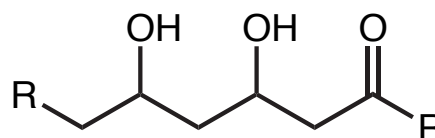
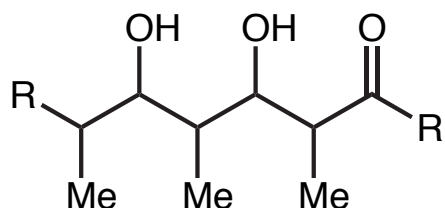


Non-Aldol Approaches to the Synthesis of Polyketide Natural Products



Evans Group Evening Seminar
Friday June 21, 2002
Travis Dunn

Keywords: Polypropionate, Polyol, Total Synthesis

Outline of Seminar

Approaches covered in this seminar:

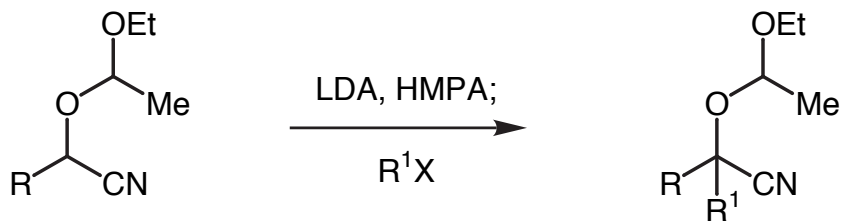
- 1) Cyanohydrin acetonide alkylation (Rychnovsky)
- 2) Dithiane alkylation (Mori, Smith)
- 3) Acyl halide/aldehyde cyclocondensation (Nelson)
- 4) Hemiacetal oxymercuration (Leighton)
- 5) Silylformylation (Leighton)
- 6) Methylketene dimer ring opening (Calter)
- 7) Oxabicyclic ring opening (Lautens)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

Bond constructions not covered in this seminar:

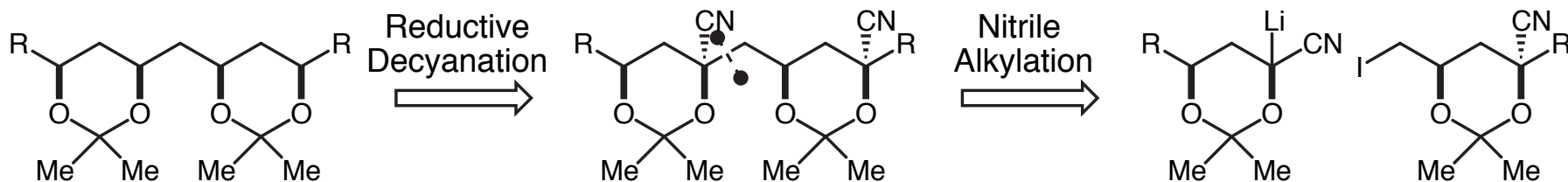
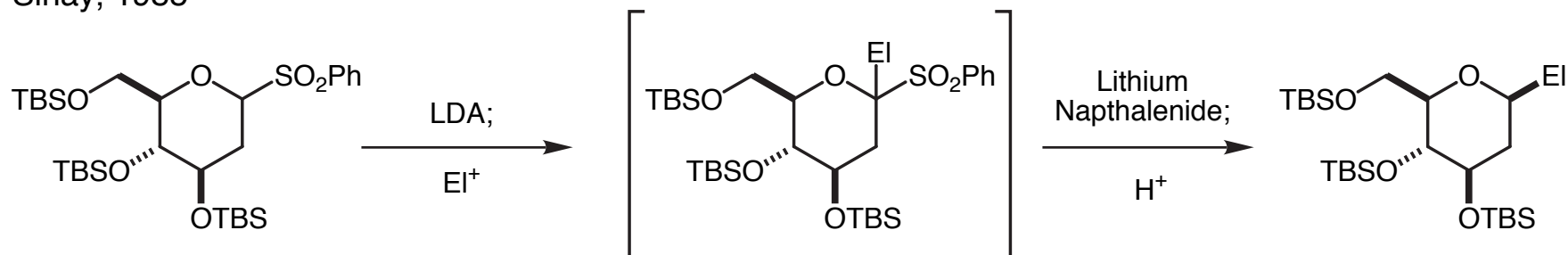
- 1) Metal enolate reactions
- 2) Mukaiyama aldol reactions
- 3) Allylmetal based reactions
(e.g. silanes, stannanes, boranes, borinates)

Rychnovsky's Cyanohydrin Acetonide Alkylation

Stork, 1971

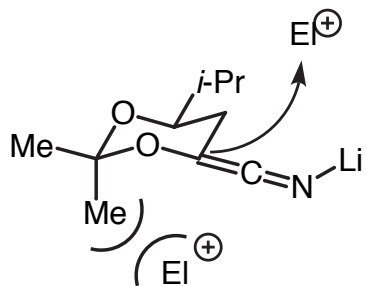
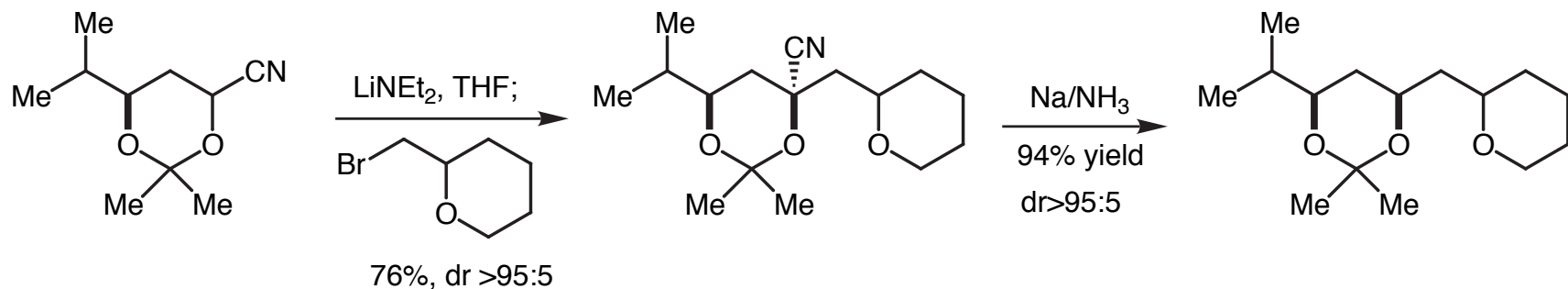
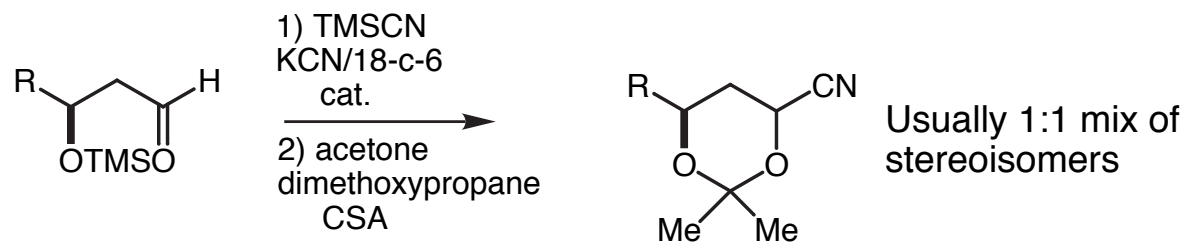


Sinay, 1985

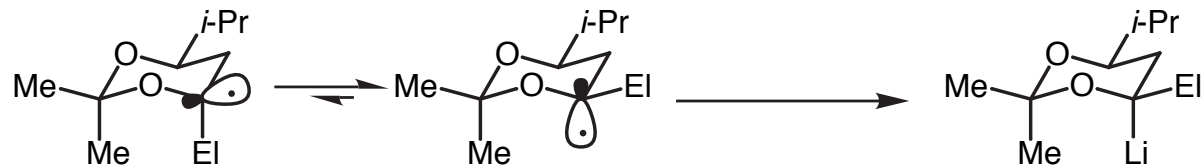


Rychnovsky and Sinz, *Topics in Current Chem.* **2001**, 216, 51-92.

Rychnovsky's Cyanohydrin Acetonide Alkylation



Equatorial alkylation due to steric shielding by methyl of acetonide.



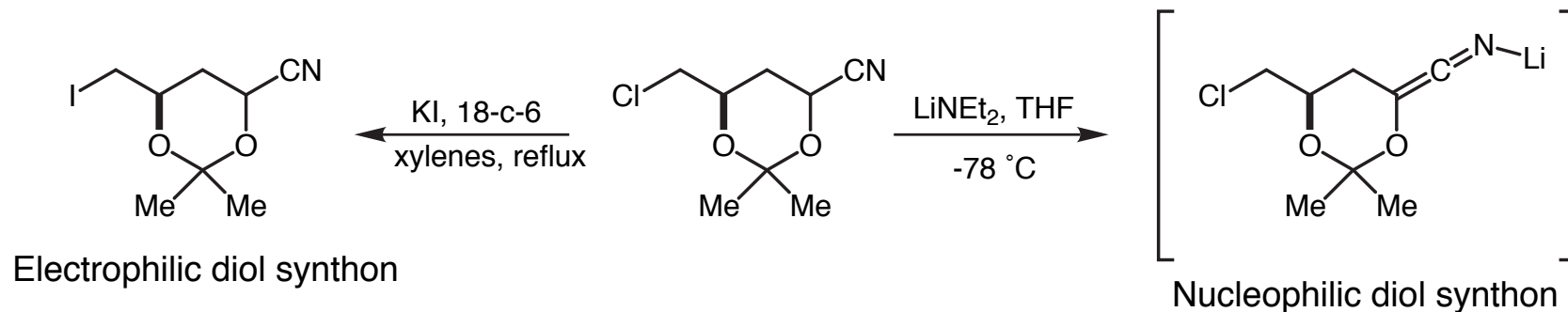
Axial radical more stable by ca. 3.5 kcal/mol (calc.)

Configurationally stable at low temperature

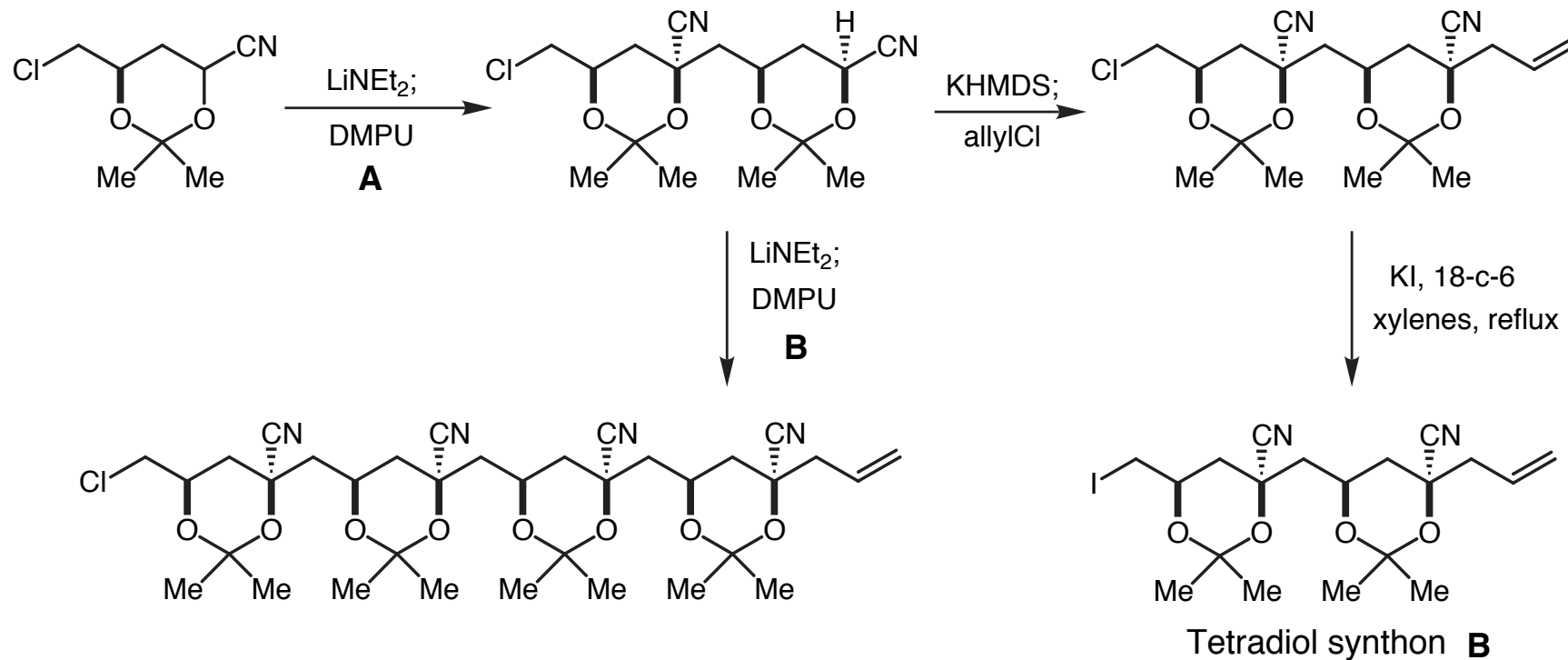
Rychnovsky and Sinz, *Topics in Current Chem.* **2001**, 216, 51-92.

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

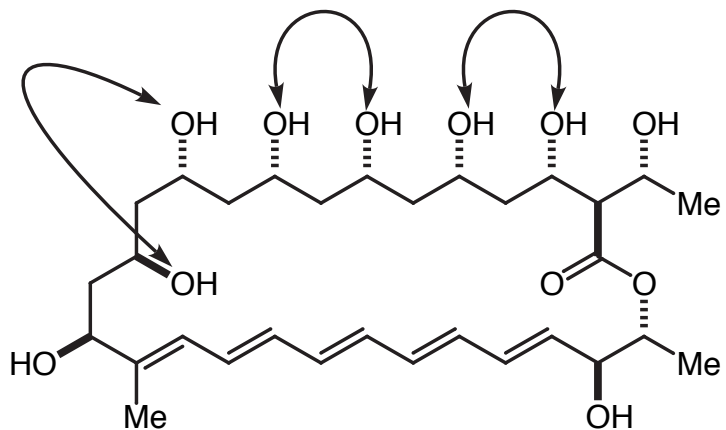
Iterative and Convergent Syn Polyol Synthesis



A

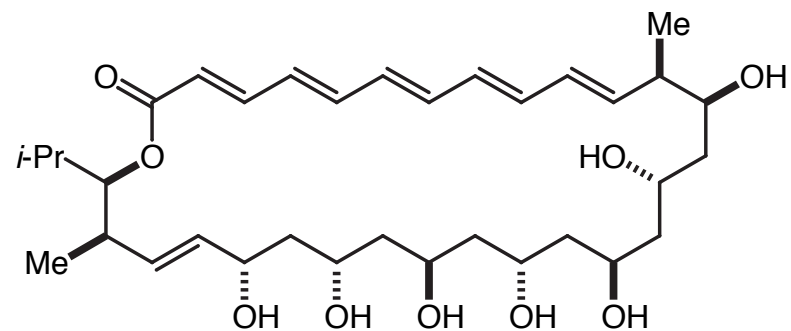


Total Syntheses Using Cyanohydrin Acetonide Methodology



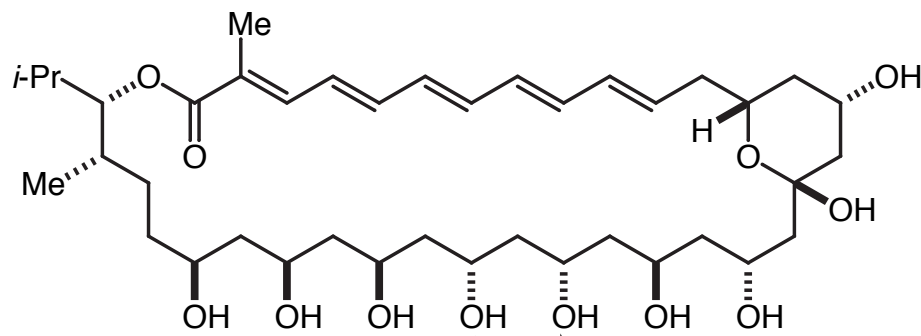
Filipin III

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



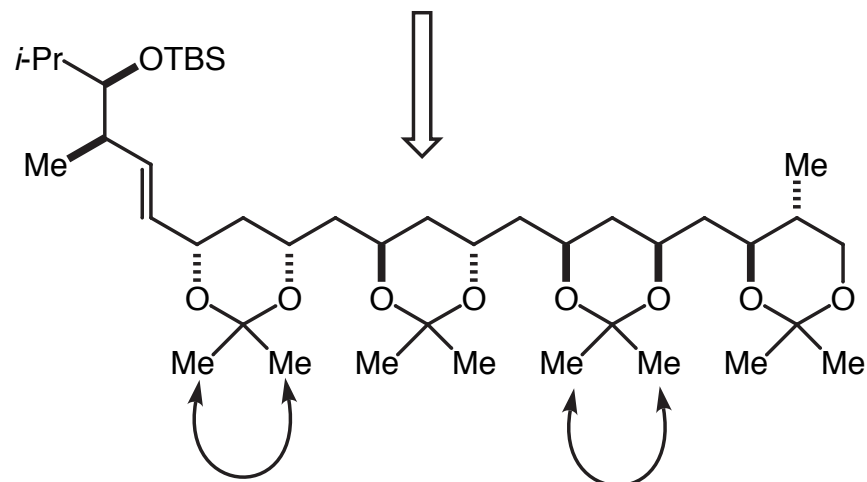
(-)-Roxaticin

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

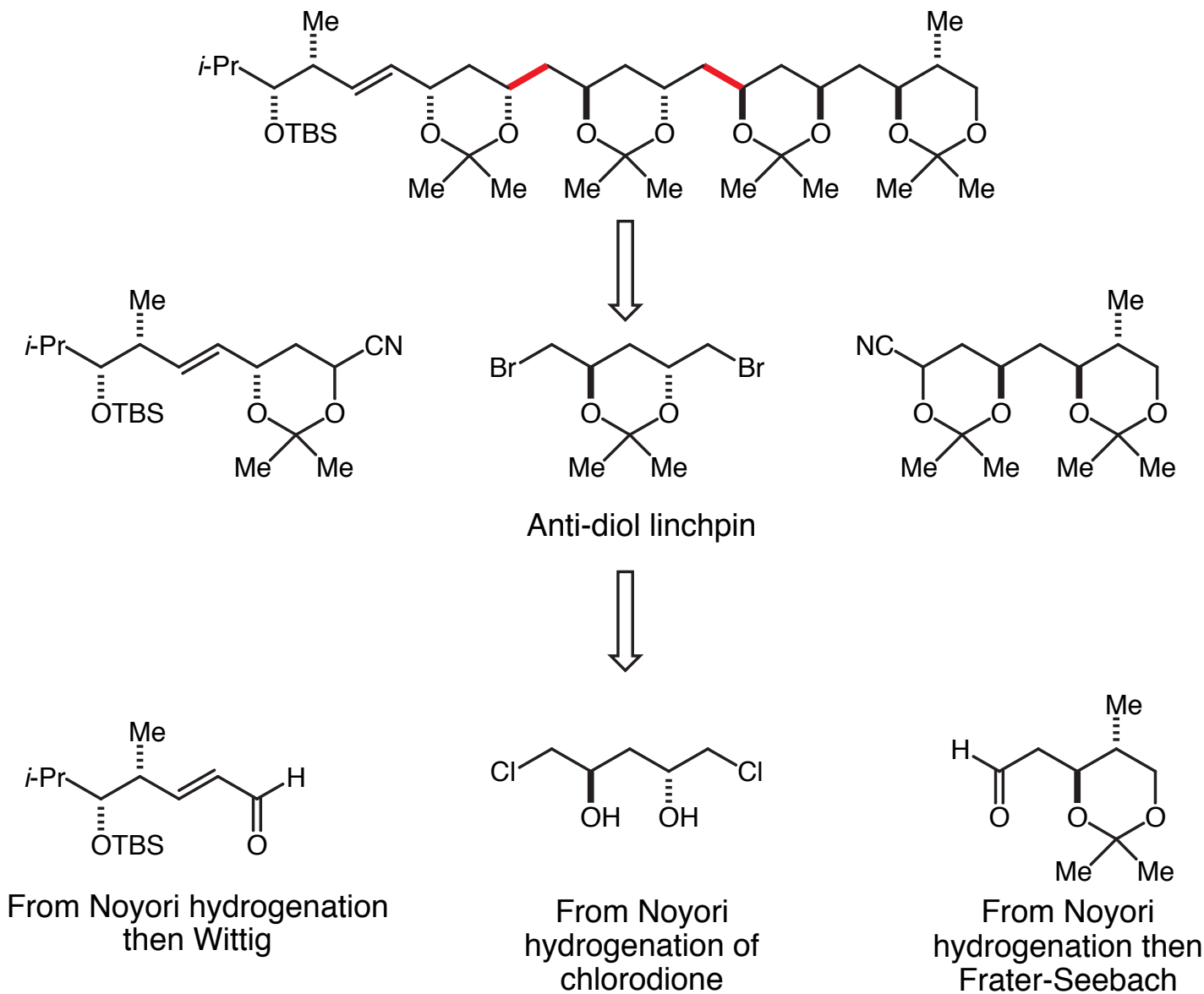


Roflamycoin

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

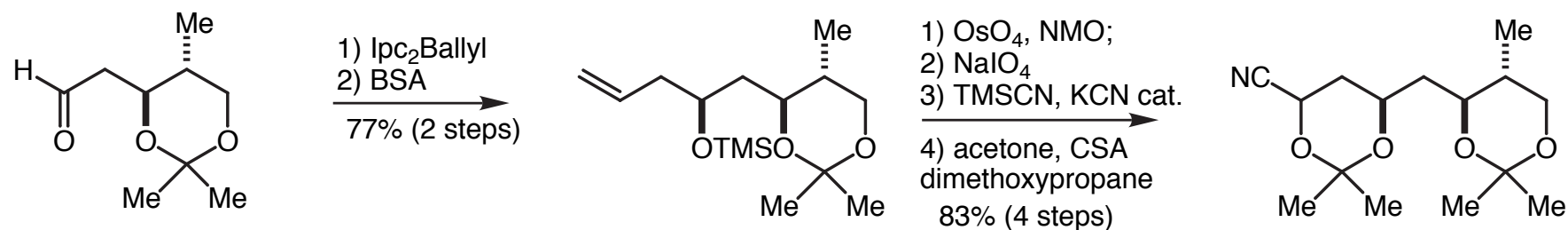
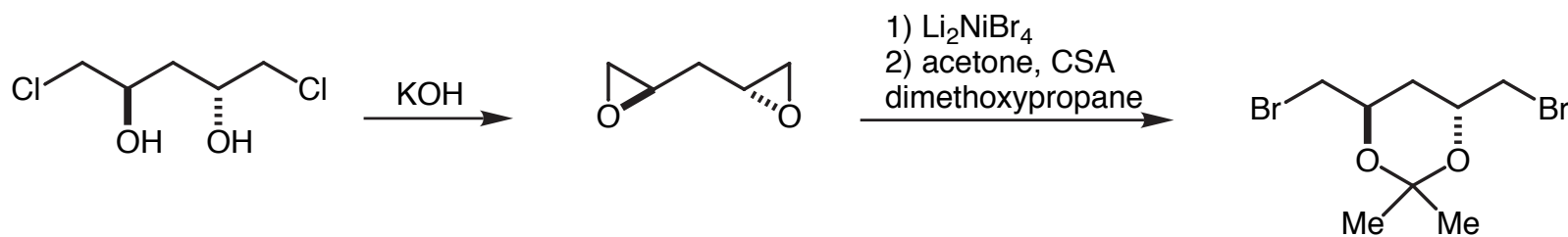
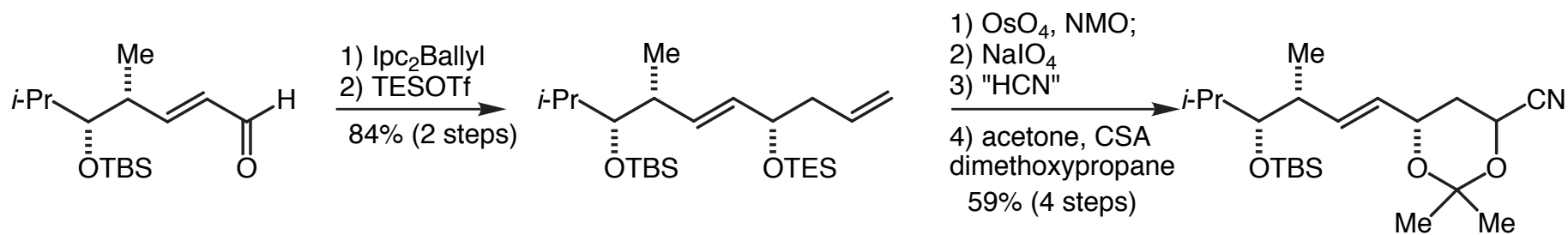


Roxaticin Polyol Segment Retrosynthesis



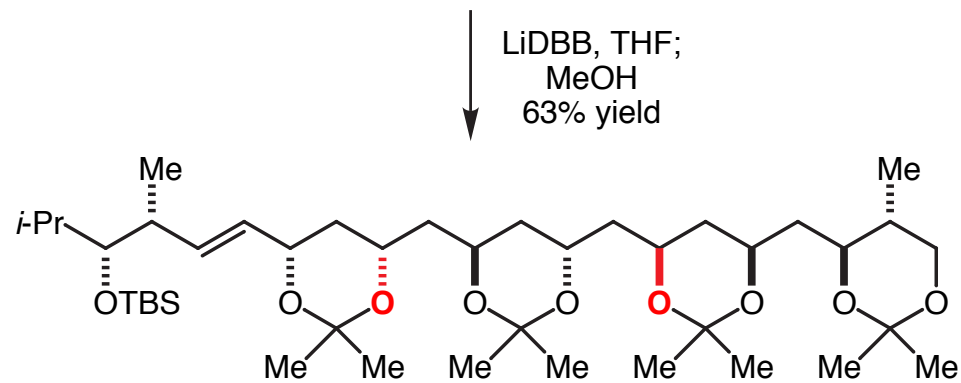
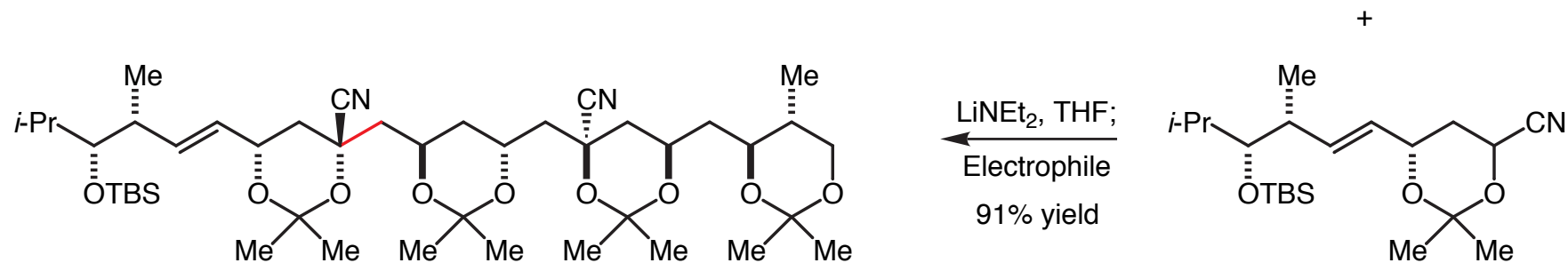
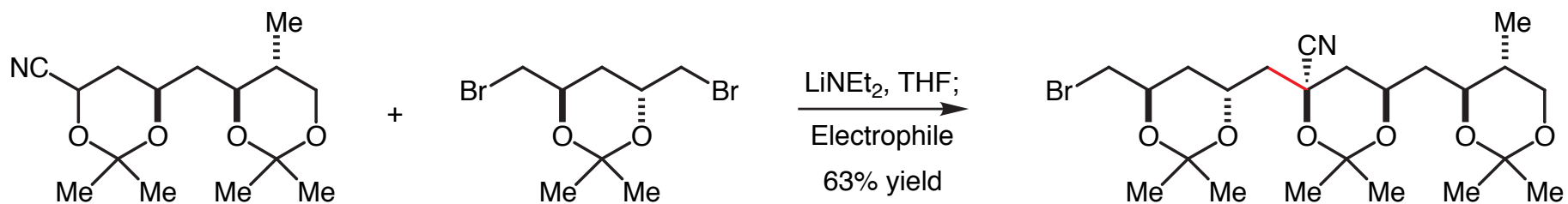
Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, 116, 1753.

Roxaticin Polyol Segment Fragment Synthesis



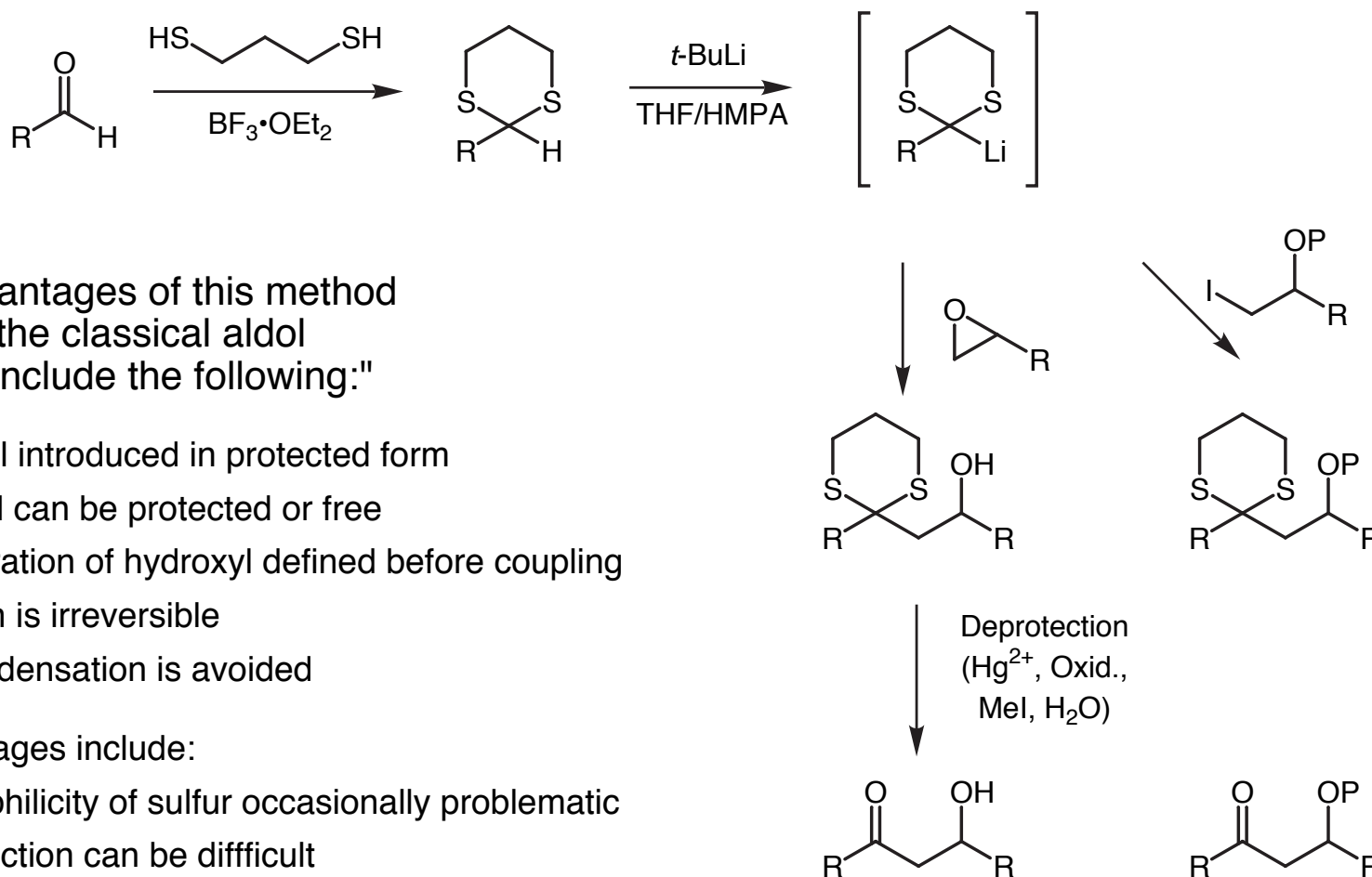
Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, 116, 1753.

Roxaticin Polyol: Fragment Coupling



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

Smith: Dithiane Coupling



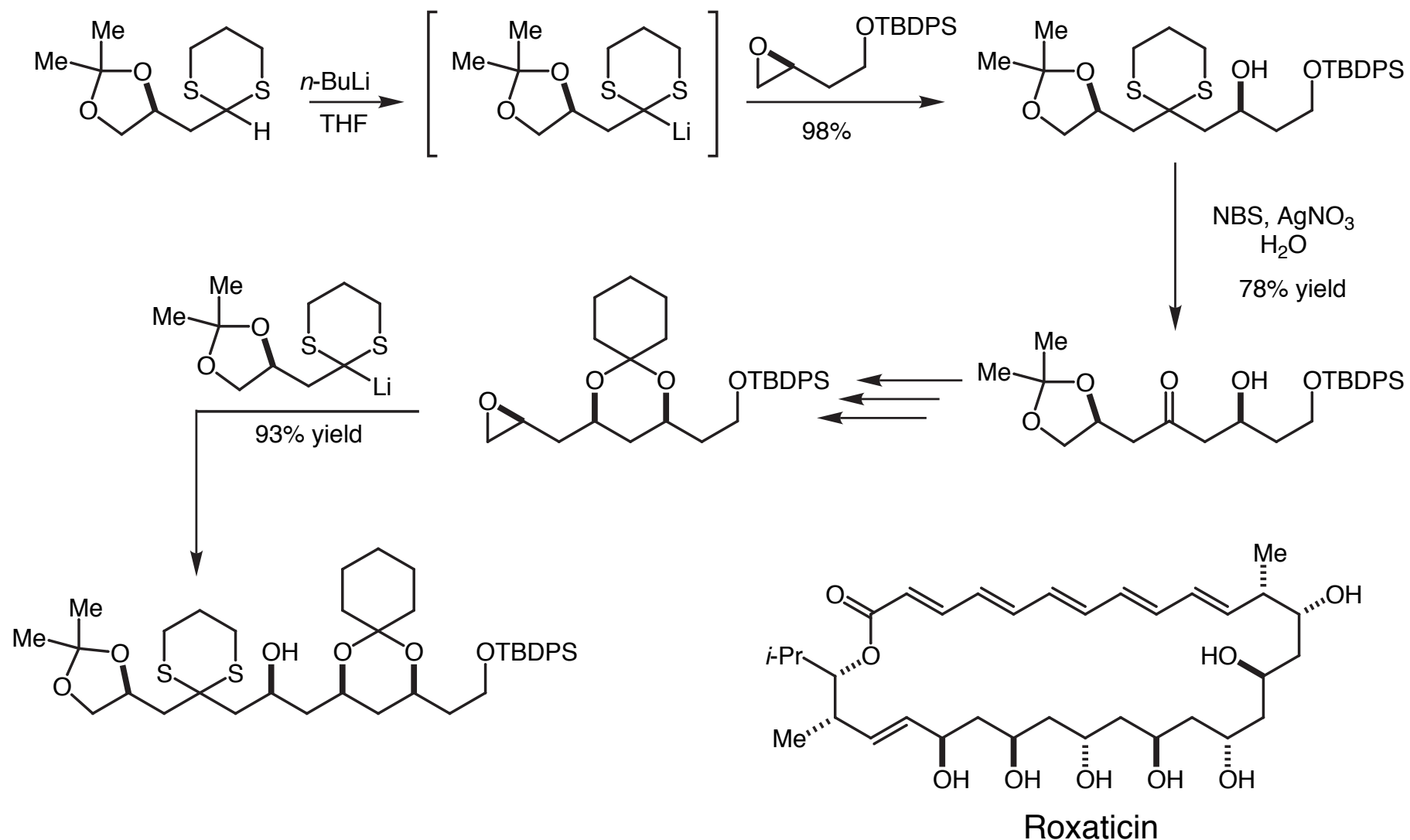
"The advantages of this method vis-a-vis the classical aldol reaction include the following:"

- 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



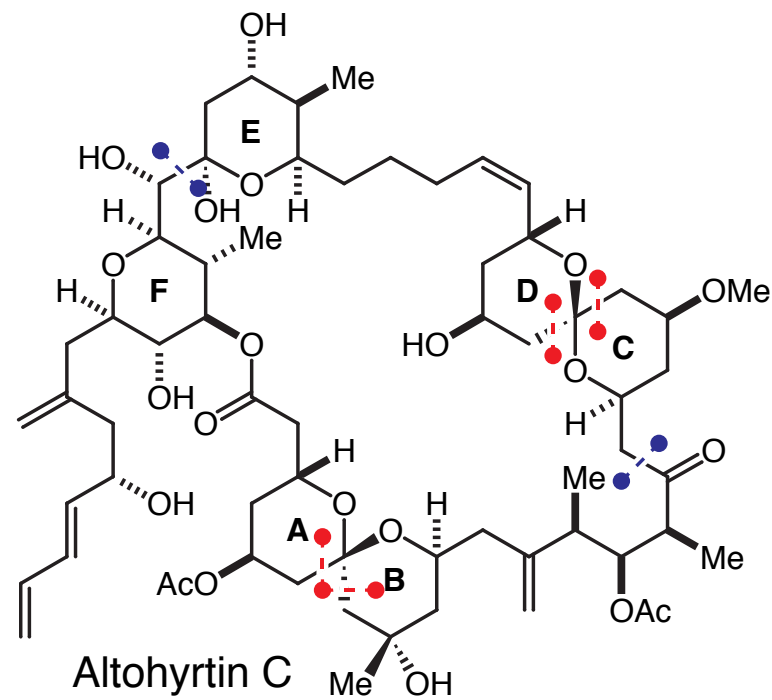
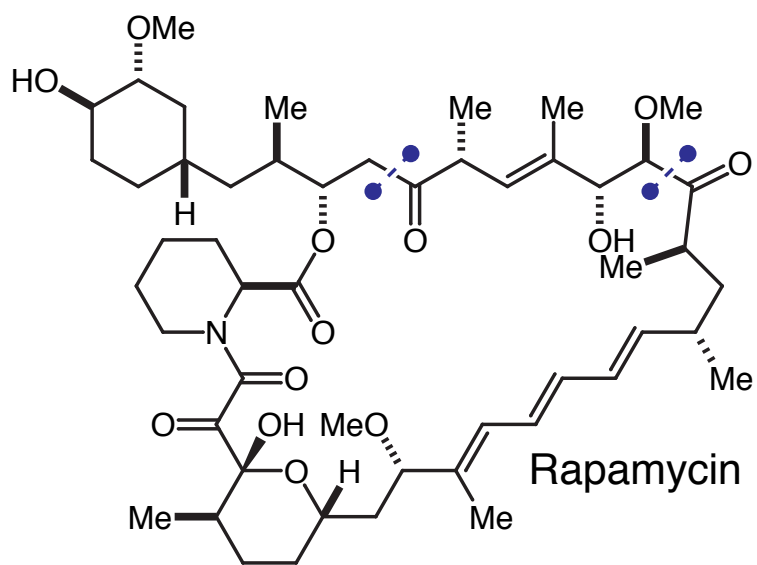
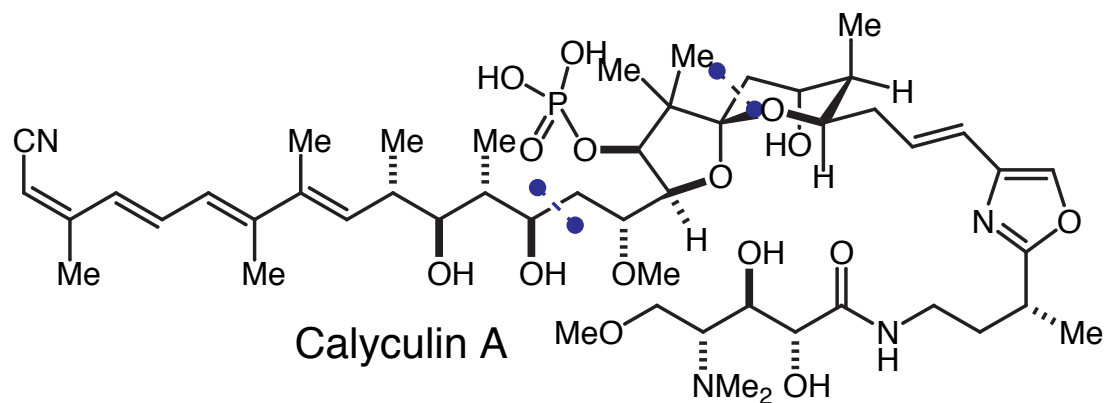
Tet. Lett. **1988**, 29, 5419, 5423.

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

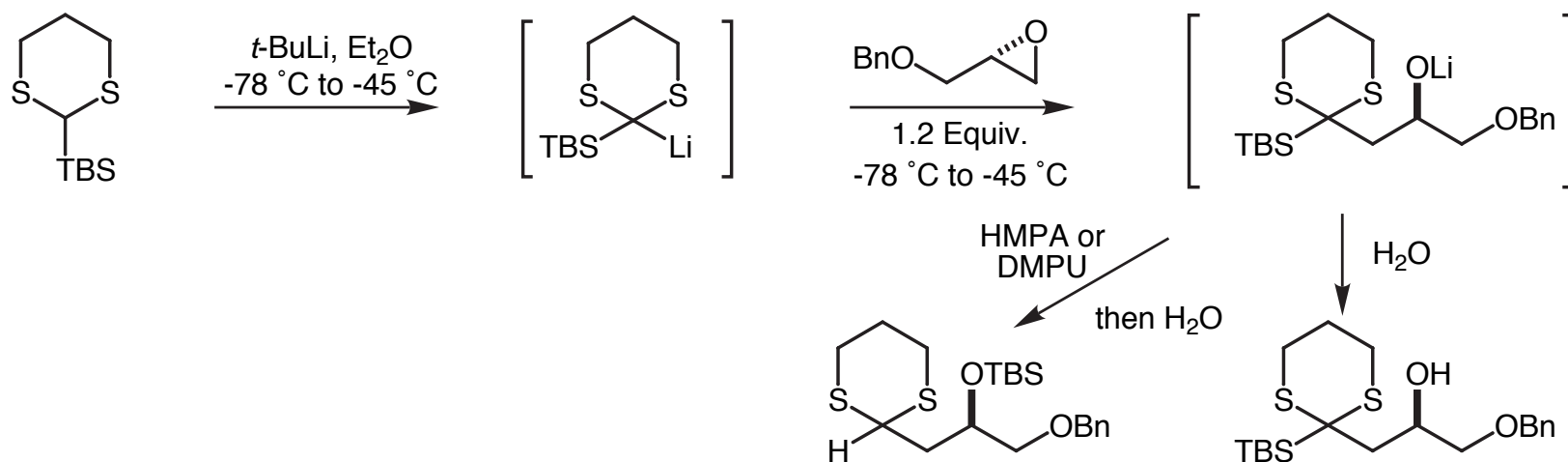
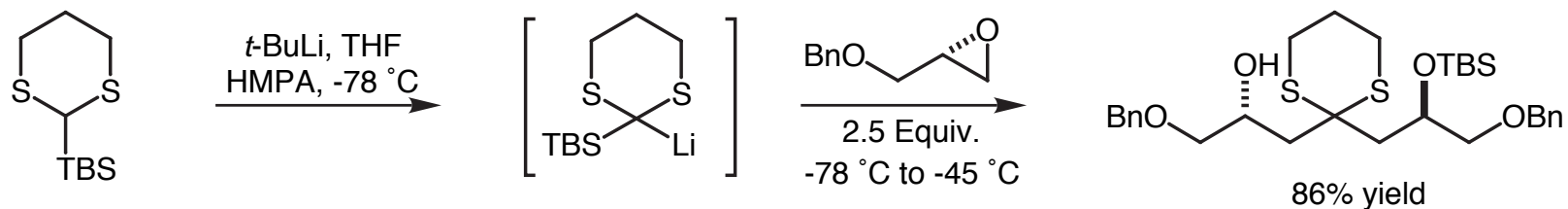
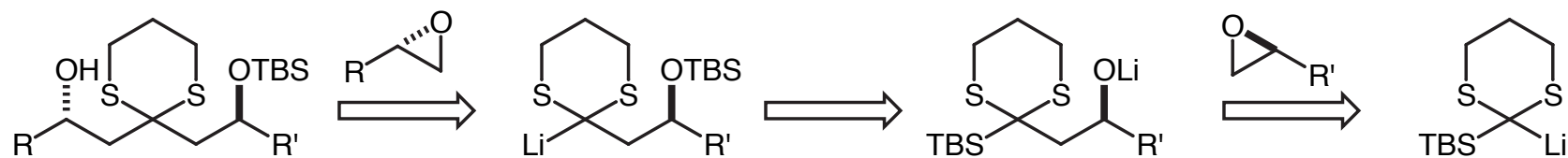
Roxaticin synthesis

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

Smith Syntheses Utilizing Dithiane Coupling



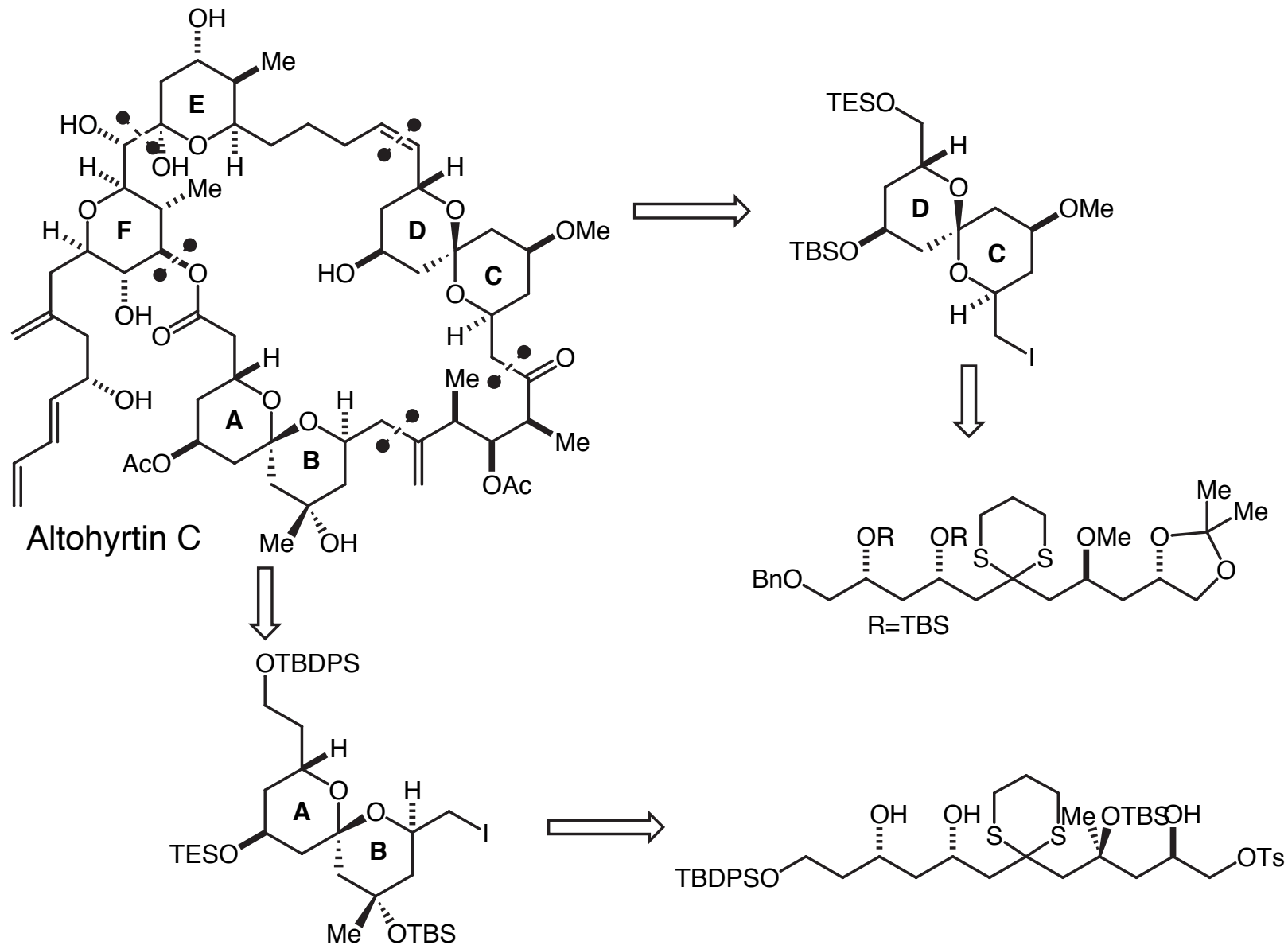
Smith: Multicomponent Dithiane Coupling via Brook Rearrangement



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

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

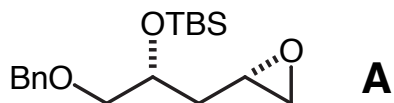
Smith: Altohyrtin C Fragment Retrosyntheses



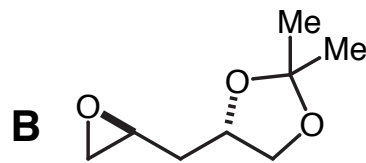
Smith et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 191.

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

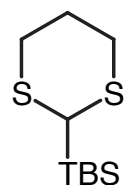
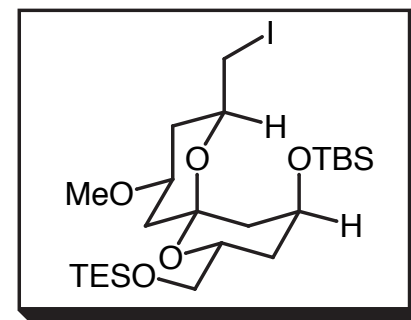
Smith: Altohyrtin C CD Ring Fragment



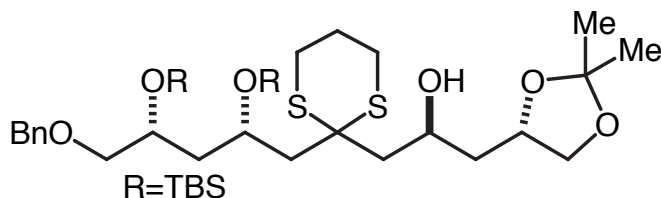
9 steps from glycerol acetonide



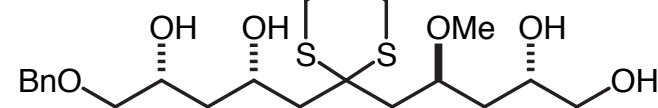
6 steps from glyceraldehyde acetonide



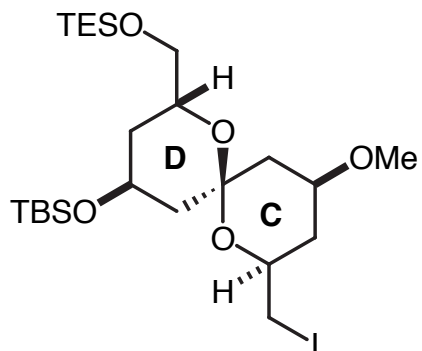
$t\text{-BuLi, Et}_2\text{O}$;
A;
B, HMPA
72%



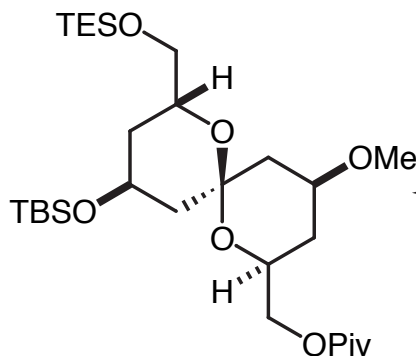
1) NaH, MeI
2) HCl, MeOH
80% (2 steps)



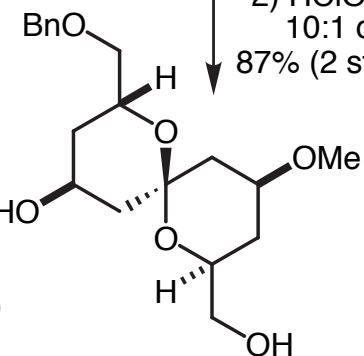
1) $\text{Hg}(\text{ClO}_4)_2$
 CaCO_3
2) HClO_4
10:1 dr
87% (2 steps)



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

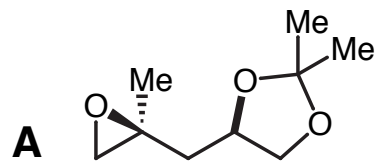


1) PivCl
2) TBSCl
3) H_2 , Pd/C
4) TESCl
57% (4 steps)

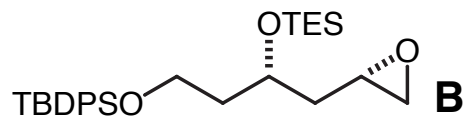


Smith et al., *Tet. Lett.* **1997**, 38, 8671.

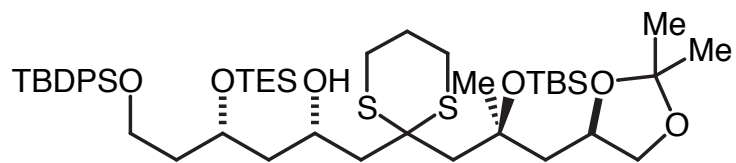
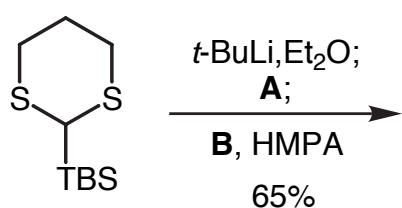
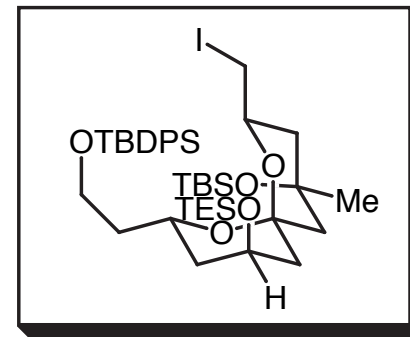
Smith: Althohyrtin C AB Ring Fragment



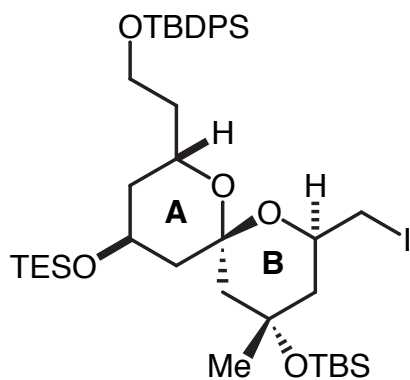
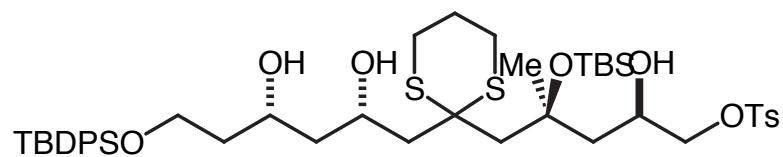
5 steps from glyceraldehyde acetonide



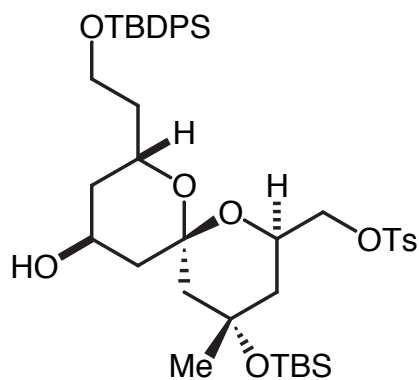
5 steps from (+)lpc₂Ballyl



1) TFA/H₂O
2) TsCl
79% (2 steps)



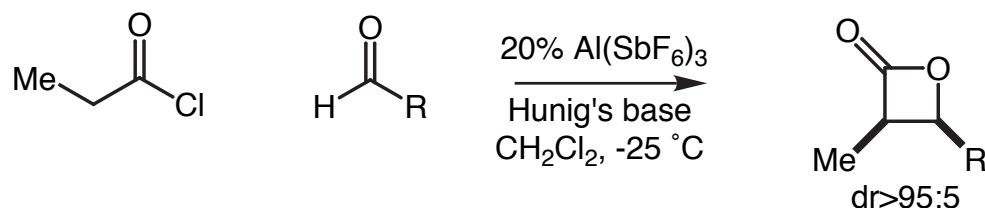
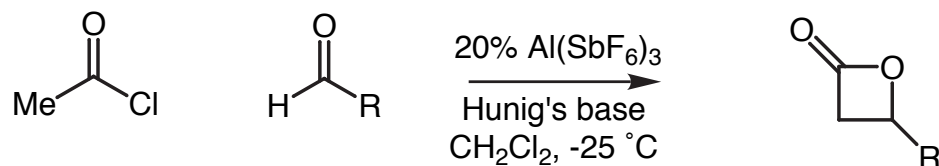
1) TESOTf
2) Lil
96% (2 steps)



Hg(ClO₄)₂
CaCO₃
81%, 26:1 dr

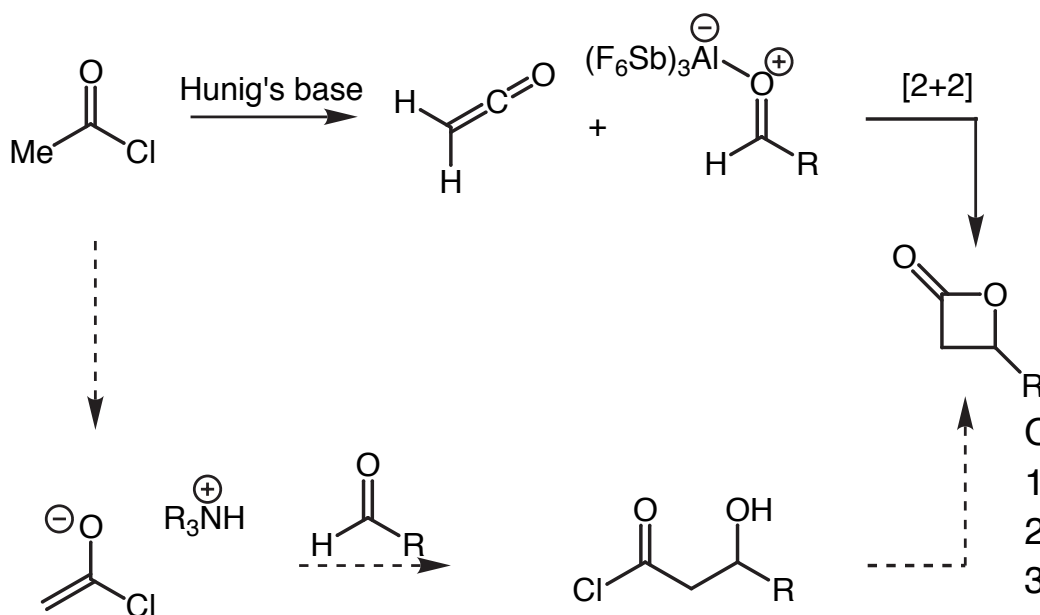
Smith et al., *Tet. Lett.* **1997**, 38, 8675.

Nelson's Acyl Halide/Aldehyde Cyclocondensation



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

Mechanism:



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

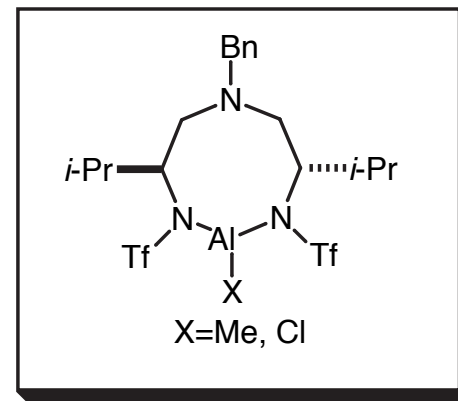
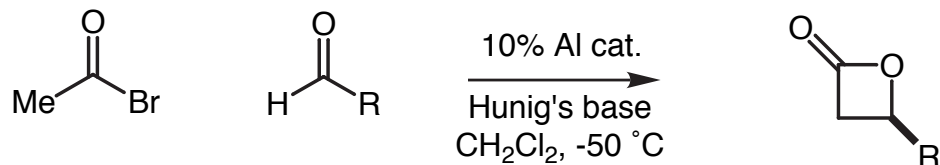
Observations:

- 1) Ketene observed in ¹³C NMR
- 2) Enolate not observed in ¹³C NMR
- 3) No lactone formed in absence of Al³⁺

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

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

Nelson's Enantioselective Acyl Halide/Aldehyde Cyclocondensation

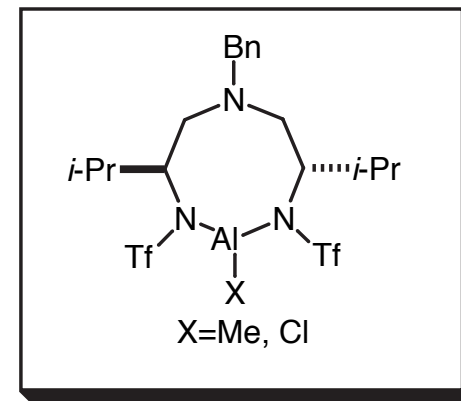
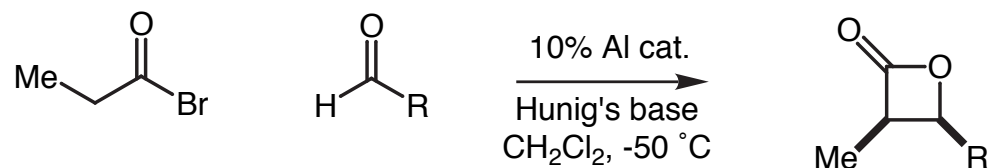


Alpha branched, unsaturated aldehydes afford low ee, yield

Aldehyde	%ee	% yield
PhCH ₂ CH ₂ CHO	92	93
Me ₂ CHCH ₂ CHO	93	80
BnOCH ₂ CHO	91	91
CH ₂ =CH(CH ₂) ₈ CHO	91	91
TBDPSOCH ₂ CHO	89	74
BnOH ₂ 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

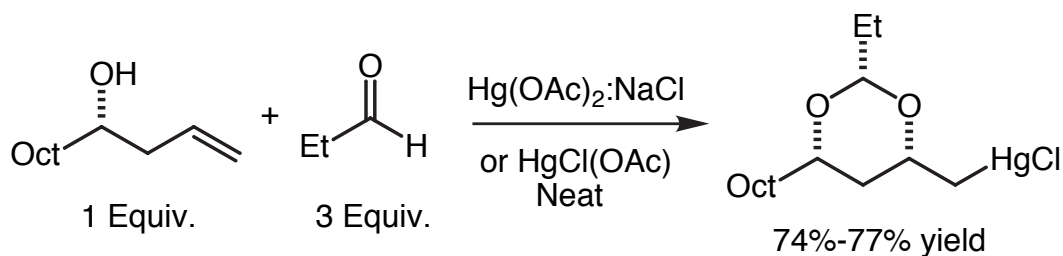
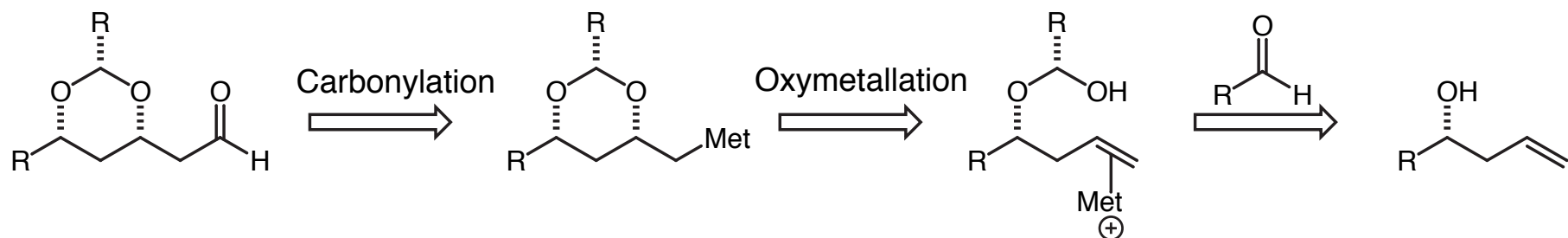


Other aliphatic aldehydes, unsaturated enals afford low yields, ee's.

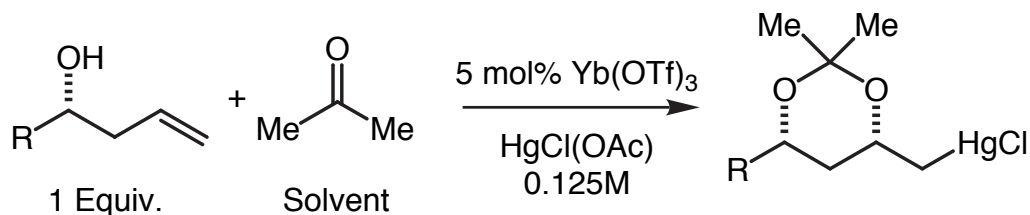
Aldehyde	%ee	dr	% yield
BnOCH ₂ CHO	94	88:12	78
BnOH ₂ CC≡CCHO	94	91:9	85
C ₆ H ₁₁ C≡CCHO	93	98:2	85
TMSC≡CCHO	93	99:1	90
PhC≡CCHO	91	99:1	83

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.

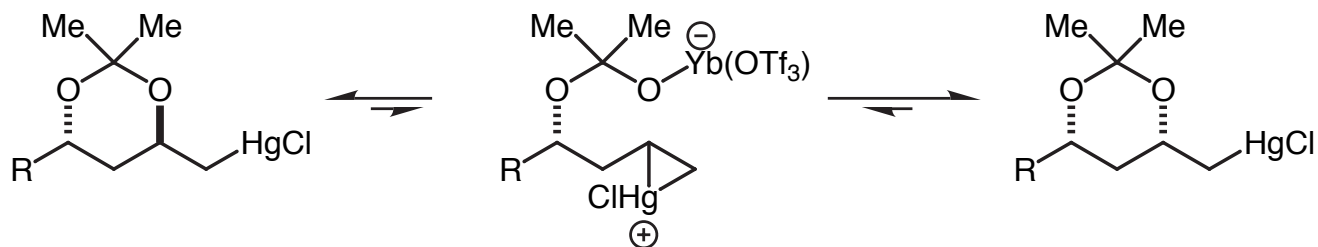
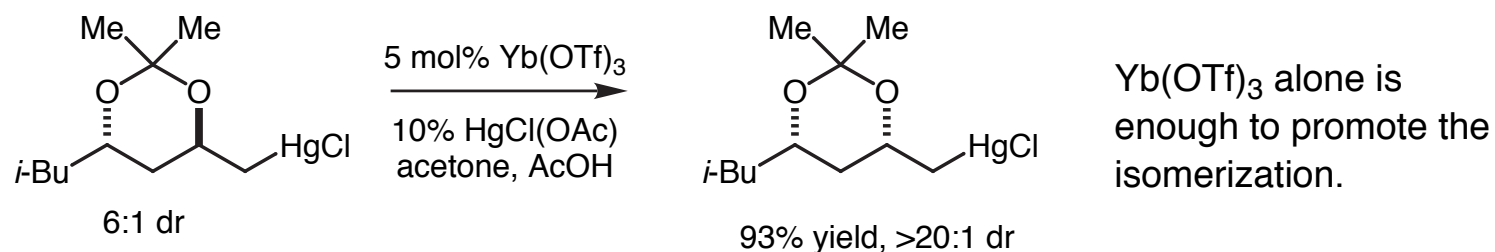
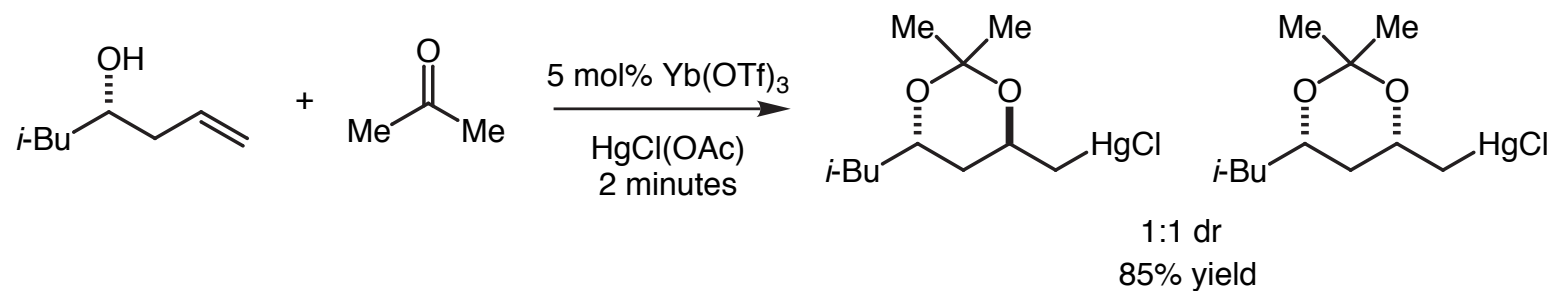


Acetone, benzaldehyde now useful substrates. Yields typically 70-85%, dr at least 20:1.

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

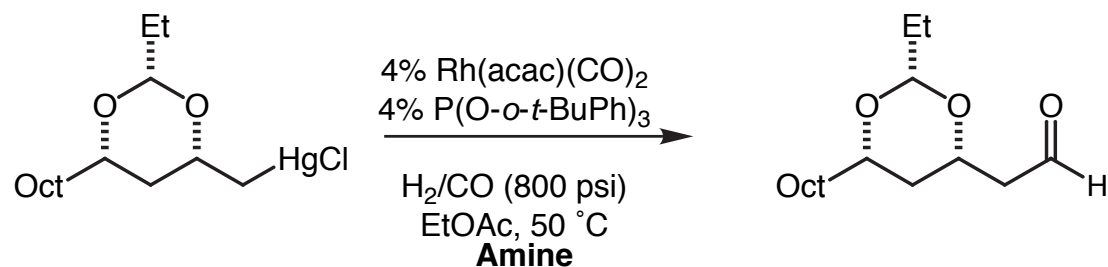
Leighton's Oxymercuration of Hemiacetals

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

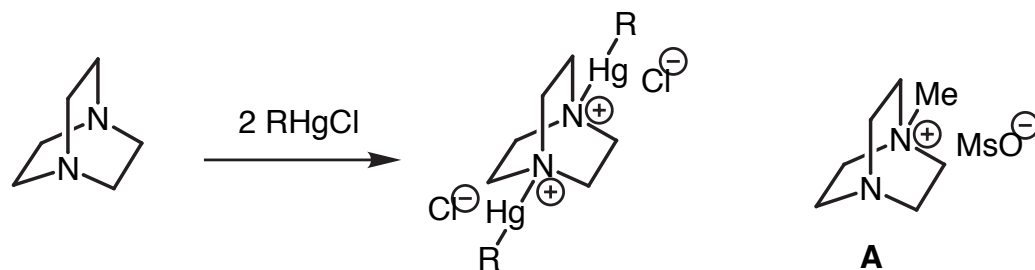


Leighton and Sarraf, *Org. Lett.* **2000**, 2, 403.
Leighton et al., *Org. Lett.* **2000**, 2, 3197.

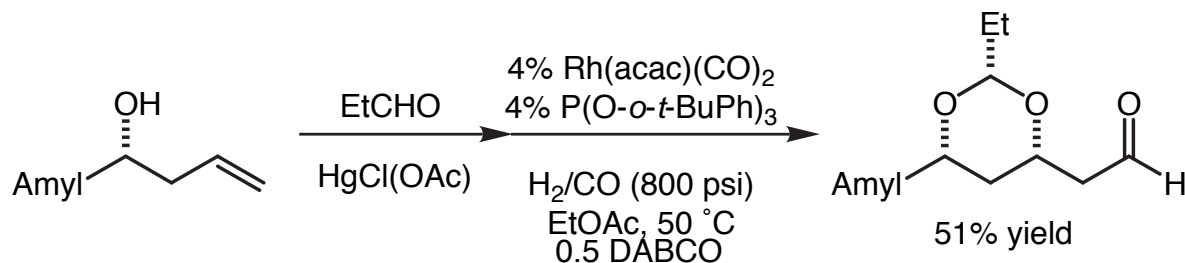
Leighton's Formylation of Mercurials



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

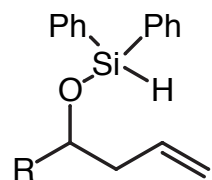
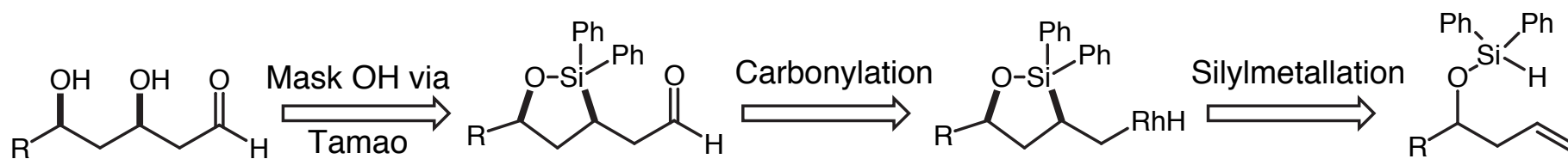


Also compatible with acetonides.
Yields typically 60-80%

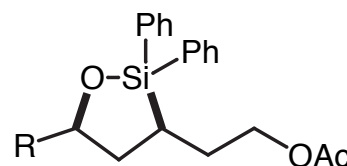


One pot procedure delivers aldehyde in comparable yield to two step procedure, without isolation of mercurial intermediate.

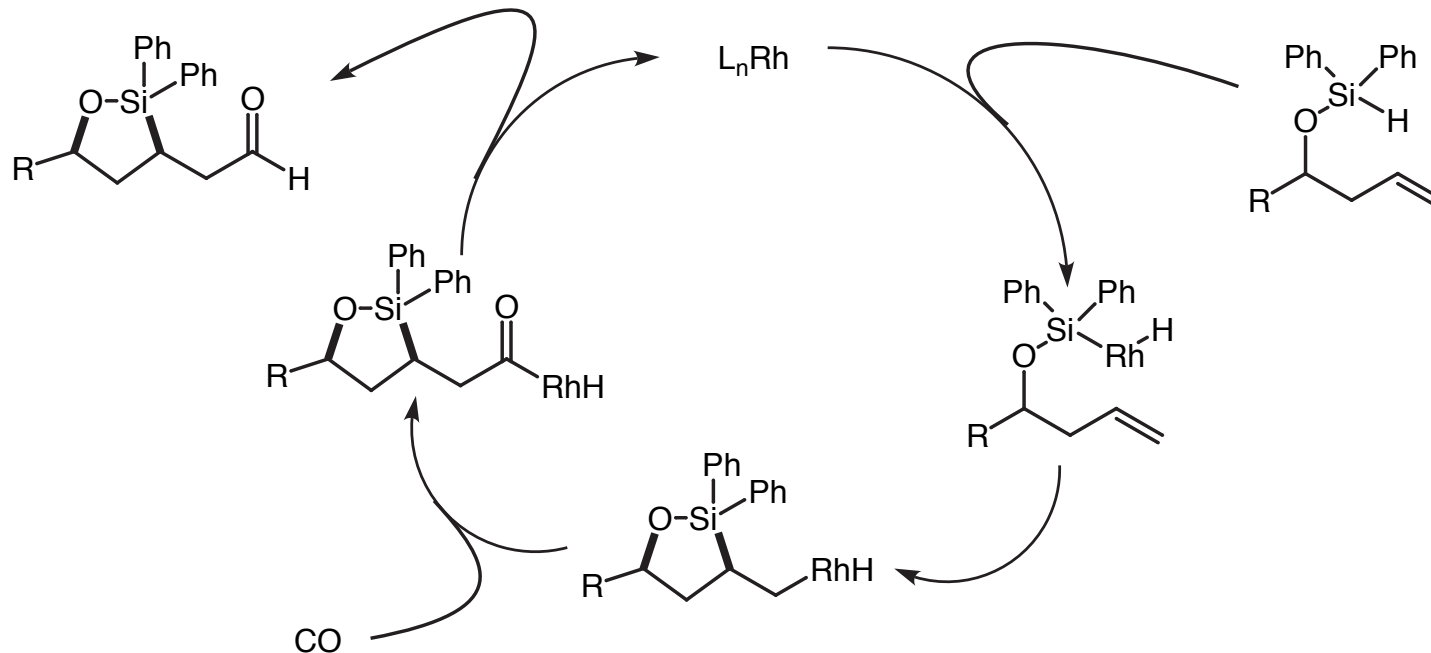
Leighton's Silylformylation



1) 1% $Rh(acac)(CO)_2$
 1000 psi CO , $60^\circ C$, C_6H_6
 2) $LiEt_3BH$
 3) Ac_2O

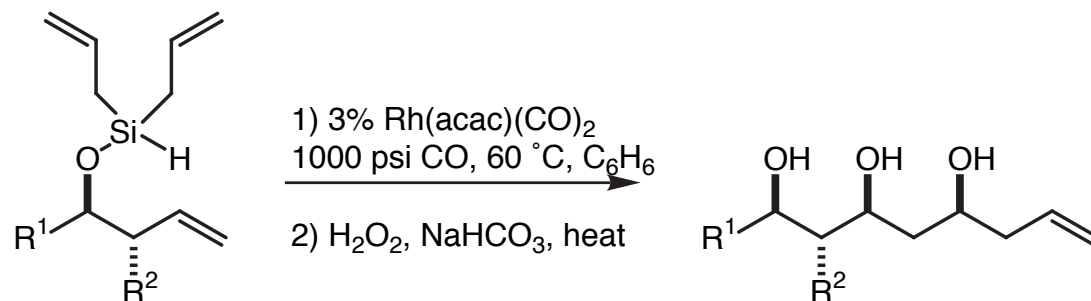
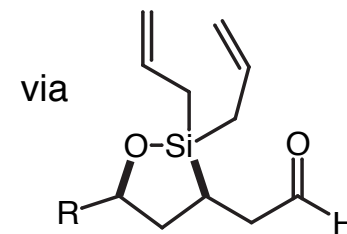
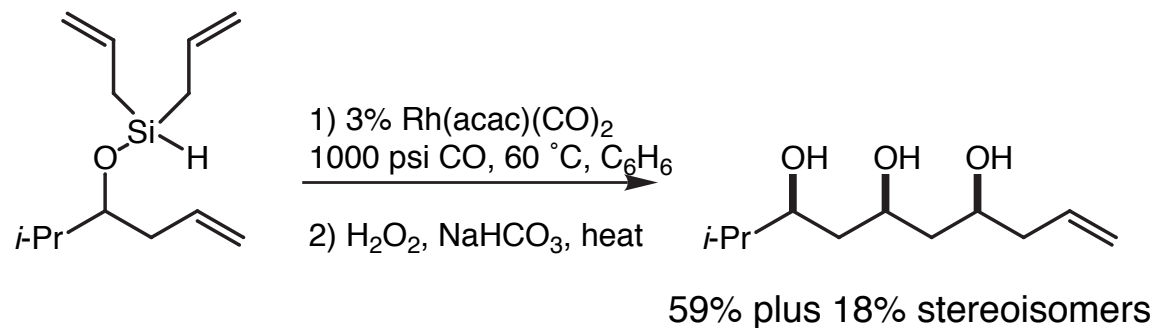


R	dr	Yield
Me	4.5:1	67%
Allyl	4:1	64%
<i>i</i> -Pr	6:1	79%
TBSOEt	4:1	60%



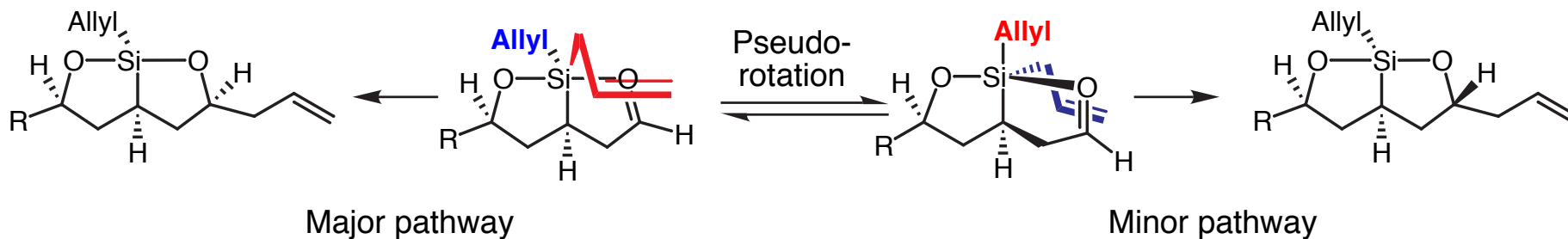
Leighton and Chapman, *J. Am. Chem. Soc.* **1997**, *119*, 12416.

Leighton's Silylformylation/Allylation



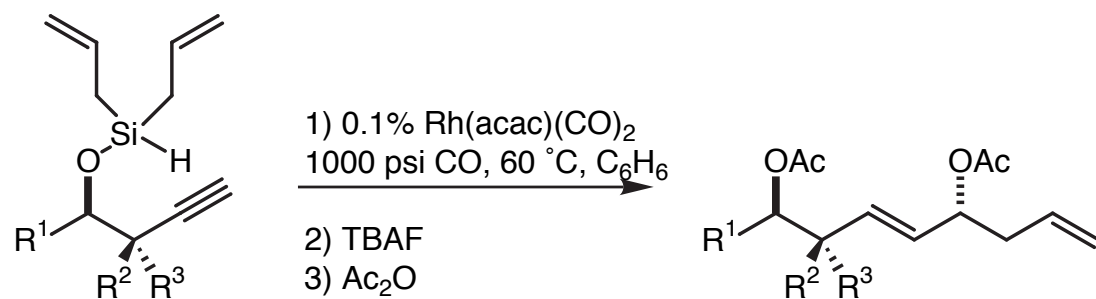
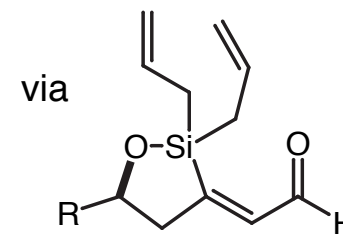
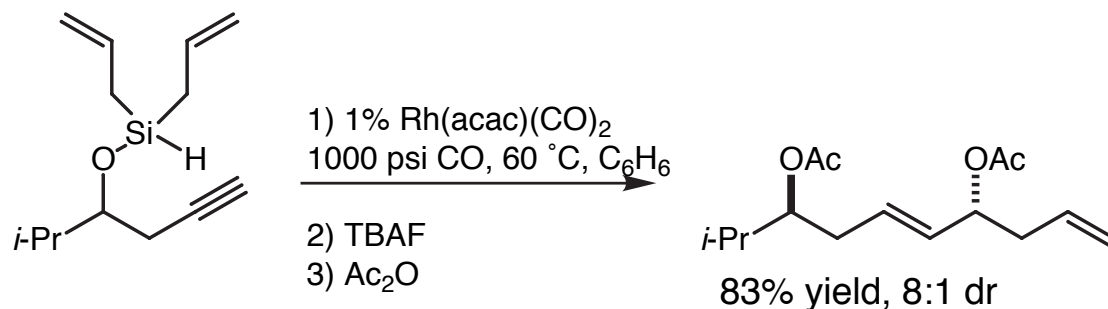
R ¹	R ²	dr	yield
<i>i</i> -Pr	H	77:23	59%
Allyl	H	69:31	50%
TBSOEt	H	71:29	45%
<i>i</i> -Pr	Me	92:8	59%

Stereochemical rationale:

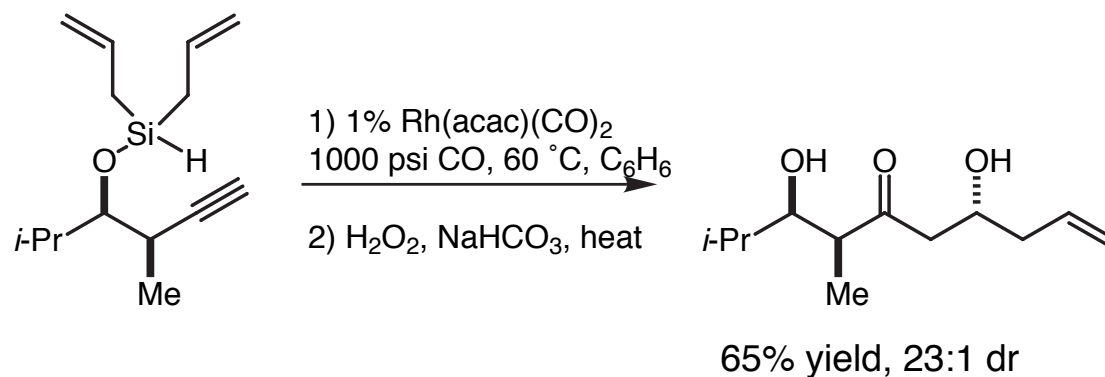


Leighton and Zacuto, *J. Am. Chem. Soc.* **2000**, 122, 8587.

Leighton's Alkyne Silylformylation/Allylation



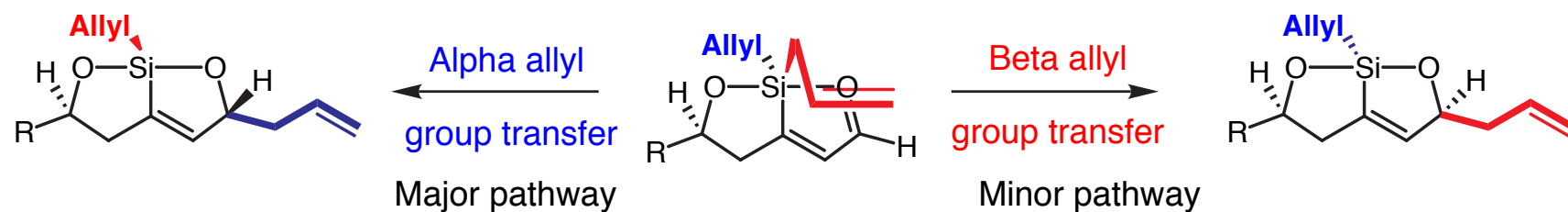
R ¹	R ²	R ³	dr	Yield
Propargyl	H	H	4:1	63%
<i>n</i> -Pr	H	H	4:1	68%
<i>t</i> -Bu	H	H	10:1	66%
<i>i</i> -Pr	H	H	8:1	83%
<i>i</i> -Pr	H	Me	7:1	70%
<i>i</i> -Pr	Me	H	23:1	70%



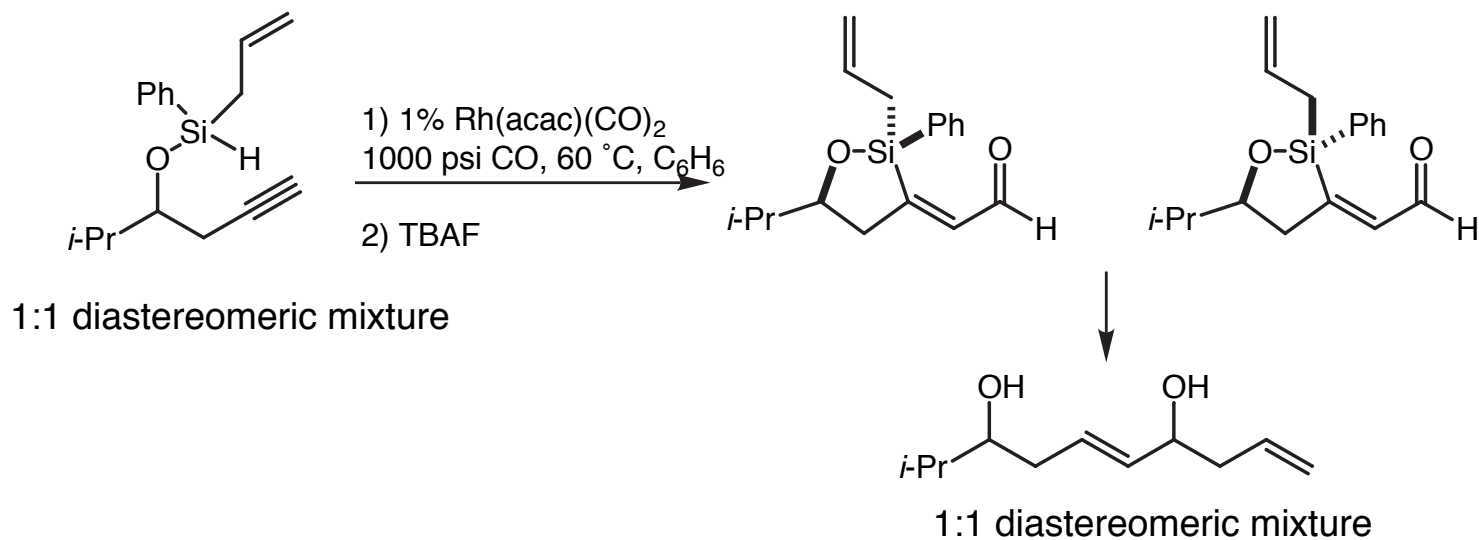
Leighton and O'Malley, *Angew. Chem. Int. Ed.* **2001**, *40*, 2915.

Leighton's Alkyne Silylformylation/Allylation

Stereochemical rationale:

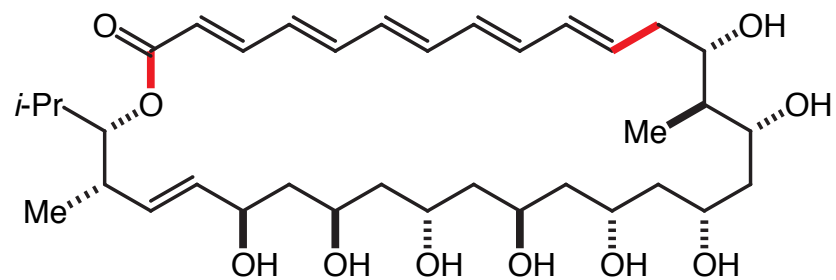


Top allyl group experiences steric repulsion with R group

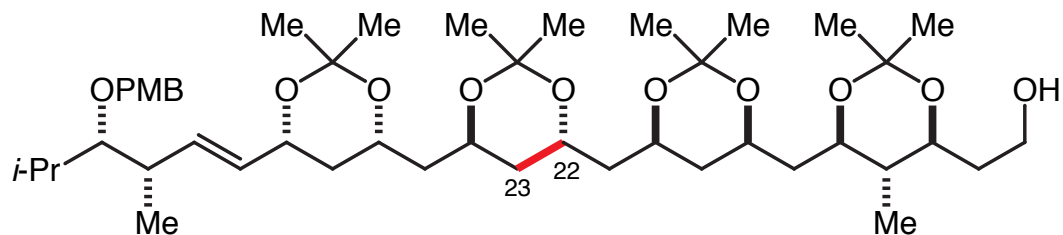


Leighton and O'Malley, *Angew. Chem. Int. Ed.* **2001**, 40, 2915.

Leighton's Retrosynthesis of Mycoticin A



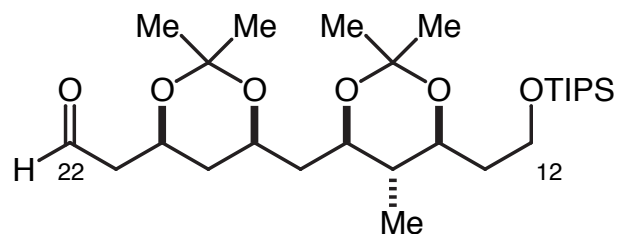
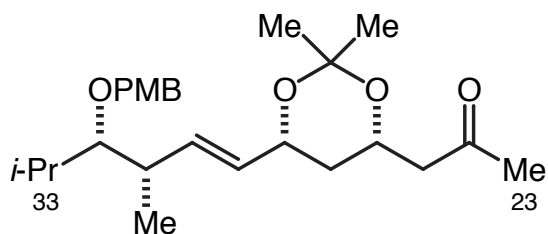
Mycoticin A



Schreiber's polyol segment

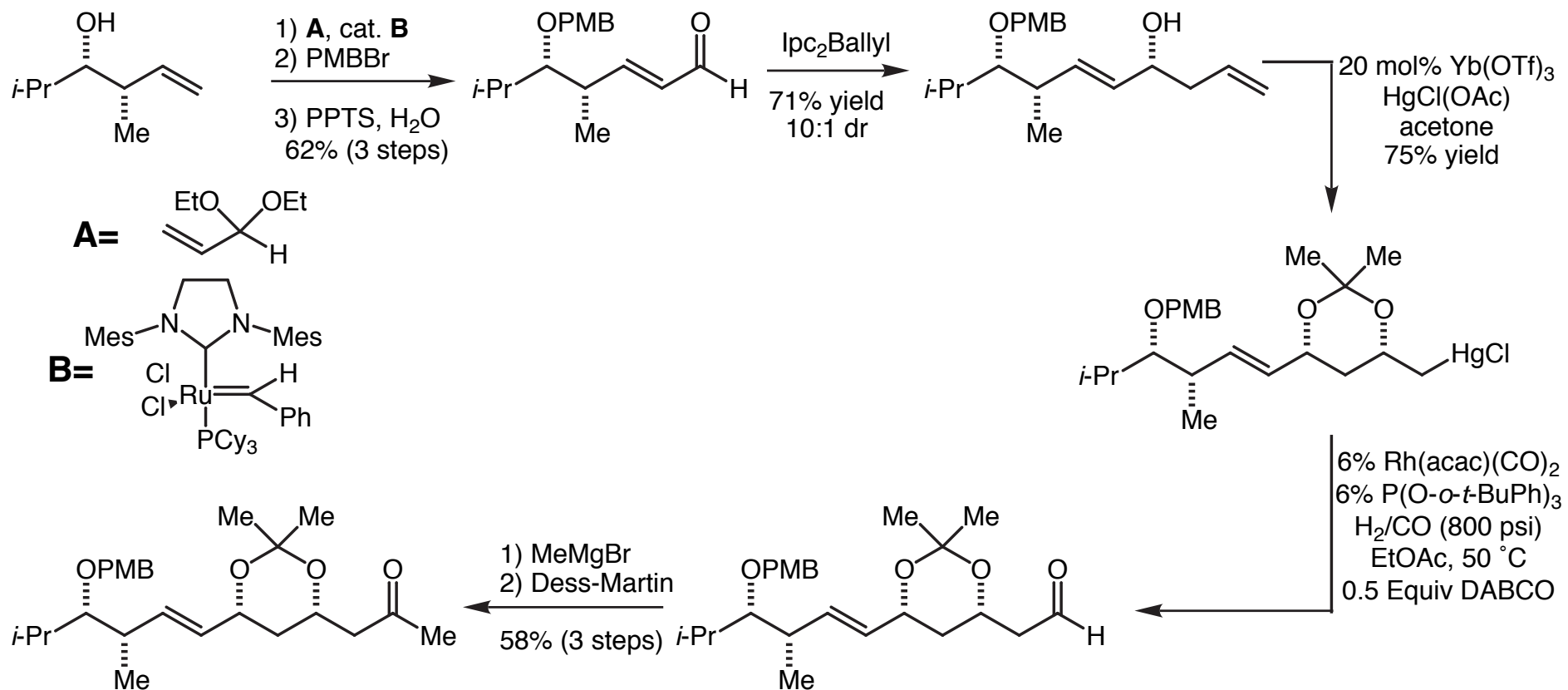


1,3 anti aldol

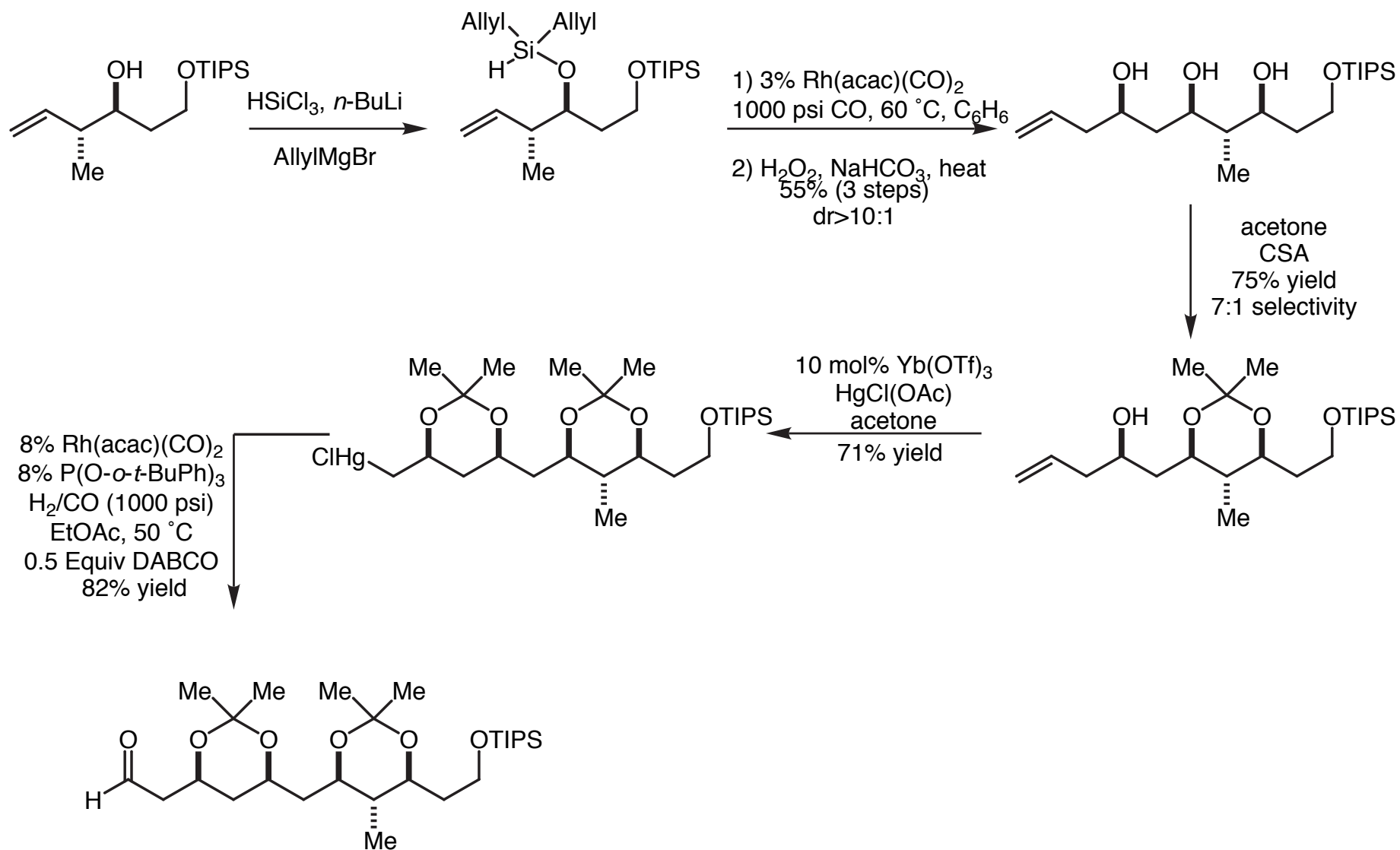


Leighton and Dreher, *J. Am. Chem. Soc.* **2001**, 123, 341.

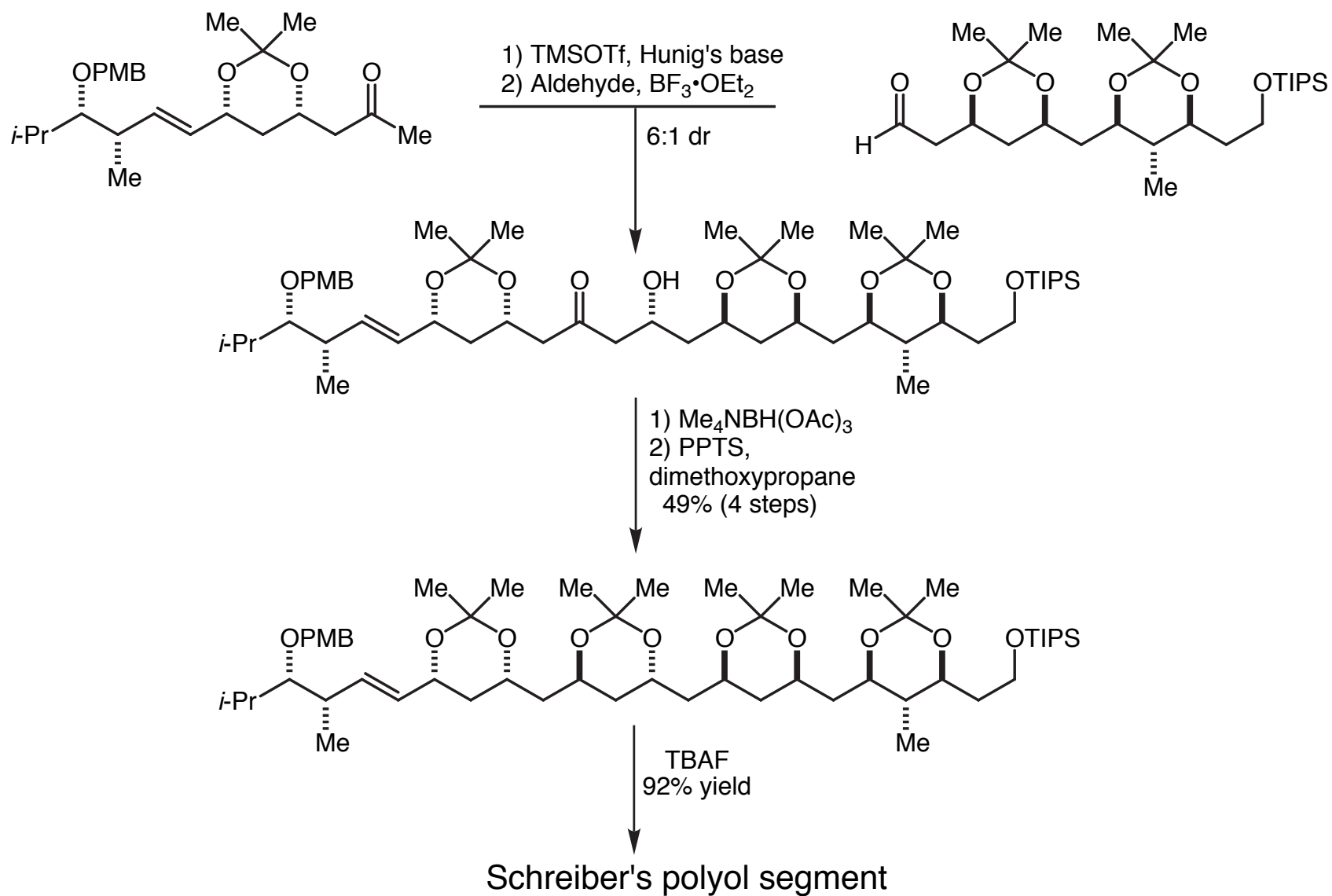
Leighton's Synthesis of the C₂₃-C₃₃ Methyl Ketone



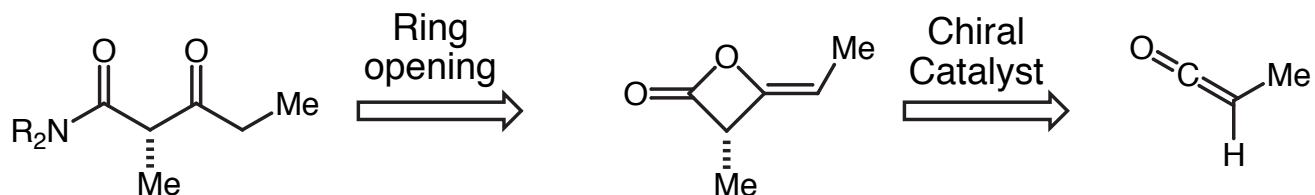
Leighton's Synthesis of the C₁₂-C₂₂ Aldehyde



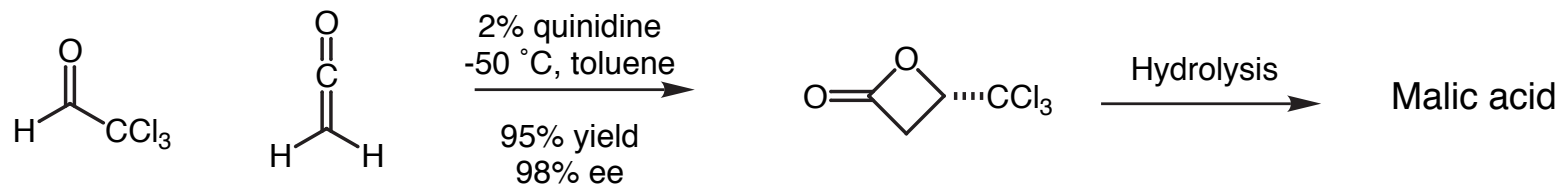
Leighton's Formal Synthesis of Mycoticin A



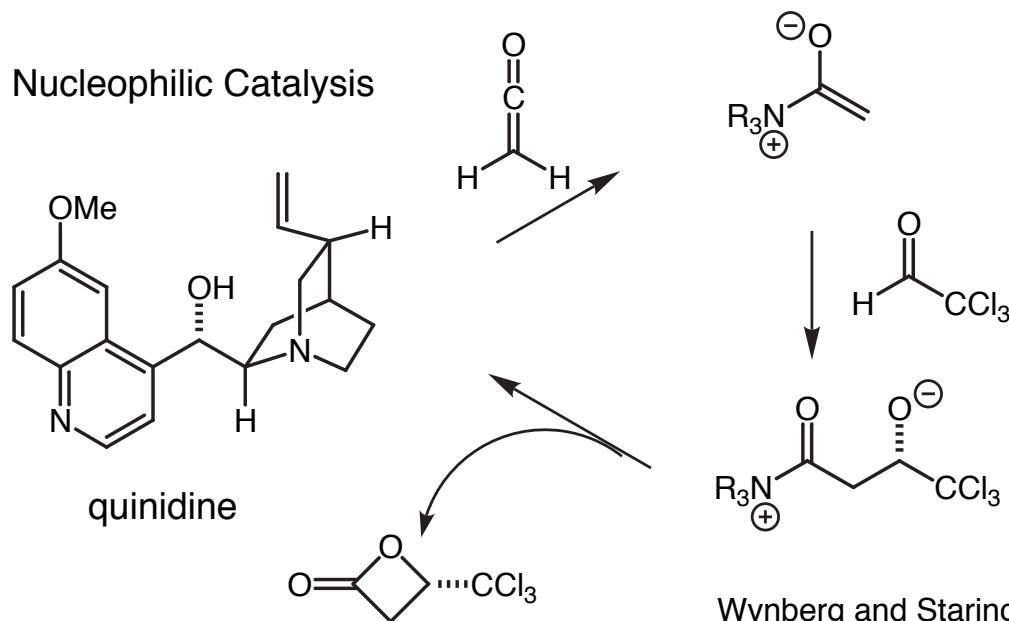
Calter: Asymmetric Methylketene Dimerization



Wynberg's precedent: 1982

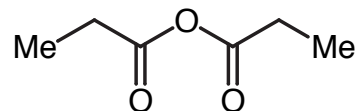
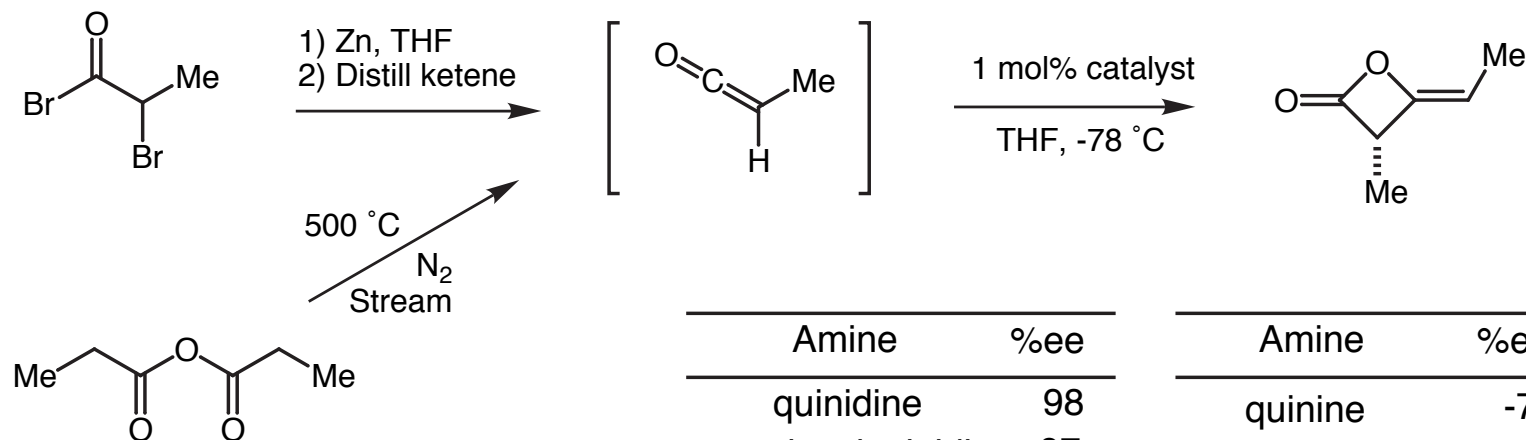


Mechanism: Nucleophilic Catalysis



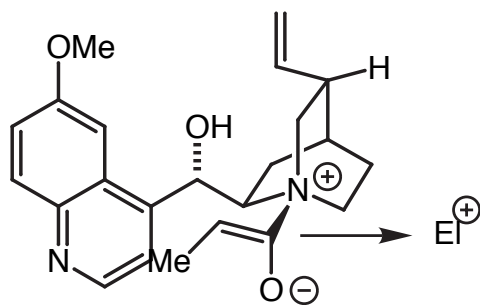
Wynberg and Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166.

Calter: Asymmetric Methylketene Dimerization

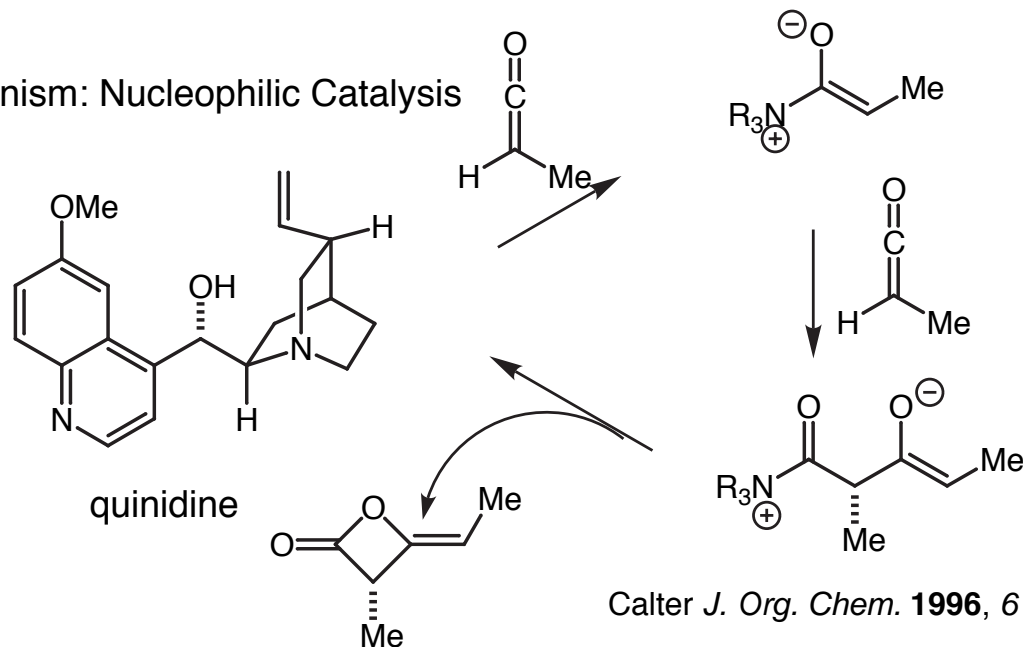


Amine	%ee	Amine	%ee
quinidine	98	quinine	-70
propionylquinidine	97	propionylquinine	-54
TMS-quinidine	98	TMS-quinine	-93

Model for stereoinduction

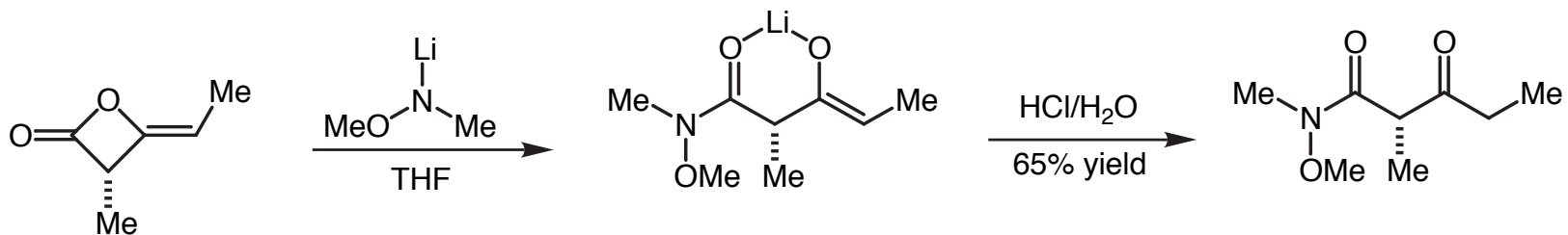


Mechanism: Nucleophilic Catalysis

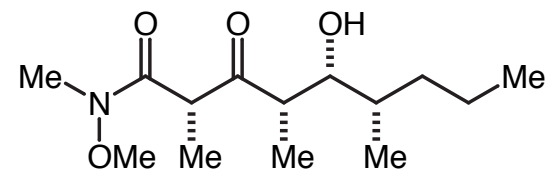
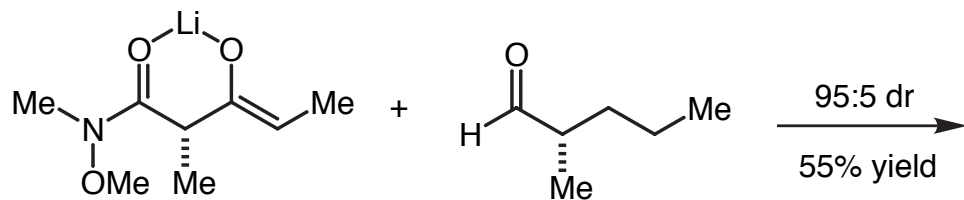
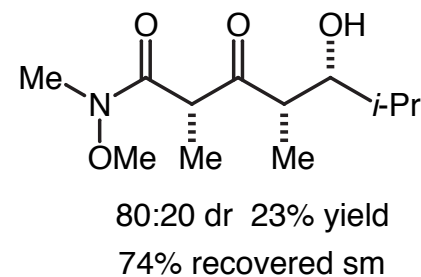
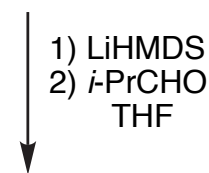
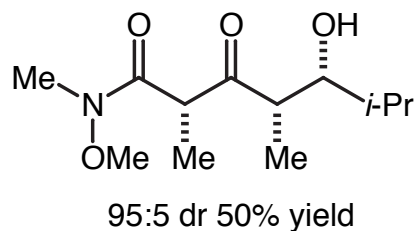
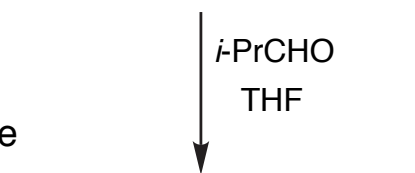


Calter *J. Org. Chem.* **1996**, *61*, 8006.

Calter: Tandem Ring Opening/Aldol Reaction



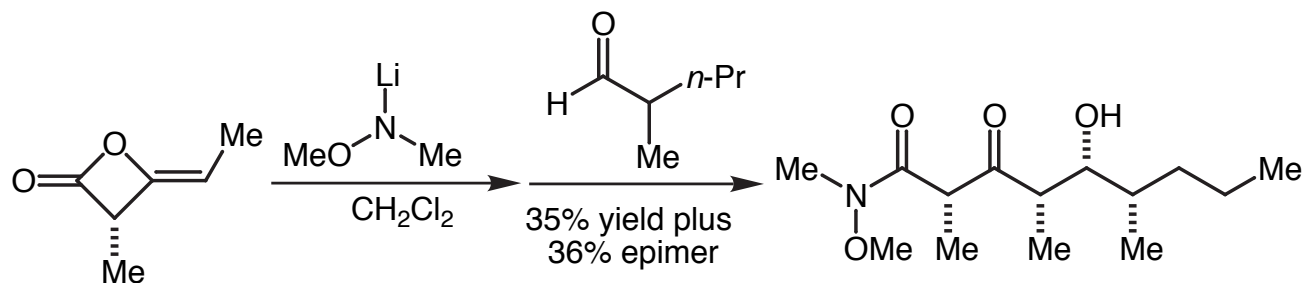
Yields around 50% based on ketene dimer, dr between 85:15 and 90:1.



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

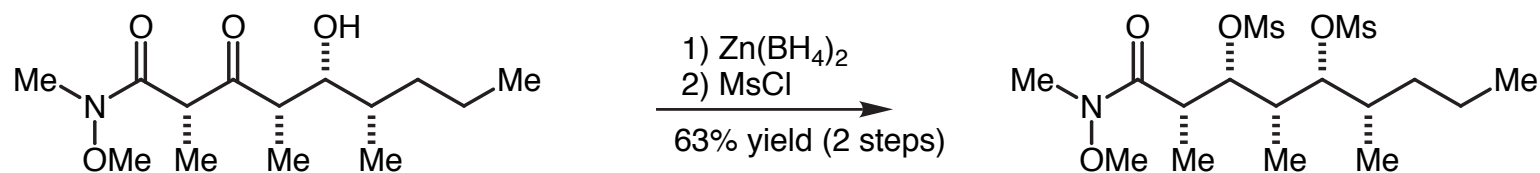
Calter et al., *J. Org. Chem.* **2001**, 66, 7500.

Calter: Synthesis of Siphonarienal

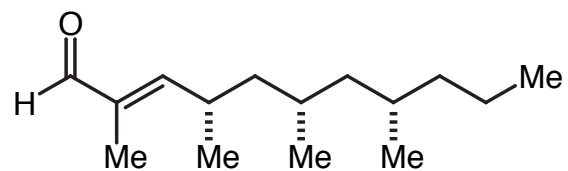


Starting materials:
All commercially available

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

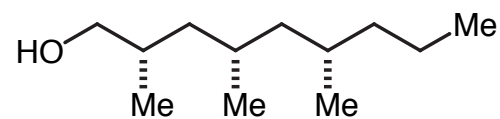


1) LiAlH_4 , THF
2) LiAlH_4 , Et_2O
72% (2 steps)

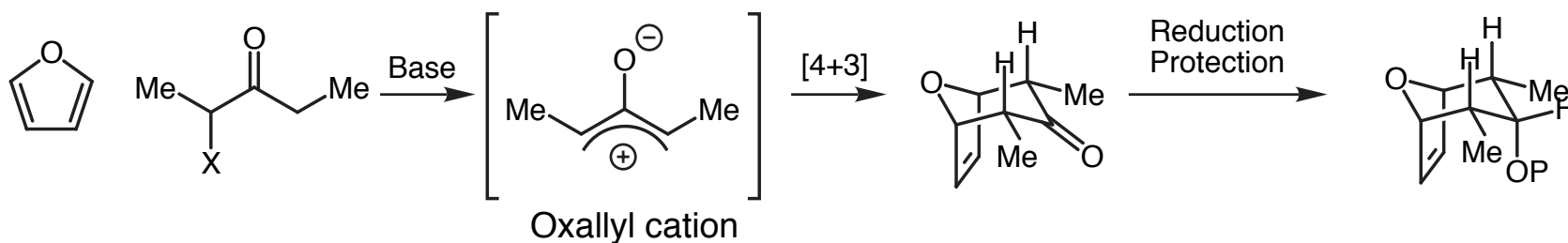
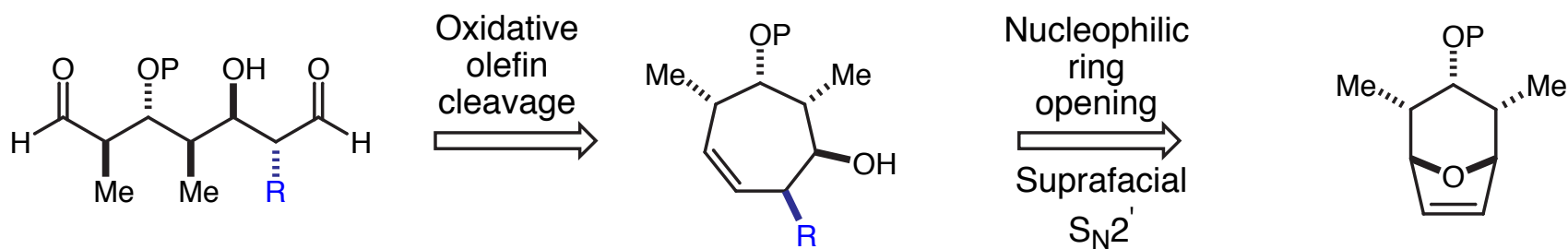


Siphonarienal

1) TEMPO, $\text{PhI}(\text{OAc})_2$
2) Wittig
3) DIBAL-H
4) MnO_2
64% yield (4 steps)

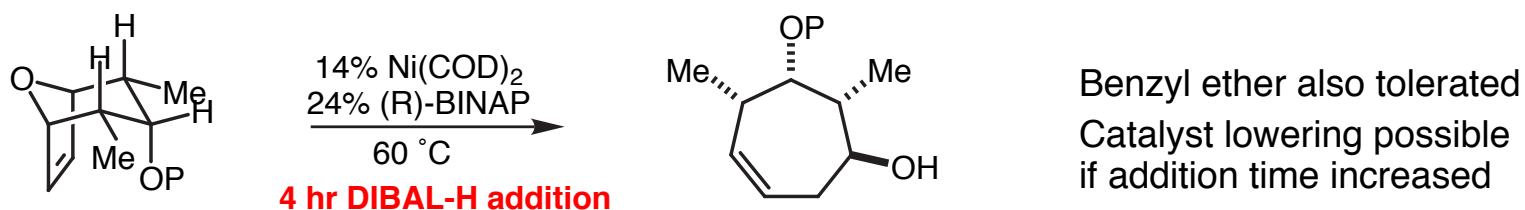
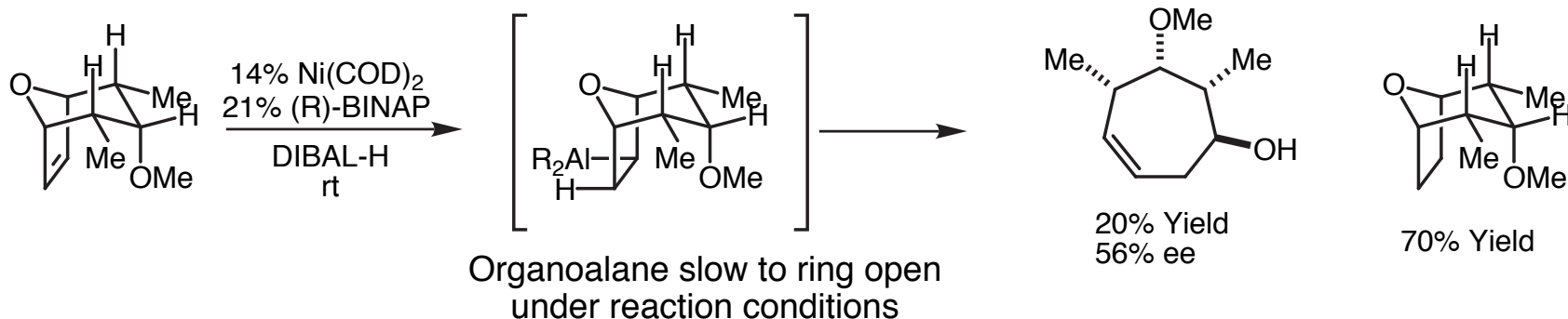
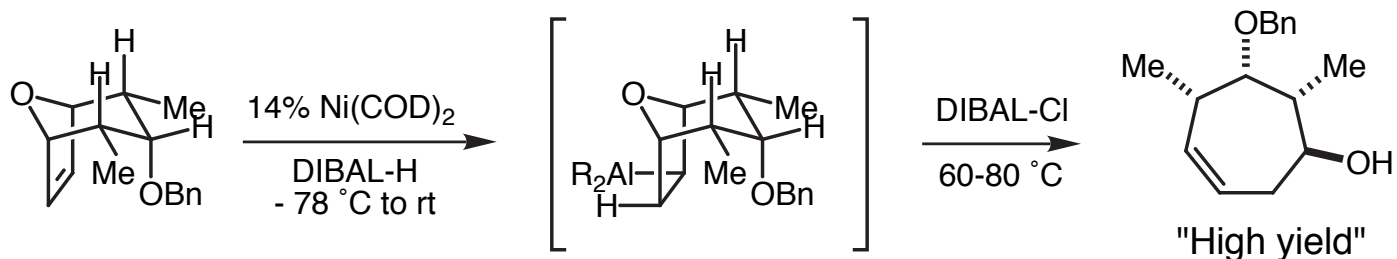


Lautens' Oxabicyclic Ring Opening



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

Lautens' Enantioselective Oxabicyclic Ring Opening: Hydride Reduction



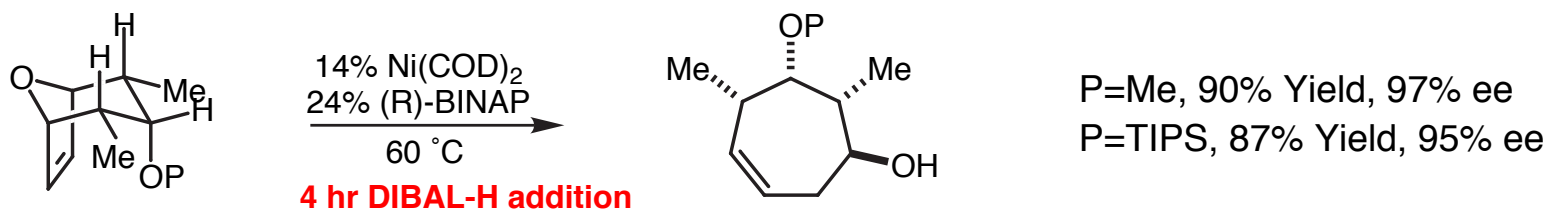
P=Me, 90% Yield, 97% ee

P=TIPS, 87% Yield, 95% ee

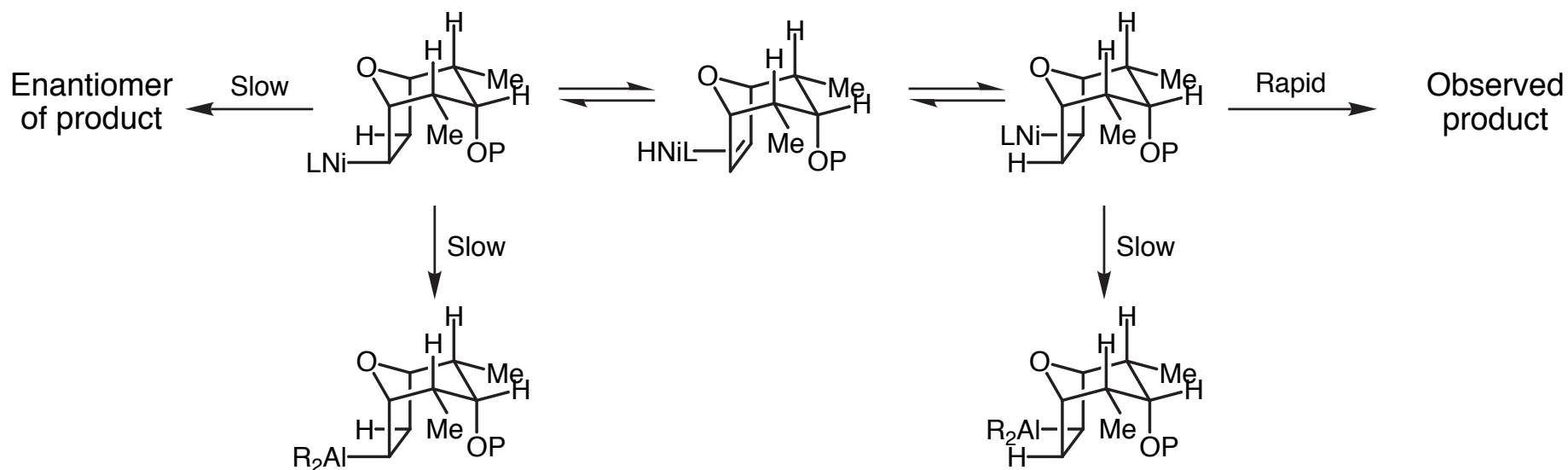
Lautens et al., *J. Am. Chem. Soc.* **1995**, 117, 532.

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

Lautens' Enantioselective Oxabicyclic Ring Opening: Hydride Reduction



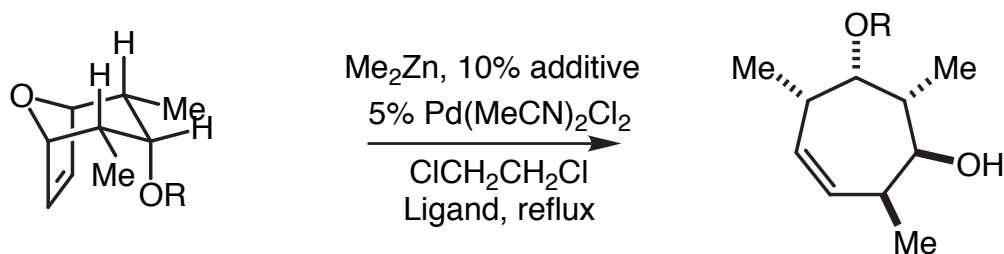
Initial hydrometallation rapid and reversible.
Organoalanes not implicated as intermediates.
Elimination is enantioselective event.



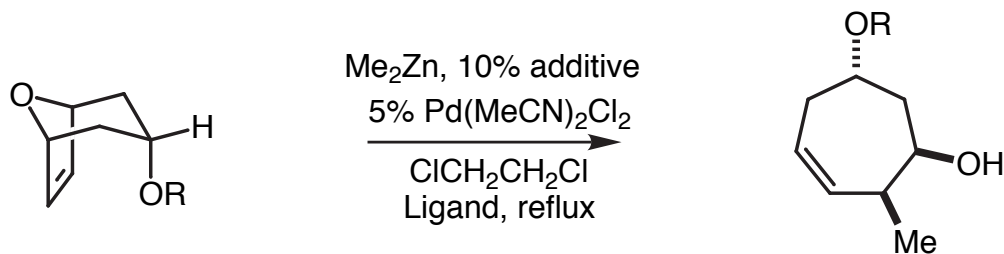
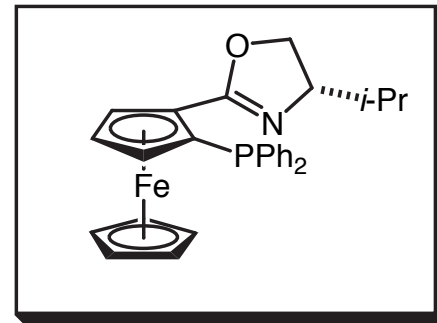
Lautens et al., *J. Am. Chem. Soc.*, **1995**, 117, 532.

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

Lautens' Enantioselective Oxabicyclic Ring Opening: Methyl Addition



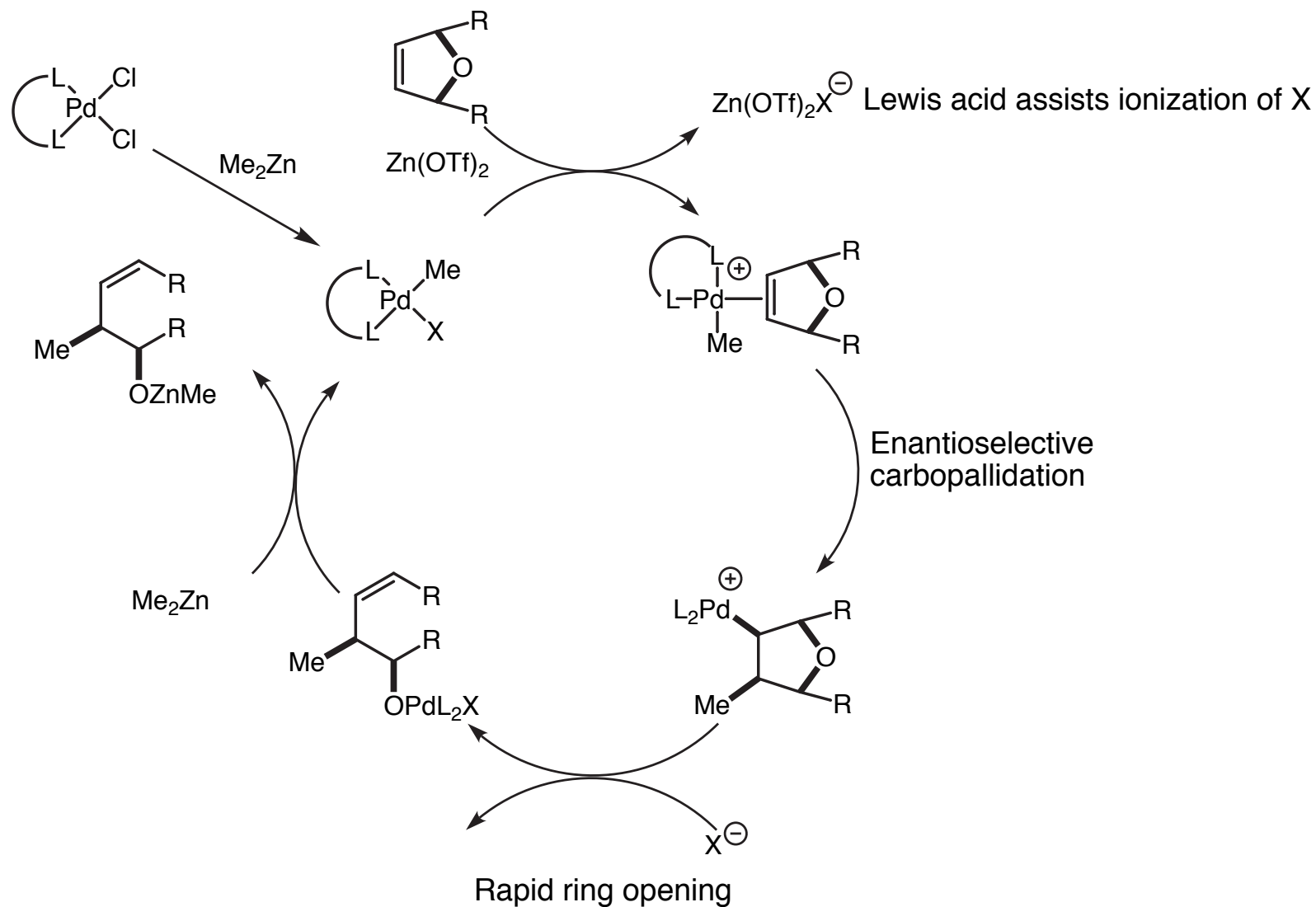
R	Additive	%ee	%yield
H	none	95	84
TBDPS	$\text{Zn}(\text{OTf})_2$	87	70
TIPS	$\text{Zn}(\text{OTf})_2$	93	73



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

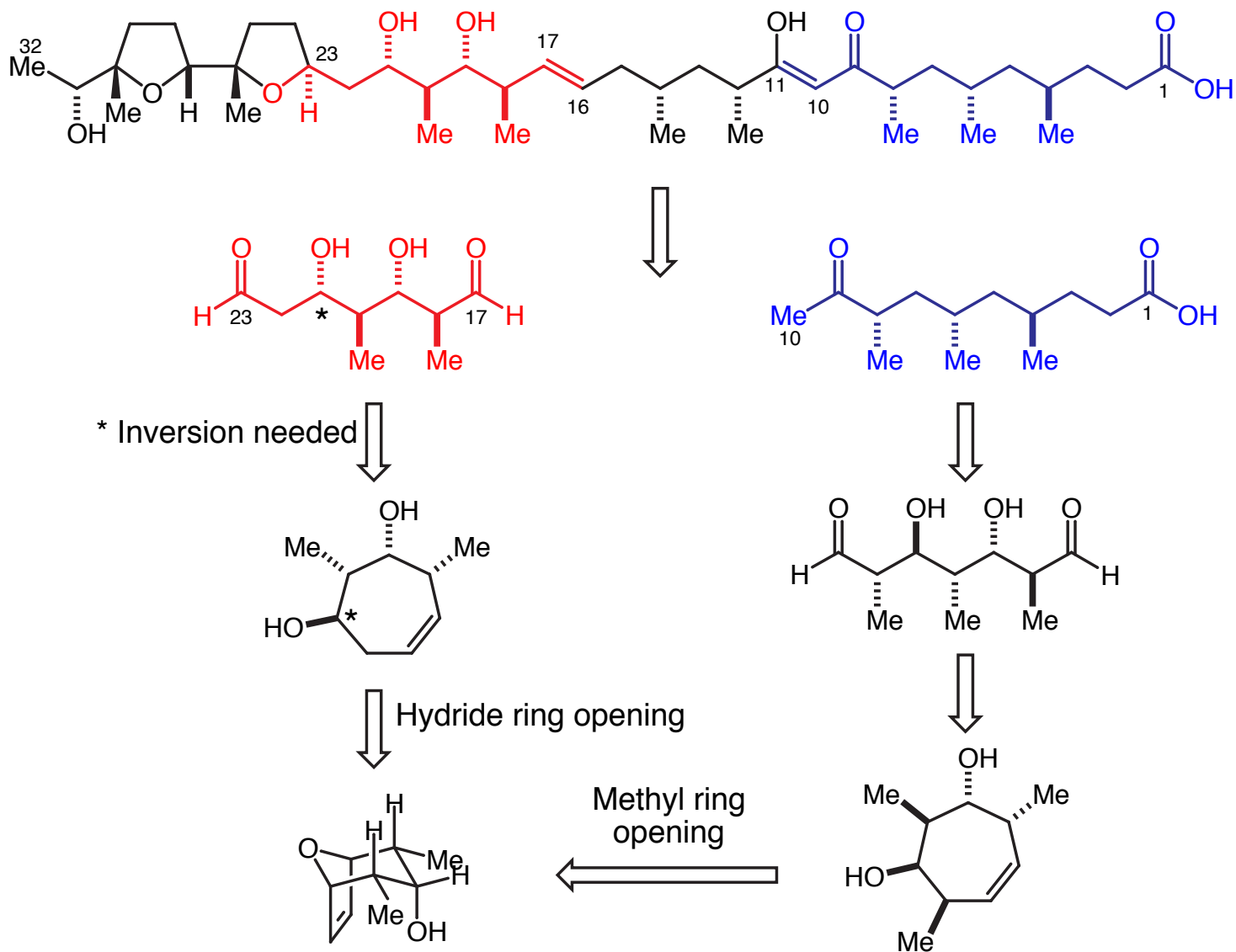
Lautens et al., *J. Am. Chem. Soc.* **2000**, 122, 1804.
 Lautens et al., *Org. Lett.* **2000**, 2, 1971.

Lautens' Enantioselective Oxabicyclic Ring Opening: Mechanism



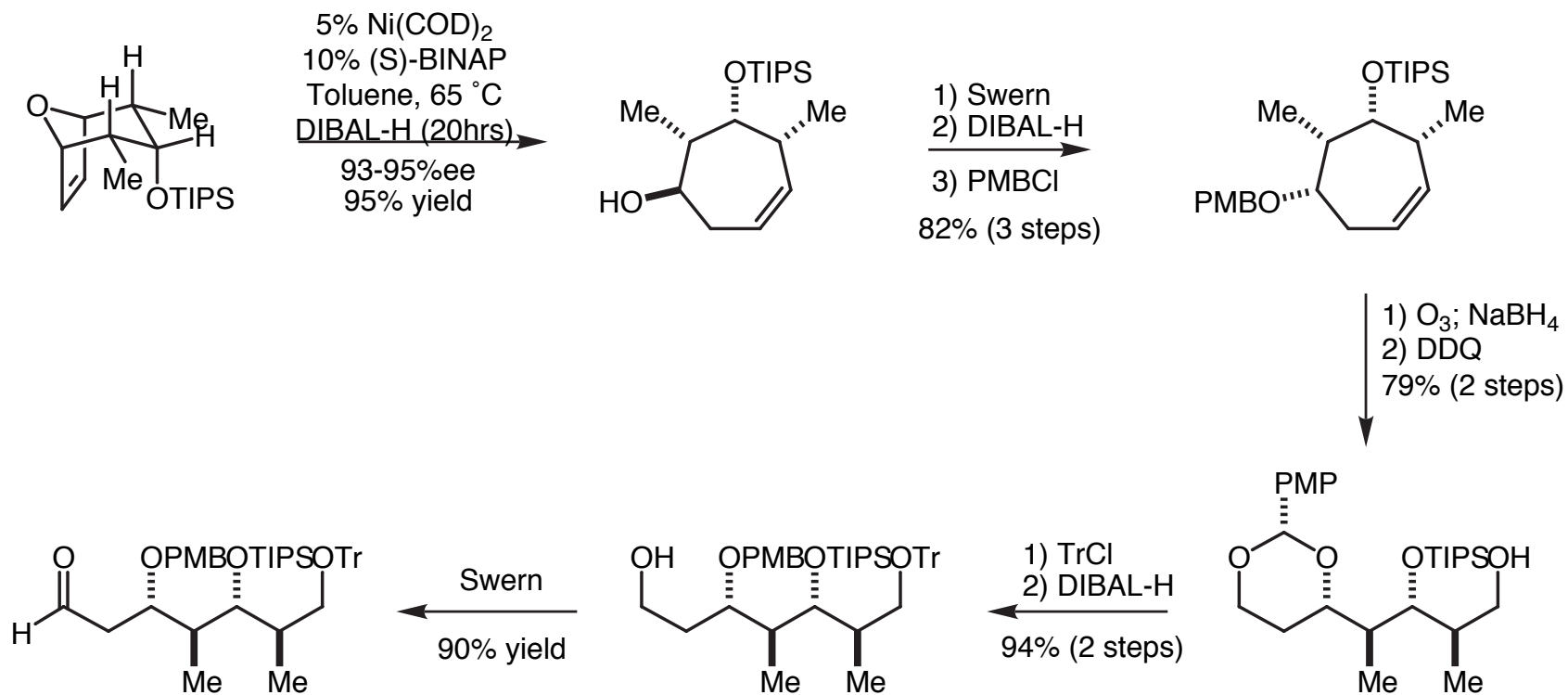
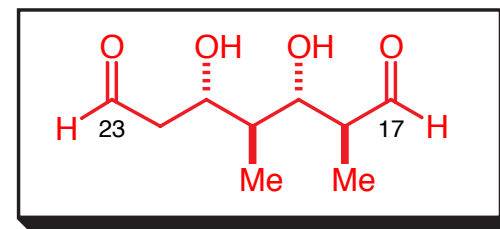
Lautens et al., *J. Am. Chem. Soc.* **2001**, 123, 6834.

Lautens' Total Synthesis of Ionomycin



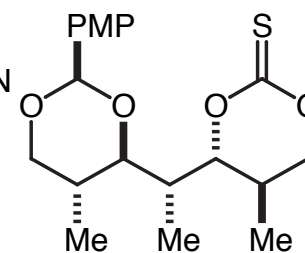
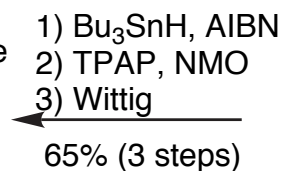
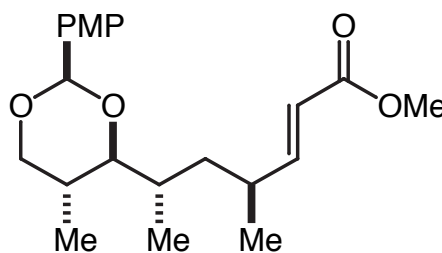
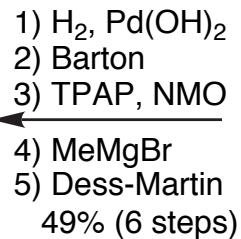
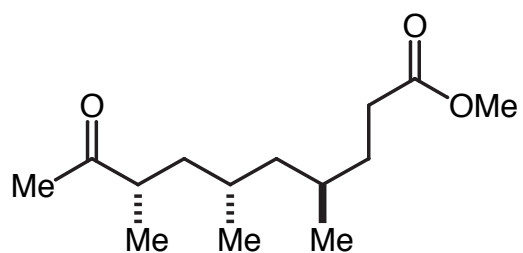
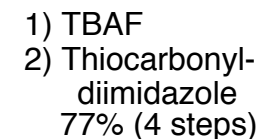
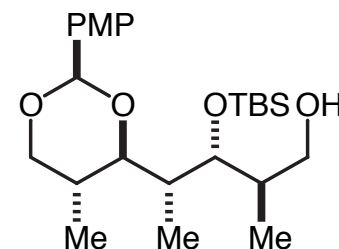
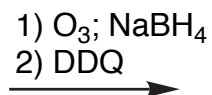
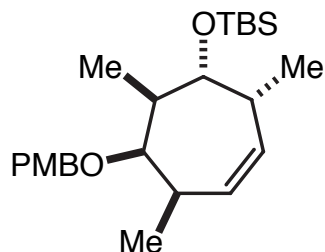
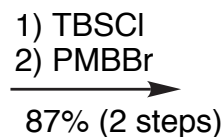
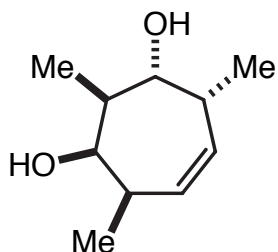
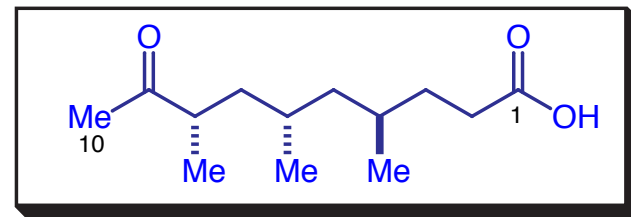
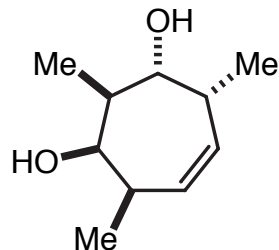
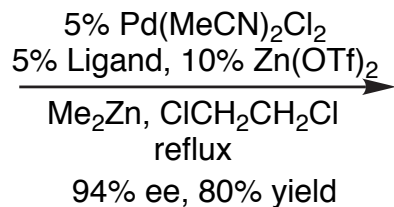
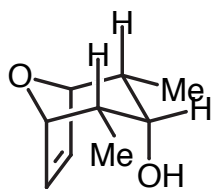
Lautens et al., *Org. Lett.* **2002**, 4, 1879.

Ionomycin: C₁₇-C₂₃ Fragment

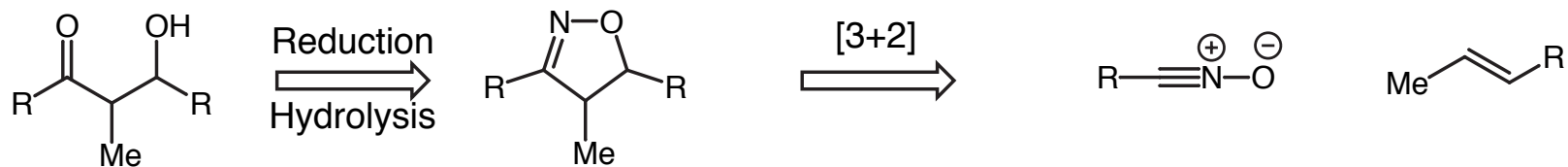


Lautens et al., *Org. Lett.* **2002**, *4*, 1879.

Ionomycin: C₁₇-C₂₃ Fragment

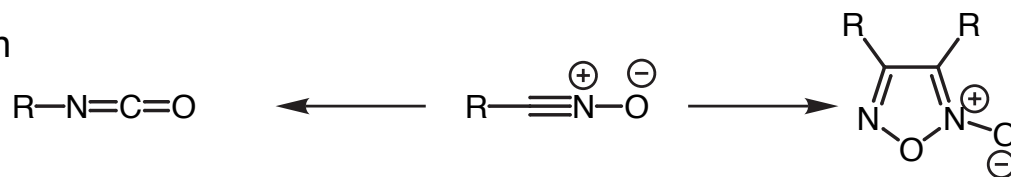


Carreira's Hydroxyl Directed Nitrile Oxide Cycloaddition

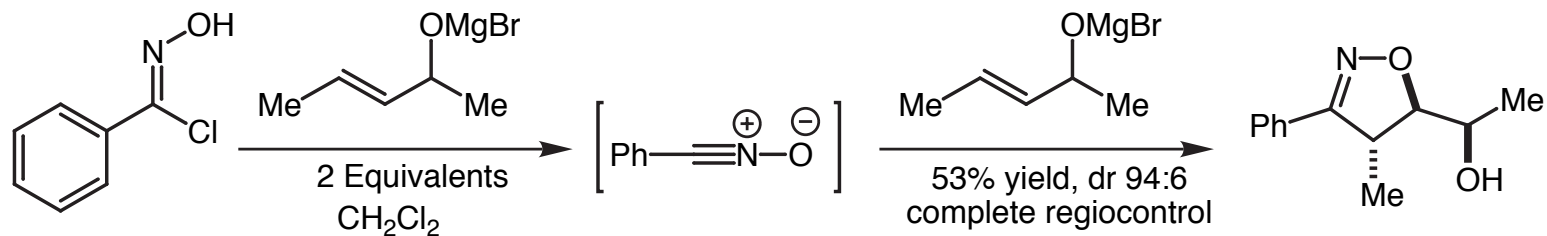


Problems:

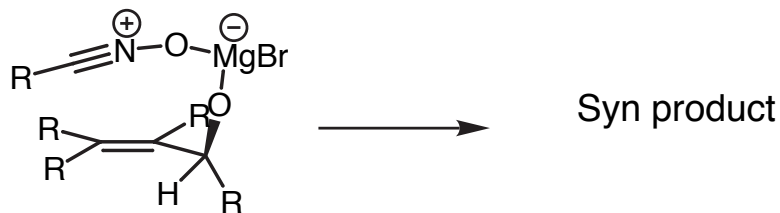
- 1) Nitrile oxides unstable; prone to dimerization, decomposition
- 2) Internal alkenes sluggish
- 3) Mixtures of regioisomers
- 4) Mixtures of stereoisomers



Kanemasa, 1994:



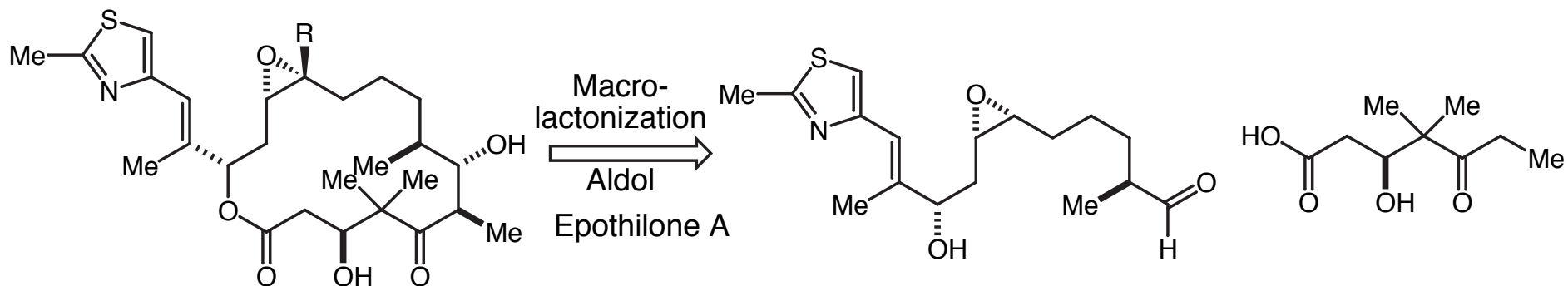
Stereochemical rationale:



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

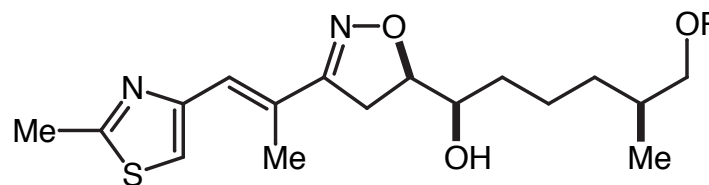
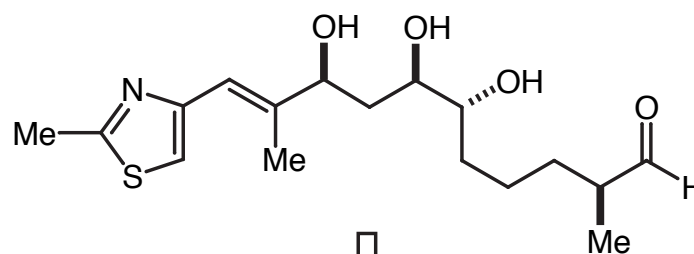
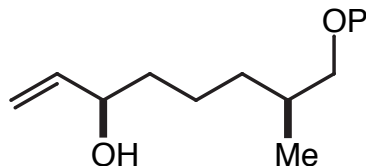
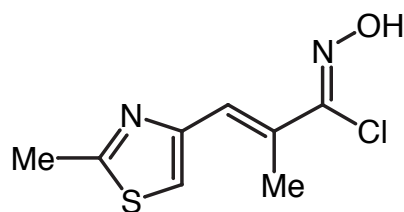
Kanemasa et al., *J. Am. Chem. Soc.* **1994**, 116, 2324.
Carreira et al., *Angew. Chem. Int. Ed.* **2001**, 40, 2082.

Carreira's Epothilone Retrosynthesis



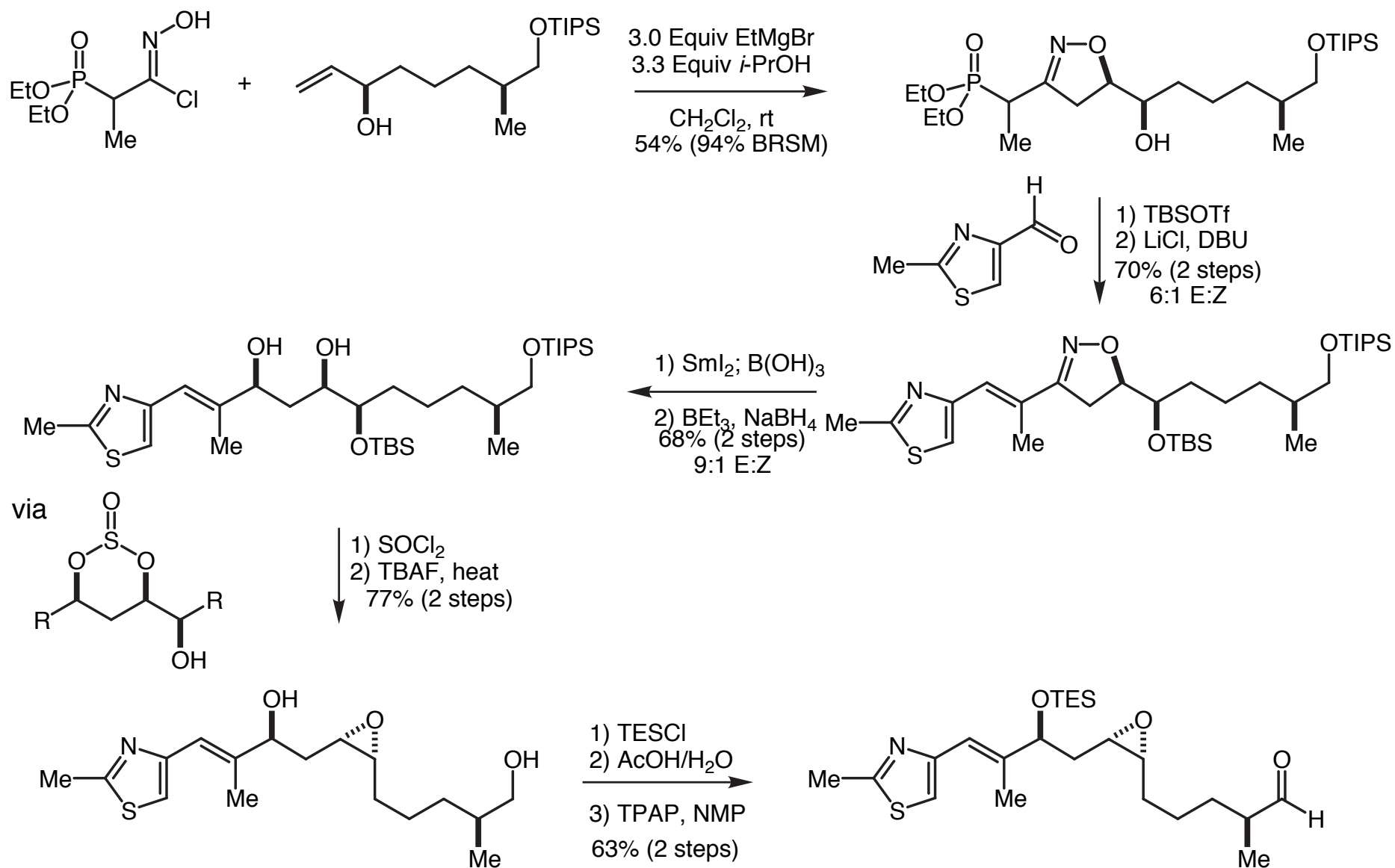
Epothilone A (R=H)
Epothilone B (R=Me)

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.

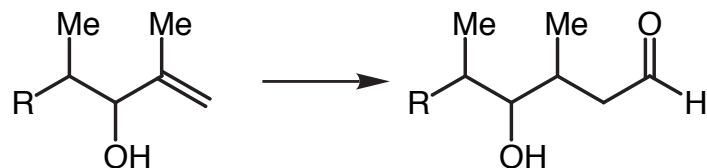
Carreira's Epothilone A Fragment Synthesis



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. ←

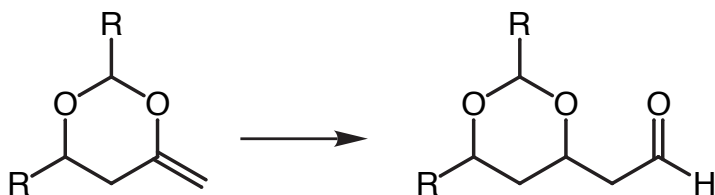
Chem. Eur. J. **1999**, 5, 2819.

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

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

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

James Leighton: Hydroformylation

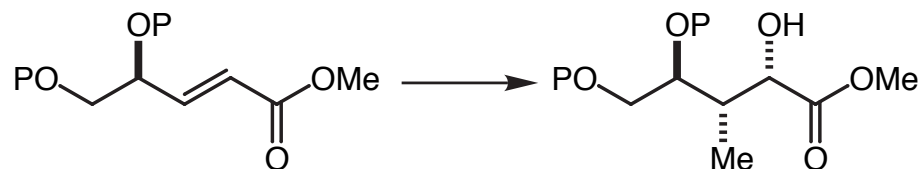


J. Am. Chem. Soc. **1997**, 119, 11118.

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

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

Stephen Hanessian: Conjugate Addition/Enolate Oxidation



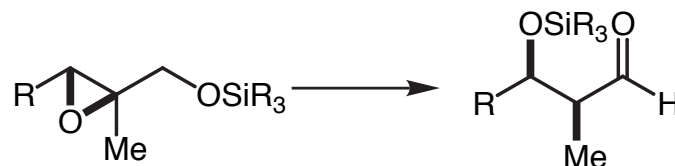
Tet. Lett. **1996**, 37, 7473.

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.

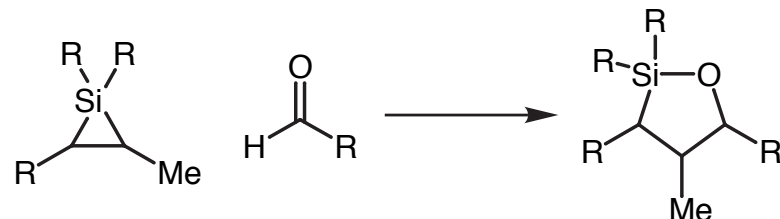
Org. Lett. **1999**, 1, 307.

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.

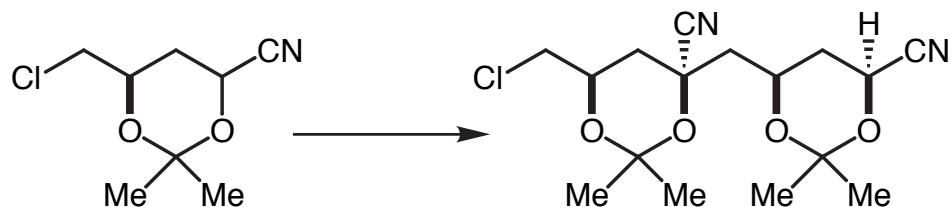
Angew. Chem. Int. Ed. **2000**, 39, 4295.

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

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

Summary

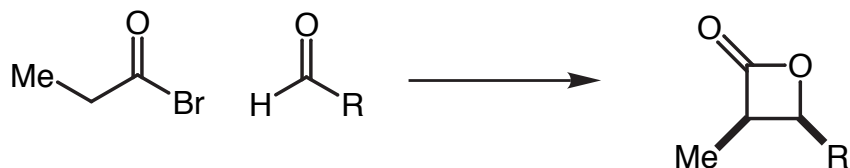
Rychnovsky: Cyanohydrin acetonide



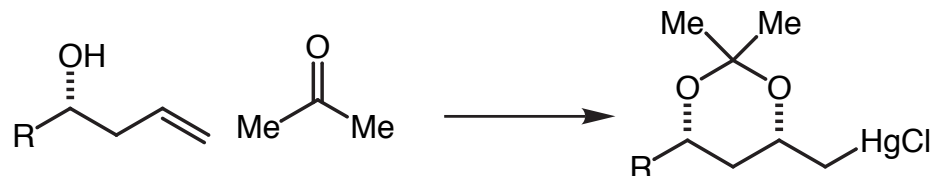
Smith: Dithiane linchpin



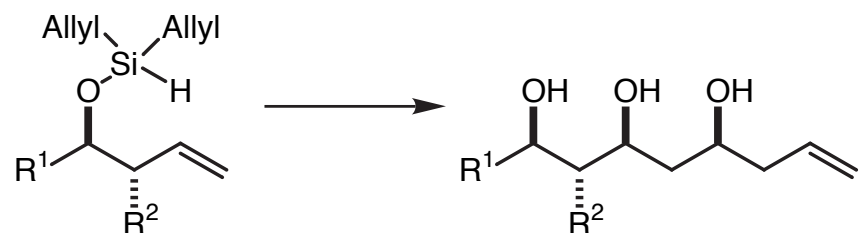
Nelson: Cyclocondensation



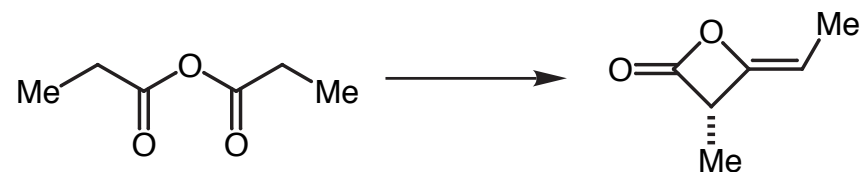
Leighton: Hemiacetal oxymercuration



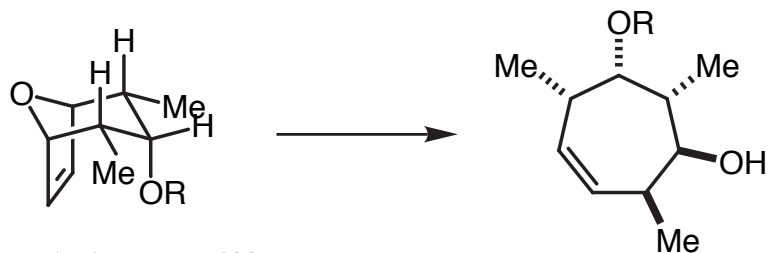
Leighton: Silylformylation



Calter: Methylketene dimerization



Lautens: Enantioselective ring opening



Carreira: Directed nitrile oxide cycloaddition

