Convergent Total Synthesis of Principinol D, a Rearranged Kaurane Diterpenoid

A. Biosynthesis of the kauranes, their precursors, and derivatives

Grayananes diterpenoids have recently been identified as structurally novel allosteric inhibitors of carbonic anhydrases and phosphatase.

Potential therapeutic development could span numerous disease areas from neurological dysfunction to cancer.

Synthetic efforts toward the grayananes have been especially limited to linear cyclization strategies.

Newhouse group speculated that a convergent retrosynthetic strategy, which isolates the two main constellations of stereocenters, would yield a laboratory route that could enable synthesis of grayanane analogs.

Herein, they report the first total synthesis of the grayanane analog principinol D.

Grayananes diterpenoids are among a broader class of rearranged kauranes. They are formed by rearrangement of the kaurane 6,6- ring system to a 5,7-ring system.

The kauranes are derived from rearrangement and cyclization of pimaranes via the beyeranes.
The principinol D possess a highly oxidized tetracyclic framework, including a bicyclo[3.2.1]octane ring system.

Four stereocenters proximal to the left-most five-membered ring.

Additional five stereocenters that decorate the bicyclo[3.2.1]octane ring system.
Synthesis of Cyclopentyl fragment 4 (SI)

(O)-CBS catalyst, catecholeborane
Et$_2$NPh (72% yield, 86% ee)

\[ \text{SI-1} \xrightarrow{(O)-CBS} \text{SI-2} \]

imidazole, DMAP, TBSCI (95%)

\[ \text{SI-2} \xrightarrow{\text{imidazole, DMAP, TBSCI}} \text{SI-3} \]

IBX, NMO (84%)

\[ \text{SI-3} \xrightarrow{\text{IBX, NMO}} \text{SI-4} \]

Corey-Bakshi-Shibata Reduction (Borane as reductant and oxazaboroiidine as catalyst)

Oxidation of ketone to enone

\[ \text{Me} \xrightarrow{\text{HCl, MeOH}} \text{Me} \]

\[ \text{Oxazaboroiidine} \xrightarrow{\text{SET}} \text{Enone} \]

\[ \text{Enone} \xrightarrow{\text{H2O}} \text{Ketone} \]
Synthesis of Bicyclo[3.2.1]octane Fragment Coupling Partner 3

1. Vicinal difunctionalization

2. Allylation

3. Selective reduction of esters in the presence of ketone
Ni catalyzed C-vinylation

4. TBSCI (35%, 3 steps)

5. LiHMDS, NiCl₂(PCy₃)₂ then HCl (74%)

NiCl₂(PCy₃)₂

Reductive elimination

Oxidative addition

Nucleophilic substitution

- LiBr
Sml$_2$-mediated diastereoselective ketone reduction

Appel reaction
Total Synthesis of Principinol D (1) via Fragment Coupling and Reductive Cyclization

1,2-addition, MOM protection

TBS deprotection and DMP

Selective oxidative cleavage of monosubstituted alkene (Mechanism see next page)
Selective oxidative cleavage of monosubstituted alkene (Lemieux-Johnson Oxidation)

Sml2-mediated ring-closing and DMP
Peterson adduct

Mukaiyama Hydration

Global MOM deprotection