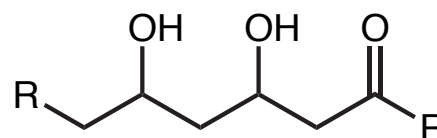
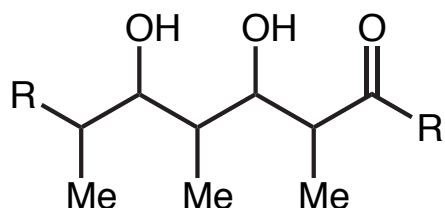


# *Non-Aldol Approaches to the Synthesis of Polyketide Natural Products*



Evans Group Evening Seminar  
Friday June 21, 2002  
Travis Dunn

Keywords: Polypropionate, Polyol, Total Synthesis

## *Outline of Seminar*

Approaches covered in this seminar:

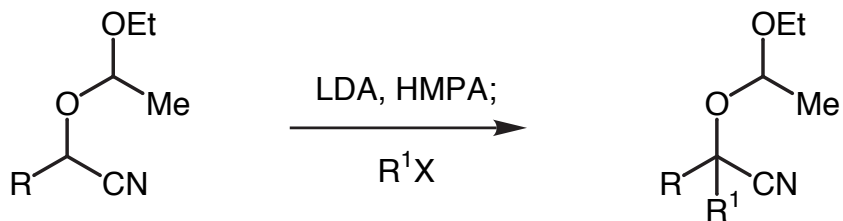
- 1) Cyanohydrin acetonide alkylation (Rychnovsky)
- 2) Dithiane alkylation (Mori, Smith)
- 3) Acyl halide/aldehyde cyclocondensation (Nelson)
- 4) Hemiacetal oxymercuration (Leighton)
- 5) Silylformylation (Leighton)
- 6) Methylketene dimer ring opening (Calter)
- 7) Oxabicyclic ring opening (Lautens)
- 8) Directed nitrile oxide cycloaddition (Carreira)

Bond constructions not covered in this seminar:

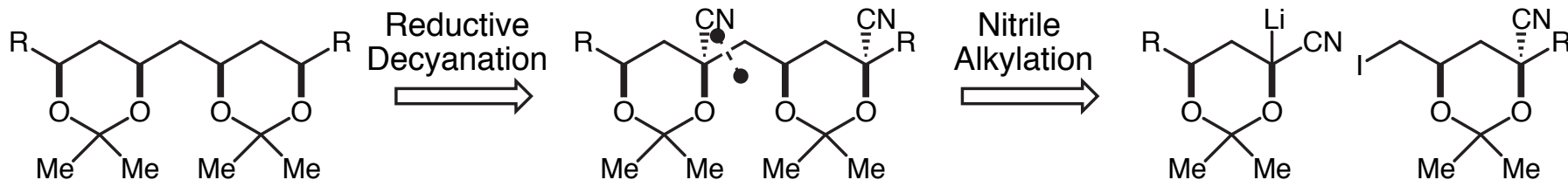
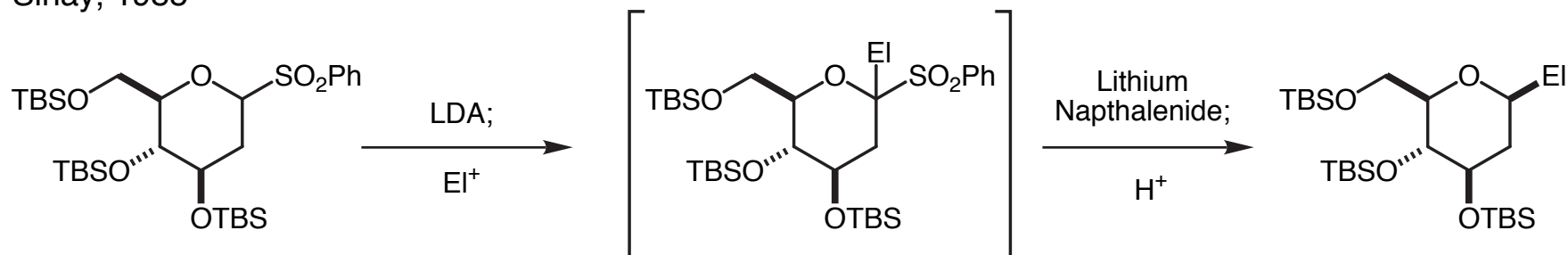
- 1) Metal enolate reactions
- 2) Mukaiyama aldol reactions
- 3) Allylmetal based reactions  
(e.g. silanes, stannanes, boranes, borinates)

# Rychnovsky's Cyanohydrin Acetonide Alkylation

Stork, 1971

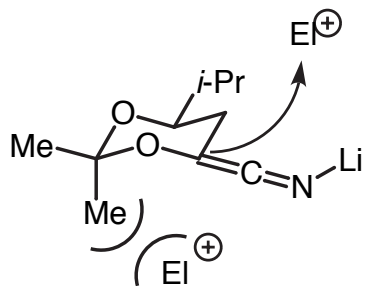
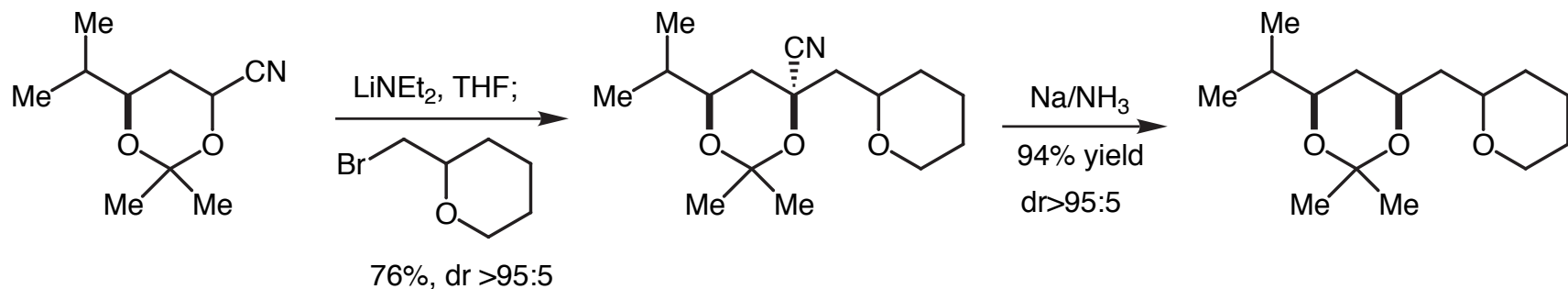
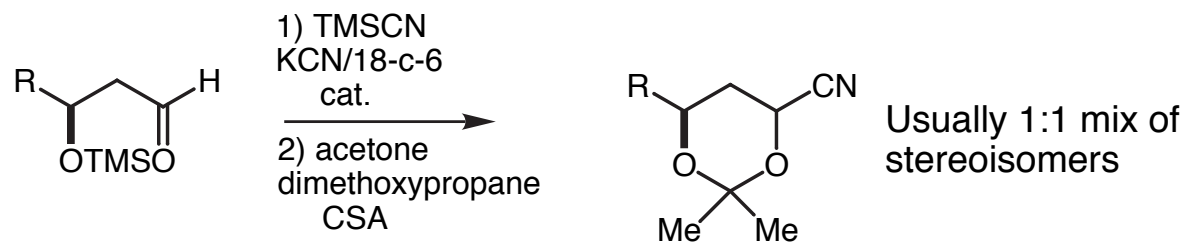


Sinay, 1985

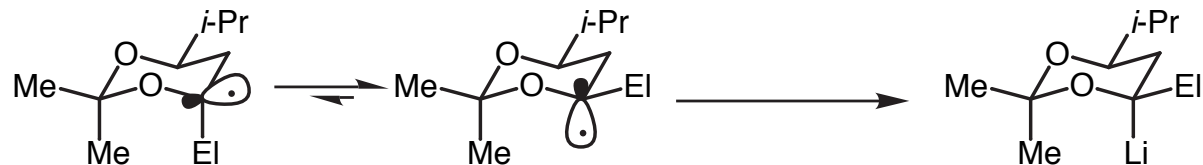


Rychnovsky and Sinz, *Topics in Current Chem.* **2001**, 216, 51-92.

# Rychnovsky's Cyanohydrin Acetonide Alkylation



Equatorial alkylation due to steric shielding by methyl of acetonide.



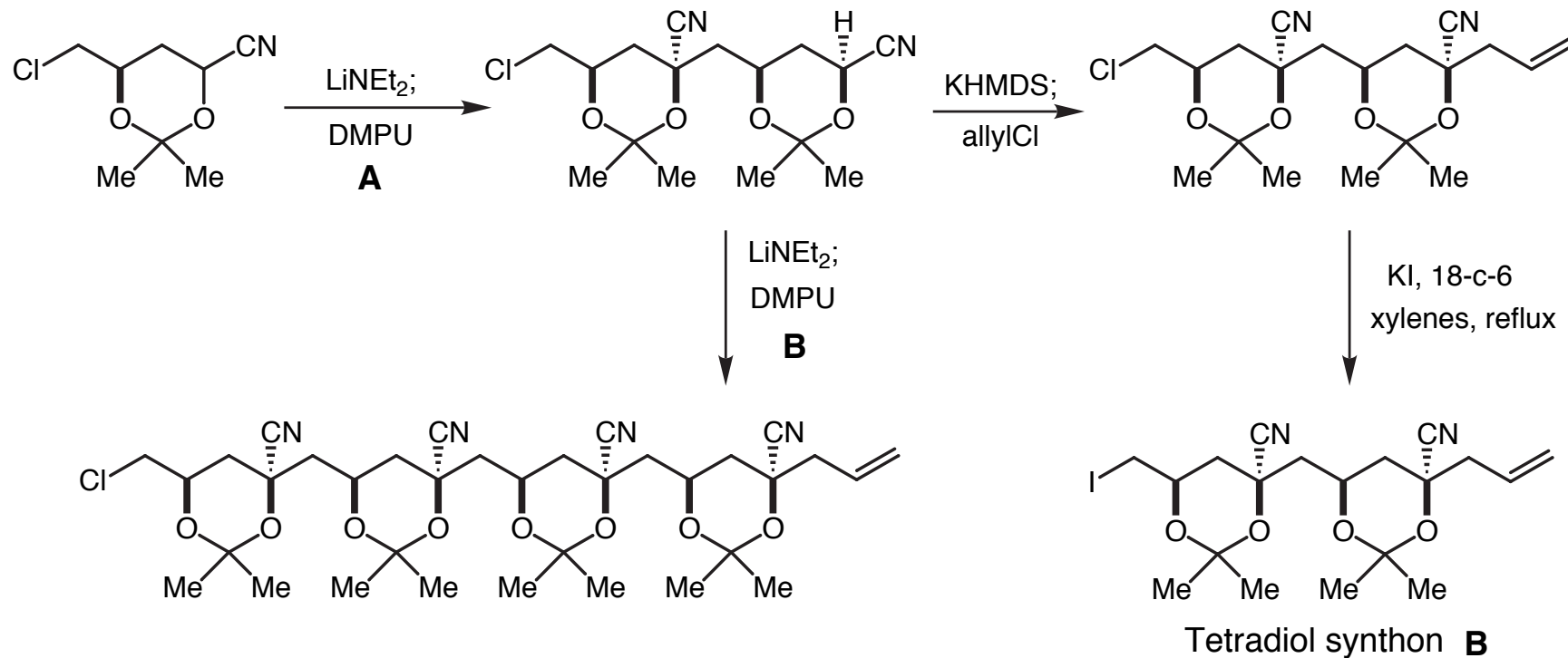
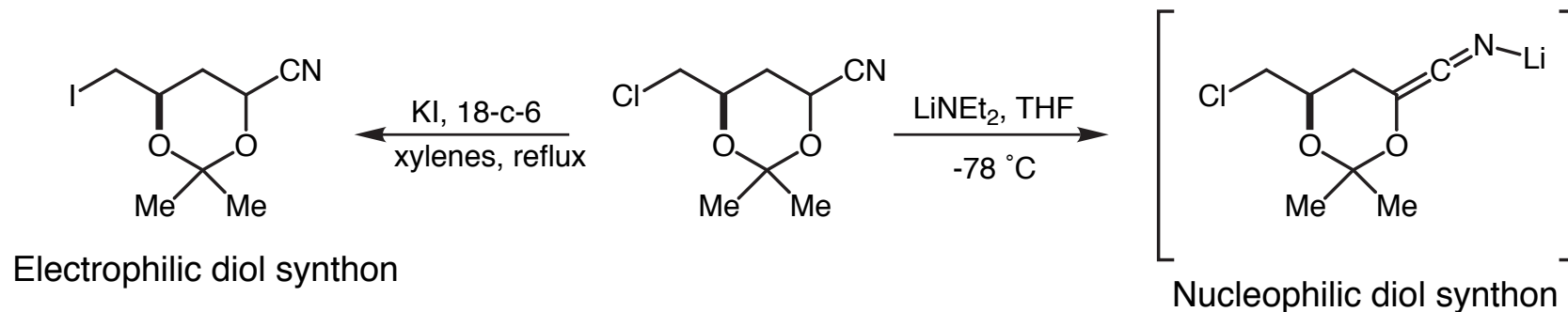
Axial radical more stable by ca. 3.5 kcal/mol (calc.)

Configurationally stable at low temperature

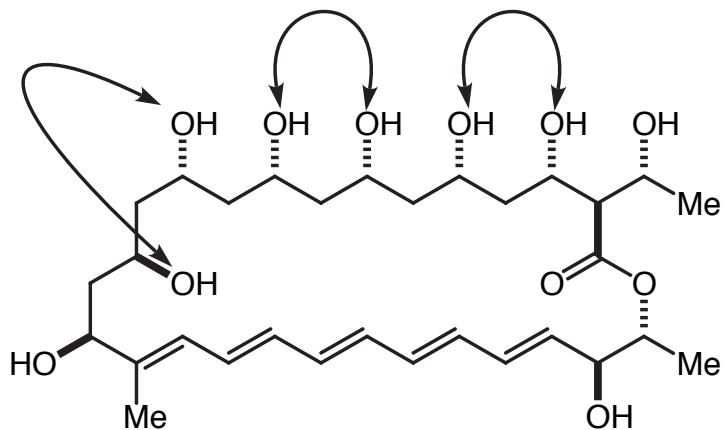
Rychnovsky and Sinz, *Topics in Current Chem.* **2001**, 216, 51-92.

Rychnovsky et al., *J. Org. Chem.* **1990**, 55, 5550.

# Iterative and Convergent Syn Polyol Synthesis

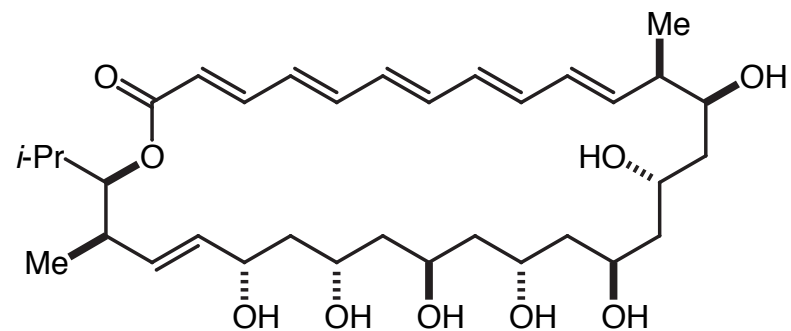


# Total Syntheses Using Cyanohydrin Acetonide Methodology



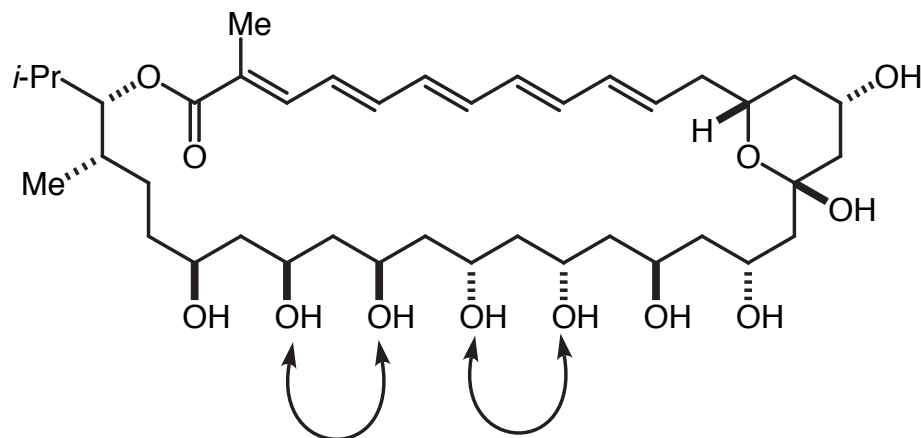
Filipin III

Rychnovsky and Richardson, *J. Am. Chem. Soc.* **1997**, *119*, 12360.  
Rychnovsky and Richardson, *Tetrahedron* **1999**, *55*, 8977.



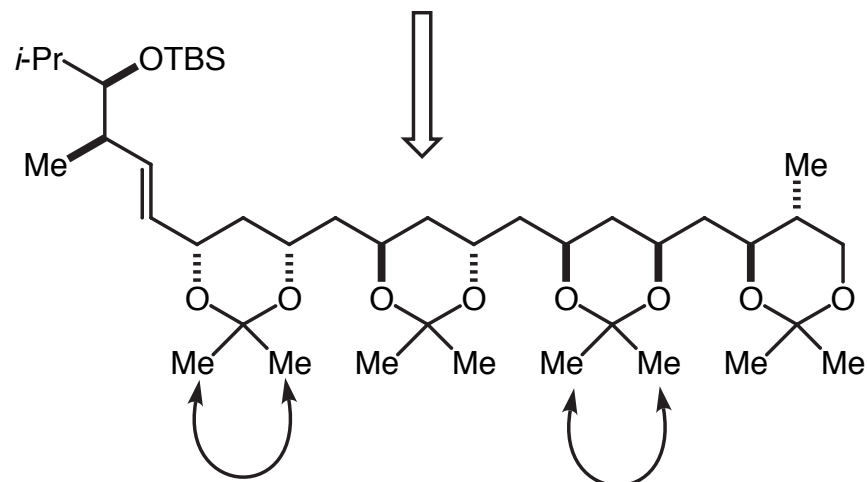
(-)-Roxaticin

Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, *116*, 1753.

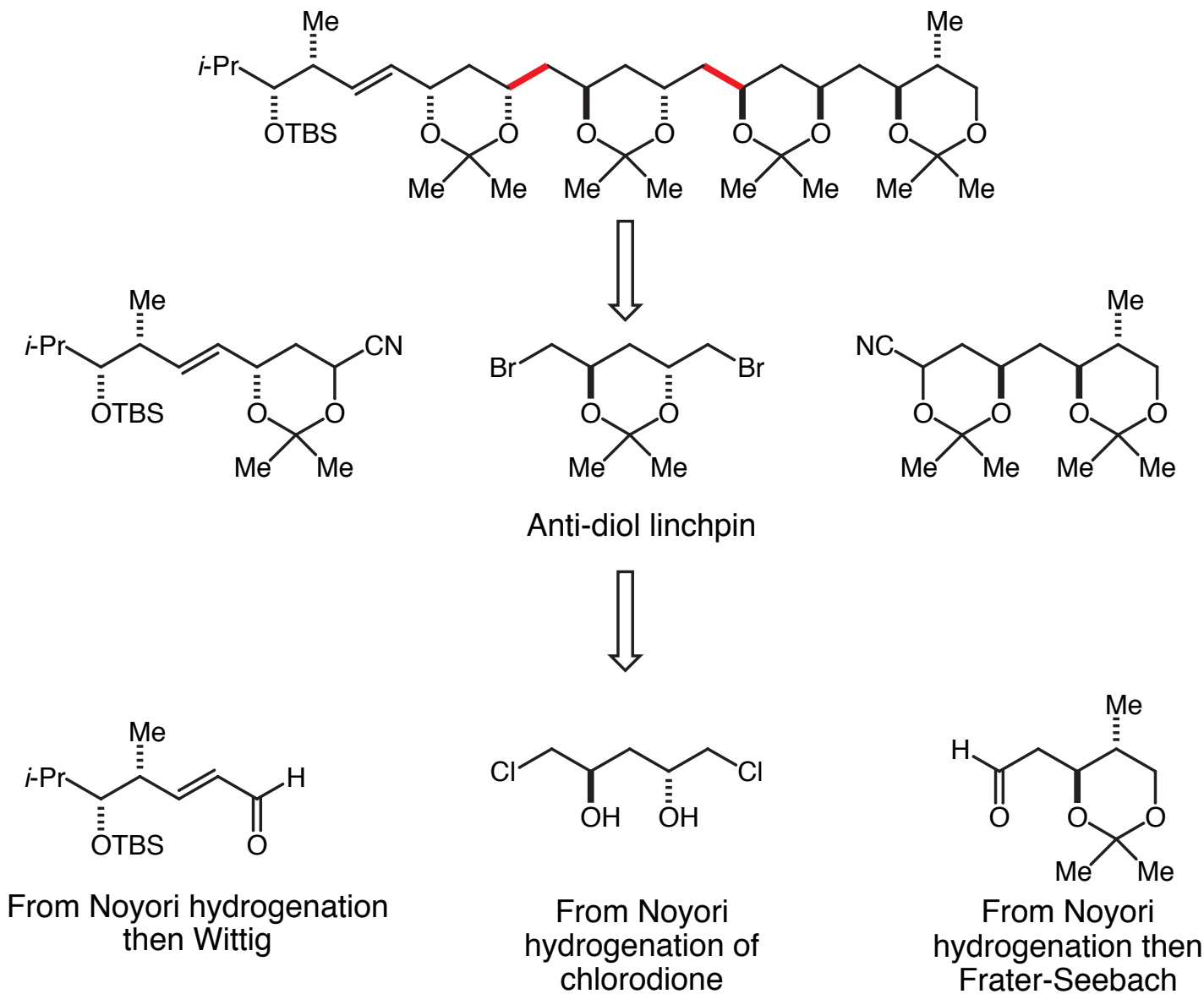


Roflamycoin

Rychnovsky et al., *J. Am. Chem. Soc.* **1997**, *119*, 2058.

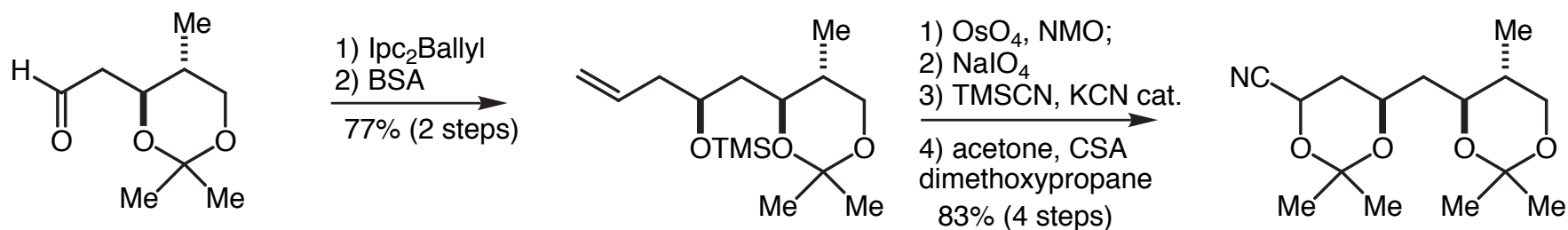
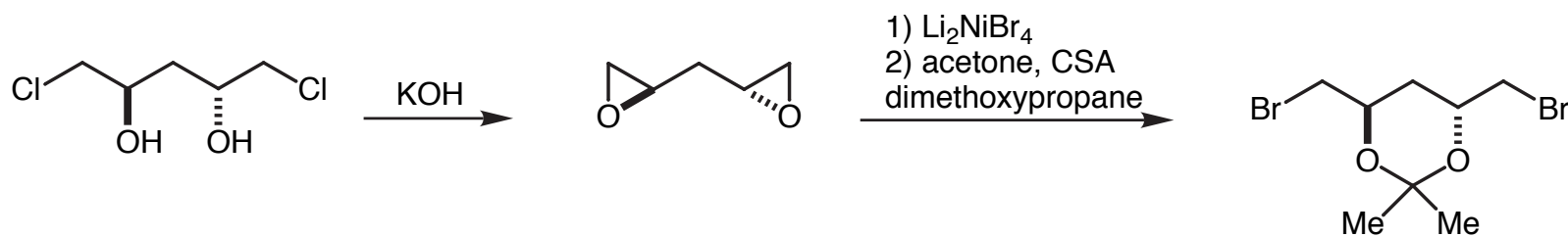
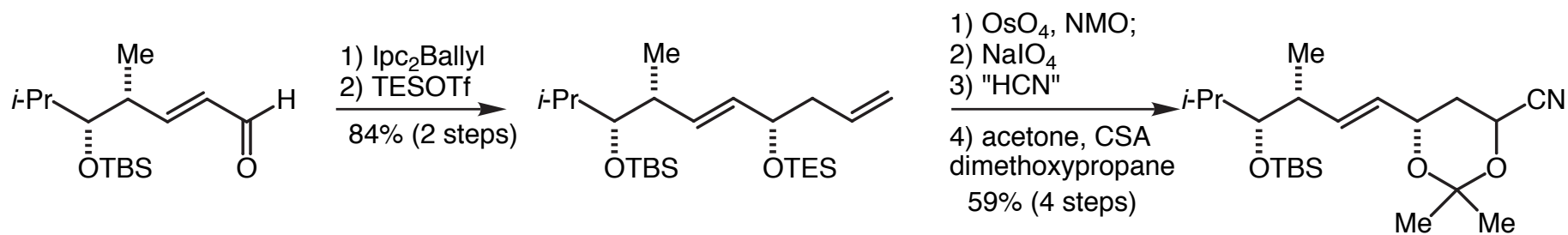


# Roxaticin Polyol Segment Retrosynthesis



Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, 116, 1753.

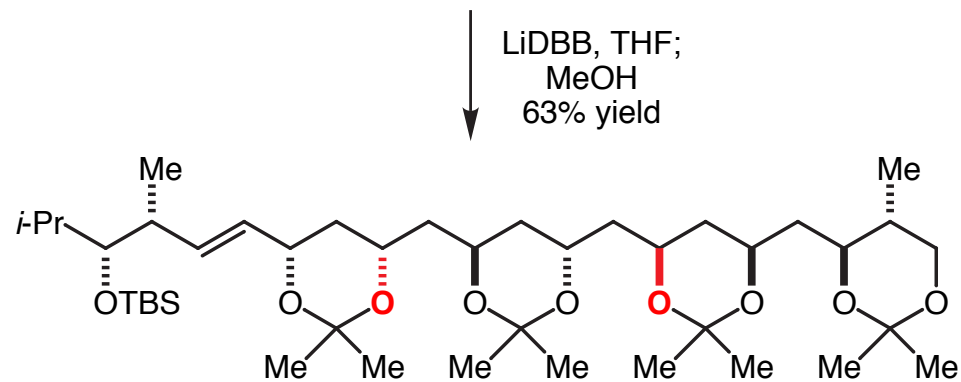
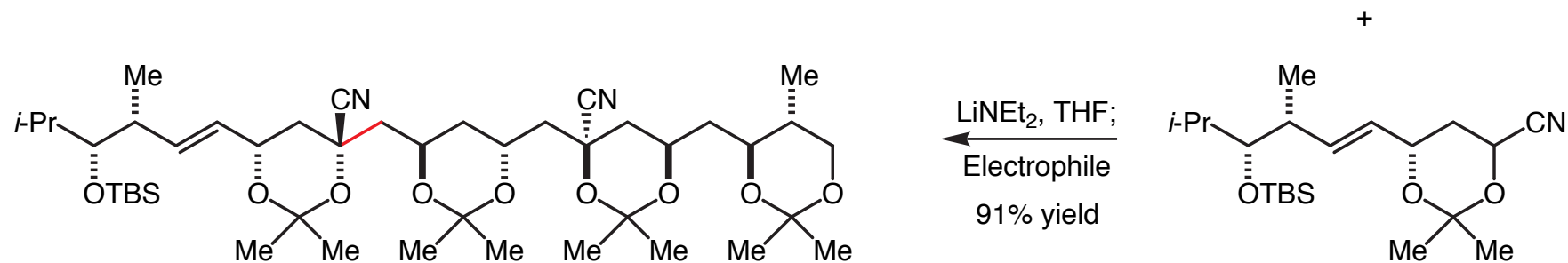
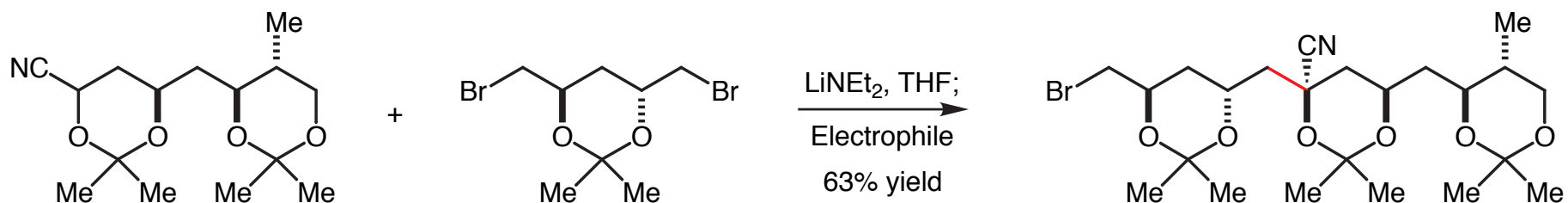
# Roxaticin Polyol Segment Fragment Synthesis



Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, 116, 1753.



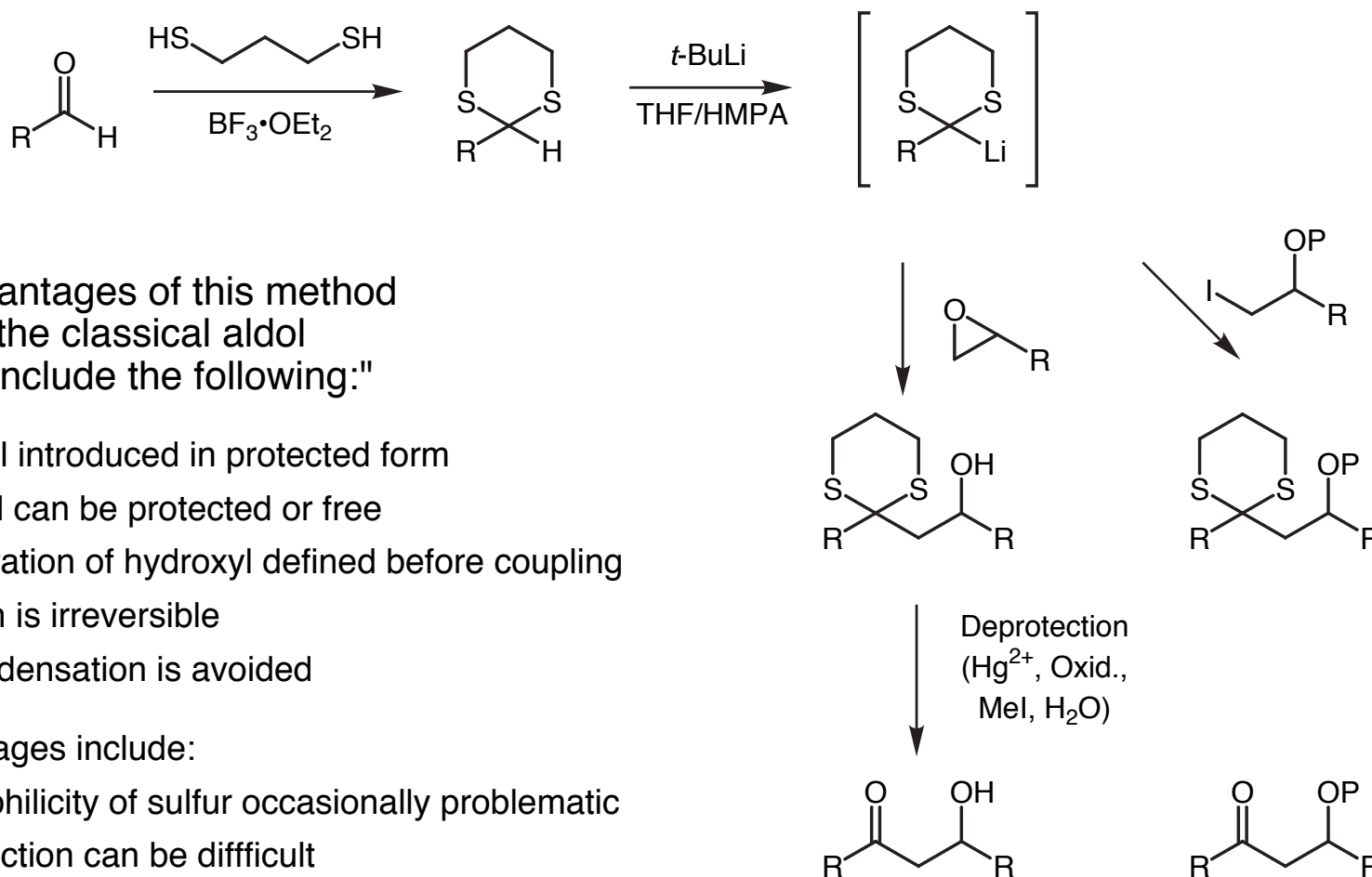
# Roxaticin Polyol: Fragment Coupling



(-)-Roxaticin

Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, 116, 1753.

# Smith: Dithiane Coupling



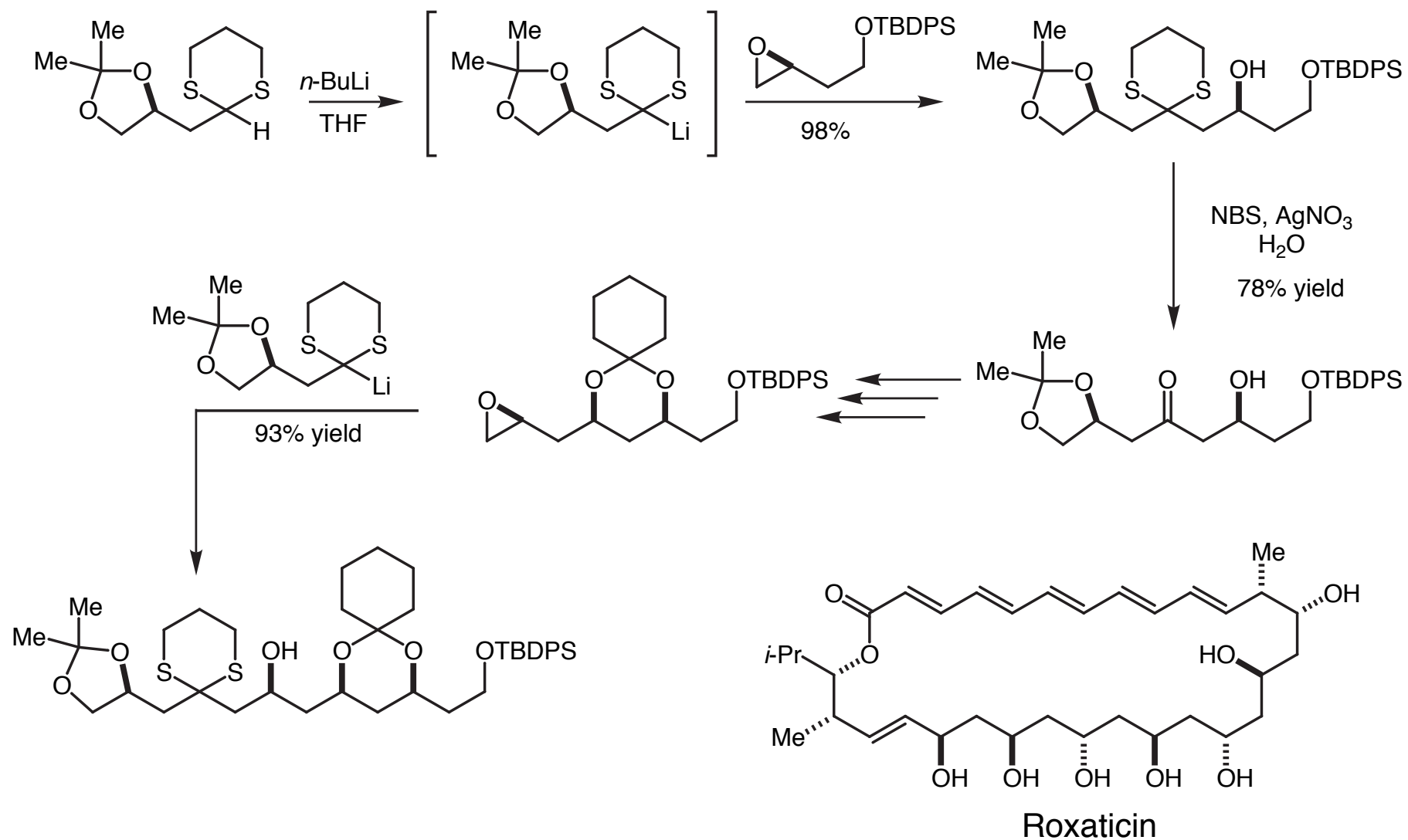
"The advantages of this method vis-a-vis the classical aldol reaction include the following:"

- 1) Carbonyl introduced in protected form
- 2) Hydroxyl can be protected or free
- 3) Configuration of hydroxyl defined before coupling
- 4) Reaction is irreversible
- 5) Self-condensation is avoided

Disadvantages include:

- 1) Nucleophilicity of sulfur occasionally problematic
- 2) Deprotection can be difficult
- 3) Metallation of dithiane sometimes difficult

# Mori's Diacetate Synthone



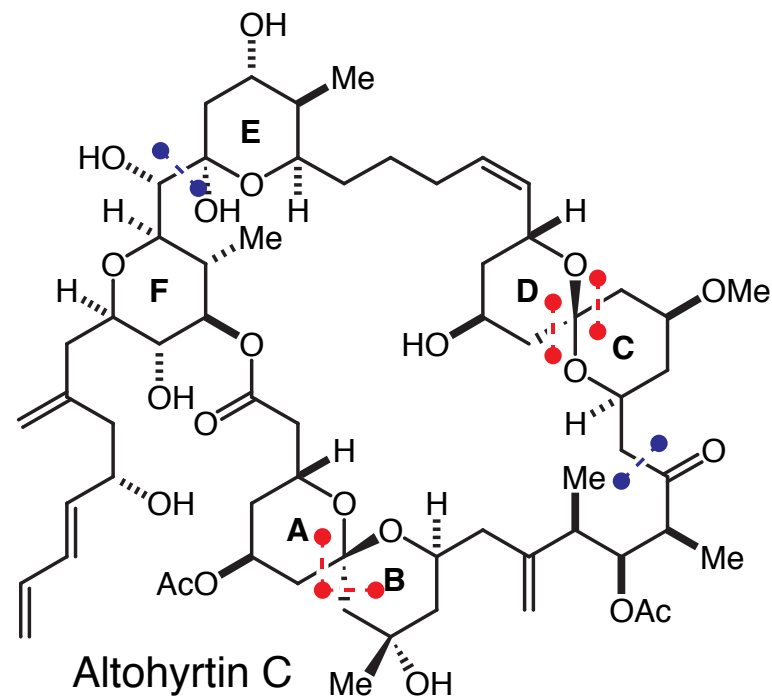
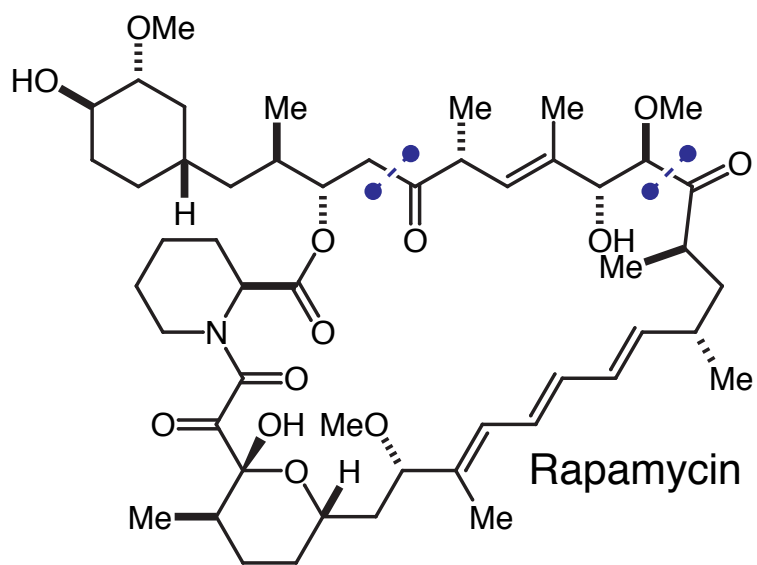
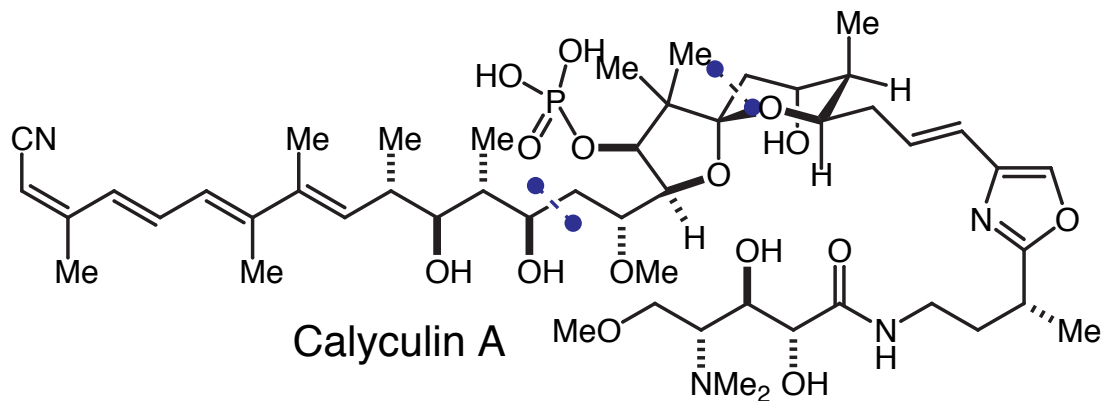
*Tet. Lett.* **1988**, 29, 5419, 5423.

*Tet. Lett.* **1989**, 30, 4383, 4387.

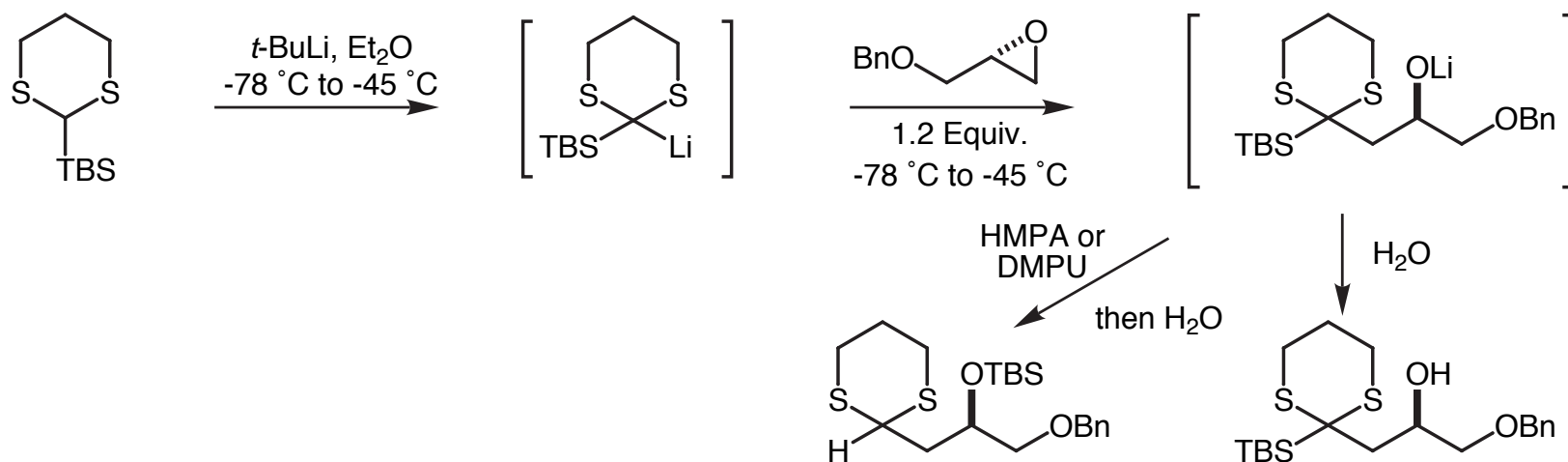
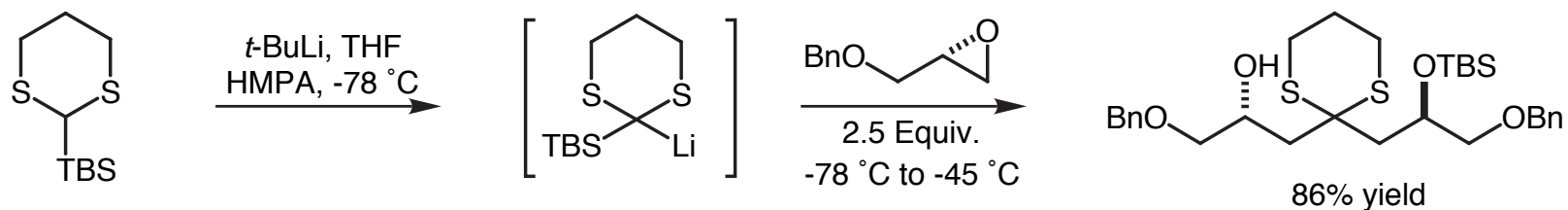
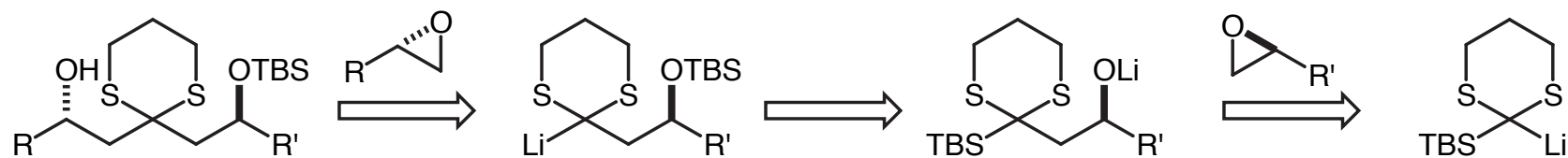
Roxaticin synthesis

*Tetrahedron* **1995**, 51, 5299, 5315.

# Smith Syntheses Utilizing Dithiane Coupling



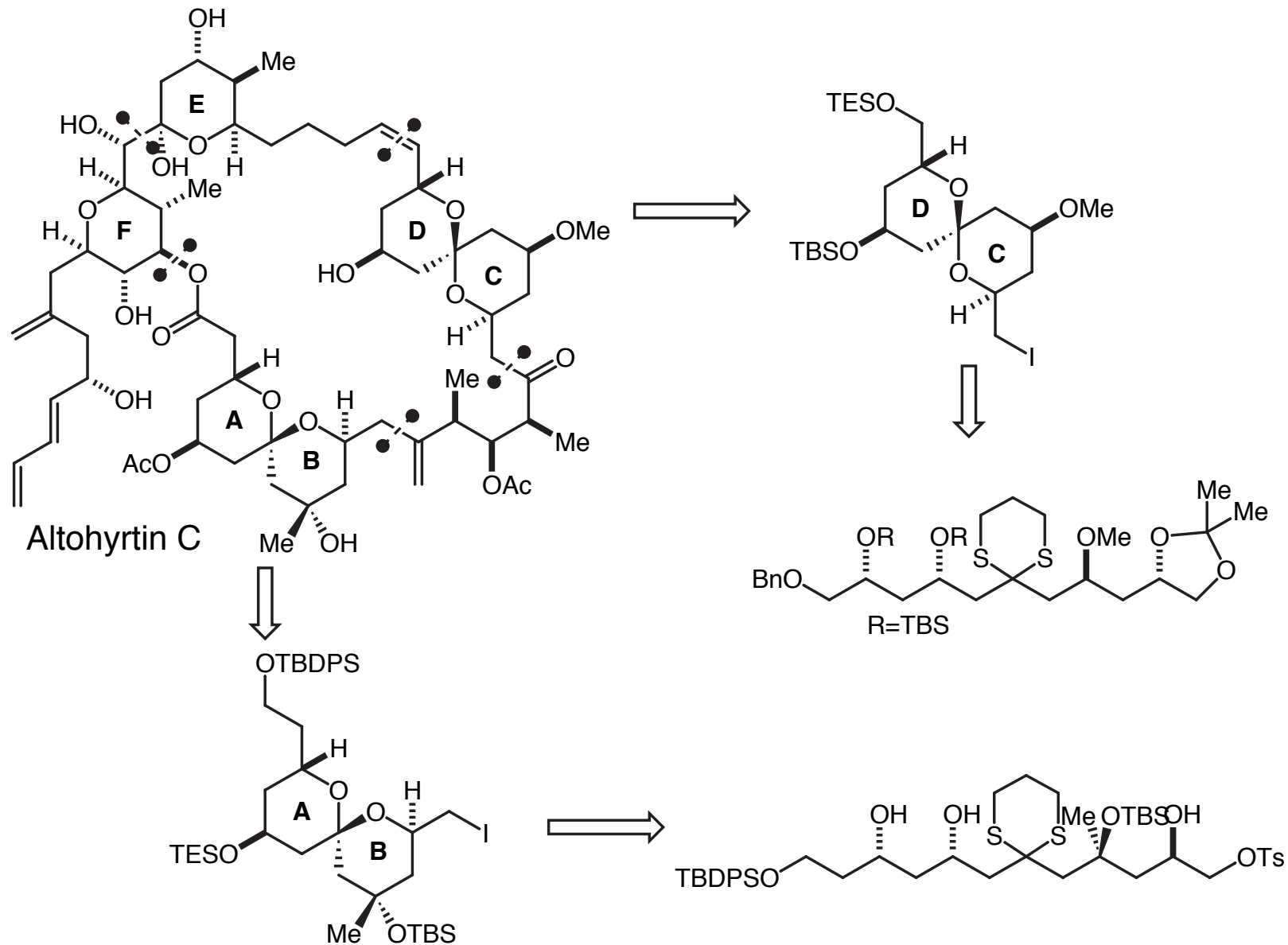
# Smith: Multicomponent Dithiane Coupling via Brook Rearrangement



Smith et al., *J. Am. Chem. Soc.* **1997**, 119, 6925.

See also: Smith et al., *Org. Lett.* **1999**, 1, 2001.

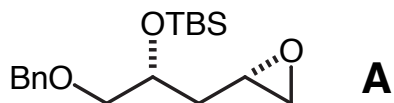
# Smith: Altohyrtin C Fragment Retrosyntheses



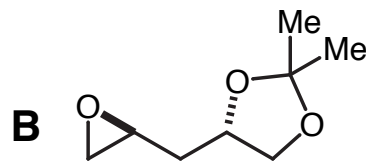
Smith et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 191.

Smith et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 196.

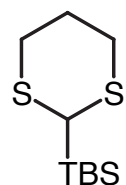
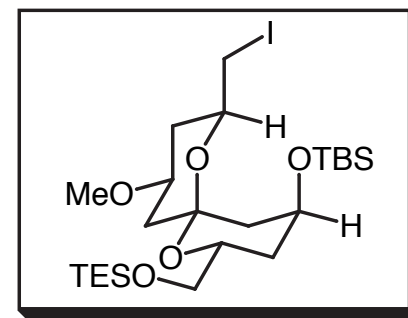
# Smith: Althohyrin C CD Ring Fragment



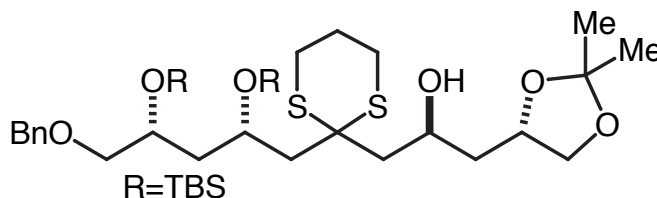
9 steps from glycerol acetonide



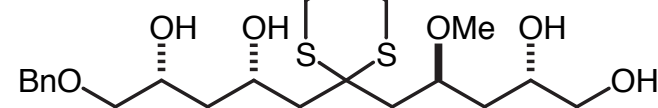
6 steps from glyceraldehyde acetonide



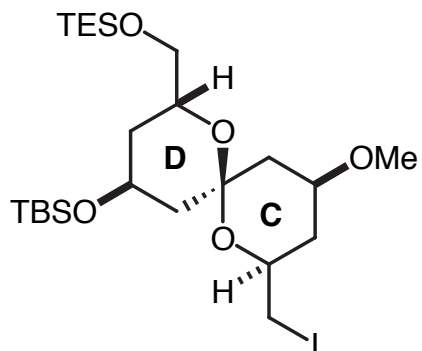
$t\text{-BuLi, Et}_2\text{O}$ ;  
**A**;  
**B**, HMPA  
72%



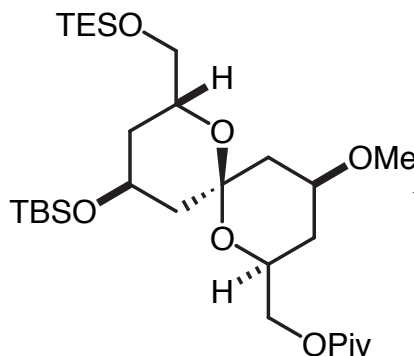
1) NaH, MeI  
2) HCl, MeOH  
80% (2 steps)



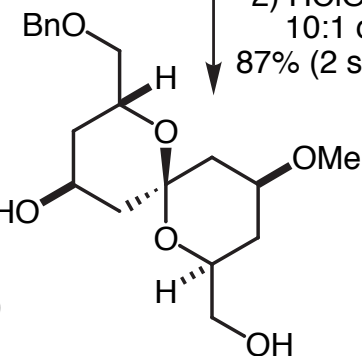
1)  $\text{Hg}(\text{ClO}_4)_2$   
 $\text{CaCO}_3$   
2)  $\text{HClO}_4$   
10:1 dr  
87% (2 steps)



1) DIBAL-H  
2) TsCl  
3) NaI  
4) TESOTf  
66% (4 steps)

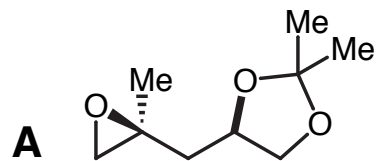


1) PivCl  
2) TBSCl  
3)  $\text{H}_2$ , Pd/C  
4) TESCl  
57% (4 steps)

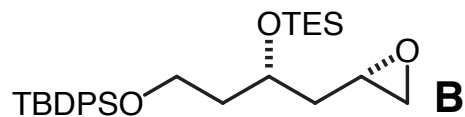


Smith et al., *Tet. Lett.* **1997**, 38, 8671.

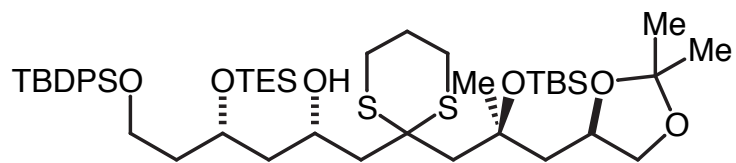
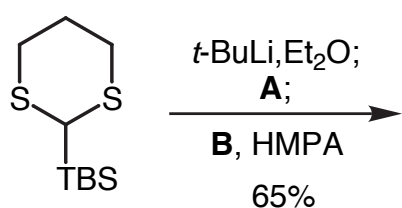
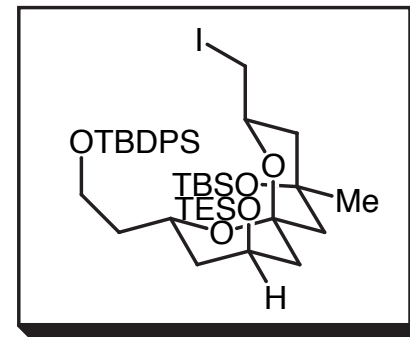
# Smith: Althoyrtin C AB Ring Fragment



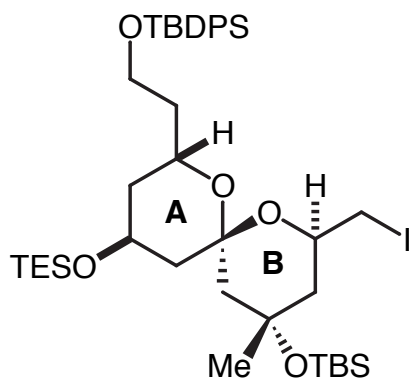
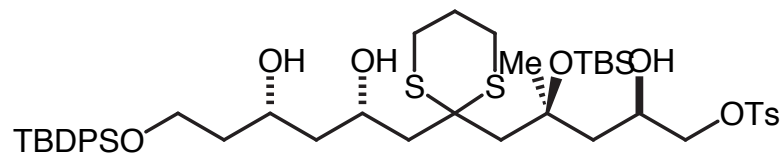
5 steps from glyceraldehyde acetonide



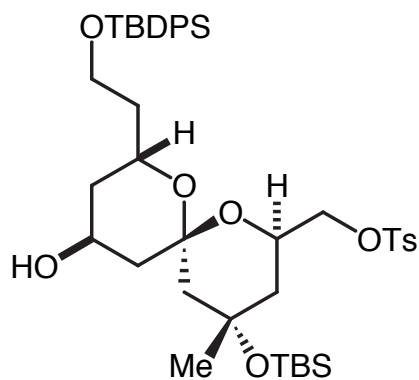
5 steps from (+)lpc<sub>2</sub>Ballyl



1) TFA/H<sub>2</sub>O  
2) TsCl  
79% (2 steps)



1) TESOTf  
2) Lil  
96% (2 steps)

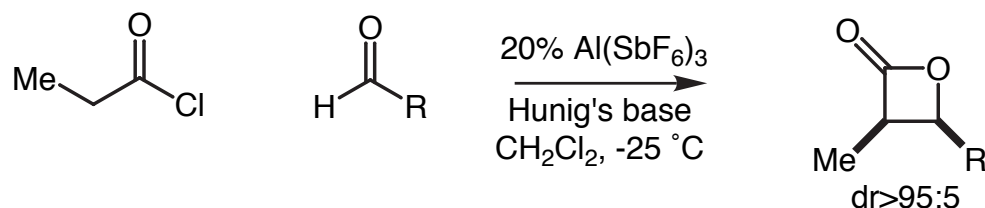
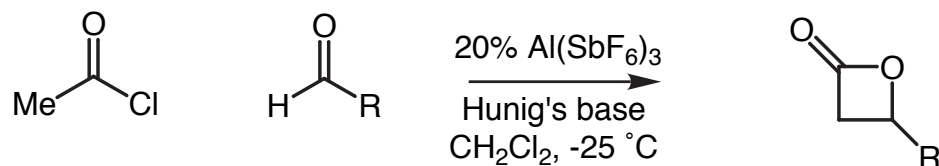


Hg(ClO<sub>4</sub>)<sub>2</sub>  
CaCO<sub>3</sub>  
81%, 26:1 dr

Smith et al., *Tet. Lett.* **1997**, 38, 8675.

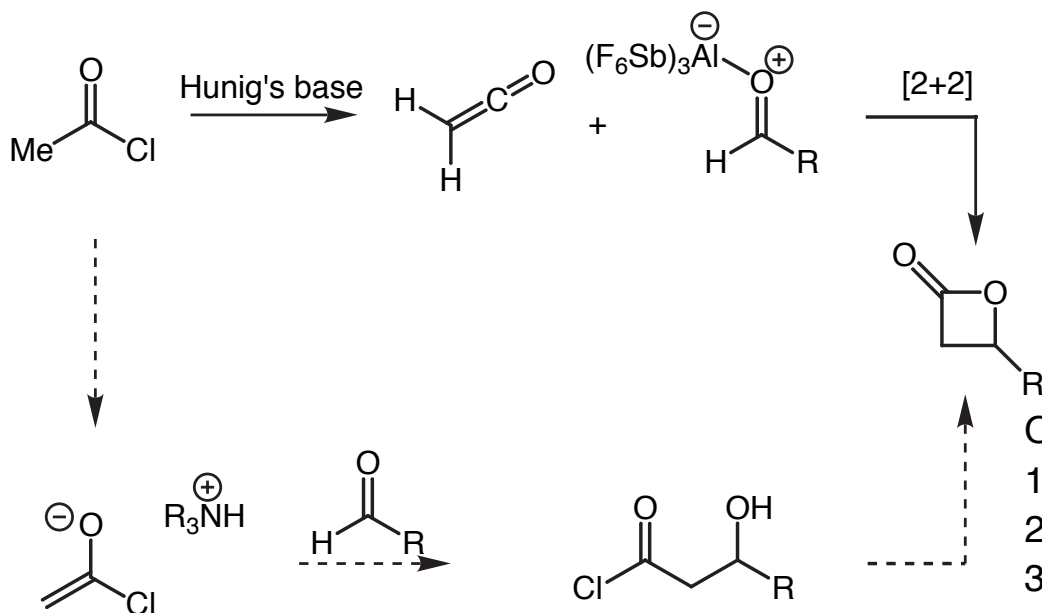


# Nelson's Acyl Halide/Aldehyde Cyclocondensation



Aldehyde	Yield
PhCH <sub>2</sub> CH <sub>2</sub> CHO	93%
C <sub>6</sub> H <sub>11</sub> CHO	90%
BnOCH <sub>2</sub> CHO	83%
CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>8</sub> CHO	81%

Mechanism:



Aldehyde	Yield
C <sub>6</sub> H <sub>11</sub> CHO	65%
CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>8</sub> CHO	80%

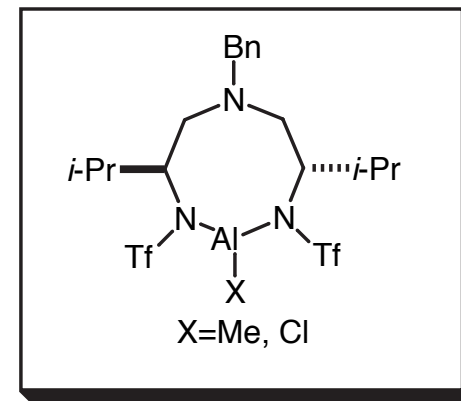
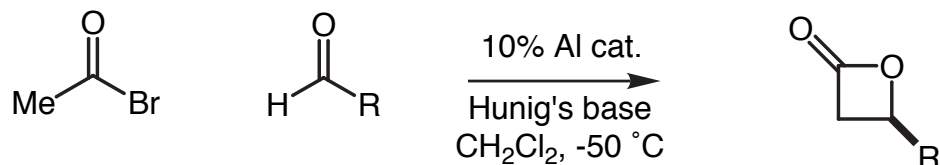
Observations:

- 1) Ketene observed in <sup>13</sup>C NMR
- 2) Enolate not observed in <sup>13</sup>C NMR
- 3) No lactone formed in absence of Al<sup>3+</sup>

Nelson et al., *Tet. Lett.* **1999**, *40*, 6535.

Nelson et al., *Tet. Lett.* **1999**, *40*, 6539.

# Nelson's Enantioselective Acyl Halide/Aldehyde Cyclocondensation

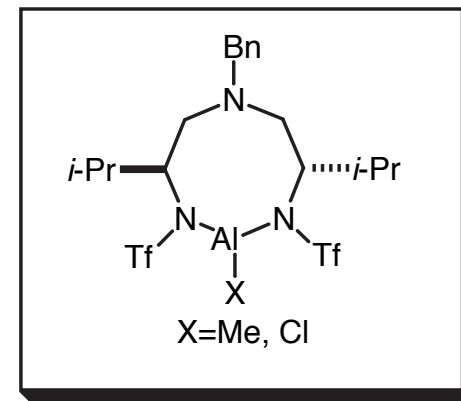
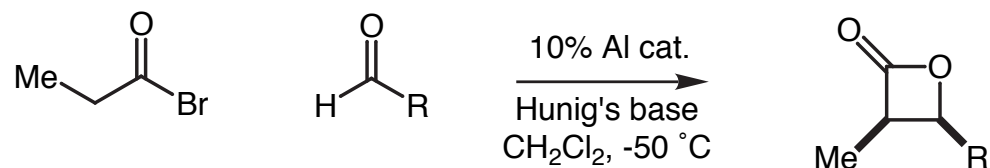


Alpha branched, unsaturated aldehydes afford low ee, yield

Aldehyde	%ee	% yield
PhCH <sub>2</sub> CH <sub>2</sub> CHO	92	93
Me <sub>2</sub> CHCH <sub>2</sub> CHO	93	80
BnOCH <sub>2</sub> CHO	91	91
CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>8</sub> CHO	91	91
TBDPSOCH <sub>2</sub> CHO	89	74
BnOH <sub>2</sub> CC≡CCHO	93	86

Nelson et al., *J. Am. Chem. Soc.* **1999**, *121*, 9742.  
 Nelson and Wan, *Org. Lett.* **2000**, *2*, 1883.

# Nelson's Enantioselective Acyl Halide/Aldehyde Cyclocondensation

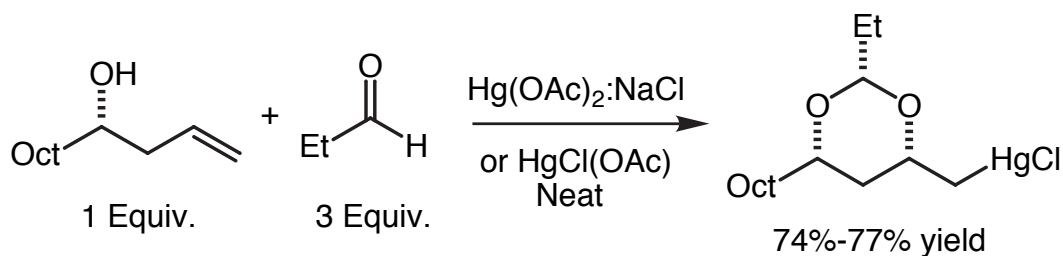
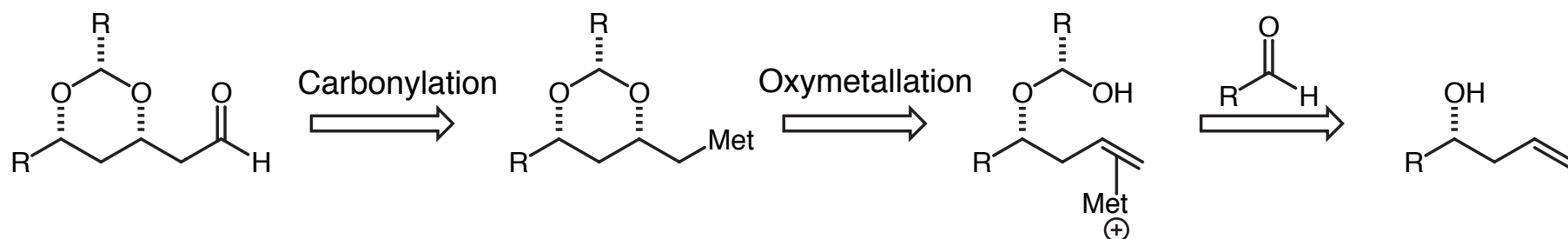


Other aliphatic aldehydes, unsaturated  
enals afford low yields, ee's.

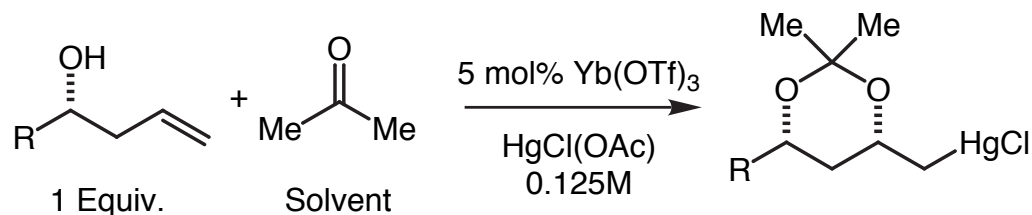
Aldehyde	%ee	dr	% yield
BnOCH <sub>2</sub> CHO	94	88:12	78
BnOH <sub>2</sub> CC≡CCHO	94	91:9	85
C <sub>6</sub> H <sub>11</sub> C≡CCHO	93	98:2	85
TMSC≡CCHO	93	99:1	90
PhC≡CCHO	91	99:1	83

Nelson et al., *J. Am. Chem. Soc.* **1999**, 121, 9742.  
Nelson and Wan, *Org. Lett.* **2000**, 2, 1883.

# Leighton's Oxymercuration of Hemiacetals



Works for aliphatic aldehydes. Ketones, aromatic aldehydes (e.g. benzaldehyde) not synthetically useful. Yields typically 65-75%, dr at least 10:1.

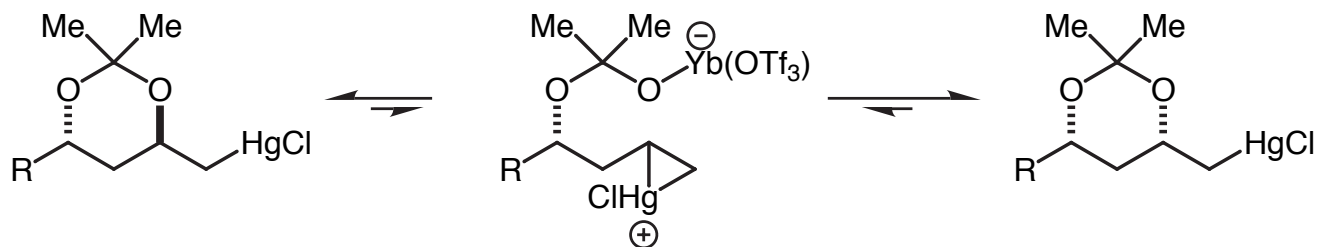
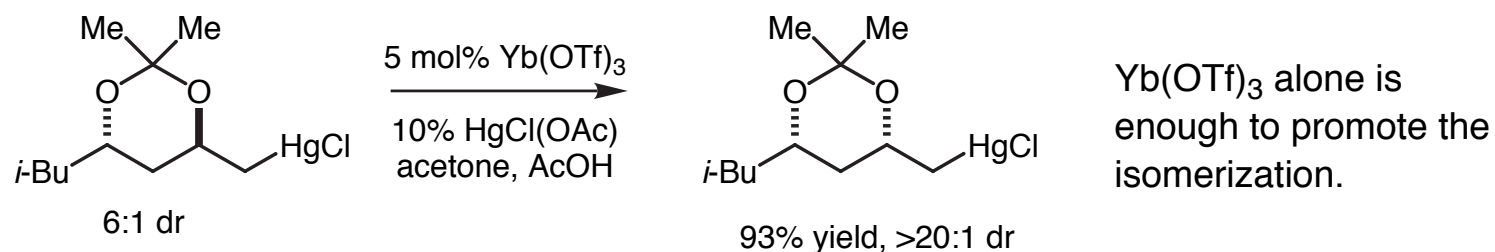
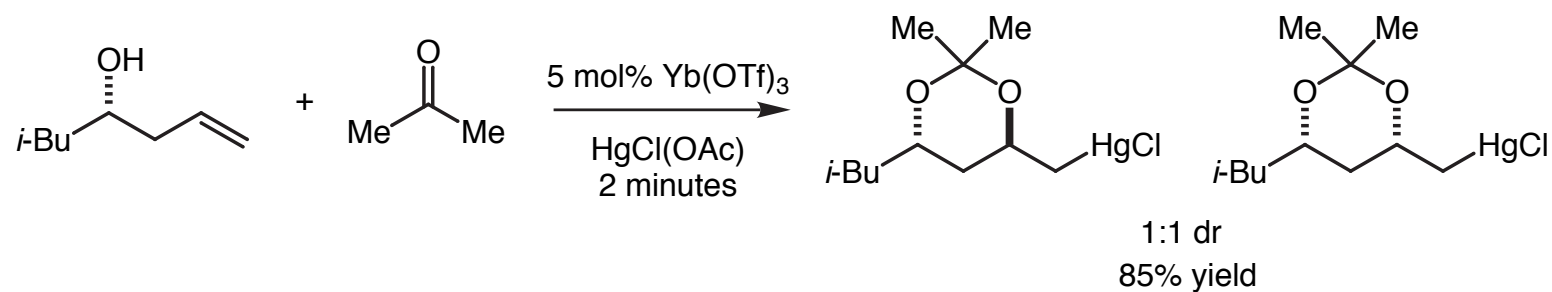


Acetone, benzaldehyde now useful substrates. Yields typically 70-85%, dr at least 20:1.

Leighton and Sarraf, *Org. Lett.* **2000**, 2, 403.  
Leighton et al., *Org. Lett.* **2000**, 2, 3197.

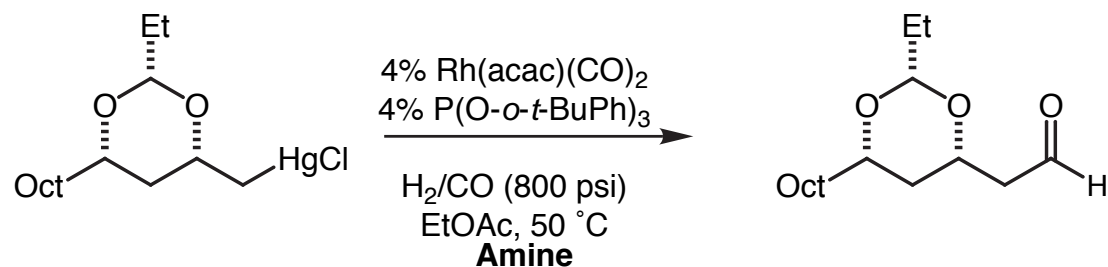
# Leighton's Oxymercuration of Hemiacetals

Is  $\text{Yb}(\text{OTf})_3$  simply increasing the rate of hemiacetal formation?

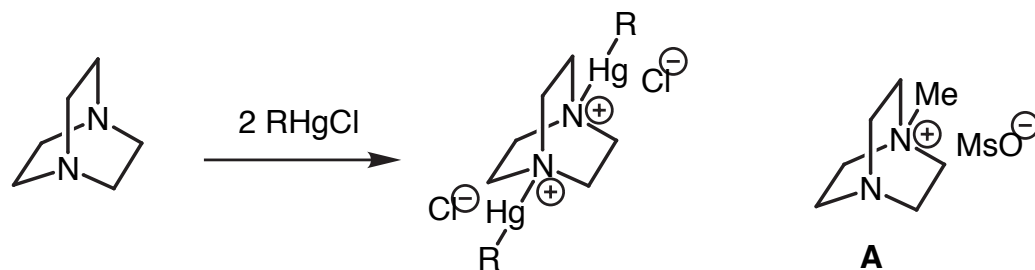


Leighton and Sarraf, *Org. Lett.* **2000**, 2, 403.  
Leighton et al., *Org. Lett.* **2000**, 2, 3197.

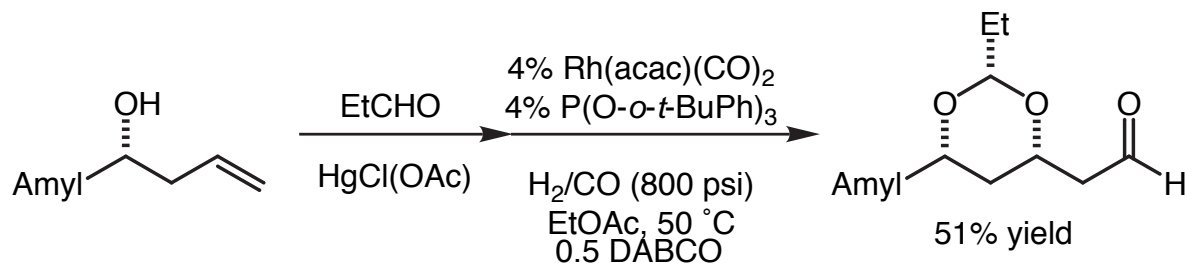
# Leighton's Formylation of Mercurials



Amine	Equiv.	Yield
pyridine	1	0
quinuclidine	1	46
TMEDA	0.5	36
DABCO	1	46
DABCO	0.5	70
Ammonium salt <b>A</b>	1	77

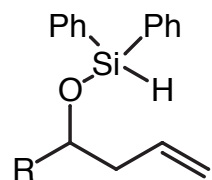
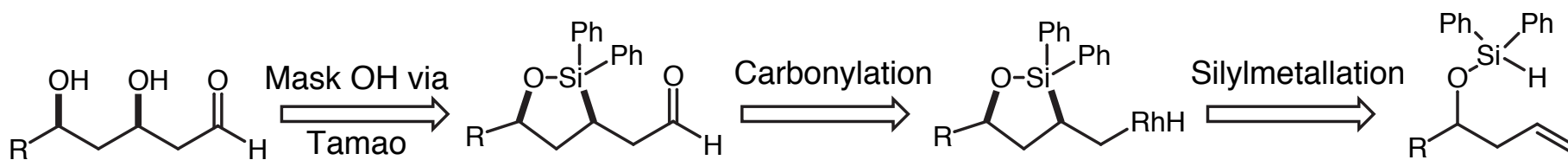


Also compatible with acetonides.  
Yields typically 60-80%



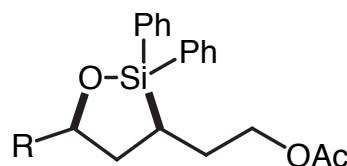
One pot procedure delivers aldehyde in comparable yield to two step procedure, without isolation of mercurial intermediate.

# Leighton's Silylformylation

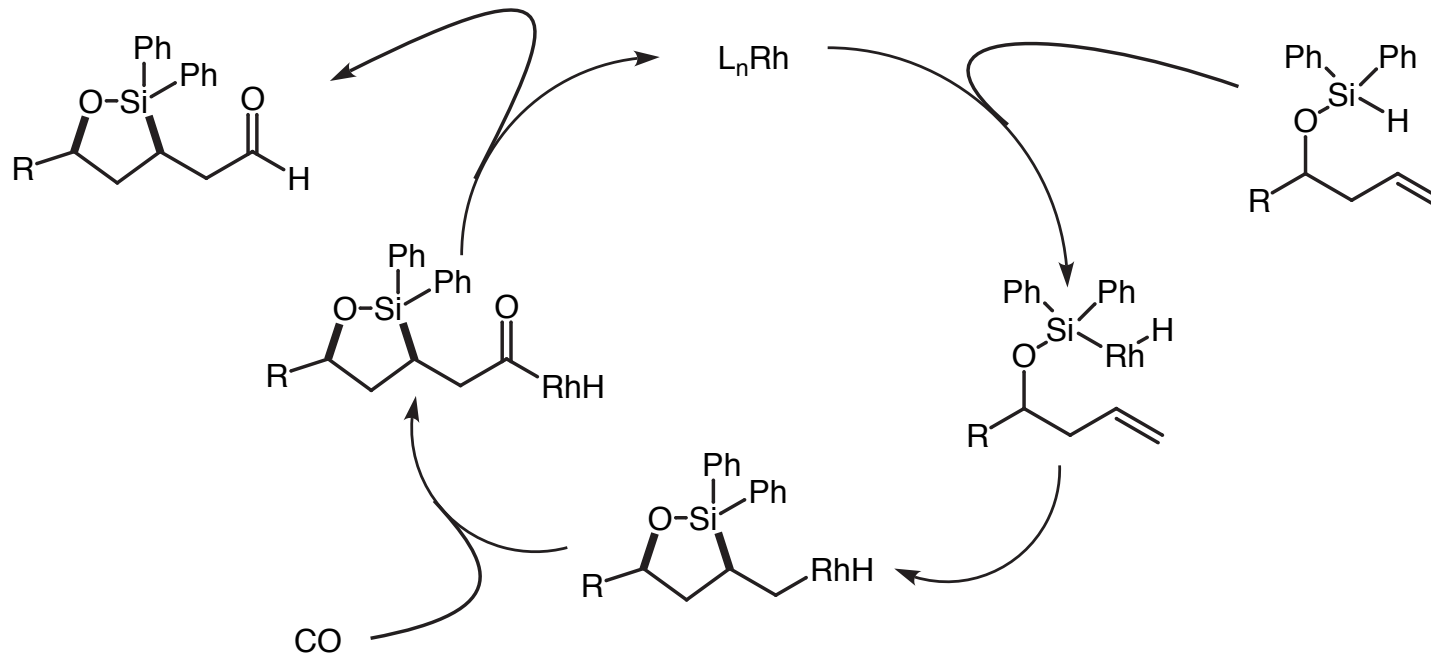


1) 1%  $Rh(acac)(CO)_2$   
1000 psi  $CO$ ,  $60^\circ C$ ,  $C_6H_6$

2)  $LiEt_3BH$   
3)  $Ac_2O$

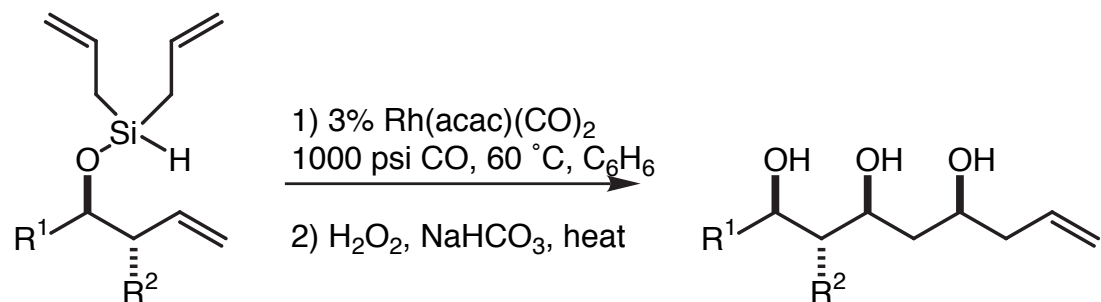
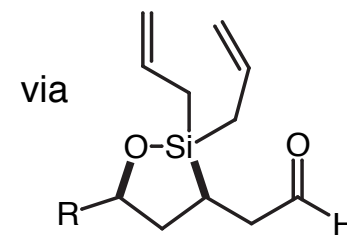
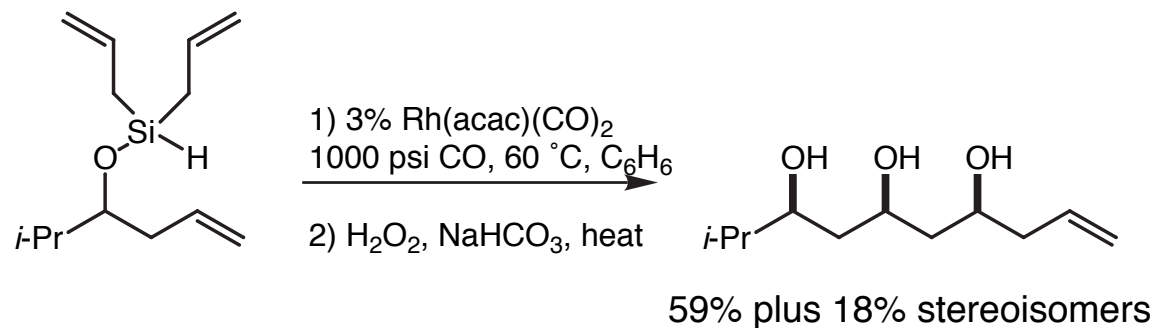


R	dr	Yield
Me	4.5:1	67%
Allyl	4:1	64%
<i>i</i> -Pr	6:1	79%
TBSOEt	4:1	60%



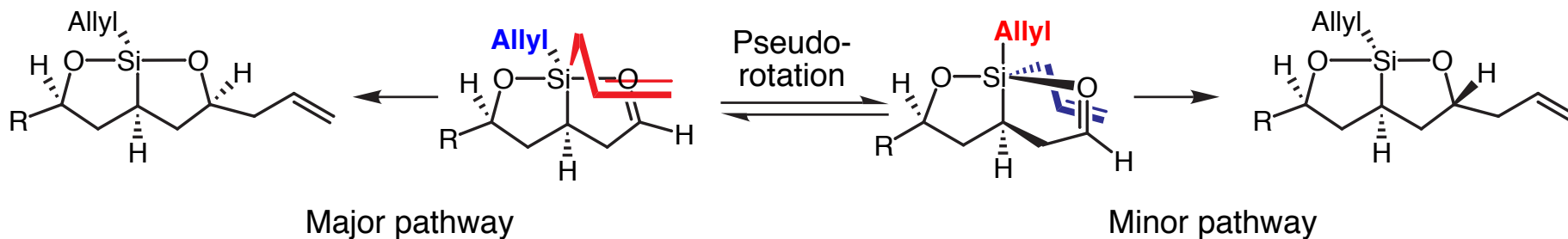
Leighton and Chapman, *J. Am. Chem. Soc.* **1997**, *119*, 12416.

# Leighton's Silylformylation/Allylation



R <sup>1</sup>	R <sup>2</sup>	dr	yield
<i>i</i> -Pr	H	77:23	59%
Allyl	H	69:31	50%
TBSOEt	H	71:29	45%
<i>i</i> -Pr	Me	92:8	59%

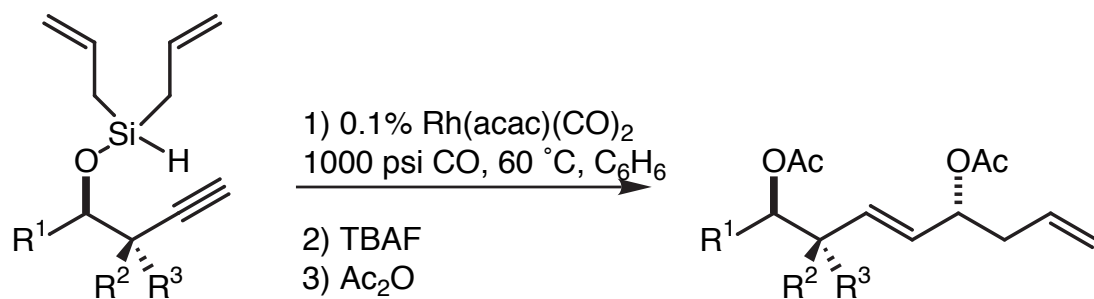
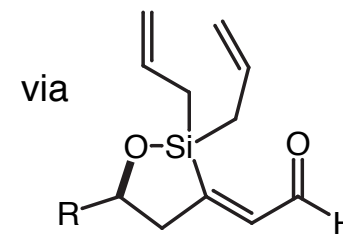
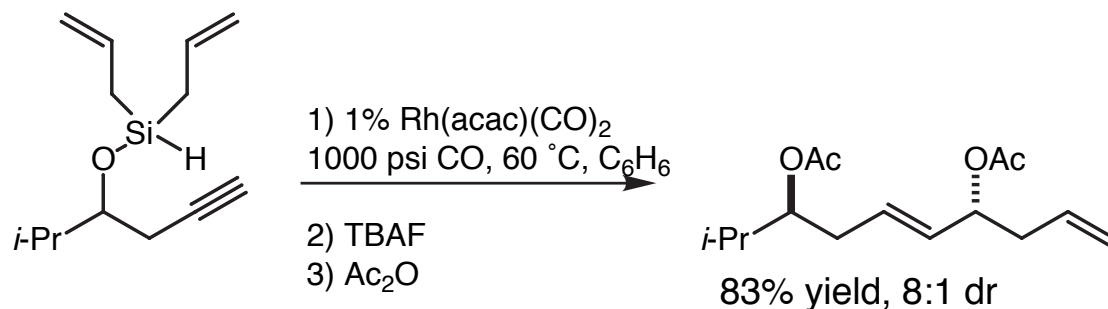
Stereochemical rationale:



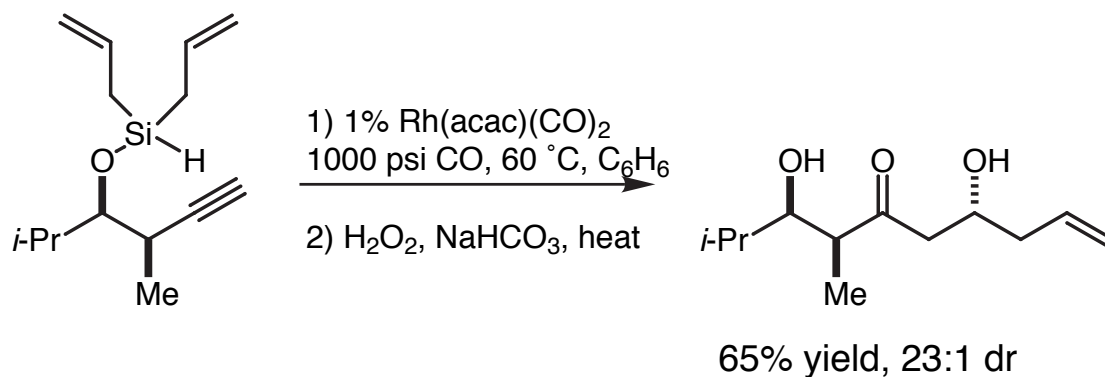
Leighton and Zacuto, *J. Am. Chem. Soc.* **2000**, 122, 8587.



# Leighton's Alkyne Silylformylation/Allylation



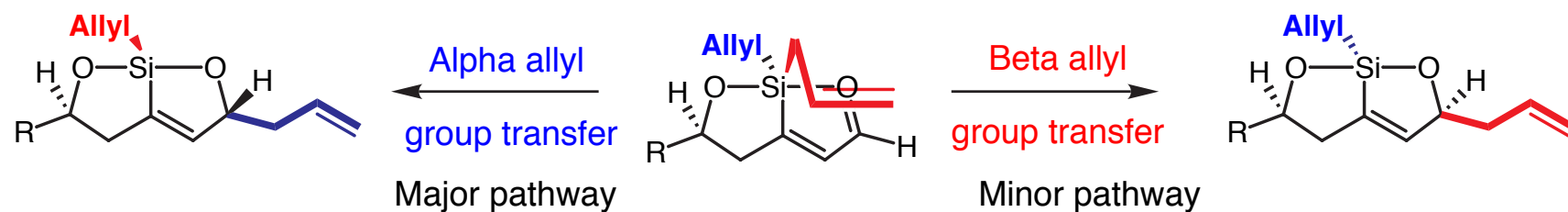
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	dr	Yield
Propargyl	H	H	4:1	63%
<i>n</i> -Pr	H	H	4:1	68%
<i>t</i> -Bu	H	H	10:1	66%
<i>i</i> -Pr	H	H	8:1	83%
<i>i</i> -Pr	H	Me	7:1	70%
<i>i</i> -Pr	Me	H	23:1	70%



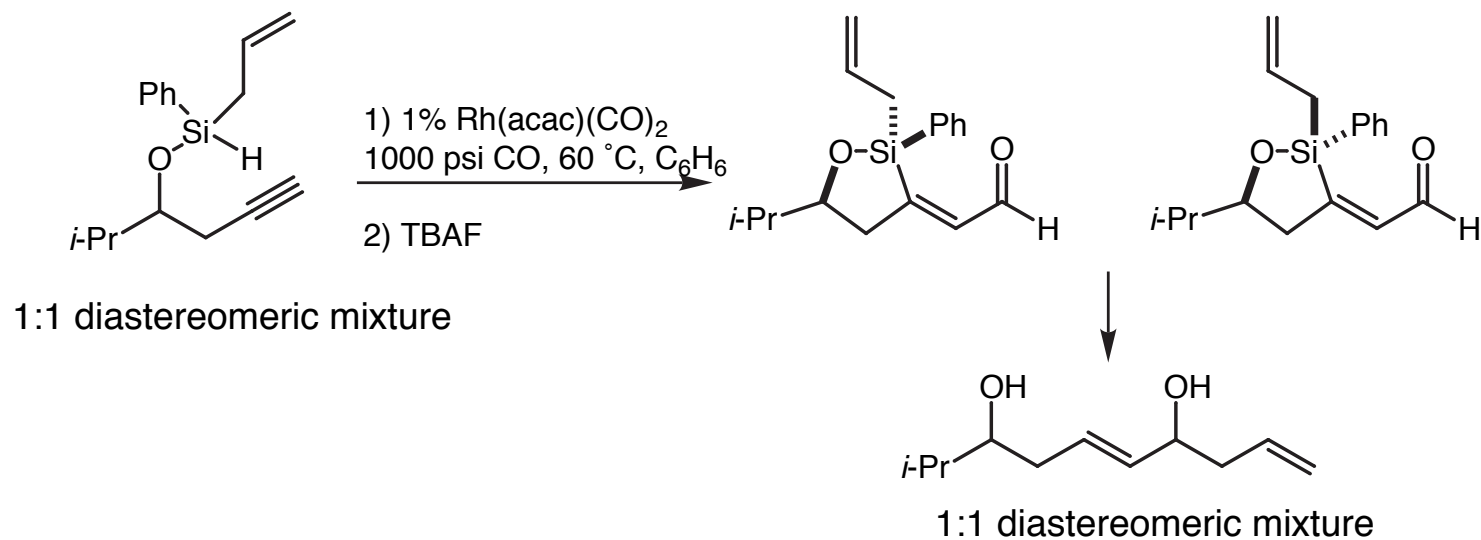
Leighton and O'Malley, *Angew. Chem. Int. Ed.* **2001**, *40*, 2915.

# Leighton's Alkyne Silylformylation/Allylation

Stereochemical rationale:

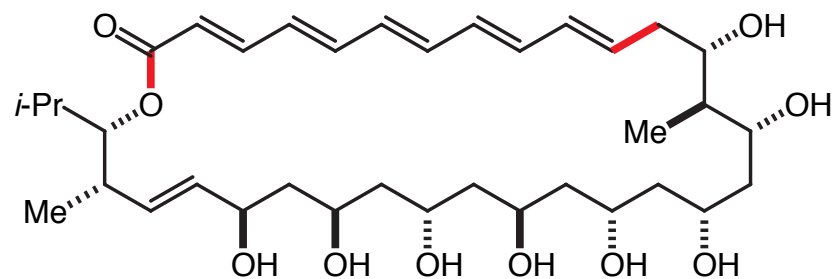


Top allyl group experiences steric repulsion with R group

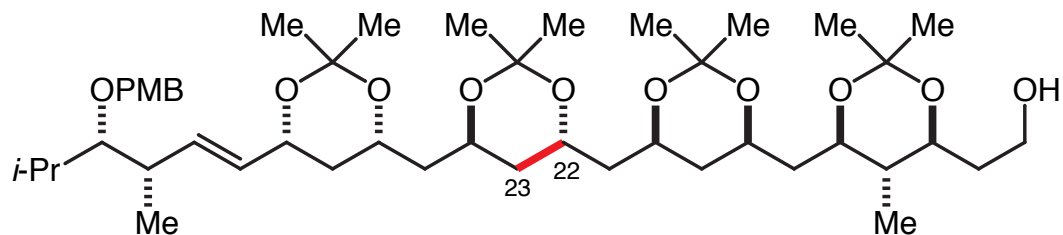


Leighton and O'Malley, *Angew. Chem. Int. Ed.* **2001**, 40, 2915.

# Leighton's Retrosynthesis of Mycoticin A



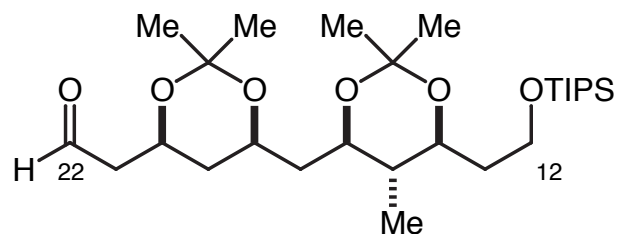
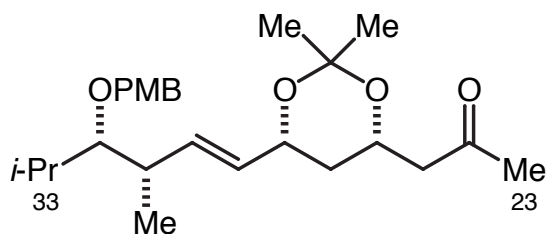
Mycoticin A



Schreiber's polyol segment

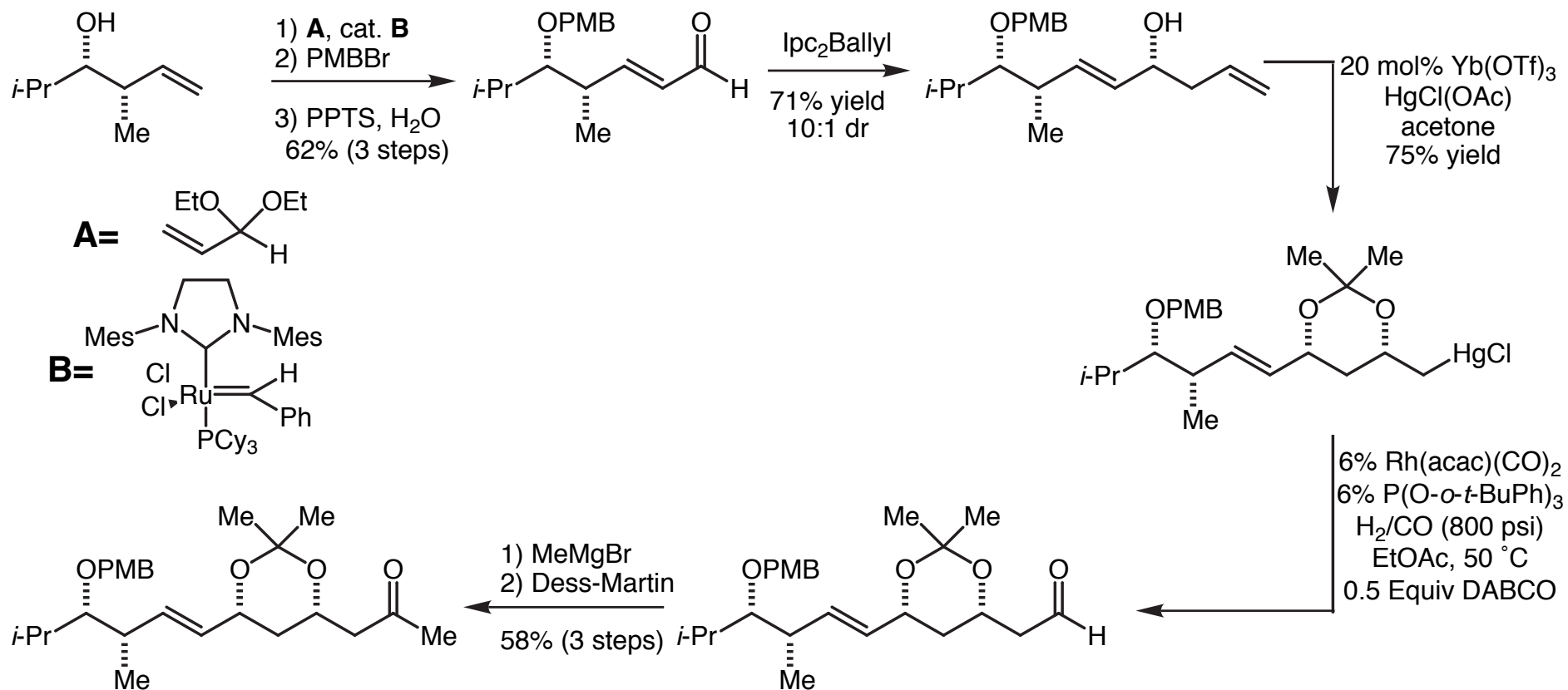


1,3 anti aldol

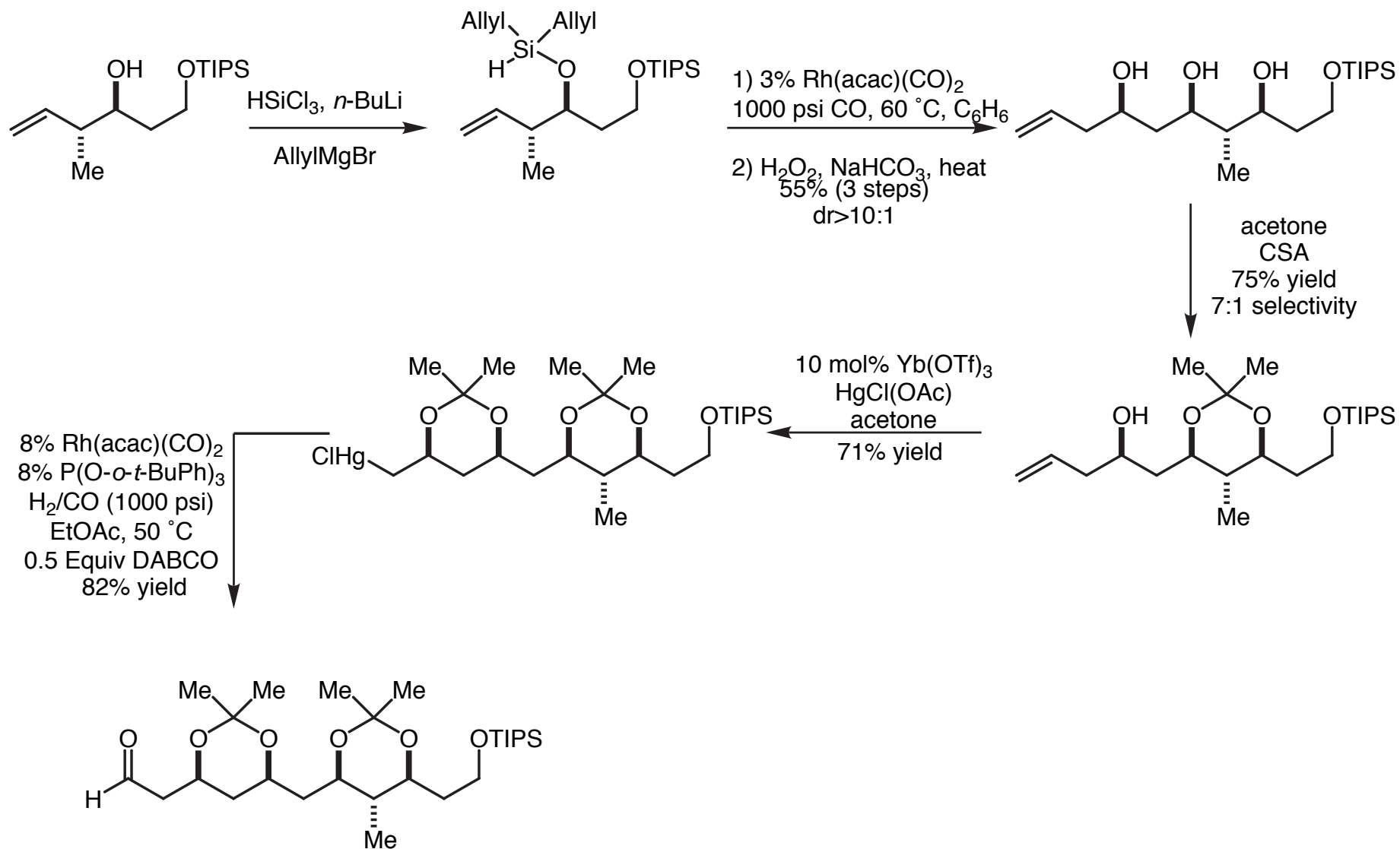


Leighton and Dreher, *J. Am. Chem. Soc.* **2001**, 123, 341.

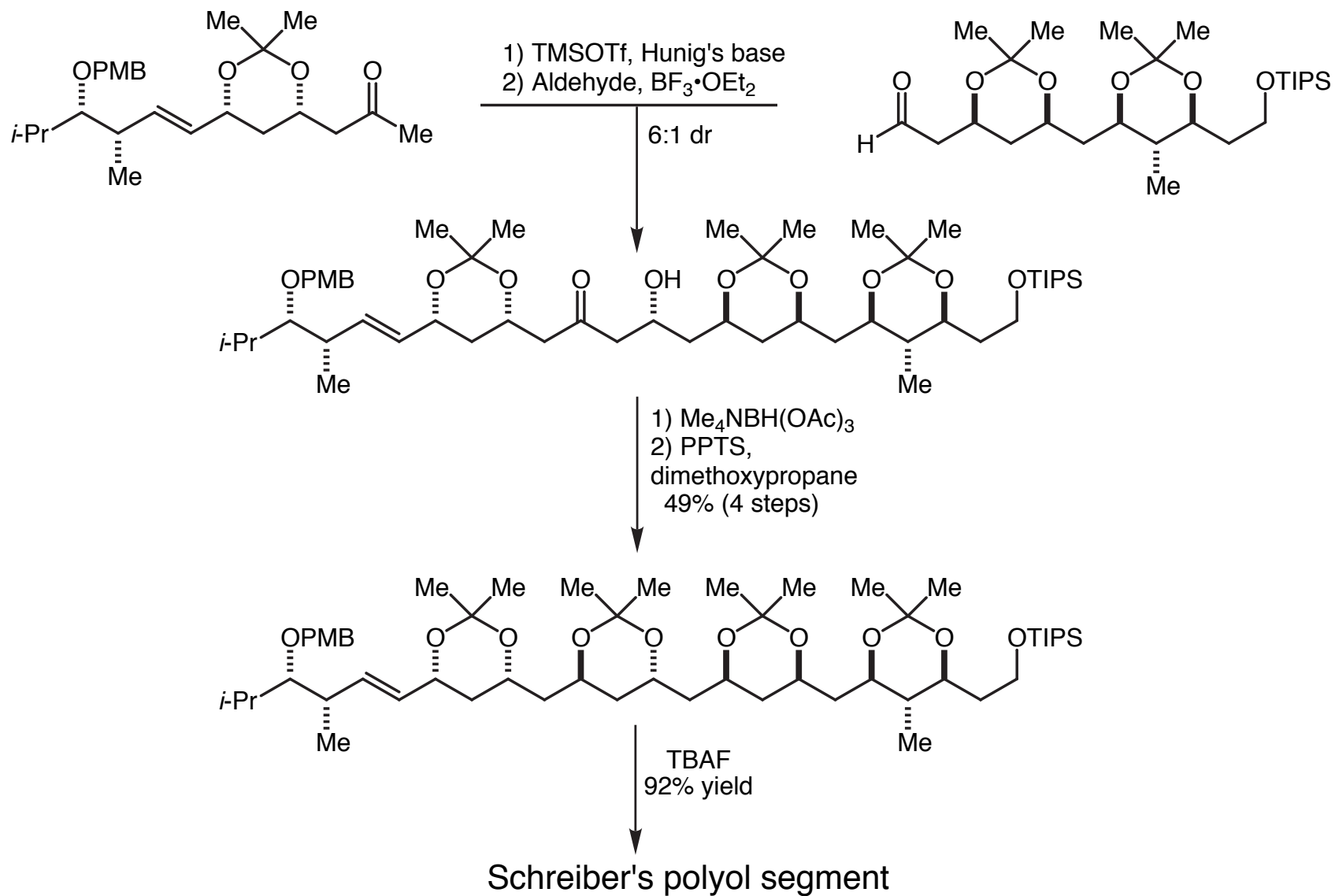
# Leighton's Synthesis of the C<sub>23</sub>-C<sub>33</sub> Methyl Ketone



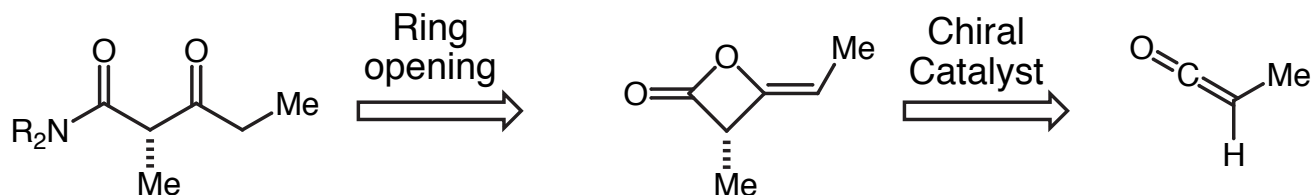
# Leighton's Synthesis of the C<sub>12</sub>-C<sub>22</sub> Aldehyde



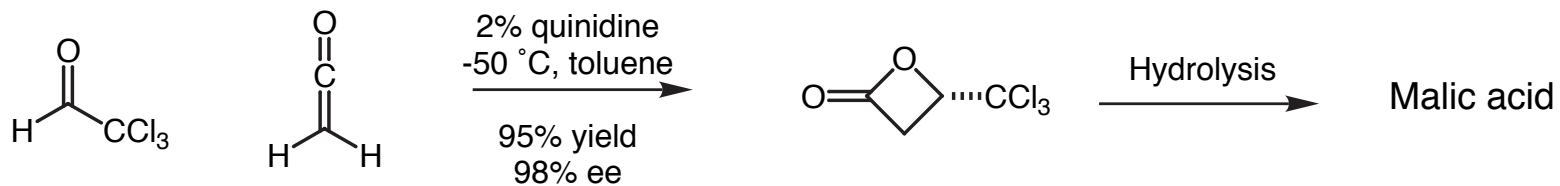
# Leighton's Formal Synthesis of Mycoticin A



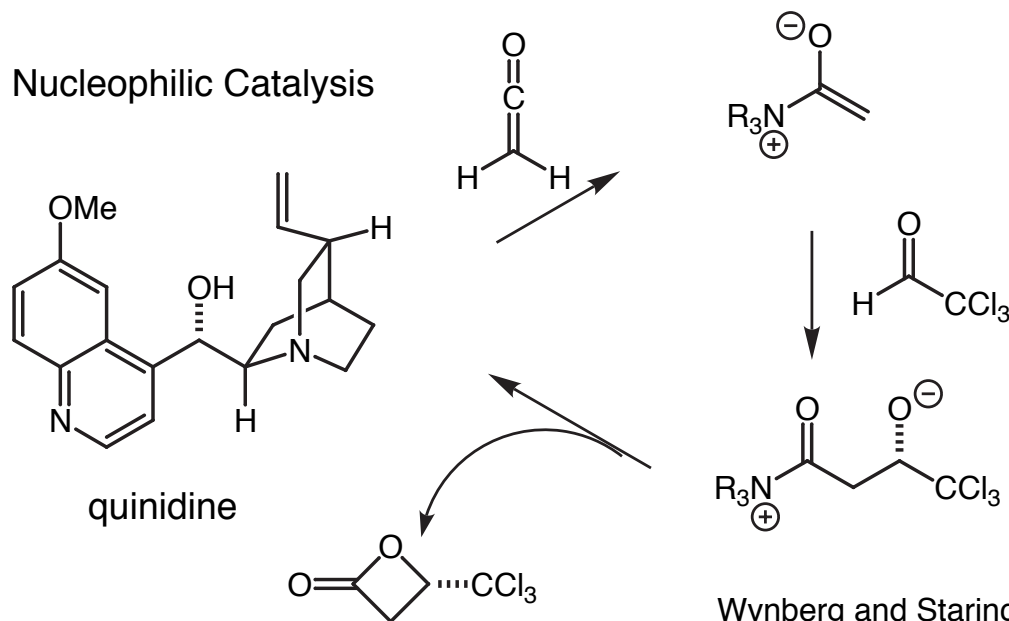
# Calter: Asymmetric Methylketene Dimerization



Wynberg's precedent: 1982

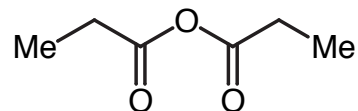
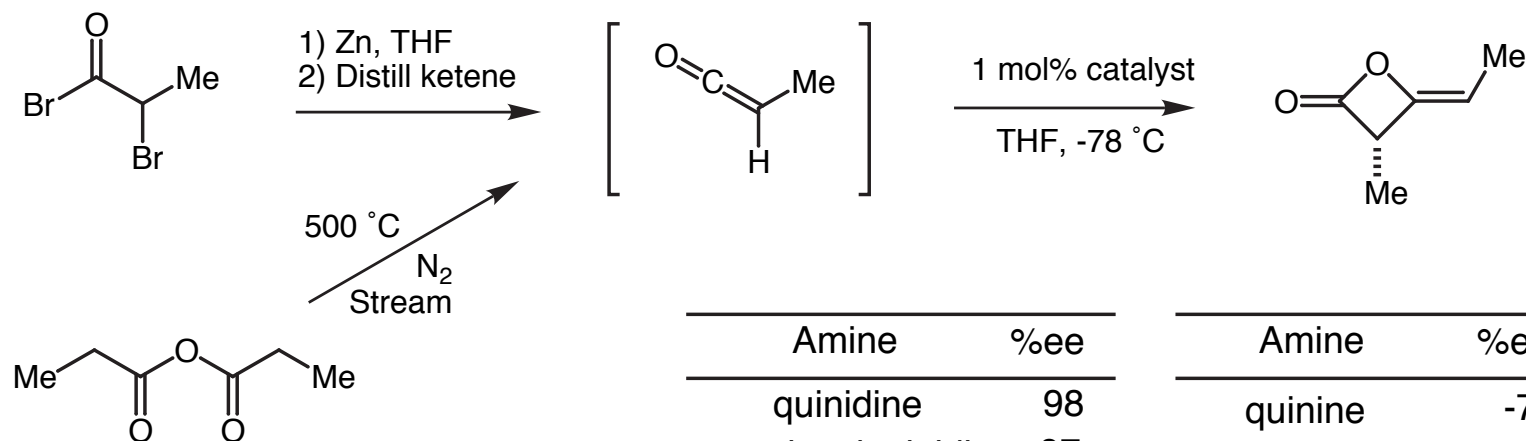


Mechanism: Nucleophilic Catalysis



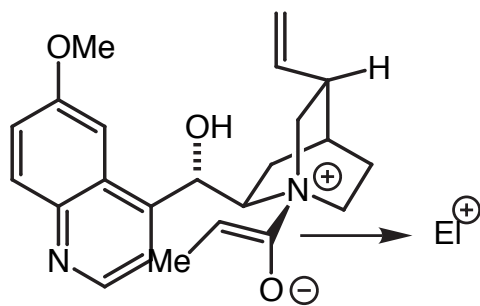
Wynberg and Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166.

# Calter: Asymmetric Methylketene Dimerization

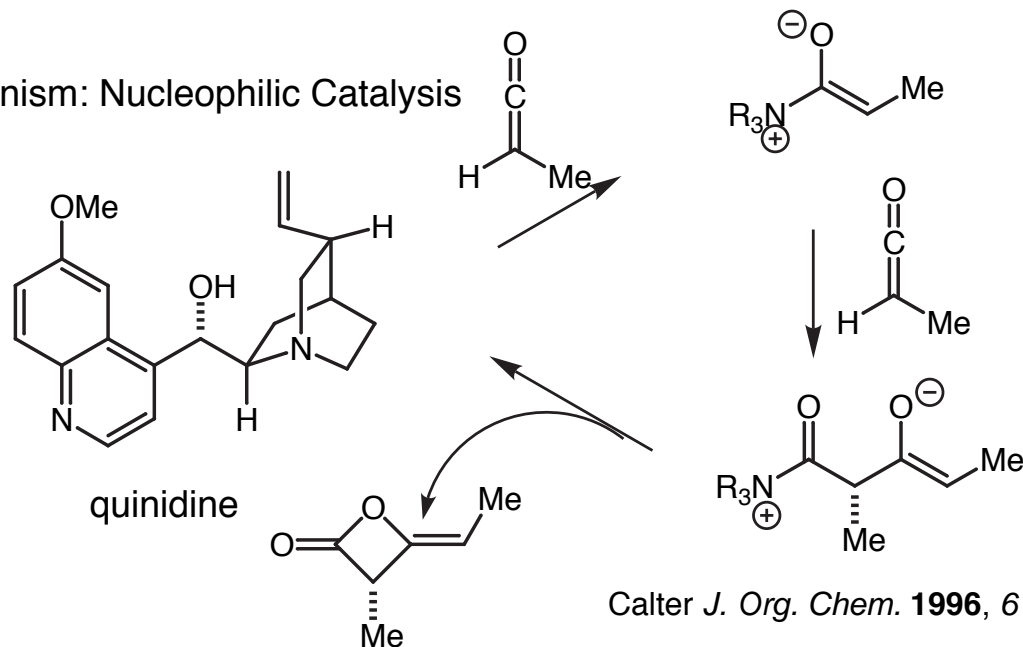


Amine	%ee	Amine	%ee
quinidine	98	quinine	-70
propionylquinidine	97	propionylquinine	-54
TMS-quinidine	98	TMS-quinine	-93

## Model for stereoinduction



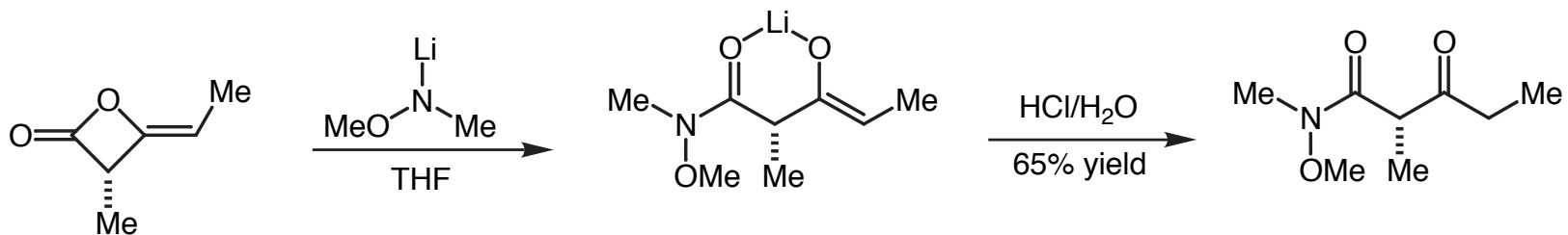
## Mechanism: Nucleophilic Catalysis



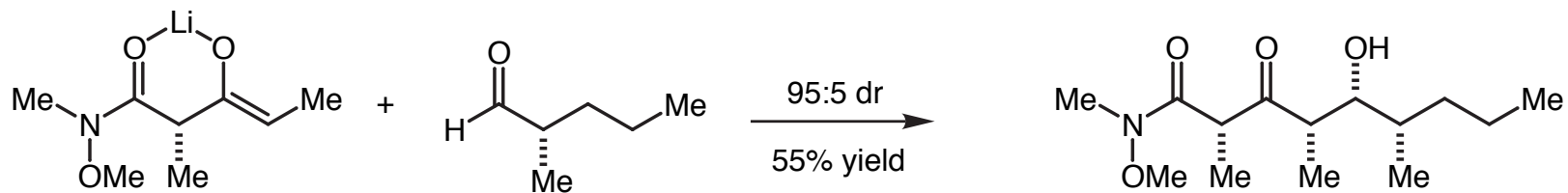
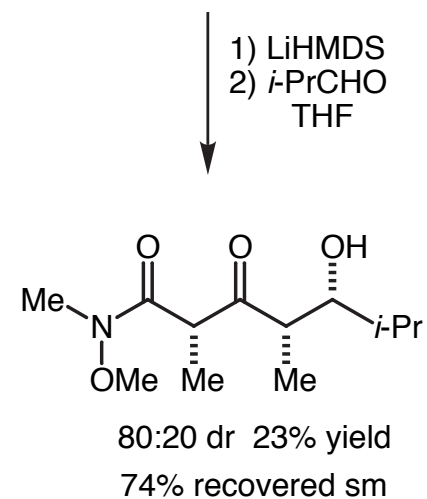
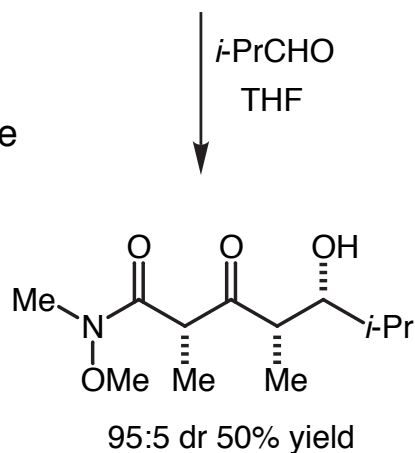
Calter *J. Org. Chem.* **1996**, *61*, 8006.



# Calter: Tandem Ring Opening/Aldol Reaction



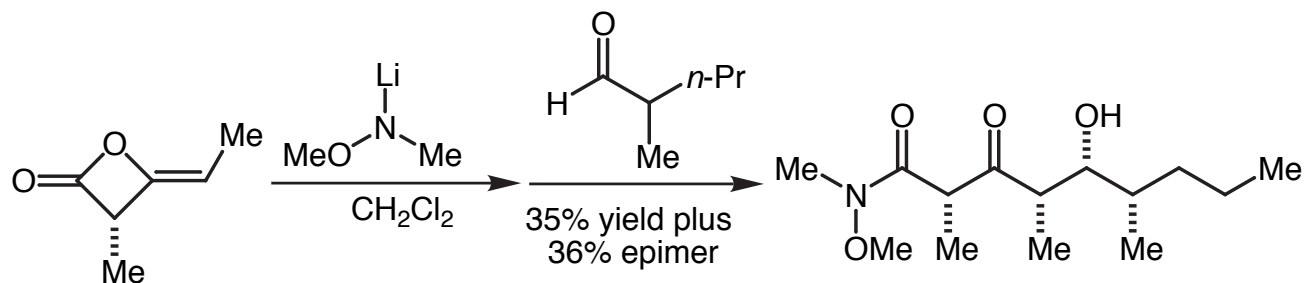
Yields around 50% based on ketene dimer, dr between 85:15 and 90:1.



Calter et al., *Org. Lett.* **2001**, 3, 1499.

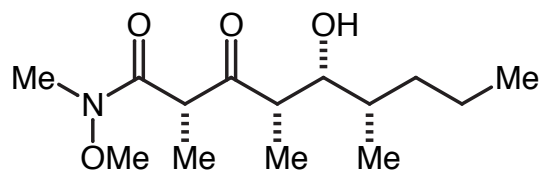
Calter et al., *J. Org. Chem.* **2001**, 66, 7500.

# Calter: Synthesis of Siphonarienal

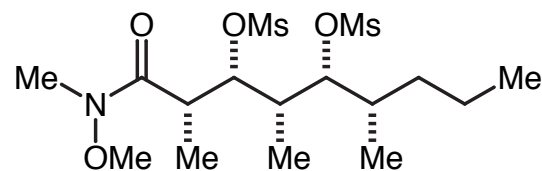


Starting materials:  
All commercially available

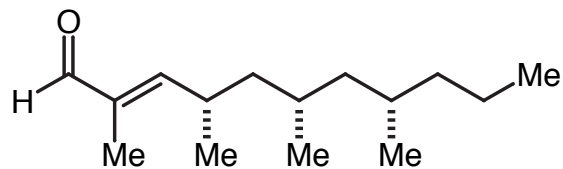
propionic anhydride  
quinidine  
*N,O*-dimethylhydroxylamine  
*n*-BuLi  
*(rac)*-2-methylpentanal



1)  $\text{Zn}(\text{BH}_4)_2$   
2) MsCl  
63% yield (2 steps)

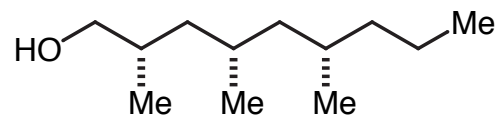


1)  $\text{LiAlH}_4$ , THF  
2)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$   
72% (2 steps)



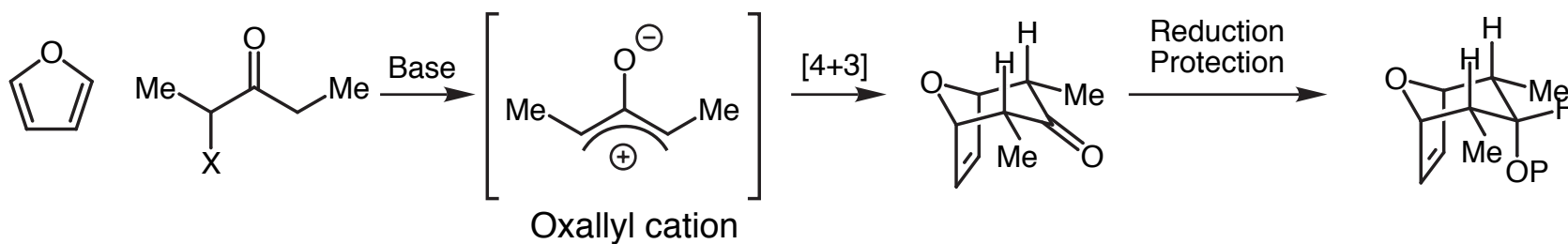
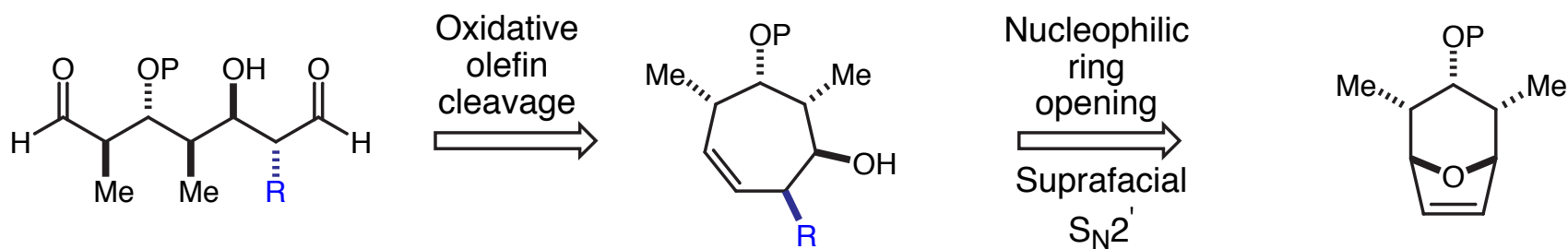
Siphonarienal

1) TEMPO,  $\text{PhI}(\text{OAc})_2$   
2) Wittig  
3) DIBAL-H  
4)  $\text{MnO}_2$   
64% yield (4 steps)



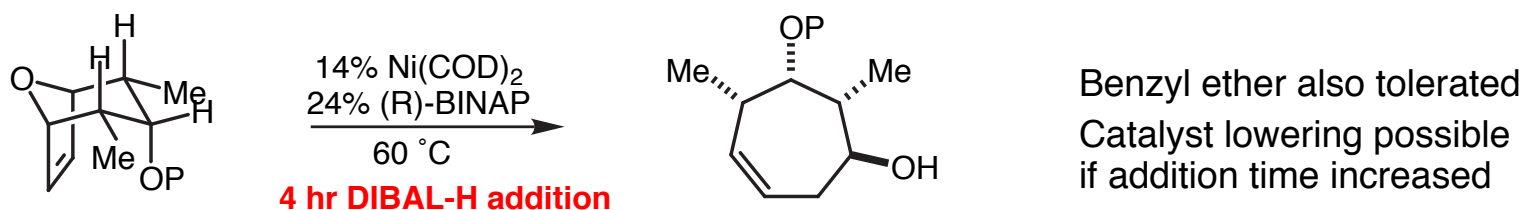
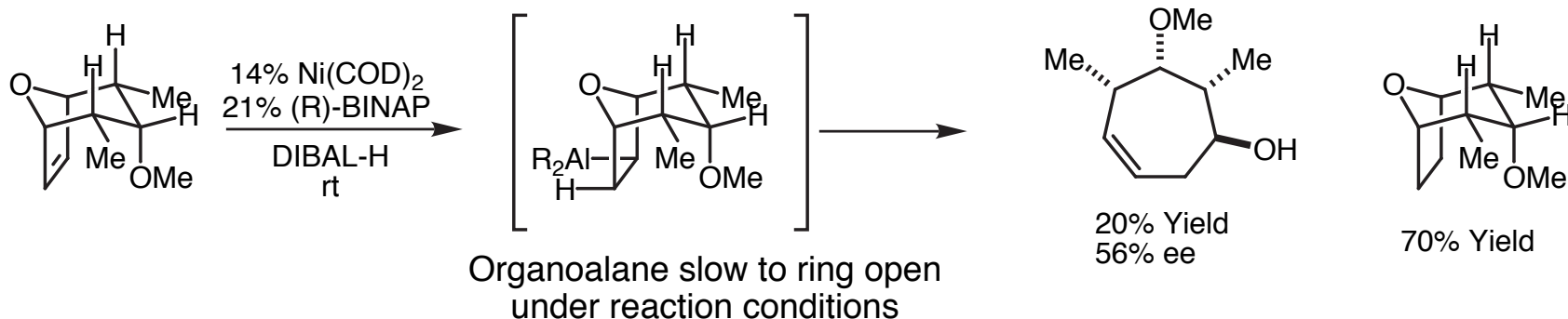
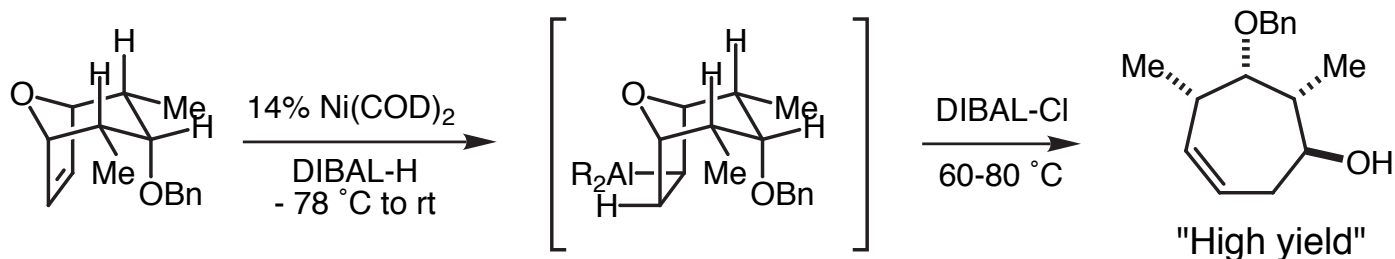
Calter et al., *J. Org. Chem.* **2001**, 66, 7500.

# Lautens' Oxabicyclic Ring Opening



Lautens and Chiu, *Topics in Current Chemistry* **1997**, 190, 1-85.

# Lautens' Enantioselective Oxabicyclic Ring Opening: Hydride Reduction



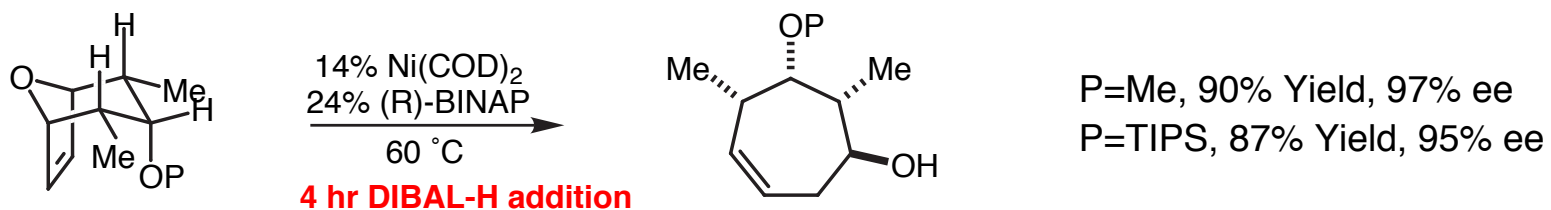
P=Me, 90% Yield, 97% ee

P=TIPS, 87% Yield, 95% ee

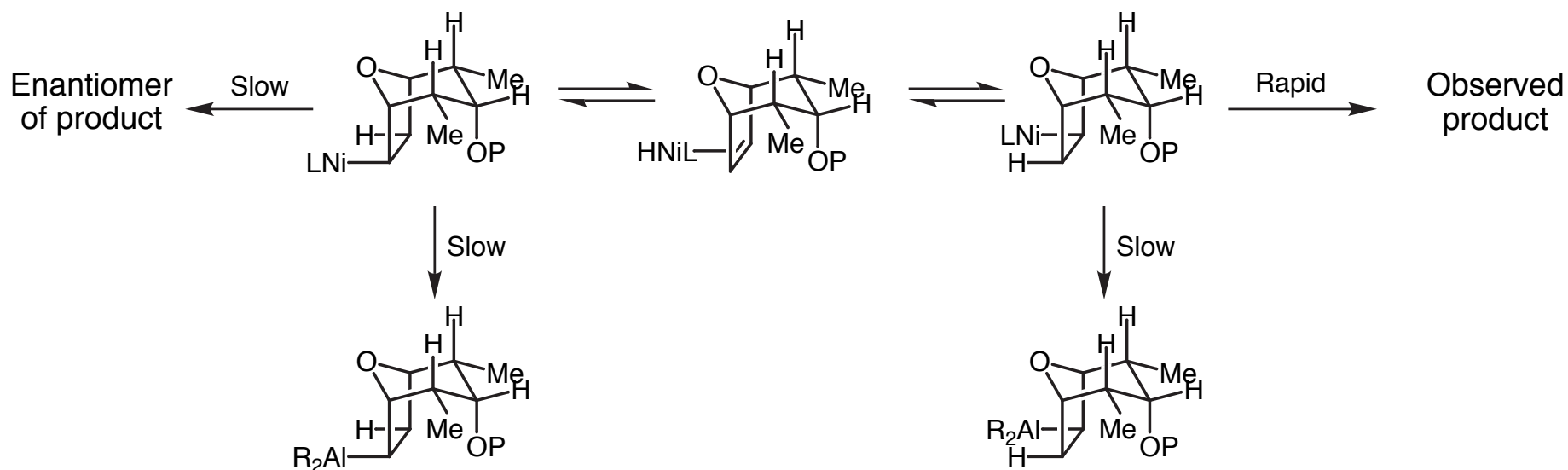
Lautens et al., *J. Am. Chem. Soc.* **1995**, 117, 532.

Lautens and Rovis, *J. Am. Chem. Soc.* **1997**, 119, 11090.

# Lautens' Enantioselective Oxabicyclic Ring Opening: Hydride Reduction



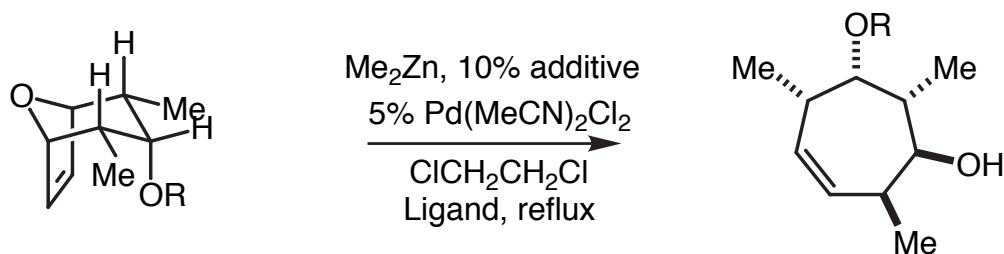
Initial hydrometallation rapid and reversible.  
 Organoalanes not implicated as intermediates.  
 Elimination is enantioselective event.



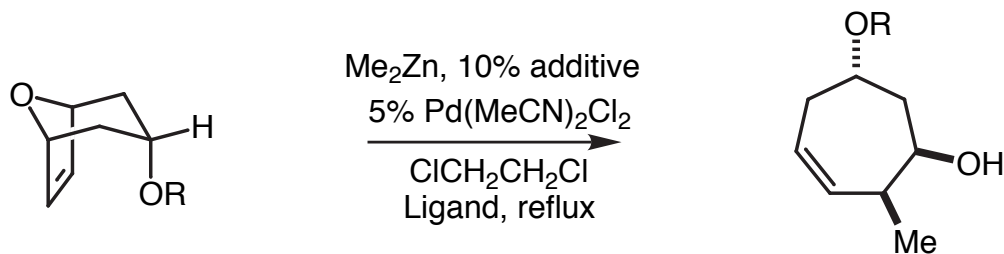
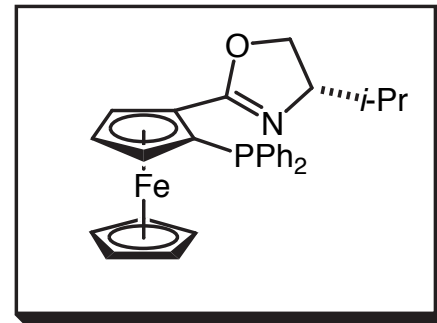
Lautens et al., *J. Am. Chem. Soc.*, **1995**, 117, 532.

Lautens and Rovis, *J. Am. Chem. Soc.*, **1997**, 119, 11090.

# Lautens' Enantioselective Oxabicyclic Ring Opening: Methyl Addition



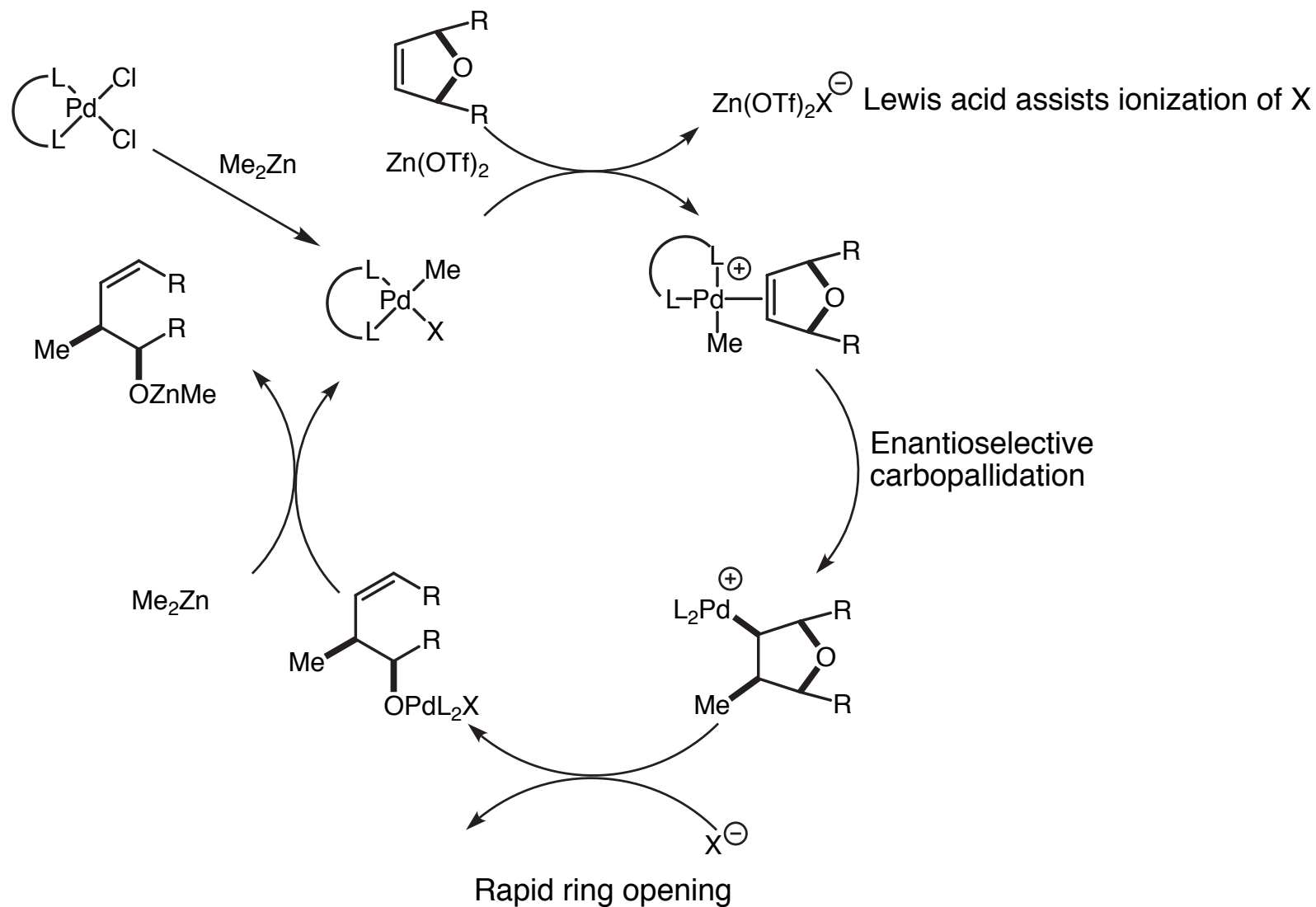
R	Additive	%ee	%yield
H	none	95	84
TBDPS	$\text{Zn}(\text{OTf})_2$	87	70
TIPS	$\text{Zn}(\text{OTf})_2$	93	73



R	Additive	%ee	%yield
H	none	90	84
TBDPS	$\text{Zn}(\text{OTf})_2$	88	92

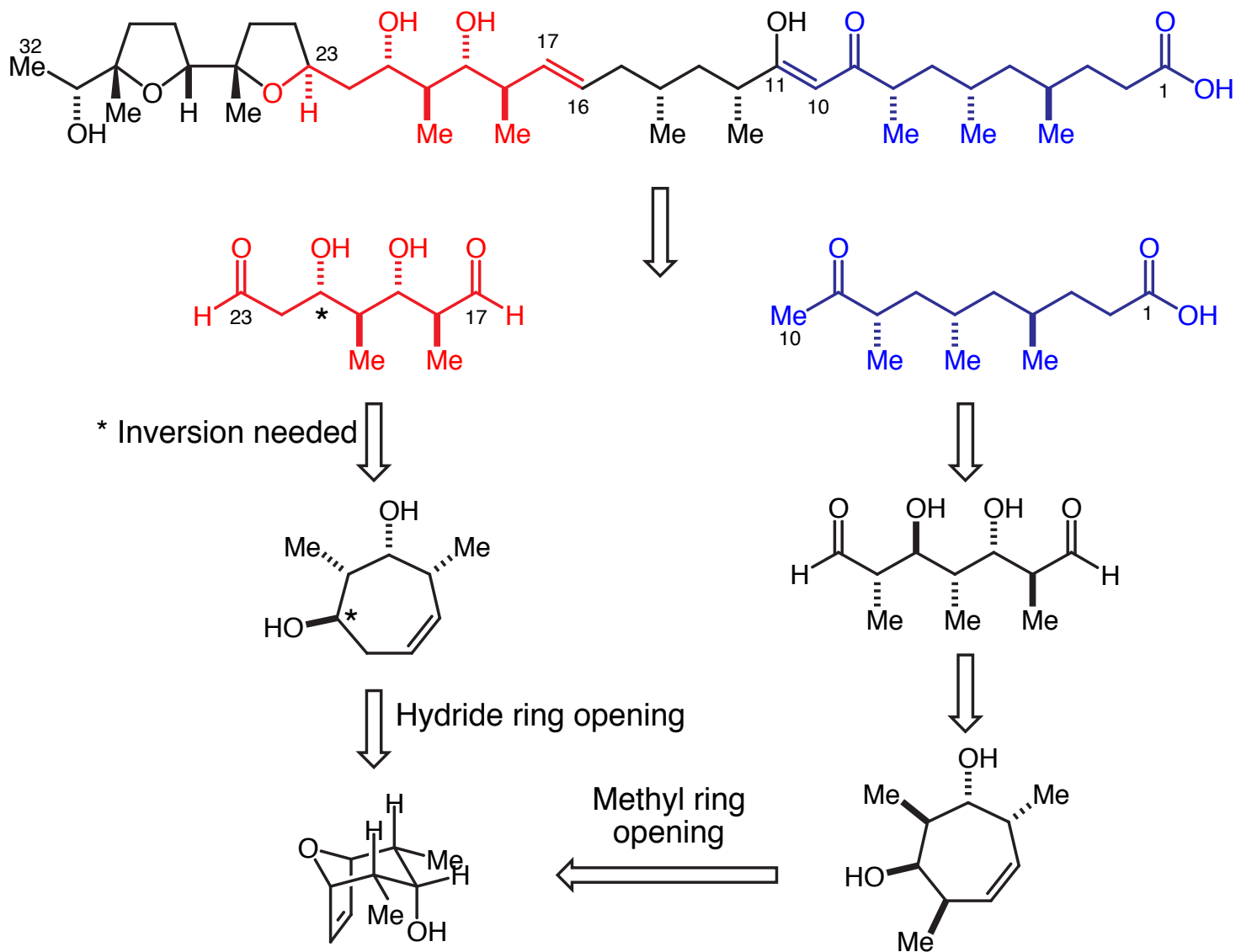
Lautens et al., *J. Am. Chem. Soc.* **2000**, 122, 1804.  
 Lautens et al., *Org. Lett.* **2000**, 2, 1971.

# Lautens' Enantioselective Oxabicyclic Ring Opening: Mechanism



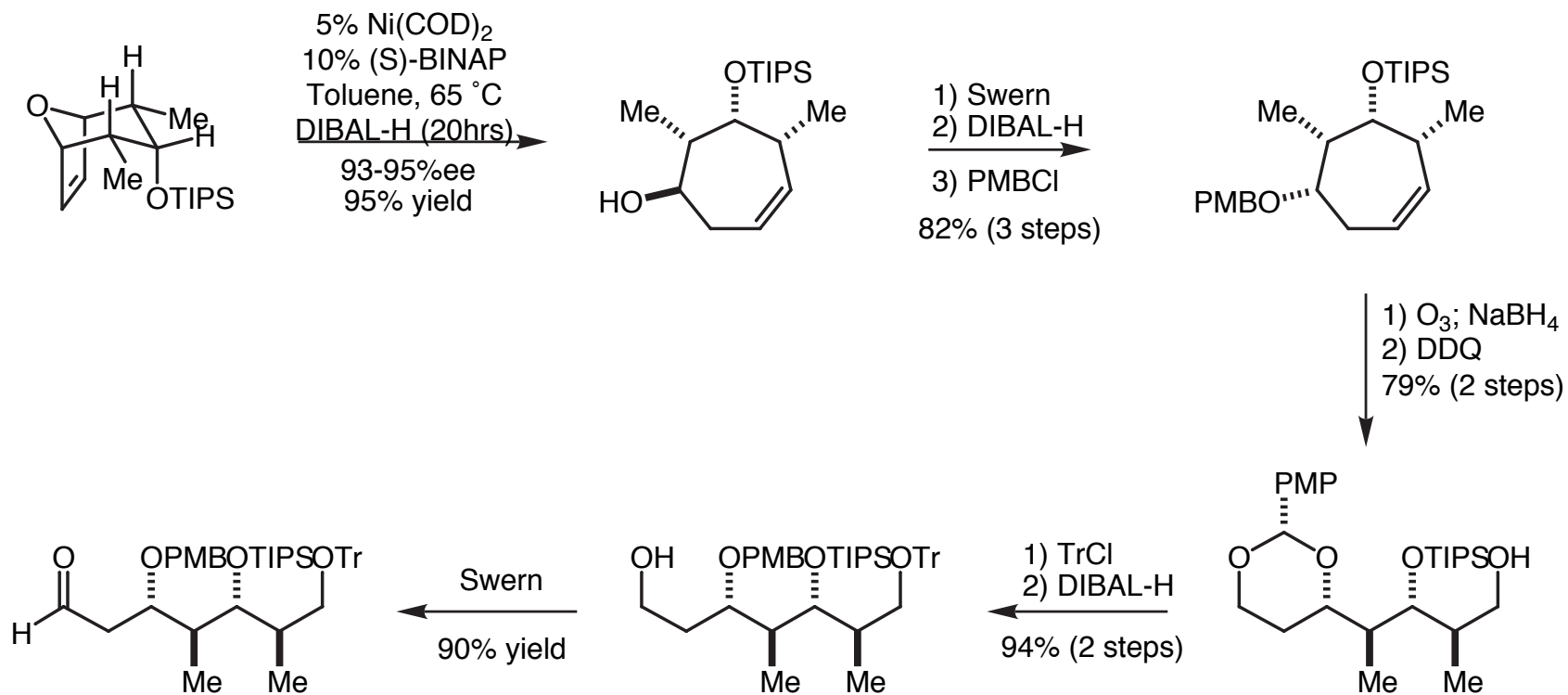
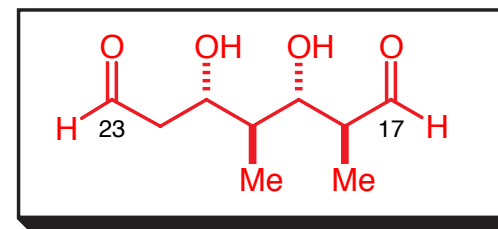
Lautens et al., *J. Am. Chem. Soc.* **2001**, 123, 6834.

# Lautens' Total Synthesis of Ionomycin



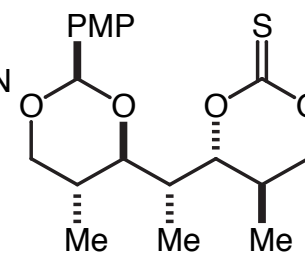
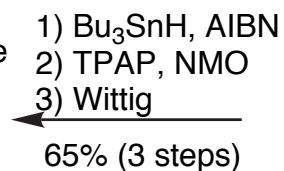
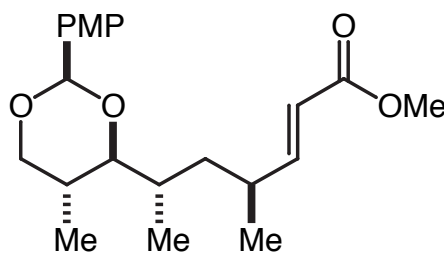
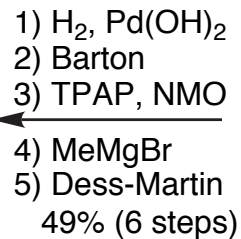
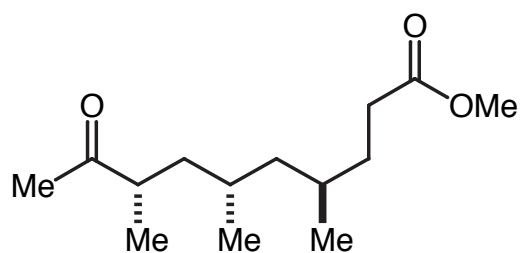
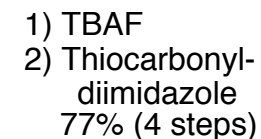
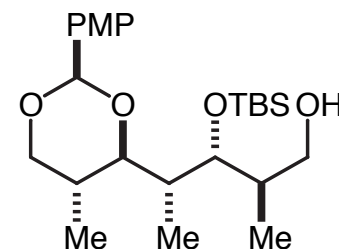
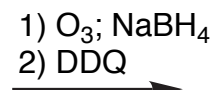
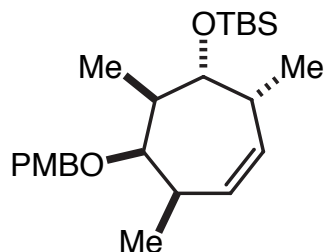
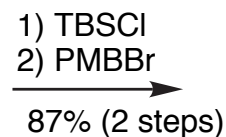
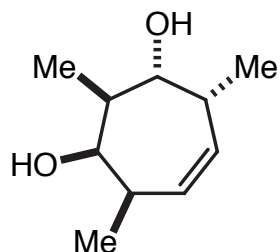
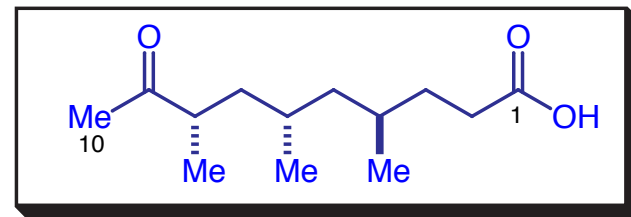
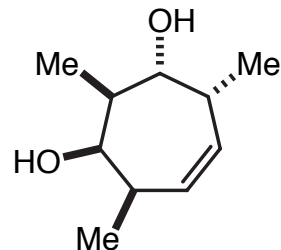
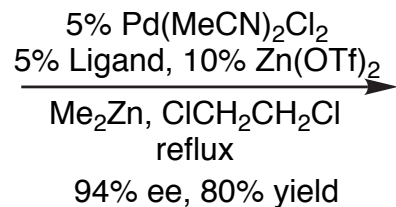
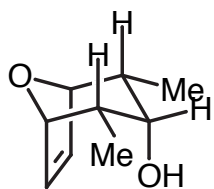


# Ionomycin: C<sub>17</sub>-C<sub>23</sub> Fragment

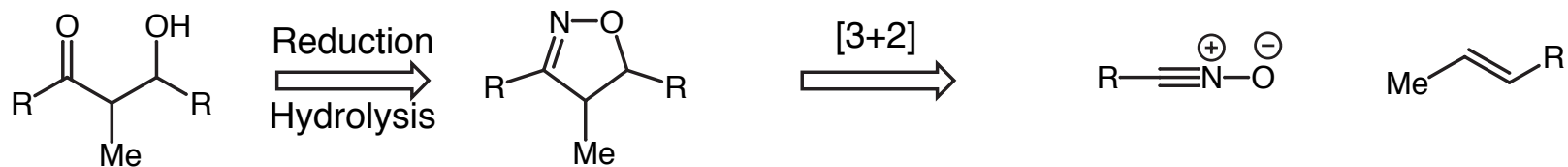


Lautens et al., *Org. Lett.* **2002**, *4*, 1879.

# Ionomycin: C<sub>17</sub>-C<sub>23</sub> Fragment

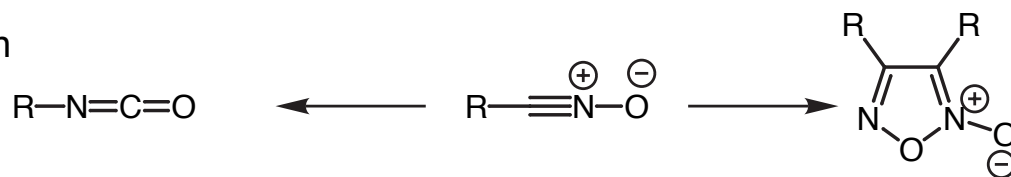


# Carreira's Hydroxyl Directed Nitrile Oxide Cycloaddition

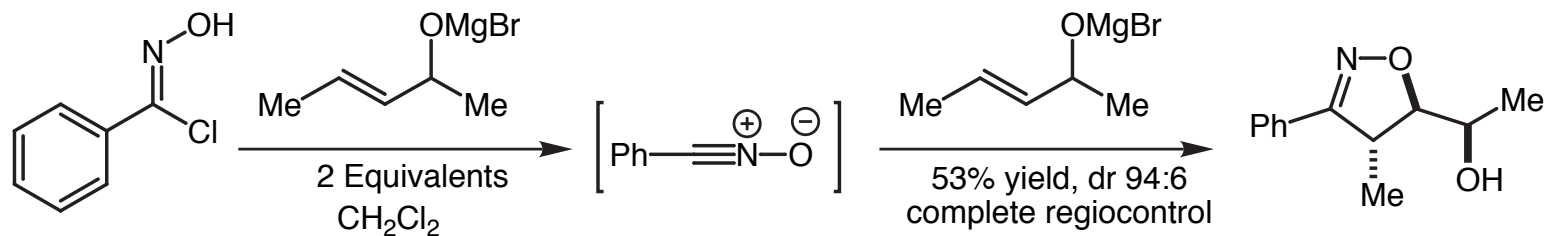


Problems:

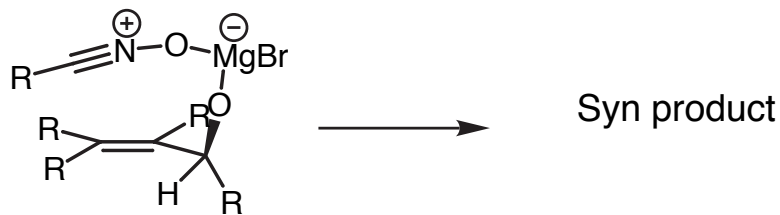
- 1) Nitrile oxides unstable; prone to dimerization, decomposition
- 2) Internal alkenes sluggish
- 3) Mixtures of regioisomers
- 4) Mixtures of stereoisomers



Kanemasa, 1994:



Stereochemical rationale:

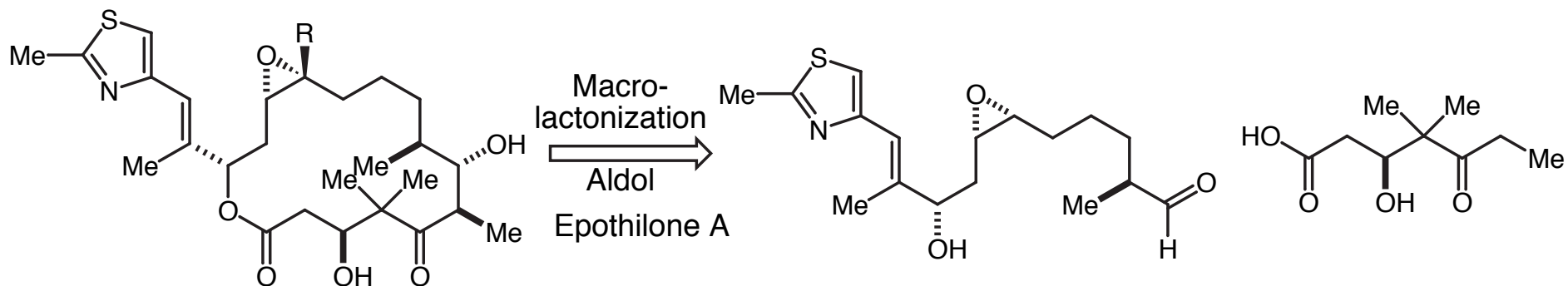


Magnesium alkoxides of allylic alcohols are substrates showing enhanced rate, regioselectivity and diastereoselectivity. Only aromatic nitrile oxides examined.

Kanemasa et al., *J. Am. Chem. Soc.* **1994**, 116, 2324.  
 Carreira et al., *Angew. Chem. Int. Ed.* **2001**, 40, 2082.

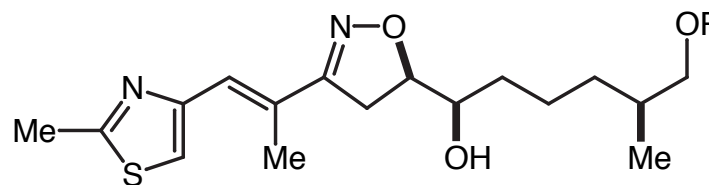
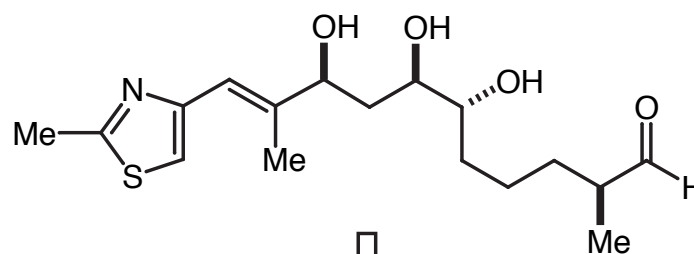
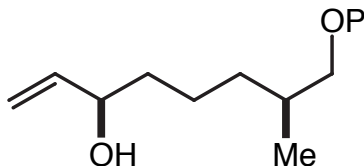
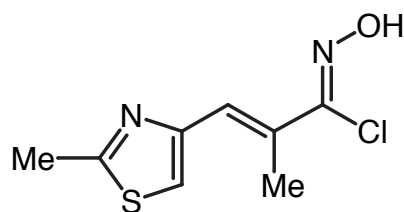


# Carreira's Epothilone Retrosynthesis



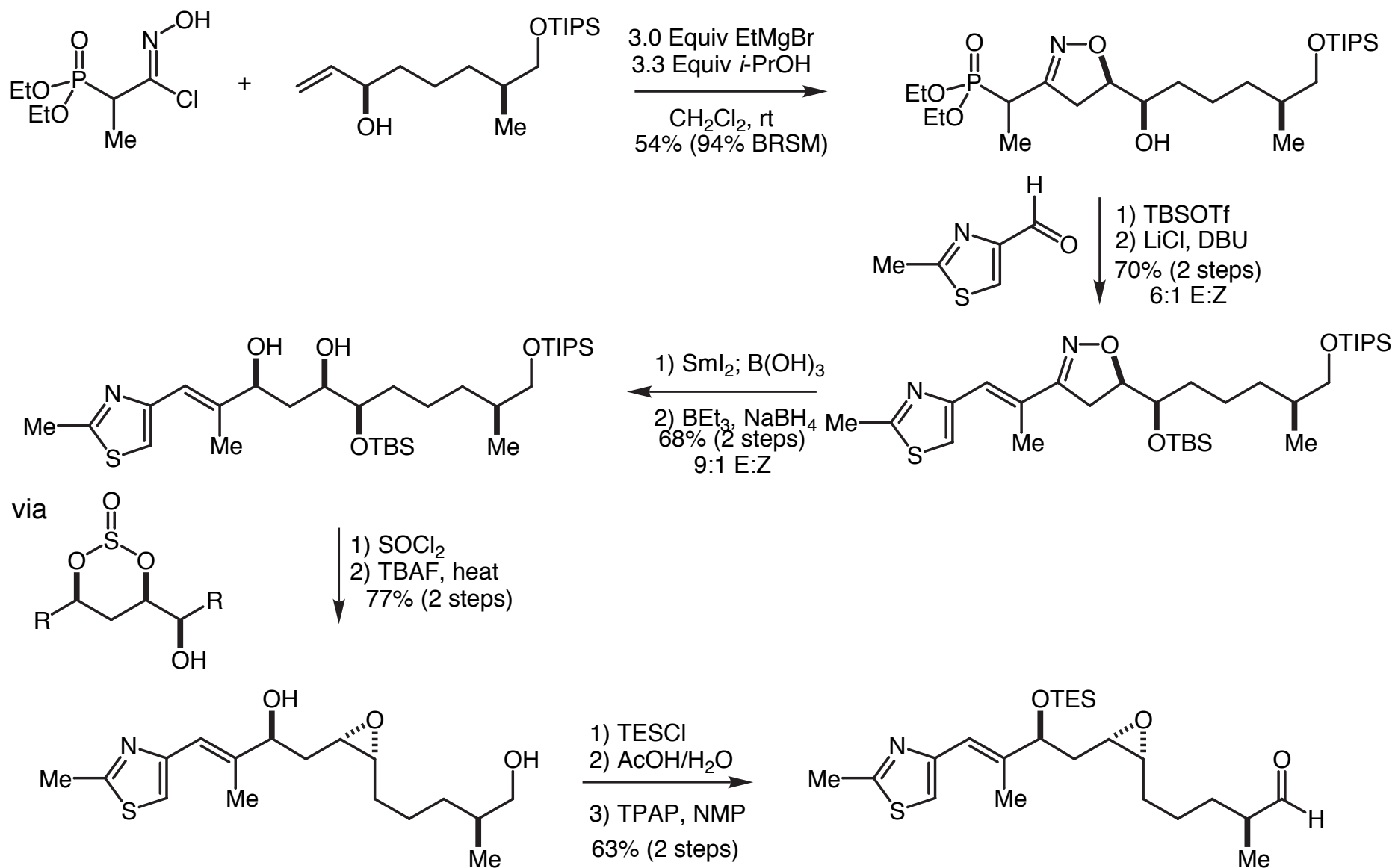
Epothilone A (R=H)  
Epothilone B (R=Me)

This hydroximinoyl chloride could not be prepared from the corresponding aldehyde.



Carreira and Bode, *J. Am. Chem. Soc.* **2001**, 123, 3611.  
Carreira and Bode, *J. Org. Chem.* **2001**, 66, 6410.

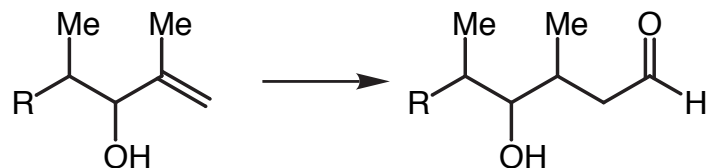
# Carreira's Epothilone A Fragment Synthesis



Carreira and Bode, *J. Am. Chem. Soc.* **2001**, 123, 3611.  
 Carreira and Bode, *J. Org. Chem.* **2001**, 66, 6410.

# Approaches Not Covered

## Bernhard Breit: Hydroformylation



*J. Org. Chem.* **2001**, 66, 4870. ←

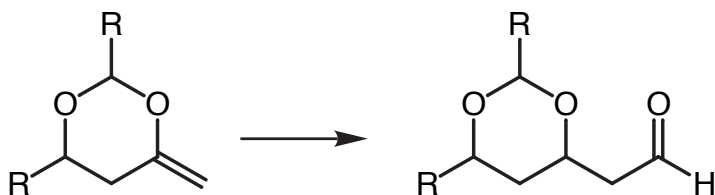
*Chem. Eur. J.* **1999**, 5, 2819.

*Eur. J. Org. Chem.* **1998**, 1123.

*Tet. Lett.* **1998**, 39, 1901.

*Liebigs Ann. Chem.* **1997**, 1841.

## James Leighton: Hydroformylation

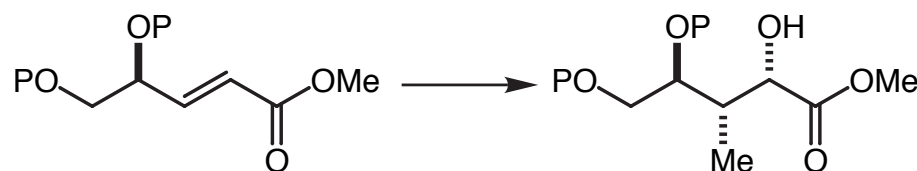


*J. Am. Chem. Soc.* **1997**, 119, 11118.

*Tet. Lett.* **1998**, 39, 6423.

*J. Am. Chem. Soc.* **2001**, 123, 11514.

## Stephen Hanessian: Conjugate Addition/Enolate Oxidation



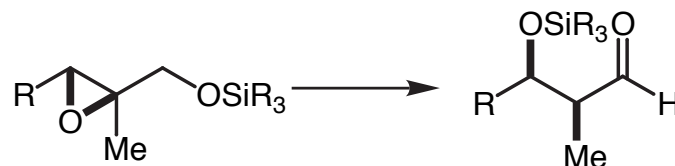
*Tet. Lett.* **1996**, 37, 7473.

*J. Am. Chem. Soc.* **1997**, 119, 10034.

*Tet. Lett.* **1999**, 40, 4627.

*J. Am. Chem. Soc.* **2001**, 123, 10200. ←

## Michael Jung: "Non-Aldol Aldol"



*Org. Lett.* **2001**, 3, 333.

*Tet. Lett.* **2000**, 41, 9719.

*Org. Lett.* **2000**, 2, 1669.

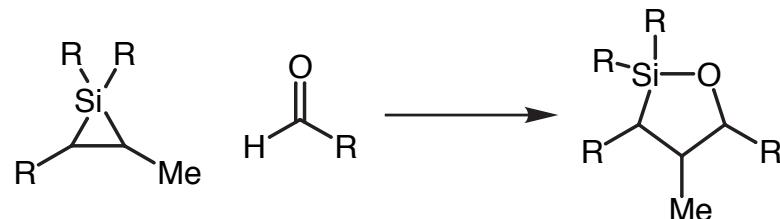
*Org. Lett.* **1999**, 1, 307.

*Tet. Lett.* **1999**, 40, 3129.

*J. Am. Chem. Soc.* **1997**, 119, 12150.

*J. Am. Chem. Soc.* **1993**, 115, 12208.

## Keith Woerpel: Silirane Ring Opening



*J. Am. Chem. Soc.* **1995**, 117, 10575.

*J. Org. Chem.* **1997**, 62, 4737.

*Tetrahedron* **1997**, 53, 16597.

*J. Am. Chem. Soc.* **1999**, 121, 949.

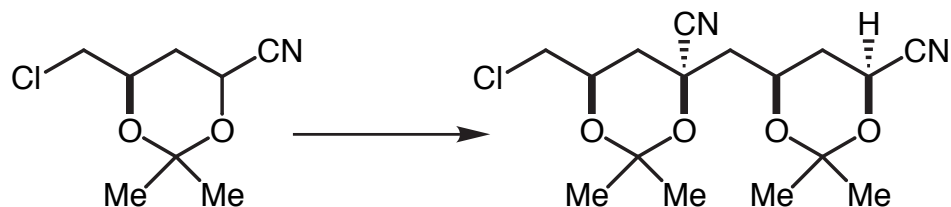
*Angew. Chem. Int. Ed.* **2000**, 39, 4295.

*Acc. Chem. Res.* **2000**, 33, 813.

*J. Am. Chem. Soc.* **2002**, 124, 6524.

# Summary

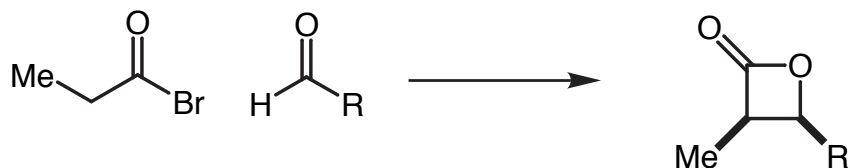
Rychnovsky: Cyanohydrin acetonide



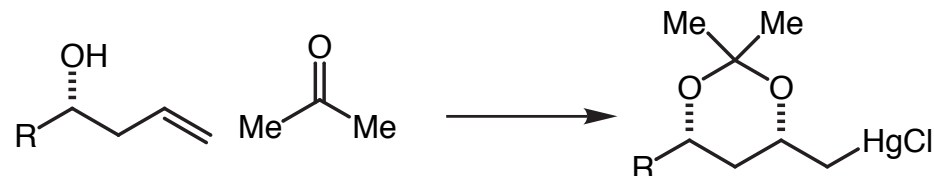
Smith: Dithiane linchpin



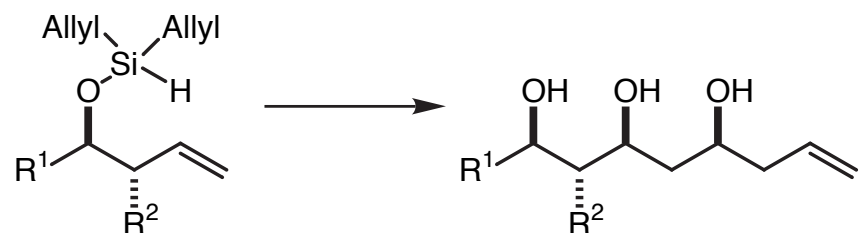
Nelson: Cyclocondensation



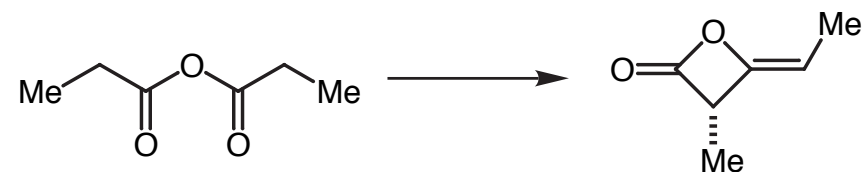
Leighton: Hemiacetal oxymercuration



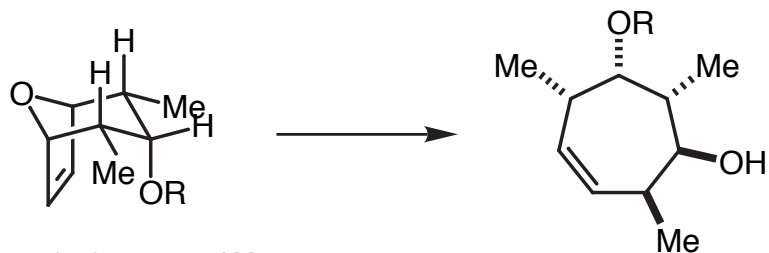
Leighton: Silylformylation



Calter: Methylketene dimerization



Lautens: Enantioselective ring opening



Carreira: Directed nitrile oxide cycloaddition

