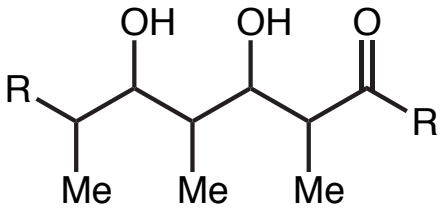
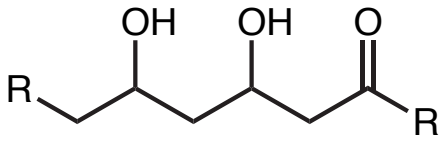
Non-Aldol Approaches to the Synthesis of Polyketide Natural Products





Evans Group Evening Seminar
Friday June 21, 2002
Travis Dunn

Keywords: Polypropionate, Polyol, Total Synthesis

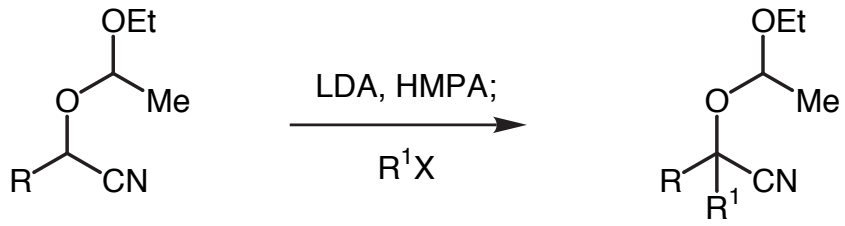
Outline of Seminar

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)

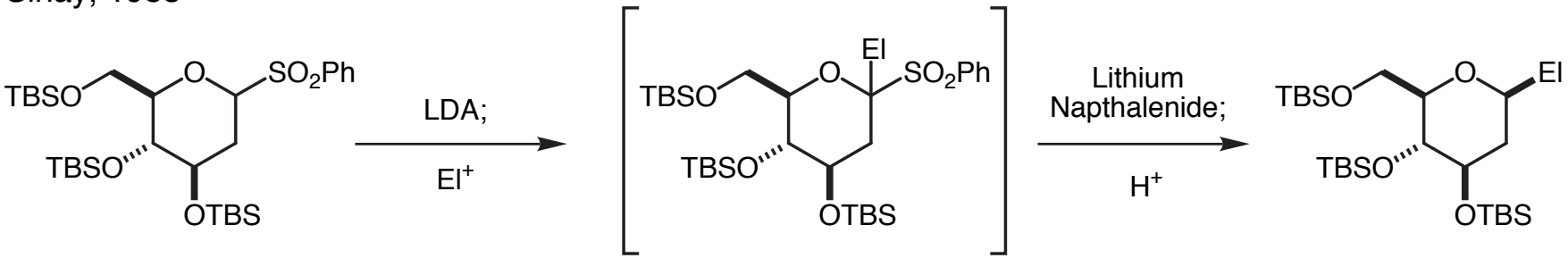
Bond constructions not covered in this seminar:
1) Metal enolate reactions
2) Mukaiyama aldol reactions
3) Allylmetal based reactions
(e.g. silanes, stannanes, boranes, borinates)

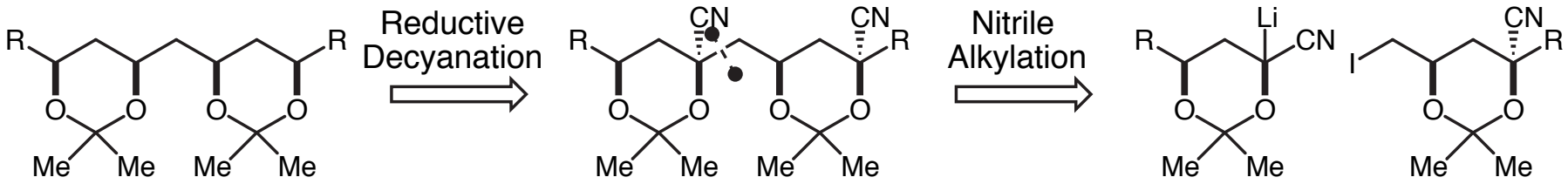
Rychnovsky's Cyanohydrin Acetonide Alkylation

Stork, 1971



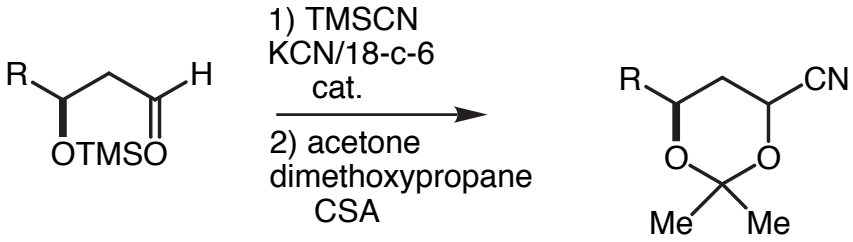
Sinay, 1985



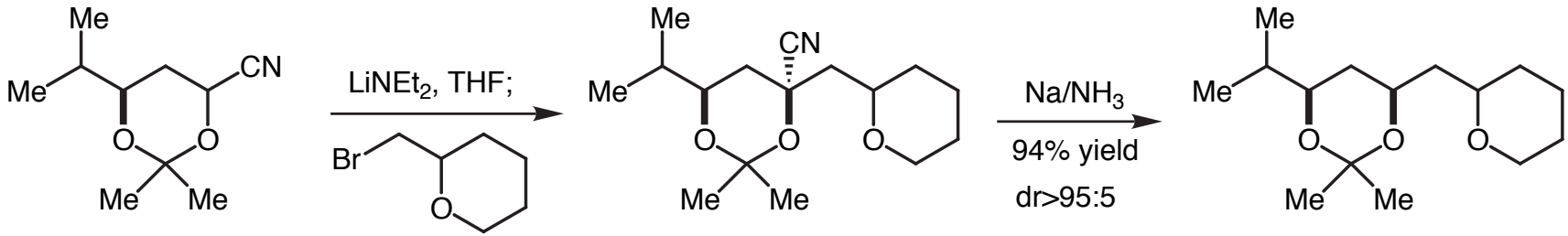


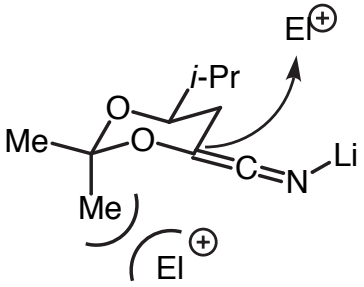
Rychnovsky and Sinz, *Topics in Current Chem.* **2001**, *216*, 51-92.

Rychnovsky's Cyanohydrin Acetonide Alkylation

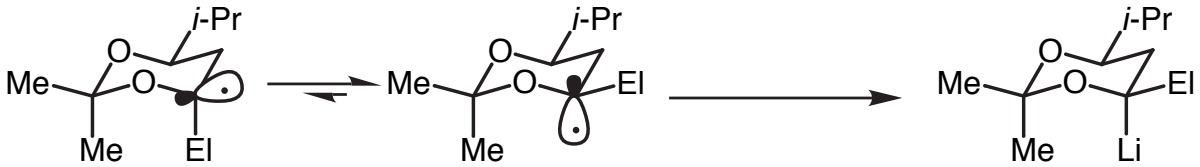


Usually 1:1 mix of stereoisomers





Equatorial alkylation due to steric shielding by methyl of acetonide.



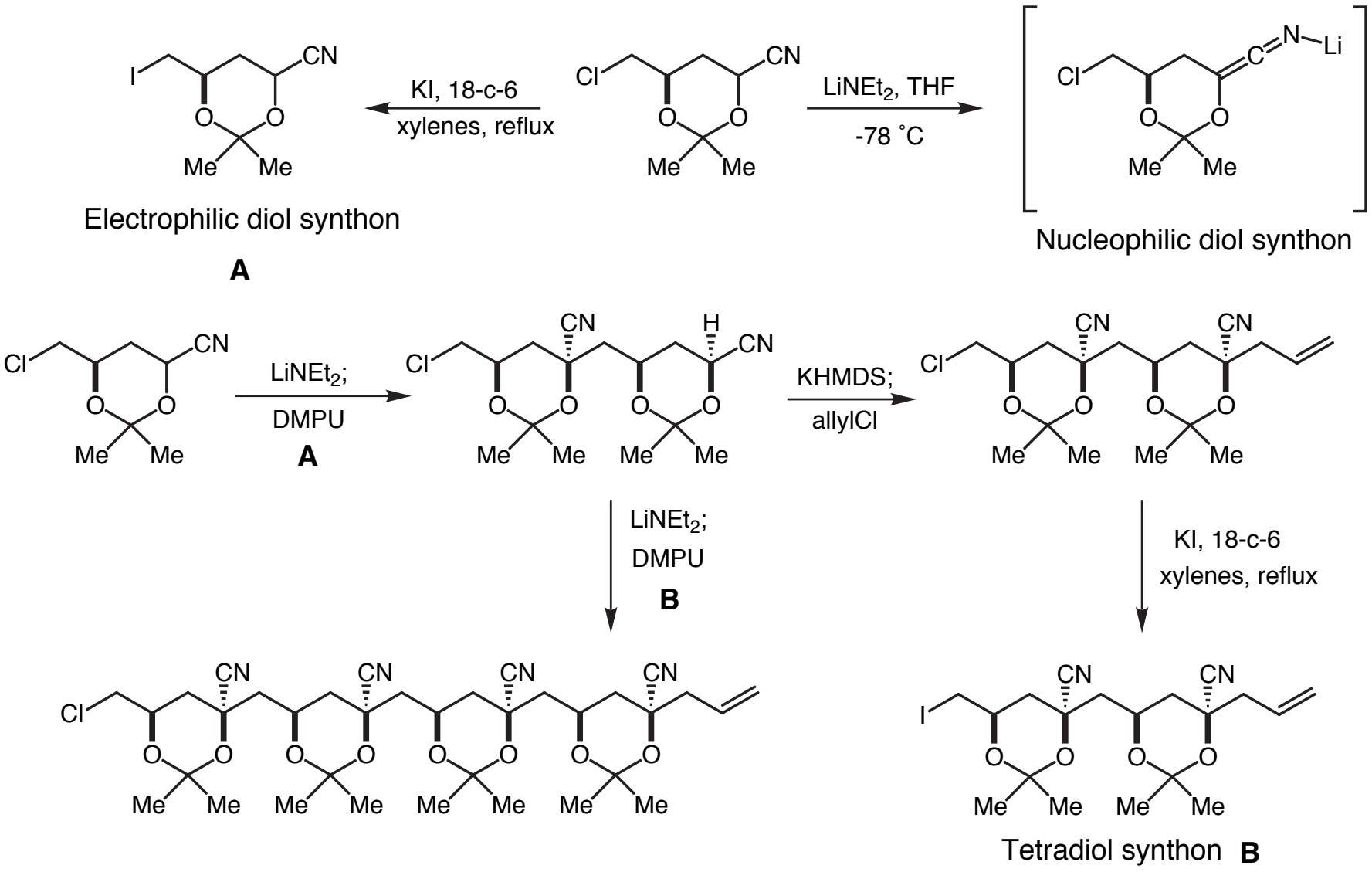
Axial radical more stable by ca. 3.5 kcal/mol (calc.)

Configurationally stable at low temperature

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

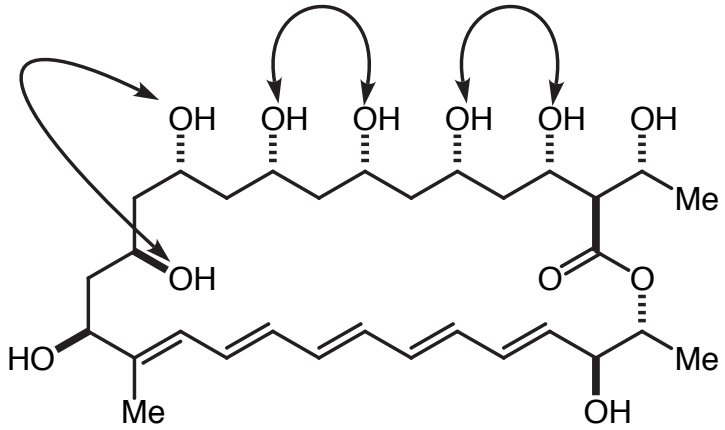
Rychnovsky et al., *J. Org. Chem.* **1990**, *55*, 5550.

Iterative and Convergent Syn Polyol Synthesis



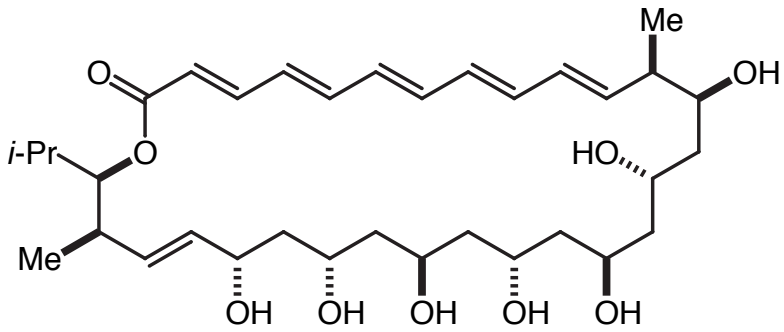
Rychnovsky et al., *J. Org. Chem.* **1992**, *57*, 1559.

Total Syntheses Using Cyanohydrin Acetonide Methodology



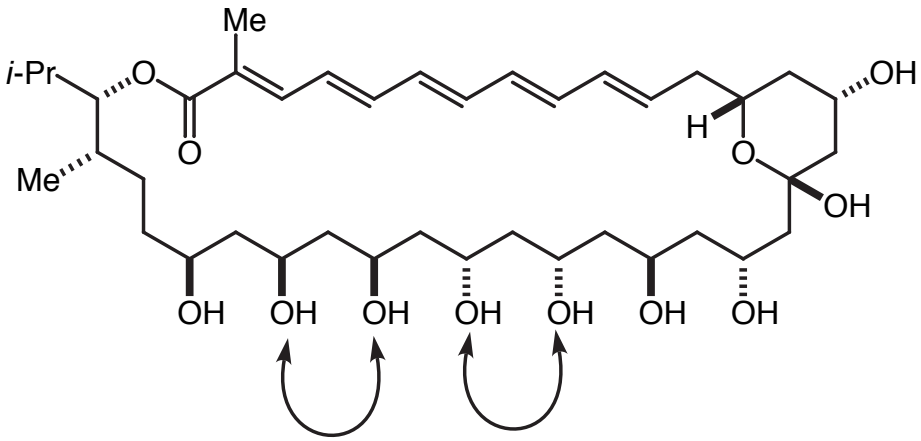
Filipin III

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

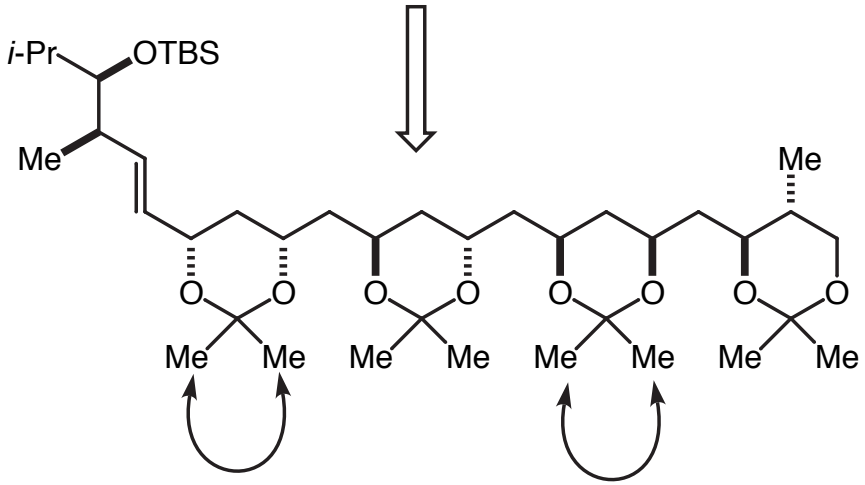


(-)-Roxaticin

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

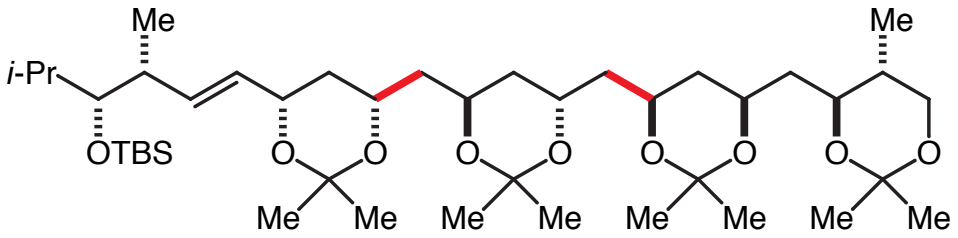


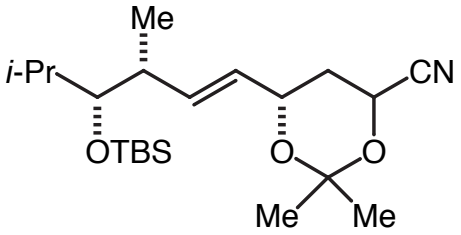
Roflamycoin

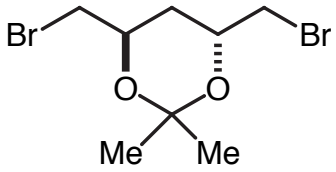


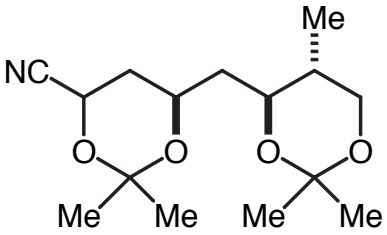
Rychnovsky et al., *J. Am. Chem. Soc.* **1997**, *119*, 2058.

Roxaticin Polyol Segment Retrosynthesis

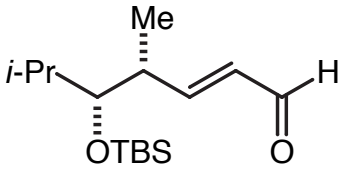




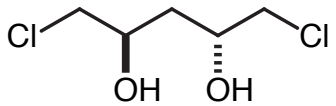




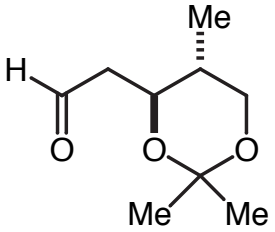
Anti-diol linchpin



From Noyori hydrogenation then Wittig



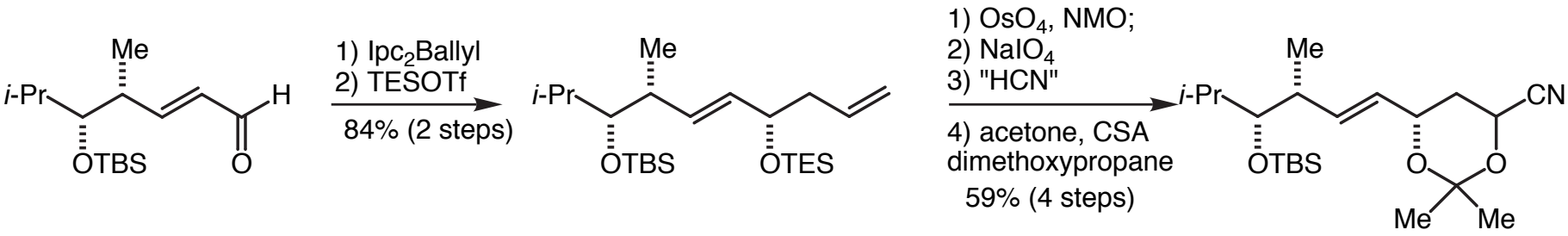
From Noyori hydrogenation of chlorodione

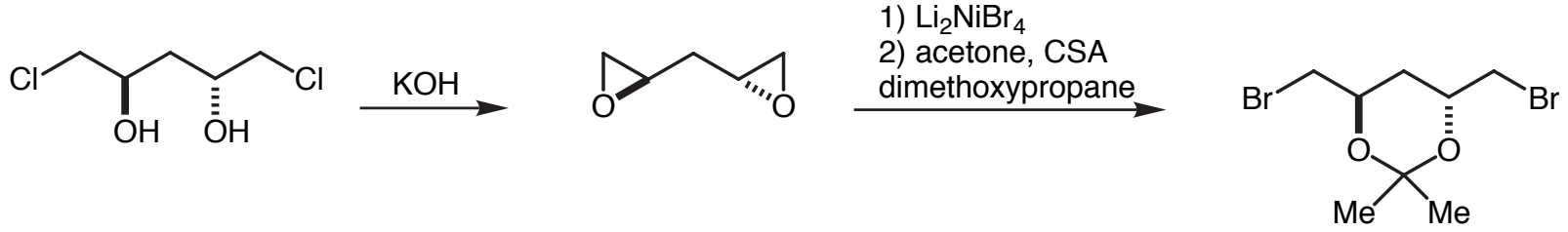


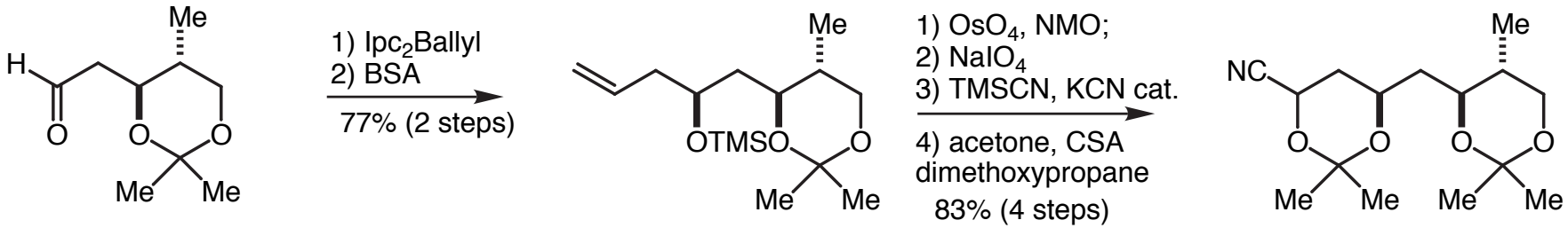
From Noyori hydrogenation then Frater-Seebach

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

Roxaticin Polyol Segment Fragment Synthesis

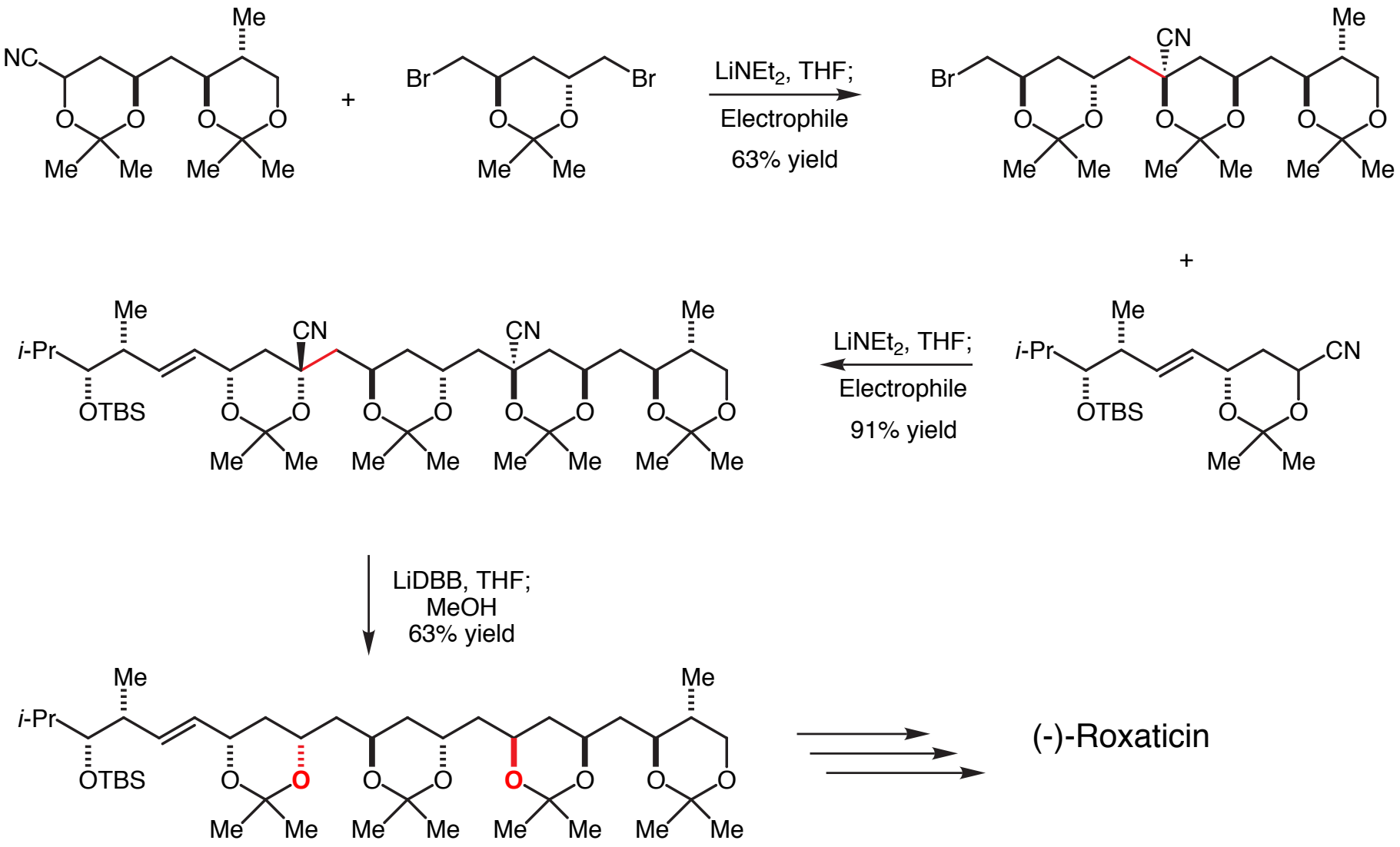






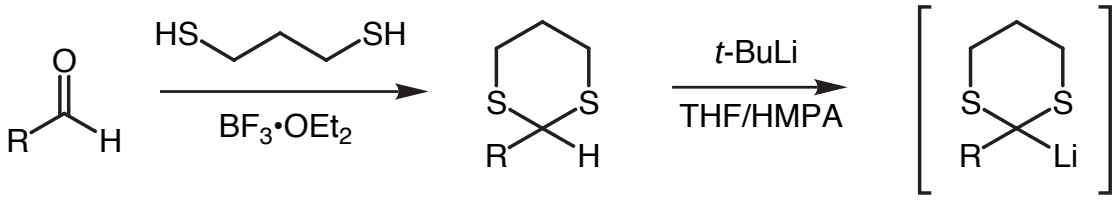
Rychnovsky and Hoye, *J. Am. Chem. Soc.* **1994**, *116*, 1753.

Roxaticin Polyol: Fragment Coupling



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

Smith: Dithiane Coupling

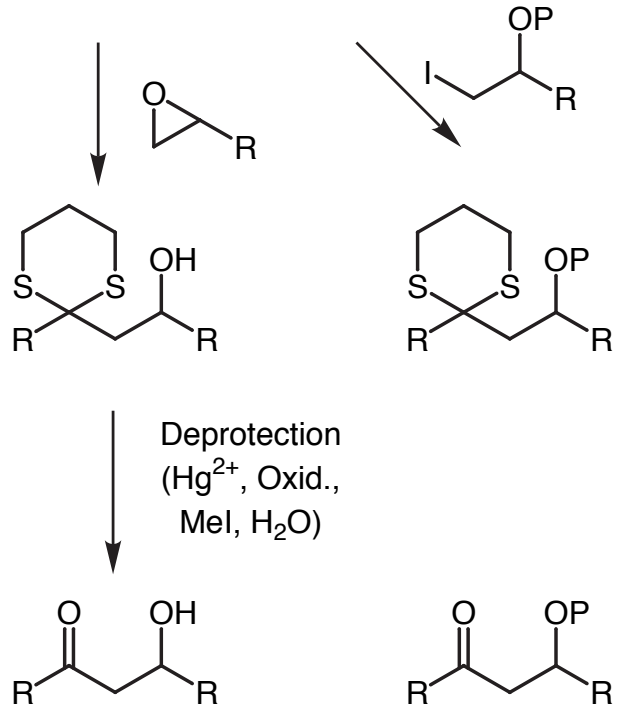


"The advantages of this method vis-a-vis the classical aldol reaction include the following:"

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

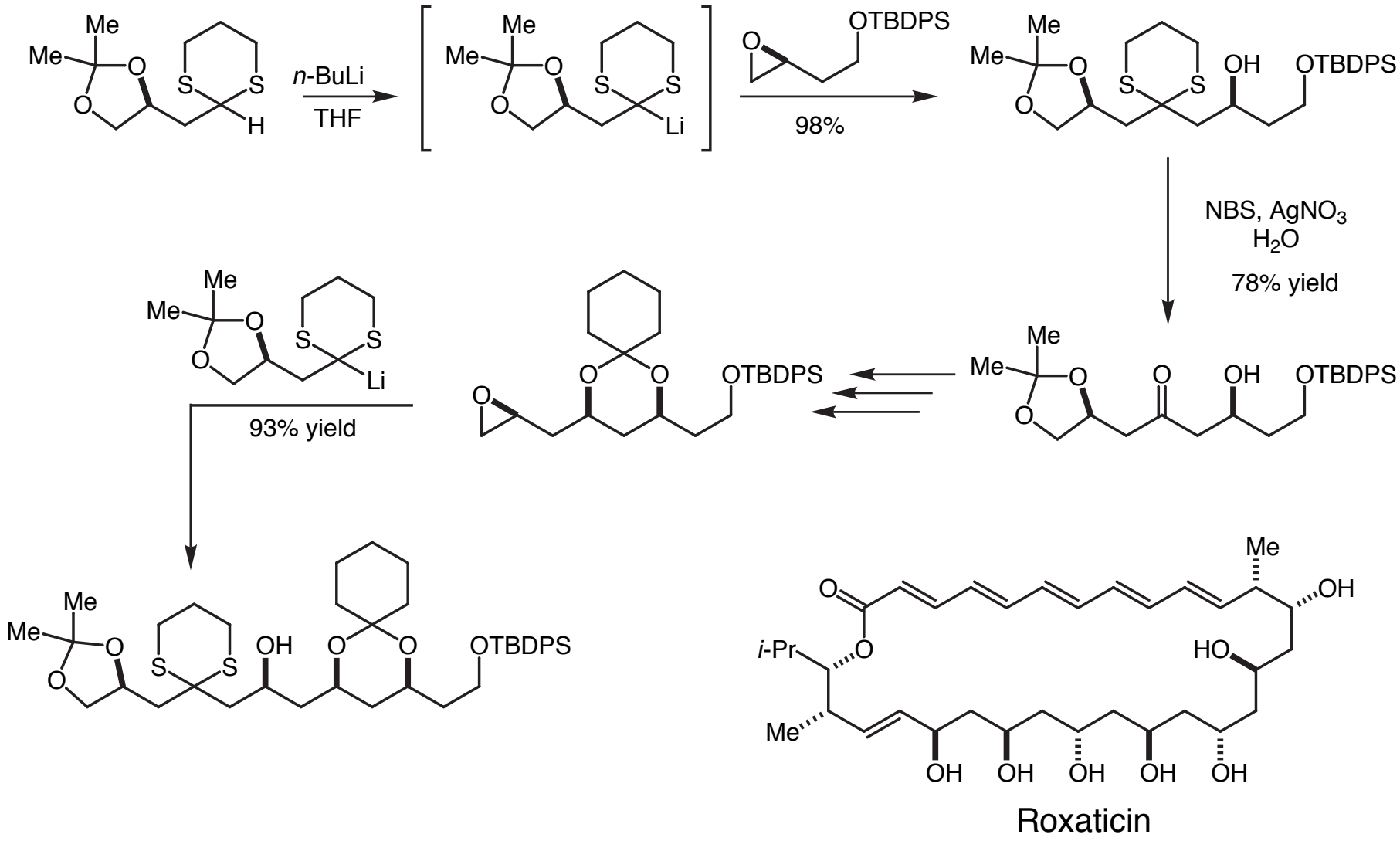
Disadvantages include:

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



Smith et al., *Acc. Chem. Res.* **1998**, *31*, 35.

Mori's Diacetate Synthon



Roxaticin

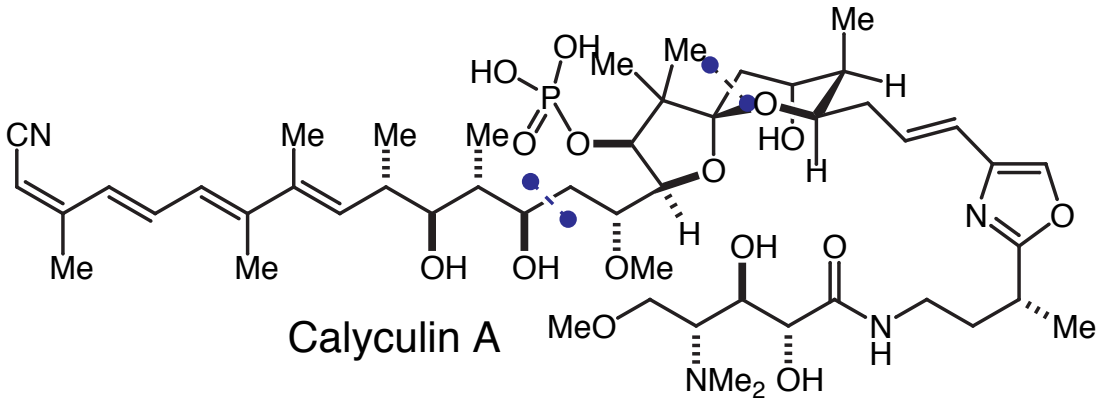
Tet. Lett. **1988**, *29*, 5419, 5423.

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

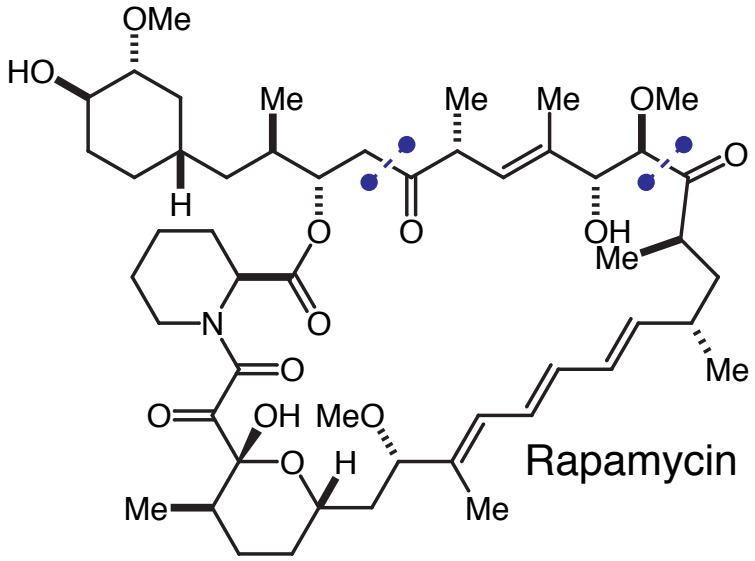
Roxaticin synthesis

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

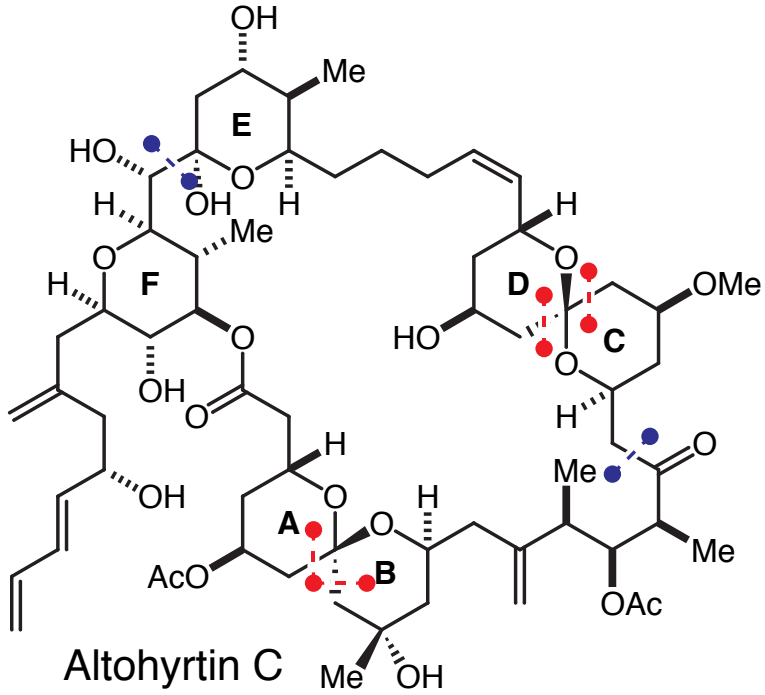
Smith Syntheses Utilizing Dithiane Coupling



Calyculin A

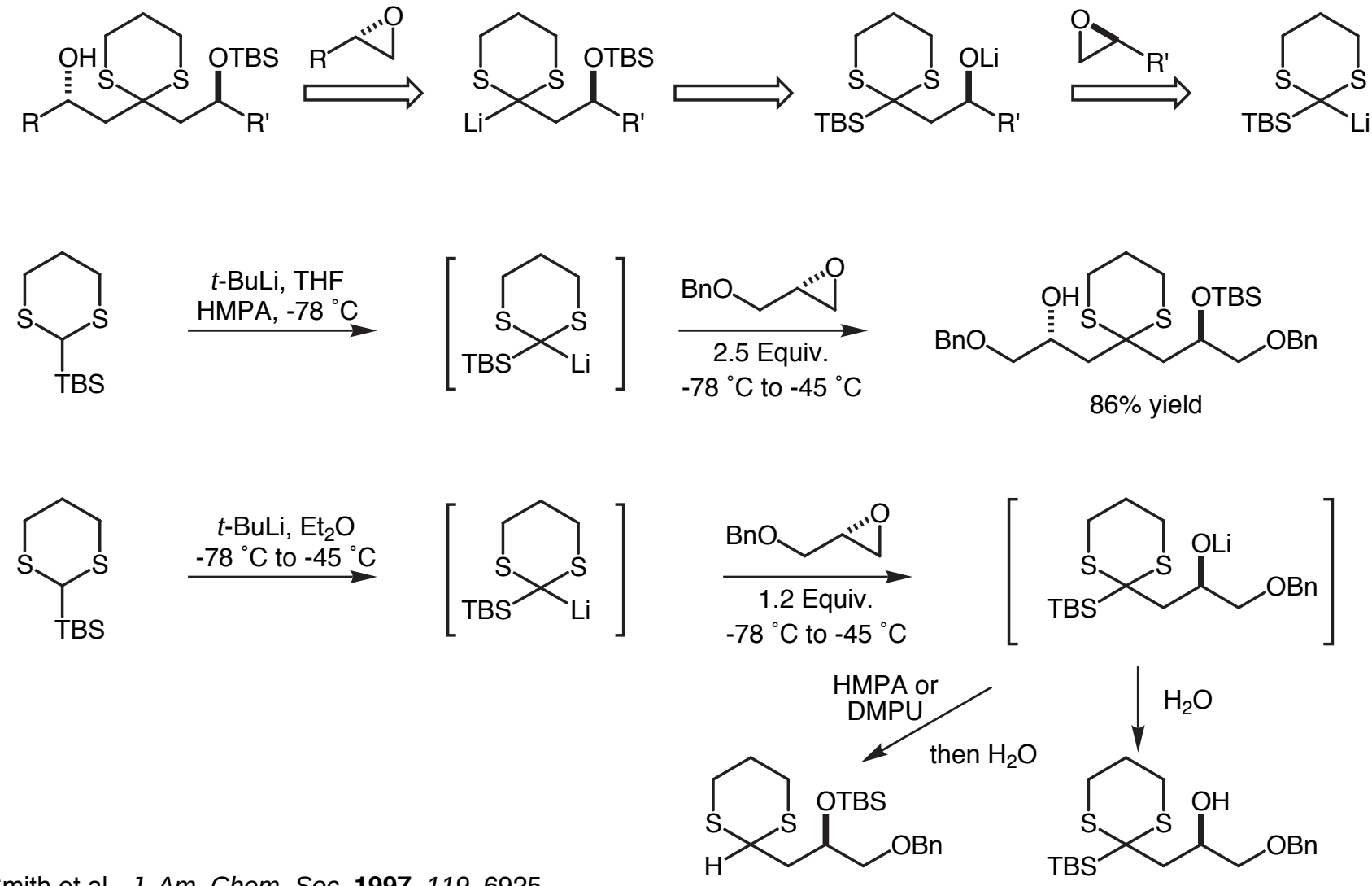


Rapamycin



Altohyrtin C

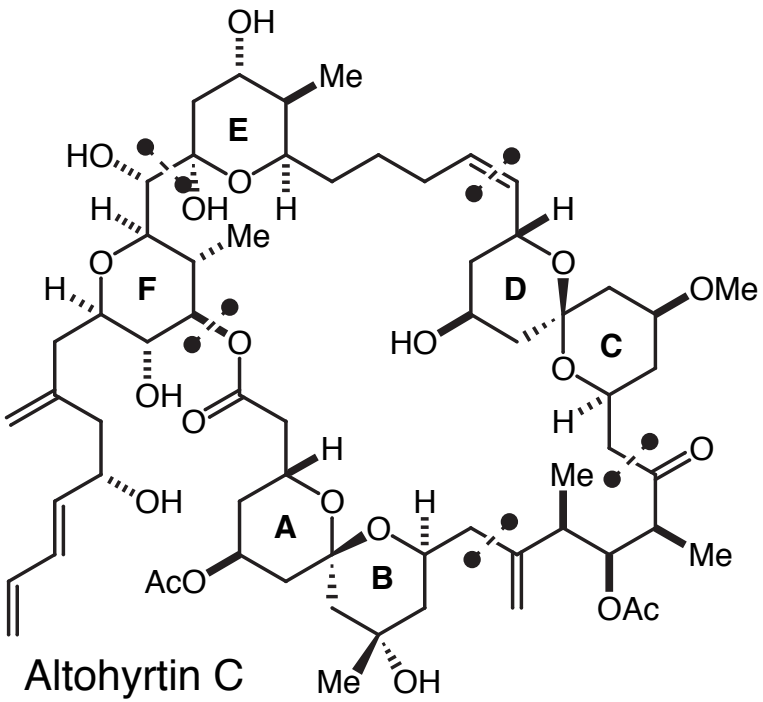
Smith: Multicomponent Dithiane Coupling via Brook Rearrangement



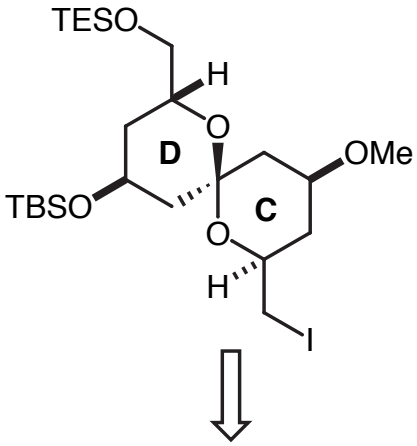
Smith et al., *J. Am. Chem. Soc.* **1997**, *119*, 6925.

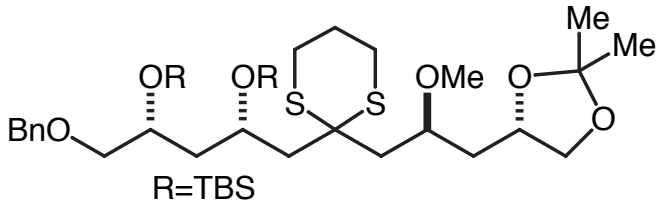
See also: Smith et al., *Org. Lett.* **1999**, *1*, 2001.

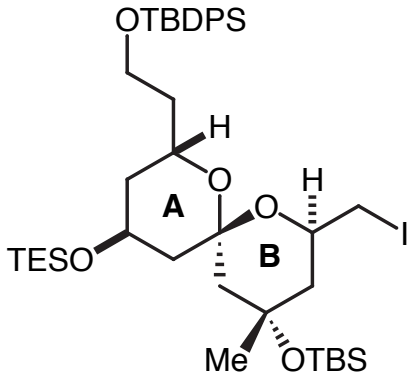
Smith: Altohyrtin C Fragment Retrosyntheses

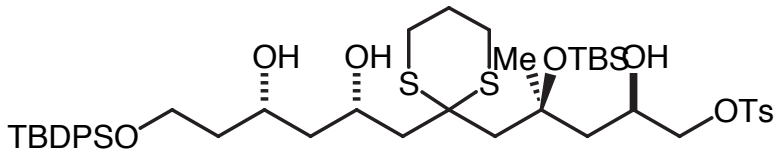


Altohyrtin C





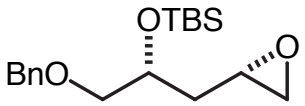




Smith et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 191.

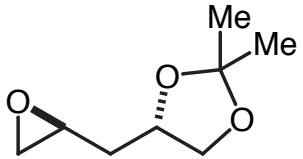
Smith et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 196.

Smith: Altohyrtin C CD Ring Fragment



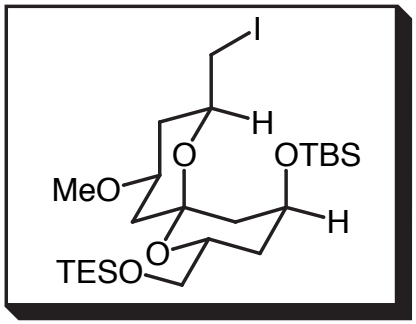
A

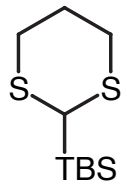
9 steps from glycerol acetonide



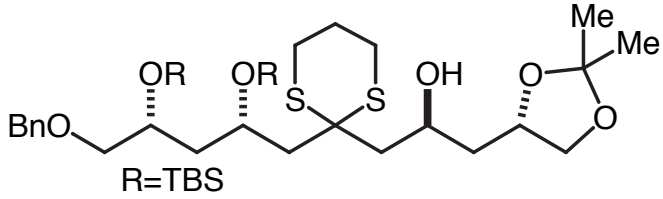
B

6 steps from glyceraldehyde acetonide

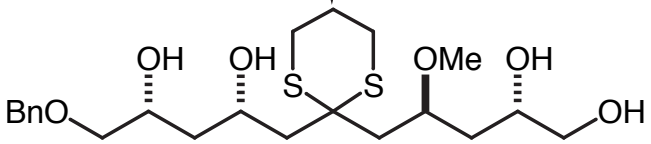




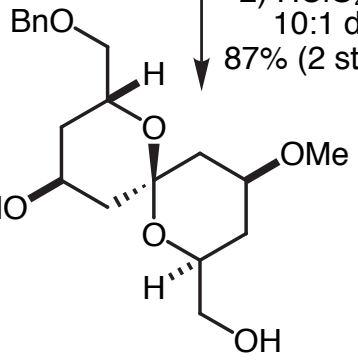
t-BuLi,Et_2O;
A;
B, HMPA
72%



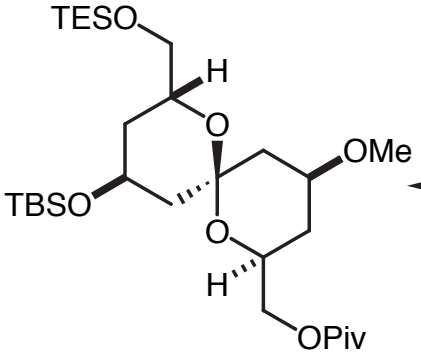
1) NaH, MeI
2) HCl, MeOH
80% (2 steps)



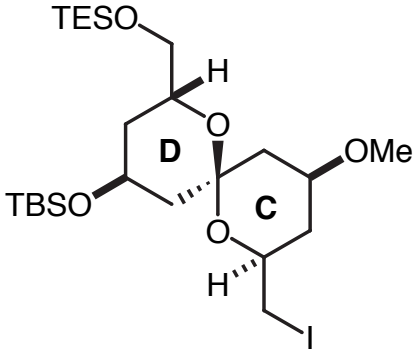
1) $Hg(ClO_4)_2$
$CaCO_3$
2) $HClO_4$
10:1 dr
87% (2 steps)



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

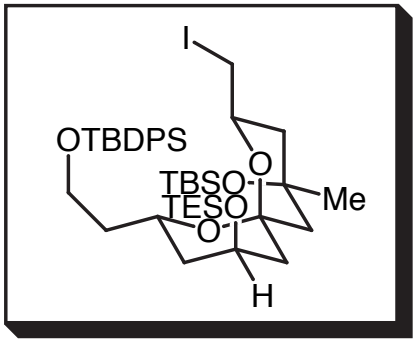


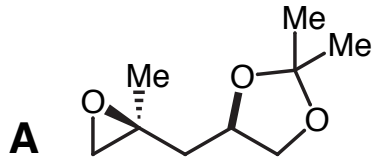
1) DIBAL-H
2) TsCl
3) NaI
4) TESOTf
66% (4 steps)



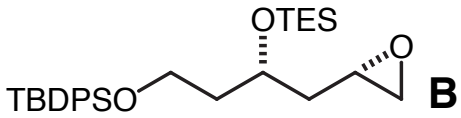
Smith et al., *Tet. Lett.* **1997**, *38*, 8671.

Smith: Altohyrtin C AB Ring Fragment

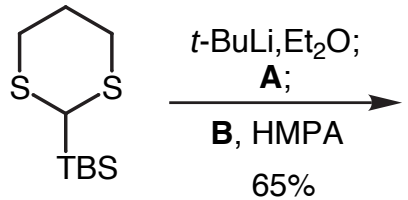




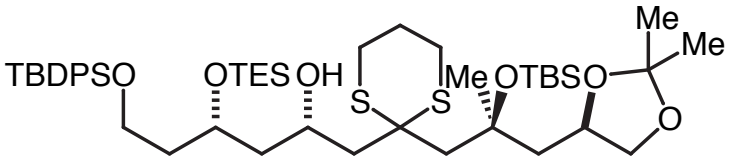
5 steps from glyceraldehyde acetonide



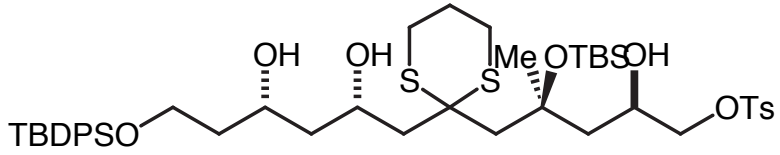
5 steps from (+)Ipc_2Allyl



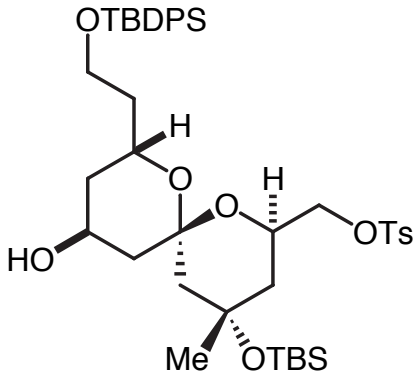
t-BuLi,Et_2O;
A;
B, HMPA
65%



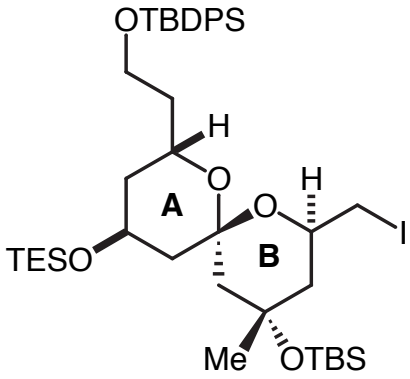
1) TFA/H_2O
2) TsCl
79% (2 steps)



$Hg(ClO_4)_2$
$CaCO_3$
81%, 26:1 dr

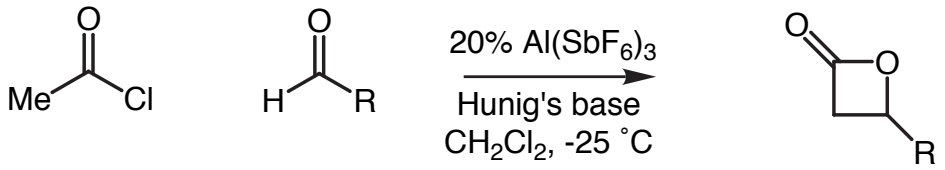


1) TESOTf
2) LiI
96% (2 steps)

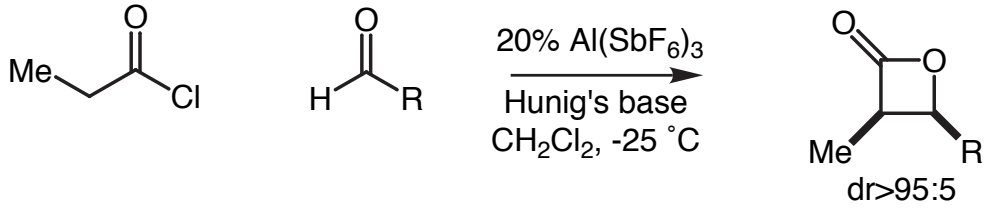


Smith et al., *Tet. Lett.* **1997**, *38*, 8675.

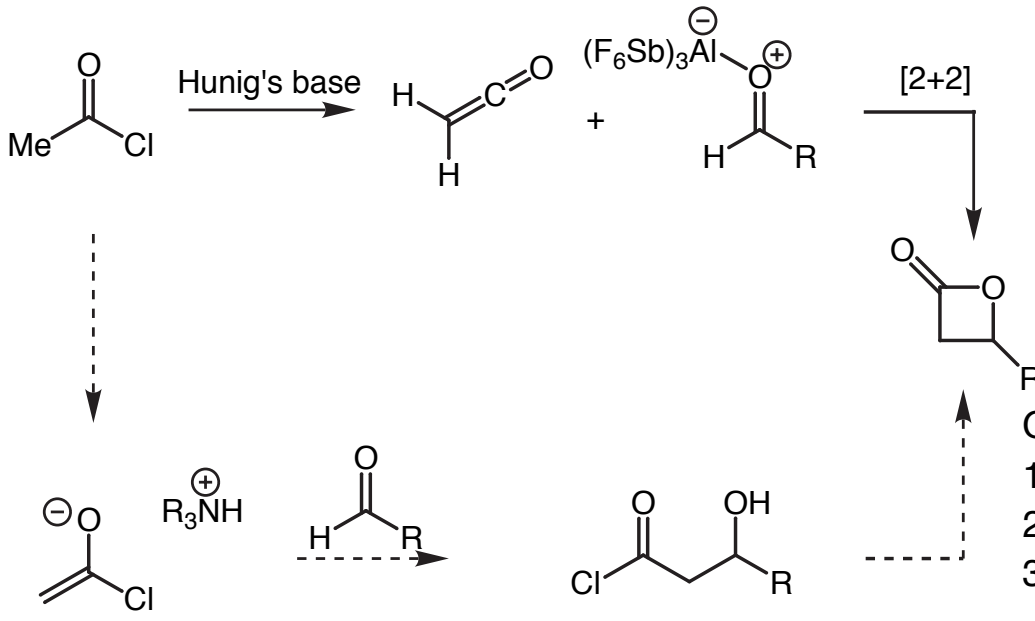
Nelson's Acyl Halide/Aldehyde Cyclocondensation



Aldehyde	Yield
$PhCH_2CH_2CHO$	93%
$C_6H_{11}CHO$	90%
$BnOCH_2CHO$	83%
$CH_2=CH(CH_2)_8CHO$	81%



Mechanism:



Aldehyde	Yield
$C_6H_{11}CHO$	65%
$CH_2=CH(CH_2)_8CHO$	80%

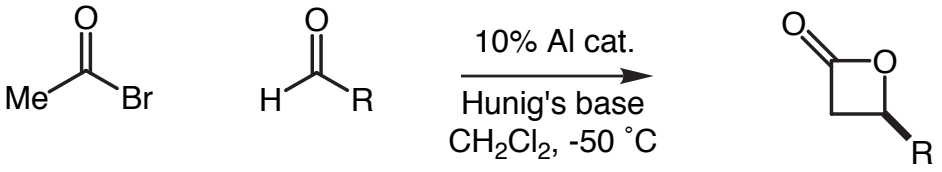
Observations:

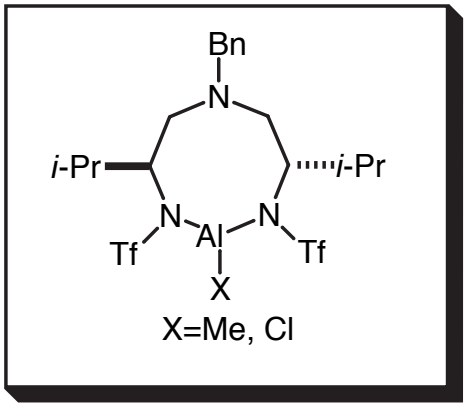
1) Ketene observed in ^{13}C NMR
2) Enolate not observed in ^{13}C NMR
3) No lactone formed in absence of Al^{3+}

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

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

Nelson's Enantioselective Acyl Halide/Aldehyde Cyclocondensation



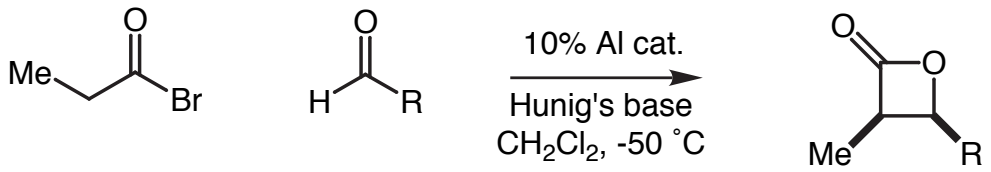


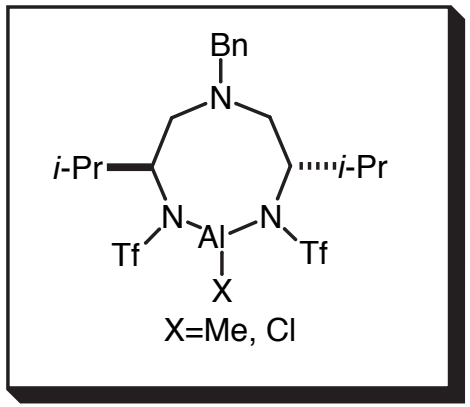
Alpha branched, unsaturated aldehydes afford low ee, yield

Aldehyde	%ee	% yield
$PhCH_2CH_2CHO$	92	93
Me_2CHCH_2CHO	93	80
$BnOCH_2CHO$	91	91
$CH_2=CH(CH_2)_8CHO$	91	91
$TBDPSOCH_2CHO$	89	74
$BnOH_2CC{\equiv}CCHO$	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





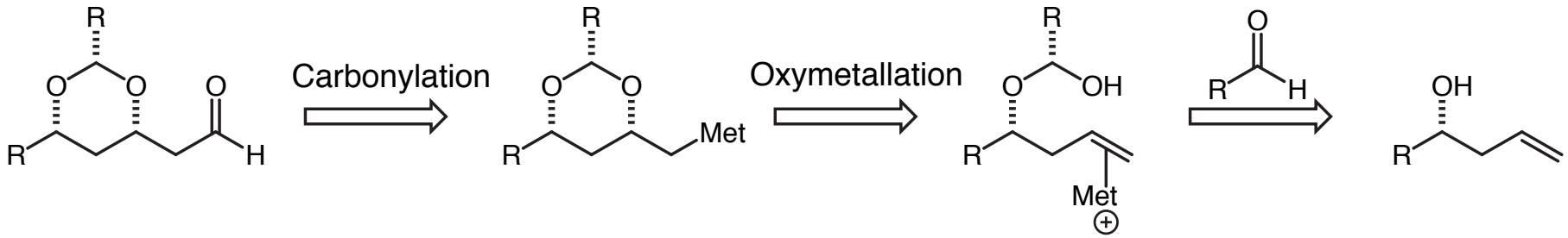
Other aliphatic aldehydes, unsaturated enals afford low yields, ee's.

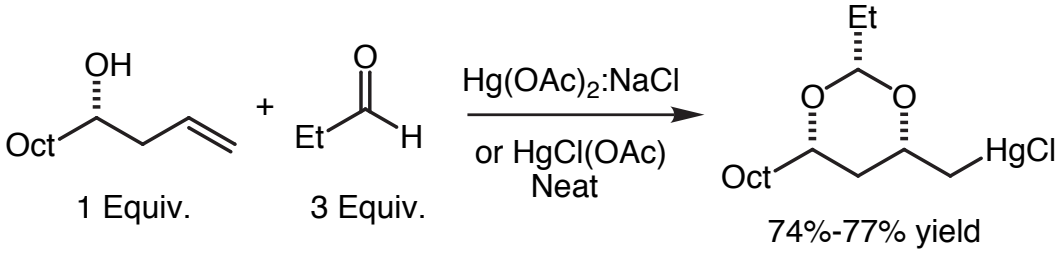
Aldehyde	%ee	dr	% yield
$BnOCH_2CHO$	94	88:12	78
$BnOH_2CC{\equiv}CCHO$	94	91:9	85
$C_6H_{11}C{\equiv}CCHO$	93	98:2	85
$TMSC{\equiv}CCHO$	93	99:1	90
$PhC{\equiv}CCHO$	91	99:1	83

Nelson et al., *J. Am. Chem. Soc.* **1999**, *121*, 9742.

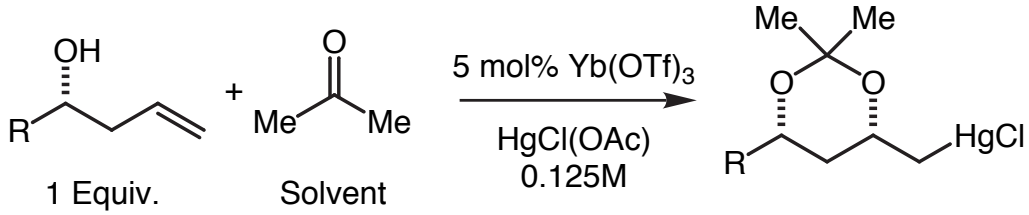
Nelson and Wan, *Org. Lett.* **2000**, *2*, 1883.

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.

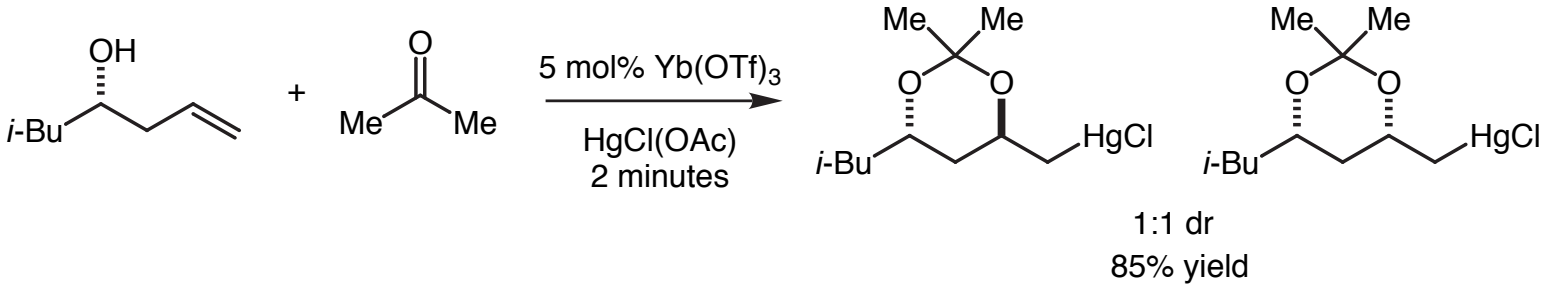


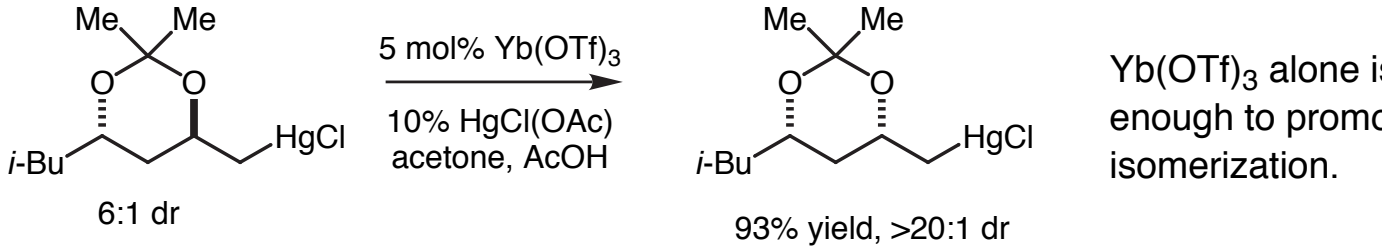
Acetone, benzaldehyde now useful substrates.
Yields typically 70-85%, dr at least 20:1.

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

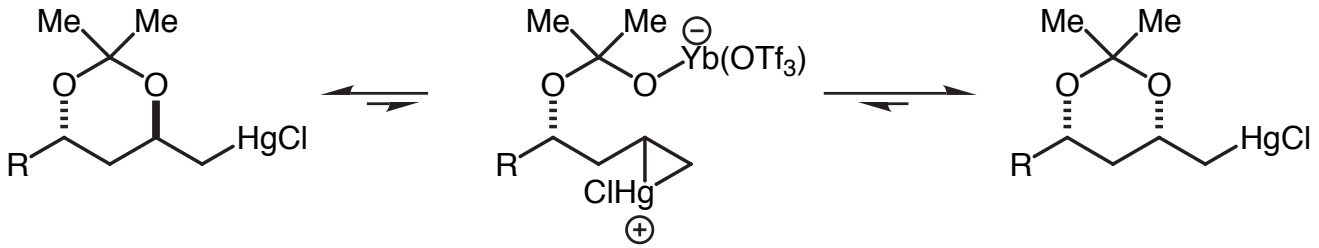
Leighton's Oxymercuration of Hemiacetals

Is $Yb(OTf)_3$ simply increasing the rate of kemiketal formation?





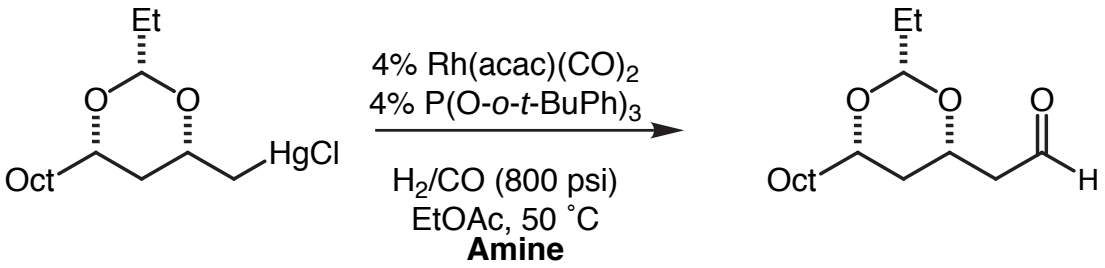
$Yb(OTf)_3$ alone is enough to promote the isomerization.



Leighton and Sarraf, *Org. Lett.* **2000**, *2*, 403.

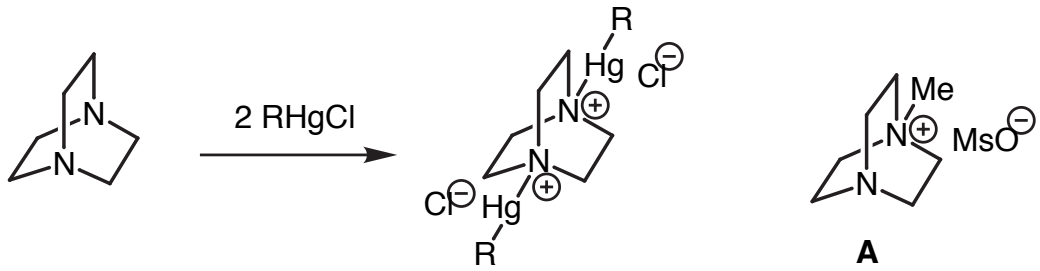
Leighton et al., *Org. Lett.* **2000**, *2*, 3197.

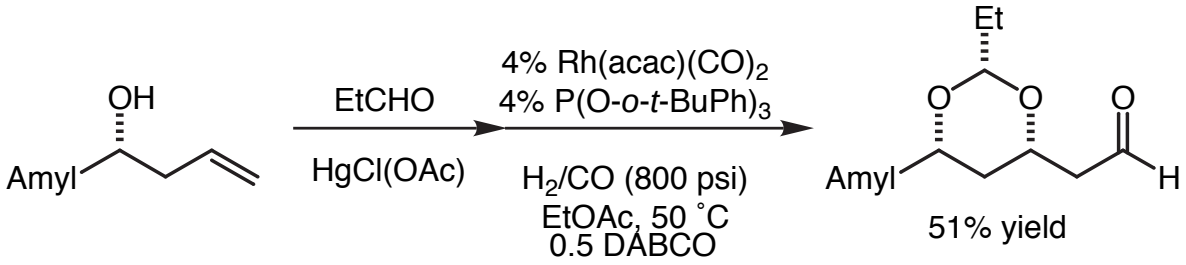
Leighton's Formylation of Mercurials



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%

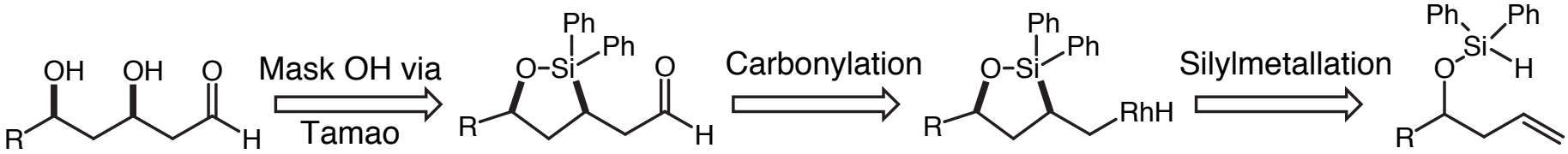


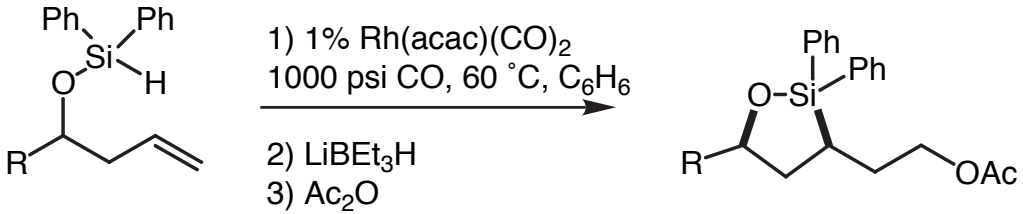


One pot procedure delivers aldehyde in comparable yield to two step procedure, without isolation of mercurial intermediate.

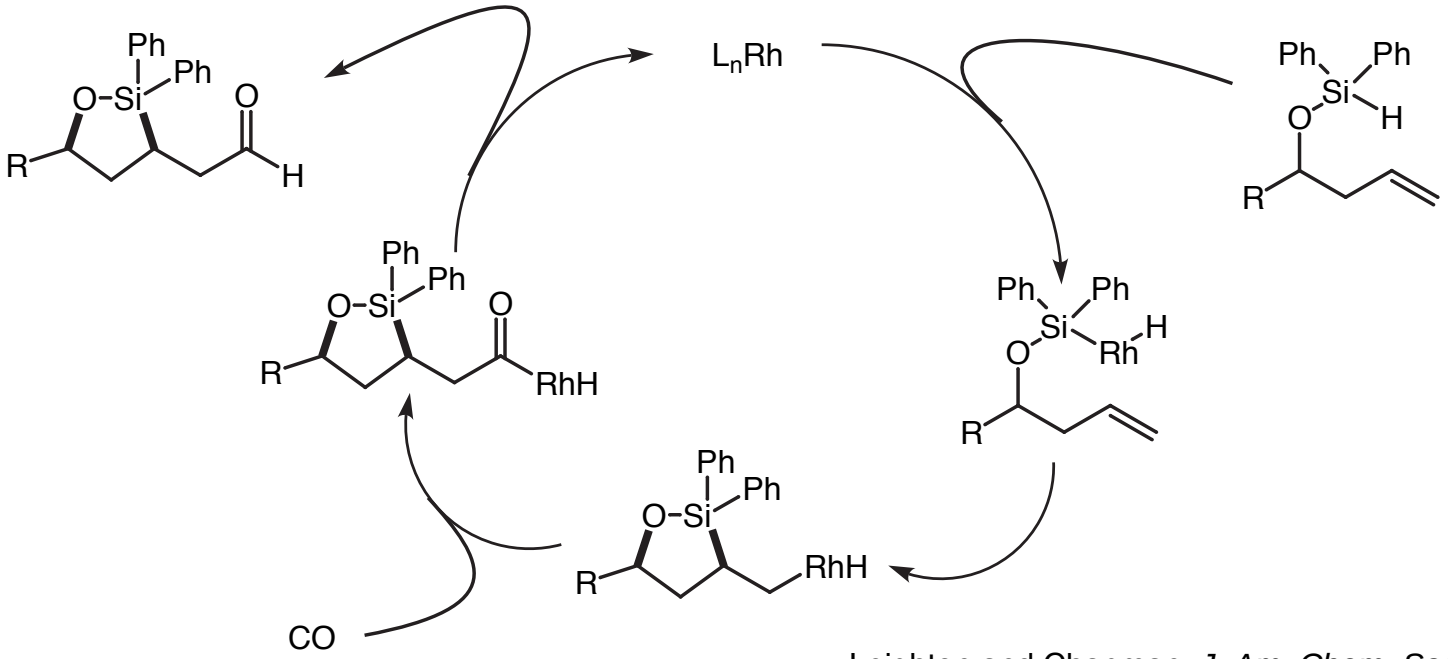
Leighton et al., *Org. Lett.* **2000**, *2*, 3205.

Leighton's Silylformylation



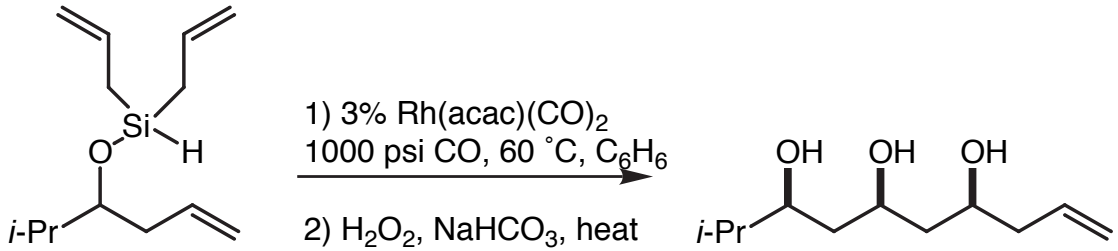


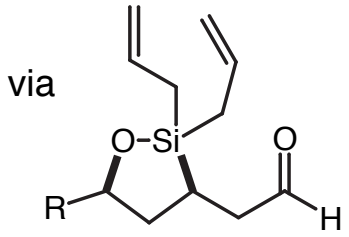
R	dr	Yield
Me	4.5:1	67%
Allyl	4:1	64%
i-Pr	6:1	79%
TBSOEt	4:1	60%



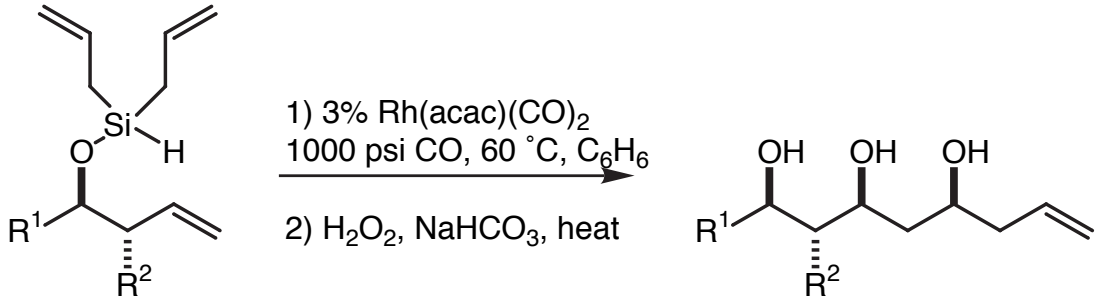
Leighton and Chapman, *J. Am. Chem. Soc.* **1997**, *119*, 12416.

Leighton's Silylformylation/Allylation



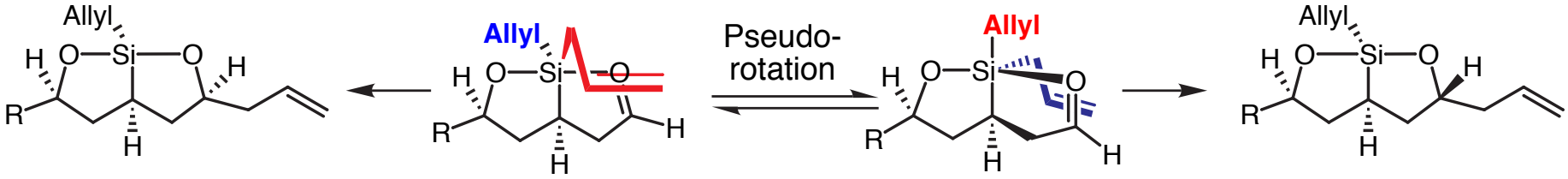


59% plus 18% stereoisomers



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

Stereochemical rationale:

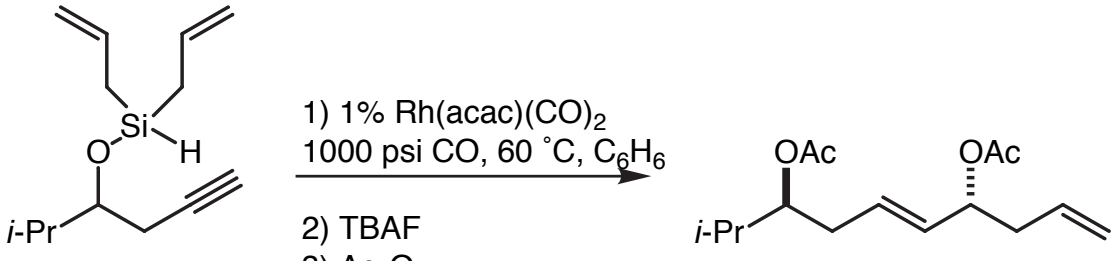


Major pathway

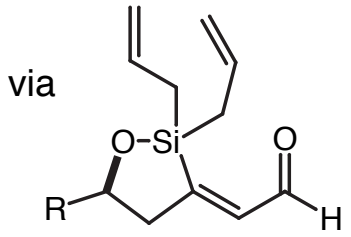
Minor pathway

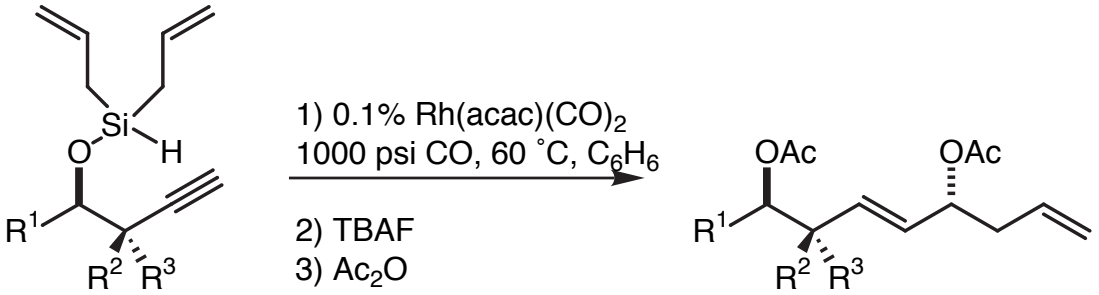
Leighton and Zacuto, *J. Am. Chem. Soc.* **2000**, *122*, 8587.

Leighton's Alkyne Silylformylation/Allylation

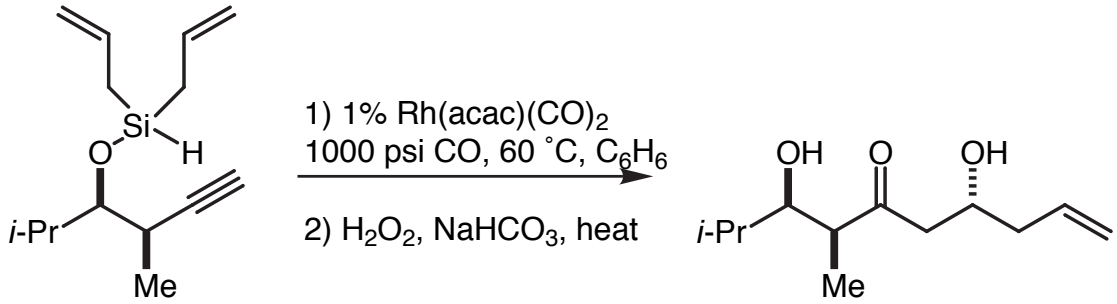


83% yield, 8:1 dr





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

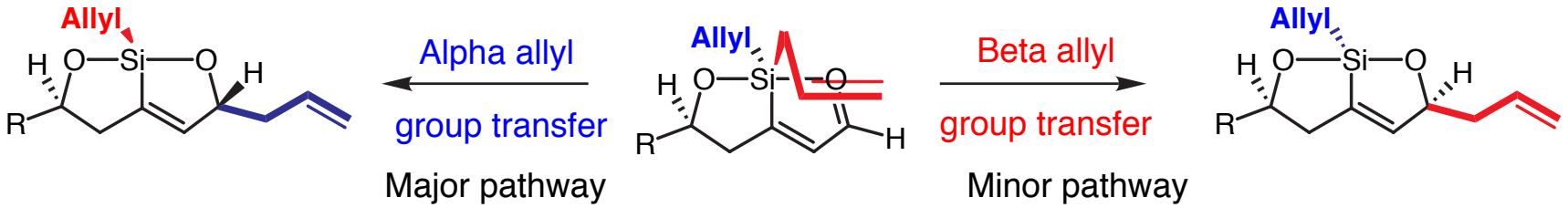


65% yield, 23:1 dr

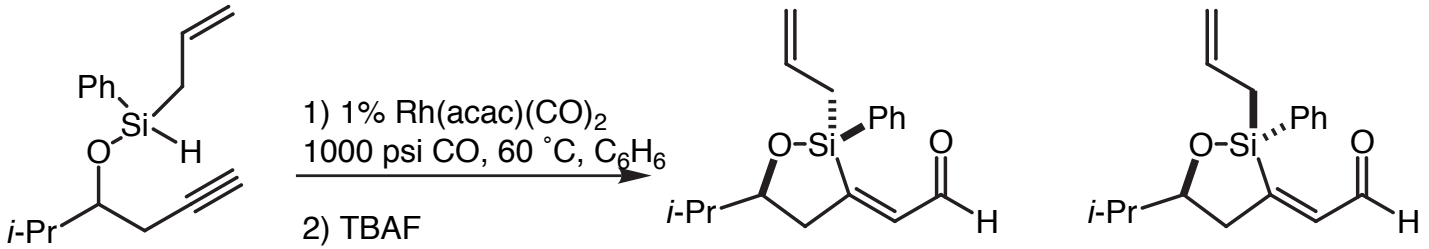
Leighton and O'Malley, *Angew. Chem. Int. Ed.* **2001**, *40*, 2915.

Leighton's Alkyne Silylformylation/Allylation

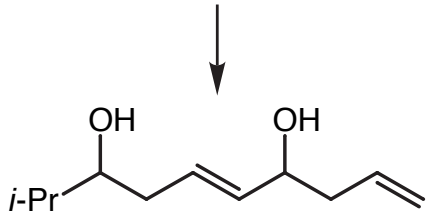
Stereochemical rationale:



Top allyl group experiences steric repulsion with R group



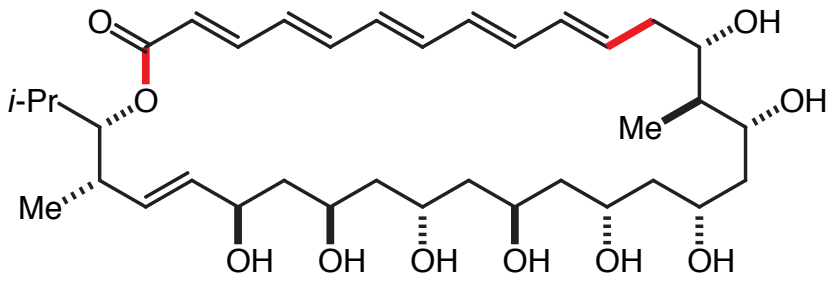
1:1 diastereomeric mixture



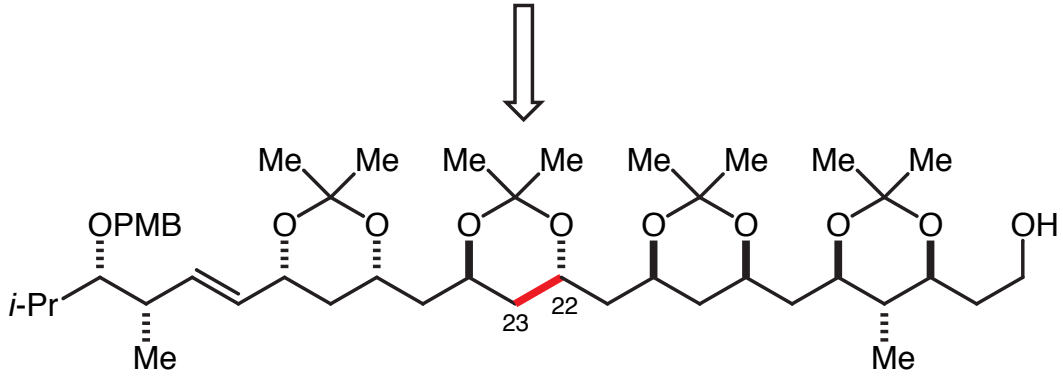
1:1 diastereomeric mixture

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

Leighton's Retrosynthesis of Mycoticin A

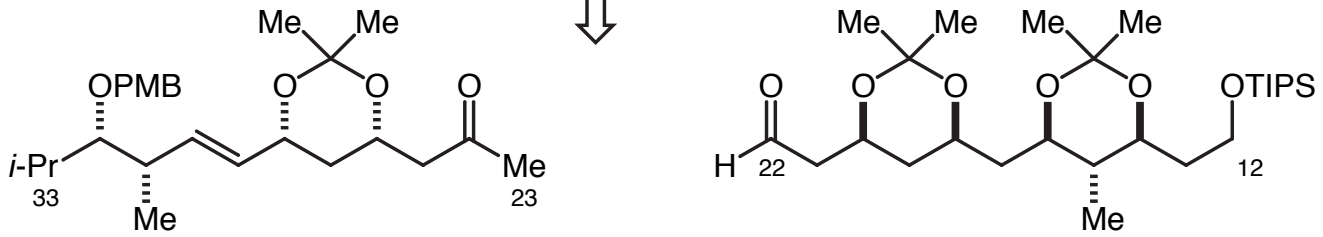


Mycoticin A



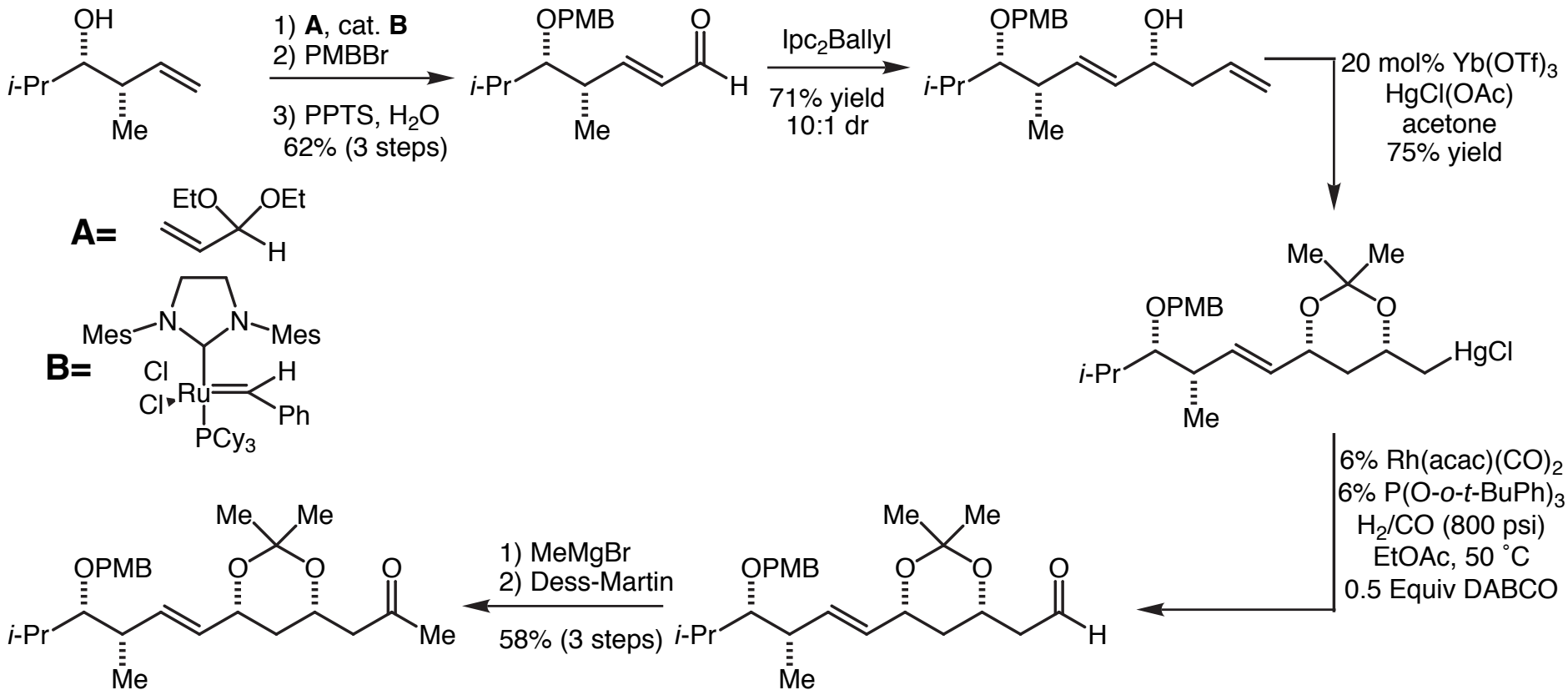
Schreiber's polyol segment

1,3 anti aldol



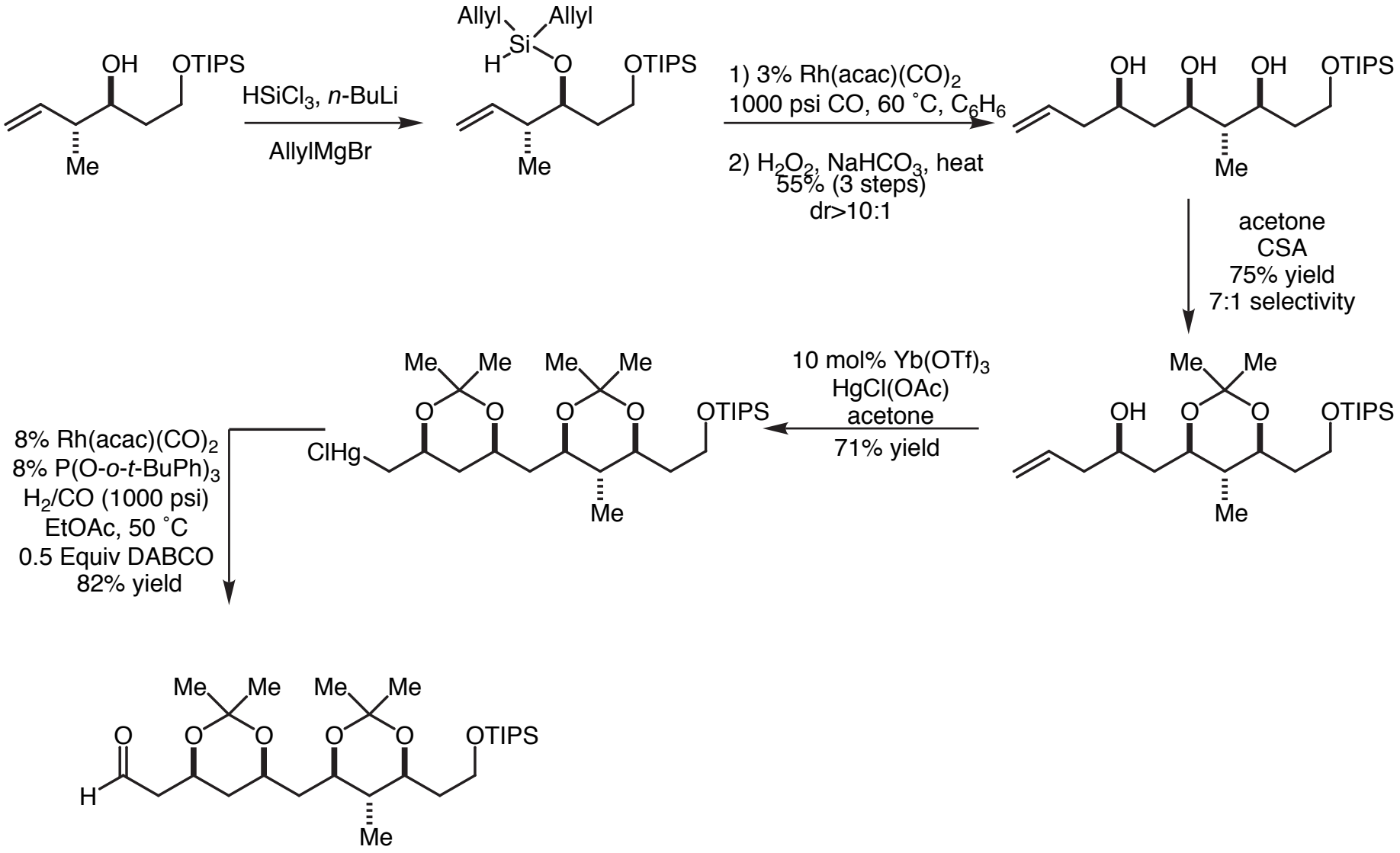
Leighton and Dreher, *J. Am. Chem. Soc.* **2001**, *123*, 341.

Leighton's Synthesis of the C_{23}-C_{33} Methyl Ketone



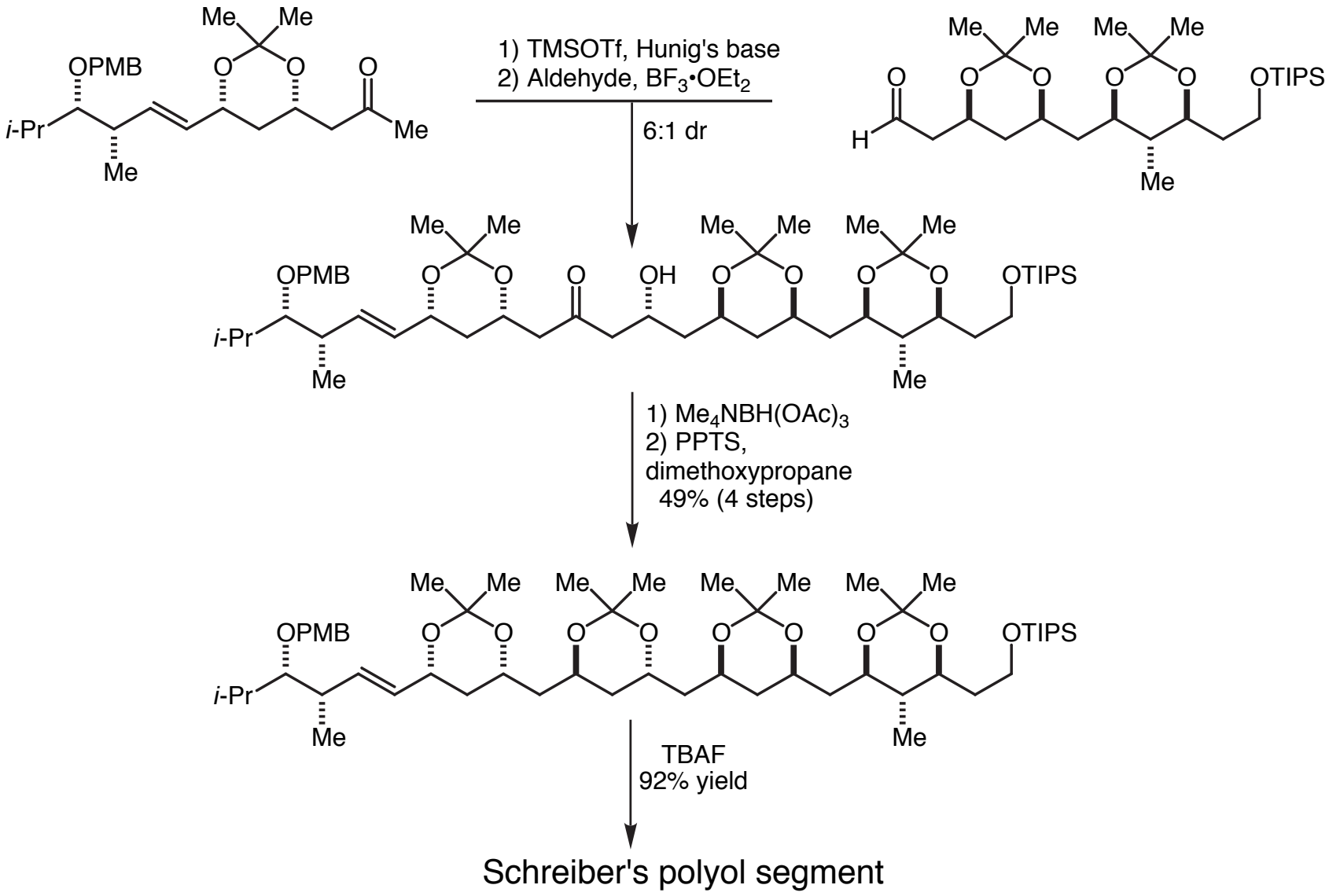
Leighton and Dreher, *J. Am. Chem. Soc.* **2001**, *123*, 341.

Leighton's Synthesis of the C_{12}-C_{22} Aldehyde



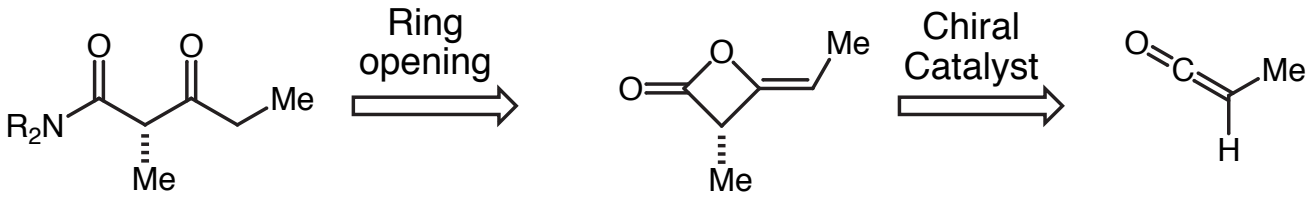
Leighton and Dreher, *J. Am. Chem. Soc.* **2001**, *123*, 341.

Leighton's Formal Synthesis of Mycoticin A

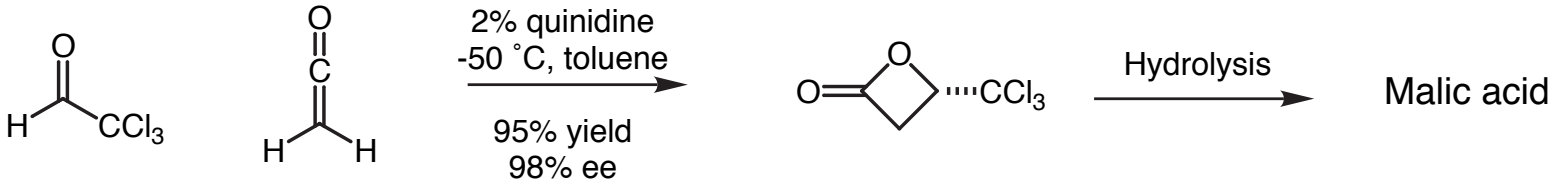


Leighton and Dreher, *J. Am. Chem. Soc.* **2001**, *123*, 341.

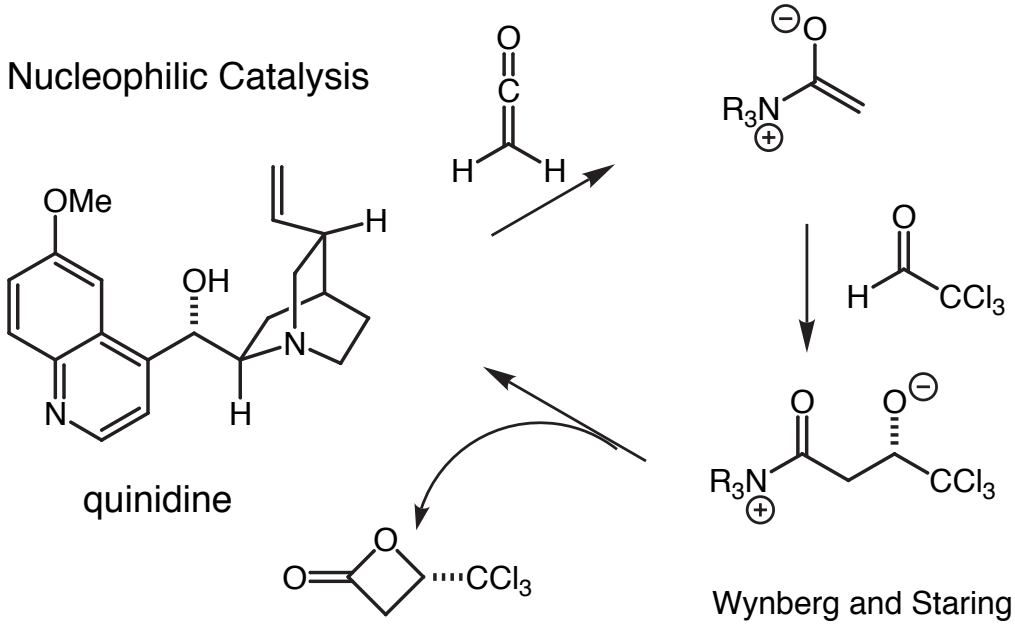
Calter: Asymmetric Methylketene Dimerization



Wynberg's precedent: 1982

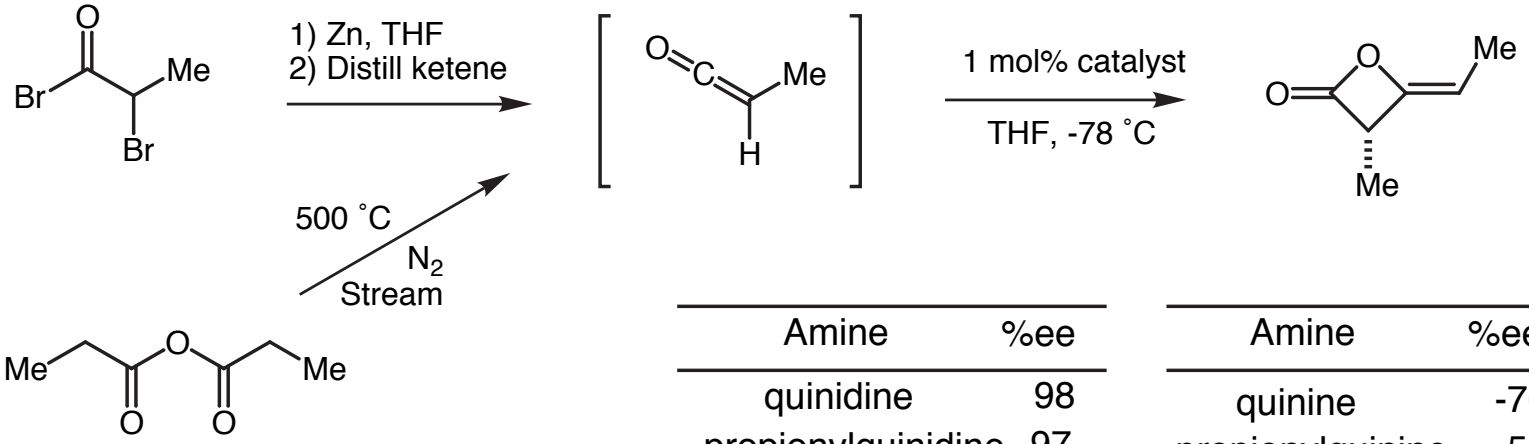


Mechanism: Nucleophilic Catalysis



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

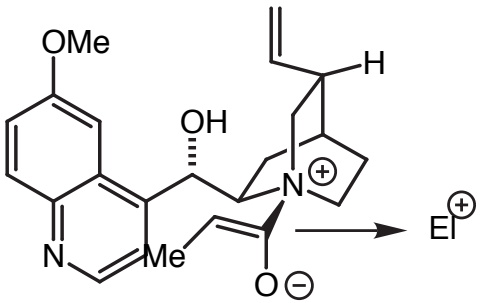
Calter: Asymmetric Methylketene Dimerization



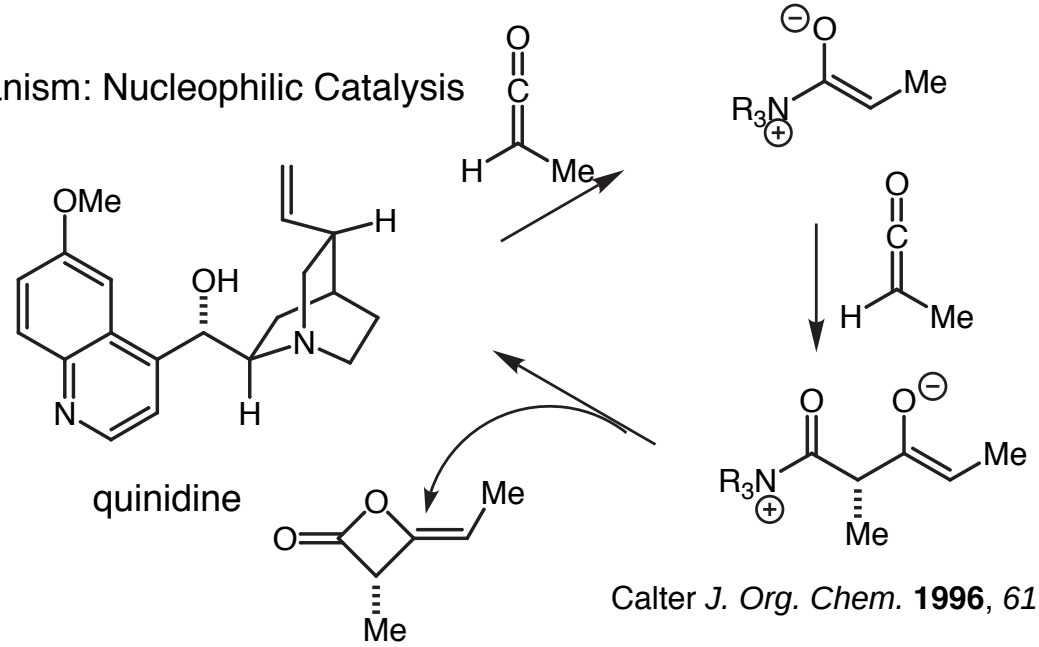
Amine	%ee
quinidine	98
propionylquinidine	97
TMS-quinidine	98

Amine	%ee
quinine	-70
propionylquinine	-54
TMS-quinine	-93

Model for stereoinduction

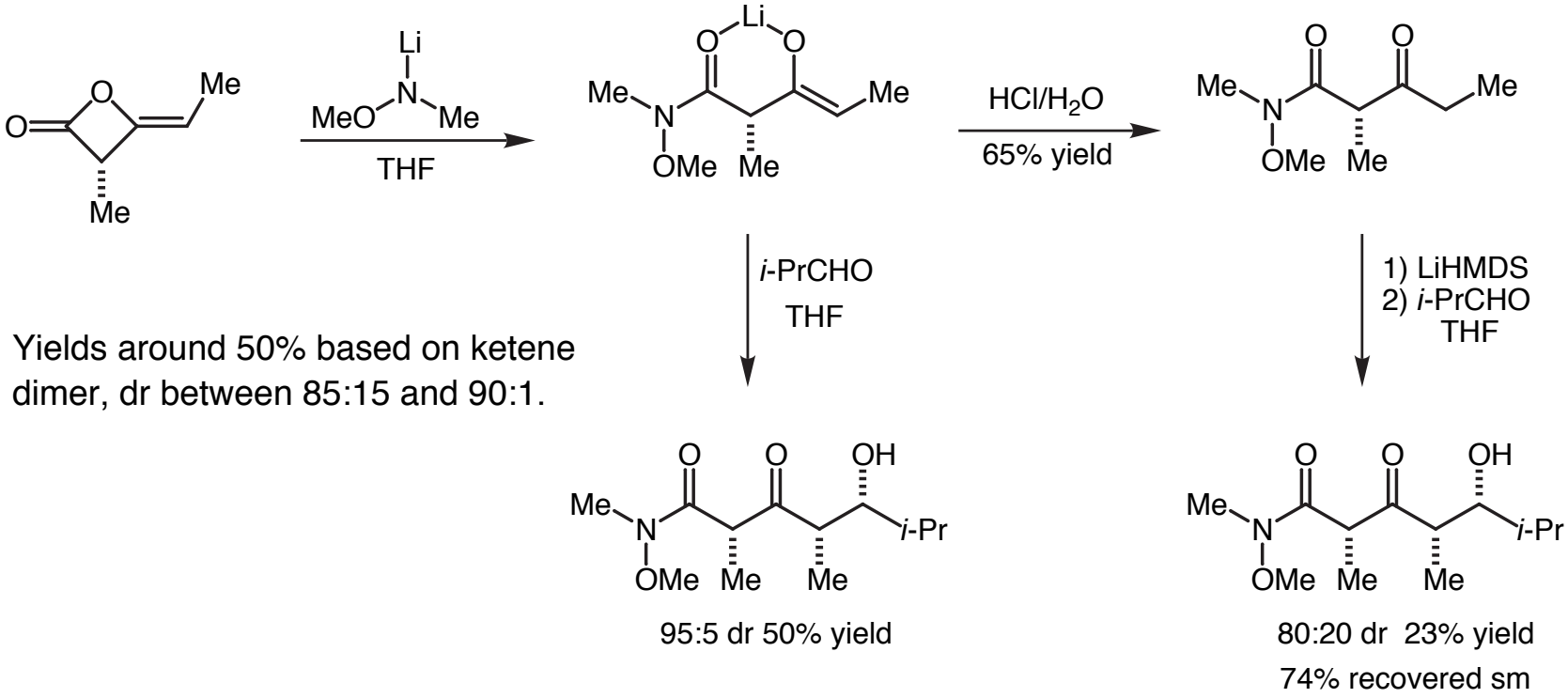


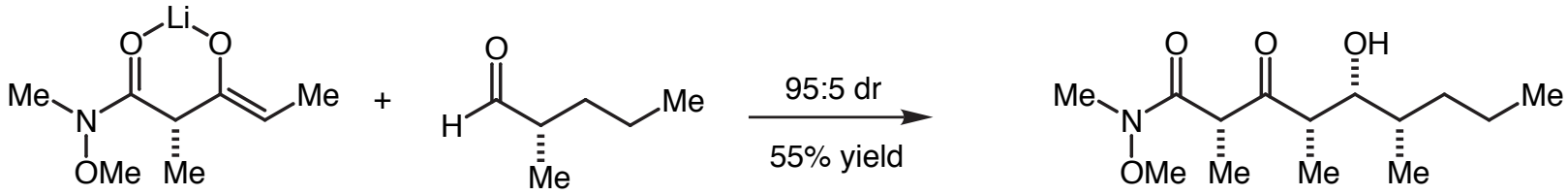
Mechanism: Nucleophilic Catalysis



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

Calter: Tandem Ring Opening/Aldol Reaction

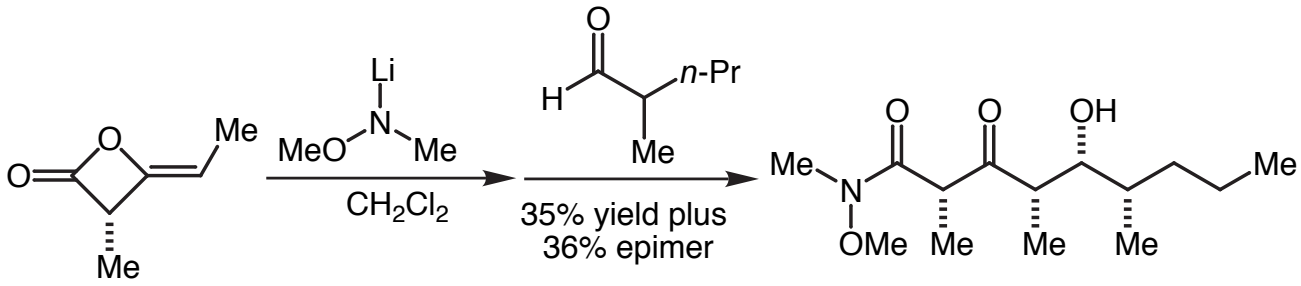




Calter et al., *Org. Lett.* **2001**, *3*, 1499.

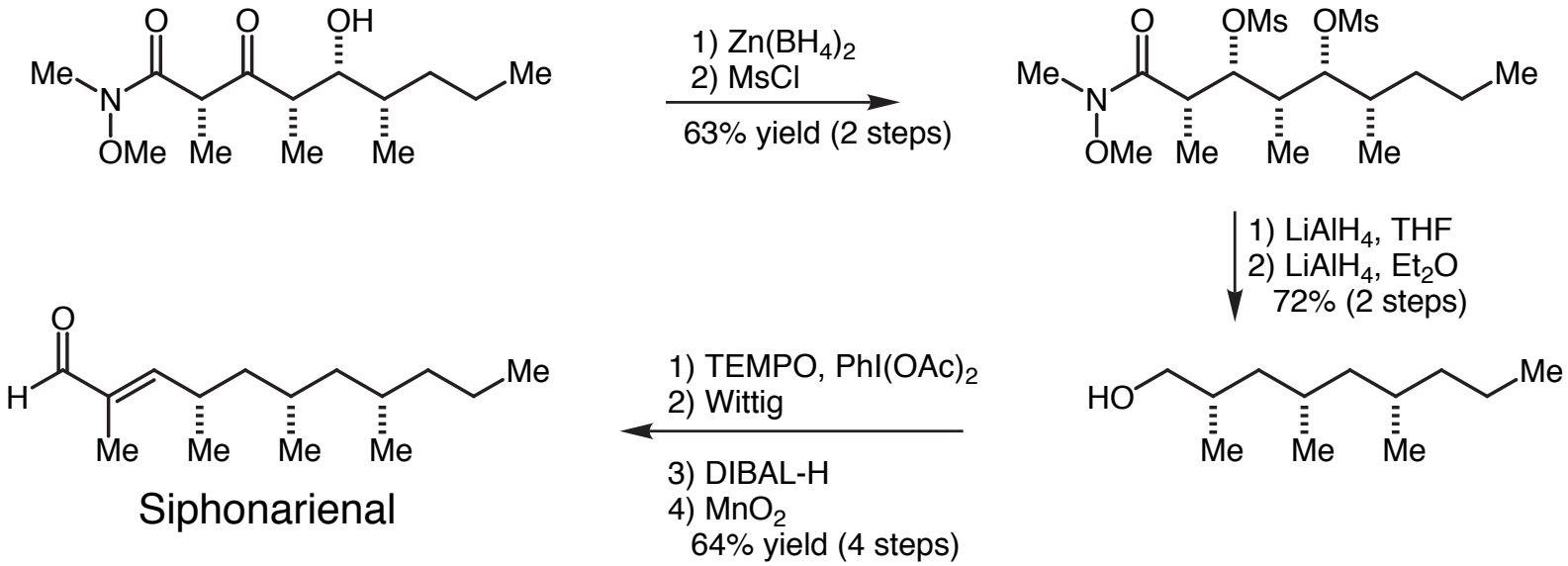
Calter et al., *J. Org. Chem.* **2001**, *66*, 7500.

Calter: Synthesis of Siphonarienal



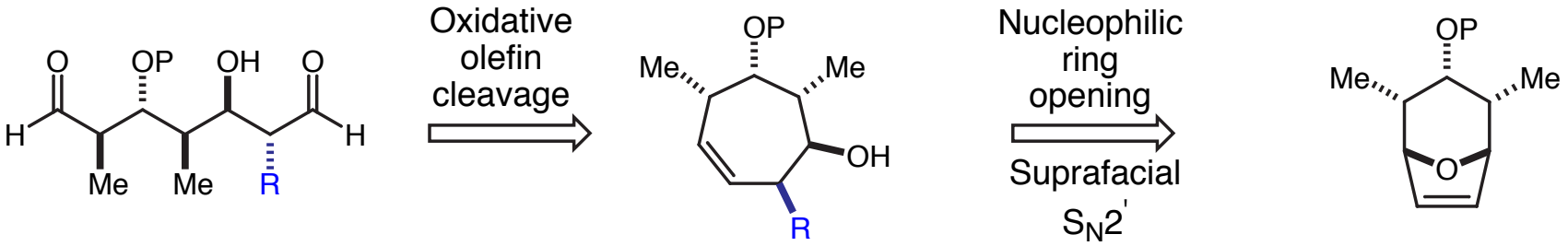
Starting materials:
All commercially available

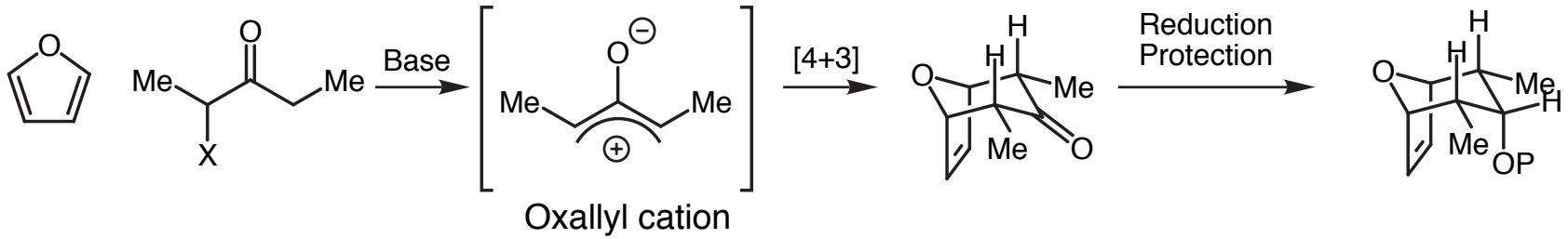
propionic anhydride
quinidine
N,O-dimethylhydroxylamine
n-BuLi
(rac)-2-methylpentanal



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

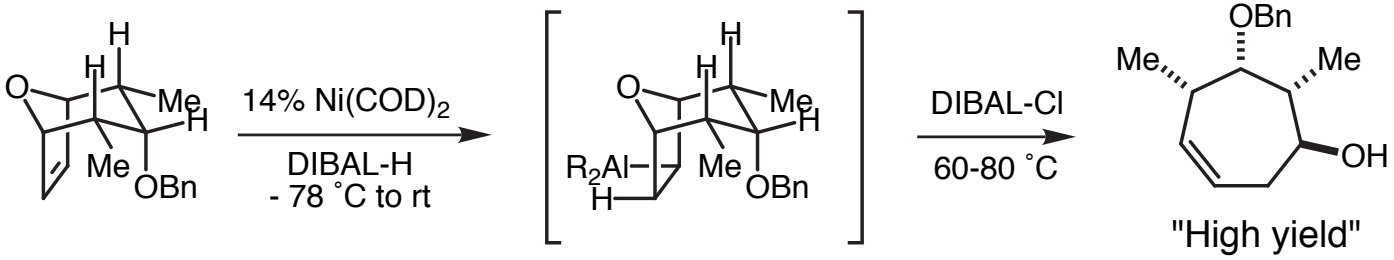
Lautens' Oxabicyclic Ring Opening

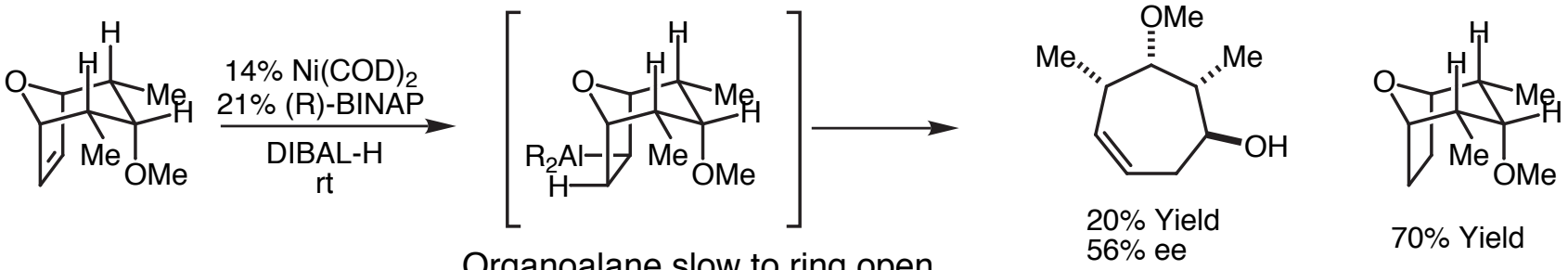




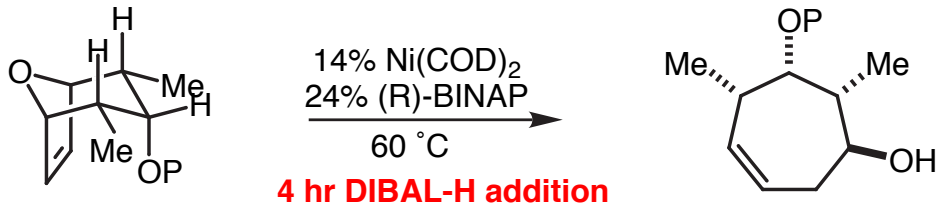
Lautens and Chiu, *Topics in Current Chemistry* **1997**, *190*, 1-85.

Lautens' Enantioselective Oxabicyclic Ring Opening: Hydride Reduction





Organoalane slow to ring open under reaction conditions



Benzyl ether also tolerated

Catalyst lowering possible if addition time increased

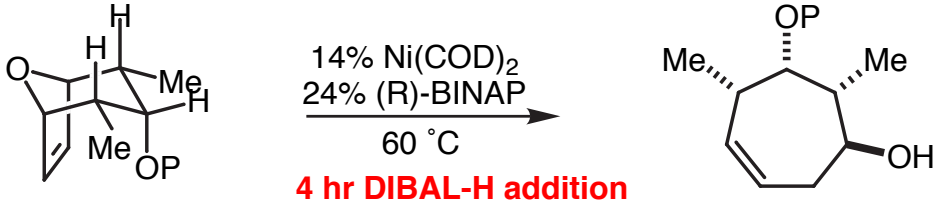
P=Me, 90% Yield, 97% ee

P=TIPS, 87% Yield, 95% ee

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

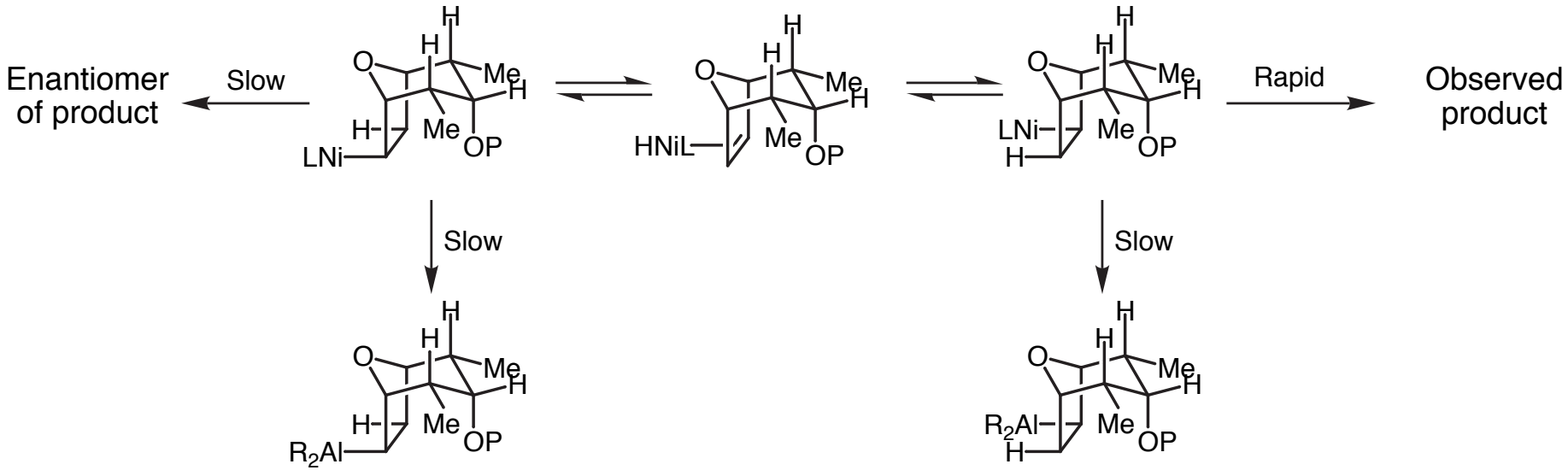
Lautens and Rovis, *J. Am. Chem. Soc.* **1997**, *119*, 11090.

Lautens' Enantioselective Oxabicyclic Ring Opening: Hydride Reduction



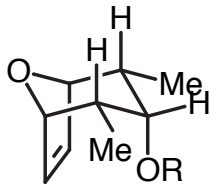
P=Me, 90% Yield, 97% ee
P=TIPS, 87% Yield, 95% ee

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

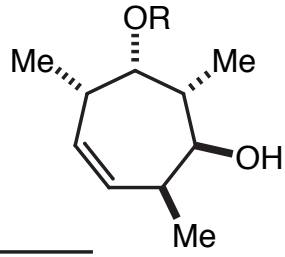


Lautens et al., *J. Am. Chem. Soc.*, **1995**, *117*, 532.
Lautens and Rovis, *J. Am. Chem. Soc.*, **1997**, *119*, 11090.

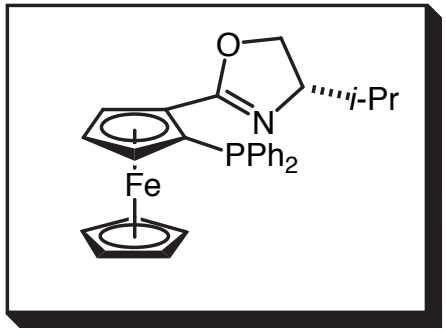
Lautens' Enantioselective Oxabicyclic Ring Opening: Methyl Addition

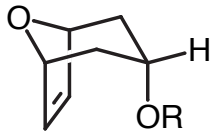


Me_2Zn, 10% additive
5% $Pd(MeCN)_2Cl_2$
$ClCH_2CH_2Cl$
Ligand, reflux

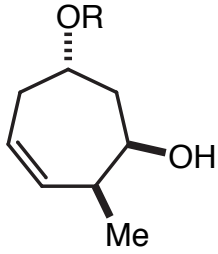


R	Additive	%ee	%yield
H	none	95	84
TBDPS	$Zn(OTf)_2$	87	70
TIPS	$Zn(OTf)_2$	93	73





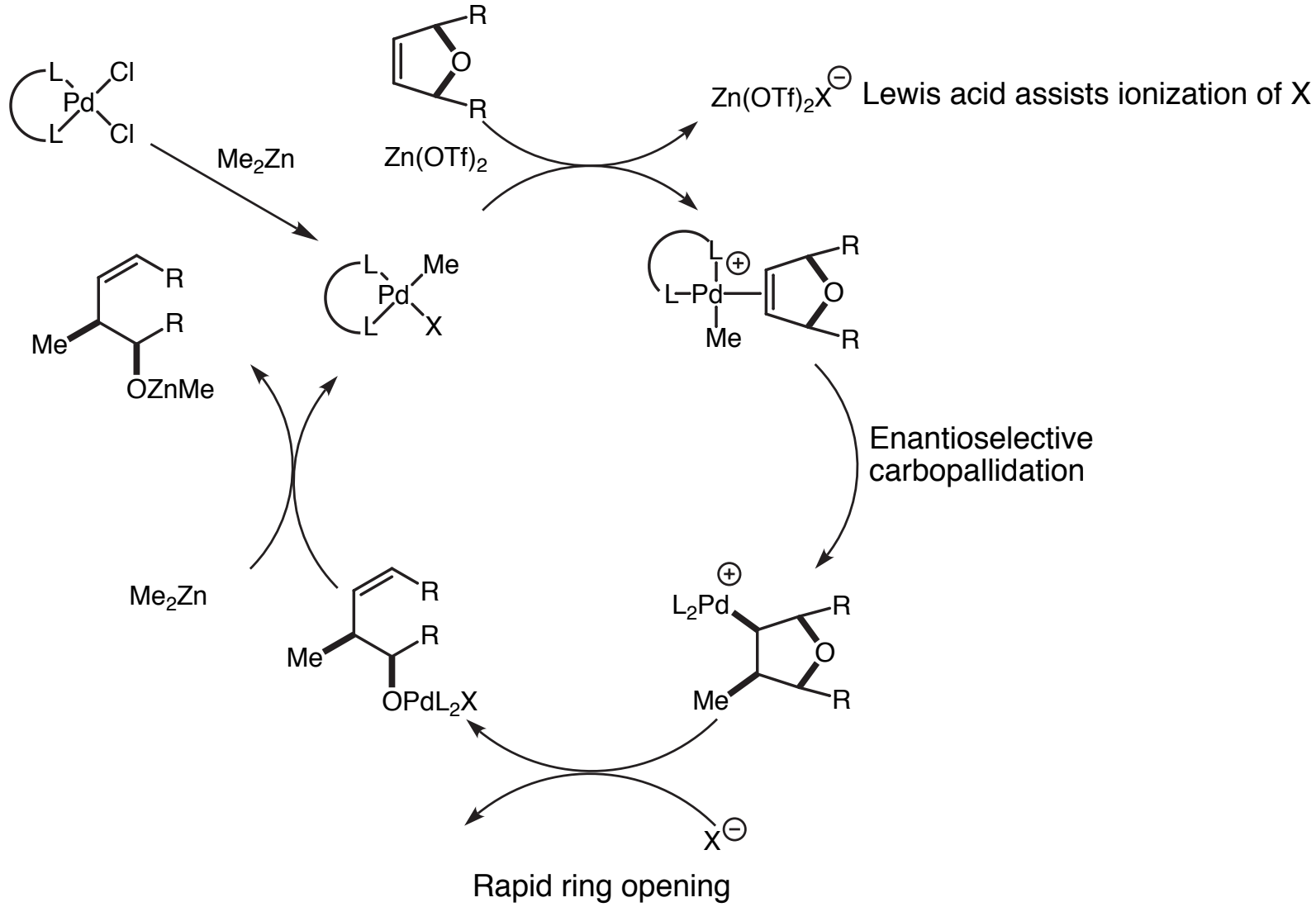
Me_2Zn, 10% additive
5% $Pd(MeCN)_2Cl_2$
$ClCH_2CH_2Cl$
Ligand, reflux



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

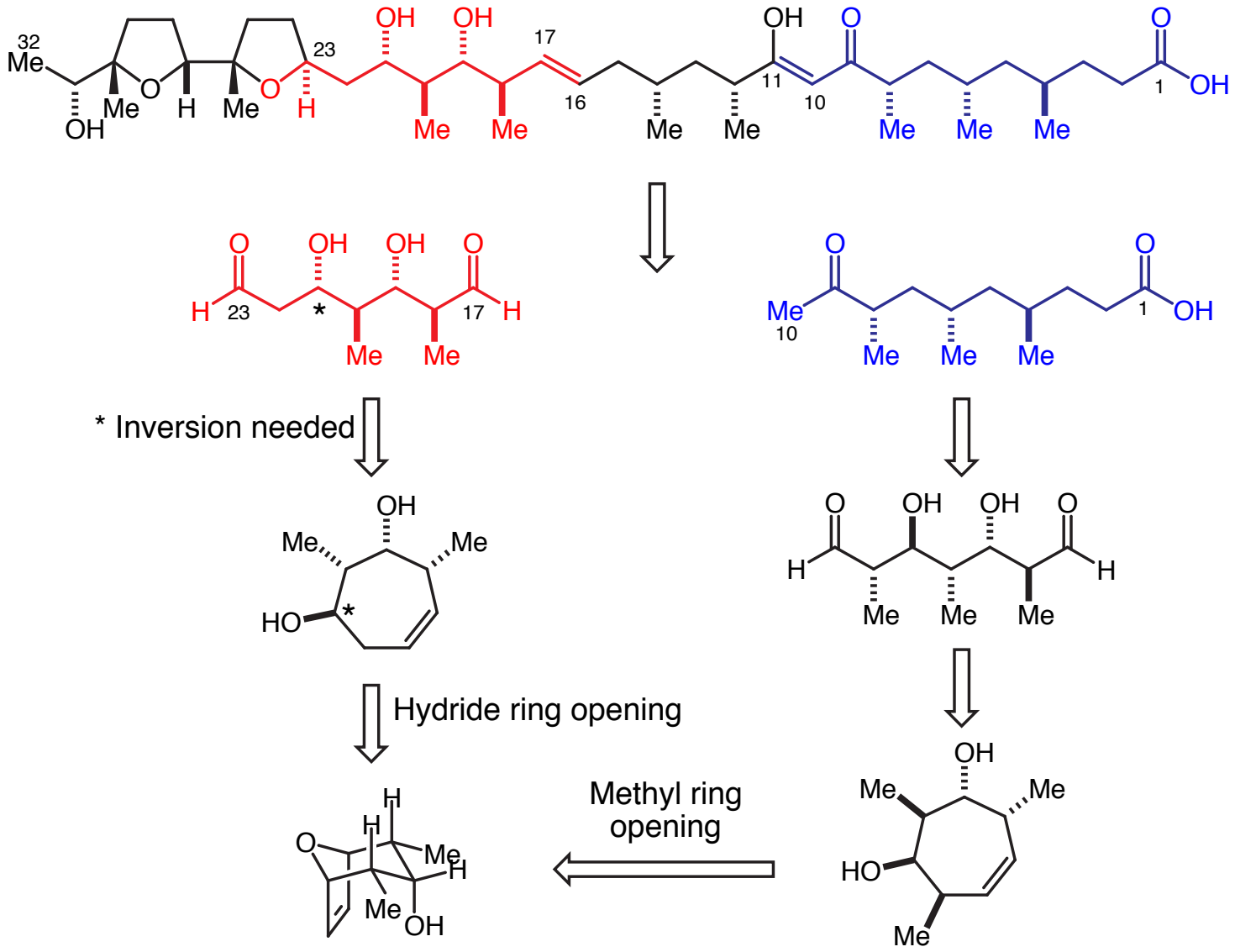
Lautens et al., *J. Am. Chem. Soc.* **2000**, *122*, 1804.
Lautens et al., Org. Lett. **2000**, *2*, 1971.

Lautens' Enantioselective Oxabicyclic Ring Opening: Mechanism



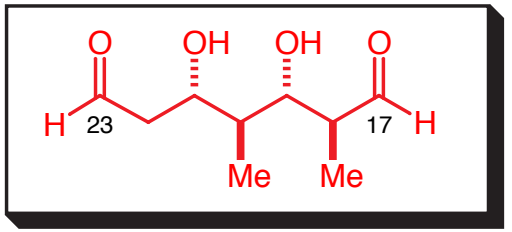
Lautens et al., *J. Am. Chem. Soc.* **2001**, *123*, 6834.

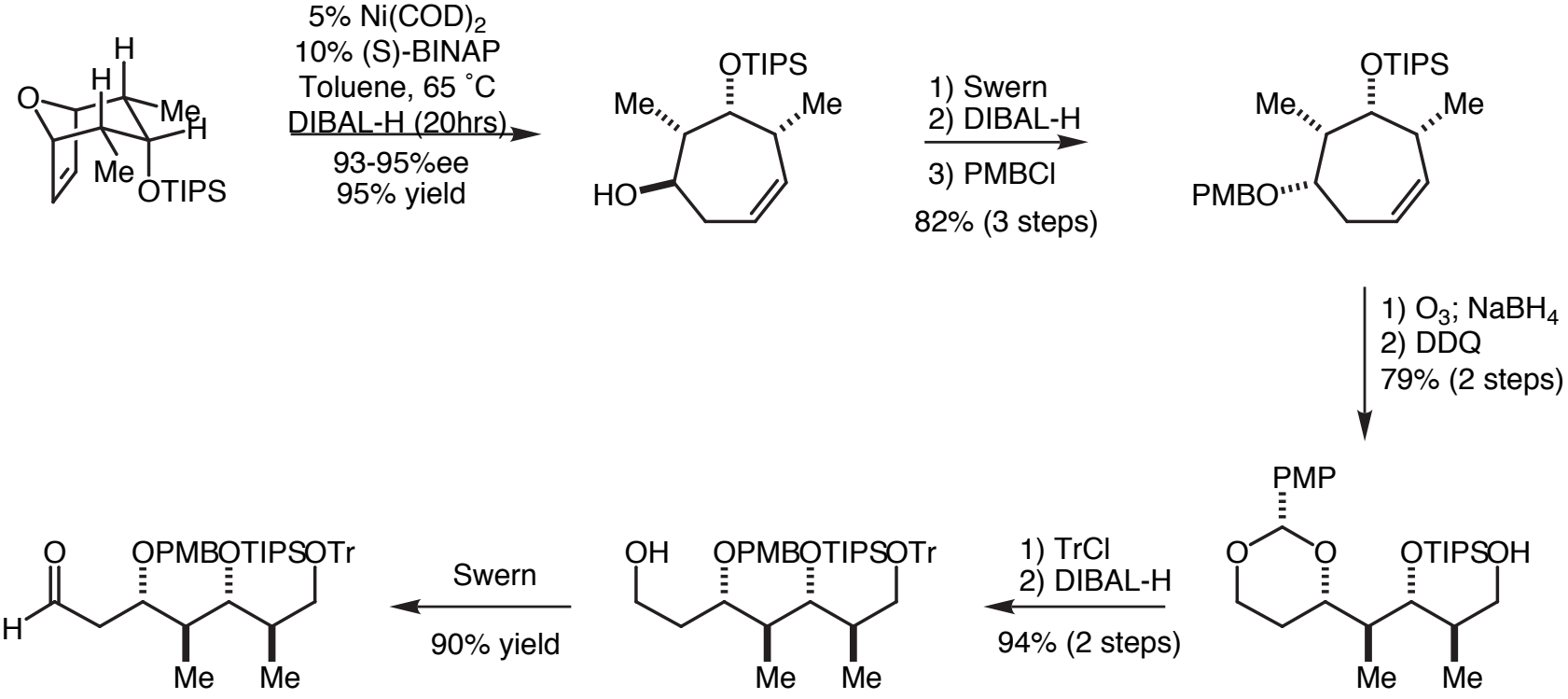
Lautens' Total Synthesis of Ionomycin



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

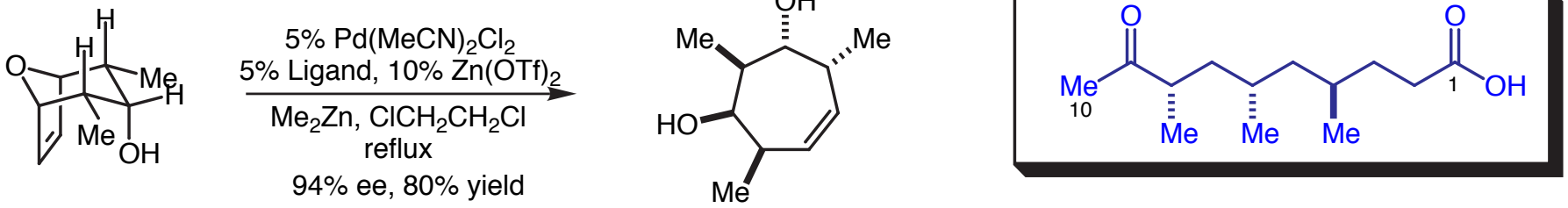
Ionomycin: C_{17}-C_{23} Fragment





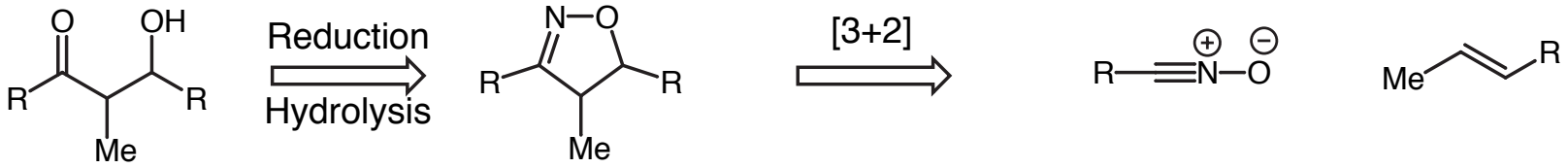
Lautens et al., *Org. Lett.* **2002**, *4*, 1879.

Ionomycin: C_{17}-C_{23} Fragment

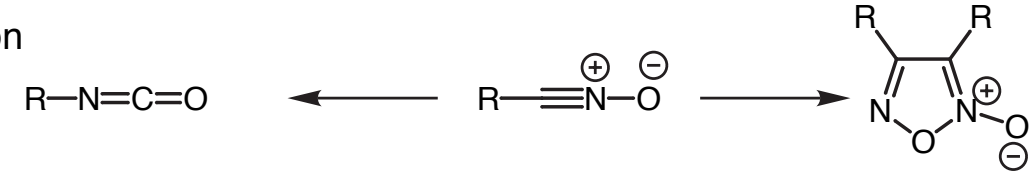


Lautens et al., *Org. Lett.* **2002**, *4*, 1879.

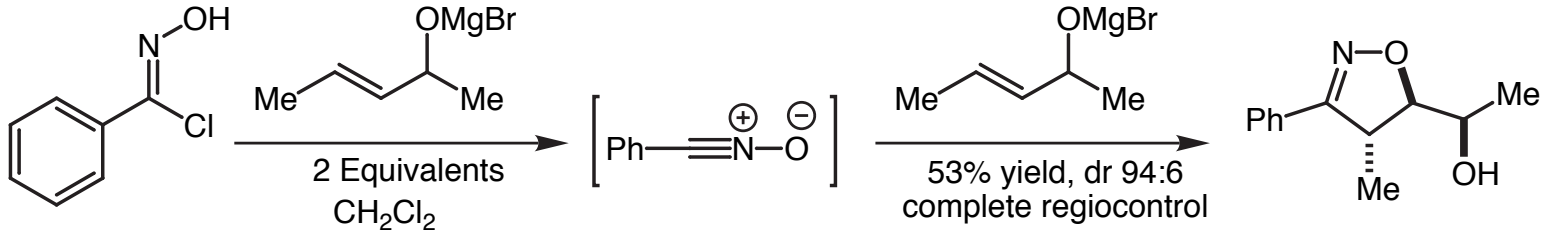
Carreira's Hydroxyl Directed Nitrile Oxide Cycloaddition



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

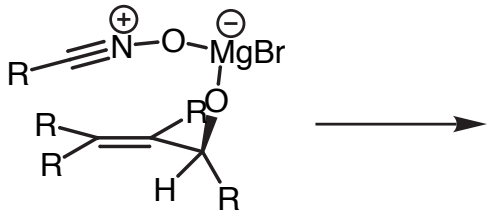


Kanemasa, 1994:



Stereochemical rationale:

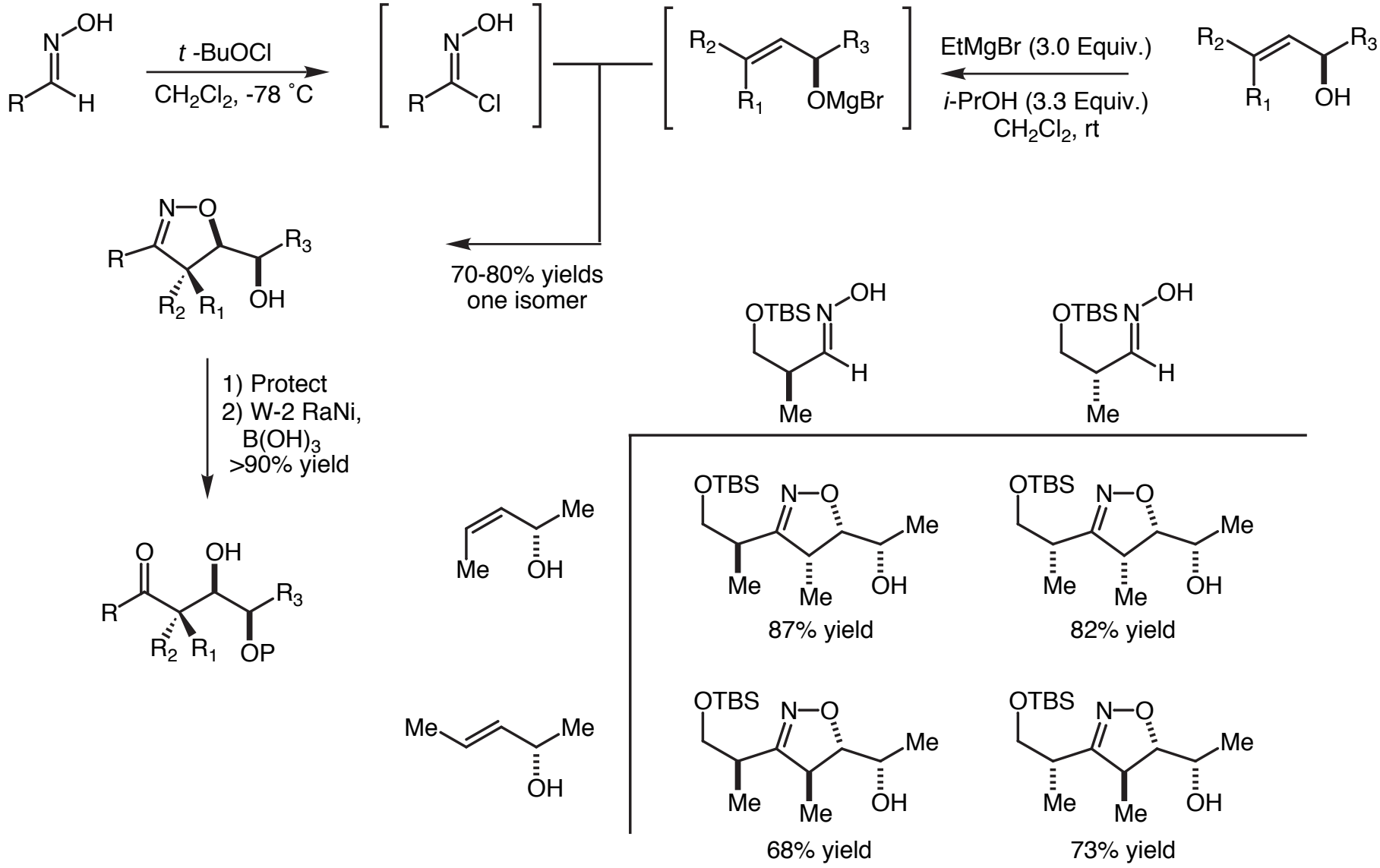
Magnesium alkoxides of allylic alcohols are substrates showing enhanced rate, regioselectivity and diastereoselectivity. Only aromatic nitrile oxides examined.



Syn product

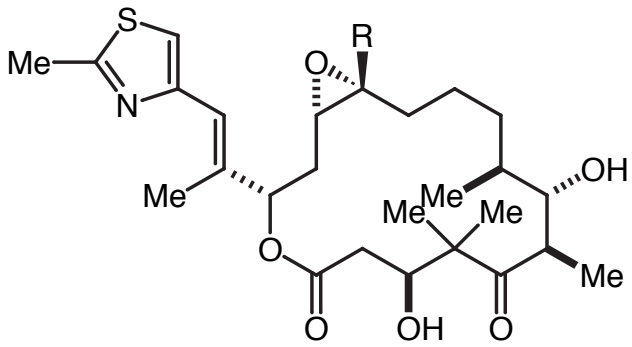
Kanemasa et al., *J. Am. Chem. Soc.* **1994**, *116*, 2324.
Carreira et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 2082.

Carreira's Hydroxyl Directed Nitrile Oxide Cycloaddition



Carreira et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 2082.

Carreira's Epothilone Retrosynthesis

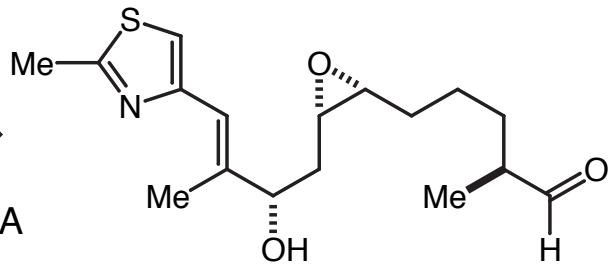


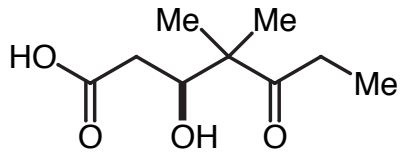
Epothilone A (R=H)
Epothilone B (R=Me)

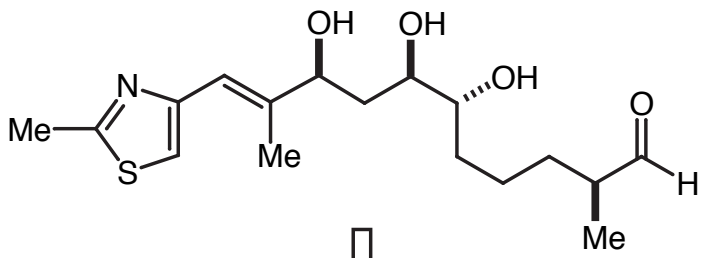
Macro-lactonization

Aldol

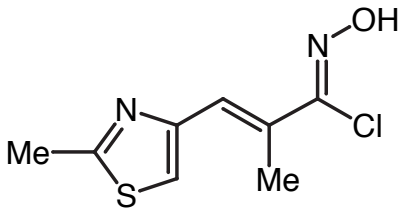
Epothilone A

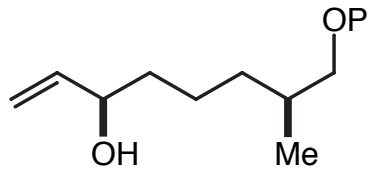


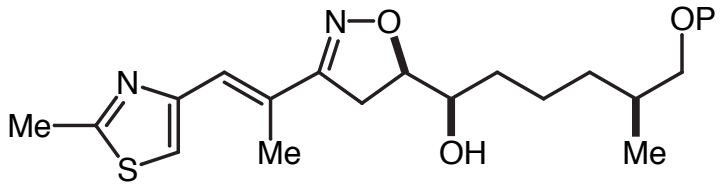




This hydroximinoyl chloride could not be prepared from the corresponding aldehyde.

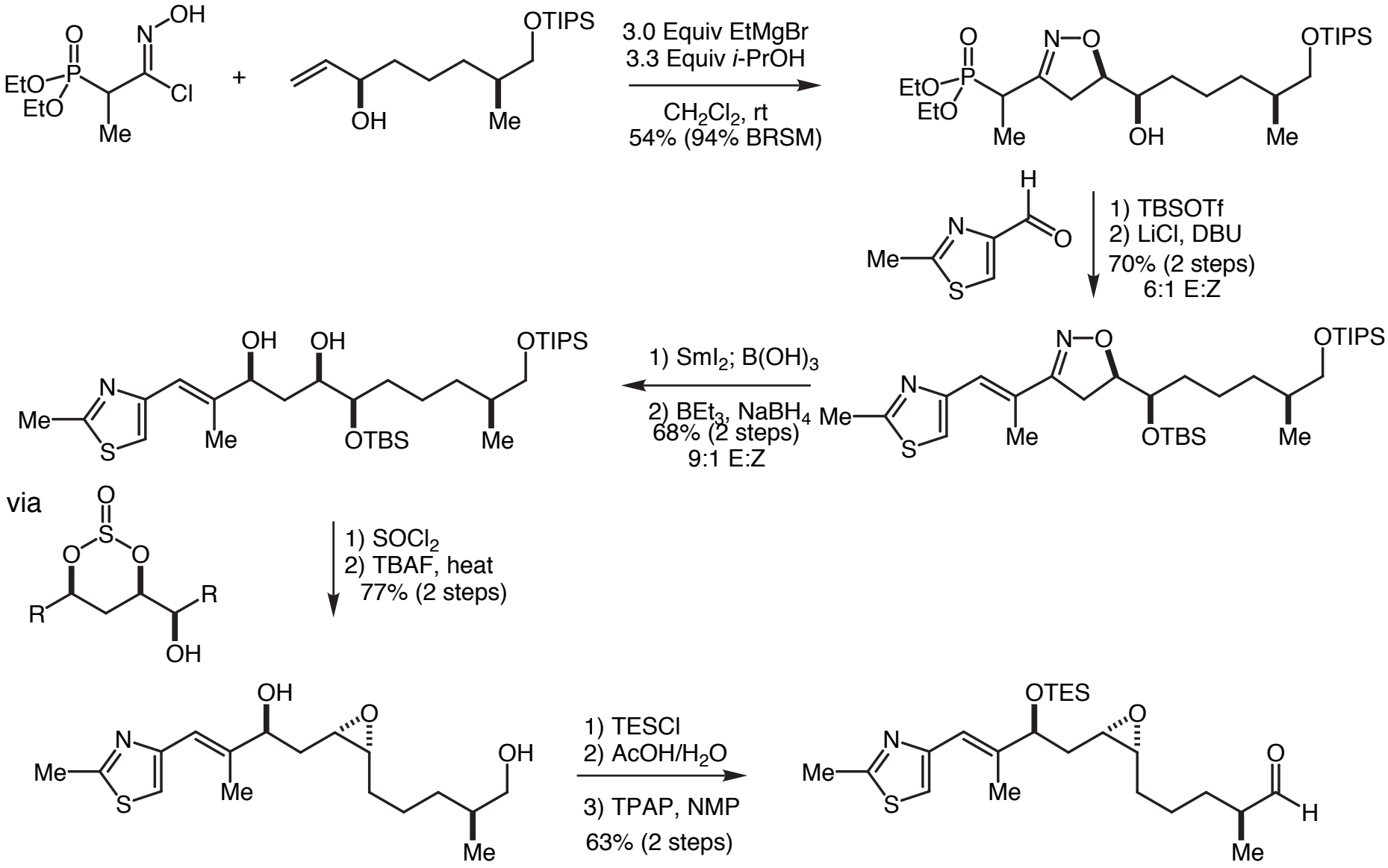






Carreira and Bode, *J. Am. Chem. Soc.* **2001**, *123*, 3611.
Carreira and Bode, *J. Org. Chem.* **2001**, *66*, 6410.

Carreira's Epothilone A Fragment Synthesis

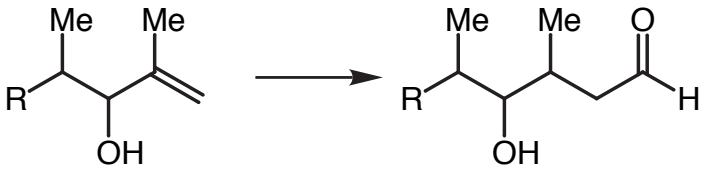


Carreira and Bode, *J. Am. Chem. Soc.* **2001**, *123*, 3611.

Carreira and Bode, *J. Org. Chem.* **2001**, *66*, 6410.

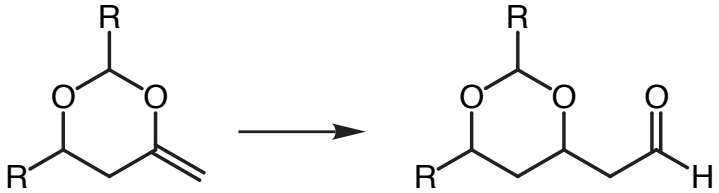
Approaches Not Covered

Bernhard Breit: Hydroformylation



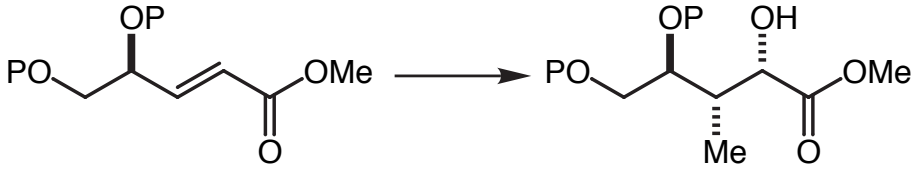
J. Org. Chem. **2001**, *66*, 4870.
Chem. Eur. J. **1999**, *5*, 2819.
Eur. J. Org. Chem. **1998**, 1123.
Tet. Lett. **1998**, *39*, 1901.
Liebigs Ann. Chem. **1997**, 1841.

James Leighton: Hydroformylation



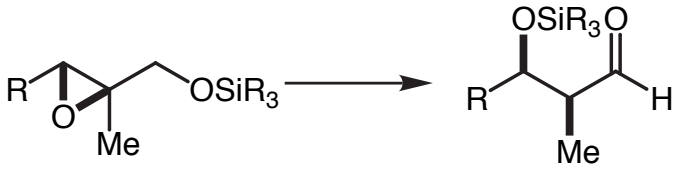
J. Am. Chem. Soc. **1997**, *119*, 11118.
Tet. Lett. **1998**, *39*, 6423.
J. Am. Chem. Soc. **2001**, *123*, 11514.

Stephen Hanessian: Conjuage Addition/Enolate Oxidation



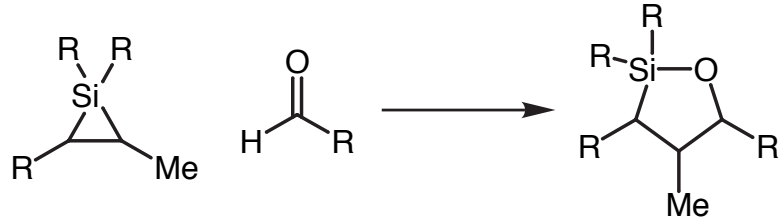
Tet. Lett. **1996**, *37*, 7473.
J. Am. Chem. Soc. **1997**, *119*, 10034.
Tet. Lett. **1999**, *40*, 4627.
J. Am. Chem. Soc. **2001**, *123*, 10200.

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.

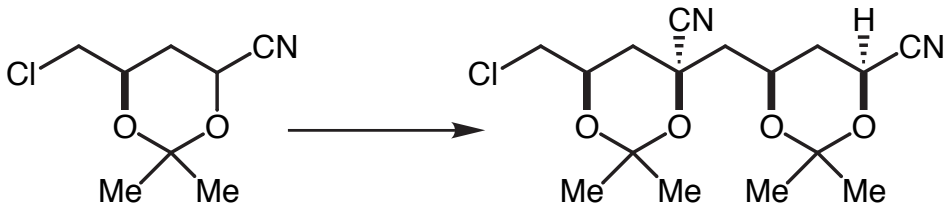
Keith Woerpel: Silirane Ring Opening



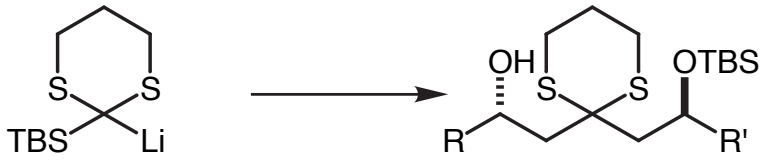
J. Am. Chem. Soc. **1995**, *117*, 10575.
J. Org. Chem. **1997**, *62*, 4737.
Tetrahedron **1997**, *53*, 16597.
J. Am. Chem. Soc. **1999**, *121*, 949.
Angew. Chem. Int. Ed. **2000**, *39*, 4295.
Acc. Chem. Res. **2000**, *33*, 813.
J. Am. Chem. Soc. **2002**, *124*, 6524.

Summary

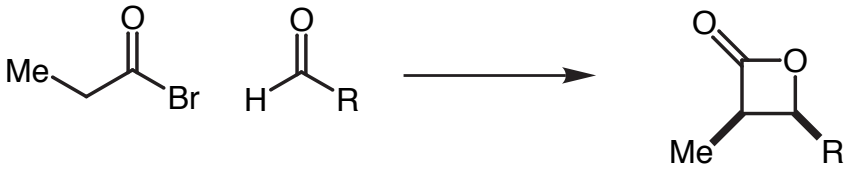
Rychnovsky: Cyanohydrin acetonide



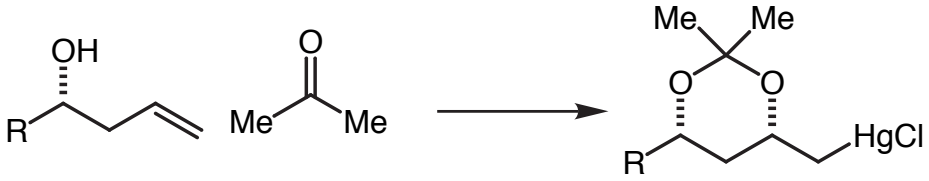
Smith: Dithiane linchpin



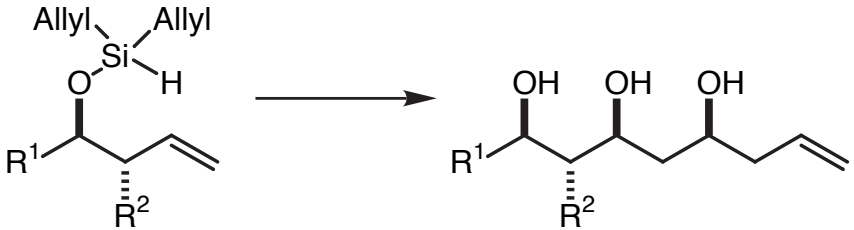
Nelson: Cyclocondensation



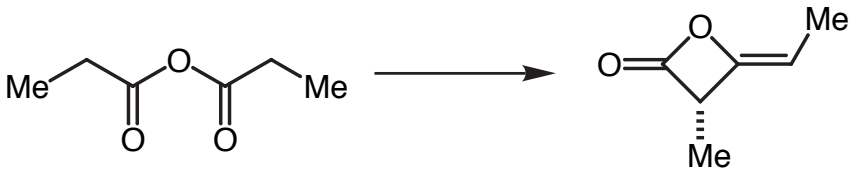
Leighton: Hemiacetal oxymercuration



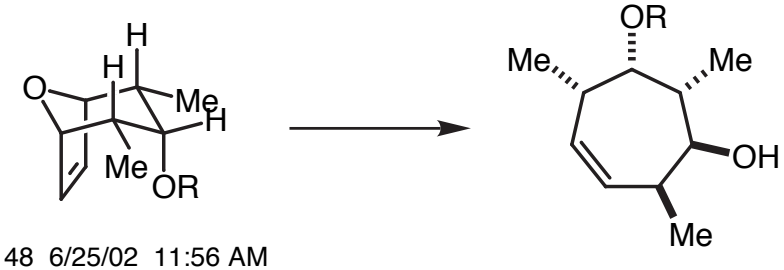
Leighton: Silylformylation



Calter: Methylketene dimerization



Lautens: Enantioselective ring opening



Carreira: Directed nitrile oxide cycloaddition