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

Michael A. Corsello, Junyong Kim, and Neil K. Garg
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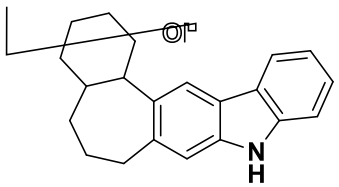
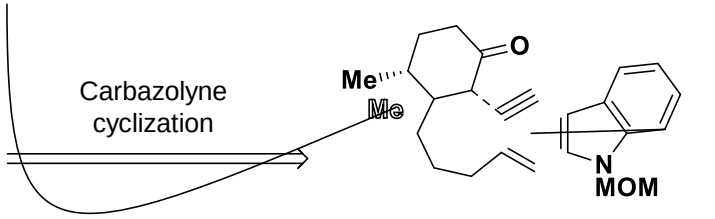
- An indole diterpenoid isolated from the fungus *Aspergillus tubingensis* in 1989.
- Exhibits activity against crop pests, cytotoxicity against cervical cancer cells, and *in vitro*

Retrosynthesis



Tubingensin B (**1**)

Radical cyclization
and functional group
manipulations



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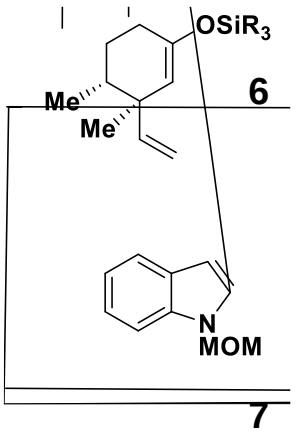

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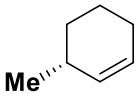
Fragment
coupling

5

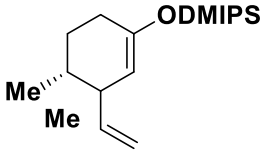


SI-**1**

i. vinylMgBr, CuI
THF, -78 ºC

ii. HMPA, *i*-PrMe$_2$SiCl
-78 to 23 ºC
(quantitative yield)

(-)-**11**



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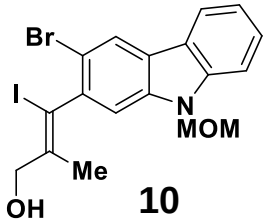
(i) MeMgBr, CuI
THF, -78 to 23 ºC

(ii) I_2, THF
-78 to 23 ºC
(71% yield)



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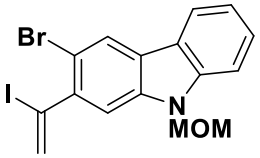
1. MsCl, Et_3N
CH_2Cl_2, 0 to 23 ºC

2. $LiEt_3BH$,
-78 to 23 ºC
(81% yield, 2 steps)



7

9-BBN

THF
-78 to 50 ºC

(-)-**11**

12

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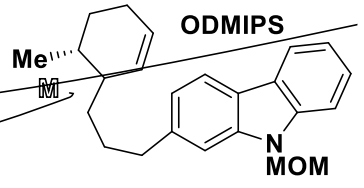
$Pd_2(dba)_3$, $AsPh_3$

K_3PO_4, DMF, 23 ºC
(76% yield)



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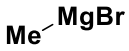
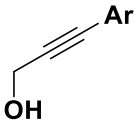
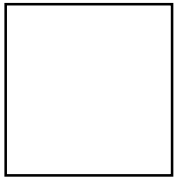
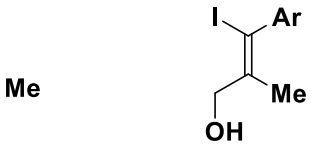
Carbometallation/Iodination

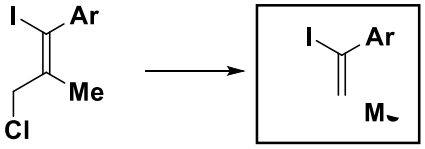


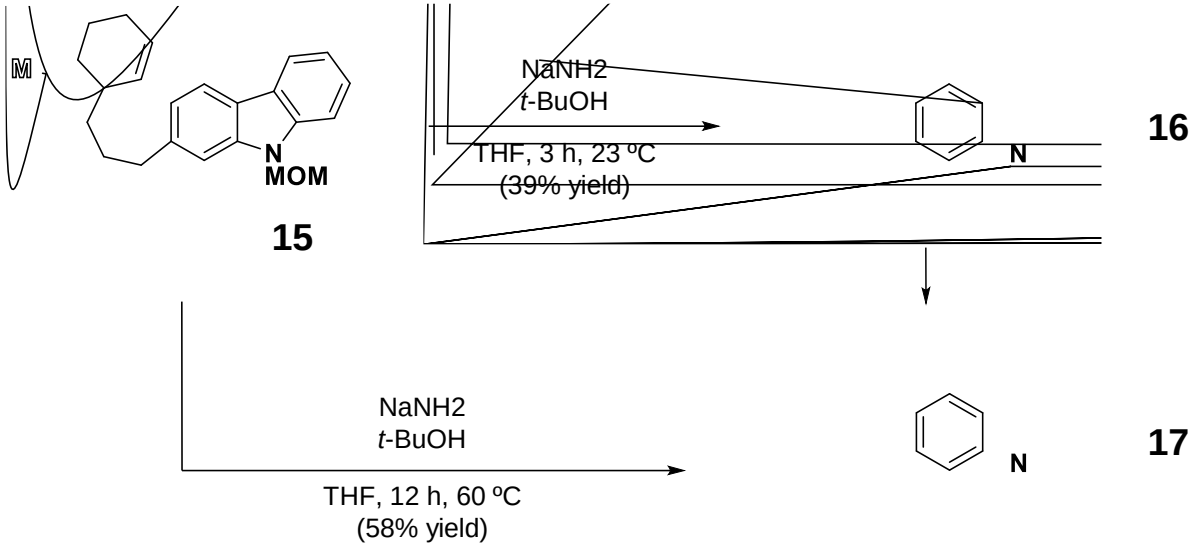




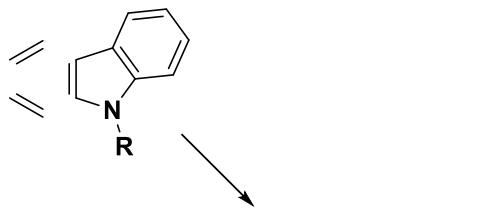
Two-step Deoxygenation protocol

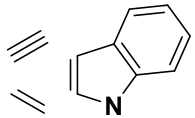






Carbazolyne (heteroaryne) cyclization





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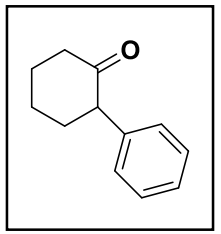

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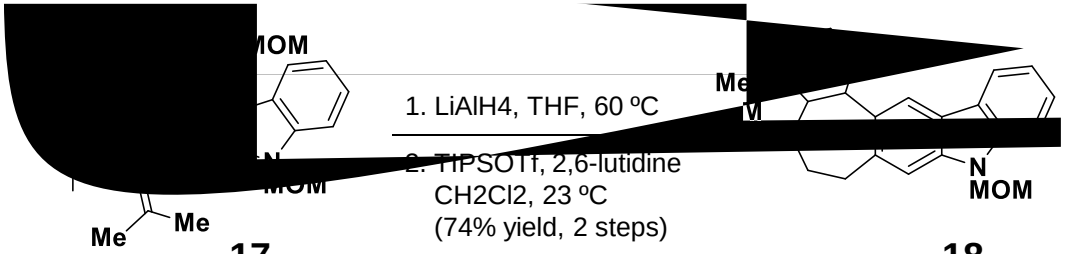
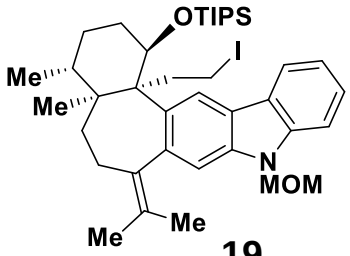


17 **18** **19**

Reduction and silyl protection



19

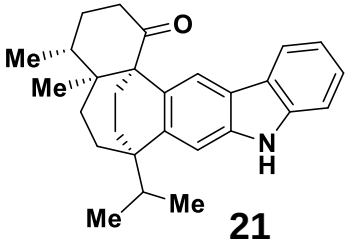
Bu_3SnH, AIBN

Toluene, 110 C
(89% yield)

20

1. TBAF, THF 60 ºC
2. DMP, $NaHCO_3$, CH2Cl2

3. 3 N HCl, $(HOCH_2)_2$
THF, 55 ºC
(46% yield, 3 steps)

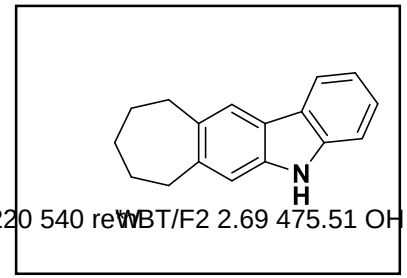


21

EtOH, 60 ºC
(quantitative yield)

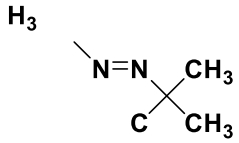
1 : 4

(qu27/P /AMCID 29>BDC 77.28 8220 540 reWBT/F2 2.69 475.51 OH



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

Radical cascade



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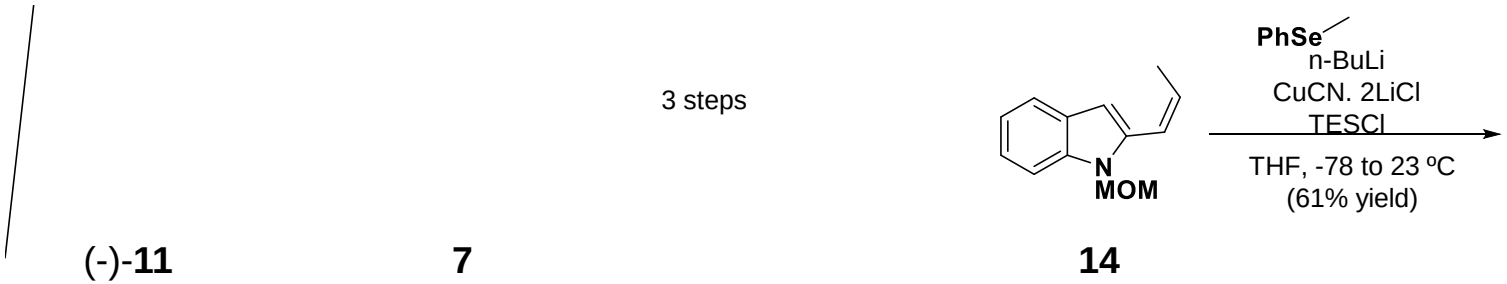
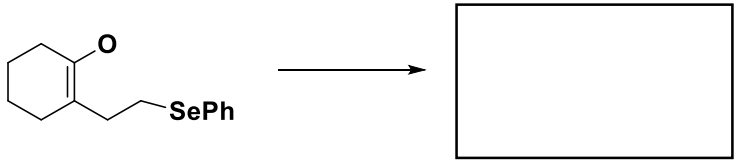
Alternative route in order to provide better product yield, utilizing phenyl-Selenium



(-)-**11** **7** **14** **22**

Phenyl-Selenium addition and silyl trapping



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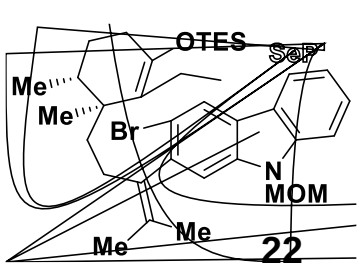

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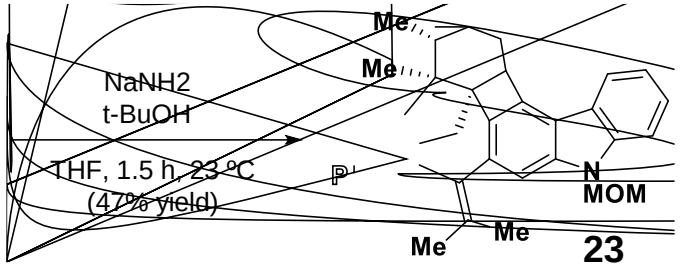
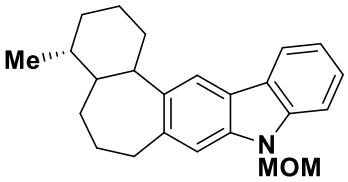


23

$[Rh(OH)cod]_2$

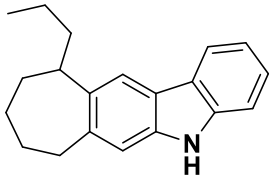
Toluene, 100 ºC
(53% yield)



24

Bu_3SnH, AIBN

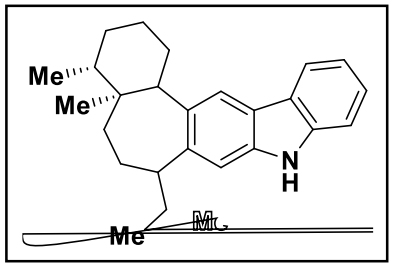
Toluene, 110 C
(54% yield)



21

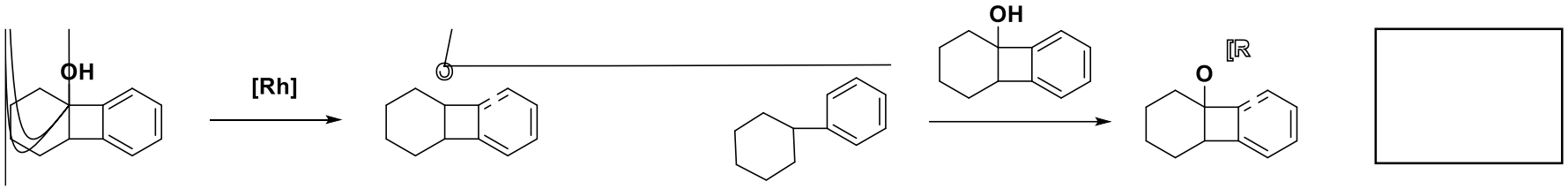
(*S*)-$Ru(OAc)_2$(DM-SEGPHOS)
H_2 (1,500 psi), KOH

i-PrOH, 23 C
(37% yield; 43% yield based on recovered **21**)



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

Murakami's Rhodium-catalyzed ring opening



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