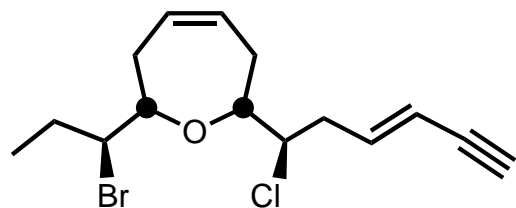


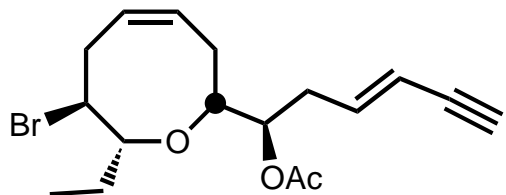
# Approaches to the Synthesis of Medium Ring Ethers

## Contents

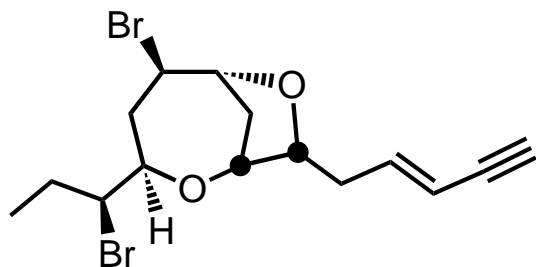
- Introduction to Medium Ring Synthesis
- Cyclization by C-O Bond Formation
- Cyclization by C-C Bond Formation
- Rearrangement Reactions
- Ring Expansion Reactions
- Modification of Lactones



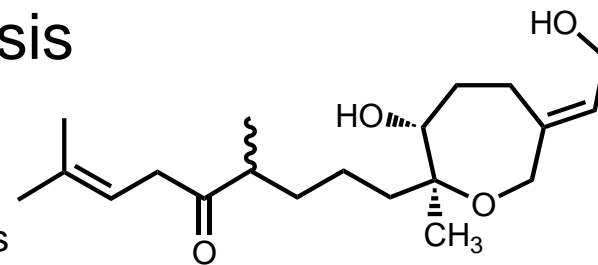
Isolaurepinnacin



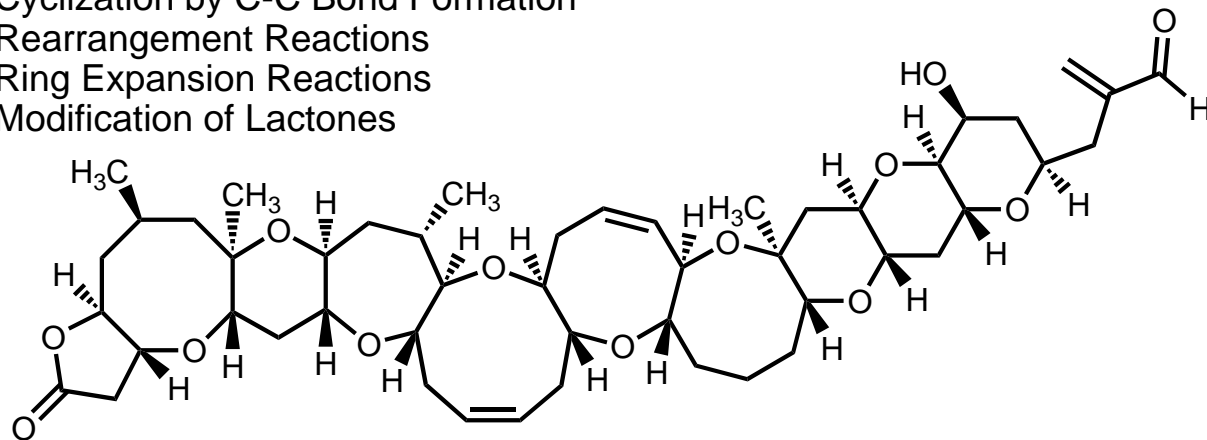
Laurencin



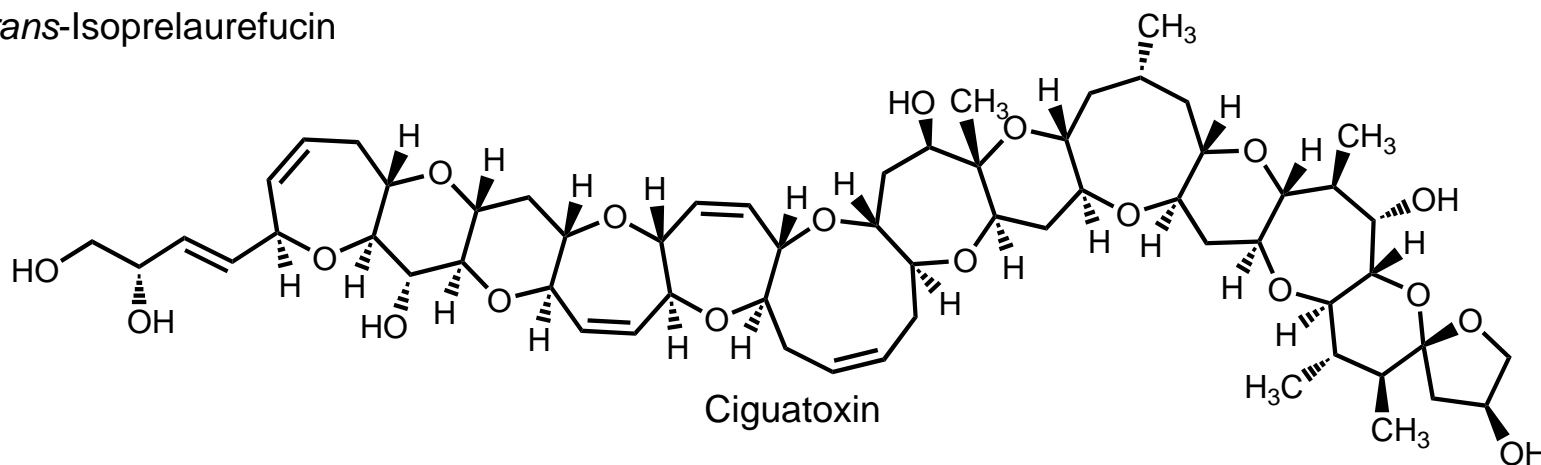
*trans*-Isoprelaurefucin



Zoapantanol



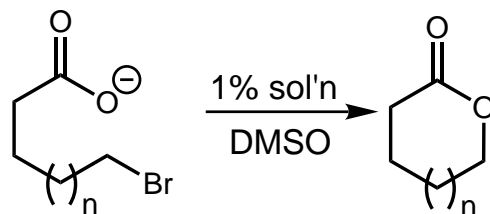
Brevetoxin A



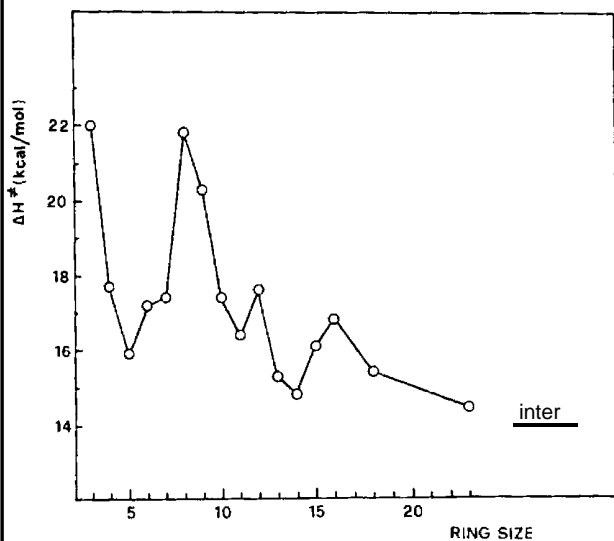
Ciguatoxin

Brian Connell  
Evans Group Seminar  
3/13/98

## The Problem of Medium Ring Synthesis Energetics of Ring Closure Reactions



### $\Delta H^\ddagger$ of Cyclization



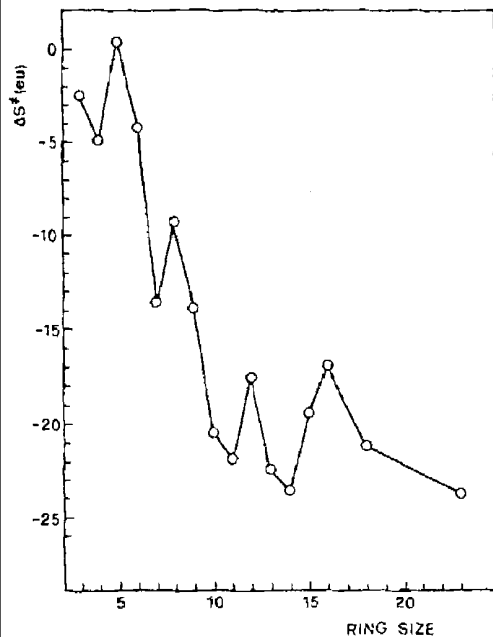
• an indicator of ring strain

Sources of Strain:

- 1) Imperfect staggering (Pitzer)
- 2) Deformation of bond <'s (Baeyer)
- 3) Transannular strain

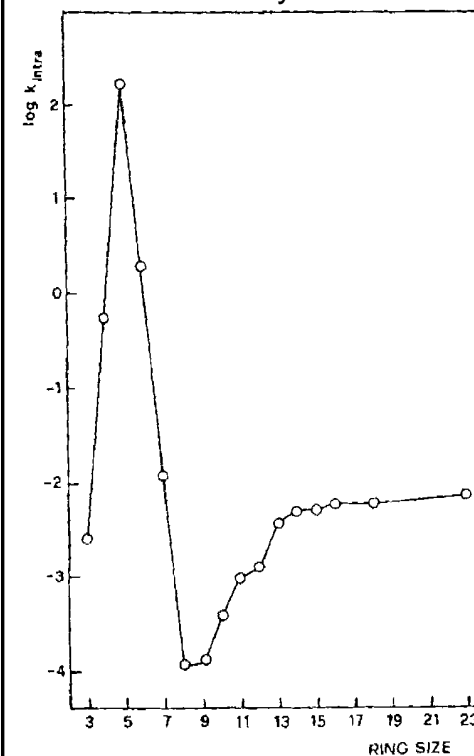
#1 and #3 are especially severe for medium rings

### $\Delta S^\ddagger$ of Cyclization



• a measure of the probability of end-to-end encounters

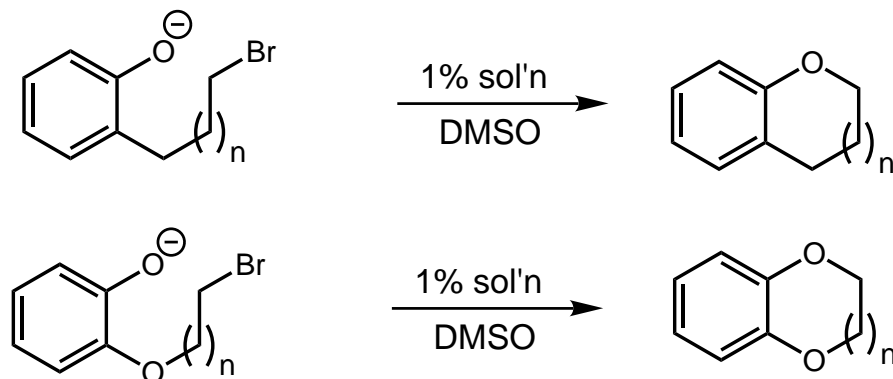
### Rates of Cyclization



• a million-fold decrease in rate from 5- to 10-membered cyclization reaction

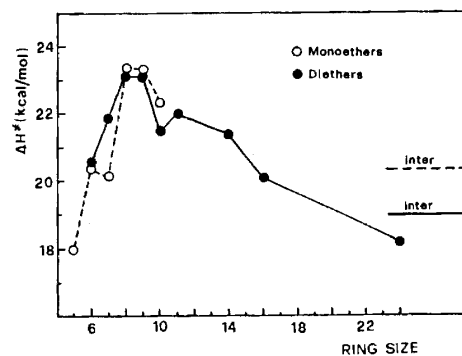
• Note: These data can NOT necessarily be extrapolated to other cyclization reactions or to substrates with differing degrees of substitution.

## The Problem of Medium Ring Synthesis Energetics of Ring Closure Reactions

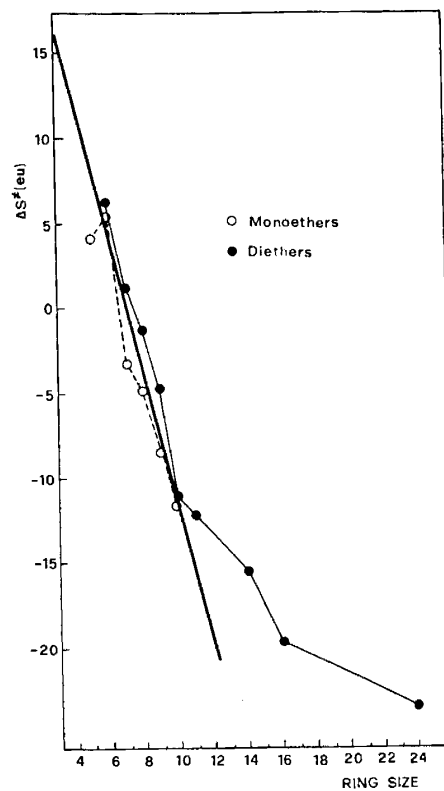


transannular CH---O interactions are less unfavorable than the corresponding CH---HC interactions

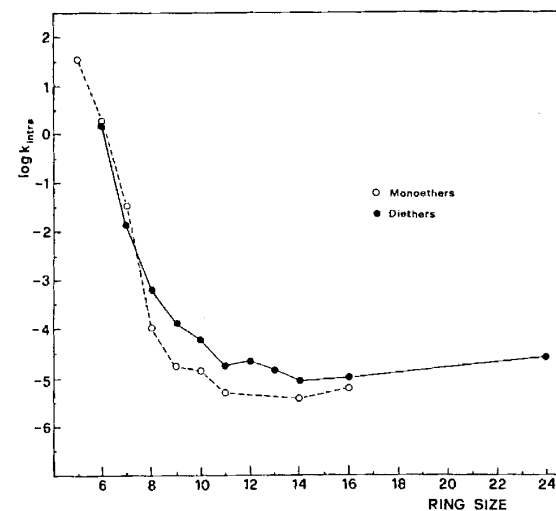
### $\Delta H$ of Cyclization



### $\Delta S^\ddagger$ of Cyclization



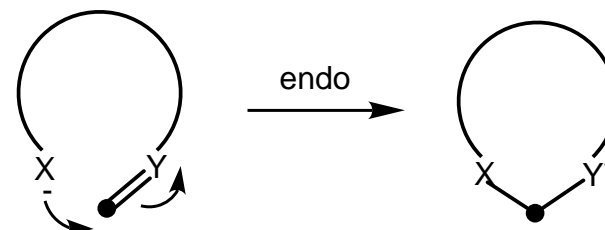
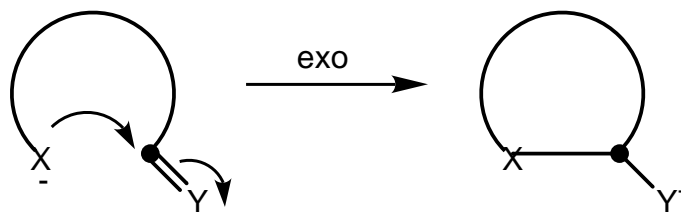
### Rates of Cyclization



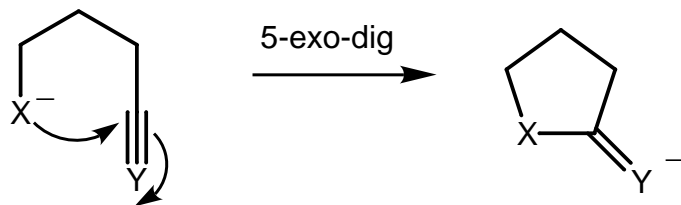
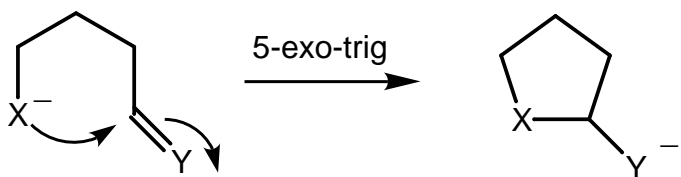
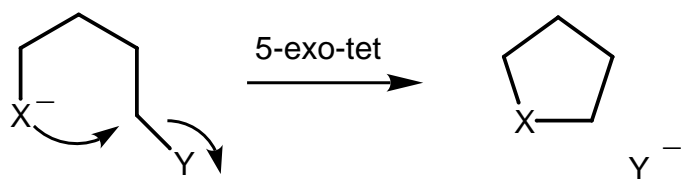
# Ring Closure Basics

General definitions/underlying concepts:

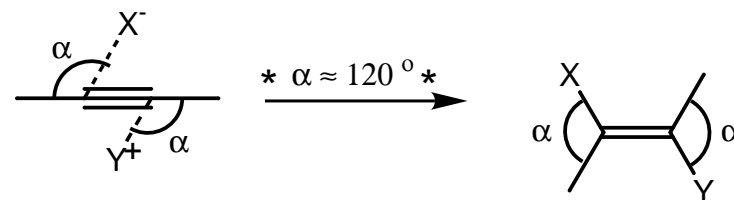
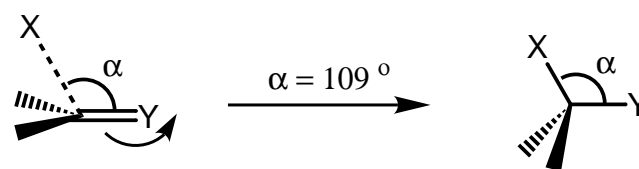
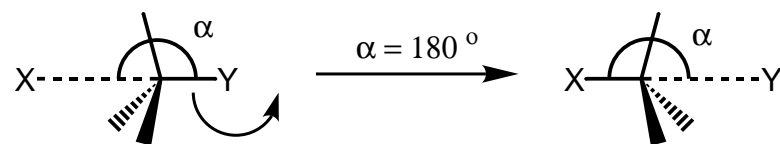
Cyclization modes:



Hybridization at atom undergoing attack:



Required trajectories:



Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

## Conclusions and Caveats

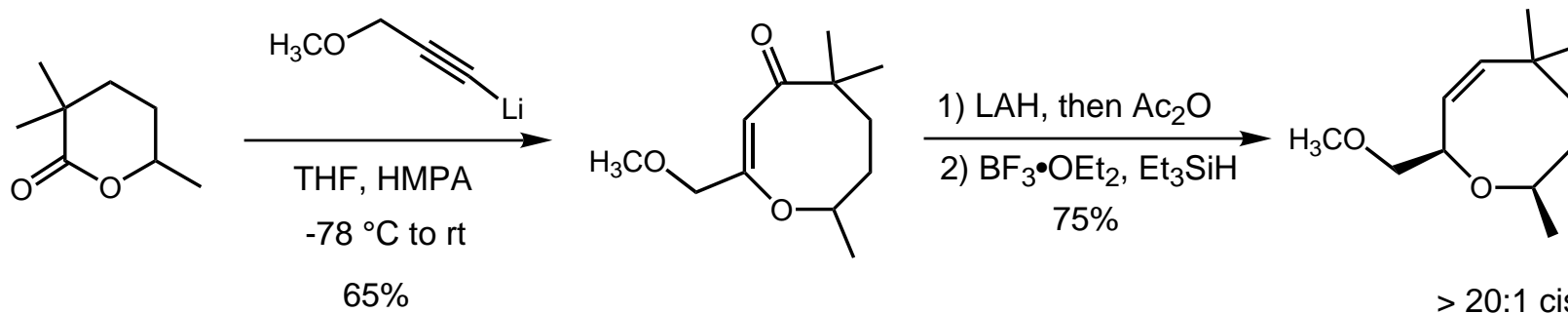
- Baldwin's Rules are an effective first line of analysis in evaluating the stereoelectronics of a given ring closure
- Baldwin's Rules have provided an important foundation for the study of reaction mechanism
- Competition studies between different modes of cyclization only give information about relative rates, and are not an absolute indicator of whether a process is "favored" or "disfavored"
- Structural modifications can dramatically affect the cyclization mode; beware of imines and epoxides

	EXO			ENDO		
	Tet	Trig	Dig	Tet	Trig	Dig
3	√	√	X		X	√
4	√	√	X		X	√
5	√	√	√	X	X	√
6	√	√	√	X	√	√
7	√	√	√	X	√	√

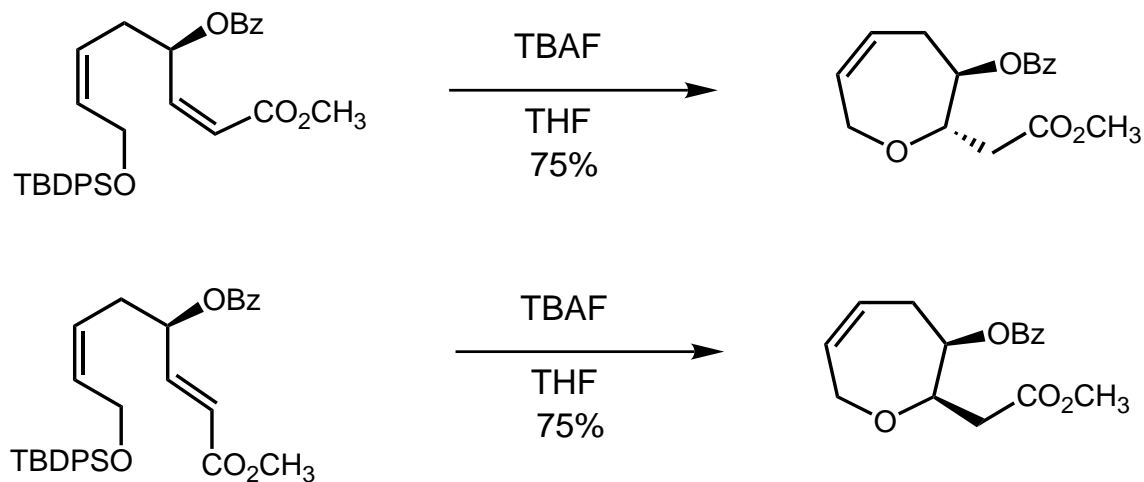
This and the previous slide taken from Jeff Johnson's seminar of 3/29/96:  
*Ring Closure and Stereoelectronics: An Examination of Baldwin's Rules*

# Cyclization By C-O Bond Formation

## Hetero-Michael Reactions



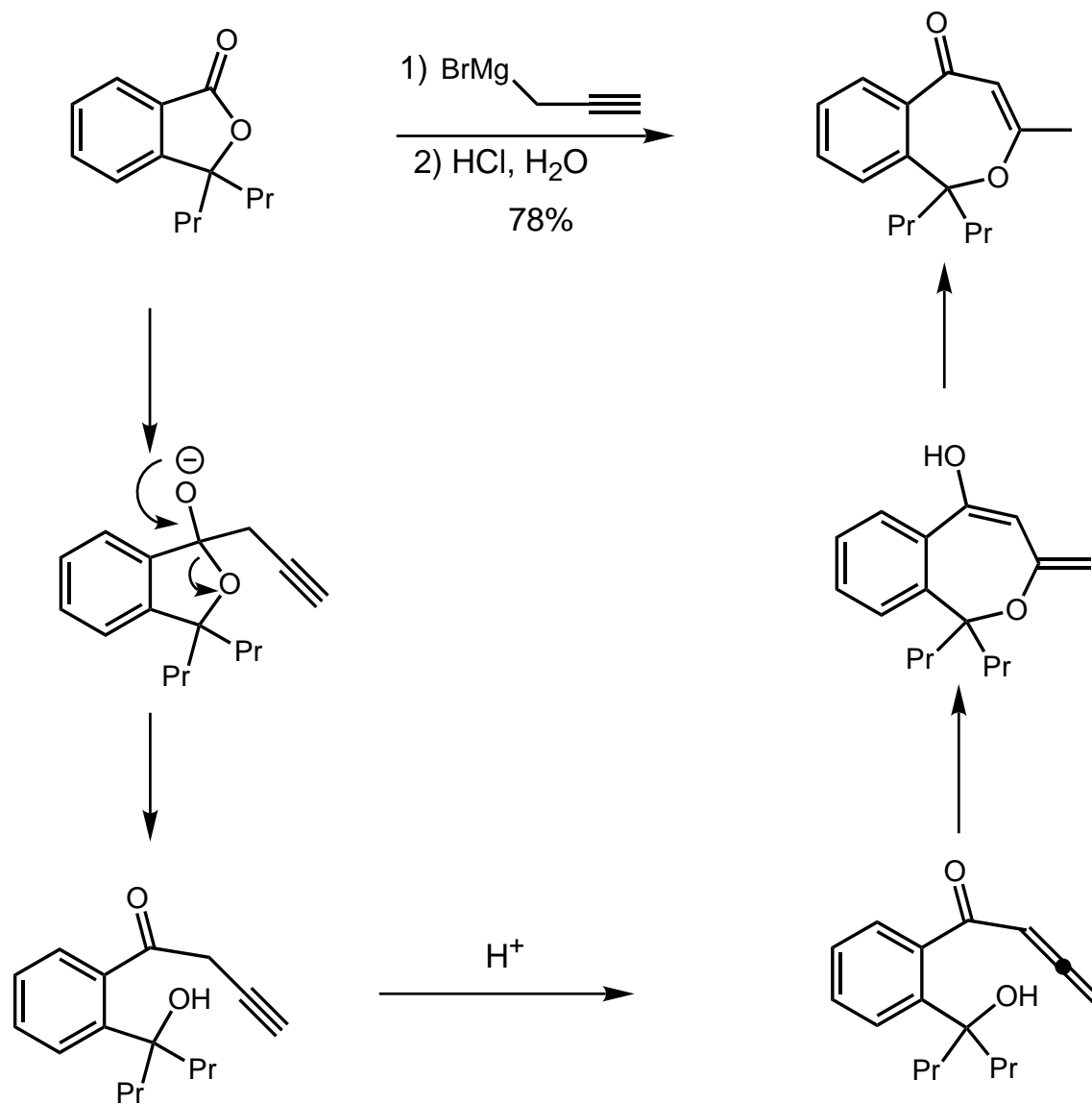
Schreiber  
TL 1984, 1757.  
JACS 1988, 6210.



• *cis* olefin was necessary for cyclization to occur

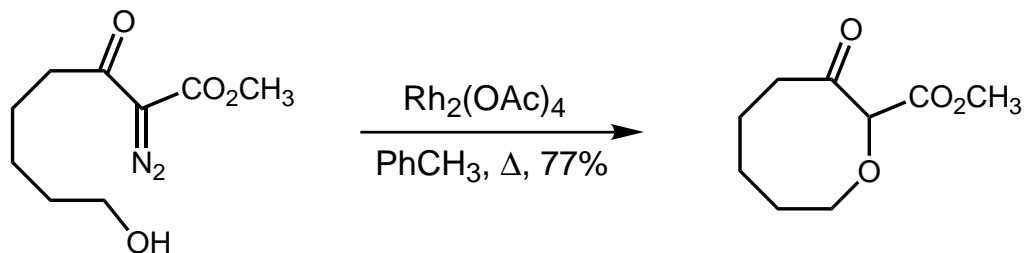
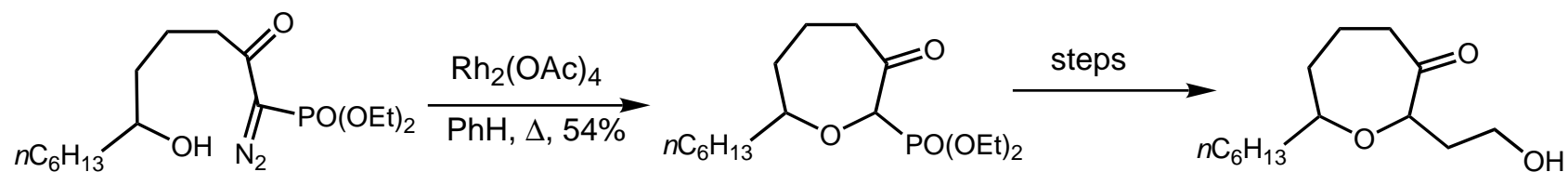
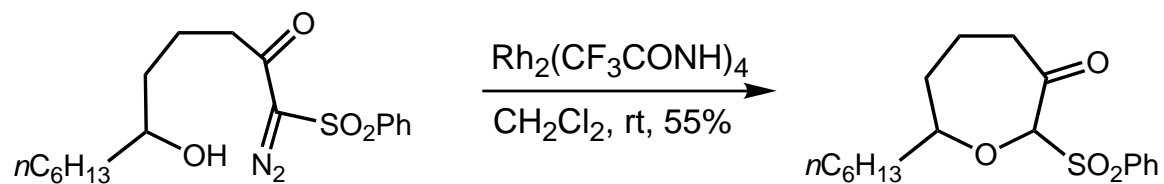
V.S. Martin TL 1993, 5471.

## Another Hydroxy Allene Cyclization



Nagao  
Chem. Comm. 1996, 19.

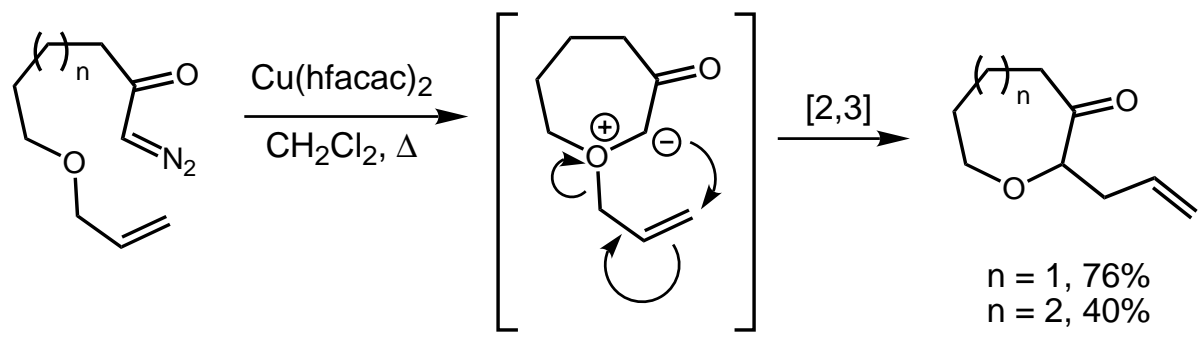
## O-H Insertion



C. J. Moody  
Synlett, 1992, 975.  
JCS Perkin I, 1991, 1.  
JCS Perkin I, 1994, 501.



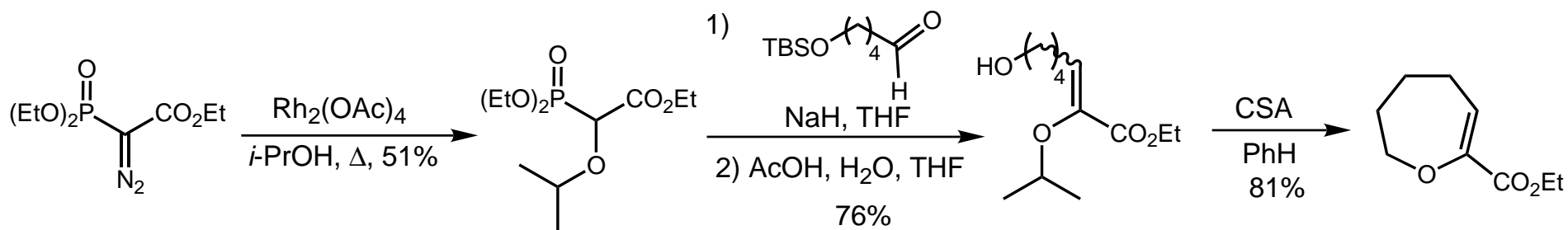
### O-H Insertion



Cu catalysts give fewer by-products derived from C-H insertions than Rh catalysts

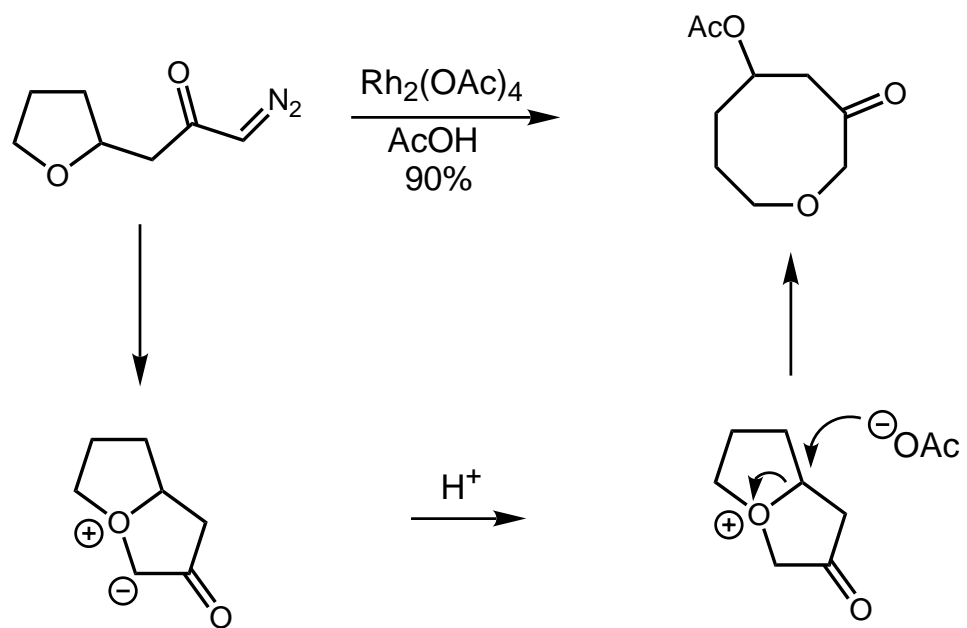
$n = 1, 76\%$   
 $n = 2, 40\%$

J. S. Clark  
TL 1993, 4385.



C. J. Moody  
Tetrahedron, 1992, 3991.

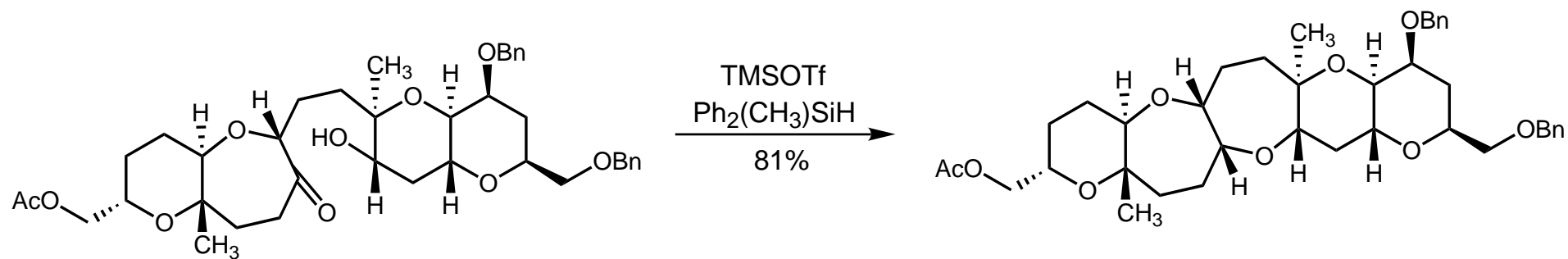
### O-H Insertion



Oku  
Chem. Comm. 1996,1077.

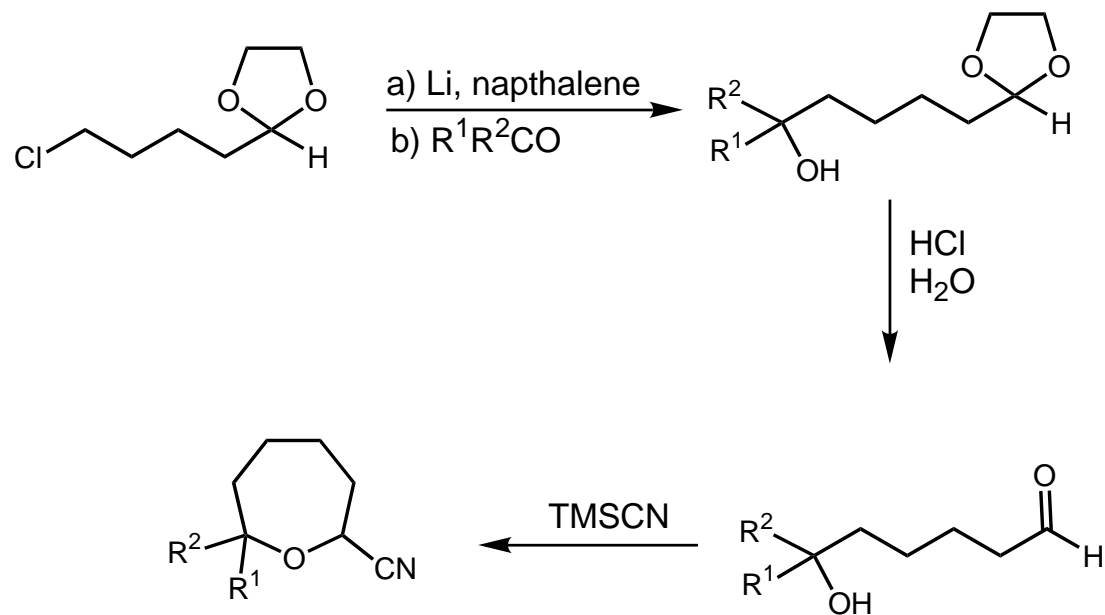
## Reductive Cyclization

Both the synthesis of Hemibrevetoxin B and 7-epi-Hemibrevetoxin B have utilized this reaction:



not universally applicable

## TMSCN Induced Cyclizations of Aldehydes



Three step yields

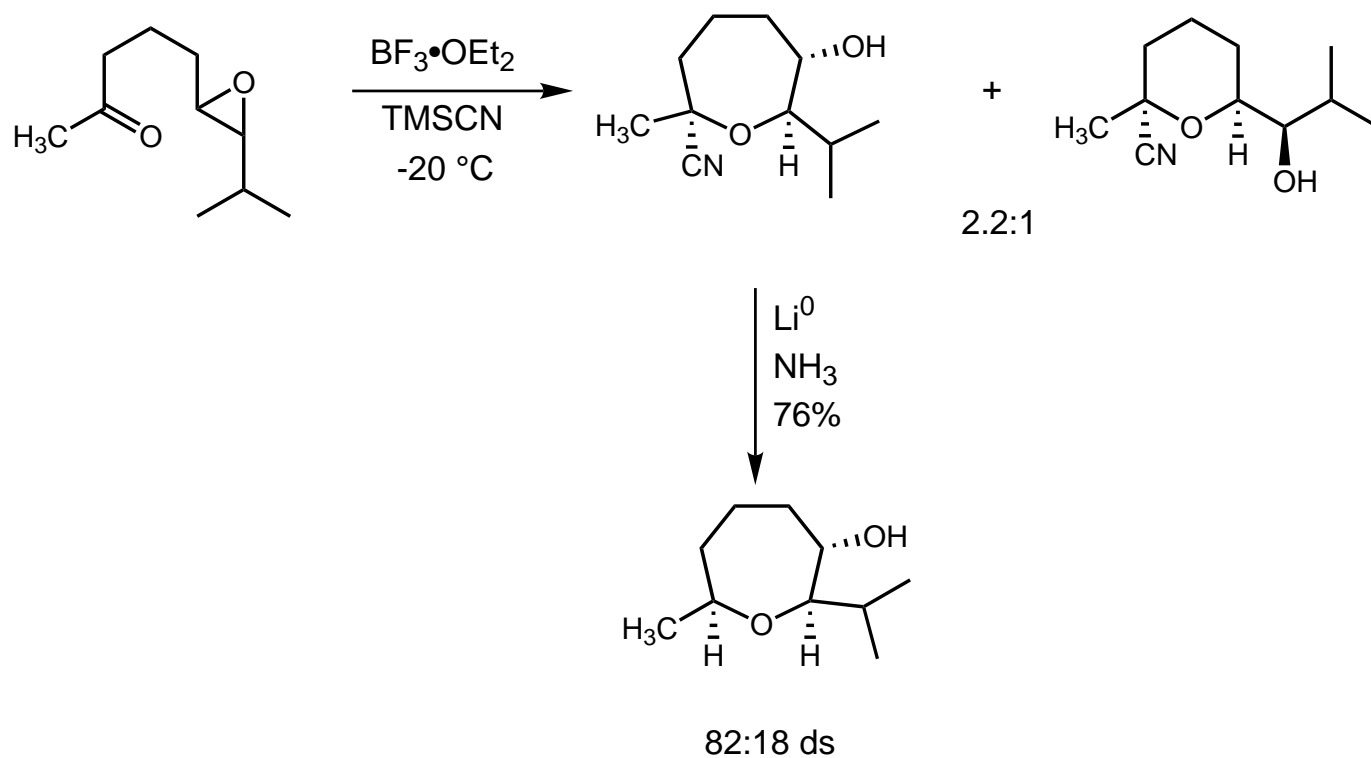
$R^1 = H, R^2 = Ph, 36\%$

$R^1 = R^2 = CH_3, 22\%$

$R^1 = R^2 = CH_2CH_3, 39\%$

$R^1R^2 = (CH_2)_5, 34\%$

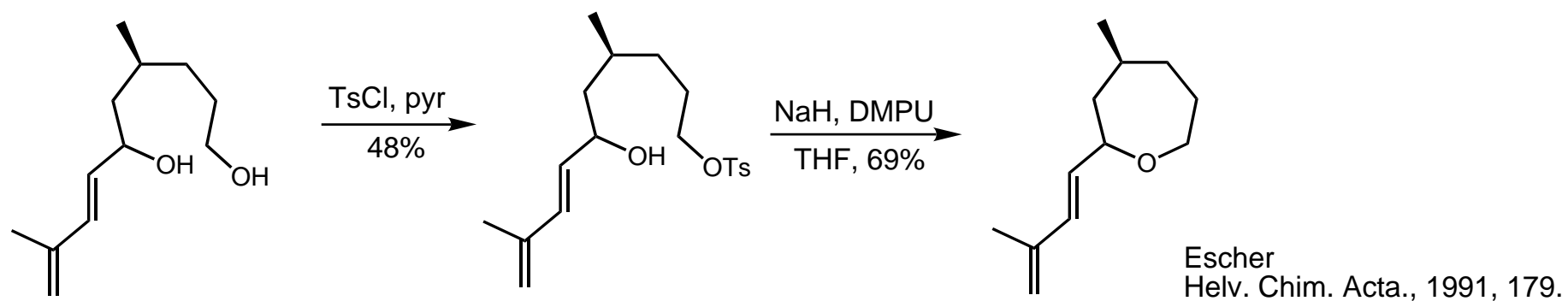
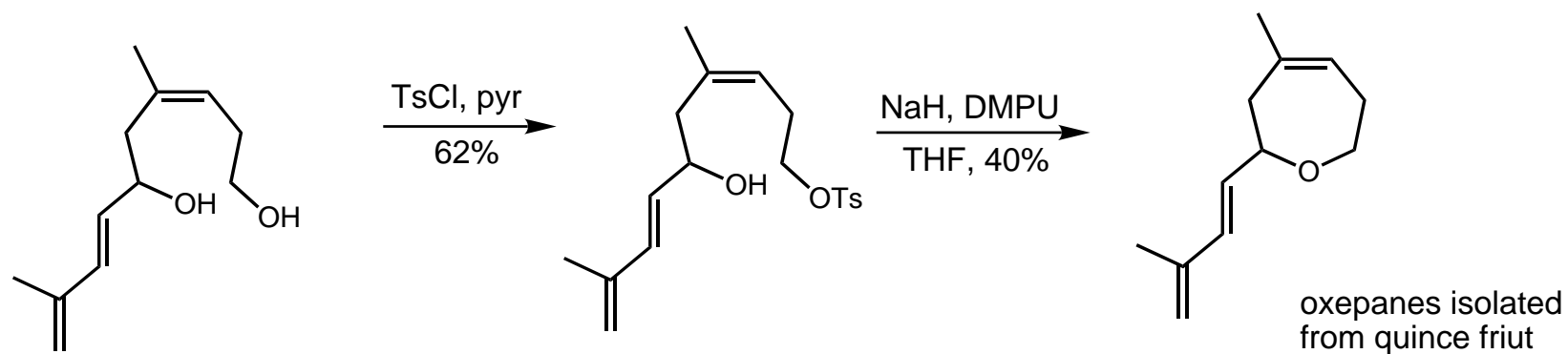
## TMSCN Induced Cyclizations of Ketones



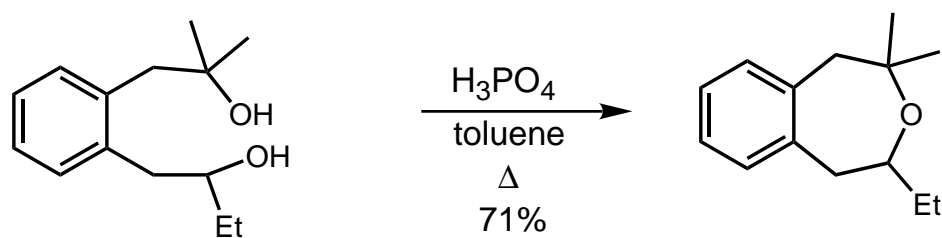
reagents other than TMSCN only  
give mixtures THPs

Rychnovsky  
TL, 1996, 339.  
based on  
Chamberlin  
JOC 1991, 4141.

### Tosylate Displacement

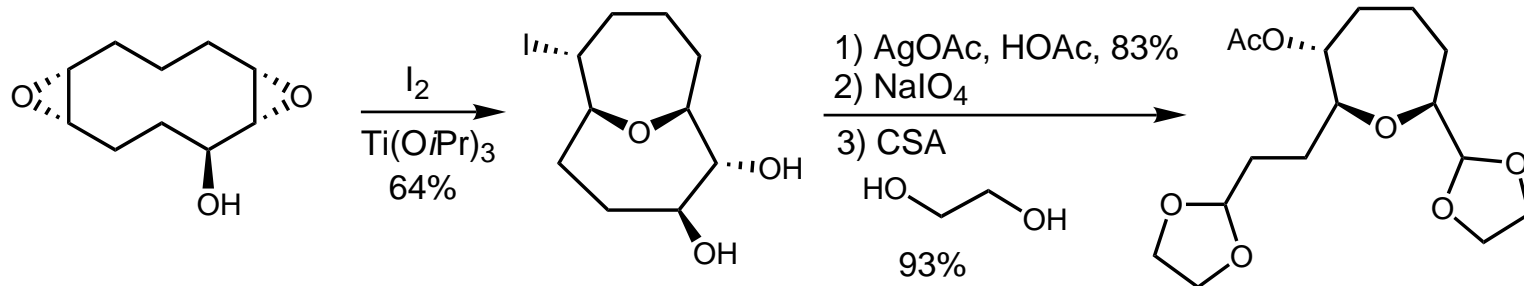
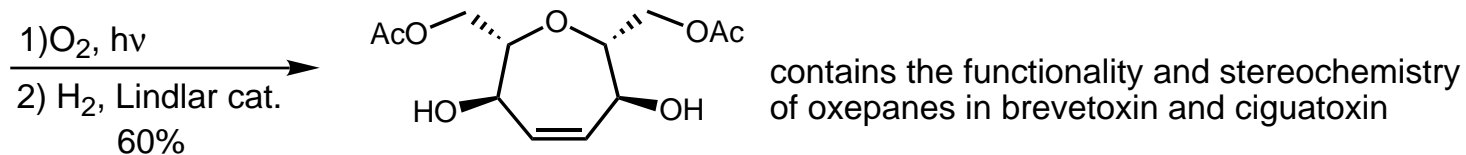
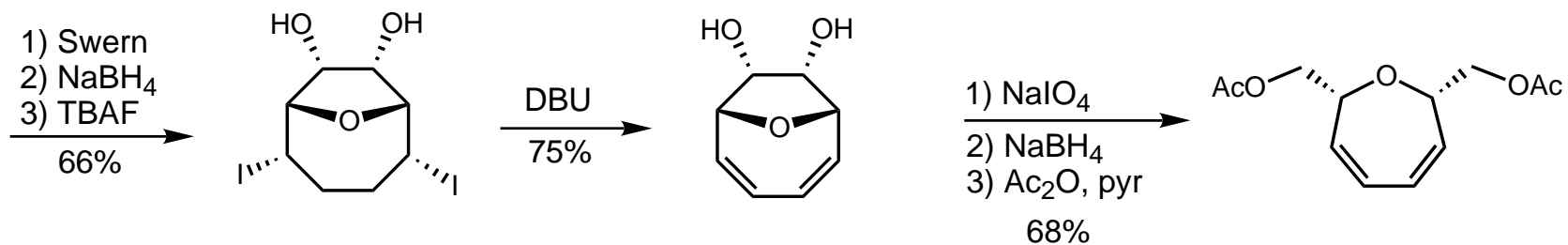
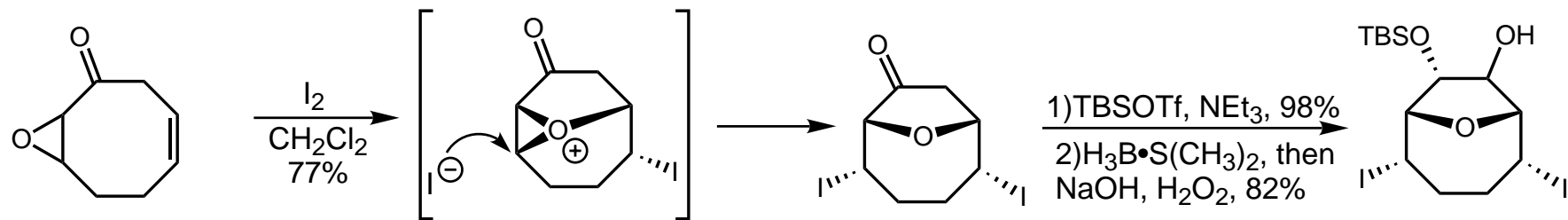


### Protic Acid Cyclization



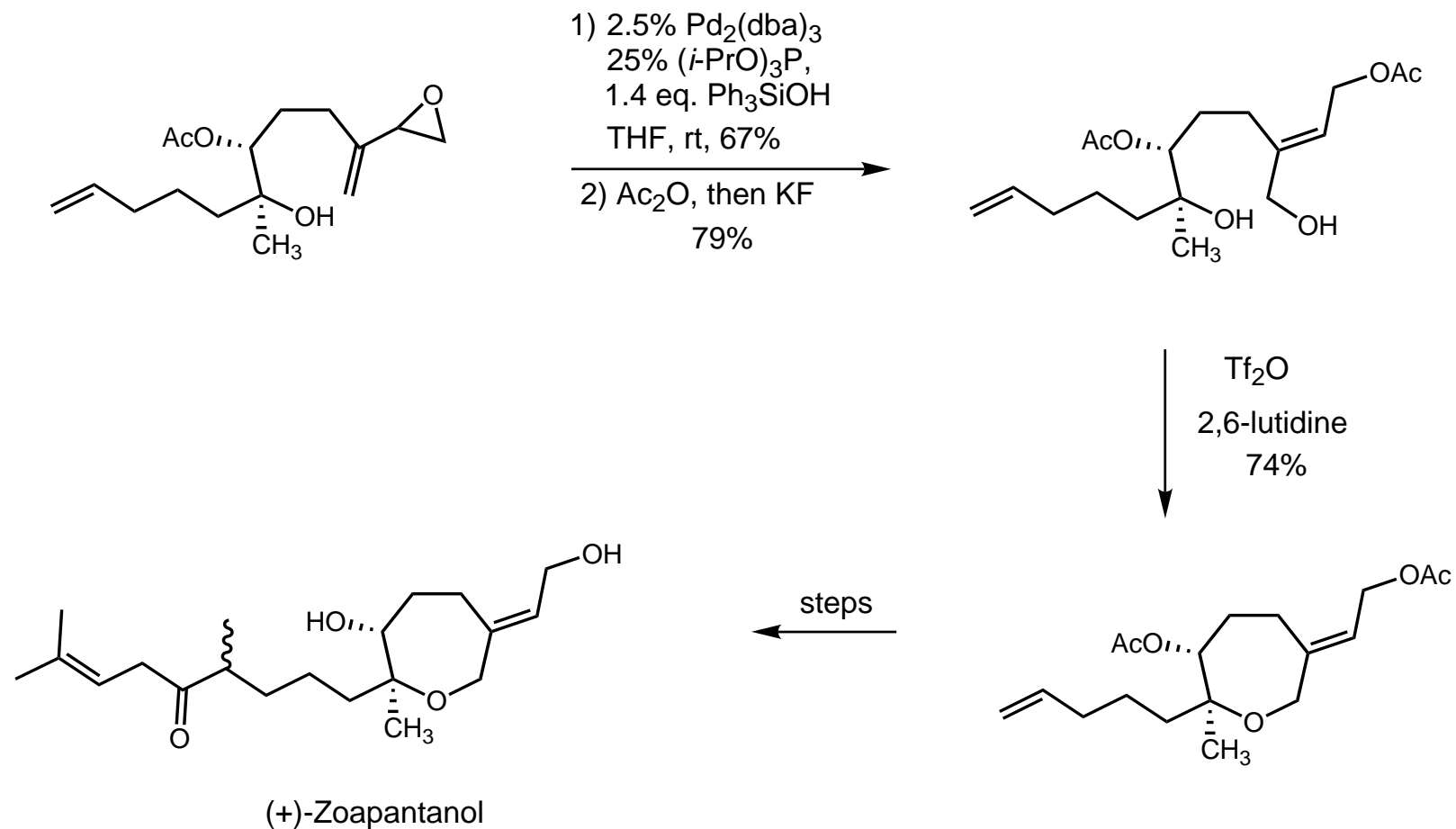
C. J. Moody  
JCS Perkin I, 1995, 1137.

## Transannular Ether Formation



J.D. Martin  
 TL 1990, 1629.  
 TL 1991, 2241.  
 TL 1991, 2245.

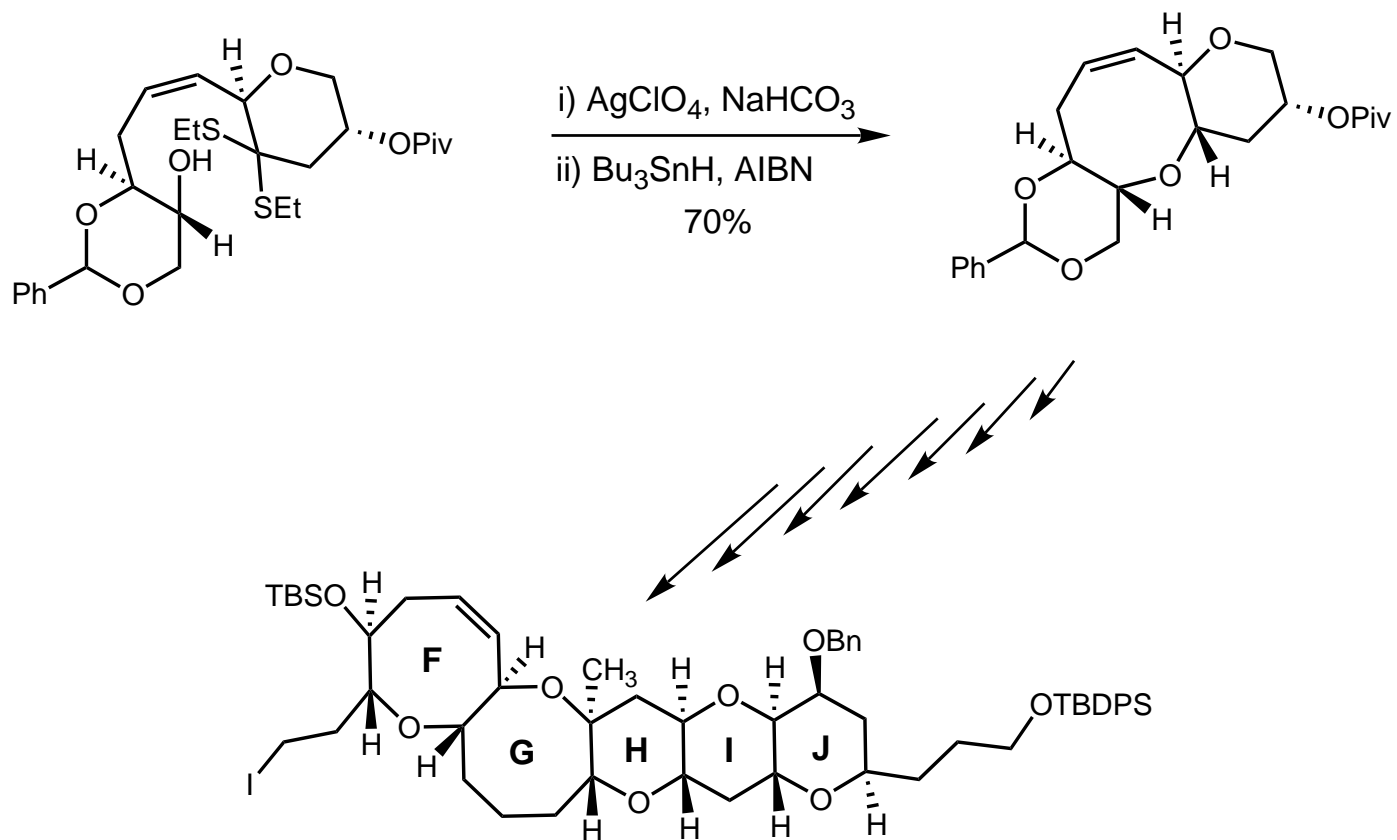
## Zoapantanol Synthesis



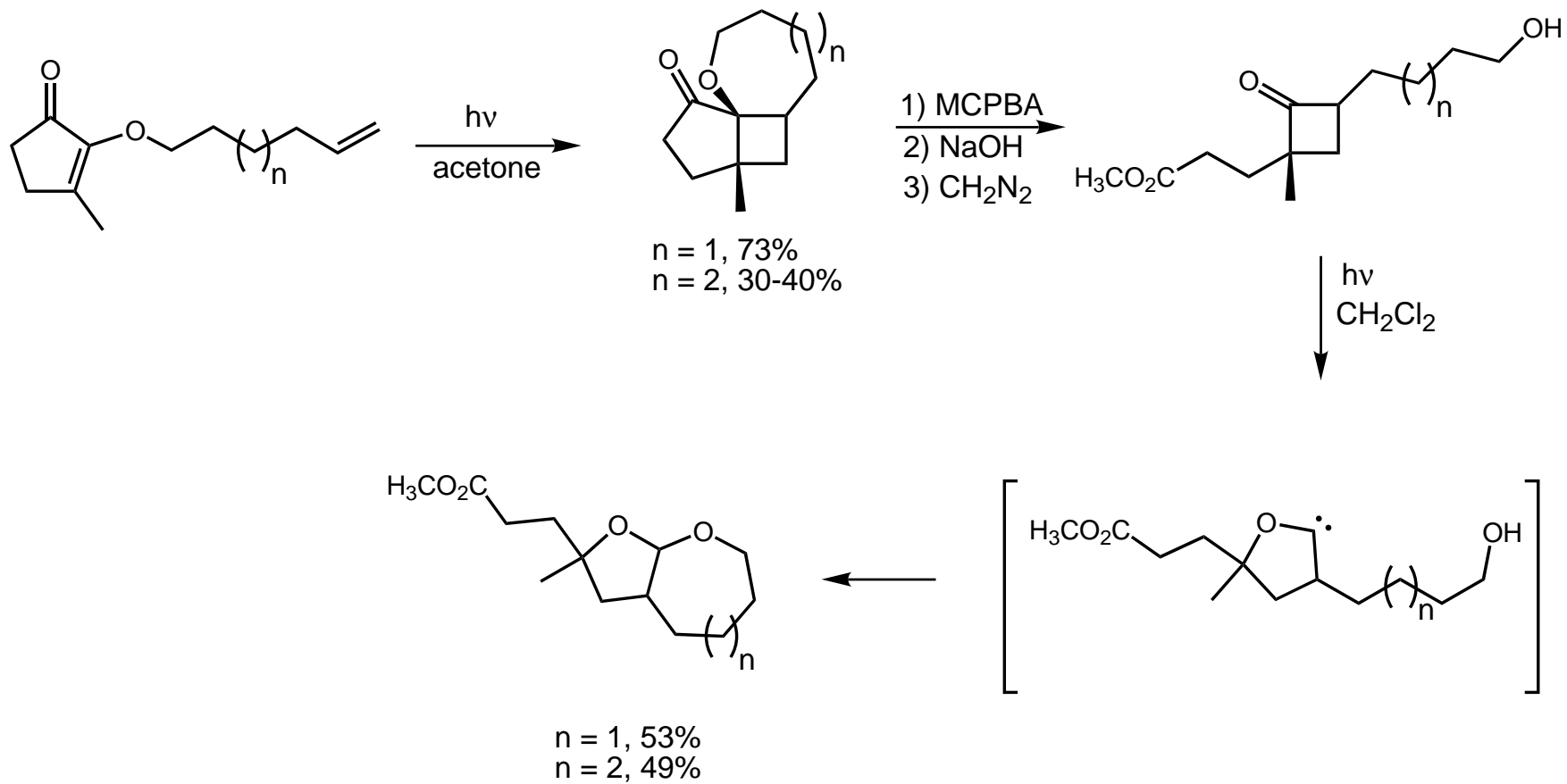


## Cyclization onto a Dithioketal

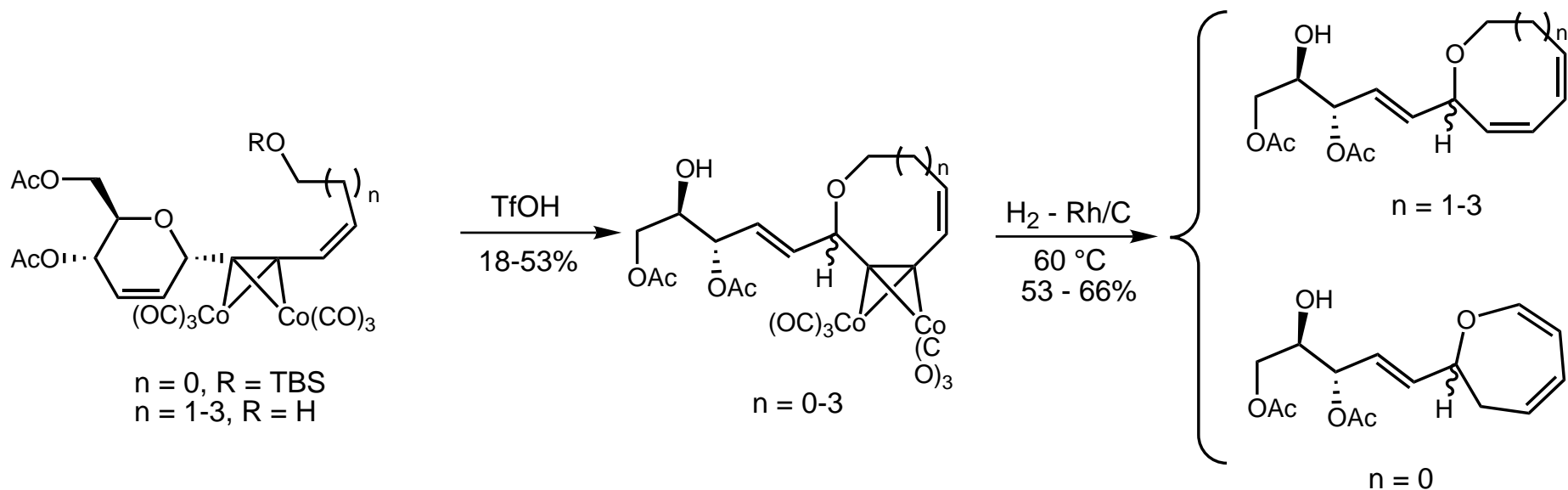
Both oxacanes of Brevetoxin B were formed by cyclization of an alcohol onto a dithioketal:



### Photolysis



## Intramolecular Nicolas Reaction



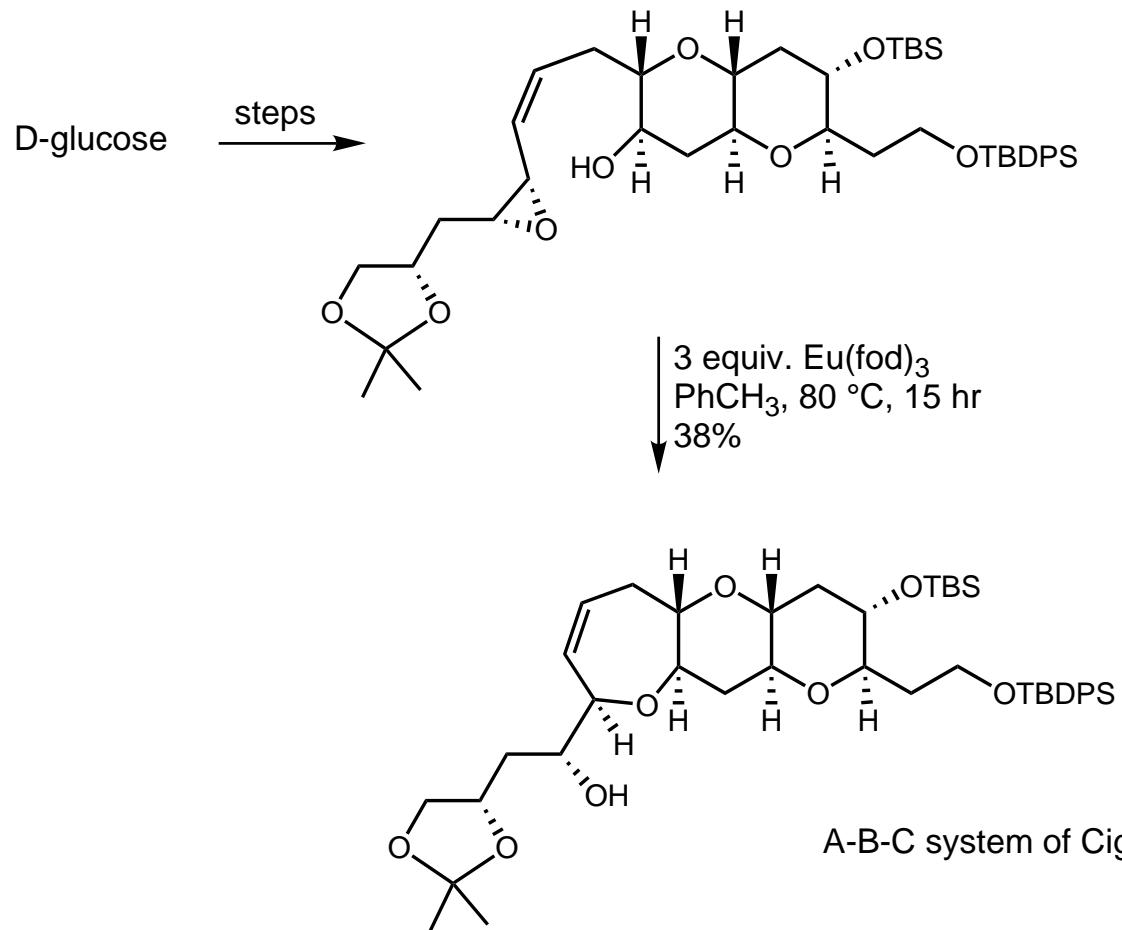
Several similar cyclizations have been used w/ limited success.

Isobe  
 Synlett 1995, 1179.  
 Synlett 1995, 351.  
 Chem Lett 1996, 473.

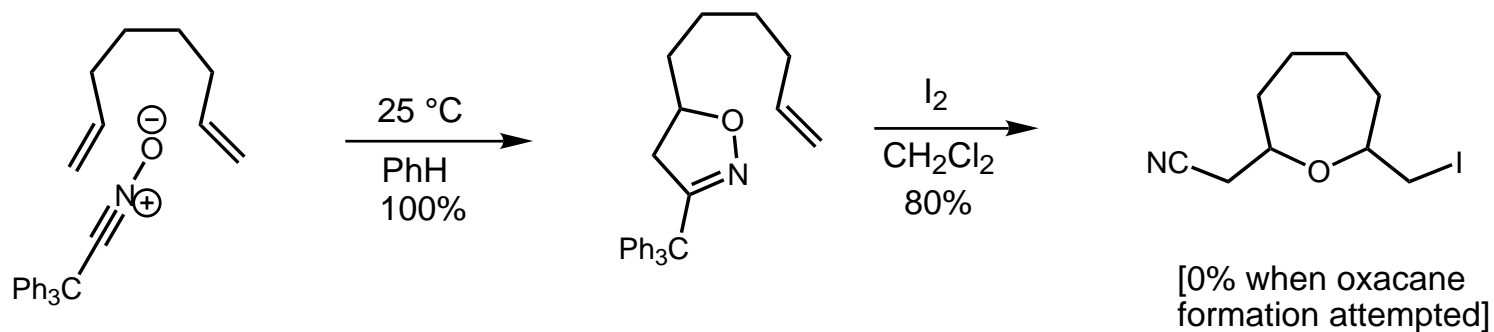
V. S. Martin  
 TL 1995, 3549.

Greé  
 JOC 1995, 2316.

## Epoxide Opening

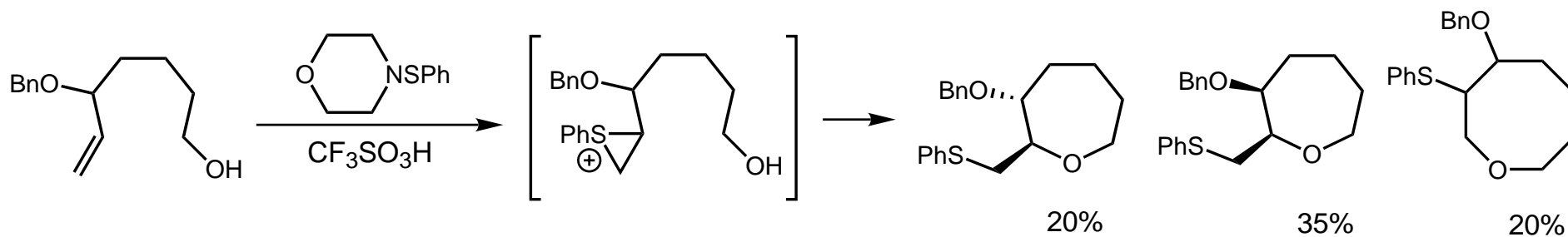


### From Isoxazolines

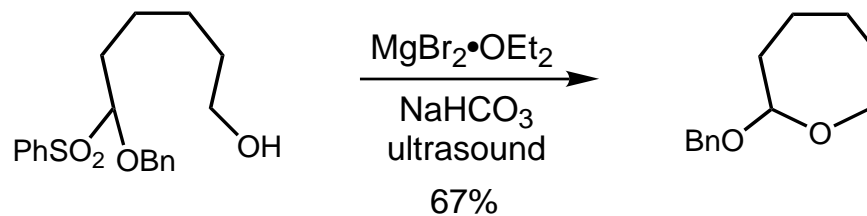


Kurth  
JOC 1990, 283.

### From Hydroxy Olefins



### From $\alpha$ -Sulphonyl Ethers

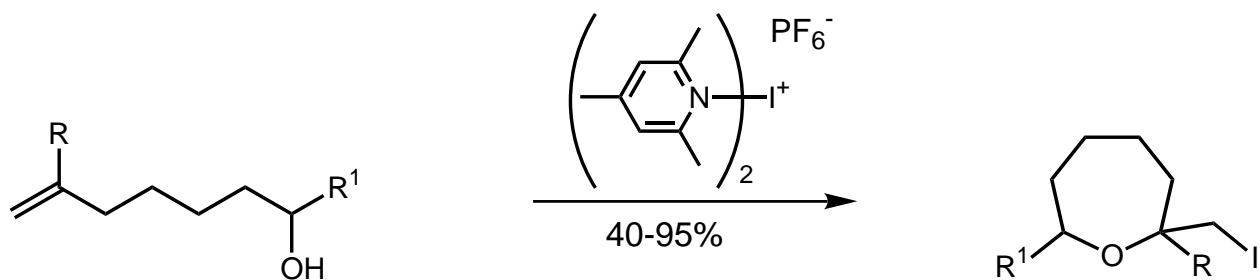


K. Jones  
TL 1991, 2261.

works for 5-8 membered rings

Ley  
Synlett, 1991, 415.

## Misc Cyclizations

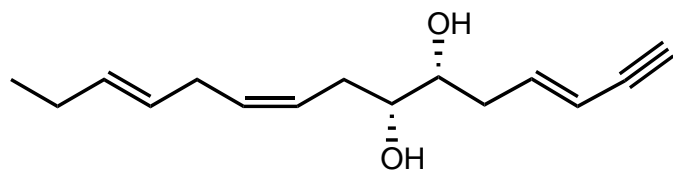


R, R<sup>1</sup> = alkyl

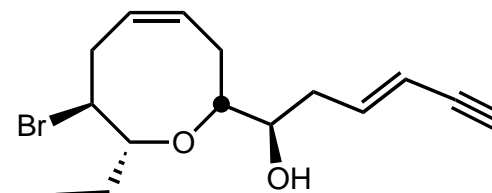
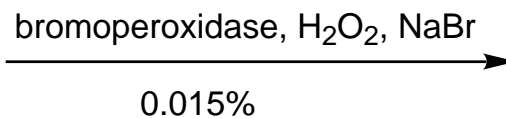
oxacanes could not be formed  
under these conditions

Rousseau  
JOC 1996, 5793.

## Enzymes



101 mg

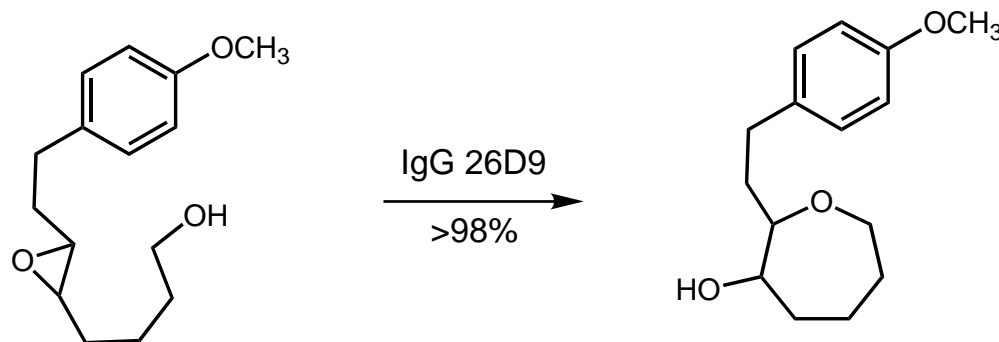


0.02mg

deacetyllaurencin  
among a number of  
other compounds

Murai  
Chem Lett 1994, 2307.

## Catalytic Antibody Mediated Cyclization

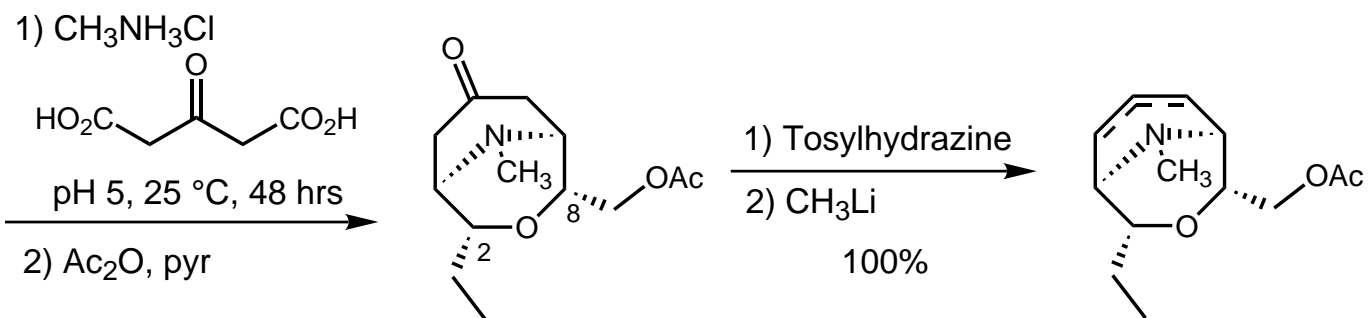
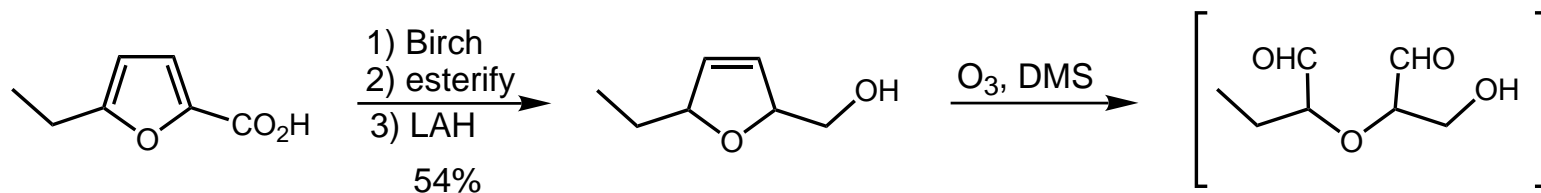


normally observed THP (6-exo-tet) not observed

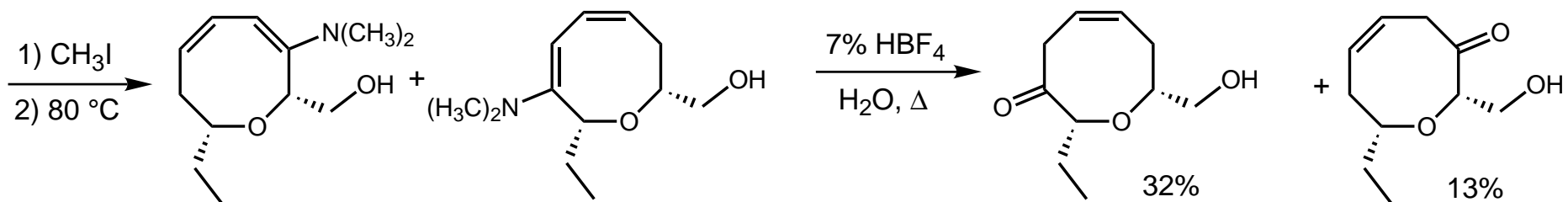
Lerner, Janda  
JACS 1995, 2659.

# Cyclization By C-C Bond Formation

## The Epic Assault



2.2% (plus 0.6% other  
2,8 isomers)



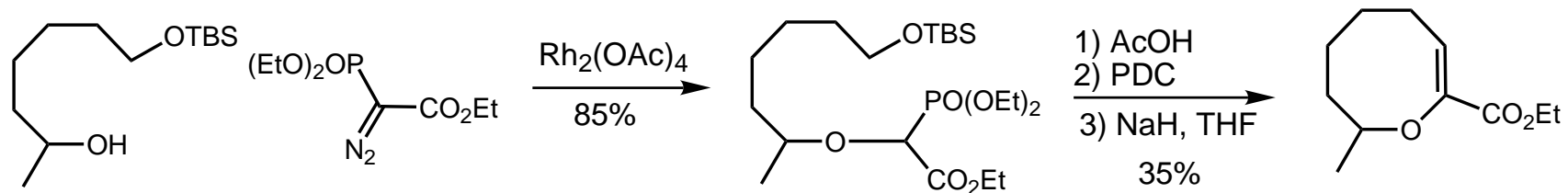
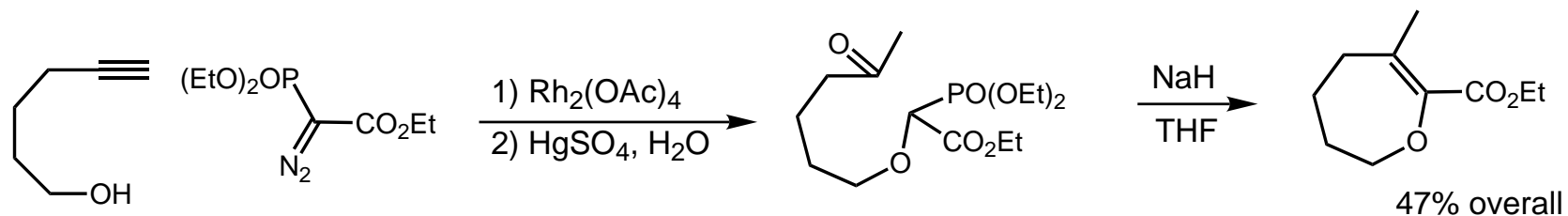
11 steps

(±)-laurencin  
0.0047%

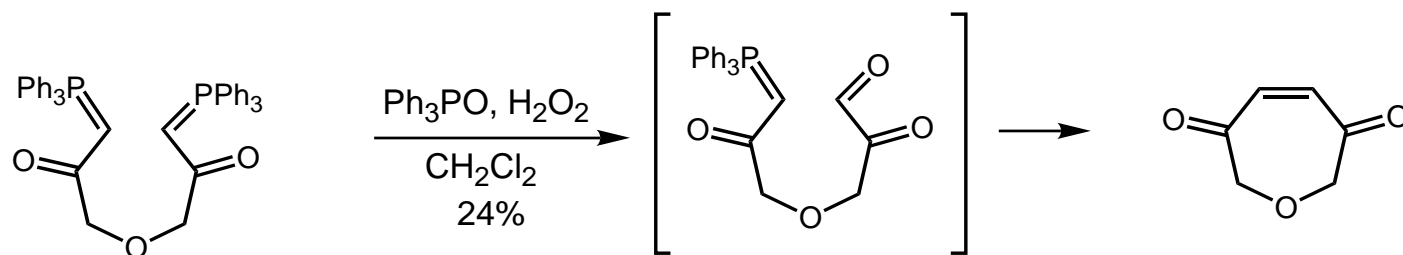
Masamune  
TL 1977, 2507.  
Chem Lett, 1975, 895.



## Wadsworth-Emmons Cyclization



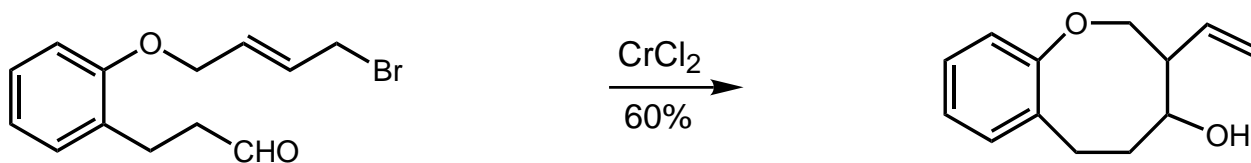
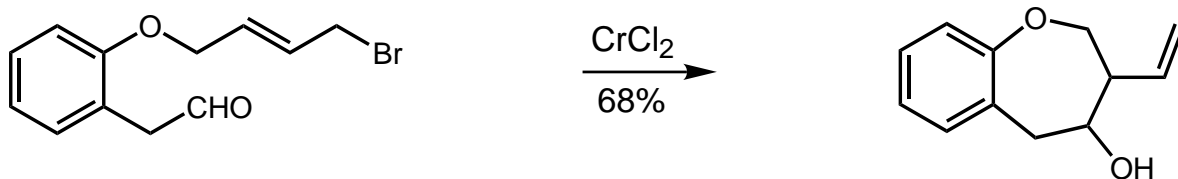
C. J. Moody  
TL 1991, 6947.



Bestmann  
Chem. Ber. 1993, 725.

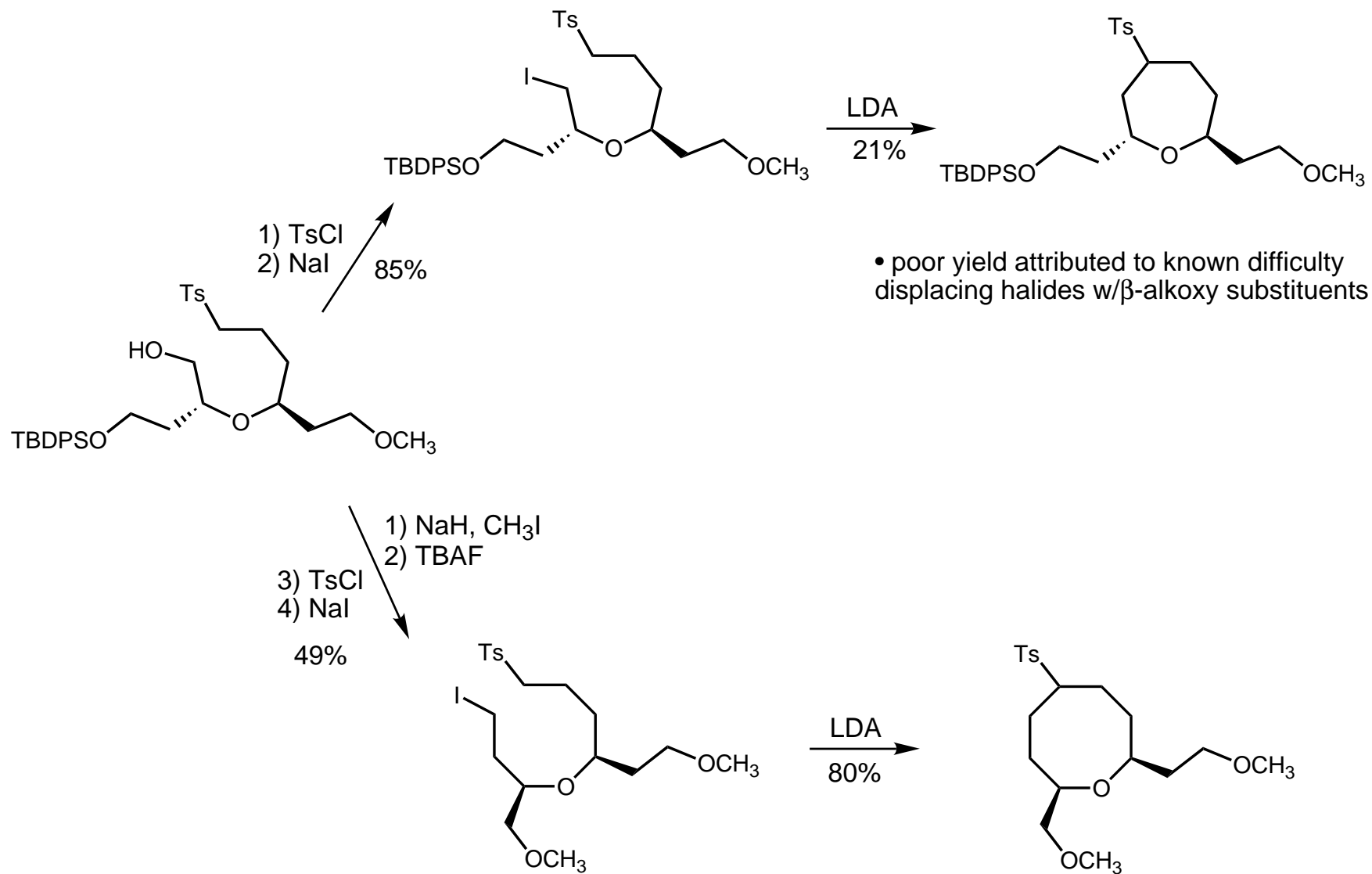
- The HWE reaction is general for aldehyde and ketone carbonyl components, and phosphonyl-ketones and -sulfones, bis-phosphonates and phosphonoacetates as nucleophiles.

## Chromium Mediated Cyclizations

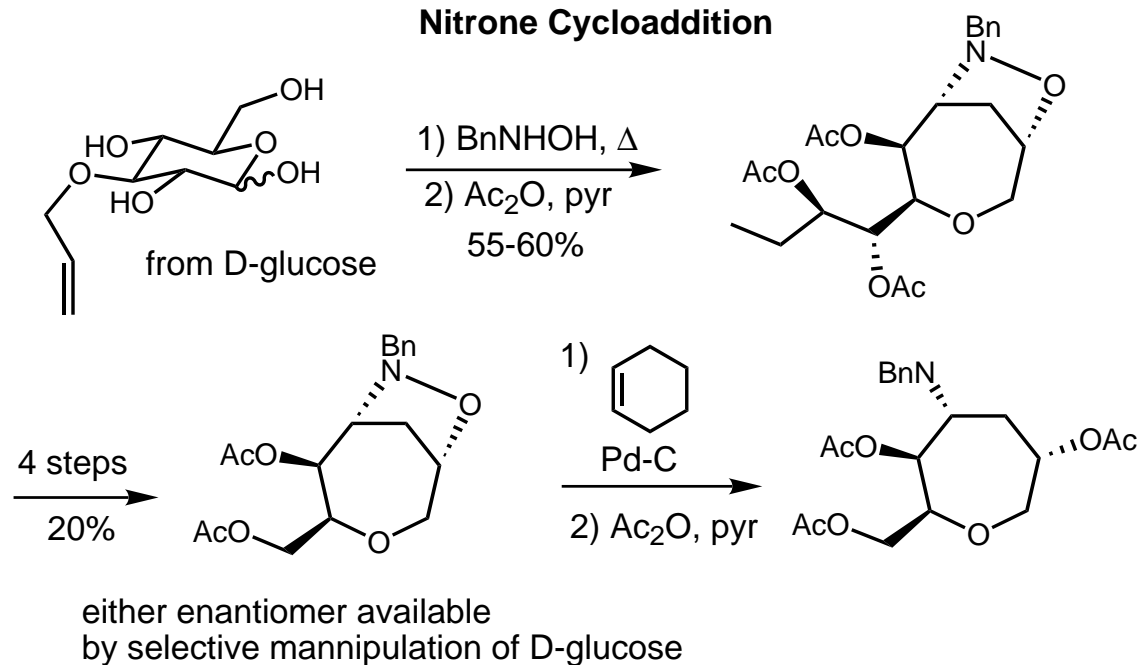


- attempted formation of a benzopyran failed due to formation of the elimination product salicylaldehyde

## Oxapanes and Oxacanes from a Common Precursor

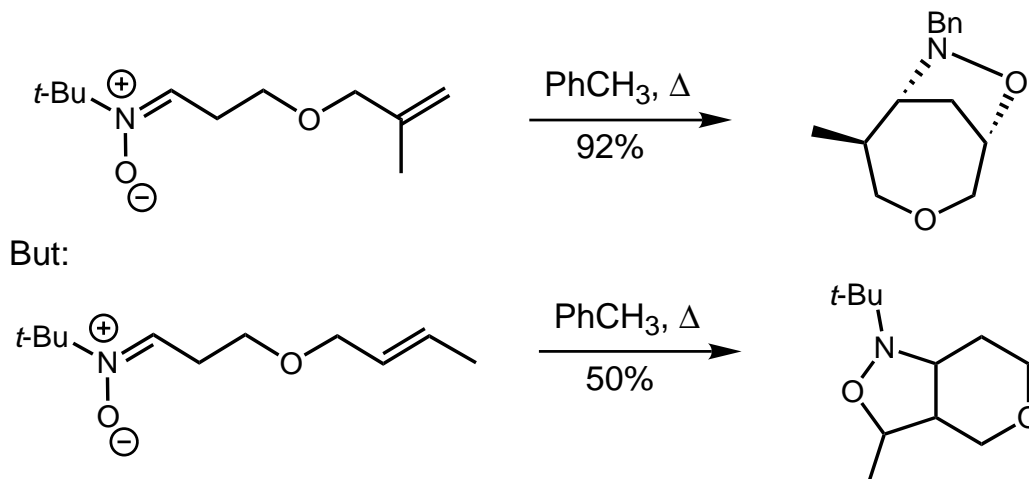


## Nitrone Cycloaddition



Bhattacharjya  
 Chem. Comm. 1990, 1508.  
 TL 1993, 3585.

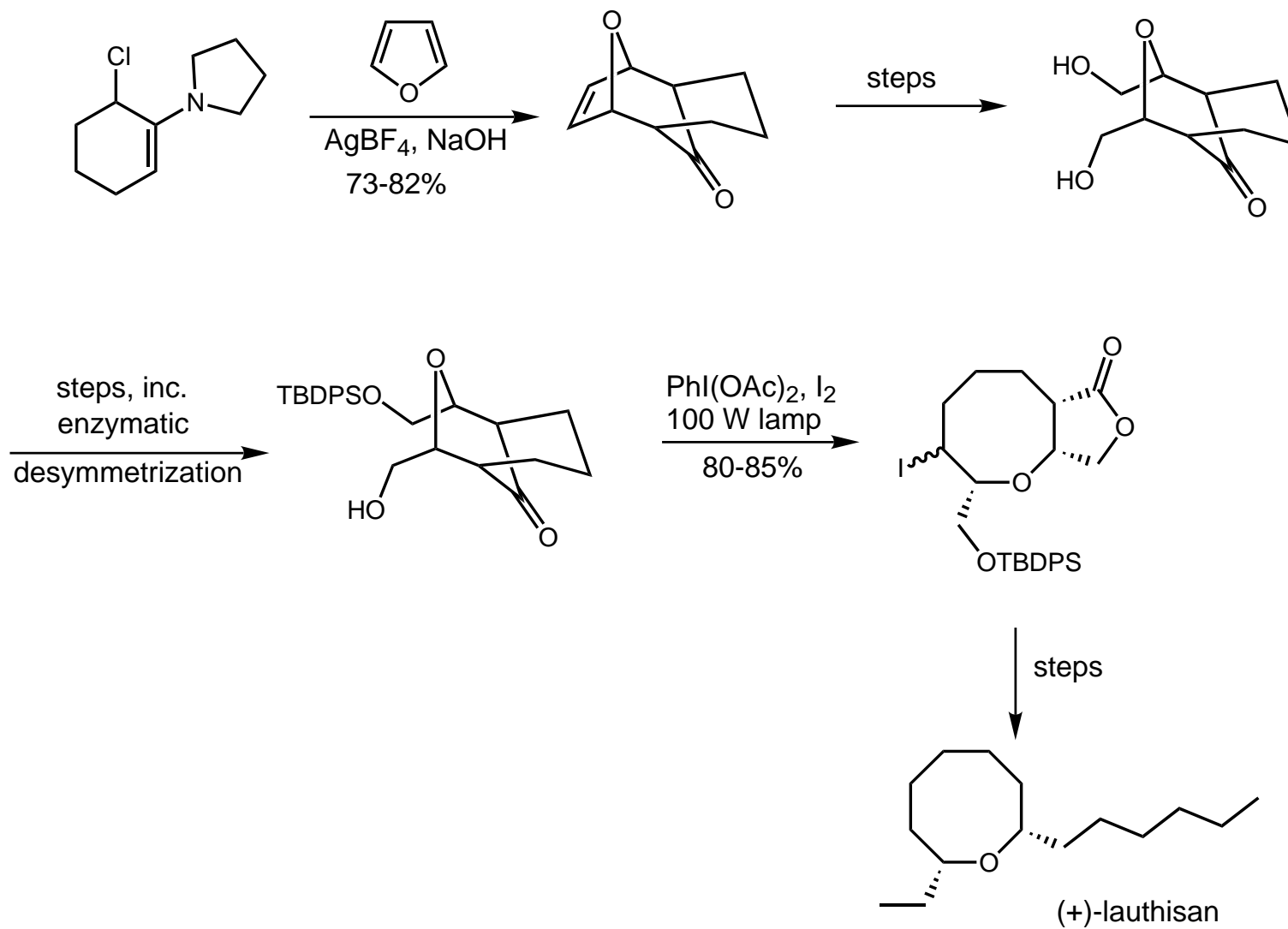
### Minor Structural Changes can have a Major Impact on Reactivity



Aurich  
 Chem. Ber. 1990, 1508.

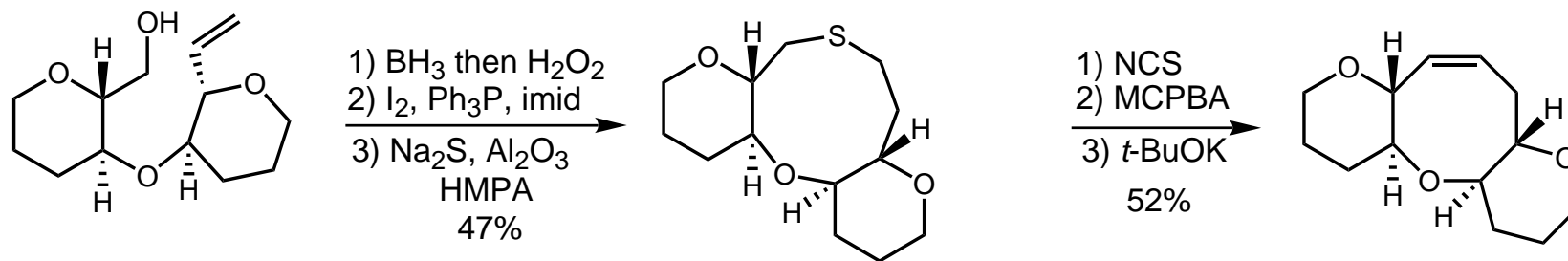
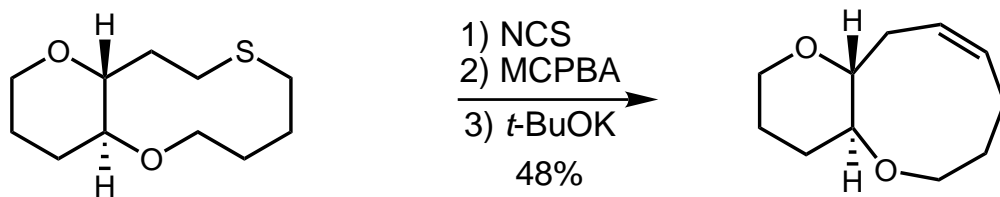
Other nitrone cycloadditions:  
 Shing  
 Tetrahedron: Asymmetry, 1996, 1323.

## [4+3] Cycloaddition Chemistry



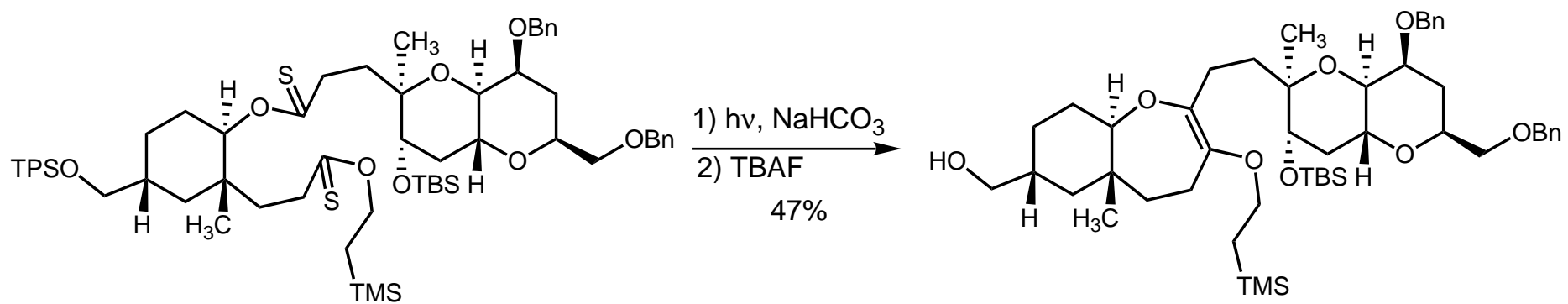
Cha  
JOC 1995, 792.

## Ramberg-Bäcklund Reaction



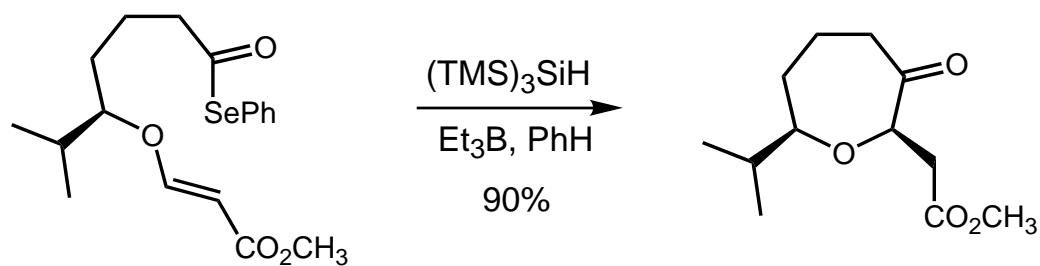
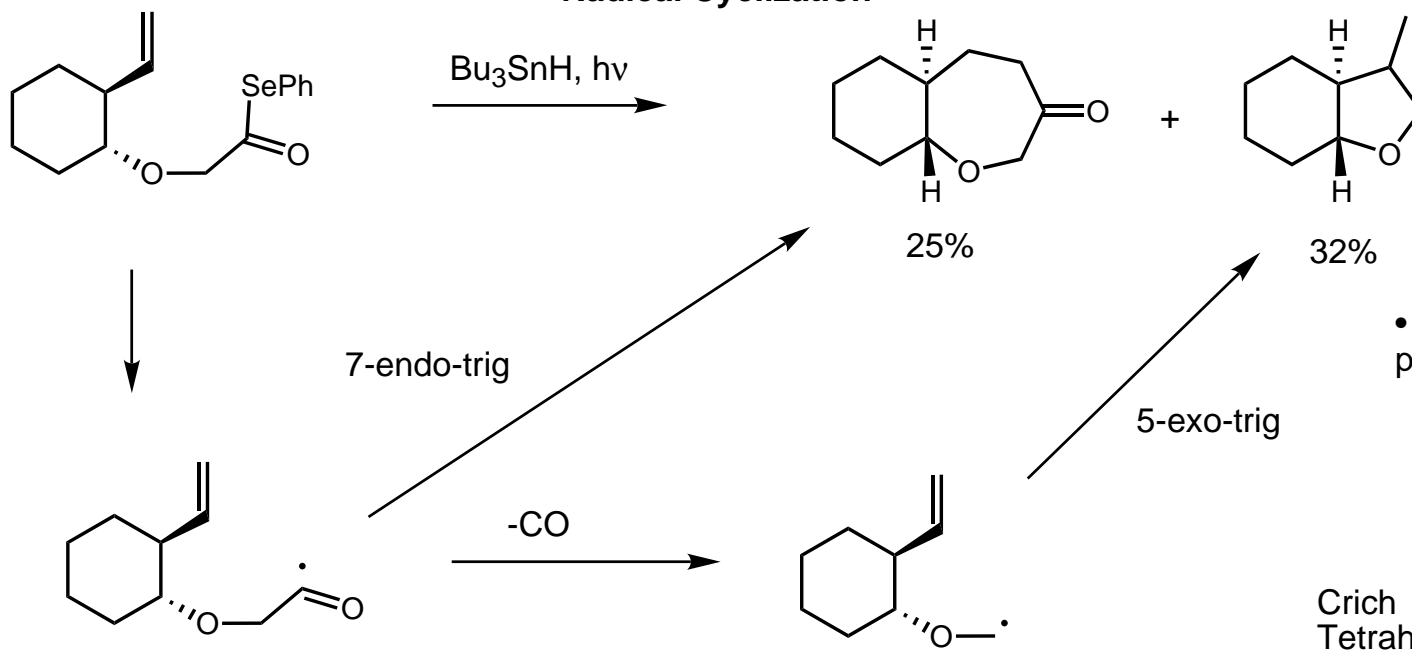
J. D. Martin  
TL 1996, 2869.  
JACS 1995, 1437.  
JOC 1994, 2848.

### Photochemical Cyclization of a bis-Thionoester



towards hemibrevetoxin  
Nicolaou  
JACS 1993, 3558.

### Radical Cyclization

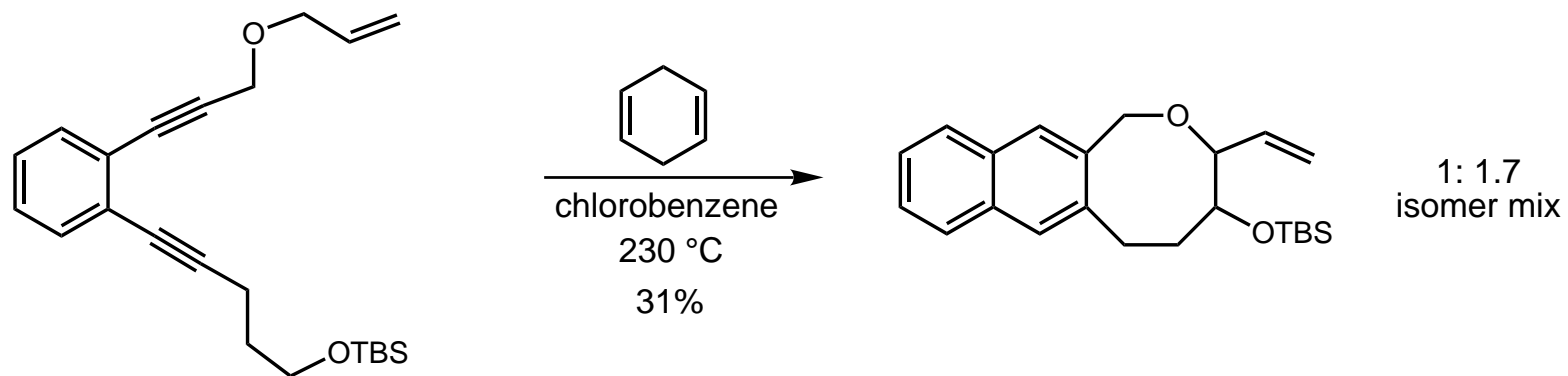


similar conditions used to form a THP  
relevant to the brevetoxins in 99% yield.

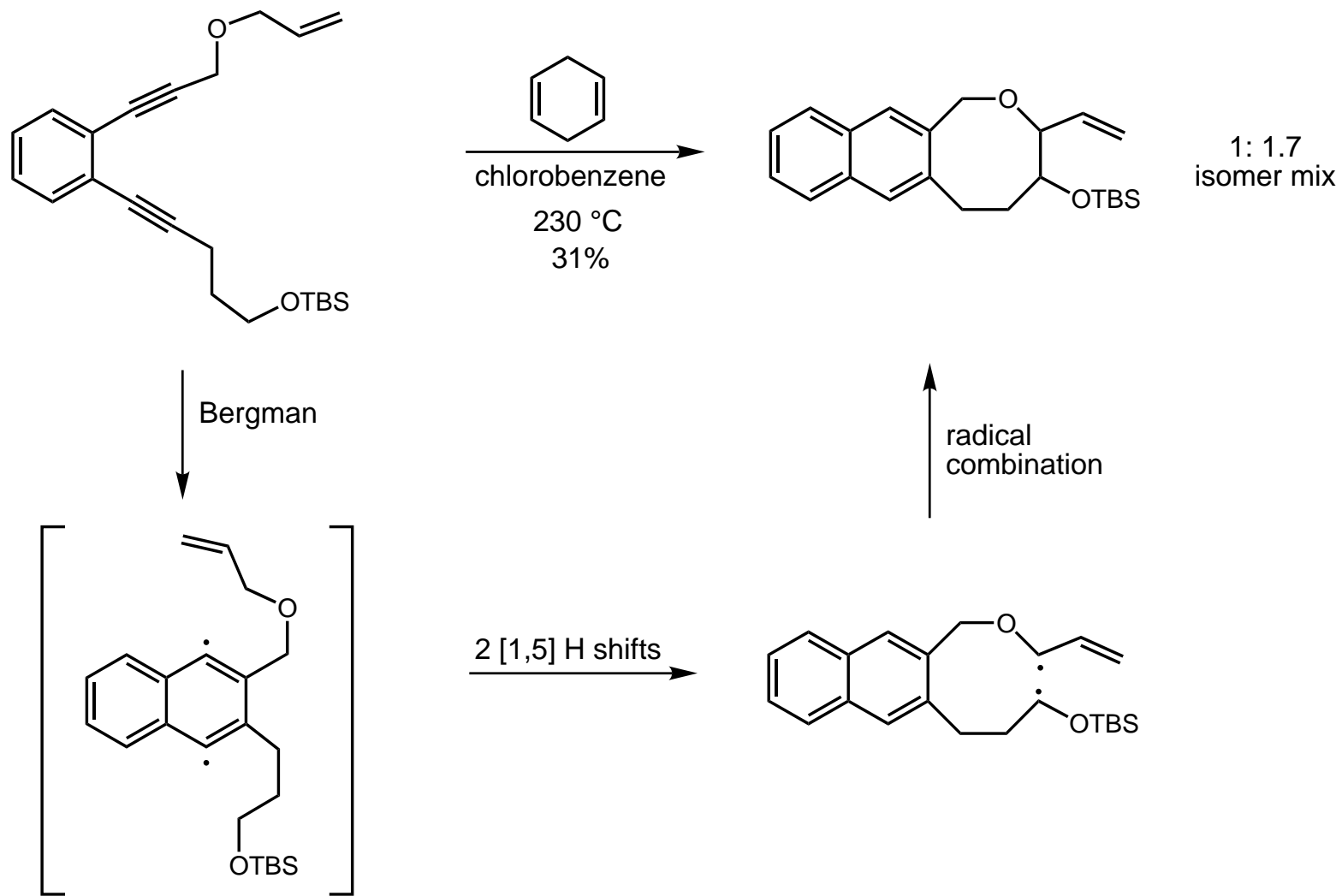
P. A. Evans  
JOC 1996, 2252.  
JOC 1996, 4880.



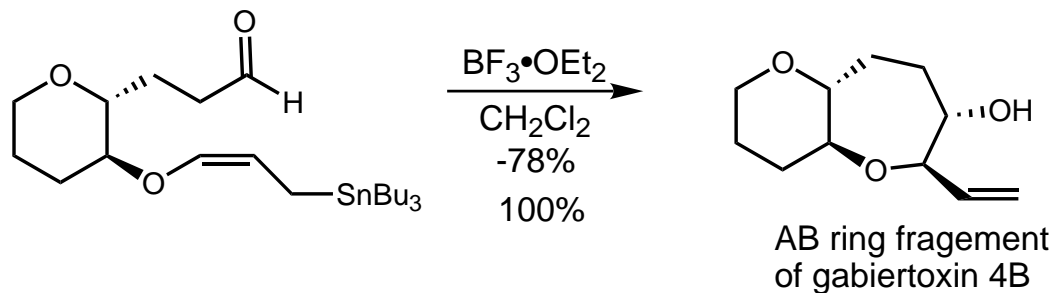
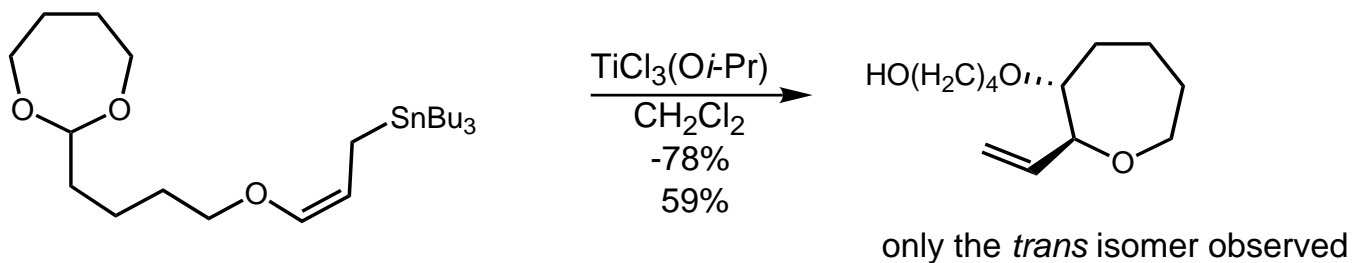
## An Interesting Cyclization



## Bergman Cyclization

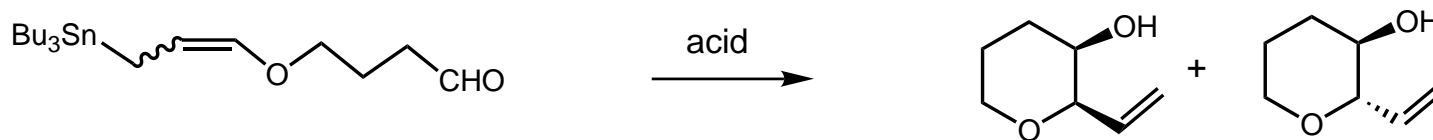


## Allyl Stannations



- fusion to 6 membered ring reduces conformational mobility of acyclic precursor
- cyclizations onto aldehydes are generally accompanied by higher stereocontrol and yields than onto acetals
- $\text{TiCl}_4$  doped with  $\text{Ph}_3\text{P}$  can be used to increase levels of diastereoselectivity
- Yamamoto has prepared the 6-7-7-6 and 7-7-6-6 systems of brevetoxin B and hemibrevetoxin respectively using this methodology

This reaction has extensively been studied under a wide range of conditions for THP synthesis:



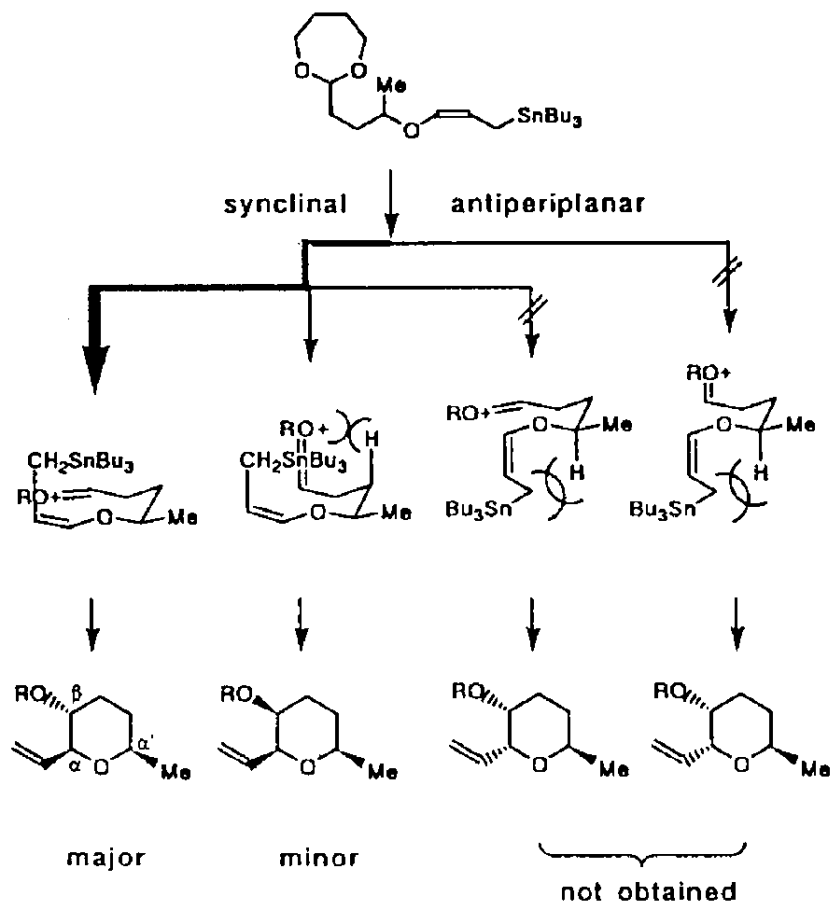
protic acid (TfOH) (Z-stannane) major  
 protic acid (TfOH) (E-stannane) minor  
 Lewis Acids (Z- or E-stannane) minor

minor  
 major  
 major

Y. Yamamoto  
 TL 1993, 1313.  
 Chem Comm 1993, 1638.  
 TL 1991, 4505.  
 TL 1991, 7069.  
 JOC 1990, 6066.

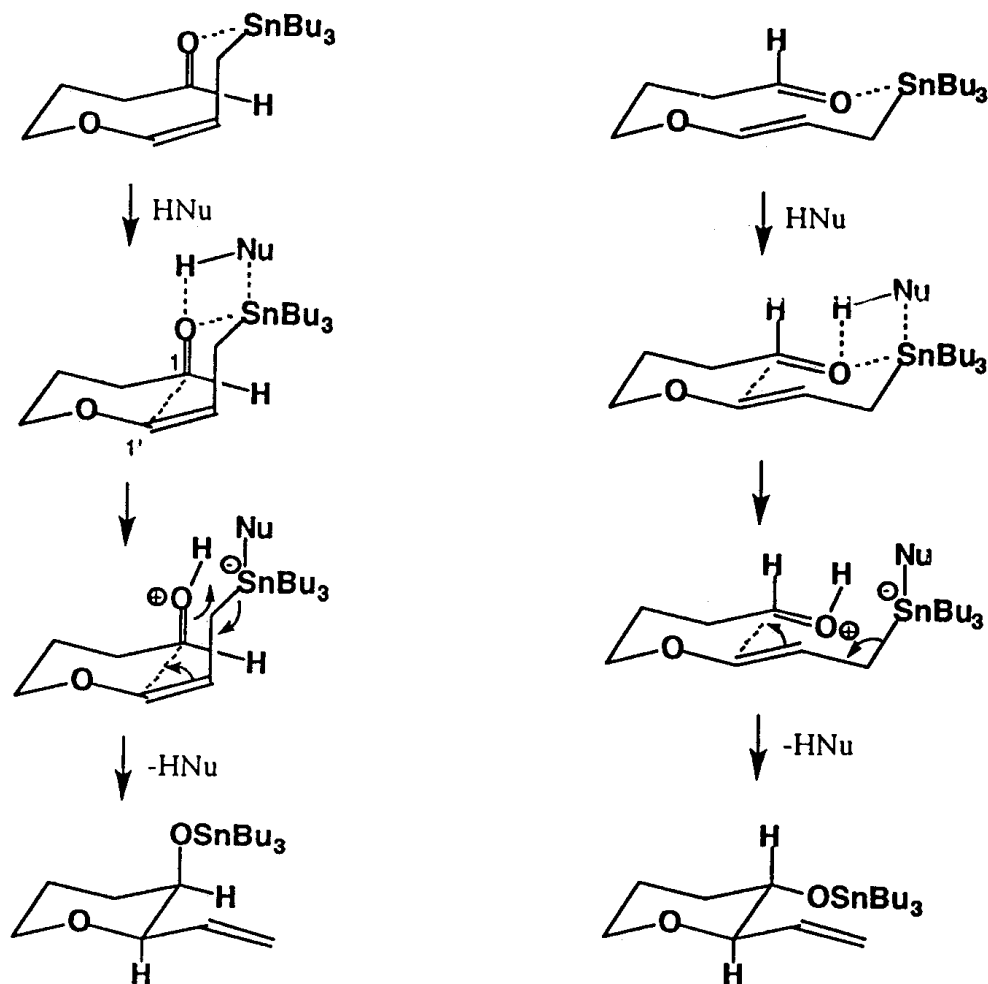
## Allyl Stannations: Mechanism and Stereochemistry

6-membered rings always give *anti* products when promoted with Lewis Acid

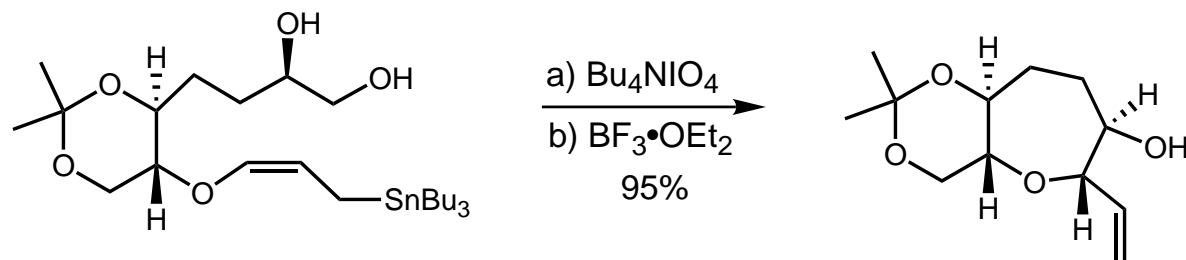
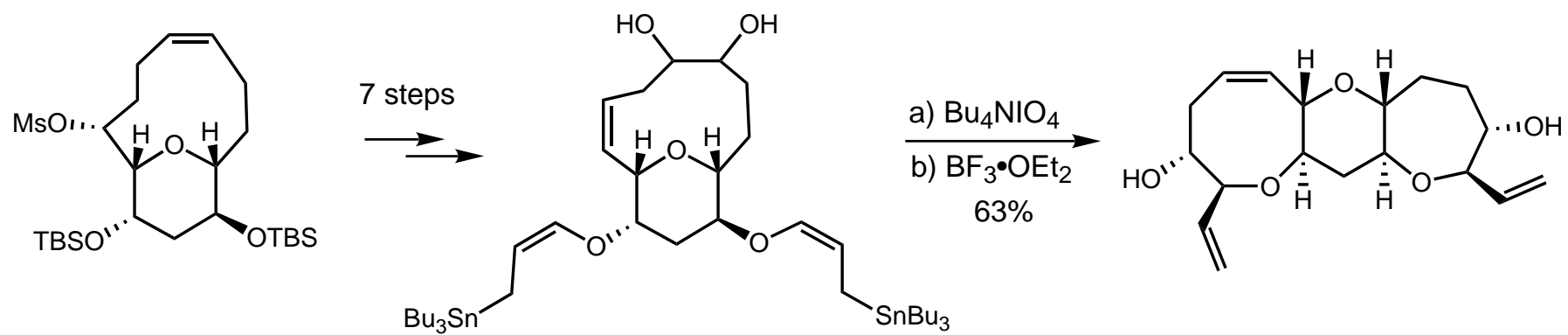


"In the 7-membered cyclization, the transition state geometry becomes more flexible, being able to give a thermodynamically stable *trans* isomer with high diastereoselectivity".

6-membered rings give *anti* or *syn* products when promoted with protic acid, depending on allylstannane geometry

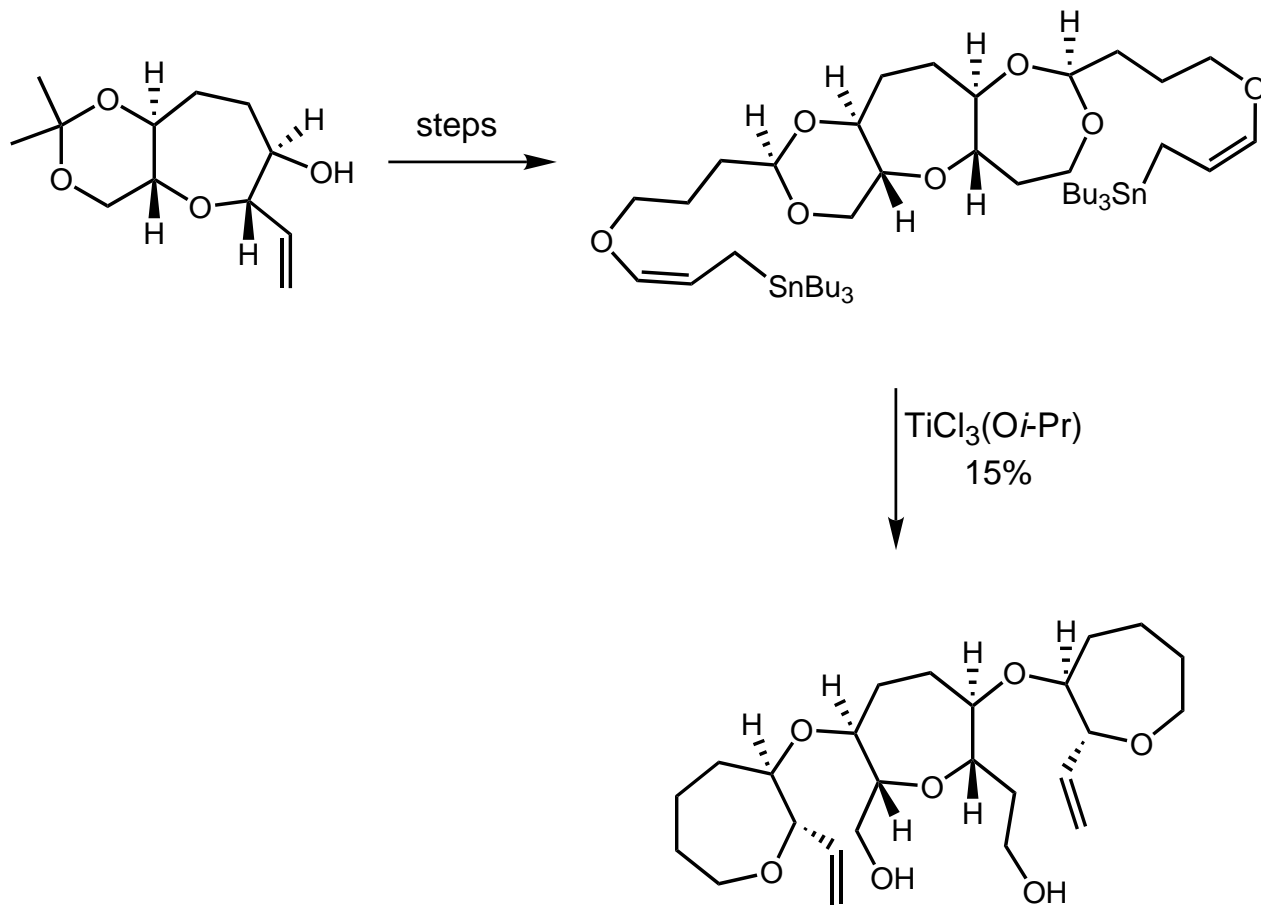


## One-Pot Oxidation-Cyclization



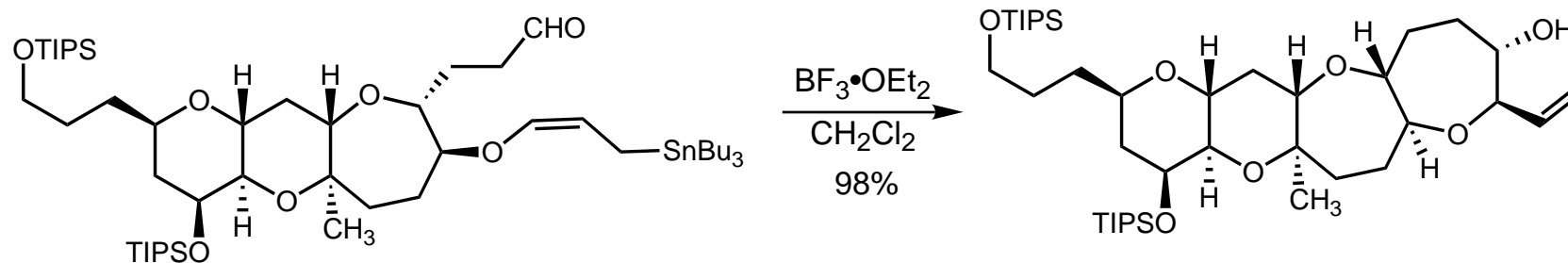
J. D. Martin  
TL 1992, 3389.  
TL 1996, 2869.

## A Disappointing Allyl Stannation



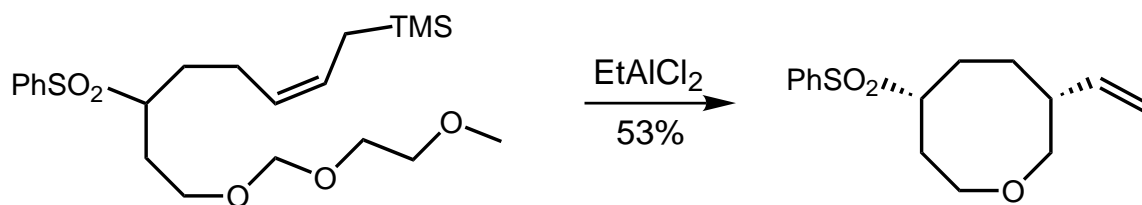
## A More Complex Allyl Stannation

Both 7-membered rings of hemibrevetoxin B formed using this method; The latter is shown here:



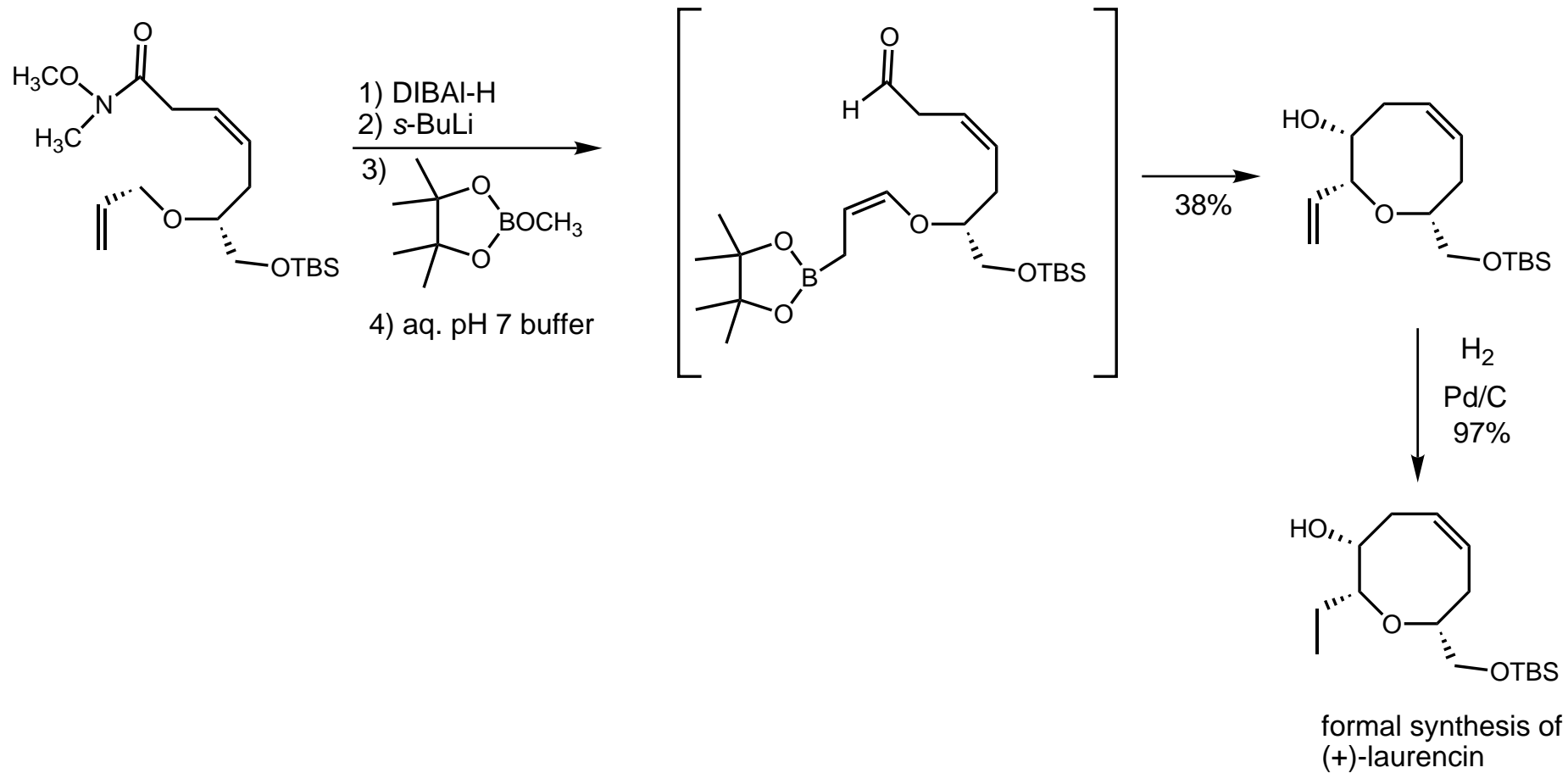
Yamamoto  
TL 1995, 5777.

## A Lone Allyl Silylation



Simpkins  
Tetrahedron, 1991, 7689.

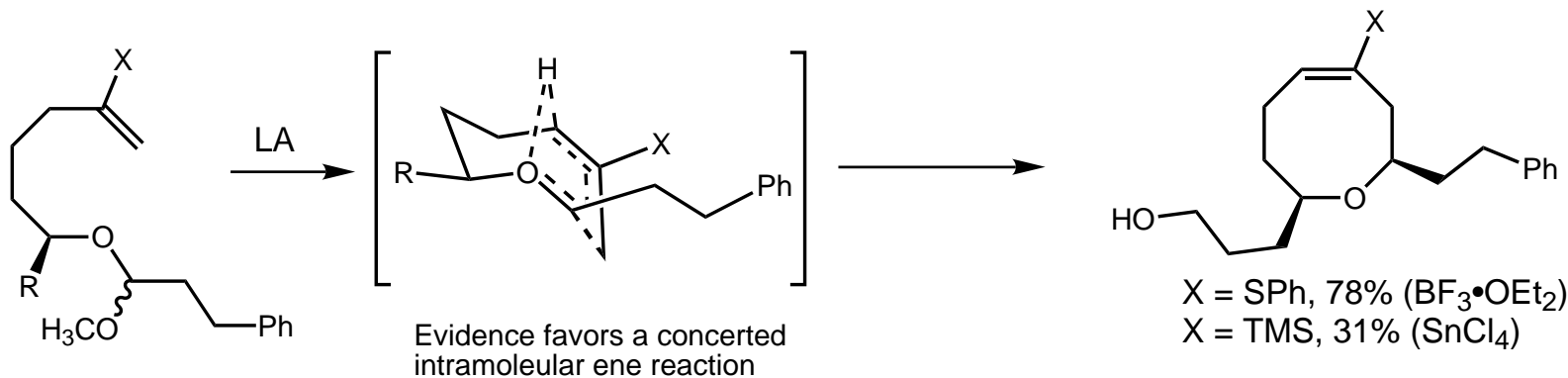
## Intramolecular Allylboration



R. W. Hoffmann  
JACS 1997, 7499.

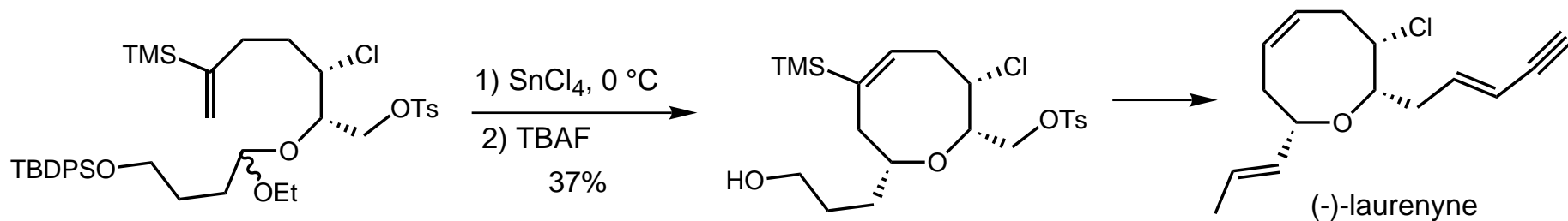


## Overman Acetal Alkene Cyclizations



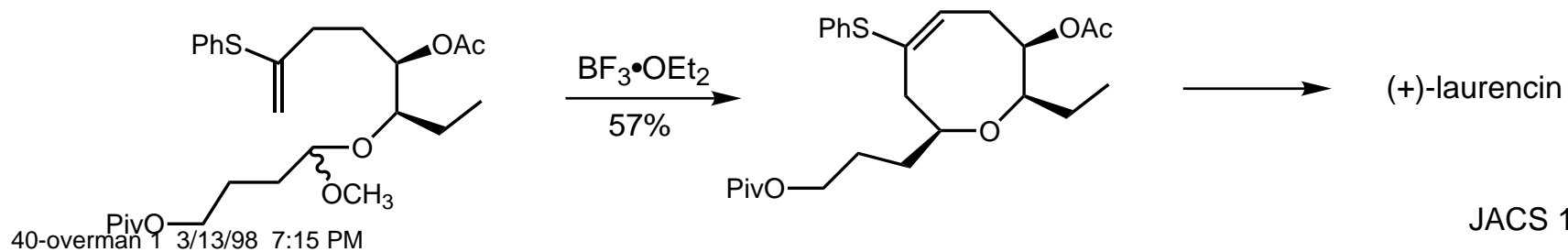
JACS 1986, 3516.  
JACS 1990, 4386.  
JACS 1990, 4399.

## Laurenyne



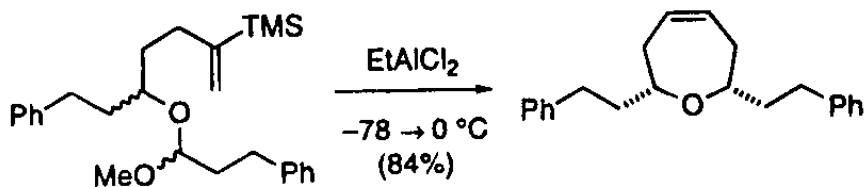
JACS 1988, 2248.

## Laurencin



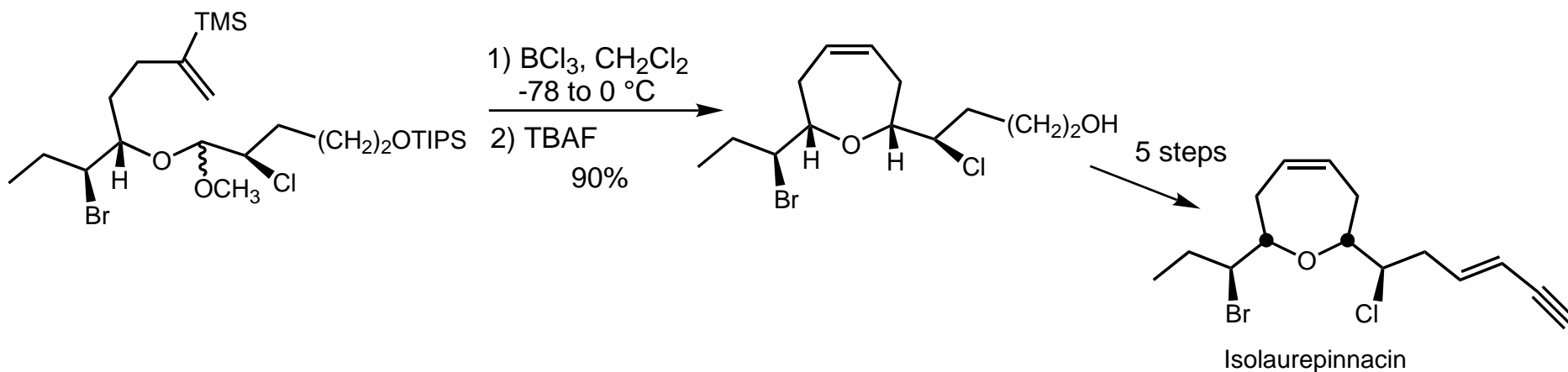
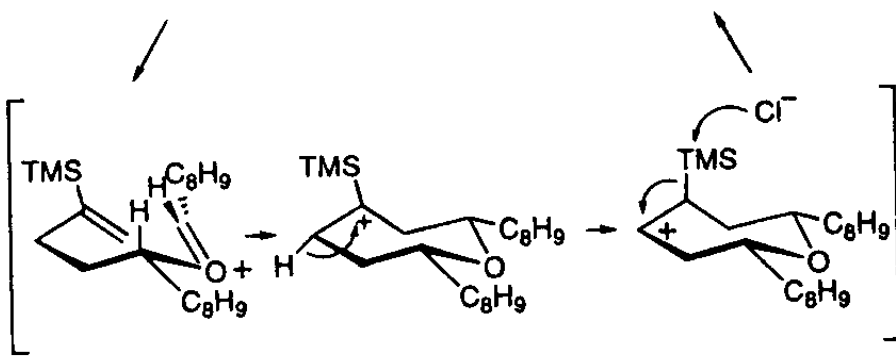
JACS 1995, 5958.

## Overman Acetal Alkene Cyclizations



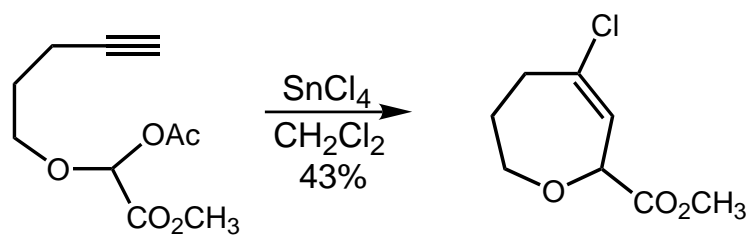
Three effects are responsible for the high yielding transformation:

- Initial Prins cyclization occurs in an endocyclic sense as a result of the greater stability of a tertiary  $\alpha$ -silyl cation than a primary  $\beta$ -silyl cation
- Cyclization of the more stable (*E*)-oxocarbenium ion occurs preferentially in the conformation which minimizes destabilizing allylic interactions
- Inductive withdrawal by the ring oxygen controls the regioselectivity of the hydride migration



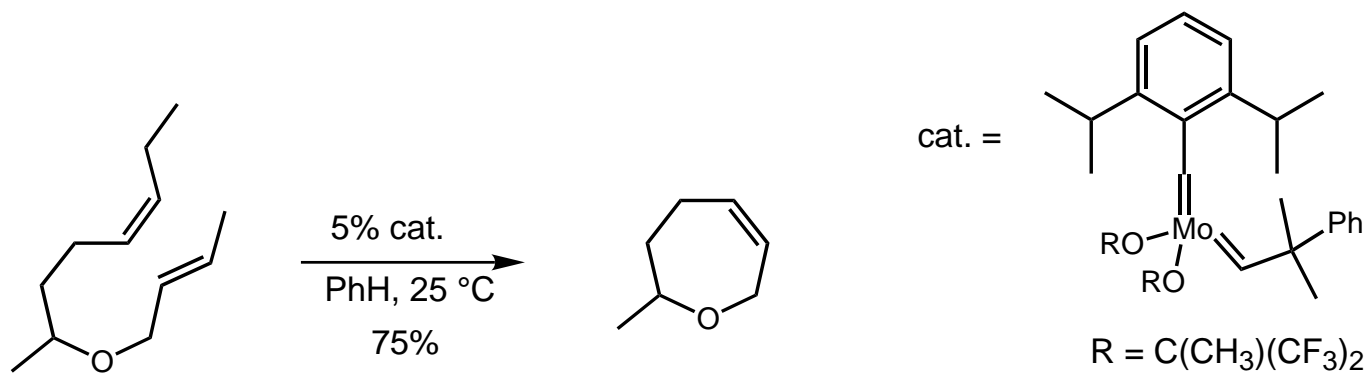
SynLett 1992, 811.  
 JACS 1993, 9305.  
 JACS 1997, 2447.

## Acetal Alkyne Cyclization



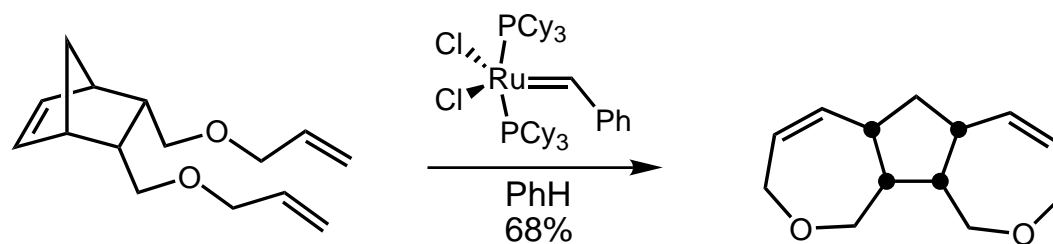
Speckamp  
Tetrahedron 1994, 7115.

### Ring Closing Metathesis



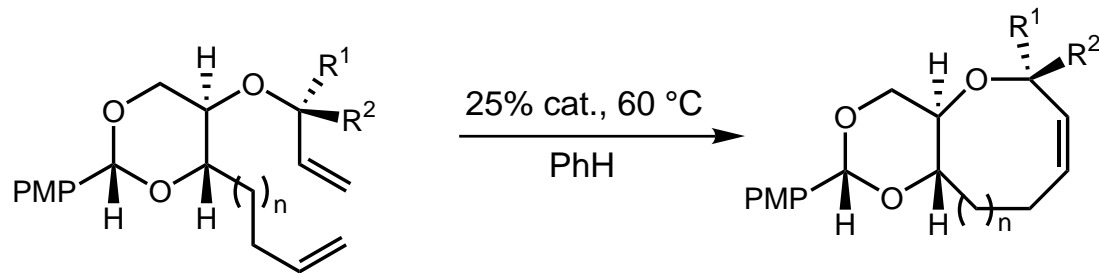
Grubbs  
JACS 1992, 5426.  
JACS 1993, 9856.

### Ring Opening - Ring Closing Metathesis



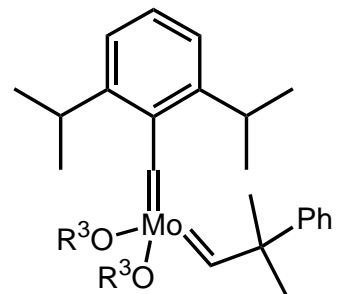
Grubbs  
JACS 1996, 6634.

### RCM for Brevetoxin and Ciguatoxin



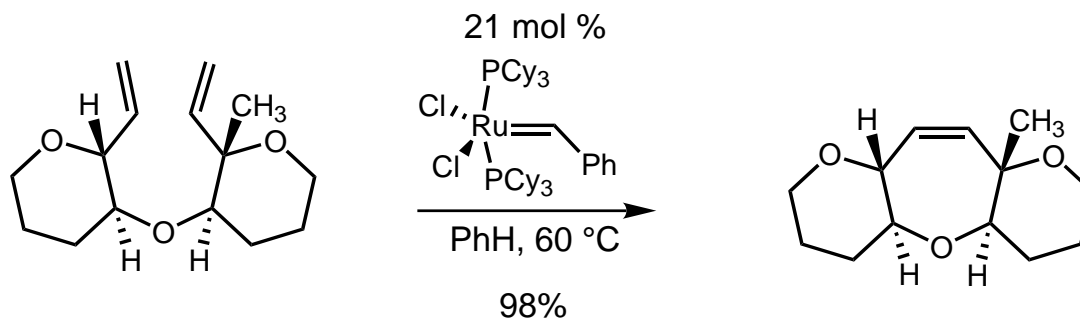
$n = 1, R^1 = H, R^2 = Et, 97\%$   
 $n = 1, R^1 = Et, R^2 = H, 86\%$   
 $n = 2, R^1 = H, R^2 = Et, 86\%$   
 $n = 2, R^1 = Et, R^2 = H, 14\%$   
 $n = 2, R^1 = H, R^2 = H, 58\%$

cat. =



$R^3 = C(CH_3)(CF_3)_2$

Clark  
TL 1997, 127.



Hirama  
Synlett 1997, 980.

## Ring Closing Metathesis

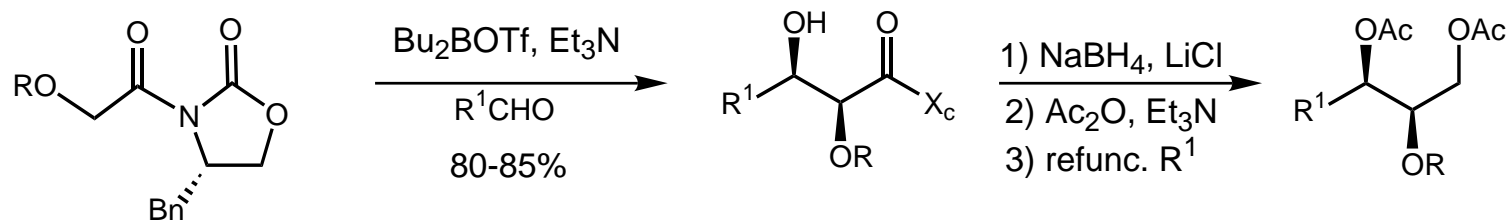


Table 1

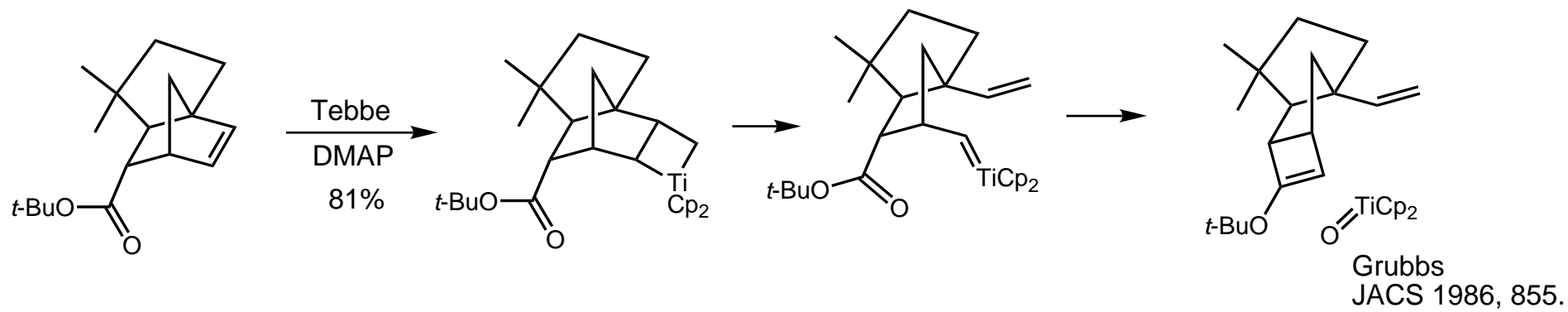
Diene	Product	Yield <sup>a,b</sup>
 4a	 8	90% 1 h
 4b	 9	95% 2 h
 4c	 10	73% (17% dimer) 2 h
 7a	 11	94% 30 min
 7b	 12	89% (10% dimer) 1 h

<sup>a</sup> Reactions were carried out in dichloromethane at 40 °C with 5–7 mol %  $(\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$ . <sup>b</sup> Yields are for isolated, chromatographically purified products.

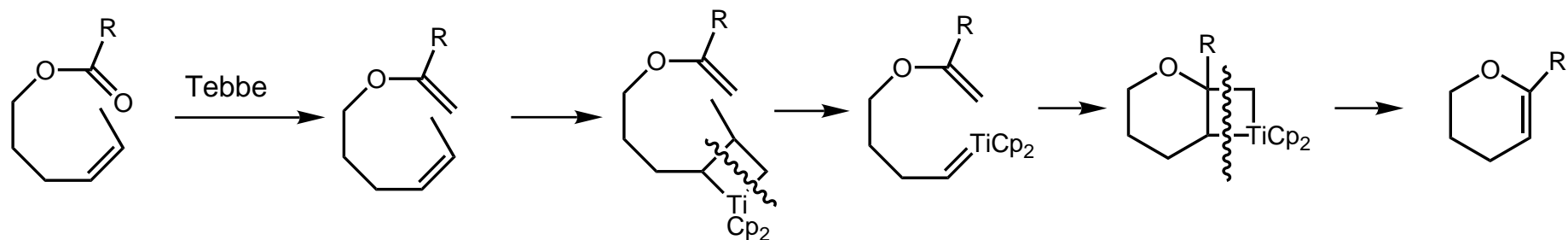
Crimmins  
JOC 1997, 7549.

## Tandem Methylenation - Metathesis of Olefinic Esters

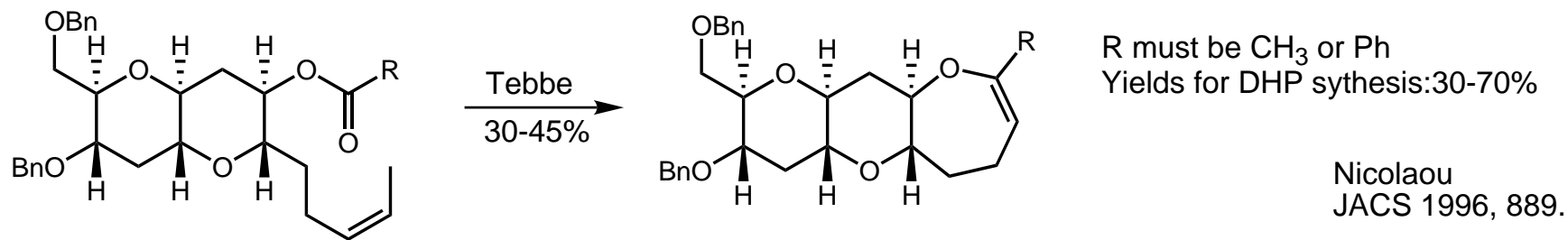
The Precedent:



The General Scheme:



The Example:

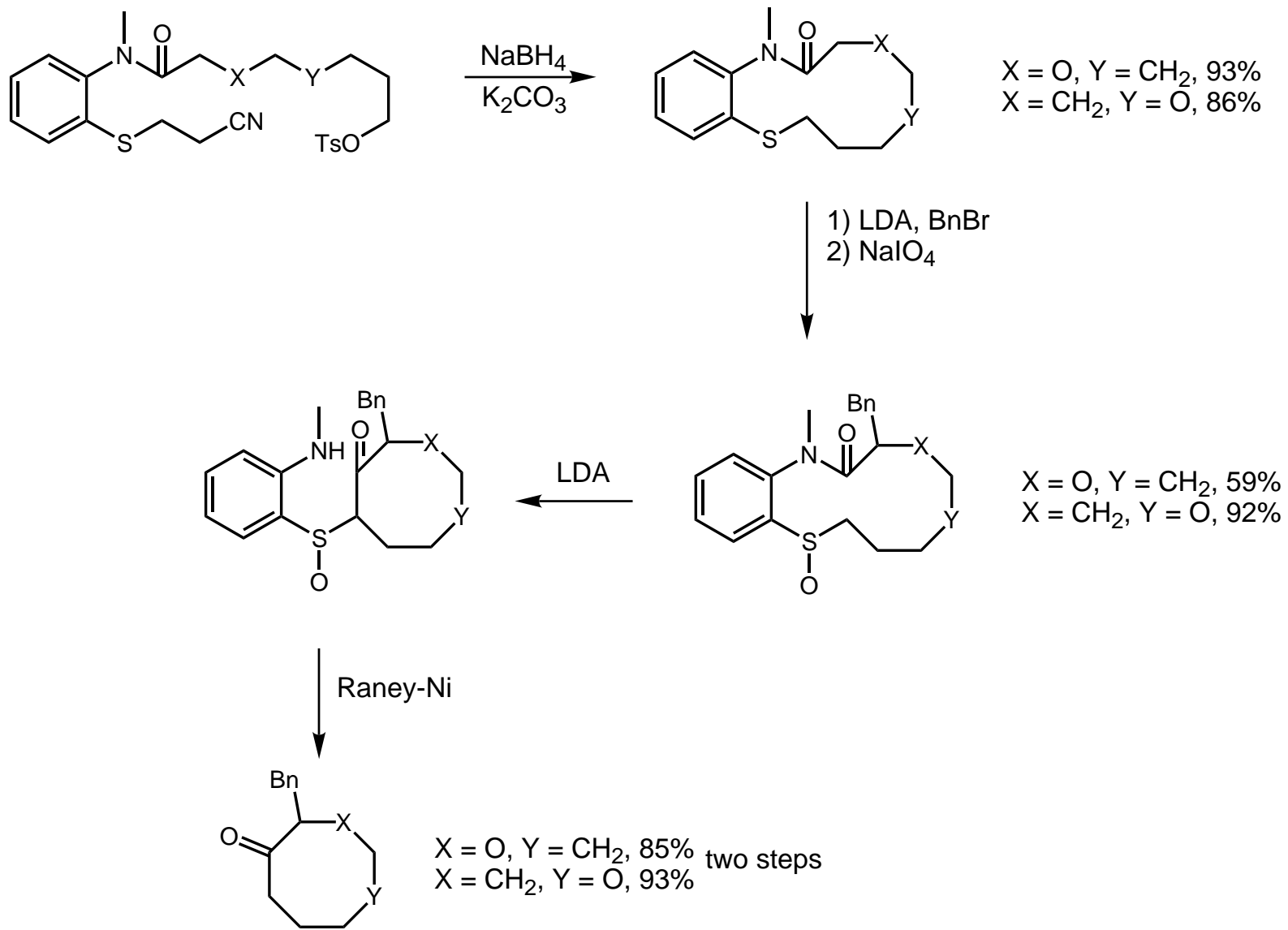


The Critique:

The reaction awaits further vigorous development before being regarded as widely applicable...  
...improvement in the efficiency is necessary.

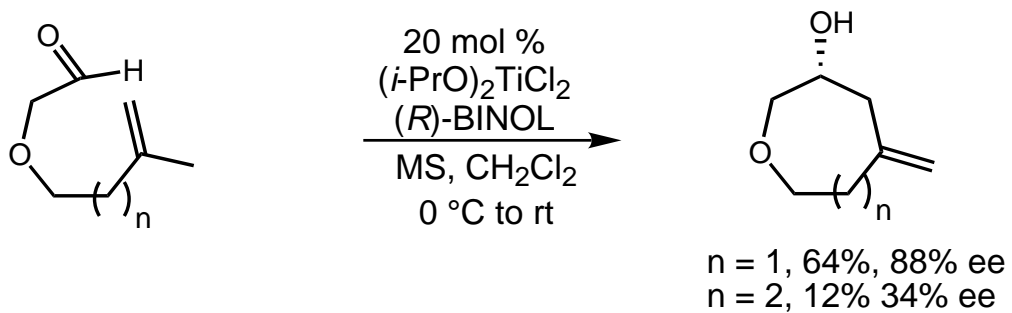
Paquette  
Chemtracts, 1997, 14.

## Use of a Tether

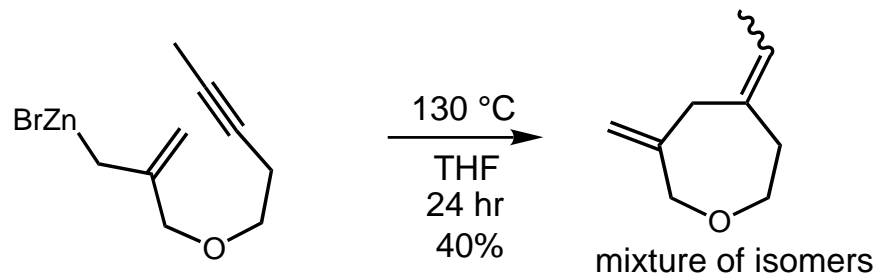




## Ene Reactions

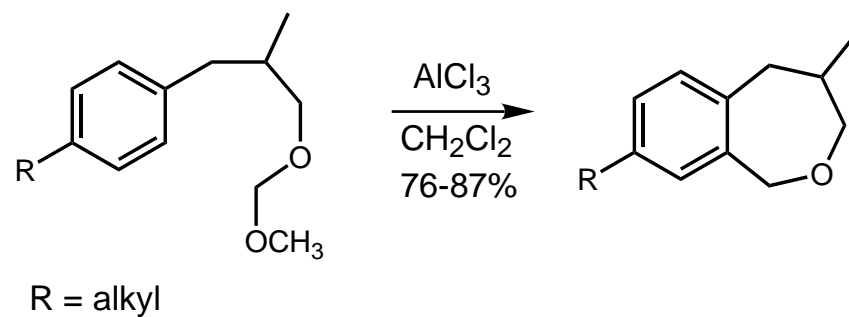


Mikami  
Tetrahedron:Asymmetry, 1991, 1403.



Klumpp  
Tetrahedron, 1992, 6105.

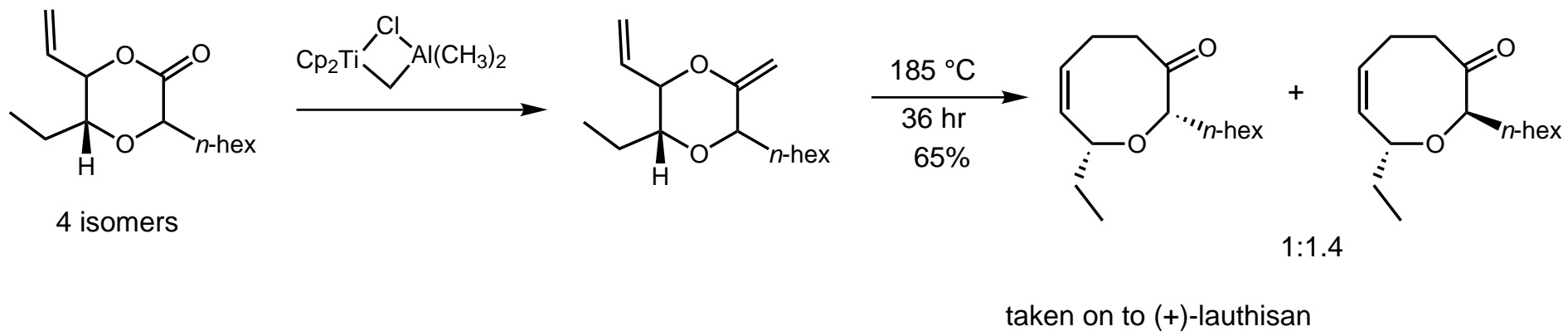
## Friedel Crafts Alkylation



Skouroumounis  
Helv. Chim. Acta, 1996, 1095.

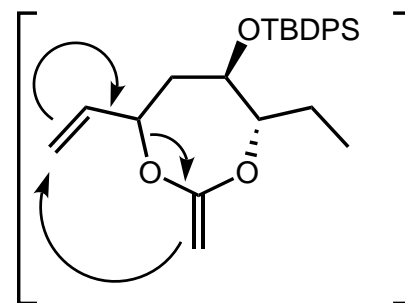
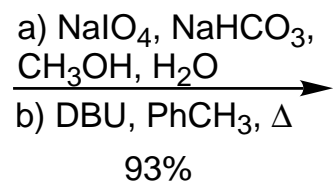
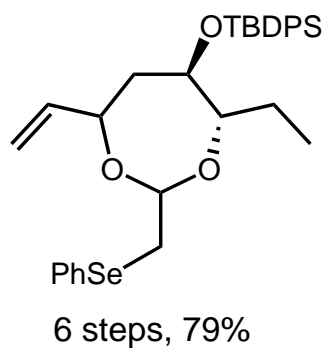
# Rearrangement Reactions

## Claisen Rearrangement

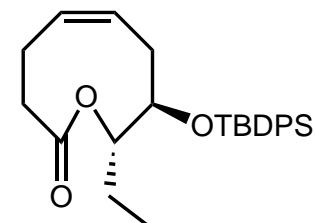


Paquette  
JOC 1990, 1703.  
Tetrahedron 1990, 4487.

## Ketene Acetal Claisen Rearrangement

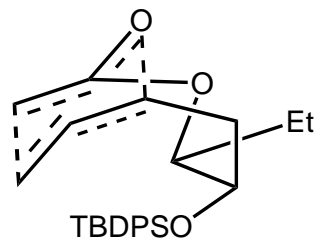
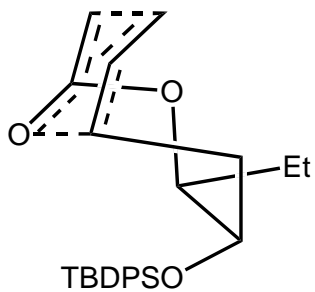


mixture of ketene acetals

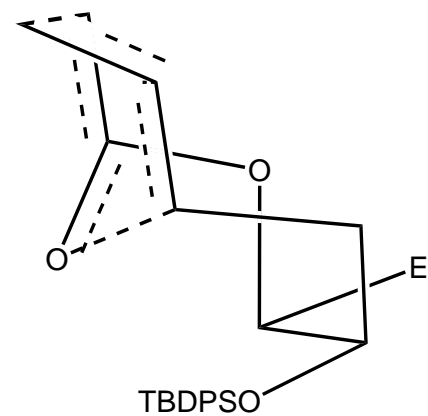


one isomer

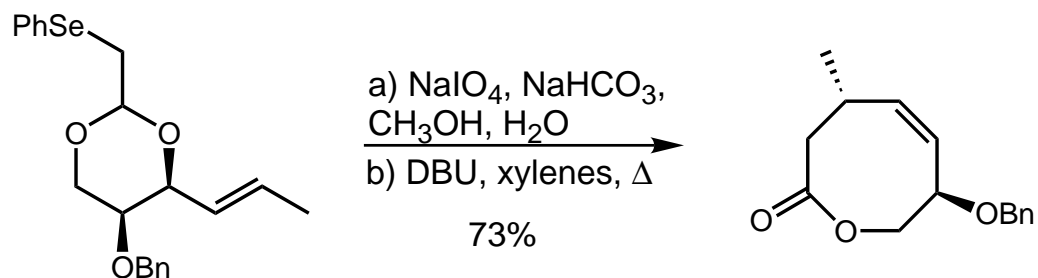
A chair TS for each isomer leads to the same product:



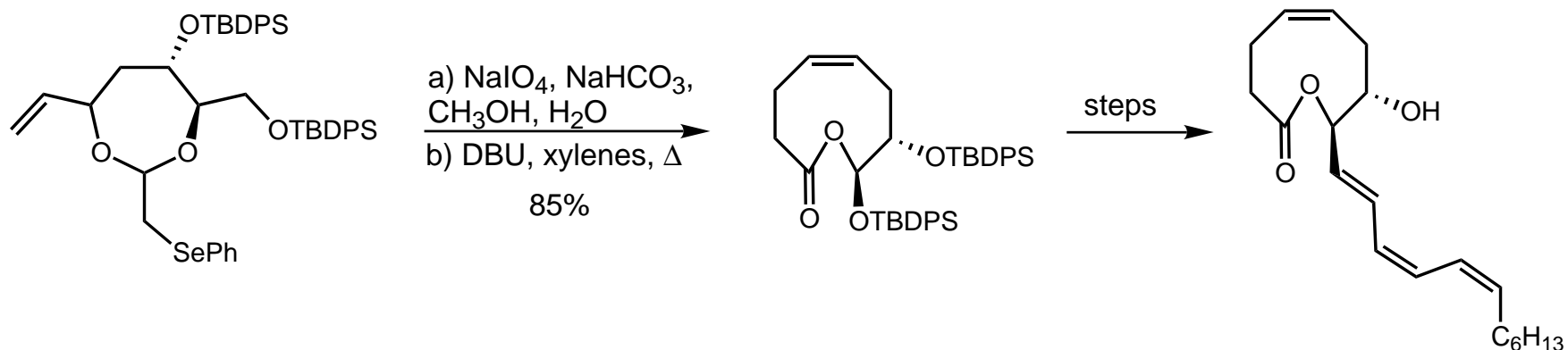
A boat TS would lead to a *trans* double bond (not observed)



## Substituted Double Bonds



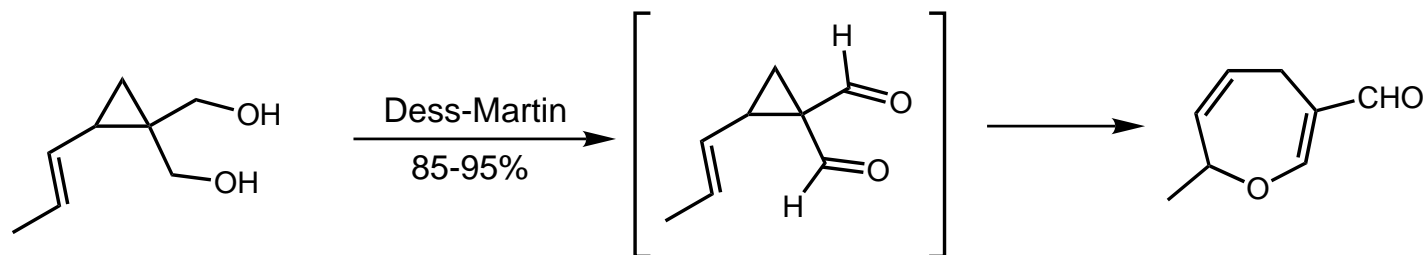
## Asciatrienolide A: Disproof of Structure



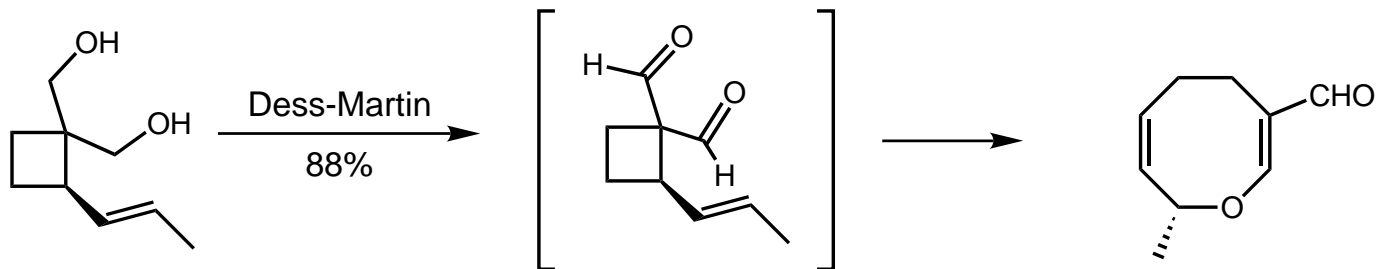
proposed structure of Asciatrienolide A - not identical to the natural product (which was shown to be a 10-membered lactone (with one more methylene))

Holmes  
JCS Perkin I, 1993, 2743.  
JACS 1993, 5815.

## Retro-Claisen Rearrangement



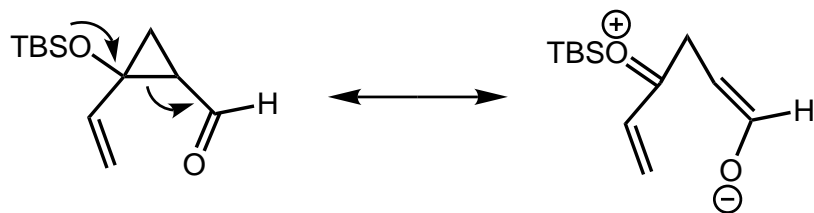
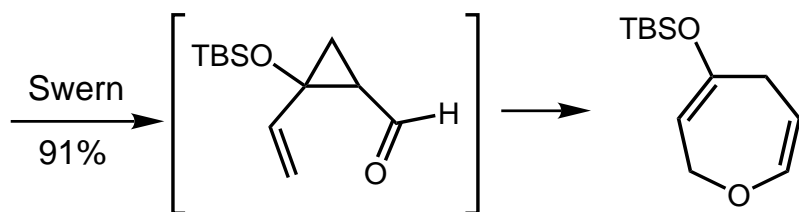
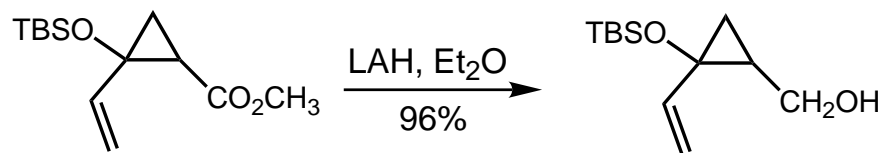
- substitution at all positions of the cyclopropane and olefin are tolerated



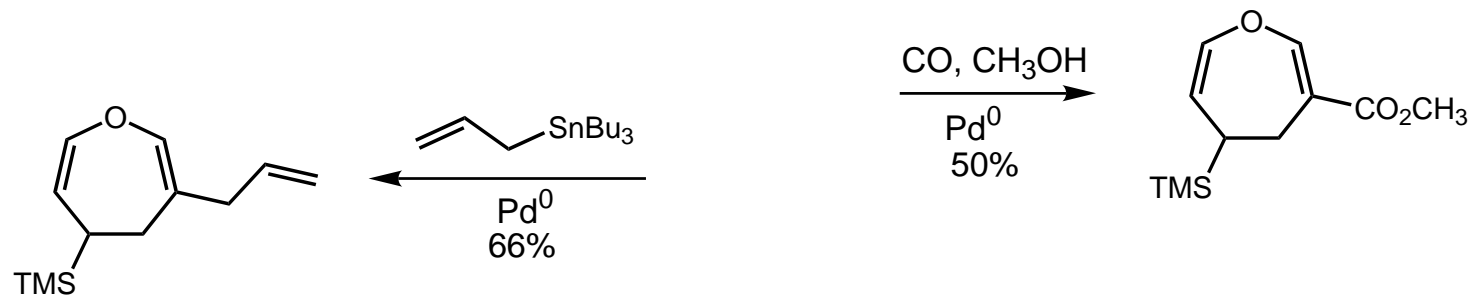
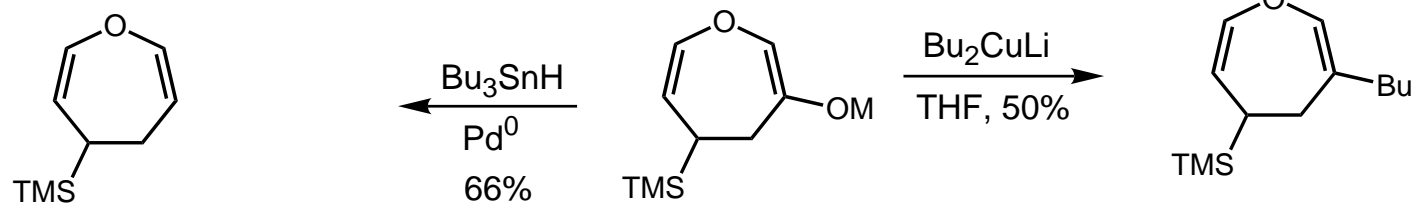
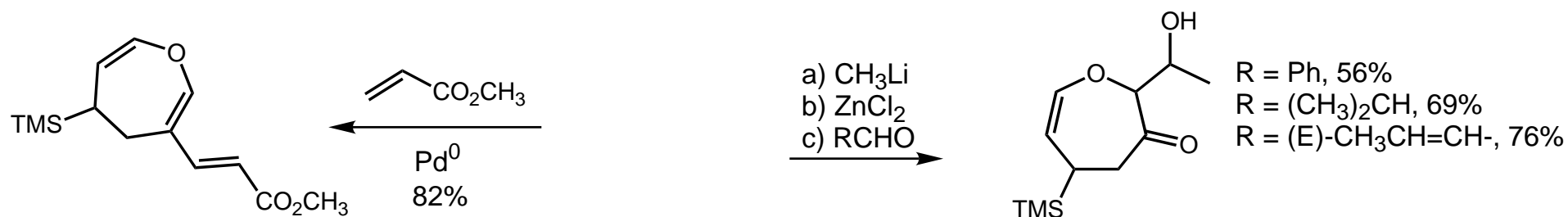
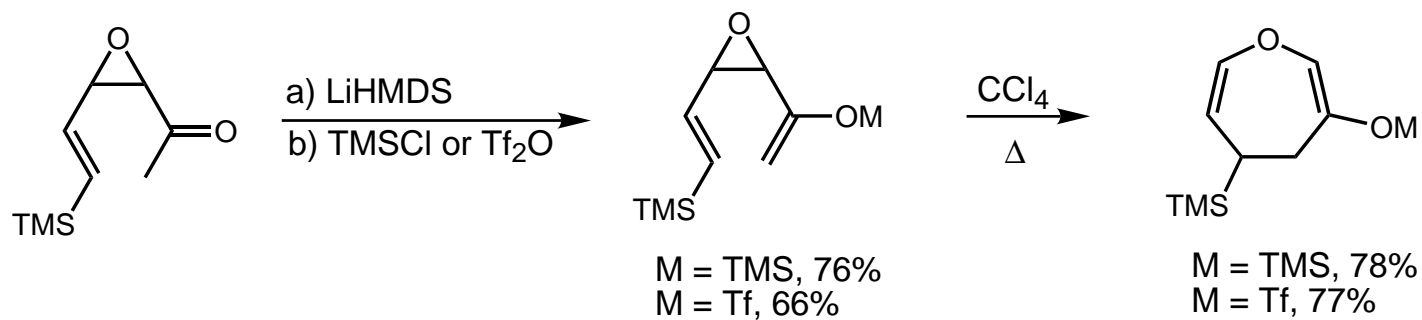
- enantiopure cyclobutane delivers enantiopure dihydrooxacenes

Boeckman  
JOC 1993, 1295.  
JOC 1997, 6456.

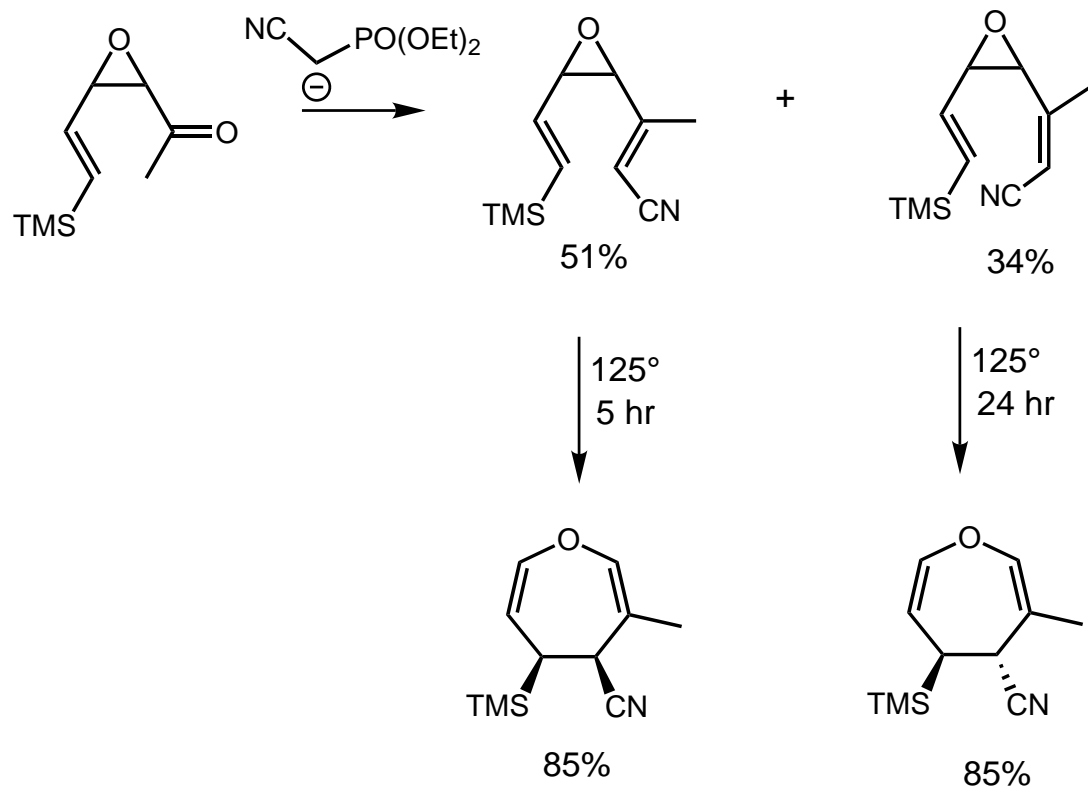
## Retro-Claisen Rearrangement



### Cope Rearrangement of Divinylepoxides



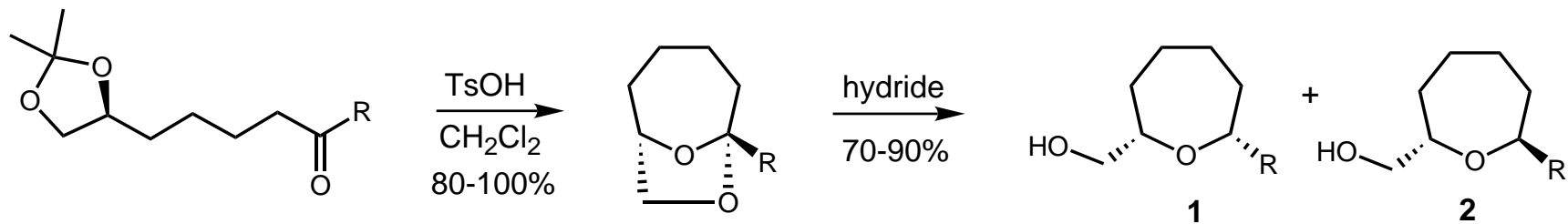
## More Substituted Cope Rearrangements





# Ring Expansion Reactions

## Bicyclic Ketal Reduction

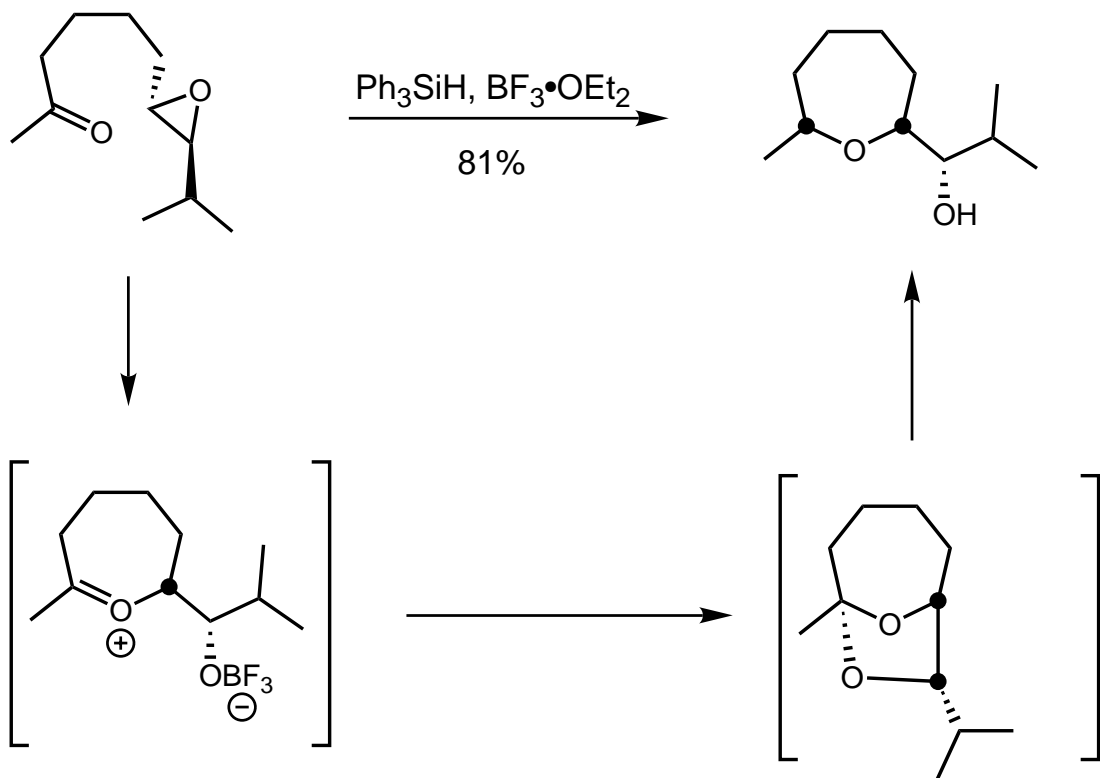


Reducing Agent  
TiCl<sub>4</sub>/Et<sub>3</sub>SiH, -78 °C  
DIBAL-H, rt

Ratio **1:2**  
~10:1  
<2:98

R = C<sub>2</sub>H<sub>4</sub>OBn

## Bicyclic Ketals: One Pot Processes



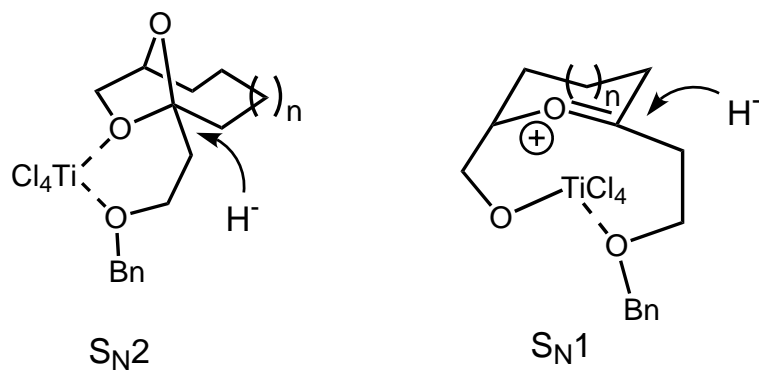
works well for 6-membered rings as well

Kotsuki  
JOC 1989, 5153.  
Synlett, 1992, 97.

## Stereochemical Rationale

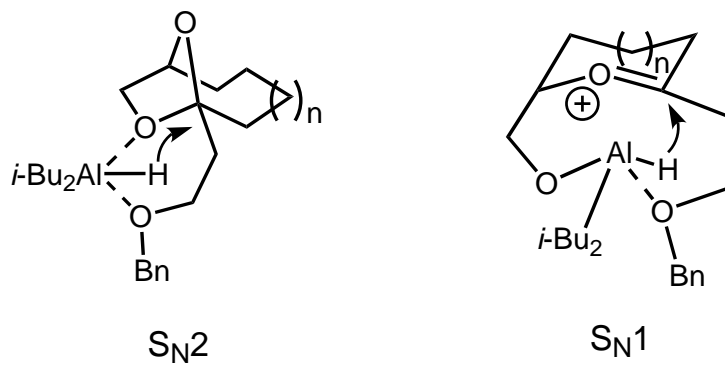
TiCl<sub>4</sub>/Et<sub>3</sub>SiH

Hydride delivery from behind coordinated metal

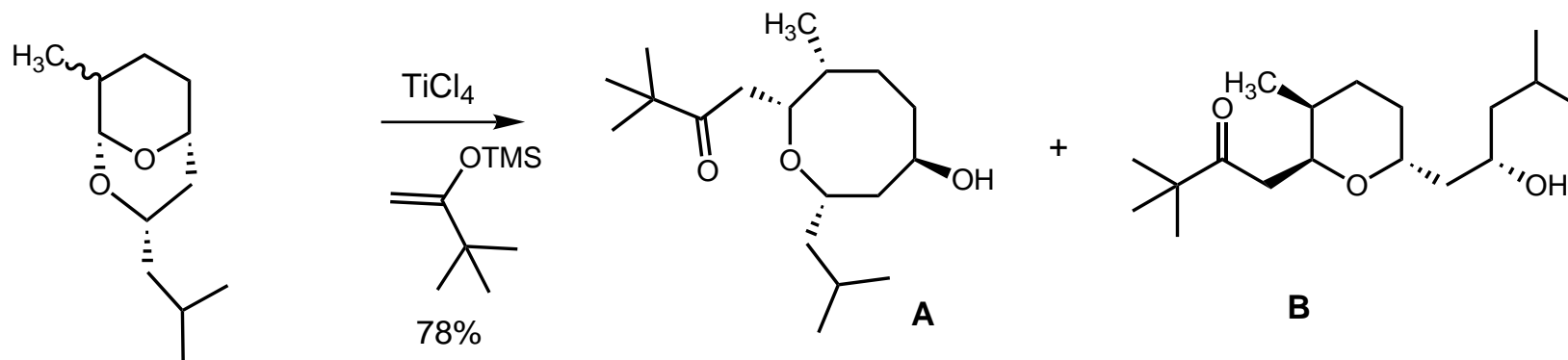


DIBAL-H

Hydride delivery from same face as coordinated metal

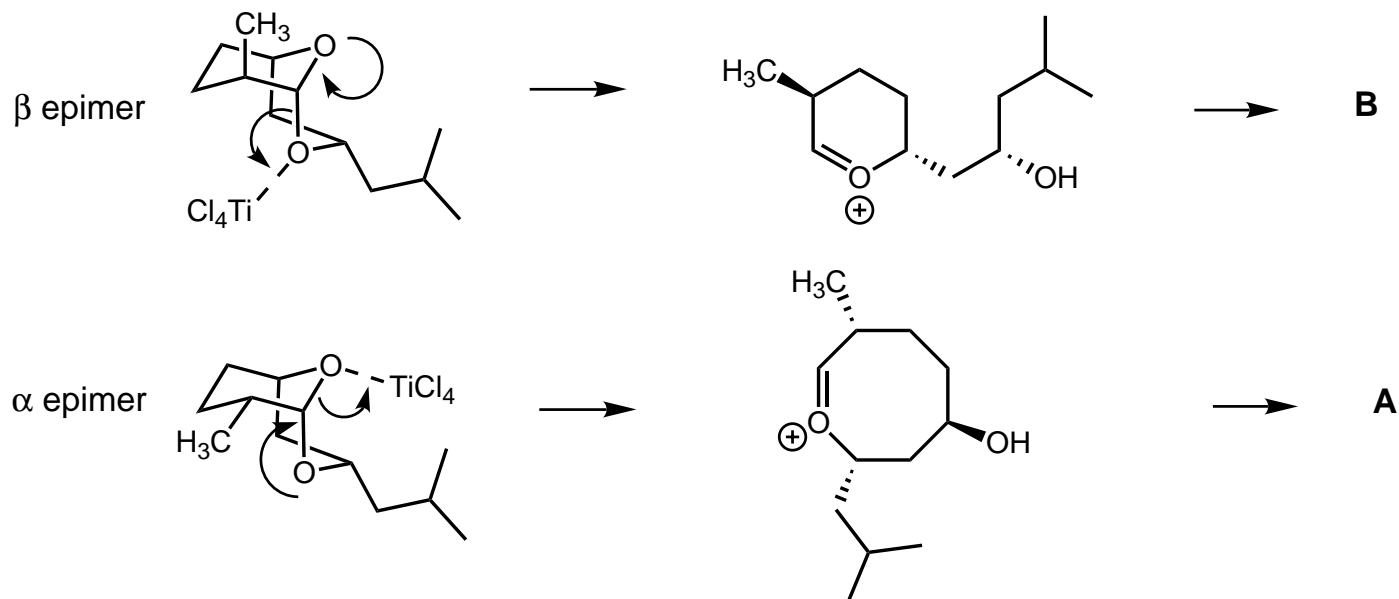


## Acetal Cleavage



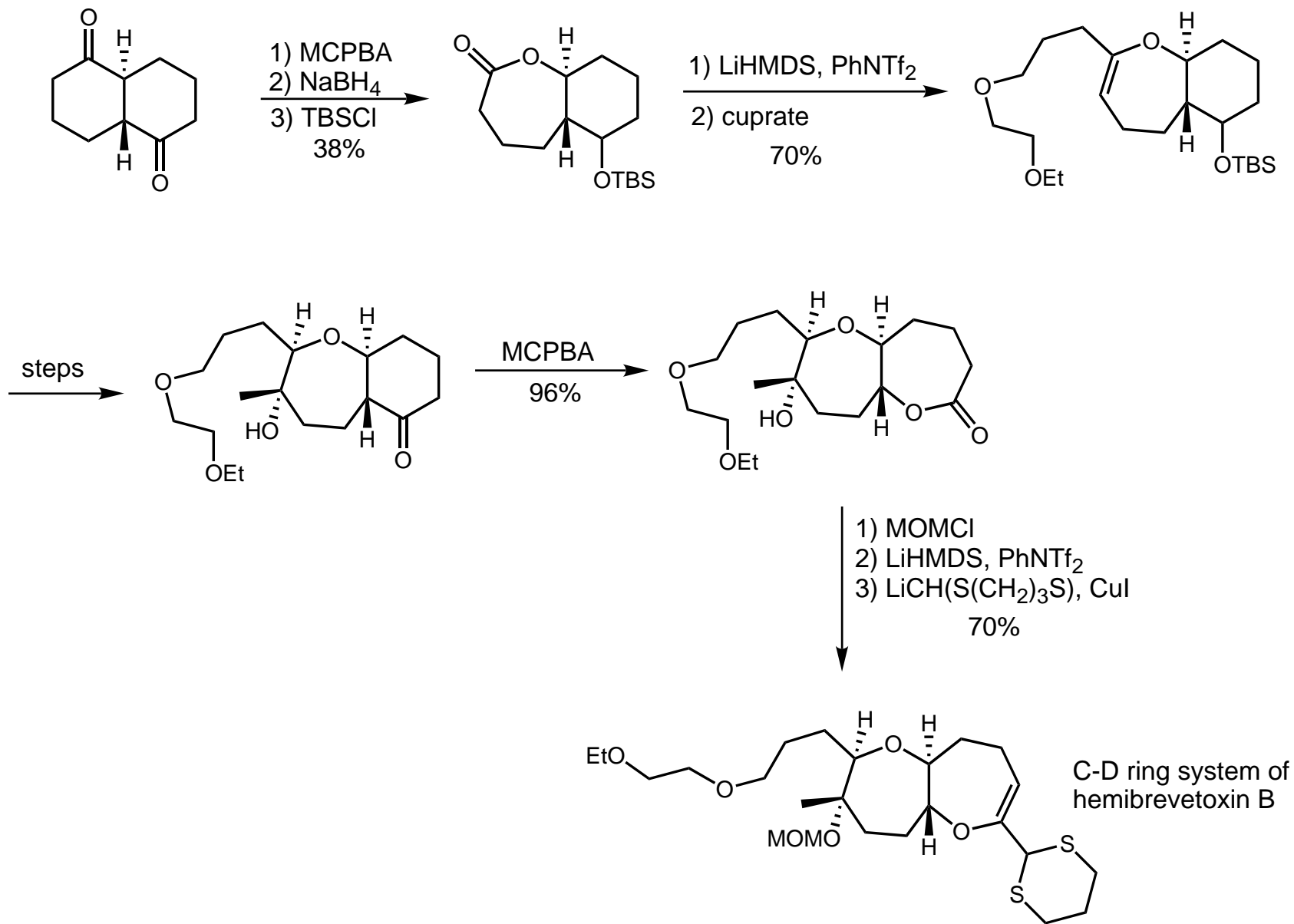
$\alpha:\beta$ $\text{CH}_3$ Ratio	Product <b>A</b> : <b>B</b> Ratio
78:22	77:23
>95:<5%	>95%:<5%

Methyl group directs LA to least hindered acetal oxygen:



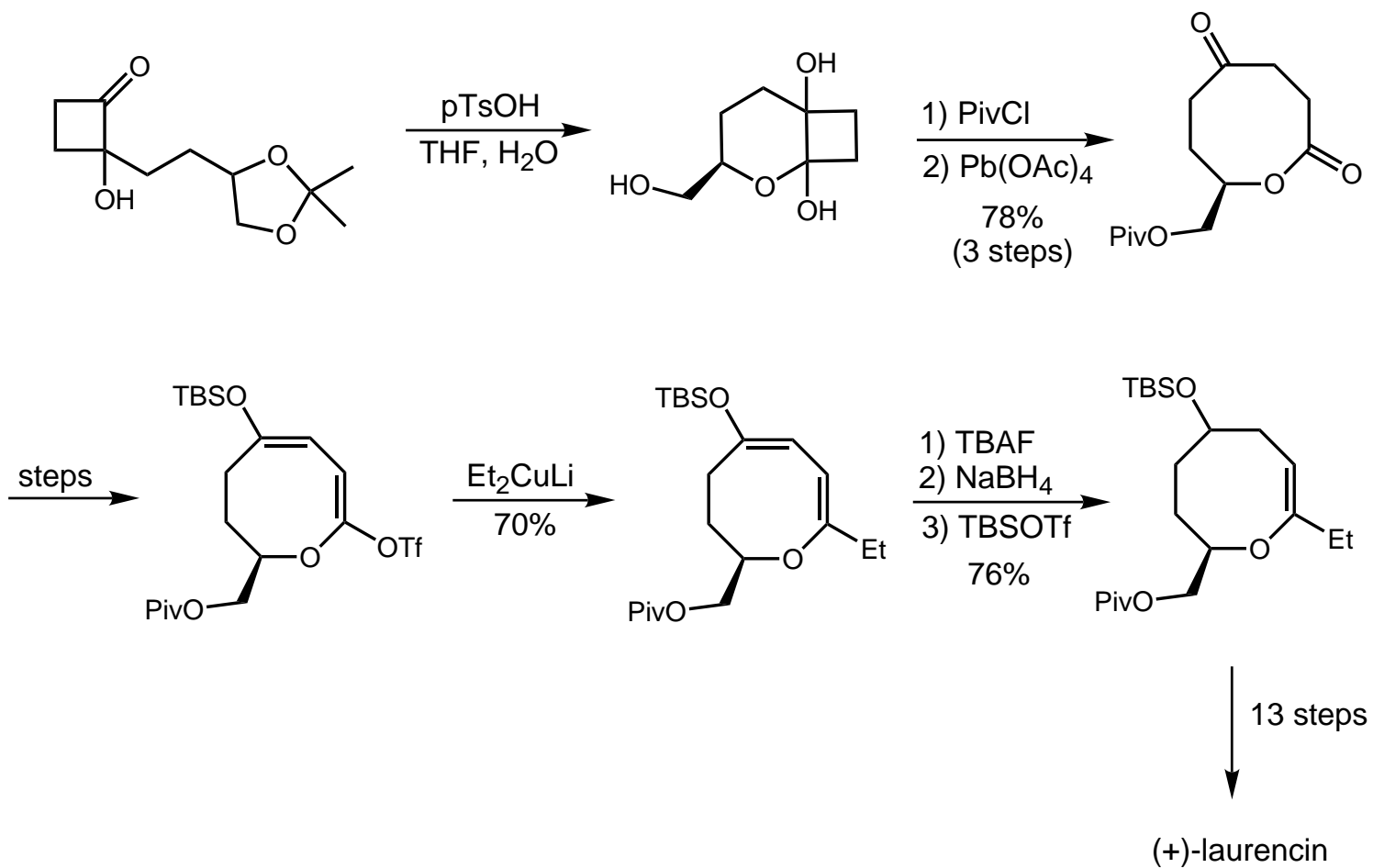
P. A. Bartlett  
JOC 1989, 98.

## Baeyer-Villiger Expansion

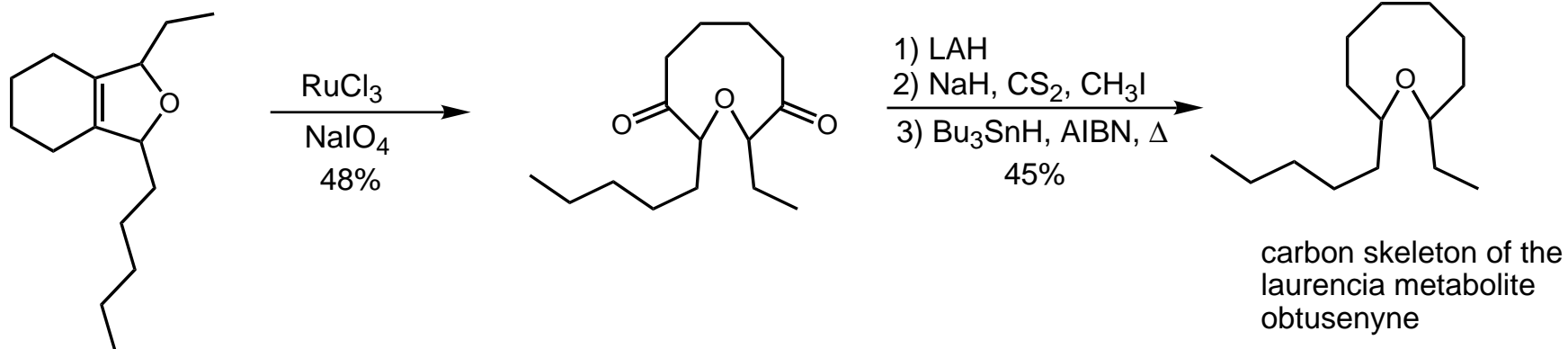
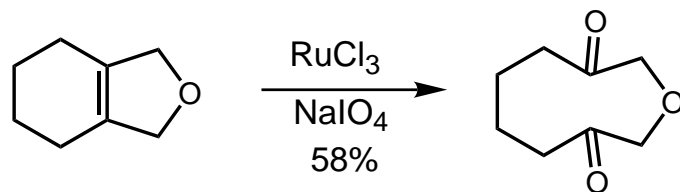


Murai  
Chem. Lett., 1992, 1587.

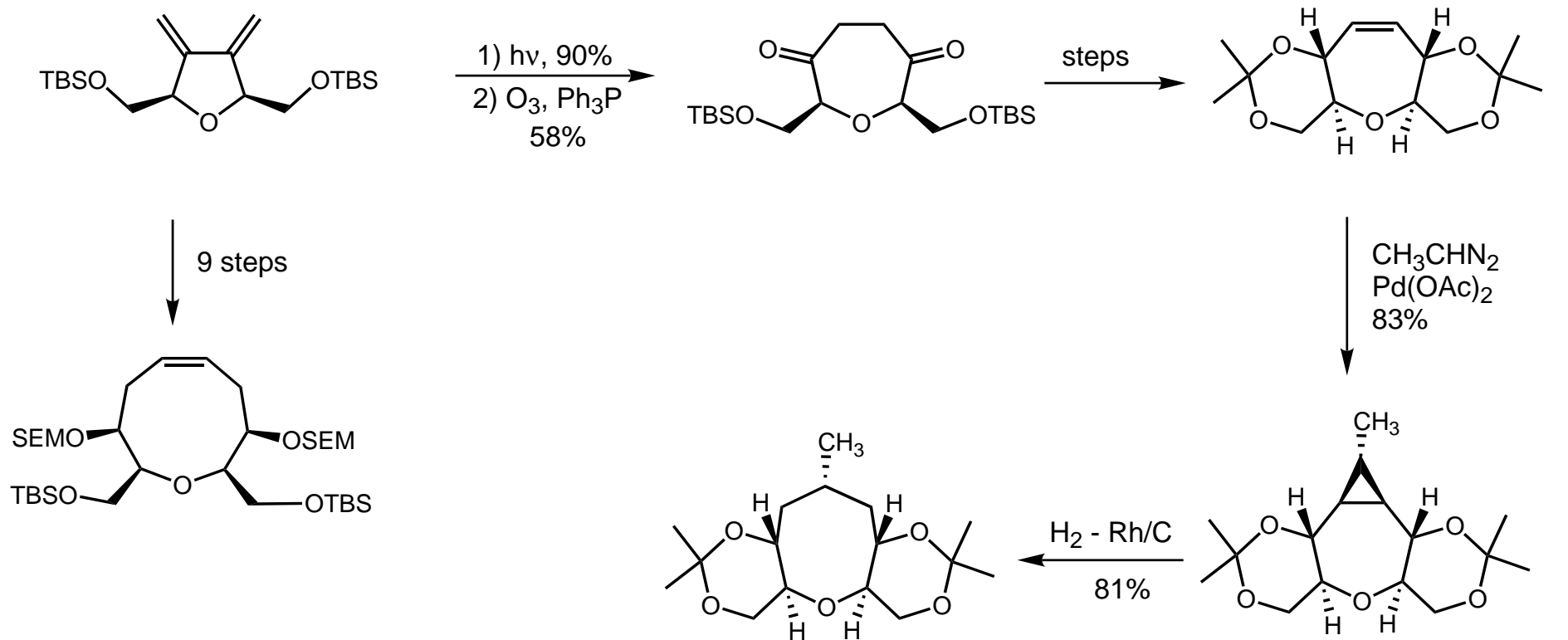
## Oxidative Ring Expansions



## Oxidative Cleavage of Tetrahydrophthalans



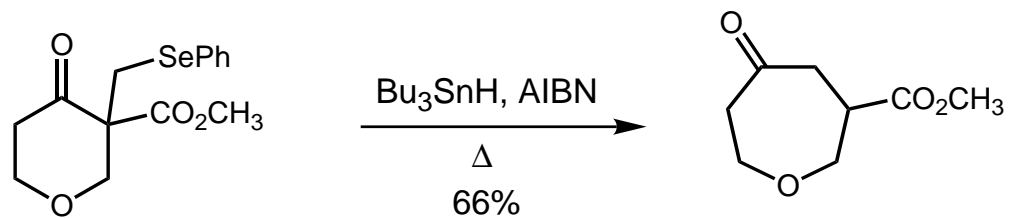
## Ring Expansions Toward Ciguatoxin



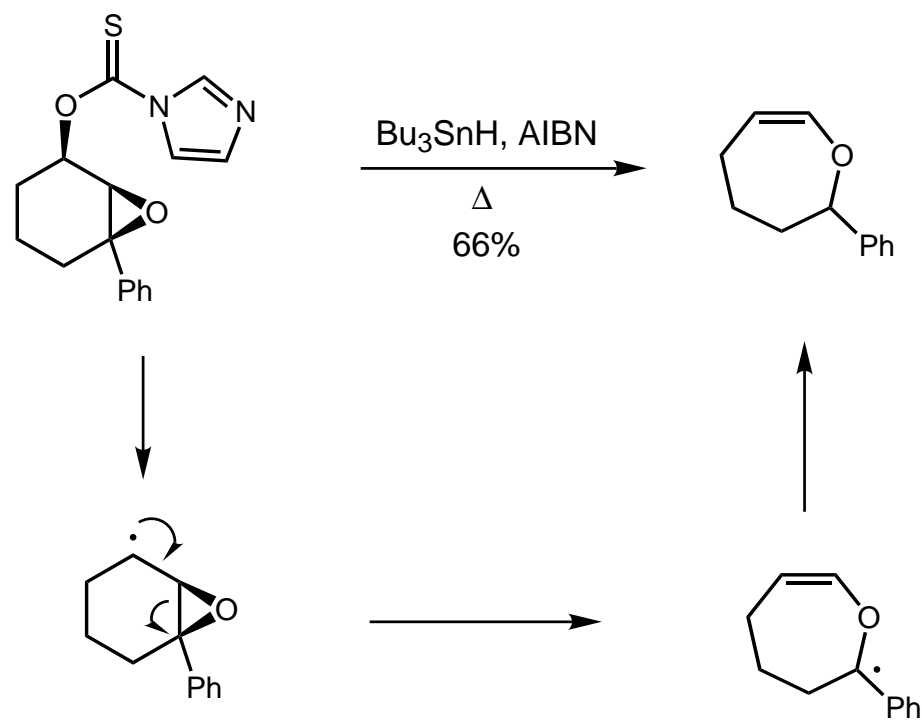
only add'n from  $\beta$  face  
 3:1 exo:endo  
 Simmoms-Smith gives  
 only  $\alpha$  face addition

Hirama  
 Synlett 1996, 1165.  
 Synlett, 1997, 980.

## Free Radical Expansions



Dowd  
Tetrahedron, 1991, 4847.

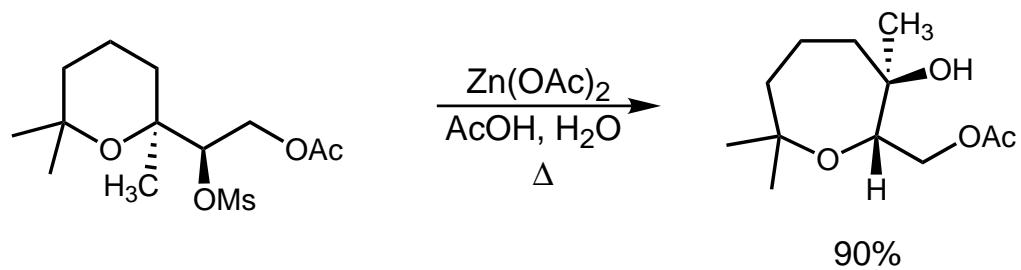
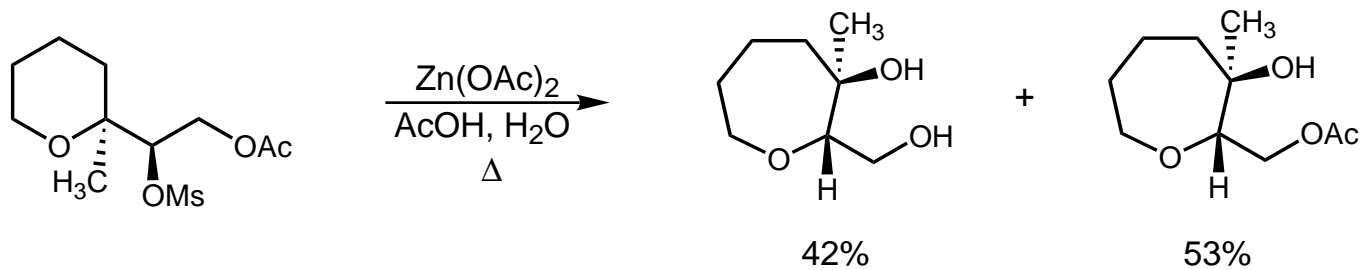


- phenyl group needed to stabilize the radical, or else competing C-O bond cleavage occurs

Dart  
Synlett, 1992, 987.

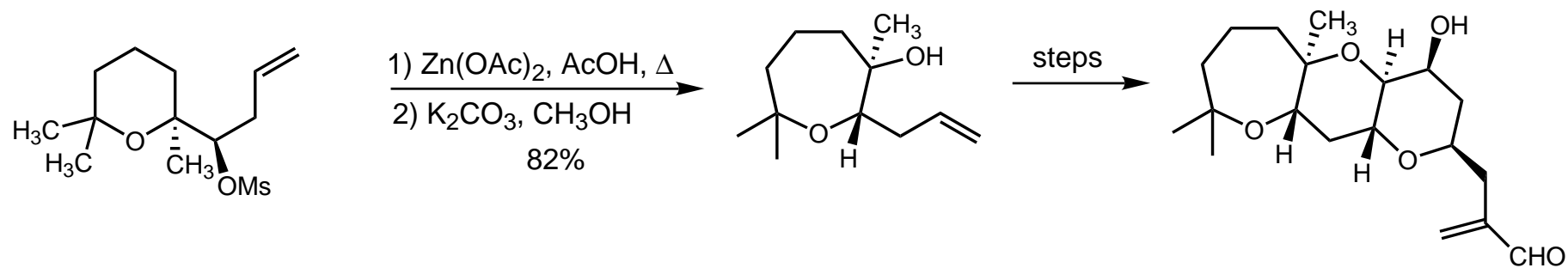
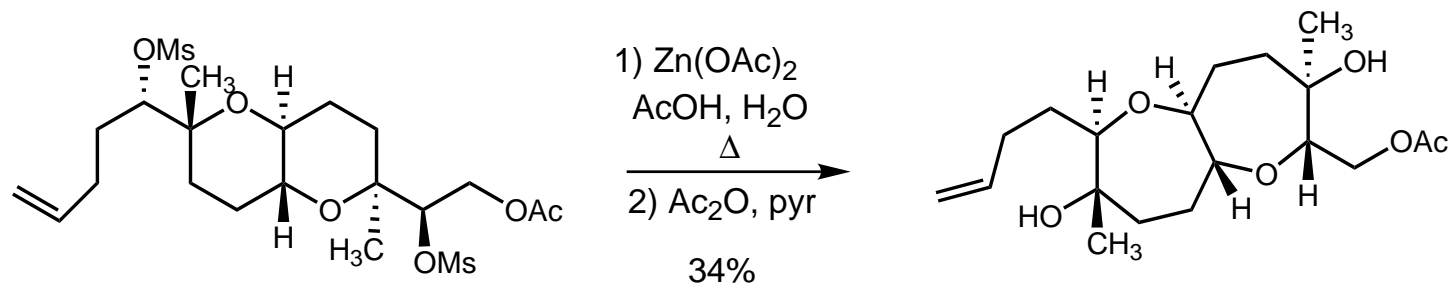


## Tetrahydropyran Expansion



enhanced reaction rate in this case prevents extended reaction times and acetate cleavage

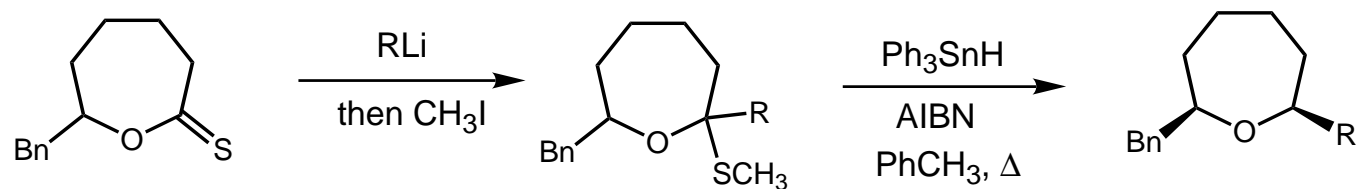
## THP Expansion: Application to Hemibrevetoxin B Intermediates



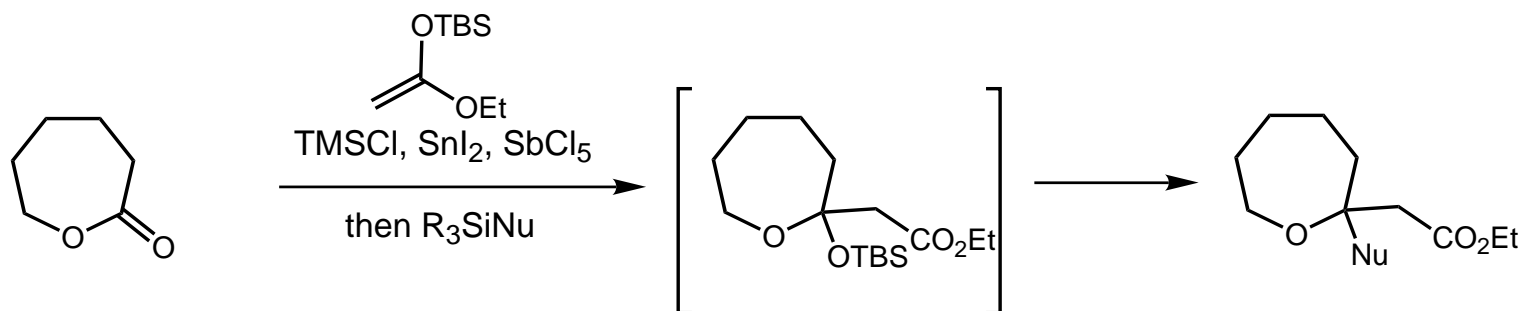
Nakata  
TL 1996, 217.  
Chem. Lett. 1996, 487.



## Modification of Lactones



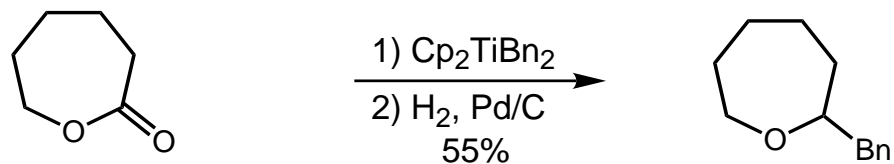
Nicoloau  
 JACS 1987, 2506.  
 JACS1990, 6263.



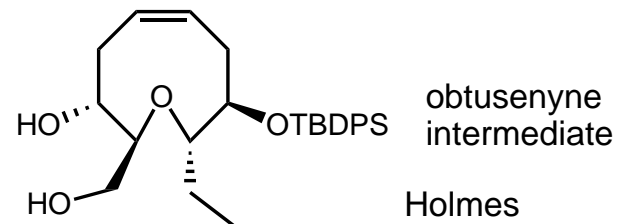
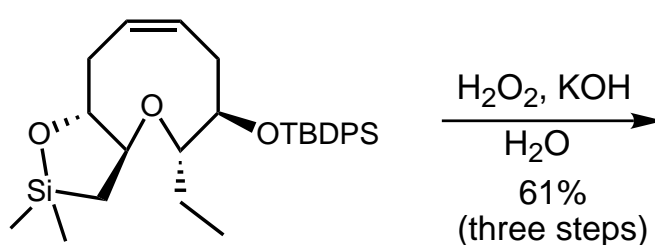
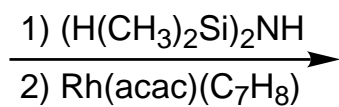
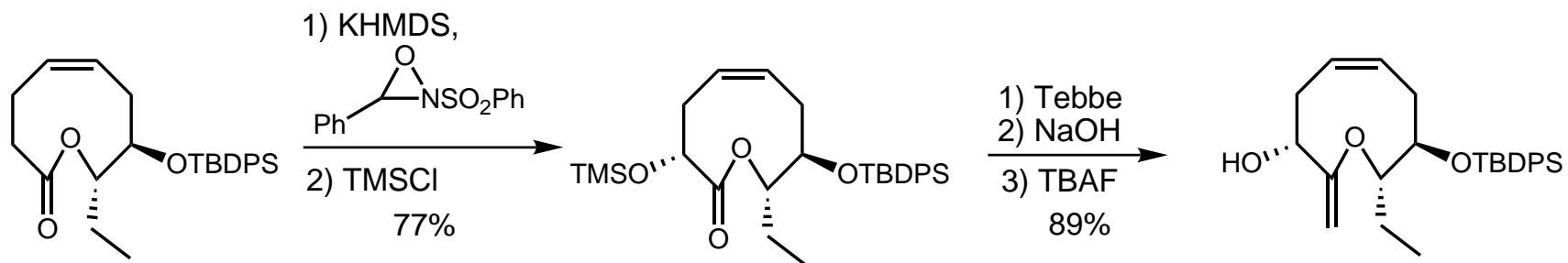
R = Et, Nu = H, 90%  
 R = CH<sub>3</sub>, Nu = allyl, 67%  
 R = CH<sub>3</sub>, Nu = CN, 62%

Mukaiyama  
 Bull. Chem. Soc. Jpn. 1990, 1898.

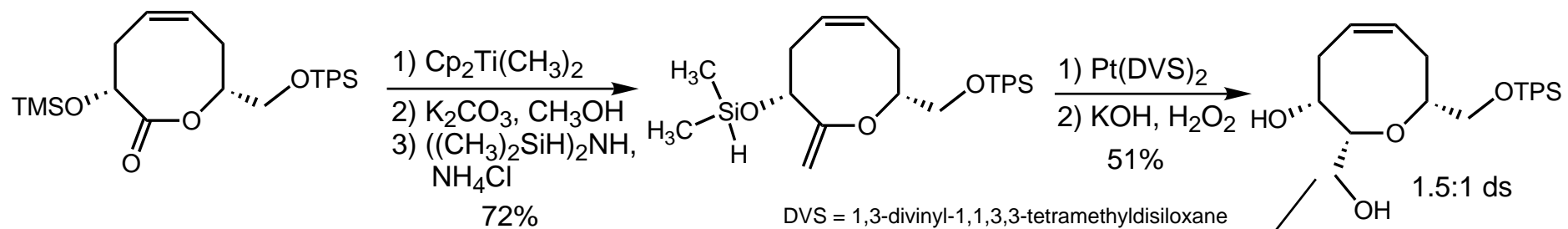
## Enol Ethers from Lactones



Petasis  
JOC 1992, 1327.



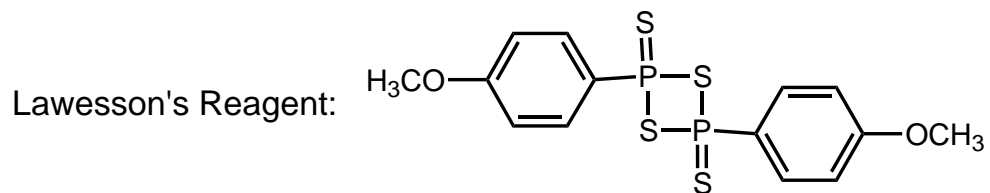
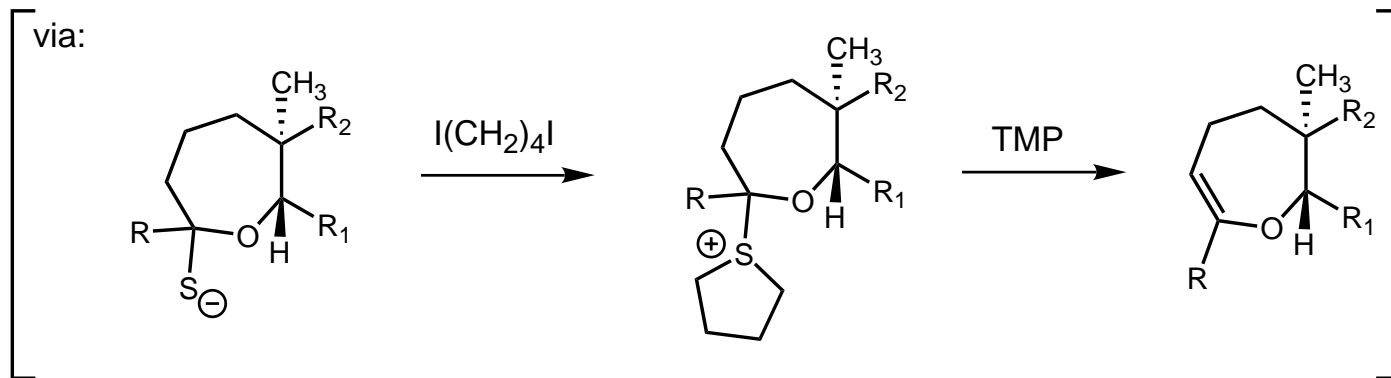
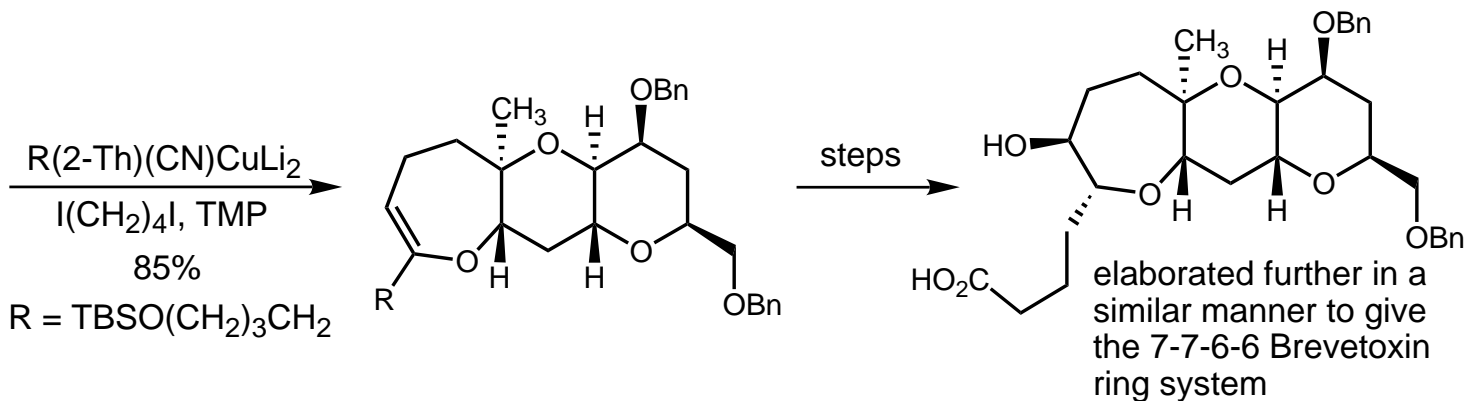
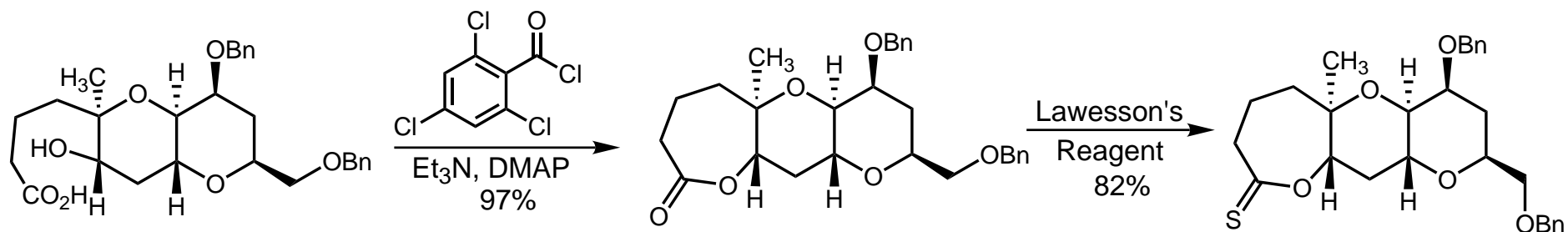
Holmes  
TL 1992, 671 & 675.



(+)-laurencin

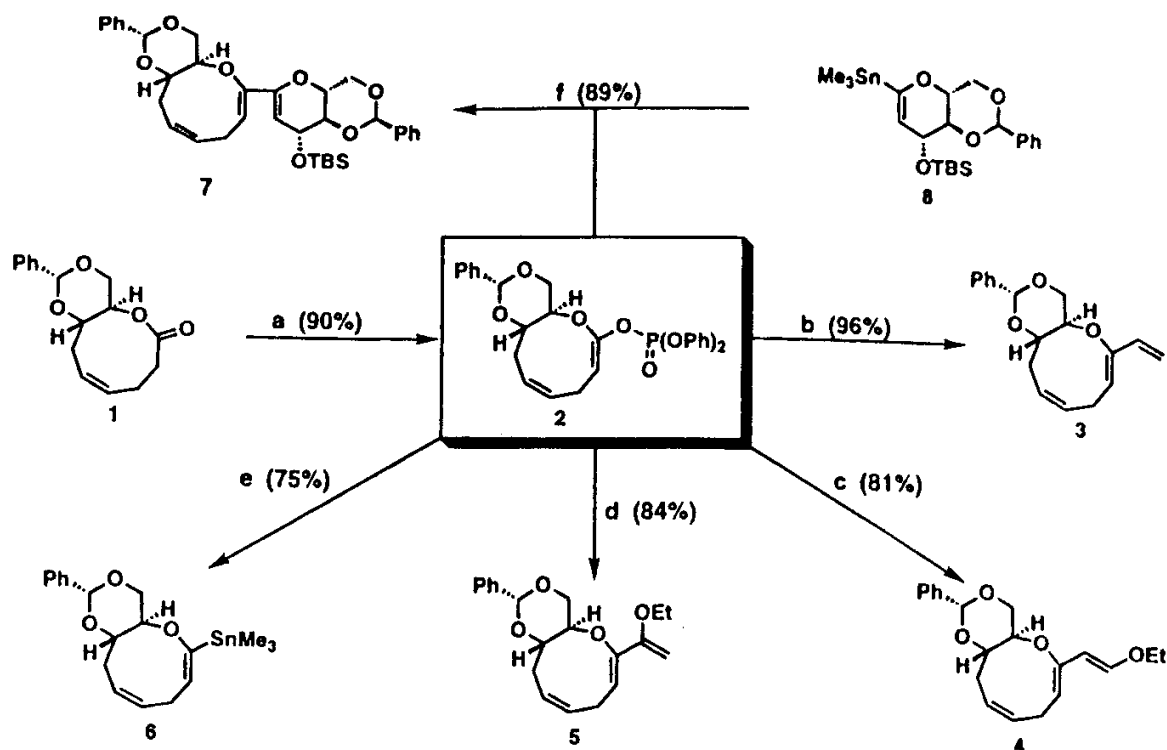
Holmes  
JACS 1997, 7483.

## More Advanced Lactone Manipulation



Nicolaou  
 JACS 1990, 4988.  
 JACS 1992, 7935.  
 JACS 1993, 3558.

## Functionalization of Lactones via Their Cyclic Ketene Acetal Phosphonates



“ Key: (a) 1.2 equiv of KHMDS, 3.0 equiv of HMPA, 2.0 equiv of (PhO)<sub>2</sub>POCl, THF, -78 °C, 0.5 h; add lactone to base, phosphoryl chloride, and HMPA; (b) 2.0 equiv of tri-*n*-butyl(vinyl)tin, 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>, 3.0 equiv of LiCl, THF, Δ, 2 h; (c) 2.0 equiv of tri-*n*-butyl(2-ethoxyvinyl)tin, 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>, 3.0 equiv of LiCl, THF, Δ, 1.5 h; (d) 2.0 equiv of tri-*n*-butyl(1-ethoxyvinyl)tin, 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>, 3.0 equiv of LiCl, THF, Δ, 6 h; (e) 2.0 equiv of hexamethylditin, 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>, 3.0 equiv of LiCl, THF, Δ, 3 h; (f) 2.0 equiv of 8, 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub>, 3.0 equiv of LiCl, THF, Δ, 7 h.

Nicolaou  
 JACS 1997, 5467.  
 JACS 1997, 8105.