

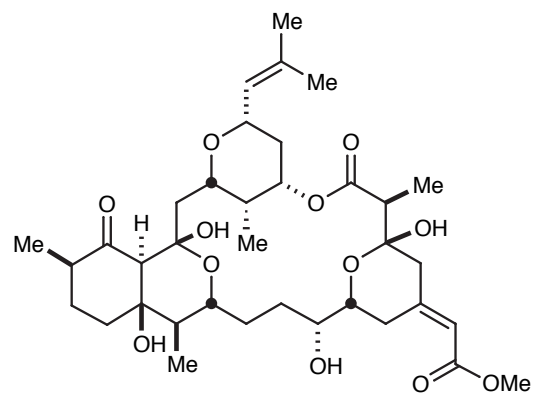
Approaches to the Synthesis of 2,6-Disubstituted Tetrahydropyran Derivatives

Duke M. Fitch
Evans' Group Seminar
May 16, 1997

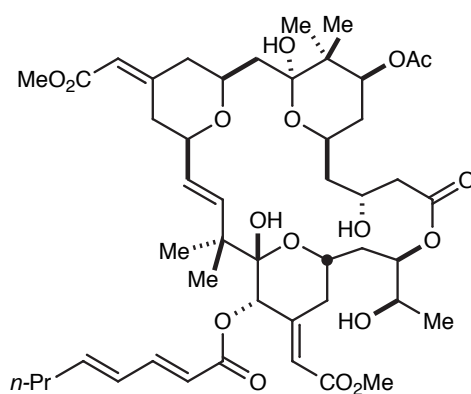
- I. Diol Cyclization
- II. Epoxide Opening
- III. Cyclization onto Activated Olefins
- IV. Heteroconjugate Addition
- V. Addition to Glycals/Dihydropyrones (Hetero-Diels-Alder)
 - A. Conjugate Addition
 - B. Carbon-Ferrier Reactions
 - C. Ireland-Claisen Rearrangement
 - D. Allyl Stannane Addition to Glycal Oxirane
- VI. Oxonium Reactions
- VII. Prins Cyclization
- VIII. Intramolecular Silyl-Modified Sakurai Reactions
- IX. Radical Cyclization

Leading References: Boivin *Tet.* **1987**, *43*, 3309.
Postema *Tet.* **1992**, *48*, 8545.
Paterson *Chem. Rev.* **1995**, *95*, 2041.
Tom Smith *Evans Group Seminar* **5/9/97**

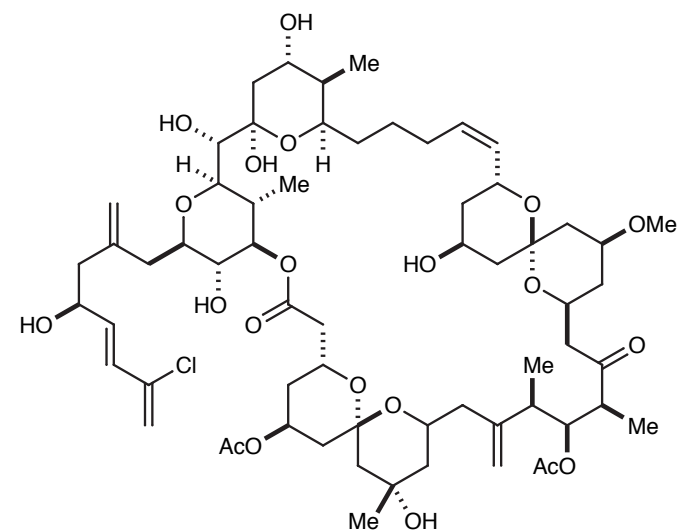
Natural Products Containing 2,6-Disubstituted Tetrahydropyran Rings



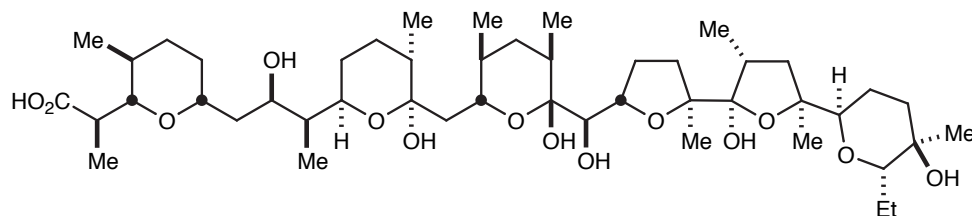
Miyakolide



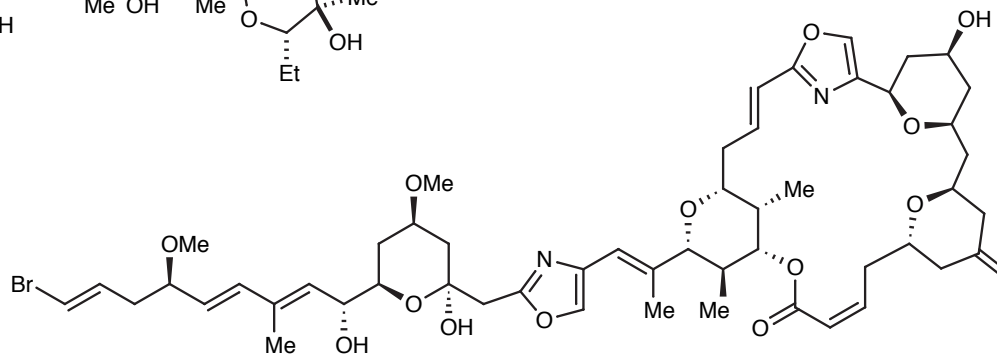
Bryostatin 1



Althoyrtin A

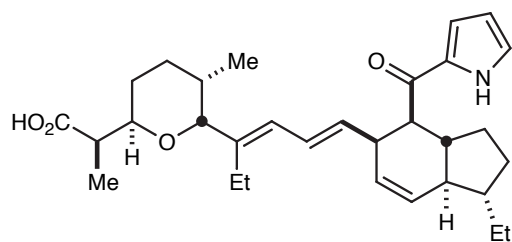


Antibiotic X-206

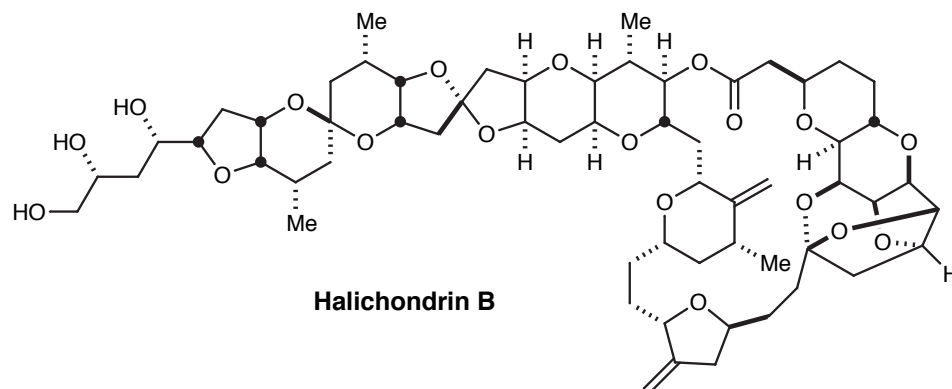


Phorboxazole B

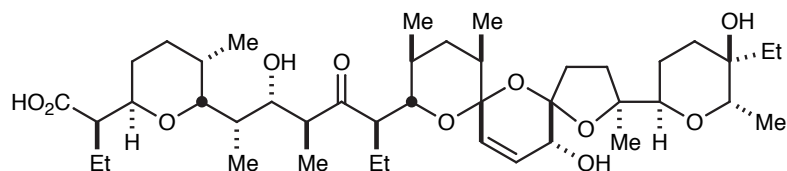
Natural Products Containing 2,6-Disubstituted Tetrahydropyran Rings



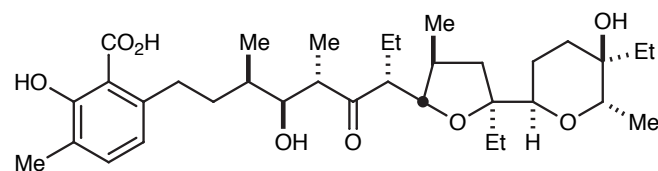
Antibiotic X-14547A



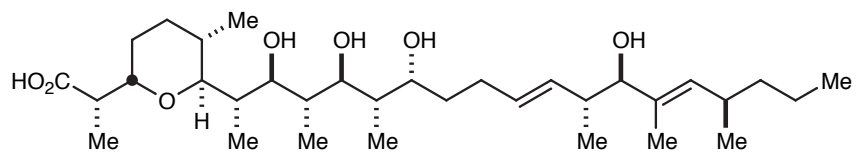
Halichondrin B



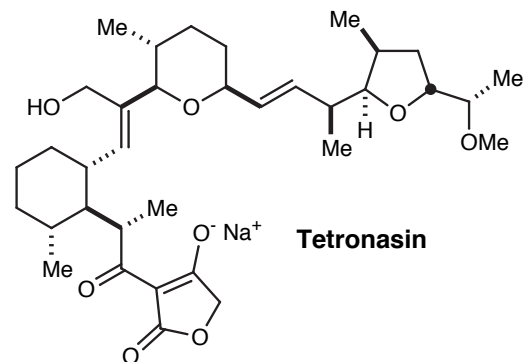
Salinomycin



Lasalocid A



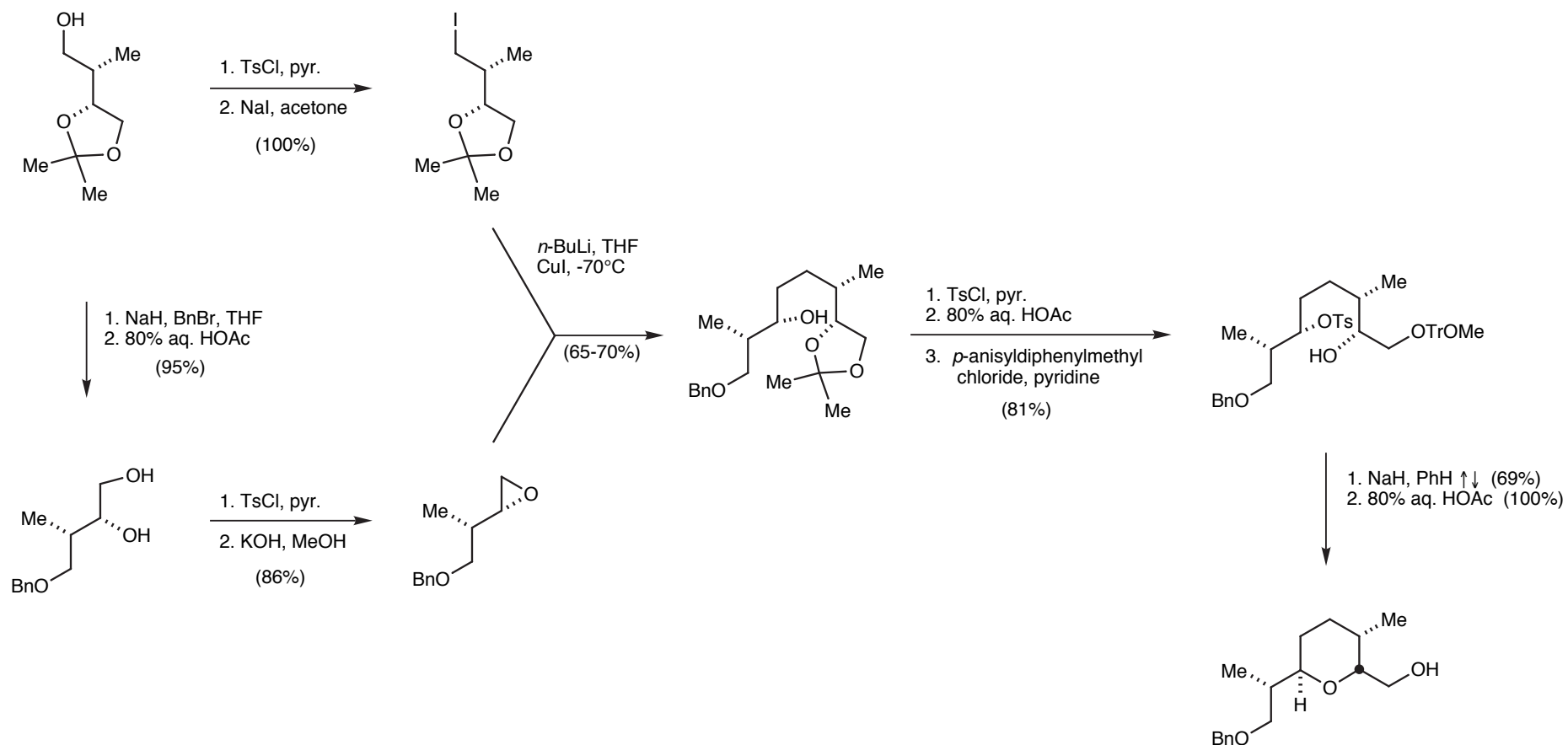
Zincophorin



Tetrinasin

Intramolecular Diol Cyclization

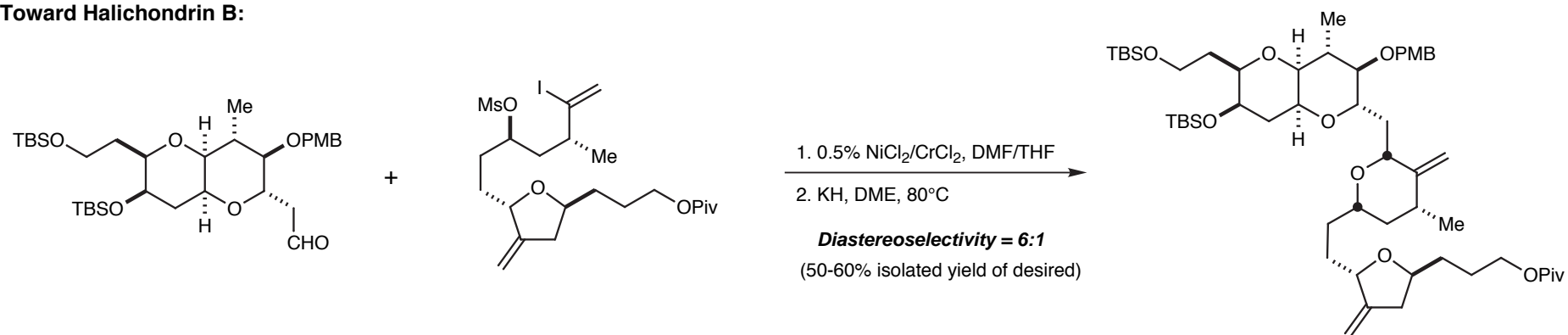
Toward Antibiotic X-14547A:



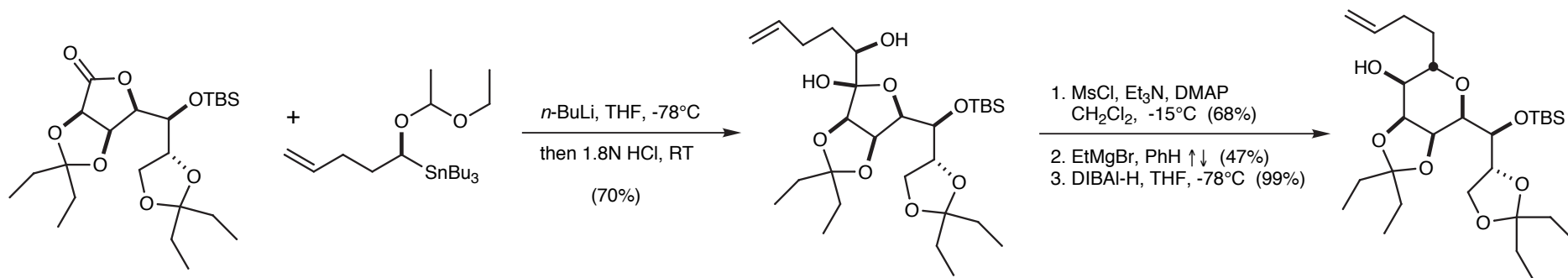
Ho *Can. J. Chem.* **1982**, 60, 90.

Intramolecular Diol Cyclization

Toward Halichondrin B:



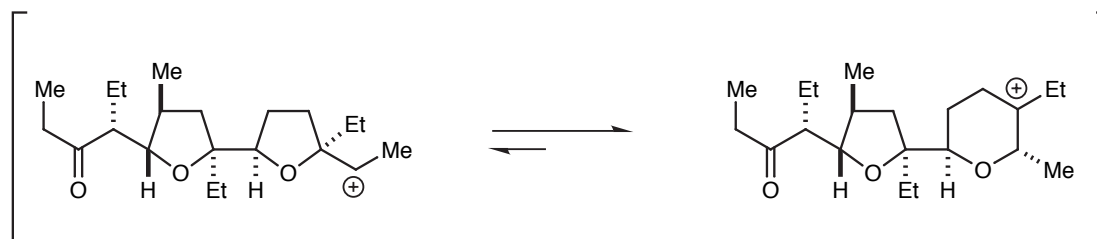
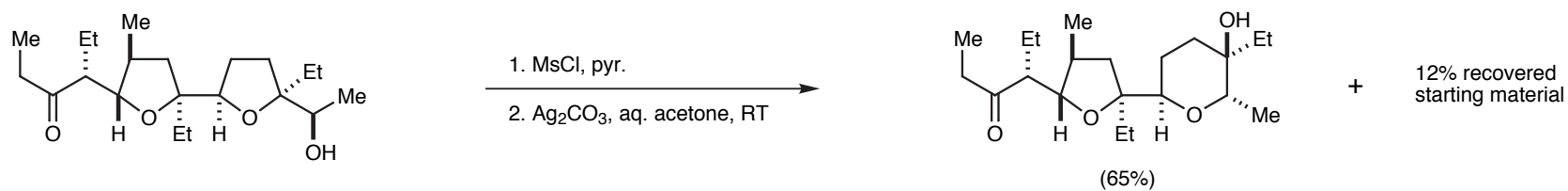
Kishi *J. Am. Chem. Soc.* **1992**, *114*, 3162.



Burke *Tet. Lett.* **1994**, *35*, 703.

Ring Expansion

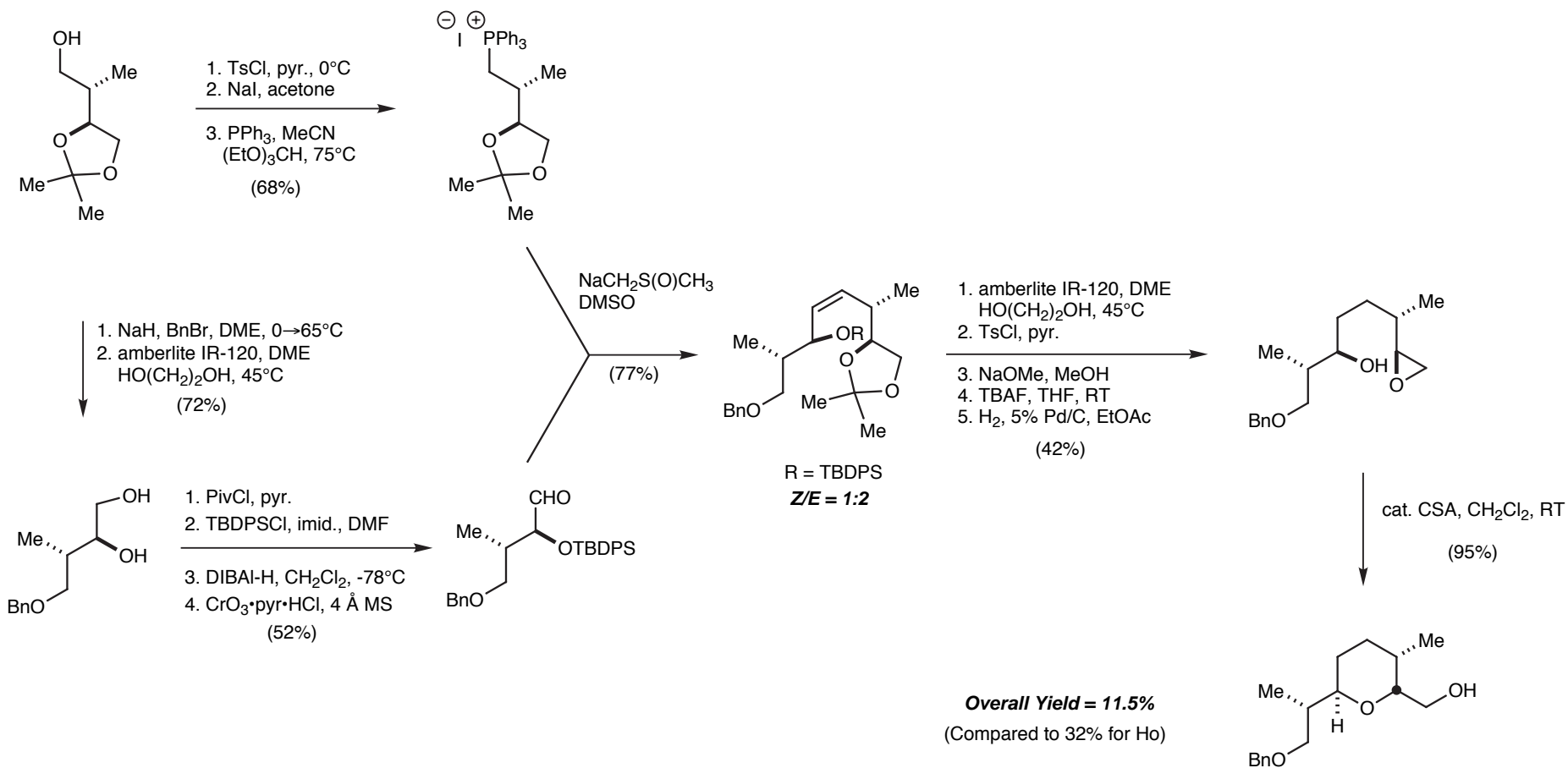
Toward Lasalocid A:



Kishi *J. Am. Chem. Soc.* **1978**, *100*, 2933.

Intramolecular Epoxide Opening

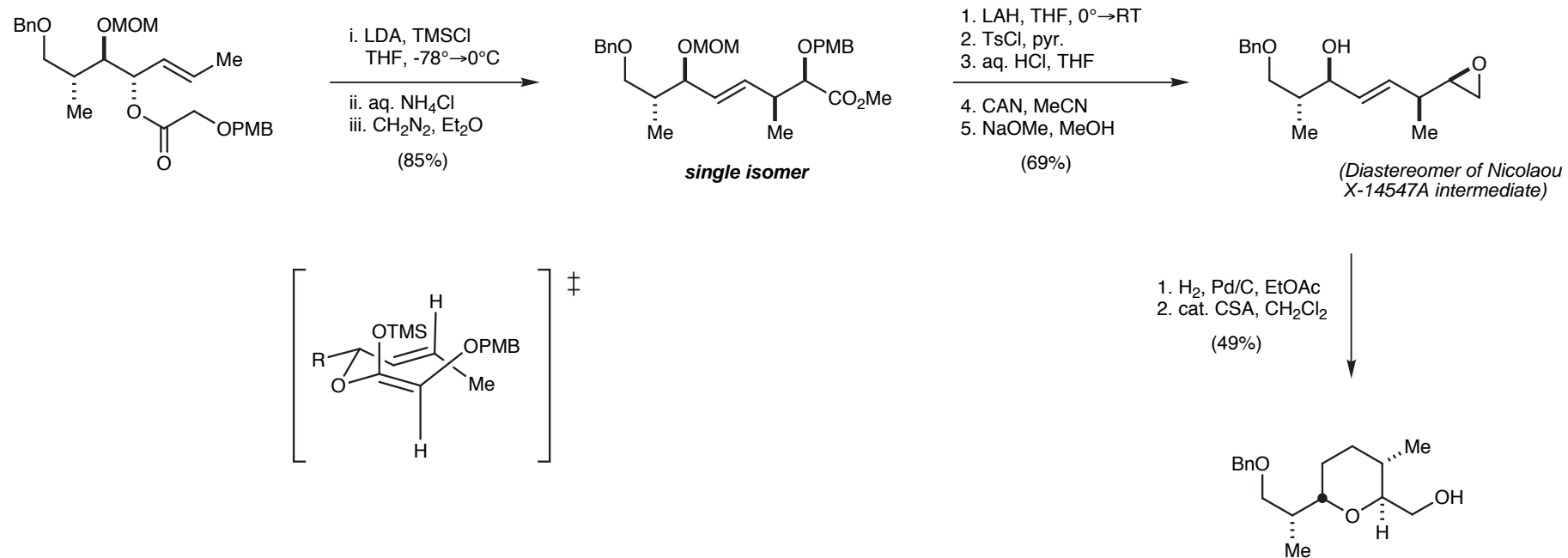
Toward Antibiotic X-14547A:



Nicolaou *J. Org.Chem.* **1985**, *50*, 1440.

Intramolecular Epoxide Opening

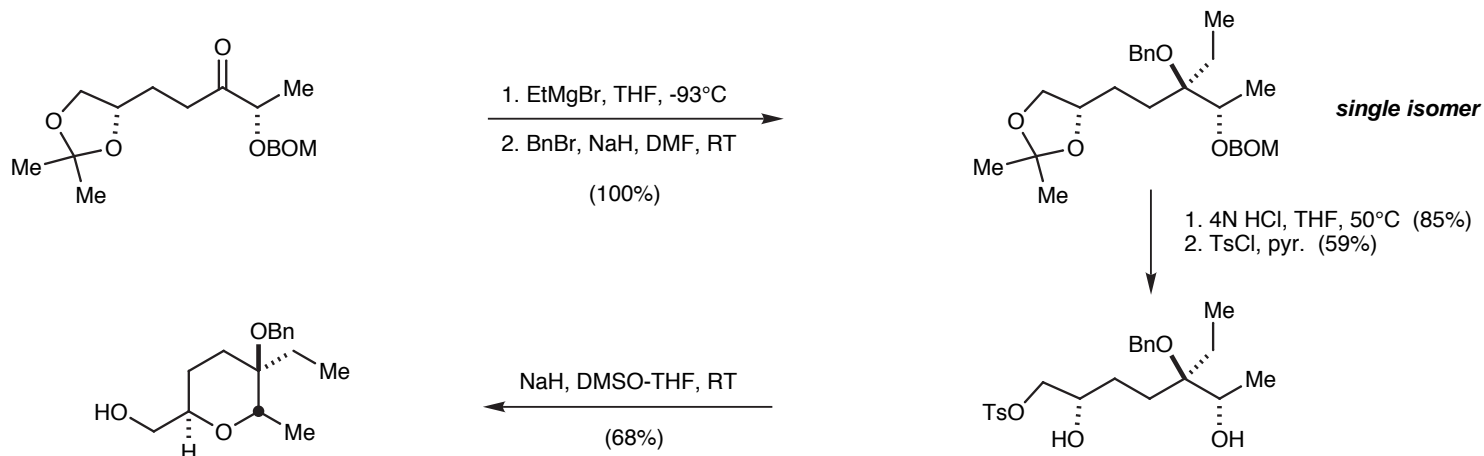
Toward Zincophorin:



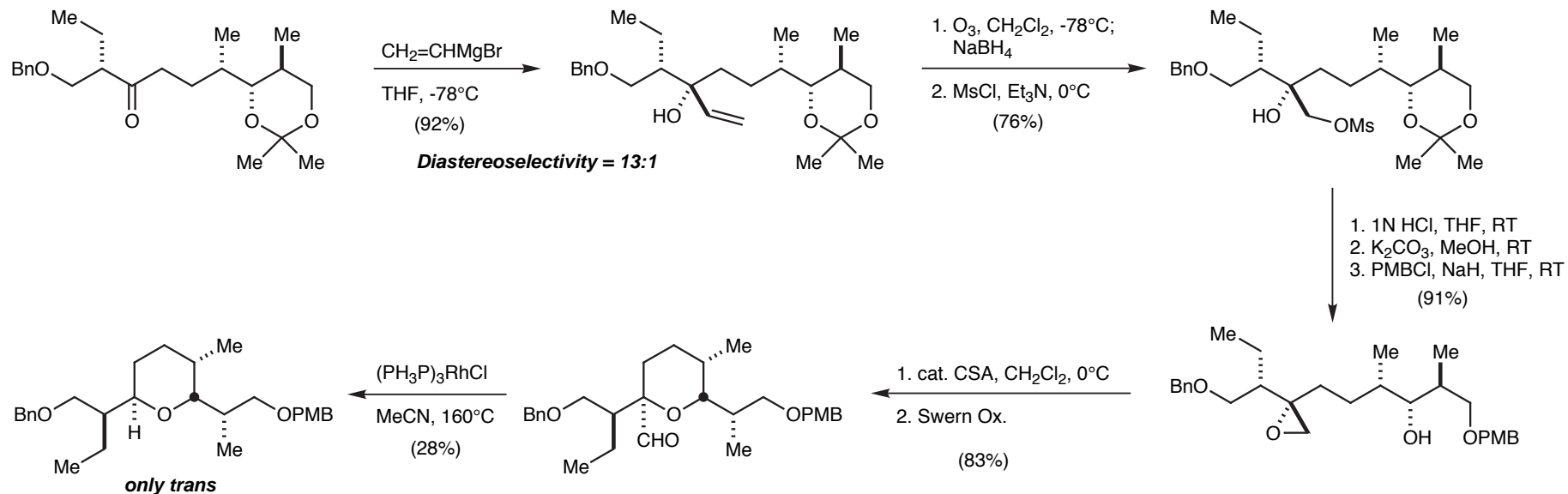
Kallmerten *Tet. Lett.* **1993**, 34, 1103.

Intramolecular Epoxide Opening

Toward Salinomycin:

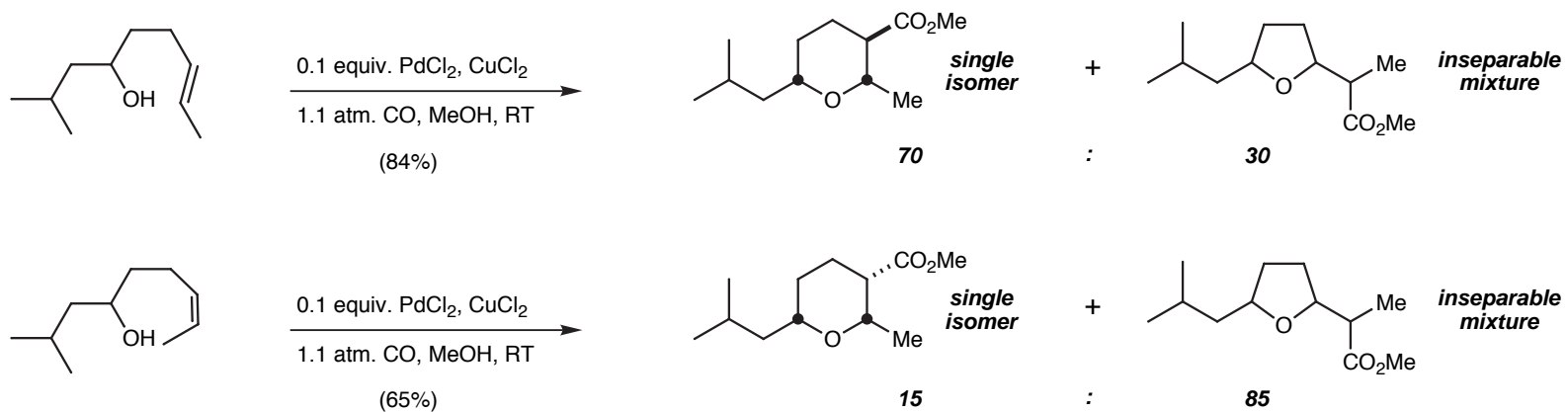


Yonemitsu *Tet. Lett.* **1987**, 28, 3253.

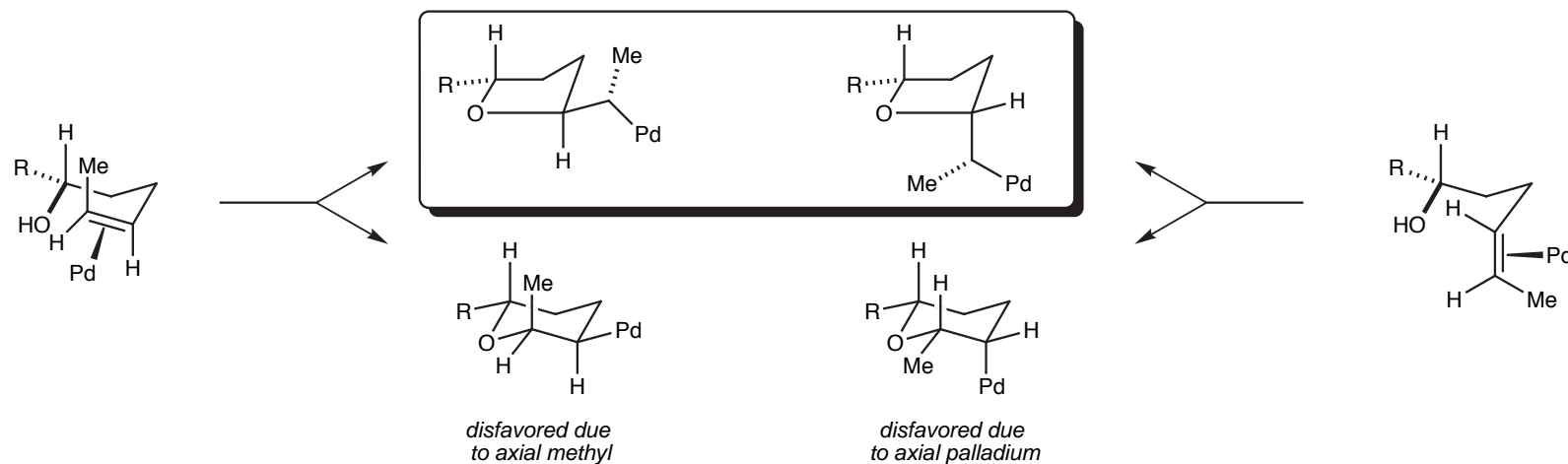


Yonemitsu *Tet. Lett.* **1988**, 29, 5143.

Intramolecular Alkoxypalladation/Carbonylation

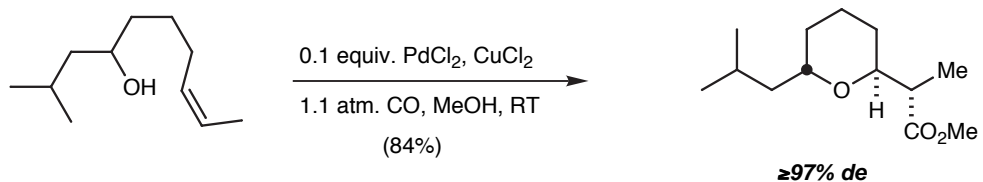
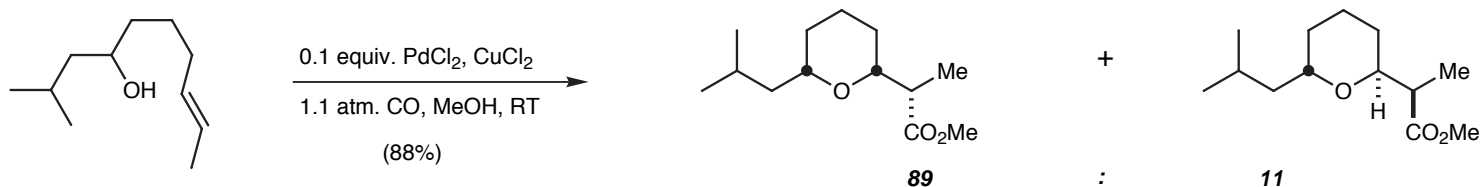


Authors' Explanation:

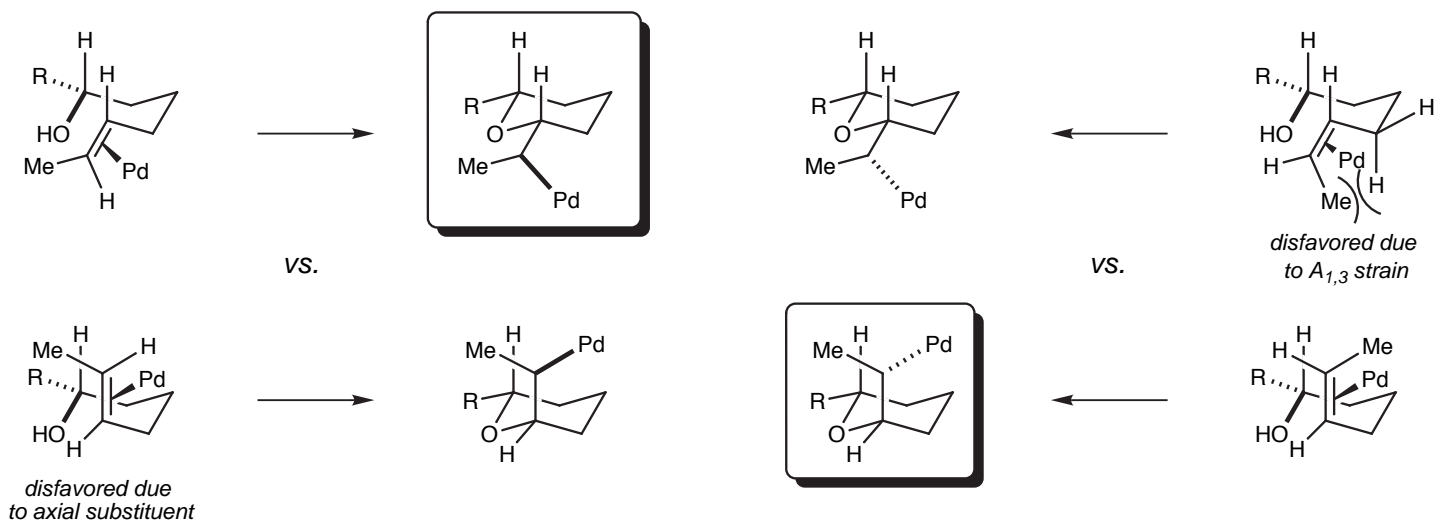


Semmelhack *J. Am. Chem. Soc.* **1984**, 106, 1496.

Intramolecular Alkoxy-palladation/Carbonylation

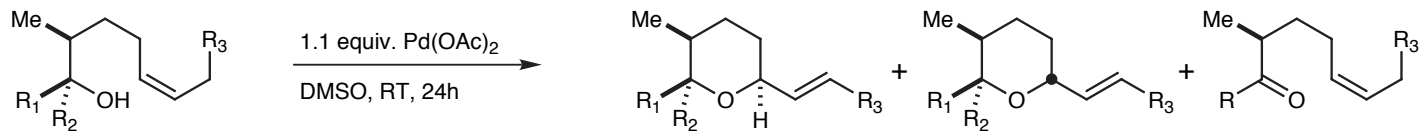


Note: No 7-membered ring products were isolated



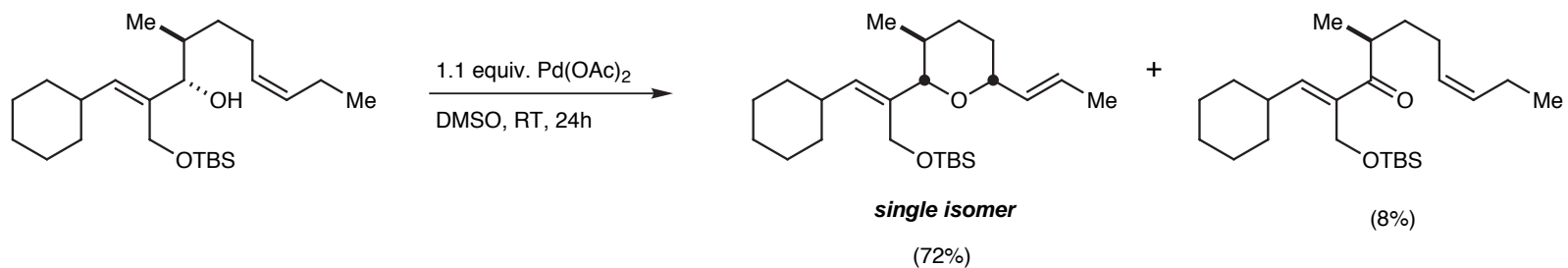
Semmelhack *J. Am. Chem. Soc.* **1984**, *106*, 1496.

Intramolecular Alkoxy-palladation



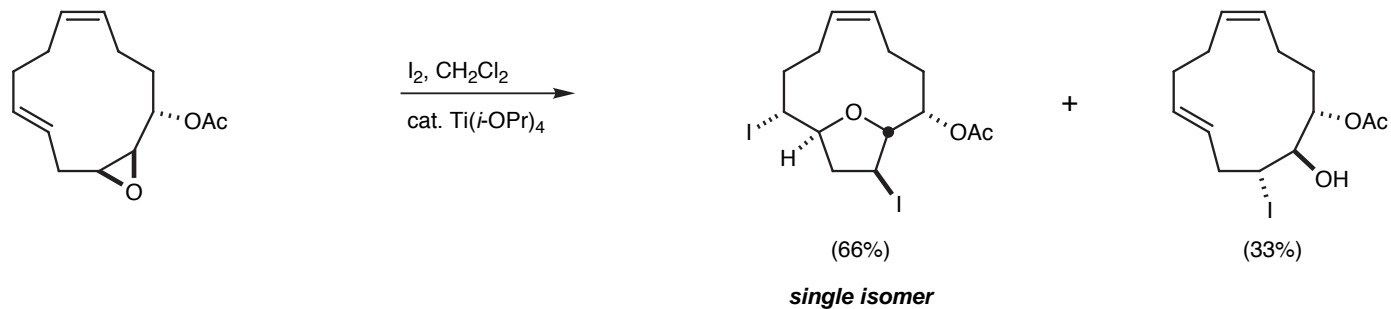
R ₁	R ₂	R ₃	% yield			
H	H	Me	93	2	98	<i>trace</i>
Me	H	H	95	56	34	10
H	Me	Me	96	3	94	3
<i>t</i> -BuCH ₂	H	Me	92	53	31	16
H	<i>t</i> -BuCH ₂	Me	96	22	64	14

Toward Tetronomycin:



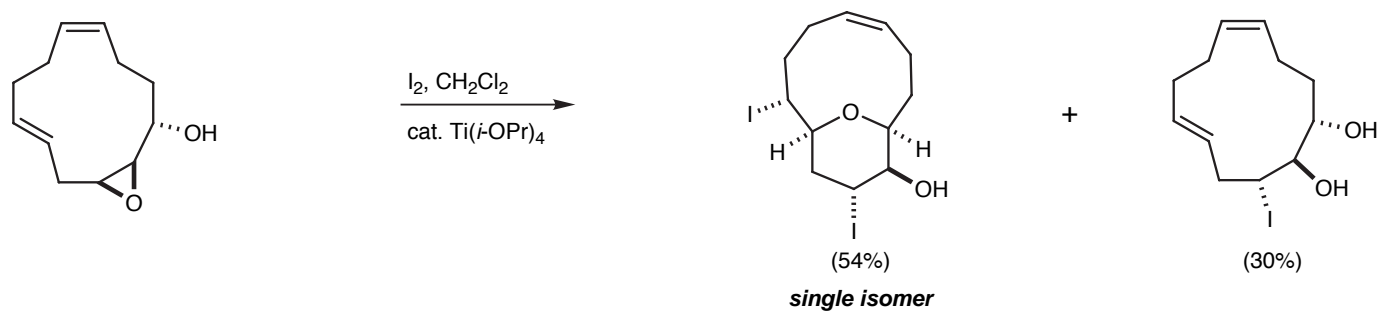
Semmelhack *Tet. Lett.* **1989**, 30, 4925.

Intramolecular Iodoetherification



Note: Byproduct of each reaction can be quantitatively recycled to the starting epoxy alcohol upon treatment with K_2CO_3 in aq. acetone.

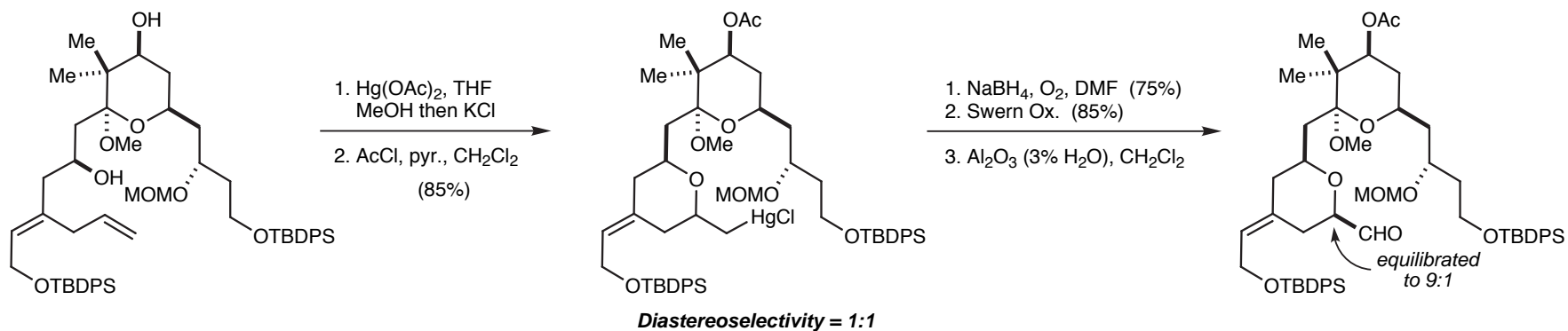
However:



Martín *Tet. Lett.* **1989**, 30, 3725.

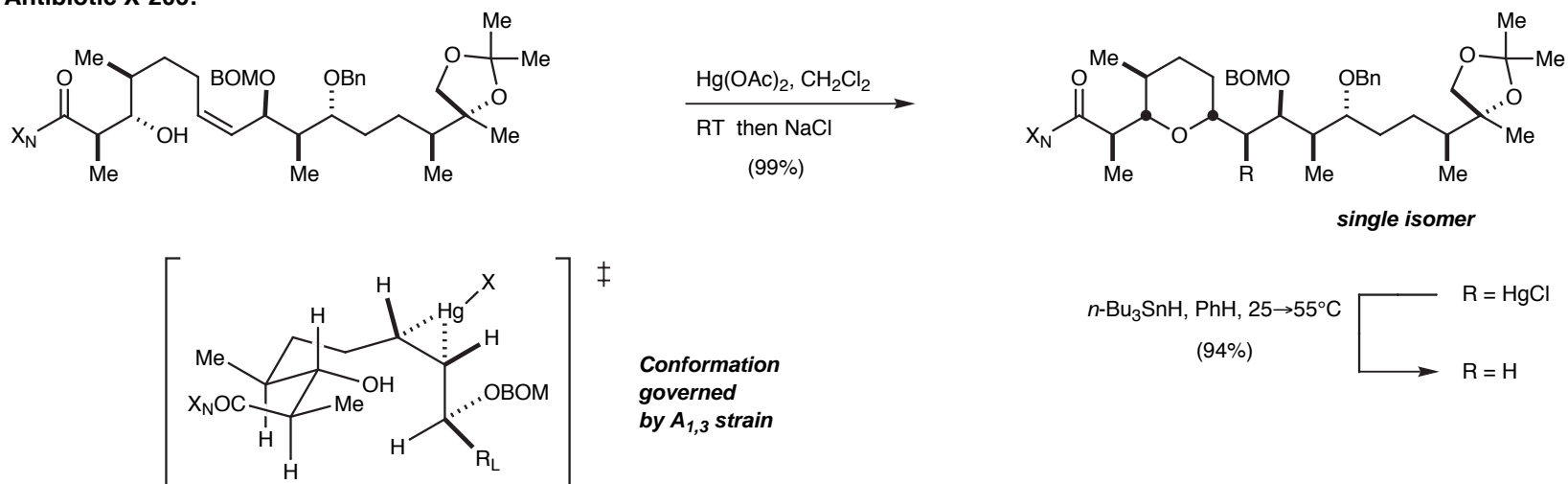
Intramolecular Alkoxymercuration

Toward Bryostatin 7:



Masamune *J. Org. Chem.* **1989**, 54, 2817.

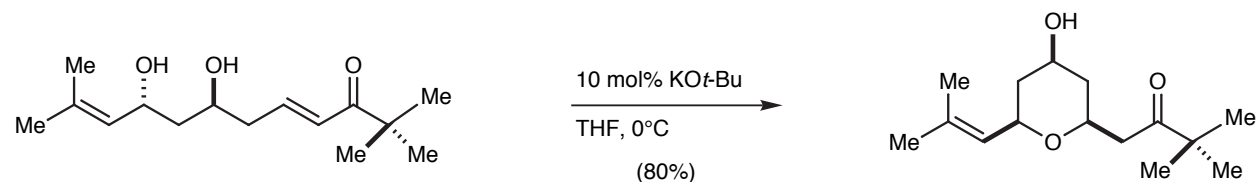
Toward Antibiotic X-206:



Evans *J. Org. Chem.* **1989**, 54, 2817.

Intramolecular Heteroconjugate Addition

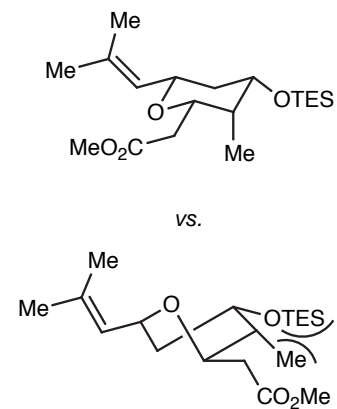
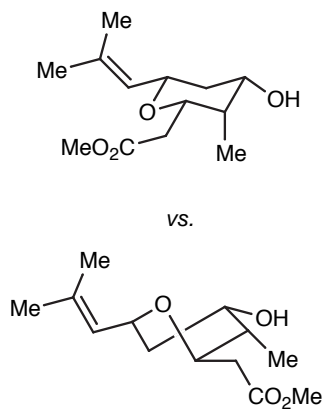
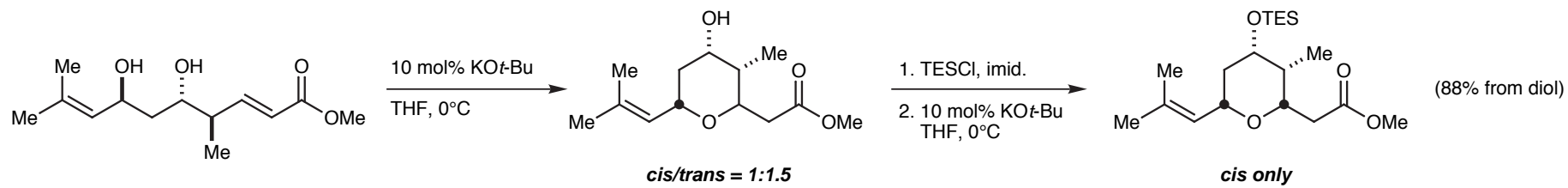
Toward Bryostatin 1:



Evans *Tet. Lett.* **1990**, 31, 4703.

Diastereoselectivity = 86:1

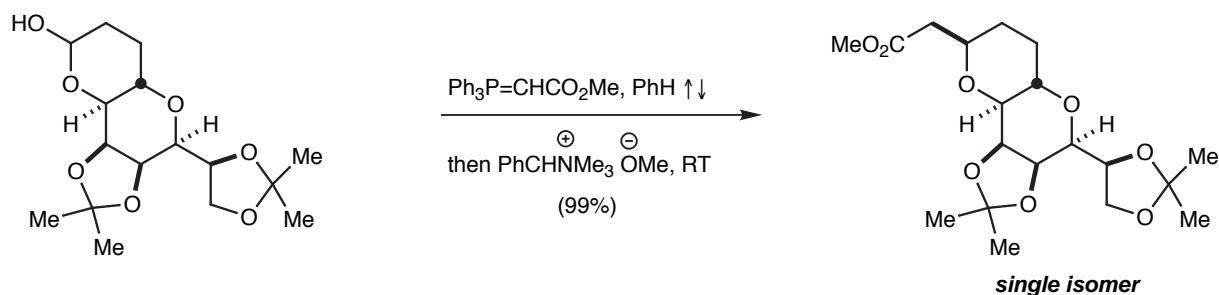
Toward Miyakolide:



Dave Ripin *Unpublished Results*

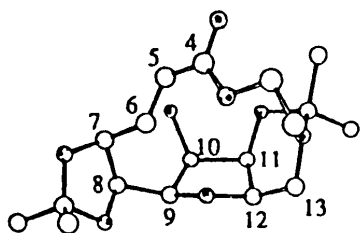
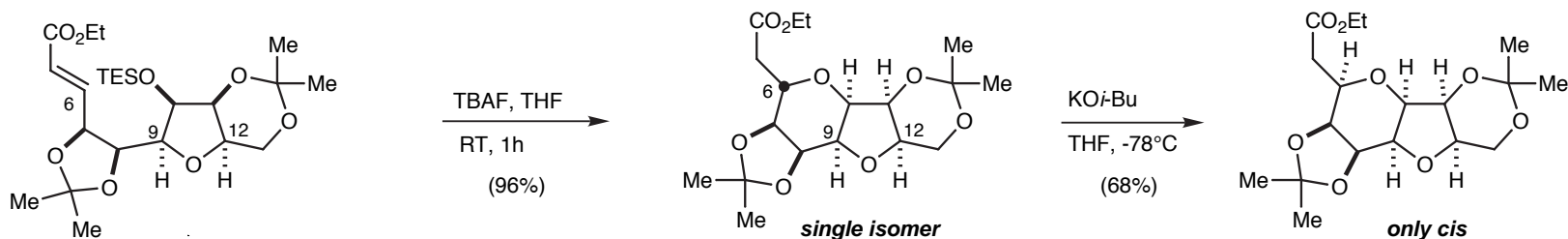
Intramolecular Heteroconjugate Addition

Toward Halichondrin B:

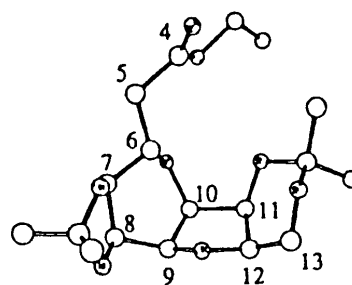


Note: In the absence of Triton B(OMe) a 1:1 mixture of epimers is obtained.

Kishi *Tet. Lett.* **1993**, 34, 7541.



Note: CONFLEX-MM2 calculations show the distance between the C10-oxygen and C6 of the major conformer of silyl deprotected starting material to be 3.1 Å when the C7/C8 diol is protected as an acetonide.

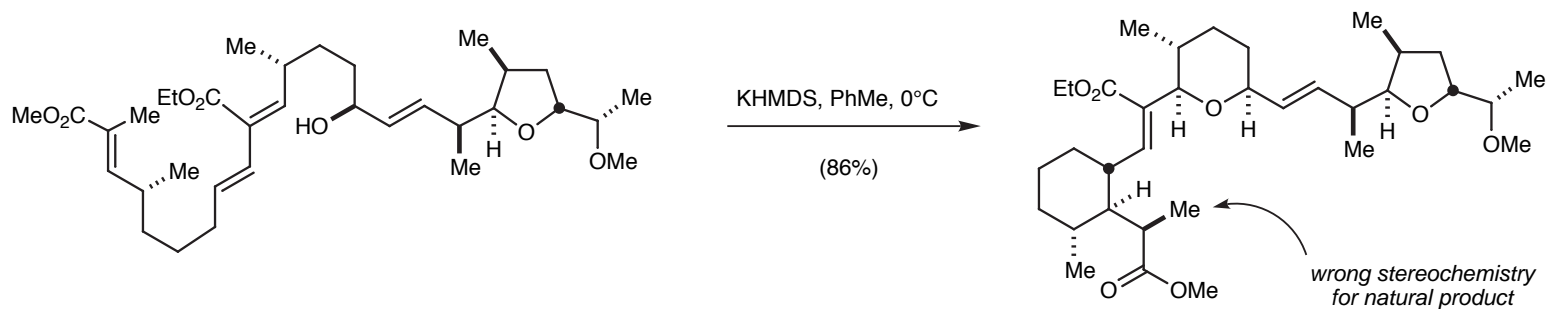


Note: CONFLEX-MM2 calculations show the major conformer of the trans isomer to be 2.48 Kcal/mol less stable than the cis.

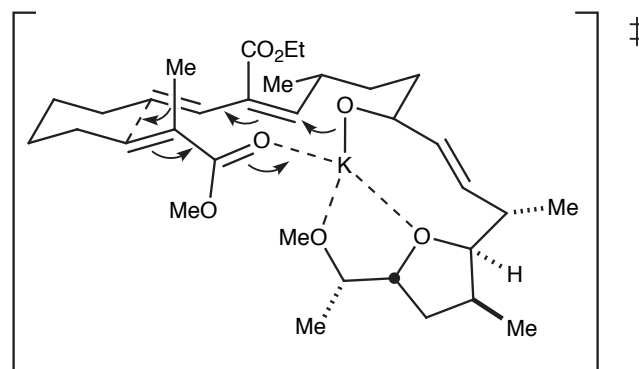
Horita/Yonemitsu *Synlett.* **1994**, 38.

Polyene Cyclization

Toward Tetronasin:

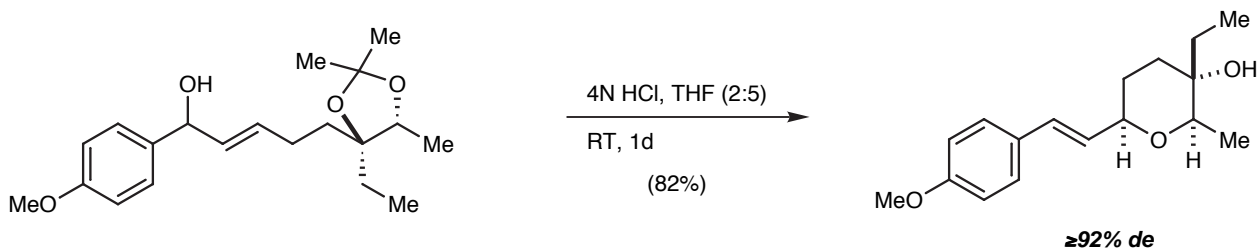


"one main diastereomer"



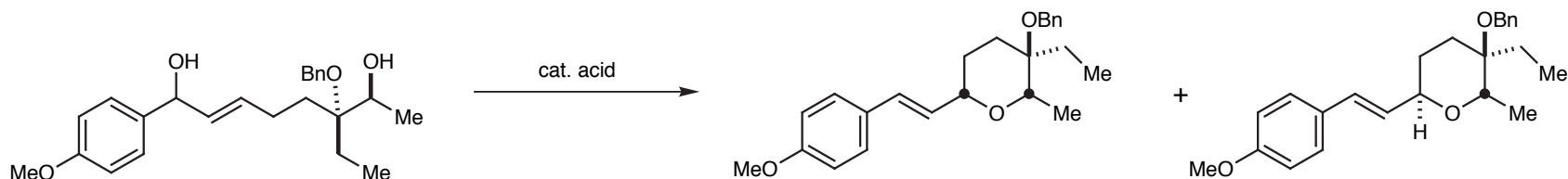
Ley *Tet. Lett.* **1994**, 35, 323.

Cyclizations of *p*-Methoxyphenylallyl Alcohols



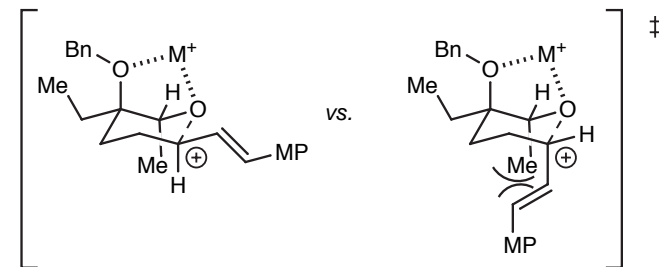
Horita/Yonemitsu *Tet. Lett.* **1986**, 27, 1917.

Toward Lasalocid A:



catalyst	solvent	temp.	time	yield	cis/trans ratio
CSA	CH ₂ Cl ₂	RT	3 min	54%	1 : 4.4
CSA	CH ₂ Cl ₂	RT	12 hr	78%	3.3 : 1
CSA	PhMe	100°C	1 day	55%	6.2 : 1
4N HCl	THF	RT	5 min	79%	1 : 1.7
ZnBr ₂	CH ₂ Cl ₂	RT	25 min	77%	1 : 4.5
ZnBr ₂	CH ₂ Cl ₂	-20°C	1.5 hr	79%	1 : 14

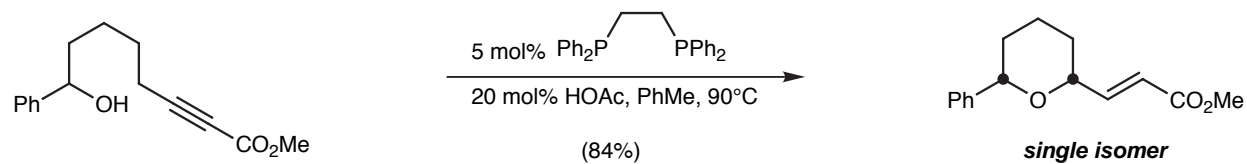
Authors' Explanation:



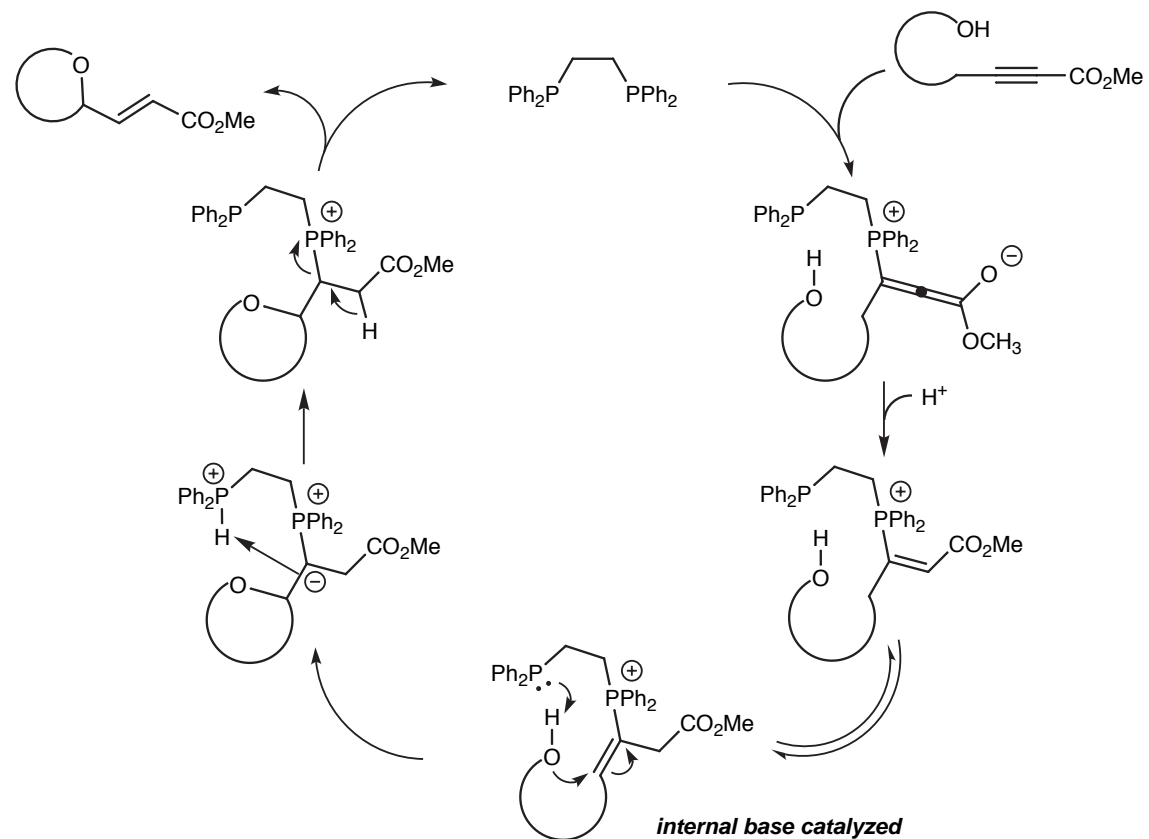
Note: Replacement of Bn with TBS in ZnBr₂ reaction gives cis/trans = 24:1.

Horita/Yonemitsu *Tet.* **1994**, 49, 5979.

Phosphine-Catalyzed Isomerization/Cyclization



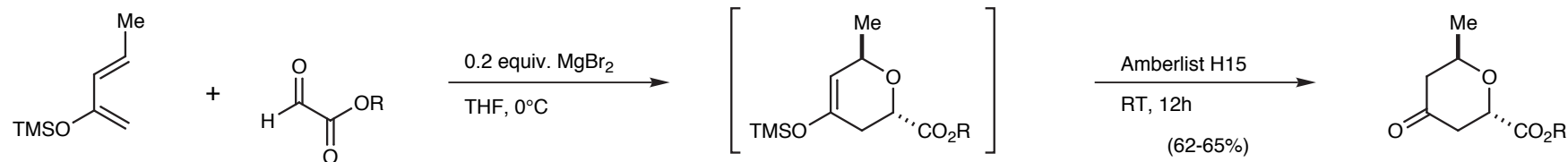
Mechanistic Rationale:



Trost *J. Am. Chem. Soc.* **1994**, 116, 10819.

Hetero-Diels-Alder

Toward Swinholide A:



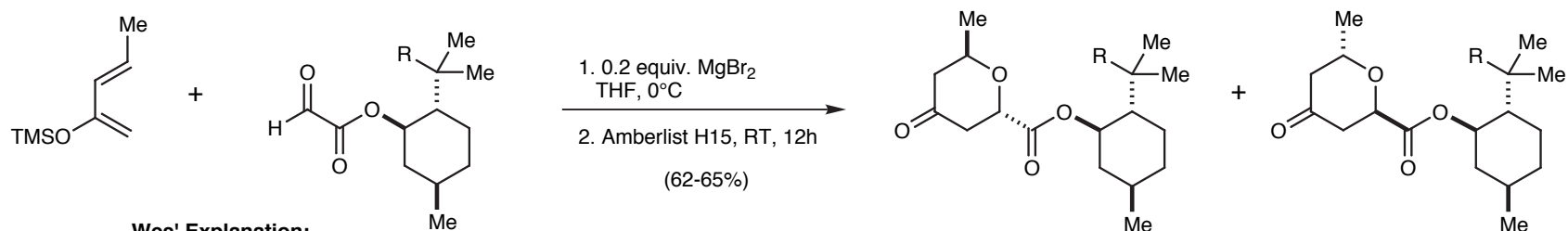
$R = \text{Et, } i\text{-Bu, endo-boranyl}$

Diastereoselectivity > 95:5

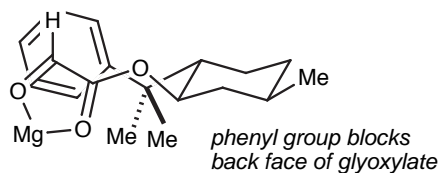
Authors' Explanation:



Note: Thermal reaction gives cis/trans = 2:1 (60-65%)



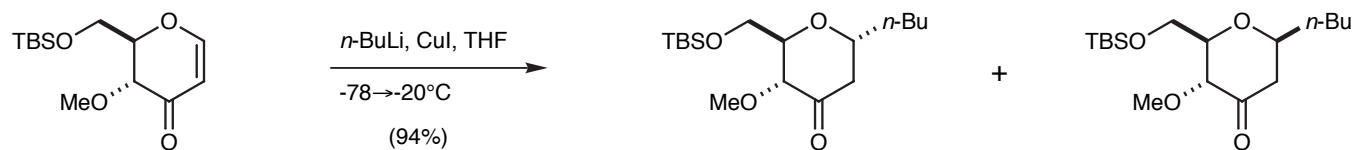
Wes' Explanation:



$R = \text{H}$	50	:	50
$R = \text{Ph}$	>99	:	1

Mulzer *Tet. Lett.* **1995**, 36, 3503.

Conjugate Addition to Dihydropyrone

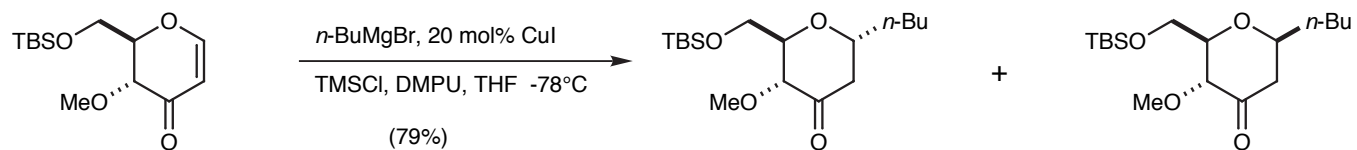


Goodwin *J. Org. Chem.* **1983**, *48*, 376.

12.9

+

1



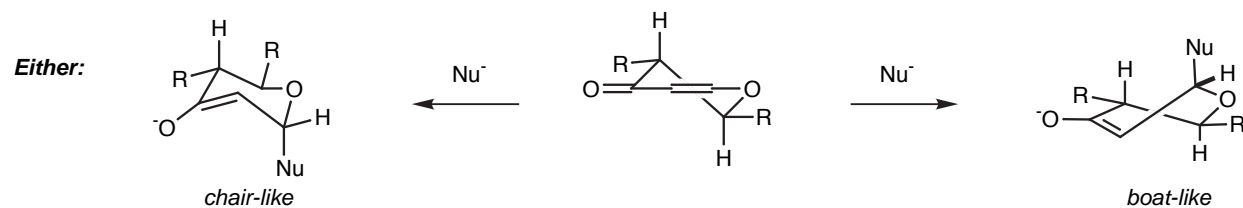
Goodwin *J. Org. Chem.* **1992**, *57*, 2469.

1

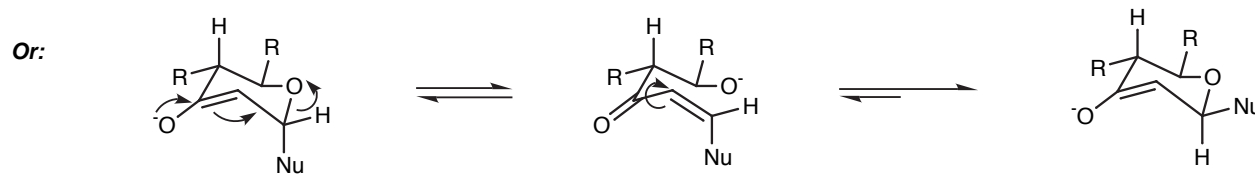
+

6.9

Authors' Explanations:



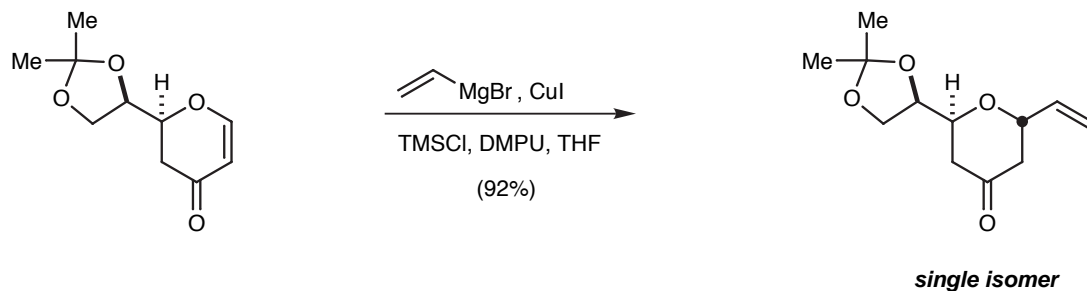
Organocopper reaction goes through chair-like TS, while copper-catalyzed Grignard goes through boat-like?



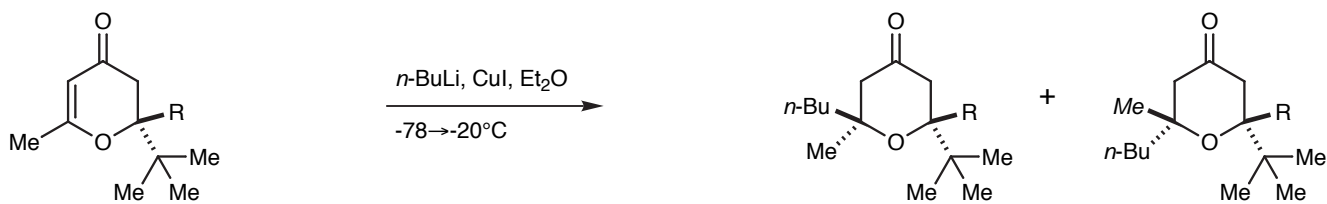
Both reactions go through chair-like TS, but copper-catalyzed Grignard equilibrates to cis isomer through ring opening/re-addition.

Conjugate Addition to Dihydropyrone

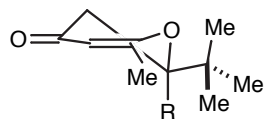
Toward Bryostatin 1:



Nishiyama/Yamamura *Tet. Lett.* **1993**, *34*, 4981.



Authors' Explanation:

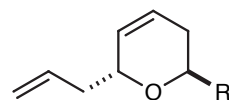
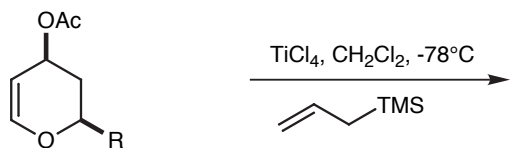


When $R = \text{Me}$, bottom face is partially blocked from attack.

$R = \text{Me}$	50	:	50	(63%)
$R = \text{H}$	>95	:	5	(78%)

Lange *J. Am. Chem. Soc.* **1994**, *116*, 3323.

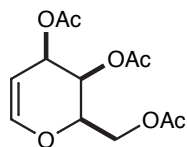
Carbon-Ferrier Reaction



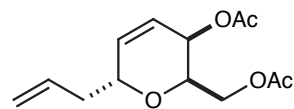
Diastereoselectivity > 95:5

Note: No regioisomers were obtained

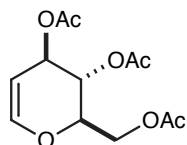
R	Yield
CH ₂ OBn	99%
Ph	60%
CH ₂ SPh	95%
n-Pr	82%



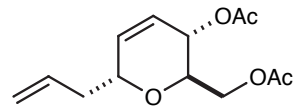
(93%)



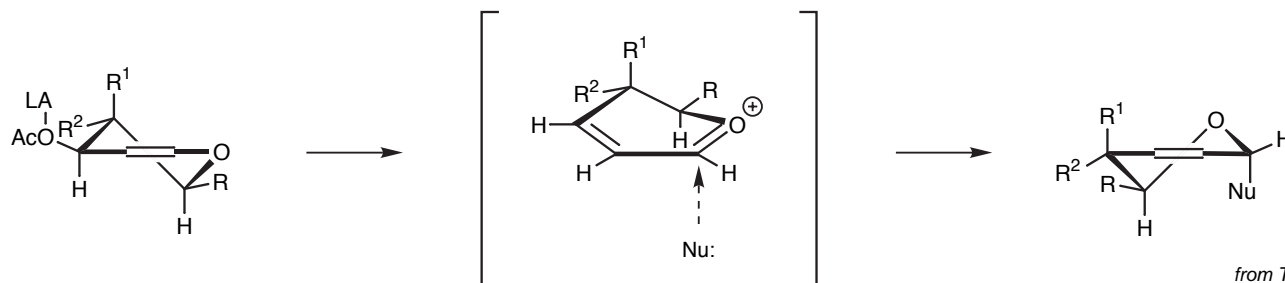
Diastereoselectivity 30:1



(85%)



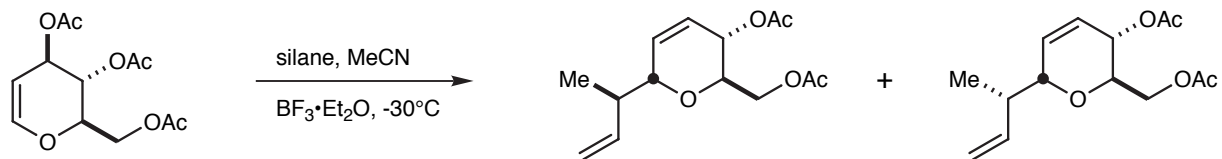
Diastereoselectivity 16:1



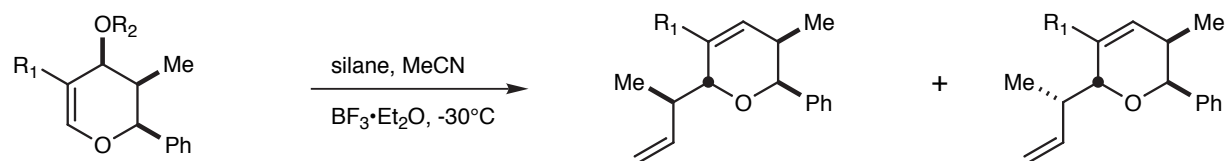
from Tom Smith seminar 5/9/97

Danishefsky *J. Org. Chem.* **1982**, *47*, 3803.

Carbon-Ferrier Reaction



Silane					
	3	:	1		
	1	:	3		
	1	:	7		

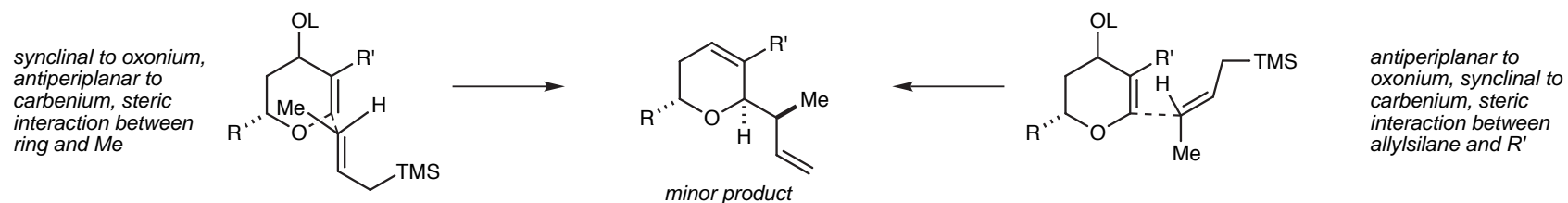
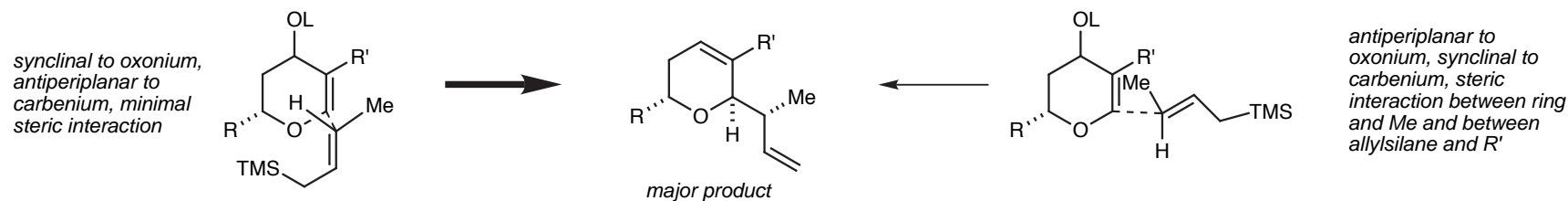


R ₁	R ₂	Silane			
H	Ac		5	:	1
H	CH(O)CHCl ₂		7	:	1
H	Ac		1	:	4
SPh	Ac		10	:	1
Me	Ac		30	:	1

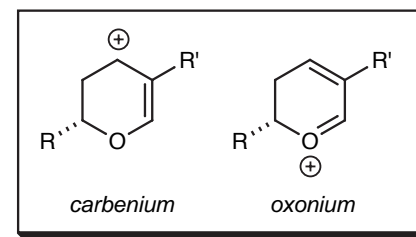
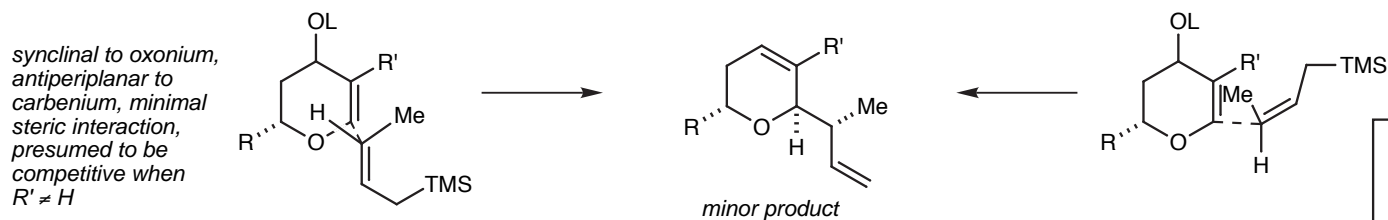
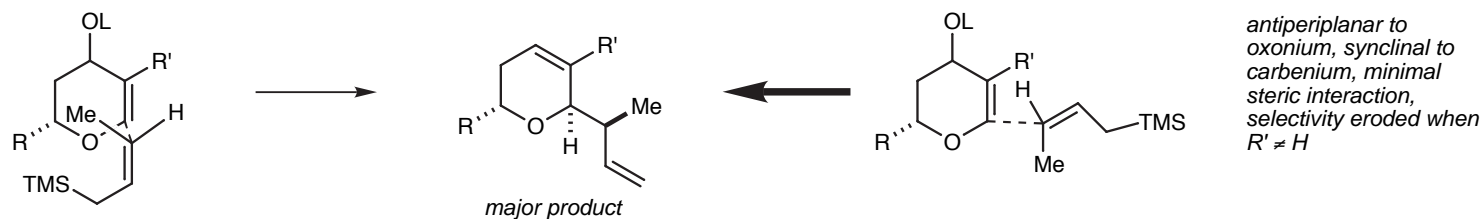
Danishefsky *J. Am. Chem. Soc.* **1987**, 109, 2082.

Stereochemical Rationale for Crotylsilane Addition

For E-silane:

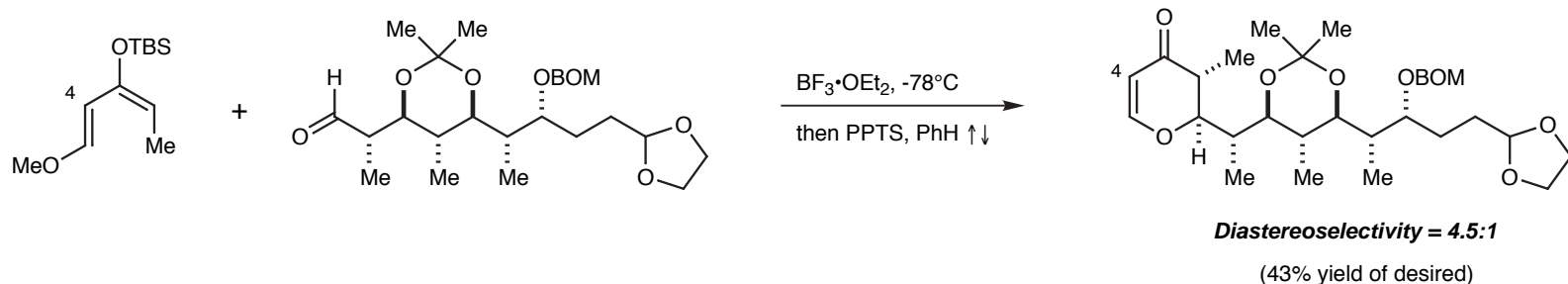


For Z-silane:

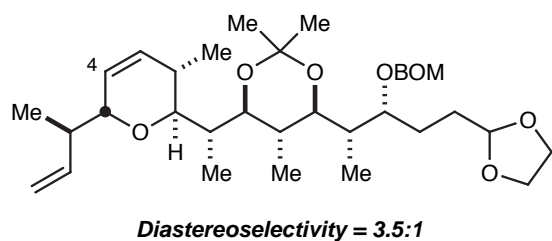


Carbon-Ferrier in Total Synthesis

Toward Zincophorin:



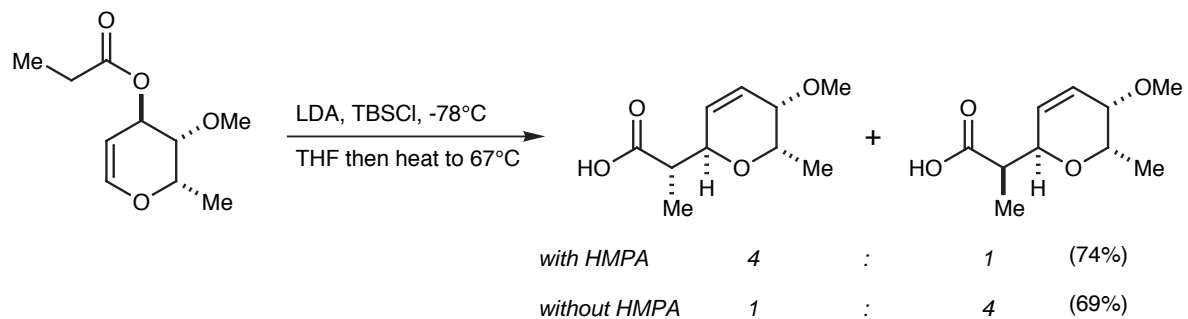
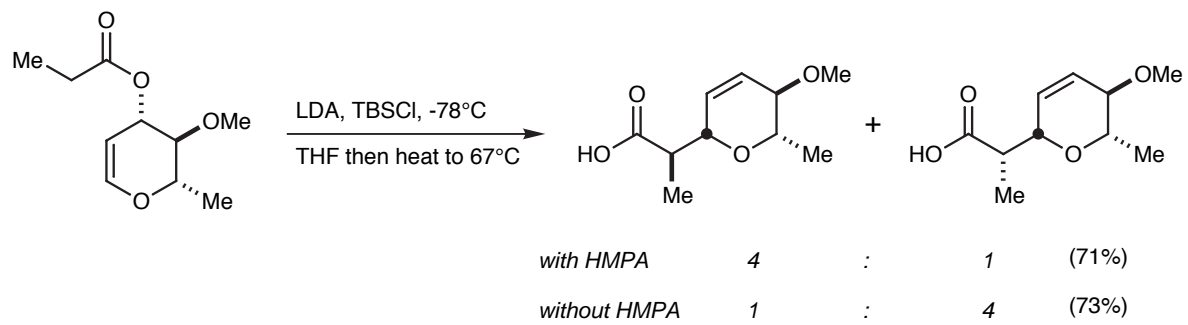
Note: Although thiophenyl substitution at C4 was expected to improve the selectivity of the carbon-Ferrier reaction, it caused a turnover in the selectivity of the hetero-Diels-Alder reaction.



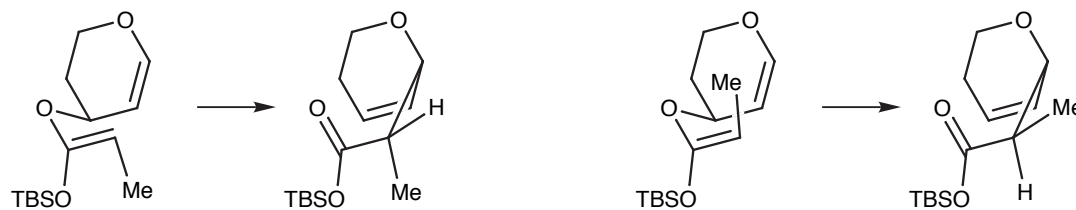
1. $\text{NaBH}_4, \text{CeCl}_3$
 2. $\text{Ac}_2\text{O}, \text{Et}_3\text{N}, \text{DMAP}$
 (90%)

Danishefsky *J. Am. Chem. Soc.* **1988**, *110*, 4368.

Ester Enolate Claisen Rearrangement



Authors' Explanation:



With HMPA, Z-enolate is formed preferentially.

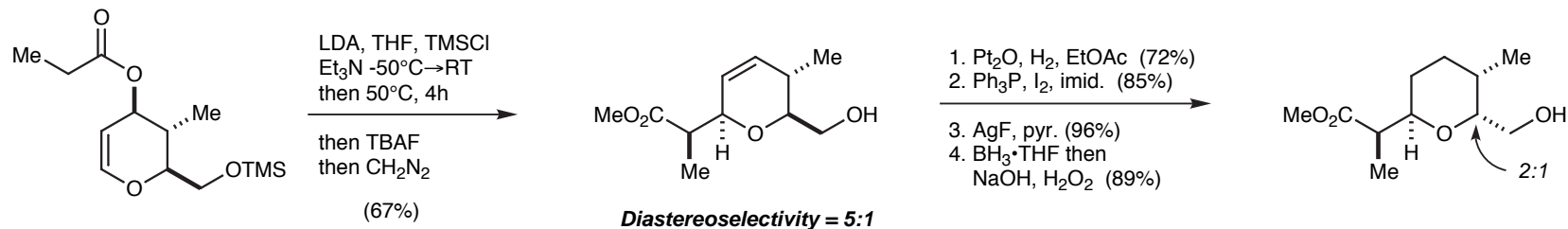
Both believed to go through boat-like TS. (See: Lythgoe, J. Chem. Soc., Perkins Trans.1 1977, 1218.)

Without HMPA, E-enolate is formed preferentially.

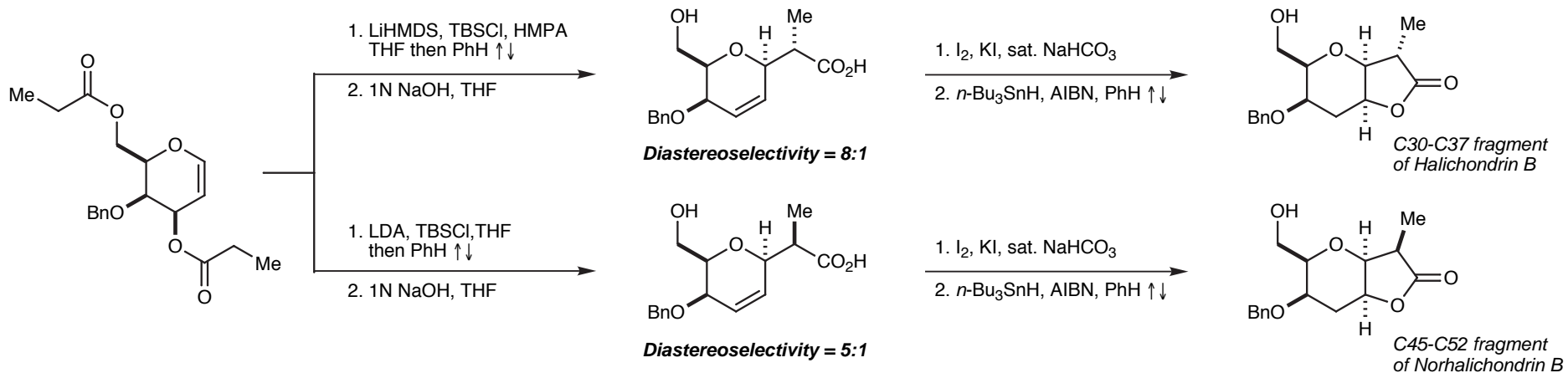
Ireland *J. Org. Chem.* **1980**, 45, 48.

Ireland-Claisen Rearrangement

Toward Antibiotic X-14547A:

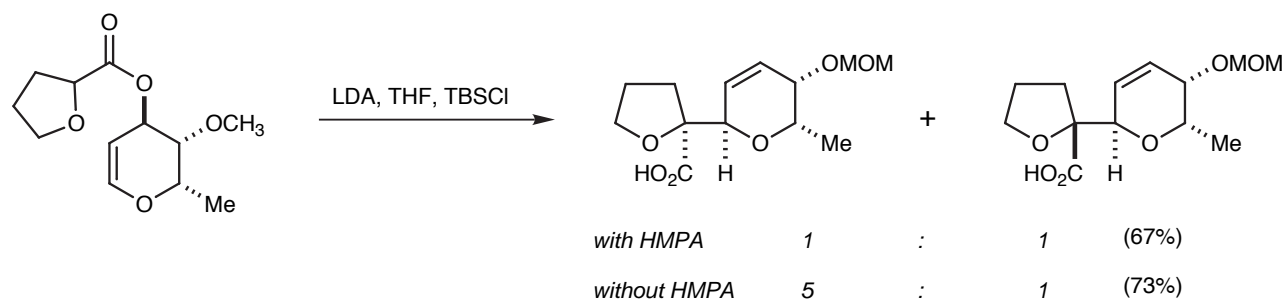


Ley *Chem. Commun.* **1983**, 630.



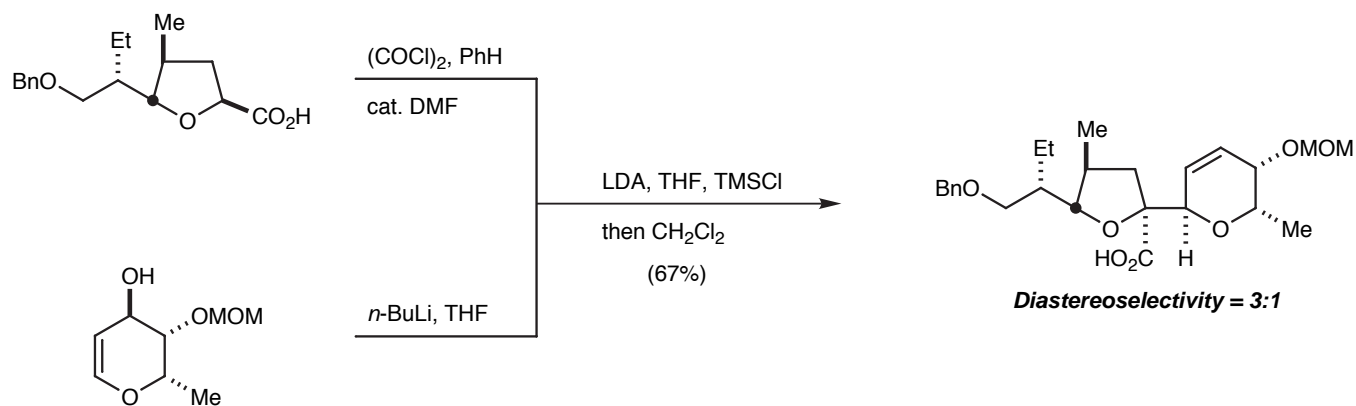
Kishi *Tet. Lett.* **1992**, 33, 1549.

Ireland-Claisen Rearrangement



Ireland *J. Org. Chem.* **1980**, *45*, 48.

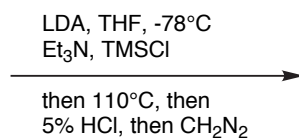
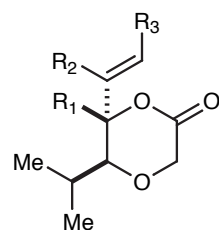
Toward Lasalocid A:



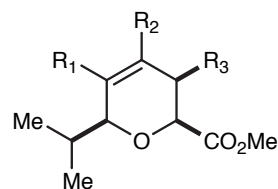
Ireland *J. Am. Chem. Soc.* **1983**, *105*, 1988.

Ireland-Claisen Rearrangement

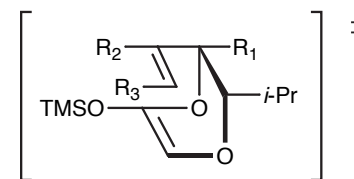
Internal Enolate:



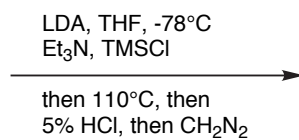
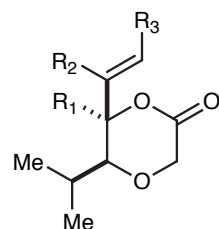
R ₁	R ₂	R ₃	Yield
H	H	H	67%
Me	H	H	90%
H	Me	H	75%
H	H	Me	70%
H	H	TMS	52%
Me	Me	H	80%



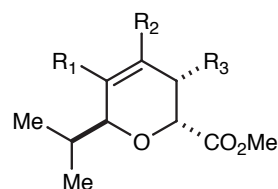
single isomer



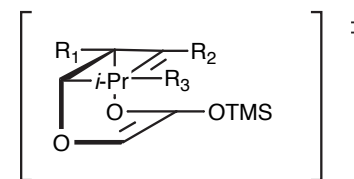
Note: Attempts at enolate Claisen rearrangement with *cis* olefin resulted in no reaction.



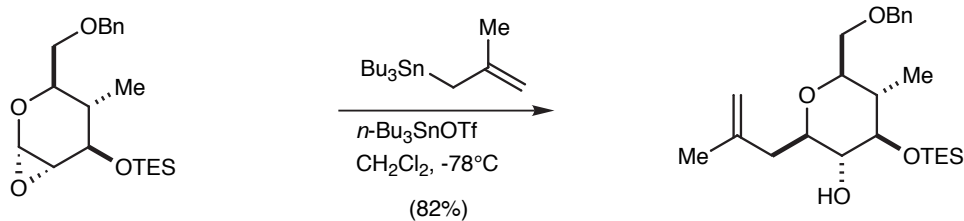
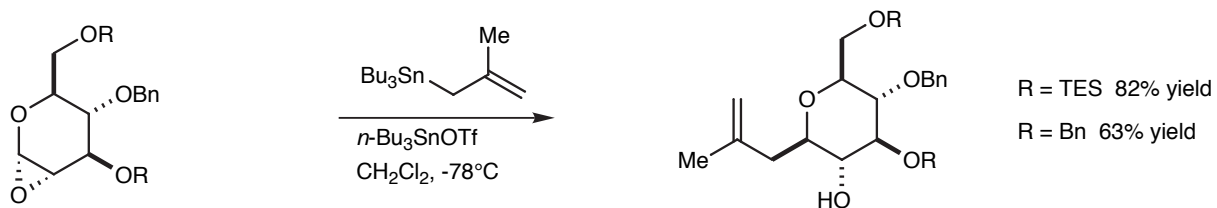
R ₁	R ₂	R ₃	Yield
H	H	H	69%
Me	H	H	91%
H	Me	H	78%
H	H	Me	81%
H	H	TMS	61%



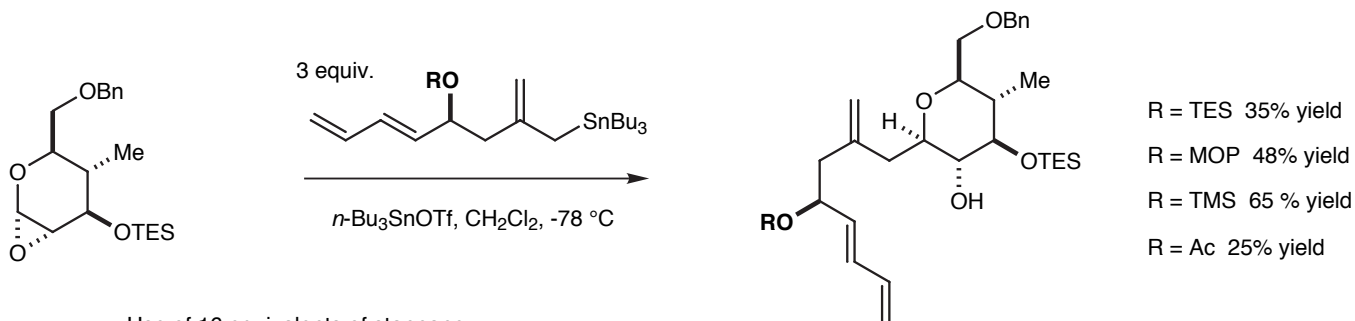
single isomer



Allyl Stannane Addition to Glycal Oxirane



Note: *In all cases*
Diastereoselectivity > 95:5

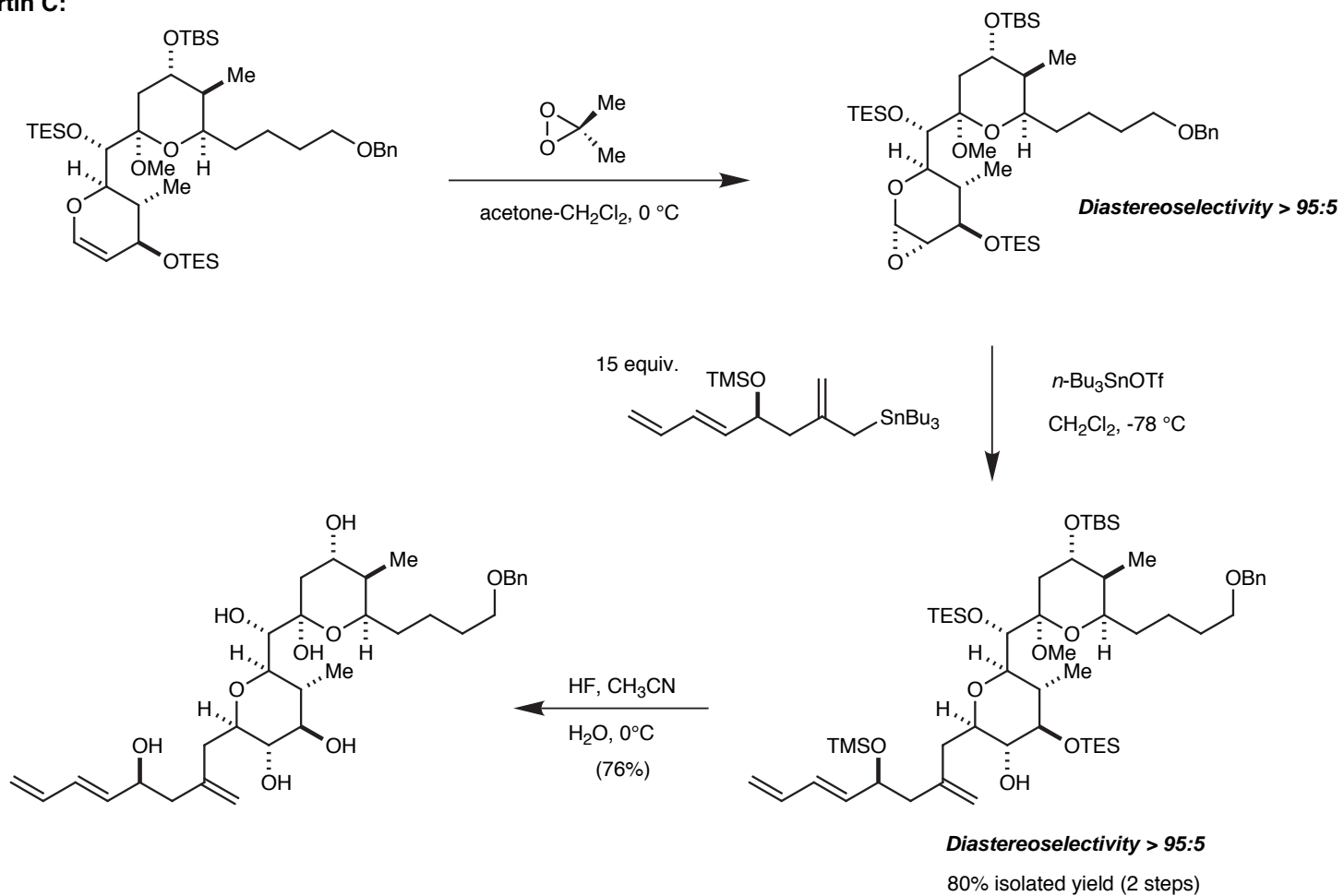


• Use of 16 equivalents of stannane increases the yield to 75% with R = TMS.

Wes Trotter *Unpublished Results*

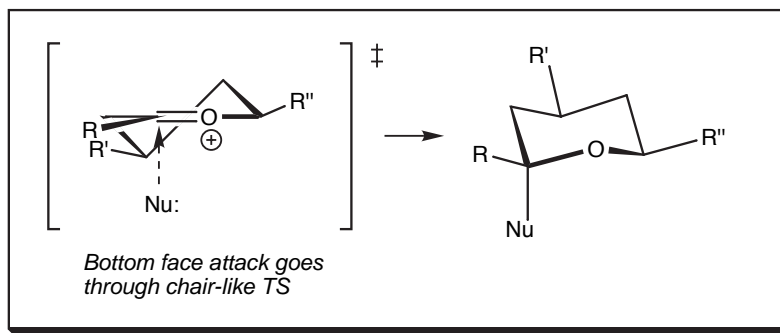
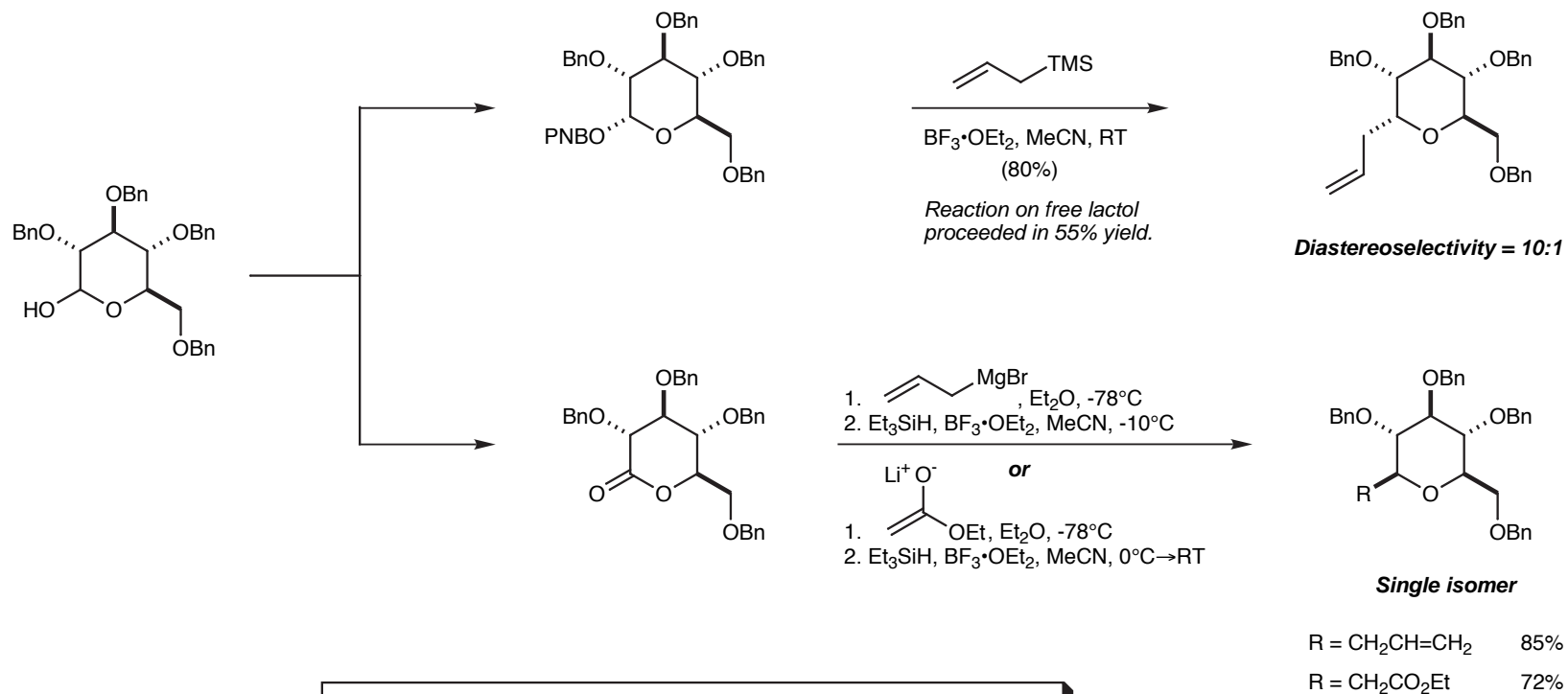
Allyl Stannane Addition to Glycal Oxirane

Toward Althoyrtin C:



Wes Trotter *Unpublished Results*

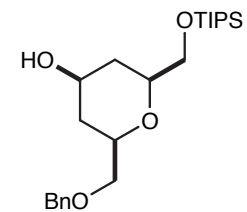
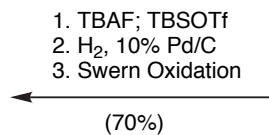
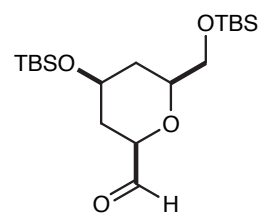
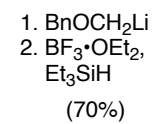
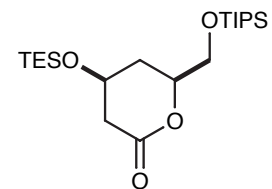
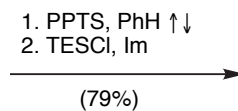
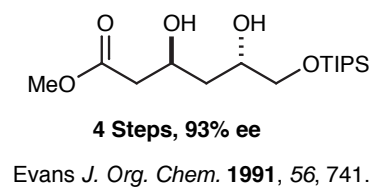
Oxonium Reactions



Kishi *J. Am. Chem. Soc.* **1982**, *104*, 4976.

Oxonium Reactions

Toward Bryostatin 1:

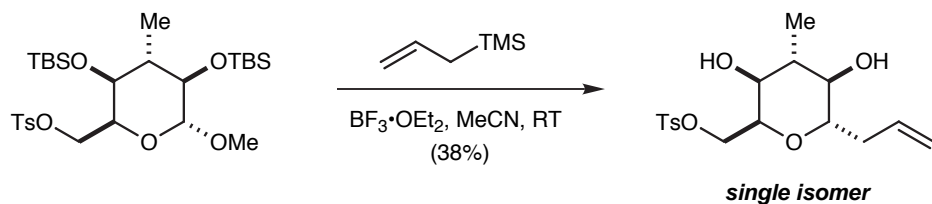
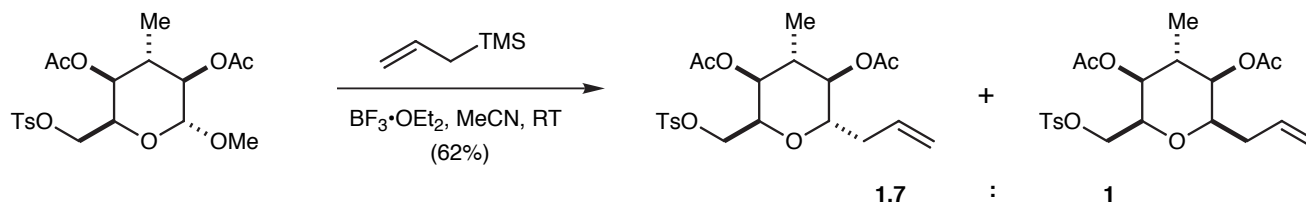


Diastereoselectivity = 95 : 5

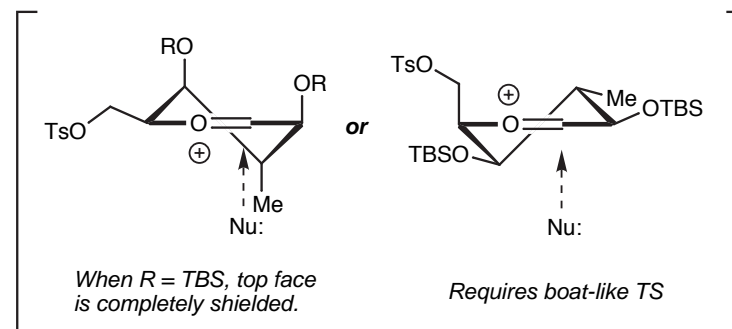
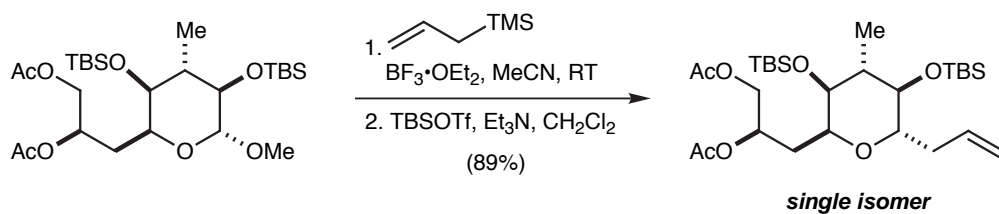
Percy Carter *Unpublished Results*

Oxonium Reactions

Toward Halichondrin B:



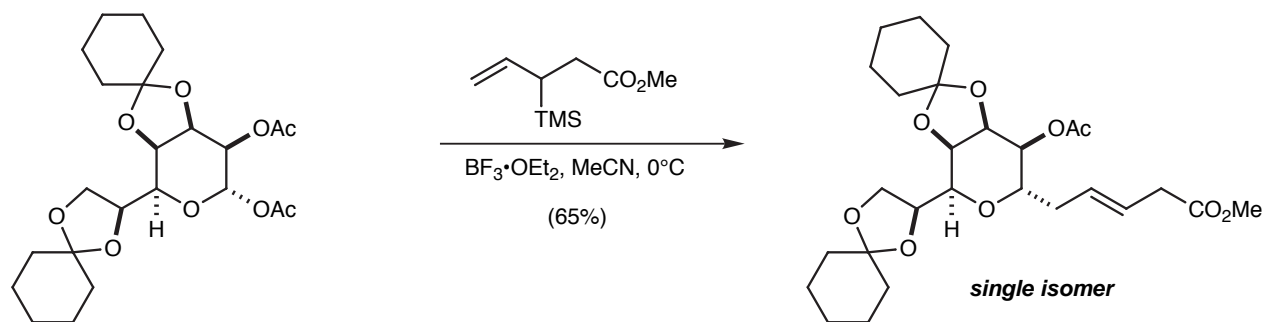
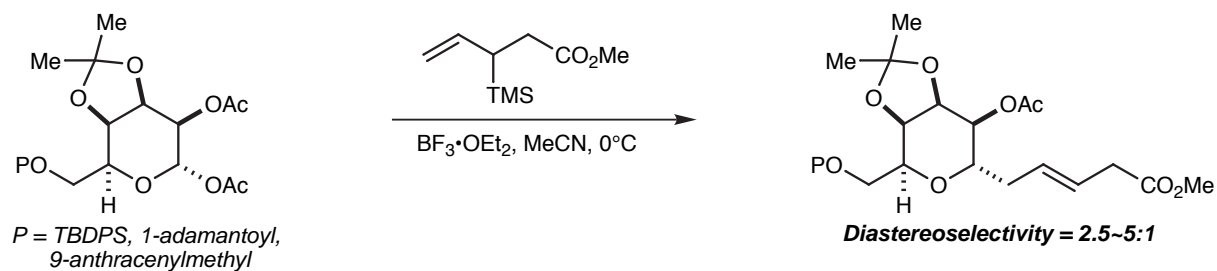
Note: ^1H NMR experiments show the TBS groups in an equatorial arrangement in the starting material, while the acetates are in the axial orientation.



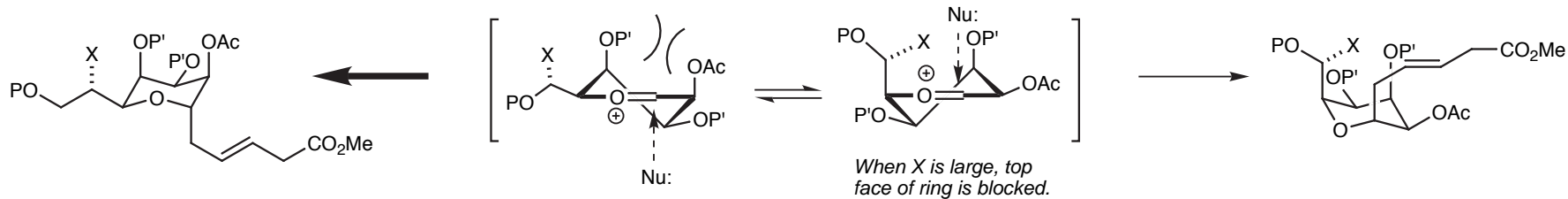
Horita/Yonemitsu *Synlett* **1994**, 43.

Oxonium Reactions

Toward Halichondrin B:

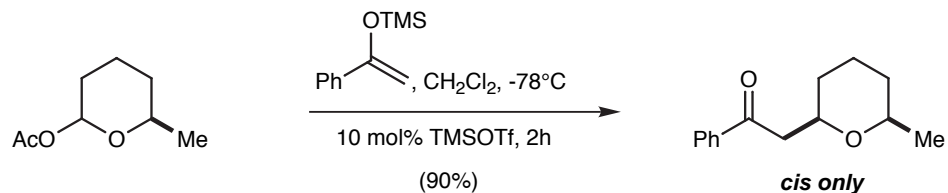


Authors' Explanation:



Kishi *Tet. Lett.* **1996**, *37*, 8643.

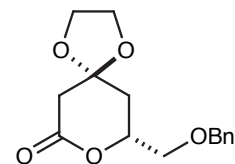
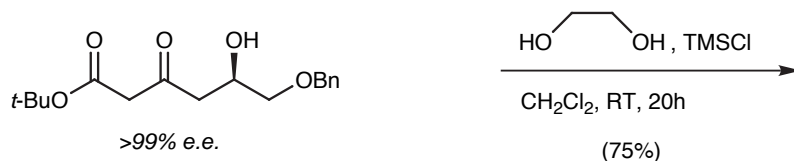
Oxonium Reactions



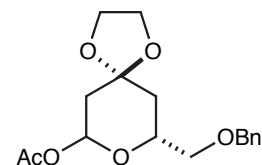
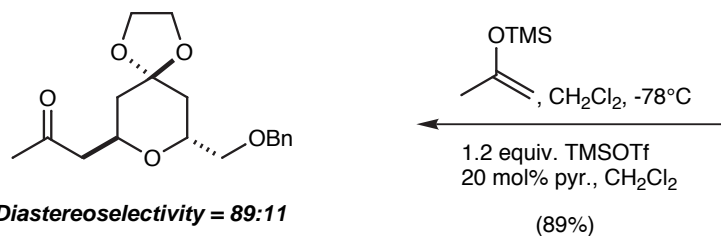
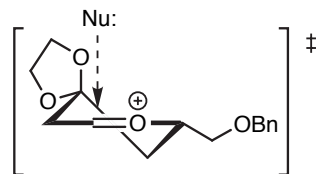
¹H NMR experiments show TMSOTf equilibrates the starting lactol acetate entirely to the axial position. Therefore, the authors claim the silyl enol ether attacks via an $\text{S}_{\text{N}}2$ -type mechanism.

Noyori *Tet. Lett.* **1982**, 23, 2601.

Toward Phorboxazole B:

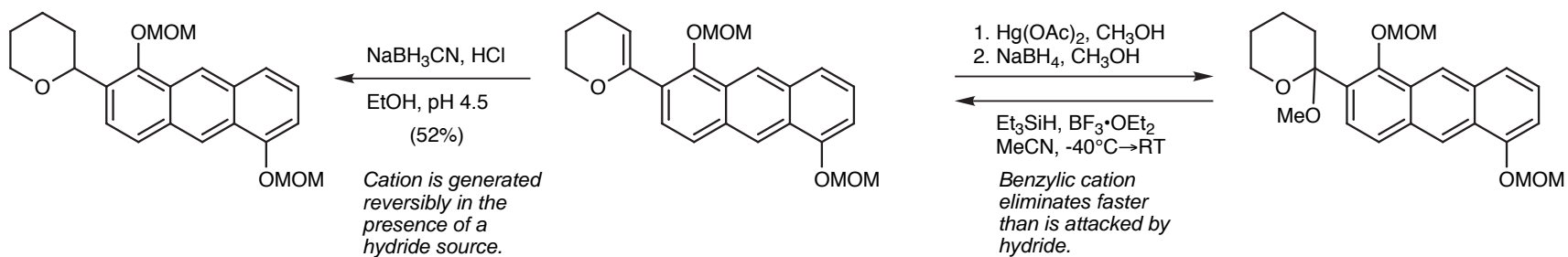


1. DIBAL-H, toluene, -78°C
 2. Ac_2O , pyr., DMAP, CH_2Cl_2
 (100%)

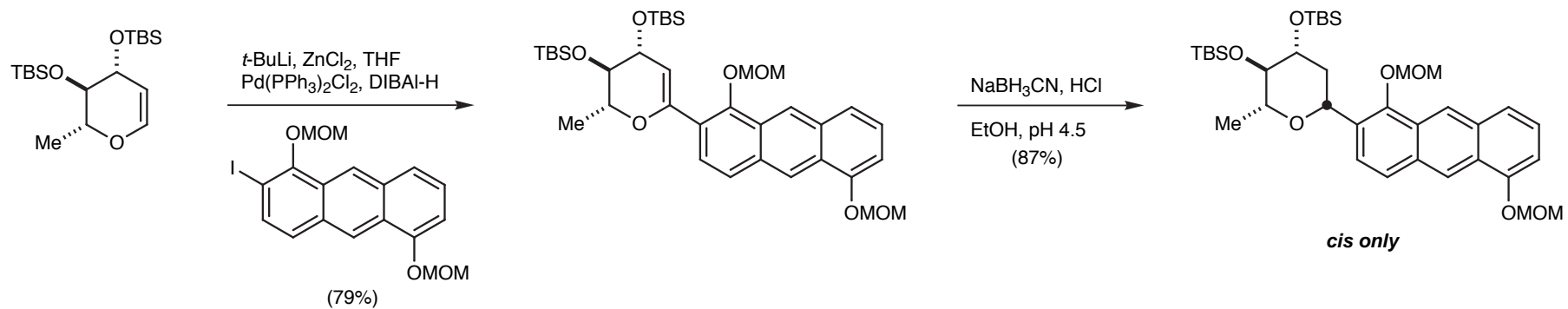


Duke Fitch *Unpublished Results*

Oxonium Reactions



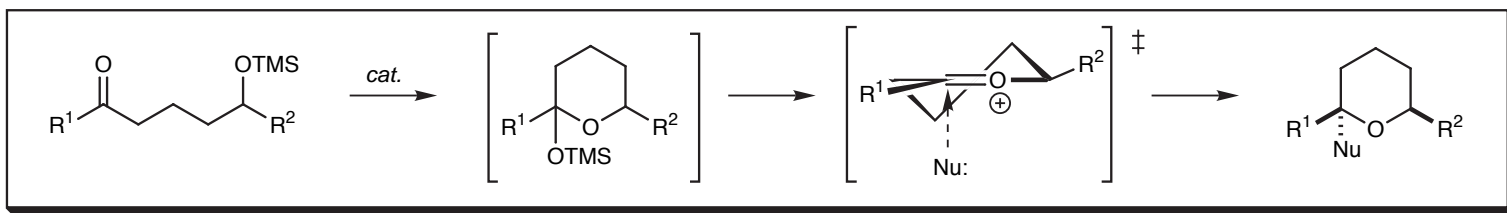
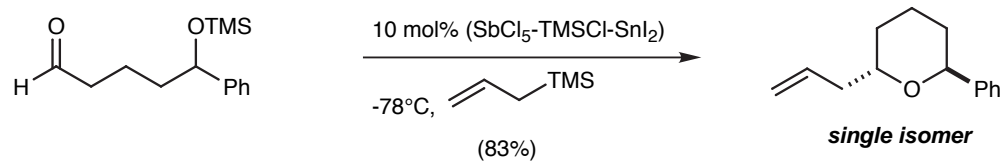
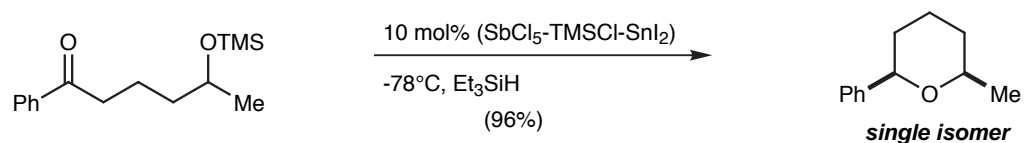
Toward Vineomycinone B2:



Tius *J. Am. Chem. Soc.* **1991**, 113, 5775.

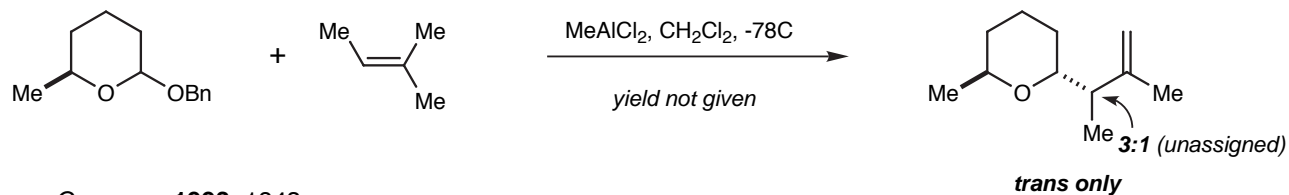
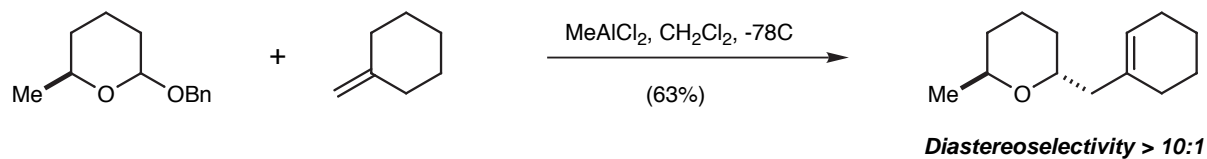
Oxonium Reactions

Acyclic Precursors:



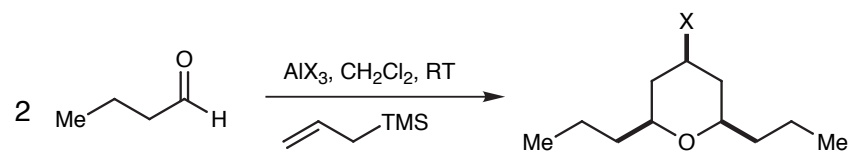
Mukaiyama *Chem. Lett.* **1989**, 259.

Oxonium-Ene:



Mikami *Chem. Commun.* **1993**, 1843.

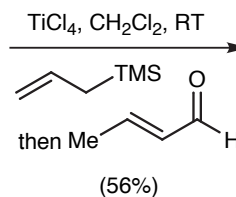
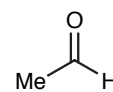
Prins Cyclization



In general, X=Cl gave higher yields.

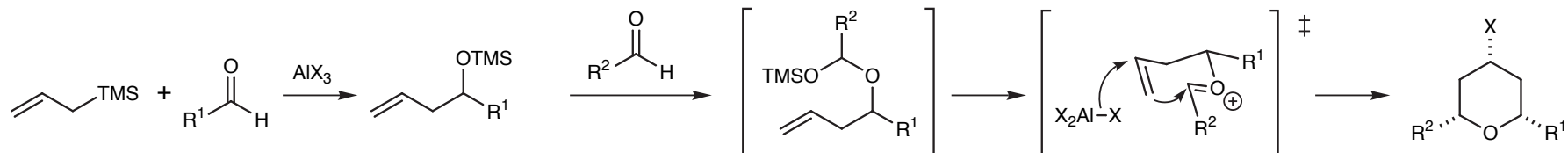
R = Cl 86% yield
R = Br 70% yield

Note: In all examples, only the all cis THP product was obtained.

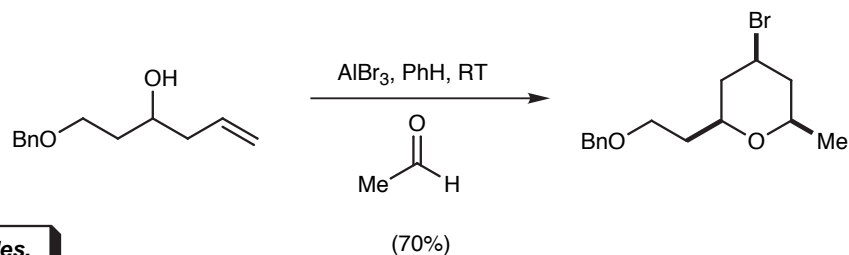
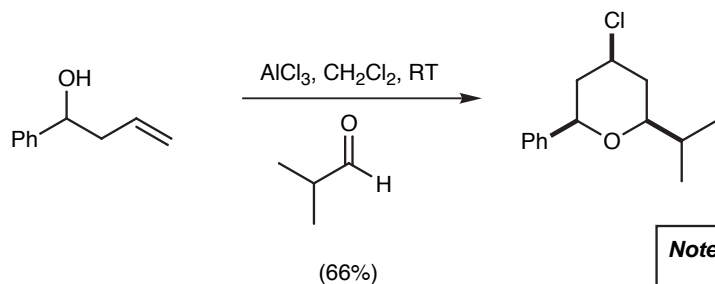


TiCl₄ was found to give minimal amounts of symmetrical byproducts.

Proposed Mechanism:



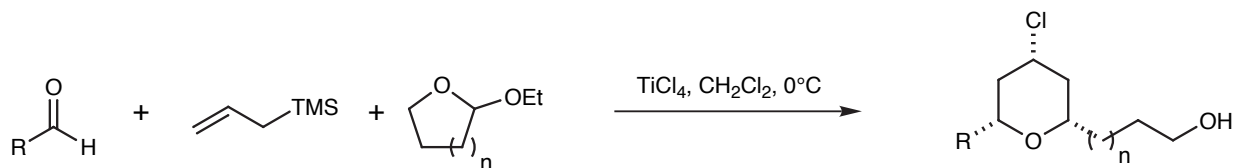
Taddei *Tet. Lett.* **1987**, 28, 973.



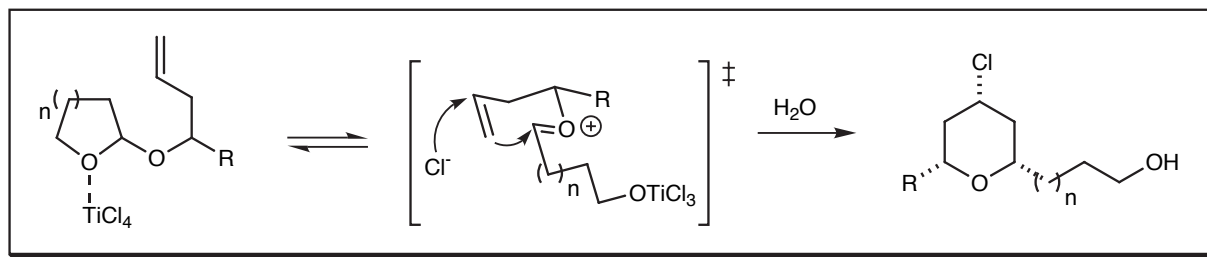
Note: In all examples, only the all cis THP product was obtained.

Taddei *J. Org. Chem.* **1988**, 53, 911.

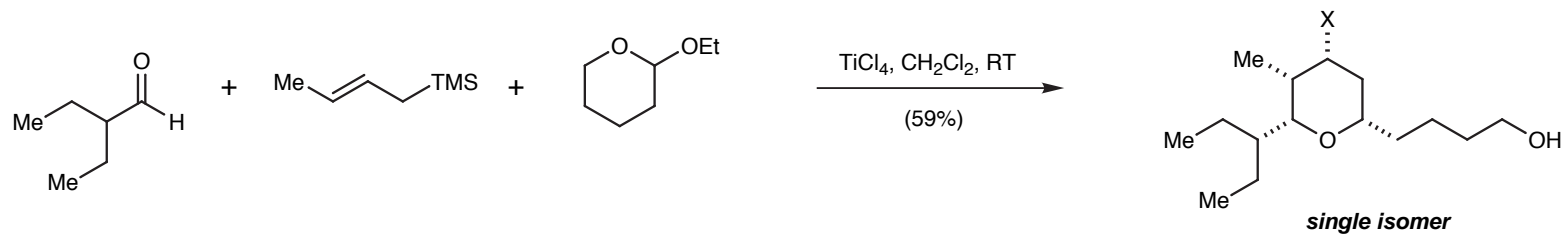
Prins Cyclization



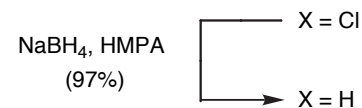
R	n	Yield
C ₆ H ₁₃ CHO	1	62%
(C ₂ H ₅) ₂ CHCHO	1	77%
C ₆ H ₁₃ CHO	2	60%
(C ₂ H ₅) ₂ CHCHO	2	60%



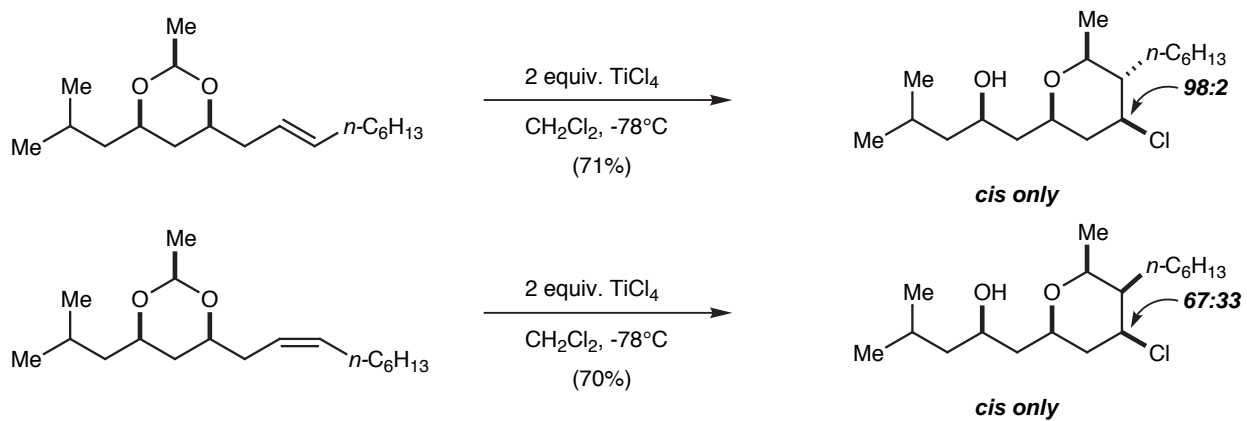
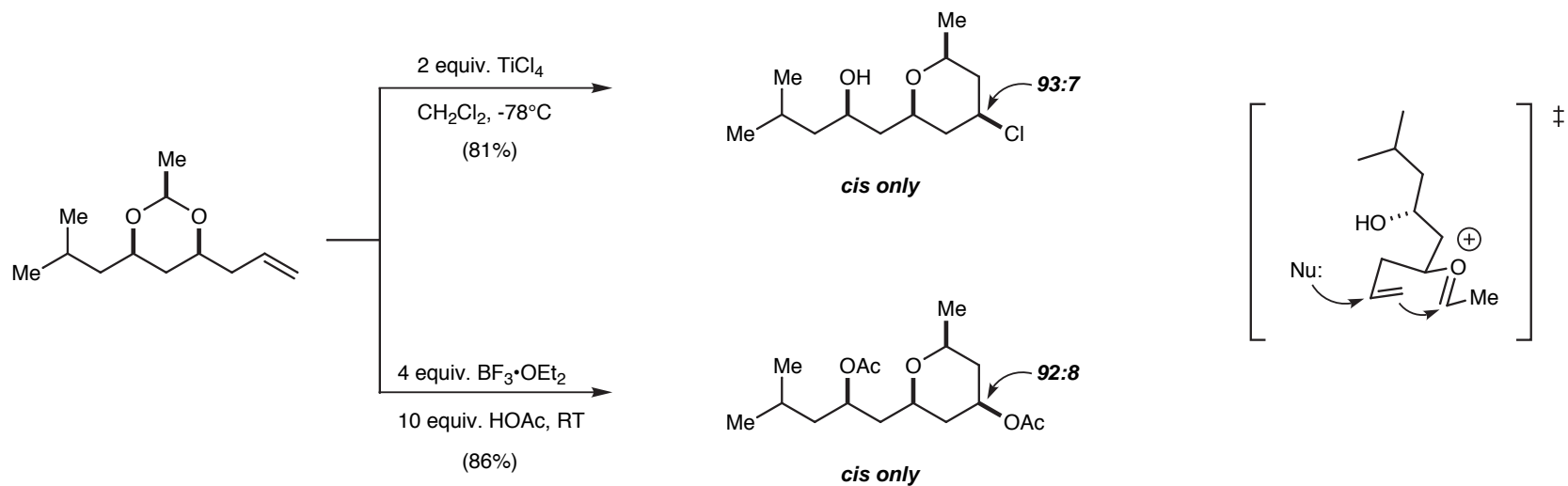
Model Study Toward Okadaic Acid:



Markó *Tet. Lett.* **1997**, *38*, 2895.



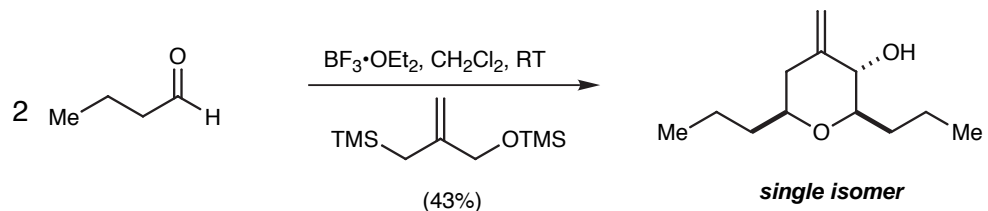
Prins Cyclization



Rychnovsky *Tet. Lett.* **1996**, 37, 8679.

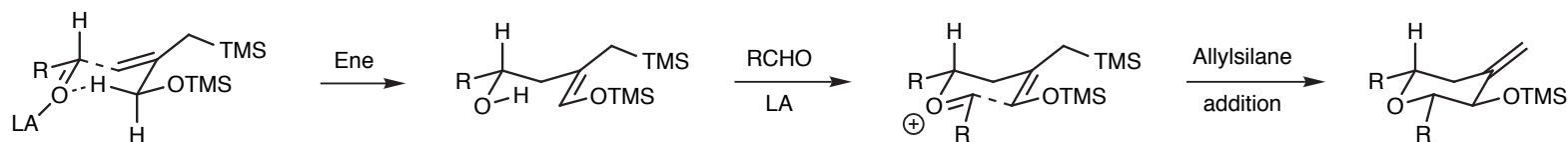
Intramolecular Silyl-Modified Sakurai Reaction

Allyl silanes:



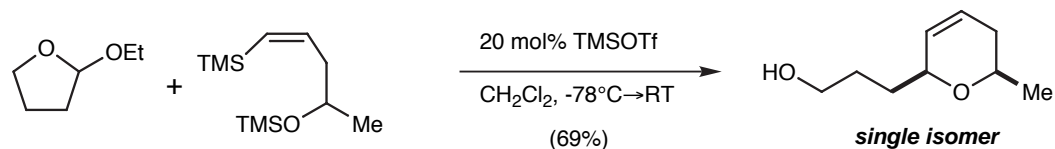
Note: In all examples, moderate yields of a single isomer were obtained. No reaction was observed for aromatic aldehydes.

Proposed Mechanism:



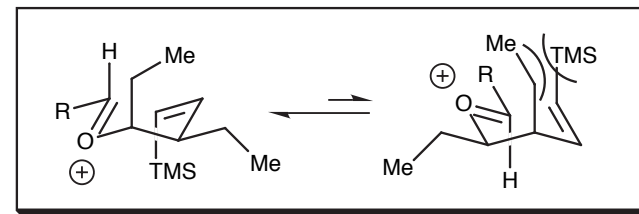
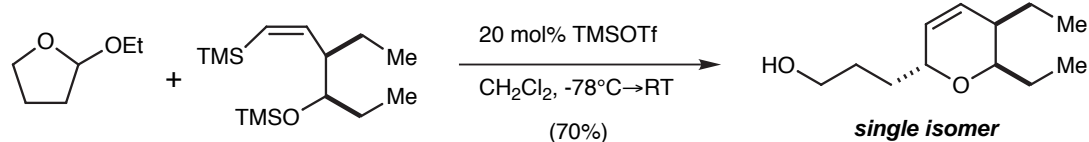
Markó *Tet. Lett.* **1993**, *34*, 6595.

Vinyl silanes:



Note: Use of aldehydes in place of acetals tended to give higher yields. In all examples of this type only the *cis* product was obtained.

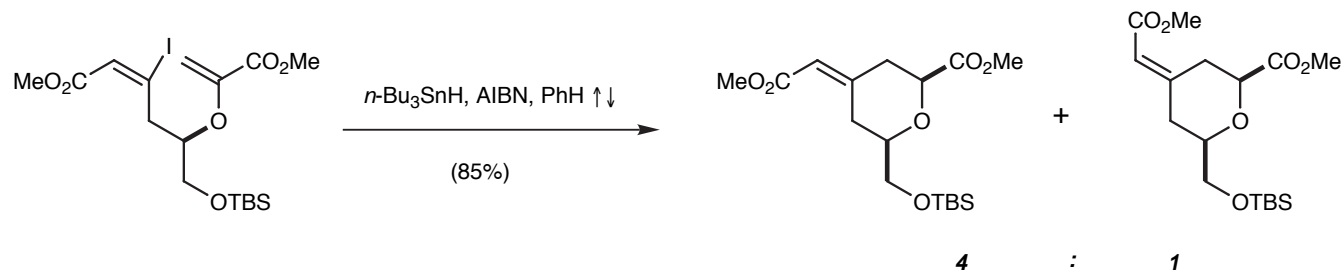
Model Study Toward Okadaic Acid:



Markó *Tet. Lett.* **1997**, *38*, 2899.

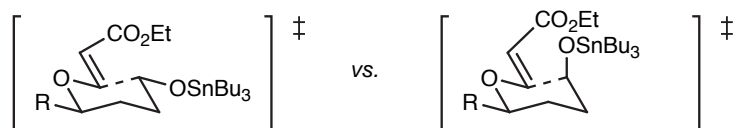
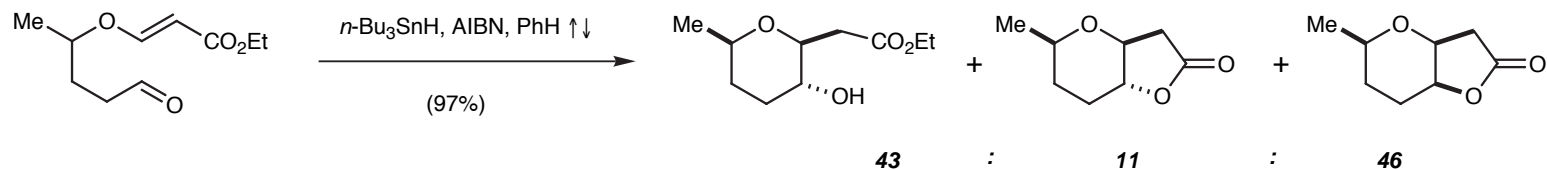
Radical Cyclization

Toward Bryostatin 1:

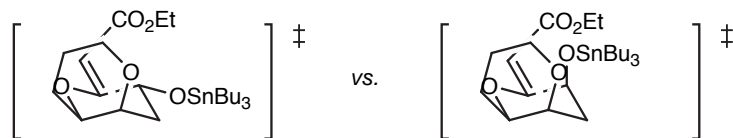
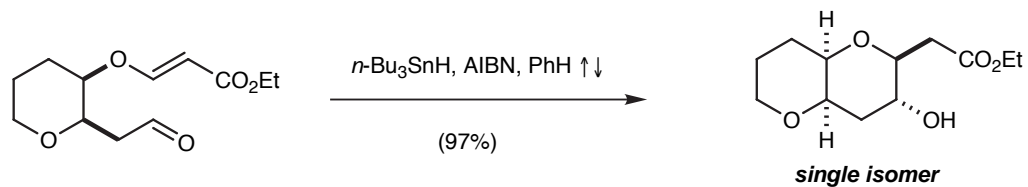


Note: Z-radicals are known to cyclize faster to 6-member rings.

Thomas *Chem. Commun.* **1989**, 480.



Note: Calculations have shown very little difference in energy between the two TS.



Lee *Tet. Lett.* **1994**, 35, 129.