Total Syntheses of Tigliane and Ingenane Diterpenoids: A Brief Survey of Synthetic Strategies and Key Discoveries

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College of Chemistry and Molecular Engineering
March 12th, 2022

Outline

- Introduction
  - Structures of Tigliane and Ingenane Diterpenoids
  - Bioactivity of Tigliane and Ingenane Diterpenoids
- Early (1989-2004) Total Synthesis of Tigliane and Ingenane Diterpenoids
  - Phorbol and Resiniferatoxin
  - Ingenol
- Wender's Semisynthesis of Prostratin from Phorbol or Crotophorbolone
- Recent (2013-2022) Total Synthesis of Tigliane and Ingenane Diterpenoids
  - Baran's Total Synthesis of Ingenol and Phorbol
  - Inoue's Total Synthesis of Crotophorbolone, Prostratin and Resiniferatoxin
  - Others
- Conclusion

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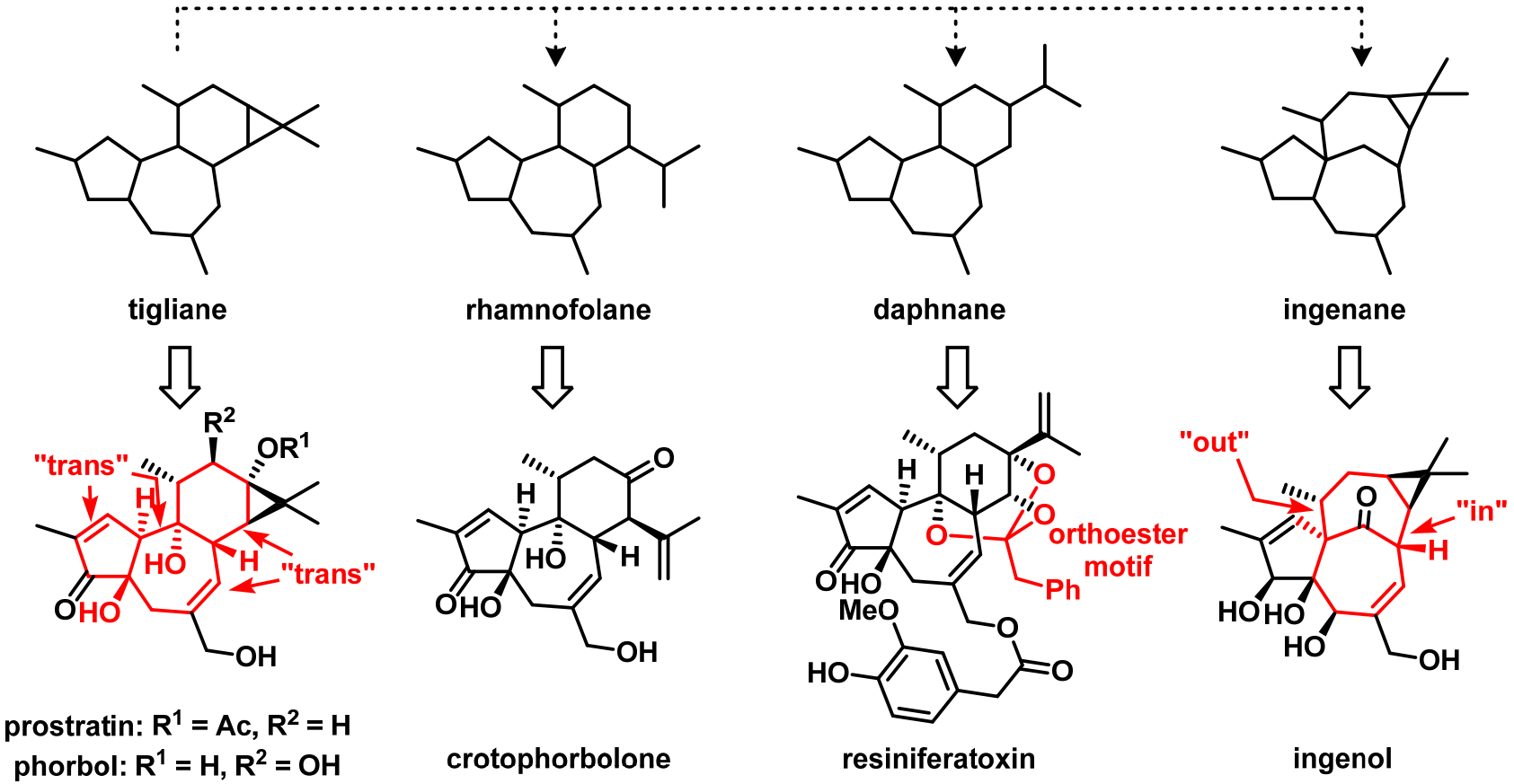
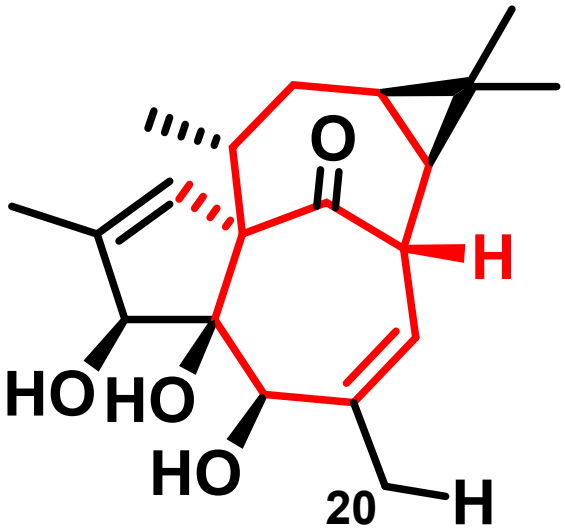
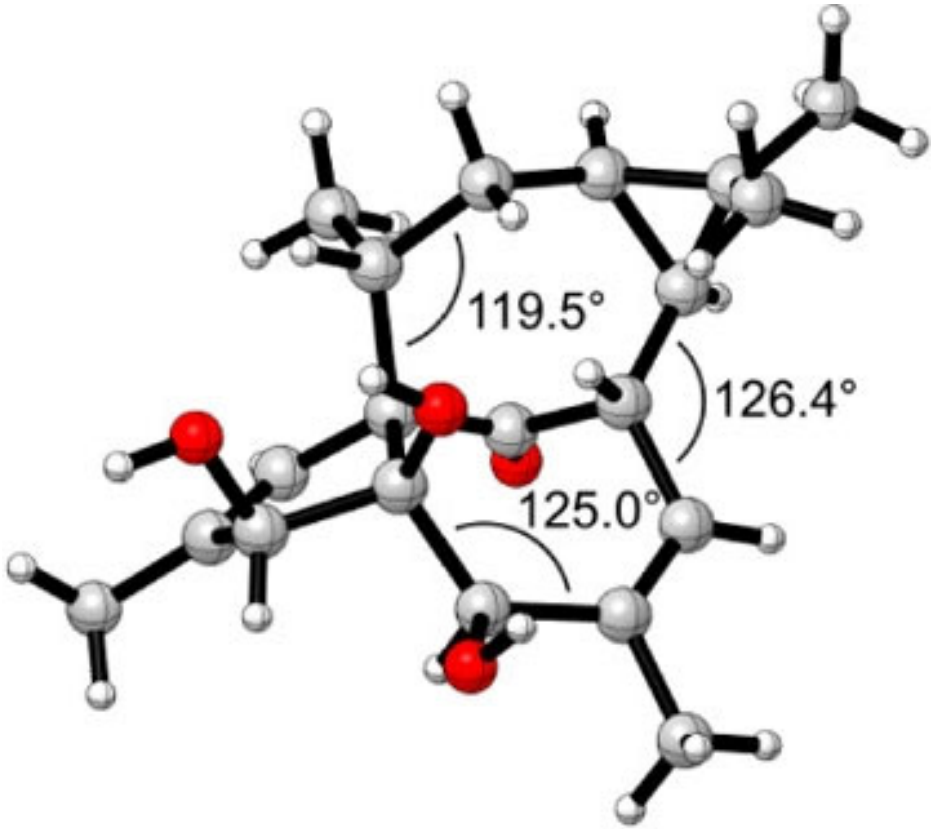
Structures of Tigliane and Ingenane Diterpenoids



X-Ray Structure of 20-Deoxyingenol



20-deoxyingenol



Jørgensen, L.; McKerrall Steven, J.; Kuttruff Christian, A.; Ungeheuer, F.; Felding, J.; Baran Phil, S. *Science* **2013,** *341*, 878-882.

Bioactivity of Tigliane and Ingenane Diterpenoids

- Prostratin: a potent activator of HIV expression in latently infected T-cell lines
- Phorbol 12-myristate 13-acetate (TPA): often employed in biomedical research to activate the protein kinase C (PKC) (similar to diacylglycerol)
- Resiniferatoxin: a potent functional analog of capsaicin (potencies 10^3 to 10^5 times greater than capsaicin) – TRPV1 activator
- Ingenol mebutate (Picato®): a first-in-class drug for the treatment of the precancerous skin condition actinic keratosis (approved by FDA in 2012)

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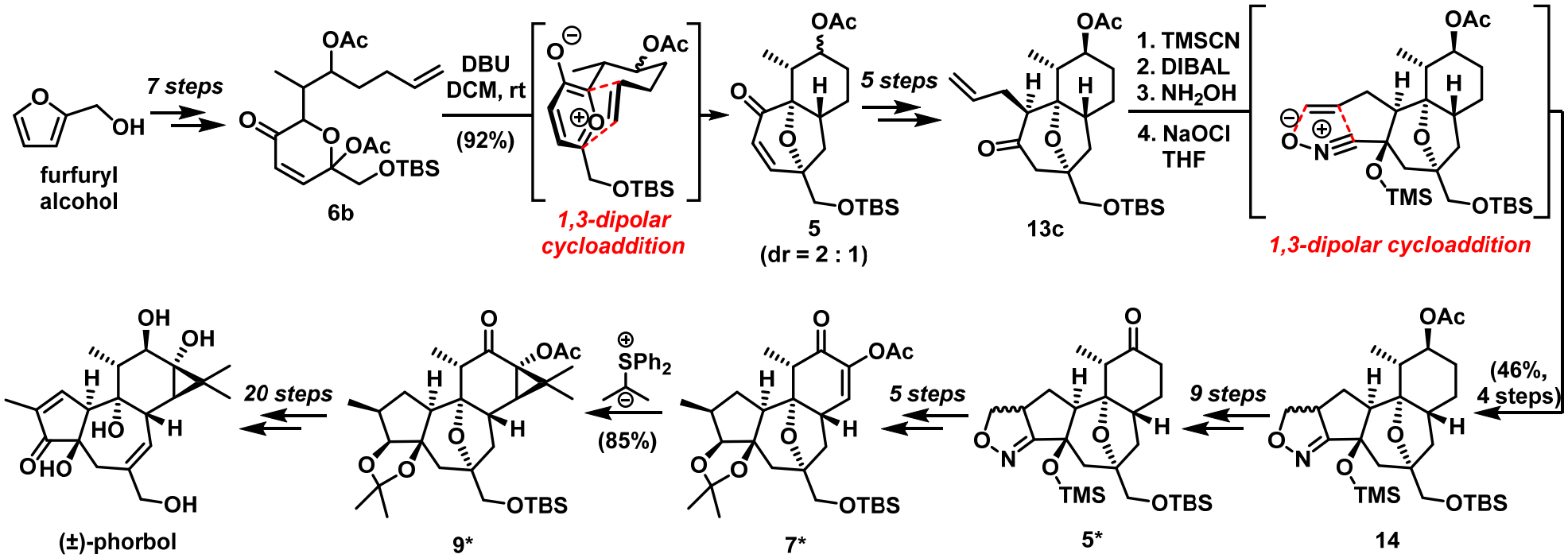
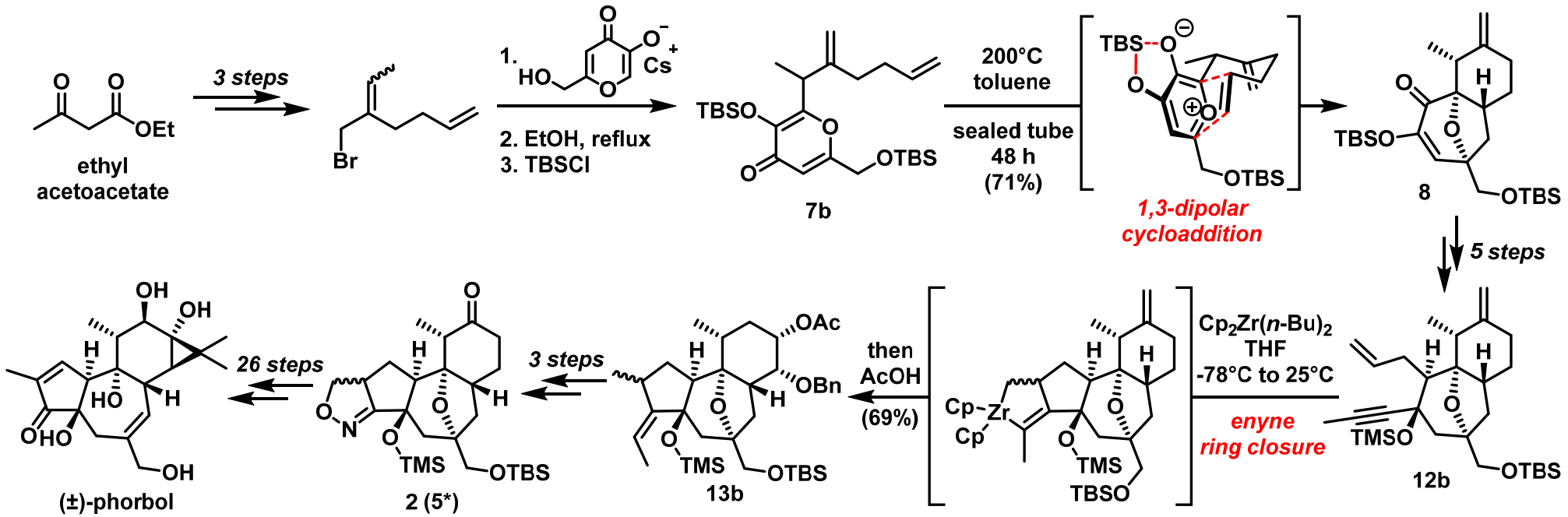
Wender's Total Synthesis of (±)-Phorbol (1989)



Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989,** *111*, 8954-8957.
Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989,** *111*, 8957-8958.

52 steps

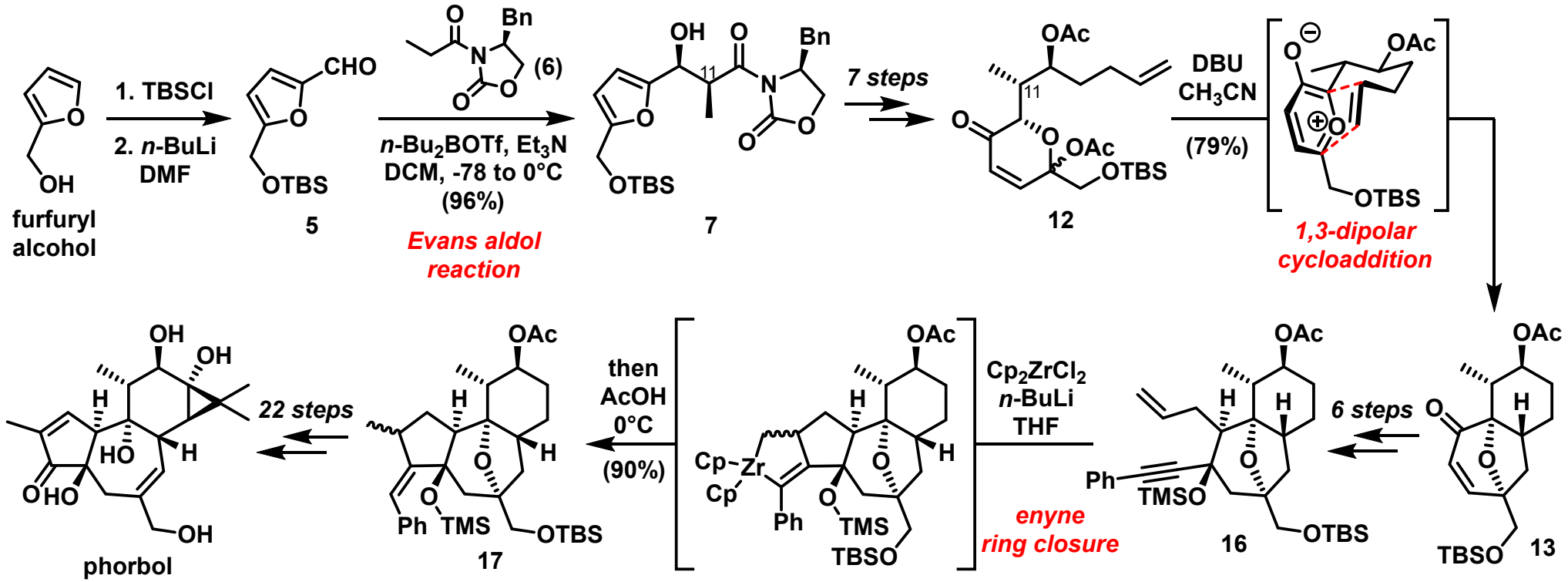
Wender's Formal Total Synthesis of (±)-Phorbol (1990)



Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990,** *112*, 4956-4958.

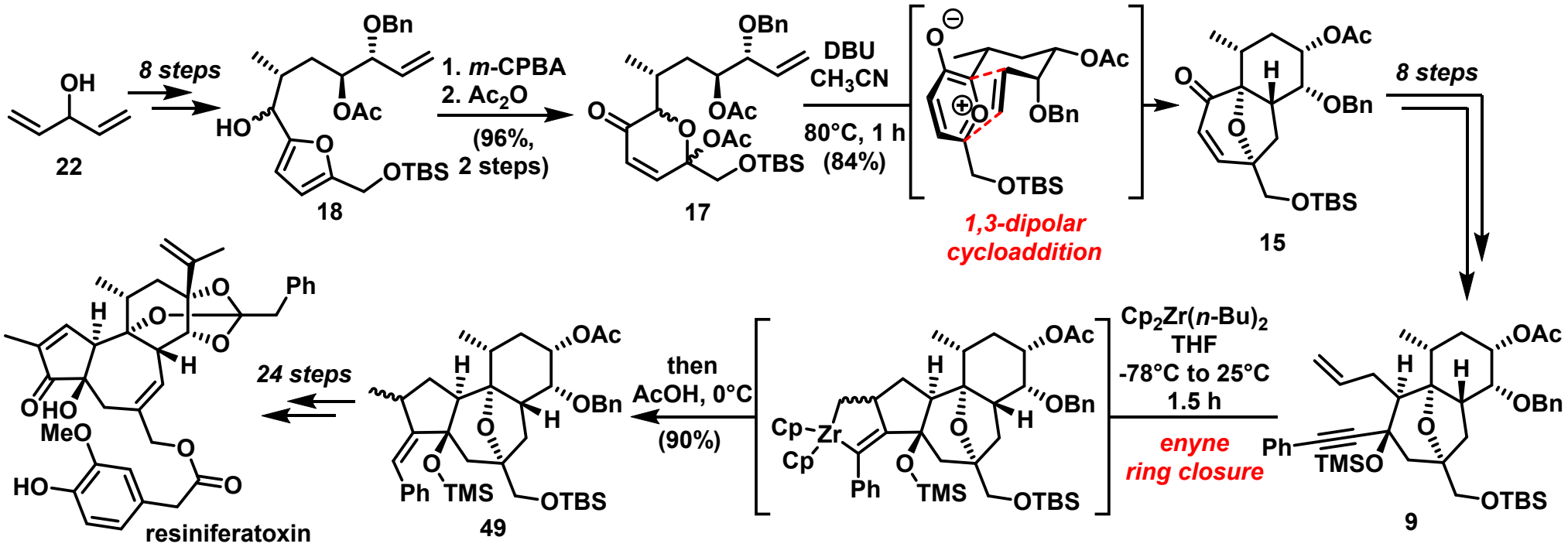
42 steps

Wender's Formal Total Synthesis of Phorbol (1997)



Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997,** *119*, 12976-12977.

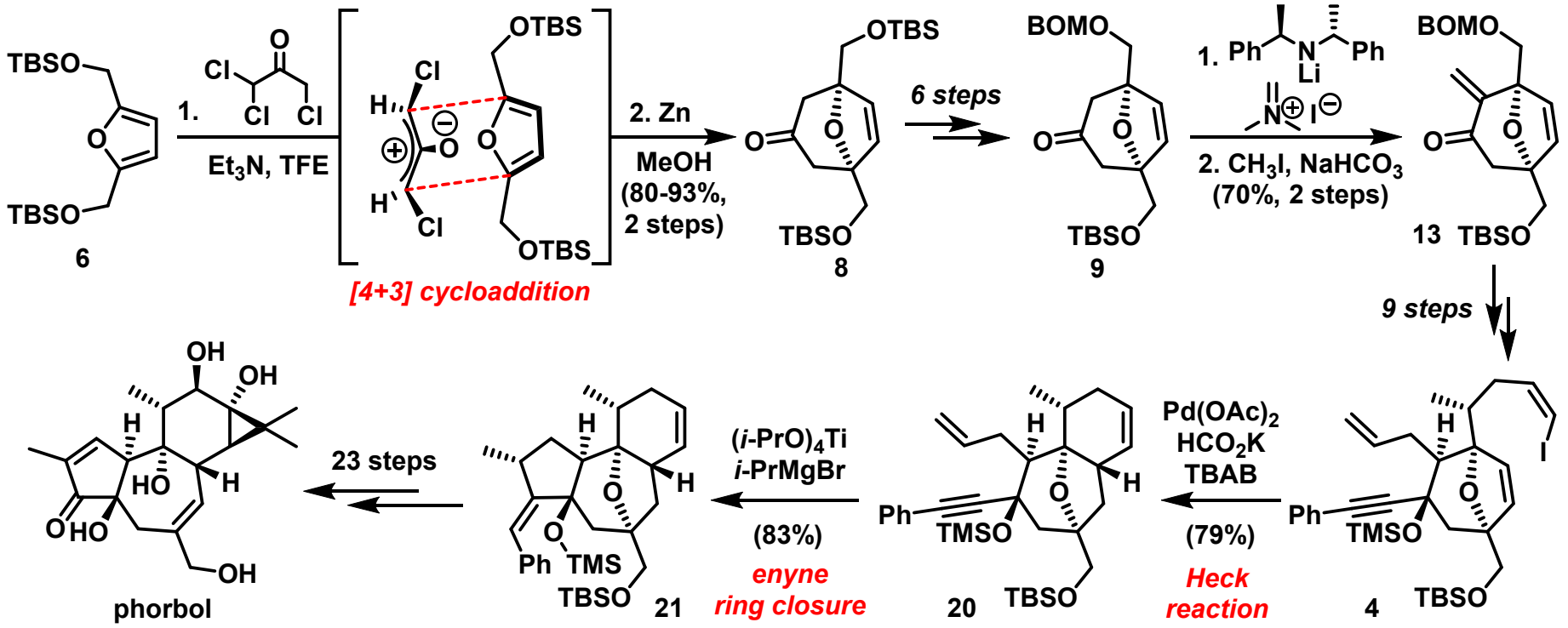
Wender's Total Synthesis of Resiniferatoxin (1997)



44 steps

Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997,** *119*, 12976-12977.

Cha's Formal Total Synthesis of Phorbol (2001)



Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001,** *123*, 5590-5591.

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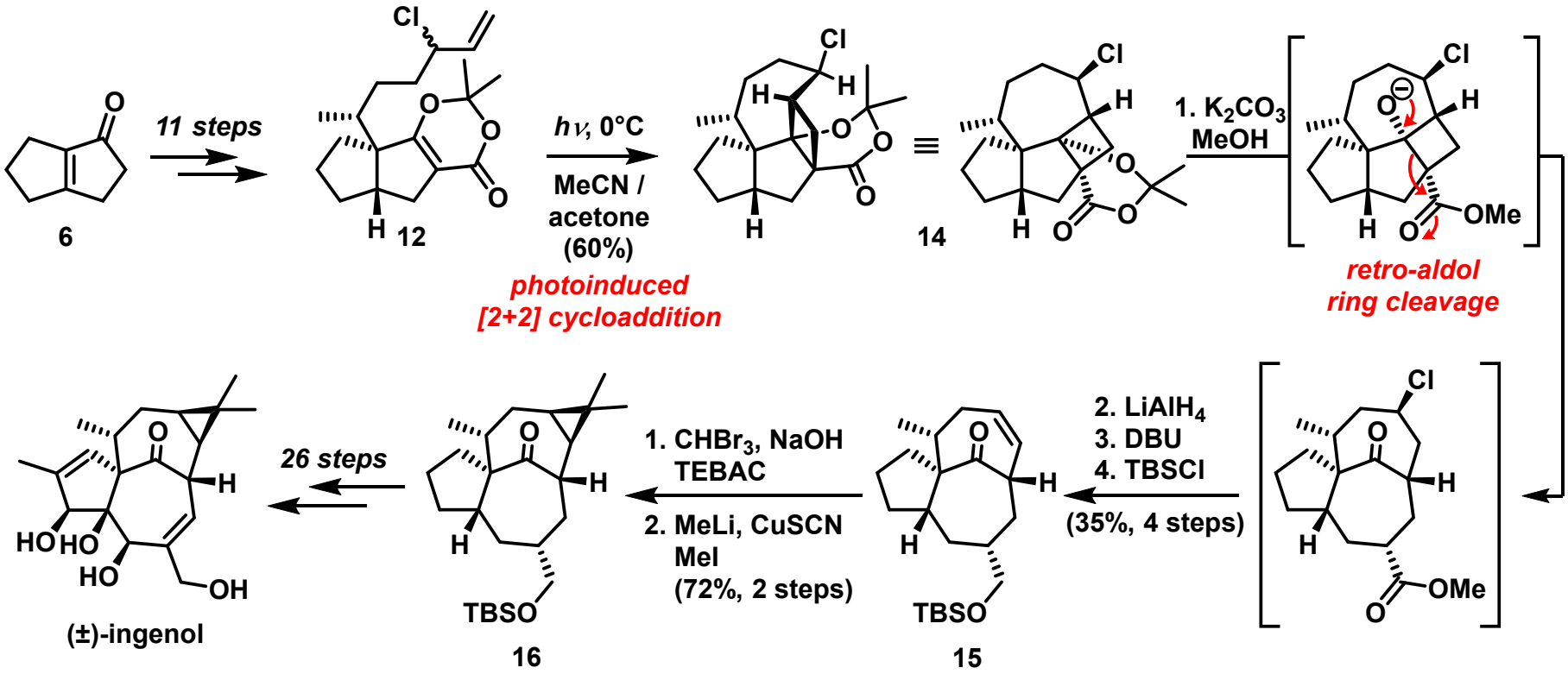
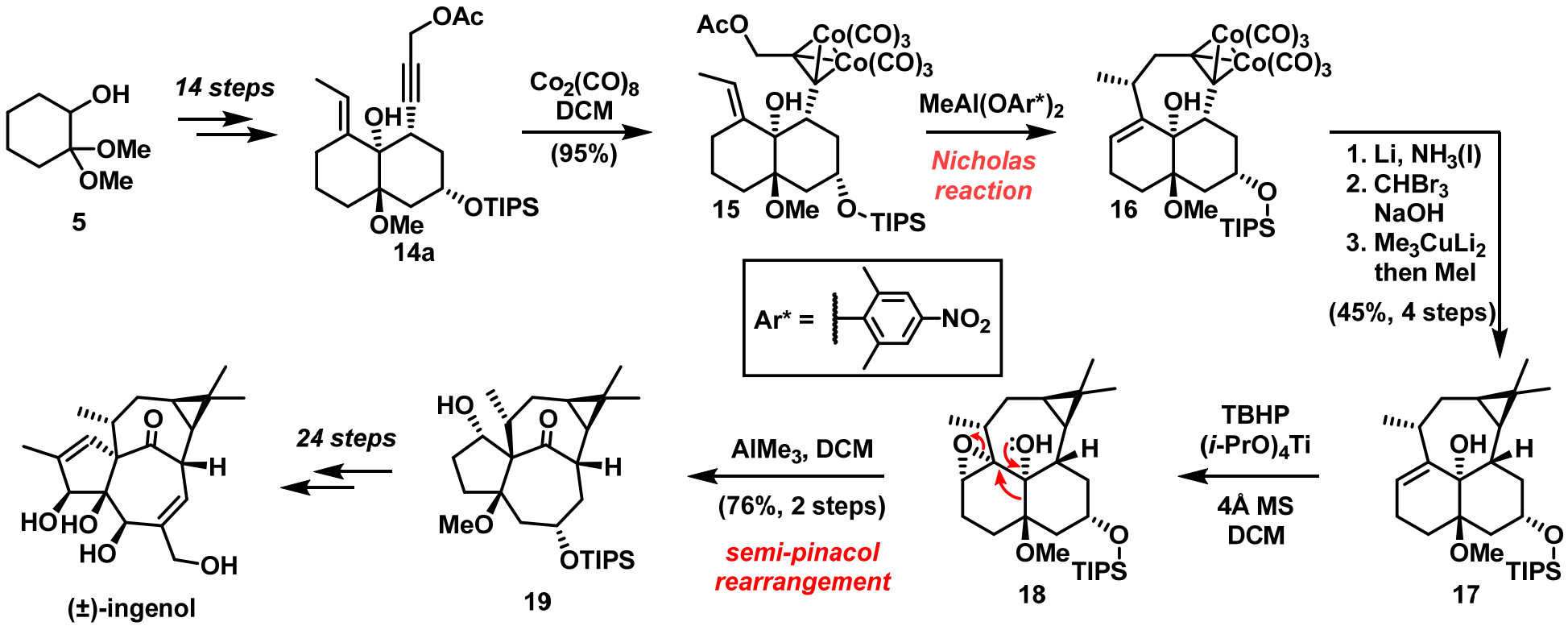
Winkler's Total Synthesis of (±)-Ingenol (2002)



44 steps

Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002,** *124* , 9726-9728.

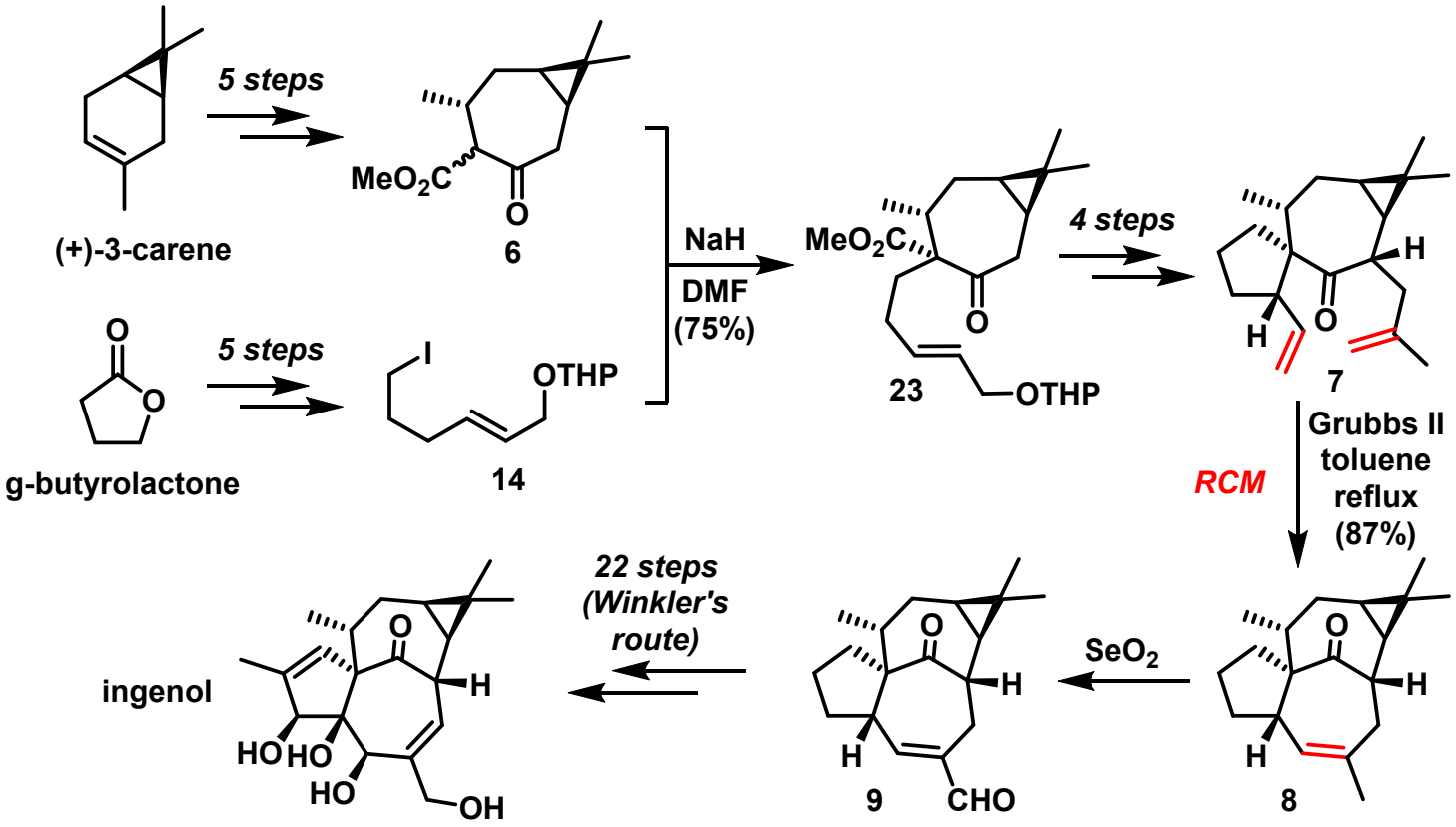
Tanino's Total Synthesis of (±)-Ingenol (2003)



45 steps

Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003,** *125*, 1498-1500.

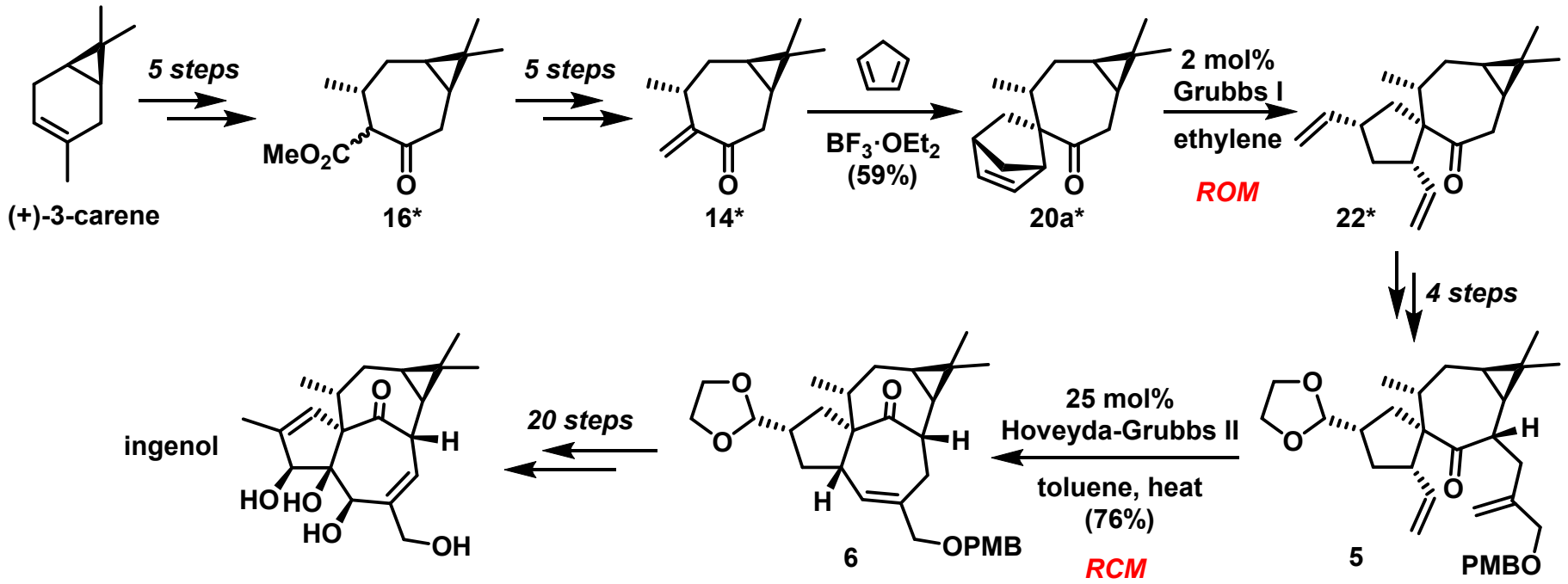
Kigoshi's Formal Total Synthesis of Ingenol (2004)



34 steps

Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004,** *69*, 7802-7808.

Wood's Total Synthesis of Ingenol (2004)



37 steps

Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004,** *126*, 16300-16301.

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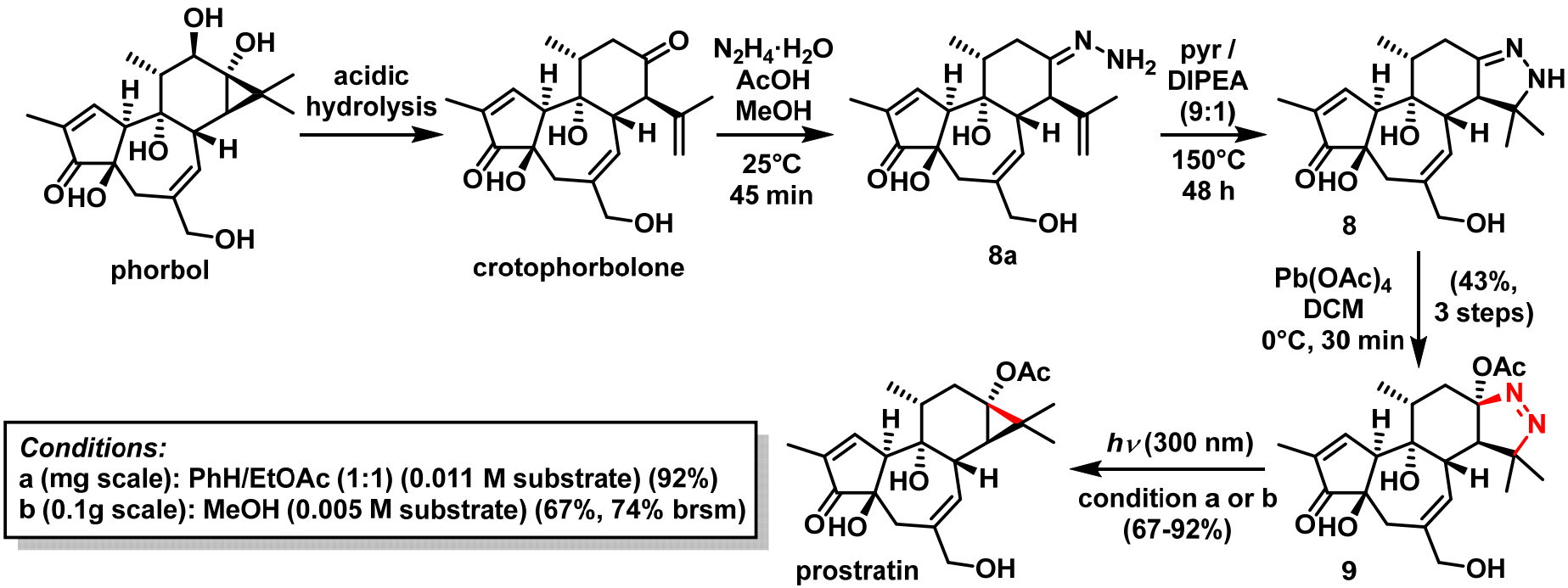
Wender's Semisynthesis of Prostratin (from Phorbol or Crotophorbolone) (2008)



Conditions:
a (mg scale): PhH/EtOAc (1:1) (0.011 M substrate) (92%)
b (0.1g scale): MeOH (0.005 M substrate) (67%, 74% brsm)

4 steps from crotophorbolone / 5 steps from phorbol

Wender Paul, A.; Kee, J.-M.; Warrington Jeffrey, M. *Science* **2008,** *320*, 649-652.

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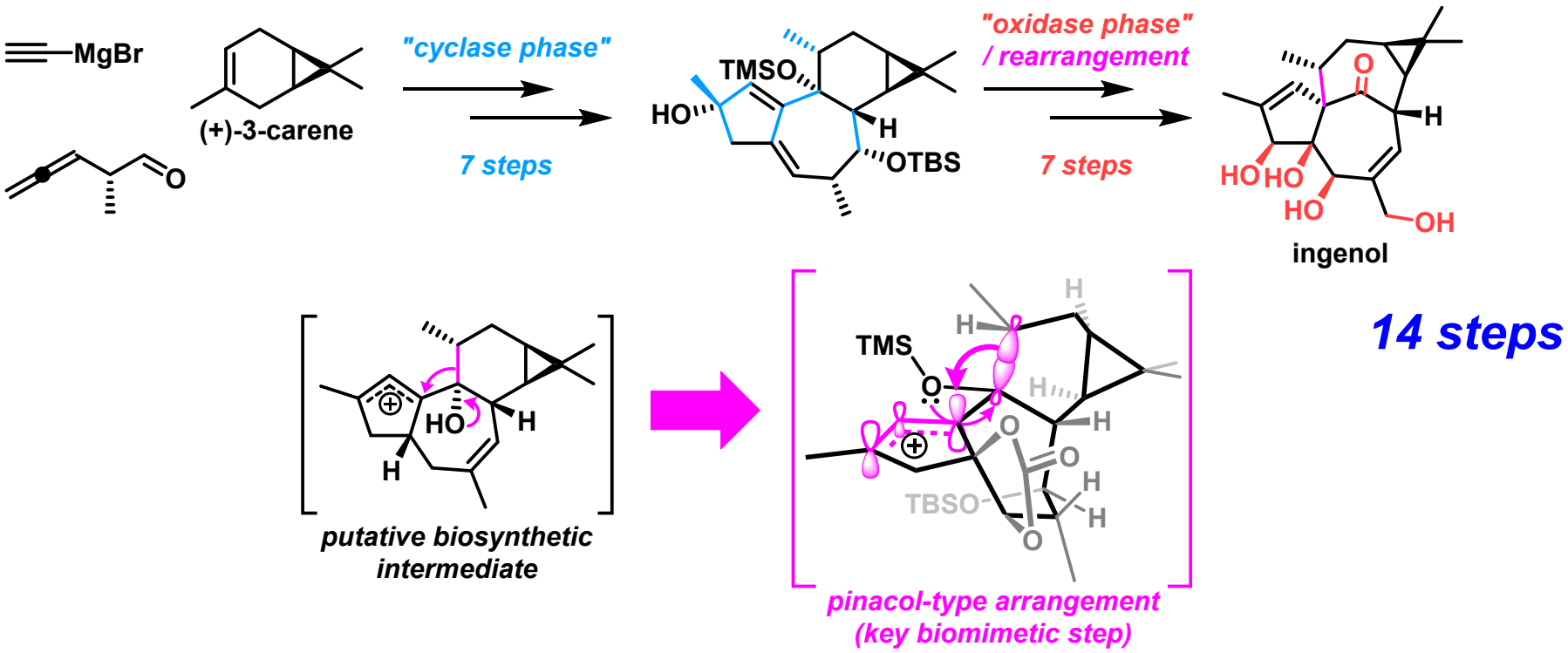
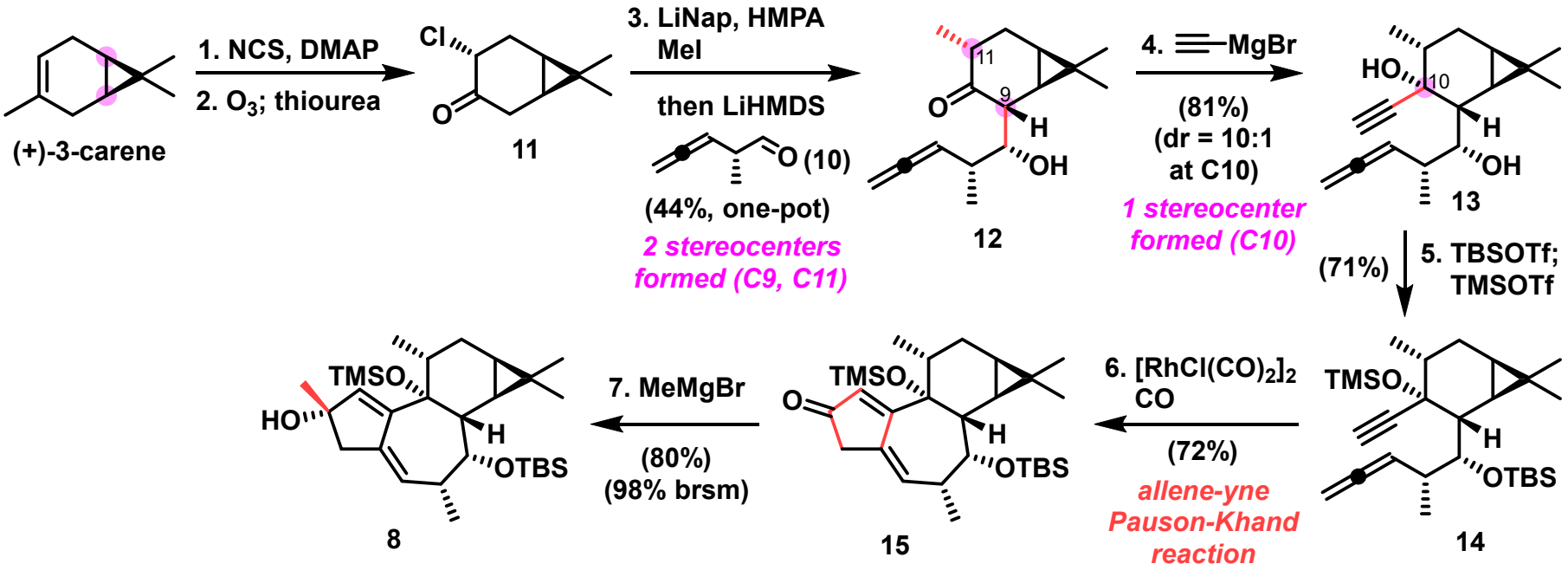
Baran's Total Synthesis of Ingenol (2013): Overview



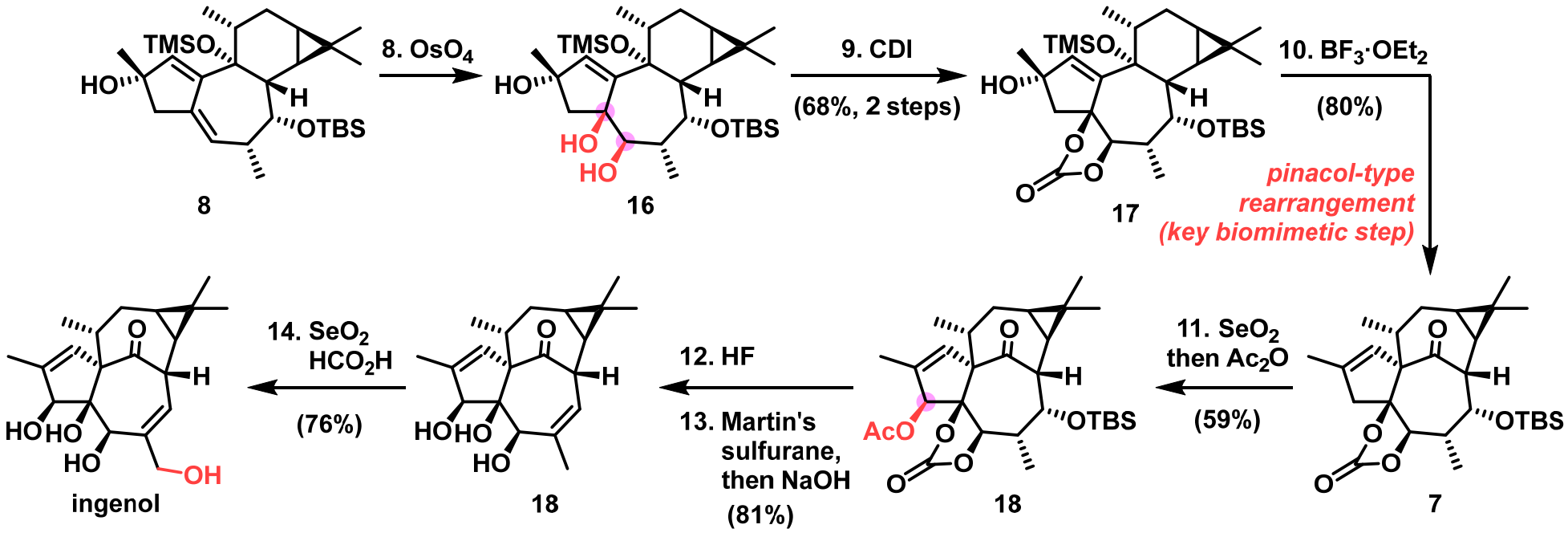
Jørgensen, L.; McKerrall Steven, J.; Kuttruff Christian, A.; Ungeheuer, F.; Felding, J.; Baran Phil, S. *Science* **2013,** *341*, 878-882.

“Cyclase Phase”



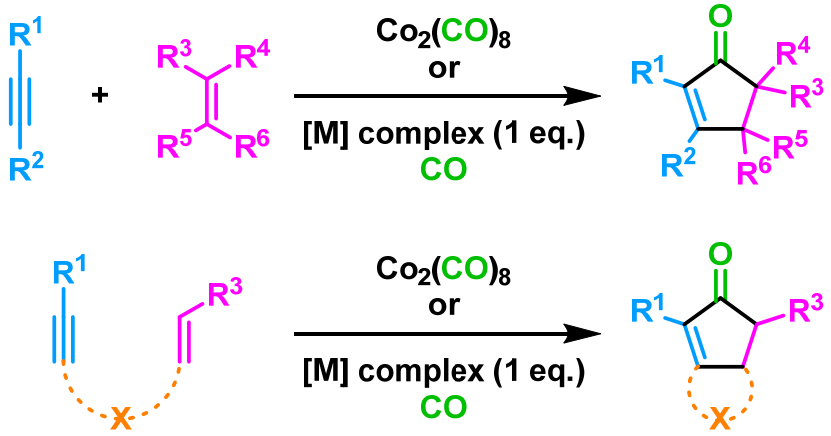
In 7 steps: 7 C-C bonds and 3 stereocenters formed!

“Oxidase Phase”

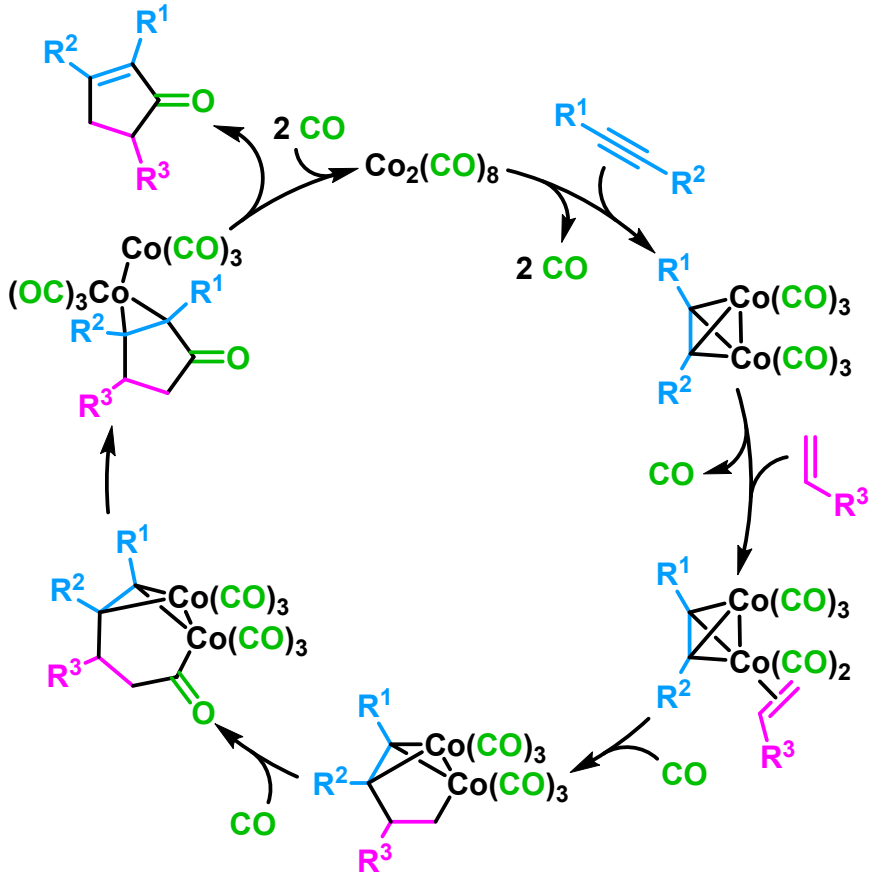


In 7 steps: 4 C-O bonds and 3 stereocenters formed!

Introduction to Pauson-Khand Reaction

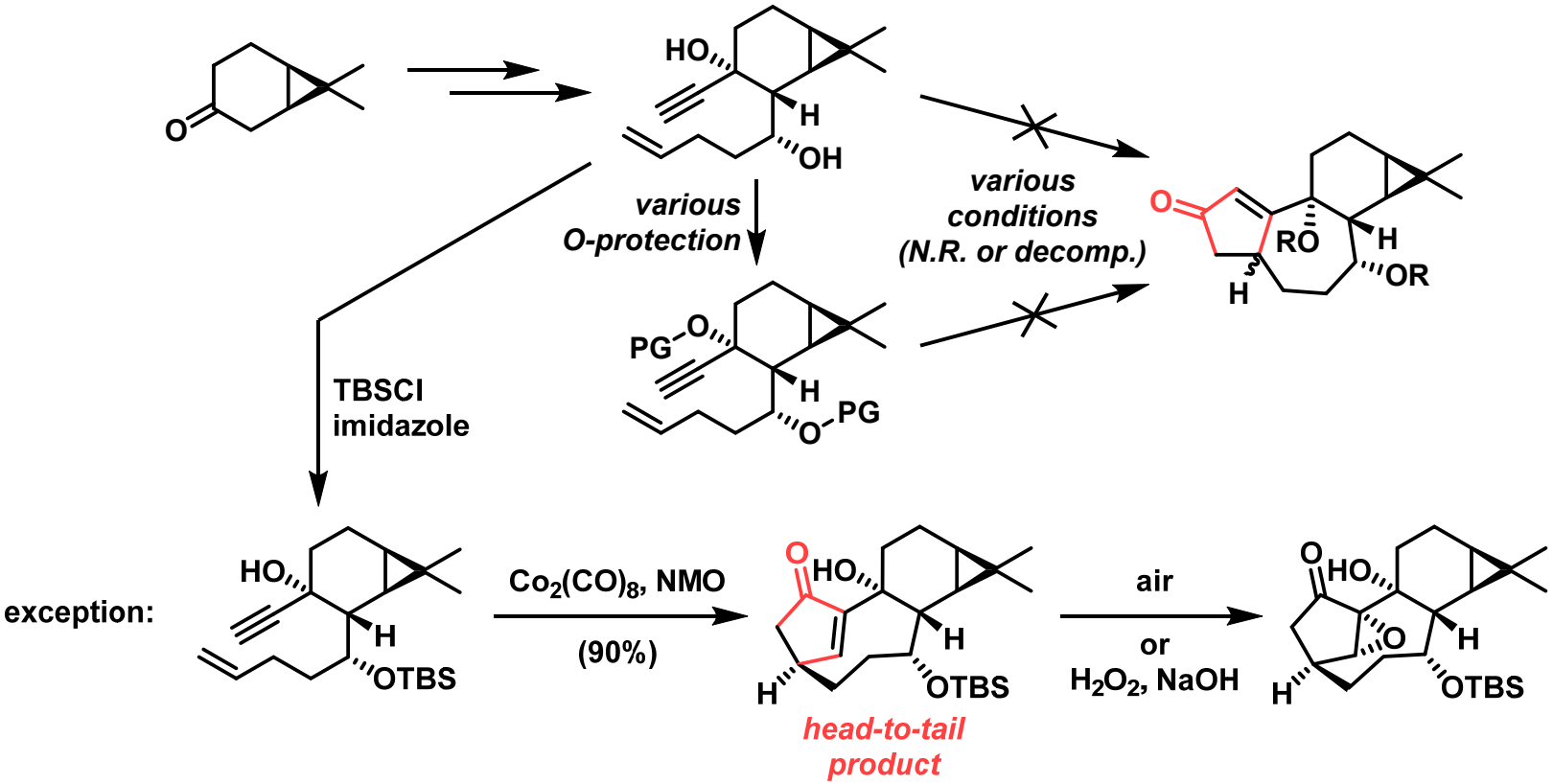


Usually X = 3 or 4-membered chain



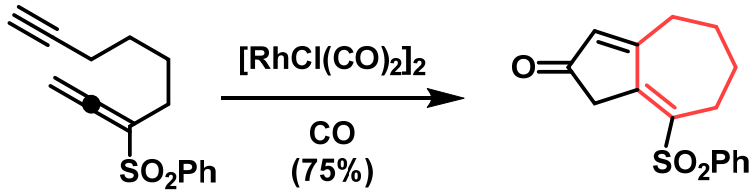
Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977,** *295*, 2-14.
Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004,** *33*, 32-42.

Model Studies of Pauson-Khand Reaction

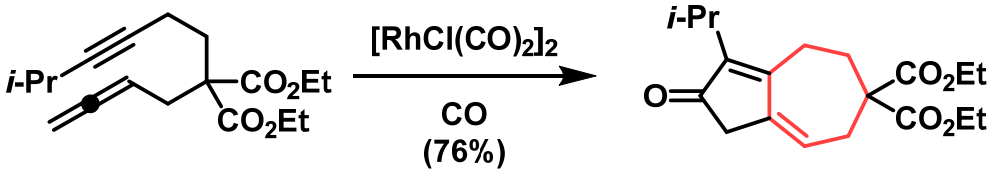


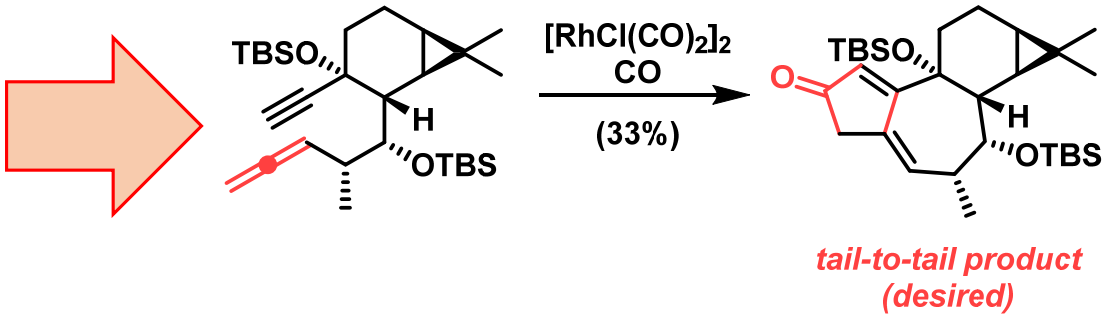
Model Studies of Pauson-Khand Reaction

Mukai[1]:



Brummond[2]:



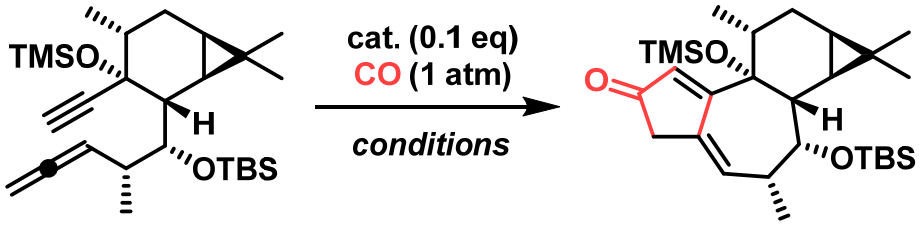


Pauson-Khand reactions with 7-membered ring forming

Success!

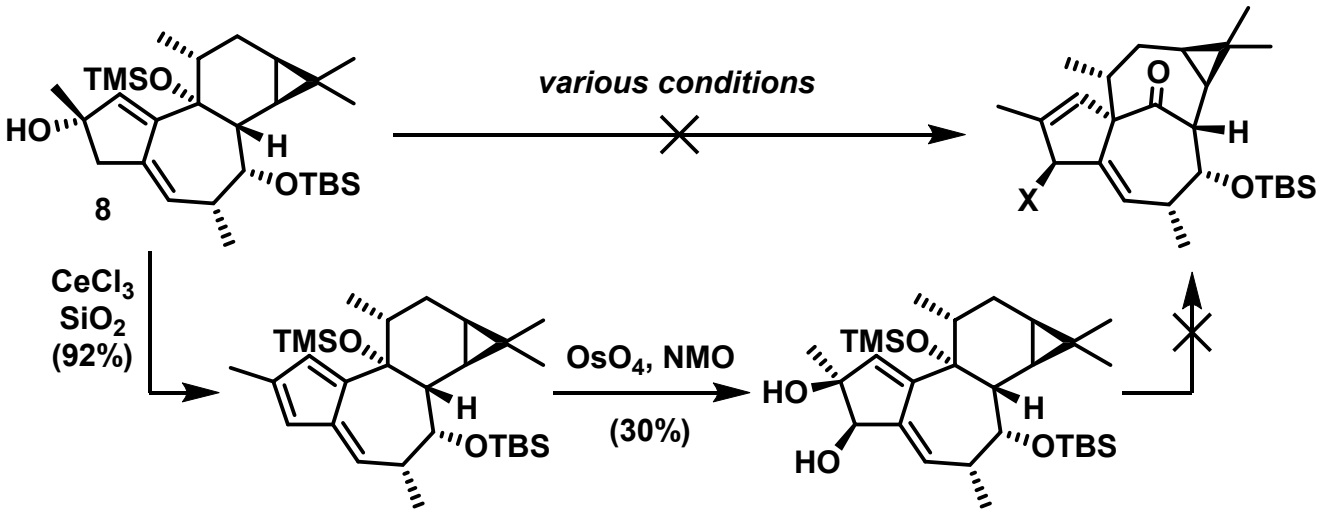
1. Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002,** *4*, 1755-1758.
2. Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. J. *Org. Lett.* **2002,** *4*, 1931-1934.

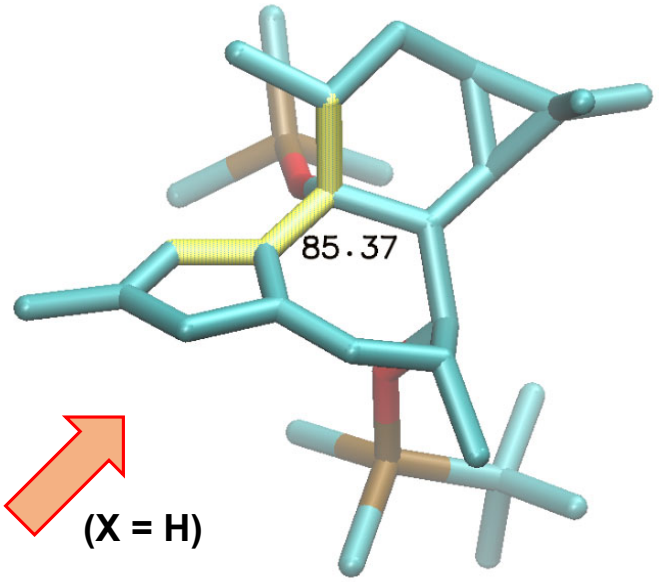
Optimization of Pauson-Khand Reaction



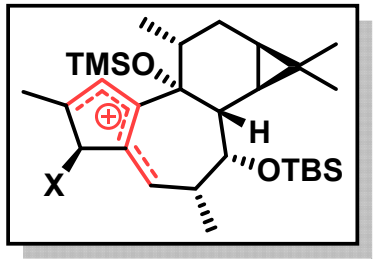
Catalyst	Additive	Solvent	T (˚C)	Concentration of Substrate (M)	Yield
$[RhCl(CO)_2]_2$	**-**	**xylenes**	**140**	**0.005**	**72%**
$[RhCl(CO)_2]_2$	-	xylenes	140	0.01	47%
$[RhCl(CO)_2]_2$	-	xylenes	140	0.05	37%
$[RhCl(CO)_2]_2$	dppp	dichloro-benzene	160	0.05	19%
$[RhCl(COD)]_2$	-	xylenes	140	0.05	26%
$[IrCl(BINAP)]_2$	-	xylenes	140	0.05	8%

Exploring the Pinacol Rearrangement





carbocation too stable

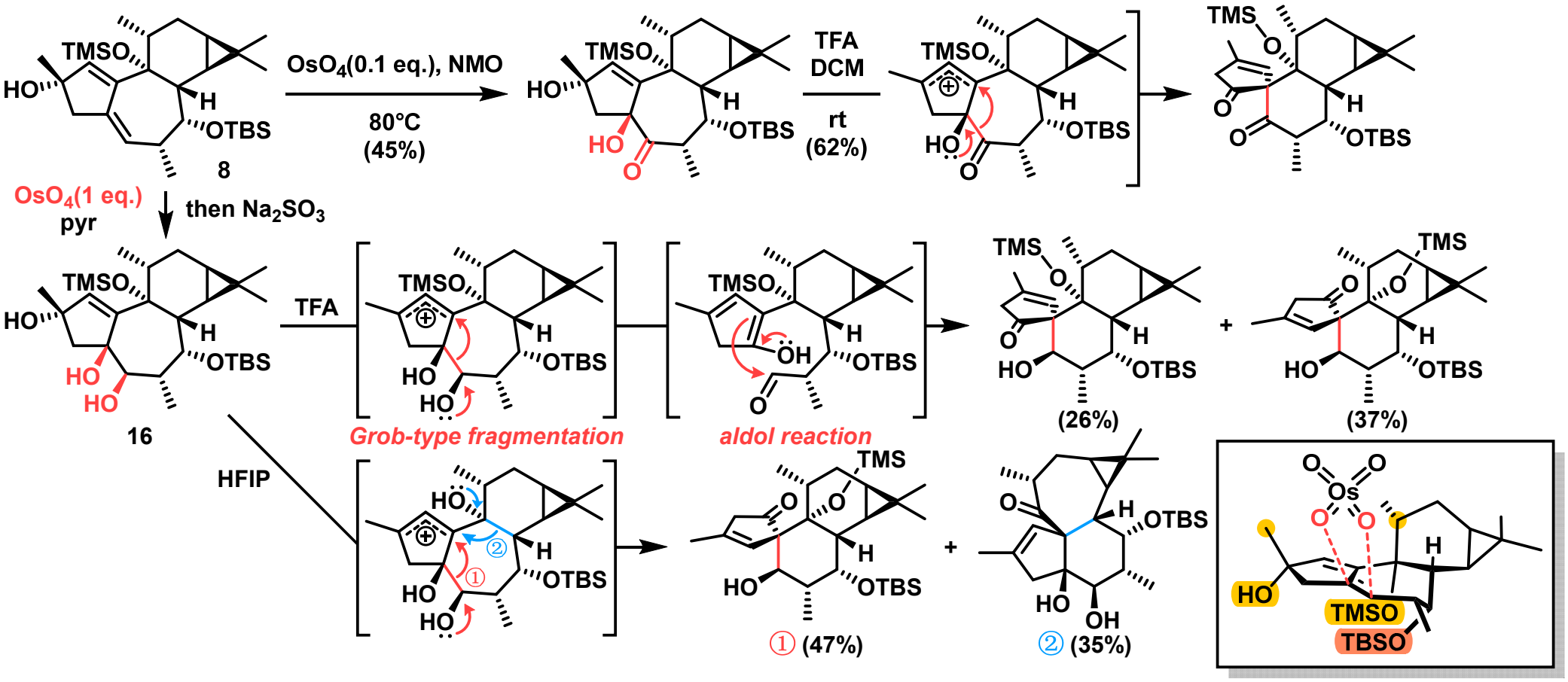


B3LYP/6-31G(d)

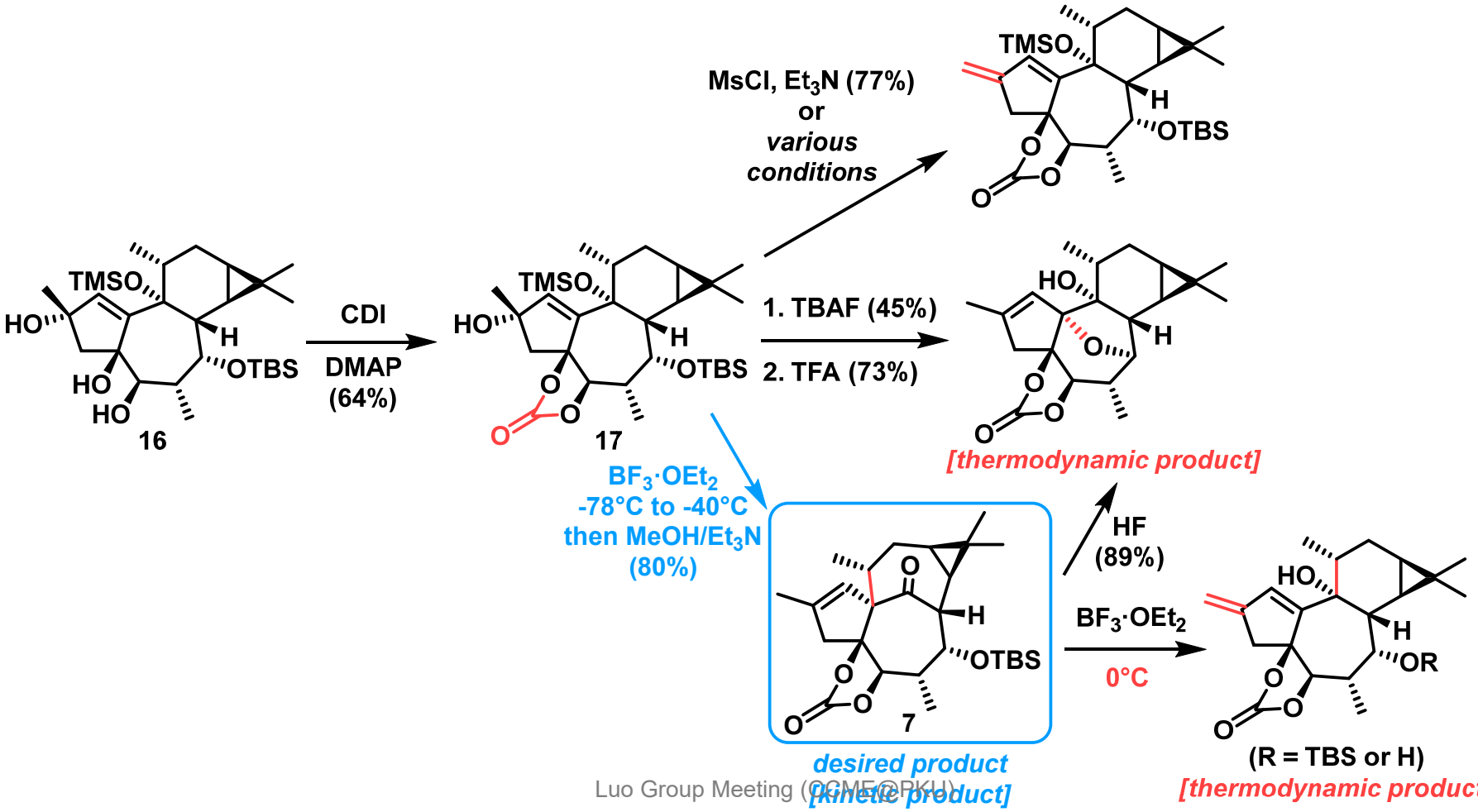
Dihedral = 85.37°

poor orbital overlap?

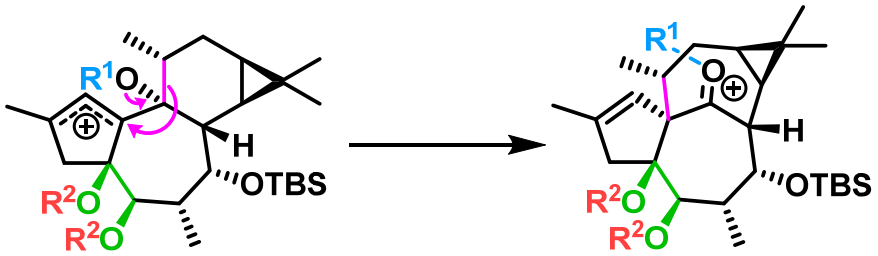
Exploring the Pinacol Rearrangement



Exploring the Pinacol Rearrangement



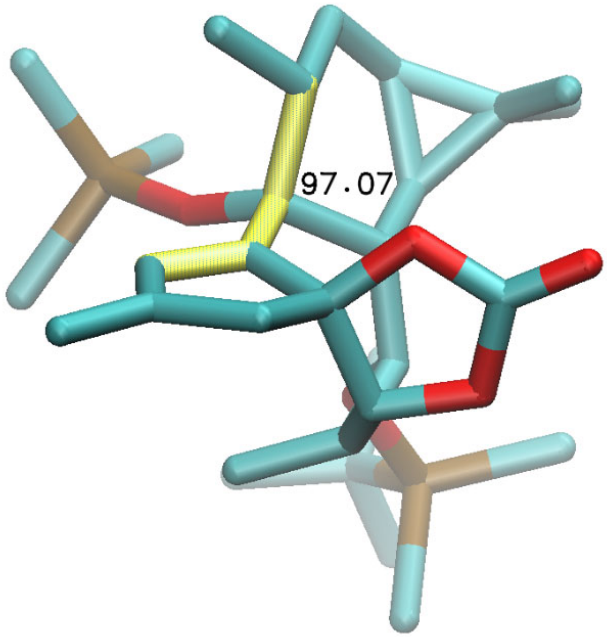
Computation Studies of the Pinacol Rearrangement



R^1	R^2	Conformation of O-C-C-O	ΔG (kcal/mol)[a]	$\Delta G^{\ddagger}$ (kcal/mol)[a]
TMS	**C=O**	**eclipsed**	**−7.0**	**4.9**
H	C=O	eclipsed	−2.3	6.8
TMS	H	gauche	1.7	13.8
TMS	H	eclipsed[b]	-3.2	5.0

[a] Calculated at M06-2X/6-31+G(d,p)//B3LYP/6-31G(d) level.
[b] The energy of substrate is 6.1 kcal/mol greater than the substrate at gauche conformation.

Computation Studies of the Pinacol Rearrangement



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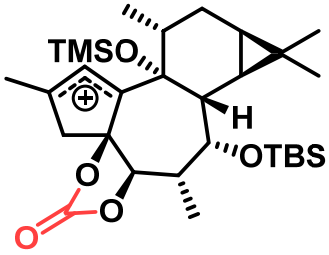

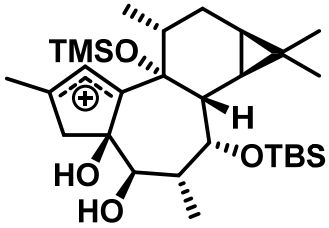

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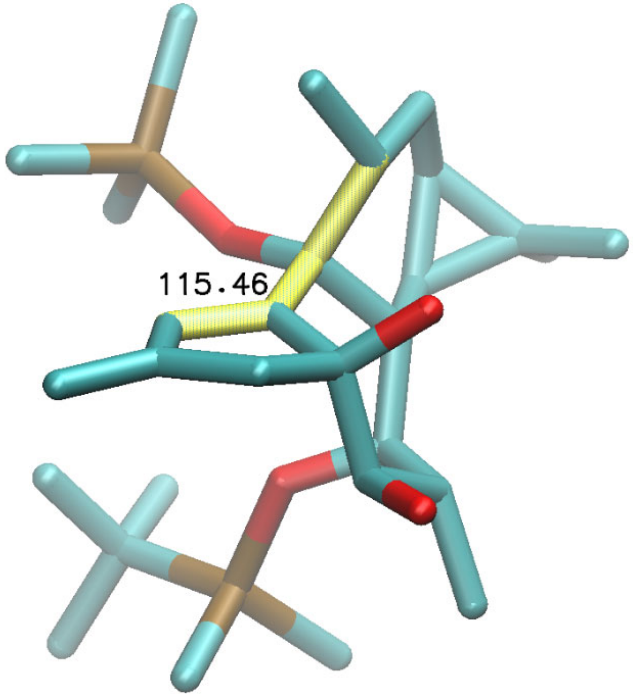


B3LYP/6-31G(d)

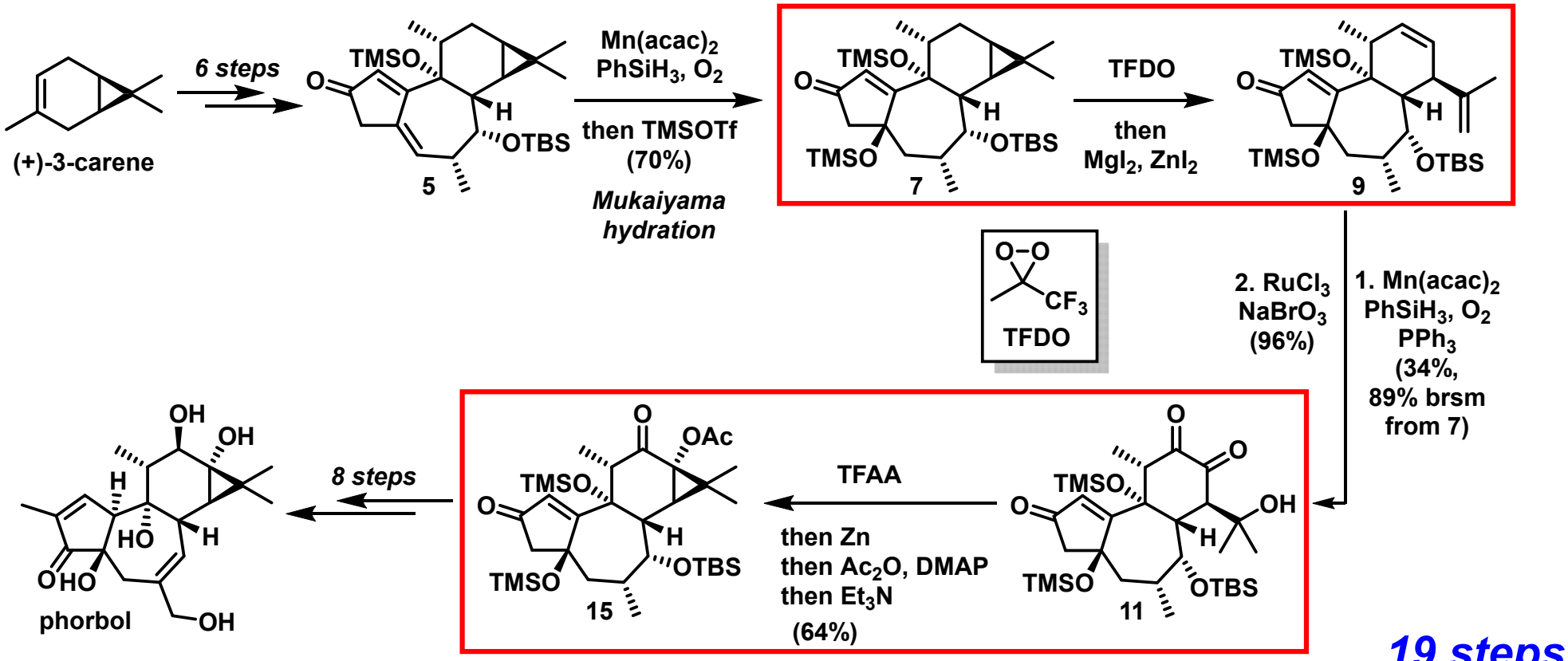
Dihedral = 97.07° *

B3LYP/6-31G(d)

Dihedral = 115.46° *

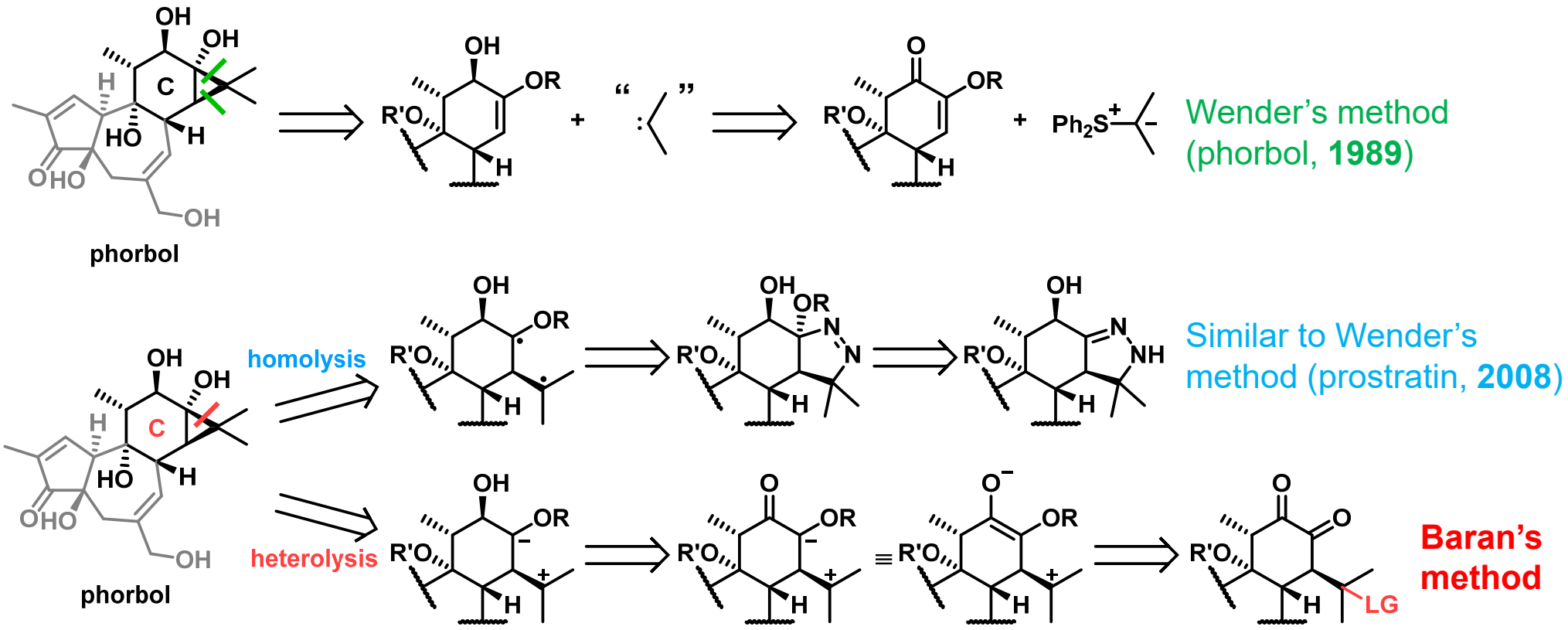
*from supporting information of
McKerrall, S. J.; Jørgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S. *J. Am. Chem. Soc.* **2014,** *136*, 5799-5810.

Baran's Total Synthesis of Phorbol (2016): Overview

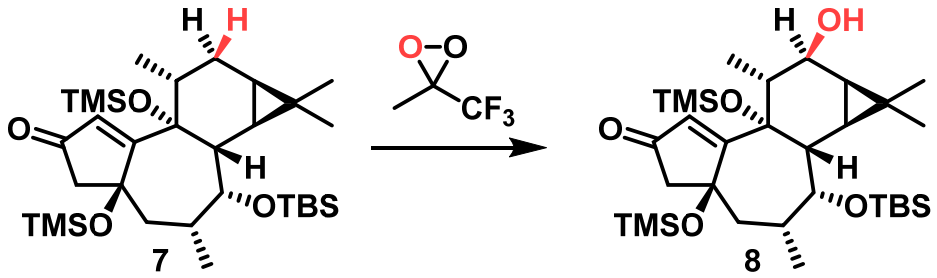


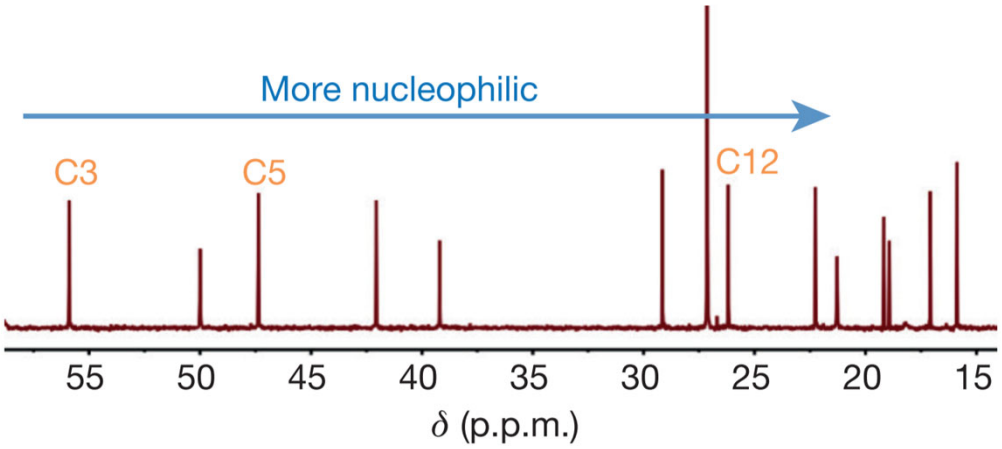
Kawamura, S.; Chu, H.; Felding, J.; Baran, P. S. *Nature* **2016,** *532*, 90-93.

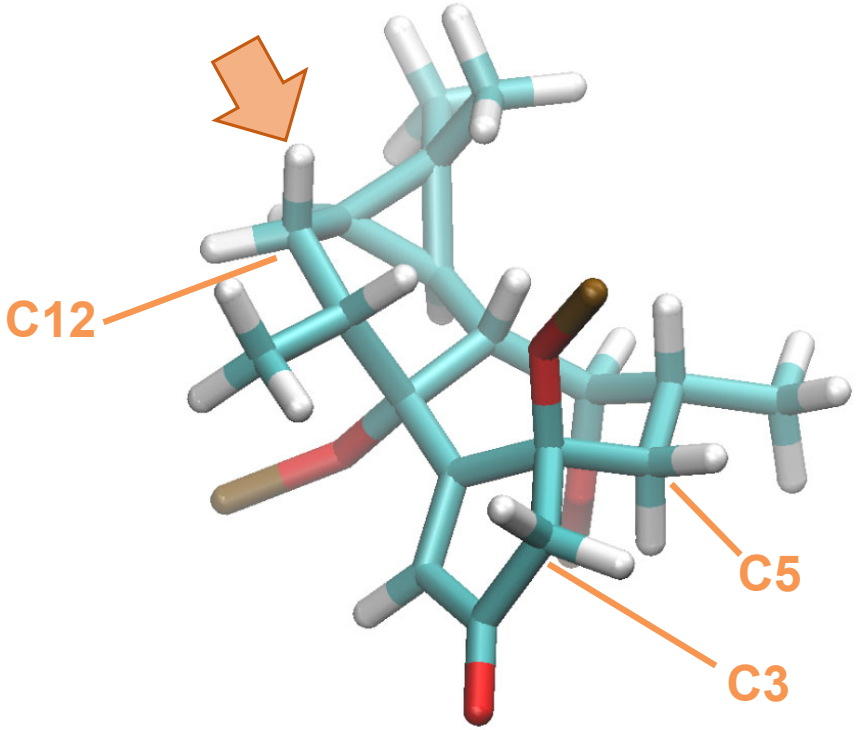
Retrosynthetic Analysis of Phorbol's C-Ring



Selective C(sp^3)-H Oxidation



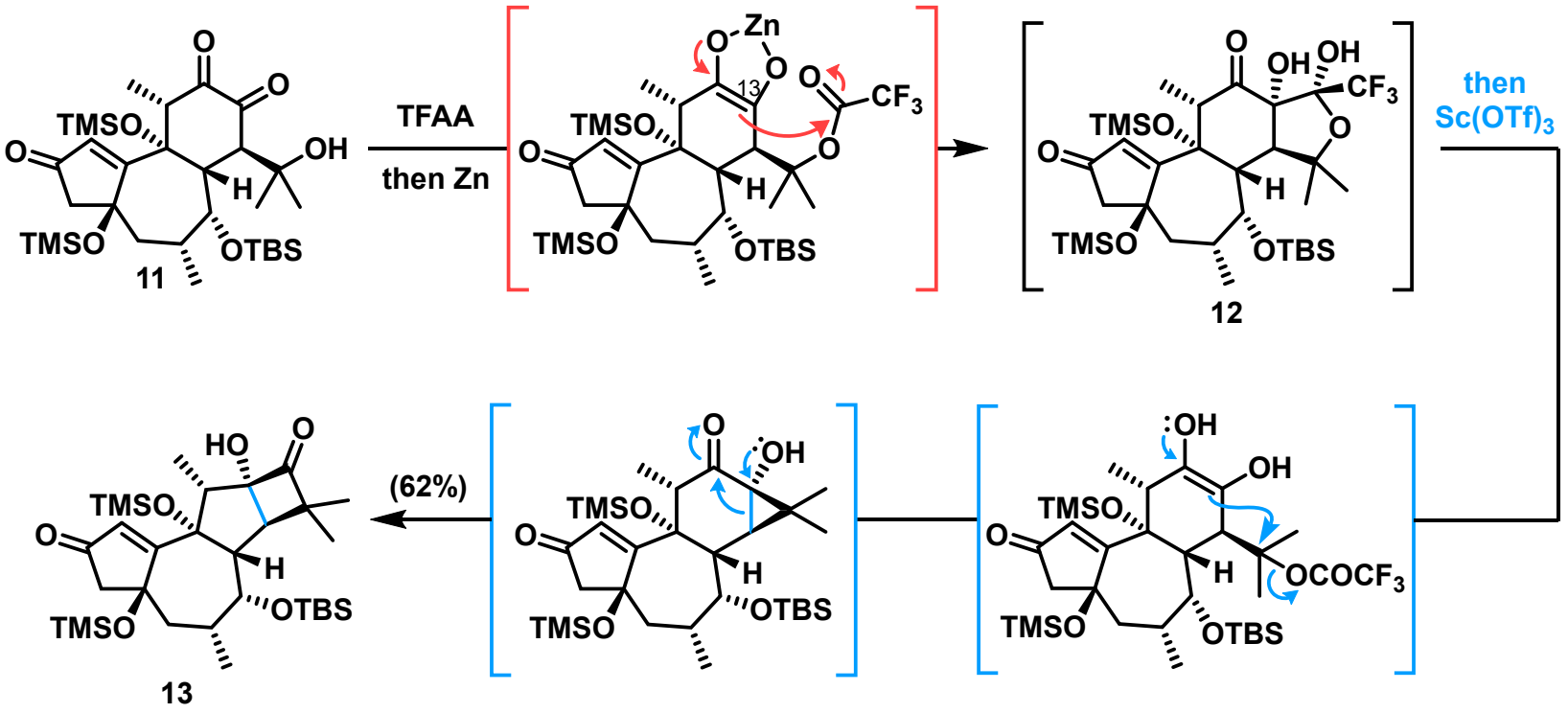




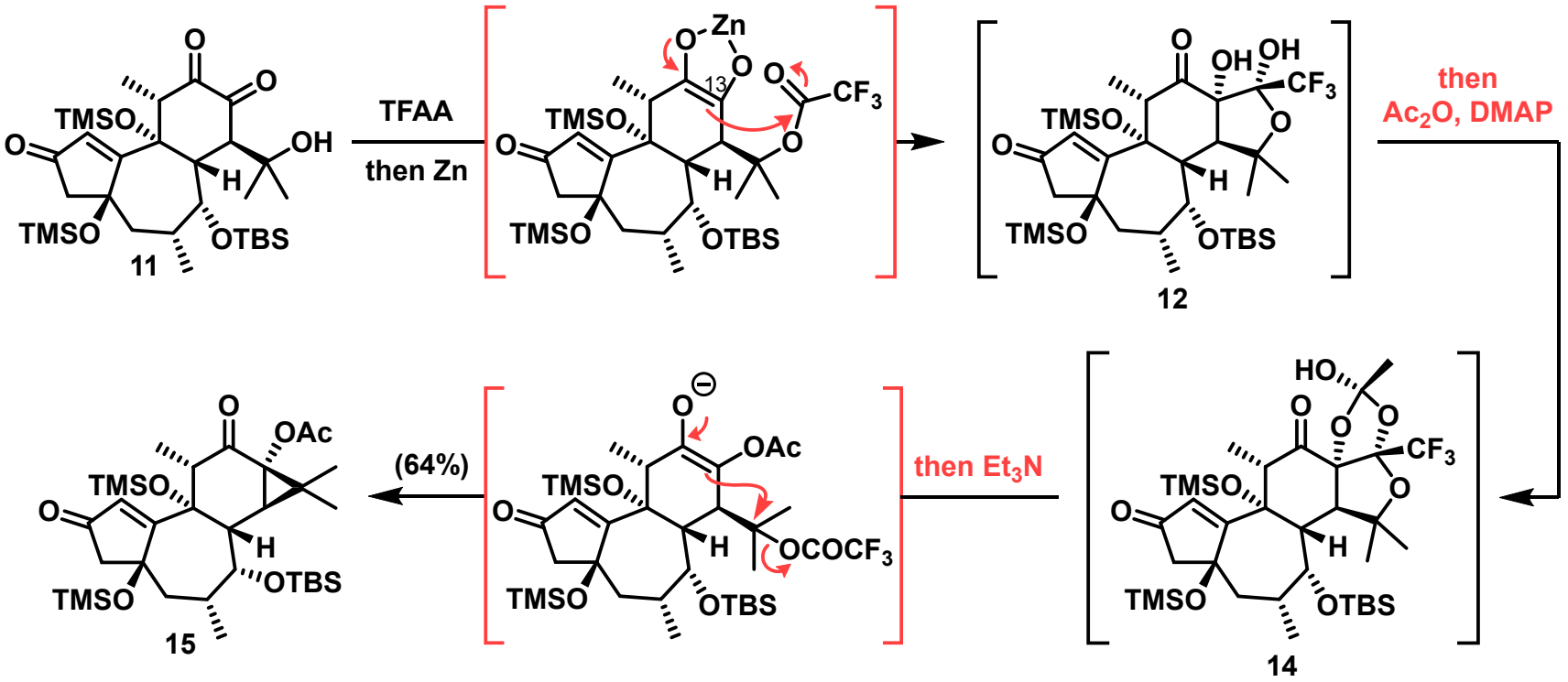
7

B3LYP/6-31g(d)

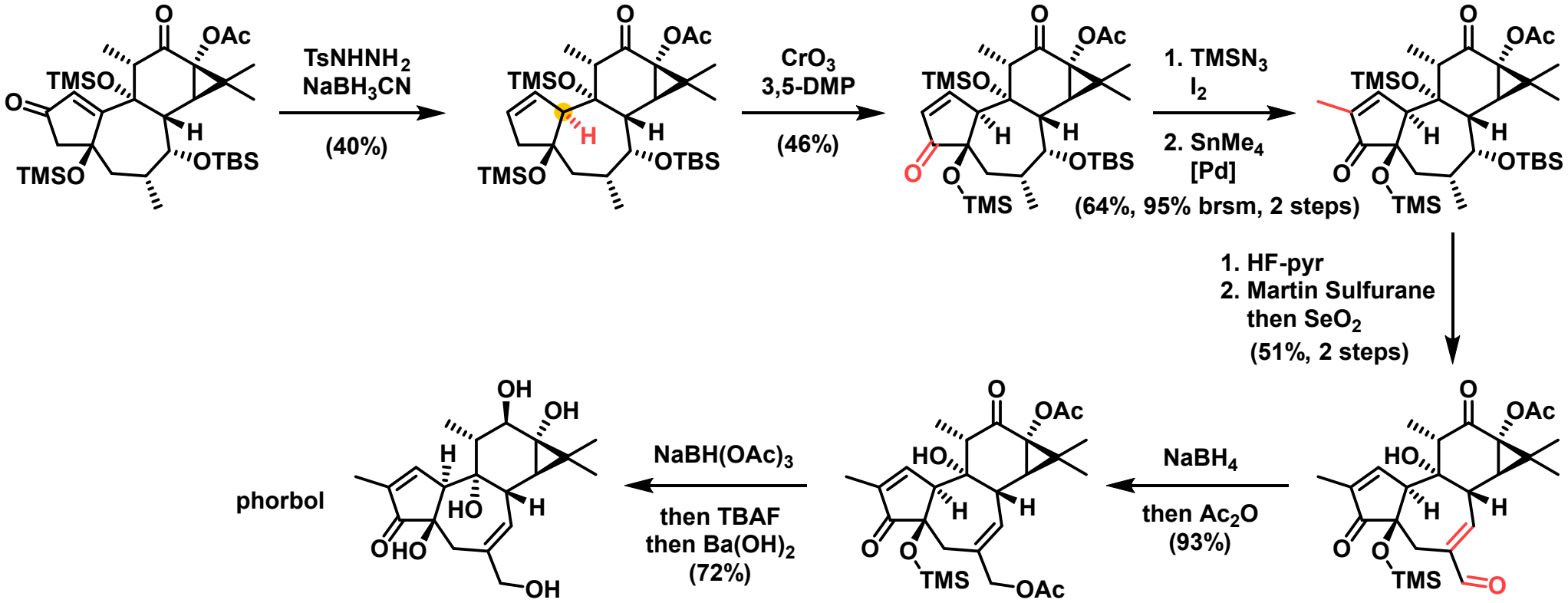
Intramolecular S_N2 Reaction: Enediol as a nucleophile



Intramolecular S_N2 Reaction: Enediol as a nucleophile



Final Steps


TsNHNH2
NaBH3CN
(40%)
CrO3
3,5-DMP
(46%)
1. TMSN3
I2
2. SnMe4
[Pd]
(64%, 95% brsm, 2 steps)
1. HF-pyr
2. Martin Sulfurane
then SeO2
(51%, 2 steps)
NaBH4
then Ac2O
(93%)
NaBH(OAc)3
then TBAF
then Ba(OH)2
(72%)
phorbol

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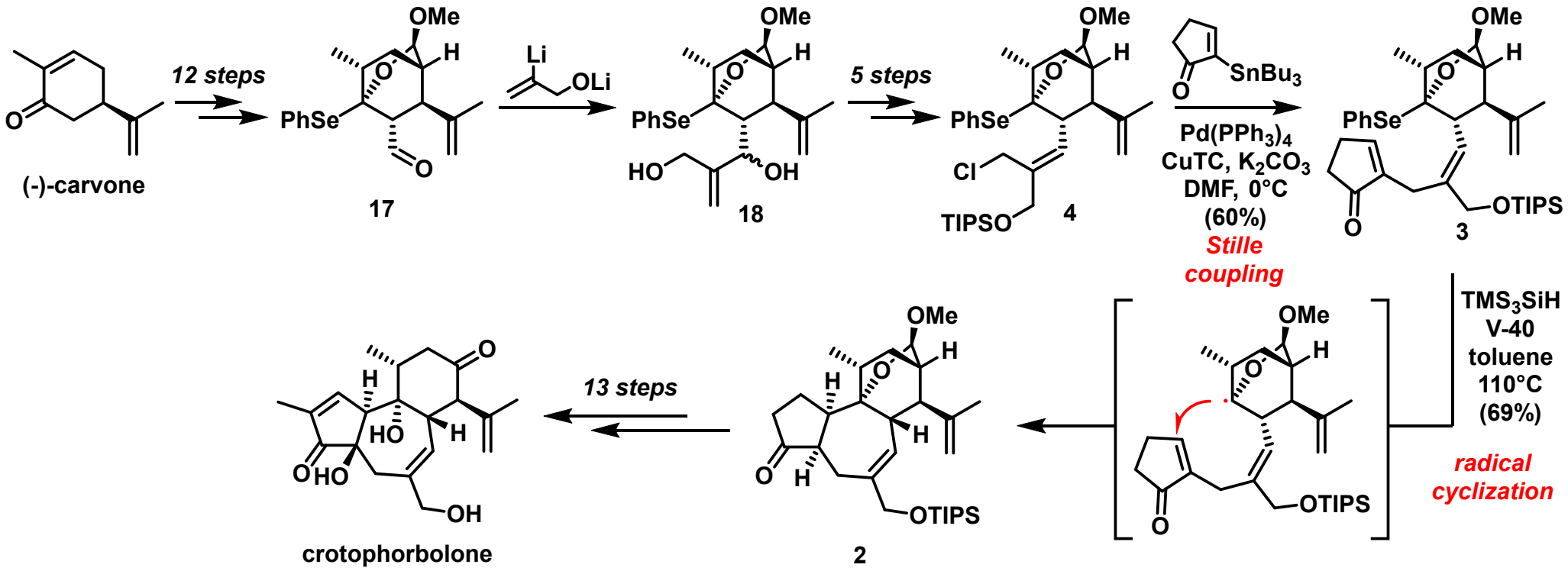
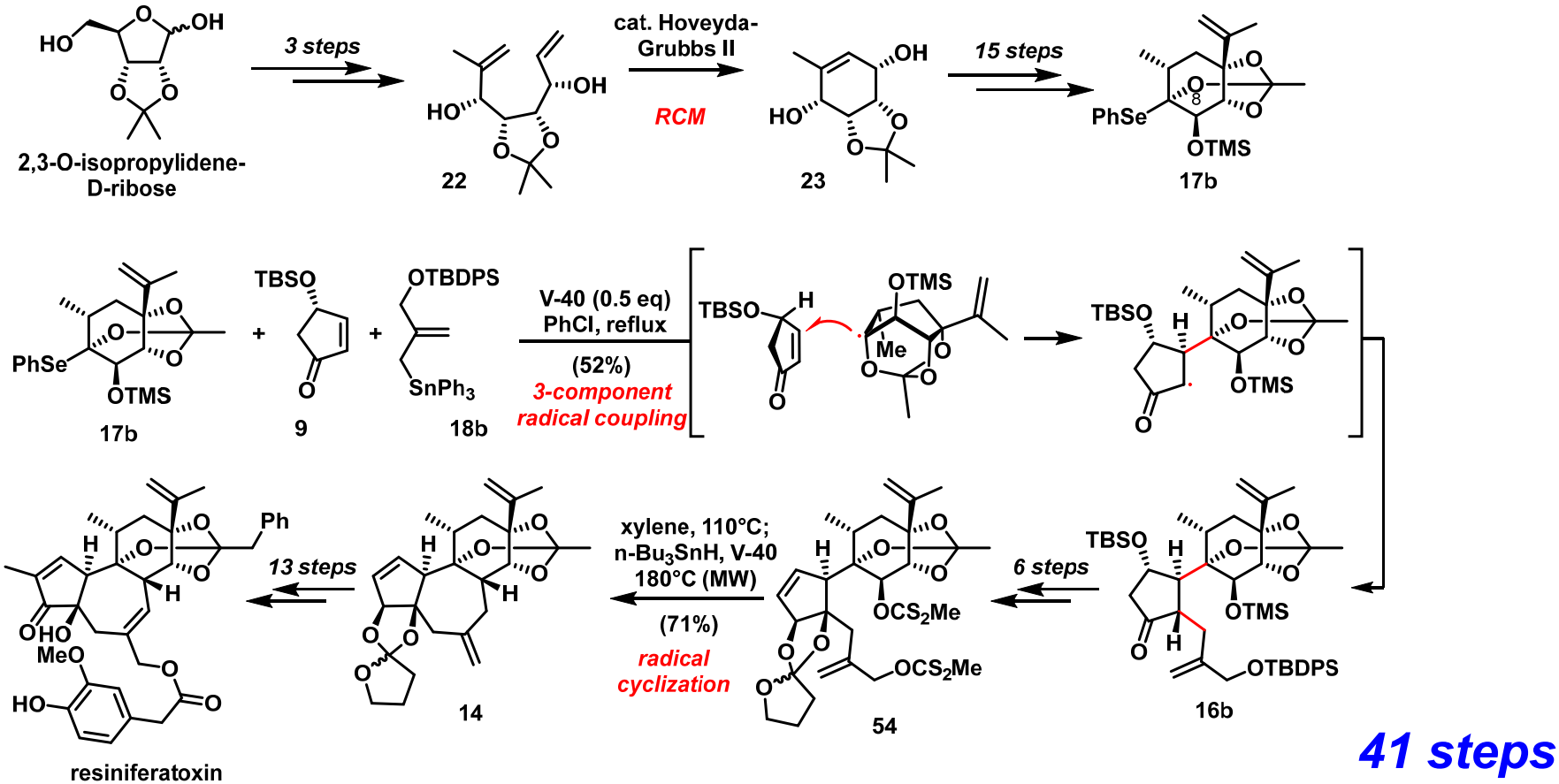
Inoue's Total Synthesis of Crotophorbolone (2015)



33 steps

Asaba, T.; Katoh, Y.; Urabe, D.; Inoue, M. *Angew. Chem. Int. Ed.* **2015,** *54*, 14457-14461.

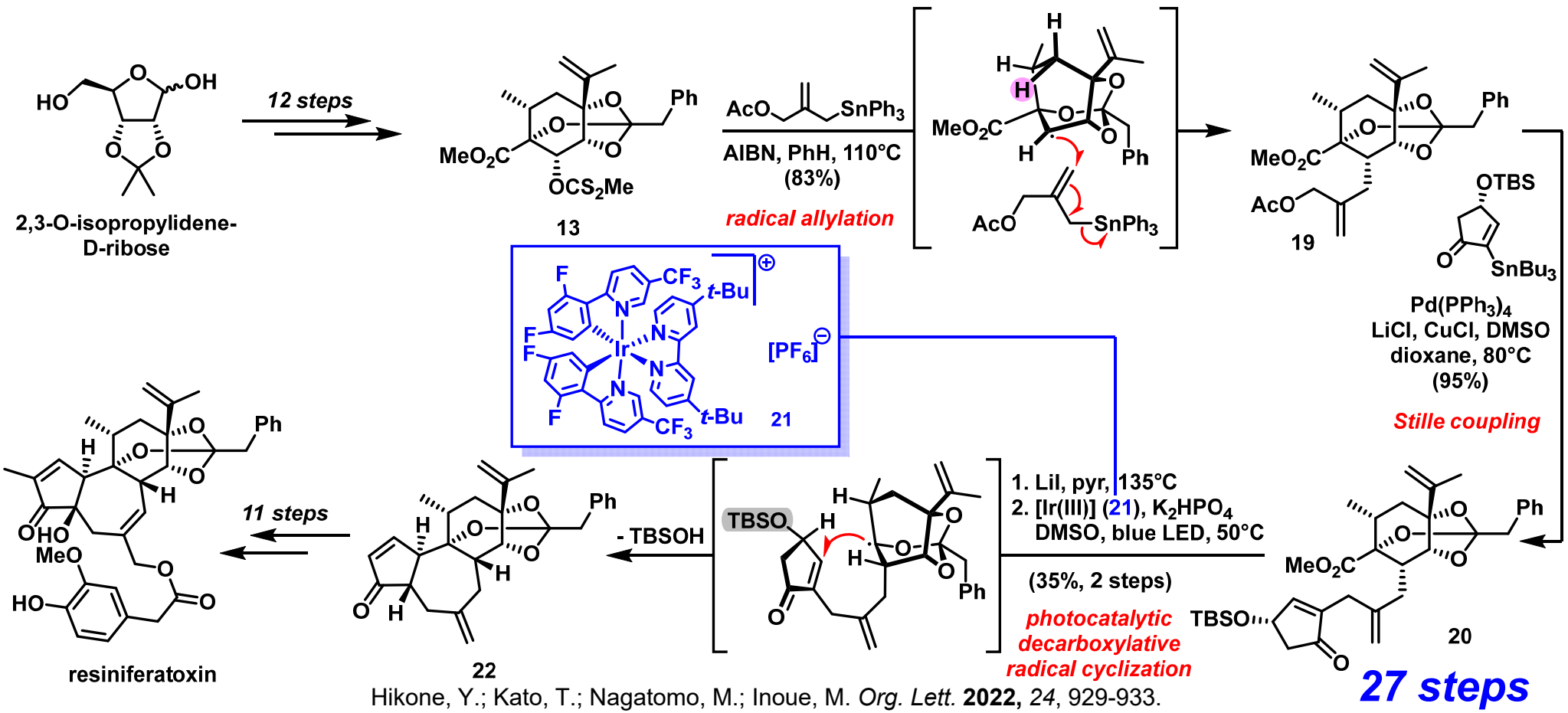
Inoue's Total Synthesis of Resiniferatoxin (2017)



41 steps

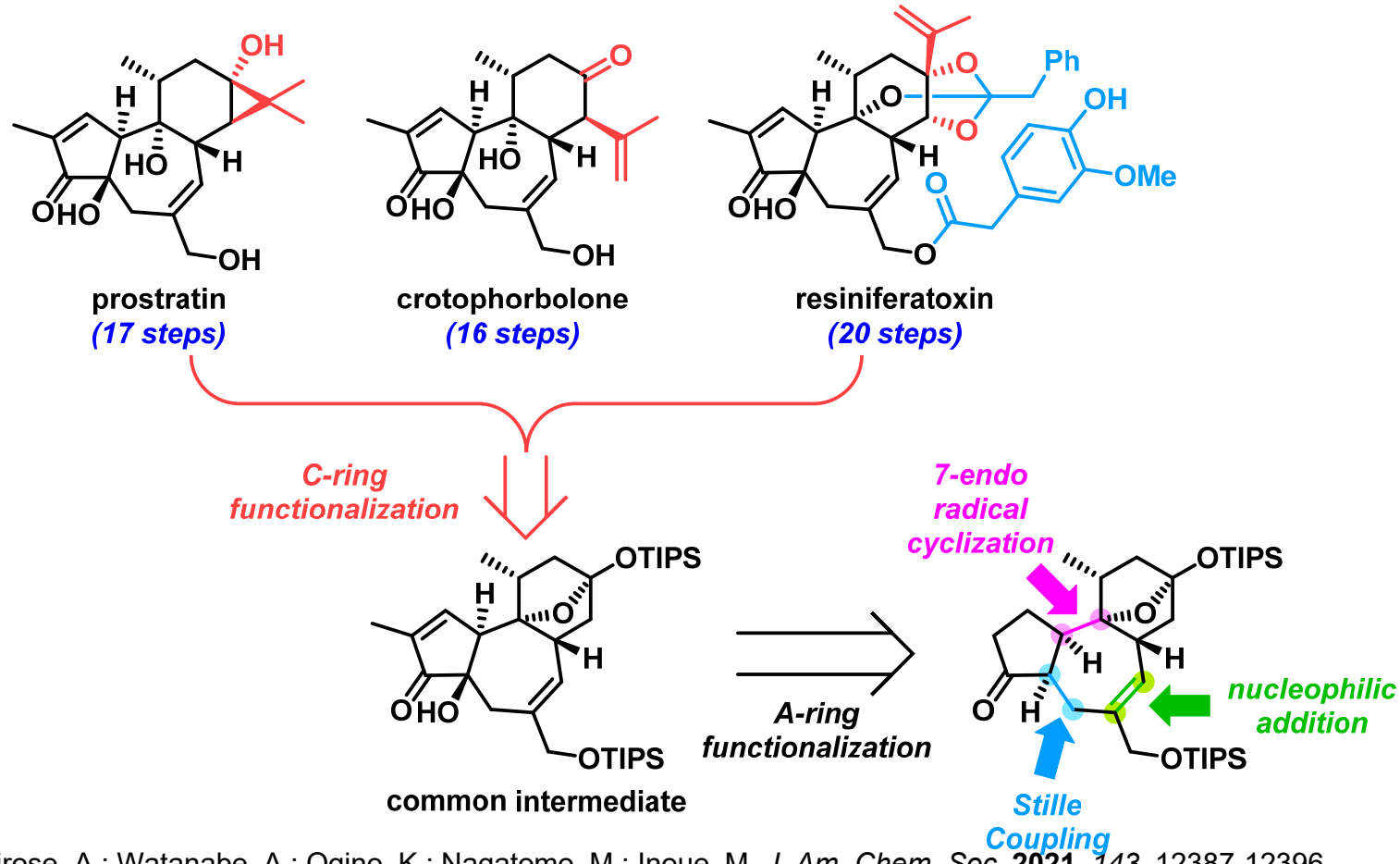
Hashimoto, S.; Katoh, S.-i.; Kato, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2017,** *139*, 16420-16429.

Inoue's Total Synthesis of Resiniferatoxin (2022)



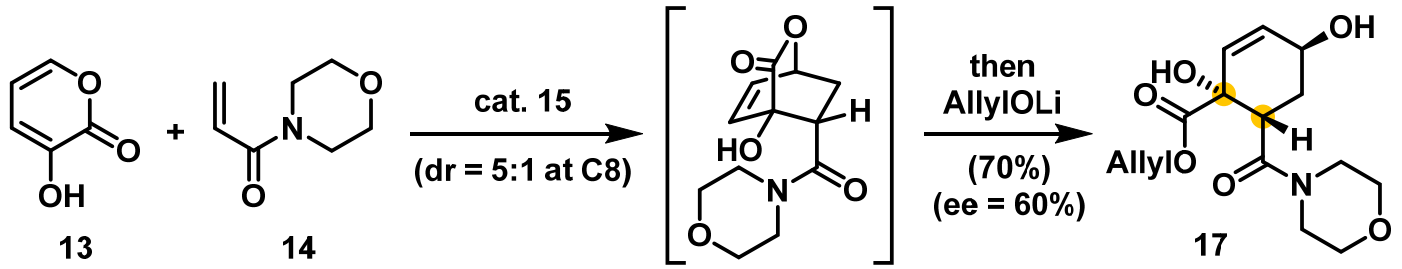
Hikone, Y.; Kato, T.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2022,** *24*, 929-933.

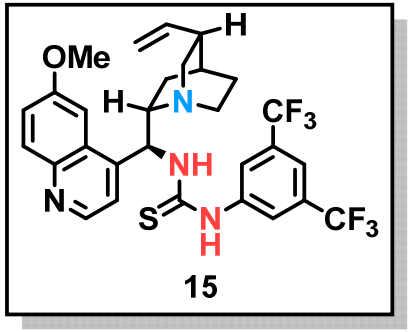
Inoue's Unified Total Synthesis of Crotophorbolone, Prostratin and Resiniferatoxin (2021): Overview

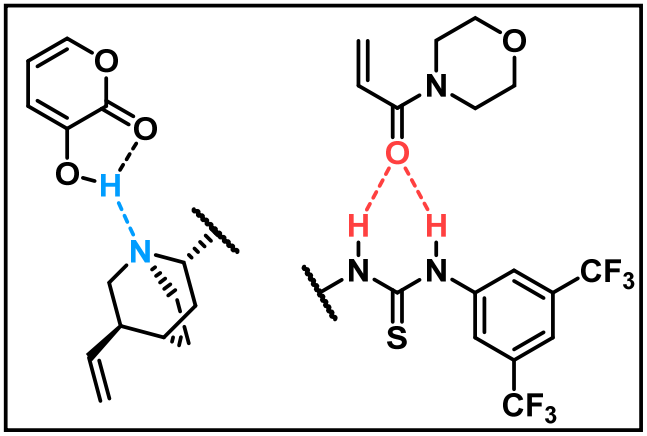


Hirose, A.; Watanabe, A.; Ogino, K.; Nagatomo, M.; Inoue, M. *J. Am. Chem. Soc.* **2021,** *143*, 12387-12396.

Organocatalytic Asymmetric Diels-Alder Reaction

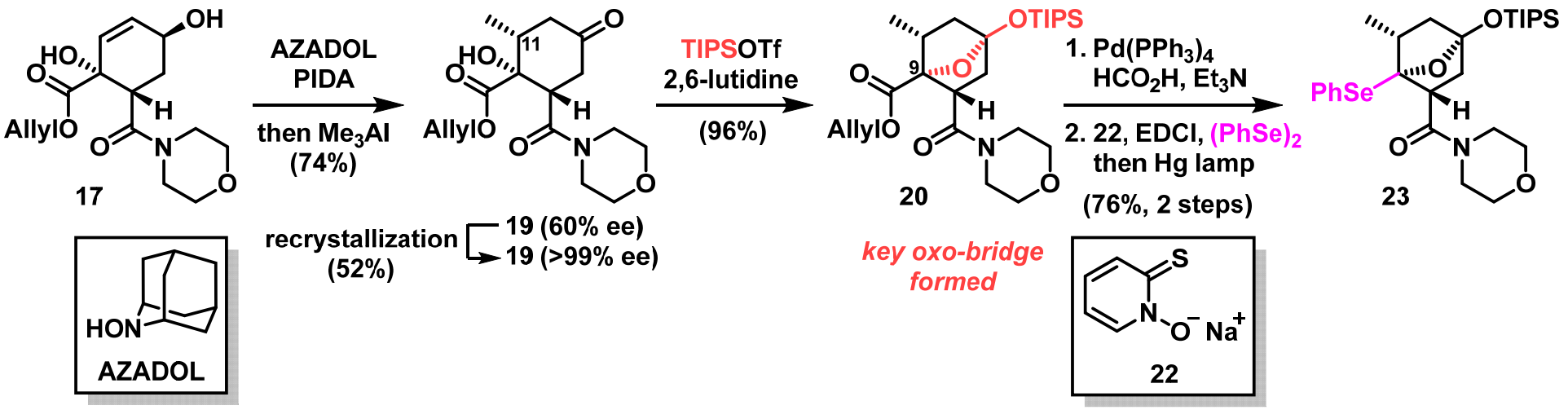






Bifunctional organocatalyst

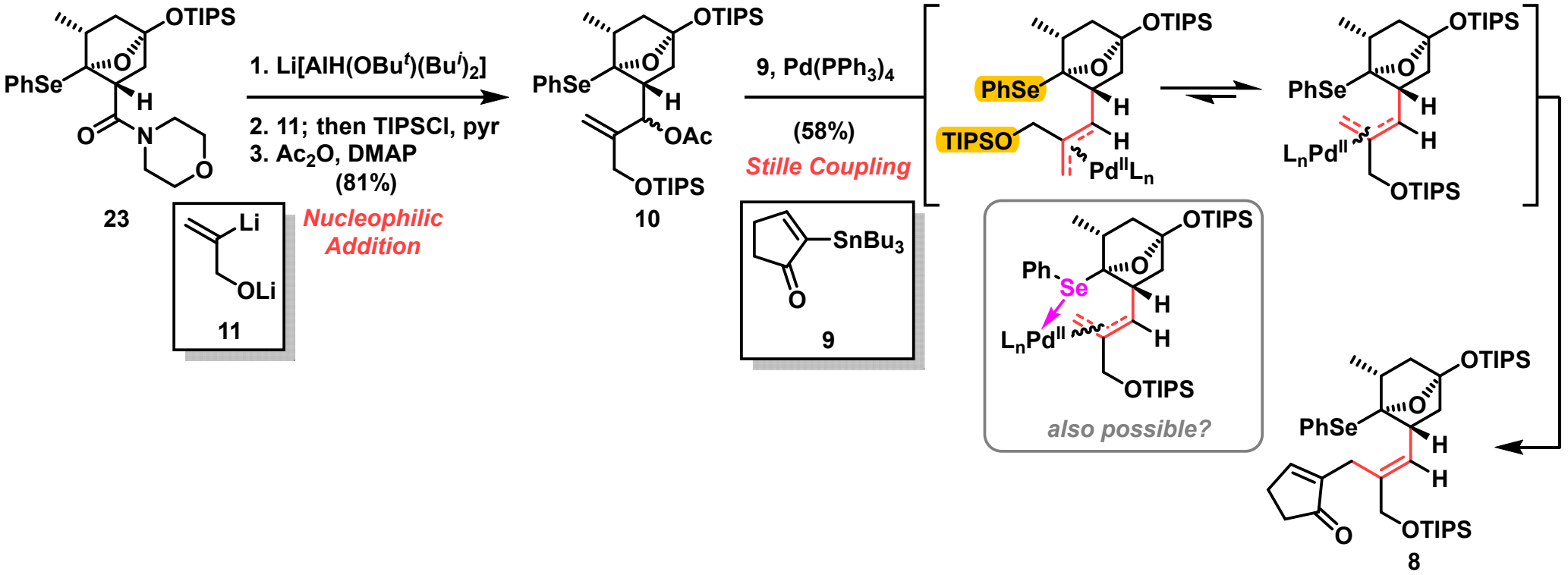
C-Ring Pre-Functionalization



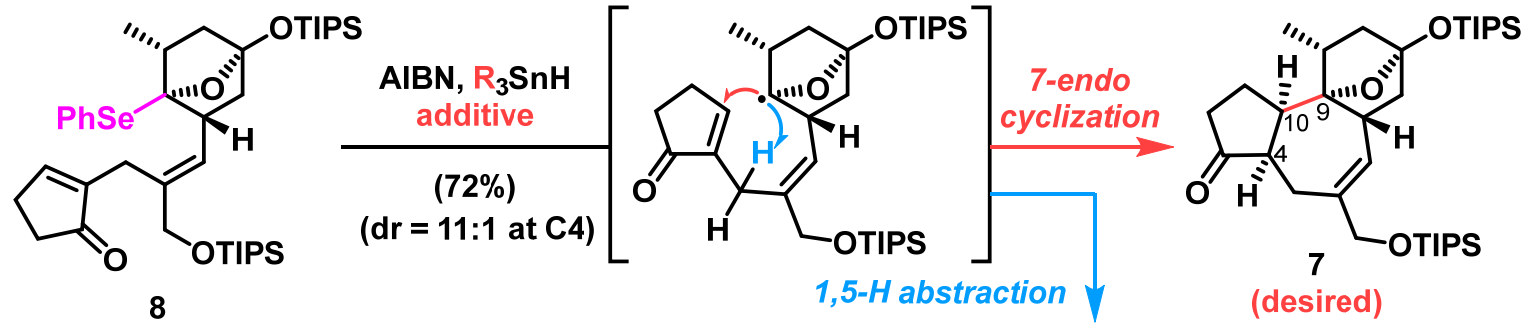
Oxo-bridge can:

1. **Protect** the **-OH** group at C9
2. **Maintain** the **configuration** of C9

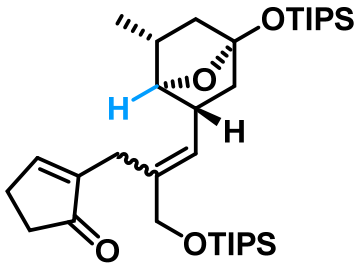
Connecting A-Ring and C-Ring



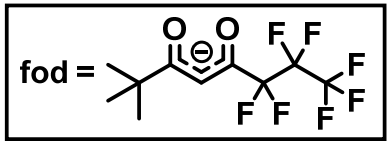
B-Ring Construction: Bridgehead Radical *7-endo* Cyclization



Additive	R	Yield of 7	Yield of 24
none	*n*-Bu	22%	11%
$Eu(fod)_3$	**Ph**	**72%**	**-**



24
(undesired)



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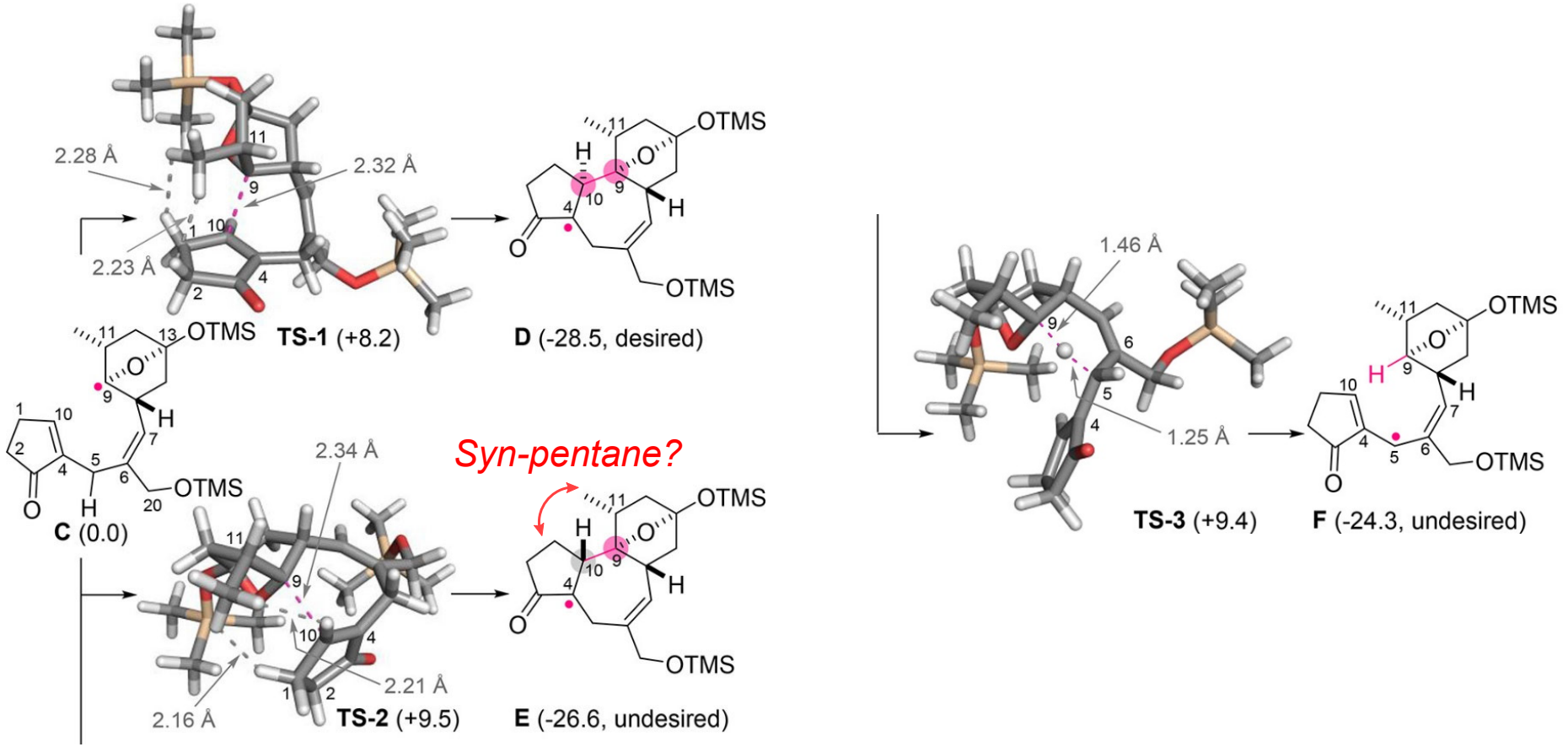
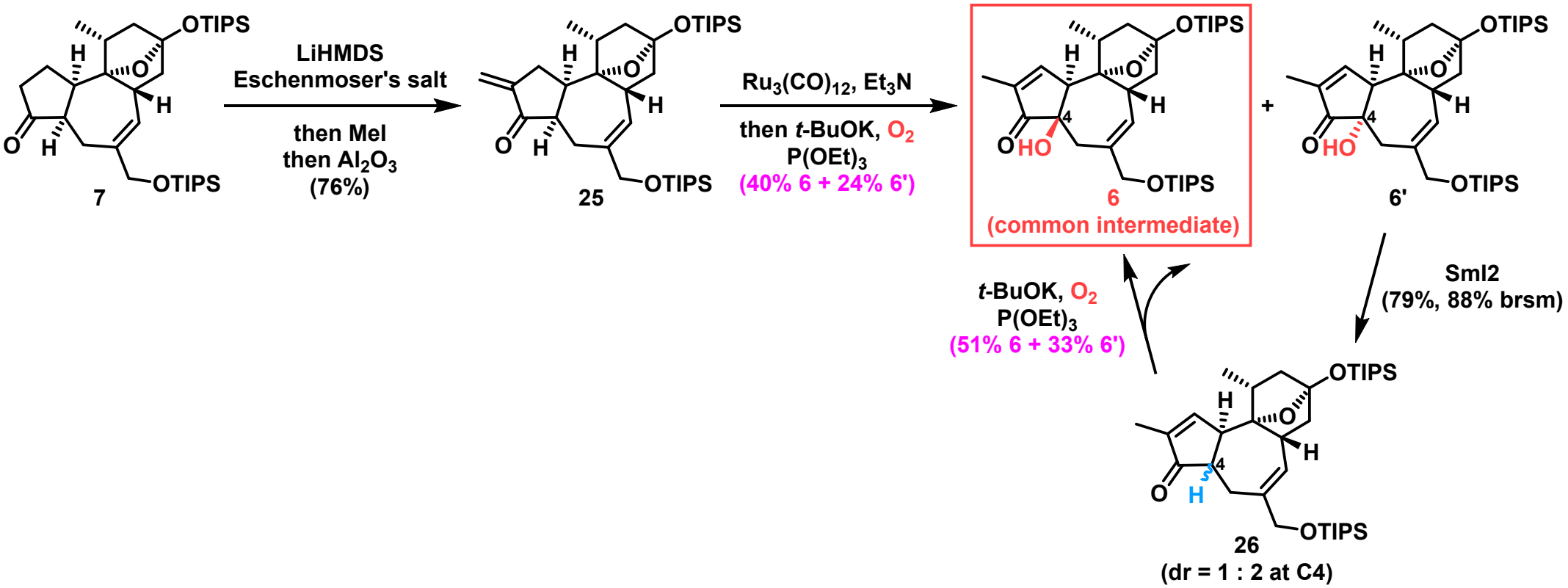
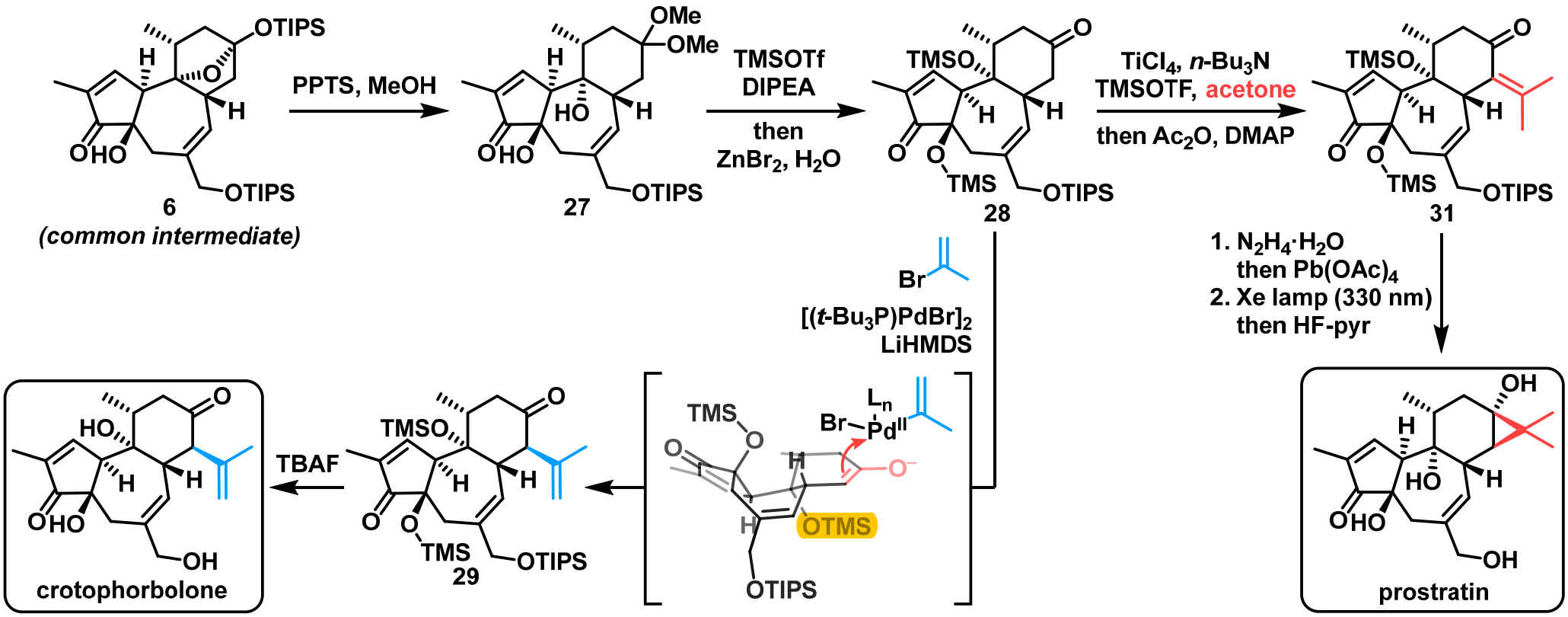


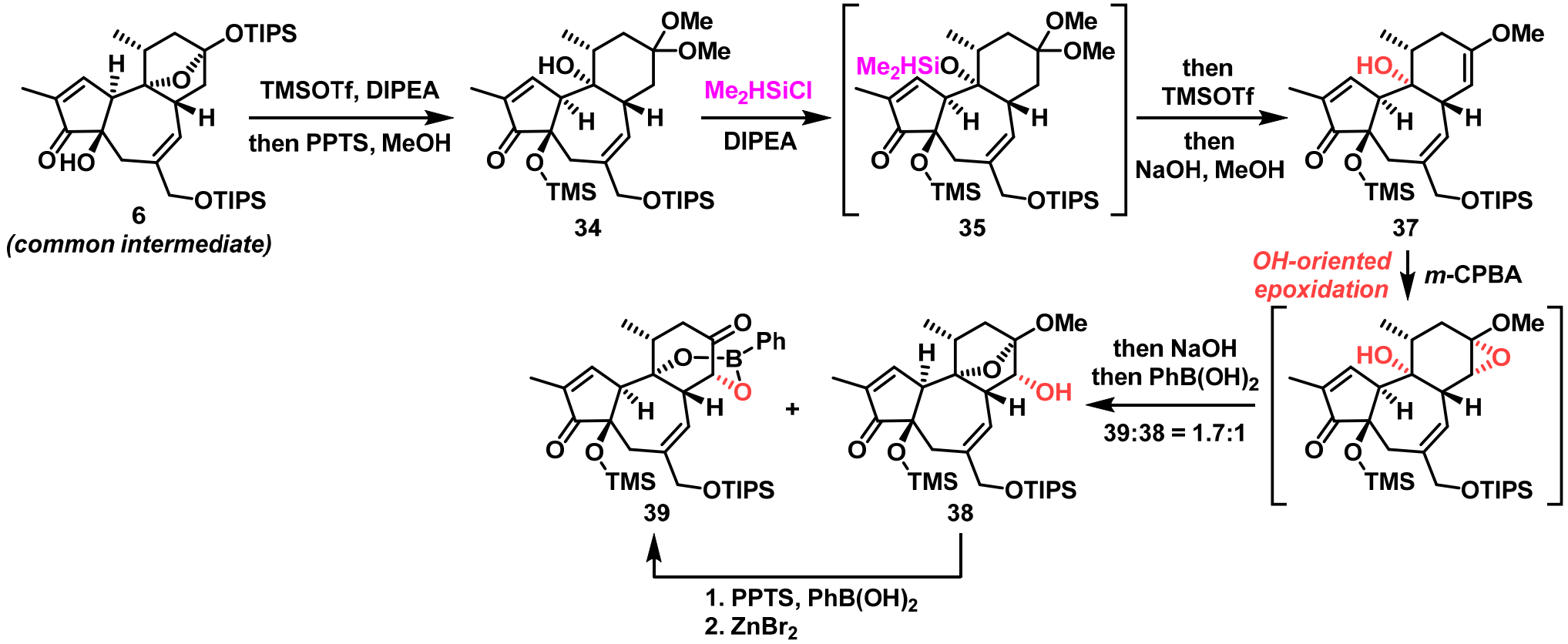
A-Ring Functionalization



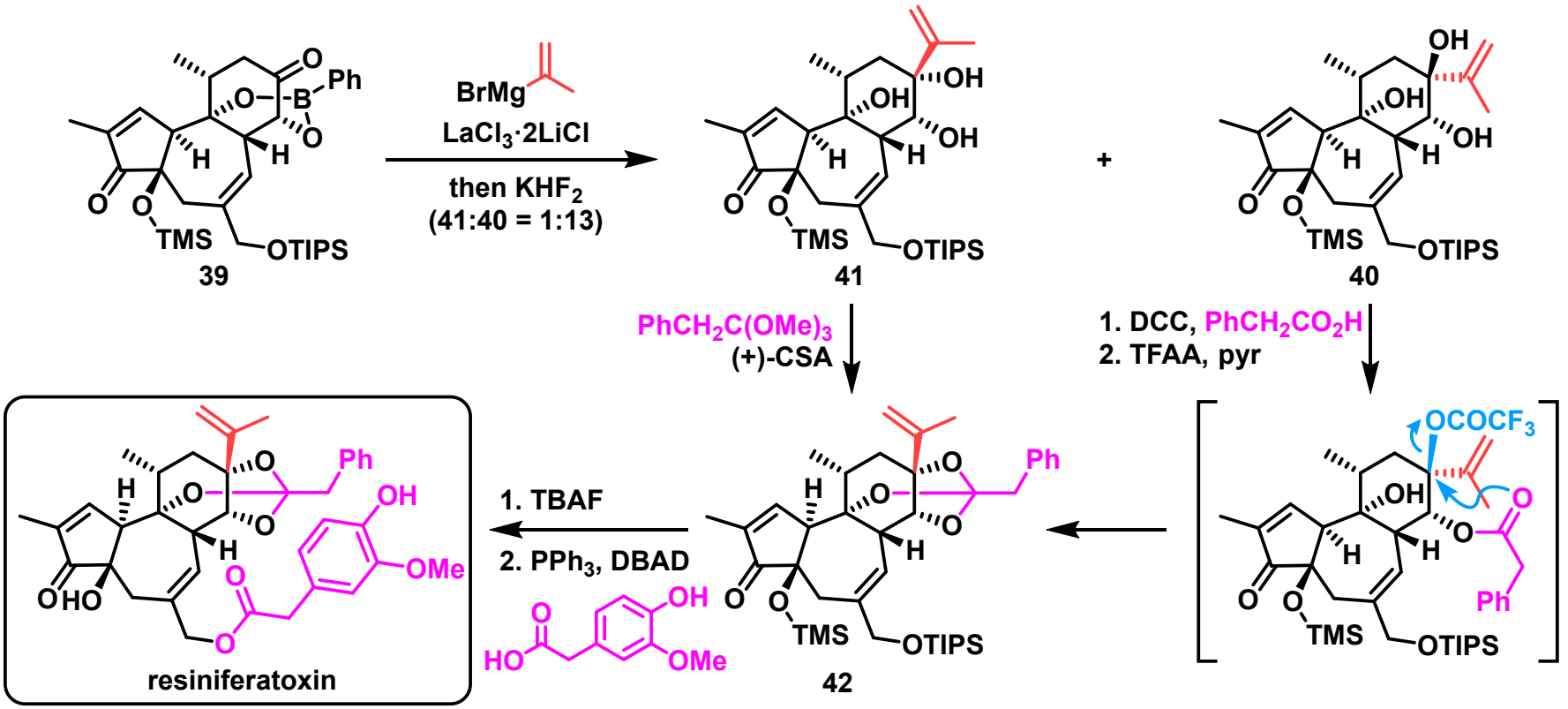
Conversion of 6 to Crotophorbolone and Prostratin



Conversion of 6 to Resiniferatoxin



Conversion of 6 to Resiniferatoxin (Continued)



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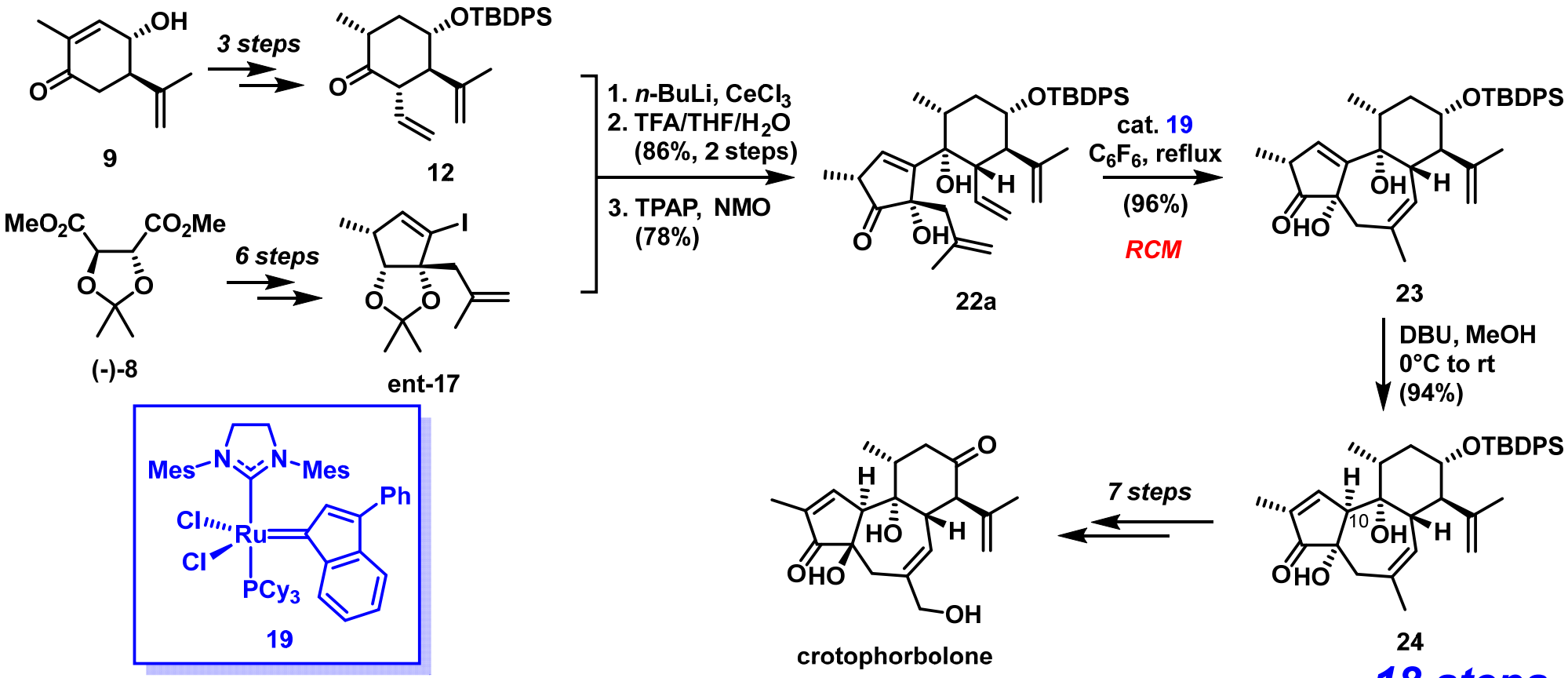
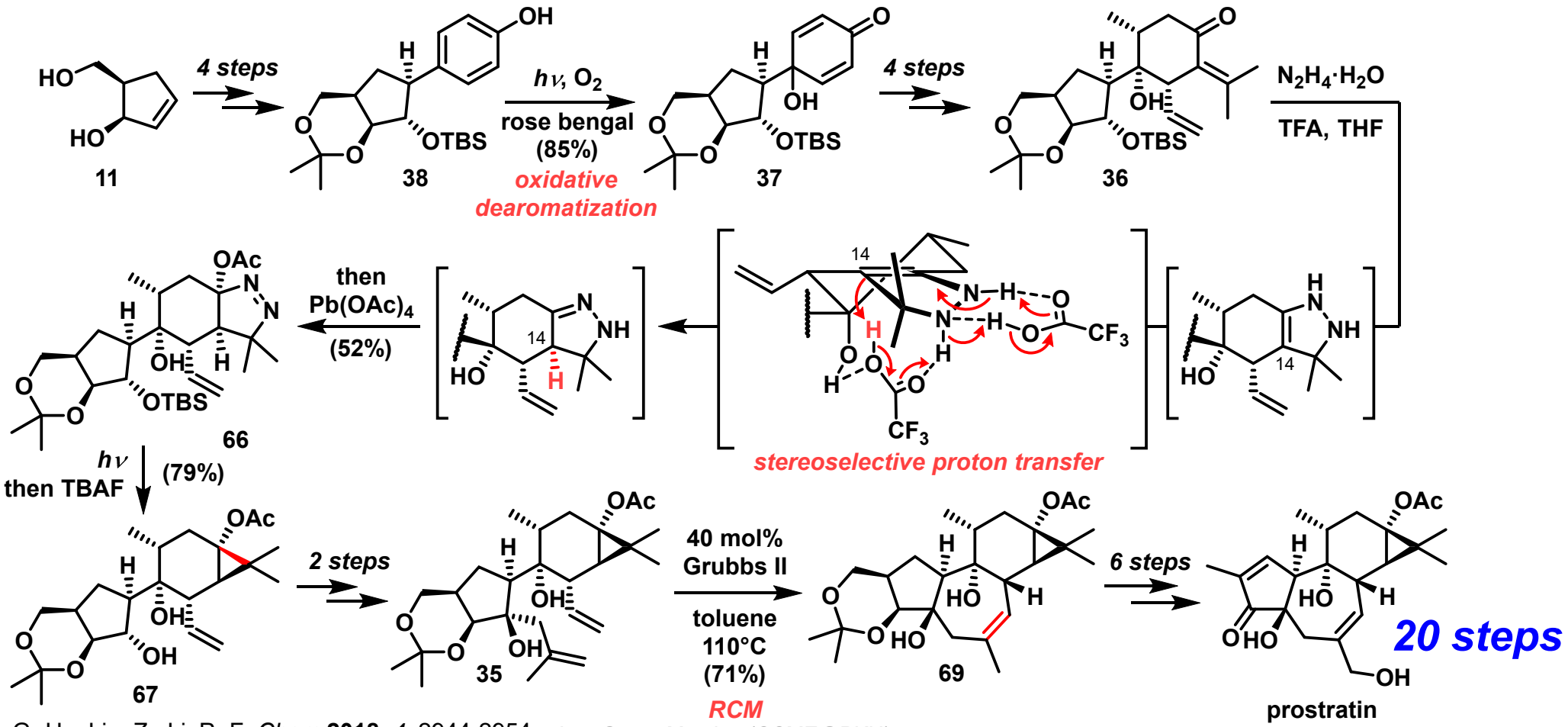
Liu's Total Synthesis of Crotophorbolone (2020)



Yu, T.-Z.; Sun, Y.; Tu, C.-H.; Chen, T.; Fu, S.-M.; Liu, B. *Chem. Sci.* **2020,** *11*, 7177-7181.

Li's Total Synthesis of Prostratin (2020)



Tong, G.-H.; Liu, Z.; Li, P.-F. *Chem* **2018,** *4*, 2944-2954.

Tong, G.-H.; Ding, Z.-W.; Liu, Z.; Ding, Y.-S.; Xu, L.; Zhang, H.-L.; Li, P.-F. *J. Org. Chem.* **2020,** *85*, 4813-4837.

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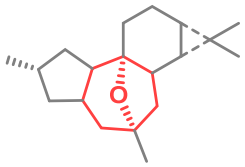
Conclusion



C-BC-ABC

- Wender's Total Synthesis of (±)-Phorbol (1989)
- Wender's Formal Total Synthesis of (±)-Phorbol (1990)
- Wender's Formal Total Synthesis of Phorbol (1997)
- Wender's Total Synthesis of Resiniferatoxin (1997)

B-BC-ABC

- Cha's Formal Total Synthesis of Phorbol (2001)

Ingenol's B-ring Various construction

- Winkler's Total Synthesis of (±)-Ingenol (2002)
- Tanino's Total Synthesis of (±)-Ingenol (2003)
- Kigoshi's Formal Total Synthesis of Ingenol (2004)
- Wood's Total Synthesis of Ingenol (2004)
- Wender's Semisynthesis of Prostratin (from Phorbol or Crotophorbolone) (2008)

Baran's efficient total synthesis

- Baran's Total Synthesis of Ingenol (2013)
- Baran's Total Synthesis of Phorbol (2016)

Inoue's radical coupling-based total synthesis

- Inoue's Total Synthesis of Crotophorbolone (2015)
- Inoue's Total Synthesis of Resiniferatoxin (2017)
- Inoue's Total Synthesis of Resiniferatoxin (2022)
- Inoue's Unified Total Synthesis of Crotophorbolone, Prostratin and Resiniferatoxin (2021)

RCM B-ring construction

- Liu's Total Synthesis of Crotophorbolone (2020)
- Li's Total Synthesis of Prostratin (2020)