Total Synthesis of Methyl Homosecodaphniphyllate

CEM 852

Yuting Zhou

Yuzuriha (*Daphniphyllum macropodum*)

- Small tree found in East Asia, China, Japan and Korea.
- Source of various type of alkaloids.
- Methyl Homosecodaphniphyllate is one of the alkaloids that isolated from this plant.

Methyl Homosecodaphniphyllate

Structure of methyl homosecodaphniphyllate was examined by X-ray crystallographic in 1971 by Sasaki and Hirata.¹

A concise total synthesis of methyl homosecodaphniphyllate was developed by Dr. Heathcock and co-workers at U.C. Berkeley.²

1: Methyl Homosecodaphniphyllate

Satisfies the structural prerequisite for an aza-Prins transform, helps to disconnect C2 and C3
Aza-diene moiety

Trisubstituted double bond
Formed from ammonia react with dialdehyde.
All the carbon atoms that needed for the target compound can be introduced via Michael addition/enolate alkylation.
Oxidized from primary alcohol

\[ \text{Oxidized from primary alcohol} \]
Hydrolysis from ester ring
Amide hydrolysis followed by esterification
Can be reduced to primary alcohol by reducing reagent.
All the carbon atoms that needed to construct the target compound was introduced.
Reduced to primary alcohol by Dibal-H

Step 2

\[ \text{OBn} \]

\[ \text{MeO}_2\text{C} \]

\[ \text{H} \]

\[ \text{OBn} \]

\[ \text{HO} \]

\[ \text{HO} \]

\[ \text{toluene, -78 °C, 1.5 h} \]

\[ \text{83%} \]

Dibal-H

\[ (\text{H}_3\text{C})_2\text{HCH}_2\text{C}-\text{Al} \]

\[ \text{H} \]

\[ \text{Al} \]

\[ \text{CH}_2\text{CH}(\text{CH}_3)_2 \]

\[ (\text{H}_3\text{C})_2\text{HCH}_2\text{C} \]
Epimerized for hydrolysis amide

Step 3

1. KOH, H₂O, EtOH, 95 °C, 2h
2. HCl, H₂O

1:1 mixture of diastereomer
Deduced to primary alcohol by LiAlH₄

Step 4

(3 equiv) LiAlH₄
ether, 5h

96%

Equimolar stereoisomeric diols
Intermediate 5 is not isolated but treated directly with NH$_3$.
NH$_3$ attacks the less hindered aldehyde.

1 mol of water is eliminated through imine-enamine tautomerization to form this aza-diene.
The crude residue of 13 is dissolved and protonated by Acetic acid.

Step 7

13

(4.5 equiv) NH₄OAc

AcOH, 25 °C

4
Step 8 (Intramolecular Diels-Alder)

\[ \text{4} \xrightarrow{[4+2]} \text{3} \]

\(25 \, ^\circ \text{C}\)
AcOH accelerated the intramolecular [4+2], reaction is complete in 5 mins
Step 9

Protonated nitrogen assist the closing up of the formed 6-membered ring

\[
\text{BnO, 70 °C}\quad \text{azap-rins}
\]

\[\text{AcOH, 70 °C}\]
Step 10

$\text{HN}$

$\text{HN}$

$77\% \text{ (from 12)}$
Step 11

Reduced by hydrogenation

Hydrogenation through adding small amount of acid

1 atm H₂, Pd-C

HCl

96%

HN

BnO

2

15
Step 12 (Jones Reagent & Fischer Esterification)

Rapid oxidation of the hydroxy group carried out by Jones reagent

The carboxylic group then undergoes Fischer esterification with methanol

\[ \text{HO} \]

1. \( \text{CrO}_3, \text{H}_2\text{SO}_4, \text{H}_2\text{O}, (\text{CH}_3)_2\text{CO} \)

2. \( \text{MeOH, H}_2\text{SO}_4 \)

\( (\pm)-1: (\pm)-\text{methyl homosecodaphniphyllate} \)

85% from 2
Mechanism: The Tetracylization I
Mechanism: The Tetracylization II

\[
\text{OBn} \quad \text{H} \quad \text{N} \quad \text{AcOH, 25 °C} \quad \text{NOAc} \quad \text{BnO} \quad \text{H} \quad \text{N} \quad \text{BnO} \quad \text{H}
\]

\[
\text{BnO} \quad \text{H} \quad \text{N} \quad \text{BnO} \quad \text{H} \quad \text{N} \quad \text{BnO} \quad \text{H}
\]
Further Studies of the Daphniphyllum Alkaloid Polycyclization Cascade

- The substitution pattern of both the dienophile and the aza-diene were examined, through a series studies of 1,5-diol cyclization precursors.
- These studies of cyclization shown that the cascade reaction can tolerant various alkyl-substituted dienophiles.
- Meanwhile, it’s also sensitive to the substitution pattern of the aza-diene.
- Alternation of the structure of the aza-diene will cause completely opposite results.