Total Synthesis of (−)-Daphenylline

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- Ph.D. in Harvard with Y. Kishi in 1977
- Assistant professor in Rice University 1978
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- Research interest: Total synthesis of complex natural product
Introduction

- *Daphniphyllum* alkaloid family

- Daphenylline was isolated from the fruit of *D. longeracemosum* by Hao in 2009

- Used in Chinese herbal medicine

- First enantioselective synthesis by Li and co-workers in 2013

Retrosynthetic Approach

Daphenylline

Azomethine ylide

MeO

HN

Me

X
Preparation of the tricyclic core

1) PCl₃, pyridine, CH₂Cl₂, –10°C
2) NiBr₂•diglyme, (S)-iPr-Pybox, DMA, 0°C
3) aq. NaOH, EtOH, rt

81% over 3 steps

99%
Installation of the side chain

1) Tf₂O, pyridine, CH₂Cl₂, 0°C
2) Propargyl alcohol, PdCl₂(dppf)•CH₂Cl₂, Pyrrolidine, TBAI, DMF, 60°C

H₂, Lindlar catalyst, quinoline, EtOAc, rt

n-butyl vinyl ether, Hg(OAc)₂, 60°C

iBu₃Al, hexane, 10°C

90% d.r. 5.9:1
Installation of the side chain

1) TBSCI, imidazole, DMF, rt
2) 9-BBN, THF, 0°C; 
   \( \text{H}_2\text{O}_2, \text{NaOH}, 0°C \text{ to } rt \)
3) AZADOL, PhI(OAc)_2, 
   Phosphate buffer (pH= 6.8), 
   MeCN, rt
4) TFA, CH_2Cl_2, rt

61% over 4 steps

LDA, THF, –78°C
Mel, HMPA, 0°C

1) LiAlH_4, THF, 0°C
2) TIPSCI, imidazole, 
   DMF, rt

64% over 2 steps
Installation of the side chain

1) PhSH, K₂CO₃, DMF, 50°C
2) TBAF, THF, rt
   Boc₂O, NaHCO₃, CH₂Cl₂, rt
3) DMP, CH₂Cl₂, rt

85% over 3 steps
Intramolecular cycloaddition

NaOAc, BHT, MS4A, Toluene, Microwave, 200°C

53%
Daphenylline

1) NH$_3$, MeOH, 70°C
2) Burgess reagent, CH$_2$Cl$_2$, rt
3) NaBH$_4$, MeOH, Reflux

Daphenylline
27% over 3 steps
Conclusion

> Key Step: Intramolecular cycloaddition of a cyclic azomethine ylide

> 24 Steps overall yield of 0.2%

→ Less efficient than the synthesis of Li (19 steps 5% overall yield)

Thank you for your attention