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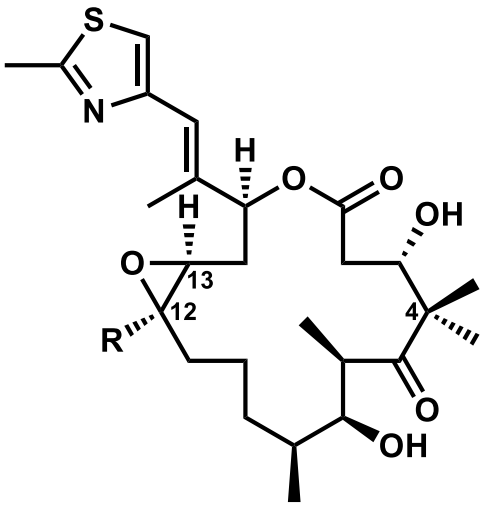

2: R = H; epothilone A
3: R = CH_3; epothilone B

Reporter: Yangyang Jiang、Jiawei Meng、Feipeng Han

Supervisors: *Prof.* Tao Ye
***Dr.* Yian Guo**

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Contents

1.Introduction

2.Total Synthesis of Epothilone

Ⅰ. **S. J. Danishefsky:** *J. Am. Chem. Soc.* **1997**, *119*, 42, 10073 - 10092.

Ⅱ. **M. Shibasaki:** *Angew. Chem.* **2000**, *39*, 209 - 213.

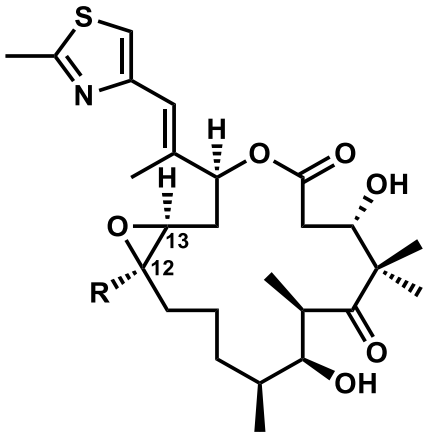
Ⅲ. **M. A. Avery:** *Org. Lett.* **2001**, *3*, 3607 - 3609.

3.Summary

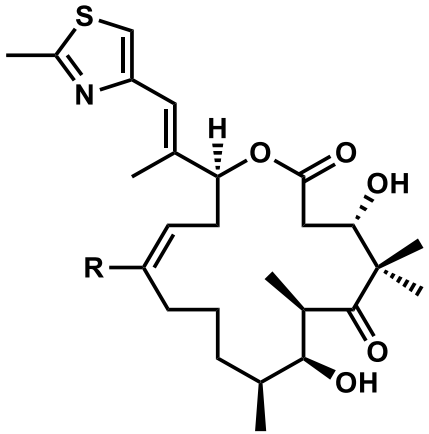
4.Acknowledgement

Introduction

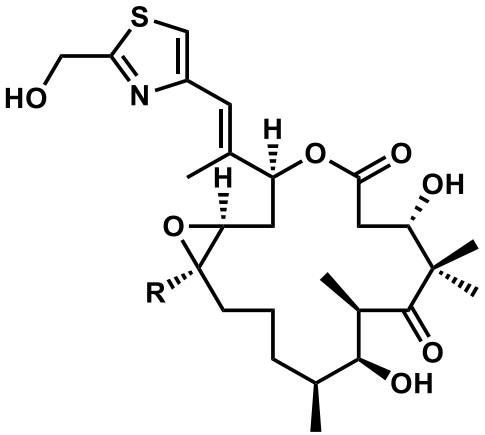
Epothilones family



2: R = H; epothilone A
3: R = CH_3; epothilone B



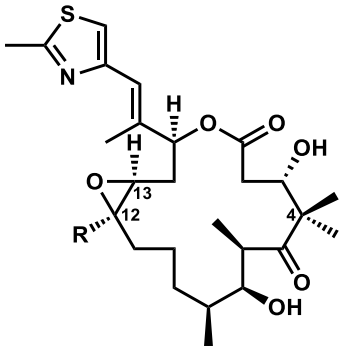
3: R = H; epothilone C
4: R = CH_3; epothilone D



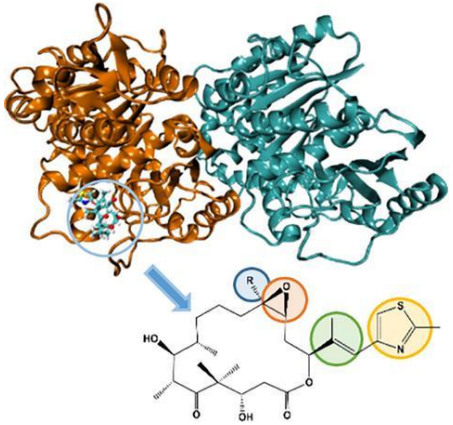
5: R = H; epothilone E
6: R = CH_3; epothilone F

Introduction

Isolation:
Metabolites produced by the soil-dwelling *myxobacterium Sorangium cellulosum*.



2: R = H; epothilone A
3: R = CH_3; epothilone B



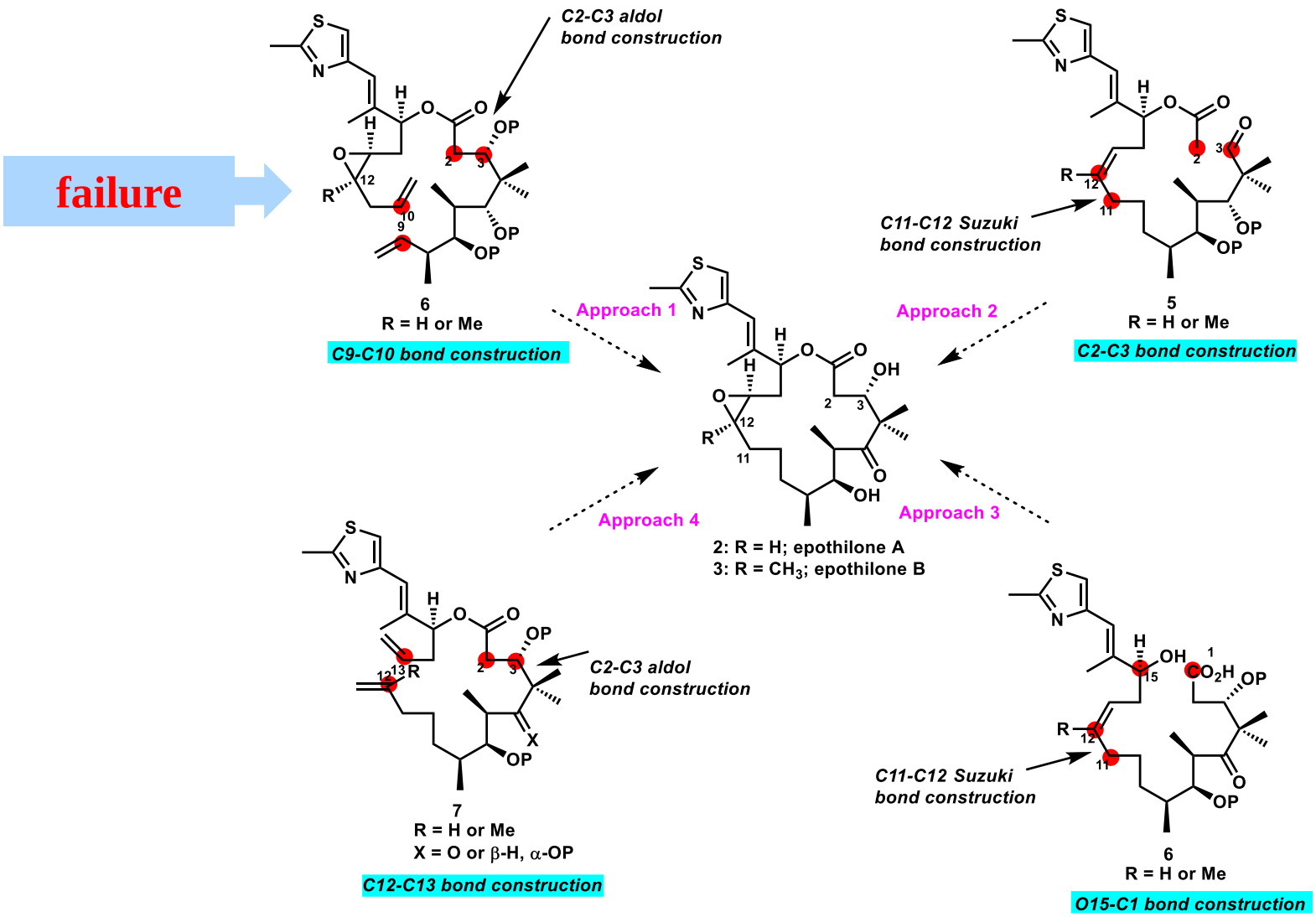
Biological activities:
- The epothilones are a class of potential cancer drugs.
- They prevent cancer cells from dividing by interfering with tubulin.
- Epothilones have better efficacy and milder adverse effects than taxanes.

Structural Features:
- 7 stereogenic centers
- A thiazole moiety, a cis-epoxide and a geminal methyl groups at C4
- A array of three contiguous methylene groups
- Acyl section containing four chiral centers.

H.Reichenbach, et al. *Angew. Chem.* **1996**, *108*, 1671 -1673.

4 possible approaches for Total Synthesis of Epothilone A (2) and B (3)

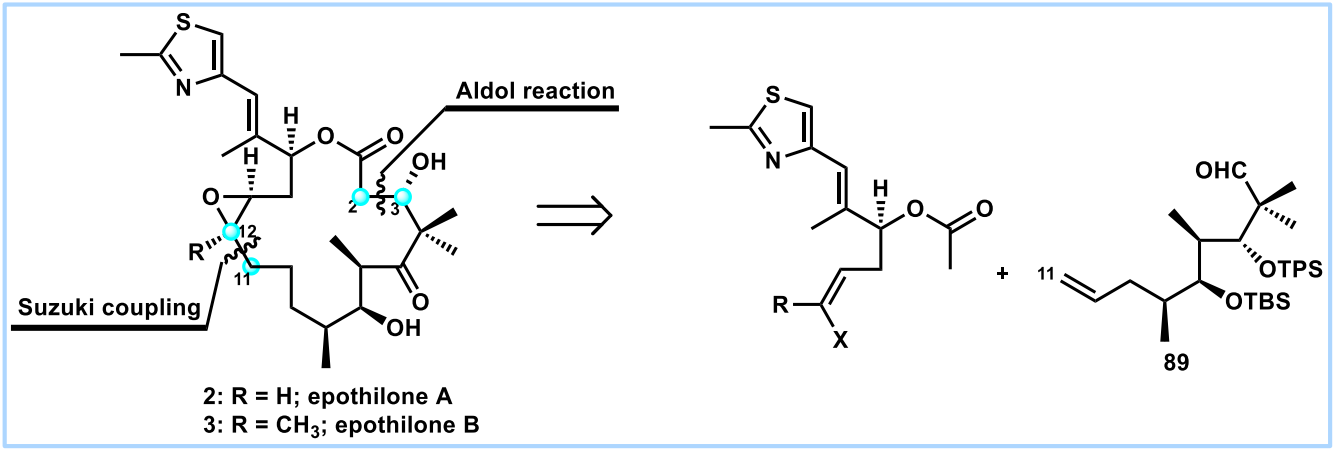
S. J. Danishefsky: *J. Am. Chem. Soc.* **1997**, *119*, 42, 10073–10092.



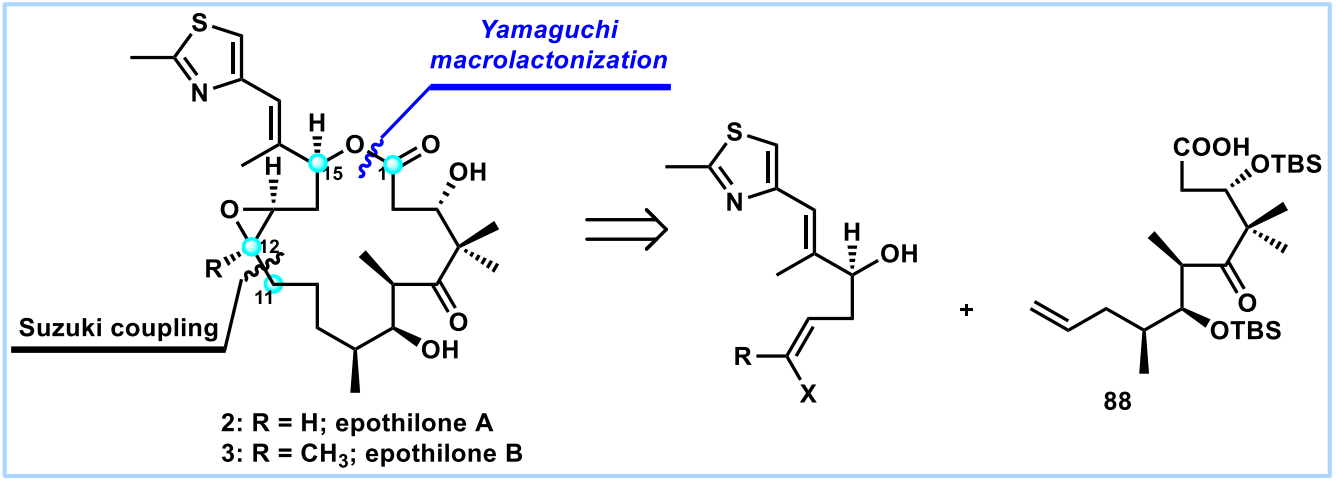
Approach 2 and 3 （Suzuki coupling Strategy)

B-Alkyl Suzuki Strategy

Approach 2:
C2-C3 bond construction strategy

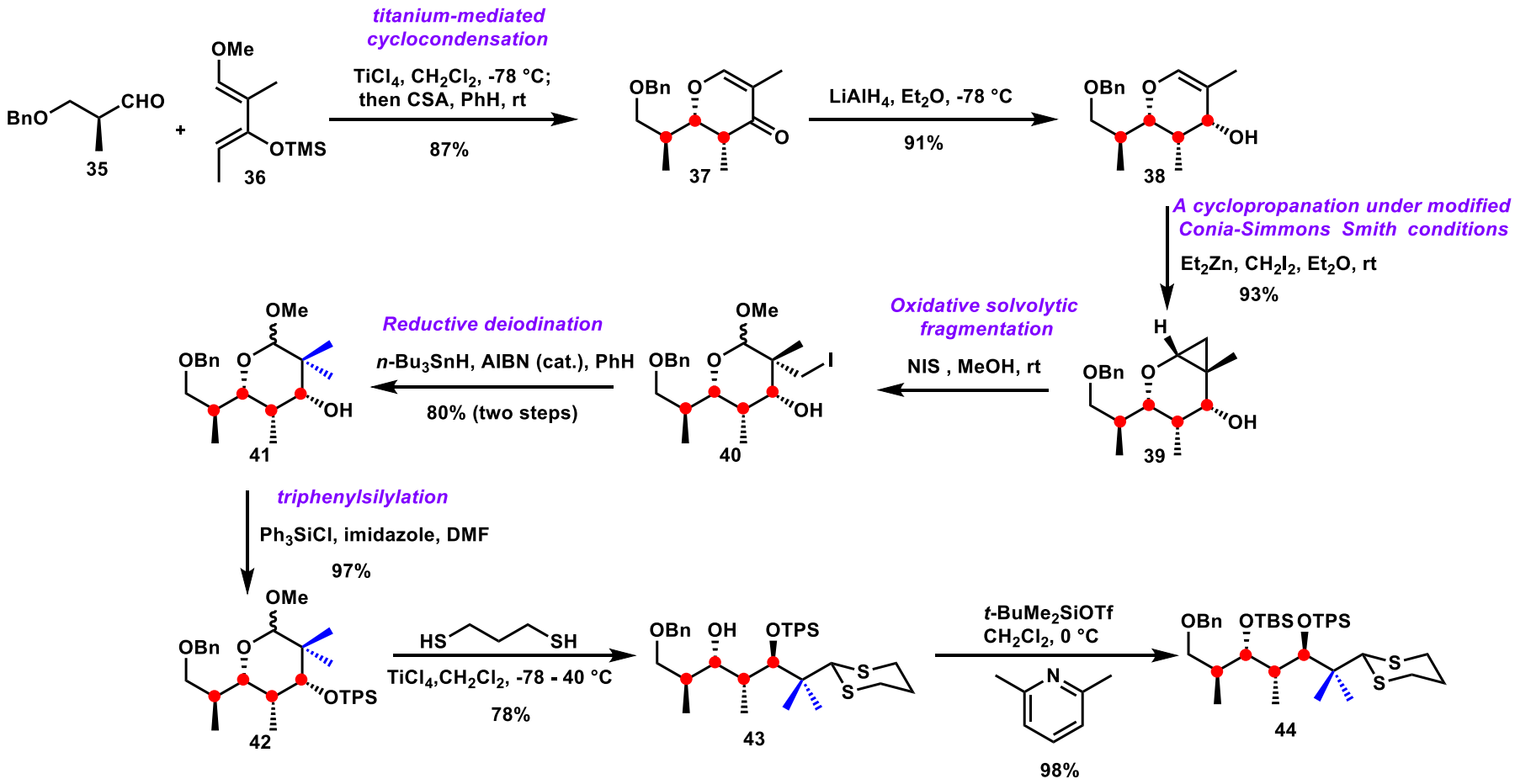


Approach 3:
O15-C1 bond construction strategy

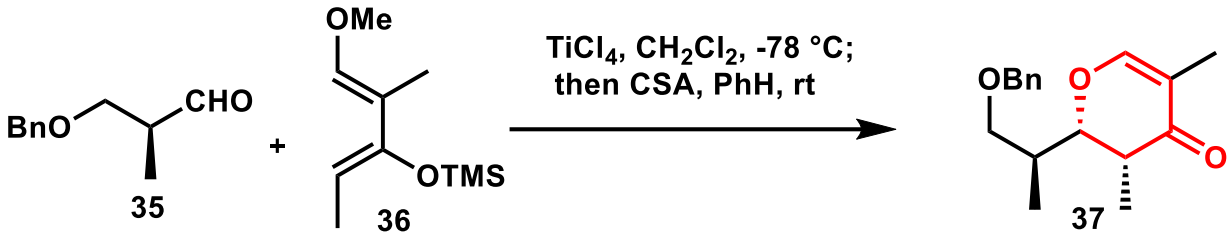


Approach 2 and 3 （Suzuki coupling Strategy)

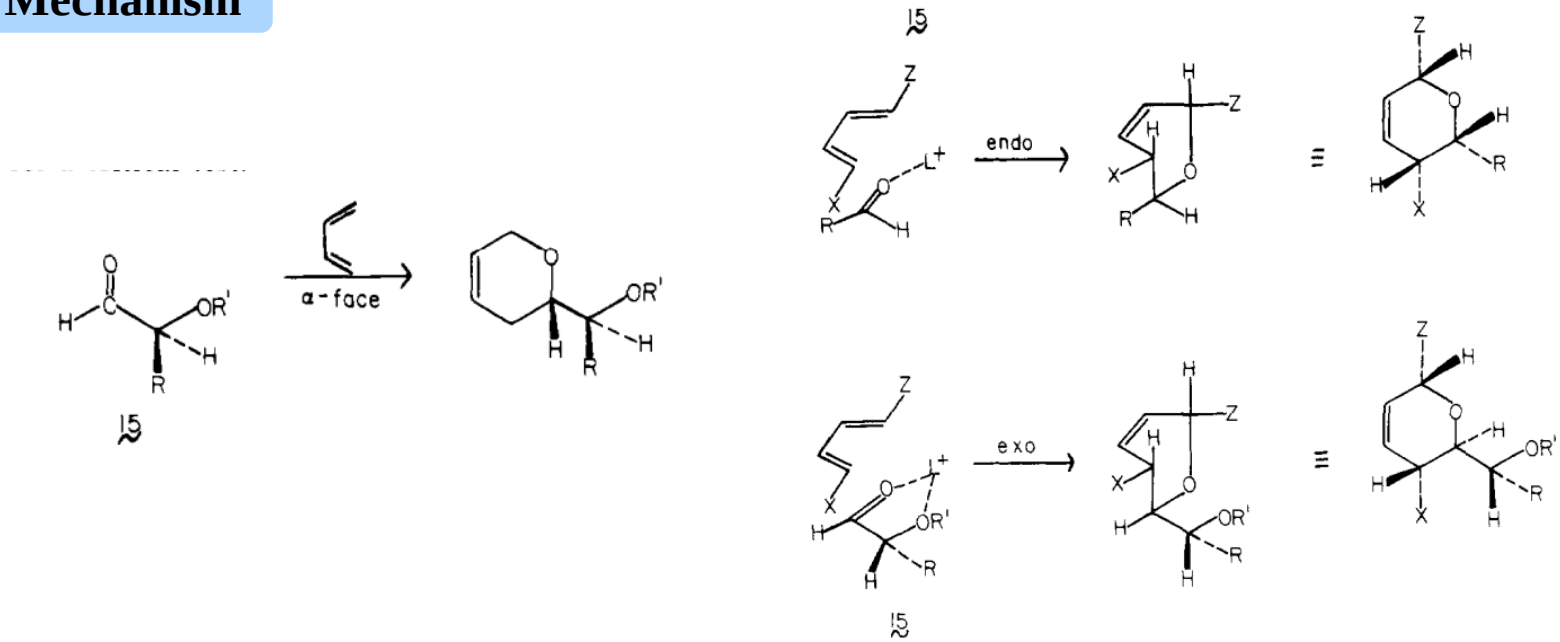
Synthesis of Suzuki coupling partner compound 68



Titanium-mediated cyclocondensation

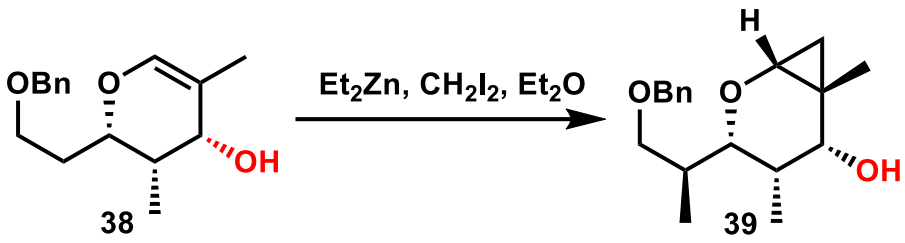


Mechanism



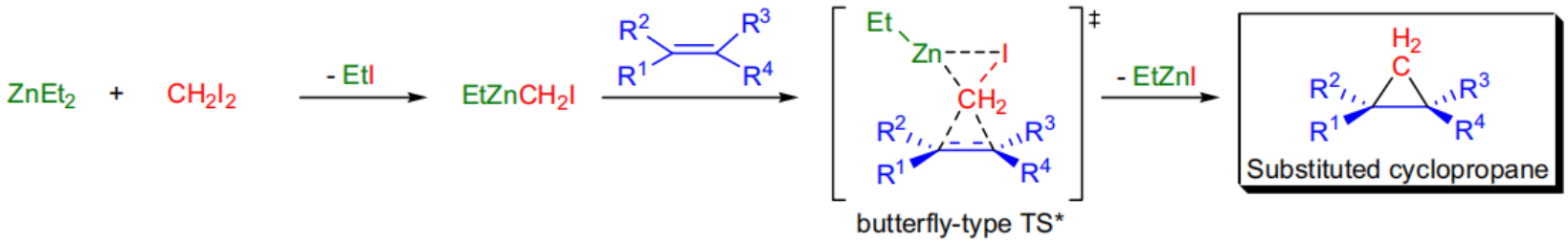
Danishefsky, S, J, et al. *J. Org. Chem.* **1996**, *61*, 8000.
Clardy, J, et al. *J. Am. Chem. Soc.* **1979**,*101*, 7001.

Simmons–Smith cyclopropanation

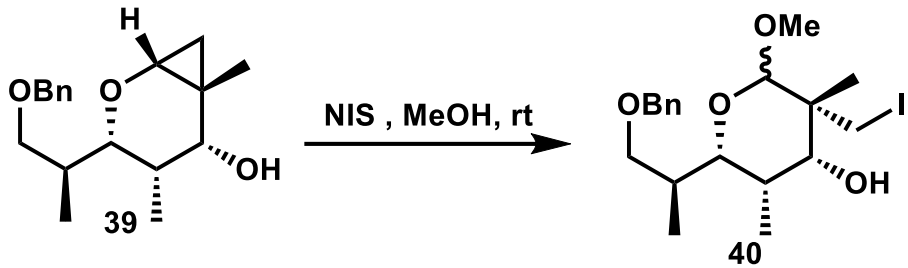


Mechanism

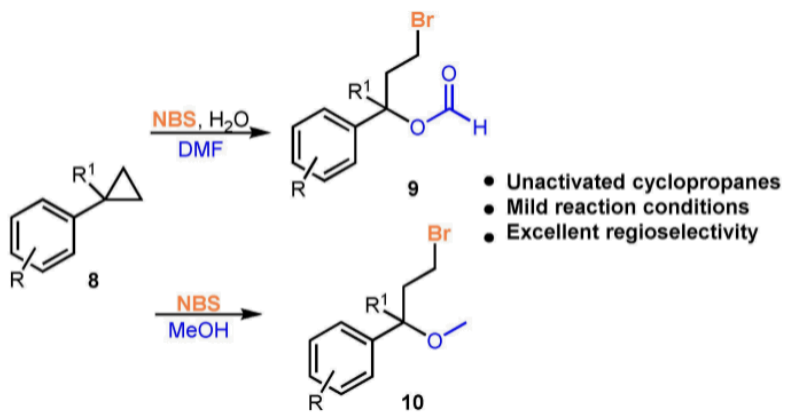
Charette asymmetric modification

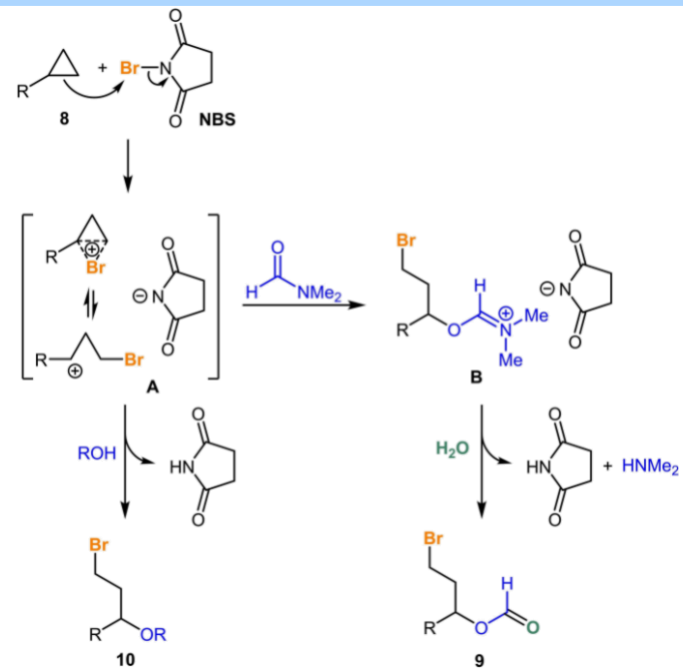


Oxidative solvolytic fragmentation with NIS



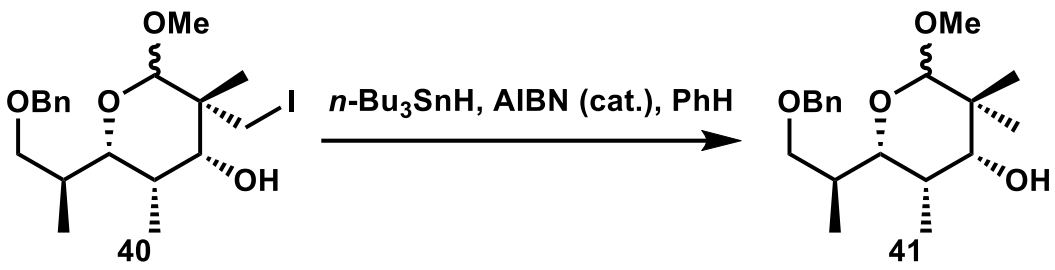
Mechanism



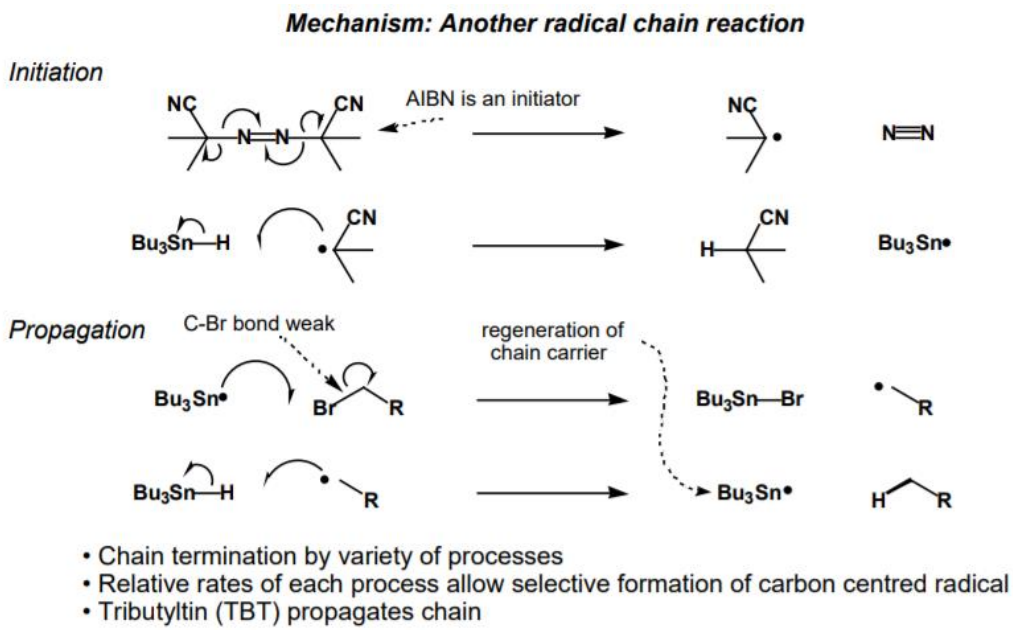


Y.-Y. Yeung, et al. *Adv. Synth. Catal.* **2020**, *362*, 2039 - 2044.

Reductive deiodination

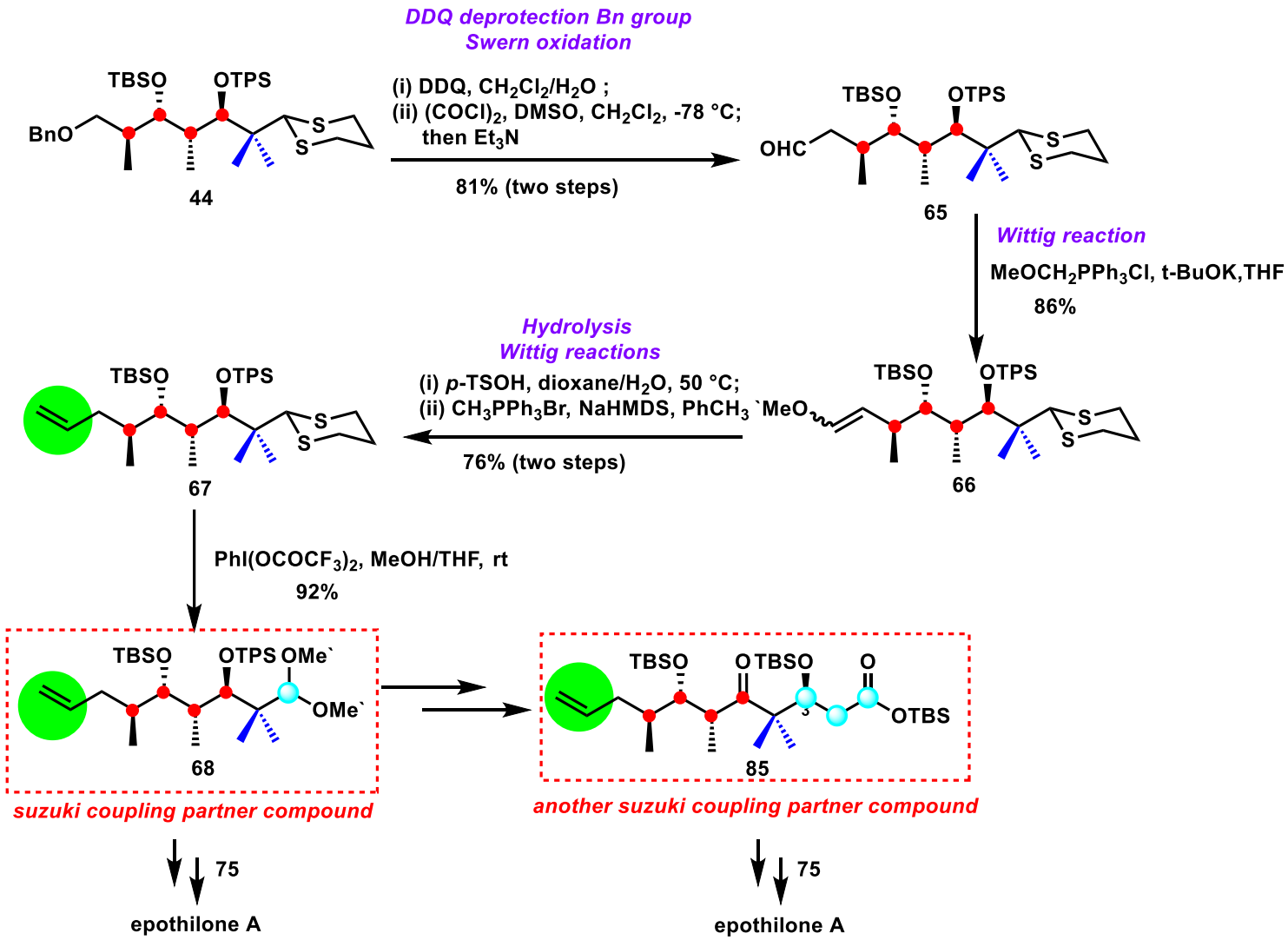


Mechanism

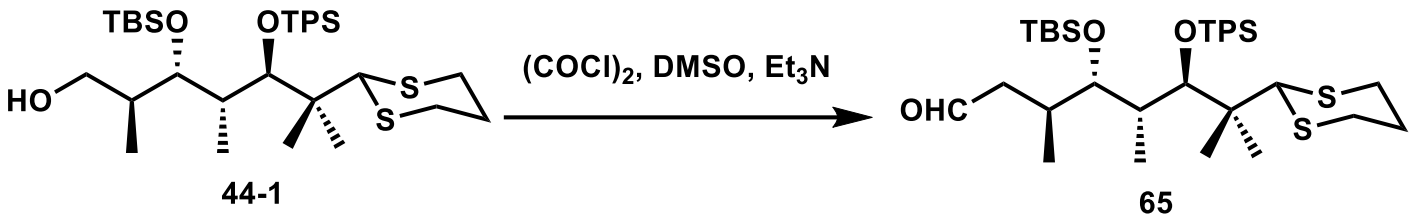


Approach 2 and 3 （Suzuki coupling Strategy)

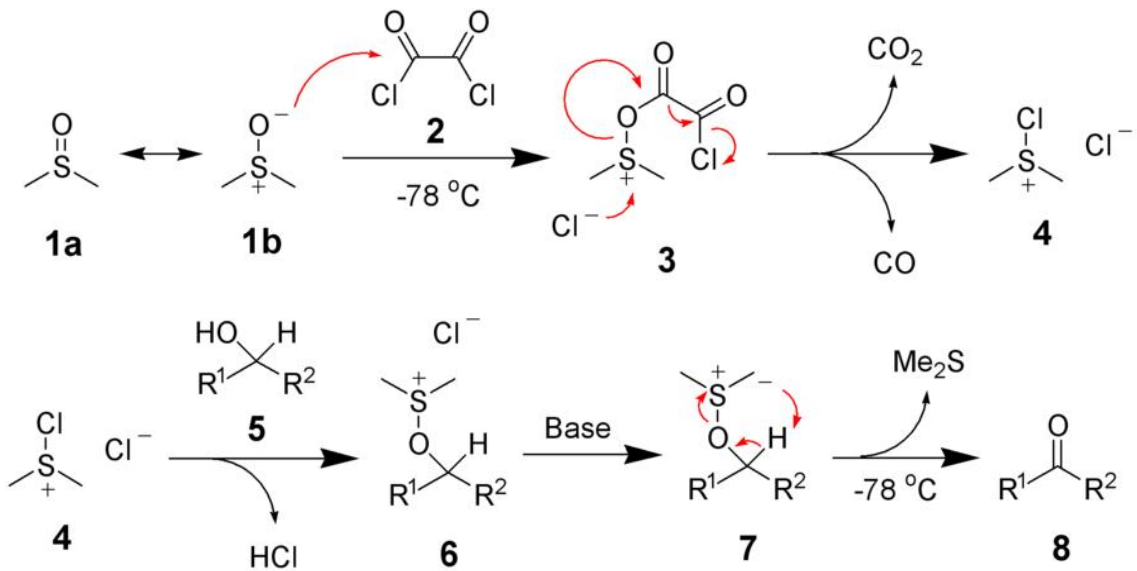
Synthesis of Suzuki coupling partner compound 68



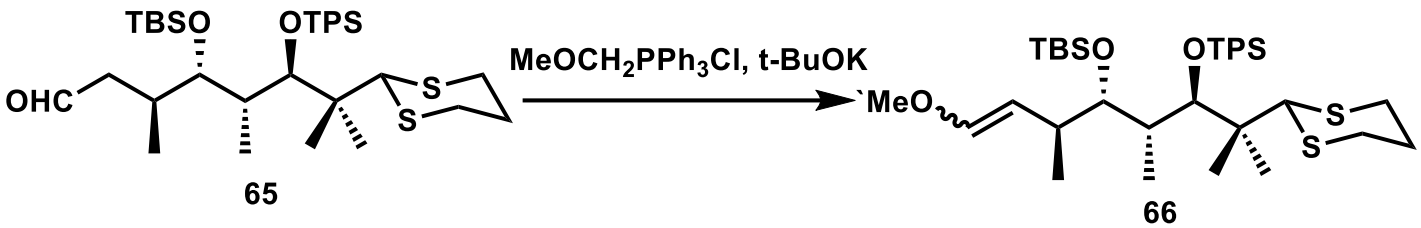
Swern oxidation



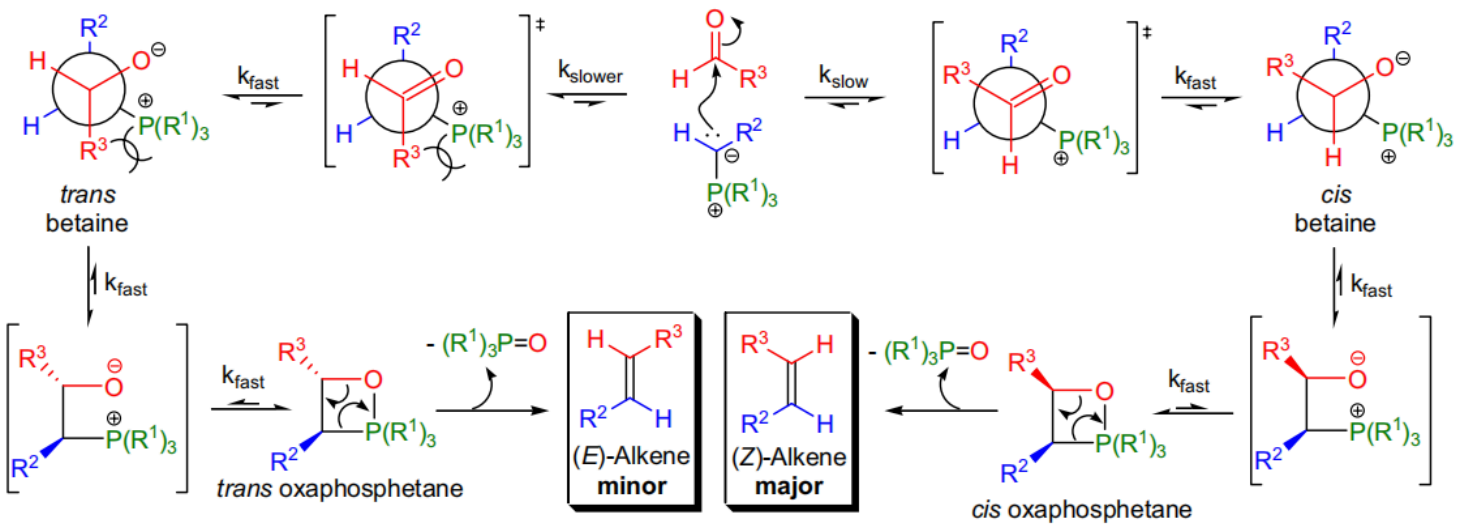
Mechanism



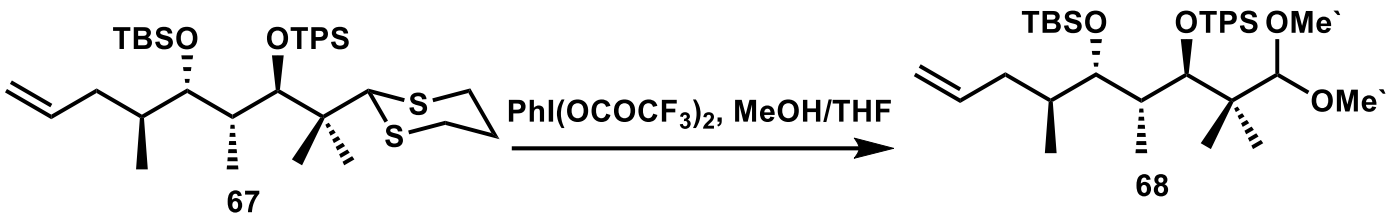
Wittig reaction



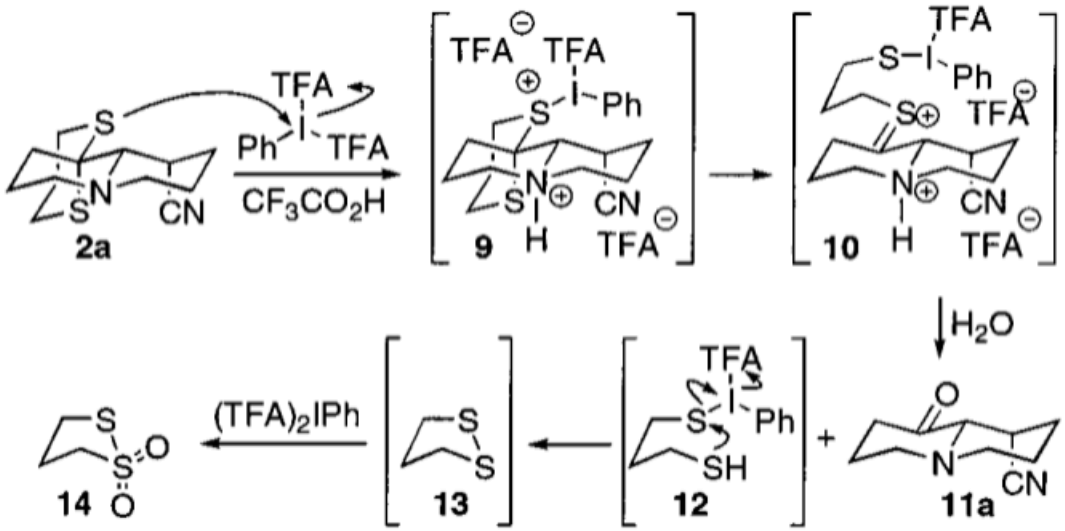
Mechanism



Deprotection of Dithiane with bis(trifluoroacetoxy)iodobenzene



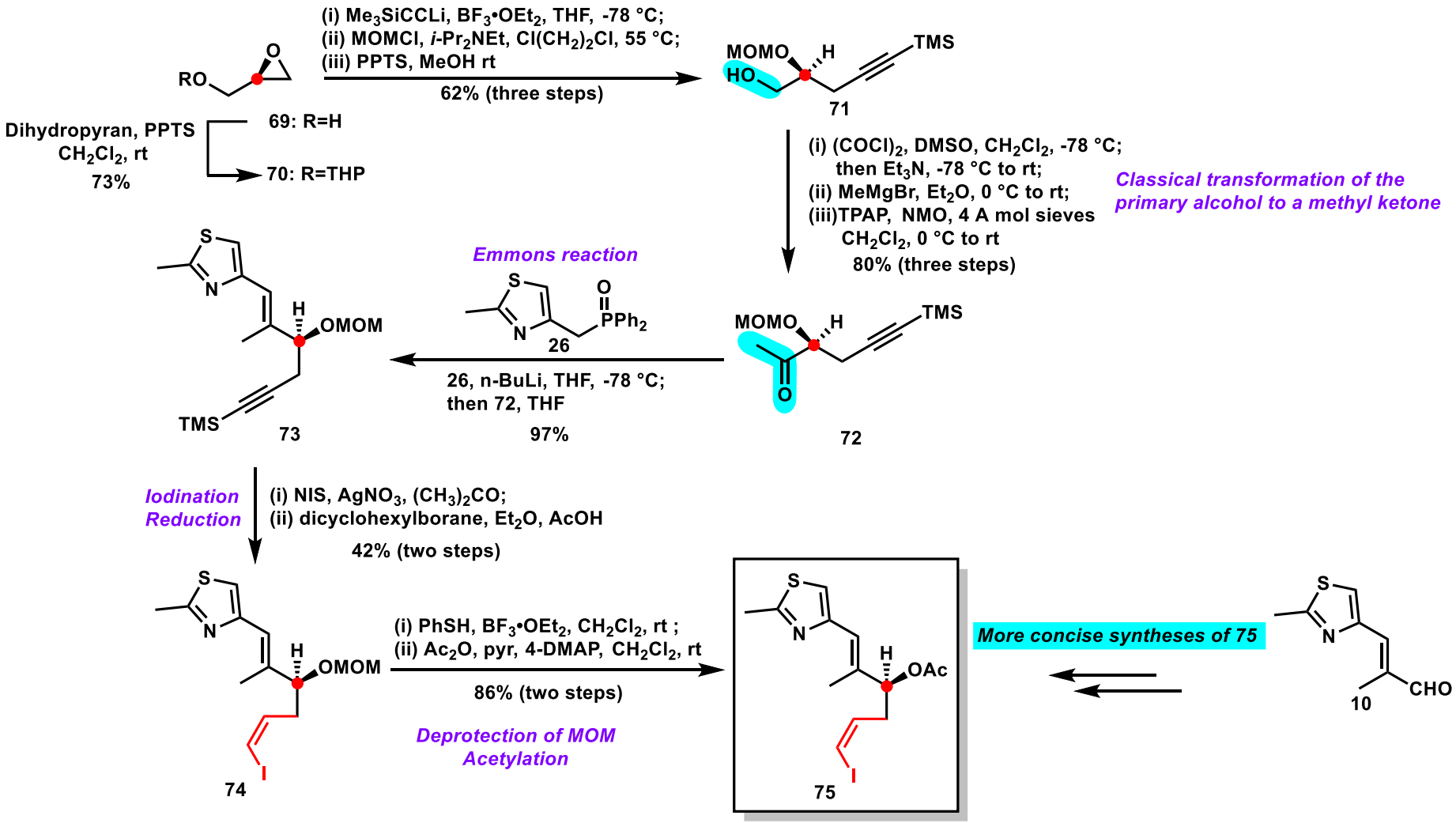
Mechanism



Y. Tu, et al. *J. Org. Chem.* **2001**, *66*, 6502 - 6504.

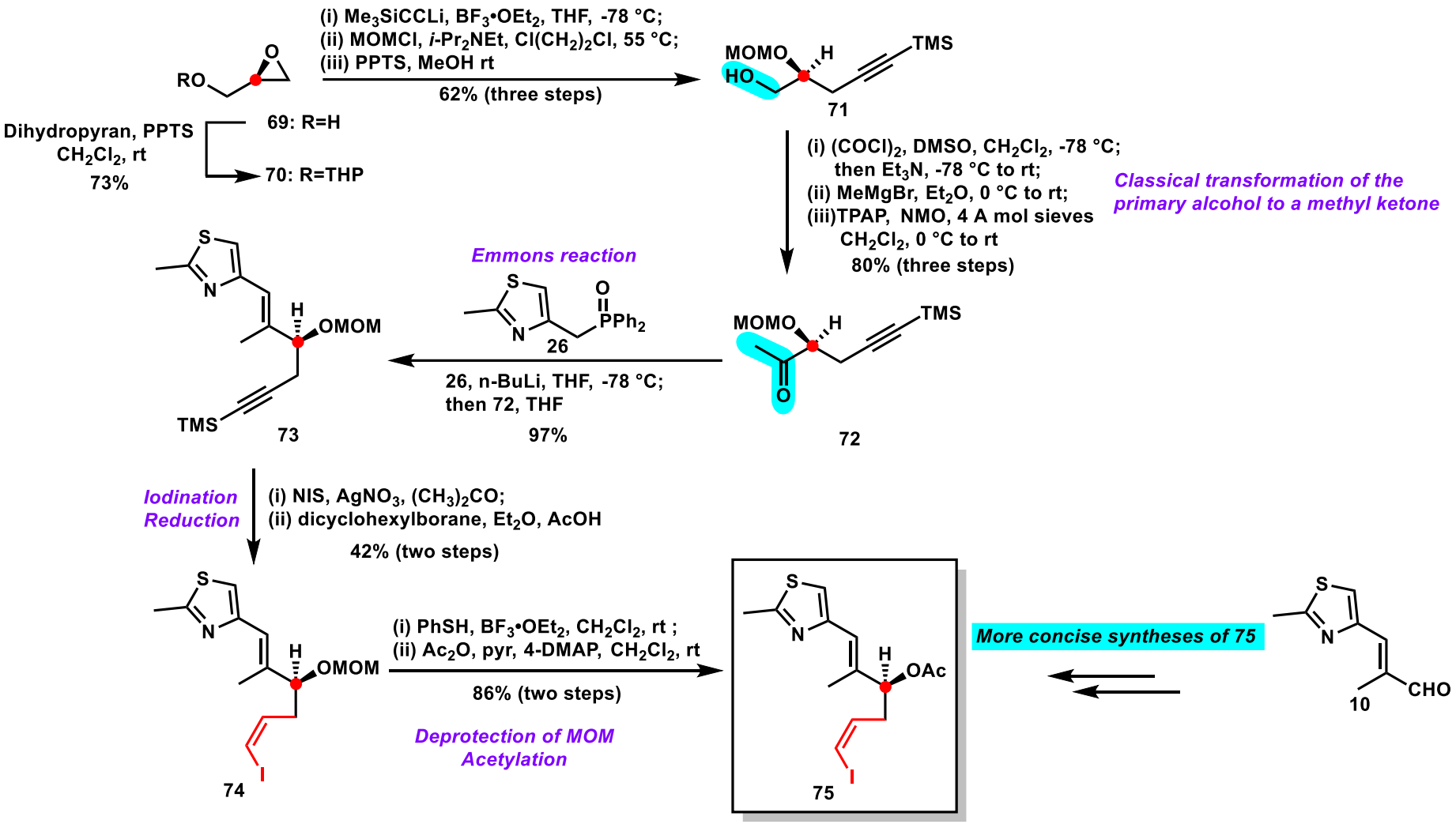
Approach 2 and 3 （Suzuki coupling Strategy)

Synthesis of Suzuki coupling partner compound 75



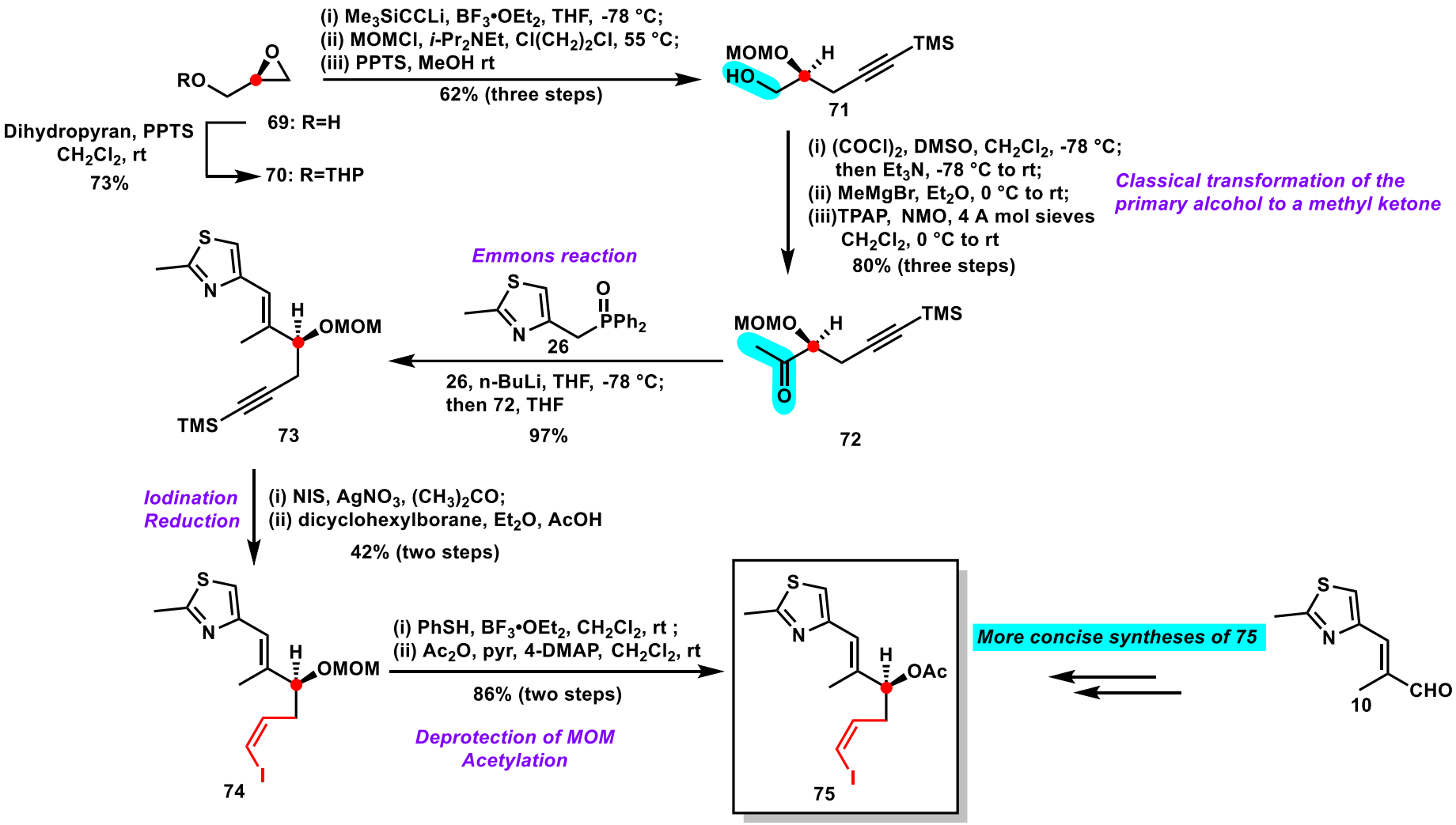
Approach 2 and 3 （Suzuki coupling Strategy)

Synthesis of Suzuki coupling partner compound 75

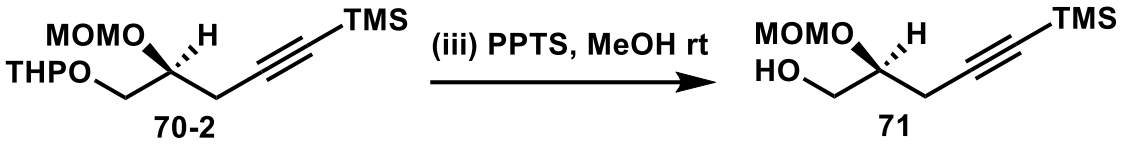


Approach 2 and 3 （Suzuki coupling Strategy)

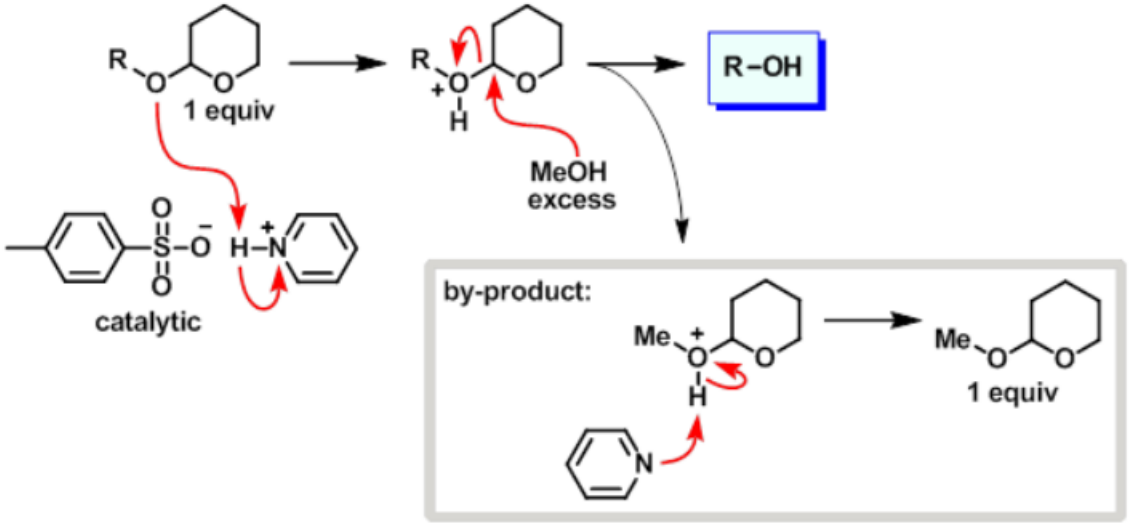
Synthesis of Suzuki coupling partner compound 75



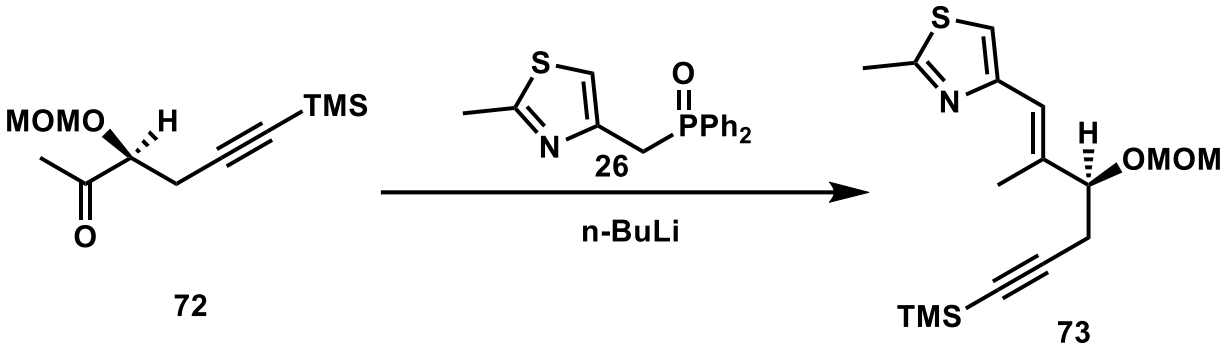
Deprotection of THP with PPTS



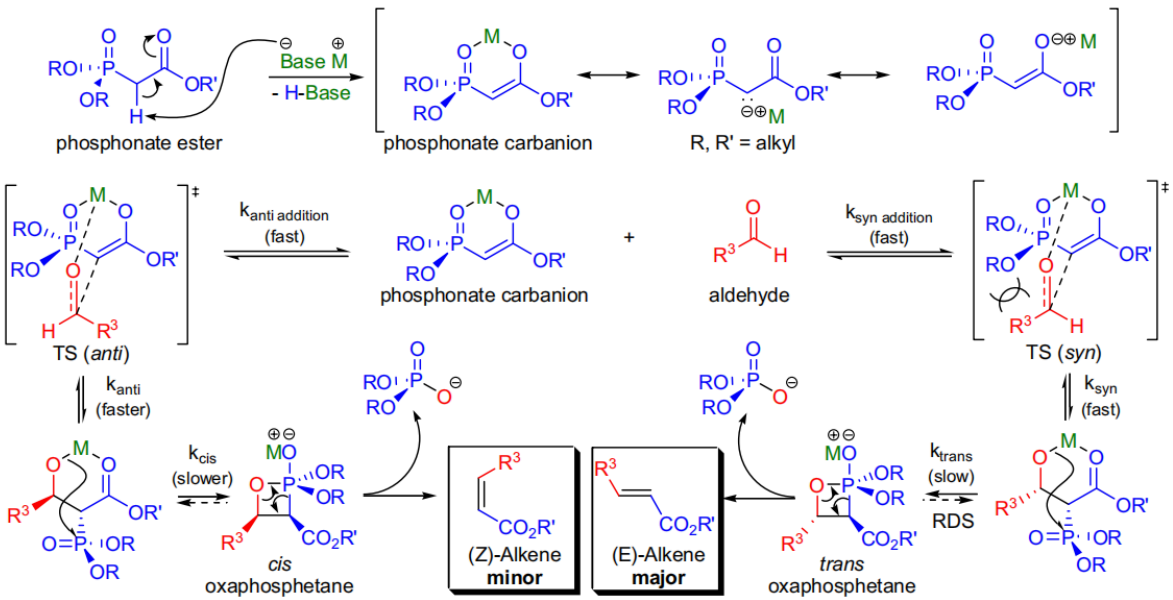
Mechanism



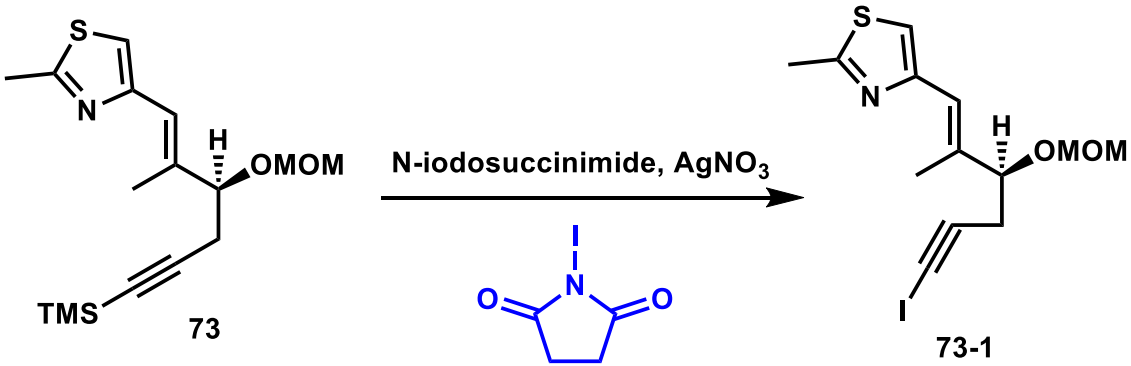
Horner–Wadsworth–Emmons



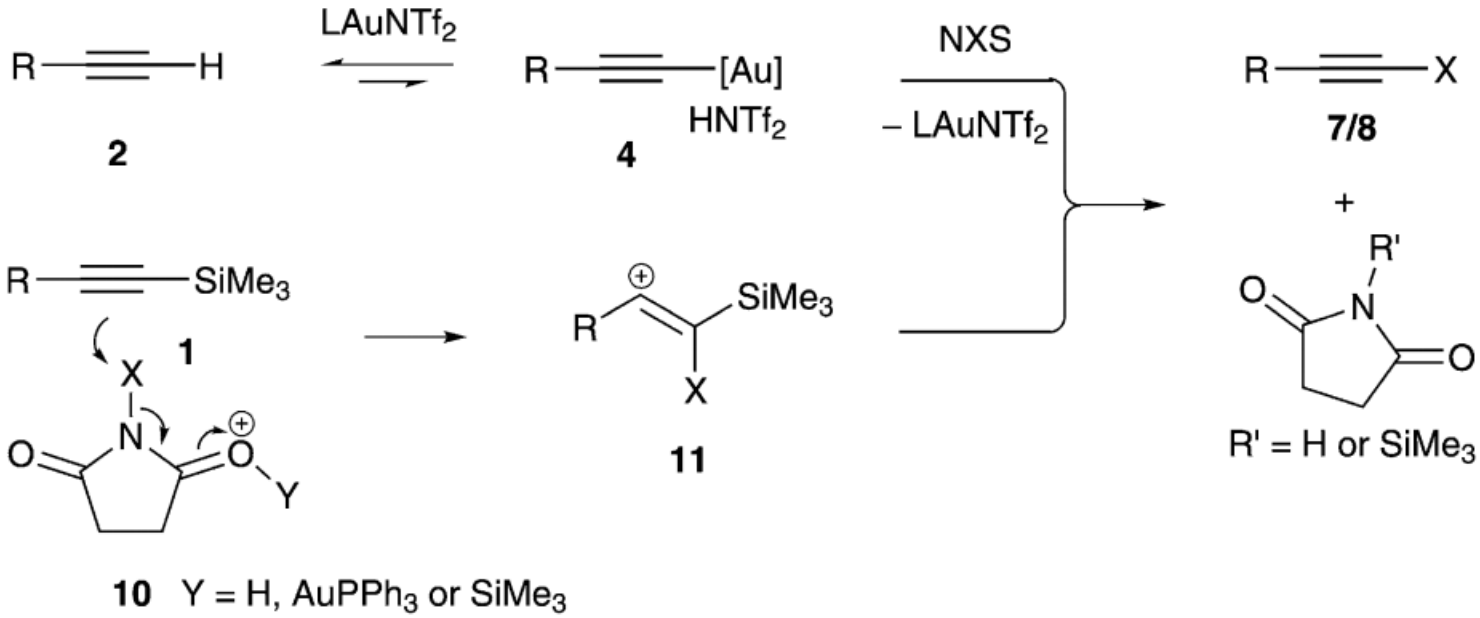
Mechanism



Mechanism of silyl acetylene to the corresponding iodoalkyne

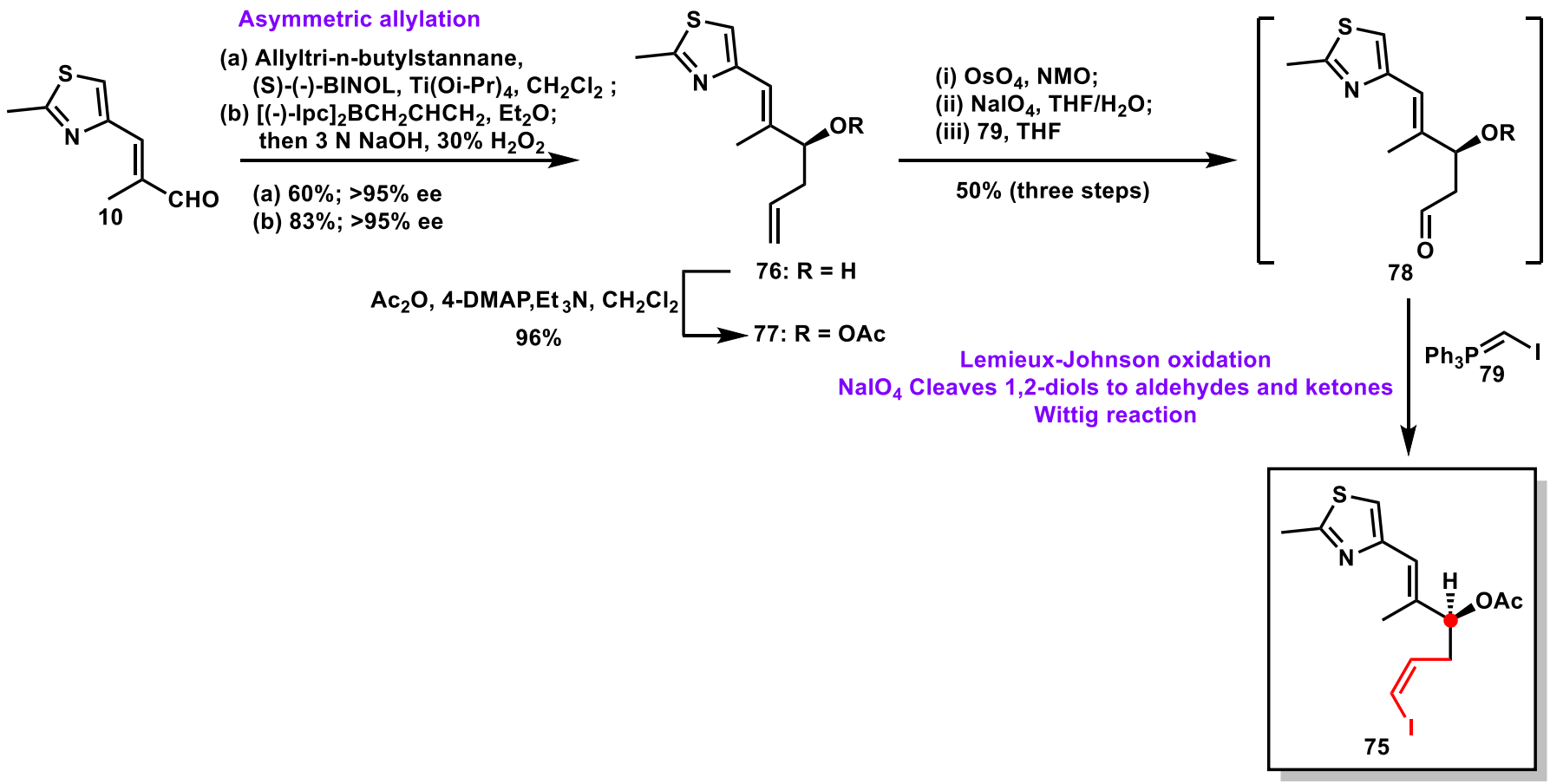


Mechanism

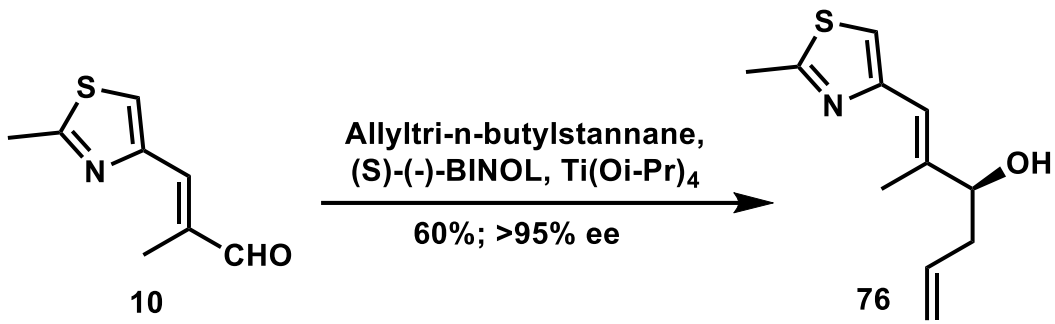


T. D. Sheppard, et al. *Adv. Synth. Catal.* **2012**, *354*, 3217 - 3224.

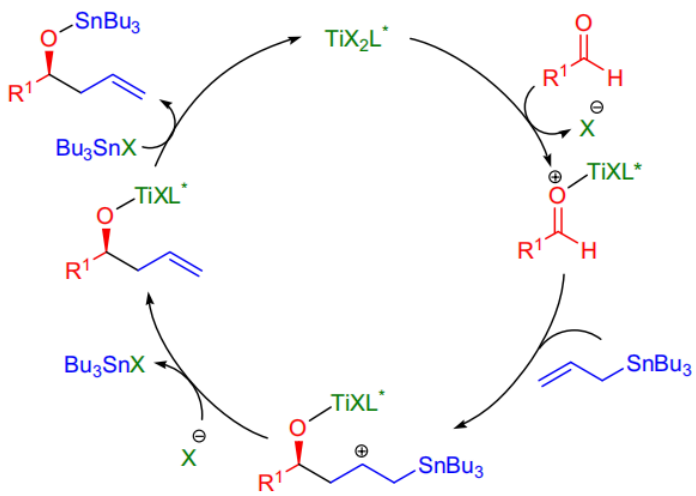
More concise syntheses of 75



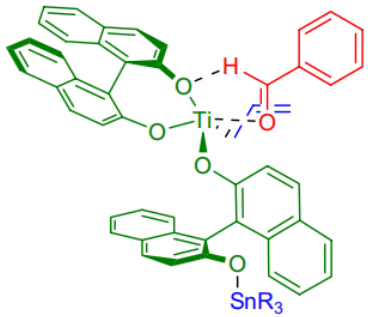
Keck asymmetric allylation



Mechanism

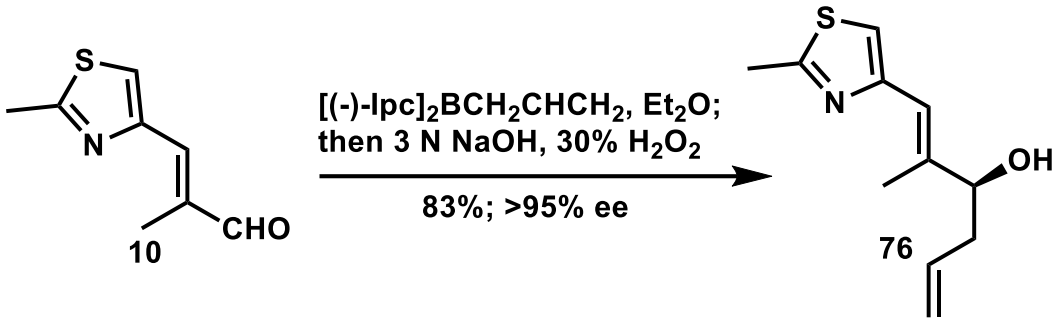


Corey's stereochemical model:

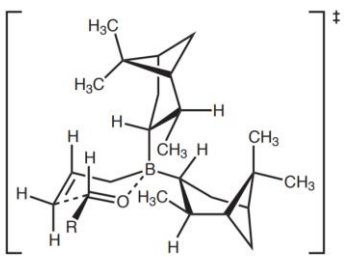


Geraci, L. S, et al. *J. Am. Chem. Soc.* **1993**,*115*, 8467.

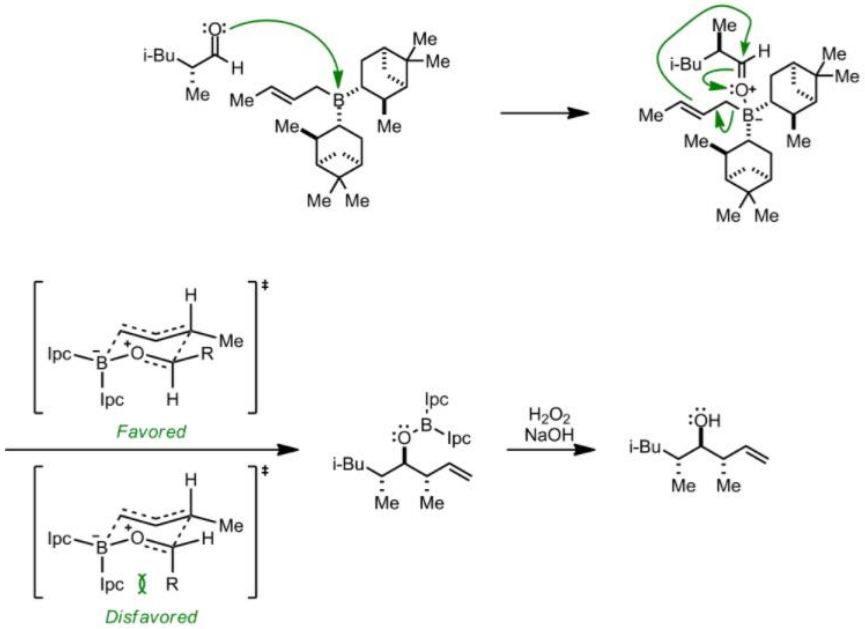
Brown Asymmetric Allylation



Mechanism

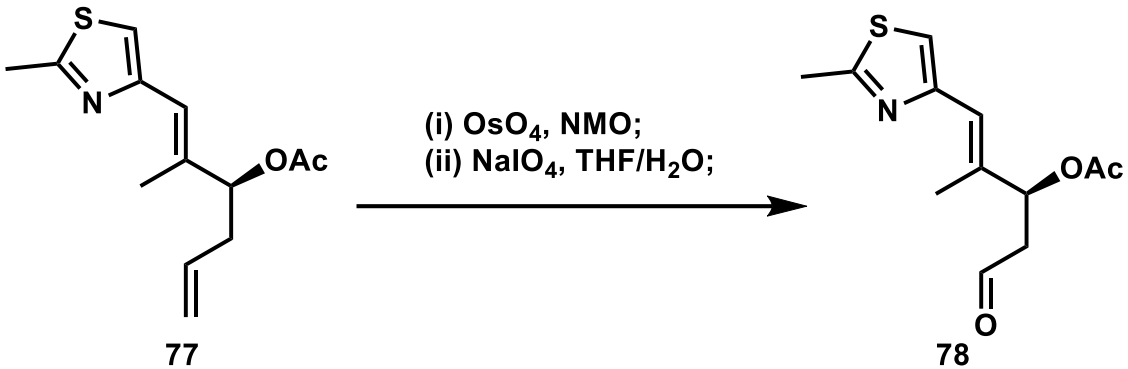


- Allylation of aldehydes proceeds through a chair-like TS where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial Ipc ligand and the allyl group.

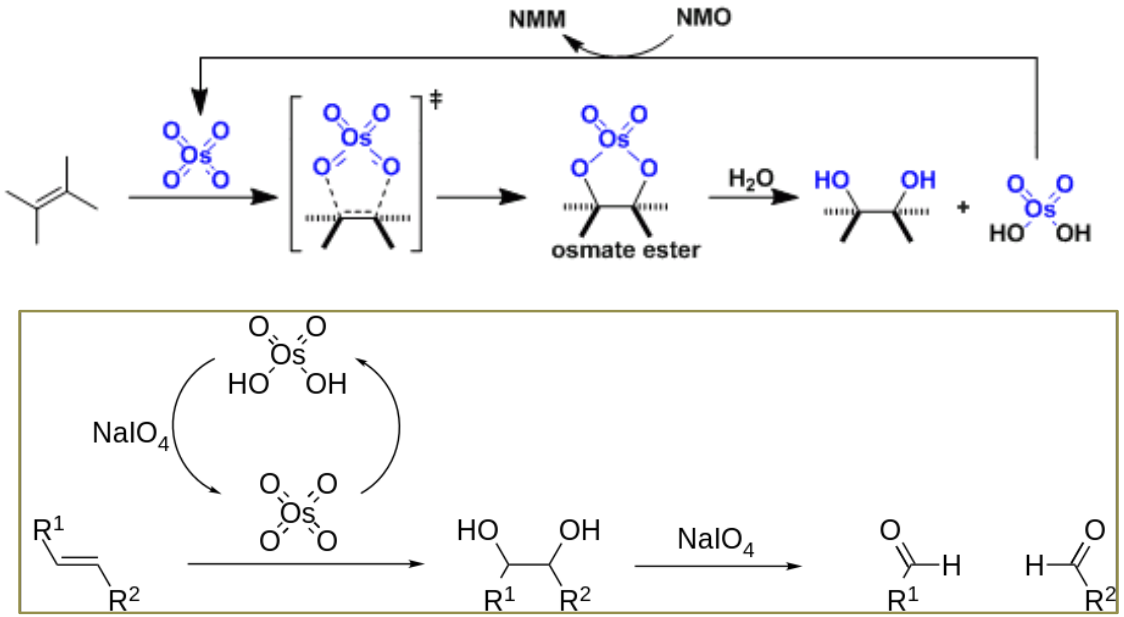


Corey, D. R, et al. *J. Am.Chem. Soc.* **1985**, *107*, 713.

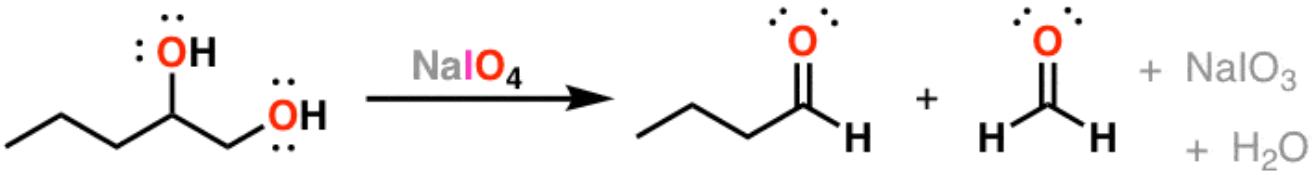
Lemieux-Johnson oxidation



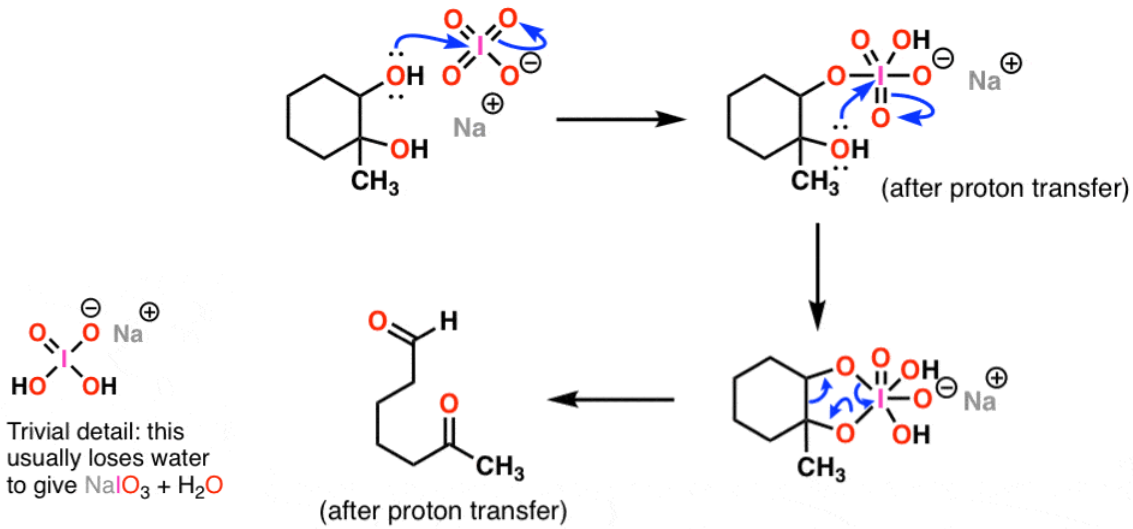
Mechanism



Malaprade reaction——NaIO4 cleaves 1,2-diols to aldehydes and ketones

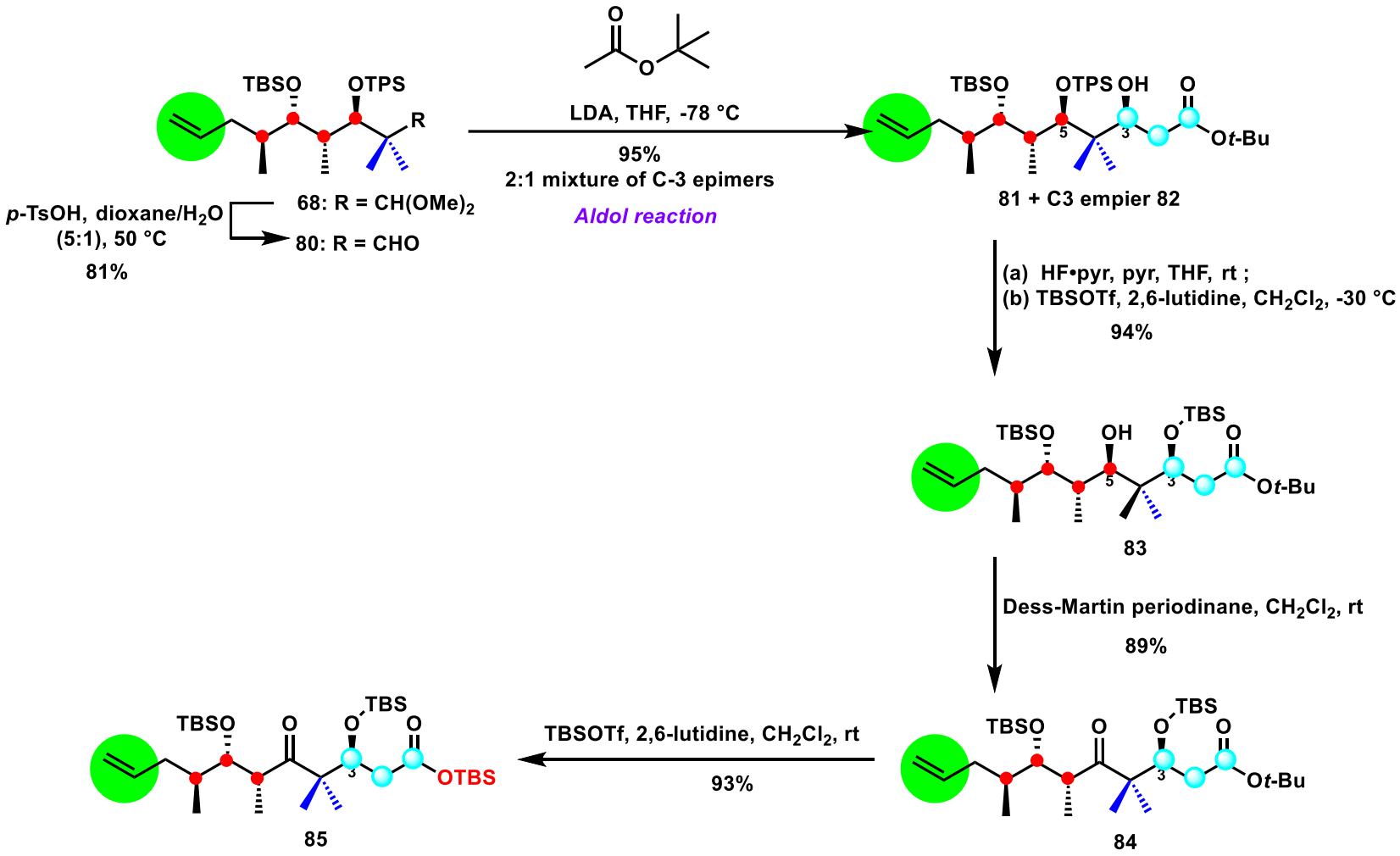


Mechanism



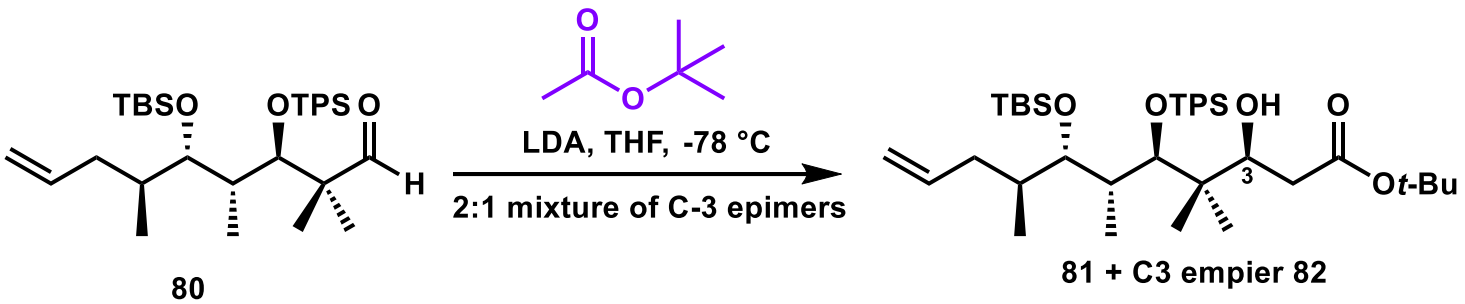
Approach 2 and 3 （Suzuki coupling Strategy)

Synthesis of a more advanced suzuki coupling partner

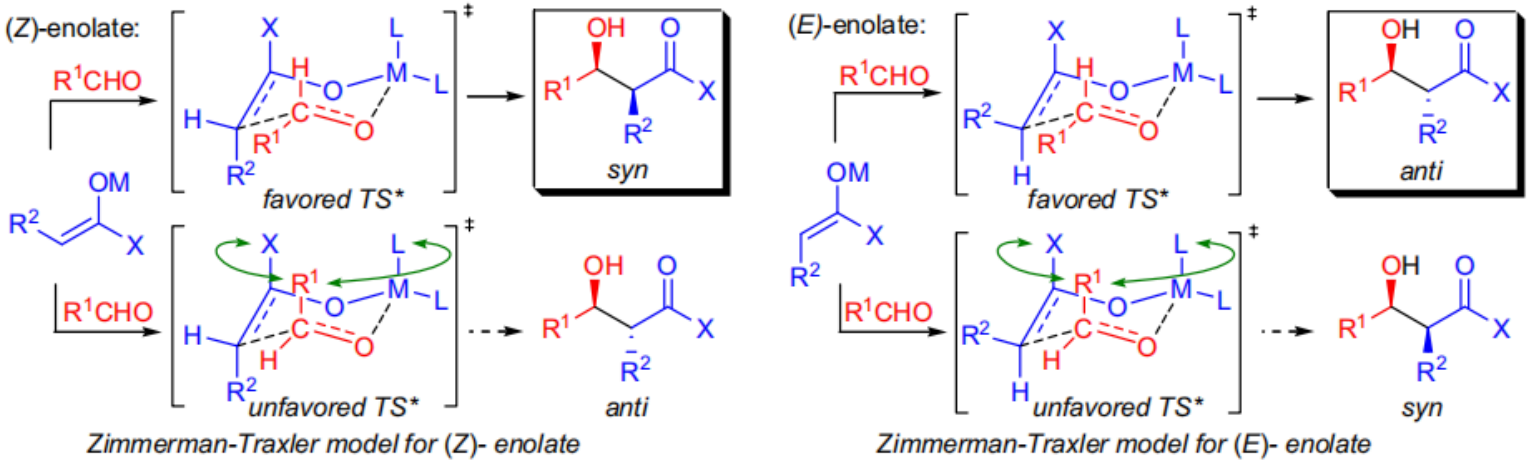


Approach 2 and 3 （Suzuki coupling Strategy)

Aldol reaction

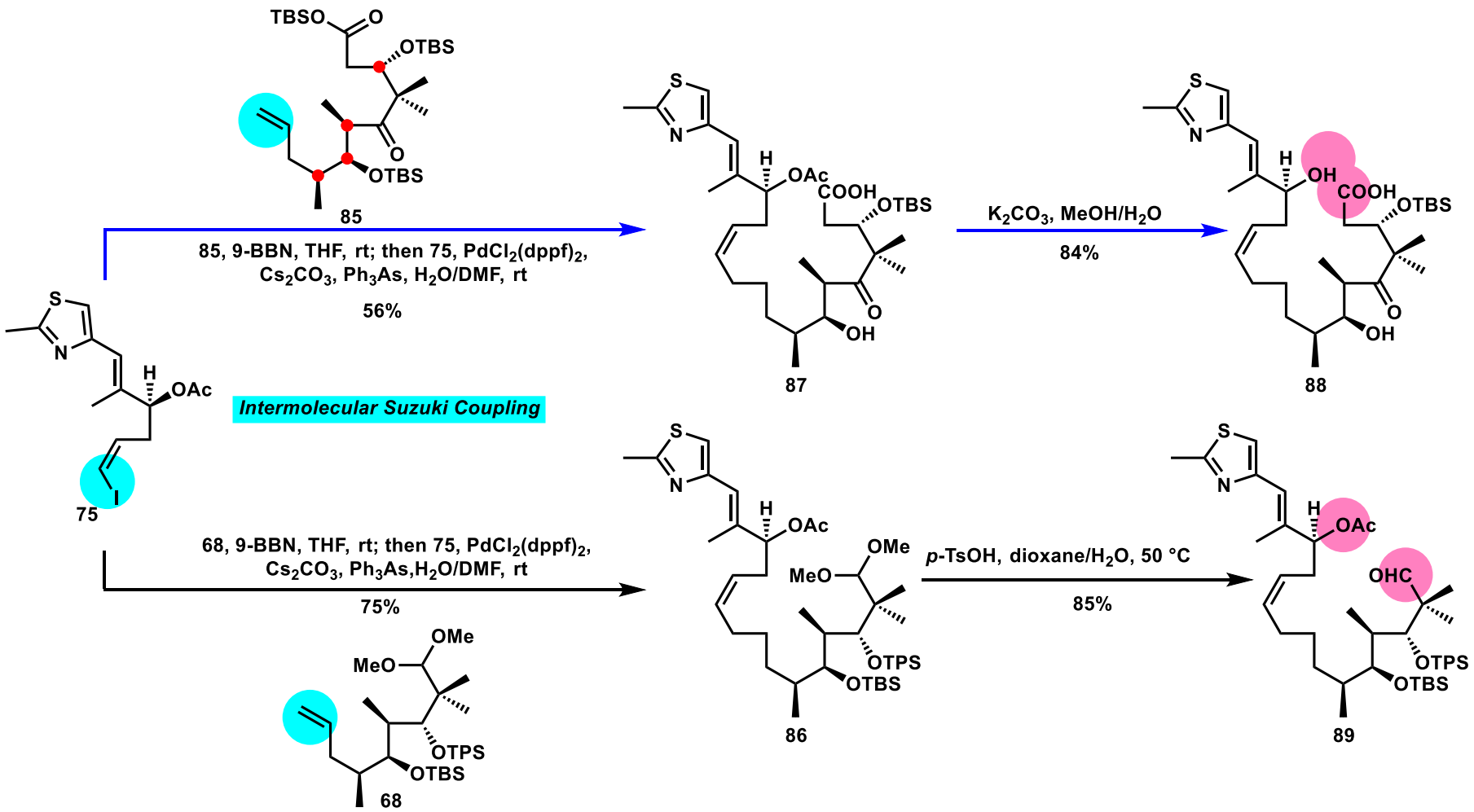


Mechanism

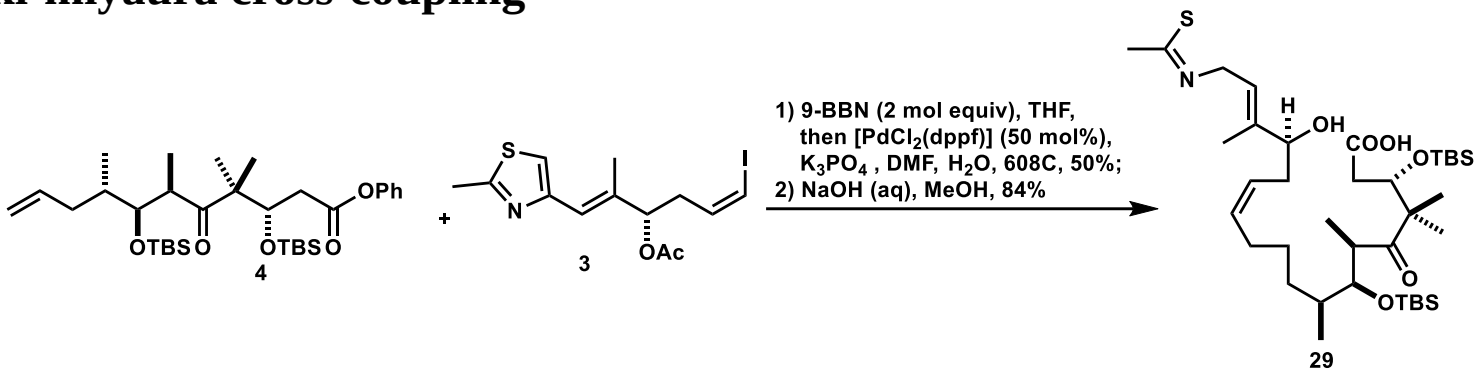


Approach 2 and 3 （Suzuki coupling Strategy)

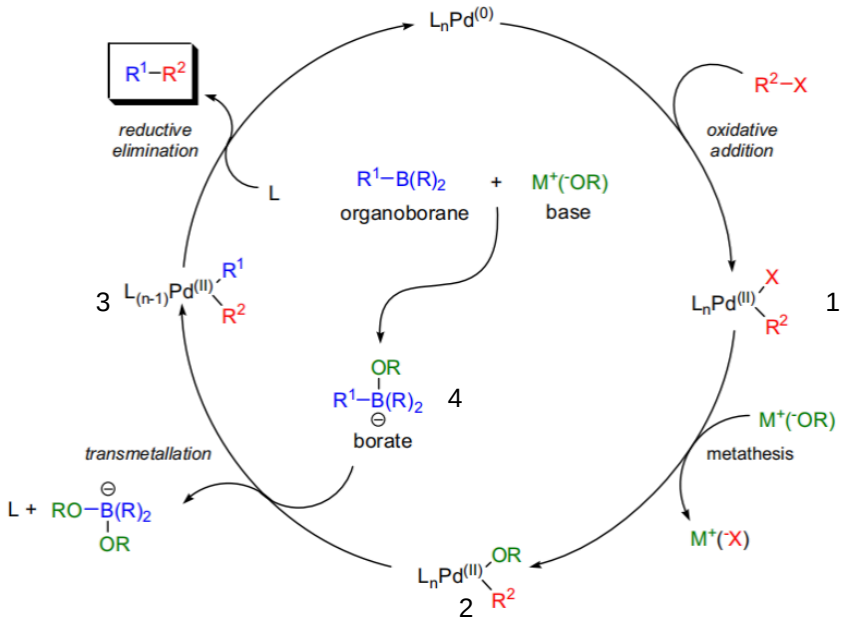
establishing the C11-C12 bond by Suzuki coupling



Suzuki-miyaura cross-coupling

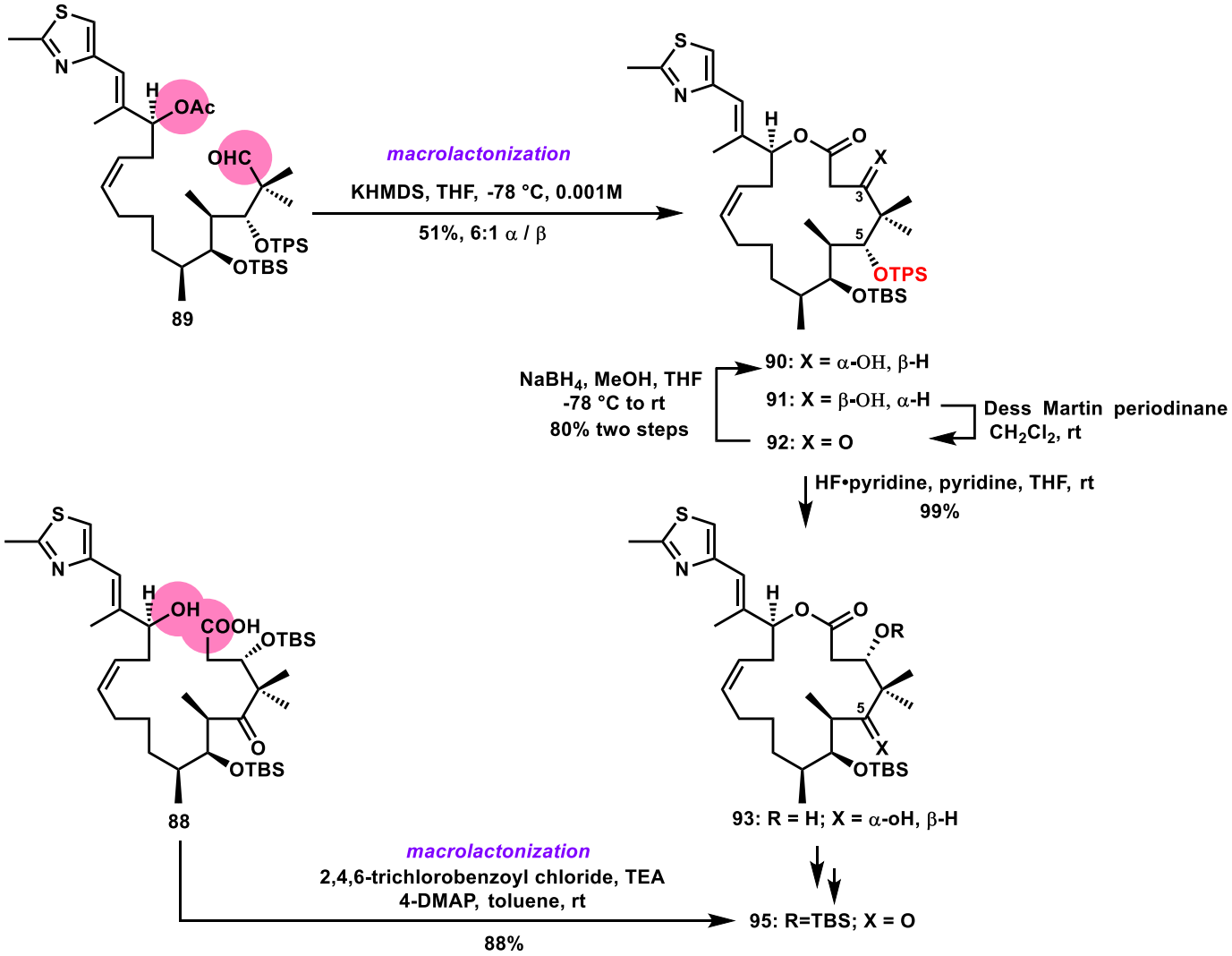


Mechanism

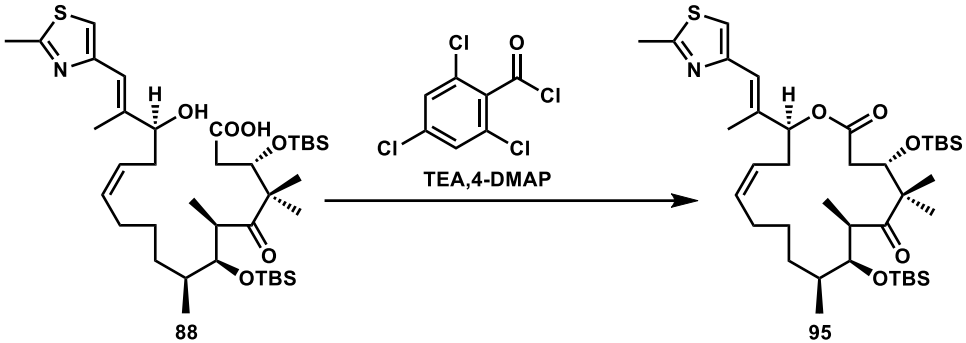


Approach 2 and 3 （Suzuki coupling Strategy)

construction ofthe 16-membered ring

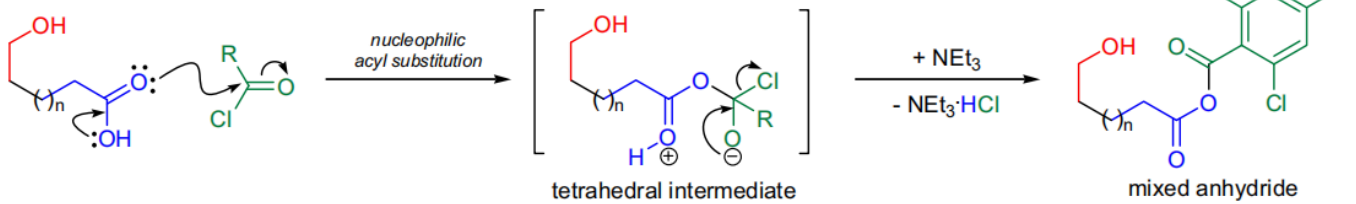


Yamaguchi macrolactonization

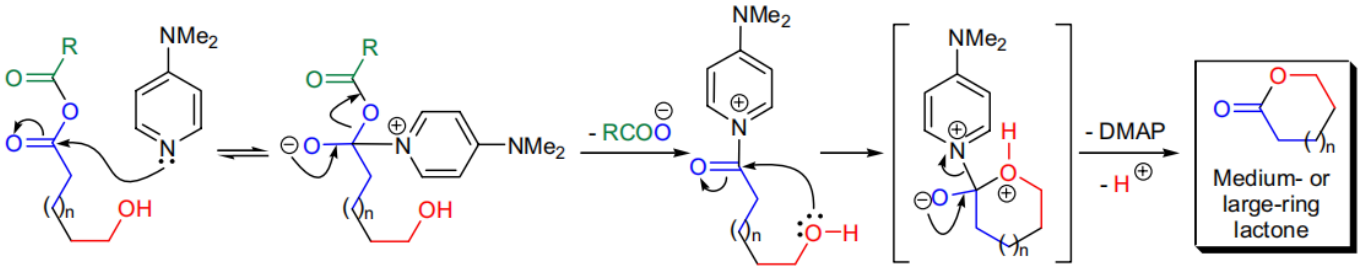


Mechanism

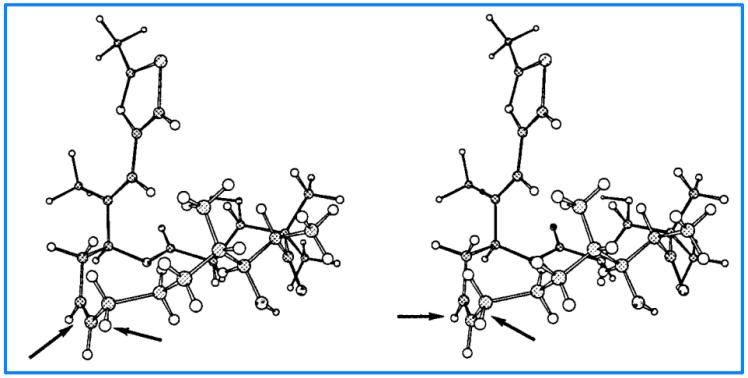
Formation of the mixed anhydride (R = 2,4,6-trichlorobenzoyl):

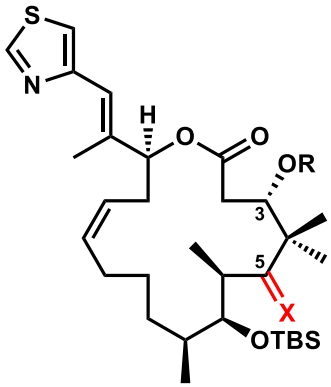


Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):



Approach 2 and 3 （Suzuki coupling Strategy)

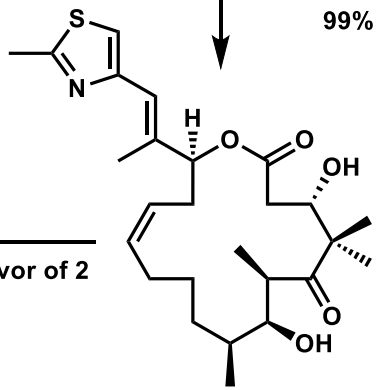




TBSOTf, 2,6-lutidine, CH_2Cl_2, -30 °C (93%) → 93: R=H; X = α-OH, β-H; 94: R=TBS; X = α-OH, β-H

Dess-Martinperiodinane, CH_2Cl_2, rt (84%) → 95: R=TBS; X = O

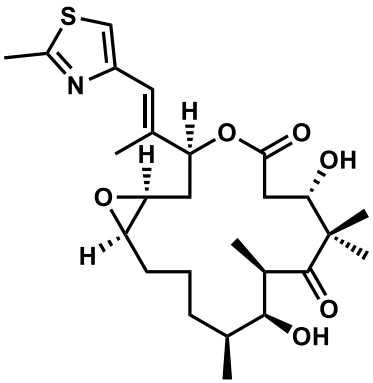
HF•pyridine, THF, rt
99%



96: desxoyepothilone A

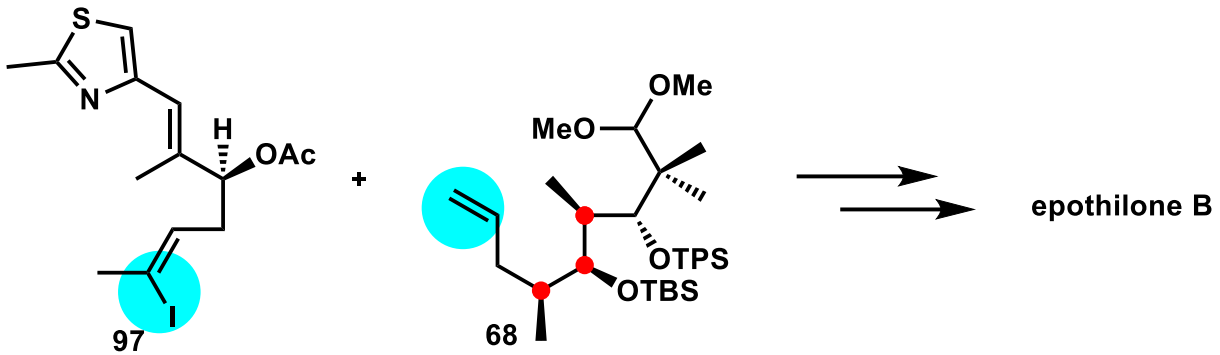
3,3-dimethyldioxirane, CH_2Cl_2, -35°C

49%; >16:1 mixture of diaster eomers in favor of 2

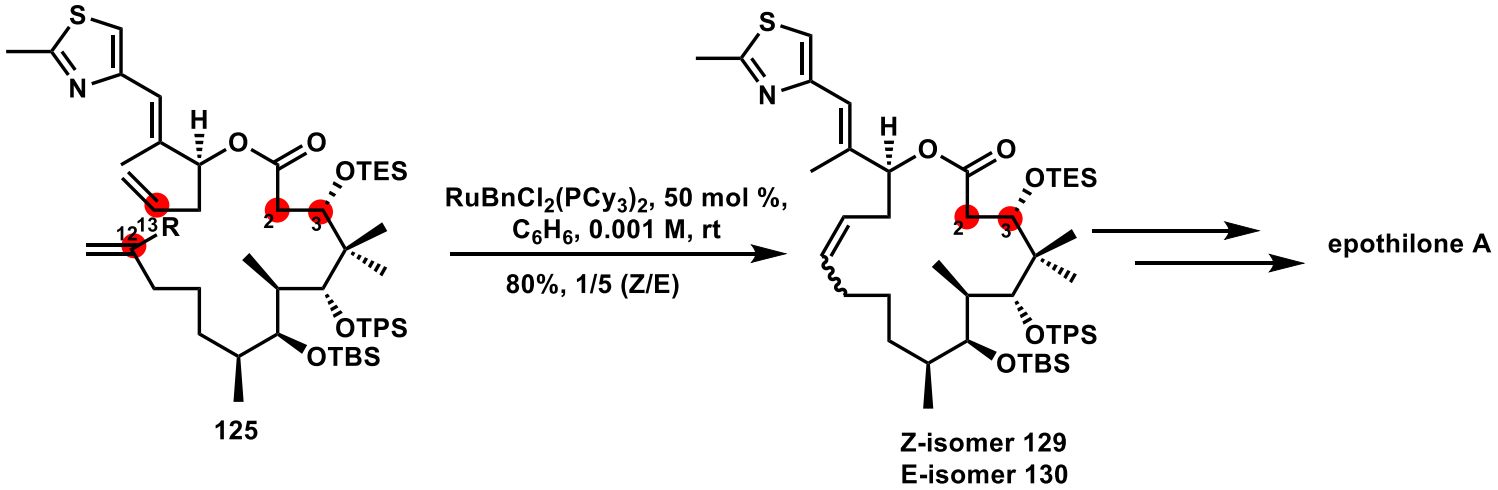


2: epothilone A

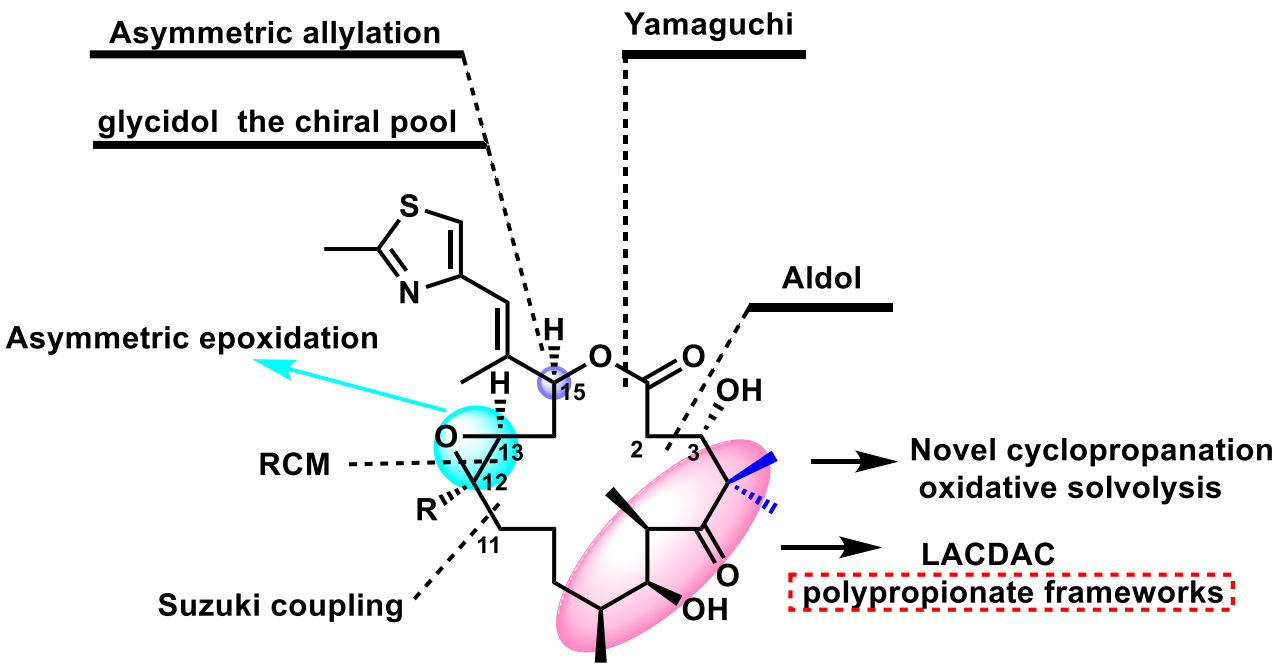
Synthesis of epothilone B by approach 2 （Suzuki coupling Strategy ）



Synthesis of epothilone A by approach 4（RCM Strategy）



Summary

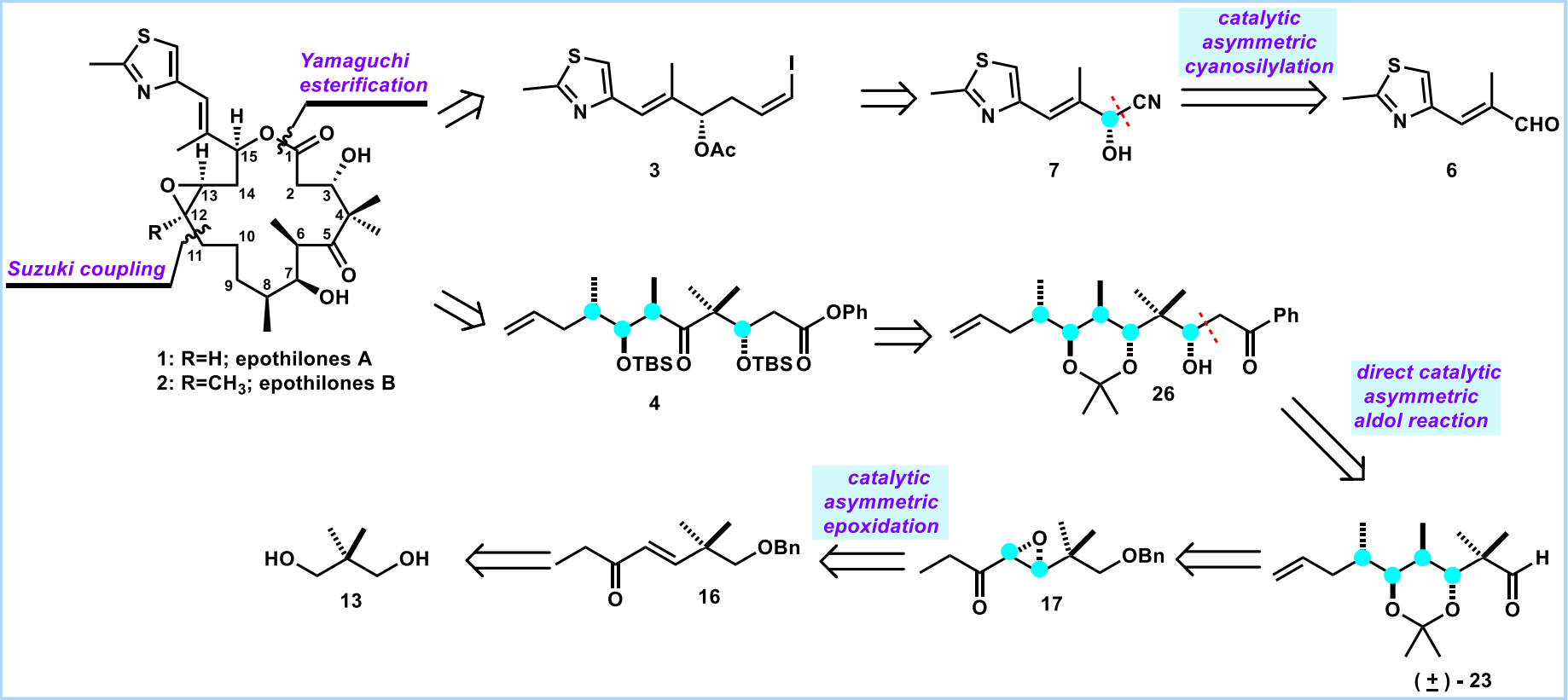


2: R = H; epothilone A
3: R = CH_3; epothilone B

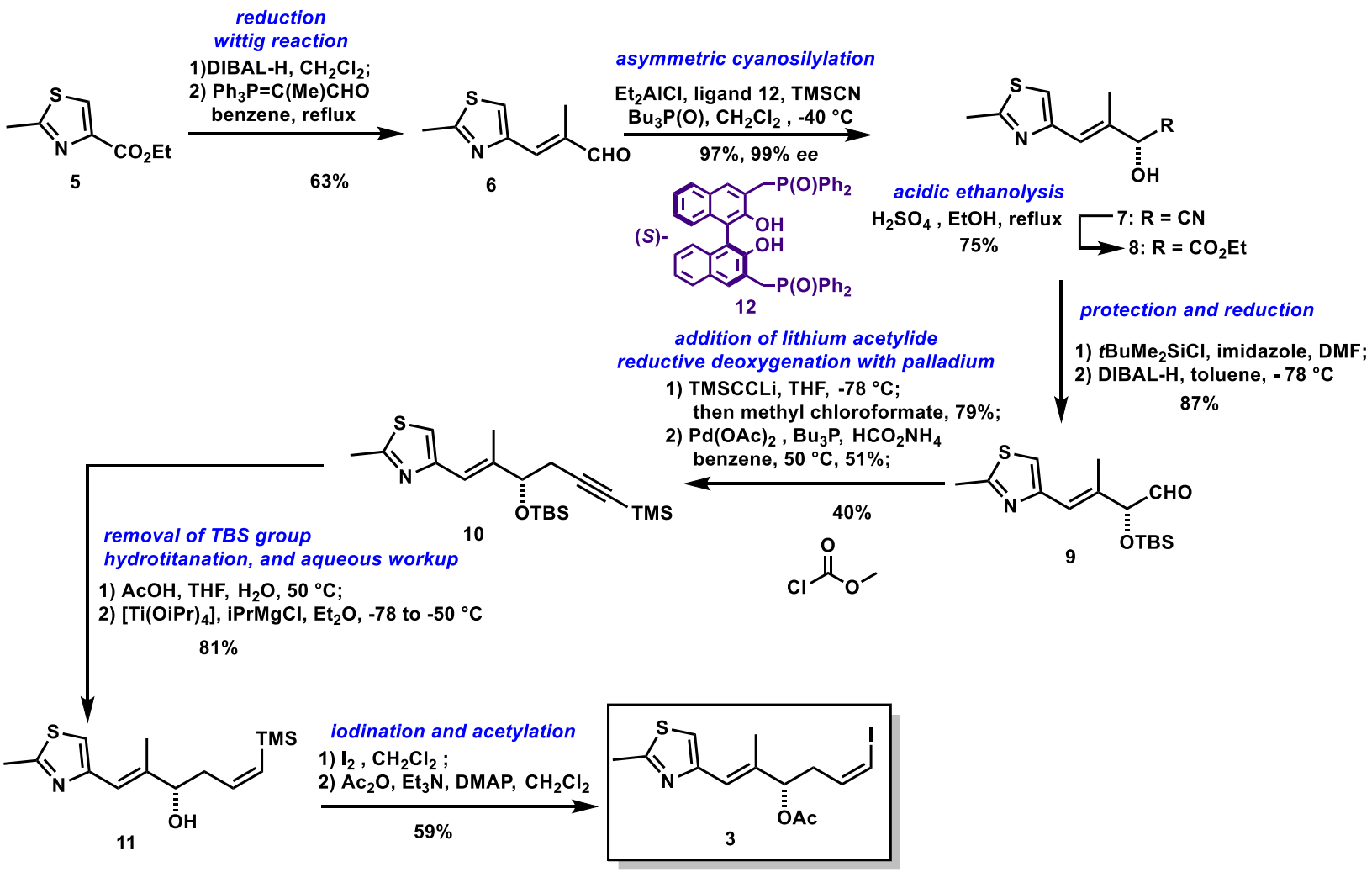
S. J. Danishefsky（1997）

M. Shibasaki: *Angew. Chem.* **2000**, *39*, 209 - 213.

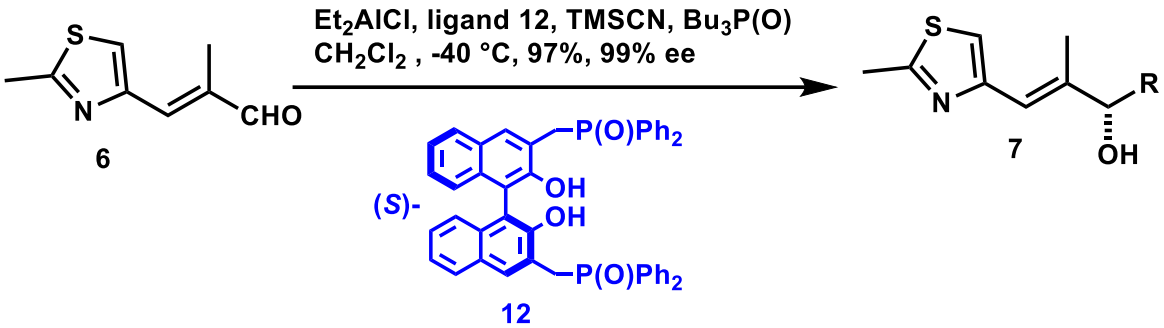
- **Enantioselective total synthesis using simple asymmetric catalysts**
- **Using multifunctional asymmetric catalyses for direct aldol reaction and cyanosilylation**



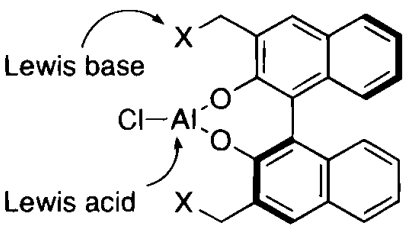
Synthesis of Fragment 3



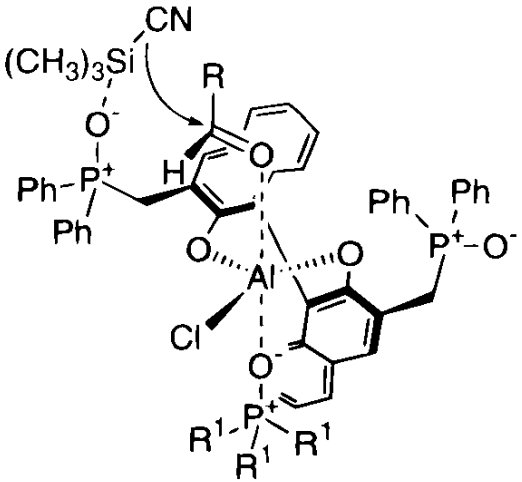
asymmetric cyanosilylation



Mechanism

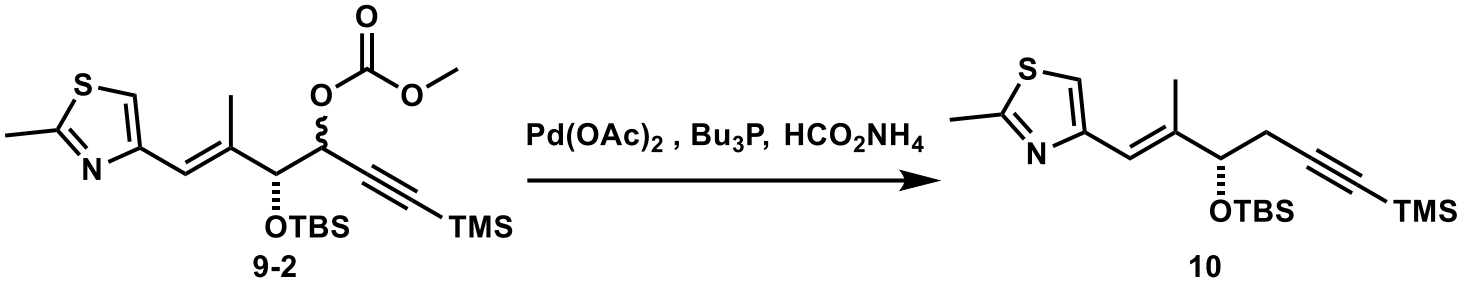


1: X = $P(O)Ph_2$
2: X = $CH_2P(O)Ph_2$
3: X = $CHPh_2$
4: X = $P(O)(PhN(CH_3)_2\text{-}p)_2$

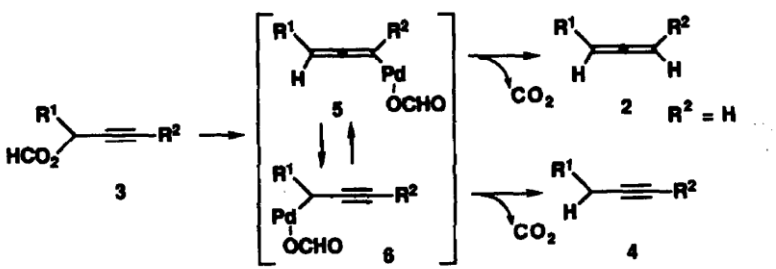


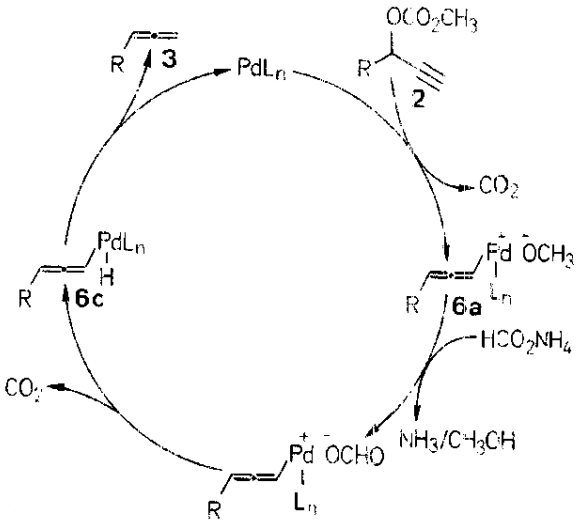
M. Shibasaki, et al. *J. Am. Chem. Soc.* **1999**, *121*, 2641 - 2642.

Reductive deoxygenation with palladium



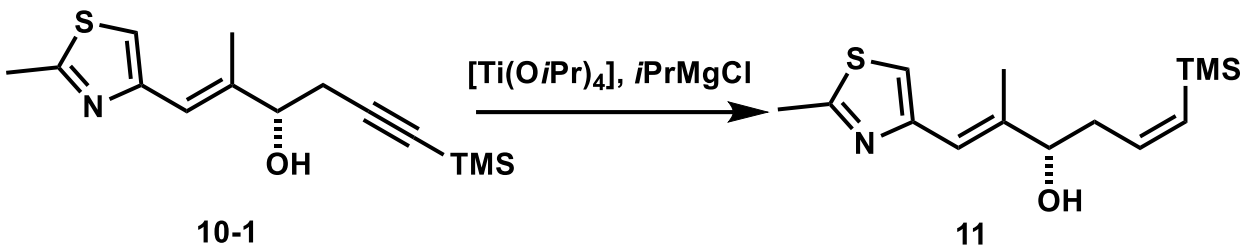
Mechanism



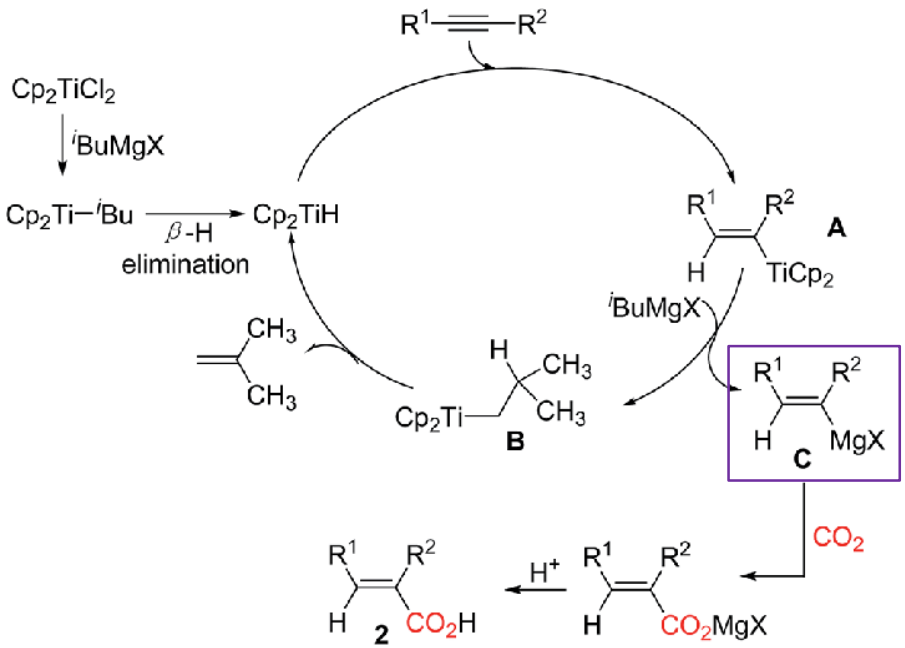


J. Tsuji, et al. *Tetrahedron Lett.* **1993**, *34*, 2161 - 2164.
I. Minami, et al. *Synthesis.* **1987**, 603 - 606.

Hydrotitanation

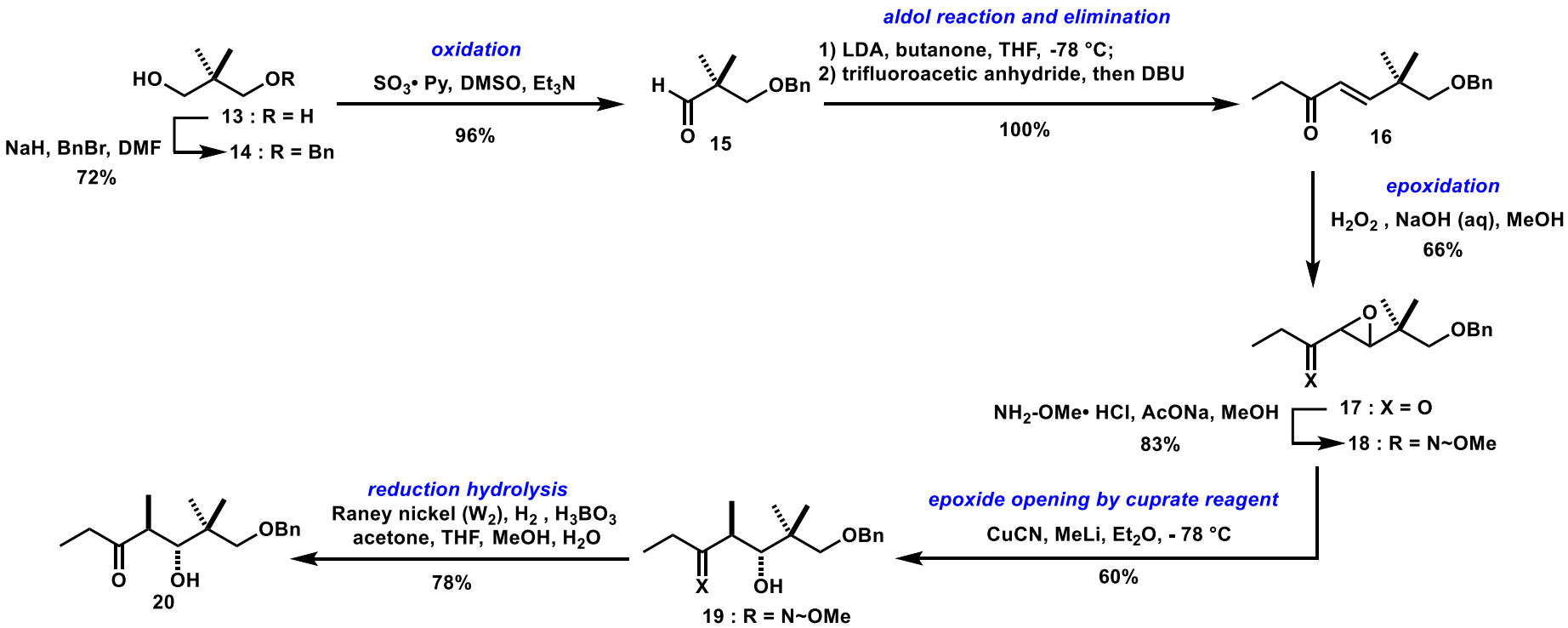


Mechanism

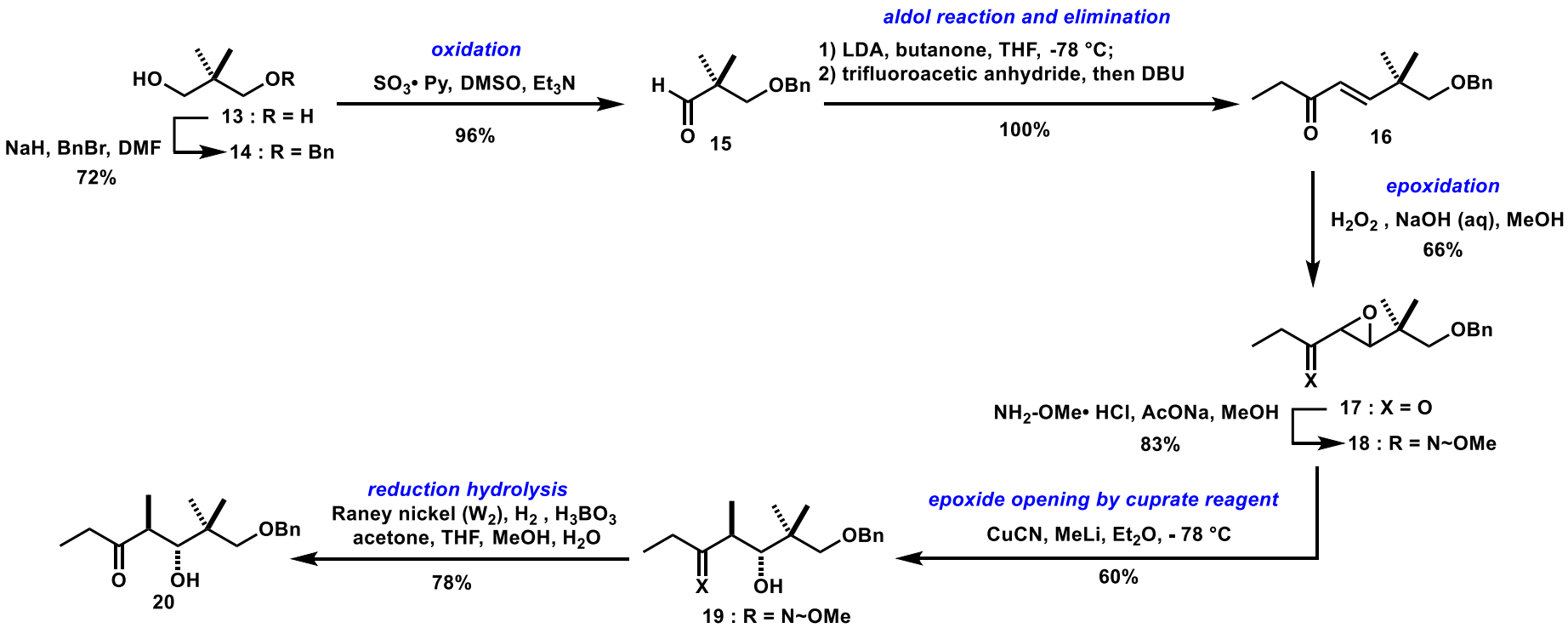


F. Sato, et al. *Tetrahedron Lett*. **1995**, *36*, 3203 - 3206.
Gaixia Du, et al. *RSC Adv*. **2017**, *7*, 3534.

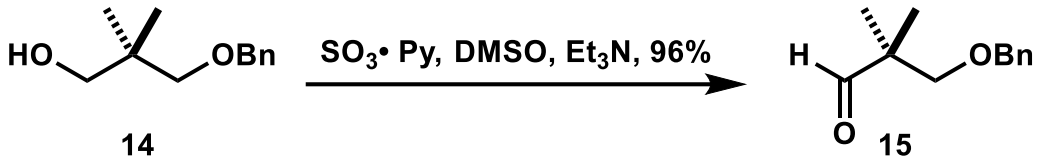
Synthesis of Fragment 4



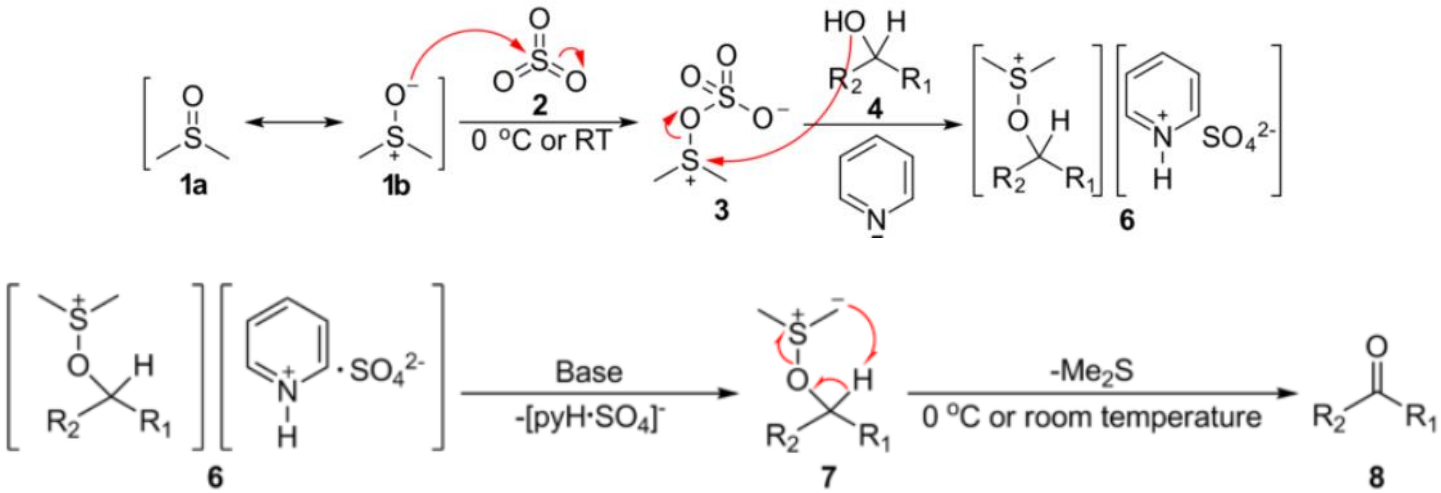
Synthesis of Fragment 4



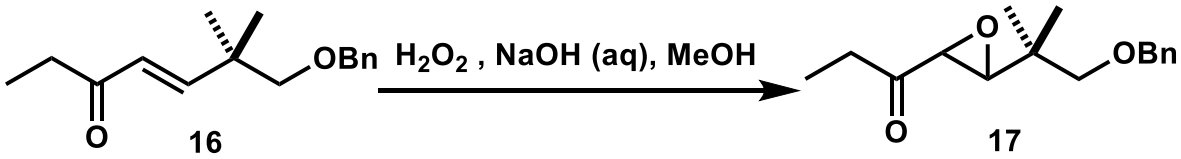
Parikh-Doering Oxidation



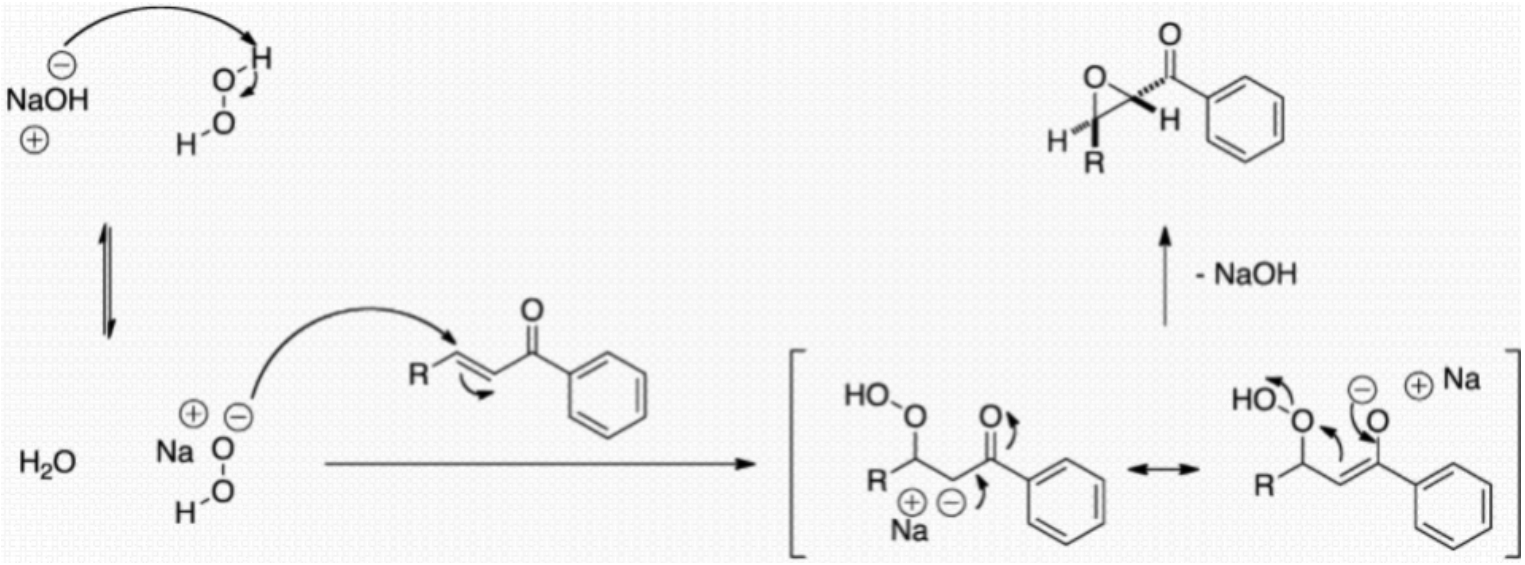
Mechanism



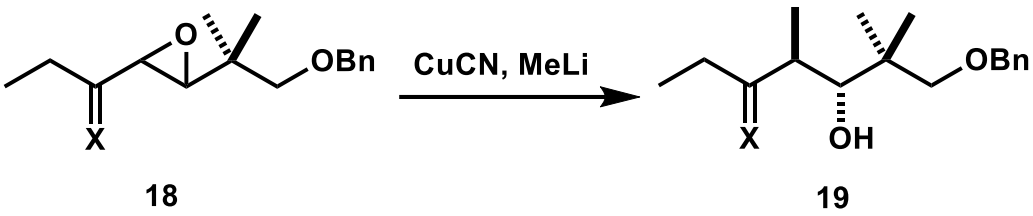
Juliá–Colonna epoxidation



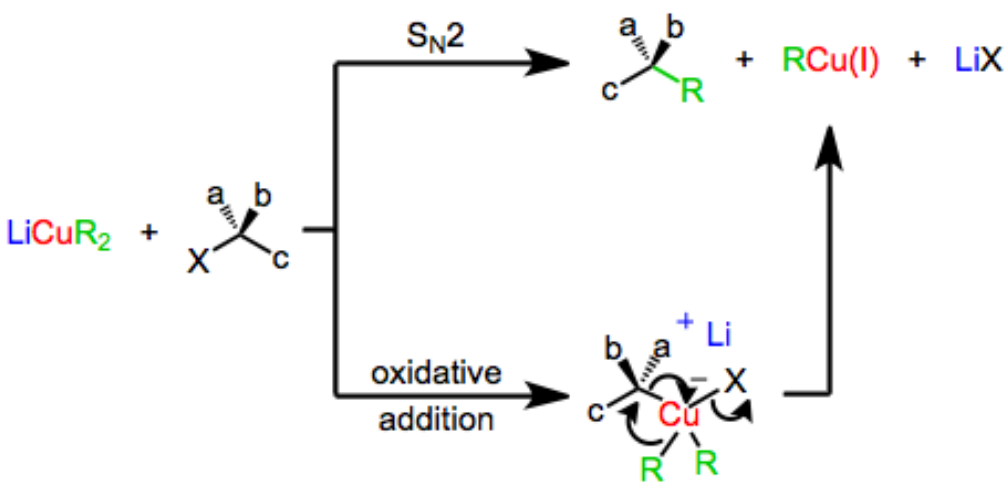
Mechanism



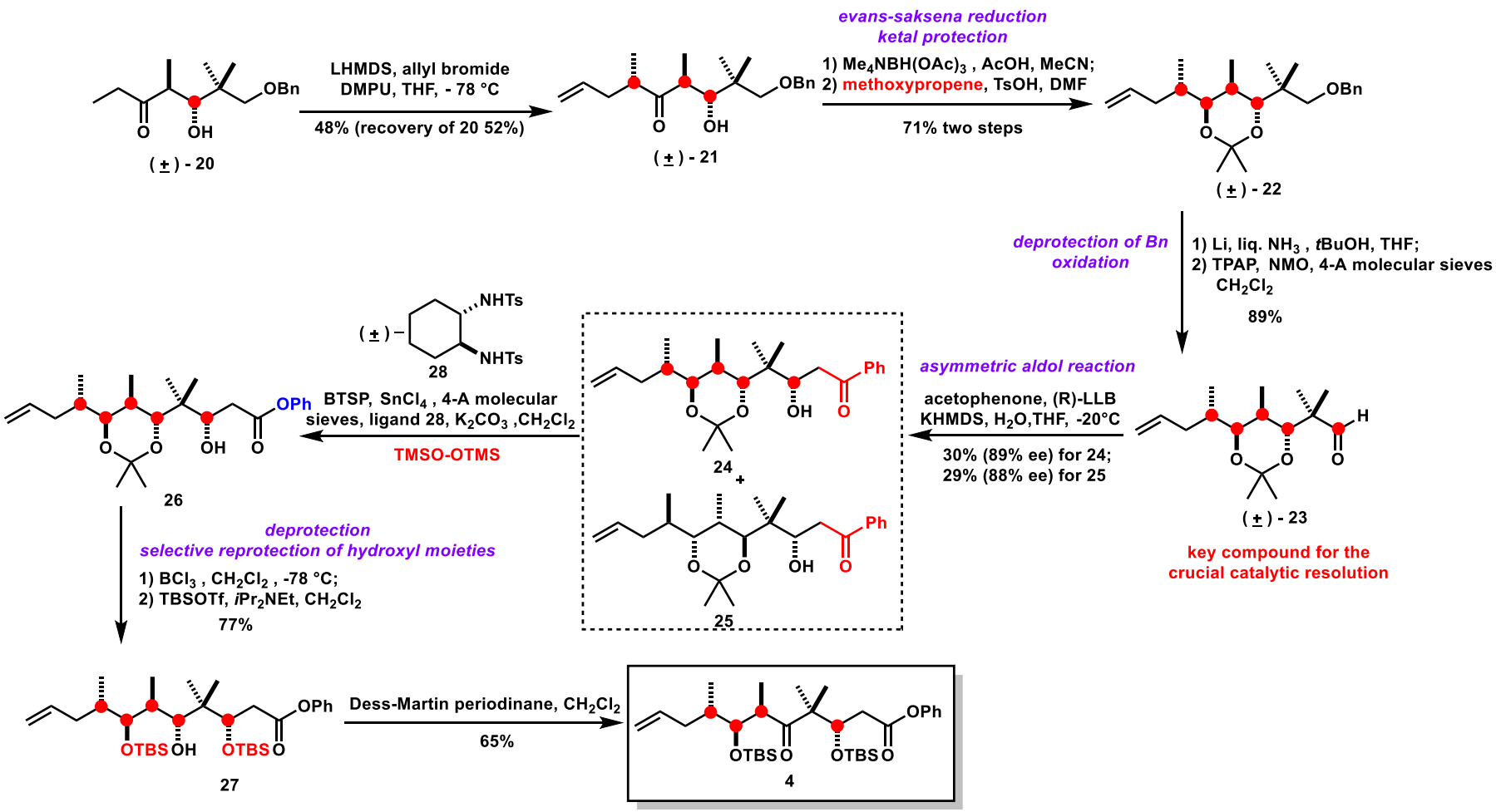
Gilman reagent



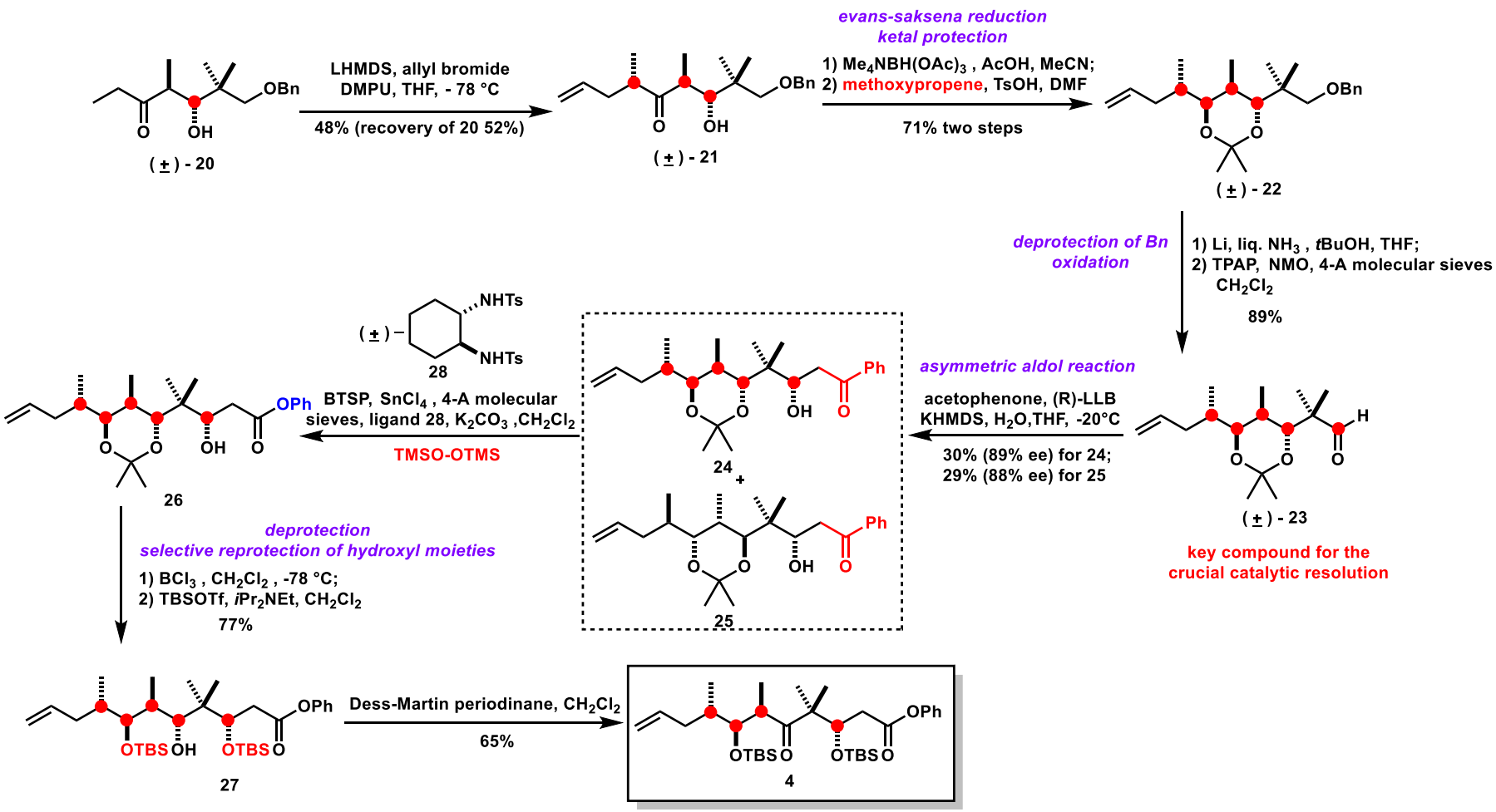
Mechanism



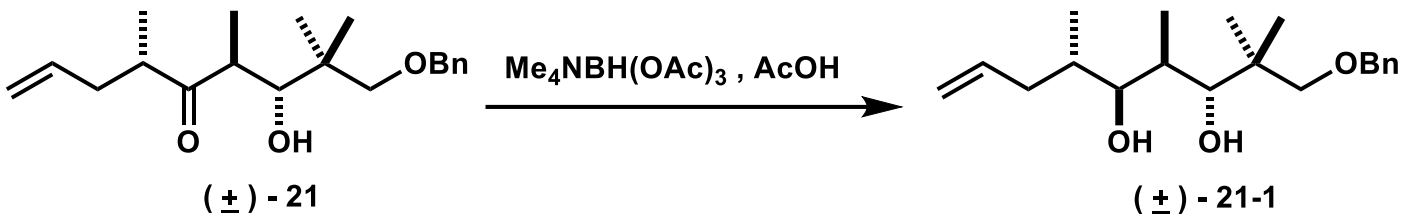
Synthesis of Fragment 4



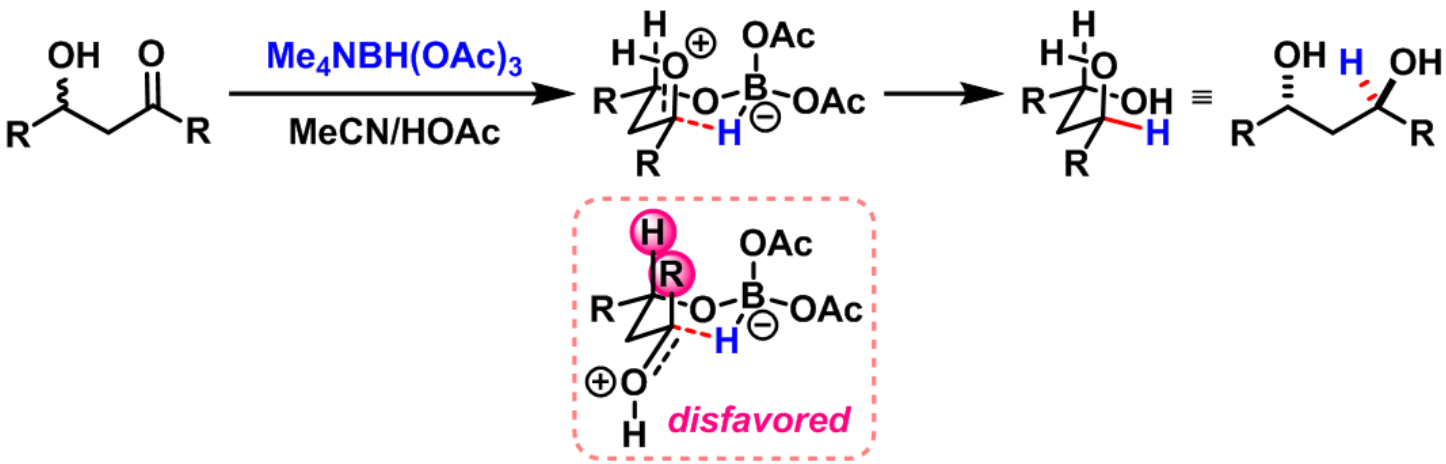
Synthesis of Fragment 4



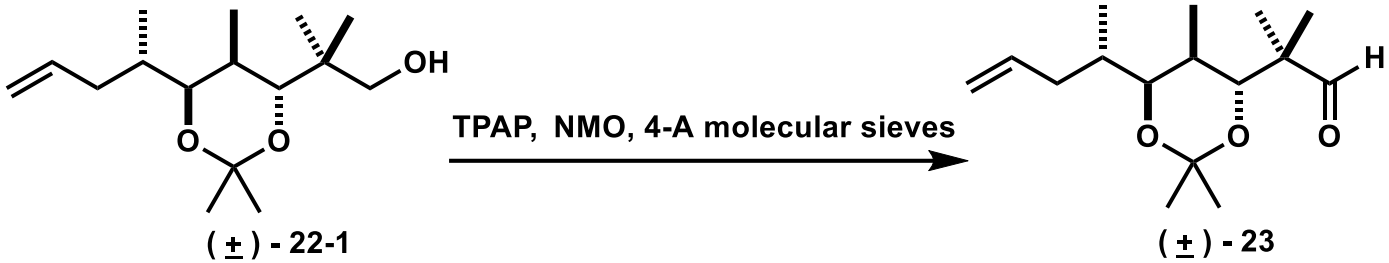
Evans–Saksena reduction



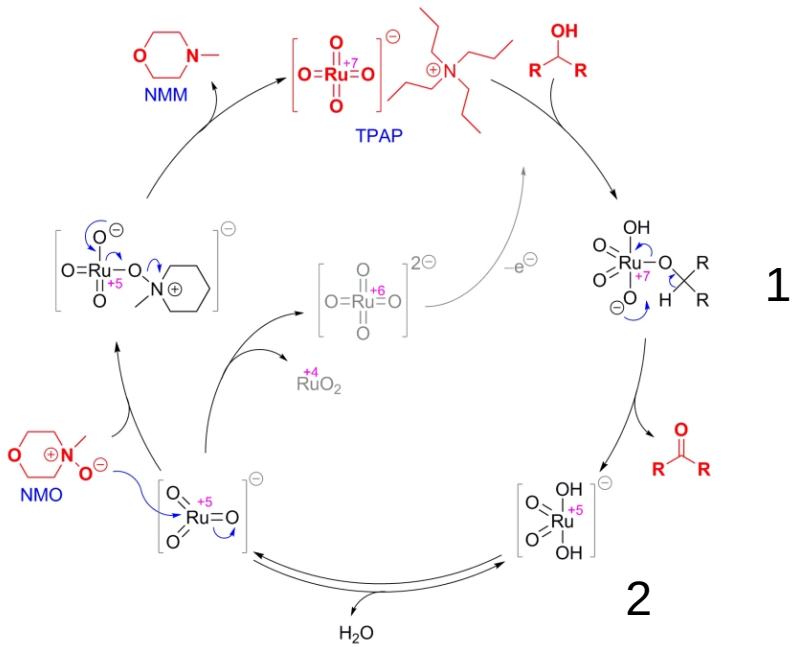
Mechanism



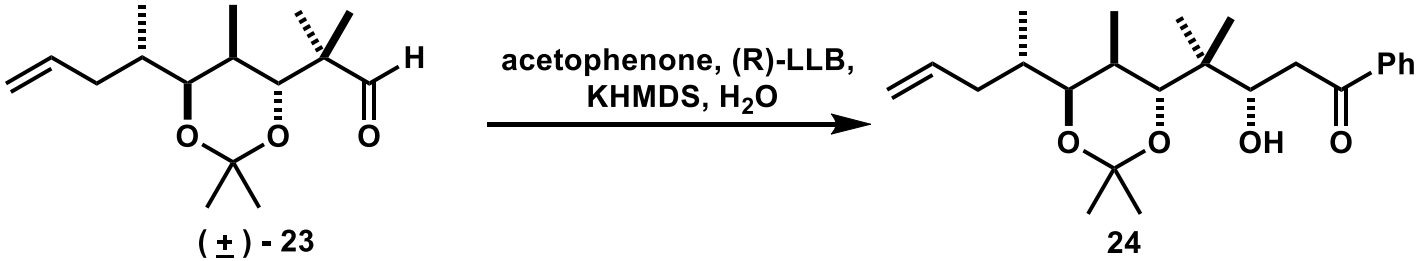
Ley-Griffith Oxidation



Mechanism

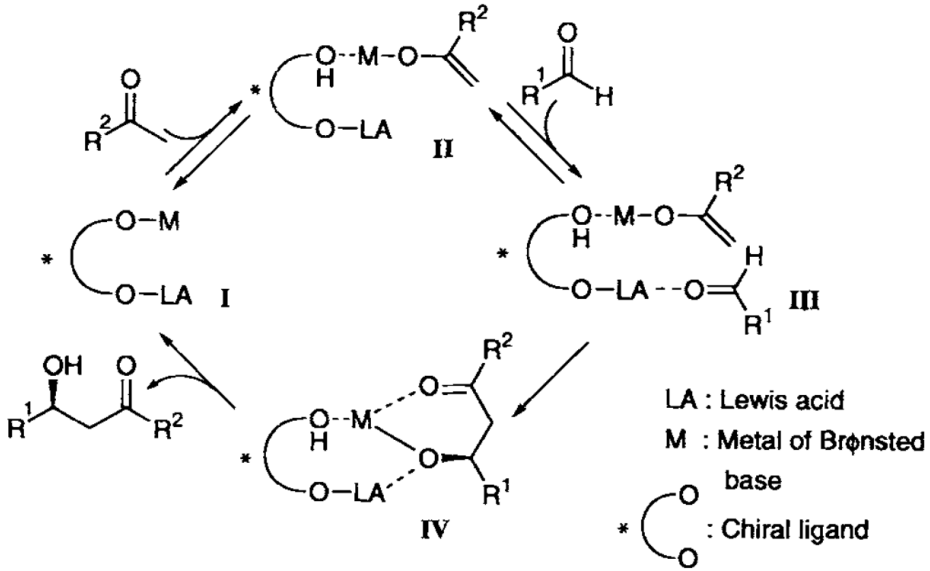


asymmetric aldol reaction



Mechanism

Direct Catalytic Asymmetric Aldol Reactions of Aldehydes with Unmodified Ketones



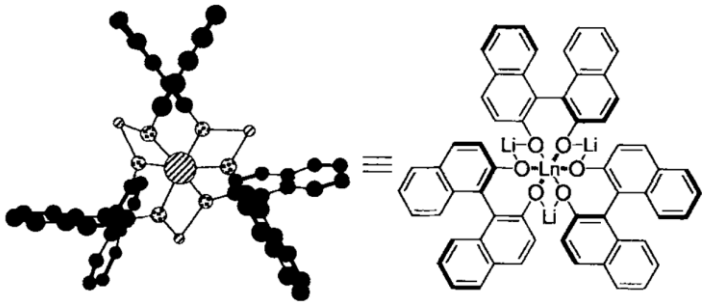
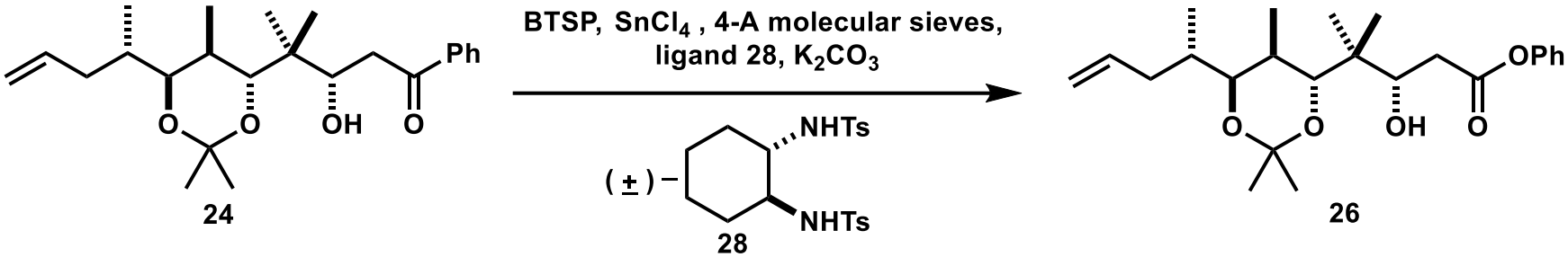


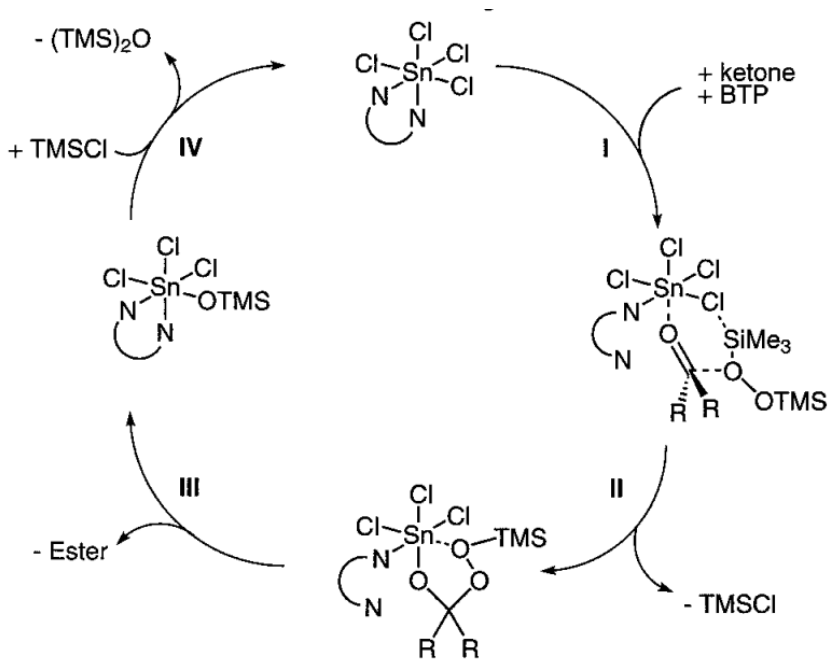
Figure 1. The structure of $LnLi_3tris[(R)$-binaphthoxide$]$ ((*R*)-LnLB).

M. Shibasaki, et al. *Angew.Chem*. **1997**, *109*, 1942 - 1944.

Baeyer–Villiger oxidation of ketones with bis(trimethylsilyl) peroxide

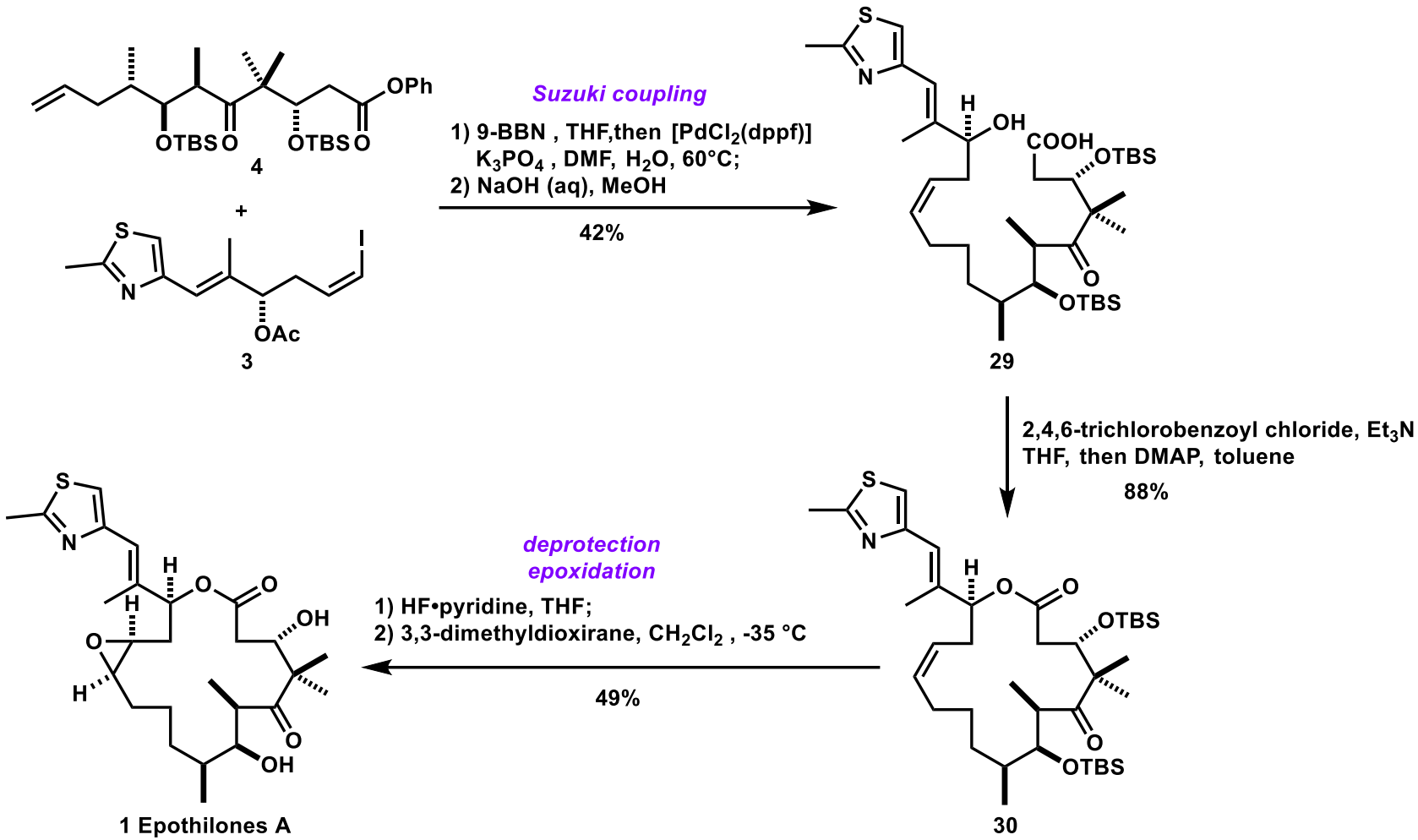


Mechanism

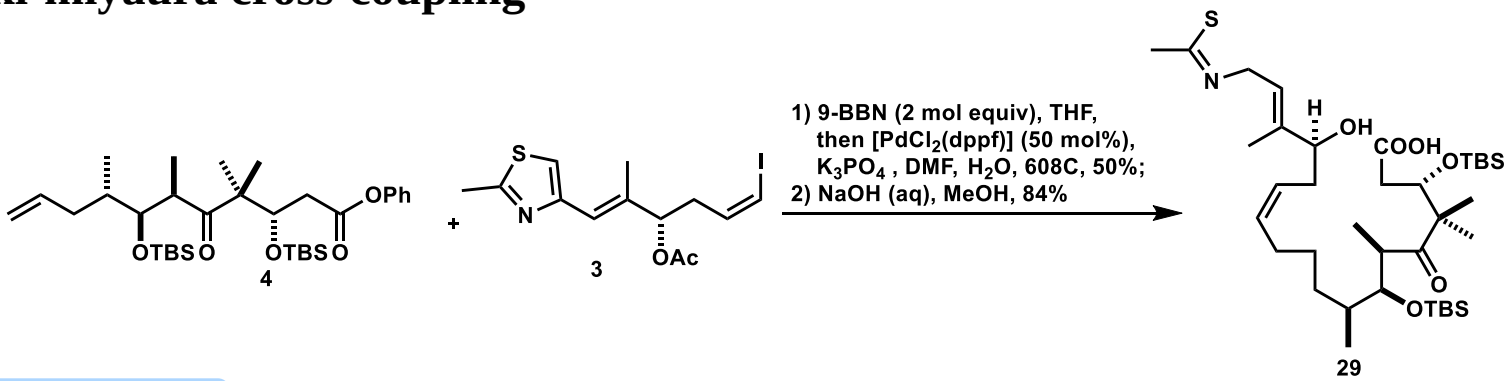


M. Shibasaki, et al. *Synlett*.**1997**, 971 - 973.

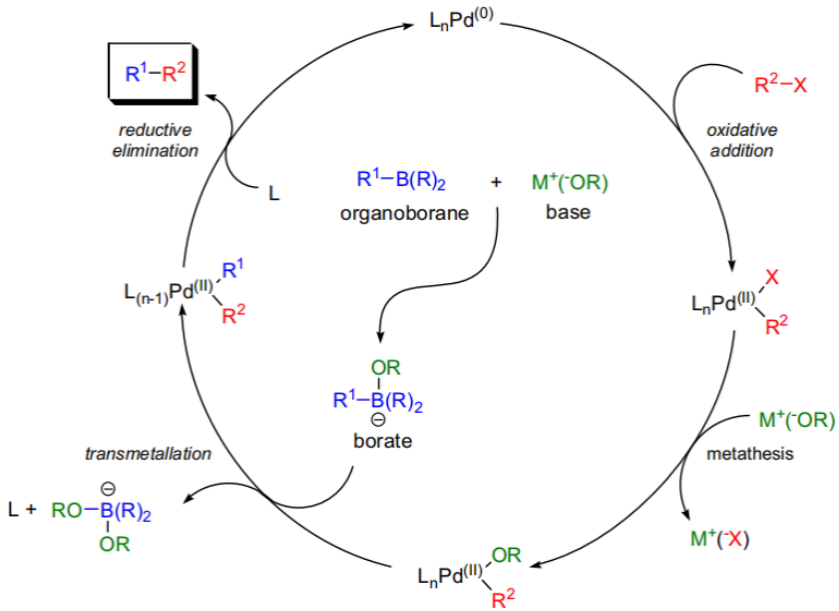
Synthesis of Epothilones A



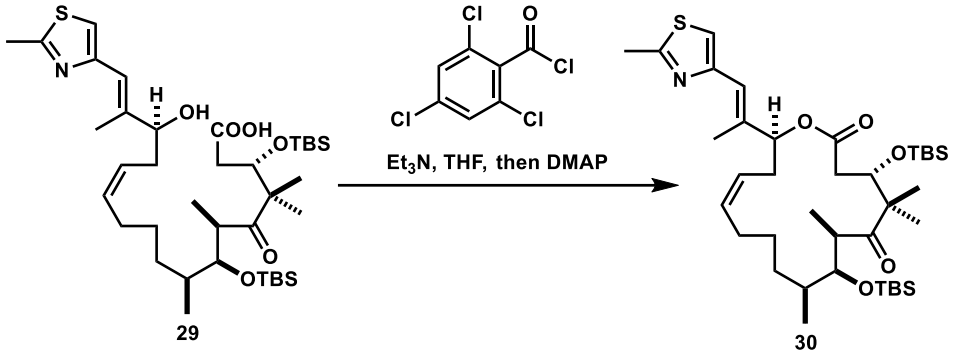
Suzuki-miyaura cross-coupling



Mechanism

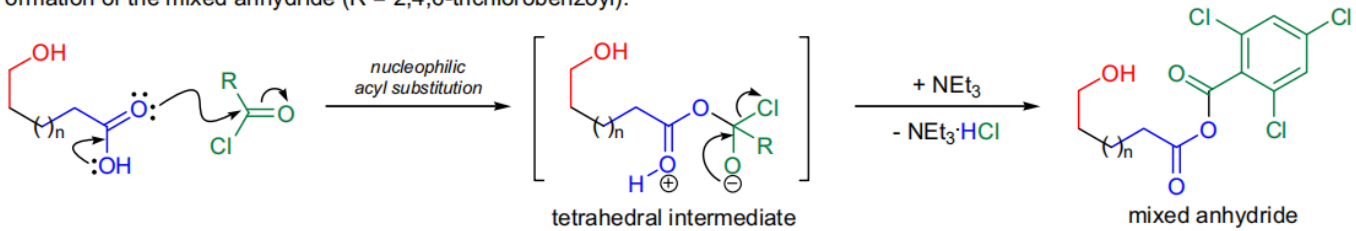


Yamaguchi macrolactonization

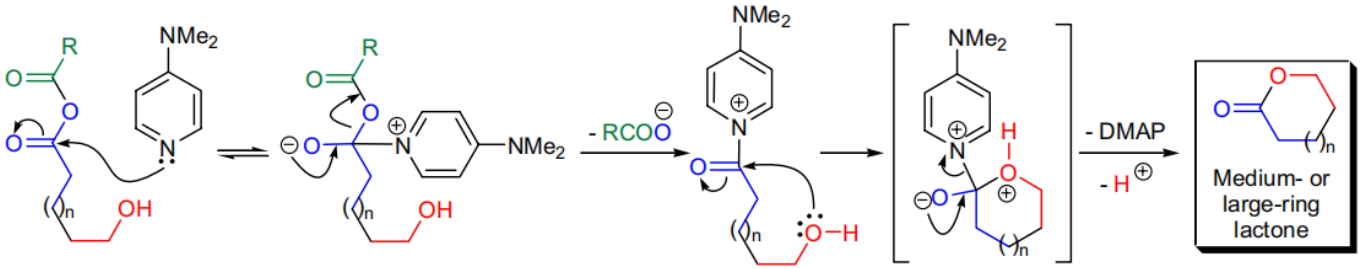


Mechanism

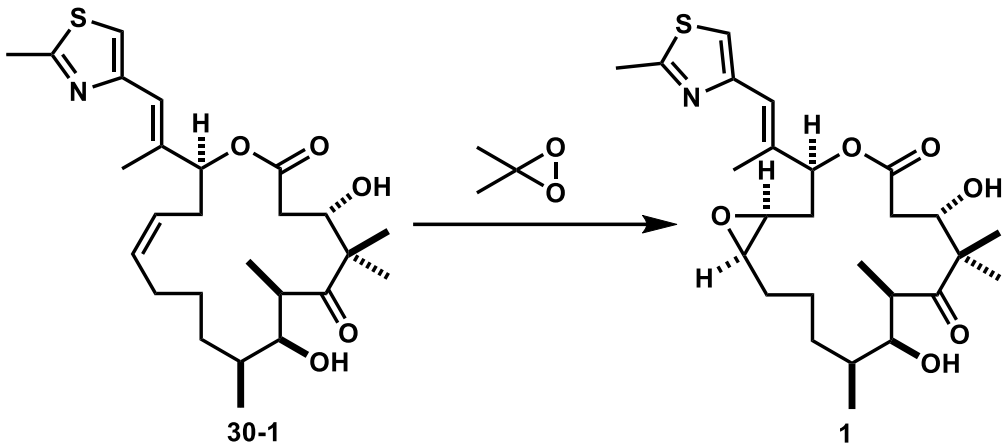
Formation of the mixed anhydride (R = 2,4,6-trichlorobenzoyl):



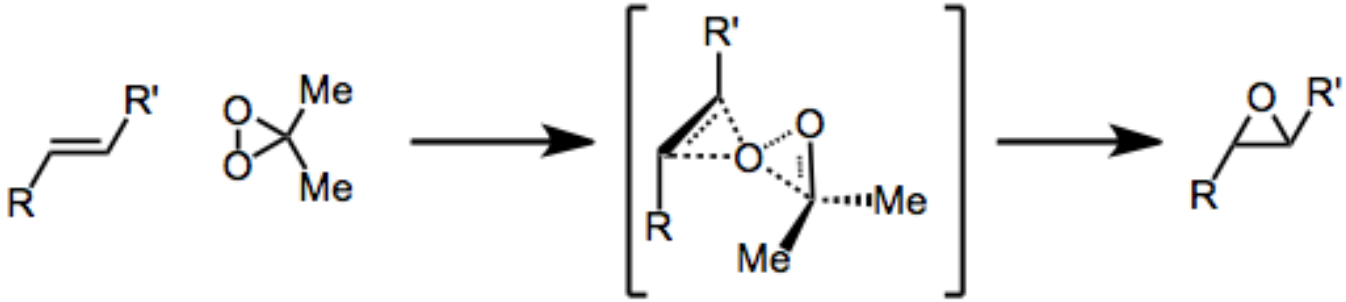
Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):



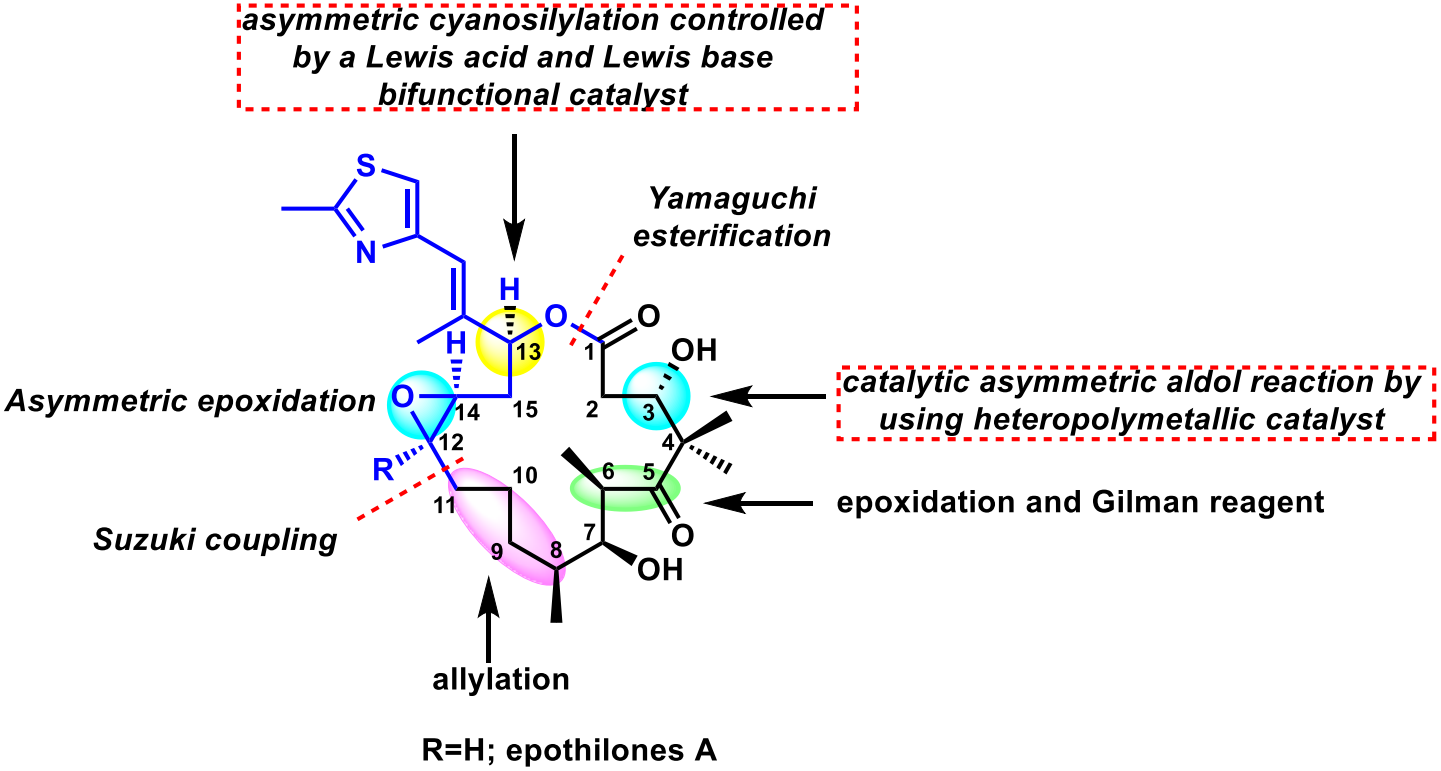
Epoxidation with 3,3-Dimethyldioxirane



Mechanism



Summary

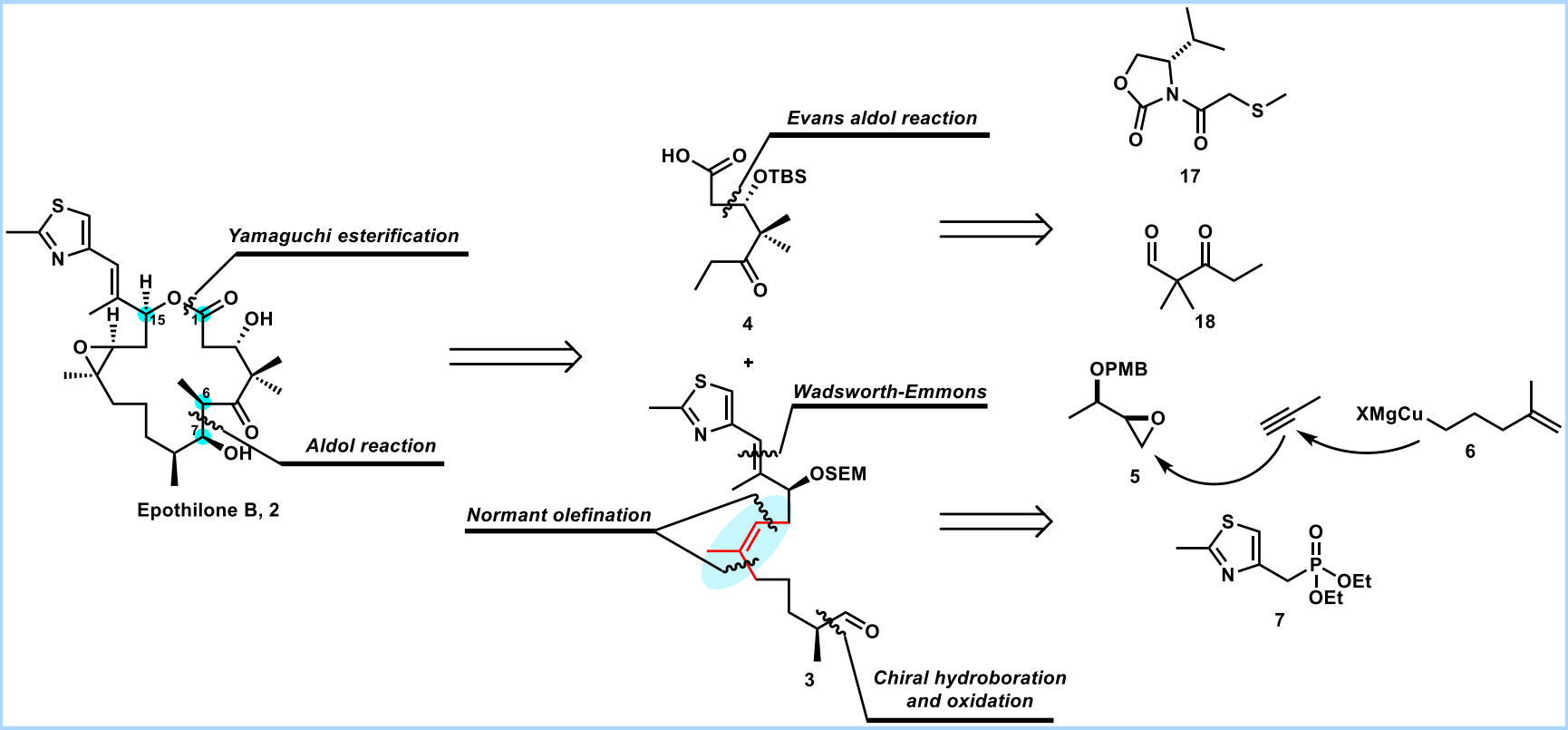


R=H; epothilones A

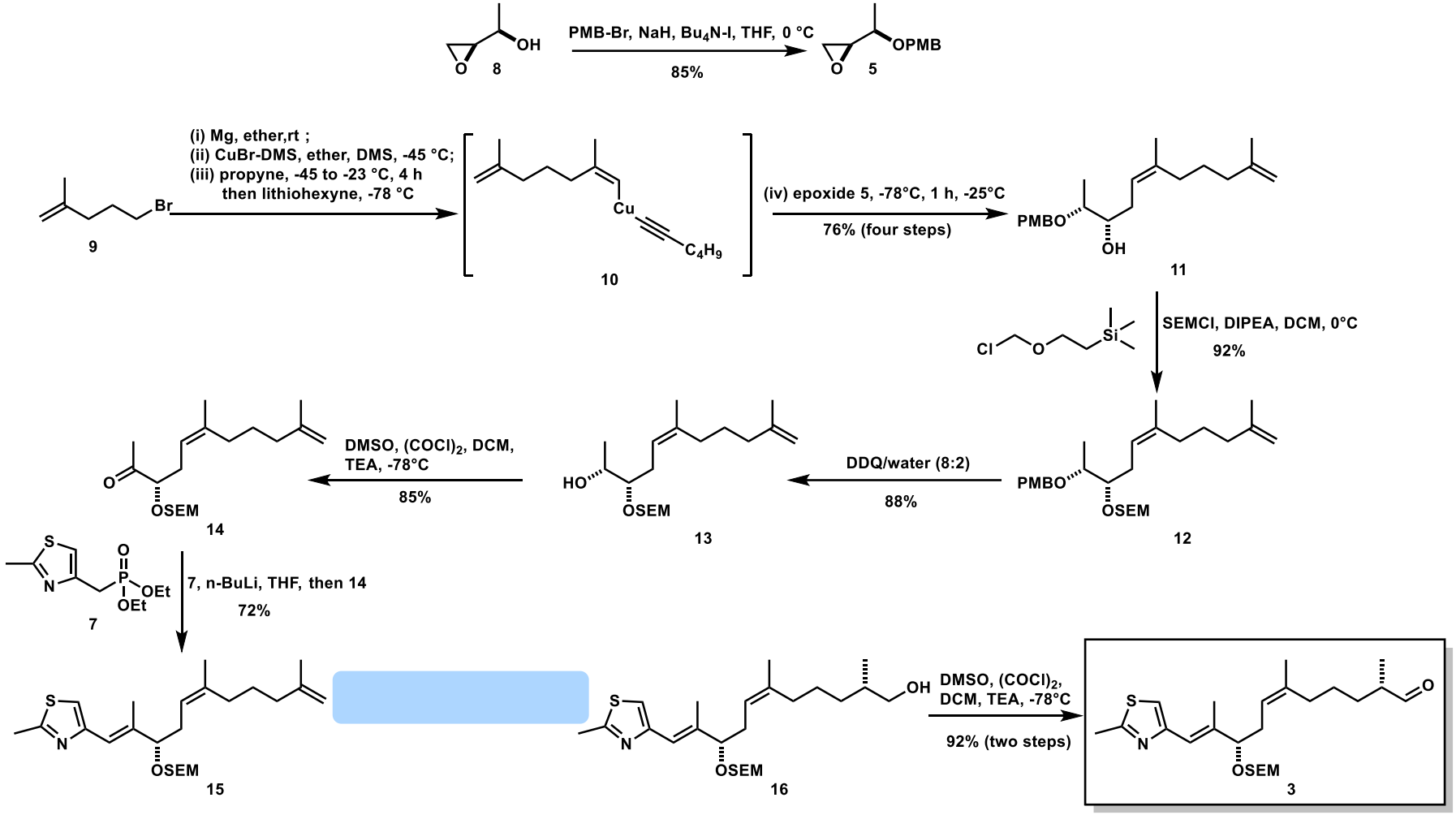
M. Shibasaki（2003）

M. A. Avery: *Org. Lett.* **2001**, *3*, 3607 - 3609.

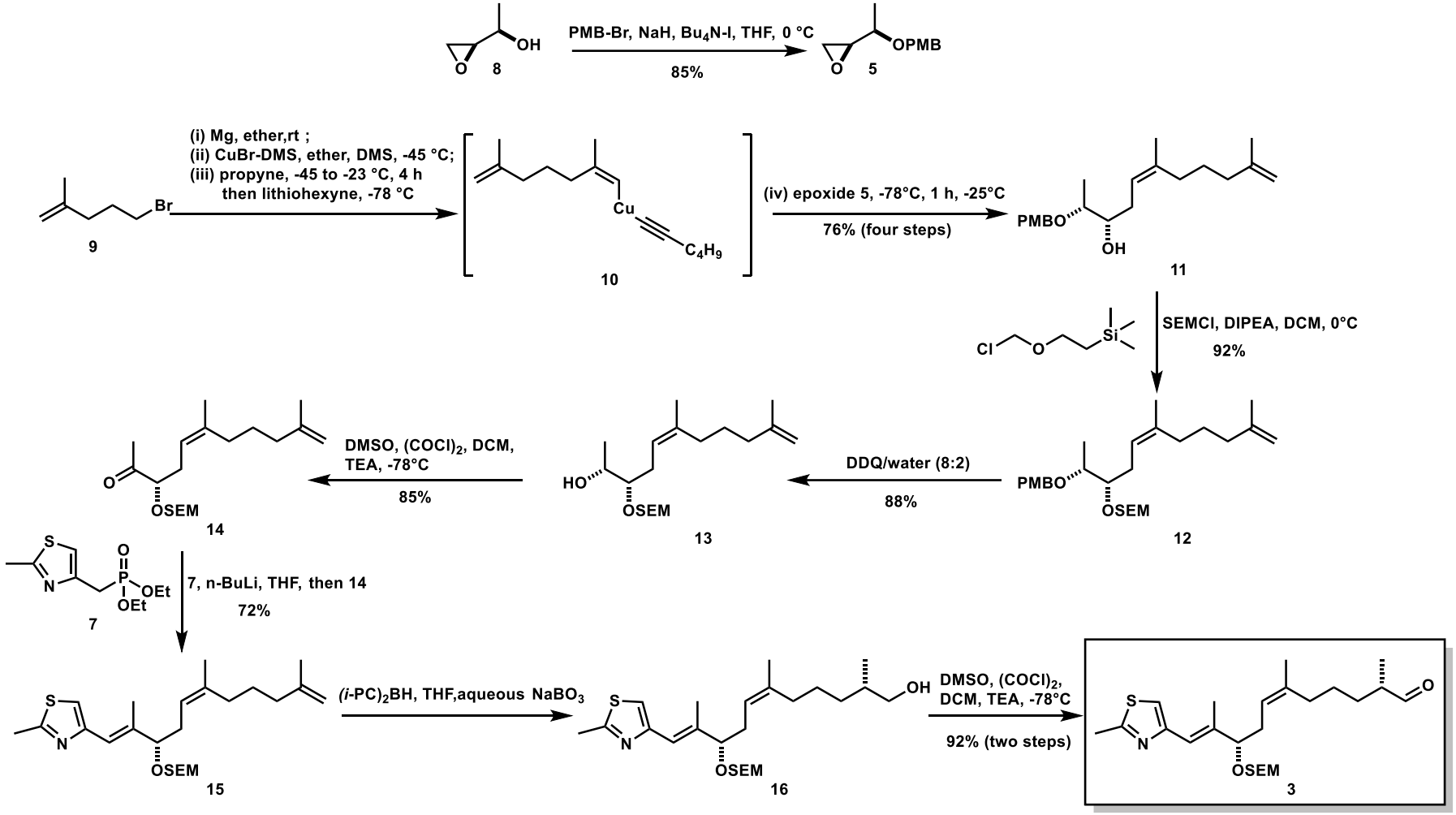
- **Closing the ring through double-diastereoselective aldol condensation and macrolactonization**
- **Synthesis of trisubstituted (Z)-olefingeometry by modifiction of a classical Normant alkynecupration and electrophile trap**



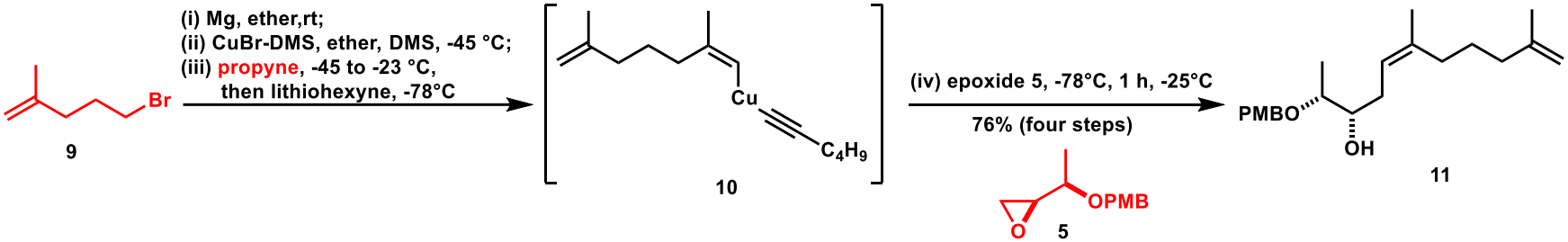
Synthesis of compound 3



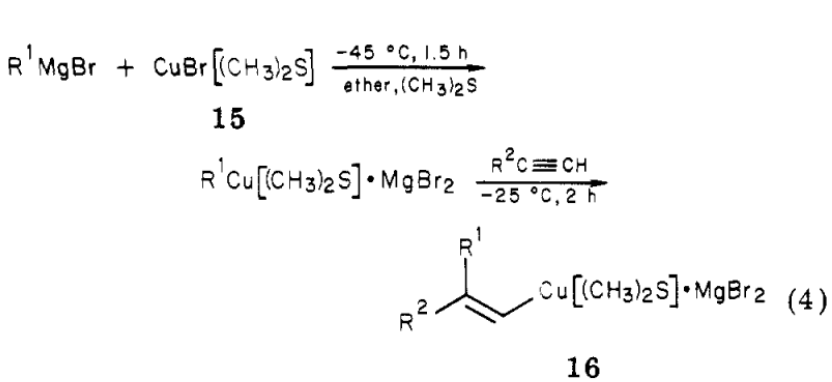
Synthesis of compound 3

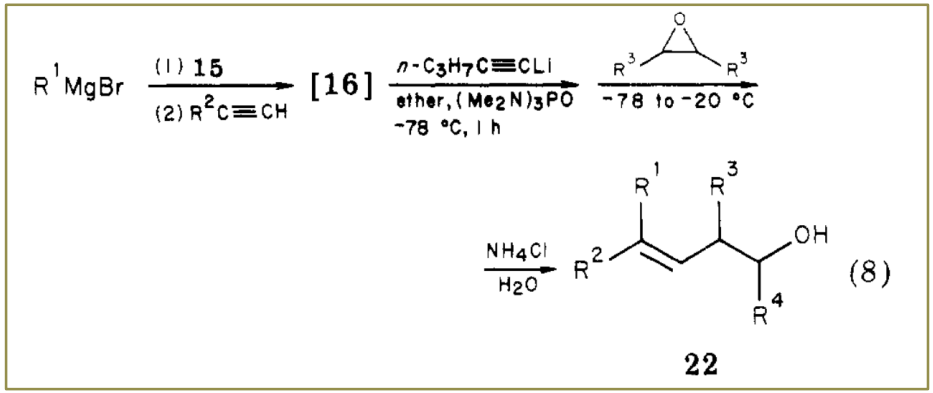


Normant coupling reaction



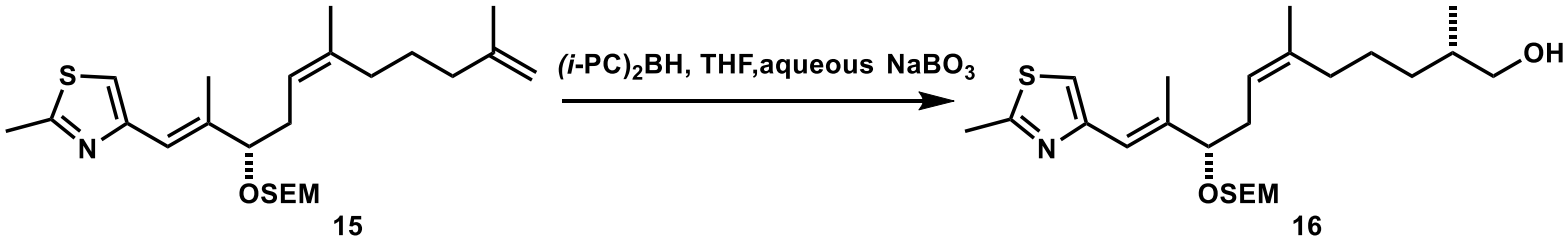
Mechanism



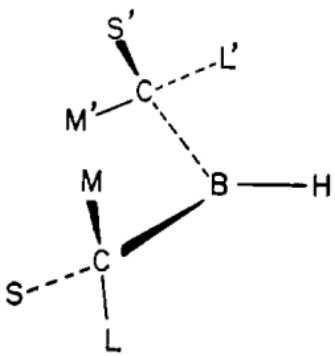


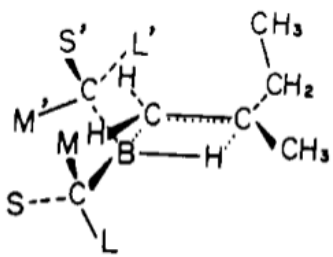
Normant, J. F, et al. *Synthesis*. **1972**, 63-80.

Diastereoselective hydroboration of the triene 15 using (*i*-PC)$_2$BH



Mechanism





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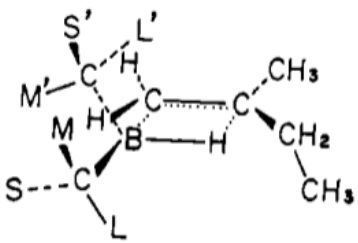

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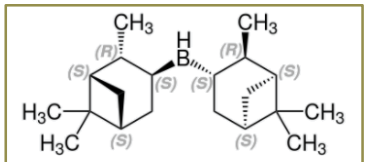
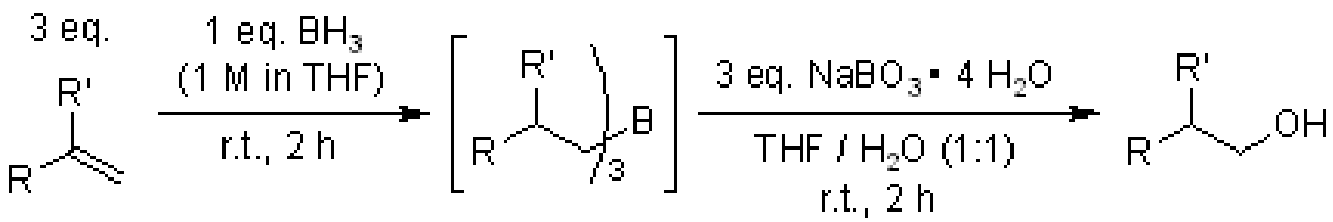


（+）-二异松香基硼烷的结构

Joshi, N. N, et al. *J. Am. Chem. Soc.* **1988**, *53*, 4059 - 4061.

Sodium perborate reagent



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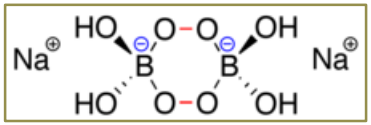
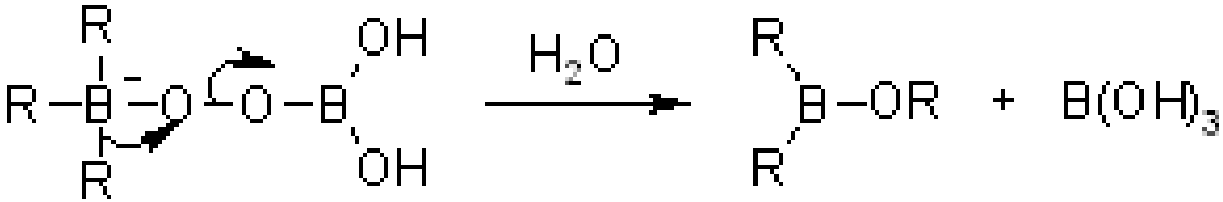
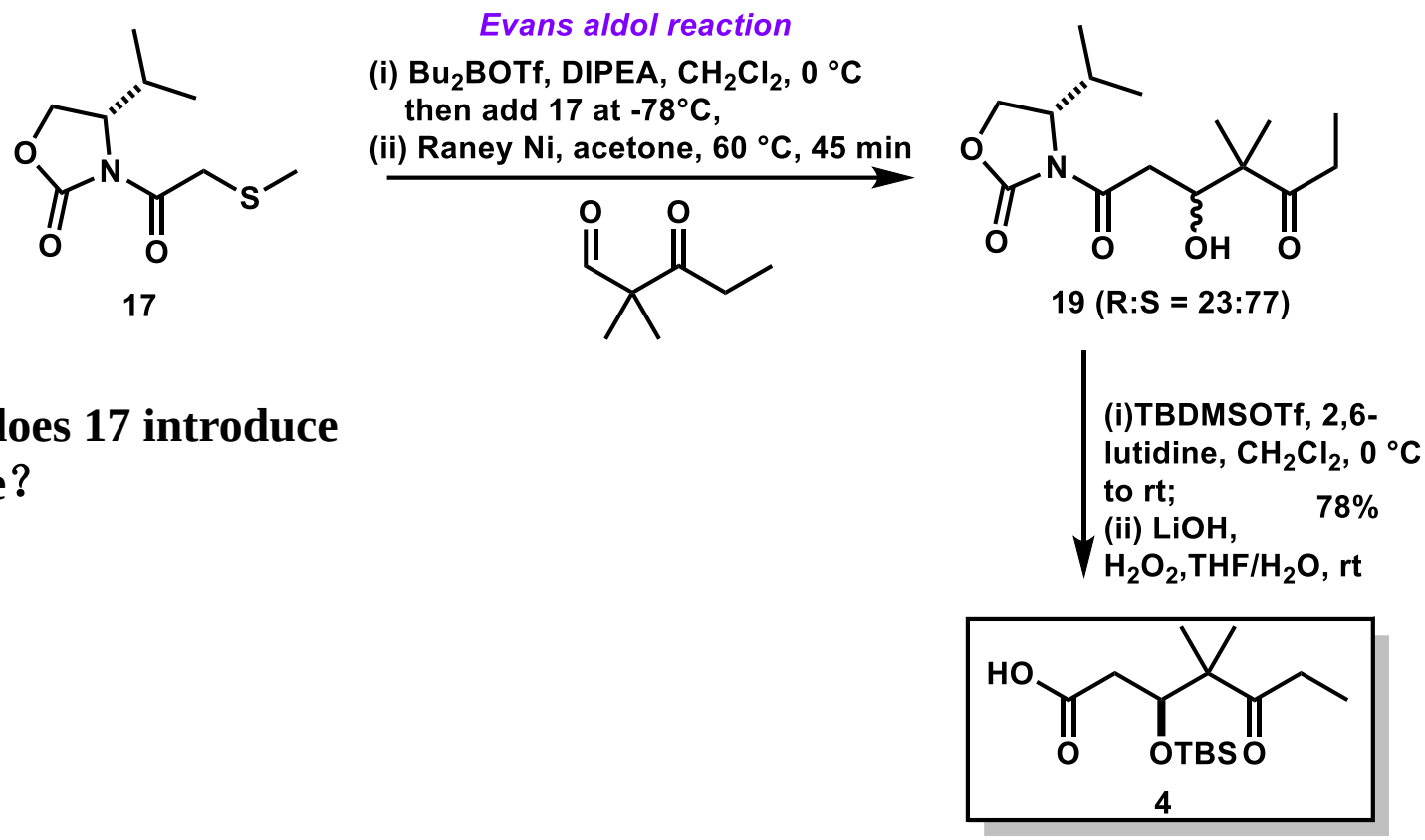


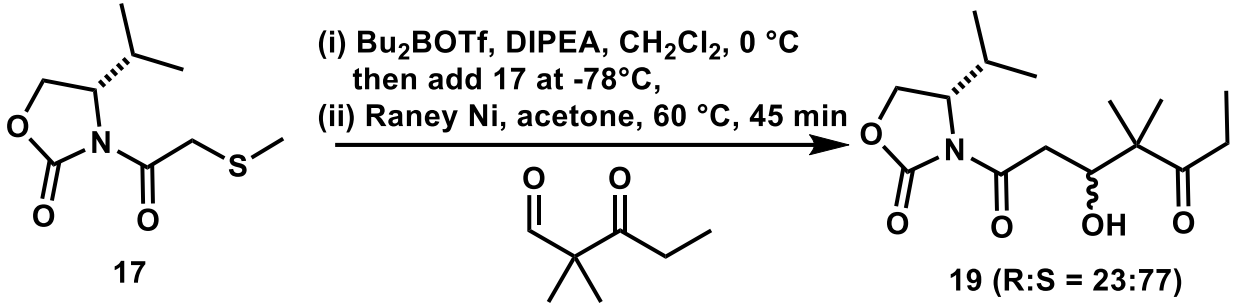


Synthesis of compound 4



Why does 17 introduce sulfide?

Evans aldol reaction



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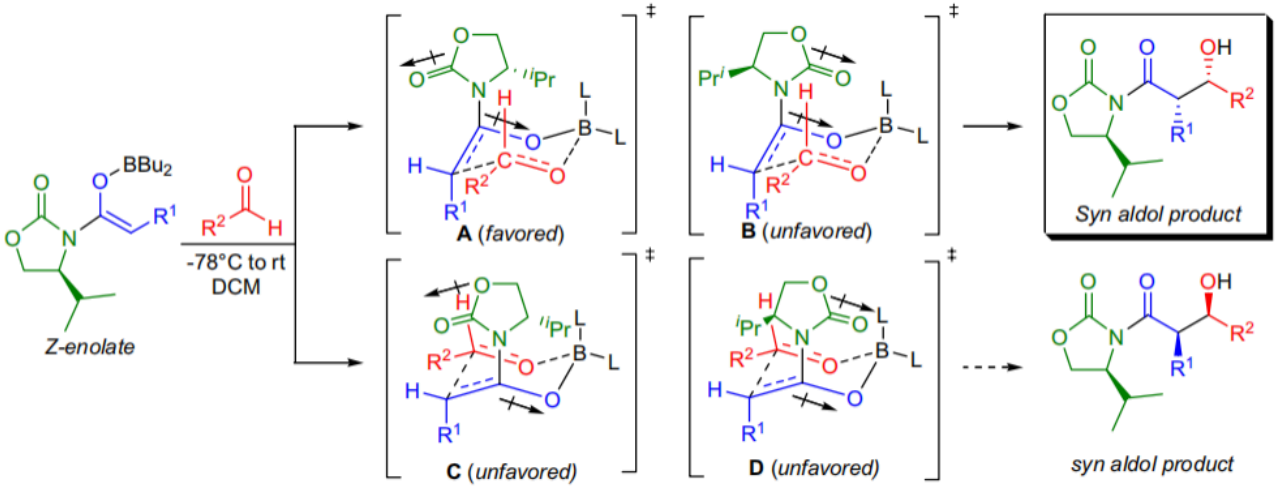
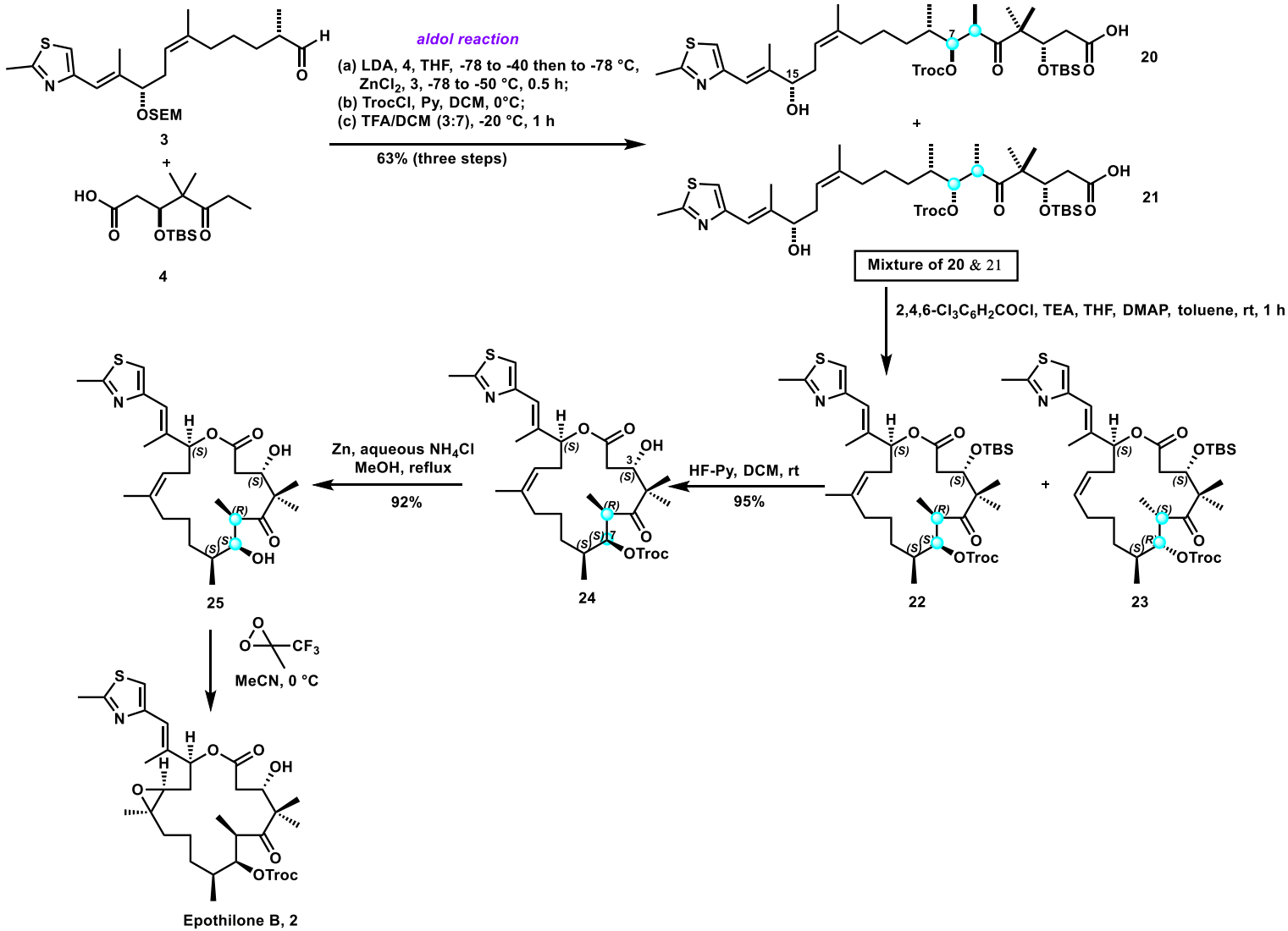
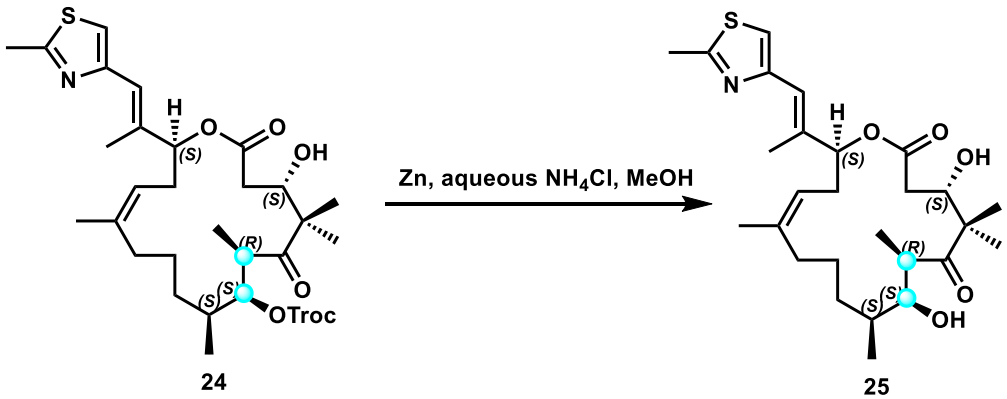


Synthesis of Epothilone B



Deprotection of Troc group using zinc metal



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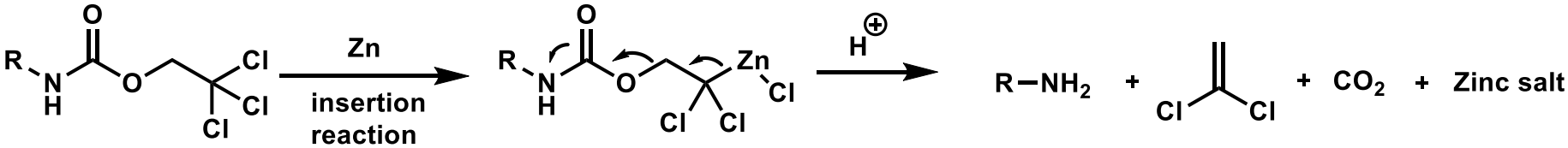
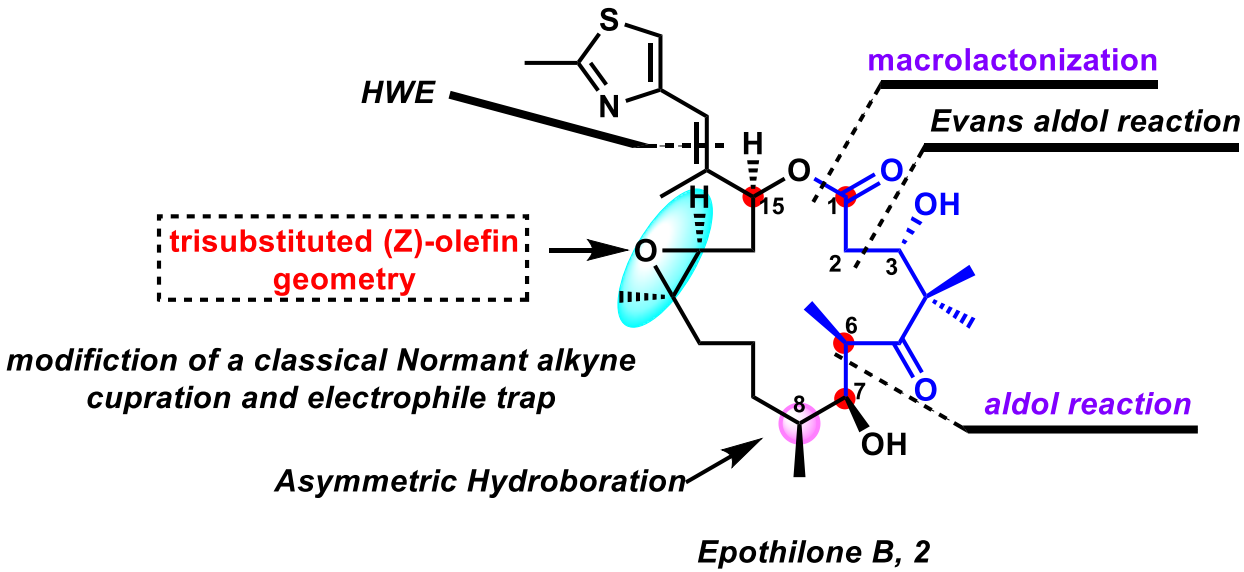


Summary



M. A. Avery（2001）

北京大學
PEKING UNIVERSITY

Contents

1. Introduction

2.Total Synthesis of Epothilone and Analogues

Ⅰ. **Richard E. Taylor:** *Org. Lett.* **2001**, No.1, 42221-2224

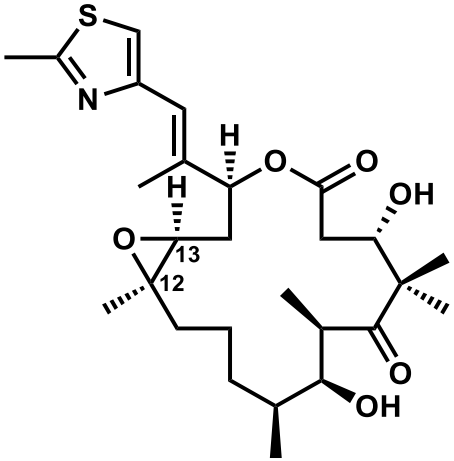
Ⅱ. **Samuel J. Danishefsky:** Angew. Chem. **2003**, 115, 4910 –4915

Ⅲ. **Ulrich Klar:** Angew. Chem. **2006**, 118, 8110 –8116

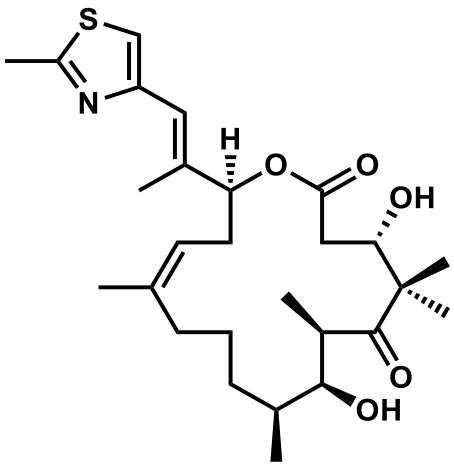
3.Summary

4.Acknowledgement

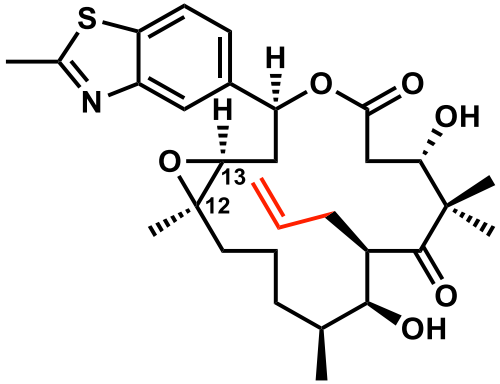
Introduction



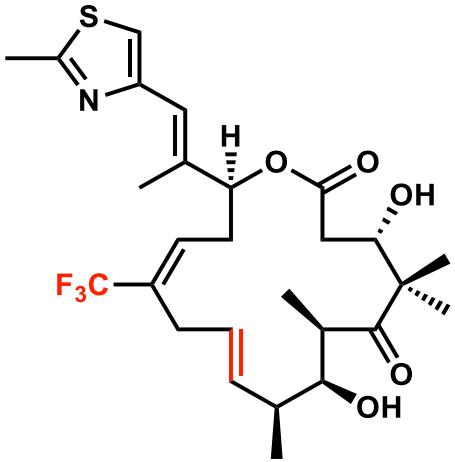
epothilone B



epothilone D



ZK-EPO



F_3-deH- epothilone D

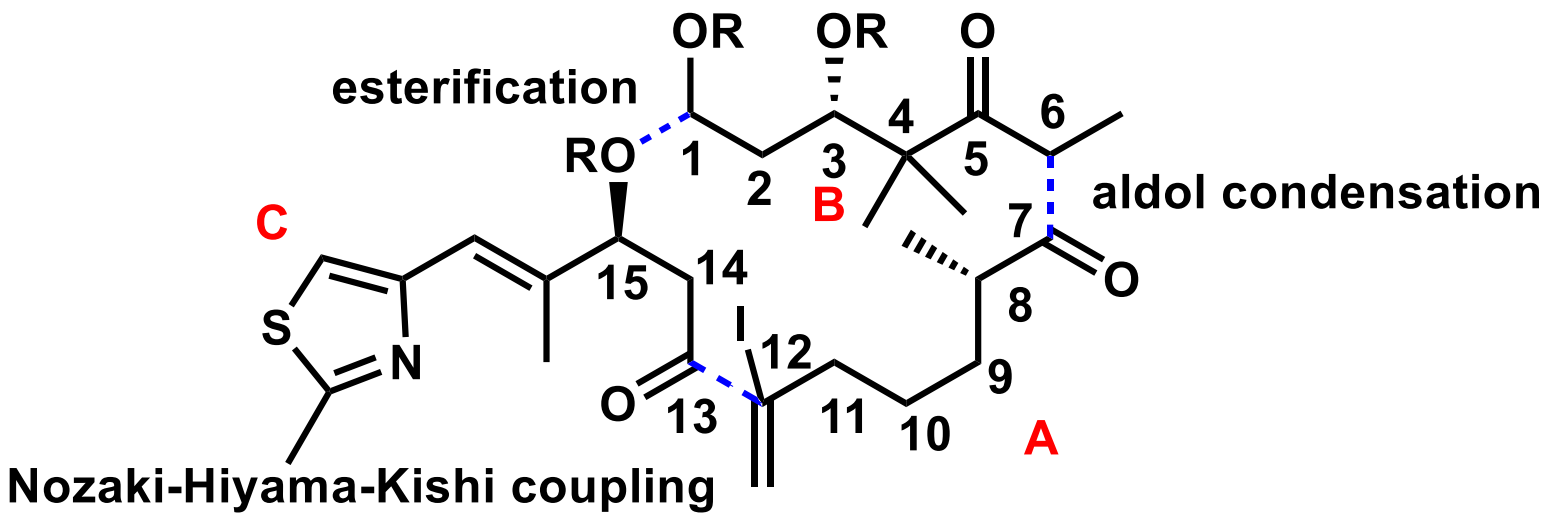
Total Systhesis of Epothilones B and D

ORGANIC LETTERS

2001
Vol. 3, No. 14
2221−2224

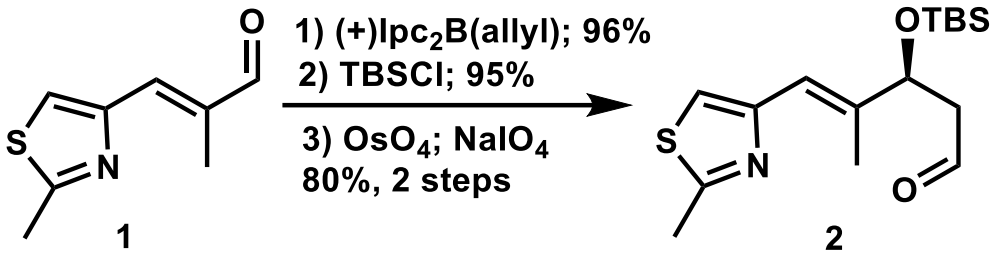
Total Synthesis of Epothilones B and D

Richard E. Taylor* and Yue Chen

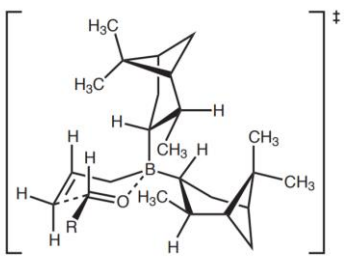


The Systhesis of Segment C

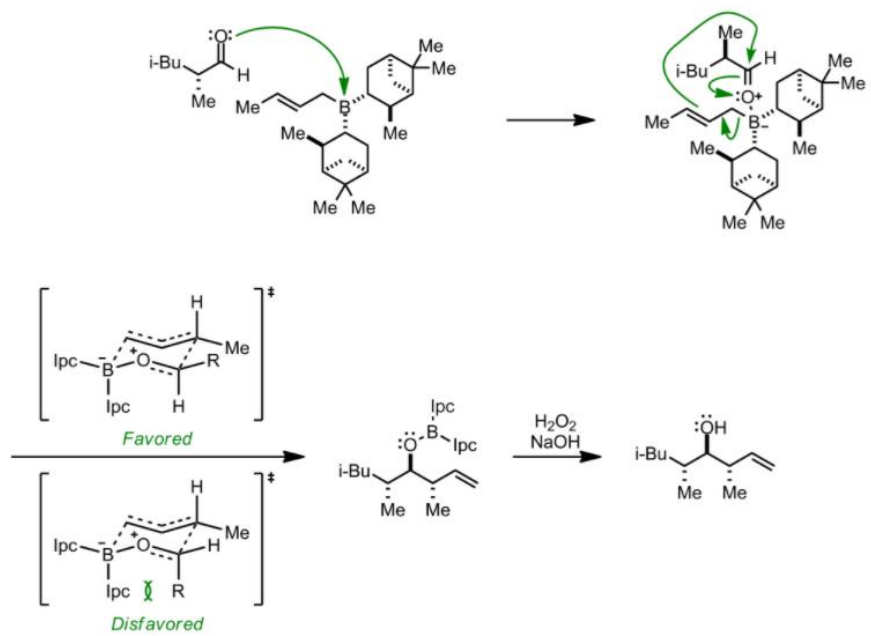
Brown Asymmetric Allylation



Mechanism



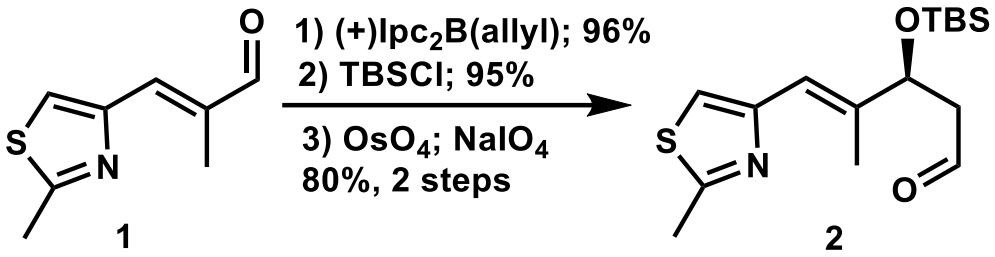
- Allylation of aldehydes proceeds through a chair-like TS where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial Ipc ligand and the allyl group.



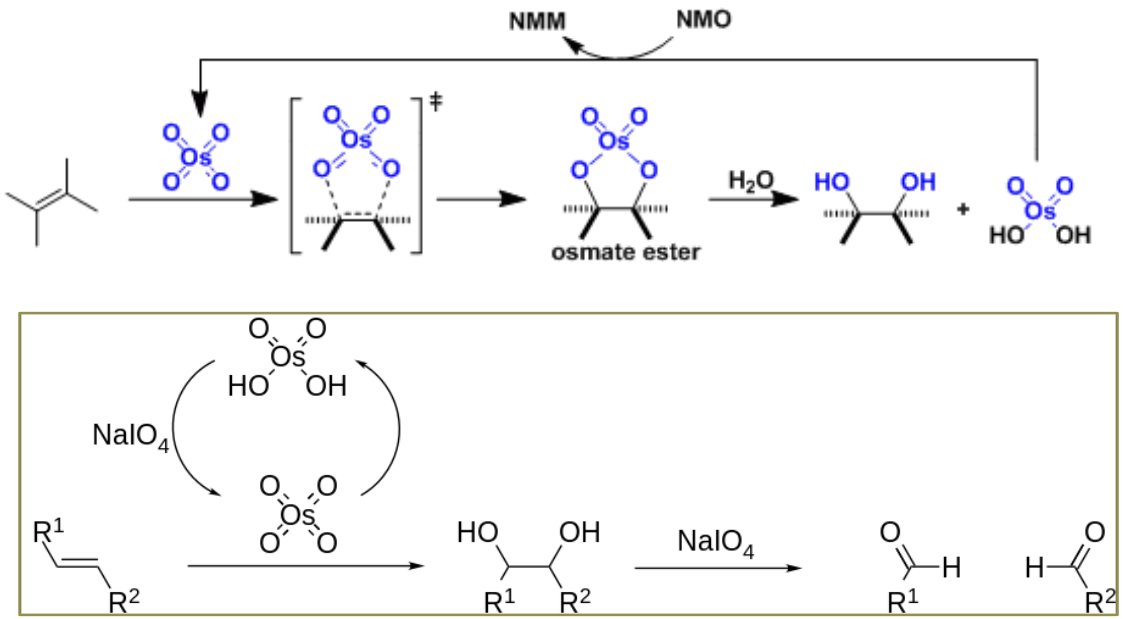
Corey, D. R, et al. *J. Am.Chem. Soc.* **1985**, *107*, 713.

The Systhesis of Segment C

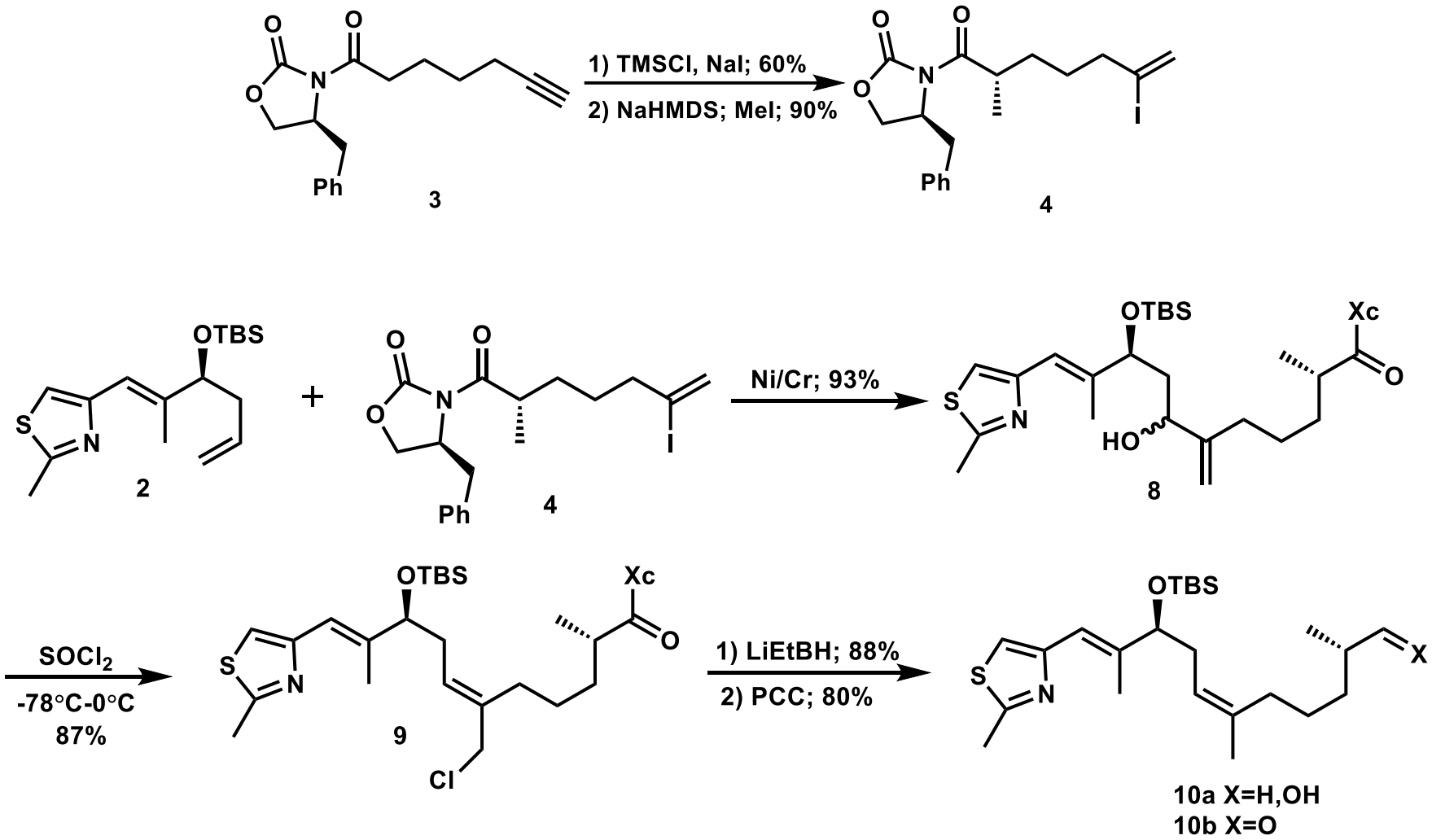
Lemieux-Johnson oxidation



Mechanism

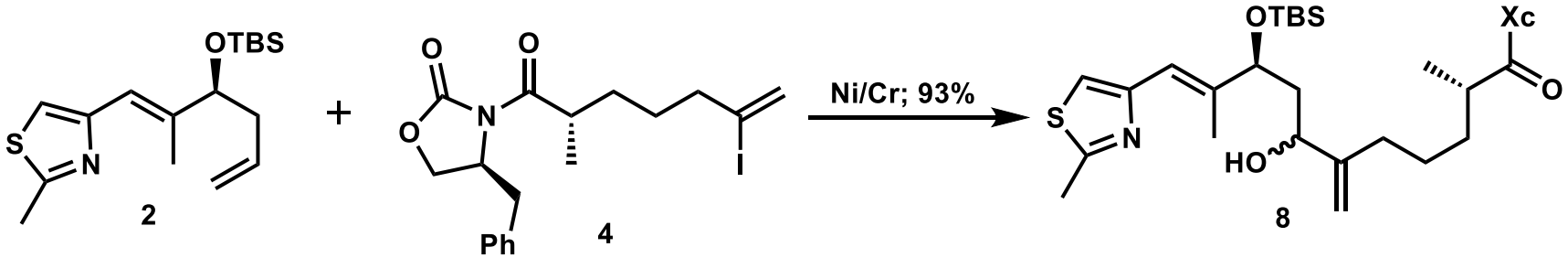


The Systhesis of Segment A and Segment AC



The Systhesis of Segment A and Segment AC

NHK reaction



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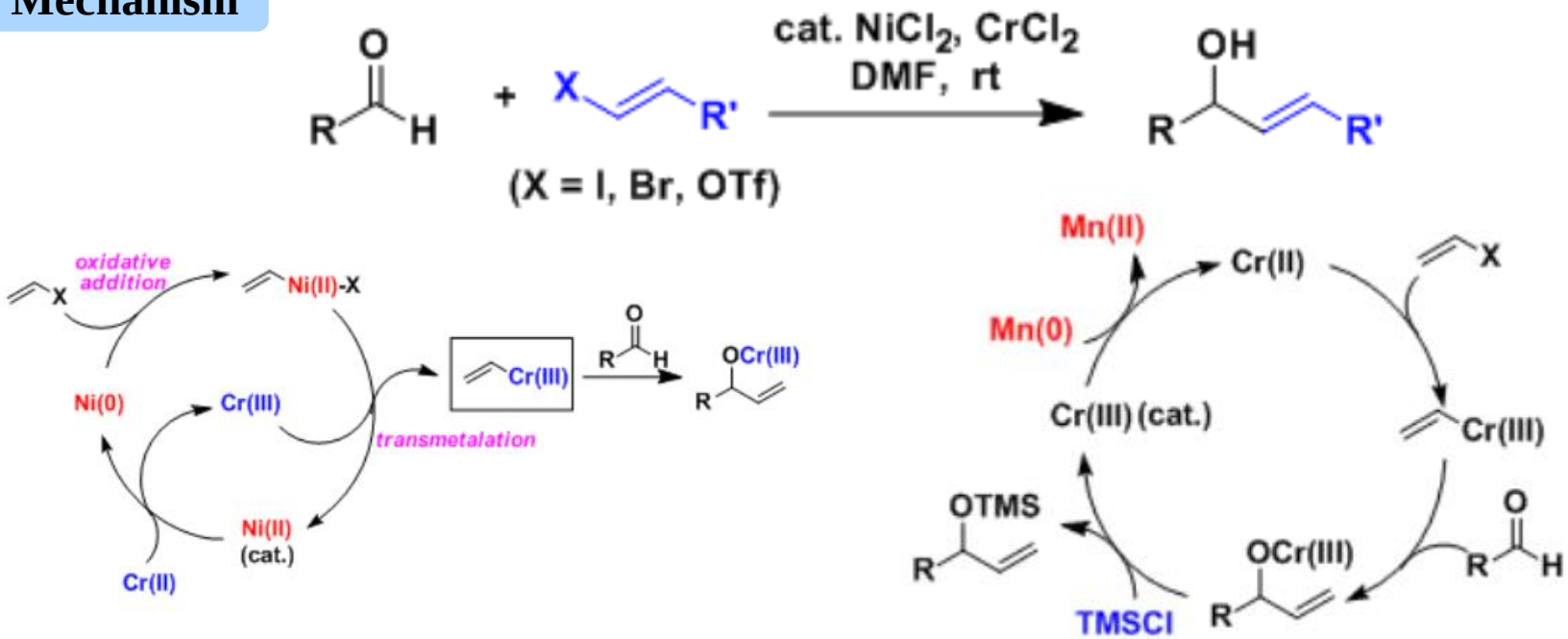
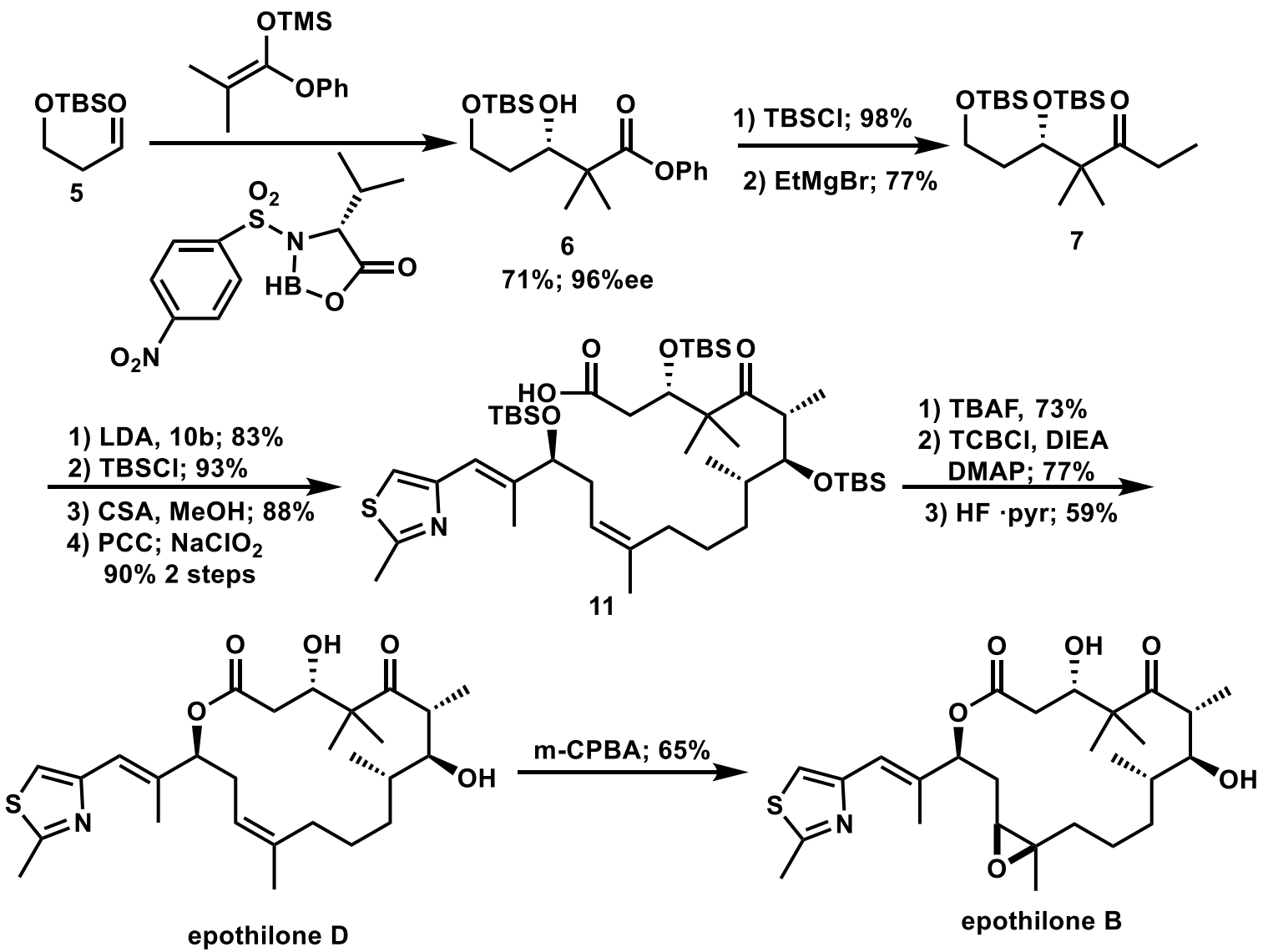
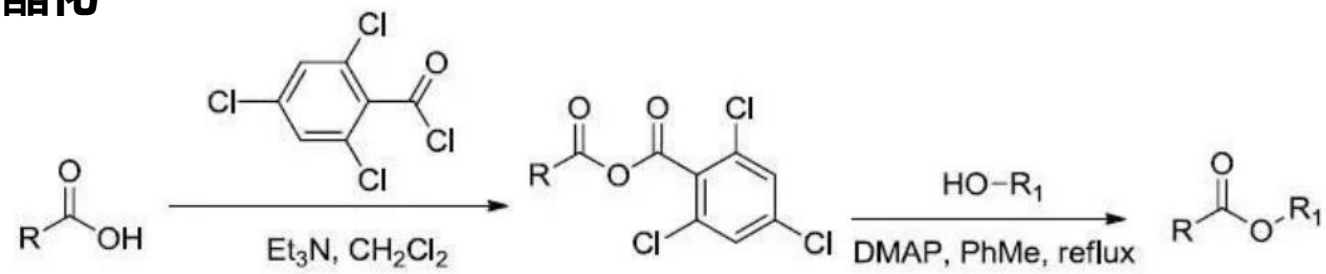


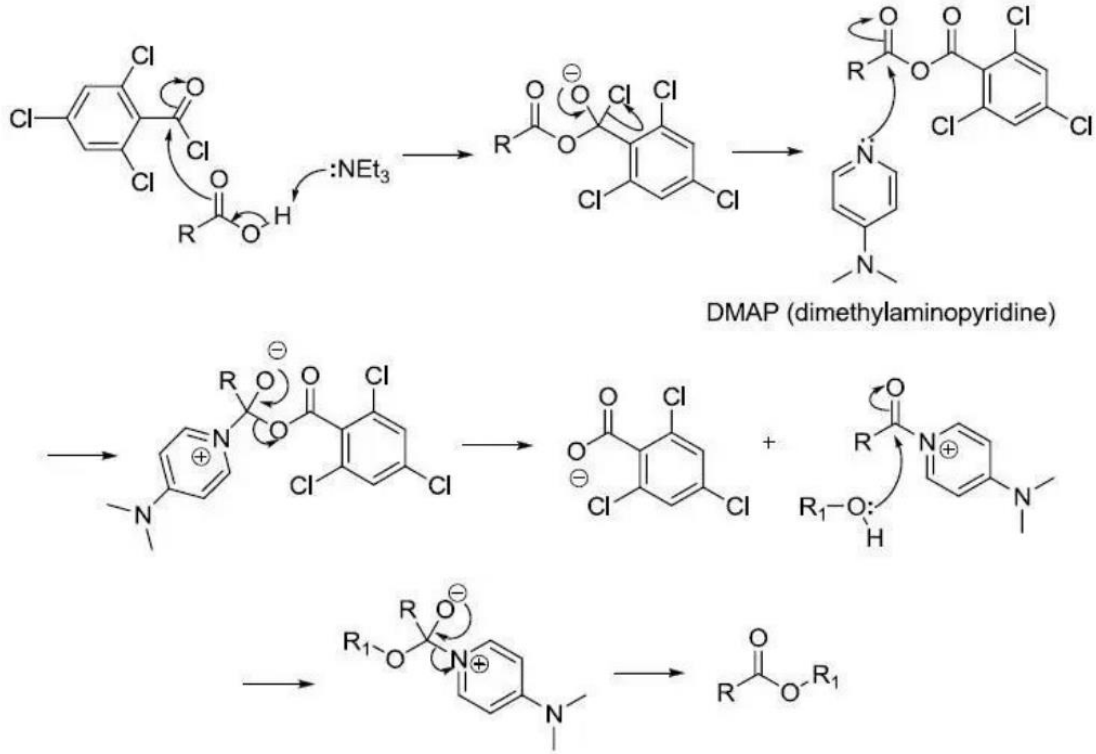
Total Systhesis of Epothilone D and Epothilone B



Total Systhesis of Epothilone D and Epothilone B

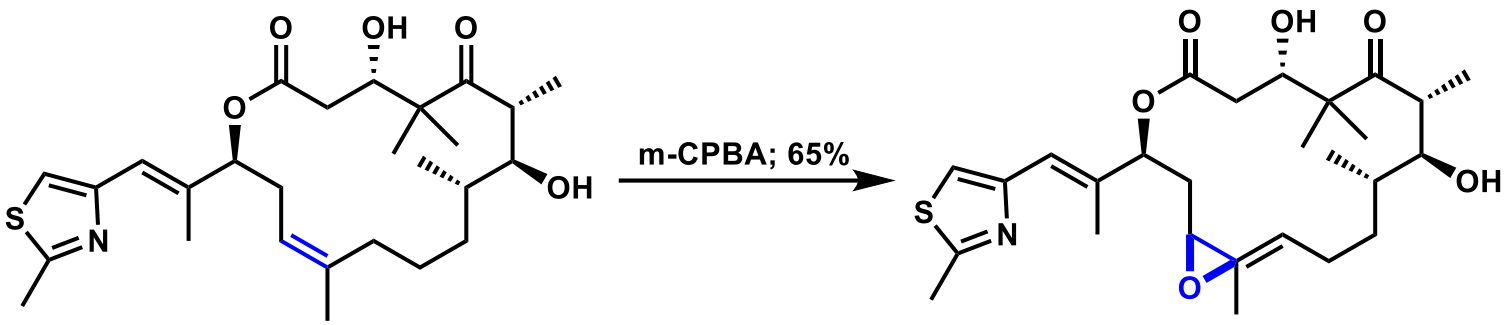
Yamaguchi酯化





Total Systhesis of Epothilone D and Epothilone B

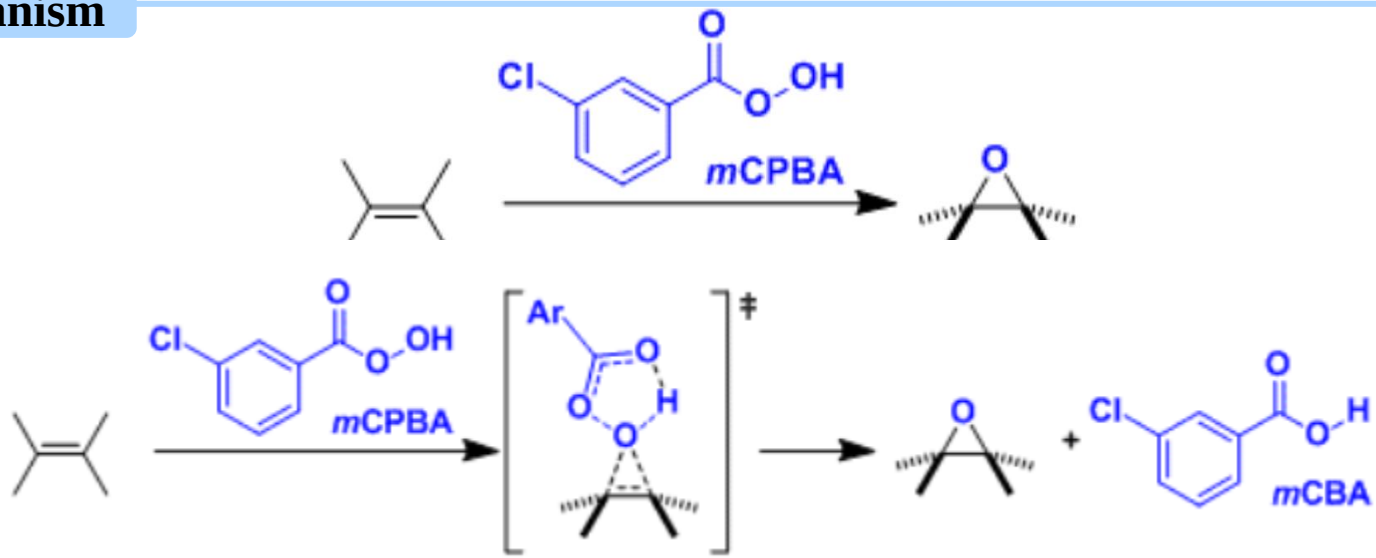
Prilezhaev Epoxidation



epothilone D

epothilone B

Mechanism



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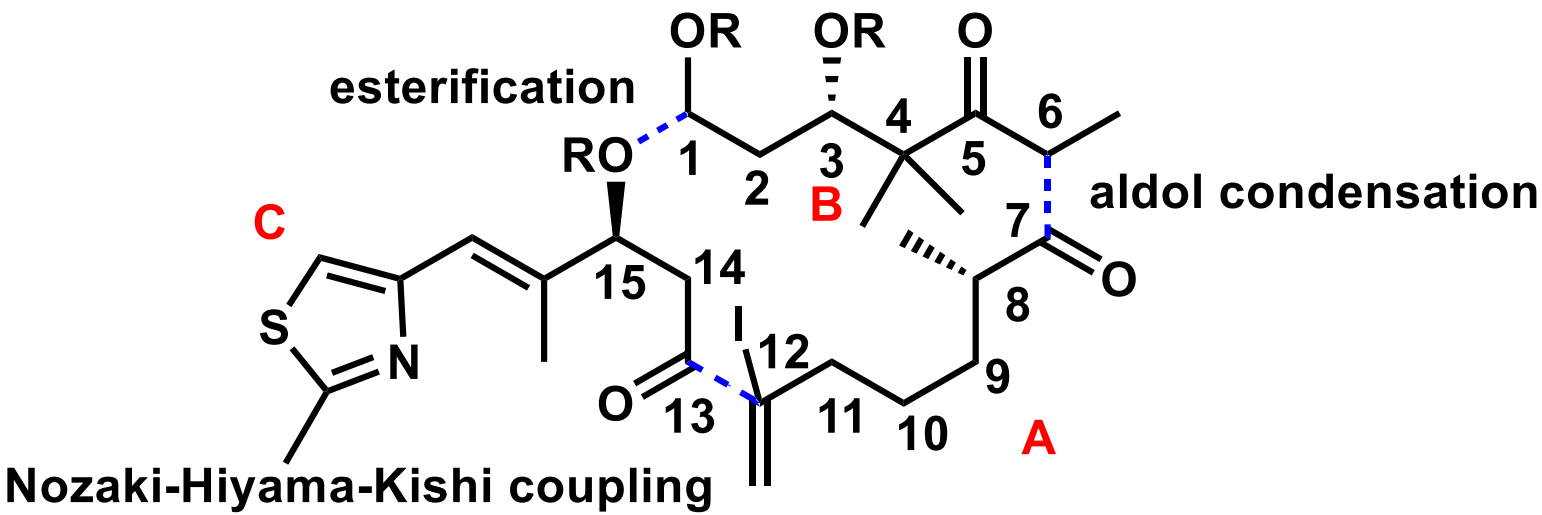


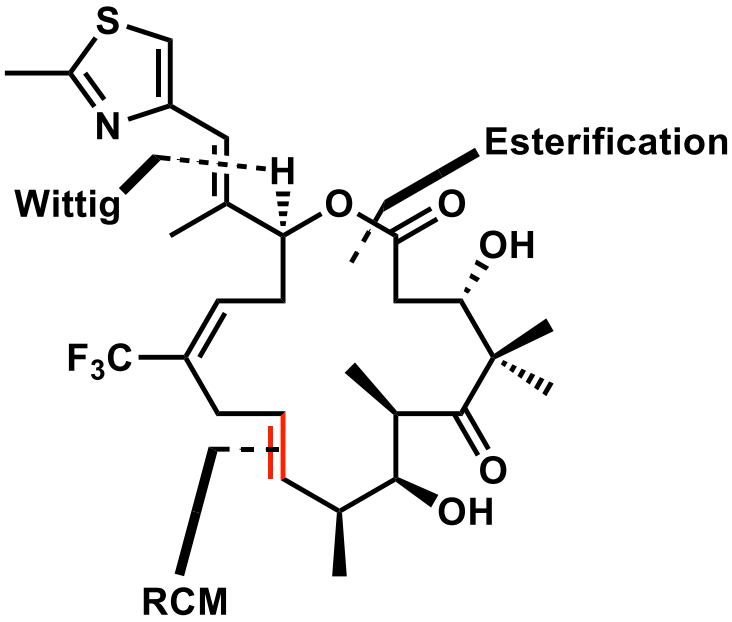
- The efficient generation of a C12-C13 trisubstituted olefin which exploits a sequential Nozaki- Hiyama-Kishi coupling
- A stereoselective thionyl chloride rearrangement.

Total Systhesis of Epothilone Analogues

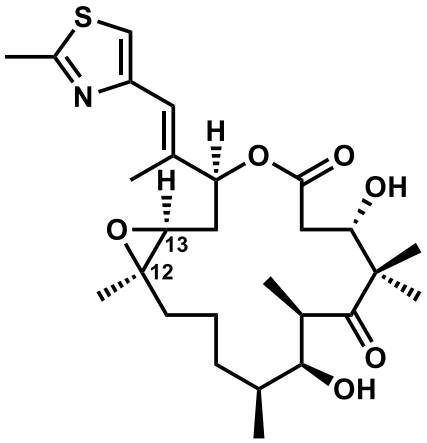
Zuschriften

Epothilones: Synthesis and Activity

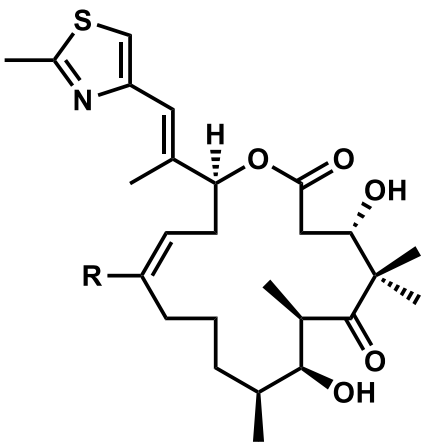
Design and Total Synthesis of a Superior Family of Epothilone Analogues, which Eliminate Xenograft Tumors to a Nonrelapsable State**



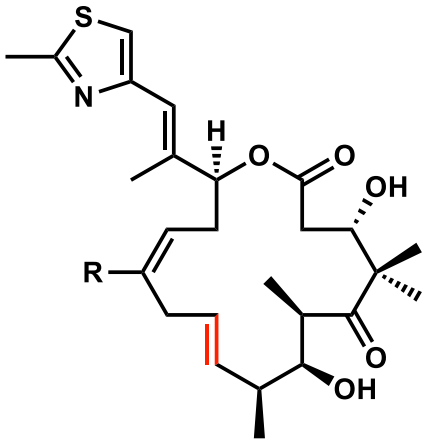
Introduction



1 epothilone B



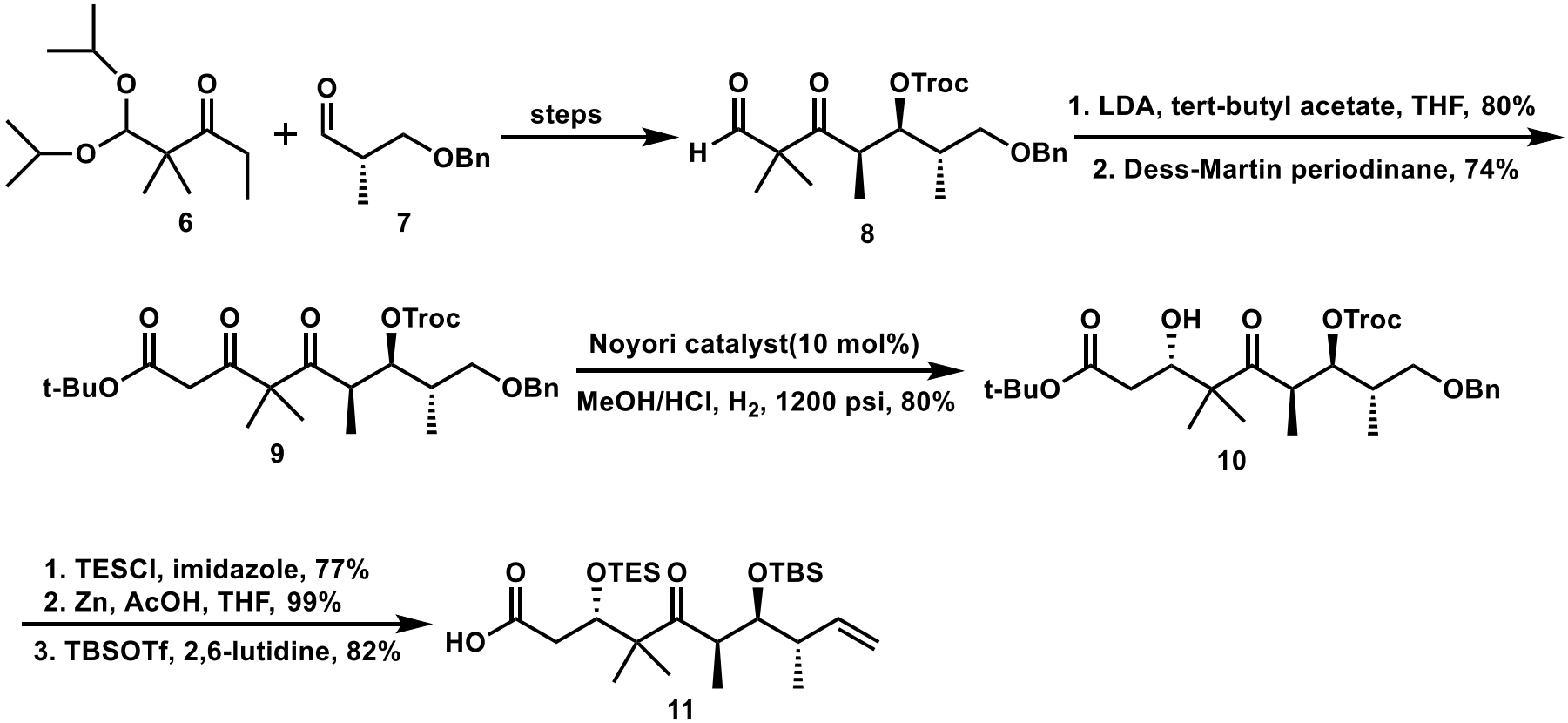
2 R=Me epothilone D
3 R=CF_3



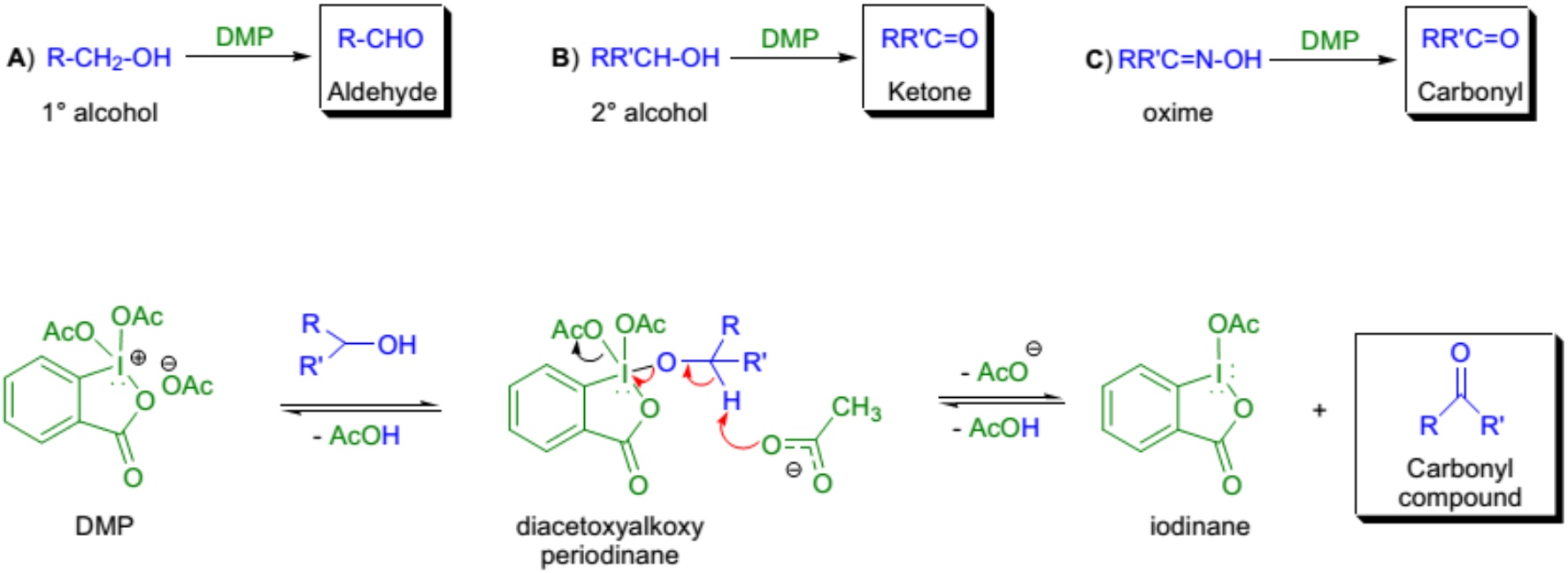
4 R=Me
5 R=CF_3

Drug	Dosage [mg kg^{-1}]	Change in body weight [%][b] day 4	day 8	Tumor-free after treatment period	Tumor reappearance[c]
2	30	−25.3 ± 2.1	−9.1 ± 4.1	10/10	5/10
paclitaxel	20	−23.9 ± 3.7	−8.7 ± 0.7	7/7	2/7
5	20	−22.4 ± 0.6	−7.3 ± 0.7	4/4	0/4[d]
5	30	−27.1 ± 2.7	−17.4 ± 5.5	4/4	0/4[e]

The Systhesis of Carboxylic Acid 11

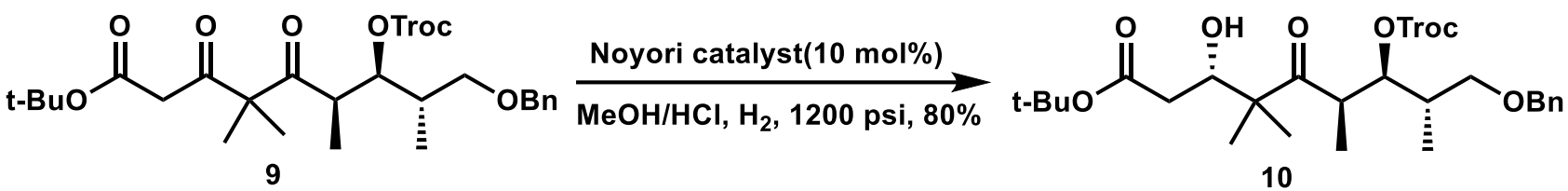


Dess-Martin

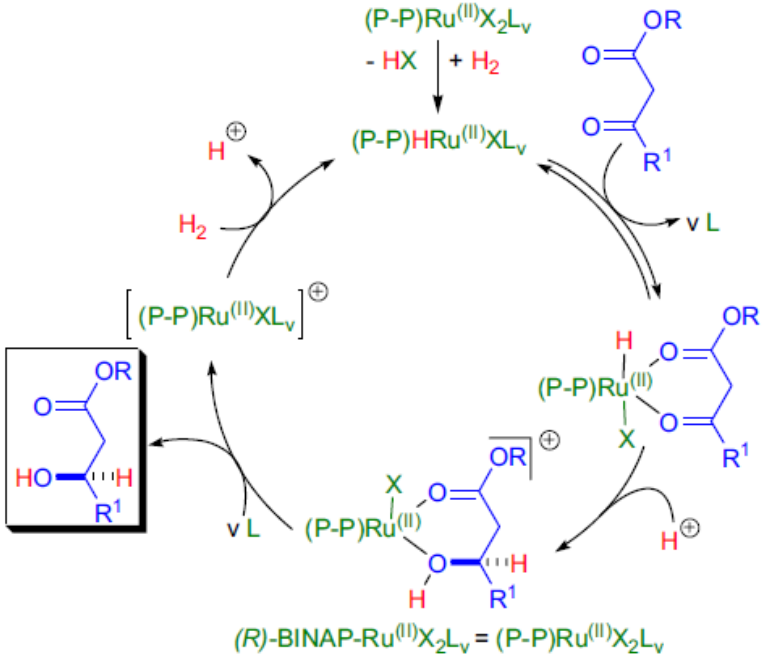

A) R-CH2-OH
DMP
R-CHO
Aldehyde
1° alcohol
B) RR'CH-OH
DMP
RR'C=O
Ketone
2° alcohol
C) RR'C=N-OH
DMP
RR'C=O
Carbonyl
oxime
AcO
OAc
OAc
DMP
R
R'
OH
- AcOH
AcO
OAc
R
R'
H
CH3
diacetoxyalkoxy
periodinane
- AcO
- AcOH
OAc
iodinane
+
R
R'
Carbonyl
compound

The Systhesis of Carboxylic Acid 11

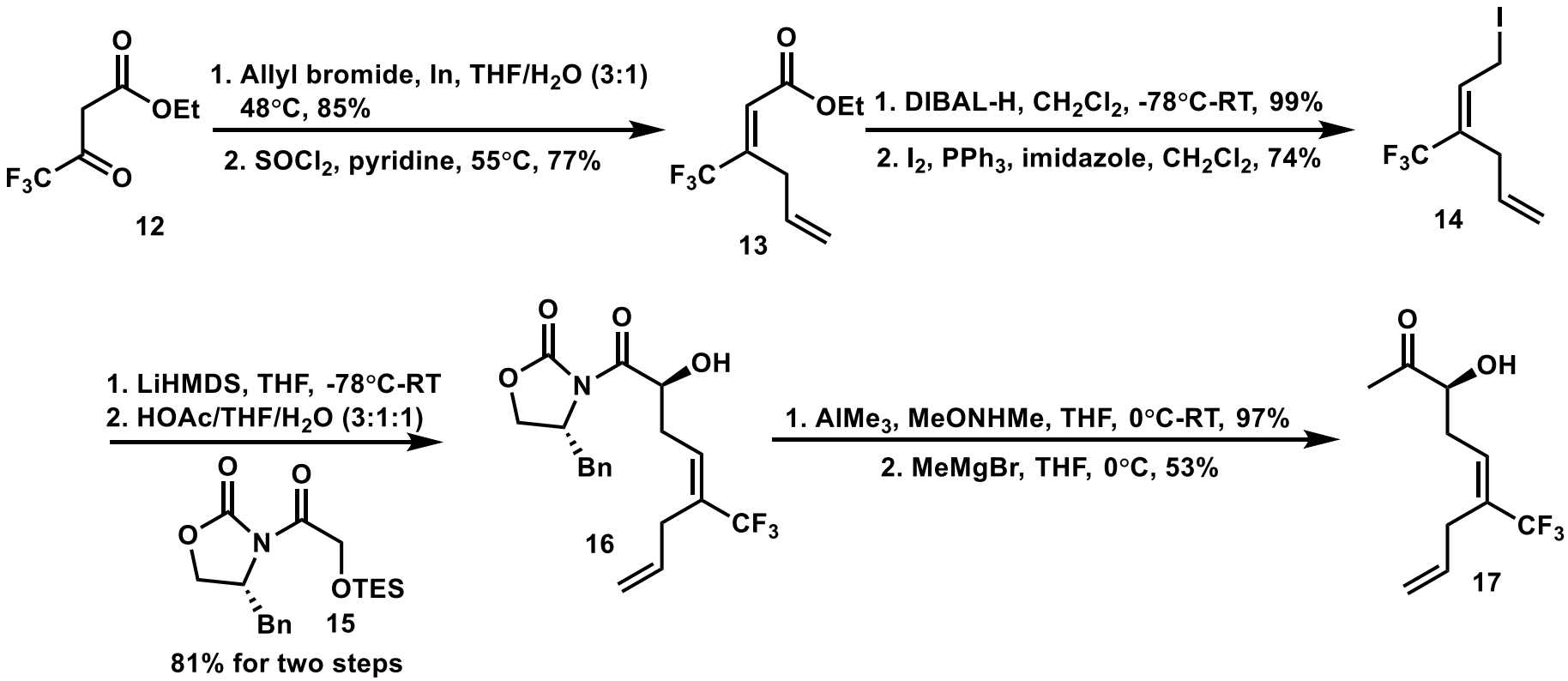
Noyori不对称氢化



Mechanism

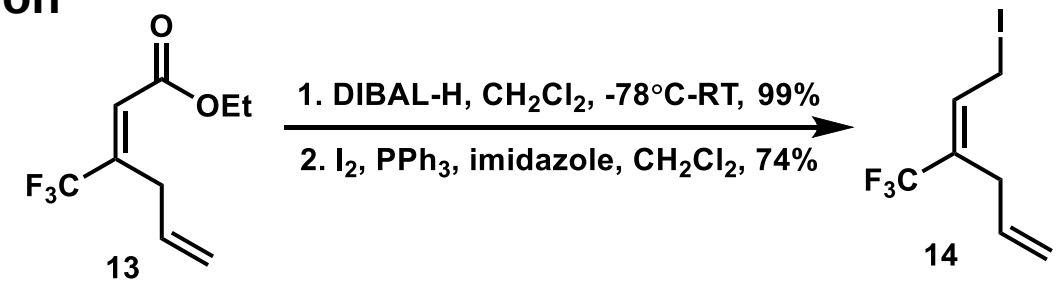


The Systhesis of Alcohol 17

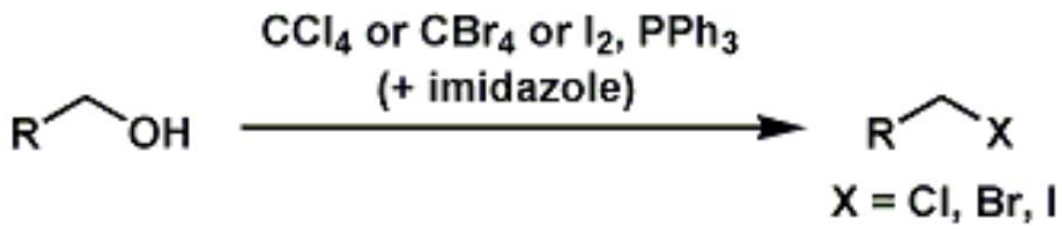


The Systhesis of Alcohol 17

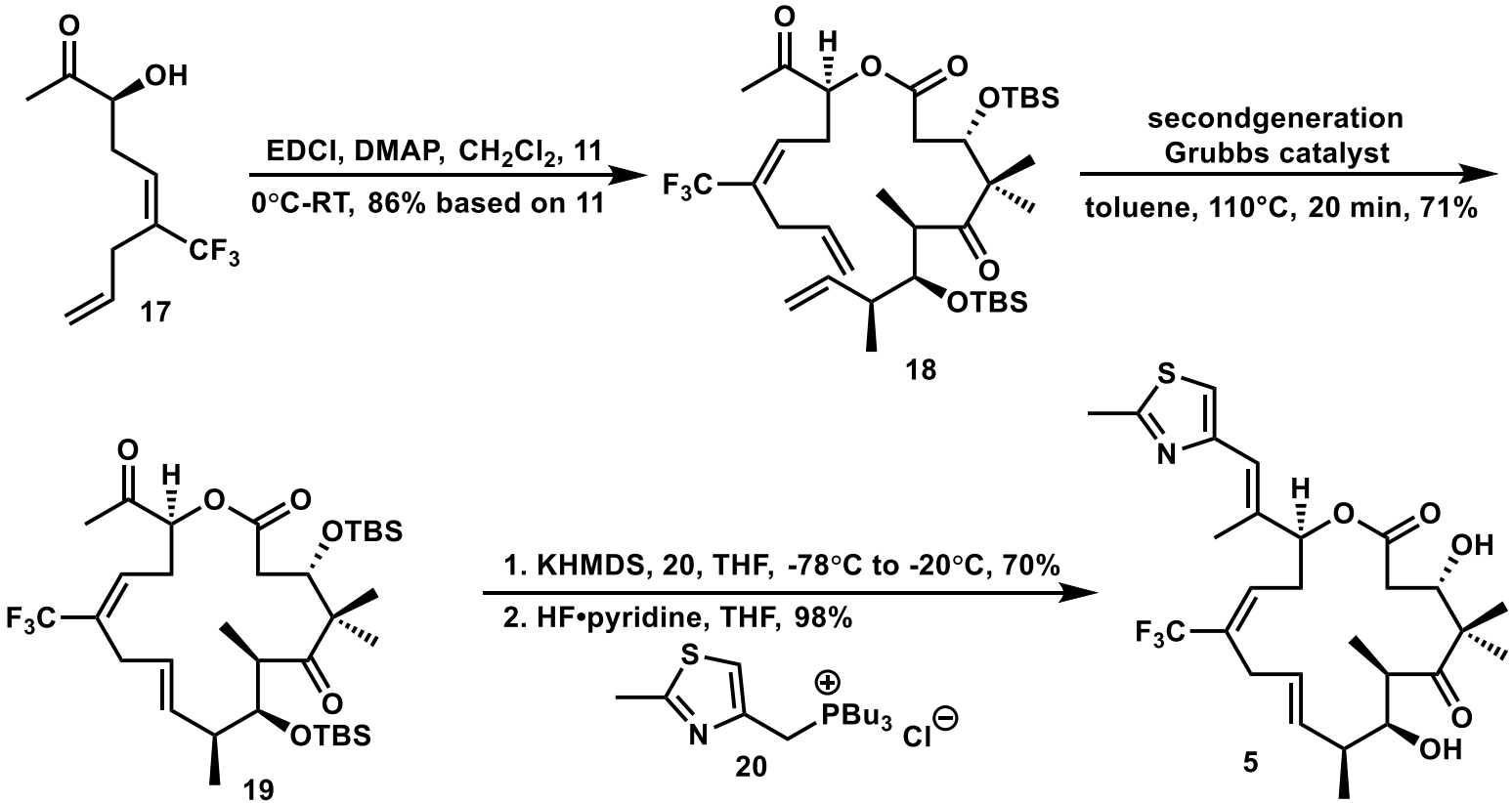
Appel reaction



Mechanism

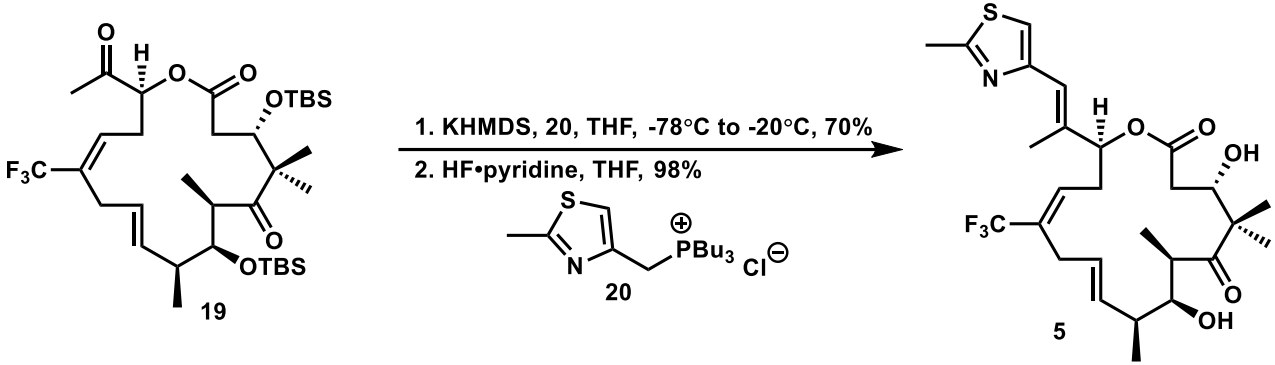


Total Systhesis of Epothilone Analogues

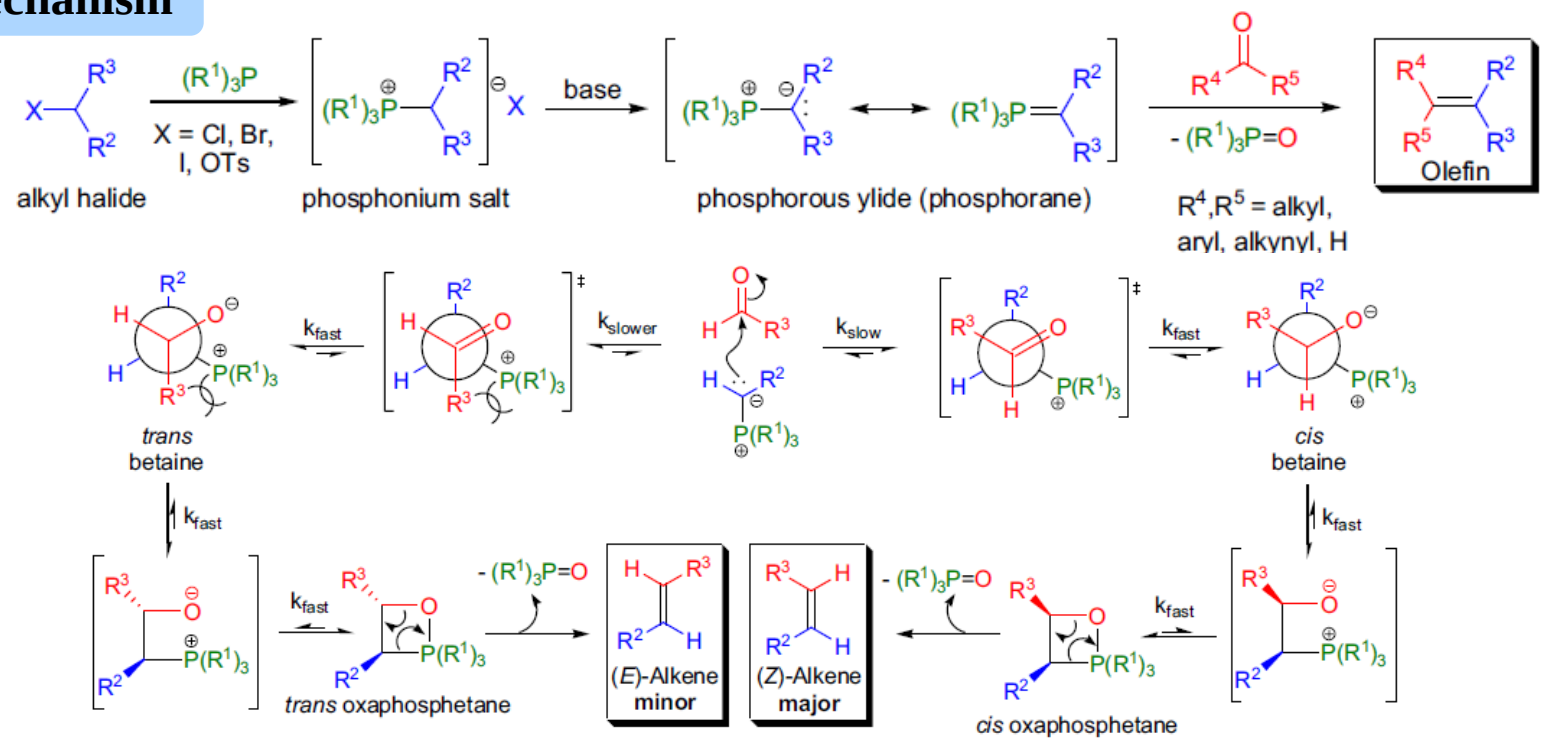


Total Systhesis of Epothilone Analogues

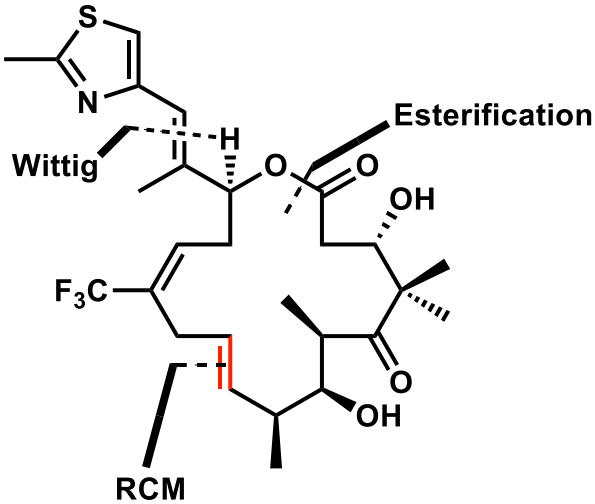
Wittig reaction

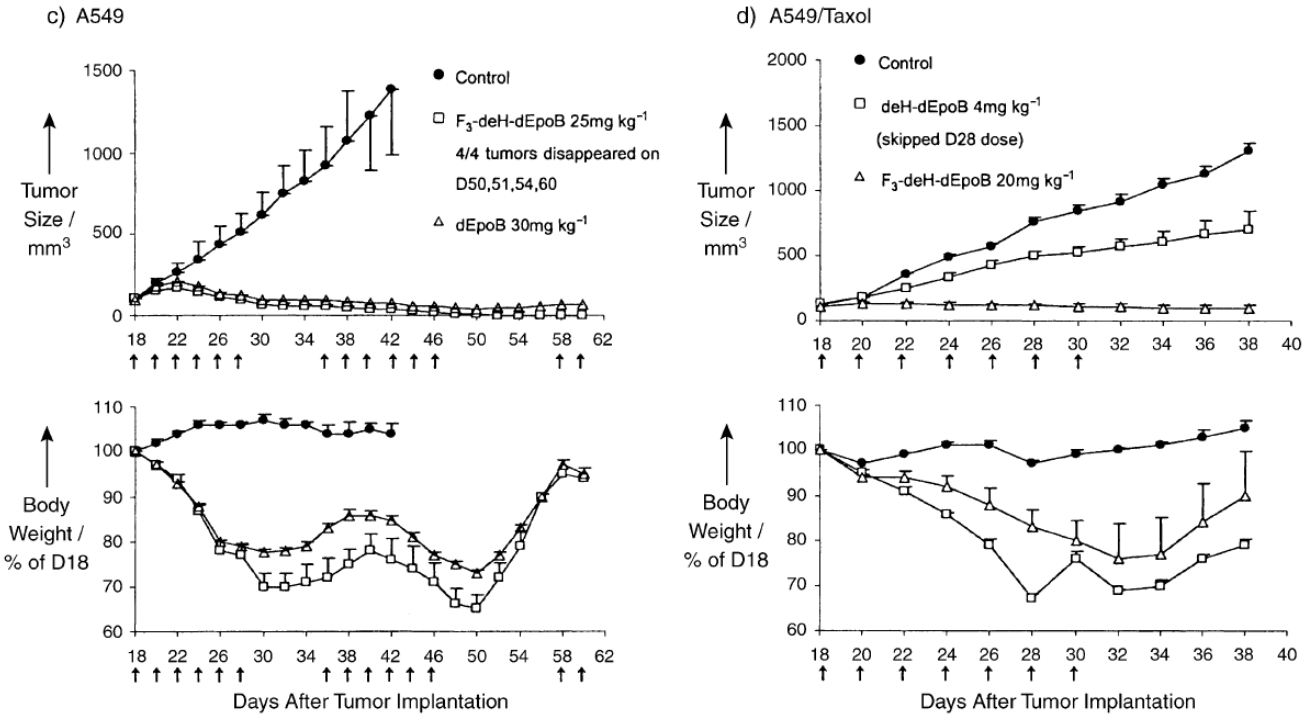


Mechanism



Summary


S
N
Wittig
H
O
O
Esterification
OH
F3C
O
OH
RCM


c) A549
Tumor Size / mm3
Control
F3-deH-dEpoB 25mg kg-1
4/4 tumors disappeared on D50,51,54,60
dEpoB 30mg kg-1
Body Weight / % of D18
Days After Tumor Implantation
d) A549/Taxol
Tumor Size / mm3
Control
deH-dEpoB 4mg kg-1
(skipped D28 dose)
F3-deH-dEpoB 20mg kg-1
Body Weight / % of D18
Days After Tumor Implantation

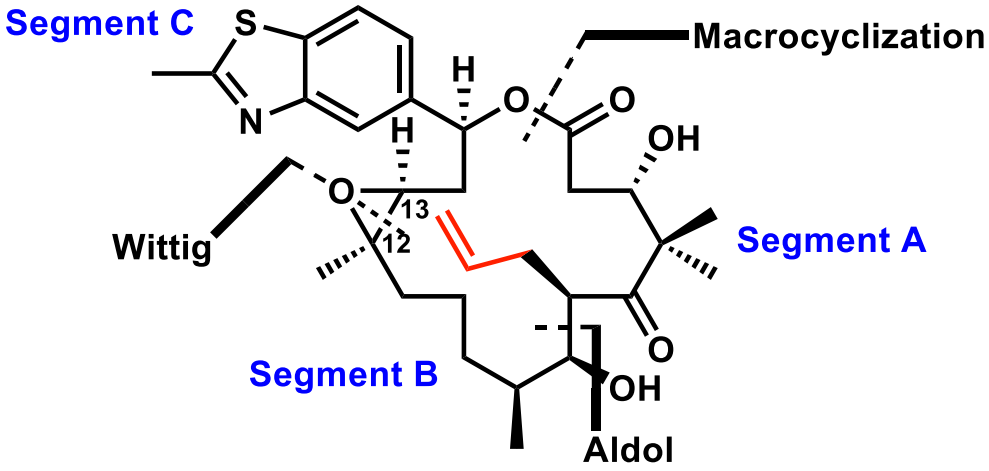
Total Systhesis of ZK-EPO

Natural Products

DOI: 10.1002/ange.200602785

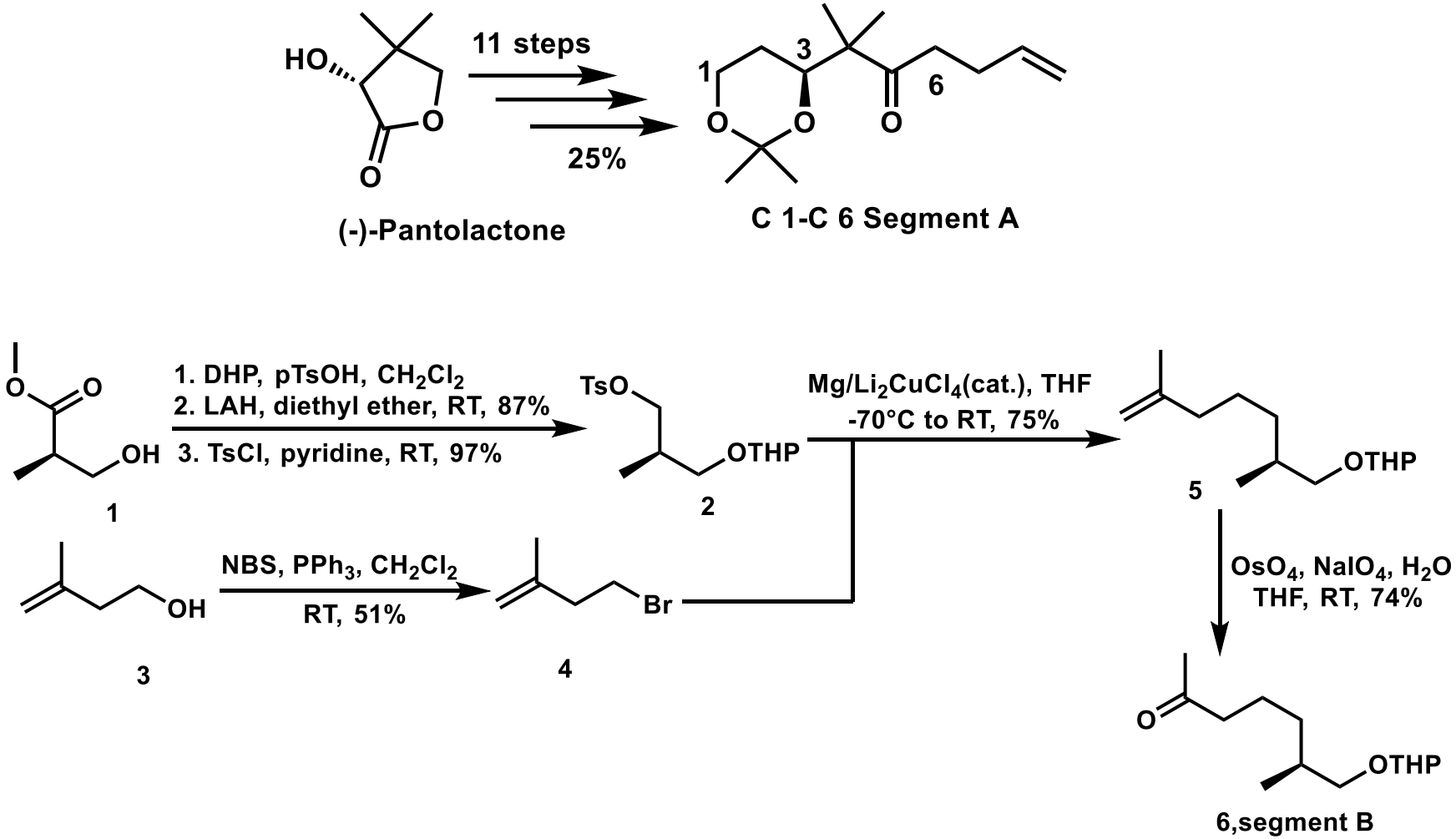
Total Synthesis and Antitumor Activity of ZK-EPO: The First Fully Synthetic Epothilone in Clinical Development**

Ulrich Klar, Bernd Buchmann, Wolfgang Schwede, Werner Skuballa, Jens Hoffmann, and Rosemarie B. Lichtner*

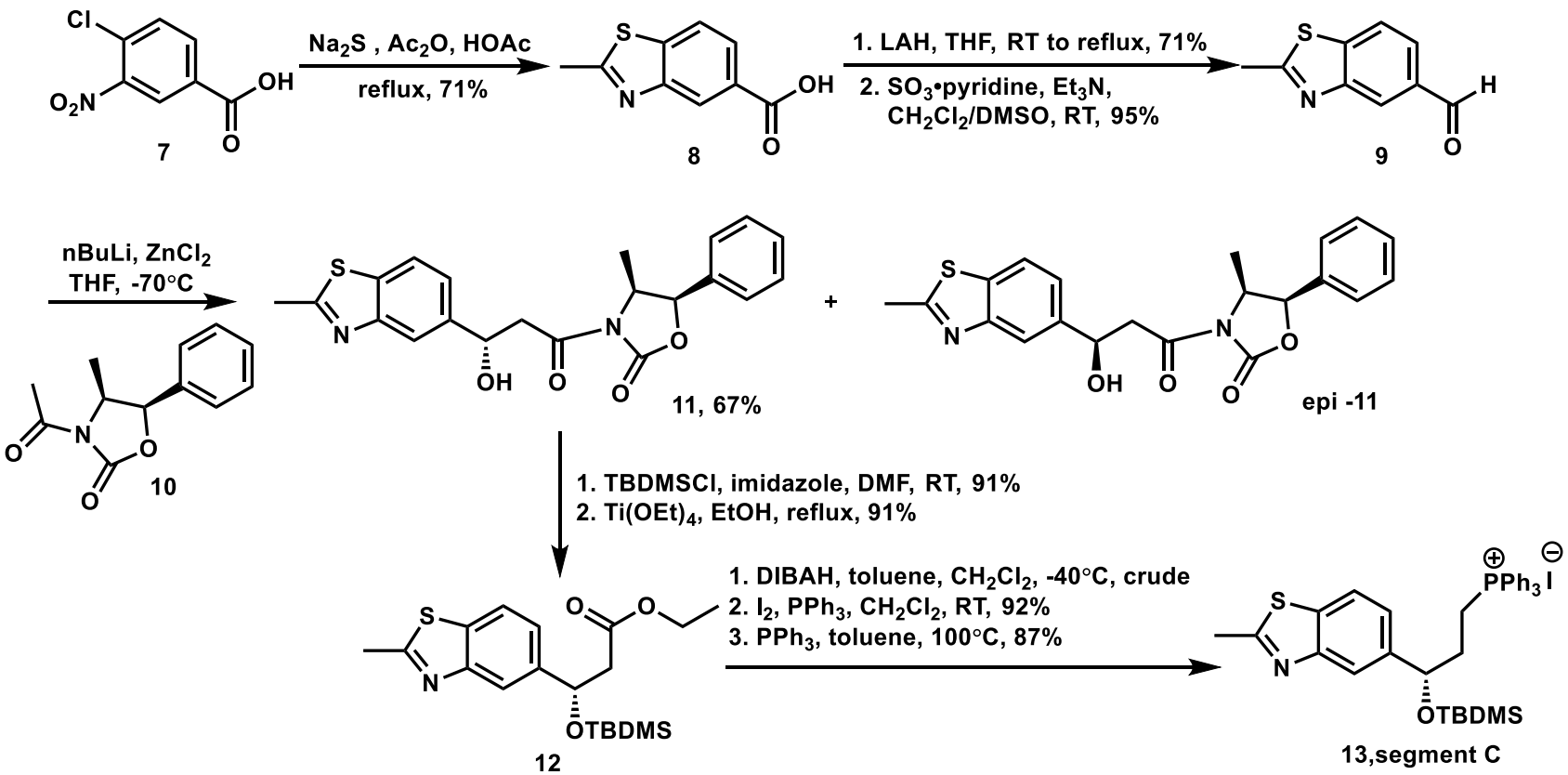


ZK-EPO

The Systhesis of Segment A and B

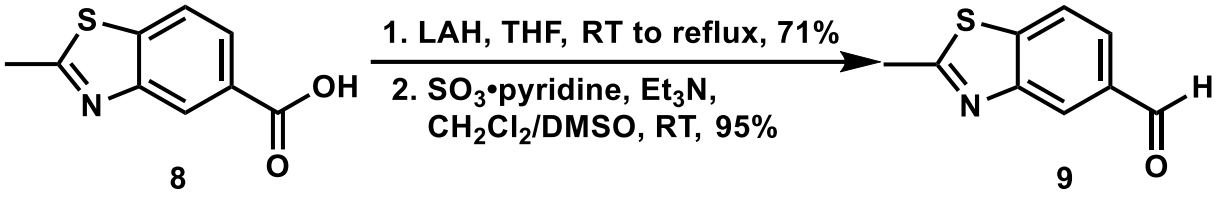


The Systhesis of Segment C

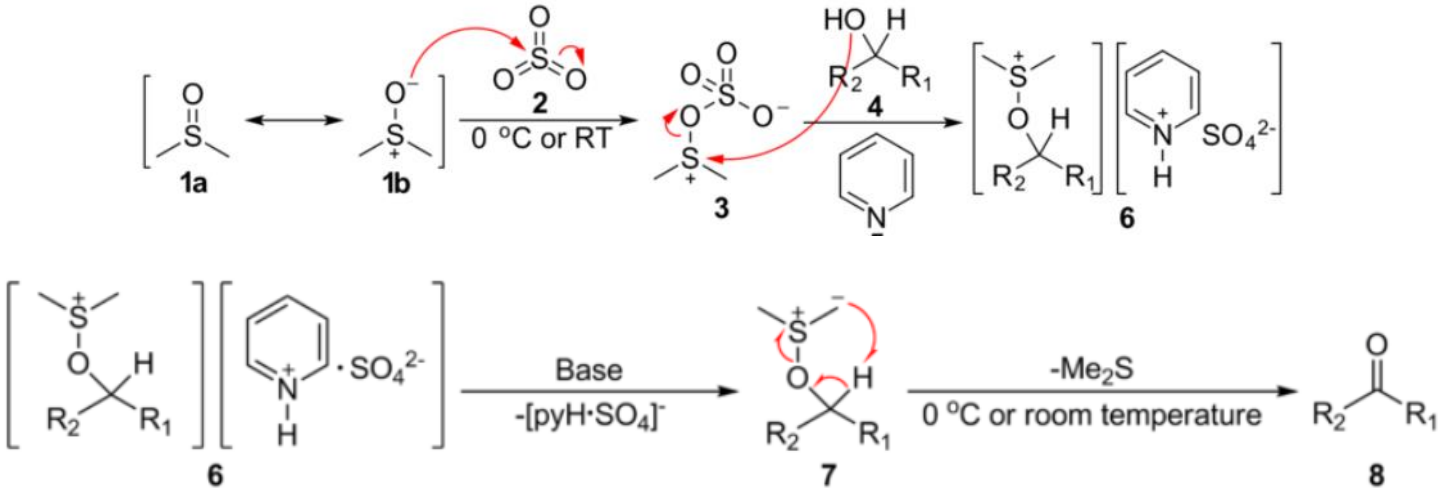


The Systhesis of Segment C

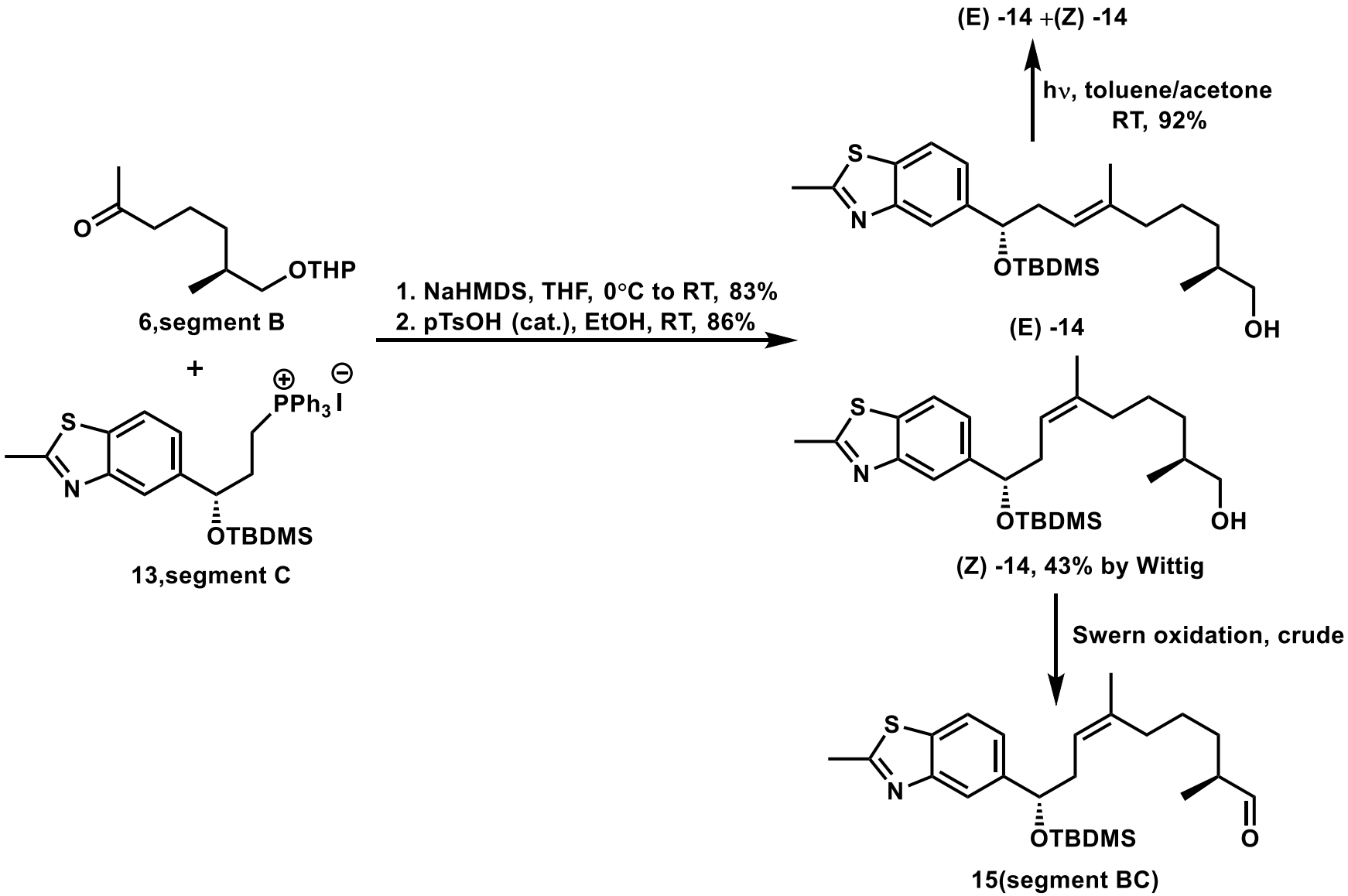
Parikh-Doering Oxidation



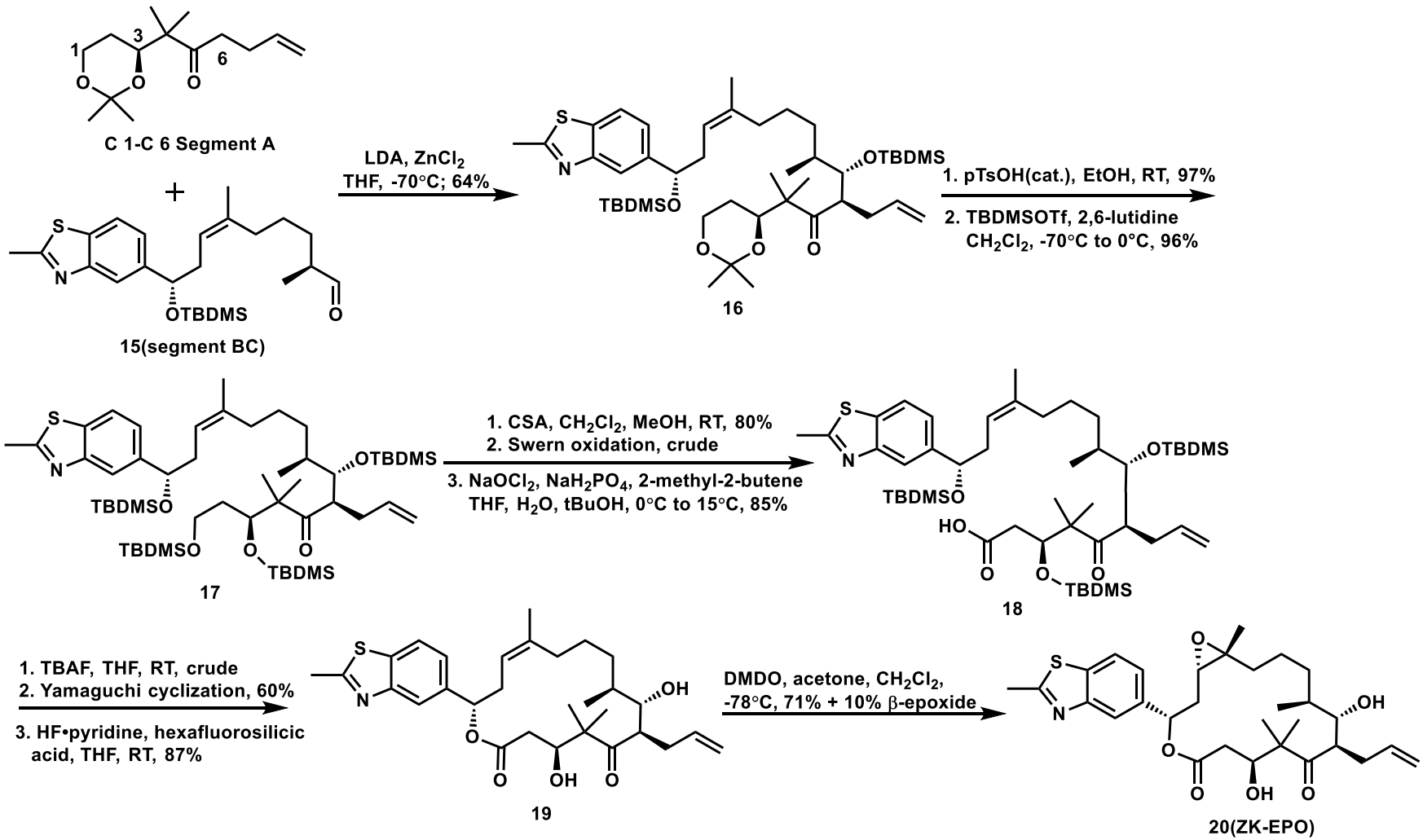
Mechanism



The Systhesis of Segment BC

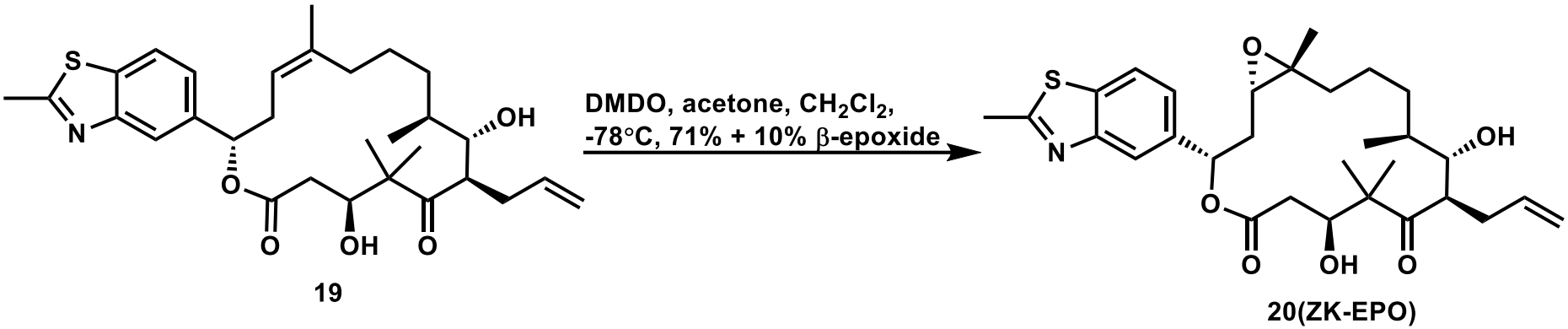


Total Systhesis of ZK-EPO

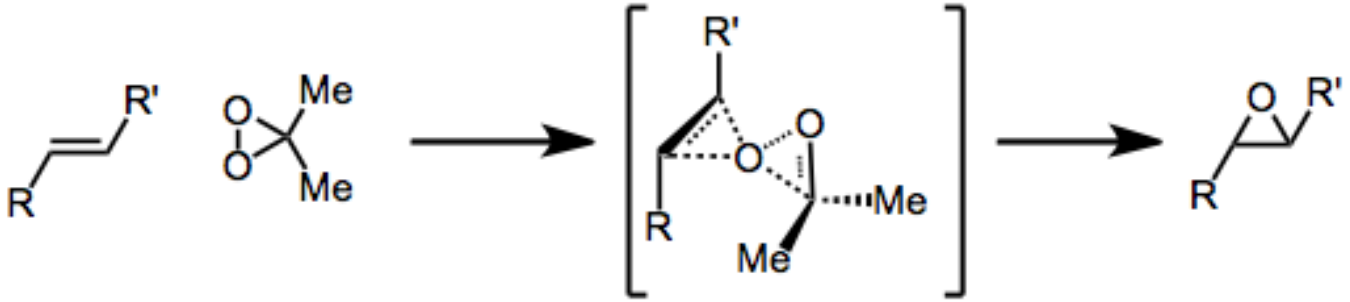


Total Systhesis of ZK-EPO

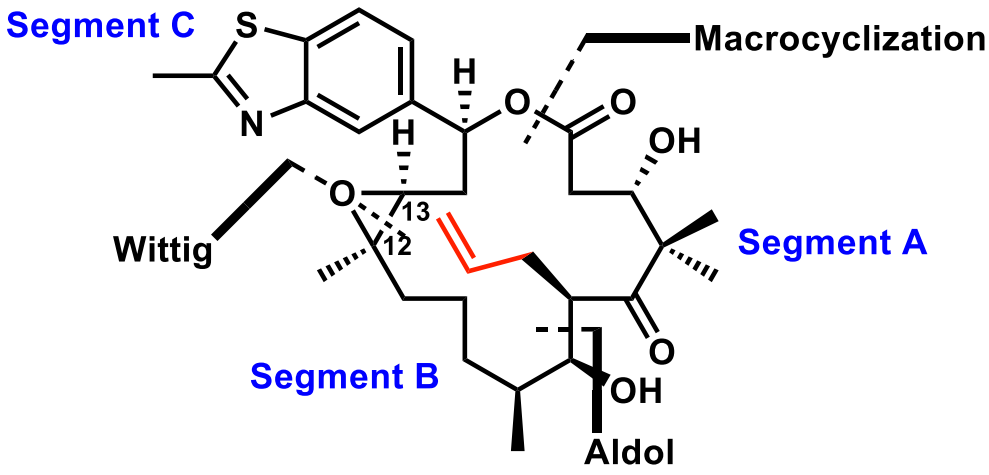
Epoxidation with 3,3-Dimethyldioxirane



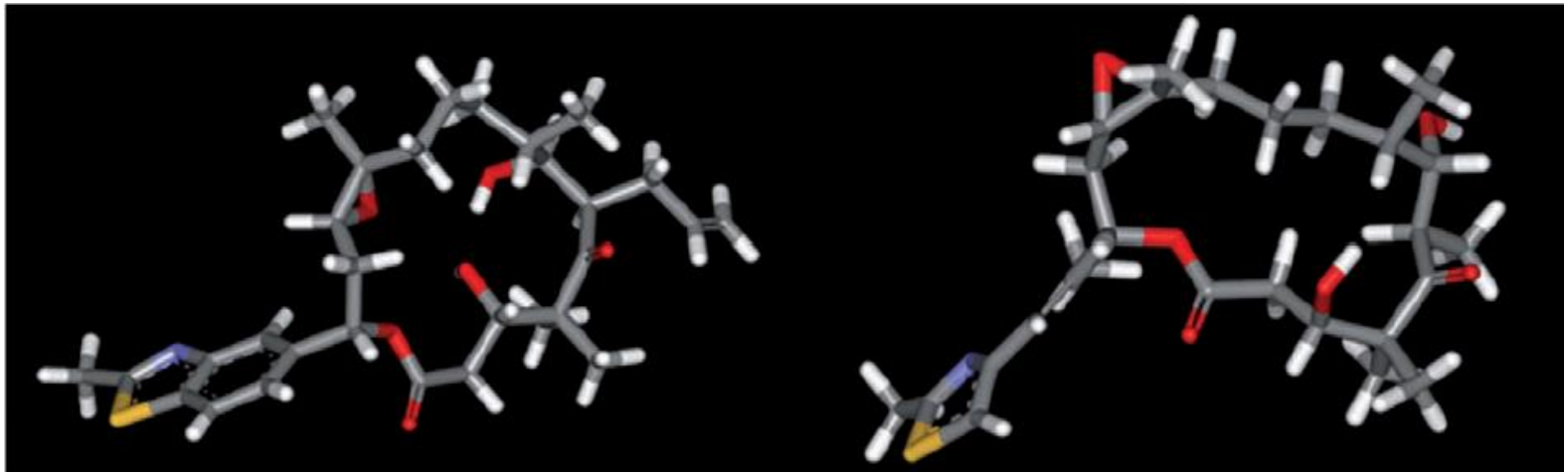
Mechanism



Summary



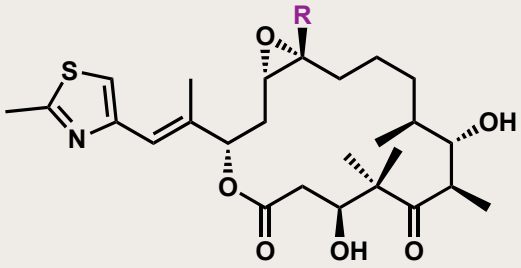
ZK-EPO



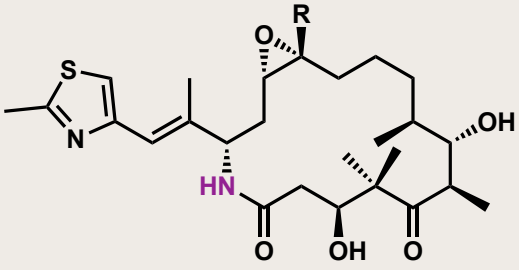
ZK-EPO

epothilone B

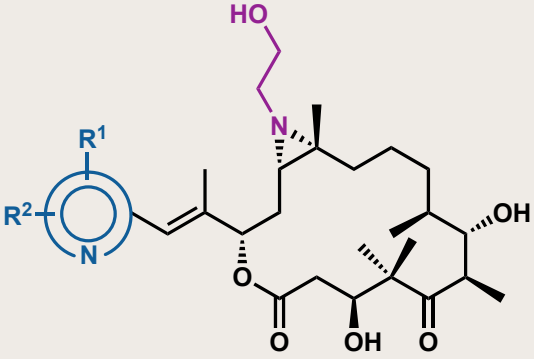
Total Synthesis of Epothilones & Analogues



epotilone A: R = H ; epotilone B: R = Me

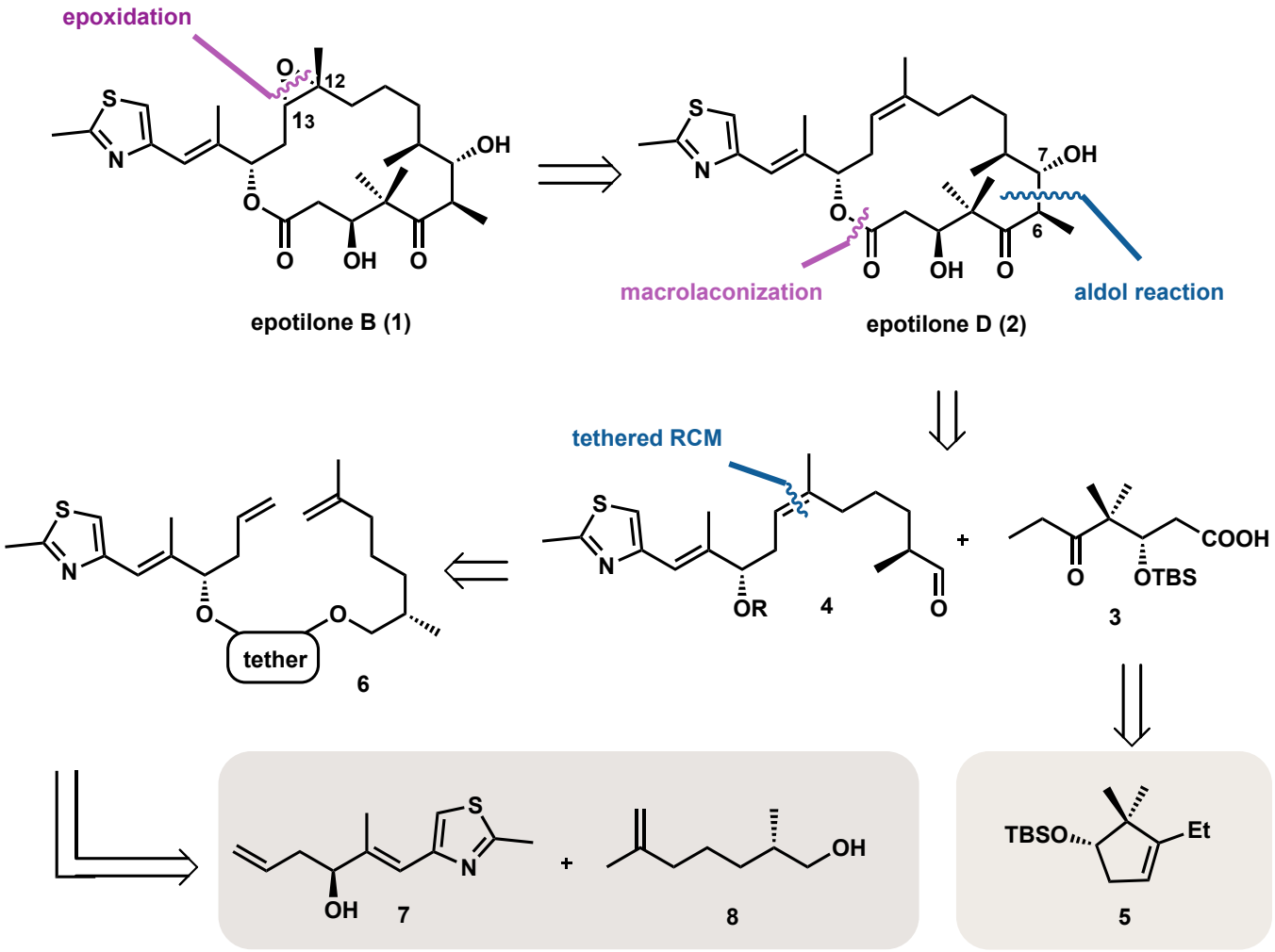


1c: R = H; 2c: R =Me (ixabepilone)



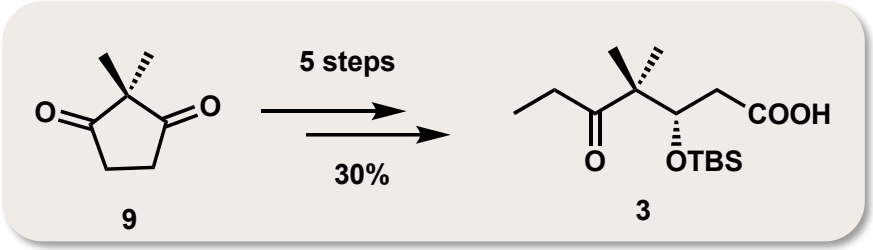
An Efficient Total Synthesis of (-)-Epothilone B

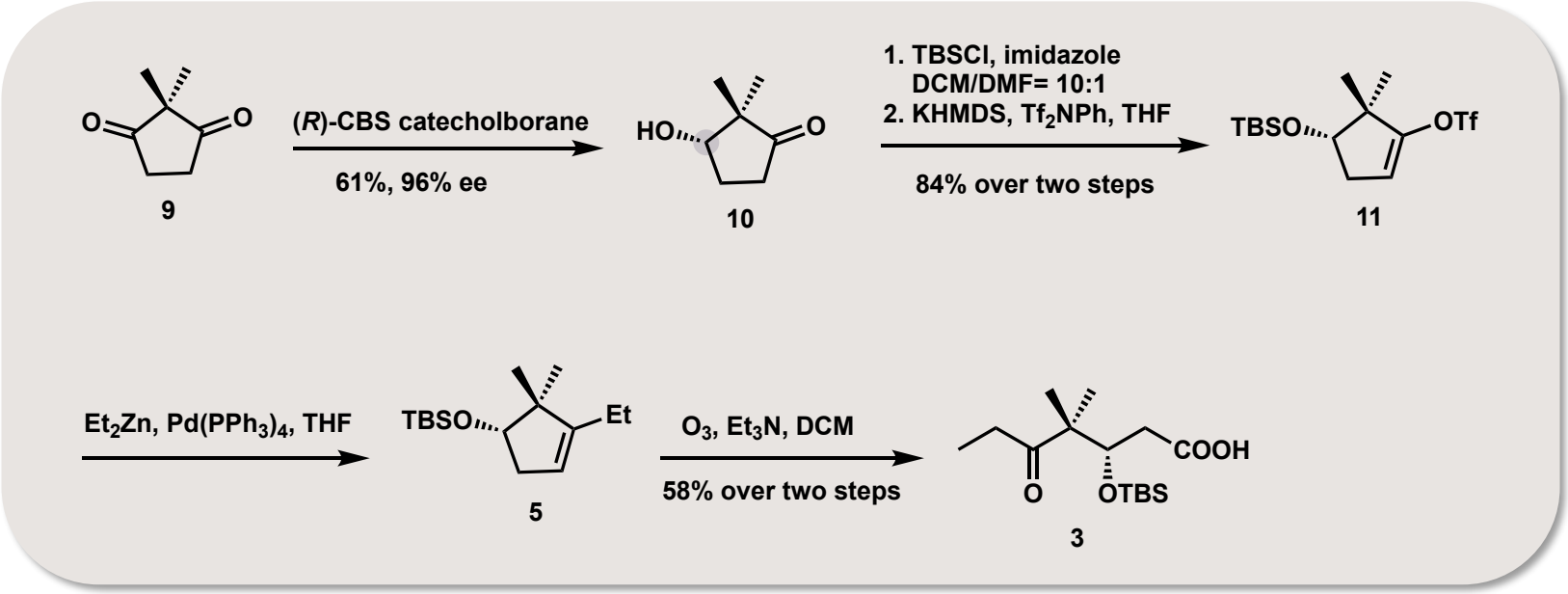
Retrosynthesis of Epothilone B (1)



Guo-Qiang Lin, et al. *Org. Lett.* **2012**, *14*, 6354-6357

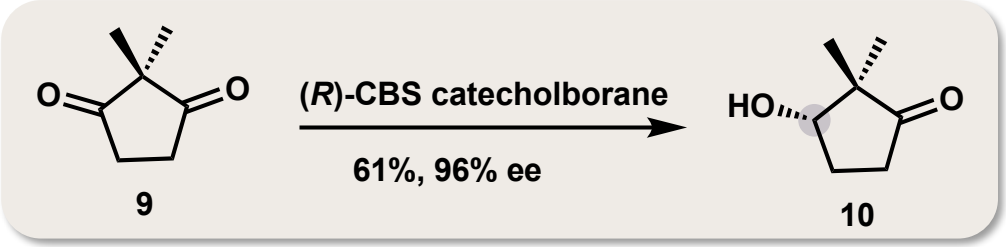
The Synthesis of Segment 3



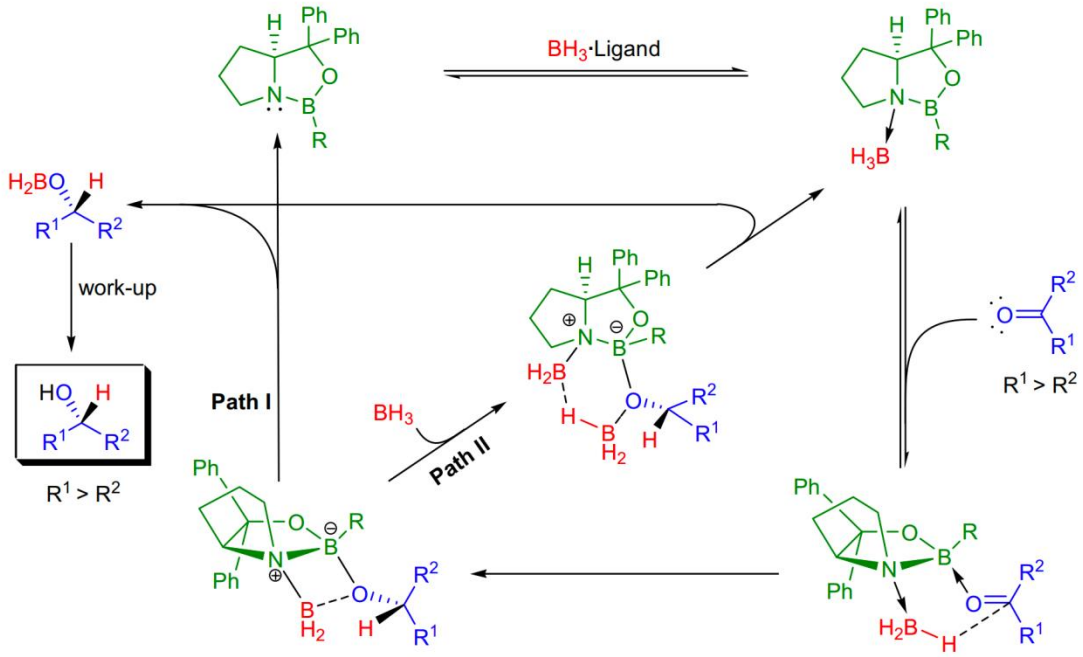


E. J. Corey, et al. *J. Am. Chem. Soc*. **2007**, 129, 10346–10347

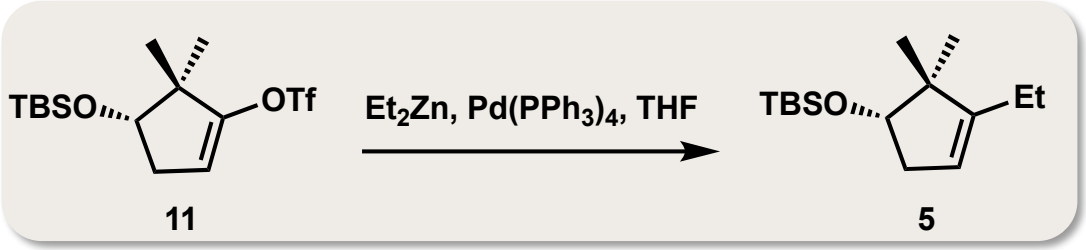
Corey-Bakshi-Shibata Reduction



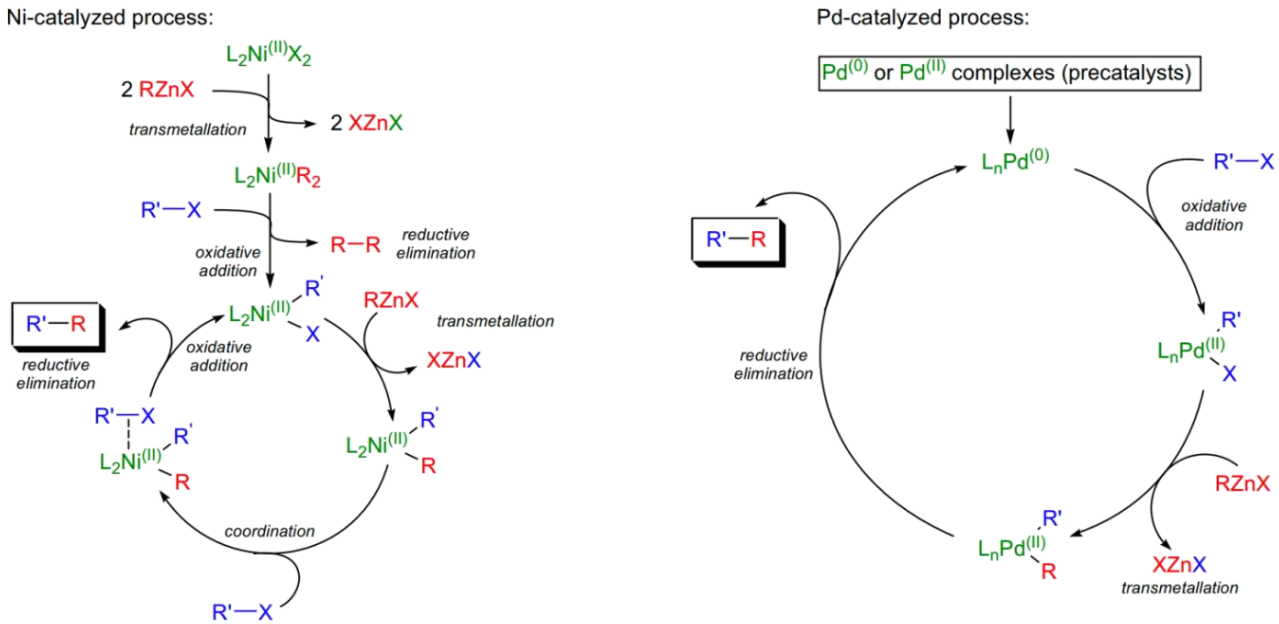
Mechanism



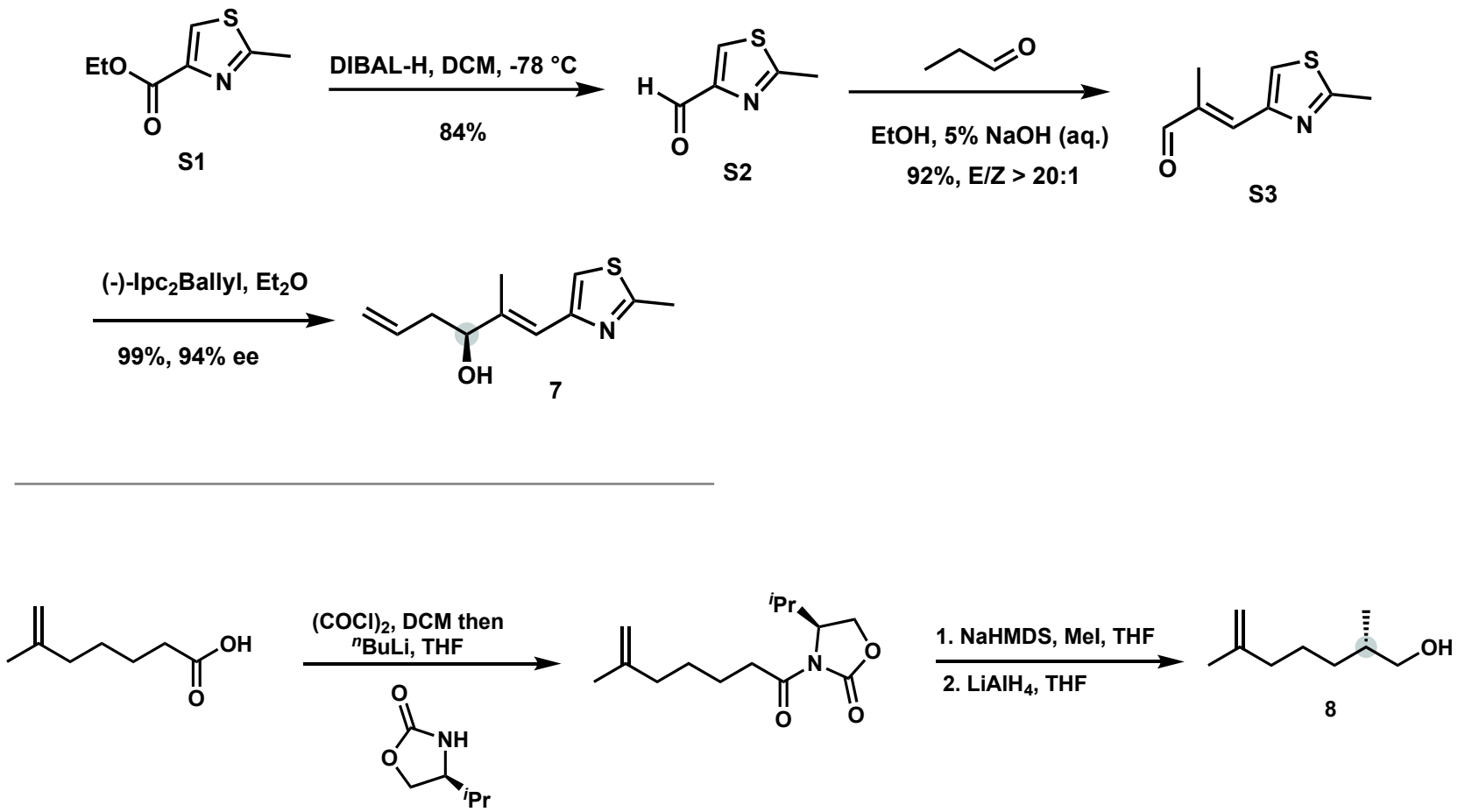
Negishi Cross-coupling



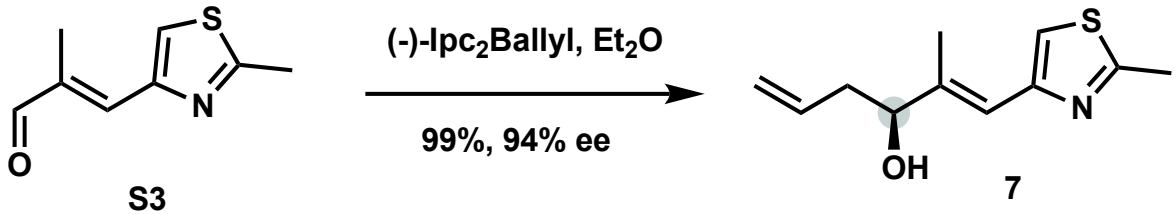
Mechanism



The Systhesis of Segment 7 and 8

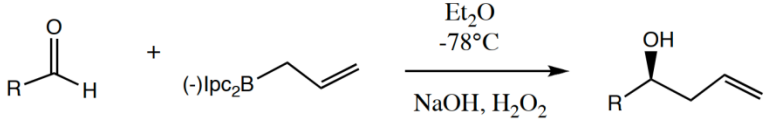


Brown Asymmetric Allylation



Mechanism

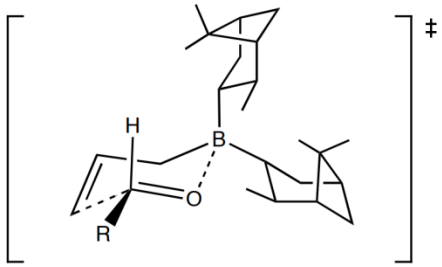
•both enantiomers commercially aailable and inexpensive



R	ee%
CH_3	>99
Bu	96
Ph	96
t-Bu	99

• low temperatures lead to increased enantioselectivity
•Allylboration of aldehydes is instantaneous at -78°C

Stereochemical Rationale:

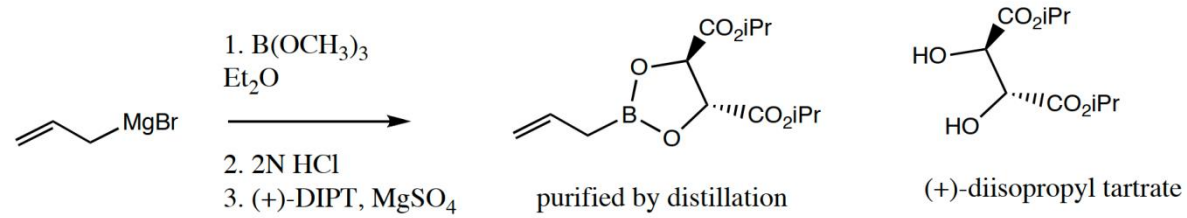


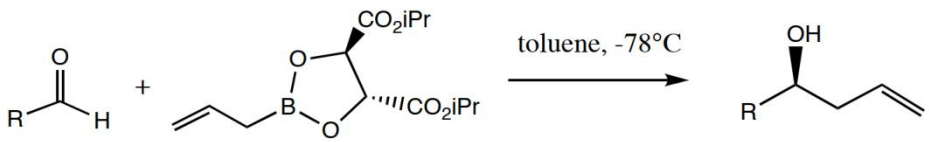
allylation proceeds through a chair-like transition state where R occupies an equatorial position, and the aldehyde facial selectivity derices from minimization of steric interactions between the Ipc ligands and the allyl group

D. R . Corey, et al. *J. Am.Chem. Soc.* **1985**, *107*, 713

Roush Asymmetric Allylation

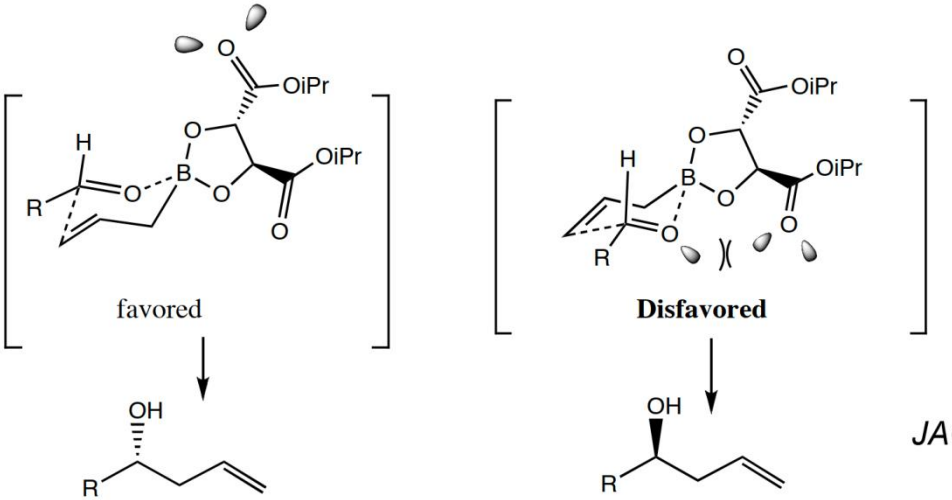
Roush Allylation and Crotylation Reactions





R	ee%
Ph	71
c-C_6H_{11}	78
C_9H_{19}	79

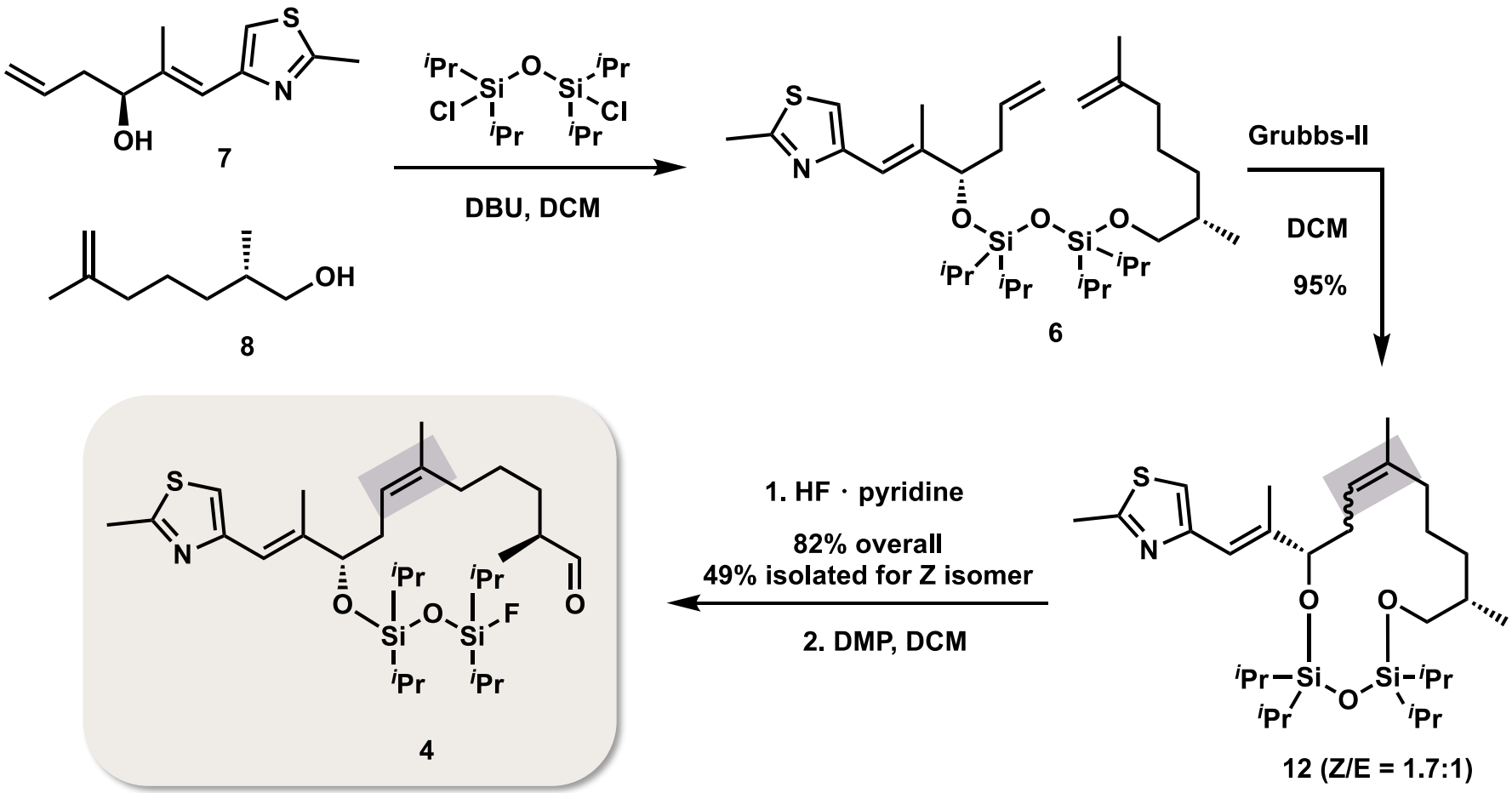
Enantioslectivities are moderate



The favored TS is believed to minimize unfavorable lone-pair lone-pair interctions

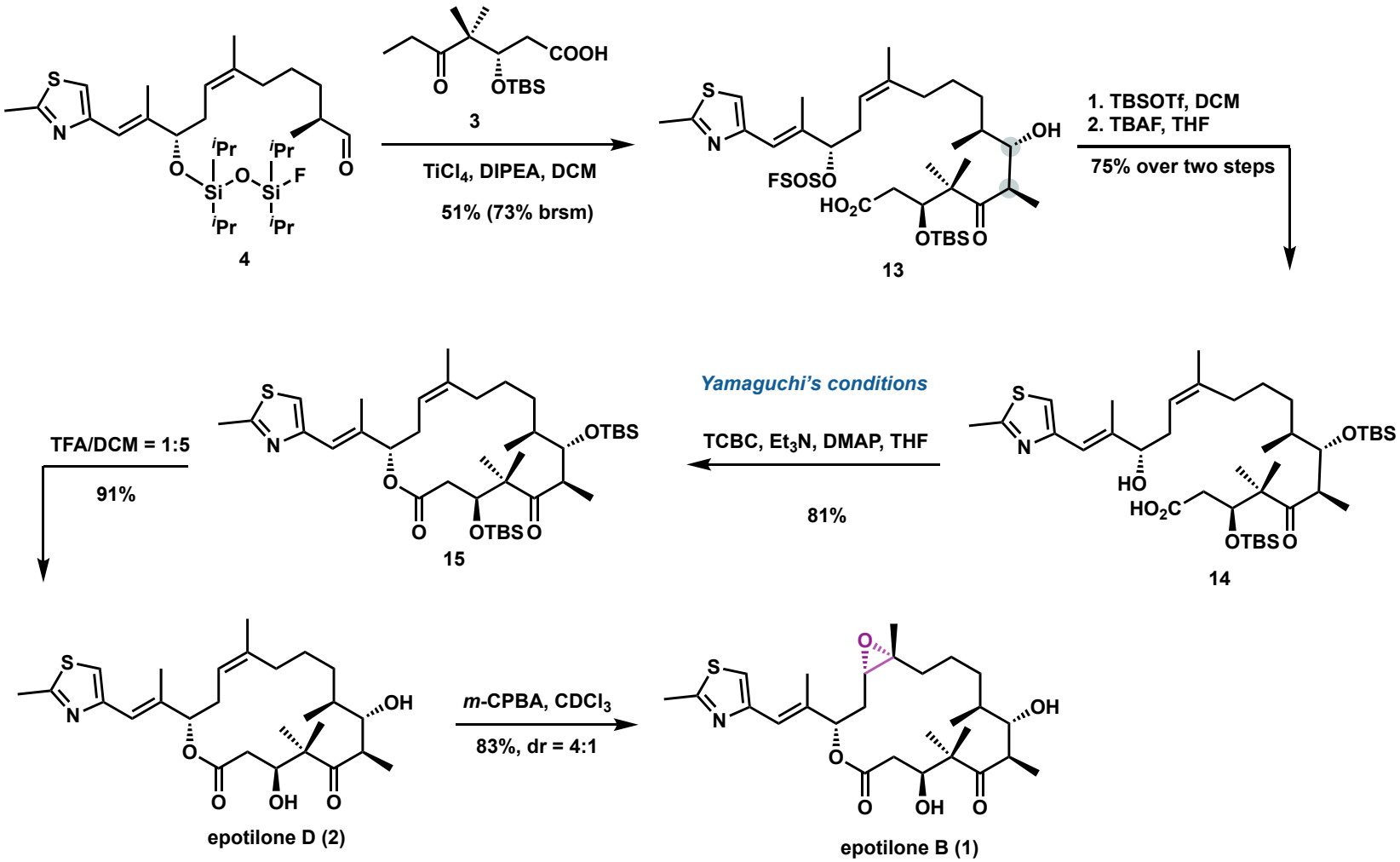
JACS, **1985,** 8186.

Synthesis of 4 via Bissiloxane-Tethered RCM Reaction



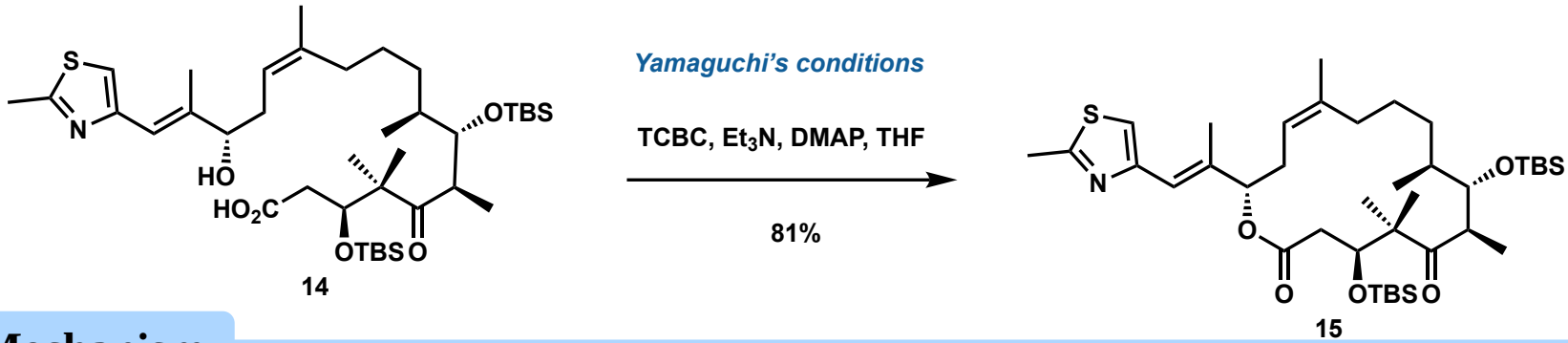
Guo-Qiang Lin, et al. *Org. Lett.* **2012**, *14*, 6354-6357

Total Synthesis of (-)-Epothilone D (2) and (-)-Epothilone B (1)

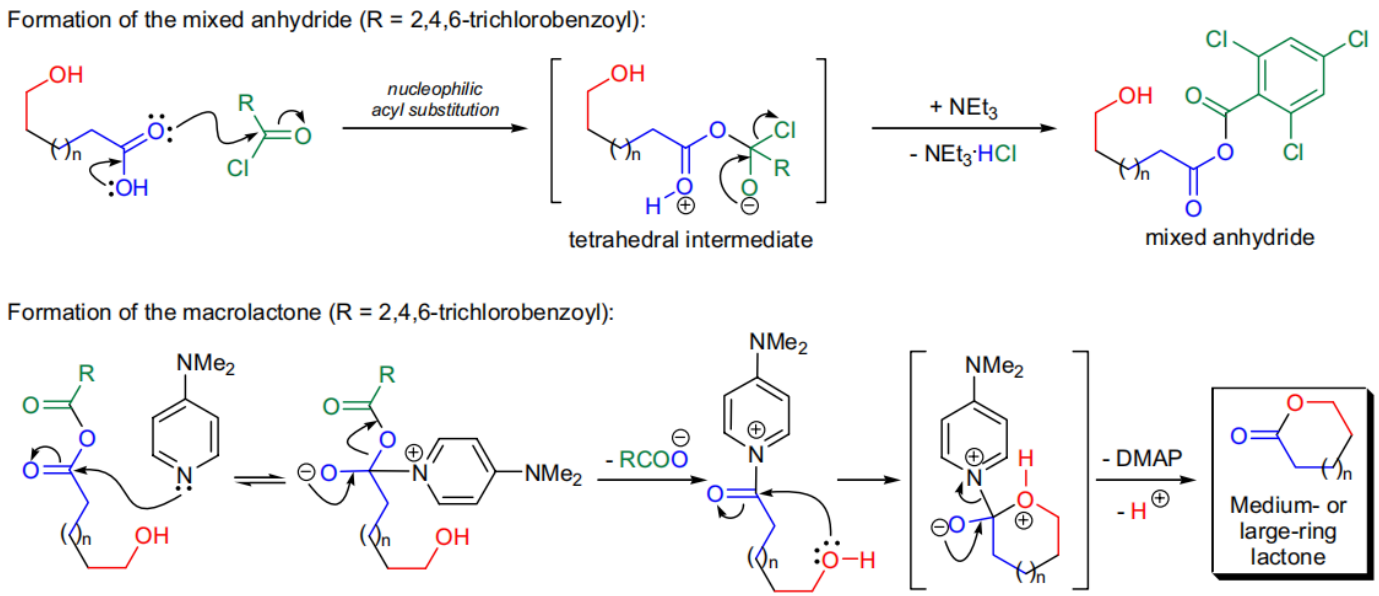


Guo-Qiang Lin, et al. *Org. Lett.* **2012**, *14*, 6354-6357

Yamaguchi's Conditions

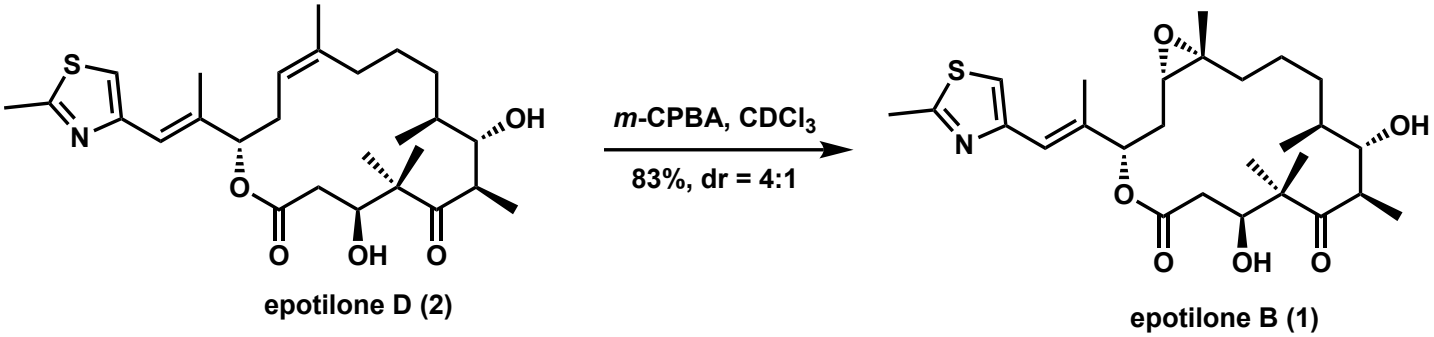


Mechanism

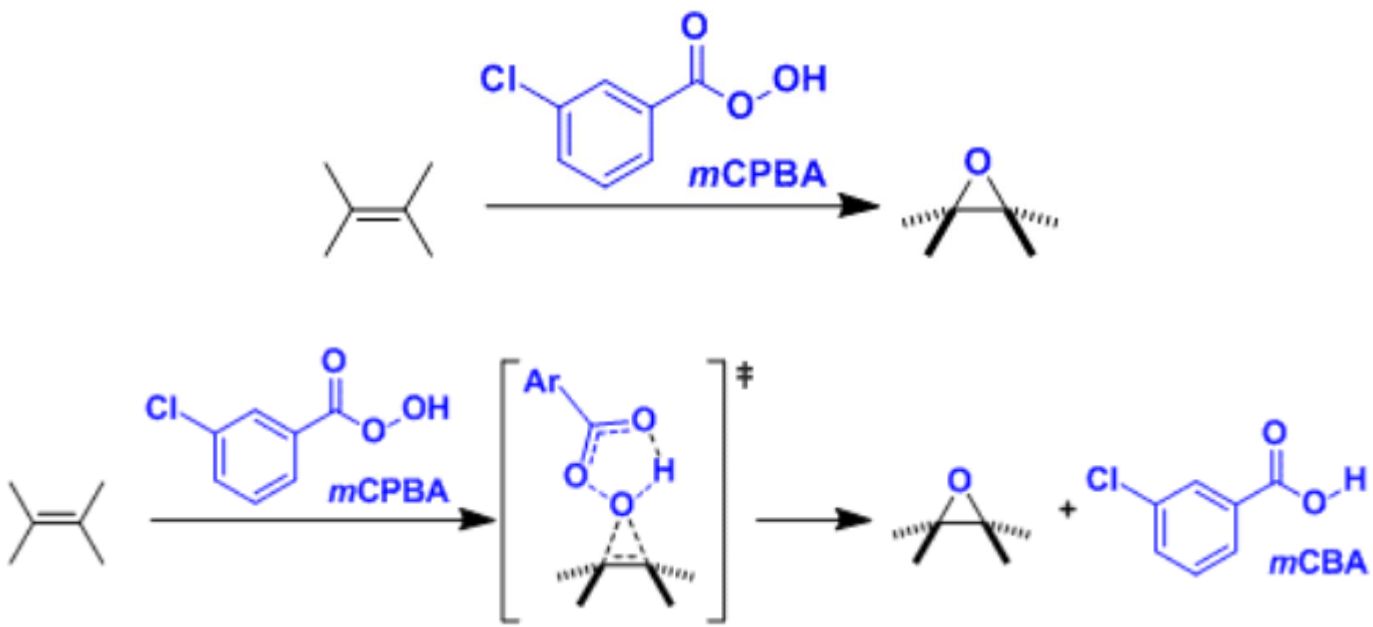


Corey, D. R, et al. *J. Am.Chem. Soc.* **1985**, *107*, 713.

Epoxidation

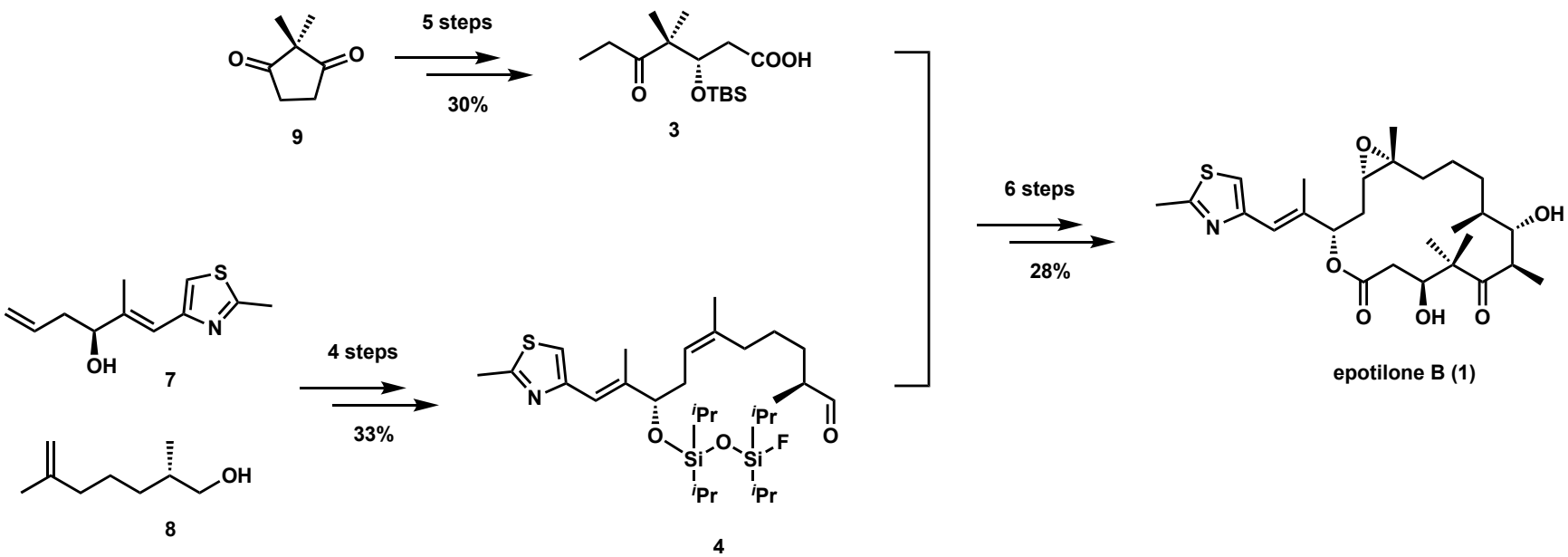


Mechanism



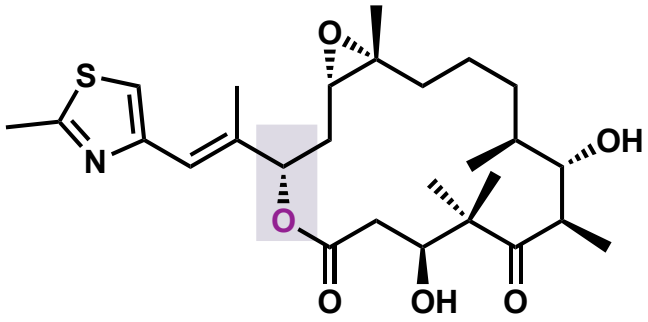
Corey, D. R, et al. *J. Am.Chem. Soc.* **1985**, *107*, 713.

Summary

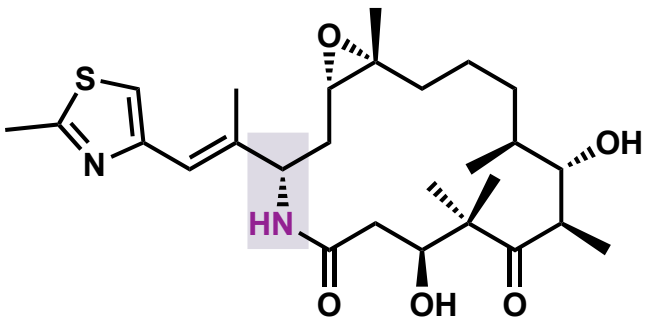


Guo-Qiang Lin, et al. *Org. Lett.* **2012**, *14*, 6354-6357

Synthesis of Lactam Analogues of the Epothilones



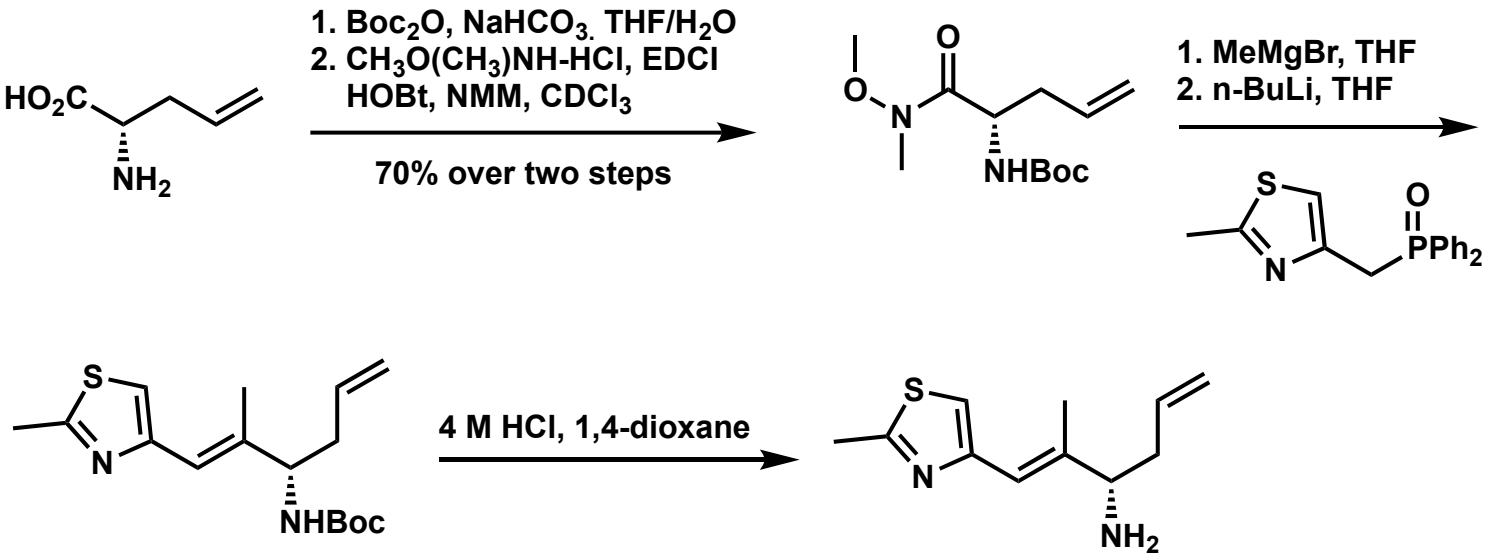
I: epotilone B



II: ixabepilone

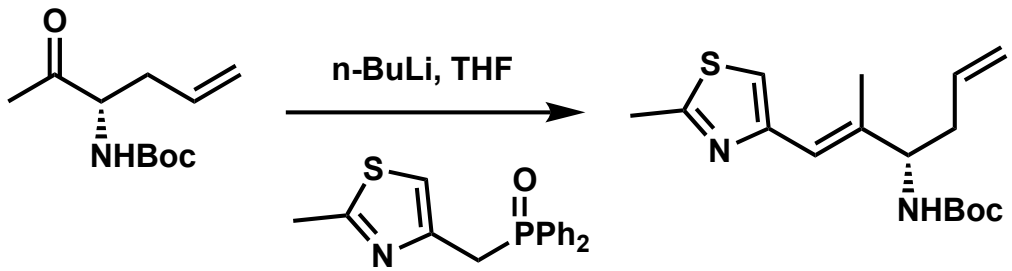
R. M. Borzilleri, et al. *J. Am. Chem. Soc*. **2000**, *122*, 8890-8897

Total Synthesis Approach

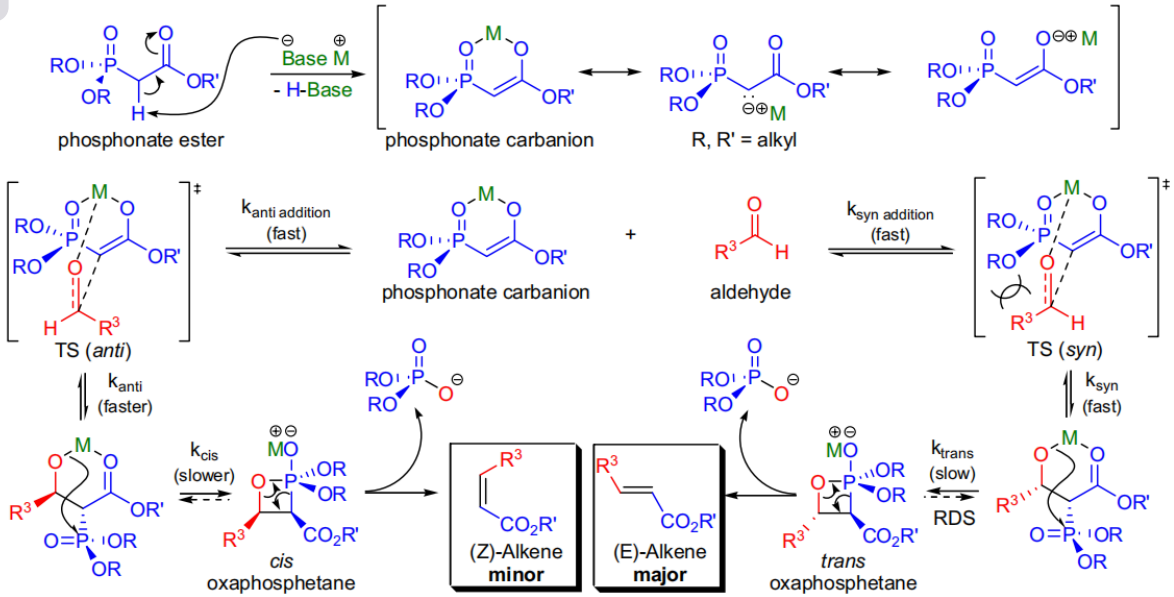


R. M. Borzilleri, et al. *J. Am. Chem. Soc*. **2000**, *122*, 8890-8897

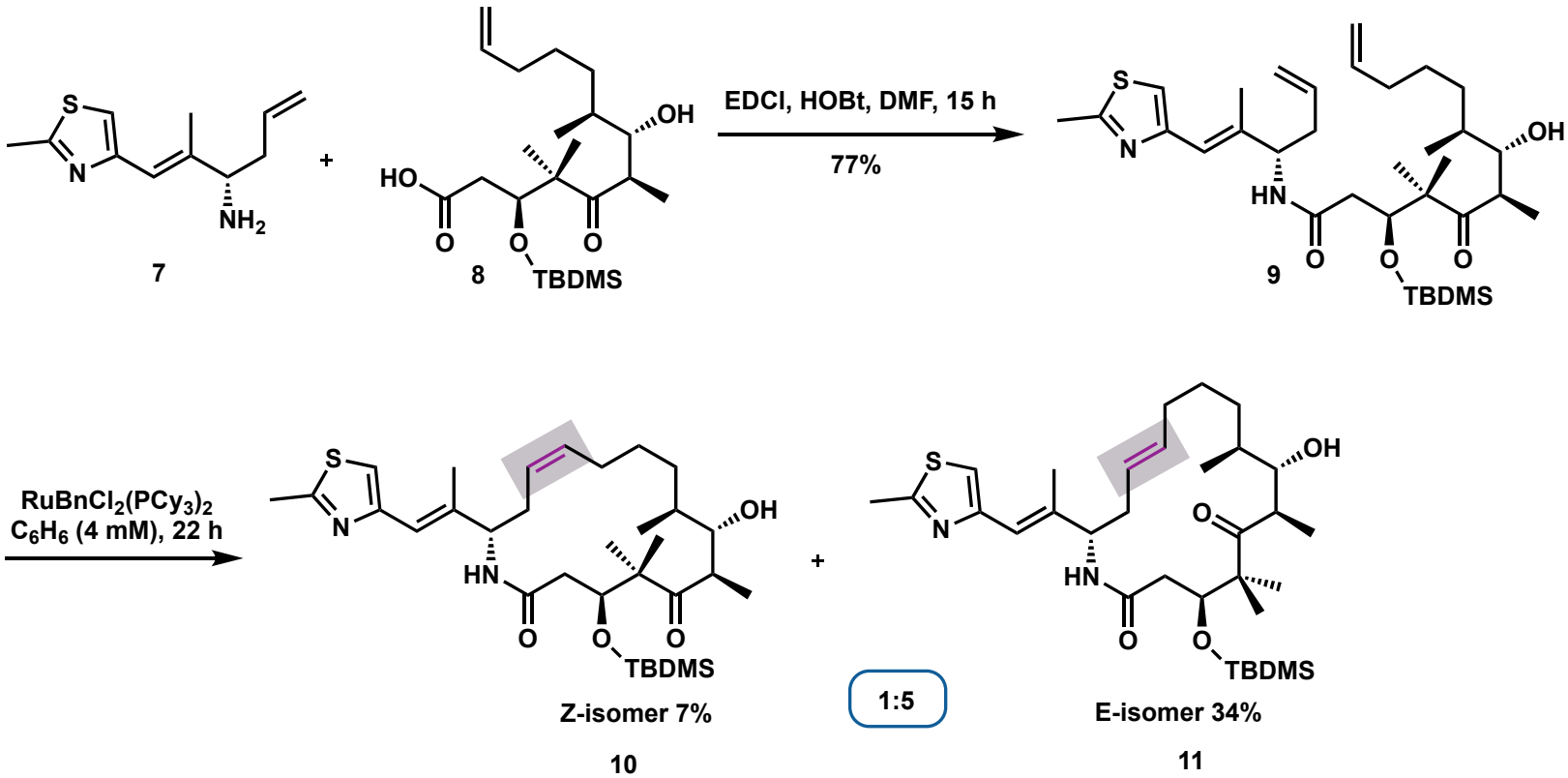
Horner–Wadsworth–Emmons



Mechanism

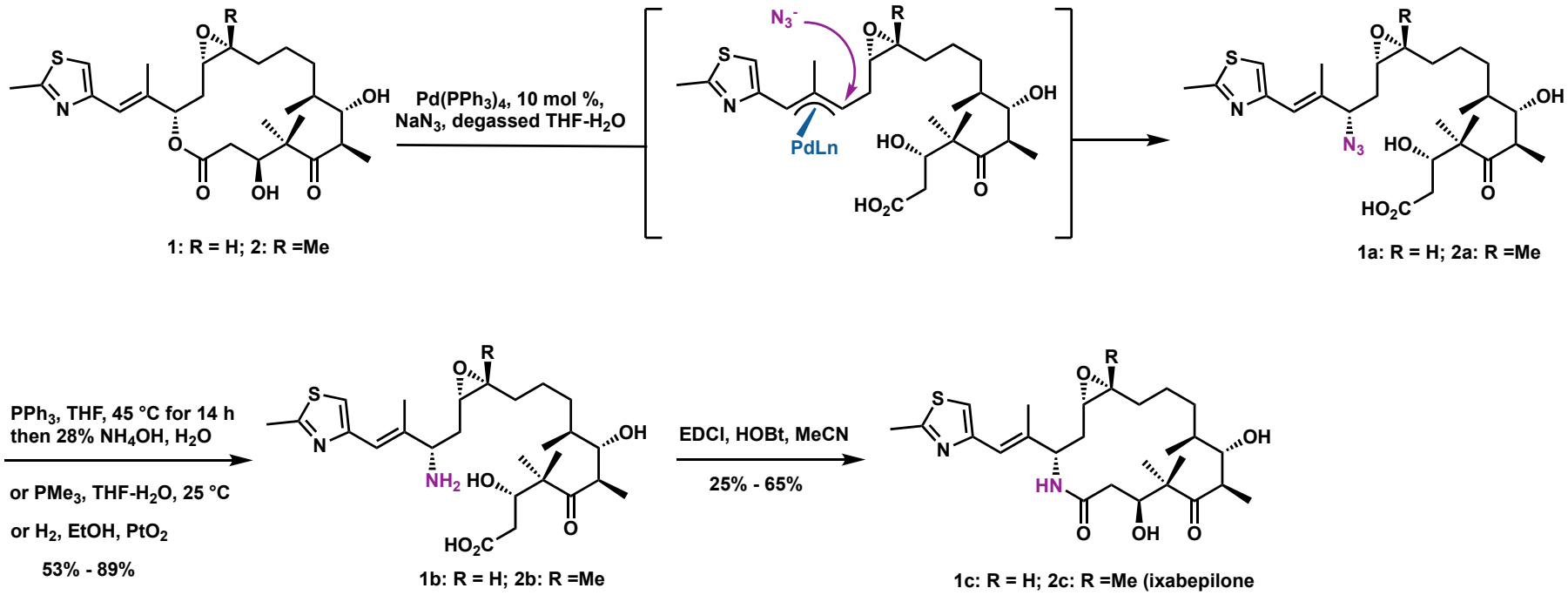


Total Synthesis Approach



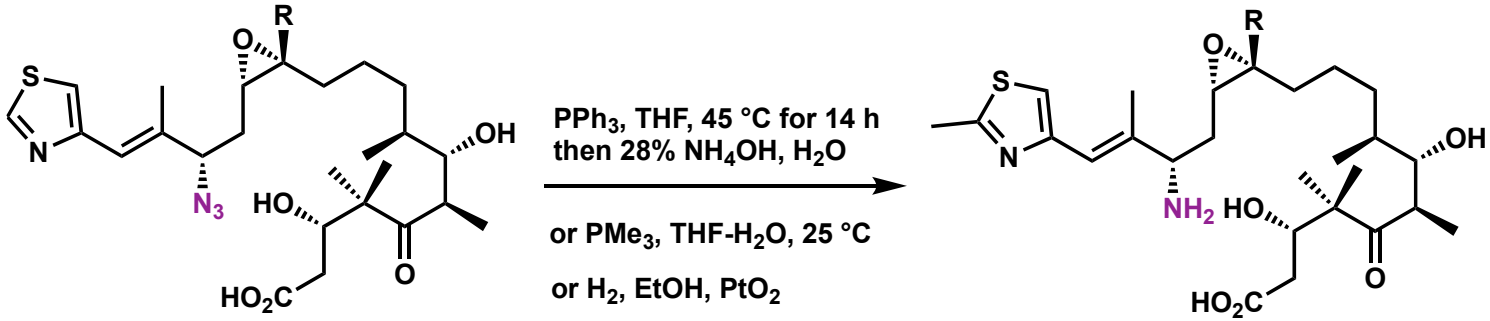
R. M. Borzilleri, et al. *J. Am. Chem. Soc*. **2000**, *122*, 8890-8897

Semi-Synthesis Approach



R. M. Borzilleri, et al. *J. Am. Chem. Soc*. **2000**, *122*, 8890-8897

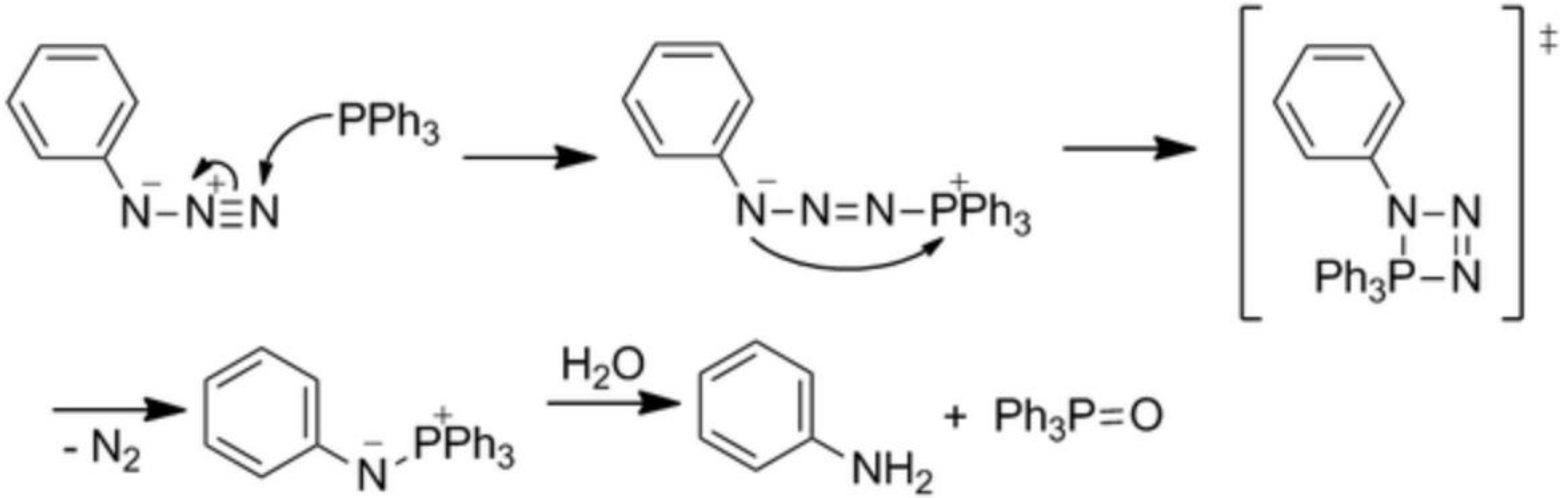
Staudinger Reaction



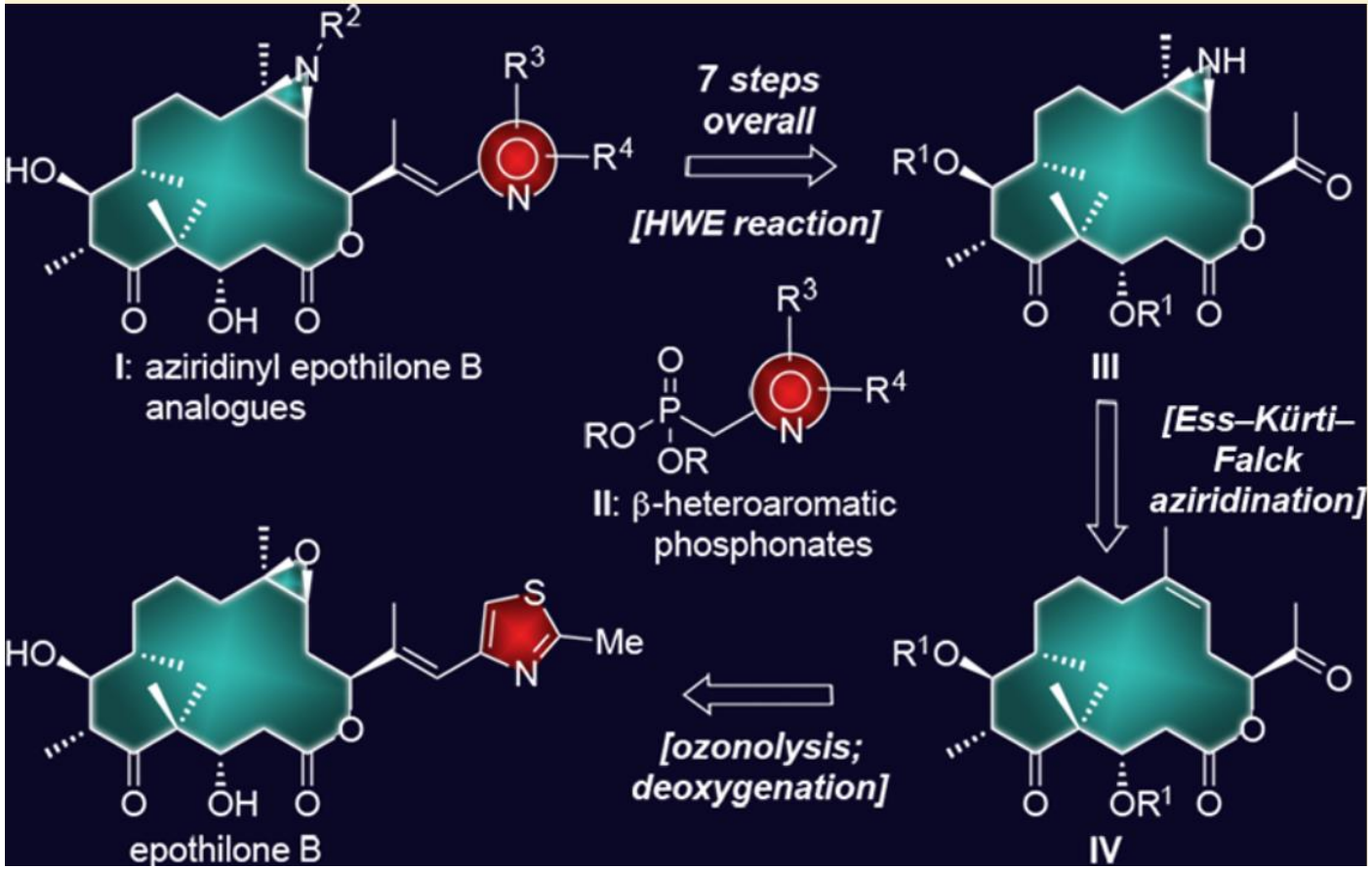
1a: R = H; 2a: R =Me

1b: R = H; 2b: R =Me

Mechanism

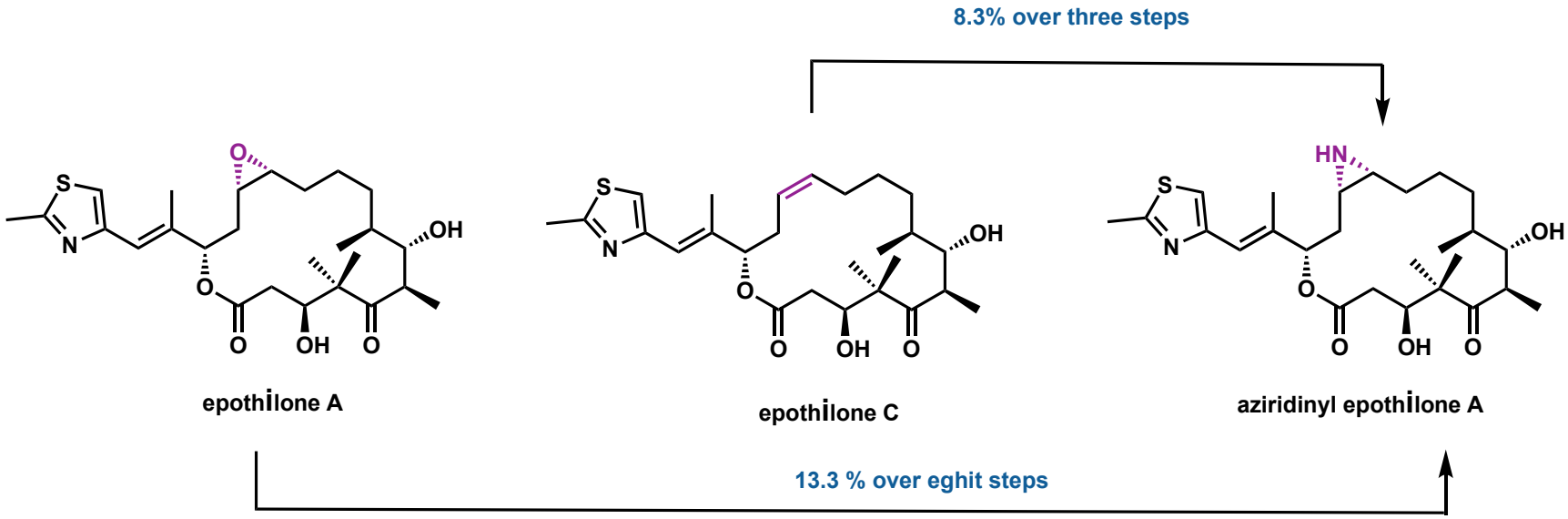


Summary



R. M. Borzilleri, et al. *J. Am. Chem. Soc*. **2000**, *122*, 8890-8897

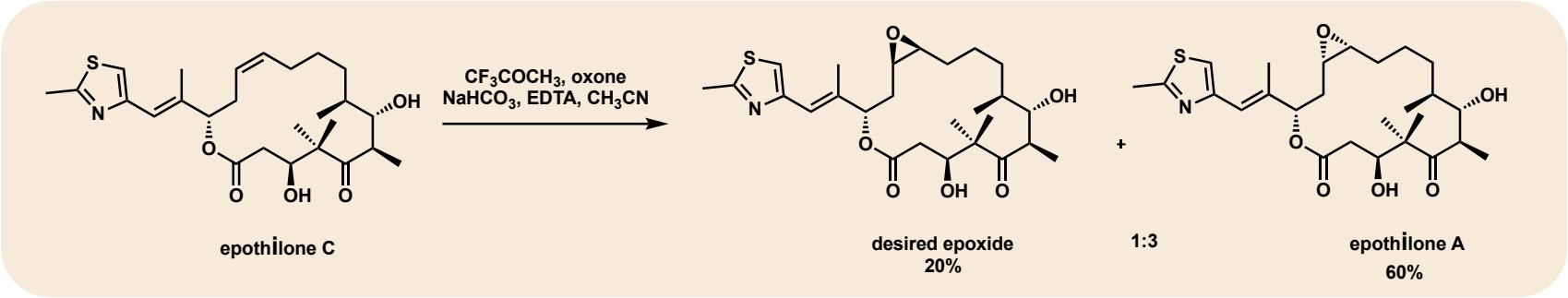
Synthesis and Biological Activity of Epothilone Aziridines



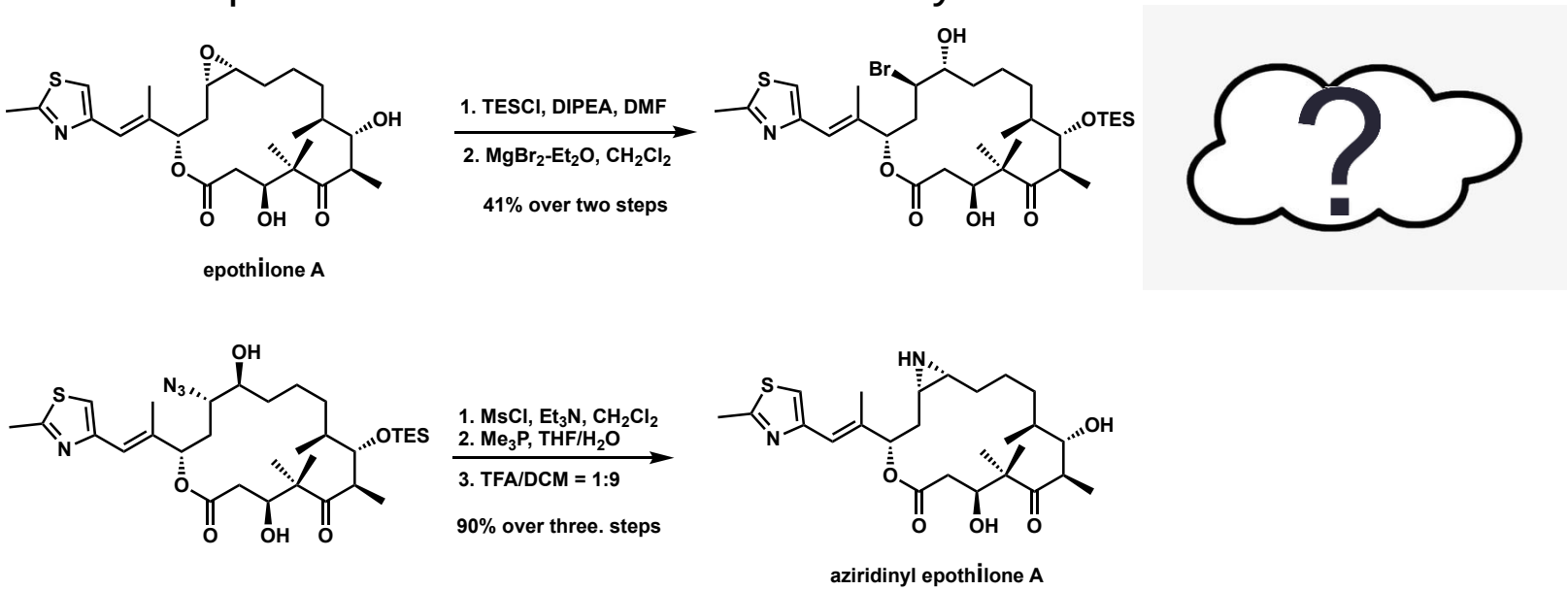
A. R. Ren, et al. *Org. Lett.* **2001**, *3*, 2693-2696

Synthesis and Biological Activity of Epothilone Aziridines

Synthesis of Epothilone A Aziridine via Diastereomeric Epoxide



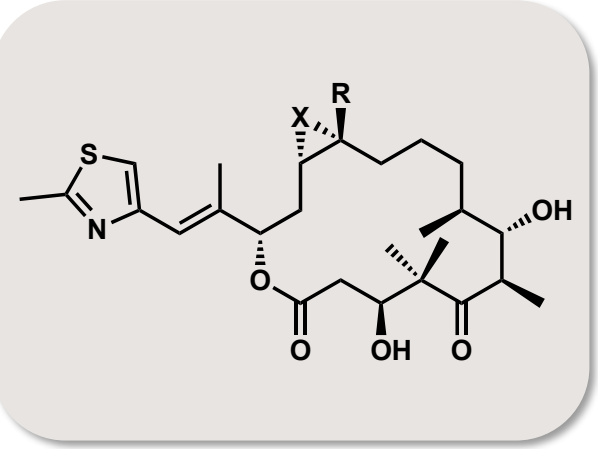
Synthesis of Epothilone A Aziridine 7 via Bromohydrin 8



A. R. Ren, et al. *Org. Lett.* **2001**, *3*, 2693-2696

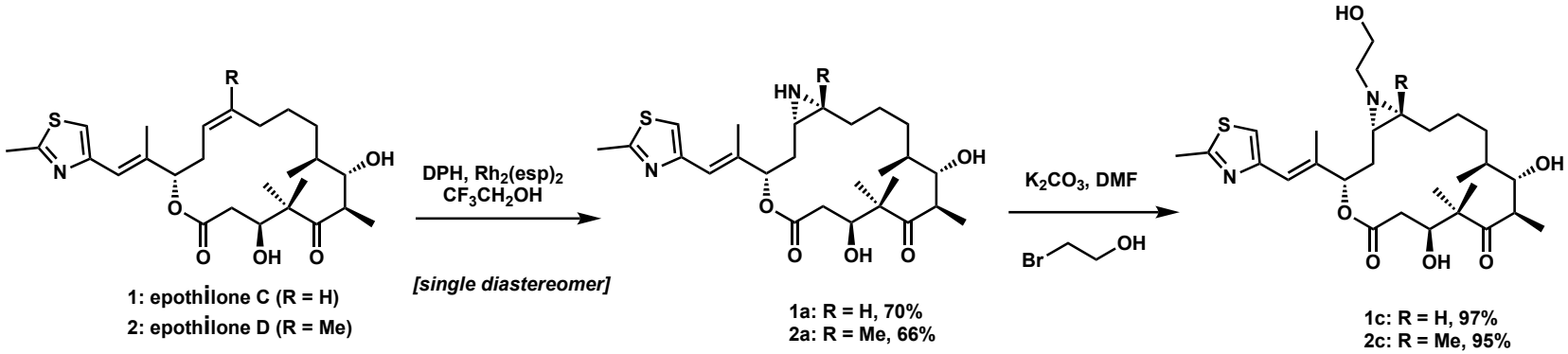
In Vitro Data for Aziridine Analogues of Epothilone A

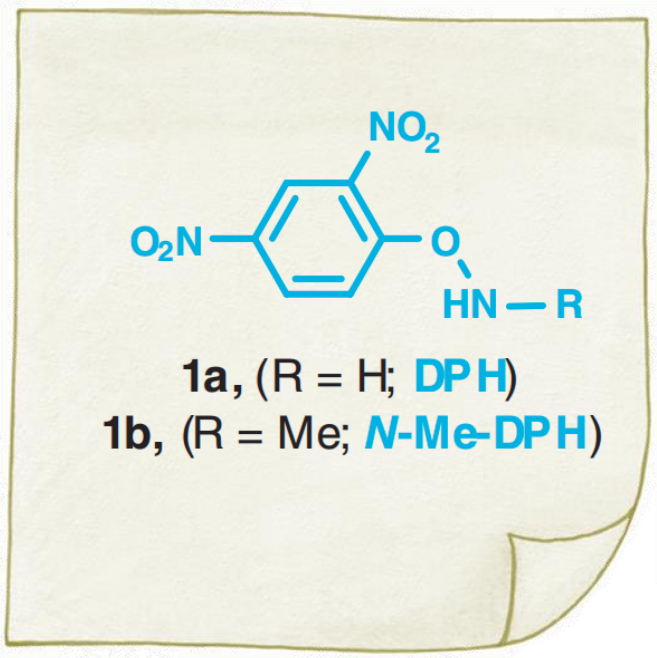
	X	R	tubulin[a] $EC_{0.01}$ (μM)	HTC-116[b] IC_{50} (nM)
taxol			4.6	2.3
1	O	H	2.0	4.4
2	O	Me	1.8	0.8
7	NH	H	14	2.7
12a	NCH_3	H	2.6	0.13
12b	$NCH_2C_6H_5$	H	35	23
13a	$NCOCH_2CH(CH_3)_2$	H	3.5	41
13b	$NCOCH_2N(CH_3)_2$	H	>1000	
13c	$NCOCH_3$	H	1.2	0.9
13d	$NCOC_6H_5$	H	1.4	3.0
13e	NCO-(2-thiophene)	H	1.2	1.6
14a	$NCOOCH_2CH_3$	H	1.2	7.7
14b	$NCOOC_6H_5$	H	1.1	1.8
15a	NSO_2CH_3	H	14	2.1
15b	$NSO_2CH_2CH_2CH_3$	H	9.4	94
15c	NSO_2-(2-thiophene)	H	4.0	30
16a	NSO_2NH_2	H	28	36
16b	NSO_2NHCH_3	H	2.3	7.8
16c	$NSO_2N(CH_3)_2$	H	1.0	0.2
16d	$NSO_2N(CH_2CH_2)_2O$	H	460	160
17	$NCONHCH_2CH_3$	H	>1000	

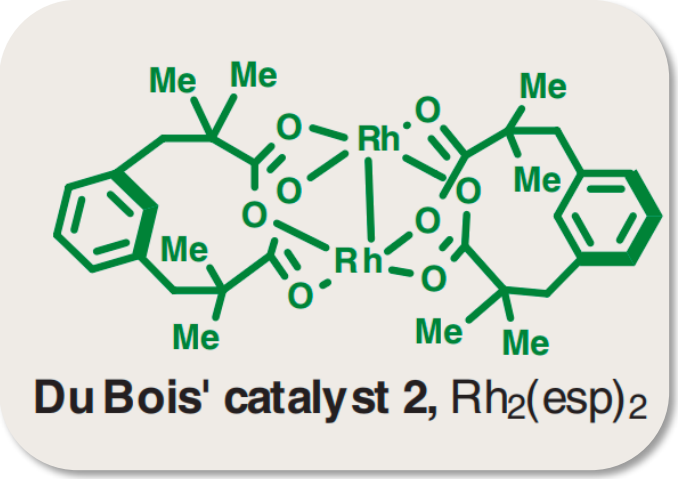


A. R. Ren, et al. *Org. Lett.* **2001**, *3*, 2693-2696

12,13-Aziridinyl Epothilones

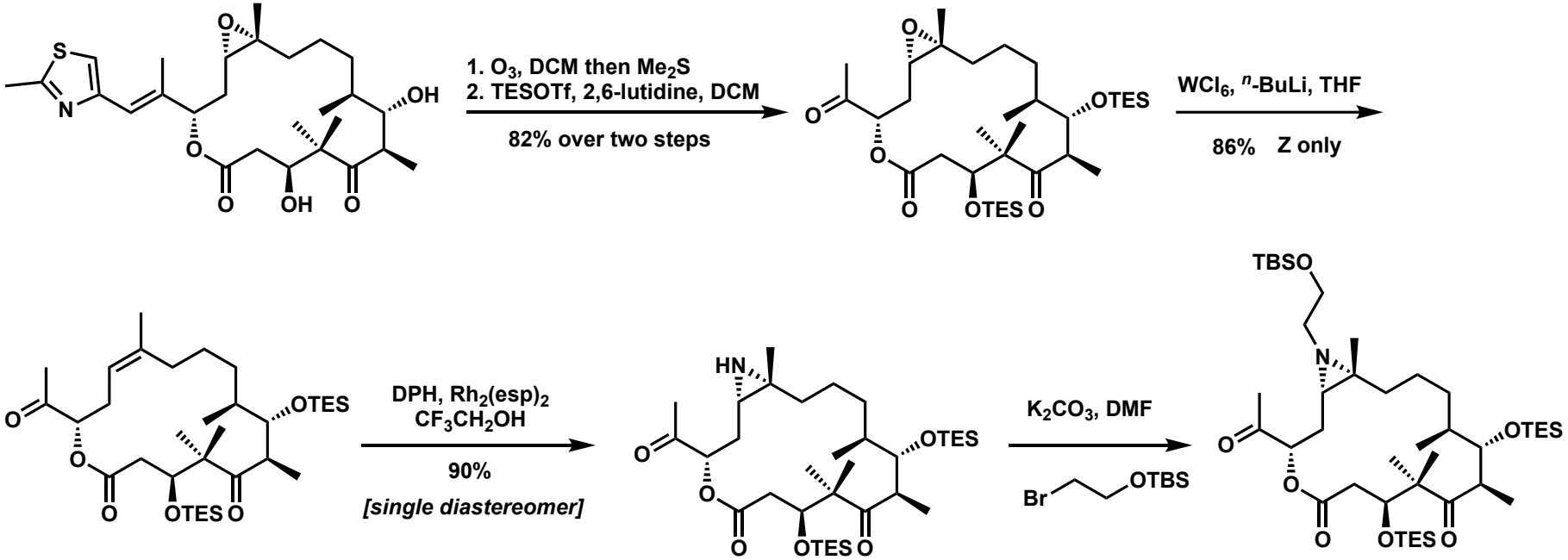






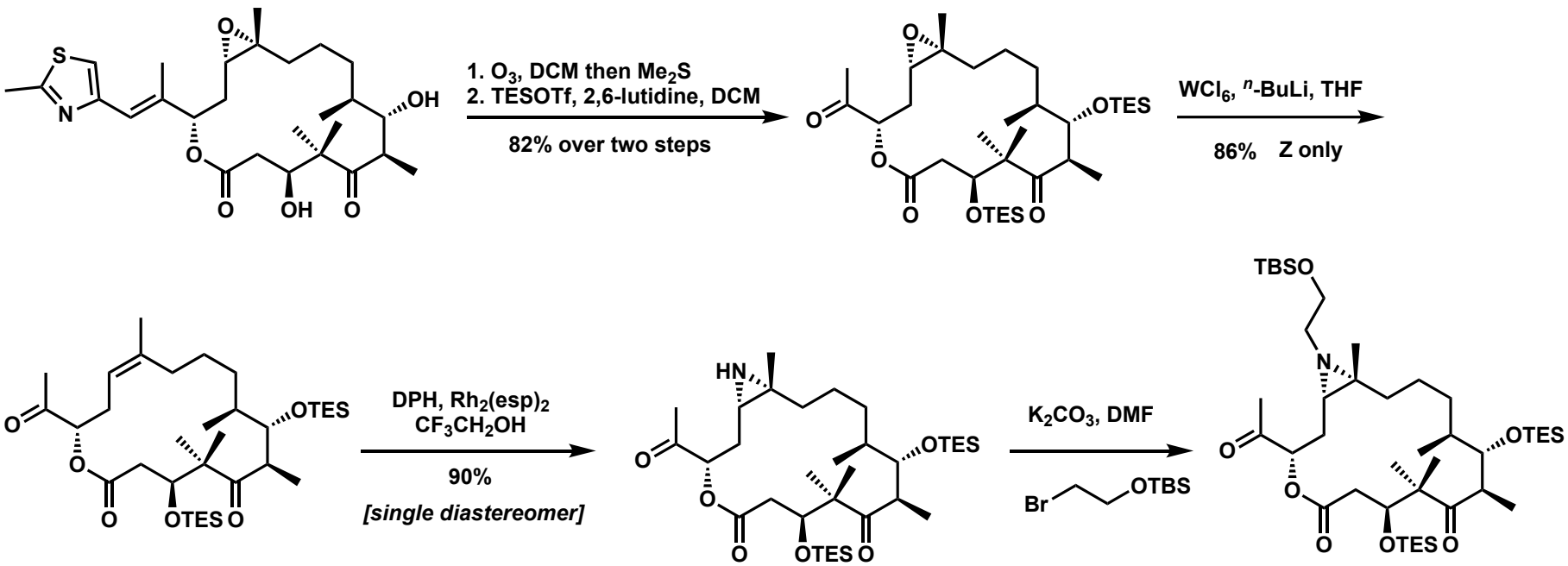
K. C. Nicolaou, et al. *J. Am. Chem. Soc*. **2017**, *139*, 7318−7334

12,13-Aziridinyl Epothilones



K. C. Nicolaou, et al. *J. Am. Chem. Soc*. **2017**, *139*, 7318−7334

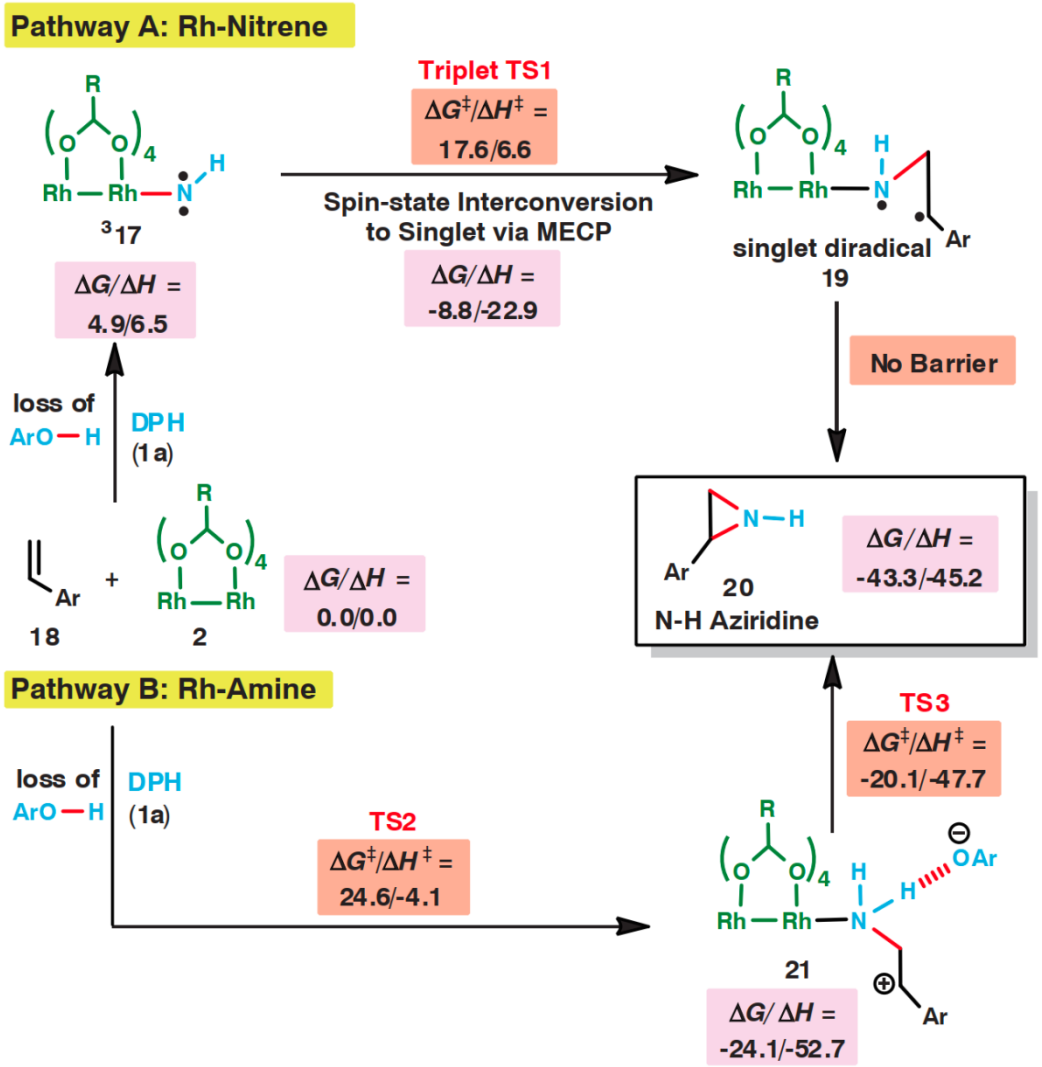
12,13-Aziridinyl Epothilones



K. C. Nicolaou, et al. *J. Am. Chem. Soc*. **2017**, *139*, 7318−7334

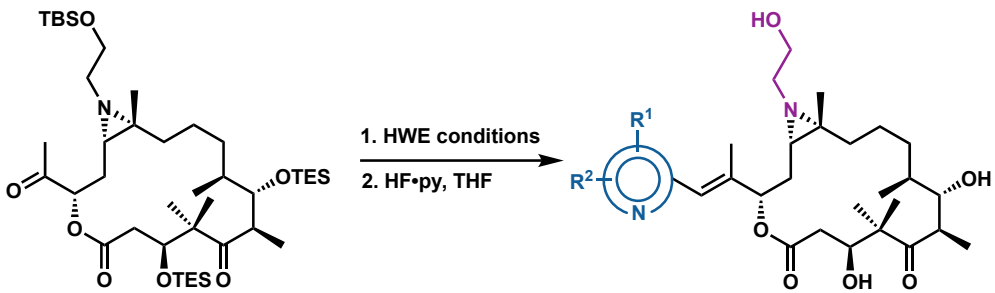
EssKürti−Falck Aziridination

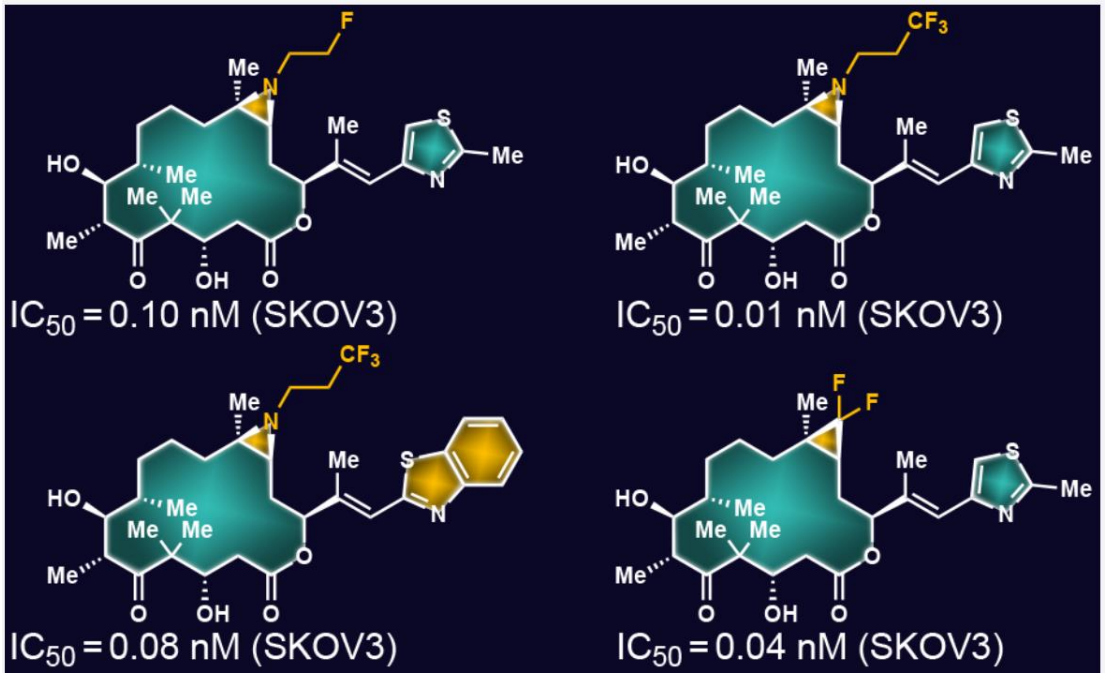
Mechanism



J.R.Falck, *Science* **2014**, *343*, 61

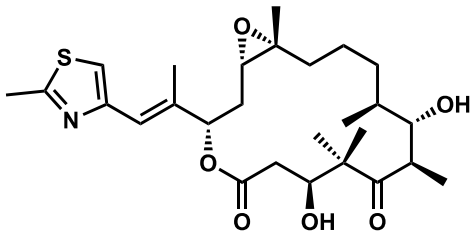
Epothilone B Analogues



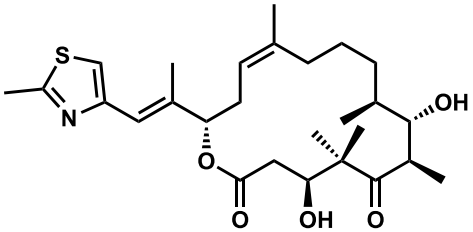


K. C. Nicolaou, et al. *J. Org. Chem.* **2020**, *85*, 2865−2917

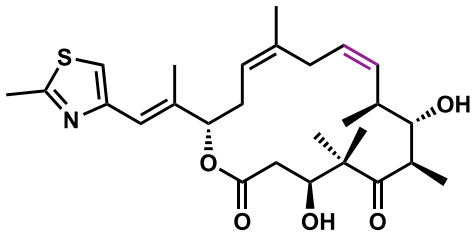
Epothilones were evaluated in the clinical setting



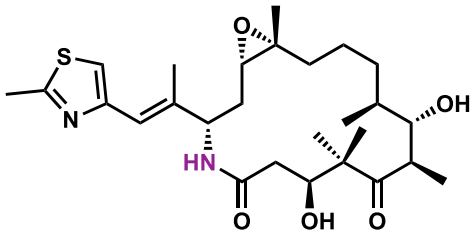
Patupilone (epotilone B)



Epotilone D (desoxyepothilone B)

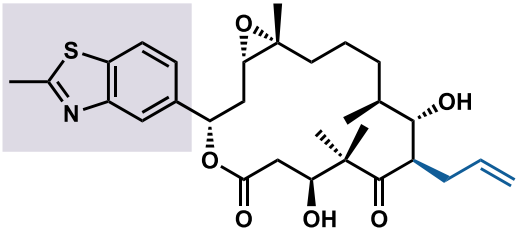


KOS-1584 (didehydroepothilone D)

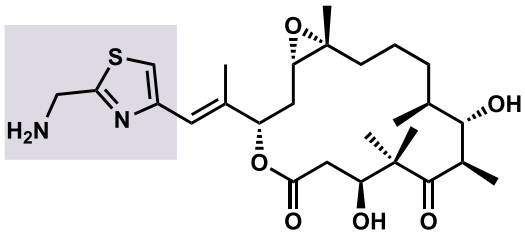


Ixabepilone (BMS-247550)

approved by the FDA as an antibreast cancer drug



Sagopilone (ZK-EPO)



BMS-310705

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Prof. Tao Ye, *Dr*. Yian Guo

All professors and faculties in SCBB

All my labmates in F211

THANK YOU !