

Stereoselective Synthesis of 2,5 Substituted Tetrahydrofurans

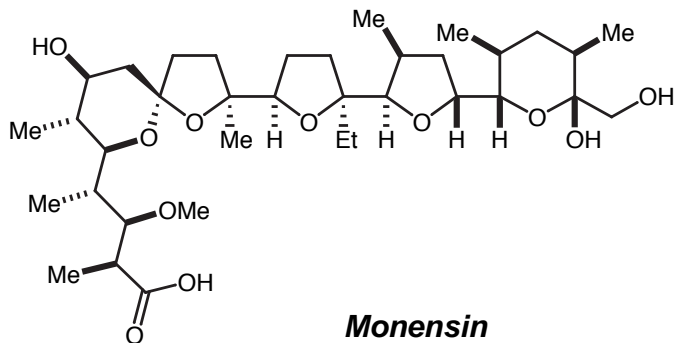
Hemaka Rajapakse
Evans Group Afternoon Seminar
Tuesday, December 8th 1998

- Tetrahydrofuran Containing Natural Products and Biosynthesis
- Oxidative Cyclizations of 1,5 Dienes
- Intramolecular Nucleophilic Substitution
- Epoxide Openings
- Haloetherifications of *bis*-Homoallylic Alcohols
- Oxonium Based Strategies
- Oxymercuration
- Miscellaneous Methods
- Multiple Tetrahydrofuran Synthesis

Leading Reviews :

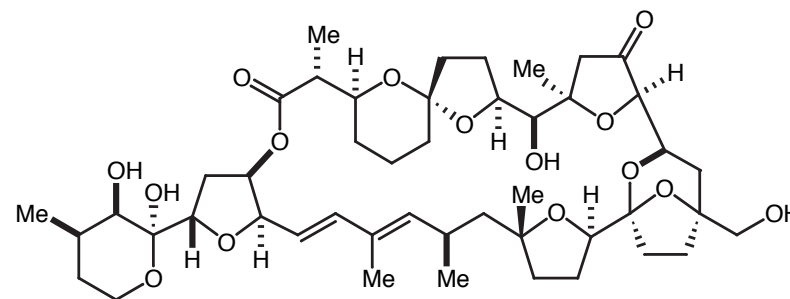
- Boivin, T. L. *Tetrahedron*, **1987**, *43*, 3362
- Figadere, B. *Tetrahedron : Asymmetry*, **1993**, *4*, 1711
- Ulrich, K. *Synthesis*, **1995**, 115

Tetrahydrofuran Ring Containing Natural Products



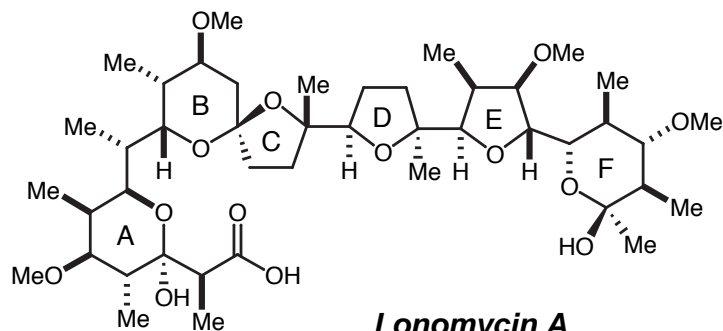
Monensin

Kishi *et al*, *JACS*, **1979**, 101, 259
 Still *et al*, *JACS*, **1980**, 102, 2117
 Ireland *et al*, *JACS*, **1993**, 115, 7152



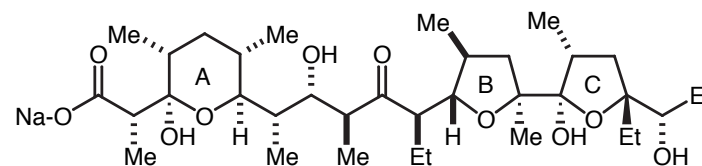
Pectenotoxin 4

Evans *et al*, In progress....



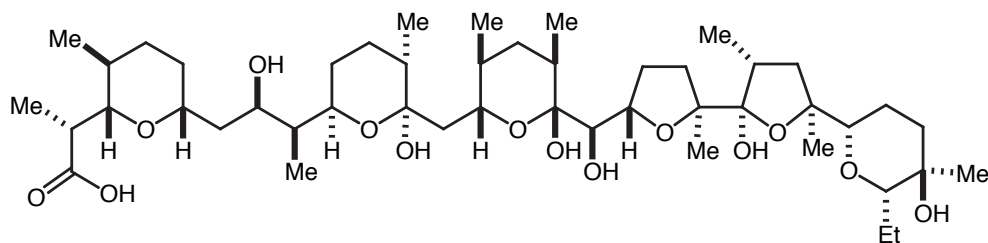
Lonomycin A

Evans *et al*, *JACS*, **1995**, 117, 3448



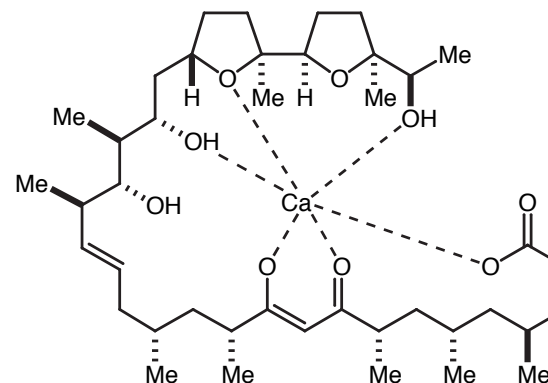
Ferensimycin B

Evans *et al*, *JACS*, **1991**, 113, 7613



Antibiotic X-206

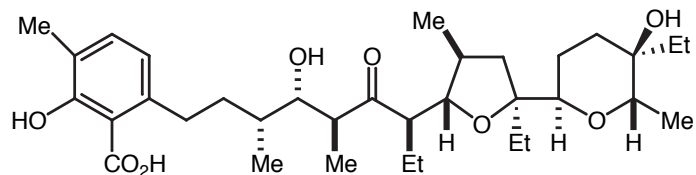
Evans *et al*, *JACS*, **1988**, 110, 2506



Ionomycin Calcium Complex

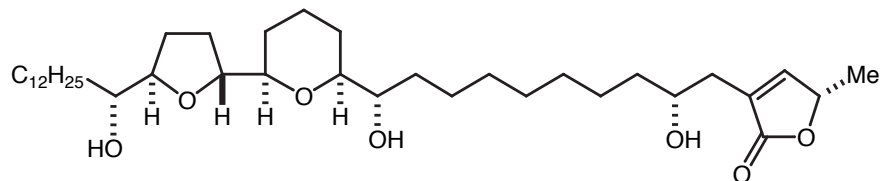
Evans *et al*, *JACS*, **1990**, 112, 5290
 Hanessian *et al*, *JACS*, **1990**, 112, 5176

More Tetrahydrofuran Ring Containing Natural Products



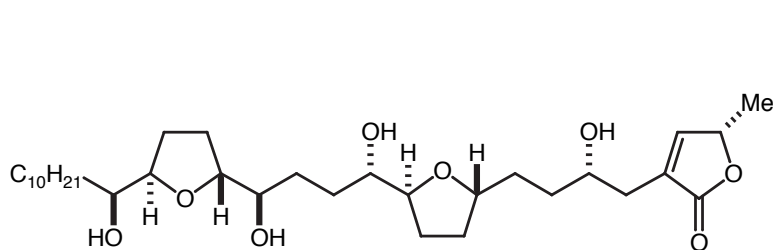
Lasalocid A

Kishi *et al*, *JACS*, **1978**, 100, 2933
Ireland *et al*, *JACS*, **1983**, 105, 1988



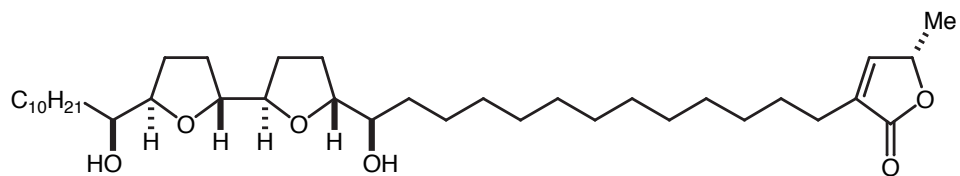
Muconin

Jacobsen *et al*, *JOC*, **1998**, 63, 4876



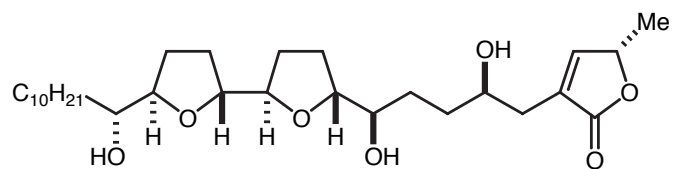
Squamostatin D

Marshall *et al*, *JOC*, **1998**, 63, 7066



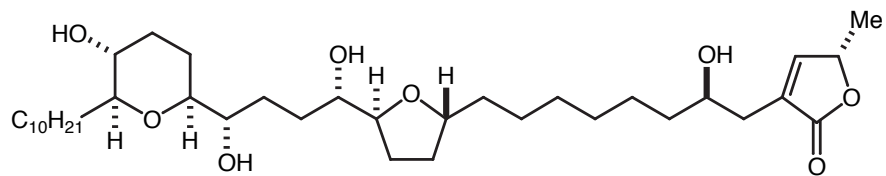
(+)-Uvaricin

Hoye *et al*, *JACS*, **1991**, 113, 9369



Asimicin

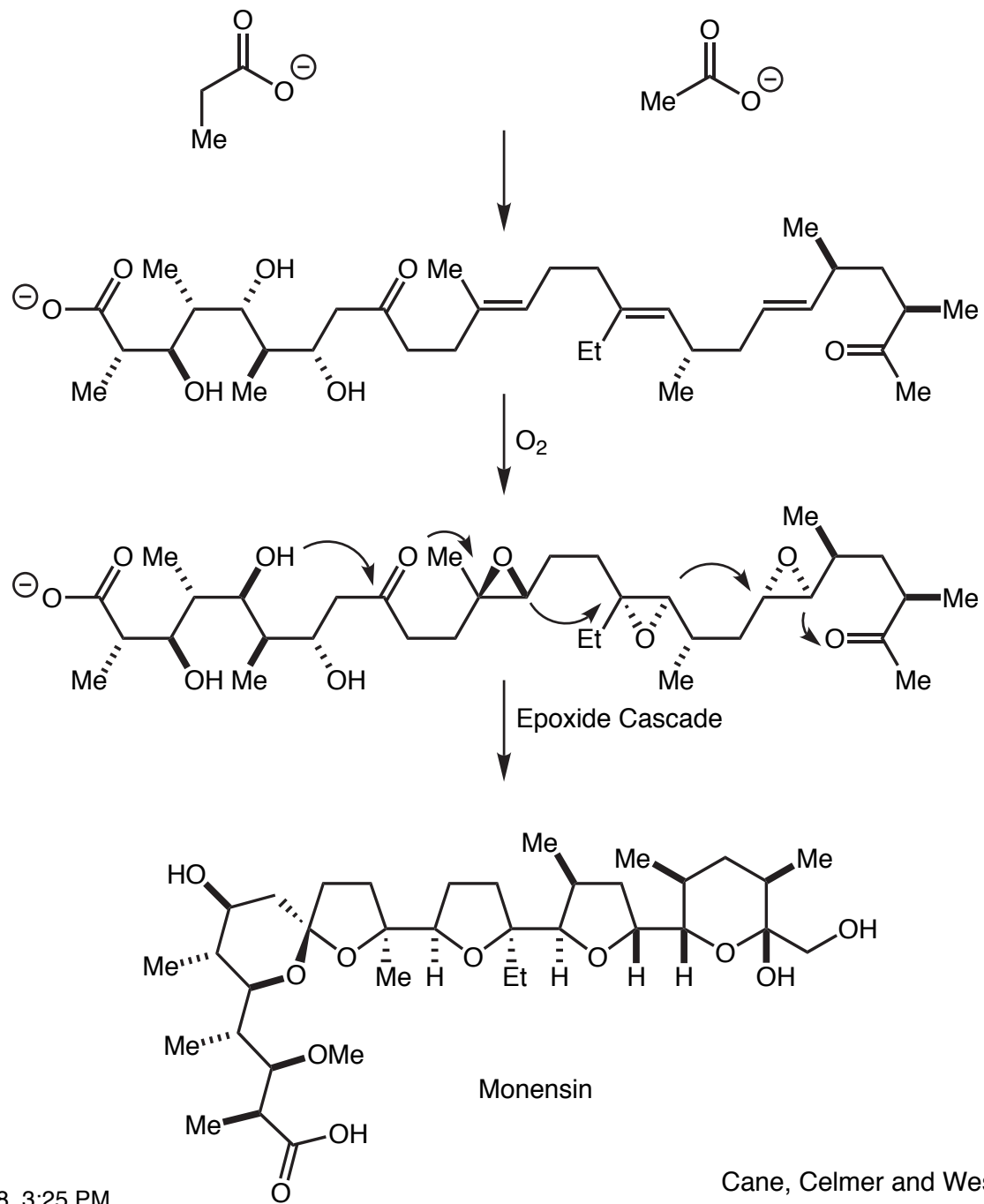
Marshall *et al*, *JOC*, **1997**, 62, 5989



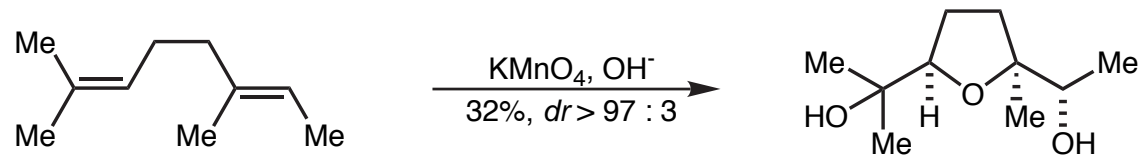
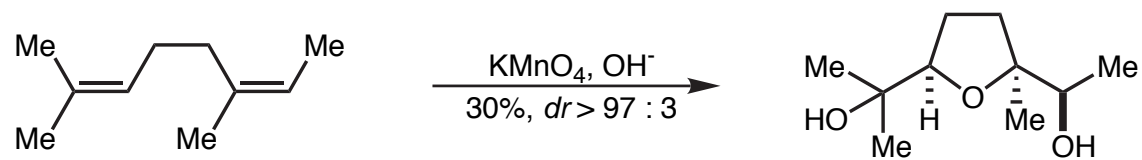
Mucocin

Keinan *et al*, *JACS*, **1998**, 120, 11279

Biosynthesis of Polyethers

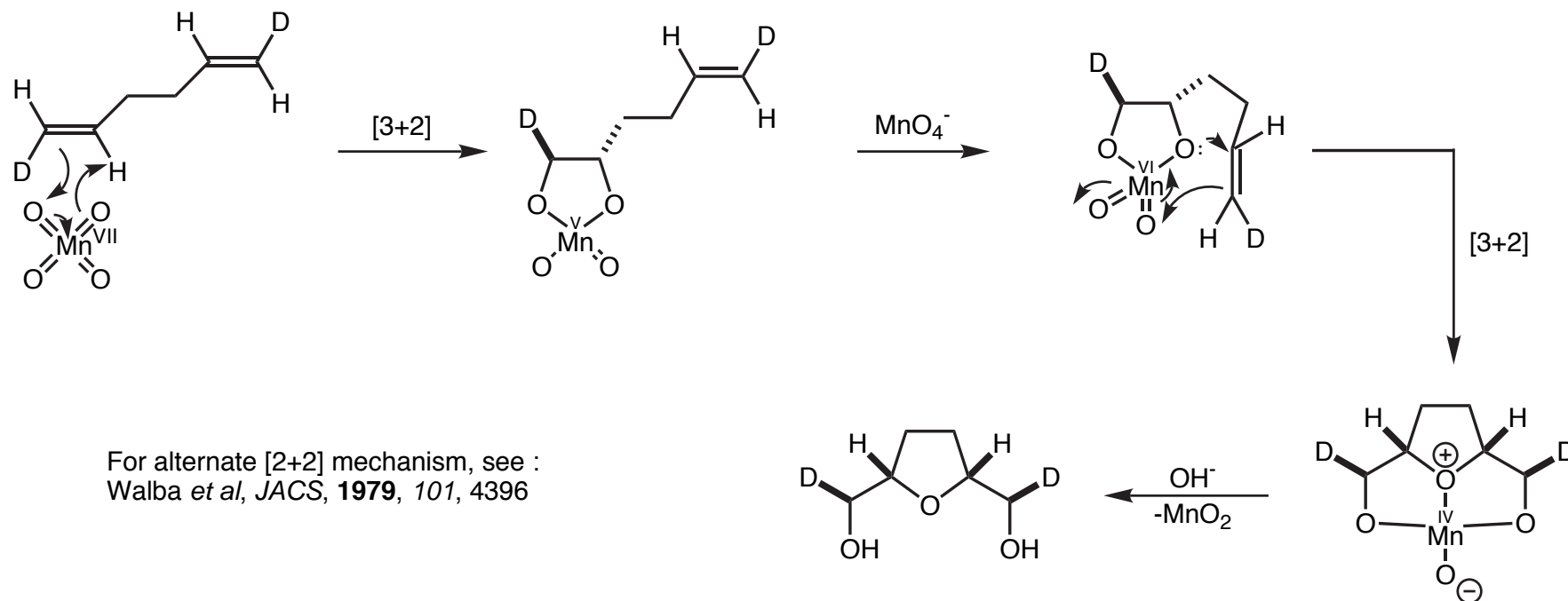


Oxidative Cyclizations of 1,5-Dienes



Klein *et al*, *Tet.*, **1965**, 21, 2353
Walba *et al*, *JACS*, **1979**, 101, 4396

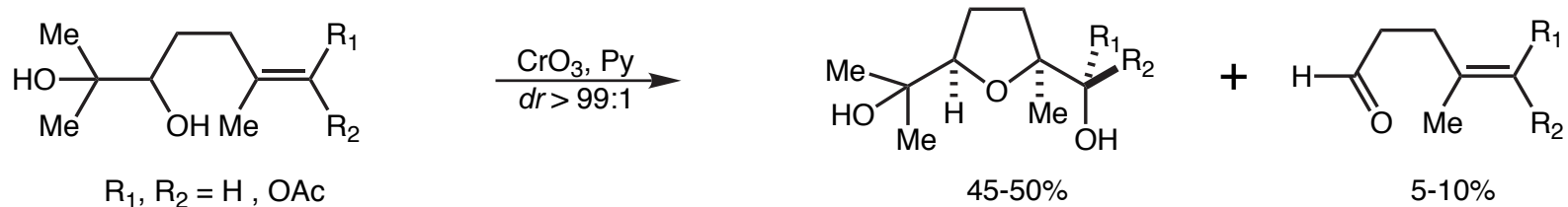
Possible Mechanism :



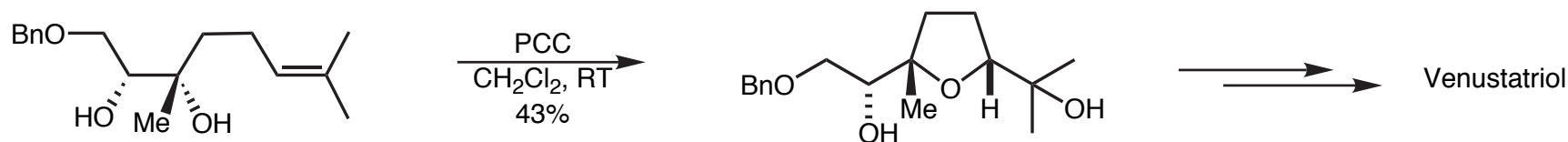
For alternate [2+2] mechanism, see :
Walba *et al*, *JACS*, **1979**, 101, 4396

Baldwin *et al*, *Chem. Comm.*, **1979**, 918

Oxidative Cyclization of 5,6-Dihydroxyolefins



Walba *et al*, *TL*, **1982**, 23, 727



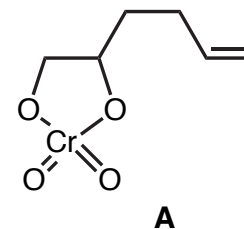
Corey *et al*, *TL*, **1988**, 29, 3171

Thought to proceed *via* chromate ester **A**, then through a [3+2] or two [2+2] rearrangements.

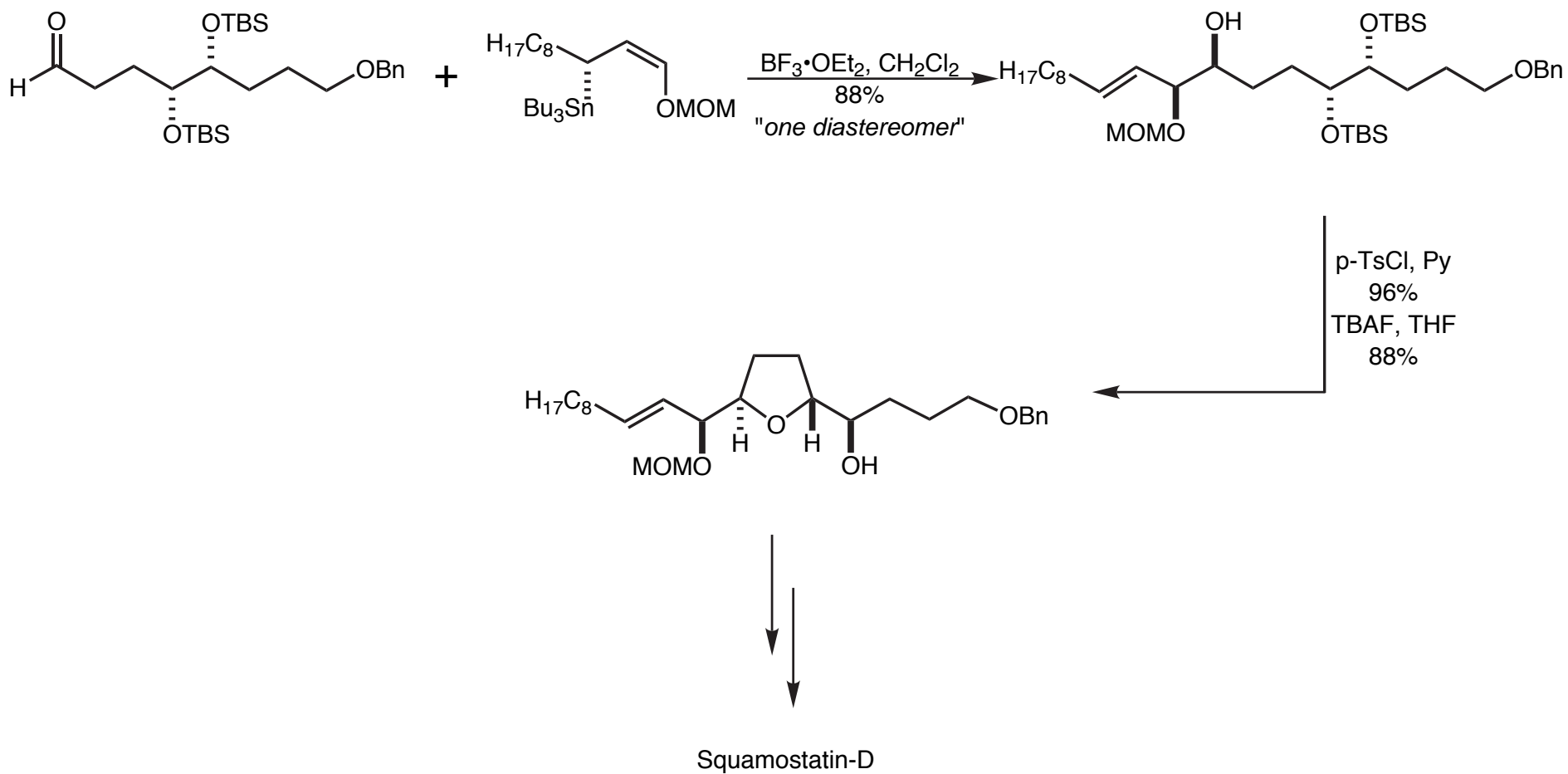
See :

Wolfe *et al*, *JACS*, **1981**, 103, 940 for [3+2] pathway

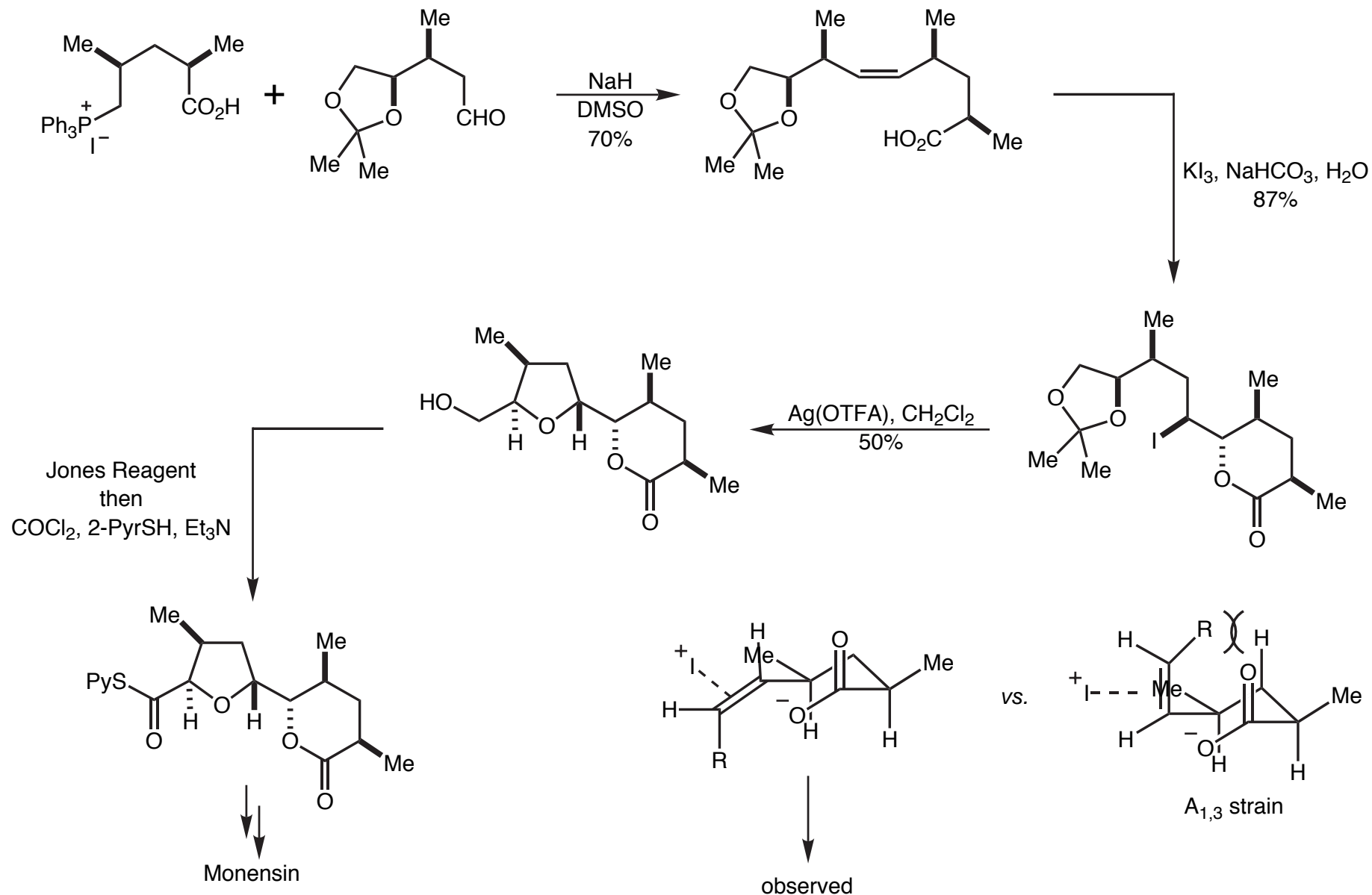
Sharpless *et al*, *JACS*, **1977**, 99, 3120 for [2+2] pathway



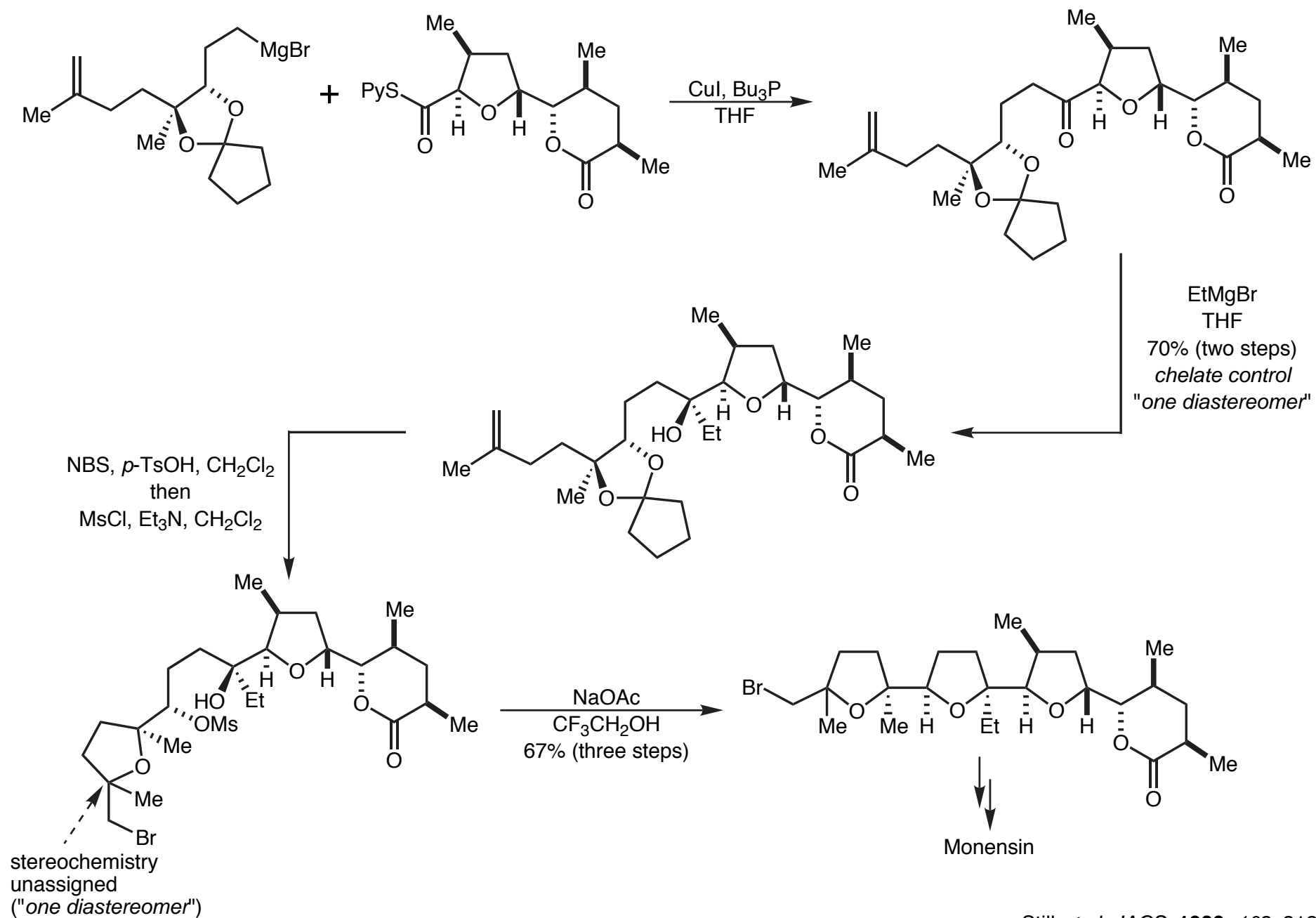
1,4-Diol Cyclization



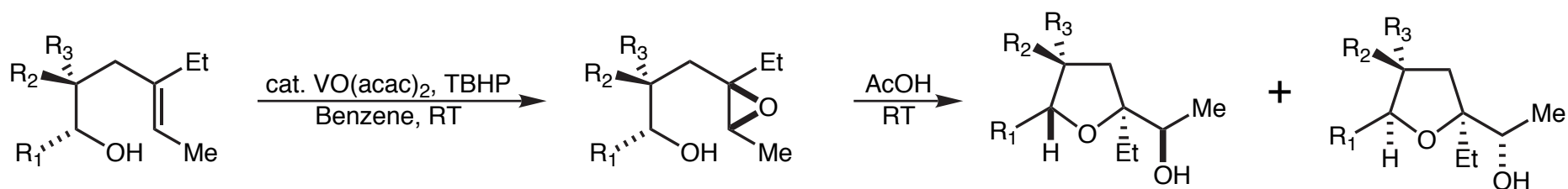
Iodide Displacement Strategy



Mesylate Displacement in the Still Monensin Synthesis

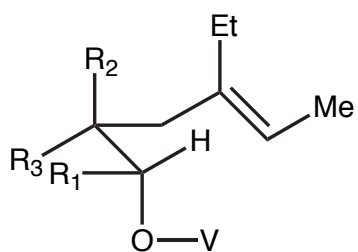


Directed Epoxidation of bis-Homoallylic Alcohols

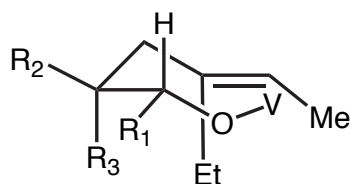


R ₁	R ₂	R ₃	<i>trans</i>	:	<i>cis</i>
<i>i</i> Pr	H	H	90	:	10
<i>i</i> Pr	CH ₃	H	84	:	16
<i>i</i> Pr	H	CH ₃	95	:	5
PMP	H	H	89	:	11
PMP	CH ₃	H	89	:	11

PMP = *para*-methoxyphenyl



A
 ↓
trans

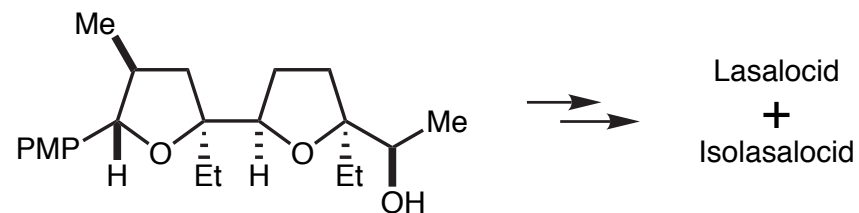
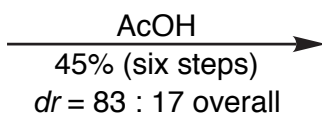
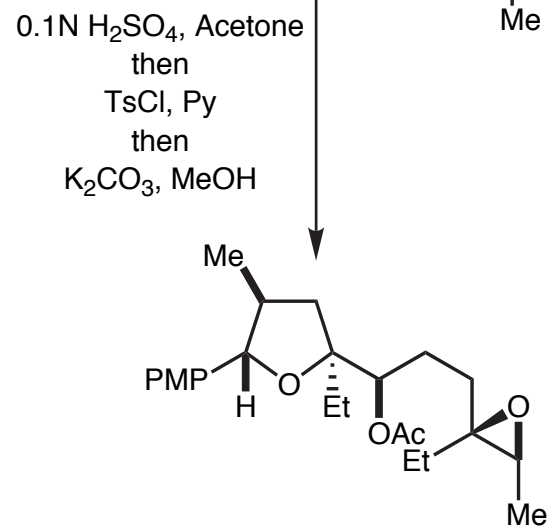
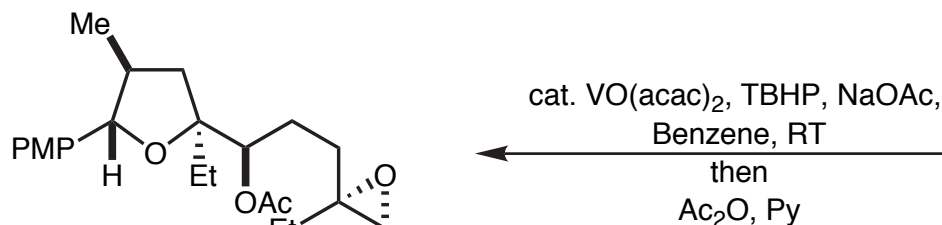
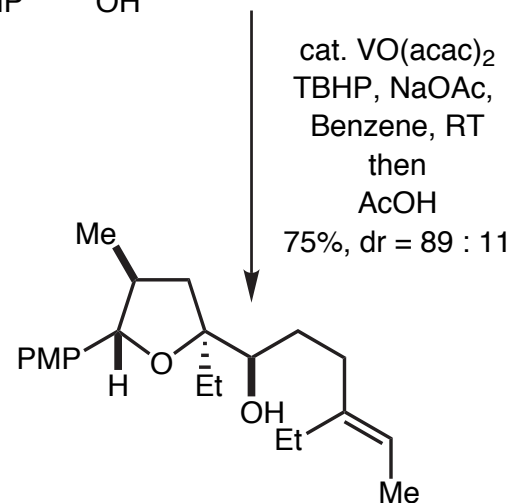
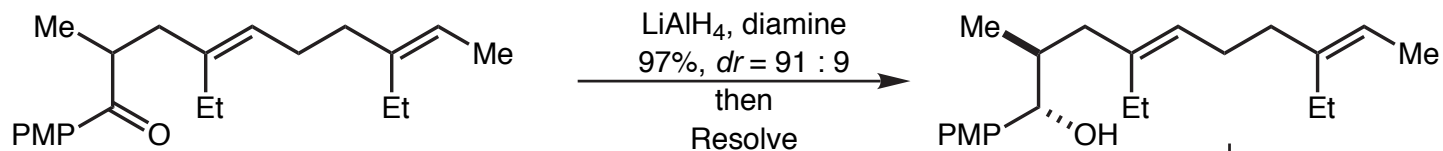
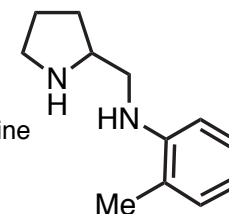


B
 ↓
cis

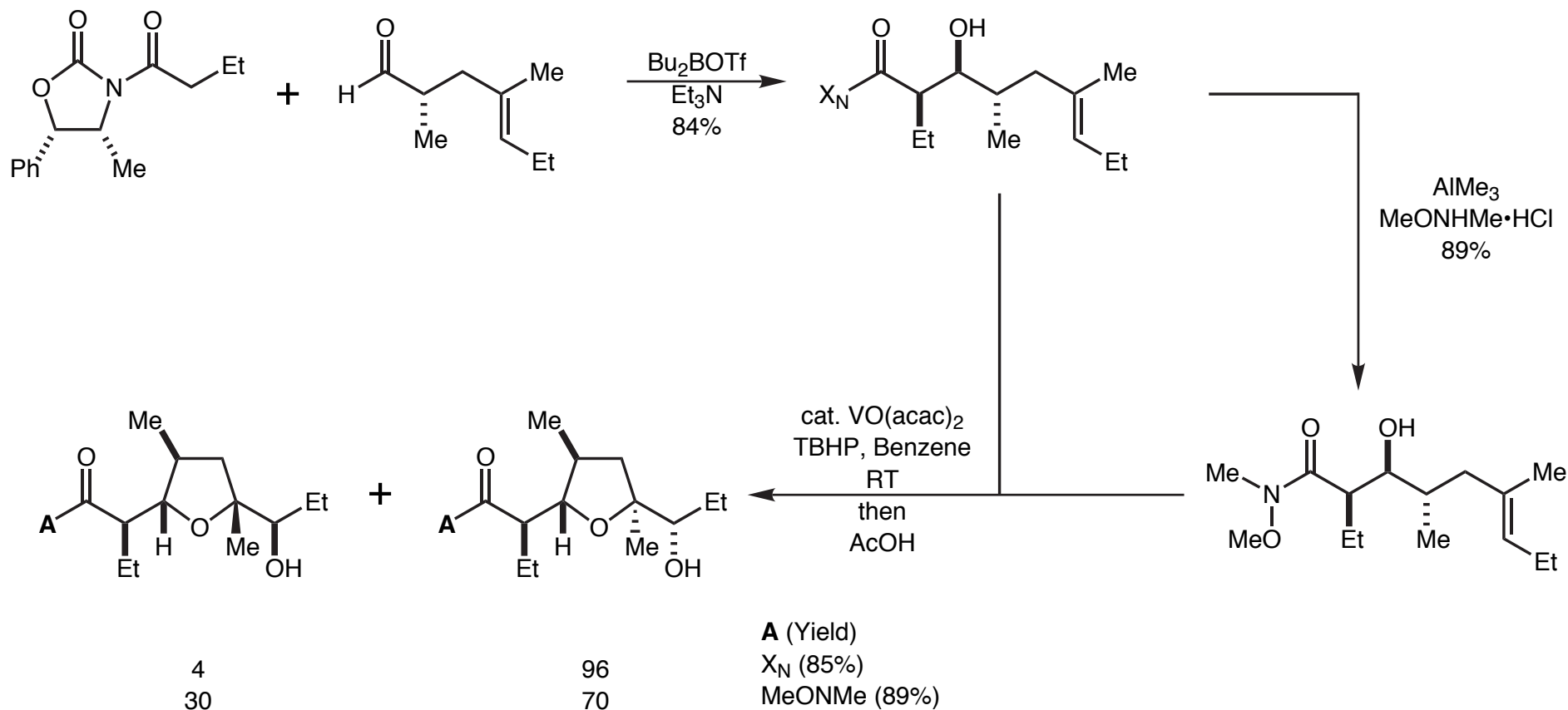
Transition state **A** best fulfills steric, stereoelectronic, and geometrical constraints for epoxidation.

Total Synthesis of Lasalocid

diamine = *dl*-2-(*o*-toluidineomethyl) pyrrolidine



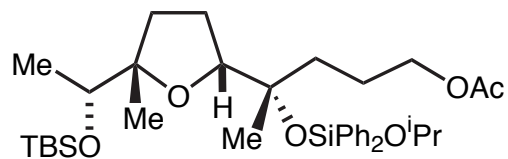
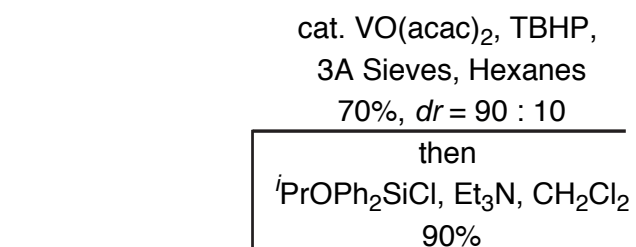
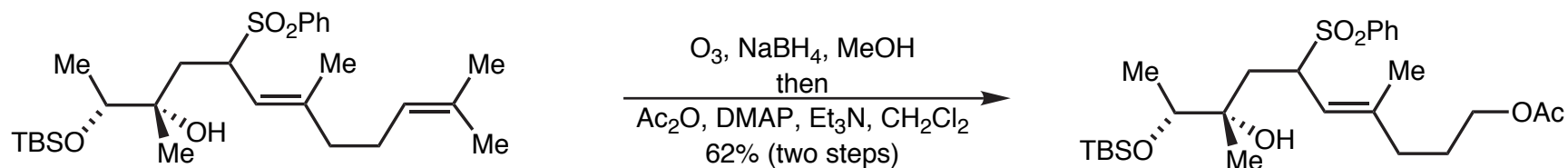
Total Synthesis of Ferensimycin B



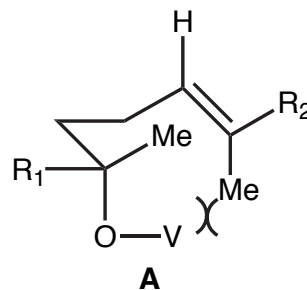
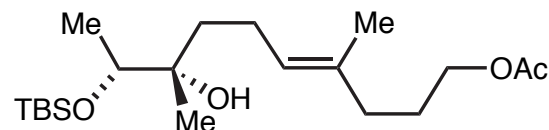
The more basic Weinreb amide carbonyl is thought to competitively chelate with vanadium, disrupting desired transition state for directed epoxidation

For a similar epoxidation/epoxide opening related to X-206 see Evans *et al*, *JACS*, **1988**, 110, 2506

Directed Epoxidation from a Tertiary Alcohol

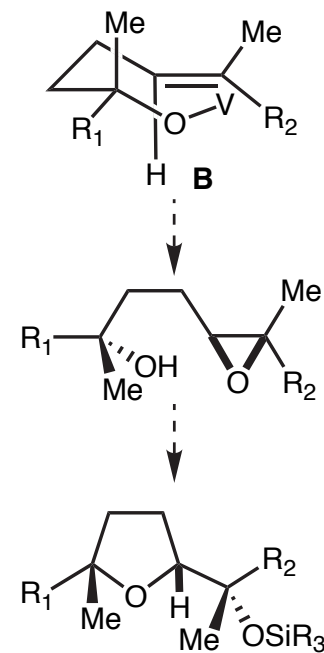


Ionomycin



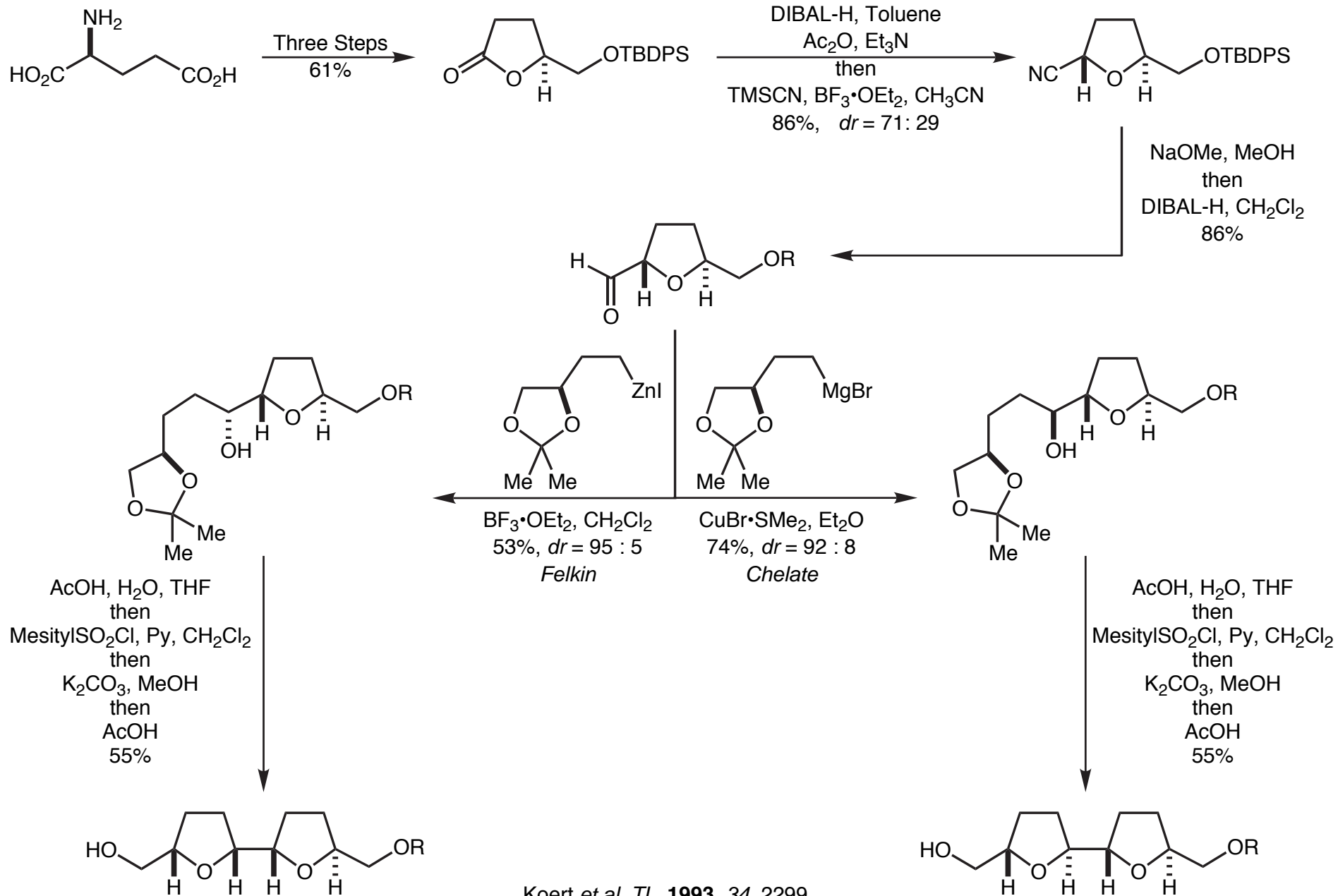
- These results are also in accord with the model proposed by Kishi.
- Steric compression between the metal and the vinylic methyl group disfavors transition state **A**.

Na⁰, NH₃
 -33 °C
 69%



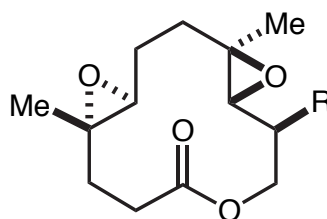
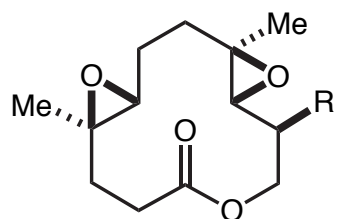
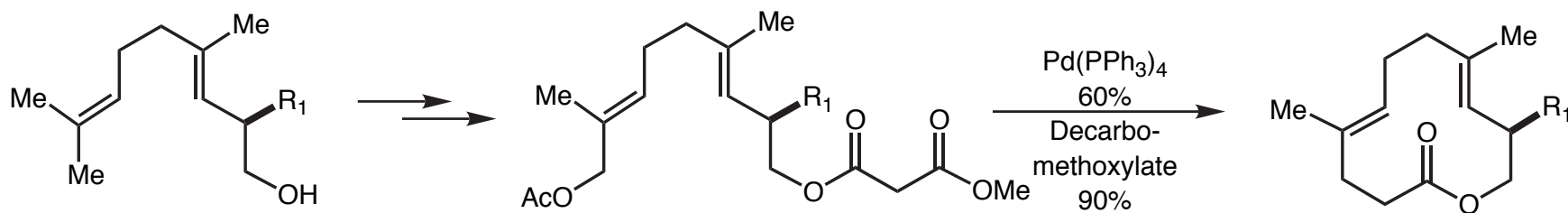
Hanessian *et al*, *JACS*, **1990**, *112*, 5276

An Iterative Epoxide Opening Sequence



Koert *et al*, *TL*, **1993**, 34, 2299
 Koert *et al*, *Chem. Ber.*, **1994**, 127, 1447

Epoxydation of Unsaturated Macrolides

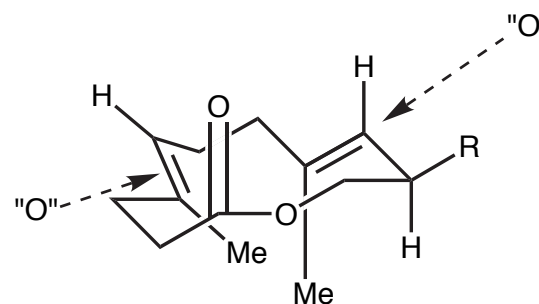


m-CPBA

R	
H	80
Me	94

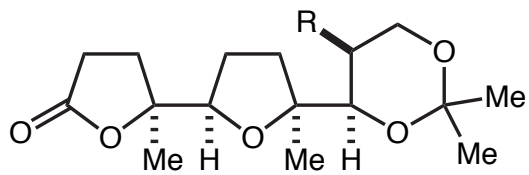
+

:	
:	20
:	06

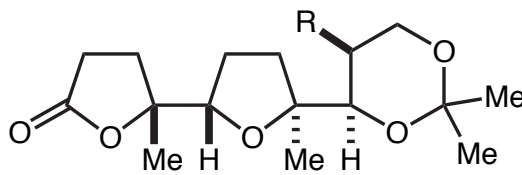


Bulky R group
rigidifies
macrolactone
conformation
through A_{1,3}
strain

KOH, MeOH
then
Acetone/H⁺
90-95%

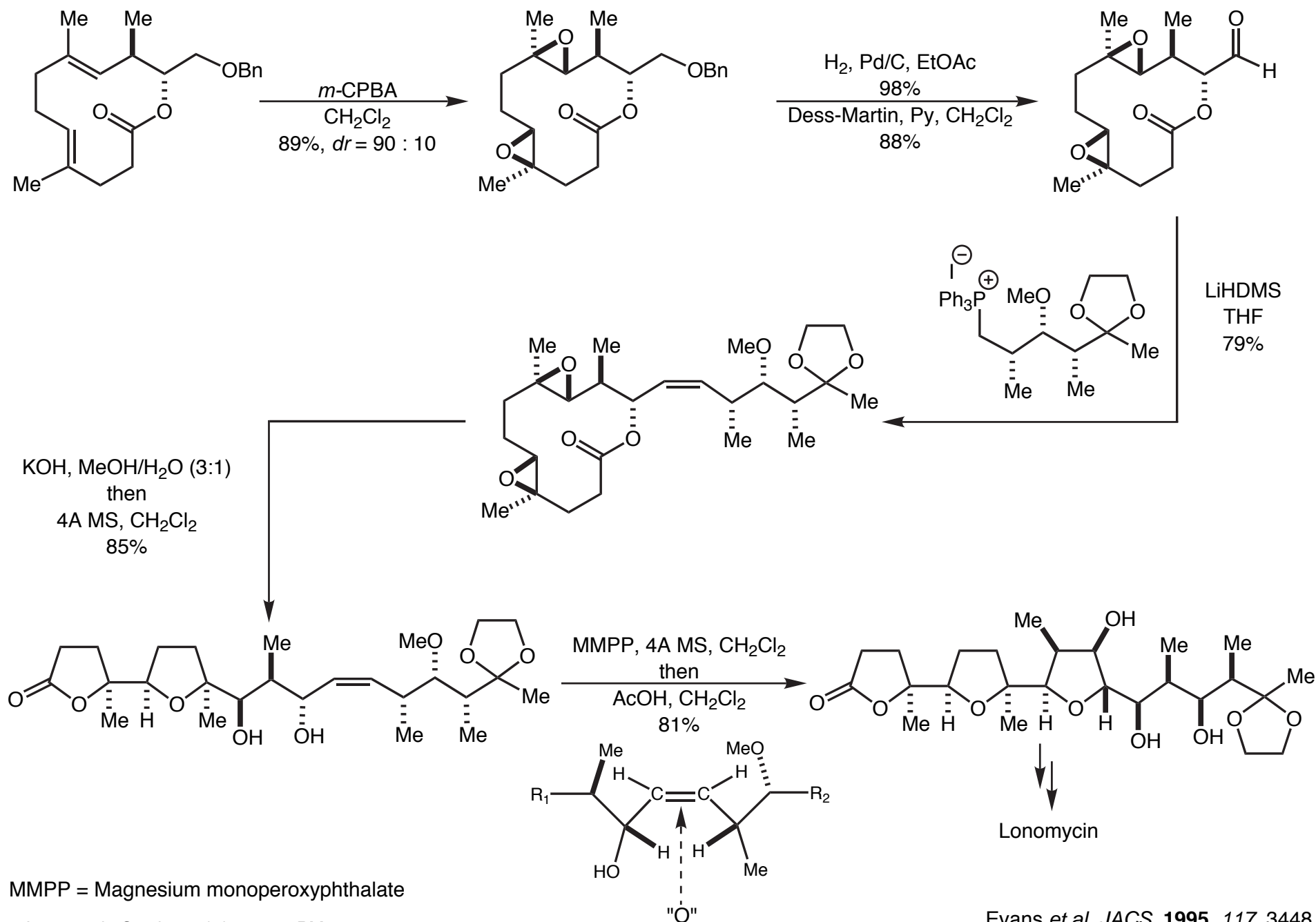


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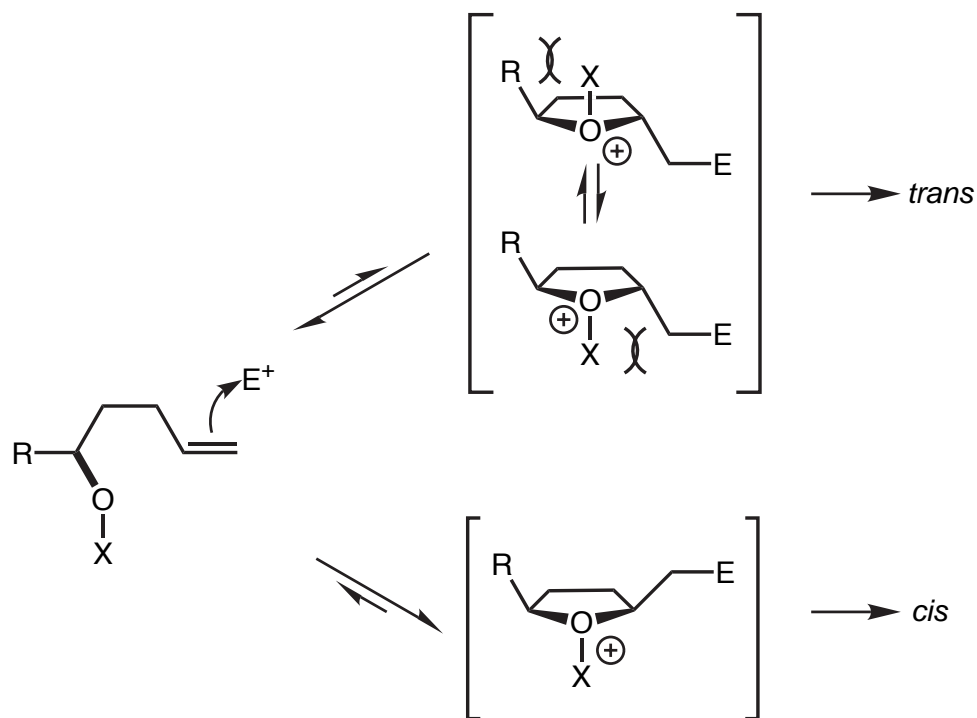
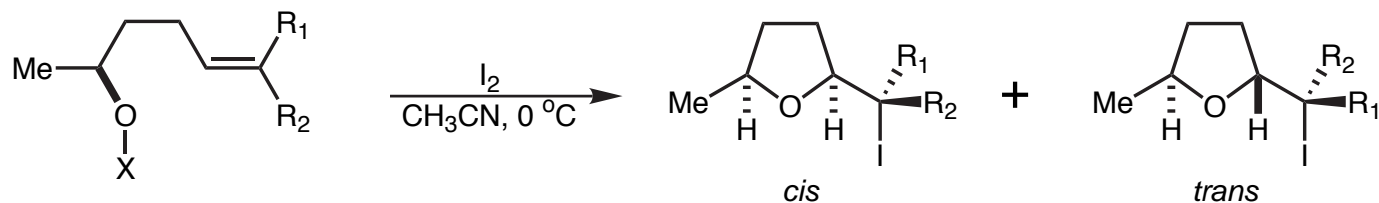
Still *et al*, *JACS*, **1986**, *108*, 2105
Schreiber *et al*, *JACS*, **1986**, *108*, 2106

The Lonomycin Synthesis



MMPP = Magnesium monoperoxyphthalate

Halocyclization of bis-Homoallylic Alcohols

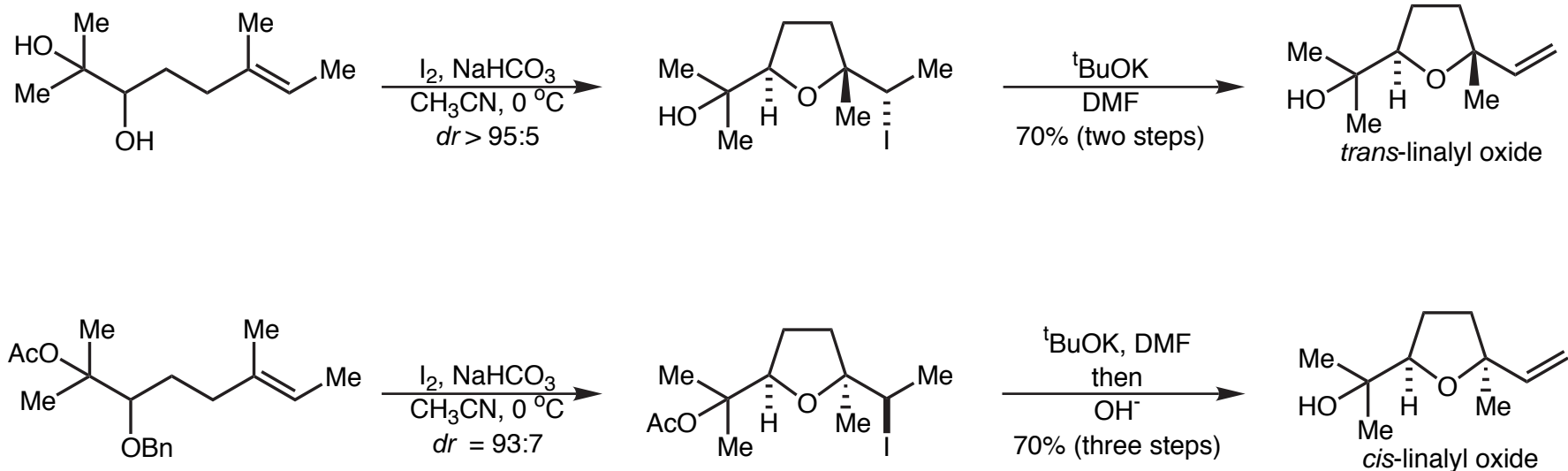


X	R ₁	R ₂	Ratio		Yield (%)
			cis	trans	
H	H	H	34	66	66
Me	H	H	34	66	15
Bn	H	H	66	34	60
TBS	H	H	75	25	43
BB	H	H	79	21	74
⇒ DCB	H	H	95	5	63
DCB	H	Me	92	8	47
DCB	CO ₂ Me	H	98	2	60

BB = 4-bromobenzyl
DCB = 2,6-dichlorobenzyl

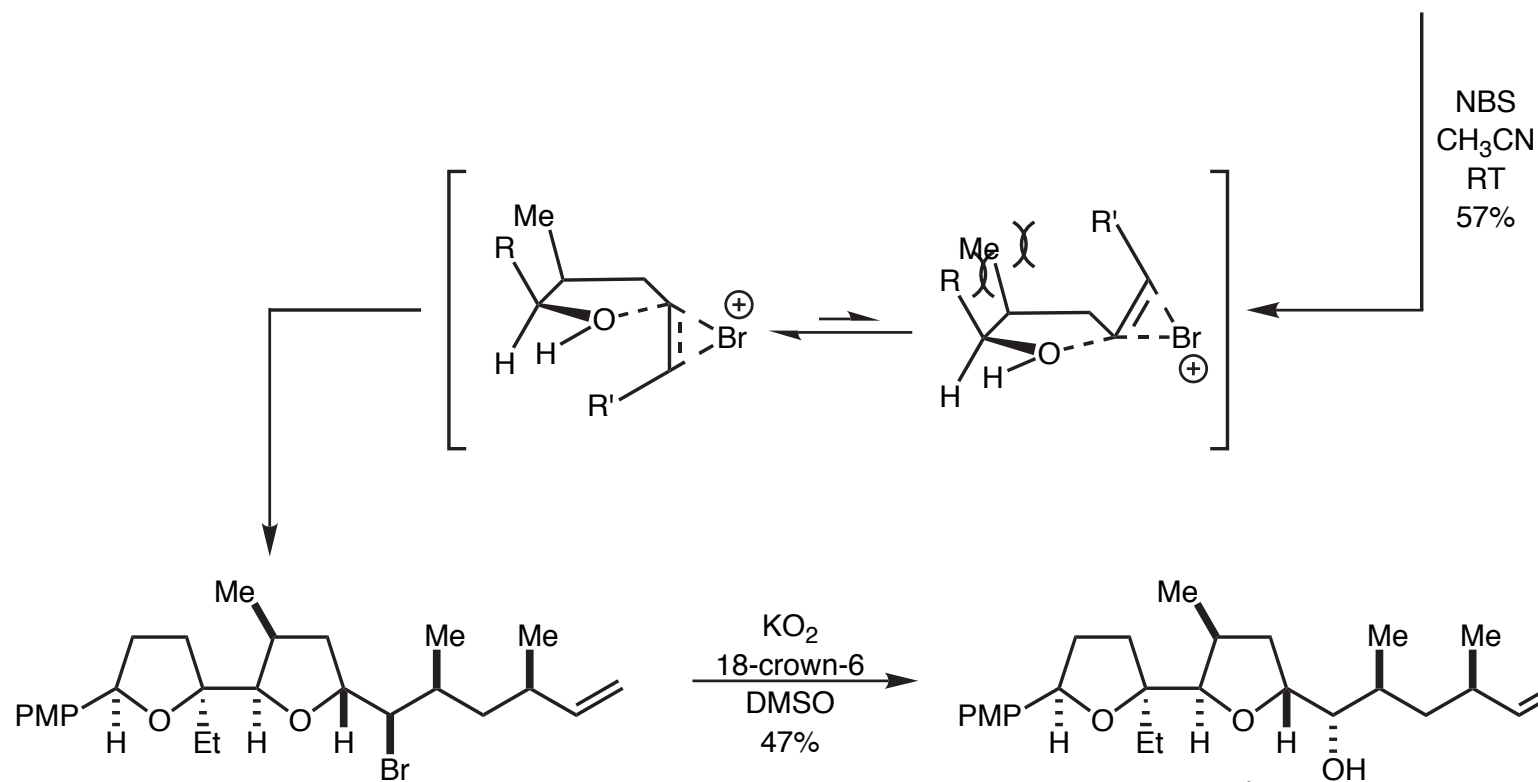
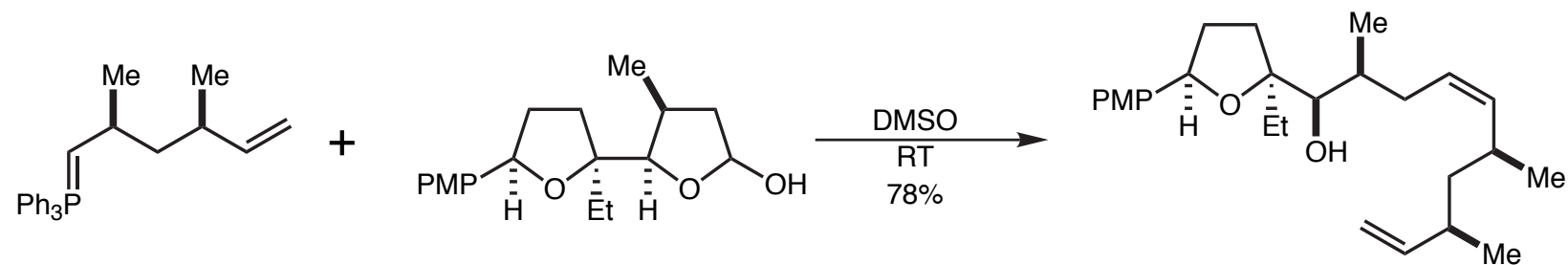
The 2,6-dichlorobenzyl group seemed to provide the best balance between sterics and reactivity for the halocyclization reaction.

Application to 2,2,5-Trisubstituted THF Rings



Authors do not comment on origin of selectivity for free diol cyclization, nor do they explain why a benzyl group was preferred for the *cis*-linalyl oxide synthesis

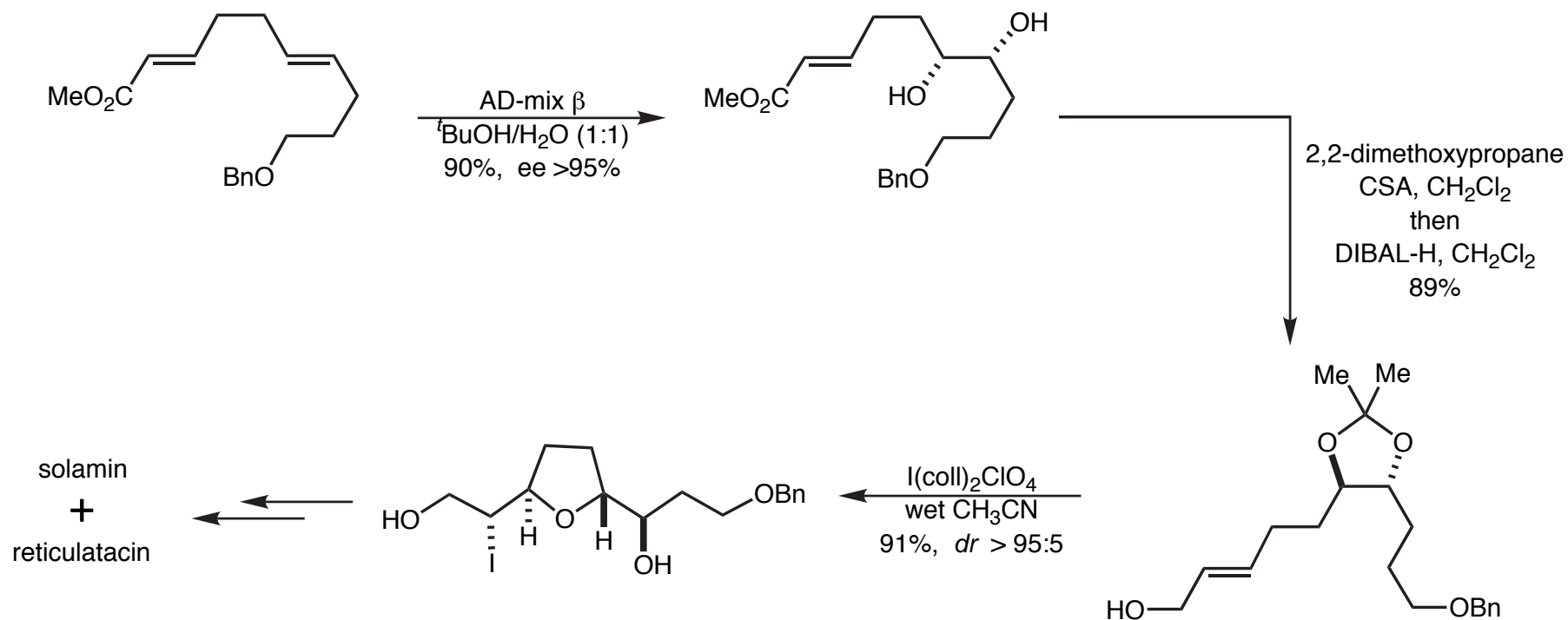
Halocyclization Application in Monensin Synthesis



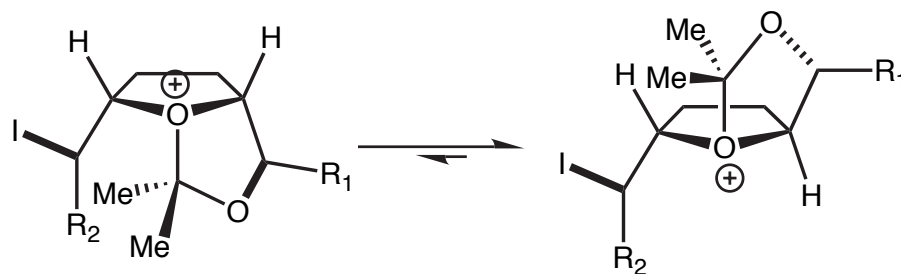
PMP = *para*-methoxyphenyl

Monensin

Dihydroxylation/Halocyclization Strategy



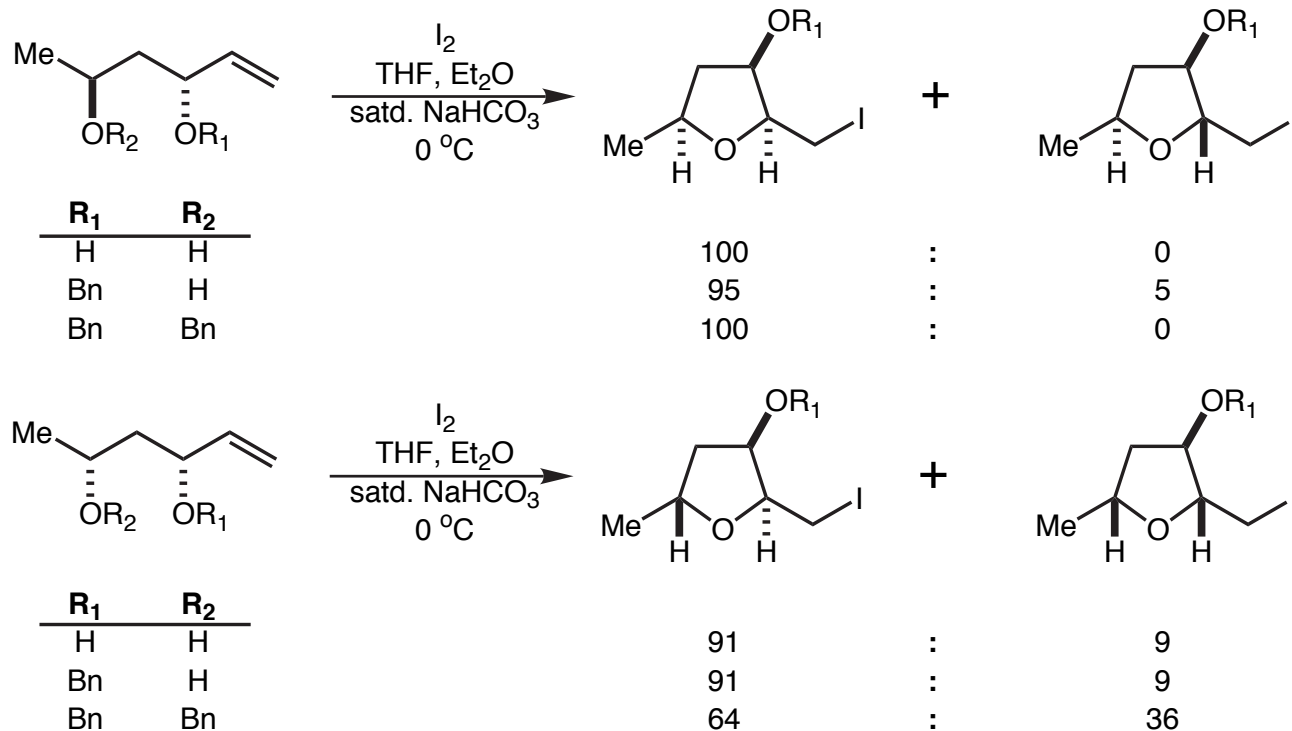
Author's Rationale :



Ketal hydrolysis is probably the rate determining step.
 Equilibration of the above oxonium intermediates would explain selectivity.

Mootoo *et al*, *JOC*, **1998**, 63, 2049
 Mootoo *et al*, *JOC*, **1995**, 60, 8134

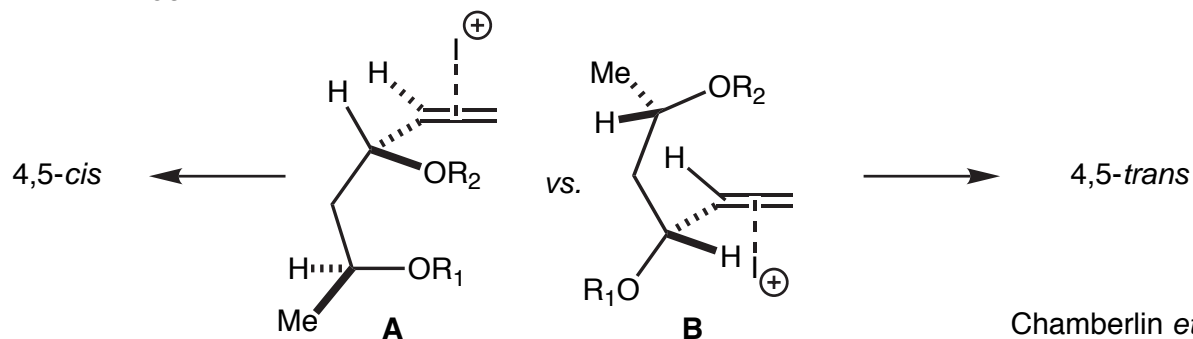
Influence of an Allylic Oxygen on Halocyclizations



Cha *et al*, *TL*, **1988**, 29, 2011

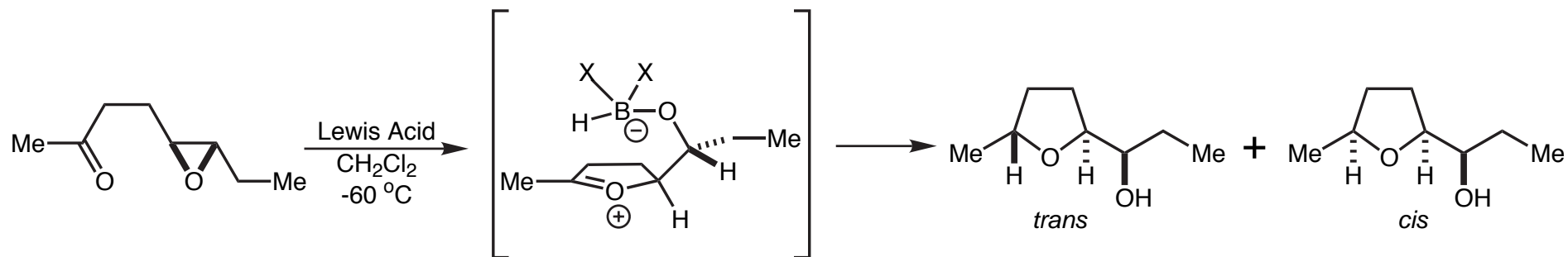
Rationale :

Reaction proceeds via an early TS through electronically favored π complex **A**, which minimizes destabilizing $\sigma^*_{CO}-\pi$ interactions.



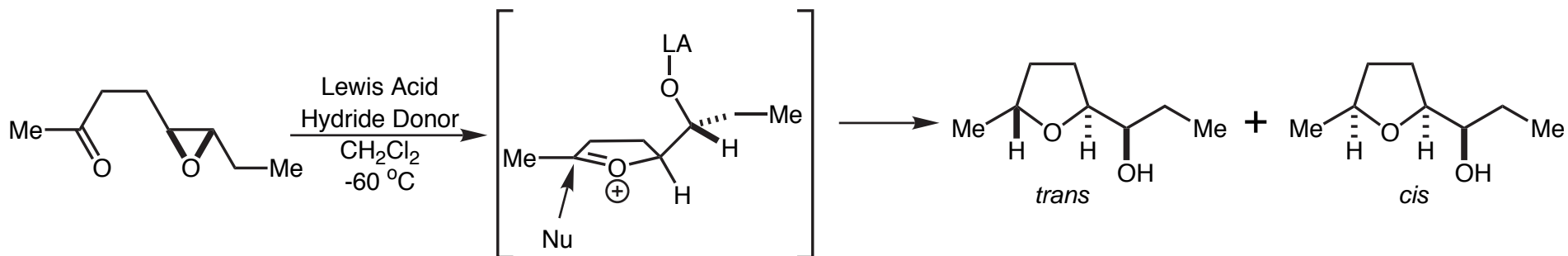
Chamberlin *et al*, *JACS*, **1987**, 109, 672
Houk *et al*, *JACS*, **1984**, 106, 3880

Oxonium Based Strategies



Lewis Acid	Concentration (M)	<i>trans</i> : <i>cis</i>	Yield (%)
$\text{BH}_3 \cdot \text{SMe}_2$	0.005	96 : 4	90
$\text{BH}_3 \cdot \text{SMe}_2$	0.012	92 : 8	58
thexylborane	0.030	90 : 10	41
catecholborane	0.016	75 : 25	85

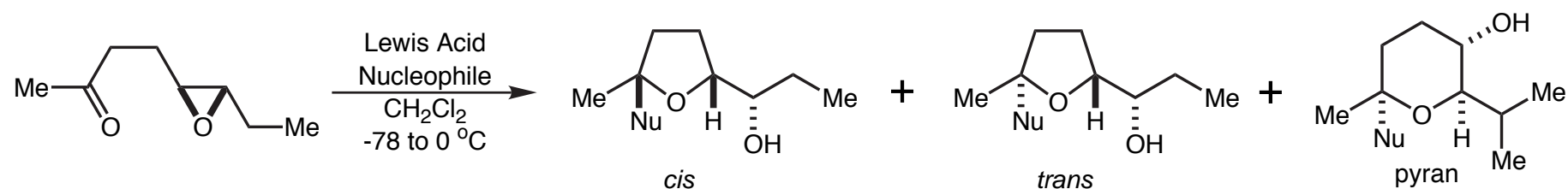
Drieding models show that intramolecular hydride delivery goes through a very strained TS



Lewis Acid	Hydride Donor	<i>trans</i> : <i>cis</i>	Yield (%)
TFA	Et_3SiH	33 : 67	90
$\text{BF}_3 \cdot \text{OEt}_2$	Et_3SiH	33 : 67	58
$\text{BF}_3 \cdot \text{OEt}_2$	Ph_3SiH	17 : 83	41
TIPSOTr	Ph_3SiH	20 : 80	85

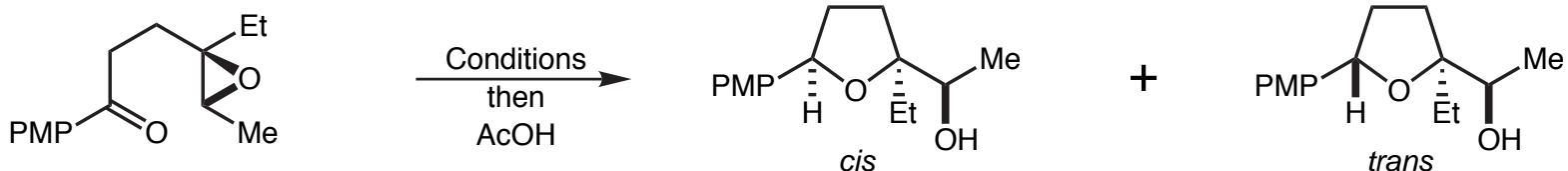
Treatment of the methyl ketone with LiAlH_4 also gives a 33:67 *trans* : *cis* ratio!
See also Kishi *et al*, *TL*, **1978**, 19, 2741

Further Extention of Chamberlin's Chemistry



Lewis Acid	Nucleophile	Combined Yield (%)	Combined		
			<i>cis</i>	<i>trans</i>	Pyran
$\text{BF}_3 \cdot \text{OEt}_2$	Ph_3SiH	67	67	: 11	: 22
TMSOTf	Ph_3SiH	81	90	: 4	: 6
TMSOTf	allylsilane	80	80	: 13	: 7
$\text{BF}_3 \cdot \text{OEt}_2$	TMSCN	68	80	: 20	: 0
$\text{BF}_3 \cdot \text{OEt}_2$	AlEt_3	68	58	: 8	: 34
$\text{BF}_3 \cdot \text{OEt}_2$	Et_2AlCCPh	60	88	: 12	: 0
$\text{BF}_3 \cdot \text{OEt}_2$	Et_2AlCN	65	50	: 50	: 0

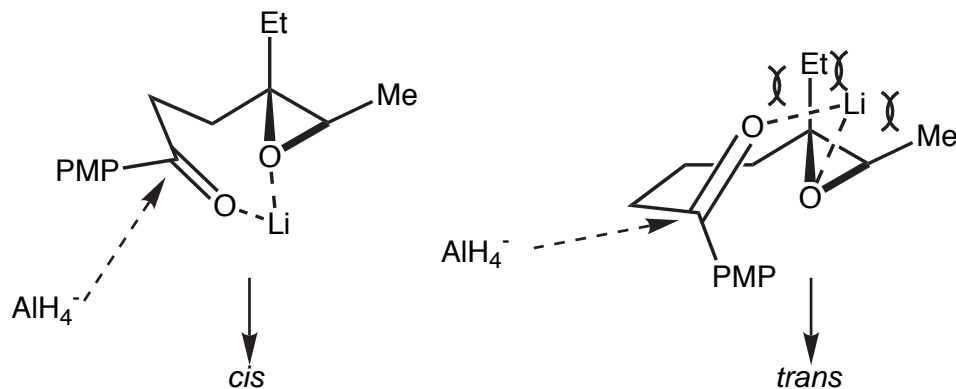
Epoxide Directed Ketone Reduction



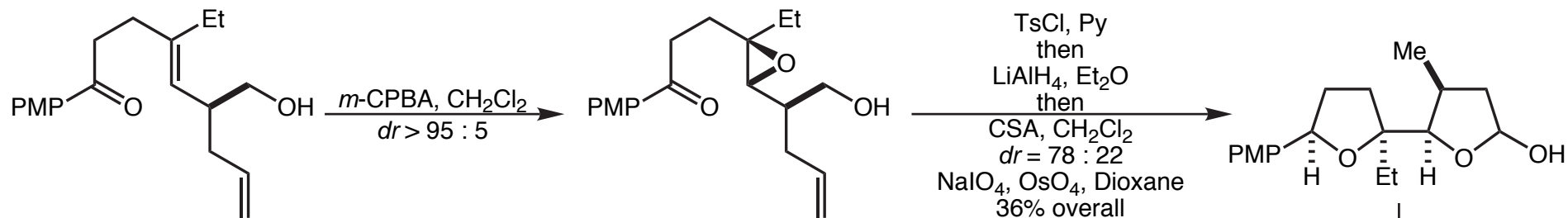
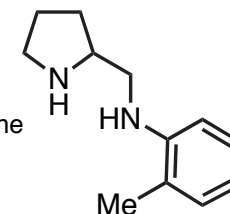
Conditions	<i>cis</i>	<i>trans</i>
NaBH ₄ , MeOH, RT	50	: 50
L-Selectride, Et ₂ O, RT	50	: 50
LiAlH ₄ , Et ₂ O, 0 °C	75	: 25
LiAl(O ^t Bu) ₃ , Et ₂ O, 0 °C	80	: 20
LiAlH ₄ , diamine, Et ₂ O, -78 °C	91	: 9

Kishi *et al*, *TL*, **1978**, 19, 2741

Possible Rationale?



diamine =
dl-2-(*o*-toluidineomethyl) pyrrolidine

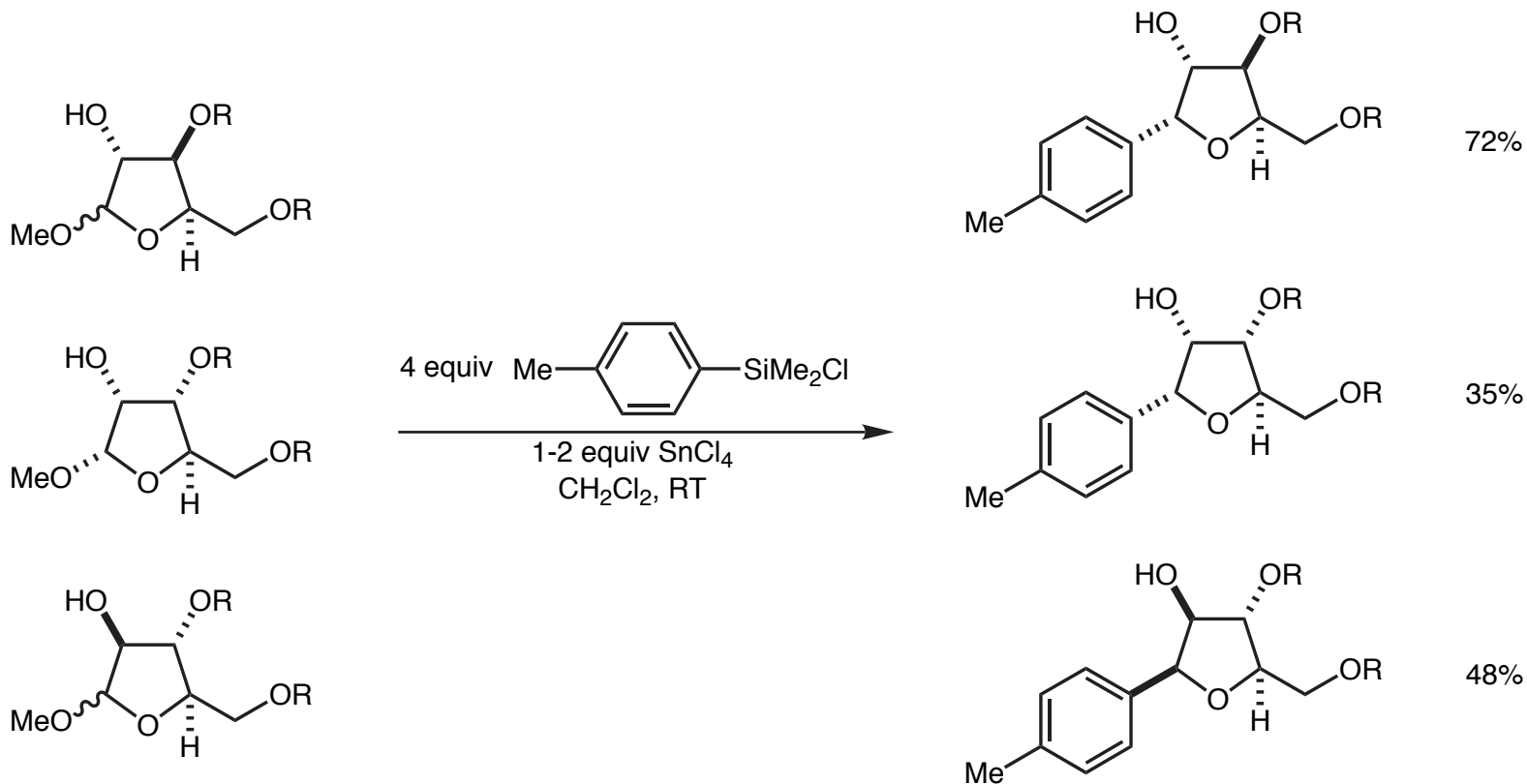


• Authors claim hydroxyl direction of *m*-CPBA (unprecedented for an acyclic homoallylic system)

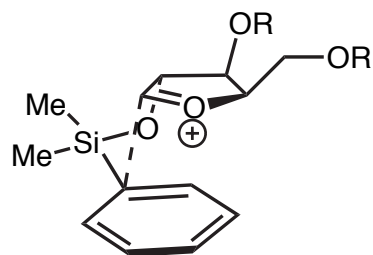
Monensin

Kishi *et al*, *JACS*, **1979**, 101, 259

Directed Aryl Silane Addition



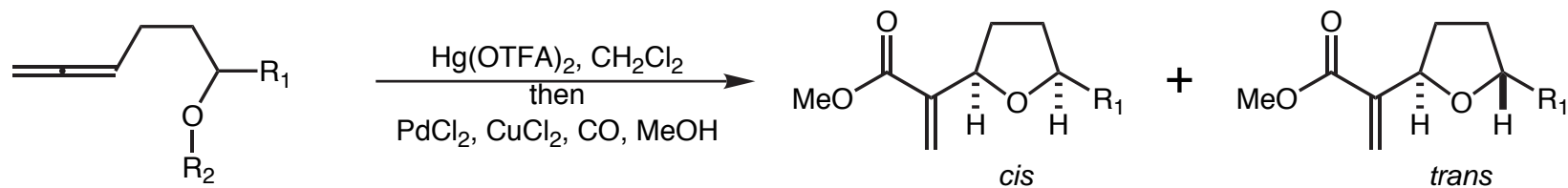
R = *p*-chlorobenzyl



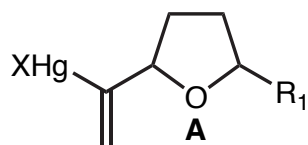
Nucleophile delivery thought to be intramolecular as :

- Protection of C₂ alcohol halts reaction
- Arylsilane must have a good leaving group
- Only observed product is always *syn* to C₂ hydroxyl

Intramolecular Oxymercuration

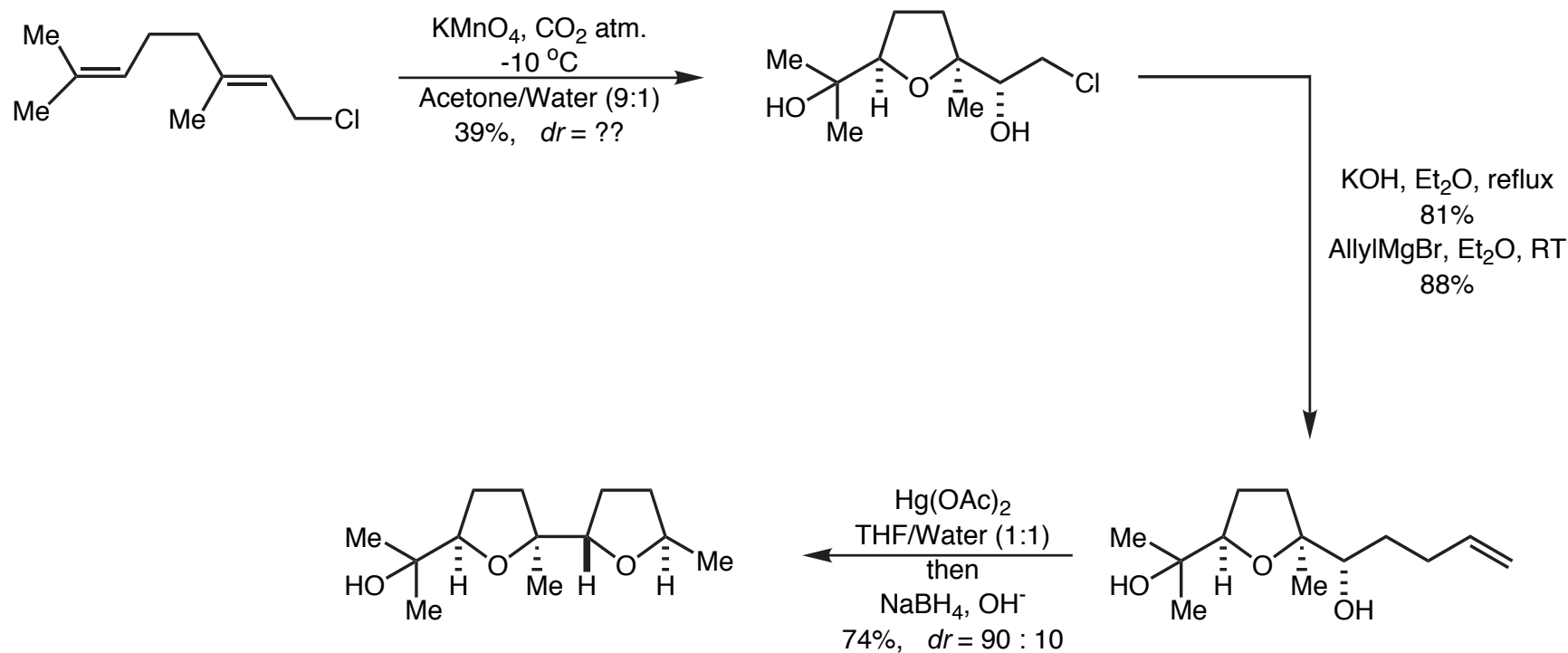


R_1	R_2	Combined Yield (%)	<i>cis</i>	:	<i>trans</i>
CH_3	TBS	53	94	:	6
$\text{CH}_2\text{CO}^t\text{Bu}$	TBS	80	92	:	8
CH_2COCH_3	TBS	70	50	:	50
$\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$	TBS	67	92	:	8



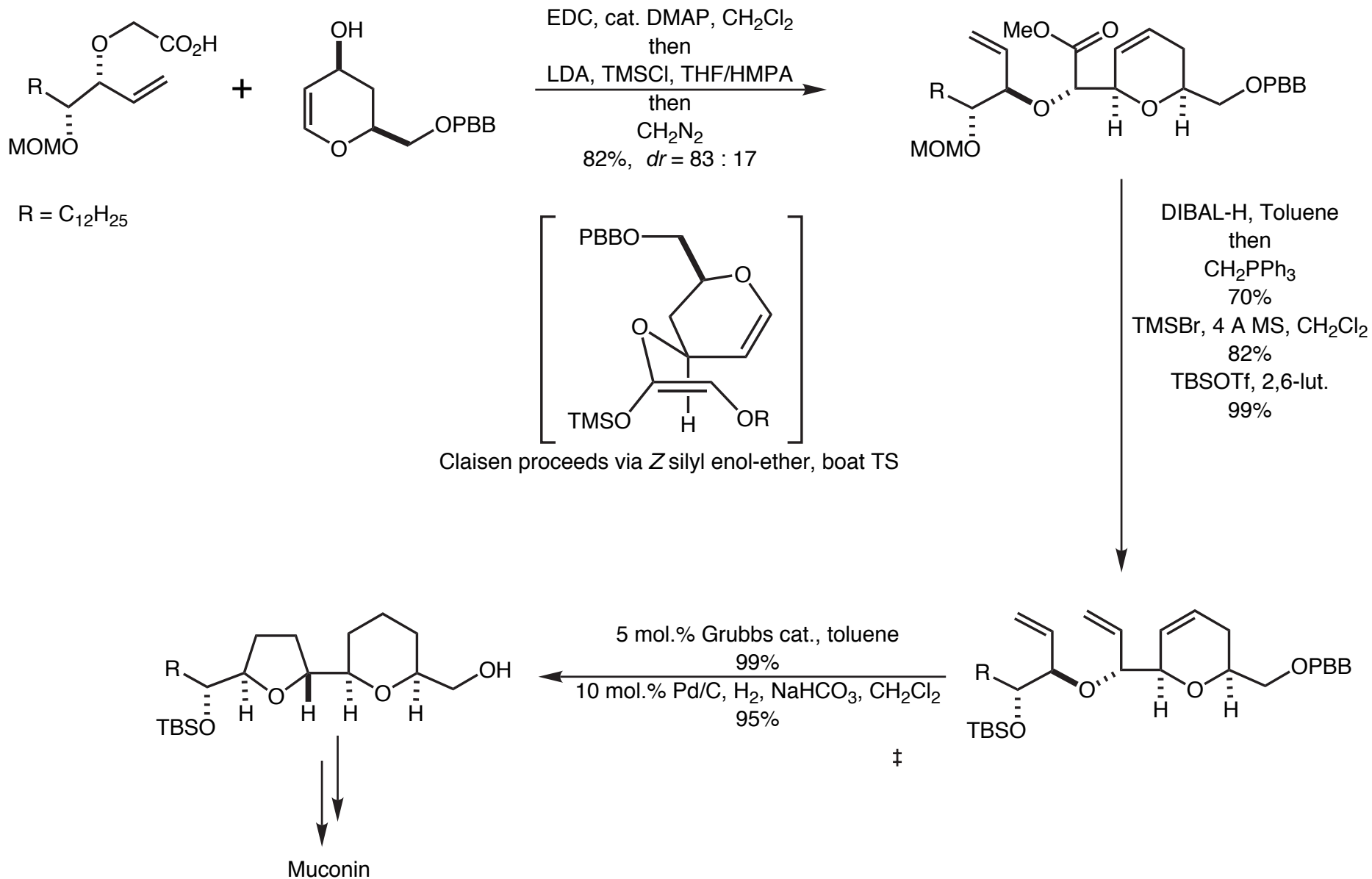
- All the above substrates cyclized nonselectively when $R_2 = \text{H}$
- The vinylmercury species **A** readily transmetalates with Pd
- PdCl_2 also effects the same reaction, but with no selectivity!
- The importance of R_2 indicates that the origin of diastereoselectivity is similar to that put forth by Bartlett.

Intramolecular Oxymercuration of a Terminal Olefin

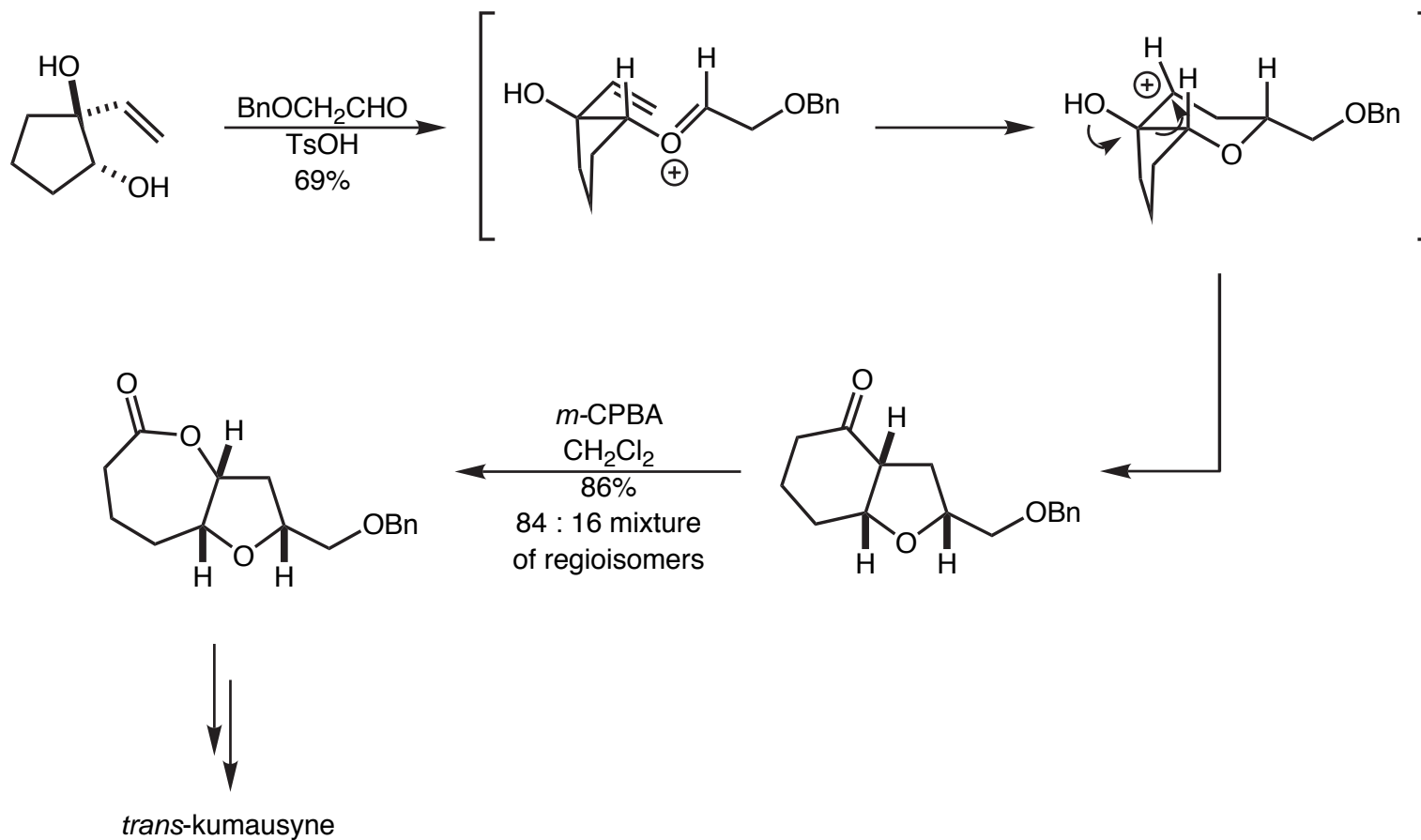


• Equilibrium driven?

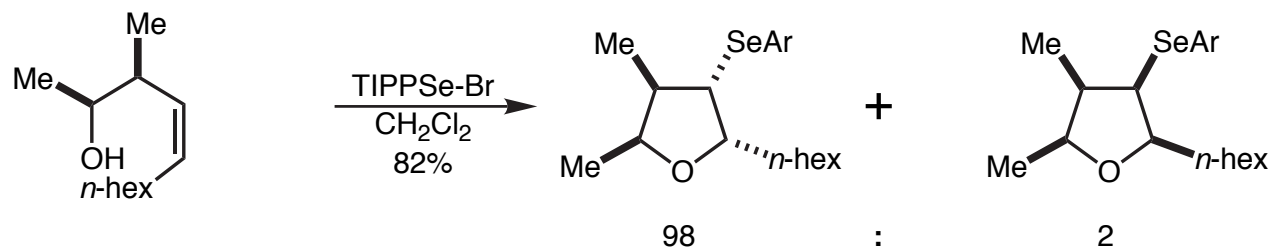
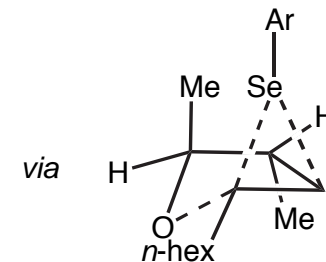
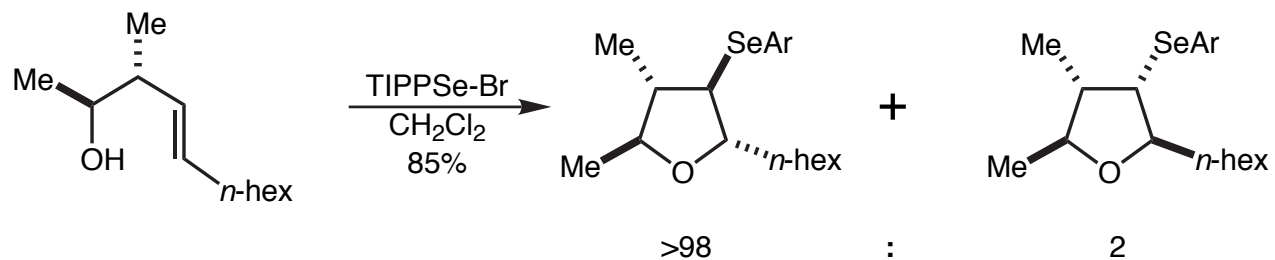
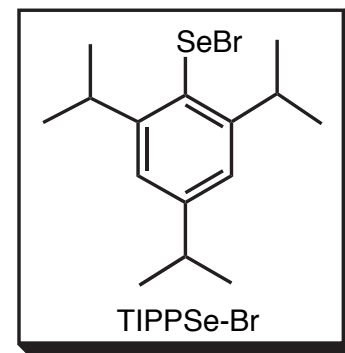
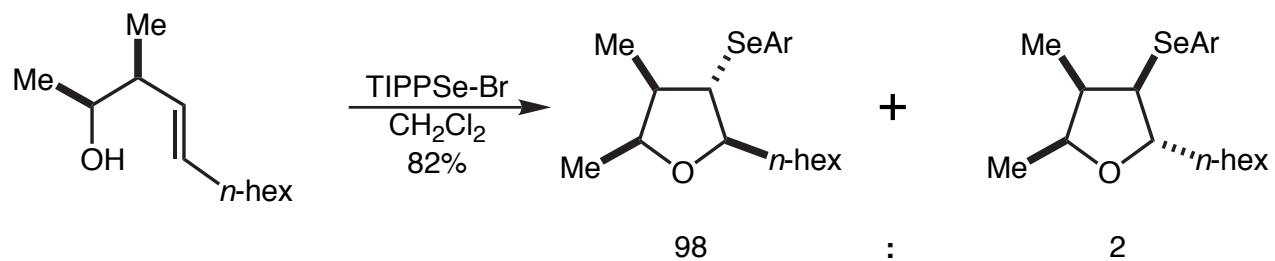
Olefin Metathesis for Tetrahydrofuran Synthesis



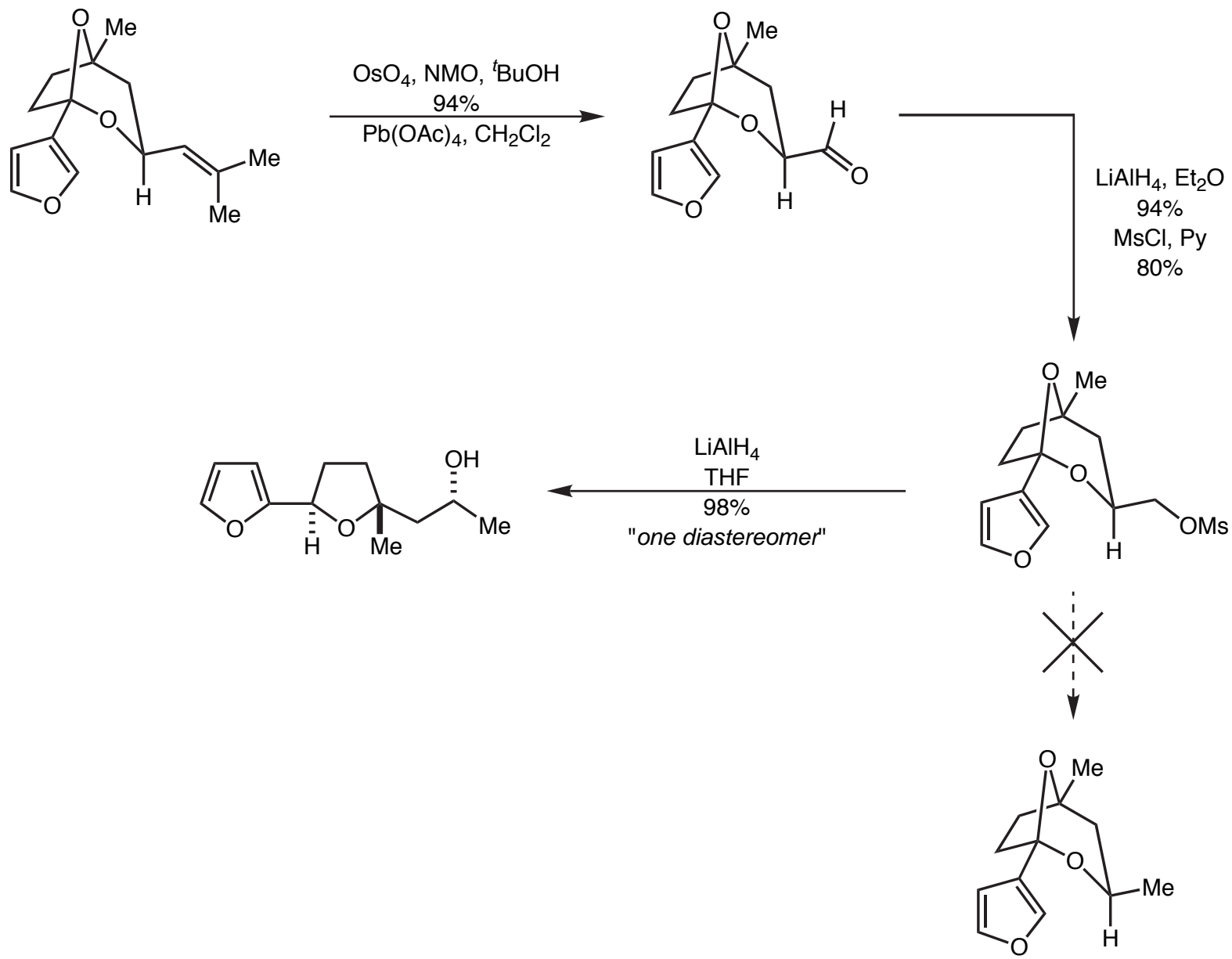
The Overman Rearrangement



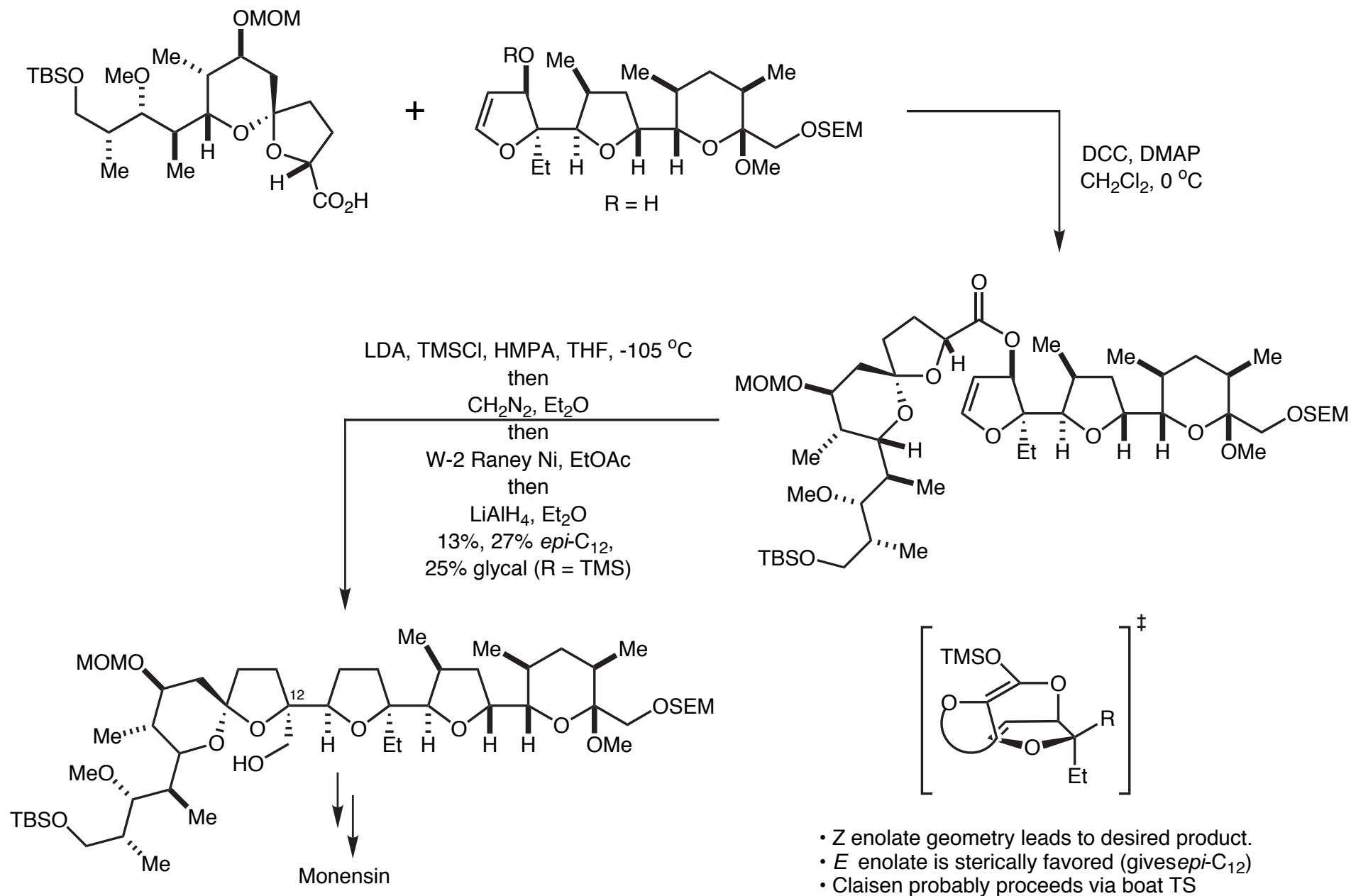
5-Endo Selenocyclizations Using TIPPSe-Br



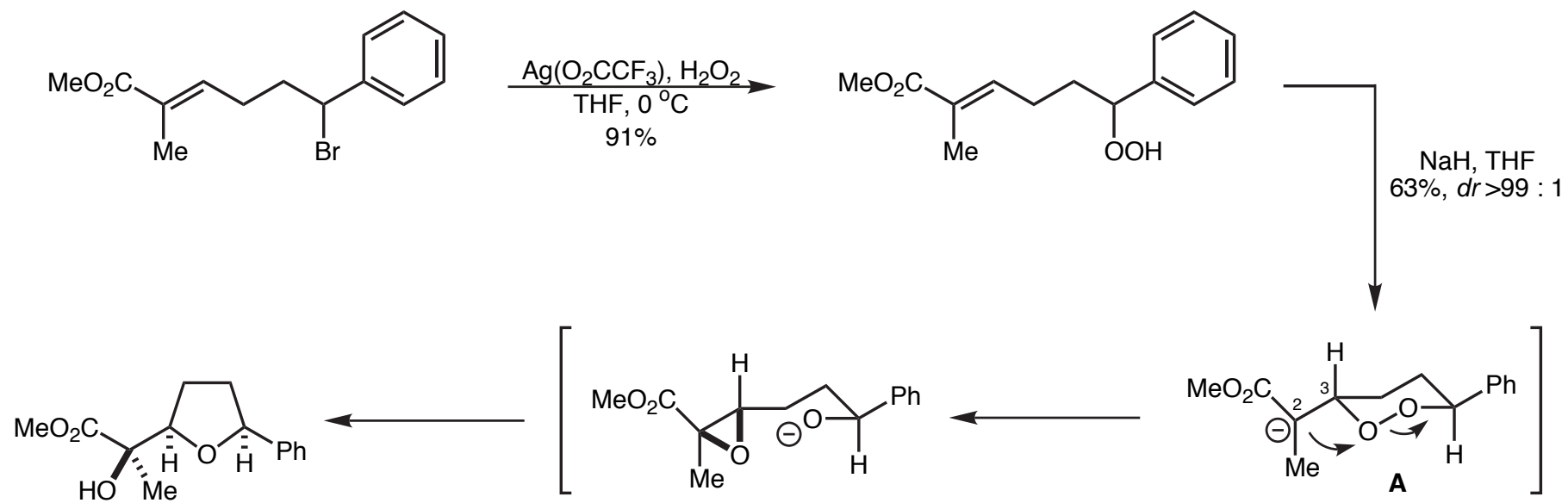
Bicyclic Ketal Opening



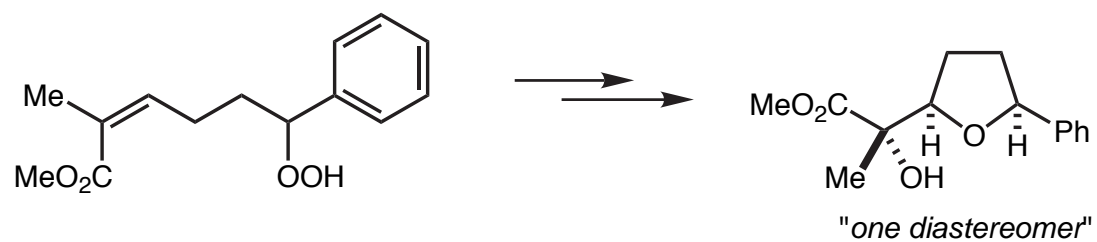
Ester Enolate Claisen Rearrangements



Hydroperoxide Cyclizations

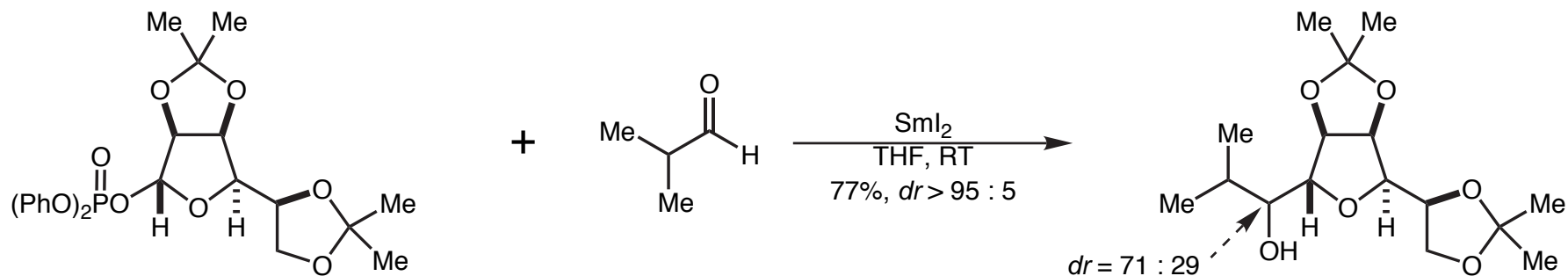
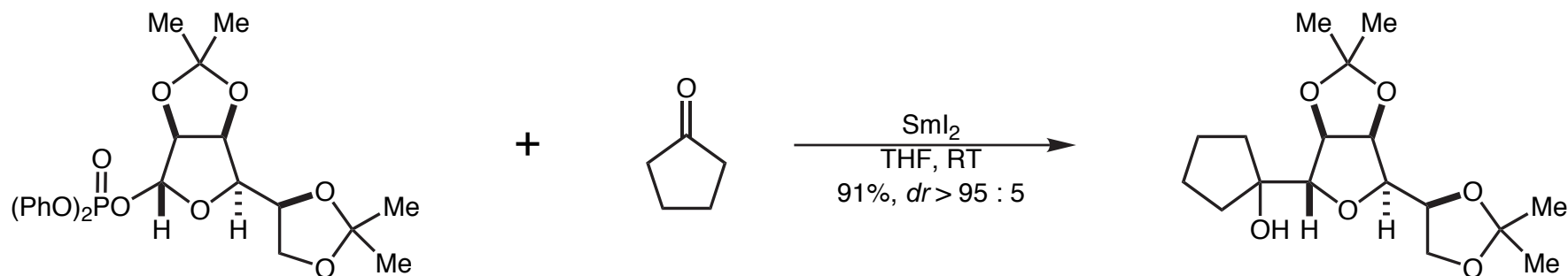
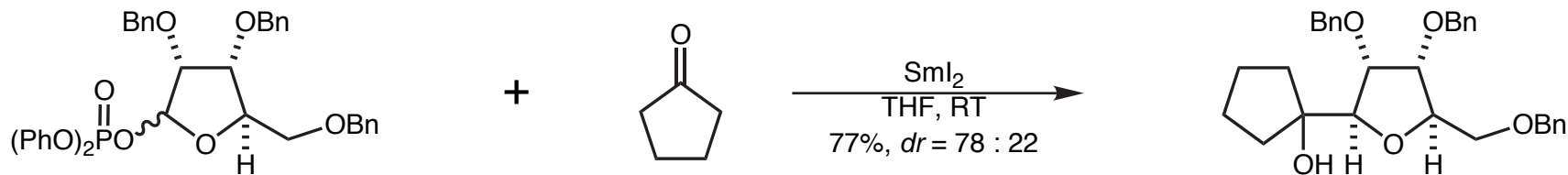


Note :



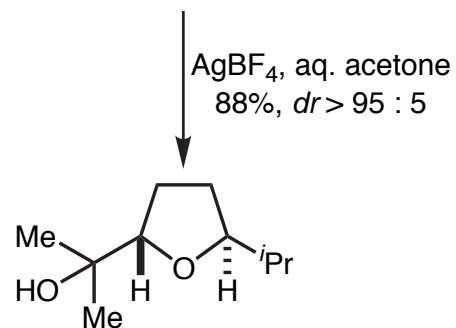
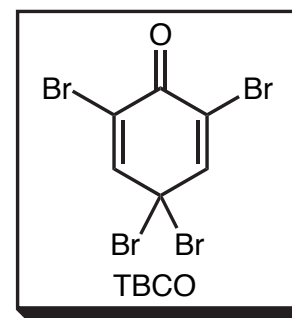
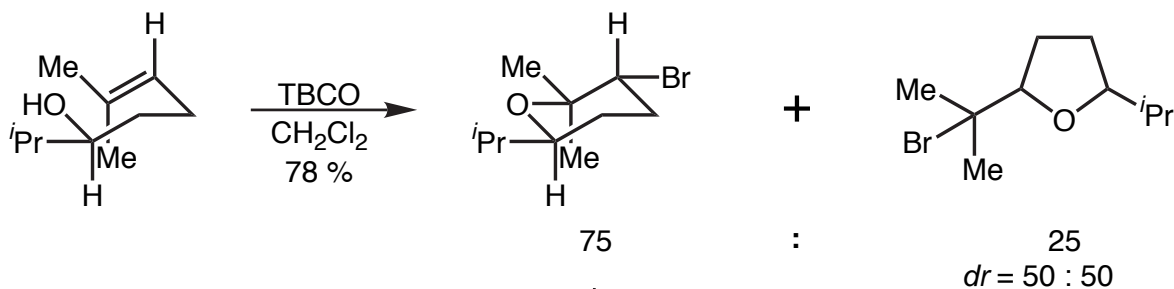
These results imply that rotation about $\text{C}_2\text{-C}_3$ bond in **A** is slower than epoxide formation.

*Sml*₂ Mediated C-Glycoside Couplings

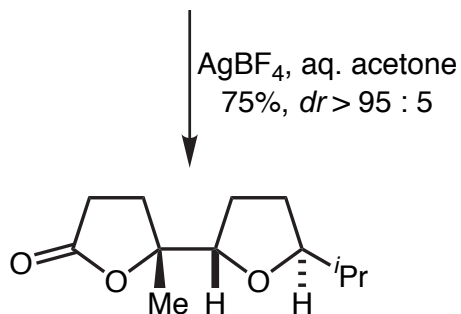
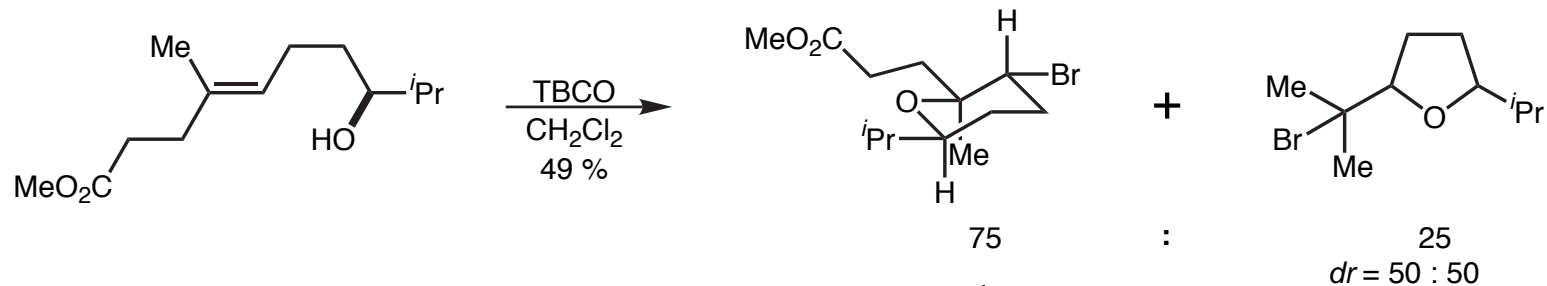


All reactions run under Barbier conditions, and are instantaneous!

Ring Contraction of Tetrahydropyrans

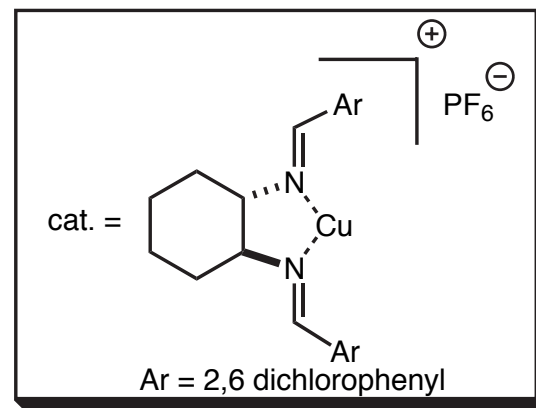
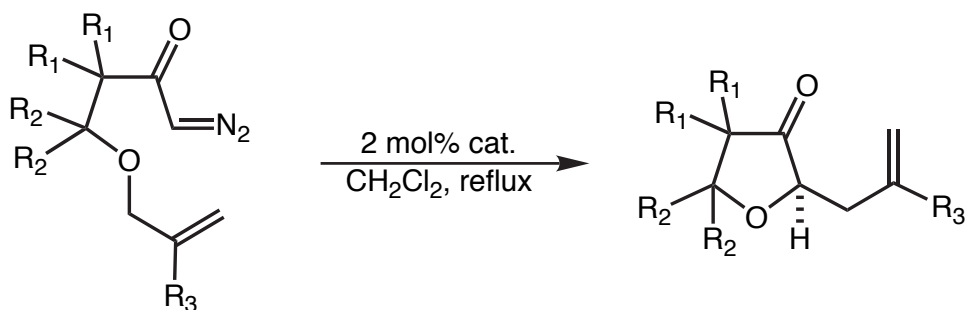


For similar, one pot TTN mediated cyclizations see:
Bartlett *et al*, *JOC*, **1985**, *50*, 2416



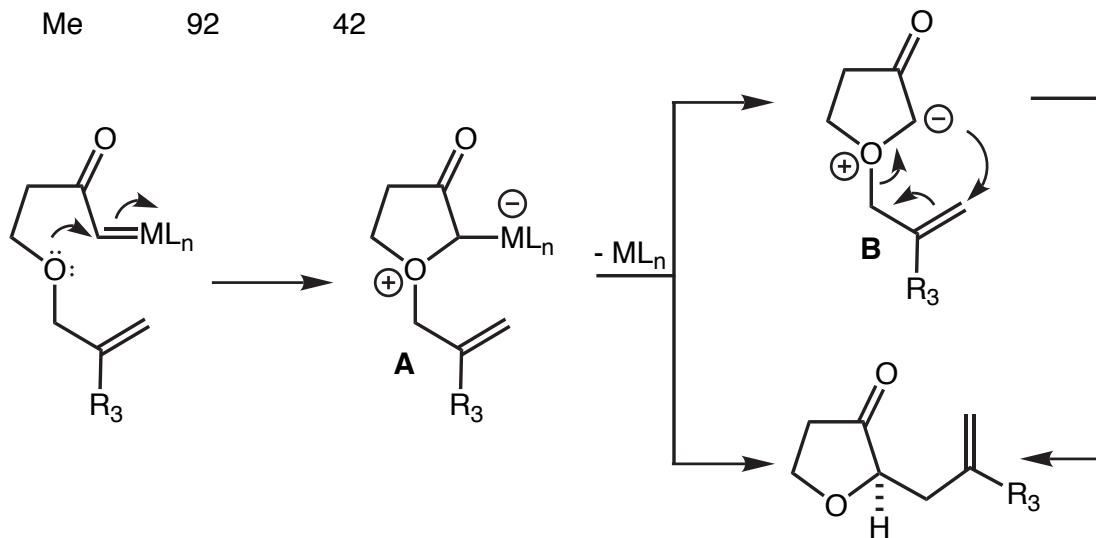
• Clean inversion at tertiary center!

A Catalytic, Modestly Enantioselective Method

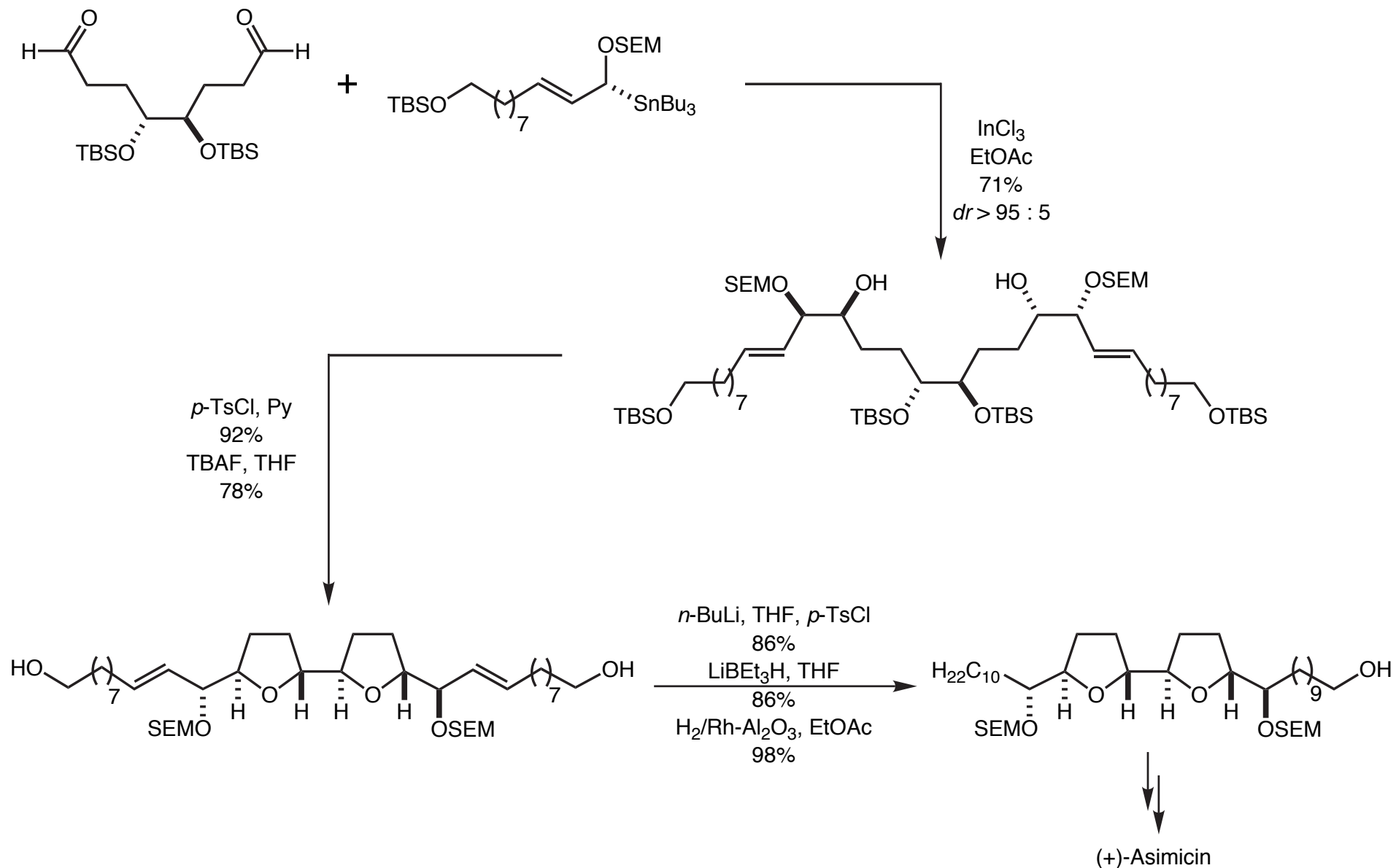


R ₁	R ₂	R ₃	Yield (%)	ee (%)
H	H	H	62	57
Me	H	H	57	56
H	Me	H	54	23
H	H	Me	62	6
Me	H	Me	92	42

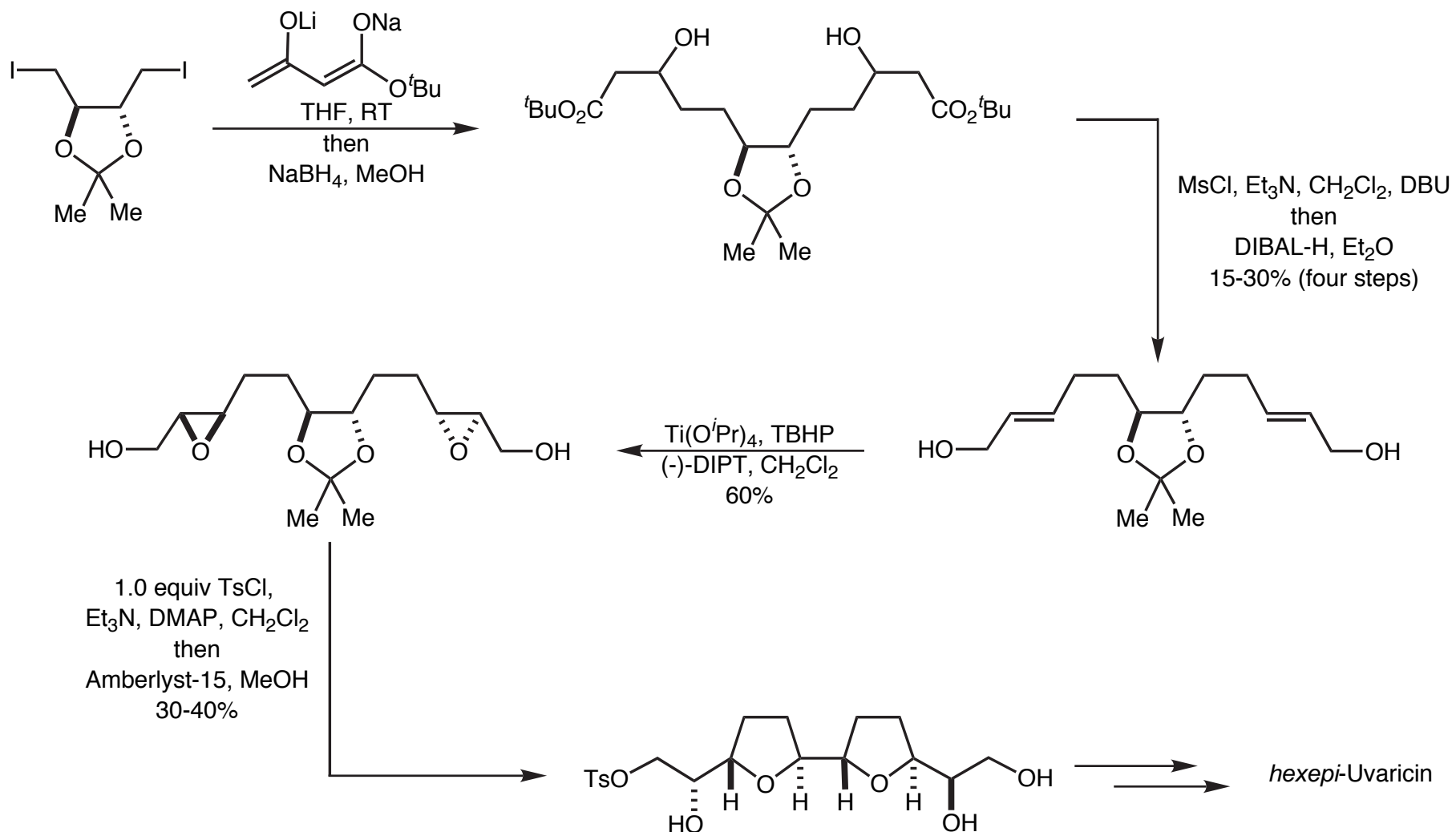
- The rearrangement could proceed directly through metal bound ylide **A** or through the free oxonium ylide **B**



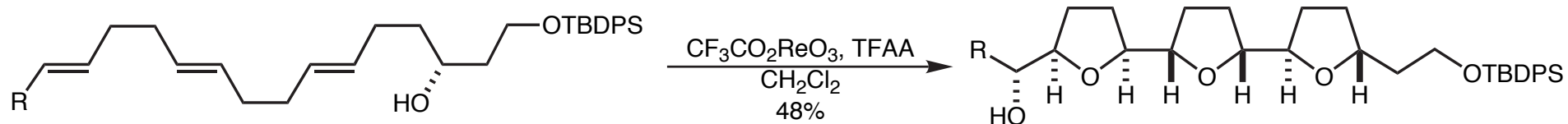
Bidirectional Approach via Tosylate Displacement



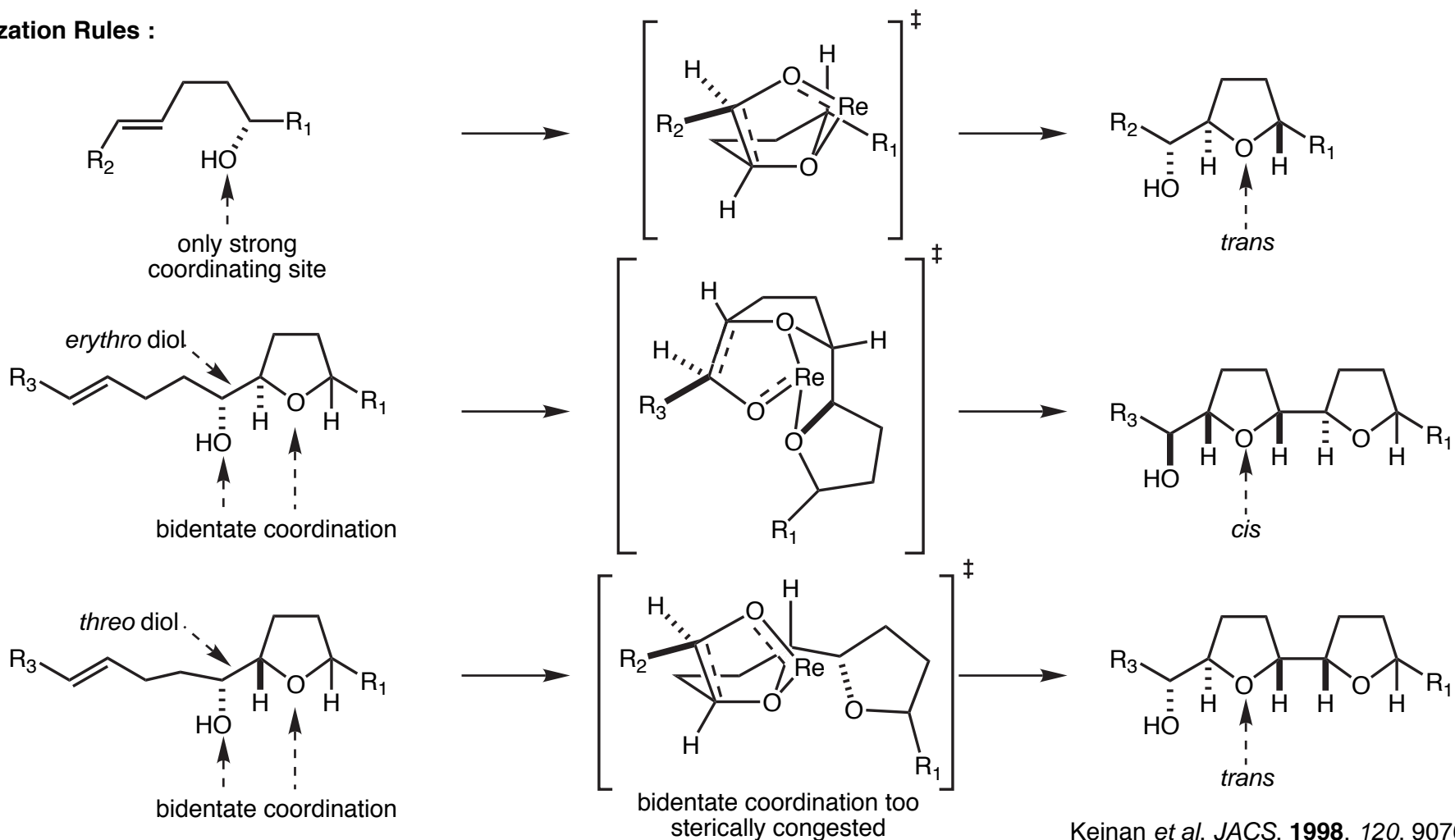
Bidirectional Synthesis via Epoxide Opening



Tandem Oxidative Cyclizations Using Re(VII) Oxides



Cyclization Rules :



Keinan *et al*, *JACS*, **1998**, 120, 9076
 McDonald *et al*, *JOC*, **1997**, 119, 6022