Model Study for The Total Synthesis of Daphniglaucin A

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Daphniphyllum alkaloids

Daphniphyllum alkaloids have highly complex polycyclic structure.

In recent years, more than 60 new Daphniphyllum alkaloids were isolated from oriental tree "Yuzuriha".

Some of these alkaloids showed cytotoxic activities against several tumor cell lines.

The unusual ring systems have attracted great interest as challenging targets for total synthesis.

Yuzuriha (Daphniphyllum macropodum; Daphniphyllaceae) dioecious evergreen trees and shrubs native to Japan.
Leaves are used as a pesticide.
Isolated from leaves of *Daphniphyllum glaucescens* in 2003.

Unprecedented fused-polycyclic skeleton containing 1-azaniatetracyclo[5.2.2.0.1,6.0.4,9]undecane ring.

Structure elucidated by MS, 1H and 13C NMR, COSY, HMBC and NOESY

Exhibited cytotoxicity against murine lymphoma L1210 cells (IC₅₀ 2.7 µg/mL) and human epidermoid carcinoma KB cells (IC₅₀ 2.0 µg/mL) in vitro.

Related compounds isolated from *Daphniphyllum glaucescens*

![Structures of Daphniglaucin B, Daphniglaucin C, Daphniglaucin D, Daphniglaucin E, Daphniglaucin F, Daphniglaucin G, Daphniglaucin H, Daphniglaucin J, Daphniglaucin K]

- **Daphniglaucin B**
  - Cytotoxicity:
  - Murine lymphoma L1210 cells (IC$_{50}$ 3.9 µg/mL)
  - Human epidermoid carcinoma KB cells (IC$_{50}$ 10.0 µg/mL).

- **Daphniglaucin C**
  - Cytotoxicity murine lymphoma L1210 cells (IC$_{50}$ 0.1 µg/mL)
  - Inhibition the polymerization of tubulin (IC$_{50}$ 25 µM)


- **Daphniglaucin D**
- **Daphniglaucin E**: R=H
- **Daphniglaucin F**: R=Ac
- **Daphniglaucin G**: R=H
- **Daphniglaucin H**: R=Ac
- **Daphniglaucin J** R=Ac
- **Daphniglaucin K** R=Ac

Proposed biogenetic pathway for Daphniglaucin A -1

Proposed biogenetic pathway -2

Total synthesis of methyl homosecodaphniphyllate

Synthetic study on Daphnilactone B

1. KF/Py, 95%
2. DMSO/SO$_3$/Py/Et$_3$N
3. EtNO$_2$/KOT-Bu, 72%

Synthetic study on Daphnilactone B

Synthetic study on Daphniglaucin D

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