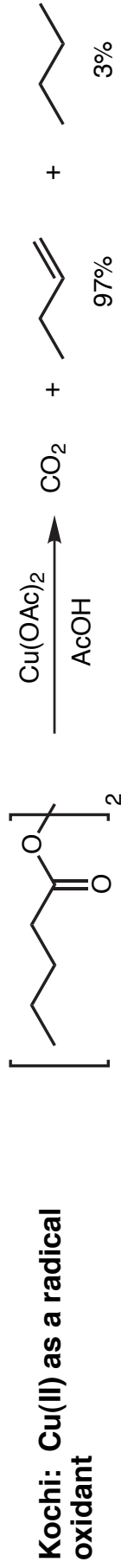


Fristad: No evidence for carbocation

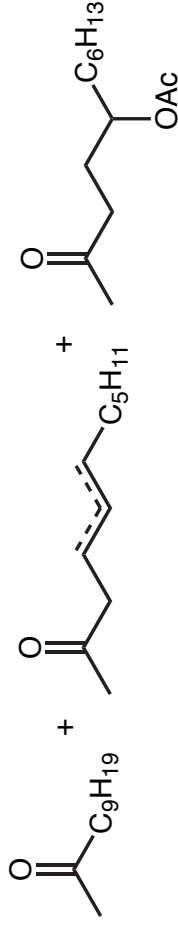
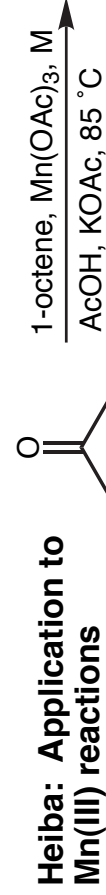


Heiba *J. Am. Chem. Soc.* **1971**, *93*, 524  
 Fristad *J. Org. Chem.* **1985**, *50*, 10

# Introduction of Copper (II)



Kochi *J. Am. Chem. Soc.* **1965**, *87*, 4855



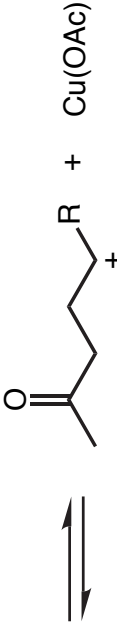
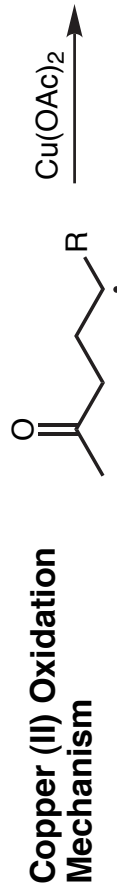
**M Oxidant**

**Relative  $k_{ox}$**

Ce(IV)  
Cu(II)

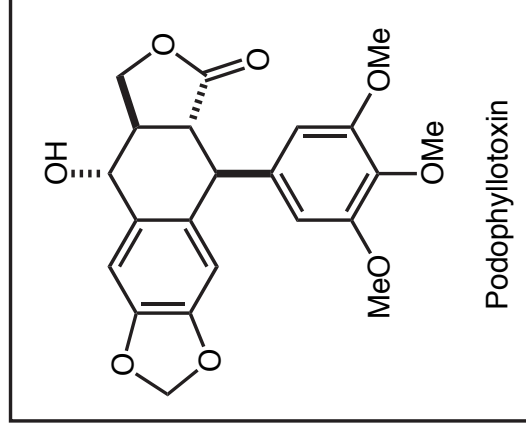
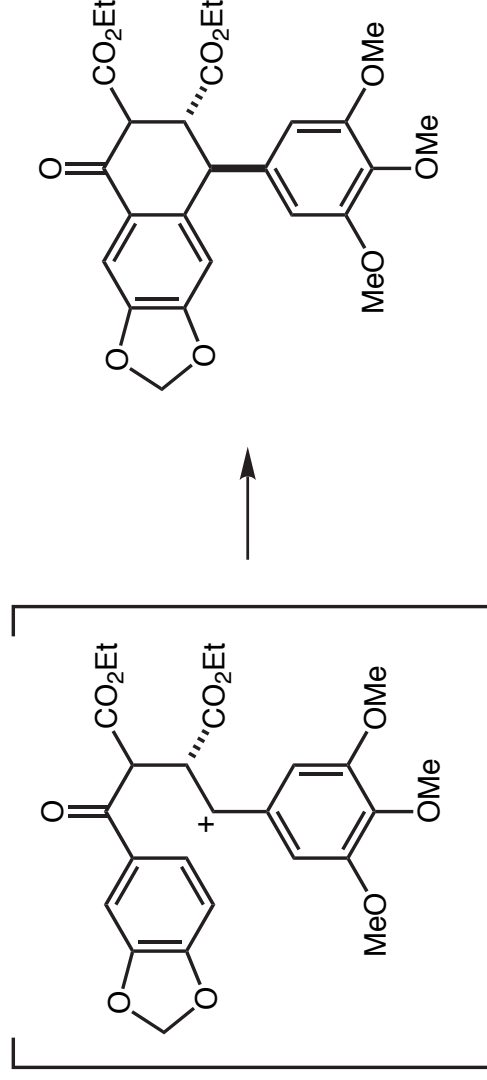
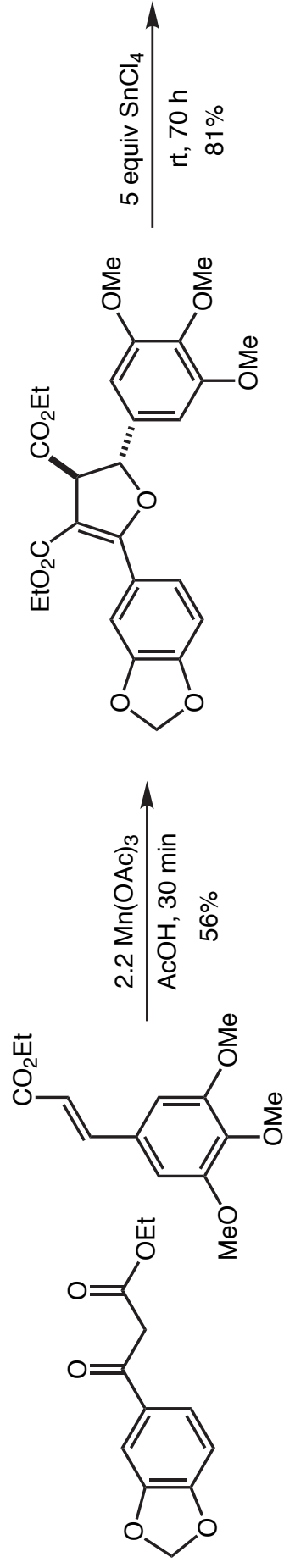
1  
12  
350

Heiba *J. Am. Chem. Soc.* **1971**, *93*, 524



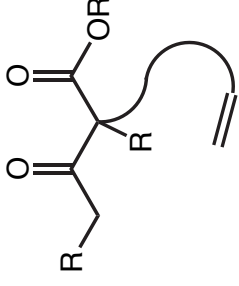
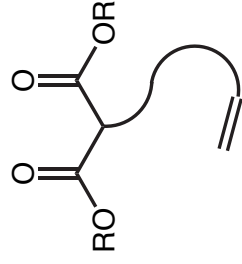
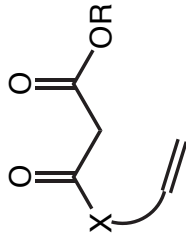
Elimination is usually the dominant pathway

# Intermolecular Cyclizations: Studies Toward Podophyllotoxin

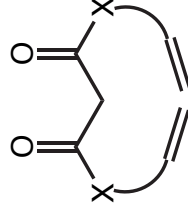
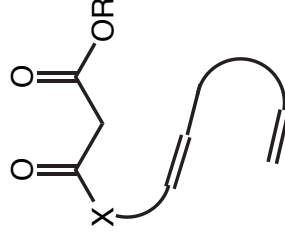
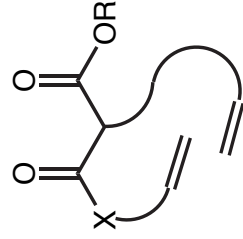


# Intramolecular Cyclizations

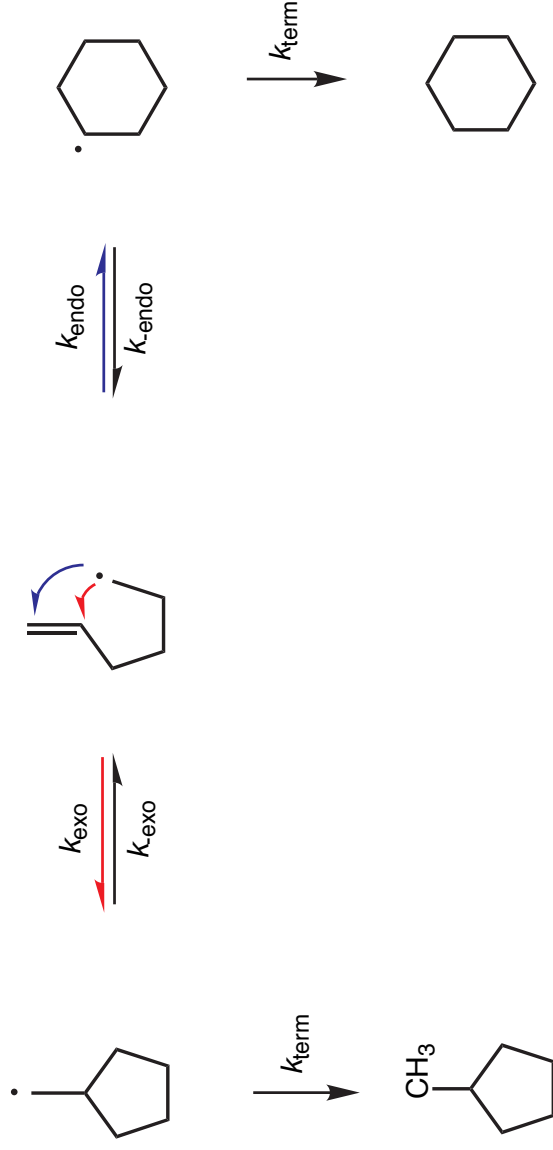
## Monocyclizations



## Higher cyclizations



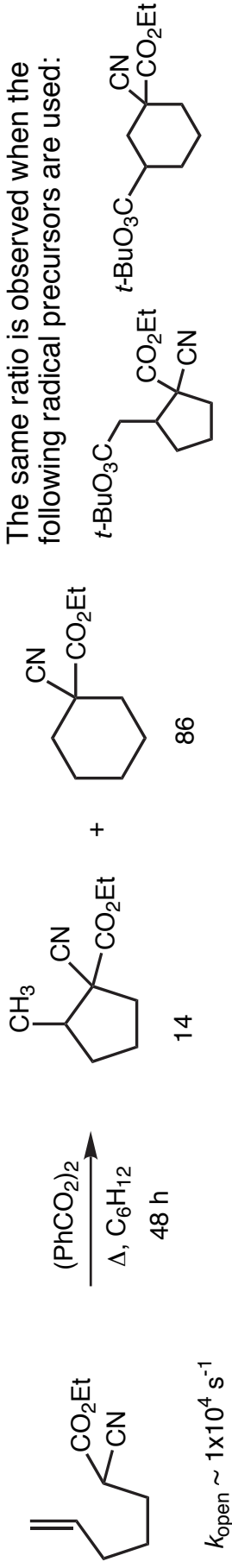
# Hexenyl Radical Cyclization - Is Equilibration Possible?



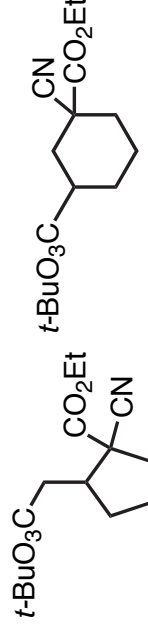
- Kinetics:  $k_{\text{exo}}/k_{\text{endo}}$  depends on substitution pattern
- Equilibration: extent of ring opening depends on relative magnitude of  $k_{\text{term}}$
- Representative rates:  $k_{\text{exo}} = 2 \times 10^5 \text{ s}^{-1}$   
 $k_{\text{endo}} = 4 \times 10^3 \text{ s}^{-1}$   
 $k_{\text{term}} = 3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$  ( $\text{Bu}_3\text{SnH}$ )

# Reversible vs. Irreversible Radical Cyclization

- Rate of H abstraction < rate of ring opening

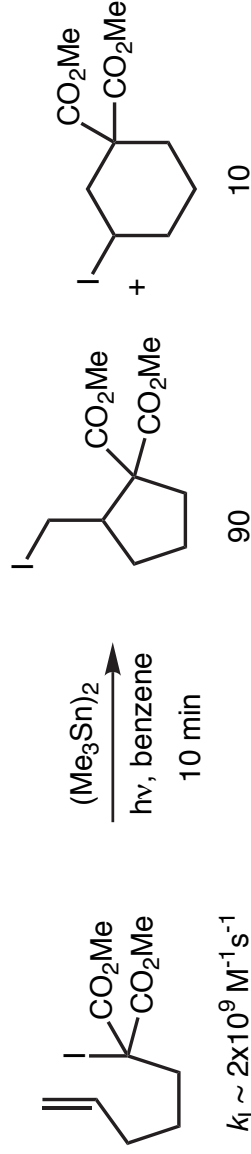


The same ratio is observed when the following radical precursors are used:

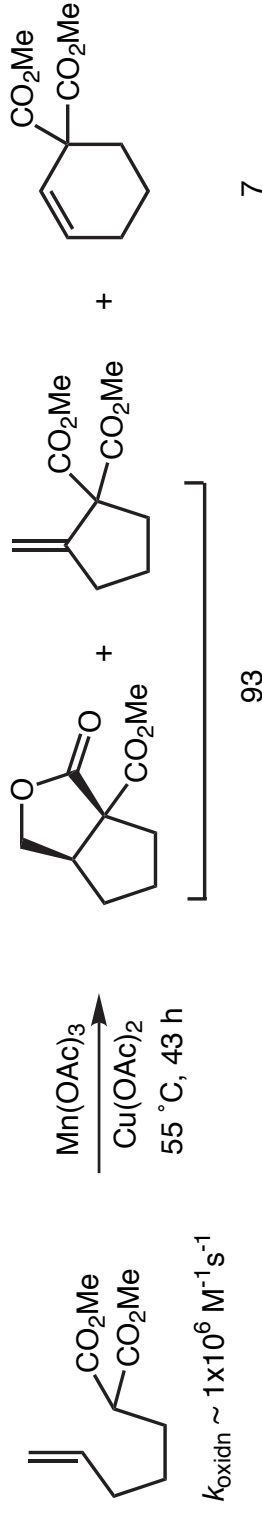


M. Julia Acc. Chem. Res. 1971, 4, 386

- Rate of iodine abstraction > rate of ring opening



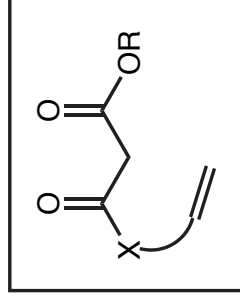
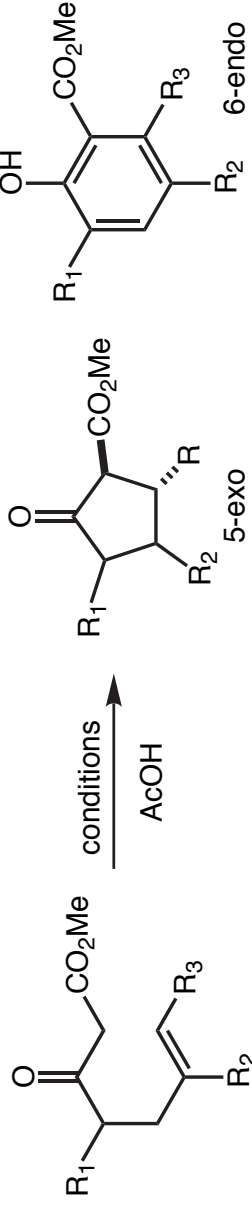
- Rate of oxidation > rate of ring opening



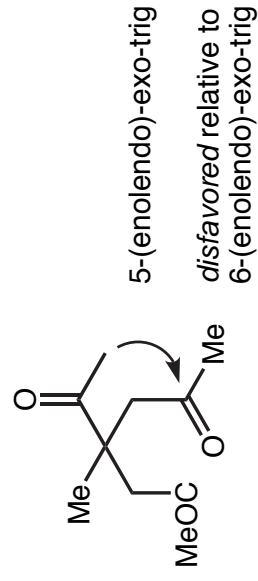
Curran J. Org. Chem. 1989, 54, 3140

Snider J. Am. Chem. Soc. 1991, 113, 6609

# Hexenyl Radical Cyclization

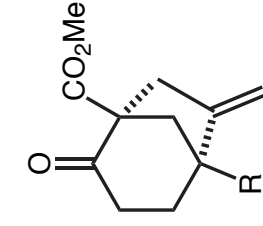
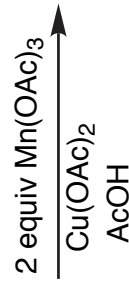
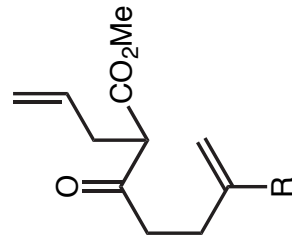
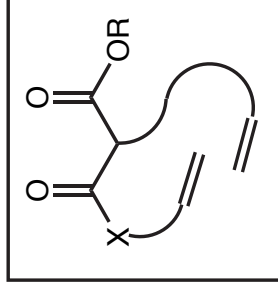


substrate			conditions	products		reference	
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>		5-exo	6-endo		R
H	H	H	4 Mn(OAc) <sub>3</sub> Cu(OAc) <sub>2</sub>	-	94%	-	Peterson <i>Tetrahedron Lett.</i> <b>1987</b> , 6109
Me	Me	H	4 Mn(OAc) <sub>3</sub> Cu(OAc) <sub>2</sub>	-	91%	-	Snider <i>J. Org. Chem.</i> <b>1989</b> , 54, 38
H	H	Me	2 Mn(OAc) <sub>3</sub> Cu(OAc) <sub>2</sub>	21%	5%		Snider <i>J. Org. Chem.</i> <b>1985</b> , 50, 3661
H	H	Ph	2 Mn(OAc) <sub>3</sub> Cu(OAc) <sub>2</sub>	70%	-		Peterson <i>Tetrahedron Lett.</i> <b>1987</b> , 6109

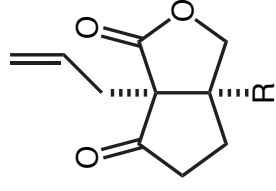


- Endocyclic ketone and the substitution pattern of the alkene control the mode of cyclization
- Similar selectivity seen for  $\alpha$ -substituted  $\beta$ -ketoesters
- Similar selectivity seen for  $\alpha$ -radicals generated by atom transfer

# Hexenyl Radical Bicyclization

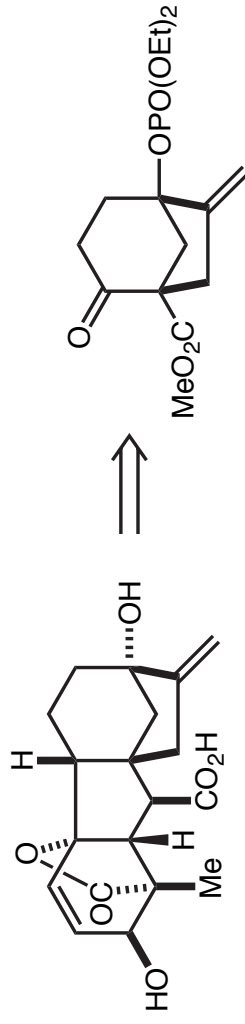


48%  
 86%  
 77%

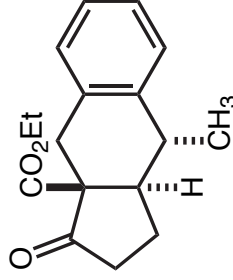
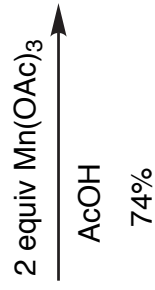
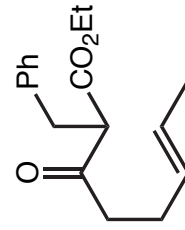


18%  
 ...

Snider *J. Org. Chem.* **1987**, 52, 5487  
*J. Org. Chem.* **1991**, 55, 5544

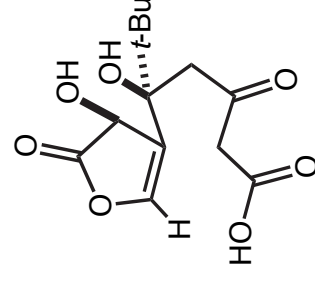
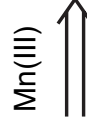
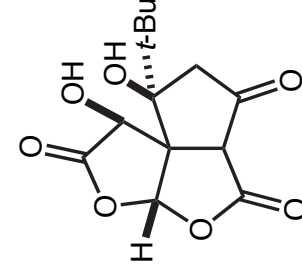
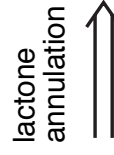
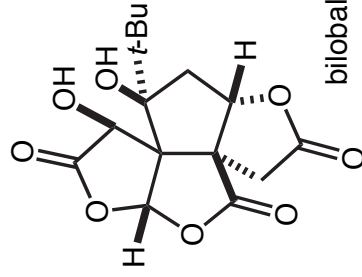
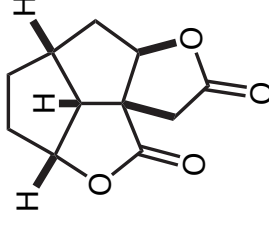
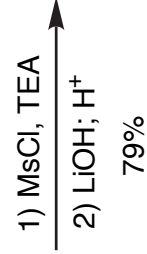
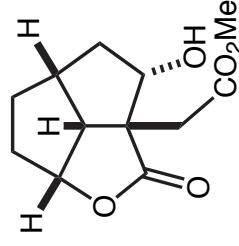
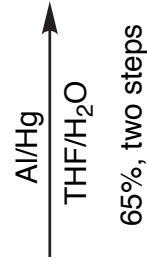
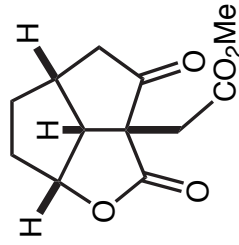
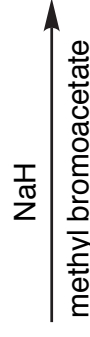
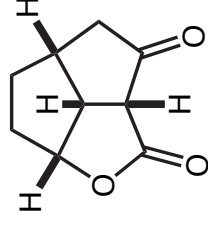
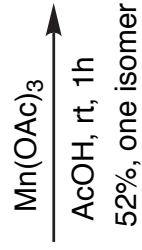
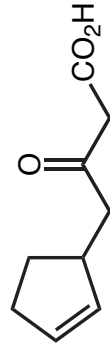
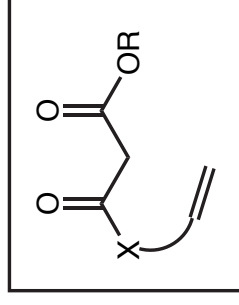


Gibberelic Acid



Snider *Tetrahedron Lett.* **1987**, 28, 845

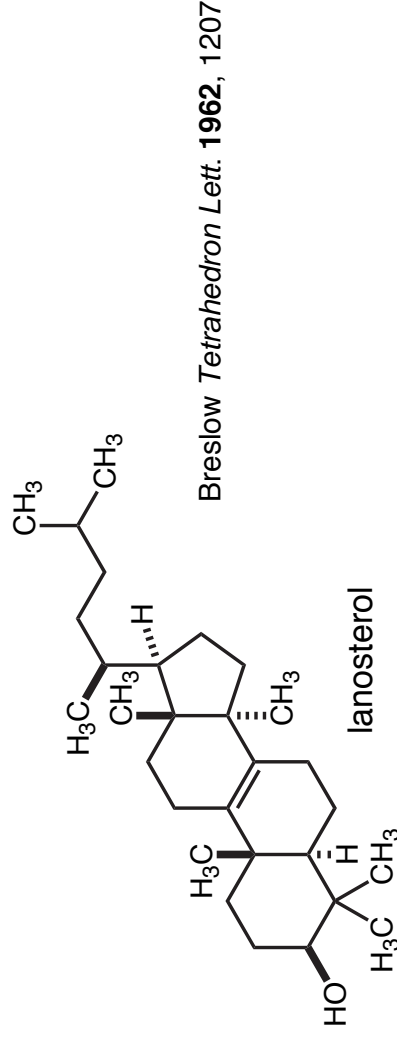
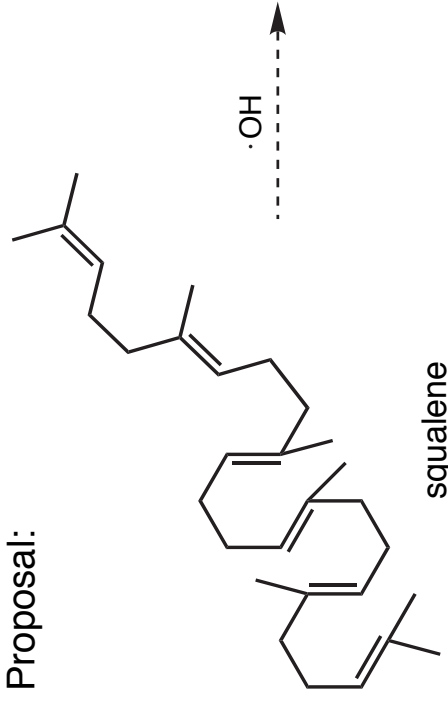
# Hexenyl Radical Cyclization: Studies Toward the Ginkgolides



bilobalide

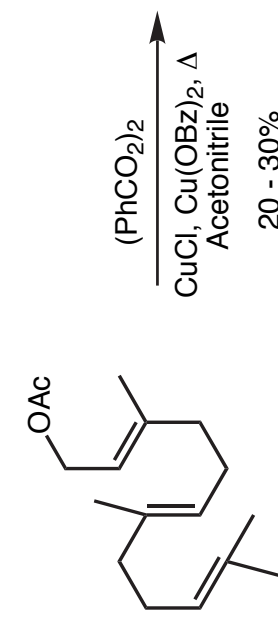
# Biosynthetic Radical Cyclization Hypothesis

Proposal:



Breslow *Tetrahedron Lett.* **1962**, 1207

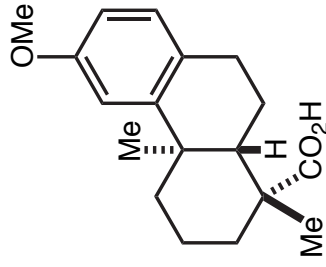
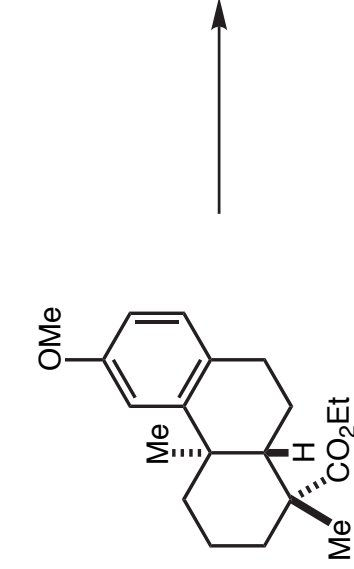
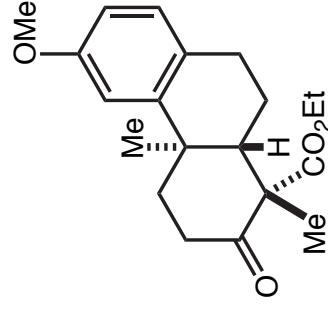
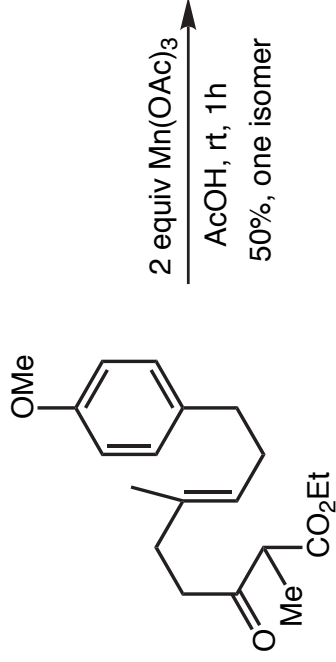
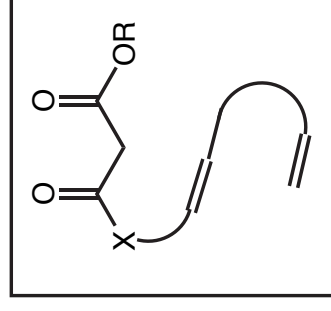
Experiment:



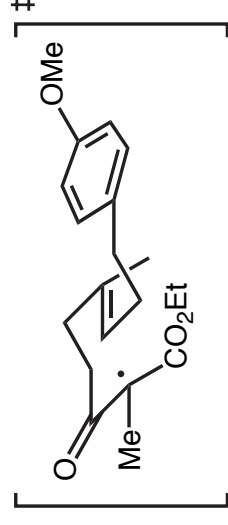
Breslow *Tetrahedron Lett.* **1968**, 1837

However, in 1966 the importance of squalene oxide was established: Corey *J. Am. Chem. Soc.* **1966**, *88*, 4750; van Tamelen, *J. Am. Chem. Soc.* **1966**, *88*, 4752

# Hexenyl Radical Bicyclization: Podocarpic Acid

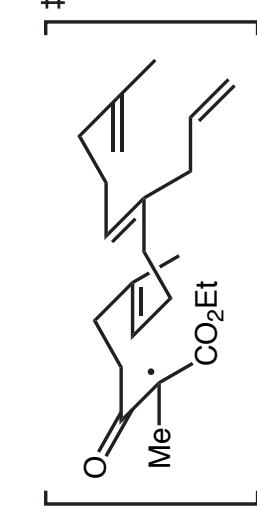
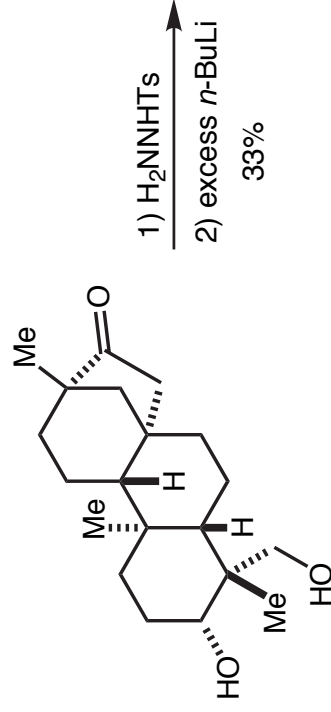
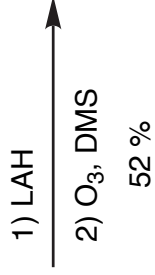
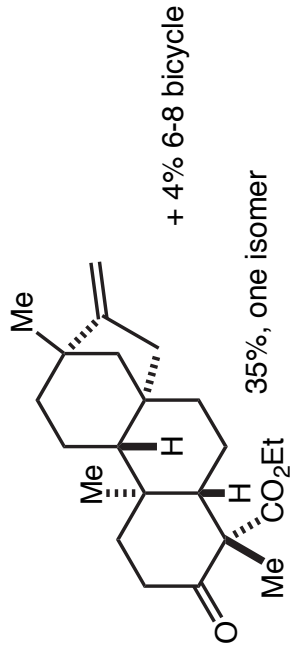
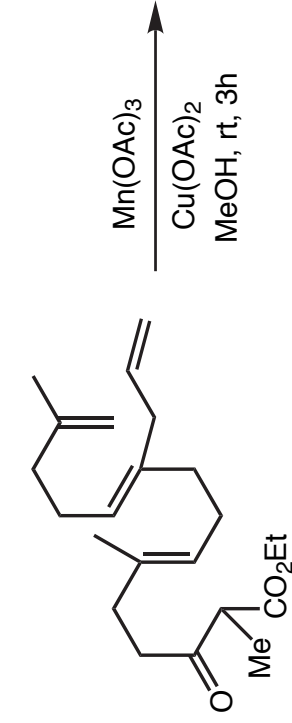
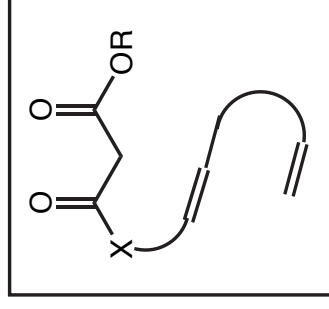


(±) Podocarpic Acid



Snider *J. Org. Chem.* **1985**, *50*, 3659  
Ester hydrolysis: Welch *J. Org. Chem.* **1977**, *42*, 2879

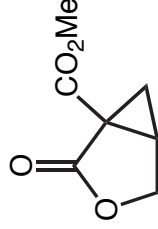
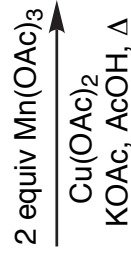
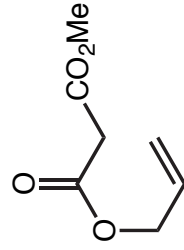
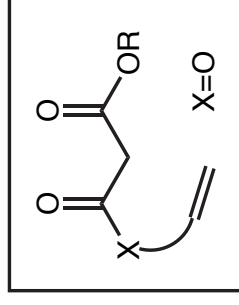
# Hexenyl Radical Tetracyclization: Beyer-15-ene-3,19-diol



Beyer-15-ene-3,19-diol

Snider *J. Org. Chem.* **1998**, 63, 7945

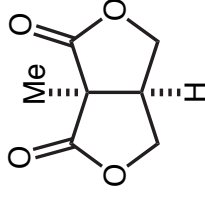
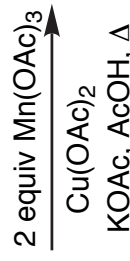
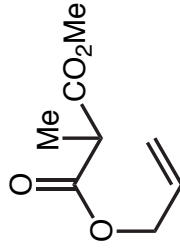
# Hexenyl Radical Cyclization: O-Substituted Malonates



43%

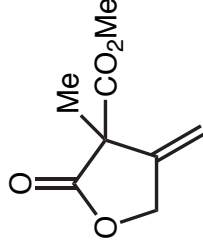
α-unsubstituted

Bertrand *Tetrahedron Lett.* **1989**, 30, 331

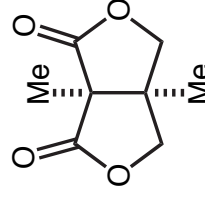
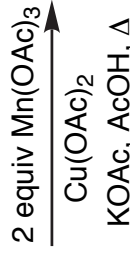
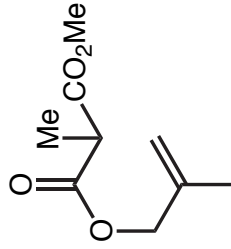


73%

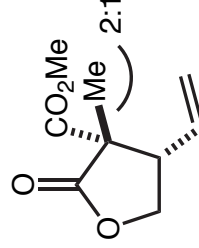
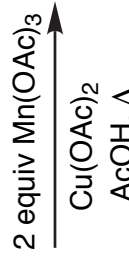
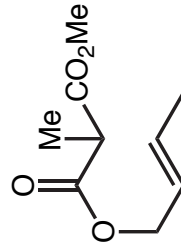
α-substituted



2 : 1



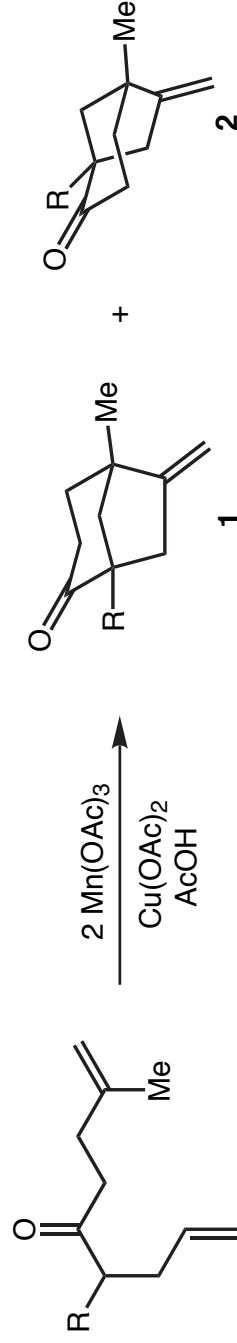
21%



54%

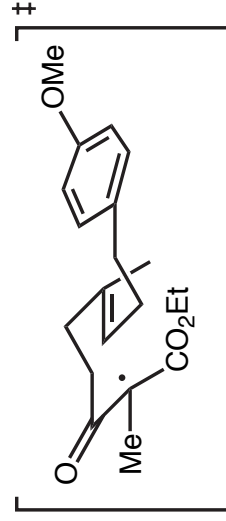
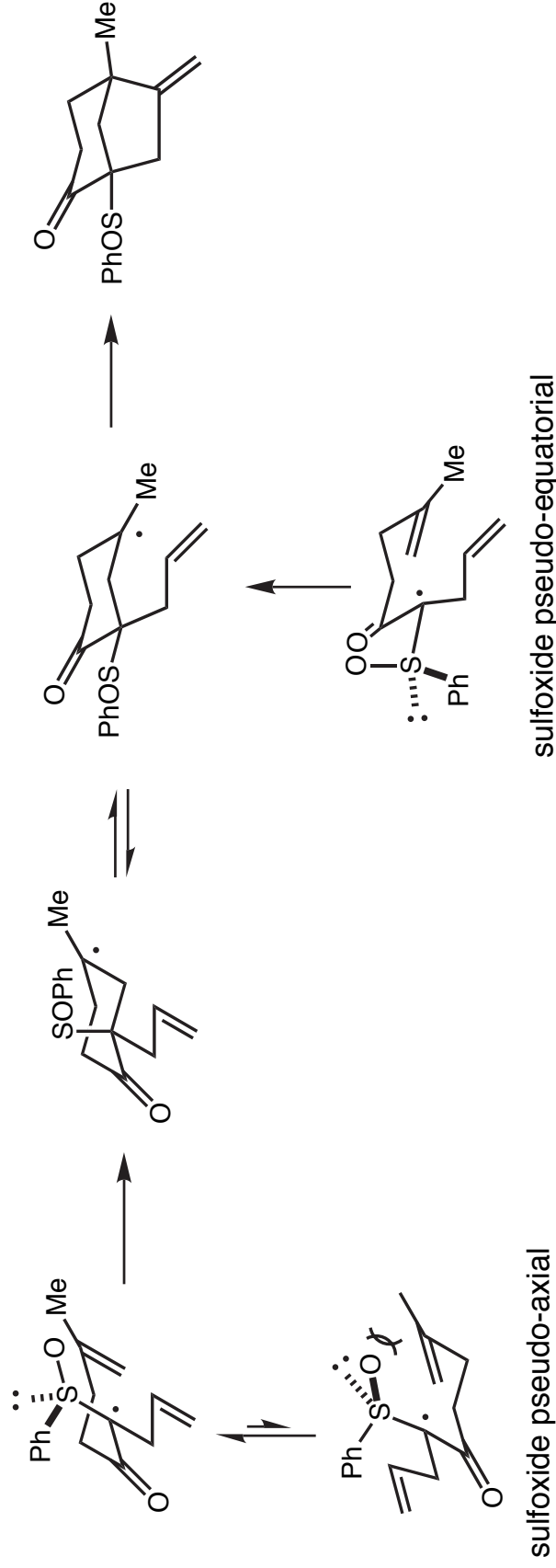
Snider *Tetrahedron* **1993**, 49, 9447

## Mn(III) Cyclizations: Chiral Auxiliaries



R	product	yield (%)	selectivity (%de)
	-	-	-
	2	28	92
	1	44	100
	2	90	86
	-	45	-

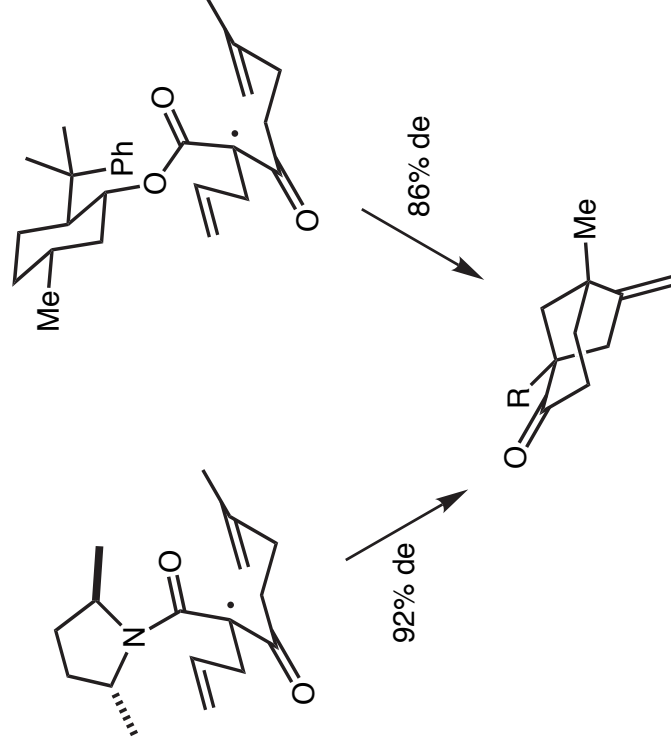
## Mn(III) Cyclizations: $\beta$ -Ketosulfoxide



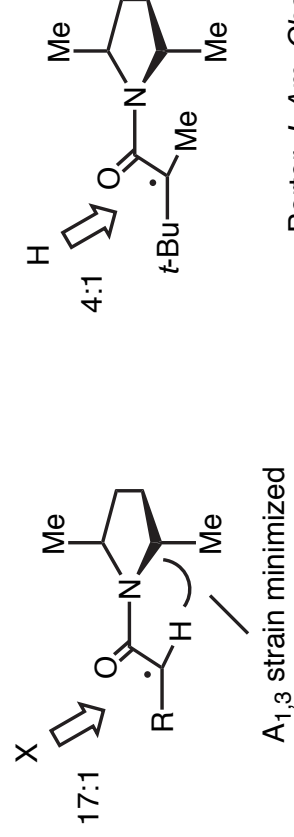
Proposed cyclization geometry in podocarpic acid synthesis

Snider *J. Org. Chem.* **1991**, 56, 328

## Mn(III) Cyclizations: $\beta$ -Ketoamide, $\beta$ -Ketoester

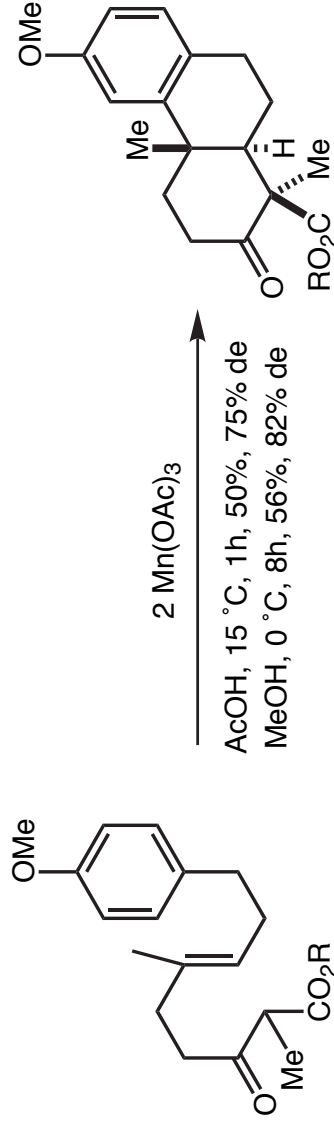


■ The origin of diastereoselectivity is difficult to rationalize when the radical center is tertiary and the conformation is controlled by  $A_{1,3}$  strain.



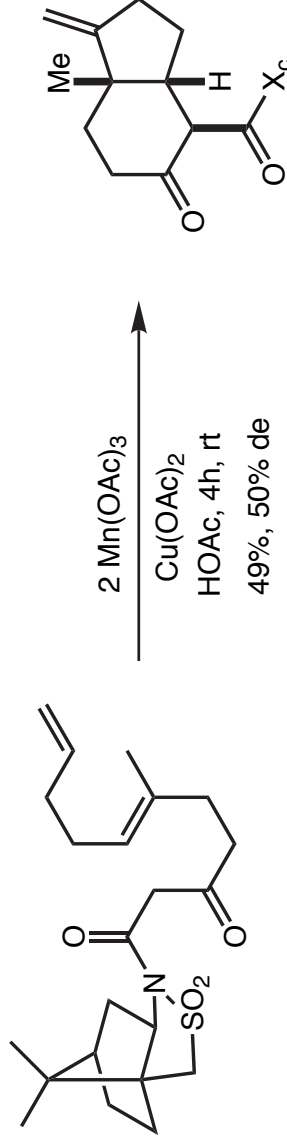
Porter *J. Am. Chem. Soc.* **1991**, 113, 7002  
Giese *Tetrahedron Lett.* **1993**, 33, 2637

# Mn(III) Cyclizations: Chiral Auxiliaries

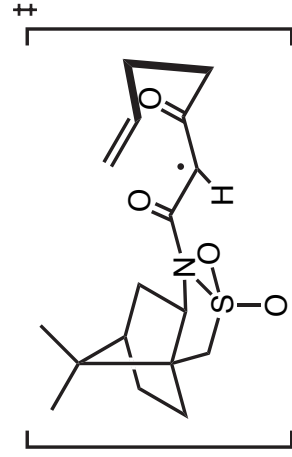


R = (-)-phenmenthyl

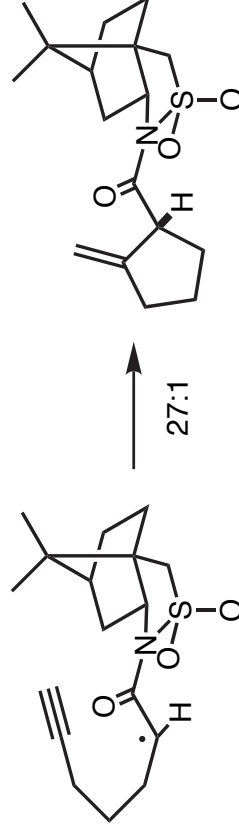
Snider *J. Org. Chem.* **1993**, *58*, 7640



Zoretic *Tetrahedron Lett.* **1992**, *33*, 2637

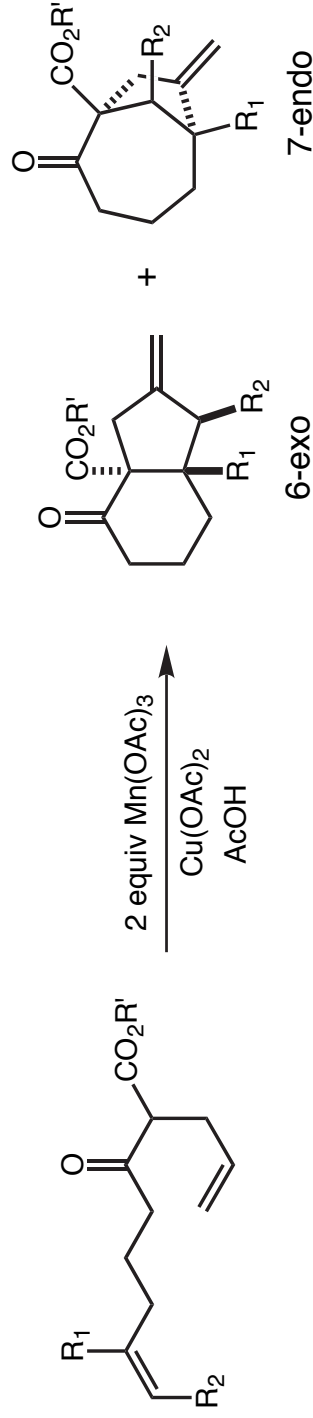
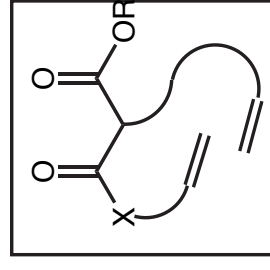


A similar example:

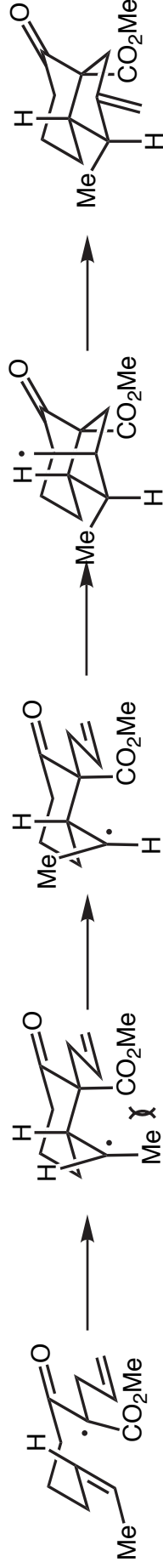


Curran; Porter; Geise In *Stereochemistry of Radical Reactions*,  
 VCH: Weinheim, 1996, 198.

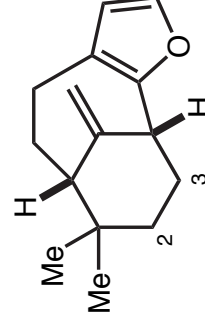
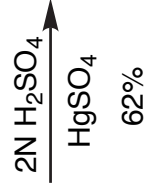
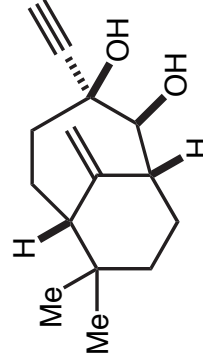
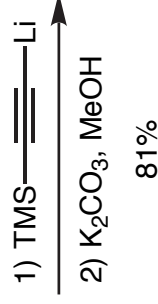
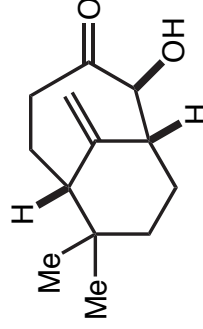
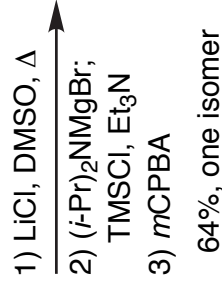
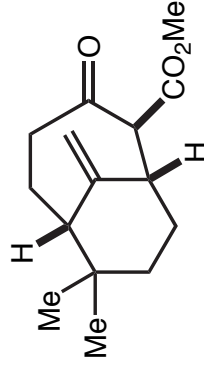
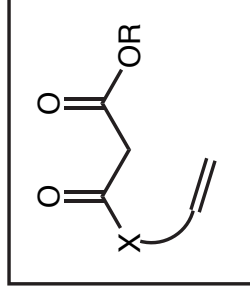
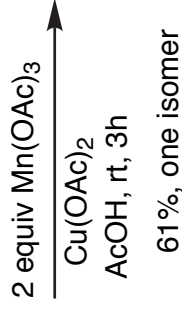
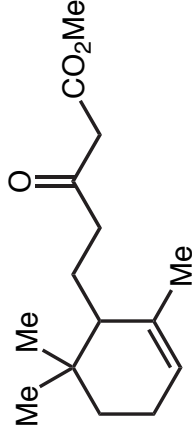
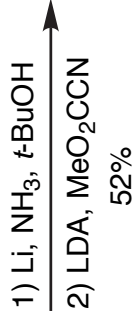
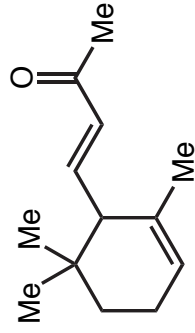
# Heptenyl Radical Bicyclization



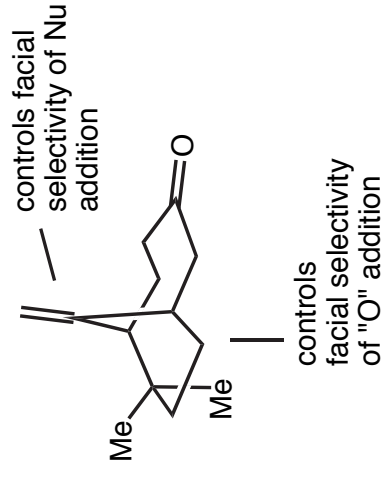
substrate	conditions	products (%yield)		reference
		6-exo	7-endo	
$R_1=R_2=H; R'=Et$	25 °C	12%	32%	Snider <i>Tetrahedron Lett.</i> <b>1988</b> , 29, 5209
$R_1=Me, R_2=H; R'=Me$	25 °C	-	68%	Snider <i>Tetrahedron</i> <b>1991</b> , 47, 8663
$R_1=H, R_2=Me; R'=Me$	25 °C, 13 h	67%	-	Snider <i>J. Org. Chem.</i> <b>1987</b> , 52, 5487



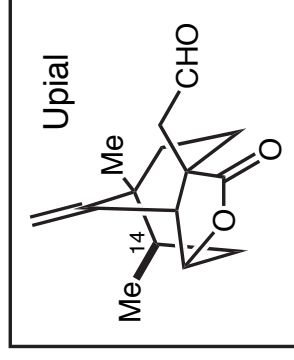
# Heptenyl Radical Cyclization: Dihydropallescensin D



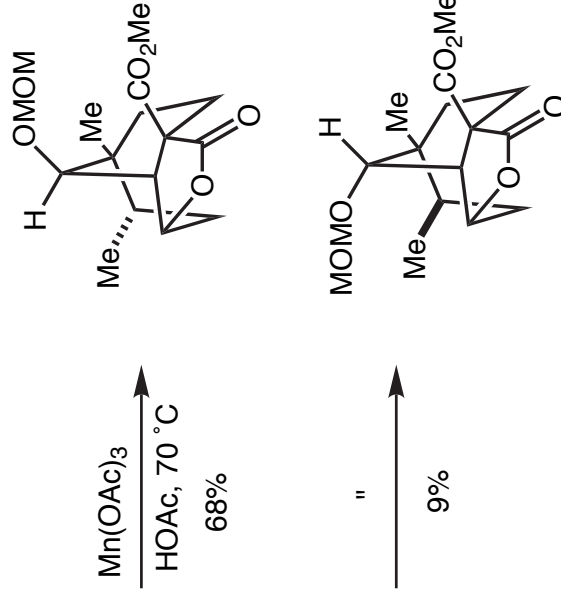
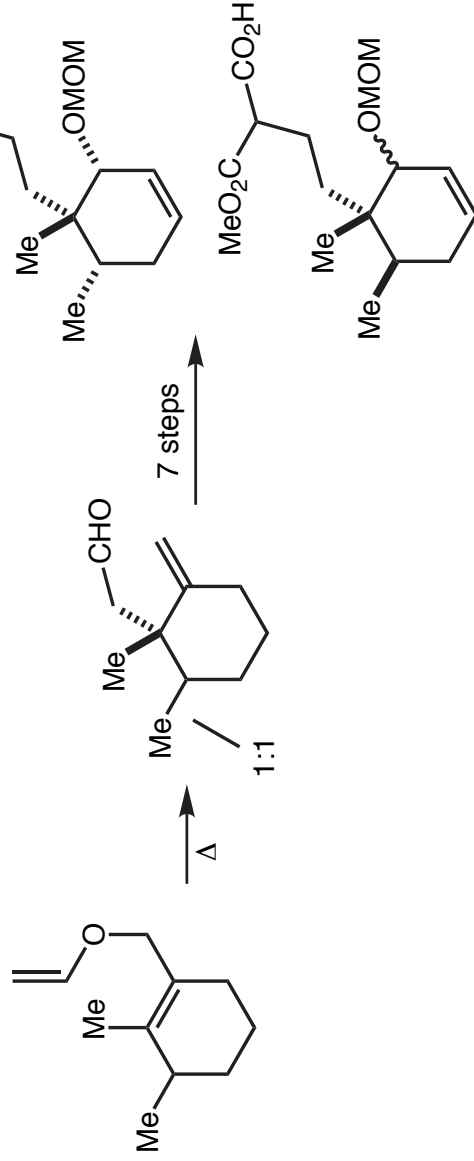
2,3-dihydropallescensin D



# Heptenyl Radical Cyclization: Upial and 14-epiUpial

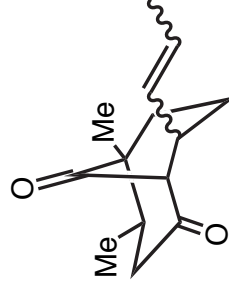
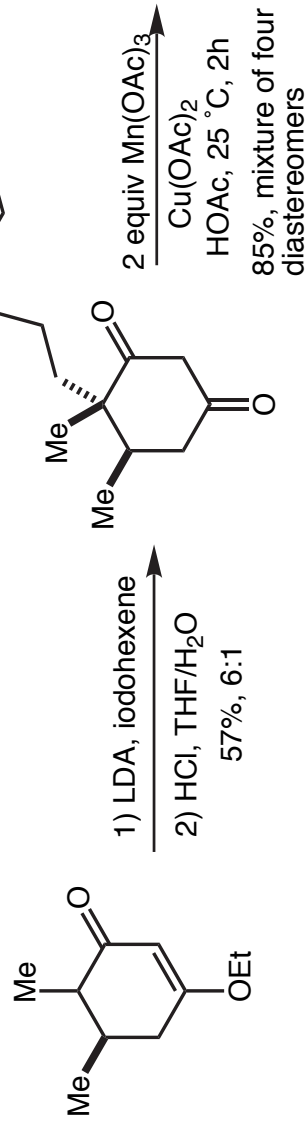


Paquette: 14-epiUpial



Paquette *Tetrahedron* **1987**, 43, 5567

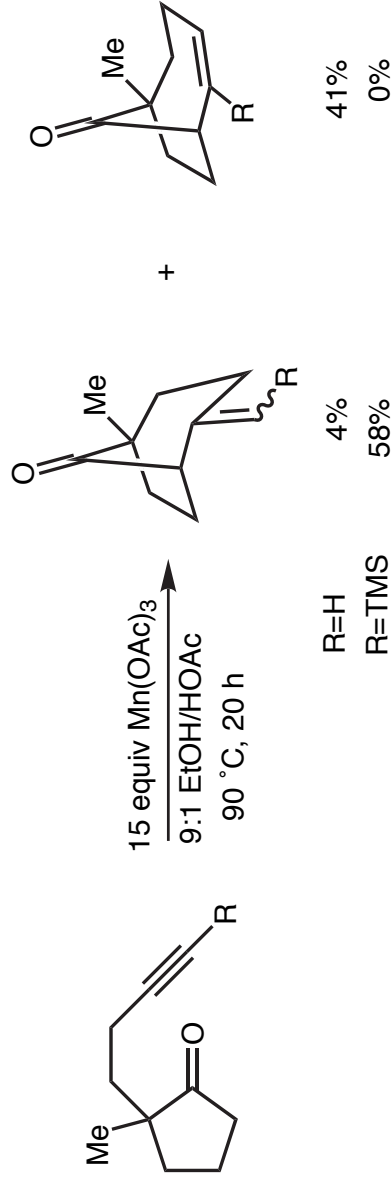
Snider: Upial Formal Synthesis



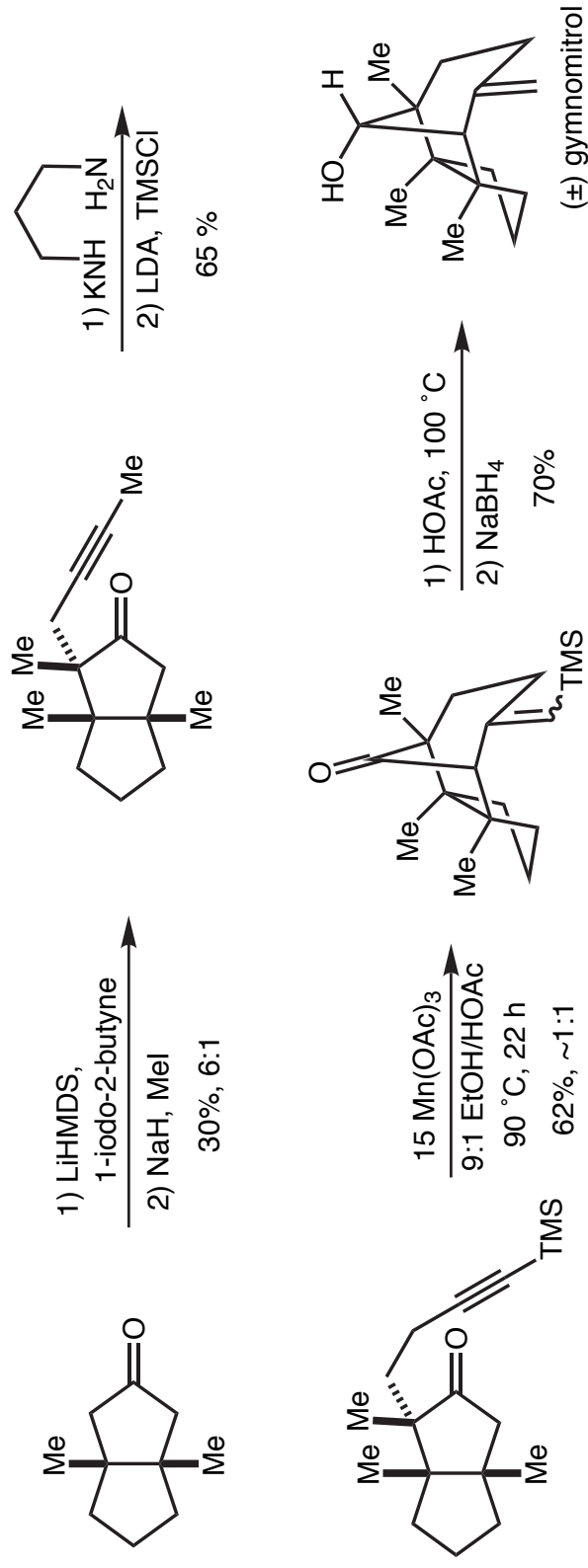
Snider *Tetrahedron* **1995**, 51, 12983  
Taschner *J. Am. Chem. Soc.* **1985**, 107, 5570

# Heptenyl Radical Cyclization: Gymnomitrol

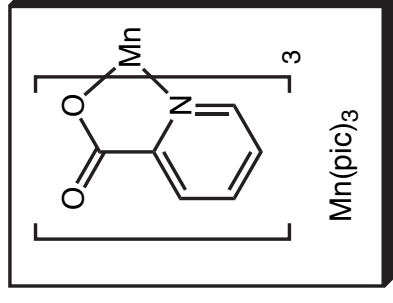
Precedent:



Synthesis:

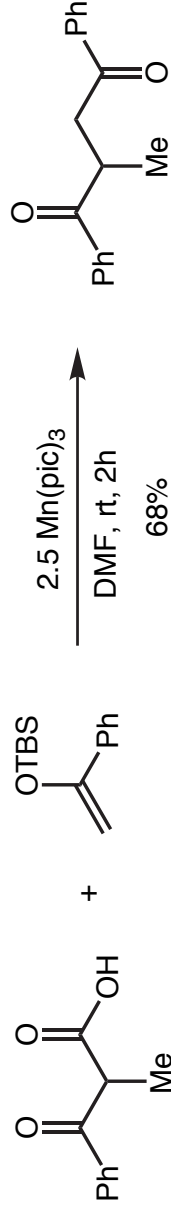


# Manganese Tris(2-pyridinecarboxylate)

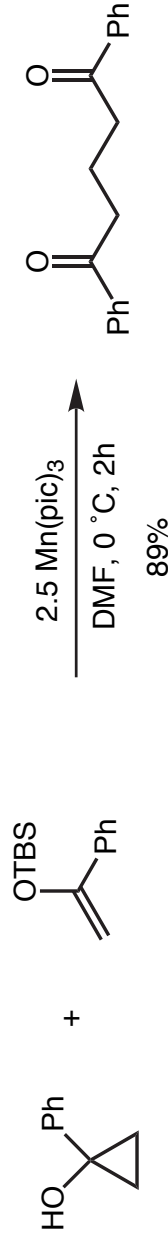


- Synthesis: Ray *Aust. J. Chem.* **1966**, 19, 1737  
Formerly a water-redox model for photosystem II.

- Introduction in synthetic chemistry: Narasaka *Chem Lett.* **1989**, 2169

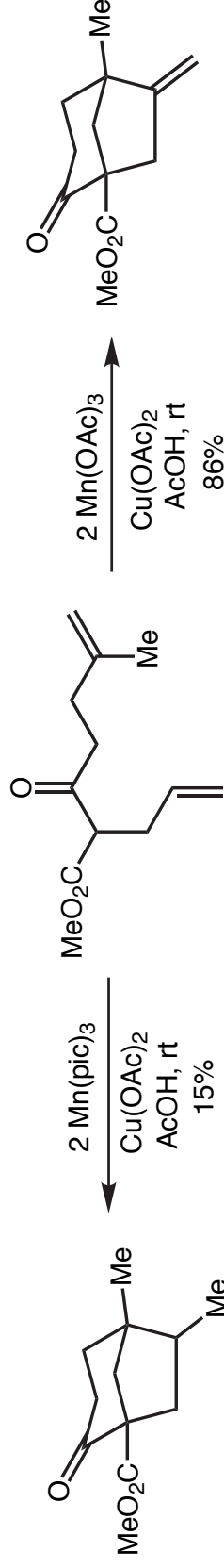


Narasaka *Chem Lett.* **1989**, 2169

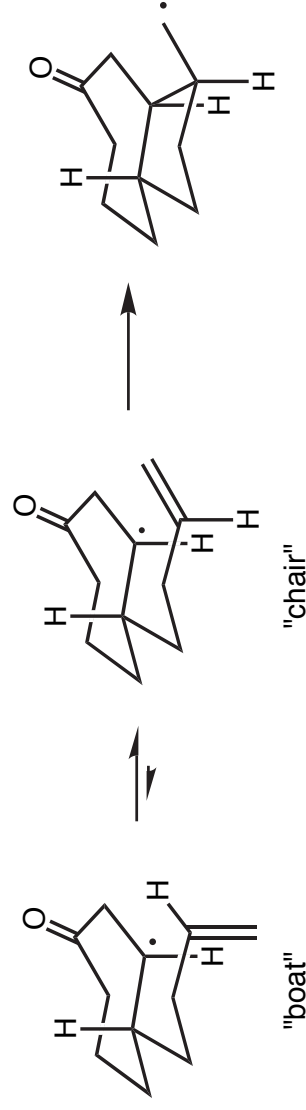
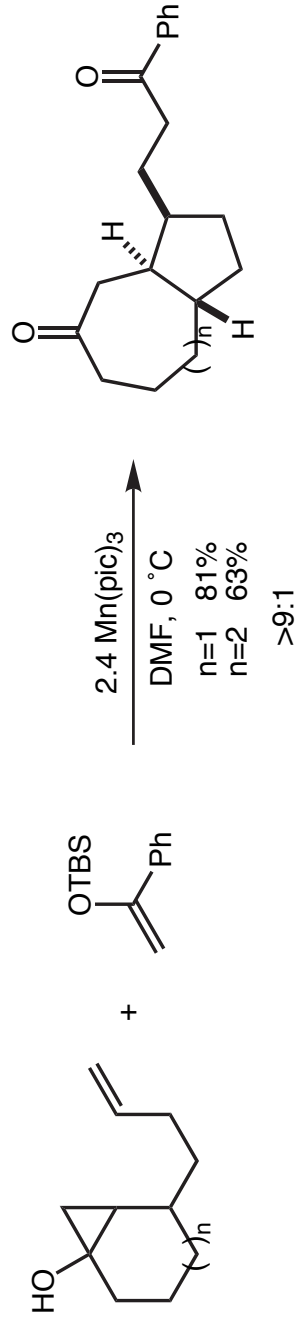
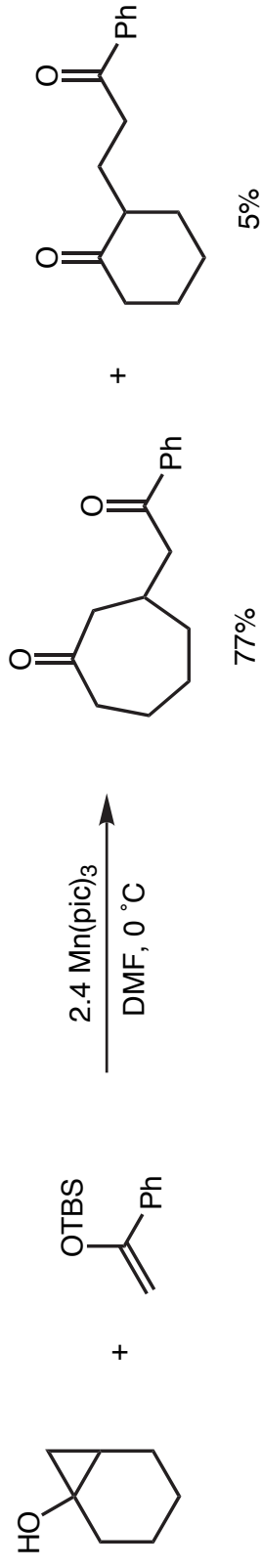


Narasaka *Chem Lett.* **1991**, 1193

- Mn(pic)<sub>3</sub> and Mn(OAc)<sub>3</sub> behave differently in acetic acid: Snider *J. Org. Chem.* **1993**, 58, 6217



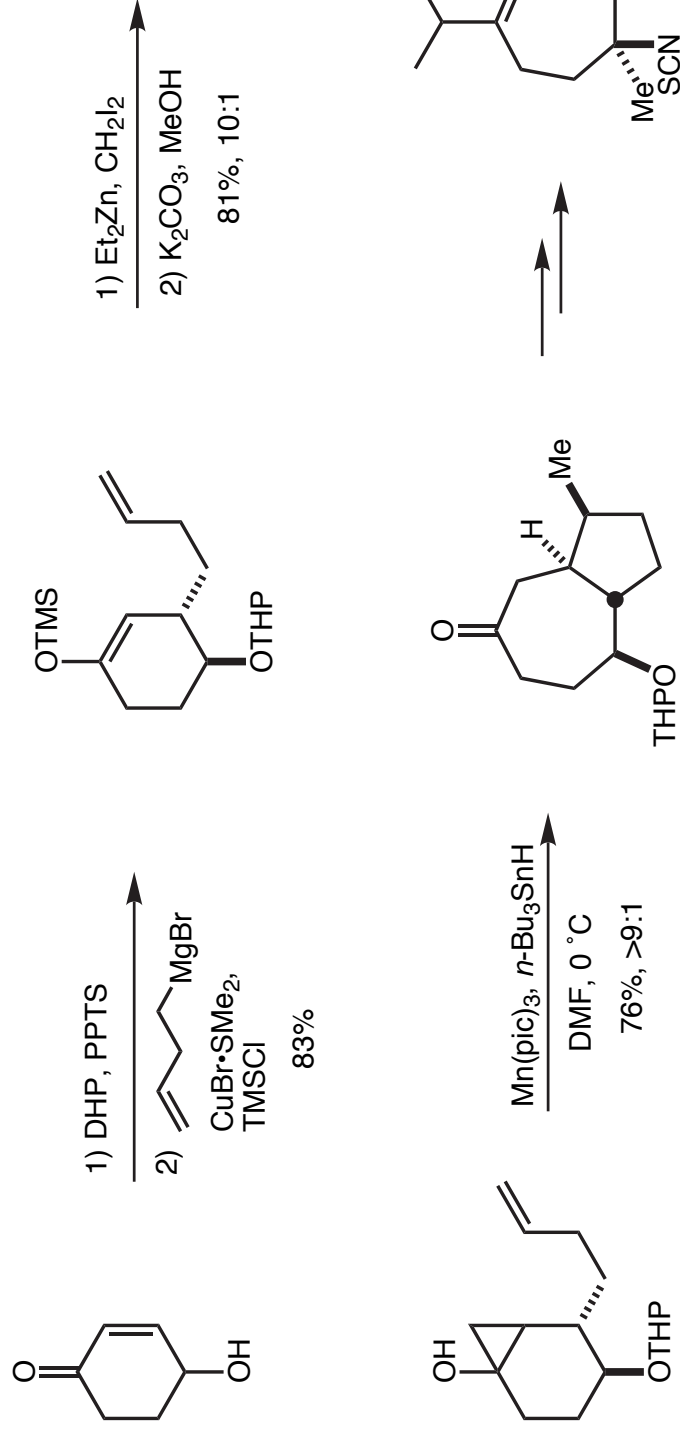
# Mn(pic)<sub>3</sub>: Oxidative Ring Expansion



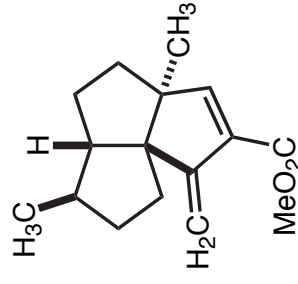
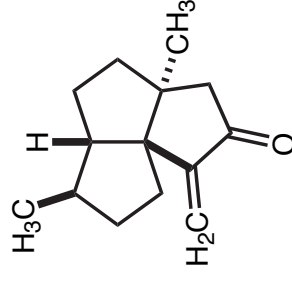
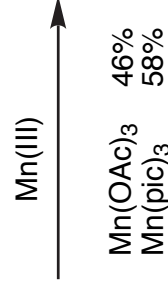
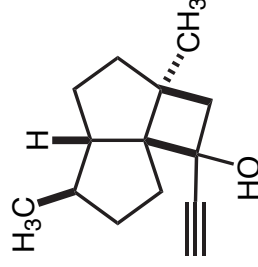
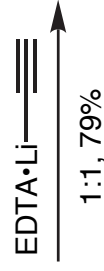
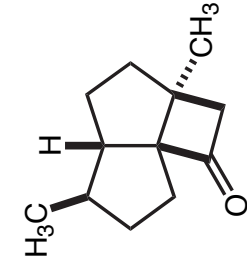
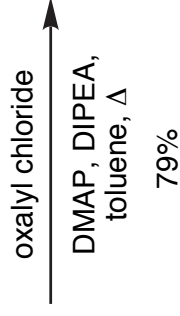
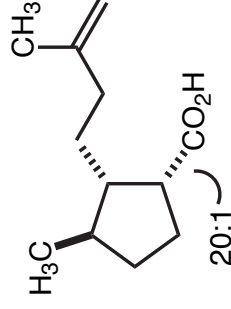
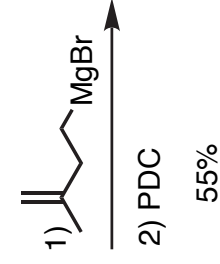
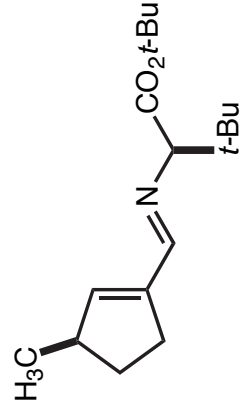
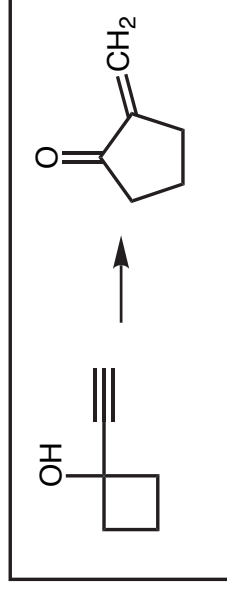
■ Cyclization selectivity is consistent with the Beckwith-Houk model

# Oxidative Ring Expansion: Synthesis of

## 10-Isothiocyanatoguaia-6-ene



# Oxidative Ring Expansion: Synthesis of (-)-Methyl Cantabradienate



■ 7 steps, 9% overall yield

(-)-methyl cantabradienate

Snider *J. Org. Chem.* **1994**, *59*, 5419

## Reflections on Mn(III)

- $\text{Mn}(\text{OAc})_3$  is a unique one-electron oxidant for acidic C-H bonds
- Important in the synthesis of fused- and bridged- polycyclic natural products, often exhibiting excellent regioselectivity in cyclizations
- Liability: polymerization and other side-reactions often lead to modest yields
- $\text{Mn}(\text{pic})_3$  offers interesting routes to natural products by oxidative cyclopropane fragmentation