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

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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* antiviral activity against herpes simplex virus type 1 (HSV-1).

• The molecule contains a carbazole unit which at first seems deceptively simple, but is in the presence of two adjacent sp2-sp3 C-C bond linkages.

• Bicyclo[3.2.2]nonane core fused to the carbazole, and a densely functionalized six-membered ring.

• The natural product possesses five stereogenic centers, four of which are contiguous, three are quaternary, and two vicinal quaternary.

• Garg group previously synthesized Tubingensin A, and adapted that procedure to synthesize Tubingensin B.

• Key reactions are a late-stage radical cyclization, as well as a carbazolyne (aryne) cyclization followed by a Rh-catalyzed fragmentation.

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October 11th, 2017
Liu Group
Retrosynthesis

Radical cyclization and functional group manipulations

Tubingensin B (1)

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Carbazolyne cyclization

4

Fragment coupling

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i. vinylMgBr, CuI
THF, -78 ºC

ii. HMPA, i-PrMe₂SiCl
-78 to 23 ºC
(quantitative yield)

SI-1

(-)-11
Two-step Deoxygenation protocol

(i) MeMgBr, Cul
THF, -78 to 23 ºC
(ii) I₂, THF
-78 to 23 ºC
(71% yield)

1. MsCl, Et₃N
CH₂Cl₂, 0 to 23 ºC
2. LiEt₃BH,
-78 to 23 ºC
(81% yield, 2 steps)

Carbometallation/Iodination

Me⁻MgBr
+ Cul
Me-[Cu] + 
CH₂Cl₂, 0 to 23 ºC

Two-step Deoxygenation protocol

Me⁻S-O
Cl
+ OH
Me⁻S-O
O=SO
OH

Pd₂(dba)₃, AsPh₃
K₃PO₄, DMF, 23 ºC
(76% yield)
Eschenmoser methenylolation

1. 18-crown-6, KF, THF, 35 °C
2. m-CPBA, CH$_2$Cl$_2$, 0 °C
(62% yield, 2 steps)

Conjugate addition with *in situ* prepared cuprate

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Carbazolyne (heteroaryne) cyclization

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\[
\text{NaNH}_2 \quad t-\text{BuOH} \quad \text{THF, 3 h, 23 °C} \quad (39\% \text{ yield})
\]

16

\[
\text{NaNH}_2 \quad t-\text{BuOH} \quad \text{THF, 12 h, 60 °C} \quad (58\% \text{ yield})
\]

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Reduction and silyl protection

MOMO deprotection with BCl₃

Appel Reaction
Radical cascade

1. TBAF, THF 60 ºC
2. DMP, NaHCO₃, CH₂Cl₂
3. 3 N HCl, (HOCH₂)₂THF, 55 ºC

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(-)-Tubingensin B (1) Epi-tubingensin B (epi-1)
Phenyl-Selenium addition and silyl trapping

Alternative route in order to provide better product yield, utilizing phenyl-Selenium
Murakami’s Rhodium-catalyzed ring opening

(-)-Tubingensin B (1)

(S)-Ru(OAc)₂(DM-SEGPHOS) H₂ (1,500 psi), KOH i-PrOH, 23 C (37% yield; 43% yield based on recovered 21)

NaNH₂ t-BuOH THF, 1.5 h, 23 ºC (47% yield)

[Rh(OH)cod]₂ Toluene, 100 ºC (53% yield)

Bu₃SnH, AIBN Toluene, 110 C (54% yield)

OH

[Rh]

O

[Rh]

O

[Rh]

[Rh]

OH

H₂

KOH

i-PrOH

24