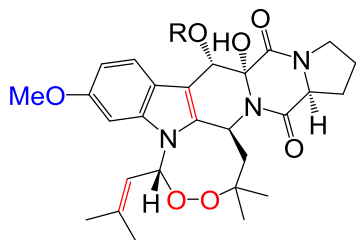


Total Synthesis of Verruculogen and Fumitremorgin A Enabled by Ligand-Controlled C–H Borylation

Yu Feng, Dane Holte, Jochen Zoller, Shigenobu Umemiya, Leah R. Simke, and Phil S. Baran
J. Am. Chem. Soc. **2015**, *137*, 10160–10163.

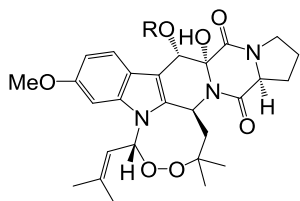
I. Introduction



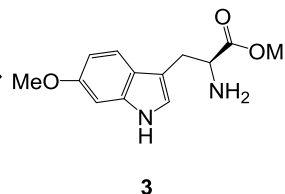
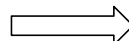
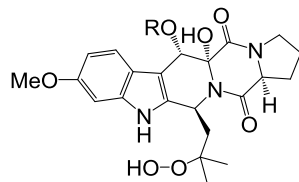
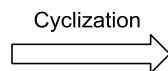
fumitremorgin A (1): R = prenyl
verruculogen (2): R = H

- Isolation and structural determination were reported in 1970s.
- They belong to the only family of alkaloids with an eight-membered endoperoxide ring.
- Structural characters: hexacyclic alkaloids with five-, six- and eight-membered rings; juxtaposition of oxidizing peroxide with two nearby prenyl groups; oxidizable 6-methoxyindole residue.
- Fumitremorgins display potent activity against multi-drug resistant (MDR) cancer cell and HIV.
- Simple family members without the endoperoxide had been synthesized.

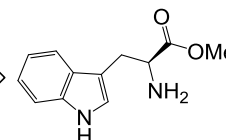
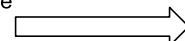
II. Retrosynthetic Analysis



fumitremorgin A (1): R = prenyl
verruculogen (2): R = H



literature gap:
regioselective
transformation



L-tryptophan methyl ester

Total Synthesis of Verruculogen and Fumitremorgin A

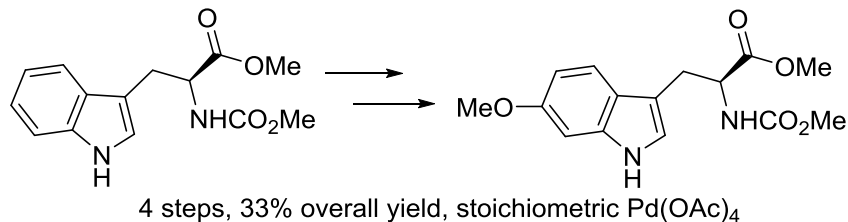
III. Synthesis

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

A short, scalable and regioselective route to compound **3** had not reported.

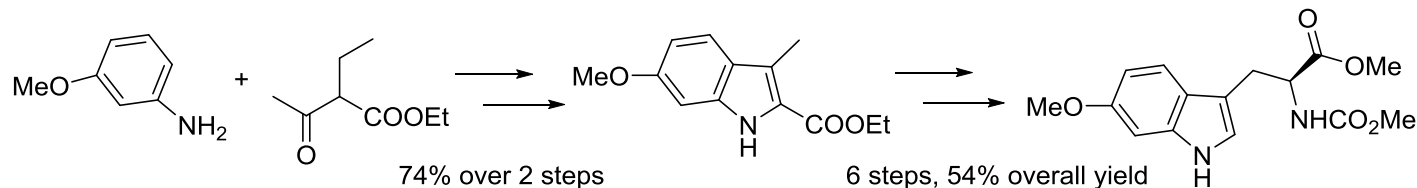
Literature summary: reported methods to 6-methoxytryptophan (see SI for details)

A: Direct C-H oxidation from tryptophan derivative

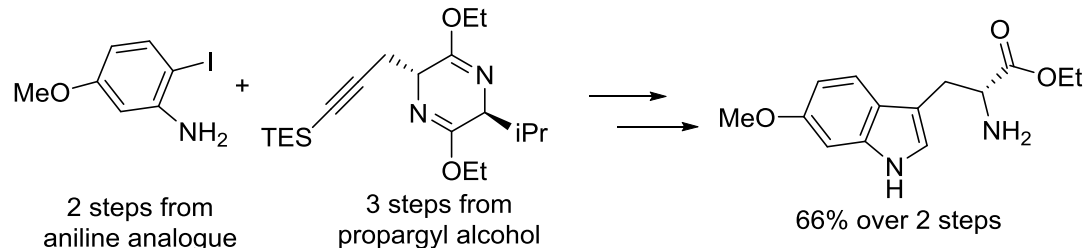


B: 6-Methoxytryptophan derivative by ring synthesis

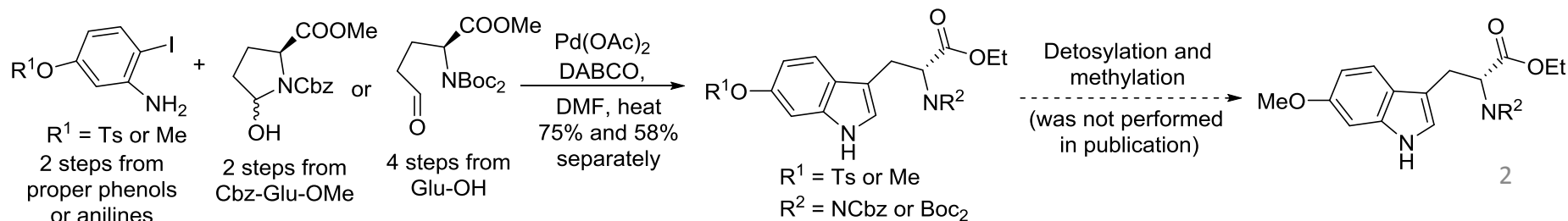
i. Japp/Klingemann/Fisher indole synthesis followed by Schollkopf amino acid synthesis



ii. Larock indole synthesis using an alkyne that has incorporated a Schollkopf auxiliary



iii. Iodoaniline/ketone cyclization



Total Synthesis of Verruculogen and Fumitremorgin A

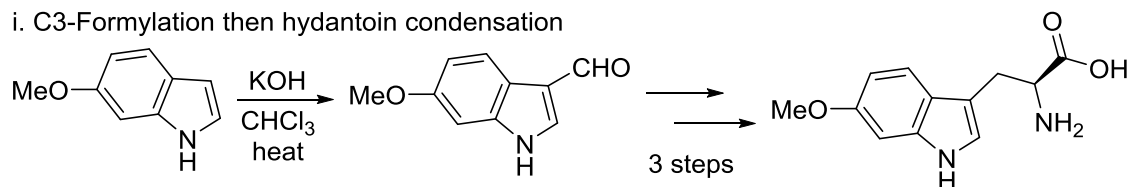
III. Synthesis

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

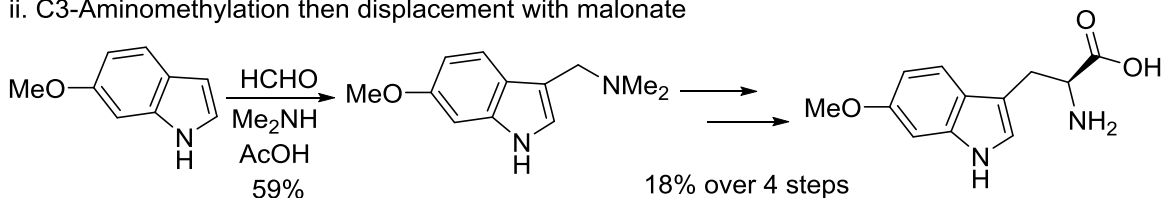
Literature summary: reported methods to 6-methoxytryptophan (continued) (see SI for details)

C: 6-Methoxytryptophan derivative by C3-substitution of 6-methoxyindole

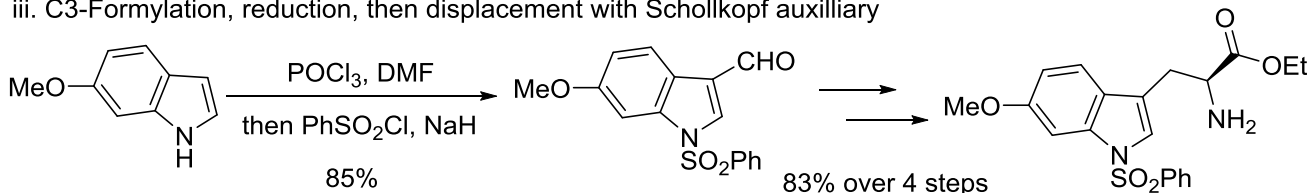
i. C3-Formylation then hydantoin condensation



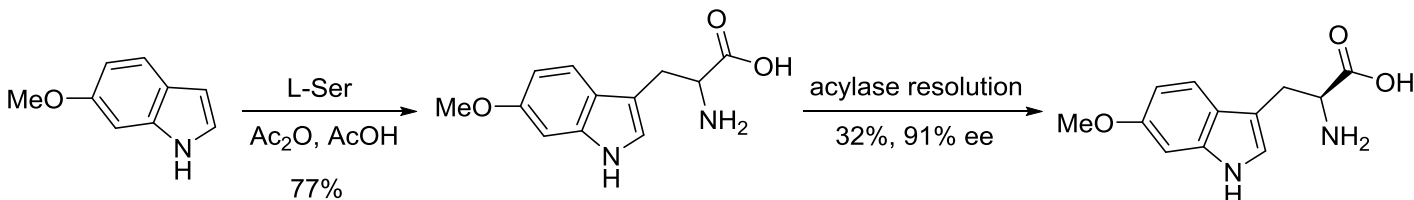
ii. C3-Aminomethylation then displacement with malonate



iii. C3-Formylation, reduction, then displacement with Schollkopf auxiliary



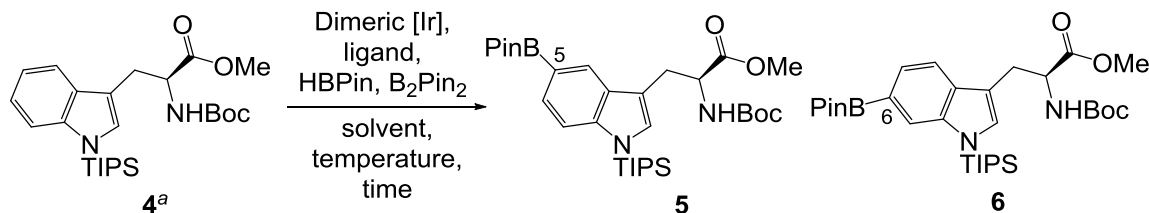
iv. C3-Substitution using serine and acetic anhydride, followed by resolution



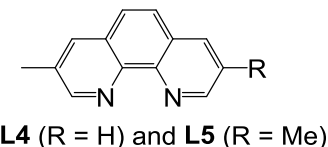
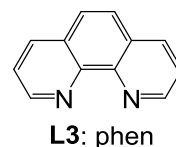
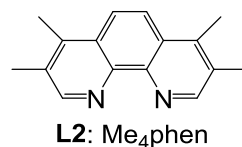
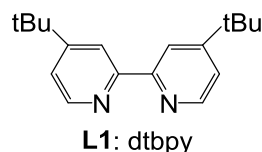
- C-H functionalization was applied to this C6 problem.
- Indole preferentially react at C2, C3 and C7. C6 is the most difficult position to directly functionalize on indole.
- C-H borylation on tryptophan system: C2 and C7
- Ligand control of regioselectivity and large blocking group on indole nitrogen for desired regioselectivity. 3

Total Synthesis of Verruculogen and Fumitremorgin A

C-H borylation of indole derivatives: optimization of ligand-controlled borylation



Entry	[Ir] catalyst	[Ir] (mol%)	Ligand	Ligand (mol%)	HBPIn (equiv.)	B ₂ Pin ₂ (equiv.)	Solvent ^b	Temp. (°C)	Time (h)	Yield (%) ^c	6 : 5 ^d	Recovered 4 (%)
1	[Ir(cod)Cl] ₂	1.5	L1	3	0	0.5	octane	80	16	5	2.0 : 1	78
2	[Ir(cod)OMe] ₂	3	L1	6	3.5	0	MTBE	23	16	0	---	~100
3	[Ir(cod)Cl] ₂	1.5	L1	3	1.0	0	octane	80	16	0	---	~100
4	[Ir(cod)OMe] ₂	3	L1	6	0	1.0	MTBE	23	16	0	---	~100
5	[Ir(cod)OMe] ₂	3	L1	6	0	1.0	hexane	23	16	23	2.0 : 1	52
6	[Ir(cod)OMe] ₂	5	L1	10	0.25	4.0	hexane	60	24	47	2.7 : 1	25
7	[Ir(cod)OMe] ₂	5	L2	10	0.25	4.0	hexane	60	24	64	3.8 : 1	7
8	[Ir(cod)OMe] ₂	5	L2	10	0	4.0	hexane	60	24	55	3.2 : 1	13
9	[Ir(cod)OMe] ₂	5	L2	10	2.0	0	hexane	60	24	0	---	~100
10	[Ir(cod)OMe] ₂	5	L2	10	0.25	4.0	hexane	60	48	66	3.9 : 1	6
11	[Ir(cod)OMe] ₂	5	L2	10	0.25	4.0	hexane	80 ^e	24	74	3.8 : 1	0
12	[Ir(cod)OMe] ₂	5	L3	10	0.25	4.0	hexane	80 ^e	24	77	8.0 : 1	0
13	[Ir(cod)OMe] ₂	5	L4	10	0.25	4.0	hexane	80 ^e	24	0	---	~100
14	[Ir(cod)OMe] ₂	5	L5	10	0.25	4.0	hexane	80 ^e	24	69	6.2 : 1	0
15	[Ir(cod)OMe] ₂	2	L3	4	0.25	4.0	hexane	80 ^e	18	72	7.5 : 1	0

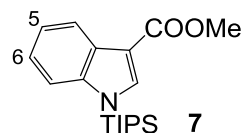


^a All reactions were performed on 0.1 mmol scale; ^b Dry solvents were used; ^c Isolated yields represent the sum of C5- and C6-borylated indole products; ^d Regioselectivity was determined by ¹H NMR; ^e Sealed tube.

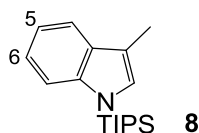
Total Synthesis of Verruculogen and Fumitremorgin A

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

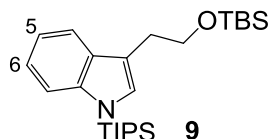
Substrate scope: indoles and carbozoles ^{a, f}



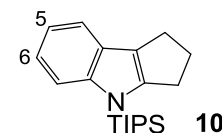
L1: 77%, 3:1 C6:C5
L2: 80%, 4:1 C6:C5
L3: 84%, 14:1 C6:C5



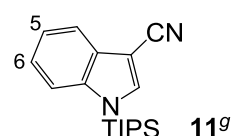
L1: 69%, 2:1 C6:C5
L2: 73%, 3:1 C6:C5
L3: 75%, 9:1 C6:C5



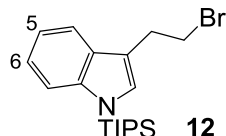
L1: 65%, 3:2 C6:C5
L2: 79%, 3:1 C6:C5
L3: 81%, 8:1 C6:C5



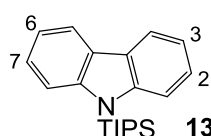
L1: 66%, 3:2 C6:C5
L2: 74%, 2:1 C6:C5
L3: 76%, 6:1 C6:C5



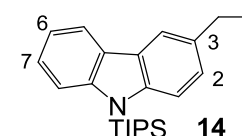
L1: 49%, 2:1 C6:C5
L2: 51%, 3:1 C6:C5
L3: 54%, 8:1 C6:C5



No reaction



L1: 55%, regioisomeric mixture
L2: 64%, regioisomeric mixture
L3: 67%, C2, C7-product major

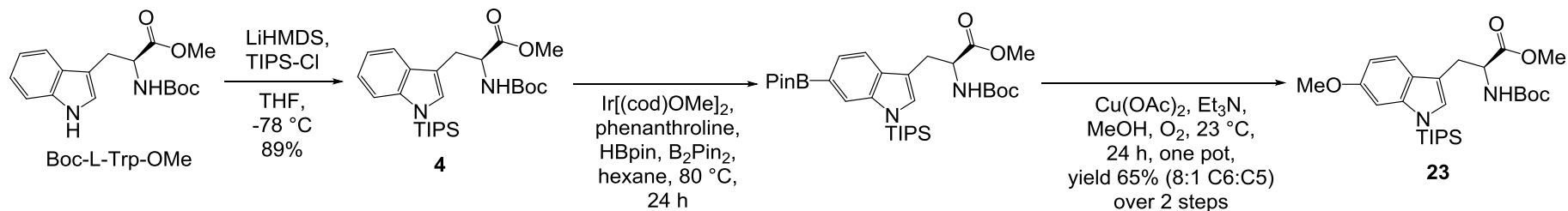


L1: 80%, 2:1 C7:C6
L2: 87%, 2:1 C7:C6
L3: 89%, 5.5:1 C7:C6

^f Conditions: 5 mol% [Ir(cod)OMe]₂, 10 mol% ligand, 0.25 equiv. HBPin, 4 equiv. B₂Pin₂, hexane, 80 °C, 24 h; ^g 50 °C

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

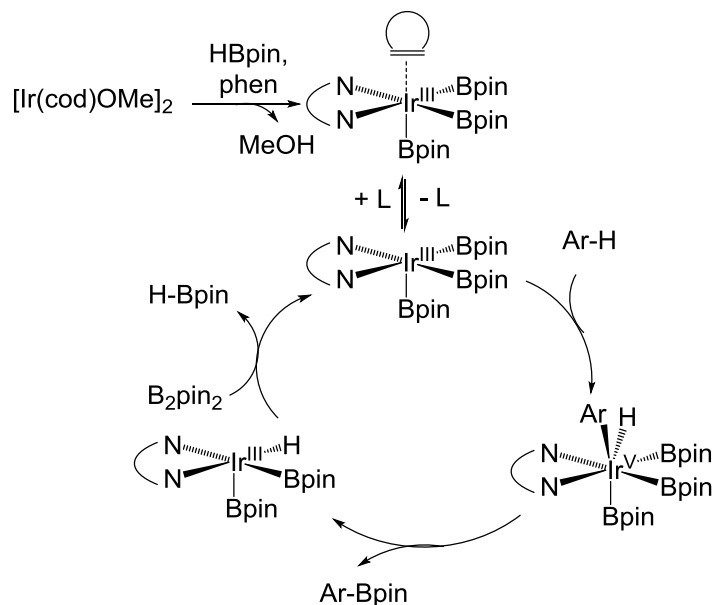
II. Total Synthesis of Verruculogen and Fumitremorgin A



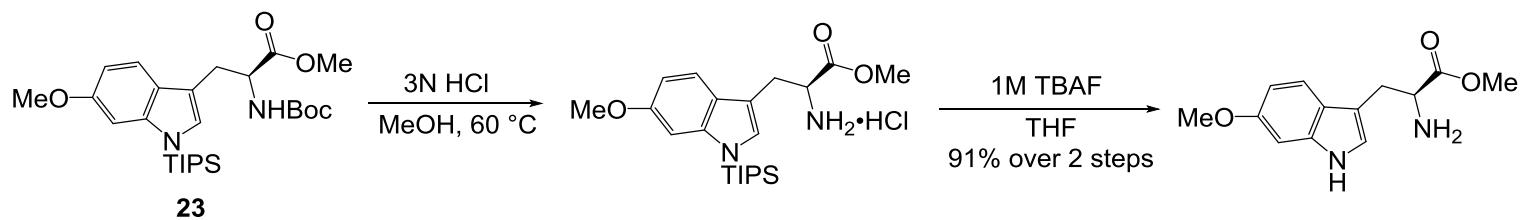
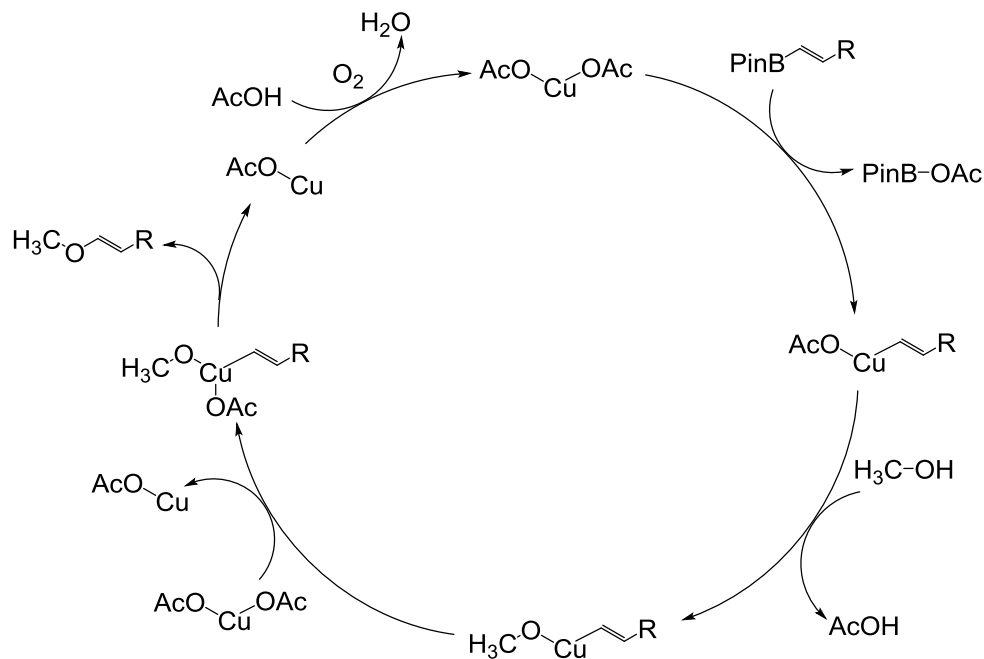
➤ Modified Chan-Evans-Lam condition by Merlic, C. A. et al: suitable for simple alkyl and allyl alcohol; BPin is better than boronic acid; only 1 equiv. boron partner.

Total Synthesis of Verruculogen and Fumitremorgin A

Iridium-Catalyzed aromatic C-H borylation

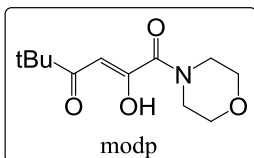
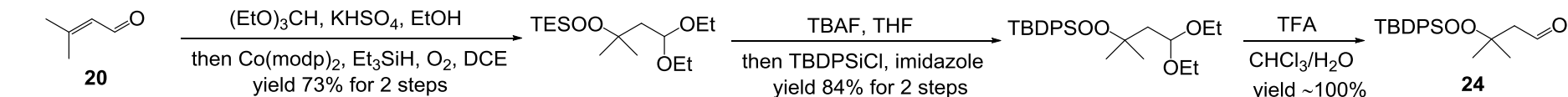


Chan-Evans-Lam coupling



Total Synthesis of Verruculogen and Fumitremorgin A

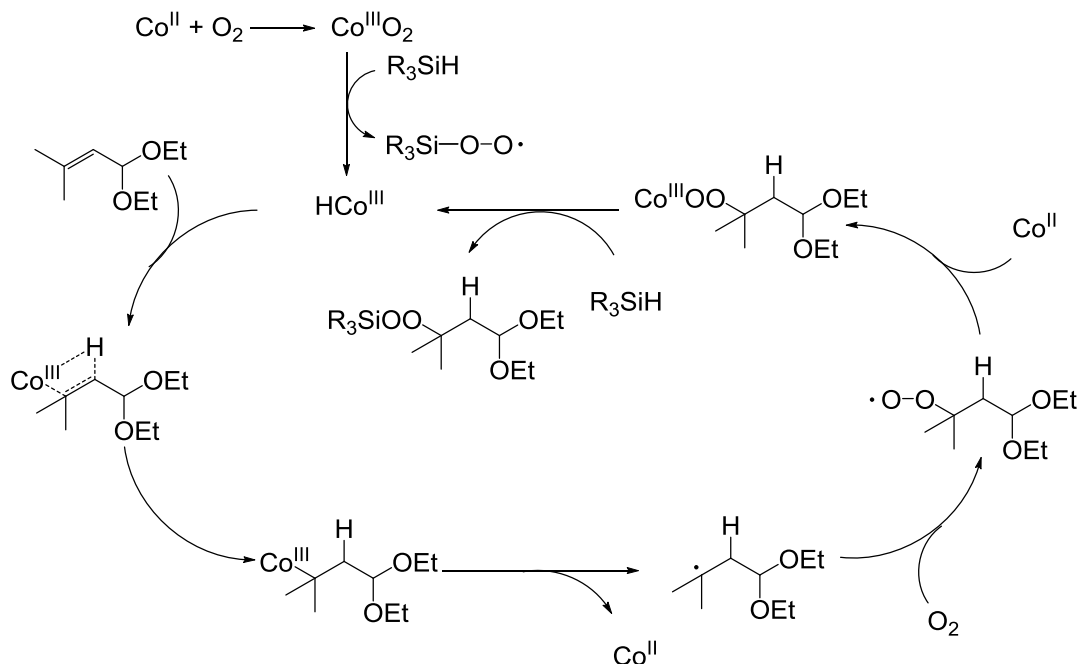
Synthesis of aldehyde 24



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

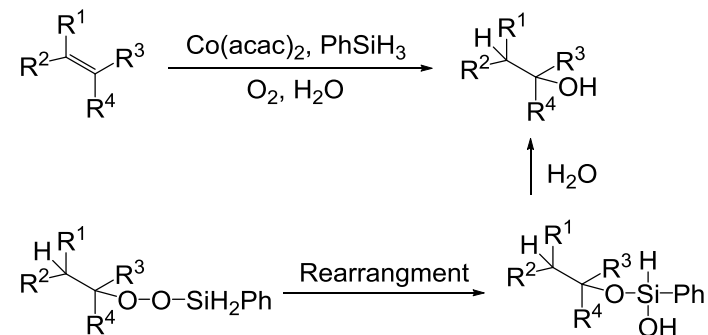
TES-TBDPS switch to make the intermediates stable in the following steps.

Isayama–Mukaiyama peroxygenation of alkenes



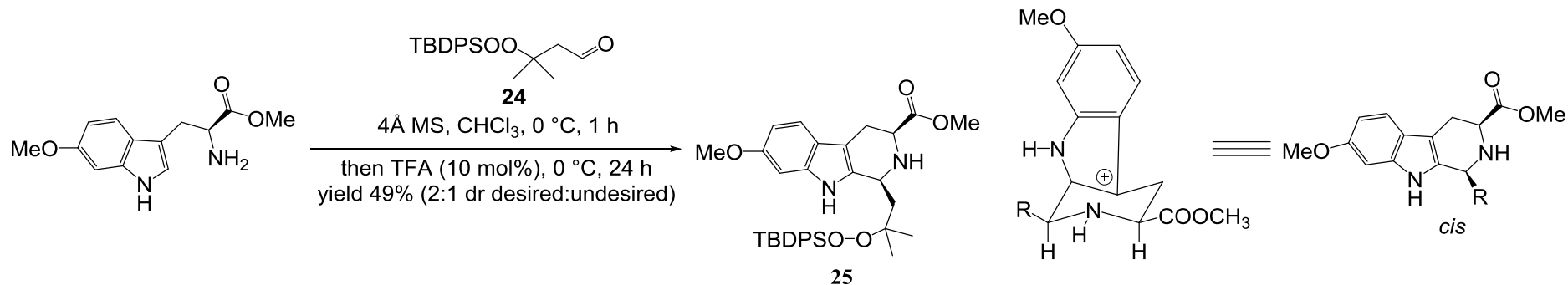
Related reaction

Mukaiyama hydration of alkenes

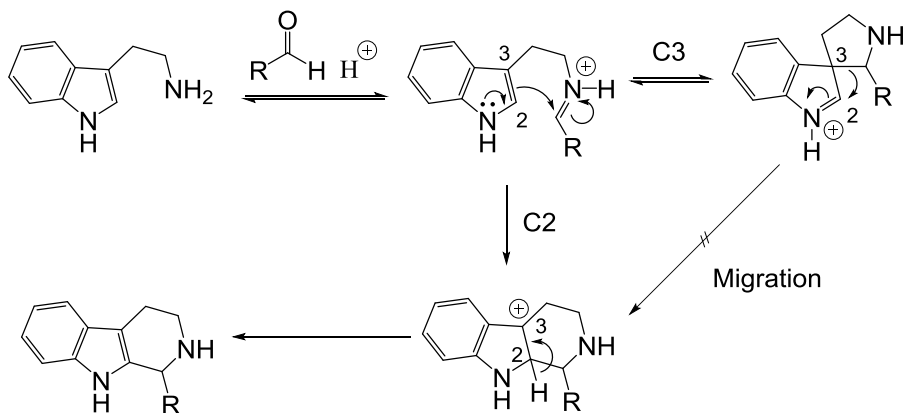


Regioselectivity in Isayama-Mukaiyama peroxygenation is based on the relative reactivity of alkene (radical stability, steric effect and electronic factor).

Total Synthesis of Verruculogen and Fumitremorgin A

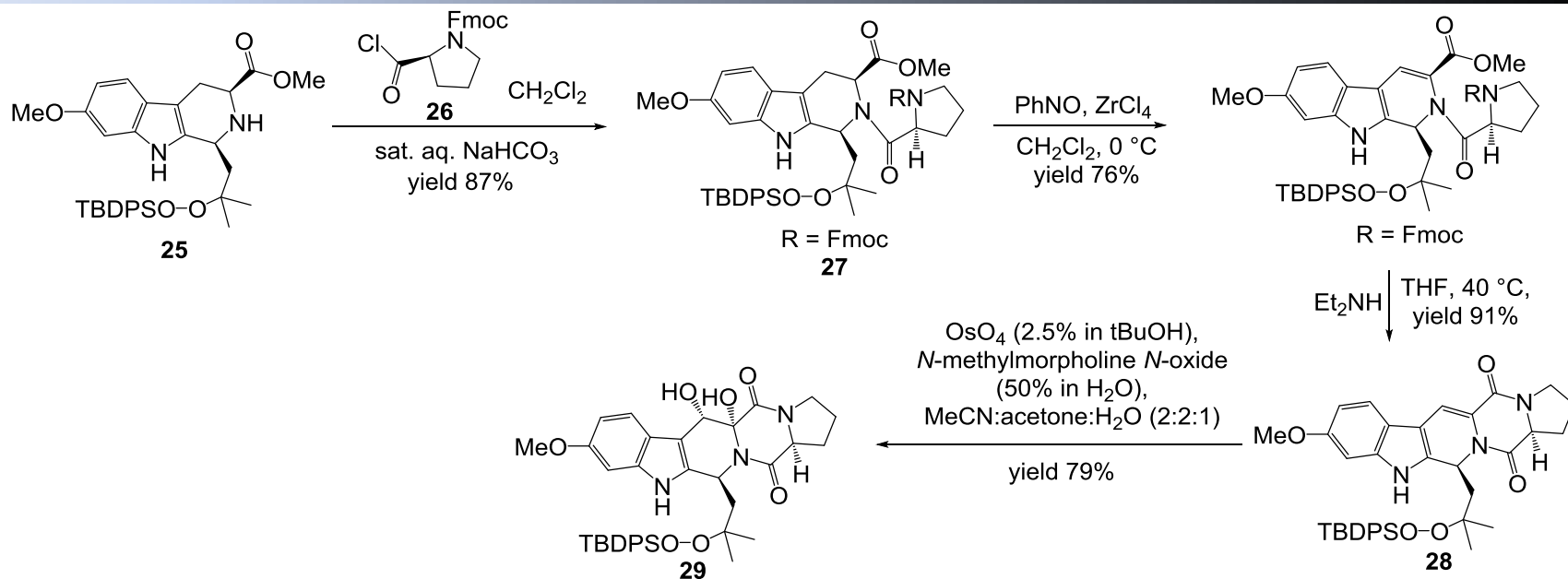


Pictet–Spengler reaction

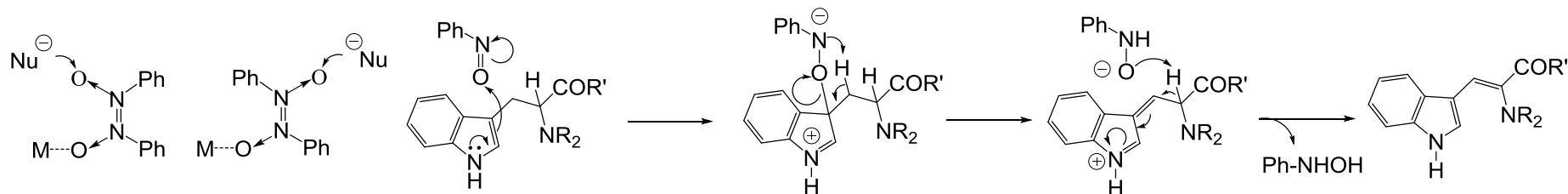


- **In favor of C3?** Most nucleophilic position in intermolecular reactions of indoles; Spiroindolinone can be isolated when C2 is substituted.
- **In favor of C2?** C3-Addition is a 5-endo-trig cyclization (disallowed by Baldwin's rules).
- Experimental evidence: Reversible C3-addition.
- Computational evidence: C2-addition is productive, while C3-Addition is non-productive.
- Rearomatization is the rate-limiting step.

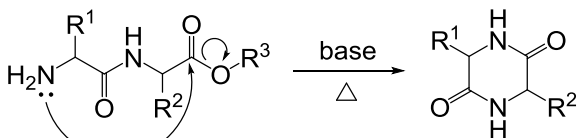
Total Synthesis of Verruculogen and Fumitremorgin A



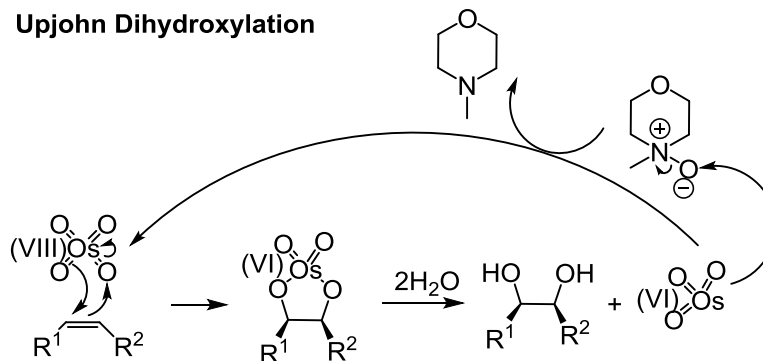
Dehydrogenation of tryptophan



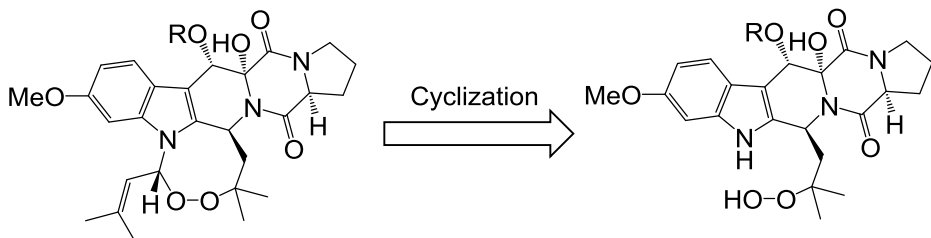
Diketopiperidine formation



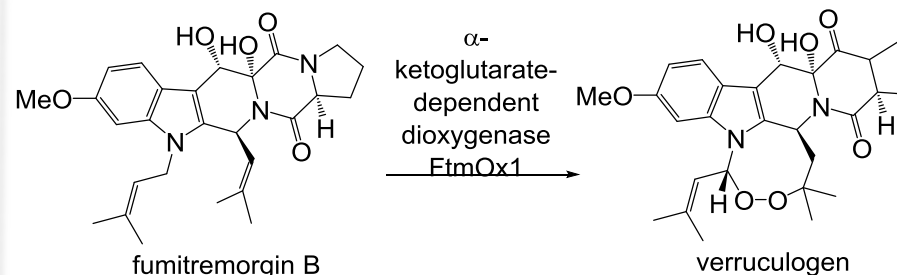
Upjohn Dihydroxylation



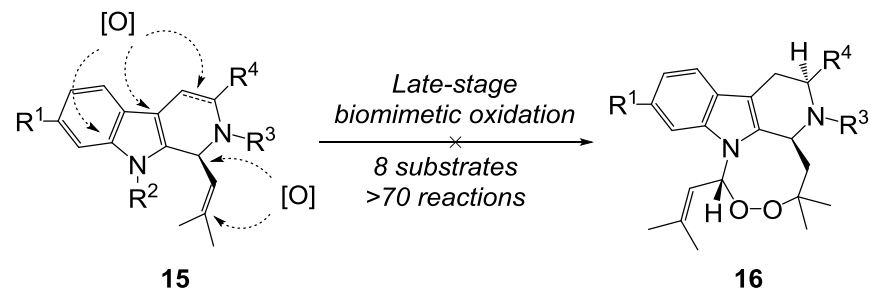
Total Synthesis of Verruculogen and Fumitremorgin A



Late-stage oxidation in biosynthetic pathway

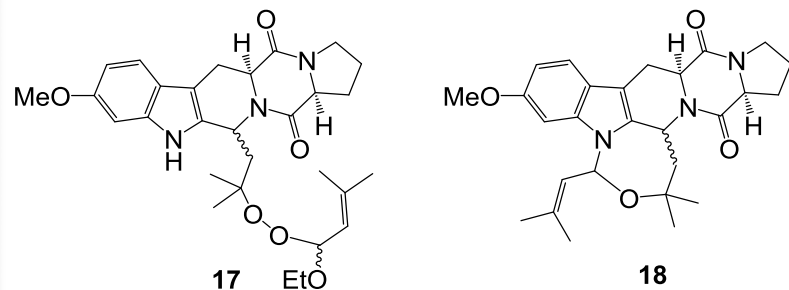


Failed attempts at the late-stage oxidation of indoles 15

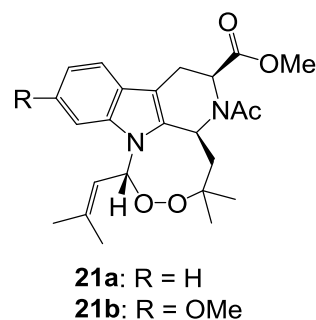
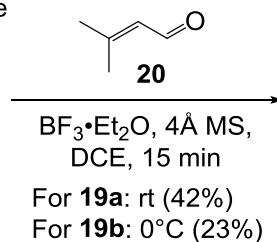
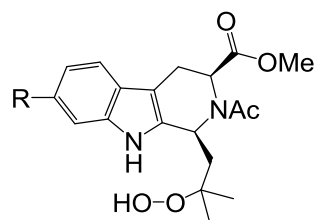
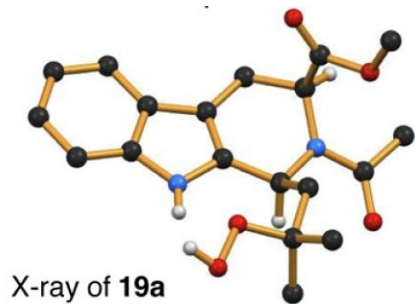


R¹ = H, OMe; R² = H, prenyl; R³ = CO₂Me, diketopiperidine
R⁴ = H, Ac, Pro-Fmoc, diketopiperidine

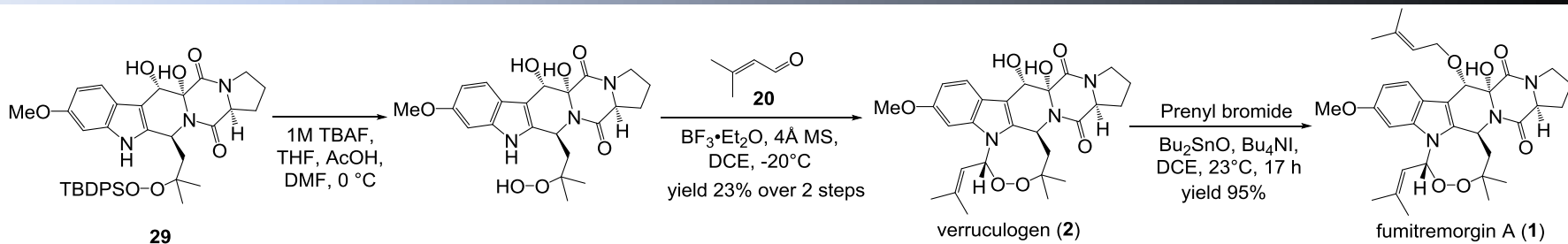
Intermediates obtained when forging the eight-membered endoperoxide



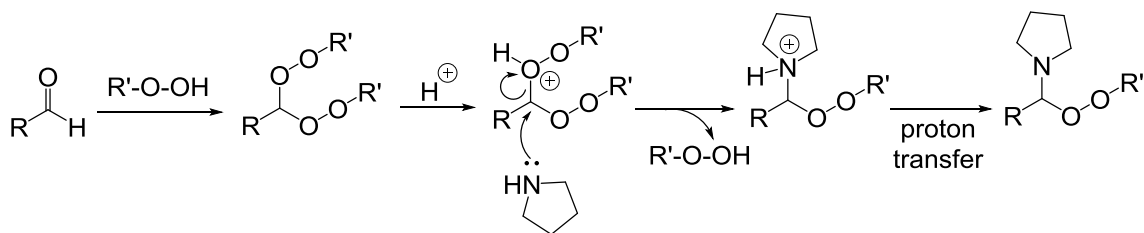
Successful endoperoxide formation on model substrates



Total Synthesis of Verruculogen and Fumitremorgin A

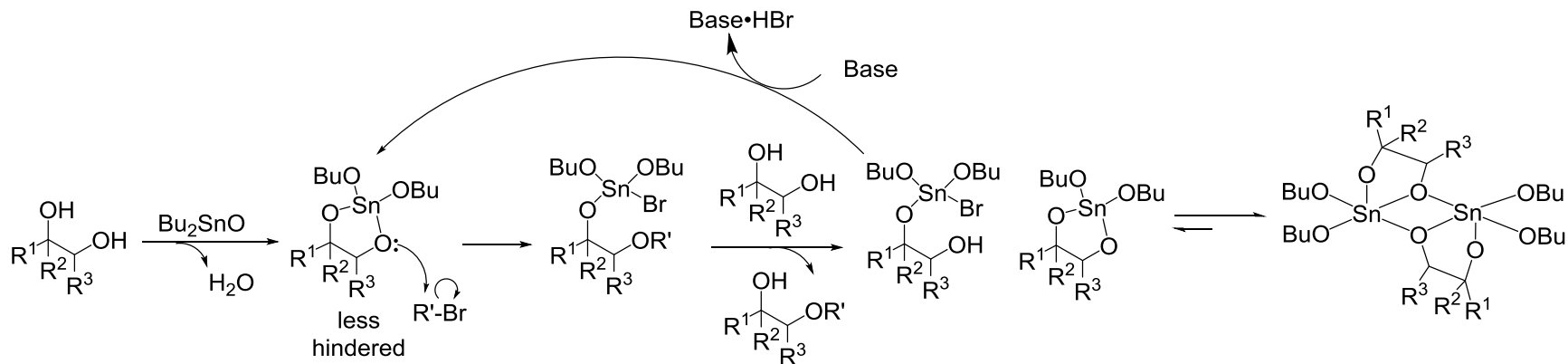


Cyclization



➤ Stereochemistry in cyclization: nitrogen attack from the bottom face

Regioselective protection of hydroxyl group by organotin derivatives



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 C–H 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.