

# **Model Study for The Total Synthesis of Daphniglaucin A**

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Research Topic Seminar  
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# Daphniphyllum alkaloids

*Daphniphyllum* alkaloids have highly complex polycyclic structure.

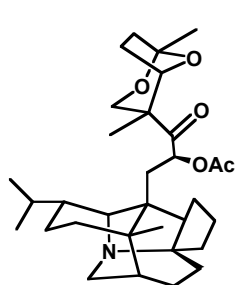
In recent year, more than 60 new *Daphniphyllum* alkaloids were isolated from oriental tree “Yuzuriha”.

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

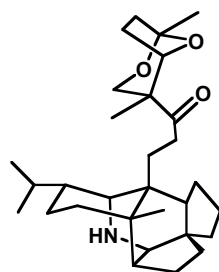
The unusual ring systems have attracted great interest as challenging targets for total synthesis.



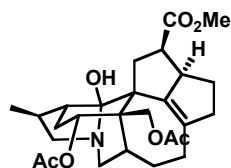
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Daphniphylline

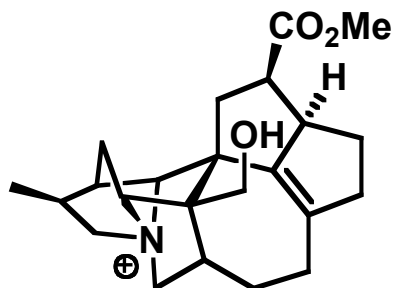


Secodaphniphylline



Yuzurimine

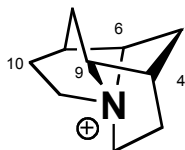
Yuzuriha (*Daphniphyllum macropodum*; Daphniphyllaceae) dioecious evergreen trees and shrubs native to Japan. Leaves are used as a pesticide.



## Daphniglaucin A

Isolated from leaves of *Daphniphyllum glaucescens* in 2003.

Unprecedented fused-polycyclic skeleton containing 1-azaniatetracyclo[5.2.2.0.<sup>1,6</sup>0.<sup>4,9</sup>]undecane ring.

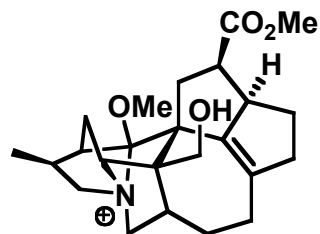


Structure elucidated by MS, <sup>1</sup>H and <sup>13</sup>C NMR, COSY, HMBC and NOESY

Exhibited cytotoxicity against murine lymphoma L1210 cells (IC<sub>50</sub> 2.7 μg/mL) and human epidermoid carcinoma KB cells (IC<sub>50</sub> 2.0 μg/mL) in vitro.

Kobayashi, J. *et al.*, *Org. Lett.*, **2003**, 5, 1733.

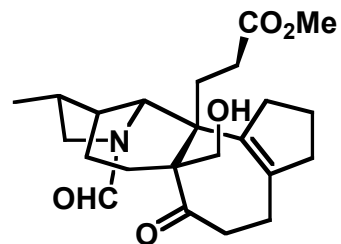
## Related compounds isolated from *Daphniphyllum glaucescens*



**Daphniglaucin B**

cytotoxicity :  
murine lymphoma L1210 cells ( $IC_{50}$  3.9  $\mu\text{g/mL}$ )  
and human epidermoid carcinoma KB cells  
( $IC_{50}$  10.0  $\mu\text{g/mL}$ ).

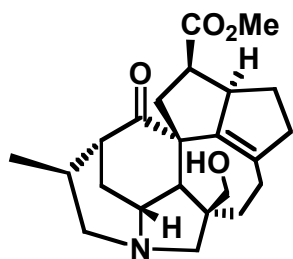
Kobayashi, J. *et al.*, *Org. Lett.*, **2003**, 5, 1733.



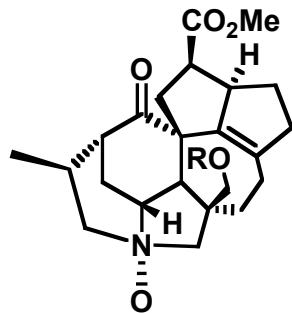
**Daphniglaucin C**

cytotoxicity murine lymphoma L1210  
cells ( $IC_{50}$  0.1  $\mu\text{g/mL}$ )  
inhibition the polymerization of tubulin  
( $IC_{50}$  25  $\mu\text{M}$ )

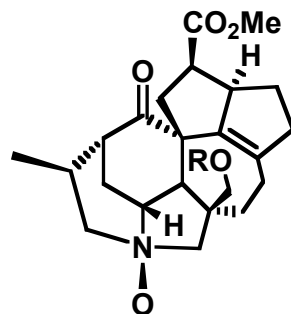
Kobayashi, J. *et al.*, *Tetrahedron Lett.*, **2004**, 45, 901.



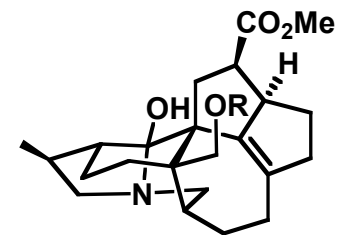
**Daphniglaucin D**



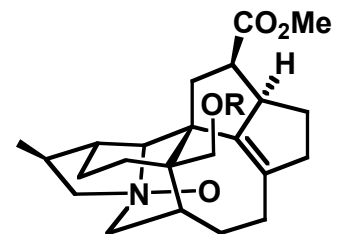
**Daphniglaucin E: R=H**  
**Daphniglaucin F: R=Ac**



**Daphniglaucin G: R=H**  
**Daphniglaucin H: R=Ac**



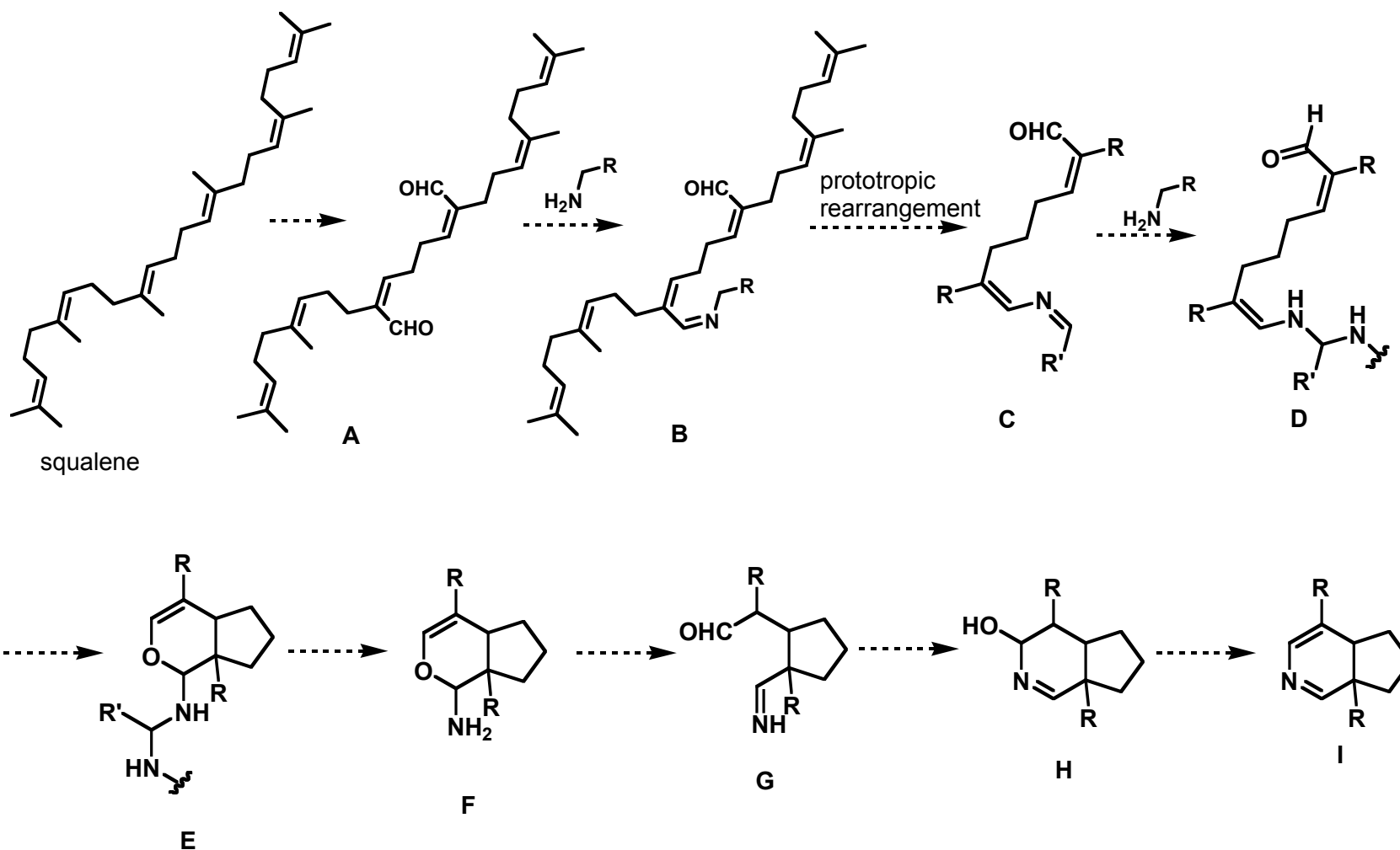
**Daphniglaucin J R=Ac**



**Daphniglaucin K R=Ac**

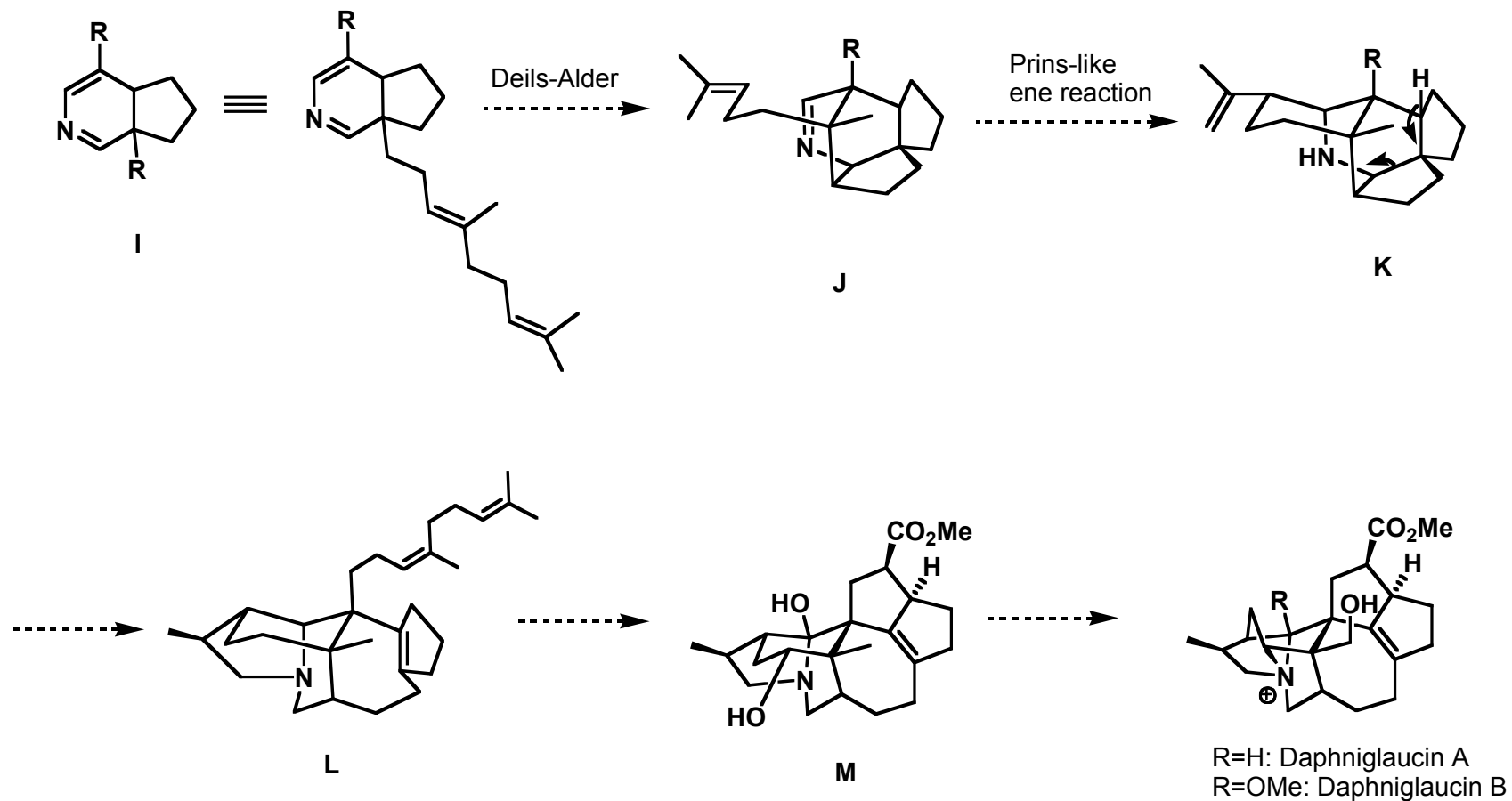
Kobayashi, J. *et al.*, *Tetrahedron*, **2004**, 60, 6279.

# Proposed biogenetic pathway for Daphniglaucin A -1



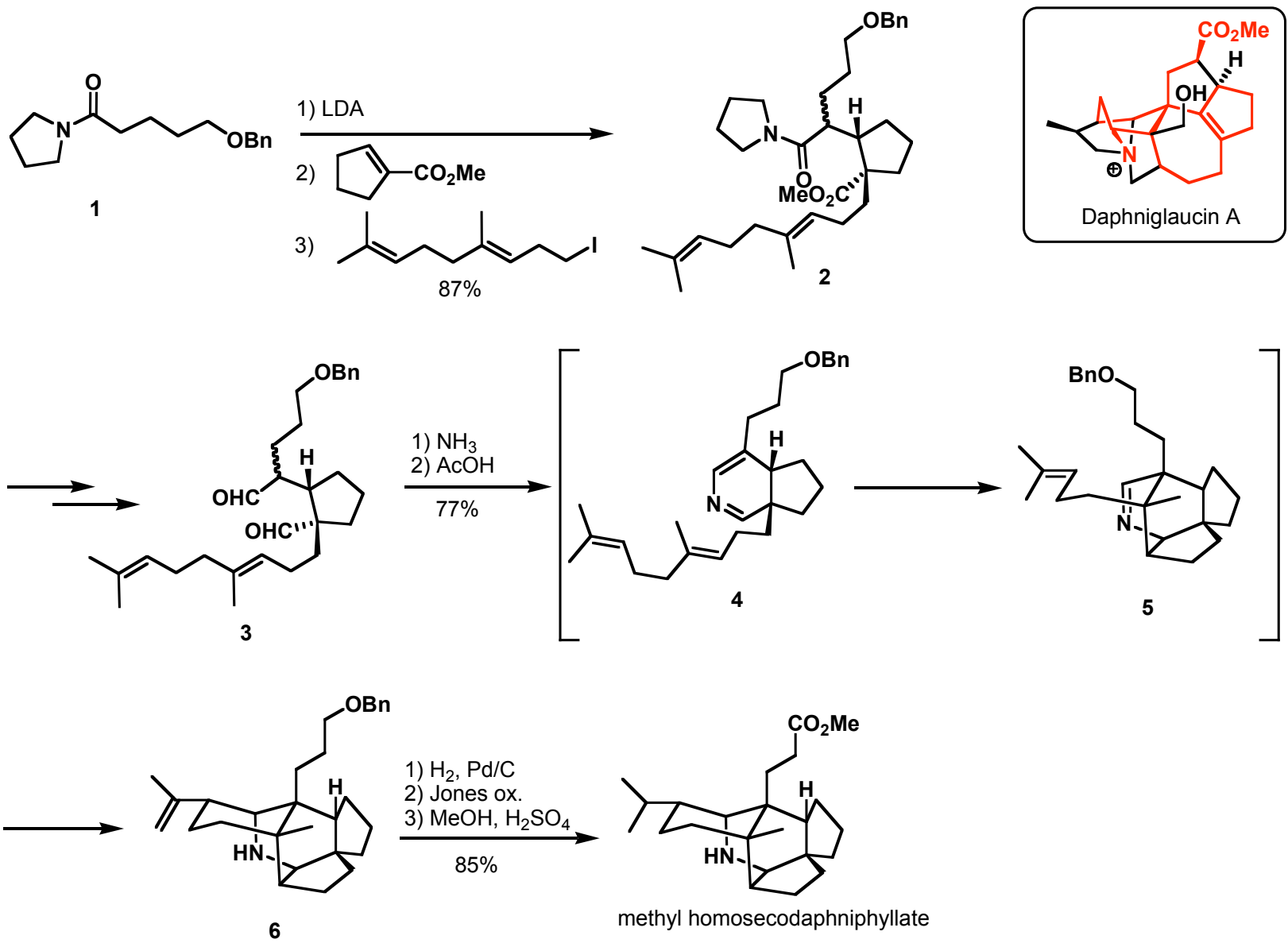
Heathcock, C. H., *Proc. Natl. Acad. Sci. USA*. **1996**, 93, 14323.

## Proposed biogenetic pathway -2



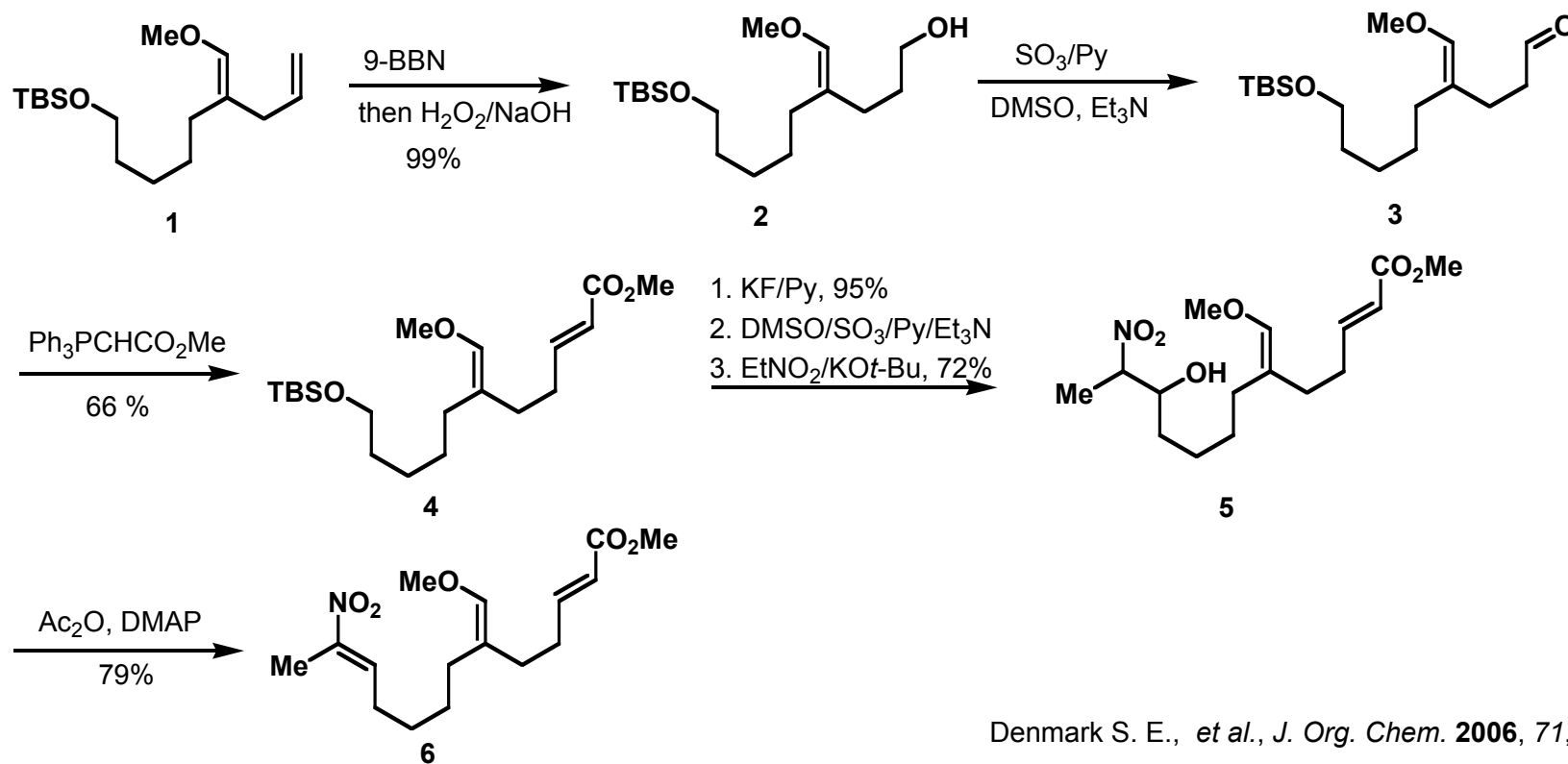
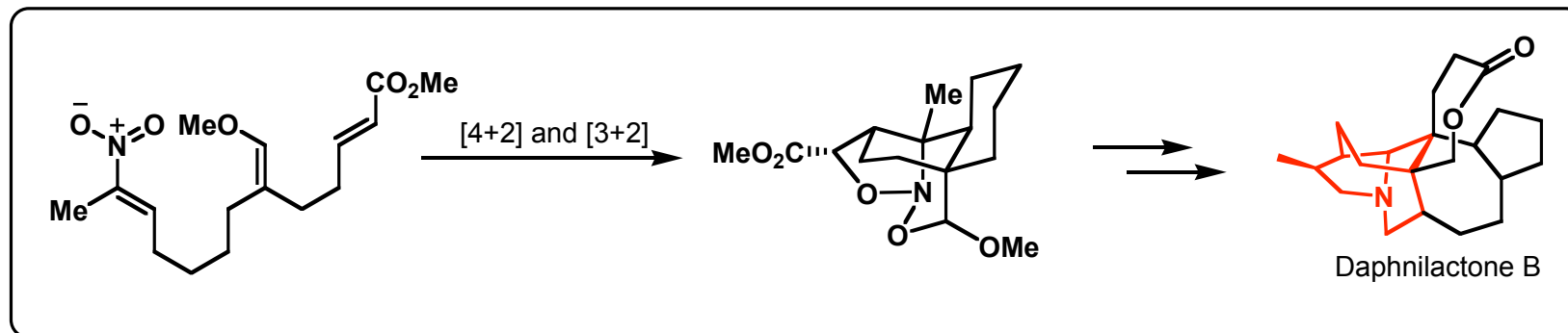
Heathcock, C. H., *Proc. Natl. Acad. Sci. USA*, **1996**, 93, 14323.  
 Kobayashi, J. *et al.*, *Org. Lett.*, **2003**, 5, 1733.

# Total synthesis of methyl homosecodaphniphyllate



Heathcock, C. H., *et al.*, *J. Am. Chem. Soc.* **1988**, *110*, 8734.

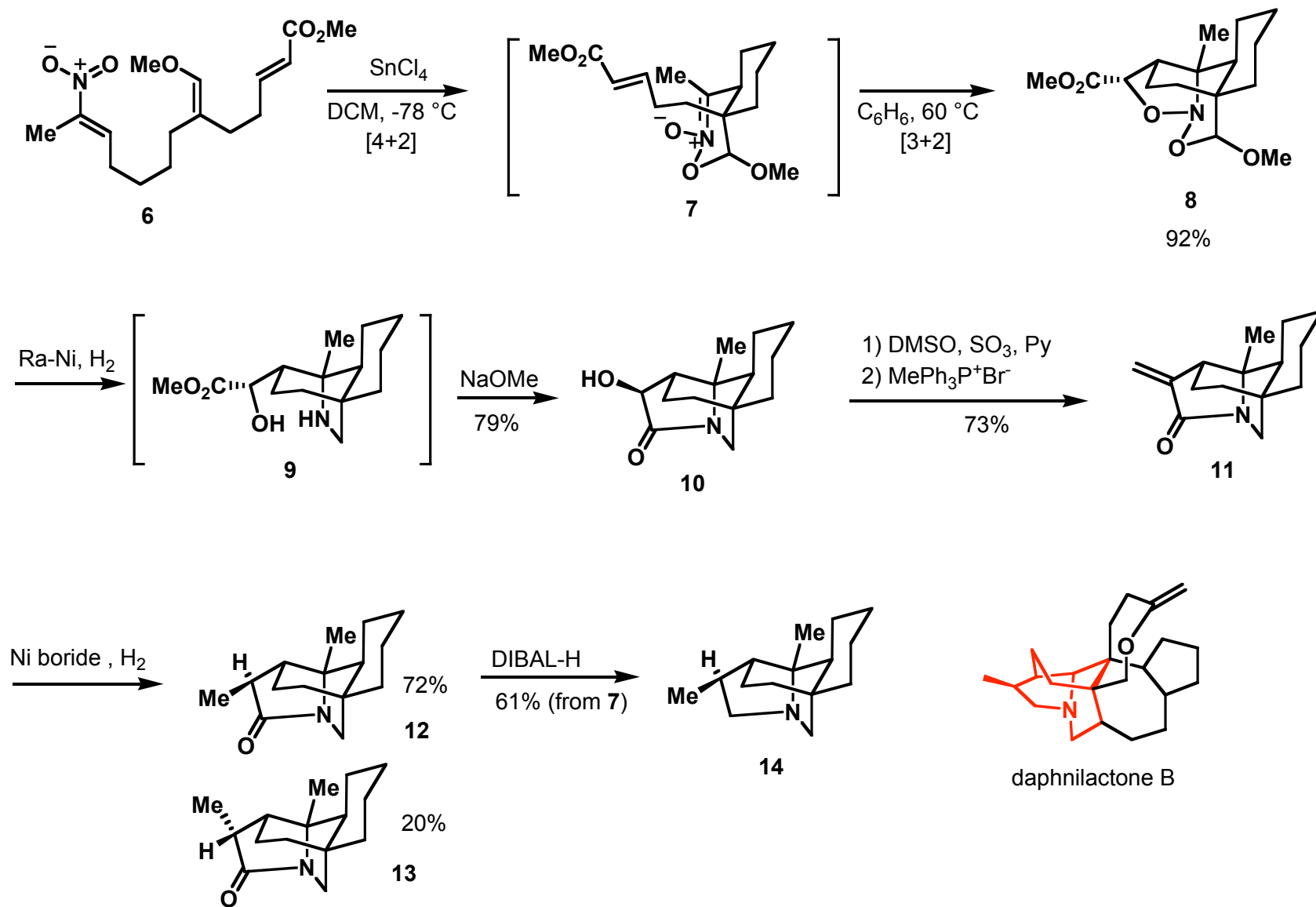
# Synthetic study on Daphnilactone B



Denmark S. E., et al., *J. Org. Chem.* **2006**, 71, 593.

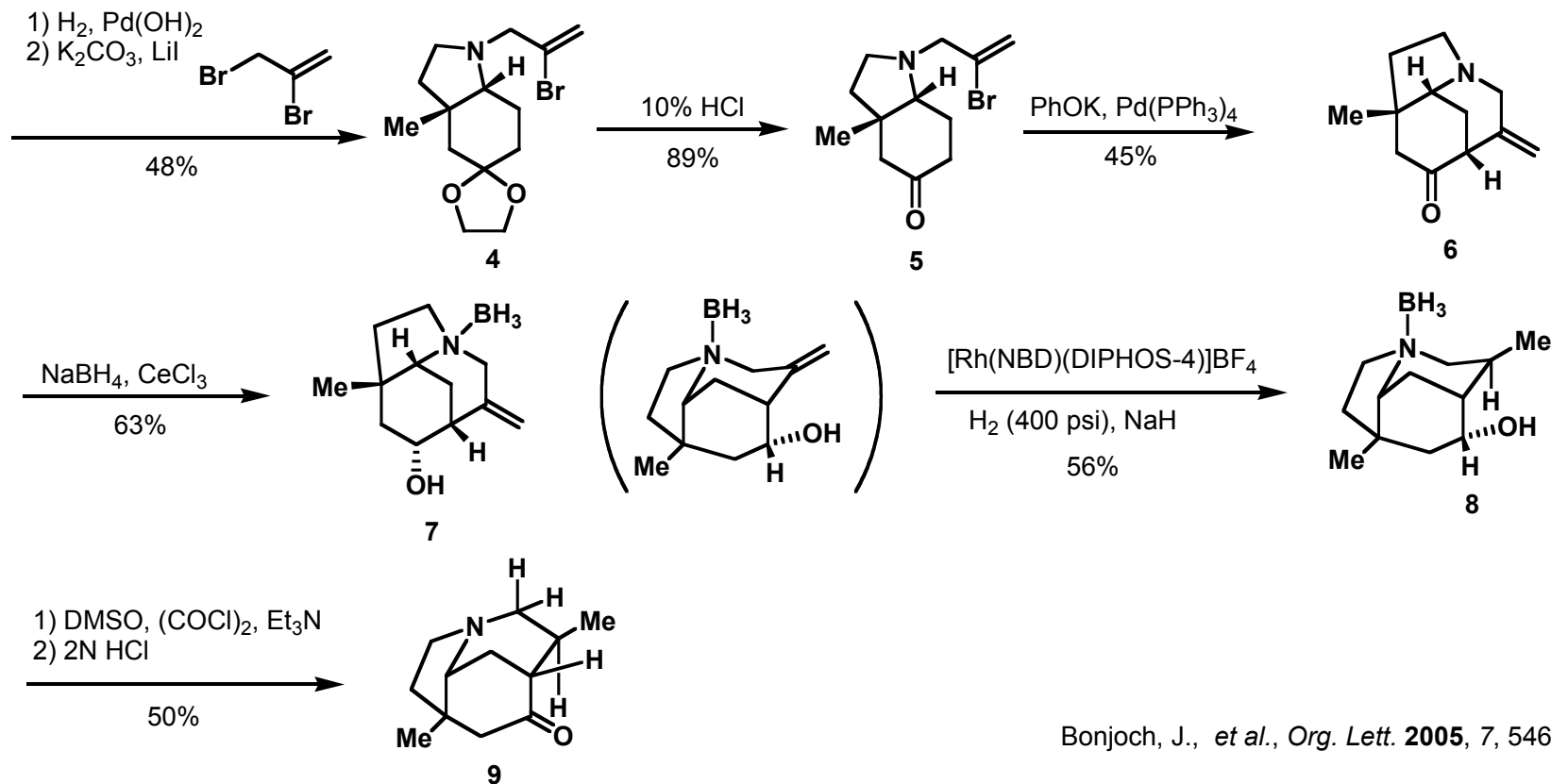
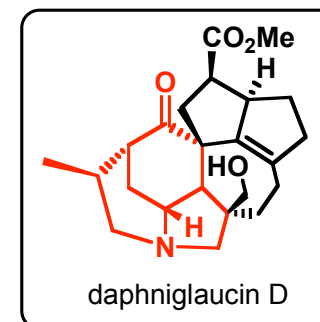
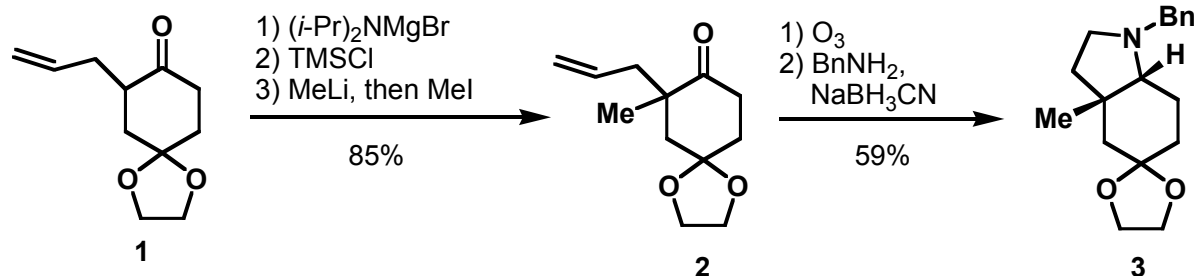


# Synthetic study on Daphnilactone B



Denmark S. E., *et al.*, *J. Org. Chem.* **2006**, *71*, 593.

# Synthetic study on Daphniglaucin D



Bonjoch, J., *et al.*, *Org. Lett.* **2005**, *7*, 5461.

# Acknowledgments

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