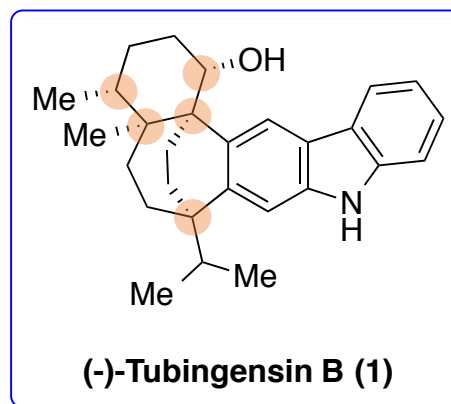


# Total synthesis of (–)-tubingensin B enabled by the strategic use of an aryne cyclization

Corsello M. A.; Kim J.; Garg N. K., *Nature Chemistry* **2017**, 9, 944-949. DOI:10.1038/nchem.2801



Emy André-Joyaux  
Renaud Group  
University of Bern  
14<sup>th</sup> December 2017

*u*<sup>b</sup>

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b  
UNIVERSITÄT  
BERN

# Neil K. Garg

## Education:

- B.S. in Chemistry from NYU in 2000, undergraduate research with Pr. Marc Walters (NYU) and Pr. Mai Wais Hosseini (University Louis Pasteur, Strasbourg)
- Ph.D. in Organic Chemistry from California Institute of Technology in 2005, under the supervision of Pr. Brian Stoltz

## Professional and academic experience:

- NIH postdoctoral scholarship at the University of California, Irvine from 2005 to 2007, under the supervision of Pr. Larry Overman
- Assistant professor at UCLA from 2007 to 2012
- Associate professor at UCLA from 2012 to 2013
- Professor at UCLA from 2013 to present



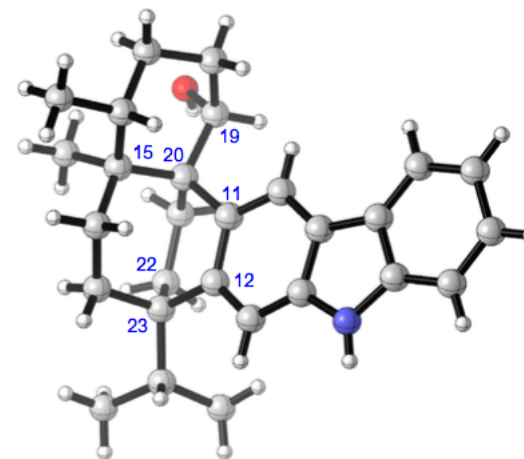
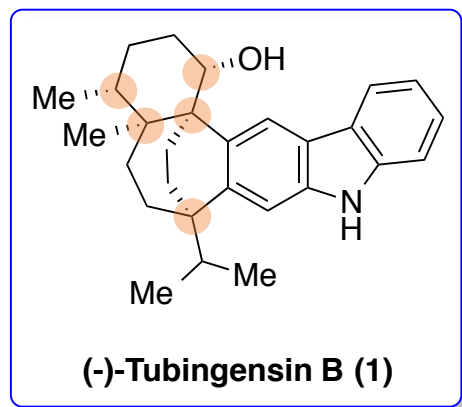
## Neil K. Garg

### Methodological interests:

- Transition-metal catalyzed cross-coupling reactions of unconventional electrophiles (esters and amides) using non-precious metal catalysis, and bench stable preparations of catalysts
- Functionalization of heterocycles, including 'interrupted Fischer indolization' cascades and the manipulation of cyclic alkynes and allenes
- Total synthesis of complex small molecules, such as drugs and natural products



# Introduction

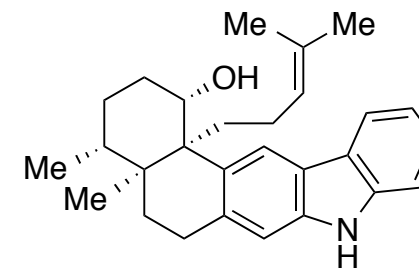
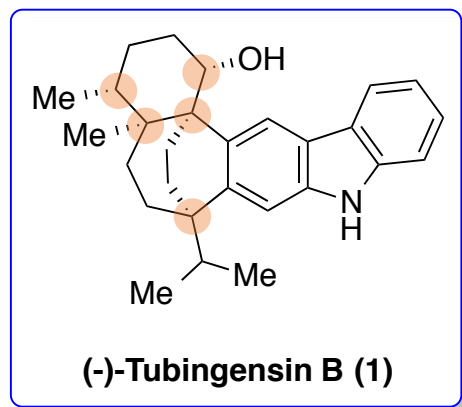


Crystal structure of (-)-Tubingensin B  
Acta Cryst. C53, 1447–1449 (1997)

- Isolated in 1989 from fungus *Aspergillus tubingensis*<sup>1</sup>
- Display antiviral, anticancer and insecticidal activity<sup>1</sup>
- No previous total syntheses reported
- Bicyclo[3.2.2]nonane core fused to the carbazole
- 5 stereogenic centers

<sup>1</sup>Tetrahedron Lett. **1989**, 30, 5965–5968

# Introduction



**Tubingensin A**

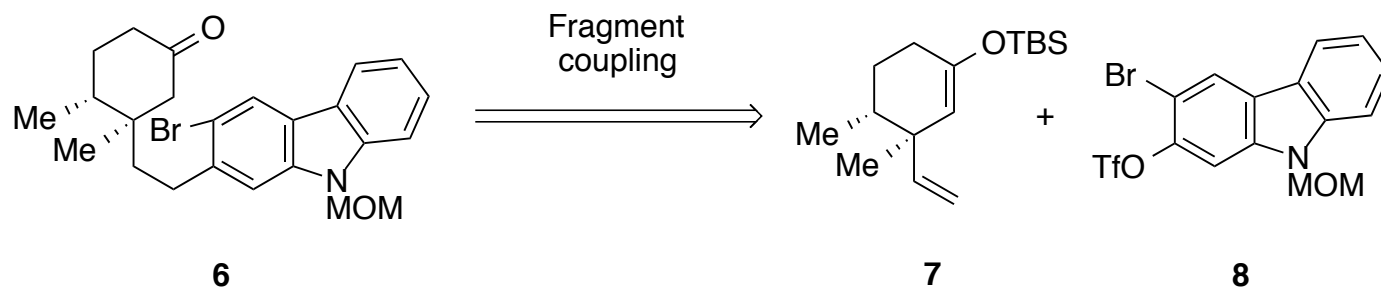
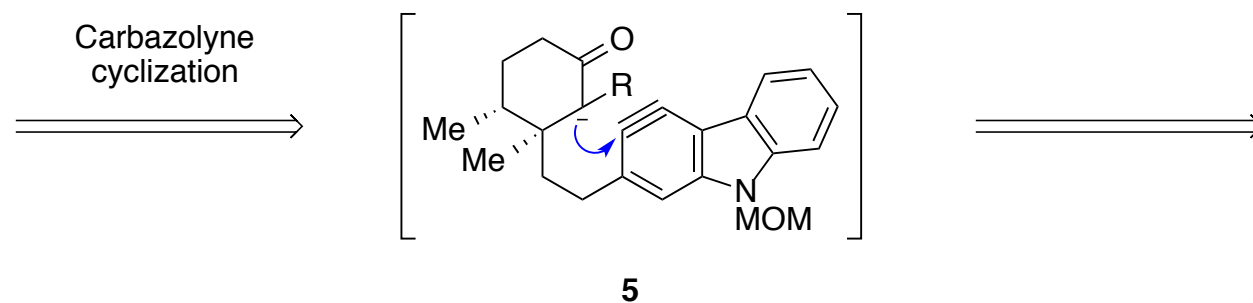
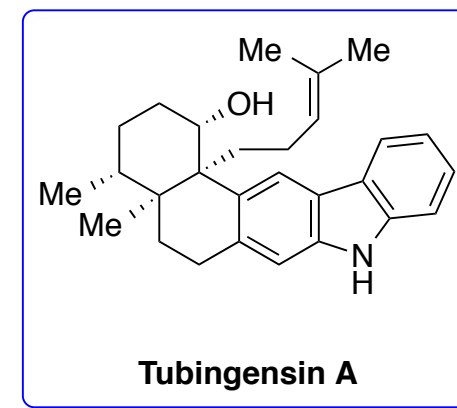
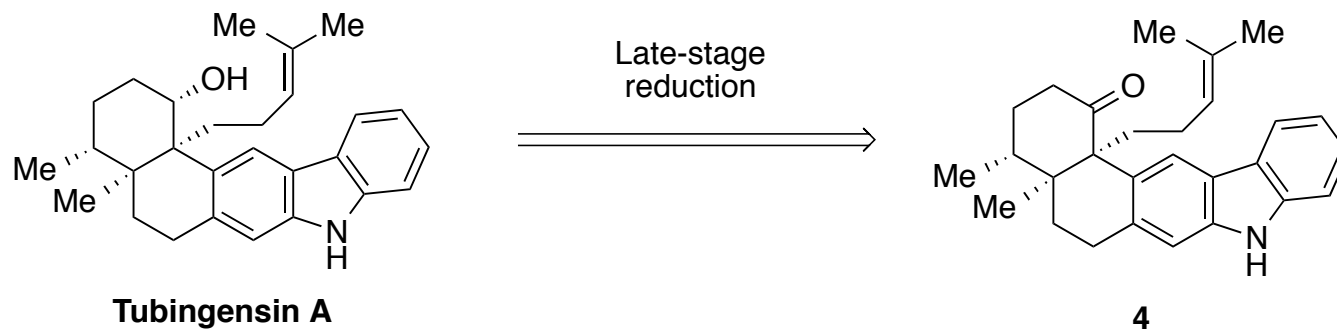
Nicolaou, K. C.; Li, A.: JACS **2012**, *134*, 8078

Garg N. C.: JACS **2014**, *136*, 3036–3039.

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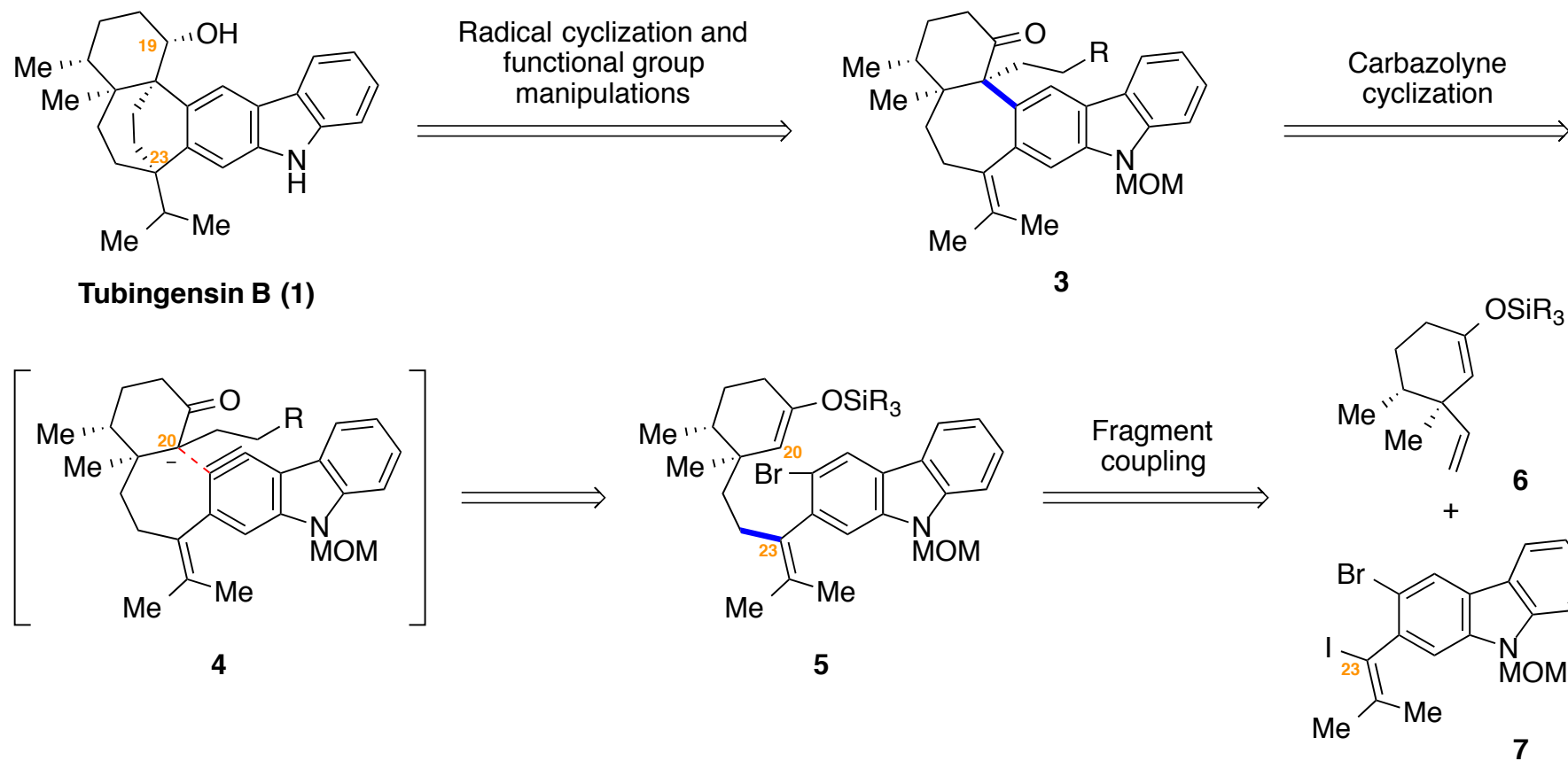
<sup>1</sup>Tetrahedron Lett. **1989**, *30*, 5965–5968

# Introduction

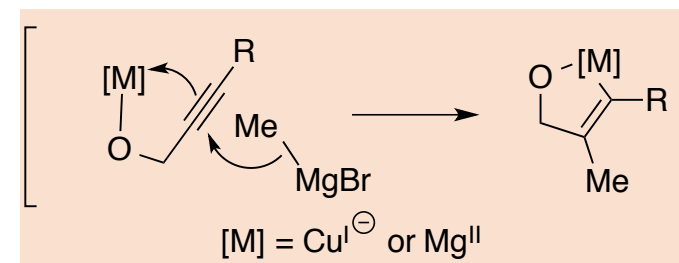
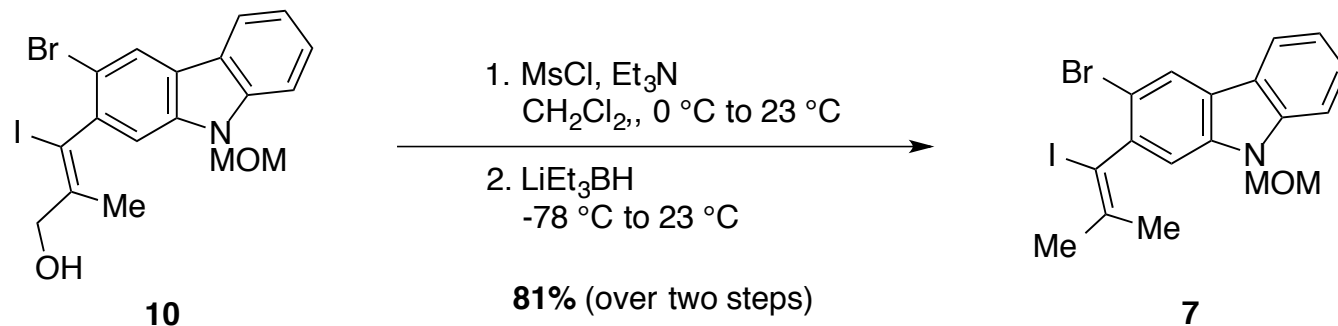
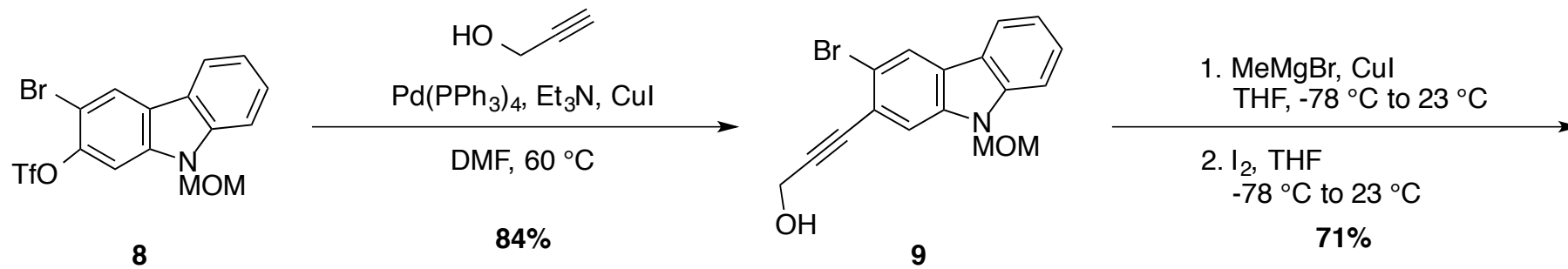


Nicolaou, K. C.; Li, A.: JACS **2012**, *134*, 8078  
Garg N. C.: JACS **2014**, *136*, 3036–3039.

# Retrosynthetic analysis of tubingensin B



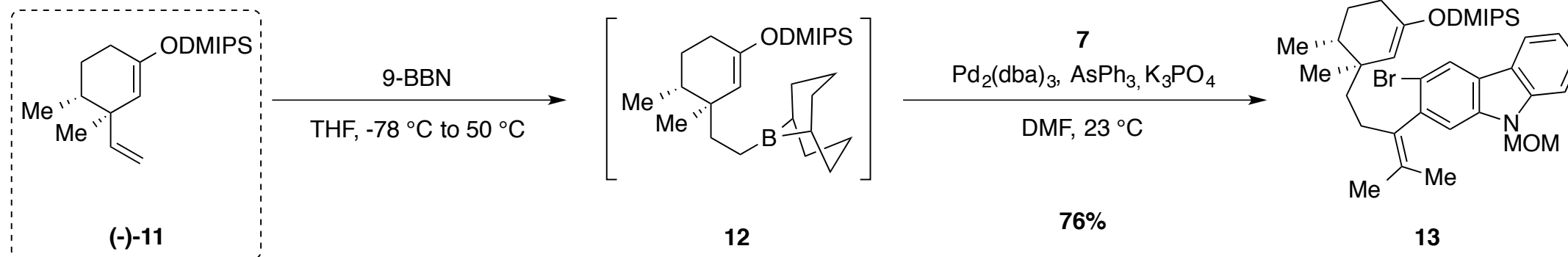
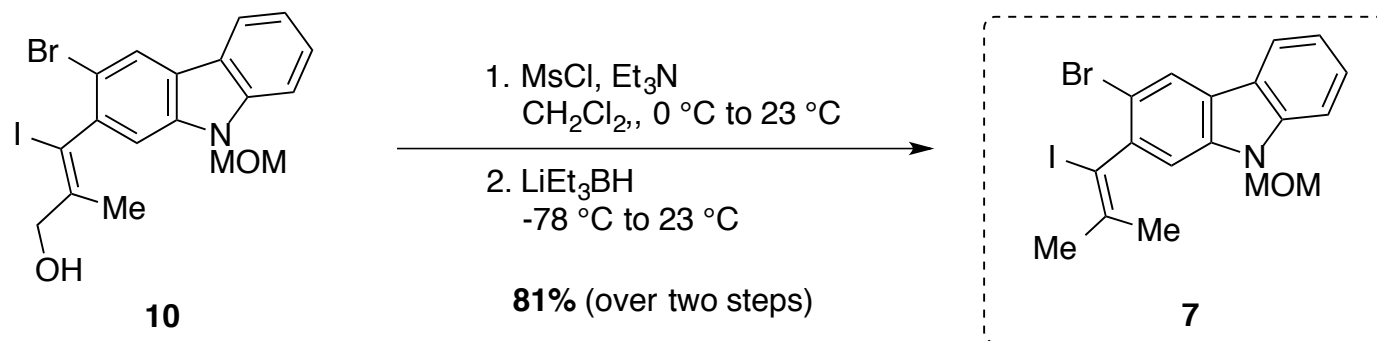
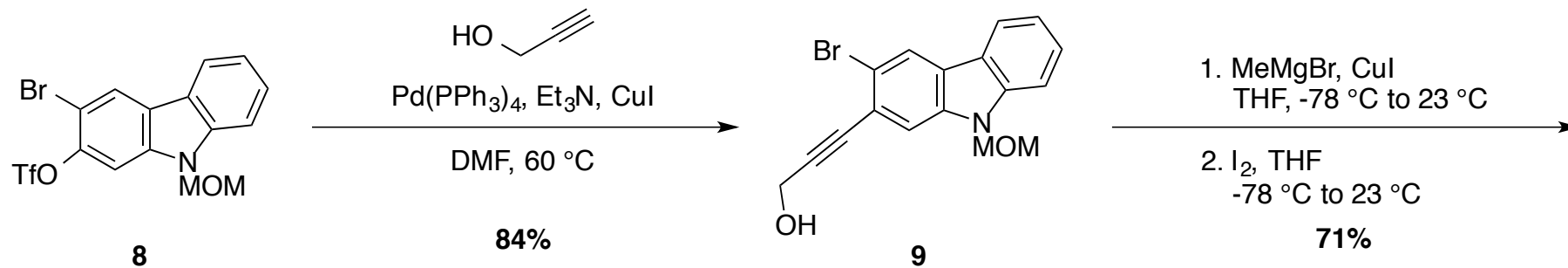
# Fragment coupling



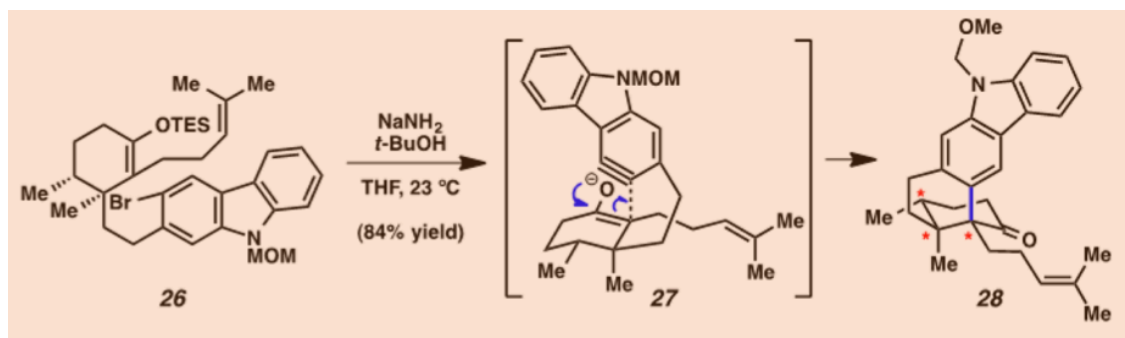
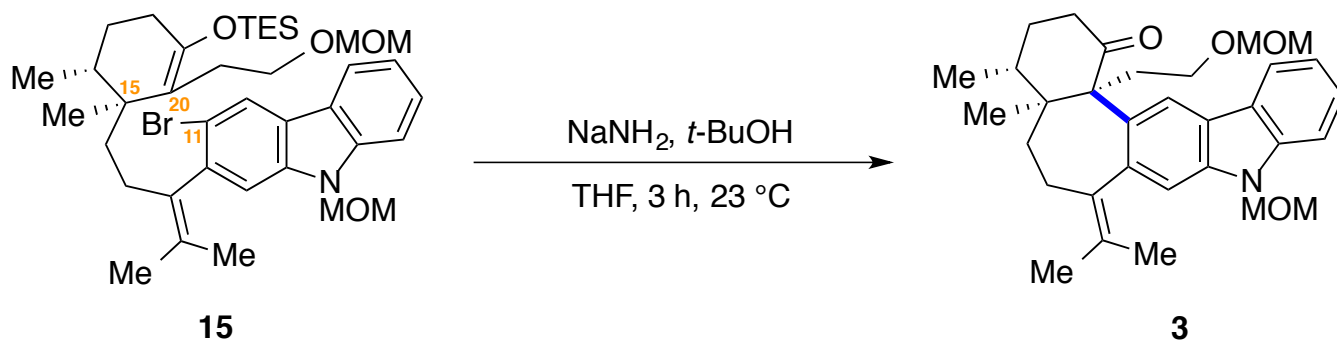
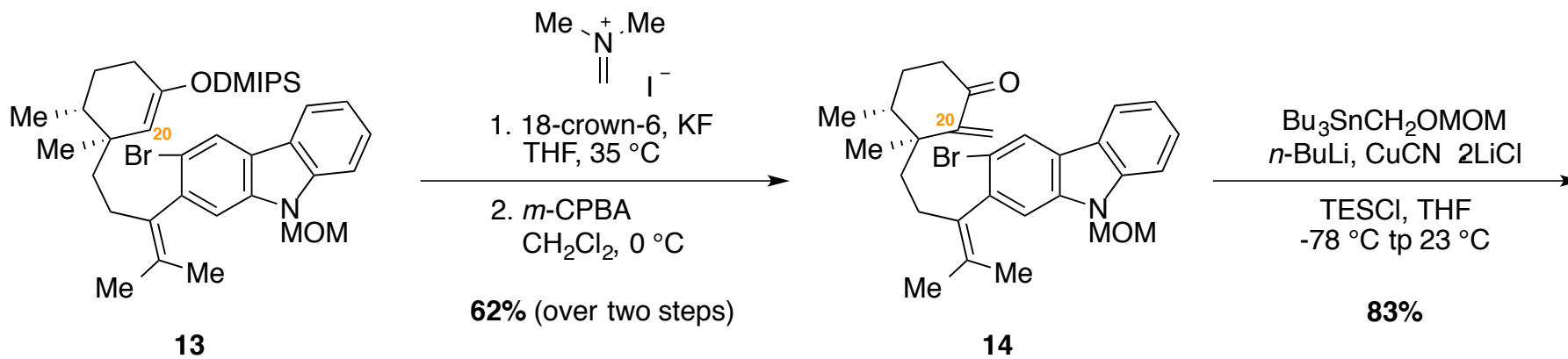
Acad. Sc. Paris, serie C 285 29 (1977)



# Fragment coupling

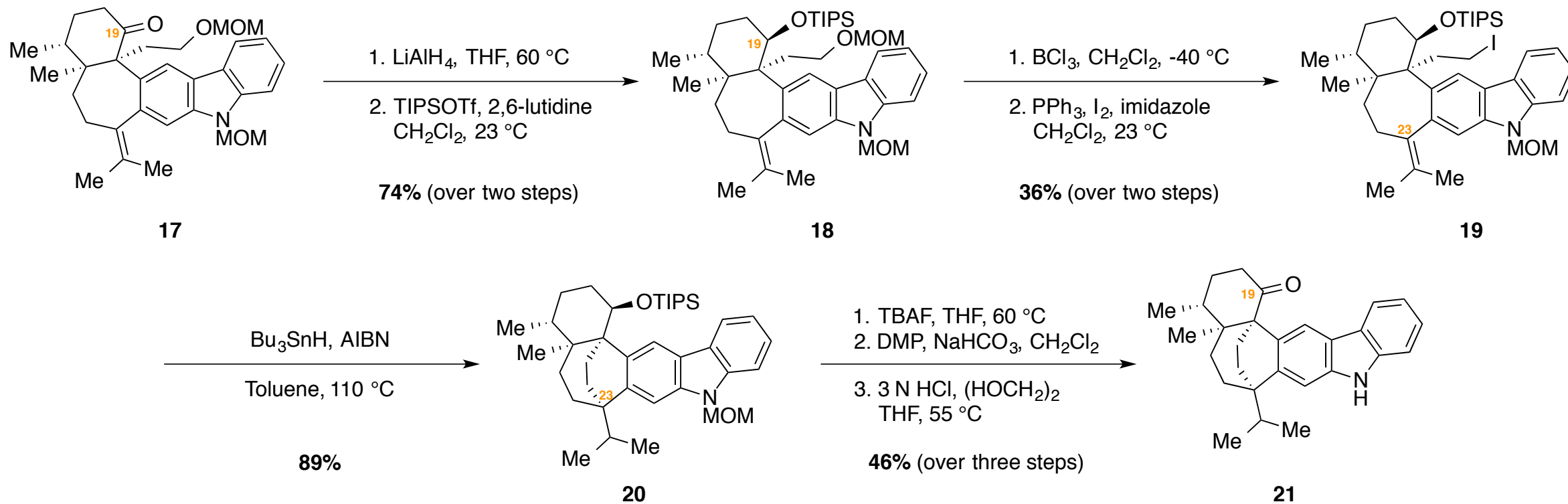


# Carbazolyne cyclization

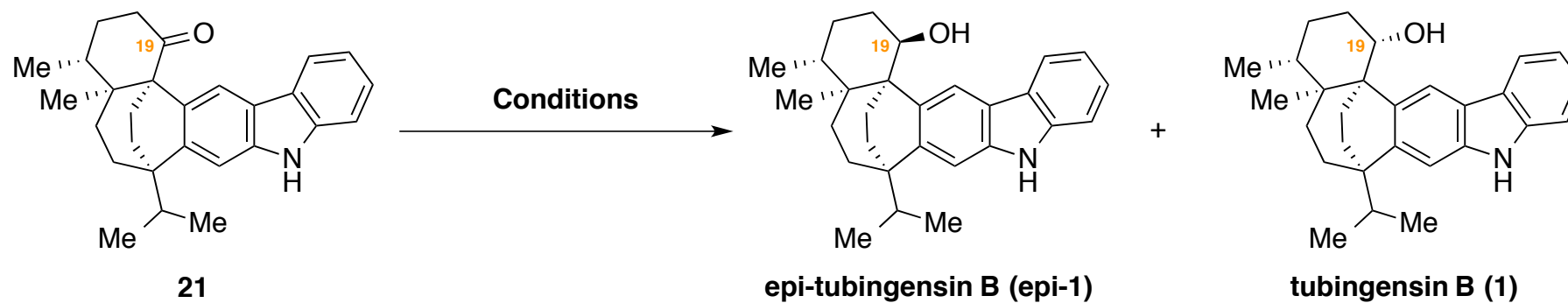




# Radical cyclization and functional group manipulations

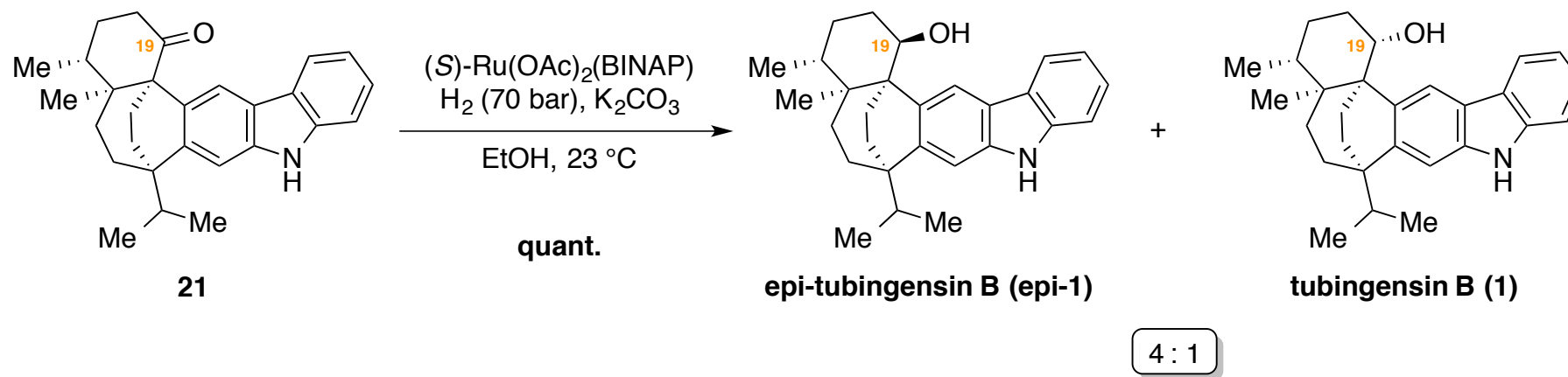


# End game

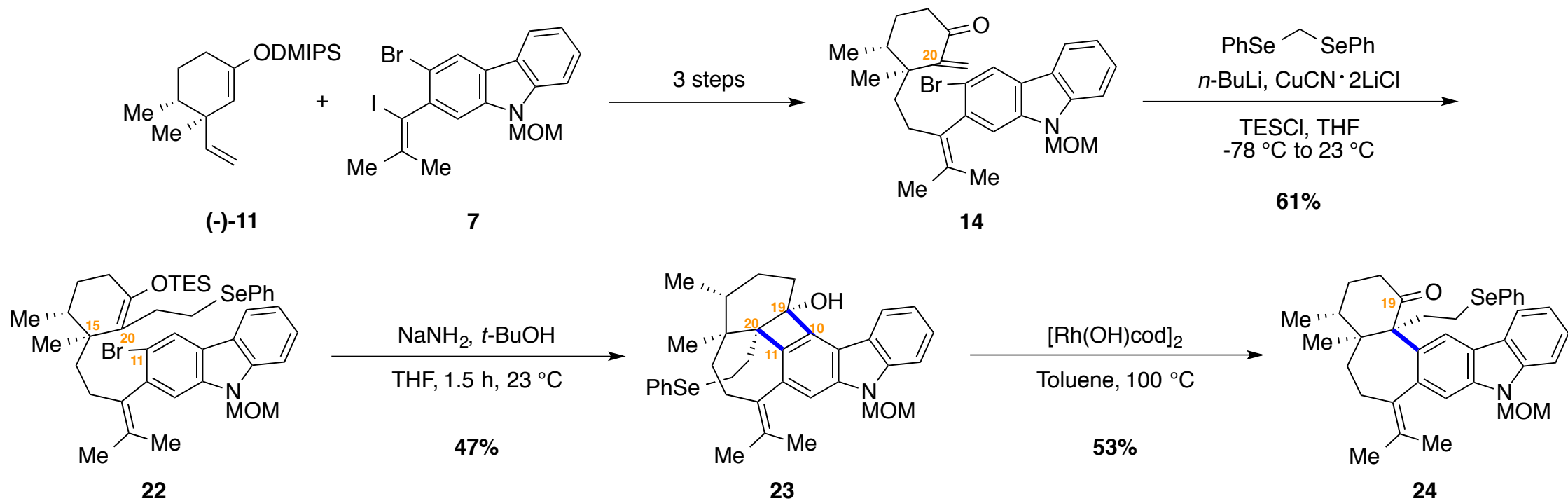


Conditions	Yield	d.r.
Na, <i>i</i> -PrOH, PhMe, 23 °C, 5 min	>99%	> 20:1
LiAlH <sub>4</sub> , THF, 23 °C, 10 min	>99%	> 20:1
DIBAL, PhMe, 23 °C, 15 min	>99%	> 20:1
L-selectride, THF, 23 °C, 25 min	no reaction	N/A
BH <sub>3</sub> •SMe <sub>2</sub> , THF, 23 °C, 2 h	>99%	> 20:1
BH <sub>3</sub> , ( <i>S</i> )- <i>B</i> -H-CBS catalyst, THF, 23 °C, 1 h	>99%	> 20:1
PtO <sub>2</sub> , H <sub>2</sub> (1 atm), AcOH, 40 °C, 1 h	decomposition	N/A
Rh/C, H <sub>2</sub> (1 atm), AcOH, 23 °C, 7 h	no reaction	N/A
Pt-black, H <sub>2</sub> (1 atm), EtOH, 23 °C, 24 h	50%	> 20:1

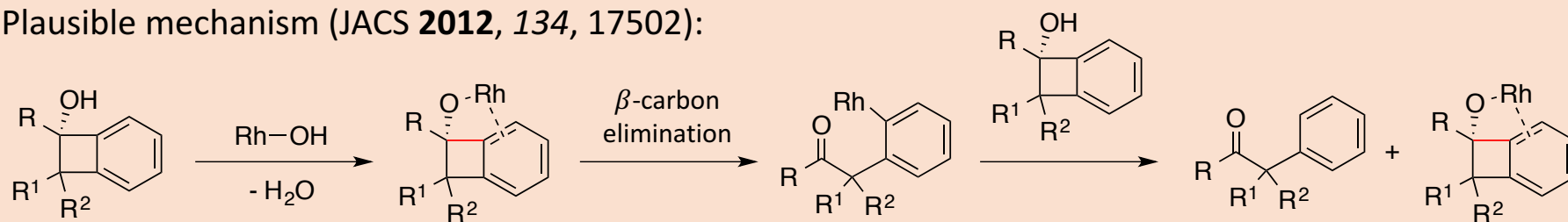
# End game



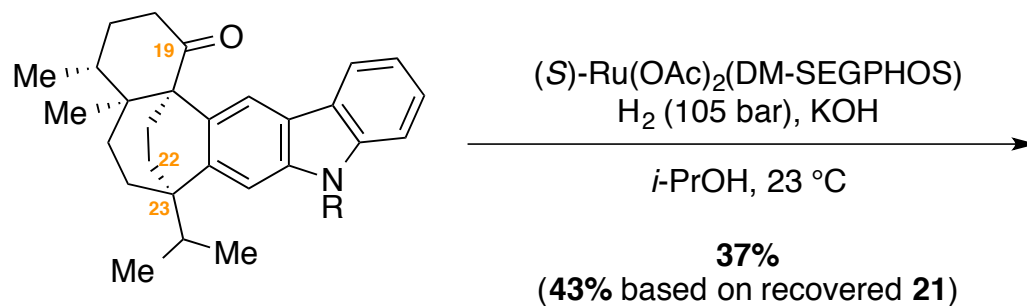
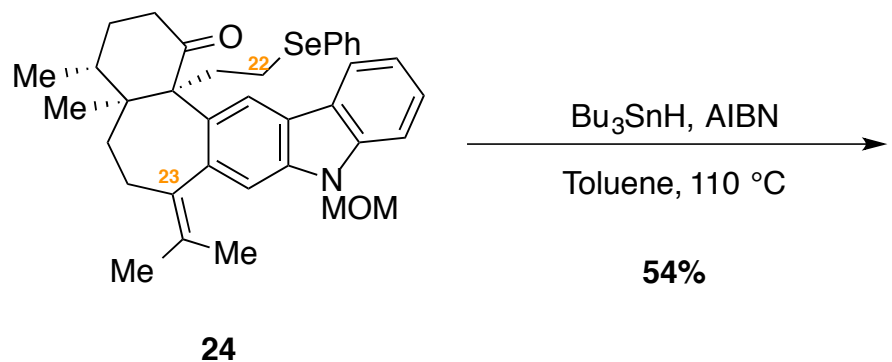
# Concise total synthesis of tubingensin B



Plausible mechanism (JACS **2012**, 134, 17502):



# Concise total synthesis of tubingensin B



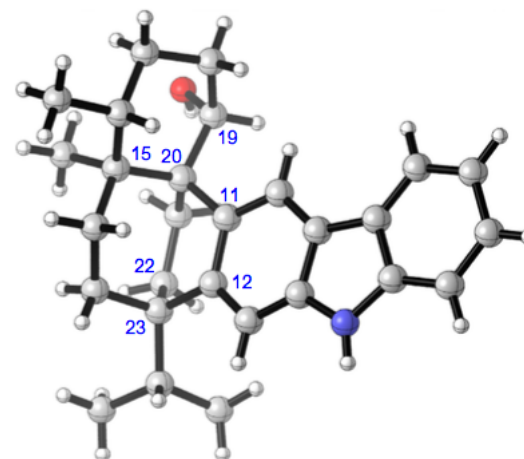
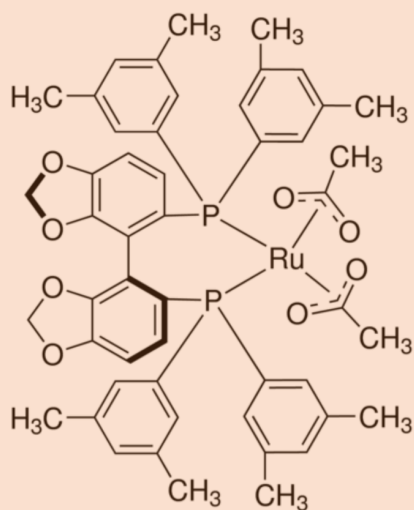
**25** (R = MOM)

**21** (R = H)

$3 \text{ N HCl}$ ,  $(\text{HOCH}_2)_2$   
 THF, 55 °C  
**67%**

**1:1.3 ratio**  
 (-)-Tubingensin B/Epi-Tubingensin B

$(S)\text{-Ru(OAc)}_2(\text{DM-SEGPHOS})$

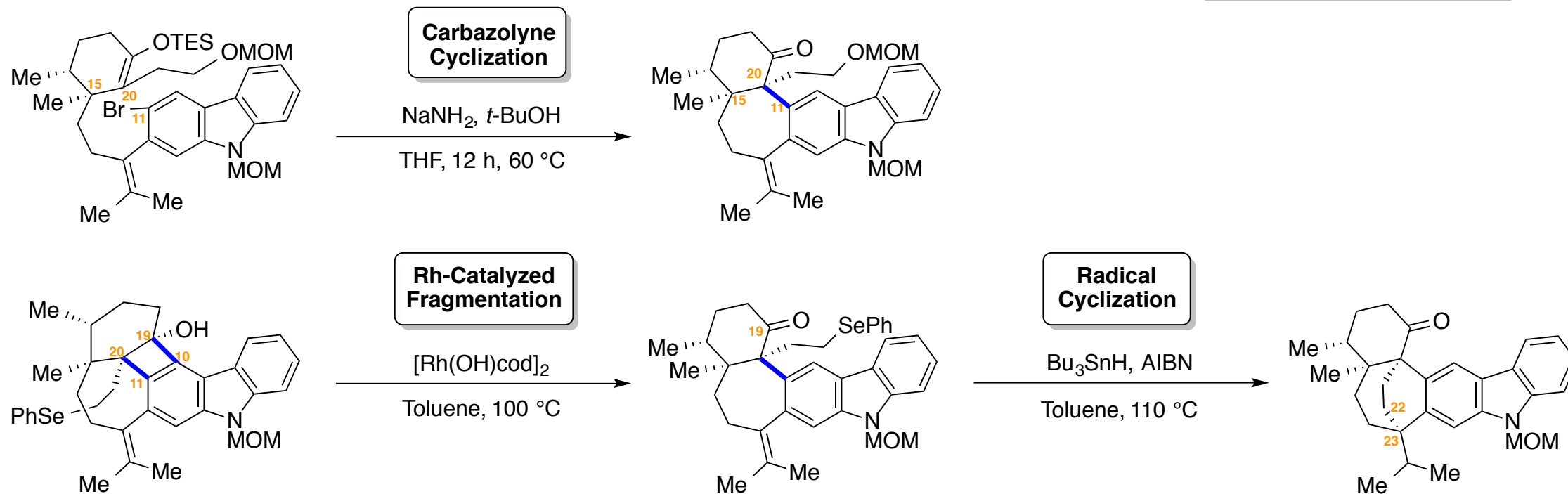
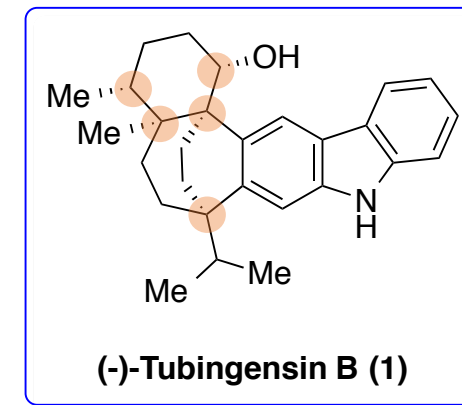


Crystal structure of (-)-Tubingensin B  
 Acta Cryst. C**53**, 1447–1449 (1997)



# Conclusion

- First total synthesis of (-)-Tubingensin B
- Concise enantiospecific route
- Several key steps



Thank you for your attention