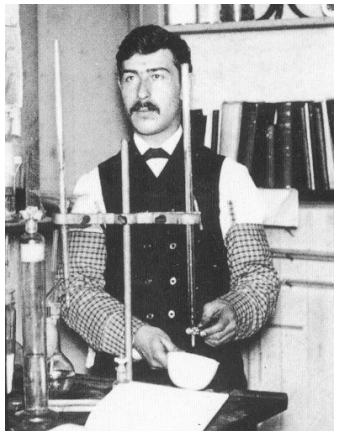
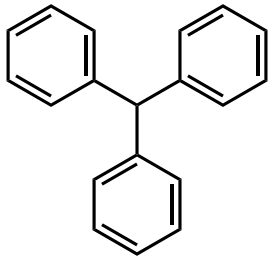
Timeless Methods for Radical Cyclizations in Total Synthesis

Patricia Zhang
MacMillan Group Meeting
Wednesday September 25th, 2013

A little history



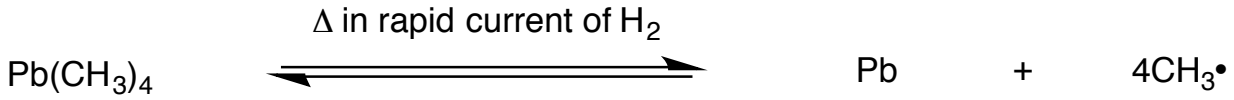
1900: Moses Gomberg



"Ph_3C" rather than "$Ph_3C\bullet$"

trivalent carbon
(discovery predated electronic theory)

1929: Paneth and Hofeditz



Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757.
Paneth, F.; Hofeditz, W. *Chem. Ber.* **1929**, *62*, 1335.

Radical Cyclizations in Total Synthesis

- A change in the synthetic community's outlook on carbon radicals

"Unruly & Uncontrollable"

- dimerization at diffusion rates
- disproportionation
- polymerization
- extremely reactive

Functional Group Transformations

- Kolbe oxidation
- Hoffman-Loffler-Freytag
- Meerwein arylation
- NBS bromination
- Kharasch reaction
- Tin Hydride

then in the 1980s.....

"Mild, Neutral and Selective"

- extremely reactive
- neutral species, good for crowded bonds
- inert to OH and NH
- no β-elimination of OR, NR, etc.
- ground state of structures good T.S. models
- easy racemic synthesis of radical precursor

Synthetic Radical Chemistry

- Giese reactions: Intermolecular Additions
- Barton's thiohydroxamates: Carbon Radicals
- Hart's pyrrolizidine synthesis
- Stork's regio- and stereoselective syntheses
- Curran's tandem syntheses

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

- Goal: General overview of major methods from the 1980s boom

Cyclizations organized by method of radical generation:

The Tin Hydride Method

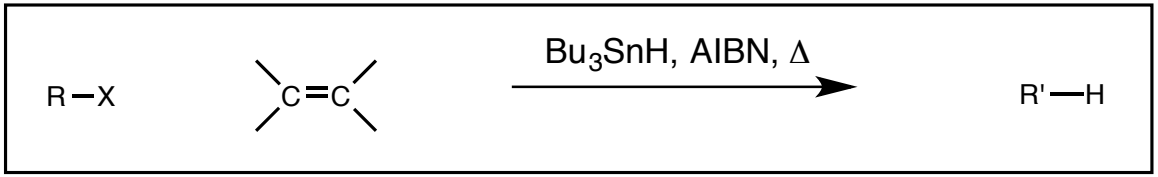
The Fragmentation Method

The Reduction Method

The Oxidation Method

Showcase power of these methods with examples from today

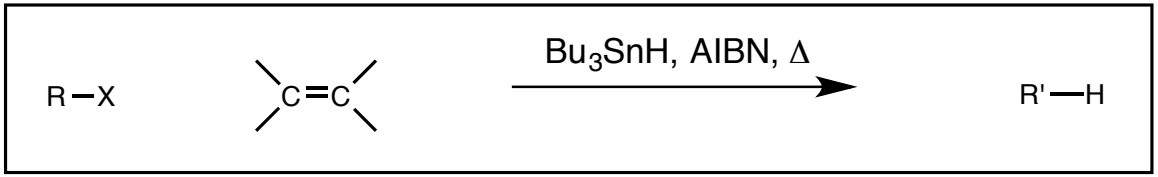
The Tin Hydride Method



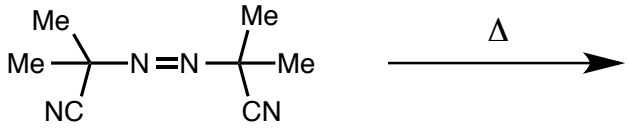
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

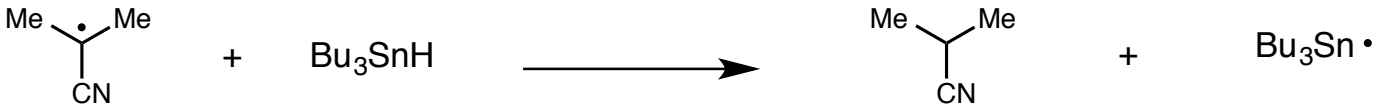
The Tin Hydride Method



Initiation:



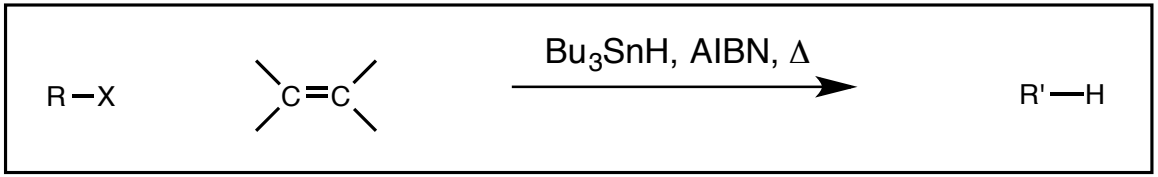
AIBN



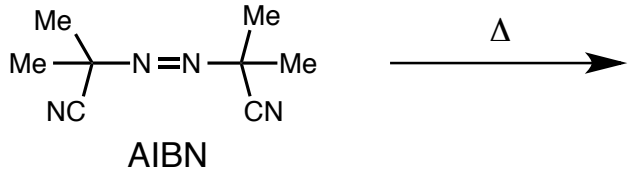
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

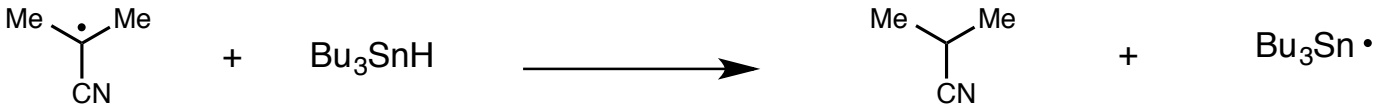
Radical Cyclizations in Total Synthesis

The Tin Hydride Method

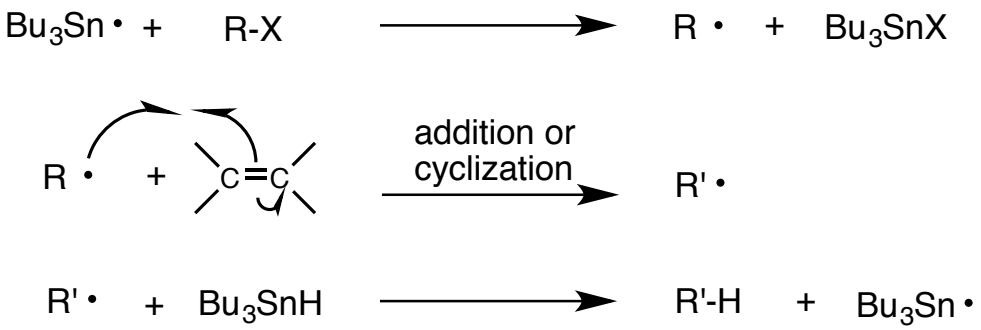


Initiation:





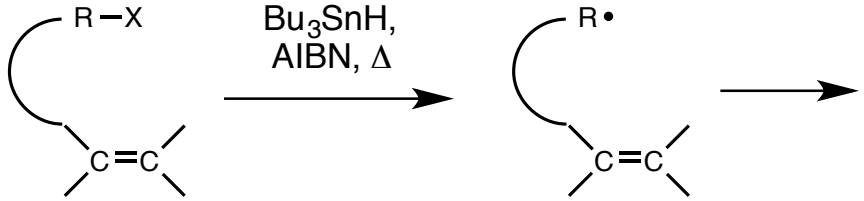
Propagation:



Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

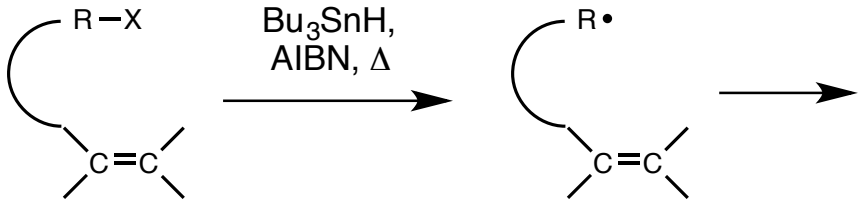
- Radical cyclizations follow Baldwin's rules



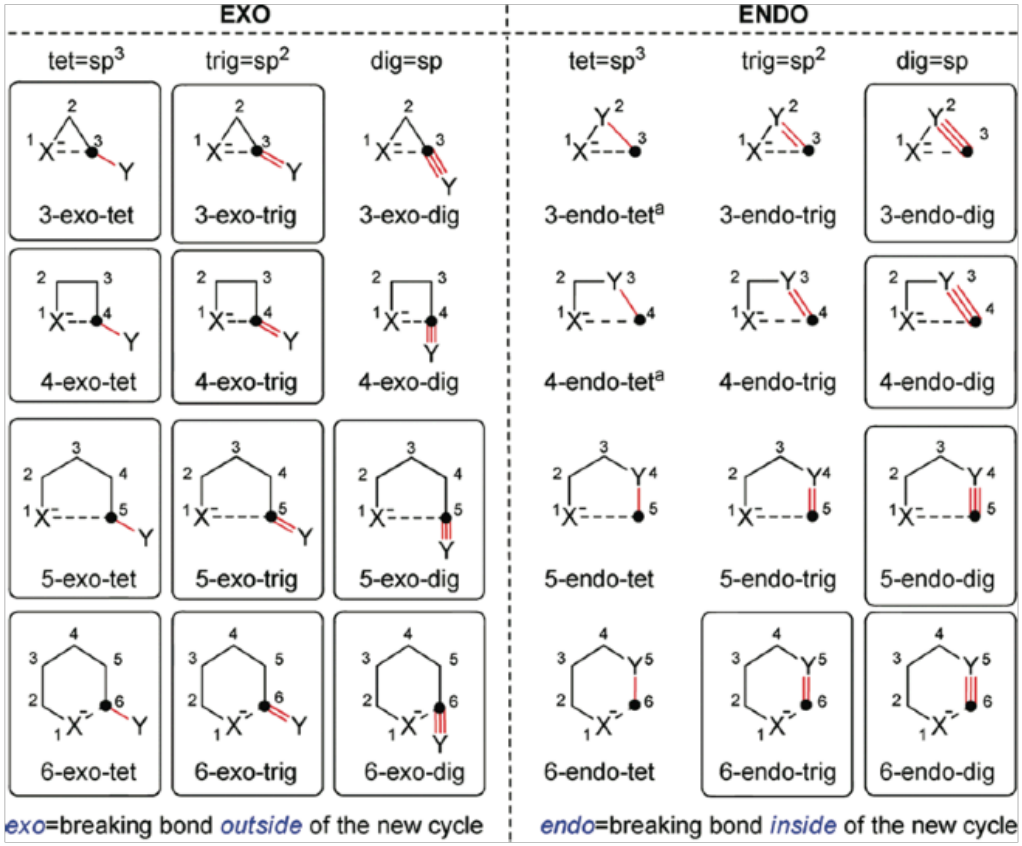
Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *11*, 6513-6556.

Radical Cyclizations in Total Synthesis

- Radical cyclizations follow Baldwin's rules

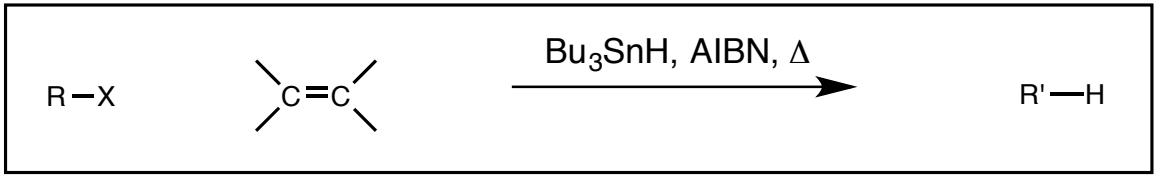


boxed structures are allowed



Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *11*, 6513-6556.

The Tin Hydride Method

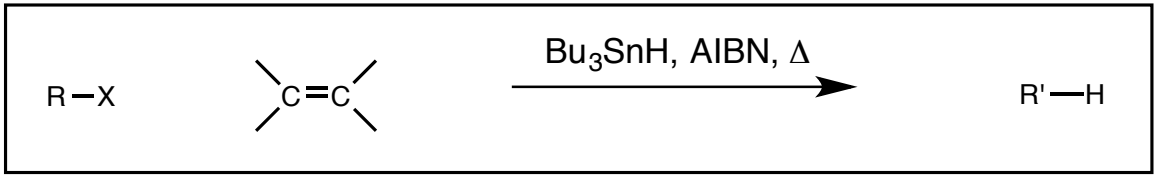


- Bu_3SnH most commonly used reagent to conduct free-radical reactions

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

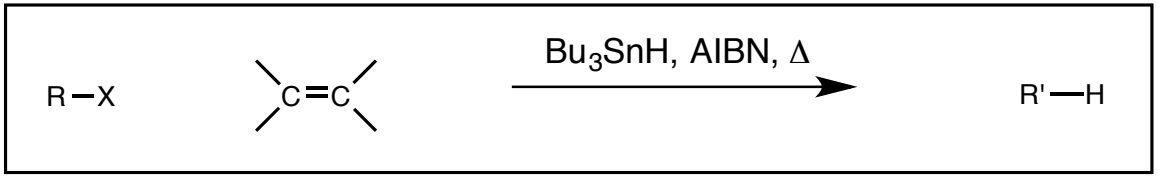
The Tin Hydride Method



- Bu_3SnH most commonly used reagent to conduct free-radical reactions
- Overall reaction: R-X for stronger R-H, Sn-H for stronger Sn-X

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

The Tin Hydride Method



- Bu_3SnH most commonly used reagent to conduct free-radical reactions
- Overall reaction: R-X for stronger R-H, Sn-H for stronger Sn-X

Substrate Trends:

- Transferability of X to $Bu_3Sn•$ is

$$X• + Bu_3Sn• \longrightarrow Bu_3Sn\text{-}X$$

I > Br > SePh > OC(S)SMe > Cl > SPh

- Reactivity of R• to Bu_3SnH is

$$R• + Bu_3SnH \longrightarrow Bu_3Sn• + R\text{-}H$$

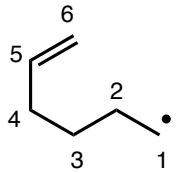
aryl ≈ vinyl > alkyl > allyl ≈ benzyl

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

Beckwith's rules

- Cyclizations containing five linking carbons or less prefers exo-mode
- Radicals add to least substituted carbon of olefin if no other geometric constraints
- Bond undergoing homolytic cleavage must lie close to the plane of the radical
- 5-Hexenyl radical ring closures are stereoselective:

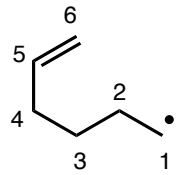


Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

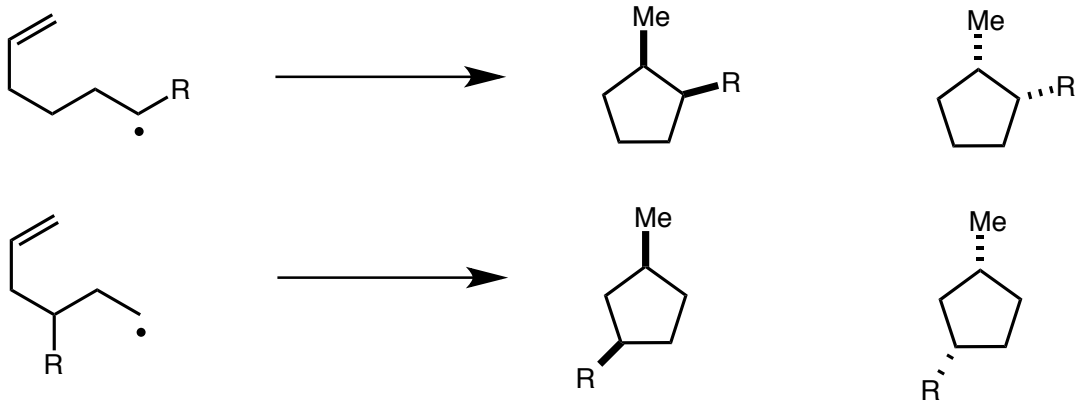
Radical Cyclizations in Total Synthesis

Beckwith's rules

- Cyclizations containing five linking carbons or less prefers exo-mode
- Radicals add to least substituted carbon of olefin if no other geometric constraints
- Bond undergoing homolytic cleavage must lie close to the plane of the radical
- 5-Hexenyl radical ring closures are stereoselective:



1-,3- substituted systems give cis

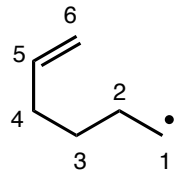


Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

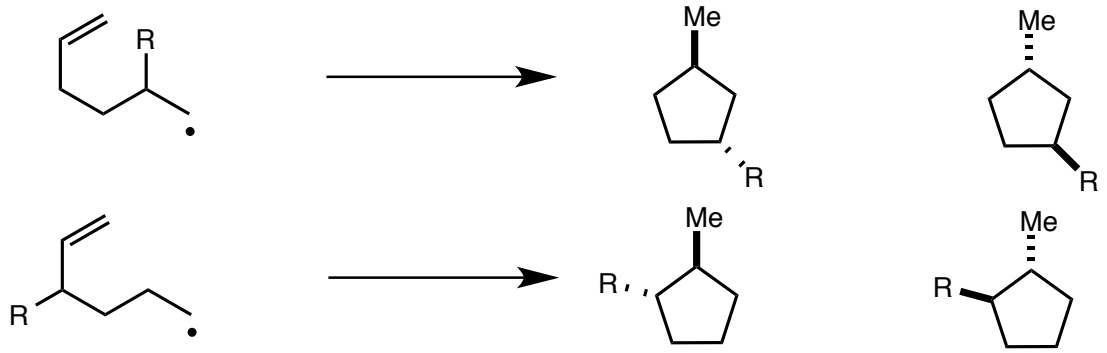
Radical Cyclizations in Total Synthesis

Beckwith's rules

- Cyclizations containing five linking carbons or less prefers exo-mode
- Radicals add to least substituted carbon of olefin if no other geometric constraints
- Bond undergoing homolytic cleavage must lie close to the plane of the radical
- 5-Hexenyl radical ring closures are stereoselective:



2-,4- substituted systems give cis

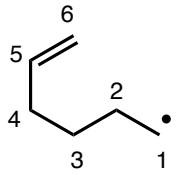


Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

Beckwith's rules

- Cyclizations containing five linking carbons or less prefers exo-mode
- Radicals add to least substituted carbon of olefin if no other geometric constraints
- Bond undergoing homolytic cleavage must lie close to the plane of the radical
- 5-Hexenyl radical ring closures are stereoselective:

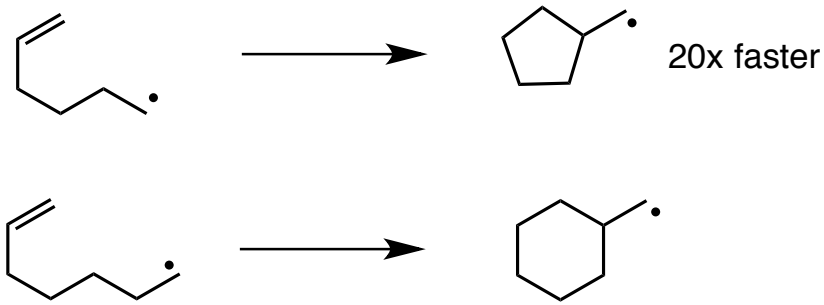


2-,3-, or 4- substitued systems reflects conformation preference of chair T.S.

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

- Carbacycle formation with tin hydride
  - Cyclizations yielding 5-membered rings are fast

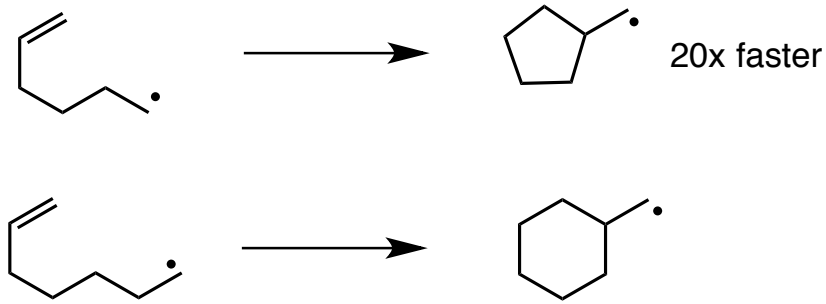


Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

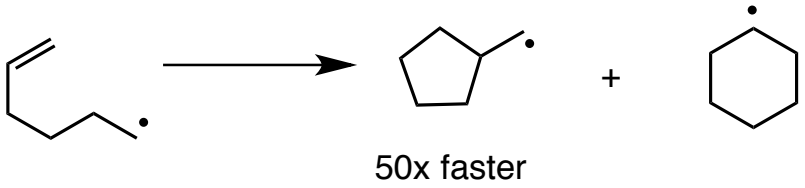
Radical Cyclizations in Total Synthesis

■ Carbacycle formation with tin hydride

- Cyclizations yielding 5-membered rings are fast



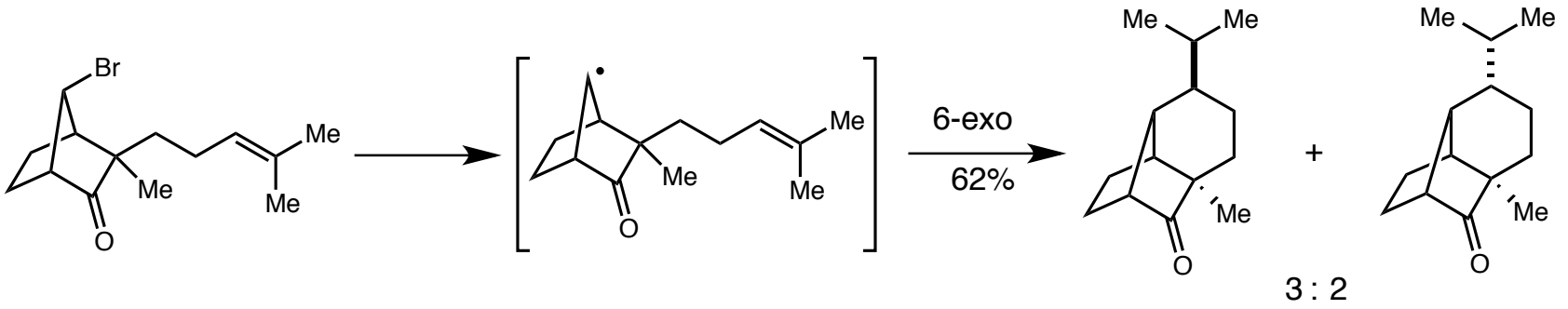
- High regioselectivity for 5-exo



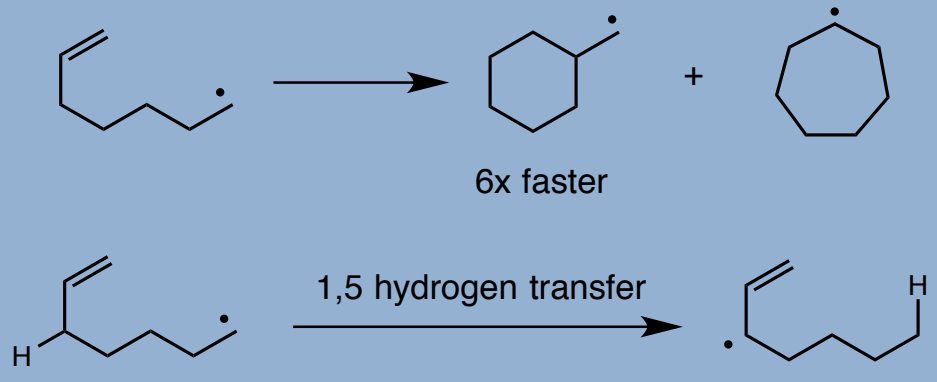
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

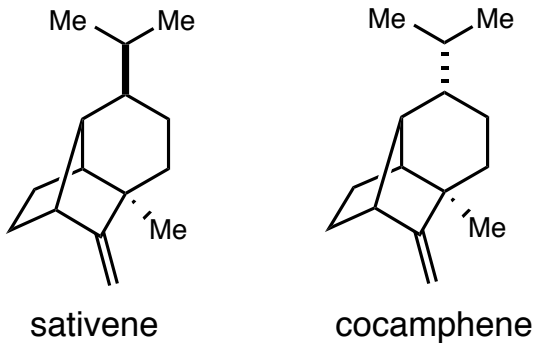
Radical Cyclizations in Total Synthesis

- First application of tin hydride in total synthesis



- 6-membered rings are less general than 5
- diminished regioselective and stereoselectivity
- more suspectible to reduction before cyclization

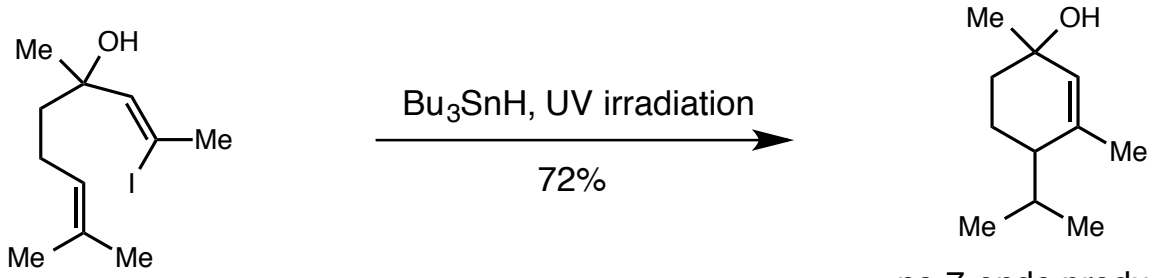




Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.
Bakuzi, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261-3264.

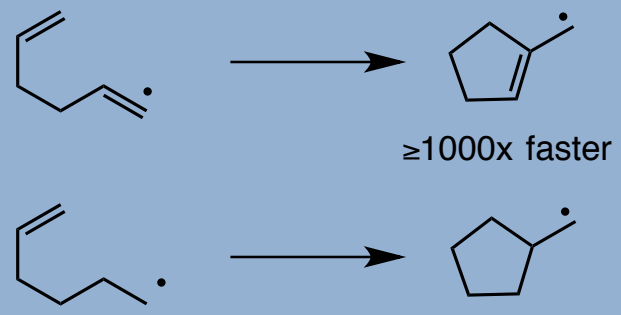
Radical Cyclizations in Total Synthesis

■ Stork improves the 6-exo cyclization

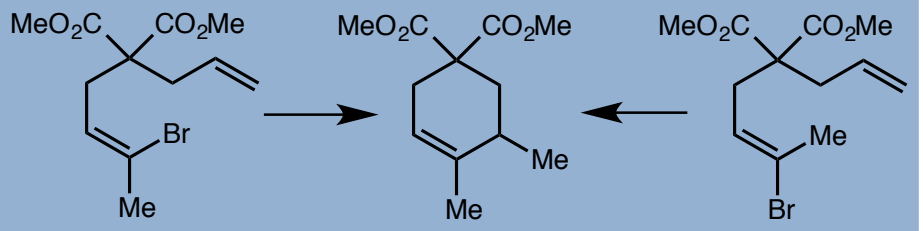


no 7-endo product
1 : 1 diastereomers

■ vinyl radicals much more reactive to cyclization



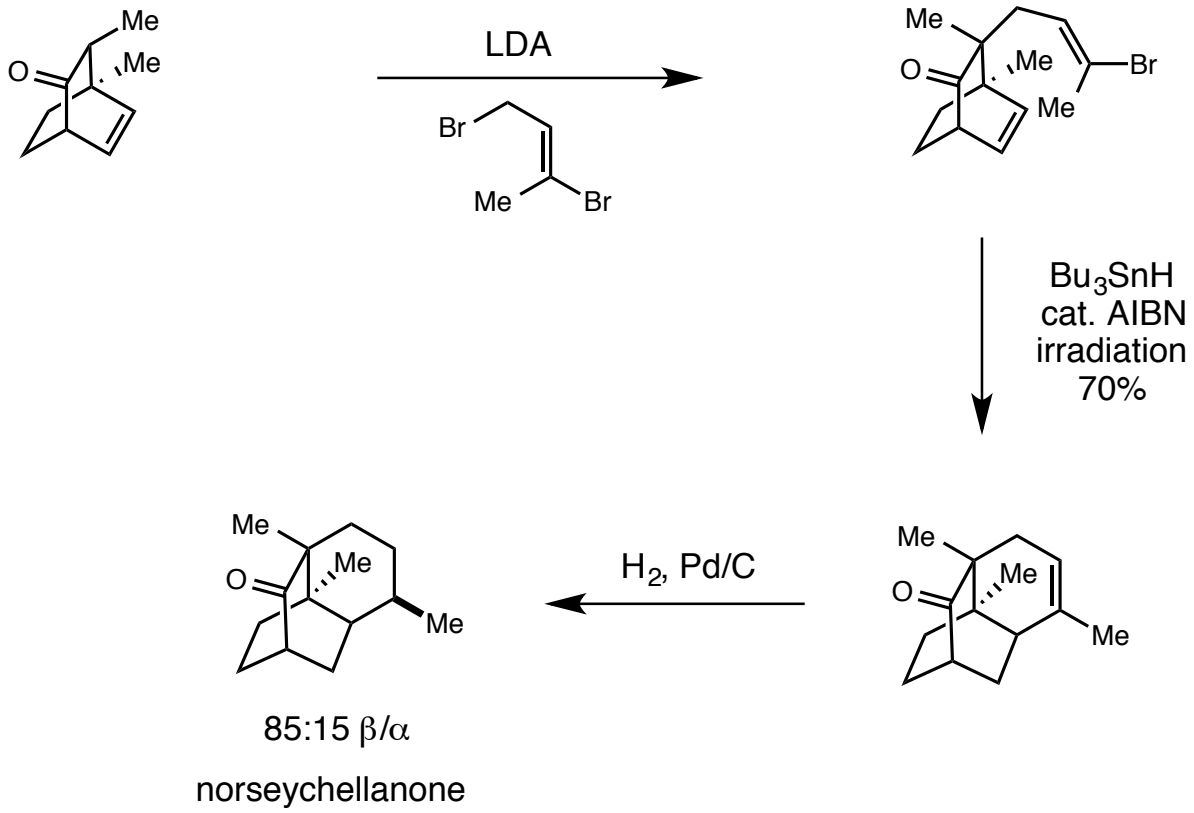
■ more suspectible to reduction and good allylic H atom abstractor
■ low inversion barrier for vinyl radical



75%

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.
Stork, G.; Baine, N. H. *J. Am. Chem. Soc* **1982**, *104*, 2323-2325.

- Vinyl radical in the total synthesis of norseychellanone



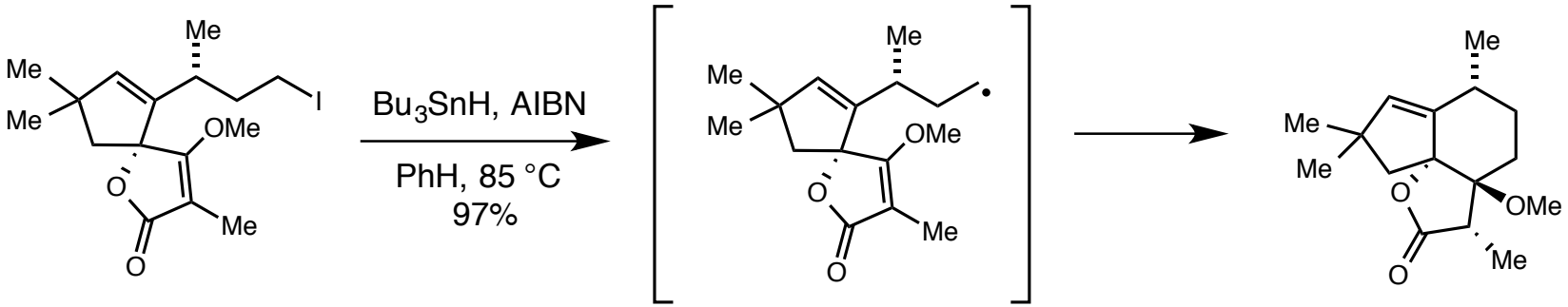
85:15 β/α

norseychellanone

Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927-5930.

- Activated olefins to aid 6-endo cyclization

EWG on "electrophile" lowers LUMO energy

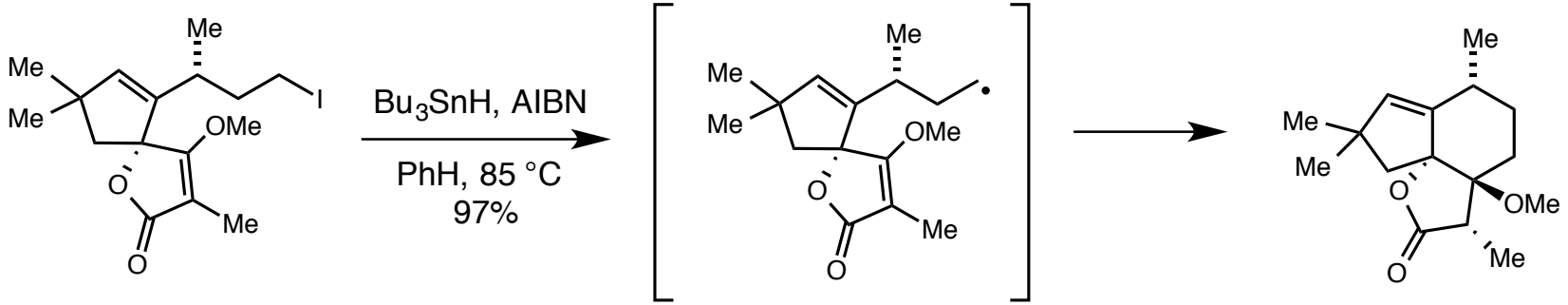


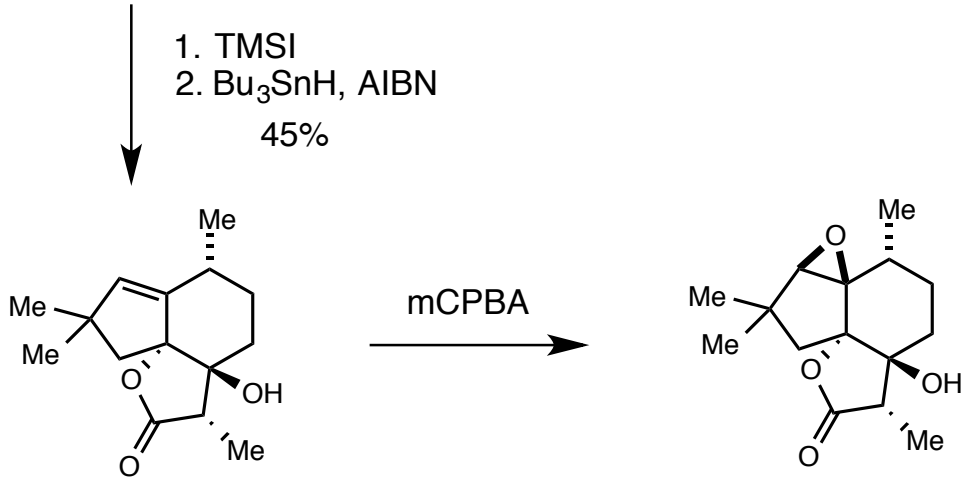
Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413-4416.

Radical Cyclizations in Total Synthesis

- Activated olefins to aid 6-endo cyclization

EWG on "electrophile" lowers LUMO energy





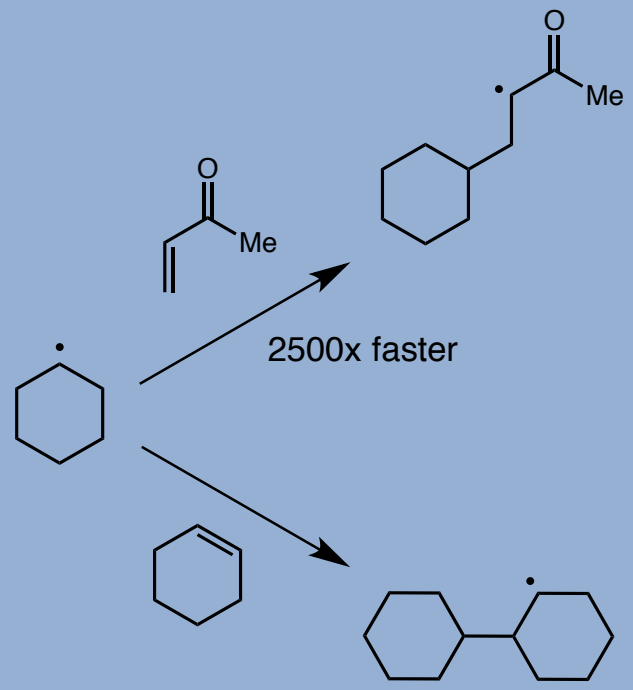
alliacolide

Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413-4416.

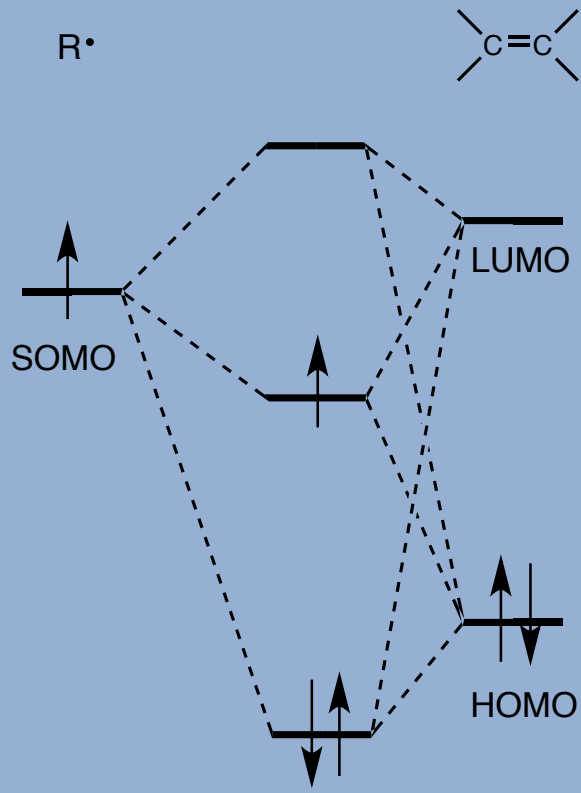
Radical Cyclizations in Total Synthesis

■ Enones as radical acceptor activators

■ Empirical evidence

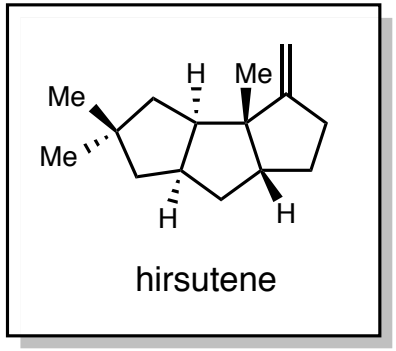


■ Frontier orbital theory explanation

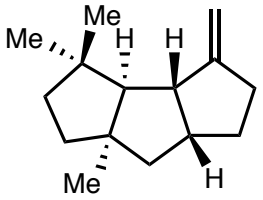


Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753-764.

The triquinane system



hirsutene

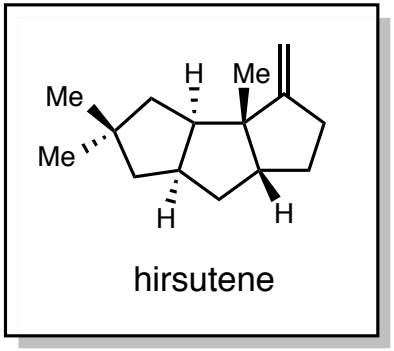


$\Delta^{9(12)}$-capnellene

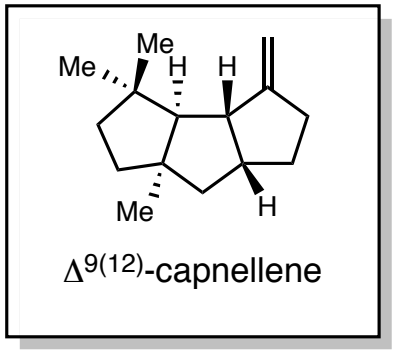
Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

Curran, D.P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.

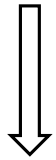
The triquinane system

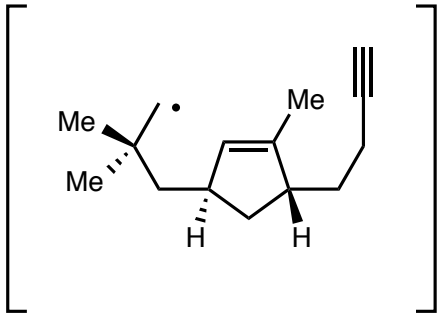


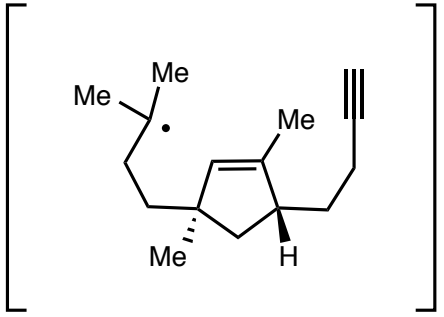
hirsutene



$\Delta^{9(12)}$-capnellene



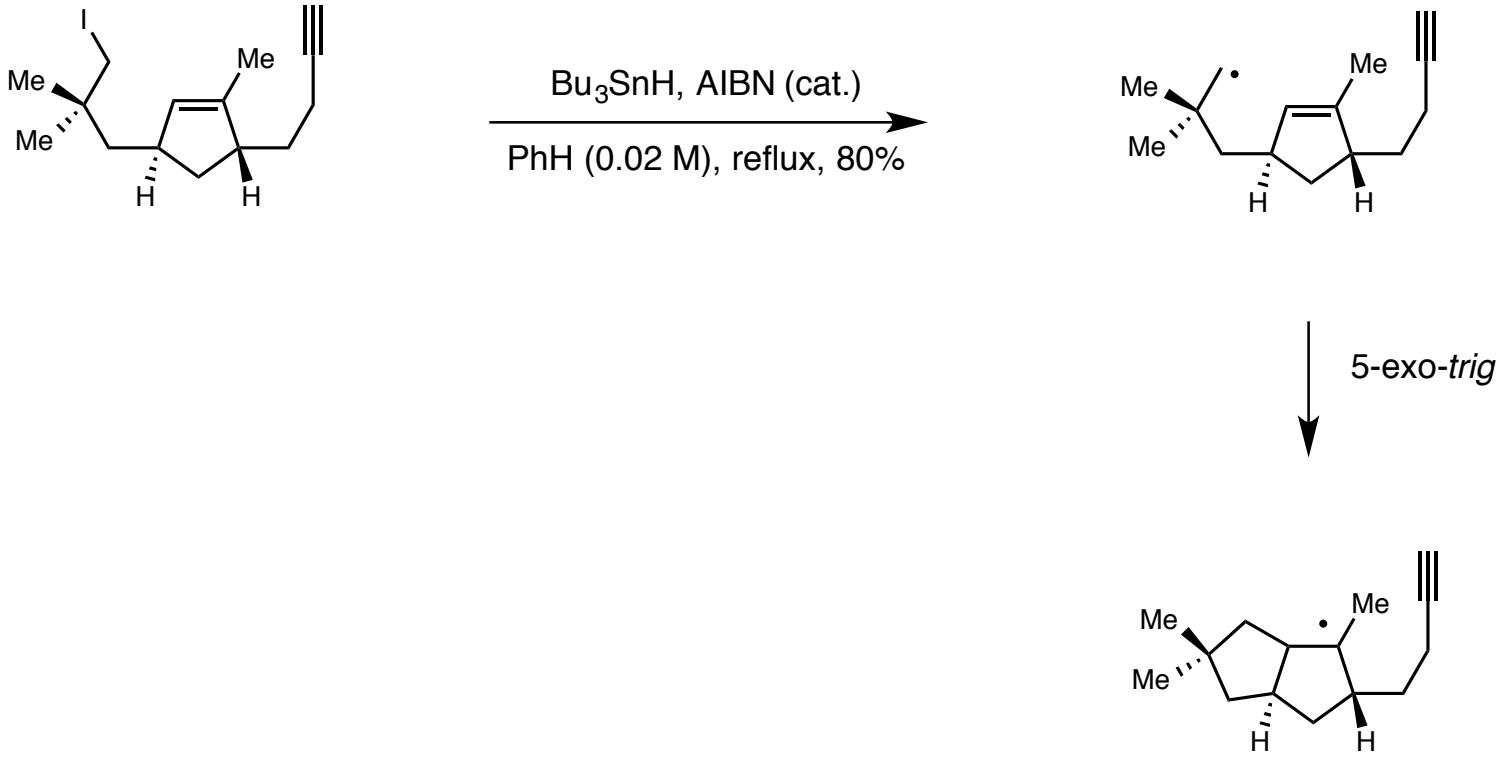




Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

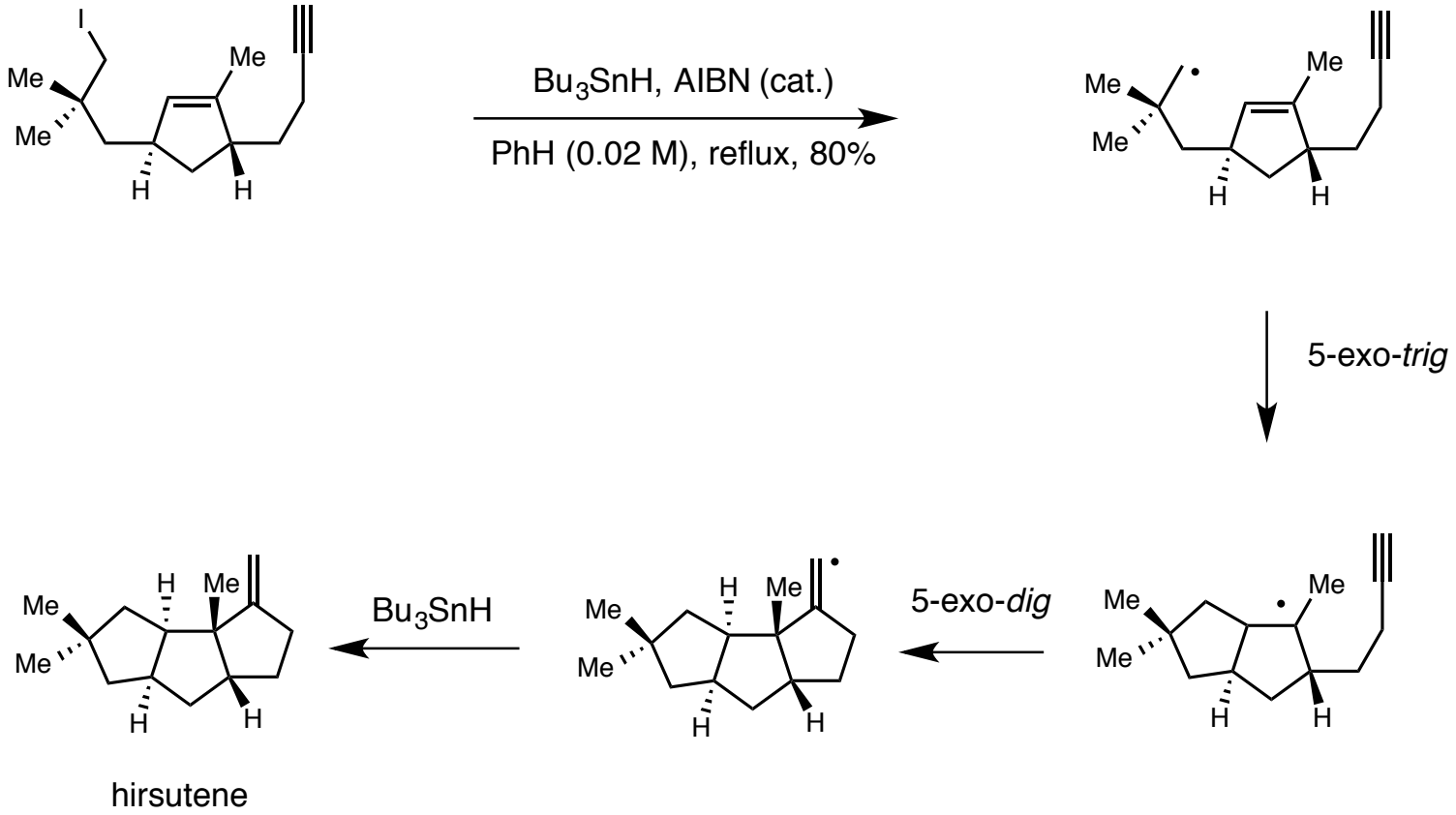
Curran, D.P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.

Radical Cyclizations in Total Synthesis



Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

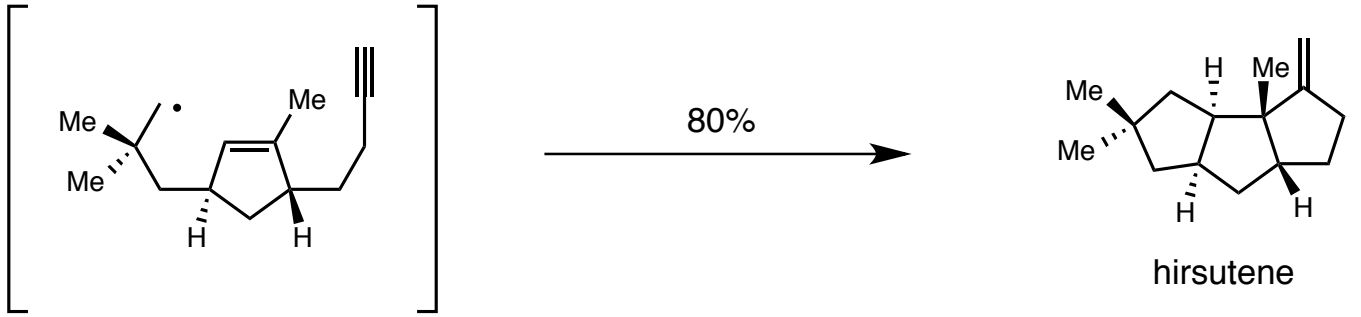
Radical Cyclizations in Total Synthesis



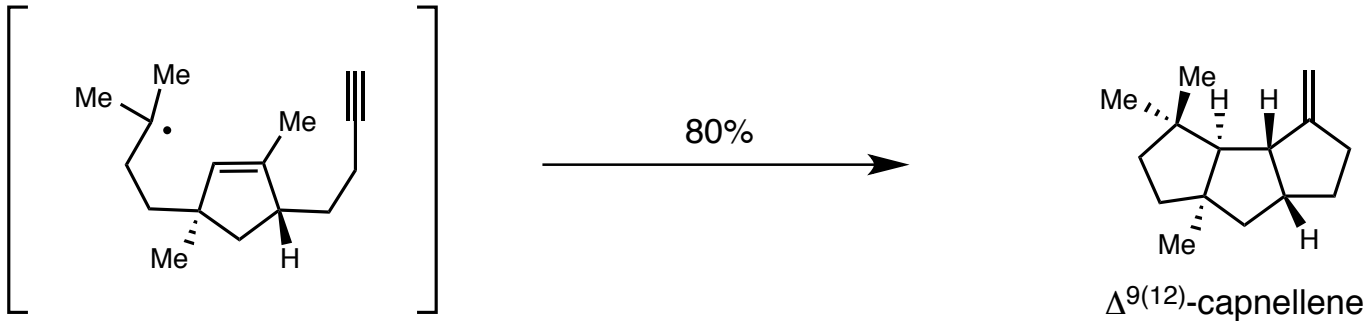
hirsutene

Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

- 1°, 2°, and 3° alkyl radicals have similar reactivities



hirsutene

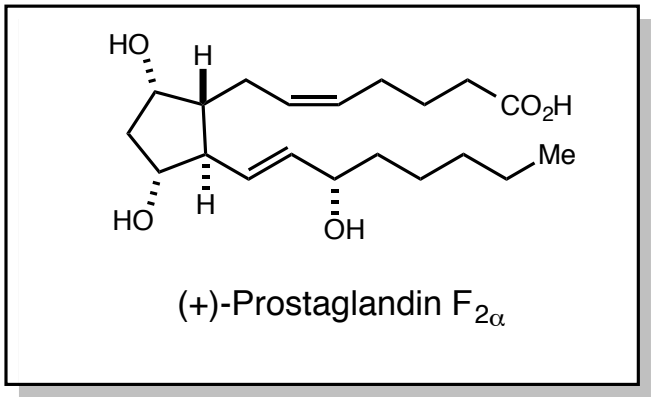


$\Delta^{9(12)}$-capnellene

Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

Curran, D.P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.

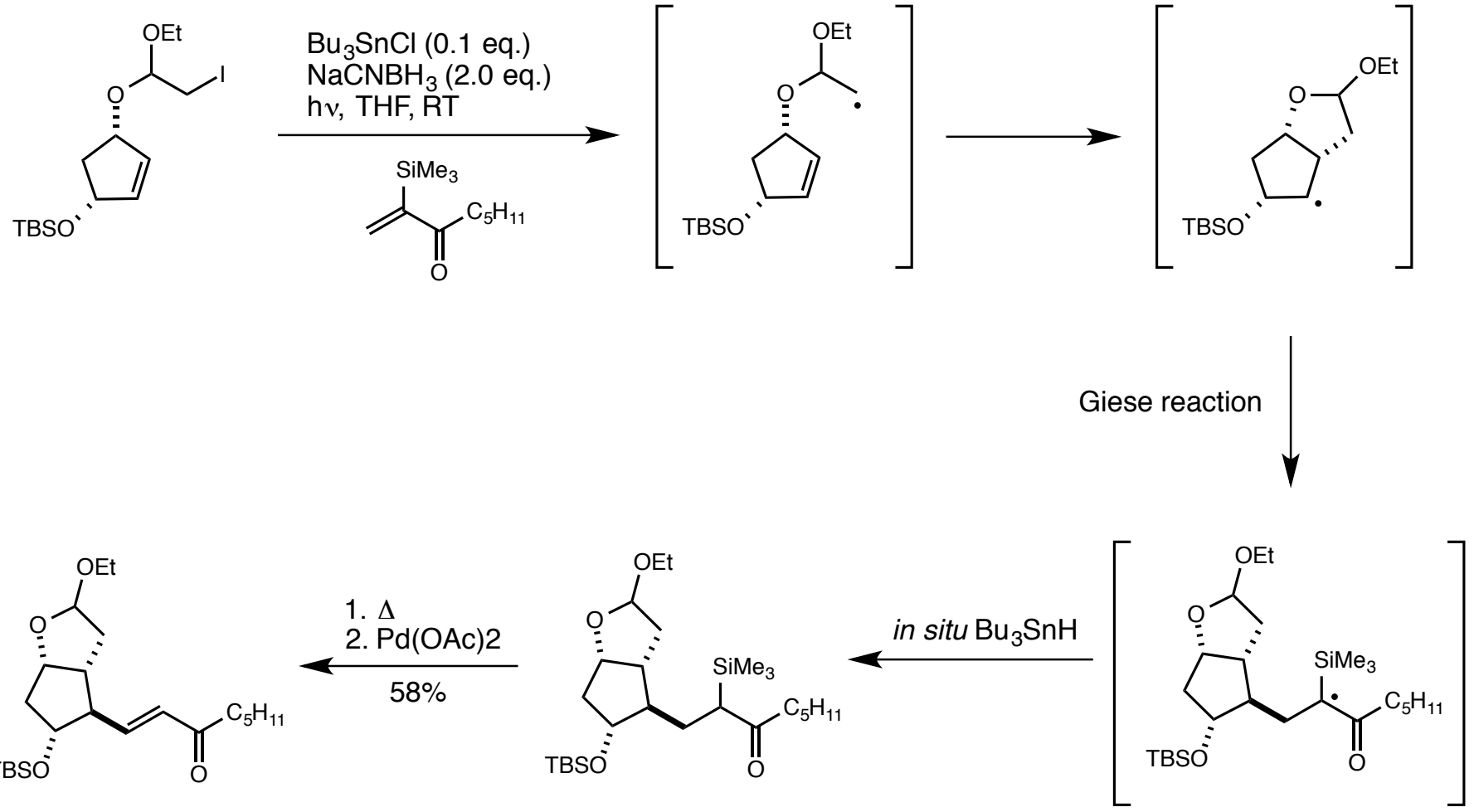
- A common natural product for radical cyclization strategies



(+)-Prostaglandin $F_{2\alpha}$

Radical Cyclizations in Total Synthesis

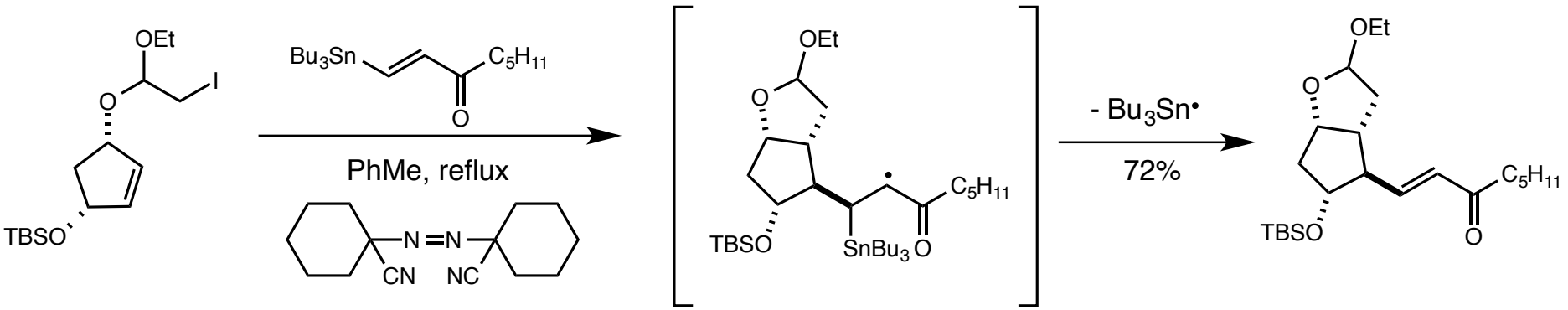
■ Stork's tandem vicinal difunctionalization strategy



Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384-6387.

Radical Cyclizations in Total Synthesis

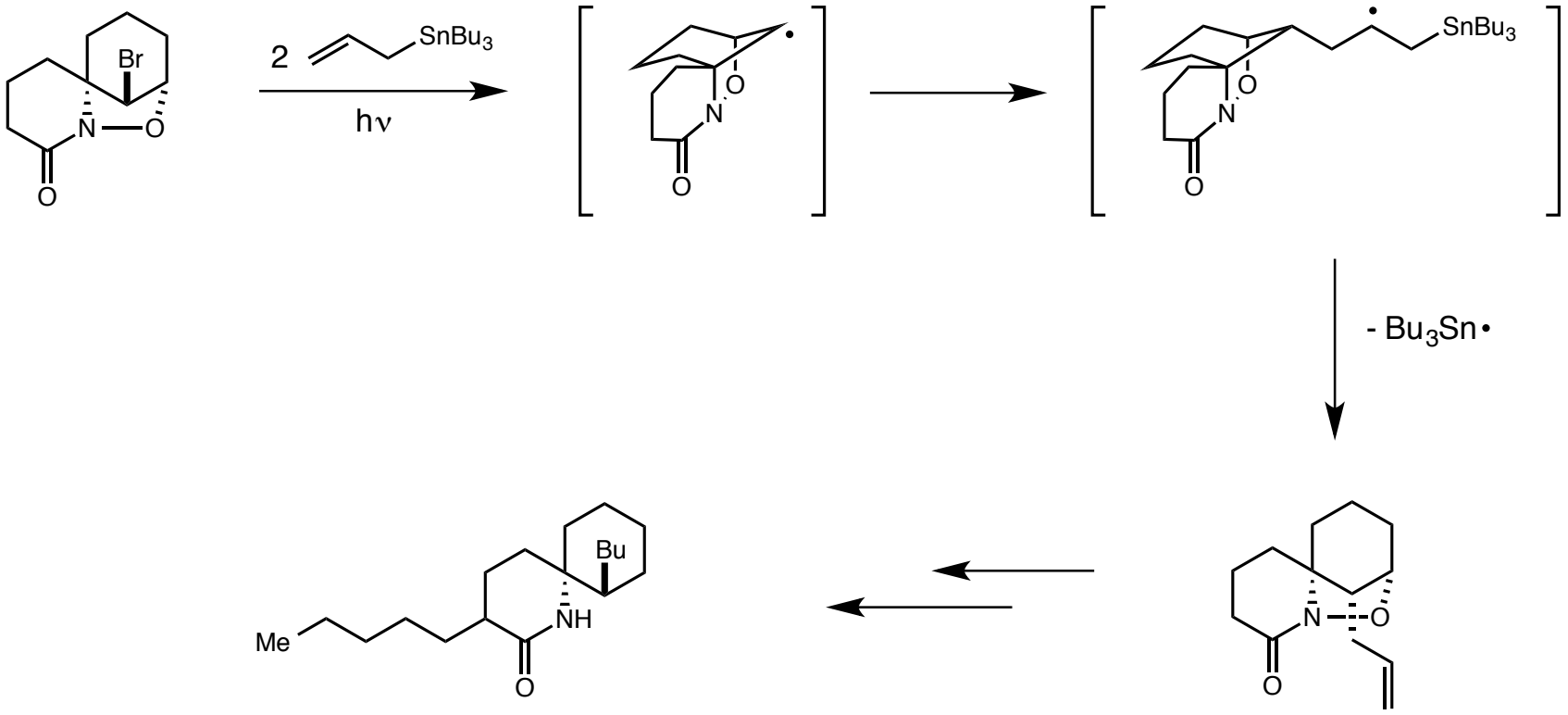
■ Keck's attempt at $PGF_{2\alpha}$



Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

The fragmentation method

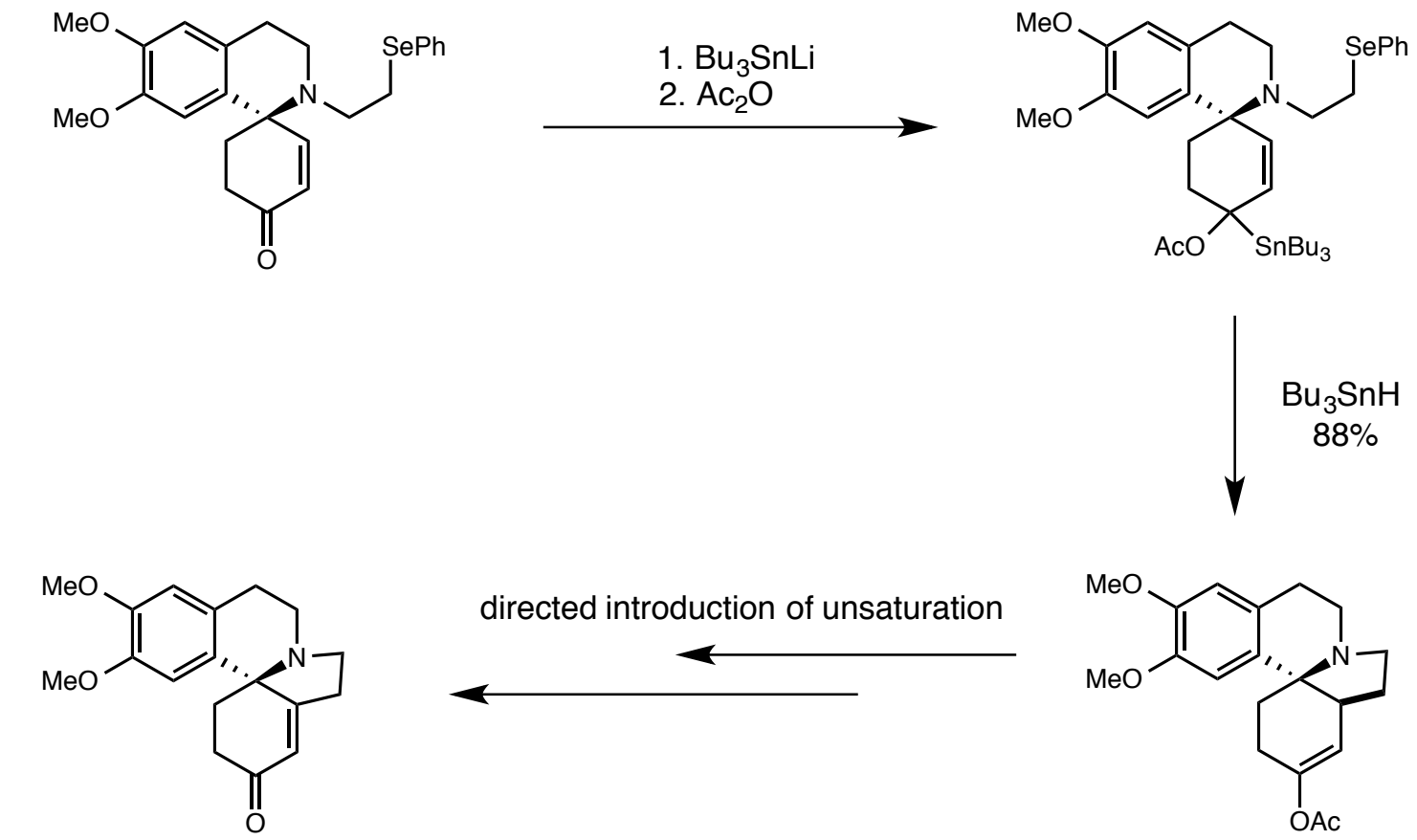
- Keck applies allylation to perhydrohistrionicotoxin synthesis



perhydrohistrionicotoxin

Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590.

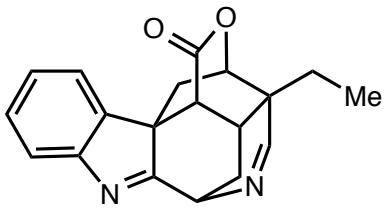
■ Intramolecular Keck allylation



3-demethoxyerythratidinone

Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917.

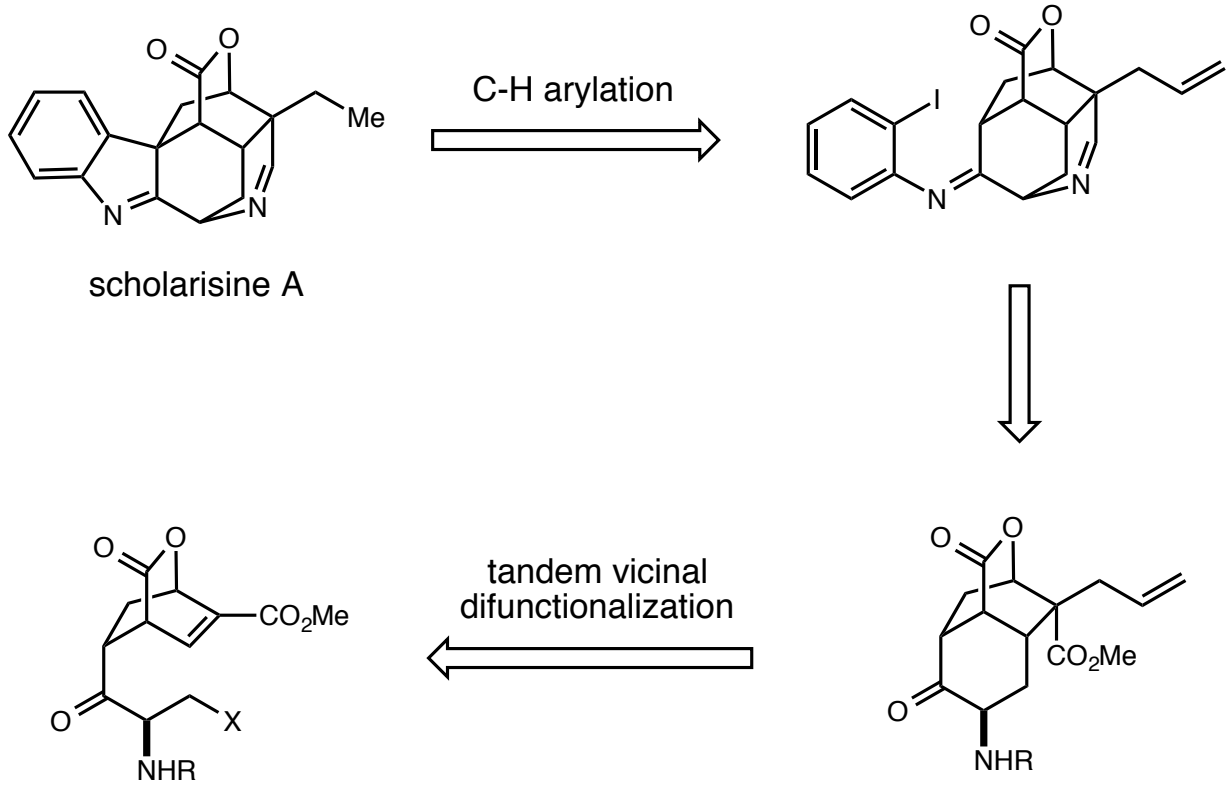
- Keck allylation for use in scholarisine A



scholarisine A

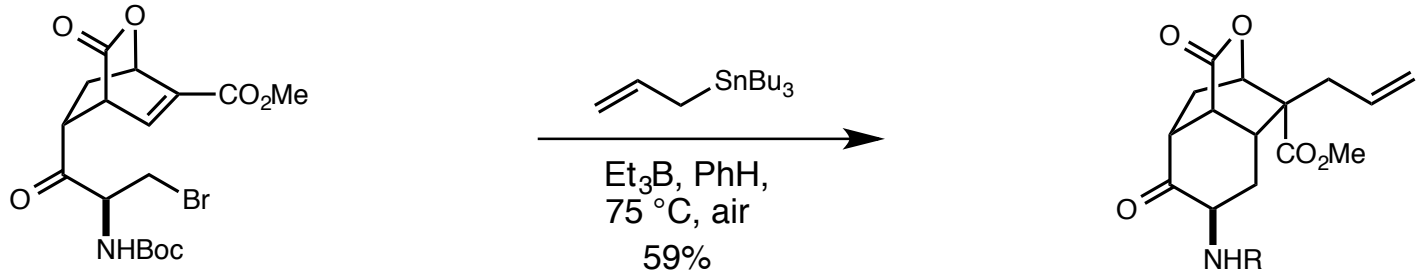
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

■ Keck allylation for use in scholarisine A



Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

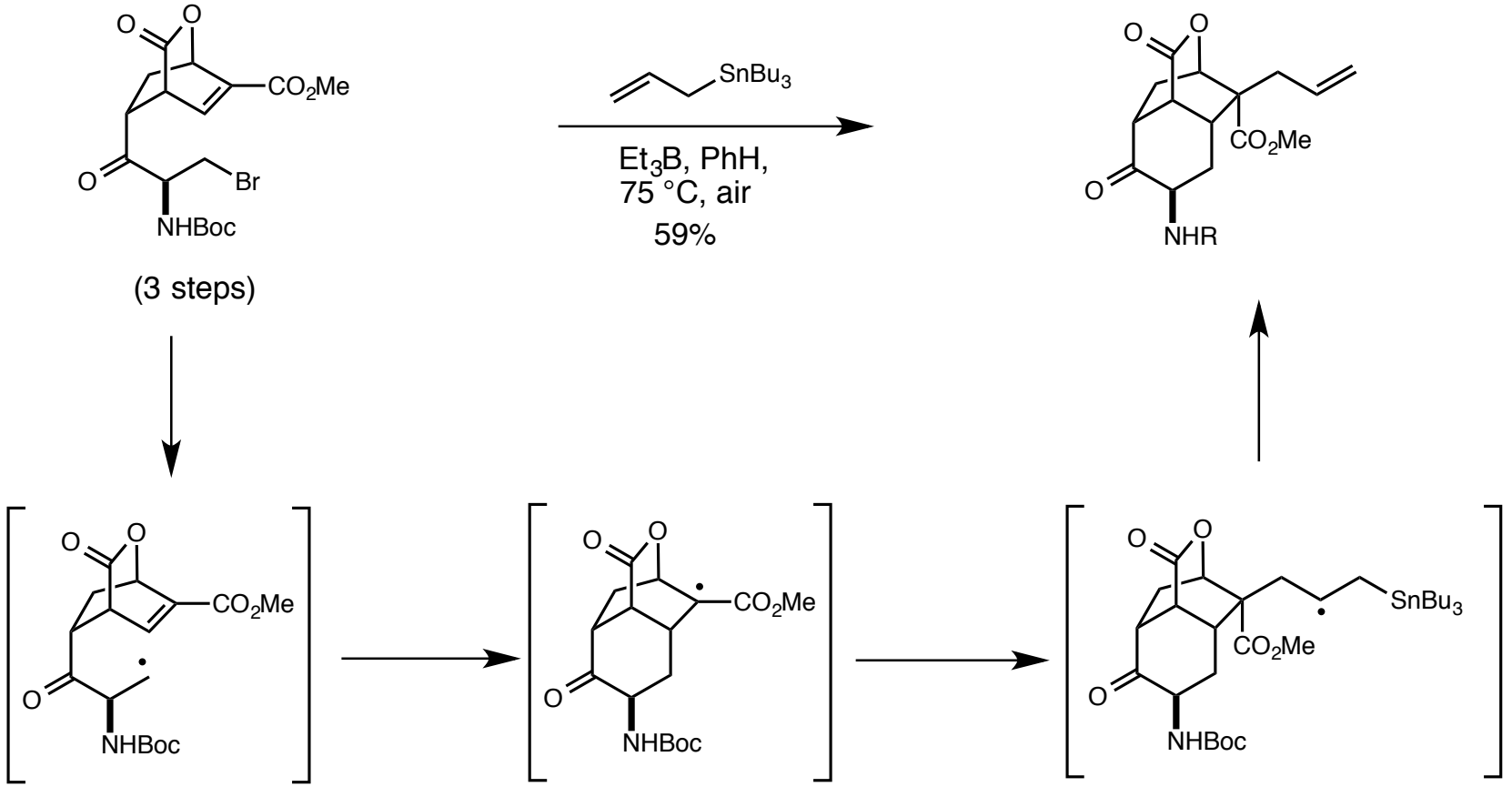
Keck allylation for use in scholarisine A



Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

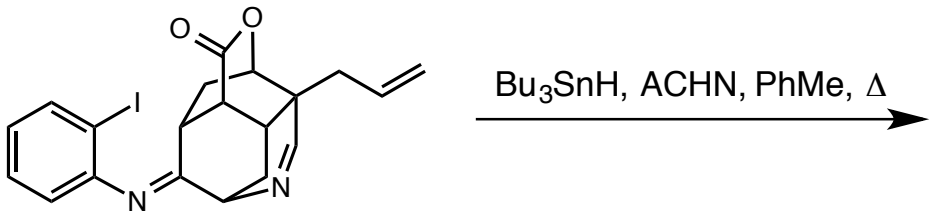
Radical Cyclizations in Total Synthesis

■ Keck allylation for use in scholarisine A



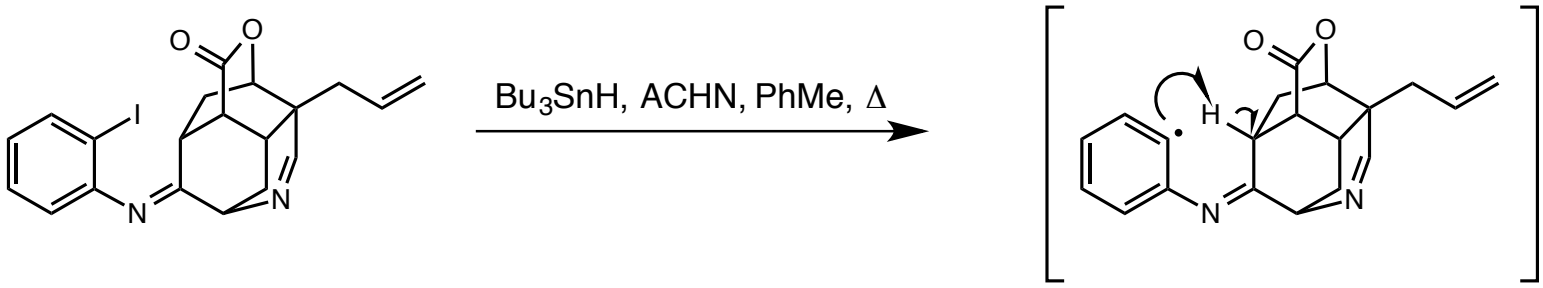
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

- Keck allylation for use in scholarisine A



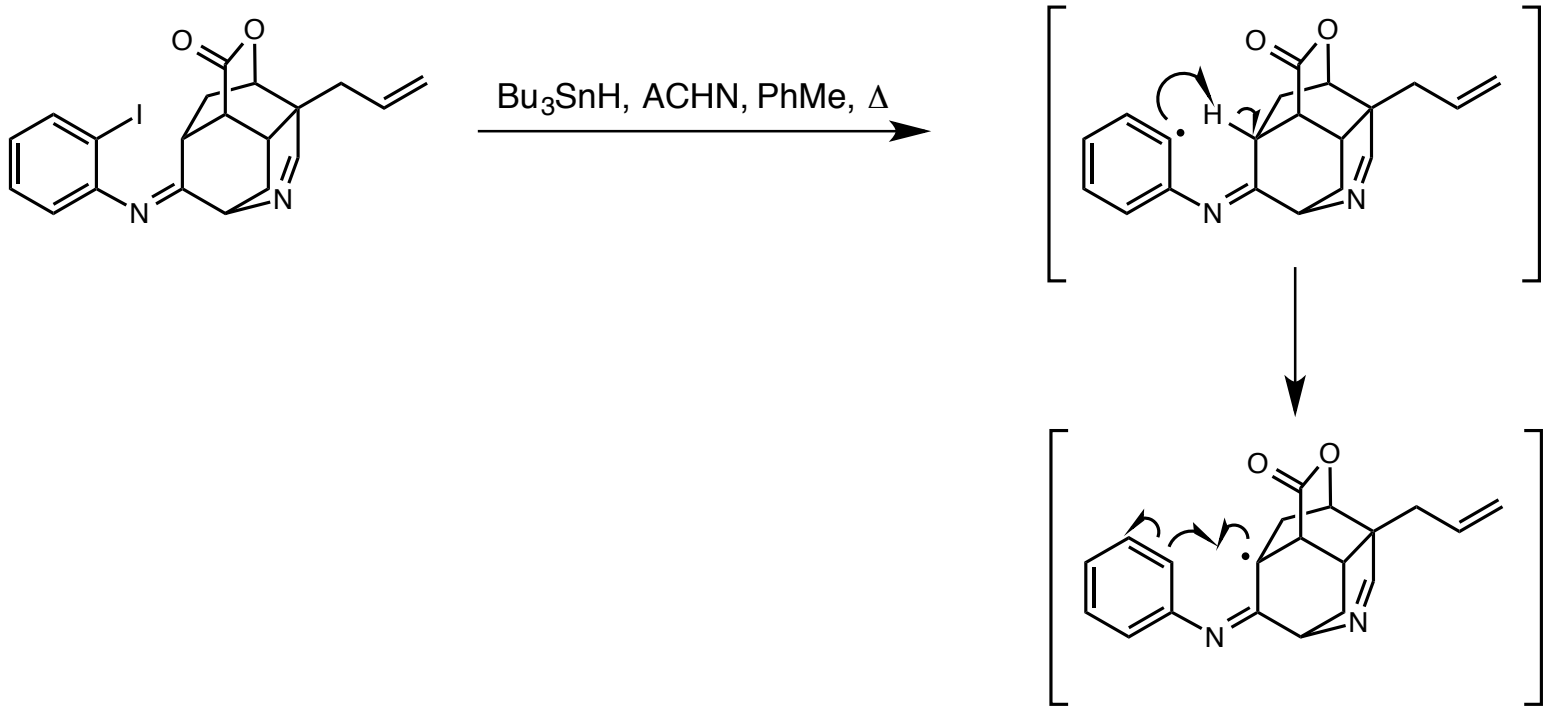
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

■ Keck allylation for use in scholarisine A



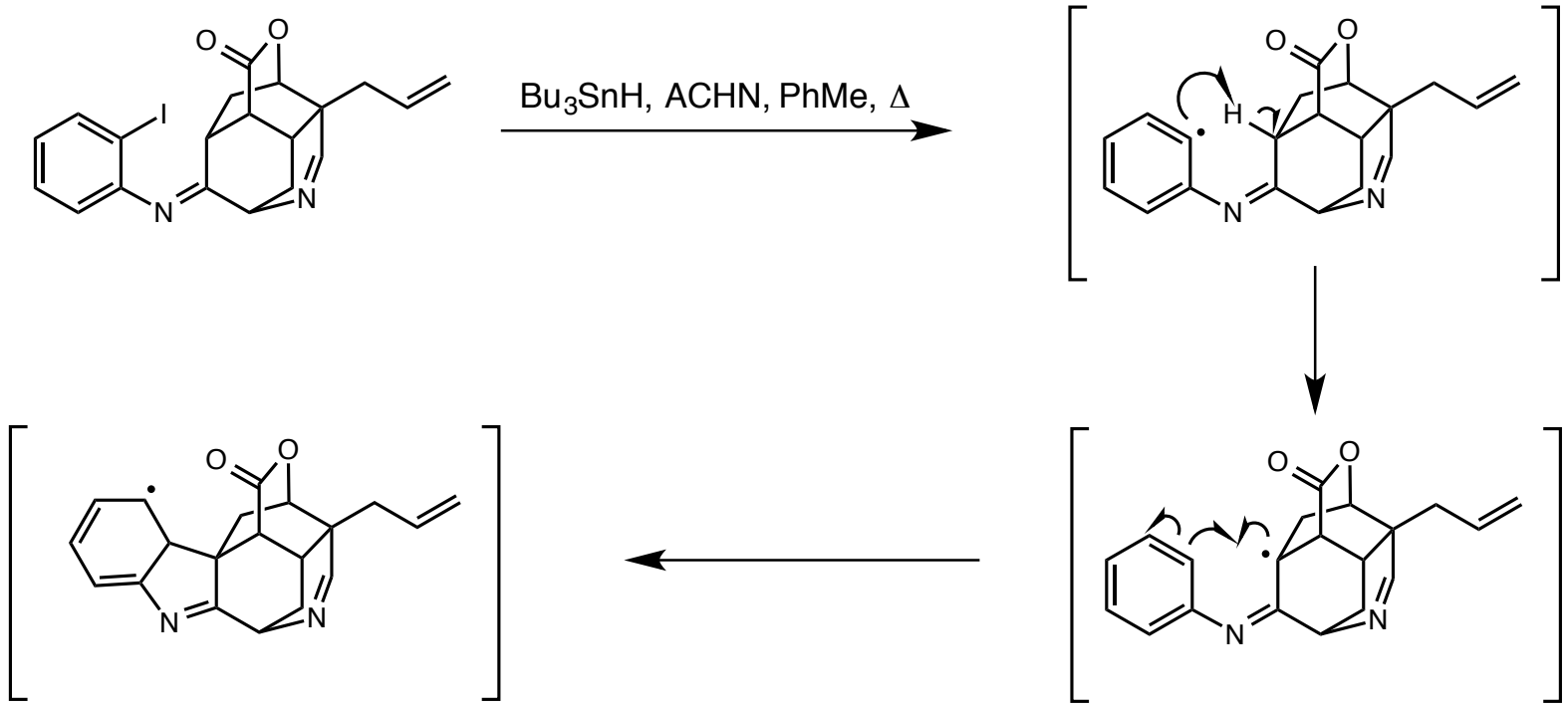
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

■ Keck allylation for use in scholarisine A



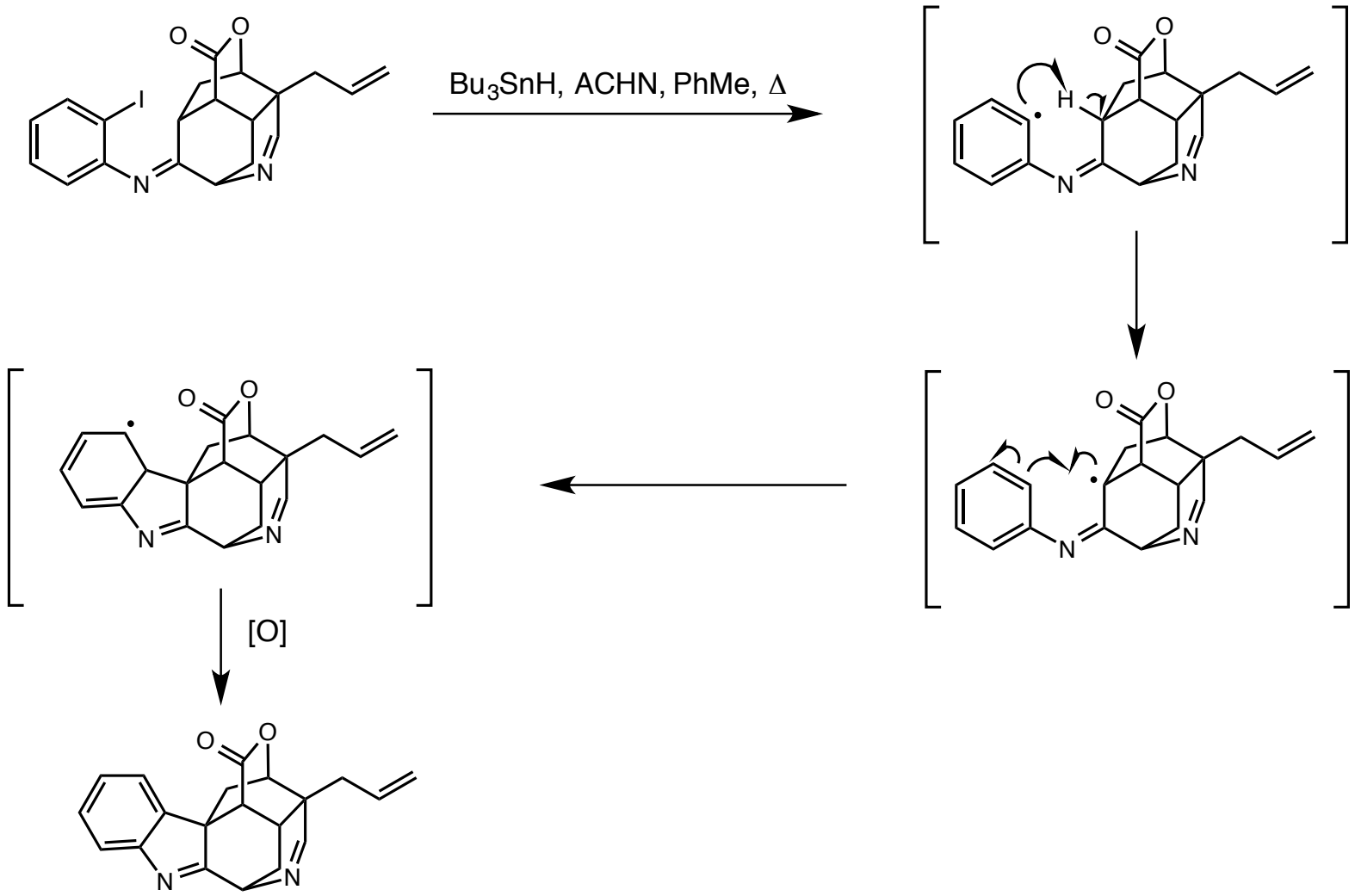
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

■ Keck allylation for use in scholarisine A



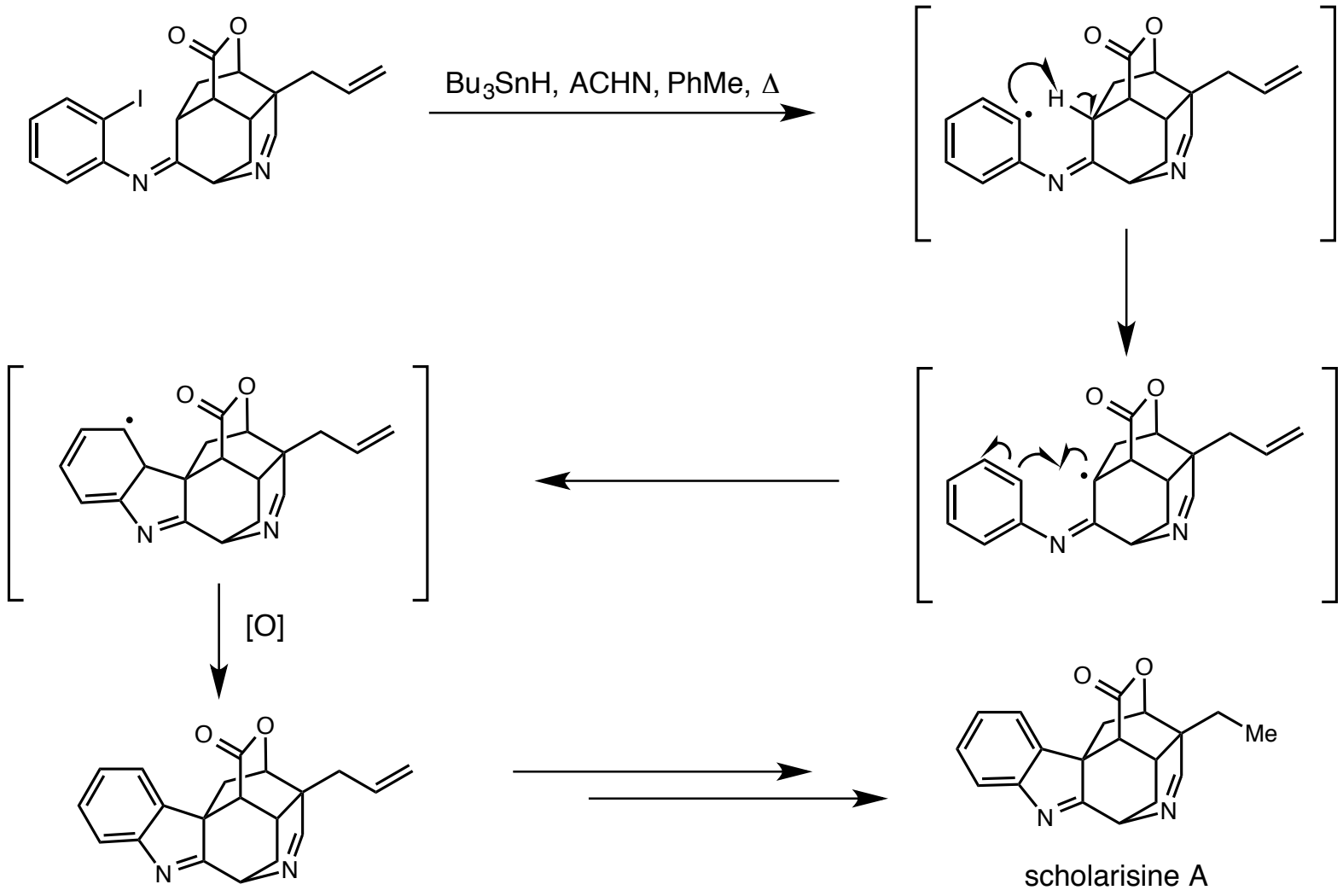
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

■ Keck allylation for use in scholarisine A



Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

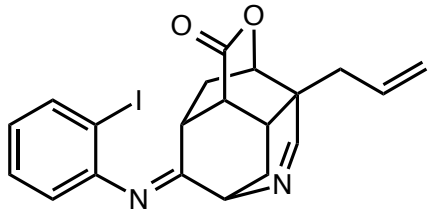
■ Keck allylation for use in scholarisine A



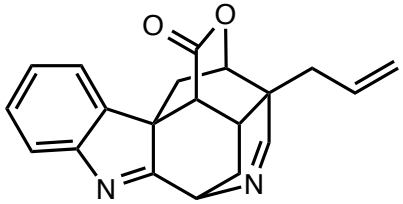
Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

Radical Cyclizations in Total Synthesis

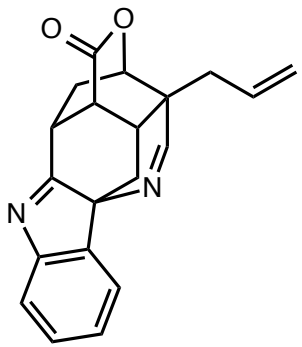
- Aryl radicals utilized as hydrogen atom abstractors



Bu_3SnH, ACHN, PhMe, Δ



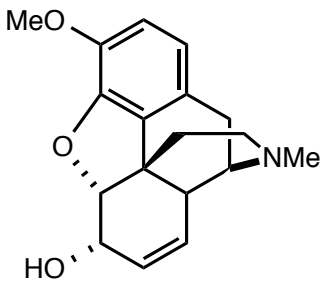
18%



6%

Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964-12967.

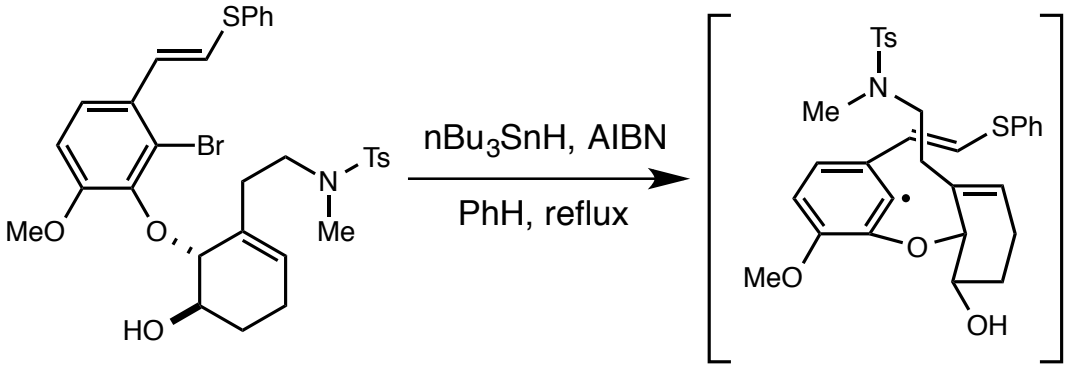
- Parker and Fokas: (-)-morphine via radical cyclization and fragmentation

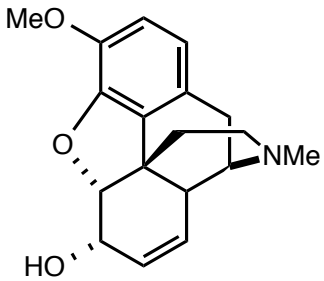


(-)-morphine

Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.

- Parker and Fokas: (-)-morphine via radical cyclization and fragmentation



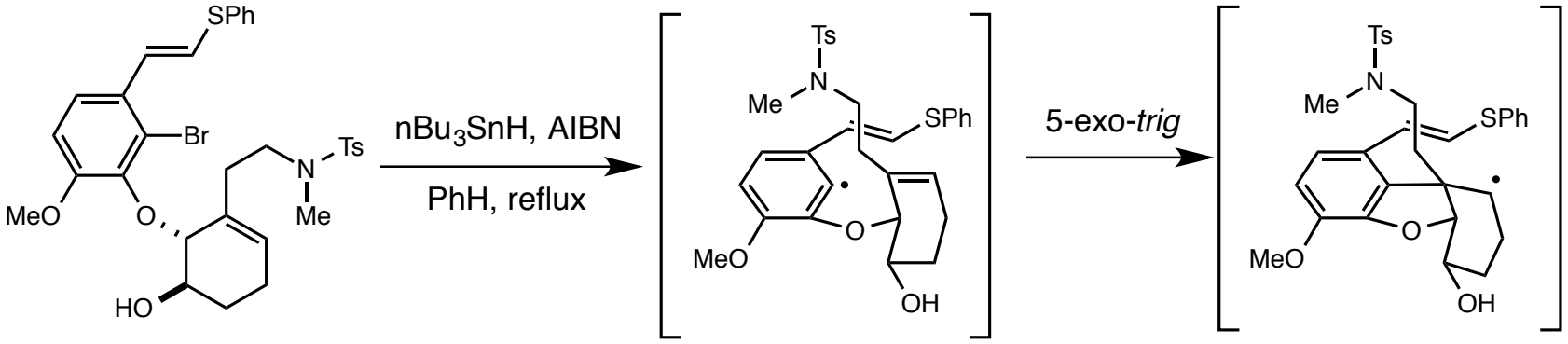


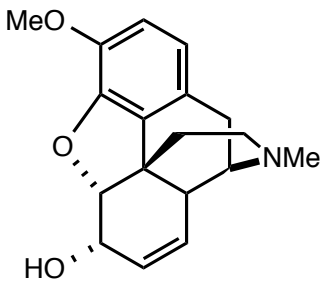
(-)-morphine

Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.

Radical Cyclizations in Total Synthesis

■ Parker and Fokas: (-)-morphine via radical cyclization and fragmentation



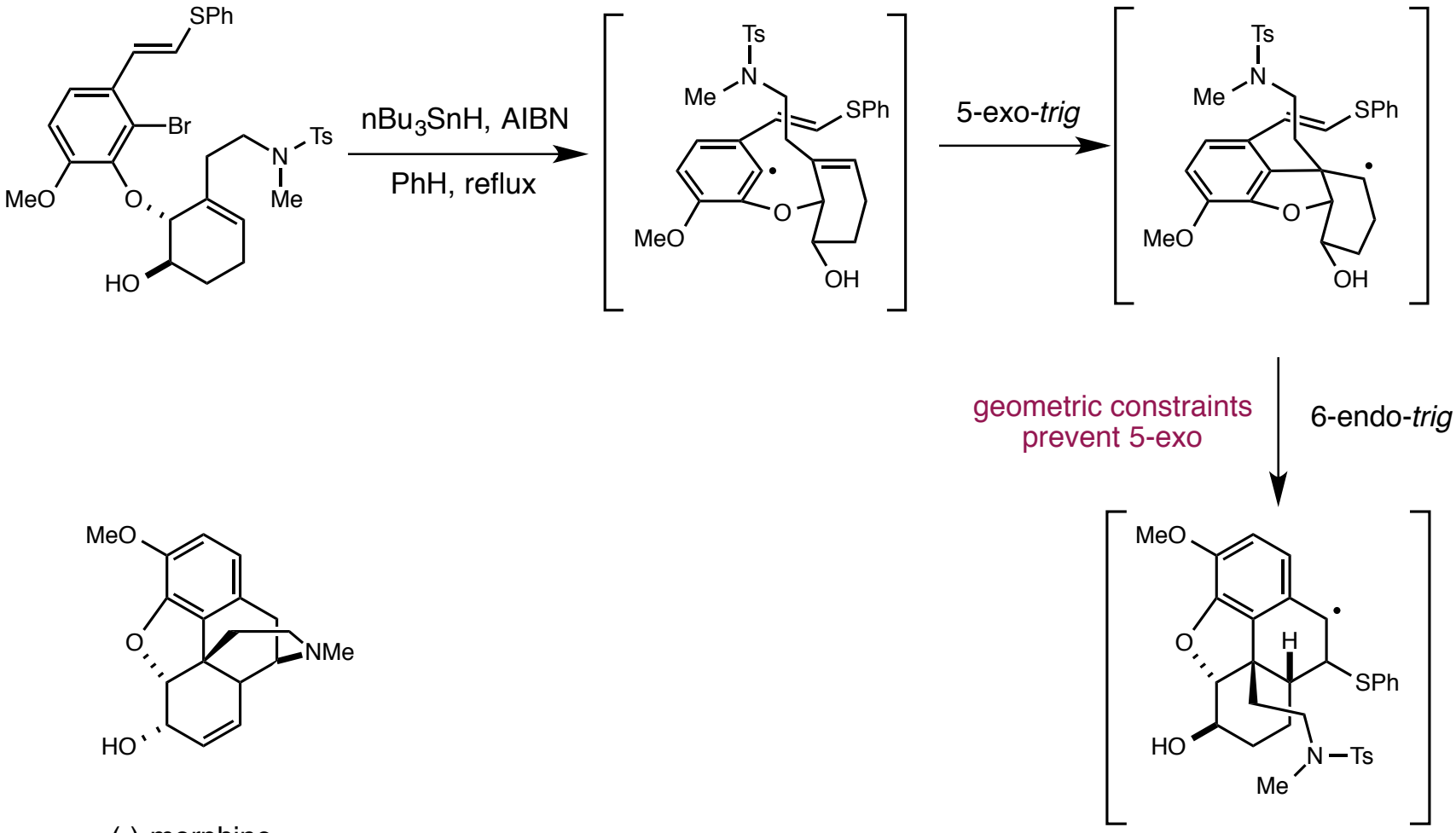


(-)-morphine

Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.

Radical Cyclizations in Total Synthesis

■ Parker and Fokas: (-)-morphine via radical cyclization and fragmentation

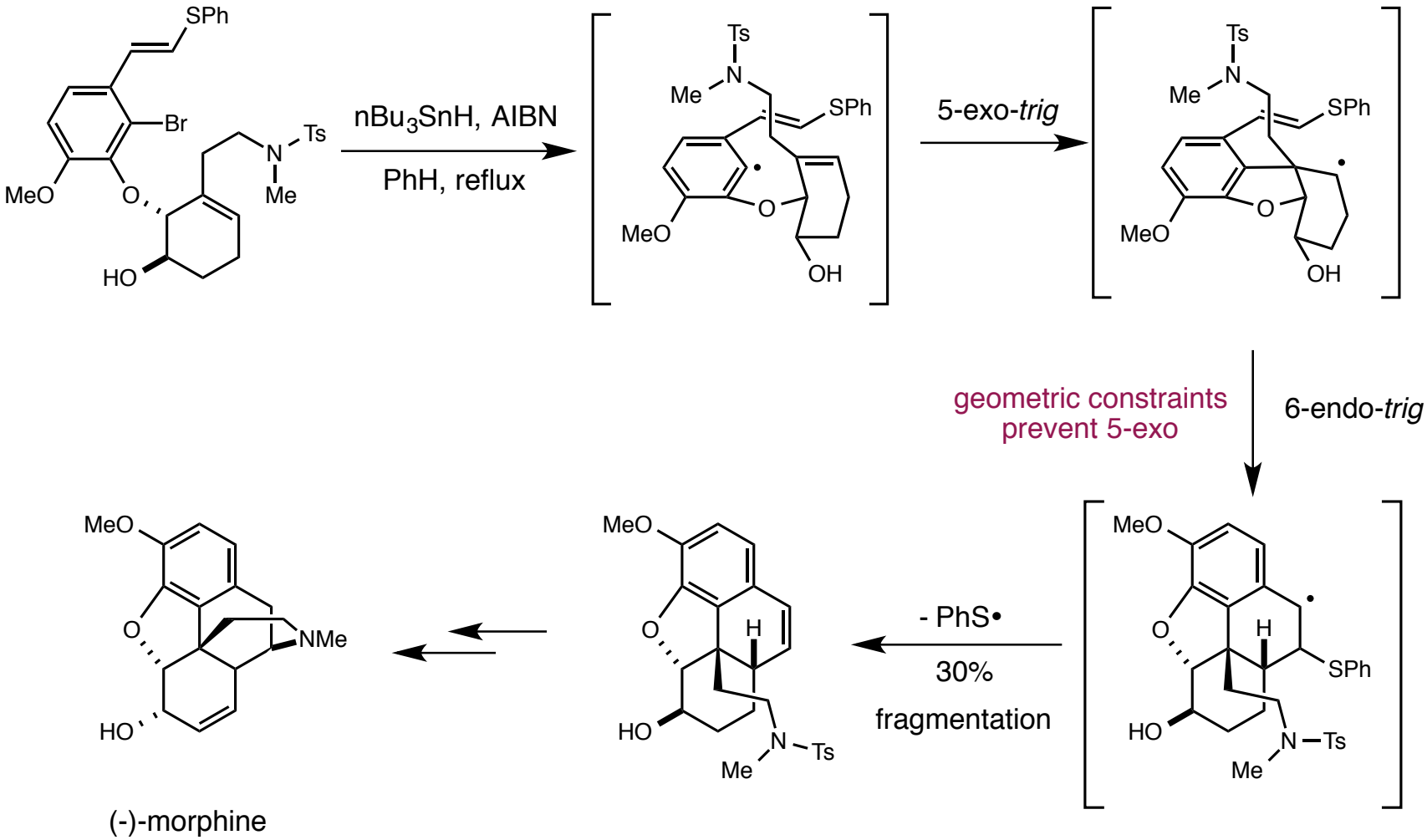


(-)-morphine

Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.

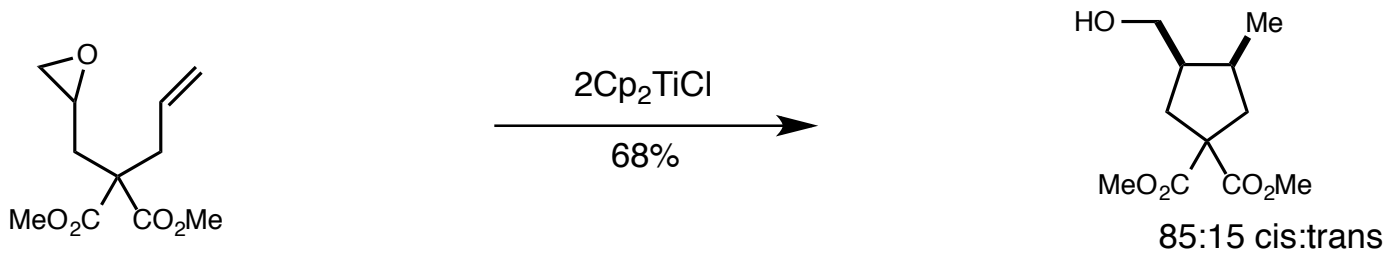
Radical Cyclizations in Total Synthesis

■ Parker and Fokas: (-)-morphine via radical cyclization and fragmentation



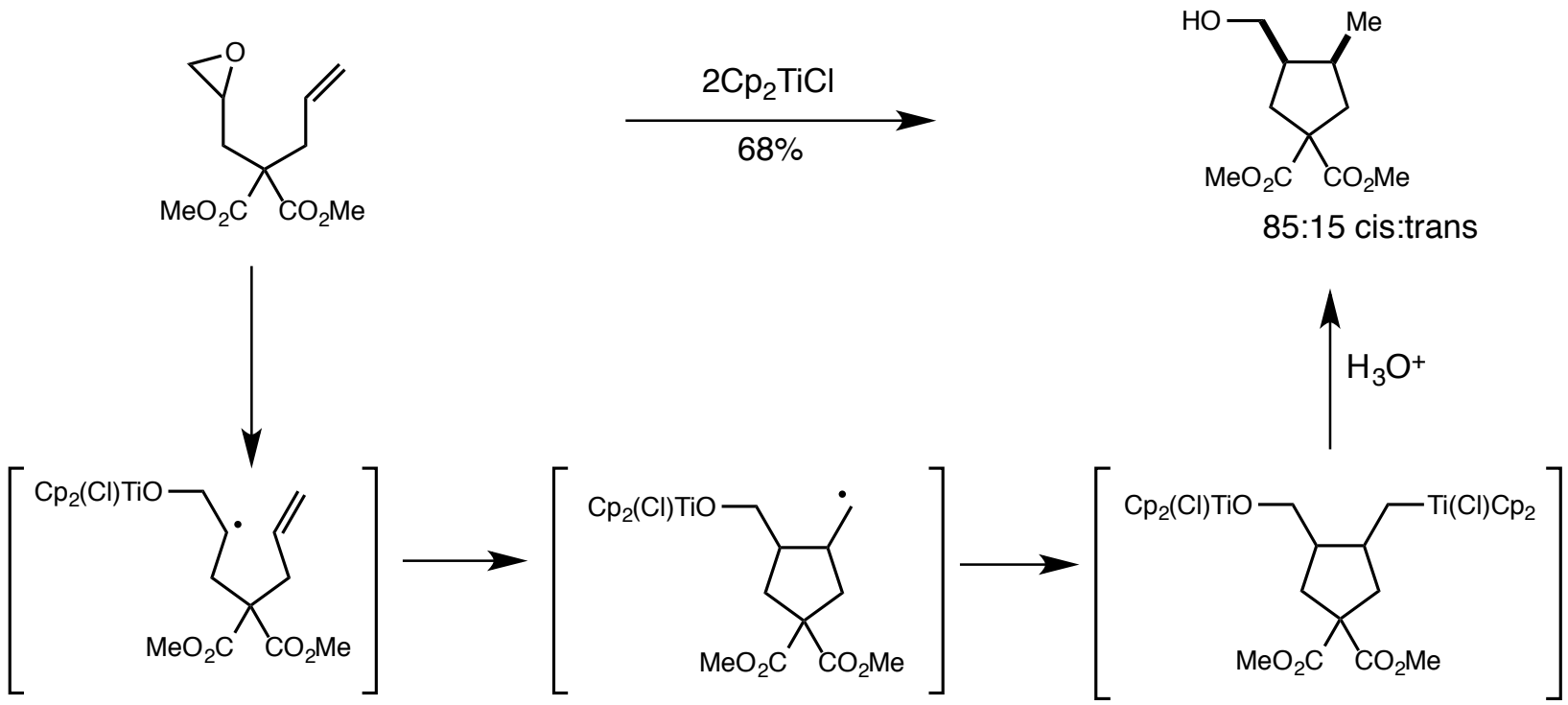
Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689.

■ Titanium(III)-induced cyclization of epoxyolefins



Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561-8562.

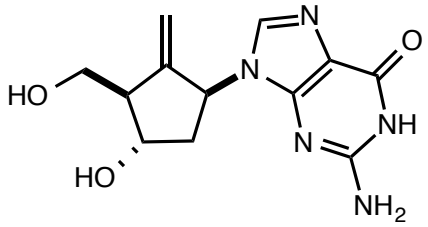
■ Titanium(III)-induced cyclization of epoxyolefins



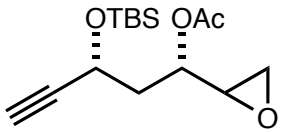
Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561-8562.

Radical Cyclizations in Total Synthesis

■ Epoxides as β-alkoxy radical cyclization precursors

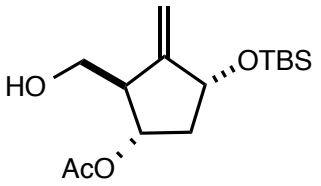


Entecavir
Antiviral agent against Hepatitis B
BMS patent to expire in 2015 in U.S.



20 mol% Cp_2TiCl_2, 10 mol% $IrCl(CO)(PPh_3)_2$

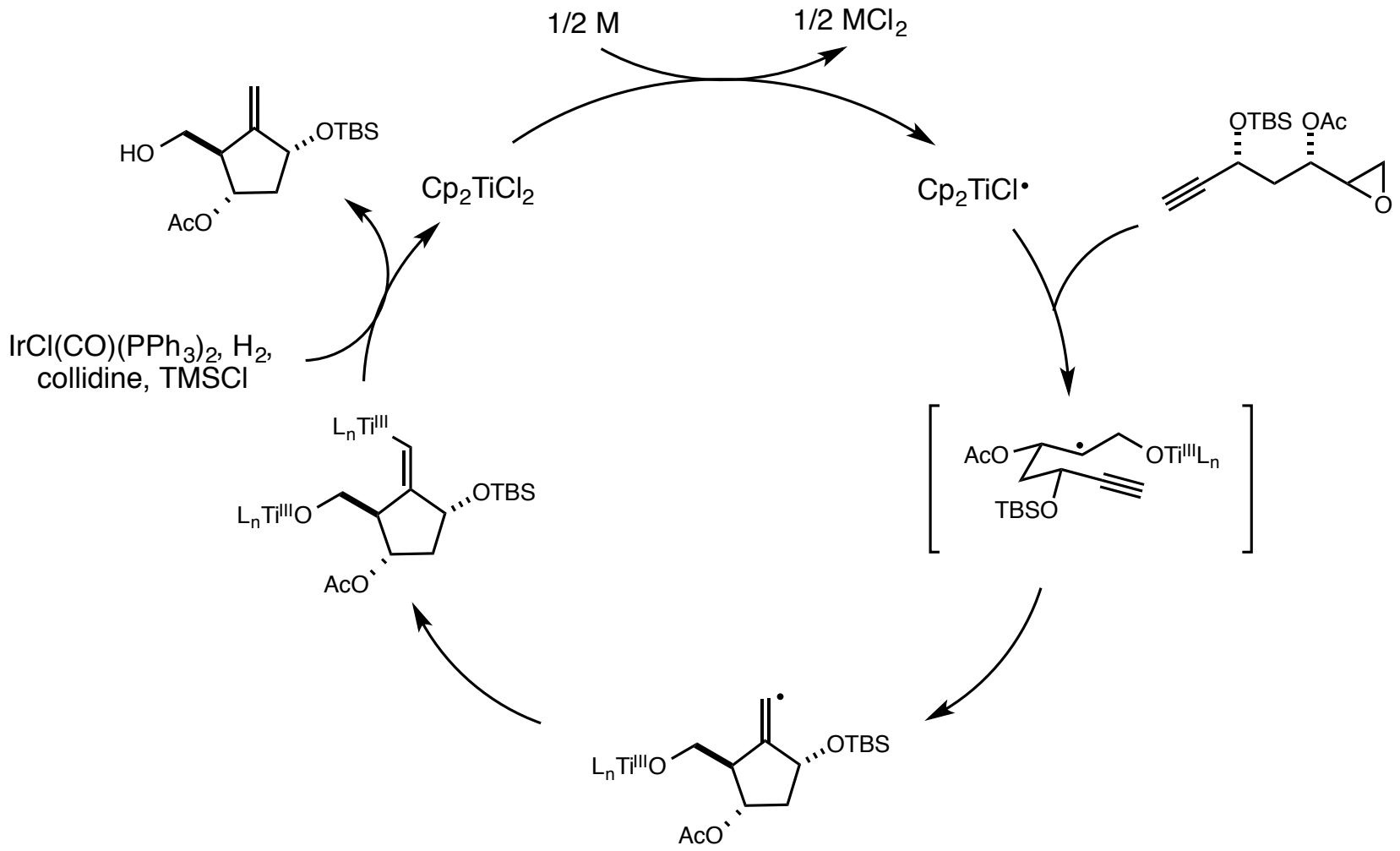
Mn (2 eq.), collidine, TMSCl, H_2 (4 bar), THF, 4 hr. RT
58%



Velasco, J. et. al. *J. Org. Chem.* **2013**, *78*, 5482-5491.

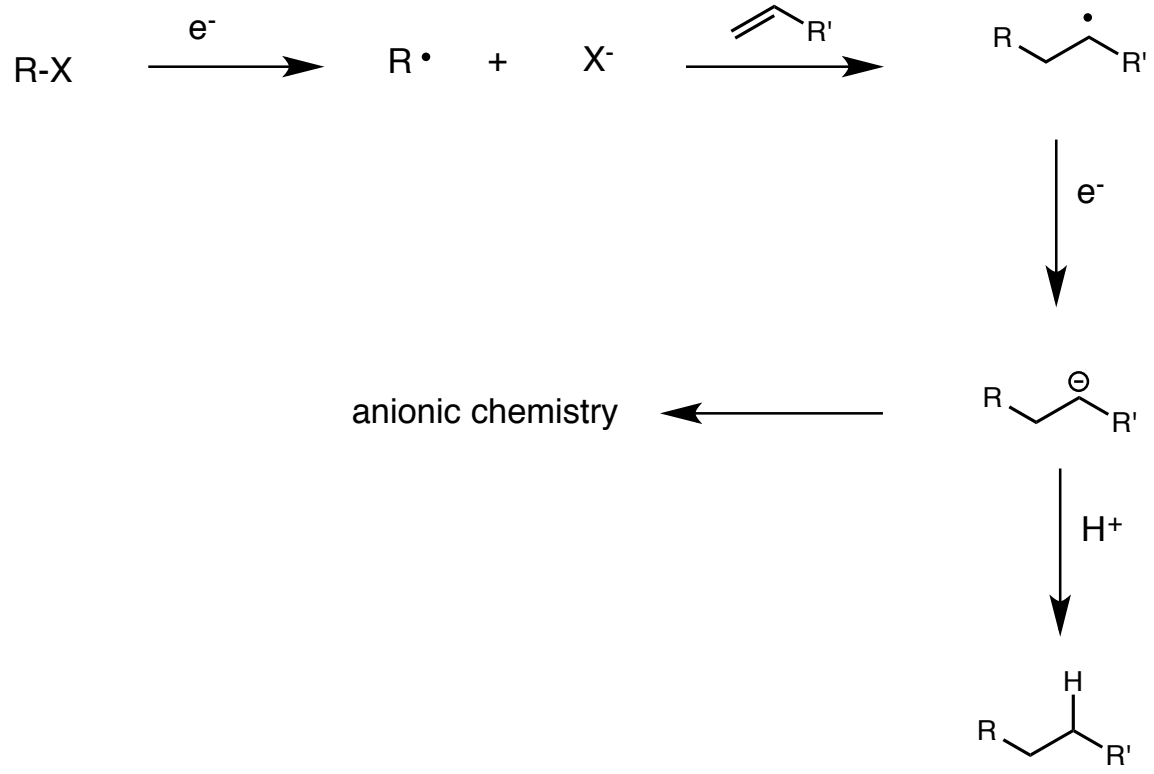
Radical Cyclizations in Total Synthesis

■ Epoxides as β-alkoxy radical cyclization precursors



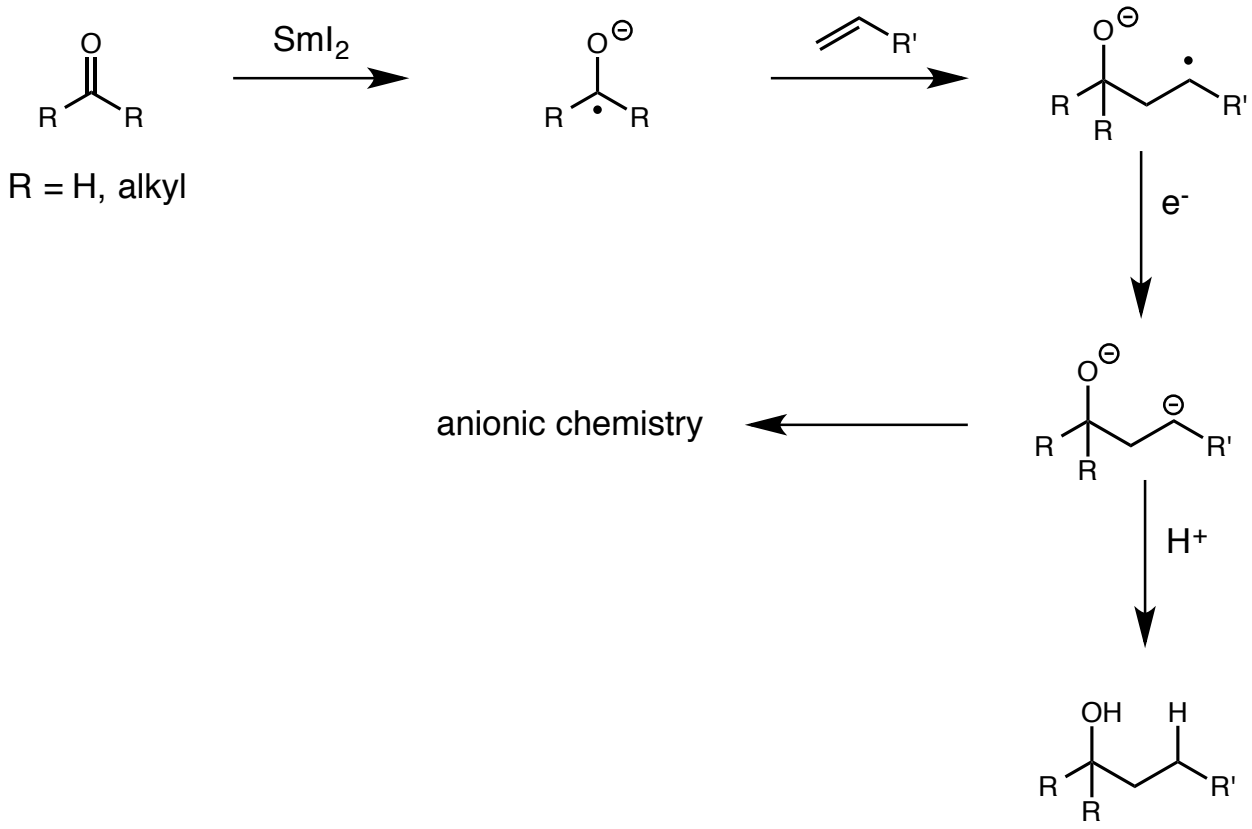
Velasco, J. et. al. *J. Org. Chem.* **2013**, *78*, 5482-5491.

The reductive method



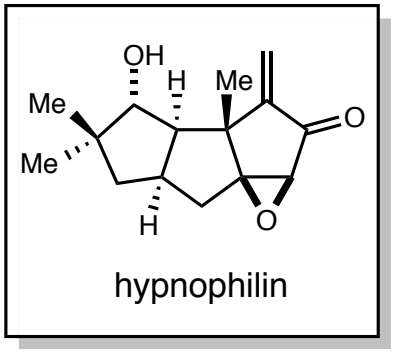
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

- The reductive method more commonly used to generate ketyl radicals



Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

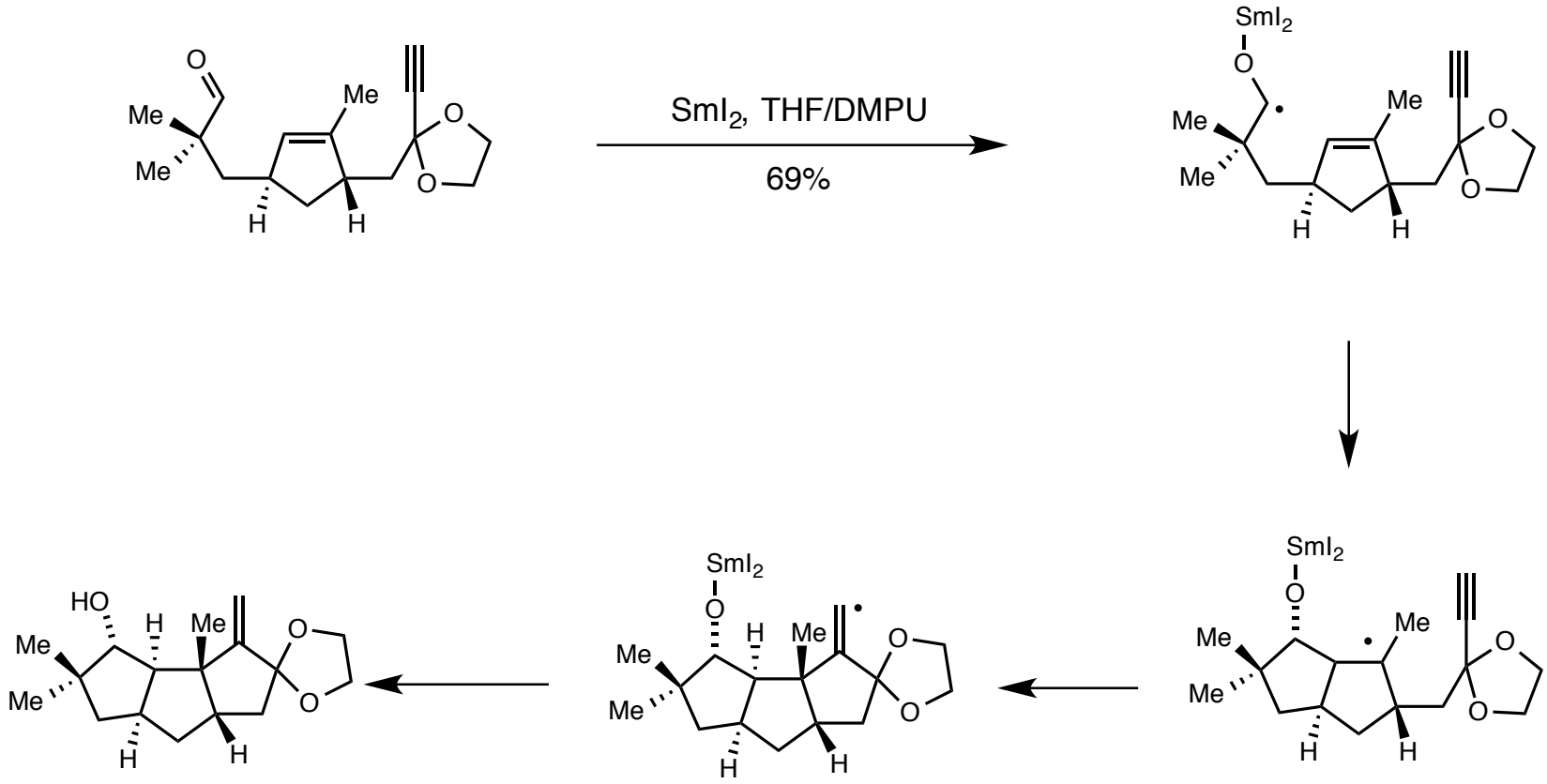
- The triquinane system using SmI_2



hypnophilin

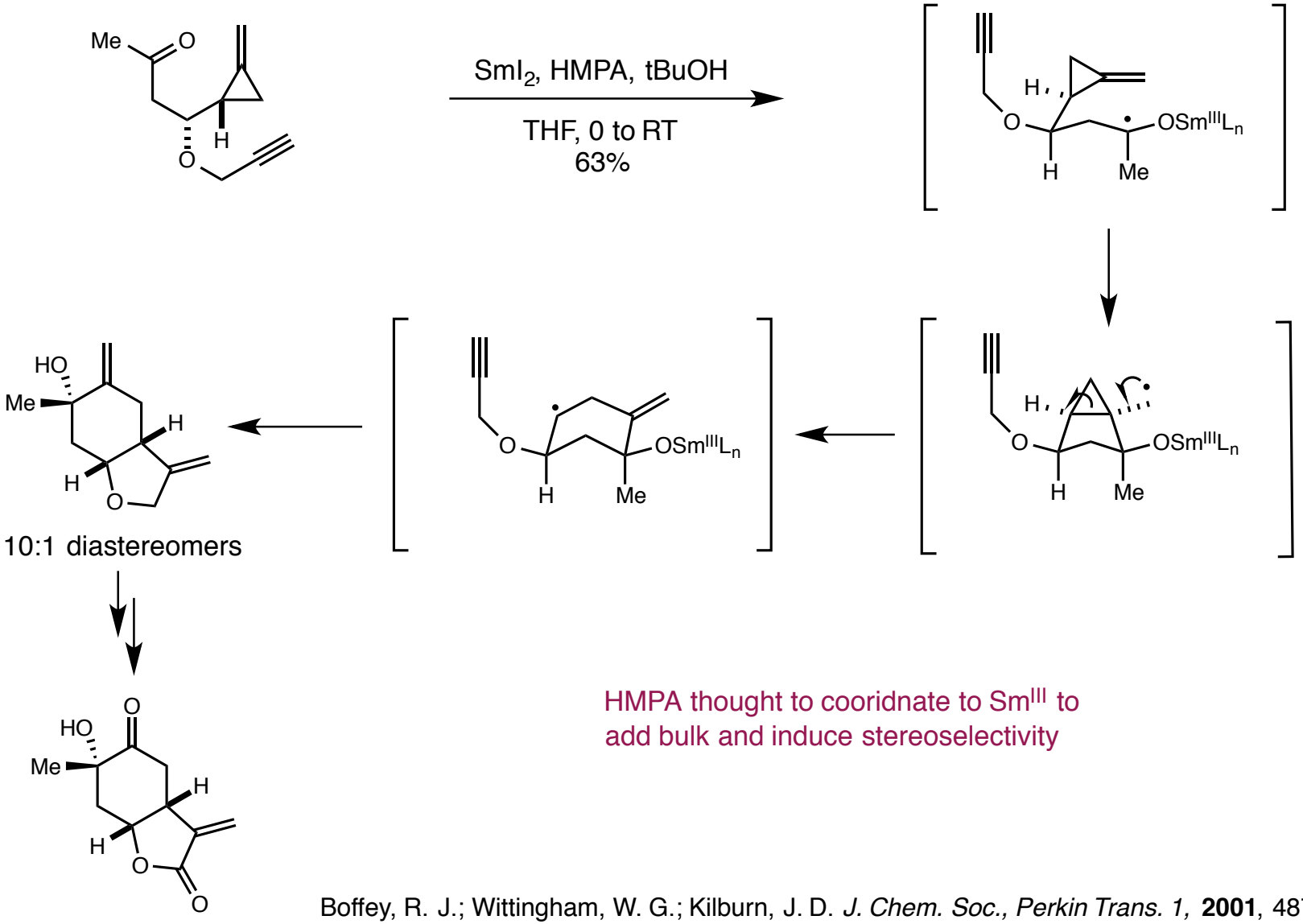
Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064-5067.

■ The triquinane system using SmI_2



Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064-5067.

■ Kilburn's stereoselective synthesis of paeonilactone B via a SmI_2 cyclization

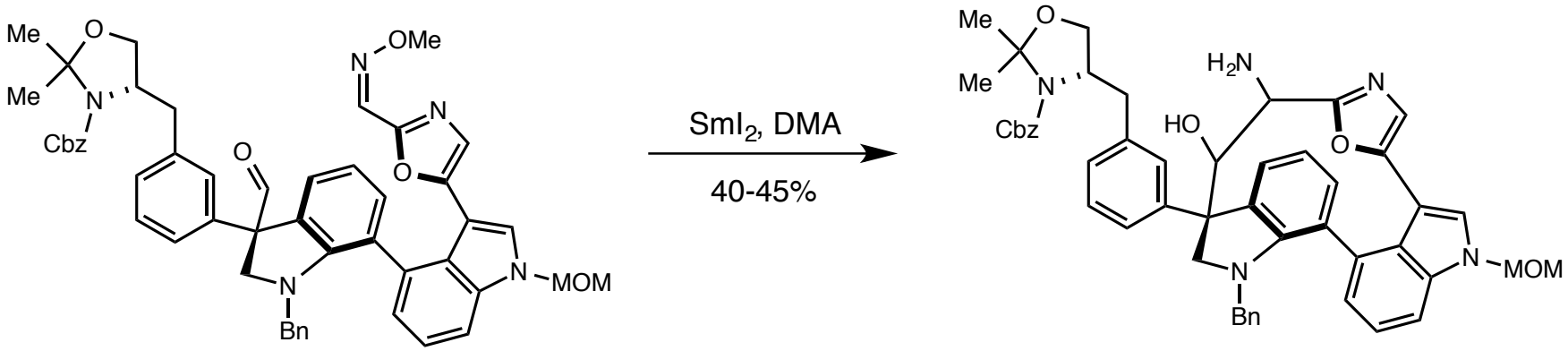


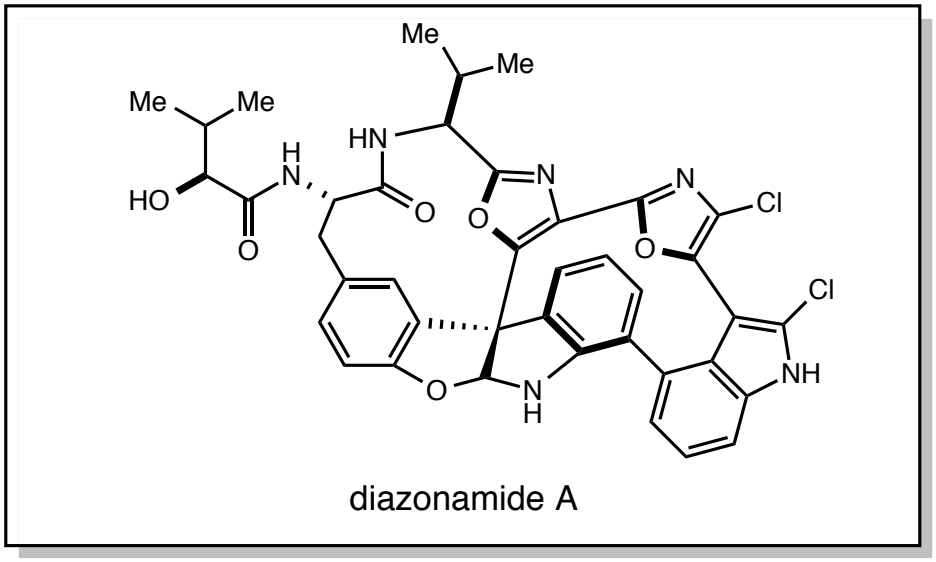
HMPA thought to cooridnate to Sm^{III} to add bulk and induce stereoselectivity

Boffey, R. J.; Wittingham, W. G.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1,* **2001**, 487-496.

Radical Cyclizations in Total Synthesis

■ SmI_2 for macrocyclizations in Diazonamide A



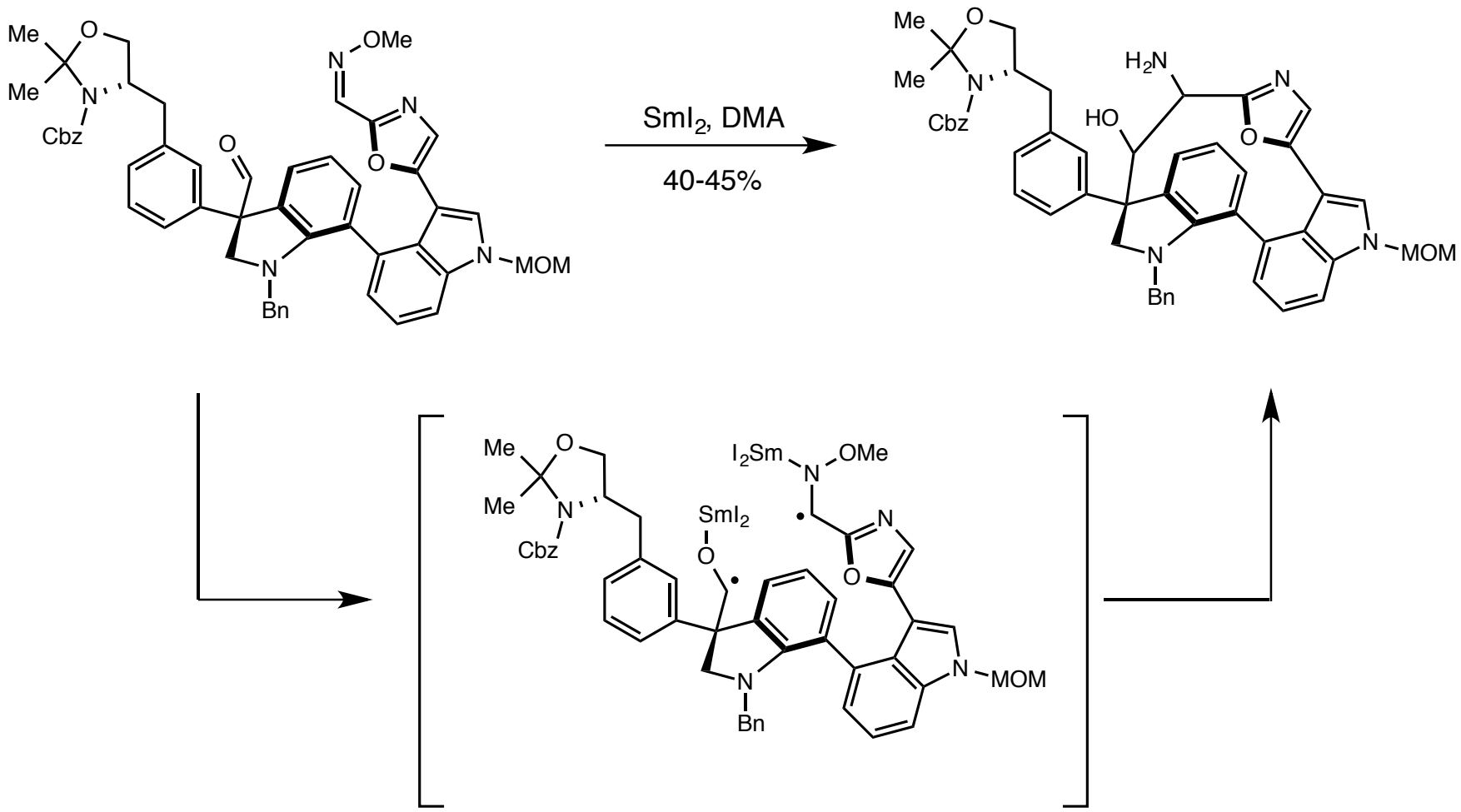


diazonamide A

Nicolaou, K. C. et. al. *ACIEE* **2003**, *42*, 1753.

Radical Cyclizations in Total Synthesis

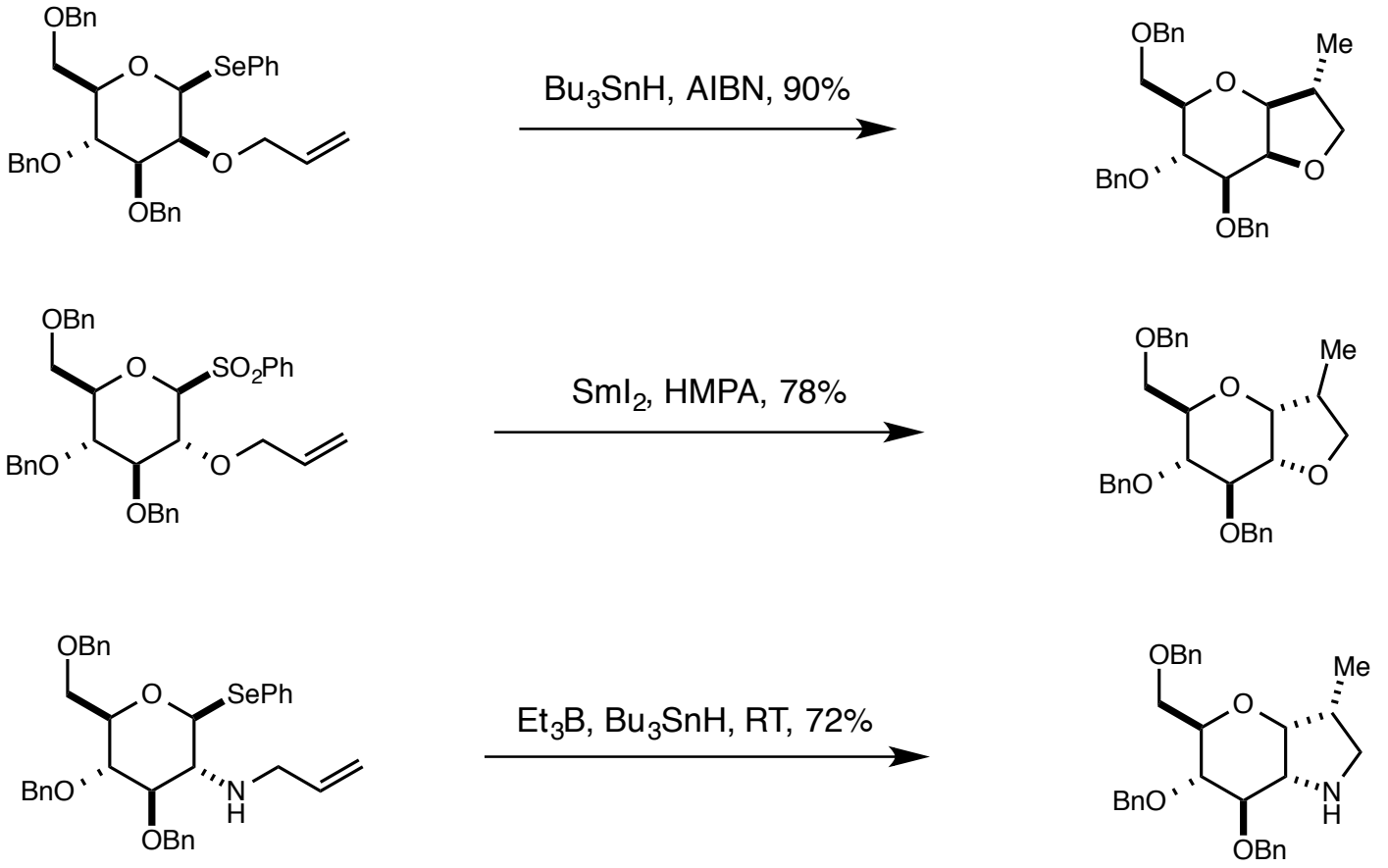
■ SmI_2 for macrocyclizations in Diazonamide A



Nicolaou, K. C. et. al. *ACIEE* **2003**, *42*, 1753.

Radical Cyclizations in Total Synthesis

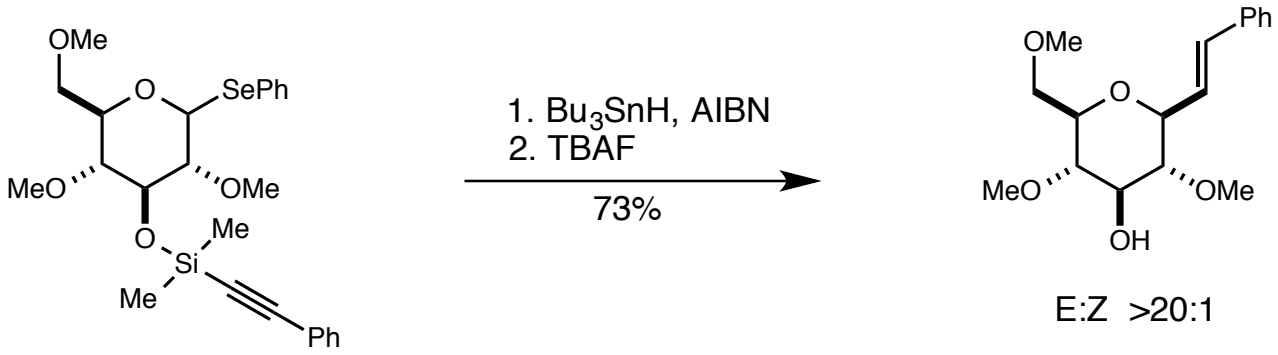
■ Radical cyclizations in sugar chemistry

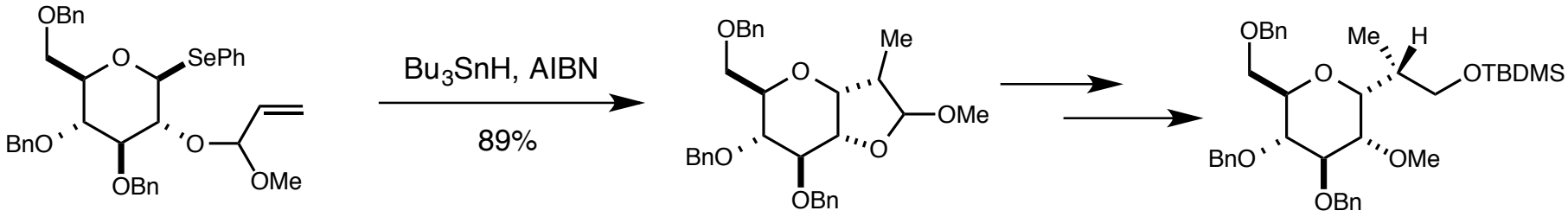


De Mesmaeker, A. et. al. *Tetrahedron Lett.* **1989**, *30*, 6307-6310.
Sinay, P. et. al. *Tetrahedron Lett.* **1992**, *33*, 8065-8068.
Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193-9194.

Radical Cyclizations in Total Synthesis

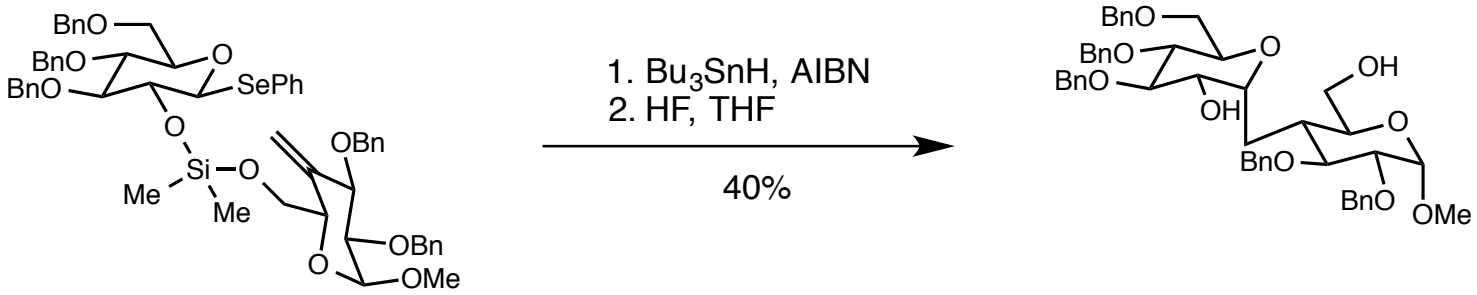
■ Tethered alkene and alkyne radical acceptors





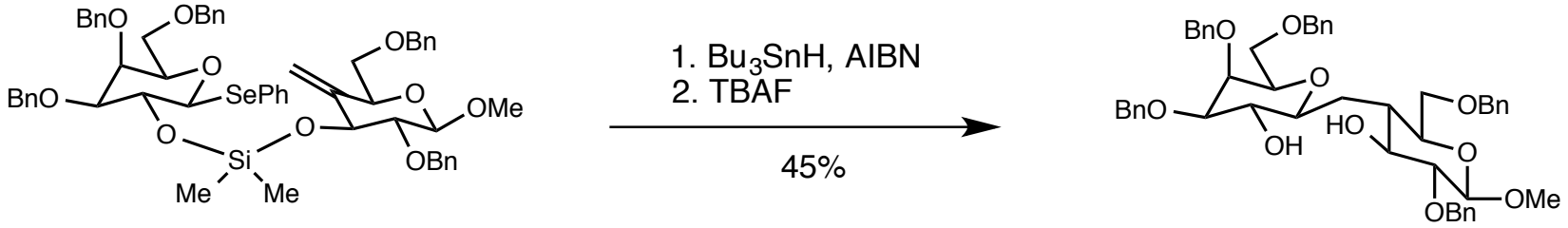
De Mesmaeker, A. et. al. *Tetrahedron Lett.* **1989**, *30*, 6311-6314.
Stork, G.; Suh, H. S.; Kim G. *J. Am. Chem. Soc.* **1991**, *113*, 7054-7056.

9-*endo* cyclization for α–*C*-disaccharides



6, 2' adduct

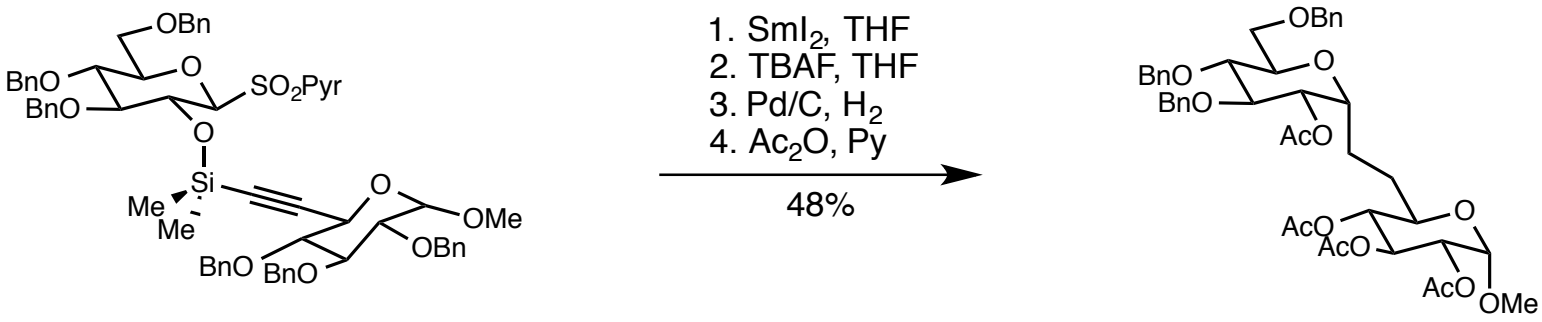
8-*endo* cyclization for β–*C*-disaccharides



3, 2' adduct

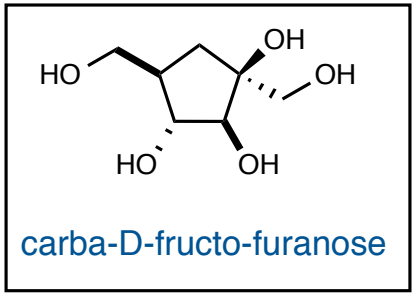
Xin, Y. C.; Mallet, J.-M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1993**, 864-865.

5-*exo* SmI_2 cyclization for *C*-disaccharides



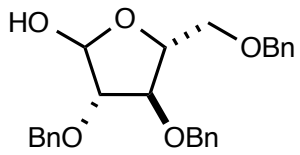
- no HMPA makes SmI_2 weaker reductant
- LUMO π^* of SO_2Ar lowered with 2-pyridine
- less toxic conditions

Mazeas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J.-M. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1383-1386.

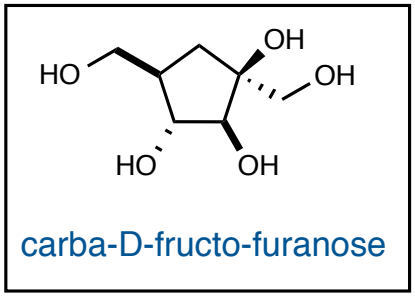


carba-D-fructo-furanose

Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.



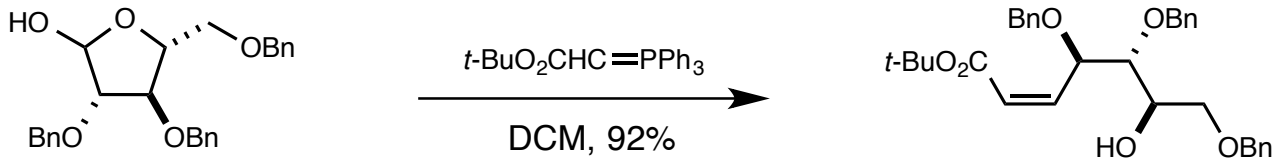
commercially available



carba-D-fructo-furanose

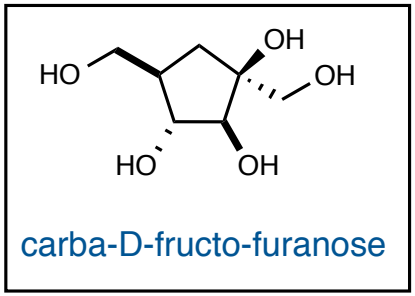
Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.

Radical Cyclizations in Total Synthesis



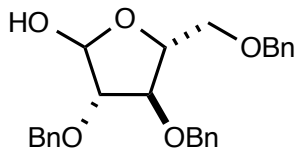
commercially available

2:3 E:Z

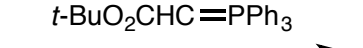


Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.

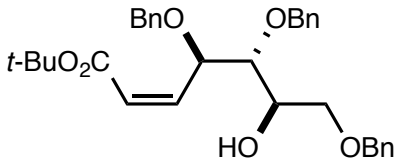
Radical Cyclizations in Total Synthesis



commercially available

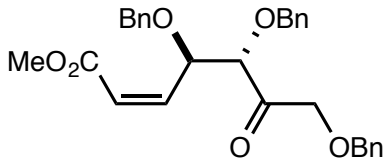


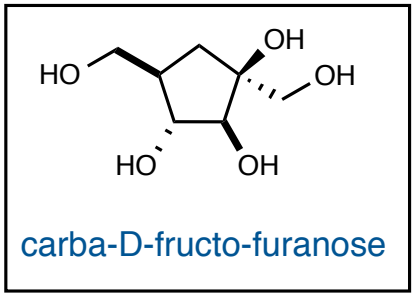
DCM, 92%



2:3 E:Z

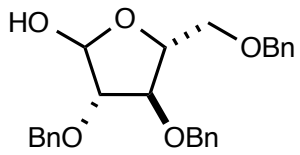
1. Me_2SO, $(COCl)_2$, NEt_3, 96%
2. TFA, DCM, 0 °C, 93%



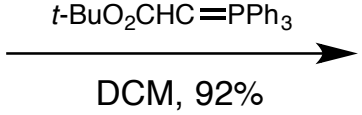


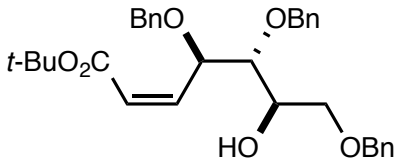
Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.

Radical Cyclizations in Total Synthesis

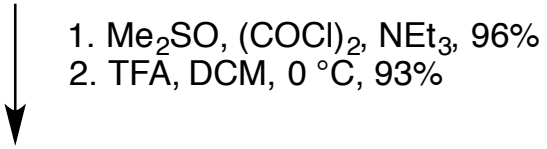


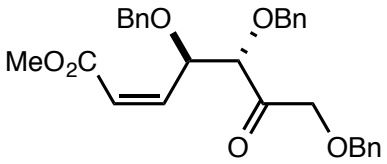
commercially available

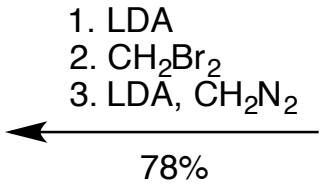


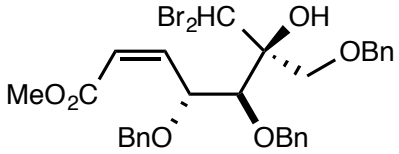


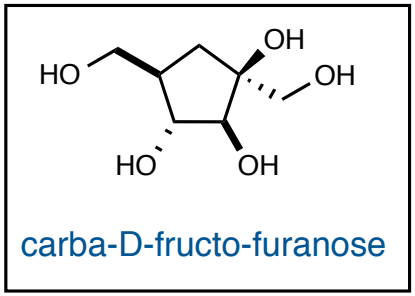
2:3 E:Z





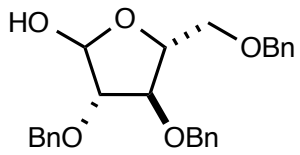




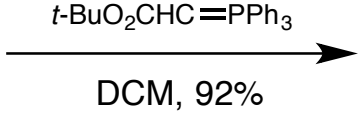


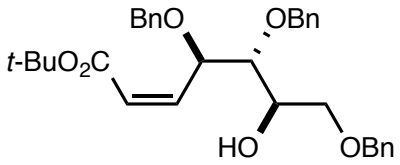
Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.

Radical Cyclizations in Total Synthesis

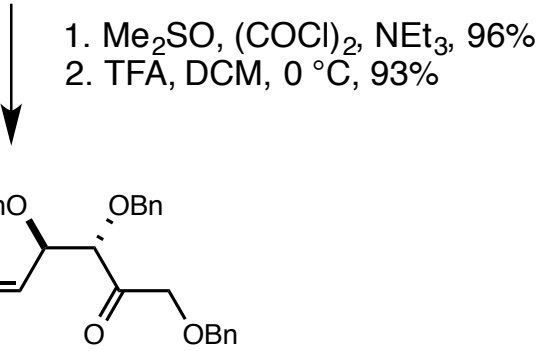


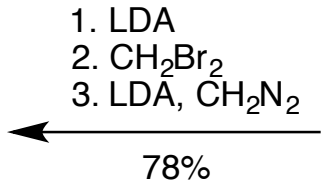
commercially available

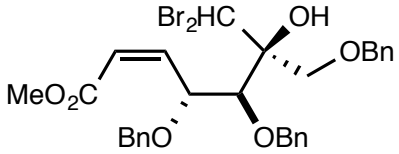


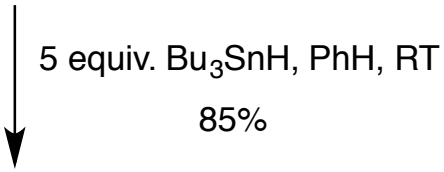


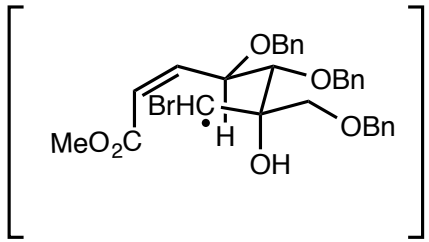
2:3 E:Z

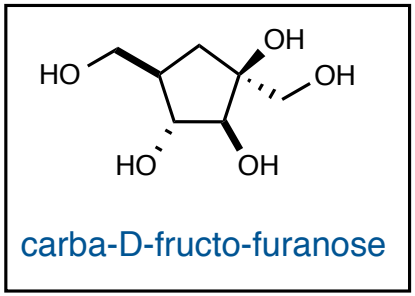






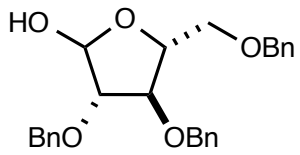




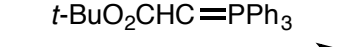


Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.

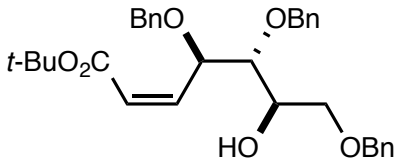
Radical Cyclizations in Total Synthesis



commercially available

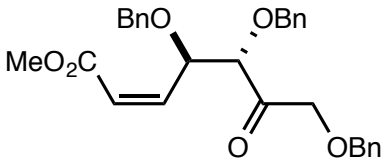


DCM, 92%



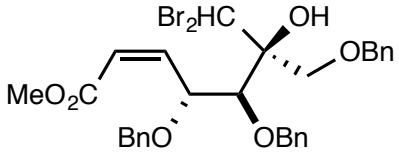
2:3 E:Z

1. Me_2SO, $(COCl)_2$, NEt_3, 96%
2. TFA, DCM, 0 °C, 93%



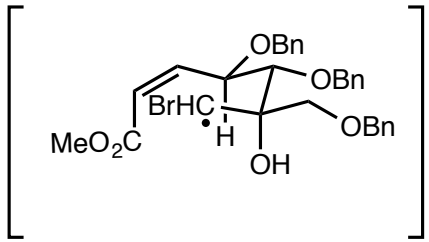
1. LDA
2. CH_2Br_2
3. LDA, CH_2N_2

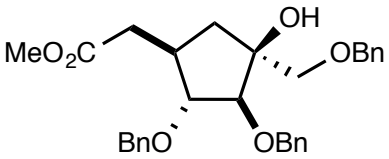
78%

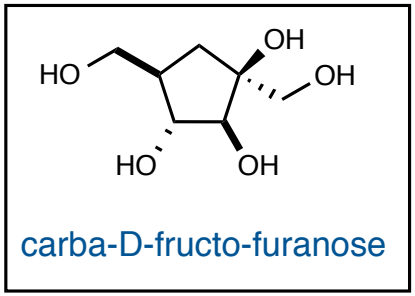


5 equiv. Bu_3SnH, PhH, RT

85%







Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3104-3105.

Radical Cyclizations in Total Synthesis

- The oxidative method
  - Chemical oxidation
  - Electrochemical oxidation

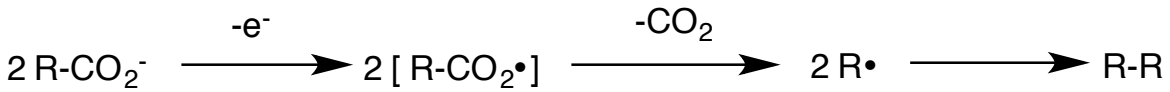
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

The oxidative method

Chemical oxidation

Electrochemical oxidation

Kolbe electrolysis

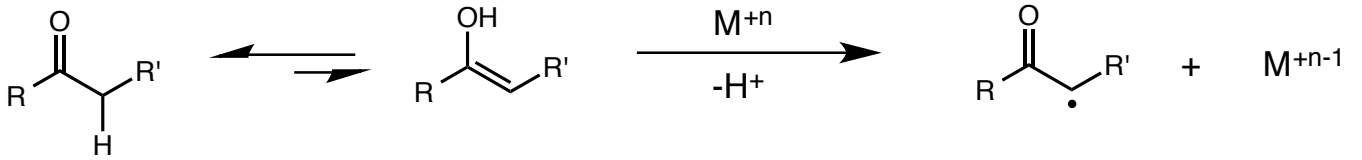


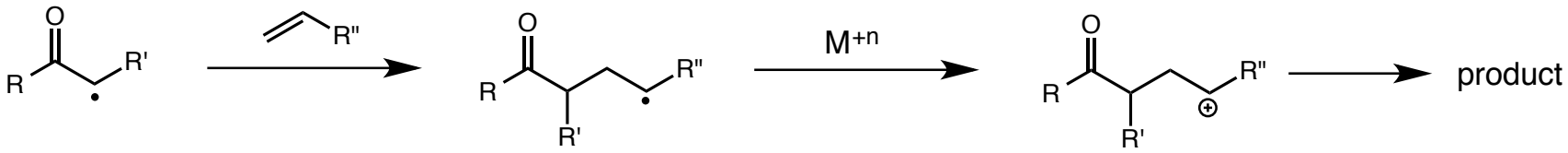
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

Radical Cyclizations in Total Synthesis

The oxidative method

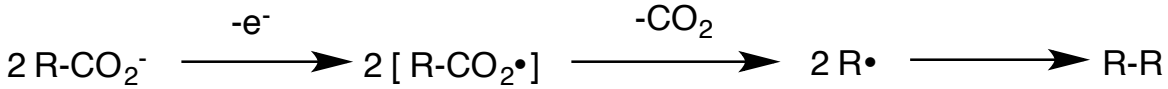
Chemical oxidation





Electrochemical oxidation

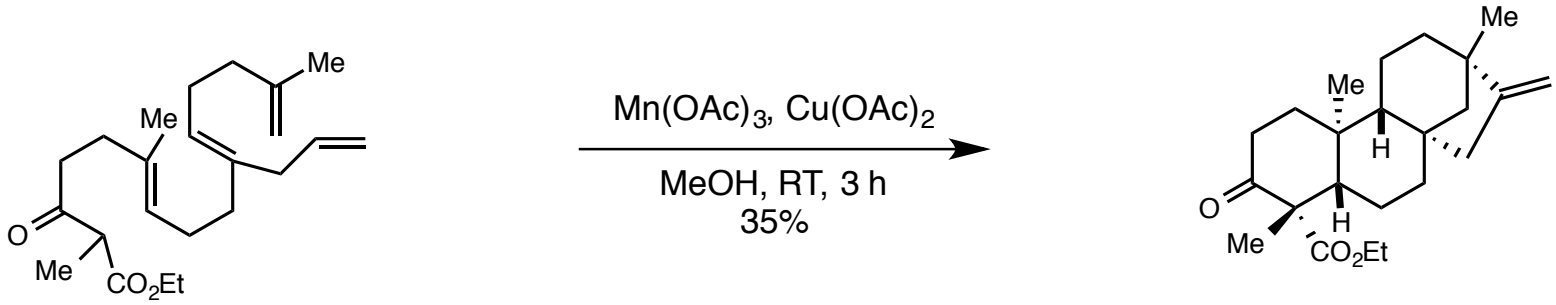
Kolbe electrolysis

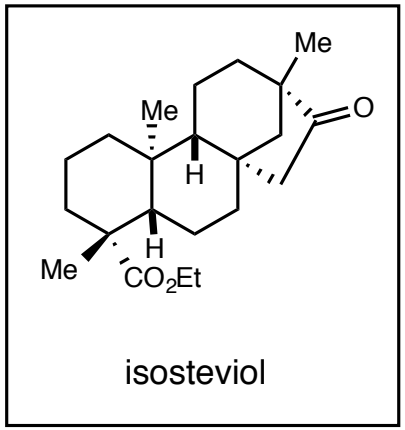


Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.

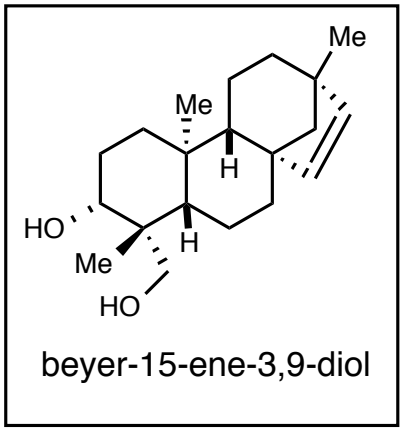
Radical Cyclizations in Total Synthesis

■ Oxidative quadruple cyclization to prepare tetracyclic diterpenes





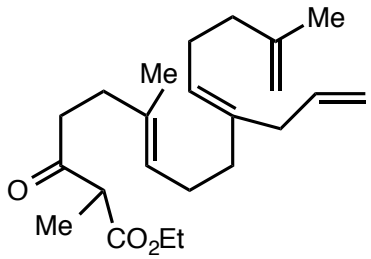
isosteviol



beyer-15-ene-3,9-diol

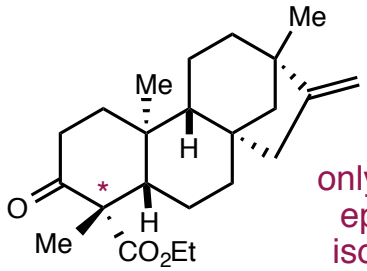
Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

■ Oxidative quadruple cyclization by Snider



$Mn(OAc)_3$, $Cu(OAc)_2$

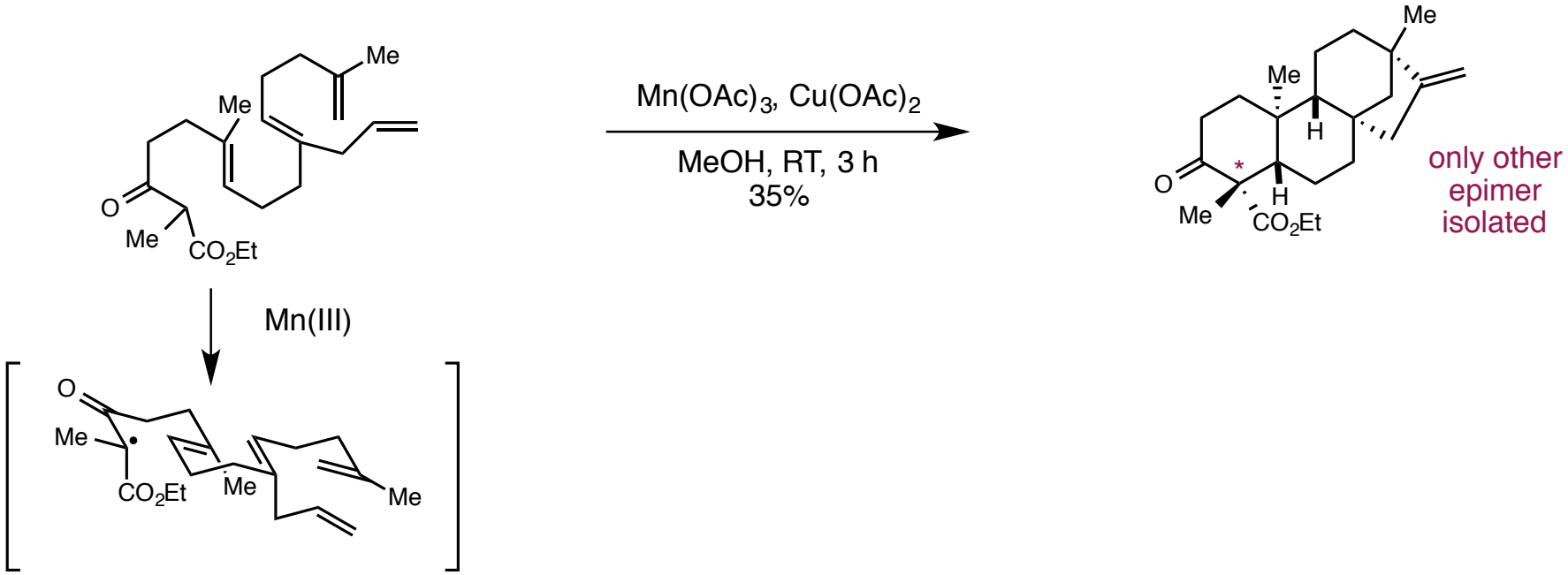
MeOH, RT, 3 h
35%



only other epimer isolated

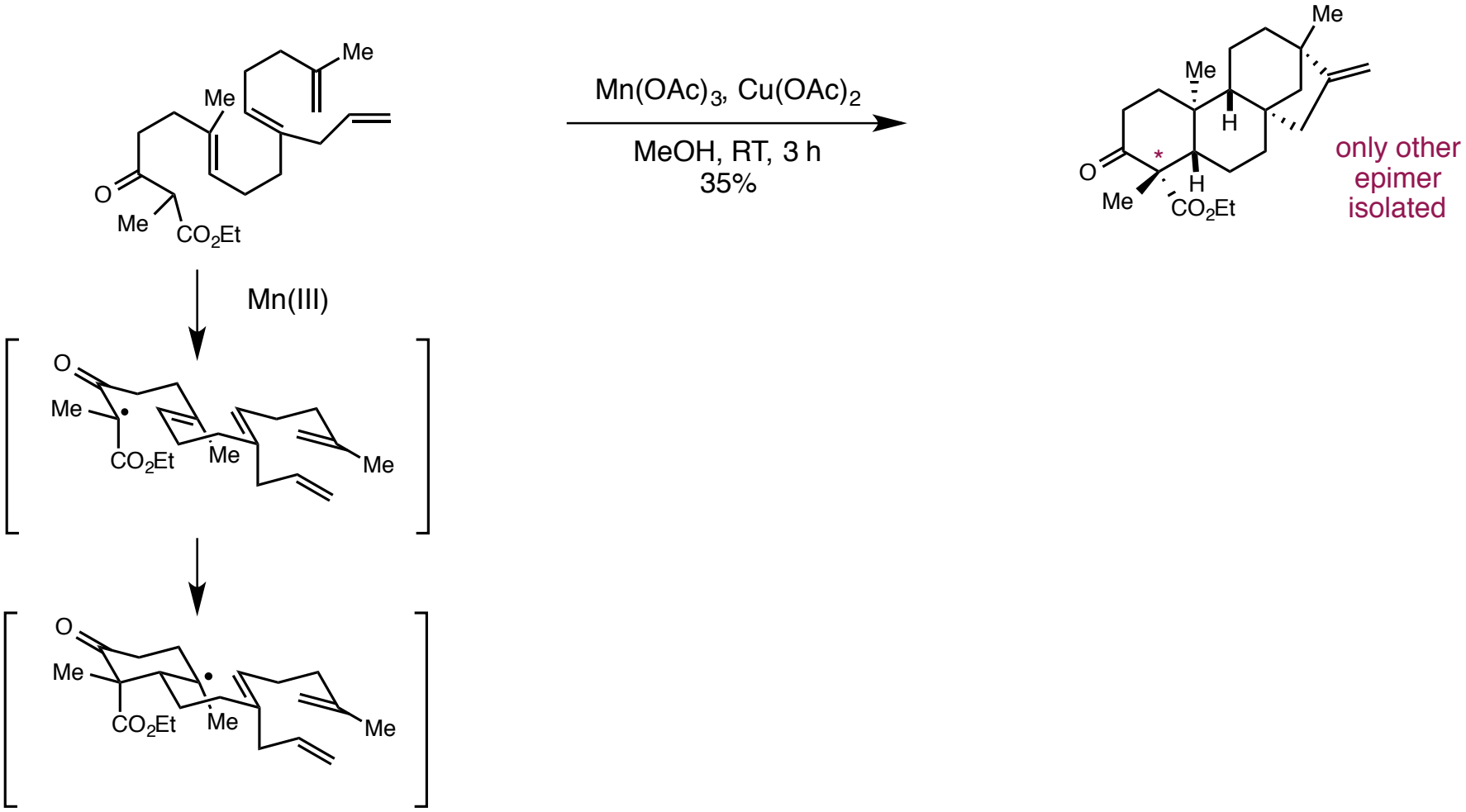
Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

■ Oxidative quadruple cyclization by Snider



Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

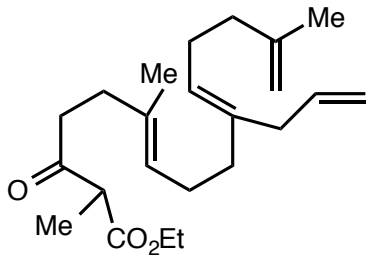
■ Oxidative quadruple cyclization by Snider



Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

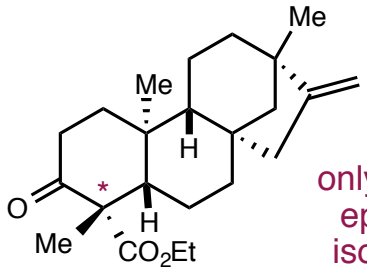
Radical Cyclizations in Total Synthesis

■ Oxidative quadruple cyclization by Snider



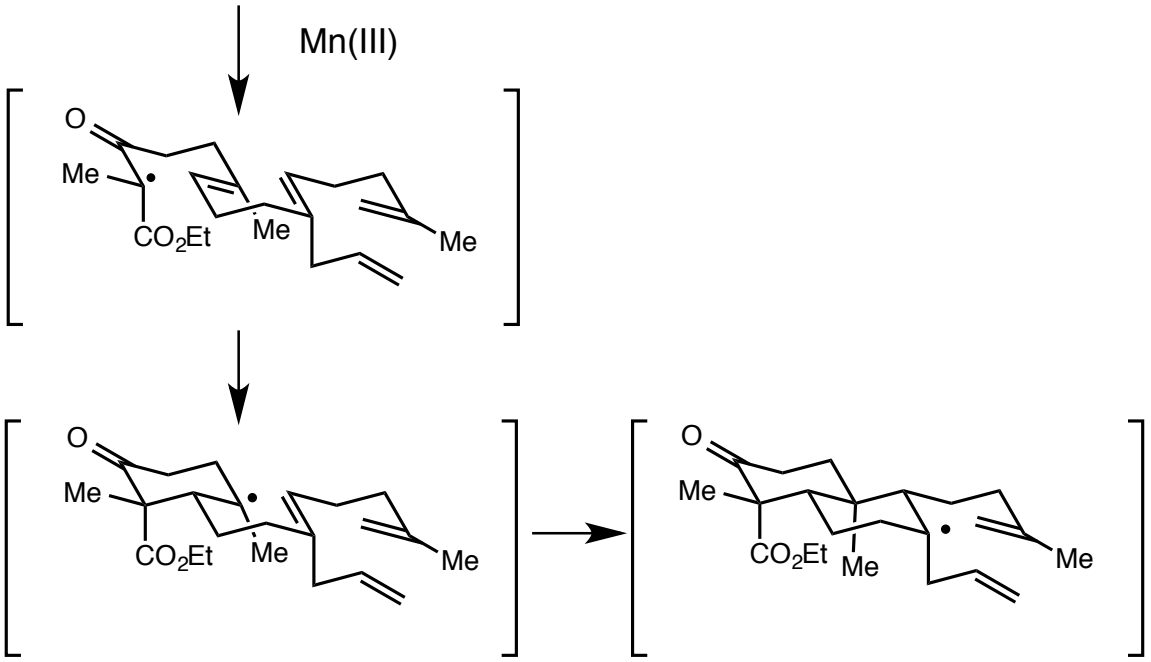
$Mn(OAc)_3$, $Cu(OAc)_2$

MeOH, RT, 3 h
35%



only other epimer isolated

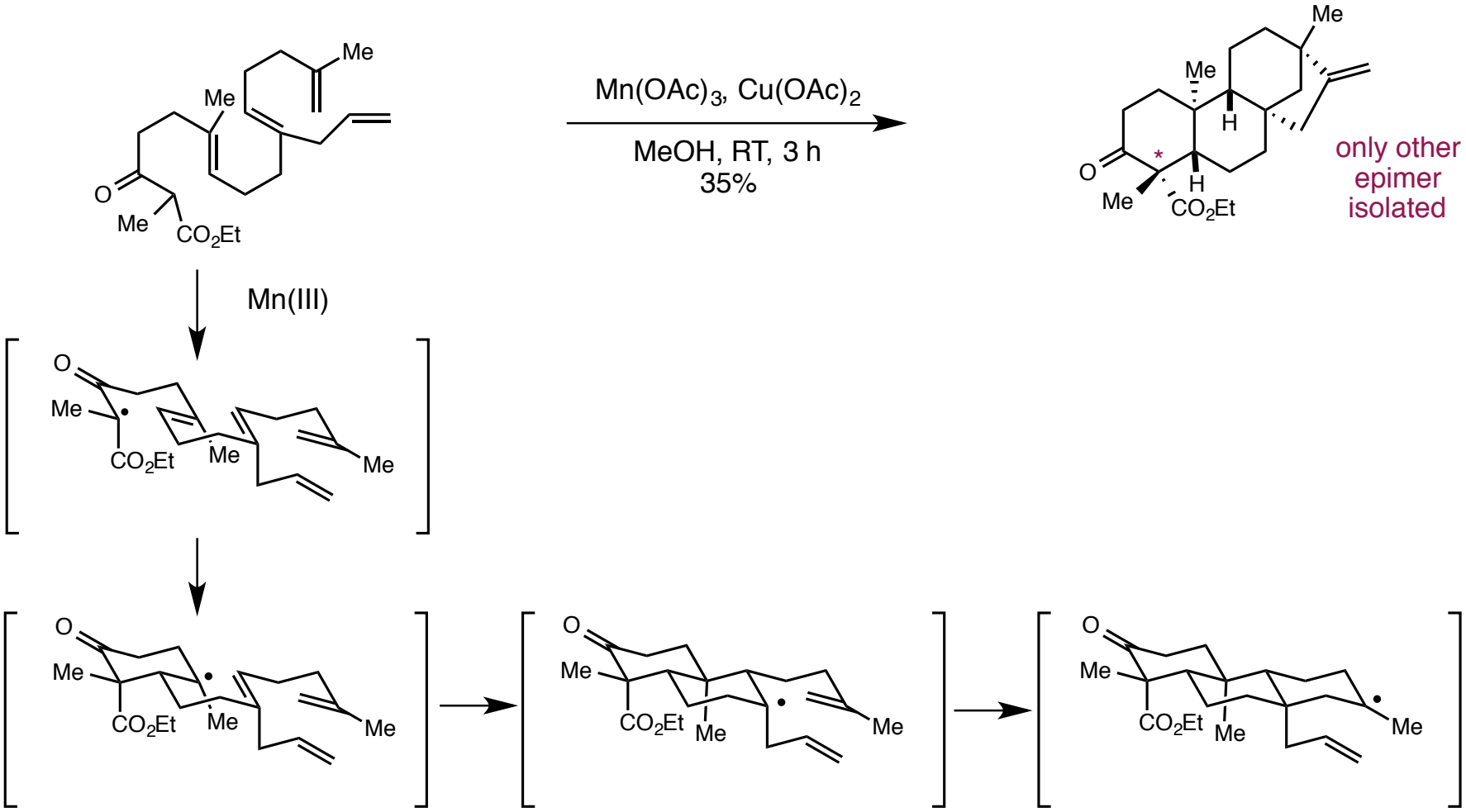
Mn(III)



Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

Radical Cyclizations in Total Synthesis

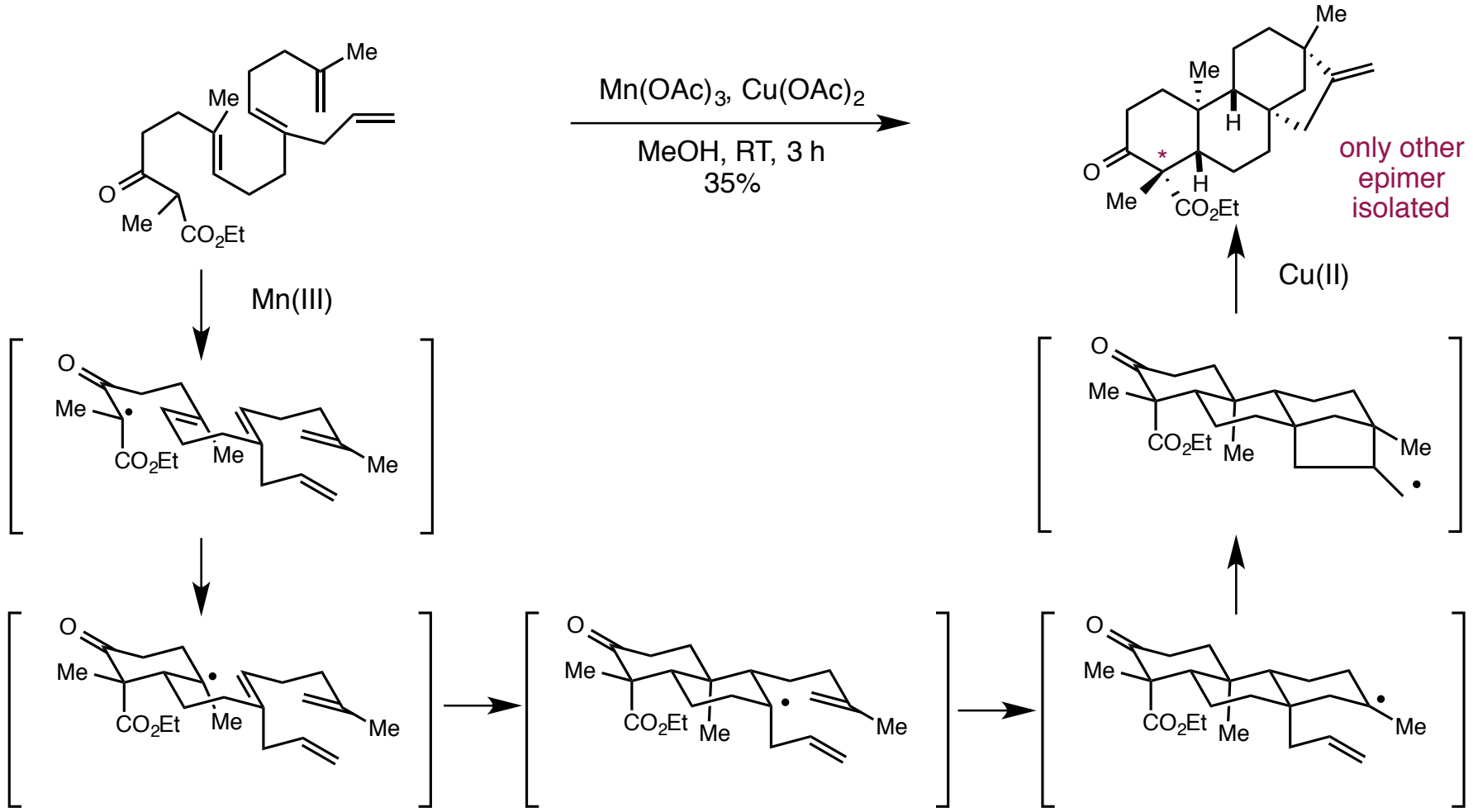
■ Oxidative quadruple cyclization by Snider



Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

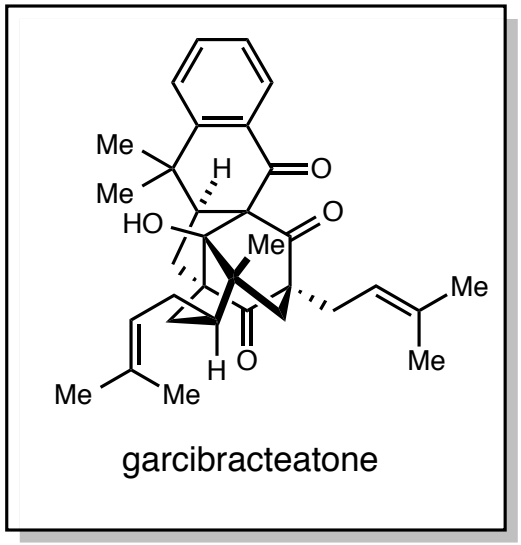
Radical Cyclizations in Total Synthesis

■ Oxidative quadruple cyclization by Snider



Snider, B.B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1990**, *112*, 4003-4008.

Radical Cyclizations in Total Synthesis

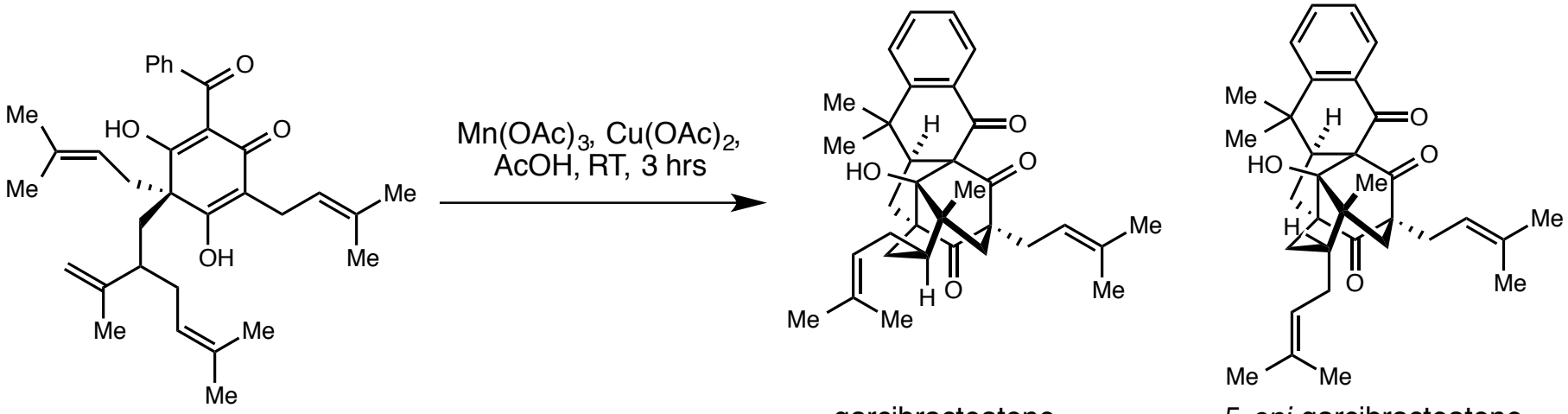


garcibracteatone

Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162-5164.

Radical Cyclizations in Total Synthesis

■ The oxidative method



garcibracteatone

14%

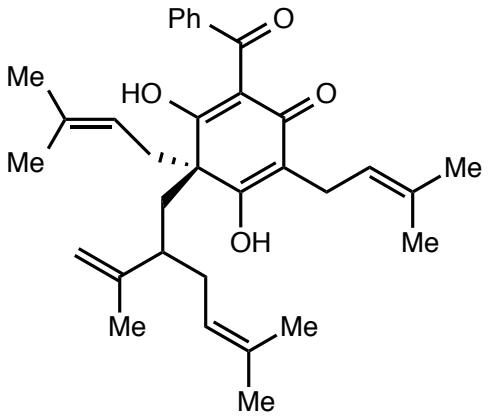
5-*epi*-garcibracteatone

8%

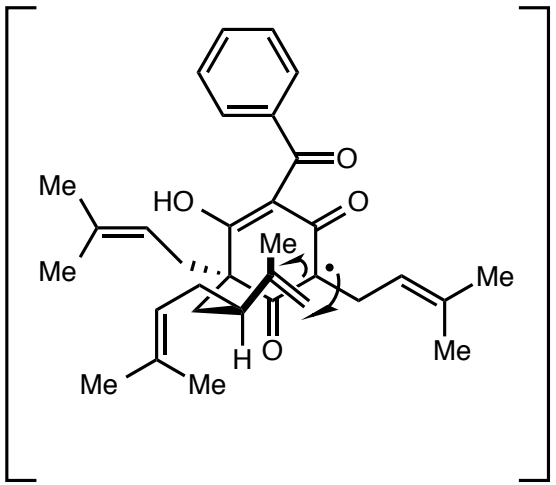
- 4 C-C bonds formed
- no protecting groups
- 5 stereocenters formed
- biomimetic pathway

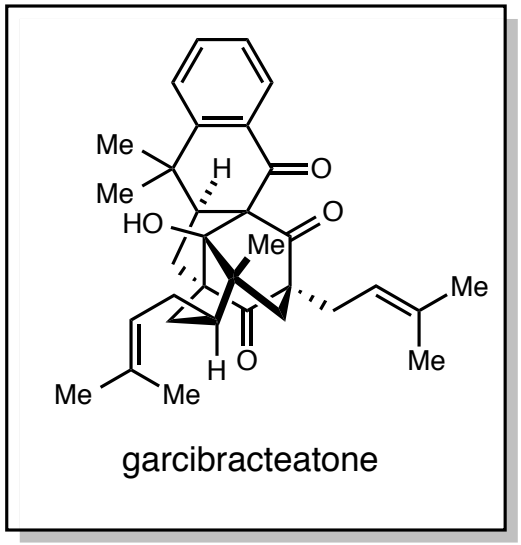
Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162-5164.

Radical Cyclizations in Total Synthesis



$Mn(OAc)_3$, $Cu(OAc)_2$,
AcOH, RT, 3 hrs

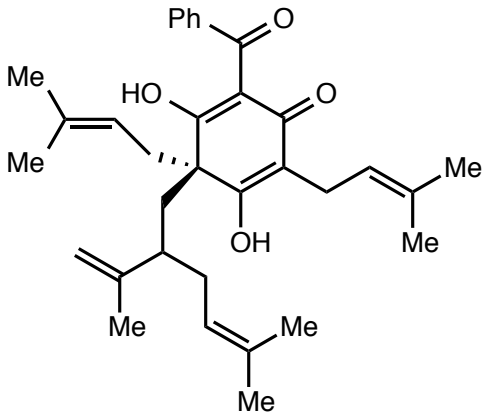


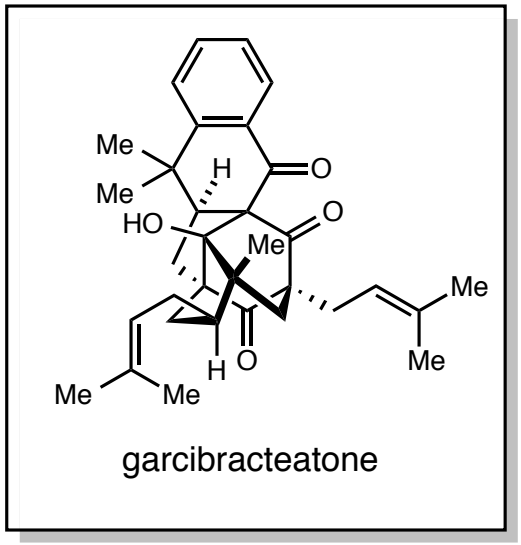


garcibracteatone

Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162-5164.

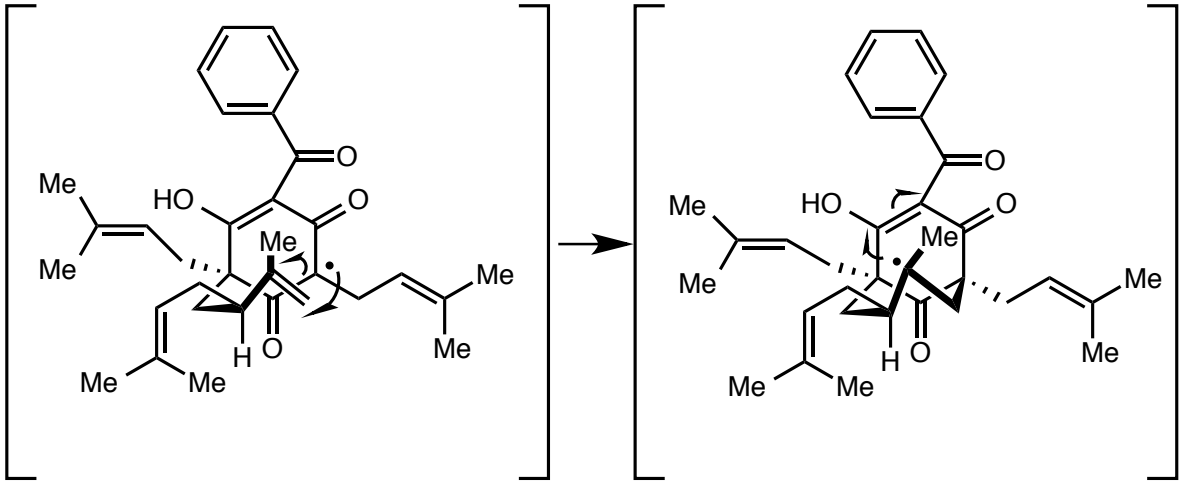
Radical Cyclizations in Total Synthesis





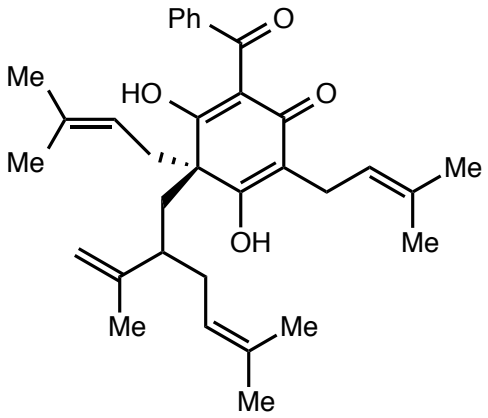
garcibracteatone

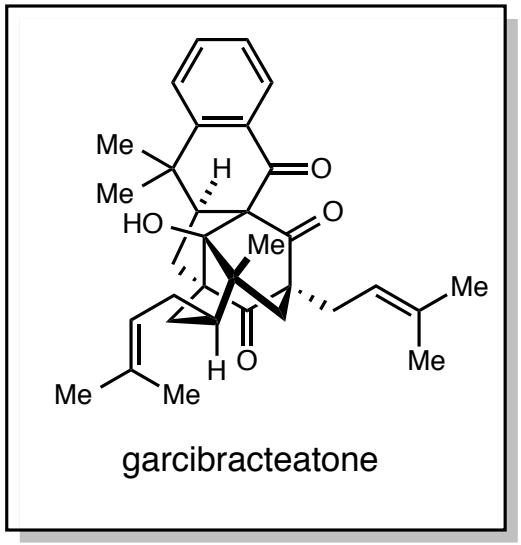
$Mn(OAc)_3$, $Cu(OAc)_2$,
AcOH, RT, 3 hrs



Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162-5164.

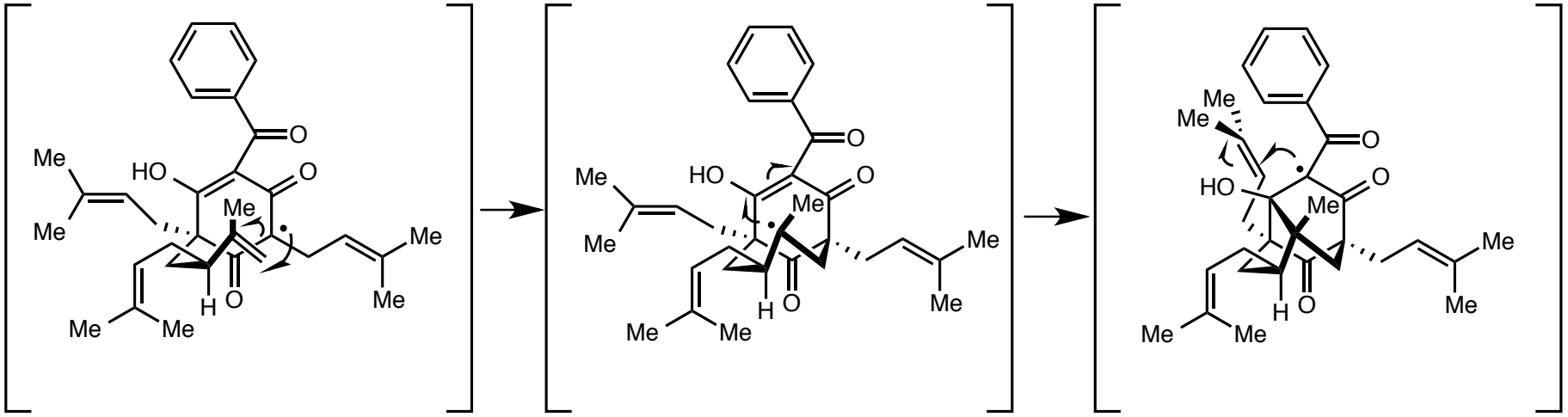
Radical Cyclizations in Total Synthesis





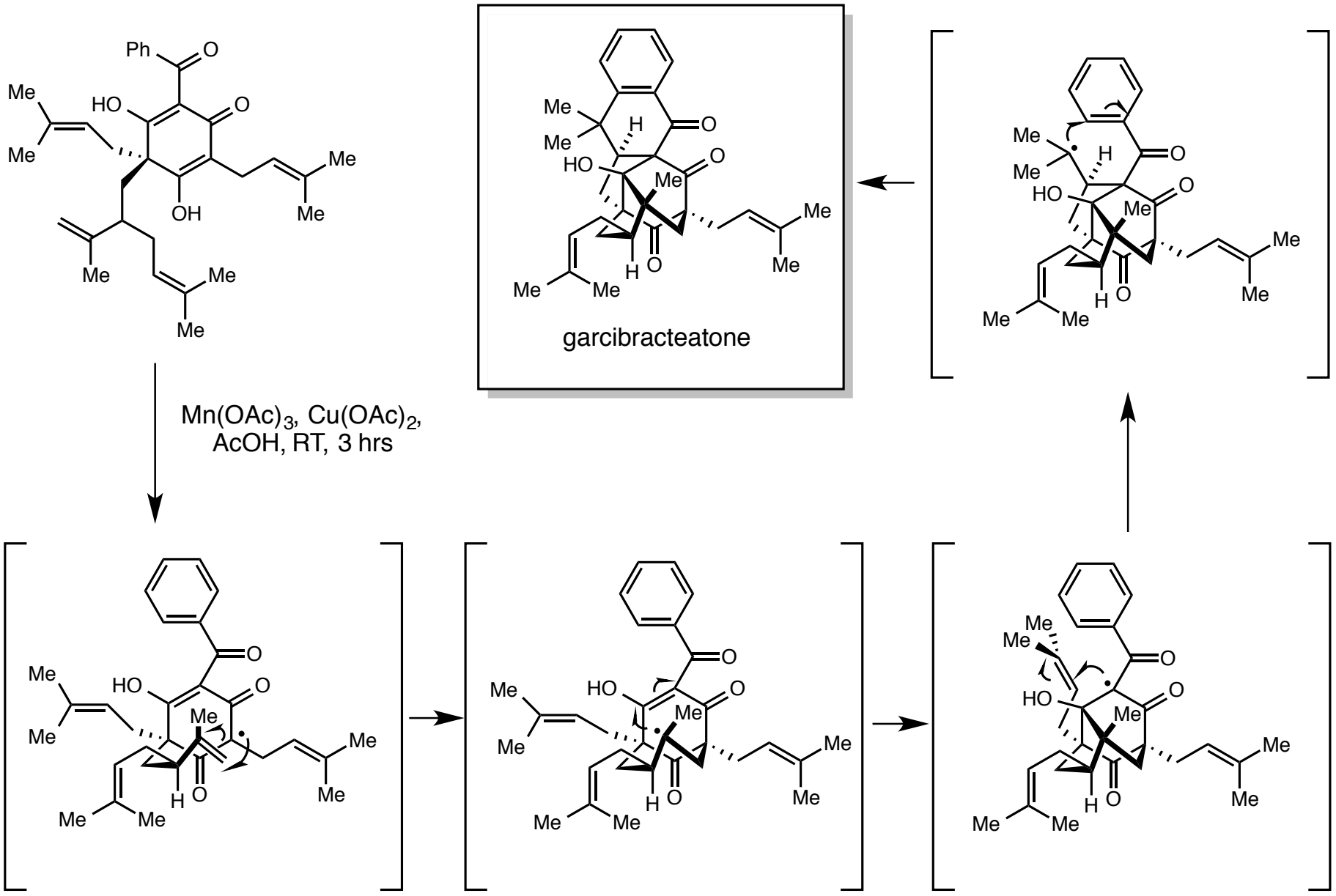
garcibracteatone

$Mn(OAc)_3$, $Cu(OAc)_2$,
AcOH, RT, 3 hrs



Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162-5164.

Radical Cyclizations in Total Synthesis



Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162-5164.

Radical Cyclizations in Total Synthesis

- So what is "radical" now?

- Total syntheses with radical cyclizations method in the last year:

  Tin Reagent: 8 reported Reduction: 6 reported Oxidation: 6 reported

- No photoredox radical cyclization in total synthesis yet
- Radical cyclization still primarily for carbon-carbon bond formations
- Many use fragmentation method - for functional handle after
- Total syntheses with tandem radical cyclization in the last year:

  Tandem: 5