Total synthesis of the *Daphniphyllum* alkaloid: daphenylline


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Introduction

- Isolated from the fruits of *D. longeracemosum* (Hao, 2009)

- 6 stereogenic centers

- 6 cycles with 1 bridge 6,1,5-tricyclic motif
Retrosynthesis

8 Daphenylline

\[
\begin{align*}
\text{Pd-catalysed} & \quad \Rightarrow \\
\text{Radical} & \quad \Rightarrow \\
\text{6π-electrocyclization/aromatization} & \\
\end{align*}
\]

9

10

11

12

22
Retrosynthesis

Michael addition

Amidation

Au-catalyzed alkyne cyclization

Mitsunobu reaction

16 + 17 → 15

13 + 14
Synthesis of fragment 20

1. **Synthesis of 15**: Compound 16 is treated with 17, Ph₃P, DIAD, at 0 °C to yield 15 in 86% yield. Compound 16 has 98% ee.

2. **Synthesis of 20**: Compound 15 is treated with TBDPSOTf in 2,6-lutidine at -78 °C, followed by Au(PPh₃)Cl·AgOTf in MeOH. The overall process yields 70% over 2 steps (29% recovery S.M.) for 20.

Other compounds:
- 18: TBDPS ether (not observed)
- 19: TBDPS ether (not observed)
Synthesis of fragment 23

1/ K₂CO₃
p-thiocresol

2/ 14, t-BuOH
EDC•HCl, Et₃N
72% (over 2 steps)

K₂CO₃, 100 °C
86%

1/ KHMDS, PhNTf₂
-78 °C

2/ 22, Pd(PPh₃)₄ cat.
K₂CO₃, 60 °C
73% (over 2 steps)
Synthesis of fragment 25

1/ $h\nu$ (Hg lamp, 500 W), $0 \degree C$, 71%
2/ DBU, air, $60 \degree C$, 67%

single diastereoisomere
Synthesis of fragment 31

1/ HF•Py, 0 °C
2/ I₂, PPh₃, imidazole

93% (over 2 steps)

1/ TMSOTf, Et₃N, -78 °C
2/ Pd(OAc)₂

81% (over 2 steps)

(TMS)₃SiH, AIBN, 75°C

98%
End of the Synthesis

1/ H₂, Cabtree's catalyst
2/ LiCl•H₂O, 160 °C
86% (over 2 steps)

1/ Pd/C, MeOH
2/ LAH, 40 °C
66% (over 2 steps)

Daphenylline
Conclusion

• 19 linear steps: overall Yield = 5%

• 3 key-steps:
  
  • gold-catalyzed cyclization
  
  • photoinduced isomerization/electrocyclization cascade
  
  • 7-exo-trig radical cyclization
Thank you for your attention
Synthesis of Methyl Homosecodaphniphyllate

Synthesis of Methyl Homosecodaphniphyllate

Synthesis of 16

$m$-methylanisole $\xrightarrow{\text{Li/NH}_3} m$-CPBA

$\xrightarrow{\text{oxalic acid MeOH/H}_2\text{O}}$ $\xrightarrow{m$-$\text{CPBA}}$

$\xrightarrow{\text{Ac}_2\text{O}, i$-$\text{Pr}_2\text{NEt DMAP}}$ $\xrightarrow{\text{Pig Liver esterase}}$ $\xrightarrow{\text{Na}_2\text{CO}_3 \text{MeOH}}$

$\xrightarrow{\text{ent-16}}$ $\xrightarrow{98\% \text{ ee}}$

Synthesis of fragment 20
(Mechanism)
Amidation

Nakajima, N.; Ikada, Y. Bioconjugate Chem. 1995, 6, 123.
Without DBU
Introduction

- Isolated from Daphniphyllum (Asian Plants)
- More of 250 alkaloids
- 20 subfamilies
- Daphnicyclidin A: anticancer