UNIVERSITÄT BERN

Total Synthesis of (–)-Daphenylline

Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed. Engl.* **2016**, *55* (20), 6067.

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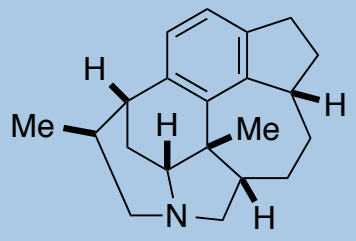


Nicolas Volkoff
26/05/2016

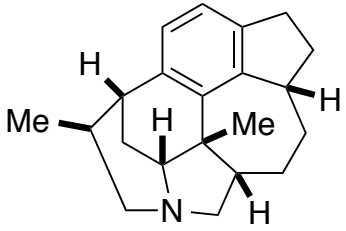
Tohru Fukuyama

- Ph.D. in Harvard with Y. Kishi in 1977

- Assistant professor in Rice University 1978
- Full professor in Rice University 1988
- Full professor in University of Tokyo since 1995

- Research interest :Total synthesis of complex natural product

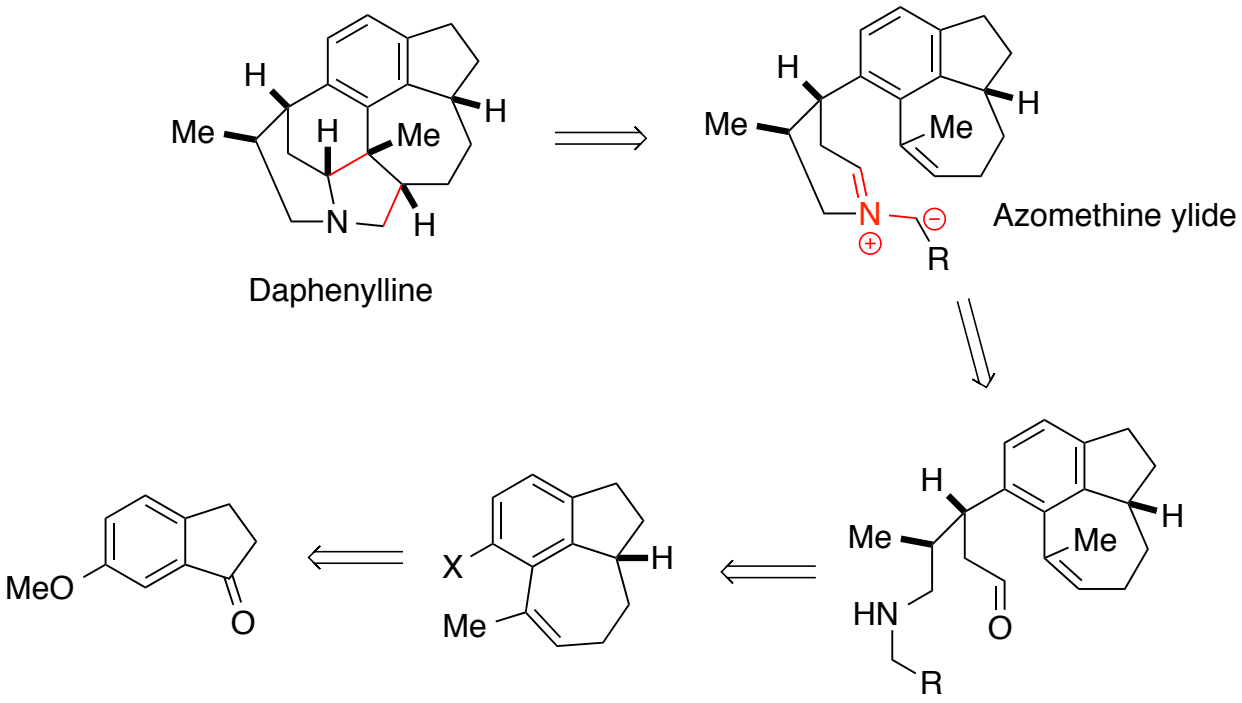
Introduction



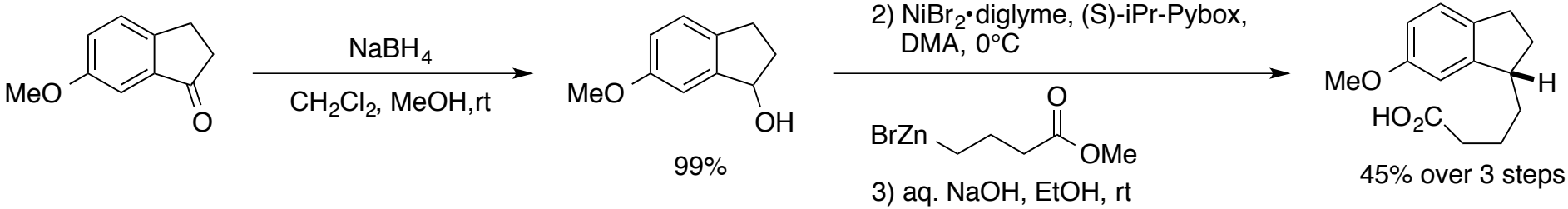
- *Daphniphyllum* alkaloid family
- Daphenylline was isolated from the fruit of *D. longeracemosum* by Hao in 2009
- Used in Chinese herbal medicine
- First enantioselective synthesis by Li and co-workers in 2013

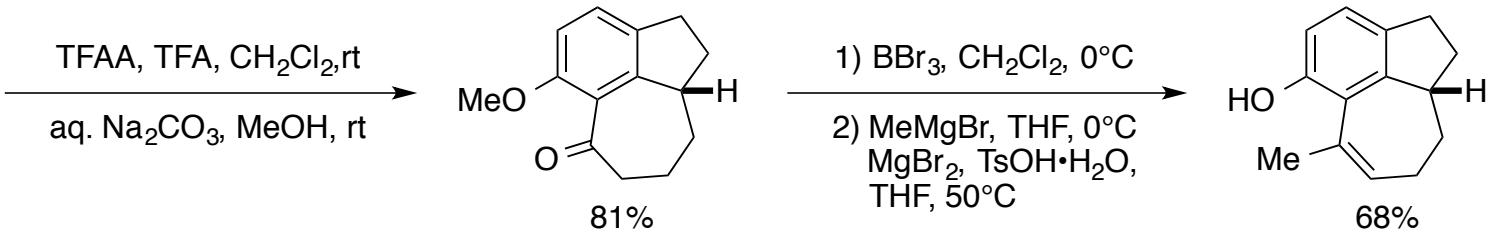
Zhang, Q.; Di, Y.-T.; Li, C.-S.; Fang, X.; Tan, C.-J.; Zhang, Z.; Zhang, Y.; He, H.-P.; Li, S.-L.; Hao, X.-J. *Org. Lett.* **2009**, *11* (11), 2357.
Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat Chem* **2013**, *5* (8), 679.

Retrosynthetic Approach

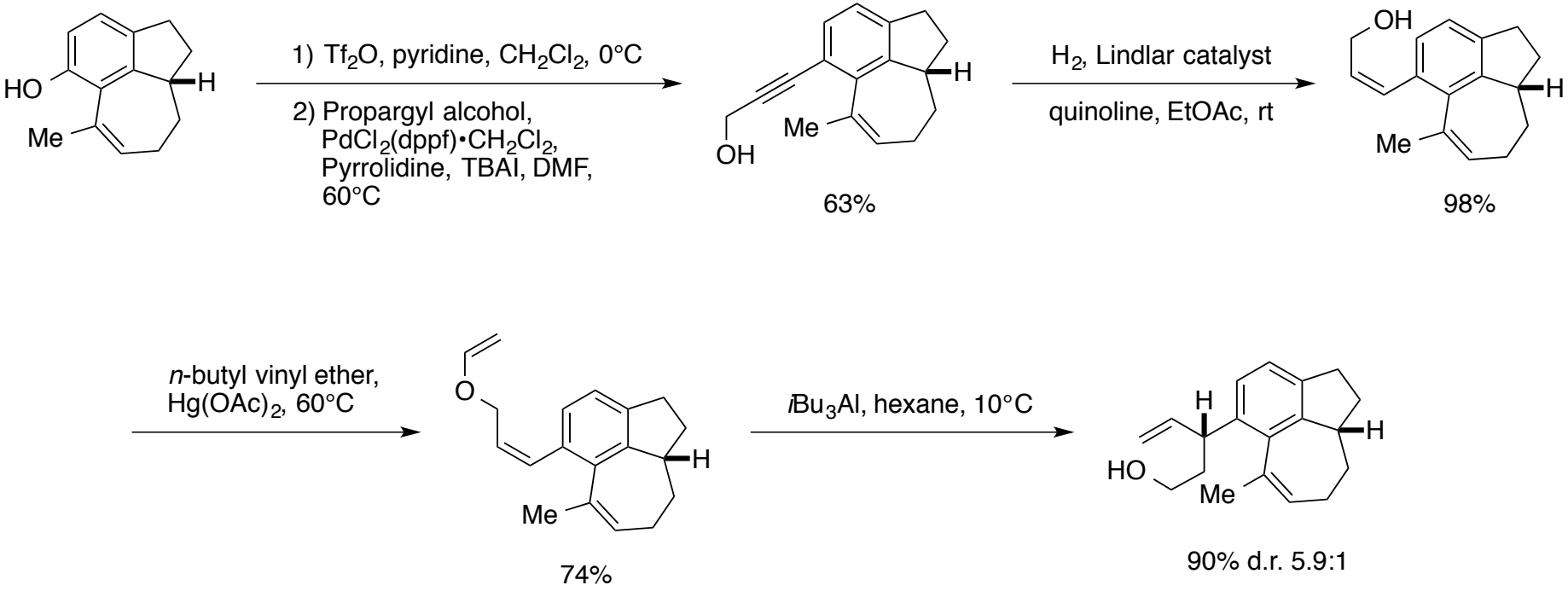


Preparation of the tricyclic core

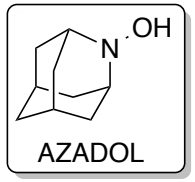


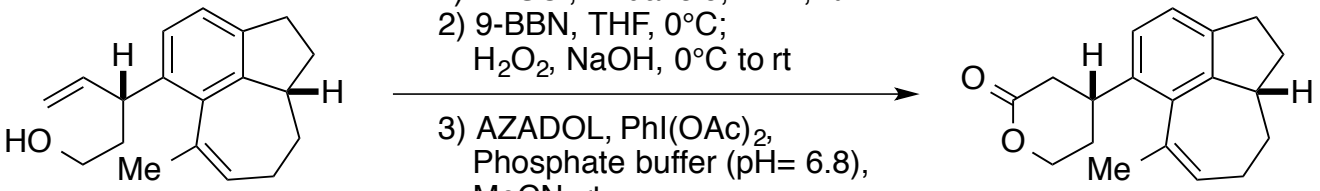


Installation of the side chain

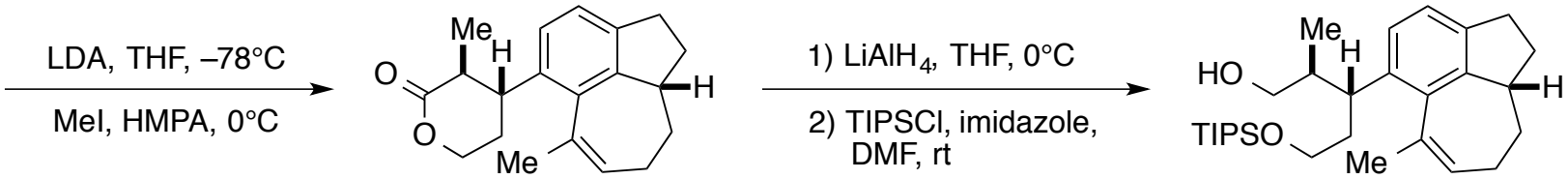


Installation of the side chain



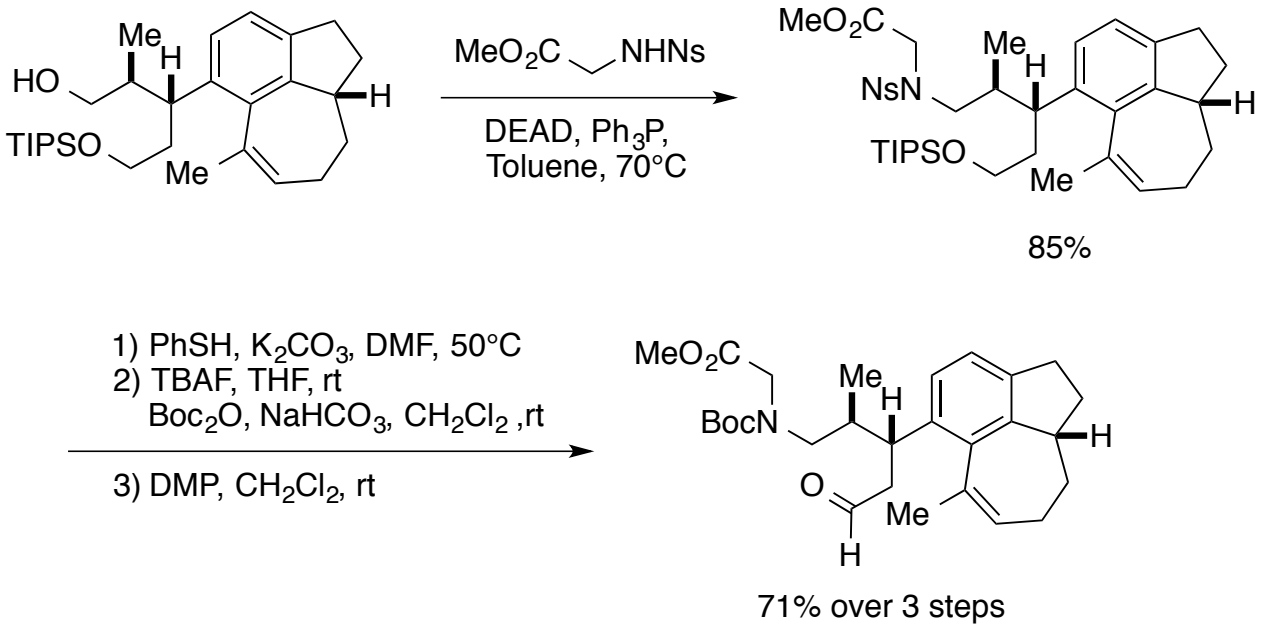


61% over 4 steps

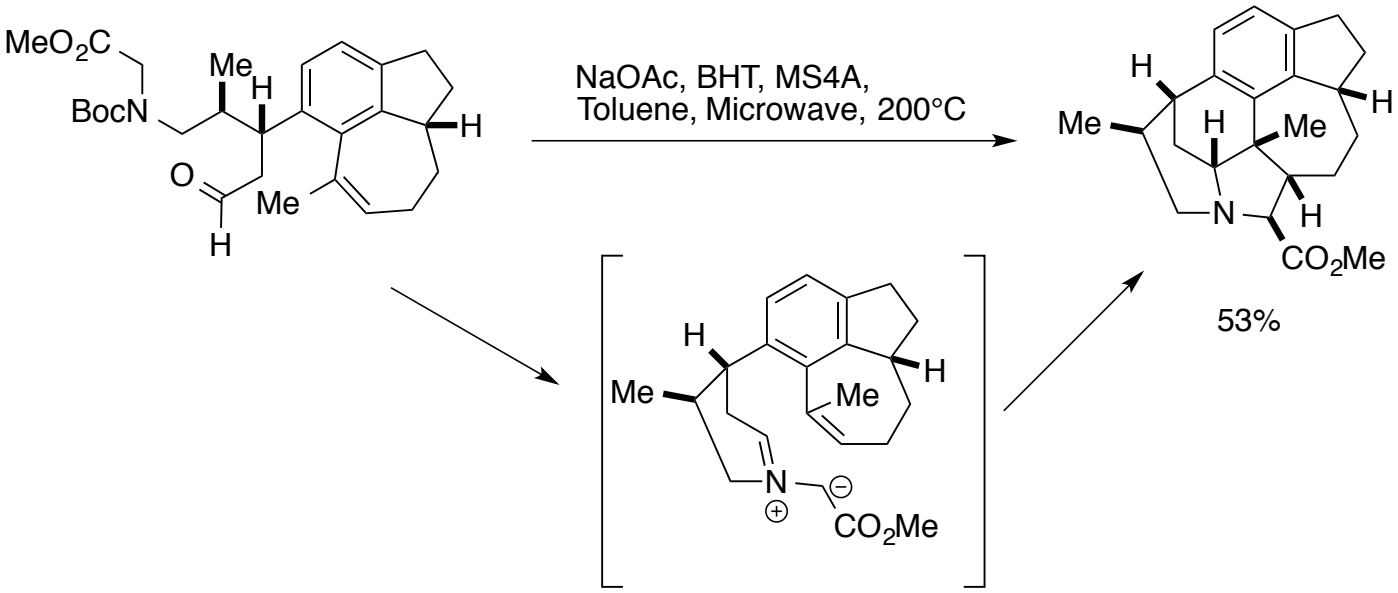


64% over 2 steps

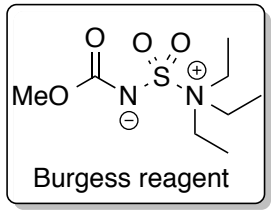
Installation of the side chain

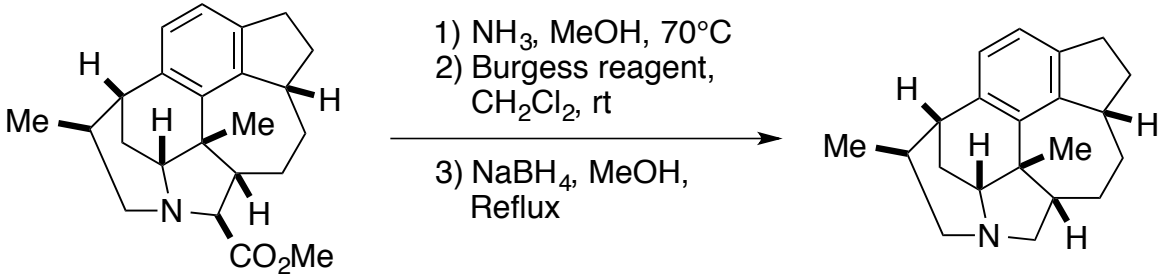


Intramolecular cycloaddition



Daphenylline





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