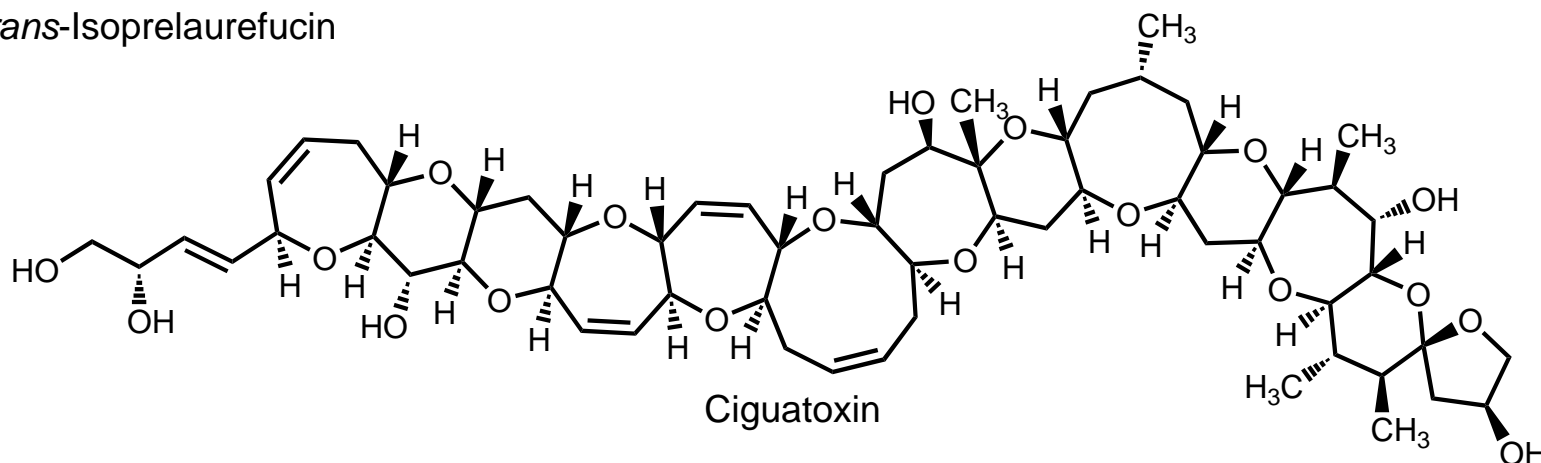
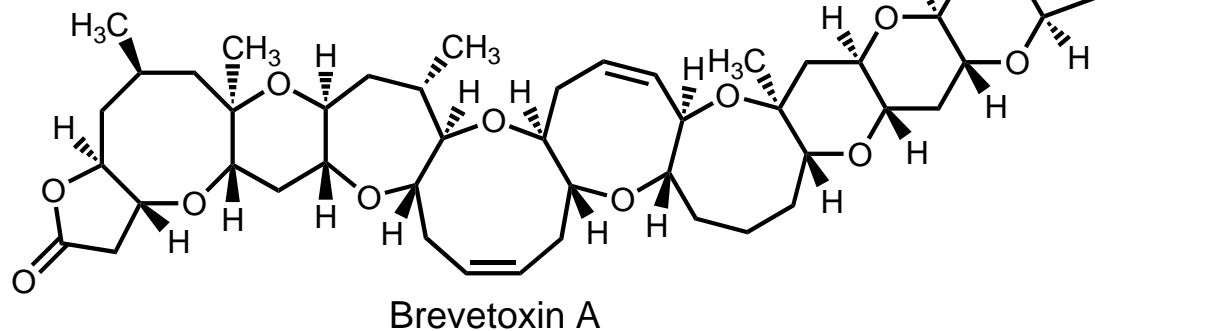
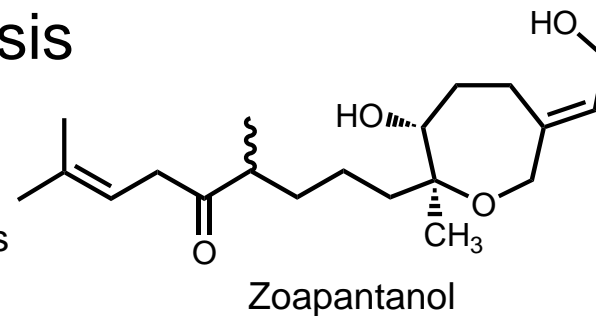
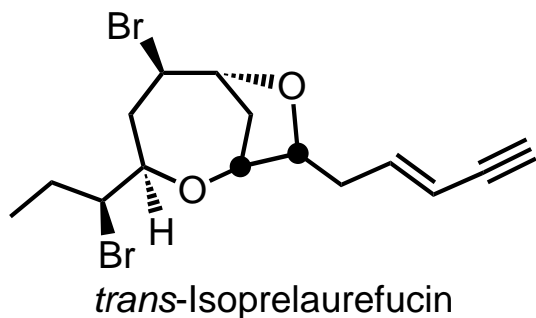
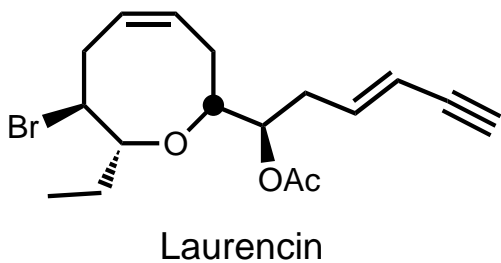
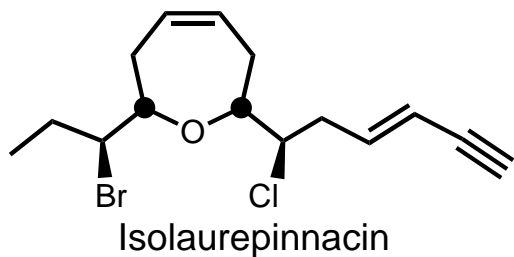


Approaches to the Synthesis of Medium Ring Ethers

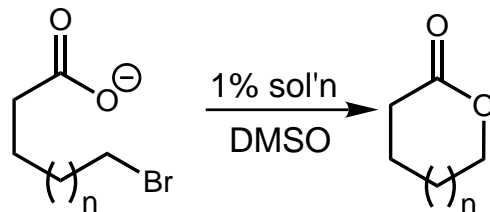
Contents

- 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

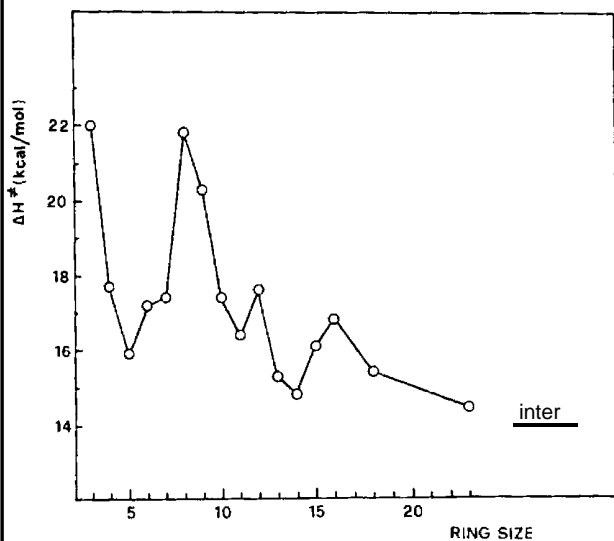


Brian Connell
Evans Group Seminar
3/13/98

The Problem of Medium Ring Synthesis Energetics of Ring Closure Reactions



ΔH^\ddagger of Cyclization



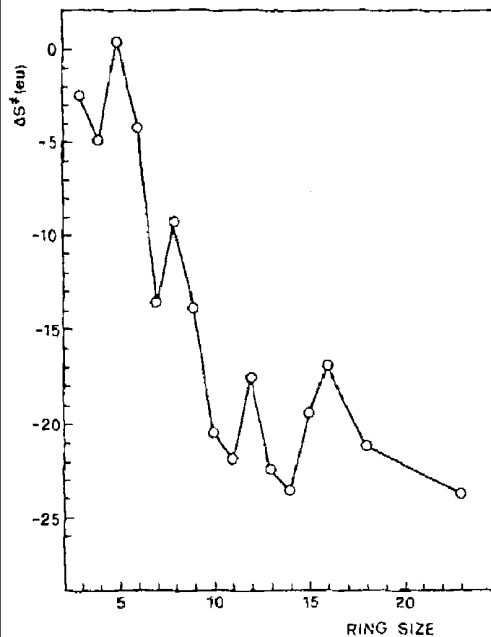
• an indicator of ring strain

Sources of Strain:

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

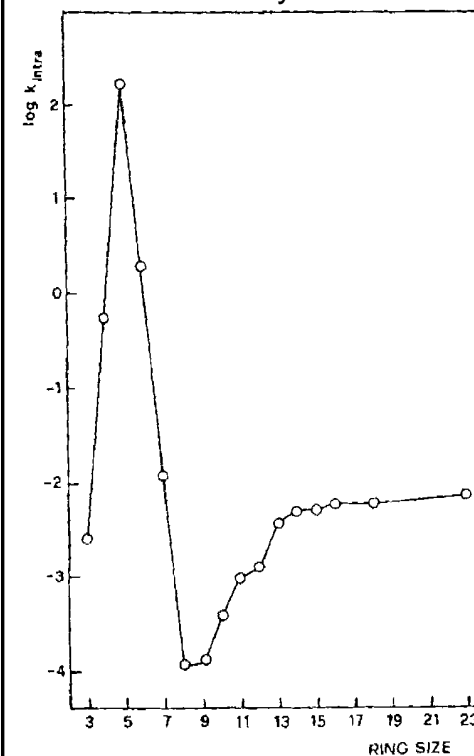
#1 and #3 are especially severe for medium rings

ΔS^\ddagger of Cyclization



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

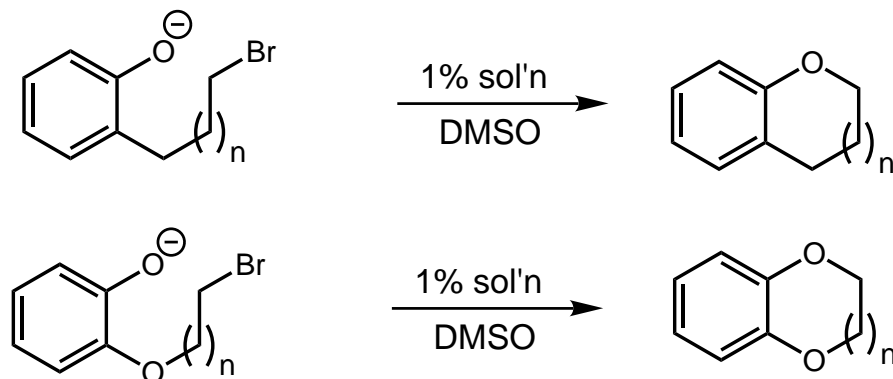
Rates of Cyclization



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

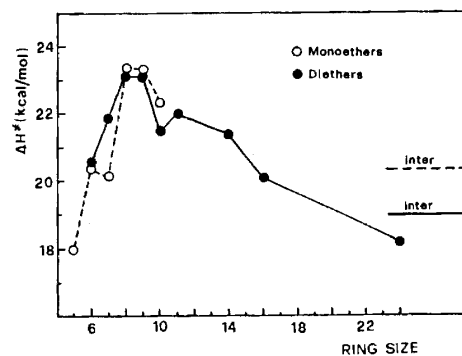
• Note: These data can NOT necessarily be extrapolated to other cyclization reactions or to substrates with differing degrees of substitution.

The Problem of Medium Ring Synthesis Energetics of Ring Closure Reactions

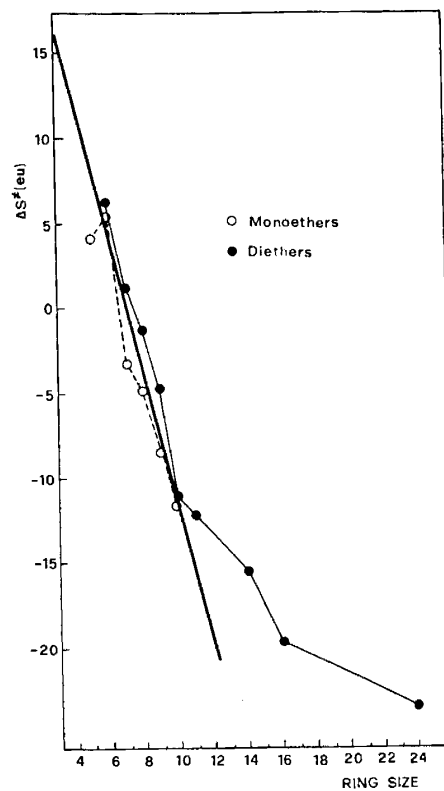


transannular CH---O interactions are less unfavorable than the corresponding CH---HC interactions

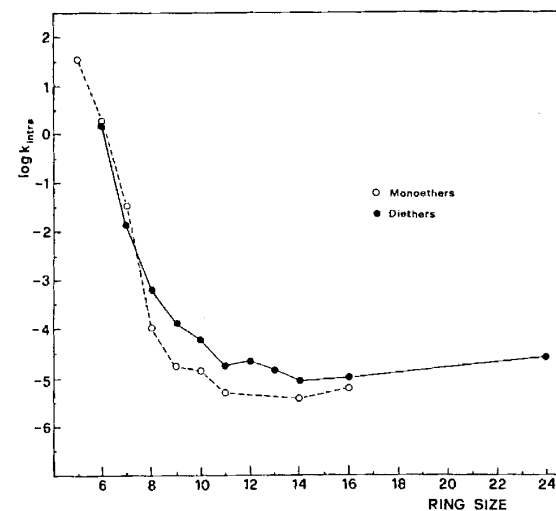
ΔH of Cyclization



ΔS^\ddagger of Cyclization



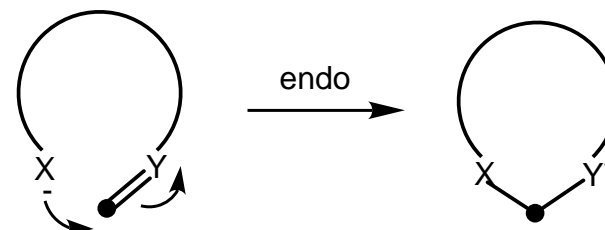
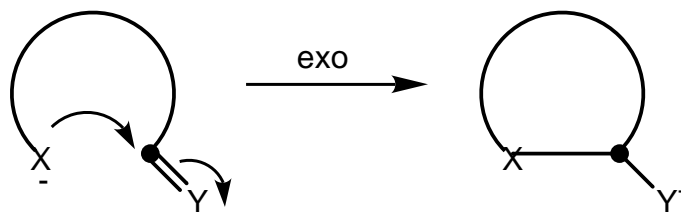
Rates of Cyclization



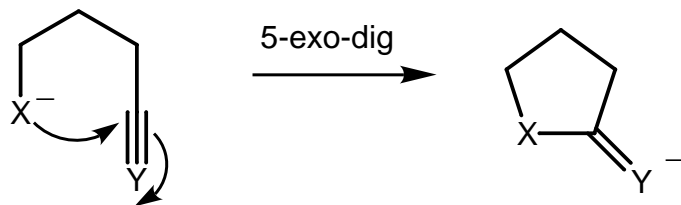
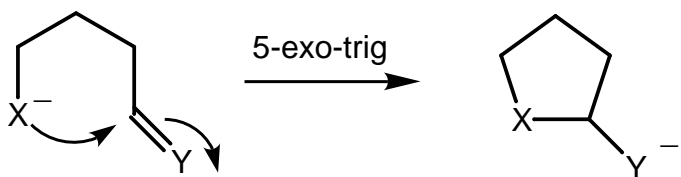
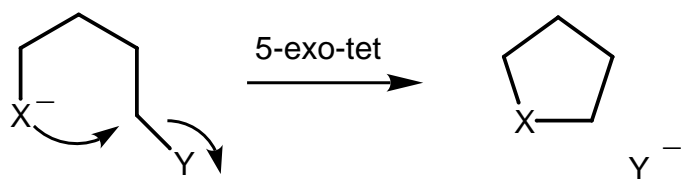
Ring Closure Basics

General definitions/underlying concepts:

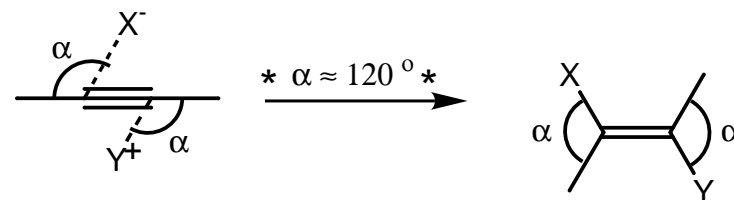
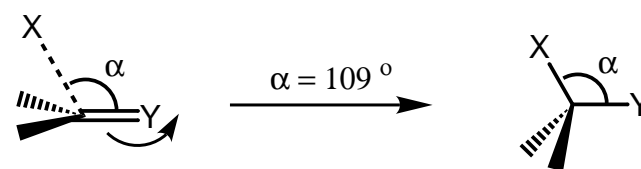
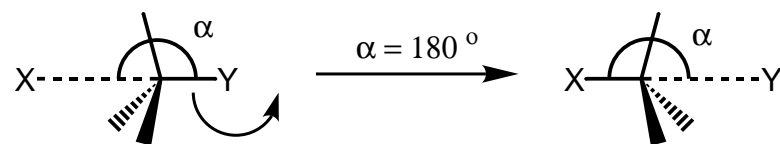
Cyclization modes:



Hybridization at atom undergoing attack:



Required trajectories:



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

Conclusions and Caveats

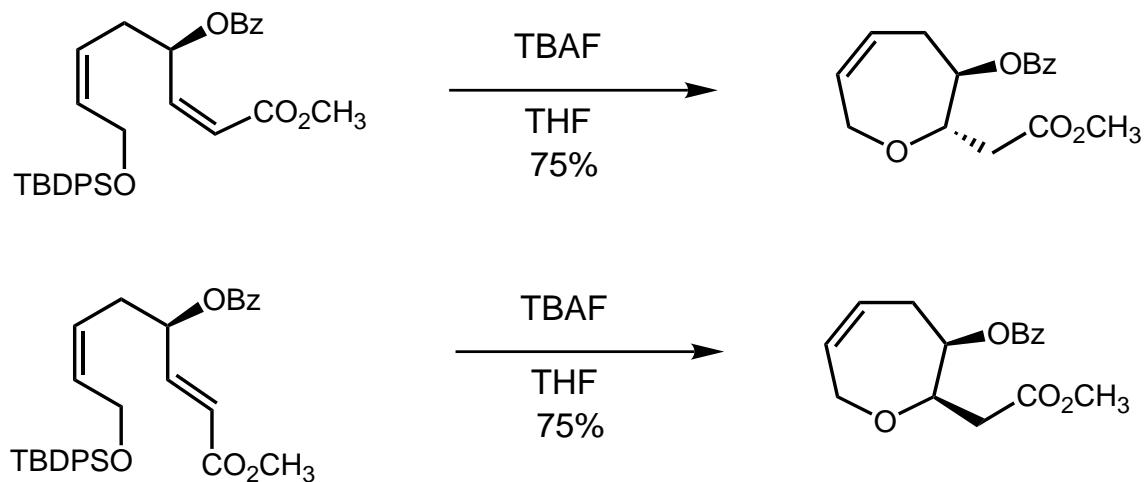
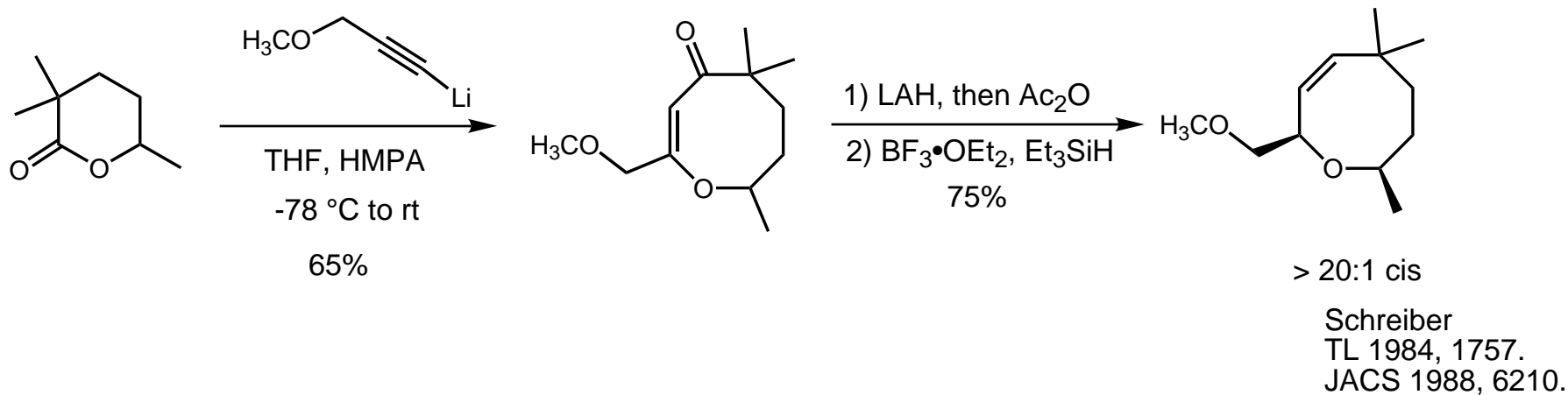
- Baldwin's Rules are an effective first line of analysis in evaluating the stereoelectronics of a given ring closure
- Baldwin's Rules have provided an important foundation for the study of reaction mechanism
- Competition studies between different modes of cyclization only give information about relative 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

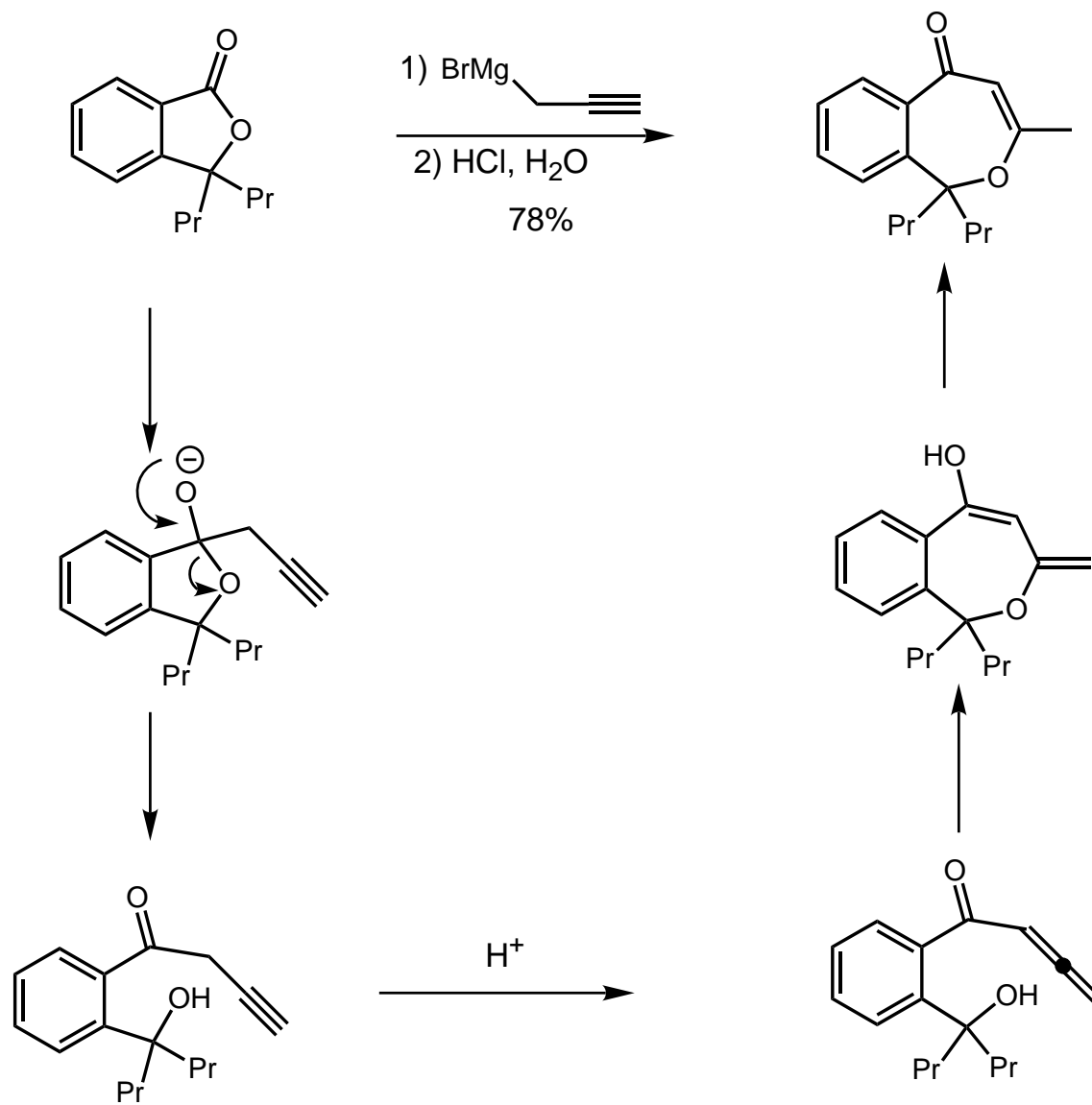
Hetero-Michael Reactions



• *cis* olefin was necessary for cyclization to occur

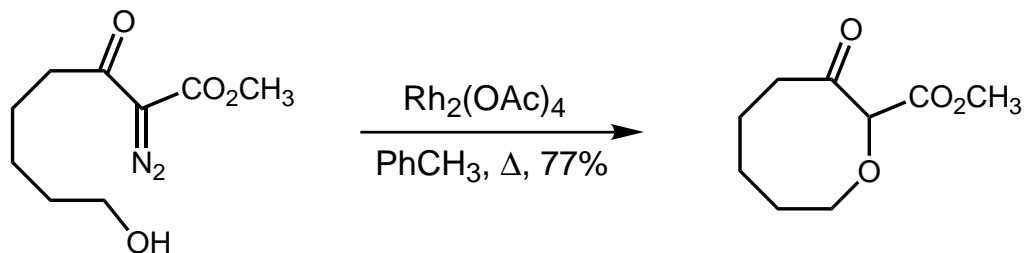
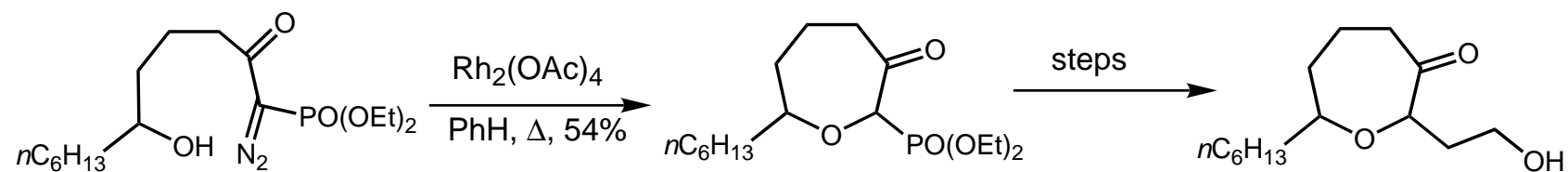
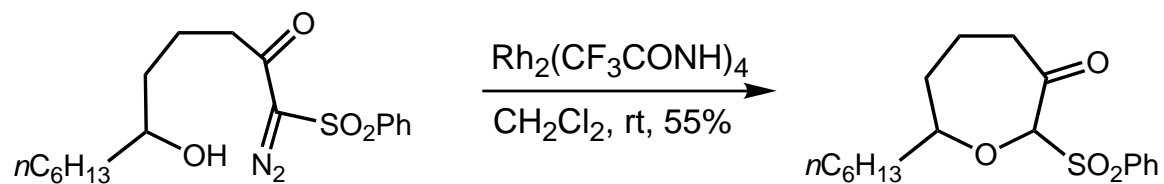
V.S. Martin TL 1993, 5471.

Another Hydroxy Allene Cyclization



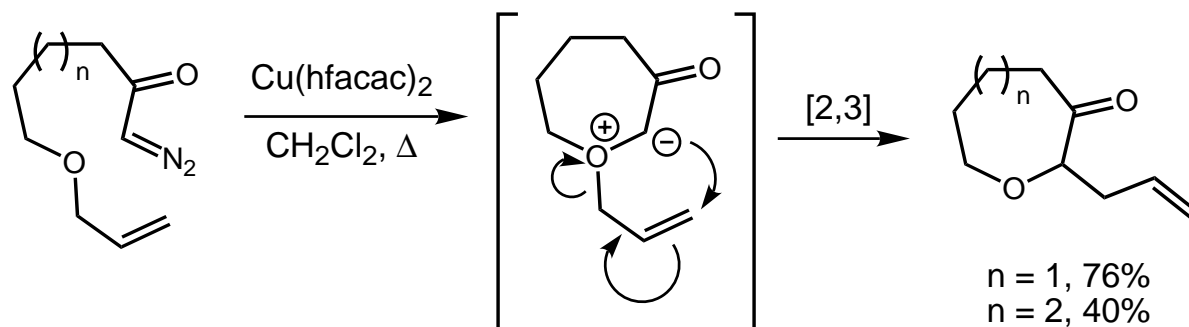
Nagao
Chem. Comm. 1996, 19.

O-H Insertion



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

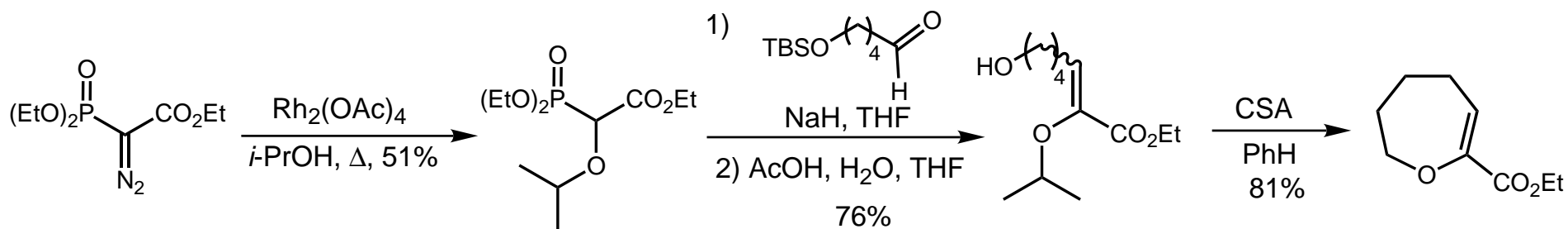
O-H Insertion



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

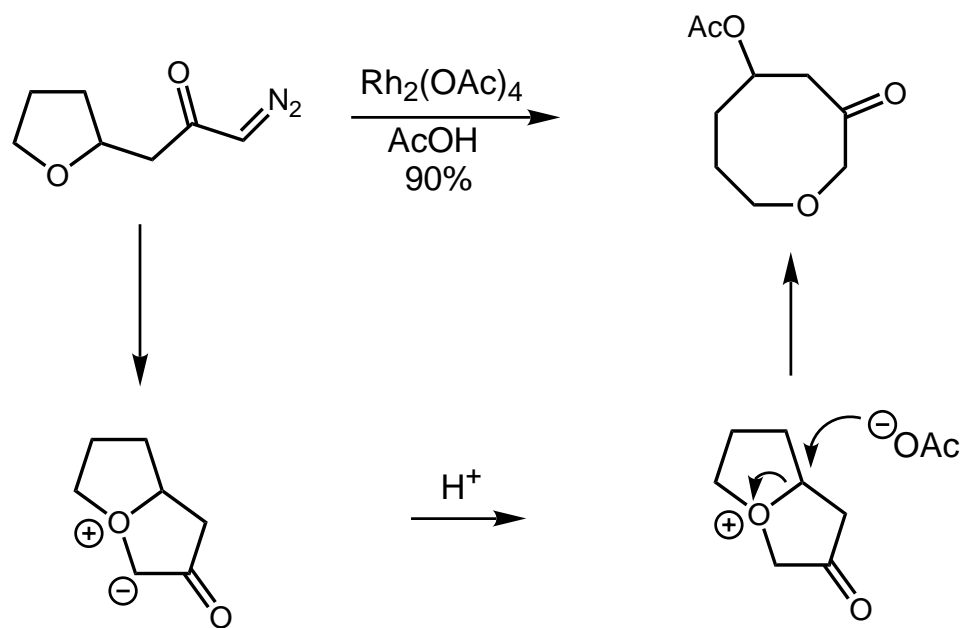
$n = 1, 76\%$
 $n = 2, 40\%$

J. S. Clark
TL 1993, 4385.



C. J. Moody
Tetrahedron, 1992, 3991.

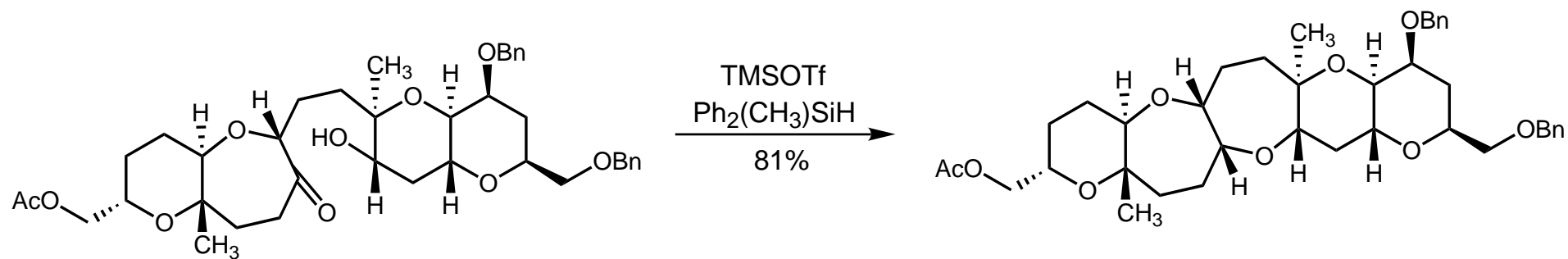
O-H Insertion



Oku
Chem. Comm. 1996,1077.

Reductive Cyclization

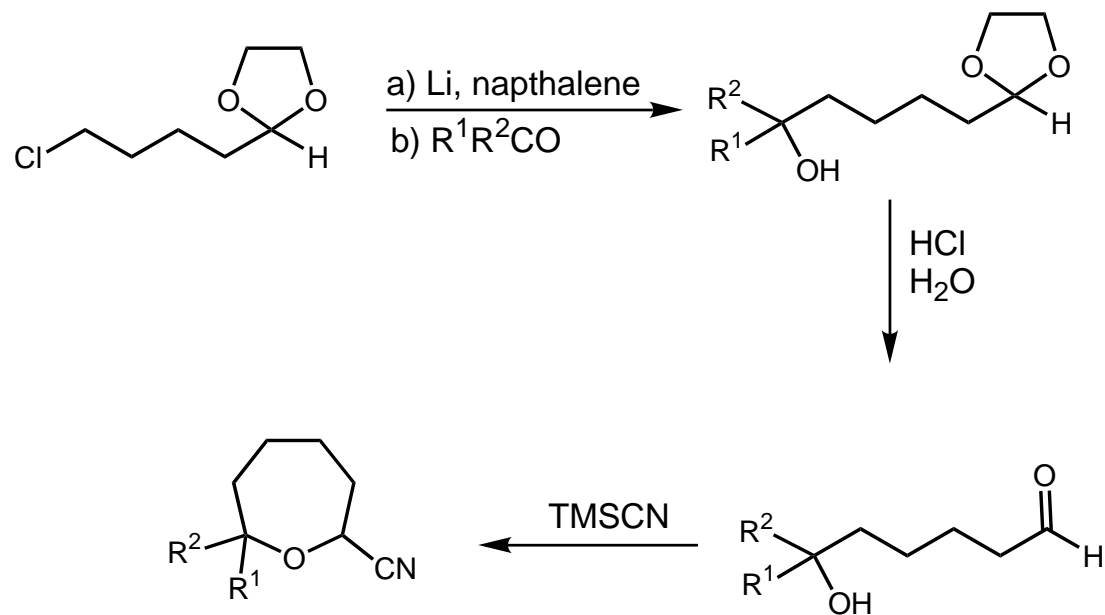
Both the synthesis of Hemibrevetoxin B and 7-epi-Hemibrevetoxin B have utilized this reaction:



not universally applicable

Nicolaou
JACS 1993, 3558.
The Brevetoxin Odyssey:
ACIEE 1996, 589.

TMSCN Induced Cyclizations of Aldehydes



Three step yields

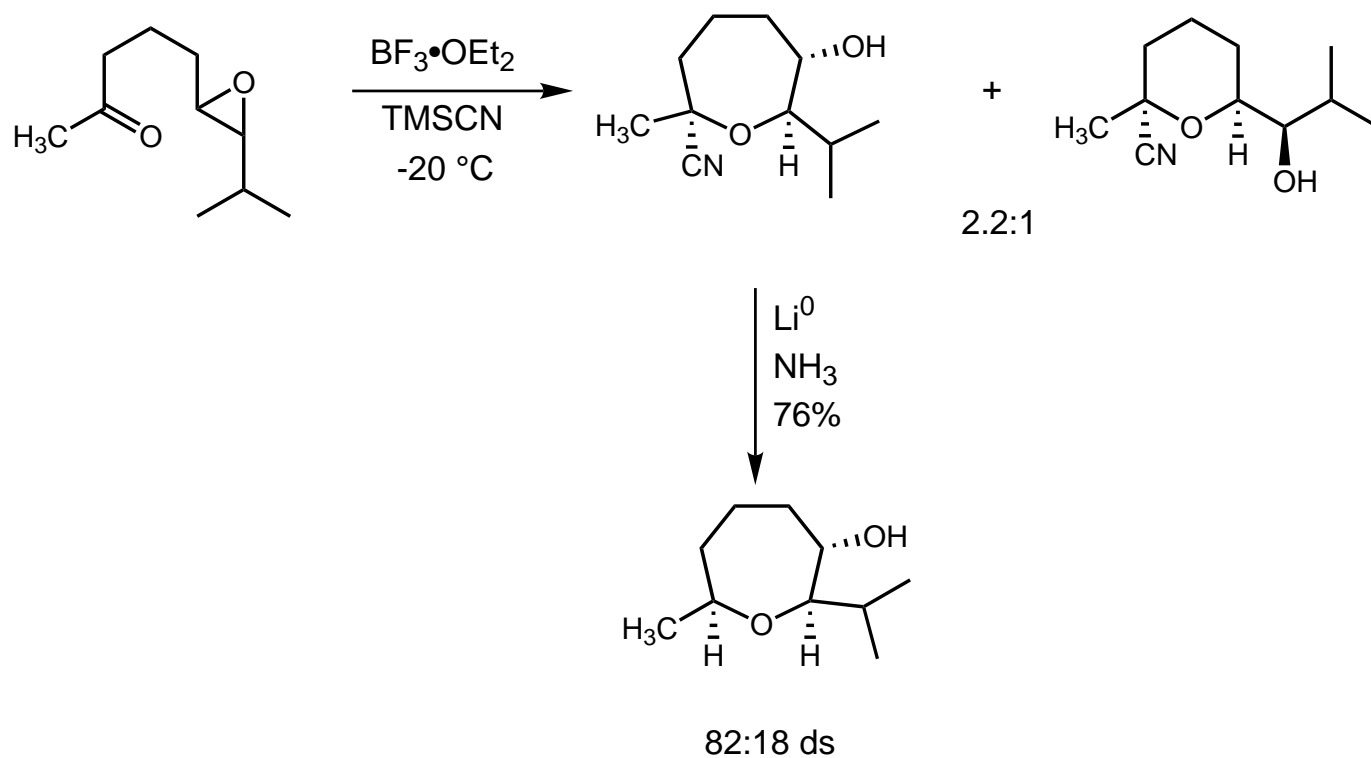
$R^1 = H, R^2 = Ph, 36\%$

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

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

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

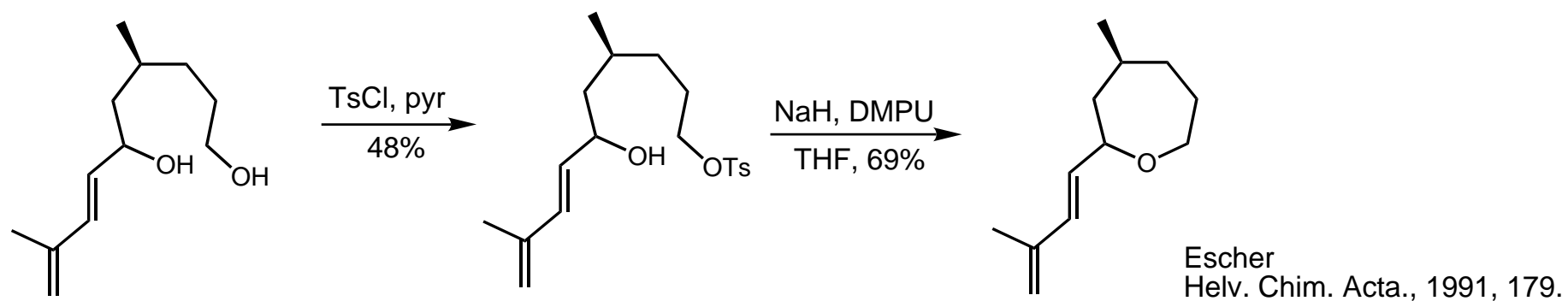
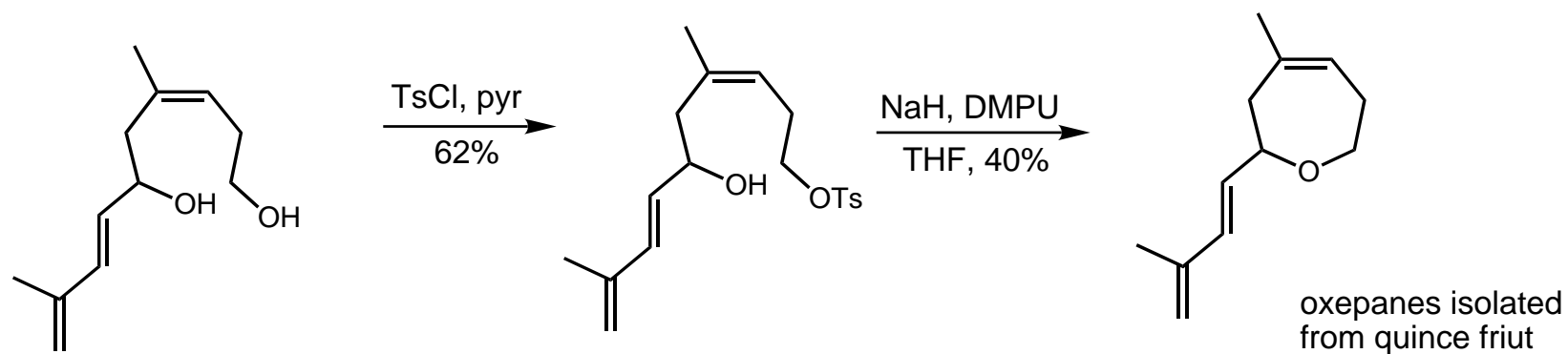
TMSCN Induced Cyclizations of Ketones



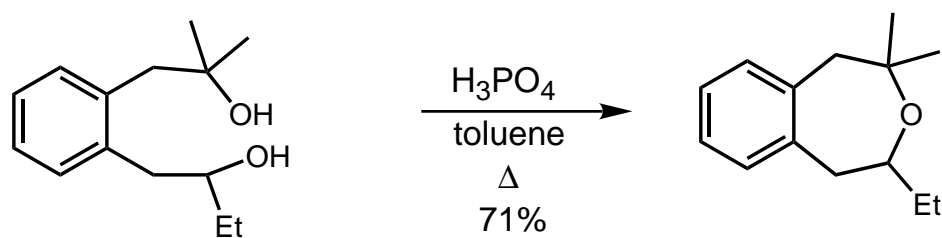
reagents other than TMSCN only
give mixtures THPs

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

Tosylate Displacement

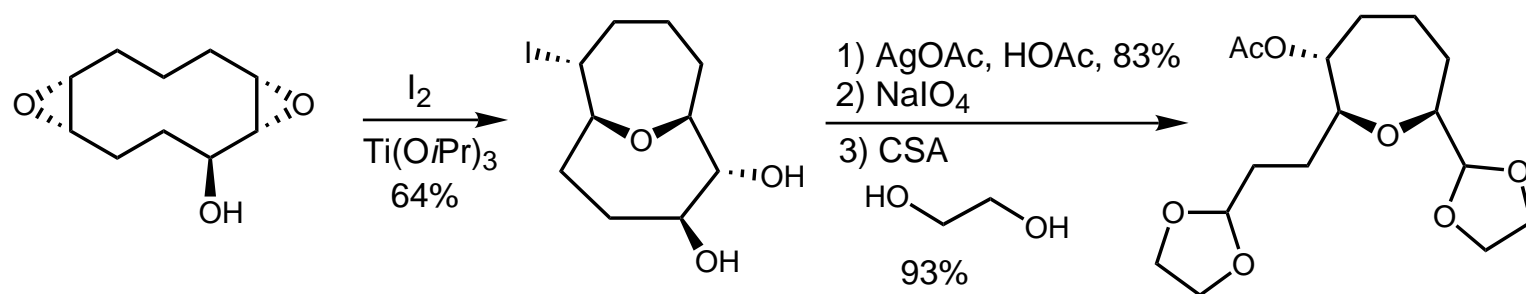
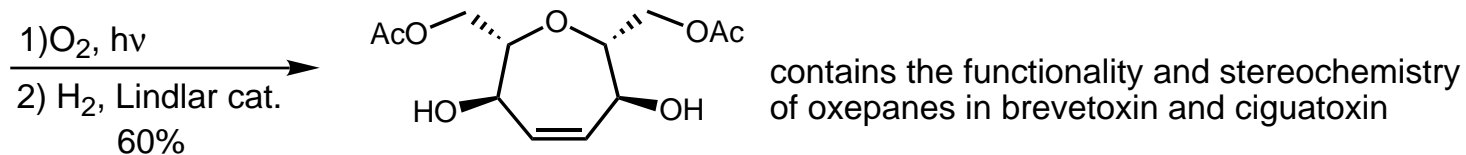
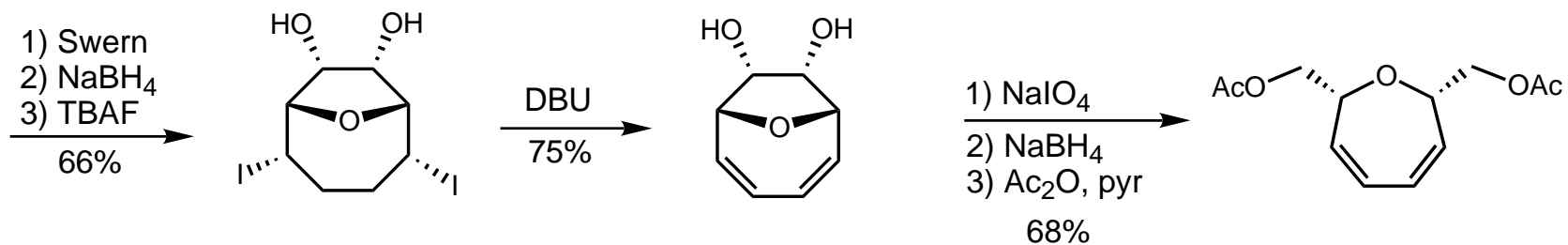
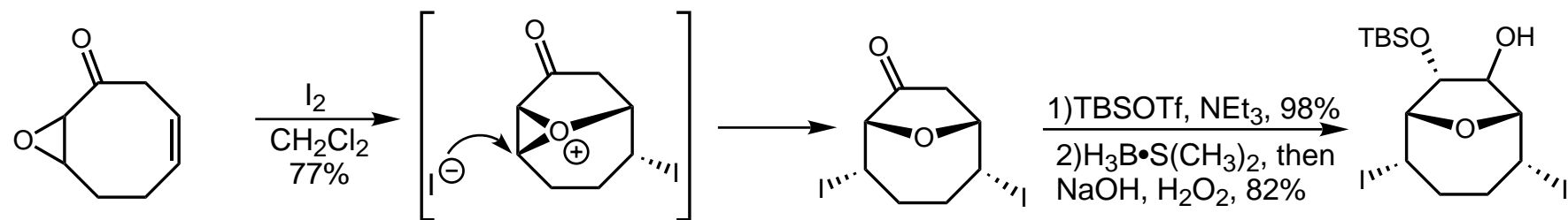


Protic Acid Cyclization



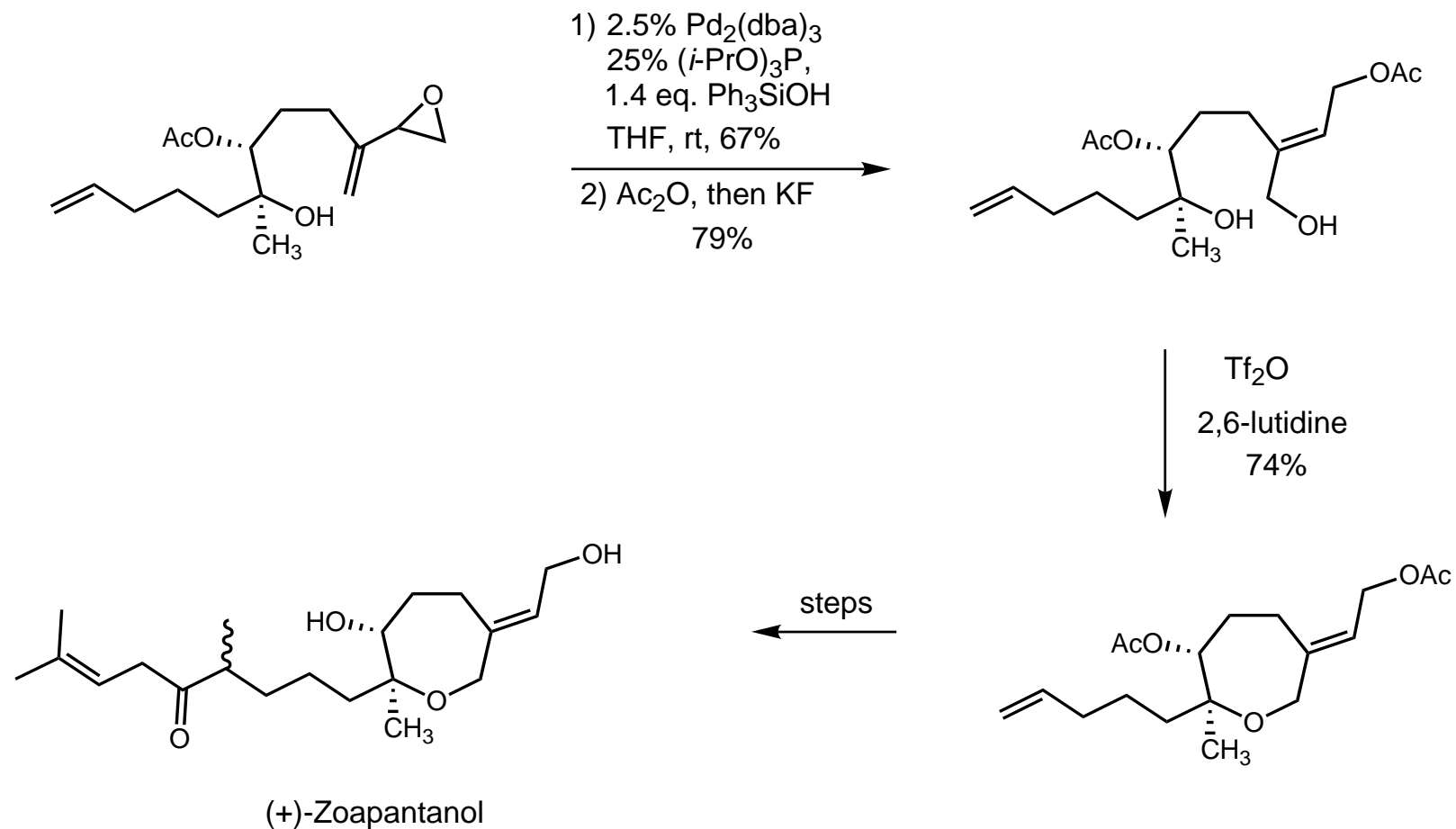
C. J. Moody
JCS Perkin I, 1995, 1137.

Transannular Ether Formation



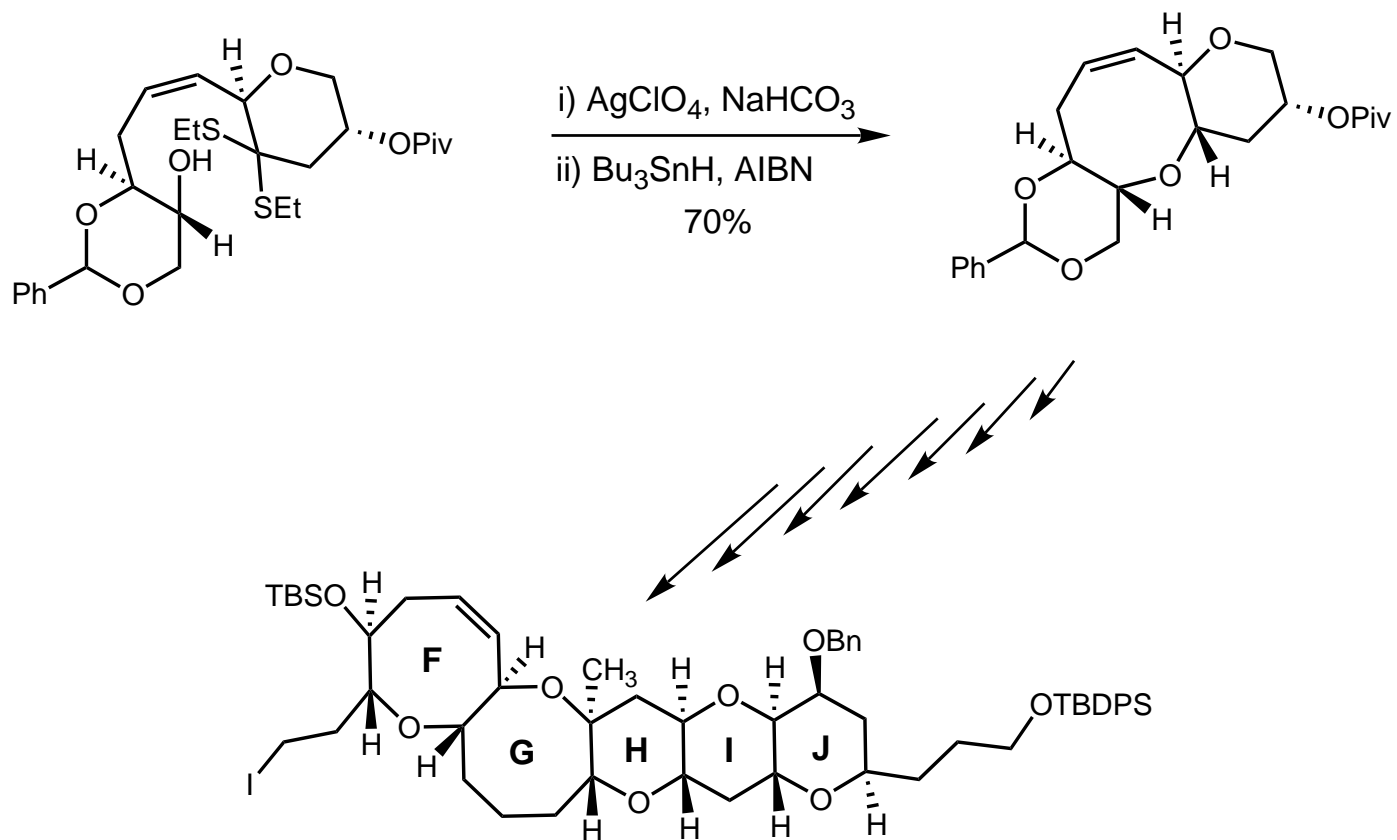
J.D. Martin
 TL 1990, 1629.
 TL 1991, 2241.
 TL 1991, 2245.

Zoapantanol Synthesis

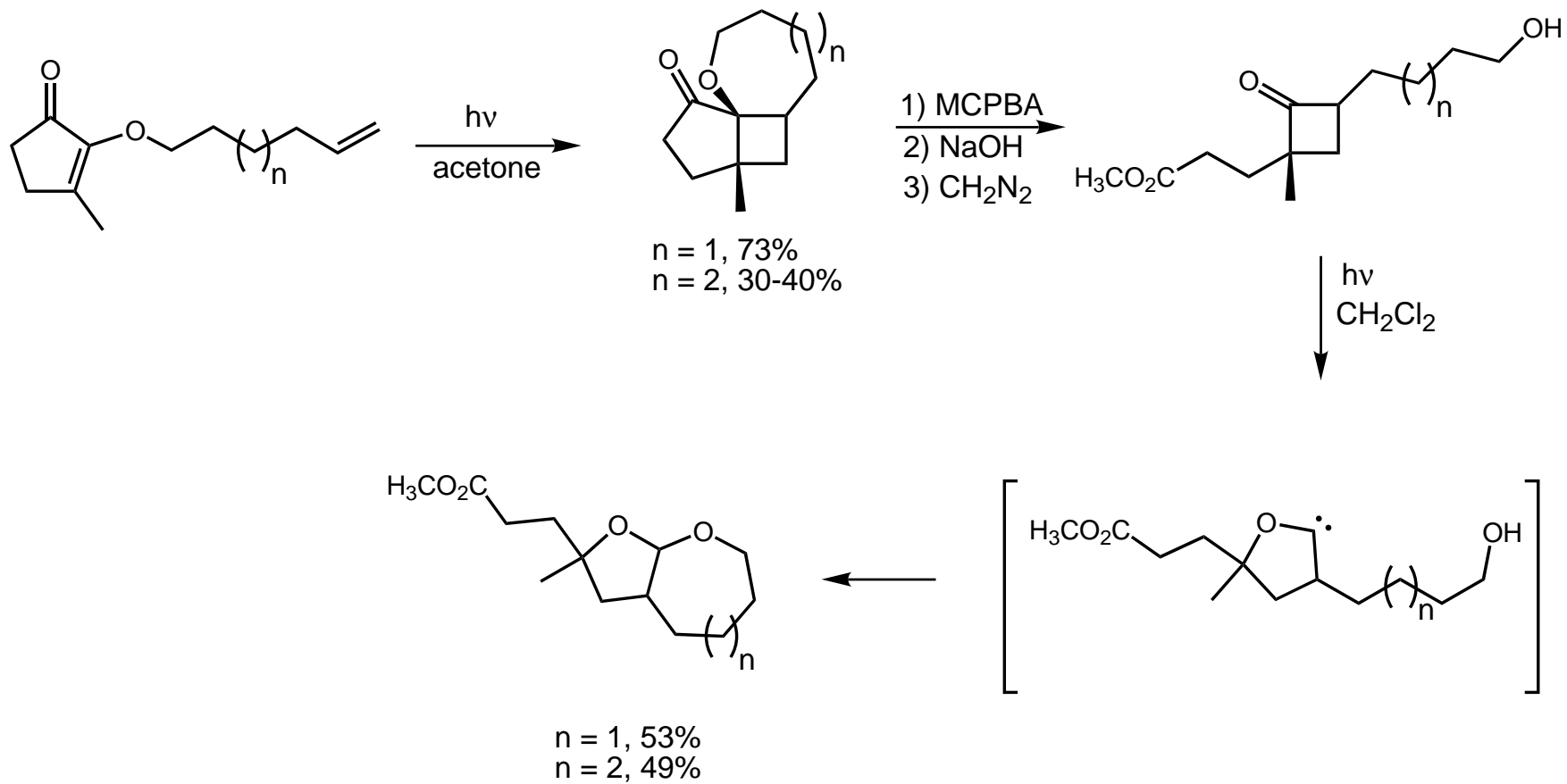


Cyclization onto a Dithioketal

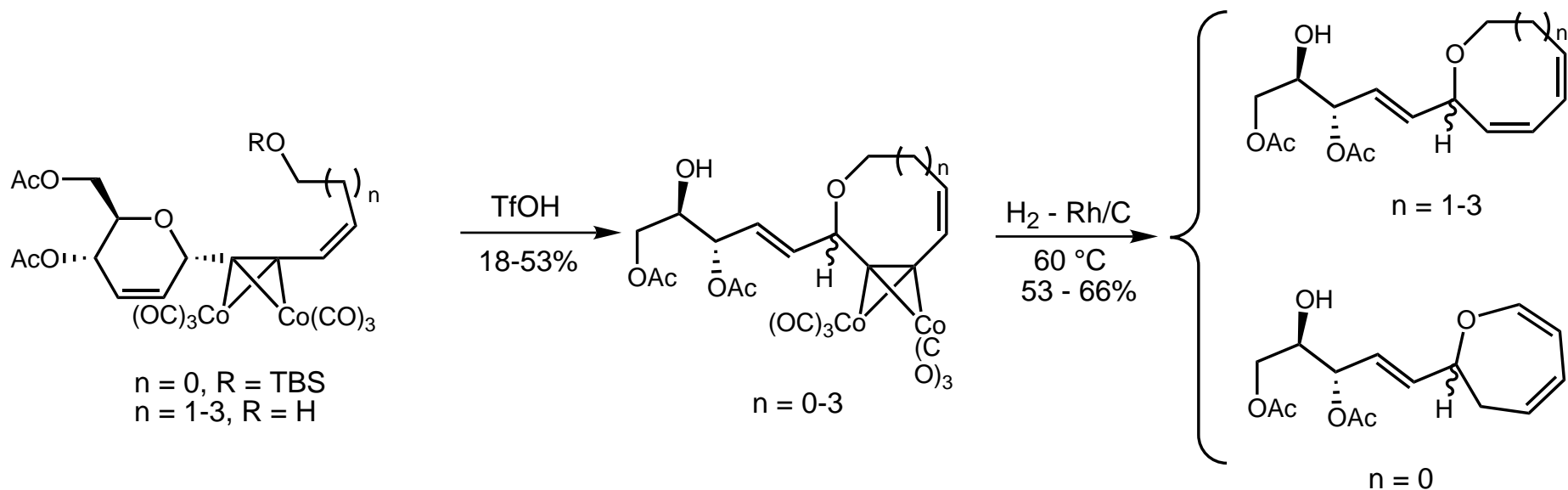
Both oxacanes of Brevetoxin B were formed by cyclization of an alcohol onto a dithioketal:



Photolysis



Intramolecular Nicolas Reaction



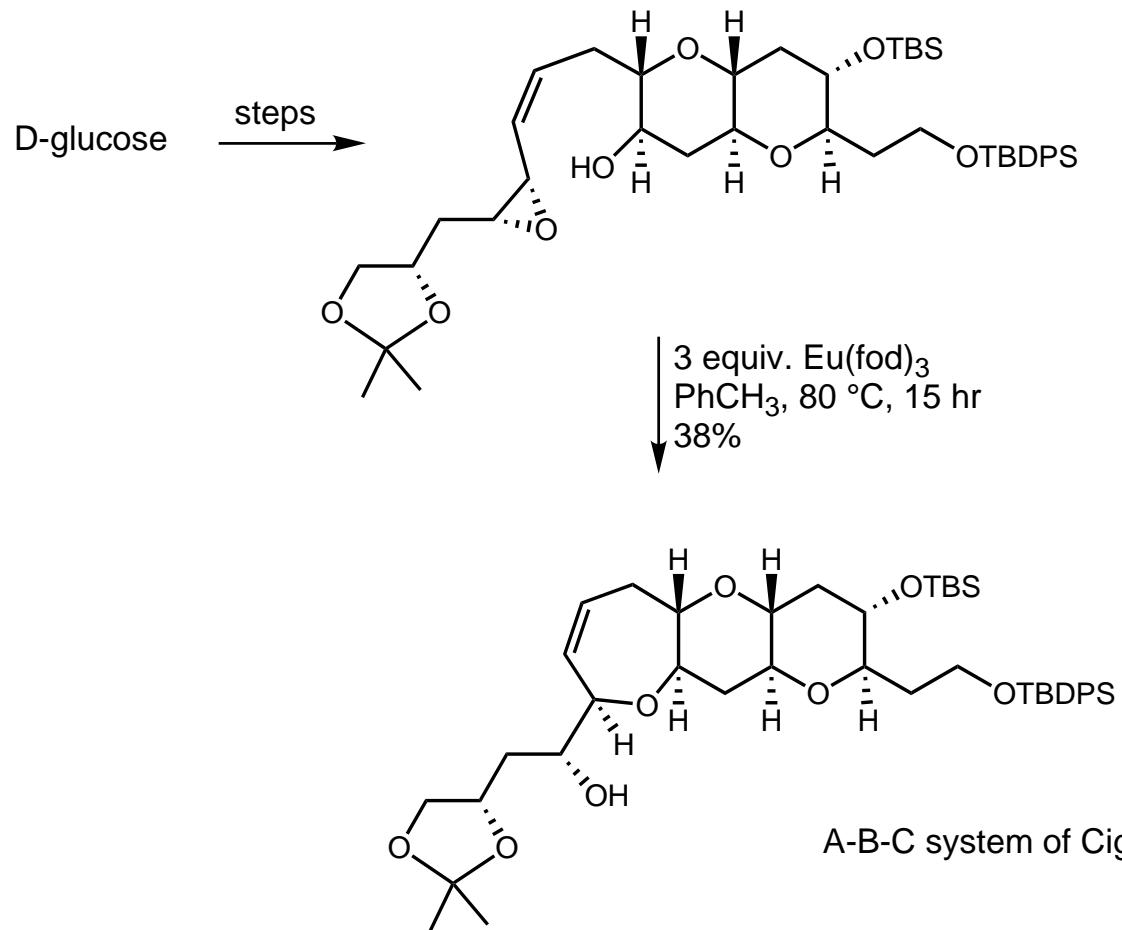
Several similar cyclizations have been used w/ limited success.

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

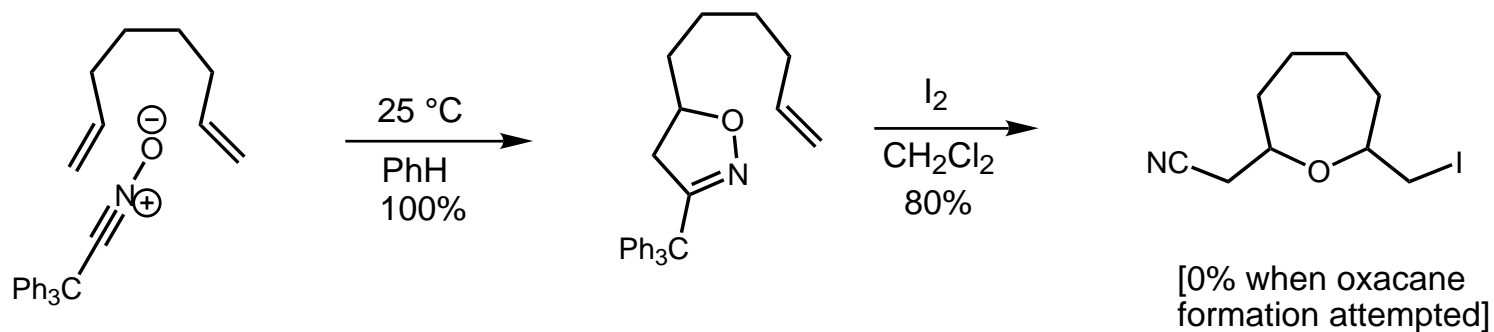
V. S. Martin
 TL 1995, 3549.

Greé
 JOC 1995, 2316.

Epoxide Opening

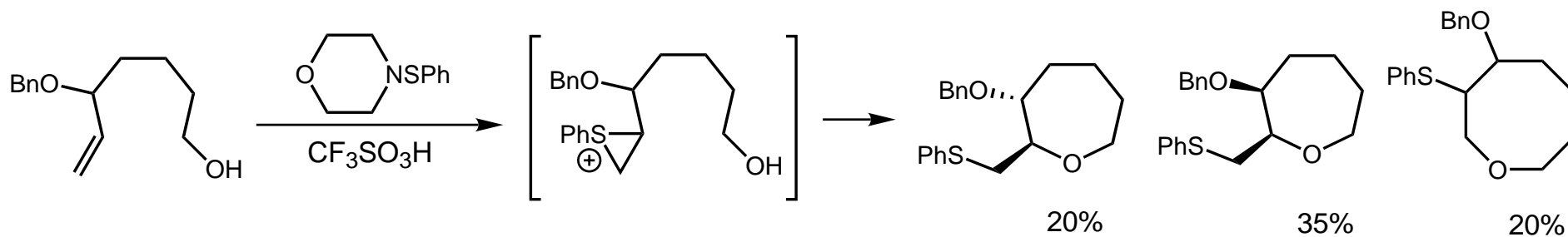


From Isoxazolines

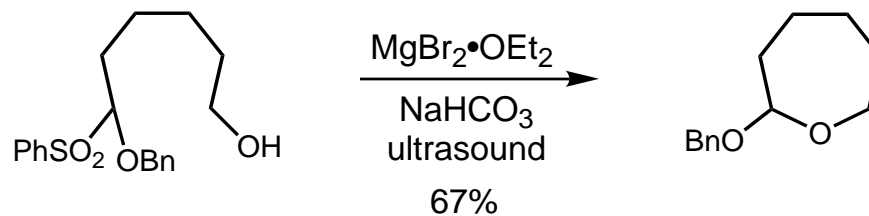


Kurth
JOC 1990, 283.

From Hydroxy Olefins



From α -Sulphonyl Ethers

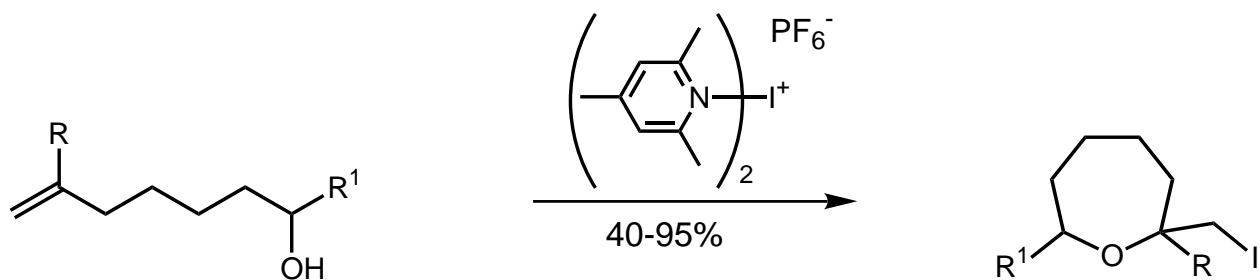


K. Jones
TL 1991, 2261.

works for 5-8 membered rings

Ley
Synlett, 1991, 415.

Misc Cyclizations

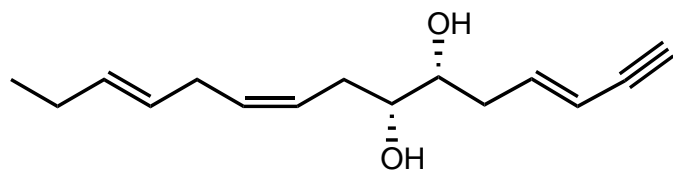


R, R¹ = alkyl

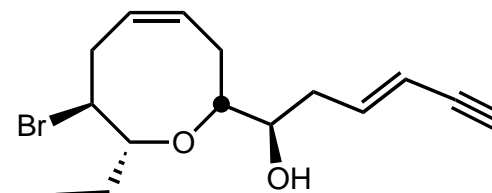
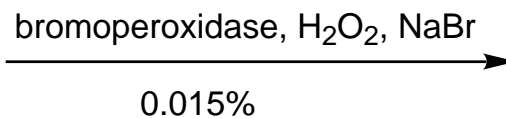
oxacanes could not be formed
under these conditions

Rousseau
JOC 1996, 5793.

Enzymes



101 mg

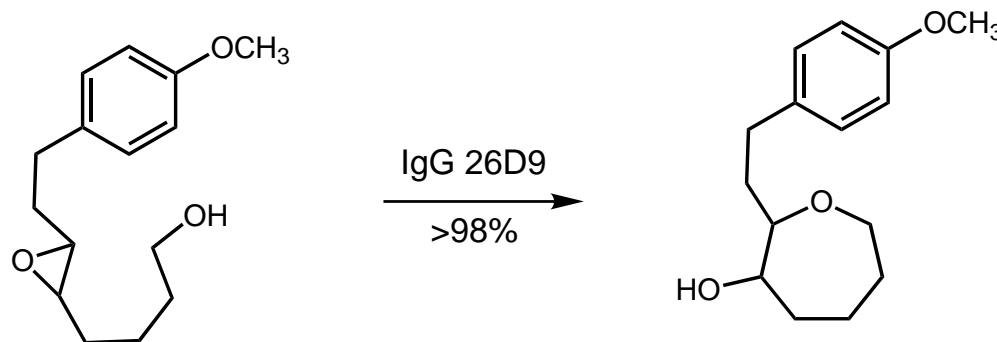


0.02mg

deacetylauricin
among a number of
other compounds

Murai
Chem Lett 1994, 2307.

Catalytic Antibody Mediated Cyclization

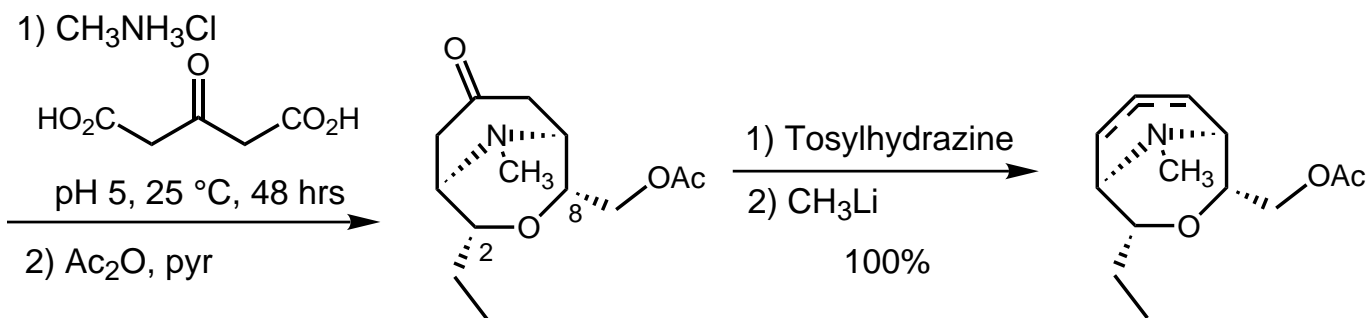
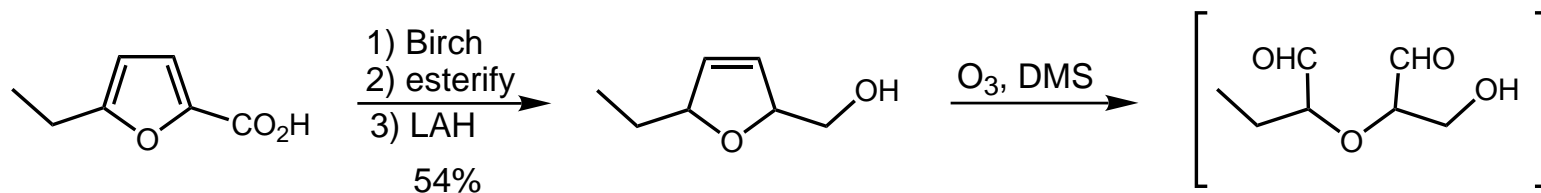


normally observed THP (6-exo-tet) not observed

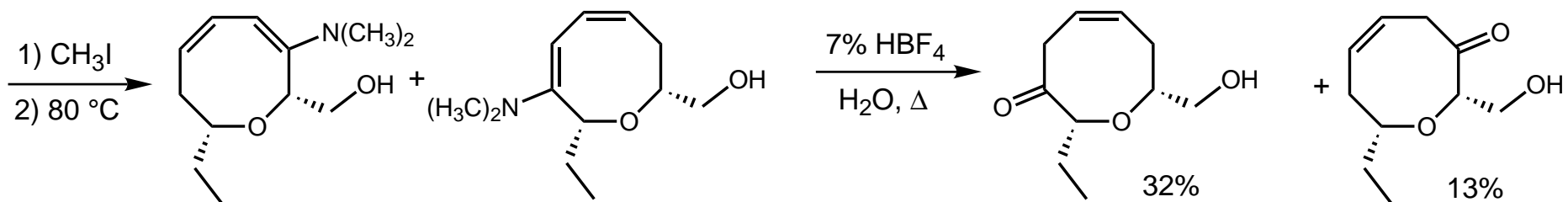
Lerner, Janda
JACS 1995, 2659.

Cyclization By C-C Bond Formation

The Epic Assault



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

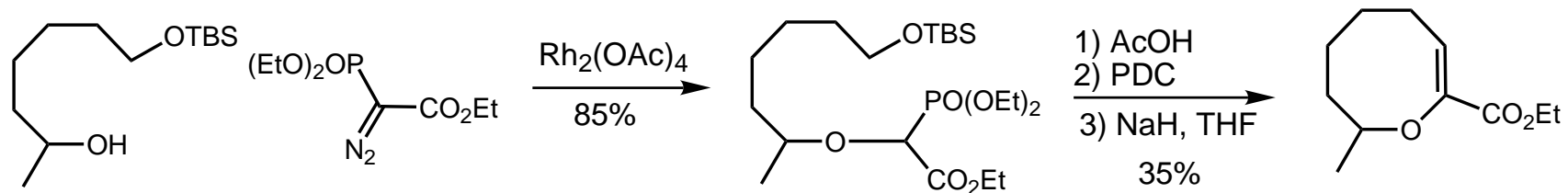
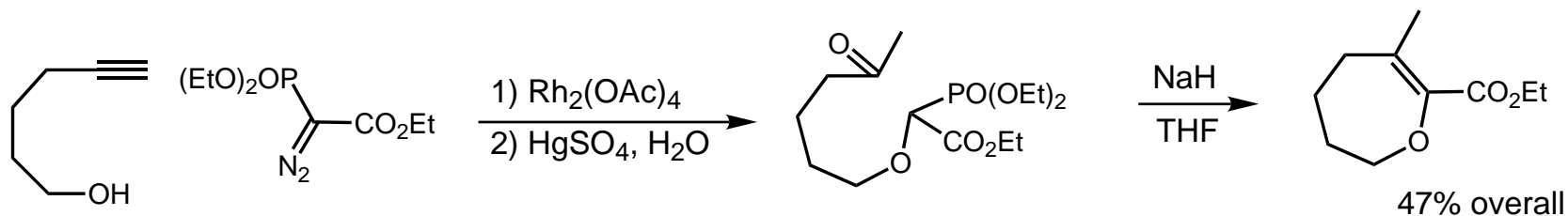


11 steps

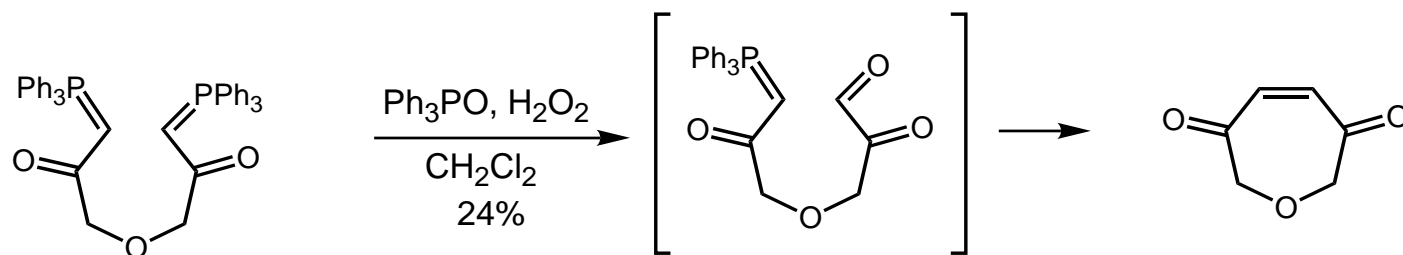
(±)-laurencin
0.0047%

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

Wadsworth-Emmons Cyclization



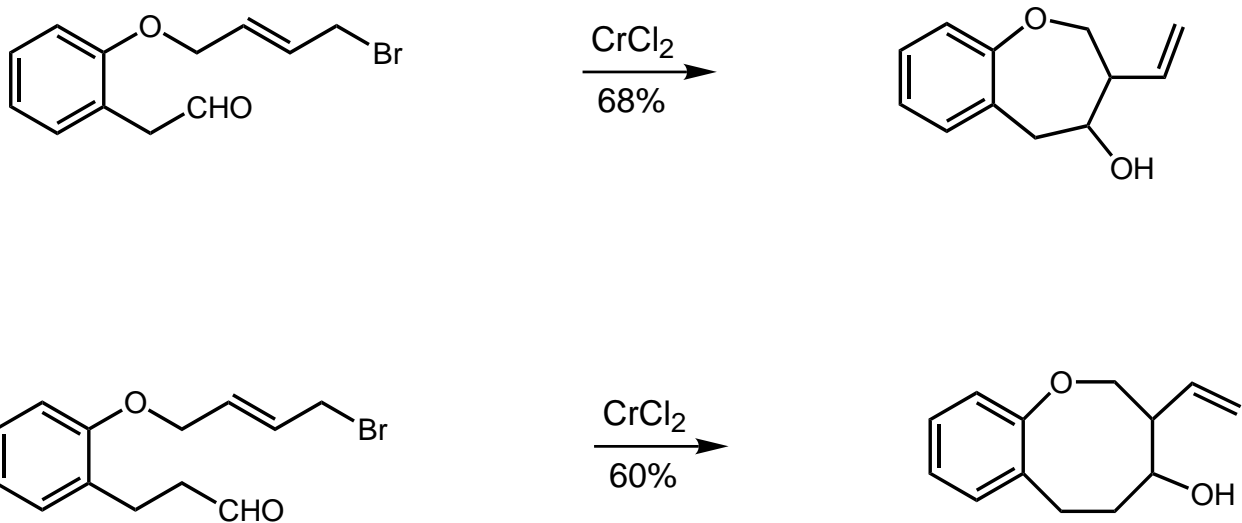
C. J. Moody
TL 1991, 6947.



Bestmann
Chem. Ber. 1993, 725.

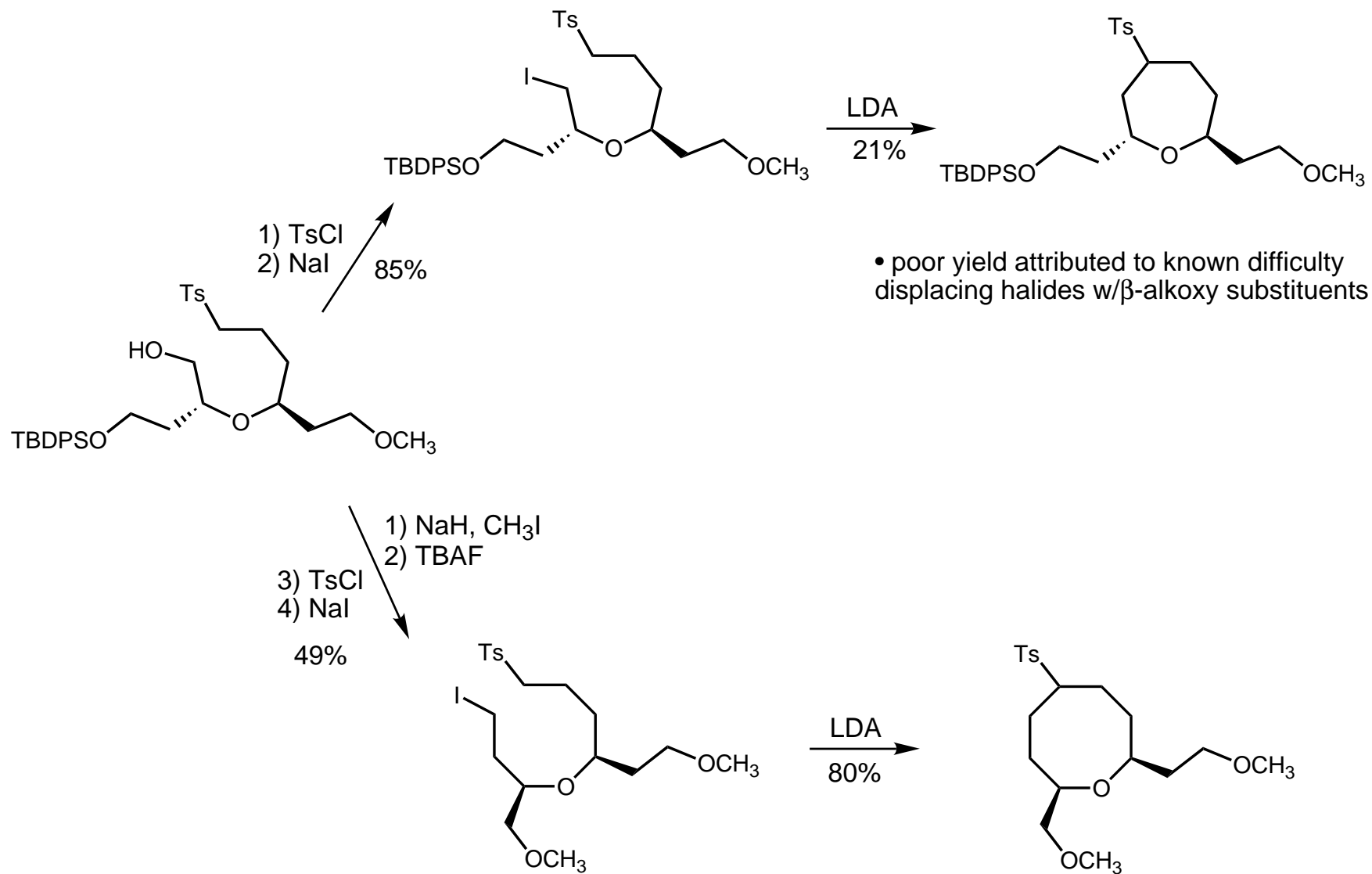
- The HWE reaction is general for aldehyde and ketone carbonyl components, and phosphonyl-ketones and -sulfones, bis-phosphonates and phosphonoacetates as nucleophiles.

Chromium Mediated Cyclizations

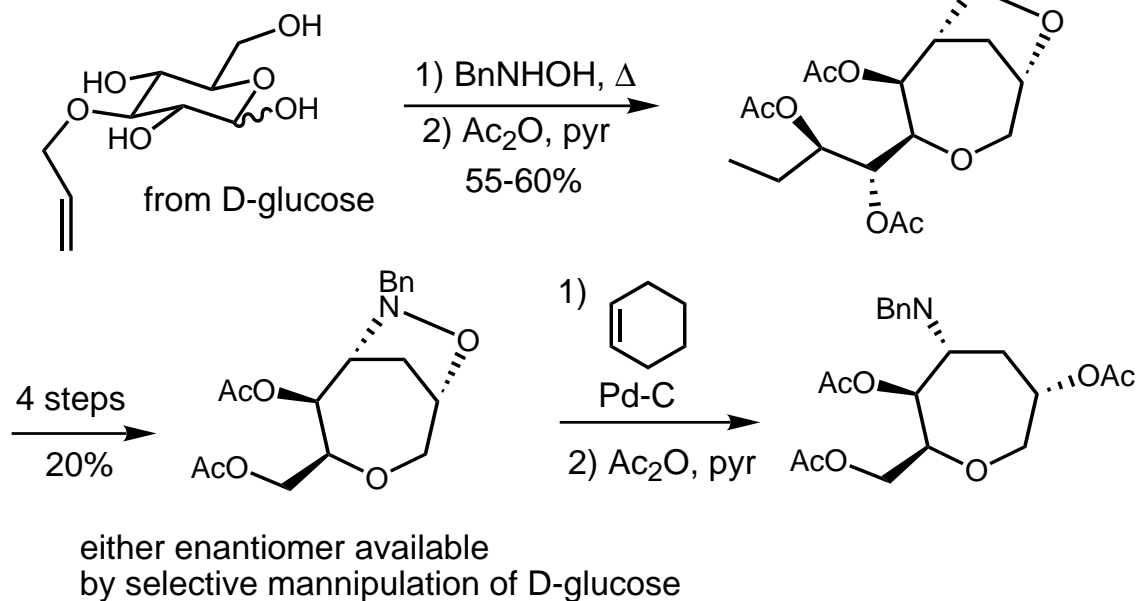


- attempted formation of a benzopyran failed due to formation of the elimination product salicylaldehyde

Oxapanes and Oxacanes from a Common Precursor

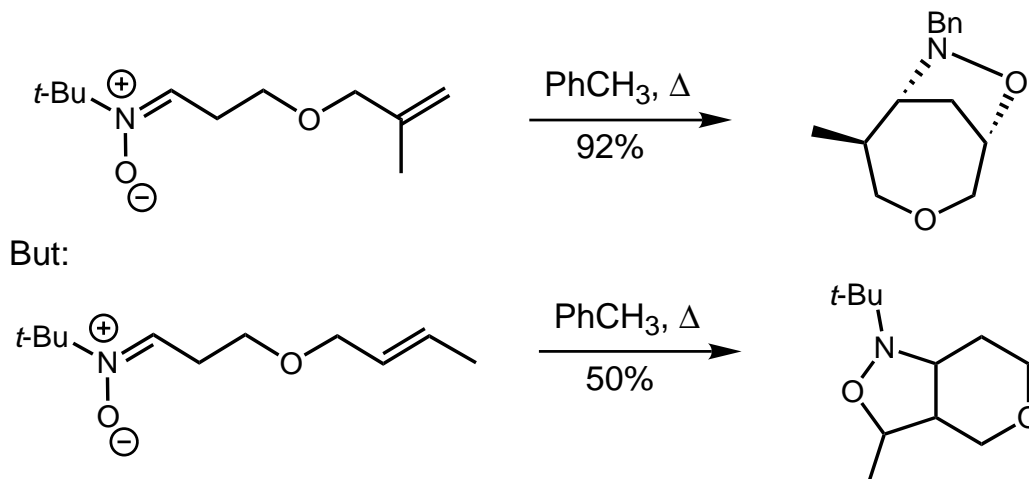


Nitrone Cycloaddition



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

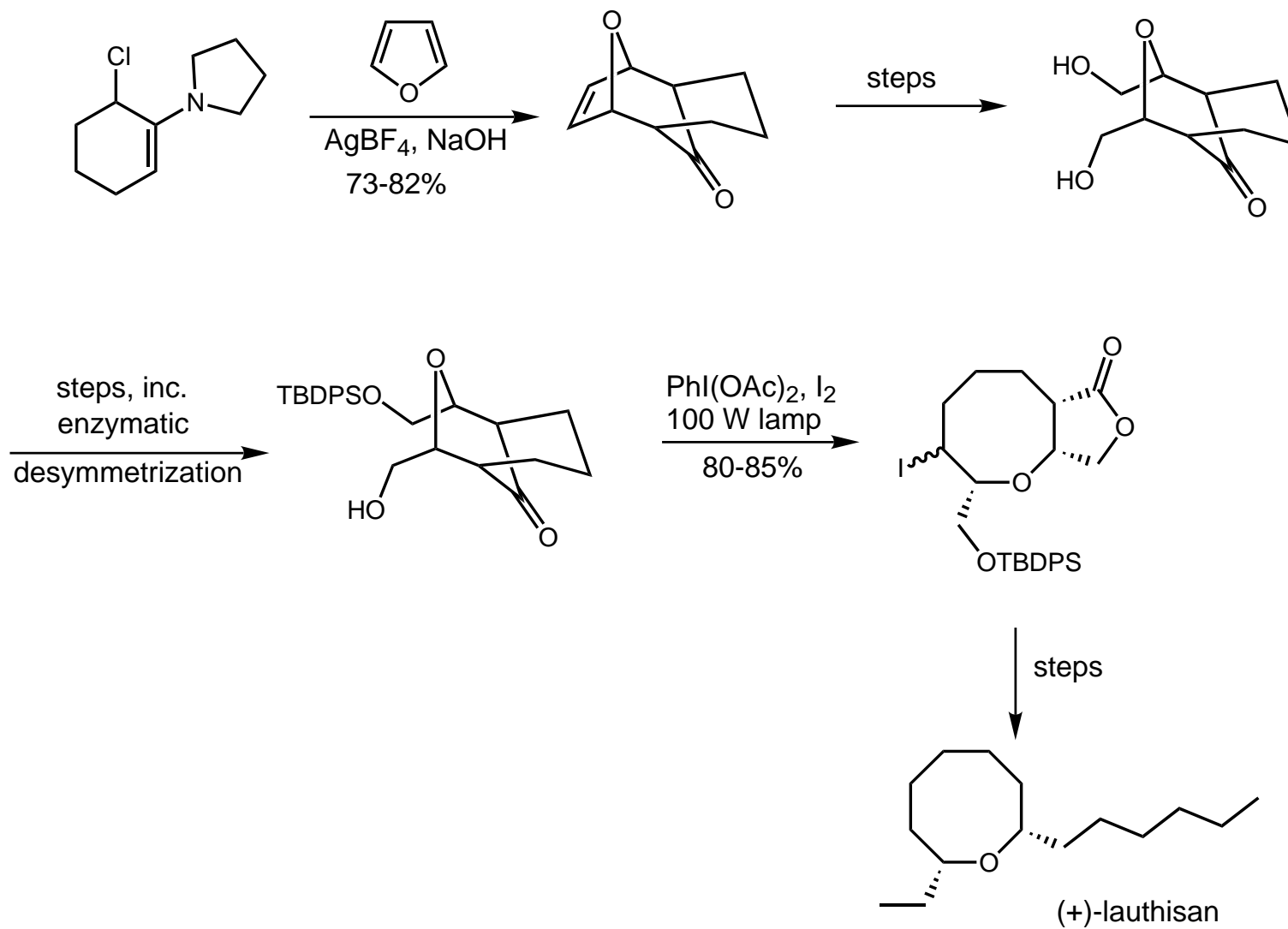
Minor Structural Changes can have a Major Impact on Reactivity



Aurich
 Chem. Ber. 1990, 1508.

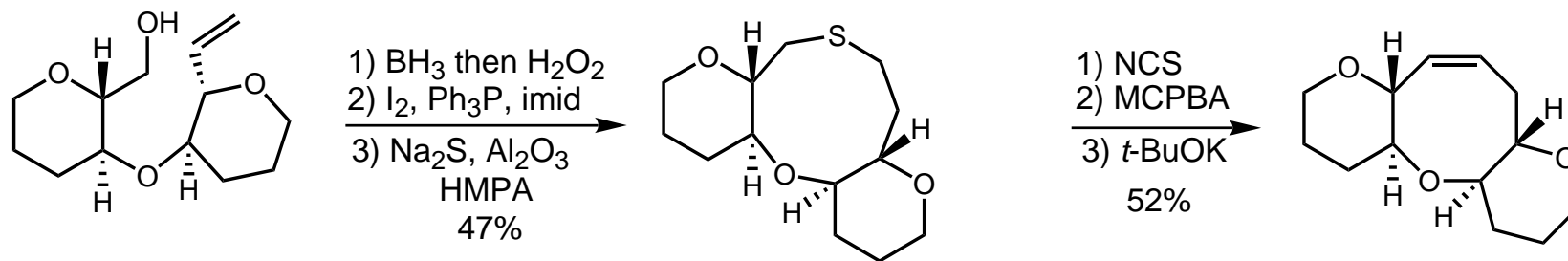
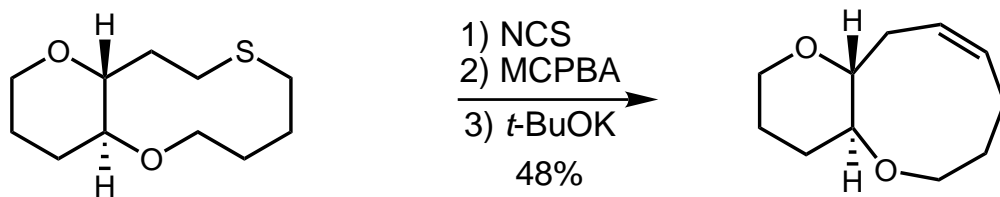
Other nitrile oxide cycloadditions:
 Shing
 Tetrahedron: Asymmetry, 1996, 1323.

[4+3] Cycloaddition Chemistry



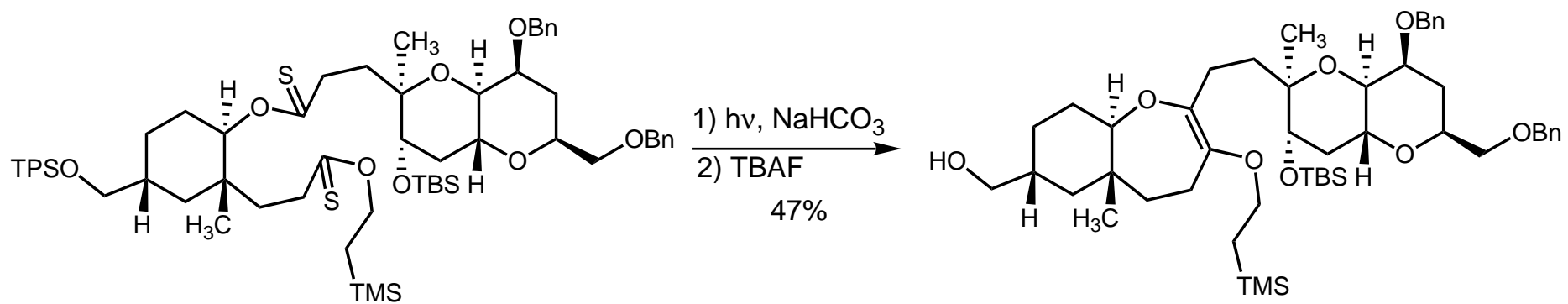
Cha
JOC 1995, 792.

Ramberg-Bäcklund Reaction



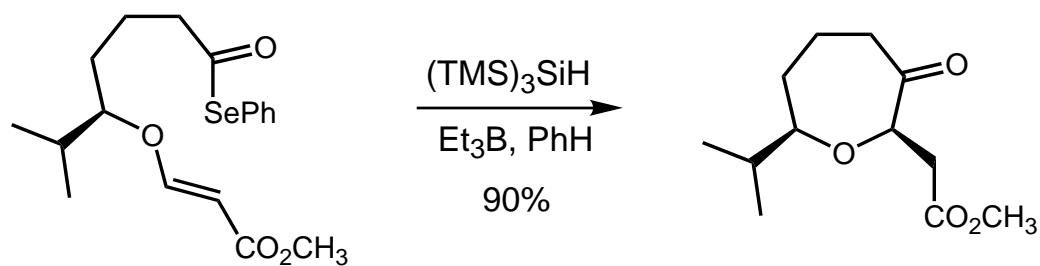
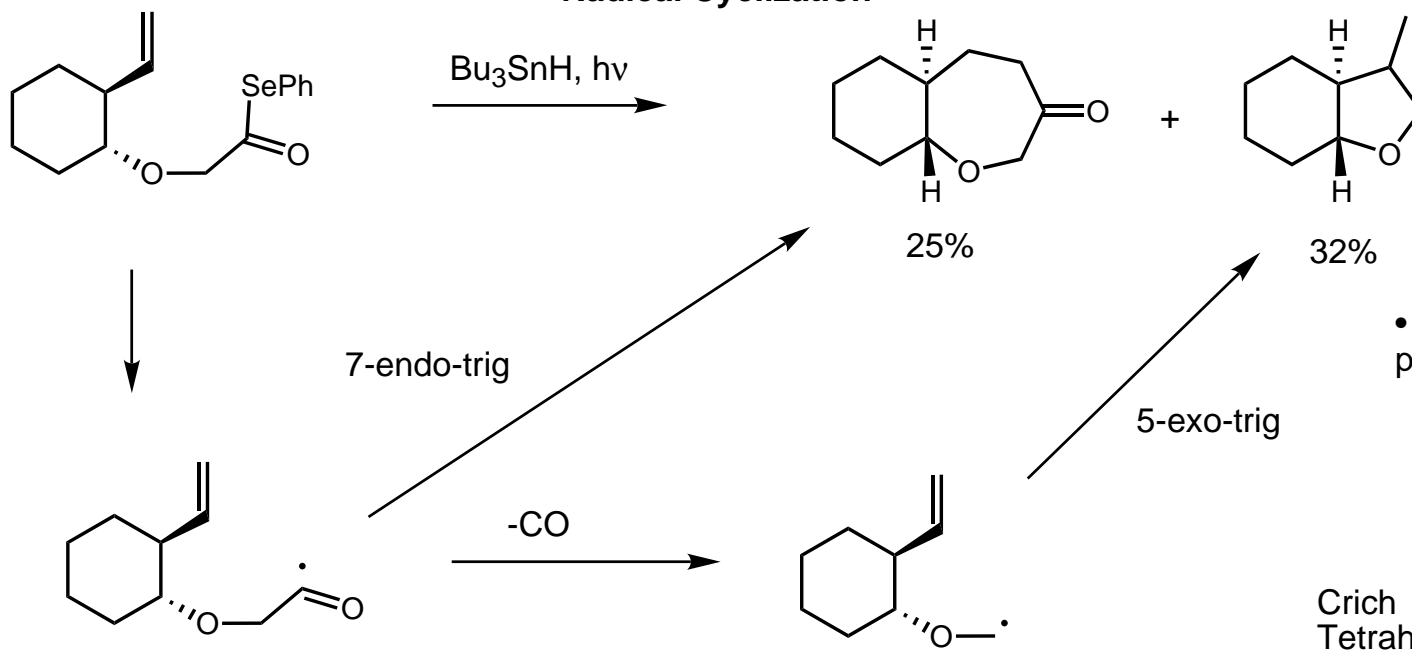
J. D. Martin
TL 1996, 2869.
JACS 1995, 1437.
JOC 1994, 2848.

Photochemical Cyclization of a bis-Thionoester



towards hemibrevetoxin
Nicolaou
JACS 1993, 3558.

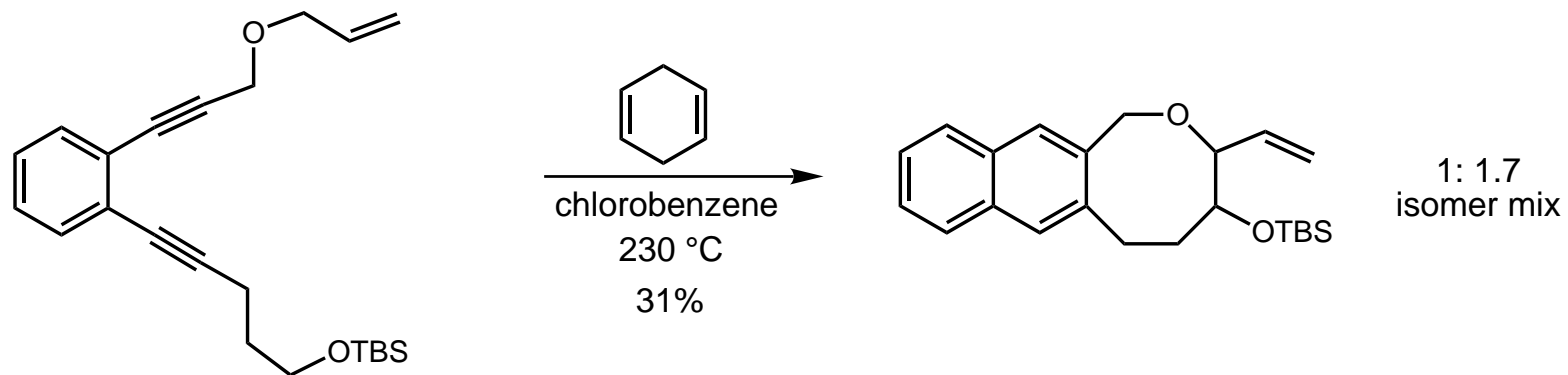
Radical Cyclization



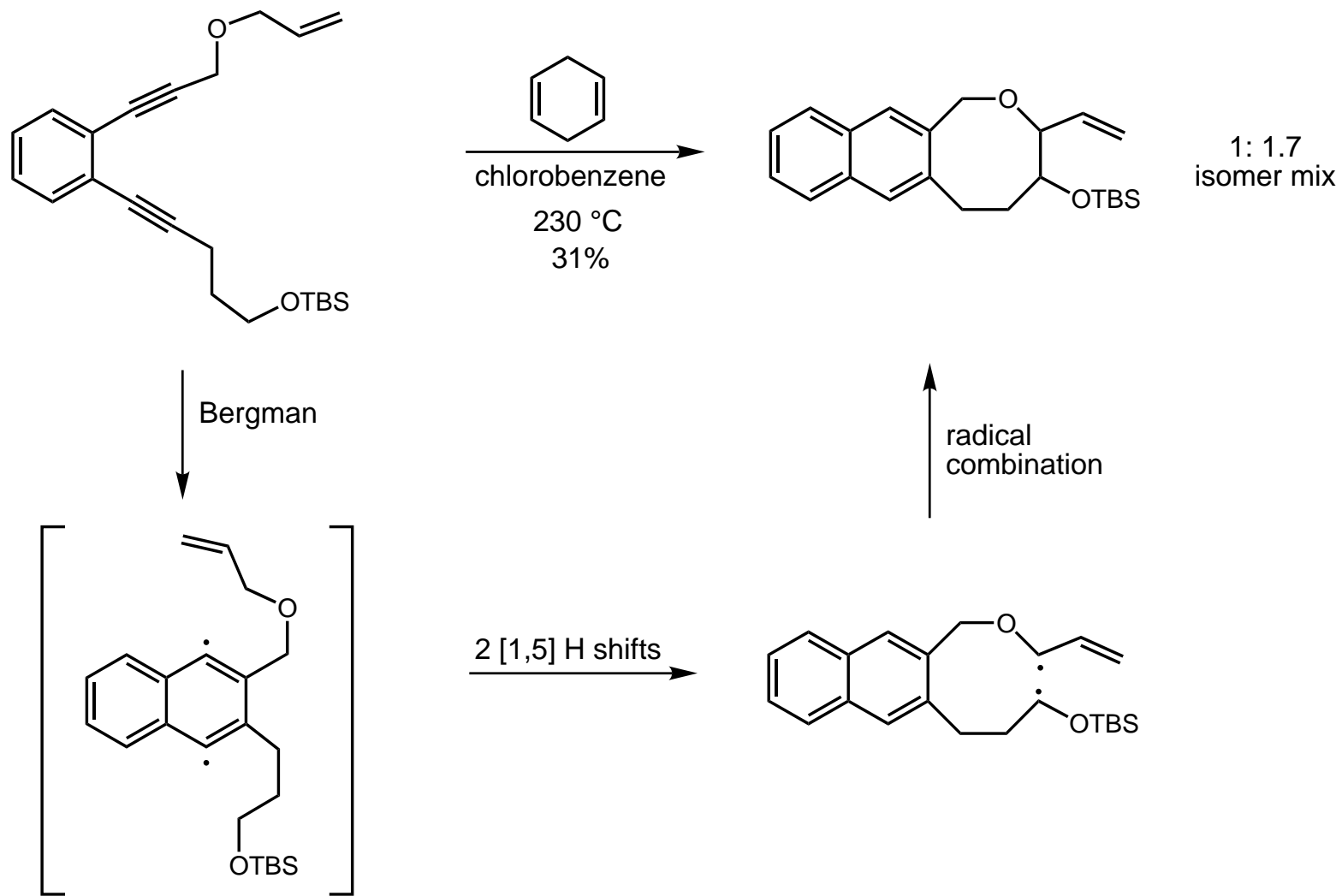
similar conditions used to form a THP relevant to the brevetoxins in 99% yield.

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

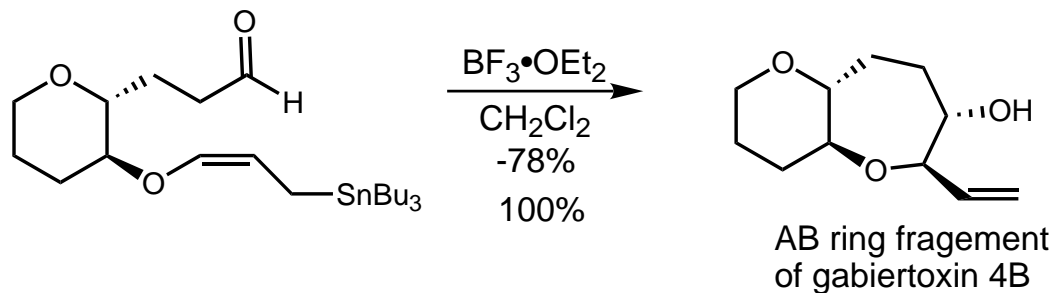
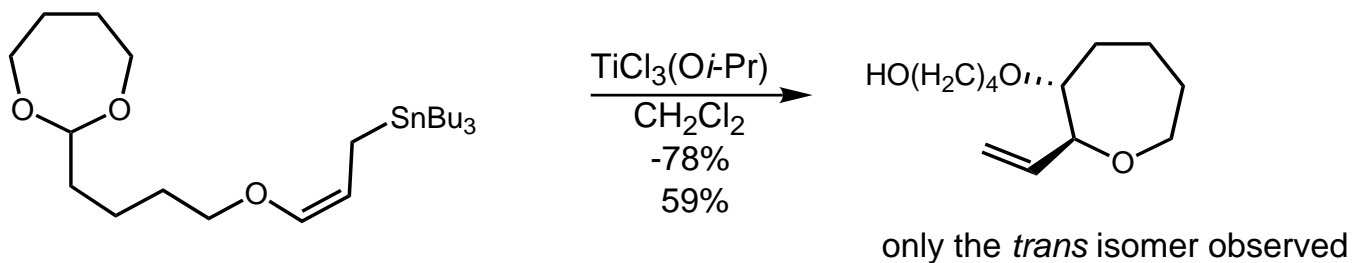
An Interesting Cyclization



Bergman Cyclization

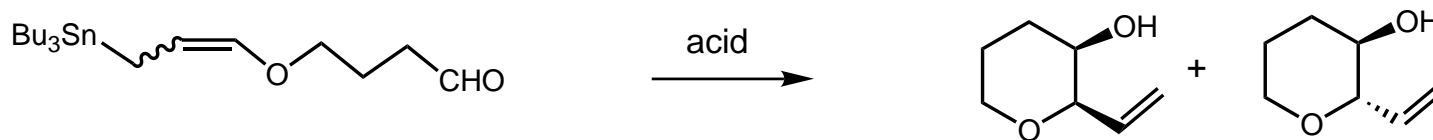


Allyl Stannations



- 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
- TiCl_4 doped with Ph_3P 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:



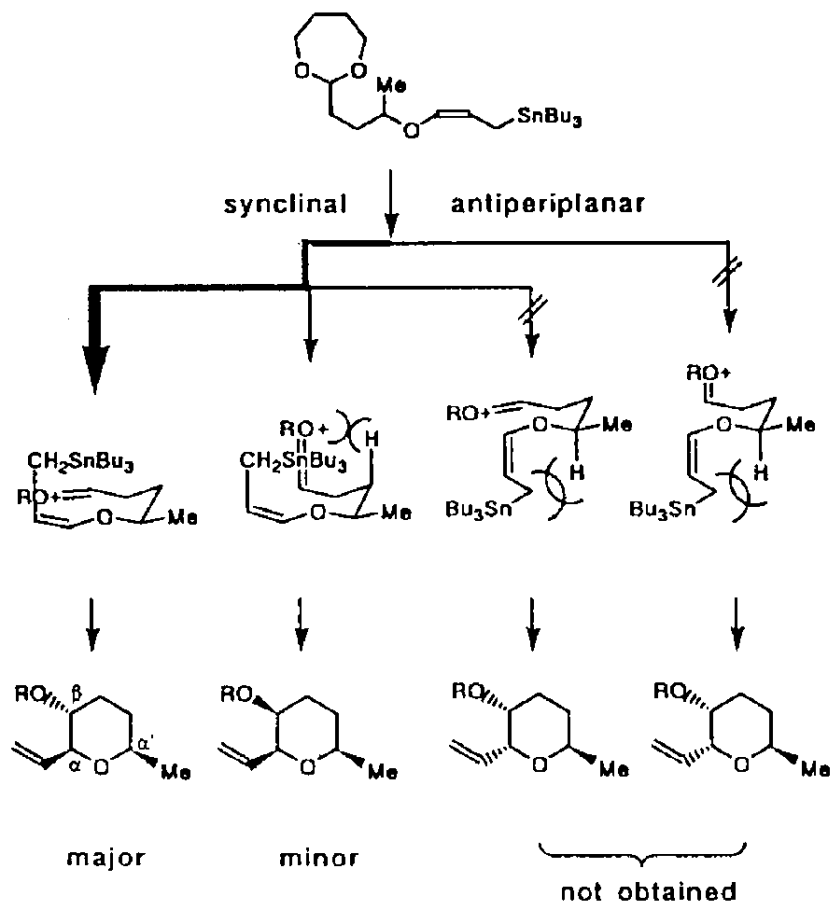
protic acid (TfOH) (Z-stannane) major
 protic acid (TfOH) (E-stannane) minor
 Lewis Acids (Z- or E-stannane) minor

minor
 major
 major

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

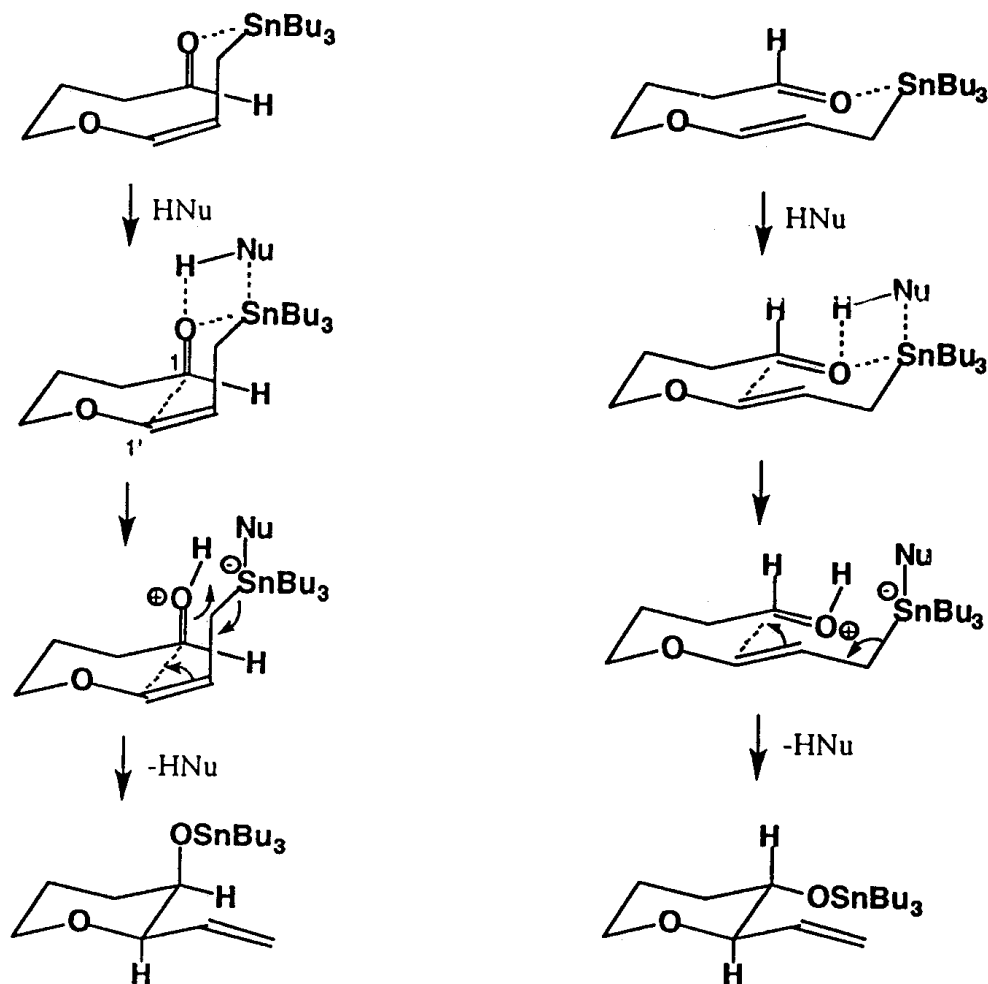
Allyl Stannations: Mechanism and Stereochemistry

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

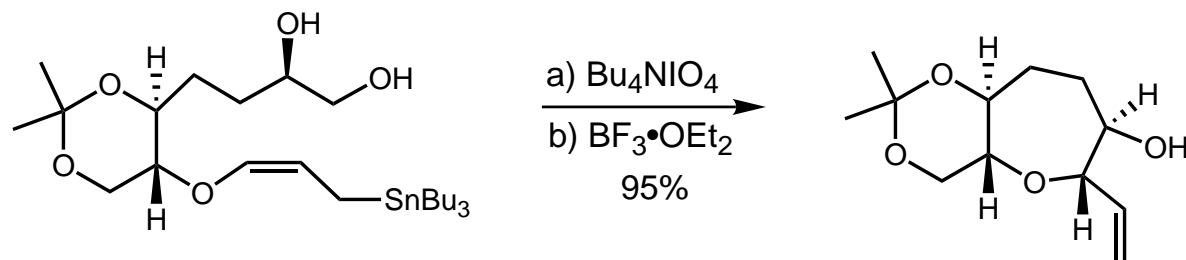
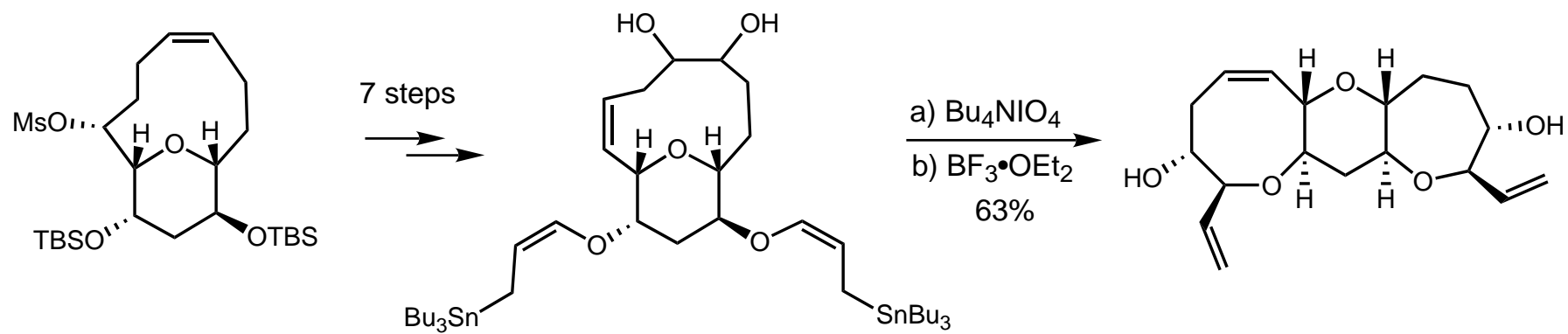


"In the 7-membered cyclization, the transition state geometry becomes more flexible, being able to give a thermodynamically stable trans isomer with high diastereoselectivity".

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

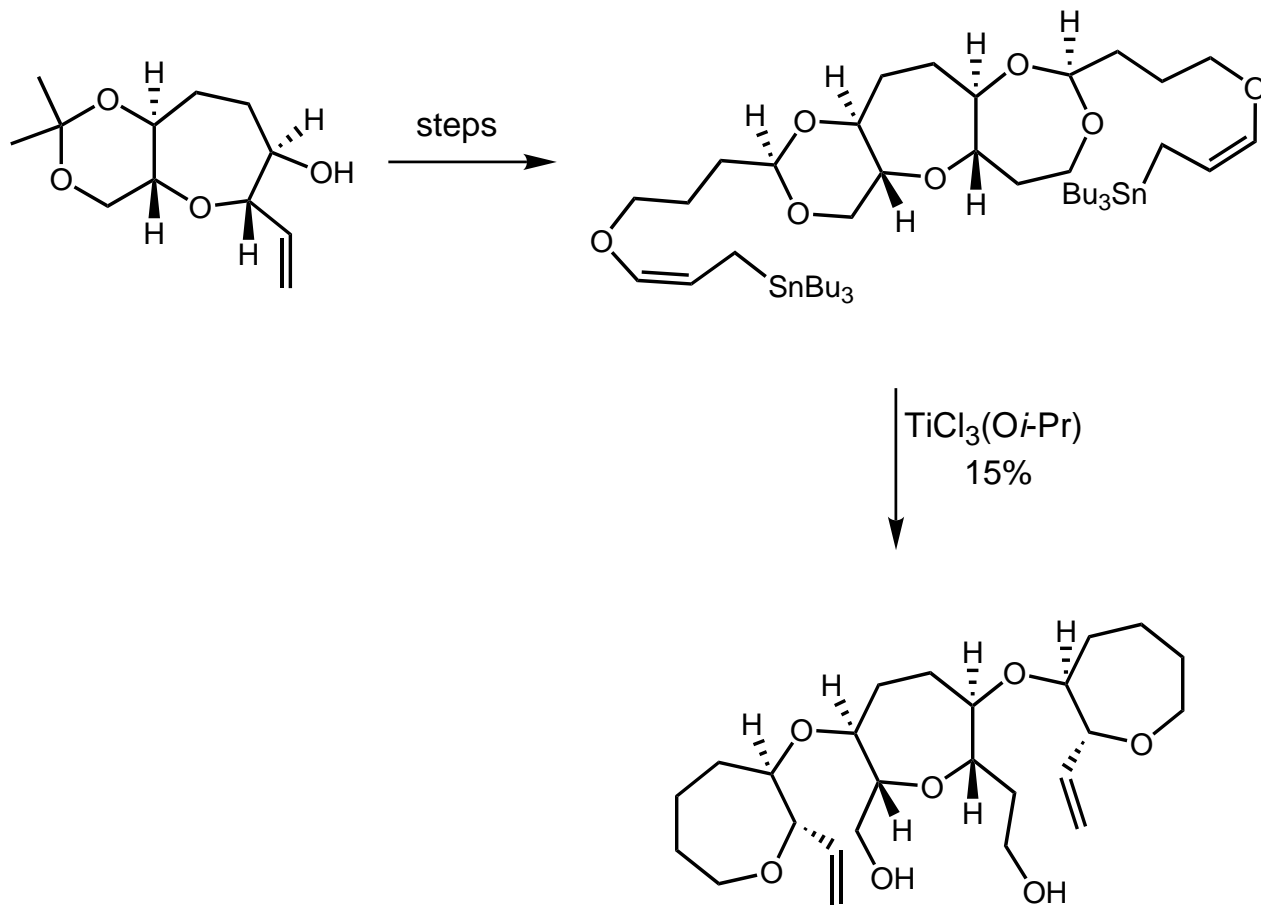


One-Pot Oxidation-Cyclization



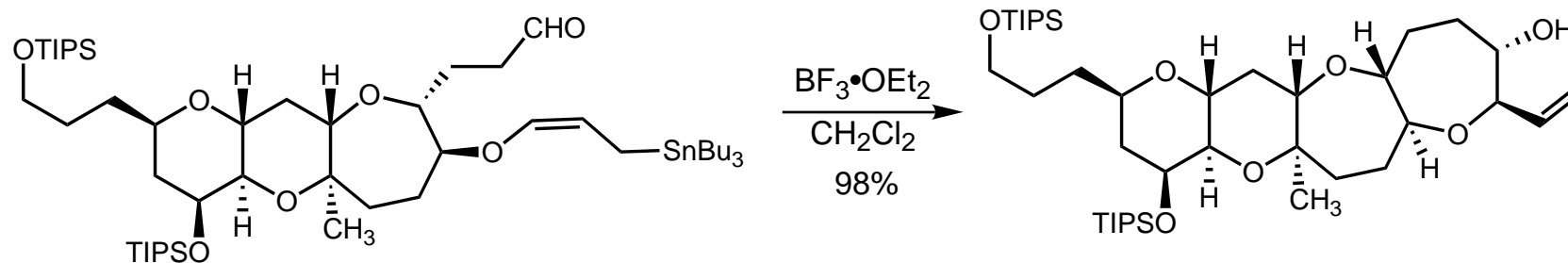
J. D. Martin
TL 1992, 3389.
TL 1996, 2869.

A Disappointing Allyl Stannation



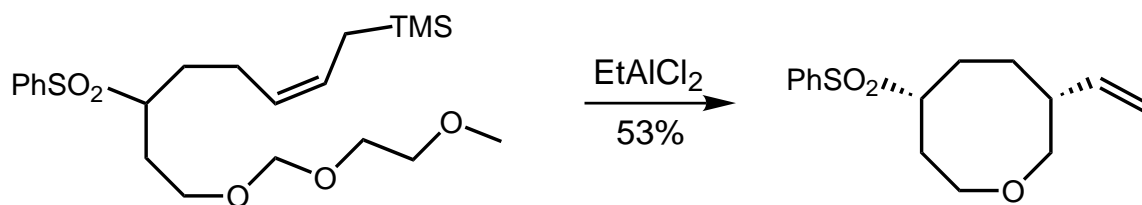
A More Complex Allyl Stannation

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



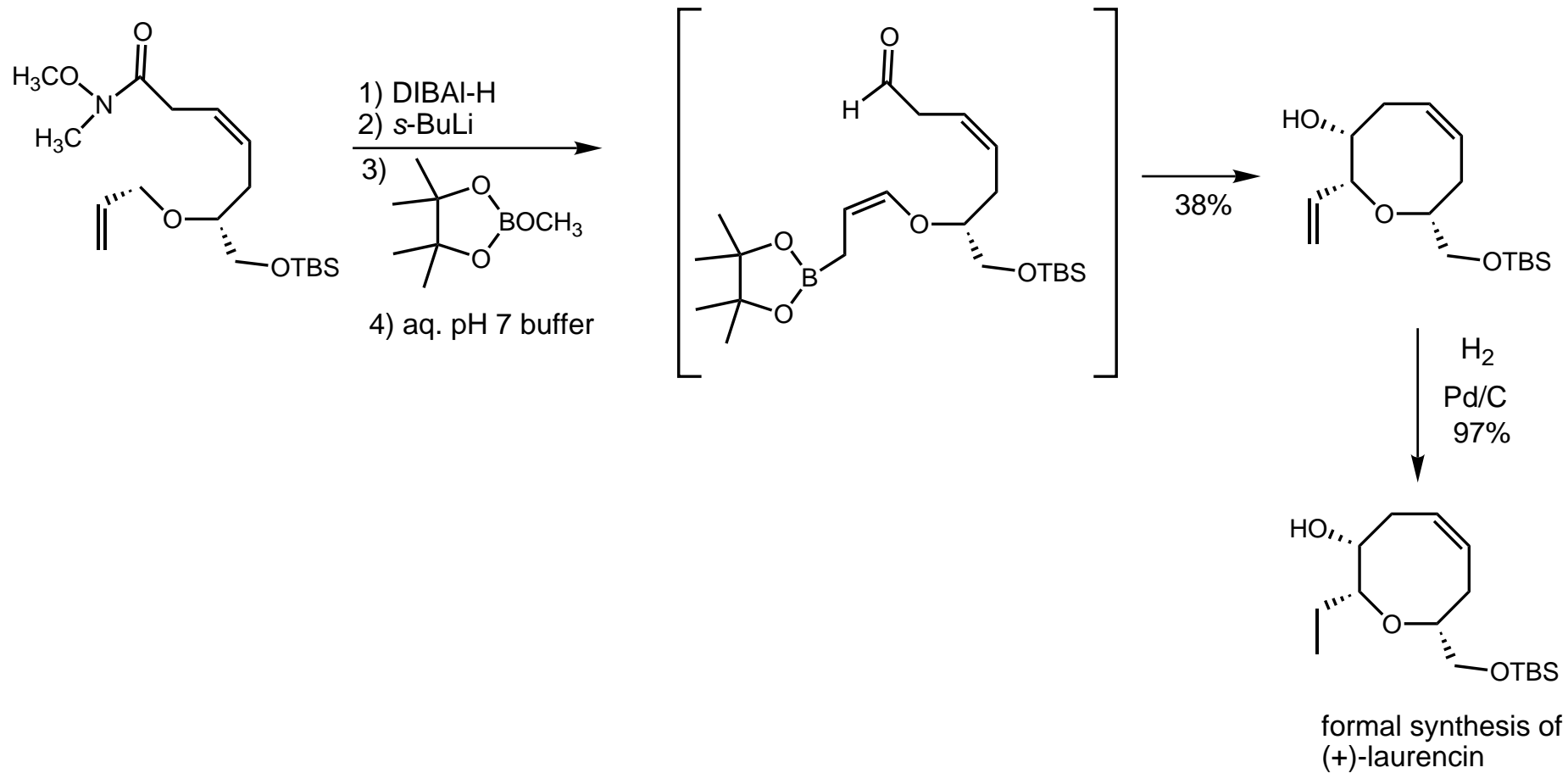
Yamamoto
TL 1995, 5777.

A Lone Allyl Silylation



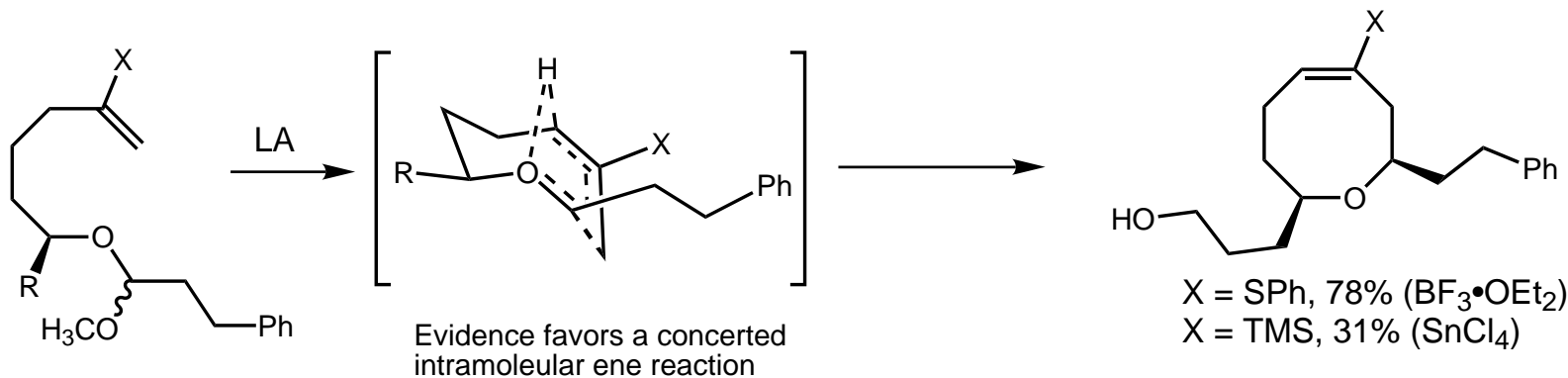
Simpkins
Tetrahedron, 1991, 7689.

Intramolecular Allylboration



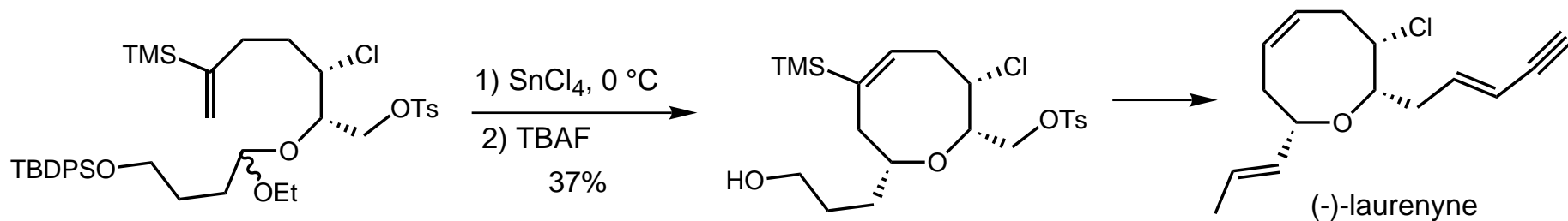
R. W. Hoffmann
JACS 1997, 7499.

Overman Acetal Alkene Cyclizations



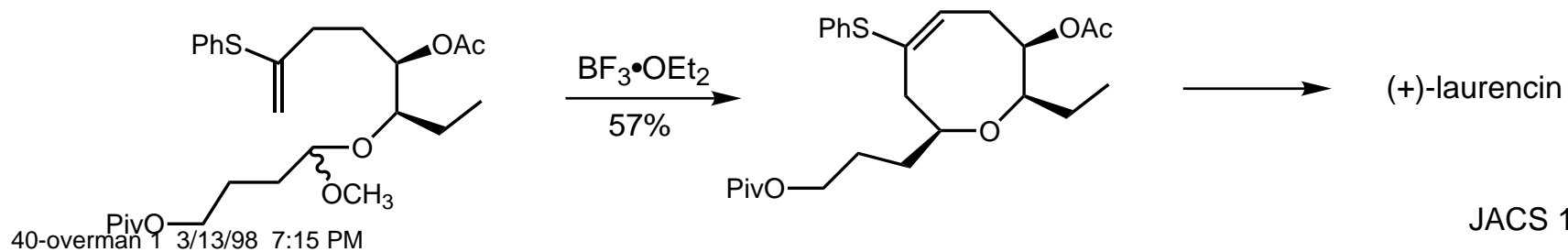
JACS 1986, 3516.
 JACS 1990, 4386.
 JACS 1990, 4399.

Laurenyne



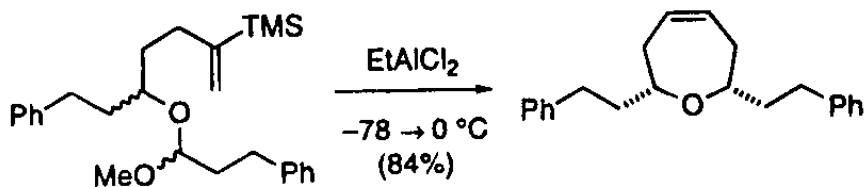
JACS 1988, 2248.

Laurencin



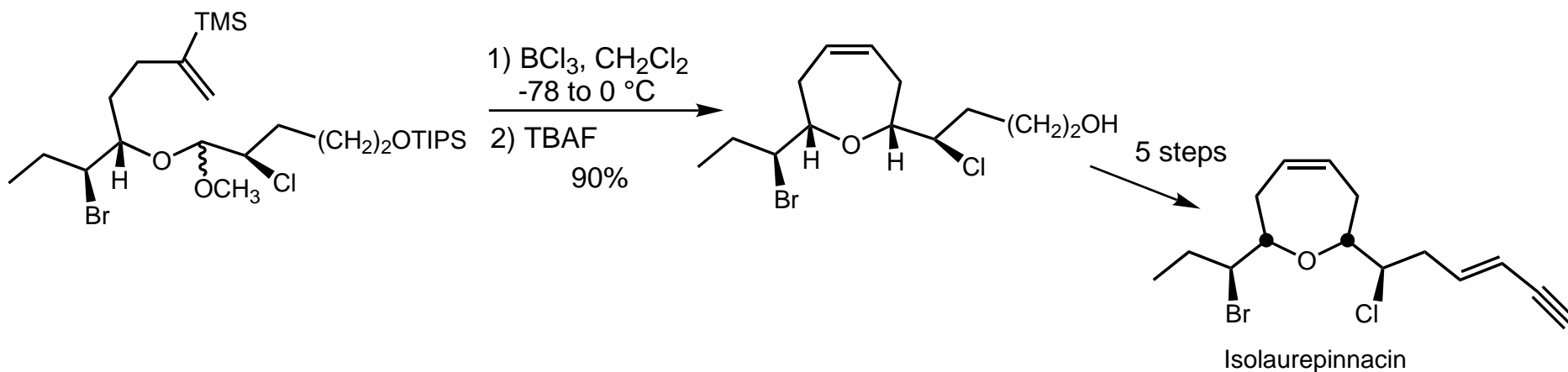
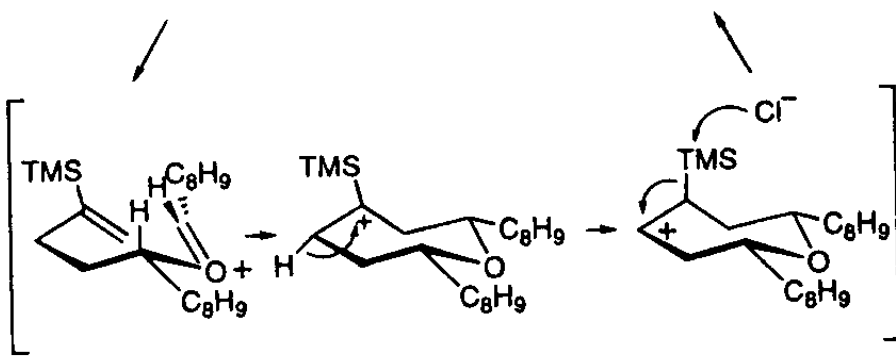
JACS 1995, 5958.

Overman Acetal Alkene Cyclizations



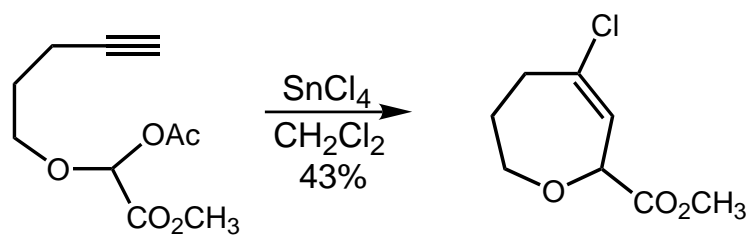
Three effects are responsible for the high yielding transformation:

- Initial Prins cyclization occurs in an endocyclic sense as a result of the greater stability of a tertiary α -silyl cation than a primary β -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



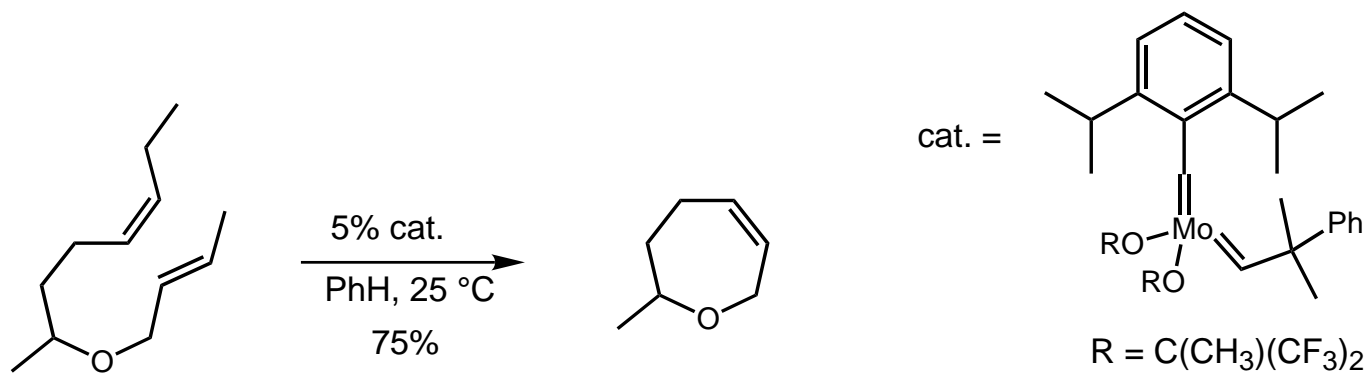
SynLett 1992, 811.
JACS 1993, 9305.
JACS 1997, 2447.

Acetal Alkyne Cyclization



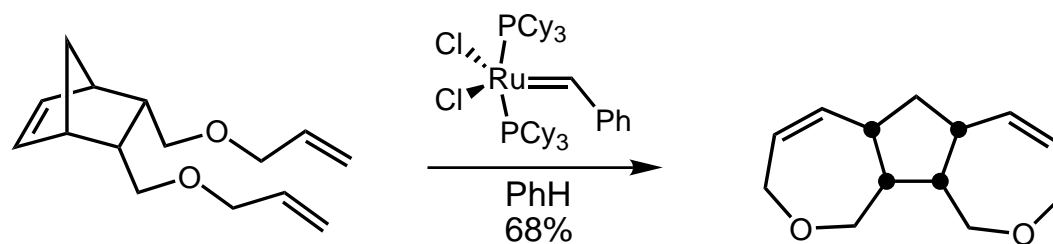
Speckamp
Tetrahedron 1994, 7115.

Ring Closing Metathesis



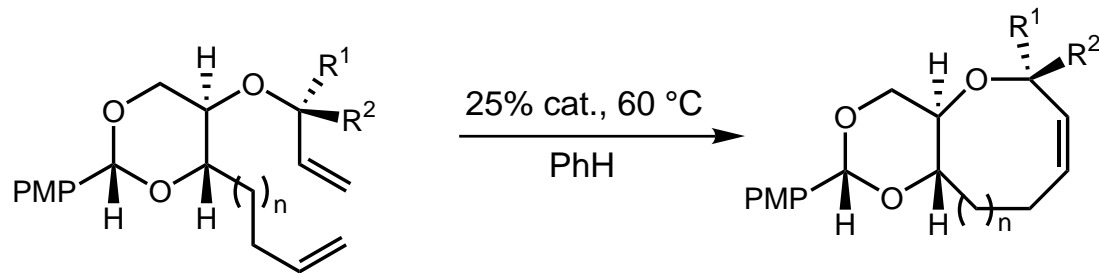
Grubbs
JACS 1992, 5426.
JACS 1993, 9856.

Ring Opening - Ring Closing Metathesis



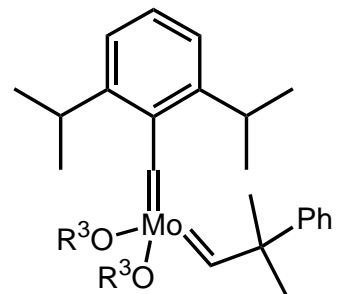
Grubbs
JACS 1996, 6634.

RCM for Brevetoxin and Ciguatoxin



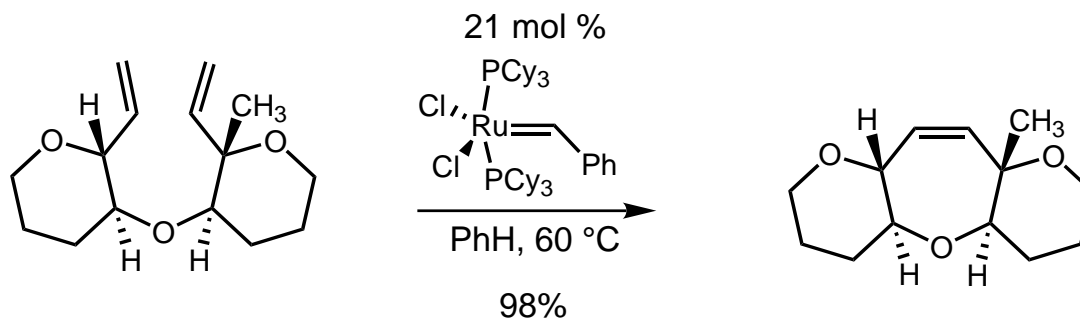
$n = 1, R^1 = H, R^2 = Et, 97\%$
 $n = 1, R^1 = Et, R^2 = H, 86\%$
 $n = 2, R^1 = H, R^2 = Et, 86\%$
 $n = 2, R^1 = Et, R^2 = H, 14\%$
 $n = 2, R^1 = H, R^2 = H, 58\%$

cat. =



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

Clark
TL 1997, 127.



Hirama
Synlett 1997, 980.

Ring Closing Metathesis

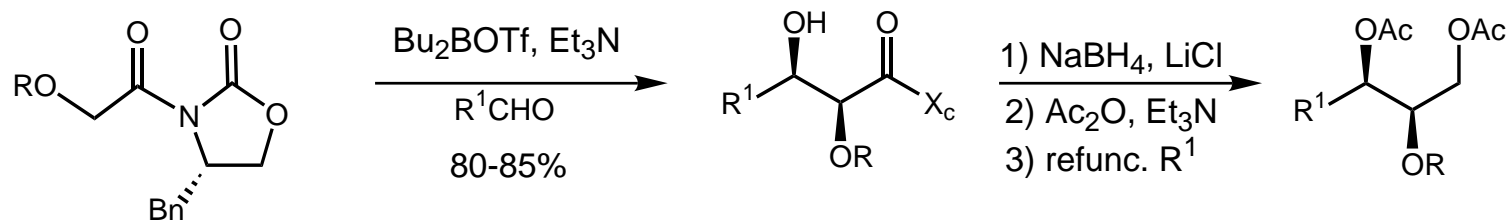


Table 1

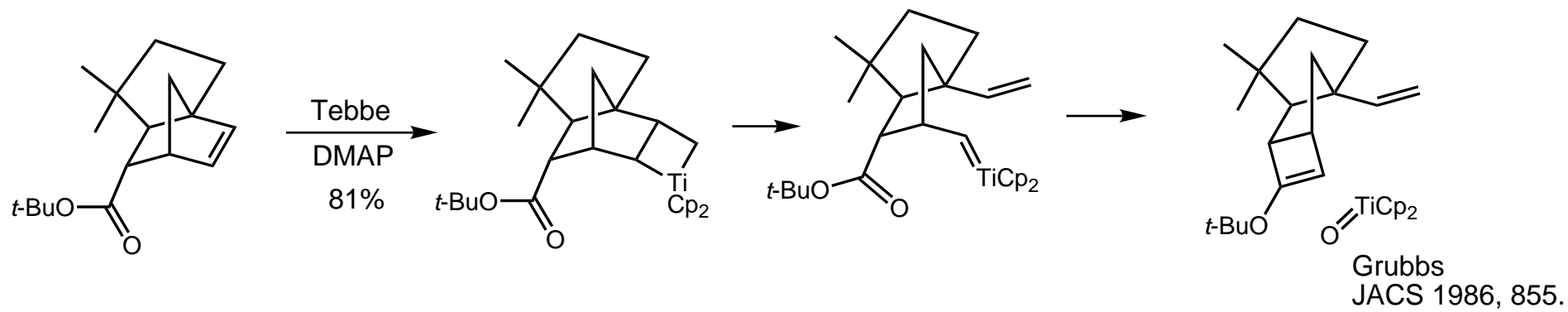
Diene	Product	Yield ^{a,b}
		90% 1 h
		95% 2 h
		73% (17% dimer) 2 h
		94% 30 min
		89% (10% dimer) 1 h

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

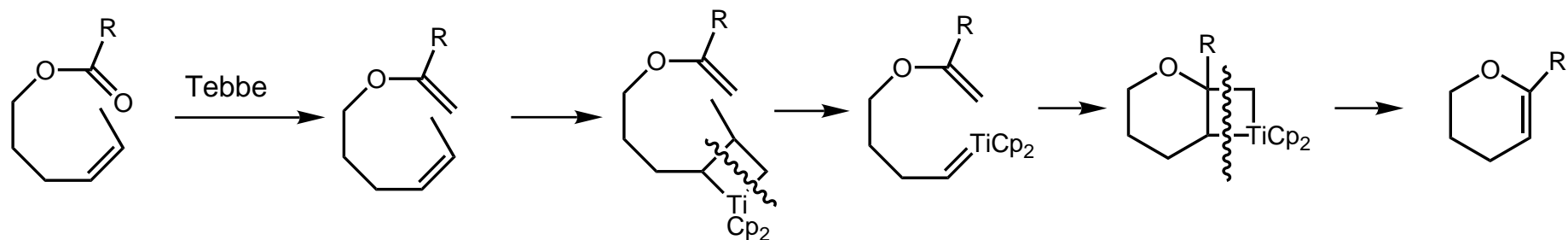
Crimmins
JOC 1997, 7549.

Tandem Methylenation - Metathesis of Olefinic Esters

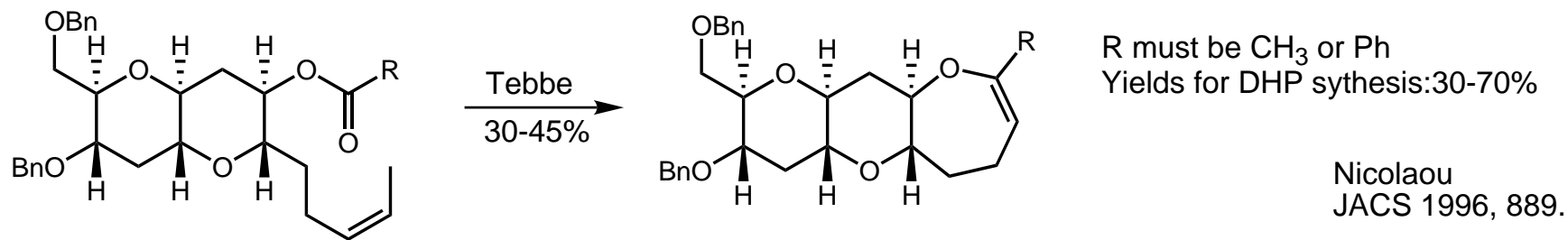
The Precedent:



The General Scheme:



The Example:

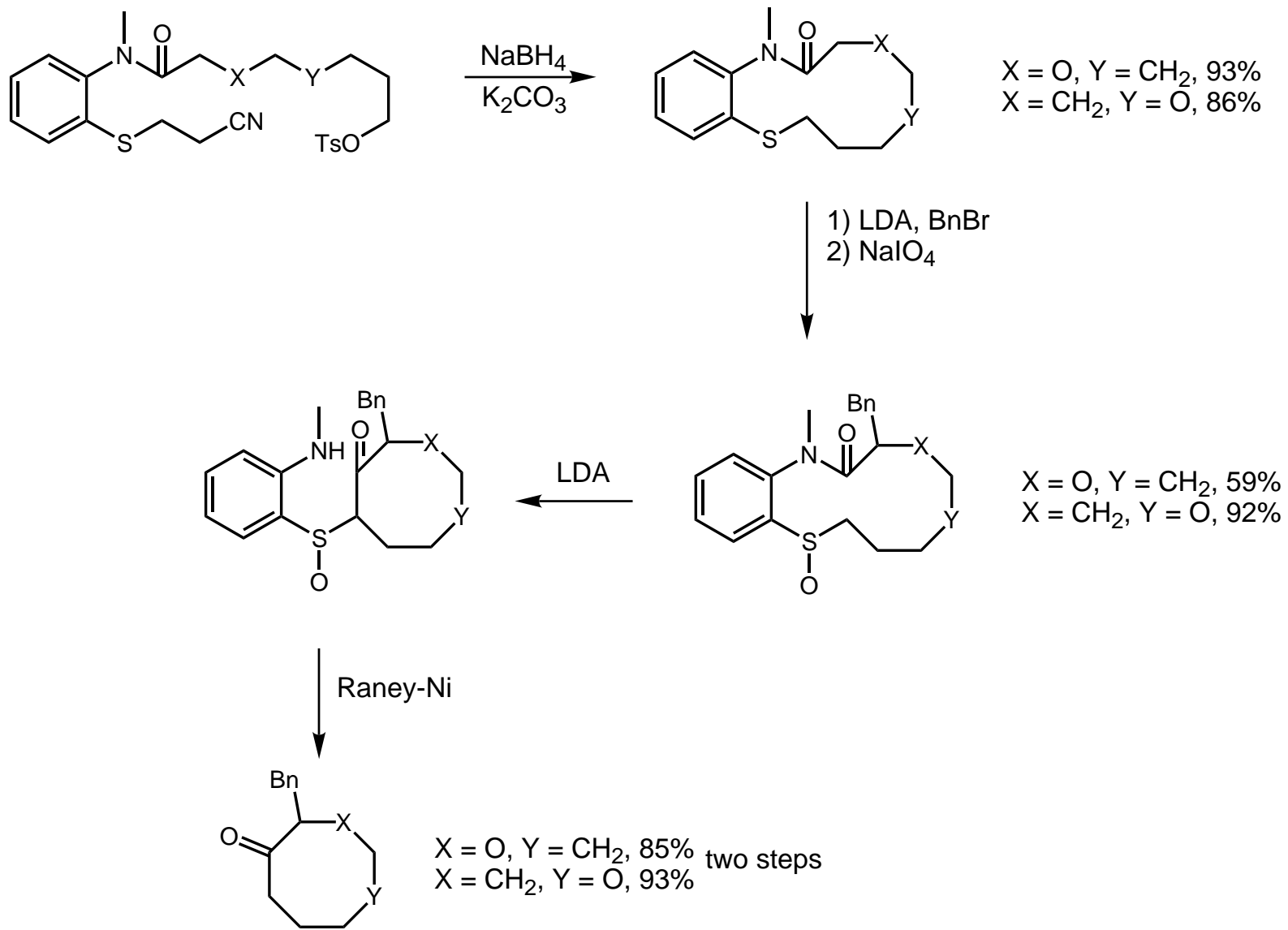


The Critique:

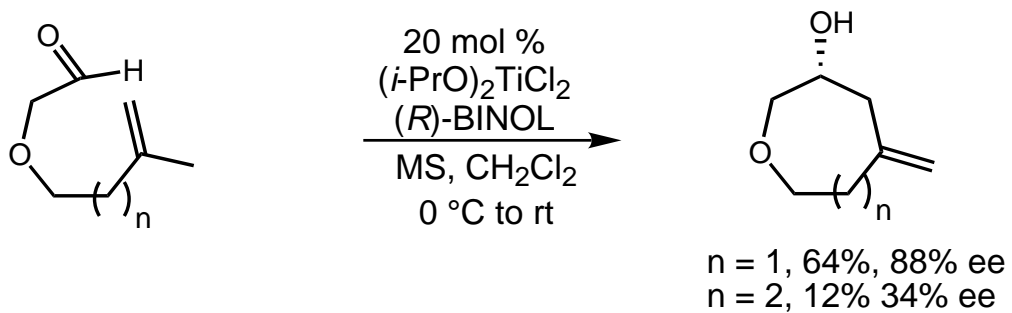
The reaction awaits further vigorous development before being regarded as widely applicable...
...improvement in the efficiency is necessary.

Paquette
Chemtracts, 1997, 14.

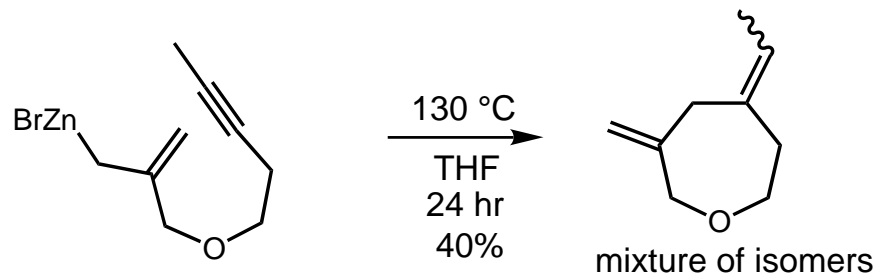
Use of a Tether



Ene Reactions

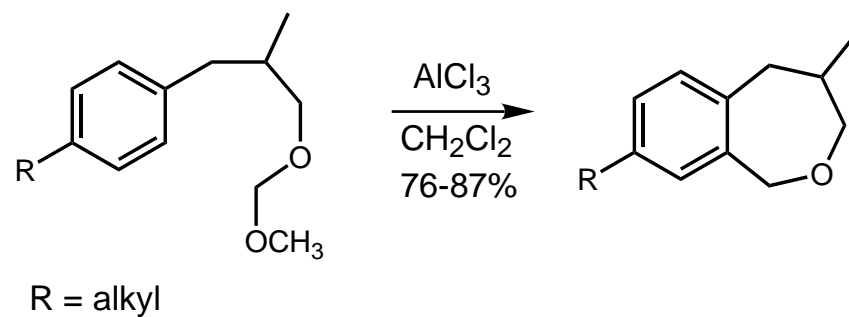


Mikami
Tetrahedron:Asymmetry, 1991, 1403.



Klumpp
Tetrahedron, 1992, 6105.

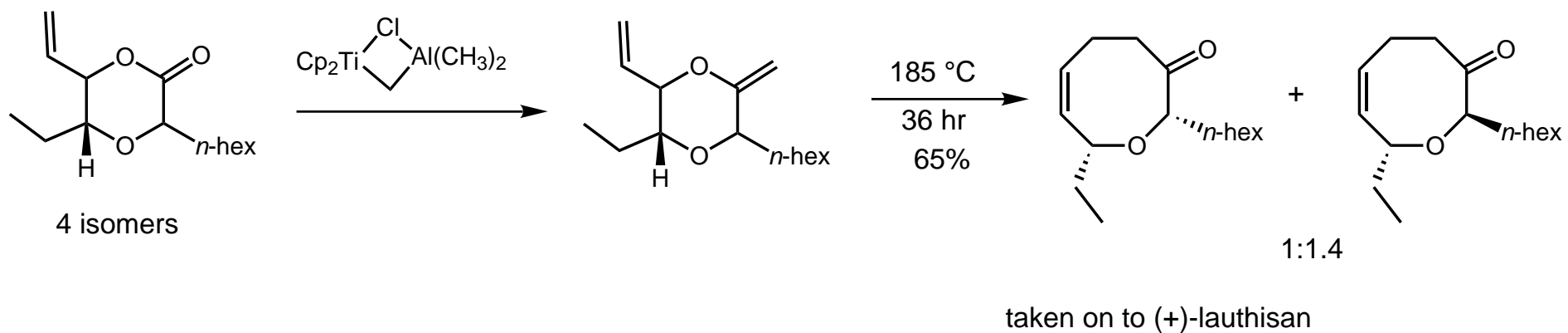
Friedel Crafts Alkylation



Skouroumounis
Helv. Chim. Acta, 1996, 1095.

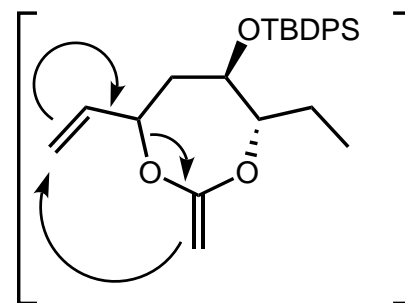
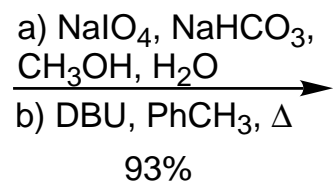
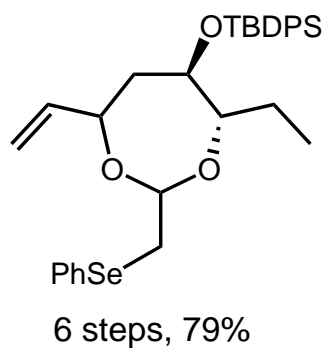
Rearrangement Reactions

Claisen Rearrangement

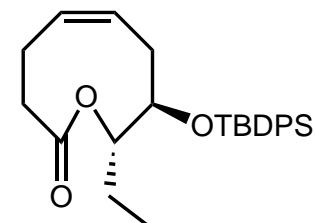


Paquette
JOC 1990, 1703.
Tetrahedron 1990, 4487.

Ketene Acetal Claisen Rearrangement

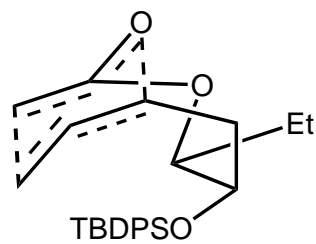
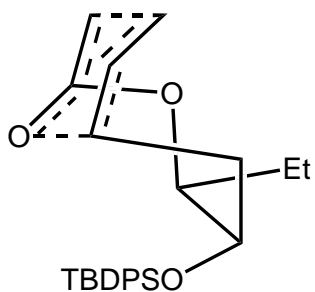


mixture of ketene acetals

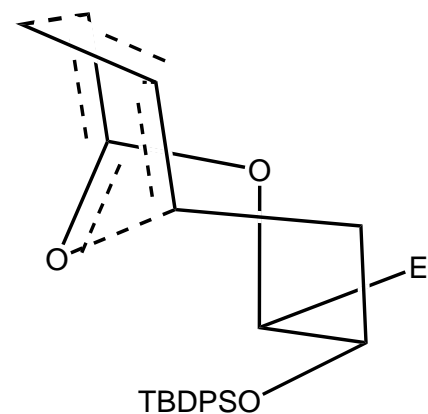


one isomer

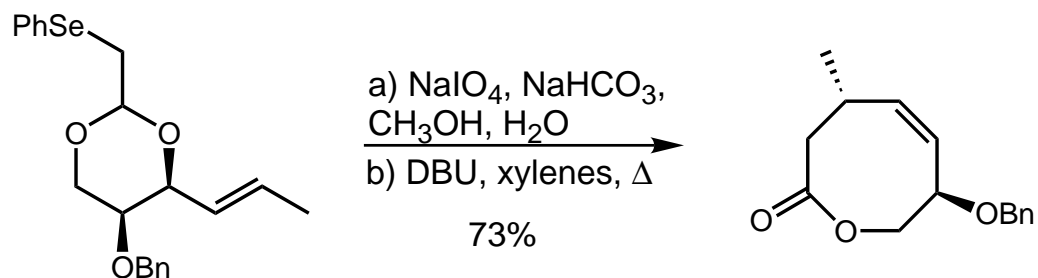
A chair TS for each isomer leads to the same product:



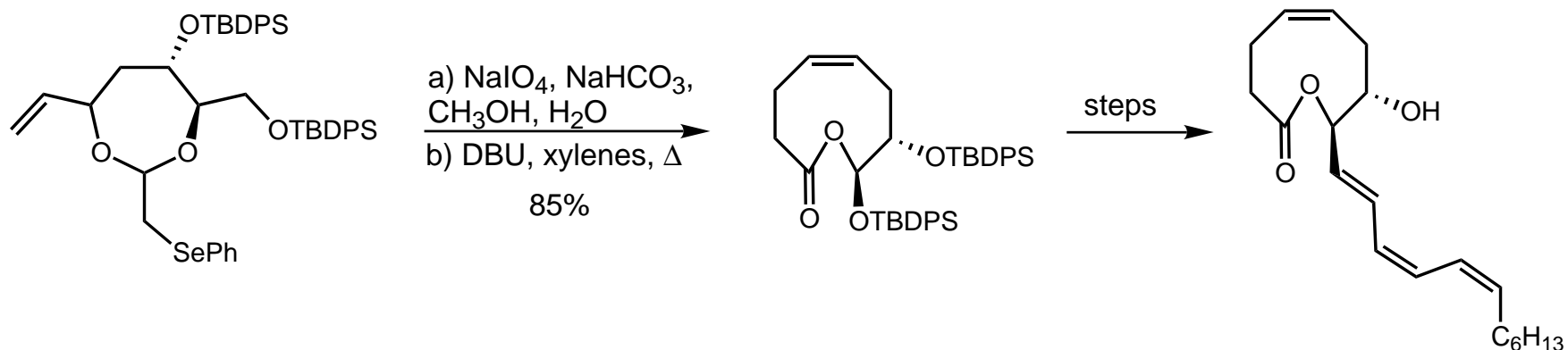
A boat TS would lead to a *trans* double bond (not observed)



Substituted Double Bonds



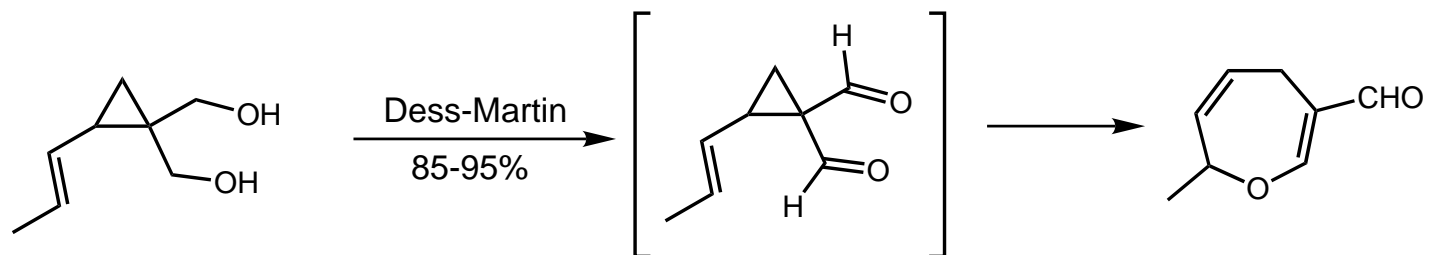
Asciatrienolide A: Disproof of Structure



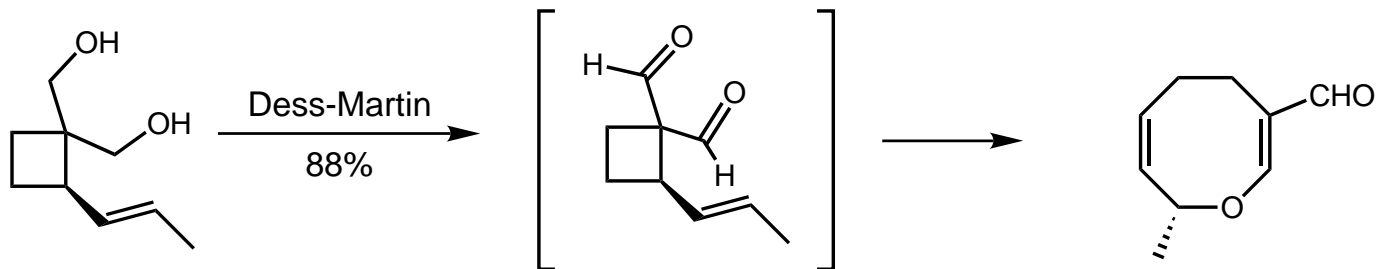
proposed structure of Asciatrienolide A - not identical to the natural product (which was shown to be a 10-membered lactone (with one more methylene))

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

Retro-Claisen Rearrangement



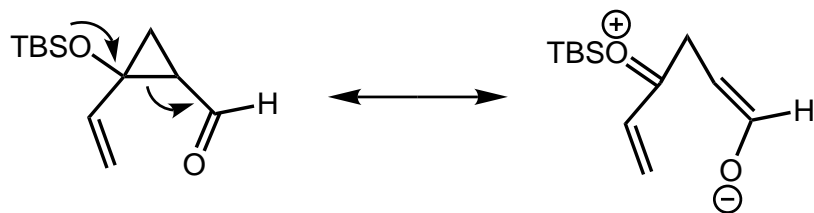
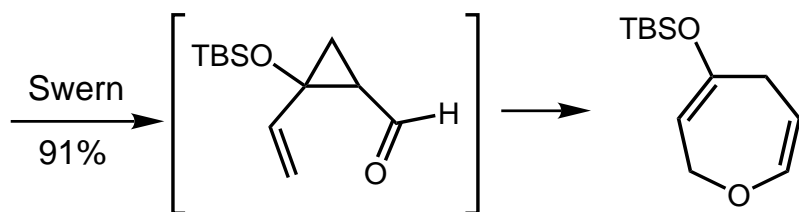
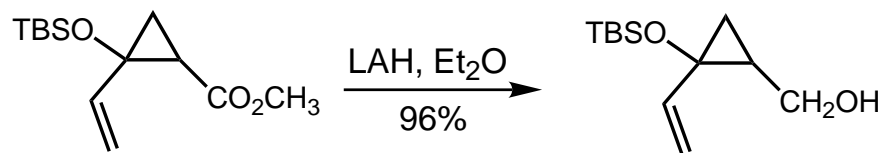
- substitution at all positions of the cyclopropane and olefin are tolerated



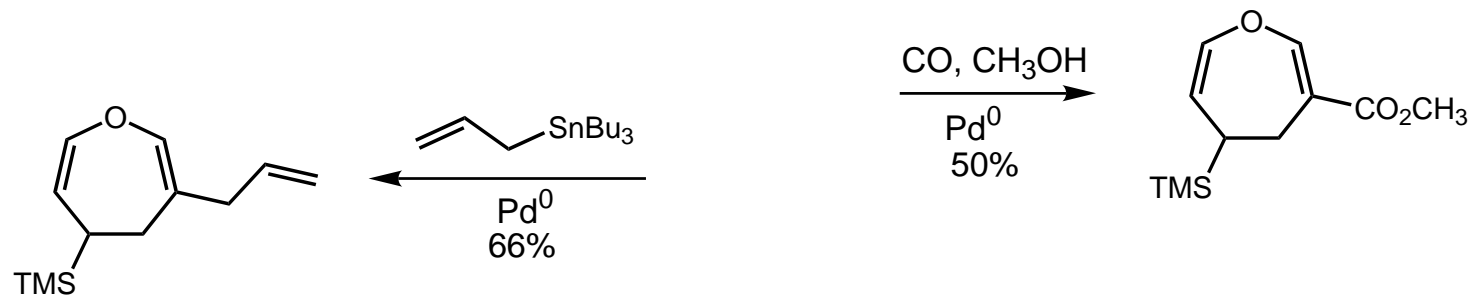
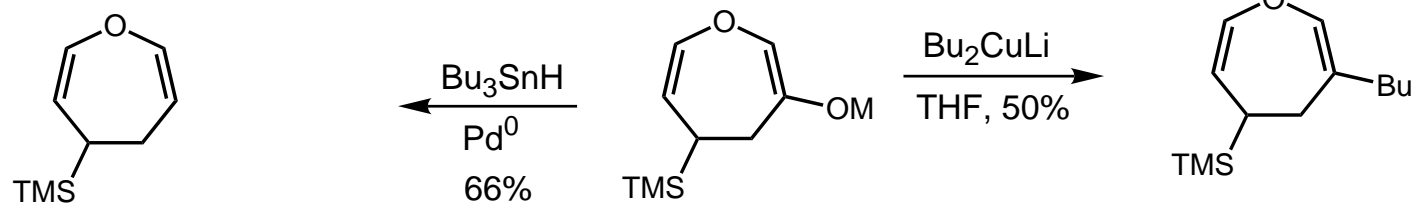
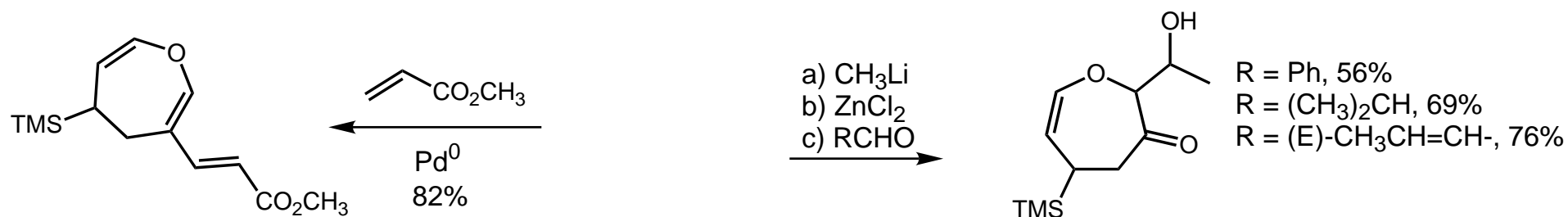
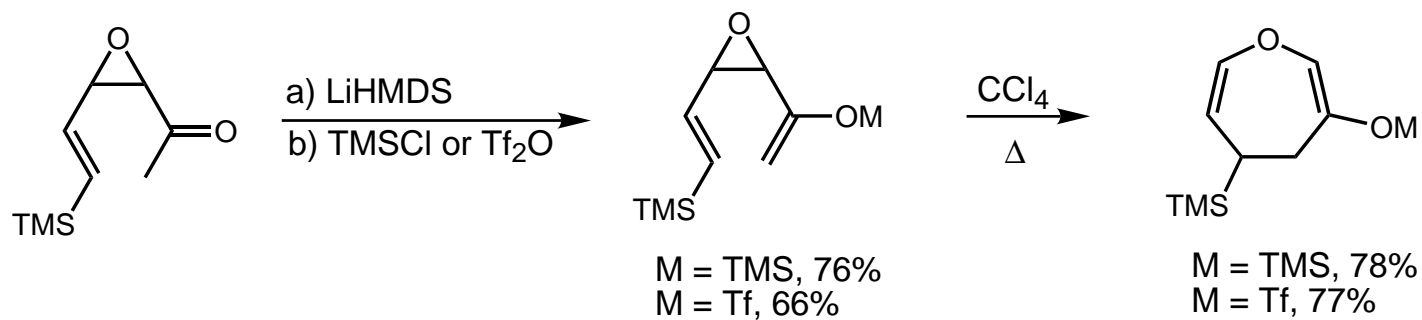
- enantiopure cyclobutane delivers enantiopure dihydrooxacenes

Boeckman
JOC 1993, 1295.
JOC 1997, 6456.

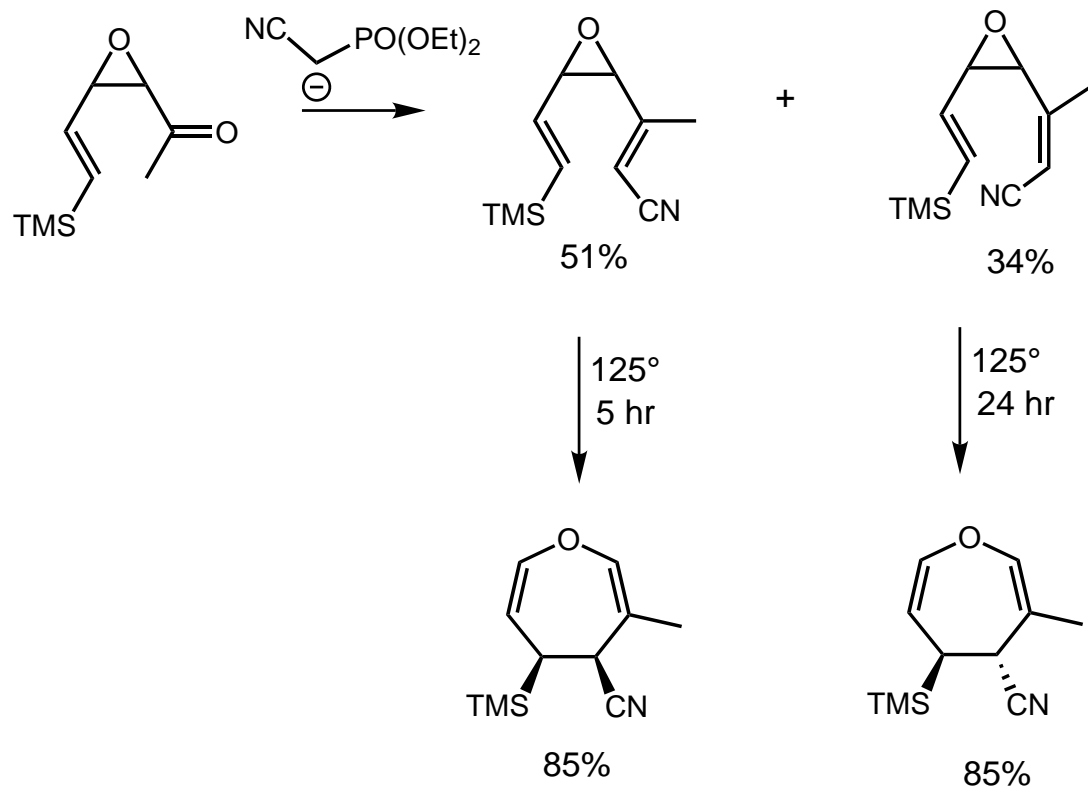
Retro-Claisen Rearrangement



Cope Rearrangement of Divinylepoxides

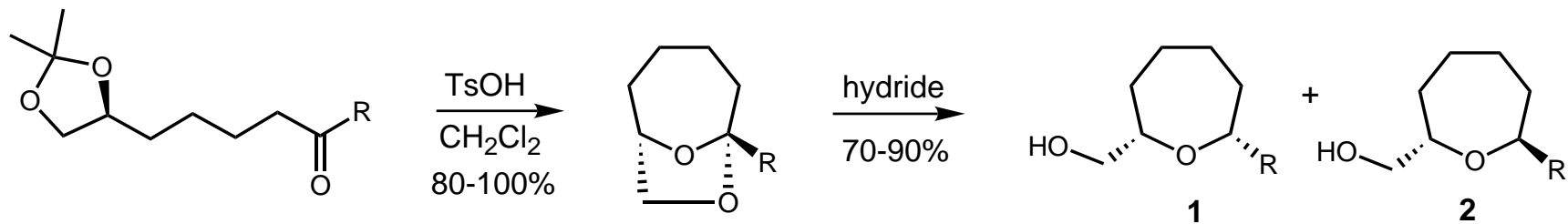


More Substituted Cope Rearrangements



Ring Expansion Reactions

Bicyclic Ketal Reduction

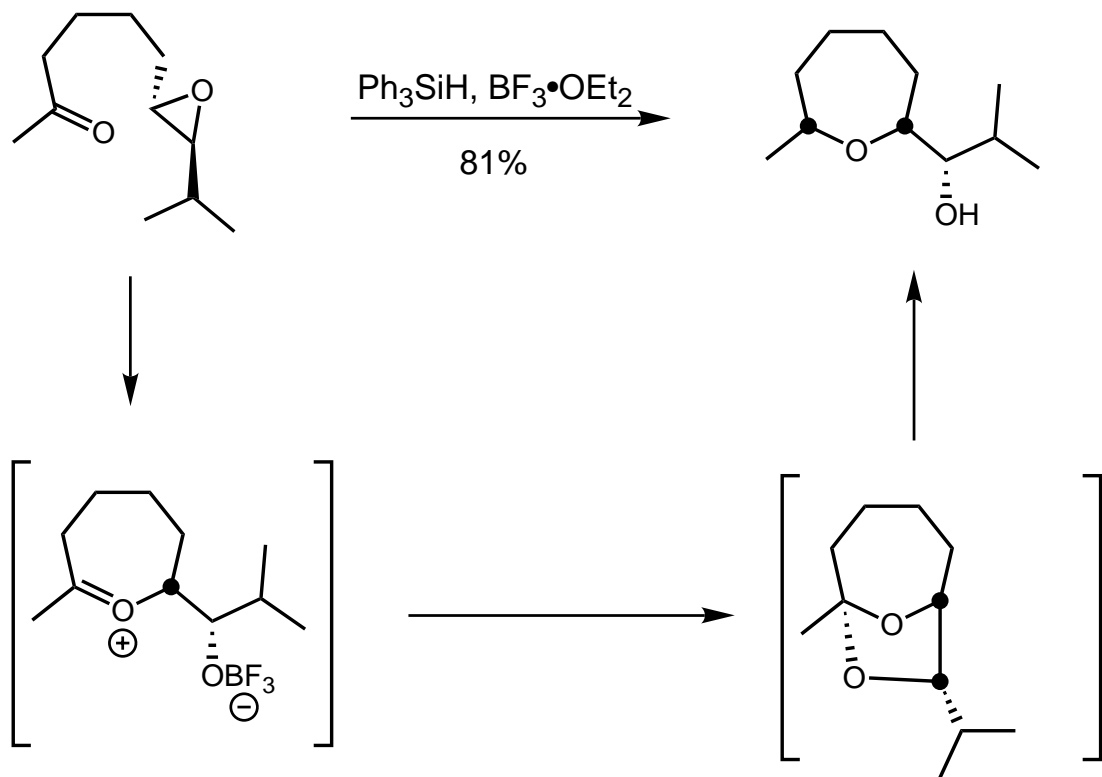


Reducing Agent
 $\text{TiCl}_4/\text{Et}_3\text{SiH}$, -78°C
 DIBAL-H , rt

Ratio **1:2**
 $\sim 10:1$
 $< 2:98$

$\text{R} = \text{C}_2\text{H}_4\text{OBn}$

Bicyclic Ketals: One Pot Processes

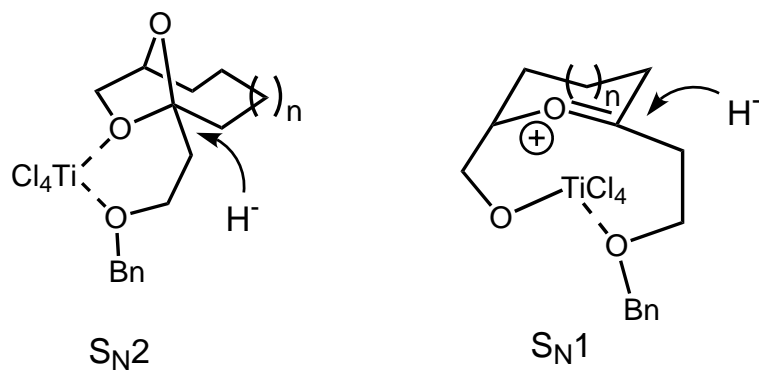


Kotsuki
 JOC 1989, 5153.
 Synlett, 1992, 97.

Stereochemical Rationale

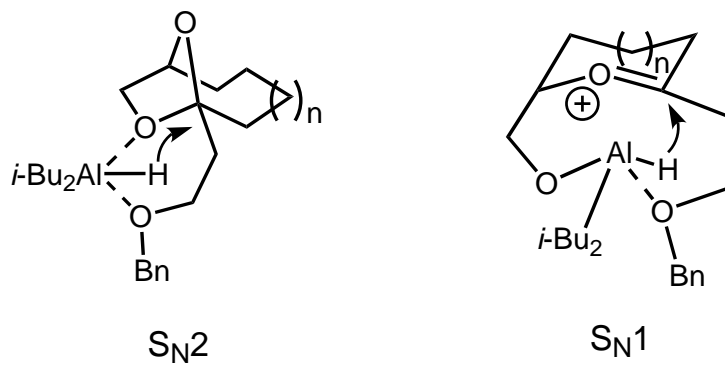
TiCl₄/Et₃SiH

Hydride delivery from behind coordinated metal

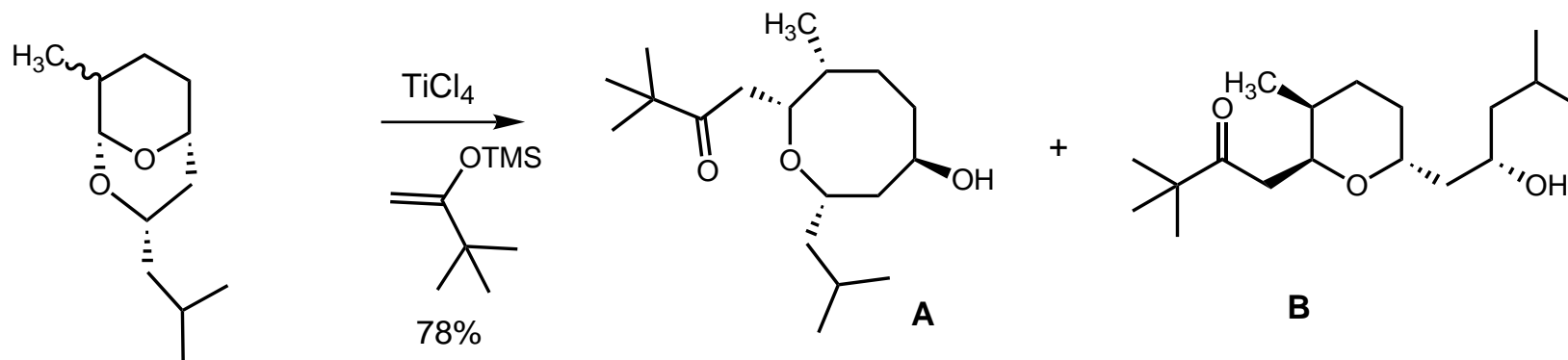


DIBAL-H

Hydride delivery from same face as coordinated metal

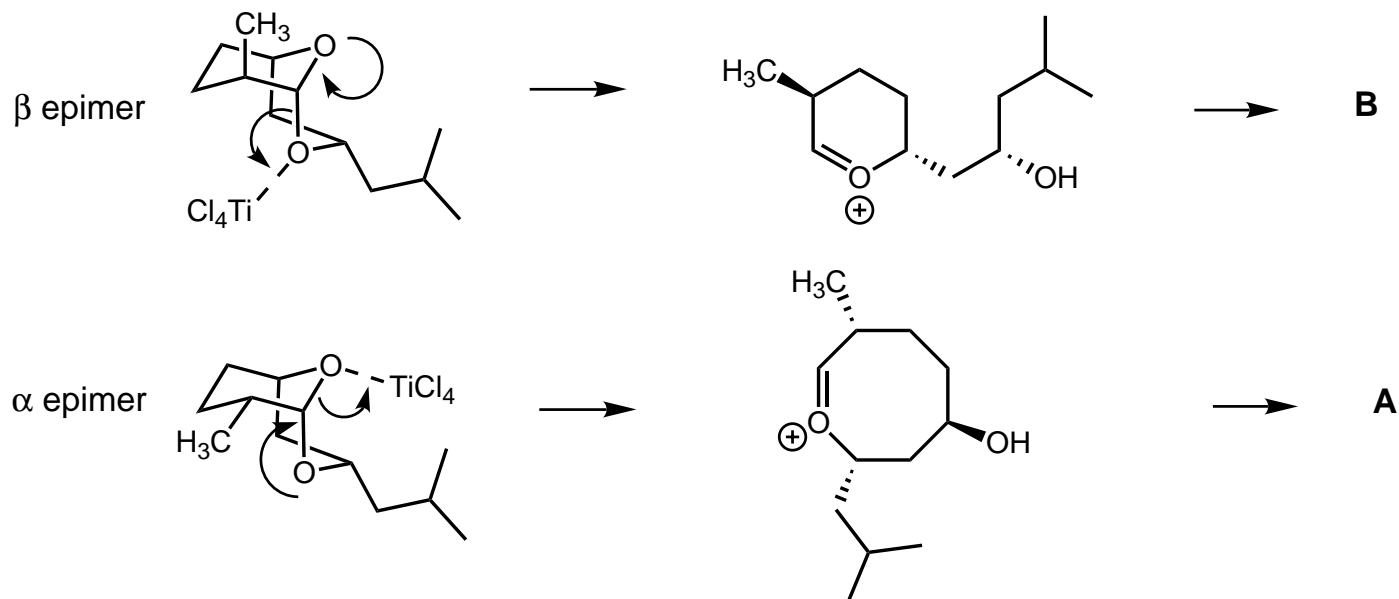


Acetal Cleavage



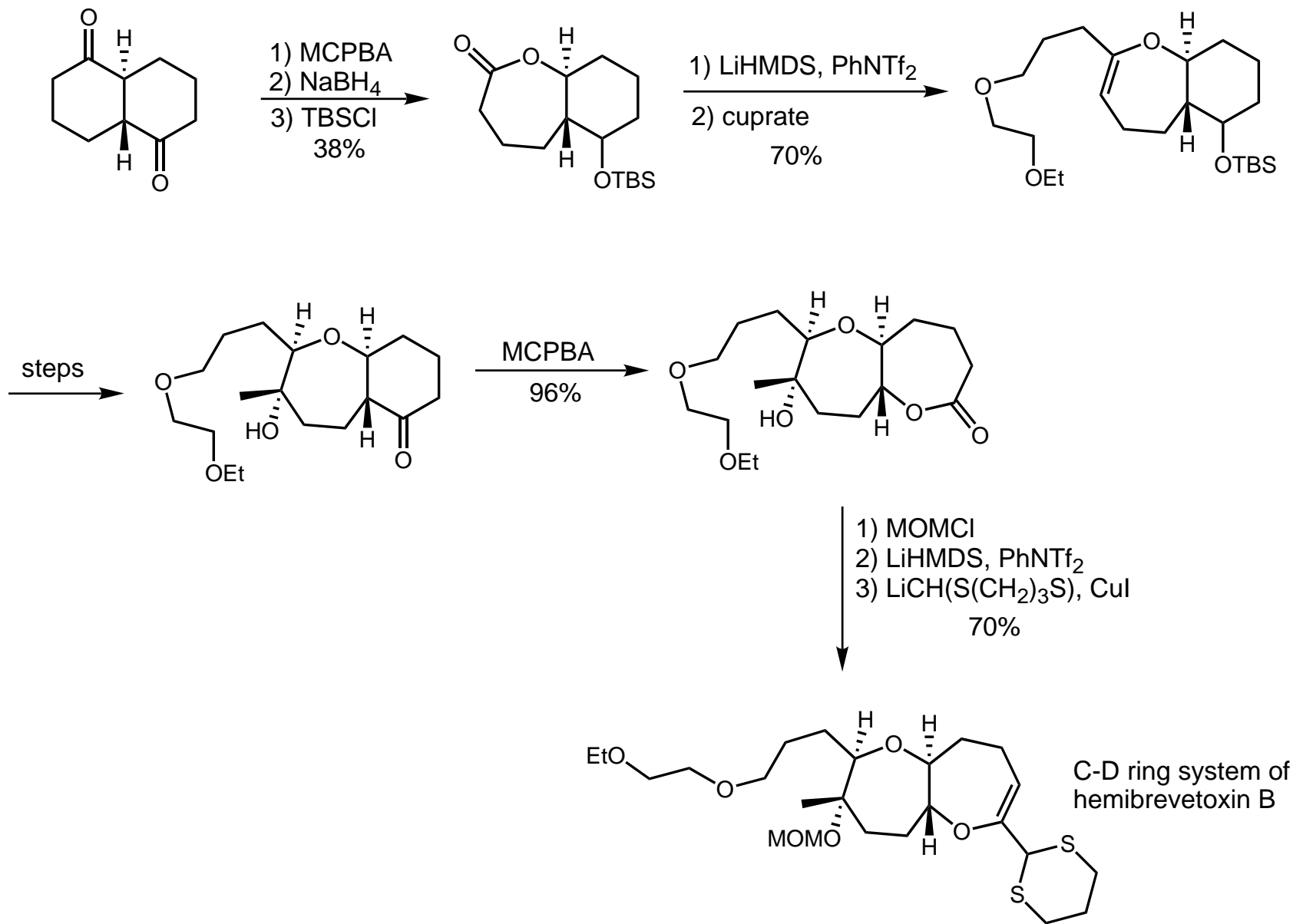
$\alpha:\beta$ CH_3 Ratio	Product A : B Ratio
78:22	77:23
>95:<5%	>95%:<5%

Methyl group directs LA to least hindered acetal oxygen:

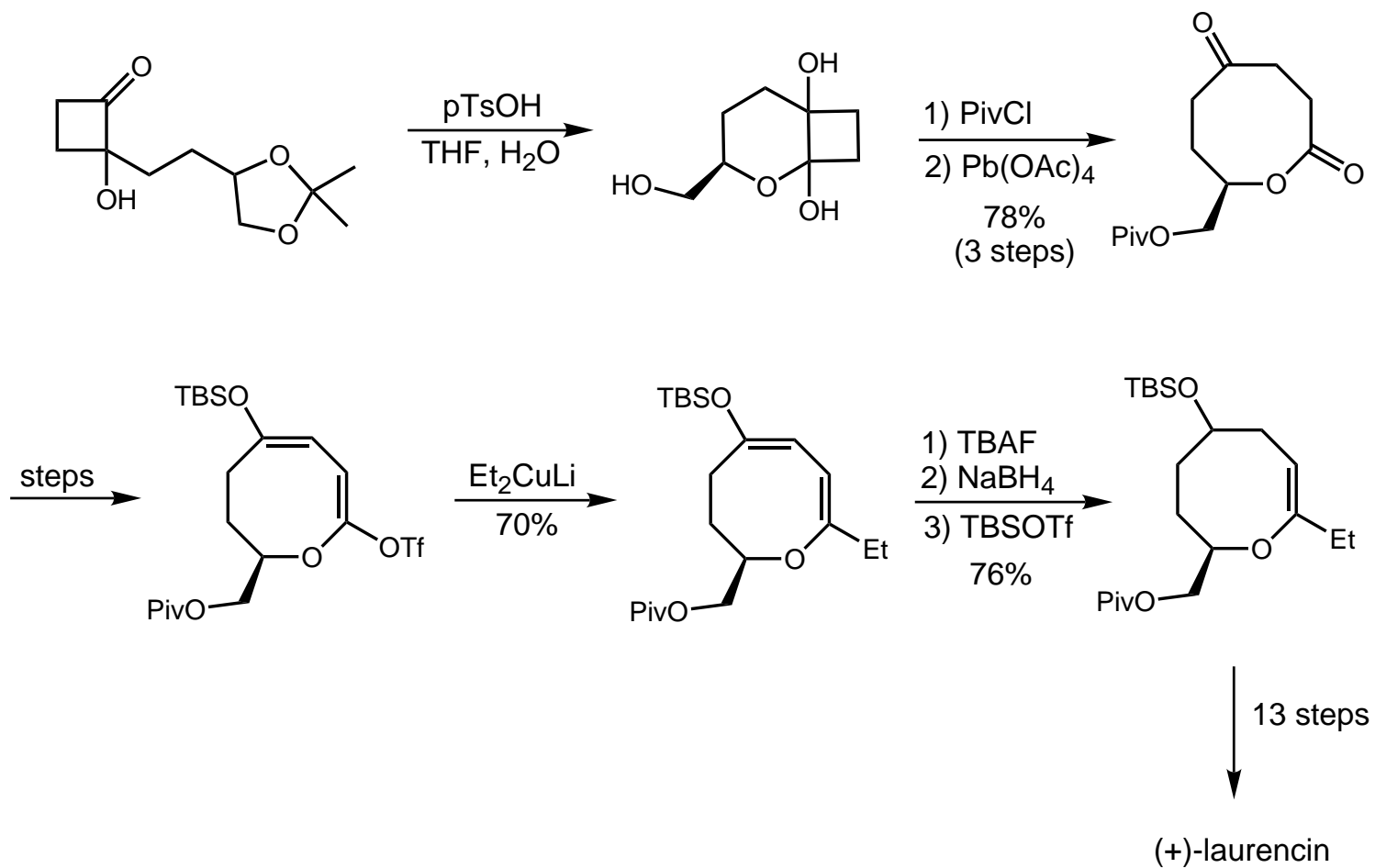


P. A. Bartlett
JOC 1989, 98.

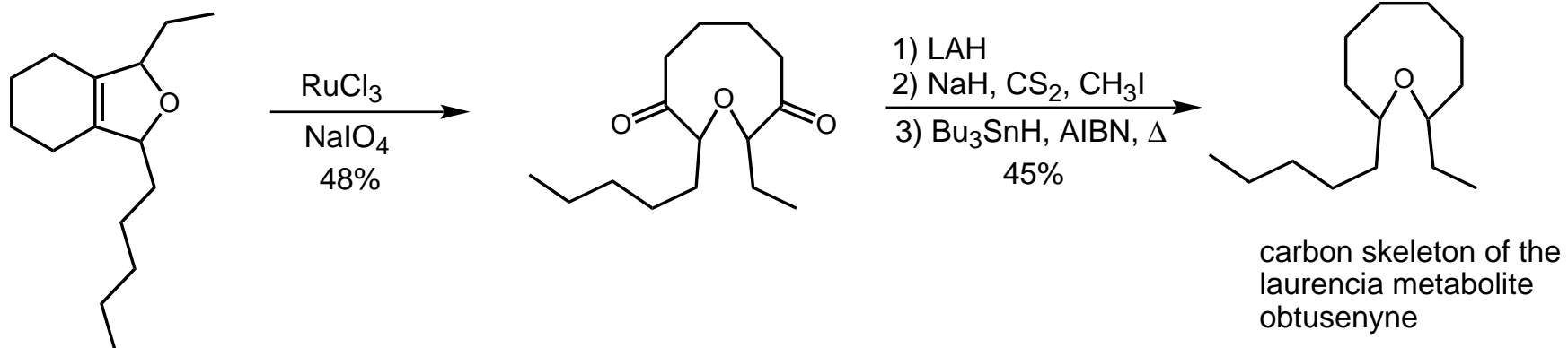
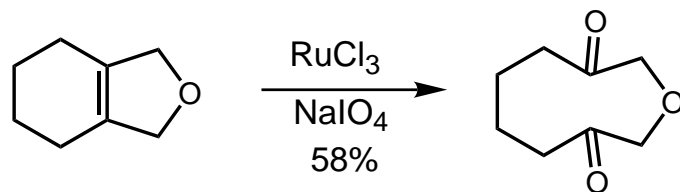
Baeyer-Villiger Expansion



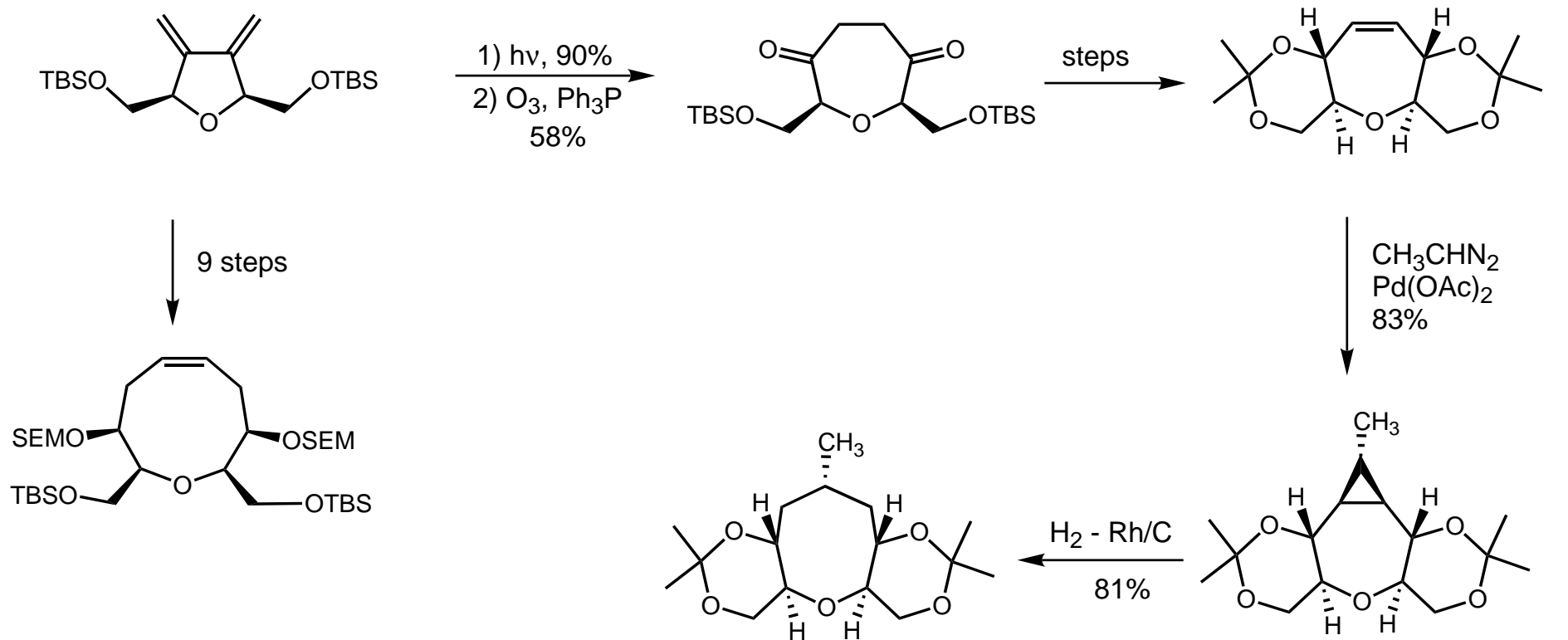
Oxidative Ring Expansions



Oxidative Cleavage of Tetrahydrophthalans



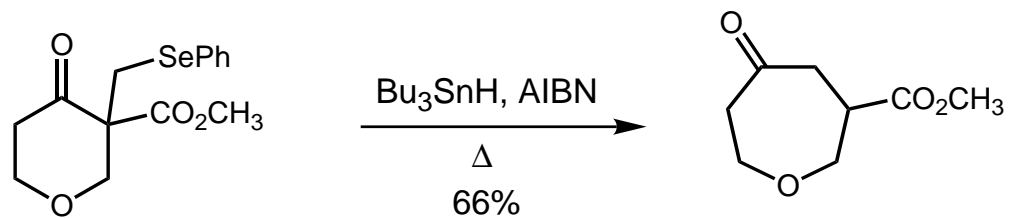
Ring Expansions Toward Ciguatoxin



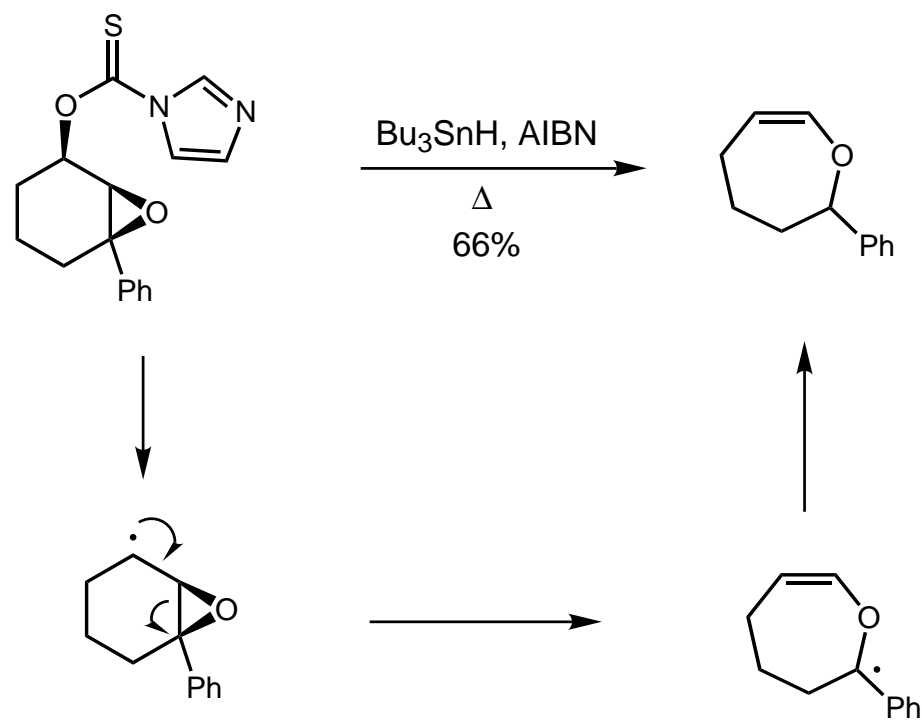
only add'n from β face
 3:1 exo:endo
 Simmons-Smith gives
 only α face addition

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

Free Radical Expansions



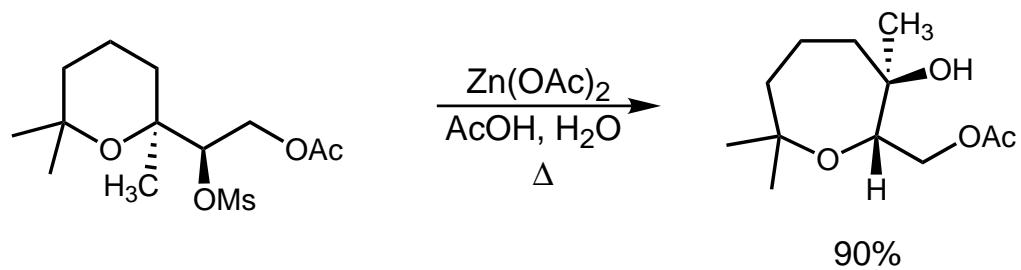
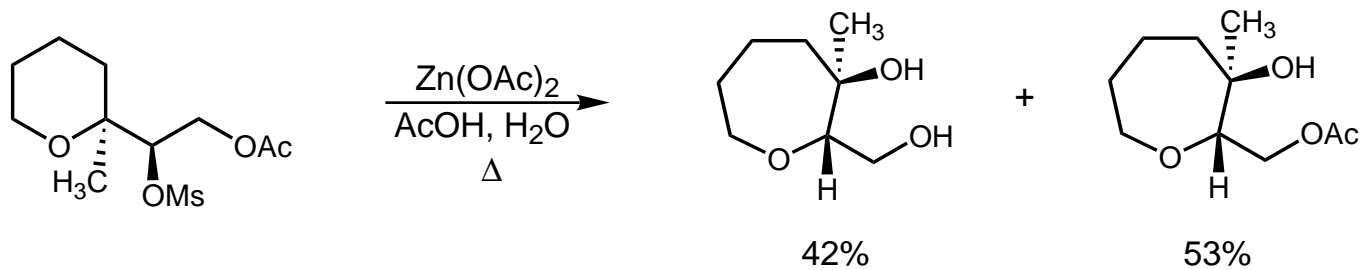
Dowd
Tetrahedron, 1991, 4847.



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

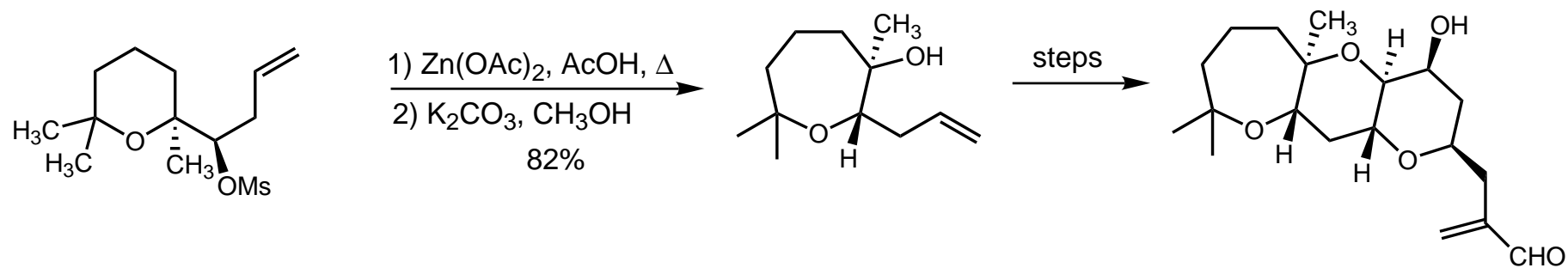
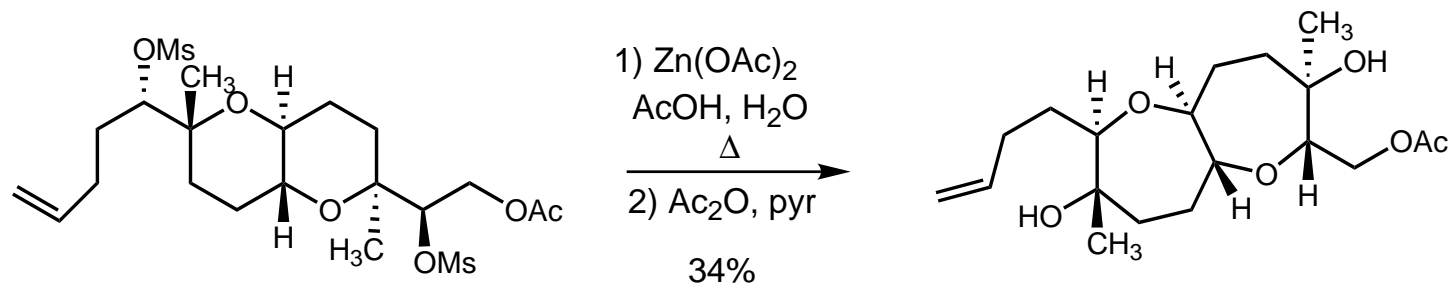
Dart
Synlett, 1992, 987.

Tetrahydropyran Expansion



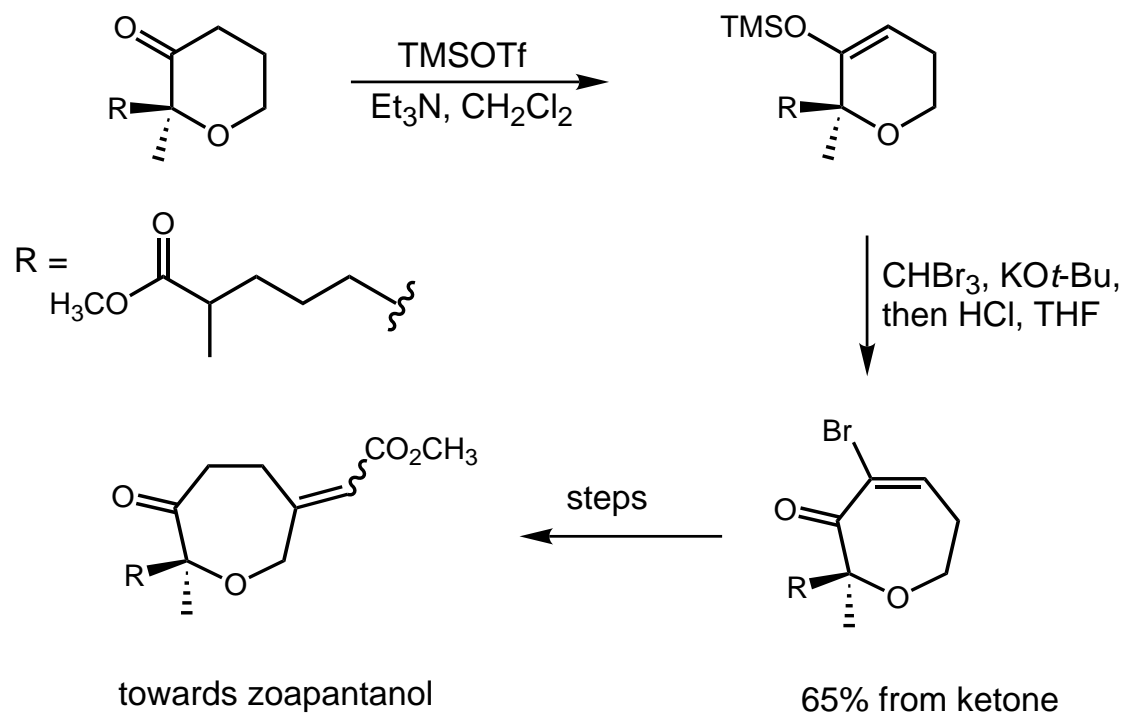
enhanced reaction rate in this case prevents extended reaction times and acetate cleavage

THP Expansion: Application to Hemibrevetoxin B Intermediates

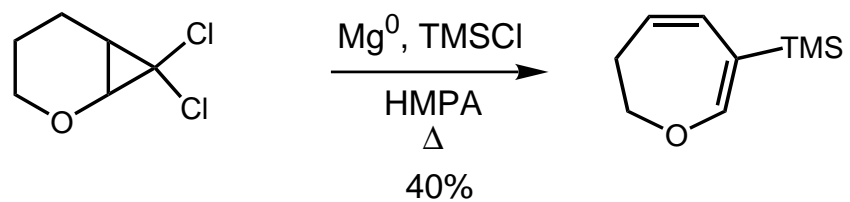


Nakata
TL 1996, 217.
Chem. Lett. 1996, 487.

Expansion of cyclopropanes

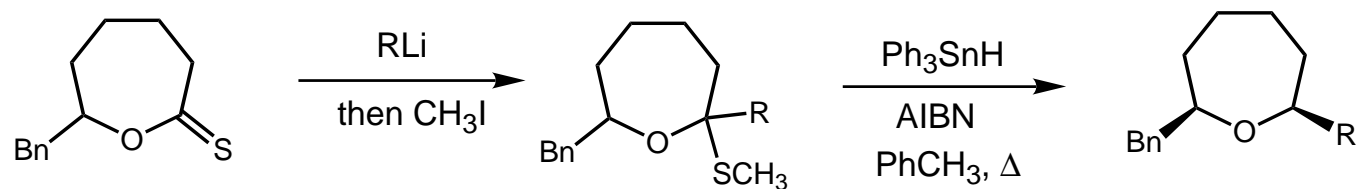


d'Angelo
TL, 1994, 3085.

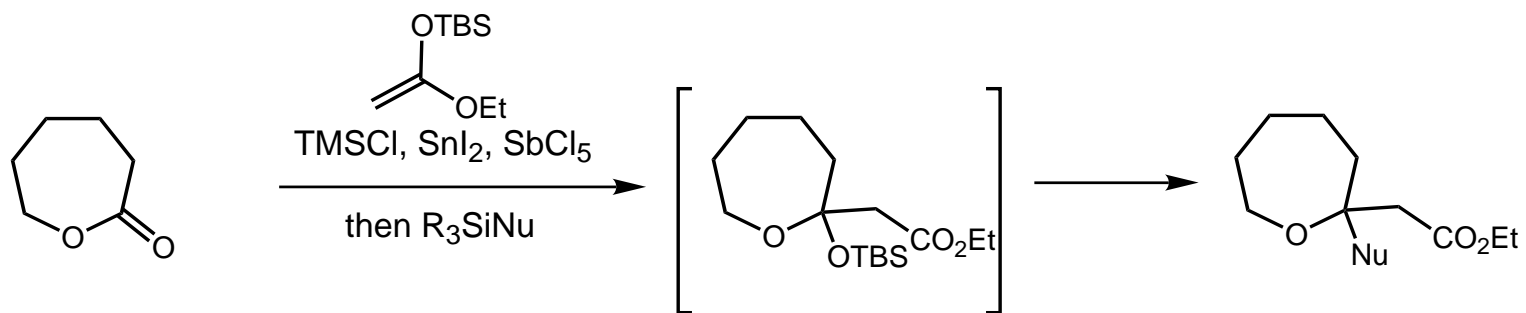


Grignon-Dubois
Can. J. Chem. 1991, 2014.

Modification of Lactones



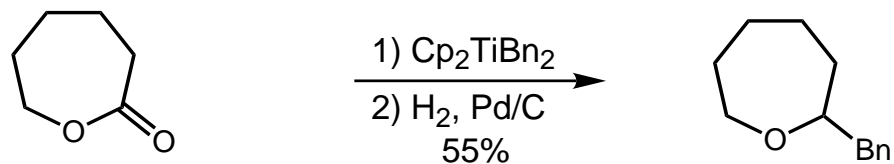
Nicoloau
 JACS 1987, 2506.
 JACS1990, 6263.



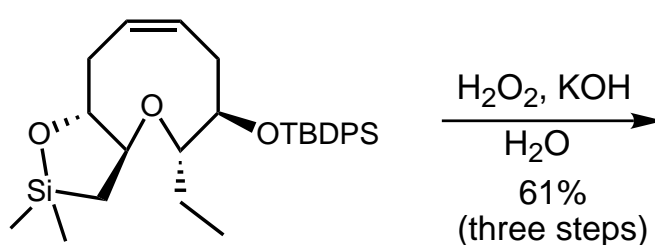
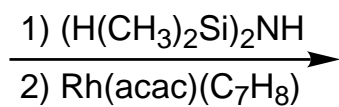
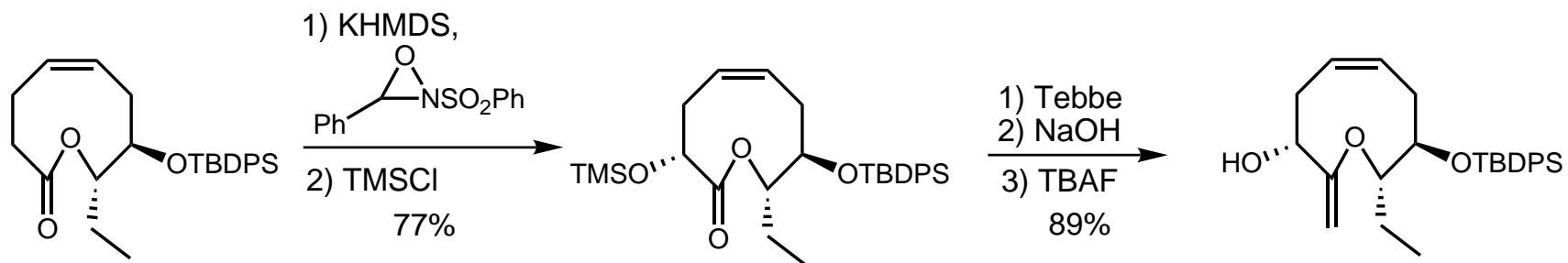
R = Et, Nu = H, 90%
 R = CH₃, Nu = allyl, 67%
 R = CH₃, Nu = CN, 62%

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

Enol Ethers from Lactones

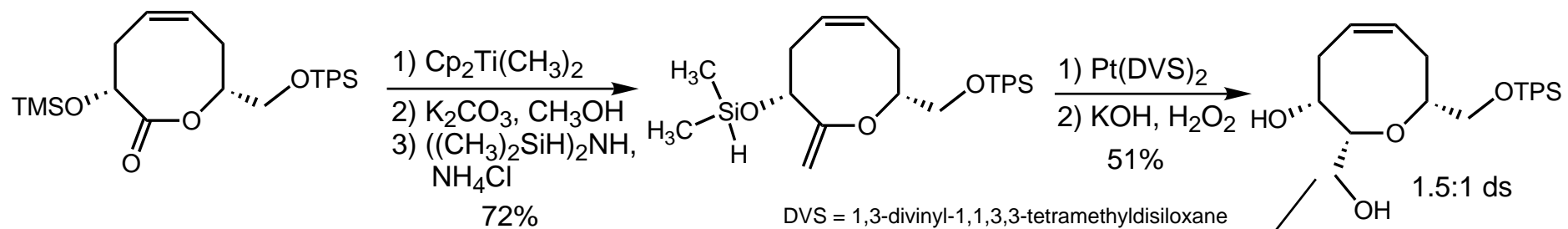


Petasis
JOC 1992, 1327.



obtusenylene
intermediate

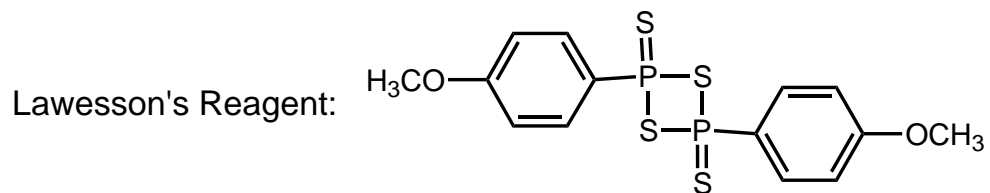
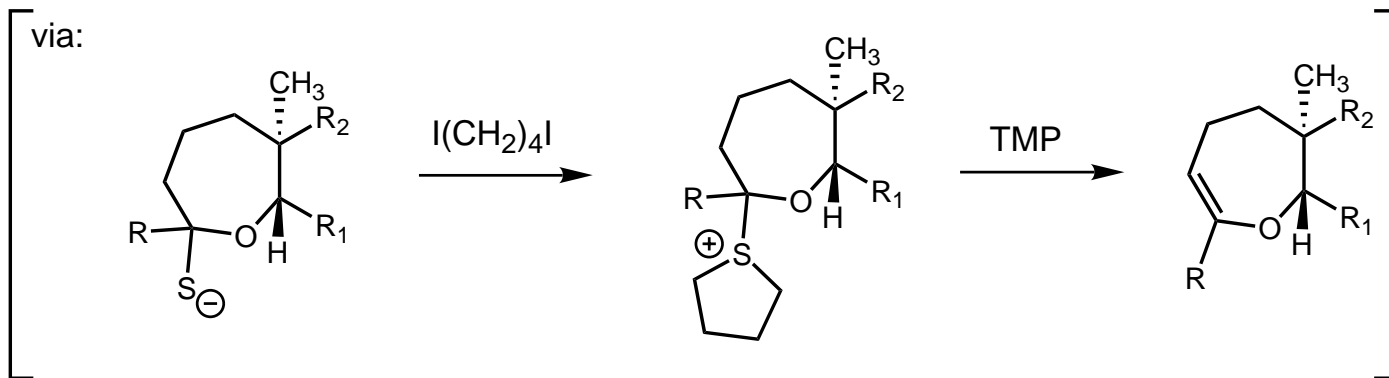
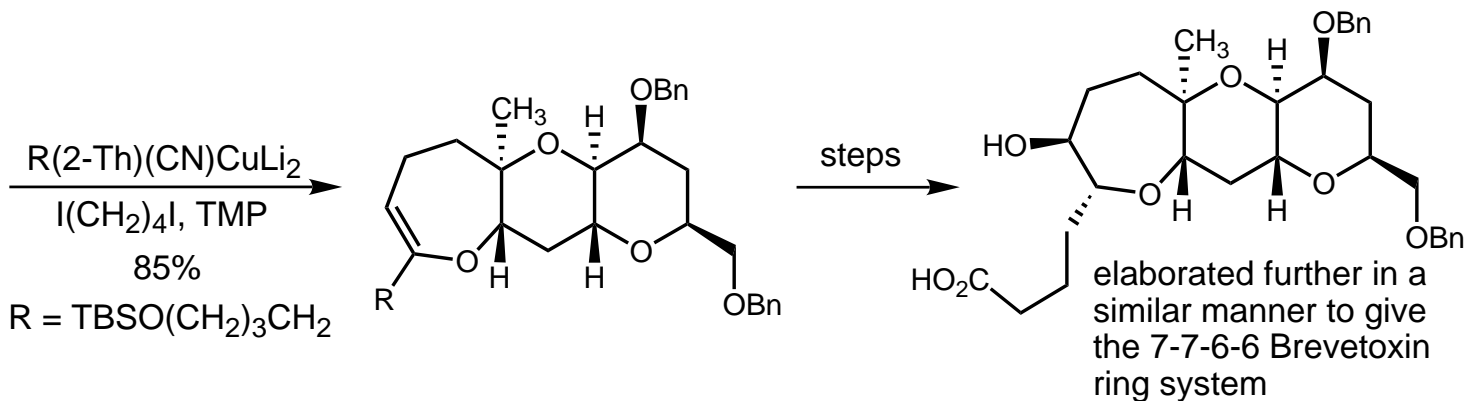
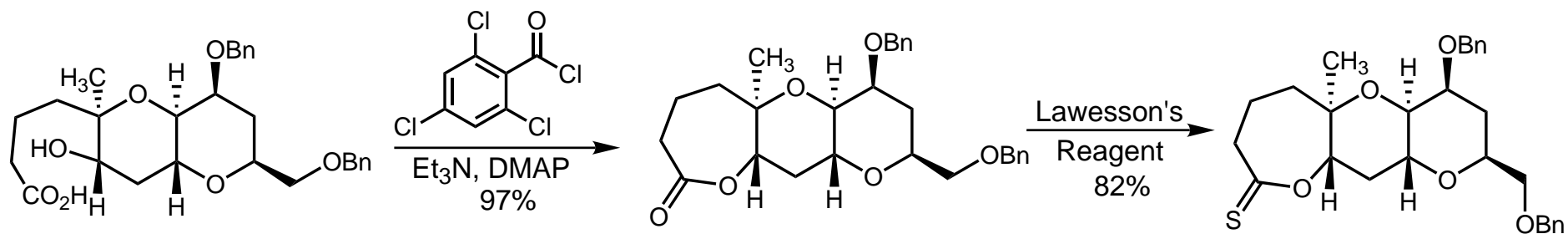
Holmes
TL 1992, 671 & 675.



(+)-laurencin

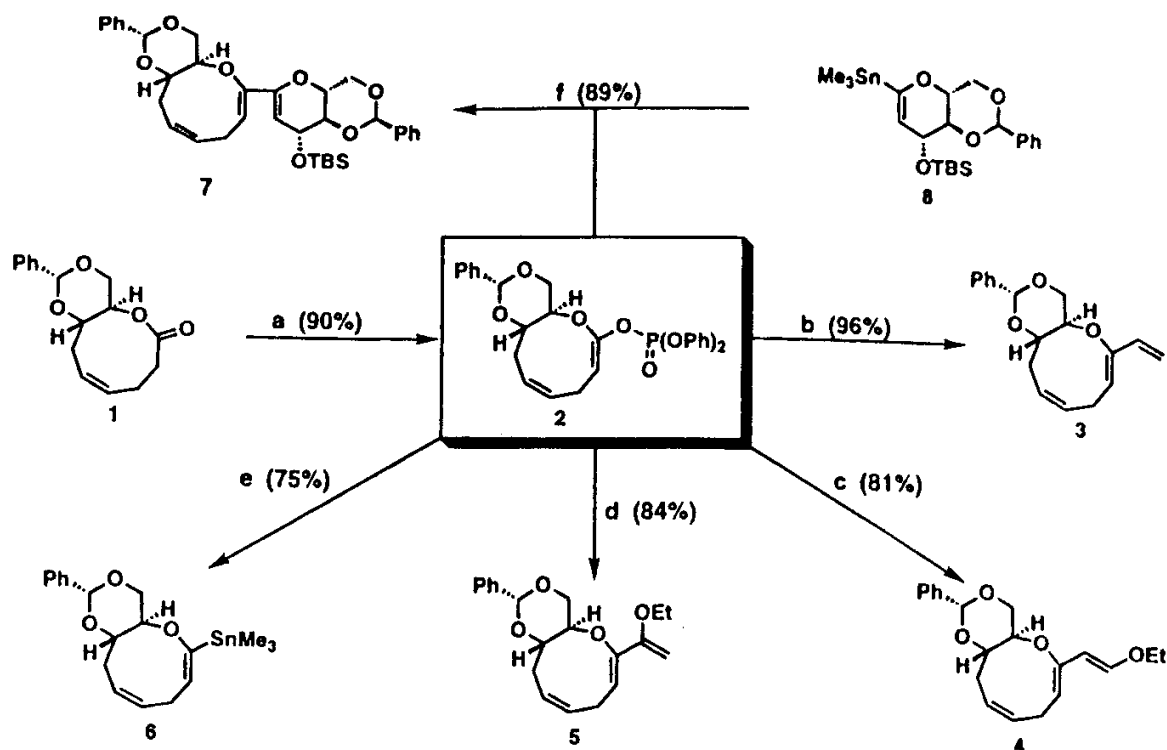
Holmes
JACS 1997, 7483.

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)₂POCl, 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(PPh₃)₄, 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(PPh₃)₄, 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(PPh₃)₄, 3.0 equiv of LiCl, THF, Δ, 6 h; (e) 2.0 equiv of hexamethylditin, 0.05 equiv of Pd(PPh₃)₄, 3.0 equiv of LiCl, THF, Δ, 3 h; (f) 2.0 equiv of 8, 0.05 equiv of Pd(PPh₃)₄, 3.0 equiv of LiCl, THF, Δ, 7 h.

Nicolaou
 JACS 1997, 5467.
 JACS 1997, 8105.