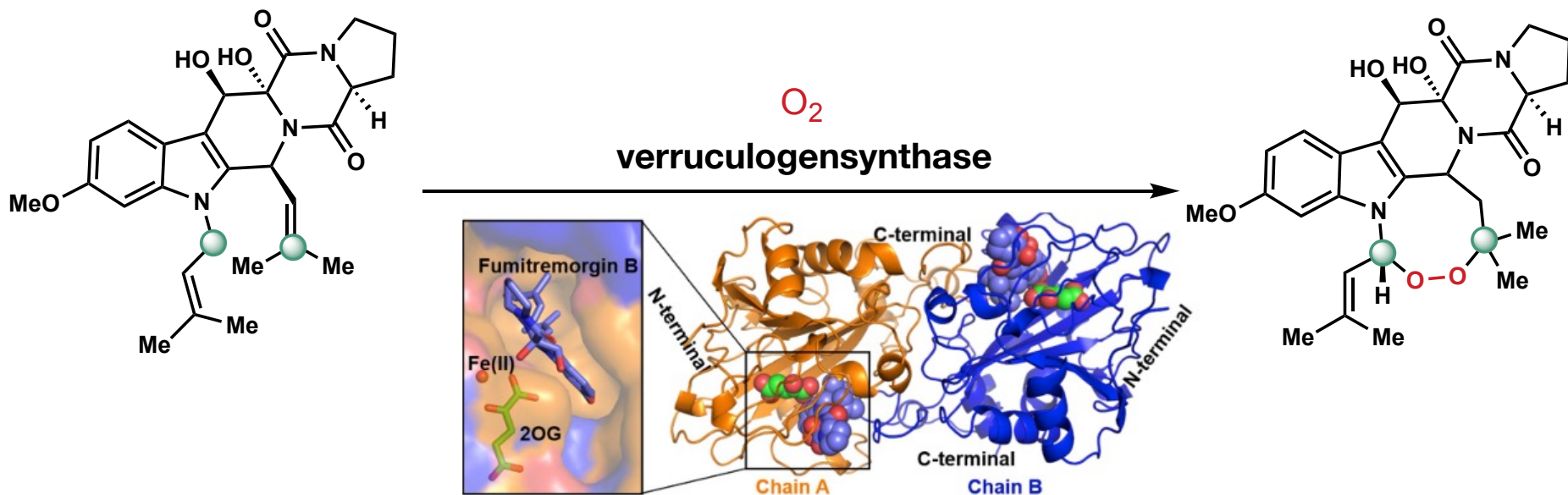




## Chemoenzymatic Synthesis of 13-Oxoverruculogen Via FtmOx1



September 1<sup>st</sup>, 2023

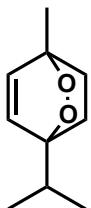
Group Meeting

Kevin Zong

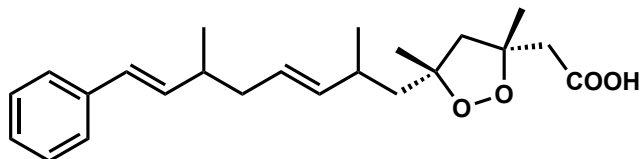
Shenvi Lab



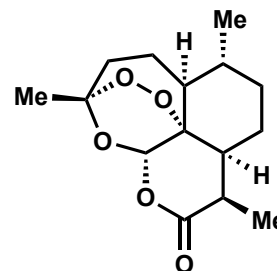
# Endoperoxy-Containing Natural Products



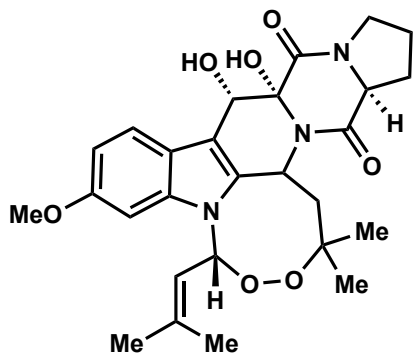
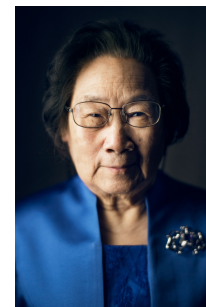
**ascaridole**  
complete inhibition of  
*Sclerotium Rolfsii*



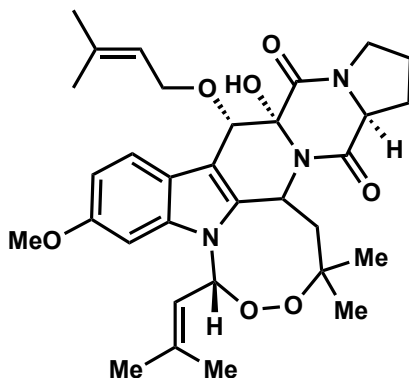
**plakinic acid A**  
antifungal and anti-parasitic



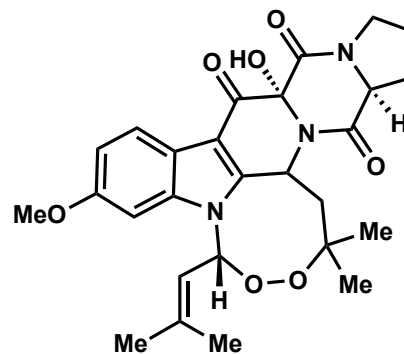
**artemisinin**  
2015 nobel prize  
for malaria treatment  
Youyou Tu



**verruculogen**



**fumitremorgen A**



**13-Oxoverruculogen**



*aspergillus fumigatus*

tremor inducing

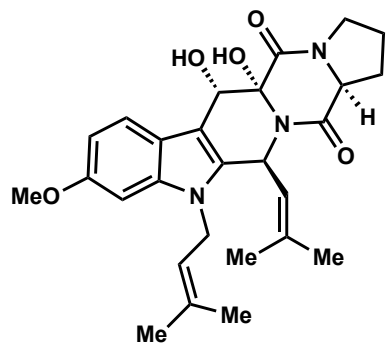
cytotoxicity against cancer cell line



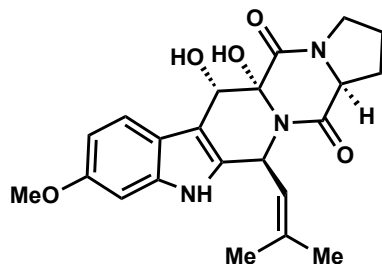
# Prior Work

Synthesized by:

Nakagawa (Biomimetic)  
Goto-Nakatsuka (Convergent)  
and more, including analogs



fumitremorgen B

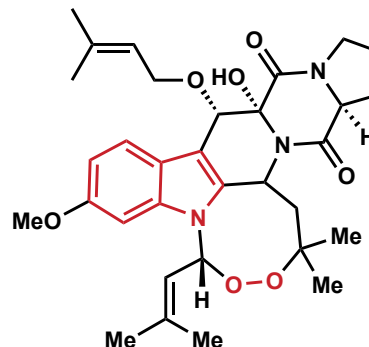


fumitremorgen C

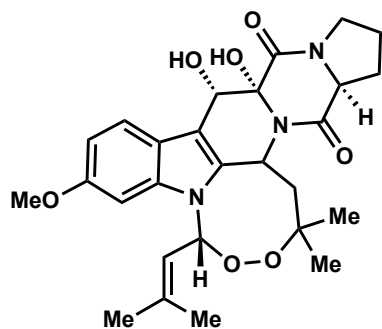
Why was this synthesis so “impossible?”

Presence of indole and 8-membered endoperoxide

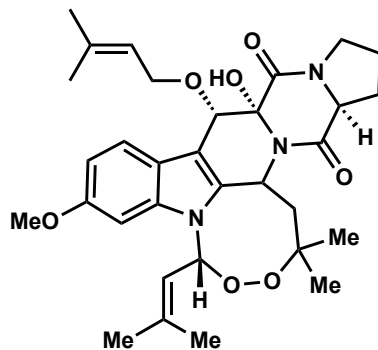
Protecting group reliant



Synthesized by Baran et al, 2015

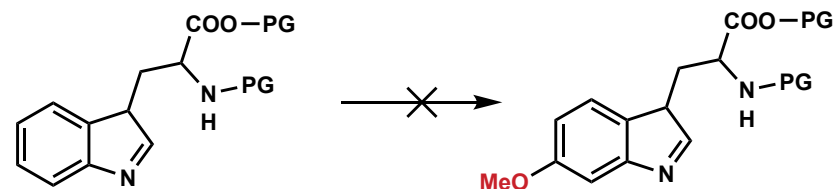


verrucologen



fumitremorgen A

No reliable method for installing methoxy on C6

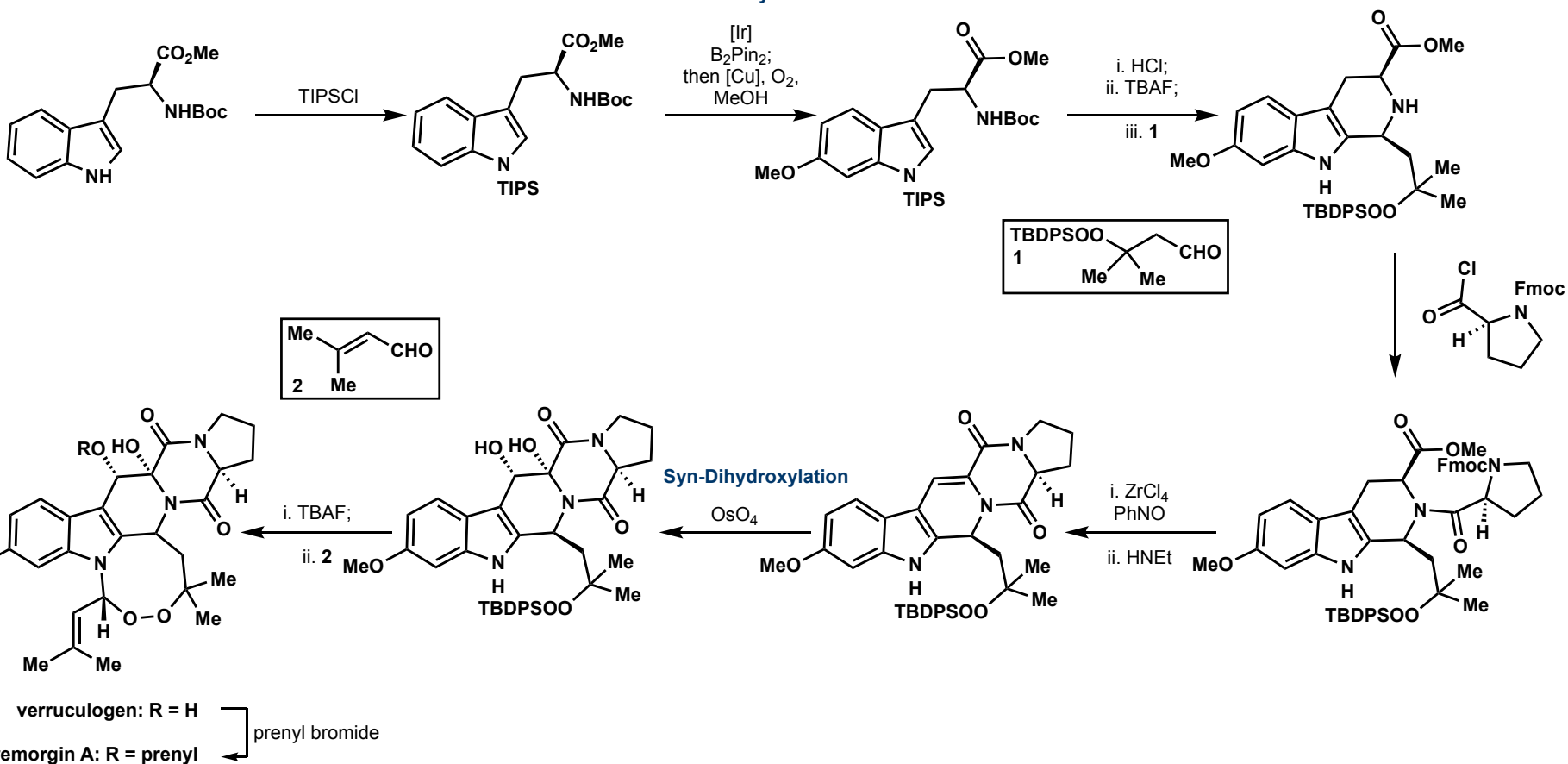




# Baran Group's Synthesis

Iridium catalyzed  
C-H Borylation

Pictet-Spengler

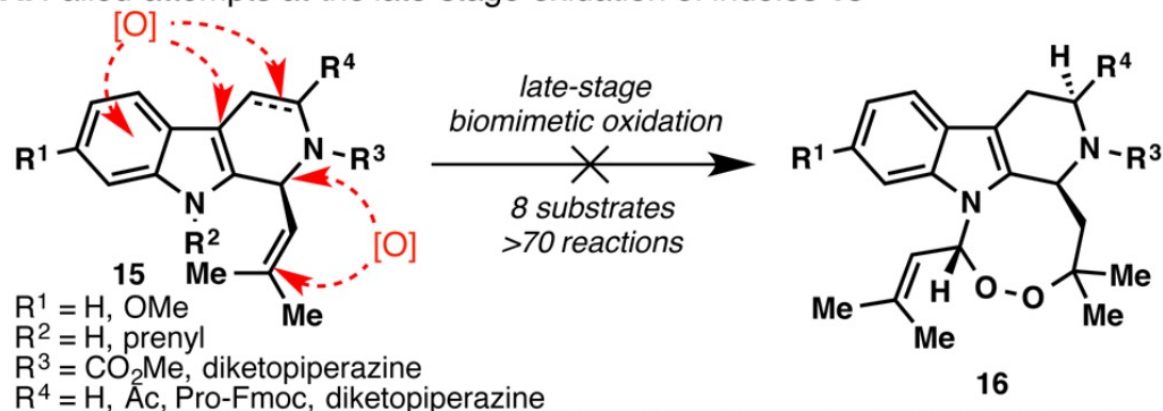




# Baran Group's Synthesis

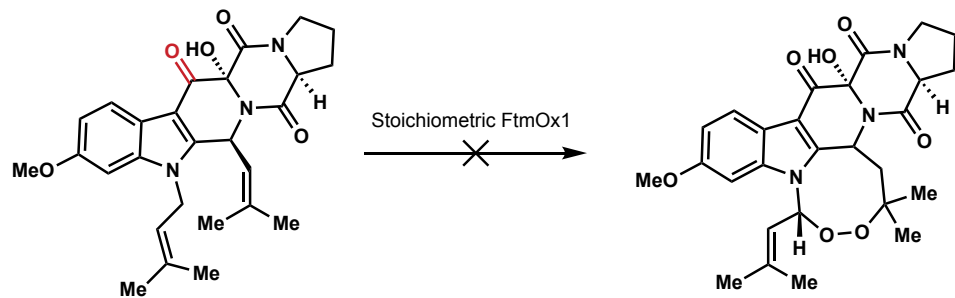
Baran lab was aware of FtmOx1, and attempted the biomimetic oxidation, but was overall unsuccessful...

## A. Failed attempts at the late-stage oxidation of indoles **15**

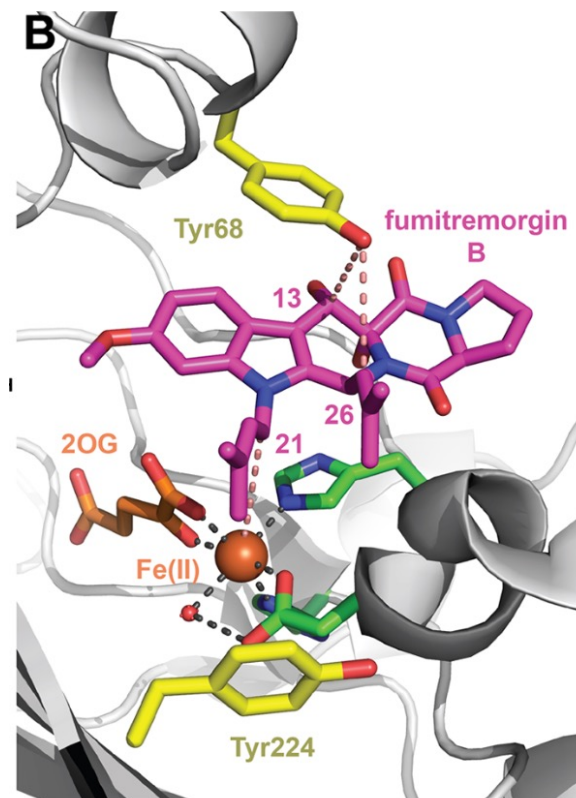


The specific reactions attempted was not documented but trials likely failed due to substrate compatibility.

Hydrogen bonding from Try68 required to initiate HAT

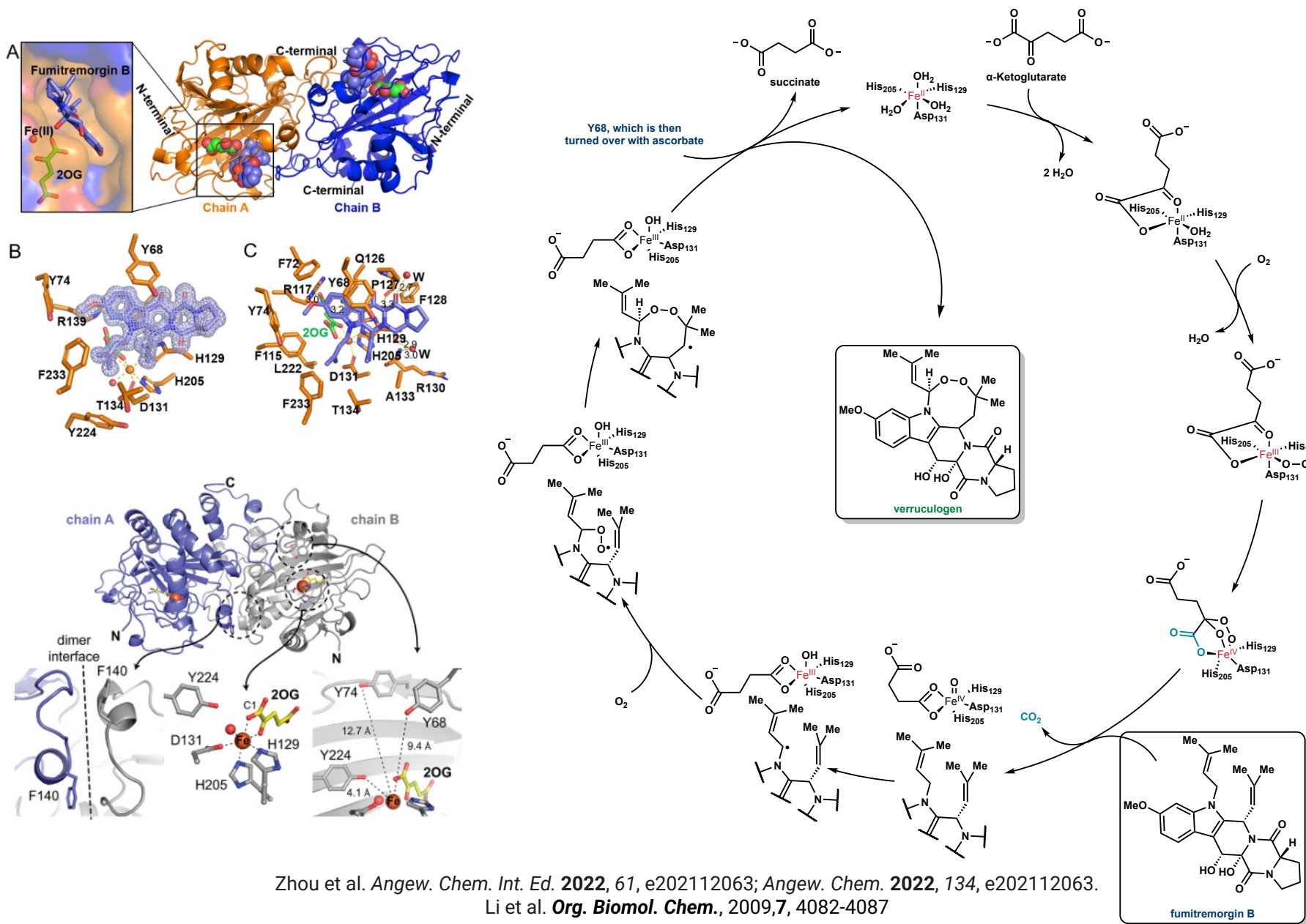


13-oxofumitremorginB





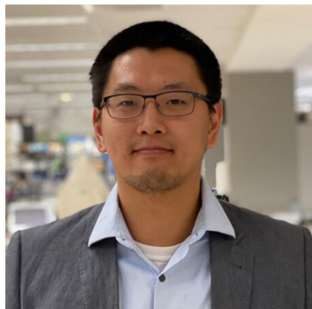
# FtmOx1 Mechanism



Zhou et al. *Angew. Chem. Int. Ed.* **2022**, 61, e202112063; *Angew. Chem.* **2022**, 134, e202112063.

Li et al. *Org. Biomol. Chem.*, 2009,7, 4082-4087

# Ting Group's Synthesis – Retrosynthetic Analysis



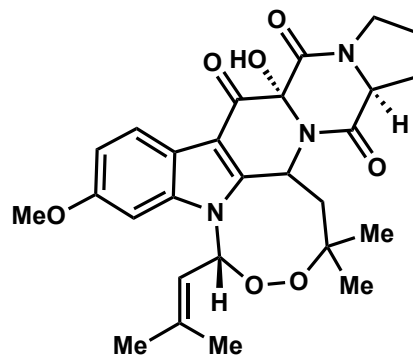
**Chi P. Ting**

Brandeis University

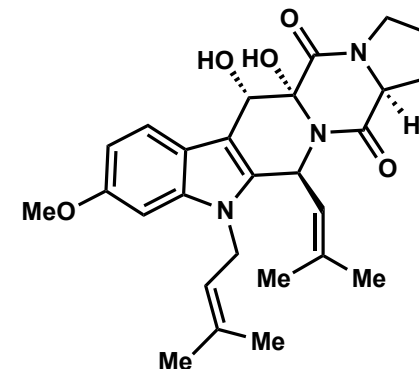
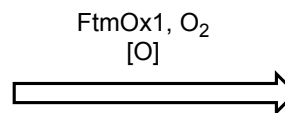
UIUC, Postdoc (Wilfred A. van der Donk)

UC Berkeley, PhD (Tom Maimone)

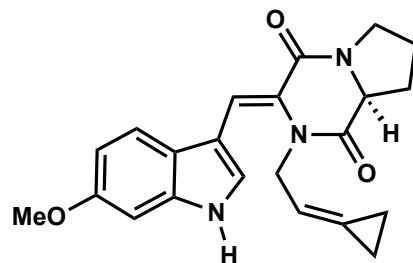
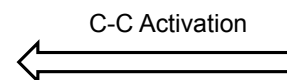
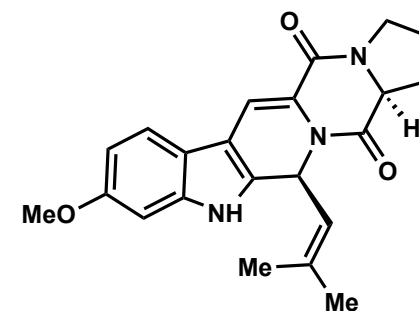
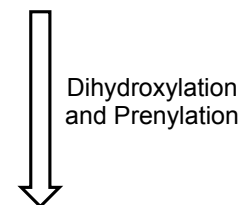
UIUC, BS (Steven Zimmerman)



**13-oxoverruculogen**

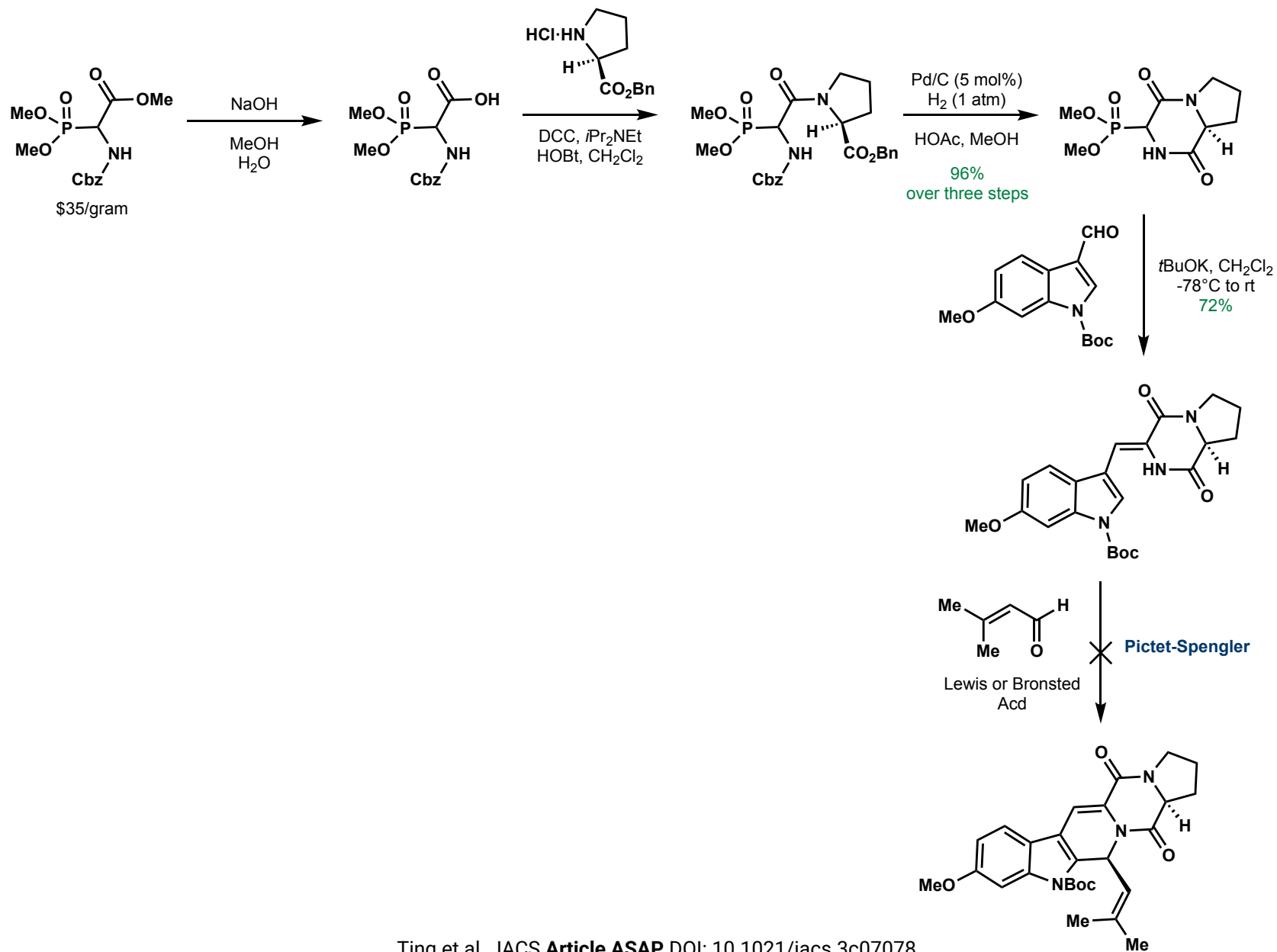


**fumitremorgin B**





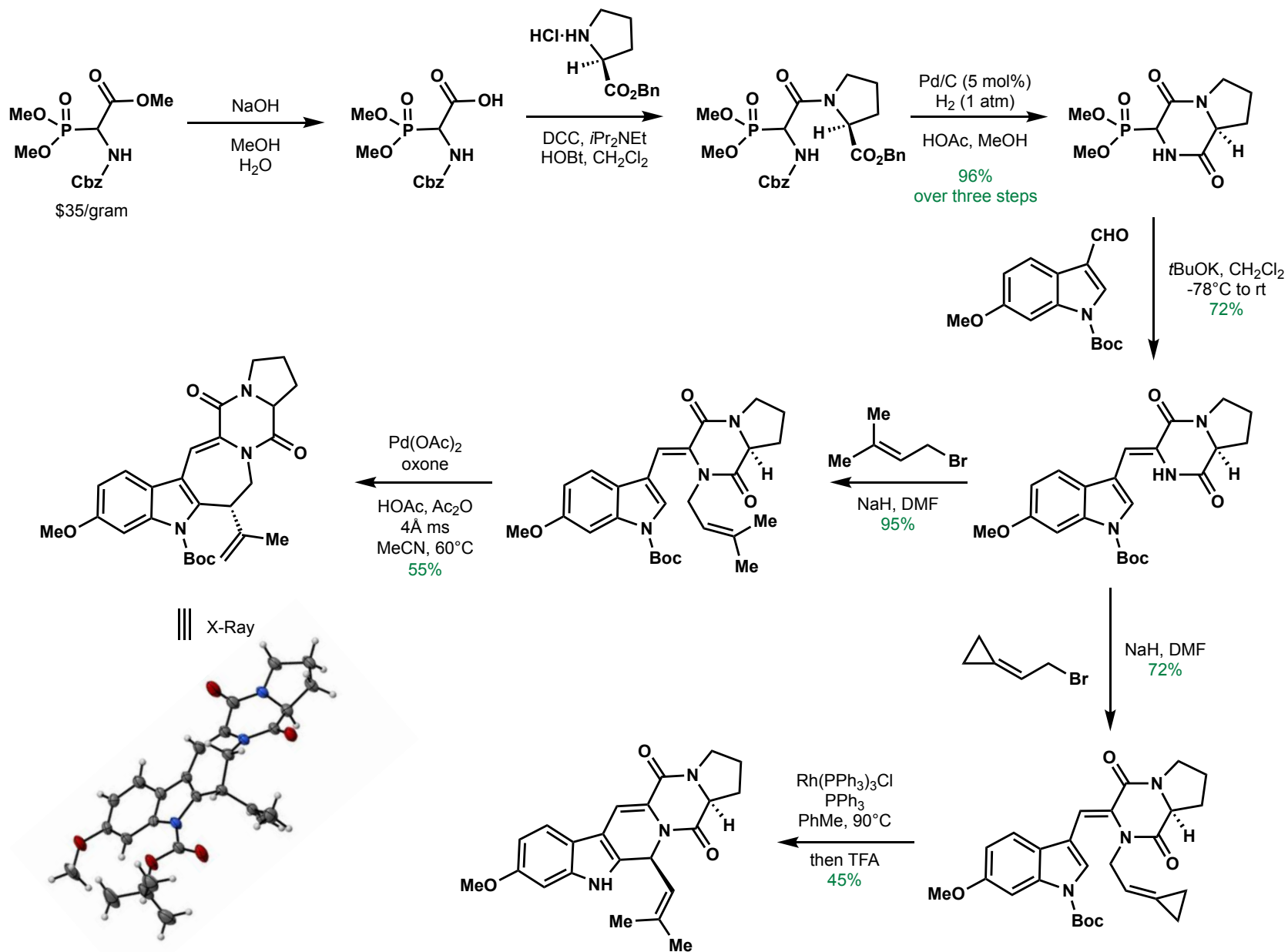
# Ting Group's Synthesis – Forward Route





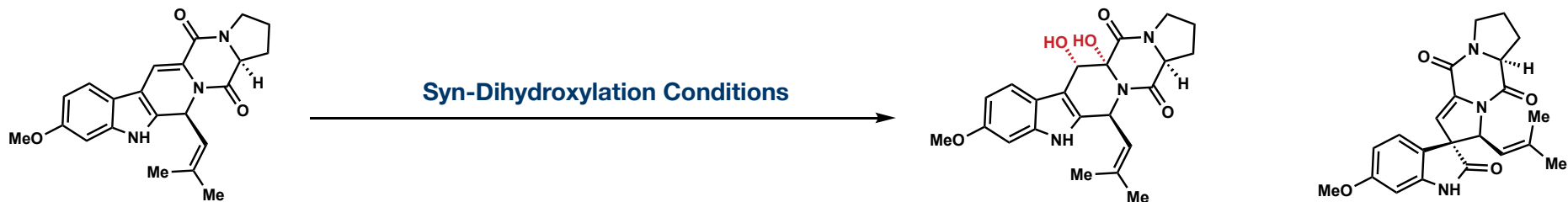


# Ting Group's Synthesis – Forward Route

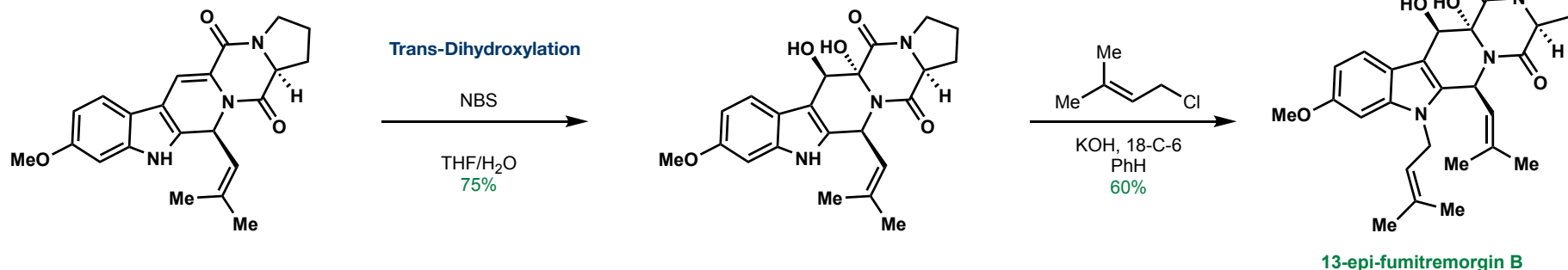




# Ting Group's Synthesis - Dihydroxylation



Entry	Conditions	Solvent	Yield of Syn-Dihydroxy	Yield of 6-methoxyspirotryprostatin B
1	OsO <sub>4</sub> , NMO·H <sub>2</sub> O, pyridine, 30°C	THF/H <sub>2</sub> O (10:1)	10	30
2	OsO <sub>4</sub> , NMO·H <sub>2</sub> O, pyridine, rt	THF/H <sub>2</sub> O (10:1)	9	29
3	OsO <sub>4</sub> , NMO·H <sub>2</sub> O, rt	MeCN/Acetone/H <sub>2</sub> O (2:2:1)	4	26
4	OsO <sub>4</sub> , NMO·H <sub>2</sub> O, rt	Acetone/H <sub>2</sub> O (4:1)	8	19
5	AD-mix- $\alpha$ , MsNH <sub>2</sub> , rt	<i>t</i> BuOH (1:1)	0	ND
6	AD-mix- $\beta$ , MsNH <sub>2</sub> , rt	<i>t</i> BuOH (1:1)	0	ND
7	OsO <sub>4</sub> , TMEDA, -45°C	CH <sub>2</sub> Cl <sub>2</sub>	Decomp.	ND
8	OsO <sub>4</sub> , dihydroquinine, pyridine	THF/H <sub>2</sub> O (10:1)	9	ND
9	4-nitrobenzonitrile, 390 nm LEDs, rt	EtOAc	N.R.	-
10	4-nitrobenzonitrile, 390 nm LEDs, rt	MeCN	N.R.	-

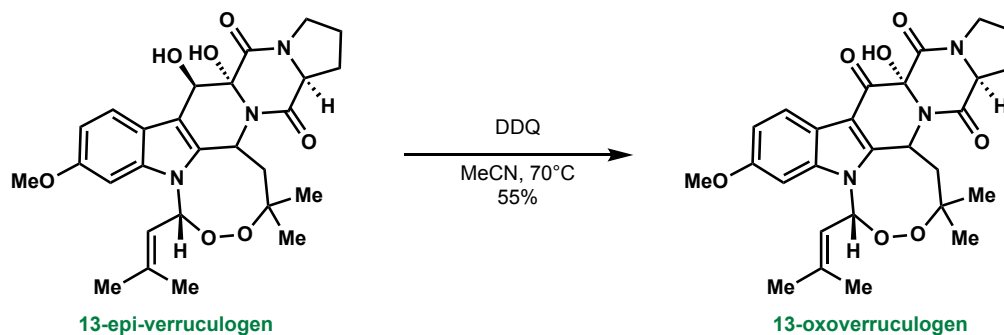




# Ting Group's Synthesis - Endgame



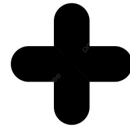
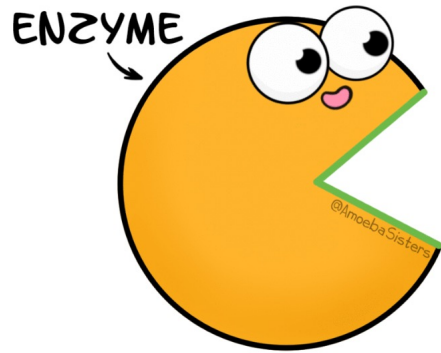
Entry	Deviations from standard	Yield of endoperoxide	Yield of Deprenylation
1	none	9	2
2	no L-ascorbate	0	0
3	HEBES buffer, pH 7.5	0	0
4	37°C	19	ND
5	$(\text{NH}_4)_2\text{Fe}(\text{SO}_4)_2$	28	ND
6	$(\text{NH}_4)_2\text{Fe}(\text{SO}_4)_2$ , 37°C	62	7
7	Other non-enzymatic conditions	Decomp. or N.R.	-







# Conclusion



**Thank you! Any Questions?**