

Recent Progress in Macrocyclizations

by Essa Hu

Evans Group Seminar

December 3, 1999

Reviews:

Direct ring closure:

Weber, E.; Vogtle, F. *Topics in Current Chemistry*; Springer-Verlag: Germany, **1992**; vol. 161, pp109-176

Large ring syntheses:

Roxburgh, C. *Tetrahedron* **1995**, 51, 9767-9822

Macrolide syntheses:

Paterson, I.; Norcross, R. D. *Chem. Rev.* **1995**, 95, 2041-2114

Macrocyclic musks syntheses:

Williams, A. S. *Synthesis* **1999**, 10, 1707-1723

Photochemical macrocyclizations:

Griesbeck, A. G.; Henz, A.; Hirt, J. *Synthesis* **1996**, 1261-1276

Ester activation and peptide coupling:

Katz, J. *Evans Group Seminar* Dec. **1998**

A-----B

Defining the Scope of This Presentation*

Field of Macrocyclizations:

I. Ring size: "Macrocycle" = medium rings (8-11), large rings (12+)*, supramolecules

II. Types of rings:

- natural products*
- polymers (polyethers, polyamines, etc.)
- polydentate molecules
- others

III. Approaches to ring construction:

- direct ring closure*
- ring enlargement/expansion
- ring contraction
- tandem macrocyclization-transannulation

IV. Medium of cyclization:

- homogeneous organic solvent*
- heterogeneous
- enzymatic
- solid phase
- zeolite

Ring Strain

Strain = observed heat of formation (or combustion) - calculated heat of formation (or combustion)

TABLE 11.4. Heat of Combustion and Ring Strain for Cyclanes.

Size of Ring (<i>n</i>)	Heat of Combustion ^a		Total Strain		Strain per CH ₂ ^d	
	(kcal mol ⁻¹)	(kJ mol ⁻¹)	(kcal mol ⁻¹) ^b	(kJ mol ⁻¹) ^c	(kcal mol ⁻¹)	(kJ mol ⁻¹)
3	499.83	2091.3	27.5	115.1	9.17	38.4
4	656.07	2745.0	26.3	110.1	6.58	27.5
5	793.40	3319.6	6.2	26.0	1.24	5.19
6	944.77	3952.9	0.1	0.5	0.02	0.09
7	1108.3	4637.3	6.2	26.2	0.89	3.74
8	1269.2	5310.3	9.7	40.5	1.21	5.06
9	1429.6	5981.3	12.6	52.7	1.40	5.86
10	1586.8	6639.1	12.4	51.8	1.24	5.18
11	1743.1	7293.3	11.3	47.3	1.02	4.30
12	1893.4	7921.9	4.1	17.2	0.34	1.43
13	2051.9	8585.0	5.2	21.5	0.40	1.66
14	2206.1 ^e	9230.9 ^e	1.9	8.0	0.14	0.57
15	2363.5	9888.7	1.9	7.8	0.13	0.51
16	2521.0	10547.7	2.0	8.0	0.12	0.50
17	2673.2	11184.5	-3.3	-13.9	-0.19	-0.82

^a Gas phase values. From *TRC Thermodynamic Tables* (1991), p. n-1960.

^b Heat of combustion minus 157.44*n*.

^c Heat of combustion minus 658.7*n*.

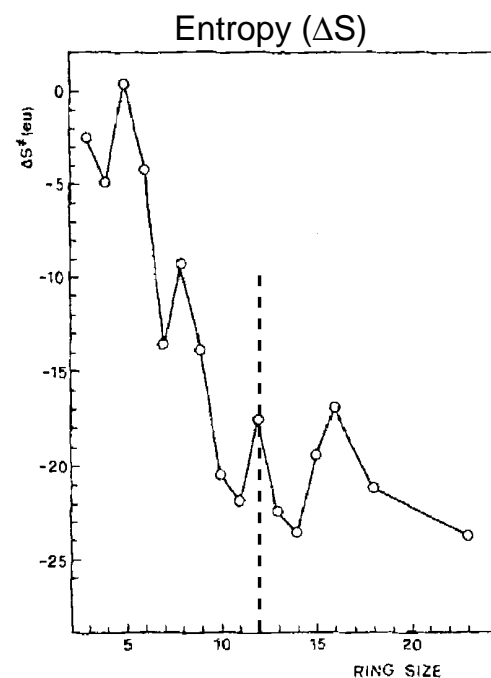
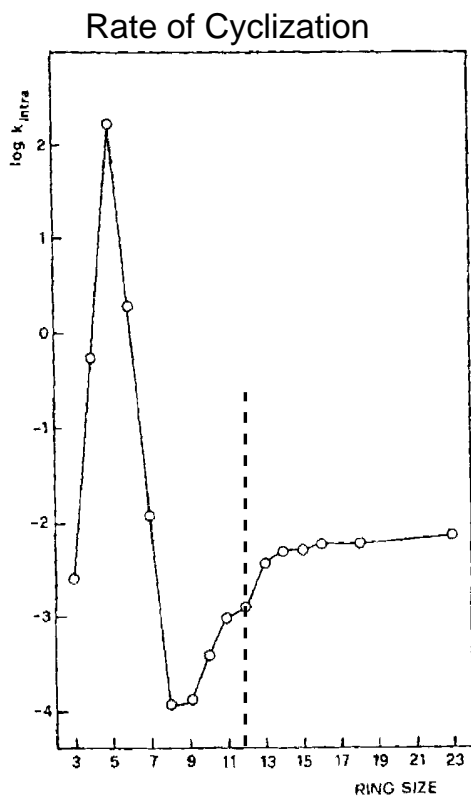
^d Total strain divided by *n*.

^e Corrected values: see Chickos, J. S., Hesse, D. G., Panshin, S. Y., Rogers, D. W., Saunders, M., Uffer, P. M., and Liebman, J. F. (1992). *J. Org. Chem.*, **57**, 1897.

==> Large rings have low ring strain.

Ease of Cyclization

Kinetics of cyclizing ω -bromoacids $\text{Br}(\text{CH}_2)_n\text{CO}_2\text{H}$:



==> Synthesis of large rings still a synthetic challenge
To cyclize: both end terminus need to overcome their high conformational entropy
Competing routes: dimerization or oligomerization

Other Cyclization Series

Kinetics of ring formation, comparison with related cyclization series:

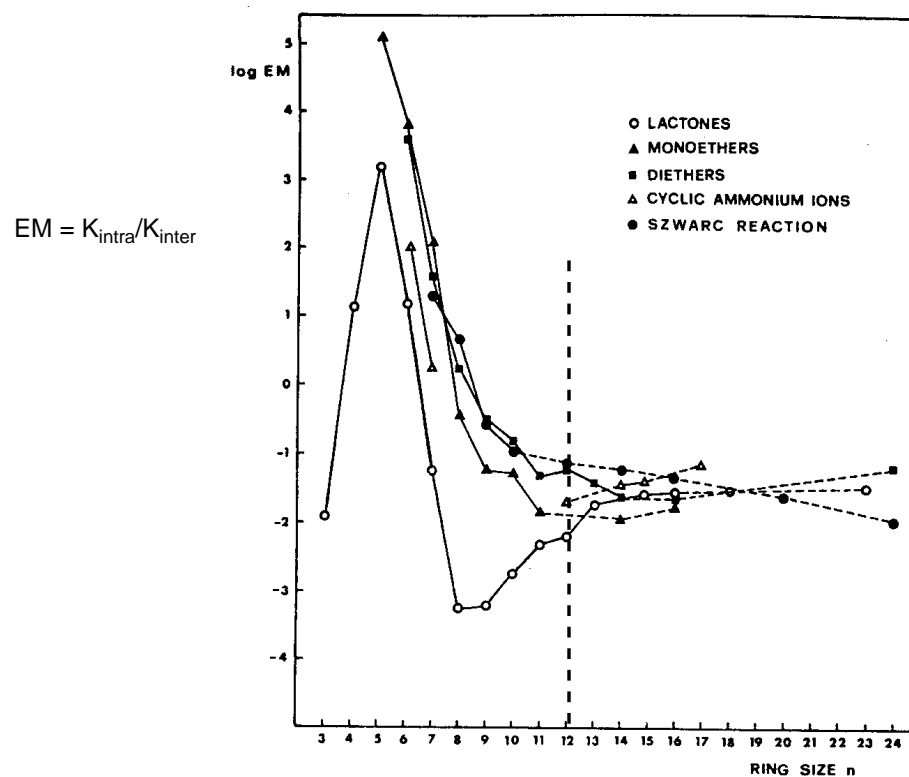


Figure 4. EM profiles vs. ring size for different cyclization reaction series. Data from different sources (see Table III).

==> Similar ring formation kinetics for other cyclization series.

Thorpe-Ingold Effect

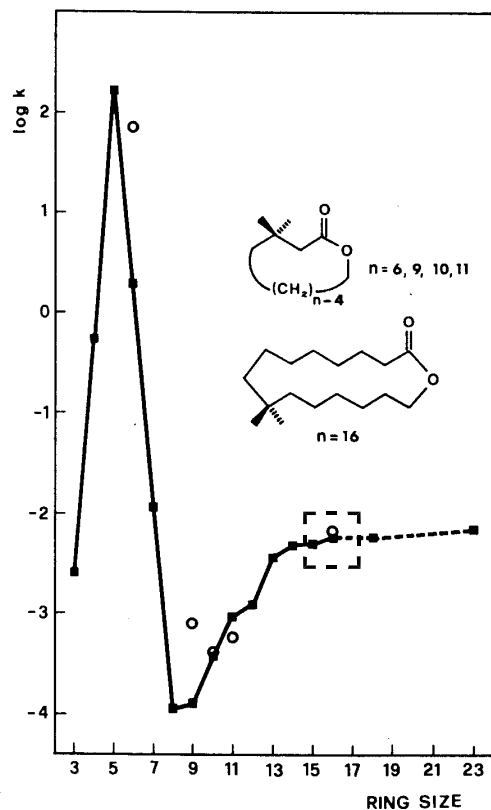


Figure 1. Plot of the *gem*-dimethyl effect on lactone formation from ω -bromoalkanoate ions in 99% aqueous Me_2SO at 50.0 °C: (○) *gem*-dimethyl compounds (this work); (■) unsubstituted compounds (ref 1 and 3b).

Table III. *gem*-Dimethyl Effect on the Rate of Lactone Formation from the Potassium Salts of ω -Bromo Acids in 99% Aqueous Me_2SO at 50.0 °C

ω -bromo acid	n^a	k, s^{-1}	ref	k_{rel}^b
$\text{Br}(\text{CH}_2)_2\text{C}(\text{CH}_3)_2\text{-CH}_2\text{CO}_2\text{H}$	6	72.4 ^c	this work	38.5
5-bromopentanoic	6	1.88	1	1.0
$\text{Br}(\text{CH}_2)_5\text{C}(\text{CH}_3)_2\text{-CH}_2\text{CO}_2\text{H}$	9	8.21×10^{-4}	this work	6.62
8-bromooctanoic	9	1.24×10^{-4}	3b	1.0
$\text{Br}(\text{CH}_2)_6\text{C}(\text{CH}_3)_2\text{-CH}_2\text{CO}_2\text{H}$	10	4.22×10^{-4}	this work	1.13
9-bromononanoic	10	3.72×10^{-4}	3b	1.0
$\text{Br}(\text{CH}_2)_7\text{C}(\text{CH}_3)_2\text{-CH}_2\text{CO}_2\text{H}$	11	5.75×10^{-4}	this work	0.61
10-bromodecanoic	11	9.45×10^{-4}	3b	1.0
$\text{Br}(\text{CH}_2)_6\text{C}(\text{CH}_3)_2\text{-(CH}_2)_7\text{CO}_2\text{H}$	16	7.06×10^{-3}	this work	1.22
15-bromopentadecanoic	16	5.77×10^{-3}	3b	1.0

^a Ring size of the ring to be formed. ^b Evaluated from the ratio of the substituted over the unsubstituted bromo acid with the same chain length. ^c See text.

==> An isolated *gem* dialkyl substitution has little influence on the cyclization of large rings.

Promoting Intramolecular Cyclization

Ways to favor Intramolecular over Intermolecular reaction pathways:

I. High dilution effect:

=> goal: minimize the concentration of reacting species

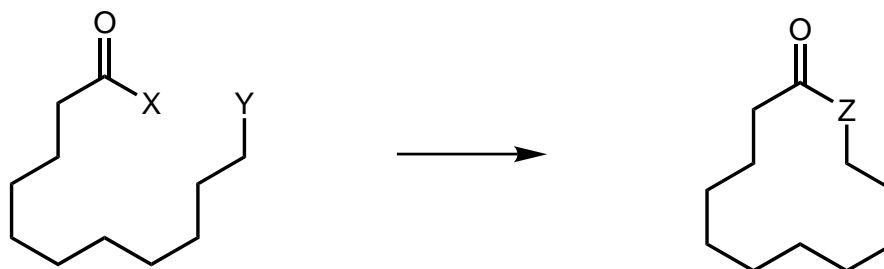
- very low reaction concentration
- high reaction temperature
- slow addition of substrate
- heterogeneous reactions: use of a low solubility component or phase transfer catalyst
- high pressure conditions (increases viscosity of reaction medium)
- catalyst on polymer support

II. Lowering the substrate entropy via conformational control:

=> goal: bring the two reacting ends to close proximity

- rigid group principle: use of functional groups and/or protecting groups
- template-directing effect

Macrocyclization I : via carbonyl formation



Lactonization & Lactamization

Industrial approaches
Activated ester methods
Corey Method
Mukaiyama Method
Keck's modified procedure
Masamune Method
Mixed anhydride methods
Yamaguchi Method
BOP-Cl
Mitsunobu Method
Ketene trapping method
 β -lactam opening
Photocyclization

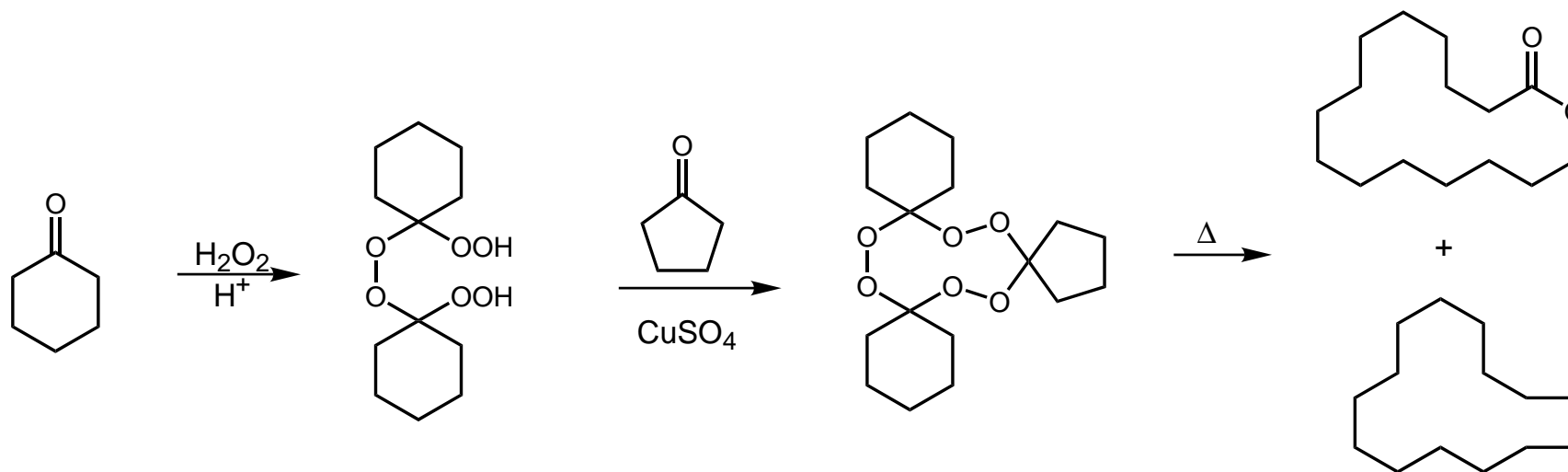
Ketone Formation

Free-radical cyclization
Stork-Takahashi Method

Industrial approaches: thermal decomposition

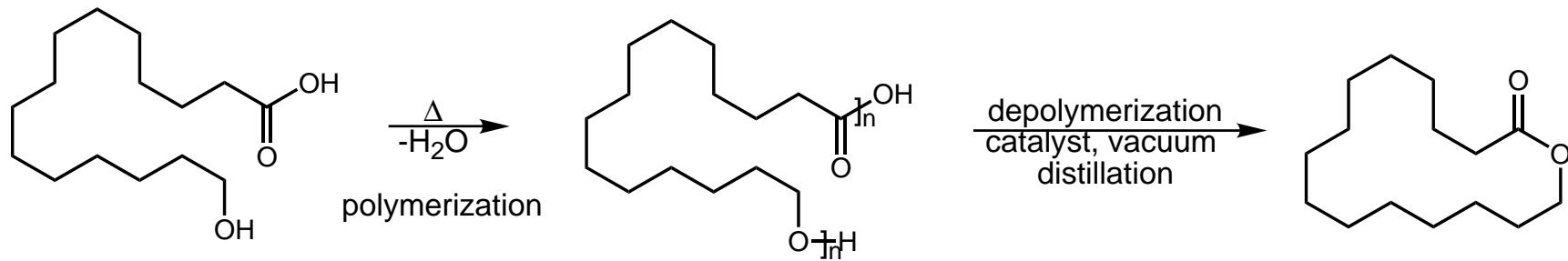
"Story" synthesis

for synthesis of Exaltolide, most widely produced macrocyclic musk lactone, 200 tons 1996

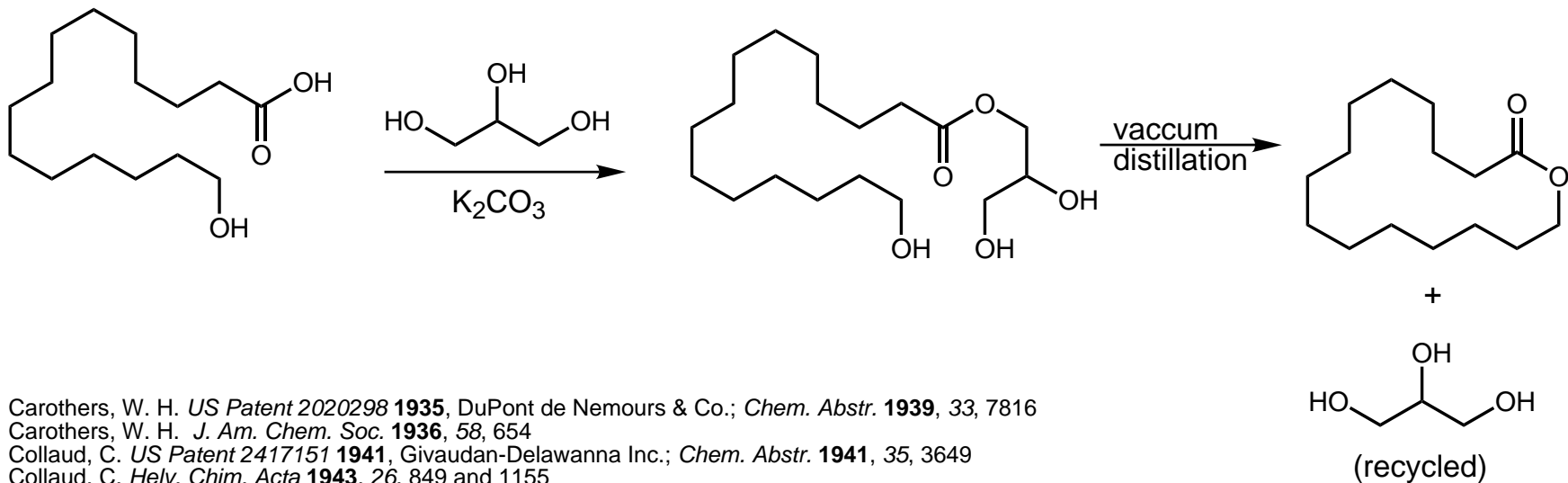


Story, P. *J. Am. Chem. Soc.* **1968**, 90, 817; *J. Org. Chem.* **1970**, 35, 3059
Story, P. *US Patent 3925421* **1973**, Research Corp.; *Chem. Abstr.* **1976**, 84, 73673
Story, P. *US Patent 3776926* **1968**, Research Corp.; *Chem. Abstr.* **1972**, 77, 61273

Industrial approaches 2: distillation



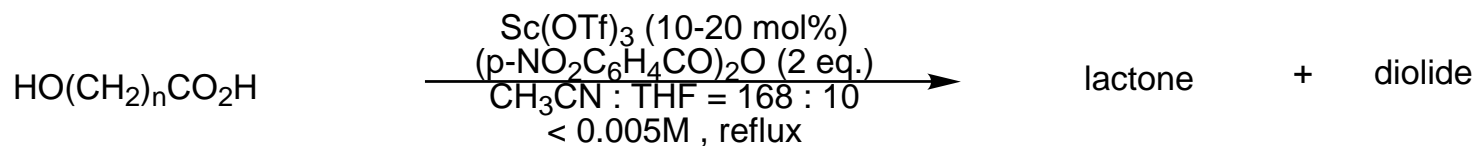
catalyst examples: Bu_2SnO , MgCl_2 , $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, $\text{Ti}(\text{OBu})_4$, PbO , $(\text{MeO})_3\text{Al}$



Carothers, W. H. *US Patent 2020298* **1935**, DuPont de Nemours & Co.; *Chem. Abstr.* **1939**, 33, 7816
 Carothers, W. H. *J. Am. Chem. Soc.* **1936**, 58, 654
 Collaud, C. *US Patent 2417151* **1941**, Givaudan-Delawanna Inc.; *Chem. Abstr.* **1941**, 35, 3649
 Collaud, C. *Helv. Chim. Acta* **1943**, 26, 849 and 1155
 Kohler, G. *EP Patent 739889* **1996**, Huls A.G.; *Chem. Abstr.* **1996**, 125, 329885

Yamamoto's Method

Yamamoto: "To our knowledge, this is the most selective monomeric lactonization method available..."



ring size	Sc(OTf) ₃ (mol%)	addn time (hr)	reaction time (hr)	yield (%) lactone	yield (%) diolide
7	20	15	5	>99	<1
8	20	15	5	71	<1
9	20	15	5	52	3
10	20	15	5	87	<5
11	20	15	5	77	2
12	10	15	0	78	2
13	10	6	0	91	3
14	10	15	5	94	<1
15	10	15	5	99	<1
16	10	9	0	99	<1
17	10	9	0	92	<1

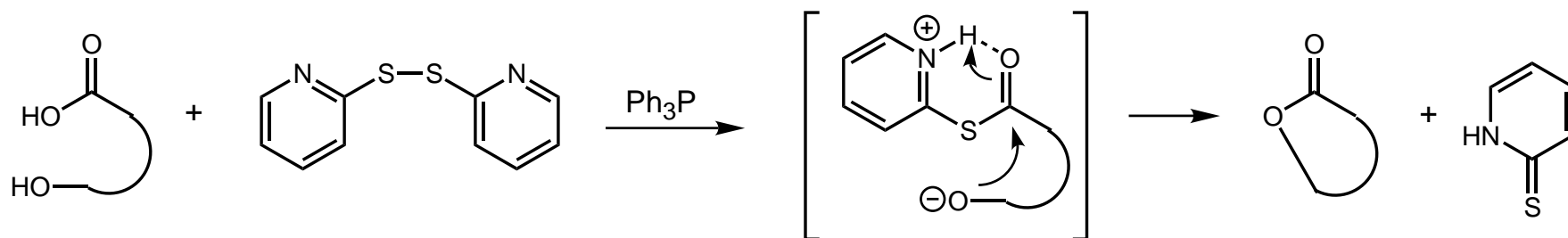
Lactonization Comparisons

Table 8. Comparison of Yield (%) in the Selective Lactonization of ω -Hydroxy Carboxylic Acids Using Typical Reagents^a

reagents	n ^b											
	5	6	7	8	9	10	11	12	13	14	15	
acidic												
Sc(OTf) ₃ /(4-NO ₂ C ₆ H ₄ CO) ₂ O	>99 (<1)	71 (<1)	52 (3)	87 (<5)	77 (2)	78 (2)	91 (3)	94 (<1)	99 (<1)	99 (<1)	92 (<1)	
TiCl ₄ (OTf) ₂ /TMSCl(4-CF ₃ C ₆ -H ₄ CO) ₂ O ^d						56 (29)	83 (10)	80 (5)	89 (3)	88 (10)	88 (2)	
TiCl ₄ -2AgClO ₄ /(4-CF ₃ C ₆ H ₄ CO) ₂ O ^{e,f}	70 (0)	0 (50)	0 (40)	33 (47)	70 (23)		75 (7)			89 (4)		
Pr ₂ BOTf ^g							83 (17)	89		94	85	
BF ₃ ·Et ₂ O/polystyrene ^h							41 ^c		46 ^c	77 ^c	77 ^c	
neutral												
Bu ₃ SnX ^j					0 (82)		45 (40)	60 (22)		74 (17)	81 (14)	
ZrO ₂ (hydrous) ^{k,l}	99 (0)	49 (51)	36 (38)				8 (<1)			52 (0)		
distannoxane ^m							(82)	20	19	78	81	
Bu ₂ SnO ⁿ			0 (20)			5	22			63(8)	60 (15)	
Me ₂ NCH(OCH ₂ Bu ^o) ₂			0 (14)								40 (17)	
basic/nucleophilic												
DMAP/Et ₃ N/(2,4,6-Cl ₃ C ₆ H ₂ CO) ₂ O ^p			36 (23)			48 (20)						
DMAP/DCC/DMAP·HCl ^q							32 (32)	77 (11)		95 (trace)	96	
cyanuric chloride/Et ₃ N ^r							70			68	85	
Bu ₃ P/DEAD ^t	40 (53)		0 (70)				63 (32)					
1-methyl-2-chloropyridinium iodide/ Et ₃ N ^u	89 (0)		13 (34)			61 (24)	69 (14)			84 (3)		
2,2'-(4- <i>t</i> -Bu- <i>N</i> -alkylimidazolyl) disulfide/Ph ₃ P ^v		0 (93)					87 ^c		90 ^c		83	
2,2'-dipyridyl disulfide/Ph ₃ P ^w	71 (7)		8 (41)			47 (30)	66 (7)	68 (6)		80 (5)	85 (15) ⁿ	

^a Isolated yield (%) of monomeric lactones is presented. Isolated yield (%) of diolides is presented in parentheses. ^b HO(CH₂)_nCO₂H. GLC yield (%). ^d Reference 11. ^e Reference 7. ^f ω -(Trimethylsiloxy) carboxylates were used. ^g Reference 20c. ^h Reference 19f. ⁱ Reference 20e. ^j 1,1,2-Trifluoroethyl esters of ω -hydroxy carboxylic acids were used. ^k Reference 20d. ^l Ethyl esters of ω -hydroxy carboxylic acids were used. ^m Reference 19l. ⁿ References 19h and 19i. ^o Reference 19e. ^p Reference 16. ^q Reference 19k. ^r Reference 19g. ^s Reference 19d. ^t Diethyl azodicarboxylate (DEAD). ^u Reference 19c. ^v Reference 19b. ^w Reference 19a.

Corey Method

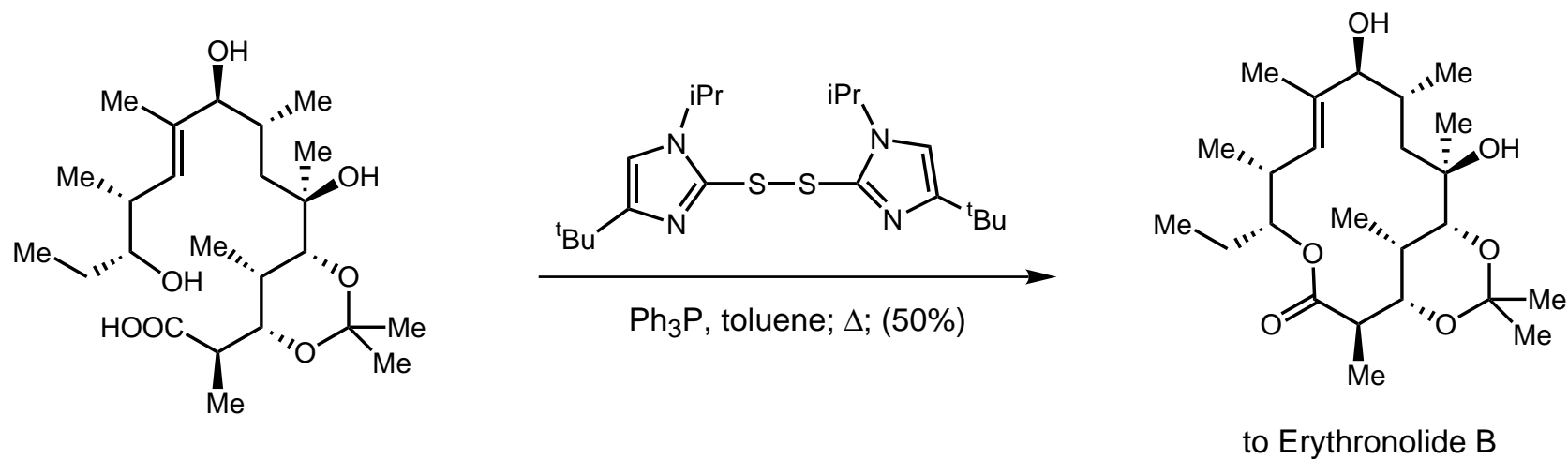


original paper: Corey, E. J. *J. Am. Chem. Soc.* **1974**, *96*, 5614

2-thiopyridyl chloroformate/ triethylamine: Corey, E. J. *Tetrahedron Lett.* **1979**, 2875

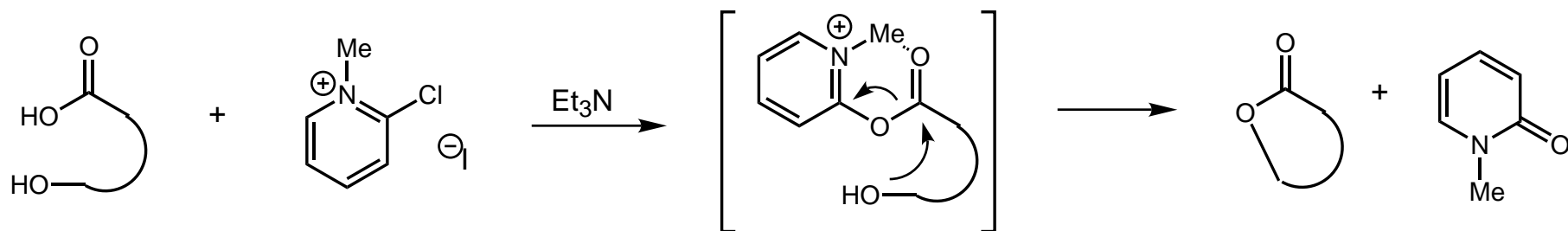
AgClO_4 or AgBF_4 additive: Gerlach, H. *Helv. Chim. Acta* **1974**, *57*, 2661

alternative disulfides: Corey, E. J. *Tetrahedron Lett.* **1976**, 3409



Corey, E. J. *J. Am. Chem. Soc.* **1978**, *100*, 4620

Mukaiyama Method

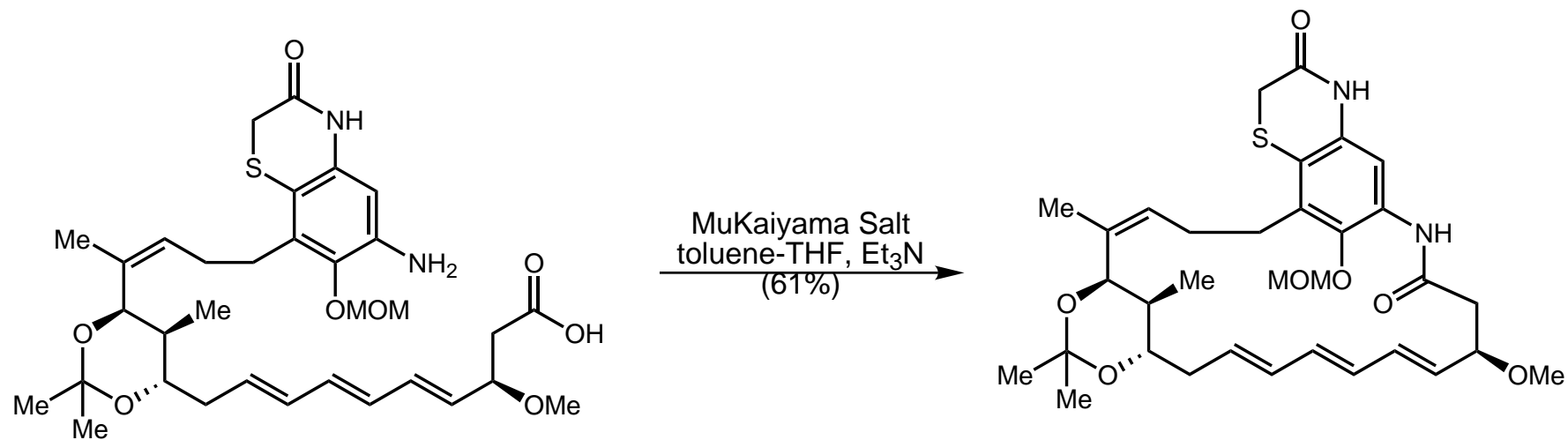


original paper: Mukaiyama, T. *Chem. Lett.* **1976**, 49

2-chloro-3-methoxymethyl-1-methylpyridinium iodide: Mukaiyama, T. *Chem. Lett.* **1977**, 763

2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate: Mukaiyama, T. *Chem. Lett.* **1978**, 885

6-phenyl-2-pyridyl esters: Mukaiyama, T. *Chem. Lett.* **1977**, 441



to (+)-Thiazinotrienomycin E

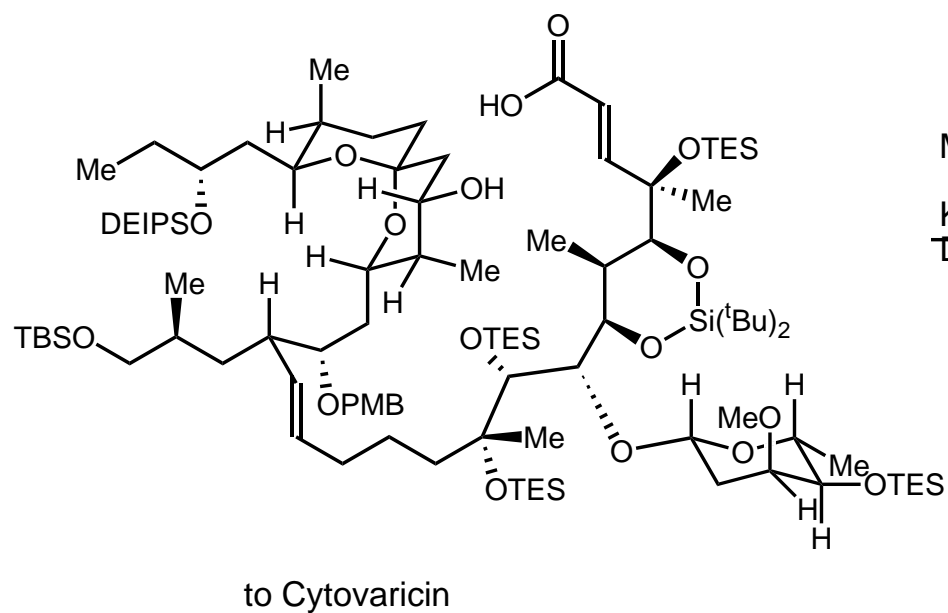
Smith, A. B., III *Organic Lett.* **1999**, 1, 1491-1494

Keck's Method

Keck's modified Steglich esterification

DCC: Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522-524

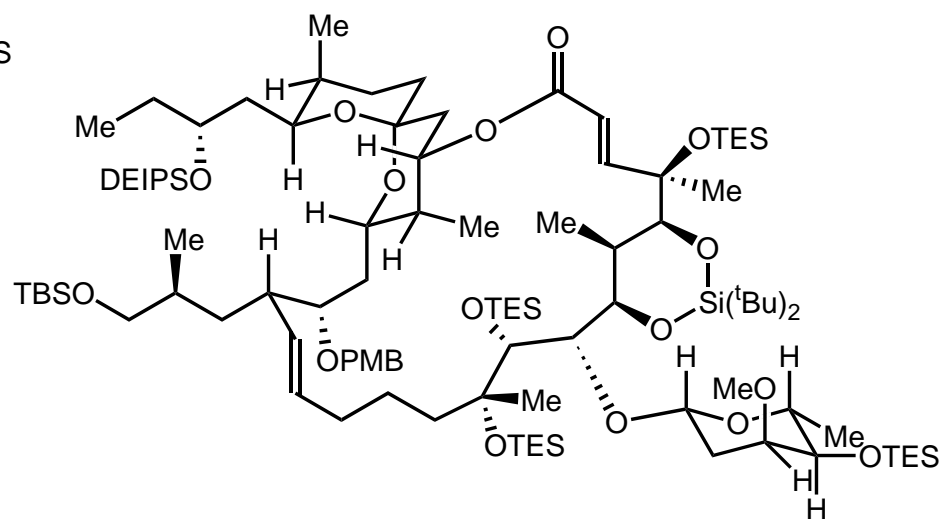
DCC, DMAP, DMAP-HCl : Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394



Mukaiyama's method did not work

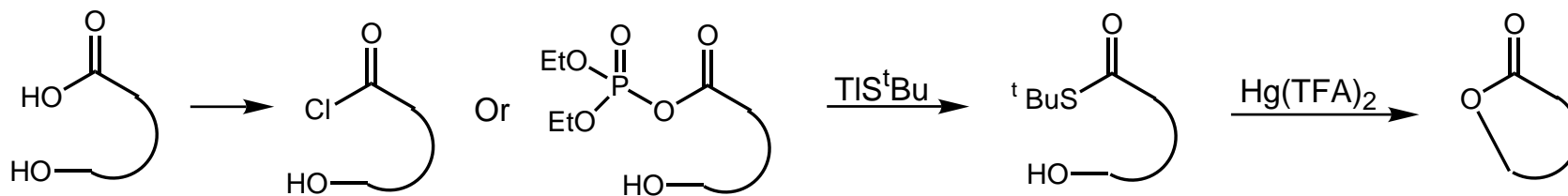
Keck's method: (92%)

~~DCC, DMAP, DMAP-HCl, CHCl₃, 61°C~~



Evans, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031

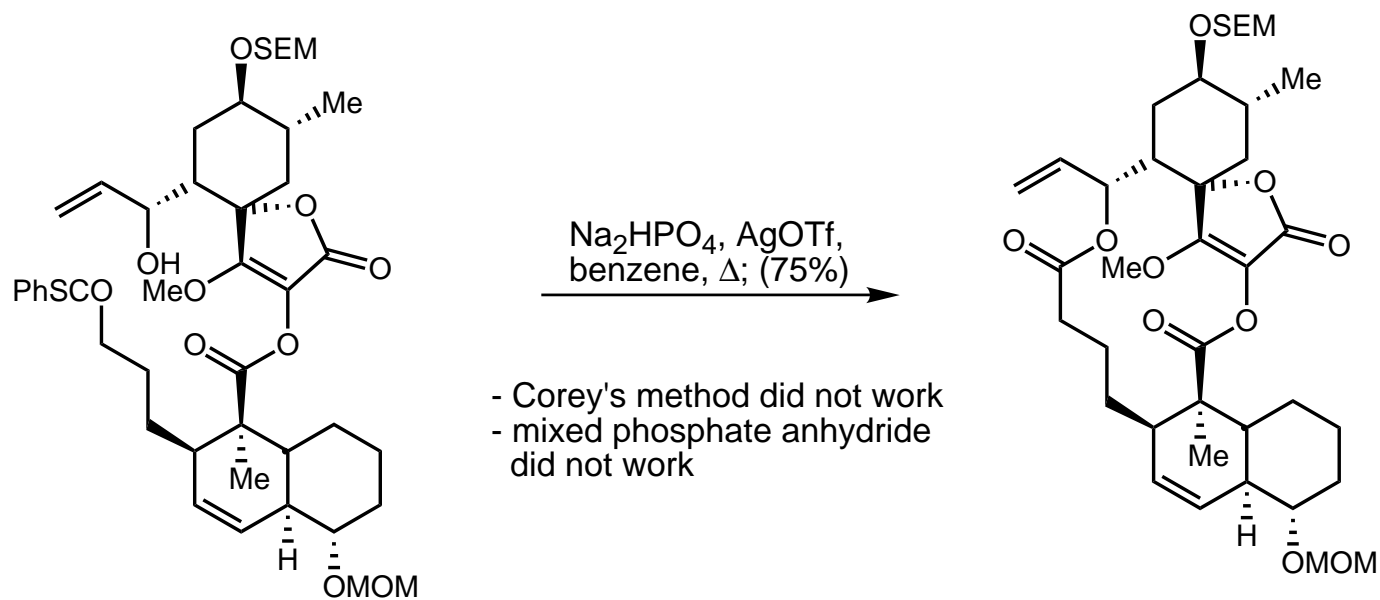
Masamune Method



original paper: Masamune, S. *J. Am. Chem. Soc.* **1975**, 97, 3512

copper(I) triflate - benzene complex additive: Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, 103, 861

benzenethiol ester: Masamune, S. *J. Am. Chem. Soc.* **1977**, 99, 6756



to synthesis of Chlorothricolide

Ireland, R. *J. Org. Chem.* **1986**, 51, 635

Yamaguchi's Method

2,4,6-trichlorobenzoyl chloride: Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989-1993

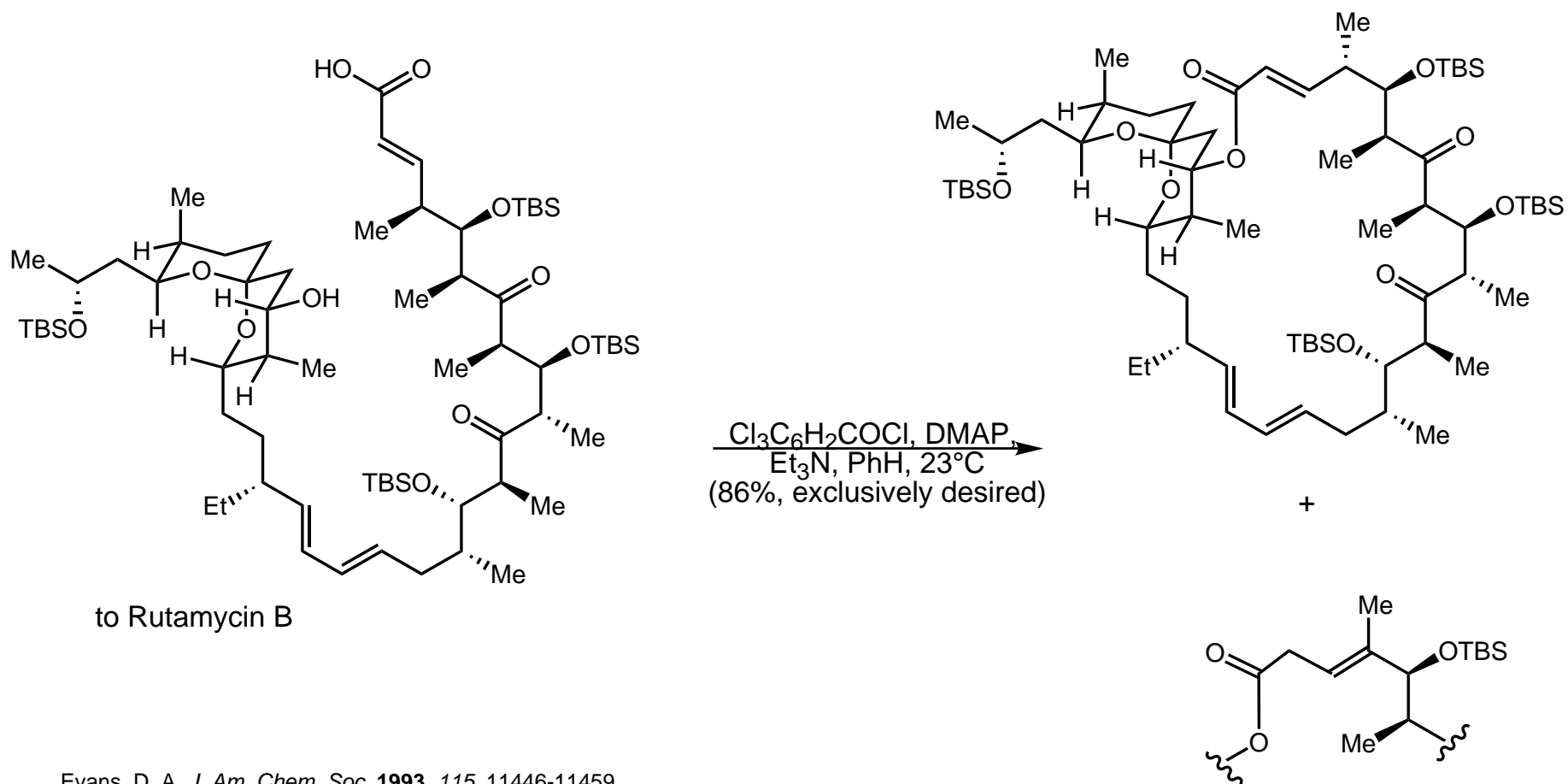
modified DMAP concentration and reaction temperature:

Yonemitsu, O. *J. Org. Chem.* **1990**, 55, 7-9; *Tetrahedron* **1990**, 46, 4613-4628

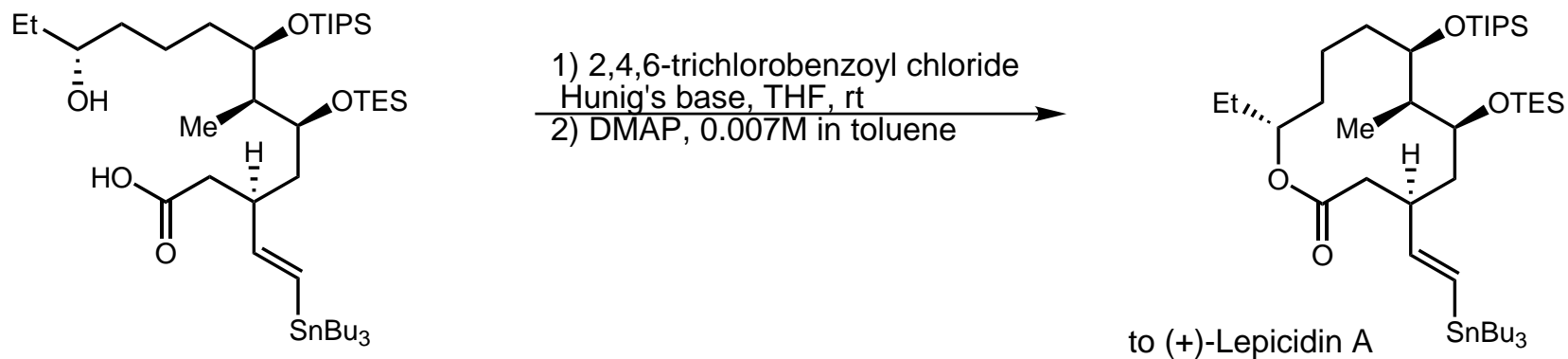
problem with olefin isomerization:

Keck, Mukaiyama, and Corey methods all afforded unfavorable ratios

only 'promising' lead, Yamaguchi's original procedures (1:1)

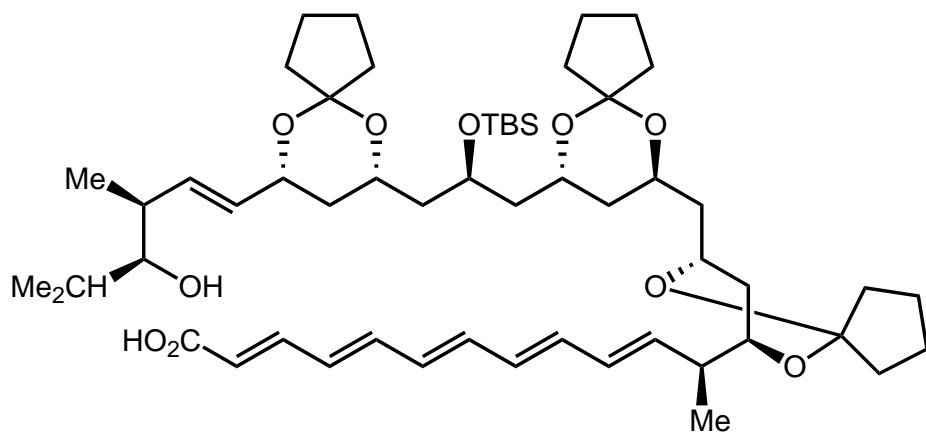


Yamaguchi 2 : effect of temperature and addition time



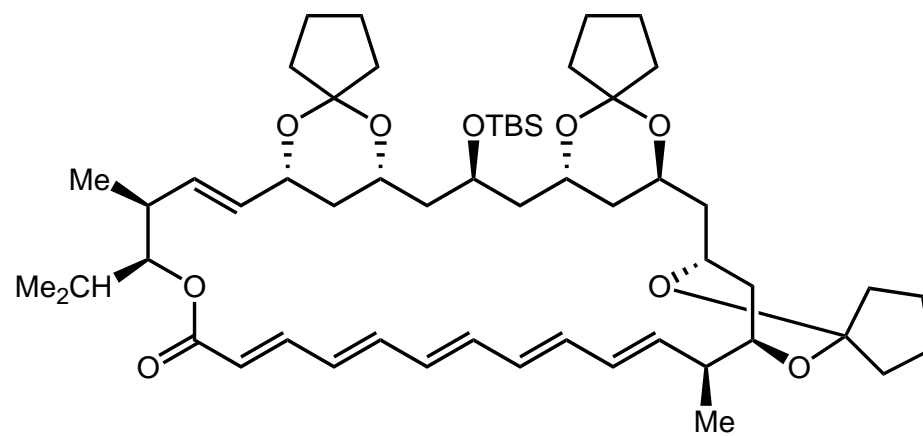
T (°C)	addn time (hr)	macrocycle prod (%)	destannylated monomer (%)	dimer (%)
25	0.5	13	0	33
70	0.5	63	7	10
110	10	10	63	1
110	1	78	3	3

Yamaguchi 3: mild conditions



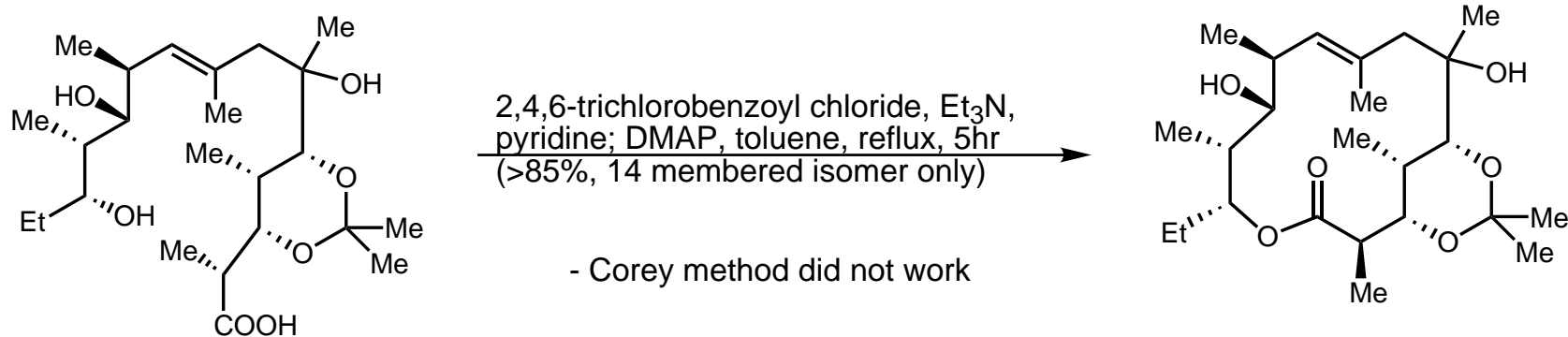
Keck and Mukaiyama methods did not work

2,4,6-trichlorobenzoyl chloride,
Et₃N, THF; DMAP, benzene, rt, 2hr
(66%)



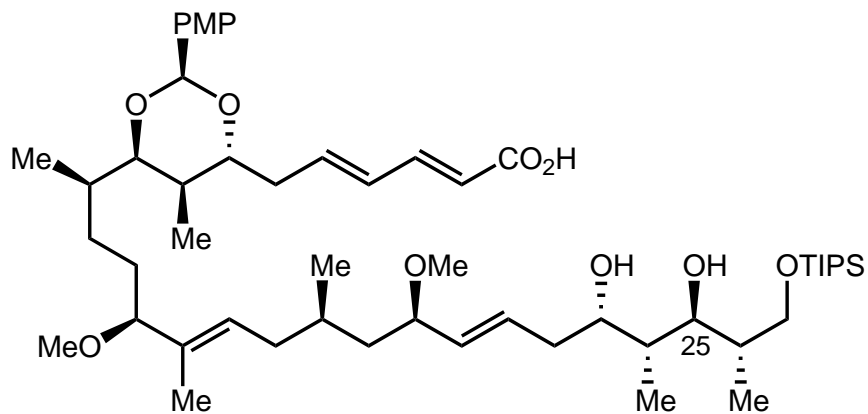
to Roxaticin

Yamaguchi 4: regioselectivity



to 9-Dihydroerythronolide B Derivatives

Mulzer, J. *J. Am. Chem. Soc.* **1991**, 113, 910-923

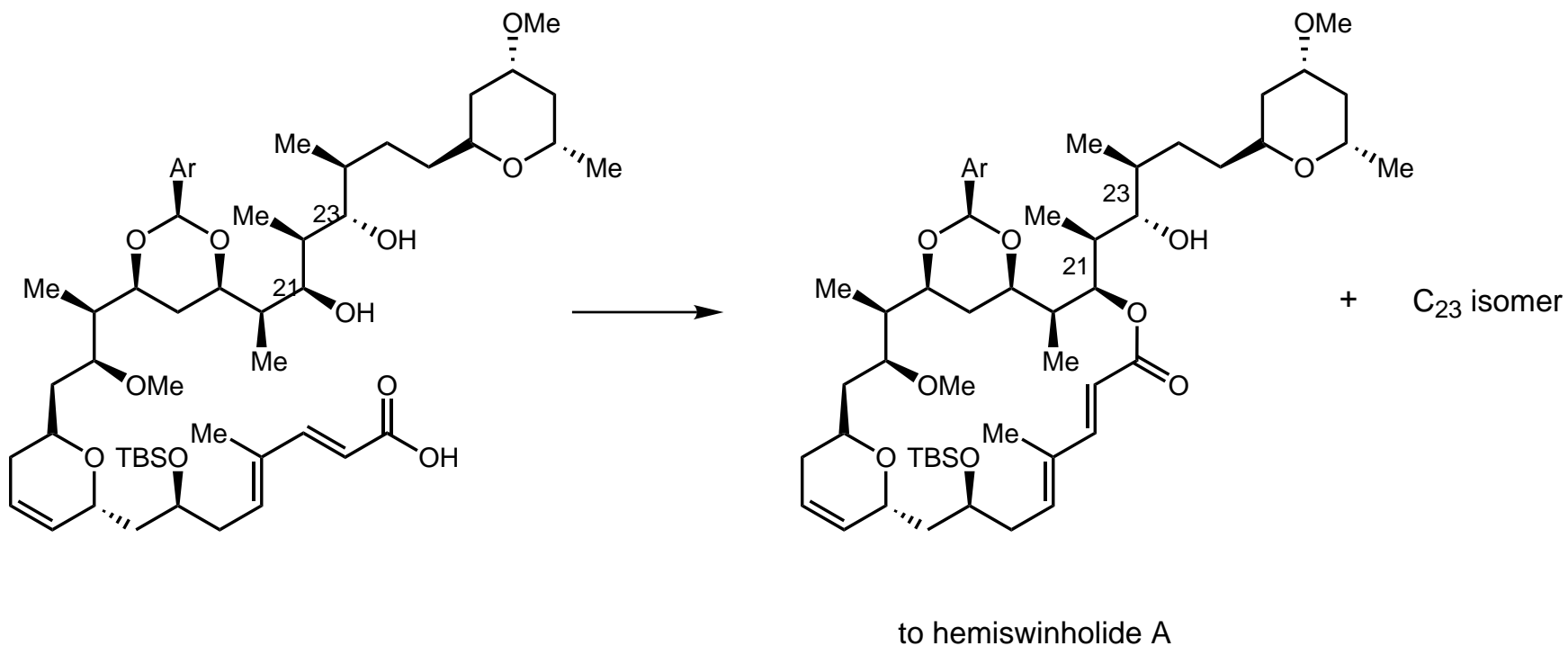


an approach to Aplyronine A

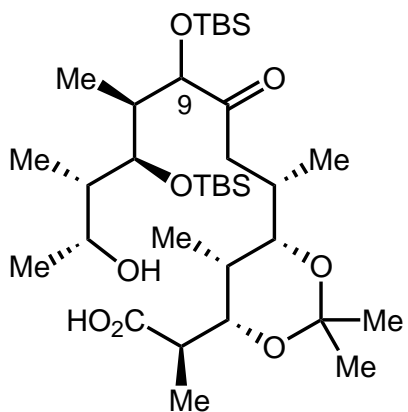
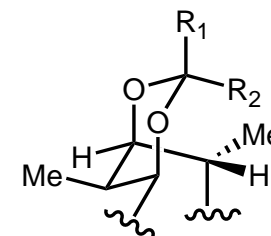
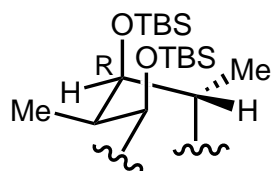
Paterson, I. *Tetrahedron Lett.* **1998**, 39, 6041-6044

Yamaguchi 5: regiocontrol?

	C ₂₁ : C ₂₃	yield (%)
Yamaguchi procedure (in toluene)	82 : 18	92
Keck's procedure (in chloroform)	05 : 95	94
Keck's procedure (in toluene)	40 : 60	73

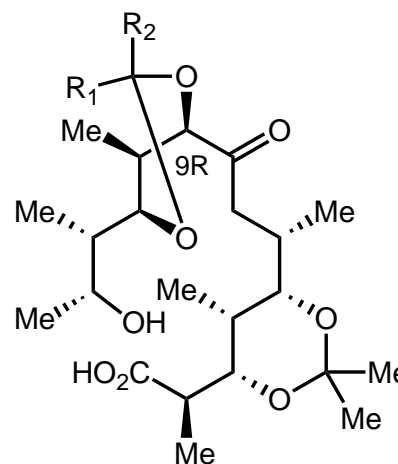


Yamaguchi 6: stereochemical effect



Yamaguchi
yield

9S :	60%
9R :	0%

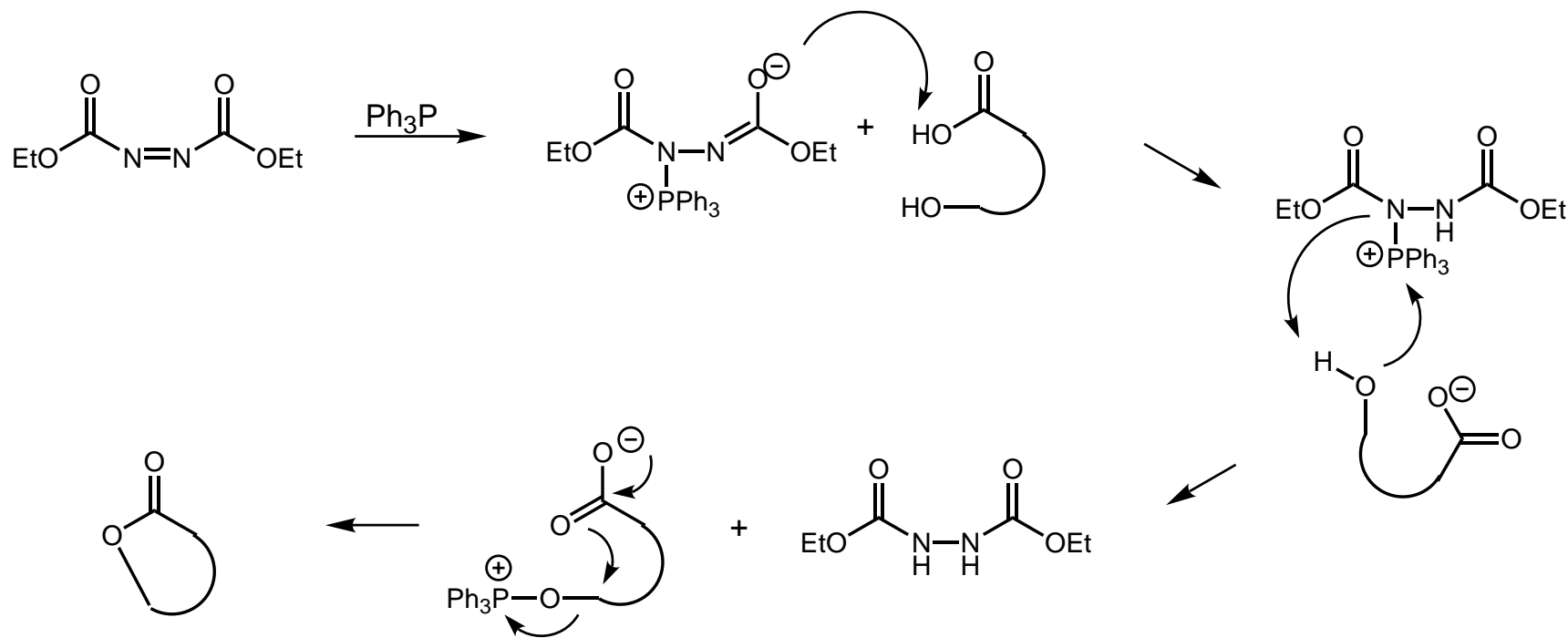


Yamaguchi
yield

R ₁ = Me, R ₂ = H :	78%
R ₁ = Me, R ₂ = Me :	0%

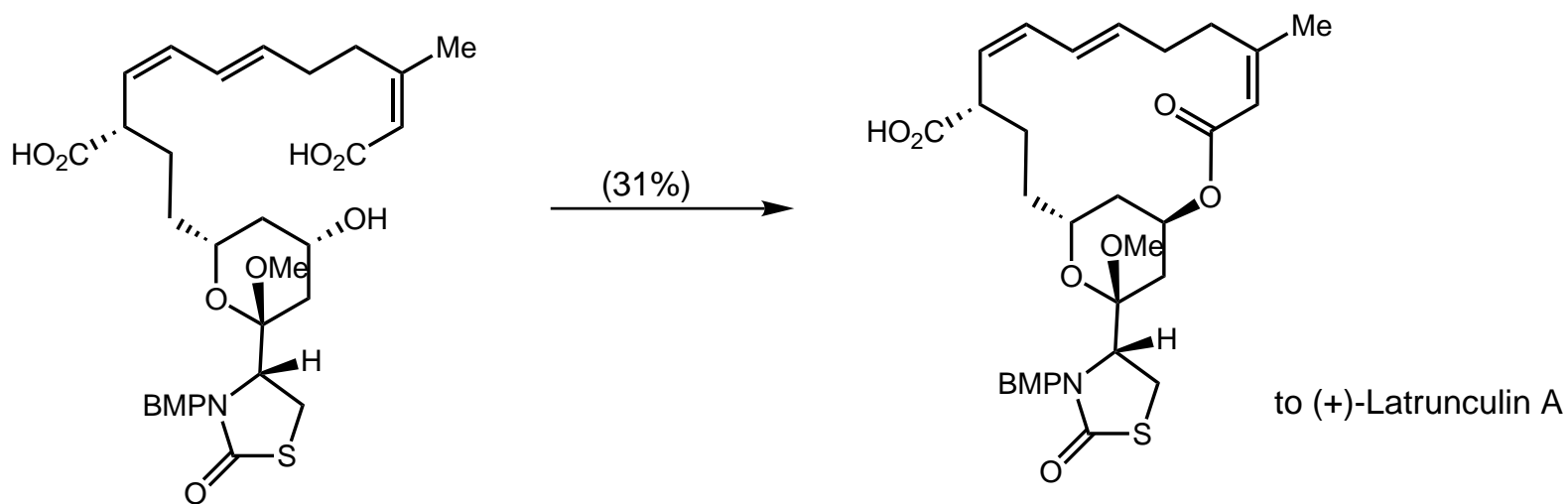
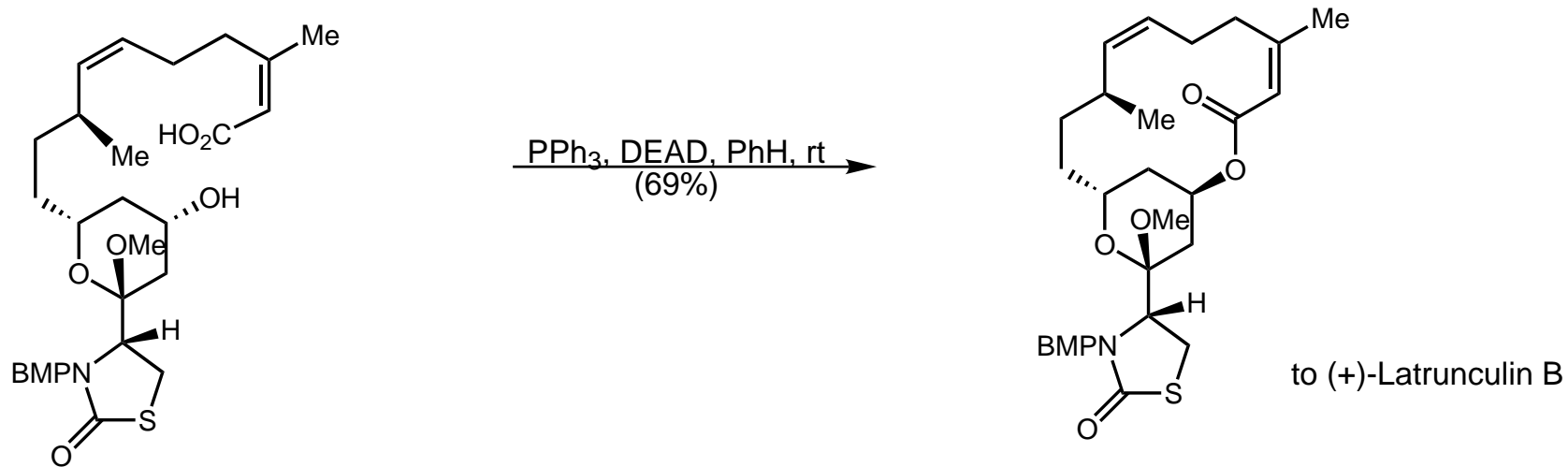
Mitsunobu Cyclization

Hydroxyl activation:



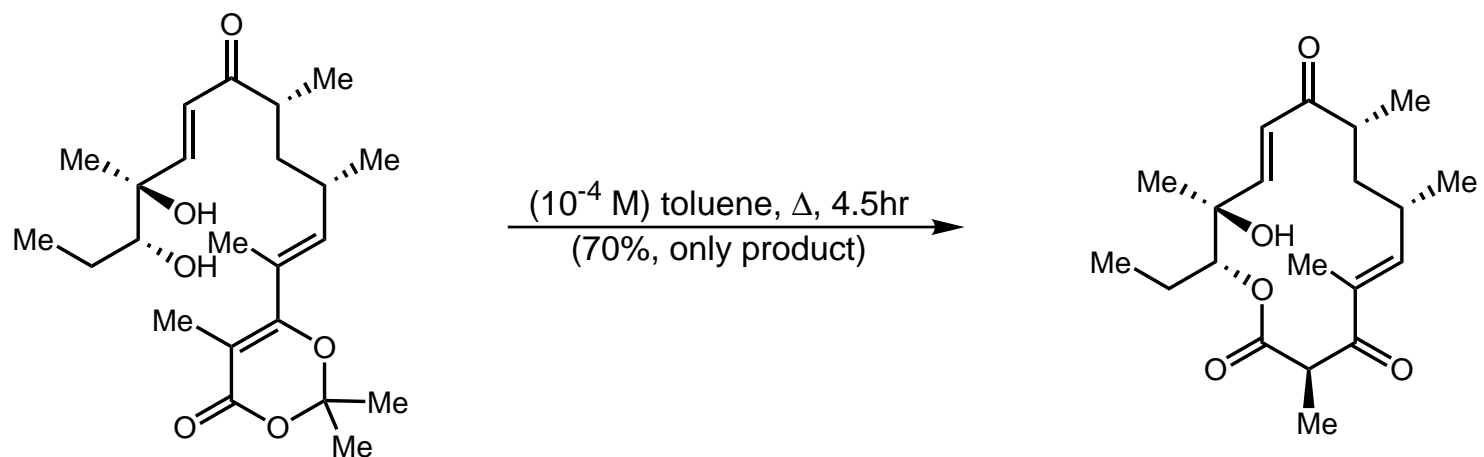
original papers: Mitsunobu, O. *Synthesis* **1981**, 1; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455
N, N-dimethylformamide dineopentylacetal: Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 876

Mitsunobu (cont'd)



Intramolecular Ketene Trapping

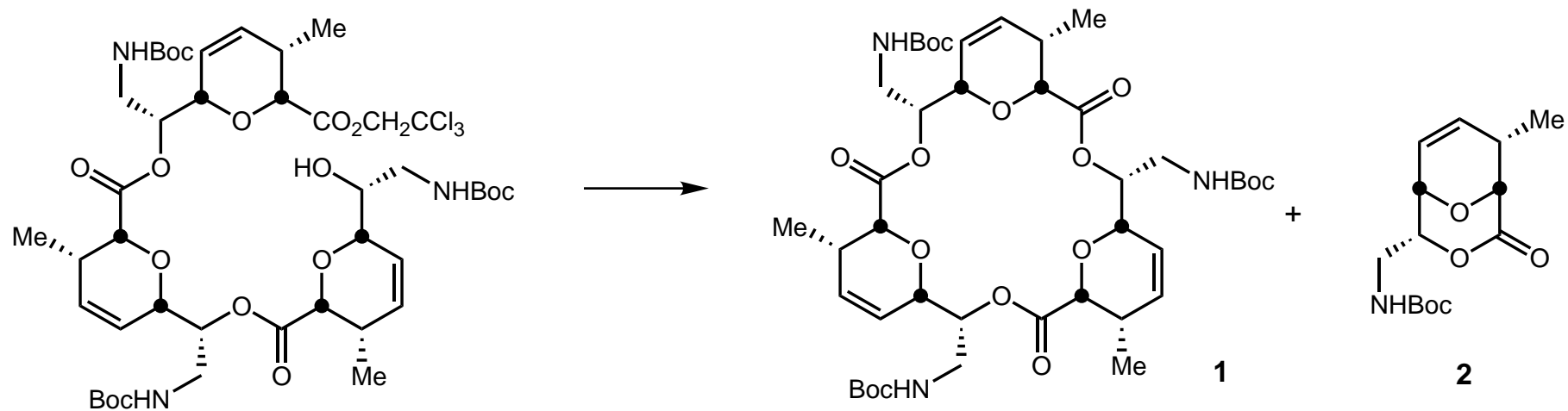
Generating β -keto lactone:



to (-)-Kromycin

Template-Directed Macrolactonization

Transesterification of trichloroethyl ester:



(10-20 eq. solid K₂CO₃)

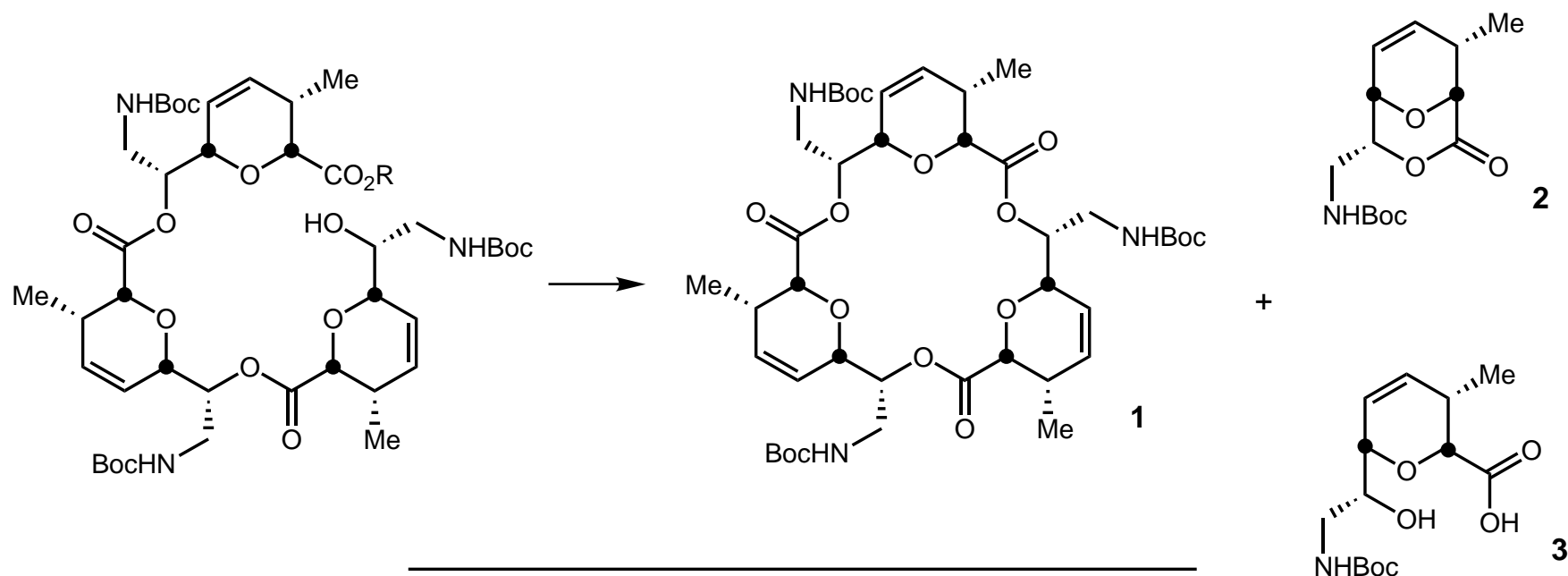
solvent	conc. (M)	time (d)	yield (% , 1 : 2)
CH ₂ Cl ₂	0.002	5	74 : 10
toluene	0.002	1	64 : 11
CH ₃ CN	0.002	1	38 : 62
THF	0.002	1	88 : 12
THF	0.005	2	69 : 07
THF	0.01	1	60 : 10
THF	0.1	1	24 : 26

(10-20eq. solid salt, 0.002 M, in THF)

salt	time (d)	yield (% , 1 : 2)
K₂CO₃	1	88 : 12
Li ₂ CO ₃	4	0
Na ₂ CO ₃	4	0
Cs ₂ CO ₃	8 hr	52 : 20
KOAc	3	47 : 0
KI	3 hr	65 : 0
NaI	4	0
KBPh ₄	3	0

Template-Directed 2

Various esters for cyclizations:

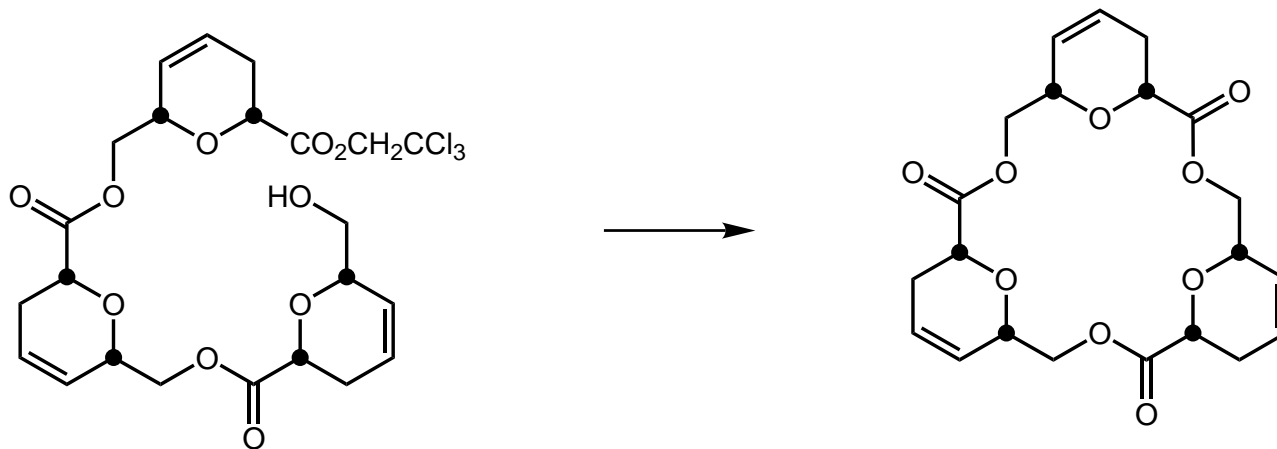


R	time (d)	yield (%; 1:2:3)
CH ₂ CCl ₃	1	88 : 12 : 0
methyl	2	18 : 50 : 20
allyl	5	39 : 28 : 17
benzyl	5	37 : 16 : 17

- Reaction conditions also do not promote intermolecular transesterification.

Template-Directed 3

Counterion effect and substituent effect:



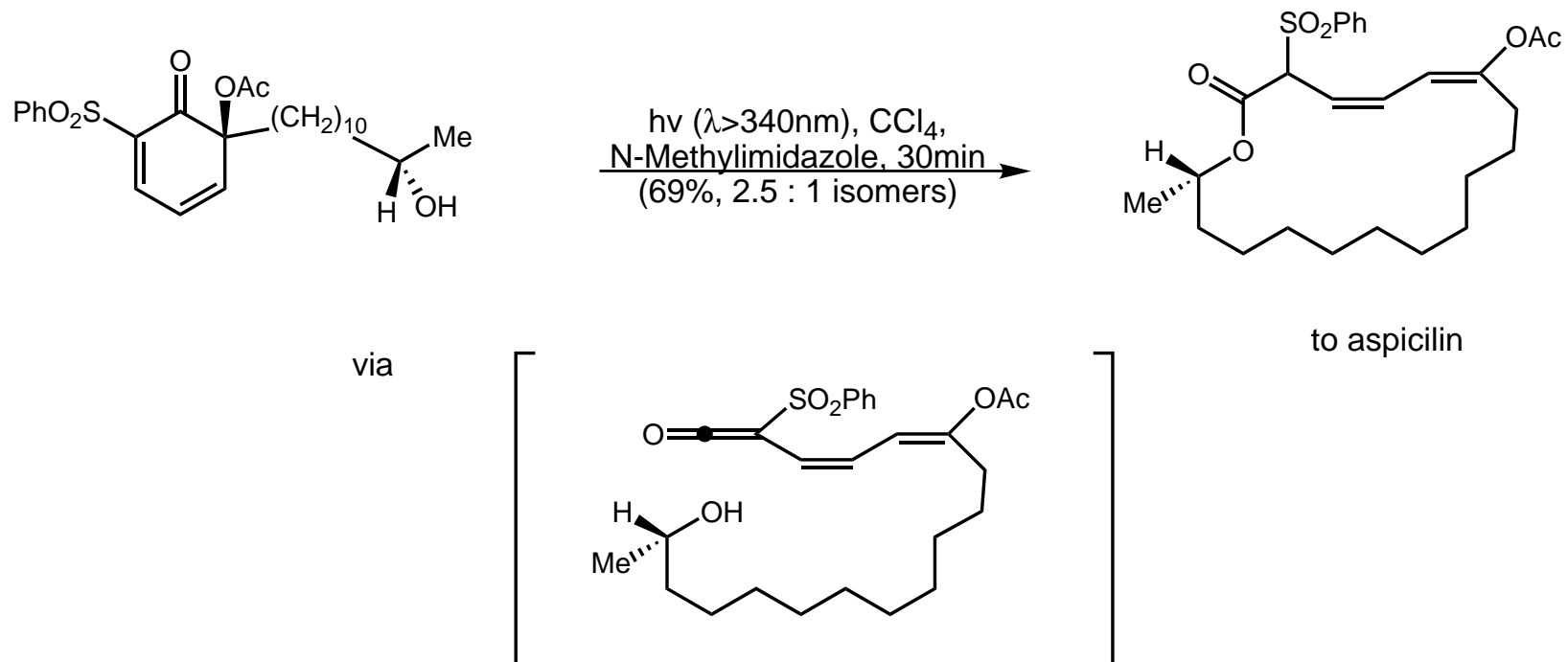
(10 eq. solid salt, 0.002 M, in THF)

salt	time (hr)	yield (%)
K ₂ CO ₃	2	90
Na ₂ CO ₃	36	73
Cs ₂ CO ₃	1	93
KOAc	1	96
KI	2	81
NaI	10 min	90
LiI	18	10
KBPh ₄	24	0

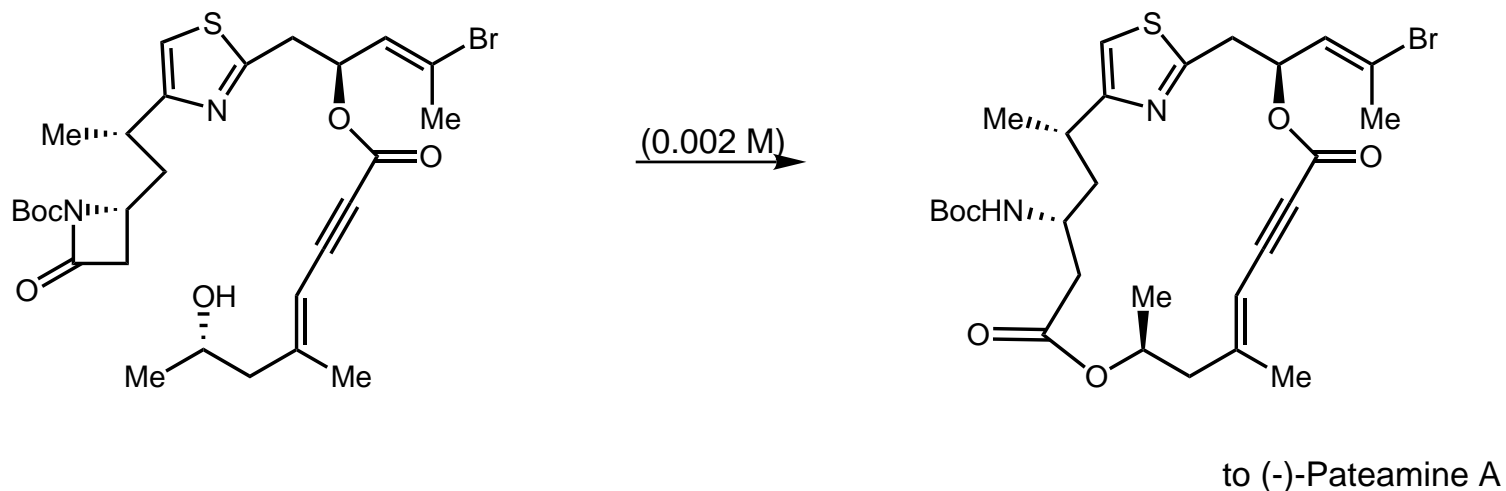
AcO ⁻ M ⁺ (equiv)	conc (M)	18-C-6 (equiv)	time (hr)	yield (%)
K (0.5)	0.002	0	1	100%
K (0.5)	0.002	1	24	97
K (0.05)	0.05	0	1	87
Bu ₄ N (0.5)	0.002	0	8	trace
Bu ₄ N (0.5)	0.002	1	18	trace

Photolactonization

Norrish Type I cleavage to dienyl ketene:

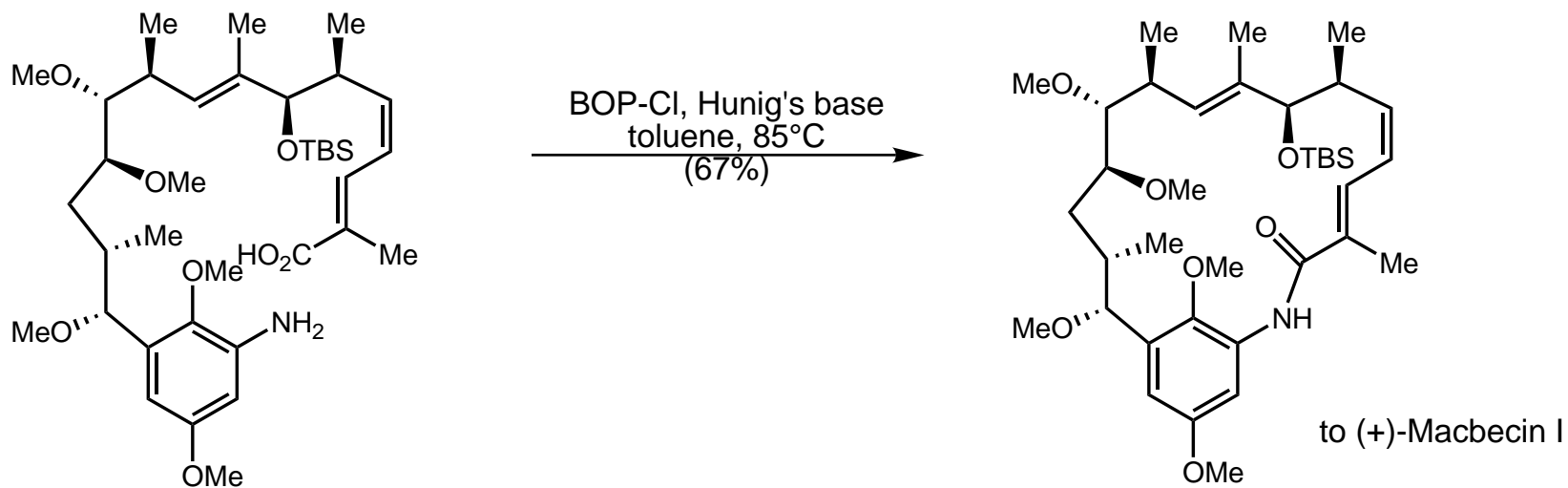


β -Lactam Based Macrocyclization

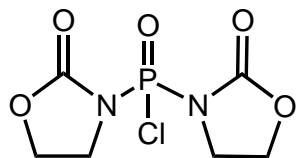


conditions (equiv)	temp ($^{\circ}$ C)	yield (%)
NaHMDS (1.1), THF, 45min	-40	37
LiHMDS (1.1), THF, 2.5hr	-40	11
NaH (1.1), THF, 1hr	-10	42
0.5-0.6 M KCN, DMF, 1-2hr	25	52-72
Et ₄ N ₄ CN (9.0), CH ₂ Cl ₂ , 4-9hr	25	59-68

Macrolactamization

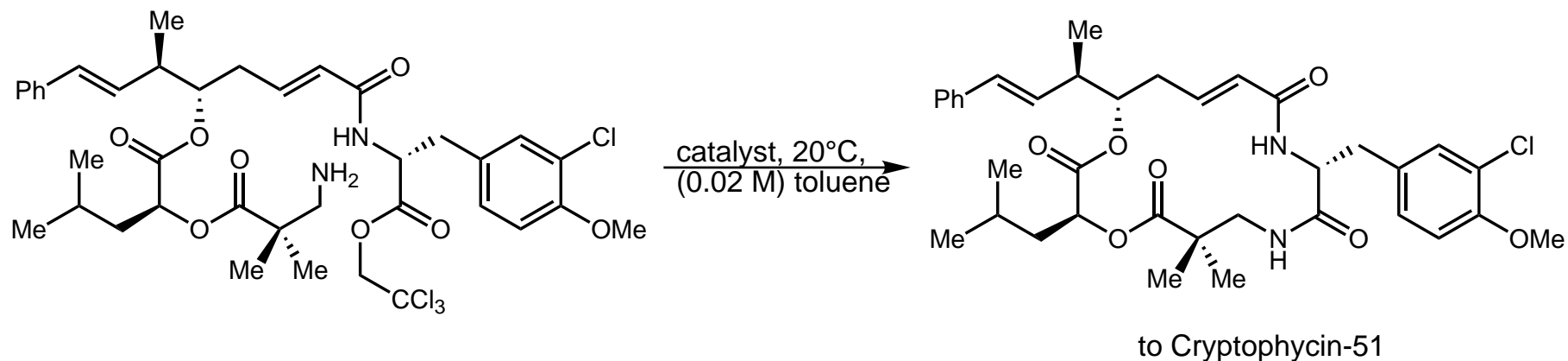


BOP-Cl = N, N' - bis(2-oxo-3-oxazolidinyl)phosphinic chloride



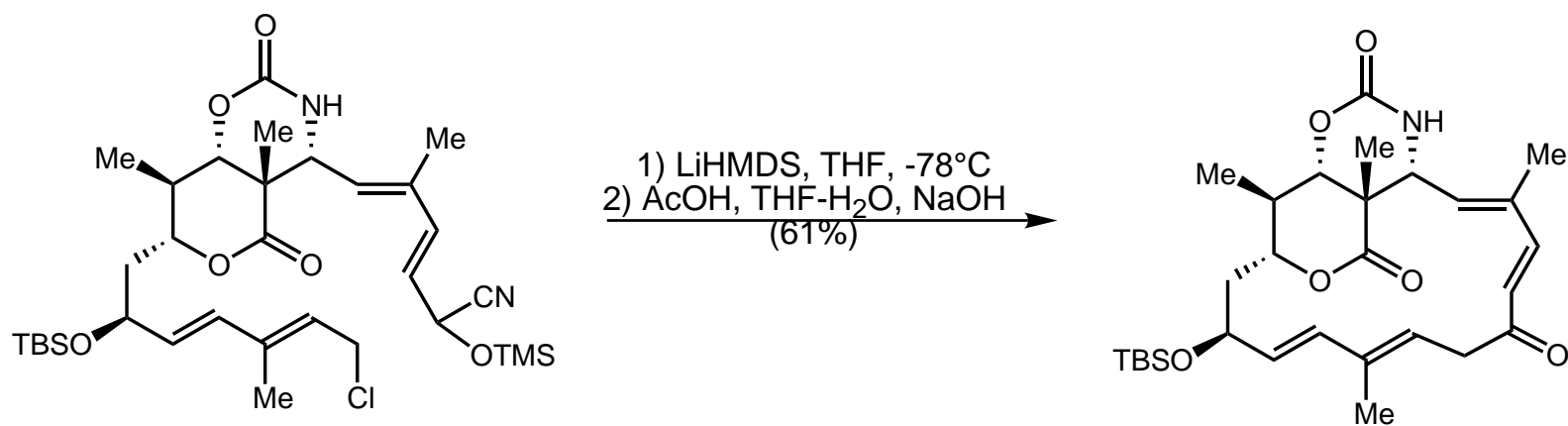
Evans, D. A. *J. Org. Chem.* **1992**, 1067
Evans, D. A. *J. Org. Chem.* **1993**, 471

Intramolecular Aminolysis of Trichloroethyl Esters



catalyst	equiv	%conv t=6hr	%conv t=25hr
none	--	3.1	15
HOBt	0.5	--	36
Imidazole	0.5	--	22
iPr ₂ NEt	0.5	7.6	--
Pyridine	0.5	4.9	--
DMAP	0.5	4.8	--
2-Hydroxypyridine	0.5	42	>99
nBu ₄ N Benzoate	0.1	37	87
TFA	1.0	00	00

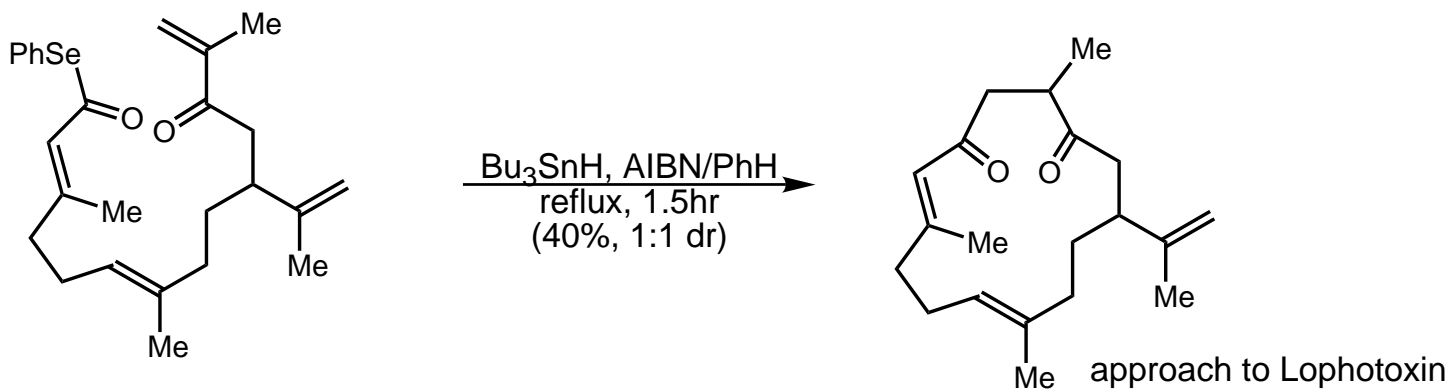
Stork-Takahashi Cyanohydrin Cyclization



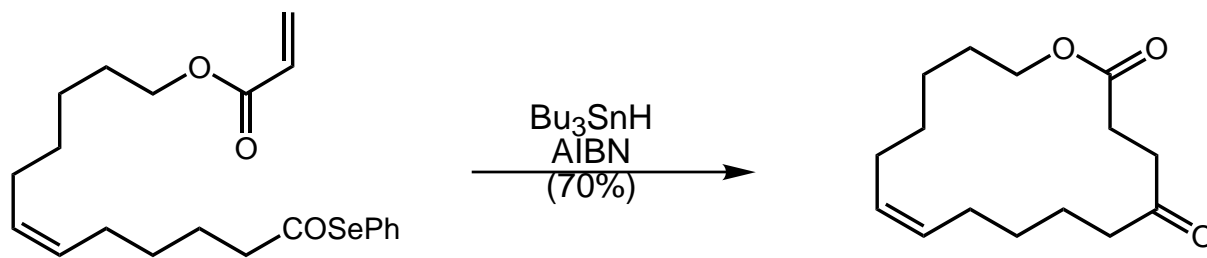
to Lankacidin C

Takahashi, T. *J. Org. Chem.* **1986**, 51, 3393
Takayanagi, H. *Tetrahedron Lett.* **1990**, 31, 3317
Kende, A. S. *J. Am. Chem. Soc.* **1995**, 117, 8258-8270

Acyl Radical Cyclizations to Ketones



Pattenden, G. *Synthesis* **1992**, 101-105



Boger, D. L. *J. Am. Chem. Soc.* **1990**, 112, 4008-4011

Macrocyclization II: via C-C bond formation

C(Sp³) - C(Sp³)

Metal mediated nucleophilic addition to carbonyl

Cr and Nozaki-Kishi

Alkenylboron / alkenylzinc

Ti Aldol

Sulfone coupling

Michael addition

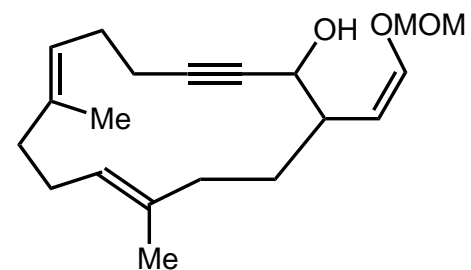
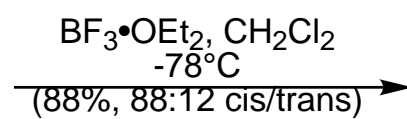
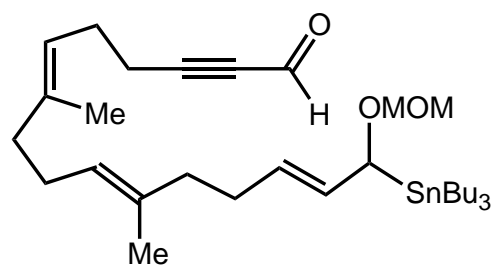
Free-radical cyclization

C(Sp^{2,3}) - C(Sp^{2,3})

Stille coupling

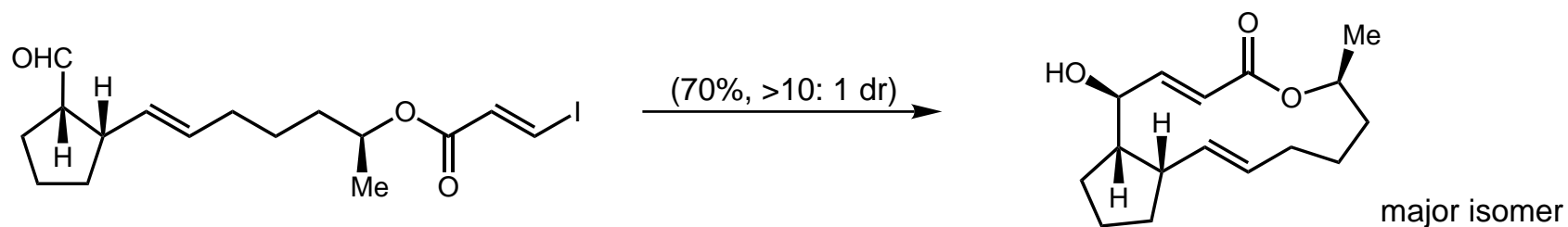
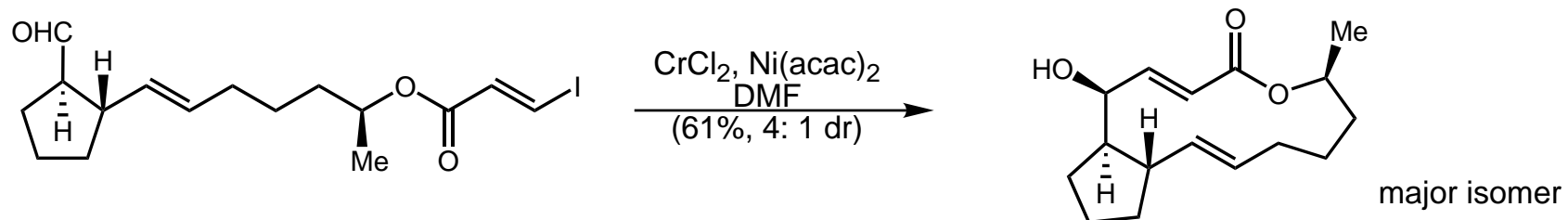
Suzuki coupling

aryl-aryl coupling



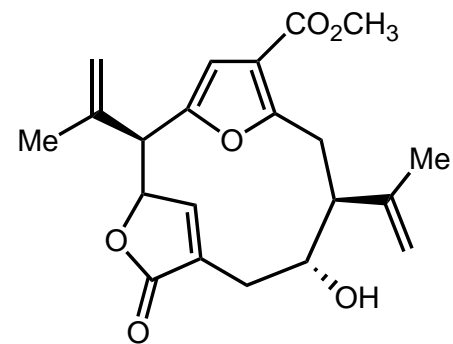
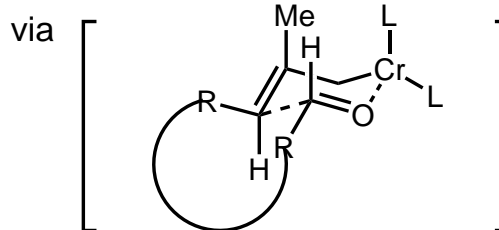
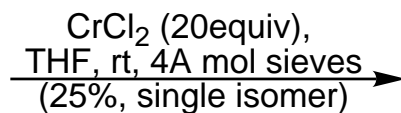
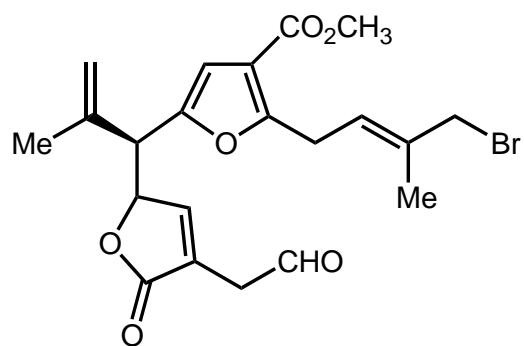
to Cembranolide

Intramolecular Nozaki-Kishi Reactions



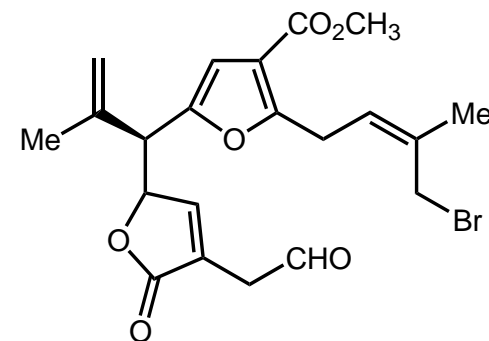
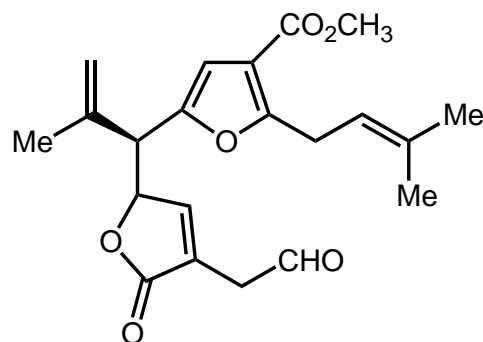
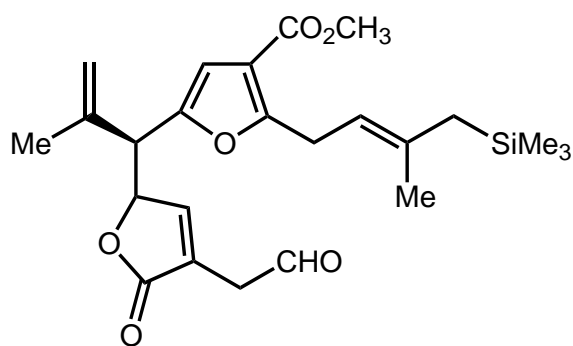
to (+)-brefeldin C

Cr(II) Mediated Macrocyclization

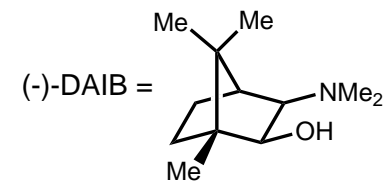


to furanocembranolides

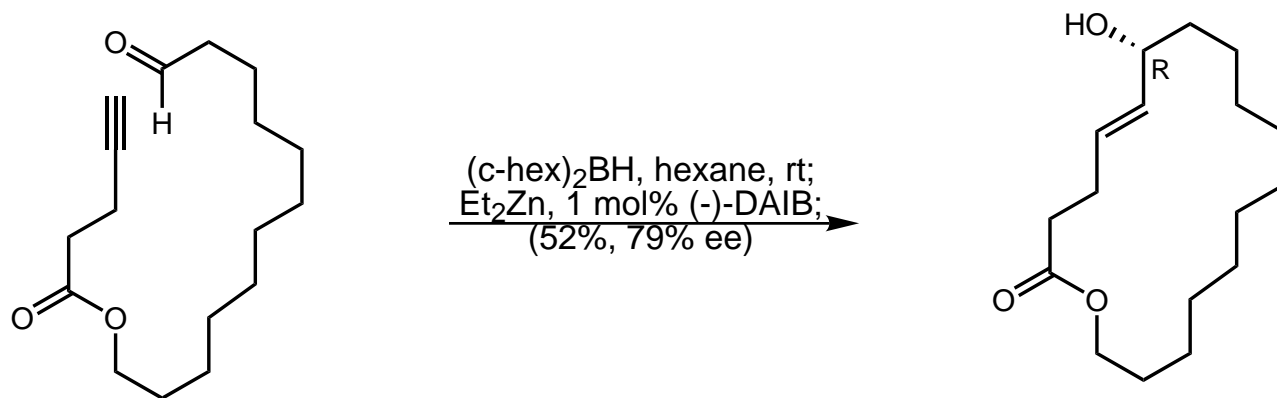
but these wouldn't cyclize...



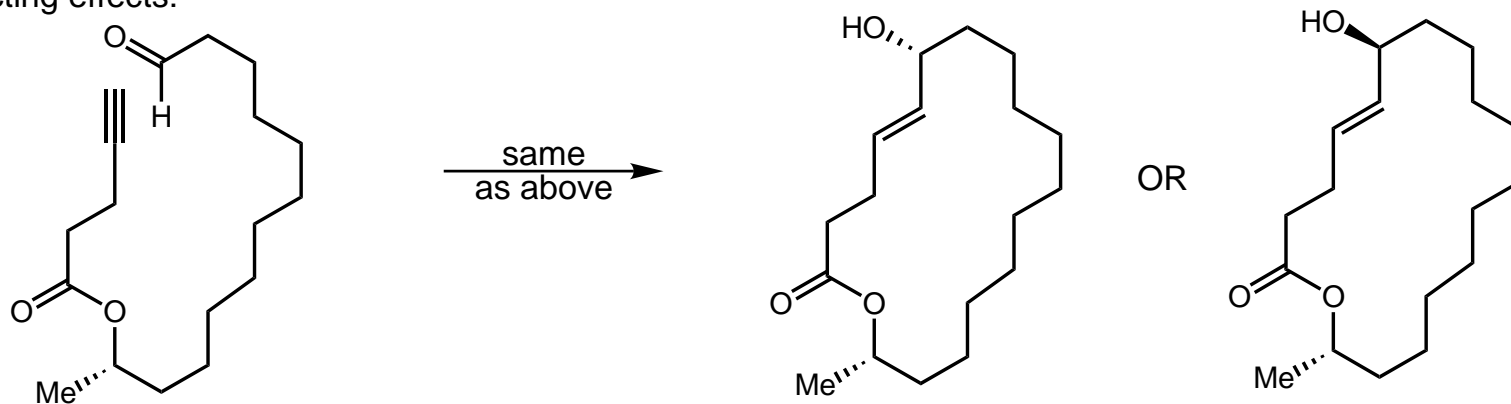
Alkenyl Zinc Macrocyclization



Catalyst control:



Stereodirecting effects:



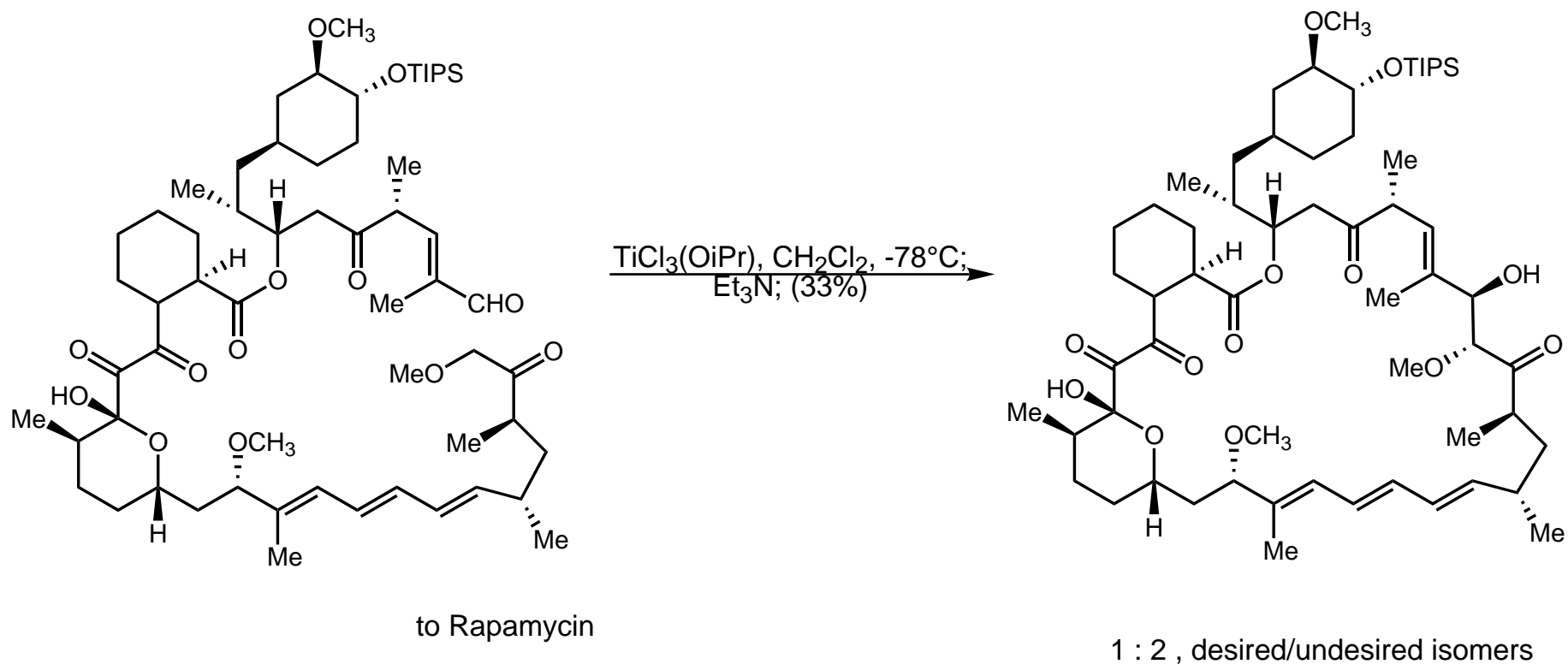
Oppolzer, W. *J. Am. Chem. Soc.* **1993**, 115, 1593-94
 Oppolzer, W. *Tetrahedron Lett.* **1995**, 36, 2607-2610

matched case
 (-)-DAIB
 60%y, 82%de
 to (+)-Aspicilin

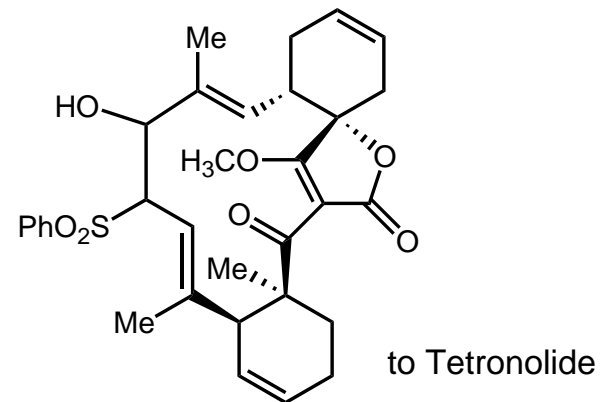
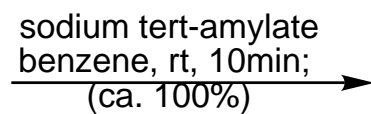
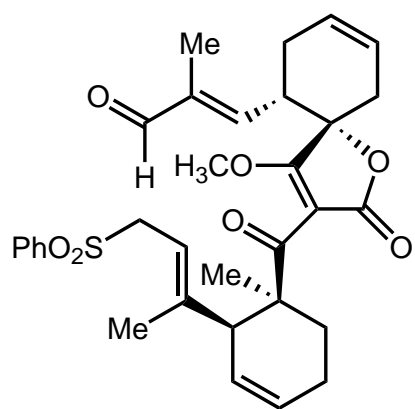
mismatched case
 (+)-DAIB
 40%y, 70%de

Titanium Aldol Macrocyclization

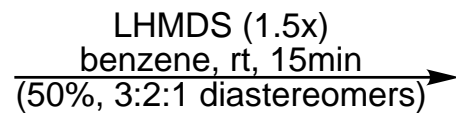
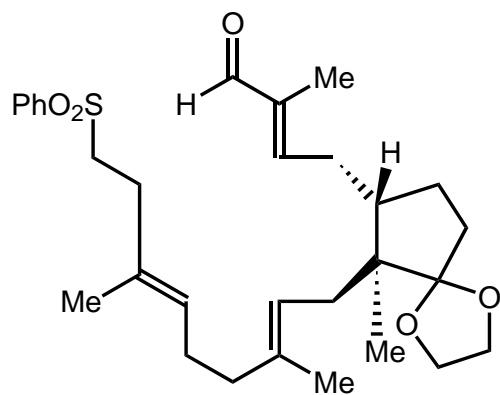
- Danishefsky: "...highly novel macroaldolization..."
- tried lithium enolates, cerium enolates, (c-hex)₂BCl, Sn(OTf)₂, Bu₃SnCl, ZnCl₂, ZrCp₂Cl₂,,, none worked
- TiCl₄, Et₃N, CH₂Cl₂, -78°C afforded 21%y, 1:2 desired/undesired isomer



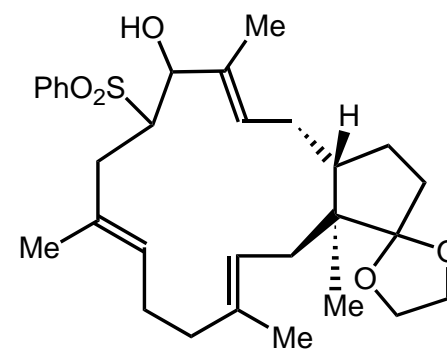
Sulfone-Aldehyde Cyclization



Takeda, K. Yoshii, E. *J. Org. Chem.* **1986**, 51, 4735



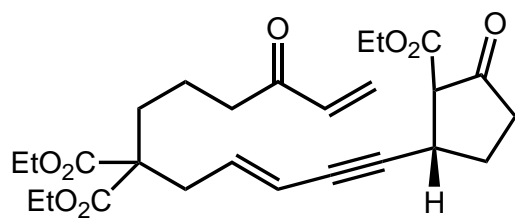
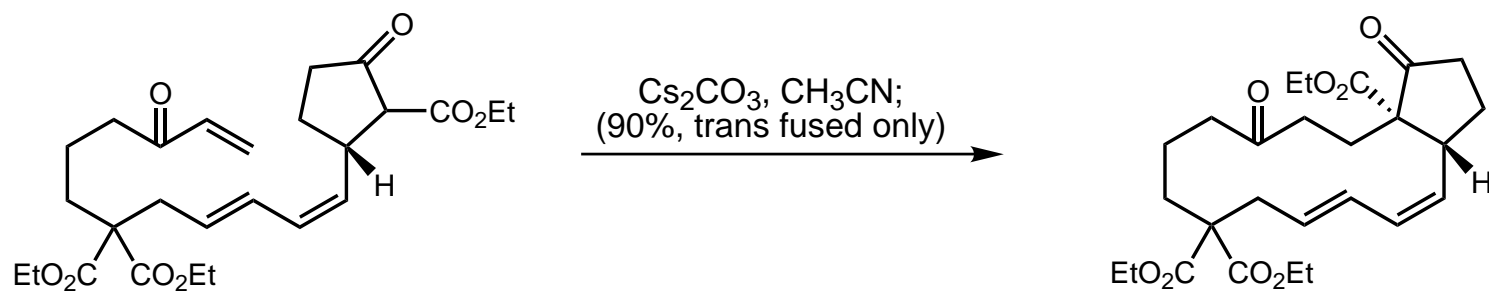
sodium tert-amylate did not work



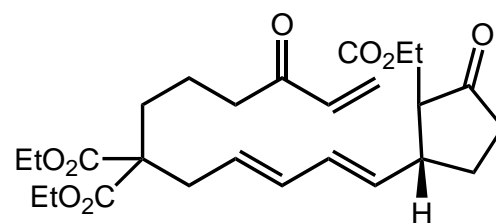
to Terpestacin

Takeda, K.; Yoshii, E. *Synlett* **1995**, 249-250

Intramolecular Michael Reaction

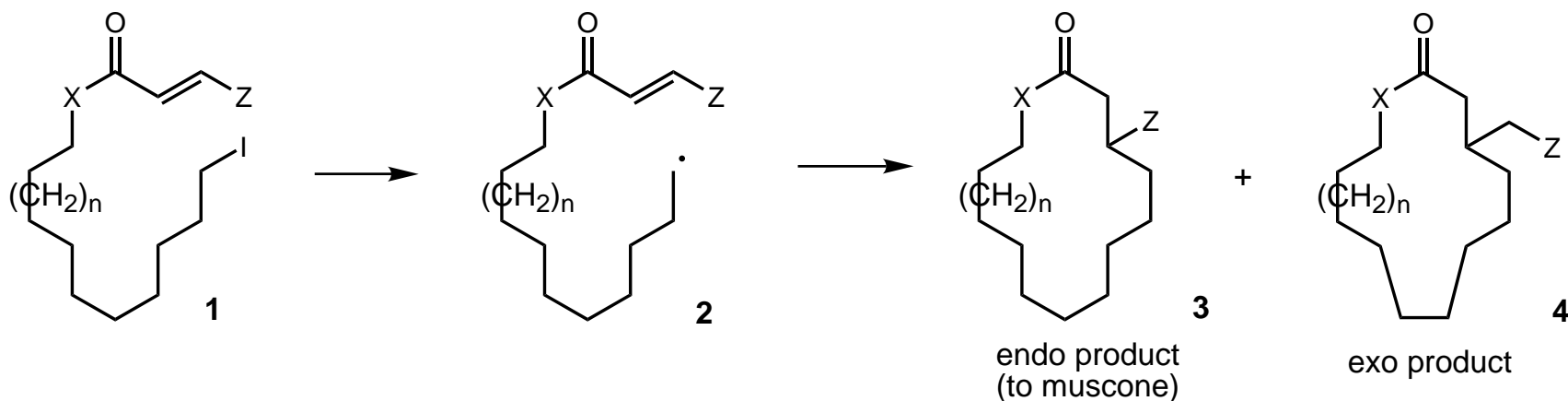


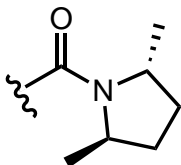
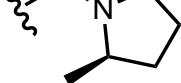
(25%, dimers only)



(48%, 1 : 0 : 4 cis:trans:dimers)

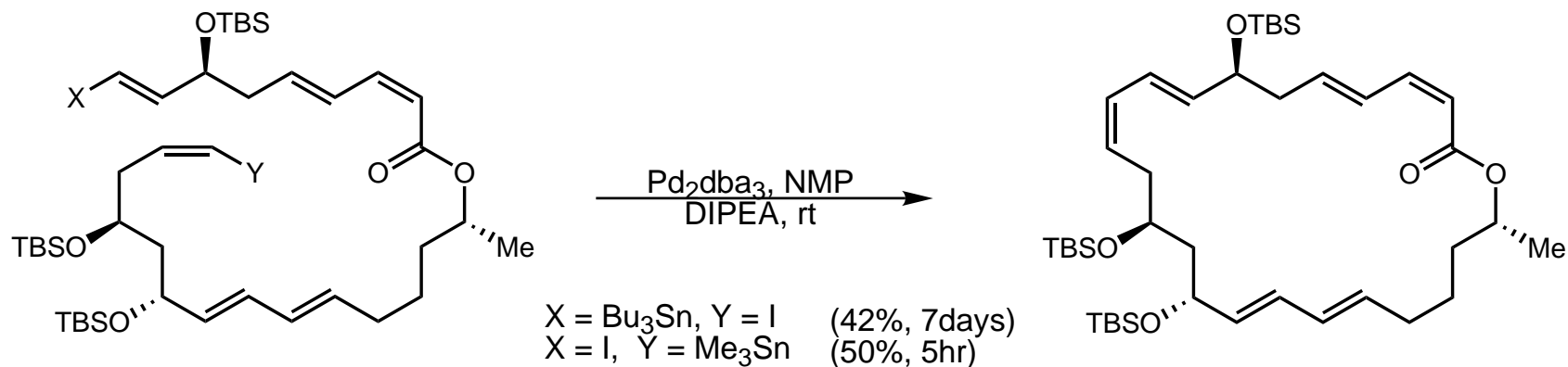
Stereoselectivity of Free Radical Cyclization



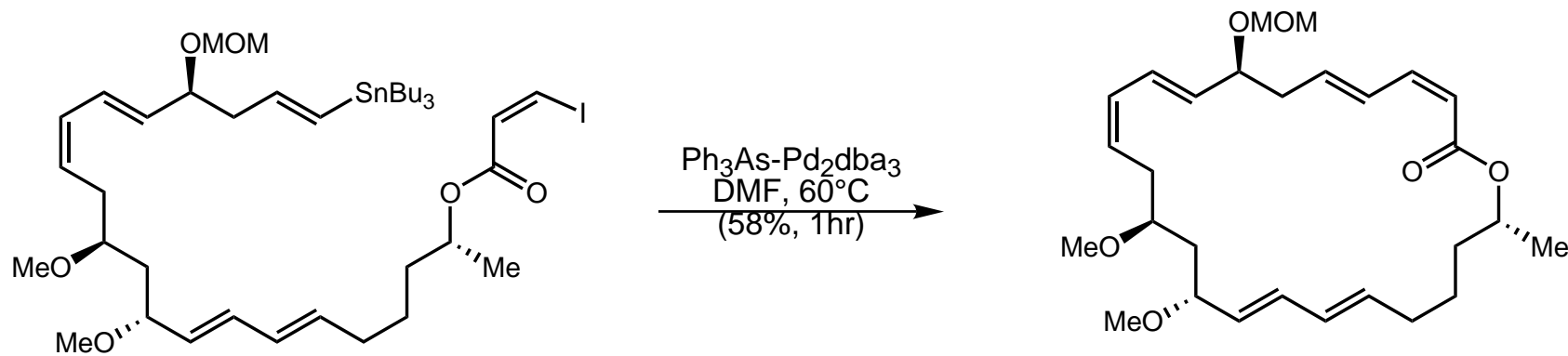
	Product Ratio	
	endo, 3	exo, 4
1a) $n=1$, $X=CH_2$, $Z=COOEt$	>98 (15)	<2 (14)
1b) $n=0$, $X=CH_2$, $Z=CONEt_2$	10 (14)	1(13)
1c) $n=0$, $X=CH_2$, $Z=$ 	14:1 R/S (14)	1:1 (13)
1d) $n=1$, $X=CH_2$, $Z=$ 	13:1 R/S (15)	1:1 (14)
1e) $n=1$, $X=O$, $Z=COOEt$	2.5 (16)	1 (15)

Stille Macrocyclization

Two different Stille macrocyclizations to (-)-Macrolactin A:

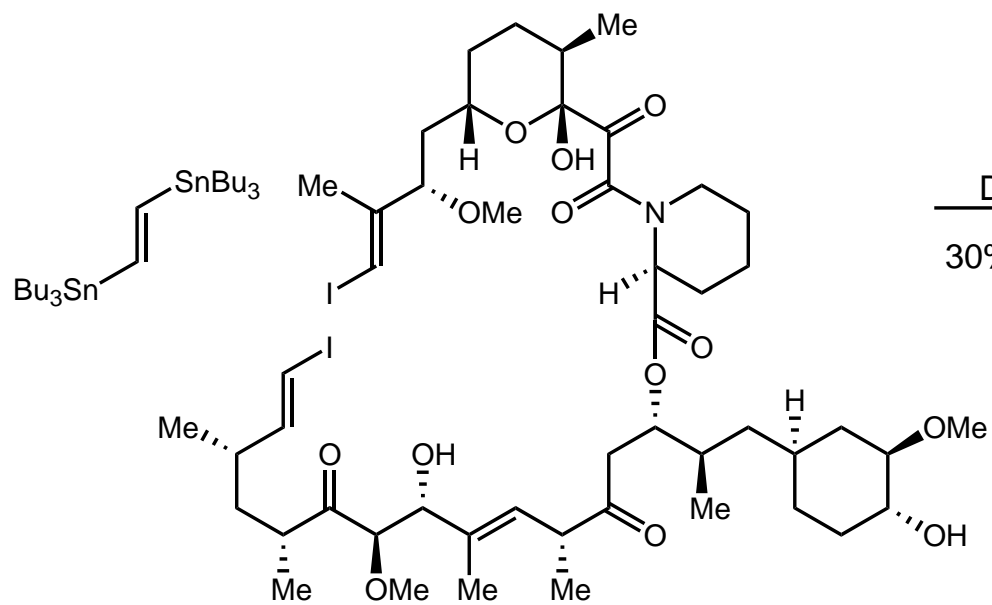


Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095-13096



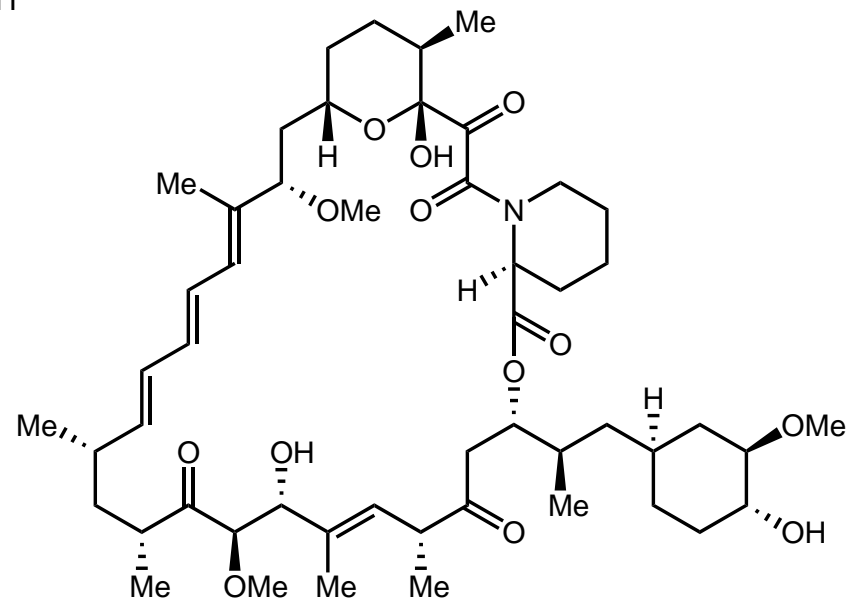
Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 3501-3504

Stille Stitching

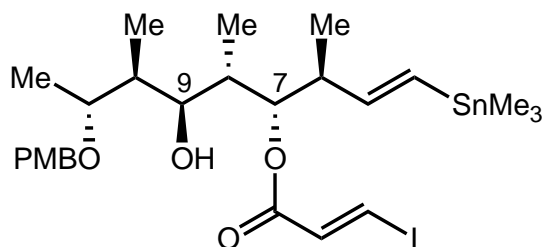


to Rapamycin

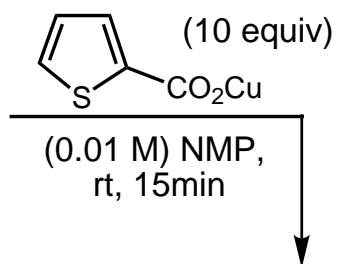
20 mol% Pd(CH₃CN)₂Cl₂, DIPEA,
DMF/THF (1:1) (0.003 M), 25°C, 24hr;
(28% product, 30% recovered SM,
30% intermediate iodostannane precursor)



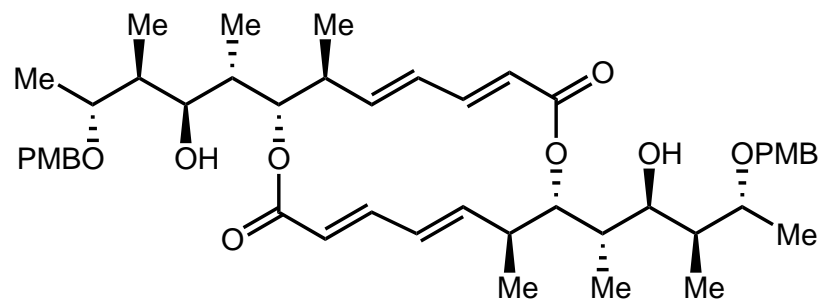
Cu(I) Promoted Stille Cyclodimerization



9.6 : 1 (C₇:C₉ regioisomer)



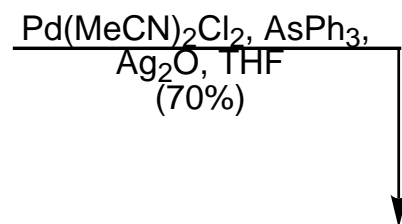
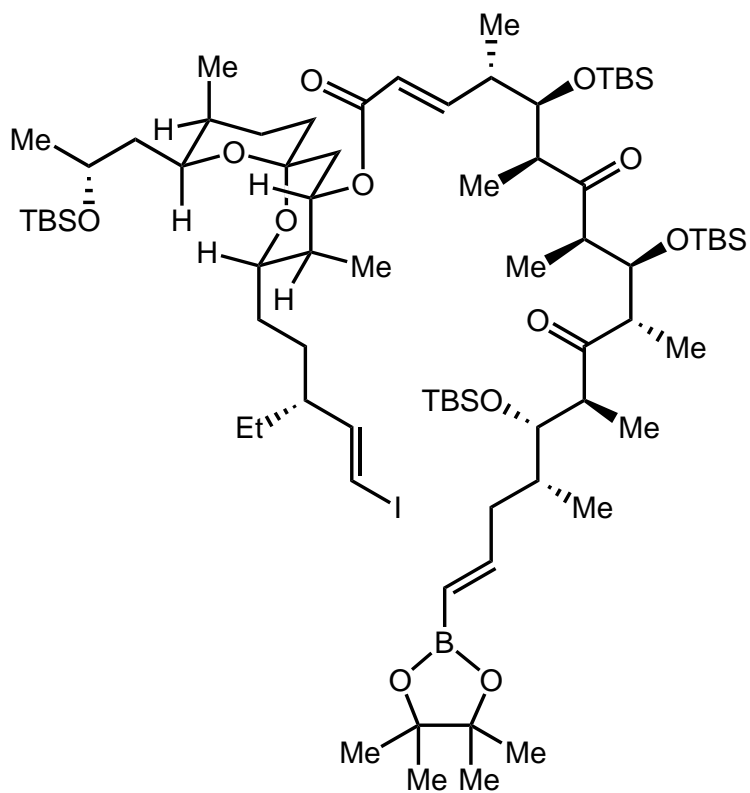
to Elaiolide



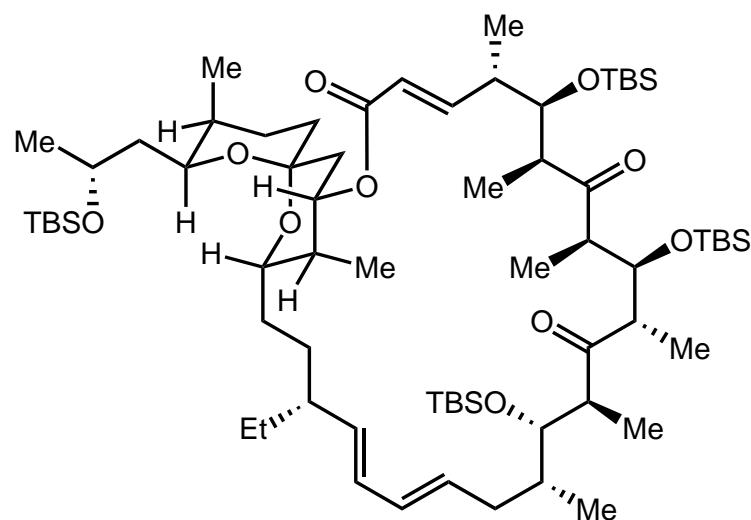
80% (88% based on C₇ regioisomer)

but (0.2 M) NMP afforded 42% dimer and 47% trimers

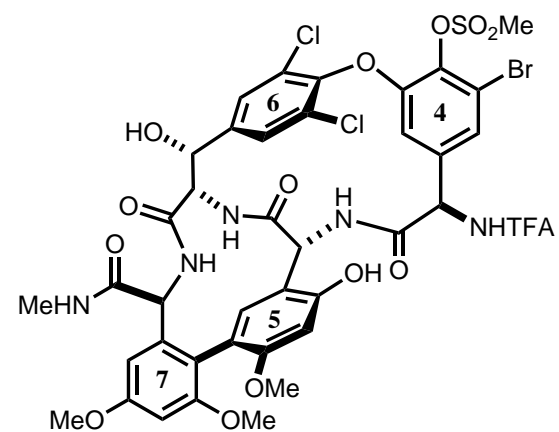
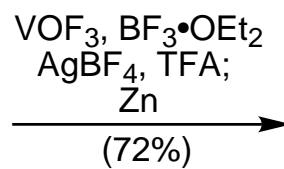
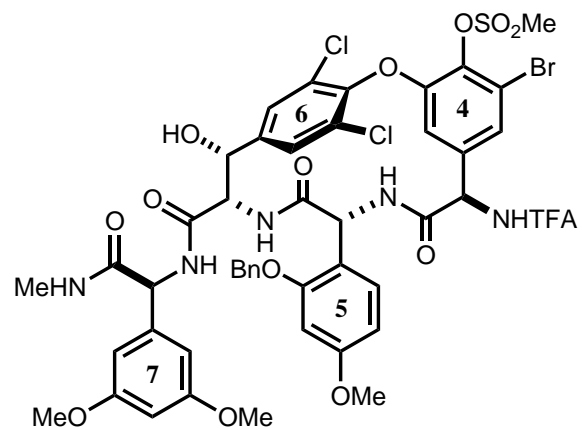
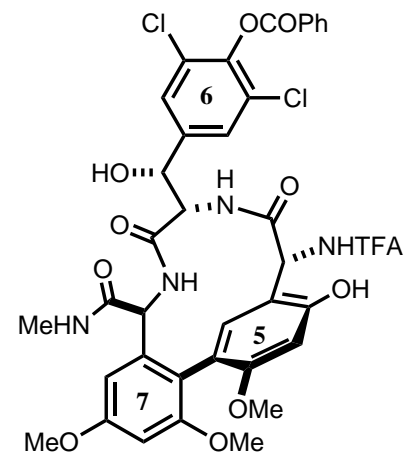
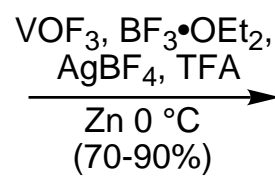
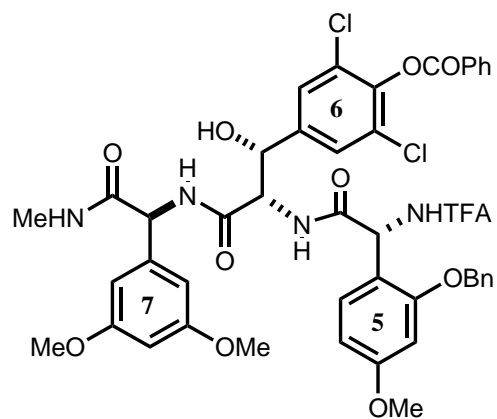
Suzuki Macrocyclization



to Rutamycin B



Aryl-Aryl Cyclization



Macrocyclization III

C-X Bond Formation

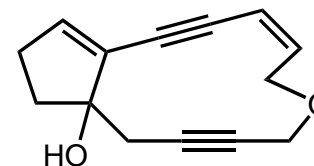
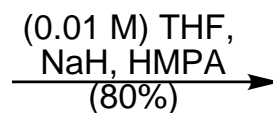
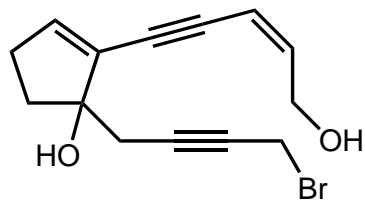
Bis-alkylation
Macrotransacetalization
Aryl-ether coupling

C=C Bond Formation

Wittig-like cyclization
Ring Closing Metathesis

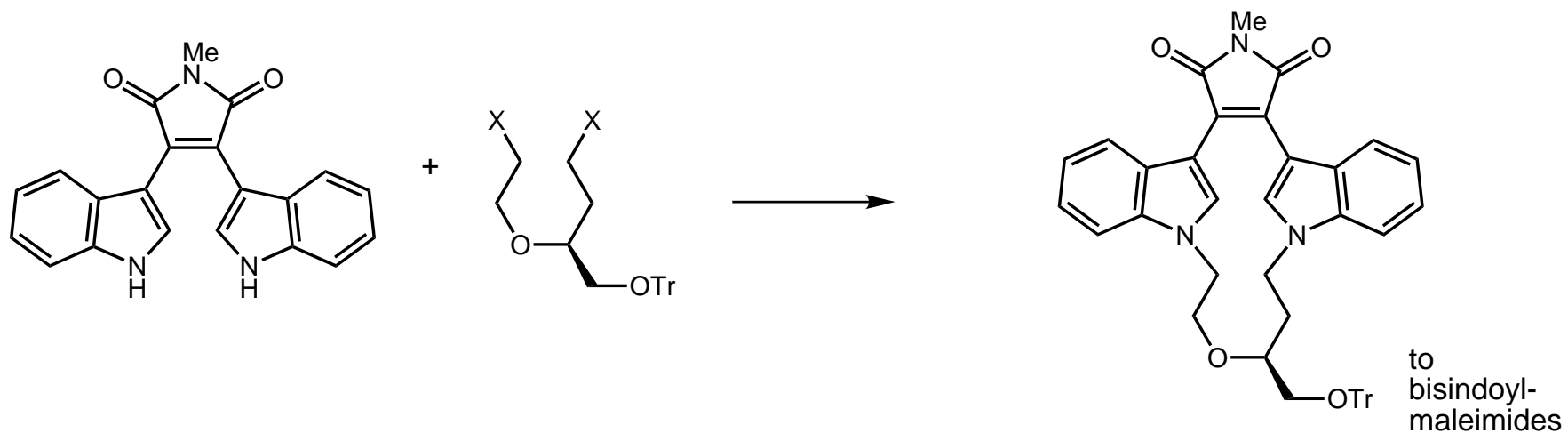
via exo-Ring Formation

Intramolecular Diels Alder
[3+2]
Intramolecular cyclopropanation



to Neocarzinostatin-Chromophore
analogues

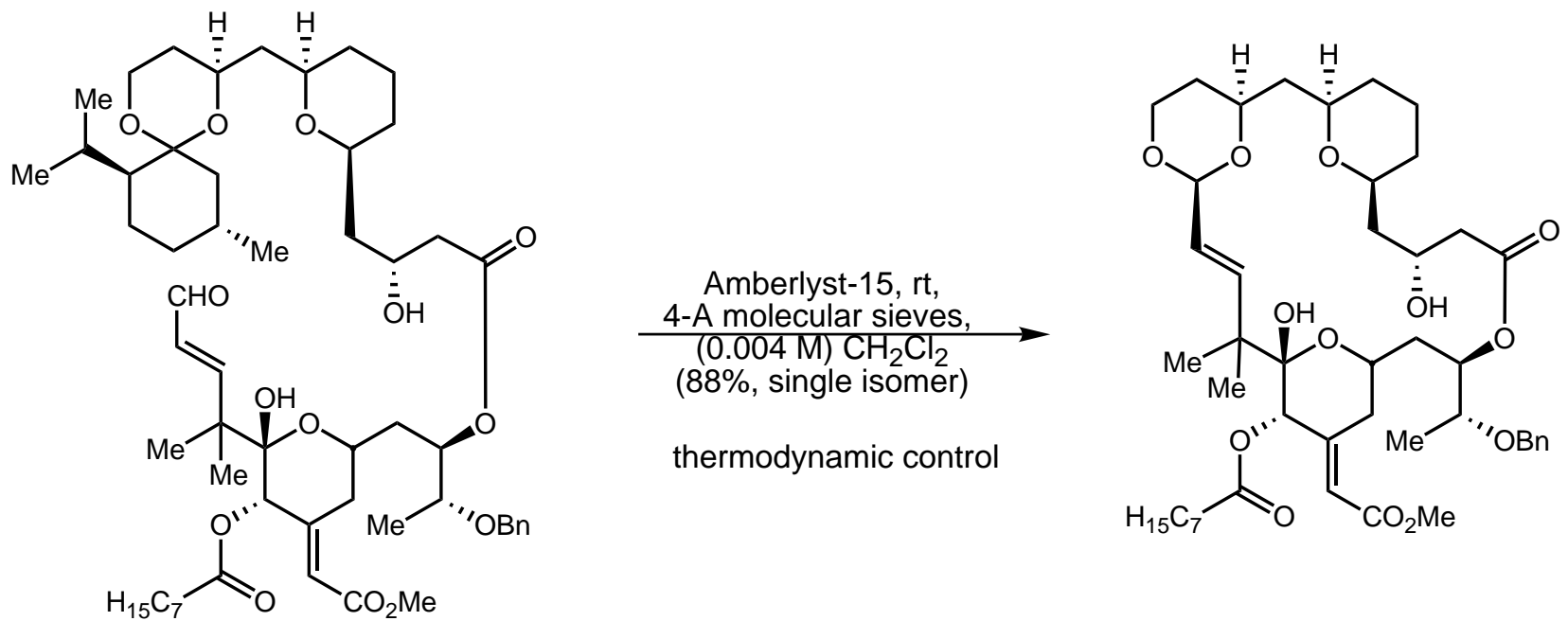
Cyclizations via Bis-Alkylation



Solvent	base	yield (%)
DMF	Cs₂CO₃	56%
THF	Cs ₂ CO ₃	0
ACN	Cs ₂ CO ₃	0
DMF	K ₂ CO ₃	40
DMF	NaH	34
THF	NaH	0
toluene	KOH	16
H ₂ O	NaOH	6

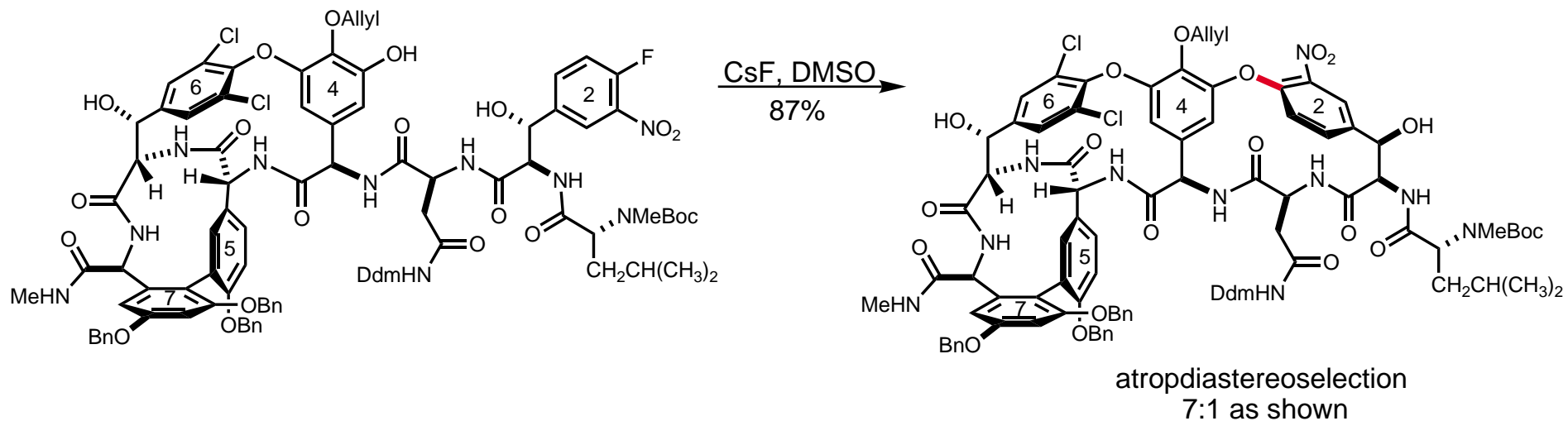
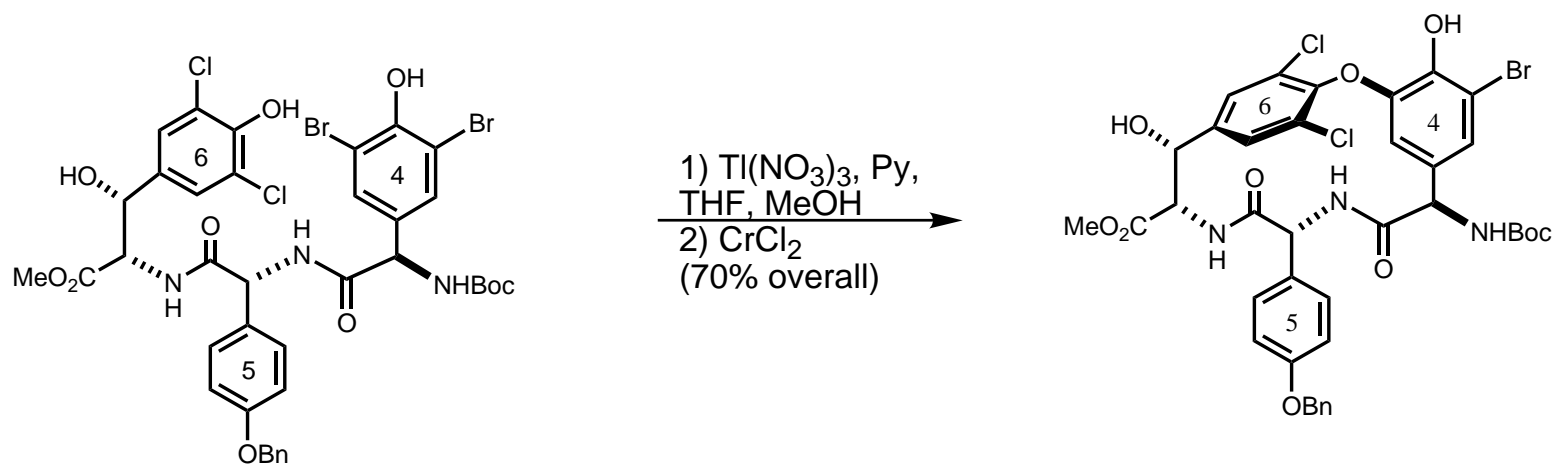
X	M	addn time (h)	yield (%)
OMs	0.0083	72	56
I	0.0083	72	48
OMs	0.029	60	66
I	0.029	60	67
OMs	0.058	60	53
OMs	0.029	6	54
Br	0.029	60	68
Cl	0.029	60	56

Macrotransacetalization

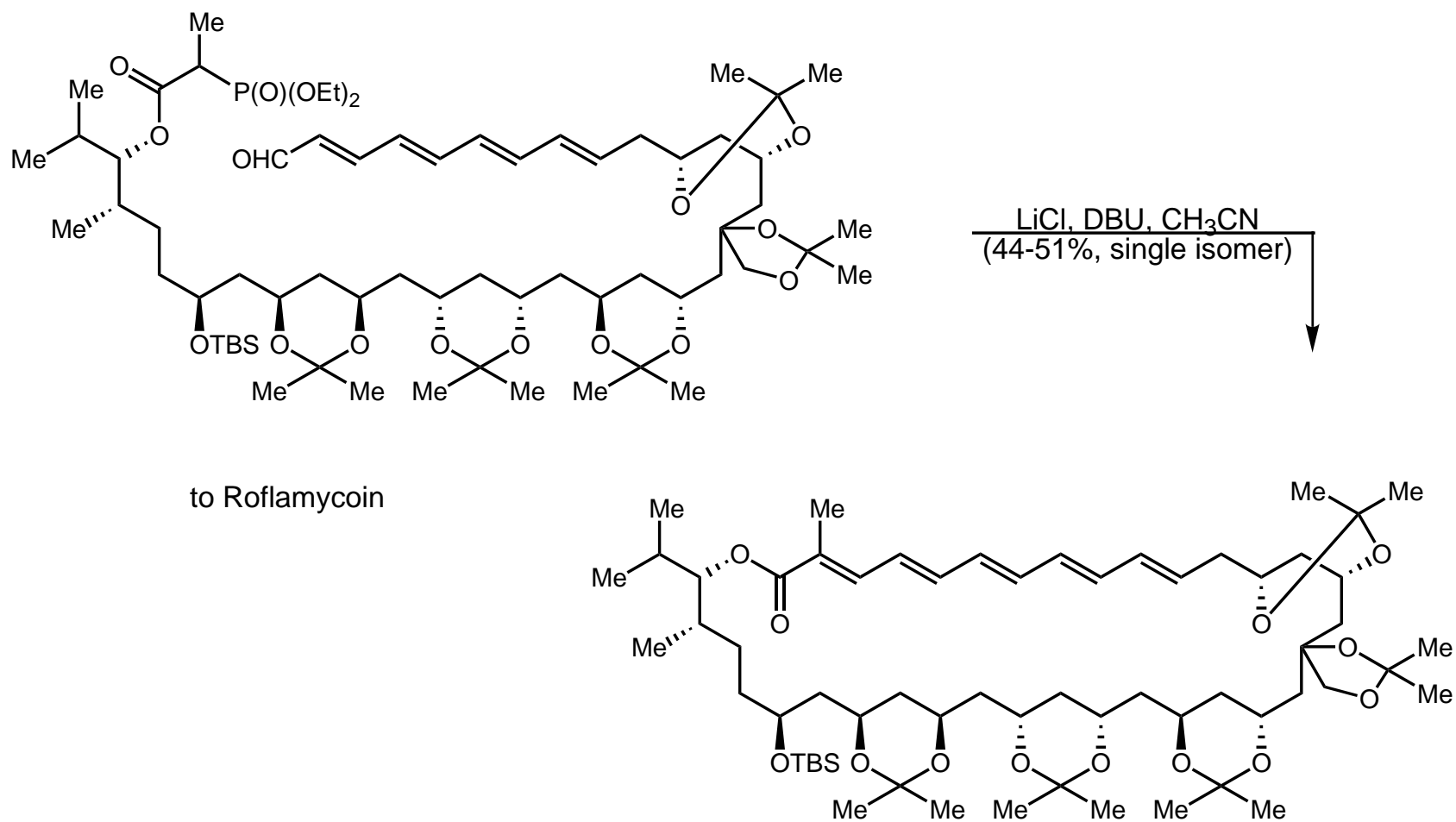


to Bryostatin analogues

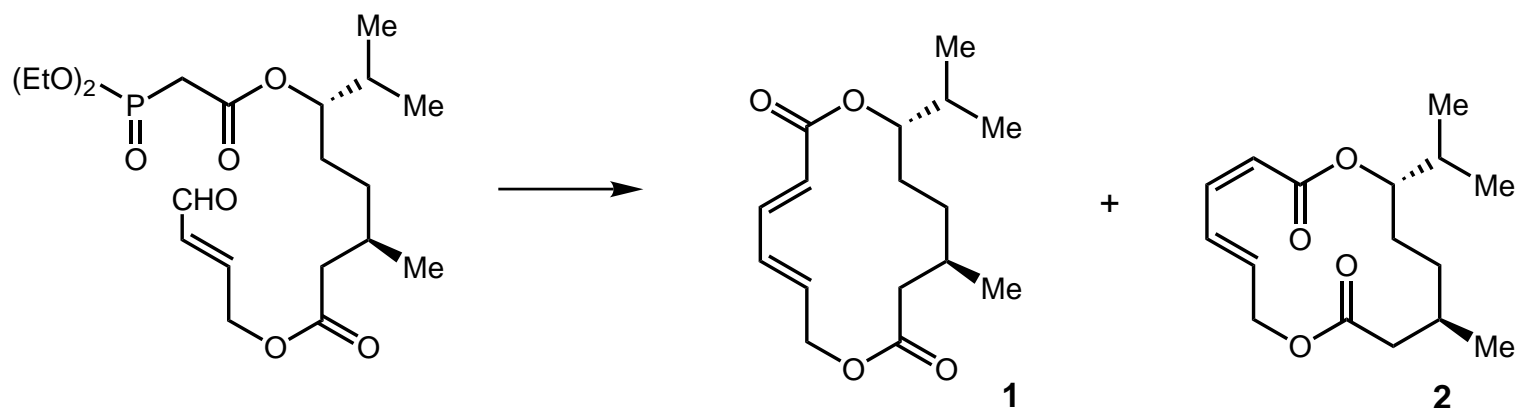
S_NAr Macrocyclization



Intramolecular Horner-Emmons Macrocyclization

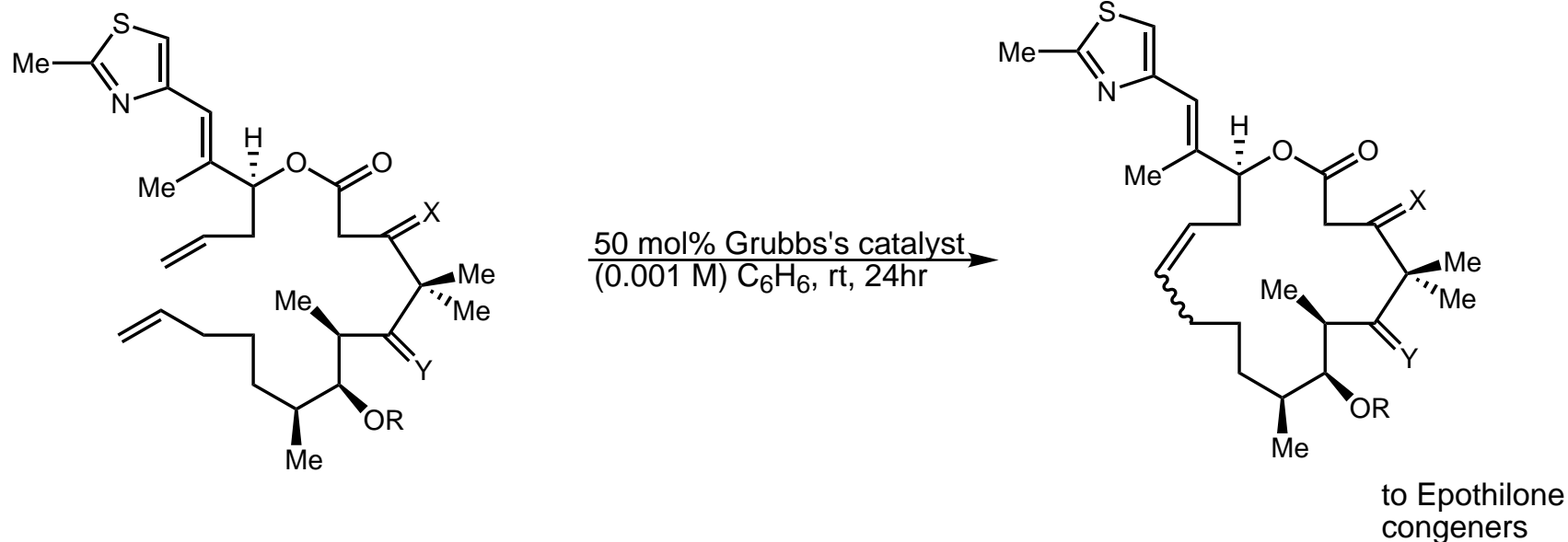


Stereodivergence in an Intramolecular Horner-Emmons Macrocyclization



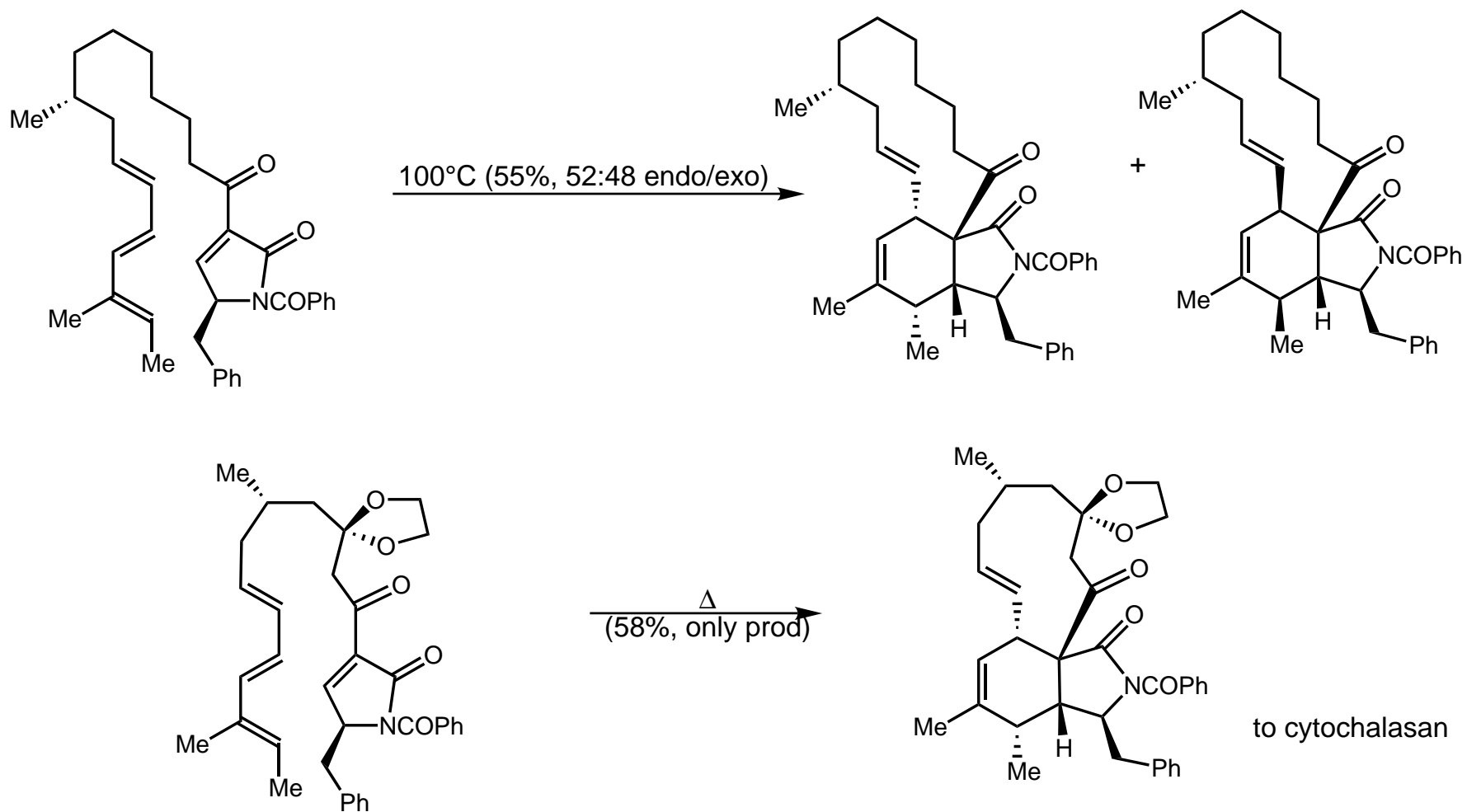
Base (equiv)	Solvent	Temp(°C)	yields (%)	
			1	2
K ₂ CO ₃ (6) / 18-crown-6 (12)	toluene	65	62	12
K ₂ CO ₃ (6) / 18-crown-6 (12)	toluene	80	mix	mix
K ₂ CO ₃ (6) / 18-crown-6 (12)	THF	65	0	0
KHMDS (1.1) / 18-crown-6 (3)	toluene	25	49	3
KHMDS (1.1) / 18-crown-6 (3)	CH ₃ CN	25	22	8
DBU (10) / LiCl (10)	CH ₃ CN	25	<3	53
NaH (1)	THF	35	51	10

Remote Effects in RCM

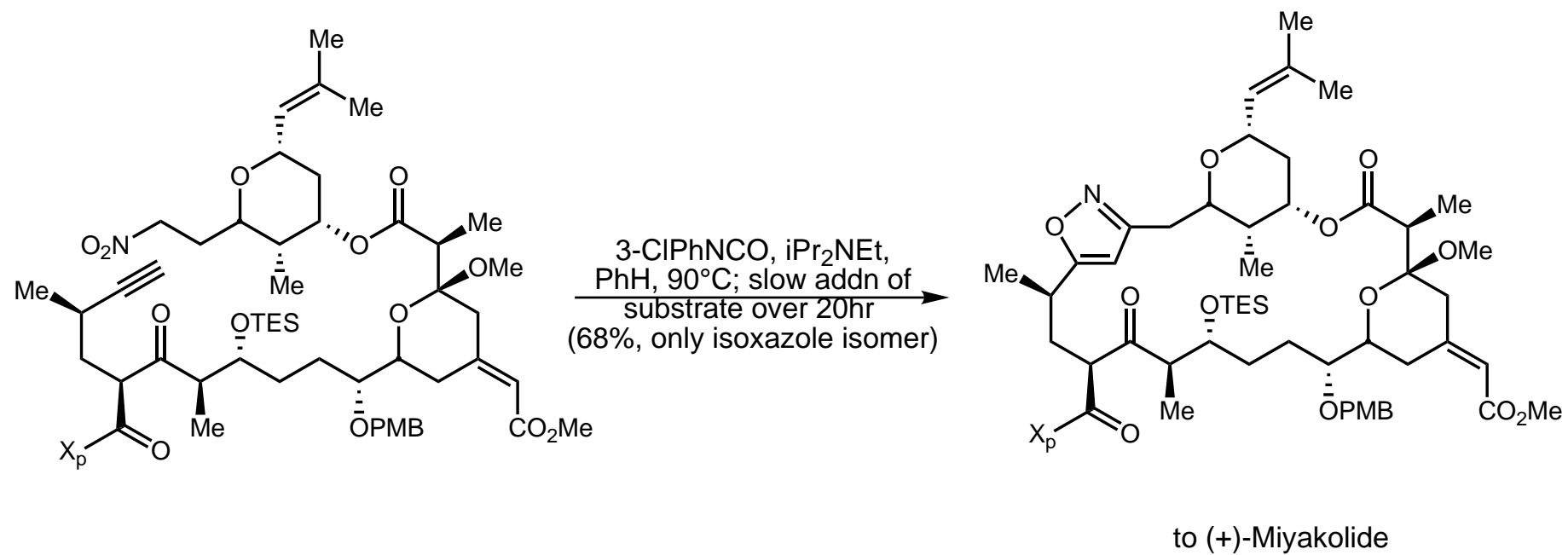


X	Y	R	E/Z (yield%)
α-OH	α-OTPS	TBS	1 : 3 (86)
α-OTES	α-OTPS	TBS	1 : 5 (80)
α-OTBS	=O	TBS	1.7 : 1 (86)
α-OH	=O	H	1 : 2 (65)
β-OH	α-OTPS	TBS	1 : 9 (81)
β-OTBS	=O	TBS	1 : 2 (88)

Intramolecular Diels-Alder Reactions

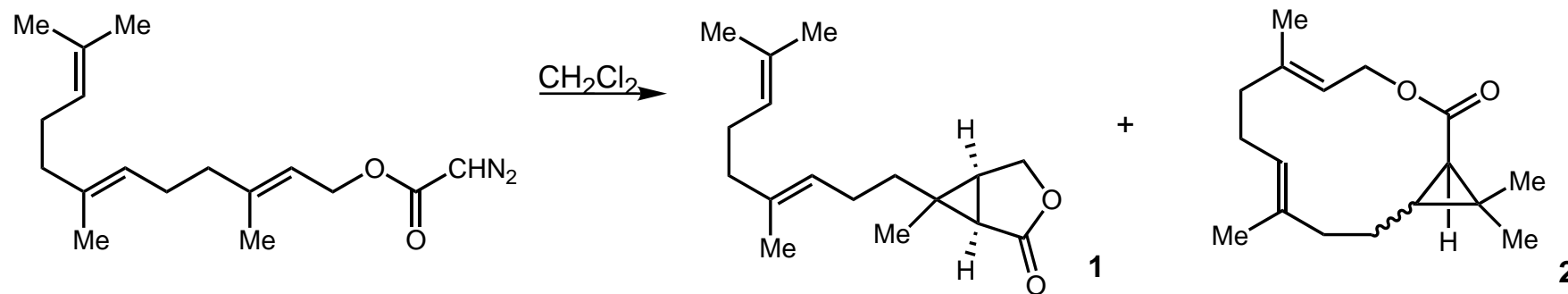


via [3+2] exo-Ring Cyclization



Catalytic Intramolecular Cyclopropanation

Catalyst ligand and product distribution:



catalyst	temp (°C)	yield (%)	1 : 2 trans : 2 cis
$\text{Rh}_2(\text{pfb})_4$	25	56	0 : 51 : 49
$\text{Rh}_2(\text{pfb})_4$	10	60	0 : 48 : 52
$\text{Rh}_2(\text{tfa})_4$	25	50	0 : 77 : 23
$\text{Rh}_2(\text{NHCOCF}_3)_4$	25	60	0 : 75 : 25
$\text{Rh}_2(\text{OAc})_4$	25	63	0 : 86 : 14
$\text{Rh}_2(\text{oct})_4$	25	50	0 : 84 : 16
$\text{Rh}_2(\text{cap})_4$	40	79	100 : 0 : 0

Table 10. Some properties of the alkali metal cations [94]

M^{\oplus}	Ionic radius Charge/Surface		Polarizability
	[Å]	[Z/Å ²]	[Å ³]
Li	0.78	0.130	0.03
Na	0.98	0.085	0.30
K	1.33	0.045	1.10
Rb	1.49	0.035	1.90
Cs	1.65	0.030	2.90
Tl	1.40 [93]		4.30 [51 a]