Stereoselective Synthesis of 2,5 Substituted Tetrahydrofurans

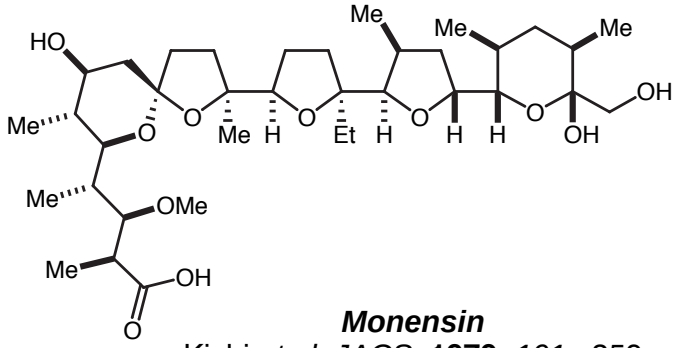
Hemaka Rajapakse
Evans Group Afternoon Seminar
Tuesday, December 8th 1998

- 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

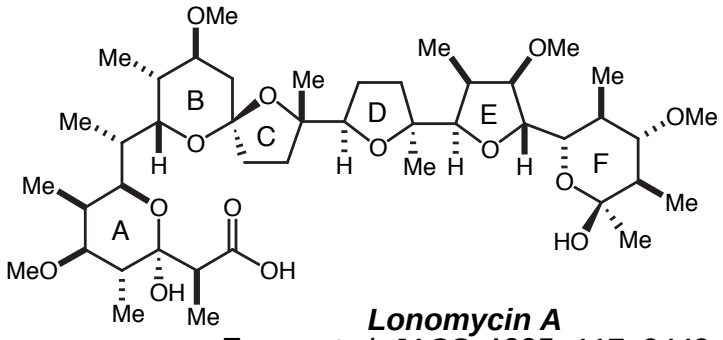
Leading Reviews :

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

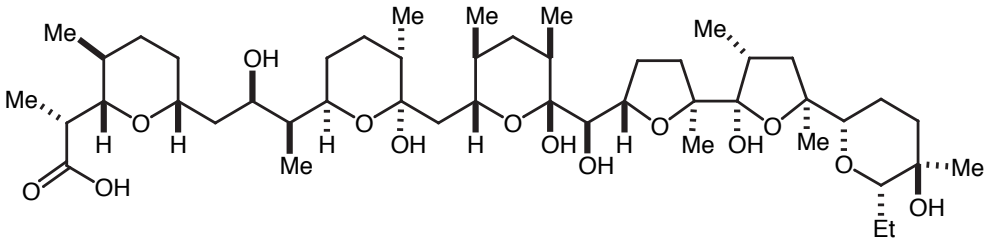
Tetrahydrofuran Ring Containing Natural Products



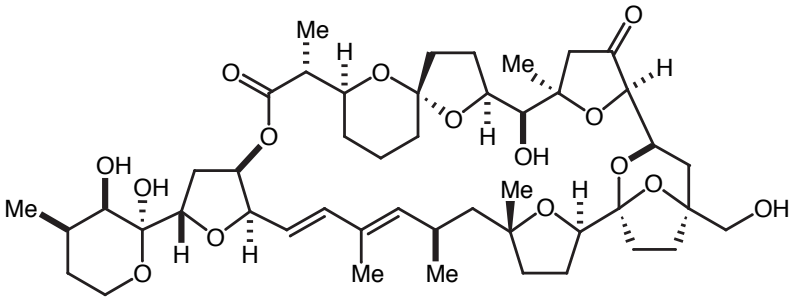
Monensin
Kishi *et al*, *JACS* ,**1979**, *101,* 259
Still *et al*, *JACS* ,**1980**, *102,* 2117
Ireland *et al*, *JACS* ,**1993**, *115,* 7152



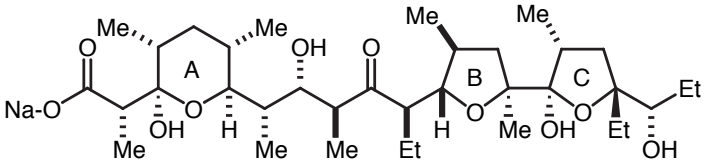
Lonomycin A
Evans *et al, JACS,* **1995**, *117, 3448*



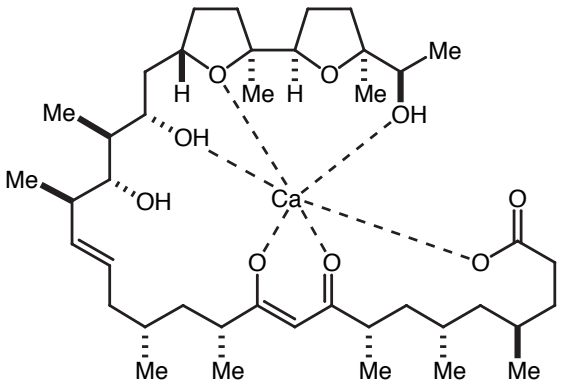
Antibiotic X-206
Evans *et al, JACS,* **1988**, *110*, 2506



Pectenotoxin 4
Evans *et al*, In progress....

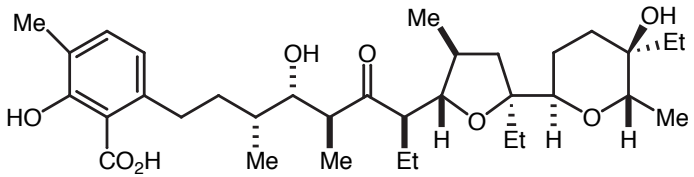


Ferensimycin B
Evans *et al*, *JACS,* **1991**, *113,* 7613

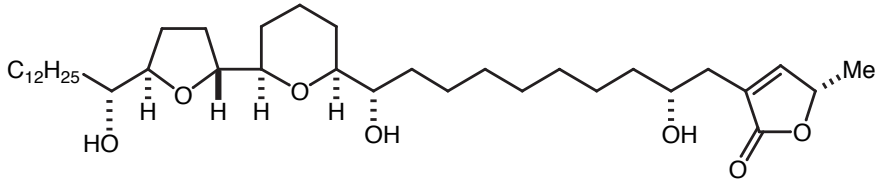


Ionomycin Calcium Complex
Evans *et al*, *JACS* ,**1990**, *112,* 5290
Hanessian *et al*, *JACS*, **1990**, *112*, 5176

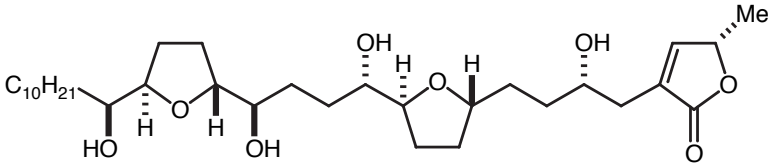
More Tetrahydrofuran Ring Containing Natural Products



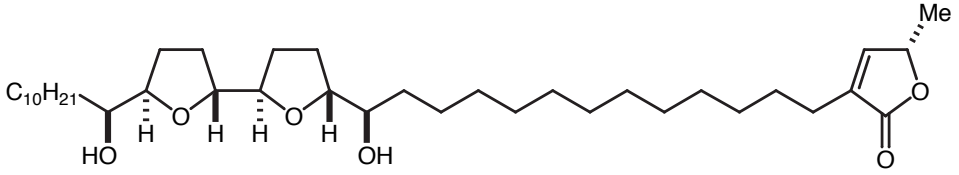
Lasalocid A
Kishi *et al*, *JACS*, **1978**, *100*, 2933
Ireland *et al*, *JACS*, **1983**, *105*, 1988



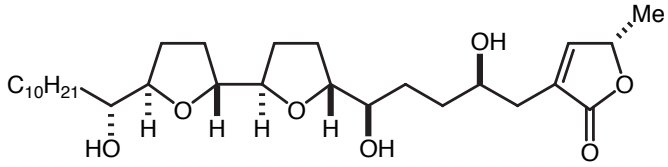
Muconin
Jacobsen *et al*, *JOC*, **1998**, *63*, 4876



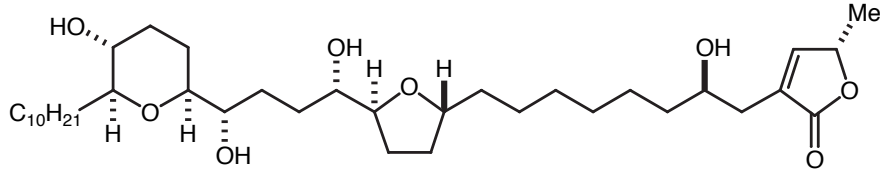
Squamostatin D
Marshall *et al*, *JOC*, **1998**, *63*, 7066



(+)-Uvaricin
Hoye *et al*, *JACS*, **1991**, *113*, 9369

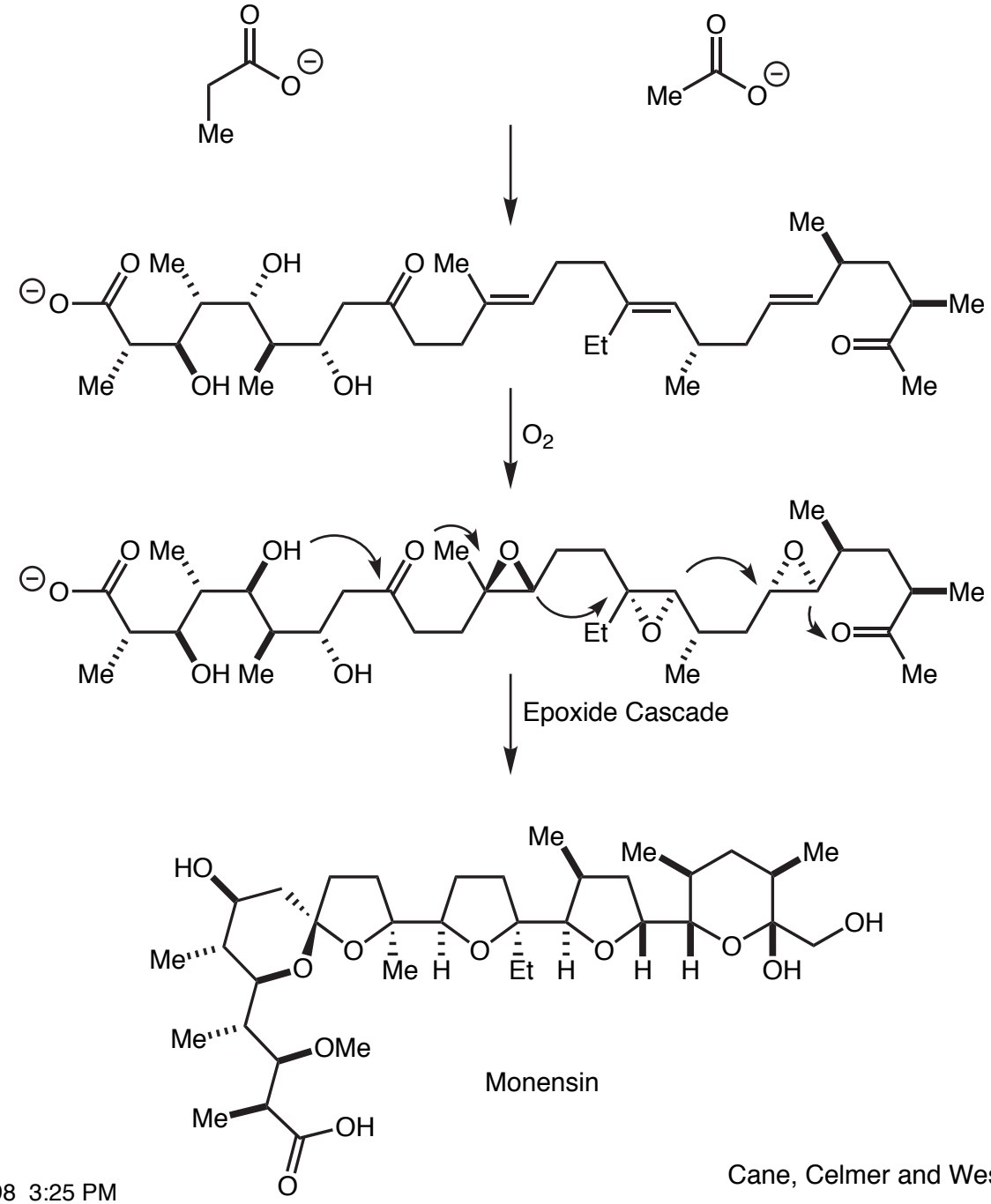


Asimicin
Marshall *et al*, *JOC*, **1997**, *62*, 5989



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

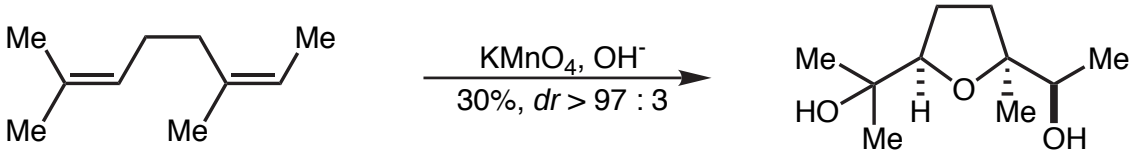
Biosynthesis of Polyethers

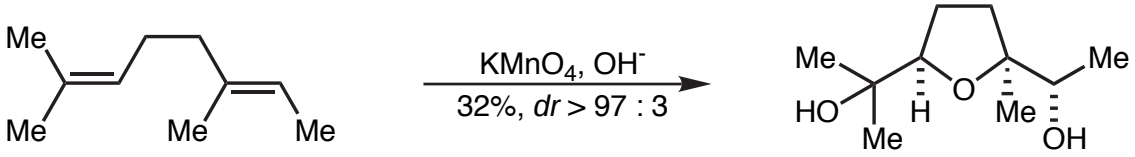


Monensin

Cane, Celmer and Westley, *JACS*, **1983**, *105*, 3594

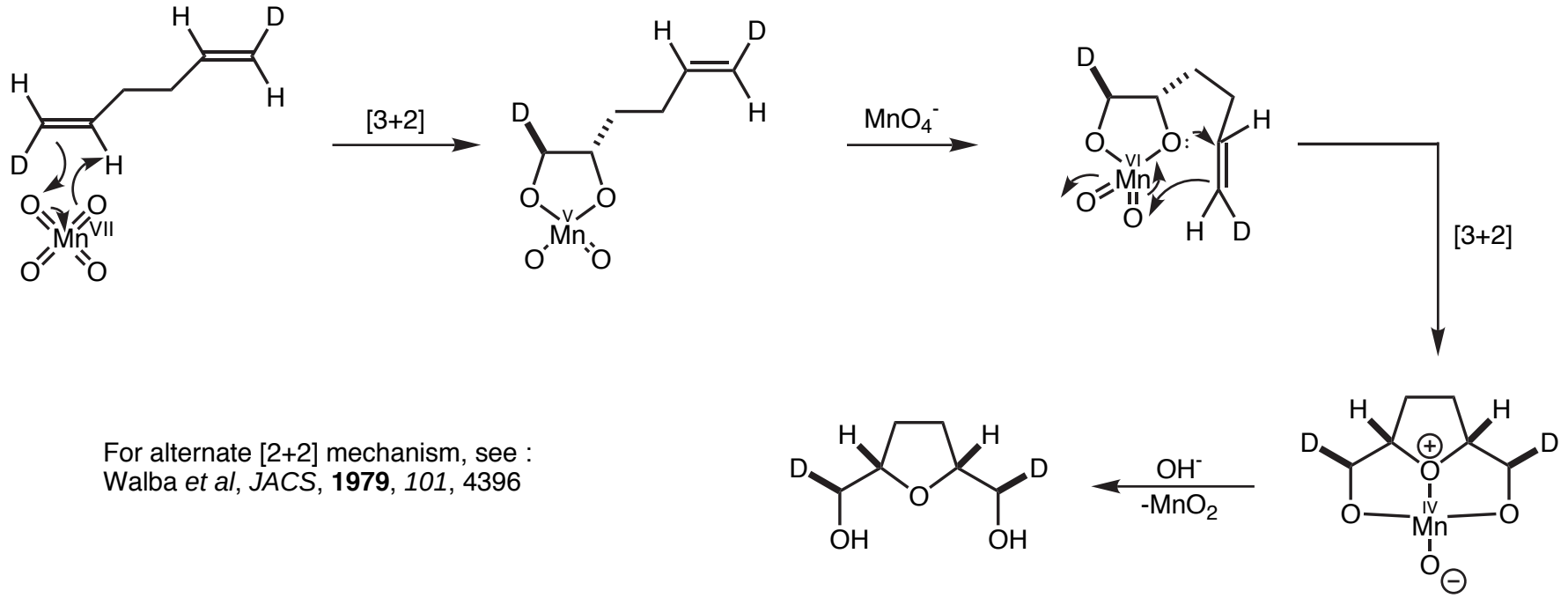
Oxidative Cyclizations of 1,5-Dienes





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

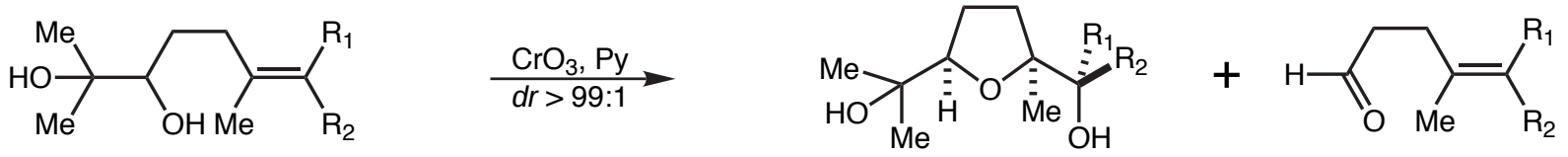
Possible Mechanism :



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

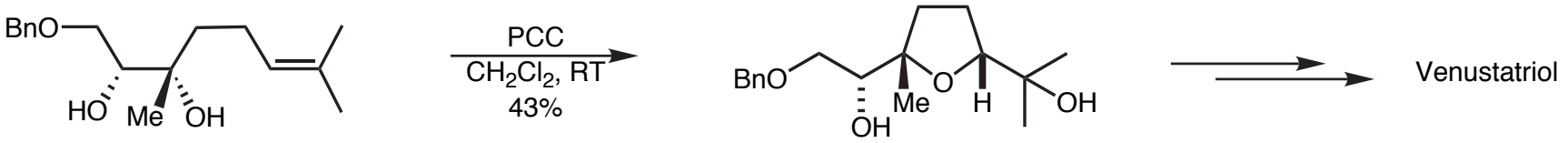


R_1, R_2 = H , OAc

45-50%

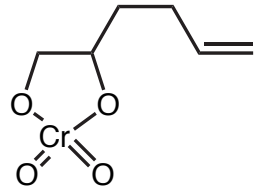
5-10%

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



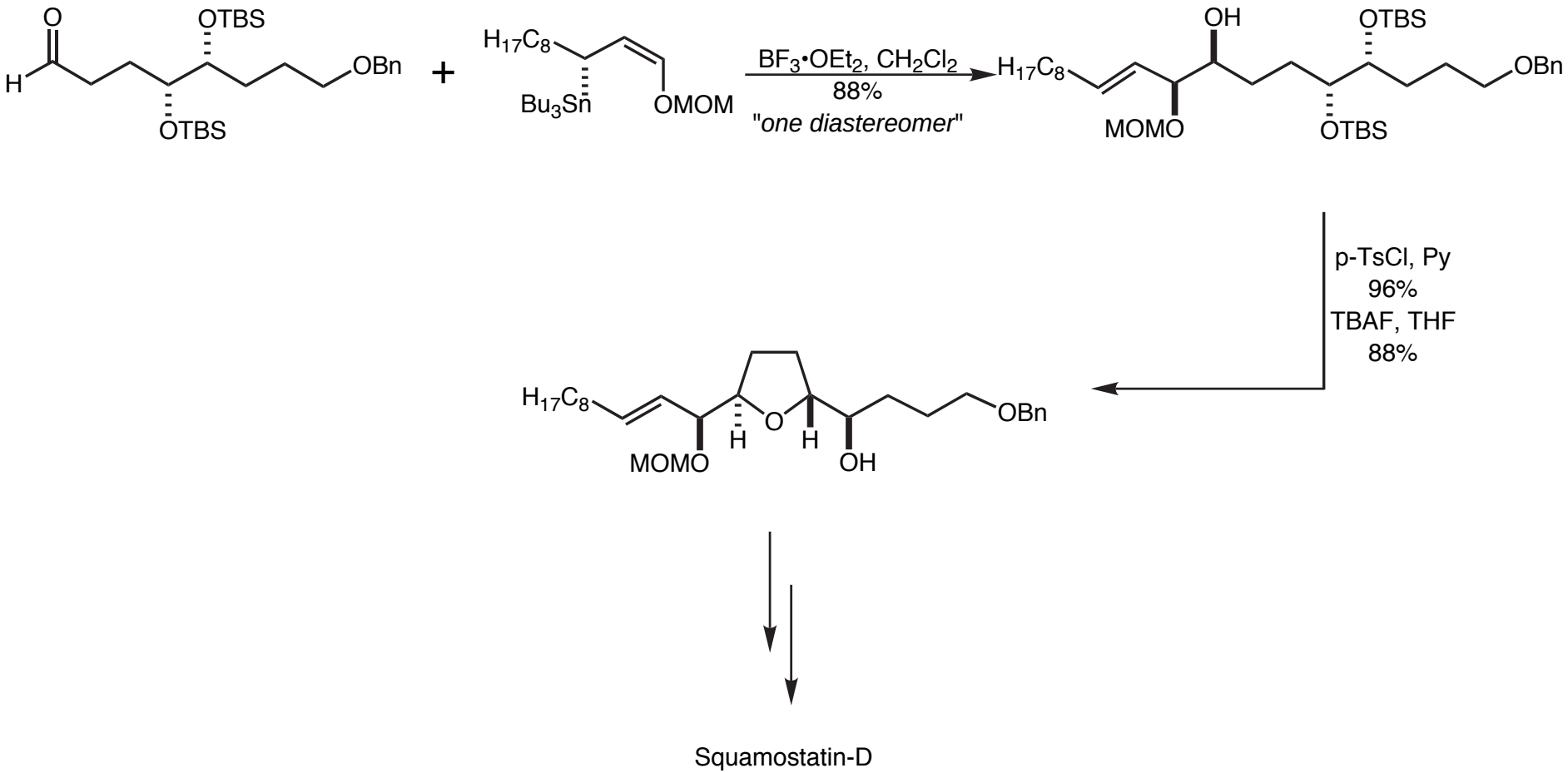
Corey et al, *TL*, **1988**, *29*, 3171

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



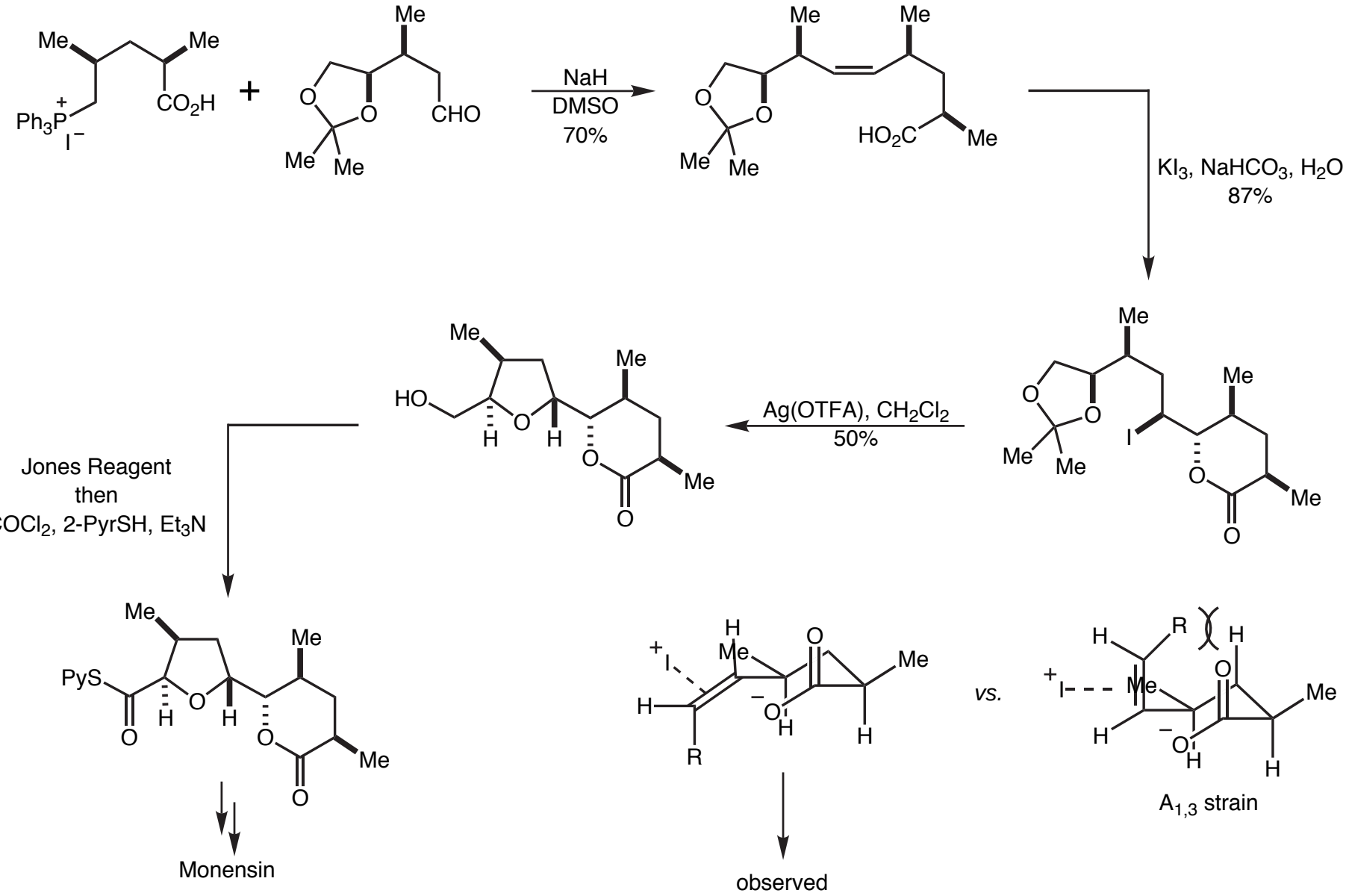
A

1,4-Diol Cyclization



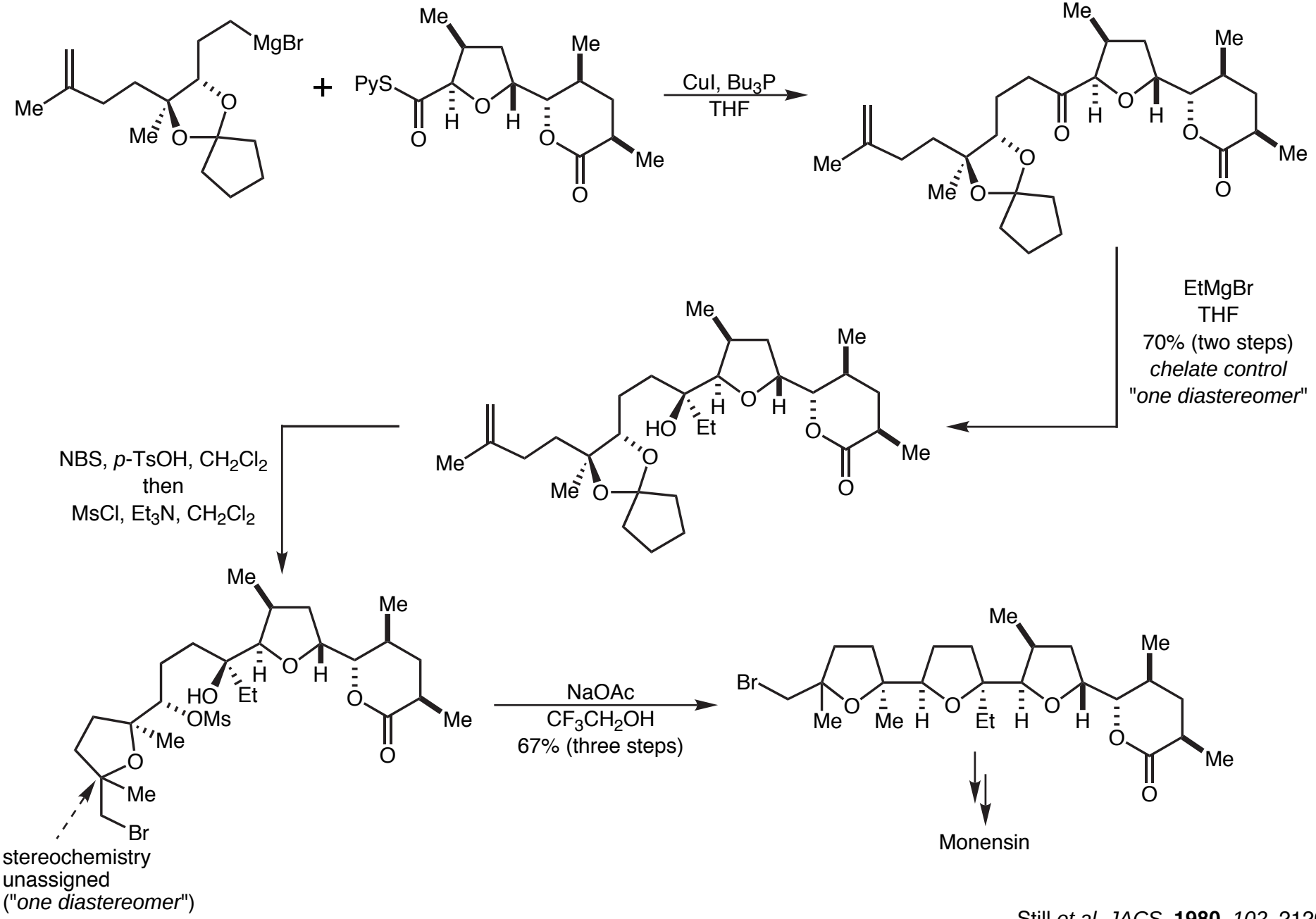
Marshall *et al*, *JOC*, **1998**, *63*, 7066

Iodide Displacement Strategy



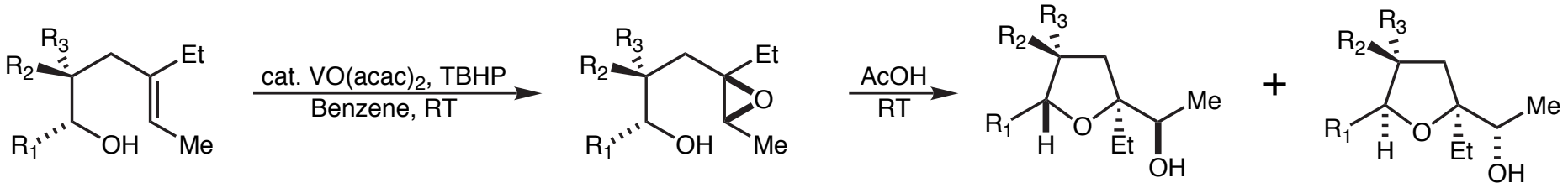
Still *et al*, *JACS*, **1980**, *102*, 2117

Mesylate Displacement in the Still Monensin Synthesis



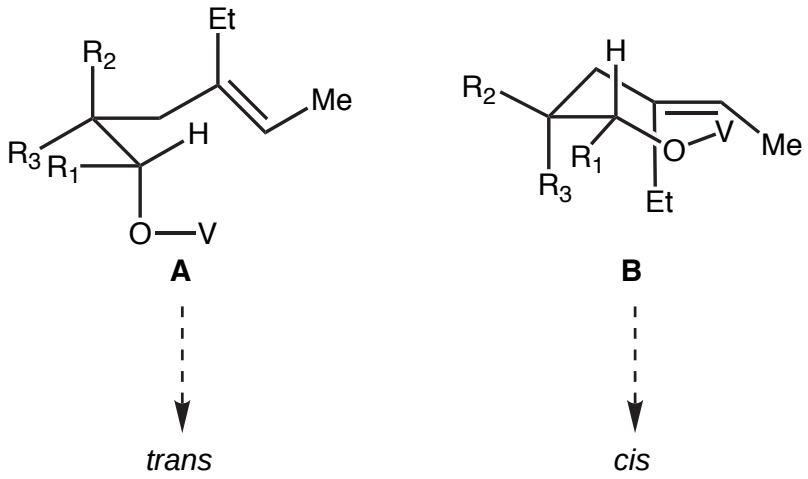
Still *et al*, *JACS*, **1980**, *102*, 2120

Directed Epoxidation of bis-*Homoallylic Alcohols*



R_1	R_2	R_3	*trans*		*cis*
^{i}Pr	H	H	90	:	10
^{i}Pr	CH_3	H	84	:	16
^{i}Pr	H	CH_3	95	:	5
PMP	H	H	89	:	11
PMP	CH_3	H	89	:	11

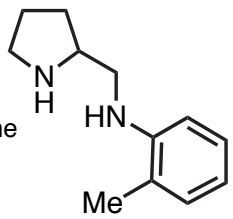
PMP = *para*-methoxyphenyl



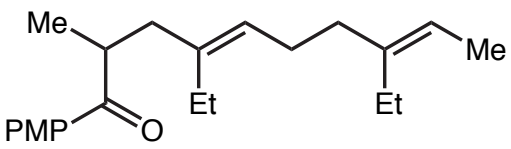
Transition state **A** best fulfills steric, stereoelectronic, and geometrical constraints for epoxidation.

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

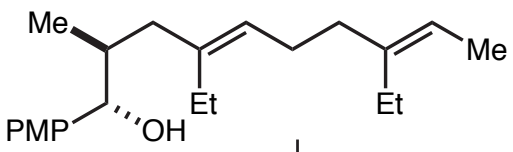
Total Synthesis of Lasalocid



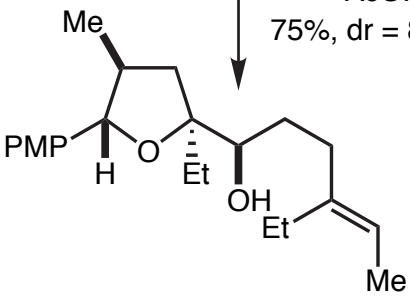
diamine =
dl-2-(o-toluidineomethyl) pyrrolidine



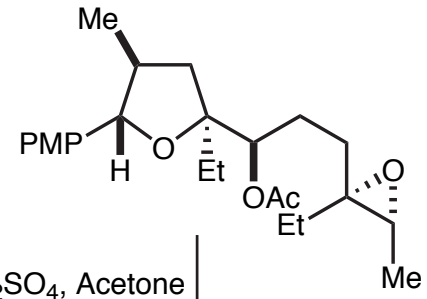
$LiAlH_4$, diamine
97%, *dr* = 91 : 9
then
Resolve



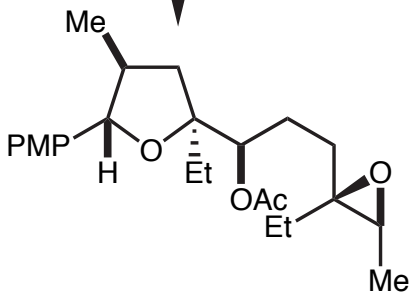
cat. $VO(acac)_2$
TBHP, NaOAc,
Benzene, RT
then
AcOH
75%, dr = 89 : 11



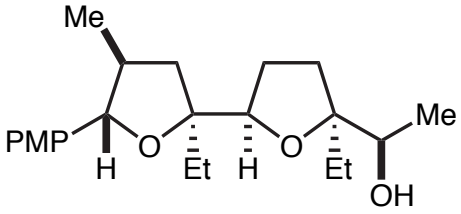
cat. $VO(acac)_2$, TBHP, NaOAc,
Benzene, RT
then
Ac_2O, Py



$0.1N\ H_2SO_4$, Acetone
then
TsCl, Py
then
K_2CO_3, MeOH



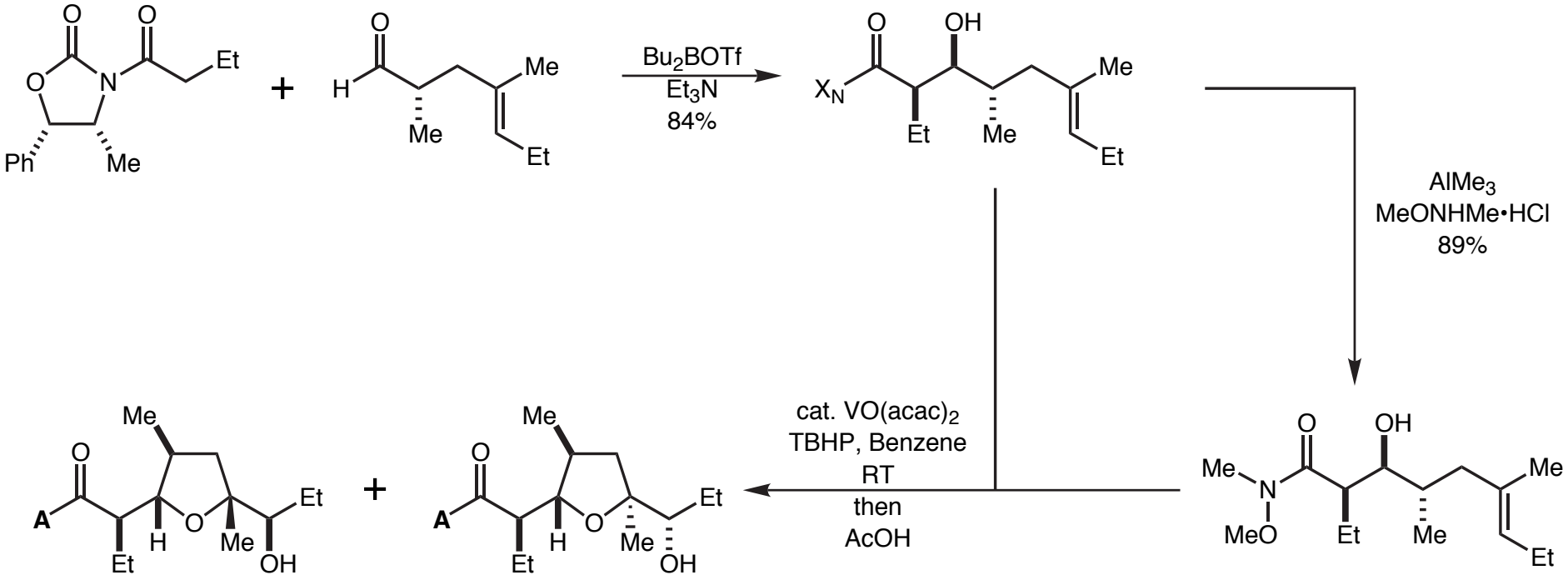
AcOH
45% (six steps)
dr = 83 : 17 overall



Lasalocid
+
Isolasalocid

Kishi et al, *JACS*, **1978**, *100*, 2933

Total Synthesis of Ferensimycin B



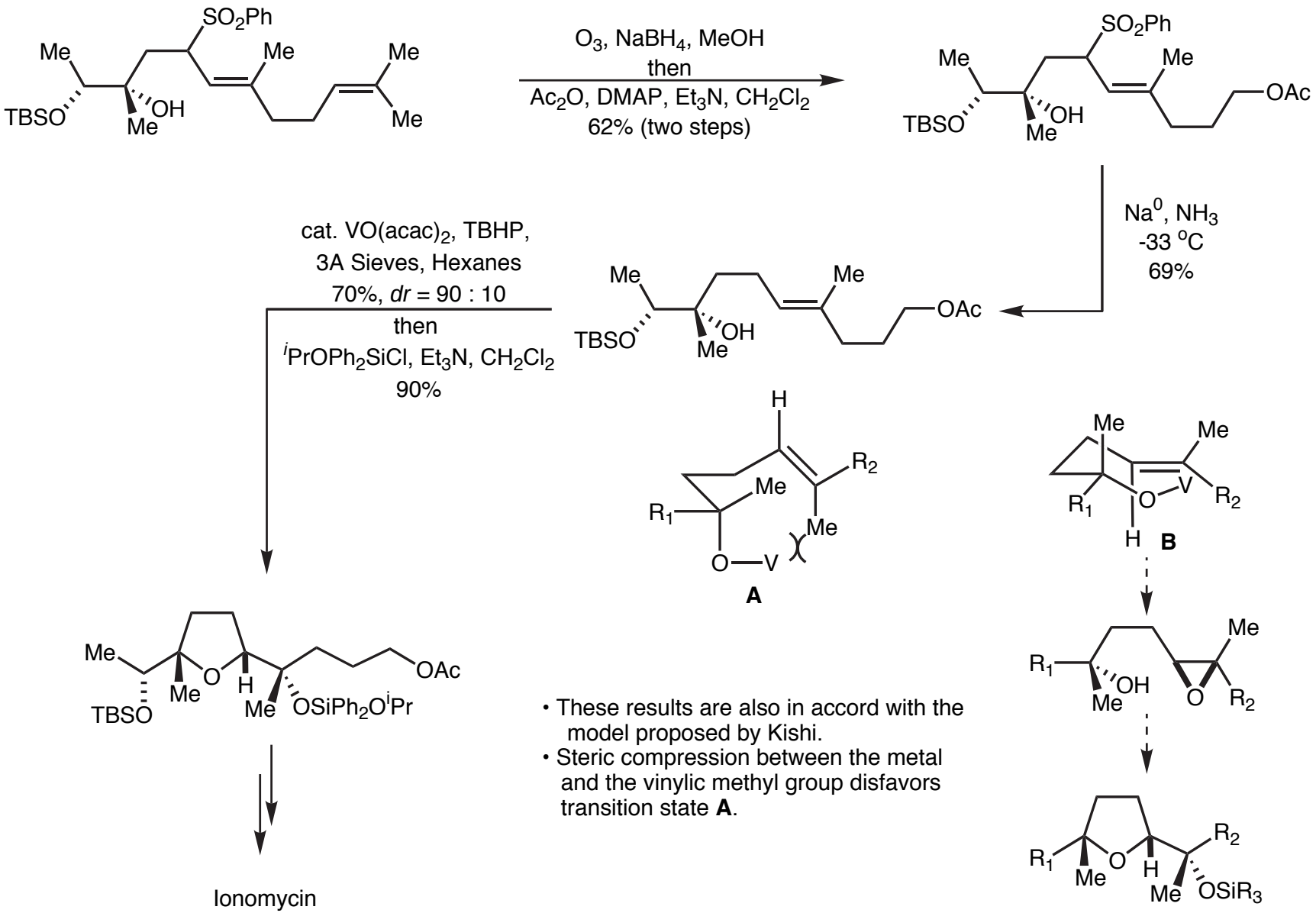
A (Yield)	4	96
X_N (85%)	30	70
MeONMe (89%)		

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

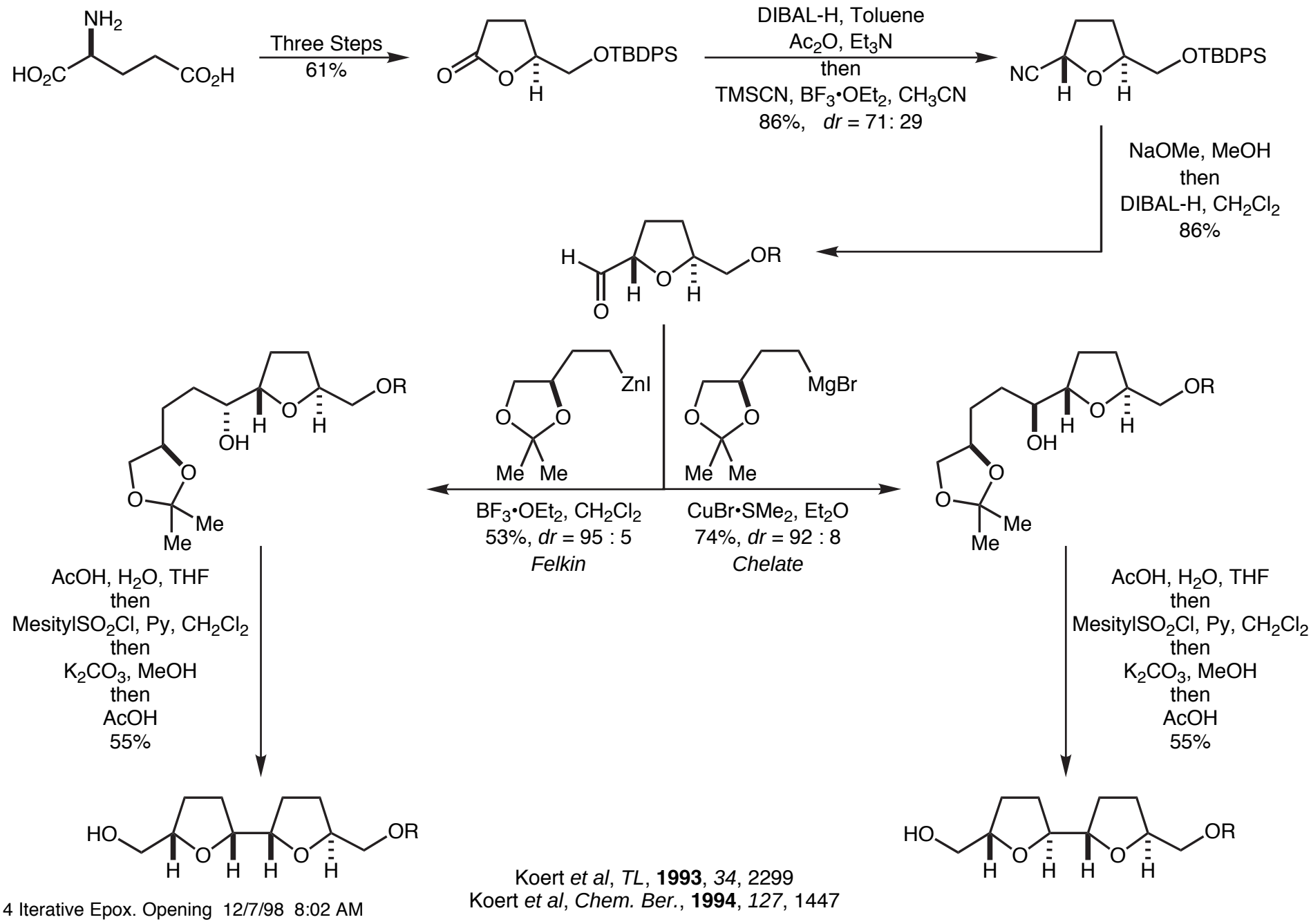
Evans *et al*, *JACS*, **1991**, *113*, 7613

Directed Epoxidation from a Tertiary Alcohol



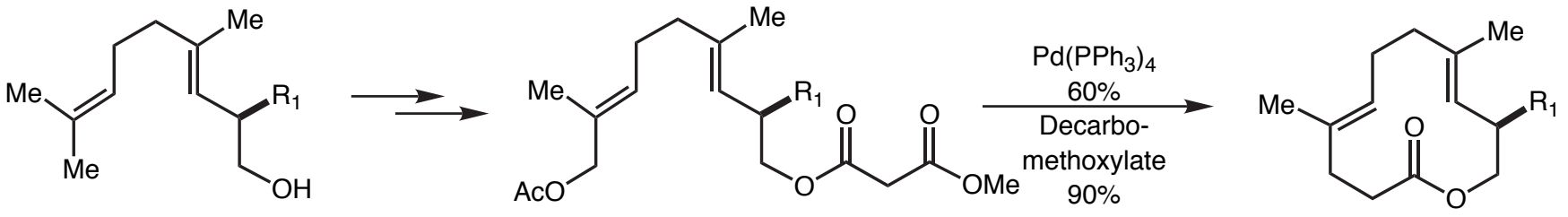
Hanessian *et al*, *JACS*, **1990**, *112*, 5276

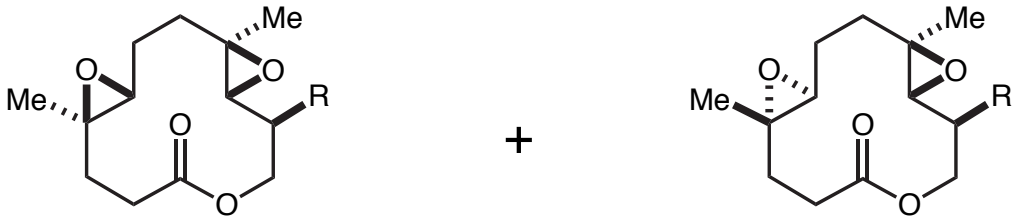
An Iterative Epoxide Opening Sequence



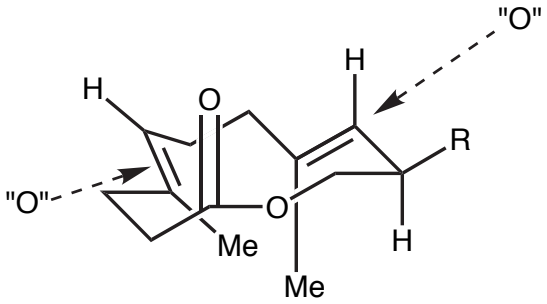
Koert *et al*, *TL*, **1993**, *34*, 2299
Koert *et al*, *Chem. Ber.*, **1994**, *127*, 1447

Epoxydation of Unsaturated Macrolides

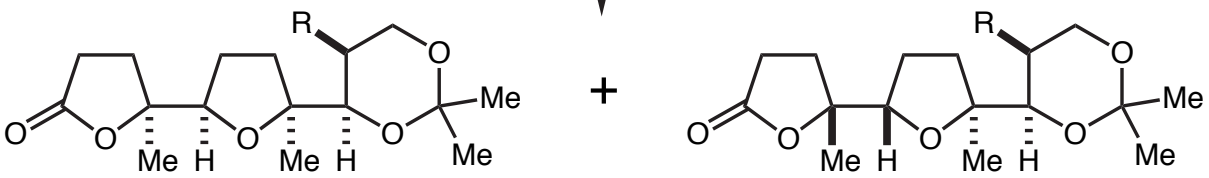




R			
H	80	:	20
Me	94	:	06

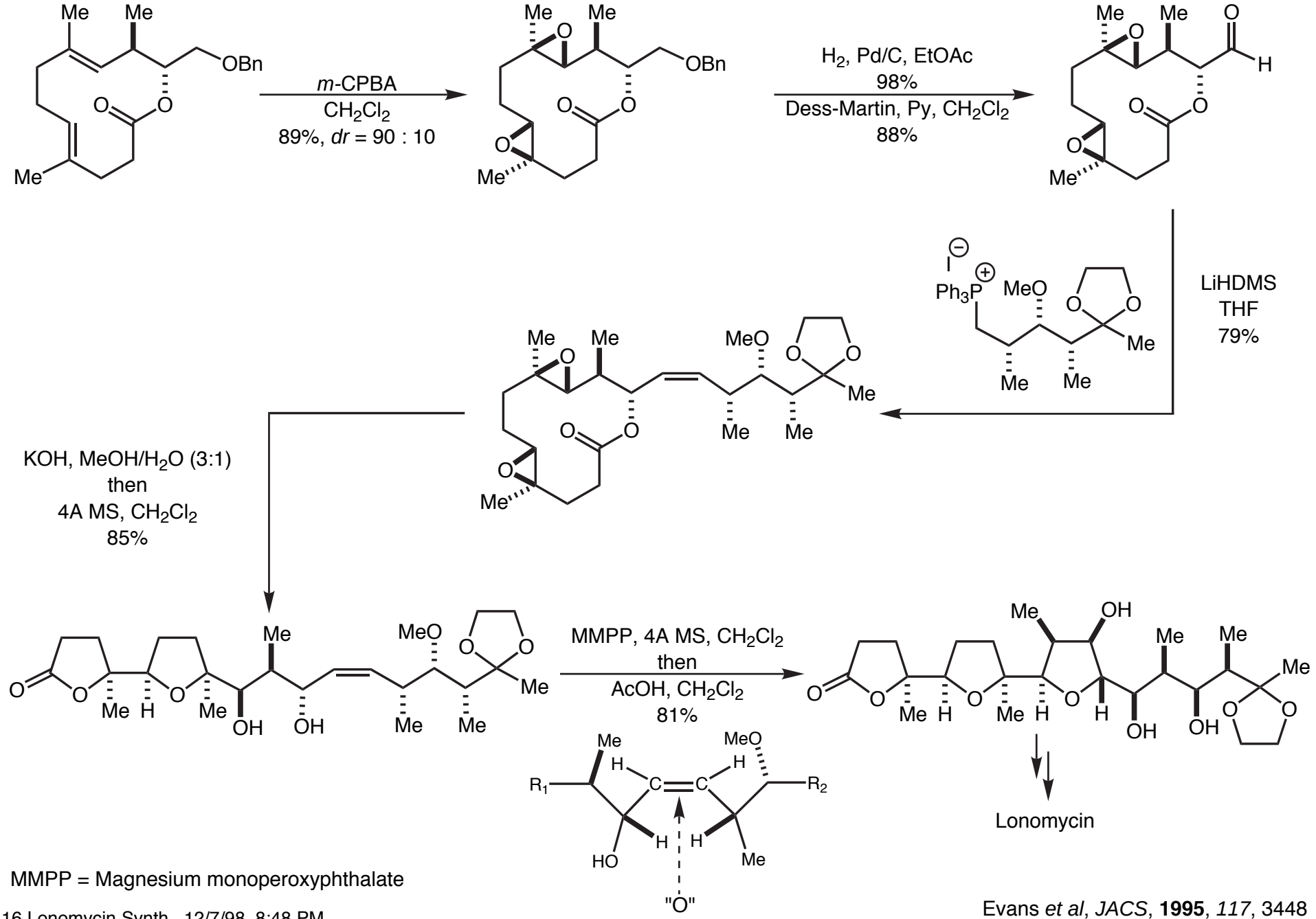


Bulky R group rigidifies macrolactone conformation through $A_{1,3}$ strain



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

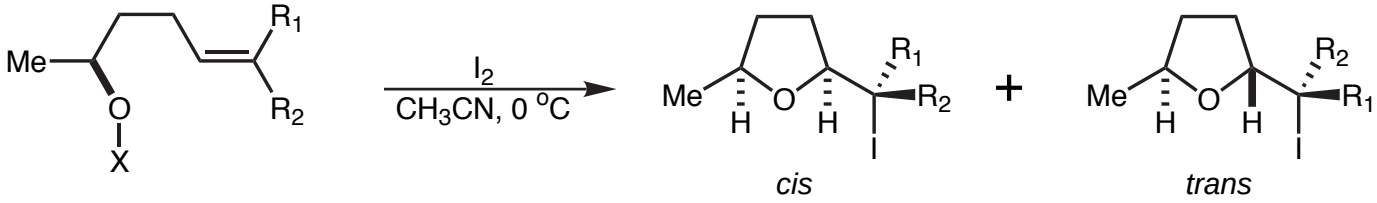
The Lonomycin Synthesis

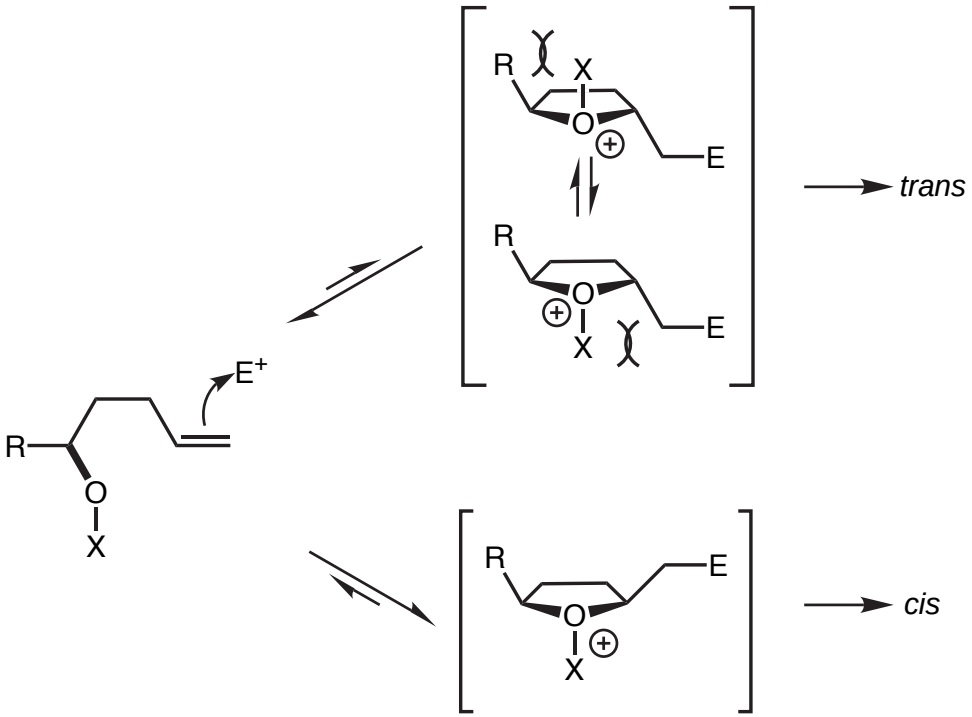


MMPP = Magnesium monoperoxyphthalate

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

Halocyclization of bis-*Homoallylic Alcohols*





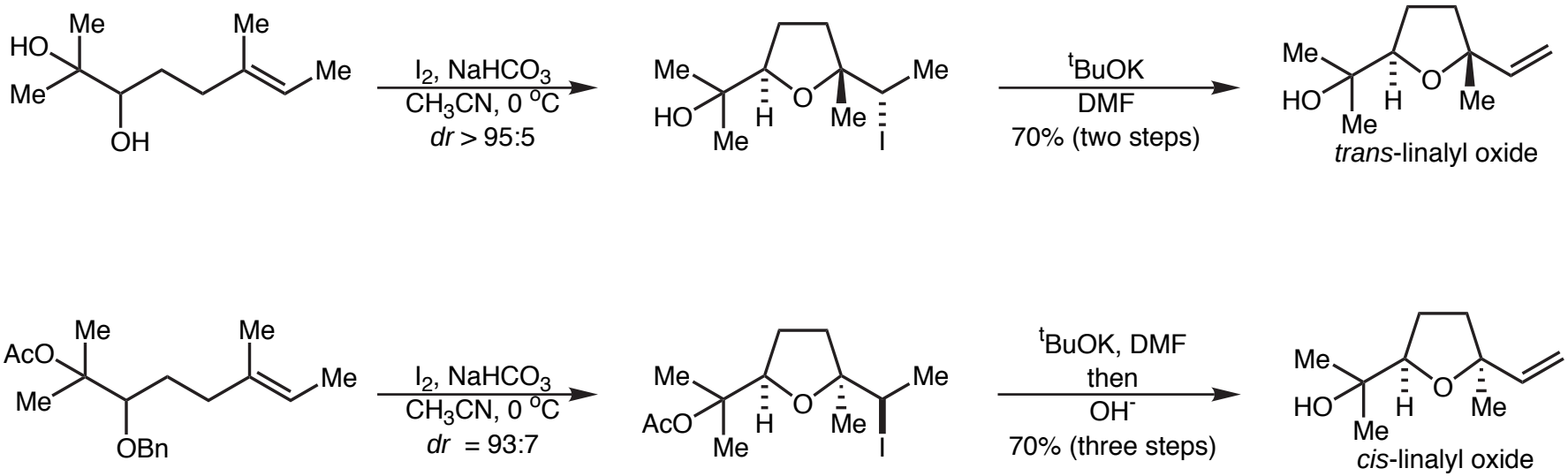
X	R_1	R_2	Ratio *cis* : *trans*	Yield (%)
H	H	H	34 : 66	66
Me	H	H	34 : 66	15
Bn	H	H	66 : 34	60
TBS	H	H	75 : 25	43
BB	H	H	79 : 21	74
⇨DCB	H	H	95 : 5	63
DCB	H	Me	92 : 8	47
DCB	CO_2Me	H	98 : 2	60

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.

Bartlett *et al*, *JACS*, **1981**, *103*, 3963

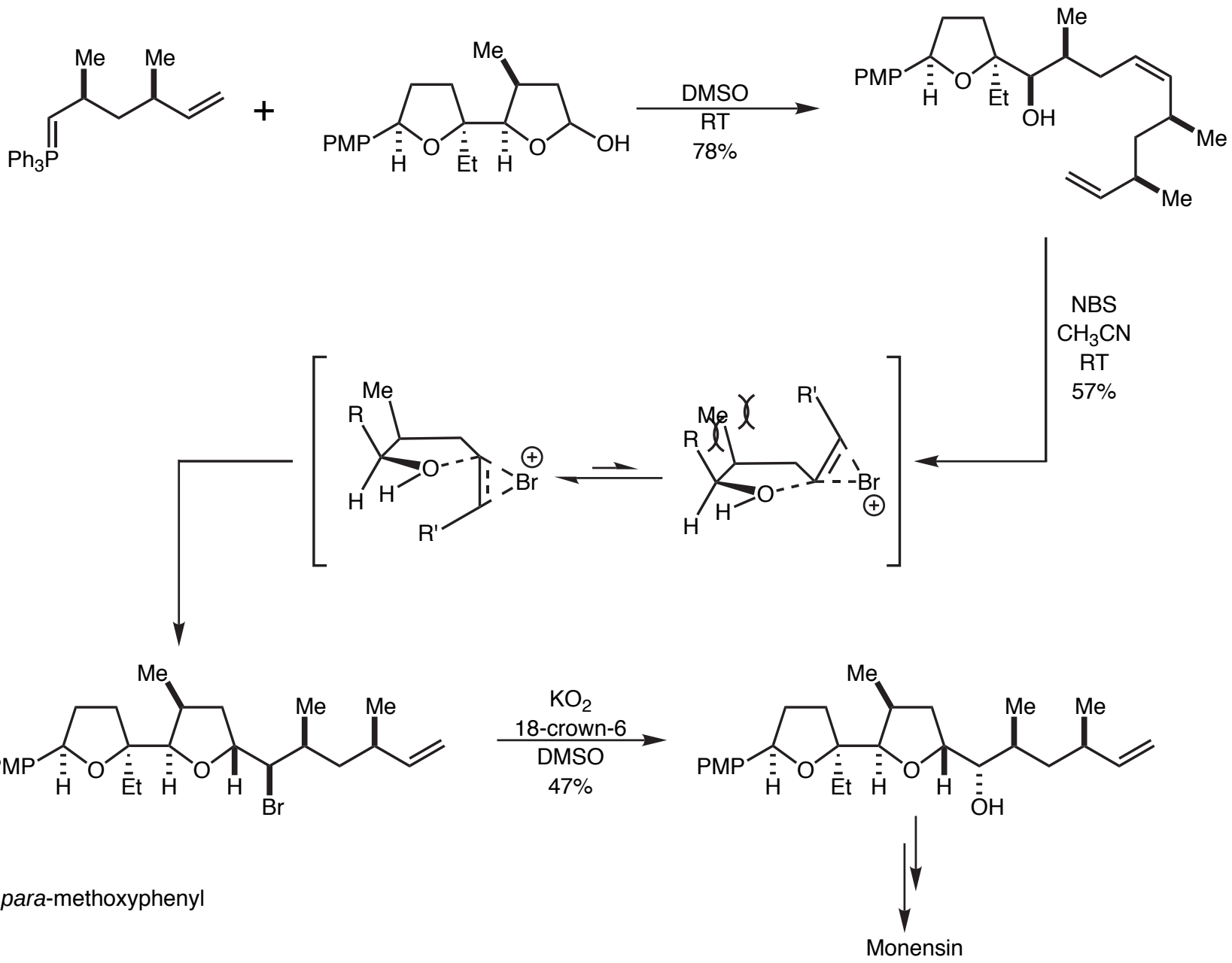
Application to 2,2,5-Trisubstituted THF Rings



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

Bartlett *et al*, *JACS*, **1981**, *103*, 3963

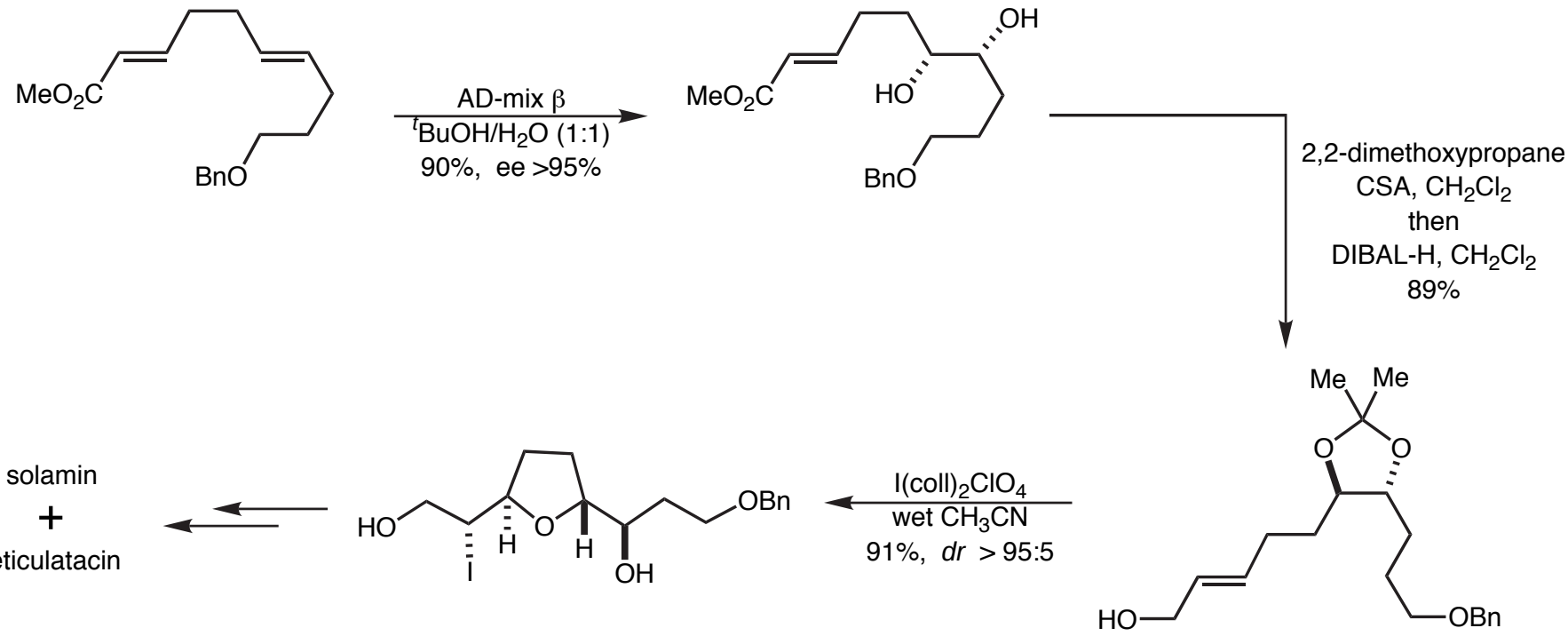
Halocyclization Application in Monensin Synthesis



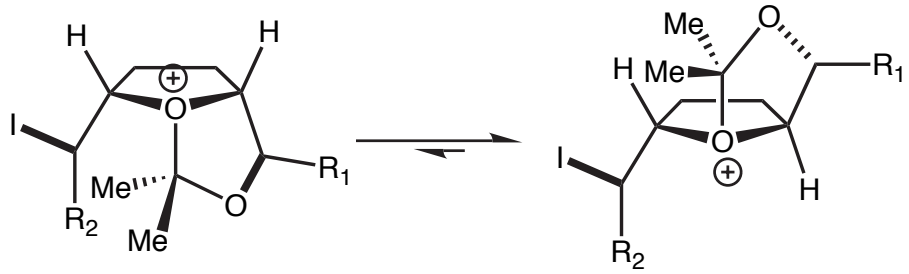
PMP = *para*-methoxyphenyl

Kishi *et al*, *JACS*, **1978**, *100*, 2933

Dihydroxylation/Halocyclization Strategy



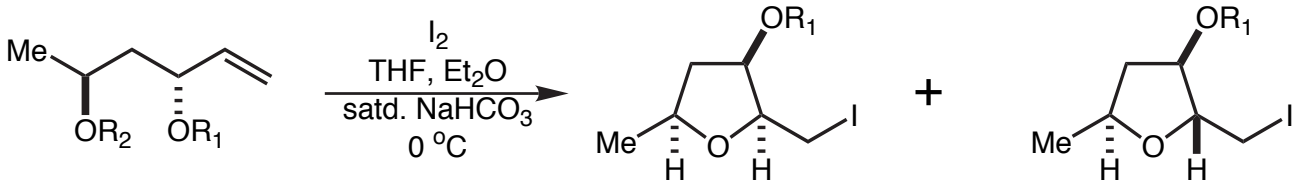
Author's Rationale :



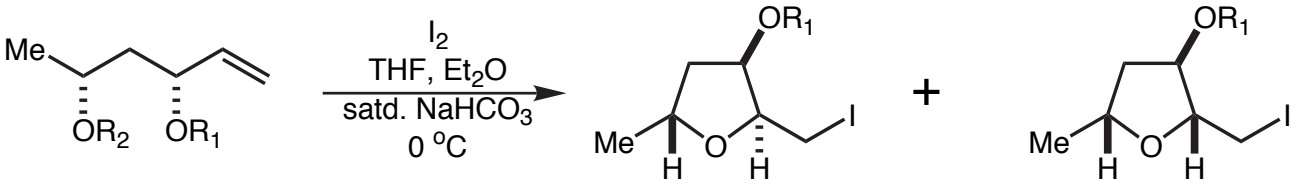
Ketal hydrolysis is probably the rate determining step. Equilibration of the above oxonium intermediates would explain selectivity.

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

Influence of an Allylic Oxygen on Halocyclizations



R_1	R_2				
H	H	100	:	0
Bn	H	95	:	5
Bn	Bn	100	:	0

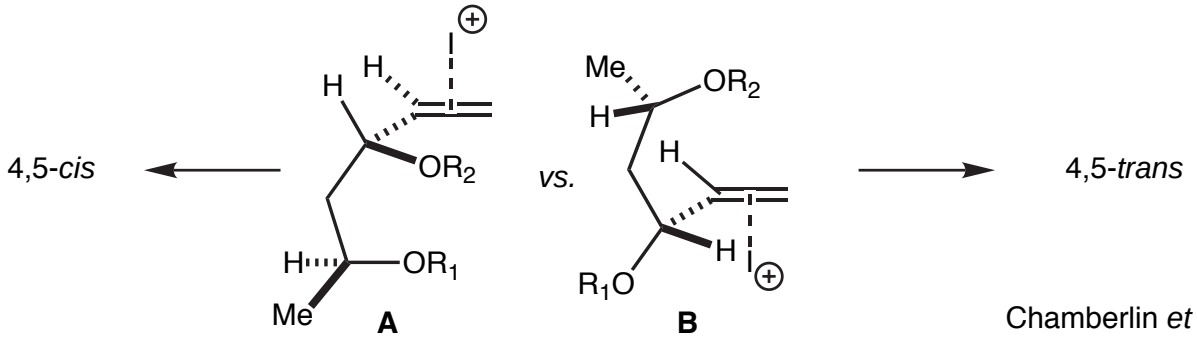


R_1	R_2				
H	H	91	:	9
Bn	H	91	:	9
Bn	Bn	64	:	36

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

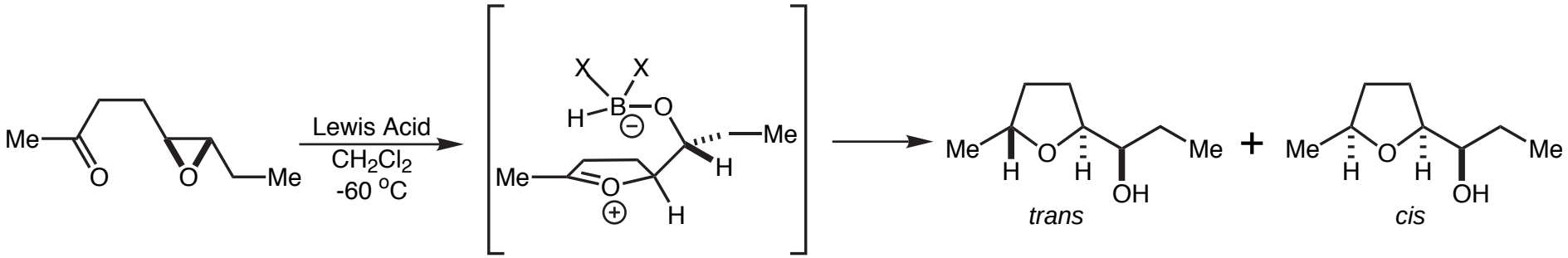
Rationale :

Reaction proceeds via an early TS through electronically favored π complex **A**, which minimizes destablizing σ^*_{CO}-π interactions.



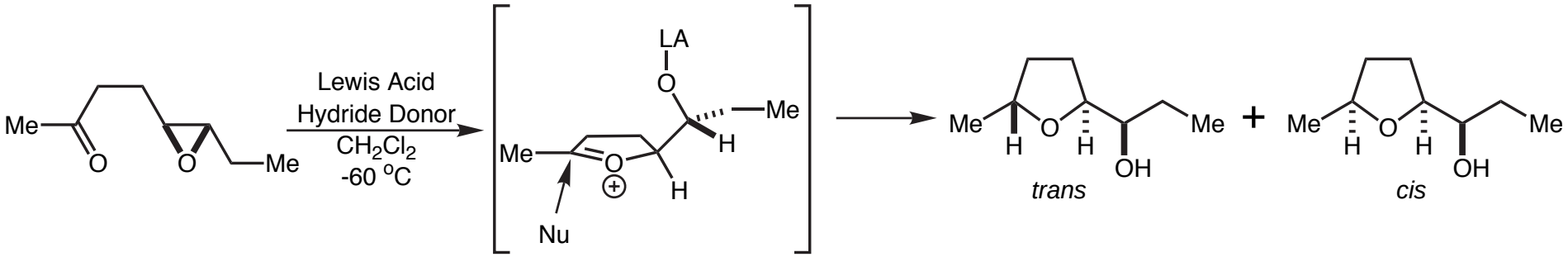
Chamberlin *et al*, *JACS*, **1987**, *109*, 672
Houk *et al*, *JACS*, **1984**, *106*, 3880

Oxonium Based Strategies



Lewis Acid	Concentration (M)	*trans* : *cis*	Yield (%)
$BH_3 \cdot SMe_2$	0.005	96 : 4	90
$BH_3 \cdot SMe_2$	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

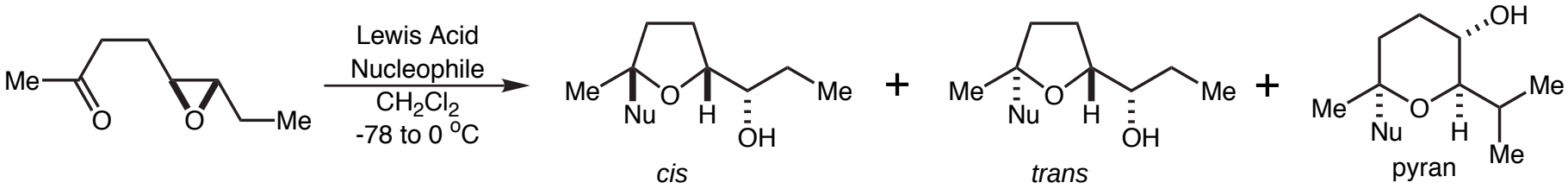


Lewis Acid	Hydride Donor	*trans* : *cis*	Yield (%)
TFA	Et_3SiH	33 : 67	90
$BF_3 \cdot OEt_2$	Et_3SiH	33 : 67	58
$BF_3 \cdot OEt_2$	Ph_3SiH	17 : 83	41
TIPSOTr	Ph_3SiH	20 : 80	85

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

Chamberlin *et al*, *JOC*, **1988**, *53*, 1082

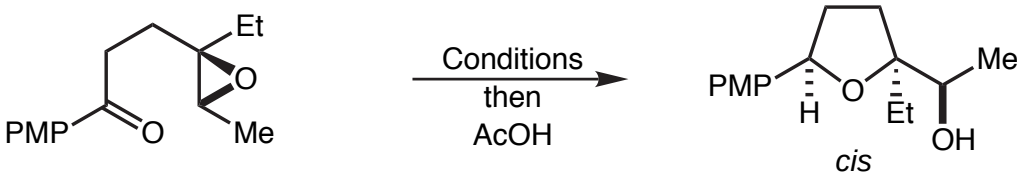
Further Extention of Chamberlin's Chemistry



Lewis Acid	Nucleophile	Combined Yield (%)	*cis*		*trans*		Pyran
$BF_3{\cdot}OEt_2$	Ph_3SiH	67	67	:	11	:	22
TMSOTf	Ph_3SiH	81	90	:	4	:	6
TMSOTf	allylsilane	80	80	:	13	:	7
$BF_3{\cdot}OEt_2$	TMSCN	68	80	:	20	:	0
$BF_3{\cdot}OEt_2$	$AlEt_3$	68	58	:	8	:	34
$BF_3{\cdot}OEt_2$	$Et_2AlCCPh$	60	88	:	12	:	0
$BF_3{\cdot}OEt_2$	Et_2AlCN	65	50	:	50	:	0

Chamberlin *et al*, *JOC*, **1991**, *56*, 4141

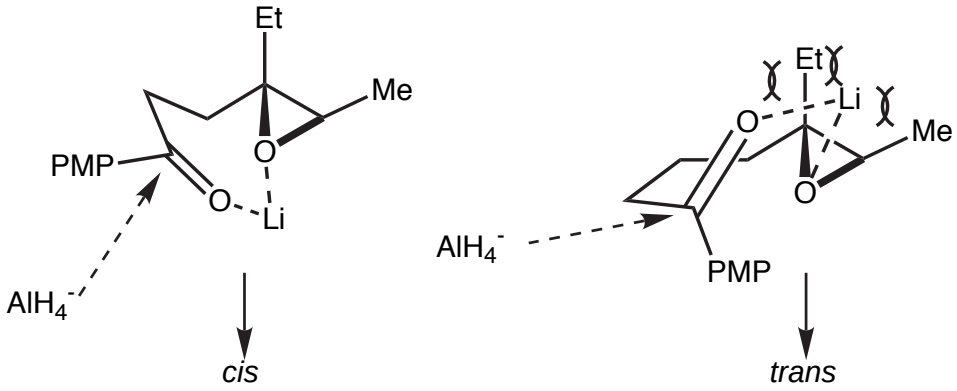
Epoxide Directed Ketone Reduction



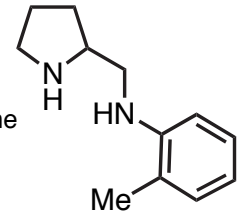
Conditions	*cis*		*trans*
$NaBH_4$, MeOH, RT	50	:	50
L-Selectride, Et_2O, RT	50	:	50
$LiAlH_4$, Et_2O, 0 °C	75	:	25
$LiAlH(O^tBu)_3$, Et_2O, 0 °C	80	:	20
$LiAlH_4$, diamine, Et_2O, -78 °C	91	:	9

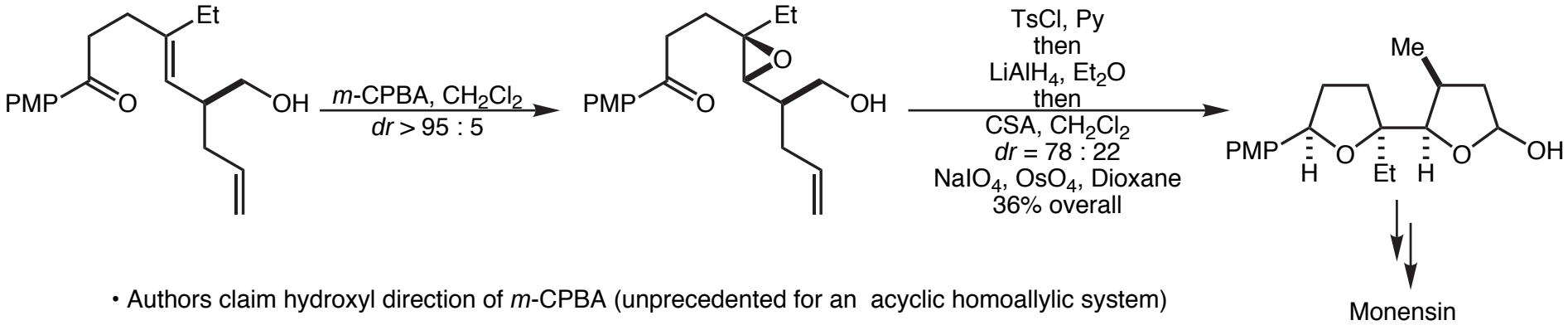
Kishi *et al*, *TL*, **1978**, *19*, 2741

Possible Rationale?



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

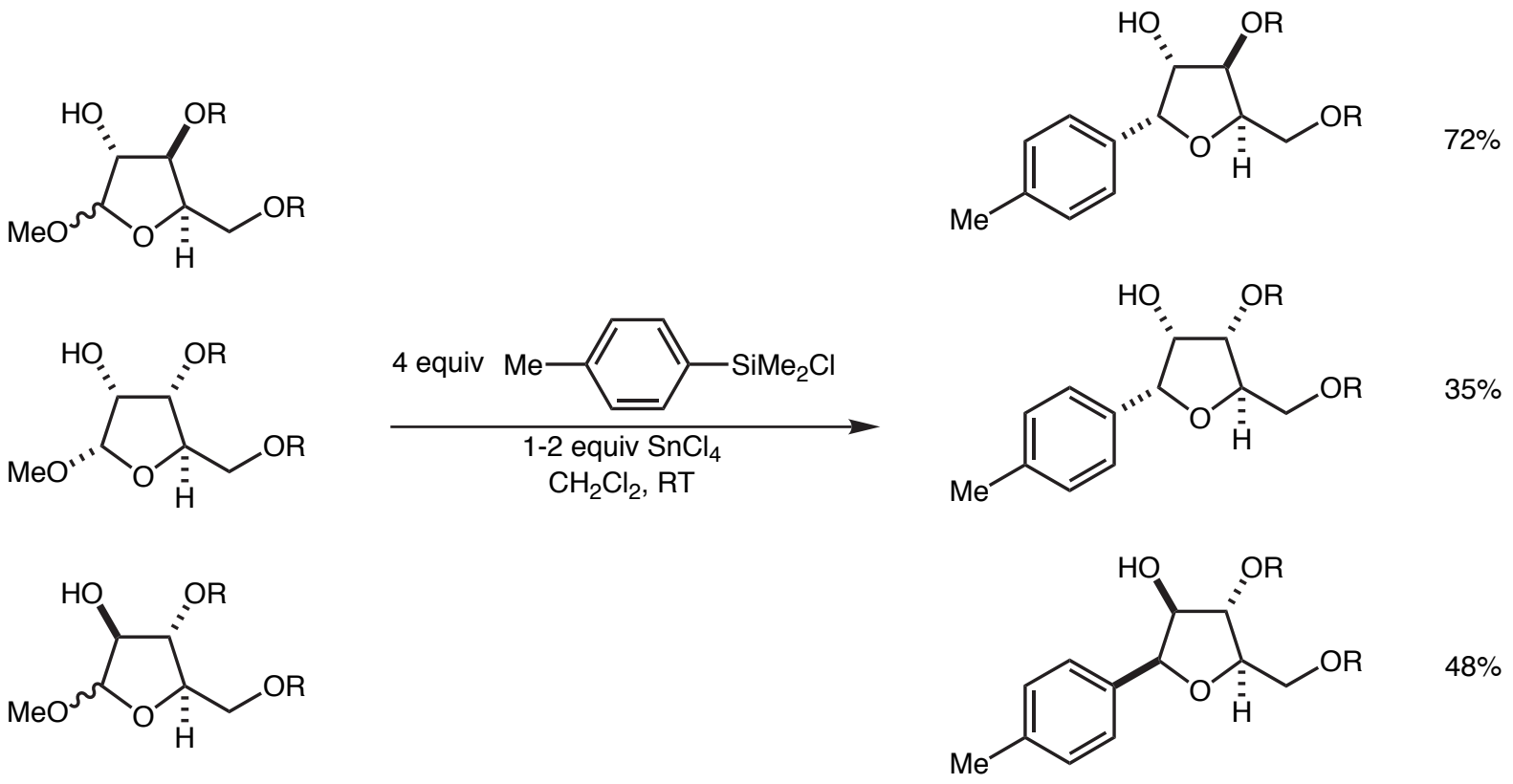




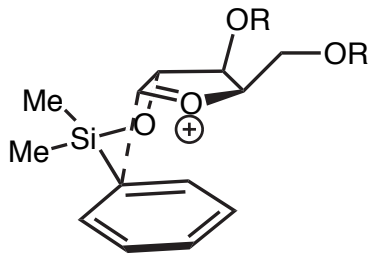
• Authors claim hydroxyl direction of *m*-CPBA (unprecedented for an acyclic homoallylic system)

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

Directed Aryl Silane Addition



R = *p*-chlorobenzyl

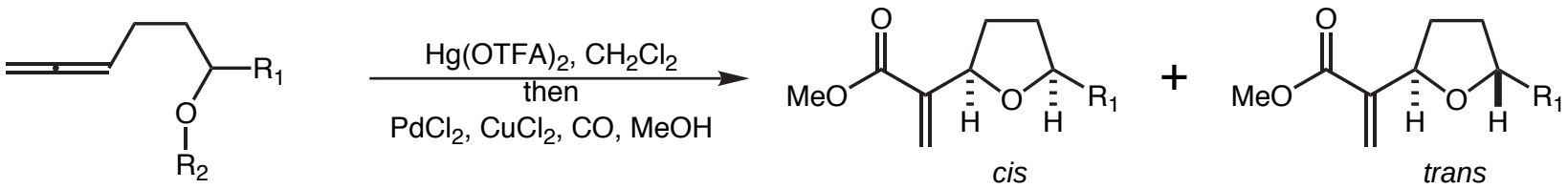


Nucleophile delivery thought to be intramolecular as :

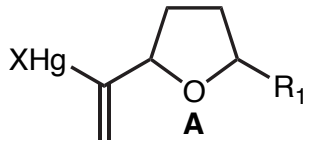
- Protection of C_2 alcohol halts reaction
- Arylsilane must have a good leaving group
- Only observed product is always *syn* to C_2 hydroxyl

Martin *et al*, *JACS*, **1988**, *110*, 8698

Intramolecular Oxymercuration



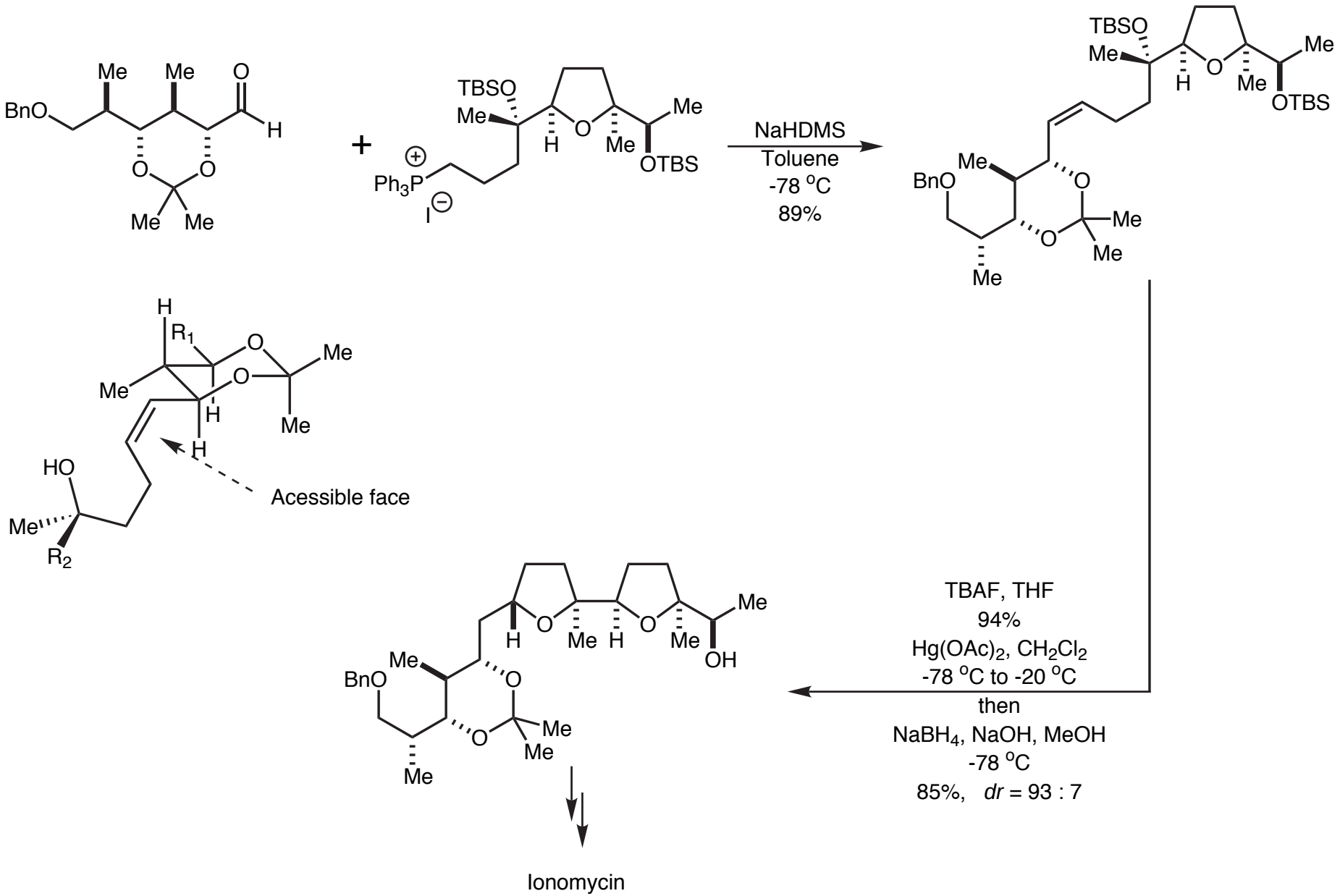
R_1	R_2	Combined Yield (%)	*cis*		*trans*
CH_3	TBS	53	94	:	6
CH_2CO^tBu	TBS	80	92	:	8
CH_2COCH_3	TBS	70	50	:	50
$CH_2CH(OH)CH_3$	TBS	67	92	:	8



- All the above substrates cyclized nonselectively when R_2 = H
- The vinylmercury species **A** readily transmetallates 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.

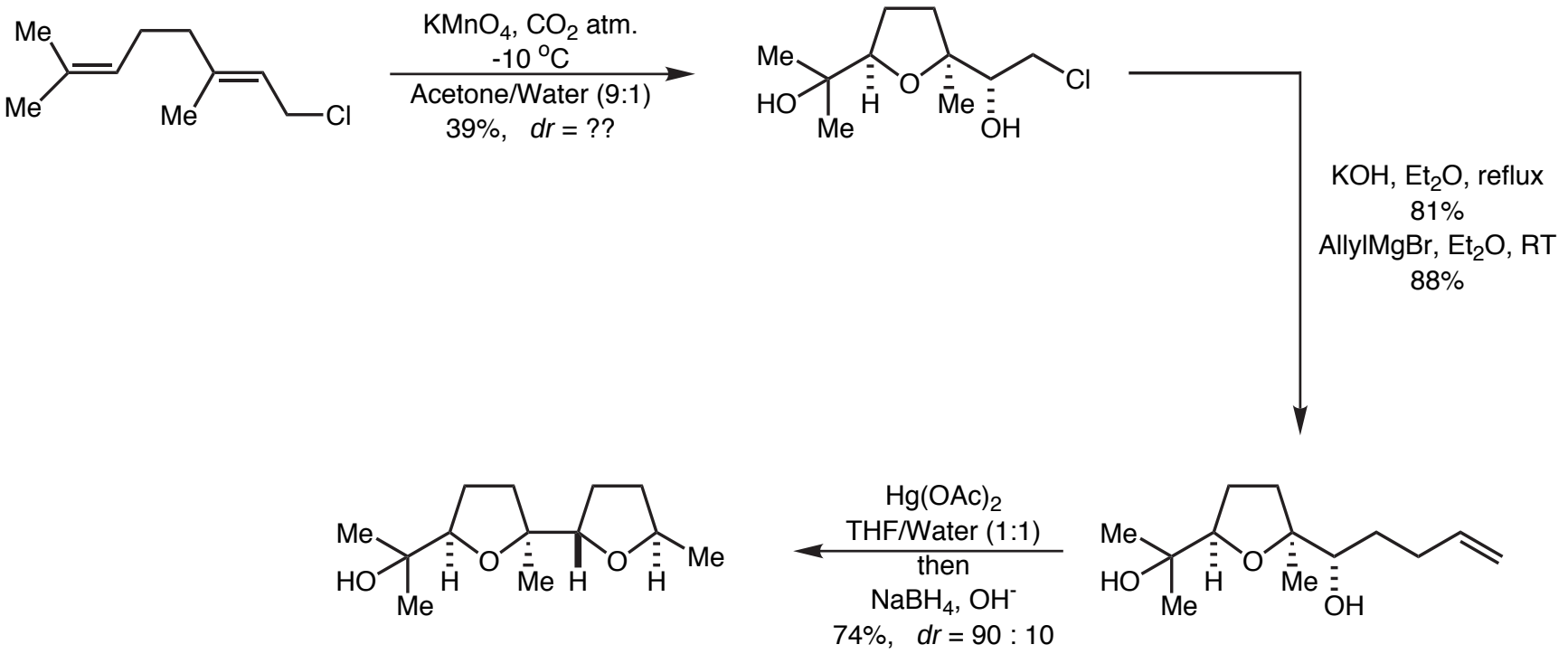
Walkup *et al*, *TL*, **1987**, *28*, 1023

Total Synthesis of Ionomycin



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

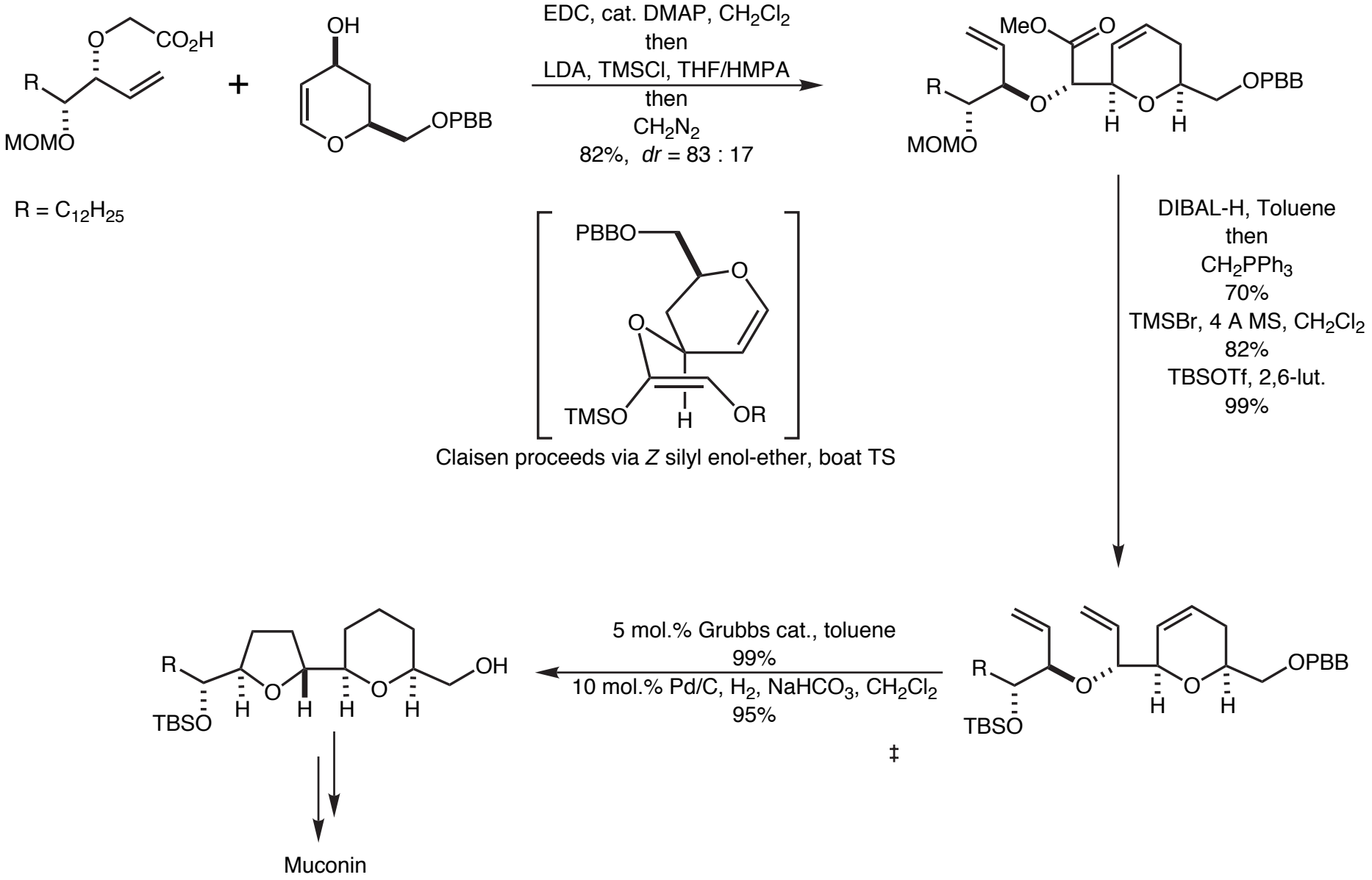
Intramolecular Oxymercuration of a Terminal Olefin



• Equilibrium driven?

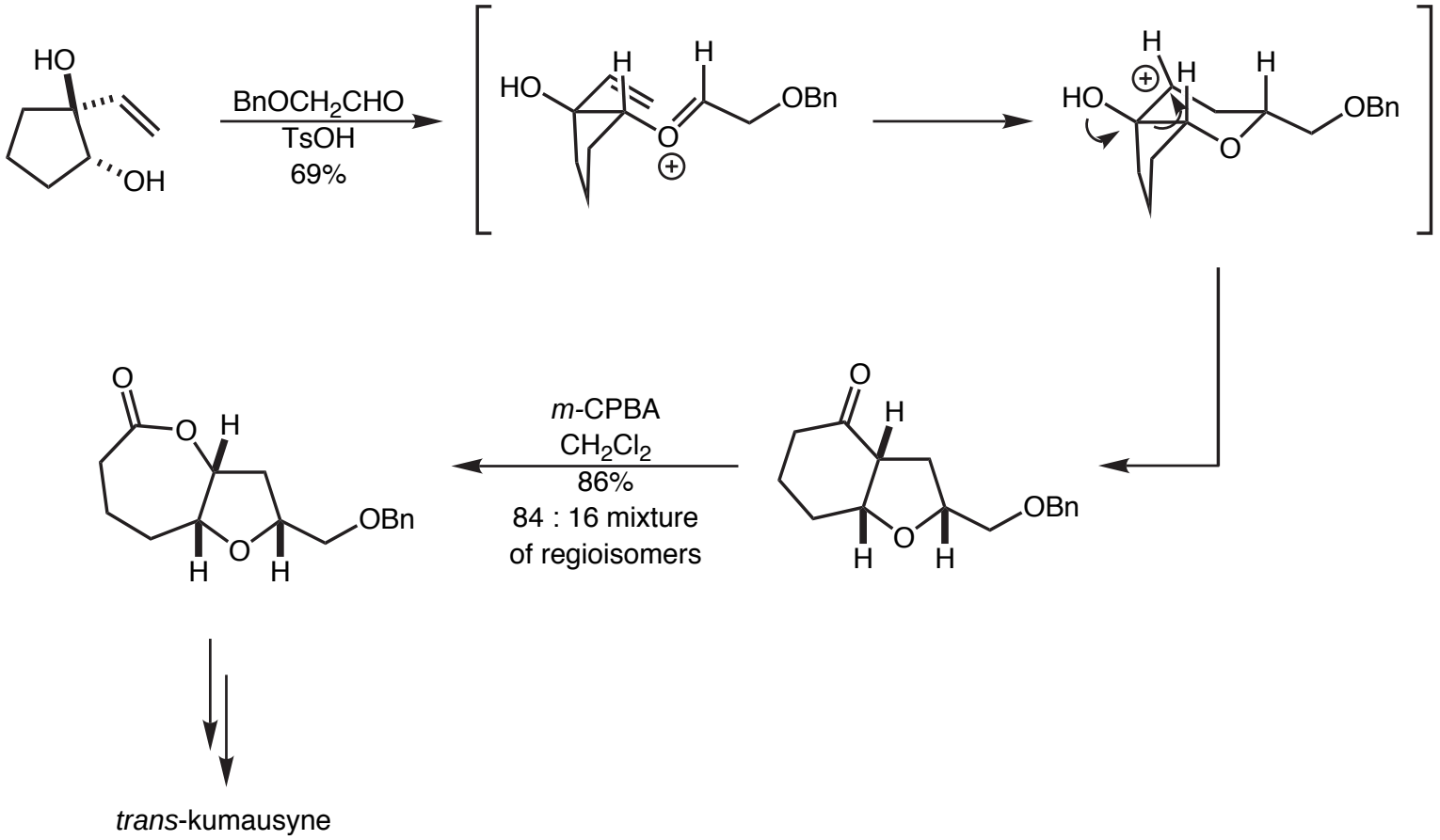
Chastrette *et al*, *TL*, **1981**, *22*, 2259

Olefin Metathesis for Tetrahydrofuran Synthesis



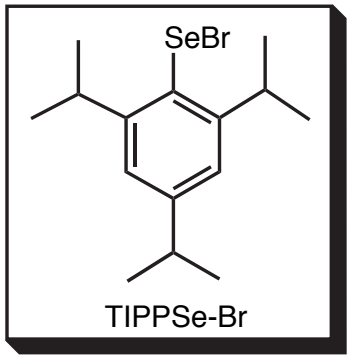
Jacobsen *et al*, *JOC*, **1998**, *63*, 4876

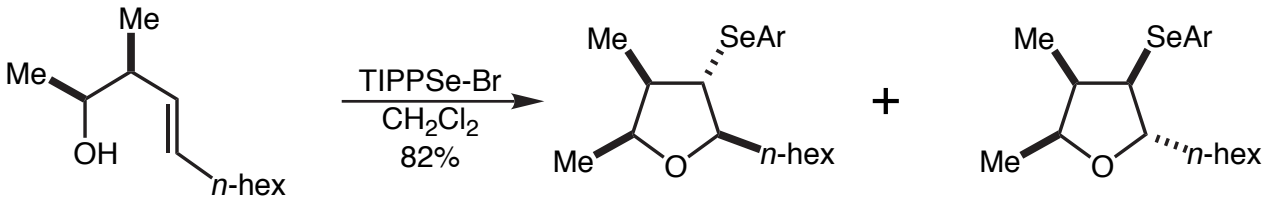
The Overman Rearrangement



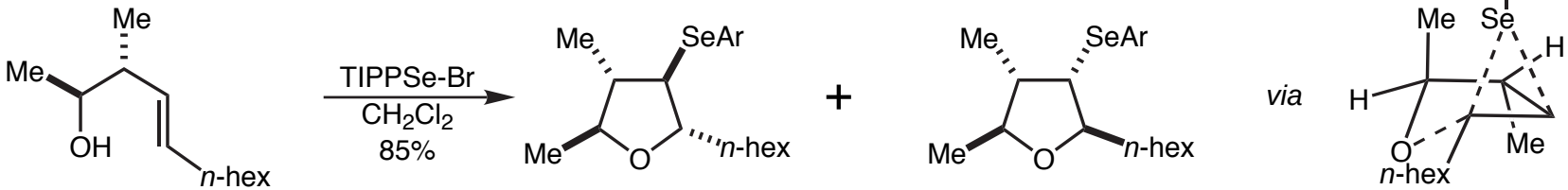
Overman *et al*, *JACS*, **1991**, *113*, 5365
Overman *et al*, *JACS*, **1991**, *113*, 5379

5-Endo *Selenocyclizations Using TIPPSe-Br*

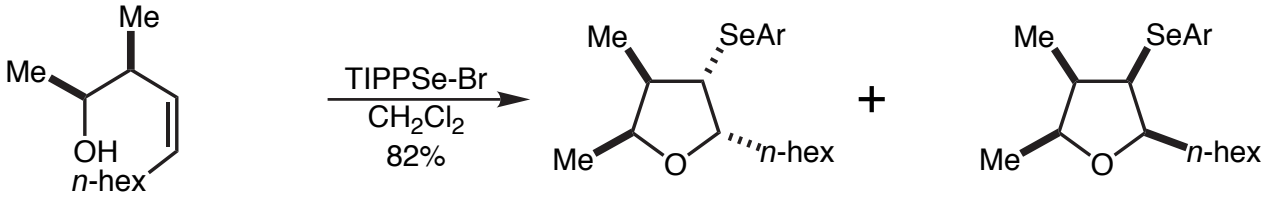




98 : 2



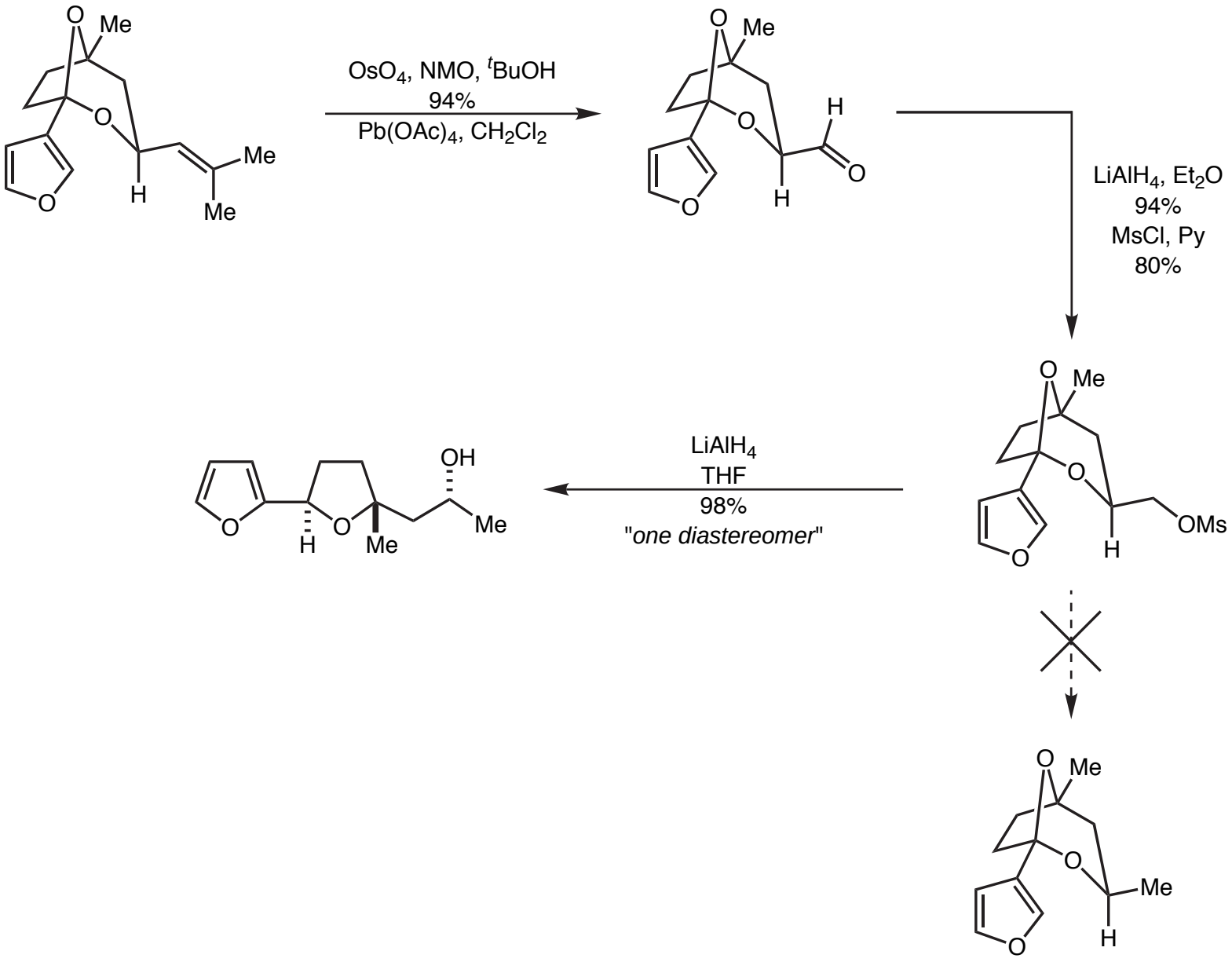
>98 : 2



98 : 2

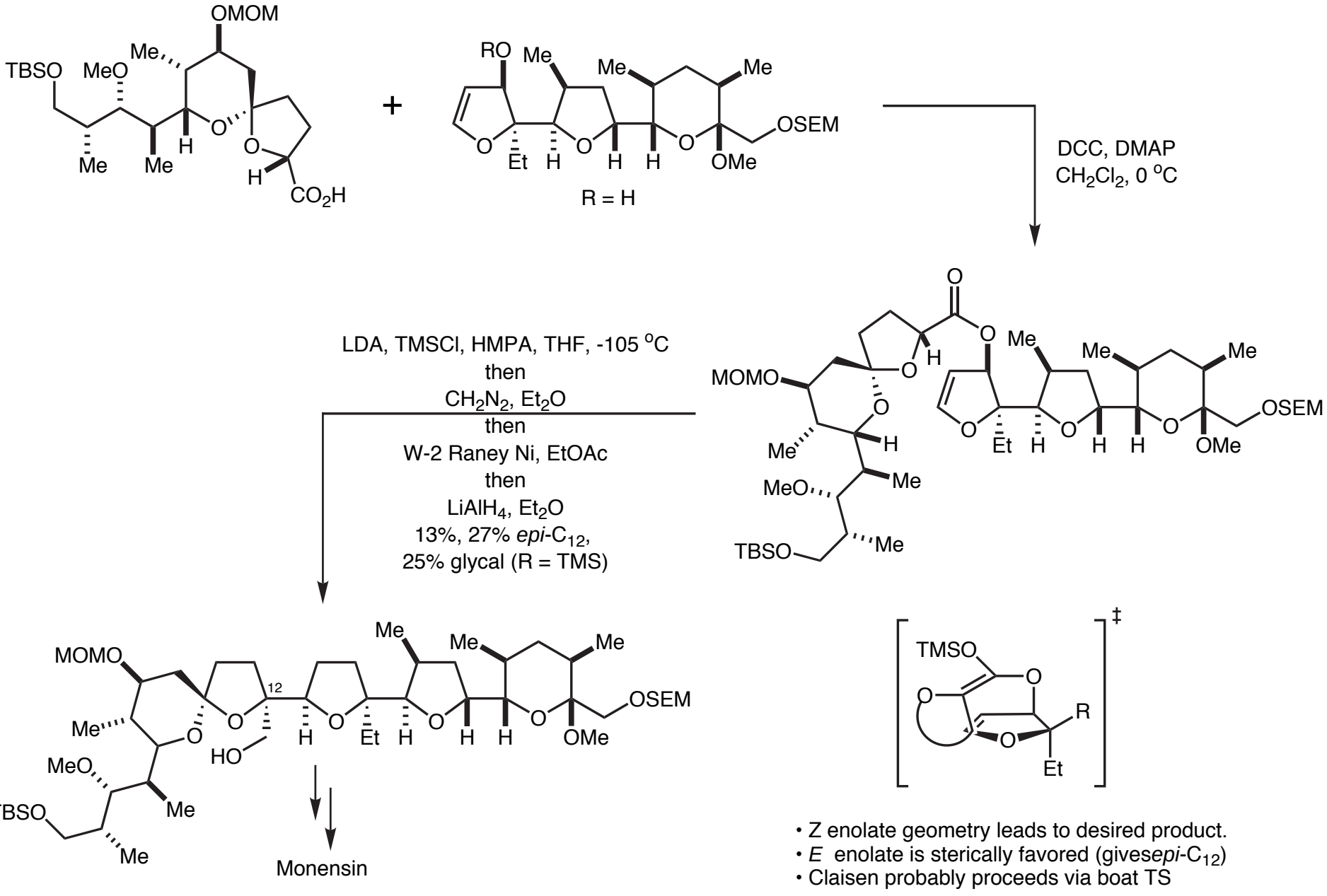
Lipshutz *et al*, *JOC*, **1995**, *60*, 3572

Bicyclic Ketal Opening



Massy-Westtropp *et al*, *Aust. J. Chem.*, **1982**, *35*, 1895

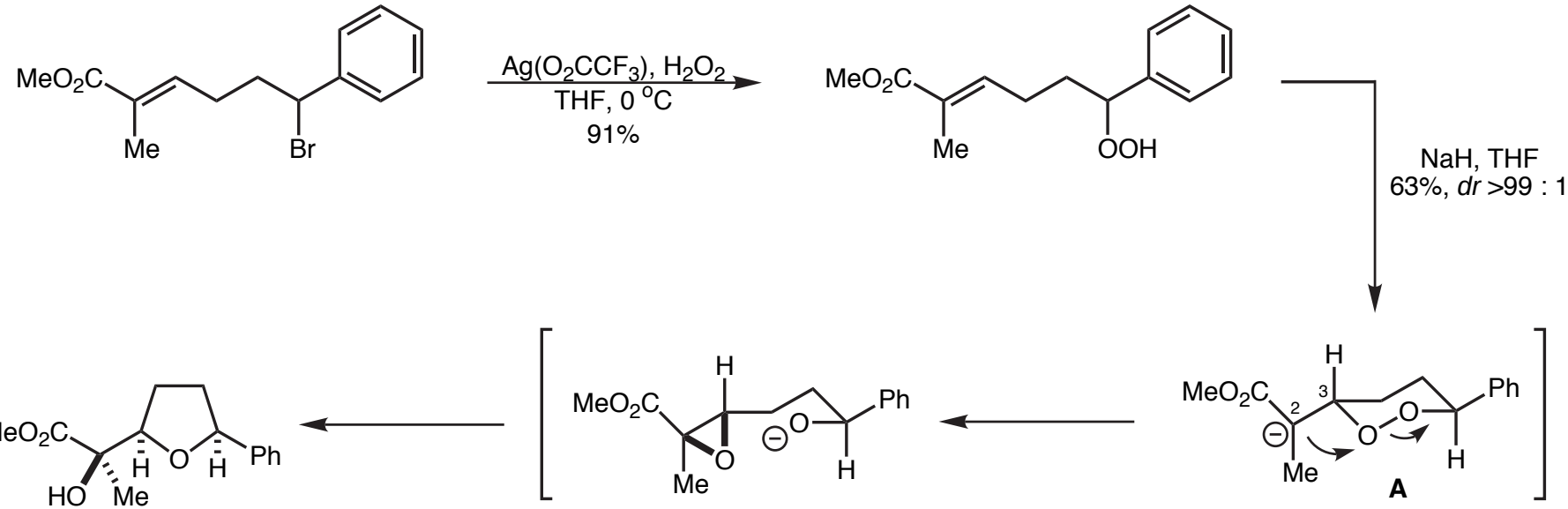
Ester Enolate Claisen Rearrangements



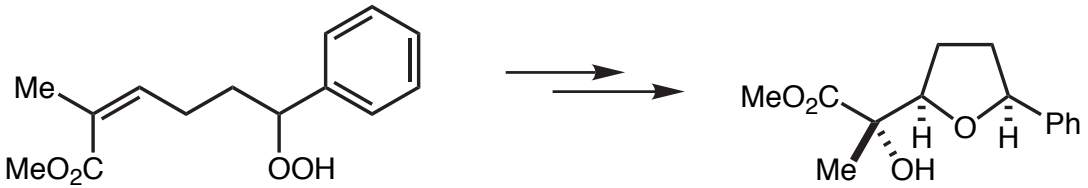
- Z enolate geometry leads to desired product.
- *E* enolate is sterically favored (gives *epi*-C_{12})
- Claisen probably proceeds via boat TS

Ireland *et al*, *JACS*, **1993**, *115*, 7152

Hydroperoxide Cyclizations



Note :

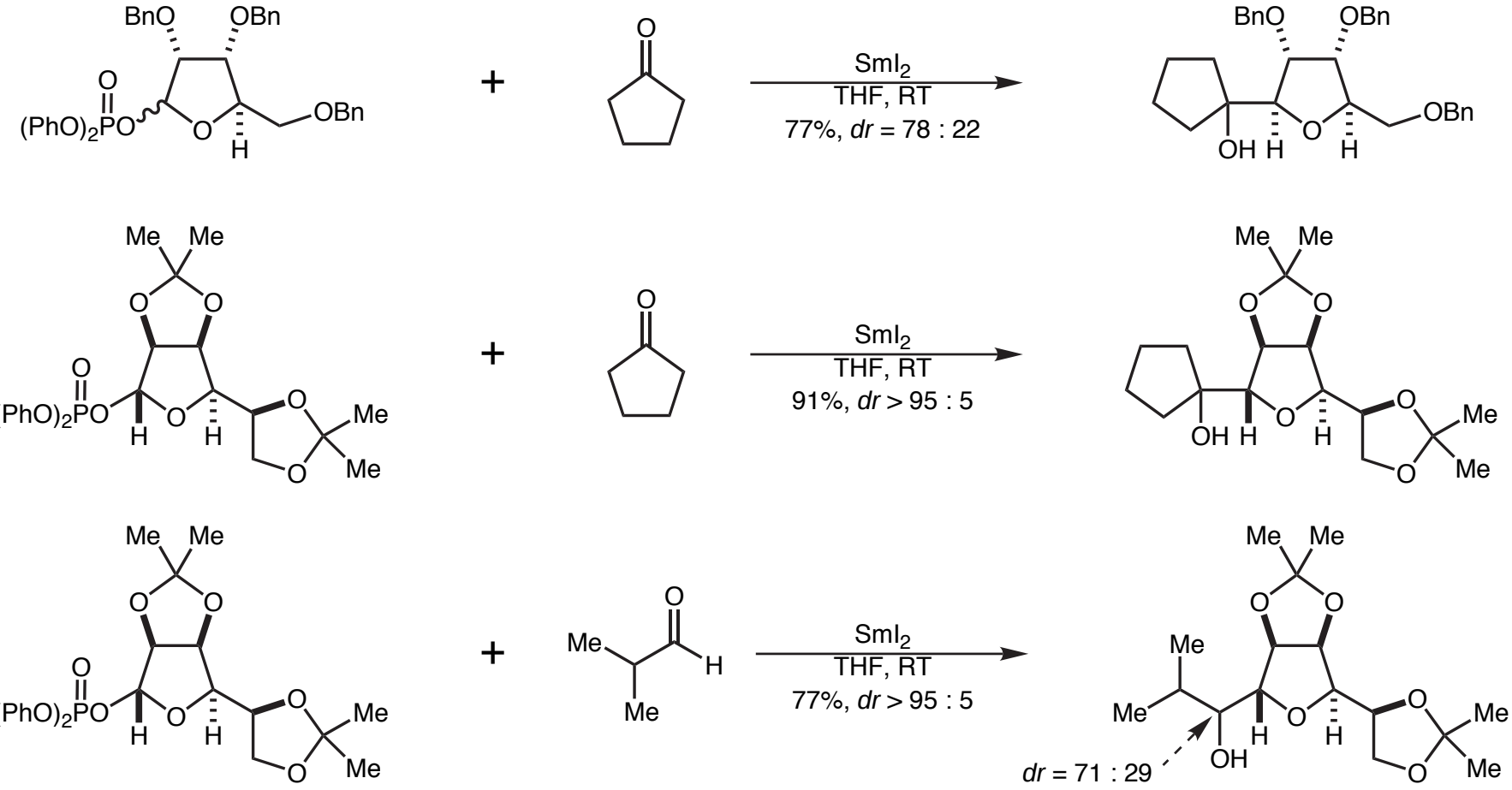


"*one diastereomer*"

These results imply that rotation about C_2-C_3 bond in **A** is slower than epoxide formation.

Bartlett *et al*, *JOC*, **1986**, *51*, 2799

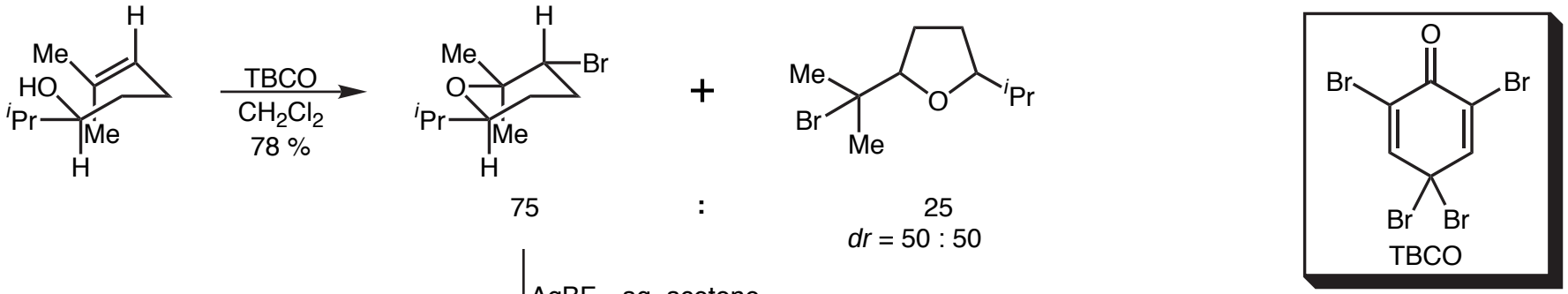
SmI_2 Mediated C-Glycoside Couplings



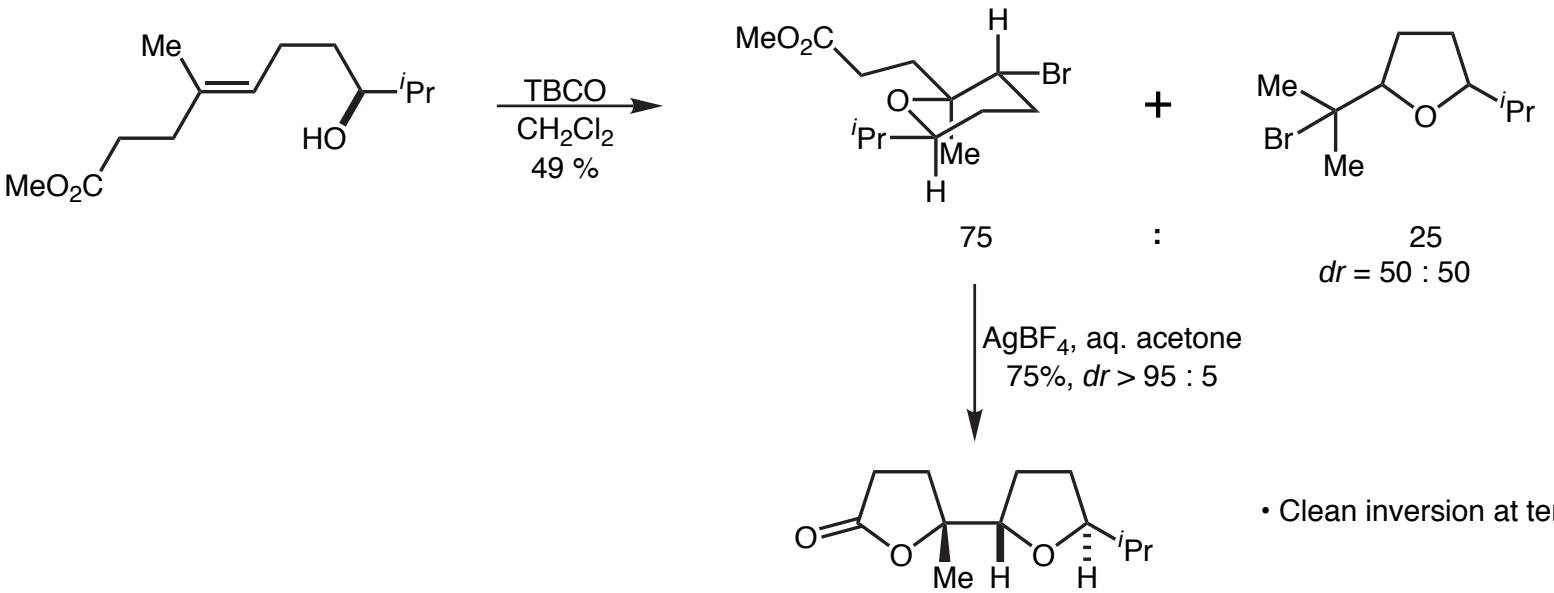
All reactions run under Barbier conditions, and are instantaneous!

Wong *et al*, *ACIEE*, **1996**, *35*, 2671

Ring Contraction of Tetrahydropyrans



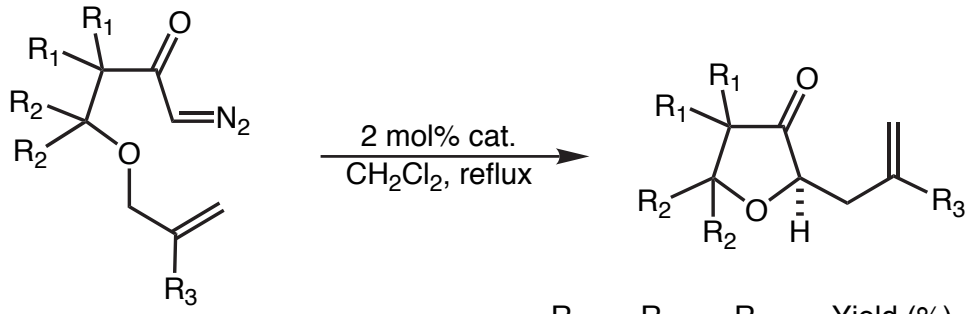
For similar, one pot TTN mediated cyclizations see:
Bartlett *et al*, *JOC*, **1985**, *50*, 2416

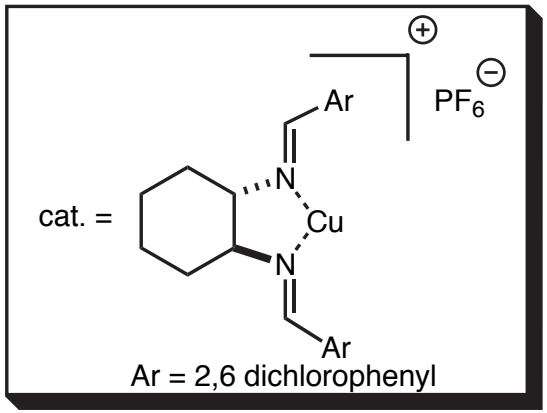


• Clean inversion at tertiary center!

Bartlett *et al*, *JACS*, **1984**, *106*, 2668

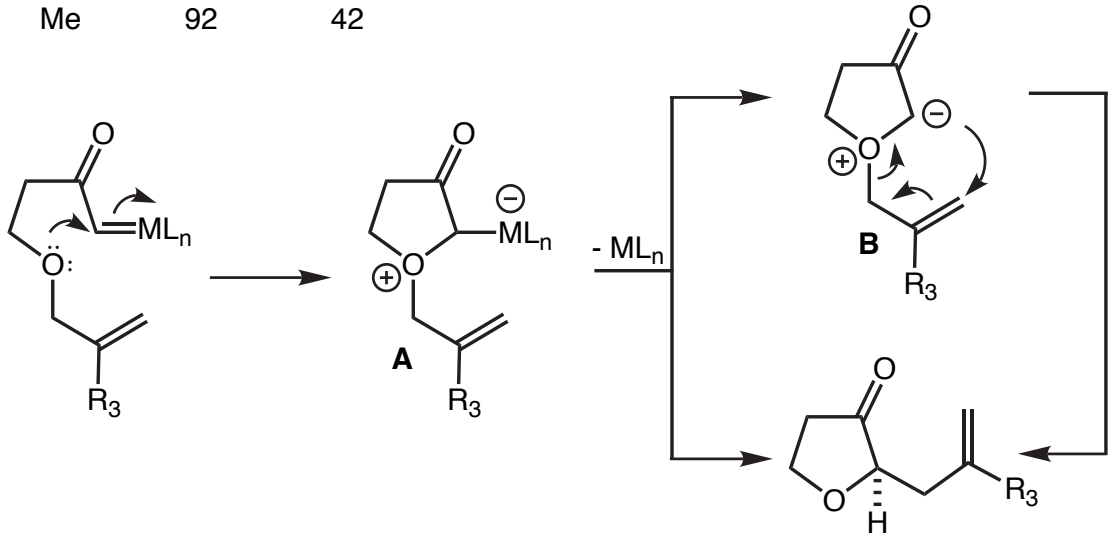
A Catalytic, Modestly Enantioselective Method





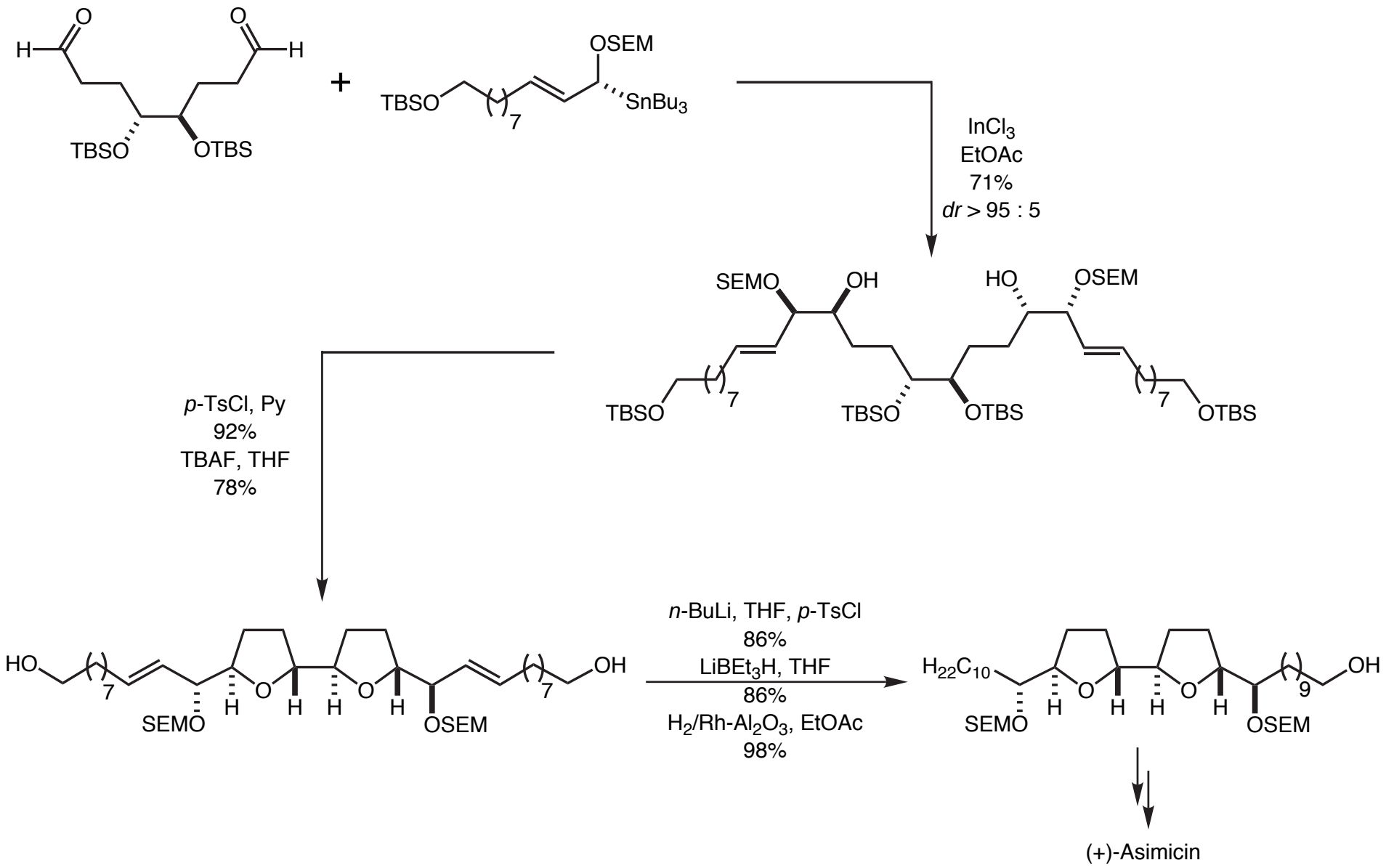
R_1	R_2	R_3	Yield (%)	*ee* (%)
H	H	H	62	57
Me	H	H	57	56
H	Me	H	54	23
H	H	Me	62	6
Me	H	Me	92	42

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



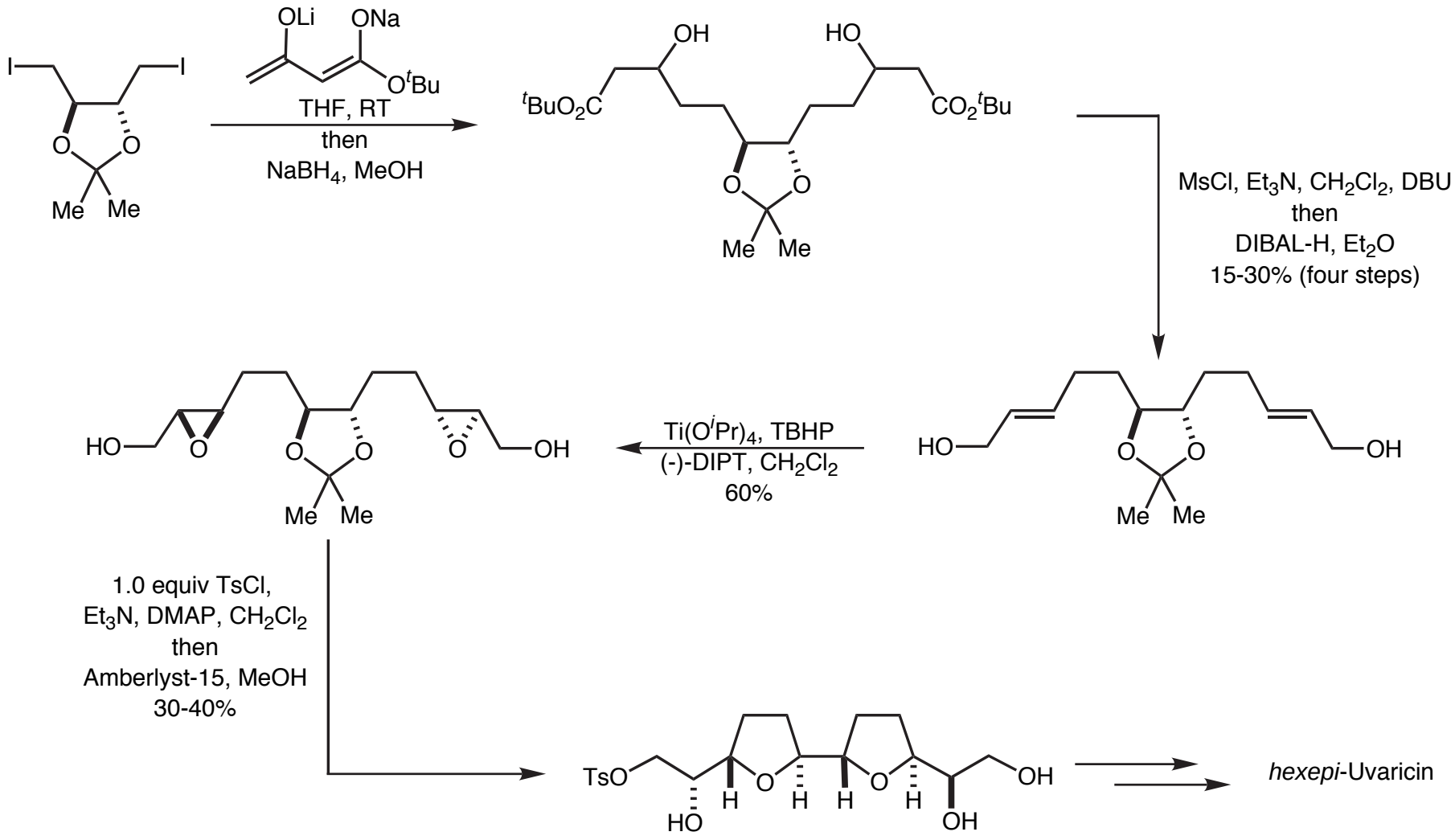
Clark *et al*, *TL*, **1998**, *39*, 97

Bidirectional Approach via *Tosylate Displacement*



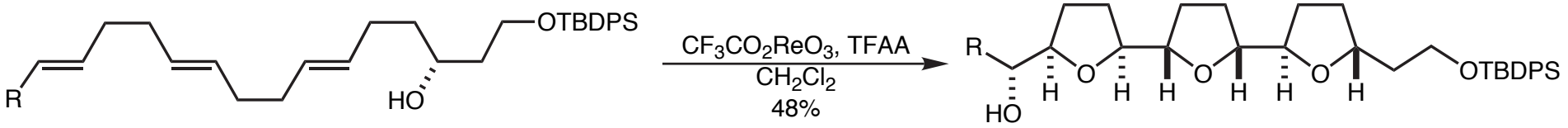
Marshall *et al*, *JOC*, **1997**, *62*, 5989

Bidirectional Synthesis via *Epoxide Opening*

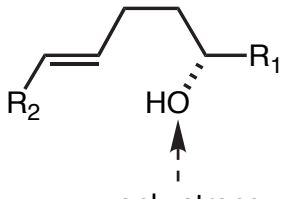


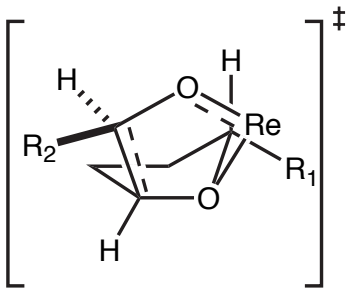
Hoye *et al*, *JACS*, **1991**, *113*, 9369

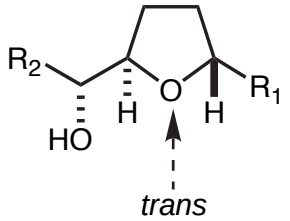
Tandem Oxidative Cyclizations Using Re(VII) Oxides

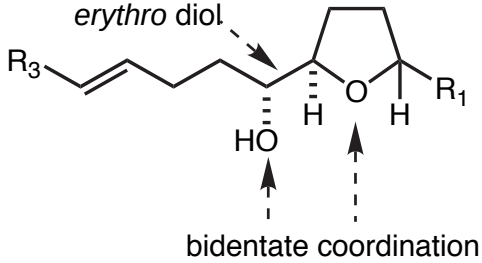


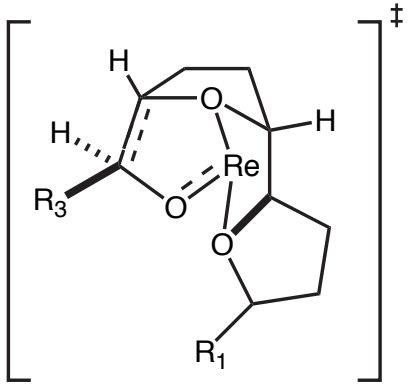
Cyclization Rules :

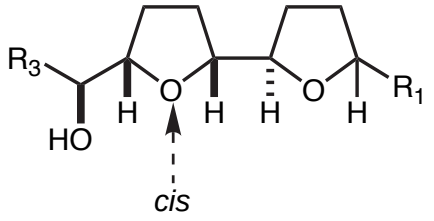


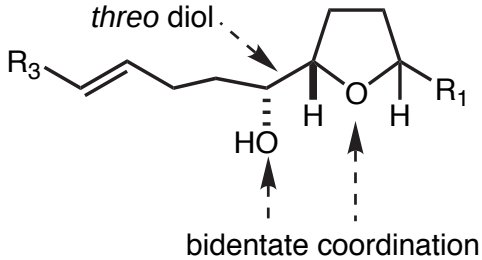


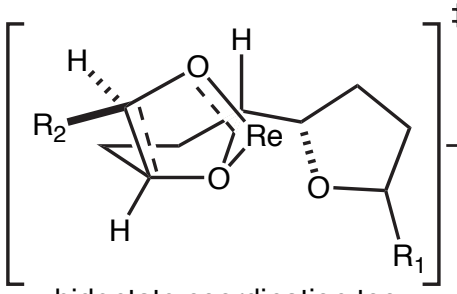


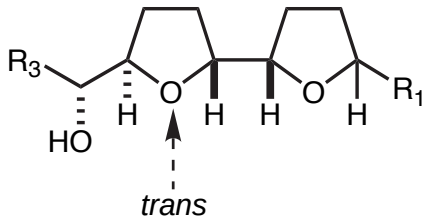












Keinan *et al*, *JACS*, **1998**, *120*, 9076
Mcdonald *et al*, *JOC*, **1997**, *119*, 6022