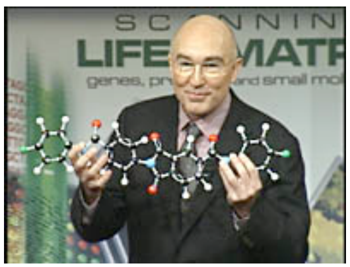
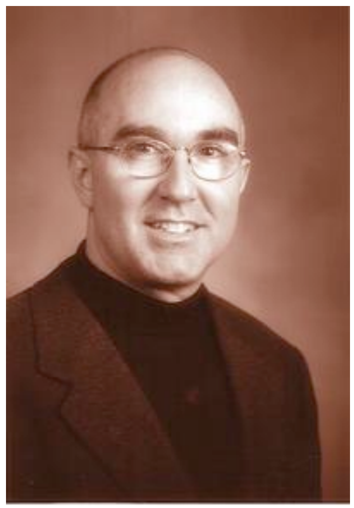
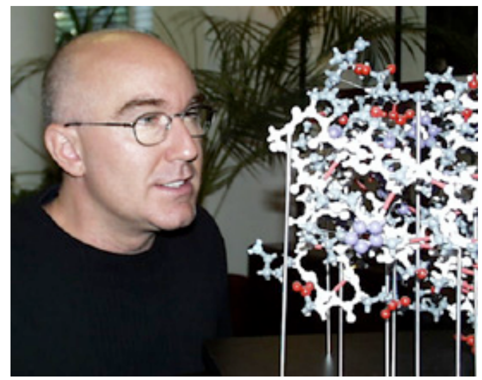
The Career of Stuart Schreiber
Part 1: Organic Chemist

Group Meeting: April 1, 2009

Benjamin D Horning







- For a complete listing of Dr. Schreiber's publications, including pdf links, please visit
  http://www.broad.harvard.edu/chembio/lab_schreiber/smdb/smdbPublicationsDissertationsForm.php

The (Chemistry) Career of Stuart L. Schreiber

Biographical Notes

- Education (b. 1956 - Virginia)

B.A. : University of Virginia (1977); R. J. Sundberg – Photocyclization of Indole Derivatives

Ph.D.: Harvard (1981); R. B. Woodward and Y. Kishi – oxidation of tertiary amines

- Hydrgogen Transfer from Tertiary Amines to Trifluoroacetic Anhydride. *Tetrahedron* **1980**, *21*, 1027
- Fragmentation Reactions of α-alkoxy Hdroperoxides and Application to the Synthesis of (±)-Recifeiolide. *J. Am. Chem. Soc*. **1980**, *102*, 6163
- Oxidation of Tertiary Amines. II. Peroxides in Organic Synthesis. Ph.D. Thesis, Harvard University, **1981**

- Career

Assistant Professor (1981-84); Associate Professor (tenured) (1984-86); Professor (1986-88); Department of Chemistry, Yale
Professor (1988-1998); Morris Loeb Professor (1998-); Department of Chemistry and Chemical Biology, Harvard
Department Chair (2001-2004); Director, Chemical Biology, and Founding Core Member of the Broad Institute of Harvard And MIT (2003-); Investigator, Howard Hughes Medical Institute (1994-); Affiliate, Department of Cell Biology, Harvard Medical School (1994-2004); Member, Graduate Programs in Biophysics and Immunology (1988-), Harvard

- Companies

Founder, Forma Therapeutics, Inc. (2008-); Founder, Co-Chair of the Scientific Advisory Board, Infinity Pharmaceuticals (2002-06); Founder and Chair of the Board of Scientific and Medical Advisers, ARIAD Pharmaceuticals (1991-); Founder, ARIAD Gene Therapeutics (1994-2008); Founder and Scientific Advisory Board Member, Vertex Pharmaceuticals (1988-90); Adviser, Theravance, 2000-04; Consultant, Pfizer, 1983-91

- Notable Awards (chemistry)

Dreyfus Newly Appointed Faculty Award, 1981; Searle Scholar, 1982; Dreyfus Teacher-Scholar Award, 1985; Fellow of the Alfred P. Sloan Foundation, 1985; NSF Presidential Young Investigator Award, 1985; ICI Pharmaceuticals Award for Excellence in Chemistry, 1986; Arthur C. Cope Scholar Award, American Chemical Society (ACS), 1986; Award in Pure Chemistry, ACS, 1989; Arun Guthikonda Memorial Award, Columbia University, 1990; Thieme-IUPAC Award in Synthetic Organic Chemistry, 1992; NIH Merit Award, 1992, Rhone-Poulenc Silver Medal, Royal Society of Chemistry, 1992; Award for Creative Work in Synthetic Chemistry, ACS, 1994; Elected to the National Academy of Sciences and the American Academy of Arts & Sciences, 1996

- Publications:
  - >425 invited lectures
  - >400 publications (h-index = 109)

http://www.broad.harvard.edu/chembio/lab_schreiber/members/smdbSchreiberBio.php

The (Chemistry) Career of Stuart L. Schreiber

H-index

Rank	Name	h-index	Field
1	Whitesides, G. M.	147	Organic
2	Corey, E. J.#	135	Organic
2	Karplus, M.	135	Theoretical
4	Heeger, A. J.#	115	Organic
4	Schleyer, P. v.	115	Organic
4	Wüthrich, K.#	115	Bio
7	Bax, A.	114	Bio
8	Huber, R.#	113	Bio
9	Hoffmann, R.#	112	Theoretical
10	Lehn, J. M. #	108	Organic
11	Bard, A. J.	106	Analytical
11	Scheraga, H. A.	106	Bio
13	Schreiber, S. L.	104	Bio
14	Clore, G. M.	99	Bio
14	Gratzel, M.	99	Physical
14	Truhlar, D. G.	99	Theoretical
17	Khorana, H. G.#	98	Bio
17	Schaefer, H. F.	98	Theoretical
19	Ertl, G.#	97	Physical

Ad Bax is the only living chemist who is both younger and has a higher H-index

http://www.rsc.org/chemistryworld/News/2007/April/23040701.asp

The (Chemistry) Career of Stuart L. Schreiber

Ex-Group Members

- Amir Hoveyda (1981-1986) (Ph.D.)
  Dissertation: "The Furan-Carbonyl Photocycloaddition Reaction and its Applications in Organic Synthesis"
  Currently Joseph T. Vanderslice Professor, Boston College
- Tim Jamison (1992-1997) (Ph.D.)
  Dissertation: "I. Consecutive Use of Two Reactions of Alkyne-$Co_2(CO)_6$ Complexes in the Total Synthesis of (+)-Epoxydictymene
  II. Studies Directed Toward the Synthesis of the Diazonamide Marine Natural Products Using Benzofuran Epoxidation-Rearrangements"
  Currently Paul M. Cook Career Development Associate Professor of Chemistry, MIT
- Glenn Micalizio (2000-2003) (post-doc)
  Currently Associate Professor, Scripps Florida
- James Morken (1995-1997) (post-doc)
  Currently Professor, Boston College
- John A. Porco Jr. (1985-1992) (Ph.D.)
  Dissertation: "Studies Toward the Synthesis of the Enediyne Antibiotics"
  Currently Assistant Professor of Chemistry, Boston University
- Daniel Romo (1991-1993) (post-doc)
  Currently Professor, Texas A&M University
- Scott Rychnovsky (1987-1988) (post-doc)
  Currently Professor, University of California, Irivine
- Matthew Shair (1995-1997) (post-doc)
  Currently Professor, Harvard University
- Martin Burke (2000-2004) (Ph.D.)
  Currently Assistant Professor, University of Illinois, Urbana-Champaign
- John Wood (1991-1993) (post-doc)
  Currently A.I. Meyers Professor of Chemistry, Colorado State University
- Marc Snapper (1990-1993) (post-doc)
  Currently Professor, Boston College

http://www.broad.harvard.edu/chembio/lab_schreiber/smdb/smdbFormerMembersForm.php








The (Chemistry) Career of Stuart L. Schreiber

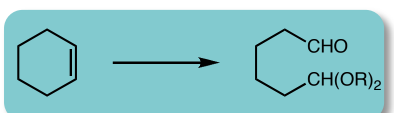
Timeline

- Research theme:

To develop chemical transformations that can be used as springboards for the synthesis of complex natural products

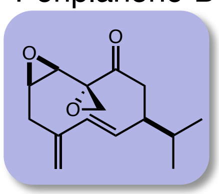
1981
Assistant Professor at Yale

1982
Ozonolytic cleavage of cycloalkenes to terminally differentiated products



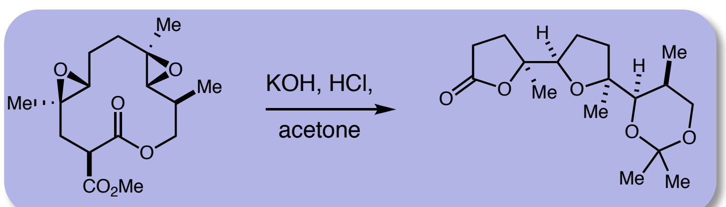
Tetrahedron Letters **1982**, *23*, 3867

1984
Total Synthesis of Periplanone-B



JACS **1984**, *106*, 4038

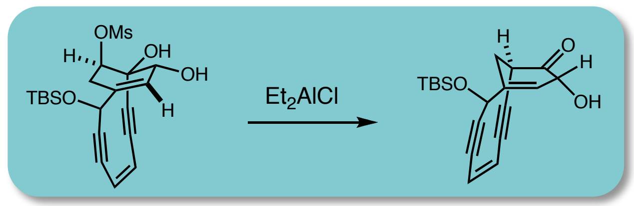
1986
Macrolide epoxidation strategy towards Monensin



JACS **1986**, *108*, 2106

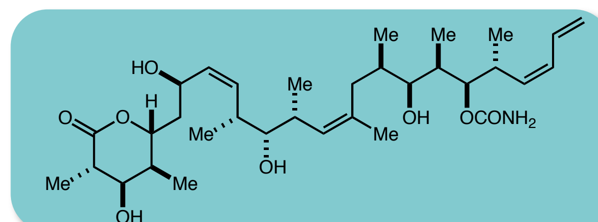
1988
Professor, Harvard

1989
Type II Diels-Alder towards Calichemicin



Tetrahedron Letters **1989**, *30*, 3765

1993
First Synthesis of Discodermolide



JACS **1993**, *115*, 12621

The (Chemistry) Career of Stuart L. Schreiber

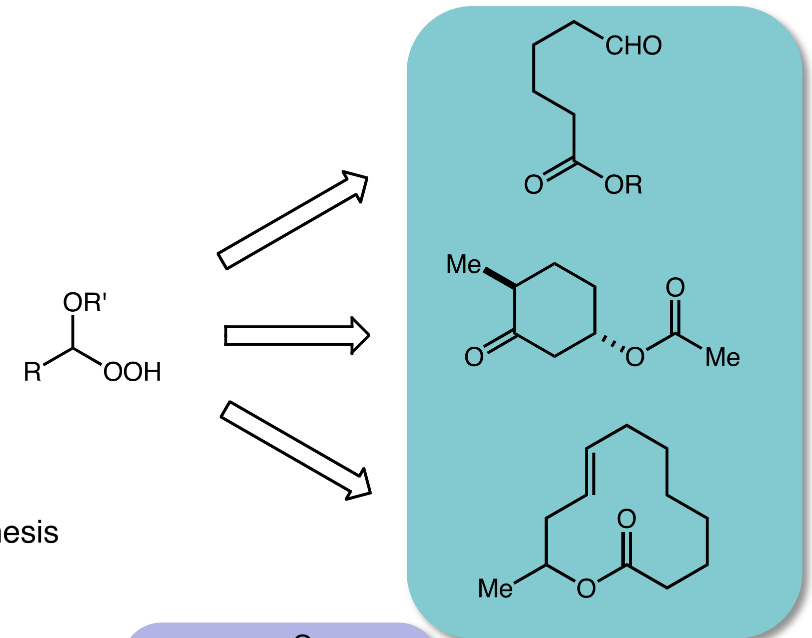
Outline

- The use of α-alkoxy hydroperoxides in organic synthesis

  Schreiber Ozonolysis

  Alkene Baeyer-Villiger

  Macrolide synthesis

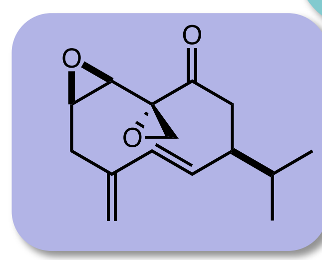


- Utilization of [2+2} photocycloaddition reactions in total synthesis

  Periplanone B

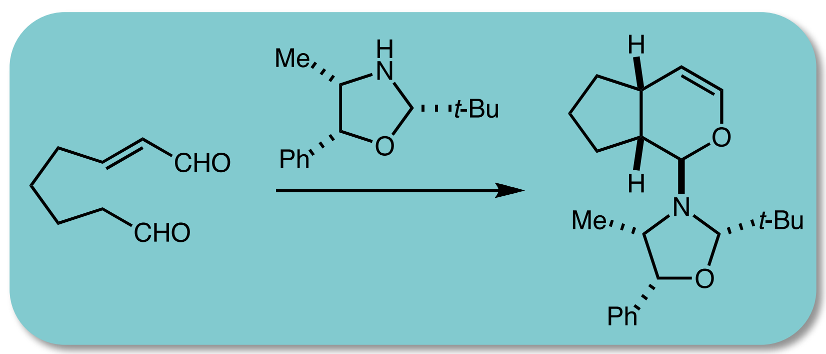
  Furan Paterno-Büchi, "photoaldol"

  Total synthesis of Asteltoxin



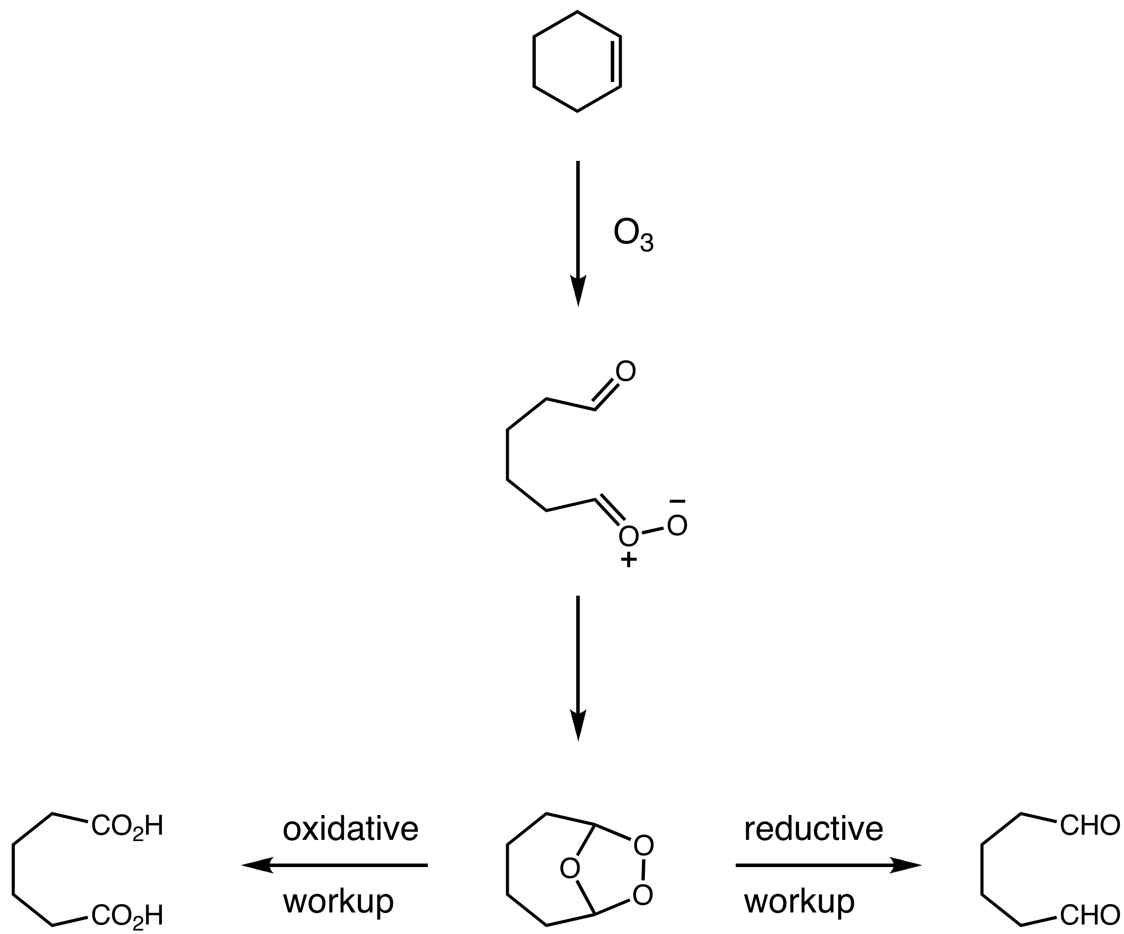
- Verging on enamine catalysis

Scaleability
"Springboard"



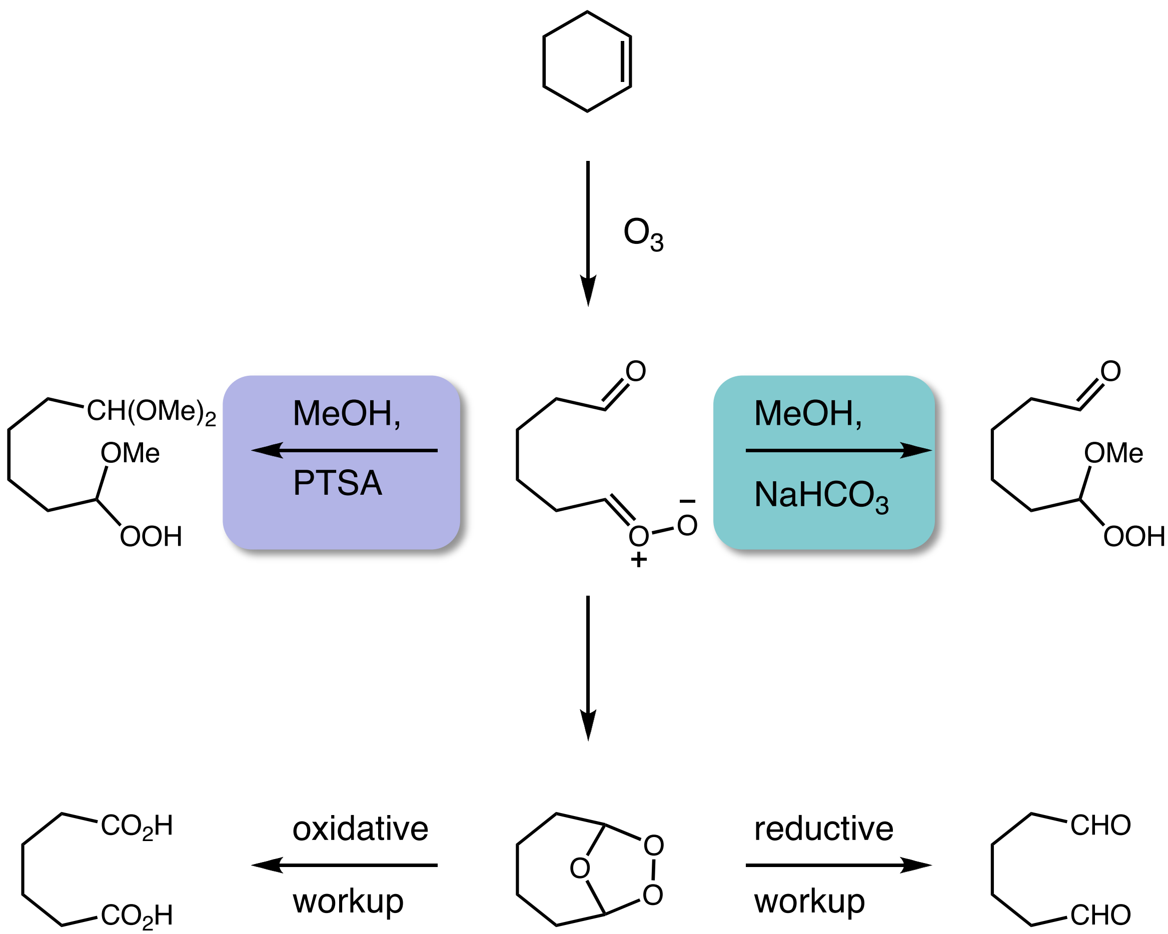
α-Alkoxy Hydroperoxides in Organic Synthesis

Schreiber Ozonolysis



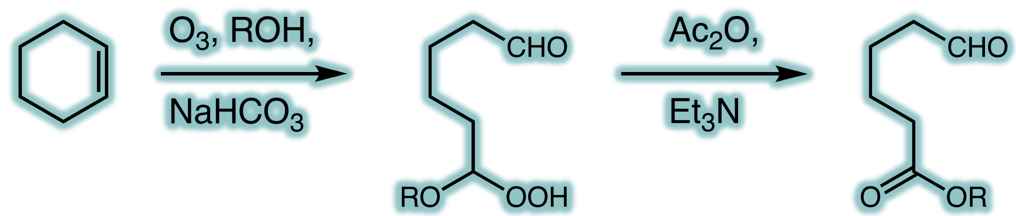
α-Alkoxy Hydroperoxides in Organic Synthesis

Schreiber Ozonolysis



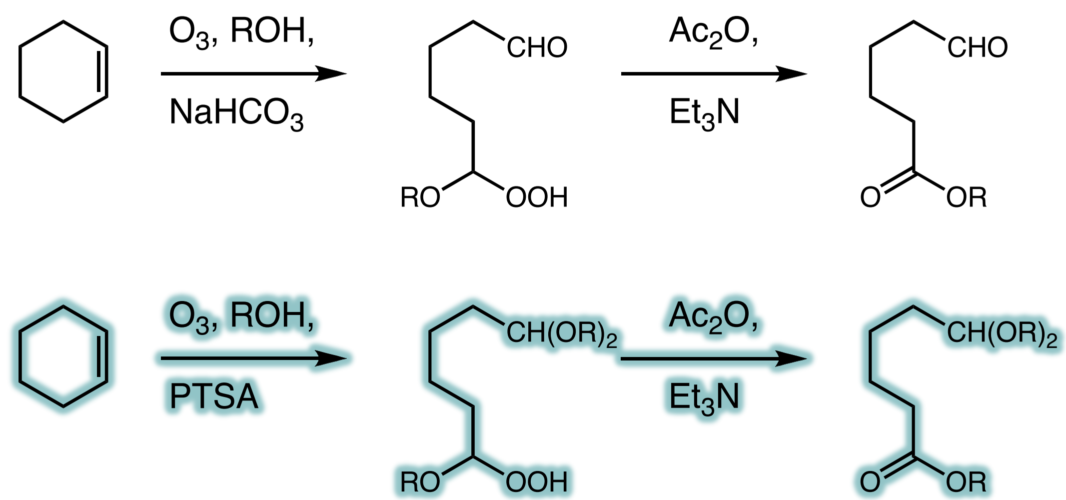
α-Alkoxy Hydroperoxides in Organic Synthesis

Schreiber Ozonolysis



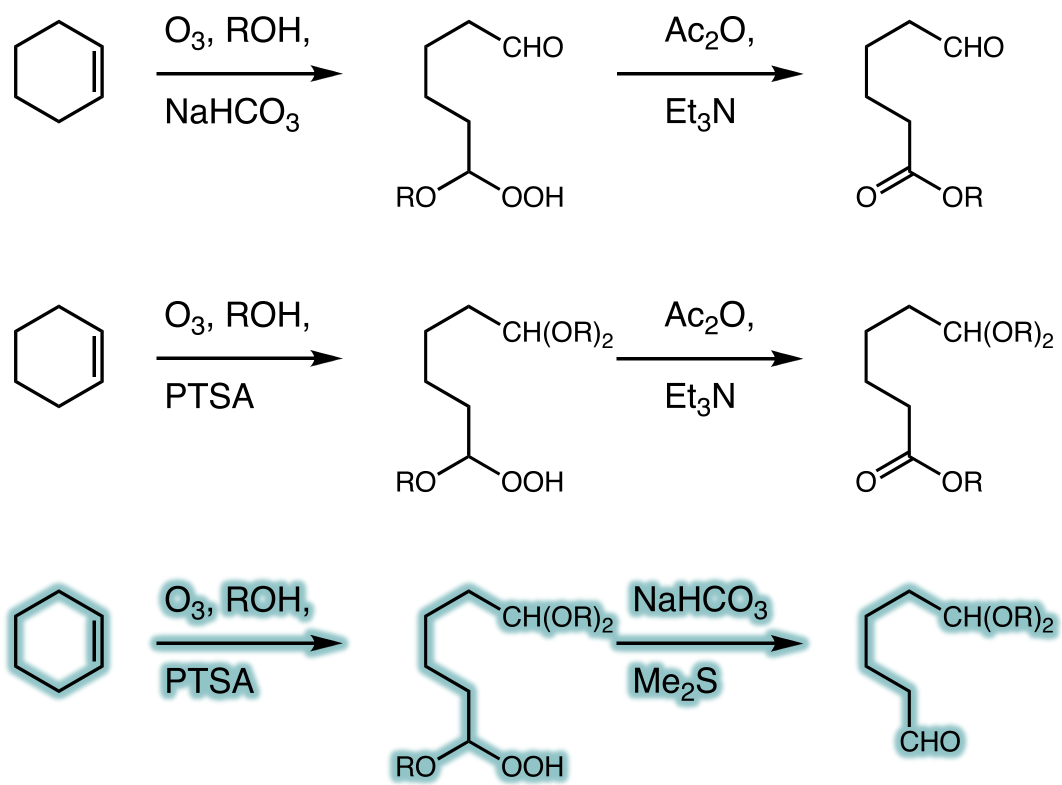
α-Alkoxy Hydroperoxides in Organic Synthesis

Schreiber Ozonolysis



α-Alkoxy Hydroperoxides in Organic Synthesis

Schreiber Ozonolysis



α-Alkoxy Hydroperoxides in Organic Synthesis

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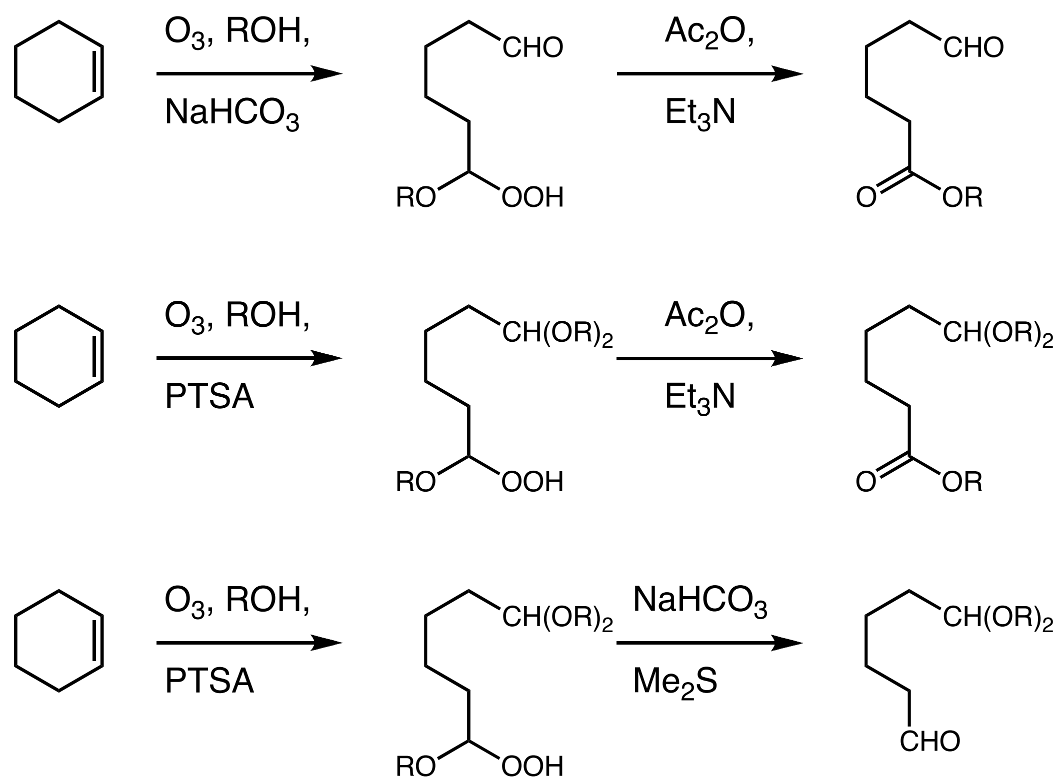


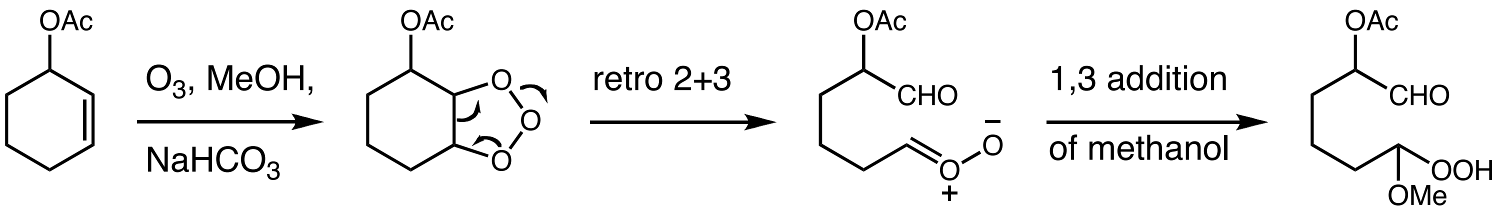
- Ozonolysis modification allows access to terminally differentiated products

Schreiber *et al. Organic Synthesis* **1984**, *64,* 168 and Schreiber *et al*. *Tetrahedron*, **1982**, *23*, 38676

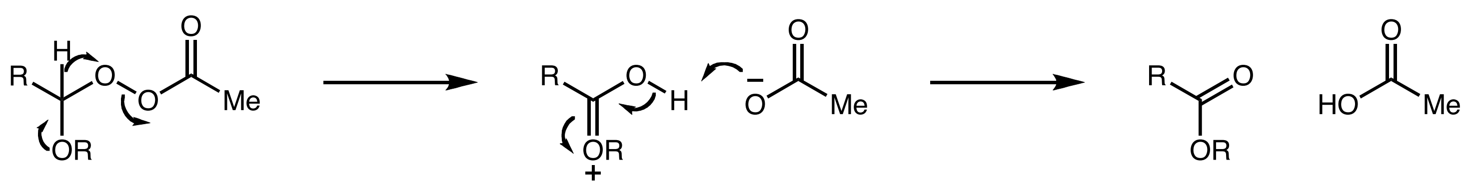
α-Alkoxy Hydroperoxides in Organic Synthesis

Schreiber Ozonolysis

- Differentially substituted alkenes can be selectively functionalized



- Ester formation depends upon hydride migration

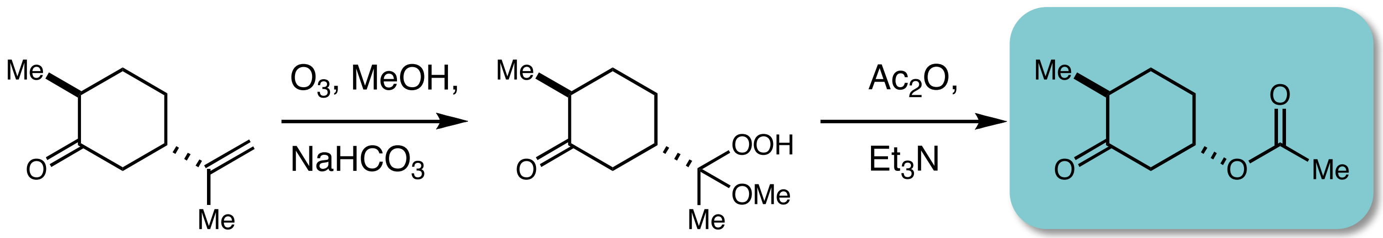


Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 660

α-Alkoxy Hydroperoxides in Organic Synthesis

Baeyer-Villiger

- Criegee rearrangement of alkoxy-hydroperoxides derived from 1,1-disubstituted olefins



Schreiber *et al. Tetrahedron* **1983**, *24*, 2363

α-Alkoxy Hydroperoxides in Organic Synthesis

Baeyer-Villiger

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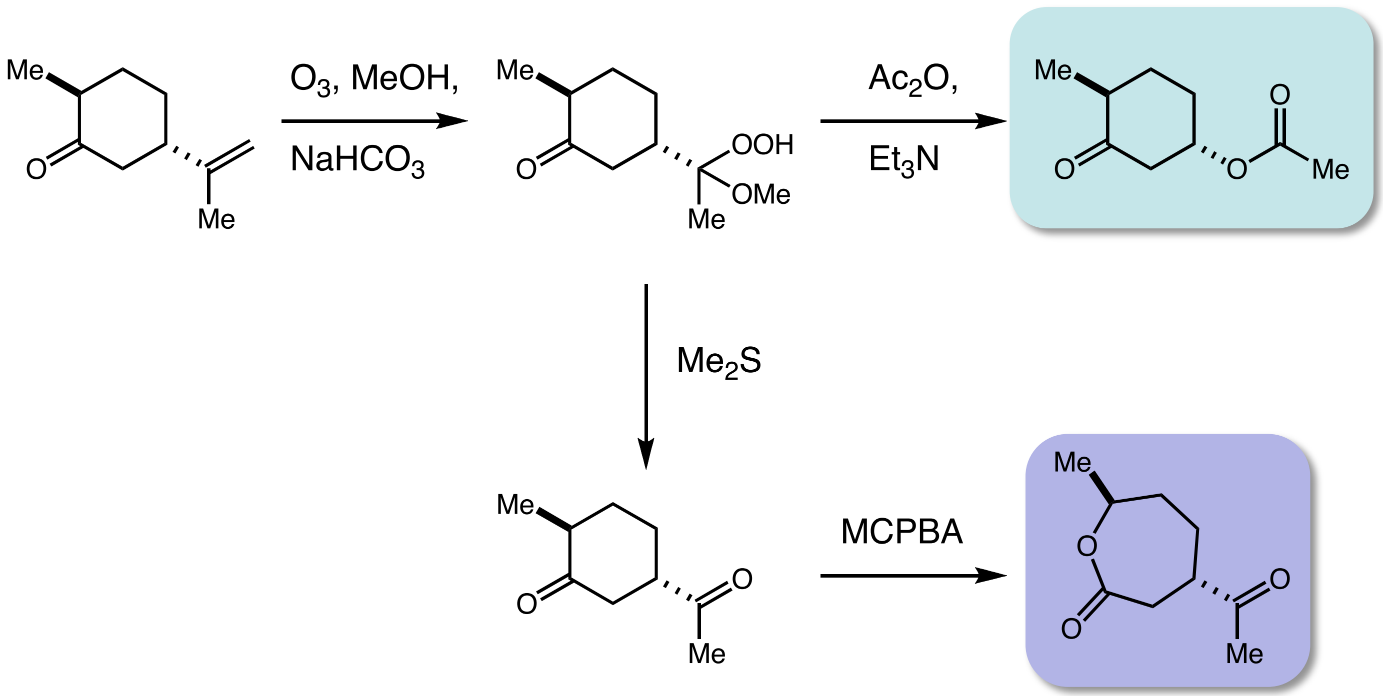
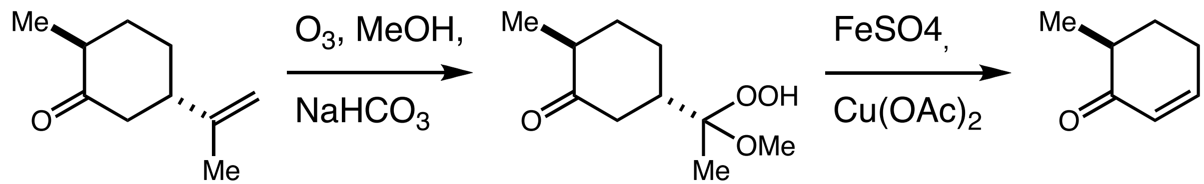


Schreiber *et al.* *Tetrahedron* **1983**, *24*, 2363

α-Alkoxy Hydroperoxides in Organic Synthesis

Iron/Copper mediated peroxide reduction/fragmentation

- Reduction of intermediate alkoxy hydroperoxides generates a highly fragmentable radical species



Schreiber *et al. J. Am. Chem. Soc.* **1980**, *102*, 6163

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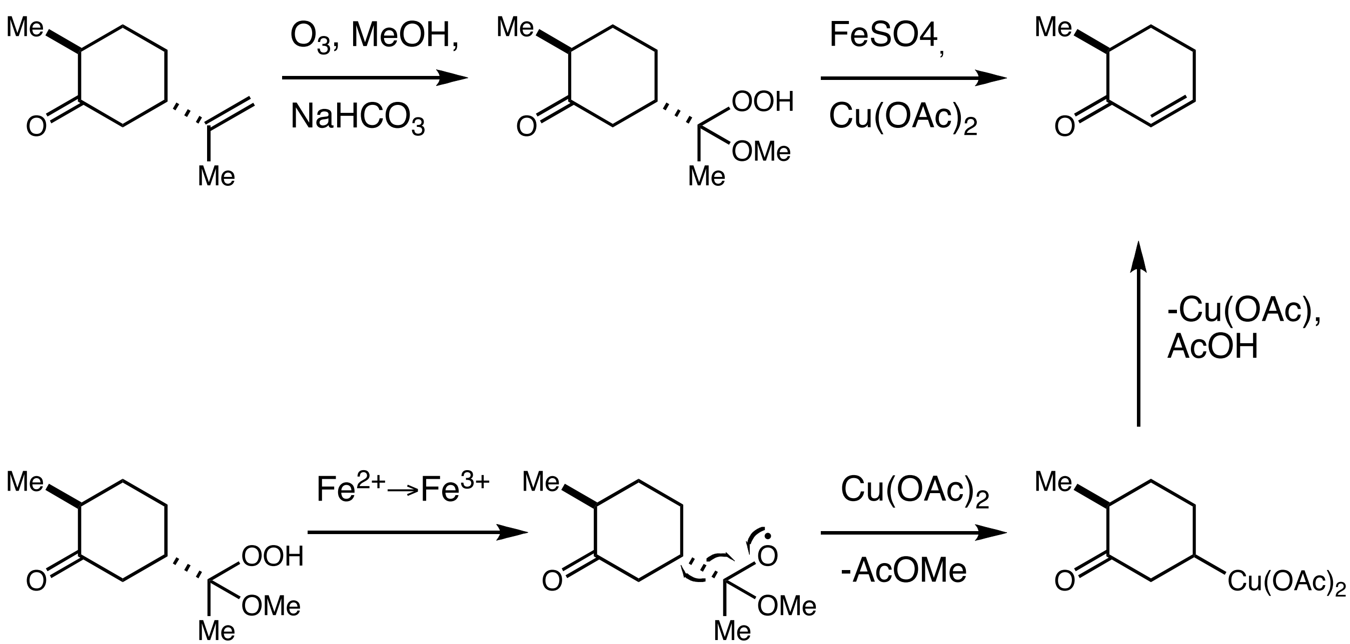
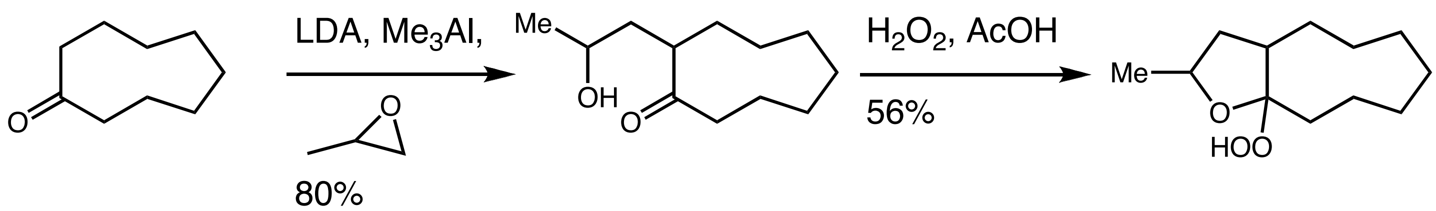


Schreiber *et al. J. Am. Chem. Soc.* **1980**, *102*, 6163

α-Alkoxy Hydroperoxides in Organic Synthesis

Application in macrolide synthesis

- Fragmentation of cyclic alkoxy-hydroperoxides can yield macrocycles



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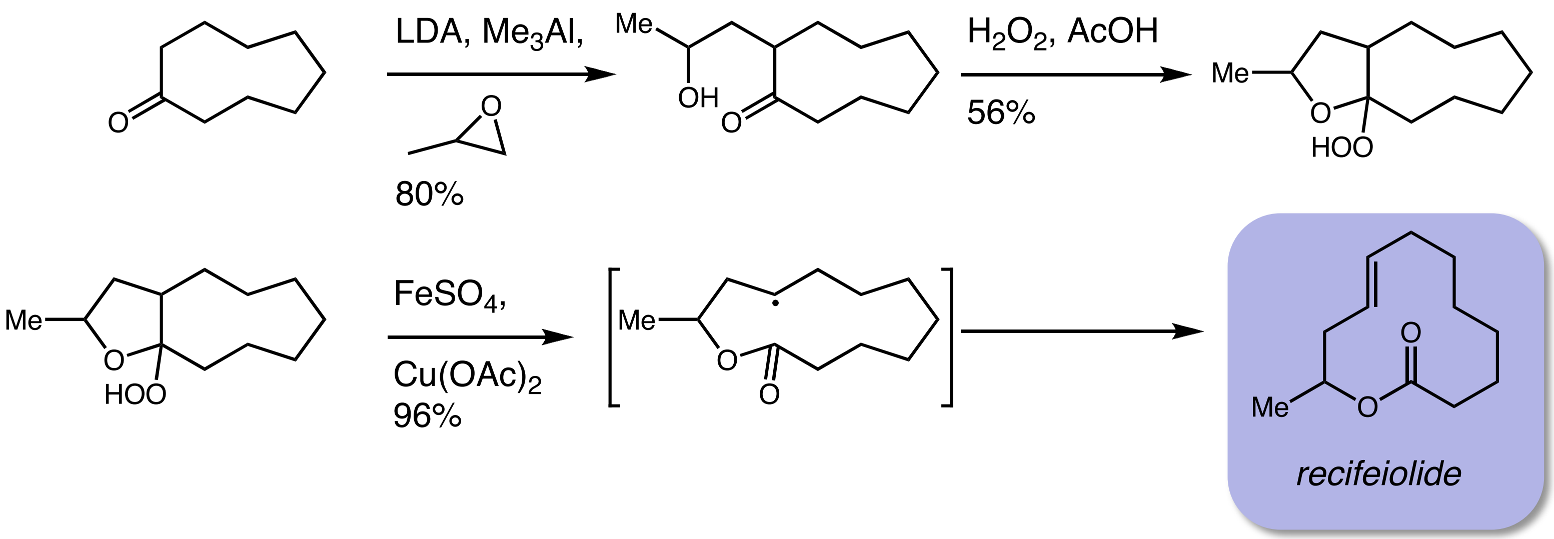
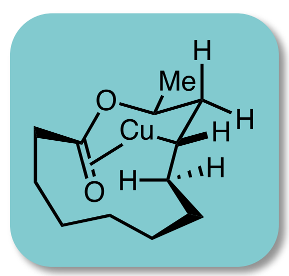


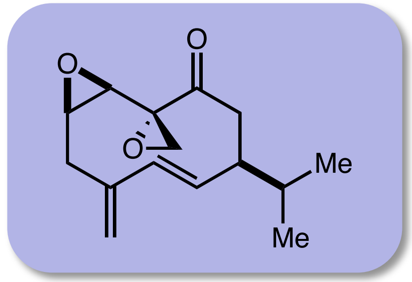
- Single olefin regio- and geometrical olefin isomer observed



Schreiber *et al. J. Am. Chem. Soc.* **1980**, *102*, 6163

[2+2] photocycloaddition reactions in natural product synthesis

Periplanone B



- Cockroach sex pheromone, used by female cockroaches to stimulate males by olfactory communication

- Isolation (<<1µg/insect) achieved by via dissection of 35,000 cockroach alimentary tracts and extraction of midguts, as well as fecal recovery and extraction from an additional 20,000 cockroaches, yielded 200 µg Periplanone B

- First synthesis and relative stereochemistry by W. C. Still in 1979

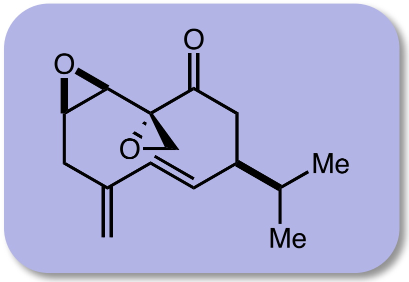
- Cyclodecanone structure containing two epoxides (one spirocyclic), two olefins and an isopropyl substituent

- First step scaleable (10.6g), involves photocycloaddition

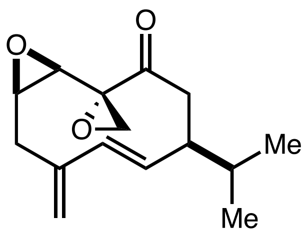
Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038

[2+2] photocycloaddition reactions in natural product synthesis

Periplanone B



- Schreiber plans on utilizing a similar end-game as found in the Still Synthesis



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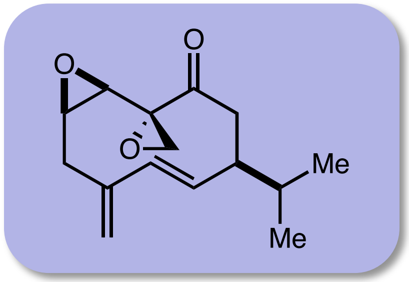

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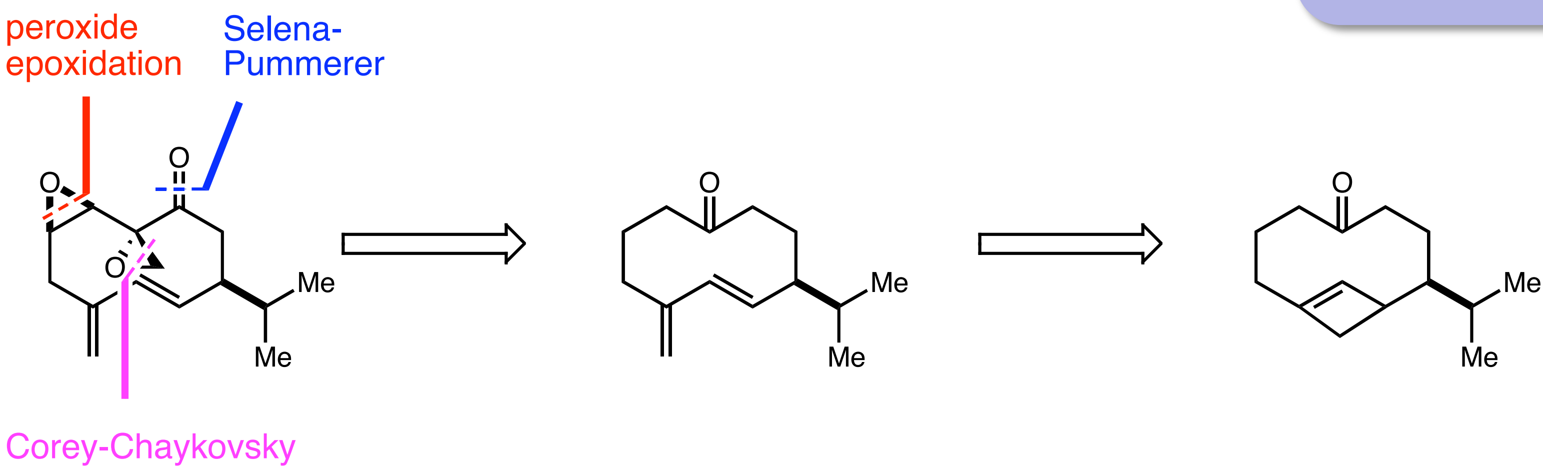

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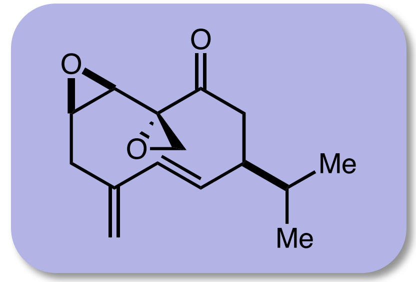
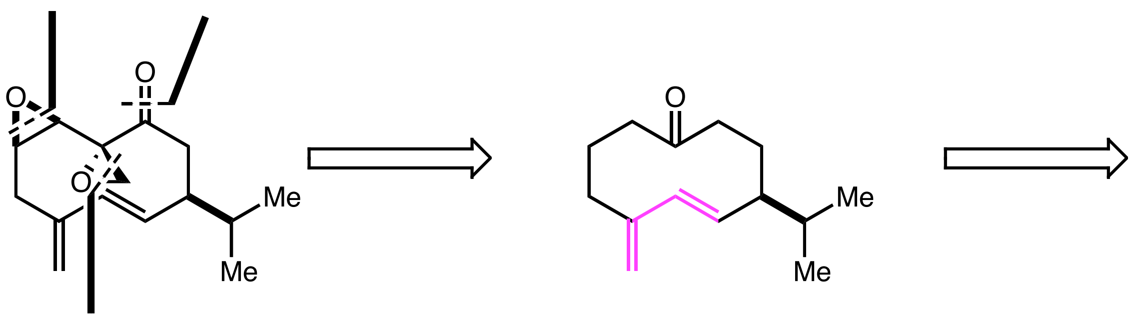
Periplanone B



- A clever synthon for a diene

peroxide epoxidation

Selena-Pummerer



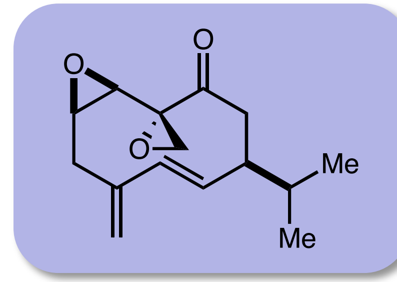
Corey-Chaykovsky

electrocyclic ring opening
olefin photoisomerization

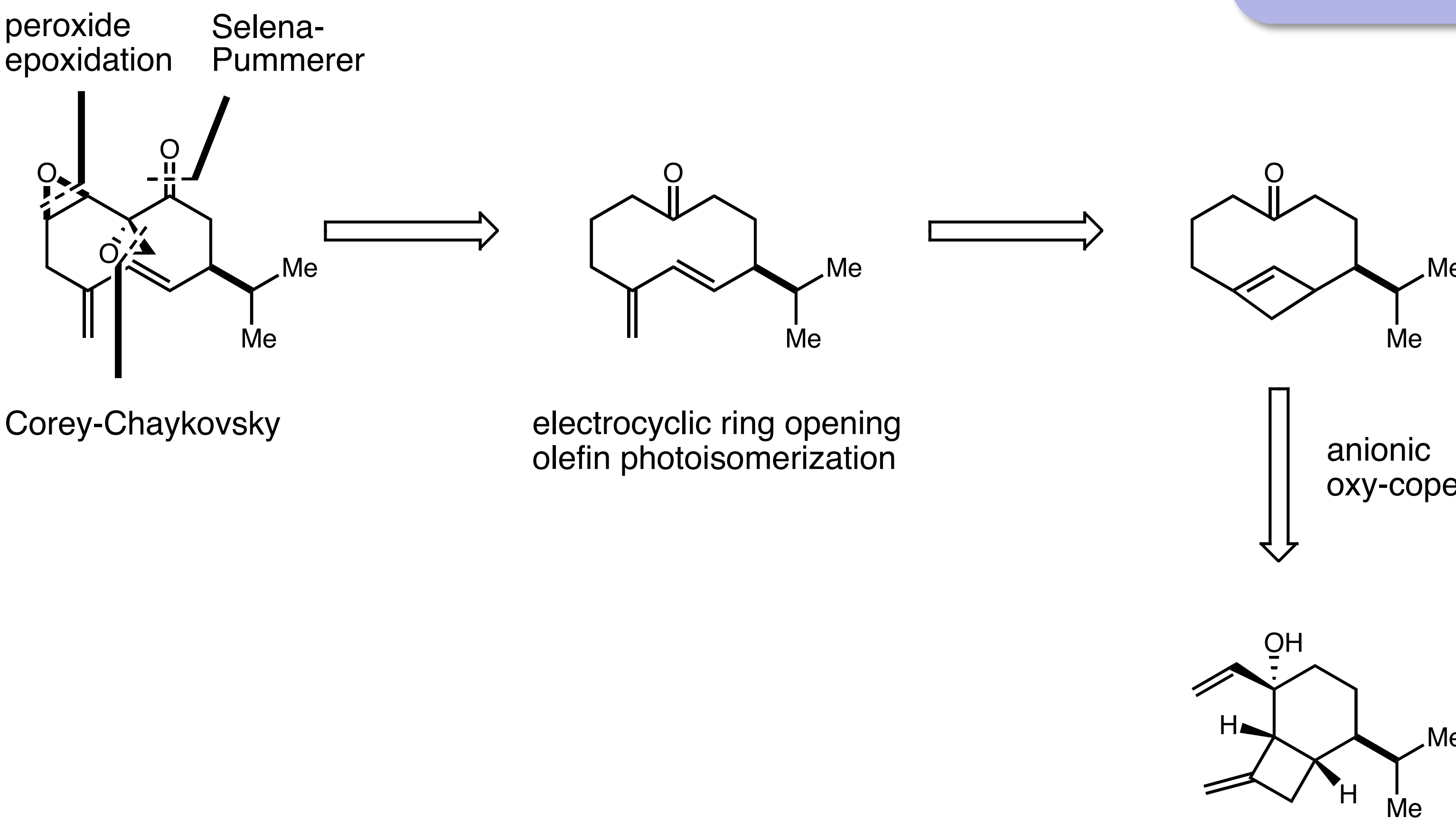
Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038

[2+2] photocycloaddition reactions in natural product synthesis

Periplanone B



- The now-classical method for forming cyclodecanes, with a twist



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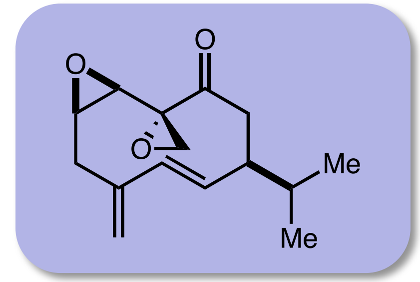
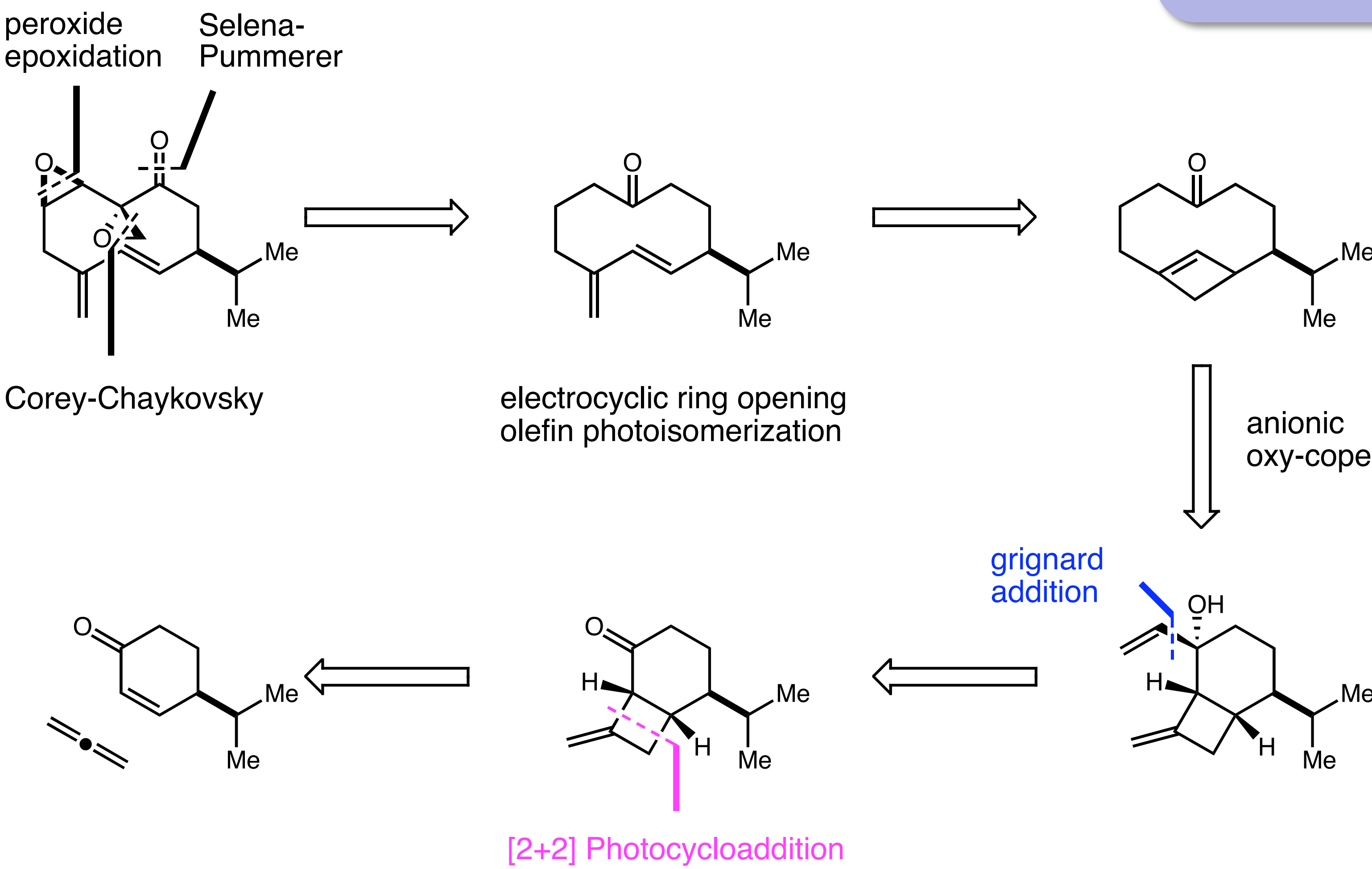
[2+2] photocycloaddition reactions in natural product synthesis

Periplanone B



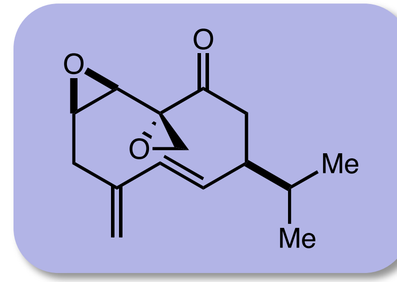
- [2+2] photocycloaddition to start things off



Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038

[2+2] photocycloaddition reactions in natural product synthesis

Periplanone B



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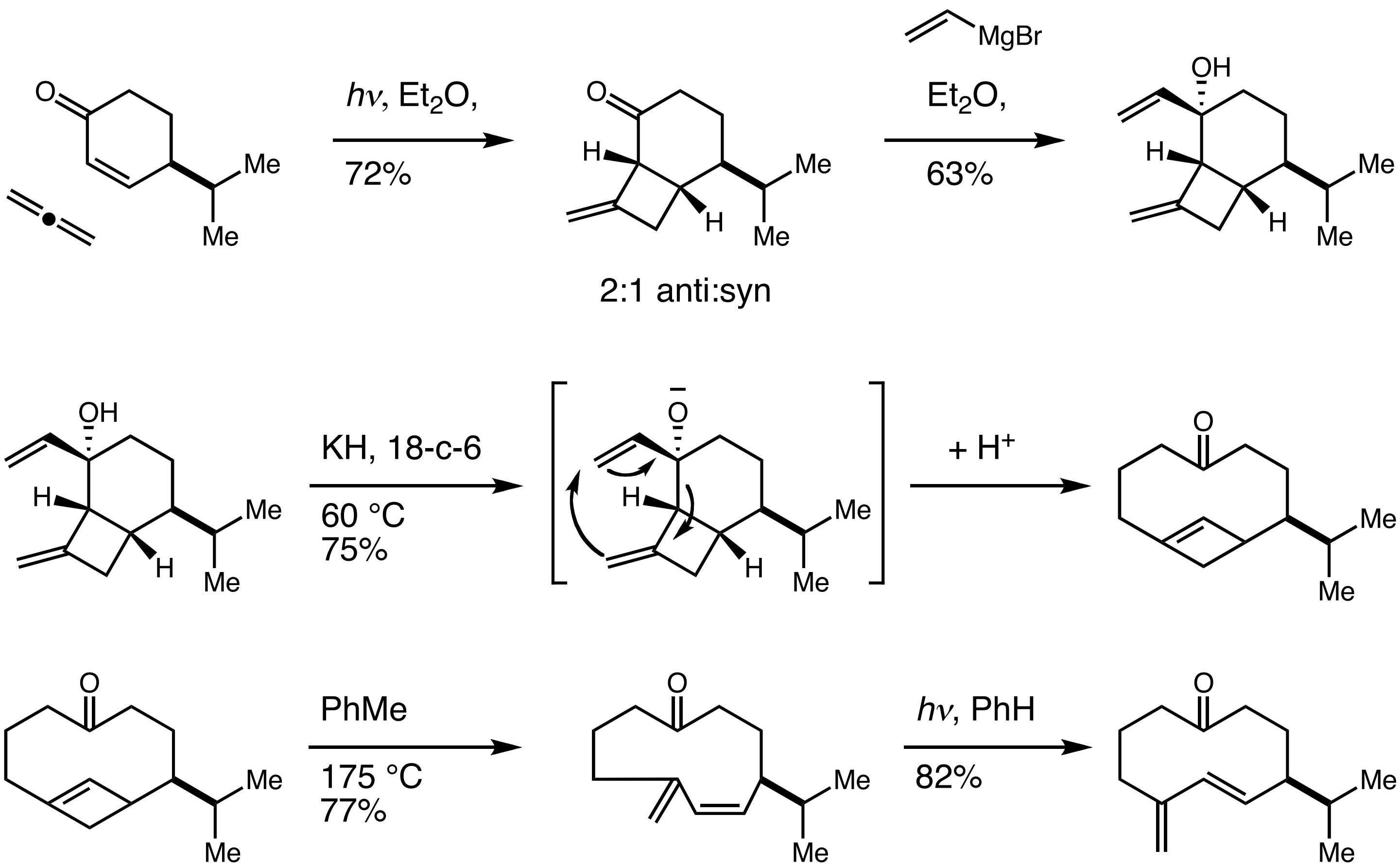
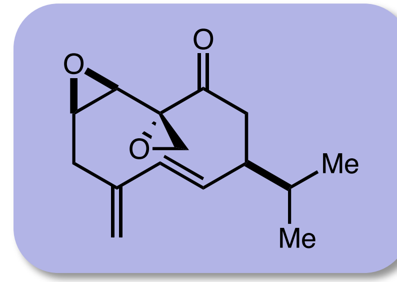


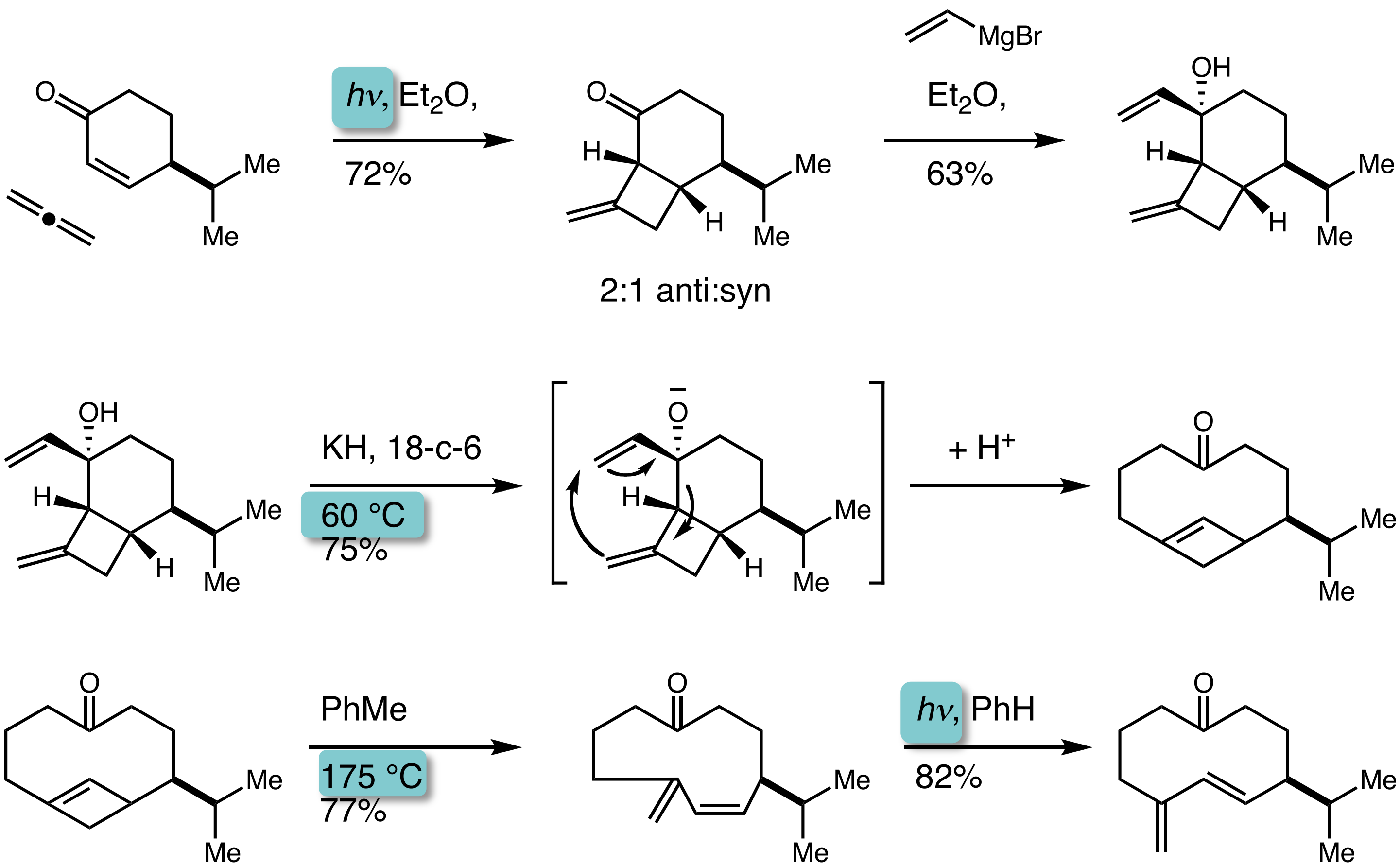
Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038

[2+2] photocycloaddition reactions in natural product synthesis

Periplanone B



- Heat and light play a commanding role in Schreiber's early steps



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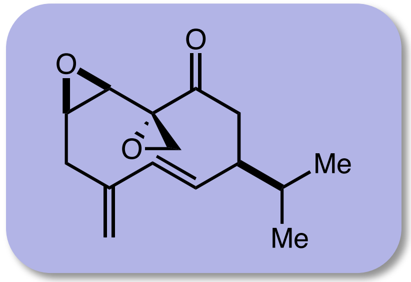
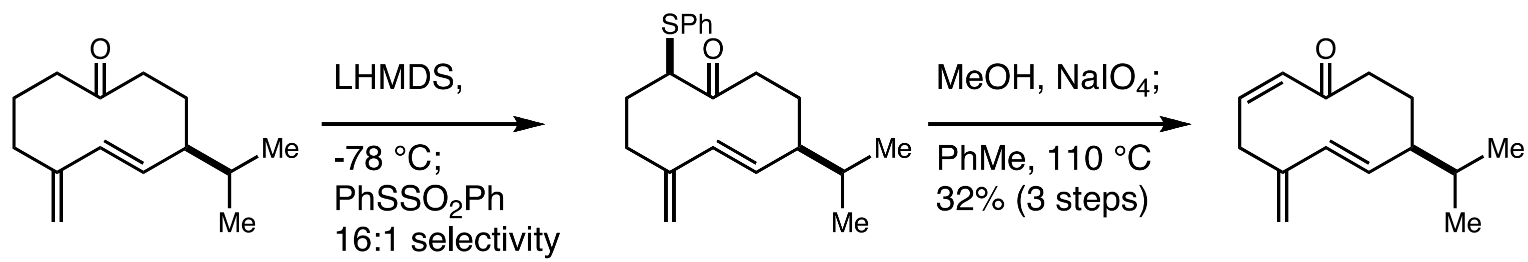
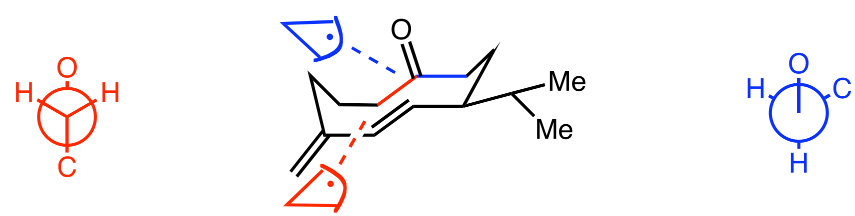


- Selective enolization/trapping allows desired olefin installation





Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038

[2+2] photocycloaddition reactions in natural product synthesis

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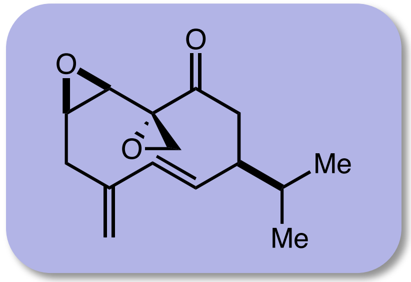
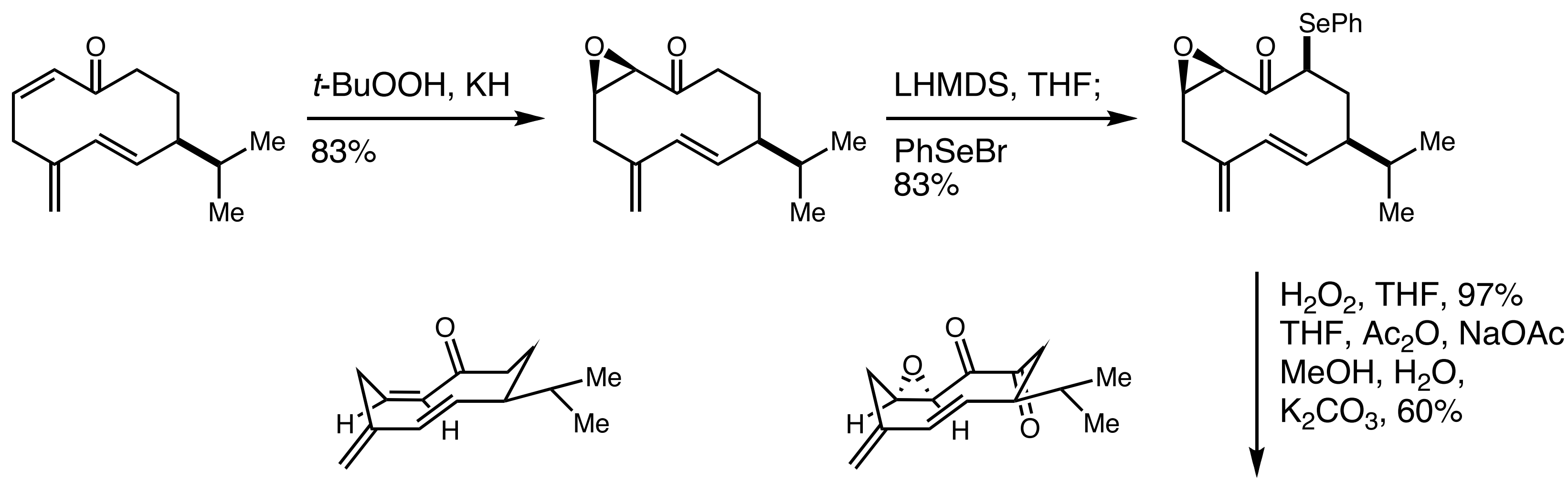
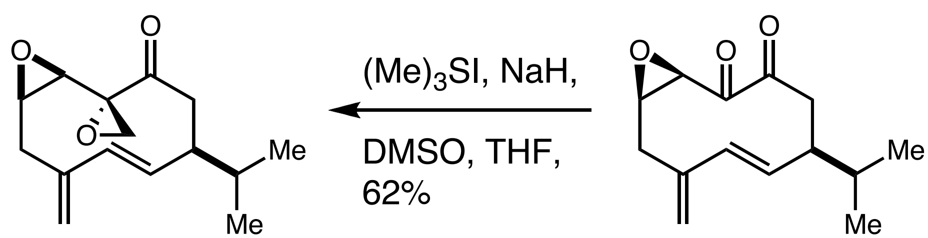


- A series of oxidations (utilizing peripheral attack) installs the remaining functionality



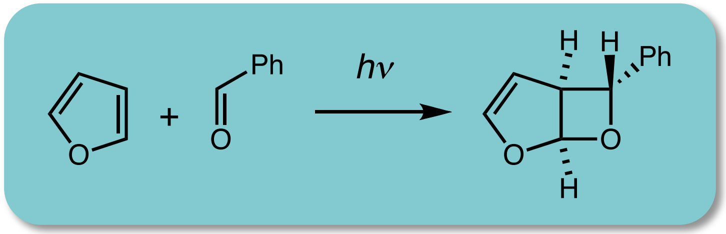
- Synthesis is completed in 13 steps, 2% yield



Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4038

[2+2] photocycloaddition reactions in natural product synthesis

Furan-aldehyde photocycloaddition, "photoaldol"



- Paterno-Büchi reaction between a furan and an aldehyde proceeds with good head-to-head and *exo-* selectivity

- Products serve as protected *threo* aldol products between a 1,4-dicarbonyl and an aldehyde

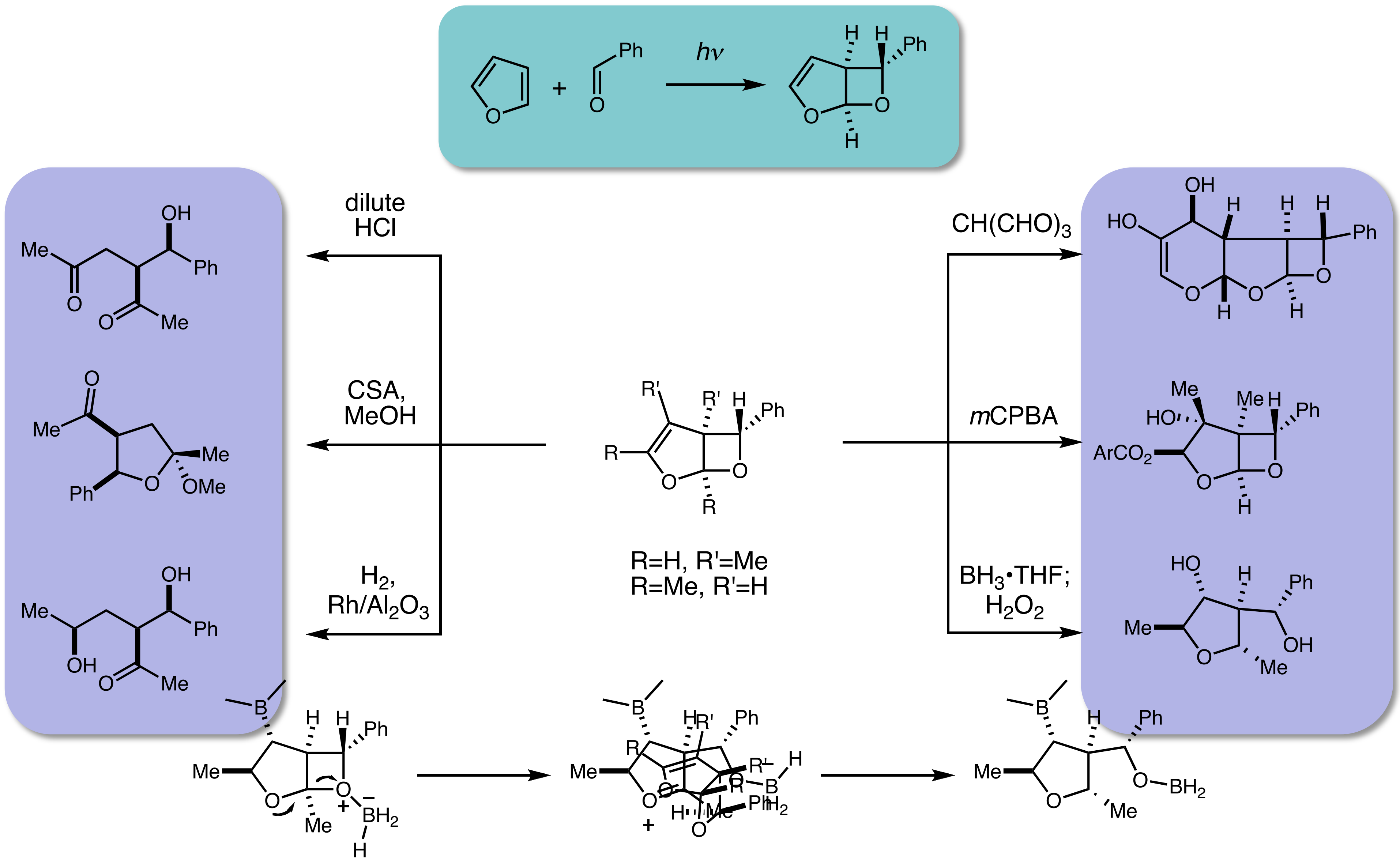
- Unfortunately, only symmetrically substituted furans are serviceable; Unsymmetrically subsituted ones proceed with low chemoselectivity

- Products serve as protected *threo* aldol products between a 1,4-dicarbonyl and an aldehyde

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 660

[2+2] photocycloaddition reactions in natural product synthesis

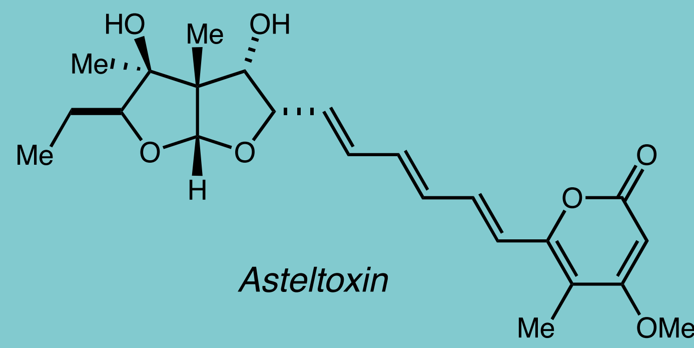
Furan-aldehyde photocycloaddition, “photoaldol”



Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 660

[2+2] photocycloaddition reactions in natural product synthesis

Asteltoxin



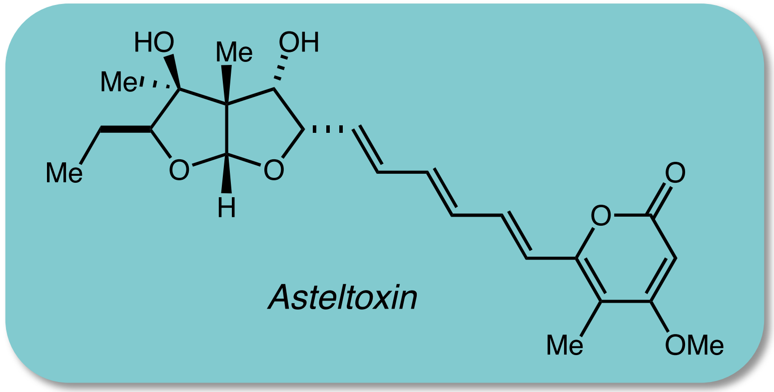
Asteltoxin

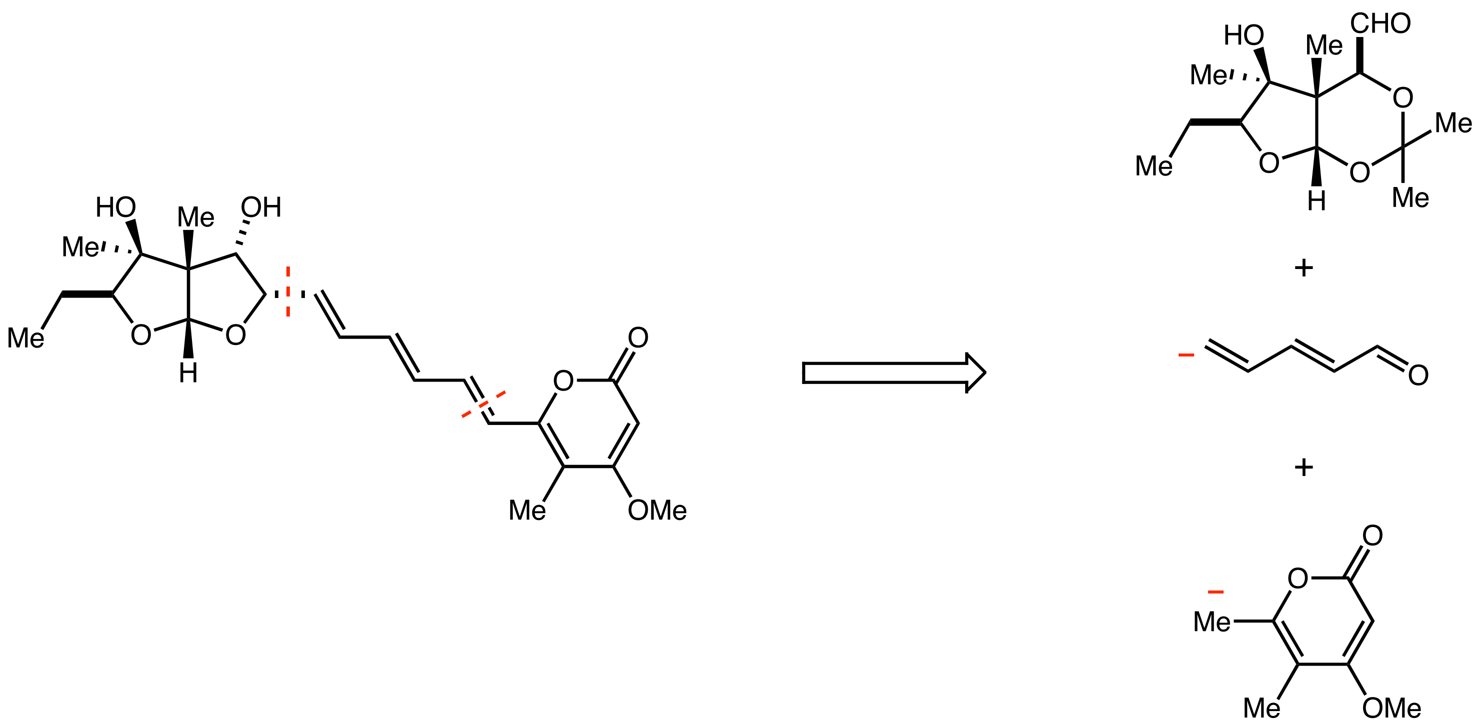
- Stereochemically complex bis-tetrahydrofuran region connection by an all-trans triene linker to a pyrone region
- Inhibitor of oxidative phosphorylation, serves as a fluorescent probe of mitochondrial F_1- and bacterial BF_1-ATPase
- No total synthesis prior to 1984
- Relative stereochemistry (and vicinal methyl groups) lends to construction via furan-aldehyde Paterno-Büchi

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

Asteltoxin

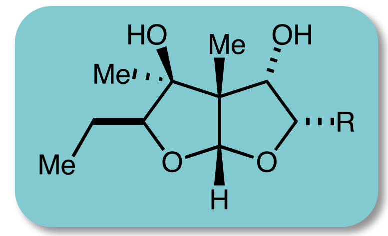


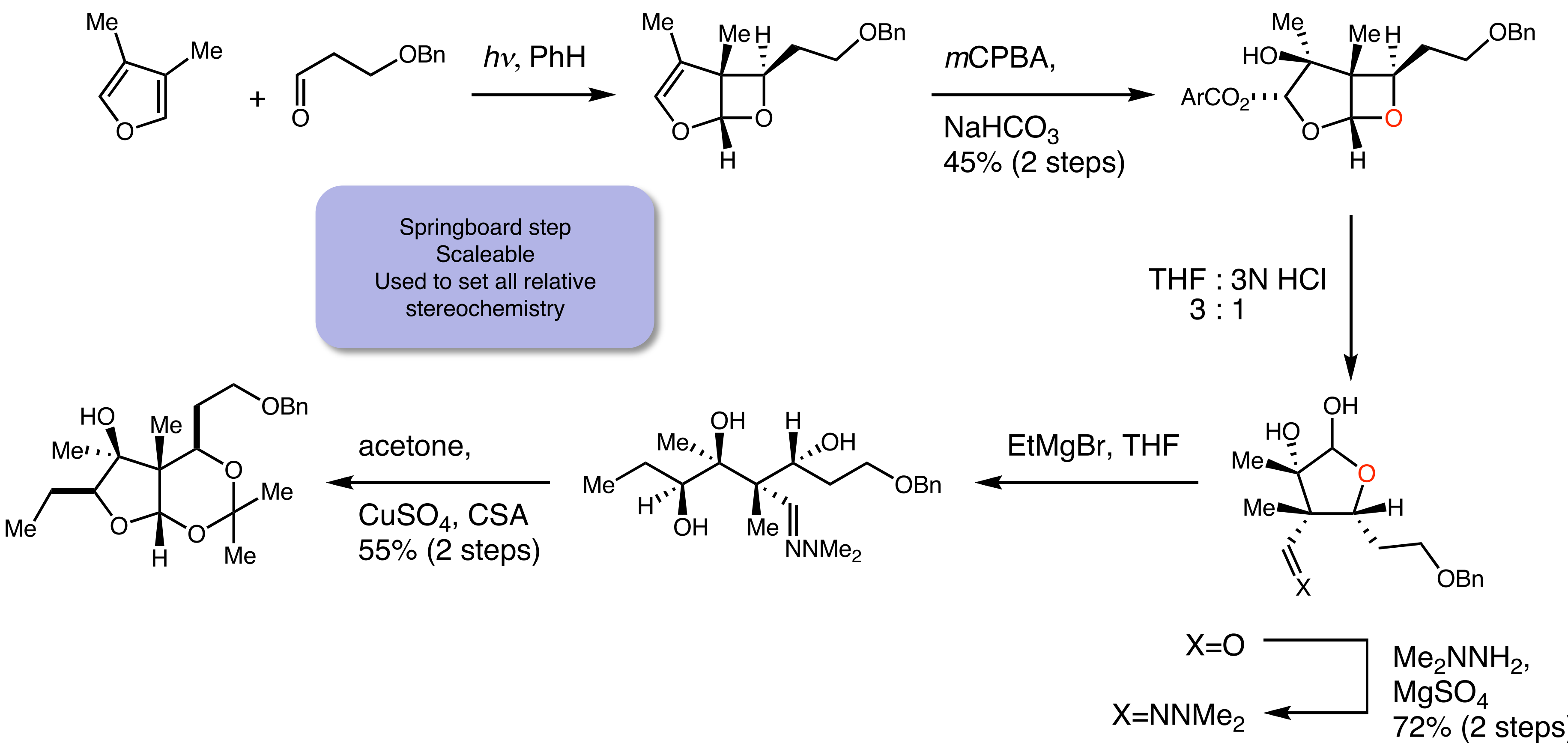


Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

Asteltoxin





Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

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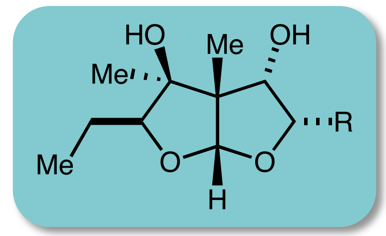

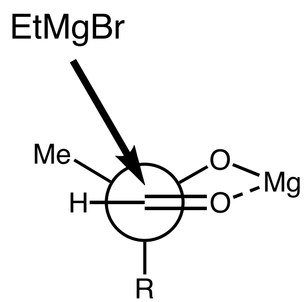

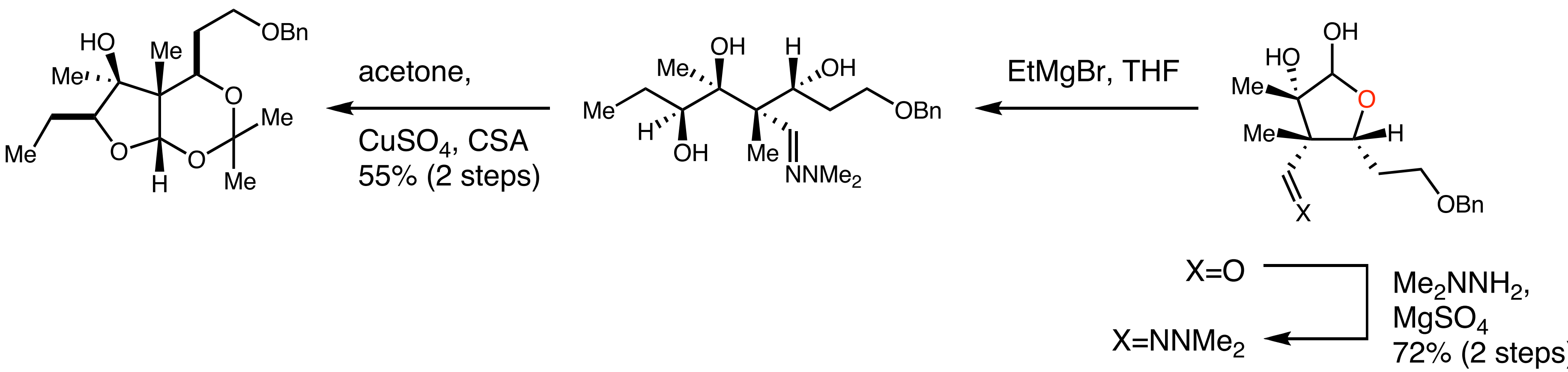

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

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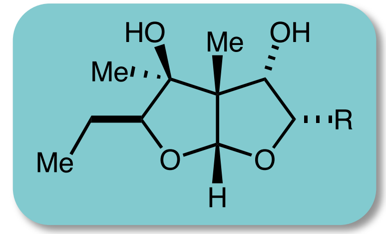

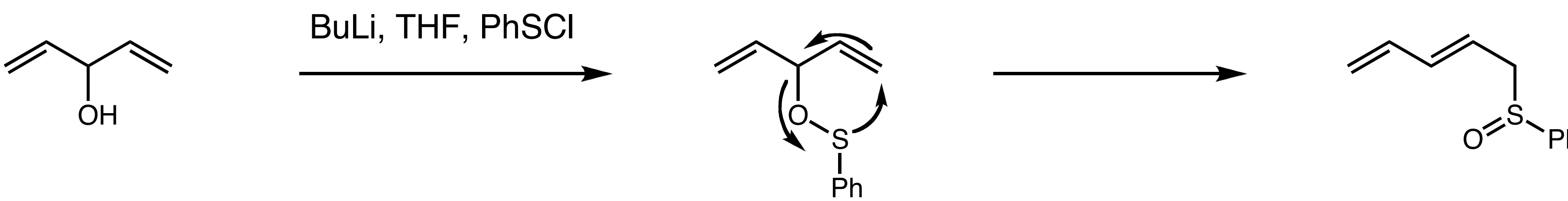

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al*. *J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

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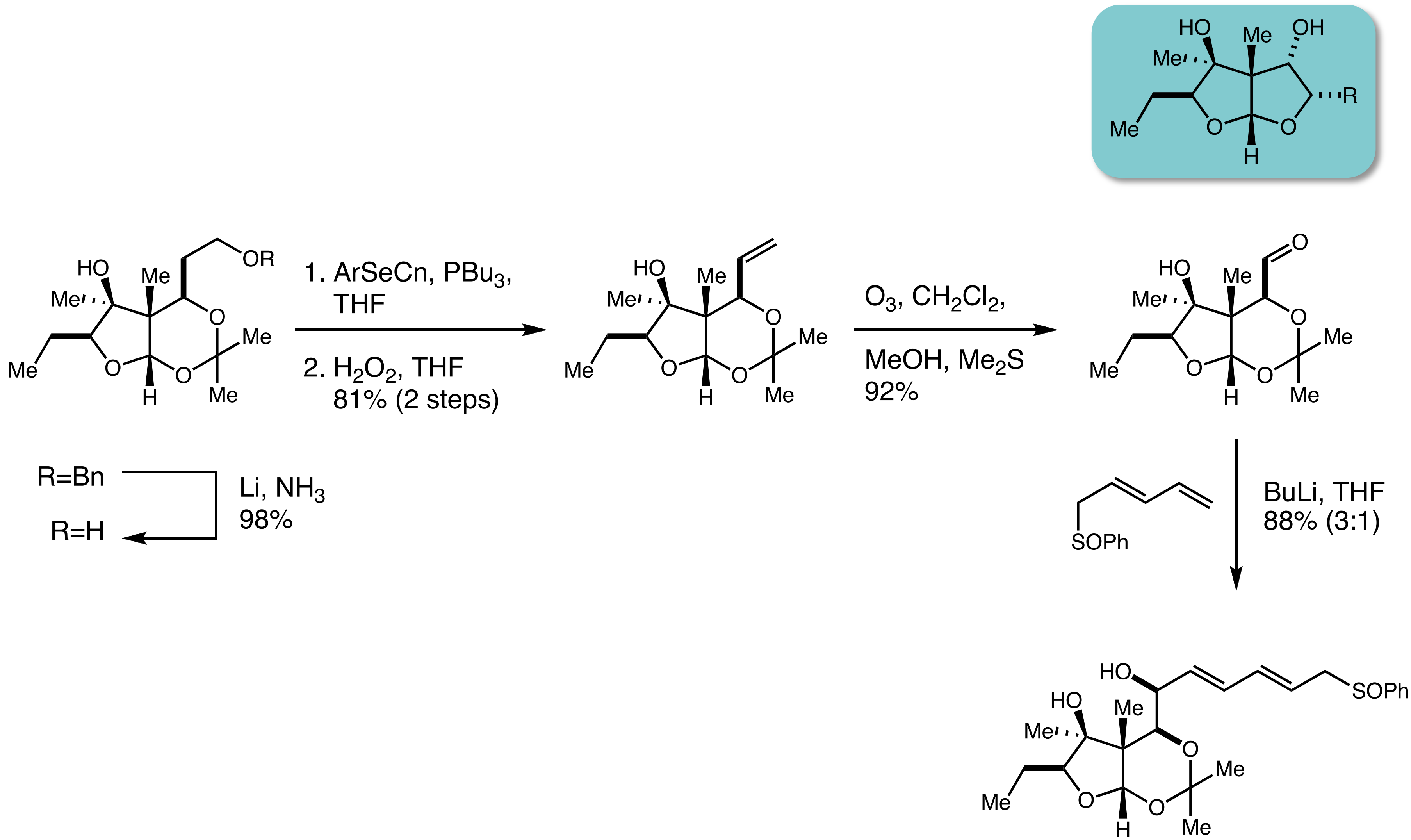

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[2+2] photocycloaddition reactions in natural product synthesis

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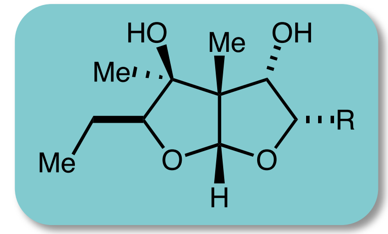

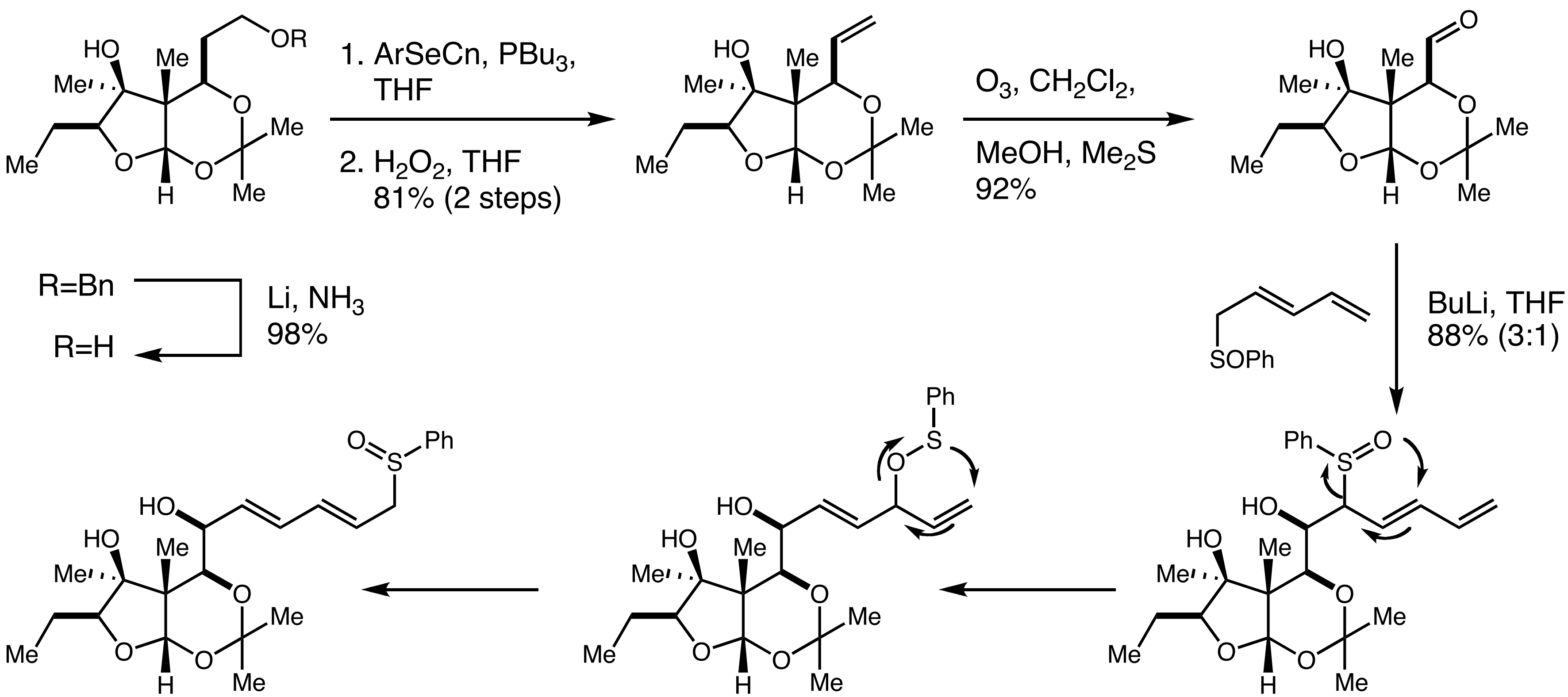

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

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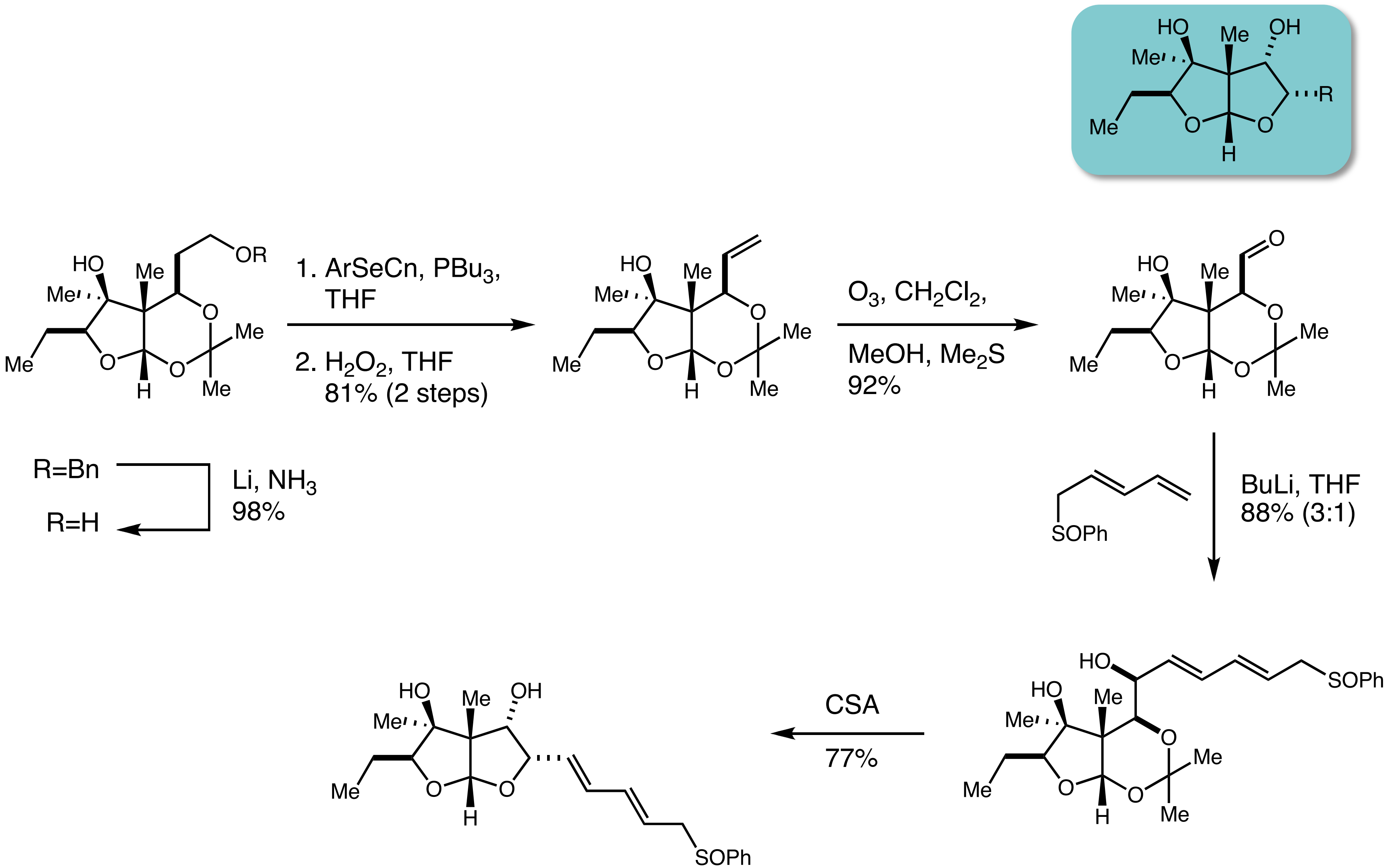

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

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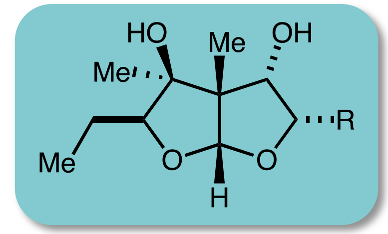

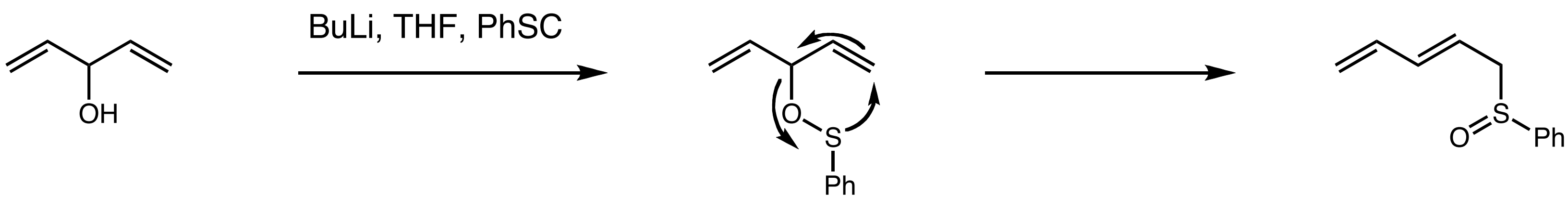

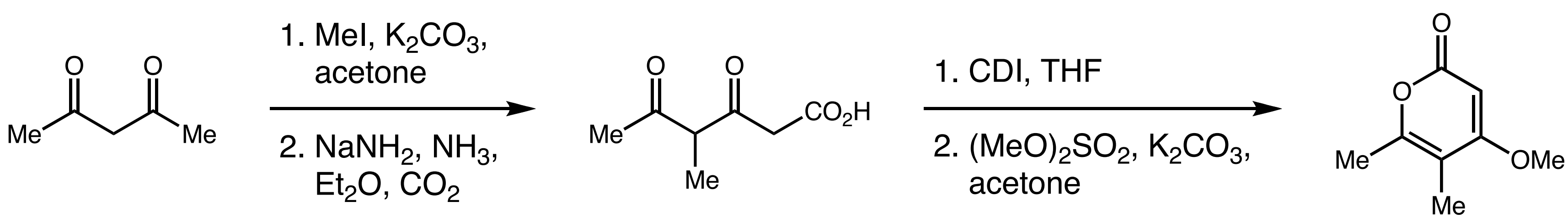

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al. J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

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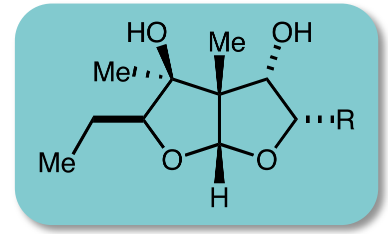

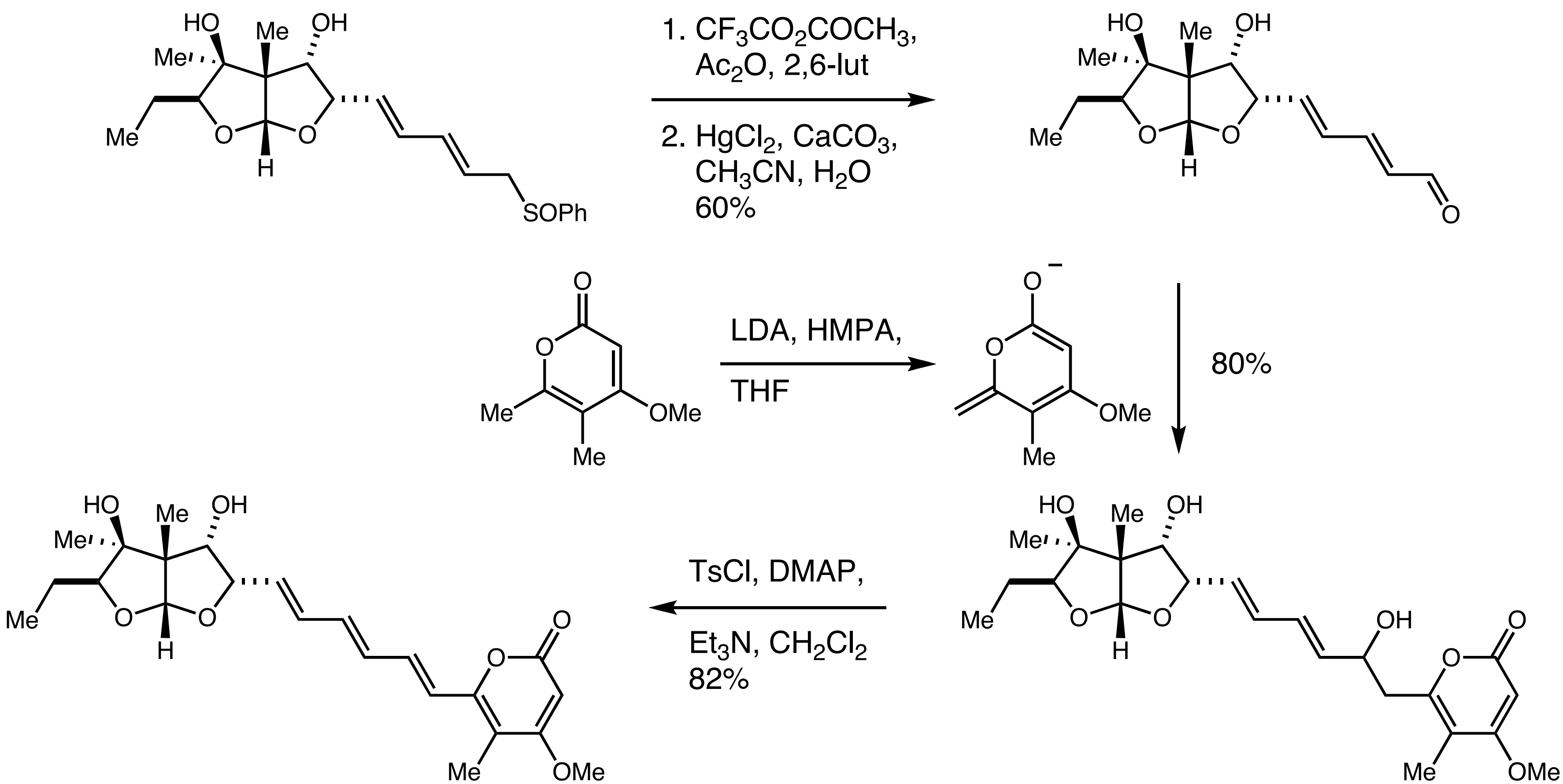

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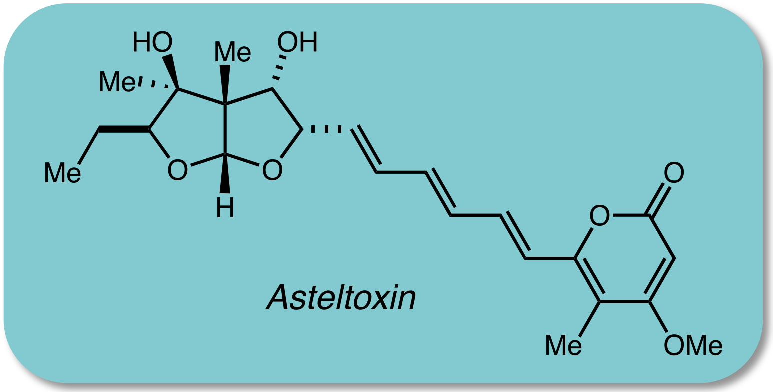


- Synthesis completed in 16 steps, 4% overall yield

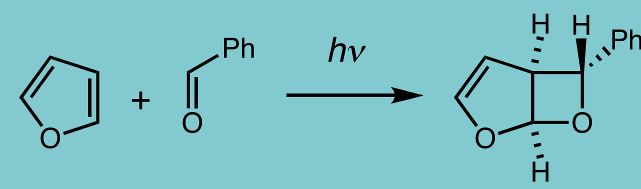
- Key steps include a furan-aldehyde Paterno-Büchi, several diastereoselective additions to aldehydes, and an addition/double 2,3-rearrangement to give net dienal addition

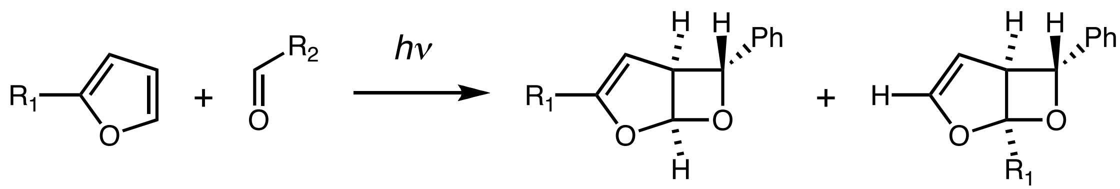
- Symmetrically substituted furan partner a necessary retrosynthetic fragment

Schreiber *et al. J. Am. Chem. Soc.* **1983**, *105*, 6723 and Schreiber *et al*. *J. Am. Chem. Soc.* **1984**, *106*, 4186

[2+2] photocycloaddition reactions in natural product synthesis

Unsymmetrically substituted furan partners



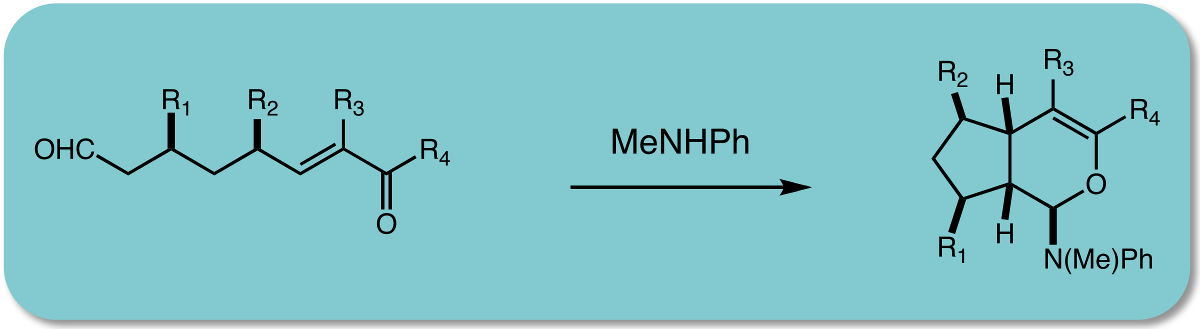


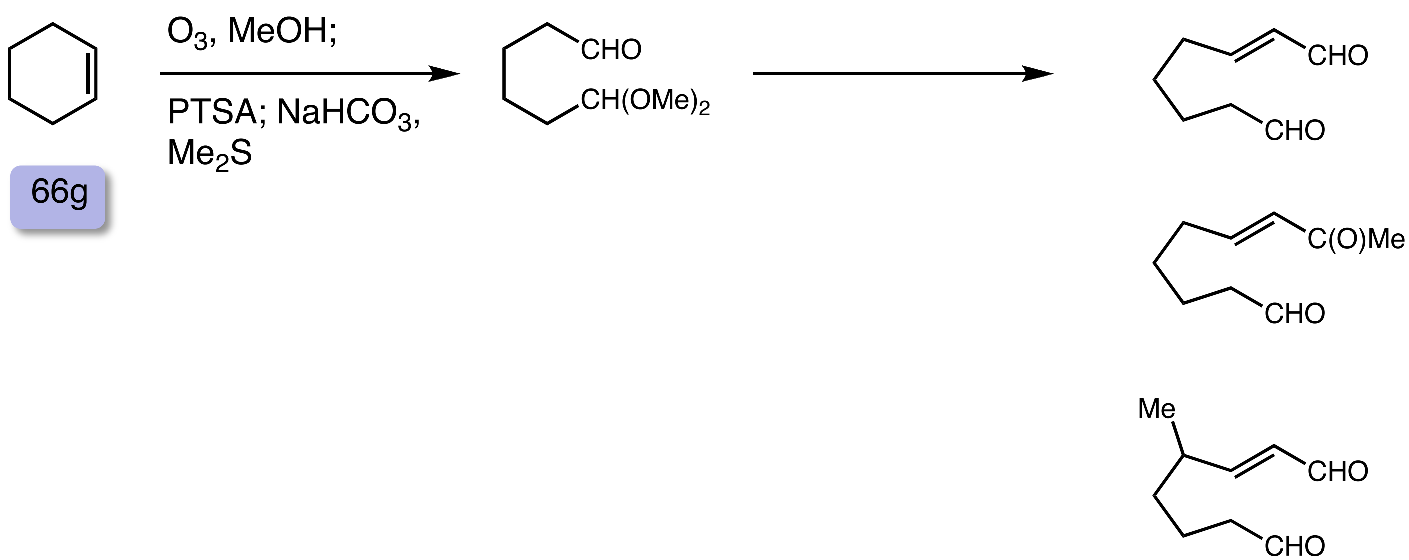
$R_1 = SiMe_3$	1.2	:	1	
$R_1 = Si\textit{i}\text{-}Pr_3$	20	:	1	
$R_1 = SnBu_3$	2.5	:	1	
$R_1 = SnBu_3$	20	:	1	(CO_2Bu instead of Ph)

Schreiber *et al. Tetrahedron Letters.* **1988**, *29*, 6689

Verging on enamine catalysis

Diastereoselective enal/enone intramolecular 4+2



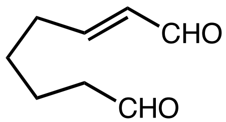
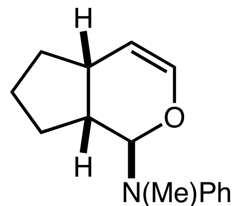
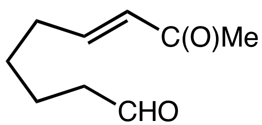
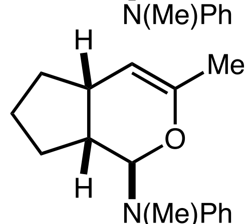
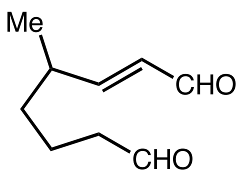
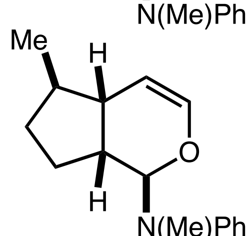
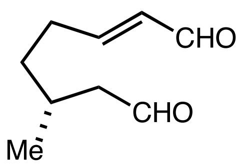
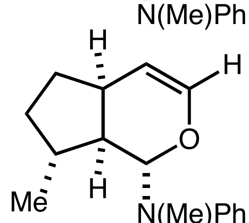
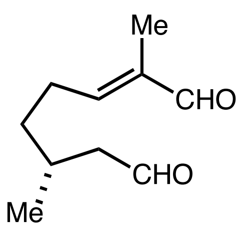
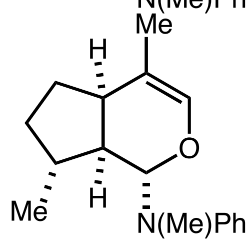


66g

Schreiber *et al. J. Am. Chem. Soc.* **1986**, *108*, 8274 and Schreiber *et al. J. Am. Chem. Soc.* **1988**, *110*, 5198

Verging on enamine catalysis

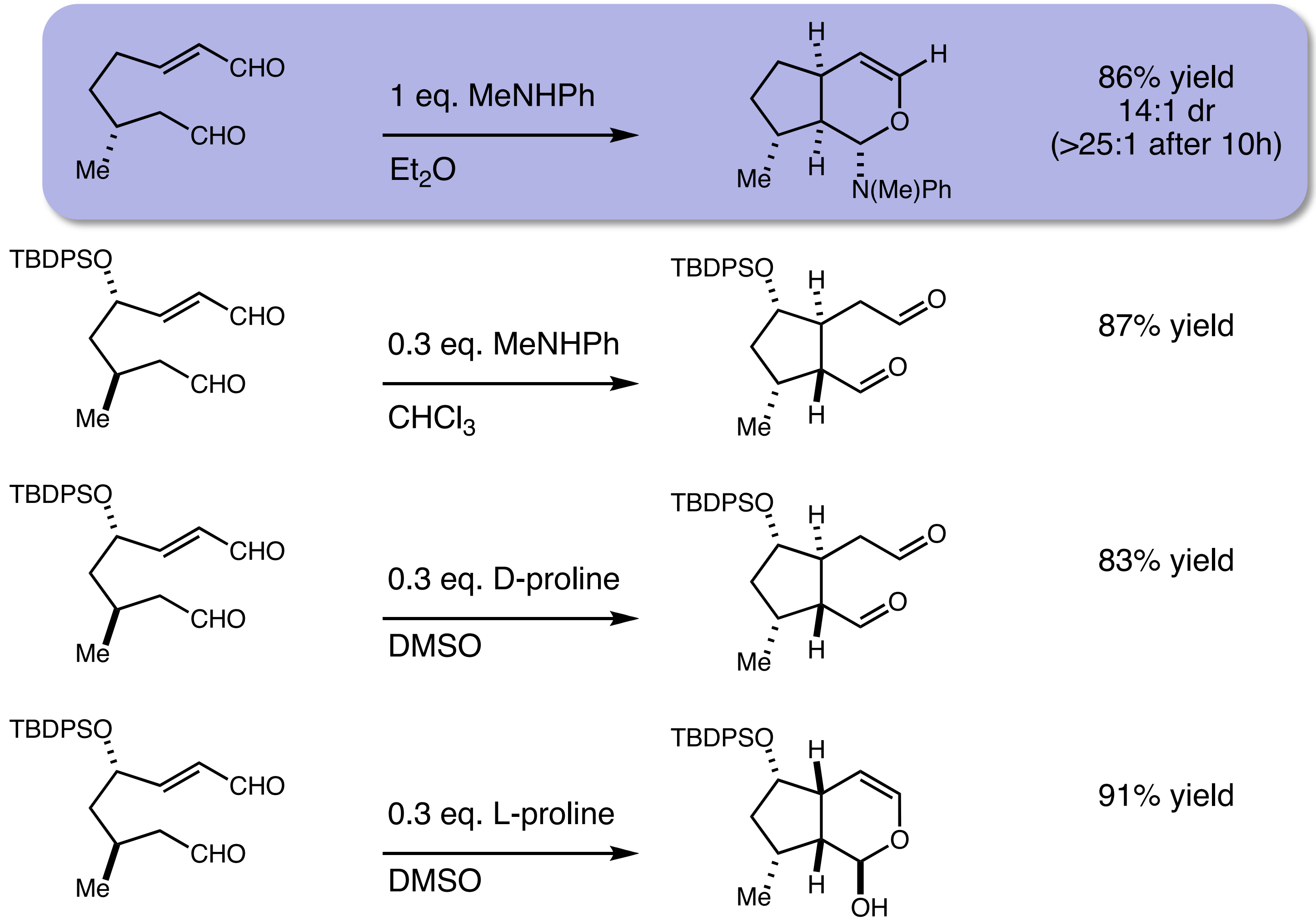
Diastereoselective enal/enone intramolecular 4+2

Starting material	product	yield	d.r.
		73	>25:1
		60	>25:1
		60	4:1 (>25:1 after 10h)
		86	14:1 (>25:1 after 10h)
		84	10:1 (>25:1 after 10h)

Schreiber *et al. J. Am. Chem. Soc.* **1986**, *108*, 8274 and Schreiber *et al*. *J. Am. Chem. Soc.* **1988**, *110*, 5198

Verging on enamine catalysis

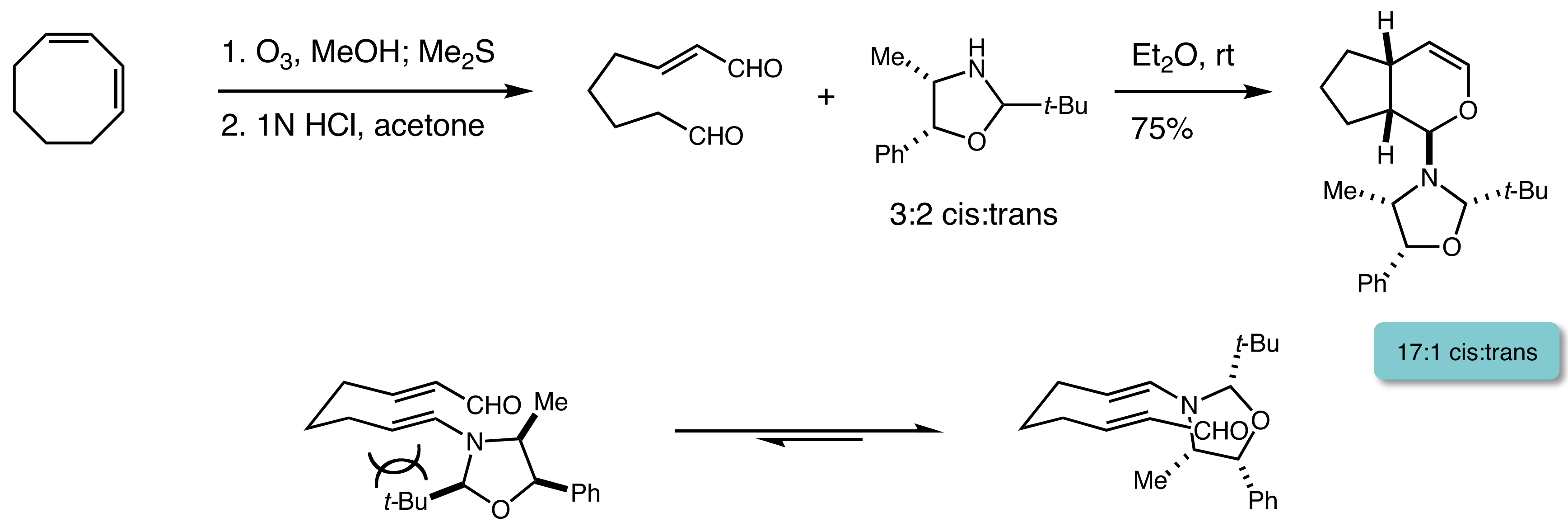
Comparison with more recent studies



Schreiber *et al. J. Am. Chem. Soc.* **1988**, *110*, 5198 and MacMillan *et al. J. Am. Chem. Soc.* **2005**, *127*, 3696

Verging on enamine catalysis

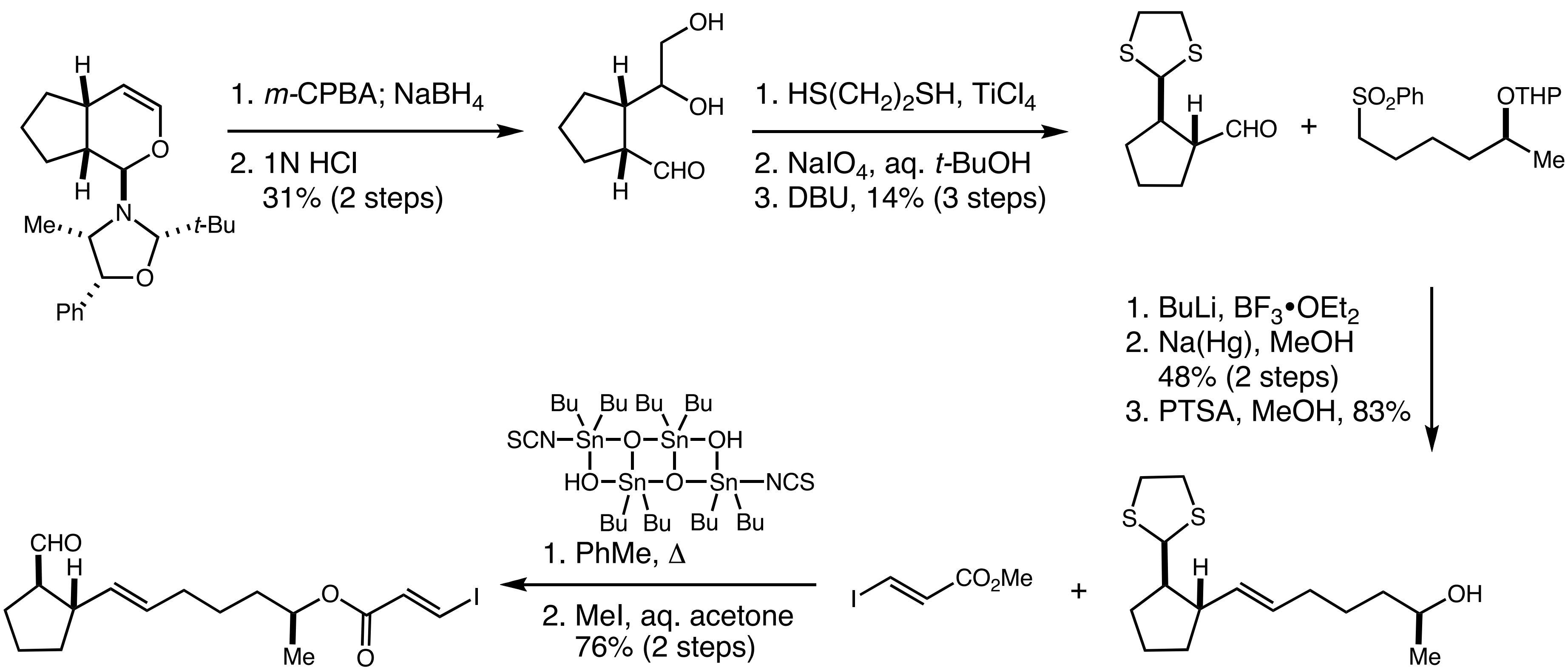
Induction of asymmetry



Schreiber *et al. J. Am. Chem. Soc.* **1988**, *110*, 5198

Verging on enamine catalysis

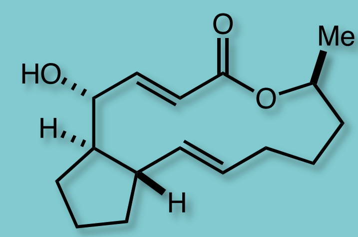
Synthesis of Brefeldin C



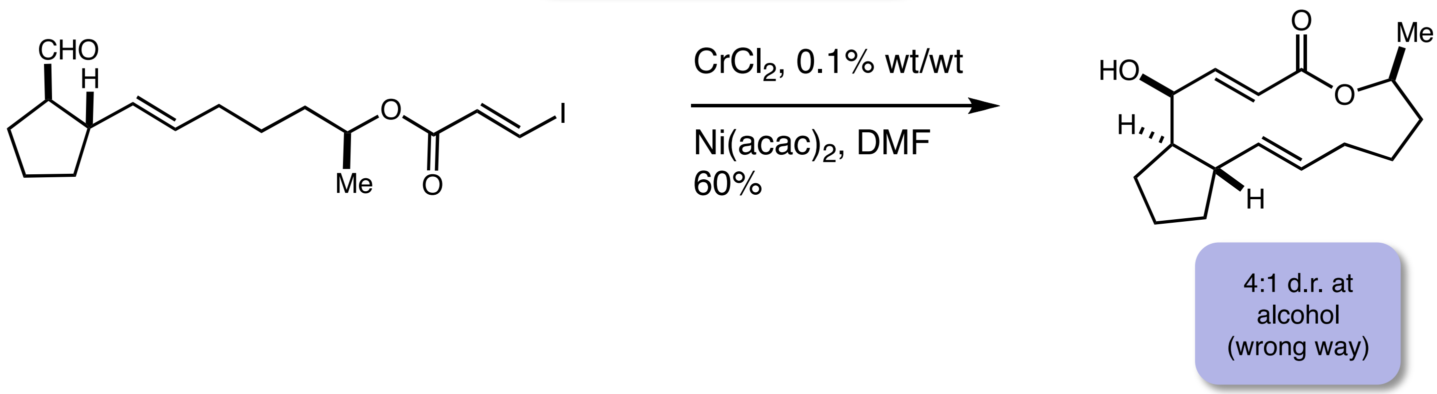
Schreiber *et al. J. Am. Chem. Soc.* **1988**, *110*, 5198

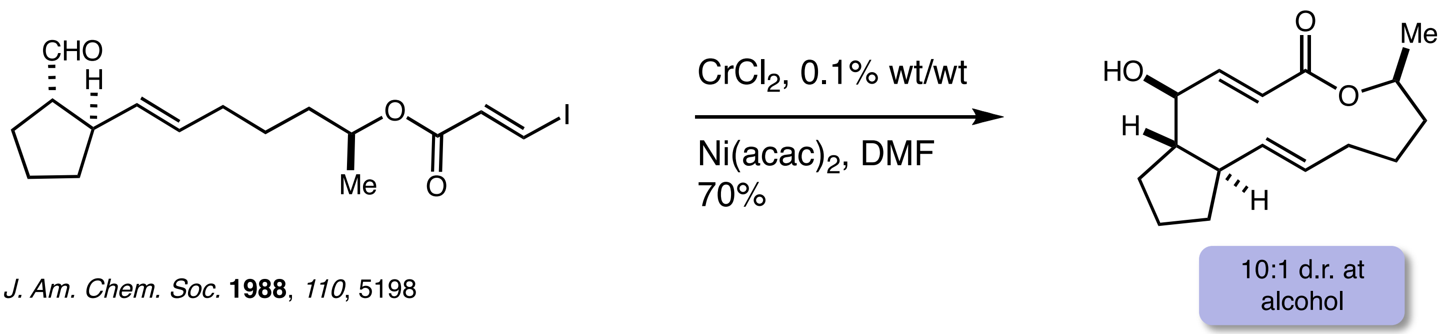
Verging on enamine catalysis

Synthesis of Brefeldin C



Brefeldin C





Schreiber *et al. J. Am. Chem. Soc.* **1988**, *110*, 5198

Stay tuned for part II: Stuart Schreiber, biologist

- Stuart Schreiber worked alongside the best in the field during the 1980s

- His synthetic work continued into the 1990s, though his focus switched mostly to biology

- His synthetic work continues today, but is focused on the synthesis of small molecules of biological interest