Introduction

• Dithiodiketopiperazines are naturally occurring complex polycyclic molecules.

• (−)-epicoccin G is isolated from the fungus *Epicoccum nigrum* and has in vitro anti-HIV-1 and antiplasmodial activities.

• (−)-rostratin A is isolated from the fungus *Exserohilum rostratum* and is cytotoxic against HCT-116 cancer cells.

• First ever synthesis of (−)-rostratin A and second synthesis of (−)-epicoccin G.
Retrosynthesis

1-2 → 5 → double C(sp³)-H alkenylation → 6 → DKP formation → 7 → regioselective epoxide opening

List enantioselective epoxidation

9 + H₂N-CO₂t-Bu → L-Ala-OtBu

8
Enantioselective epoxidation:

Enolate formation followed by opening of the epoxide:

Protection of alcohol:
Cyclodimerization mediated by BOP-Cl:

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\begin{align*}
\text{OTf}^+\text{N}^+\text{CO}_2\text{H} \quad &\xrightarrow{\text{SiO}_2, 95^\circ\text{C}, \text{then recrystallization}} \quad \text{OTf}^+\text{N}^+\text{CO}_2\text{H} \\
&\quad (83\%) \\
&\quad \text{d.r. } >99:1 \\
&\quad \text{decagram scale} \\
\text{BOP-Cl, collidine} \quad &\xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{ to } 25^\circ\text{C}} \quad \text{TFO}^+\text{N}^+\text{CO}_2\text{H} \\
&\quad (97\%) \\
&\quad \text{decagram scale}
\end{align*}
\]
C(sp^3)-H alkenylation:

\[
\begin{align*}
\text{6} & \xrightarrow{\text{Pd(PCy}_3)_2 (4 \text{ mol\%}), \text{PCy}_3 (20 \text{ mol\%}) \text{, PivOH (30 mol\%)}} \xrightarrow{\text{Cs}_2\text{CO}_3, \text{toluene, 110°C (93\%)}} \text{5}
\end{align*}
\]

decagram scale

multigram scale
51\%, 7 steps
Upjohn dihydroxylation:

IBX Oxidation:

1. OsO₄ cat., NMO·H₂O, acetone/t-BuOH/H₂O, 0 to 25°C
2. IBX, MeCN, 60°C
(96%)
Samarium (II) iodide mediated reduction of hydroxyketones:

Dimethoxyketal protection and deacylation:
Iodine mediated cleavage:

Preparation of A:

Sulfuration:

Iodine mediated cleavage:
Upjohn dihydroxylation:

TBS Protection:

Elimination:
Hydrogenation:

Deprotection of the TBS group:

IBX Oxidation:
CBS Reduction:

Deacylation:
Preparation of A:

Sulfuration:

Scandium triflate-mediated deprotection: