

# Literature Report

## Total synthesis of the *Daphniphyllum* alkaloid daphenylline

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**Checker: Zhang-Pei Chen**  
**Date: 2013-12-17**

**Li, A. *et al.***  
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## Research Interests

Divergent total synthesis of biologically active natural products based on biosynthetic hypothesis or privileged core structures

Desymmetrization strategy in natural product total synthesis

Ring strain-promoted reactions in natural product synthesis

## Professional Experience

2010–present “Bairen Jihua” Professor, Shanghai Institute of Organic Chemistry,

2010 Research fellow, Institute of Chemical and Engineering Sciences, Singapore

Advisor: Prof. K. C. Nicolaou

## Education

2004–2009 Ph.D., The Scripps Research Institute

Advisor: Prof. K. C. Nicolaou

2000–2004 B.Sc., Peking University

Advisor: Prof. Zhen Yang



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**Total synthesis of the Daphniphyllum alkaloid daphenylline**

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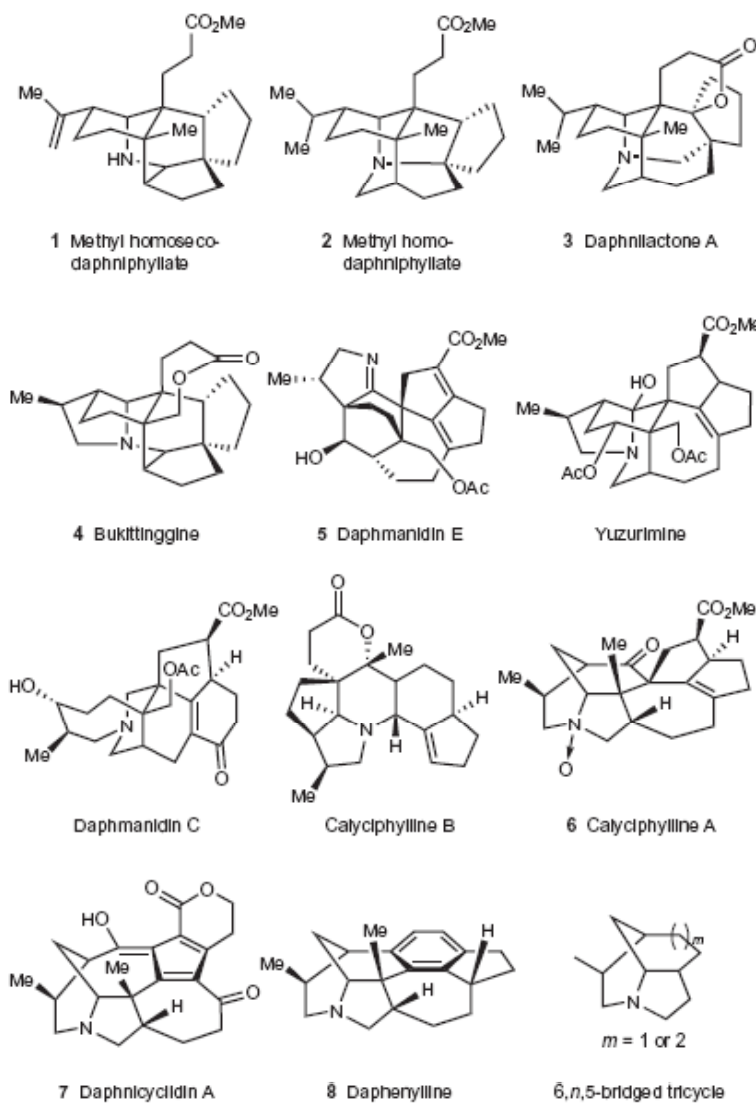
**Summary**

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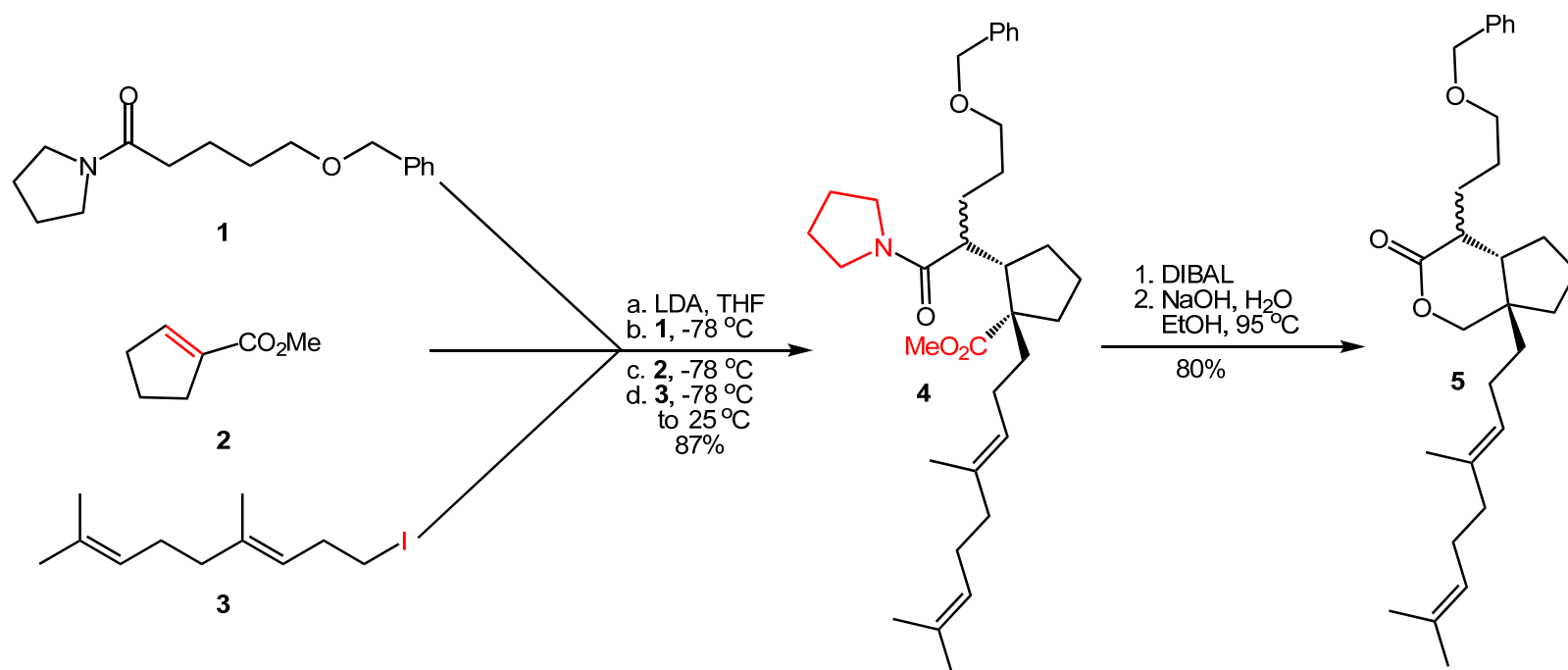
# Daphniphyllum alkaloid

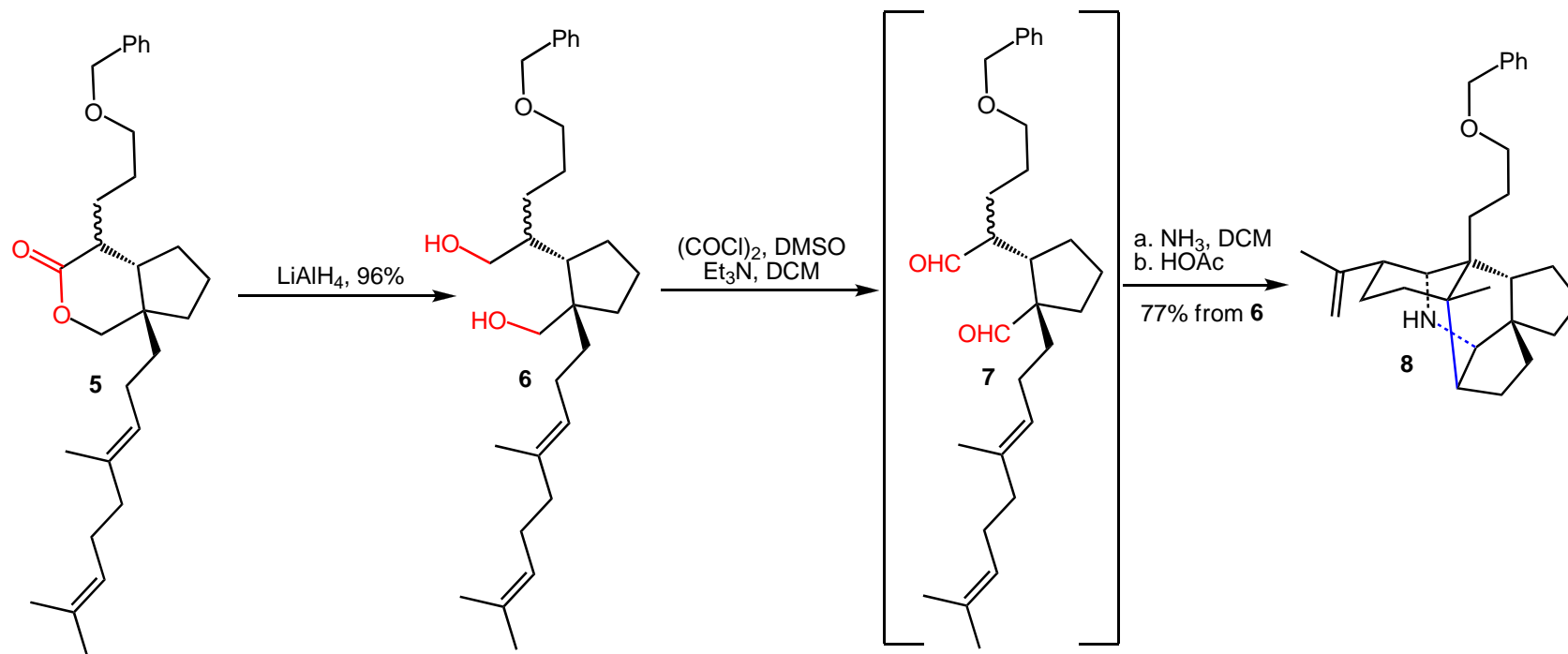


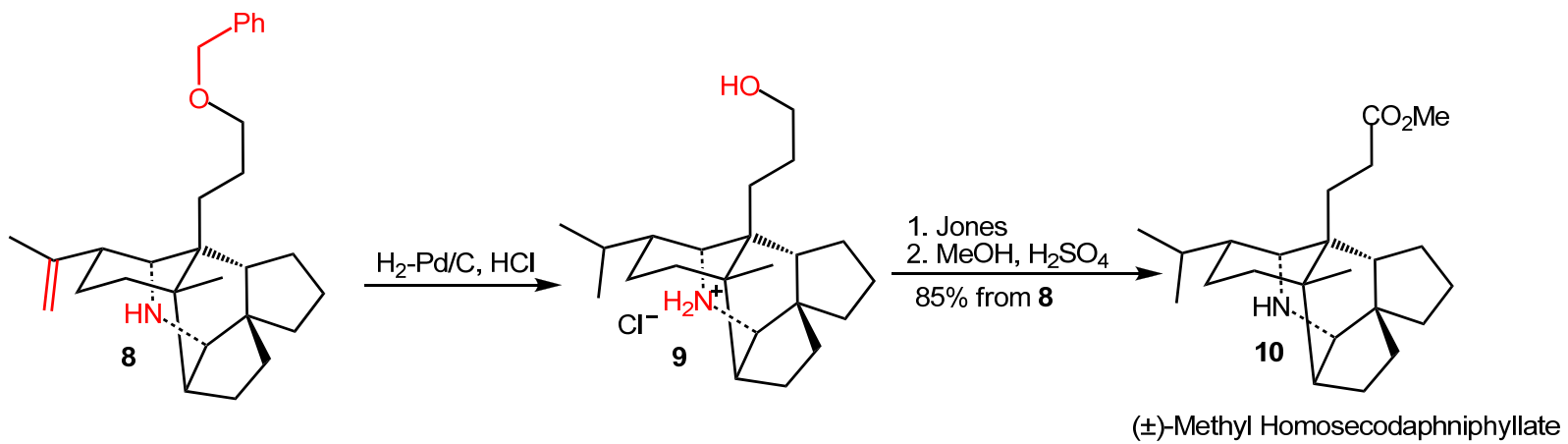
About 250 *Daphniphyllum* alkaloids have been isolated from the leaves and roots of evergreen plants



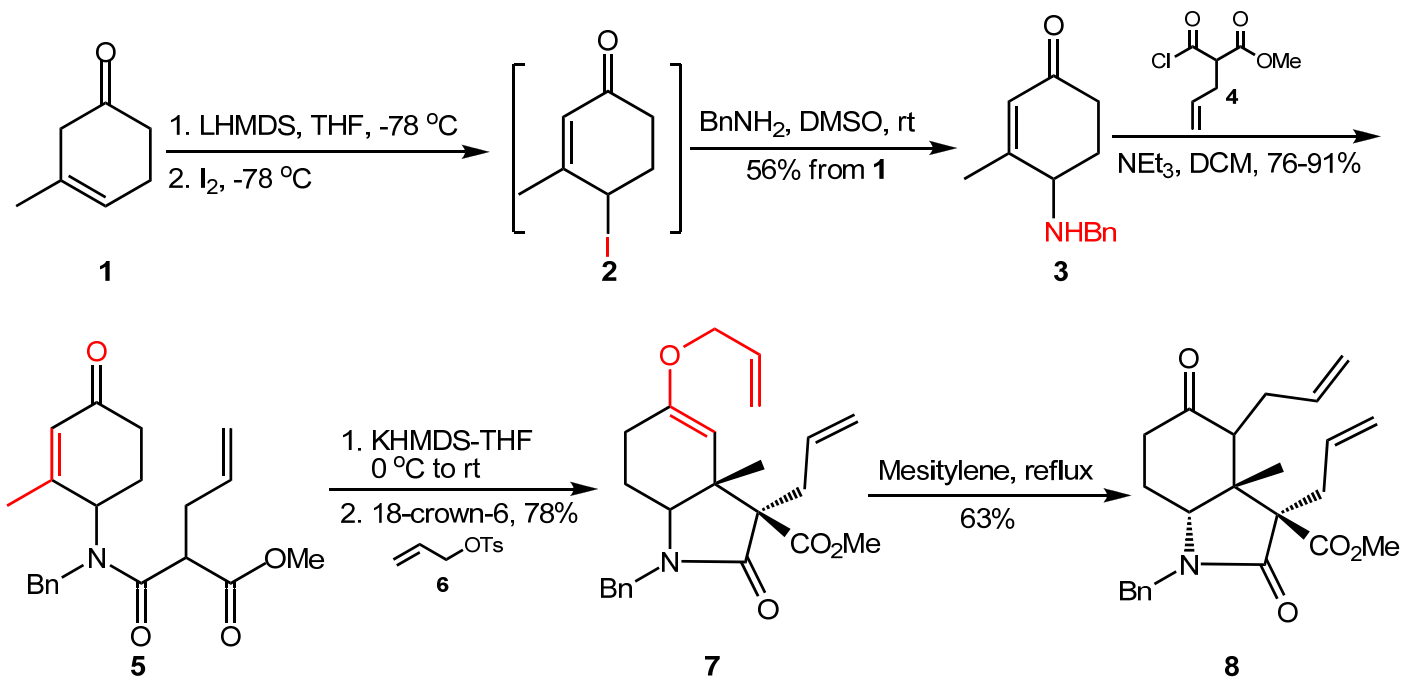
# Total synthesis of ( $\pm$ )-Methyl Homosecodaphniphyllate



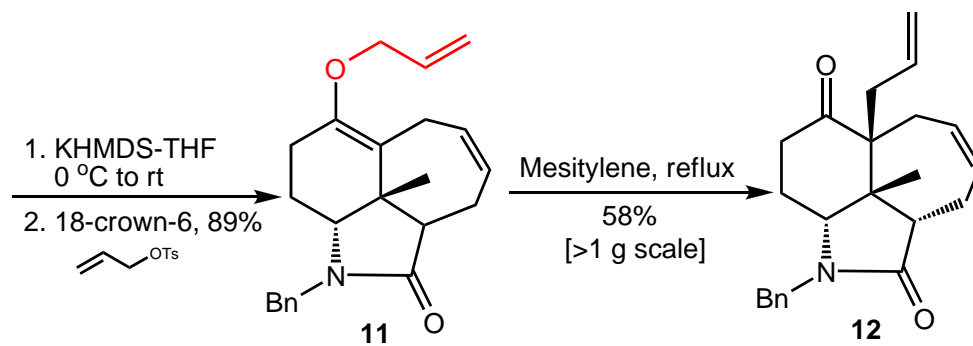
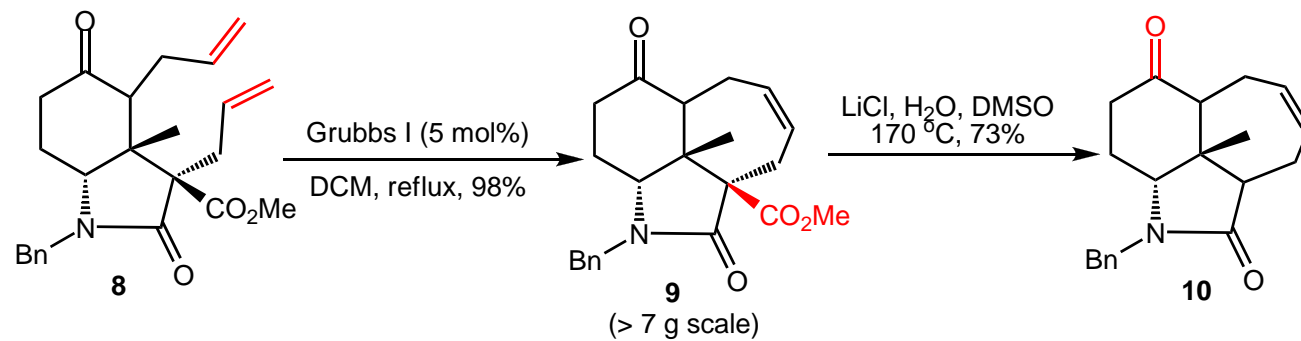


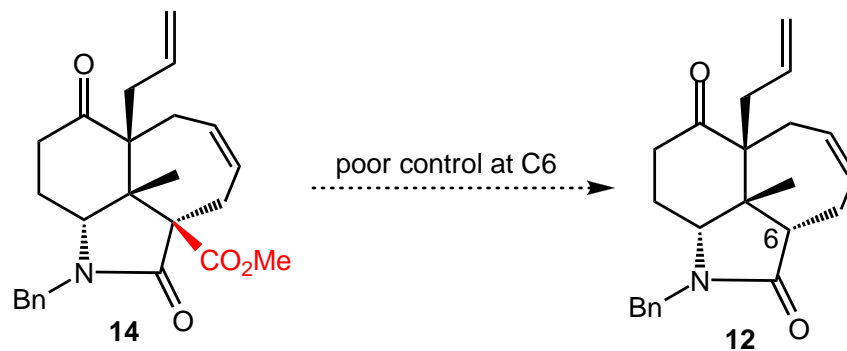
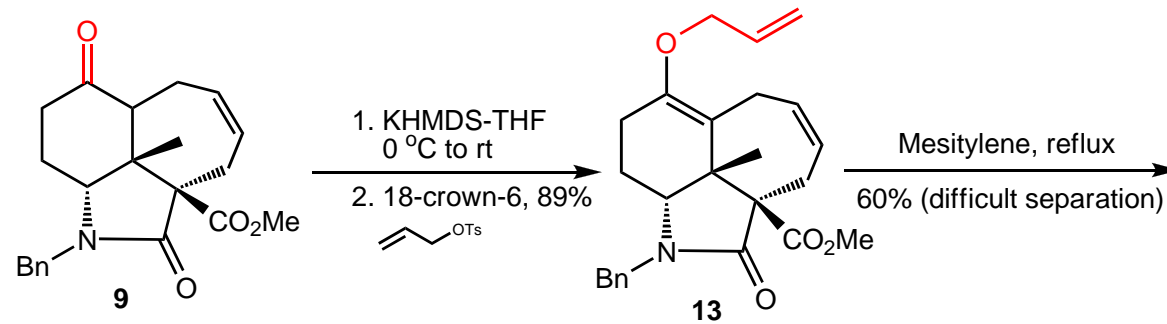


# Synthesis of the tricyclic core of Calyciphylline



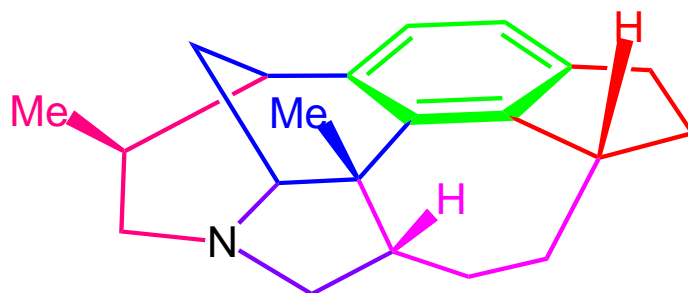






# Total synthesis of the Daphniphyllum alkaloid daphenylline

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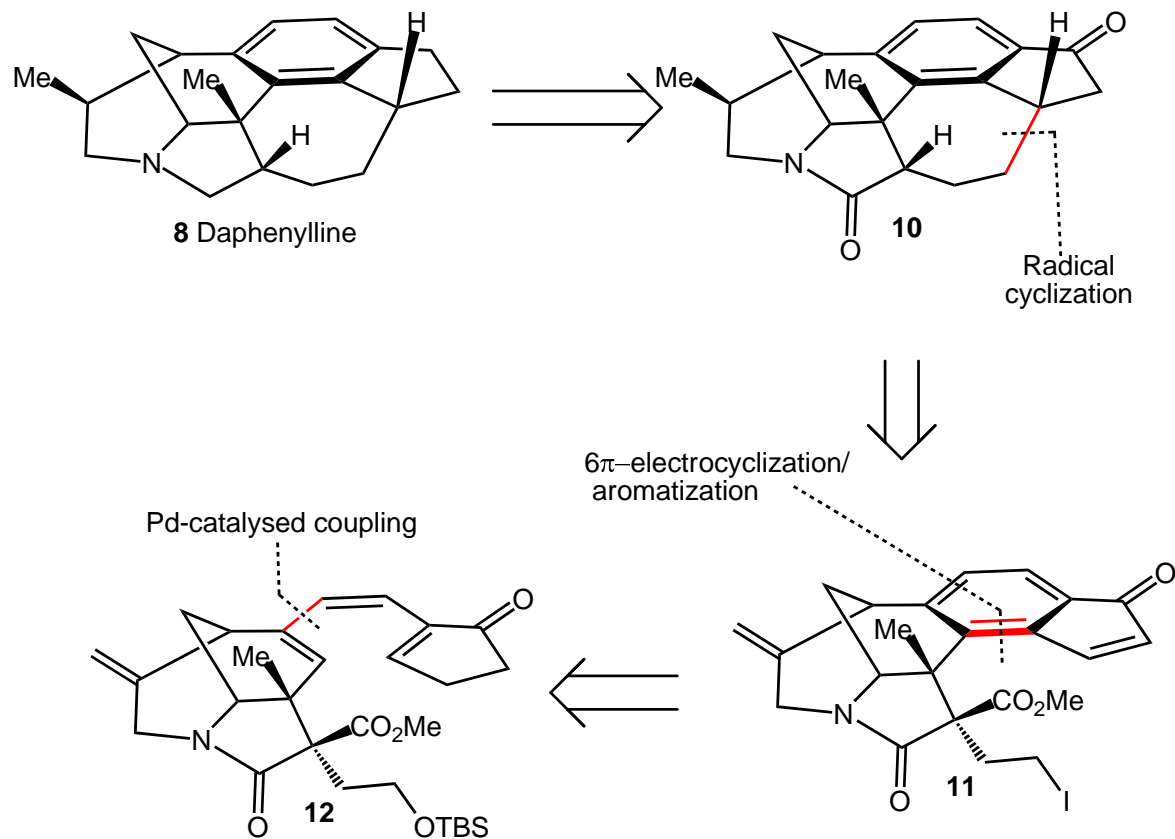


8 Daphenylline

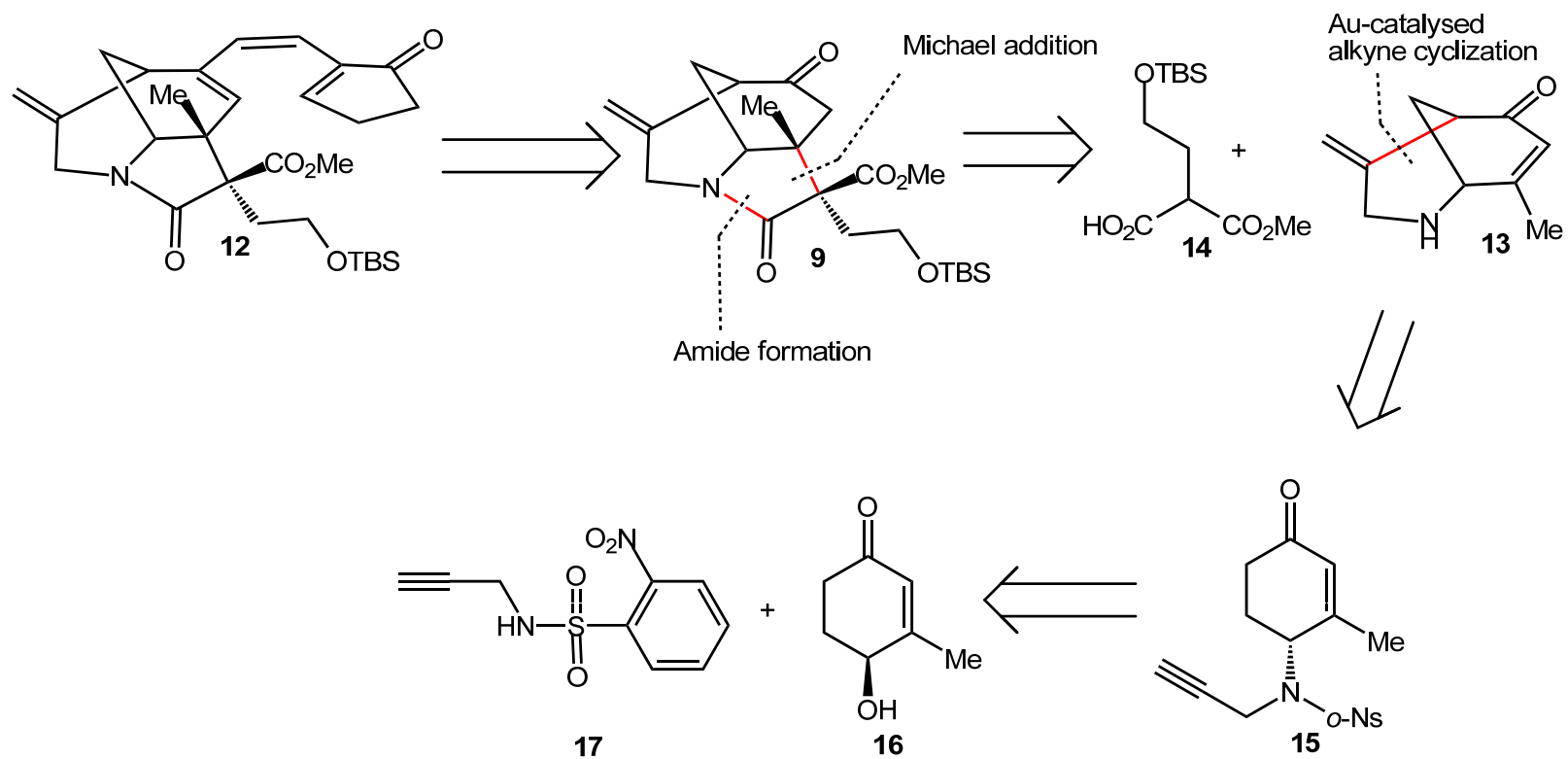
- ✦ **2009 Isolated by Hao and co-workers from the fruits of *D. longracemosum***
- ✦ **Six cyclic**
- ✦ **[3,3,1] Bicyclic and tetrasubstituted benzene ring**

# Retrosynthetic analysis of daphenylline

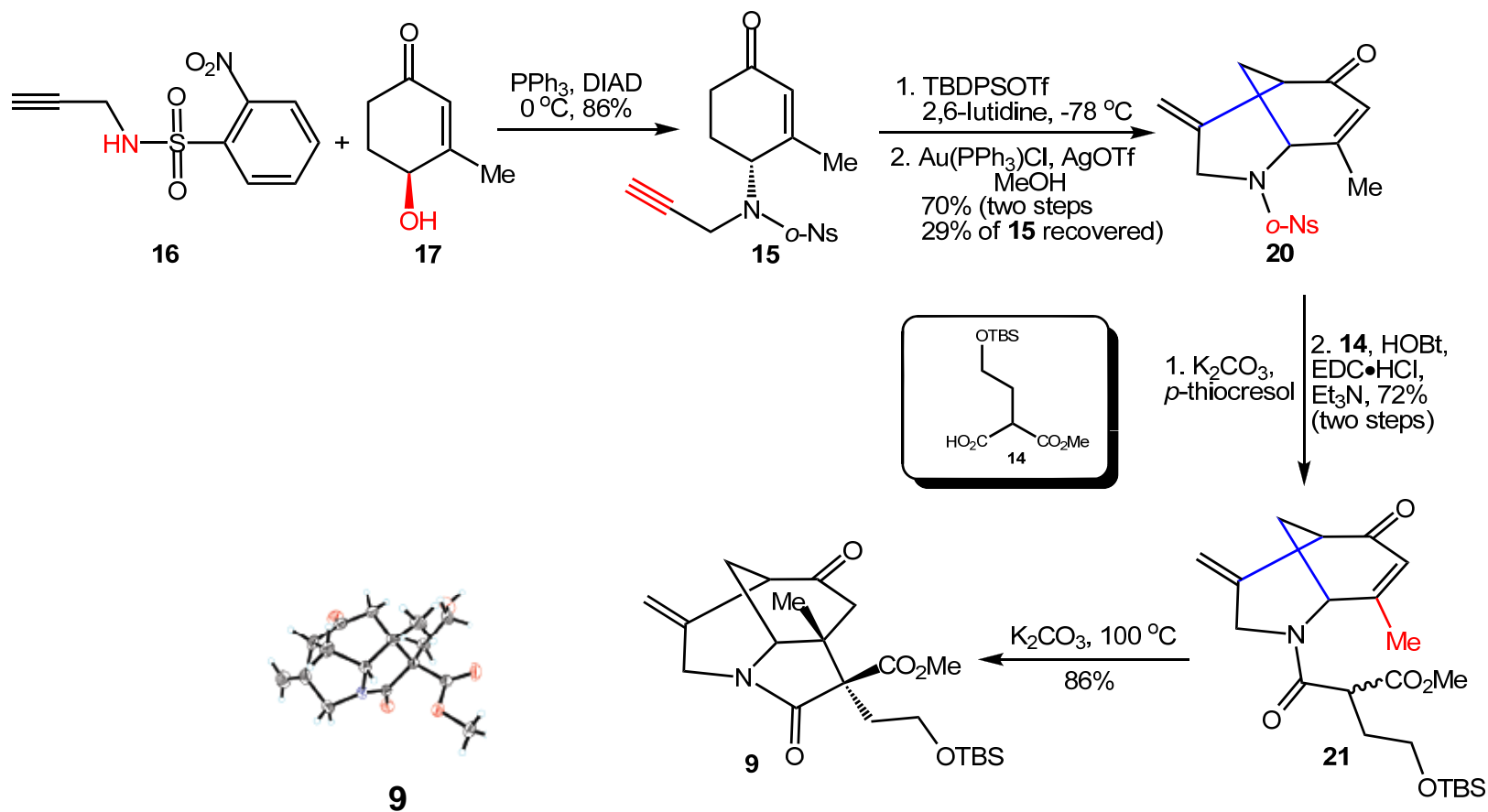
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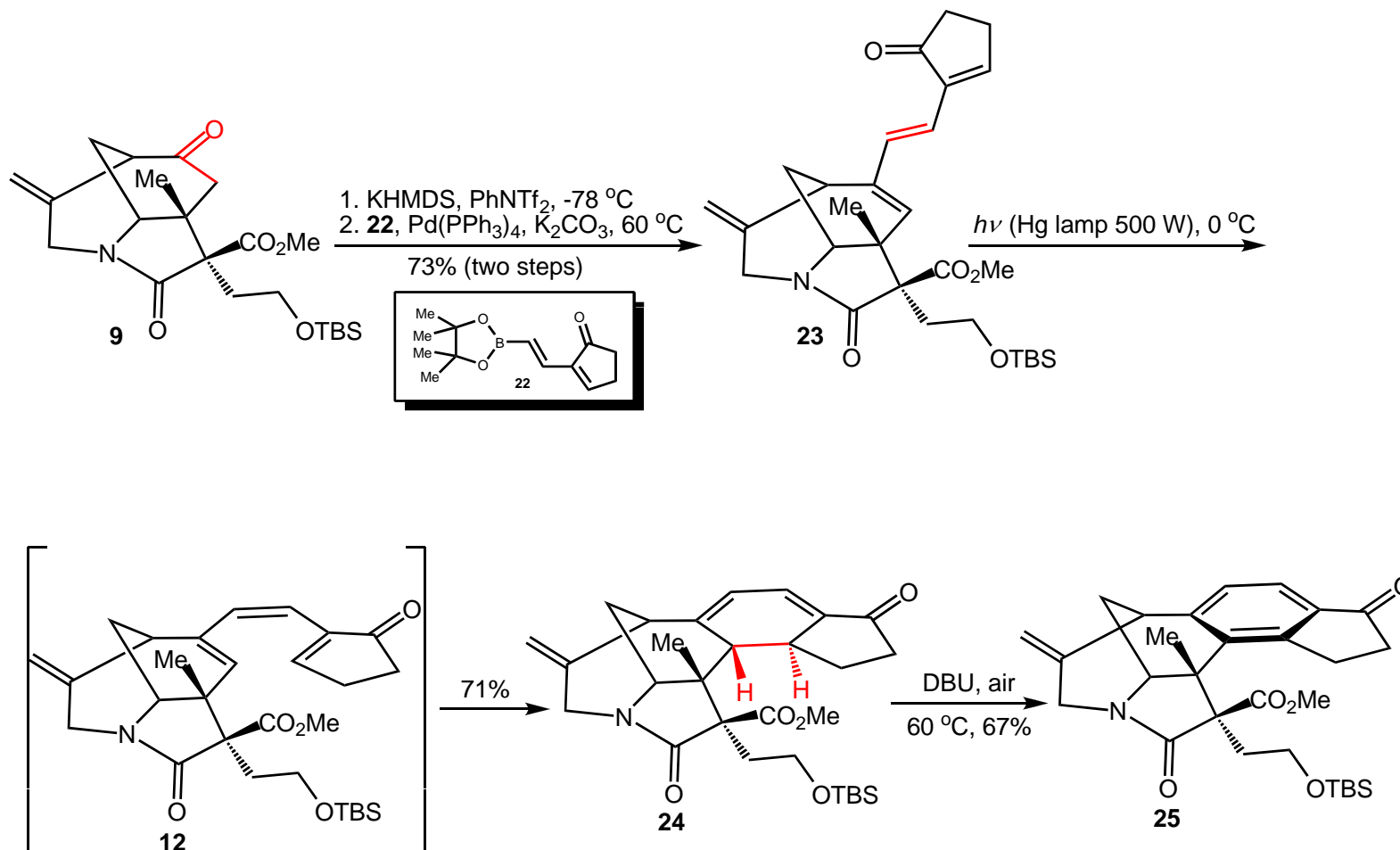
# Retrosynthetic analysis of daphenylline

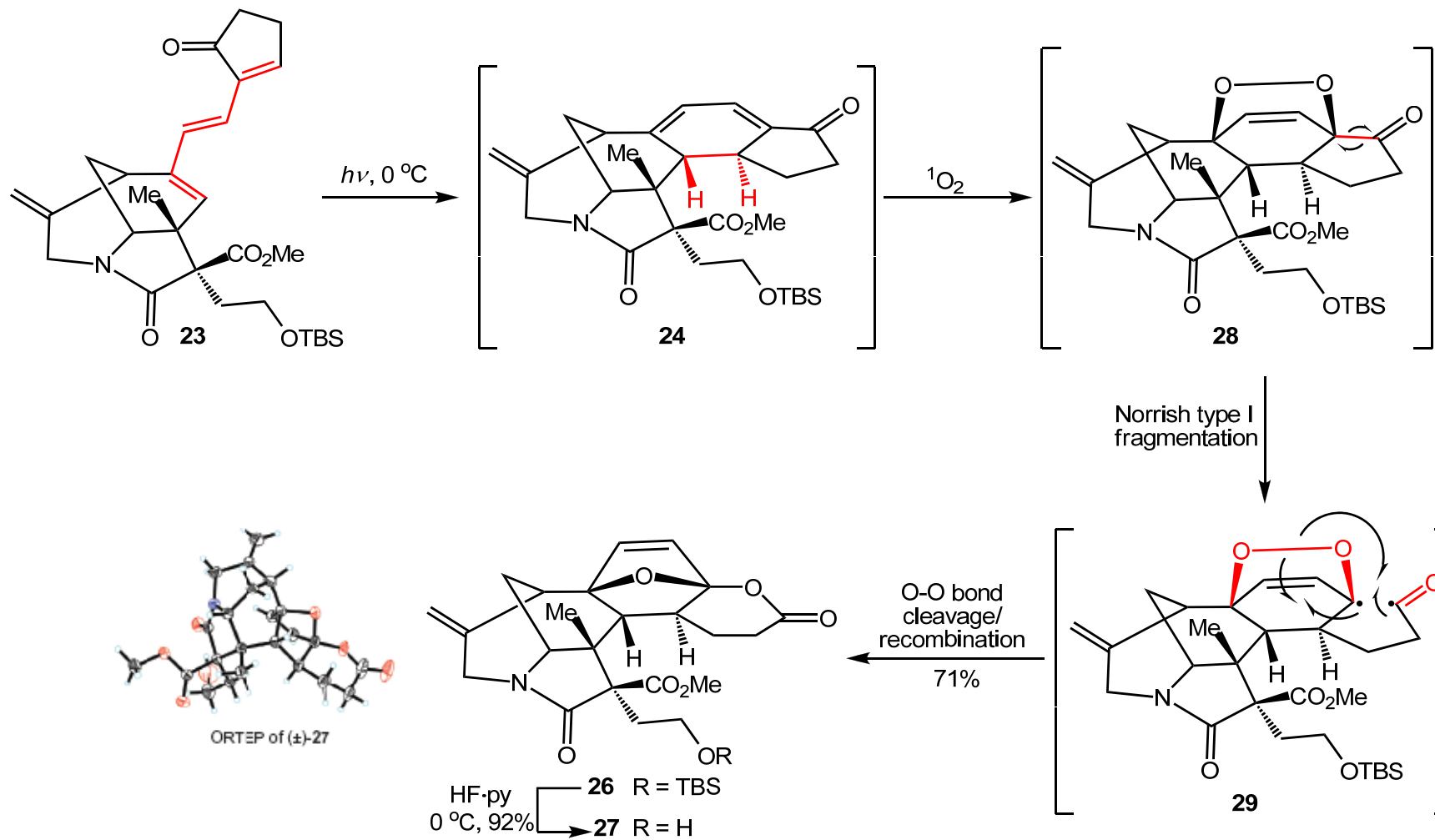


# Construction of the bridged tricycle 9



# Assembly of the pentacyclic intermediate 25

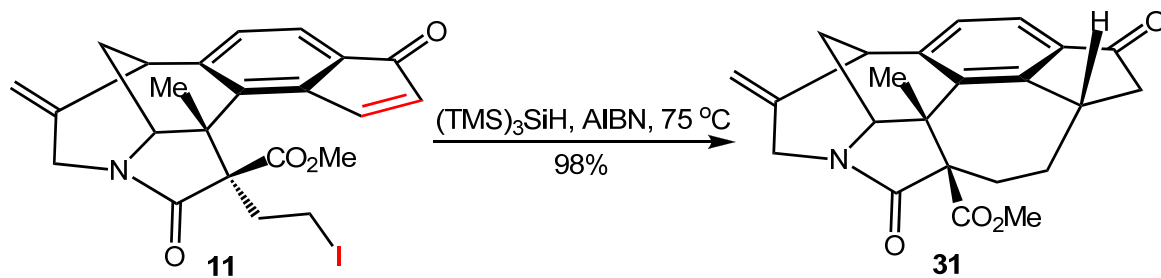
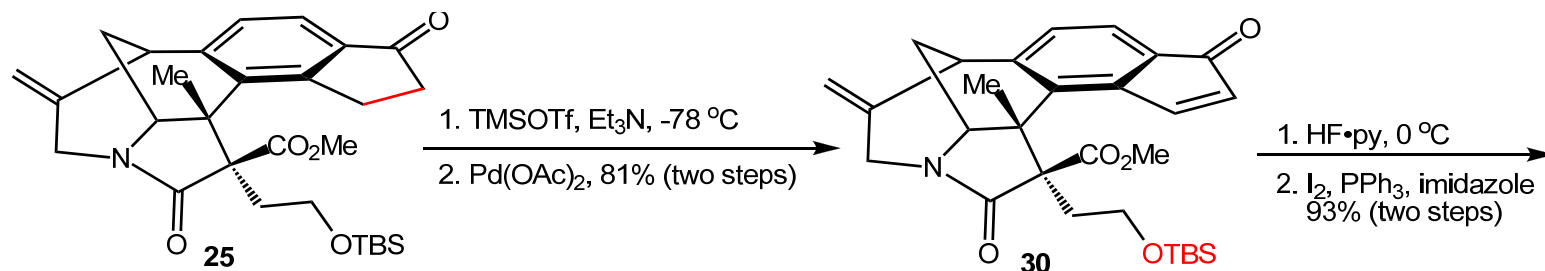


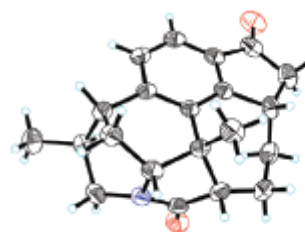
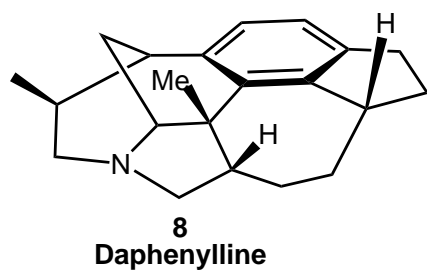
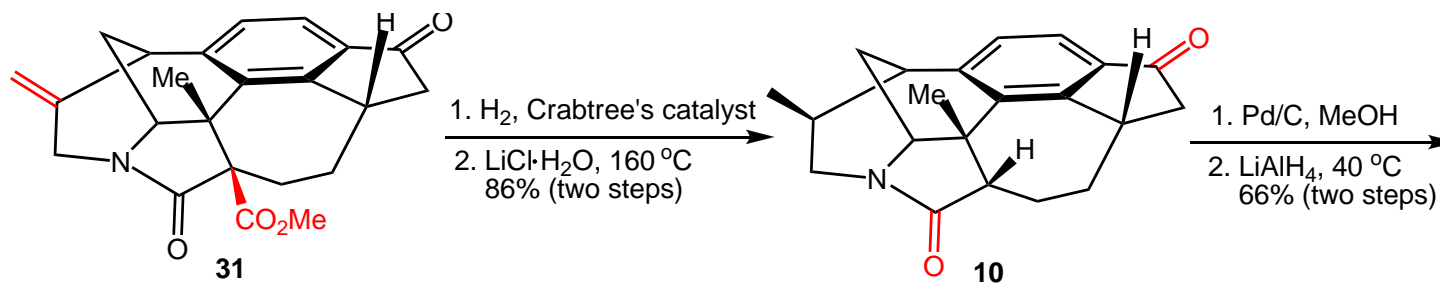




# Completion of the total synthesis of daphenylline

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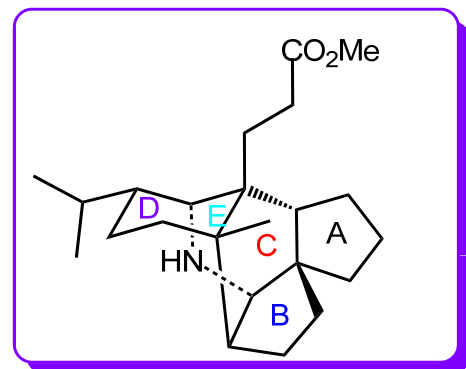
ORTEP of 10

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# Summary

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## Heathcock's work

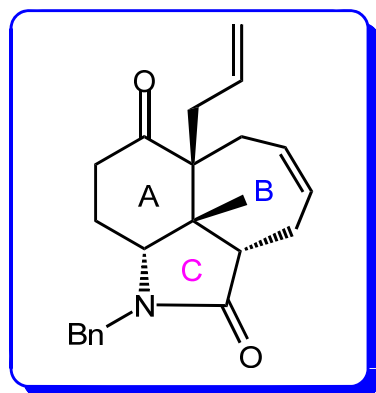


(±)-Methyl Homosecodaphniphyllate

- ▀ First biosynthesis
- ▀ Nine laboratory operations
- ▀ Overall yield: 44%

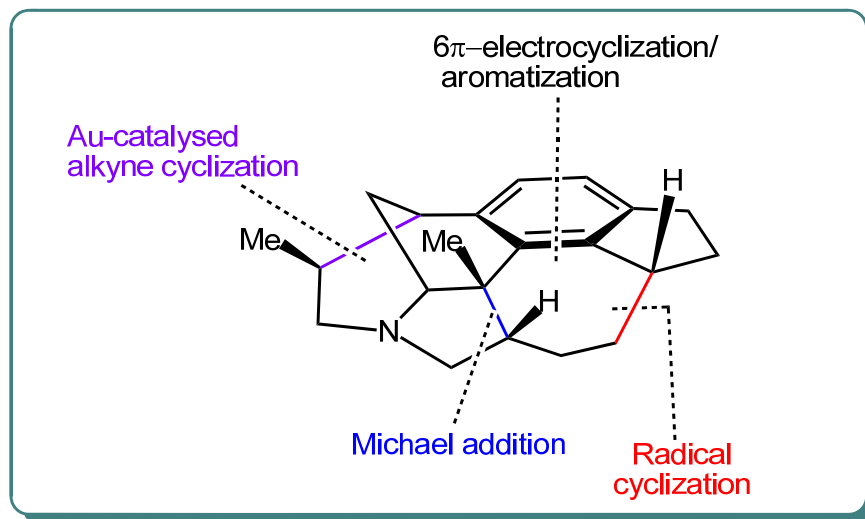
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## Dixon's work



- Intramolecular Michael addition
- Claisen rearrangement
- RCM strategy

## Li's work



8 Daphenylline

- △ The longest linear steps: 19
- △ Overall yield: 5.4%

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Plant natural products have played an important role in chemistry, biology and medical science for centuries, and chemical synthesis continues to serve as a powerful tool to understand the functions of these compounds. *Daphniphyllum* is a genus of dioecious evergreen plants native to Asia, the leaves and roots of which are used widely in Chinese herbal medicine. About 250 *Daphniphyllum* alkaloids have been isolated from this genus to date. From a structural perspective, these naturally occurring molecules usually possess a bridged and fused hexa- or pentacyclic scaffold that contains continuous stereogenic centres; based on their connectivity modes, they can be further classified into more than 20 subfamilies. Shown in Fig. 1 are the molecular architectures that represent several major subfamilies of *Daphniphyllum* alkaloids. Intrigued by these fascinating structures, a series of biosynthetic hypotheses were suggested, led by Heathcock's elegant proposal for the biosynthesis of methyl homosecodaphniphyllate (**1**; Fig. 1) from a squalene derivative.

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Although some isotopic labelling experiments were carried out, identifying the biosynthetic network that connects all the subfamilies of *Daphniphyllum* alkaloids at the biochemical level remains a formidable challenge. These structurally diverse and complex natural products display a remarkable range of biological activities, such as anticancer, antioxidation, elevation of nerve growth factor and vasorelaxation. However, the systematic biological profiling of the *Daphniphyllum* alkaloids and their derivatives is hampered by the scarce supply of these compounds from natural sources.

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We accomplished the total synthesis of the *Daphniphyllum* alkaloid daphenylline. The synthesis features a gold-catalysed 6-exo-dig cyclization reaction for the construction of a bridged bicyclic motif, and a photoinduced olefin isomerization/ $6\pi$ -electrocyclization/aromatization sequence to forge the sterically compact arene. The chemistry developed may find use in the synthesis of other polycyclic natural products and pharmaceutically interesting molecules. The above endeavour represents the first example of a chemical synthesis of a member of the *Daphniphyllum* alkaloid subfamilies that share a bridged 6,n,5-tricyclic motif. Taking advantage of the versatility of the tricyclic intermediate **9**, studies towards the total synthesis of related *Daphniphyllum* alkaloids are currently underway, which, together with this work, should accelerate further biological and biosynthetic investigations of these fascinating natural products .

