

# Total Synthesis of

---

# Total Synthesis of Verruculogen

---

# Total Synthesis of Verruculogen and Fumitremorgin A

## III. Synthesis

### I. Rationality to direct C-H functionalization on indole C6 position

Literature summary: reported methods to 6-methoxytryptophan (continued) (see SI for details)

C:

---

C-H functionalization was applied to this C6 problem.

Indole preferentially react at C2, C3 and C7. C6 is the most difficult position to directly functionalize on indole.

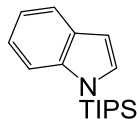
C-H borylation on tryptophan system: C2 and C7

Ligand control of regioselectivity and large blocking group on indole nitrogen for desired regioselectivity.



# Total Synthesis of Verruculogen and Fumitremorgin A

C-H borylation of indole derivatives: indoles and carbozoles substrate scope



This method has been field-tested on decagrams scale at Novartis for valuable unnatural amino acid.

## II. Total Synthesis of Verruculogen and Fumitremorgin A

Modified Chan-Evans-Lam condition by Merlic, C. A. et al: suitable for simple alkyl and allyl alcohol; BPin is better than boronic acid; only 1 equiv. boron partner.



# Total Synthesis of Verruculogen and Fumitremorgin A

Silane	Yield (%)
TESi-H	73
TBSi-H	30
TIPSi-H	No reaction
TBDPSi-H	No reaction

TES-TBDPS switch to make the intermediates stable in the following steps.

Related reaction

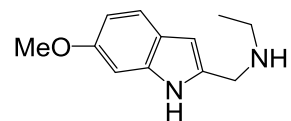
Regioselectivity in Isayama-Mukaiyama peroxygenation is based on the relative reactivity of alkene (radical stability, steric effect and electronic factor).

# Total Synthesis of Verruculogen

---



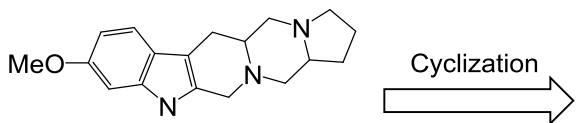
# Total Synthesis of Verruculogen and Fumitremorgin A



Upjohn

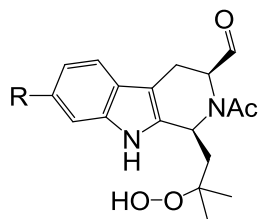
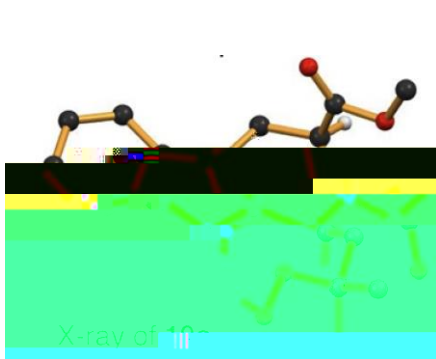
H

# Total Synthesis of Verruculogen and Fumitremorgin A



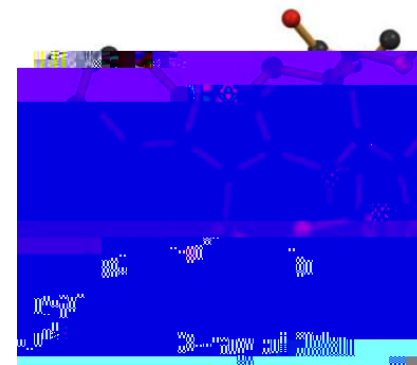
N

18



**19a:** R = H

**19b:** R = OMe



# Total Synthesis of Verruculogen and Fumitremorgin A

---

Stereochemistry in  
cyclization: nitrogen attack  
from the bottom face

Wang, X. CN104610125A

Hanessian S. et al. *Tetrahedron* **1985**, *41*, 643-663.

Martinelli, M. J. et al. *J. Am. Chem. Soc.*, **2002**, *124*, 3578-3585.

# Total Synthesis of Verruculogen and Fumitremorgin A

## IV. Summary

More than 40-years unsolved synthetic challenge posed by the peroxide-containing alkaloids, verruculogen (**2**) and fumitremorgin A (**1**), has been accomplished in 11 and 12 steps, respectively.

Iridium-catalyzed regioselective borylation of the remote C6 position of tryptophan as a general way to functionalize C6 position of an N,C3-disubstituted indole.

Hydroperoxide/indole hemiaminal cyclization to peroxide.