1. Introduction

1-1. Psychotrimine 1
- isolated from leaves of Psychotria rostrana in 2004\(^1\)
- shows activity against lung cancers
- has N1-C3 linkage between indole subunits
- first synthesized in 2008 (16 steps, 13.2 \% yield, 6.5 mg)\(^2\)

1-2. Kapakahines
• Kapakahine B (2): isolated from sponge Cribchalina olemda in 1995\(^3\)
• Kapakahine F (3): isolated from sponge C. olemda in 2003\(^4\)
• Both kapakahines show anti-leukemia (白血病) activity.
• Strained tetracycle, twisted 16-membered ring, and hindered quaternary center as well as N1-C3 linkage of indoles.
• Total synthesis has not been reported.

1-3. This work
Gram-scale total synthesis of psychotrimine and kapakahine B and F through
- development of direct indole-aniline coupling method
- making use of equilibrium between 5-membered ring and 6-membered ring

Scheme 1. Retrosynthesis of psychotrimine and kapakahines

2. Results and Discussion

2-1. Psychotrimine 1
2-1-1. Failure of direct indole dimerization
• The authors first tried dimerization of indoles, but it did not work (Scheme 2).
2-1-2. Direct coupling of indole and aniline
• Instead of indole dimerization, o-iodoaniline was screened as the nitrogen donor (Figure 2).

2-1-3. Completion of total synthesis of psychotrimine 1
Total synthesis of psychotrimine was achieved by 5 steps, 41-45% yield from 23. 2.5 g of psychotrimine was obtained from 2 g of 24.

2-2. Kapakahine B and F (2 and 3)

2-2-1. Applying direct coupling to kapakahines

The authors tried to apply the direct coupling method to kapakahines, but it only gave C2-coupled aniline isomer 30 (Figure 3A).

This is likely due to the slow rate of ring-closure of a six-membered α-carboline ring.

α-carboline ring may be obtained by isomerization (Figure 3B). Isomer A may be favored, so irreversible kinetic trap would be necessary.

Isomer A was successfully obtained with various protecting group (Figure 3C).

2-2-2. Preparation for isomerization—Synthesis of the tripeptide fragment

Knochel’s copper/zinc coupling to bromo TES-acetylene provided alkyne amino acid 35 as a single enantiomer.

2-2-3. Successful isomerization and completion of total synthesis of kapakahines
• Removal of both the Cbz group and benzyl group allowed equilibrium between 39 and 41.
• 41 is more reactive intermediate than 39 because of more reactive primary amine.
• 38 was obtained as the major product by irreversible ring closure.

2.2.4. Biological evaluation of kapakahines

Table 2: biological evaluation of kapakahines

<table>
<thead>
<tr>
<th>Tumor cell line</th>
<th>Tissue type</th>
<th>IC50(50 % inhibitory concentration) [µM] kapakahine B</th>
<th>IC50(50 % inhibitory concentration) [µM] kapakahine F</th>
</tr>
</thead>
<tbody>
<tr>
<td>DU4475 breast</td>
<td>11.7</td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>CCRF-CEM Leukemia</td>
<td>22.7</td>
<td>&gt;50.0</td>
<td></td>
</tr>
</tbody>
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• Kapakahines were expected to show activity against leukemia, but kapakahine B showed activity against breast cancer cell line rather than leukemia cell (Table 2).

3. Conclusions
• Total synthesis of psychotrimine was achieved in gram-scale (5 steps, 41-45 % yield)
• First total synthesis of kapakahine B and F were achieved (12 steps, 10 % and 12 %, respectively) through dynamic equilibrium.
• C-N bond between quaternary carbon and nitrogen was formed by direct indole-aniline coupling.

References