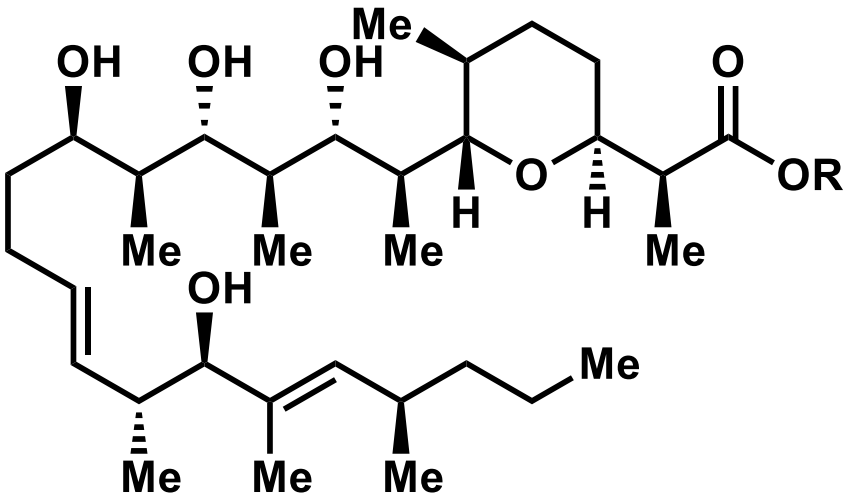
Zincophorin and its methyl ester



1 R = H, zincophorin
2 R = Me, zincophorin methyl ester

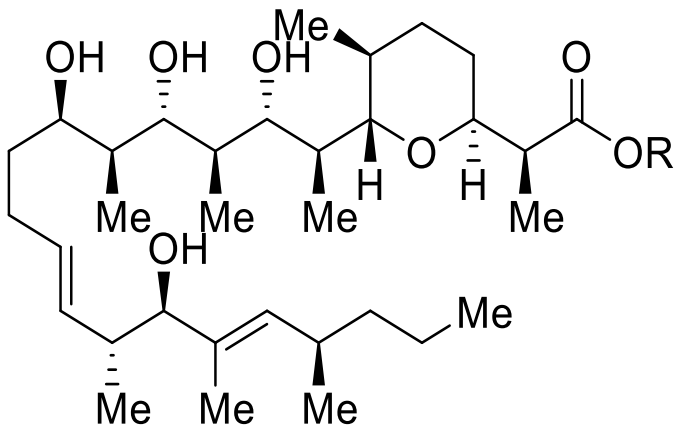


Reporters: Jiawei Meng Jie Li Fusong Wu

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

Contents

Classics in the synthesis of Zincophorin and its methyl ester



1 R = H, **zincophorin**
2 R = Me, **zincophorin methyl ester**

Reporter: Jiawei Meng

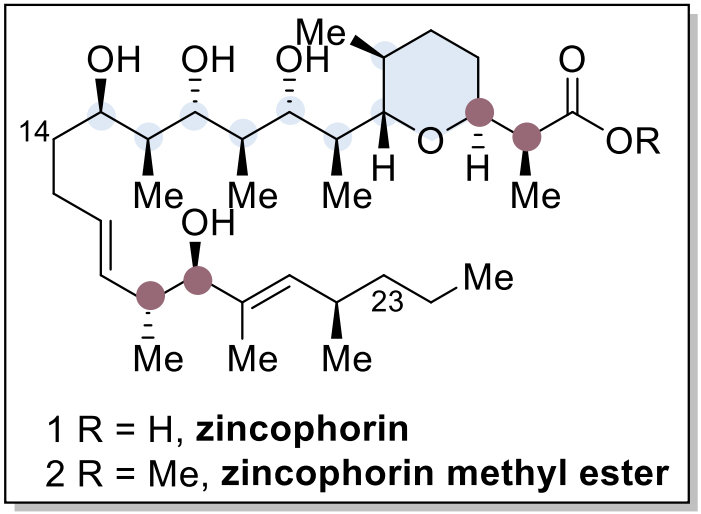
Supervisors: *Prof.* Tao Ye

Dr. Yian Guo

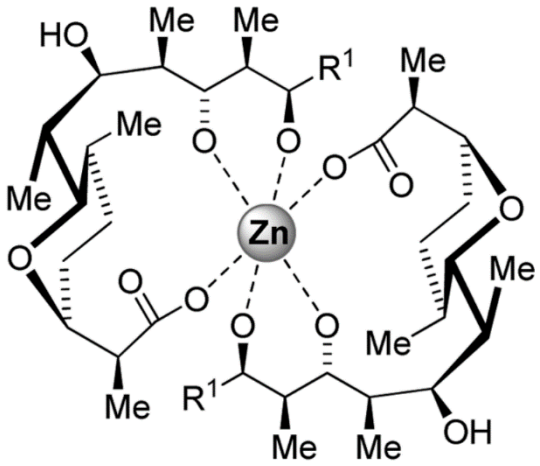
2020.09.07

Contents

Introduction



1 R = H, **zincophorin**
2 R = Me, **zincophorin methyl ester**



R^1 = C14-C25

Isolation:

- In 1984, Grafe *et al*. reported the isolation of griseocholin, from cultured strains of *Streptomyces* griseus; Poyser *et al.* reported the isolation of another ionophore named M144255 from the same strains.
- Based on its high affinity for divalent cations, especially zinc, it was given the trivial name (+)-zincophorin

Biological activities:

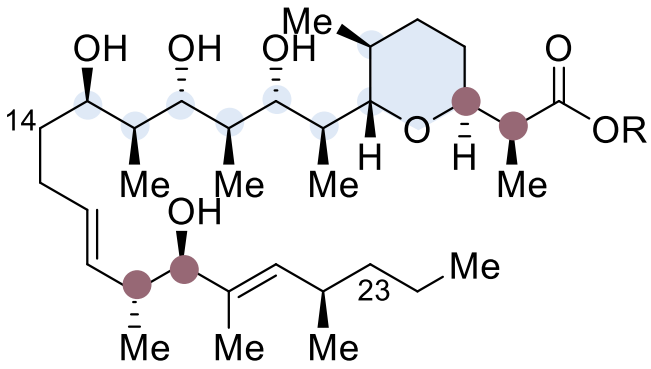
- Possesses in vivo activity against Gram-positive bacteria and Clostridium coelchii at ≤1 ppm
- Its salts exhibited anticoccidal activity against Eimeria tenella W/CAM
- Methyl ester has strong inhibitory properties against influenza WSN/virus

Structural Features:

- A challenging C8−C12 all-*anti* stereopentad embedded within the C6−C13 tetrapropionate, and the *trans*-tetrahydropyran ring
- 13 stereogenic centers (8 contiguous stereocenters)

U. Grafe, *et al. J. Antibiot*., **1984**, *37*, 836.
J. P. Poyser, *et al. J. Antibiot*., **1984**, *37*, 1501.
U. Grafe, *Ger. Pat*., **1986**, *231*, 793.

Introduction



1 R = H, **zincophorin**
2 R = Me, **zincophorin methyl ester**

Total Synthesis of Zincophorin and Its Methyl Ester

Danishefsky: *J. Am. Chem. Soc.* **1987**, *109*, 1572
J. Am. Chem. Soc. **1988**, *110*, 4368

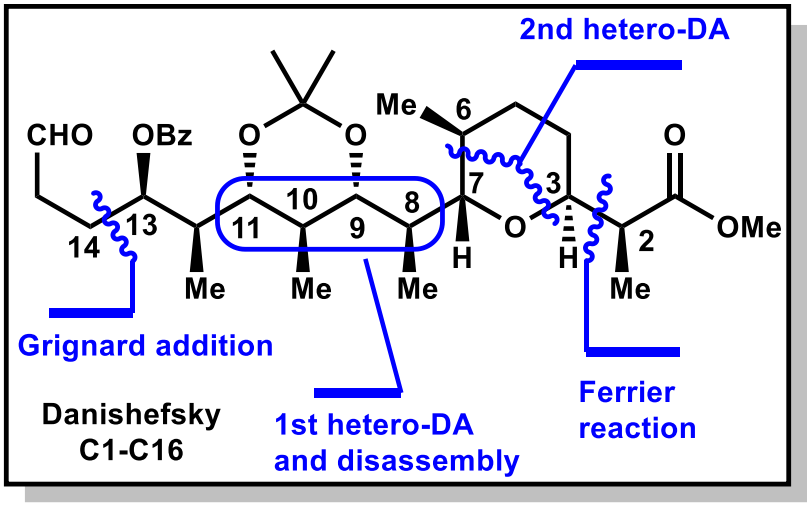
Cossy: *Org. Lett.* **2003**, *5*, 4037
J. Org. Chem. **2004**, *69*, 4626

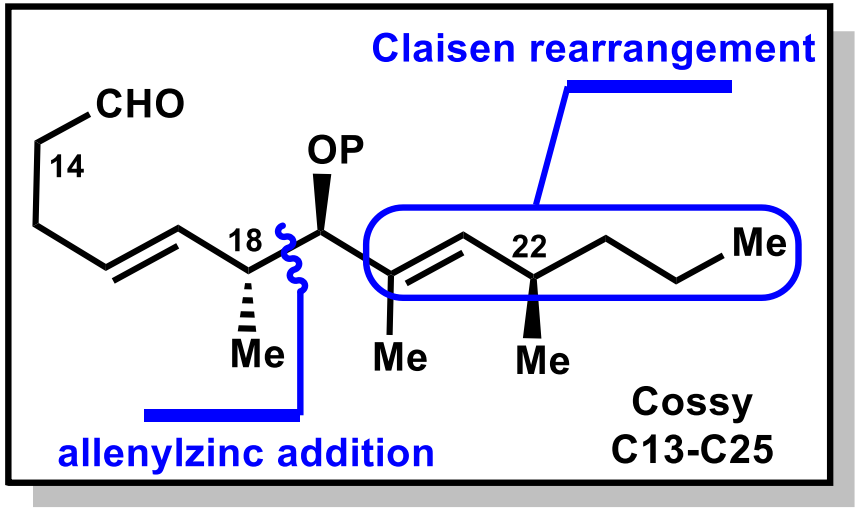
Miyashita: *Angew. Chem., Int. Ed.* **2004**, *43*, 4341

Leighton: *J. Am. Chem. Soc.* **2011**, *133*, 7308
J. Am. Chem. Soc. **2017**, *139*, 4568

Krische: *J. Am. Chem. Soc.* **2015**, *137*, 8900

Guindon: *Tetrahedron* **2015**, *71*, 709

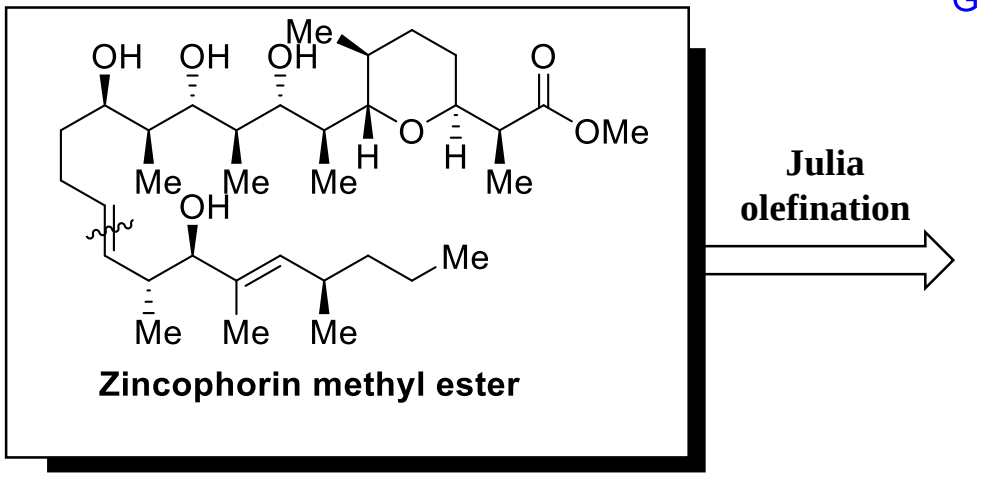




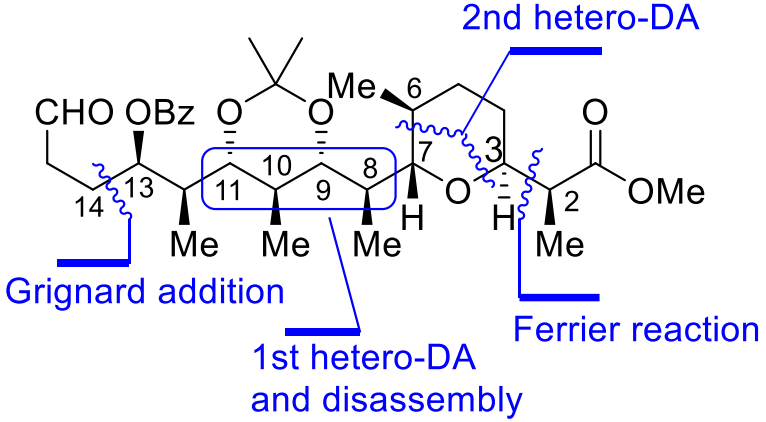
Contents

Total synthesis of zincophorin methyl ester

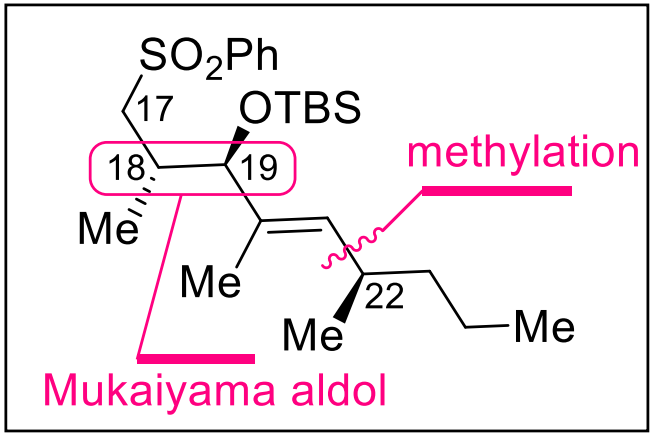
I. Danishefsky: *J. Am. Chem. Soc.* **1987**, *109*, 1572 **(the first total synthesis)**



Julia olefination



C1-C16 +

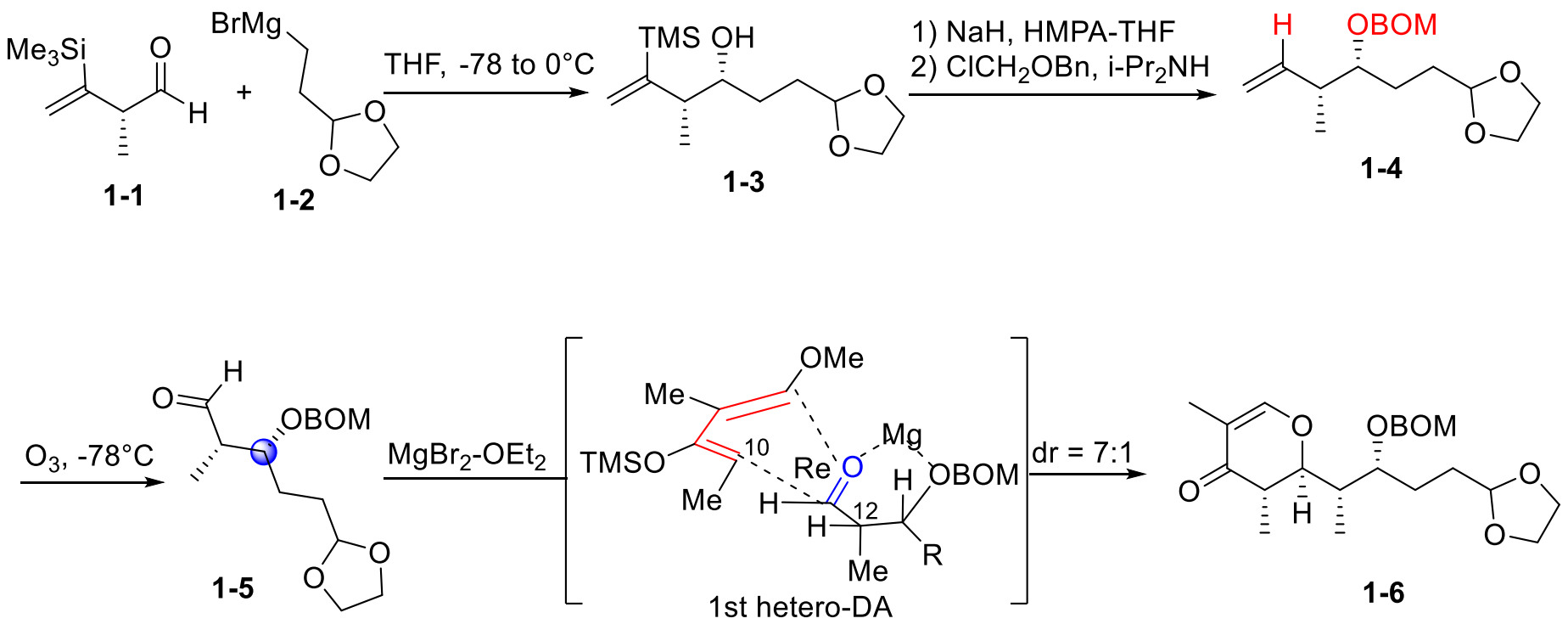


C17-C25

S. J. Danishefsky, *et al*, *J. Am. Chem. Soc.*, **1987**, *109*, 1572.
S. J. Danishefsky, *et al*, *J. Am. Chem. Soc.*, **1988**, *110*, 4368

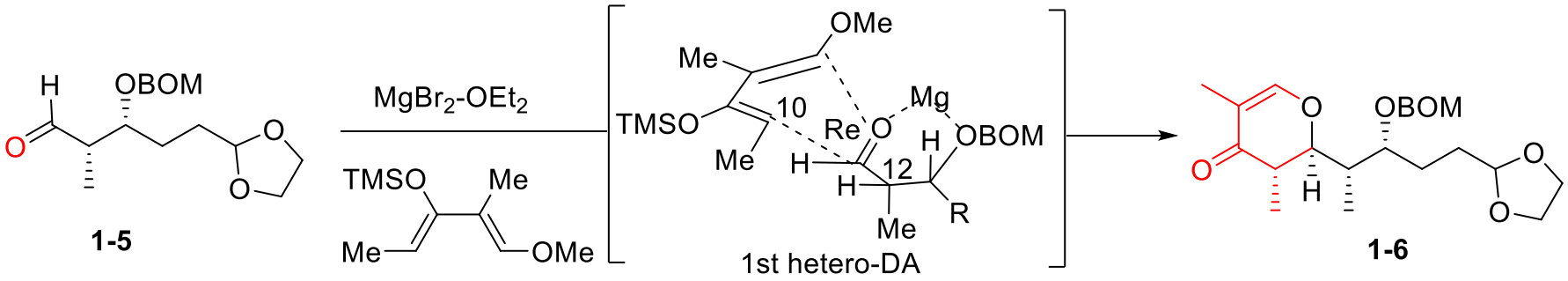
Total synthesis of zincophorin methyl ester

- Synthesis of the C1–C16 fragment (**1st hetero-DA**)

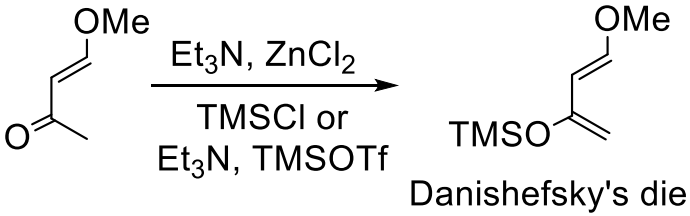


S. J. Danishefsky, *et al*, *J. Am. Chem. Soc.*, **1987**, *109*, 1572.
S. J. Danishefsky, *et al*, *J. Am. Chem. Soc.*, **1988**, *110*, 4368

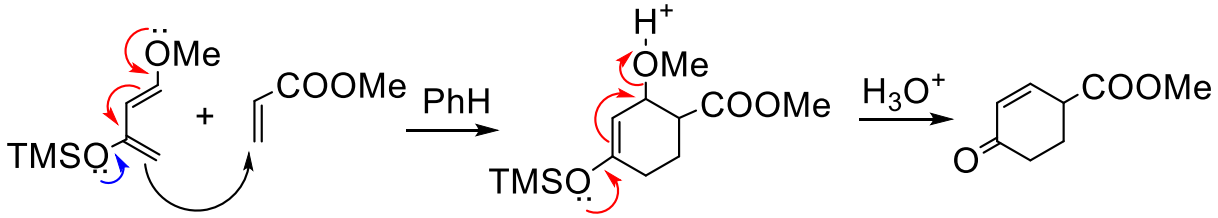
Total synthesis of zincophorin methyl ester



Mechanism

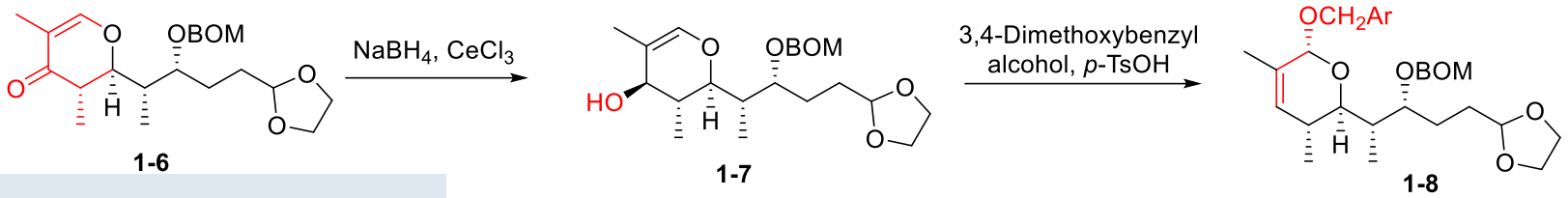


The two oxygenetaed substituents of this highly reactive diene have consonant regiodirecting capabilities



Total synthesis of zincophorin methyl ester

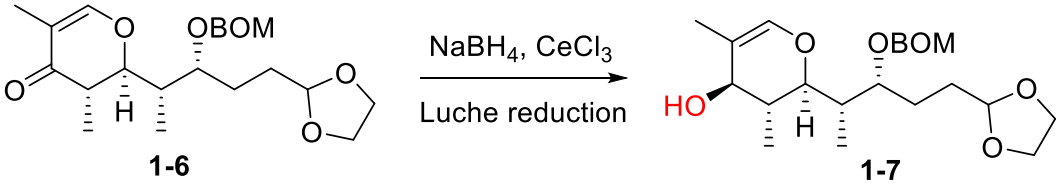
- Synthesis of the C1–C16 fragment



1-6 1-7 1-8

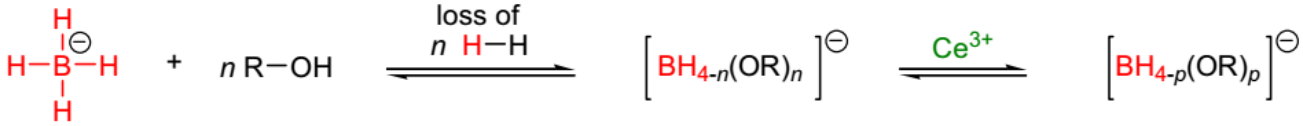
Mechanism

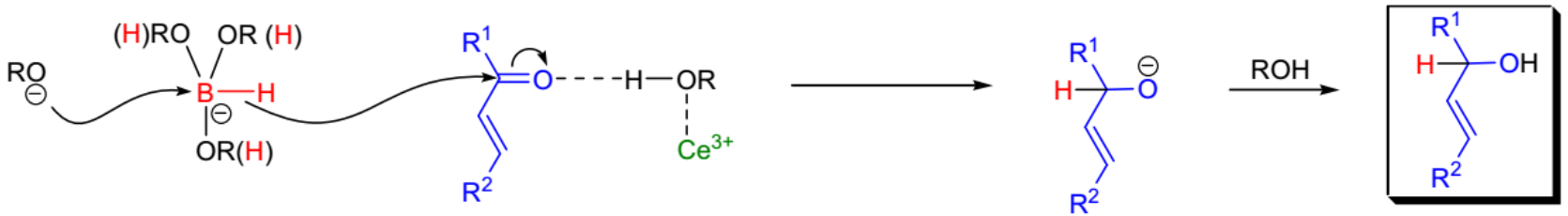
Luche reduction



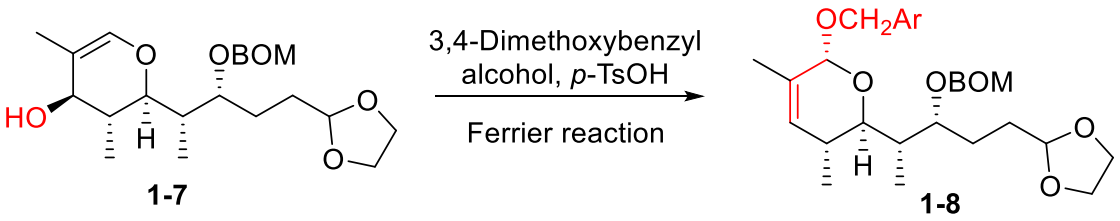
1-6 1-7

Formation of alkoxyborohydrides:

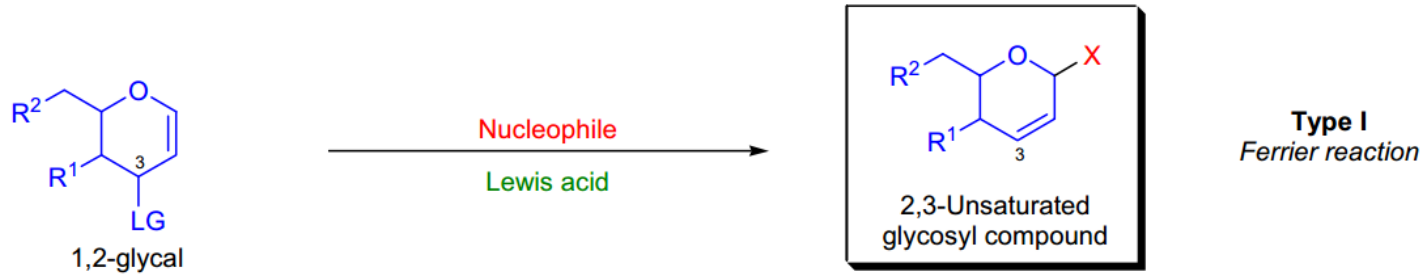




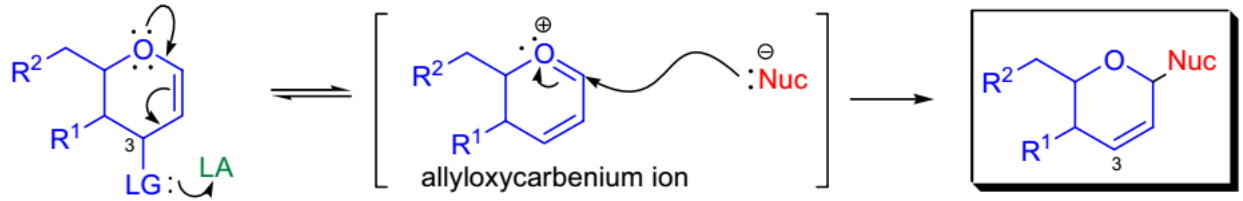
Total synthesis of zincophorin methyl ester

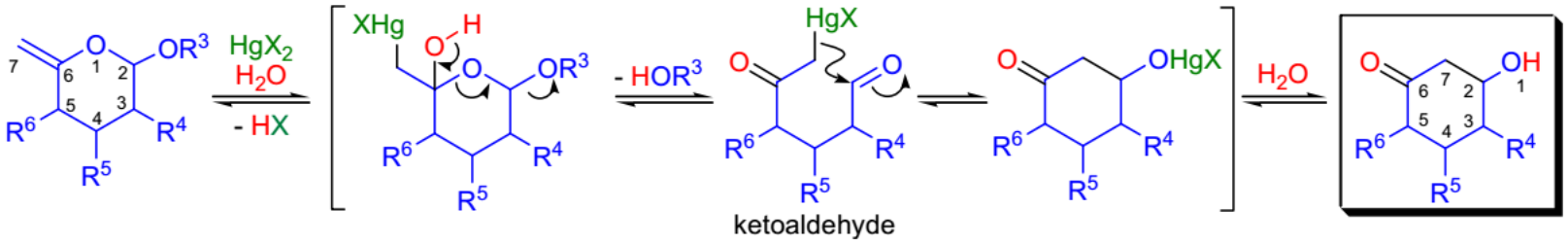


Mechanism



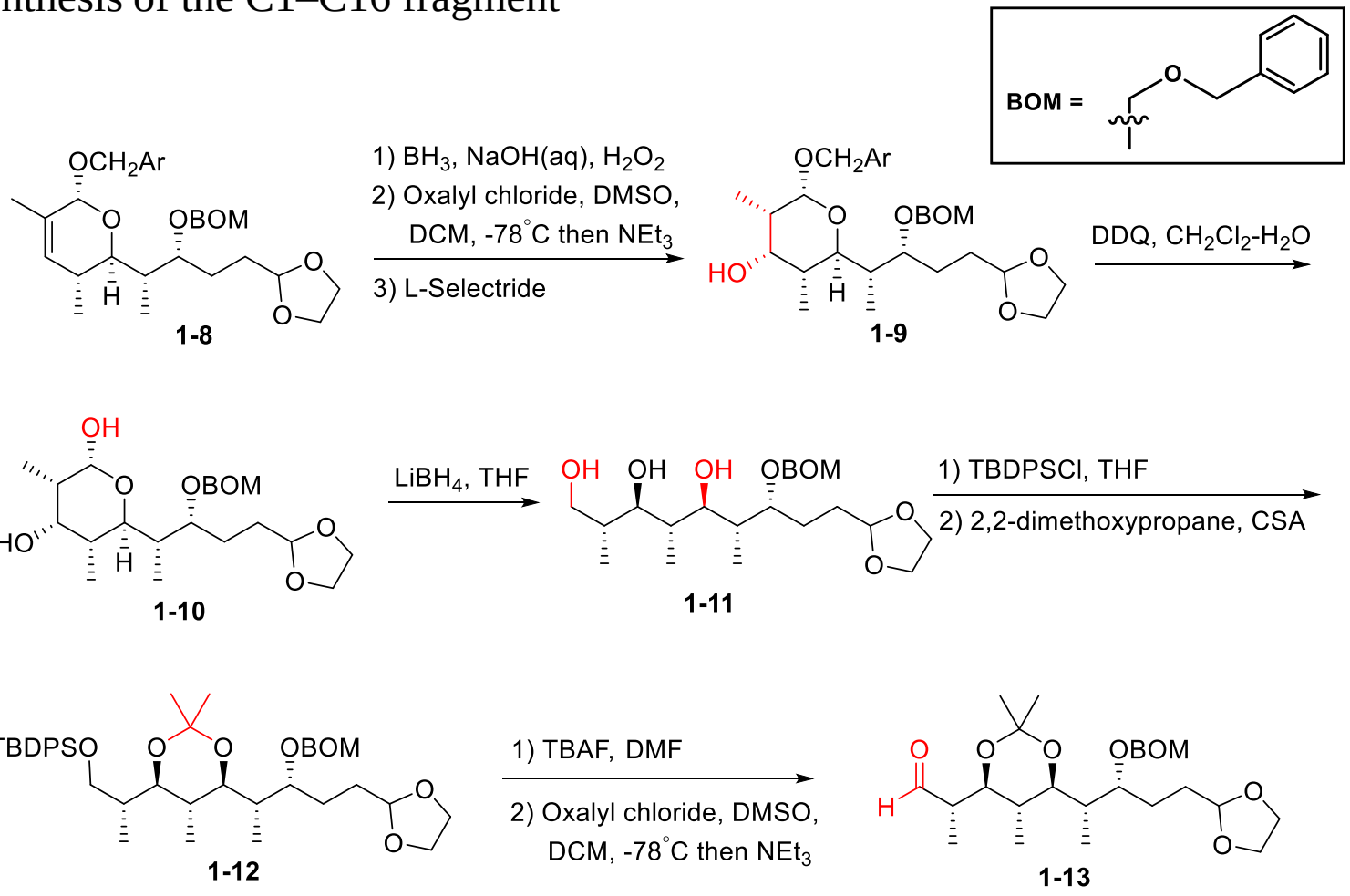
R^1, R^2 = *O*-acyl; LG = *O*-acyl, OTs, etc.; Lewis acid: $BF_3{\cdot}OEt_2$, $SnCl_4$, I_2, H_3O^+, TMSOTf, $FeCl_3$, etc.; X = OR, SR, NR_2, CR_3





Total synthesis of zincophorin methyl ester

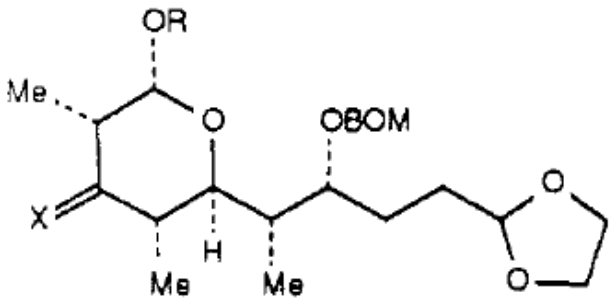
- Synthesis of the C1–C16 fragment

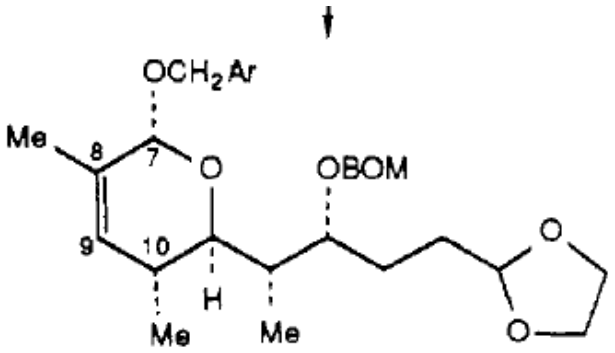


S. J. Danishefsky, *et al*, *J. Am. Chem. Soc.*, **1988**, *110*, 4368.

Total synthesis of zincophorin methyl ester

Mechanism





16 Ar = 3, 4 - dimethoxyphenyl

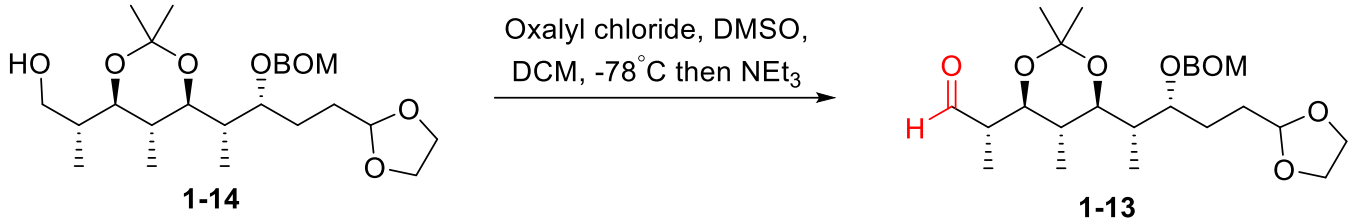
17 X = β OH, α H; R = CH_2Ar

18 X = O; R = CH_2Ar

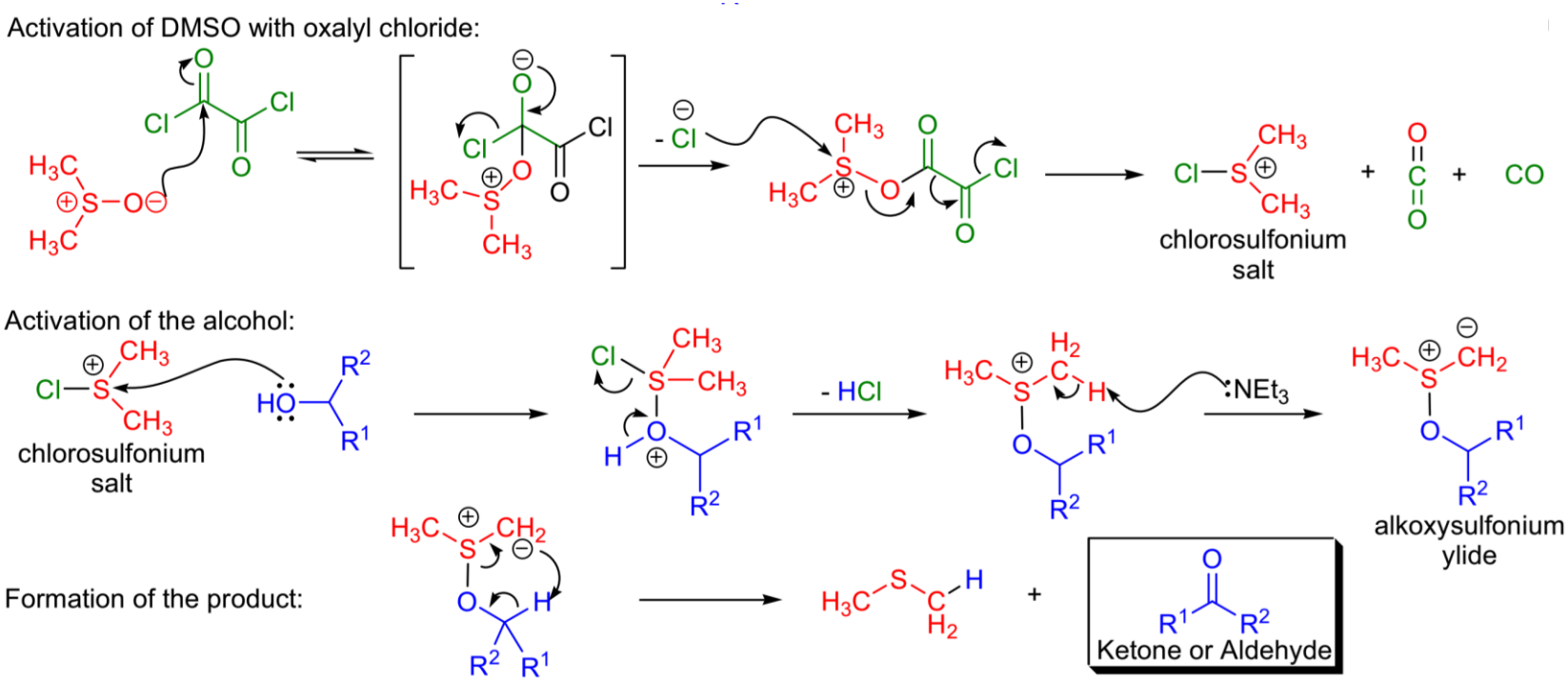
19 X = α OH, β H; R = CH_2Ar

20 X = α OH, β H; R = H (anomeric mixture)

Total synthesis of zincophorin methyl ester

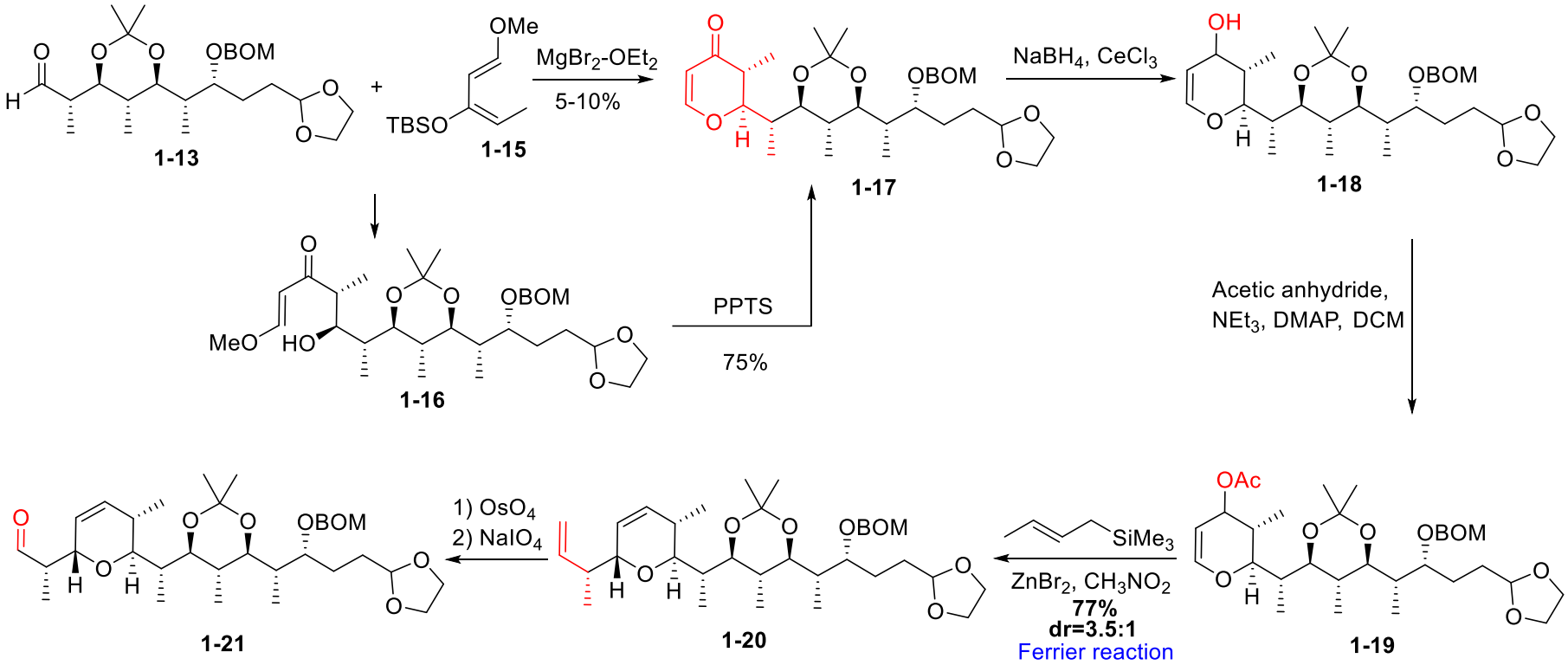


Mechanism



Total synthesis of zincophorin methyl ester

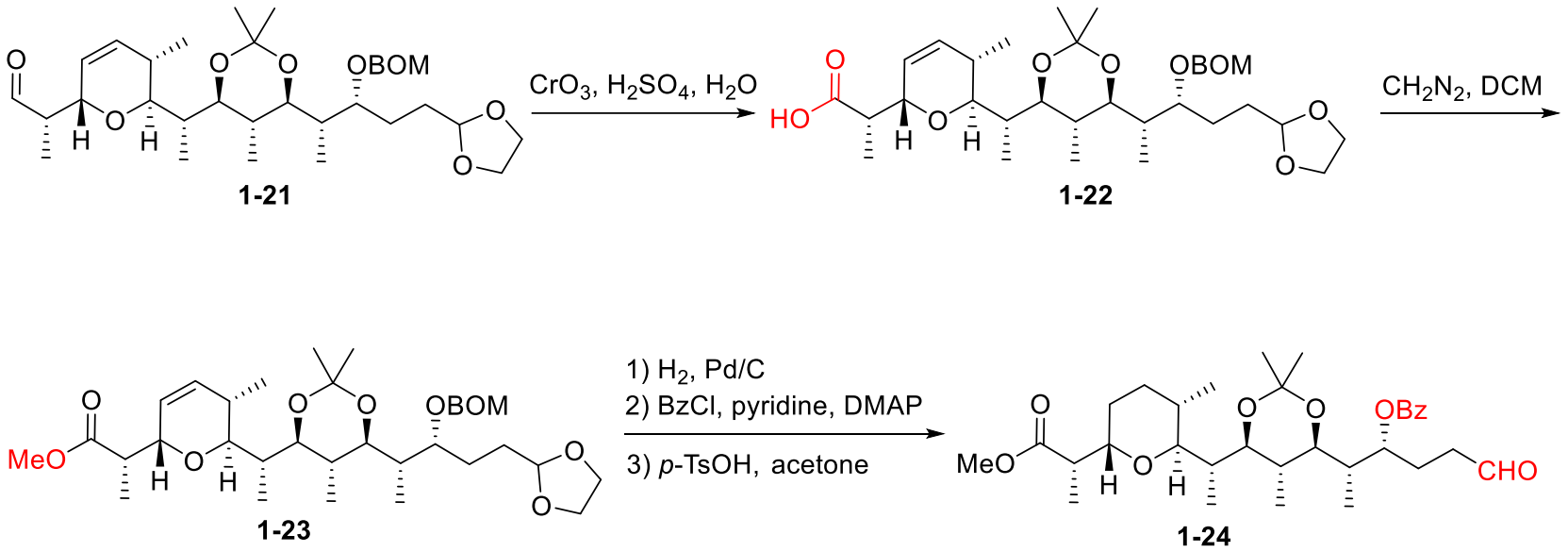
- Synthesis of the C1–C16 fragment (**2nd hetero-DA**)



S. J. Danishefsky *et al, J. Am. Chem. Soc.*, **1988**, 110, 4368.

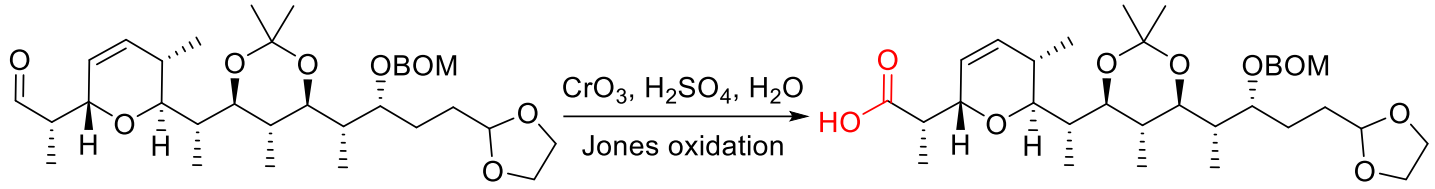
Total synthesis of zincophorin methyl ester

- Synthesis of the C1–C16 fragment



S. J. Danishefsky *et al*, *J. Am. Chem. Soc.*, **1988**, 110, 4368.

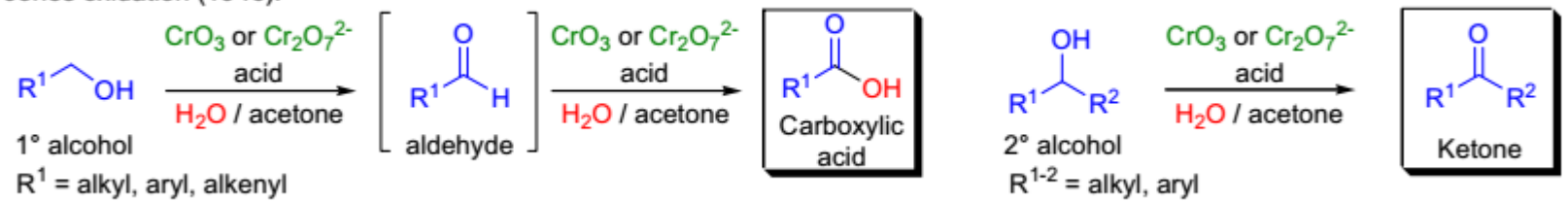
Total synthesis of zincophorin methyl ester

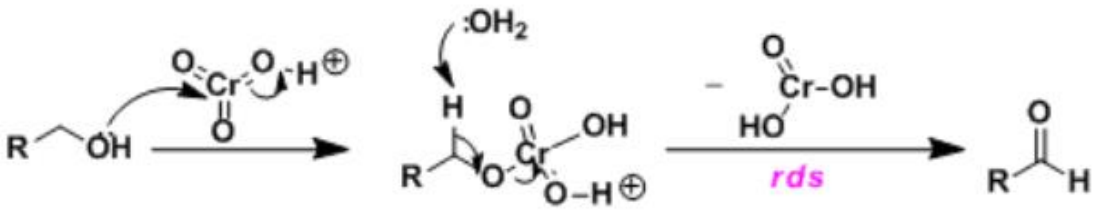


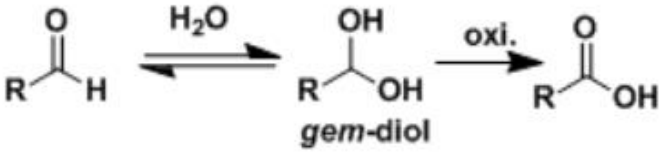
1-21 1-22

Mechanism

Jones oxidation (1946):

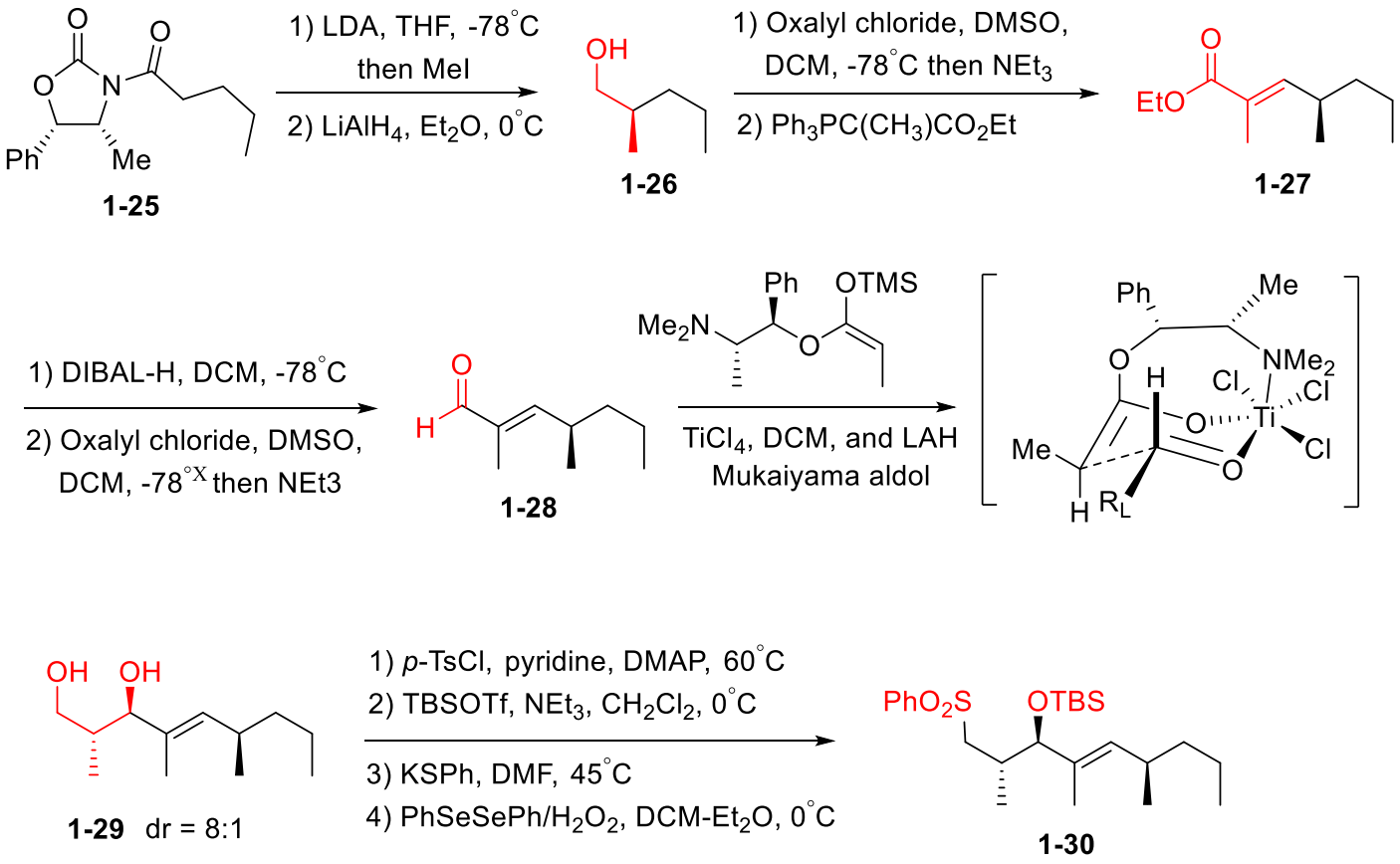






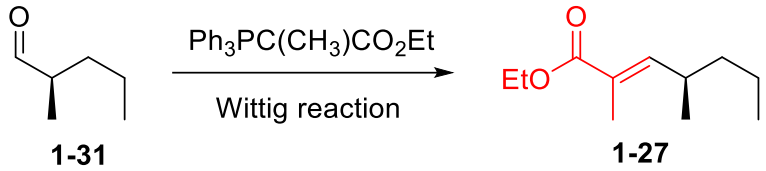
Total synthesis of zincophorin methyl ester

- Synthesis of the C17–C25 fragment

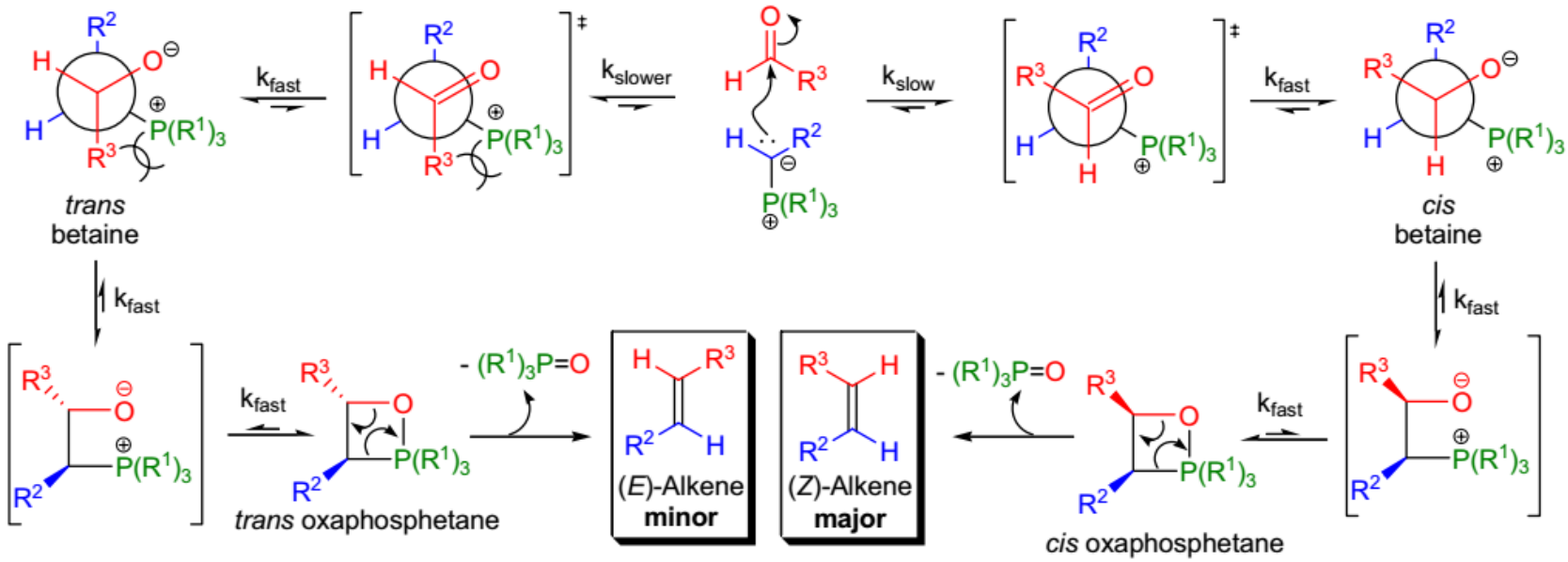


S. J. Danishefsky et al, *J. Am. Chem. Soc.*, **1988**, 110, 4368.

Total synthesis of zincophorin methyl ester

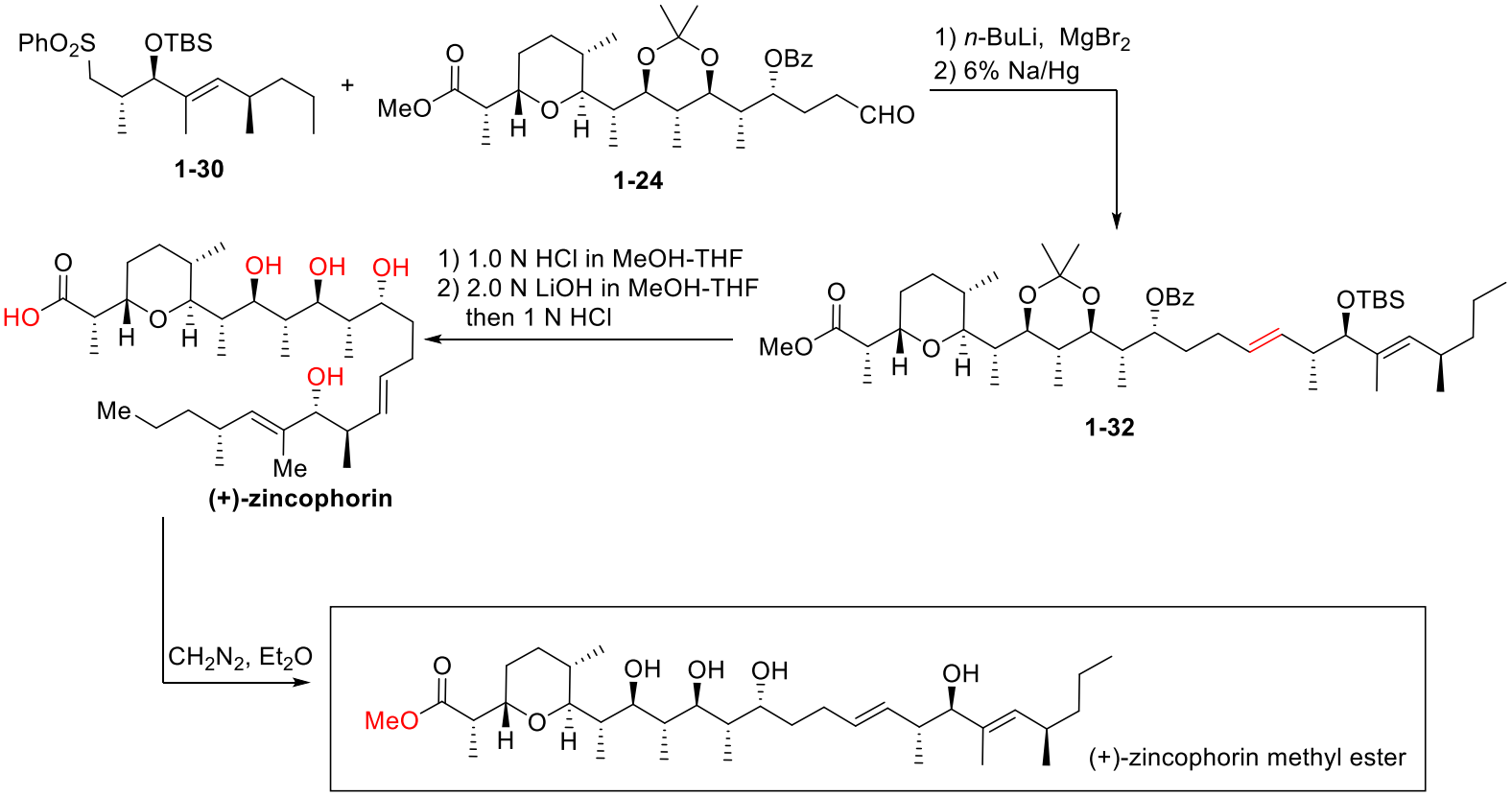


Mechanism



Total synthesis of zincophorin methyl ester

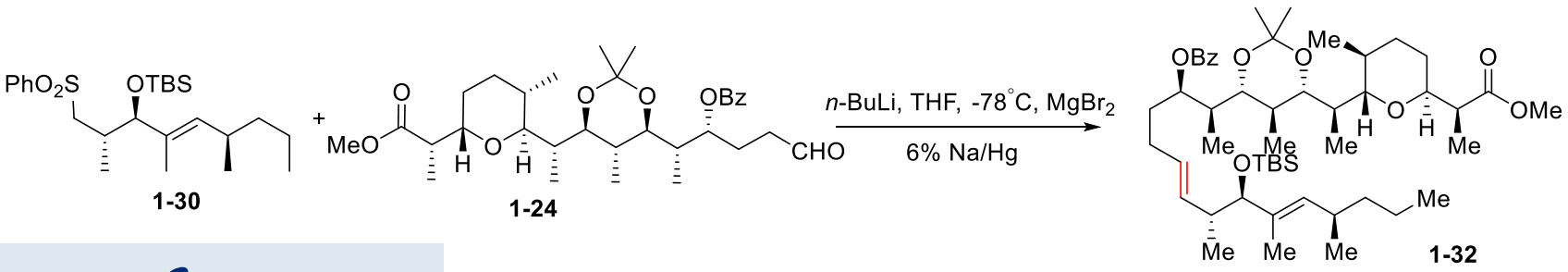
- Coupling of two fragments and synthesis of Zincophorin



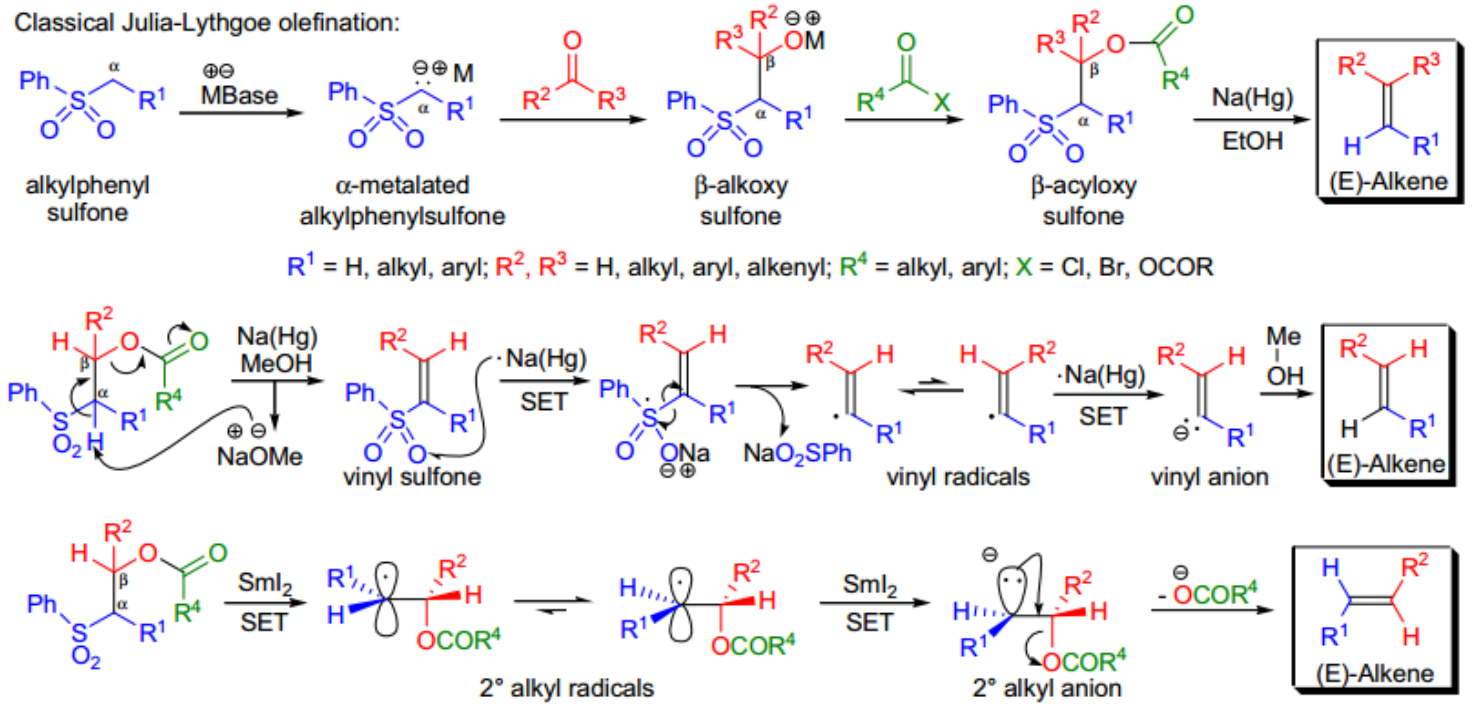
35 steps LLS

S. J. Danishefsky et al, *J. Am. Chem. Soc.*, **1988**, 110, 4368.

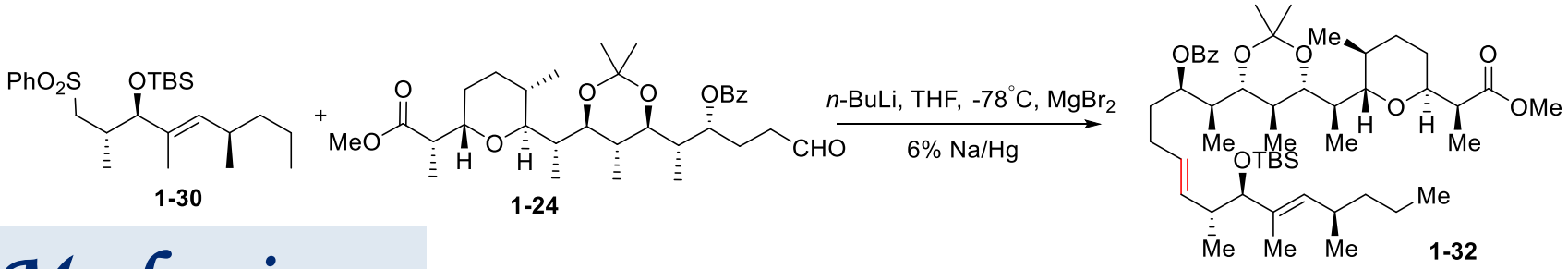
Total synthesis of zincophorin methyl ester



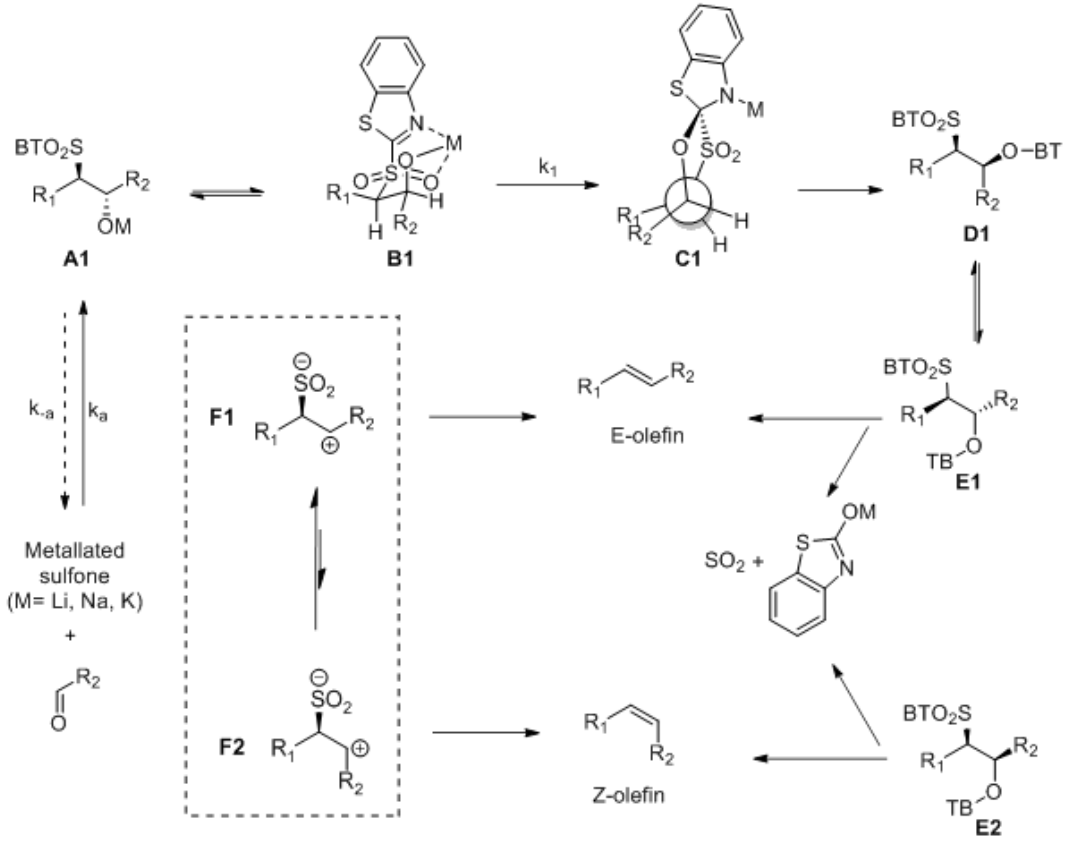
Mechanism



Total synthesis of zincophorin methyl ester



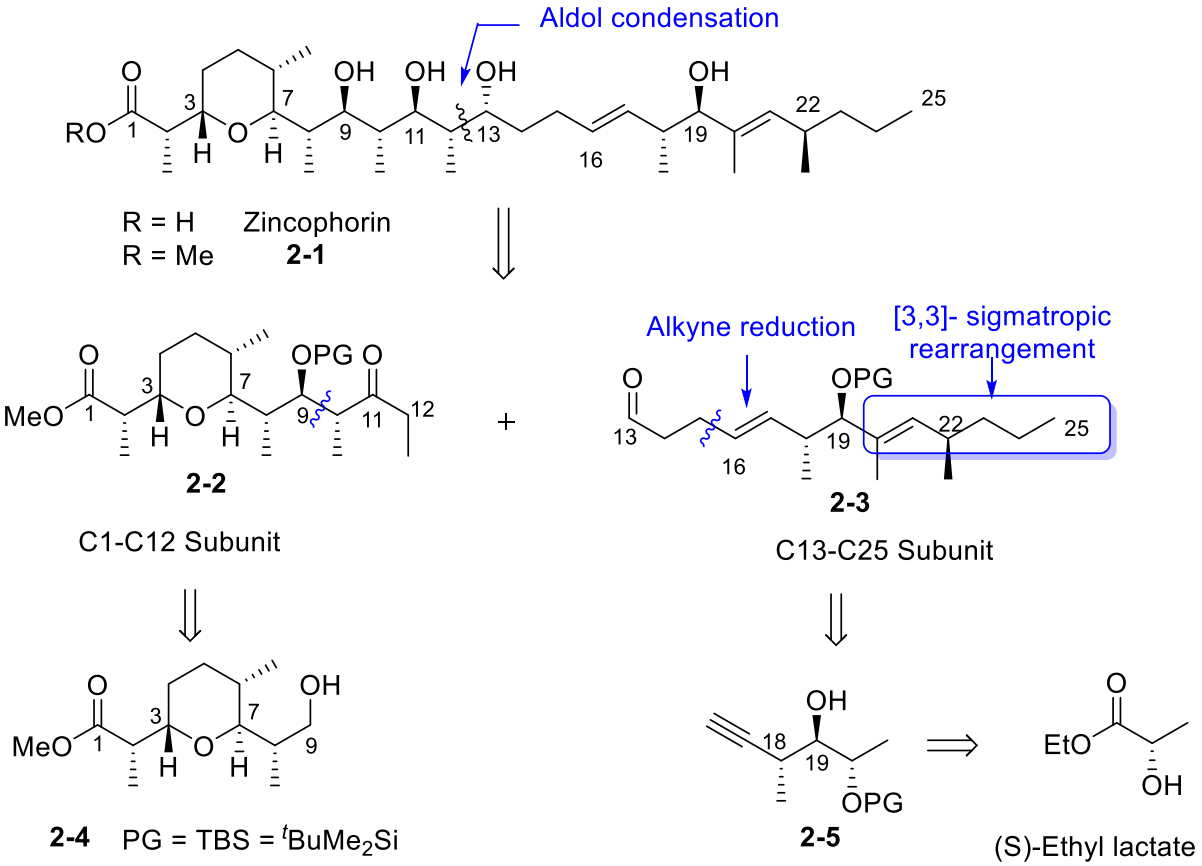
Mechanism



Total synthesis of zincophorin methyl ester

II. Cossy: *Org. Lett.* **2003**, *5*, 4037

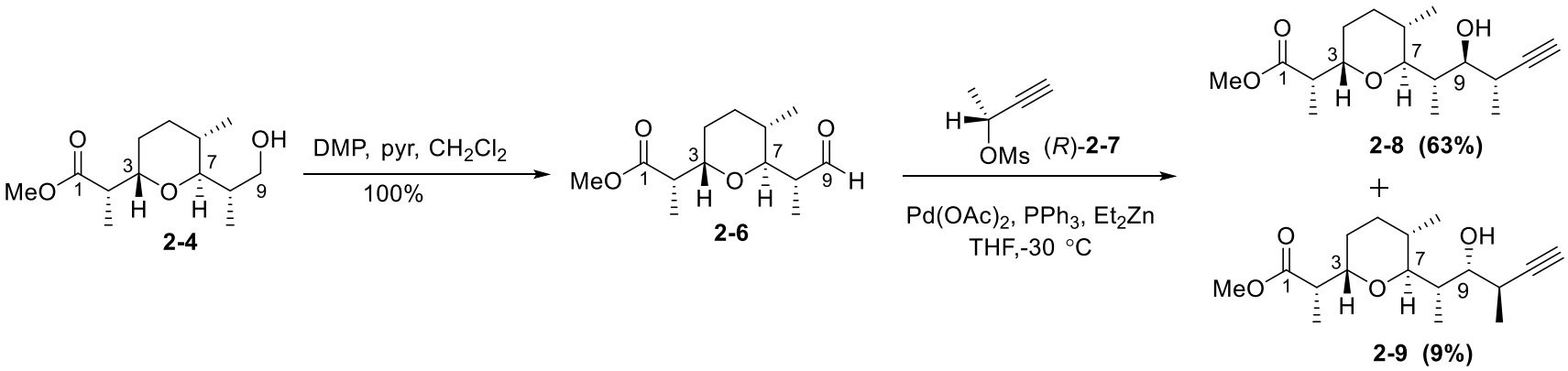
- Retrosynthetic Analysis

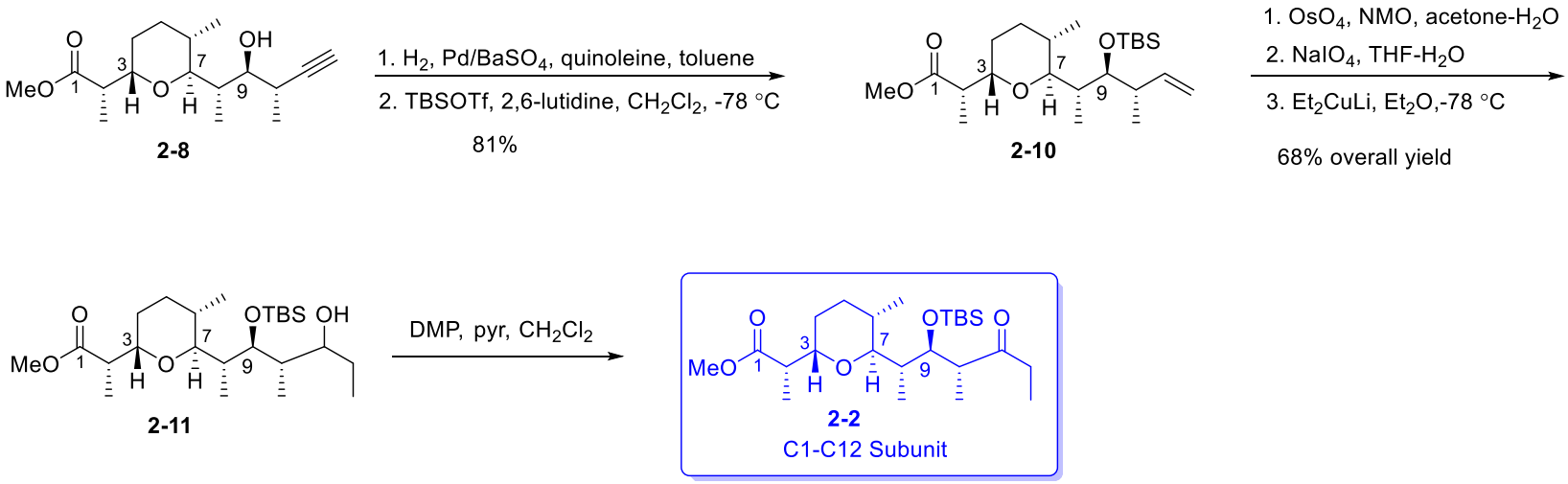


J. Cossy, *et al*. *Org.Lett.* **2003**, *5*, 4037.

Total synthesis of zincophorin methyl ester

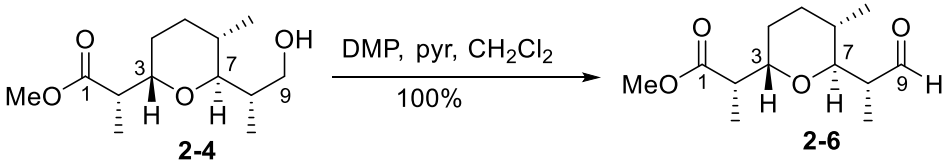
- Synthesis of the C1-C12 Subunit of Zincophorin



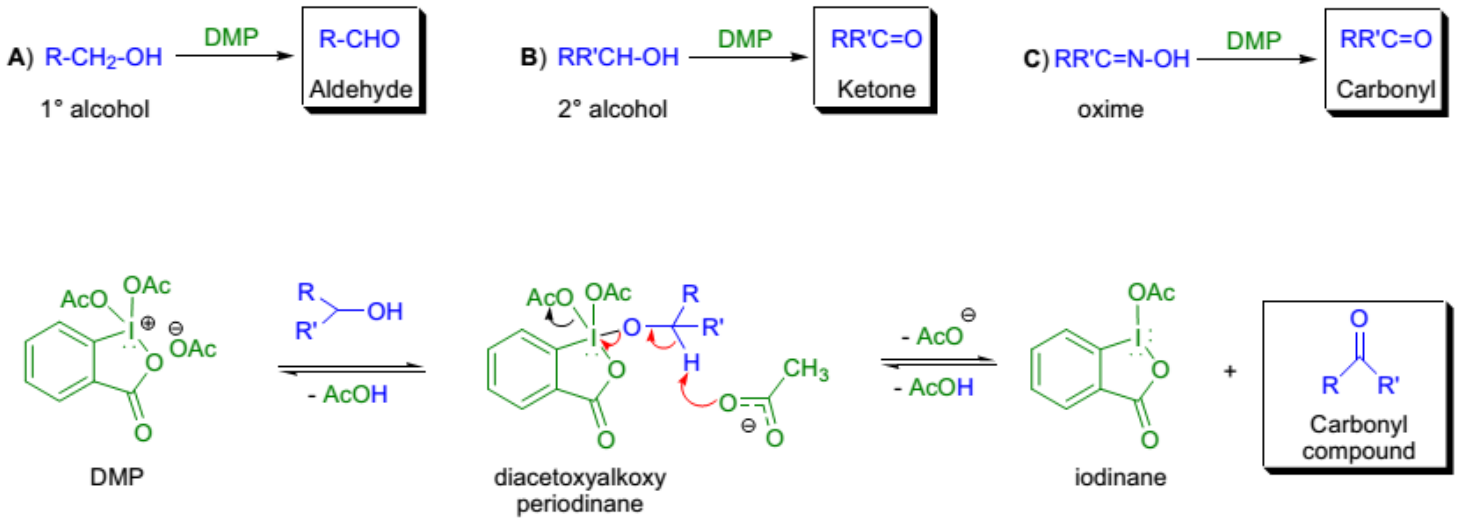


J. Cossy, *et al*. *Org.Lett.* **2003**, *5*, 4037.

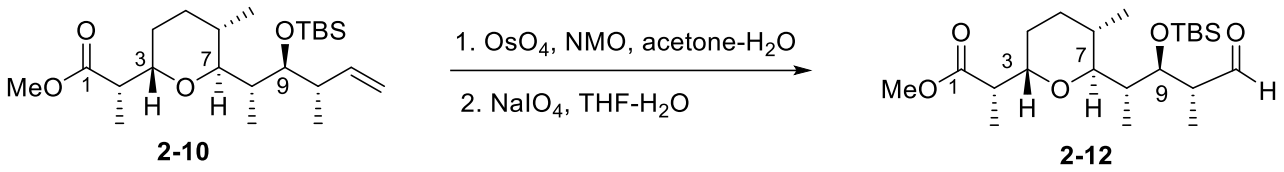
Total synthesis of zincophorin methyl ester



Mechanism

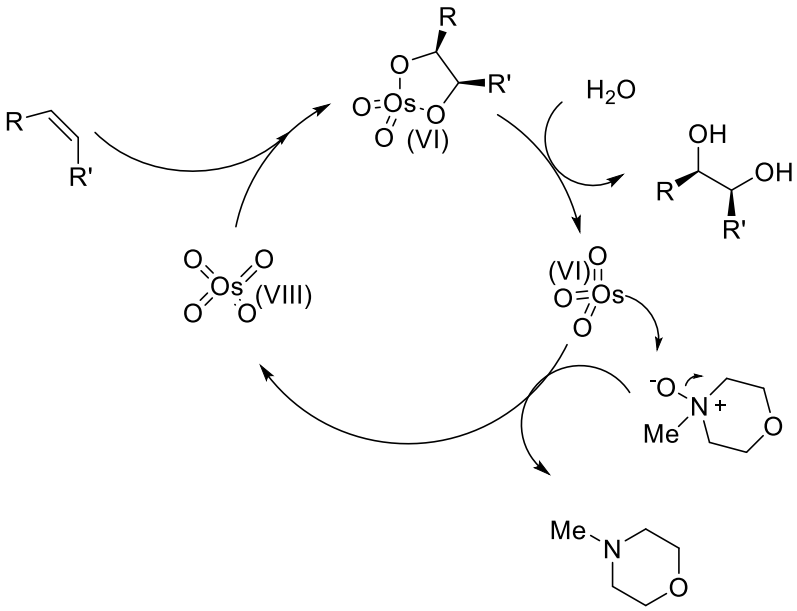


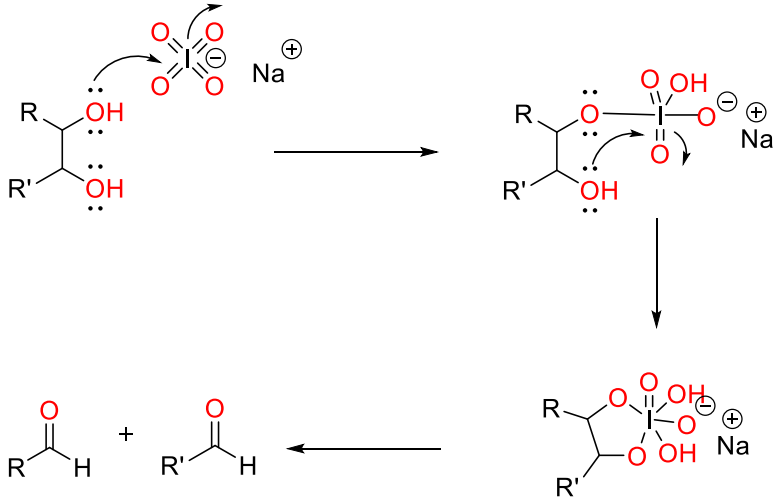
Total synthesis of zincophorin methyl ester



2-10 2-12

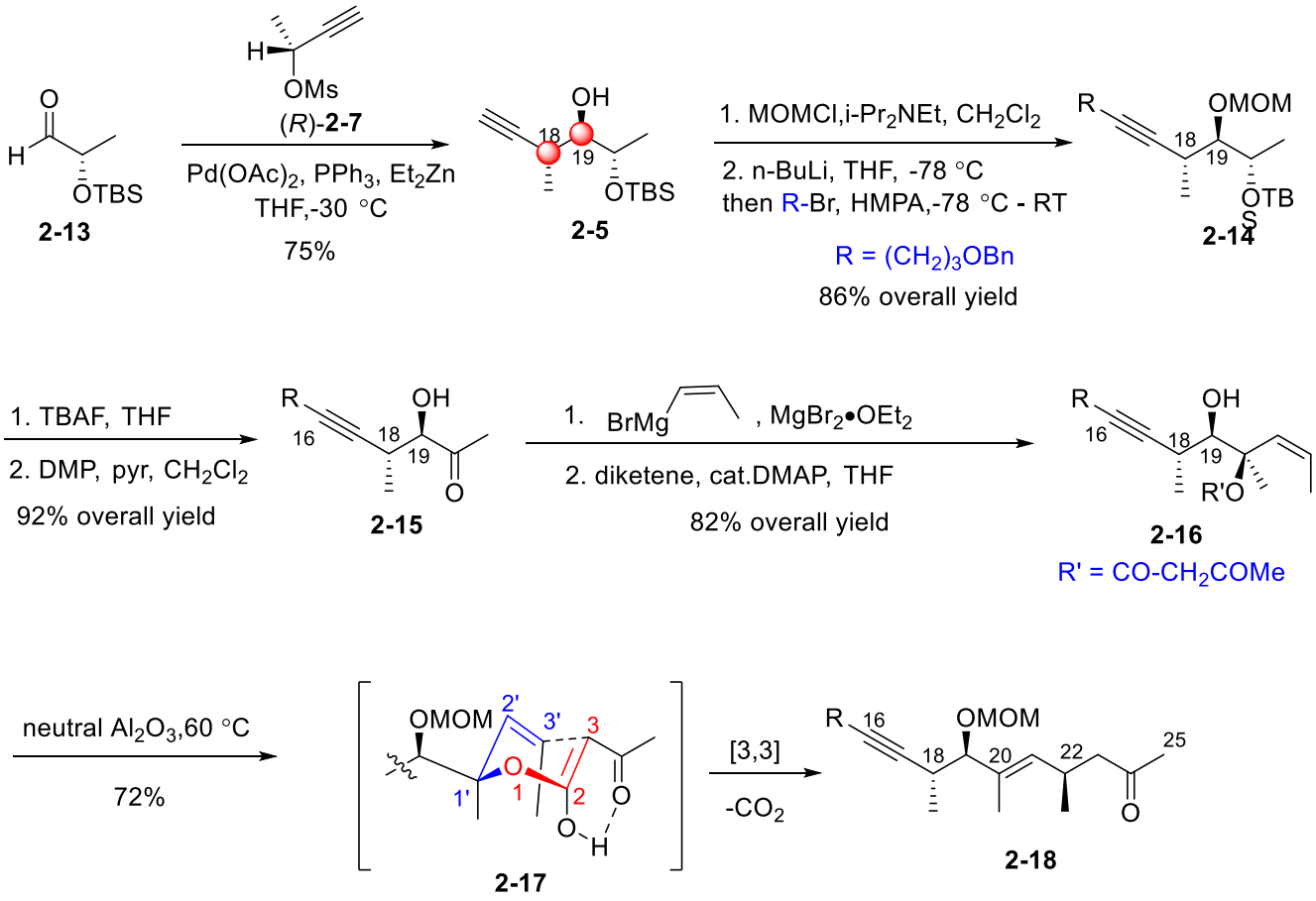
Mechanism





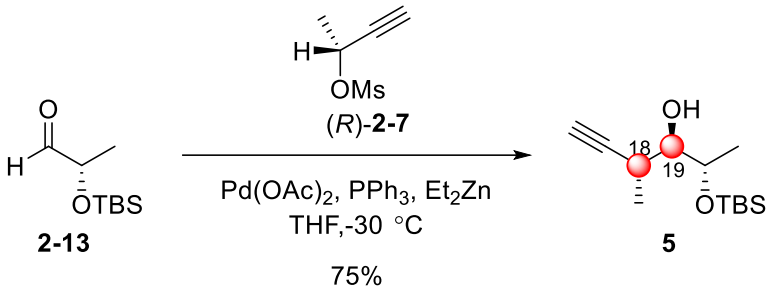
Total synthesis of zincophorin methyl ester

- Synthesis of the C13-C25 Subunit of Zincophorin

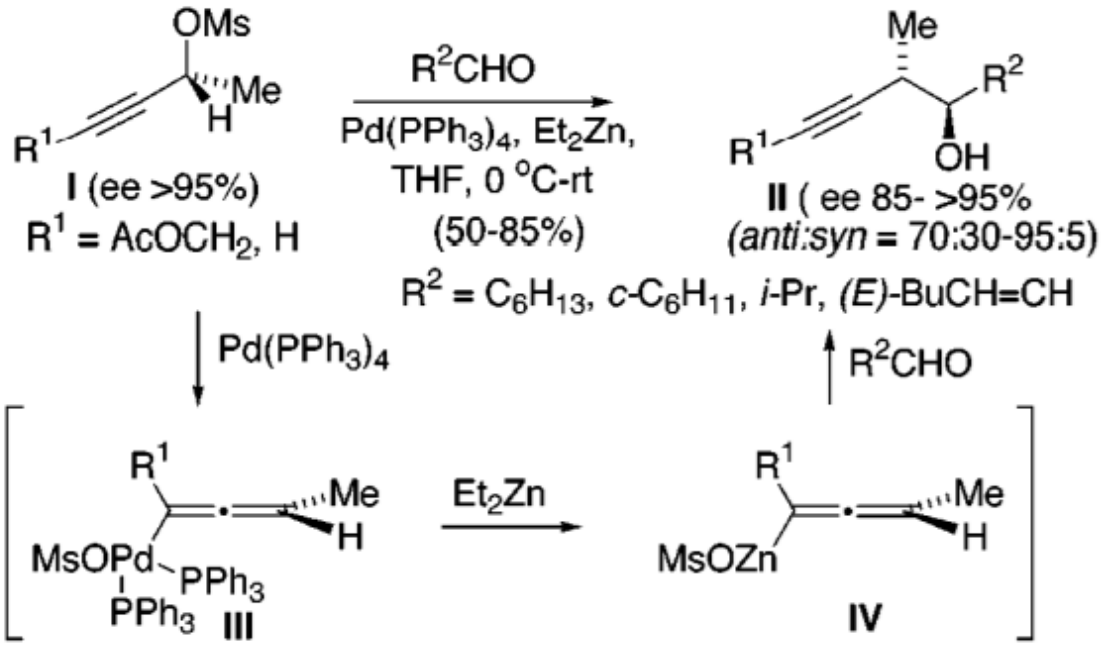


J. Cossy, *et al*. *Org.Lett.* **2003**, *5*, 4037.

Total synthesis of zincophorin methyl ester



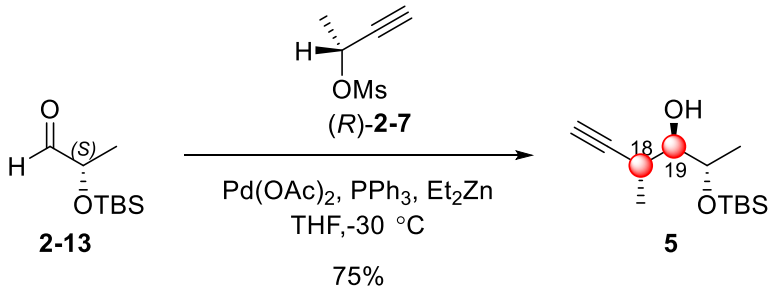
Mechanism

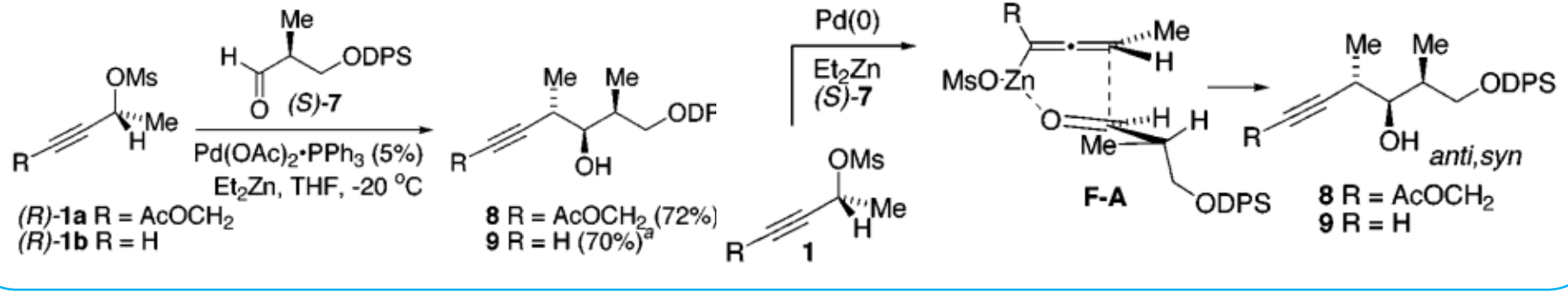


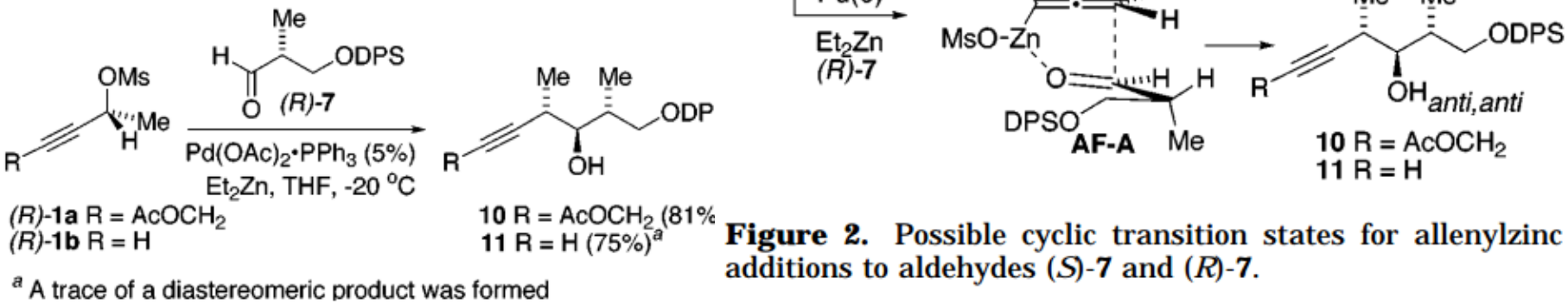
J. Marshall, N. Adams. *J. Org. Chem.***1999**, *64*, 5201.

Total synthesis of zincophorin methyl ester

Mechanism





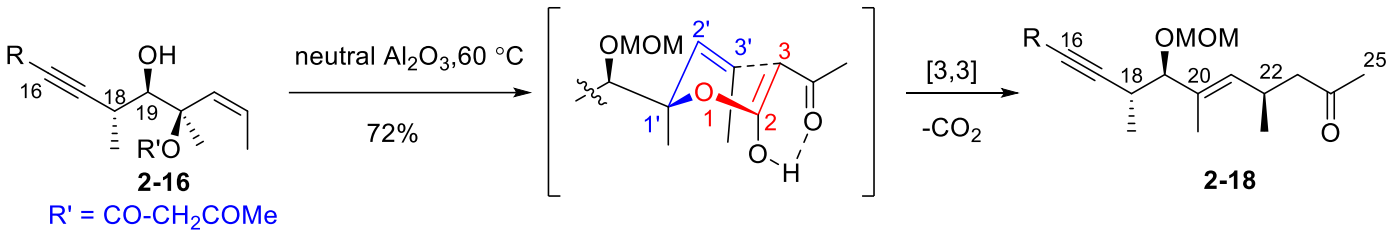


[a] A trace of a diastereomeric product was formed

Figure 2. Possible cyclic transition states for allenylzinc additions to aldehydes (*S*)-**7** and (*R*)-**7**.

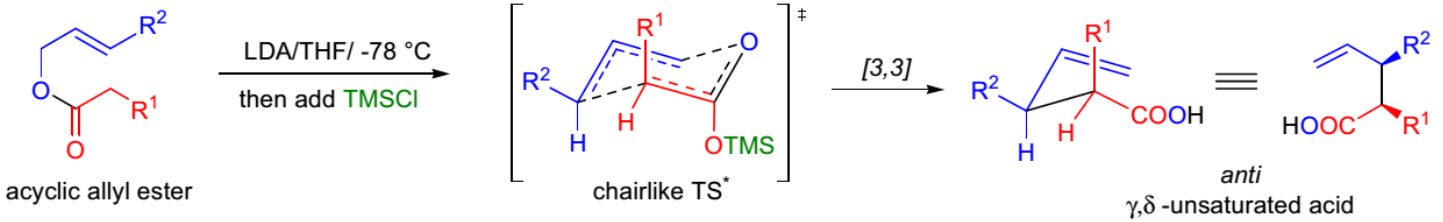
J. Marshall, N. Adams. *J. Org. Chem.***1999**, *64*, 5201.

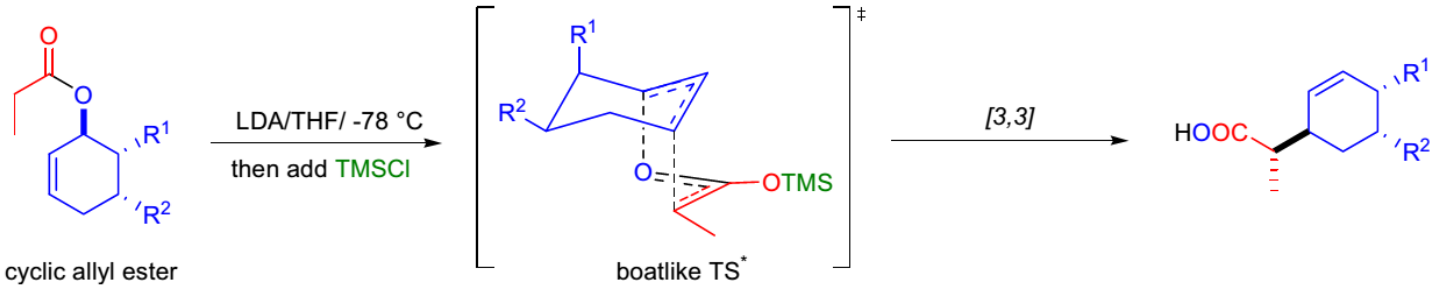
Total synthesis of zincophorin methyl ester



Mechanism

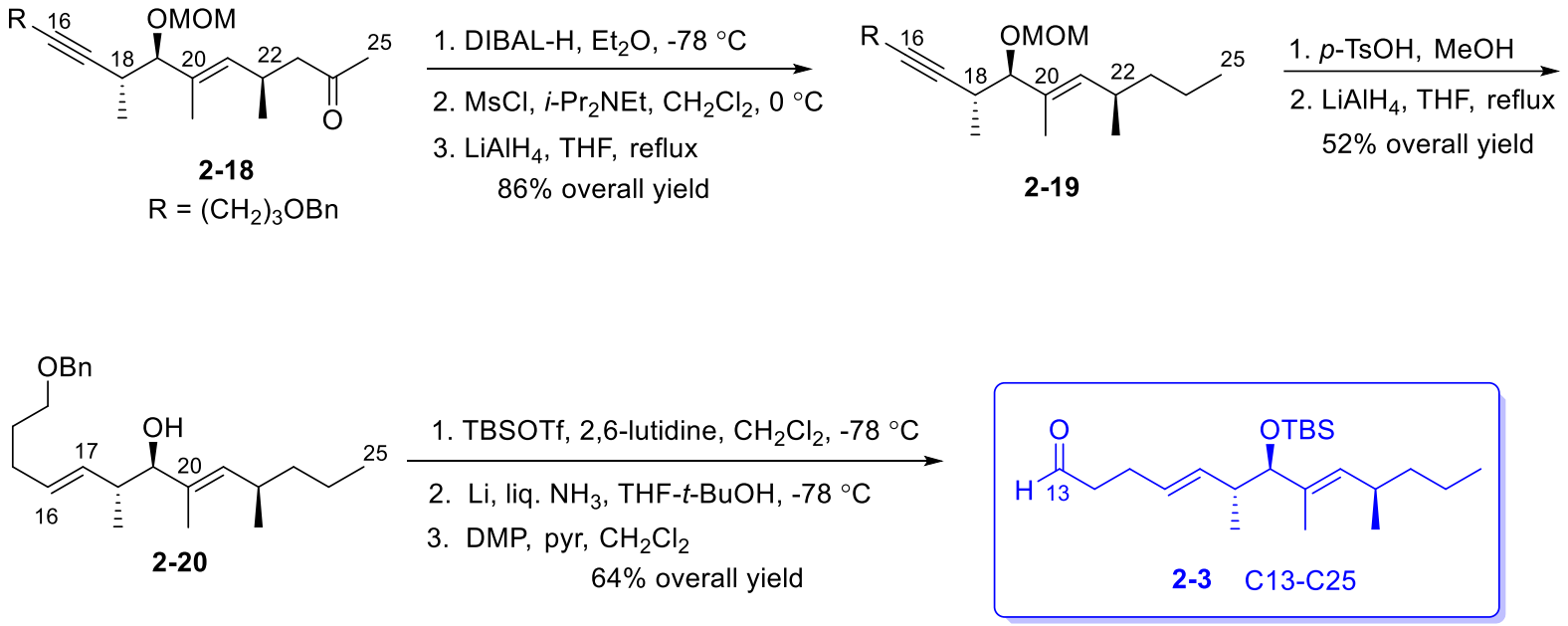
Claisen-Ireland rearrangement





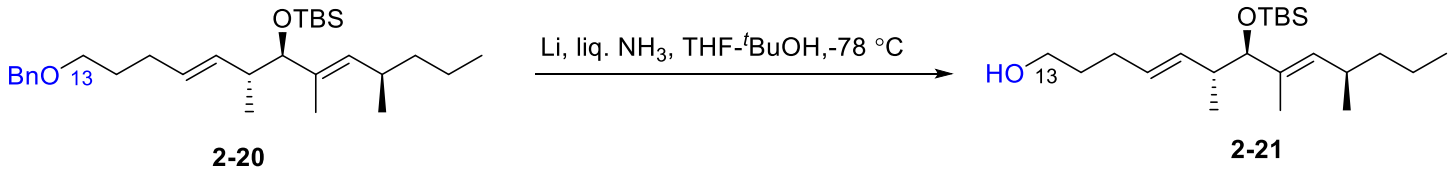
Total synthesis of zincophorin methyl ester

- Synthesis of the C13-C25 Subunit of Zincophorin



J. Cossy, *et al*. *Org.Lett.* **2003**, *5*, 4037.

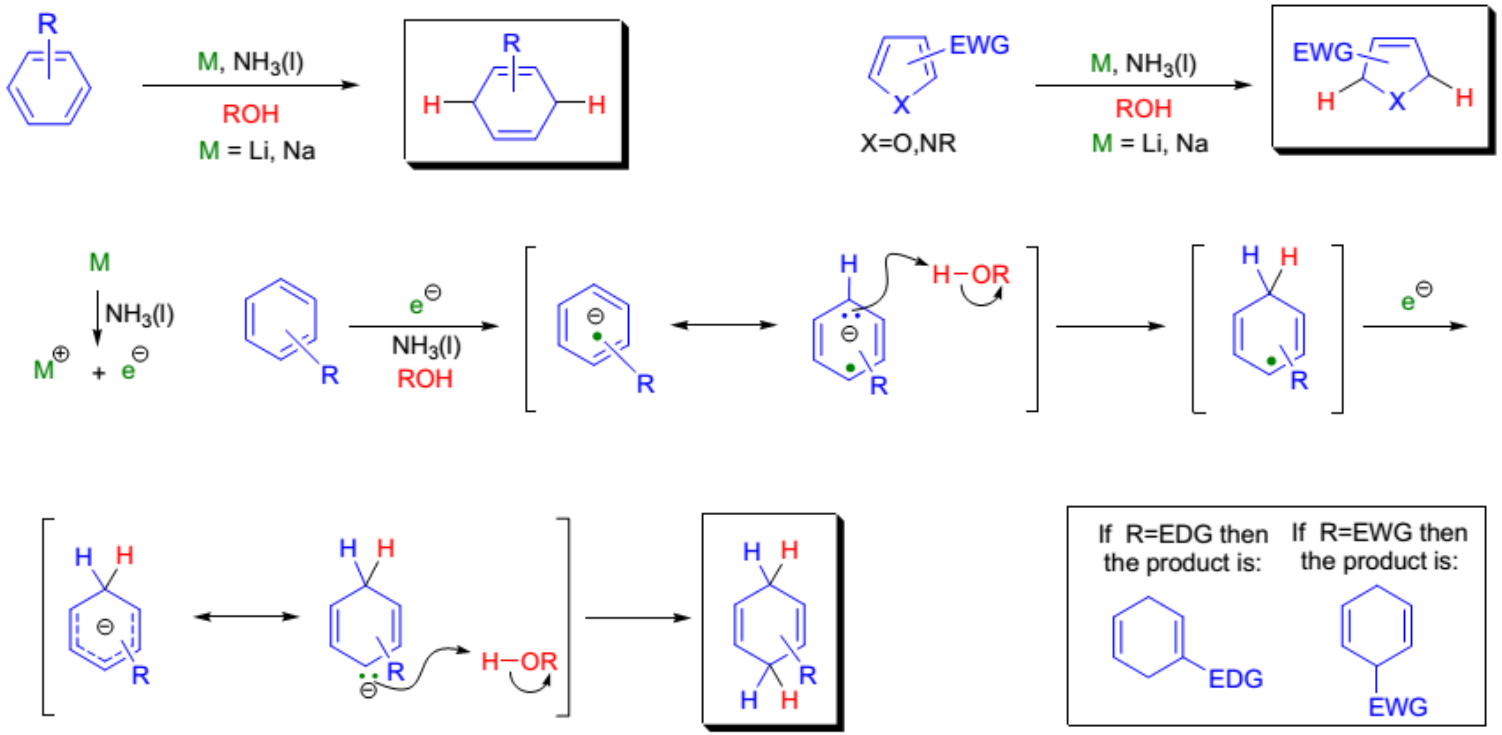
Total synthesis of zincophorin methyl ester



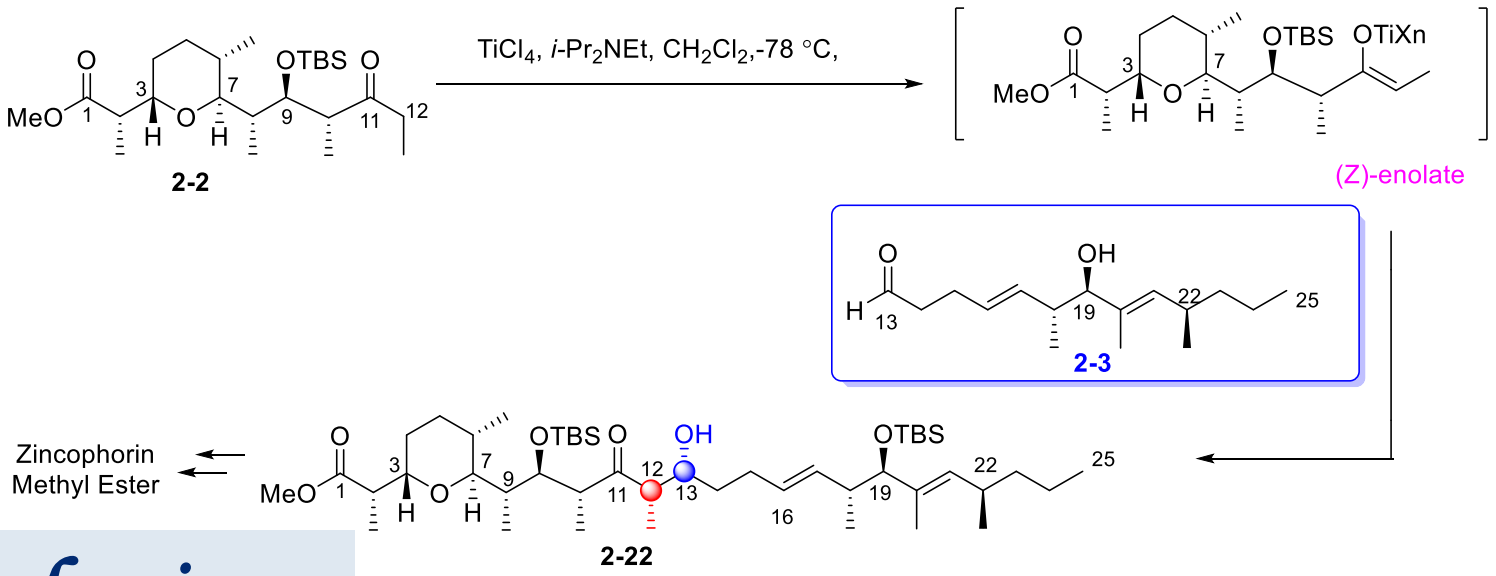
2-20 **2-21**

Mechanism

Birch reduction

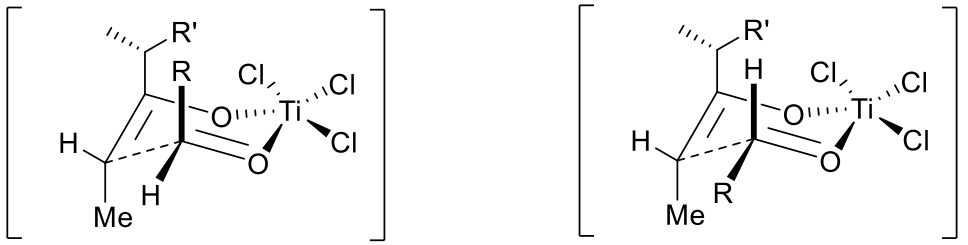


Total synthesis of zincophorin methyl ester



Mechanism

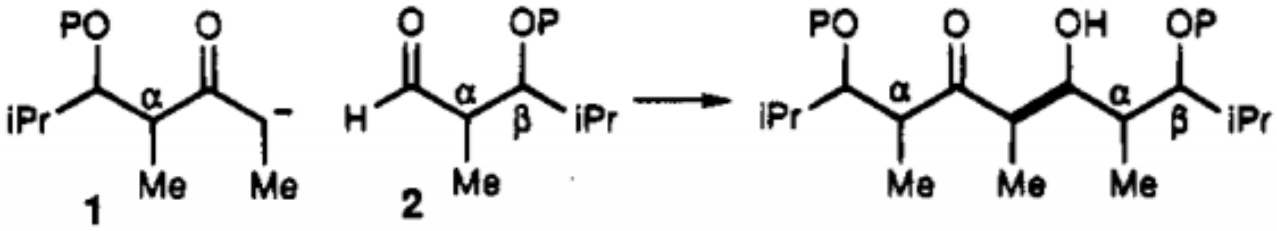
Aldol reaction



Total synthesis of zincophorin methyl ester

Mechanism

Double Stereodifferentiating Options: Three Centers

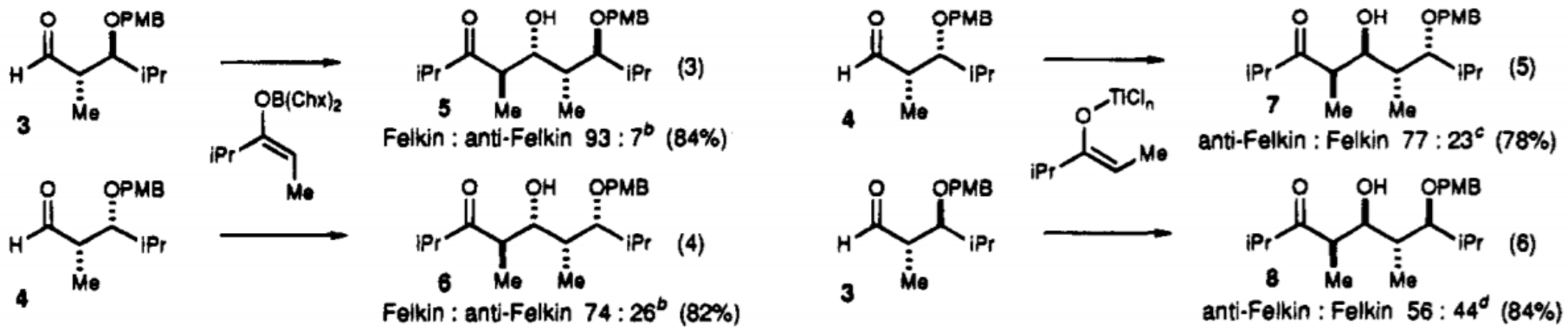


Double Stereodifferentiating Cases		Enolate α	Aldehyde α	Aldehyde β
A	Fully matched reaction	(+)	(+)	(+)
B	Partially matched reaction	(+)	(+)	(−)
C	Partially matched reaction	(+)	(−)	(+)
D	Fully mismatched reaction	(+)	(−)	(−)

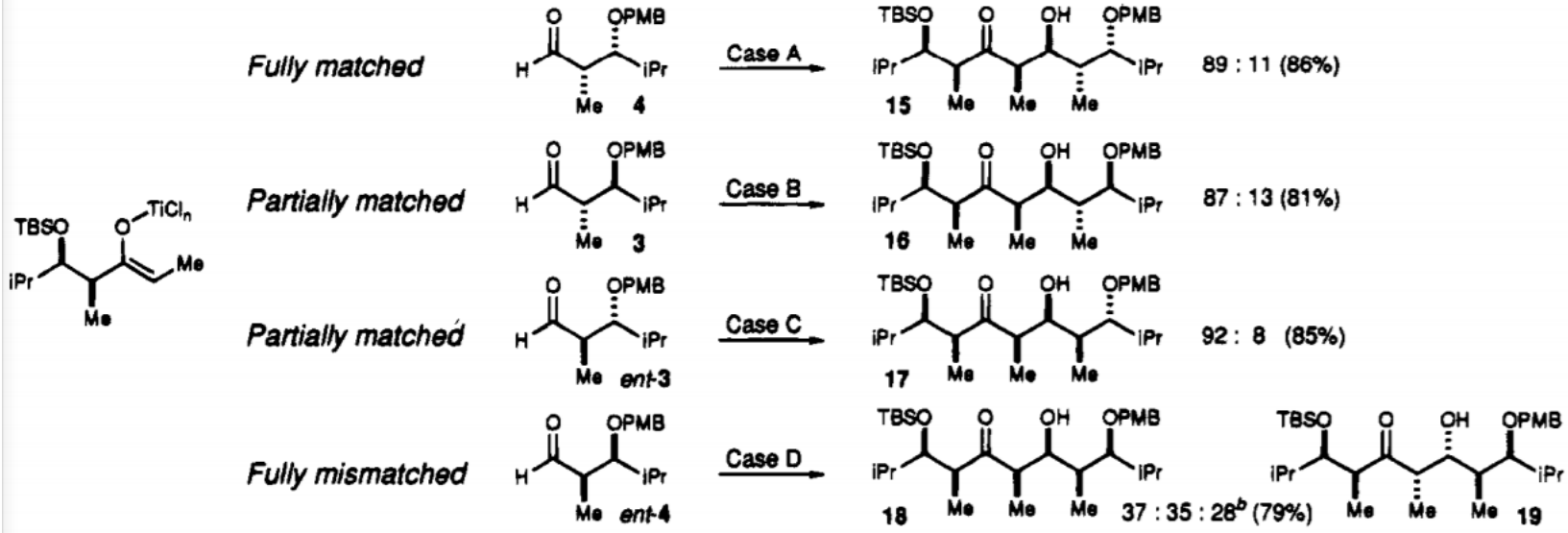
D. Evans, et al. *J. Am. Chem. Soc.* **1995**, 117, 9073-9074

Total synthesis of zincophorin methyl ester

Diastereoselective Aldol Reactions between Chiral Aldehydes and Achiral Enolates



[a] Double Stereodifferentiating *Syn* Aldol Reactions between Chiral Reaction Partners

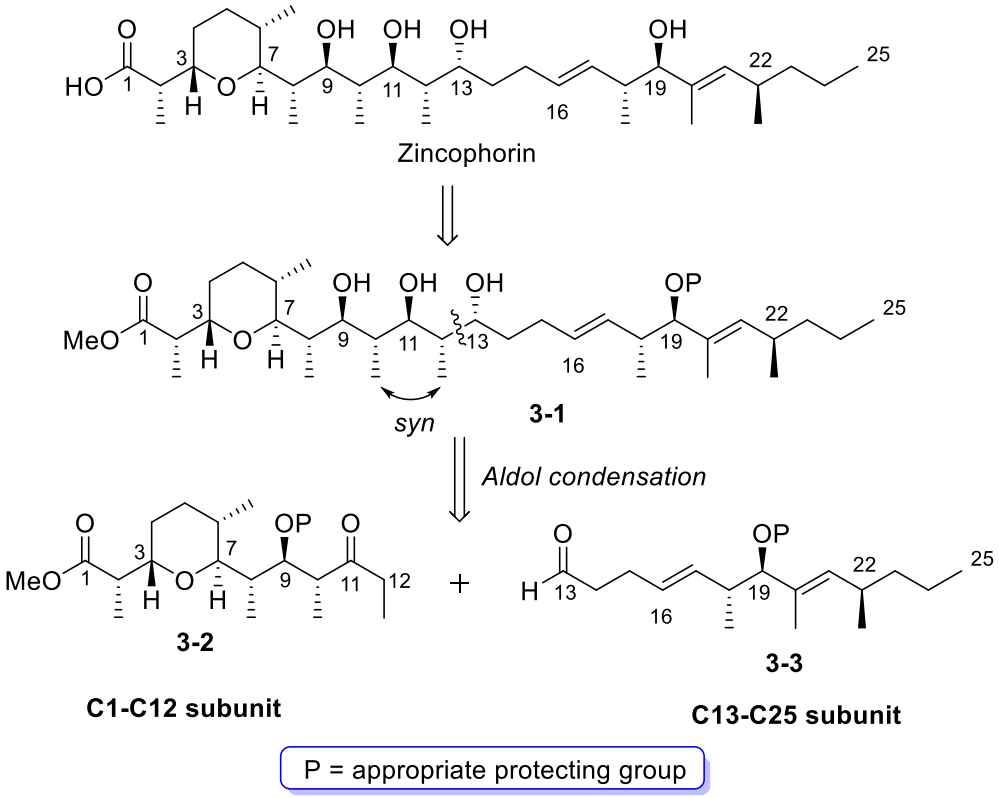


D. Evans, et al. *J. Am. Chem. Soc.* **1995**, 117, 9073-9074

Total synthesis of zincophorin methyl ester

III. Cossy: *J. Org. Chem.* **2004**, *69*, 4626

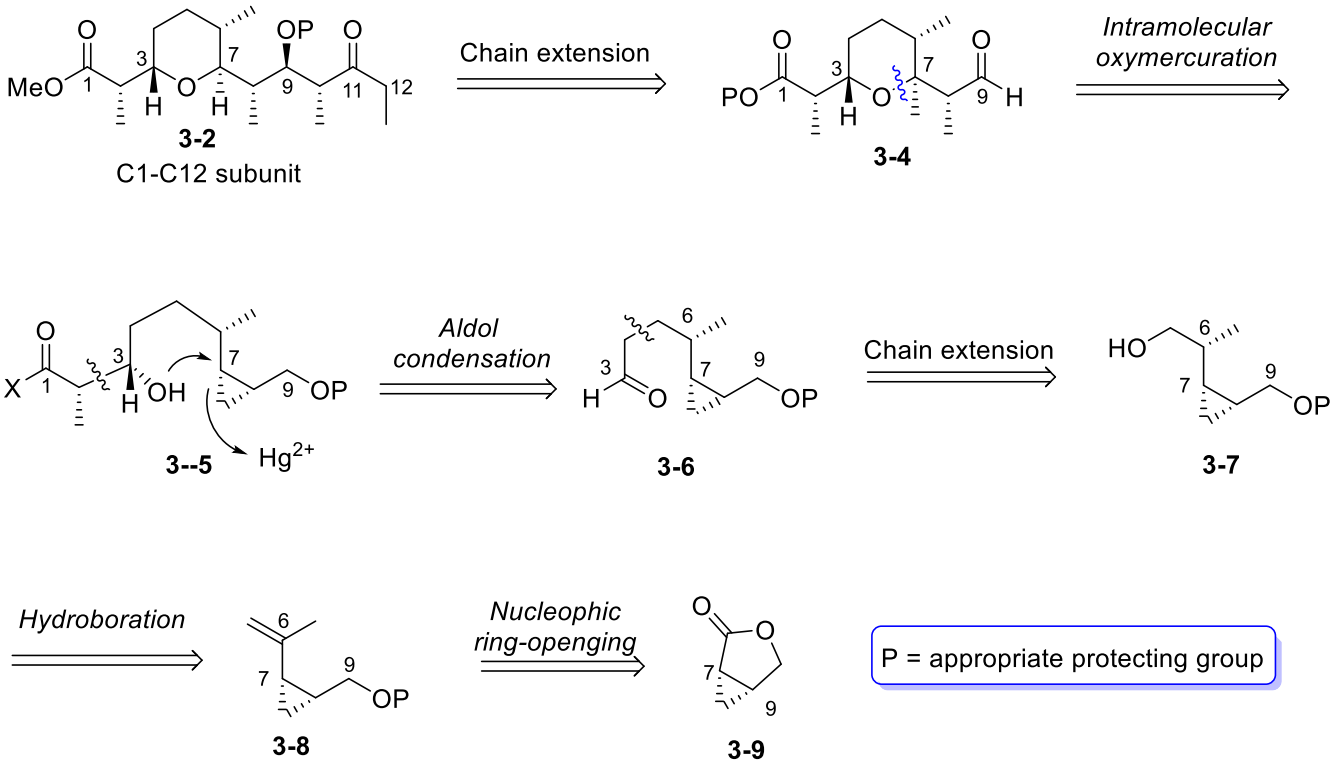
- Retrosynthetic Analysis



J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

Total synthesis of zincophorin methyl ester

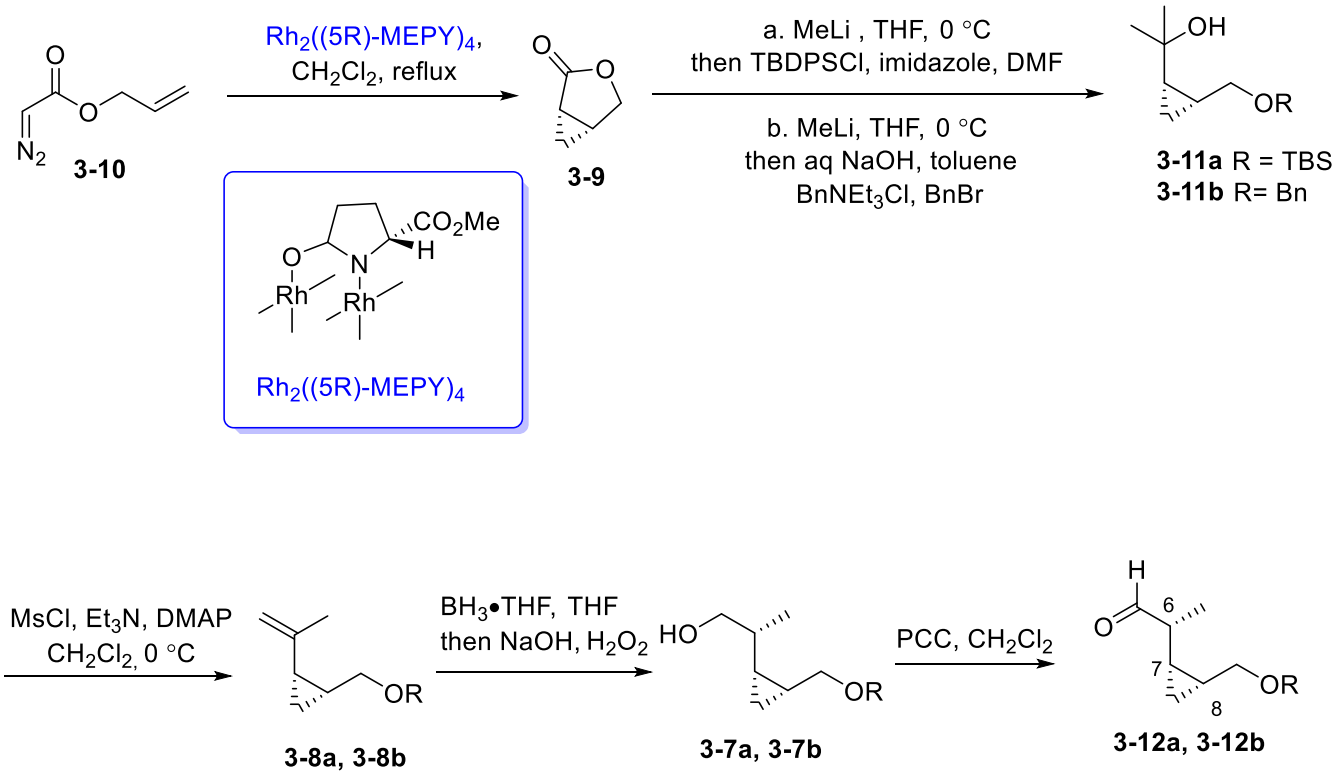
- Retrosynthetic Analysis of the C1-C12 Subunit



J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

Total synthesis of zincophorin methyl ester

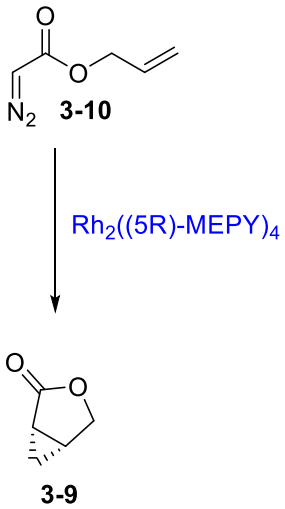
- Synthesis of the aldehyde **3-12**

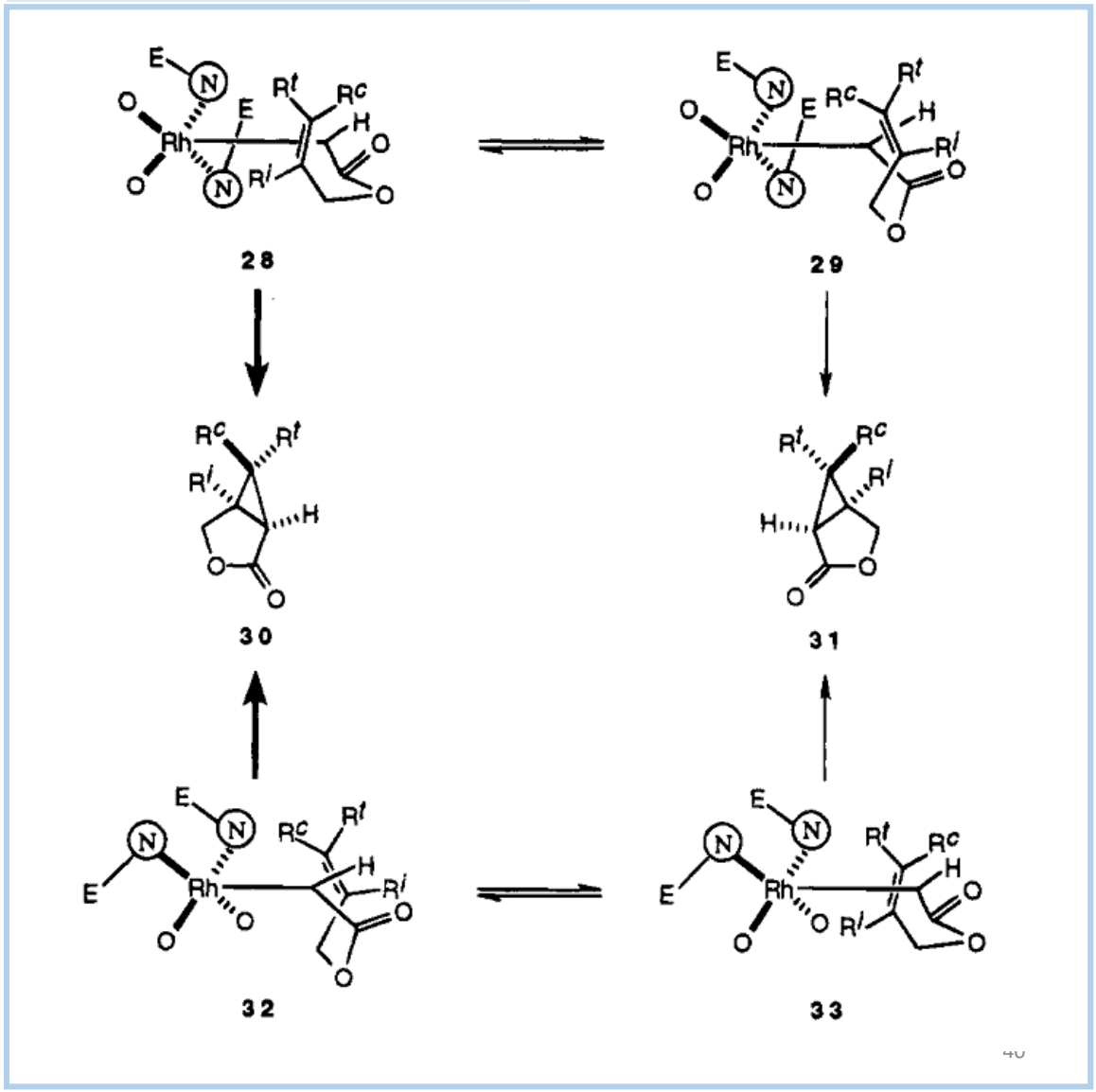


J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

Total synthesis of zincophorin methyl ester

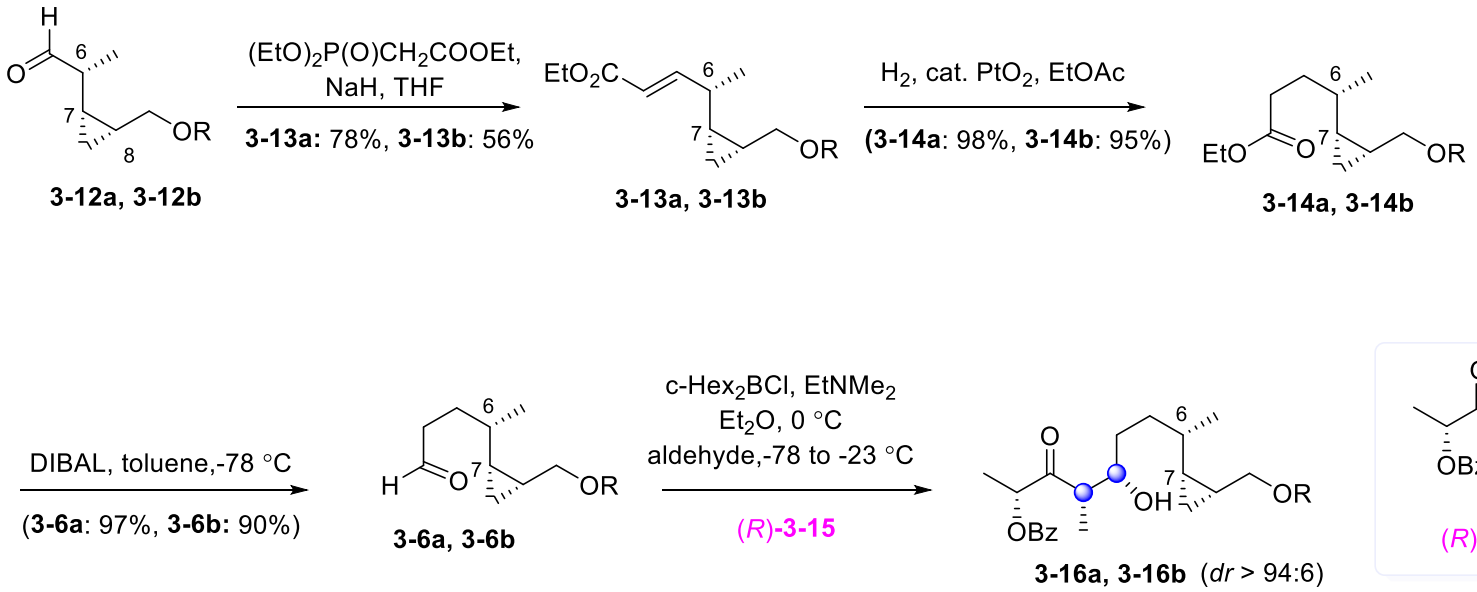
Mechanism





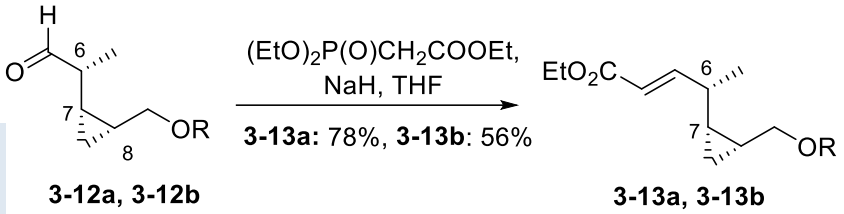
Total synthesis of zincophorin methyl ester

- Synthesis of the cyclopropanemethanol **3-16**



J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

Total synthesis of zincophorin methyl ester



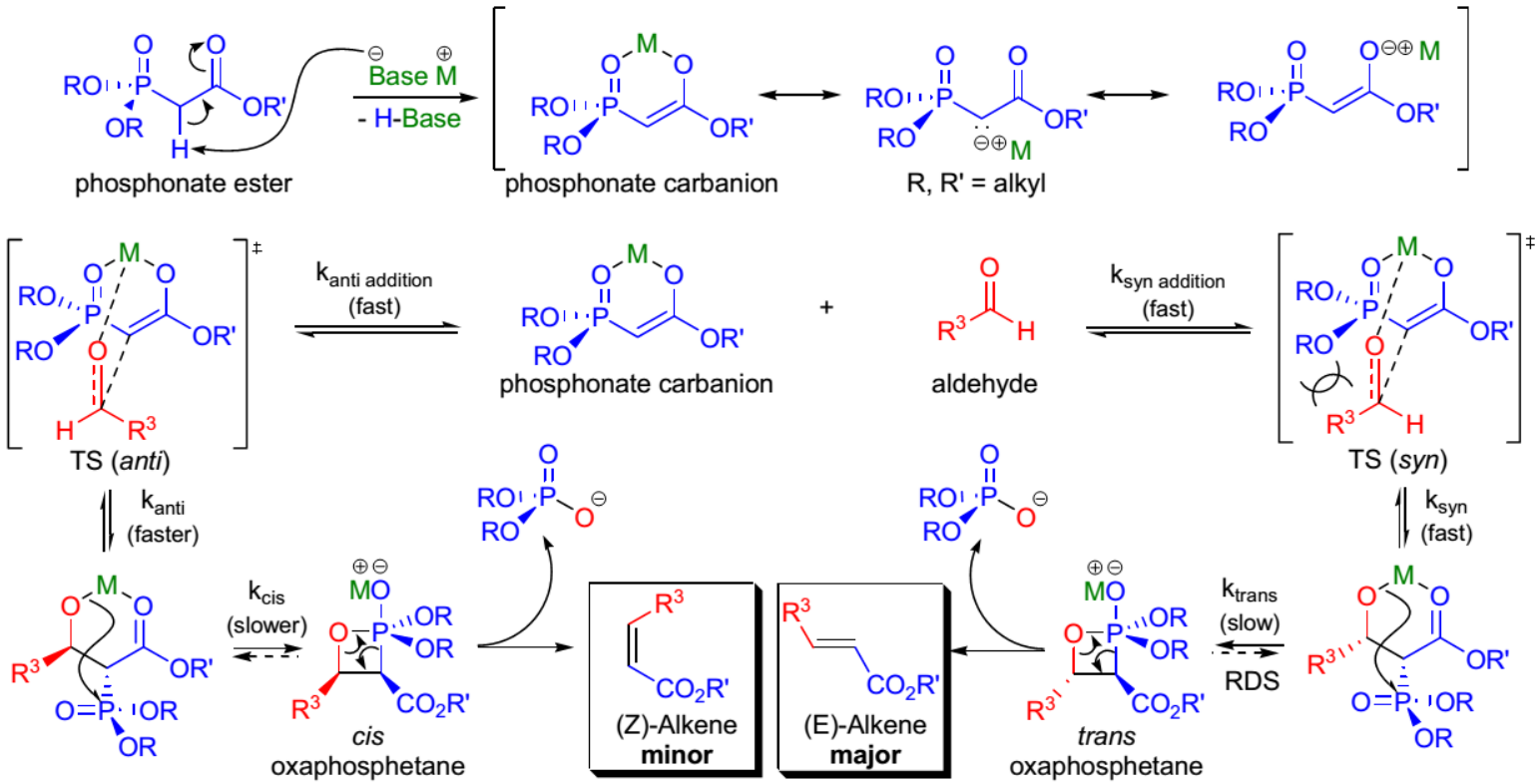
3-12a, 3-12b

3-13a, 3-13b

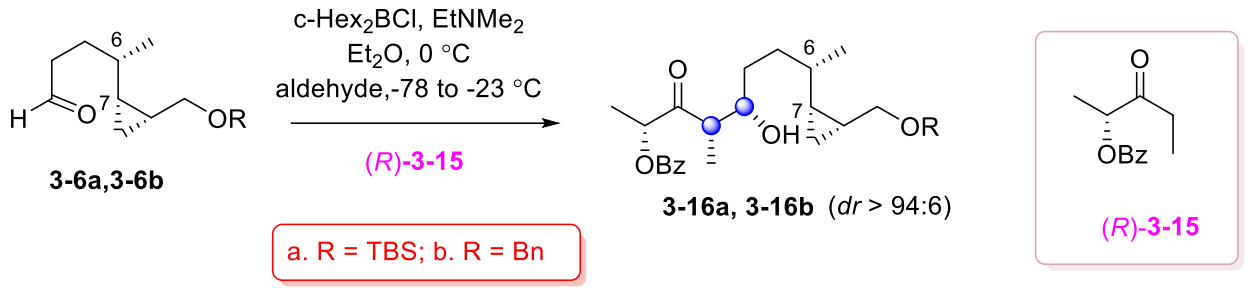
Mechanism

Mechanism: [47,9,48,11]

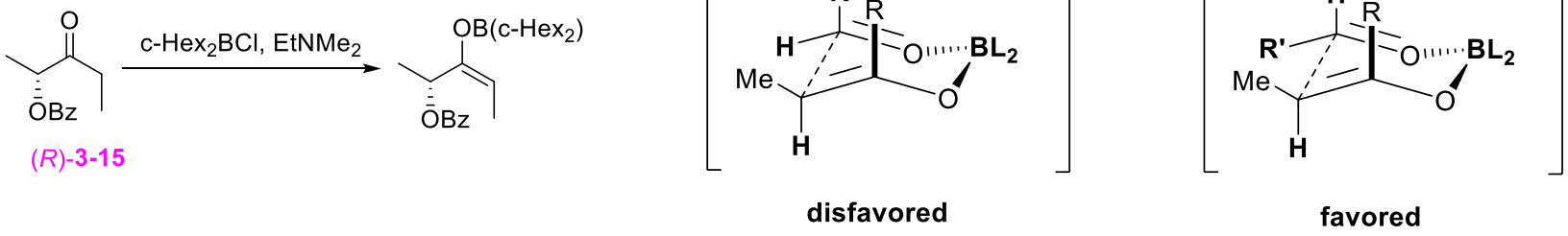
HWE olefination



Total synthesis of zincophorin methyl ester

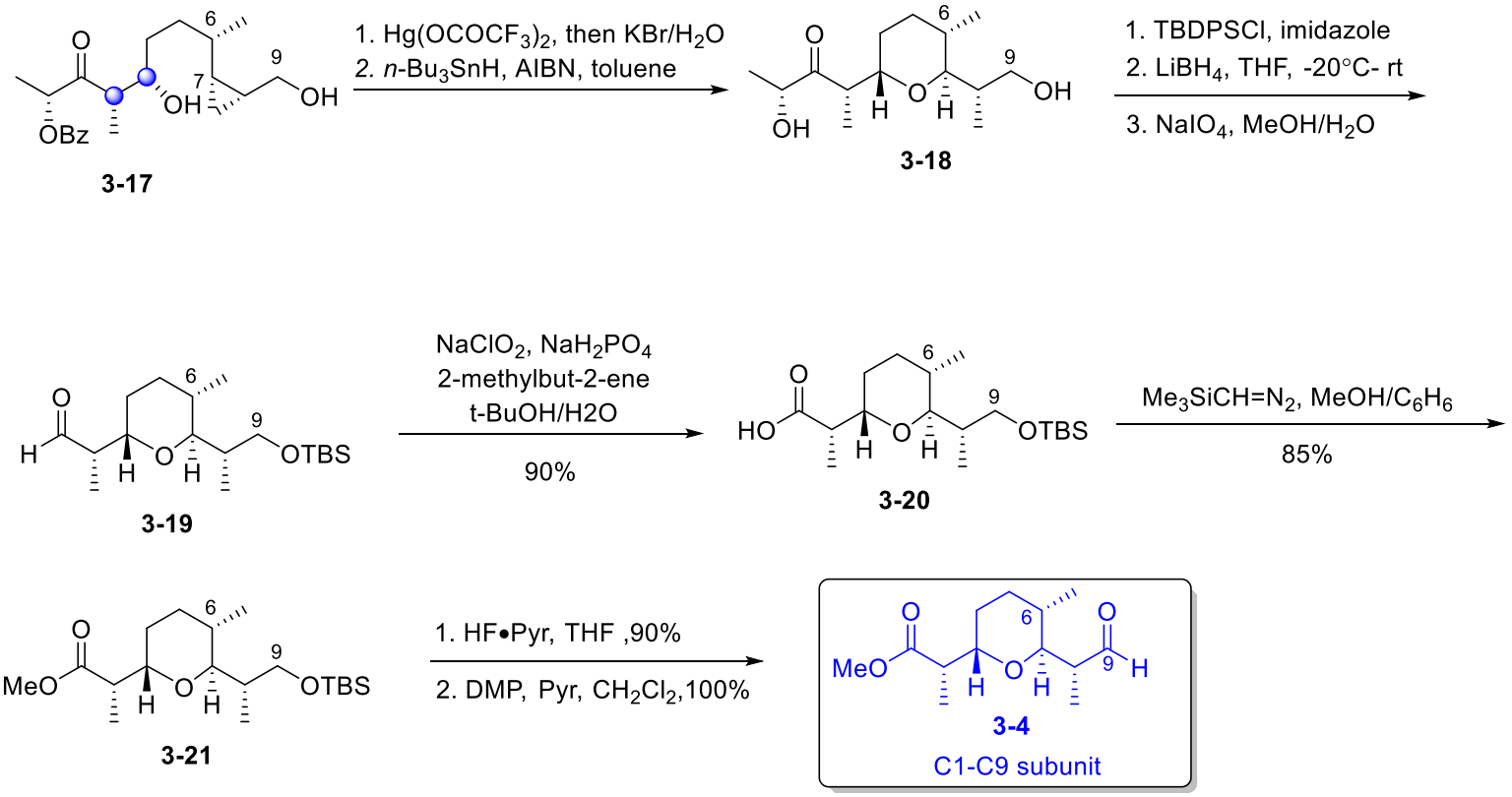


Mechanism



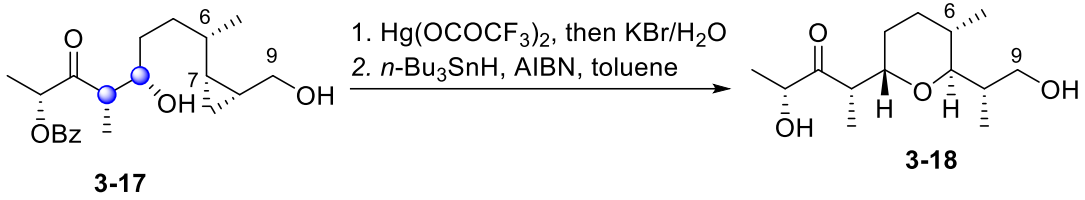
Total synthesis of zincophorin methyl ester

- Synthesis of the C1-C9 Subunit of Zincophorin

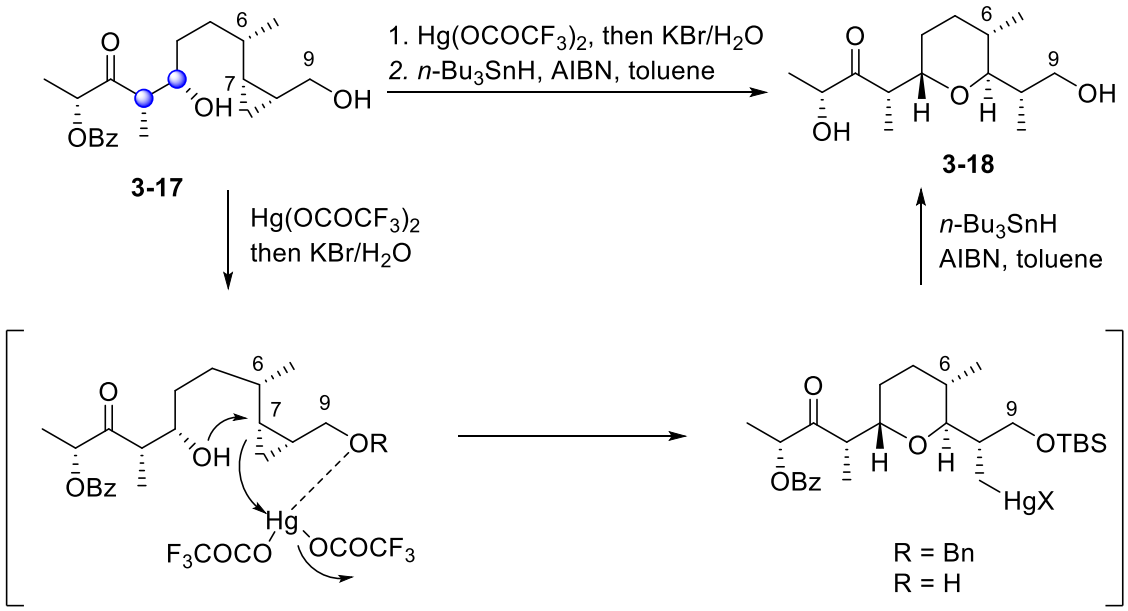


J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

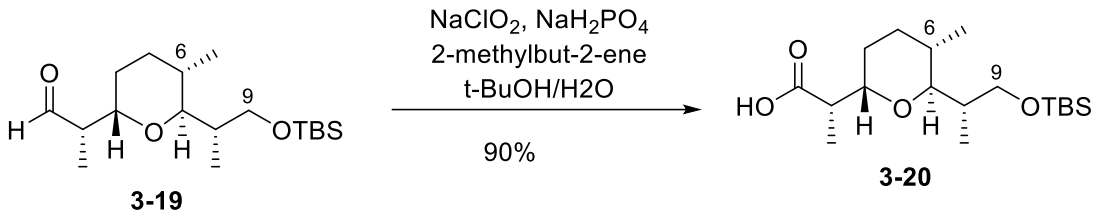
Total synthesis of zincophorin methyl ester



Mechanism



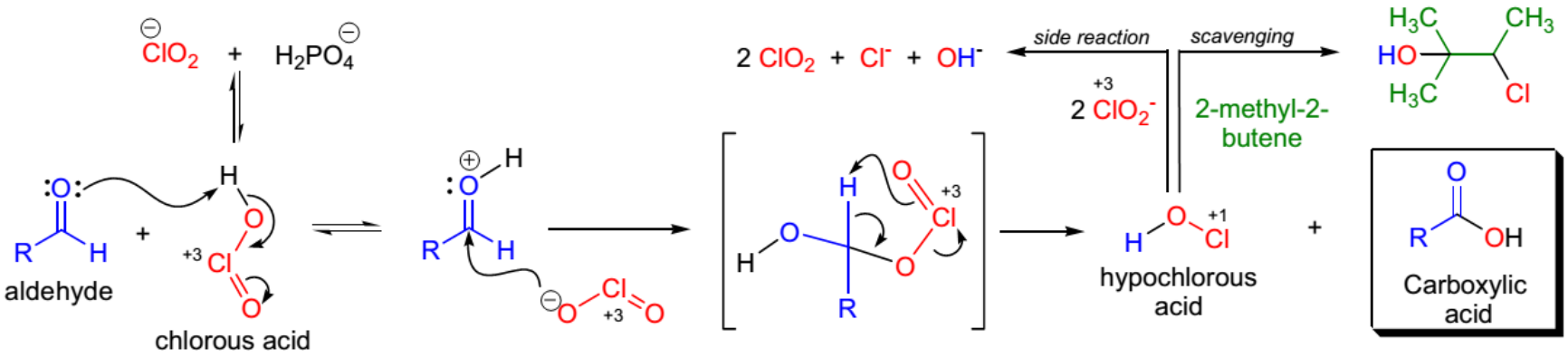
Total synthesis of zincophorin methyl ester



Mechanism

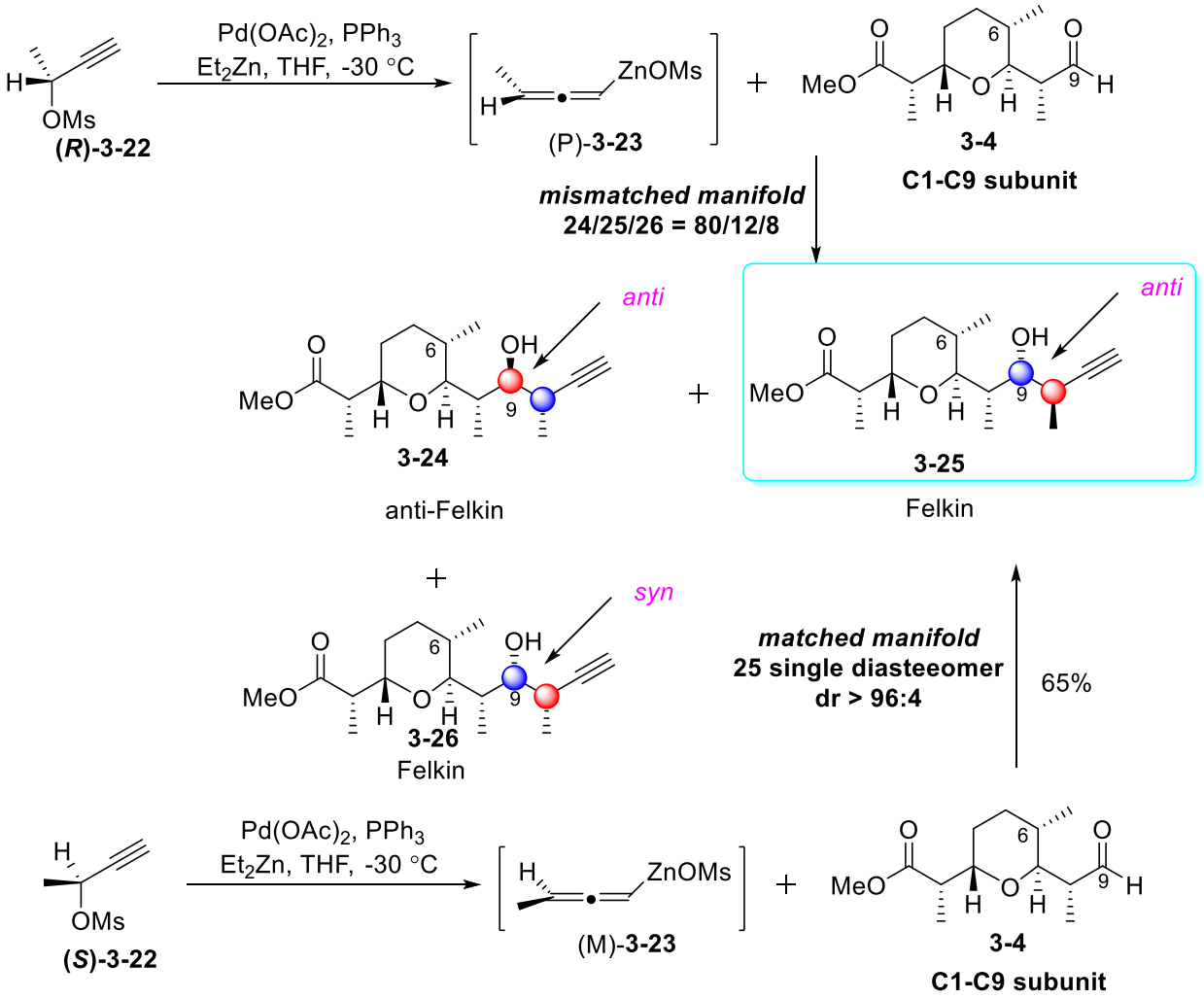
Pinnick oxidation

Mechanism: [10,6]



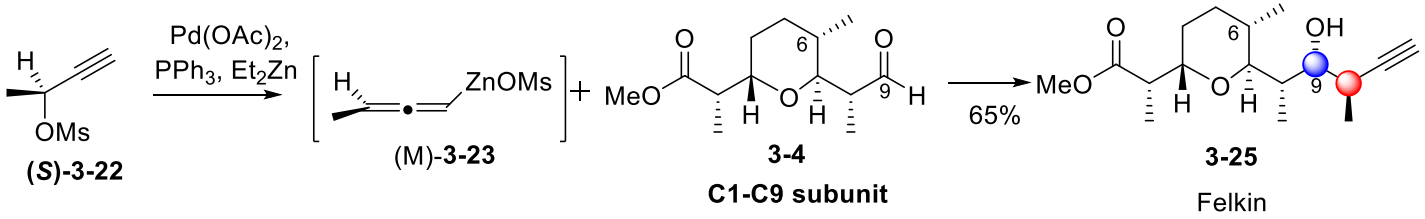
Total synthesis of zincophorin methyl ester

- Synthesis of the compound **3-25**



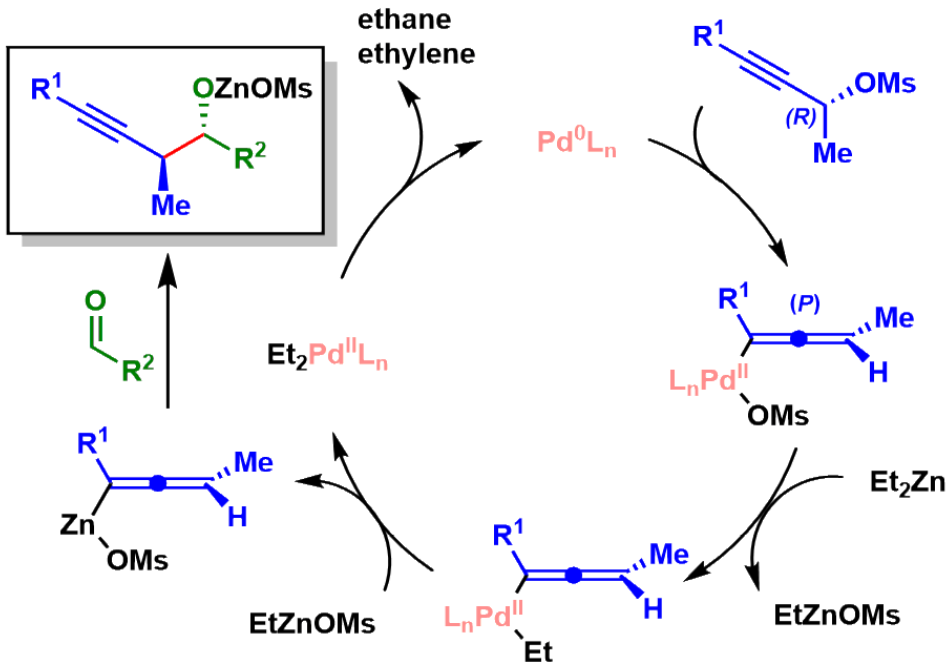
J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

Total synthesis of zincophorin methyl ester



Mechanism

Marshall propargylation



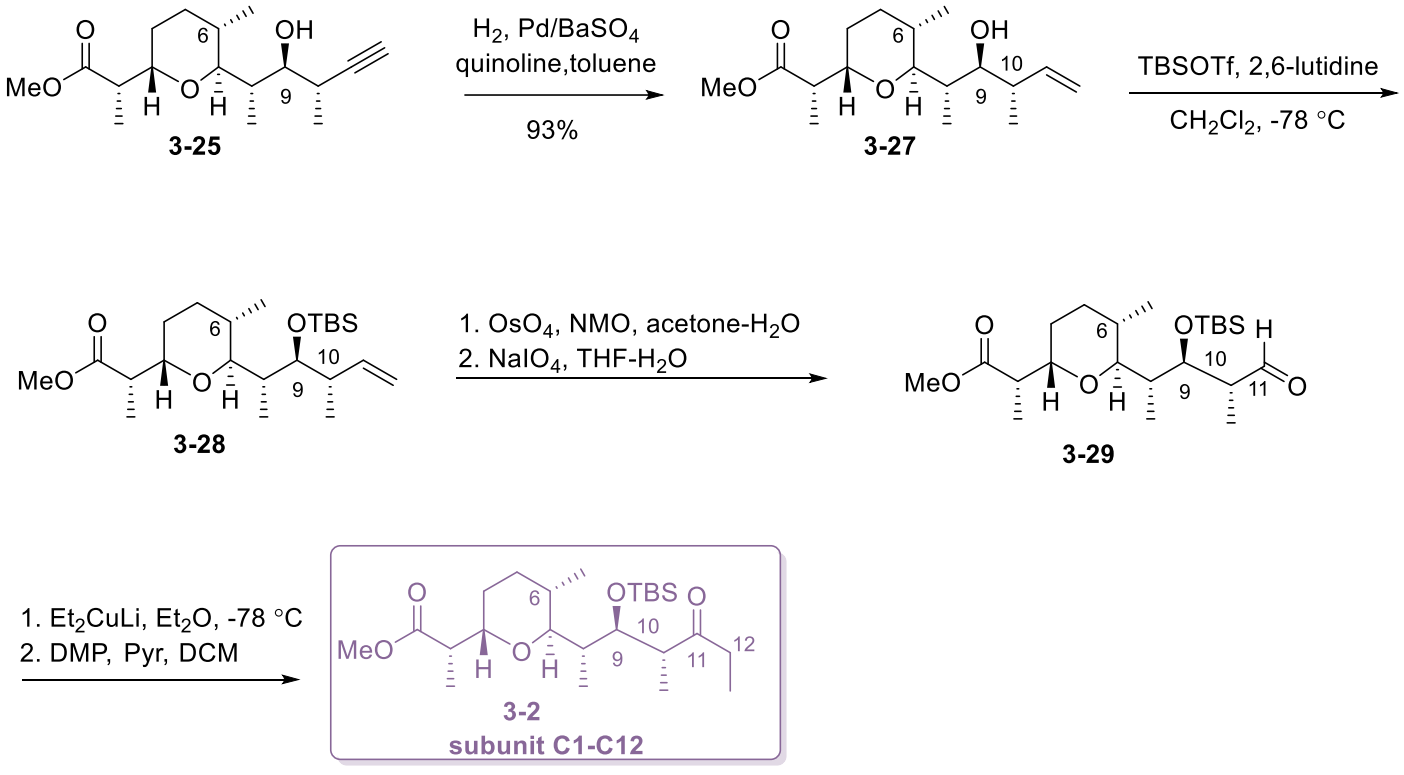
Et_2Zn is commomly utilized in traditional Marshall propargylation;

While, InI can also be employed in Marshall propargylation;

J. A. Marshall. et. al. *J. Org. Chem*. **2006**, *71*, 4840
J. A. Marshall. et. al. *J. Org. Chem*. **1998**, *63*, 3812

Total synthesis of zincophorin methyl ester

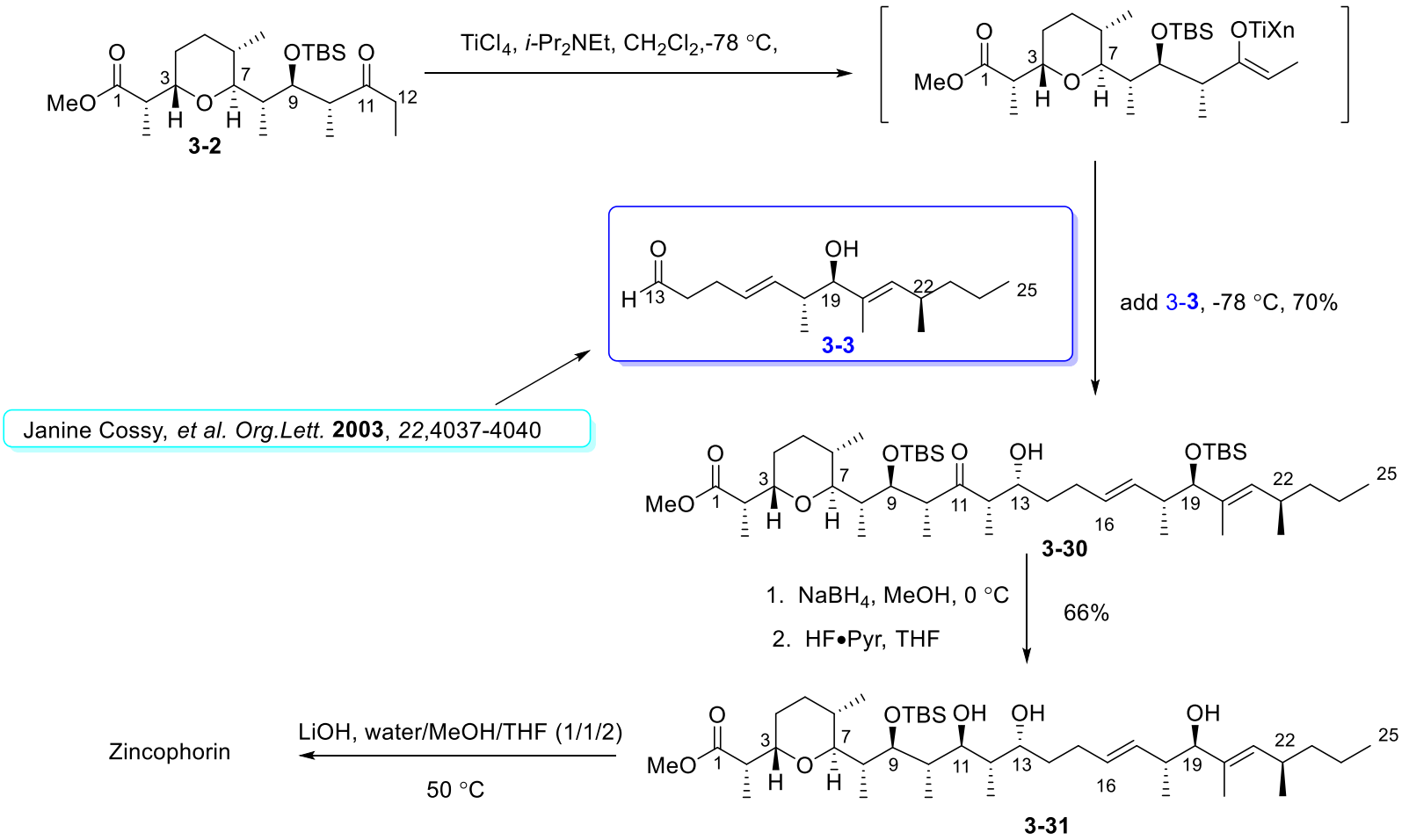
- Synthesis of the C1-C12 Subunit of Zincophorin



J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

Total synthesis of zincophorin methyl ester

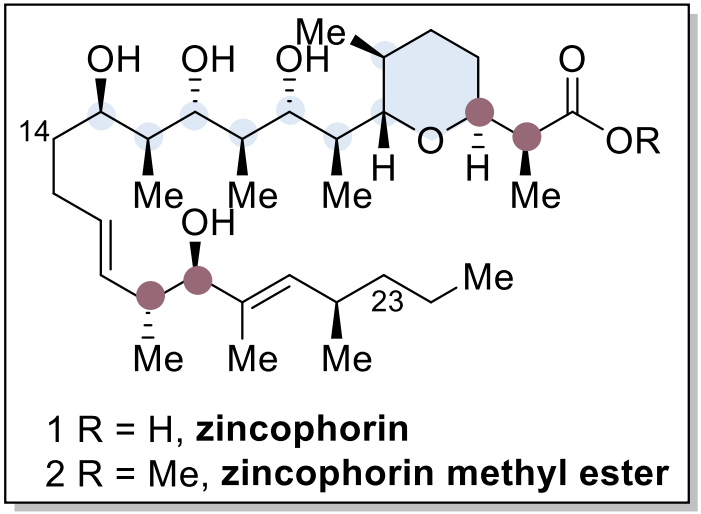
- Coupling of two fragments and synthesis of Zincophorin

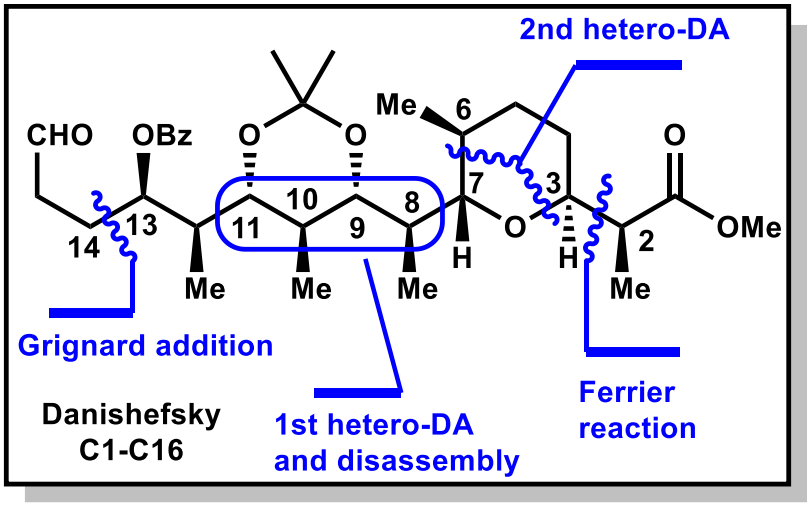


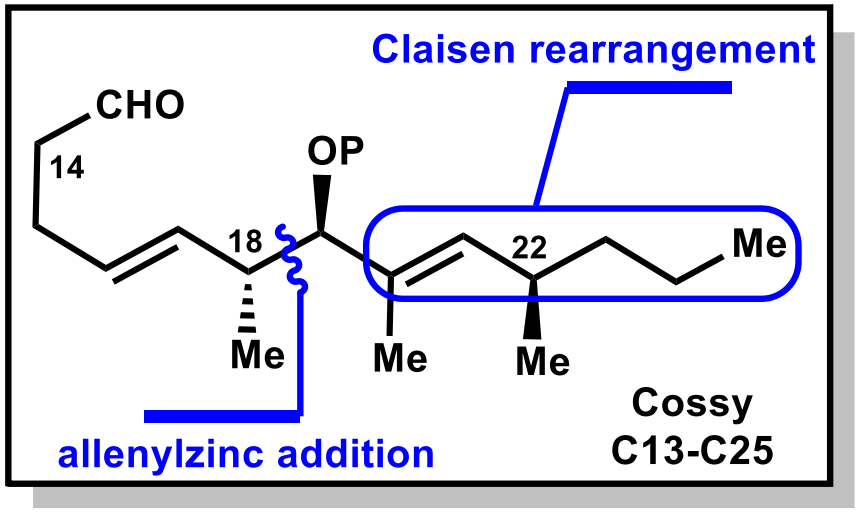
30 steps LLS

J. Cossy, *et al. J. Org. Chem.* **2004**, *69*, 4626.

Summary


Me
OH
OH
OH
O
14
O
OR
H
H
Me
Me
Me
Me
OH
Me
23
Me
Me
Me
1 R = H, **zincophorin**
2 R = Me, **zincophorin methyl ester**


2nd hetero-DA
CHO
OBz
O
O
Me
6
7
3
O
O
OMe
10
8
11
9
14
13
H
H
2
Me
Me
Me
Me
Grignard addition
Danishefsky
C1-C16
1st hetero-DA
and disassembly
Ferrier
reaction


Claisen rearrangement
CHO
OP
14
18
22
Me
Me
Me
Me
allenylzinc addition
Cossy
C13-C25

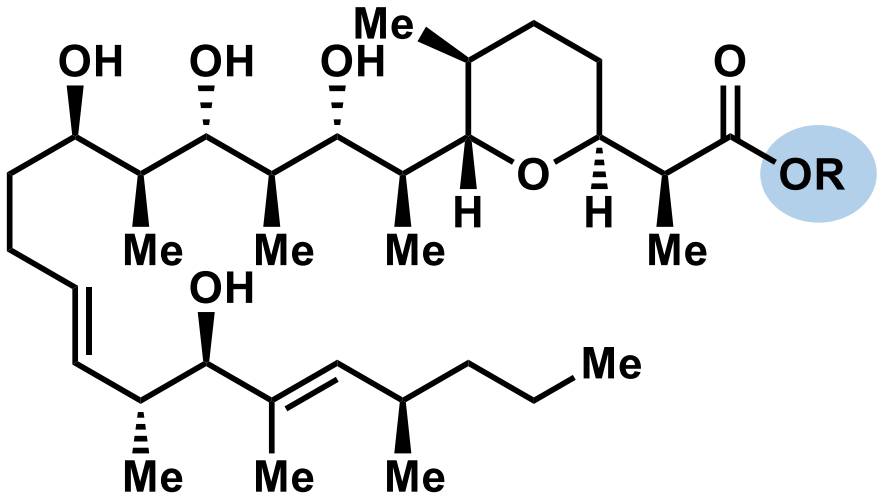
Acknowledgement

- *Prof.* Tao Ye, *Dr.* Yian Guo;
- All my labmates in F211;
- All professors and faculties in SCBB

Thank you

for your kind attention

Classics in the synthesis of Zincophorin and its methyl ester



1 R = H, zincophorin
2 R = Me, zincophorin methyl ester

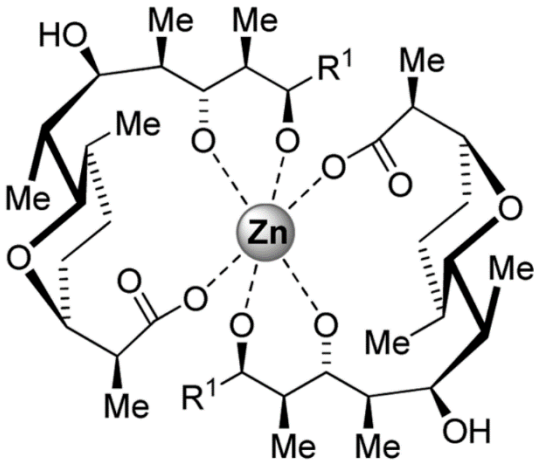
Reporter: Jie Li

Supervisors: *Prof.* Tao Ye, *Dr.* Yi-an Guo

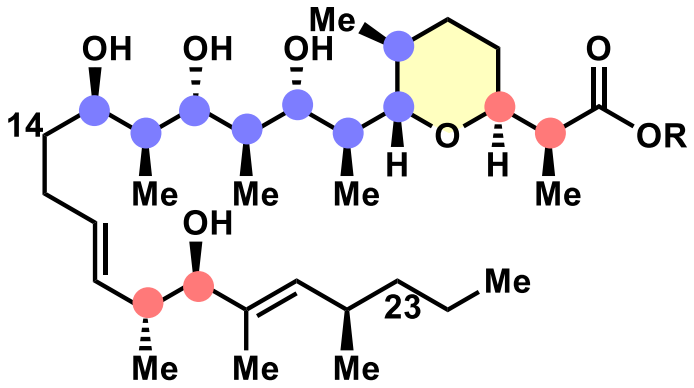
September 14th, 2020

Contents

Review-Features of Zincophorin



R^1 = C14-C25



1 R = H, zincophorin
2 R = Me, zincophorin methyl ester

Isolation:

- Seperated from strains of ***Streptomyces* griseus**
- In 1984, Grafe *et al*. and Poyser *et al.* reported the isolation.

Biological activities:

- **High affinity for divalent cations**, it was given the name of zincophorin.
- Against Gram-positive bacteria and Clostridium coelchii
- Its salts exhibited anticoccidial activity against Eimeria tenella W/CAM
- Methyl ester has strong inhibitory properties against influenza WSN/virus

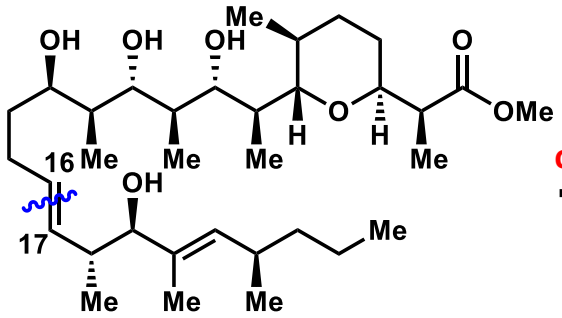
Structural Features:

- A challenging **C8–C12 all-*anti* stereopentad** embedded within the **C6–C13 tetrapropionate**, and the ***trans*-tetrahydropyran ring**
- **13 stereogenic centers** (8 contiguous stereocenters)

U. Grafe, *et al. J. Antibiot*., **1984**, *37*, 836.
J. P. Poyser, *et al*. *J. Antibiot*., **1984**, *37*, 1501.
U. Grafe, *Ger. Pat*., **1986**, *231*, 793.

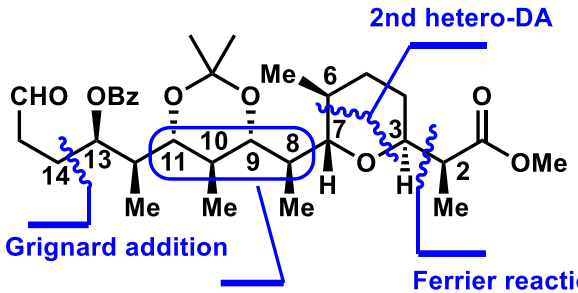
Review - Danishefsky

I. **Danishefsky:** *J. Am. Chem. Soc.* **1987**, *109*, 1572 (**the first total synthesis**)

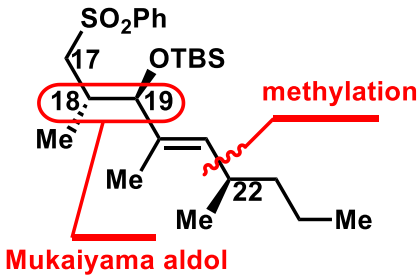


zincophorin methyl ester

Julia olefination

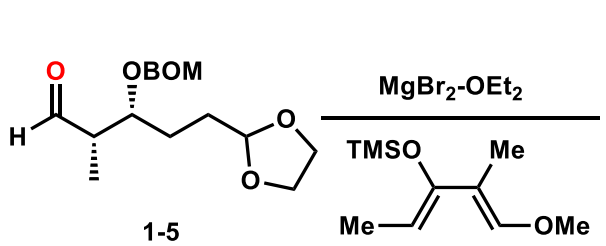


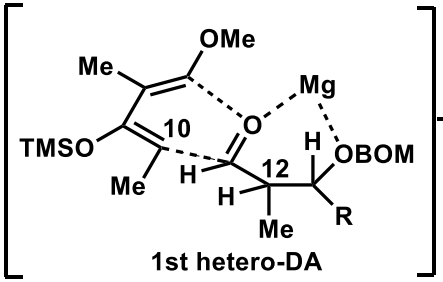
C1-C16

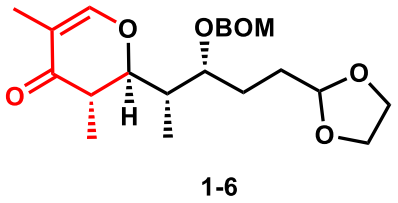


C17-C25

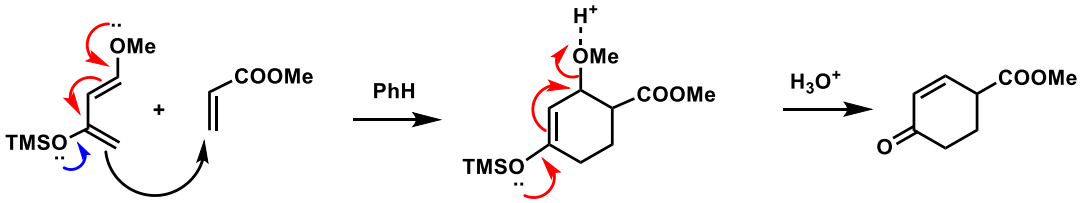
Key reaction： 1st hetero-DA







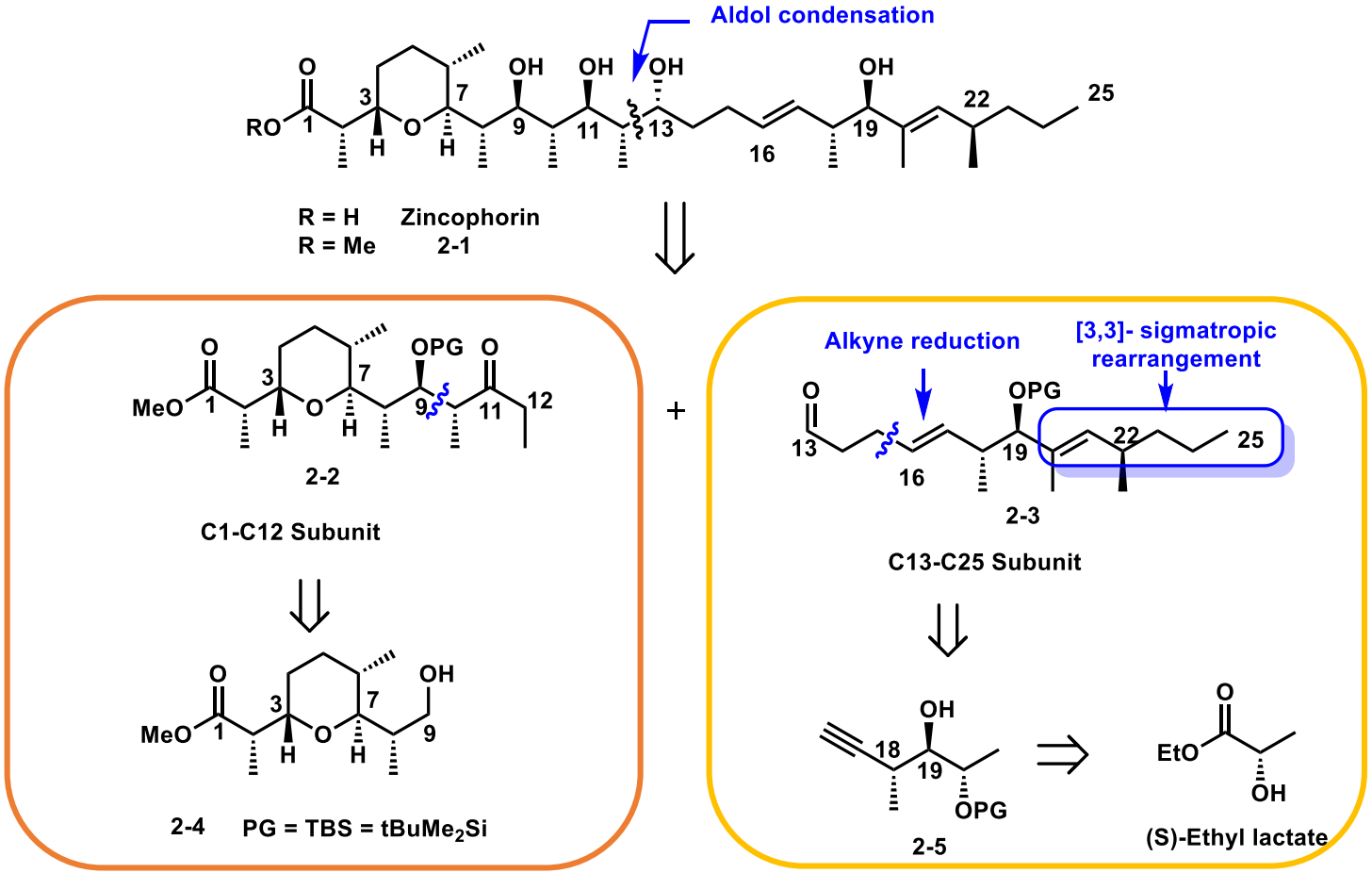
1-6



Review-Cossy

II. **Cossy**: *Org. Lett.* **2003**, *5*, 4037

III. **Cossy**: *J. Org. Chem.* **2004**, *69*, 4626

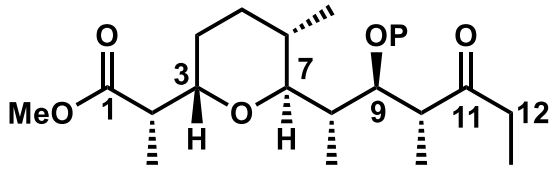


J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

J. Cossy, *et al*. *Org.Lett.* **2003**, *5*, 4037.

Review-Cossy

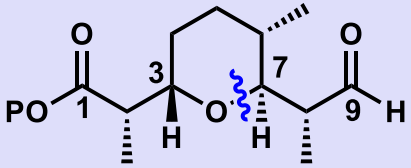
Retrosynthetic Analysis of the C1-C12 Subunit



3-2

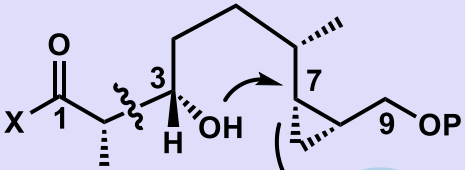
C1-C12 subunit

Chain extension



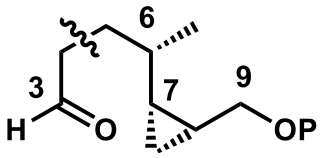
3-4

Intramolecular oxymercuration



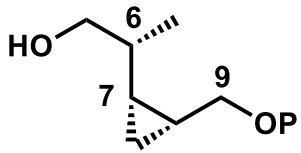
3--5

Aldol condensation



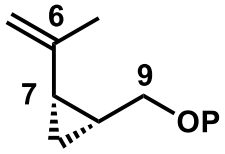
3-6

Chain extension



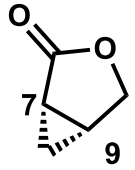
3-7

Hydroboration



3-8

Nucleophic ring-openging



3-9

P = appropriate protecting group

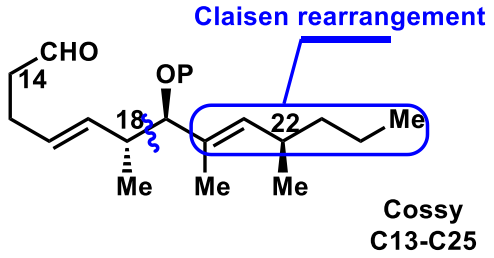
J. Cossy, *et al. J. Org. Chem.* **2004**, *69*, 4626.

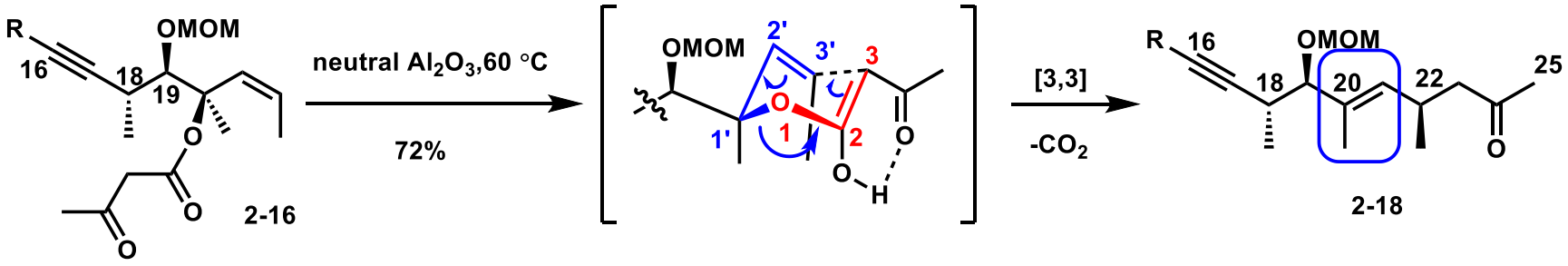
Review

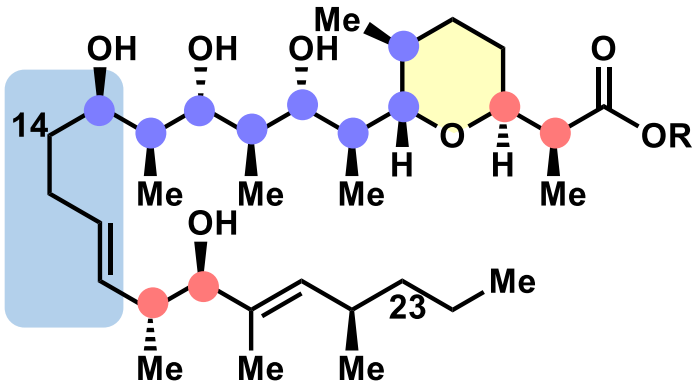
II. **Cossy**: *Org. Lett.* **2003**, *5*, 4037

III. **Cossy**: *J. Org. Chem.* **2004**, *69*, 4626

Key reaction：Claisen-Ireland rearrangement







1 R = H, zincophorin
2 R = Me, zincophorin methyl ester

Total Synthesis of Zincophorin and Its Methyl Ester

Danishefsky: *J. Am. Chem. Soc.* **1987**, *109*, 1572
J. Am. Chem. Soc. **1988**, *110*, 4368

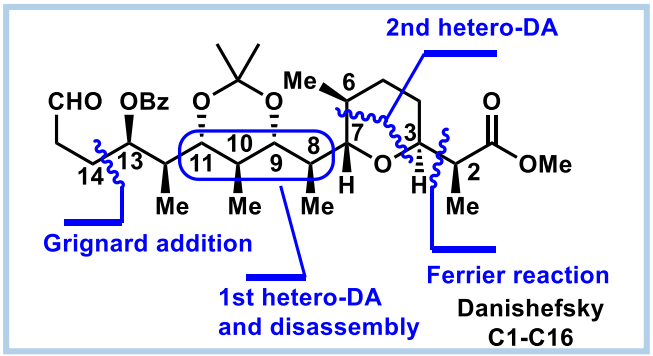
Cossy: *Org. Lett.* **2003**, *5*, 4037
J. Org. Chem. **2004**, *69*, 4626

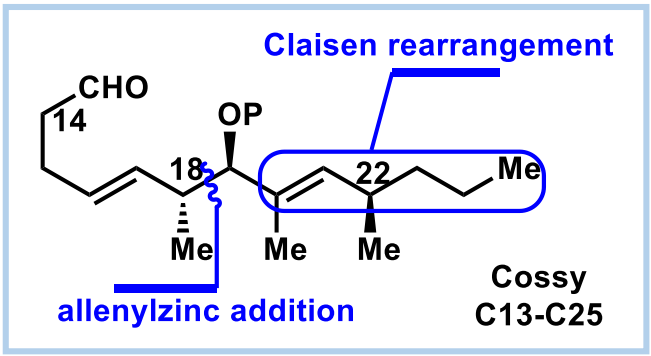
Miyashita: *Angew. Chem., Int. Ed.* **2004**, *43*, 4341

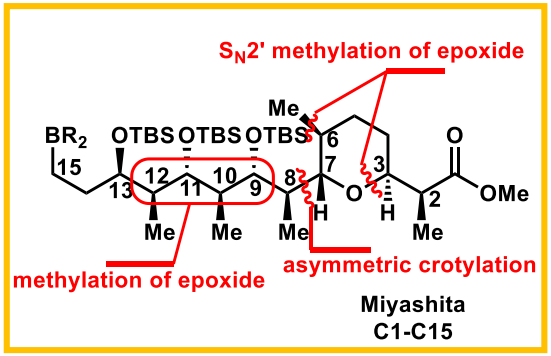
Leighton: *J. Am. Chem. Soc.* **2011**, *133*, 7308
J. Am. Chem. Soc. **2017**, *139*, 4568

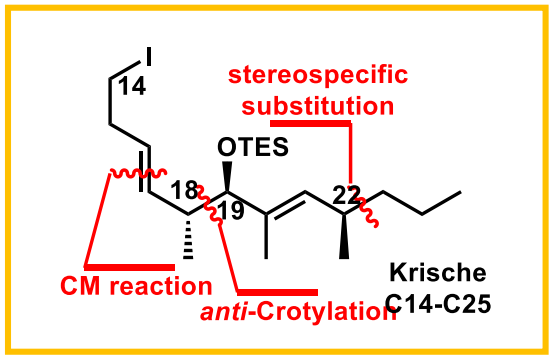
Krische: *J. Am. Chem. Soc.* **2015**, *137*, 8900

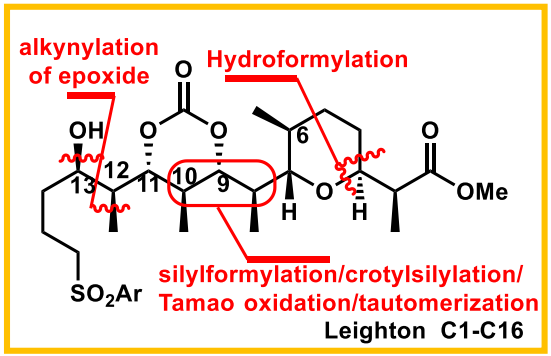
Guindon: *Tetrahedron* **2015**, *71*, 709







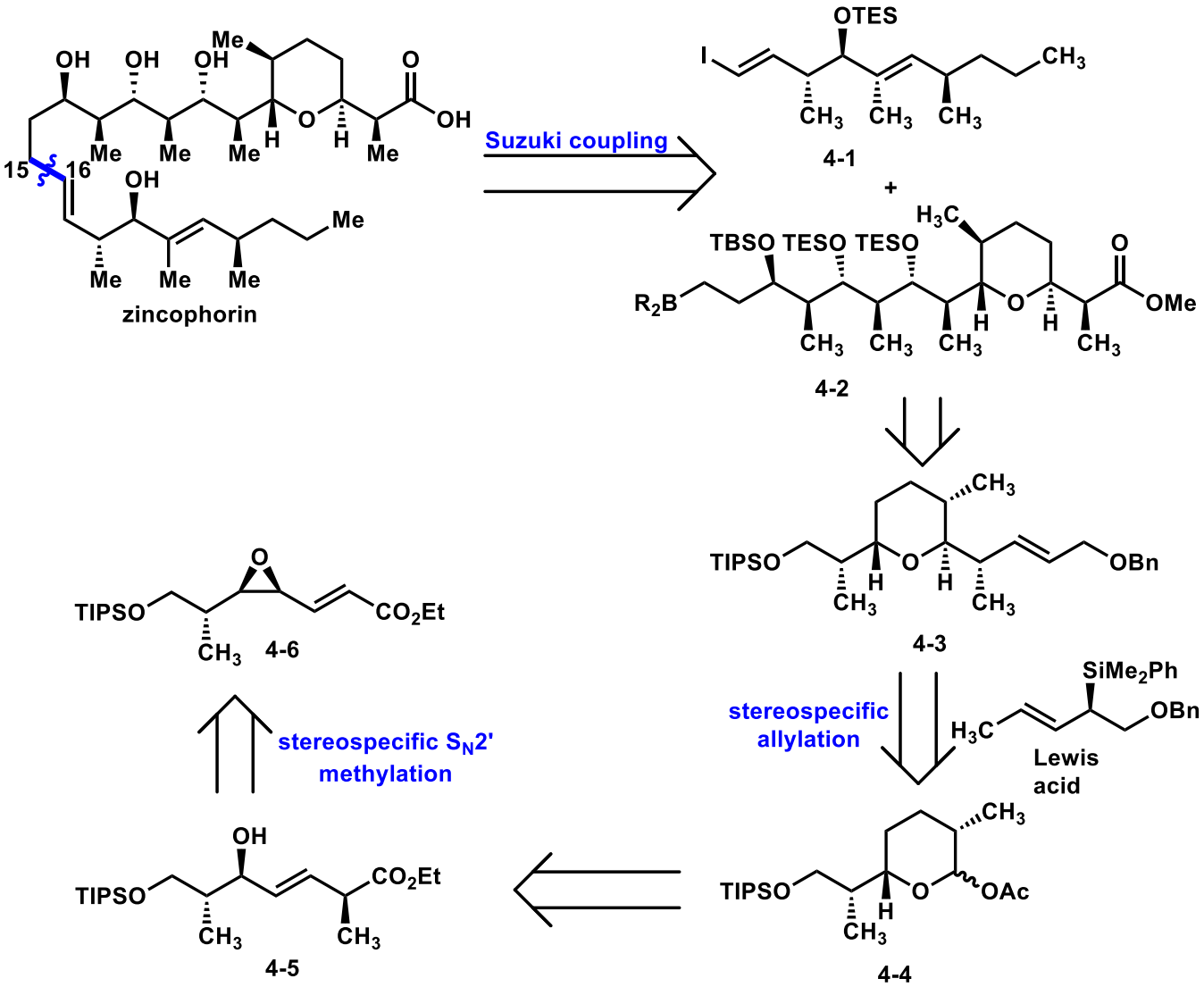




Total Synthesis of Zincophorin-Miyashita

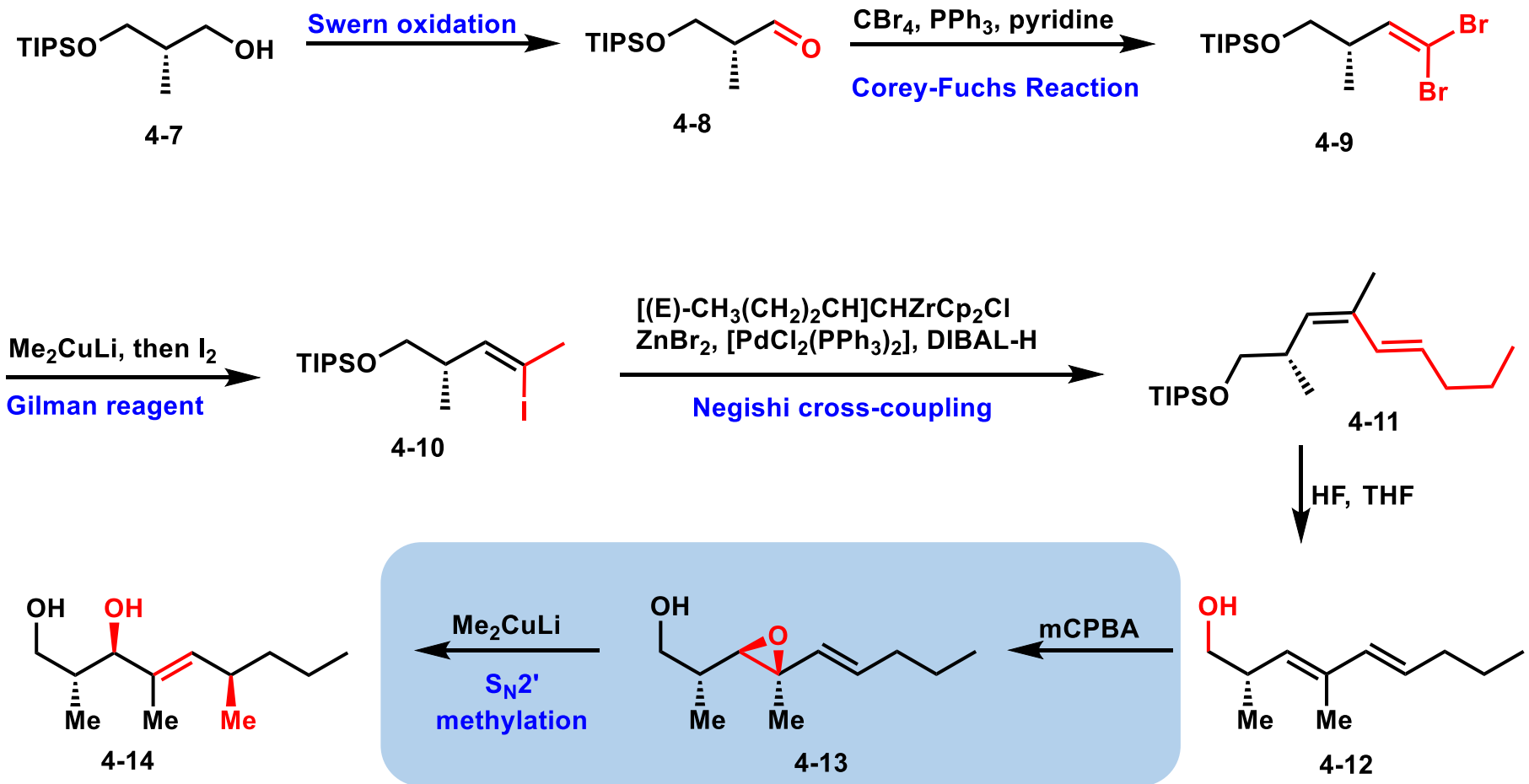
Retrosynthetic Analysis

IV. Miyashita: *Angew. Chem., Int. Ed.* **2004**, *43*, 4341



Total Synthesis of Zincophorin-Miyashita

Synthesis of the C16–C25 fragment (S_N2' methylation)

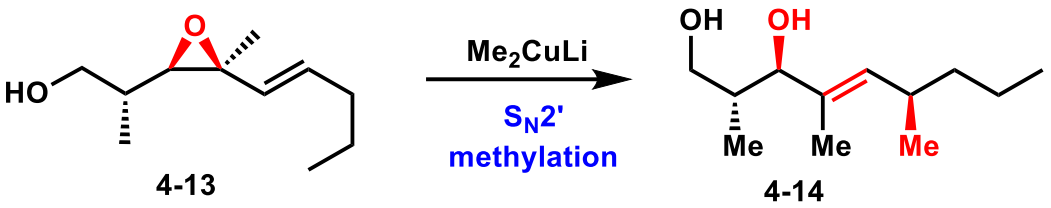


M. Miyashita, *et al*. *Angew. Chem., Int. Ed*. **2004**, *43*, 4341.

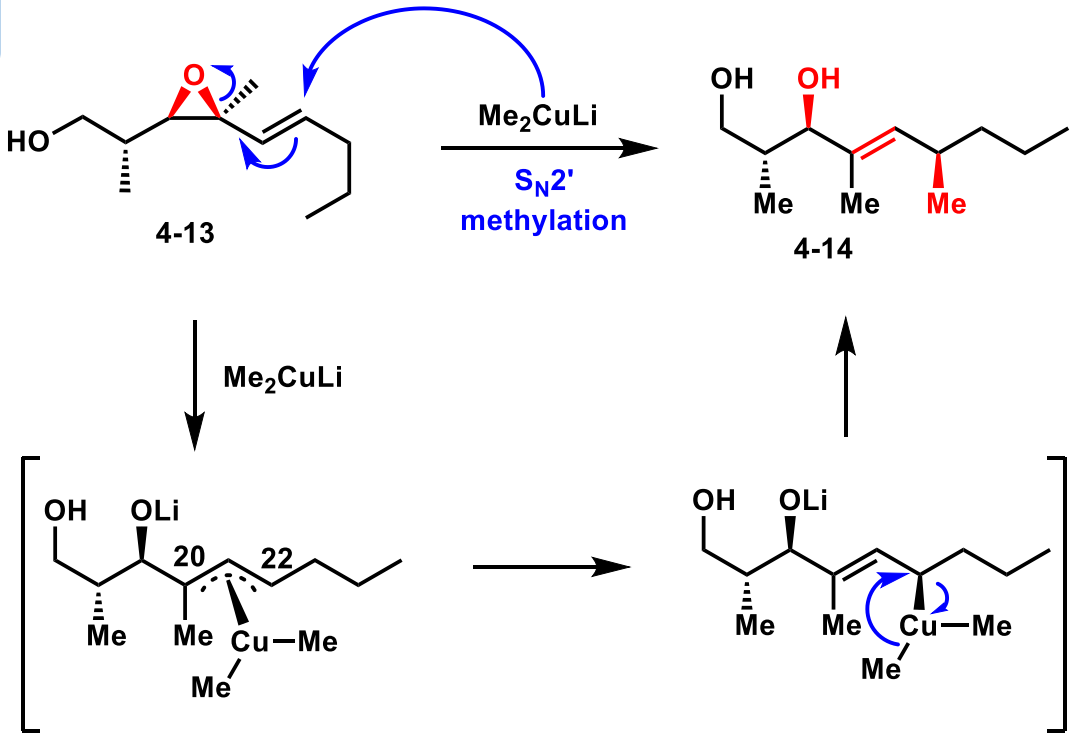
.

Total Synthesis of Zincophorin-Miyashita

Synthesis of the C16–C25 fragment (4-13 to 4-14)

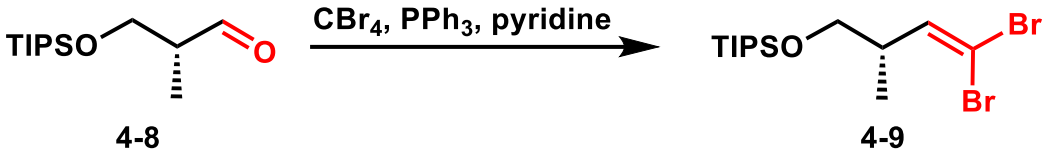


S_N2' methylation



Total Synthesis of Zincophorin-Miyashita

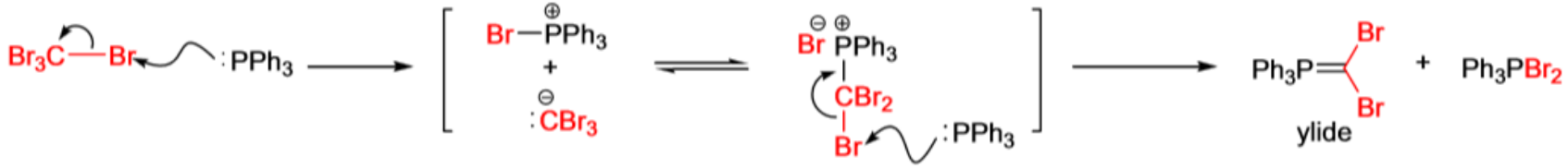
Synthesis of the C16–C25 fragment (4-8 to 4-9)



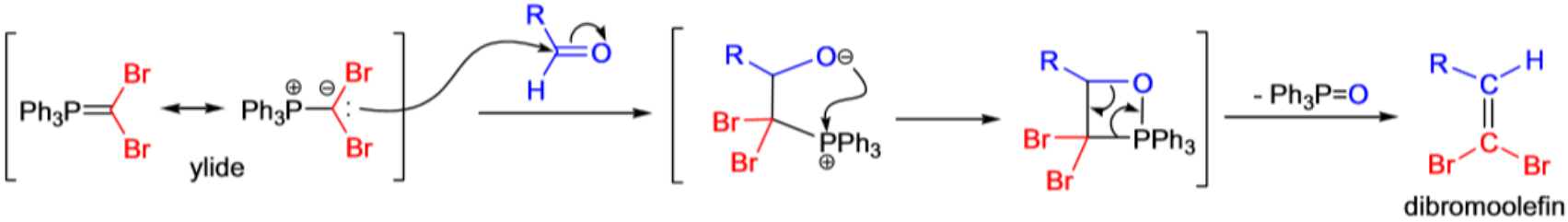
4-8 4-9

Corey-Fuchs Reaction

Generation of the phosphorous ylide:

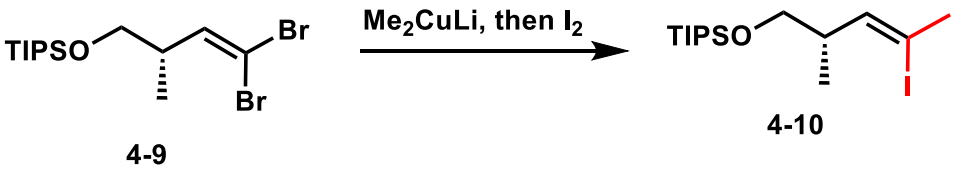


Reaction of the phosphorous ylide with the aldehyde:

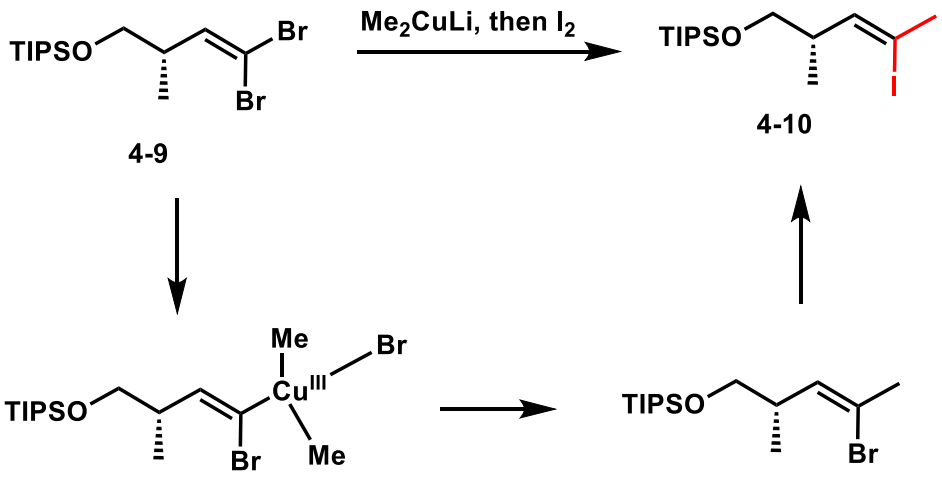


Total Synthesis of Zincophorin-Miyashita

Synthesis of the C16–C25 fragment (4-9 to 4-10)

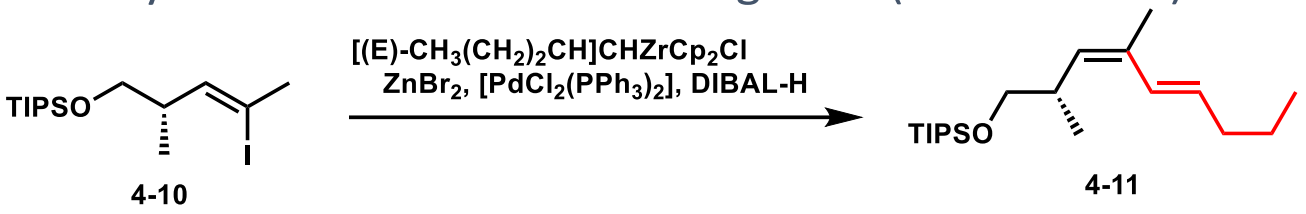


Gilman reagent：Me_2CuLi

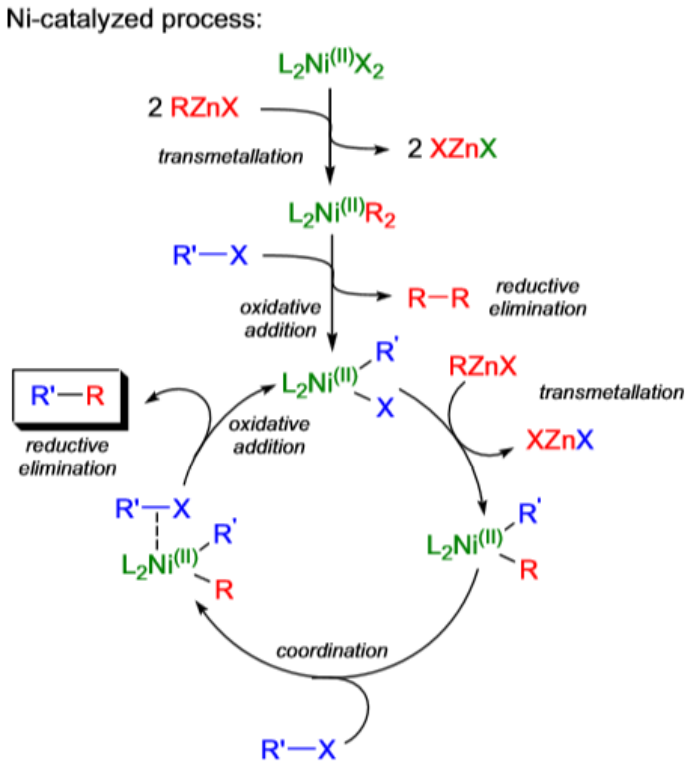


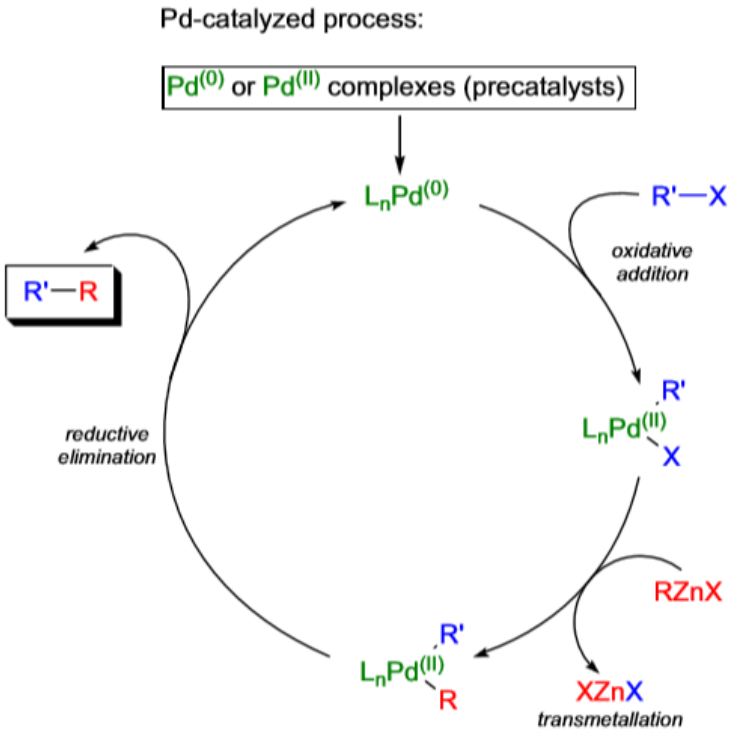
Total Synthesis of Zincophorin-Miyashita

Synthesis of the C16–C25 fragment (4-10 to 4-11)



Negishi cross-coupling

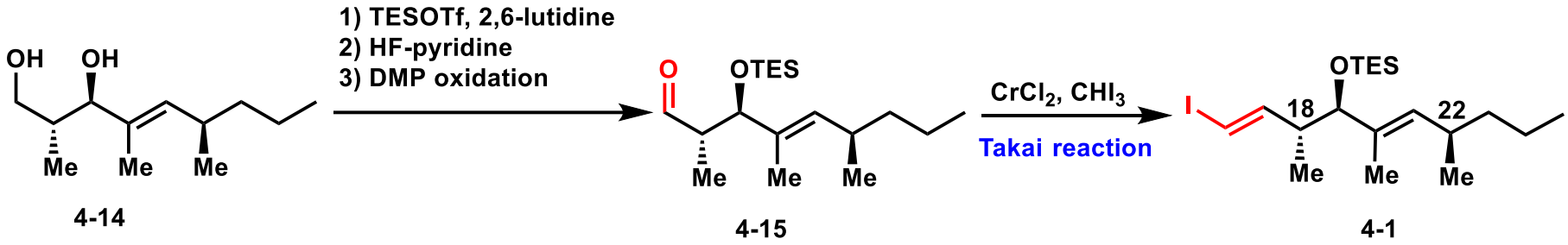




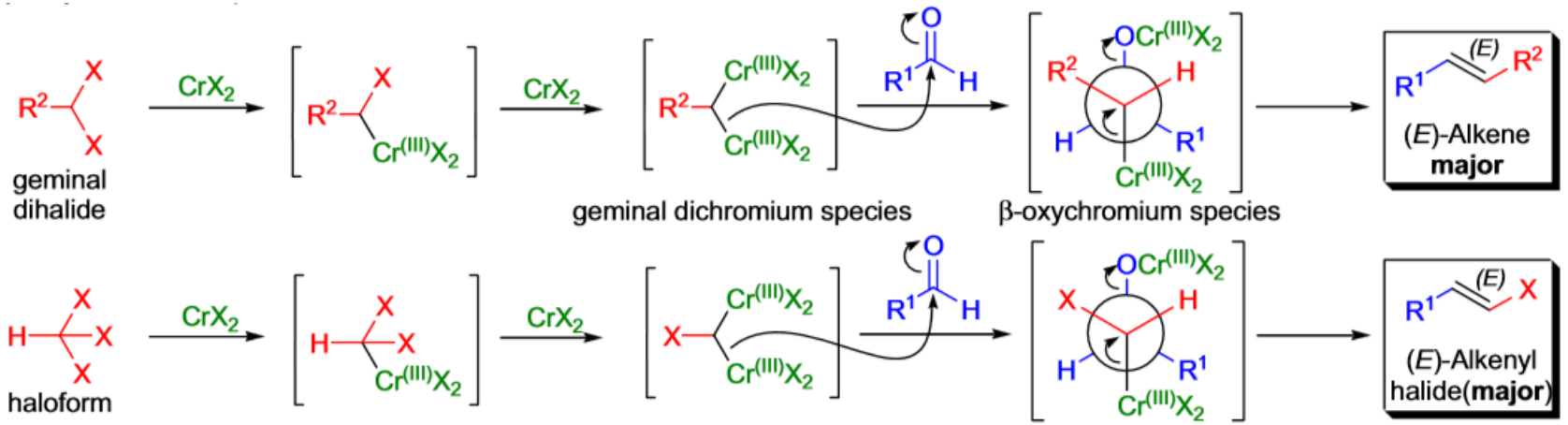
L. Kürti, B. Czakó. Strategic Applications of Named Reactions in Organic Synthesis, 2005, Elsevier Academic Press.

Total Synthesis of Zincophorin-Miyashita

Synthesis of the C16–C25 fragment (4-14 to 4-1)

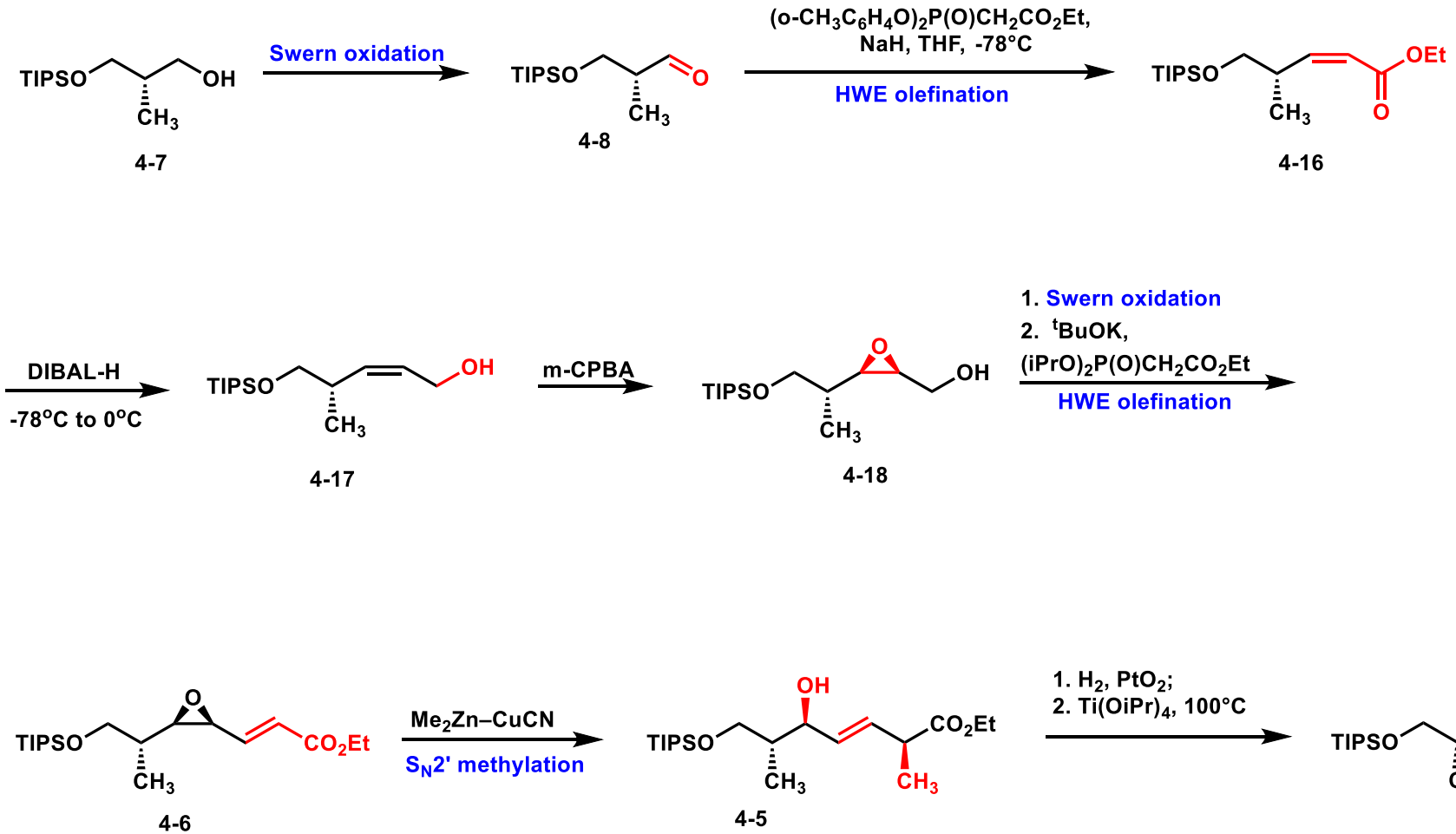


Takai reaction



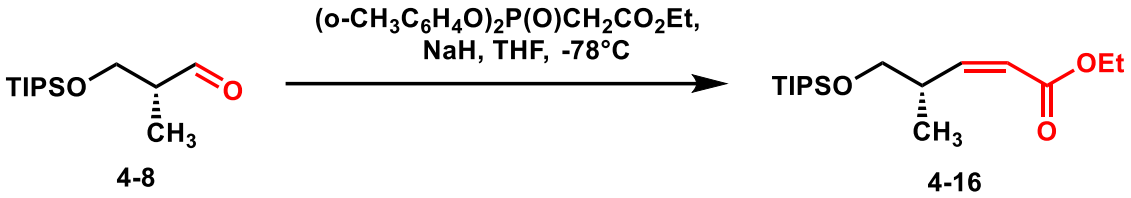
Total Synthesis of Zincophorin-Miyashita

Synthesis of the C1–C15 fragment (S_N2' methylation)

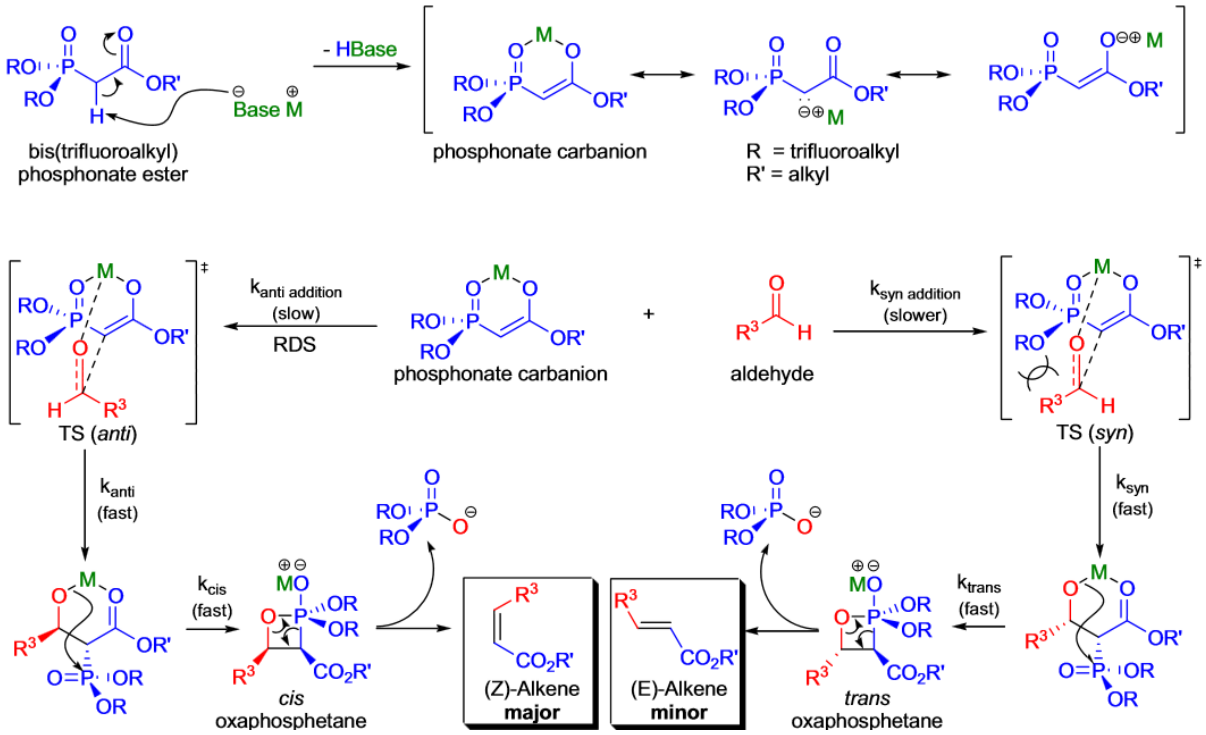


Total Synthesis of Zincophorin-Miyashita

Synthesis of the C1–C15 fragment (4-8 to 4-16、 4-18 to 4-6)



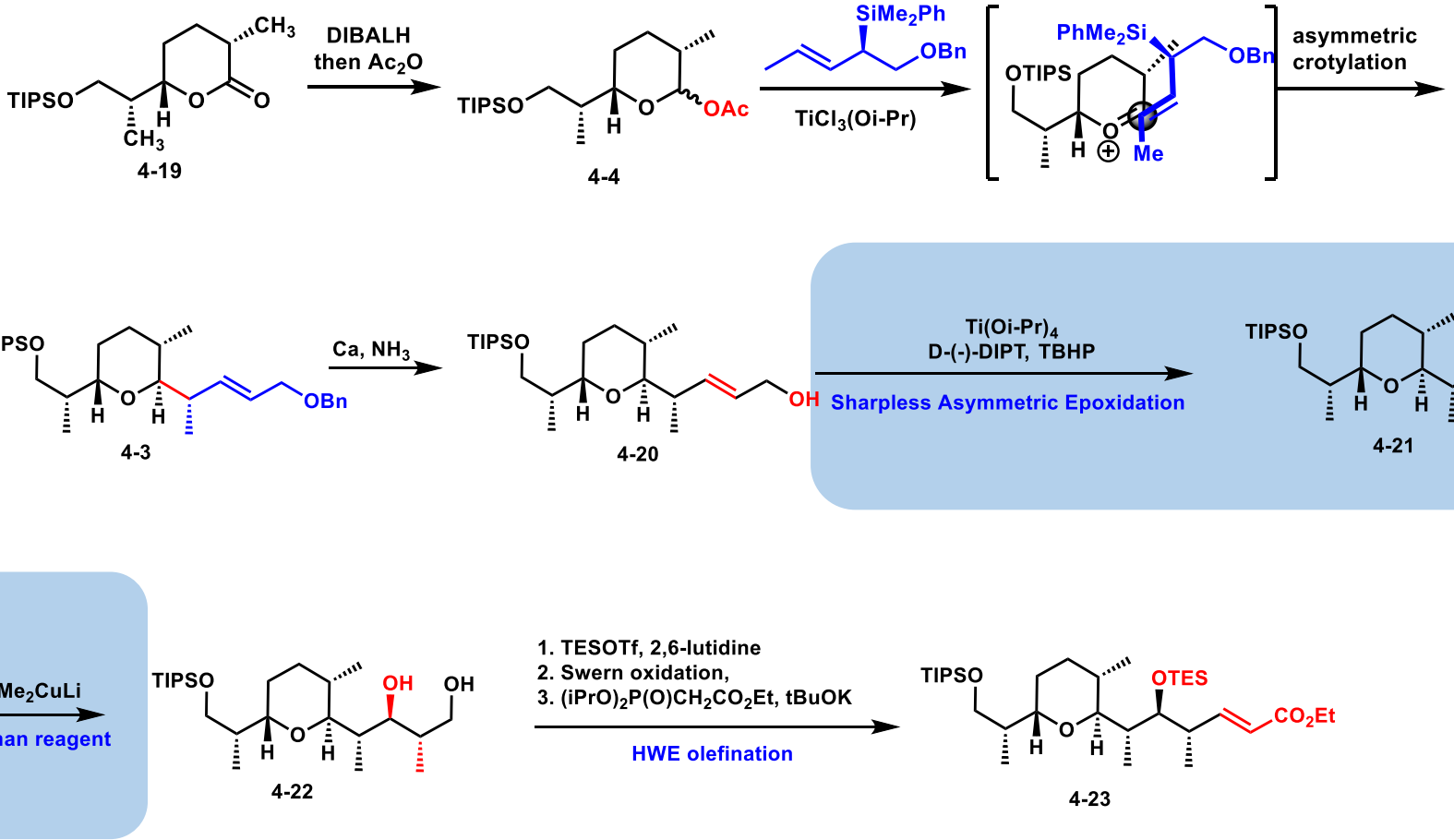
HWE olefination



L. Kürti, B. Czakó. Strategic Applications of Named Reactions in Organic Synthesis, 2005, Elsevier Academic Press.

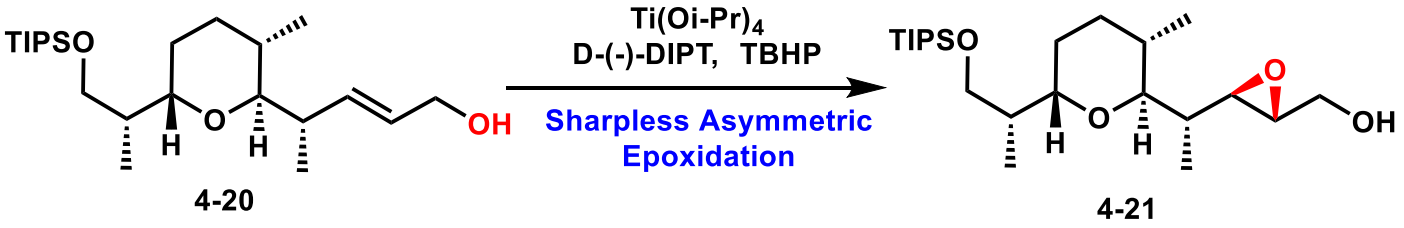
Total Synthesis of Zincophorin-Miyashita

Synthesis of the C1–C15 fragment (S_N2' methylation and methylation of epoxide)

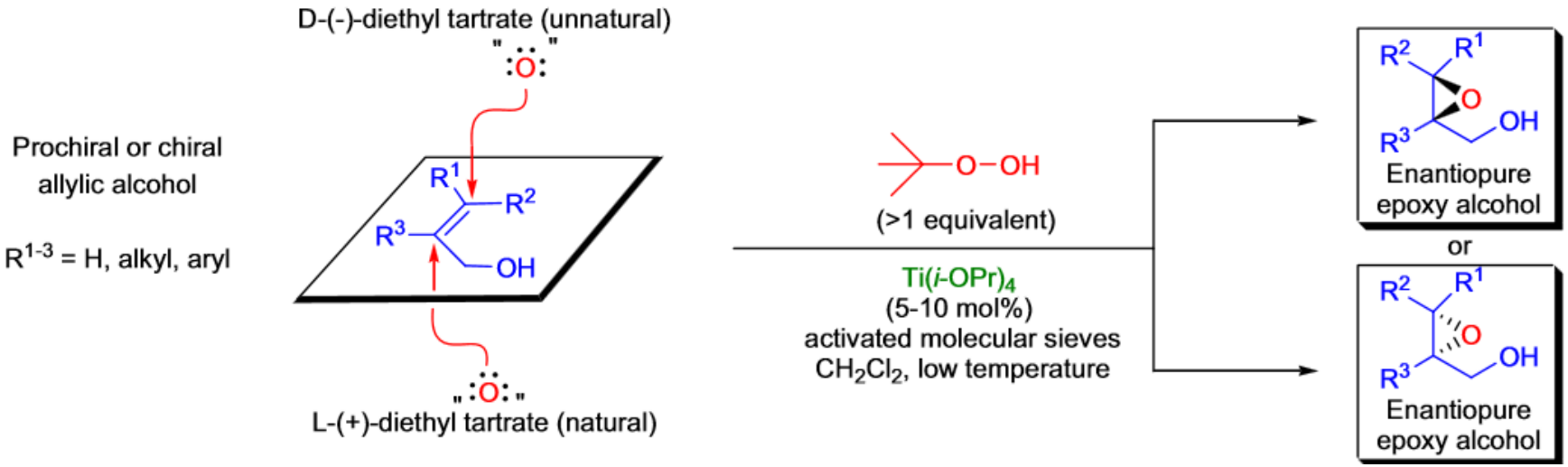


Total Synthesis of Zincophorin-Miyashita

Synthesis of the C1–C15 fragment (4-20 to 4-21)



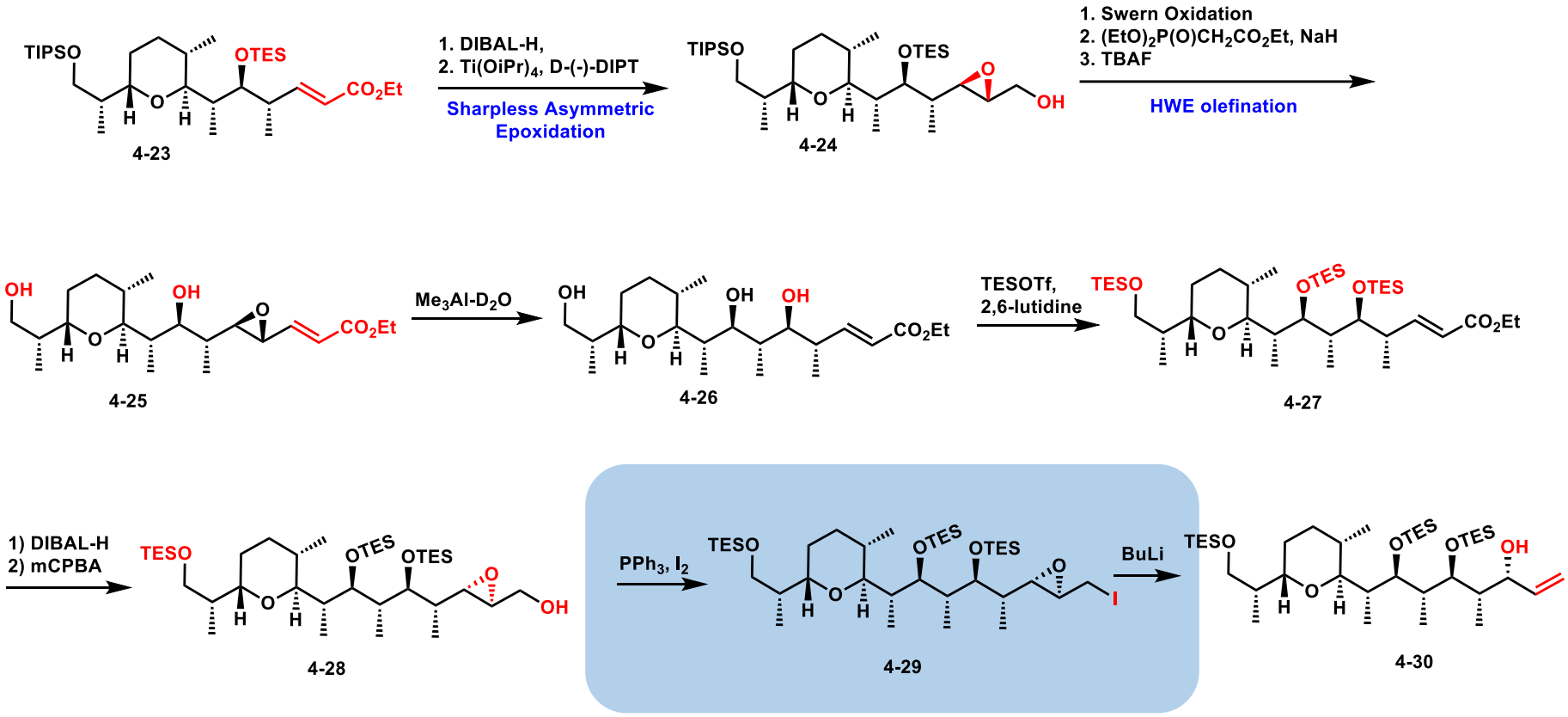
Sharpless Asymmetric Epoxidation



L. Kürti, B. Czakó. Strategic Applications of Named Reactions in Organic Synthesis, 2005, Elsevier Academic Press.

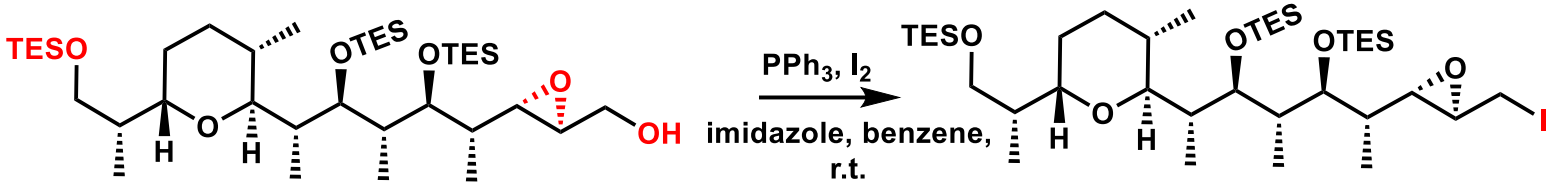
Total Synthesis of Zincophorin-Miyashita

Synthesis of the C1-C15 fragment (methylation of expoxide)

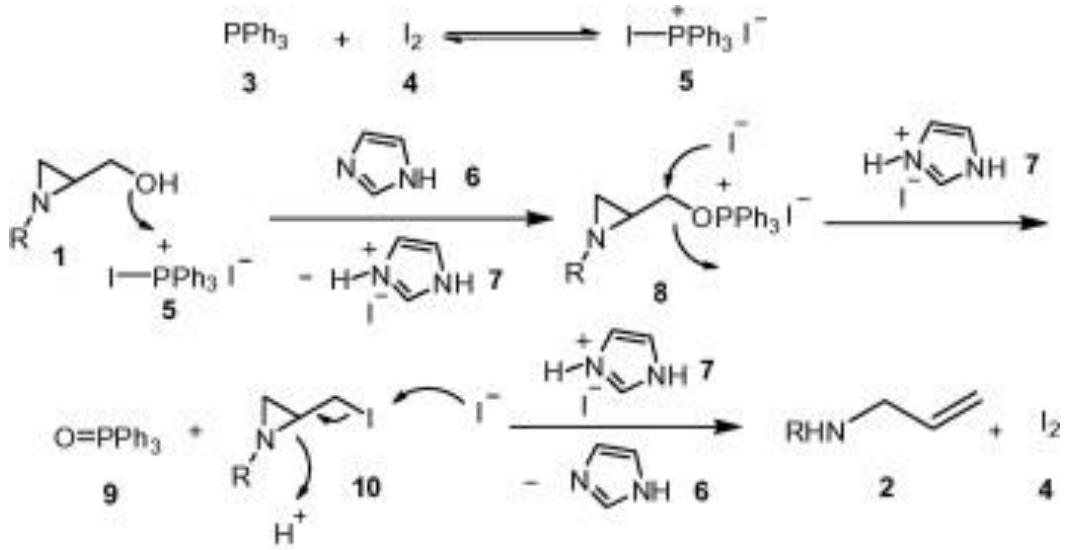


Total Synthesis of Zincophorin-Miyashita

Synthesis of the C1–C15 fragment (4-25 to 4-26)



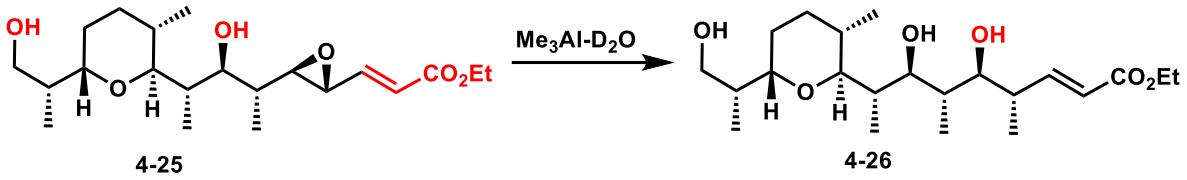
4-28 4-29



S.P. Chavan, L.B. Khairnar, P.N. Chavan. *Tetrahedron Lett.*, **2014**, *55,* 5905-5907

Total Synthesis of Zincophorin-Miyashita

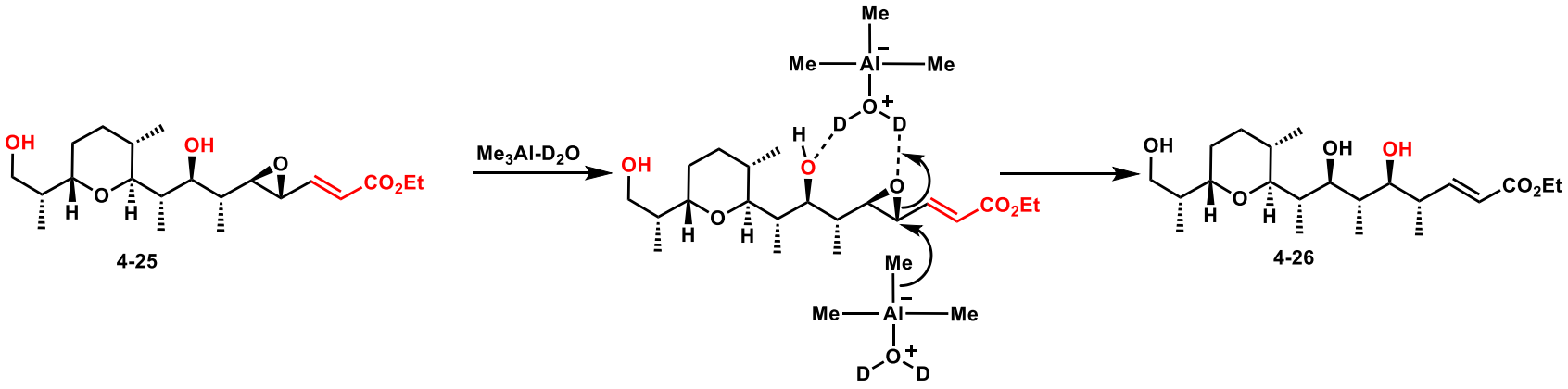
Synthesis of the C1–C15 fragment (4-25 to 4-26)



4-25 4-26

Me_3Al-D_2O Methylation

(Z)-epoxy acrylates→ anti product
(E)-epoxy acrylates→ syn product

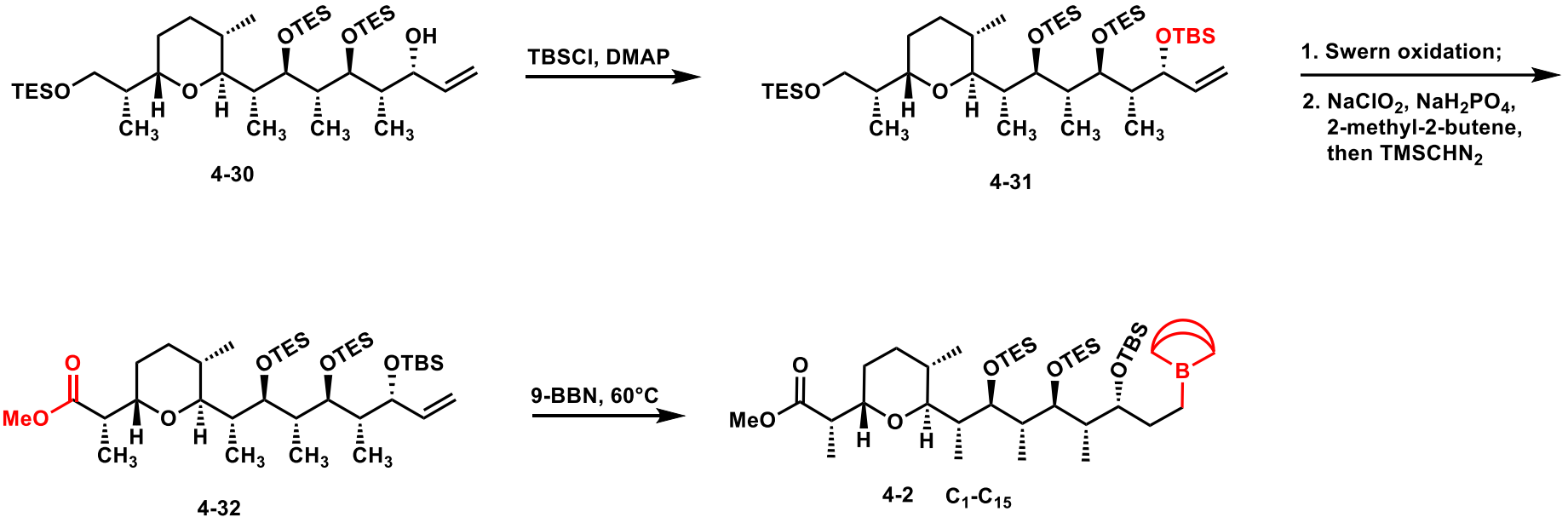


4-25 4-26

M. Miyashita, M. Hoshino, A. Yoshikoshi, *J. Org. Chem.* **1991**, *56*, 6483.

Total Synthesis of Zincophorin-Miyashita

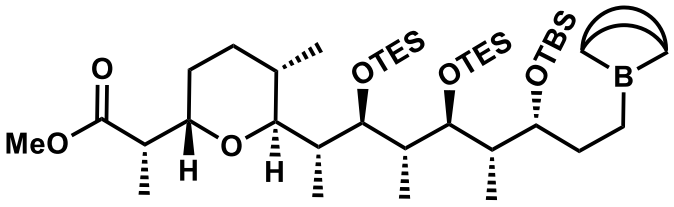
Synthesis of the C16–C25 fragment (S_N2' methylation and methylation of epoxide)



4-30 → 4-31 → 4-32 → 4-2 C_1-C_{15}

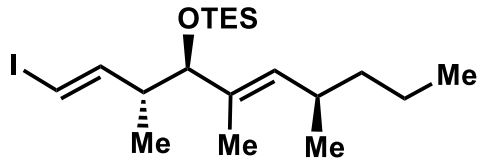
Total Synthesis of Zincophorin-Miyashita

Coupling of the C1–C15 fragment with C16–C25 fragment



4-2 C1-C15

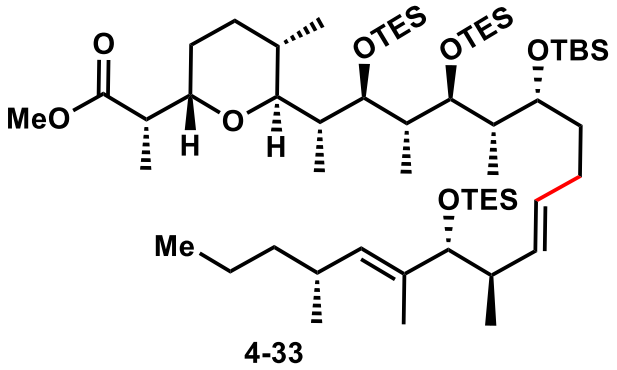
+



4-1 C16-C25

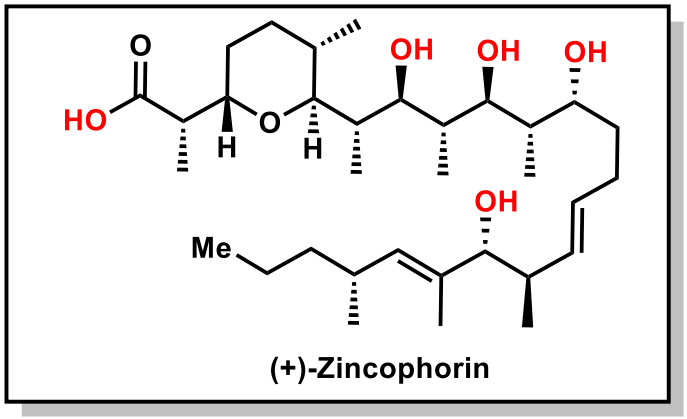
Cs_2CO_3, $AsPh_3$
$[PdCl_2(dppf)]$

Suzuki-Miyaura Coupling



4-33

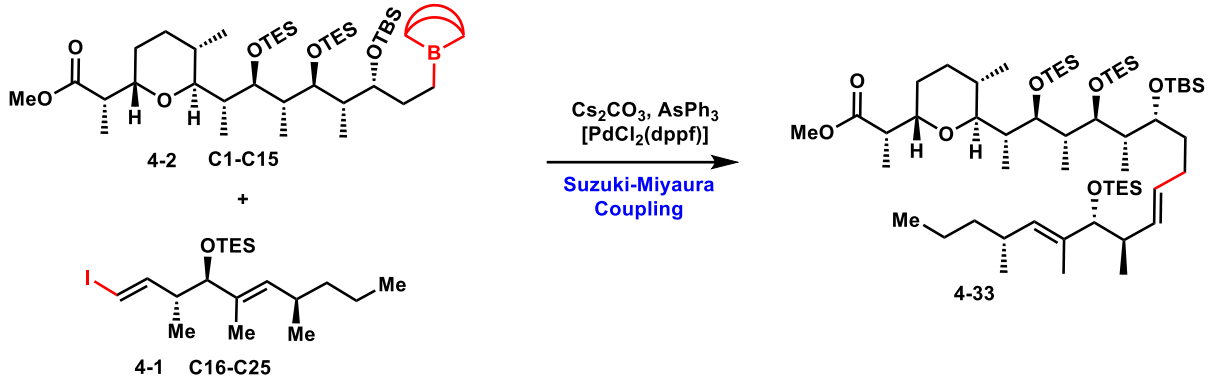
1. TEAF, DMF
2. LiOH, H_2O/MeOH/THF



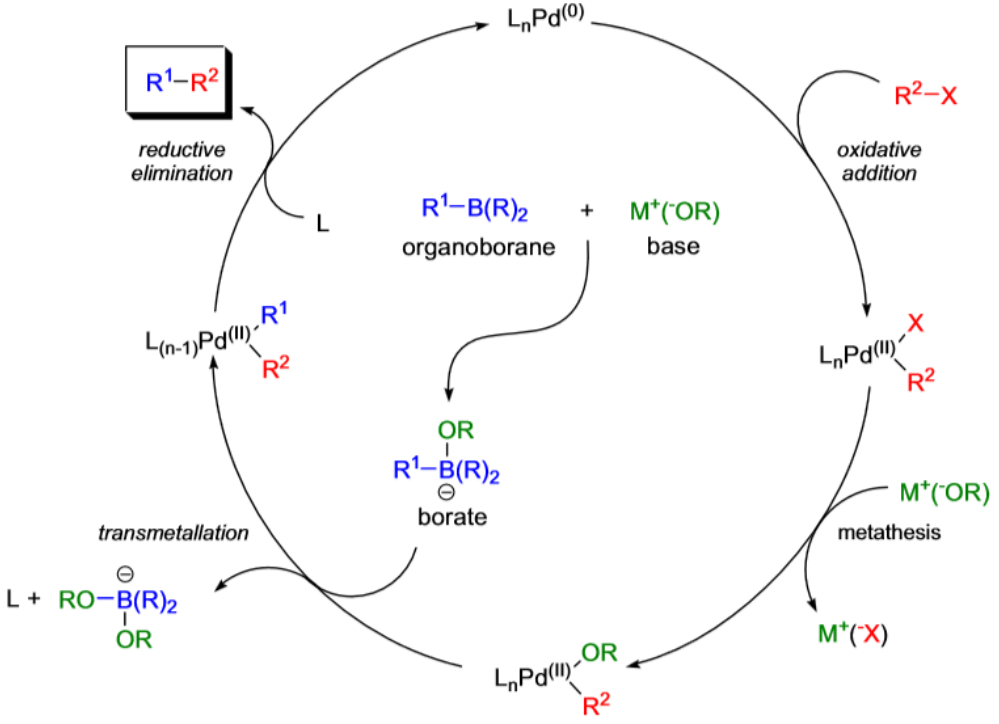
(+)-Zincophorin

Total Synthesis of Zincophorin-Miyashita

Coupling of the C1–C15 fragment with C16–C25 fragment



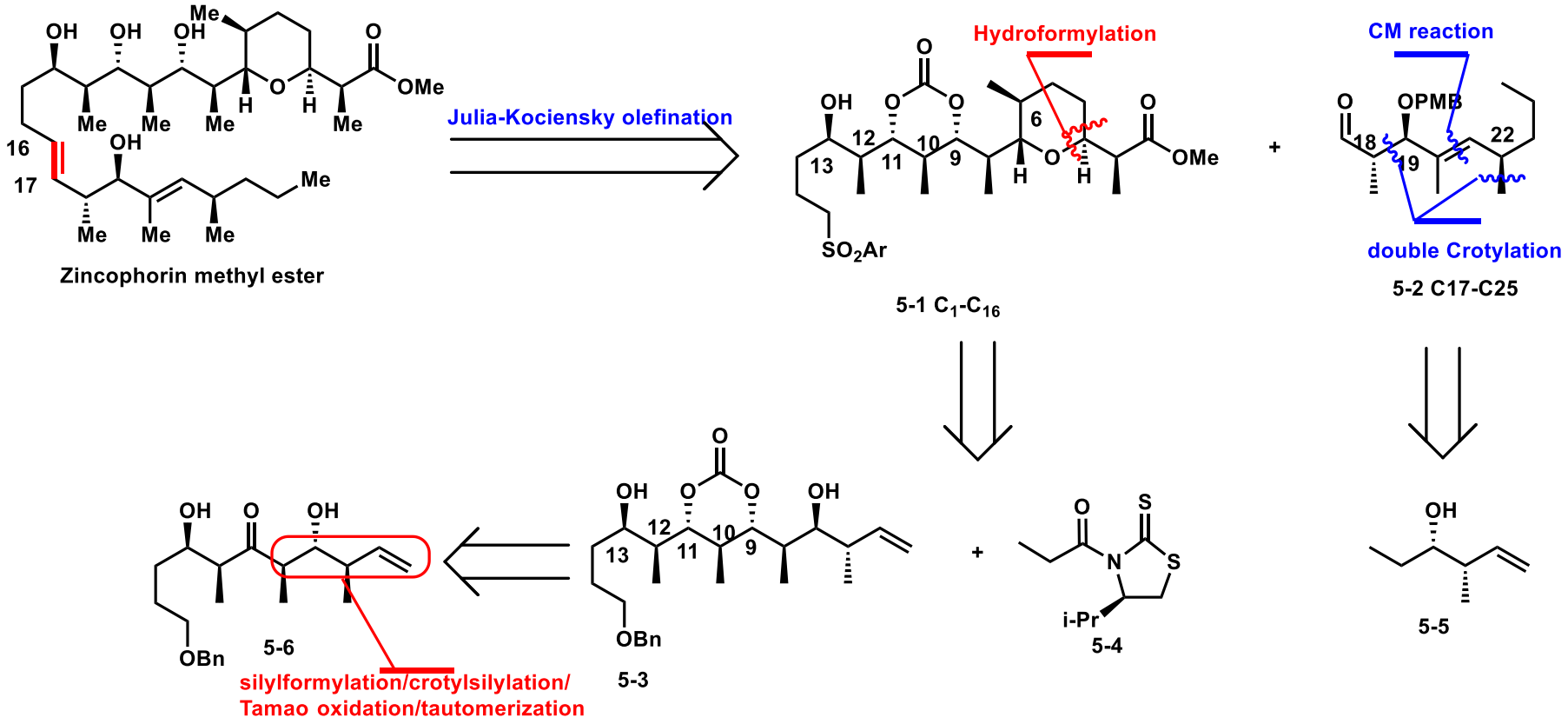
Suzuki-Miyaura Coupling



Total Synthesis of Zincophorin-Leighton

Retrosynthetic Analysis

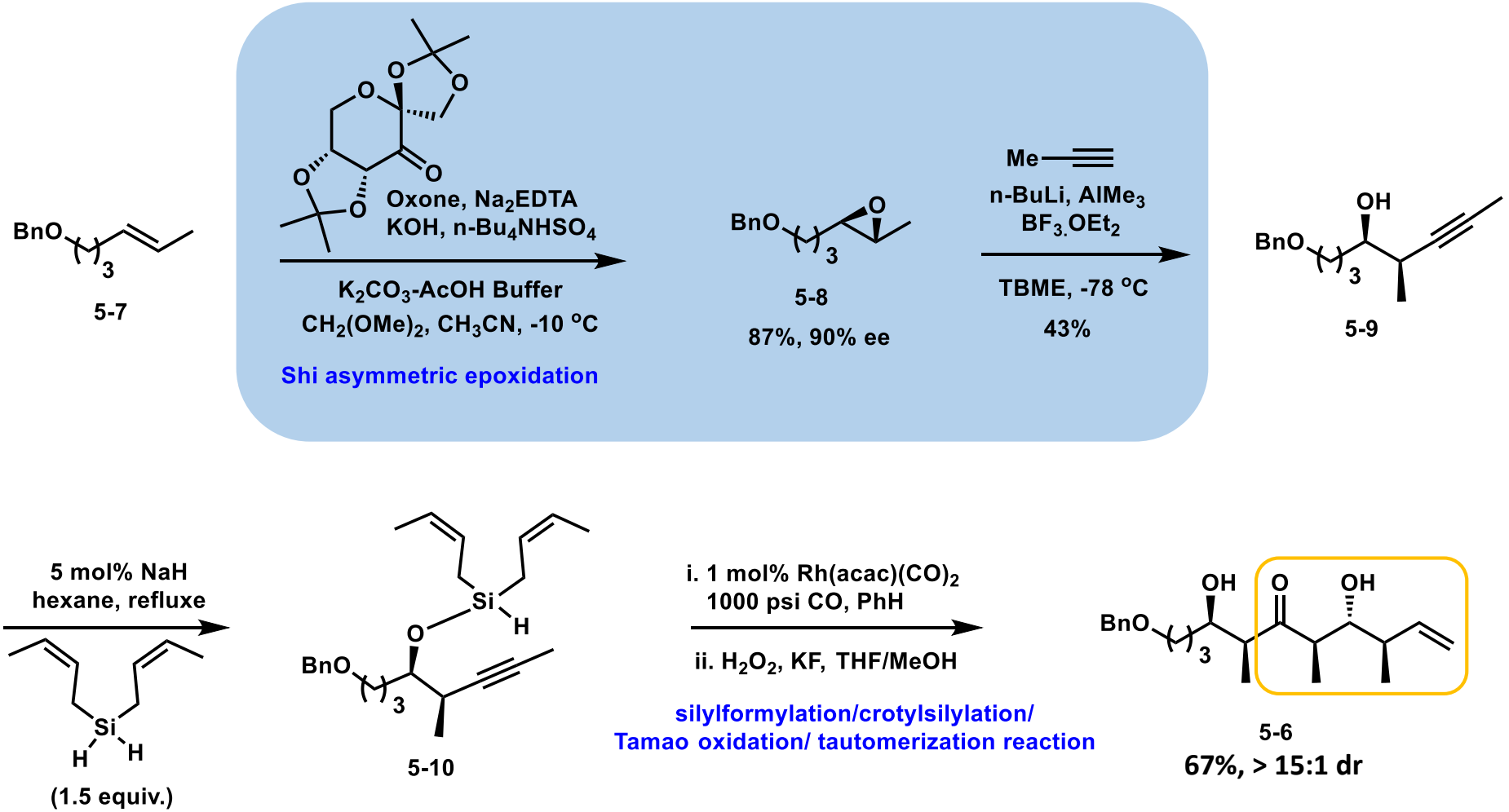
V. Leighton: *J. Am. Chem. Soc.* **2011**, *133*, 7308



J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

Total Synthesis of Zincophorin-Leighton

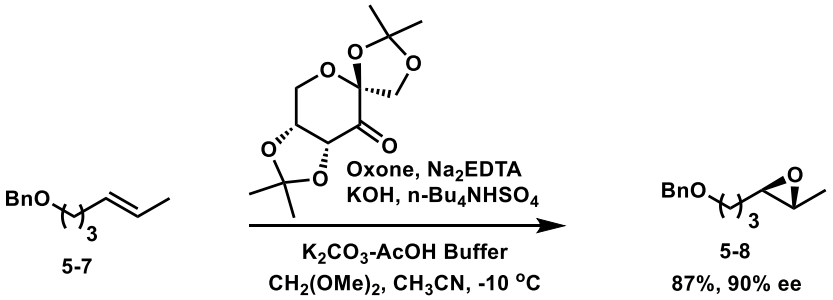
Synthesis of Tetrahydrofuran Fragment



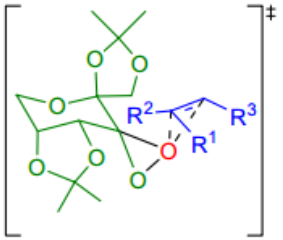
J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

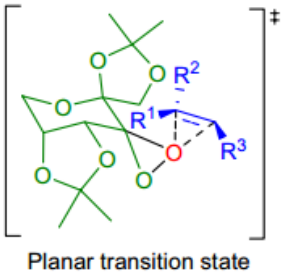
Total Synthesis of Zincophorin-Leighton

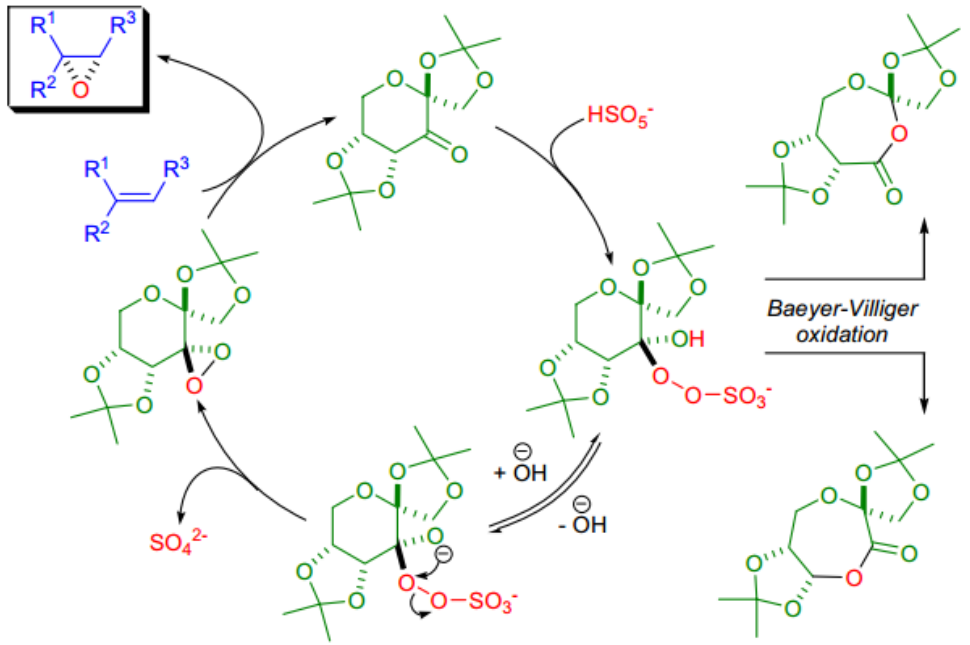
Synthesis of Tetrahydrofuran Fragment (5-7 to 5-8)



Shi asymmetric epoxidation

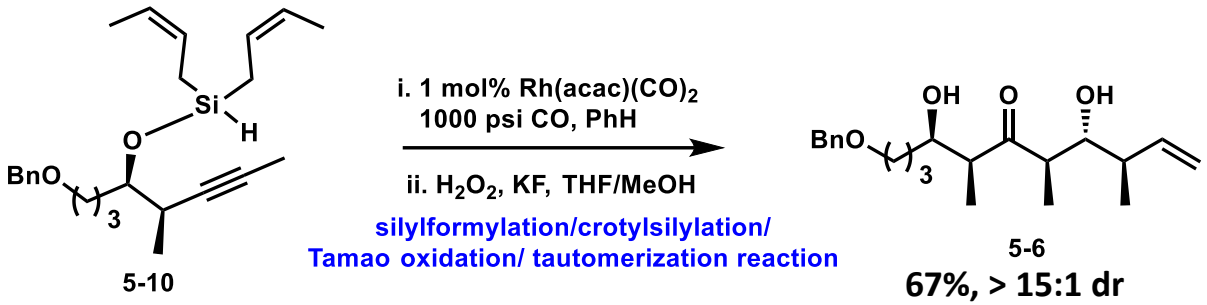


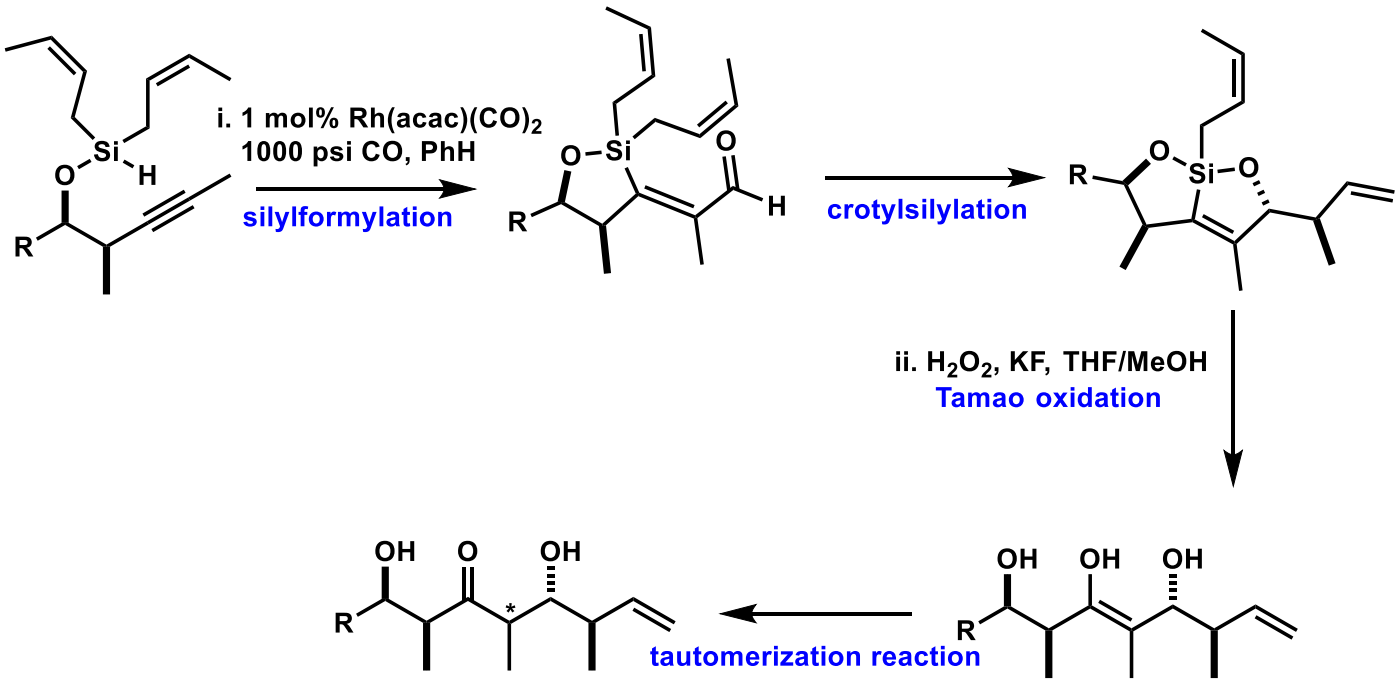




Total Synthesis of Zincophorin-Leighton

Synthesis of Tetrahydrofuran Fragment (5-9 to 5-6)

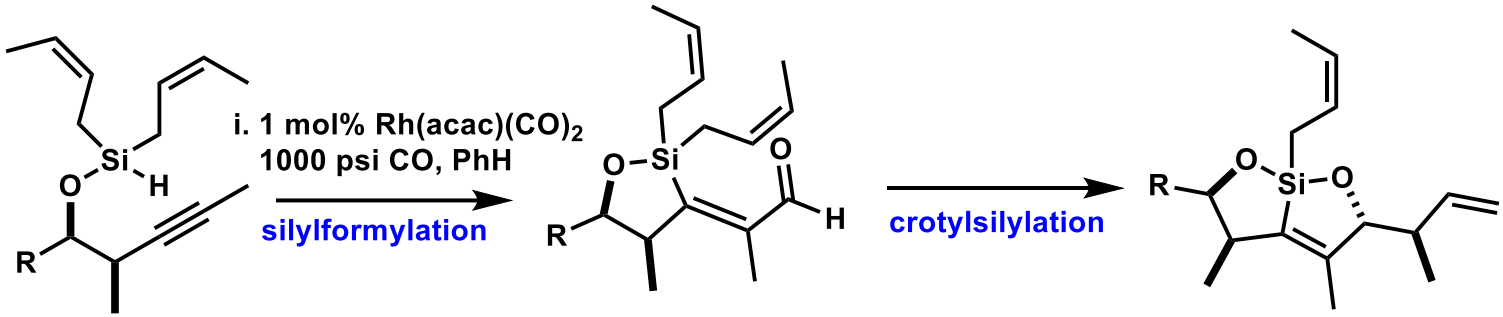


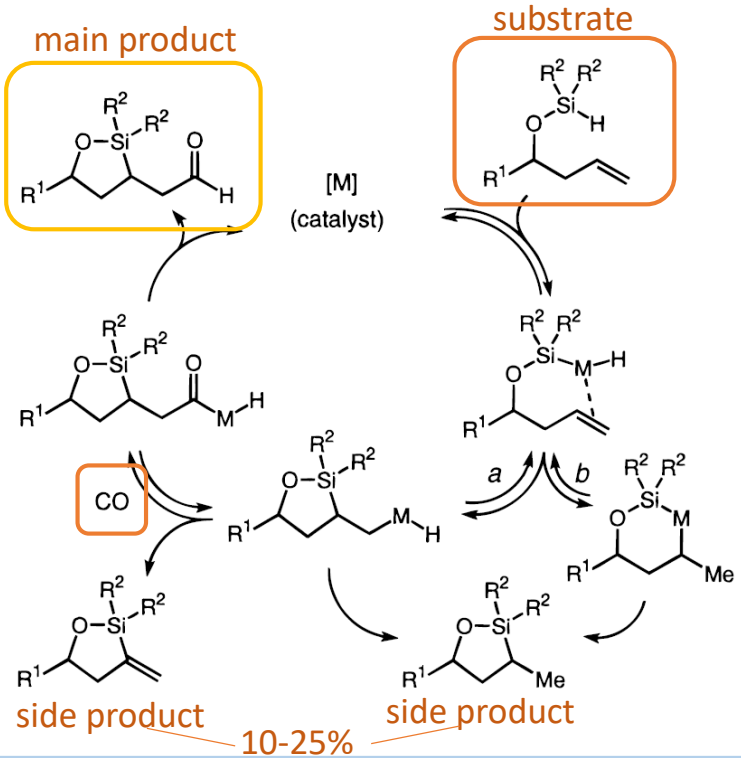


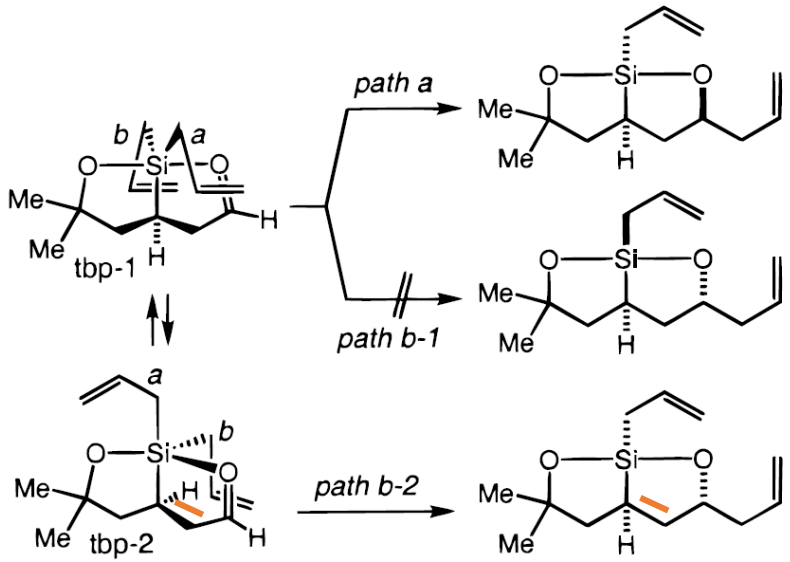
J. L. Leighton, E.Chapman. *J. Am. Chem. Soc.* **1997**, *119*, 12416.
M. J. Zacuto,J. L. Leighton. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

Total Synthesis of Zincophorin-Leighton

Synthesis of Tetrahydrofuran Fragment (5-9 to 5-6)



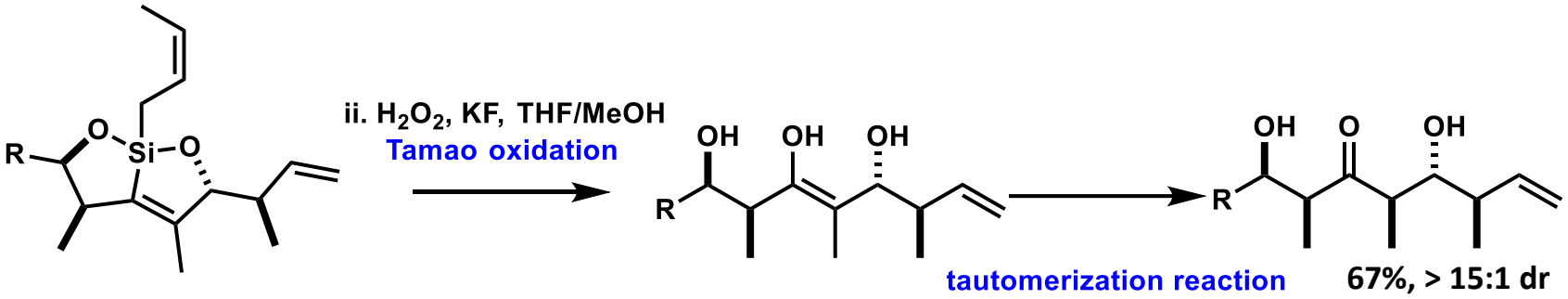




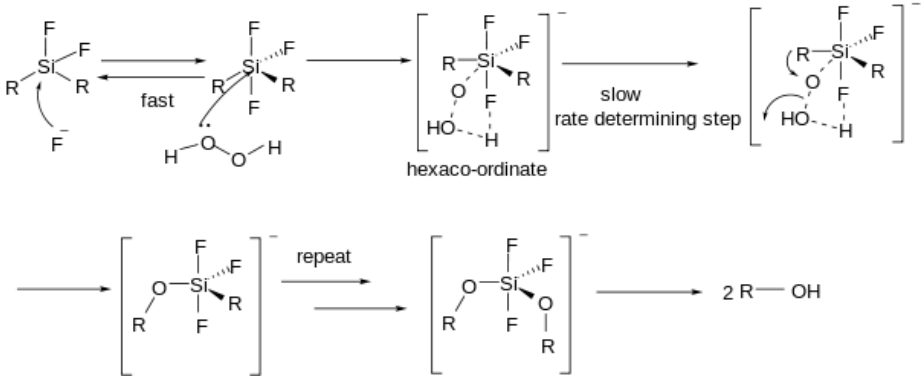
J. L. Leighton, E.Chapman. *J. Am. Chem. Soc.* **1997**, *119*, 12416.
M. J. Zacuto,J. L. Leighton. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

Total Synthesis of Zincophorin-Leighton

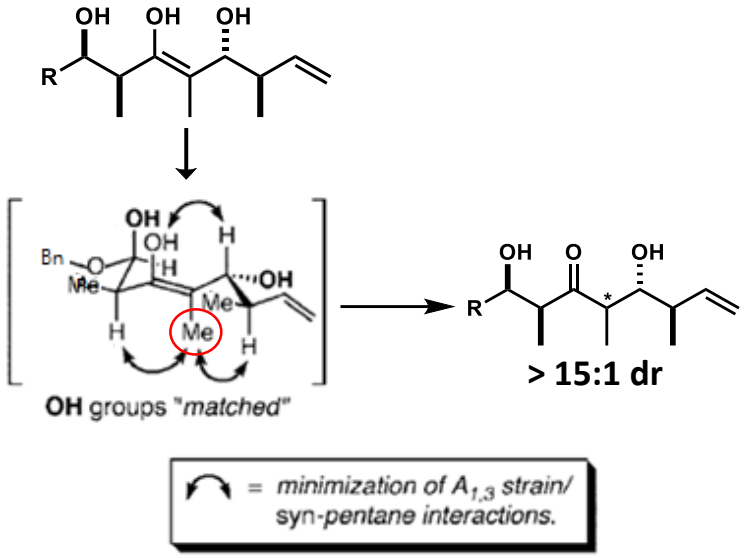
Synthesis of Tetrahydrofuran Fragment (5-9 to 5-6)



Tamao oxidation



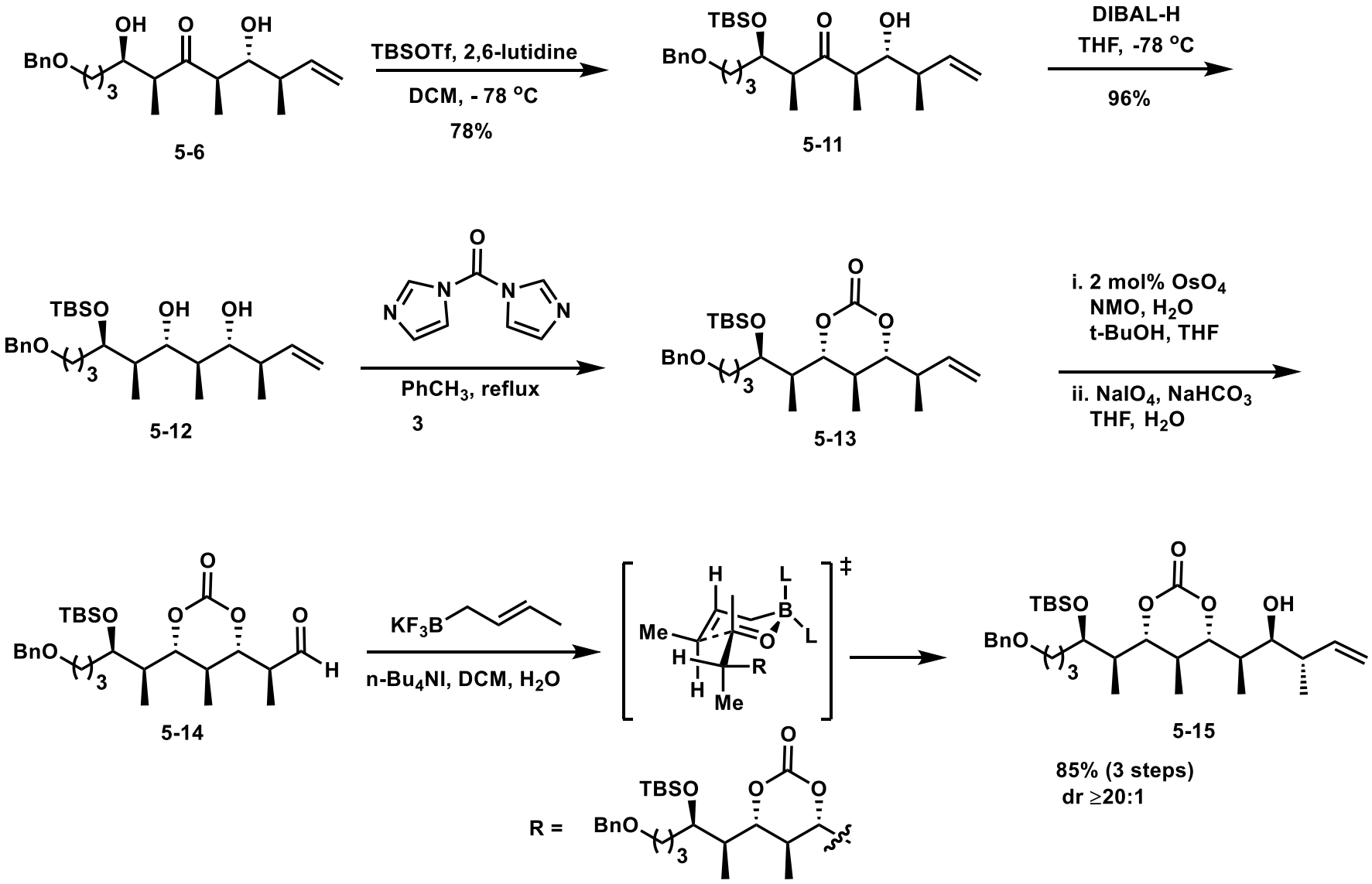
tautomerization



J. L. Leighton, E.Chapman. *J. Am. Chem. Soc.* **1997**, *119*, 12416.
M. J. Zacuto,J. L. Leighton. *J. Am. Chem. Soc.* **2000**, *122*, 8587.

Total Synthesis of Zincophorin-Leighton

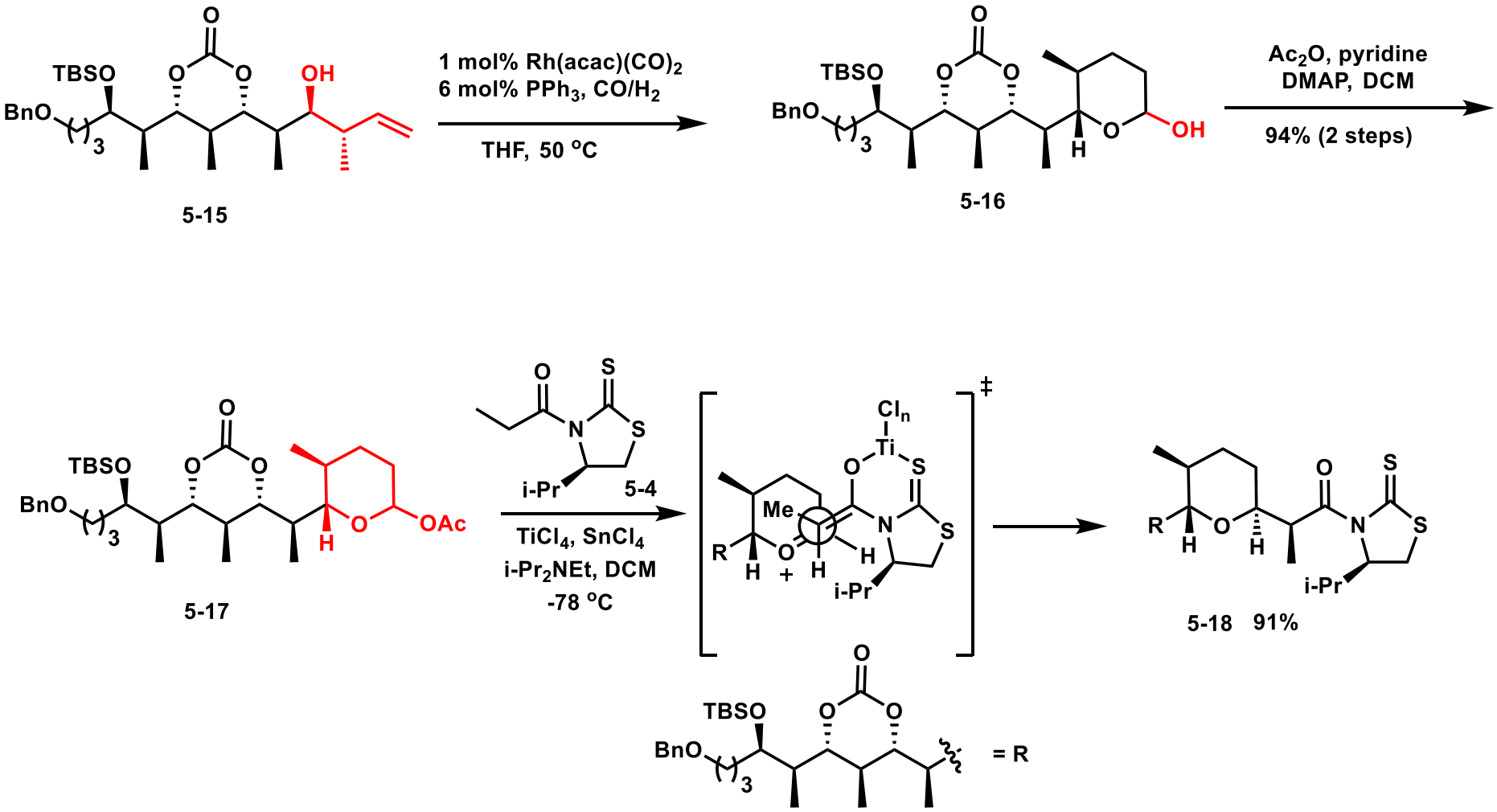
Synthesis of Tetrahydrofuran Fragment



J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

Total Synthesis of Zincophorin-Leighton

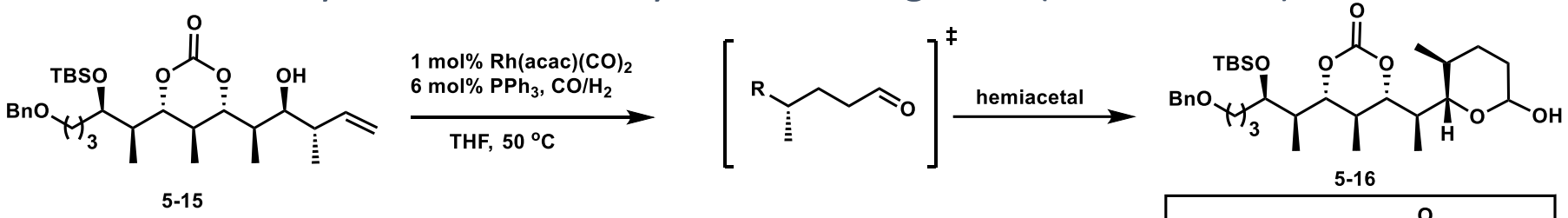
Synthesis of Tetrahydrofuran Fragment



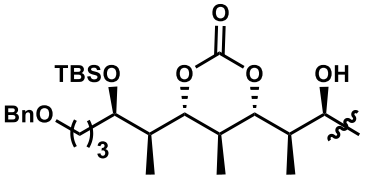
J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.
X. Solans, *et. al. Org. Lett.* **2001**, *3*, 615.

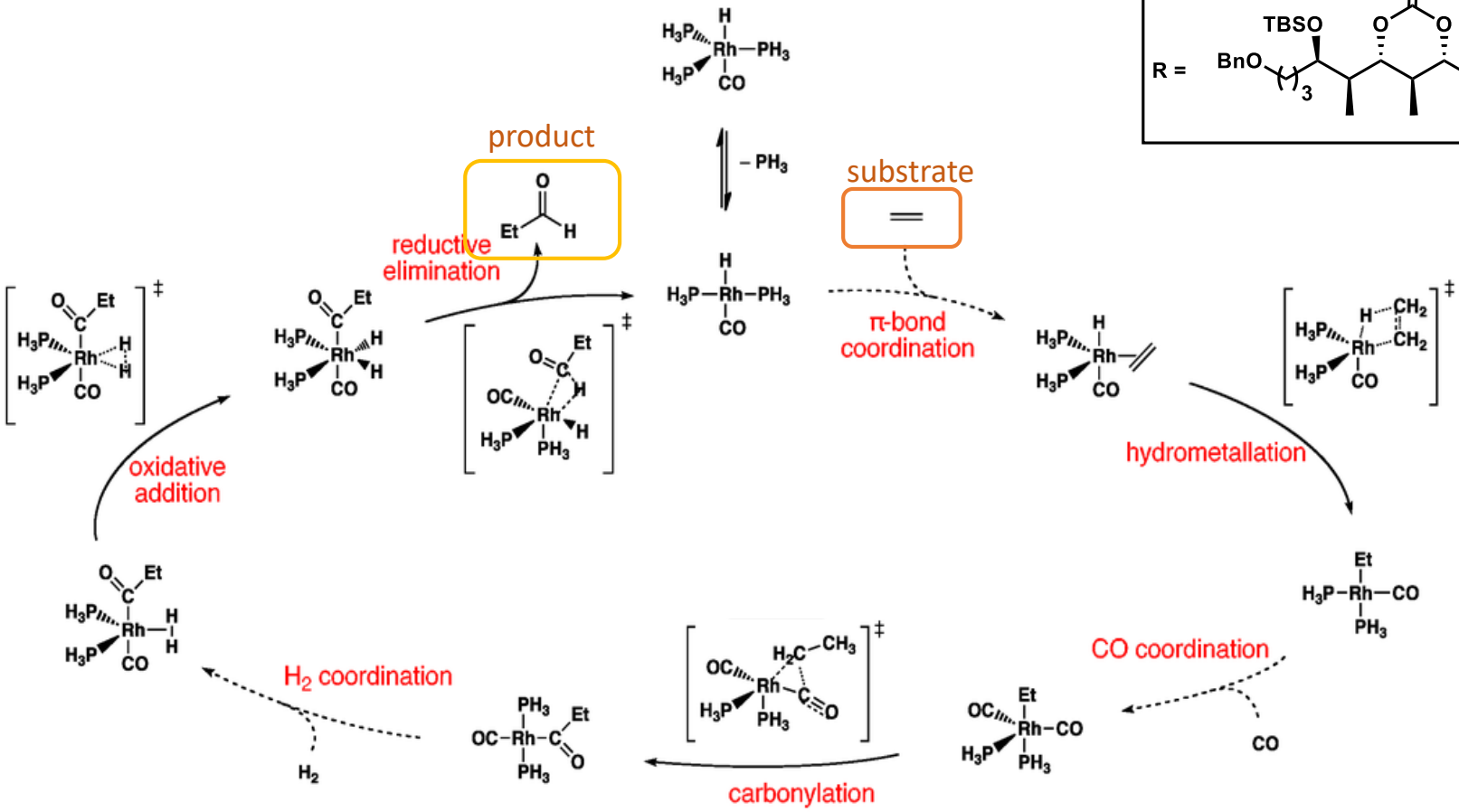
Total Synthesis of Zincophorin-Leighton

Synthesis of Tetrahydrofuran Fragment (5-15 to 5-16)



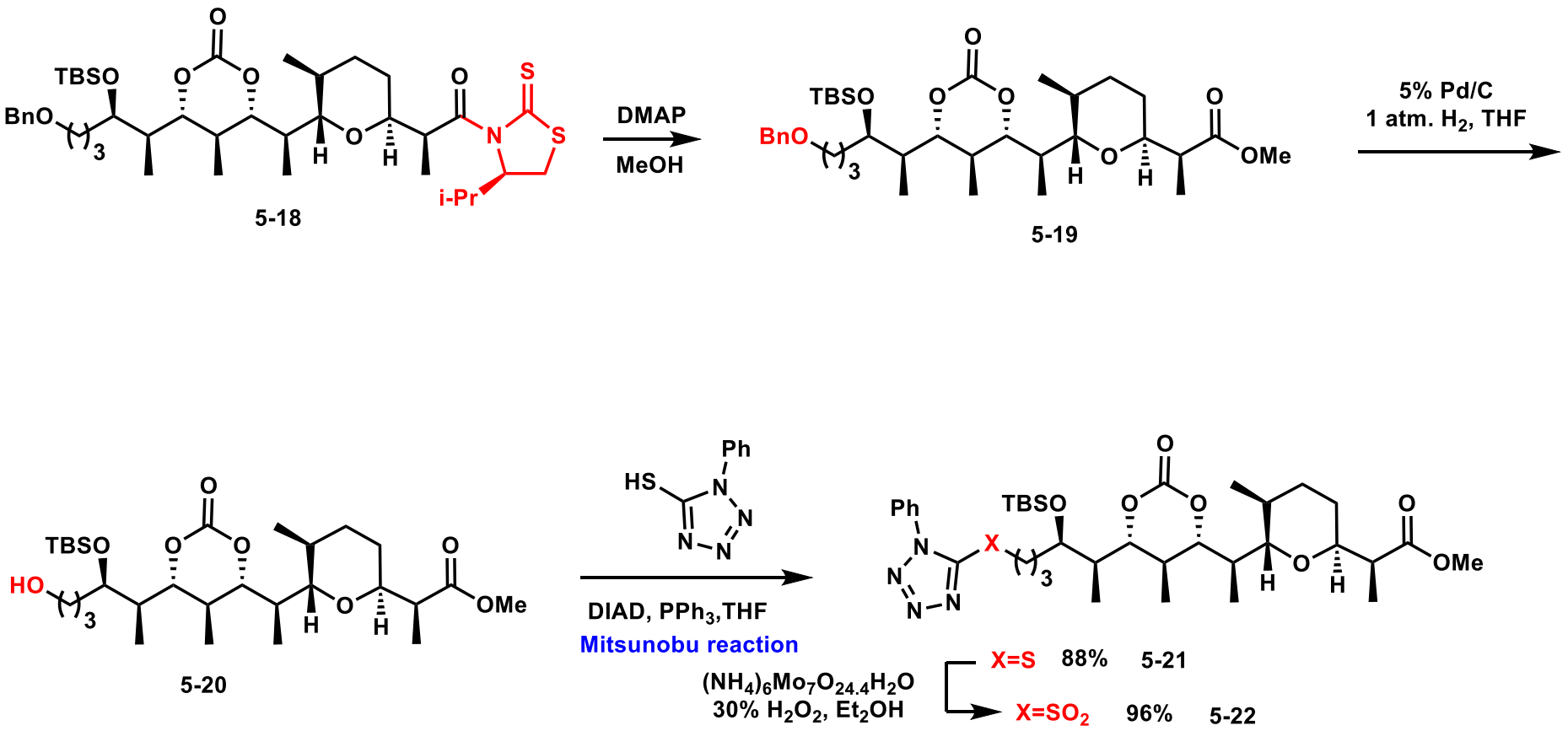
R =





Total Synthesis of Zincophorin-Leighton

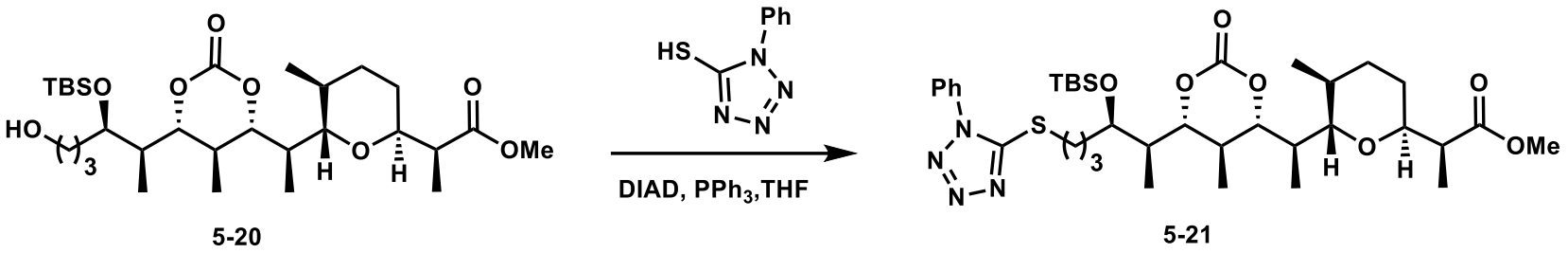
Synthesis of C1-C16 Fragment



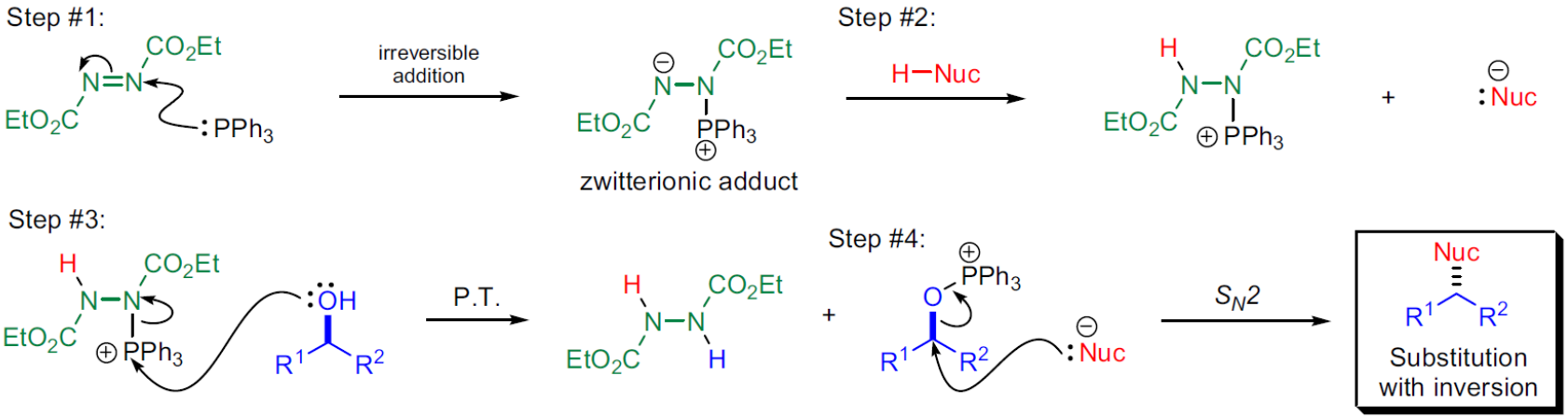
J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

Total Synthesis of Zincophorin-Leighton

Synthesis of C1-C16 Fragment (5-20 to 5-21)

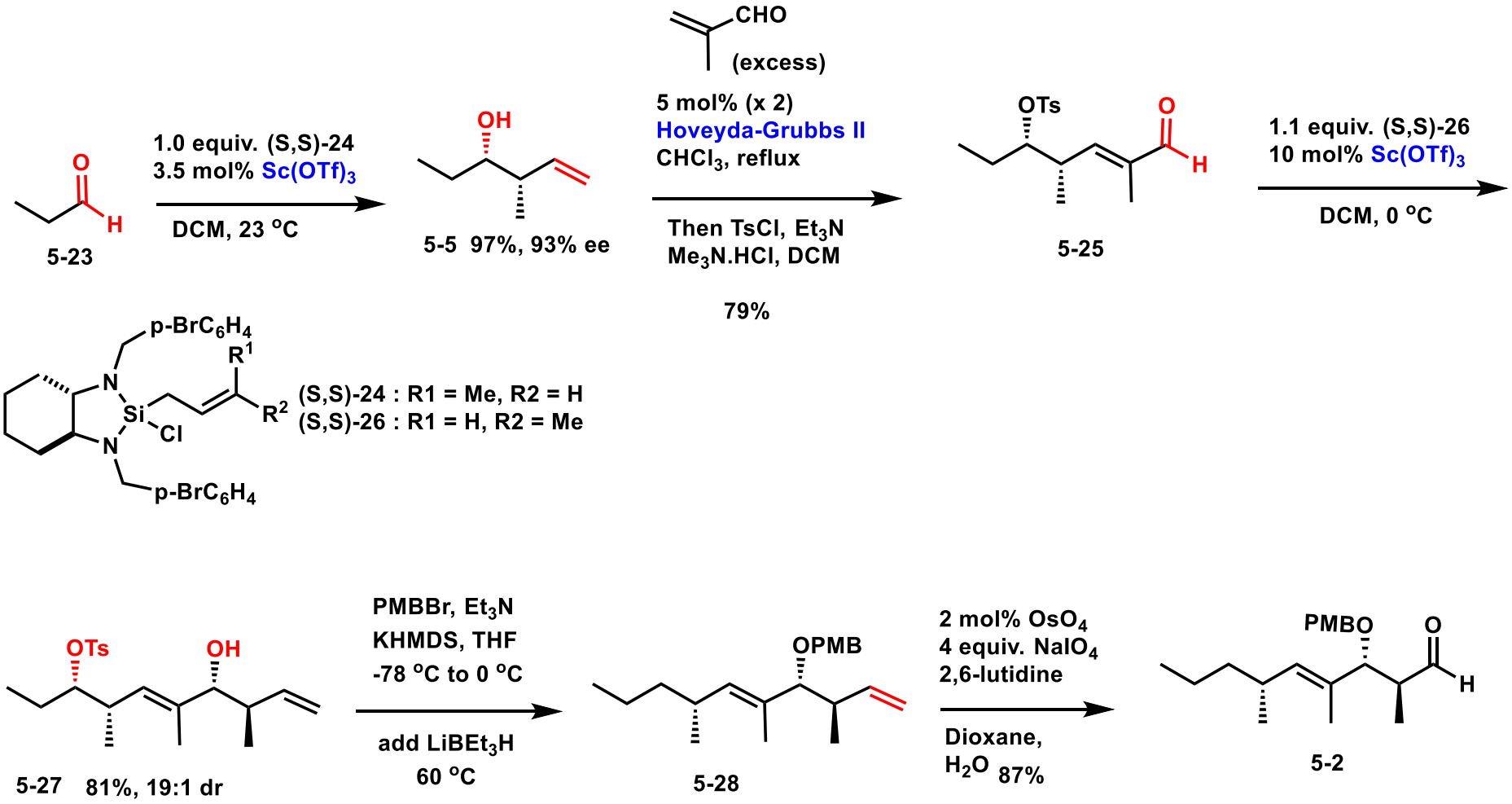


Mitsunobu reaction



Total Synthesis of Zincophorin-Leighton

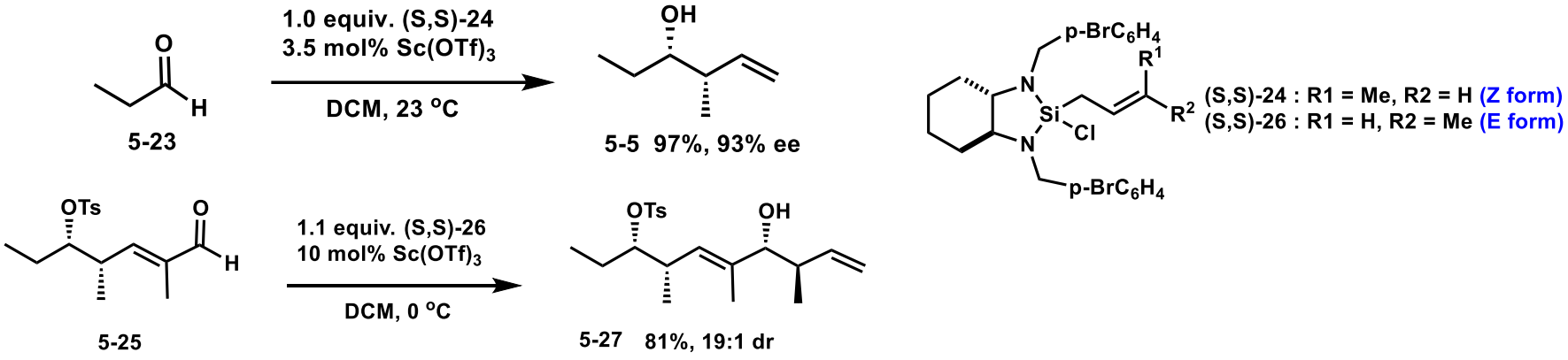
Synthesis of C17-C25 Fragment



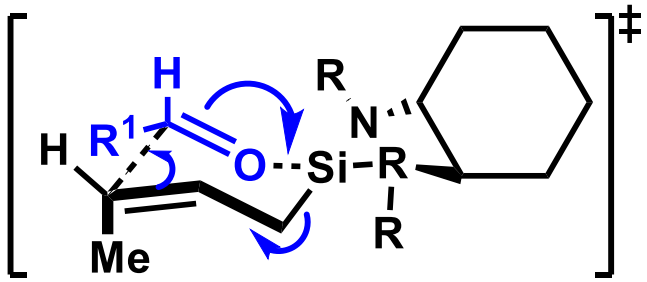
J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

Total Synthesis of Zincophorin-Leighton

Synthesis of C17-C25 Fragment



$Sc(OTf)_3$-catalyzed crotylation (5-23 to 5-5)

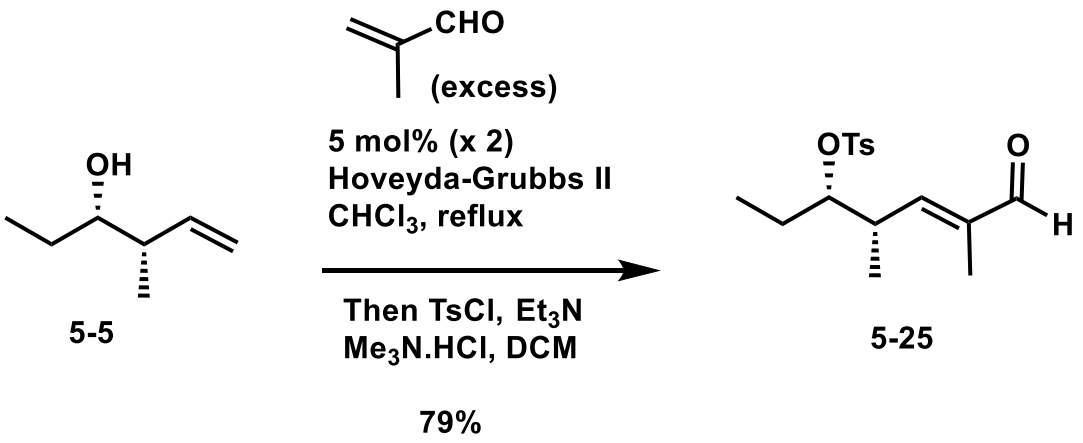


Z form catalyst → syn form product
E form catalyst → anti form product

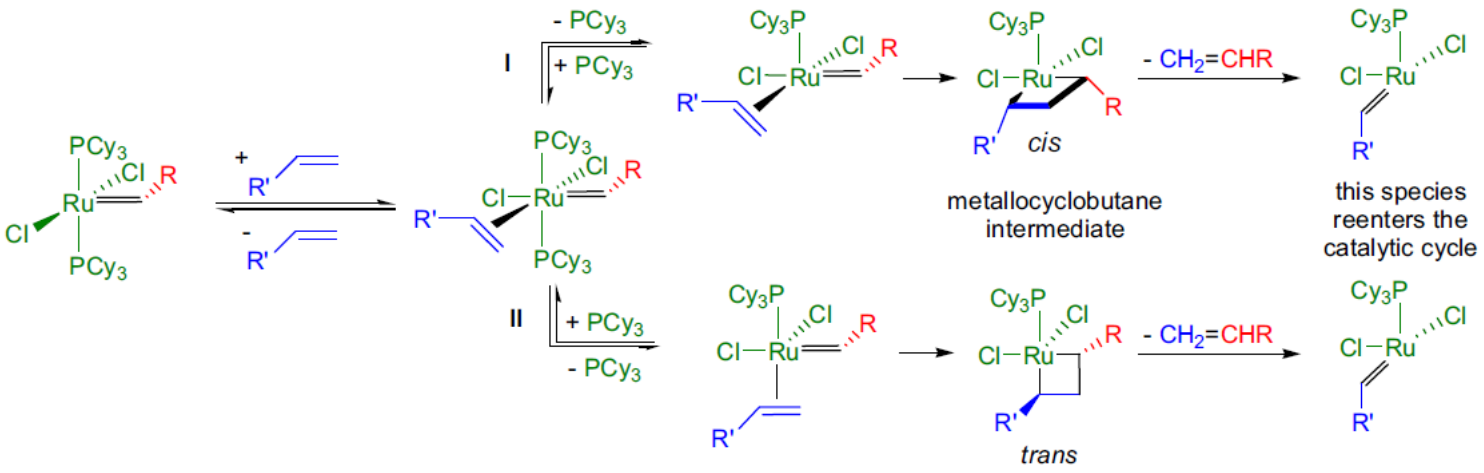
J. L. Leighton. *et. al. Angew. Chem., Int. Ed.* **2003**, *42*, 946

Total Synthesis of Zincophorin-Leighton

Synthesis of C17-C25 Fragment (5-5 to 5-25)

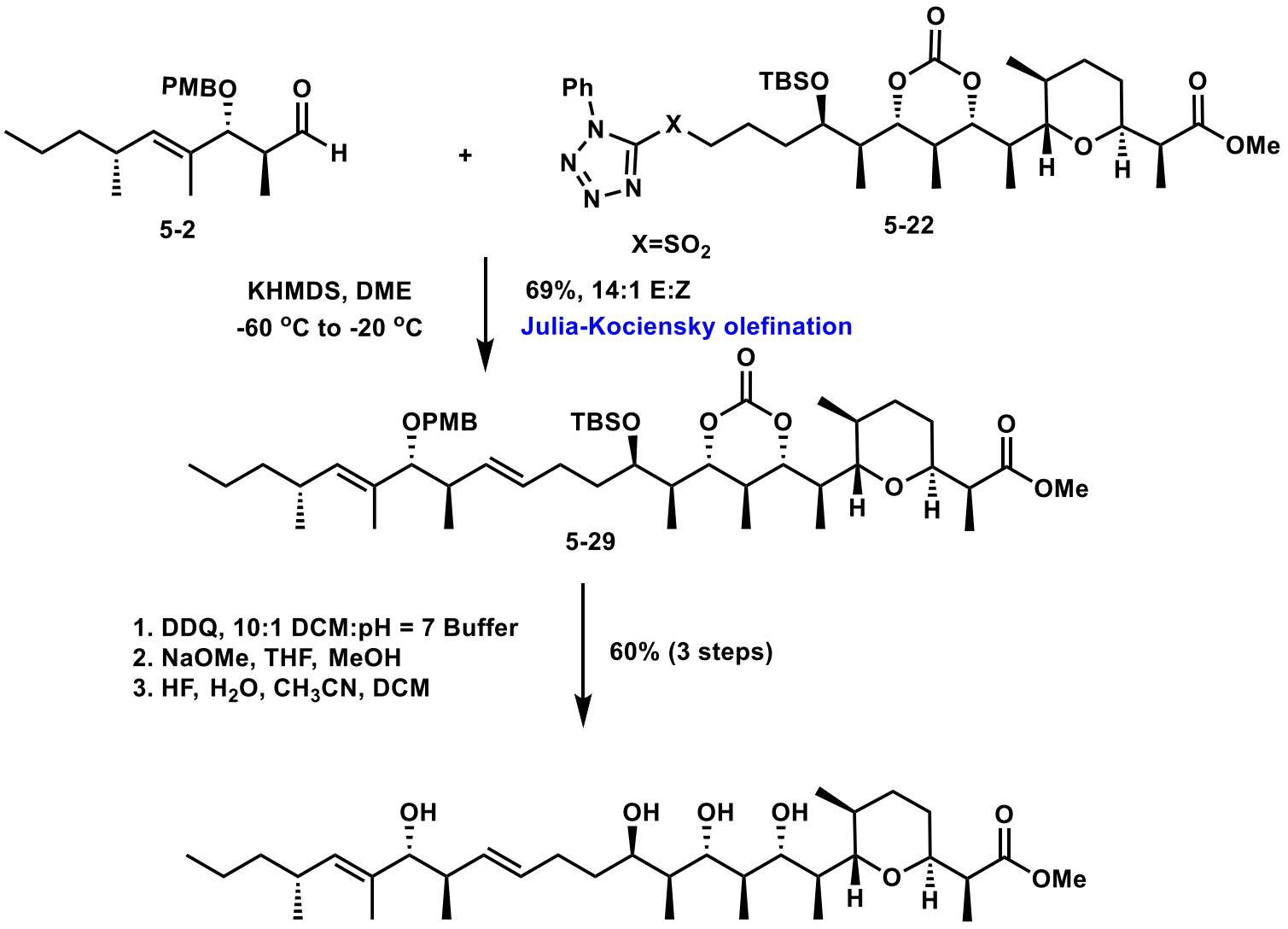


Alkene(Olefin) Metathesis (Grubbs catalyst)



Total Synthesis of Zincophorin-Leighton

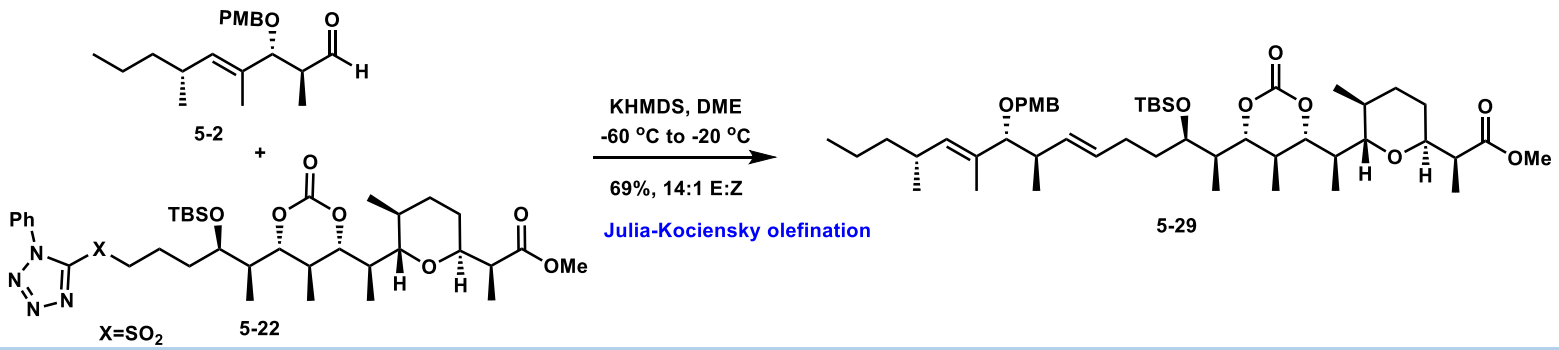
Coupling of the C1–C16 fragment with C17–C25 fragment



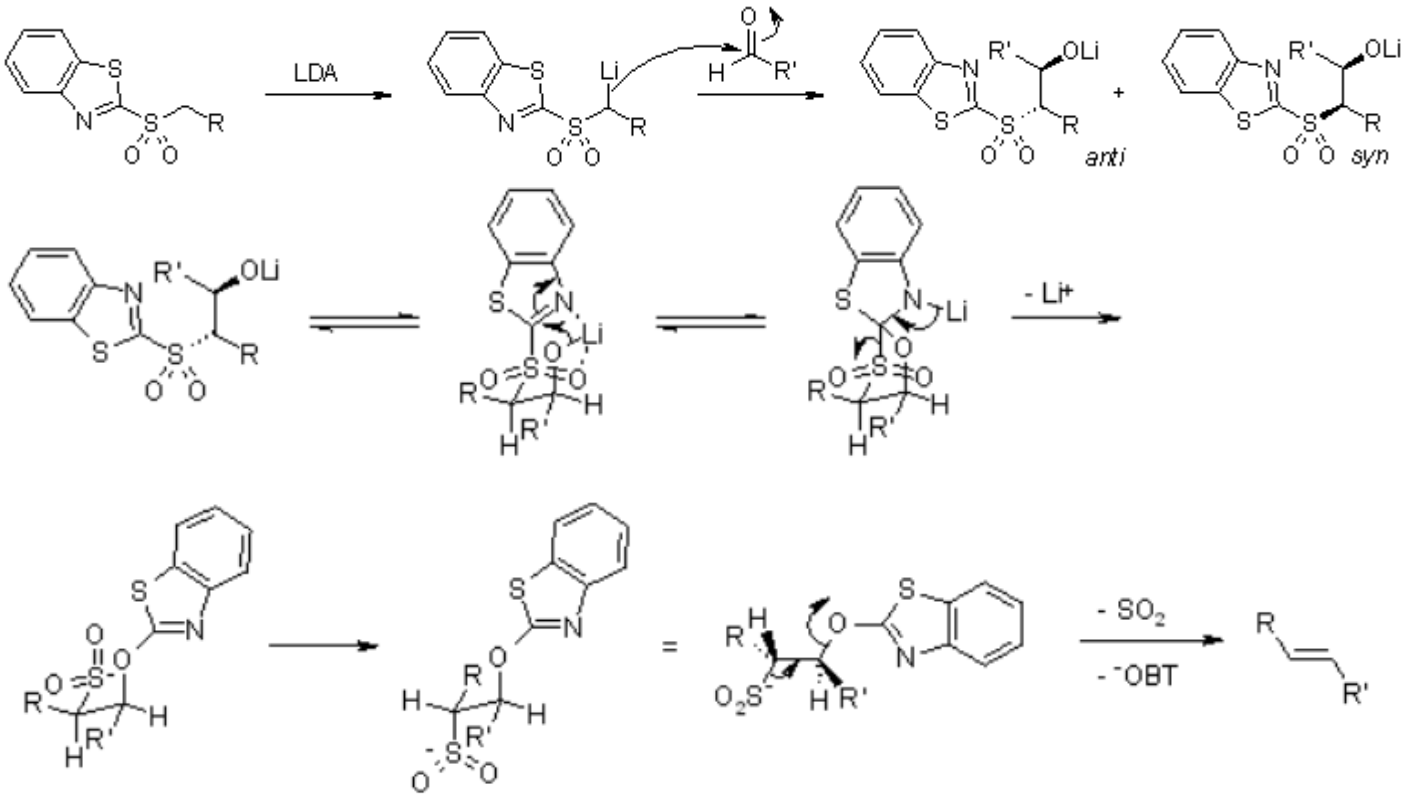
J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

Total Synthesis of Zincophorin-Leighton

Coupling of the C1–C16 fragment with C17–C25 fragment



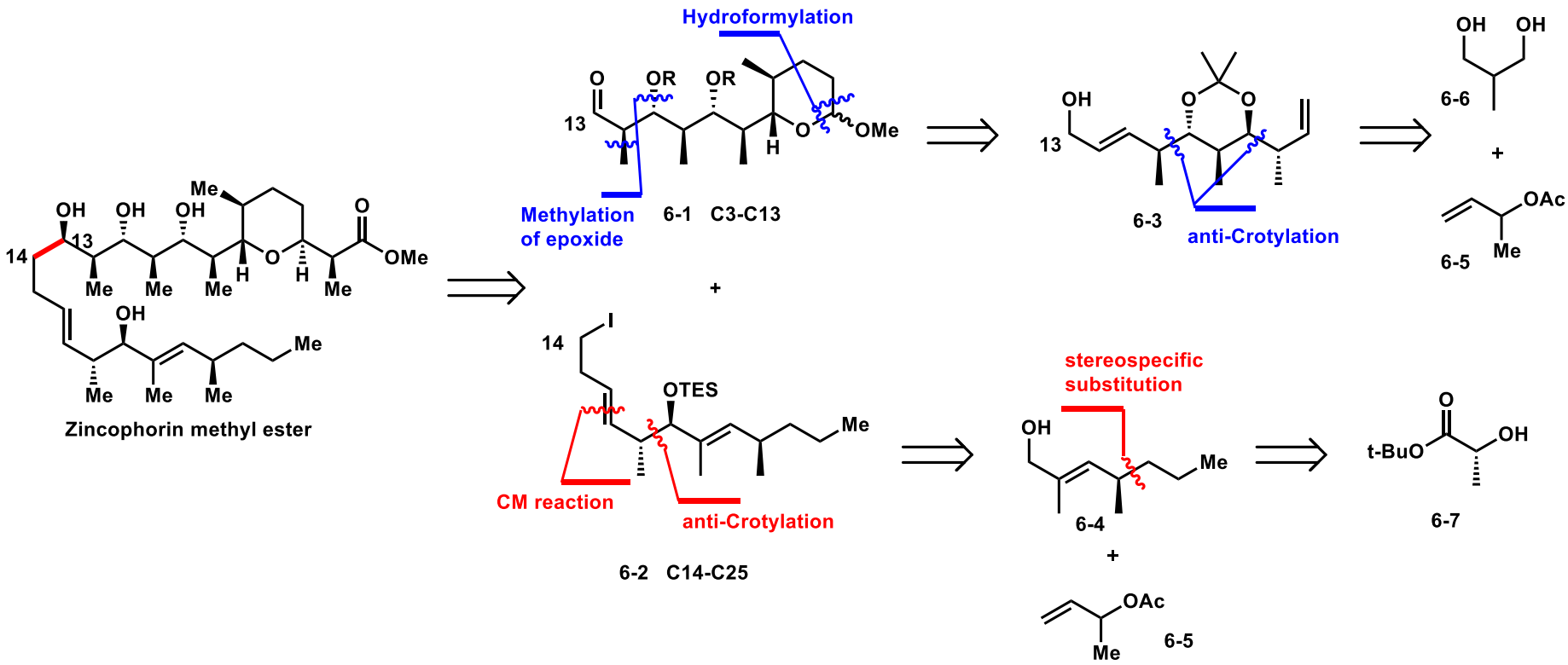
Julia-Kociensky olefination



Total Synthesis of Zincophorin-Krische

Retrosynthetic Analysis

VI. Krische: *J. Am. Chem. Soc.* **2015**, *137*, 8900

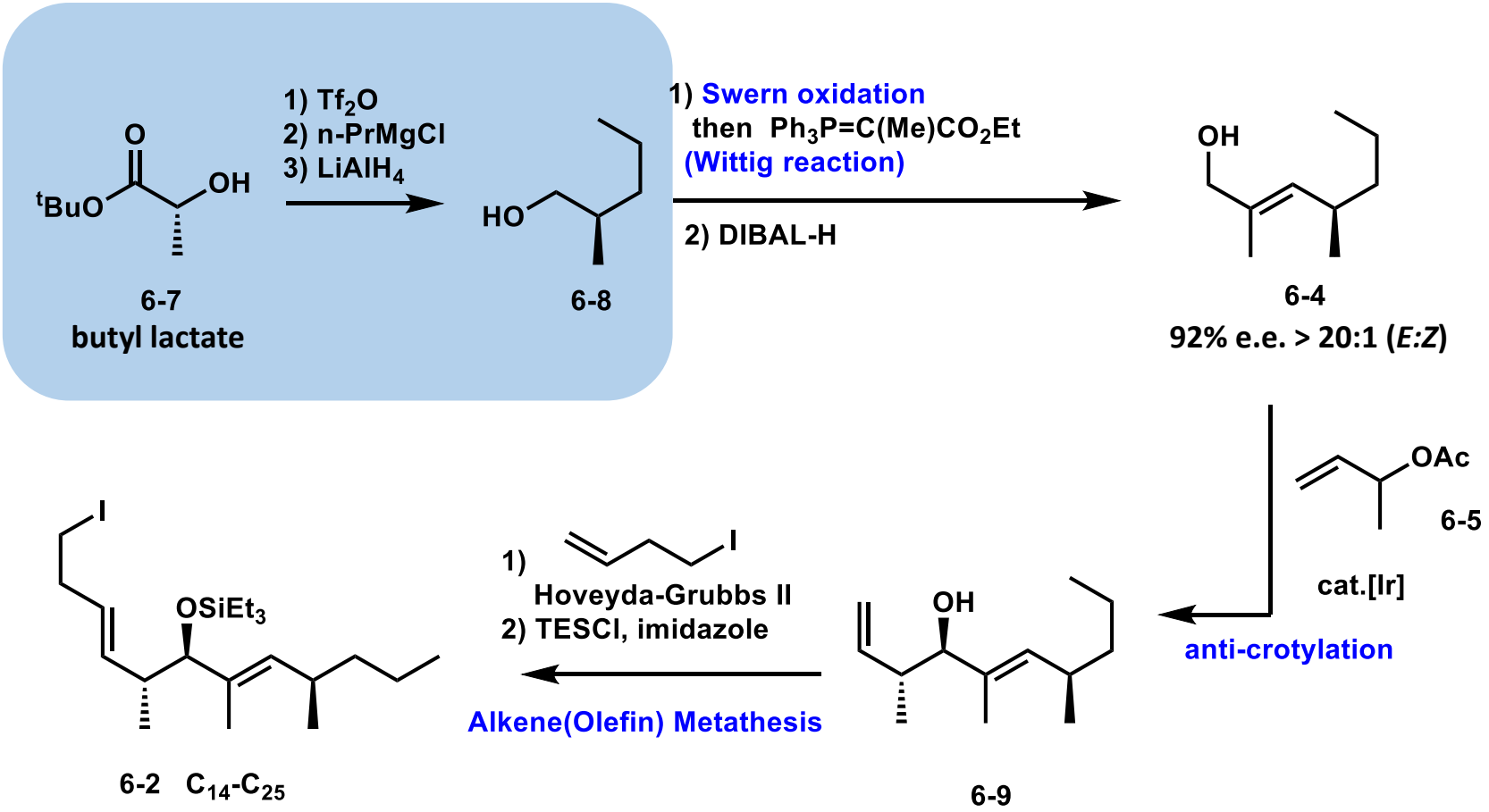


M. J. Krische, *et al*. *J. Am. Chem. Soc*. **2015**, *137*, 8900.

96

Total Synthesis of Zincophorin-Krische

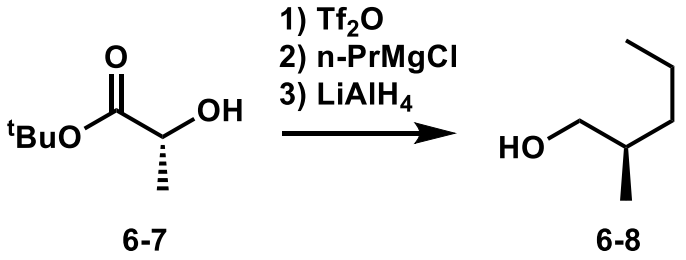
Synthesis of the C14–C25 fragment



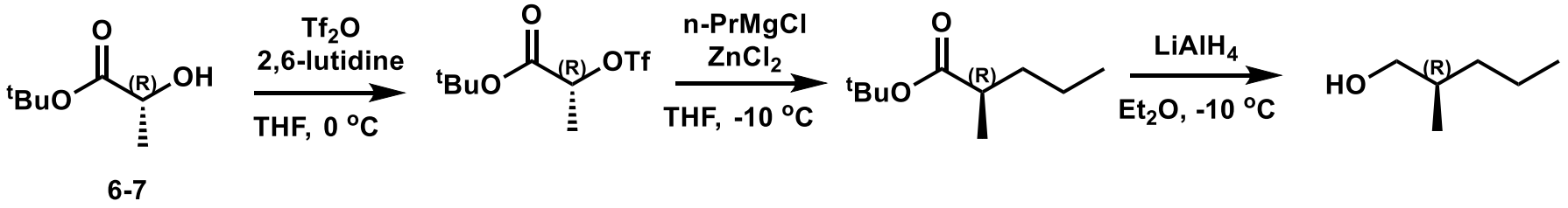
M. J. Krische, *et al*. *J. Am. Chem. Soc*. **2015**, *137*, 8900.

Total Synthesis of Zincophorin-Krische

Synthesis of the C14–C25 fragment (6-7 to 6-8)



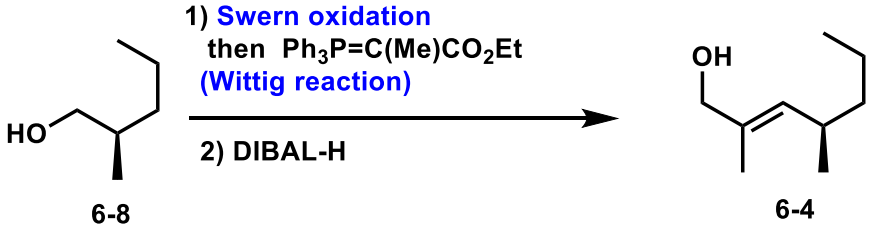
6-7 6-8



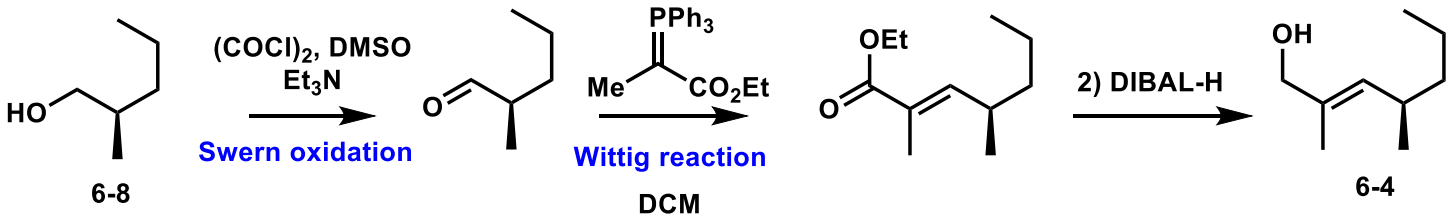
6-7

Total Synthesis of Zincophorin-Krische

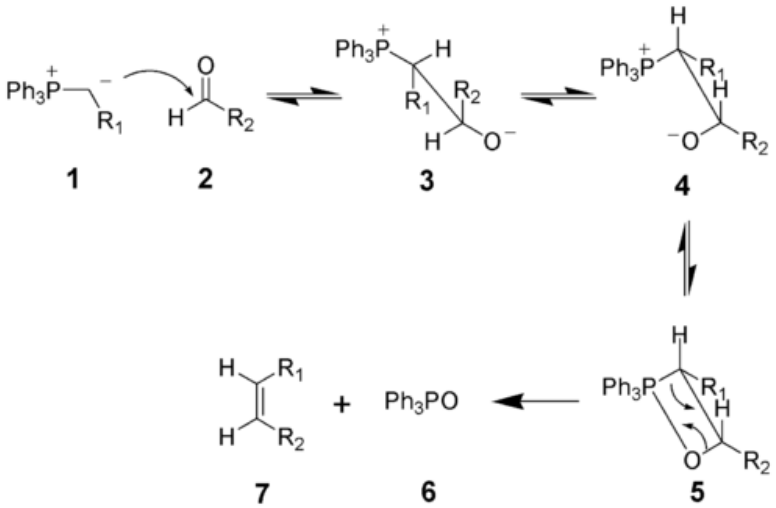
Synthesis of the C14–C25 fragment (6-8 to 6-4)



92% e.e. > 20:1 (*E:Z*)

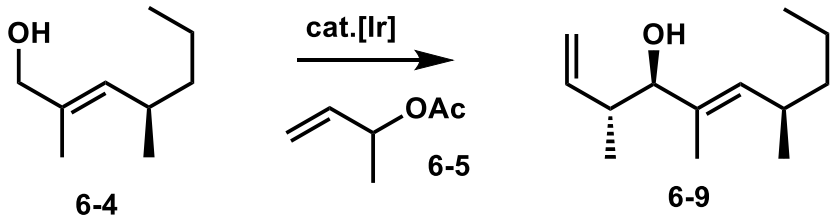


Wittig reaction

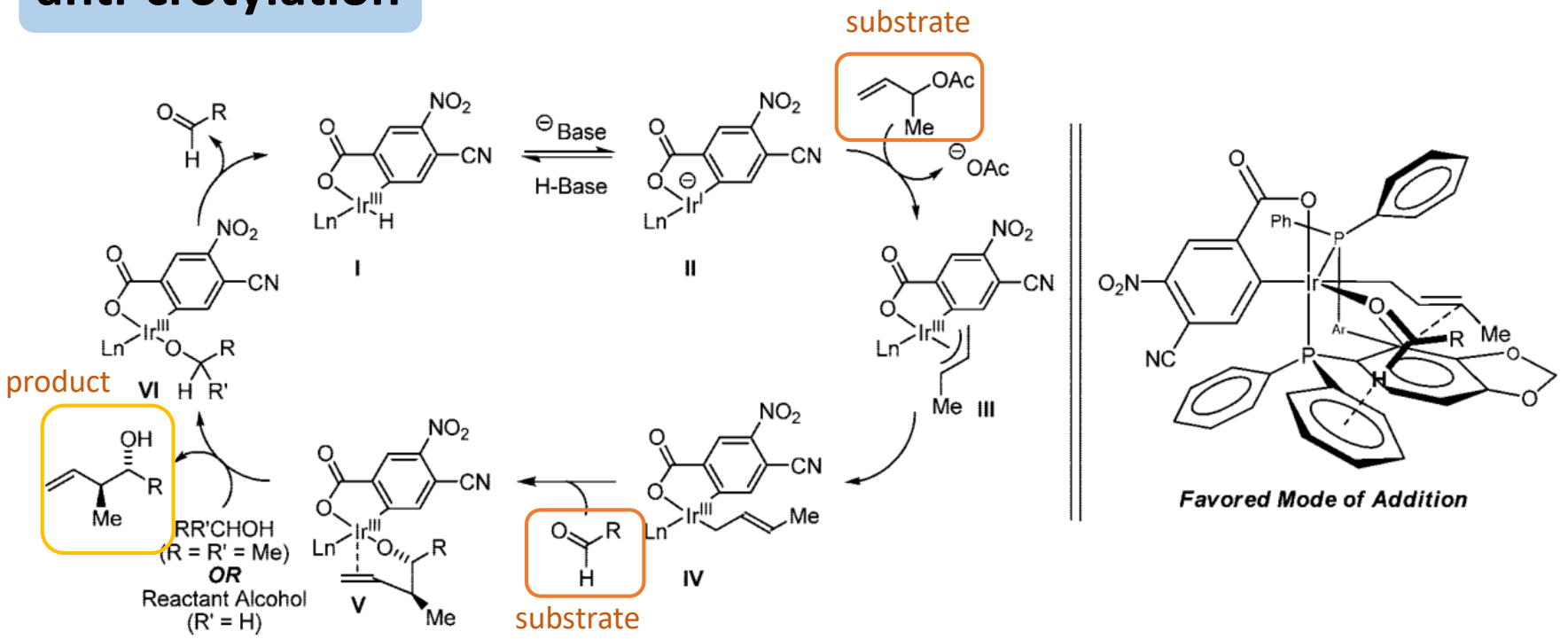


Total Synthesis of Zincophorin-Krische

Synthesis of the C14–C25 fragment (6-4 to 6-9)



anti-crotylation



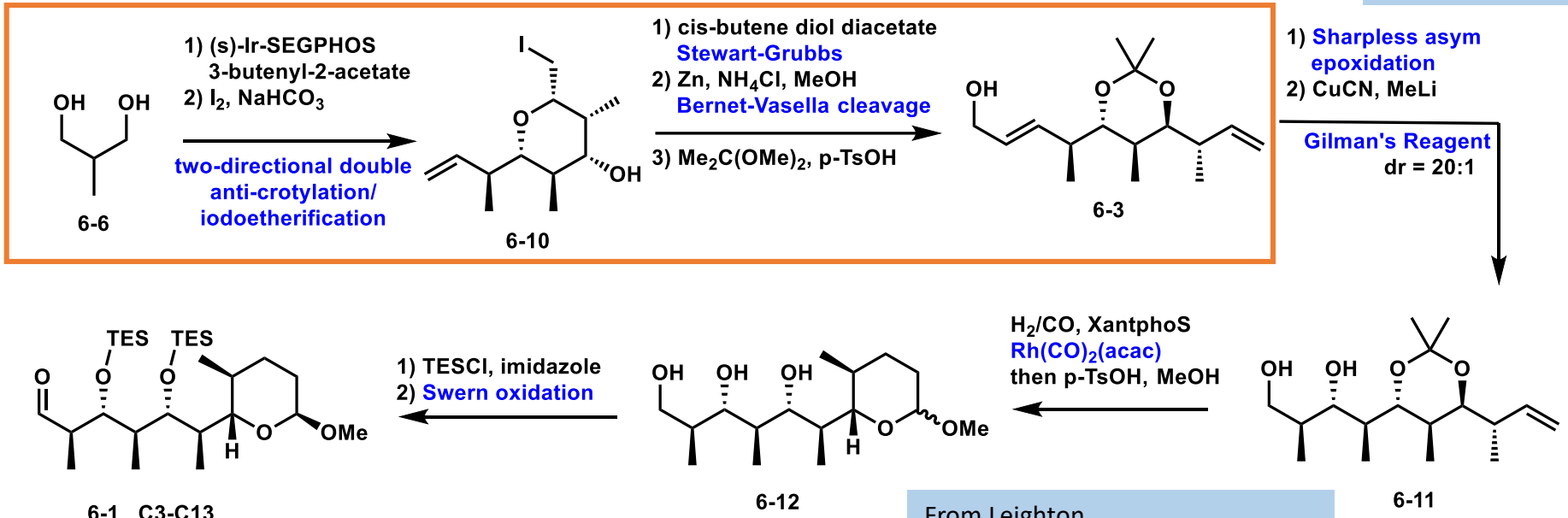
M. J. Krische, *et al. J. Am. Chem. Soc.* **2008**, *130*,14891

Total Synthesis of Zincophorin-Krische

Synthesis of the C3–C10 fragment

From Miyashita
Angew. Chem., Int. Ed. **2004**, *43*, 4341.

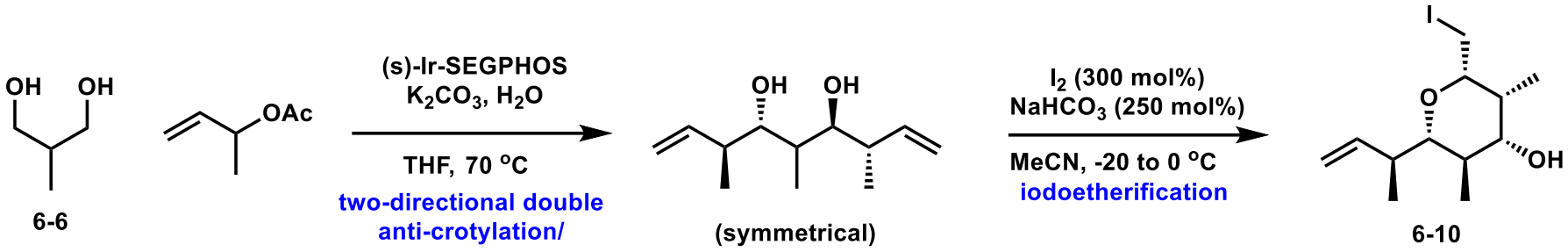
Efficient!



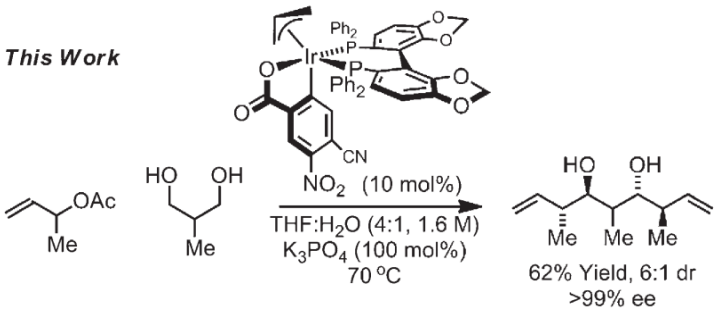
From Leighton
J. Am. Chem. Soc. **2011**, *133*, 7308.

Total Synthesis of Zincophorin-Krische

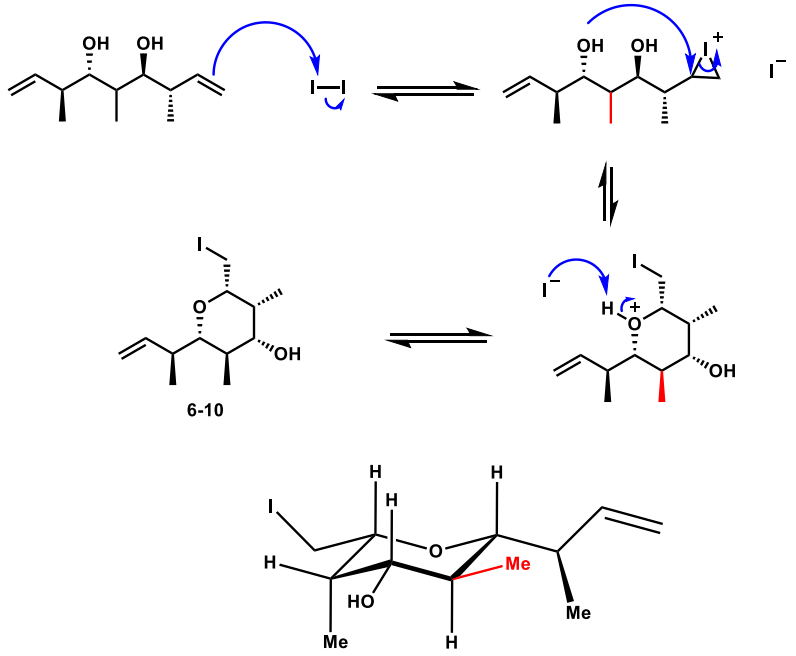
Synthesis of the C3–C10 fragment (6-6 to 6-10)



two-directional double anti-crotylation

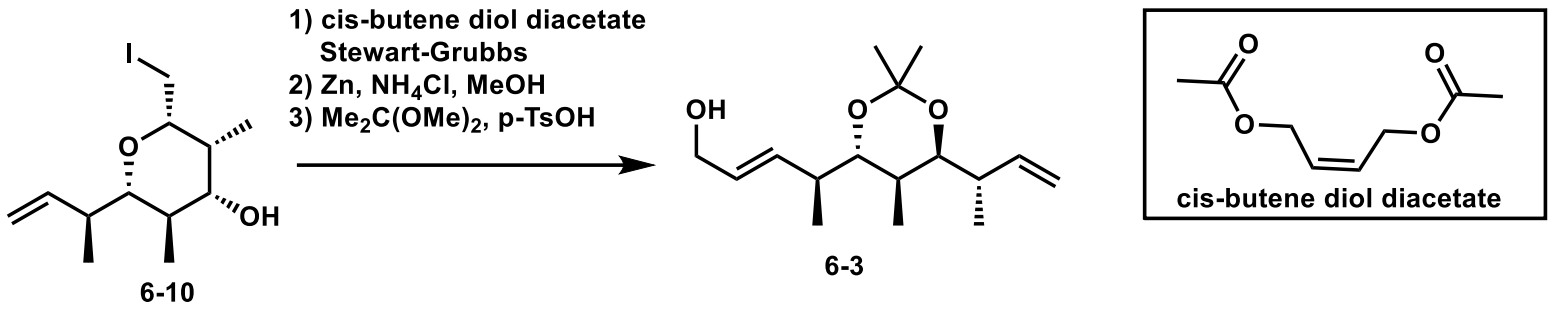


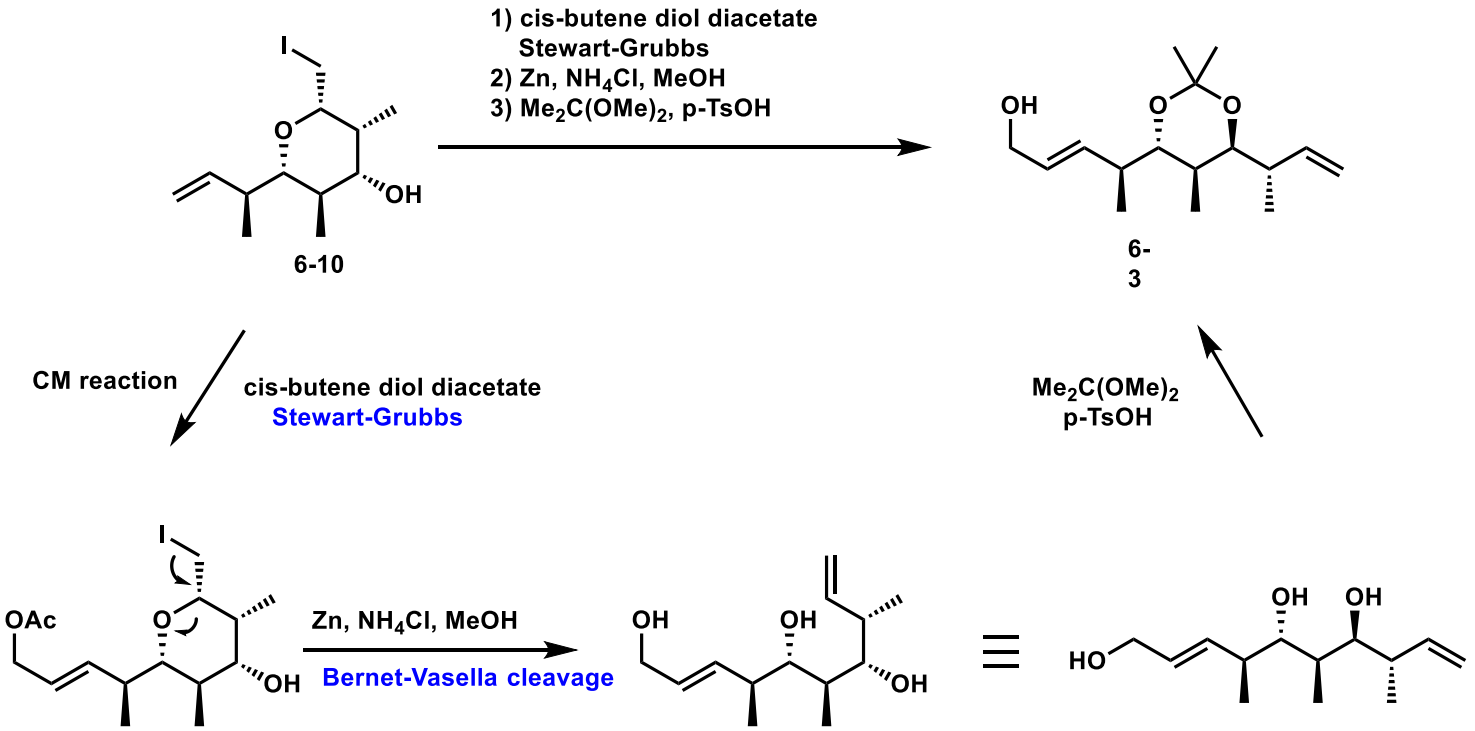
Iodoetherification



Total Synthesis of Zincophorin-Krische

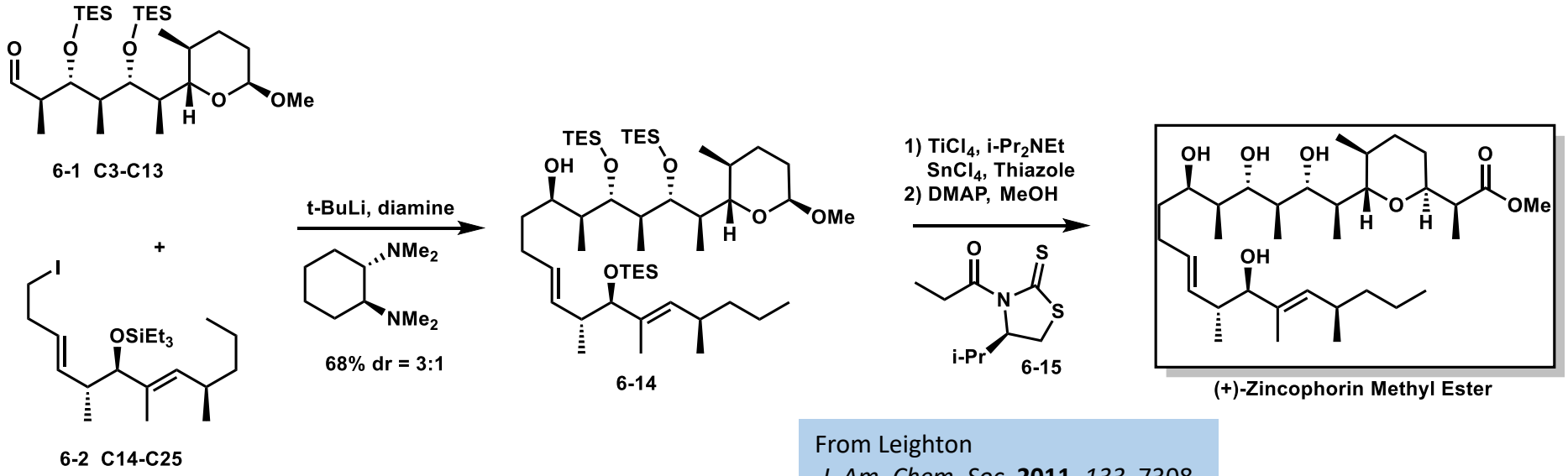
Synthesis of the C3–C10 fragment (6-10 to 6-3)





Total Synthesis of Zincophorin-Krische

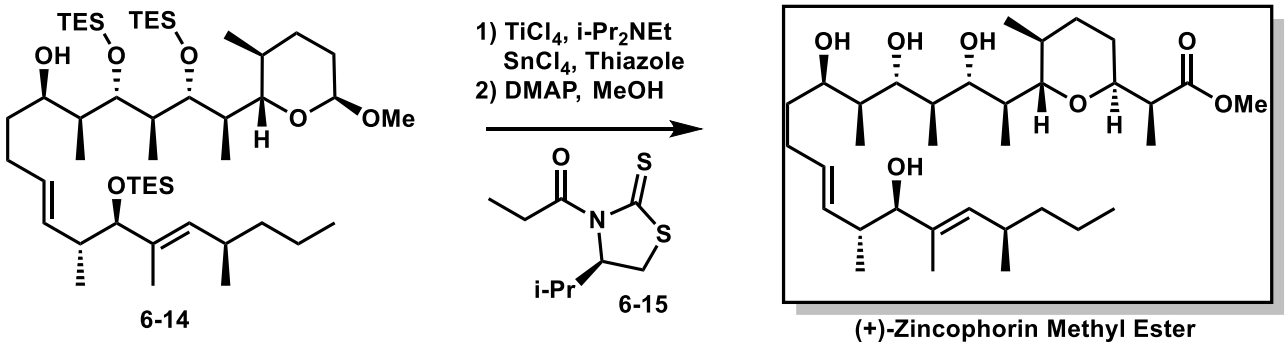
Coupling of two fragments and synthesis of Zincophorin methyl ester



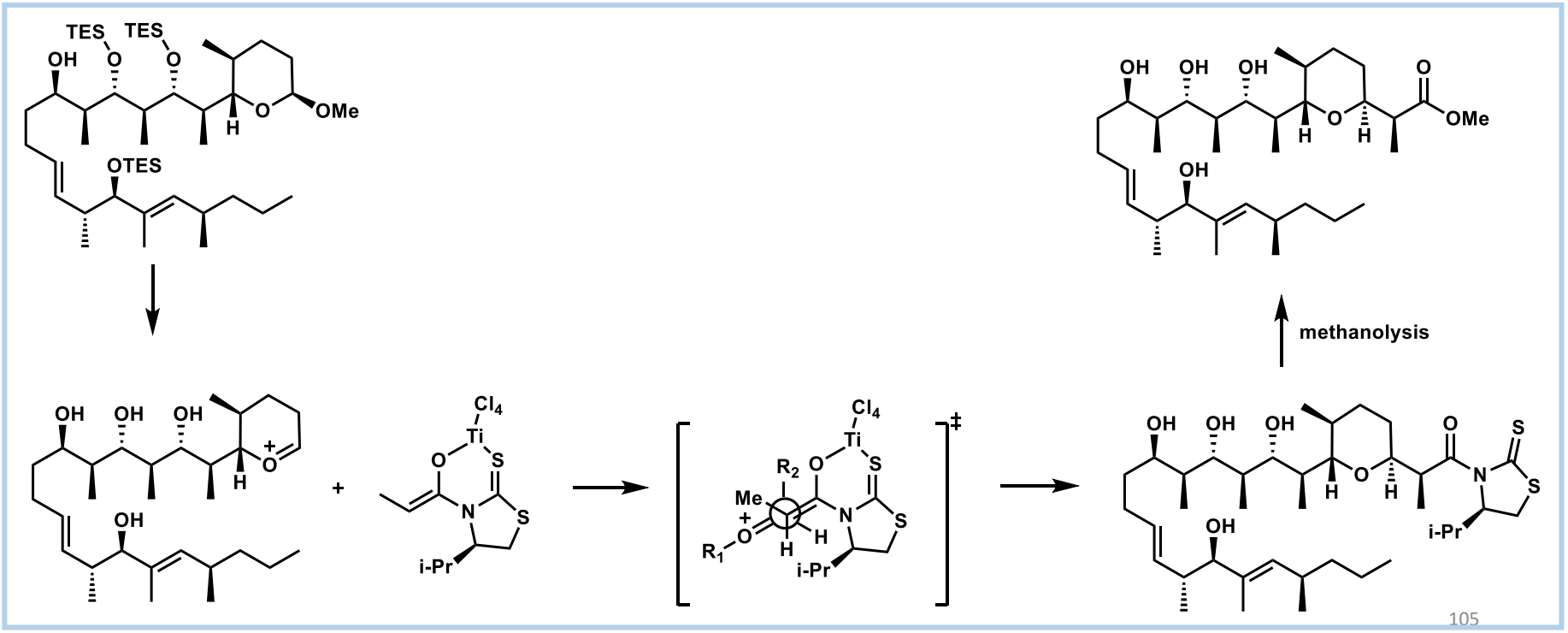
From Leighton
J. Am. Chem. Soc. **2011**, *133*, 7308.

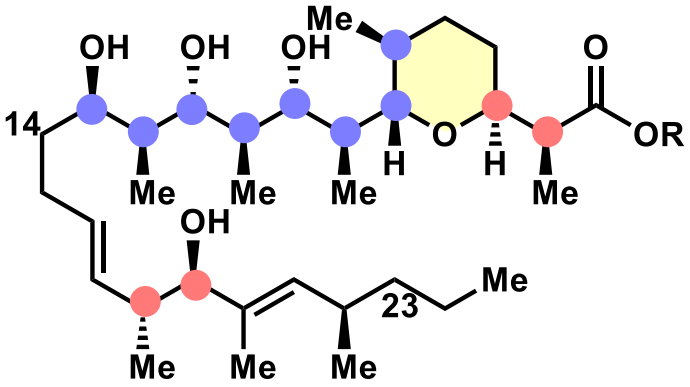
Total Synthesis of Zincophorin-Krische

Coupling of two fragments and synthesis of Zincophorin methyl ester



From Leighton
J. Am. Chem. Soc. **2011**, *133*, 7308.





1 R = H, zincophorin
2 R = Me, zincophorin methyl ester

Total Synthesis of Zincophorin and Its Methyl Ester

Danishefsky: *J. Am. Chem. Soc.* **1987**, *109*, 1572 (**35 steps LLS**)

Cossy: *J. Org. Chem.* **2004**, *69*, 4626 (**30 steps LLS**)

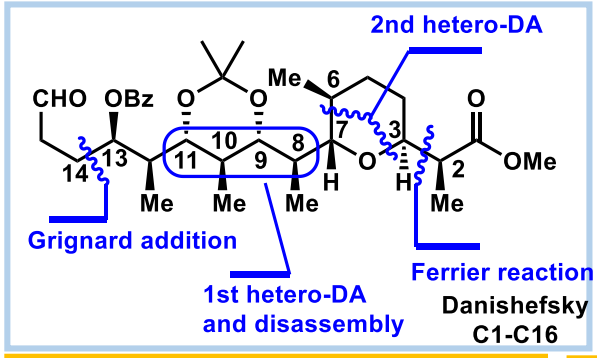
Miyashita: *Angew. Chem., Int. Ed.* **2004**, *43*, 4341 (**39 steps LLS**)

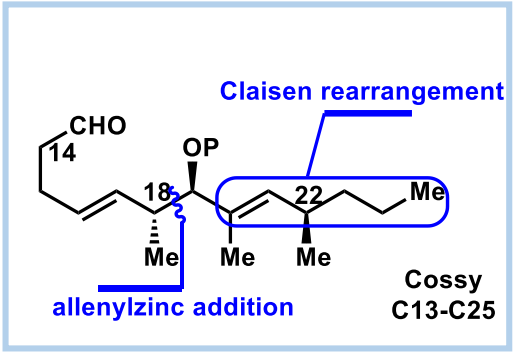
Leighton: *J. Am. Chem. Soc.* **2011**, *133*, 7308 (**21 steps LLS**)

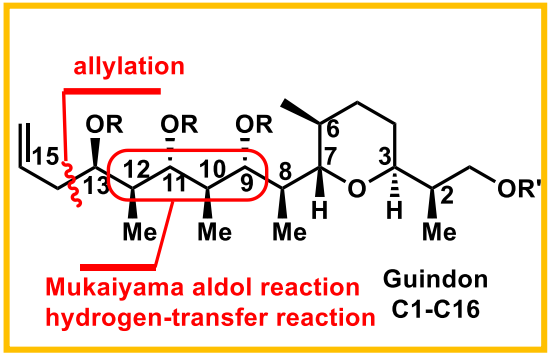
J. Am. Chem. Soc. **2017**, *139*, 4568 (**9 steps LLS**)

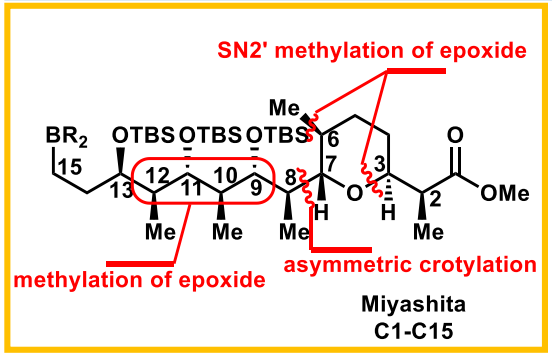
Krische: *J. Am. Chem. Soc.* **2015**, *137*, 8900 (**13 steps LLS**)

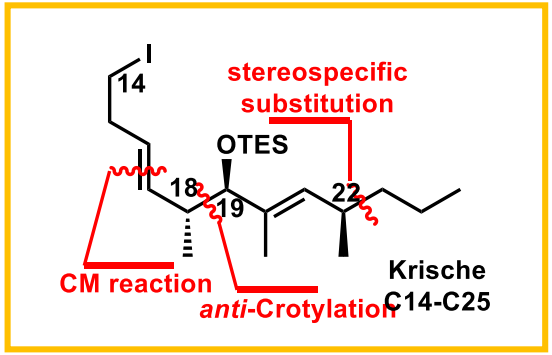
Guindon: *Tetrahedron* **2015**, *71*, 709 (**49 steps LLS**)

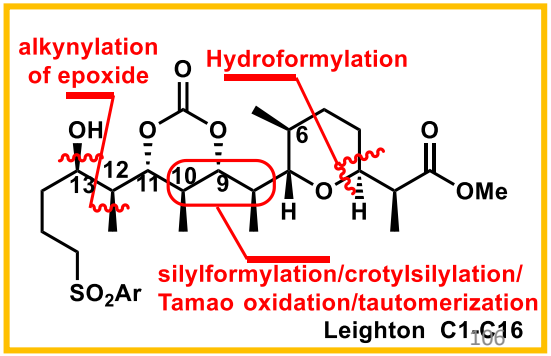












Acknowledgement

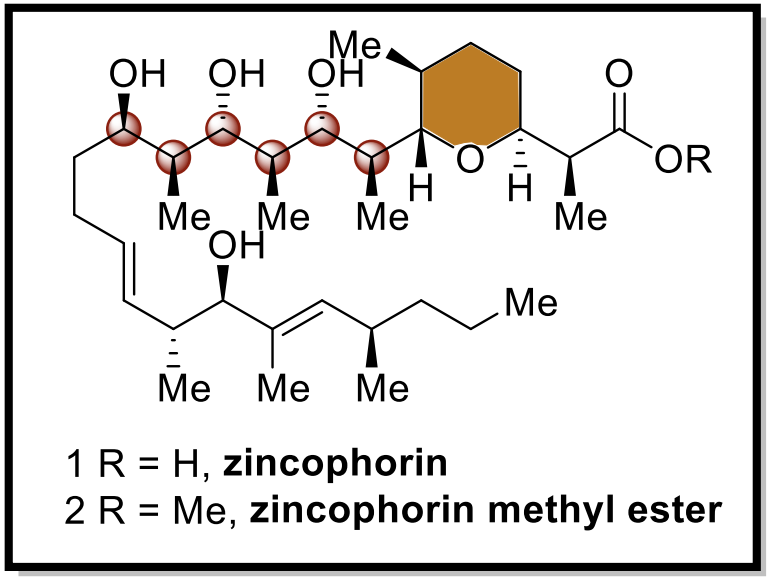
- *Prof.* Tao Ye, *Dr.* Yian Guo;
- All my labmates in F211;
- All professors and faculties in SCBB

Thank you

for your kind attention

Classics in Total Synthesis

Total synthesis of zincophorin methyl ester



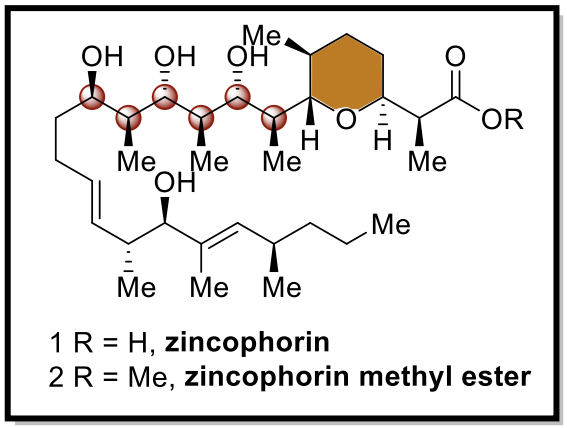
Reporter: **Fusong Wu**

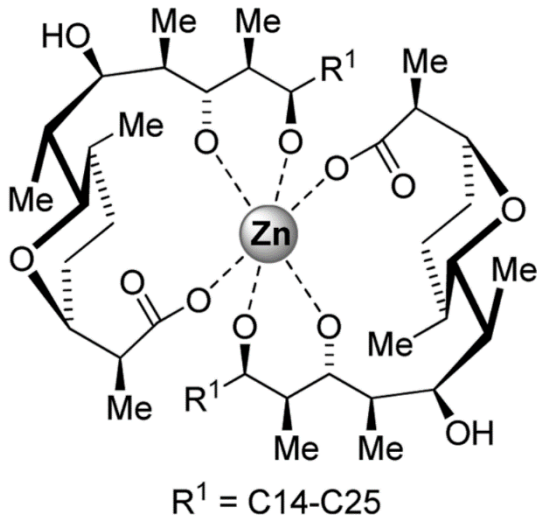
Supervisors: ***Prof.*** **Tao Ye**

Dr. **Yian Guo**

2020.9.21

Review-background of Zincophorin and Zincophorin methyl ester





Isolation:

- *Seperated from strains of Streptomyces griseus*
- *In 1984, Grafe et al. and Poyser et al. reported the isolation*

Biological activities:

- *Possesses in vivo activity against Gram-positive bacteria and Clostridium coelchii at ≤1 ppm*
- *Its salts exhibited anticoccidal activity against Eimeria tenella W/CAM*
- *Methyl ester has strong inhibitory properties against influenza WSN/virus*

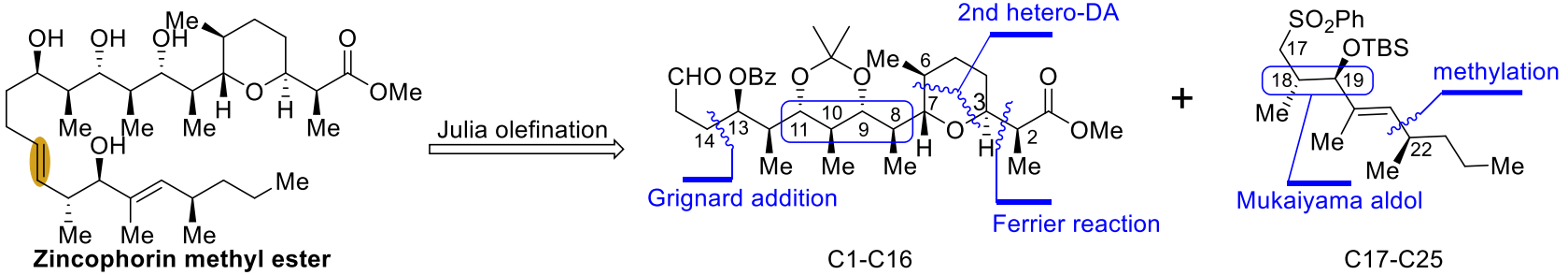
Structural Features:

- *A challenging C8–C12 all-anti stereopentad embedded within the C6–C13 tetrapropionate, and the trans tetrahydropyran ring*
- *13 stereogenic centers (8 contiguous stereocenters)*

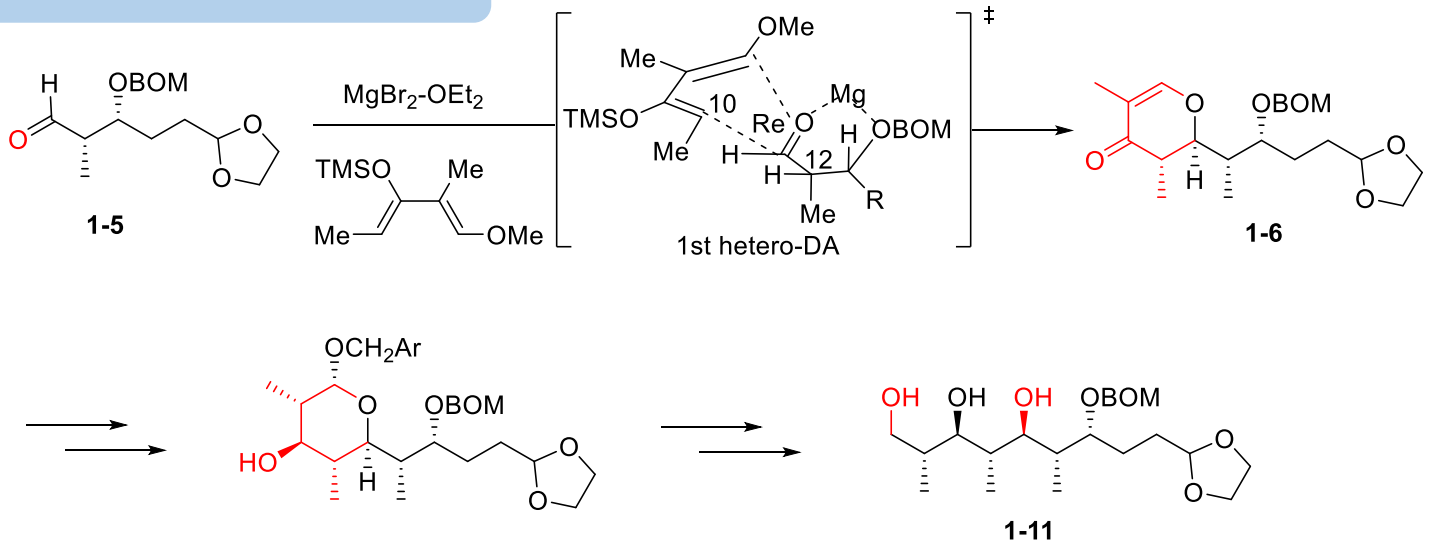
1. U. Grafe, *et al. J. Antibiot*., **1984**, *37*, 836.
2. J. P. Poyser, *et al*. *J. Antibiot*., **1984**, *37*, 1501.
3. U. Grafe, *Ger. Pat*., **1986**, *231*, 793.

Review - Danishefsky

I. **Danishefsky:** *J. Am. Chem. Soc*. **1987**, *109*, 1572 (**the first total synthesis**)



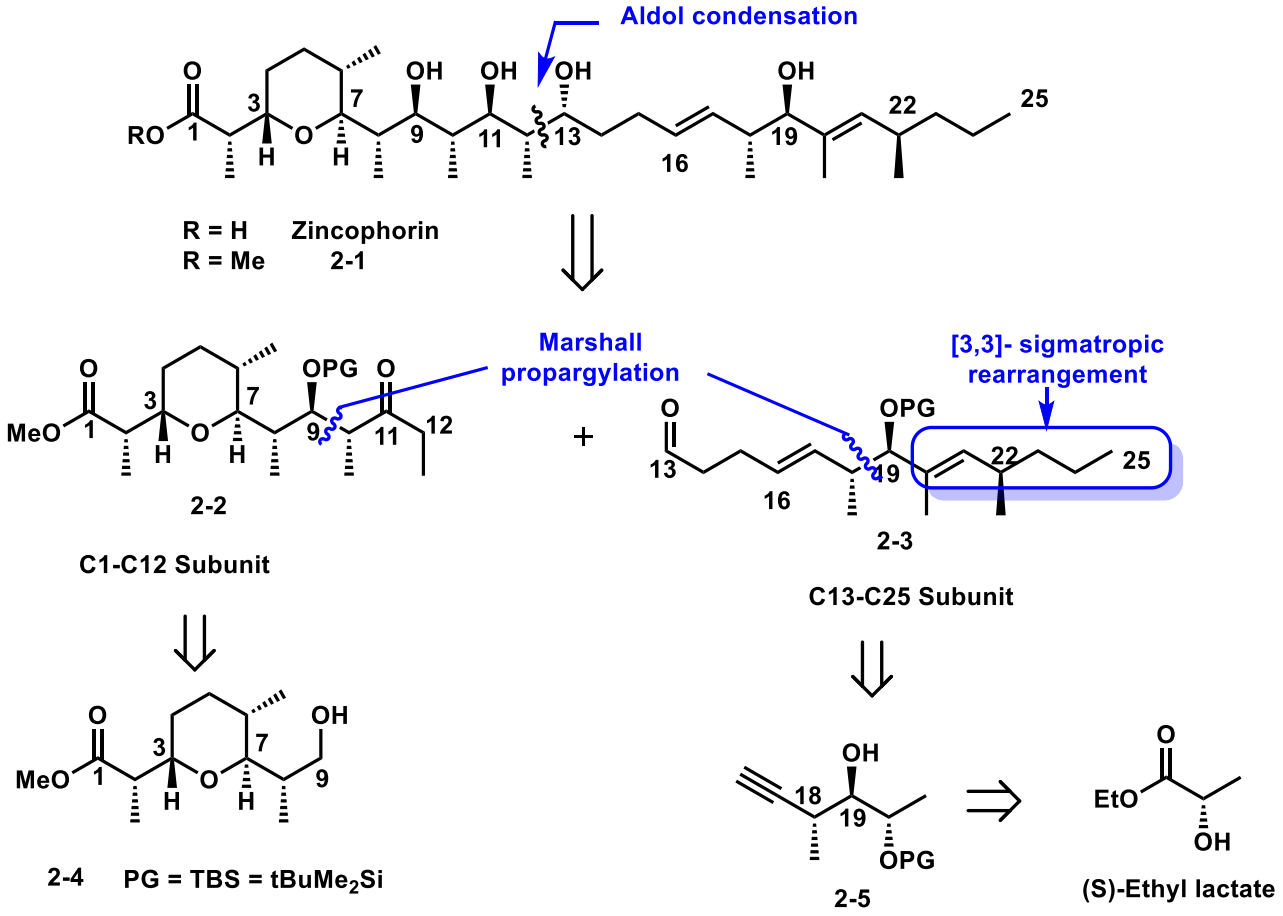
Key reaction： 1st hetero-DA



Review-Cossy

II. **Cossy**: *Org. Lett.* **2003**, *5*, 4037

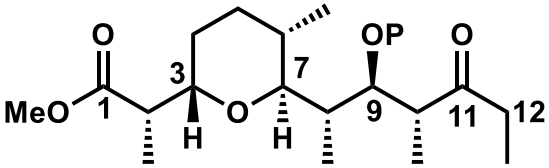
III. **Cossy**: *J. Org. Chem.* **2004**, *69*, 4626



J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

J. Cossy, *et al*. *Org.Lett.* **2003**, *5*, 4037.

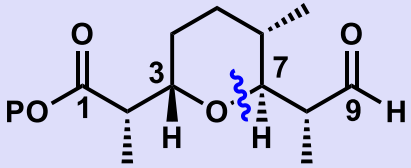
Review-Cossy



3-2

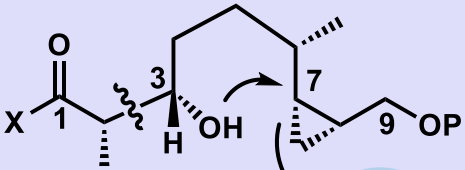
C1-C12 subunit

Chain extension



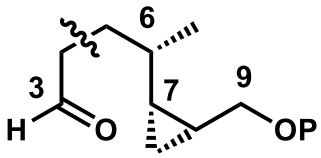
3-4

Intramolecular oxymercuration



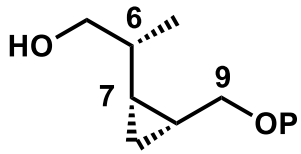
3--5

Aldol condensation



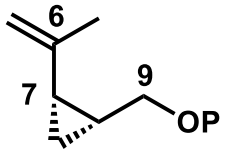
3-6

Chain extension



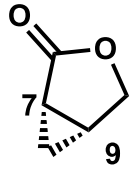
3-7

Hydroboration



3-8

Nucleophic ring-openging



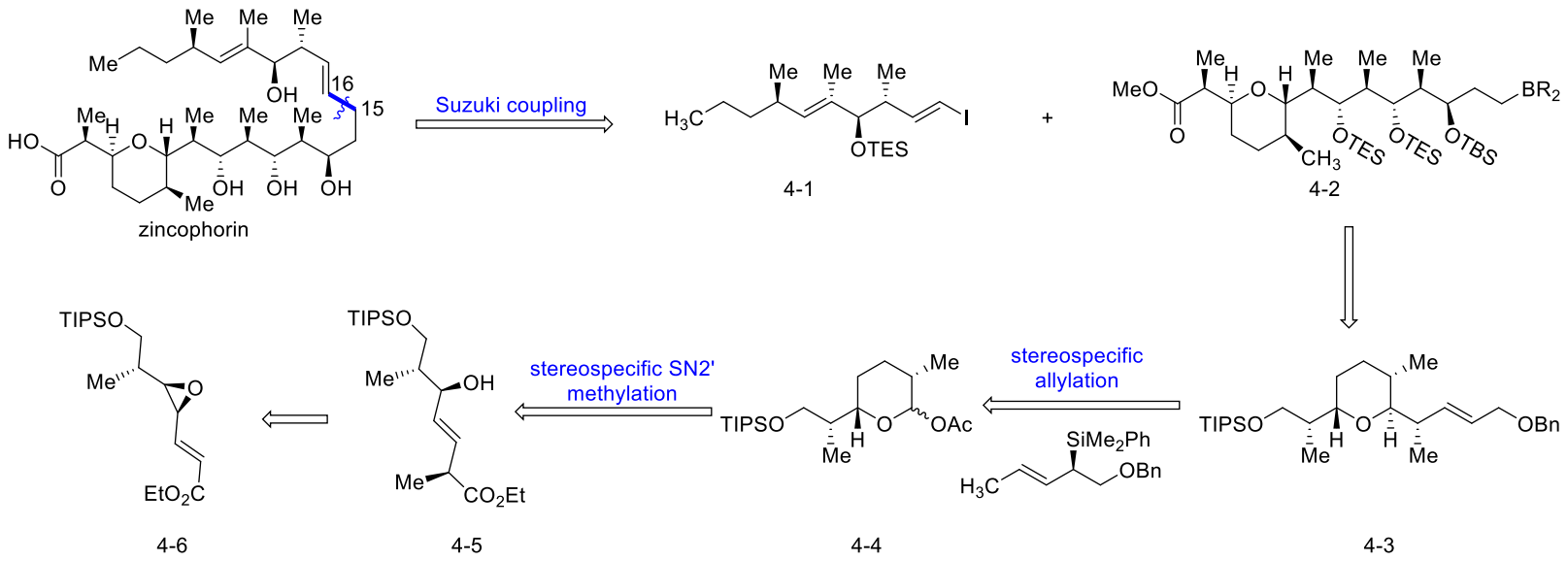
3-9

P = appropriate protecting group

J. Cossy, *et al*. *J. Org. Chem.* **2004**, *69*, 4626.

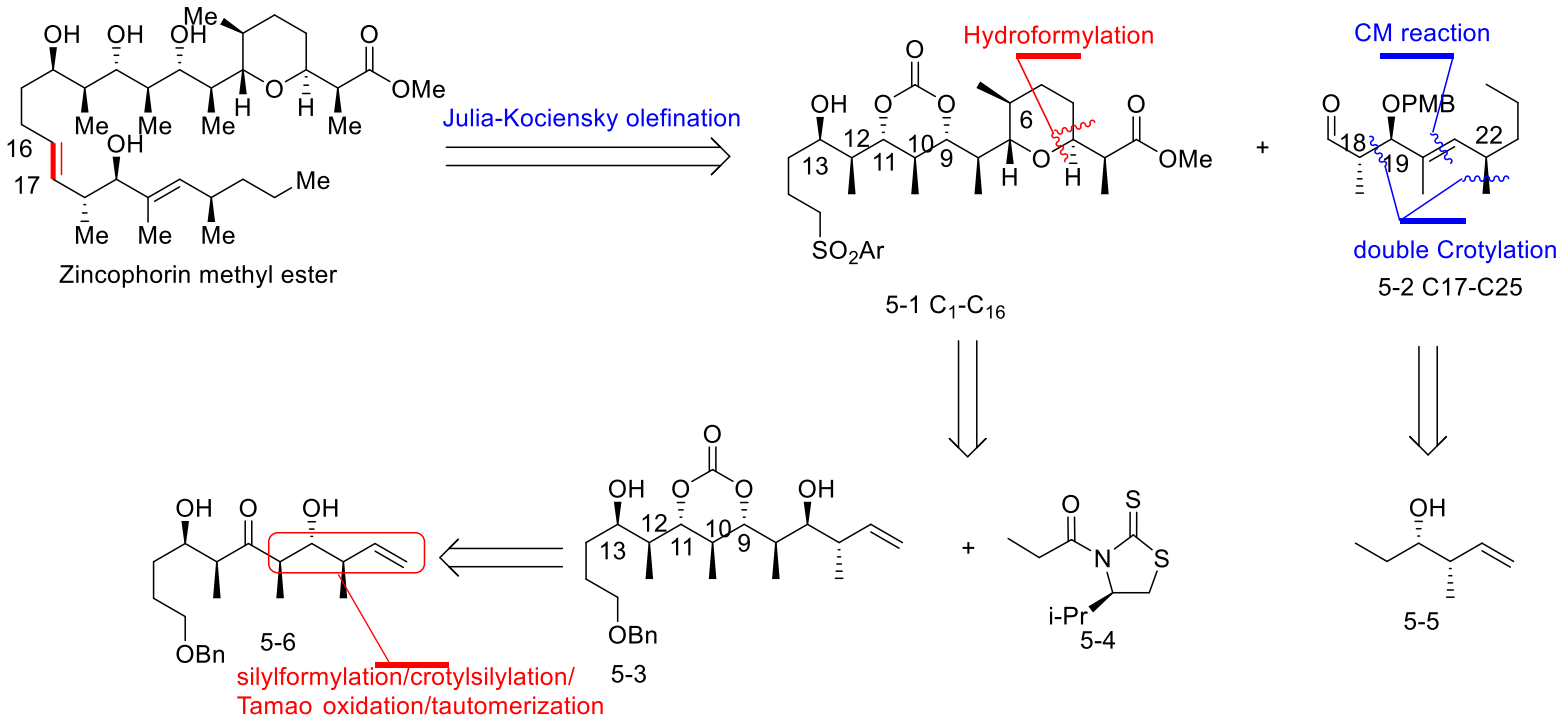
Review-Miyashita

IV. Miyashita: *Angew. Chem., Int. Ed*. **2004**, *43*, 4341



Review-Leighton

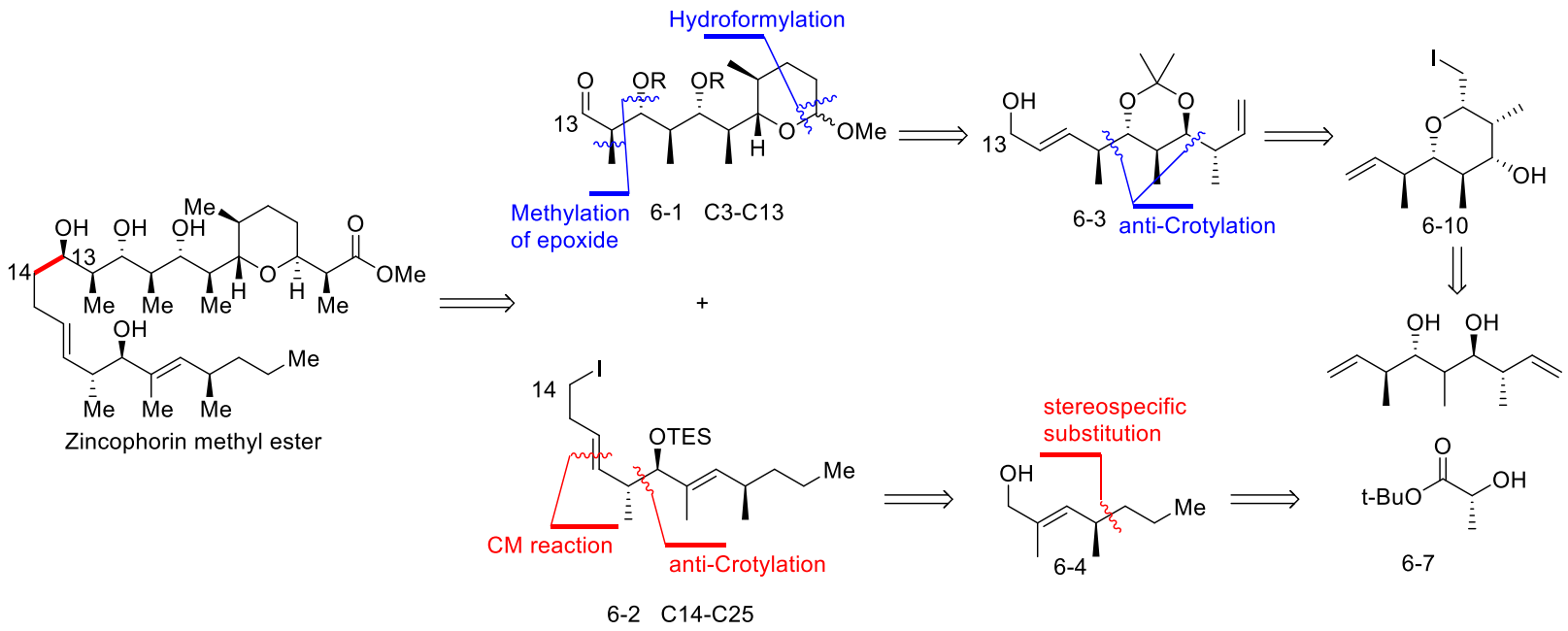
V. **Leighton:** *J. Am. Chem. Soc*. **2011**, *133*, 7308



J. L. Leighton, *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

Review-Krische

VI. Krische: *J. Am. Chem. Soc*. **2015**, *137*, 8900



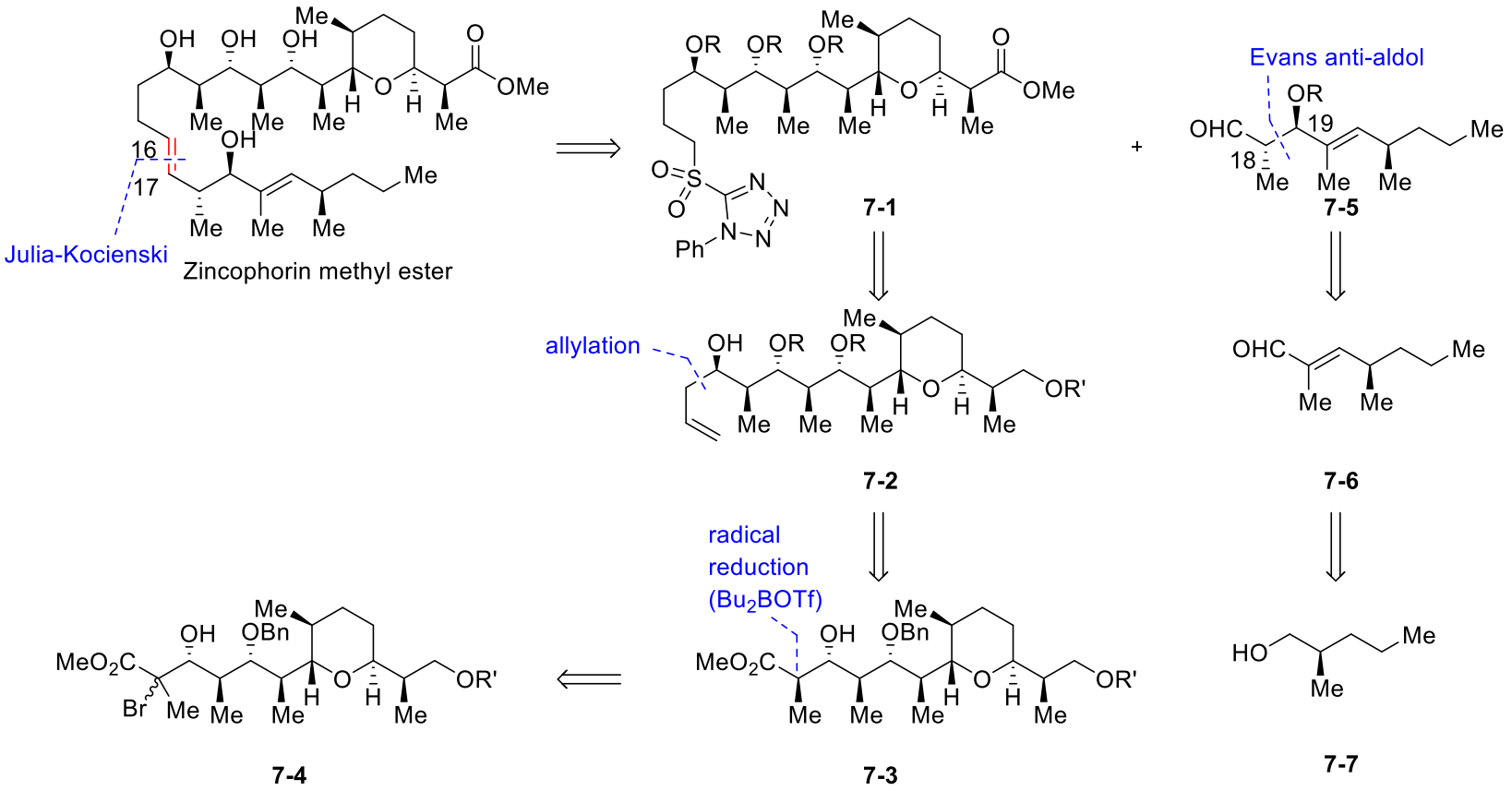
M. J. Krische, *et al*. *J. Am. Chem. Soc*. **2015**, *137*, 8900.

115

Total synthesis of zincophorin methyl ester

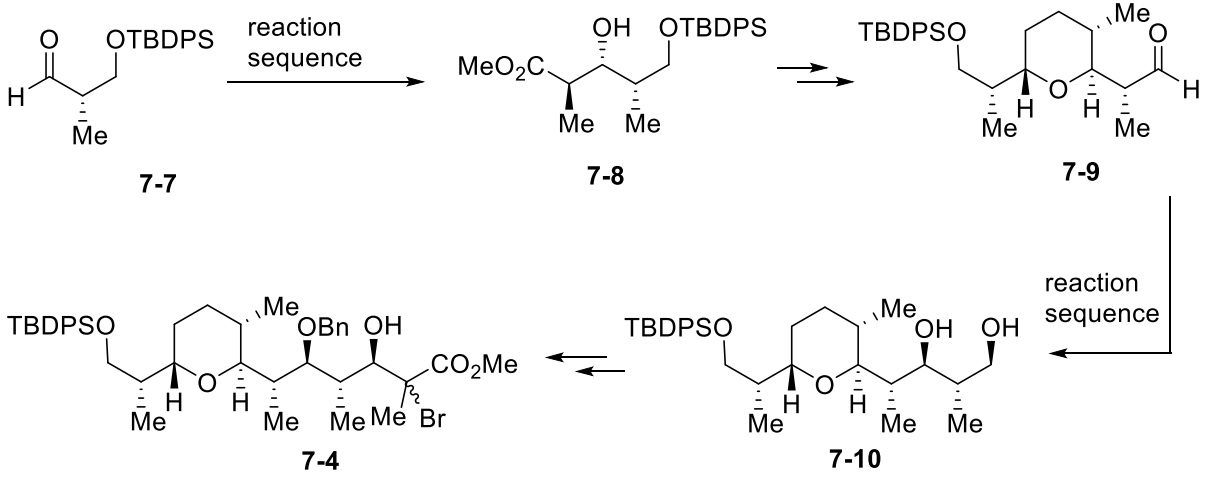
☐ Retrosynthetic Analysis

VII. Yvan Guindon : Tetrahedron 2015, 71, 709

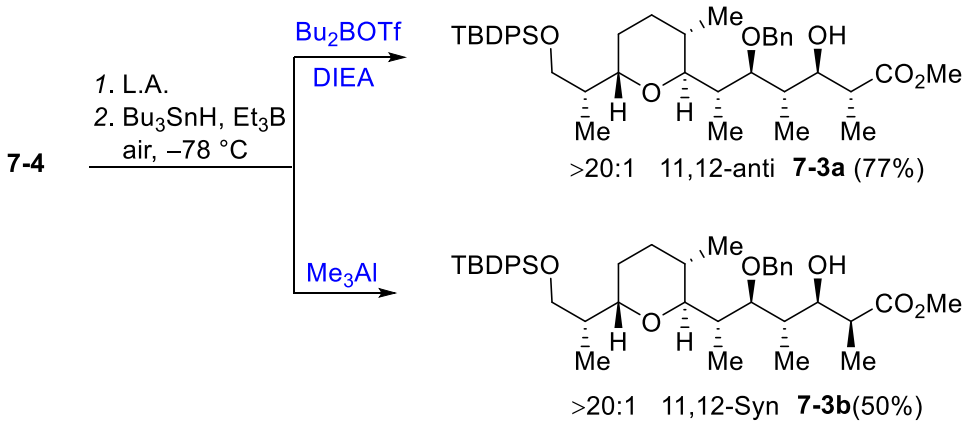


Total synthesis of zincophorin methyl ester

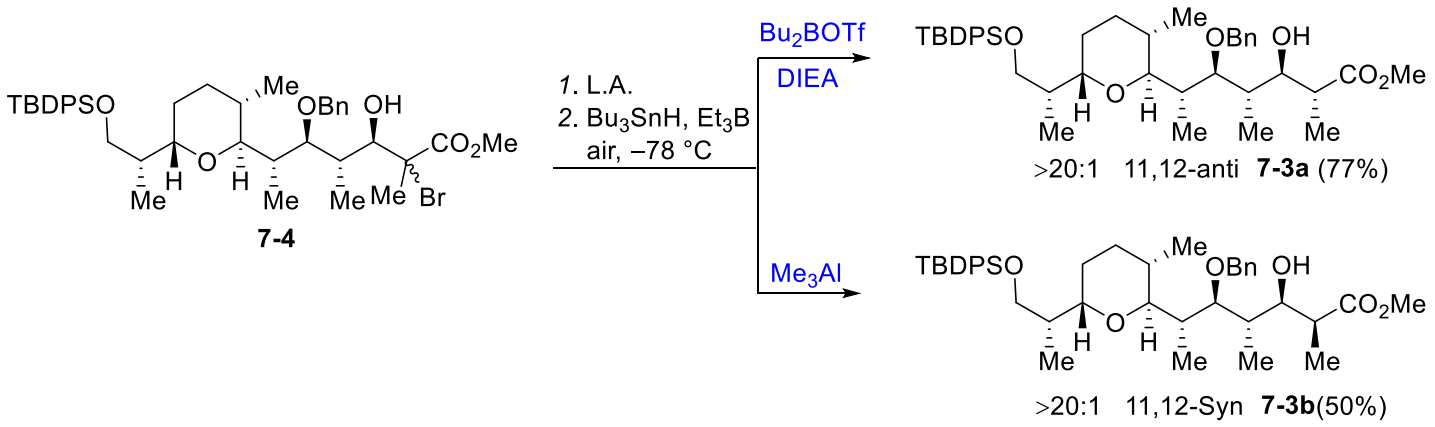
☐ Synthesis of the C1–C16 fragment



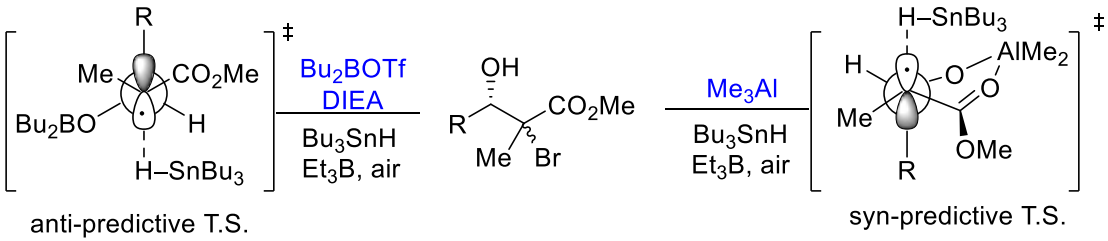
J. Org. Chem. **2011**, *76*, 7654-7676



Total synthesis of zincophorin methyl ester



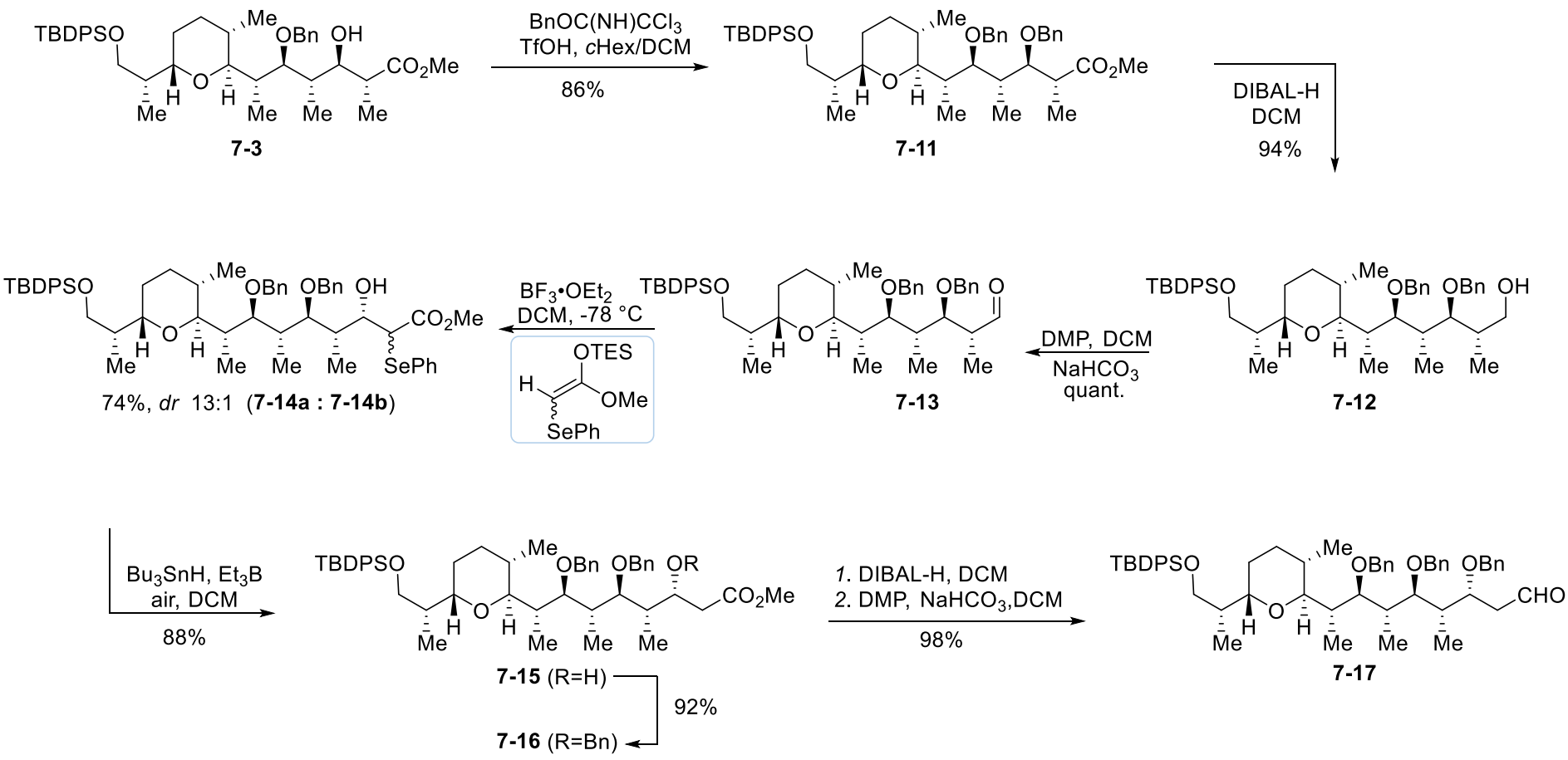
Mechanism



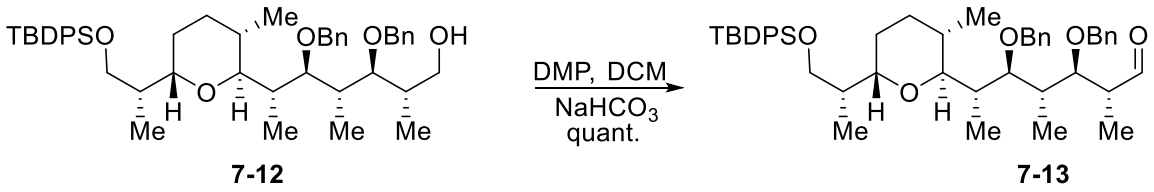
VII. Yvan Guindon : Tetrahedron 2015, 71, 709

Total synthesis of zincophorin methyl ester

☐ Synthesis of the C1–C16 fragment



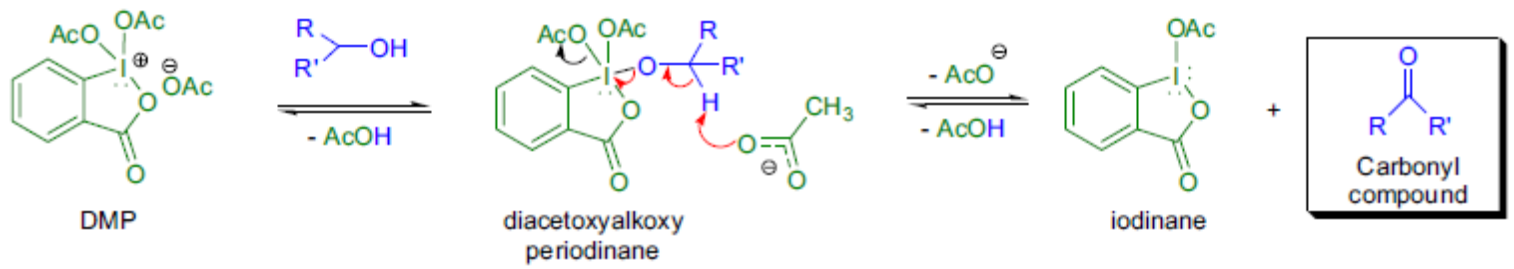
Total synthesis of zincophorin methyl ester



7-12 **7-13**

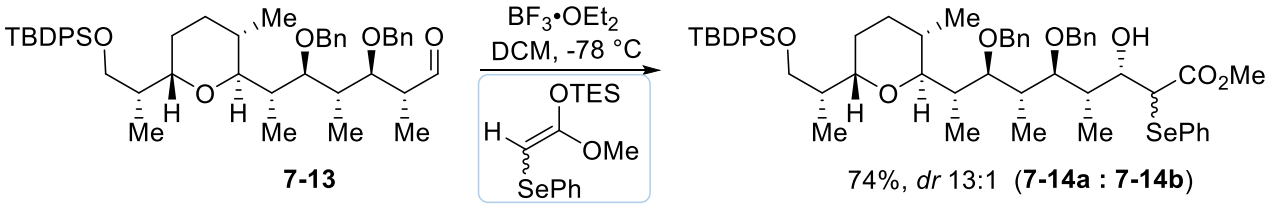
Mechanism

Dess-Martin oxidations



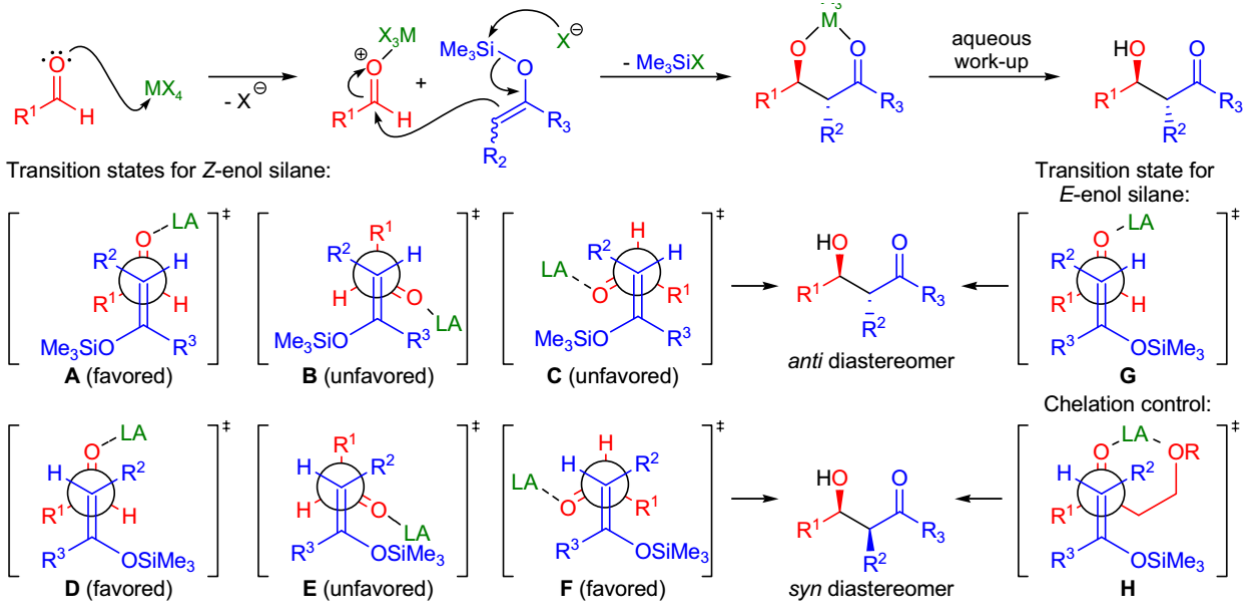
VII. Yvan Guindon : Tetrahedron 2015, 71, 709

Total synthesis of zincophorin methyl ester



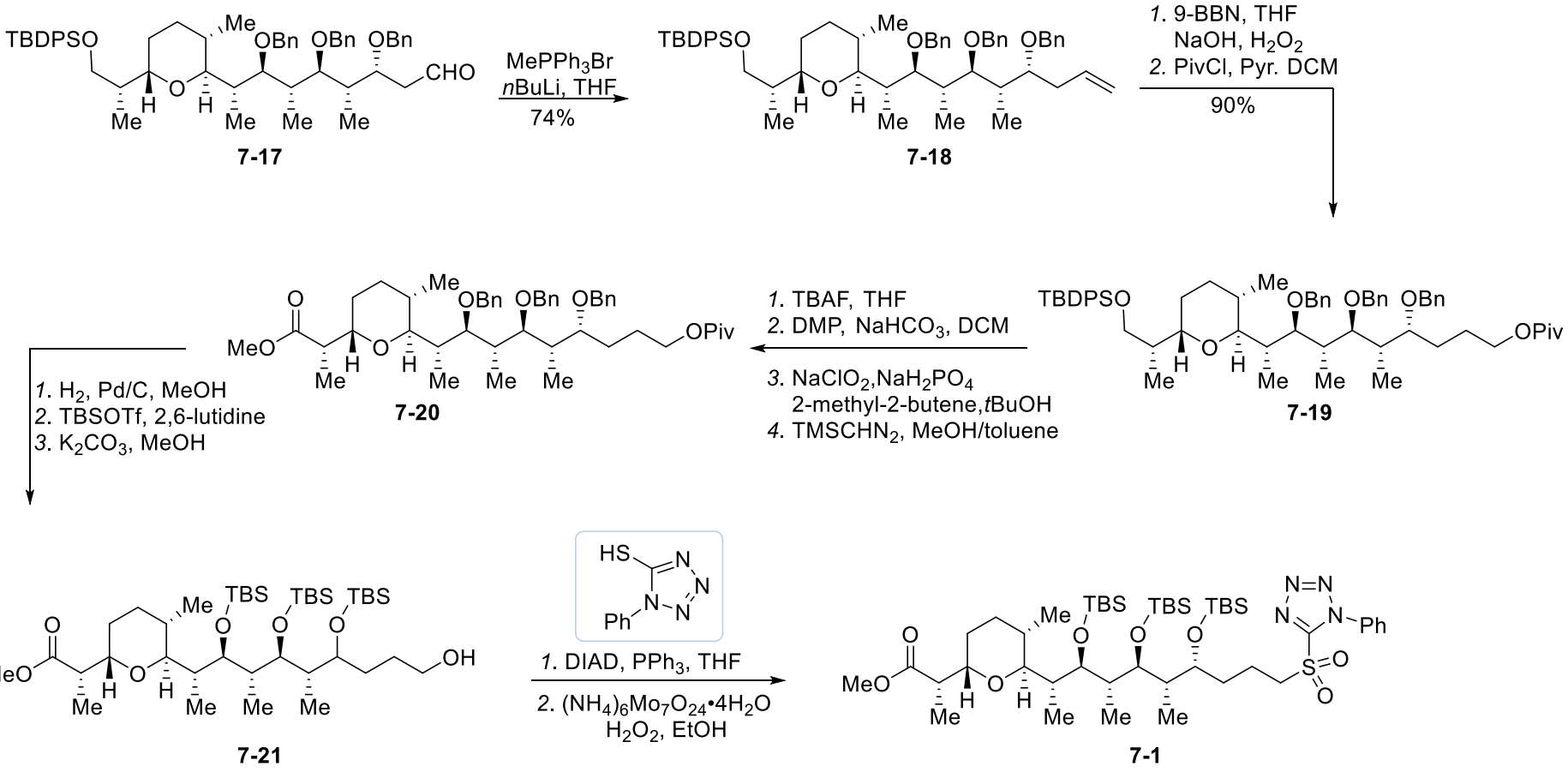
Mechanism

Mukaiyama aldol reaction



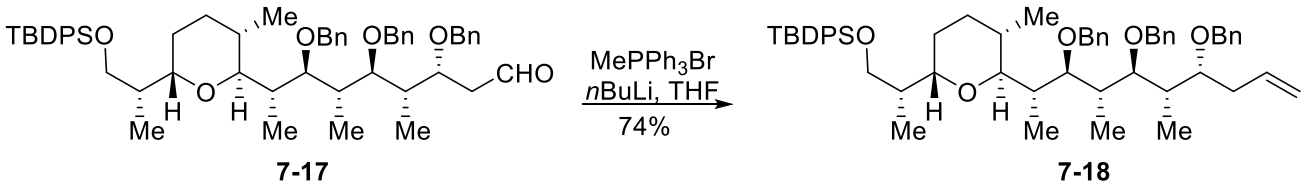
Total synthesis of zincophorin methyl ester

☐ Synthesis of the C1–C16 fragment



VII. Yvan Guindon : Tetrahedron 2015, 71, 709

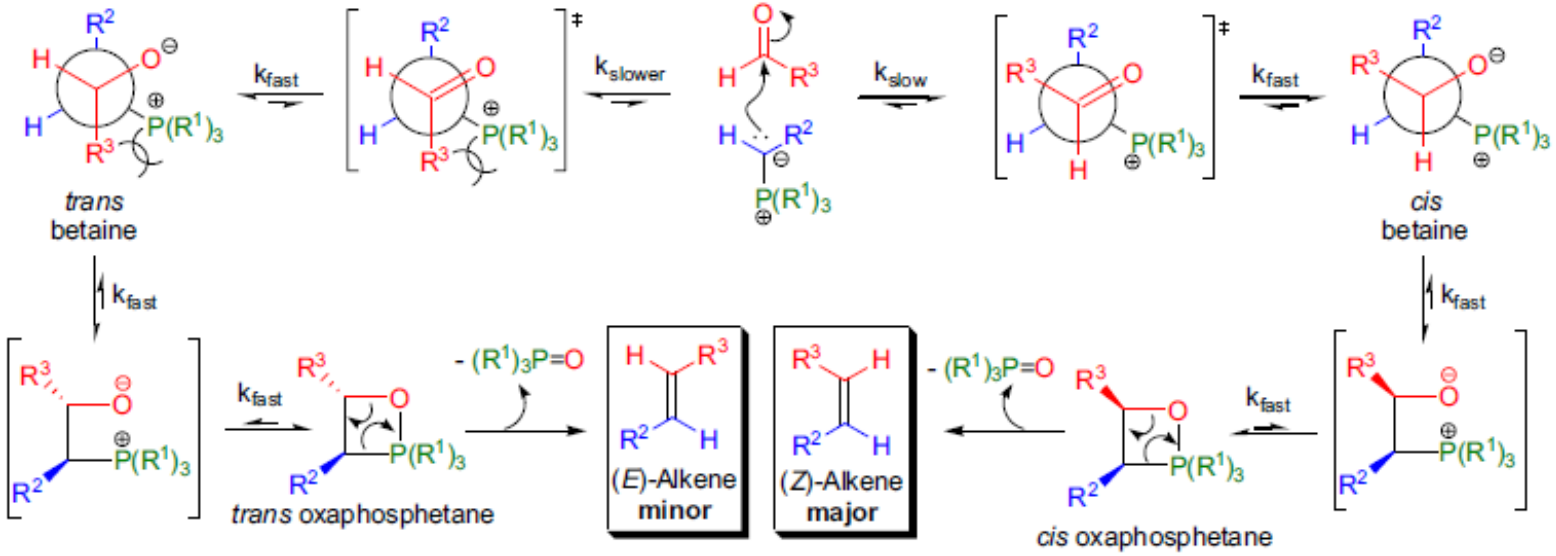
Total synthesis of zincophorin methyl ester



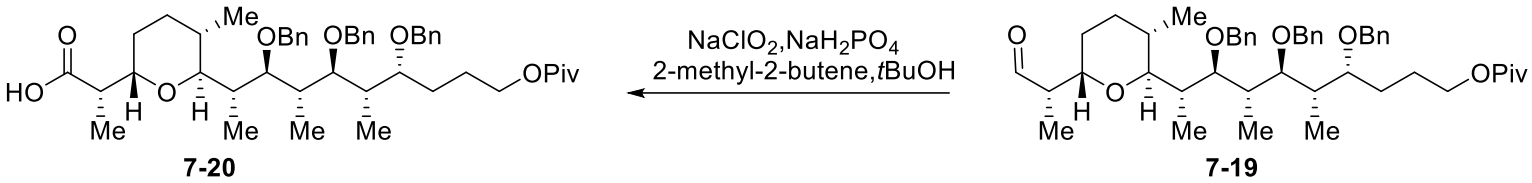
7-17 7-18

Mechanism

Wittig reaction

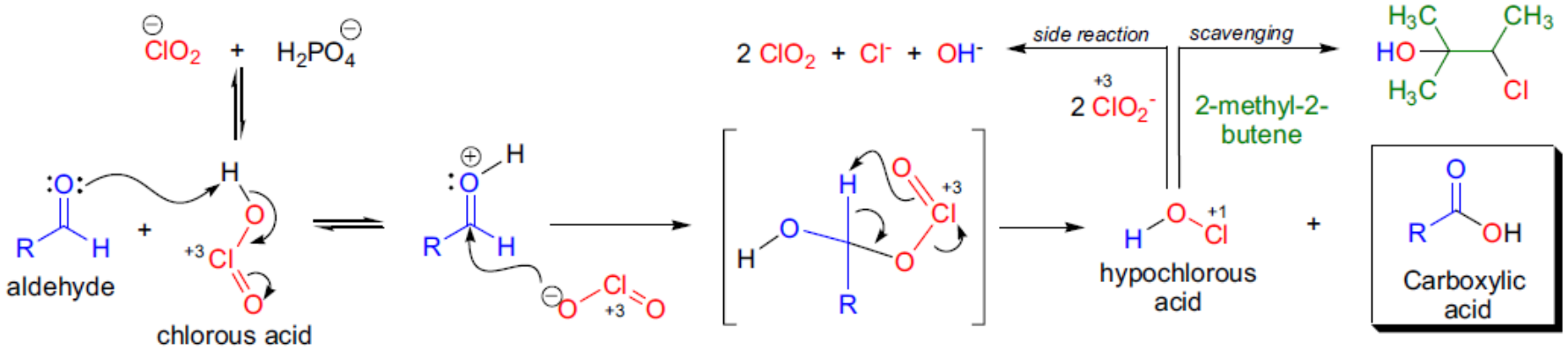


Total synthesis of zincophorin methyl ester

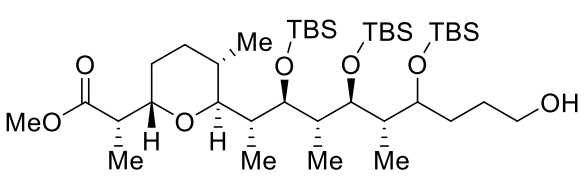


Mechanism

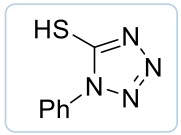
Pinnick oxidation

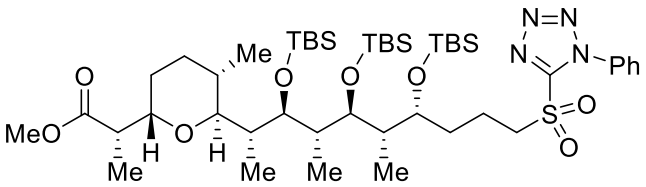


Total synthesis of zincophorin methyl ester



7-21

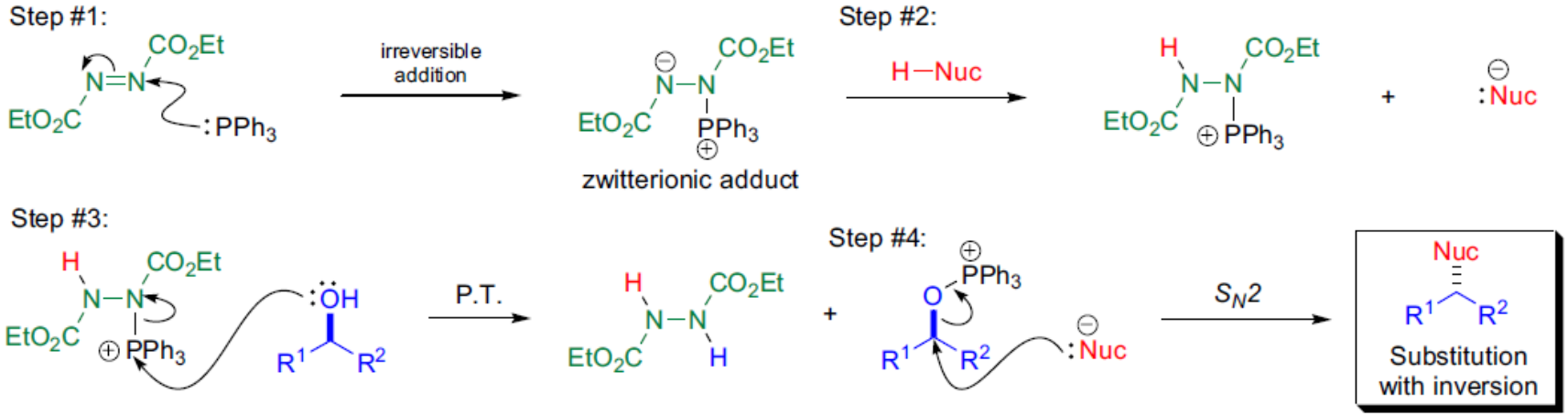




7-1

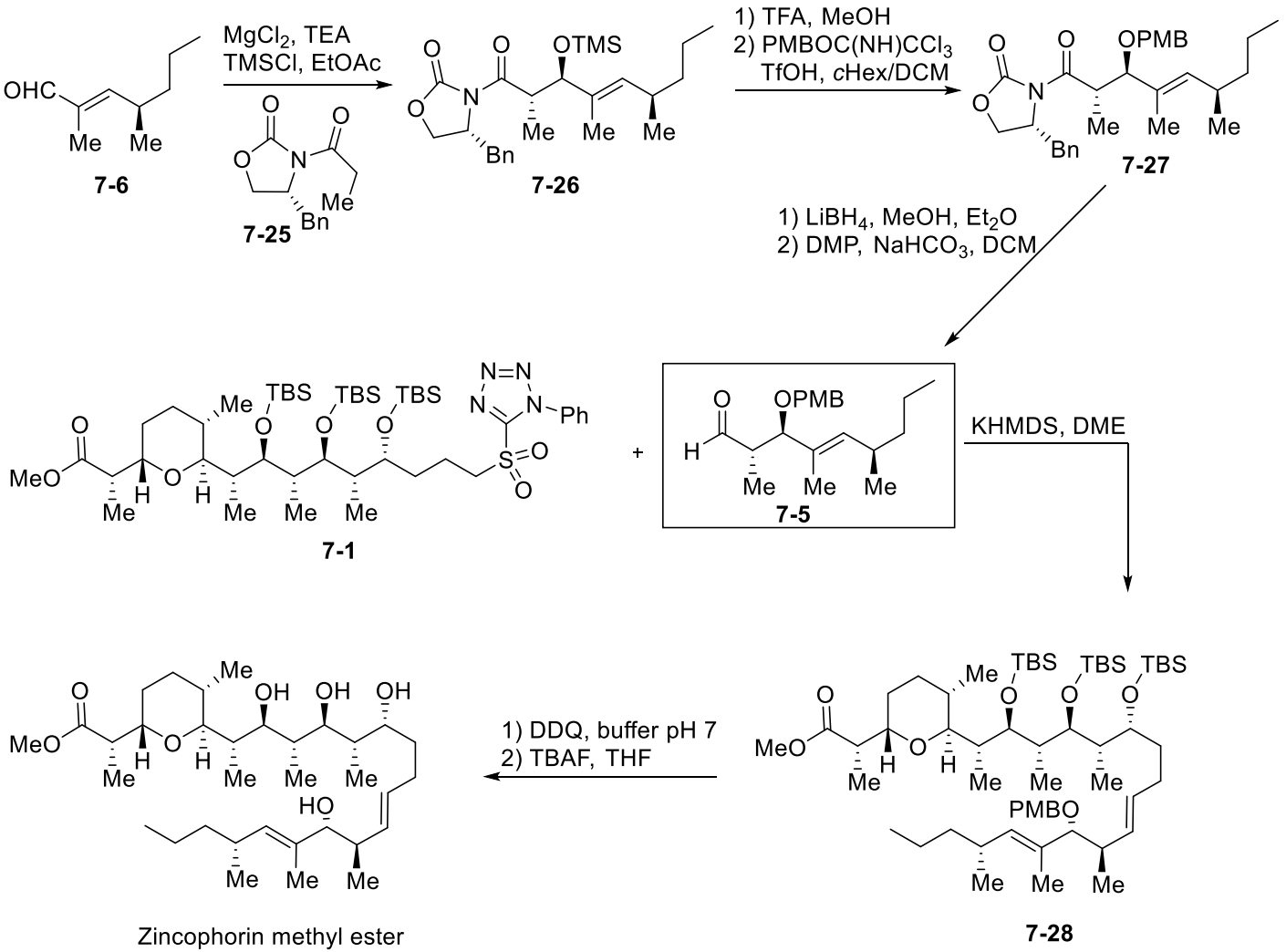
Mechanism

Mitsunobu reaction



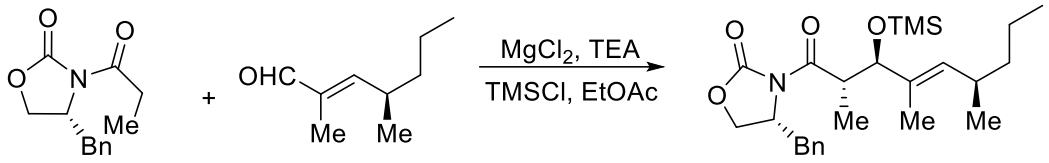
Total synthesis of zincophorin methyl ester

☐ Synthesis of the C17–C25 fragment and Coupling of two fragments



VII. Yvan Guindon : Tetrahedron 2015, 71, 709

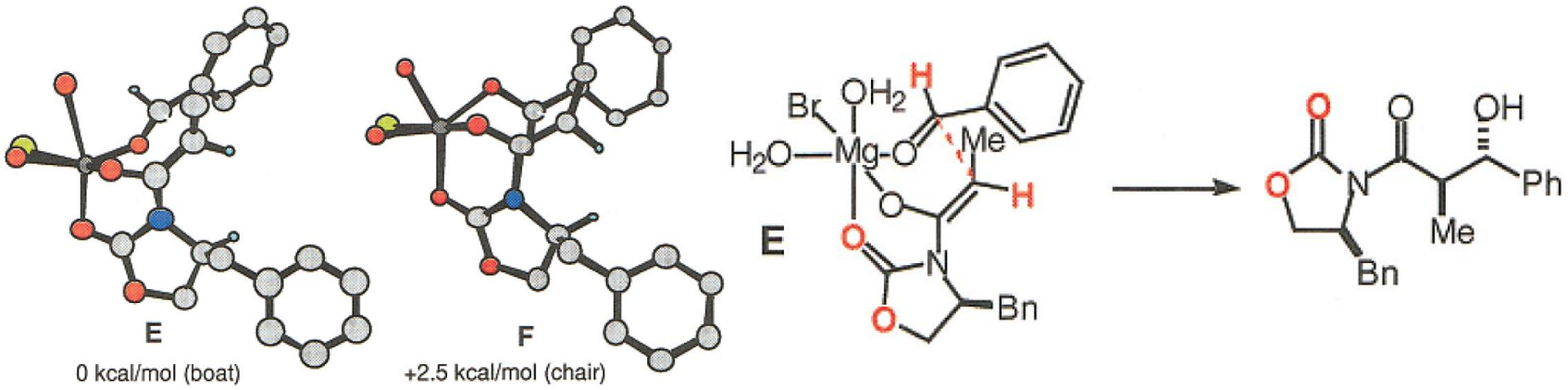
Total synthesis of zincophorin methyl ester



7-25 **7-6** **7-26**

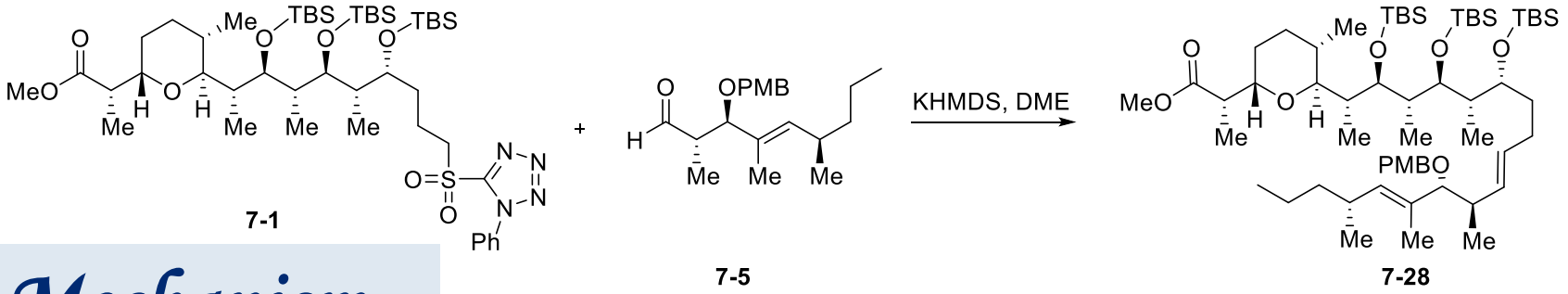
Mechanism

Evans' anti-aldol



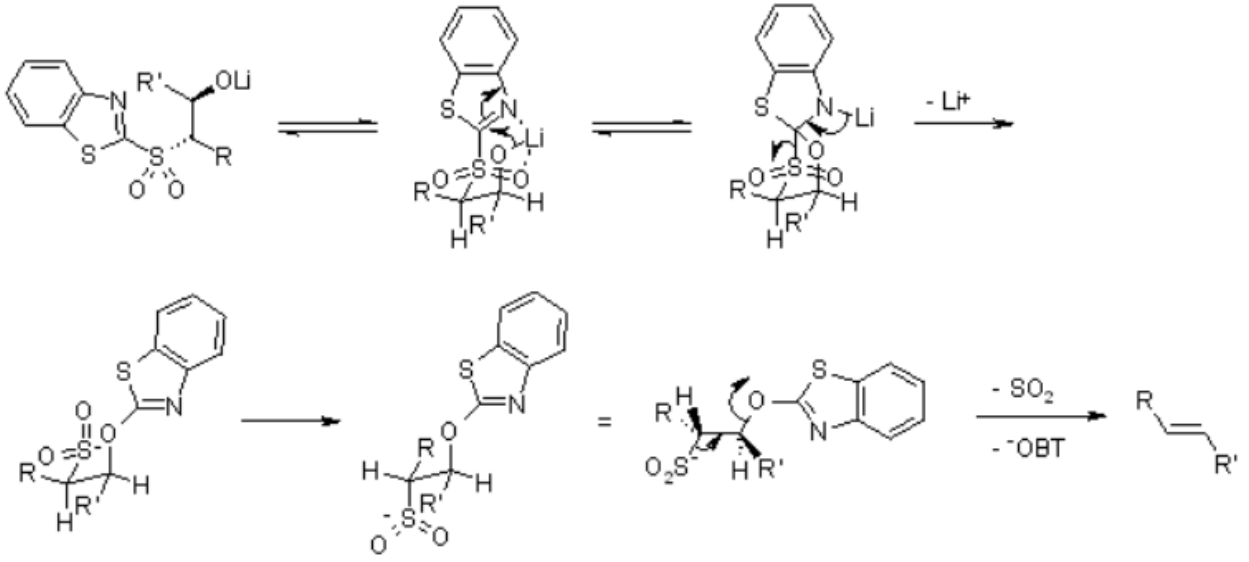
Org. Lett. **2020**, *4*, 1127

Total synthesis of zincophorin methyl ester



Mechanism

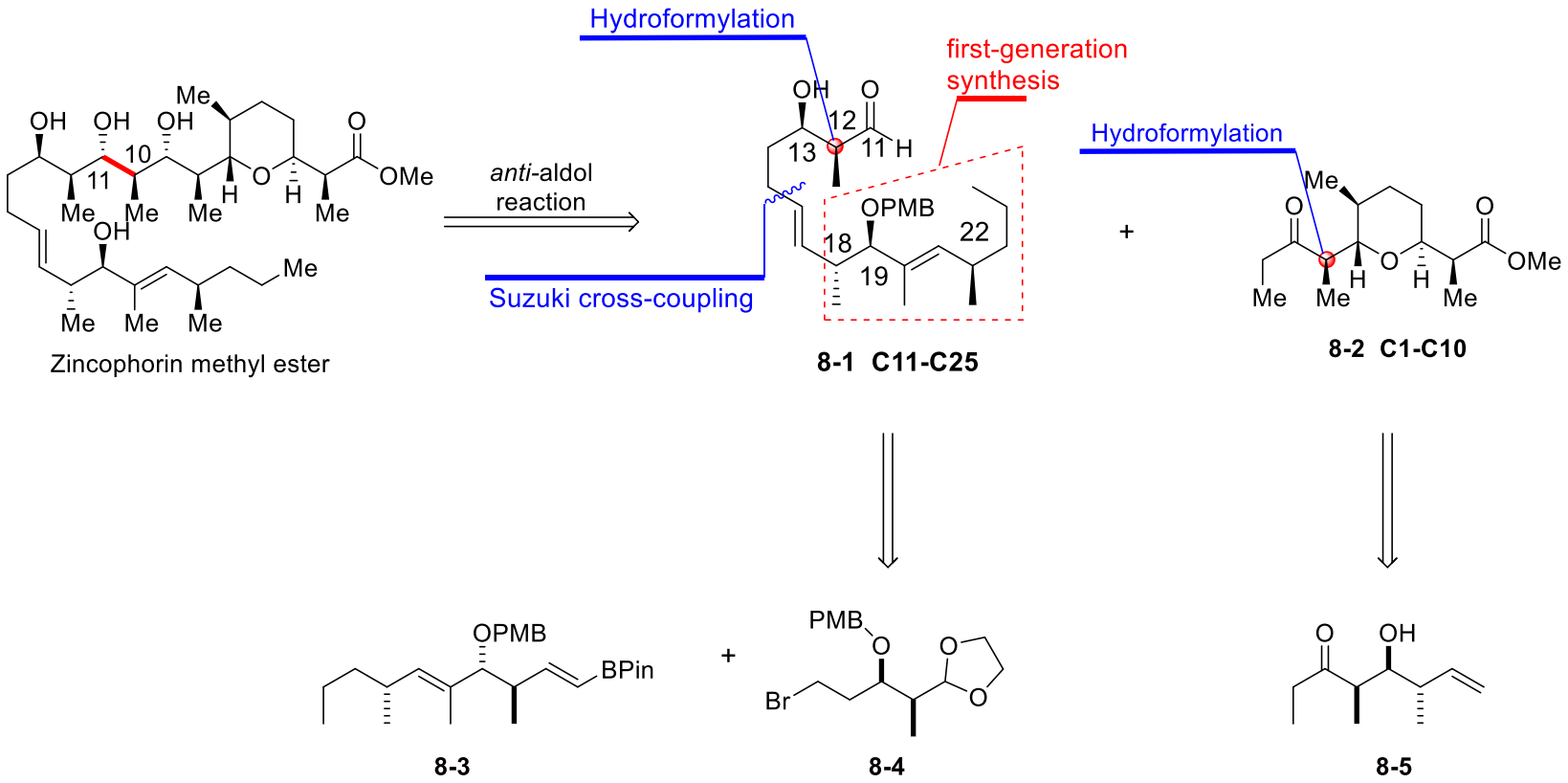
Modified (One-pot) Julia olefination



Total synthesis of zincophorin methyl ester

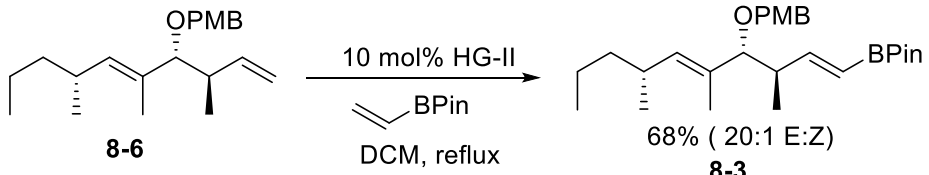
☐ Retrosynthetic Analysis

VIII. Leighton: *J. Am. Chem. Soc.* **2017**, *139*, 4568



Total synthesis of zincophorin methyl ester

☐ Synthesis of C11-C25 Fragment



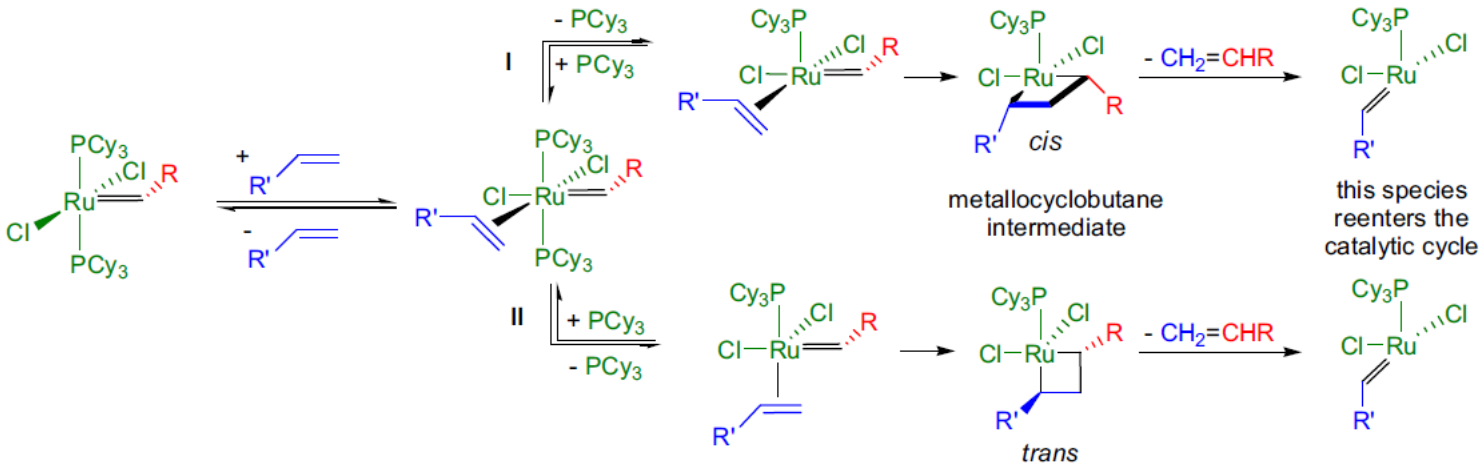
8-6

first-generation synthesis (4 steps)

8-3

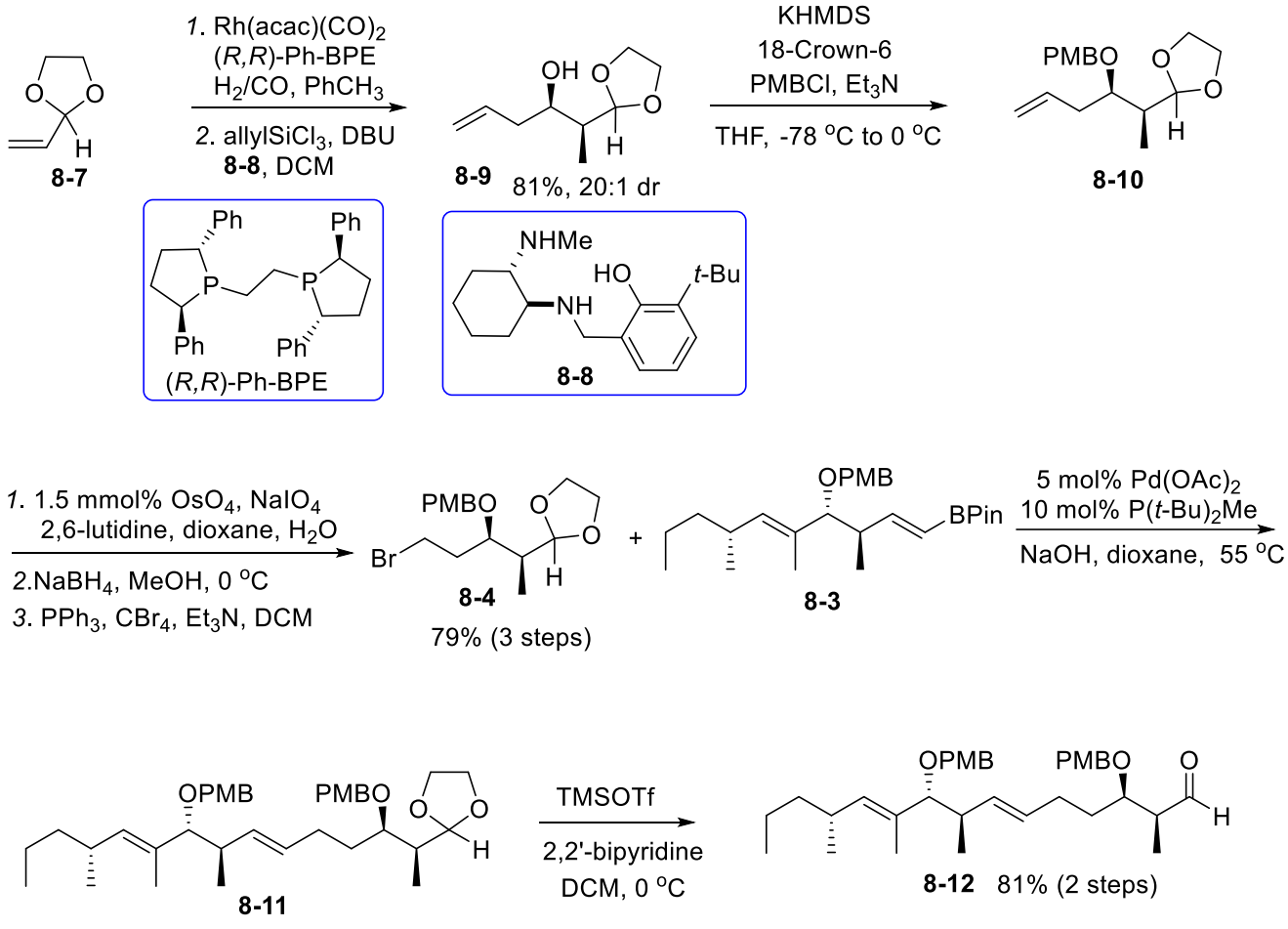
Mechanism

alkene (olefin) metathesis



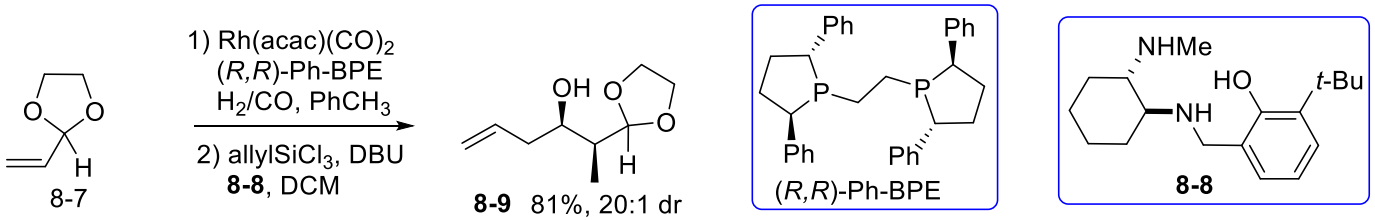
Total synthesis of zincophorin methyl ester

☐ Synthesis of C11-C25 Fragment



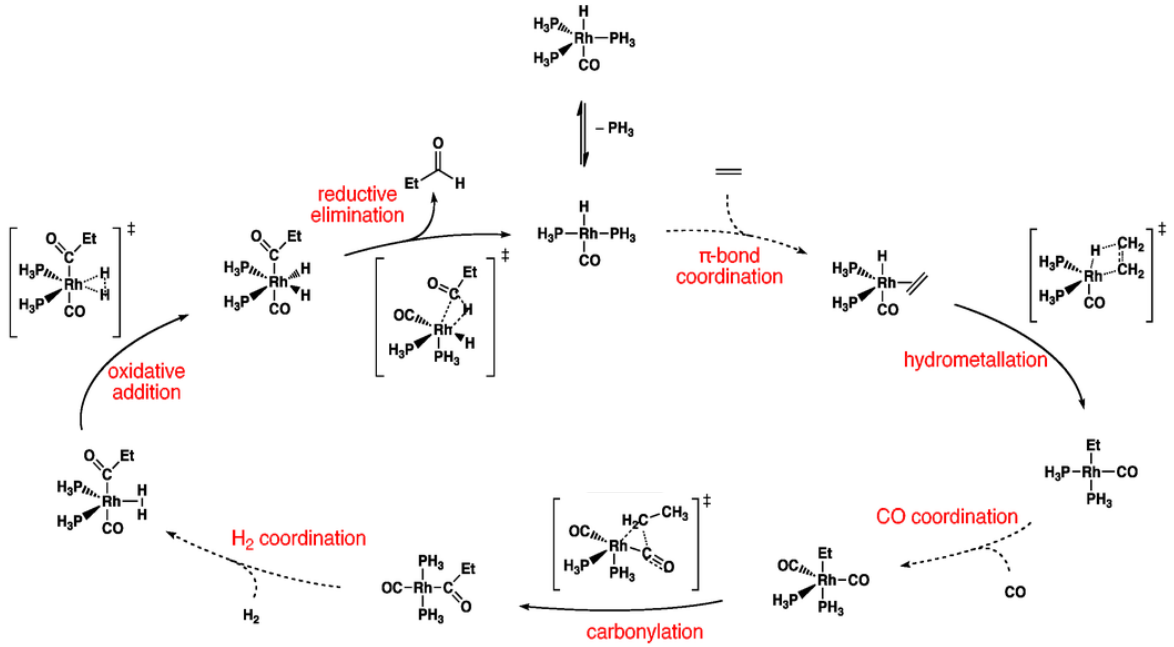
J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester



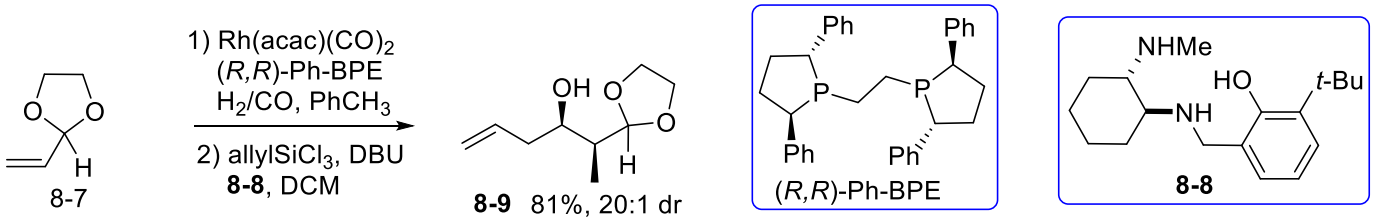
Mechanism

Hydroformylation

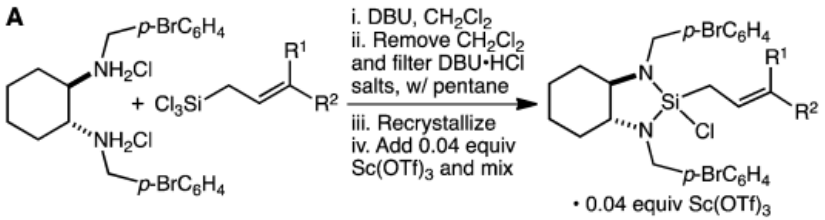


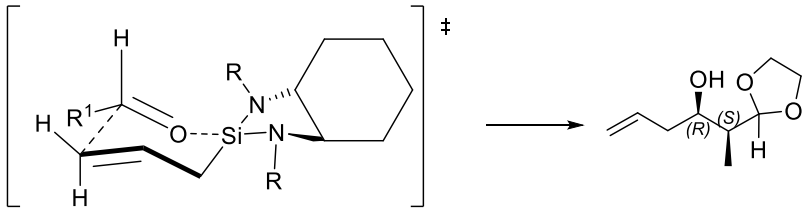
J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester



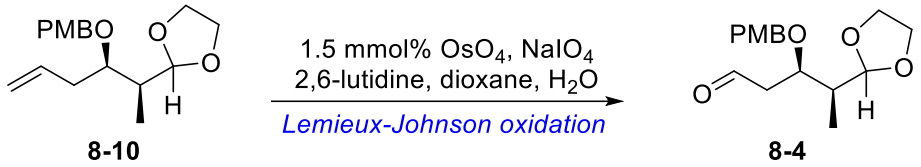
Mechanism



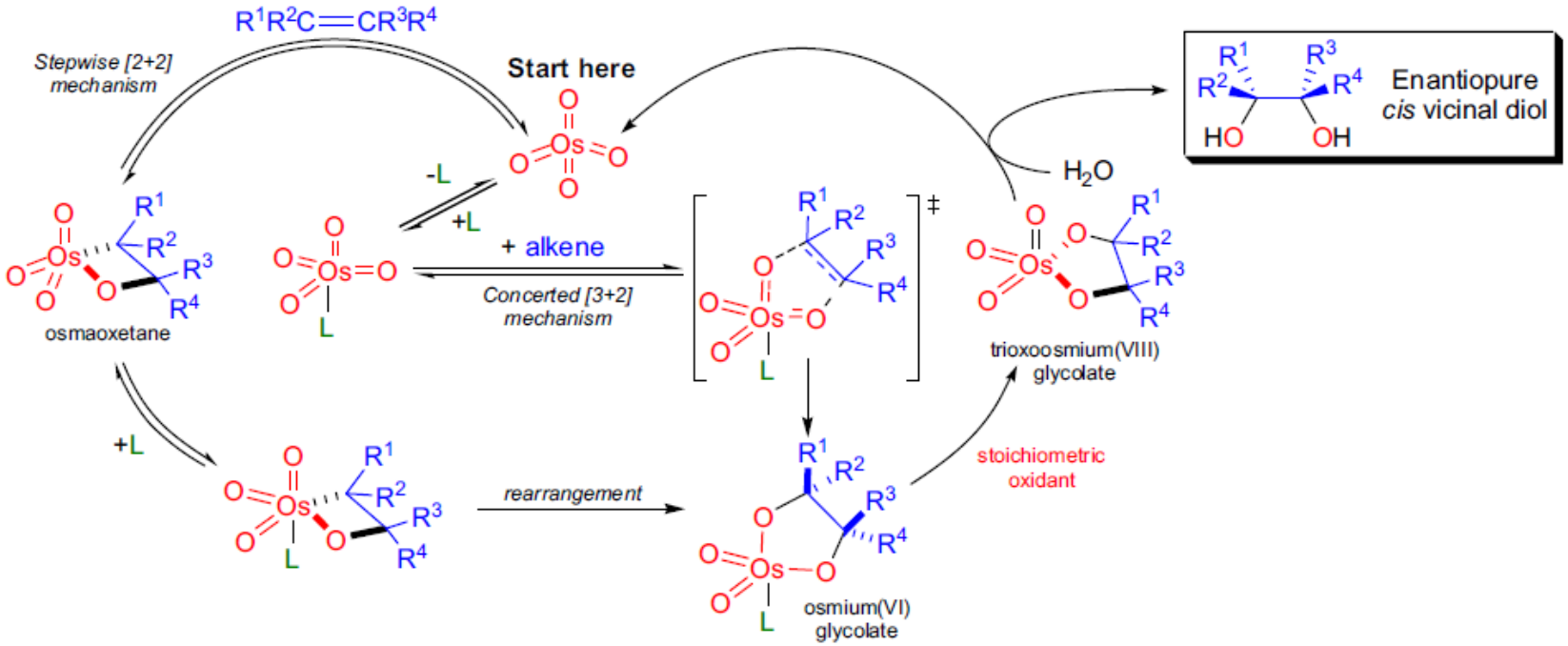


J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester

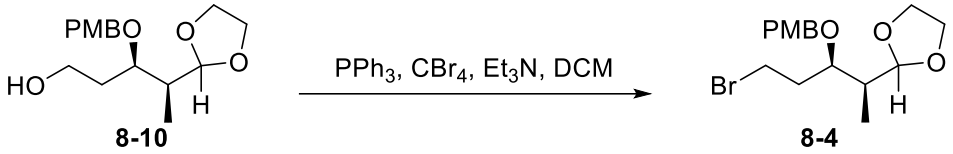


Mechanism



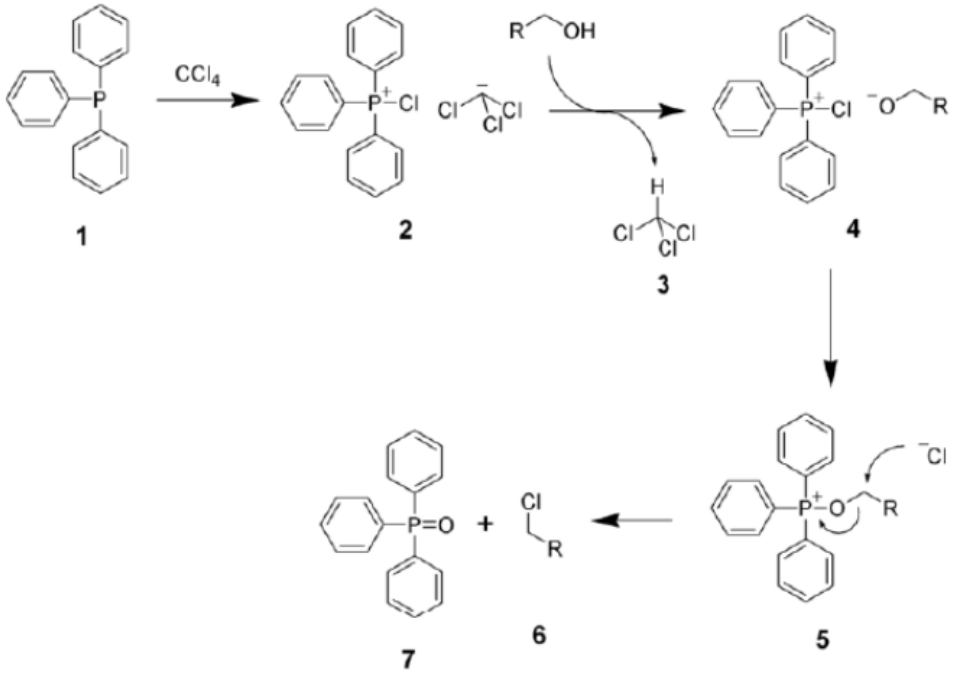
J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester



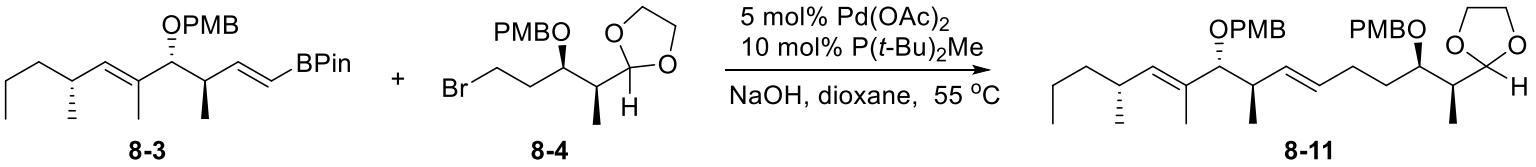
Mechanism

Appel reaction



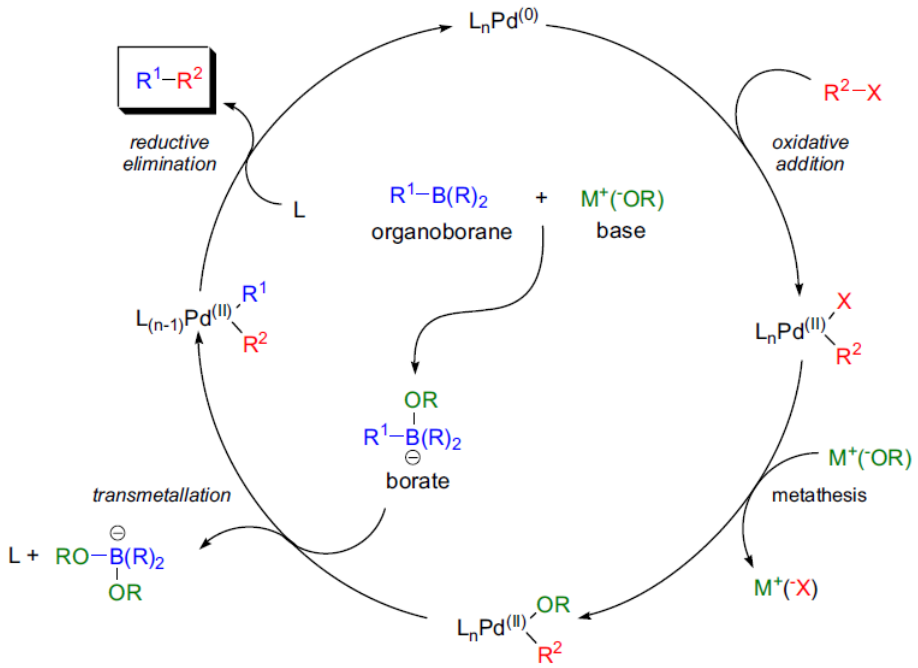
J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester



Mechanism

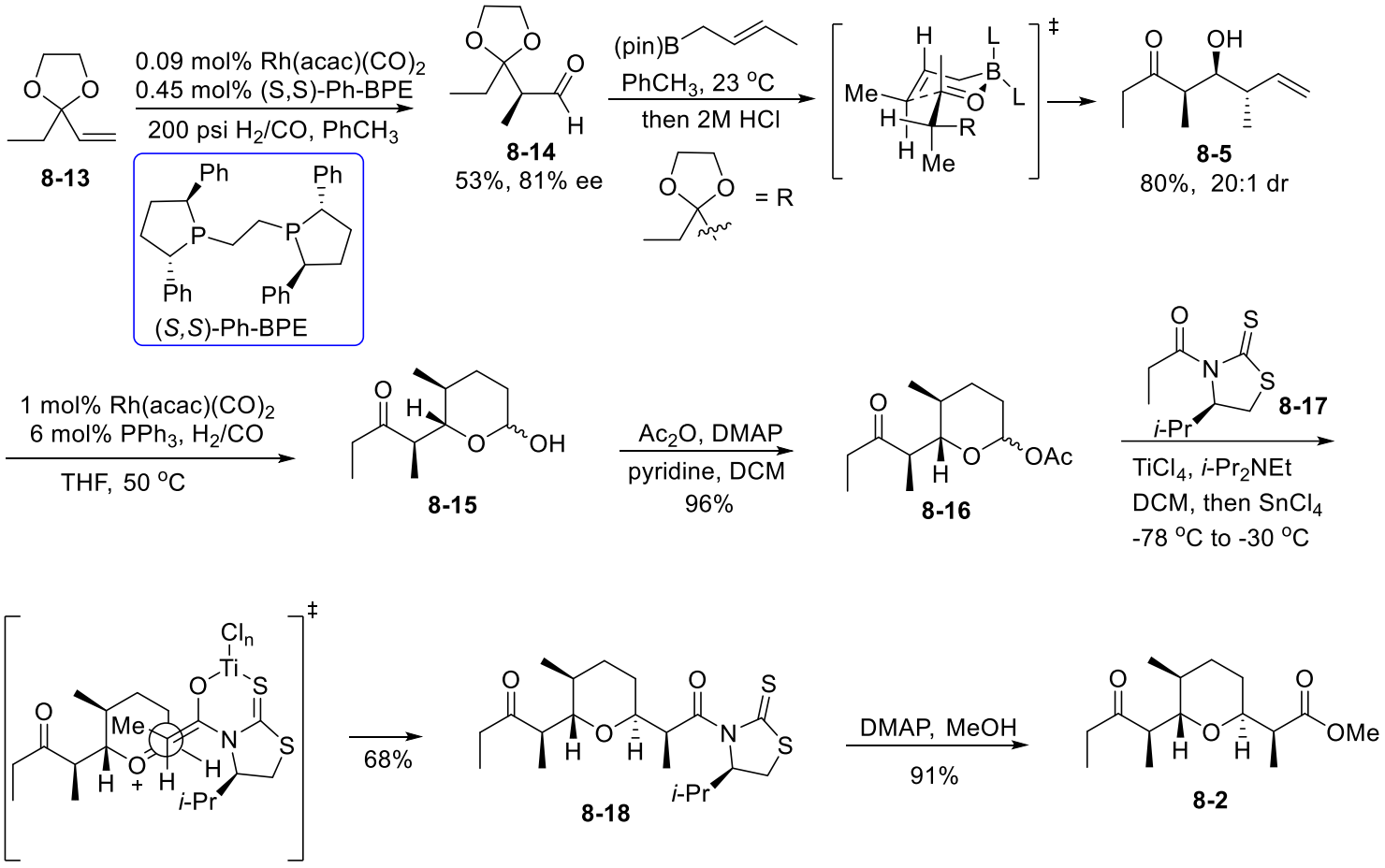
Suzuki cross-coupling



J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

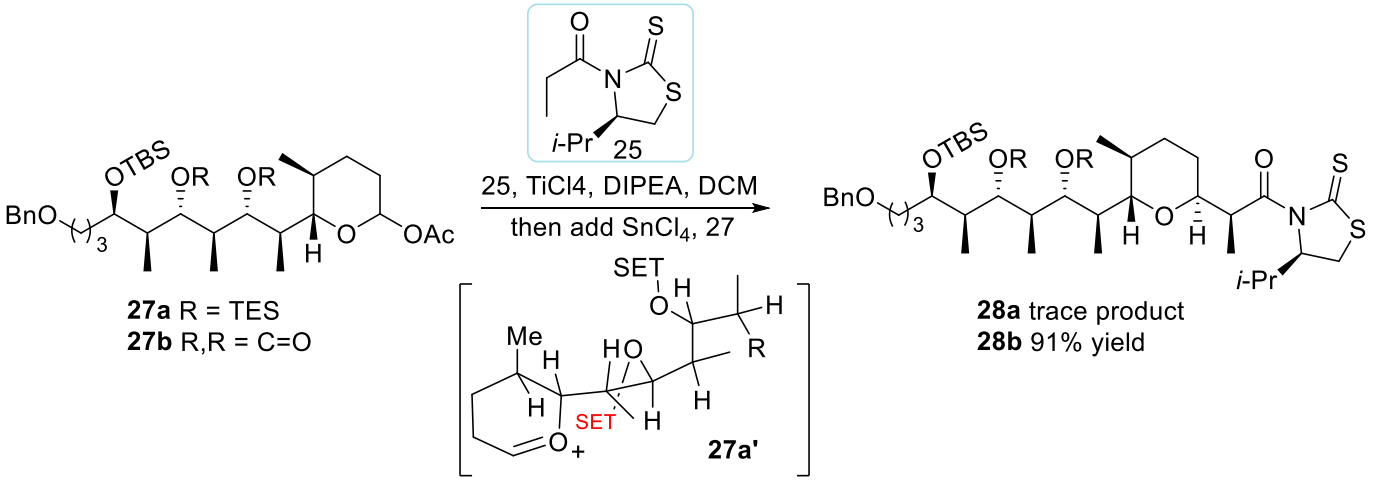
Total synthesis of zincophorin methyl ester

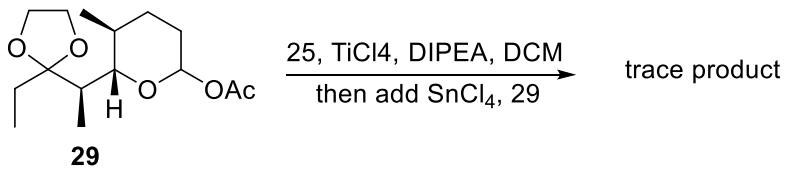
☐ Synthesis of Tetrahydrofuran Fragment



J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester

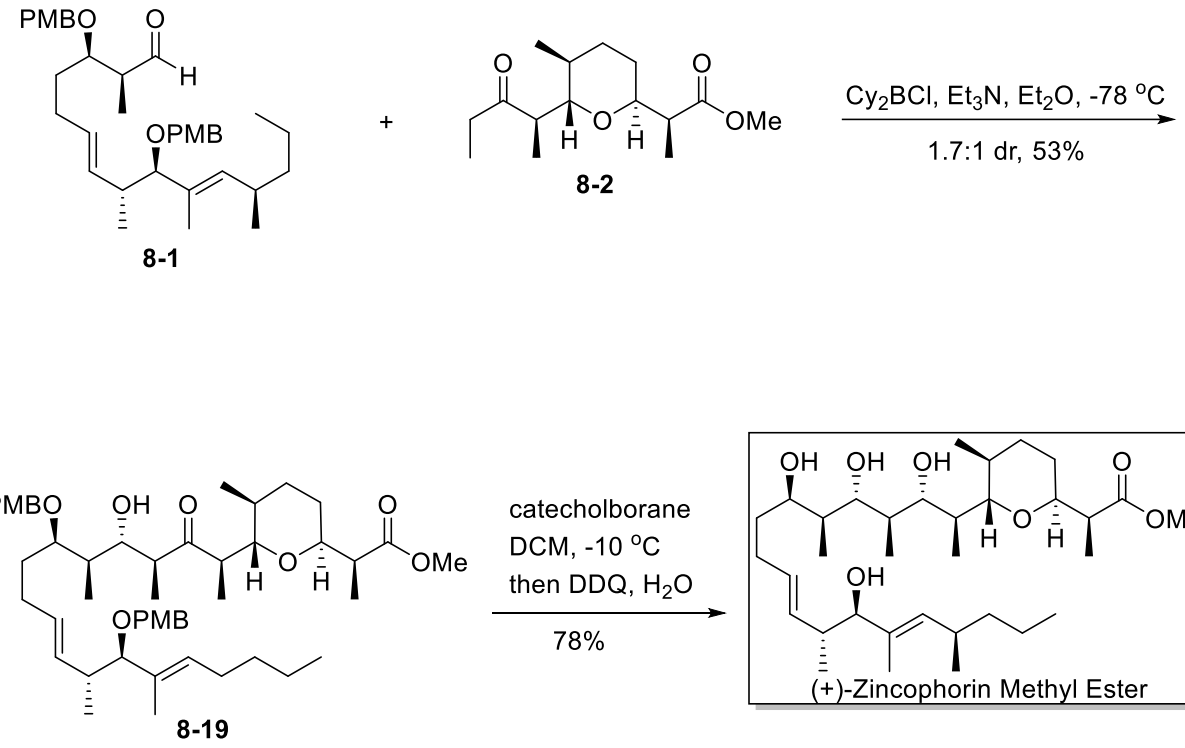




J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

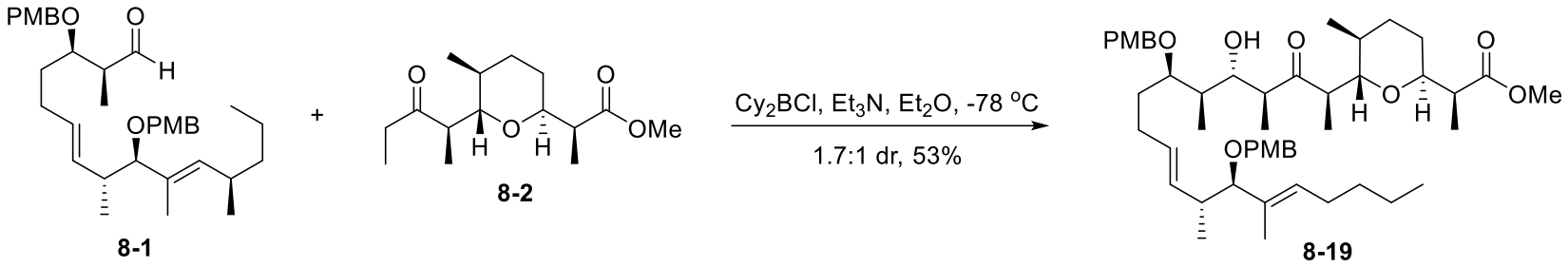
Total synthesis of zincophorin methyl ester

☐ Coupling of the C1–C10 fragment with C11–C25 fragment

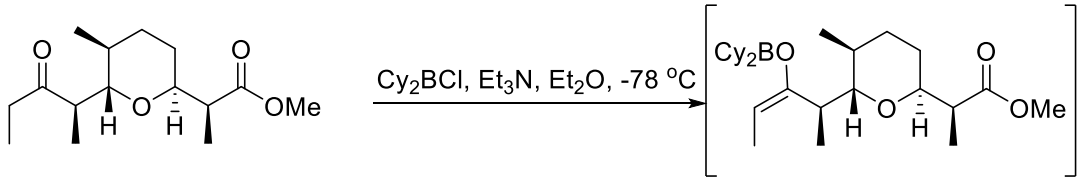


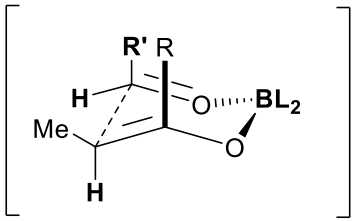
J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Total synthesis of zincophorin methyl ester

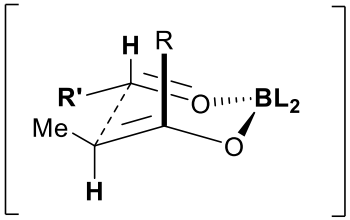


Mechanism





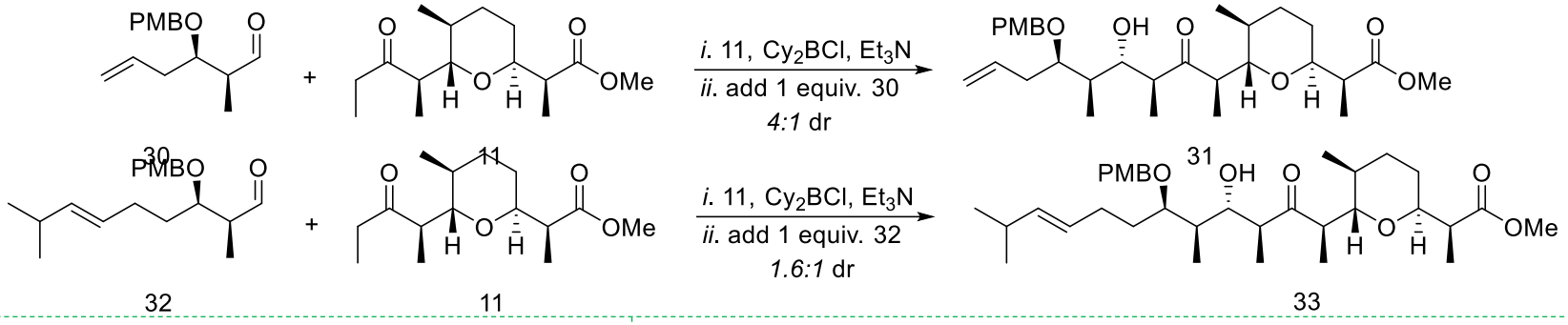
disfavored

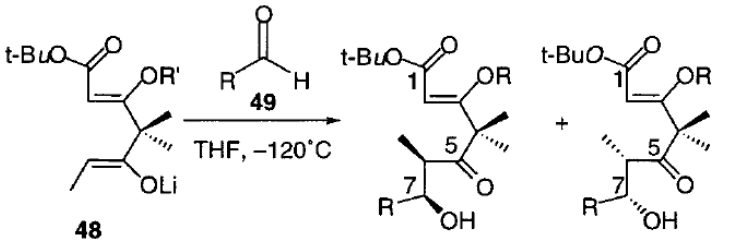


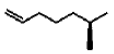
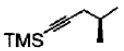
favored

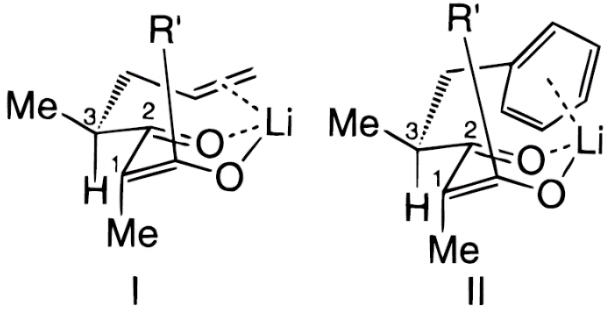
J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

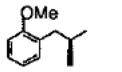
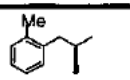
Total synthesis of zincophorin methyl ester

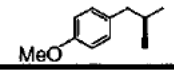
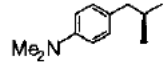
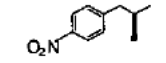




Entry	Aldehyde R =	Ratio (50:51) (C7-C8) (*syn*:*anti*)	
a		1	5.5
b		1	4.5
c		1	1.3
d		1	2.0
e		1	3.3
f		11	1.0



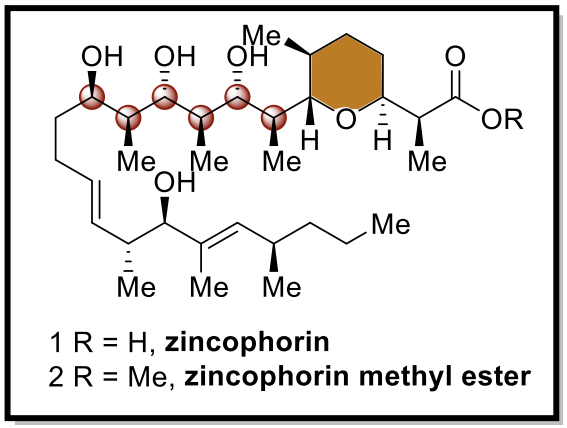
k		1	1.2
l		1	2.8

n		1	5.0
o		1	5.4
p		1	1.2

J. Am. Chem. Soc. **1999**, *121*, 7050−7062.

J. L. Leighton, et al. J. Am. Chem. Soc. 2017, 139, 4568.

Summary



Total Synthesis of Zincophorin and Its Methyl Ester

Danishefsky: *J. Am. Chem. Soc*. **1987**, *109*, 1572 (**35 steps LLS)**

Cossy: Org. Lett. 2003, 5, 4037 (**18 steps LLS)**

J. Org. Chem. **2004**, *69*, 4626 (**30 steps LLS)**

Miyashita: *Angew. Chem., Int. Ed*. **2004**, *43*, 4341 (**39 steps LLS)**

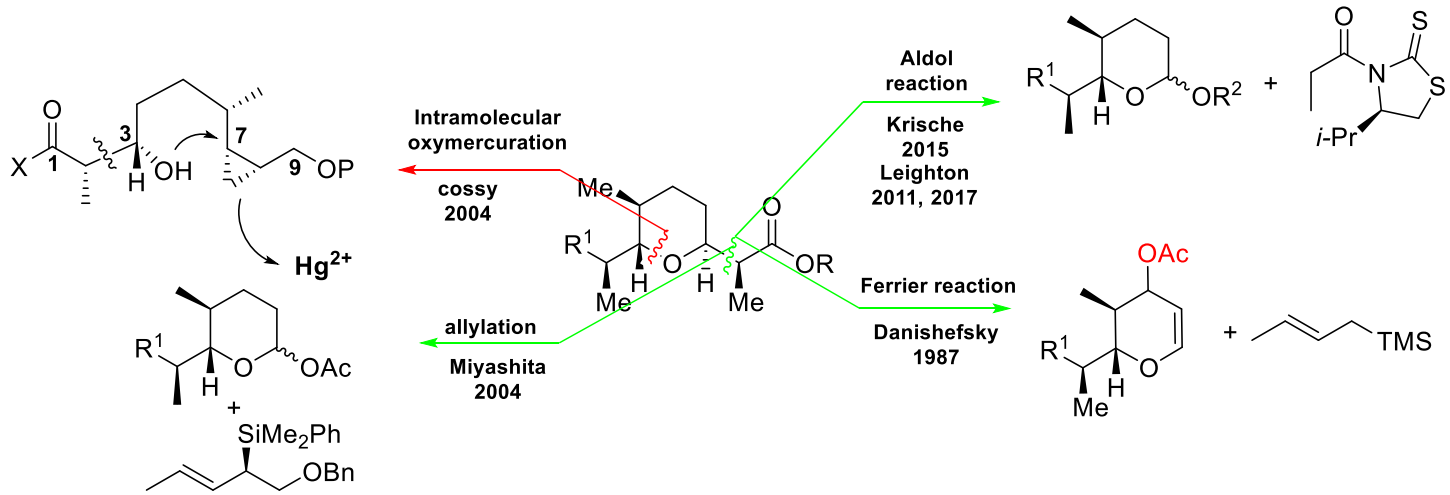
Leighton: *J. Am. Chem. Soc*. **2011**, *133*, 7308 (**21 steps LLS)**

J. Am. Chem. Soc. **2017**, *139*, 4568 (**9 steps LLS)**

Krische: *J. Am. Chem. Soc*. **2015**, *137*, 8900 (**13 steps LLS)**

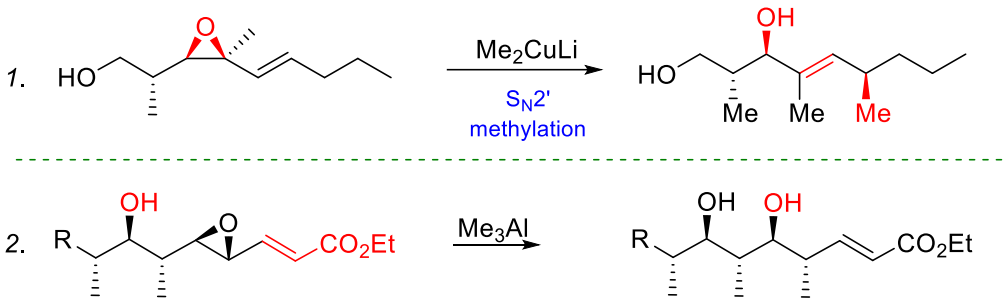
Guindon: *Tetrahedron* **2015**, *71*, 709 (**49 steps LLS)**

☐ Synthesis of Tetrahydrofuran Fragment

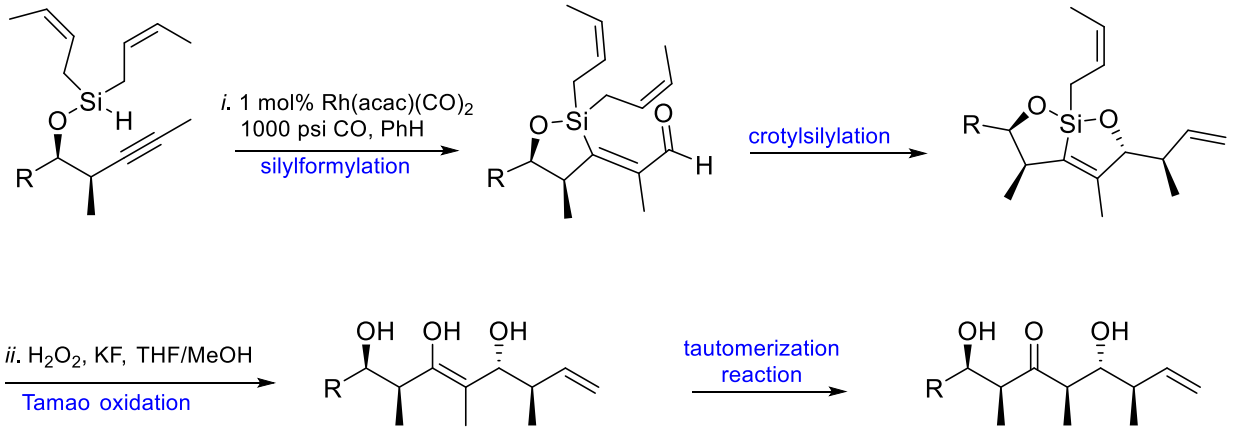


Summary

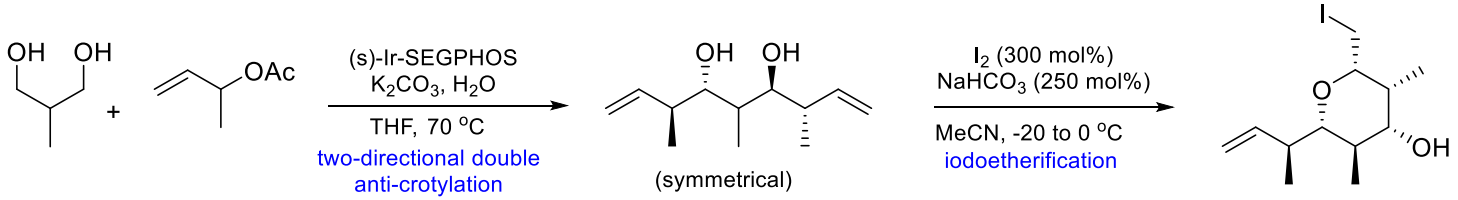
Miyashita (2004)



Leighton (2011)

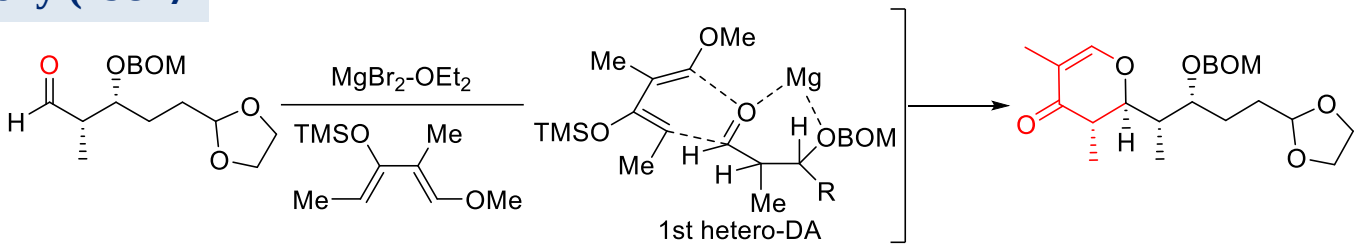


Krische (2015)

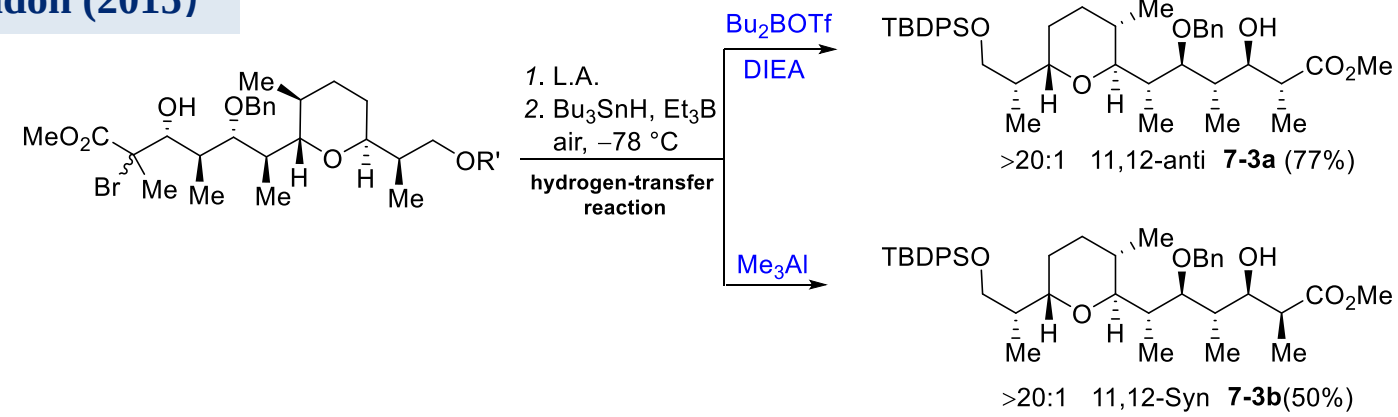


Summary

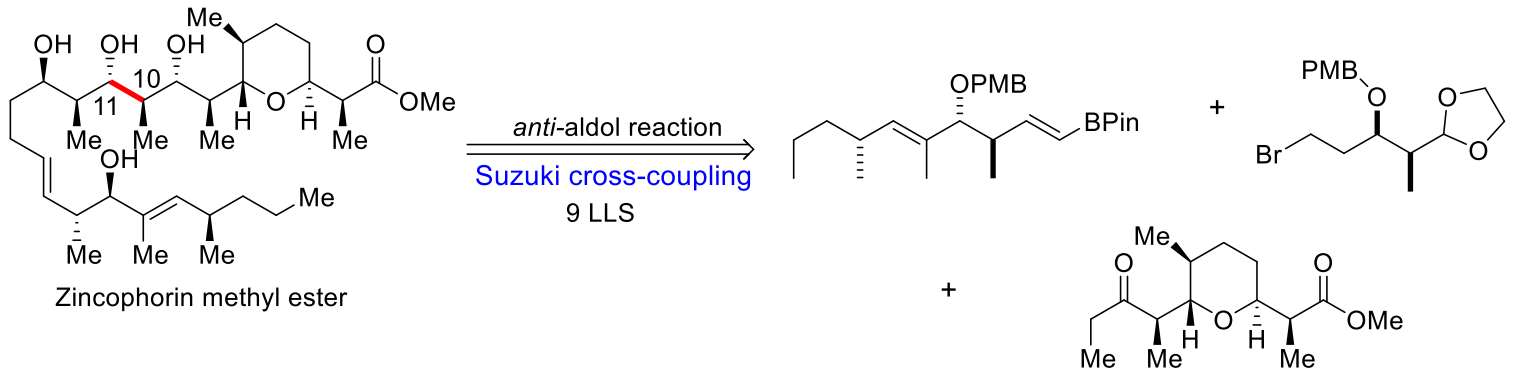
Danishefsky (1987)



Guindon (2015)



Leighton (2017)



Thank you

for your kind attention