

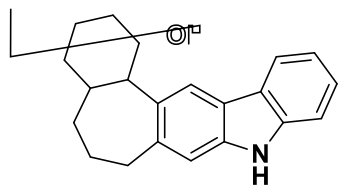
# Total synthesis of (-)-tubingensin B enabled by the strategic use of an aryne cyclization

Michael A. Corsello, Junyong Kim, and Neil K. Garg

*Nat. Chem.* **2017**, 9, 944 - 949.

- An indole diterpenoid isolated from the fungus *Aspergillus tubingensis* in 1989.
- Exhibits activity against crop pests, cytotoxicity against cervical cancer cells, and *in vitro* activity against cancer cells.

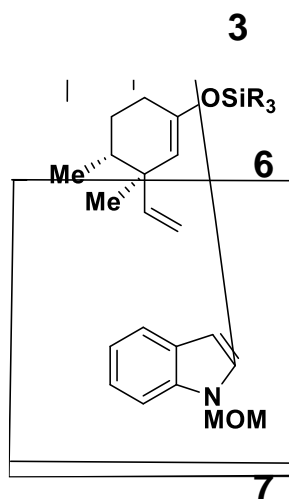
# Retrosynthesis



Tubingensin B (1)

Radical cyclization  
and functional group  
manipulations

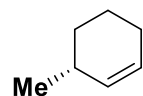
Carbazolyne  
cyclization



Fragment  
coupling

4

5



SI-1

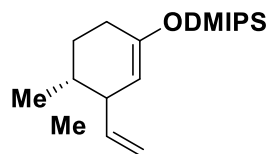
i. vinylMgBr, CuI  
THF, -78 °C  
ii. HMPA, *i*-PrMe<sub>2</sub>SiCl  
-78 to 23 °C  
(quantitative yield)

(-)-11

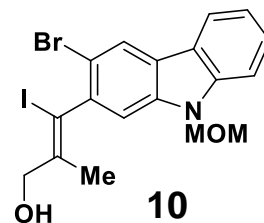
**9**

(i) MeMgBr, CuI  
THF, -78 to 23 °C

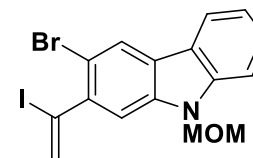
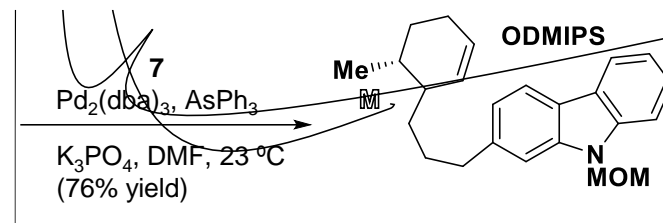
(ii) I<sub>2</sub>, THF  
-78 to 23 °C  
(71% yield)

**(-)-11**

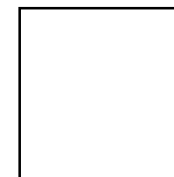
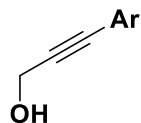
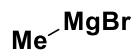
9-BBN  
THF  
-78 to 50 °C

**10**

1. MsCl, Et<sub>3</sub>N  
CH<sub>2</sub>Cl<sub>2</sub>, 0 to 23 °C  
2. LiEt<sub>3</sub>BH,  
-78 to 23 °C  
(81% yield, 2 steps)

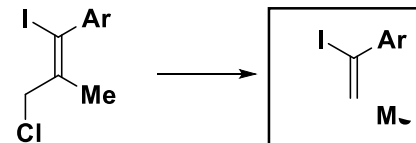
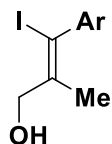
**7****13**

### Carbometallation/Iodination

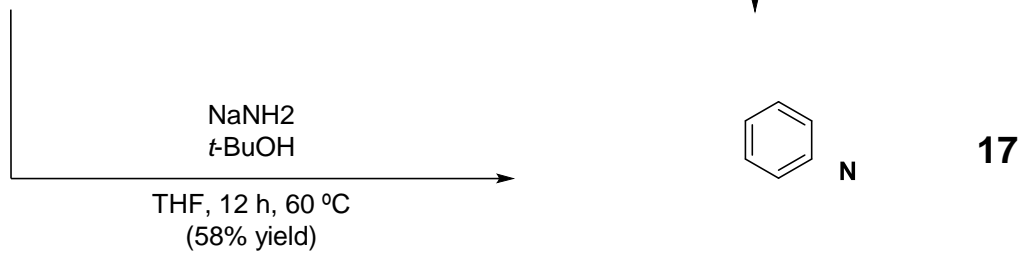
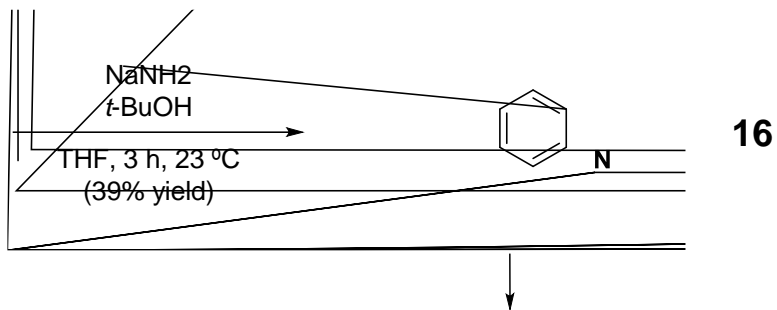
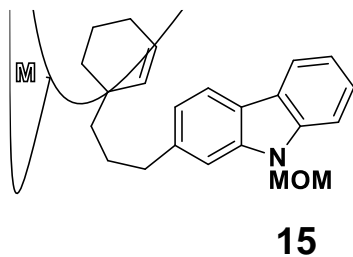


### Two-step Deoxygenation protocol

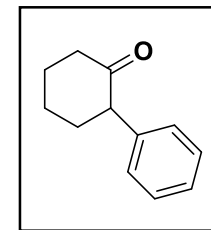
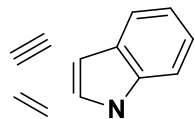
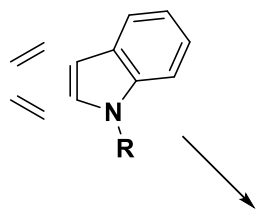
Me



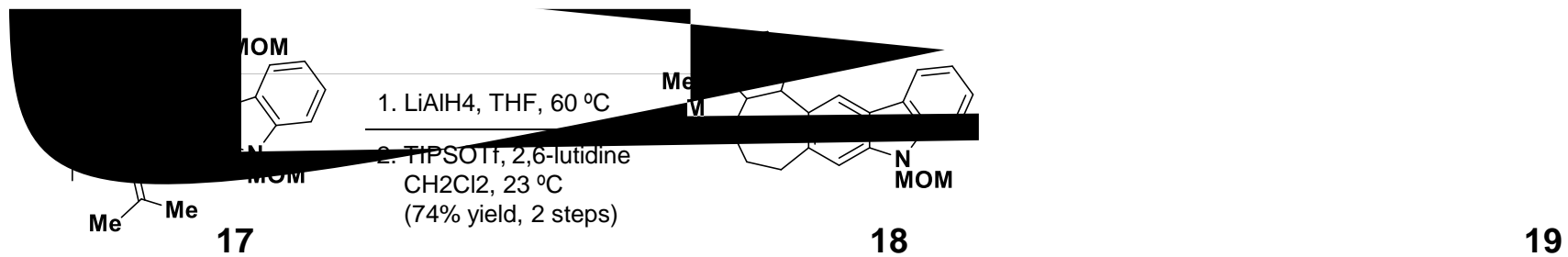




## Carbazolyne (heteroaryne) cyclization

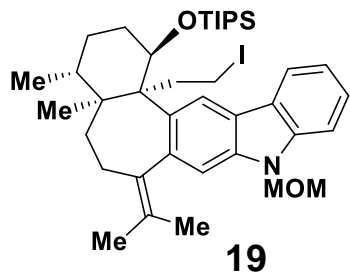


**17**



Reduction and silyl protection



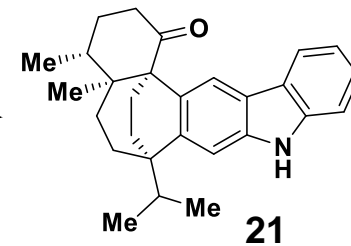


Bu<sub>3</sub>SnH, AIBN

Toluene, 110 °C  
(89% yield)

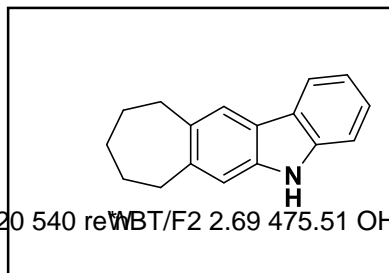
**20**

1. TBAF, THF 60 °C  
2. DMP, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>  
3. 3 N HCl, (HOCH<sub>2</sub>)<sub>2</sub>  
THF, 55 °C  
(46% yield, 3 steps)



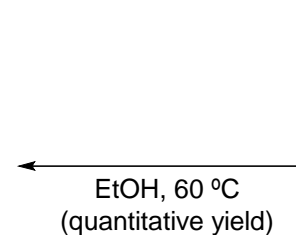
1 : 4

(qu27/P 4MCID 29>BDC 77.28 8220 540 reWB/F2 2.69 475.51 OH

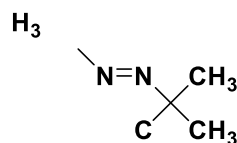


(-)-Tubingensin B (**1**)

Epi-tubingensin B (epi-**1**)

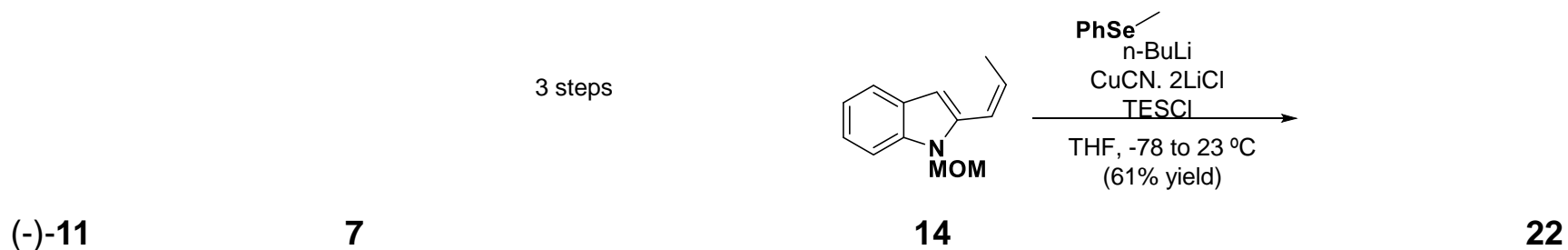


Radical cascade



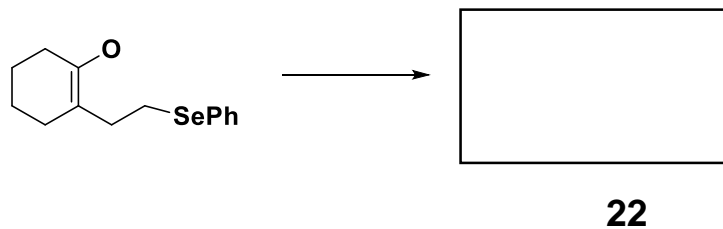
**20**

Alternative route in order to provide better product yield, utilizing phenyl-Selenium

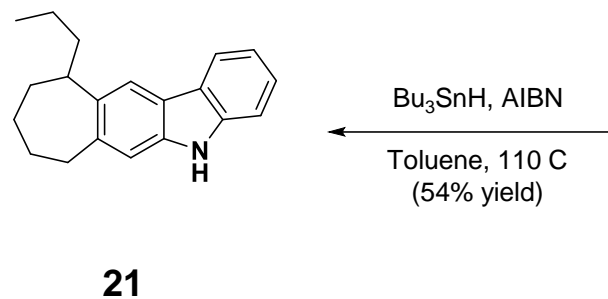
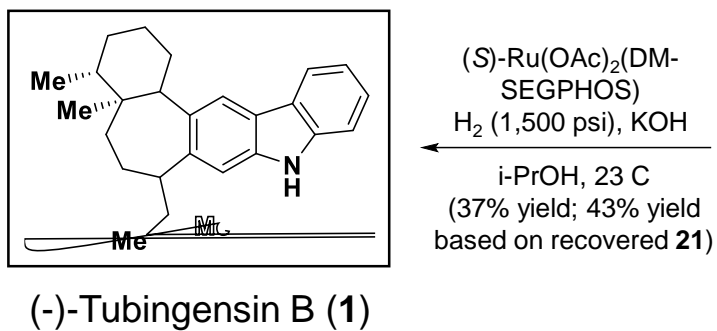
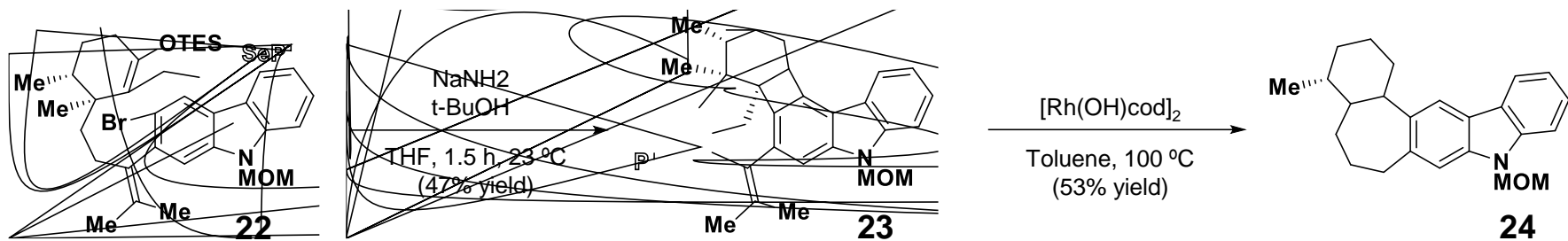


Phenyl-Selenium addition and silyl trapping

PhSe-







### Murakami's Rhodium-catalyzed ring opening

