

Prof. Ang Li

Literature Seminar 2017. 10. 28

Kosuke Minagawa (D2)

Contents

1. Introduction

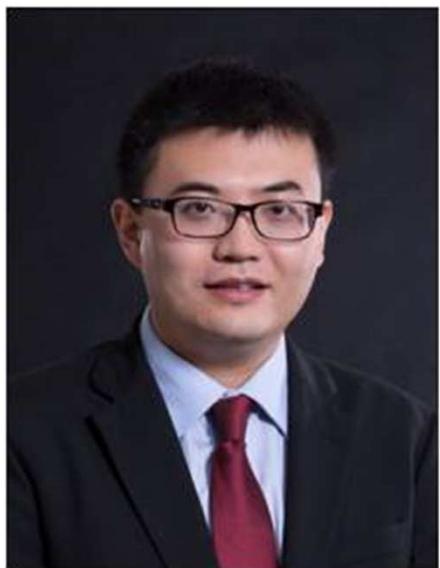
-Prof. Ang Li

-Synthetic Methodology

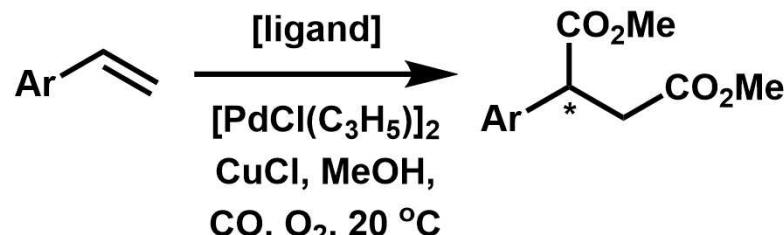
2. Total synthesis of aspidodasycarpine, Ionicerine and Lanciferine (2016)

3. Total synthesis of longeraciniphyllin A (2017, main)

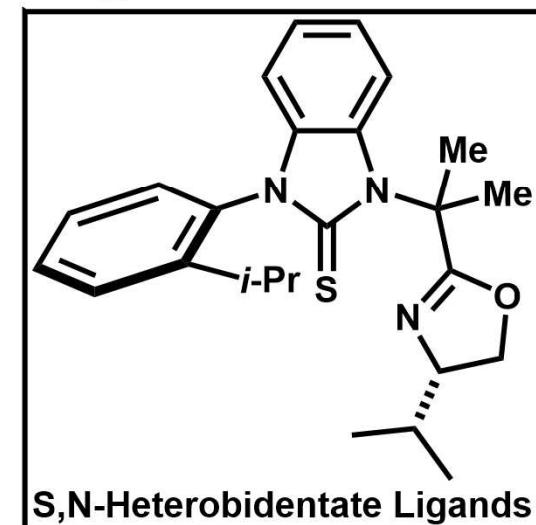
Prof. Ang Li



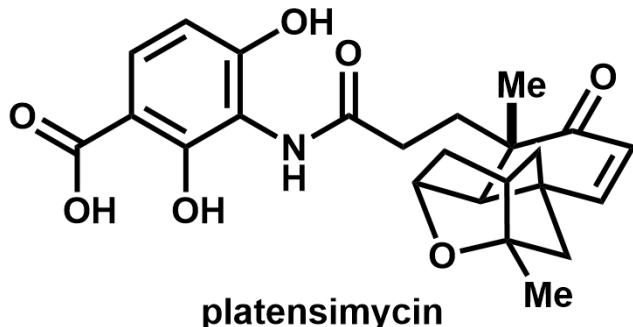
2000-2004: Peking University (B.Sc., Prof. Zhen Yang)



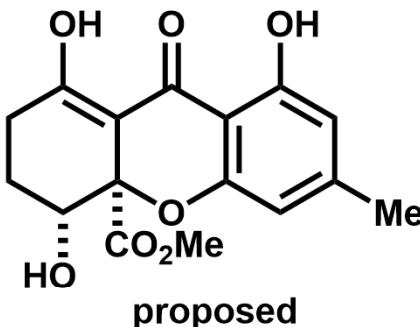
Organometallics 2007, 26, 4756.



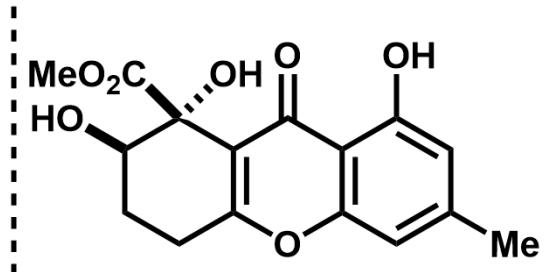
2004-2009: The Scripps Research Institute (Ph.D., Prof. K. C. Nicolaou)



Angew. Chem. Int. Ed. 2006, 45, 7086.



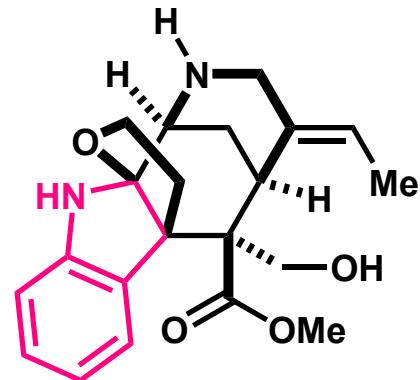
Angew. Chem. Int. Ed. 2008, 47, 6579 .6582



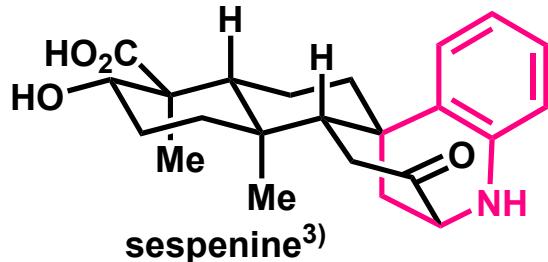
2009-2010: Institute of Chemical and Engineering Sciences
(Research fellow, Prof. K. C. Nicolaou)

2010-present: Shanghai Institute of Organic Chemistry (Professor)

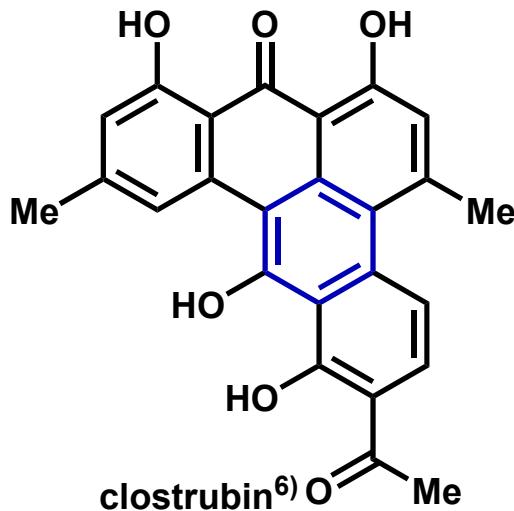
Natural Products Synthesized by Ang Li group



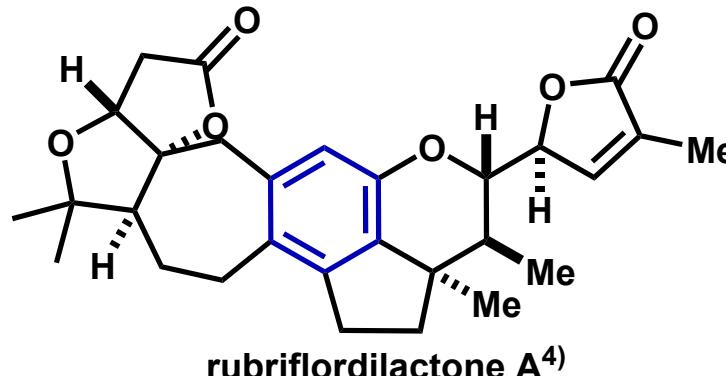
aspidodasycarpine¹⁾



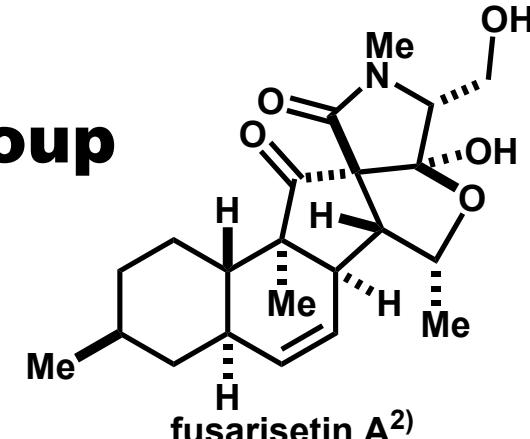
sespenine³⁾



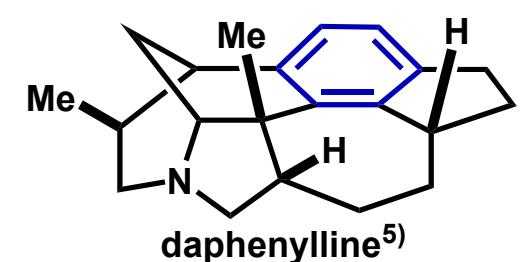
clostrubin⁶⁾



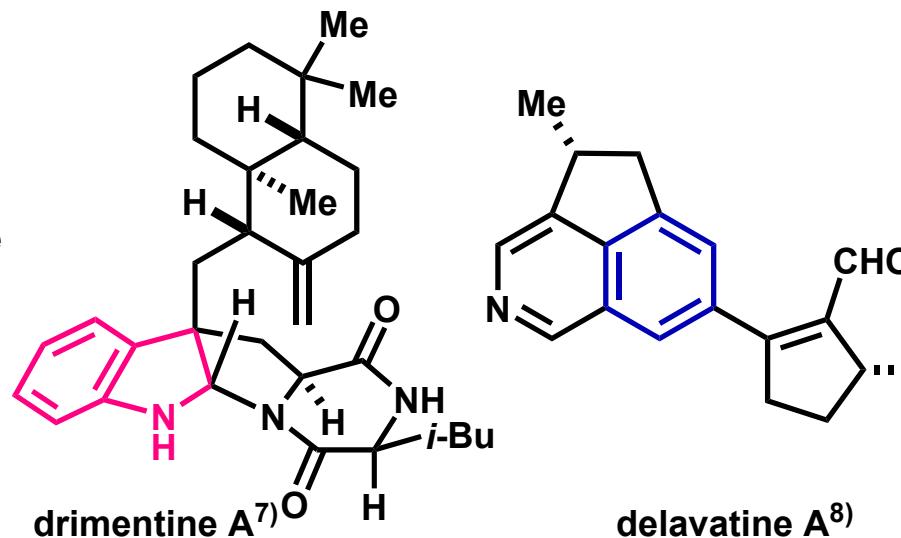
rubriflordanilactone A⁴⁾



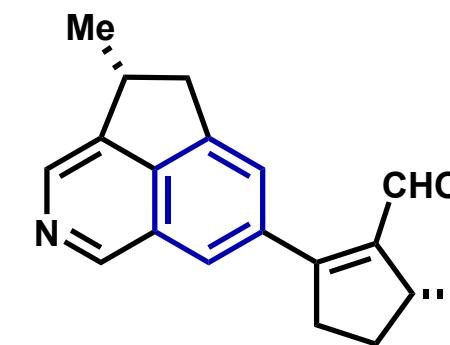
fusarisetin A²⁾



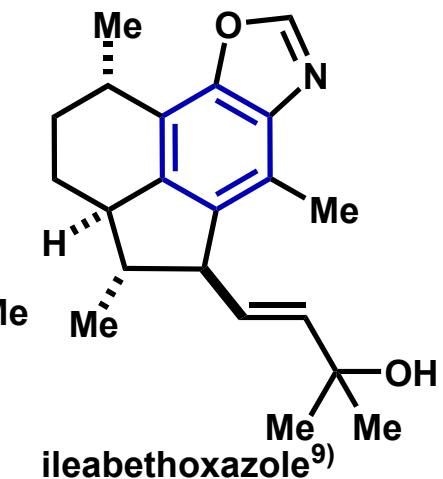
daphenylline⁵⁾



drimentine A⁷⁾



delavatine A⁸⁾



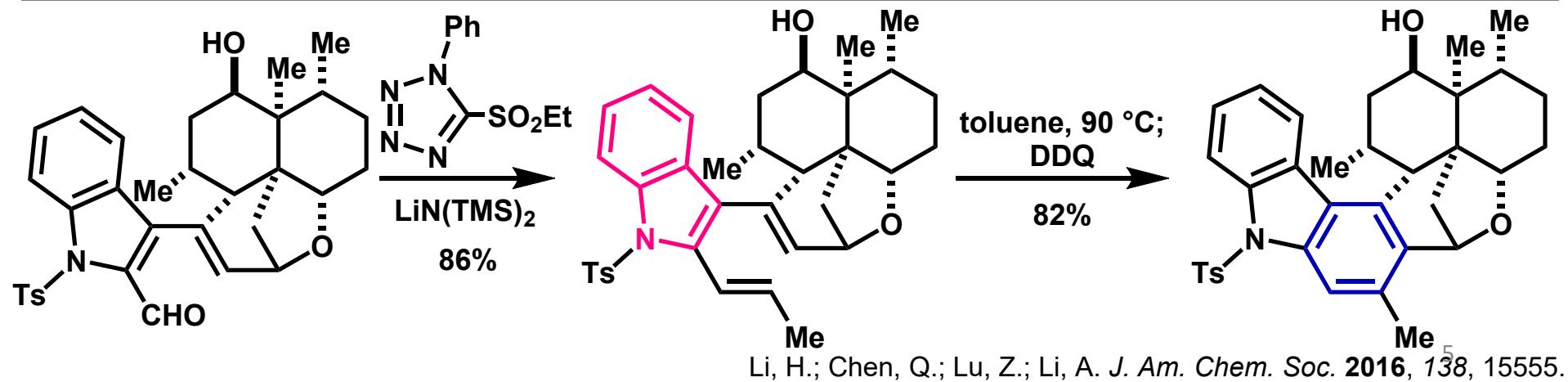
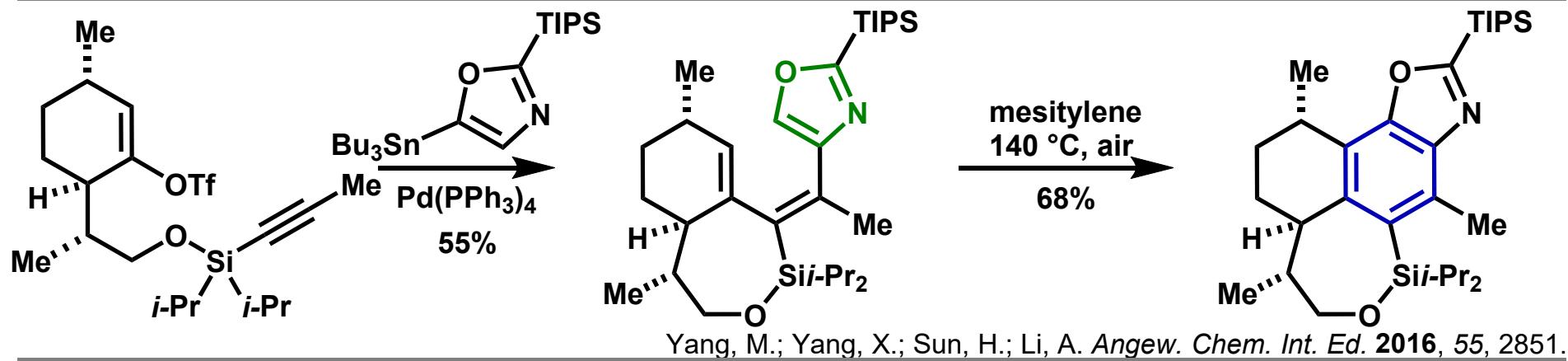
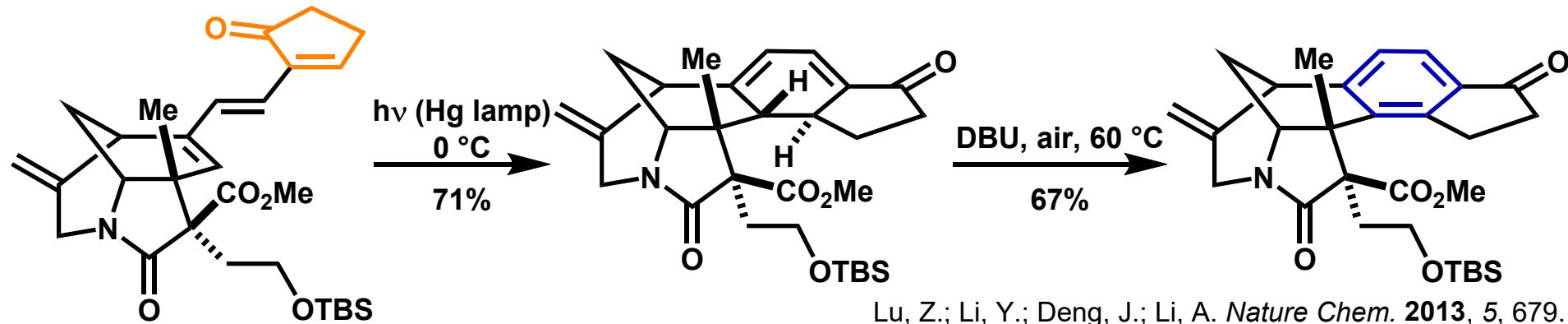
ileabethoxazole⁹⁾

1. *J. Am. Chem. Soc.* **2016**, *138*, 3982.; 2. *J. Am. Chem. Soc.* **2012**, *134*, 920.; 3. *Angew. Chem. Int. Ed.* **2014**, *53*, 9012.;

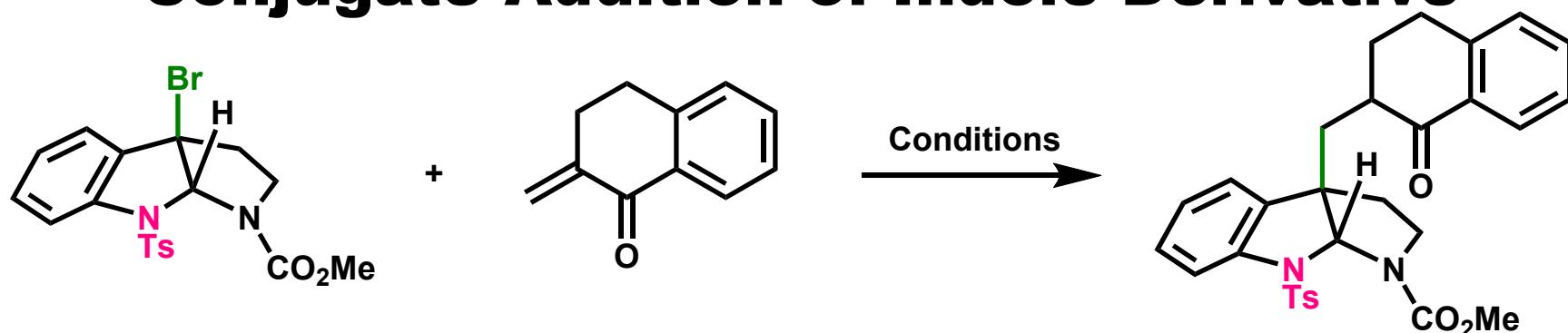
4. *J. Am. Chem. Soc.* **2014**, *136*, 16477.; 5. *Nature Chem.* **2013**, *5*, 679.; 6. *Nature commun.* **2015**, *6*, 6445.;

7. *J. Am. Chem. Soc.* **2016**, *138*, 3982.; 8. *J. Am. Chem. Soc.* **2017**, *139*, 5558.; 9. *Angew. Chem. Int. Ed.* **2016**, *55*, 2851.

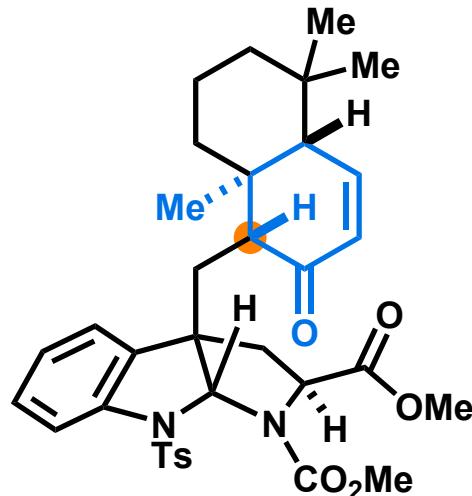
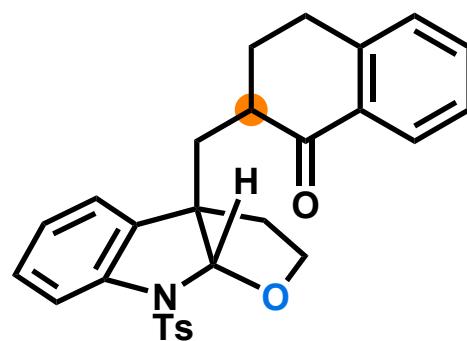
~ 6π -Electrocyclization / Aromatization ~



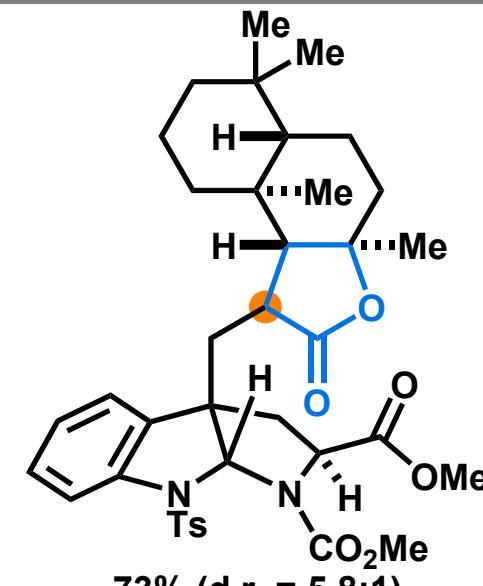
Conjugate Addition of Indole Derivative



Entry	Conditions	Yield
1	AIBN, <i>n</i> -Bu ₃ SnH, toluene, 80 °C	8%
2	Et ₃ B, O ₂ , <i>n</i> -Bu ₃ SnH, THF, 22 °C	13%
3	[Ru(bpy) ₃]Cl ₂ ·6H ₂ O, Et ₃ N, blue LED, DMF, 22 °C	11%
4	[Ir(bpy) ₂ (dtbbpy)]PF ₆ , Et ₃ N, blue LED, DMF, 22 °C	90%

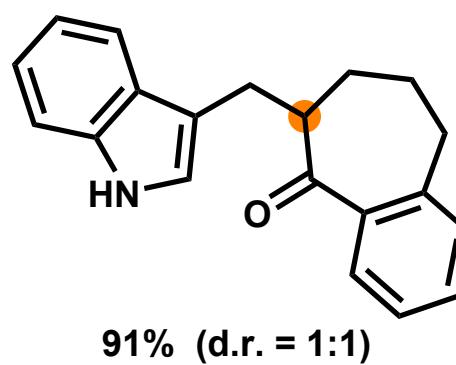
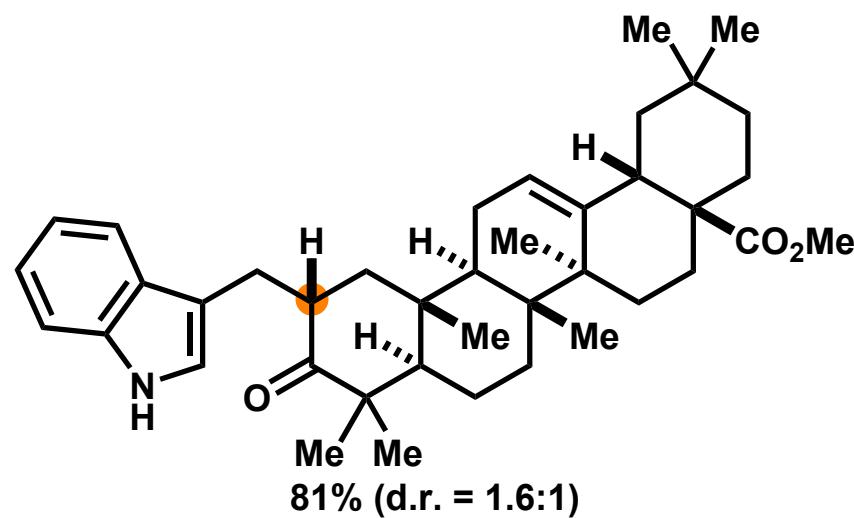
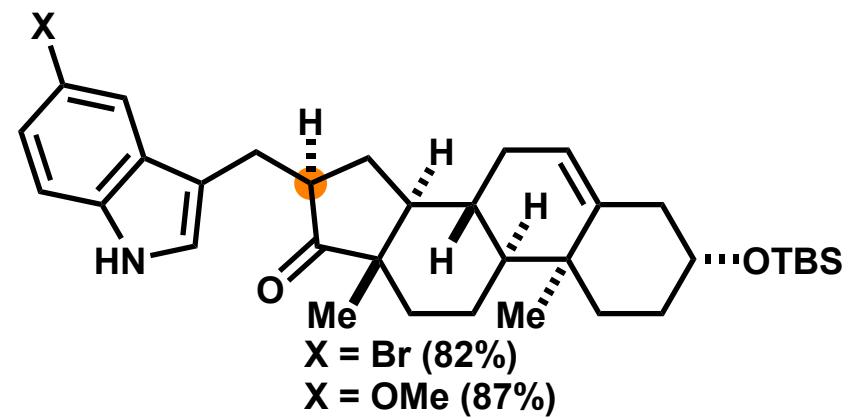
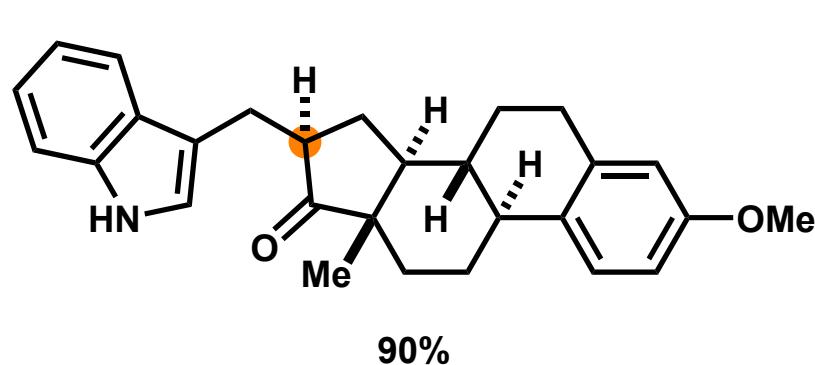
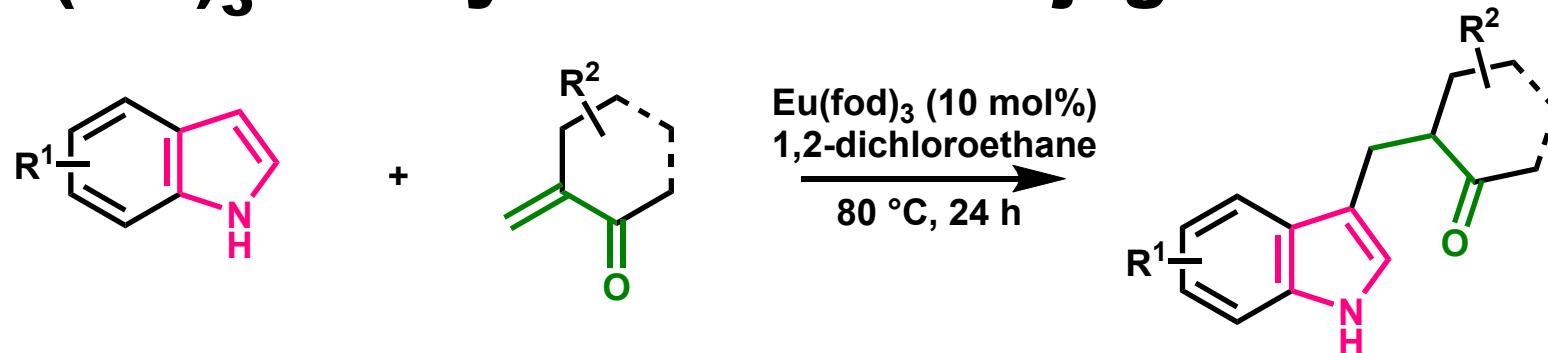


87% (d.r. = 2.2:1)



73% (d.r. = 5.8:1)

Eu(fod)₃-catalyzed Indole Conjugate Addition



Contents

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-Prof. Ang Li

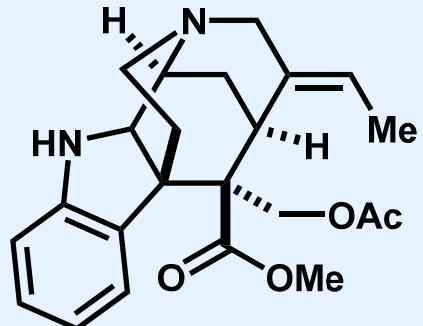
-Synthetic Methodology

2. Total synthesis of aspidodasycarpine, Ionicerine and Lanciferine (2016)

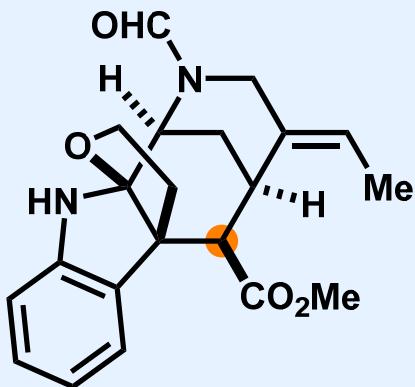
3. Total synthesis of longeraciniphyllin A (2017, main)

aspidodasycarpine, ionicerine, lanciferine

Akuammiline Indole Alkaloids



akuammiline

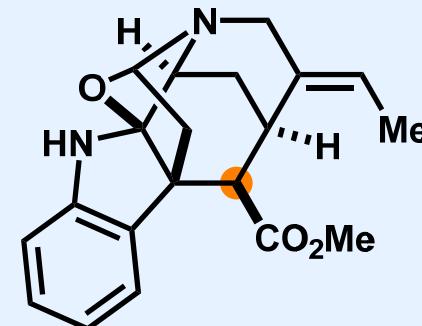


aspidophylline A

Garg, 2011^a

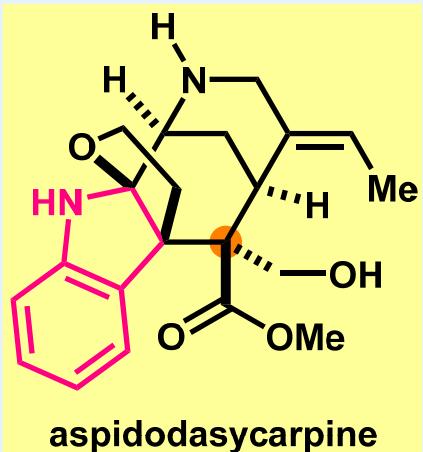
Zhu, 2014^b

Ma, 2014^c

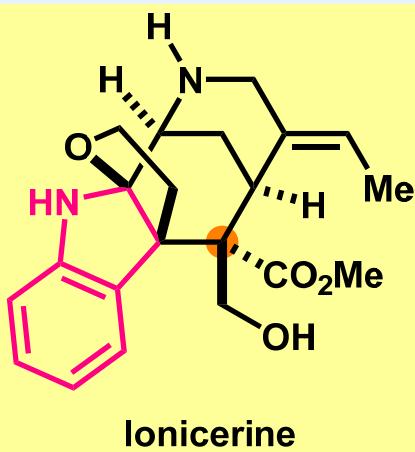


picrinine

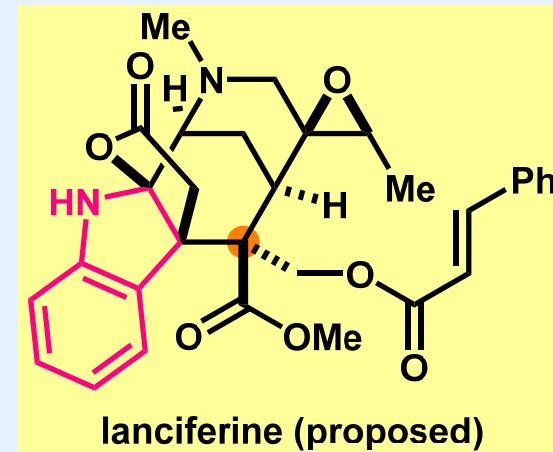
Garg, 2014^d



aspidodasycarpine



ionicerine

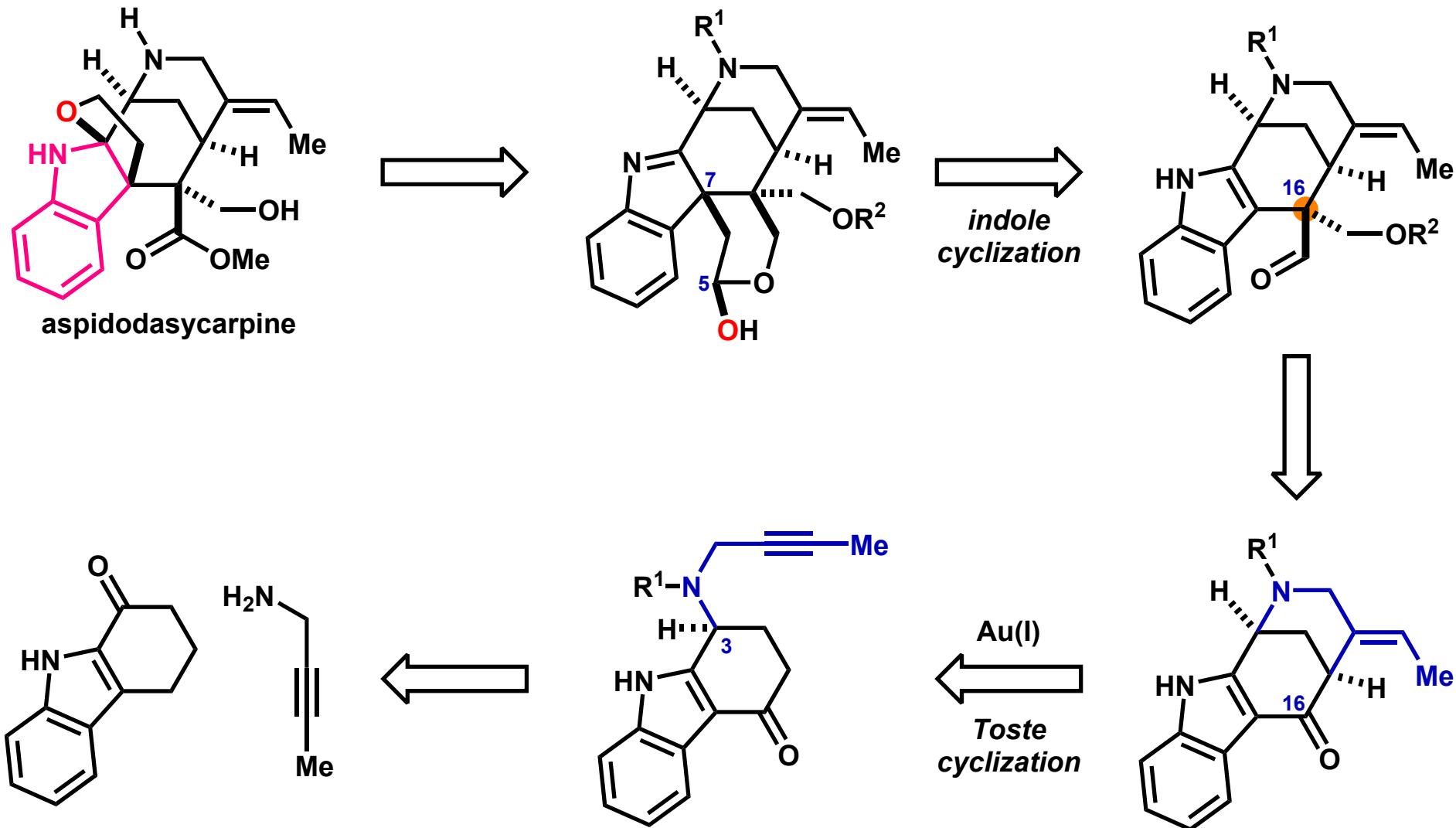


lanciferine (proposed)

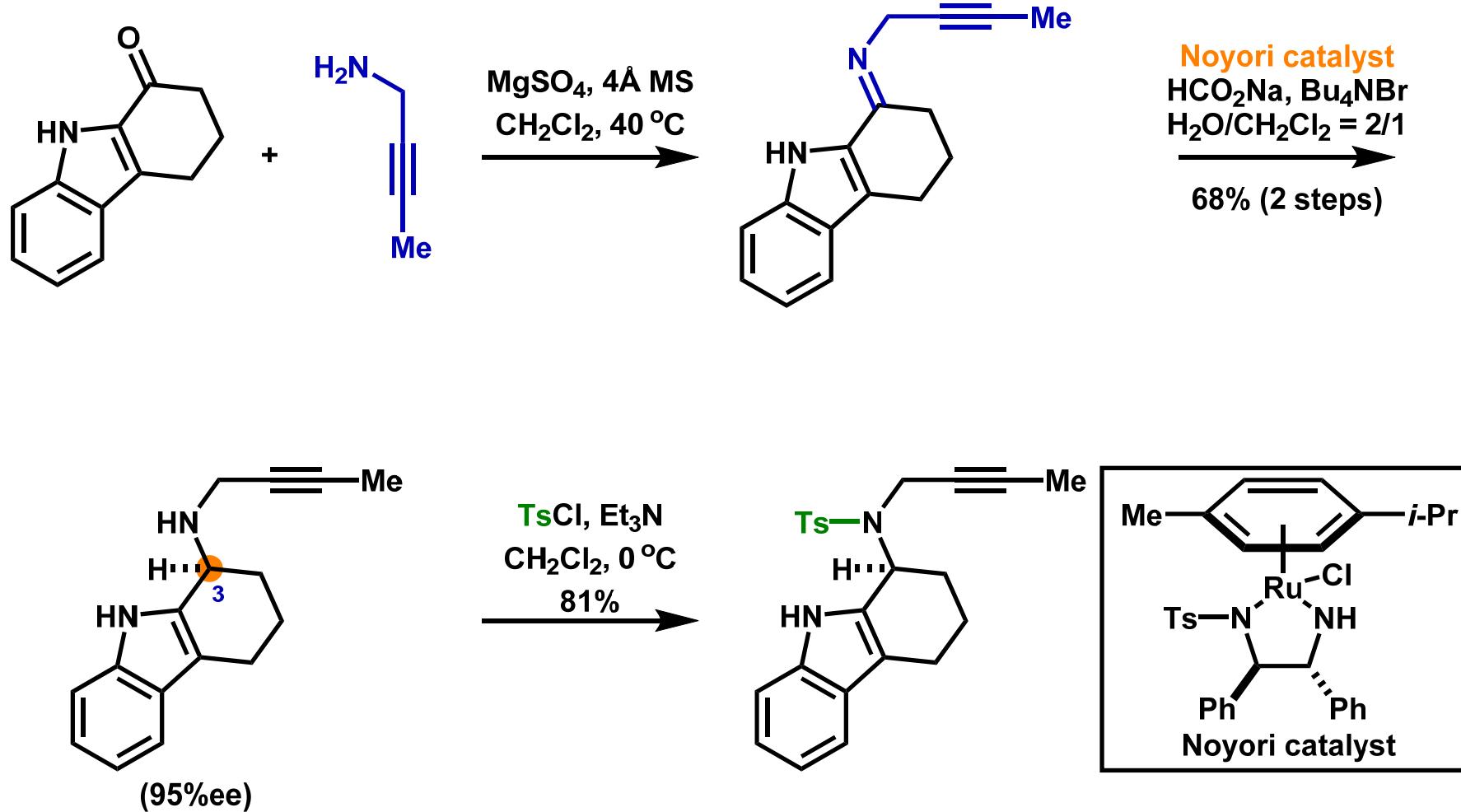
^aGarg, N. K. et al. *J. Am. Chem. Soc.* **2011**, 133, 8877. ^bZhu, J. et al. *Angew. Chem. Int. Ed.* **2014**, 53, 1818.

^cMa, D. et al. *Angew. Chem. Int. Ed.* **2014**, 53, 1814. ^dGarg, N. K. et al. *J. Am. Chem. Soc.* **2014**, 136, 4504.

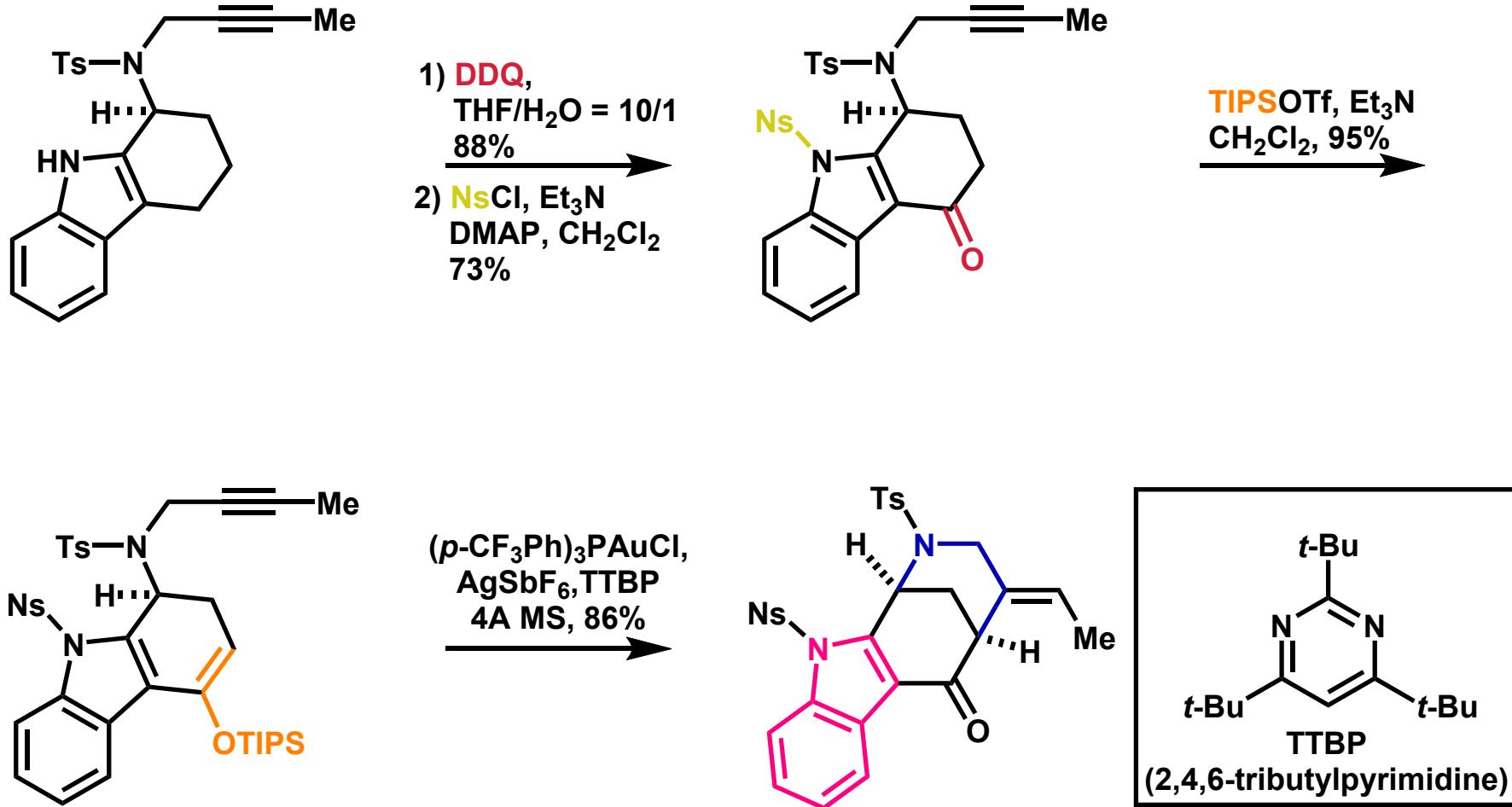
Retrosynthesis of Aspidodasicarpine



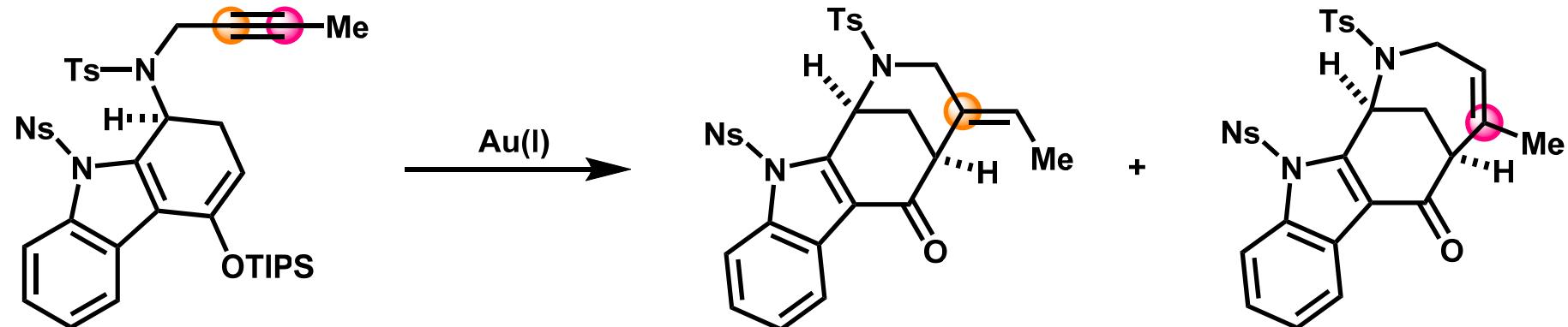
Introduction of C3-stereocenter



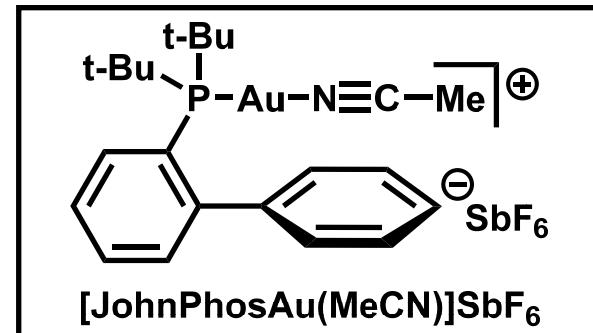
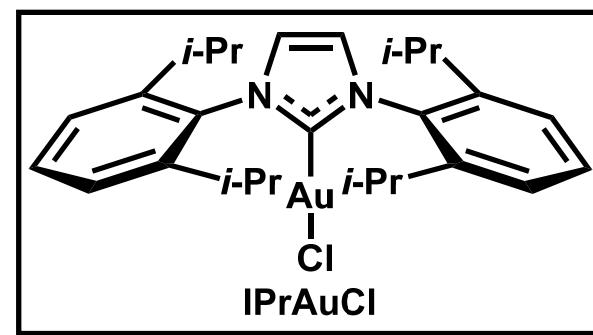
Construction of bridge tetracycle



Studies of Toste-type Cyclization



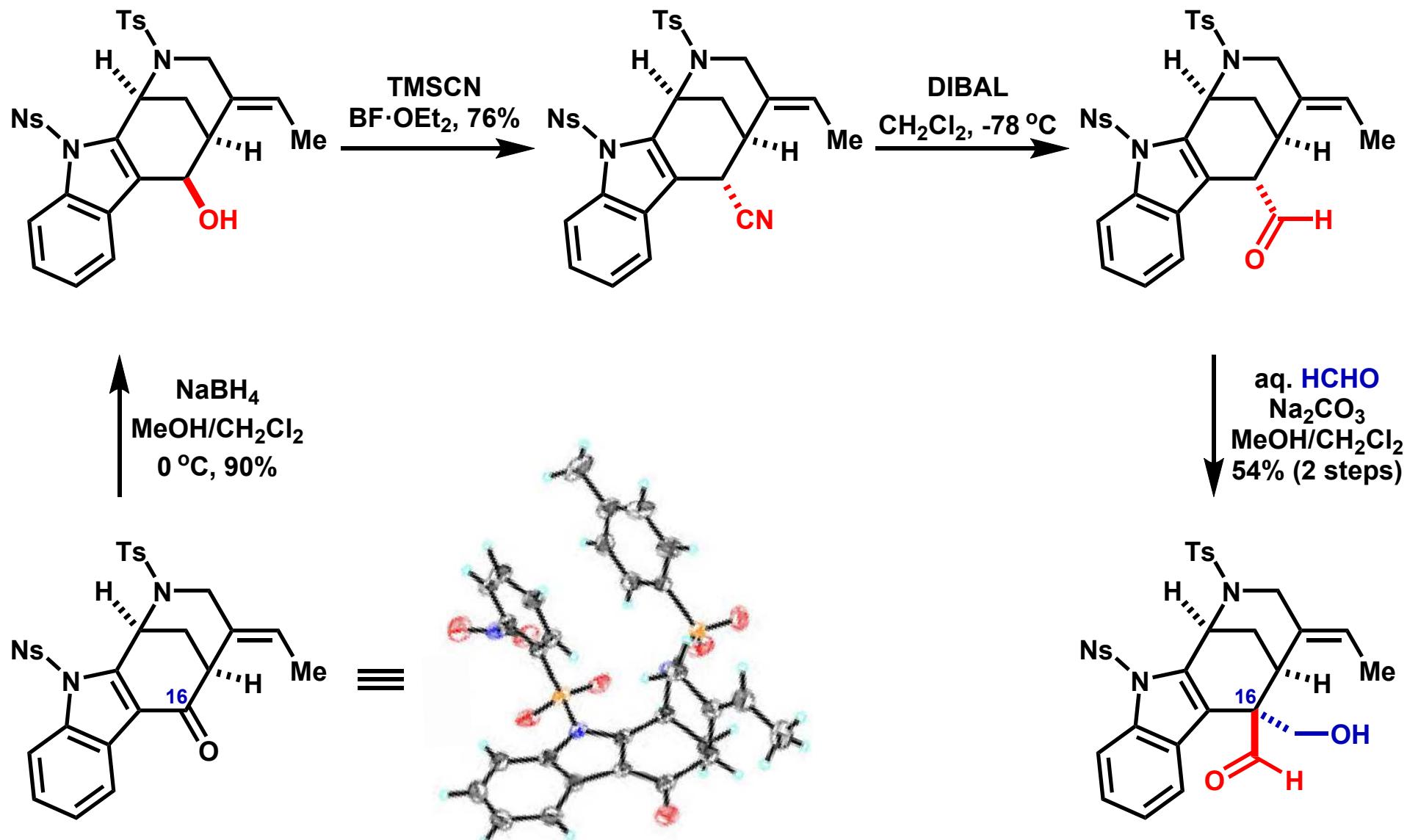
Entry	Conditions	Yield	
		6-exo	7-endo
1 ^a	Ph ₃ PAuCl, AgSbF ₆	55%	8%
2 ^a	IPrAuCl, AgSbF ₆	61%	27%
3 ^a	[JohnPhosAu(MeCN)]SbF ₆	45%	43%
4 ^a	(<i>p</i> -CF ₃ Ph) ₃ PAuCl, AgSbF ₆	62%	6%
5 ^b	(<i>p</i> -CF ₃ Ph) ₃ PAuCl, AgSbF ₆ , TTBP, 4Å MS	86%	9%



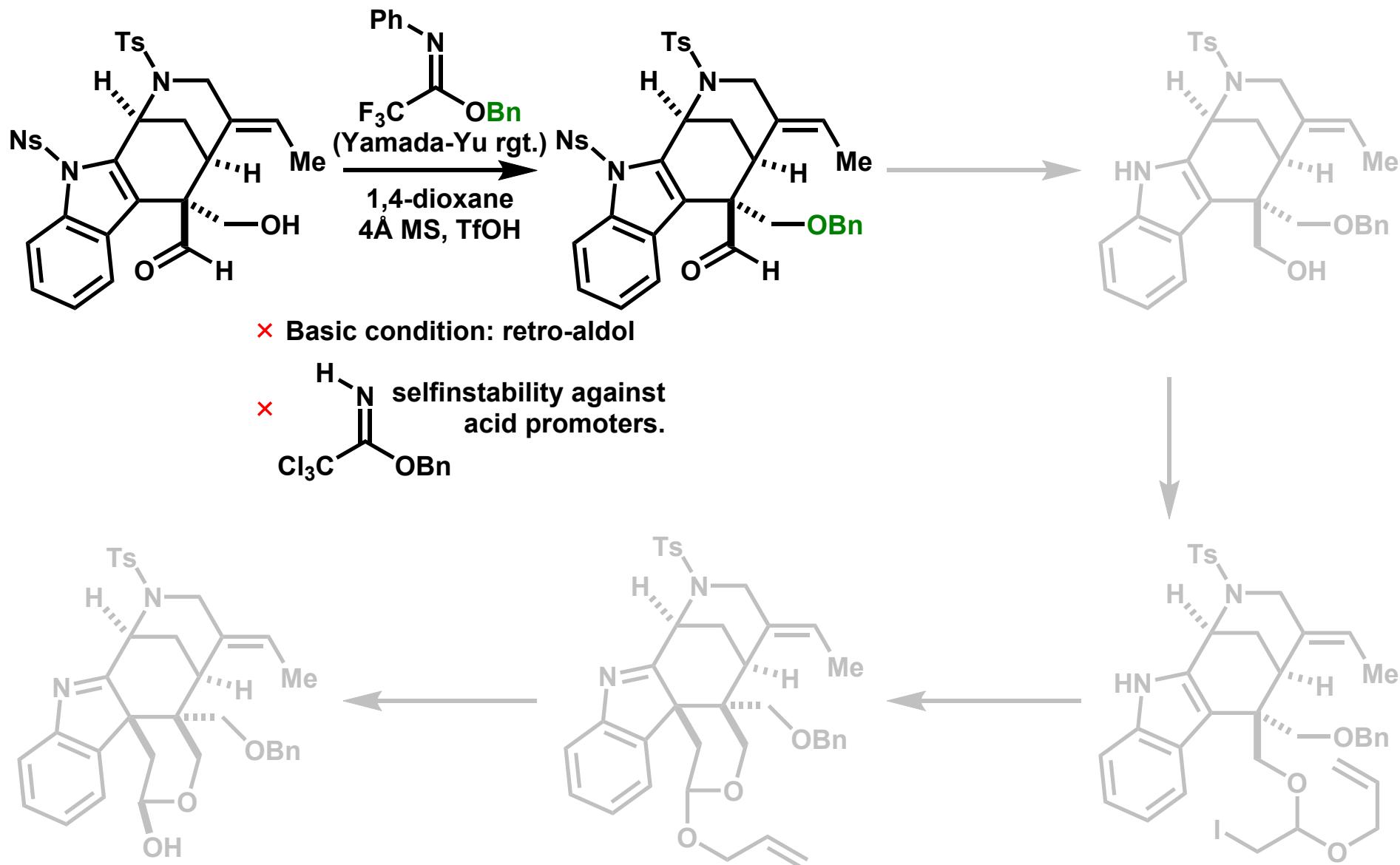
^a 5 mol% of [Au], MeOH/toluene (1/10), 3 h.

^b 3 mol% of [Au], 10 mol% of pyrimidine, *i*-PrOH/CH₂Cl₂ (7/100), 3d.

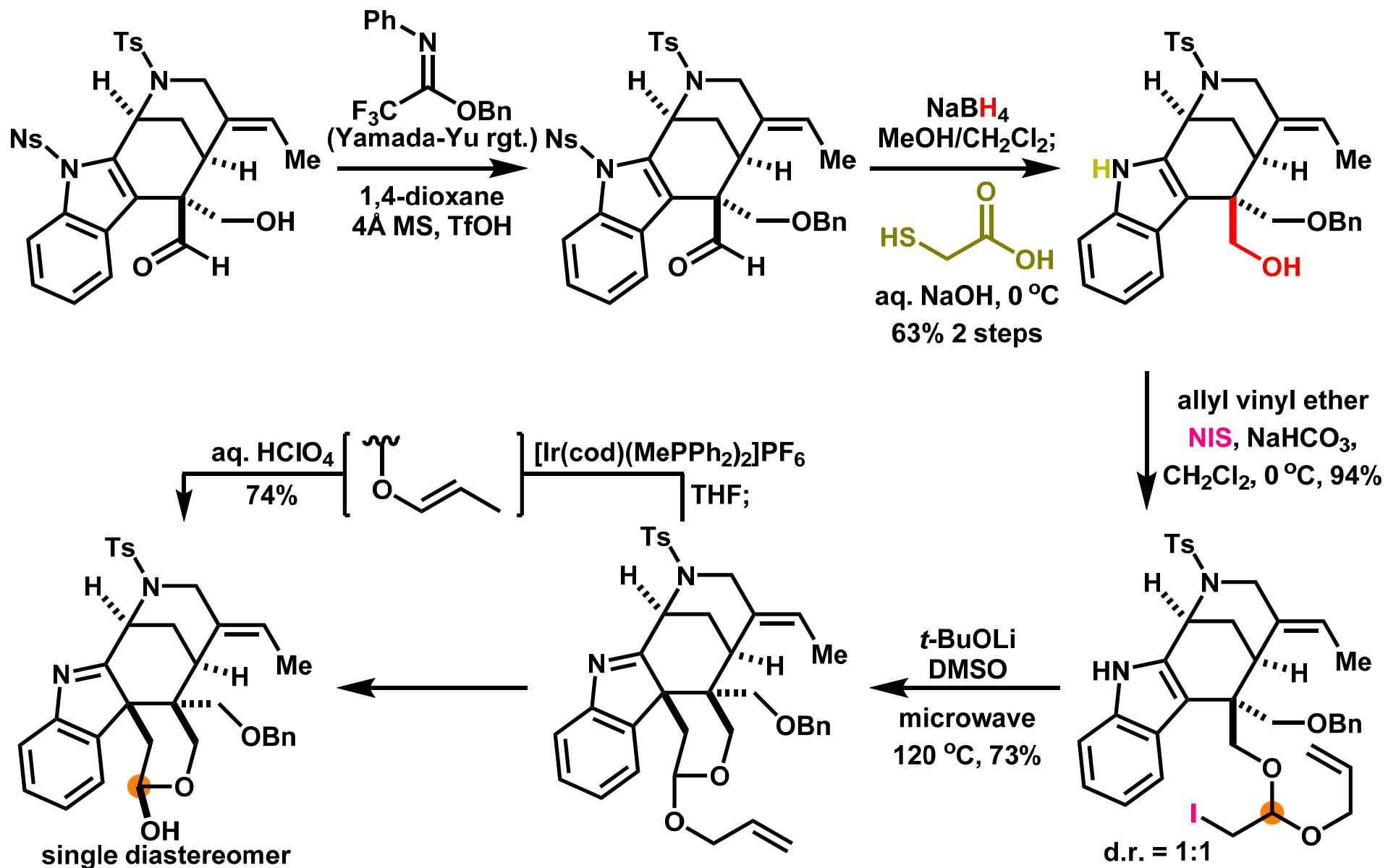
Construction of C16-quaternary Carbon



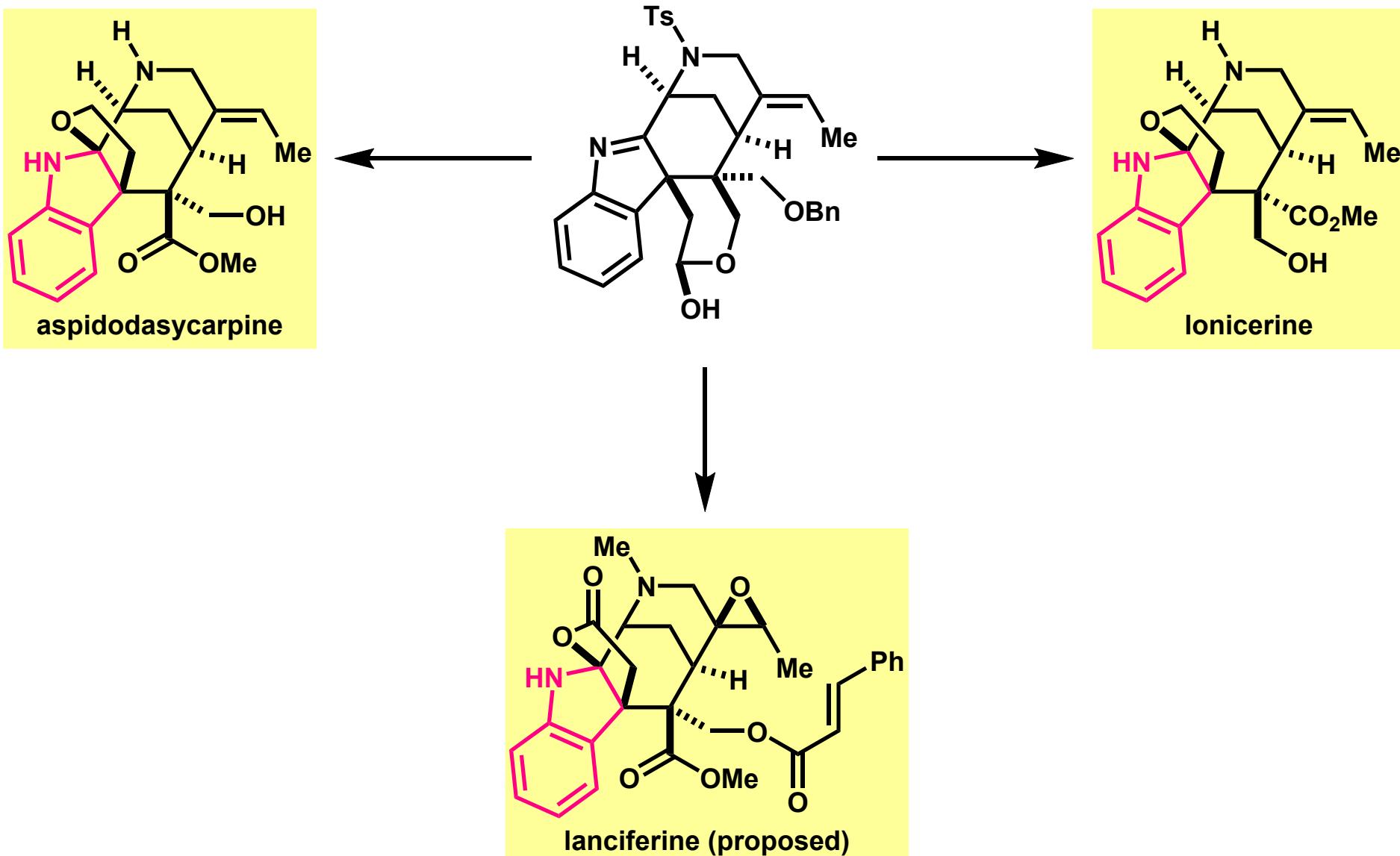
Synthesis of the lactol



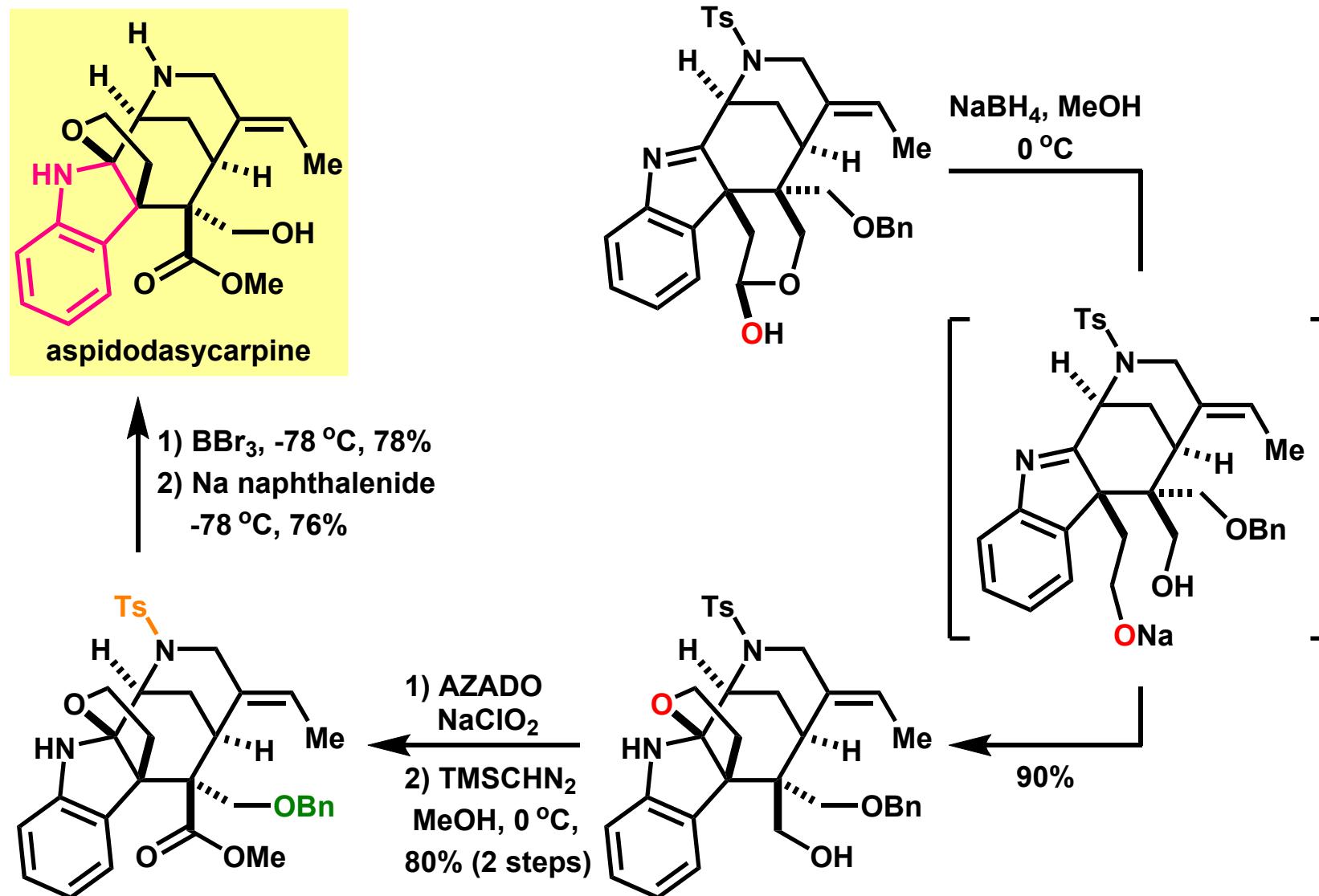
Synthesis of the lactol



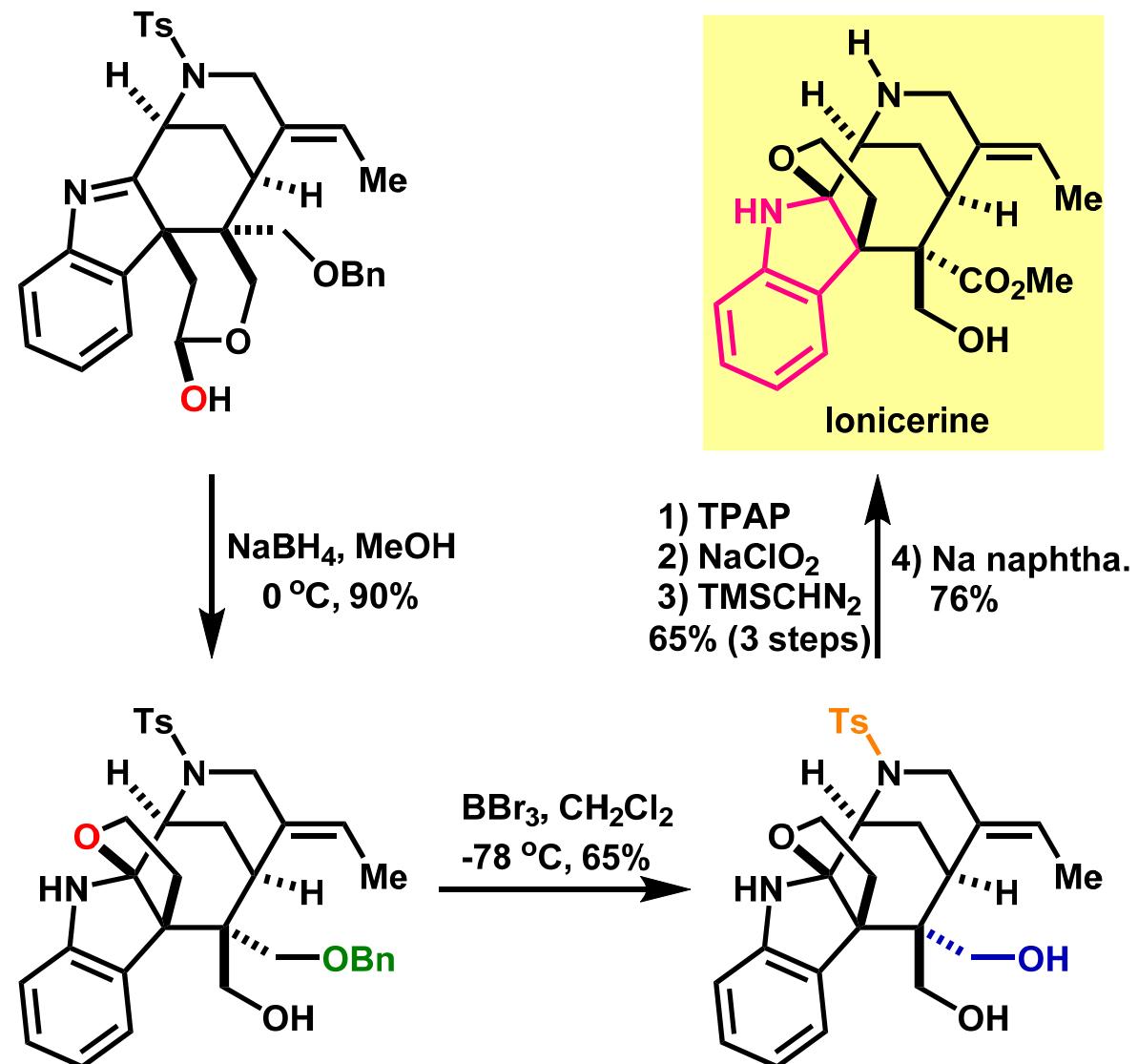
Divergent Synthesis from Common lactol



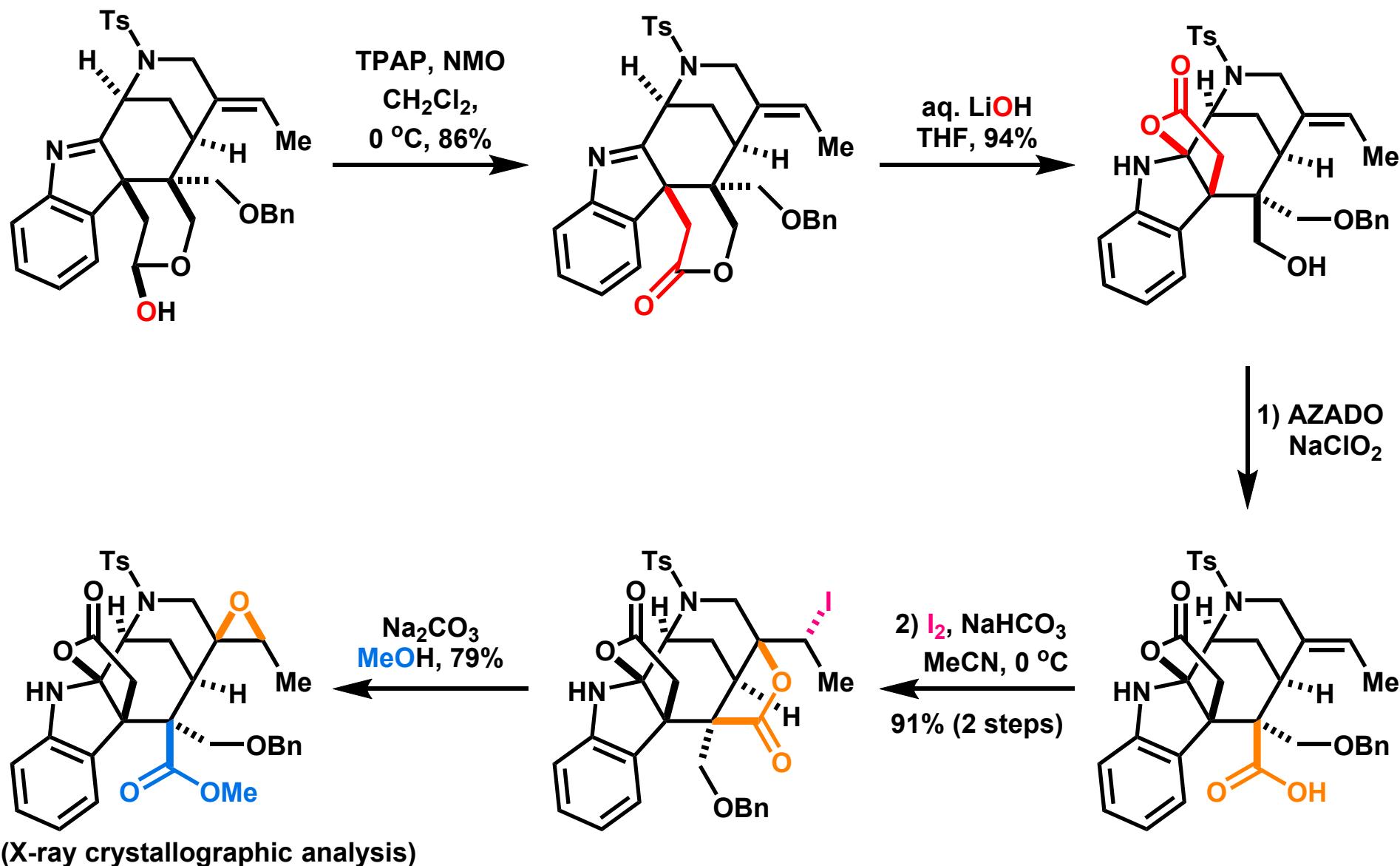
Completion of the Synthesis of aspidodasycarpine



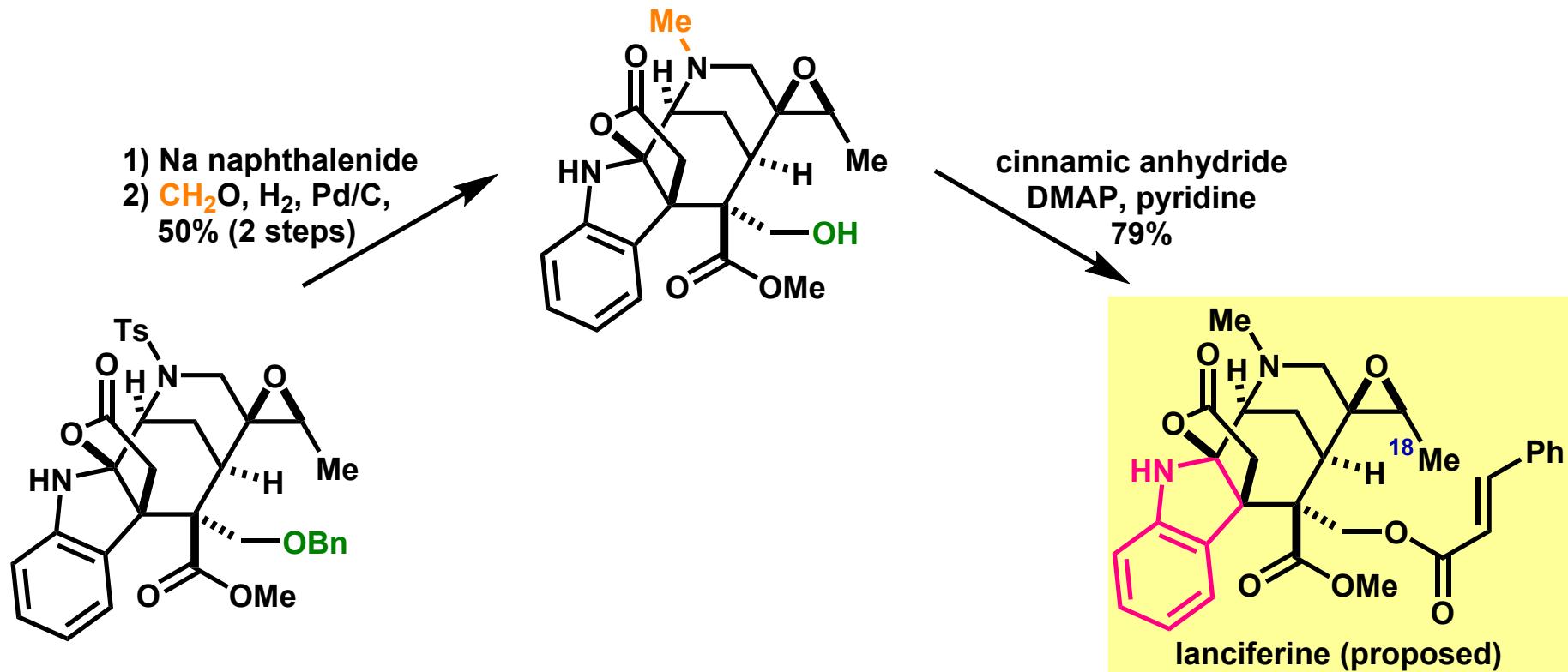
Completion of the Synthesis of Ionicerine



Formation of the Epoxide



Completion of the Synthesis of lanciferine



Ang Li et al. synthesized lanciferine (proposed), but
 ^1H NMR chemical shift of C18 methyl drastically differed from reported ($\Delta\delta = 0.2$).
(Lewin, G.; Kunesch, N.; Posson, J. *J. Indian Chem. Soc.* 1978, 55, 1096.)

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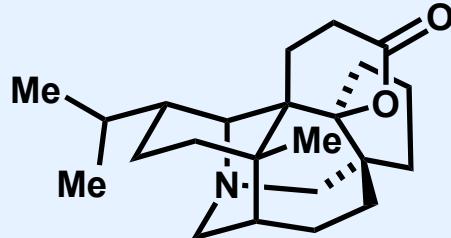
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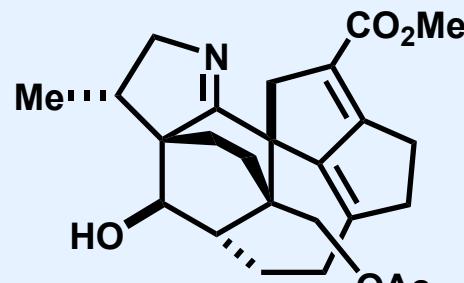
longeraciphyllin A

Daphniphyllum alkaloids



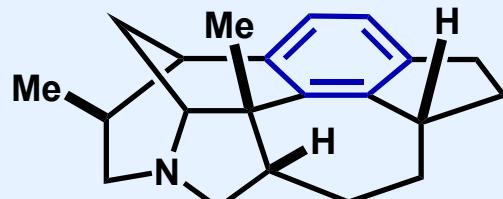
daphnilactone A

Heathcock, 1989^a



daphmanidin E

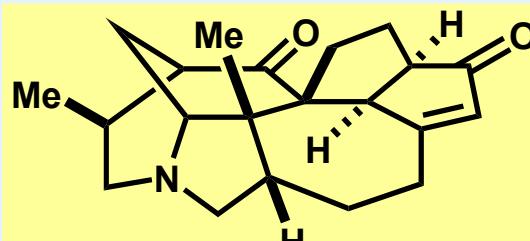
Carreira, 2011^b



daphenylline

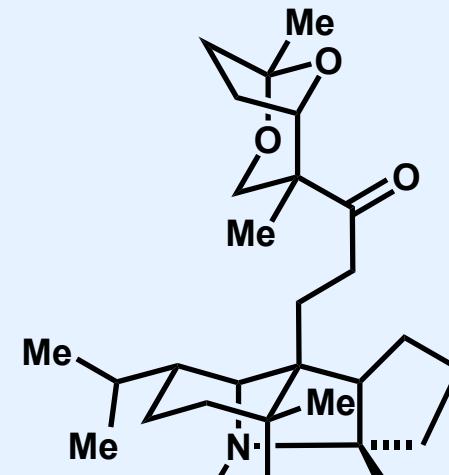
Li, 2013^d

Yokoshima & Fukuyama, 2016^e



longeraciphyllin A

Li, 2017^e



codaphniphylline

Heathcock, 1995^c

^aHethcock, C. H. et al. *J. Am. Chem. Soc.* **1989**, 111, 1530.

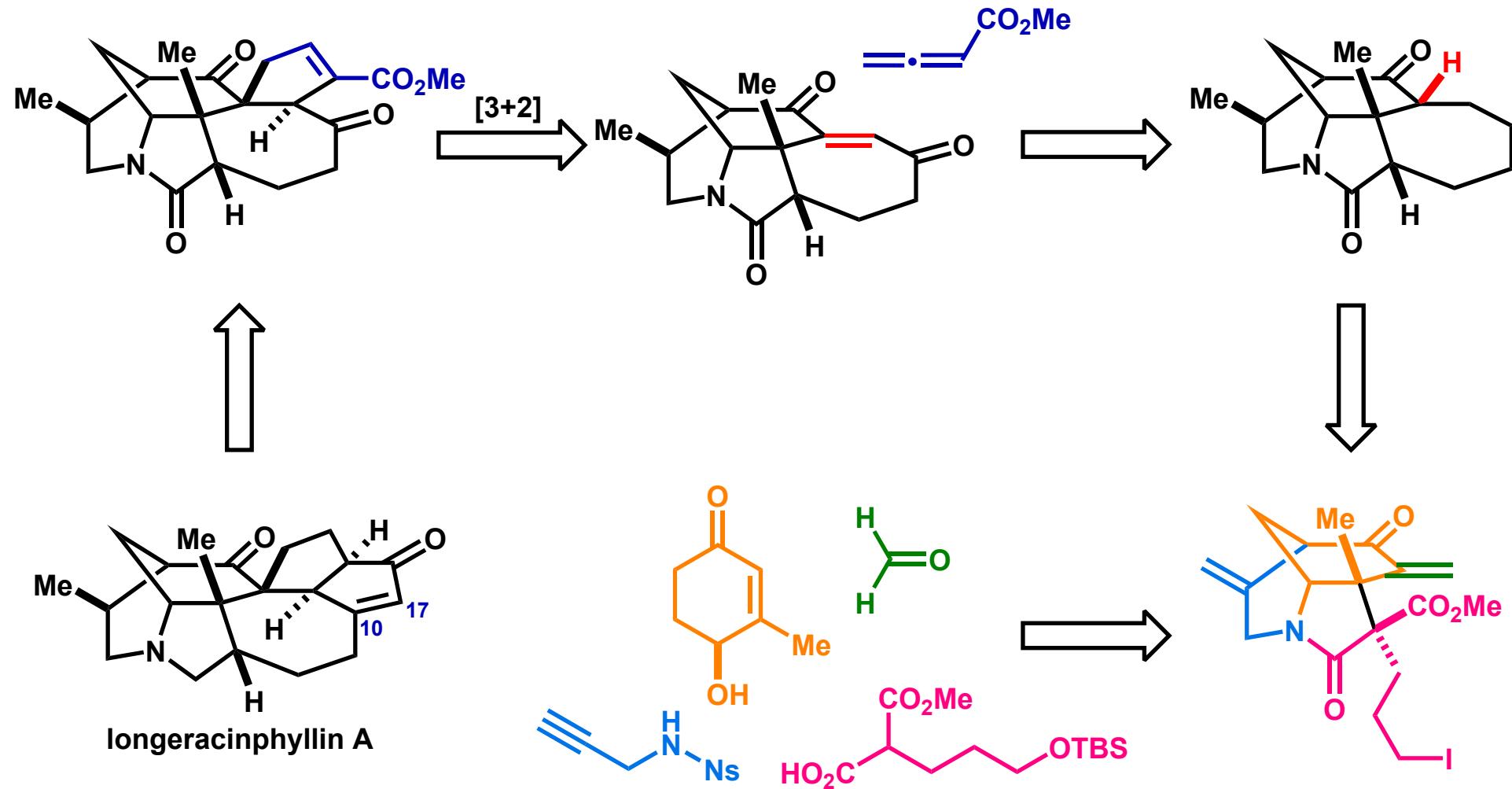
^bCarreira, E. M. et al. *Angew. Chem. Int. Ed.* **2011**, 50, 11501.

^cHethcock, C. H. et al. *J. Org. Chem.* **1995**, 60, 1120. ^dLi, A. et al. *Nat. Chem.* **2013**, 5, 679.

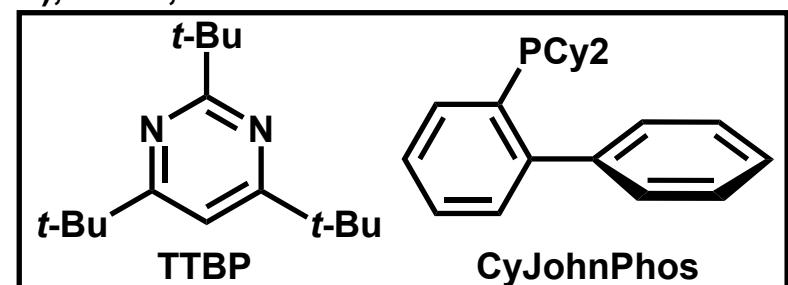
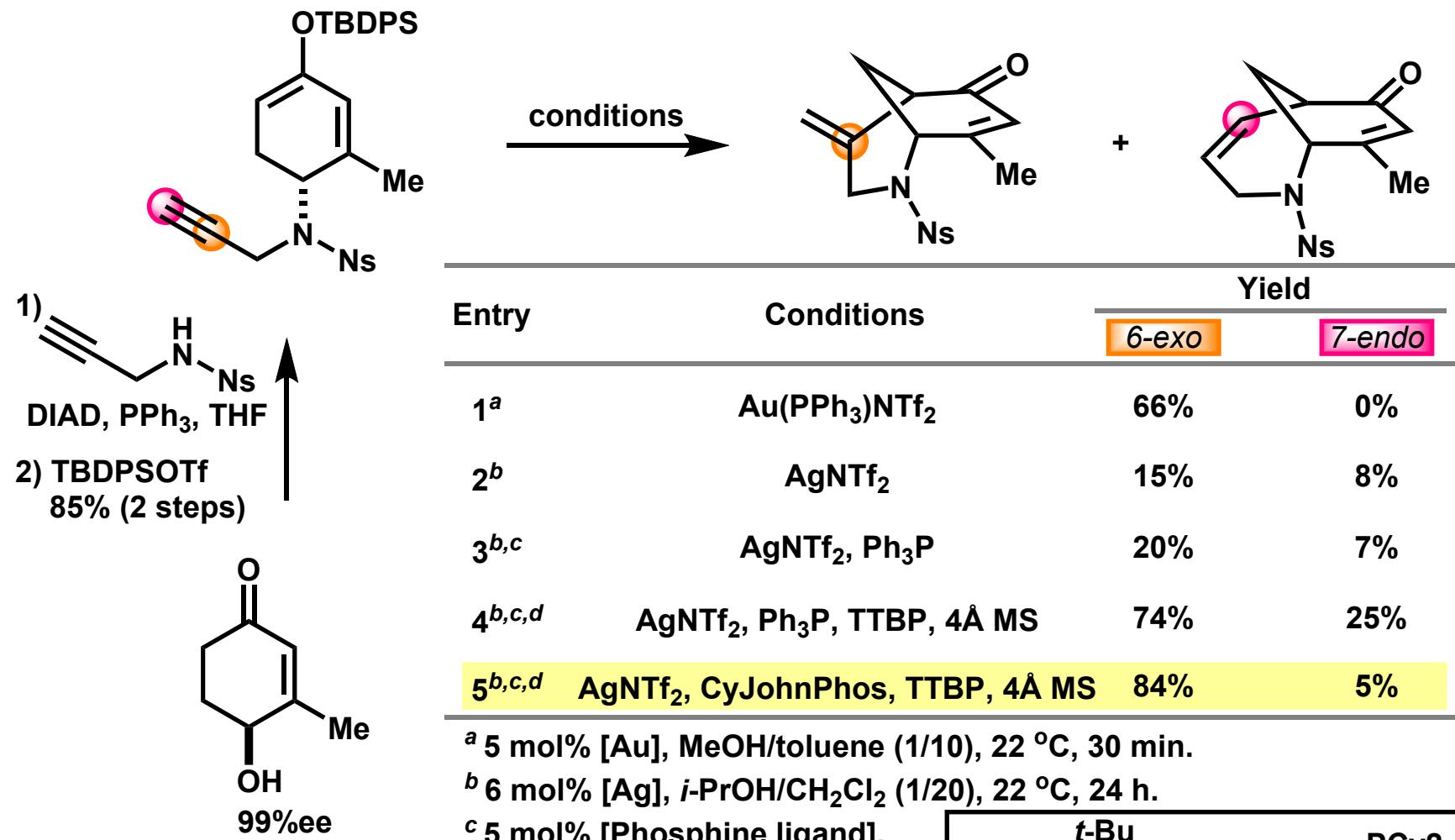
^eYokoshima, S.; Fukuyama, T. et al. *Angew. Chem. Int. Ed.* **2016**, 55, 6067.

^eLi, A. et al. DOI: 10.1021/jacs.7b09186

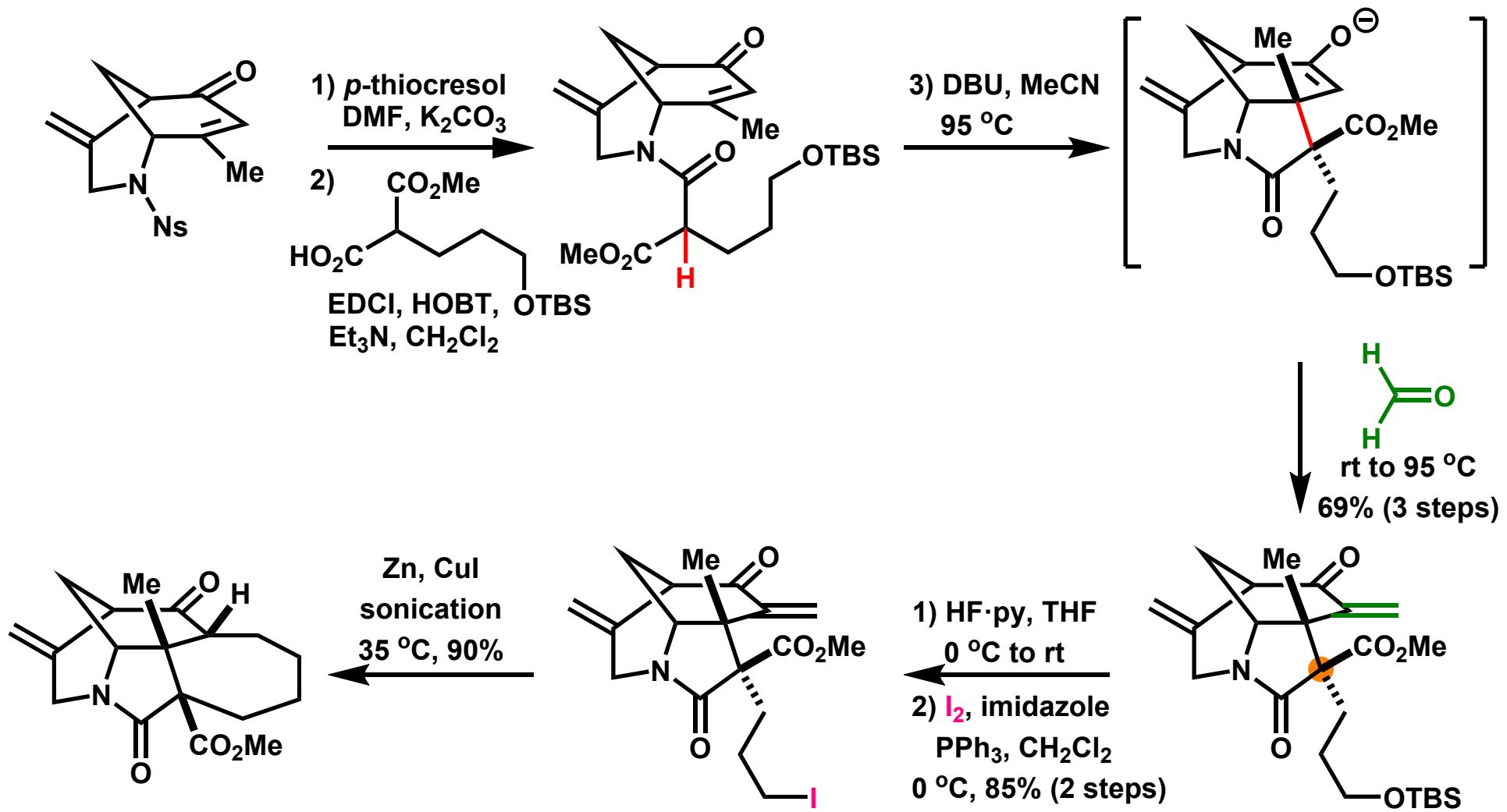
Retrosynthesis analysis of longeraciphyllin A



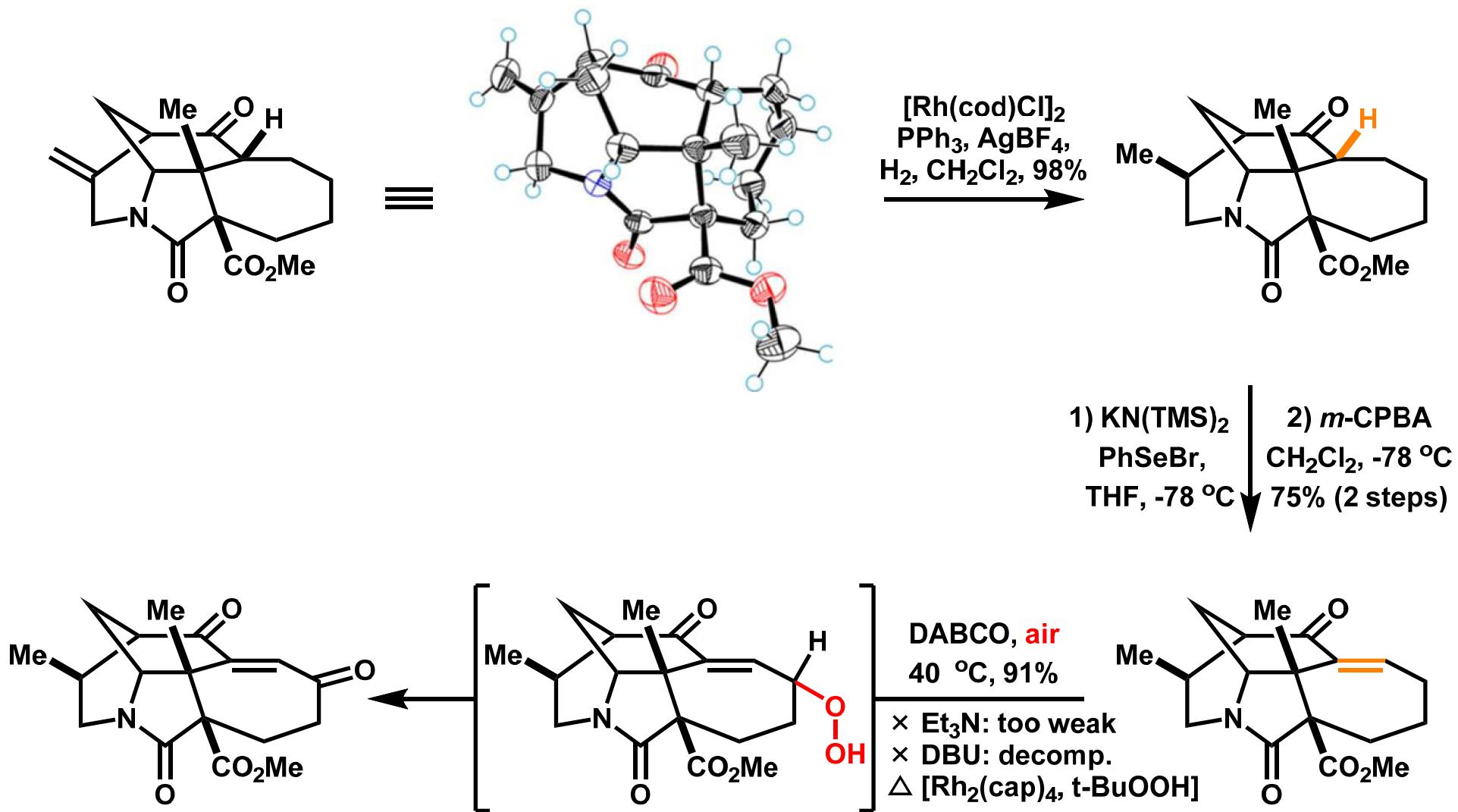
Studies of Toste-type Cyclization



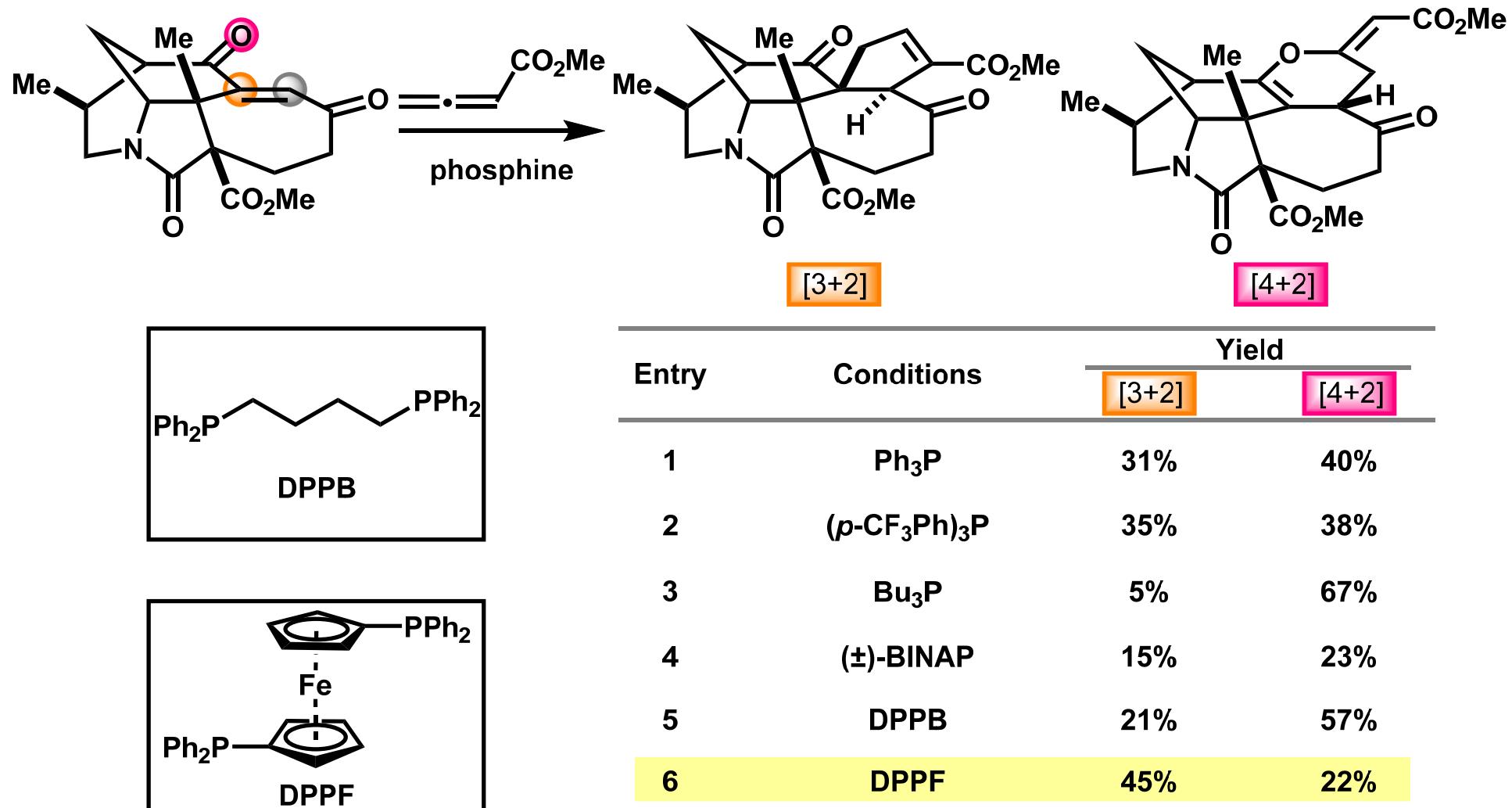
Preparation of Tetracyclic Intermediate



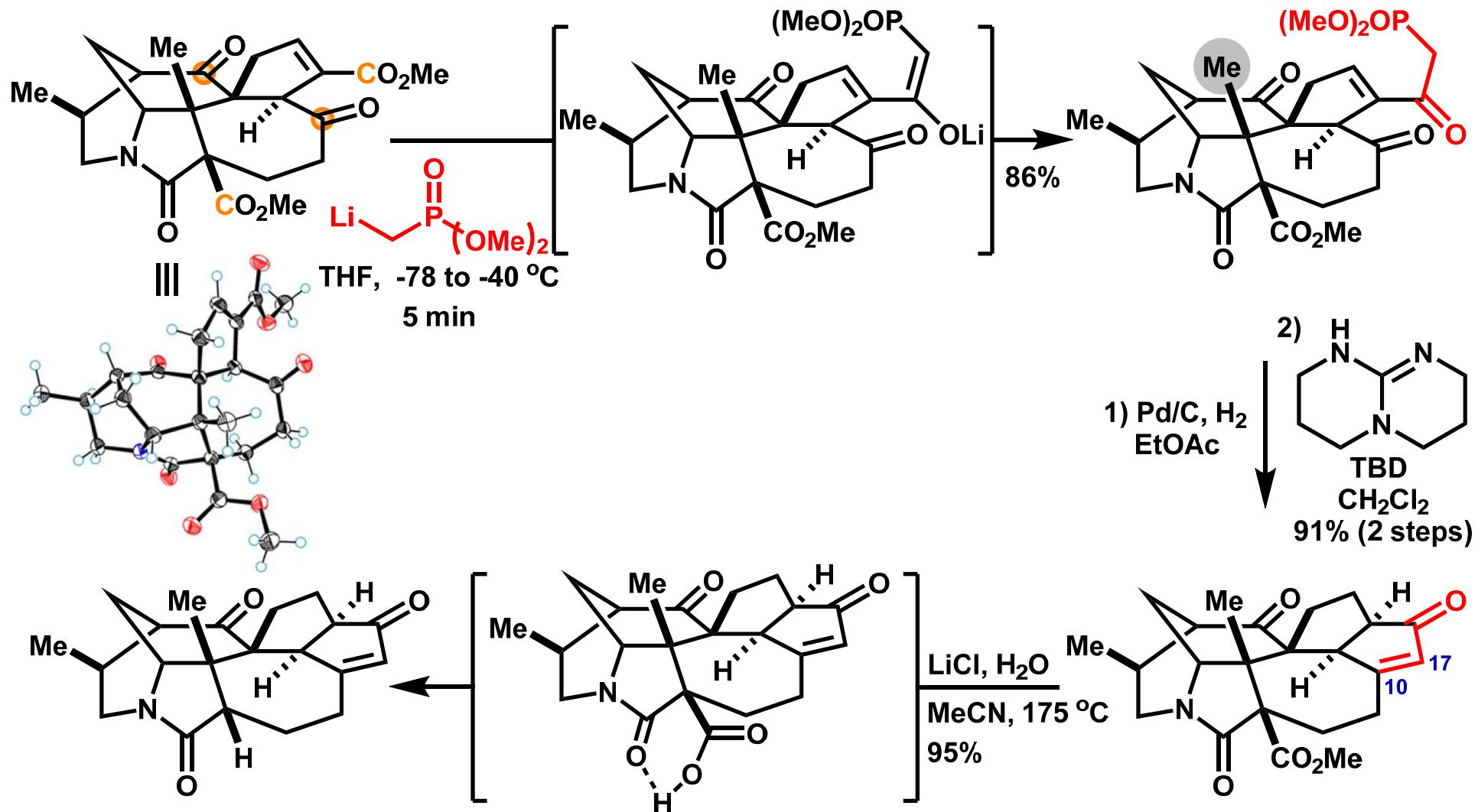
Functionalization of the seven-membered ring



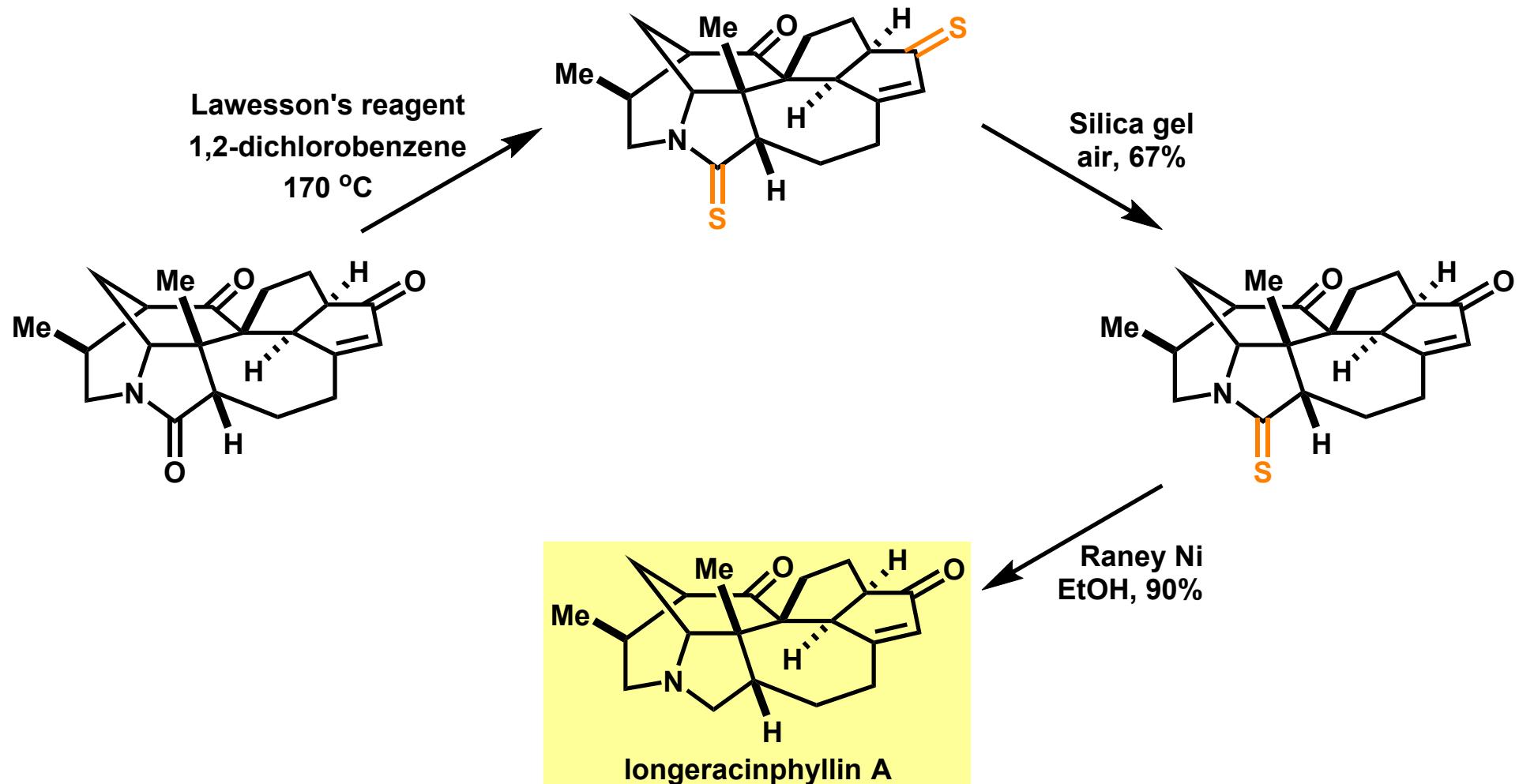
Studies of Phosphine Promoters for [3+2] Cycloaddition



Construction of Hexacyclic-ring System

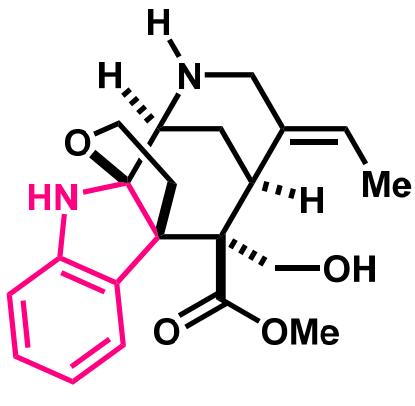


Completion of the Synthesis of longeraciphyllin A

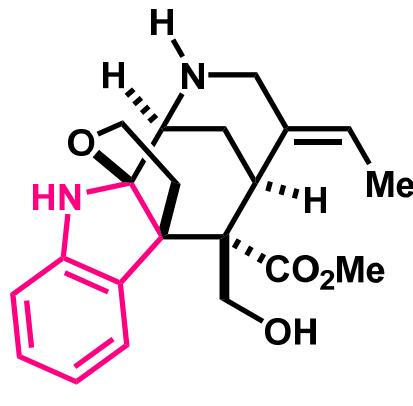


Summary

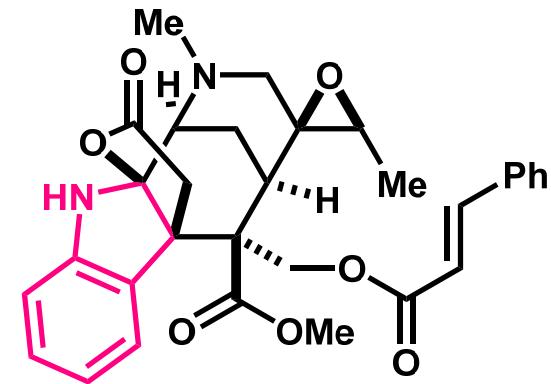
in 2016



aspidodasycarpine

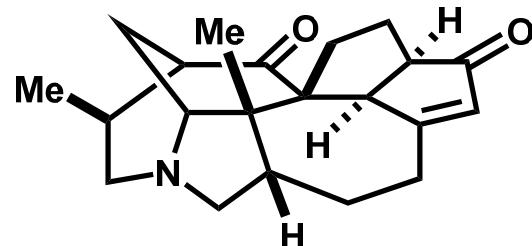


ionicerine



lanciferine (proposed)

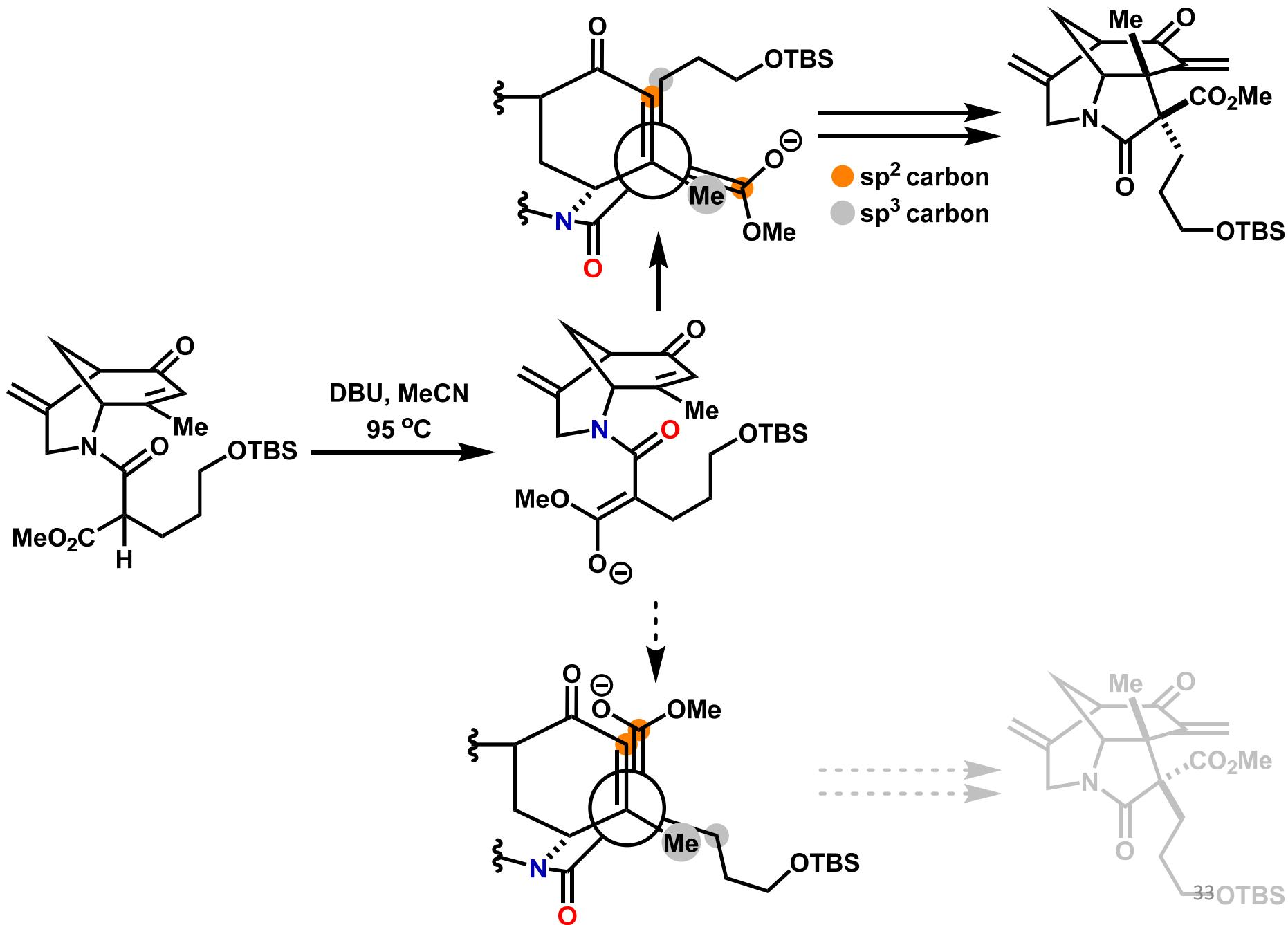
in 2017



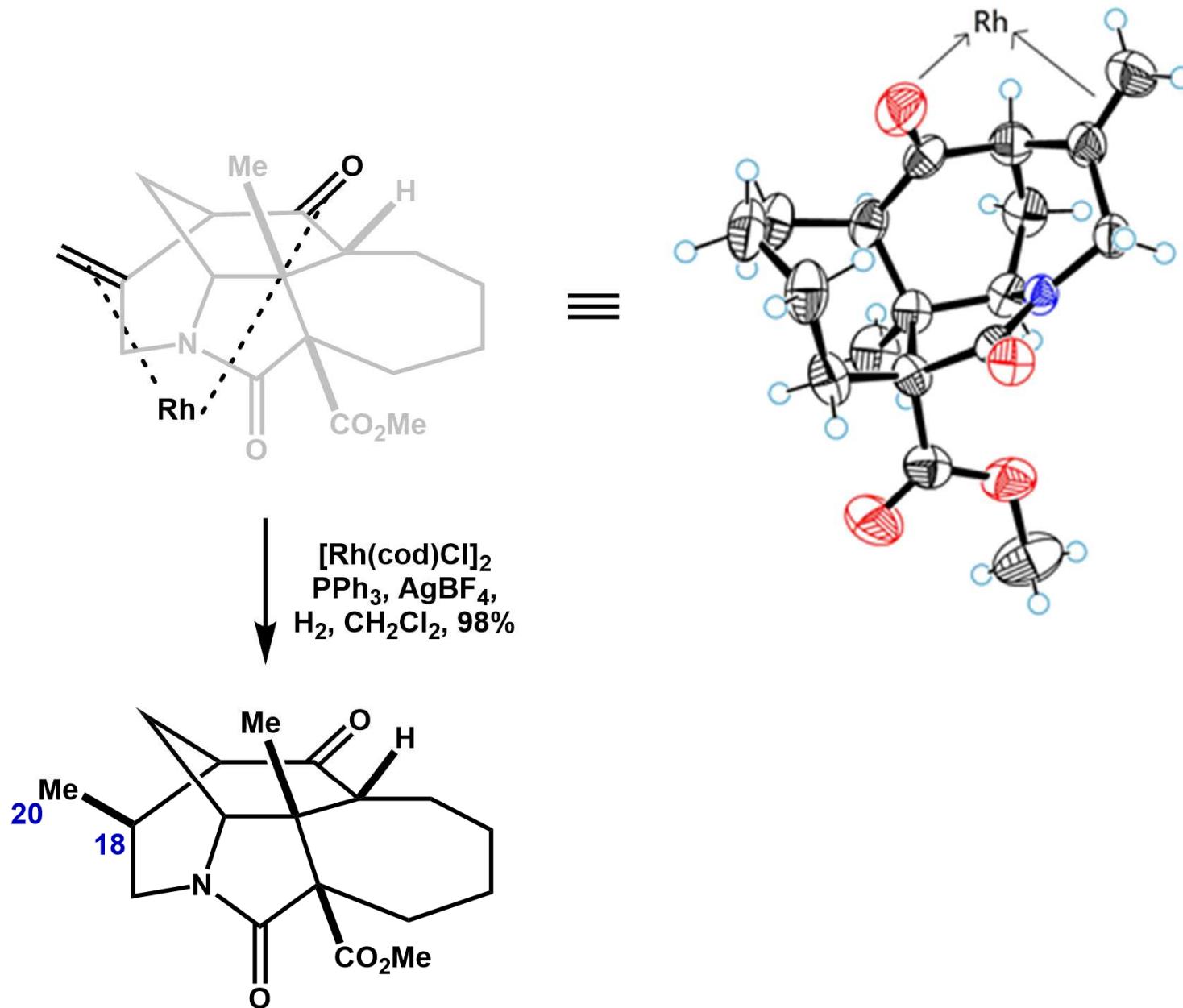
longeraciniphyllin A

Appendix

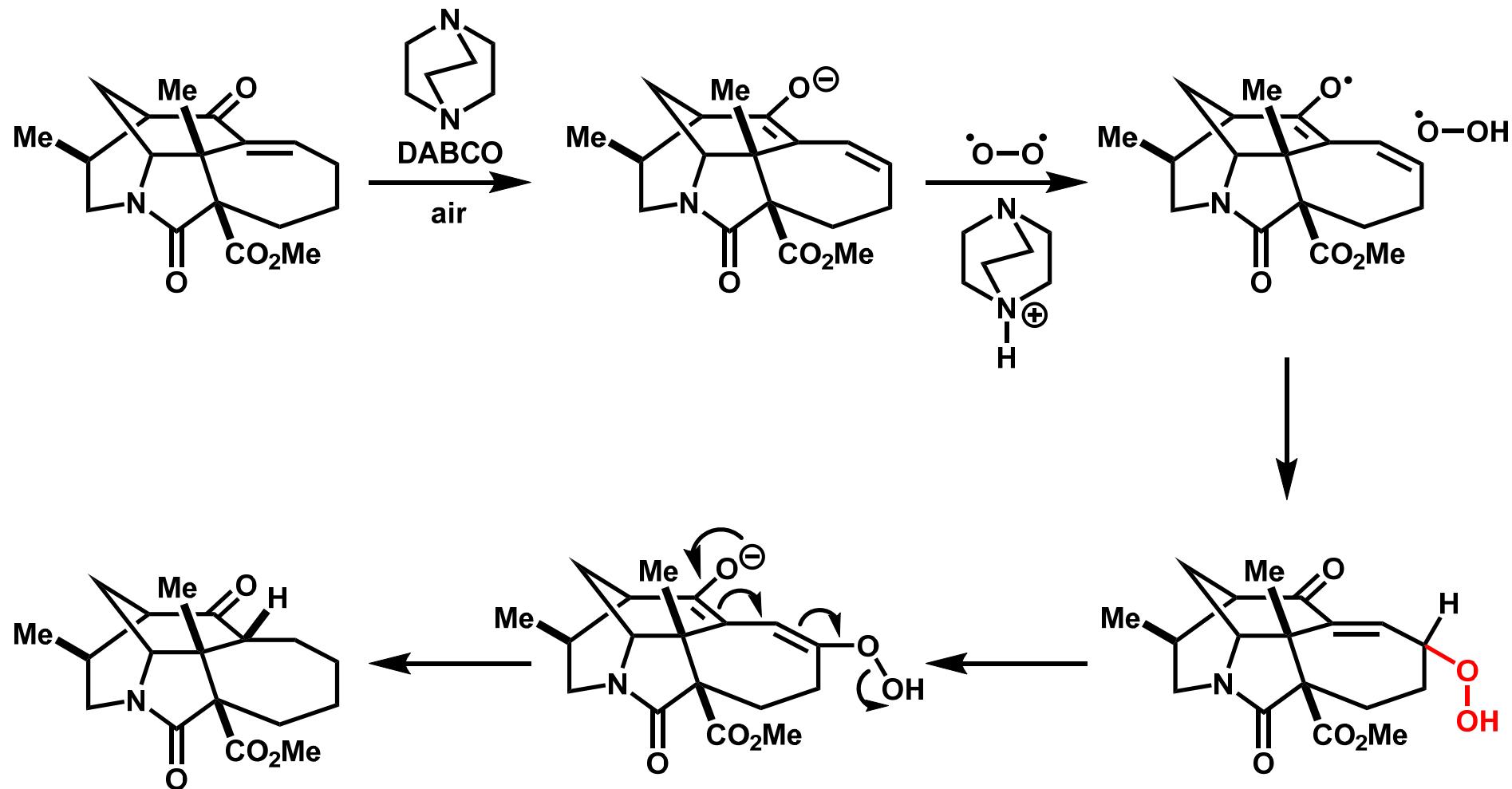
Aldol Condensation



Direceted Homogeneous Hydrogenation



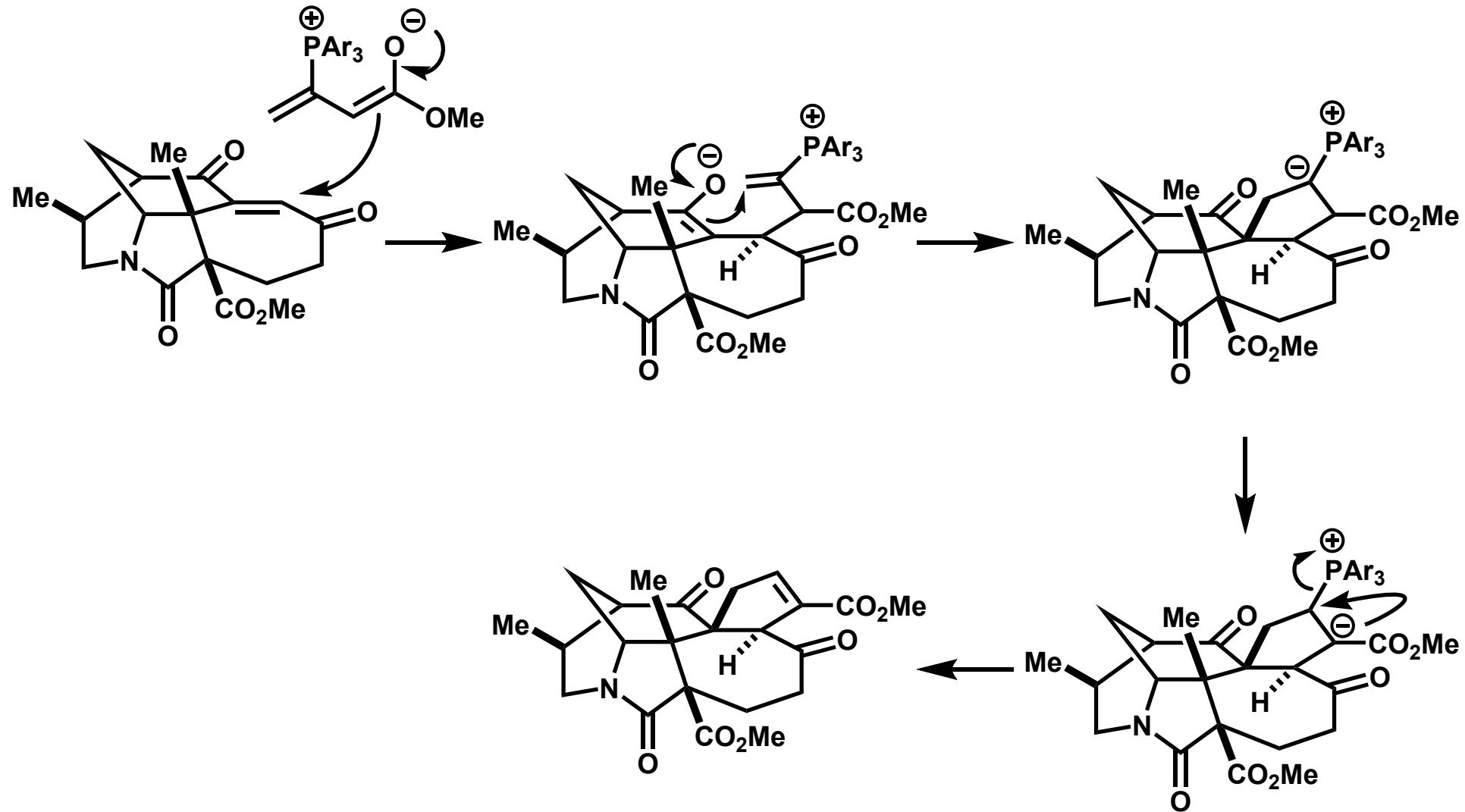
Oxidation of seven-membered ring



[3+2] stepwise mechanism

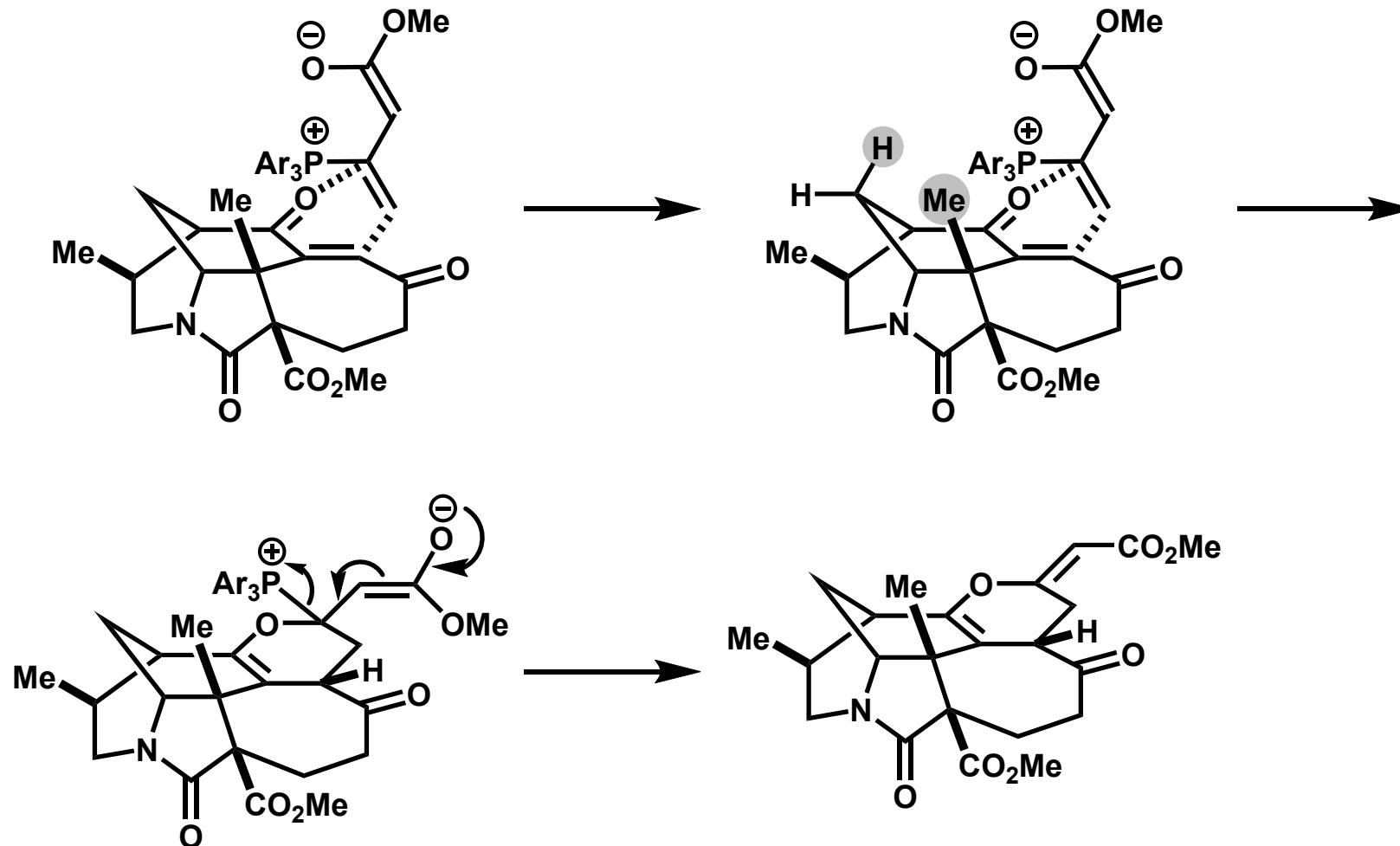
phosphine-catalyzed [3+2] reaction is generally known stepwise mechanism.

- In the first step, nucleophile attacks to less hindered carbon from convex face.



[4+2] Concerted mechanism

-the dienophile reacts from concave face, because of the steric repulsion between phosphine ligand and highlighted H and/or Me?



Mechanism of the photocatalyzed radical conjugate addition

