香港科技大學
THE HONG KONG
UNIVERSITY OF SCIENCE
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**Summary of Research Projects**

# FOD in Natural Product Synthesis and Methodology Development

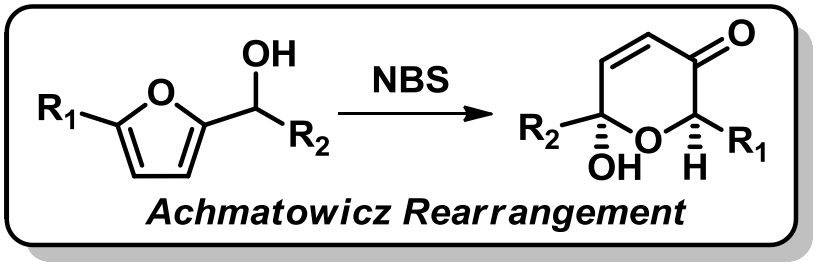
**Rongbiao Tong**

**April 19th, 2016**

# Furan Oxidative Dearomatization (FOD, Achmatowicz Rearrangement.)

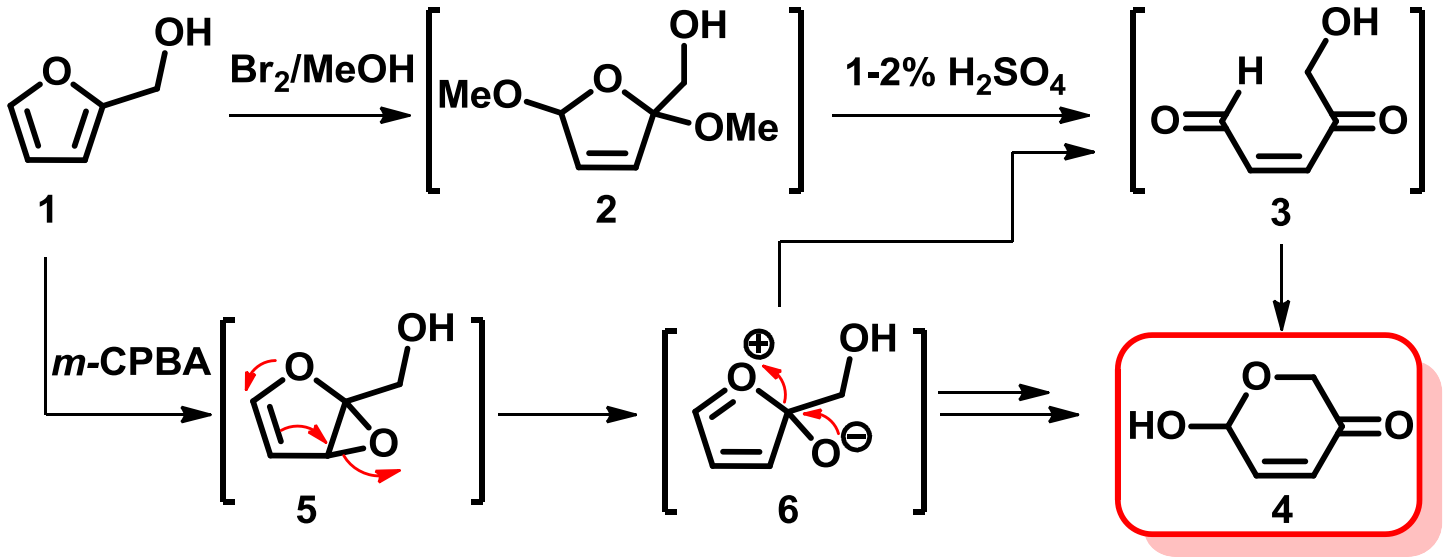
**FOD**

*Furan Oxidative Dearomatization (FOD)*



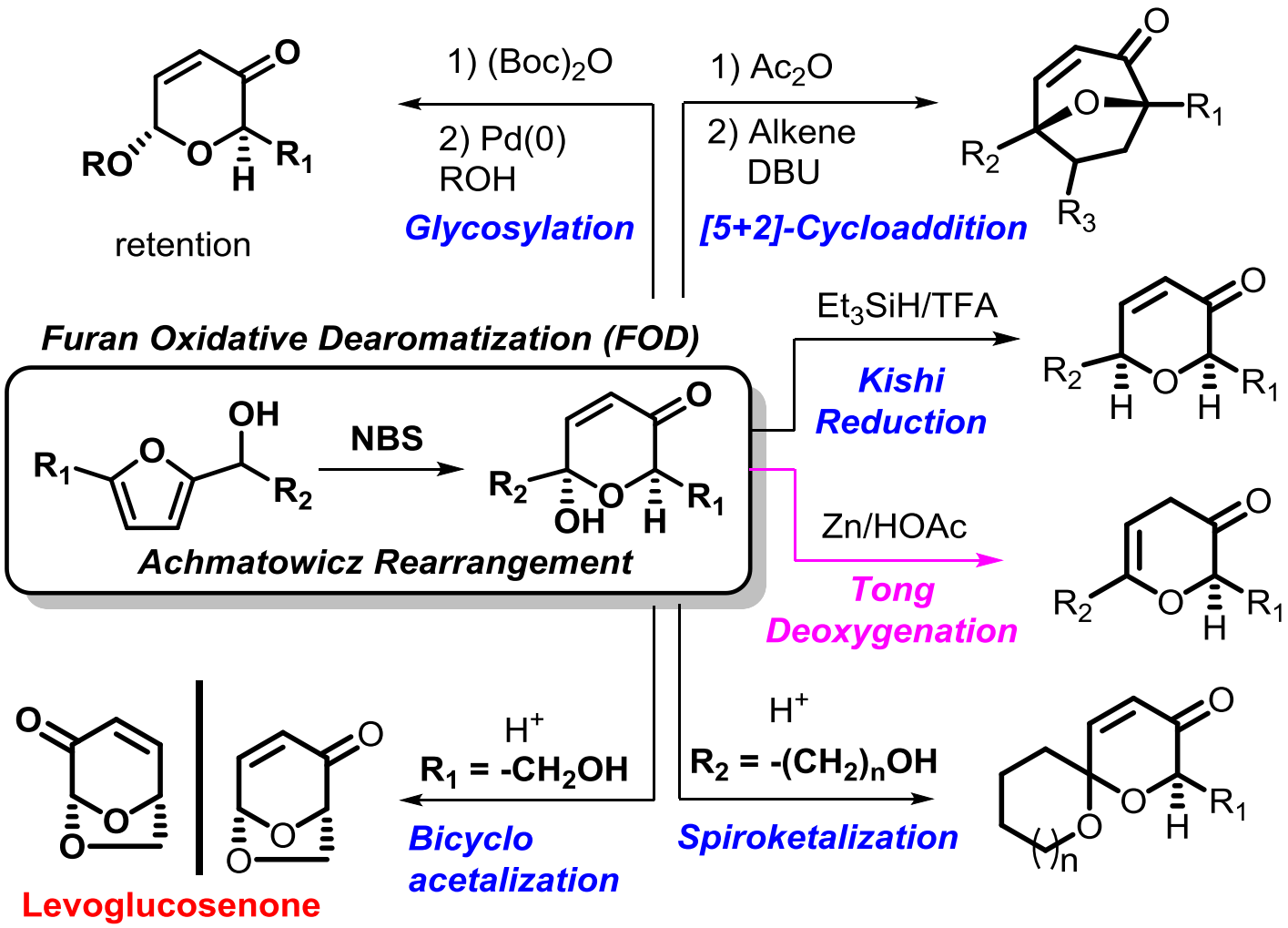

**PCC**
**Oxone**
**PhI(OAc)$_2$**
**VO(acac)$_2$, *t*-BuOOH**
**Sharpless AE**

***Scheme 1.*** **Mechanisms of Achmatowicz Rearrangement**



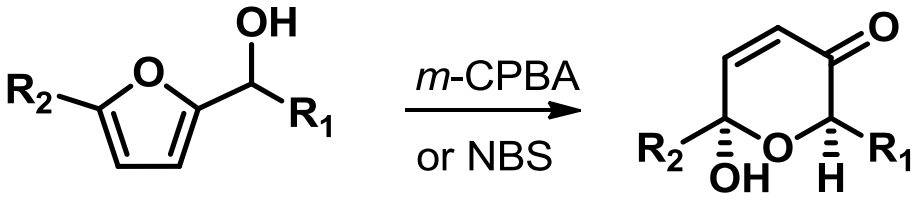

Achmatowicz, Jr., O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron*, **1971**, *27*, 1973-1996.

# Synthetic Applications of FOD

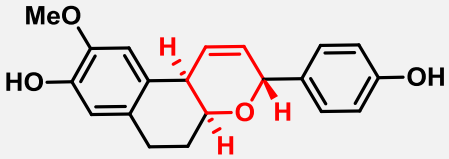


# FOD in Natural Product Synthesis (2011 – 2016)

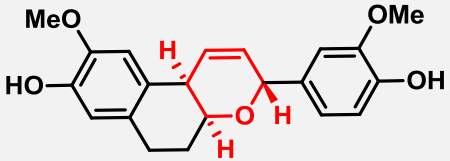
**FOD**



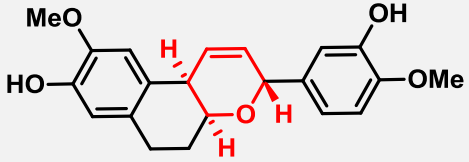

**Achmatowicz Rearrangement**



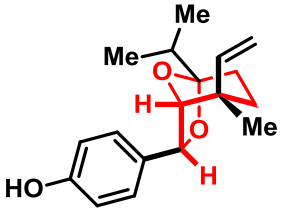

(±)-Musellarin A (B1a)
(2014) by Li, Z. & Leung, T.-F.
(–)-Musellarin A (B1b)
(2015) by Li, Z.



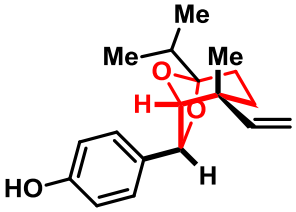

(±)-Musellarin B (B2a)
(2014) by Li, Z. & Leung, T.-F.
(–)-Musellarin A (B2b)
(2015) by Li, Z.



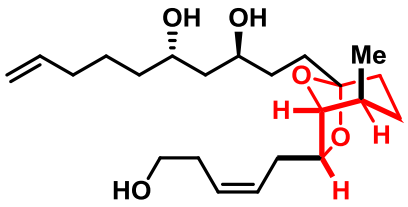

(±)-Musellarin C (B3a)
(2014) by Li, Z. & Leung, T.-F.
(–)-Musellarin A (B3b)
(2015) by Li, Z.



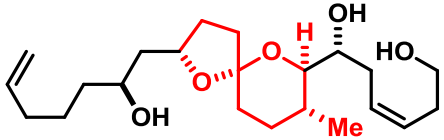

Psoracorylifol B (B8)
(2014) by Ren, J. & Liu, Y.



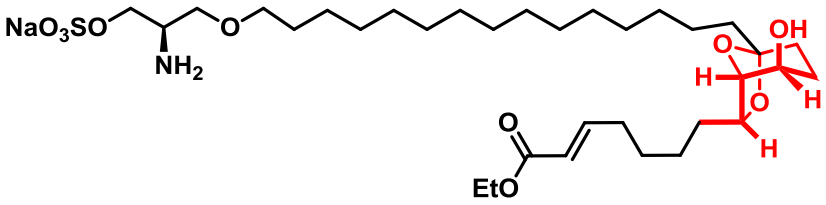

ent-Psoracorylifol C (B9)
(2014) by Ren, J. & Liu, Y.



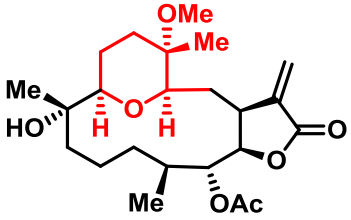

(+)-Attenol B (B9)
(2015) by Ren, J.



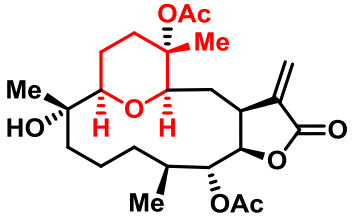

(-)-Attenol A (B10)
(2014) by Ren, J.




Didemniserinolipid B (B11)
(2014) by Ren, J.

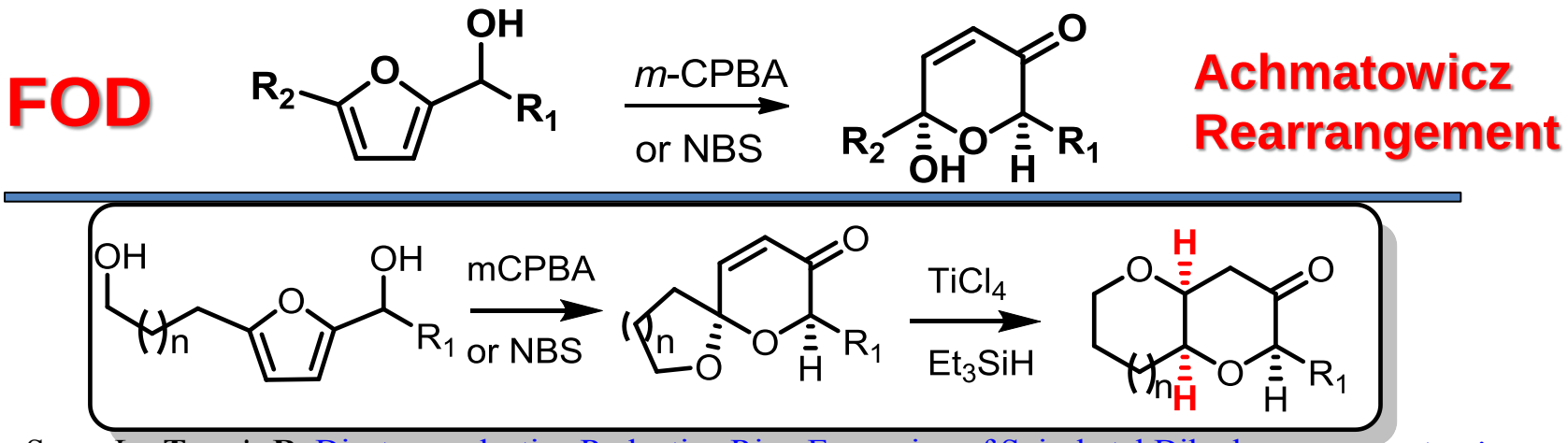



Uprolide G Acetate (B5)
(2014) by Zhu, L.

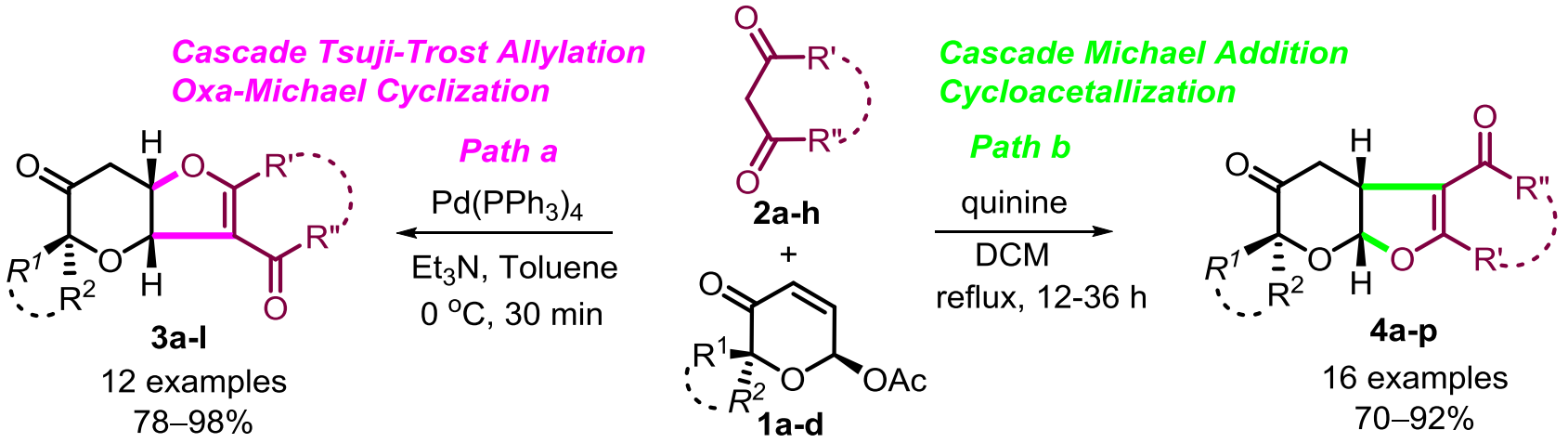



Uprolide F Diacetate (B7)
(2015) by Zhu, L.

# FOD in Methodology Development (2011 – 2016)

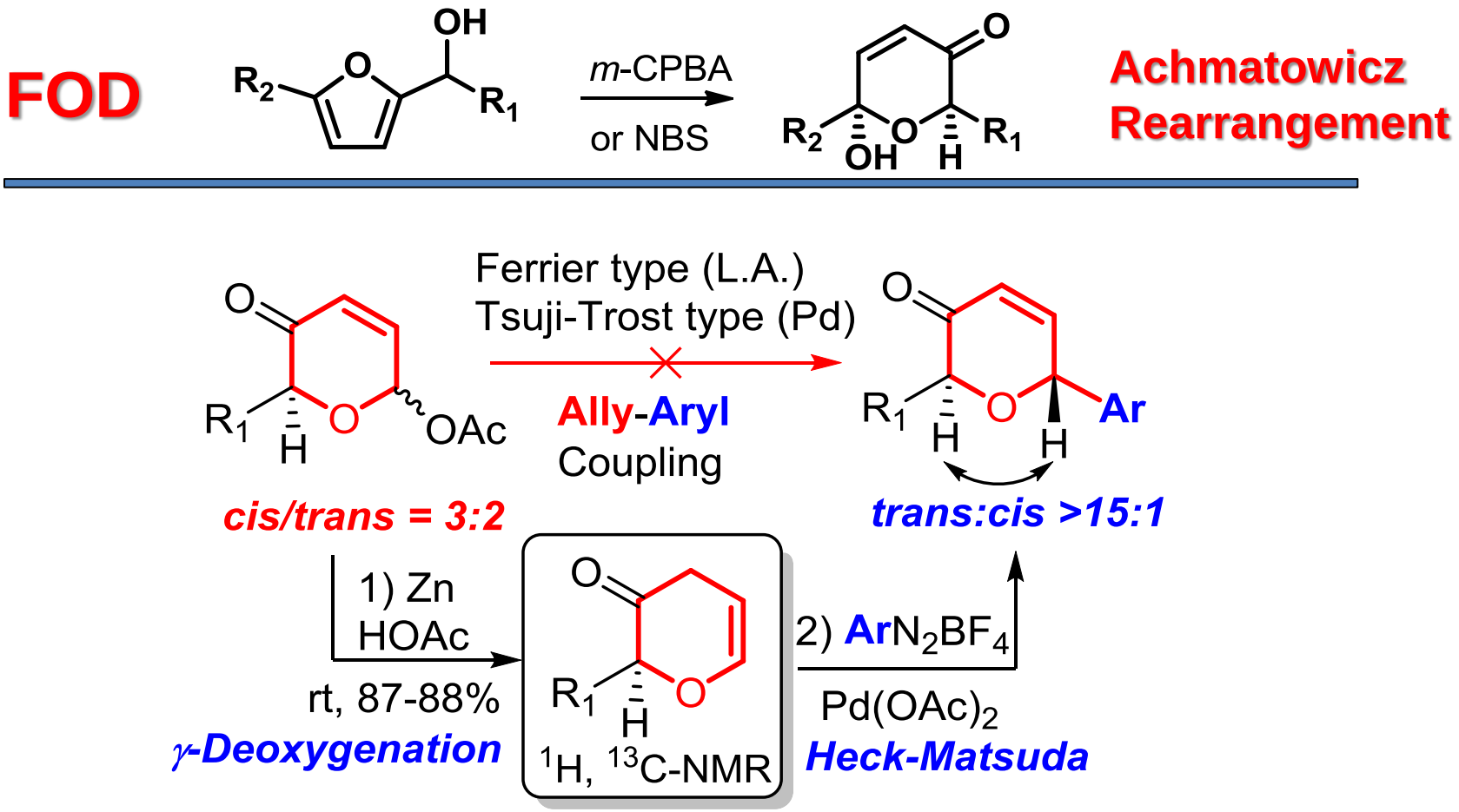



Zhu, L.; Song, L.; **Tong*, R.** Diastereoselective Reductive Ring Expansion of Spiroketal Dihydropyranones to *cis*-Fused Bicyclic Ethers. *Org. Lett.* **2012**, *14*, 5892-5895.



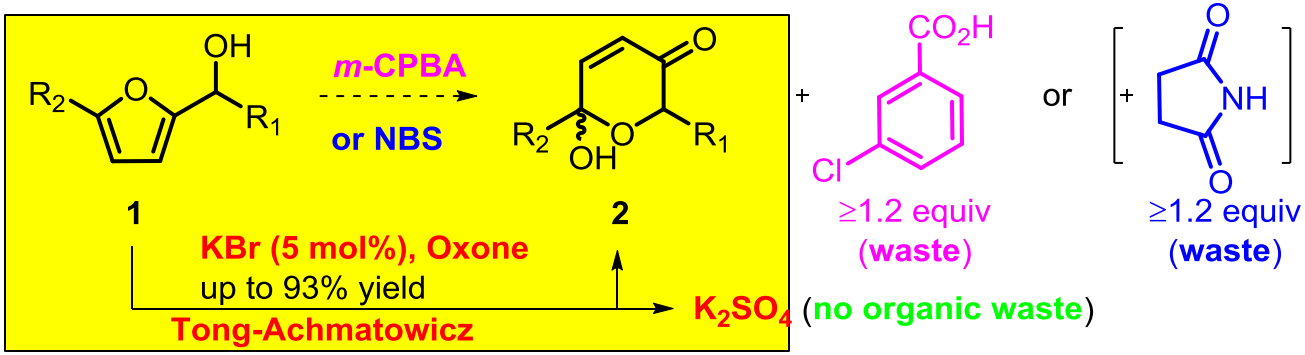

Yu, J.; Ma, H.; Yao, H.; Cheng, H.; **Tong*, R.** A General Concise Strategy Enables Collective Total Syntheses of >50 Protoberberine and 5 Aporhoeadane Alkaloids within 4-8 steps. *Org. Chem. Front.* **2016**, *3*, 714-719.

# FOD in Methodology Development (2011 – 2016)



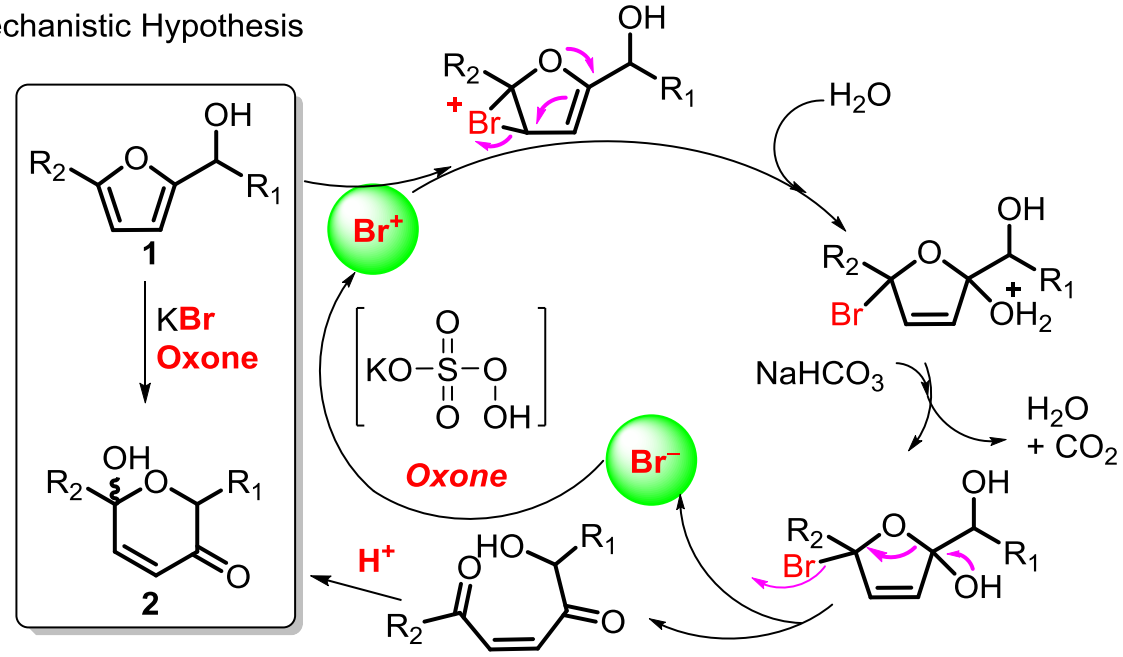

Li, Z.; **Tong*, R.** Highly *trans*-Selective Arylation of Achmatowicz Rearrangement Products by Reductive γ-Deoxygenation and Heck-Matsuda Reaction: Asymmetric Total Synthesis of (-)-Musellarins and Analogues. *Chem. Eur. J.* **2015**, 21, 11152-11157.

# New Protocol for FOD: Tong Modification (Achmatowicz Rearrangement)




NBS, *m*-CPBA, PCC
$Br_2$, Oxone
$PhI(OAc)_2$
$VO(acac)_2$, *t*-BuOOH
Sharpless AE

Mechanistic Hypothesis

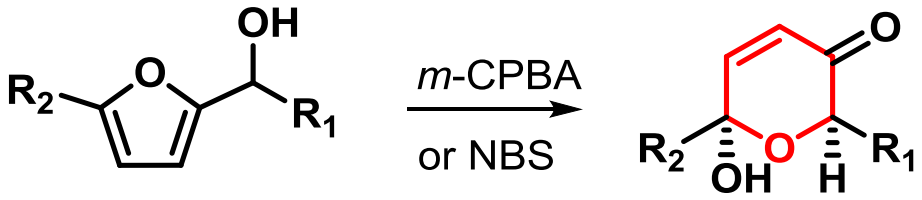



***** No TS Metals
***** No Organic Waste
*** No Column
*** Tolerance of FGs
* Tolerance of $H_2O$/Air
** Higher Yield
** Short Rx Time
*** Wide Scope

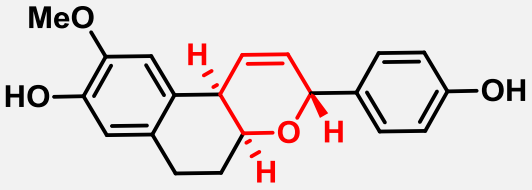
Li, Z.; **Tong*, R.** Catalytic Environmentally Friendly Protocol for Achmatowicz Rearrangement. *J. Org. Chem.* **2016**, (Accepted).

# FOD in Total Synthesis of Musellarins

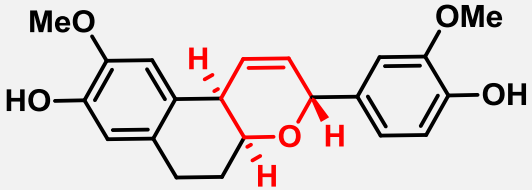
**FOD**



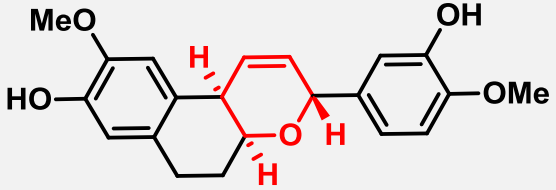

**Achmatowicz Rearrangement**




(±)-Musellarin A (B1a)
(2014) by Li, Z. & Leung, T.-F.
(–)-Musellarin A (B1b)
(2015) by Li, Z.




(±)-Musellarin B (B2a)
(2014) by Li, Z. & Leung, T.-F.
(–)-Musellarin A (B2b)
(2015) by Li, Z.

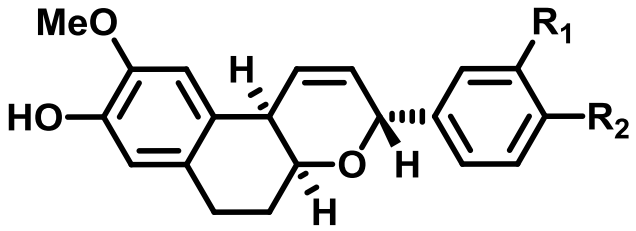



(±)-Musellarin C (B3a)
(2014) by Li, Z. & Leung, T.-F.
(–)-Musellarin A (B3b)
(2015) by Li, Z.

# Musellarins A-C

***Musellarin A*** was isolated from *Musa x paradisiaca L.* by A. Douglas Kinghorn's group

Jang, D. S.; Park, E. J.; Hawthorne, M. E.; Vigo, J. S.; Graham, J. G.; Cabieses, F.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H. S.; Mehta, R. G.; Pezzuto, J. M.; Kinghorn, A. D. *J. Agric. Food Chem.* **2002**, *50*, 6330.




*Musellarin A*: $R_1$=H, $R_2$=OH
*Musellarin B*: $R_1$=$OCH_3$, $R_2$=OH
*Musellarin C*: $R_1$=OH, $R_2$=$OCH_3$

| | CD ($\mu$g/mL) | $IC_{50}$ ($\mu$g/mL) |
|---|---|---|
| ***Musellarin A*** | 9.3 | >20 |
| ***Musellarin B*** | no significant bioactivity | |

CD is concentration required to double QR (Quinone Reductase, phase II enzyme for detoxication) activity

$IC_{50}$ / $\mu$M

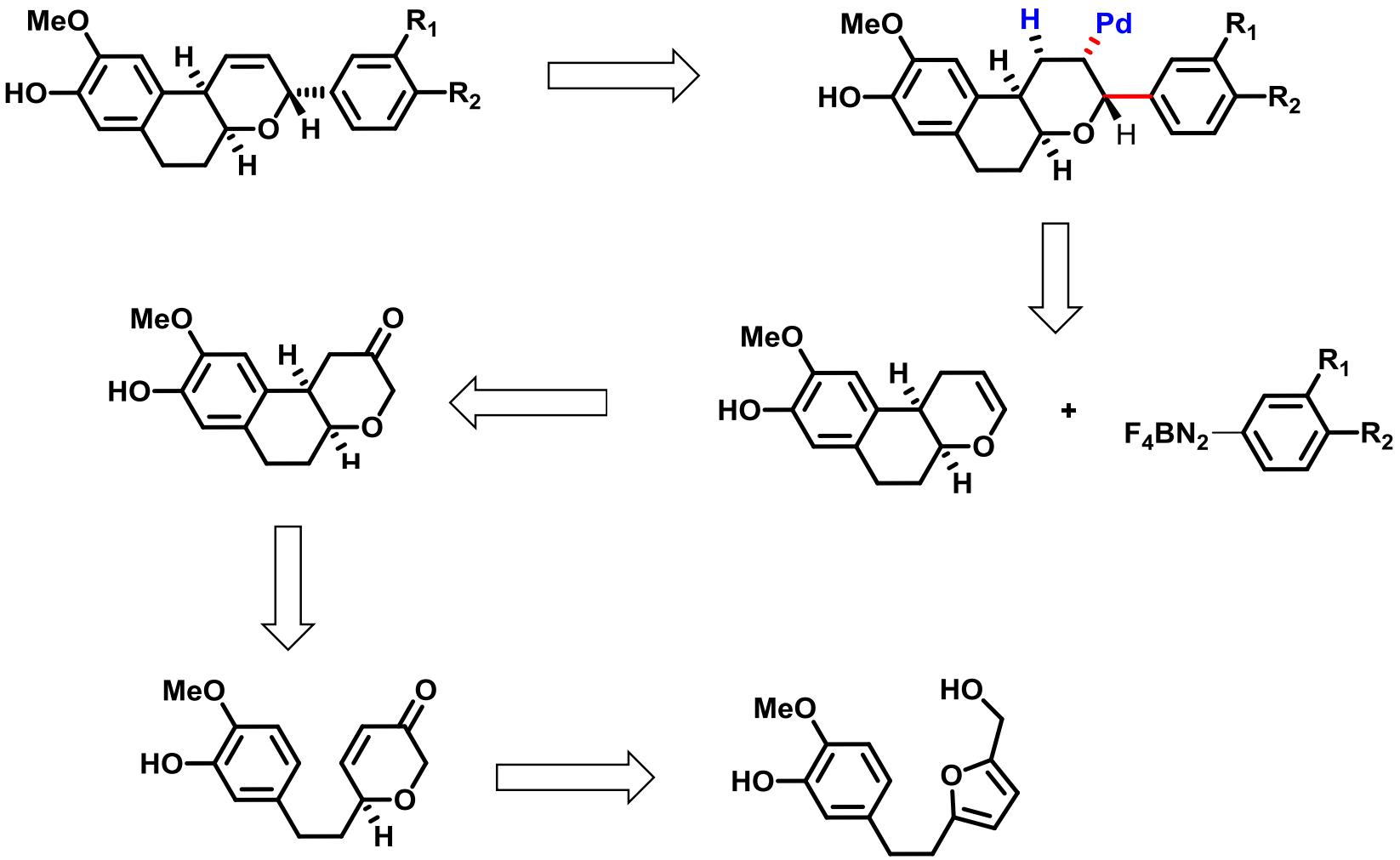
| | HL-60 | SMMC-7721 | A-549 | MCF-7 | SW480 |
|---|---|---|---|---|---|
| ***Musellarin C*** | 21.3 | 26.7 | 25.1 | > 40 | > 40 |

HL-60 acute leukemia
SMMC-7721 liver cancer
A-549 lung cancer
MCF-7 breast cancer
SW480 colon cancer

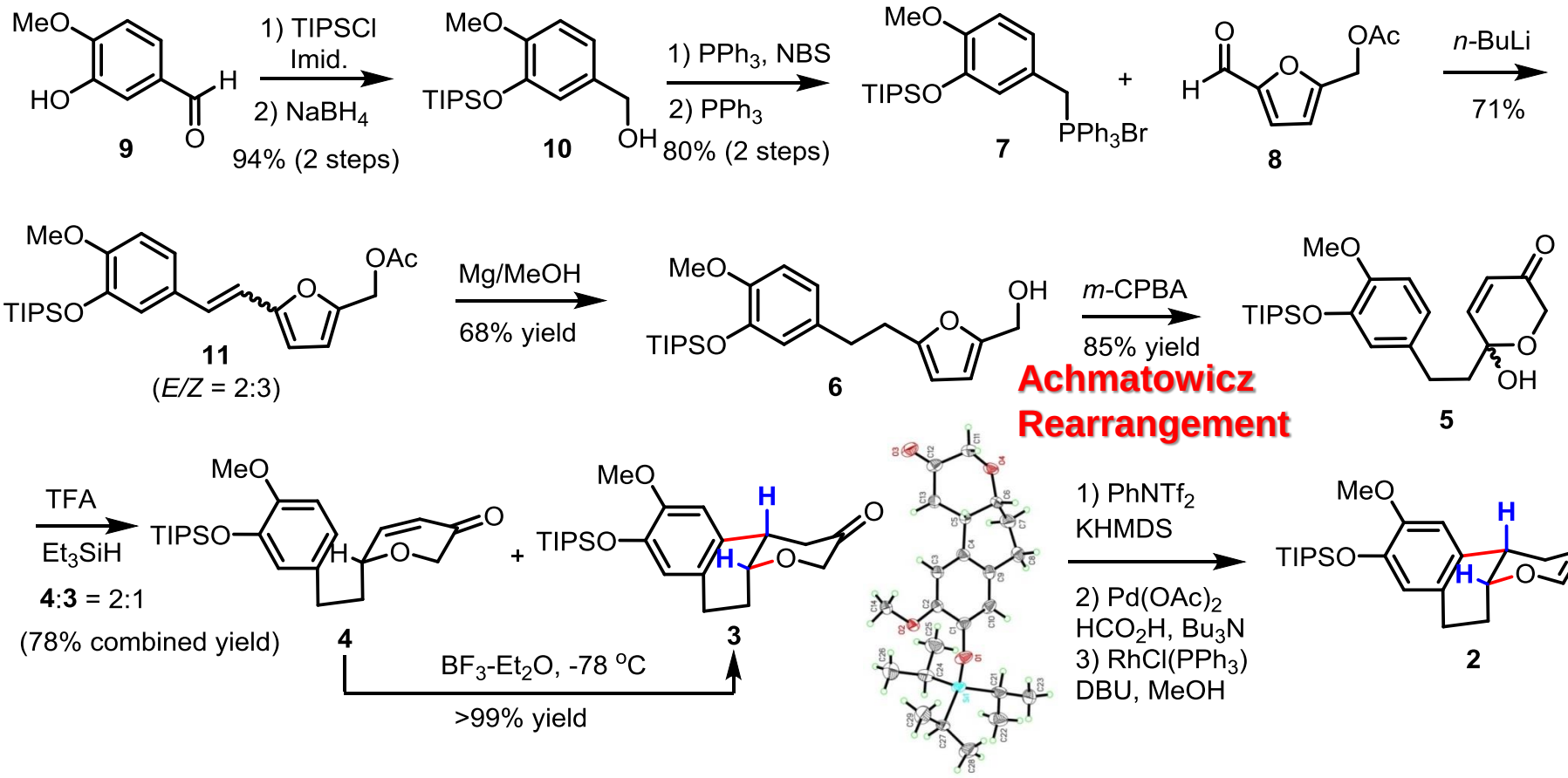
***Musellarin B and C*** were isolated from aerial parts of *Musella lasiocarpa* (地涌金蓮) by Zhao Qin-Shi's group

Dong, L.-B.; He, J.; Li, X.-Y.; Wu, X.-D.; Deng, X.; Xu, G.; Peng, L.-Y.; Zhao, Y.; Li, Y.; Gong, X.; Zhao, Q.-S. *Nat. Prod. Bioprospect.* **2011**, *1*, 41.

# Synthetic Plan of (±)-Musellarins A-C

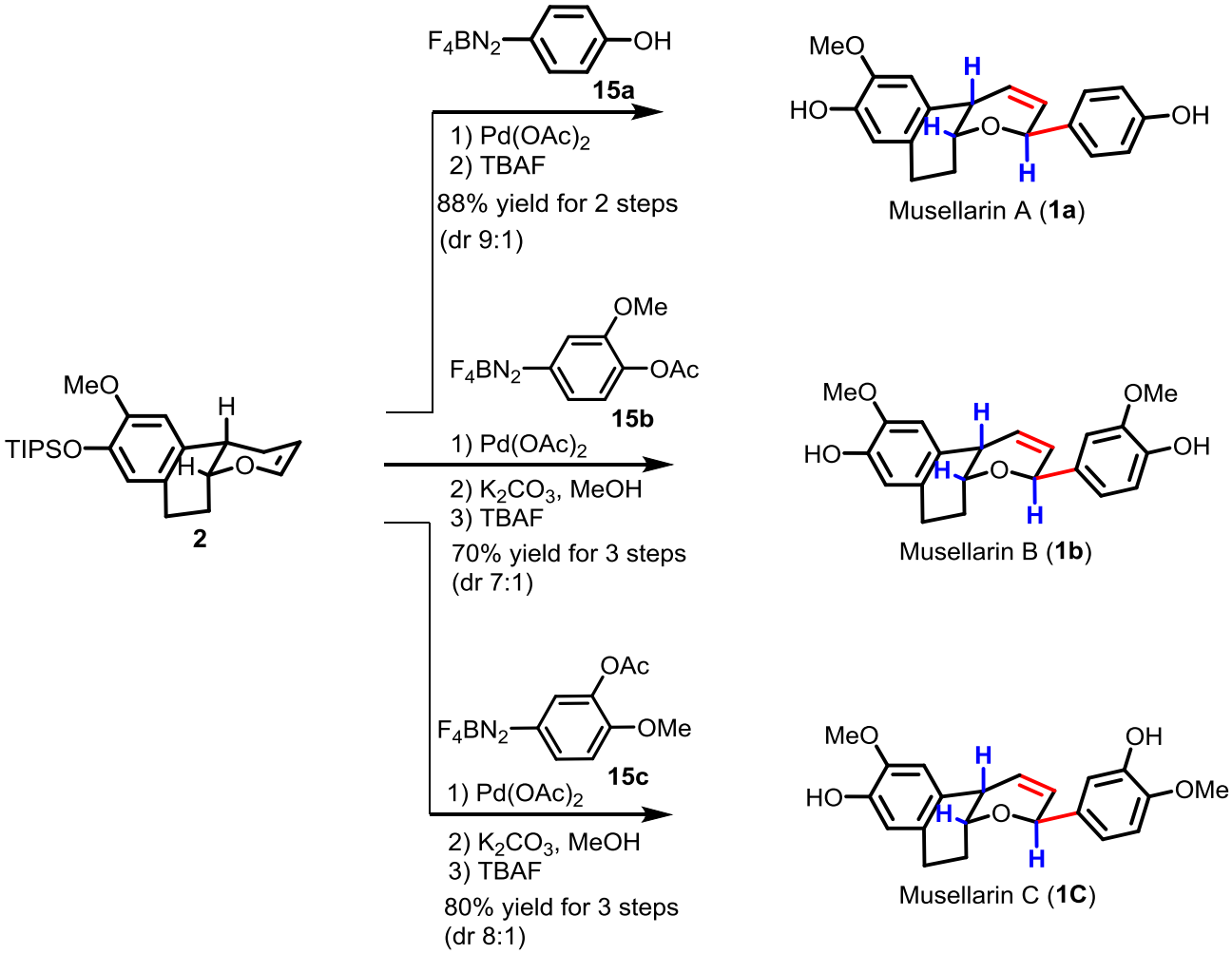


# Total Synthesis of (±)-Musellarins A-C



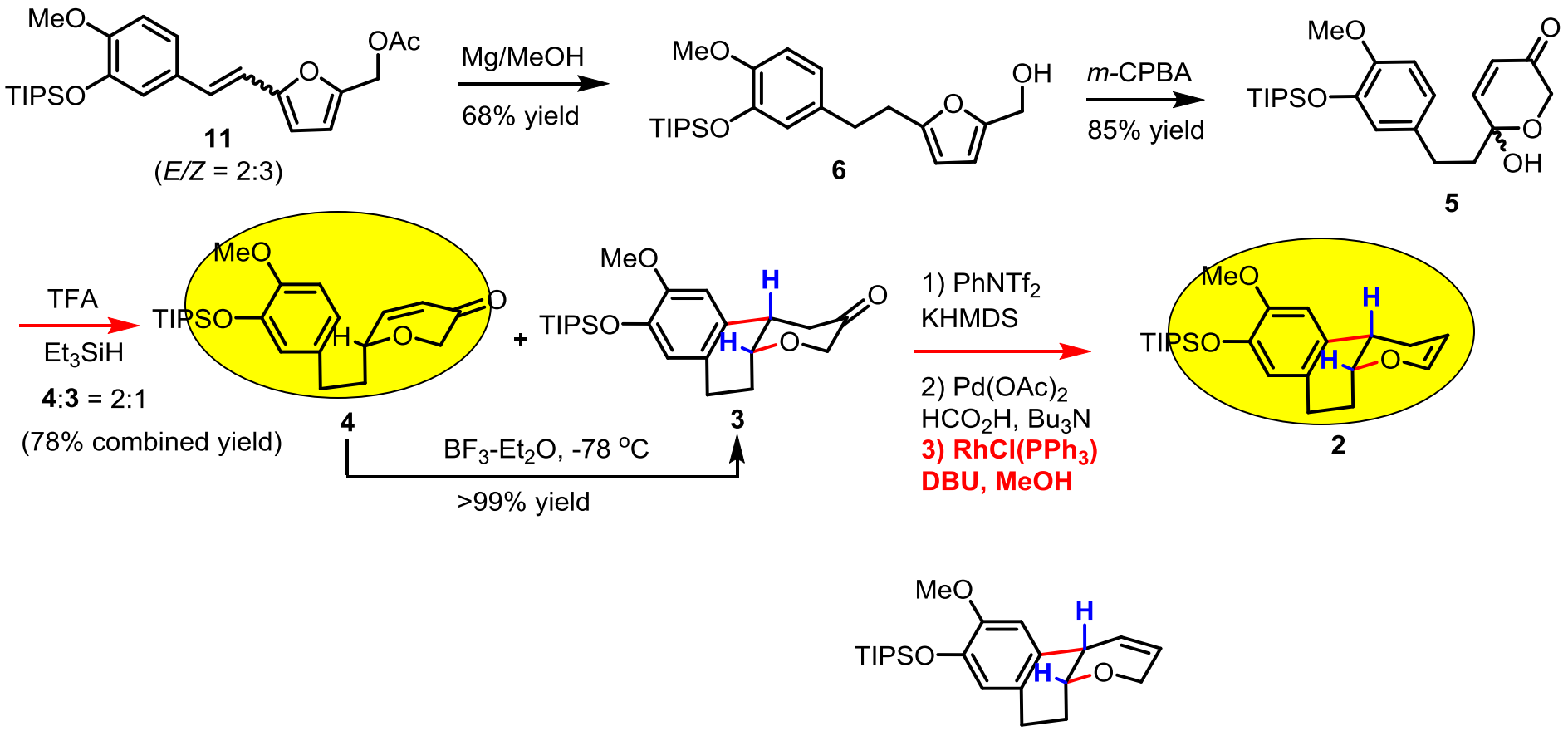

Li, Z.; Leung, T.-F.; **Tong*, R.** Total Syntheses of (±)-Musellarins A-C. *Chem. Commun.* **2014**, *50*, 10990-10993.

# Total Synthesis of (±)-Musellarins A-C



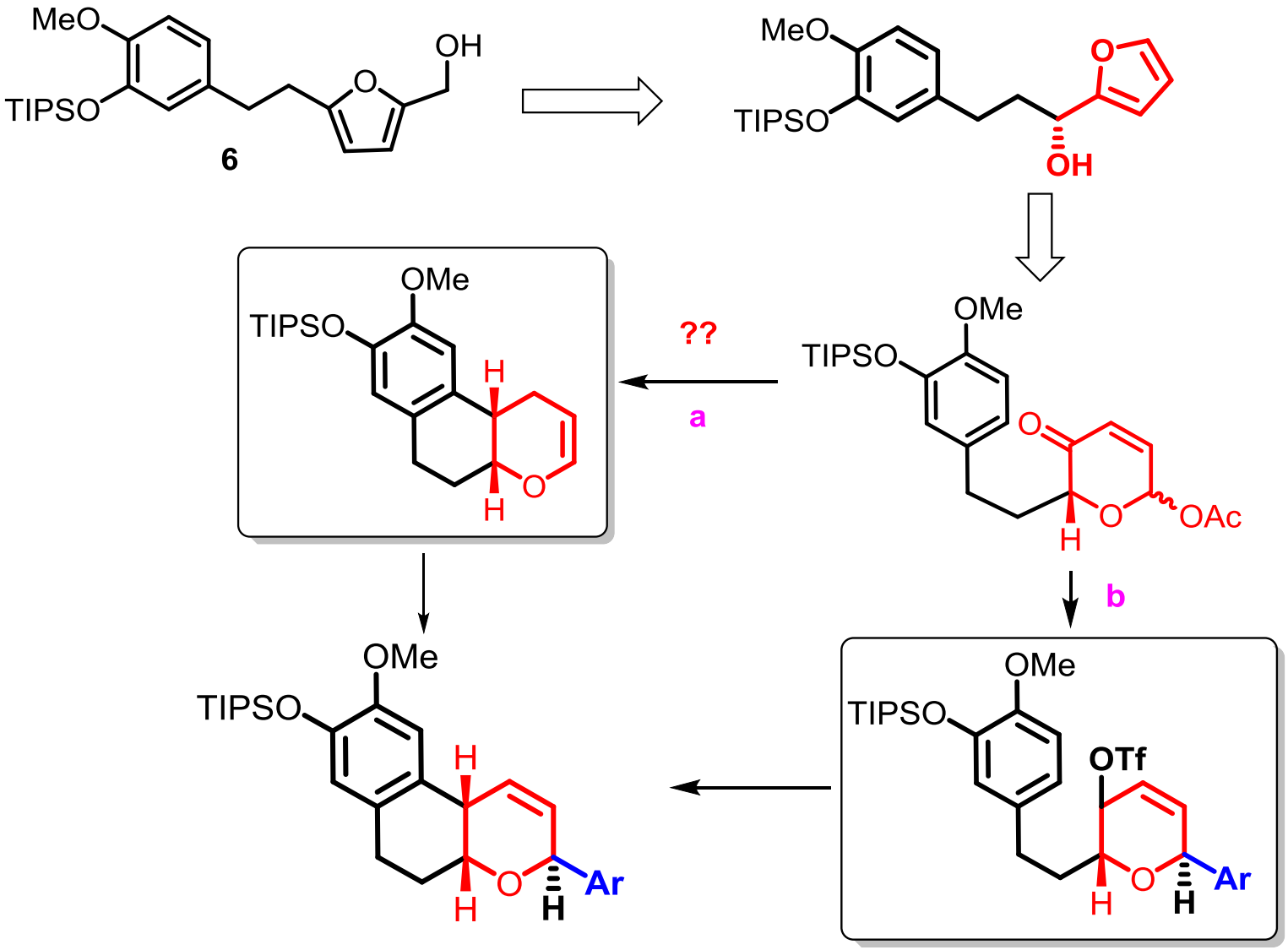

Li, Z.; Leung, T.-F.; **Tong*, R.** Total Syntheses of (±)-Musellarins A-C. *Chem. Commun.* **2014**, *50*, 10990-10993.

# Problems for Asymmetric Version

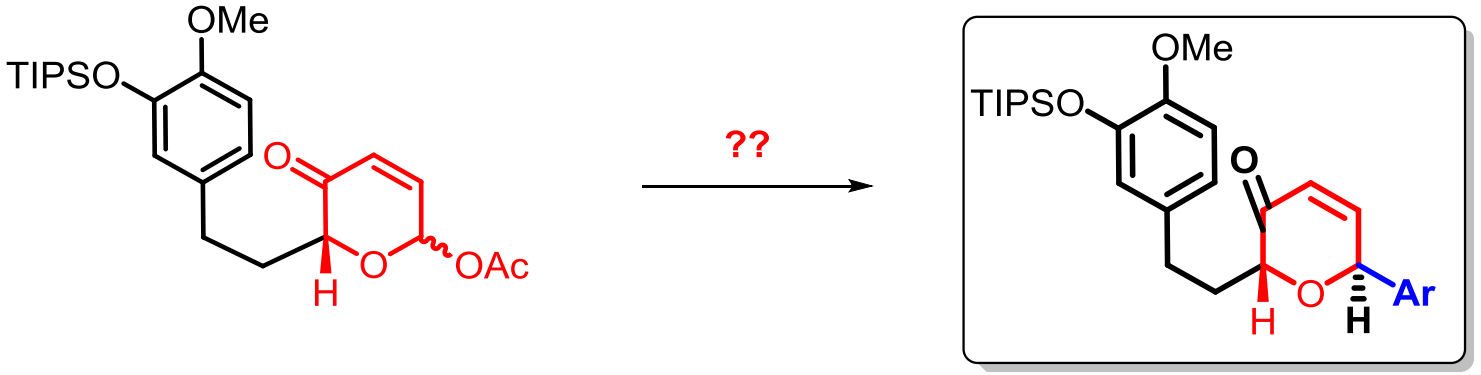


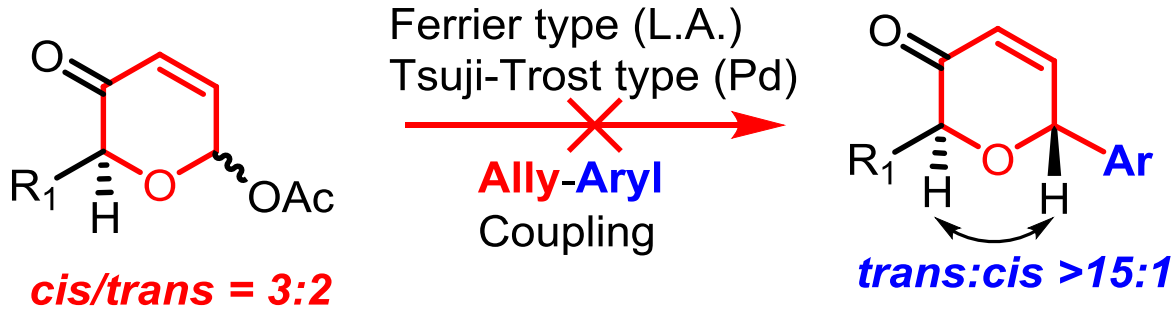

Li, Z.; Leung, T.-F.; **Tong*, R.** Total Syntheses of (±)-Musellarins A-C. *Chem. Commun.* **2014**, *50*, 10990-10993.

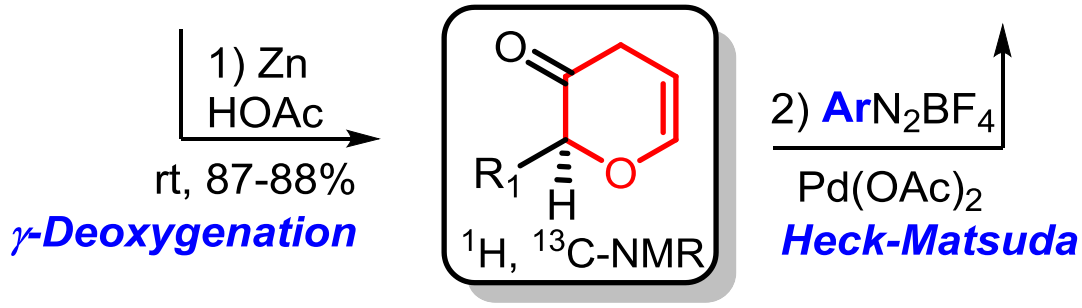
# Asymmetric Version of Musellarins A-C



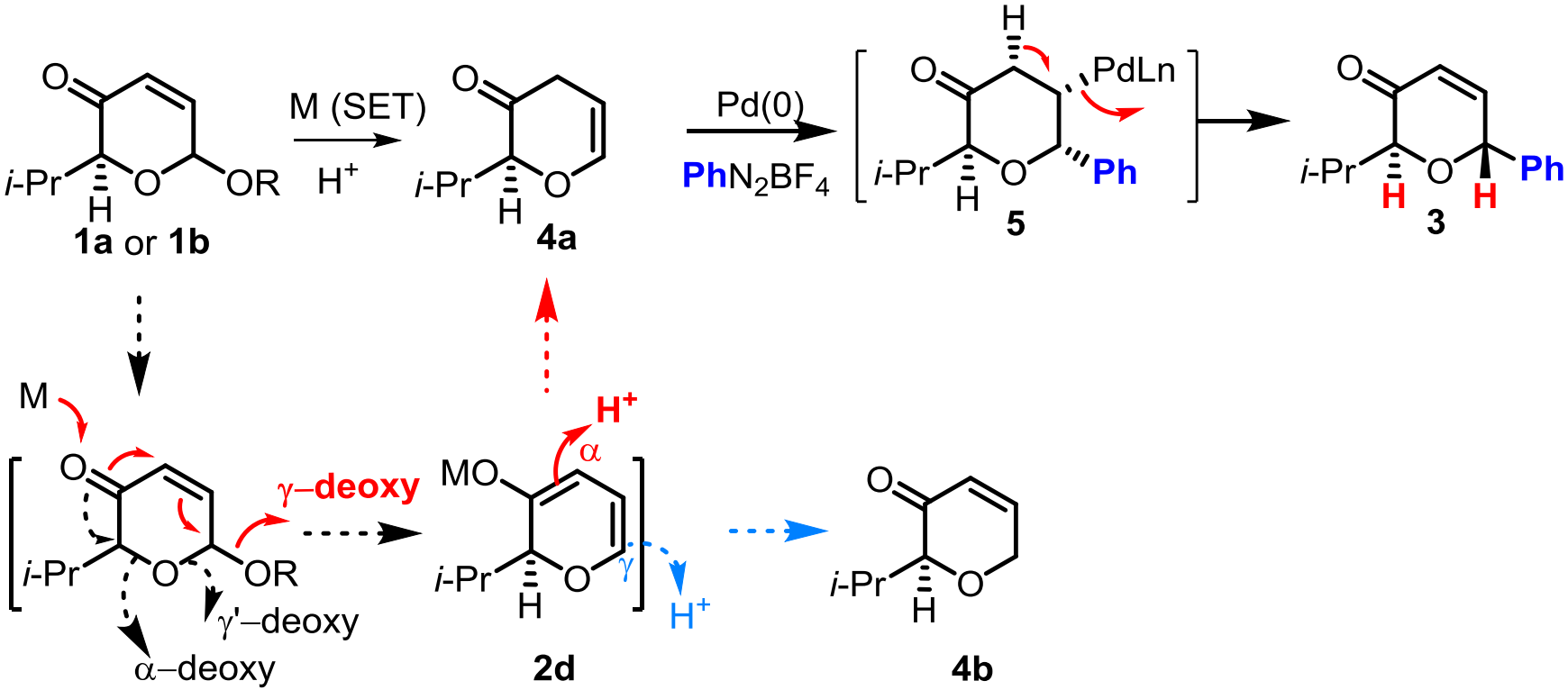
# No Precedent for Such Transformation



# Mechanistic Hypothesis of Deoxygenation




Li, Z.; **Tong*, R.** Highly *trans*-Selective Arylation of Achmatowicz Rearrangement Products by Reductive γ-Deoxygenation and Heck-Matsuda Reaction: Asymmetric Total Synthesis of (-)-Musellarins and Analogues. *Chem. Eur. J.* **2015**, 21, 11152-11157.

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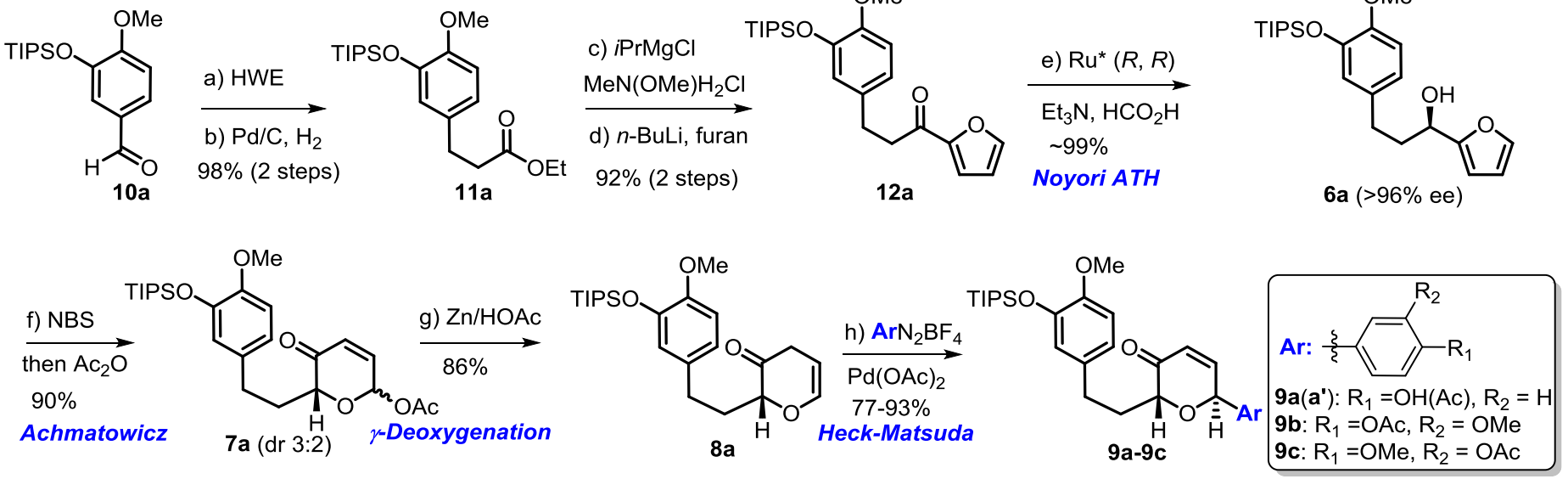
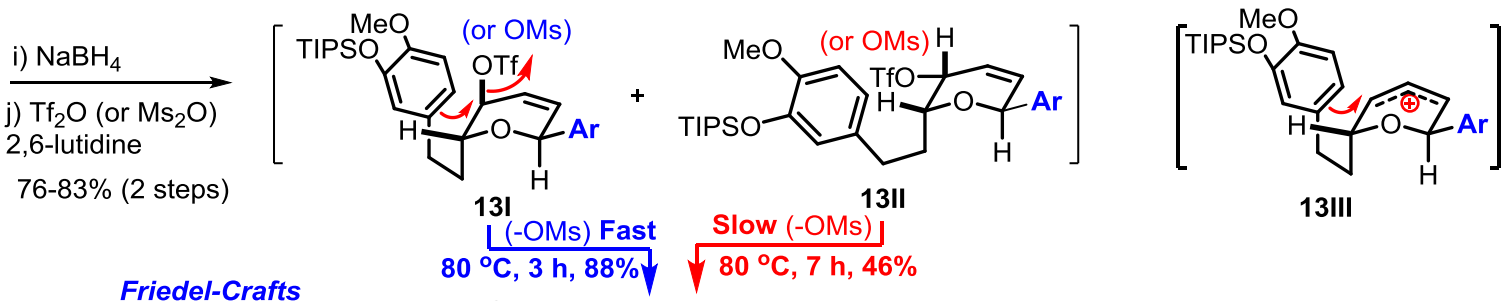
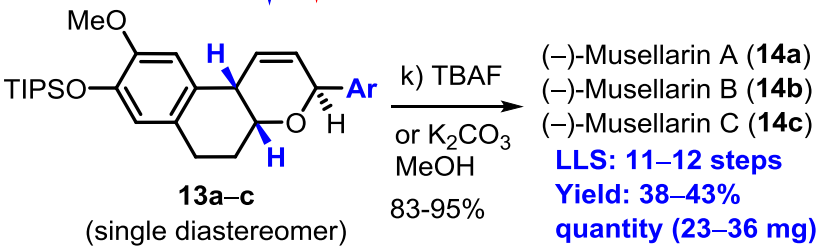
# Asymmetric Total Synthesis of Musellarins A-C



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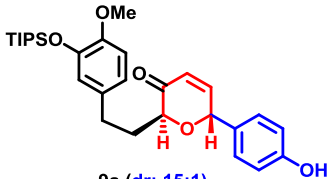
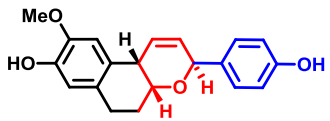
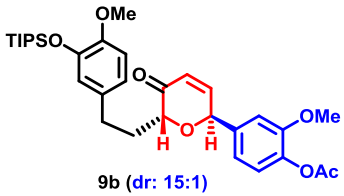
# Asymmetric Synthesis of Musellarin Analogues



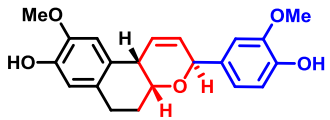
9a (dr: 15:1)



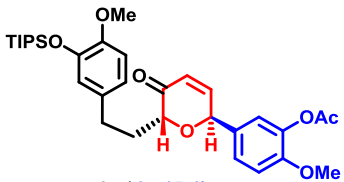
(-)- Musellarin A (14a), 98% ee
(24 mg, 10% for 11 steps)



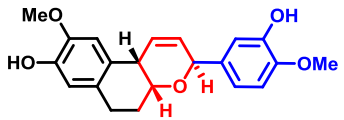
9b (dr: 15:1)



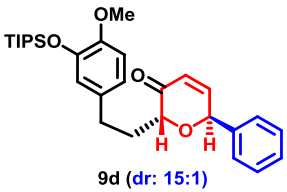
(-)-Musellarin B (14b)
(23 mg, 10% for 11 steps)



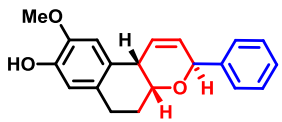
9c (dr: 15:1)



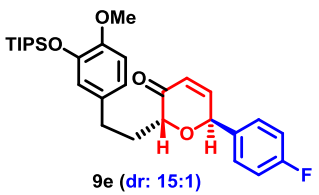
(-)-Musellarin C (14c)
(36 mg, 10% for 11 steps)



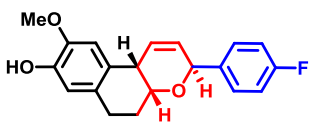
9d (dr: 15:1)



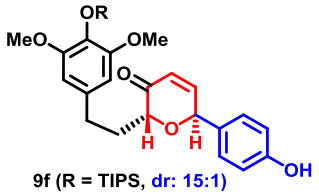
14d (45 mg)



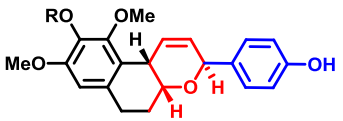
9e (dr: 15:1)



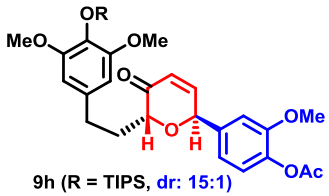
14e (56 mg)



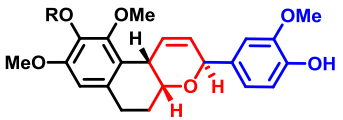
9f (R = TIPS, dr: 15:1)
9g (R = Me, dr: 15:1)



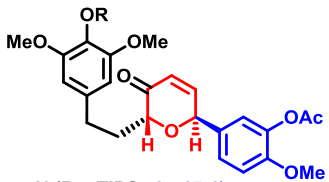
14f (R = H, 24 mg)
14g (R = Me, 45 mg)



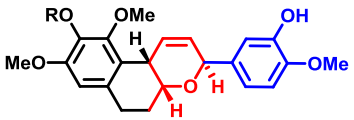
9h (R = TIPS, dr: 15:1)
9i (R = Me, dr: 15:1)



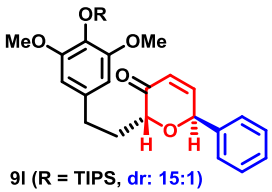
14h (R = H, 26 mg)
14i (R = Me, 39 mg)



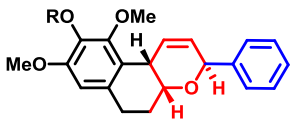
9j (R = TIPS, dr: 15:1)
9k (R = Me, dr: 15:1)



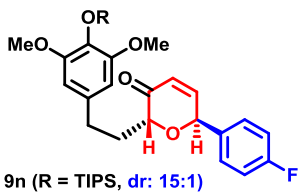
14j (R = H, 29 mg)
14k (R = Me, 20 mg)



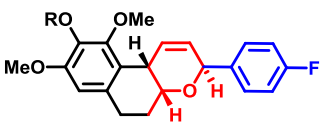
9l (R = TIPS, dr: 15:1)
9m (R = Me, dr: 15:1)



14l (R = H, 49 mg)
14m (R = Me, 41 mg)



9n (R = TIPS, dr: 15:1)
9o (R = Me, dr: 15:1)



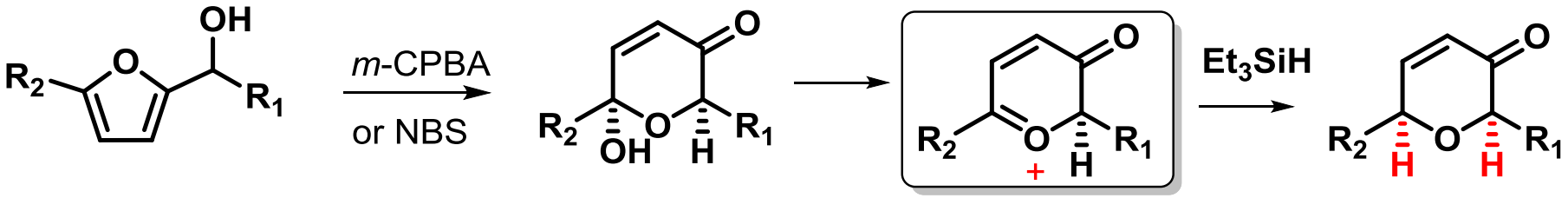
14n (R = H, 35 mg)
14o (R = Me, 50 mg)

# Cytotoxicity of Musellarin Analogues

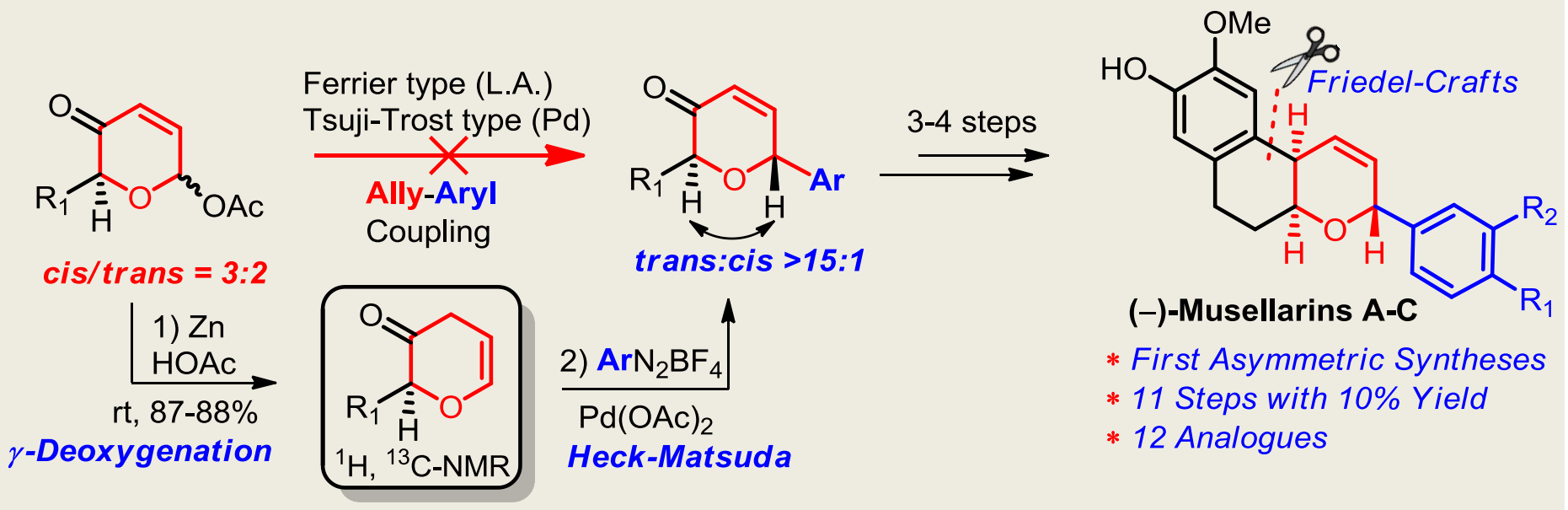
| compound | PCN[b] $IC_{50}$ (μM) | HL60 $IC_{50}$ (μM) | HepG2 $IC_{50}$ (μM) | MCF7 $IC_{50}$ (μM) |
|---|---|---|---|---|
| 14a (Musellarin A) | 23.8 | 9.7 | 44.1 | >50 |
| 14b (Musellarin B) | 65.3 | 25.9 | >50 | >50 |
| 14c (Musellarin C) | >50 | 22.0 | >50 | >50 |
| 14d | 23.6 | 7.4 | >50 | >50 |
| 14e | 33.1 | 11.9 | >50 | >50 |
| 14i | 29.6 | 10.8 | >50 | >50 |
| 14j | >50 | 23.1 | 46.1 | >50 |
| 14k | 17.7 | 3.9 | 40.4 | >50 |
| Oxaliplatin[c] | NA | 1.56 | 5.28 | 12.99 |

# Asymmetric Total Synthesis of Musellarins A-C

## Kishi Reduction



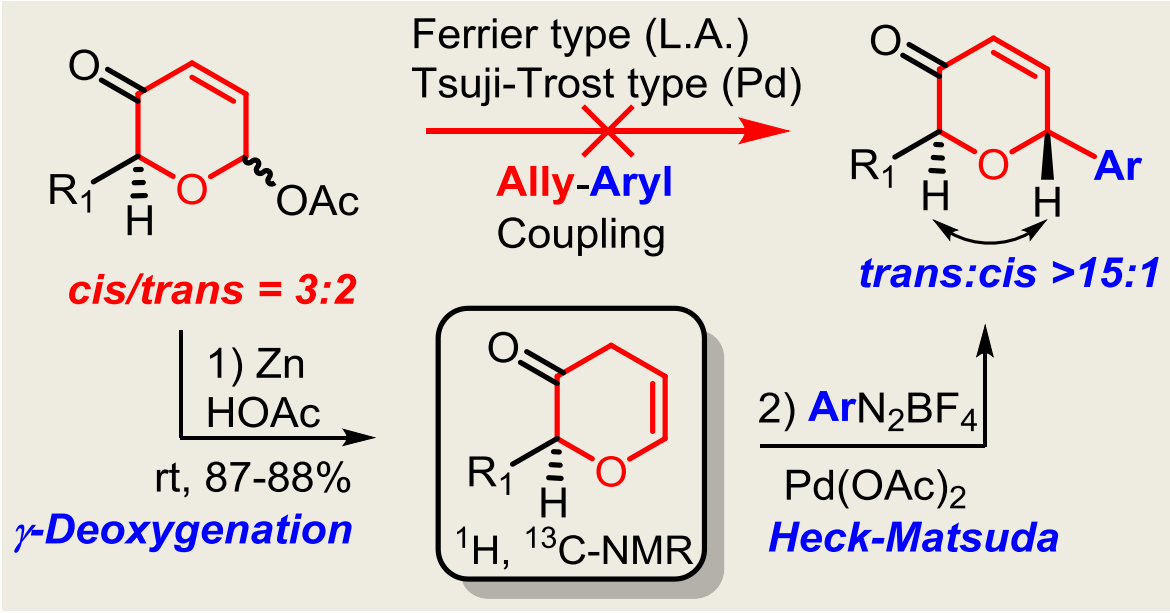

## Tong Deoxygenation/Heck-Matsuda Coupling

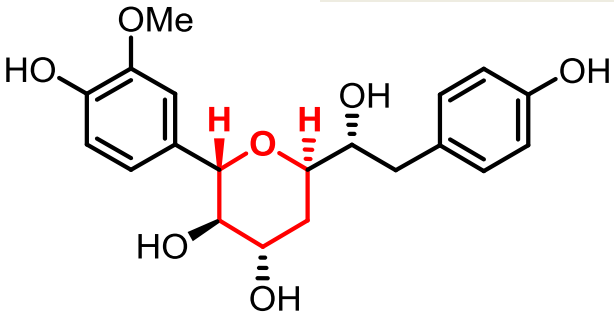



Li, Z.; **Tong*, R.** Highly *trans*-Selective Arylation of Achmatowicz Rearrangement Products by Reductive γ-Deoxygenation and Heck-Matsuda Reaction: Asymmetric Total Synthesis of (-)-Musellarins and Analogues. *Chem. Eur. J.* **2015**, 21, 11152-11157.

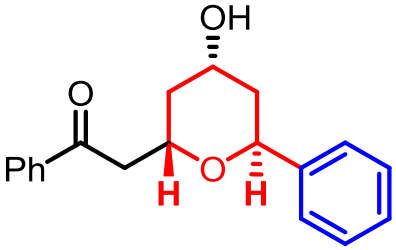
# Asymmetric Total Synthesis of Diospongin B and Parvistones D/E

## Tong Deoxygenation/Heck-Matsuda Coupling

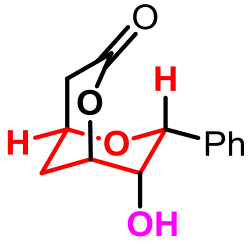


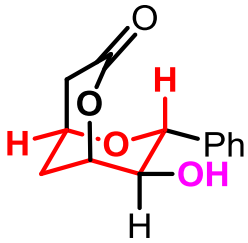
Hedycoropyran A



Diospongin B



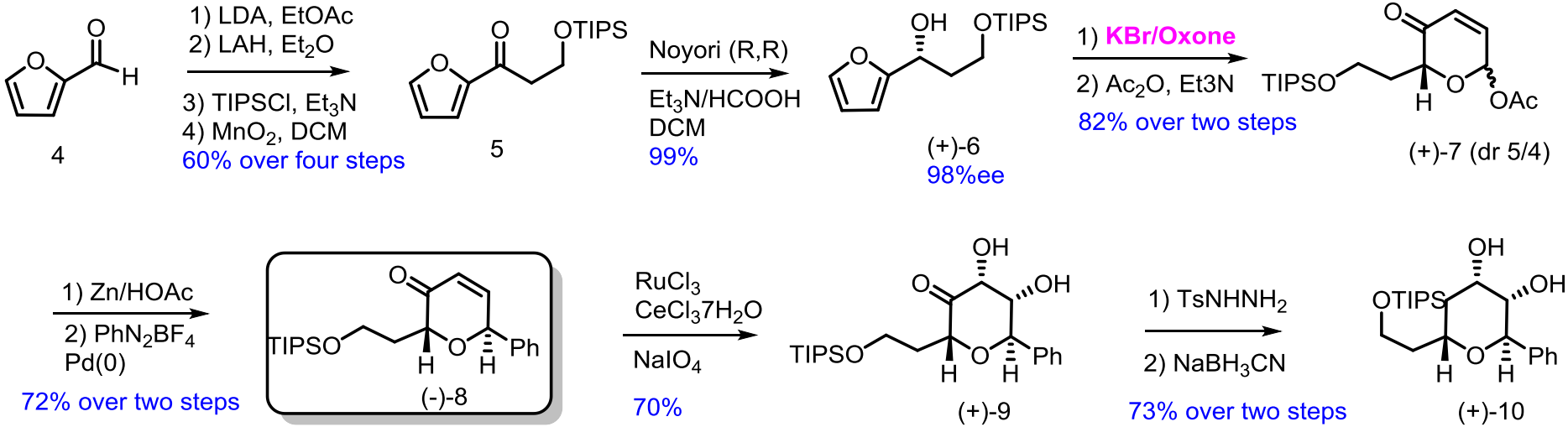
Parvistone D

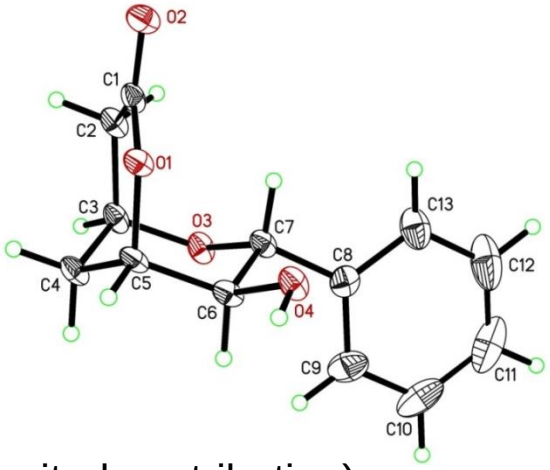


Parvistone E

Li, Z.; Tong, R. *Synthesis* **2016,** 48, 1630-1636 (Invited contribution).

# Asymmetric Synthesis of Parvistone E




Li, Z.; Tong, R. *Synthesis* **2016,** 48, 1630-1636 (Invited contribution).

# Asymmetric Synthesis of Parvistone D

(a)

*synth*-**3** → (Swern, Jones; DMP, PCC, TPAP/NMO) → a) $K_2CO_3$, MeOH; b) $NaBH(OAc)_3$ → **Parvistone D**

$S_N2$ Mitsunobu or MsCl/CsOAc

(b)

(+)-**10** → a) $RuCl_3$ (1 mol %), Oxone; **12a**/**12b** = 2:1 → **12a** + **12b** → b) $NaBH(OAc)_3$; **10**/**13** = 2:1

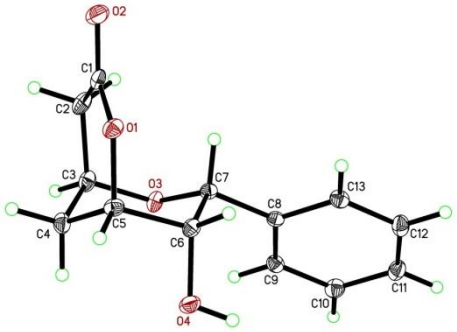
42% (71% brsm) over 2 steps

**10** + (+)-**13** → c) *p*-TsOH, $Me_2C(OMe)_2$; d) TBAF

70% over 2 steps

(+)-**14** → e) DMP; f) $NaClO_2$; g) HCl → **Parvistone D**

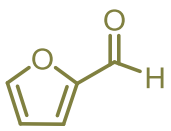
49% over 3 steps



Li, Z.; Tong, R. *Synthesis* **2016,** 48, 1630-1636 (Invited contribution).

RTONG@HKUST

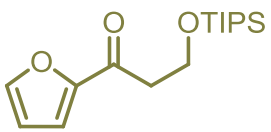
# Asymmetric Total Synthesis of Diospongin B



4

1) LDA, EtOAc
2) LAH, $Et_2O$

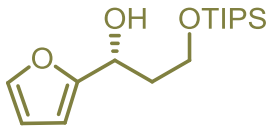
3) TIPSCl, $Et_3N$
4) $MnO_2$, DCM
60% over four steps



5

Noyori (R,R)

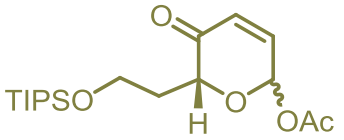
$Et_3N$/HCOOH
DCM
99%



(+)-6
98%ee

1) **KBr/Oxone**

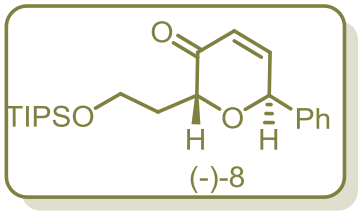
2) $Ac_2O$, Et3N
82% over two steps



(+)-7 (dr 5/4)

1) Zn/HOAc

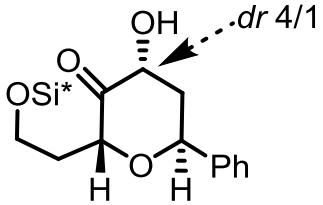
2) $PhN_2BF_4$
Pd(0)
72% over two steps



(-)-8

h) $Rh_2(OAc)_4$
$Et_3SiH$

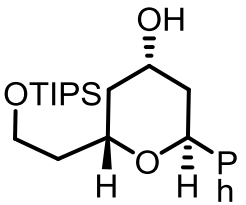
i) *m*-CPBA
65% over 2 steps



(–)-**15** (*dr* 4/1)

j) $TsNHNH_2$

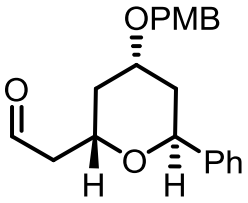
k) $NaBH_3CN$
68% over 2 steps



(–)-**16** (*dr* 4/1)

l) PMBCl
m) TBAF

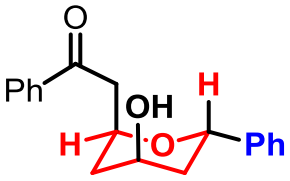
n) DMP
52% over
3 steps



(–)-**17** (*dr* 4/1)

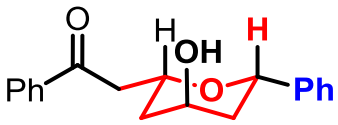
o) PhMgBr

p) DMP
r) DDQ
62% over 3 steps



(+)-diospongin B (**1**)

ref. 11, 13

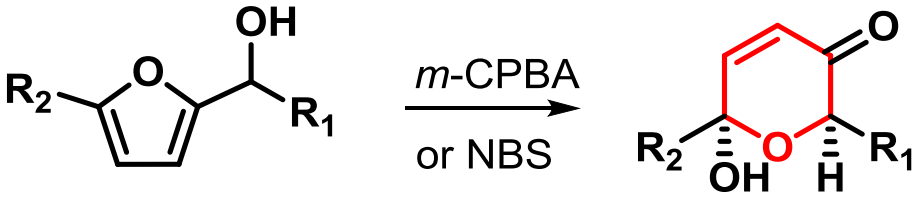


diospongin A (**1**)

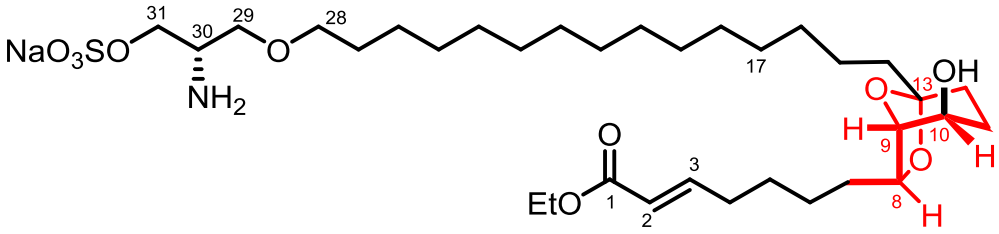
Li, Z.; Tong, R. *Synthesis* **2016,** 48, 1630-1636 (Invited contribution).

# FOD in Total Synthesis of DOBCO

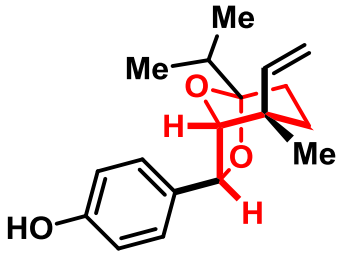
**FOD**



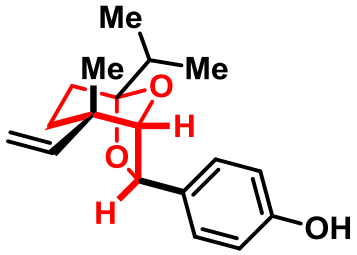

**Achmatowicz Rearrangement**



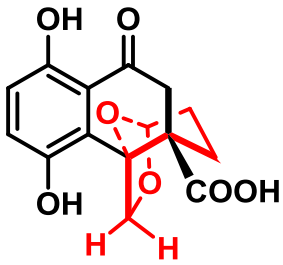

Didemniserinolipid B



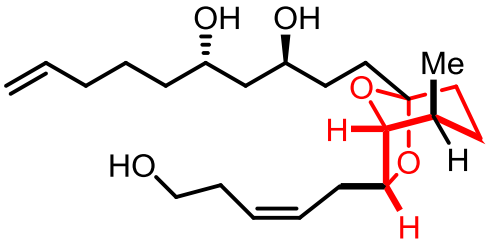

Psoracorylifol B



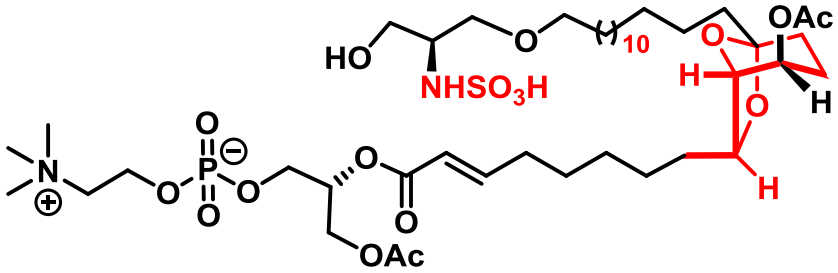

Psoracorylifol C




Cochlearols A



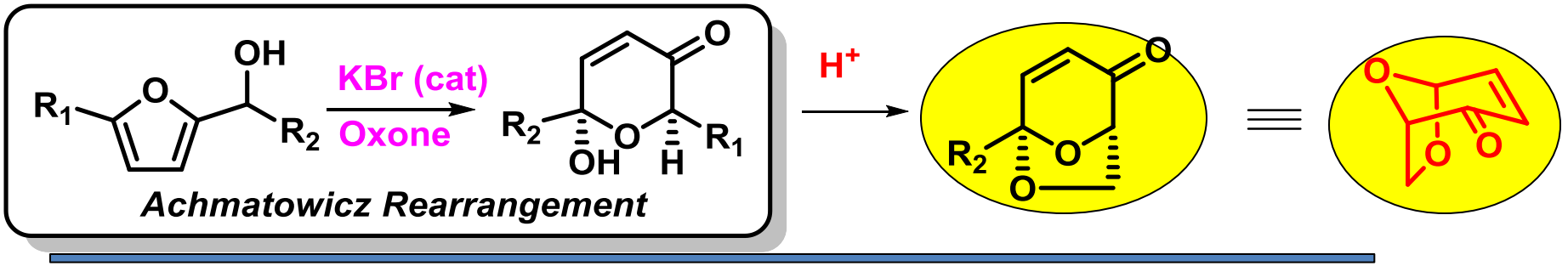

Attenol B

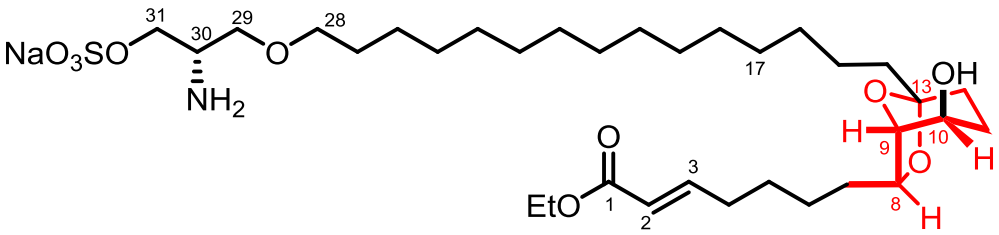



Siladenoserinol A

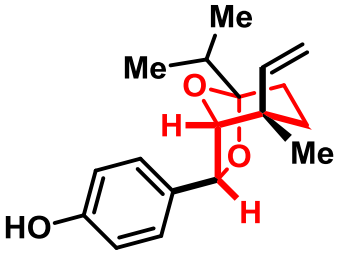
# FOD in Total Synthesis of DOBCO

***Furan Oxidative Dearomatization (FOD)***

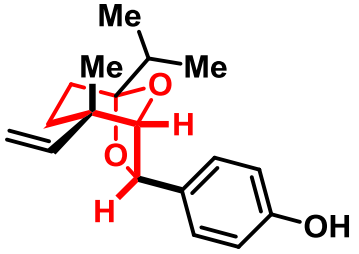


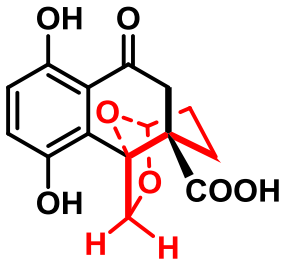

**Didemniserinolipid B**



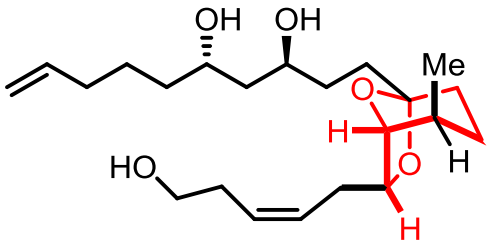

**Psoracorylifol B**



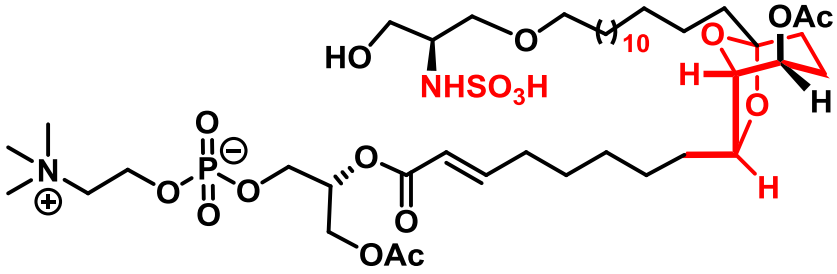

**Psoracorylifol C**




**Cochlearols A**

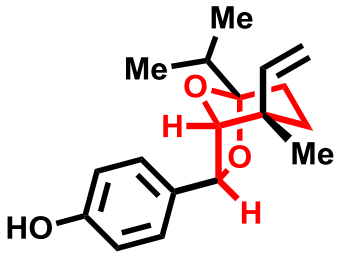



**Attenol B**

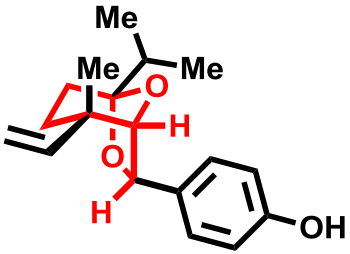



**Siladenoserinol A**

# Psoracorylifol B and *ent*-Psoracorylifol C




**Psoracorylifol B**
**MIC = 12.5 μg/mL**




**Psoracorylifol C**
**MIC = 12.5 μg/mL**

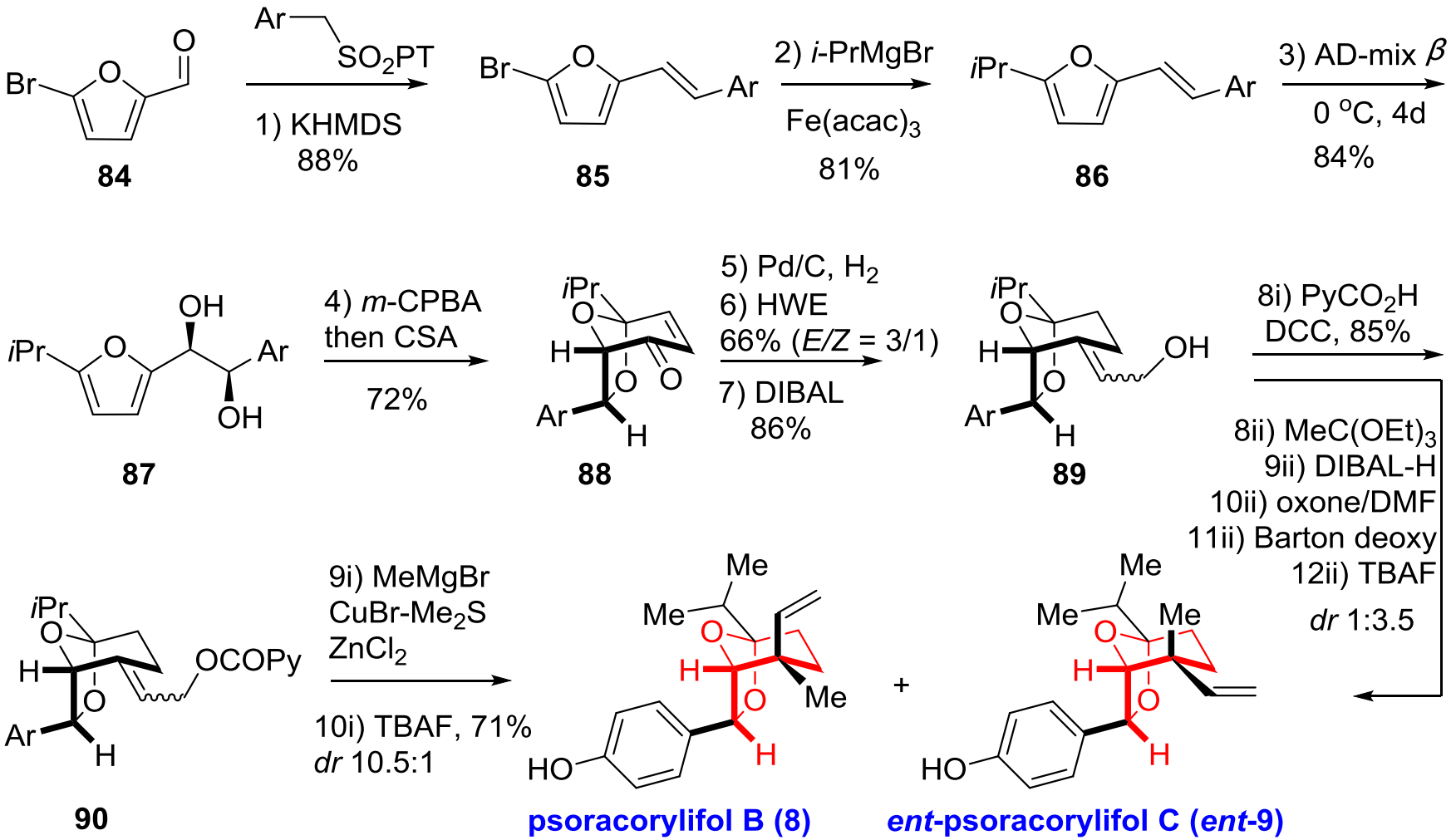
*Psoralea corylifolia* L

First isolated from the seeds of *Psoralea corylifolia* L. in 2006. In 2007, Yoshikawa and co-workers independently isolated psoracorylifols B and C again from the same source.

They showed significant antimicrobial activity *in vitro* as potent inhibitors against two strains of *Helicobacter pylori* with MICs of 12.5-25 μg/mL.

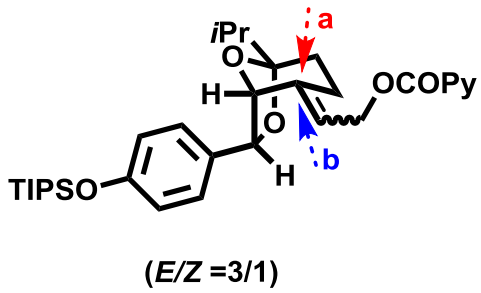
(a) Yin, S.; Fan, C. -Q.; Dong, L.; Yue, J.-M. *Tetrahedron* **2006**, *62*, 2569-2575.
(b) Matsuda, H.; Sugimoto, S.; Morikawa, T.; Matsuhira, K.; Mizugachi, E.; Nakamura, S.; Yoshikawa, M. *Chem. Pharm. Bull.* **2007**, *55*, 106.

# Asymmetric Total Synthesis of Psoracorylifol B and *ent*-Psoracorylifol C




Ren, J.; Liu, Y.; Song, L.; **Tong*, R.** Scalable Asymmetric Total Syntheses of (+)-Psoracorylifol B and (+)-ent-Psoracorylifol C. *Org. Lett.* **2014**, *16*, 2986-2989. Highlighted in Synfacts: 2014, 10, 904. And Highlighted in Organic Chemistry Portal, 2014, November 10.

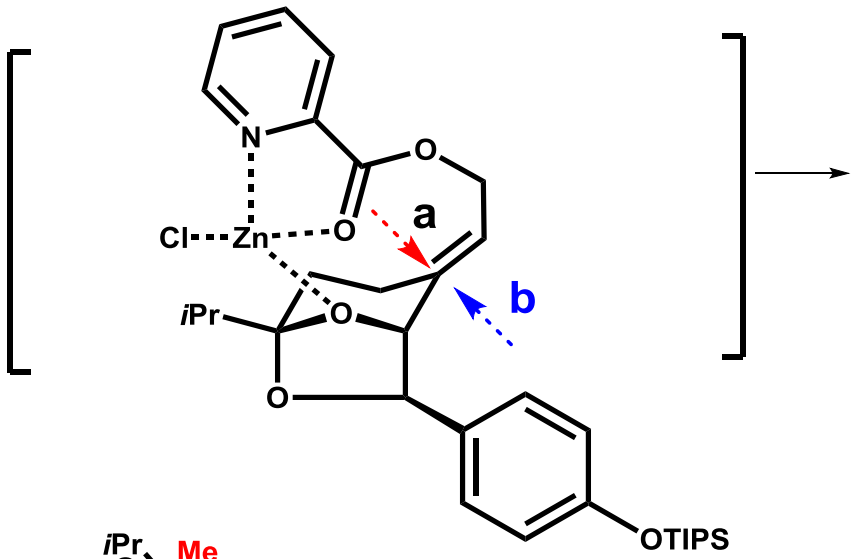
# Unusual Diastereoselectivity

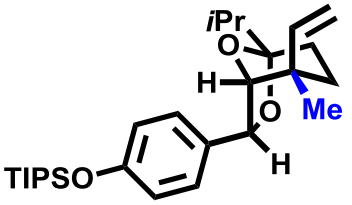



(*E*/*Z* =3/1)

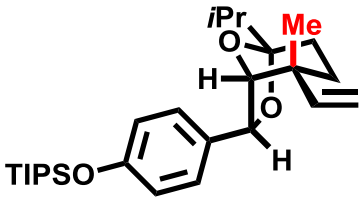
MeMgBr
CuBr-$Me_2S$
$ZnCl_2$

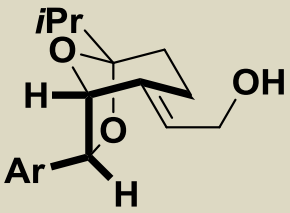
*dr* 10.5/1




+



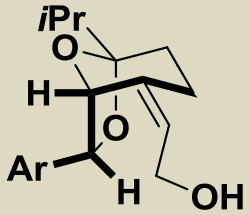

16a (*E only*)

3 steps → PsB (2) (only)

PsB (2) + *ent*-PsC (*ent*-3)

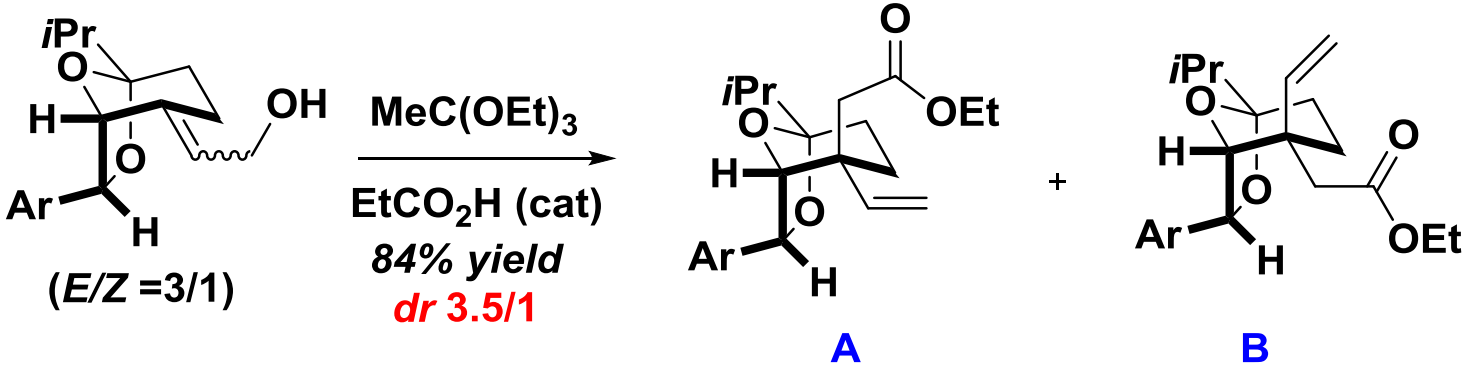
2/*ent*-3 = 2/1

3 steps ←

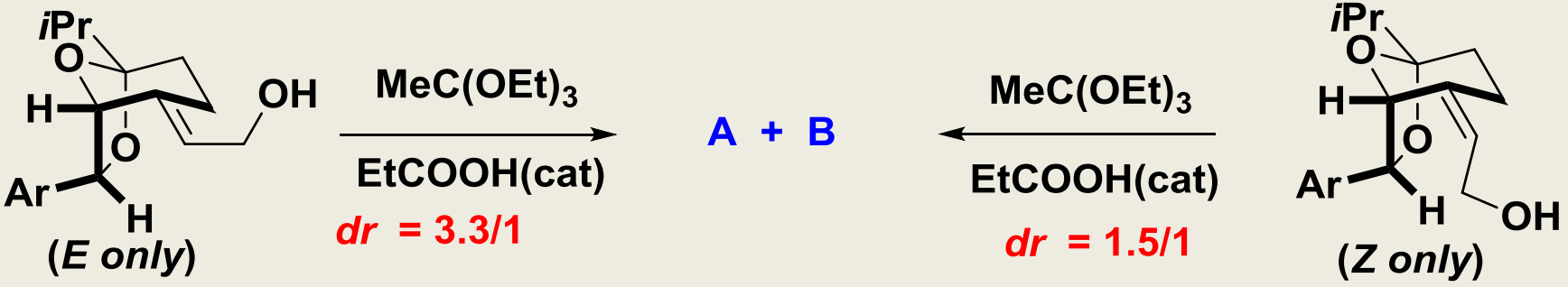



16b (*Z only*)

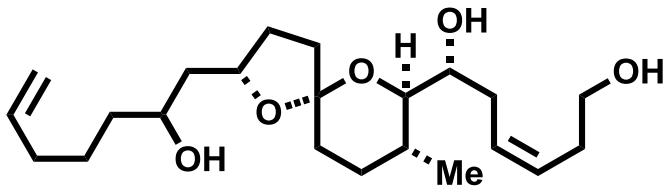
# Non-stereospecific Johnson-Claisen




## Non-Stereospecific Johnson-Claisen Rearrangement

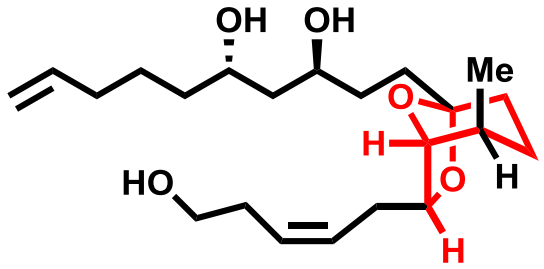


# Attenols A and B



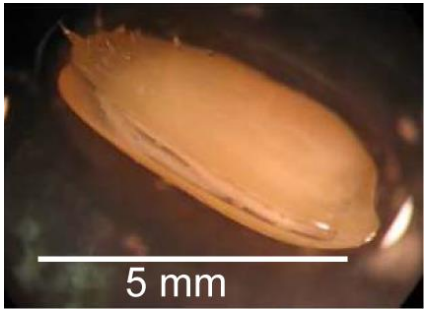

(–)-Attenol A

**$IC_{50}$ = 24 μg/mL**




(+)-Attenol B

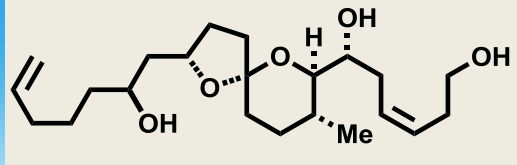
**$IC_{50}$ = 12 μg/mL**



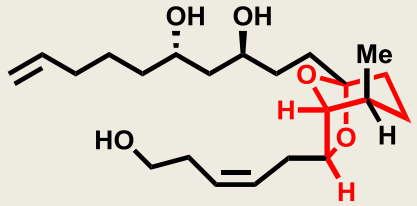

**Isolated from the Chinese bivalve *Pinna attenuata* in 1999, exhibited cytotoxicity against P388 cells ($IC_{50}$ values of 24 and 12 μg/mL, respectively).**

Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527-529.

# Previous Methods to Attenols A and B

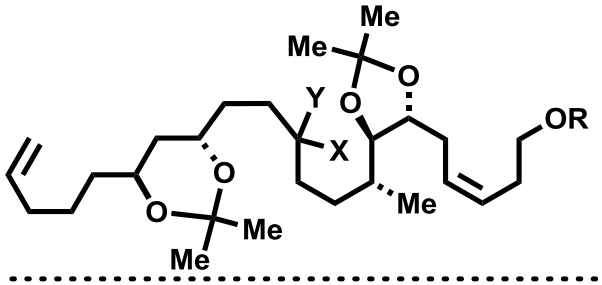



(–)-Attenol A




(+)-Attenol B

**Method A:** Suenaga, K, & *Uemura, D. & Chandrasekhar, S. & Enders, D. & Yadav, J. S*

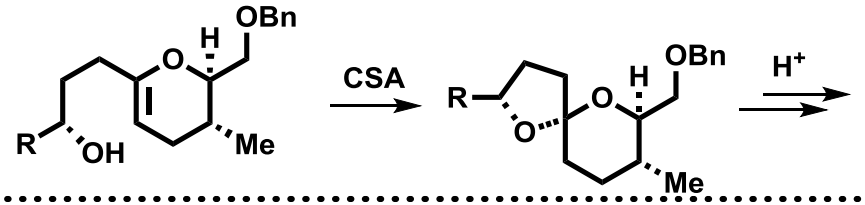



$H^+$ → Ketalization

Attenol A + Attenol B

A:B = 3.8:1 to 6.3/1

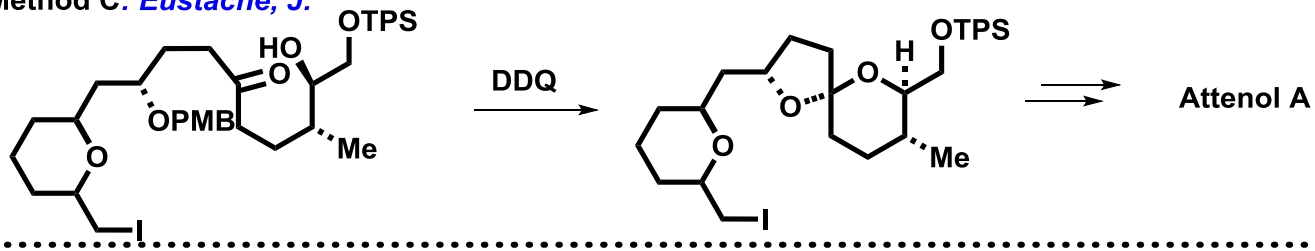
**Method B:** Fuwa, H. and Sasaki, M.




Attenol A + Attenol B

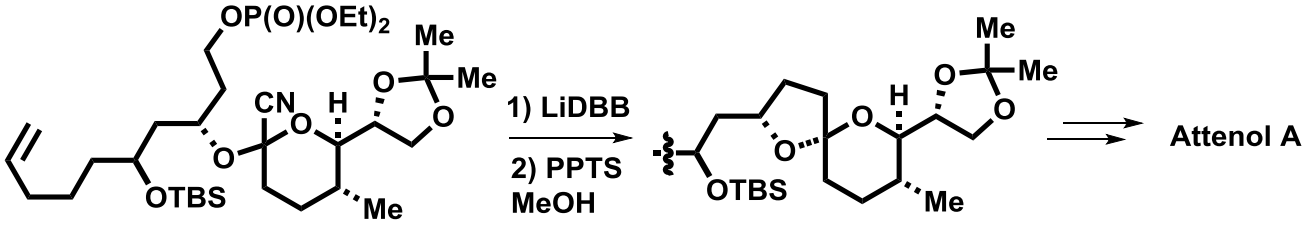
A:B = 8.6:1

**Method C***: Eustache, J.*




Attenol A

**Mehtod D:** *Rychnovsky, S. D.*

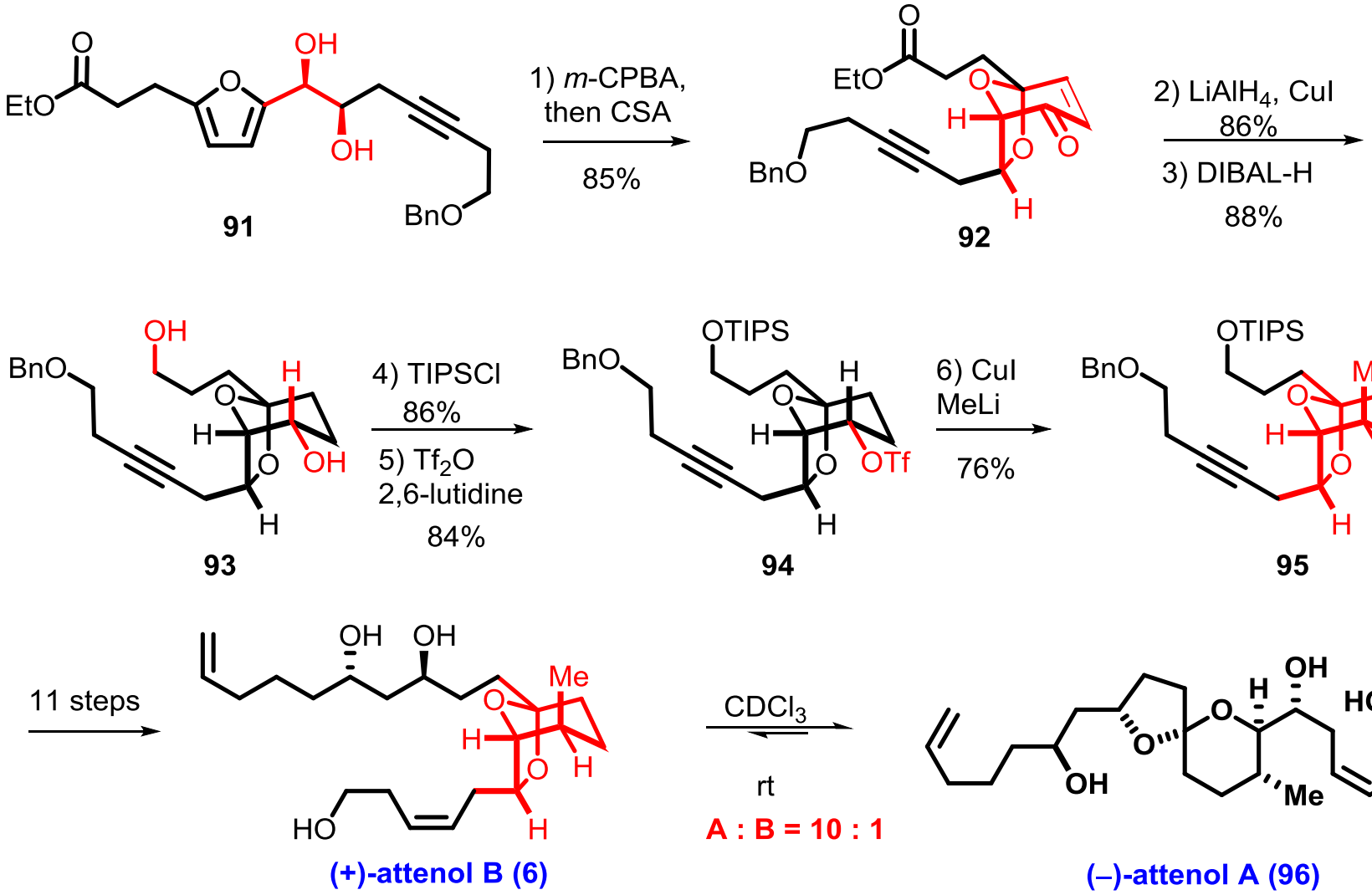



Attenol A

**7 total Synthesis of Attenols A and B**

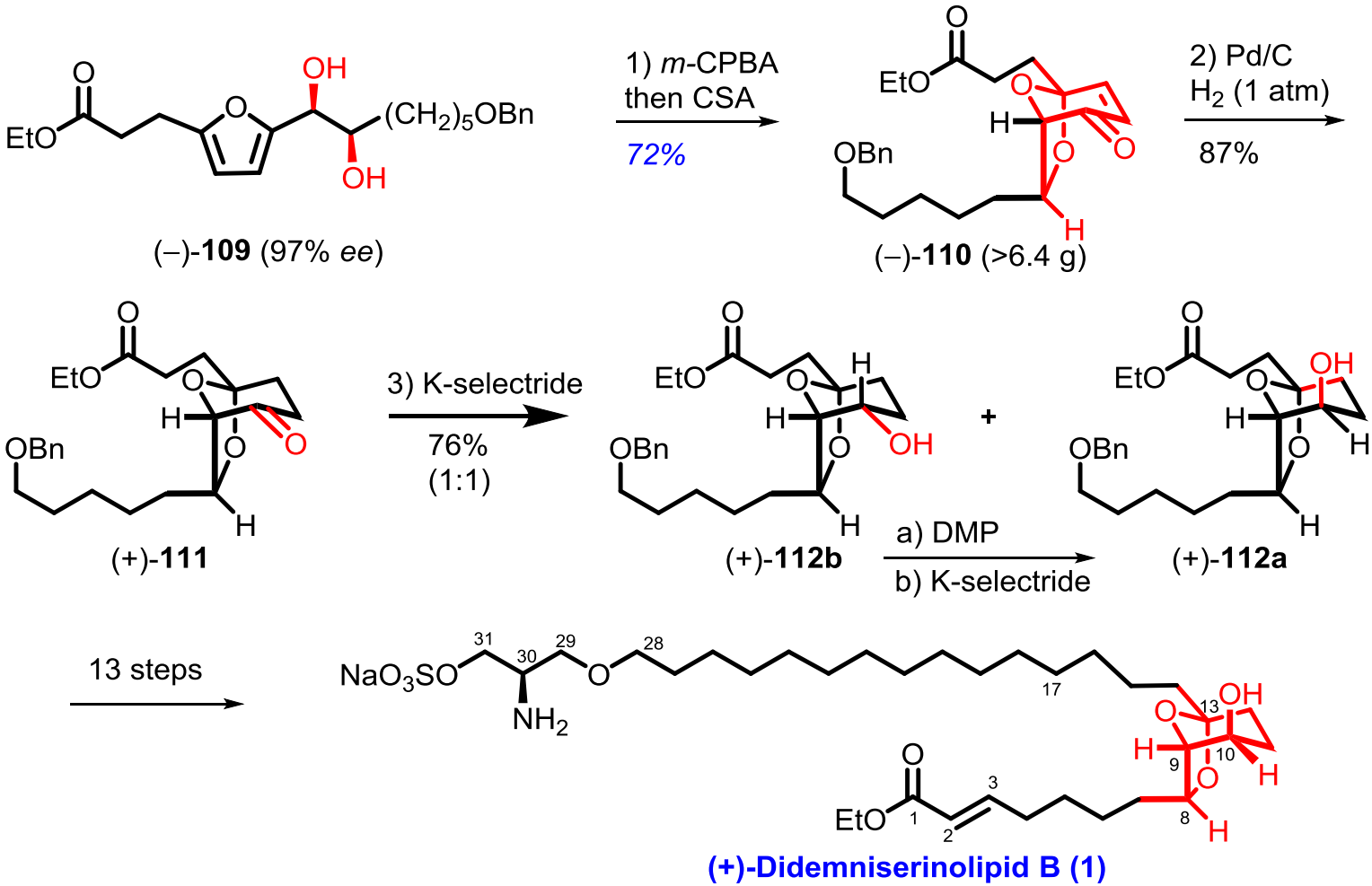
**2 Total Synthesis of Attenol A**

# Asymmetric Total Synthesis of Attenols A and B



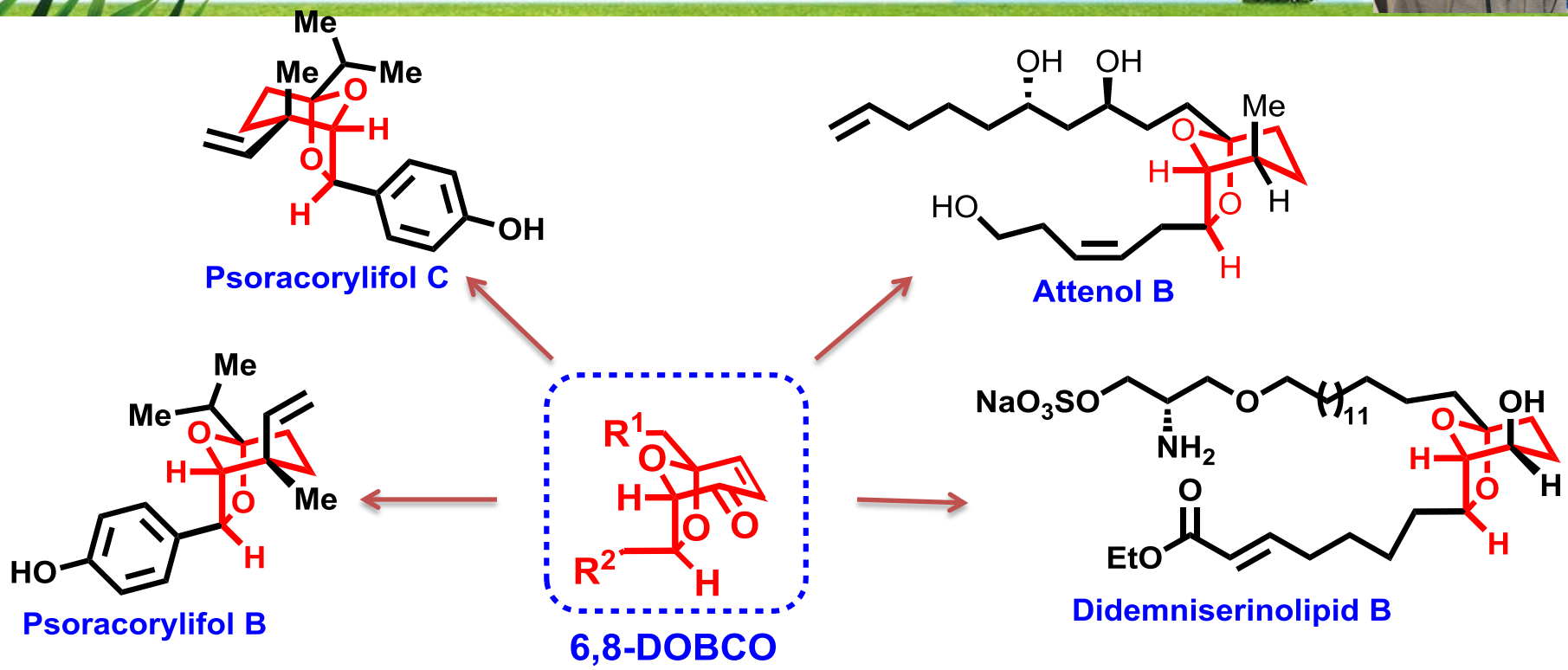

Ren, J.; Wang, J.; **Tong*, R.** Asymmetric Total Synthesis of (+)-Attenol B. *Org. Lett.* **2015**, *17*, 744-747.

# Asymmetric Total Synthesis of Didemniserinolipid B




Ren, J.; **Tong*, R.** Asymmetric Total Synthesis of (+)-Didemniserinolipid B via Achmatowicz Rearrangement/Bicycloketalization. *J. Org. Chem.* **2014**, *79*, 6987-6995. (Top 20 most downloaded JOC articles: July & August 2014). Highlighted in Organic Chemistry Portal on April 20, 2015.

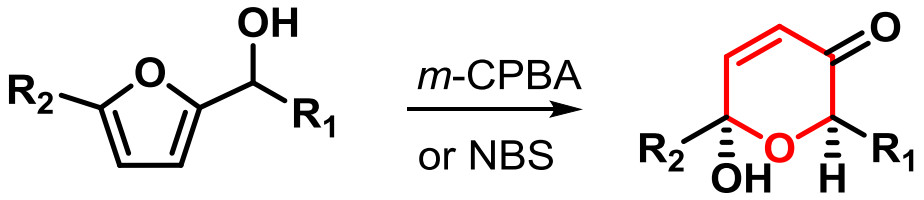
# Completed Natural Products by the Key Synthetic Strategy for 6,8-DOBCOs



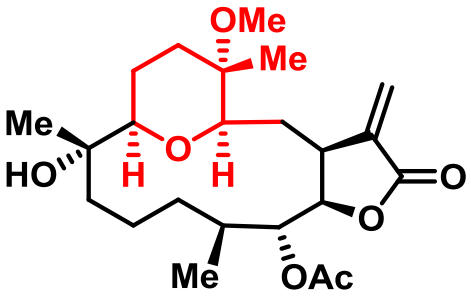

(a) Ren, J.; Wang, J.; **Tong*, R.** Asymmetric Total Synthesis of (+)-Attenol B. *Org. Lett.* **2015**, *17*, 744-747.
(b) Ren, J.; **Tong*, R.** Asymmetric Total Synthesis of (+)-Didemniserinolipid B via Achmatowicz Rearrangement/Bicycloketalization. *J. Org. Chem.* **2014**, *79*, 6987-6995. Highlighted in Organic Chemistry Portal on April 20, 2015.
(c) Ren, J.; Liu, Y.; Song, L.; **Tong*, R.** Scalable Asymmetric Total Syntheses of (+)-Psoracorylifol B and (+)-ent-Psoracorylifol C. *Org. Lett.* **2014**, *16*, 2986-2989. Highlighted in Synfacts: 2014, 10, 904. And Highlighted in Organic Chemistry Portal, 2014, November 10.

# FOD in Total Synthesis of Uprolides

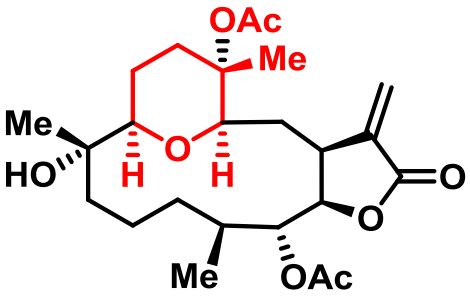
**FOD**




**Achmatowicz Rearrangement**

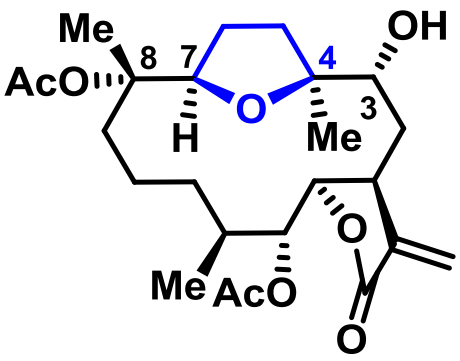



Uprolide G Acetate (B5)
(2014) by Zhu, L.

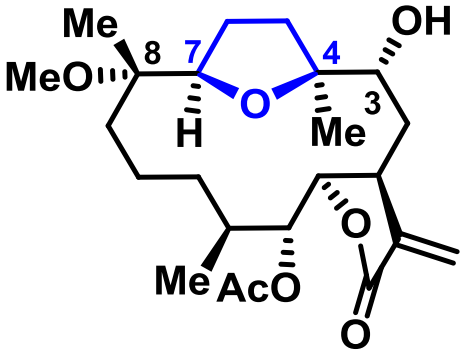



Uprolide F Diacetate (B7)
(2015) by Zhu, L.

# Isolation and Bioactivity




**Uprolide F Diacetate (UFD)**



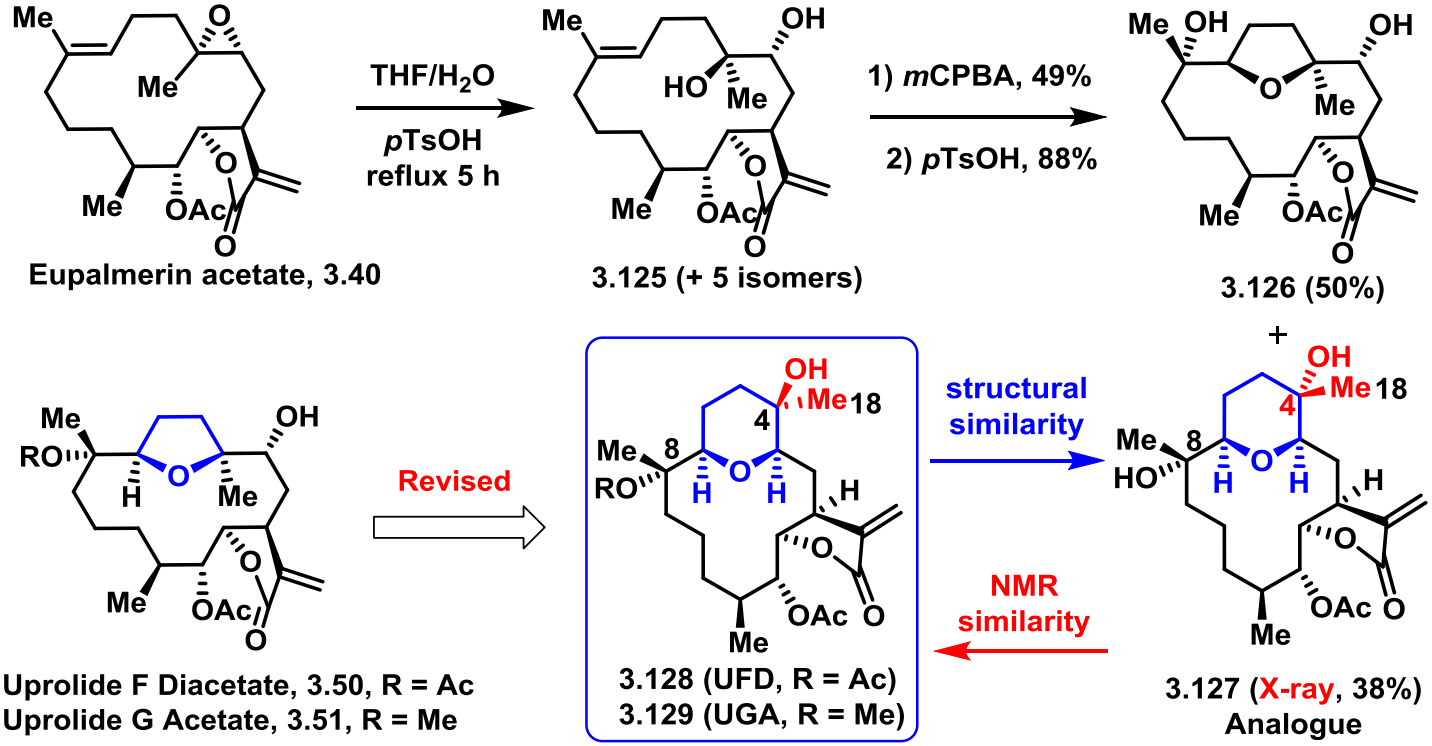

**Uprolide G Acetate (UGA)**

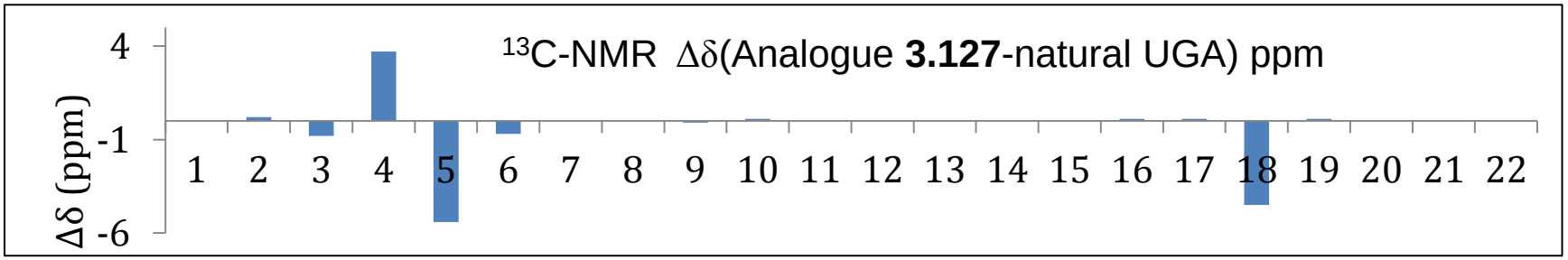
Isolated from **sea coral** *Euniceain mammosa* by **Rodríguez** and coworkers in **1995**.

They were **cytotoxic** and showed some anti-cancer properties.

Rodríguez, A. D.; Soto, J. J.; Piña, I. C. *J. Nat. Prod.* **1995**, *58*, 1209.
Rodríguez, A. D.; Piña, I. C.; Barnes, C. L. *J. Org. Chem.* **1995**, *60*, 8096.

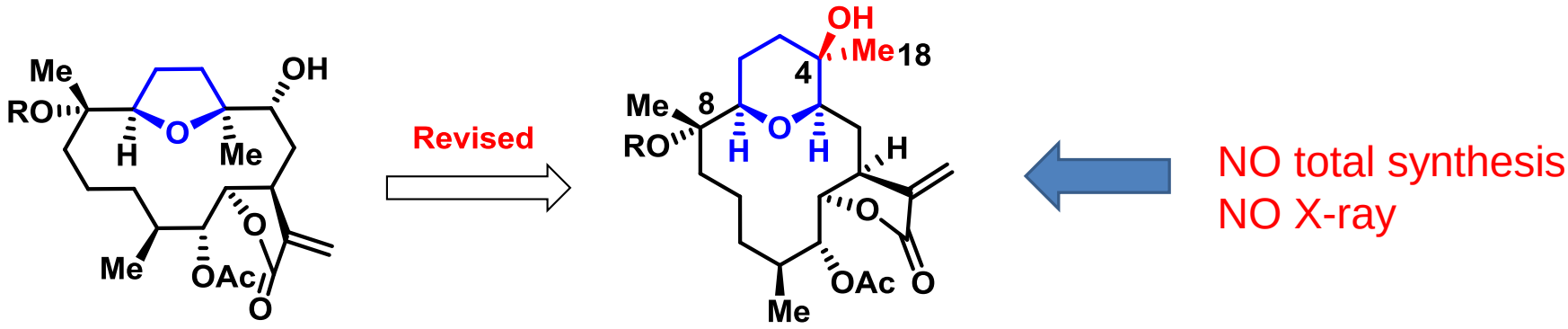
# Structural Revision by Rodríguez




Rodríguez, A. D.; Soto, J. J.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 7700.

# Structural Revision by Rodríguez



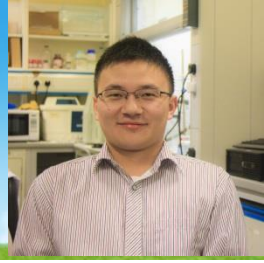

**Uprolide F Diacetate, 3.50, R = Ac**
**Uprolide G Acetate, 3.51, R = Me**

**Goals:**

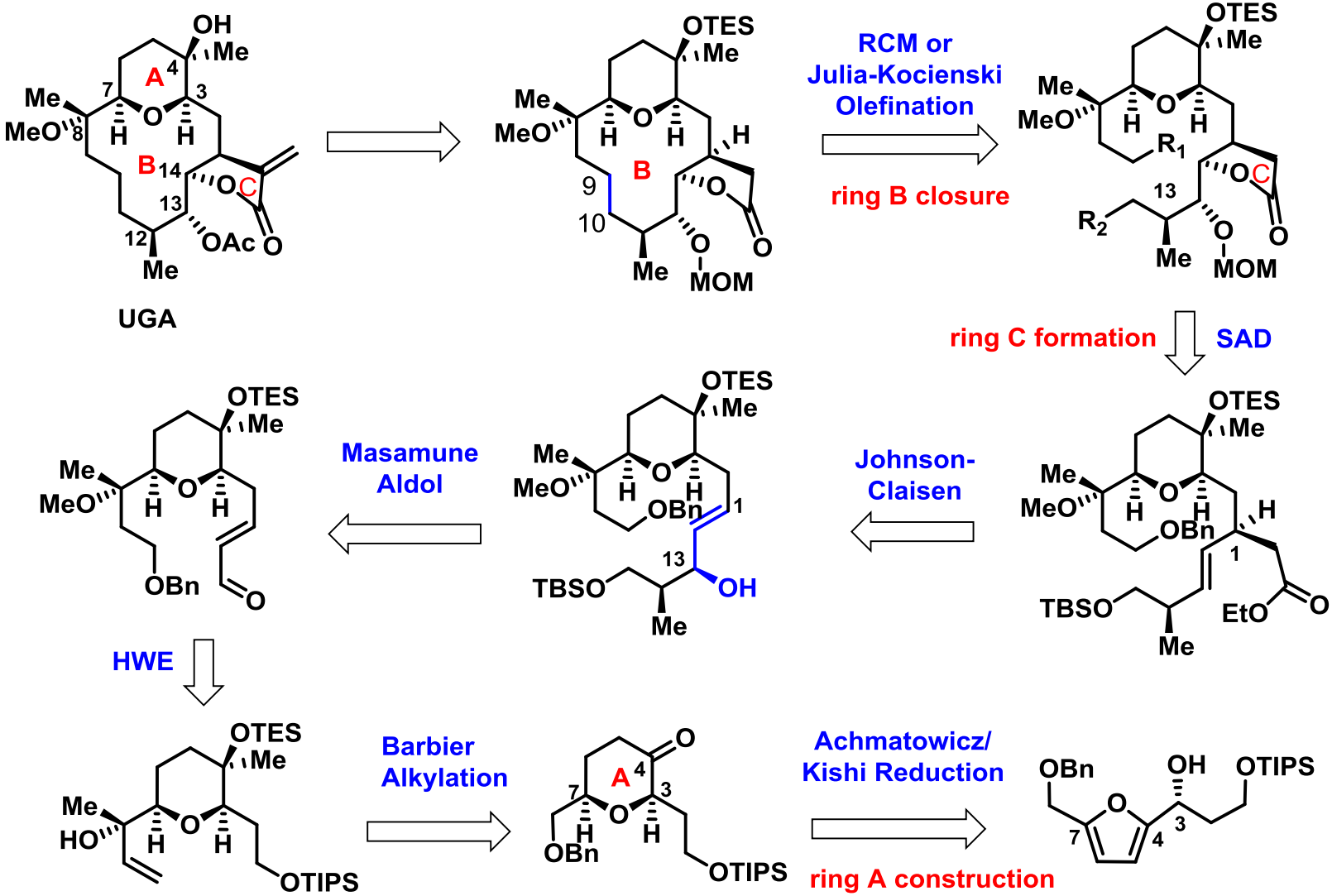
To confirm the structural revision by Rodriguez
To provide a fexible and robust synthetic strategy

Rodríguez, A. D.; Soto, J. J.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 7700.

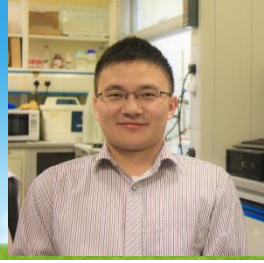
# Retrosynthetic Analysis for UGA

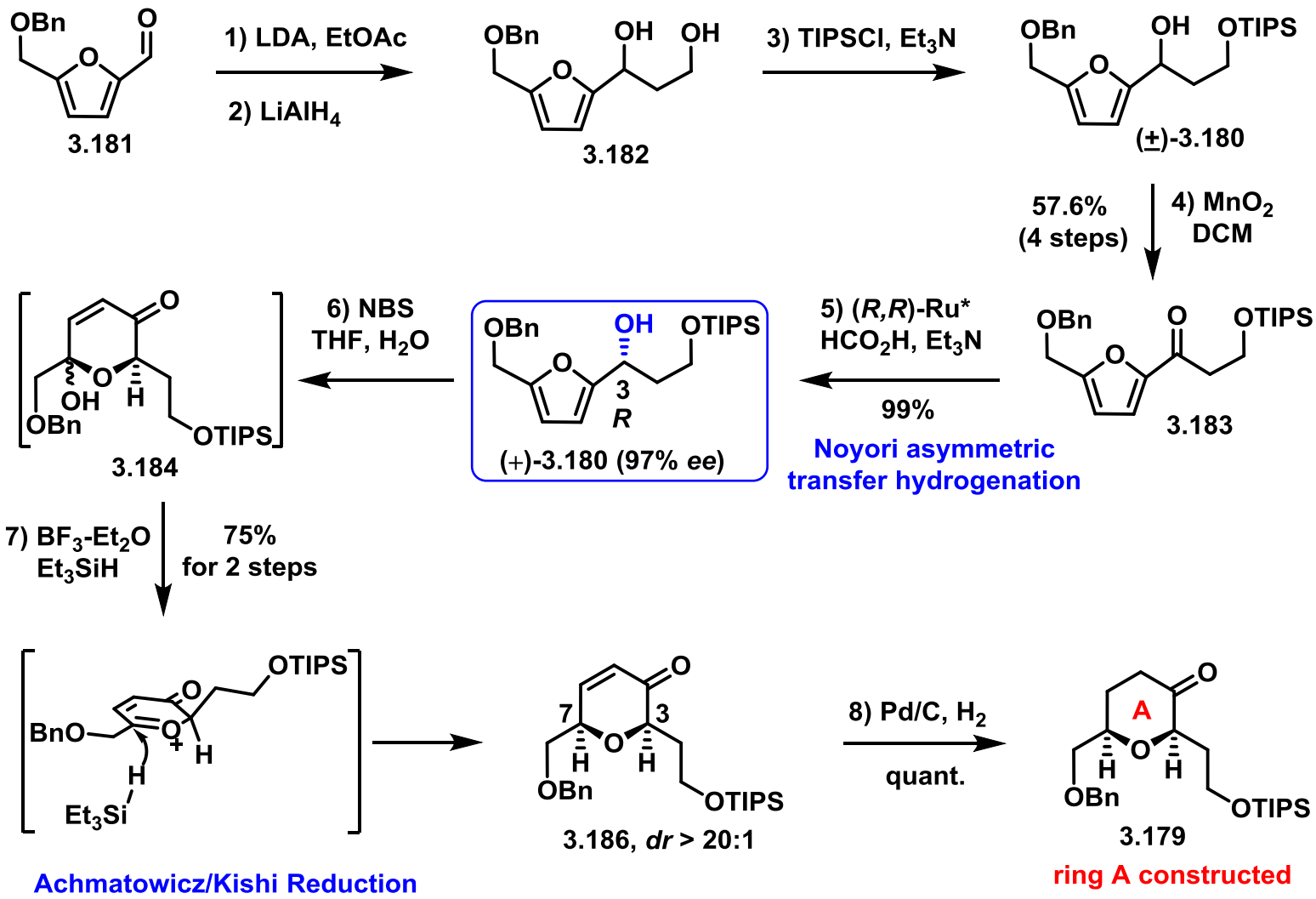


**Strategic ring construction: A → C → B**

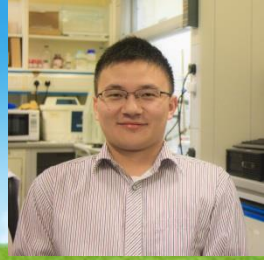


# Ring A Construction

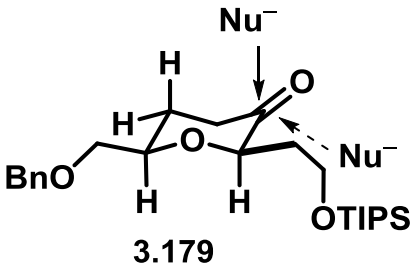





Achmatowicz Rearrangement: O. Achmatowicz, Jr., *et al*., *Tetrahedron* **1971**, *27*, 1973.
Kishi Reduction: Phillips, A. J., *et al*., *Org. Lett.* **2008**, *10*, 3769.

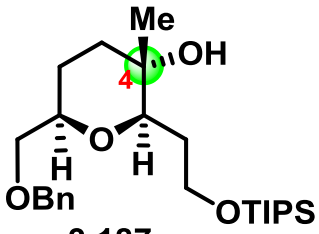


# Installation of 1st Tertiary Alcohol

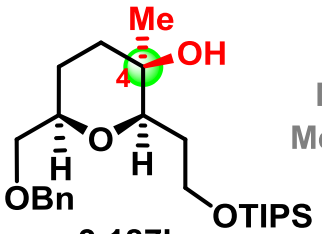



3.179

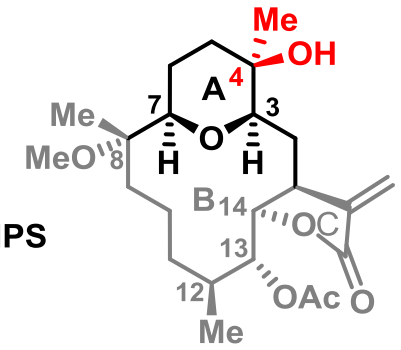
$Me^-$ reagents




3.187a

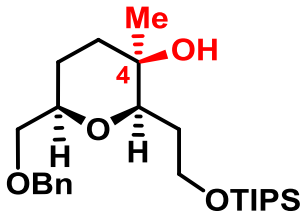



3.187b
minor isomer




UGA, 3.129

| Entry | $Me^-$ reagent | Yield (%) | 3.187a : 3.187b |
|---|---|---|---|
| 1 | $Me_2CuILi_2$ | 86 | 15 : 1 |
| 2 | MeLi | 80 | 3 : 1 |
| 3 | MeLi + $CeCl_3$ | 95 | 1.1 : 1 |

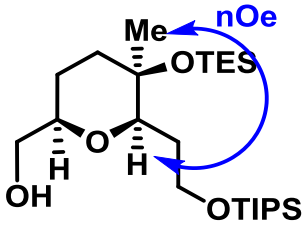



3.187b
minor isomer

1) TESOTf

2) Pd/C, $H_2$

95%
(2 steps)

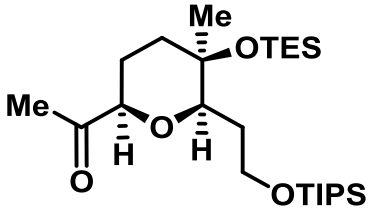



3.188

3) DMP, $NaHCO_3$
4) MeMgCl, THF

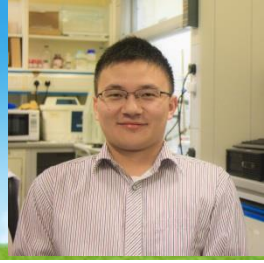
5) DMP, $NaHCO_3$

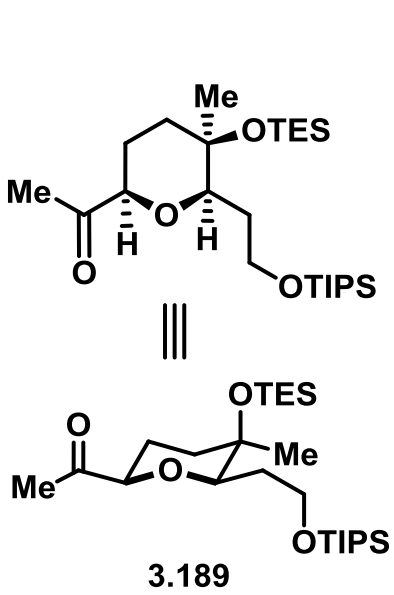
80%
(3 steps)



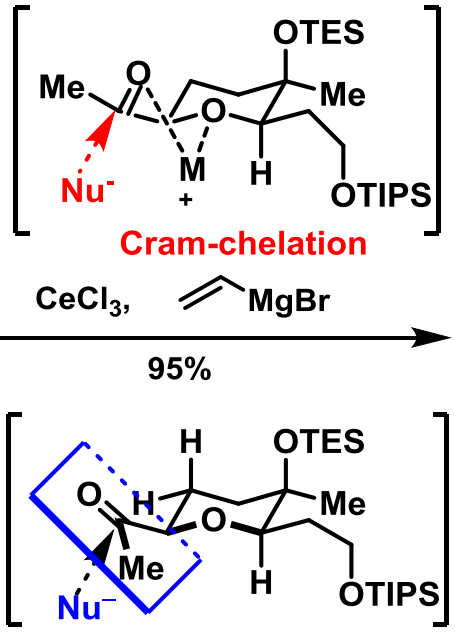

3.189

# Installation of 2nd Tertiary Alcohol






3.189



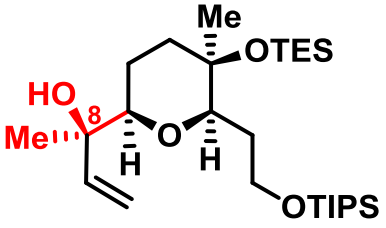

Cram-chelation

polar Felkin-Anh model

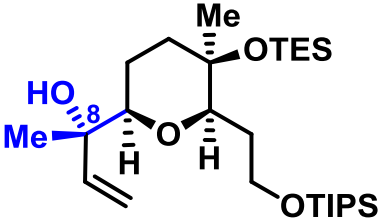
$CeCl_3$, MgBr

95%

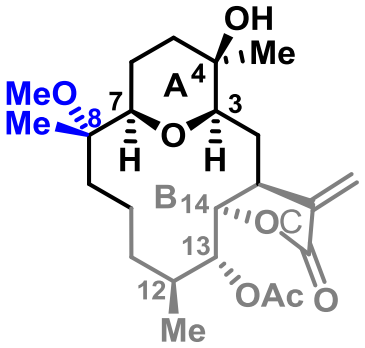
7 : 1 mixture




3.178' Undesired



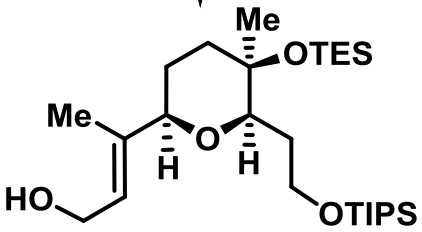

3.178 Desired




UGA, 3.129

90% over 2 steps

1) HWE
2) DIBAL-H




3.191 (*E*/*Z* >10:1)

***Diastereospecific Chemical Approach***

3) $Ti(OiPr)_4$, D-Tartrate

TBHP, DCM

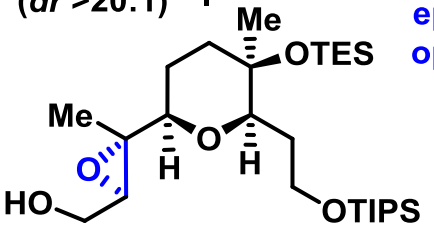
80%

Sharpless Asymmetric Epoxidation

72% over 2 steps (*dr* >20:1)

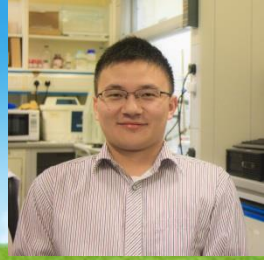
4) $PPh_3$, $CBr_4$
5) $SmI_2$

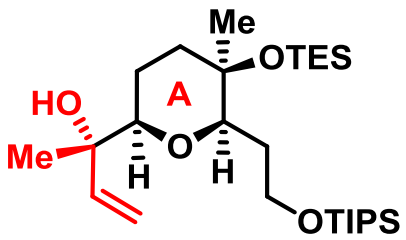
reductive epoxide opening




3.192 (*dr* >20:1)

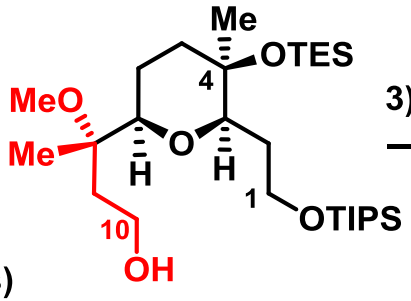
# Extension of Right Side Chain





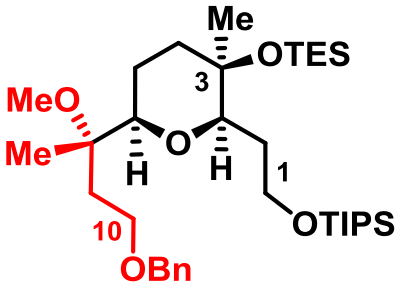

3.178
(> 5 g prepared)

1) NaH, MeI
2) 9-BBN; NaOH, $H_2O_2$
90% (2 steps)




3.193

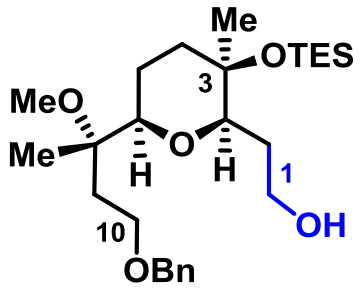
3) BnBr, NaH




3.194

80%
(4 steps)

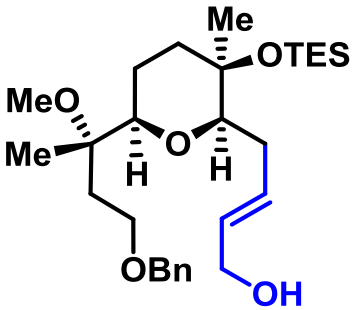
4) TBAF
5) TESOTf
6) A-21, MeOH




3.196

7) DMP
8) HWE

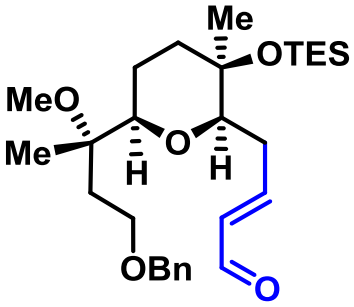
9) DIBAL




3.197

10) DMP

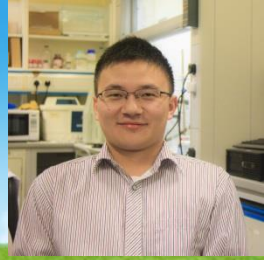
81% (4 steps)

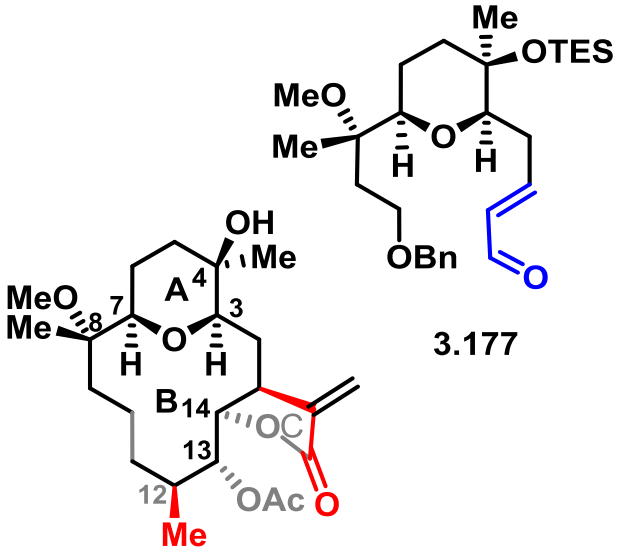



3.177
(> 2 g prepared)

2 carbon extended
10 steps, 58%

# Installation of 2 Chiral Centers

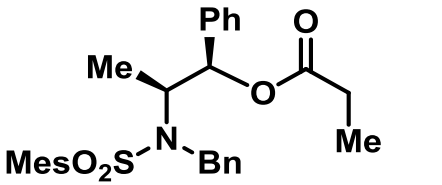





3.177

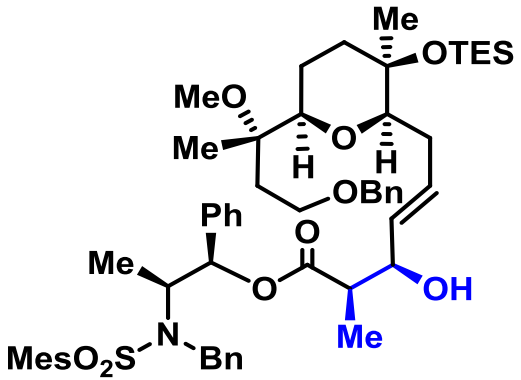
UGA, 3.129

2 chiral centers installed




1) $Cy_2BOTf$, $Et_3N$
DCM, -78°C
70%

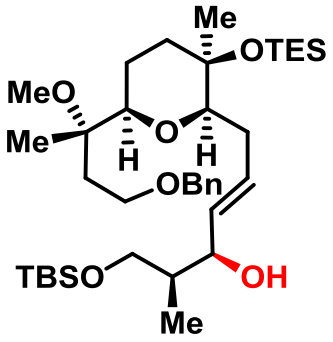
Abiko-Masamune Aldol




3.198 (*dr* >20:1)

80%
(2 steps)

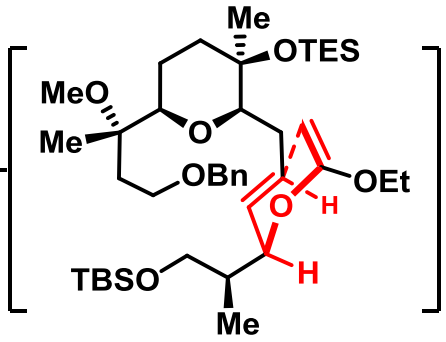
2) LAH
3) TBSCl




3.176

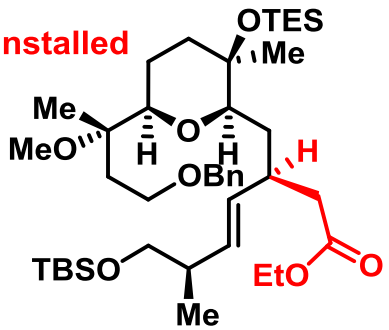
4) $MeC(OEt)_3$
$EtCO_2H$

90%




3.200

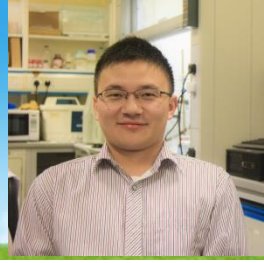
Johnson-Claisen Rearr.

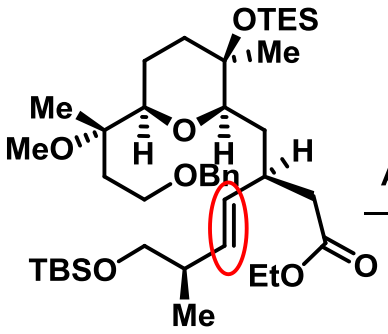



3.175

Abiko, A. *Org. Synth.* **2002**, *79*, 109 and 116.

# Installation of 2 Chiral Centers & Ring C Formation





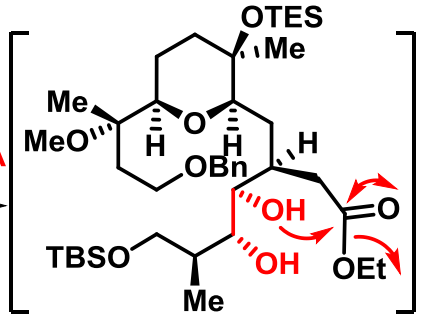

3.175

internal alkene

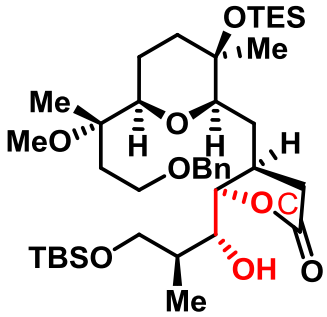
AD-mix-β

SAD

pathway A




Lactonization



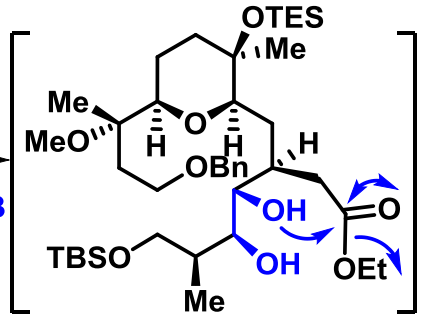

3.202a, 60%

major isomer

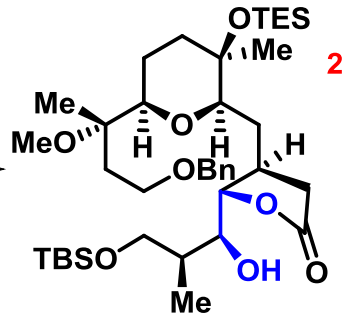
from SAD

poor selectivity, 2 : 1

pathway B



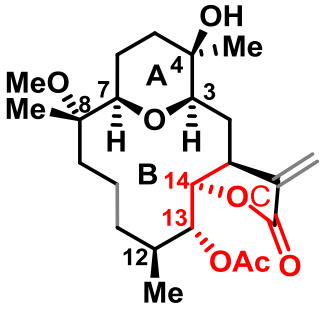

Lactonization




3.202b, 30%

minor isomer

from SAD

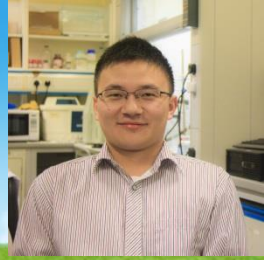


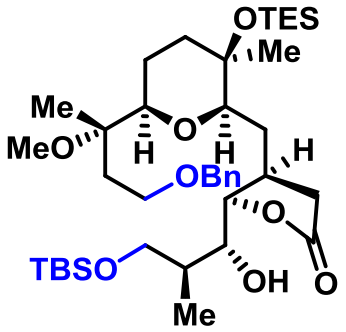

UGA, 3.129

ring C formed

2 oxy-chiral centers installed

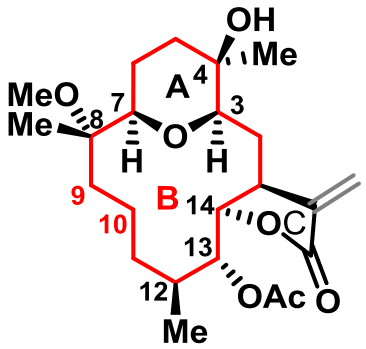
# Ring B Closure



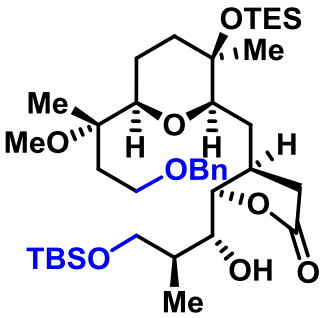



3.202a

Julia-Kocienski Olefination




UGA, 3.129

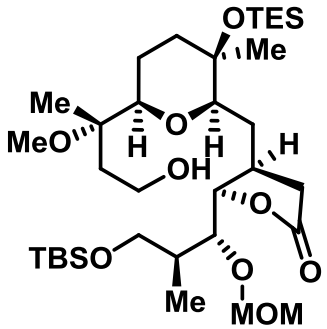



3.202a
major isomer
from SAD

1) MOMCl

2) $Pd(OH)_2/H_2$

95% (2 steps)

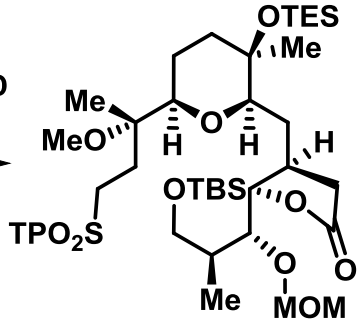



3.203a

3) PTSH, $PPh_3$, DIAD

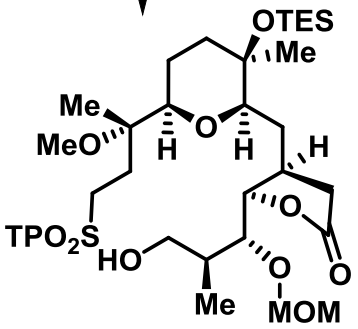
4) *m*CPBA, $NaHCO_3$

80% over 2 steps




3.204

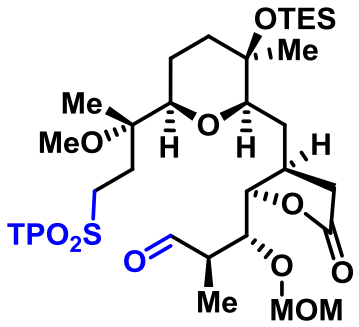
5) AcOH/THF /$H_2O$




3.205

6) DMP

80%
over 2 steps



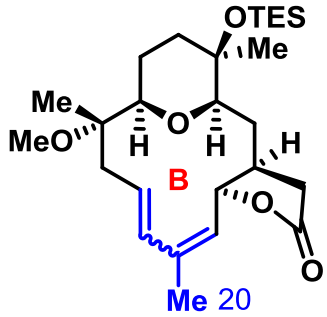

3.206

7) KHMDS, THF

(C<0.002M)

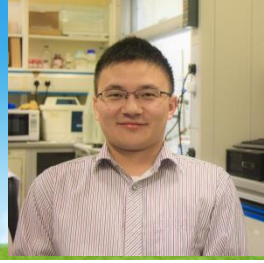
~30% yield

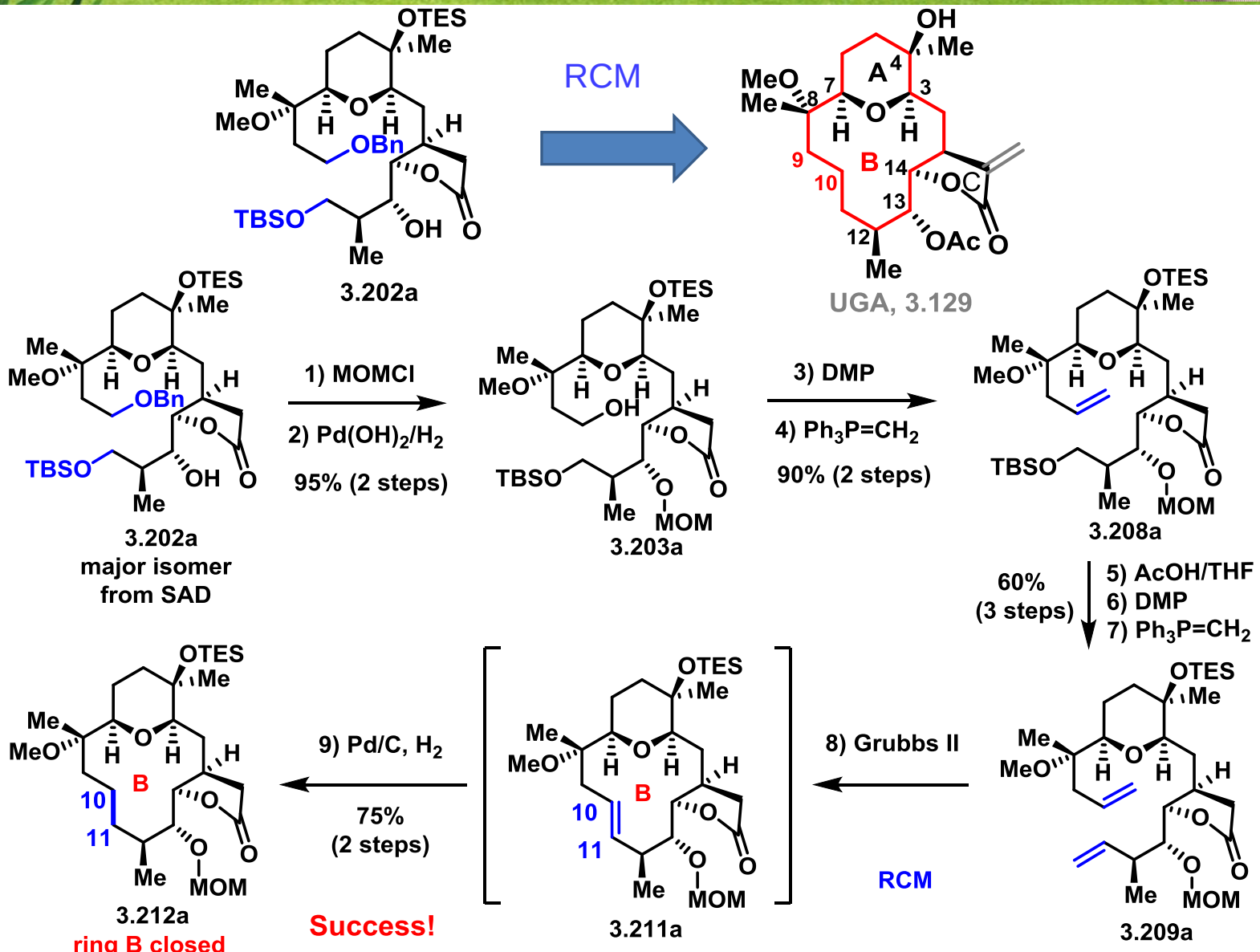
Failure!



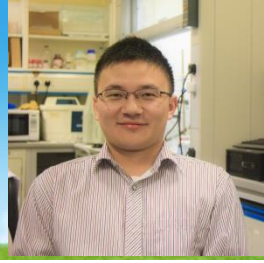

3.207, side product

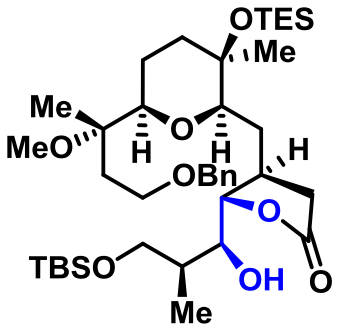
# Ring B Closure





# Study on SAD





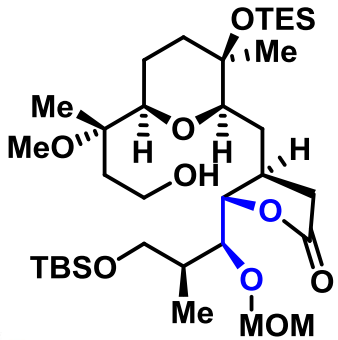

3.202b
minor isomer
from SAD

*via* pathway B

1) MOMCl

2) $Pd(OH)_2/H_2$

95% (2 steps)

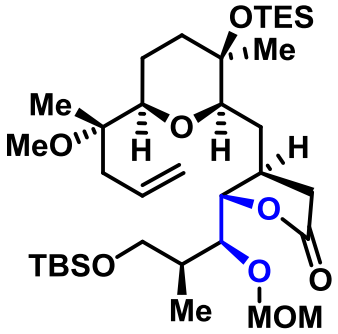



3.203b

3) DMP

4) $Ph_3P{=}CH_2$

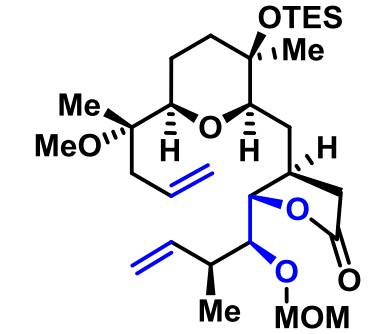
90% (2 steps)




3.208b

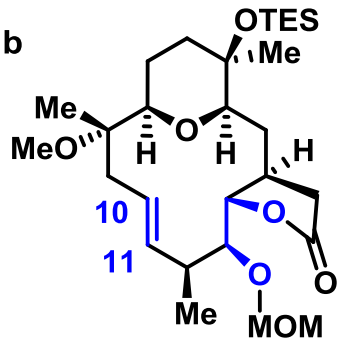
60%
(3 steps)

5) AcOH/THF
6) DMP
7) $Ph_3P{=}CH_2$




3.209b

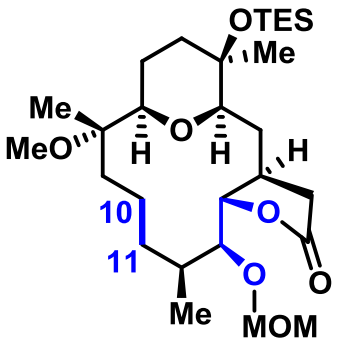
8) Grubbs II



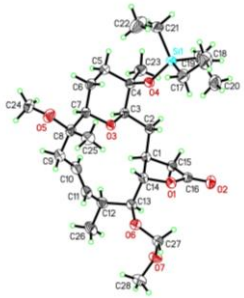

3.211b

9) Pd/C, $H_2$

75%
(2 steps)

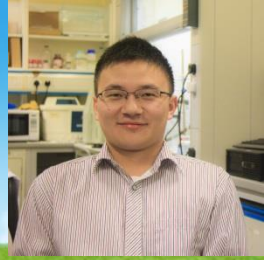


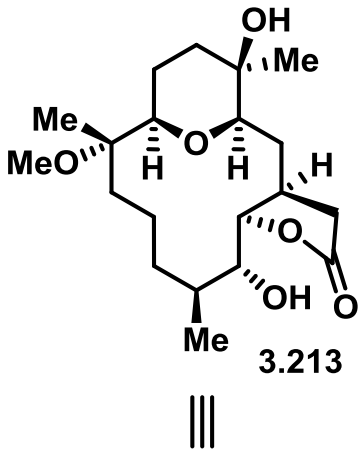

3.212b



X-ray of 3.211b

# Completion of Proposed UGA

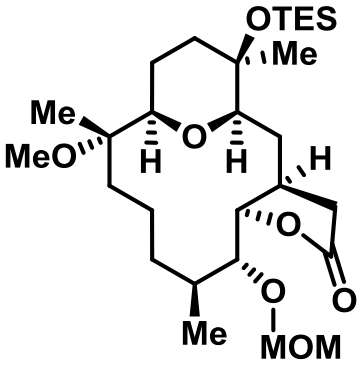





3.213

TFA

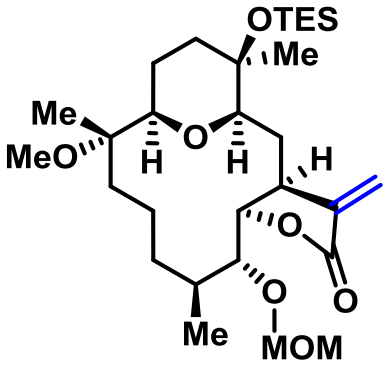
90%




3.212a

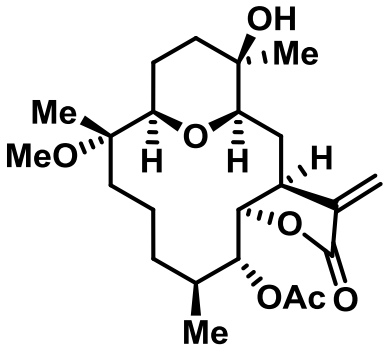
1) LDA, $CH_2O$ (g)
then, MsCl; DBU

50%



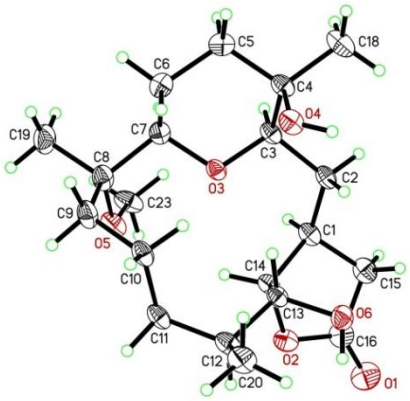

2) TFA
3) $Ac_2O$

60% (2 steps)



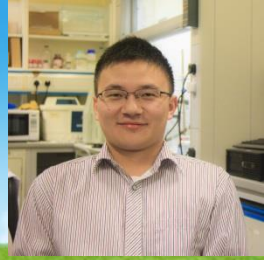

3.129
Proposed UGA

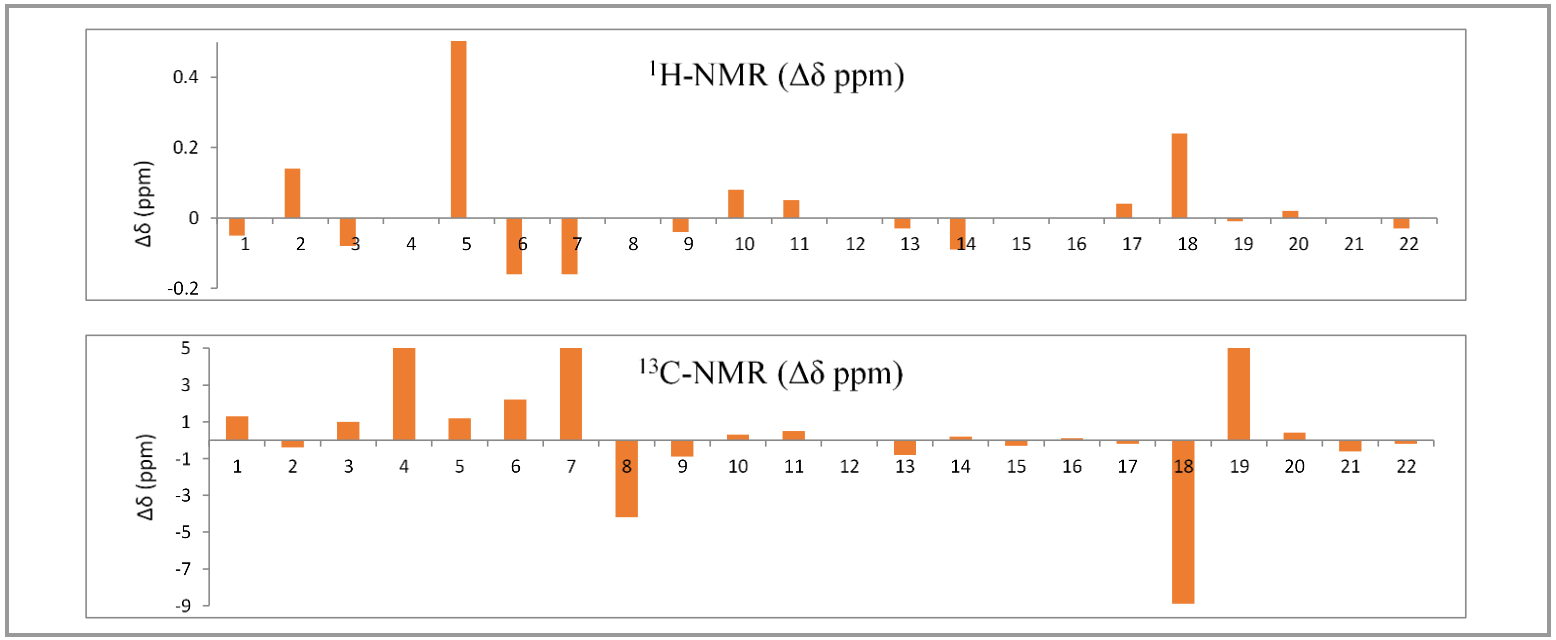
stereochemistry confirmation

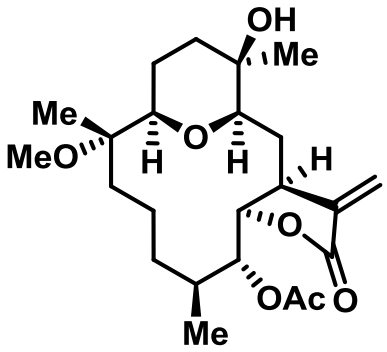



X-ray of 3.213

# Data Comparison (Proposed UGA and natural UGA)





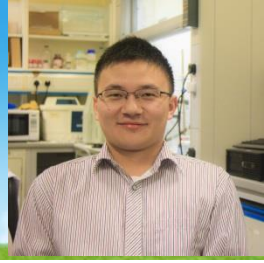



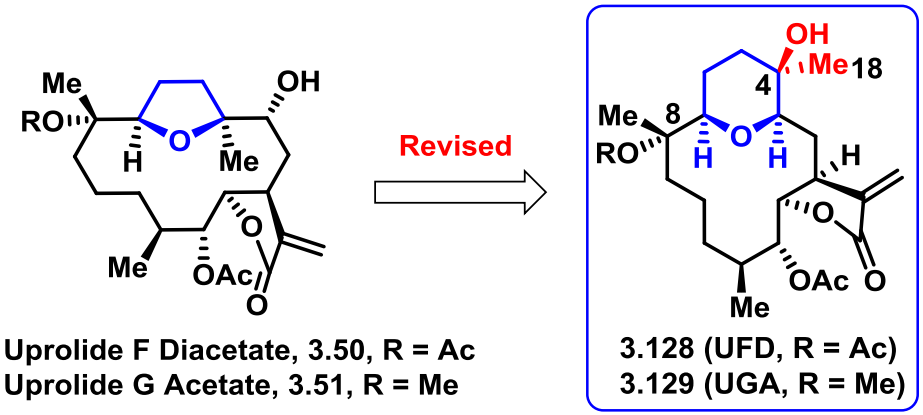

**3.129**

**Proposed UGA**

not correct for natural UGA

# Structural Revision by Rodríguez






Uprolide F Diacetate, 3.50, R = Ac
Uprolide G Acetate, 3.51, R = Me

3.128 (UFD, R = Ac)
3.129 (UGA, R = Me)

Total synthesis of Proposed UGA

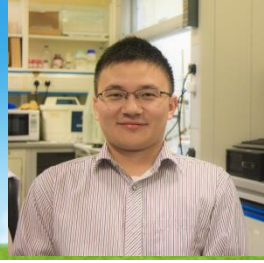
Goals: To confirm the structural revision by Rodriguez
To provide a fexible and robust synthetic strategy

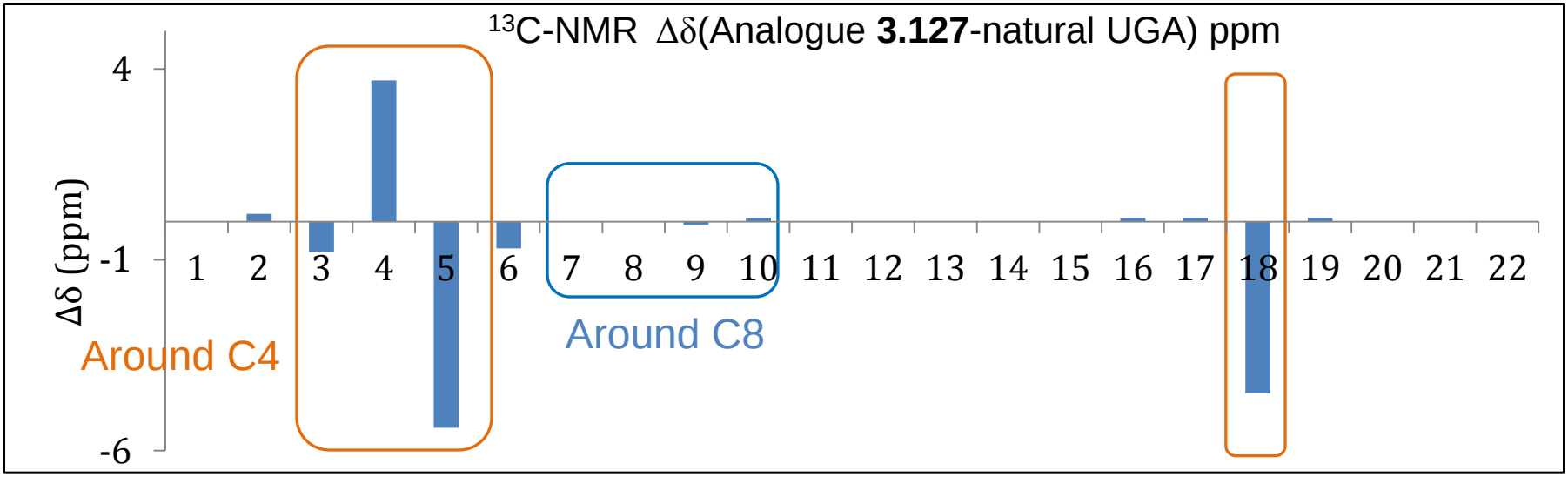
Achieved: Disproved the structural revision of UGA by Rodriguez
Developed a robust synthetic strategy

What is the true structure for natural UGA?

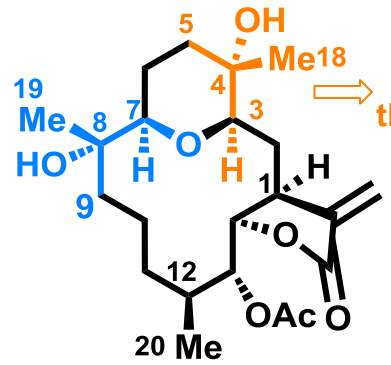
Rodríguez, A. D.; Soto, J. J.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 7700.

# Structural Revision by us





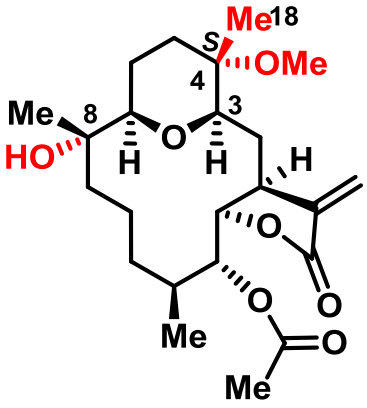

free alcohol at C8 in UGA




**3.127 (X-Ray)**

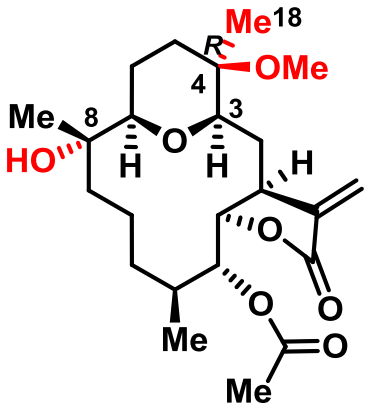
Analogue derived from natural Eupalmerin Acetate Rodriguez, 2000

methyl ether with the same or inverted stereochemistry at C4 in UGA



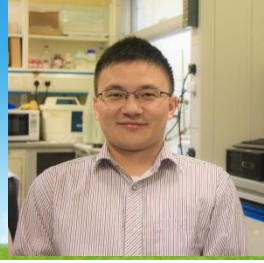

**3.215a**

or

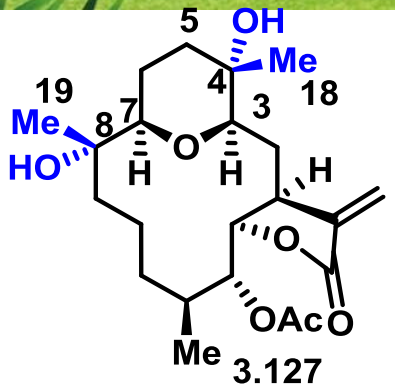



**3.215b**

revised UGA by us



# a or b: which is more likely?

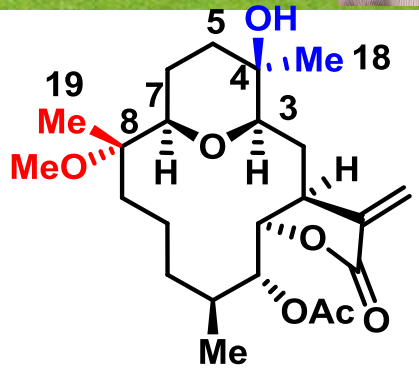



3.127

Analogue derived from natural Eupalmerin Acetate

**S effect (3.129-3.127)**
**β (8): +4.2**
**γ (7, 19): -5.1, -6.1**

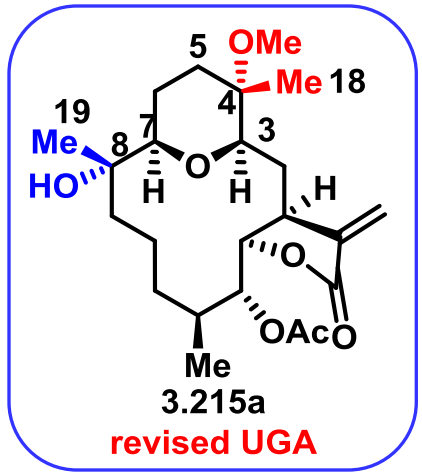
Rule: β effect: positive +
γ effect: negative -




**3.129**
**proposed UGA**

Substituent Effect of O-Me on $^{13}C$ NMR

***If UGA = 3.215a***
***S effect (UGA-3.127)***
**β (4): +3.7**
**γ (3, 5, 18): -0.8, -5.4, -4.5**

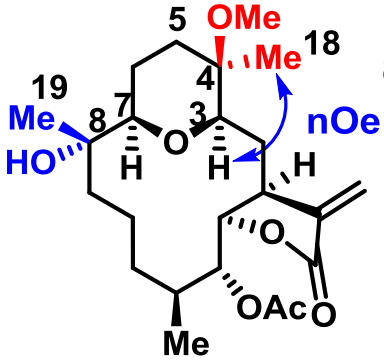



**3.215a**
**revised UGA**

normal

preferred!

***If UGA = 3.215b***
***S effect (UGA-3.129)***
***β (4): +5.5; β (8): +4.2***
***γ (3, 5, 18): +1.0, +1.2, -8.9***
***γ (7, 9): -5.1, -6.2***

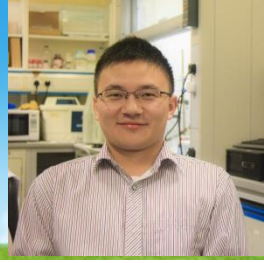


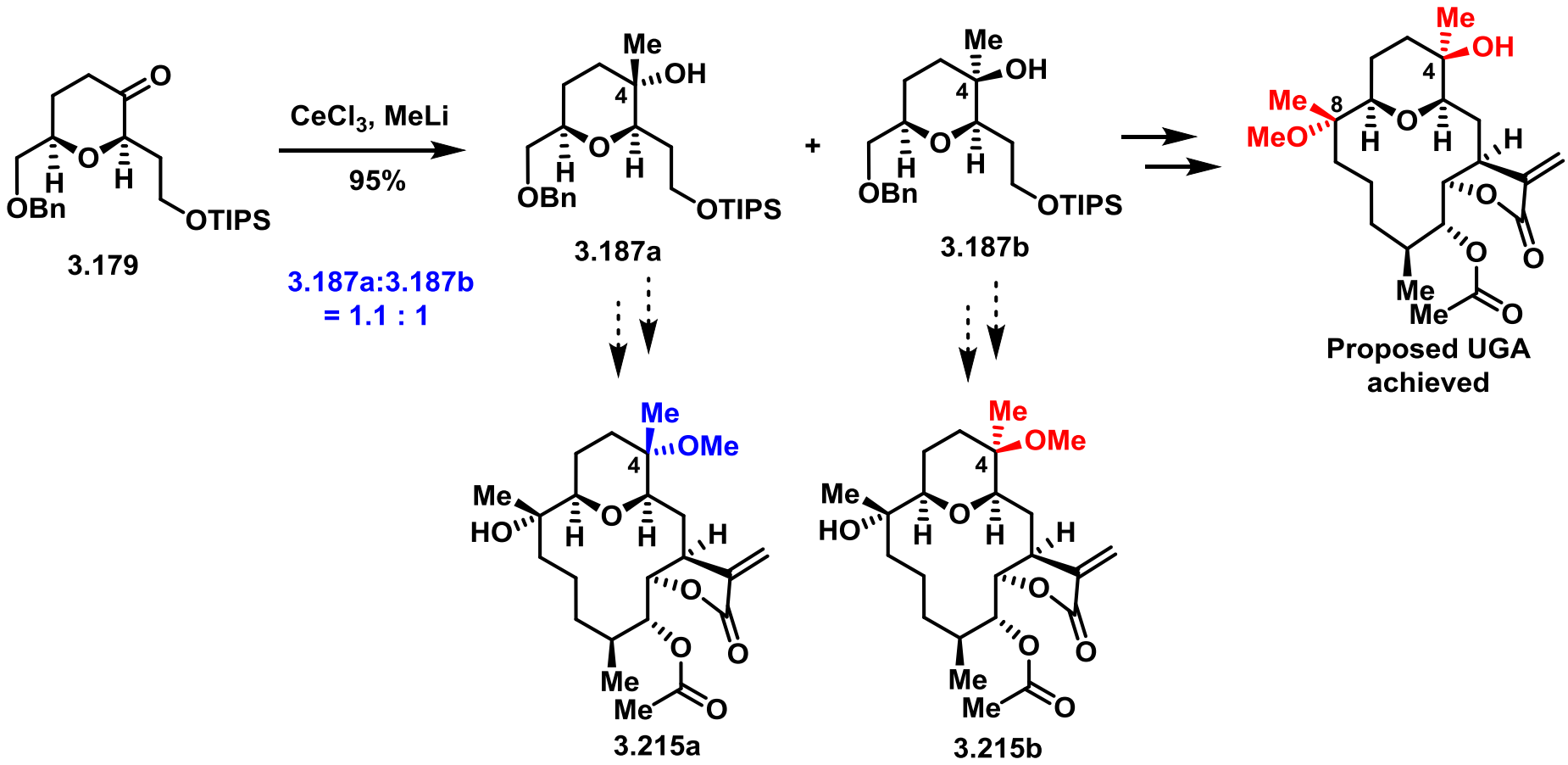

**3.215b**
**revised UGA**

abnormal

not excluded!

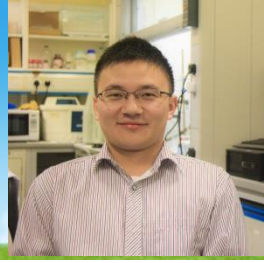
# Total Syntheses of 3.215a and 3.215b

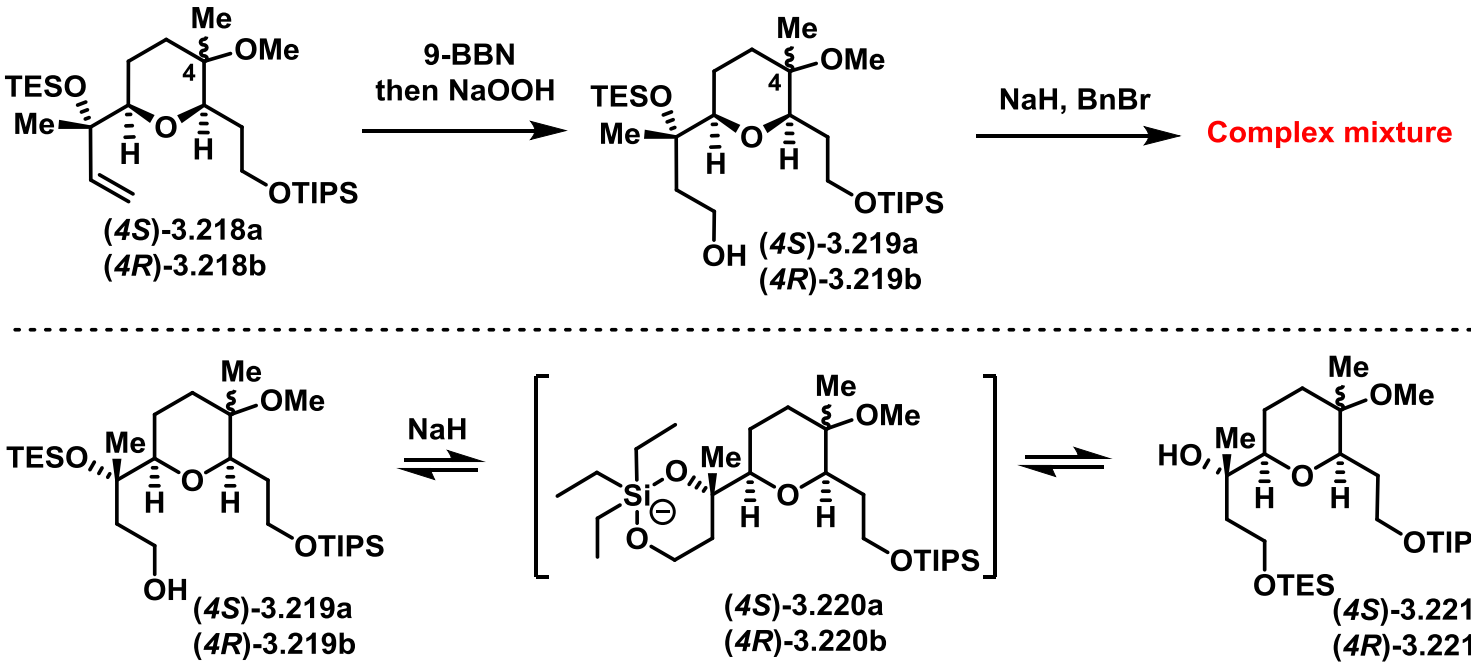




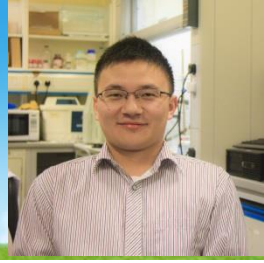

Straightforward Synthesis!

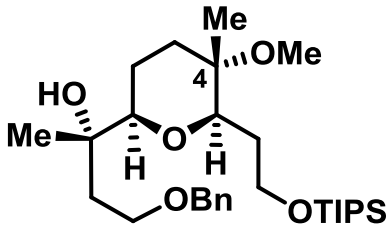
# Unexpected 1,5-Silyl Migration





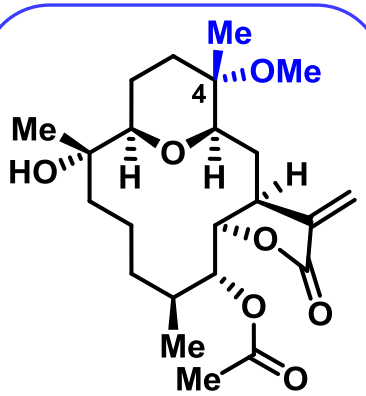
# Completion of Revised UGA






(*4S*)-3.223a

23 steps




3.215a

Correct UGA

**NMR**

$^{1}H$, $\Delta\delta$ ≤0.02 ppm

$^{13}C$, $\Delta\delta$ ≤0.1 ppm

$[\alpha]_D$

| | | |
|---|---|---|
| UGA | +125.0 | C=0.66 |
| 3.215a | +110.0 | C=0.10 |

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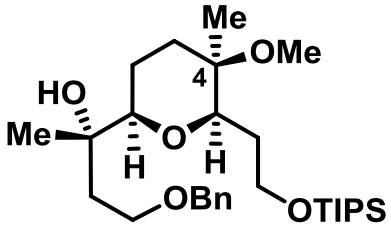
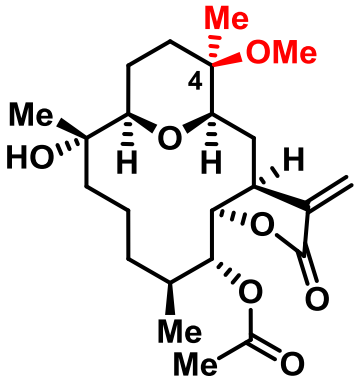


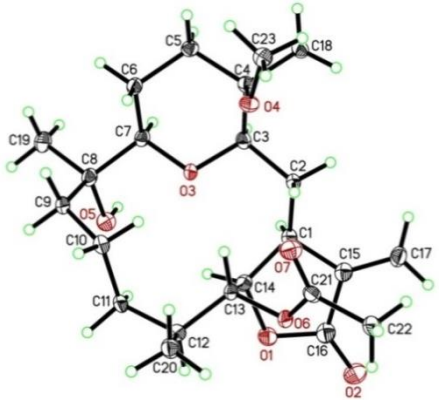

3.223b

23 steps




3.215b

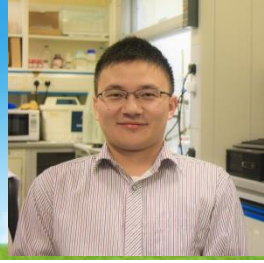
≡

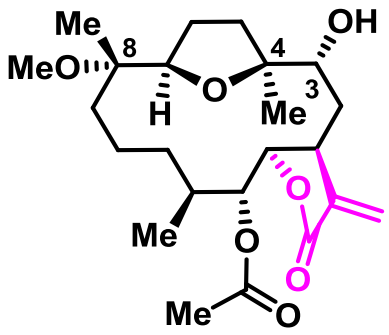



X-Ray

3.215b

# Structural Revision for Uprolide G Acetate

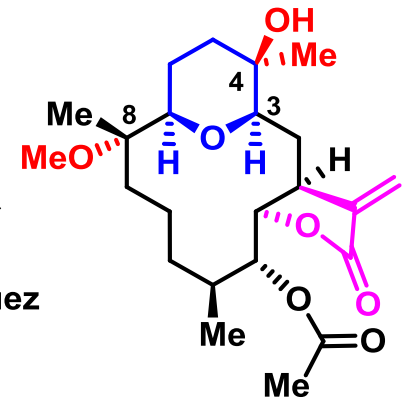





Uprolide G Acetate, 3.51
(UGA, 1995)

2000

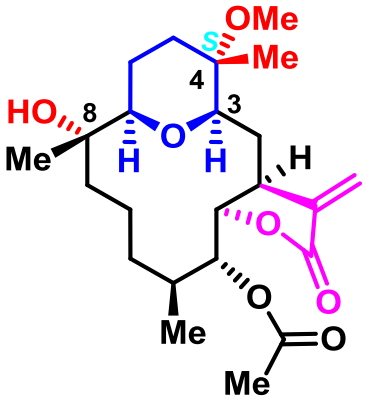
revised
by Rodriguez




Proposed Structure, 3.129
(UGA, 2000 )

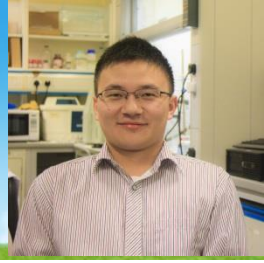
2014

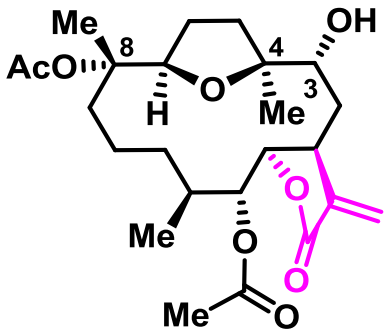
revised
by us




Correct Structure, 3.215a
(UGA, 2014)

# Structural Revision for Uprolide F Diacetate

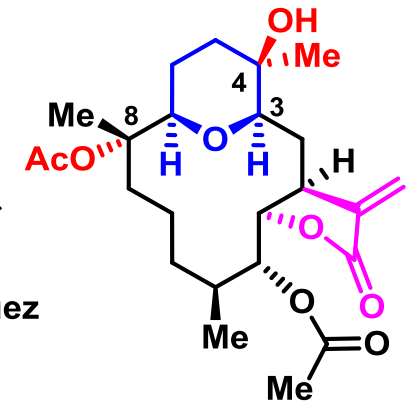





Uprolide F Diacetate, 3.50
(UFD, 1995)

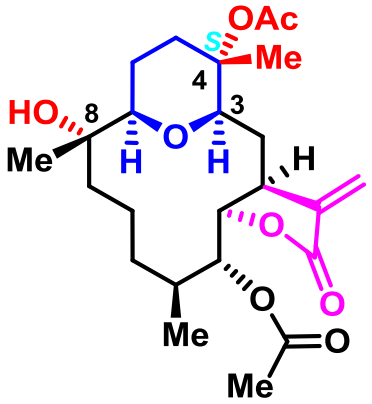
2000

revised
by Rodriguez



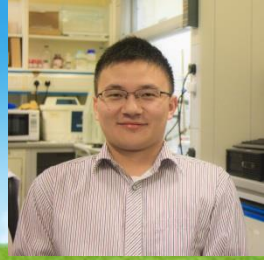

Proposed Structure, 3.128
(UFD, 2000 )

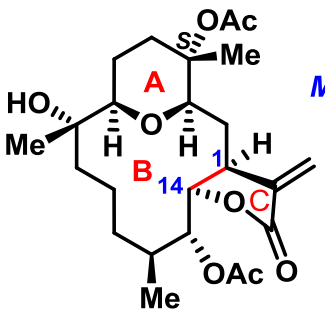
revised??
by us




Correct Structure??
(UFD, 3.233)

# Retrosynthetic Analysis

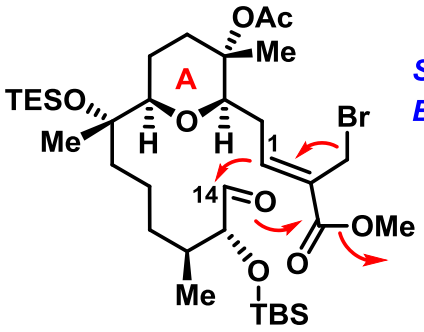





UFD, 3.233

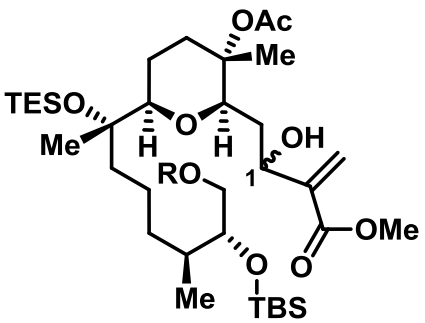
*NHK Macrocyclization/ Lactonization*

ring B+C




3.234

*$S_N2'$ Appel Bromination*

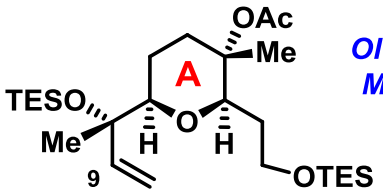



3.235

**Strategical ring construction: A → (B+C)**

*Morita-Baylis-Hillman*

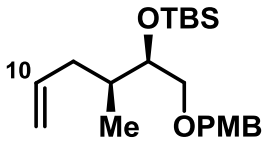
right side chain extension




ring A 3.237

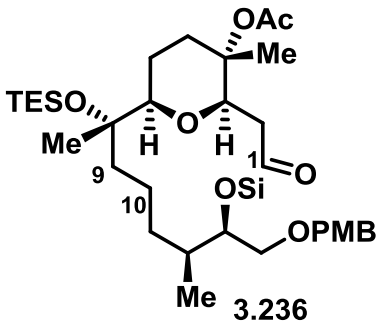
*Olefin Cross Metathesis*

+

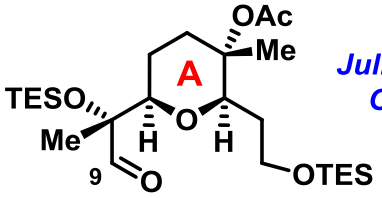



side chain 3.239

left side chain extension



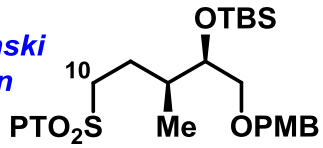

3.236




ring A 3.238

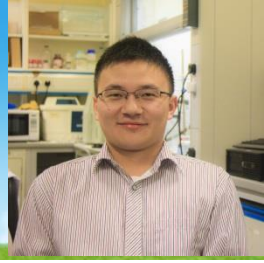
*Julia-Kocienski Olefination*

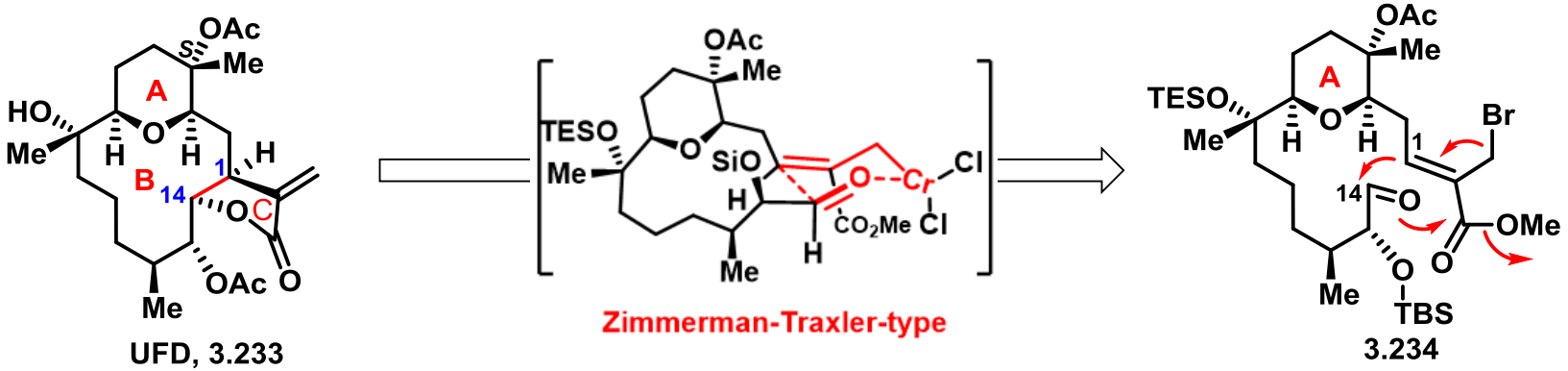
+

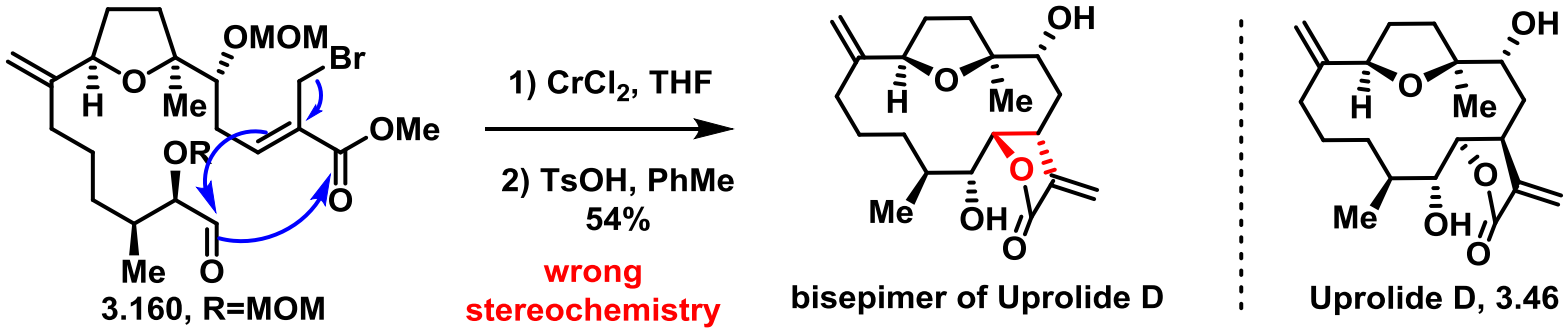



side chain 3.240

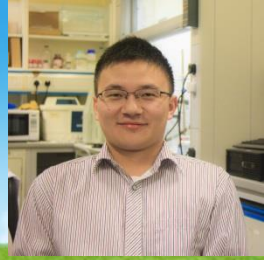
# Retrosynthetic Analysis



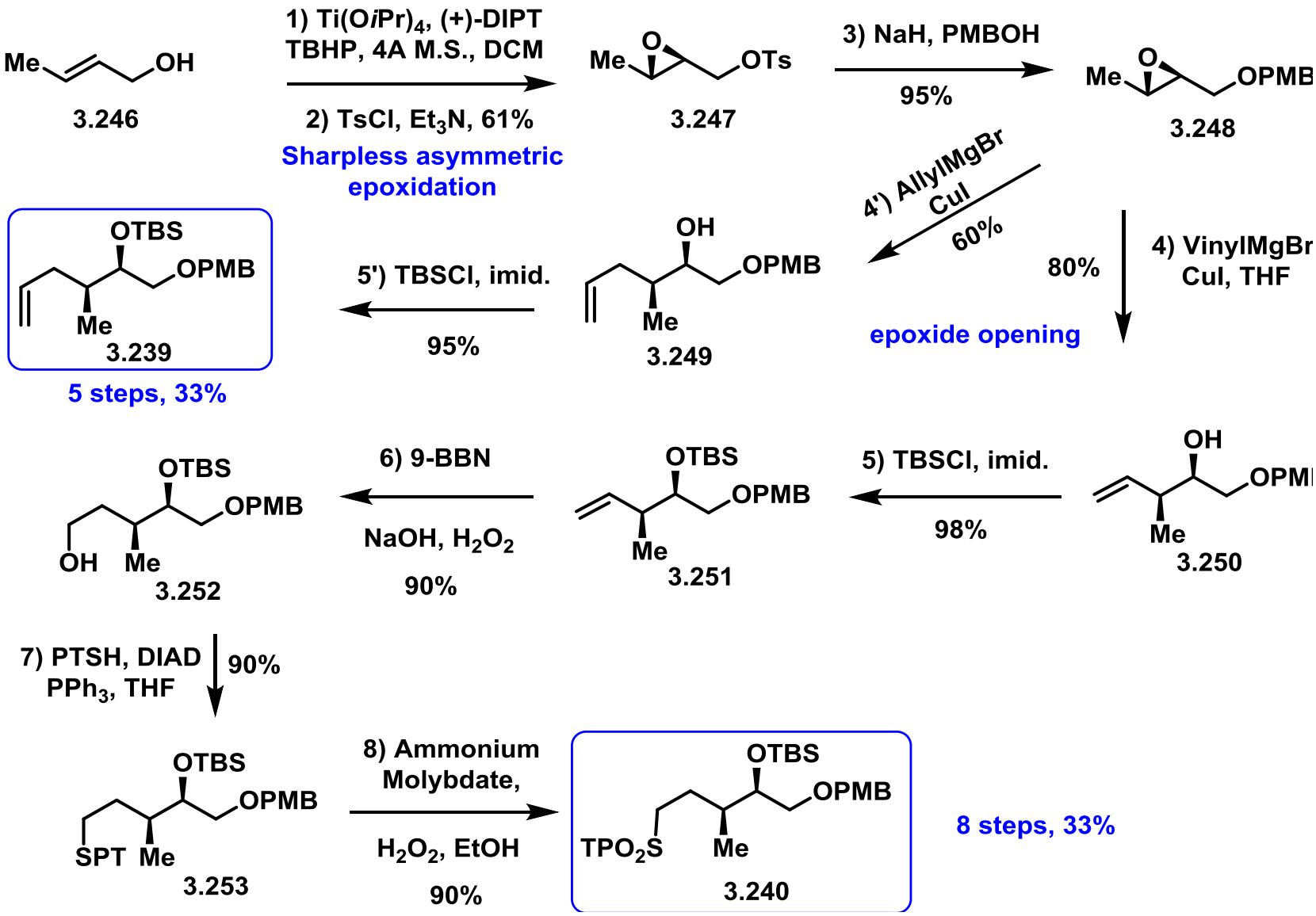


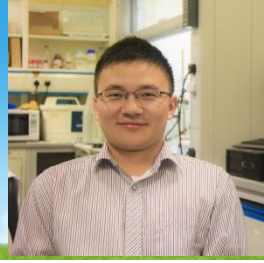




Marshall, J. A. et al. *Org. Lett.* **2010**, *12*, 4328.

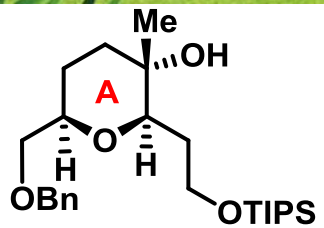


# Synthesis of Side Chains





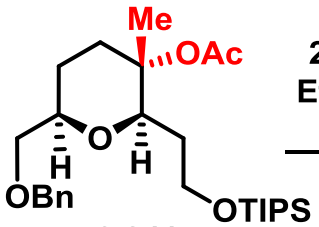
# Synthesis of Functionalized Ring A




3.187a
(9 steps)

1) DIPEA, $Ac_2O$
DMAP, DCM

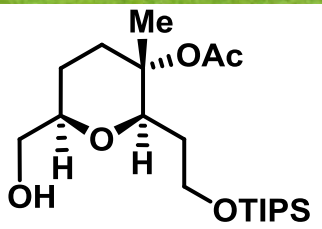
90%




3.241

2) $Pd(OH)_2/C$, $H_2$
EtOAc/MeOH=1/4,
r.t., 2h

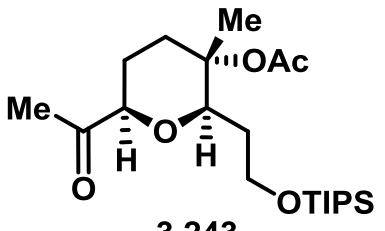
100%




3.242

68%
for 3 steps

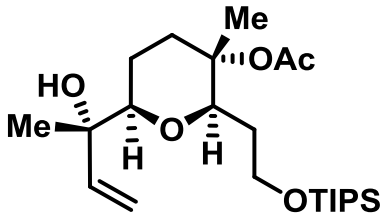
3) DMP
4) MeLi, $CeCl_3$
5) DMP




3.243

6) VinylMgBr
$CeCl_3$

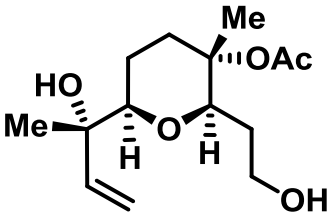
80%




3.244

7) TBAF, THF

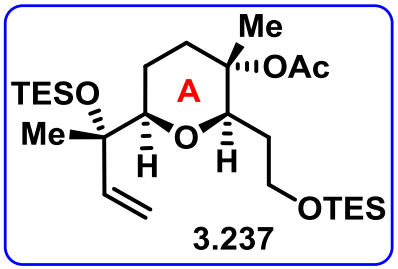
90%




3.245

8) TESOTf
2,6-lut.

95%

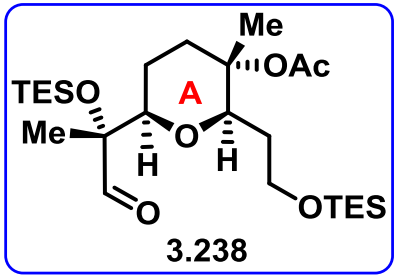



3.237

8 steps, 42%

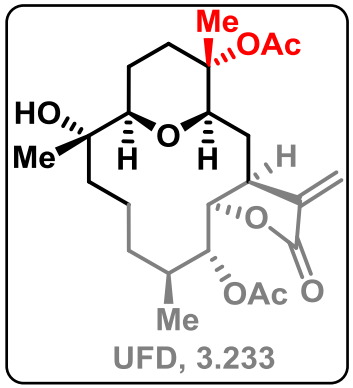
9) $O_3$, Py, DCM

80%

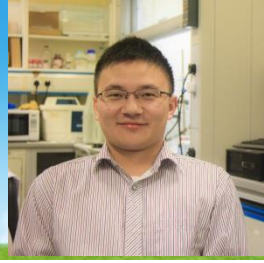



3.238

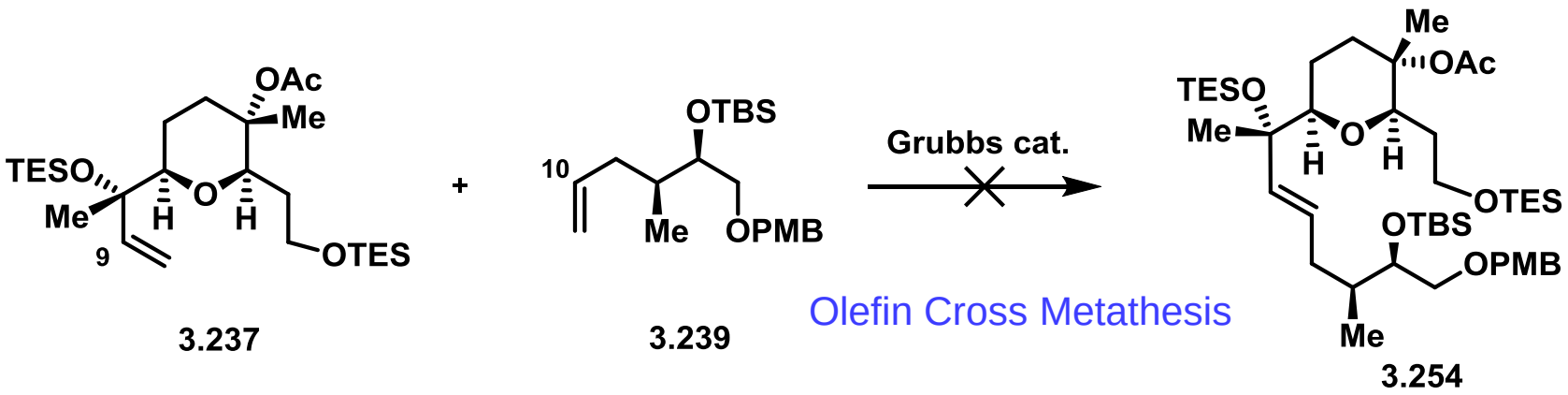
9 steps, 33%




UFD, 3.233

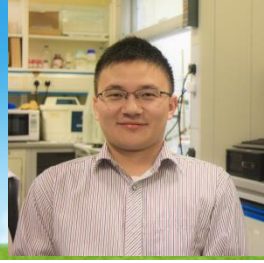


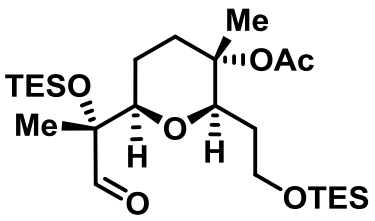
# Left Side Chain Extension




| Entry | Reaction condition | Results |
|---|---|---|
| 1 | Grubbs II, DCM, reflux, 12 h | total recovery of **3.237** |
| 2 | Grubbs II, DCM, reflux, 36 h | The same as above |
| 3 | Grubbs II, PhMe, reflux, 12 h | The same as above |
| 4 | Hoveyda-Grubbs II, PhMe, reflux, 12 h | The same as above |

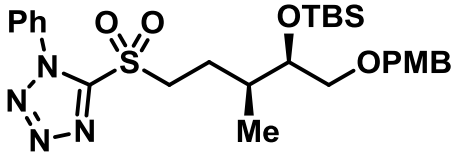
# Left Side Chain Extension






3.238

+



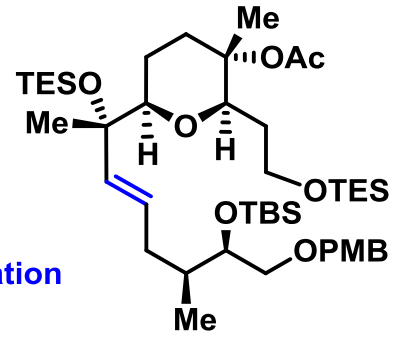

3.240

1) LiHMDS

THF, -78°C

70%

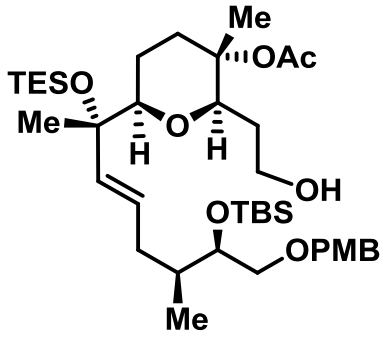
Julia-Kocienski Olefination




3.254

80%

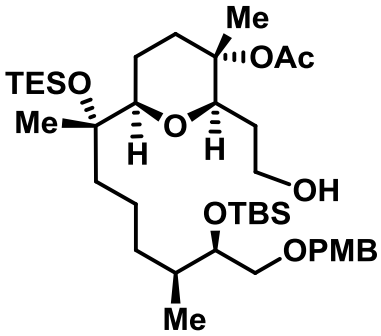
2) AcOH/
$THF/H_2O$




3.255

3) Pd/C, $H_2$

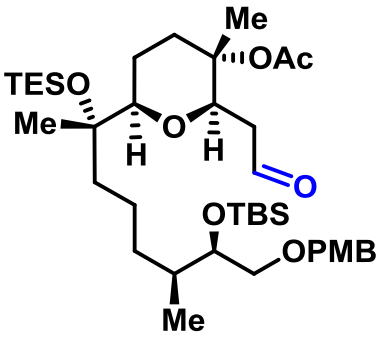
90%




3.256

4) DMP,
$NaHCO_3$, DCM

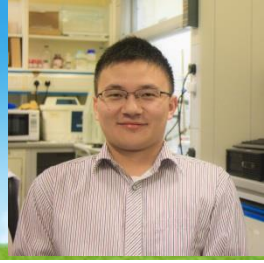
90%



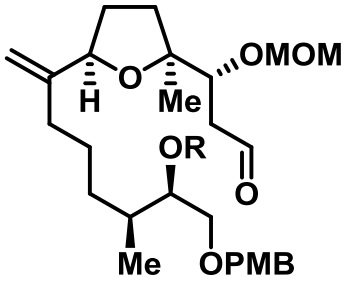

3.236

MBH substrate

# Right Side Chain Extension



## Literature example




3.156

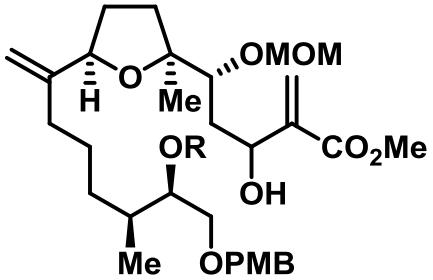
Morita-Baylis-Hillman

DABCO

$CO_2Me$

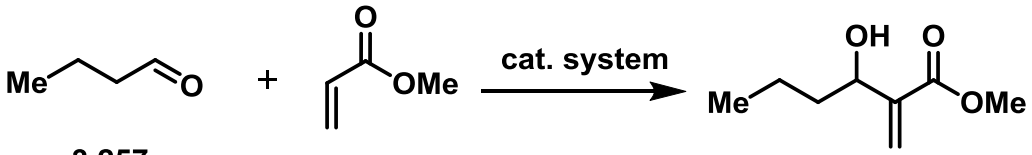
22 days
57%

Slow and low-yielding!




3.157

## Model study

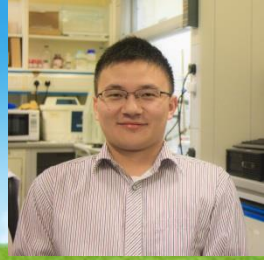


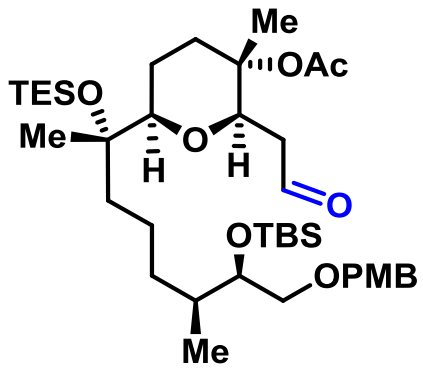

3.257 3.258 3.259, desired

| Entry | Conditions | Time/h | Yield% |
|---|---|---|---|
| 1 | DABCO, dioxane, 0°C | 12 | 10 |
| 2 | DABCO, dioxane, r.t. | 24 | 50 |
| 3 | PhSeLi, THF; *m*CPBA, $Na_2CO_3$ | 12 | 40 |
| 4 | PhSeLi, THF; BnBr, TBAI | 12 | 30~40 |
| 5 | $PBu_3$, BINOL, THF, r.t. | 4 | 40 |
| 6 | $PBu_3$, THF, r.t. | 4 | 60 |

Marshall, J. A. et al. *Org. Lett.* **2010**, *12*, 4328.

# Right Side Chain Extension



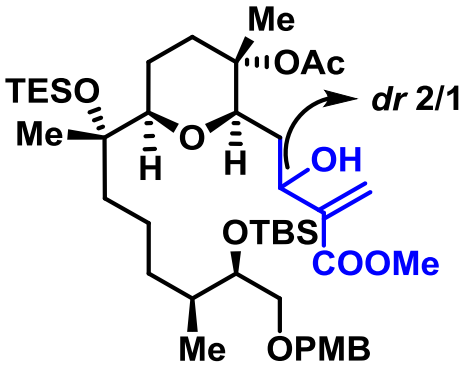



3.236

1) $PBu_3$


75%

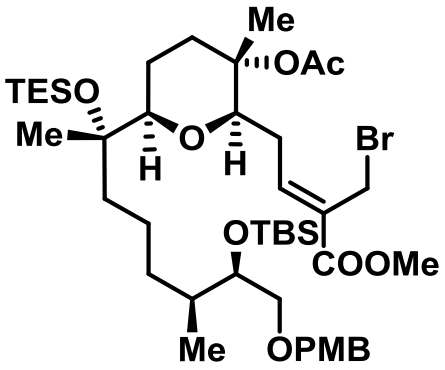
Morita-Baylis-Hillman




3.235

80%

2) $CBr_4$, $PPh_3$, DIPEA, DCM

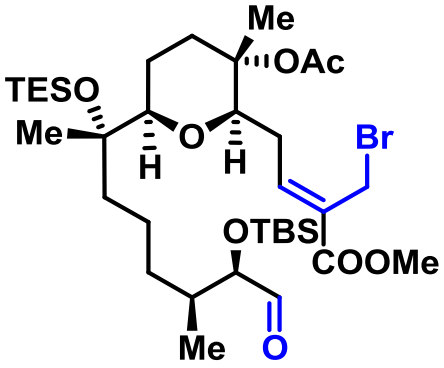



3.261

3) DDQ, pH=7 buffer

4) DMP, DCM

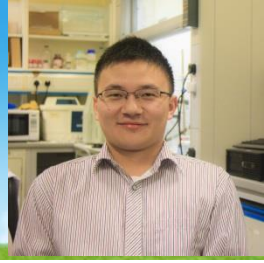
80%
over 2 steps

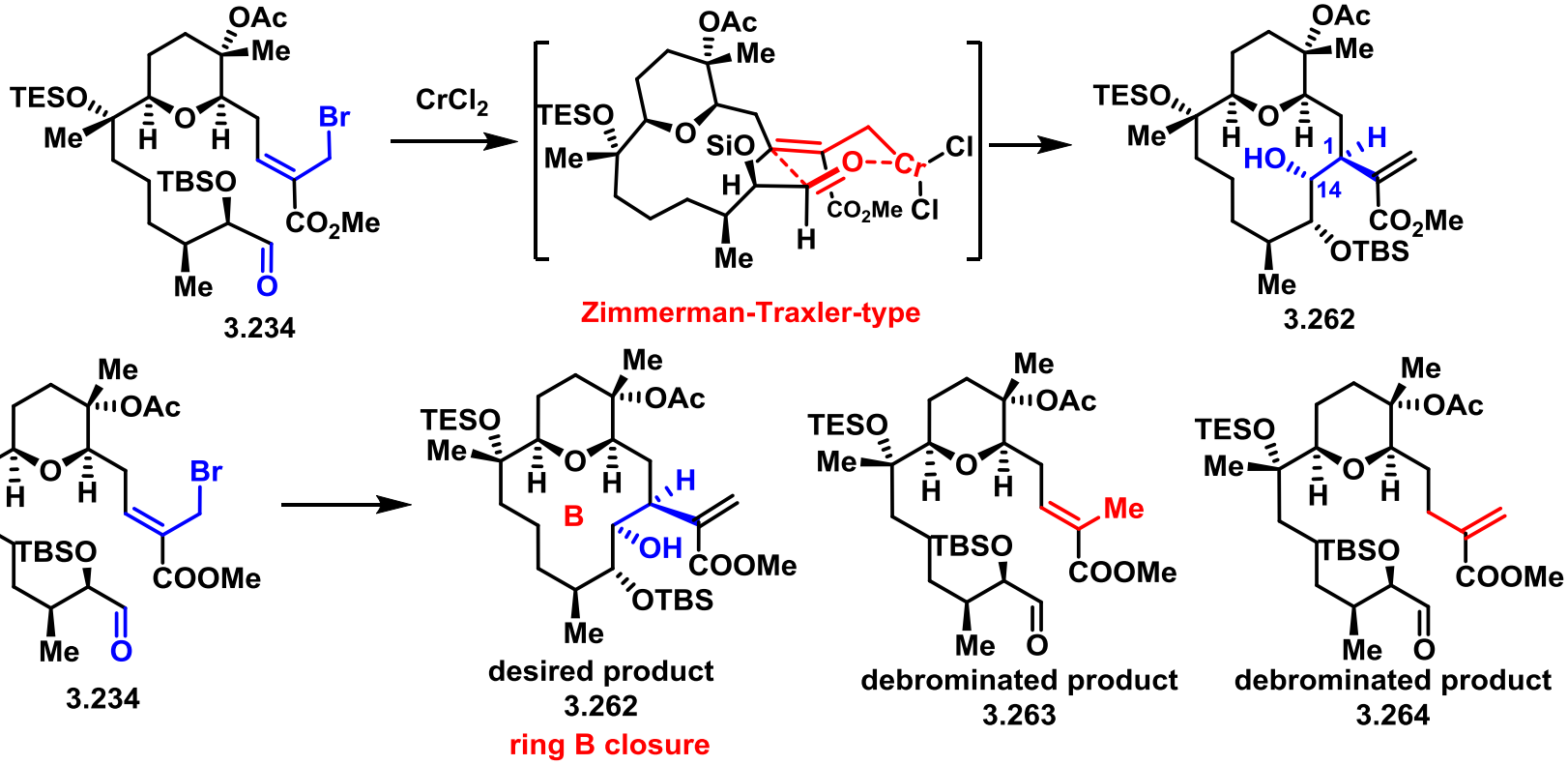



3.234

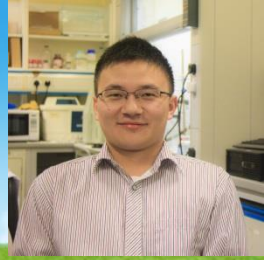
key precursor

# Ring B Closure

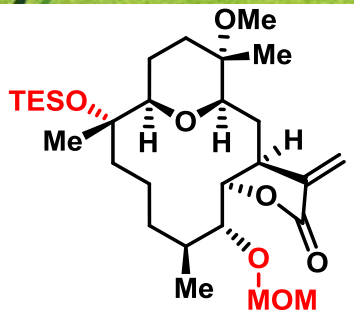





| Entry | Conditions | Conv.% | Yield% |
|---|---|---|---|
| 1 | In, $THF/H_2O$, r.t. | 0 | 0 |
| 2 | Zn, THF, r.t. | 100 | 90% **3.263/3.264**~1/1 |
| 3 | $SmI_2$, THF, 0°C | 100 | 90% **3.263** |
| 4 | $CrCl_2$, 4 Å M. S., THF, r.t. | 100 | 95% **3.262** |

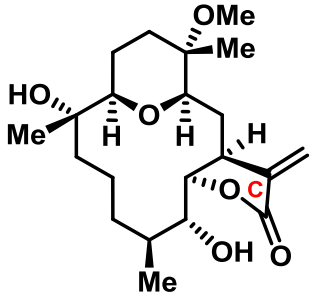


# Ring C Formation

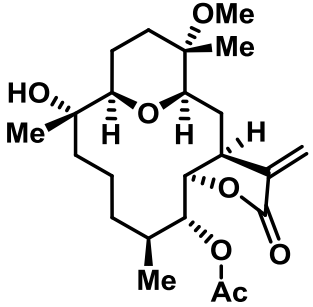



TFA

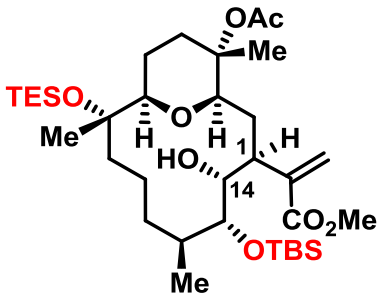
75%




γ-lactone



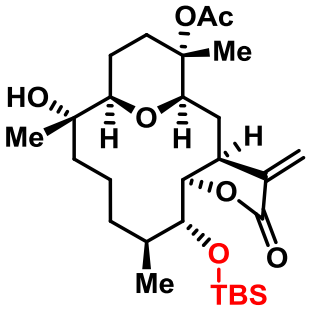

revised UGA




3.262

1) TFA

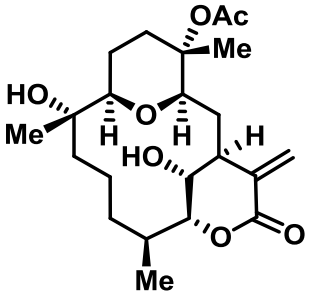
80%



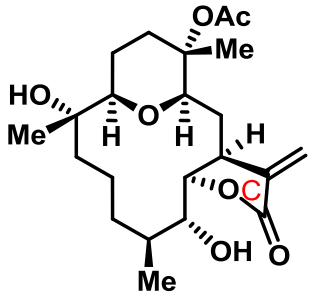

3.266

2) TBAF
or HCl/MeOH

δ:γ=10:1

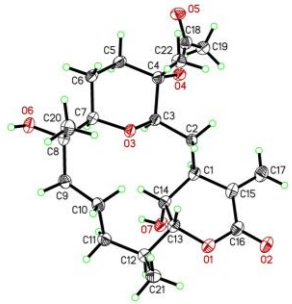



δ-lactone 3.267a



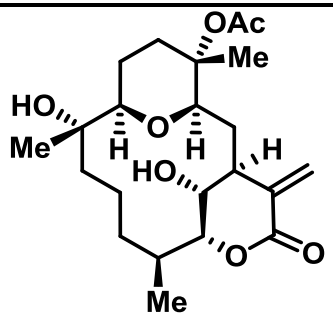

γ-lactone 3.267b

3) 1% HCl in MeOH, 90%  δ:γ = 10:1




X-ray

≡




δ-lactone

5) HOAc, $CH_2Cl_2$

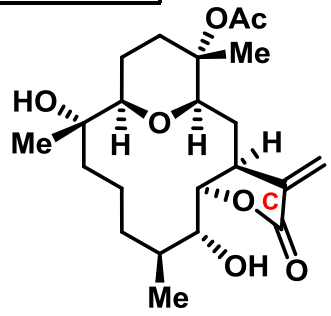
or Silica Gel

>85%

4)  NaH, 80%

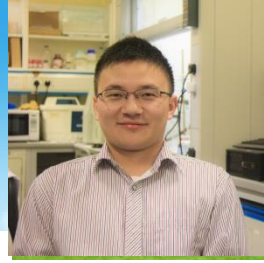
γ:δ= 10:1

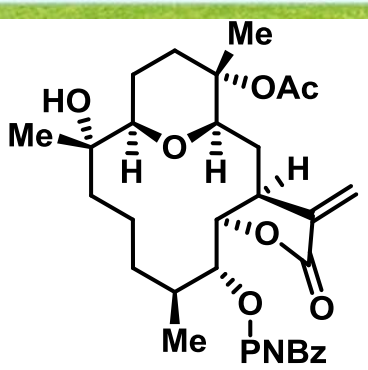
translactonization




γ-lactone
ring C formed

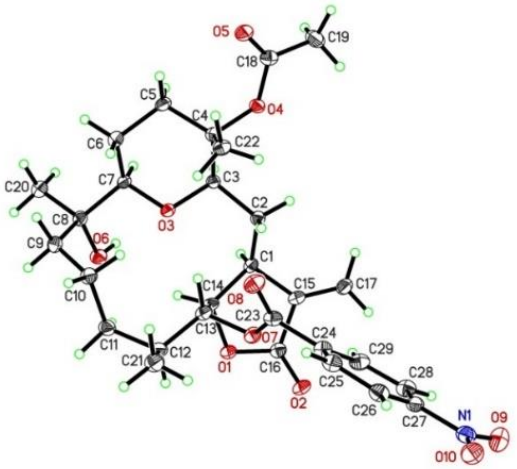
# Completion of UFD



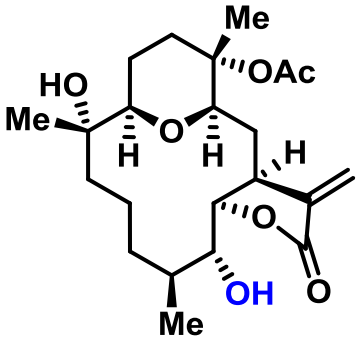



3.268

≡



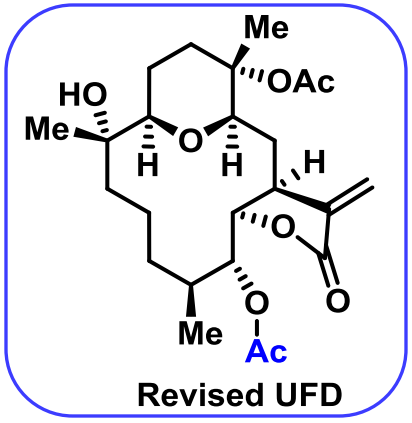

90% ↑ 4-nitrobenzoyl chloride, DIPEA, DMAP, DCM




3.267b

$Ac_2O$, DMAP, DIPEA, DCM

90%



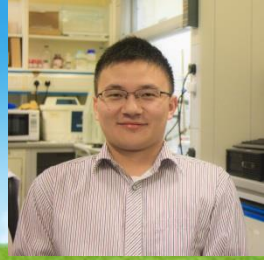

Revised UFD

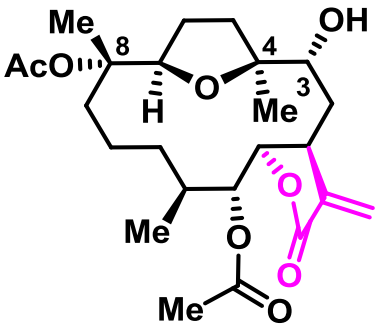
3.233

**Correct UFD**

| NMR | | $[\alpha]_D$ | |
|---|---|---|---|
| $^1H$, $\Delta\delta \leq 0.02$ ppm | natural | +145.7 | C=0.88 |
| $^{13}C$, $\Delta\delta \leq 0.1$ ppm | synthetic | +135.9 | C= 0.10 |

# Structural Revision for Uprolide F Diacetate

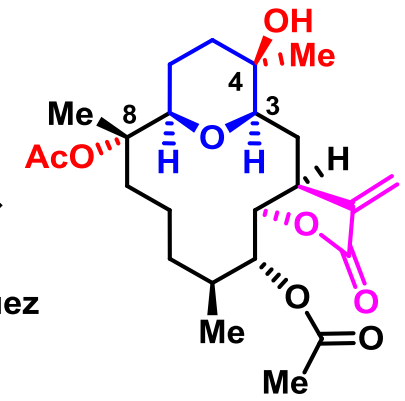





Uprolide F Diacetate, 3.50
(UFD, 1995)

2000

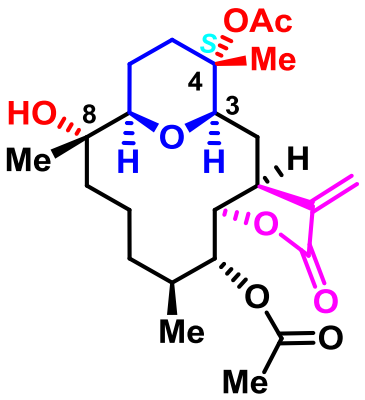
revised
by Rodriguez




Proposed Structure, 3.128
(UFD, 2000 )

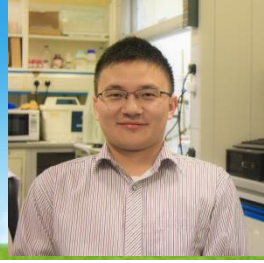
2015

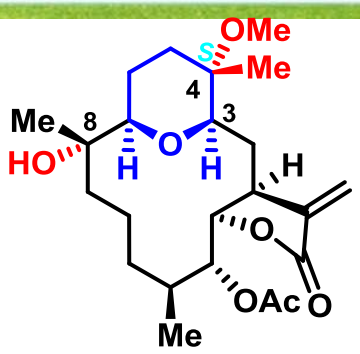
revised
by us




Correct Structure!!
(UFD, 3.233)

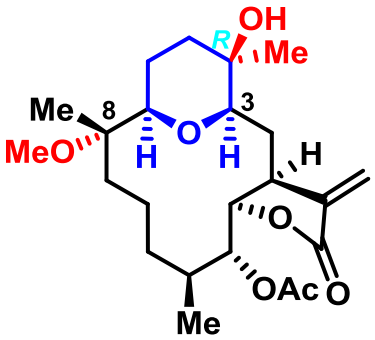
# Summary





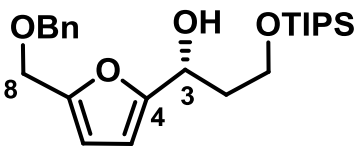

Revised UGA
(correct)

Strategy 1



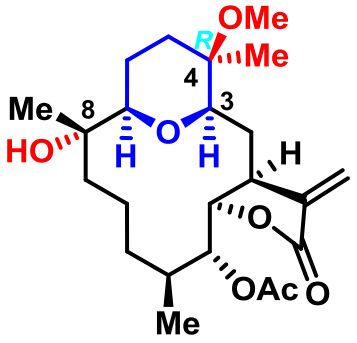

Proposed UGA

Strategy 1



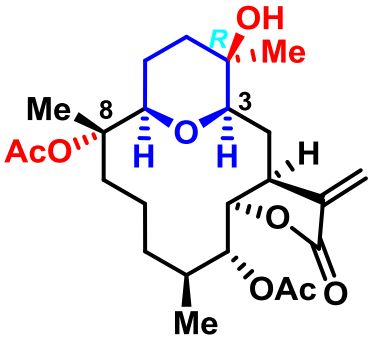

(97% *ee*)

Strategy 1




4-*epi*-UGA (X-ray)

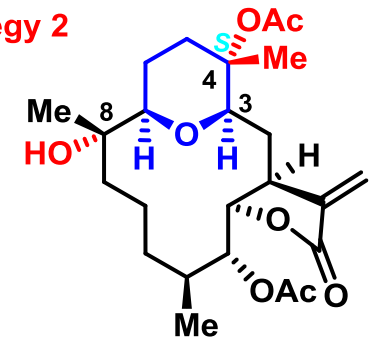
**Strategy 1**
**Ring construction:**
**A->C->B**
**43 steps (LLS)**
**47 steps (TS)**




Proposed UFD

Strategy 2

Revision




Revised UFD (correct)

**Strategy 2**
**Ring construction:**
**A->(B+C)**
**30 steps (LLS)**
**38 steps (TS)**

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