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

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I. Introduction

- 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

\[ \text{Cyclization} \rightarrow \]

- Literature gap: regioselective transformation

3

- L-tryptophan methyl ester
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

\[ R^1 = \text{Ts or Me} \]

2 steps from proper phenols or anilines

\[ R^1 = \text{Cbz-Glu-OMe} \]

2 steps from Cbz-Glu-OMe

4 steps from Glu-OH

Detosylation and methylation

(was not performed in publication)
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

\[
\begin{align*}
\text{MeO-} & \quad \text{KOH, CHCl}_3, \text{heat} & \quad \text{MeO-} & \quad \text{CHO} & \quad \text{MeO-} & \quad \text{NH}_2 \\
\end{align*}
\]

ii. C3-Aminomethylation then displacement with malonate

\[
\begin{align*}
\text{MeO-} & \quad \text{HCHO, Me}_2\text{NH, AcOH} & \quad \text{MeO-} & \quad \text{NMMe}_2 & \quad \text{MeO-} & \quad \text{NH}_2 \\
& \quad 59\% & \quad 18\% & \quad \text{over 4 steps} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{MeO-} & \quad \text{POCl}_3, \text{DMF, then PhSO}_2\text{Cl, NaH} & \quad \text{MeO-} & \quad \text{CHO} & \quad \text{MeO-} & \quad \text{NH}_2 \\
& \quad 85\% & \quad 83\% & \quad \text{over 4 steps} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{MeO-} & \quad \text{L-Ser, Ac}_2\text{O, AcOH} & \quad \text{MeO-} & \quad \text{NH}_2 & \quad \text{MeO-} & \quad \text{NH}_2 \\
& \quad 77\% & \quad \text{acylase resolution, 32%, 91% ee} \\
\end{align*}
\]

- 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: optimization of ligand-controlled borylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ir] catalyst</th>
<th>[Ir] (mol%)</th>
<th>Ligand</th>
<th>Ligand (mol%)</th>
<th>HBPin (equiv.)</th>
<th>B₂Pin₂ (equiv.)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>6 : 5</th>
<th>Recovered (%)</th>
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<td>L1</td>
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<td>16</td>
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<td>0</td>
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<td>~100</td>
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<td>L1</td>
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<td>80</td>
<td>16</td>
<td>0</td>
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<td>MTBE</td>
<td>23</td>
<td>16</td>
<td>0</td>
<td>---</td>
<td>~100</td>
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<td>72</td>
<td>7.5 : 1</td>
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</table>

<sup>a</sup> All reactions were performed on 0.1 mmol scale; <sup>b</sup> Dry solvents were used; <sup>c</sup> Isolated yields represent the sum of C5- and C6-borylated indole products; <sup>d</sup> Regioselectivity was determined by 1H NMR; <sup>e</sup> 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 $^a,f$

- **7**
  - L1: 77%, 3:1 C6:C5
  - L2: 80%, 4:1 C6:C5
  - L3: 84%, 14:1 C6:C5

- **8**
  - L1: 69%, 2:1 C6:C5
  - L2: 73%, 3:1 C6:C5
  - L3: 75%, 9:1 C6:C5

- **9**
  - L1: 65%, 3:2 C6:C5
  - L2: 79%, 3:1 C6:C5
  - L3: 81%, 8:1 C6:C5

- **10**
  - L1: 66%, 3:2 C6:C5
  - L2: 74%, 2:1 C6:C5
  - L3: 76%, 6:1 C6:C5

- **11**
  - L1: 49%, 2:1 C6:C5
  - L2: 51%, 3:1 C6:C5
  - L3: 54%, 8:1 C6:C5

- **12**
  - No reaction

- **13**
  - L1: 55%, regioisomeric mixture
  - L2: 64%, regioisomeric mixture
  - L3: 67%, C2, C7-product major

- **14**
  - L1: 80%, 2:1 C7:C6
  - L2: 87%, 2:1 C7:C6
  - L3: 89%, 5:1 C7:C6

$^f$ Conditions: 5 mol% [Ir(cod)OMe]$_2$, 10 mol% ligand, 0.25 equiv. HBPin, 4 equiv. B$_2$Pin$_2$, 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

- **4**
  - THF, -78 °C
  - 89%

- **13**
  - L1: 55%, regioisomeric mixture
  - L2: 64%, regioisomeric mixture
  - L3: 67%, C2, C7-product major

- **23**
  - L1: 80%, 2:1 C7:C6
  - L2: 87%, 2:1 C7:C6
  - L3: 89%, 5:1 C7:C6

- **MeO**
  - **23**
  - Over 2 steps

- **23**
  - Over 2 steps

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

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

CoII + O2 → CoIIIO2

CoIIIO2 + R3SiH → R3SiO•O•

HCoII

R3SiO•O• + H → R3SiOH

CoII + O2 → CoIIIO2

CoIIIO2 + R3SiH → R3SiO•O•

HCoII

R3SiO•O• + H → R3SiOH

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

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

Total Synthesis of Verruculogen and Fumitremorgin A

Failed attempts at the late-stage oxidation of indoles 15

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.