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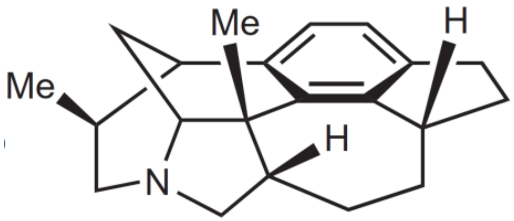
Total synthesis of the *Daphniphyllum* alkaloid daphenylline

Zhaoyong Lu†, Yong Li†, Jun Deng and Ang Li*



Daphenylline

Gilmar A. Brito Jr.

8/26/2013 – Wipf group

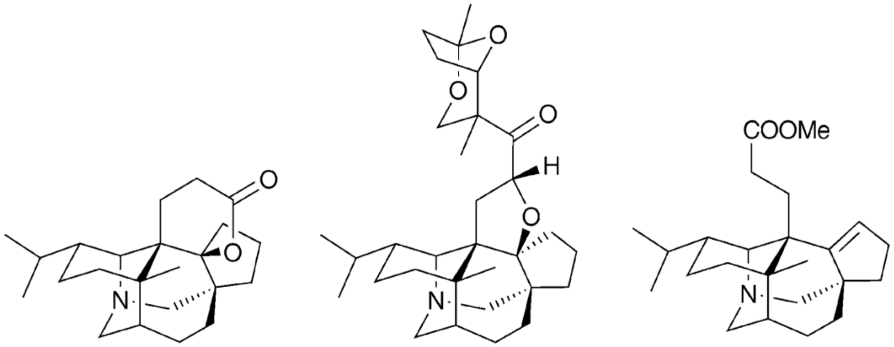
Daphniphyllum alkaloids: Introduction

- Structurally diverse group of natural products found in the genus *Daphniphyllum*

- About 250 *Daphniphyllum* alkaloids have been isolated

- Possess a bridged and fused hexa- or pentacyclic scaffold and classified into more than 20 subfamilies

- Diverse biological activities include anticancer, antioxidation, vasorelaxation and others.

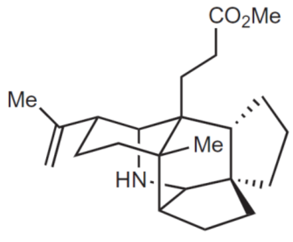


Daphnilactone A-type alkaloids.

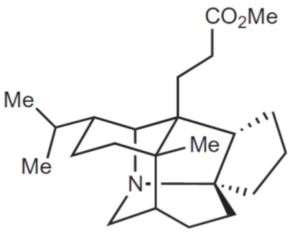
Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936

Daphniphyllum alkaloids: Introduction

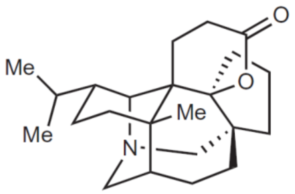
- Heathcock and co-workers accomplished the first total synthesis of an alkaloid in this family (**1**), guided by their biosynthetic hypothesis.
- Heathcock also synthetized the Daphniphyllum alkaloids **2**, **3** and **4**.



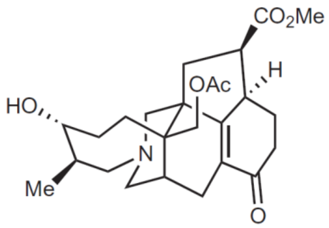
1 Methyl homoseco-daphniphyllate



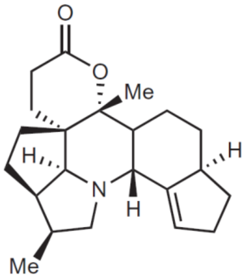
2 Methyl homo-daphniphyllate



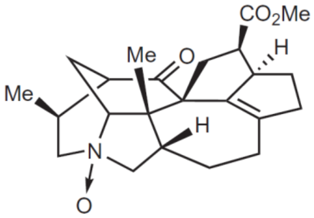
3 Daphnilactone A



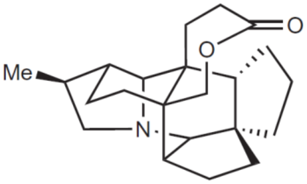
Daphmanidin C



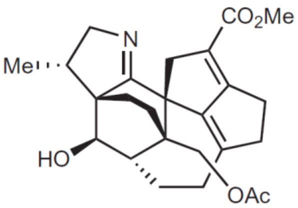
Calyciphylline B



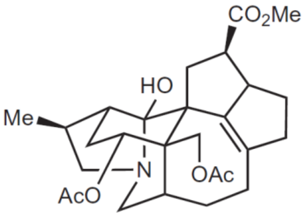
6 Calyciphylline A



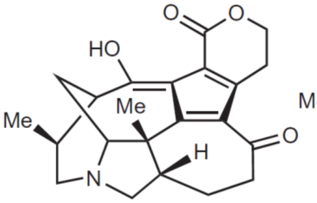
4 Bukittinggine



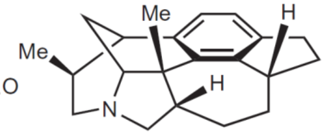
5 Daphmanidin E



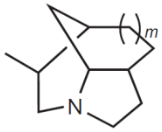
Yuzurimine



7 Daphnicyclidin A



8 Daphenylline



m = 1 or 2

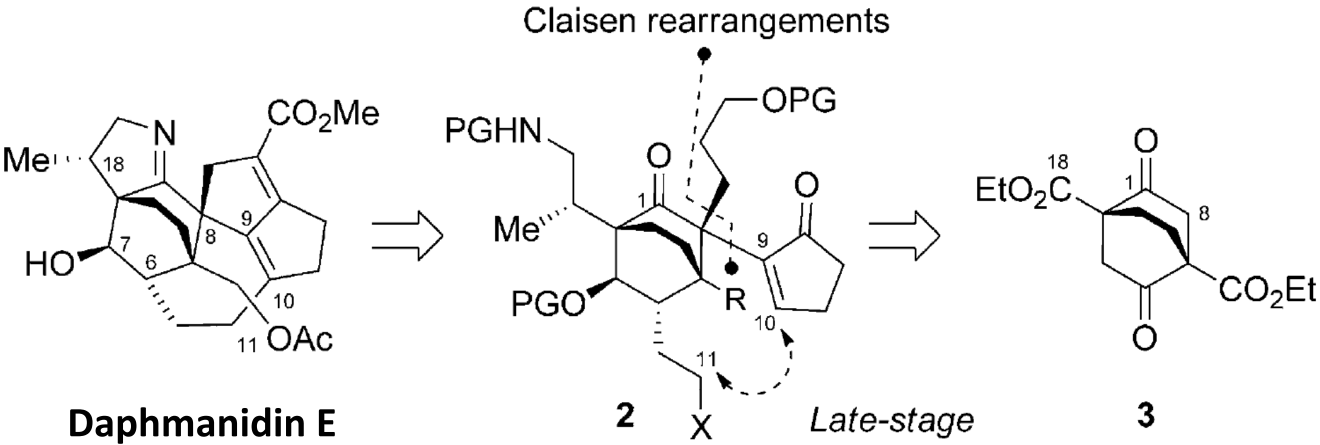
6,*n*,5-bridged tricycle

Ruggeri, R. B.; Hansen, M. M; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *110*, 8734-8736; Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714.; Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585.; Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575; Stafford, J. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5433; Heathcock, C. H. ; Kath, J.C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120.

Daphniphyllum alkaloids: Introduction

- After almost 20 years since Heathcock's contributions in *Daphniphyllum* alkaloids total synthesis, Carreira and co-workers disclosed the total synthesis of daphmanidin E.

- Their strategy was based on two Claisen rearrangements (to consctruct the remaining quaternary center) and an intramolecular 7-membered alkyl Heck coupling.



Claisen rearrangements

Daphmanidin E

2

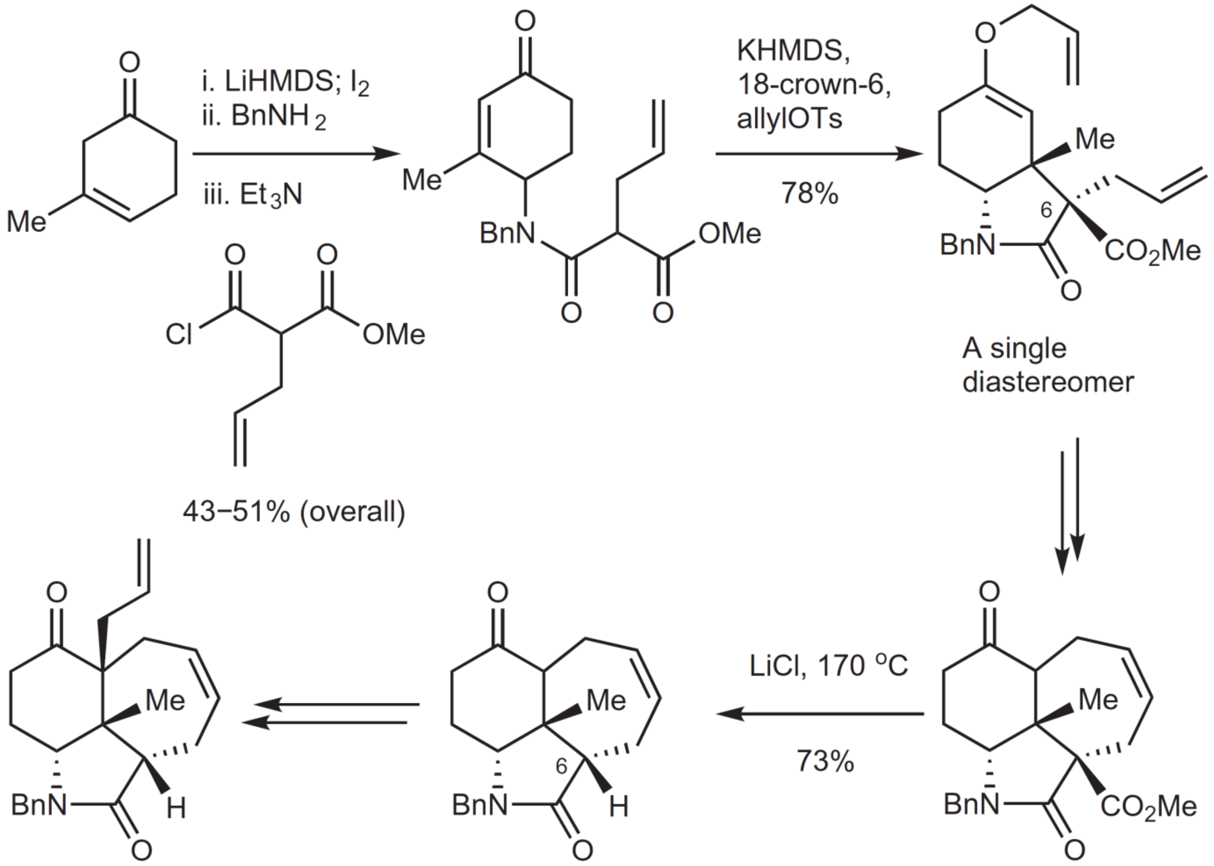
Late-stage Alkyl Heck Coupling

3

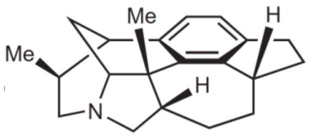
Weiss, M. E.; Carreira, E. M. *Angew. Chemie. Int. Ed.* **2011**, *50,* 11501

Daphenylline total synthesis: previous studies

- Dixon and co-workers developed an elegant synthesis of the tricyclic core of calyciphylline A-type *Daphniphyllum* alkaloids, based on a highly diastereoselective intramolecular Michael reaction

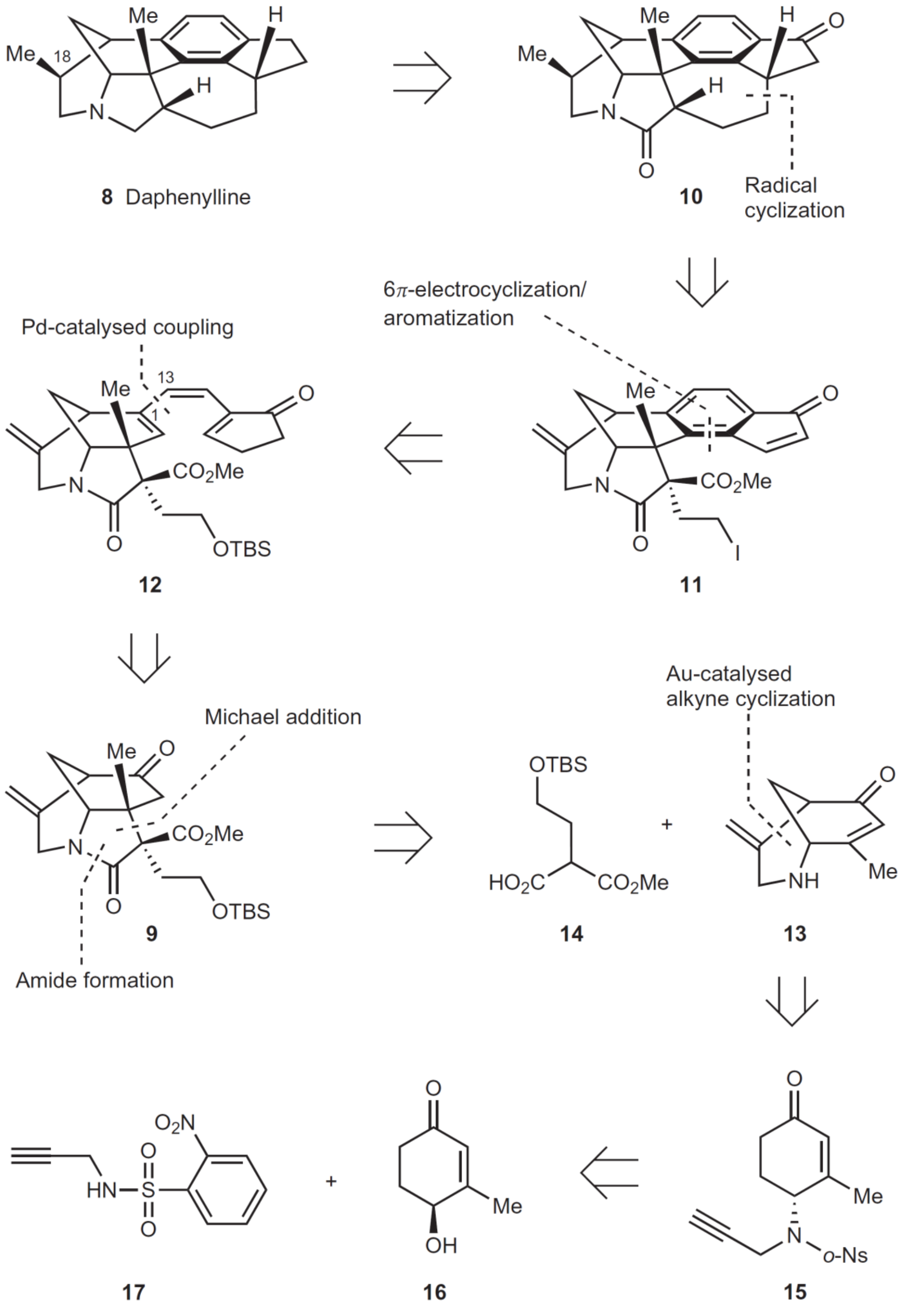


Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. *Org. Lett.* **2011**, *13,* 5132

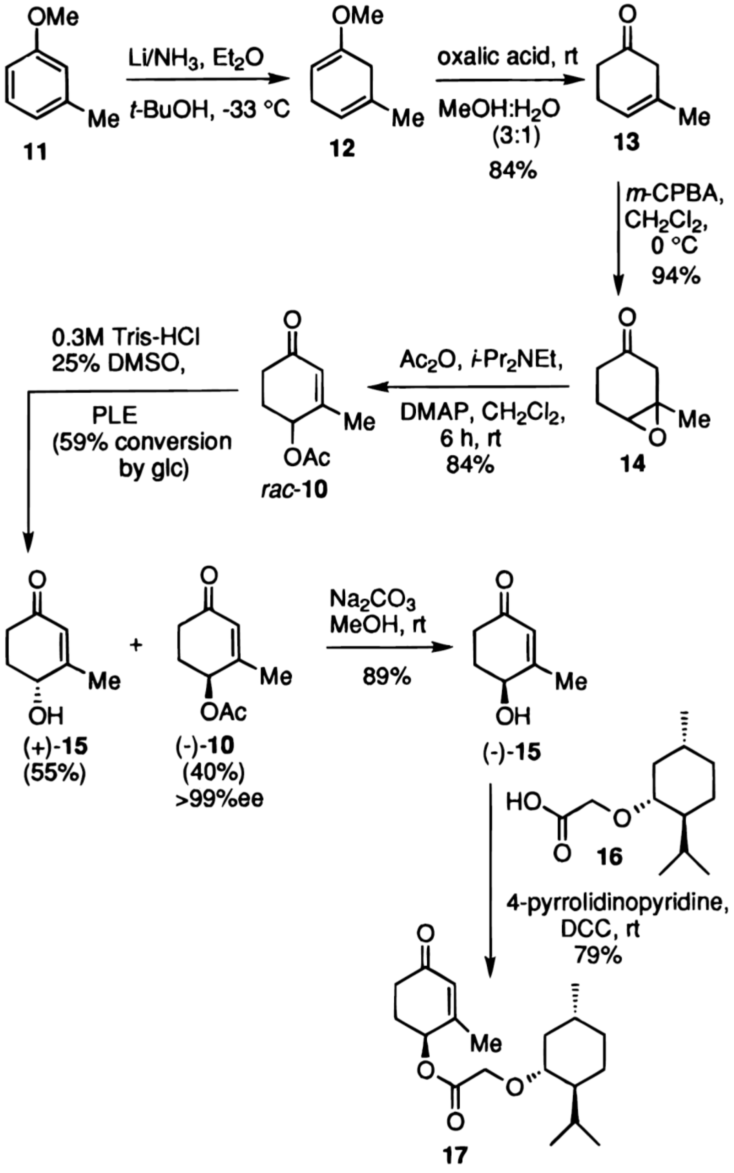


8 Daphenylline

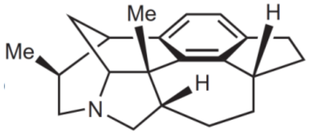
Daphenylline total synthesis: Retrosynthesis



Daphenylline total synthesis: starting material

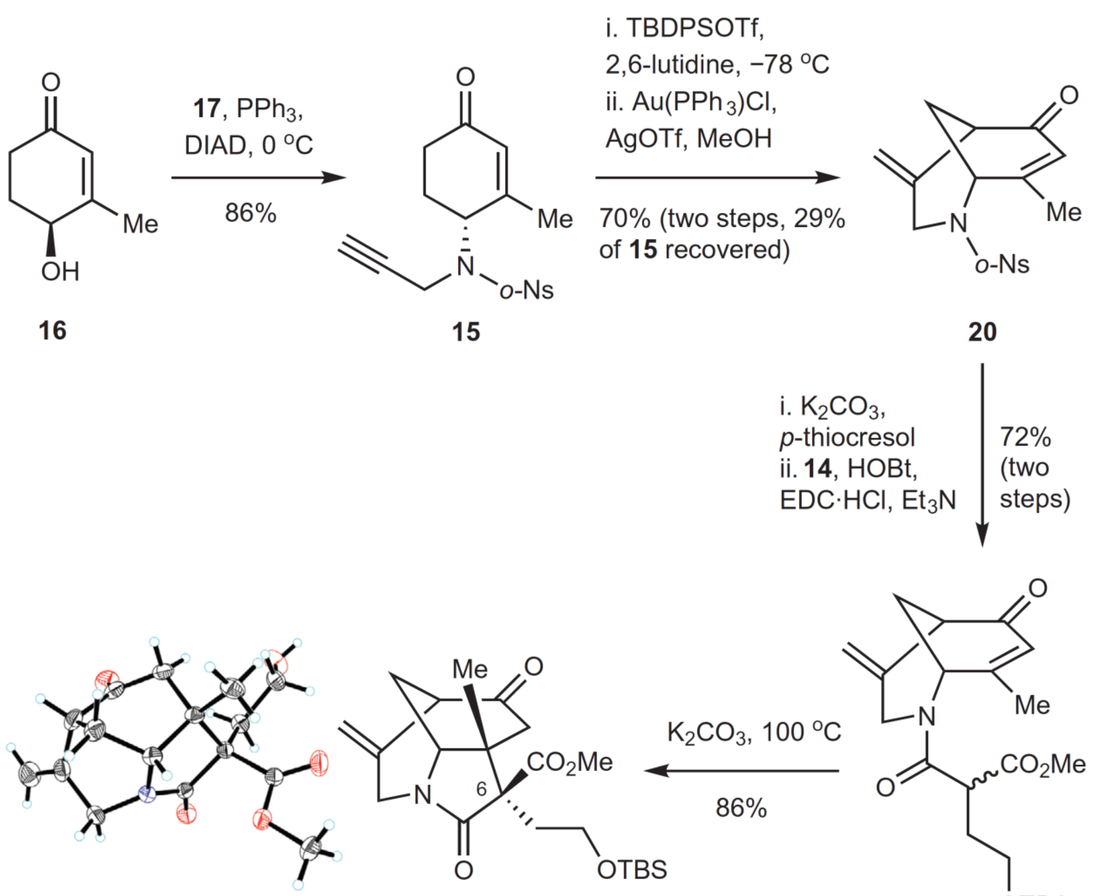


Piers, E.; Oballa, R. M. *J. Org. Chem.* **1996**, *61,* 8439



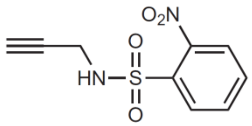
8 Daphenylline

Toste-Conia-ene reaction and intramolecular Michael addition



ORTEP of **9a** (desilylated **9**)

- Au induced 5-exo-dig cyclization to conscruct the bridged [3.3.1] bicyclic system.



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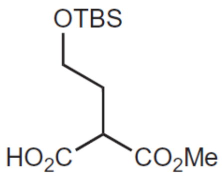

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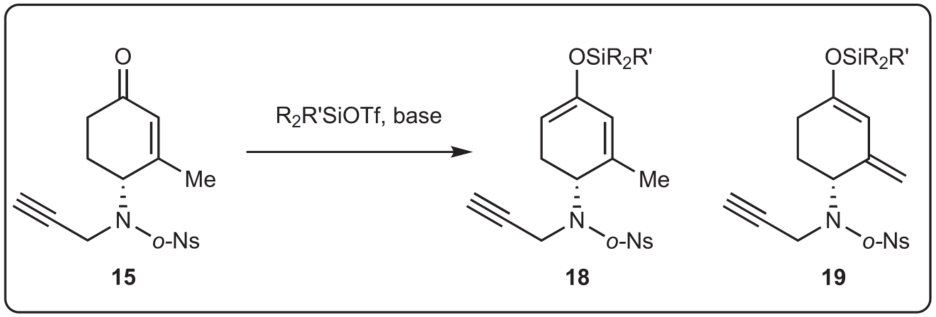

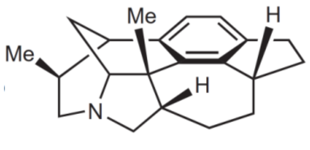

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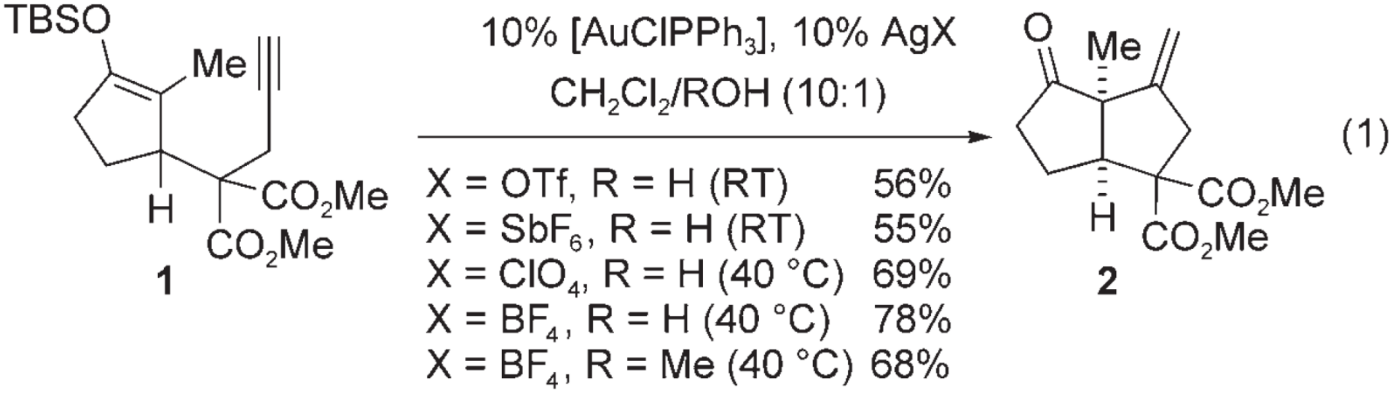
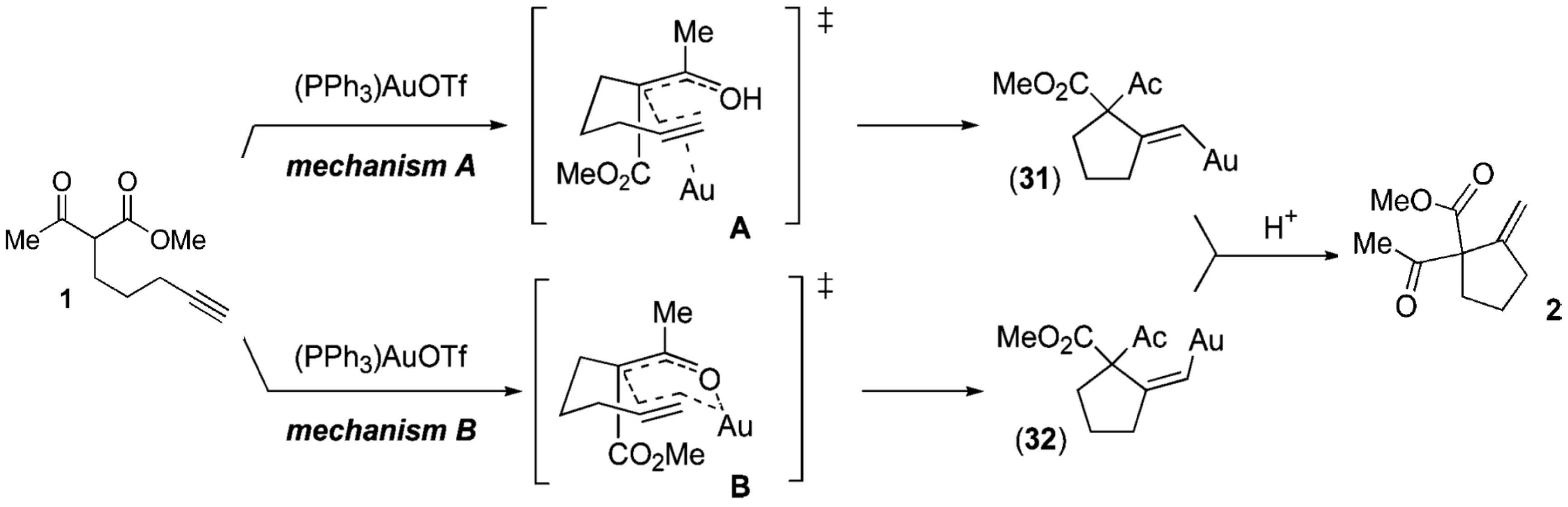
8 Daphenylline

Toste-Conia-ene reaction: Mechanism

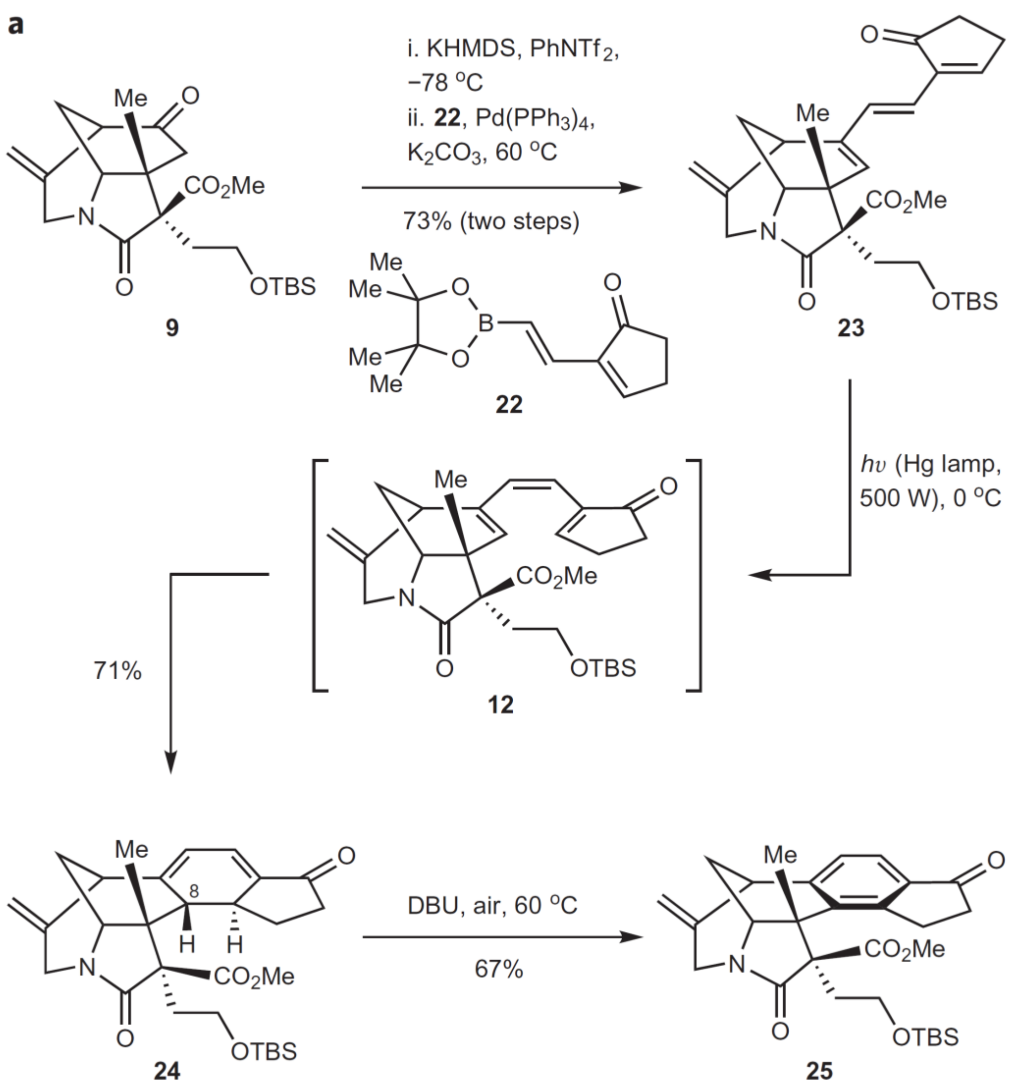


Staben. S. T.; Kenndy-Smith, J.J.; Huang, D.; Corkey, B. K.; Lalonde, R. L.; Toste, F. D. *Angew. Chemie. Int. Ed.* **2006**, *45,* 5991



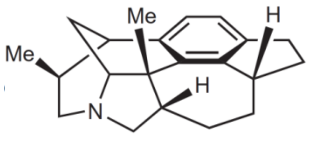
S.-K., S. J.; Staben. S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126,* 4526

6π-eletrocyclization/aromatization



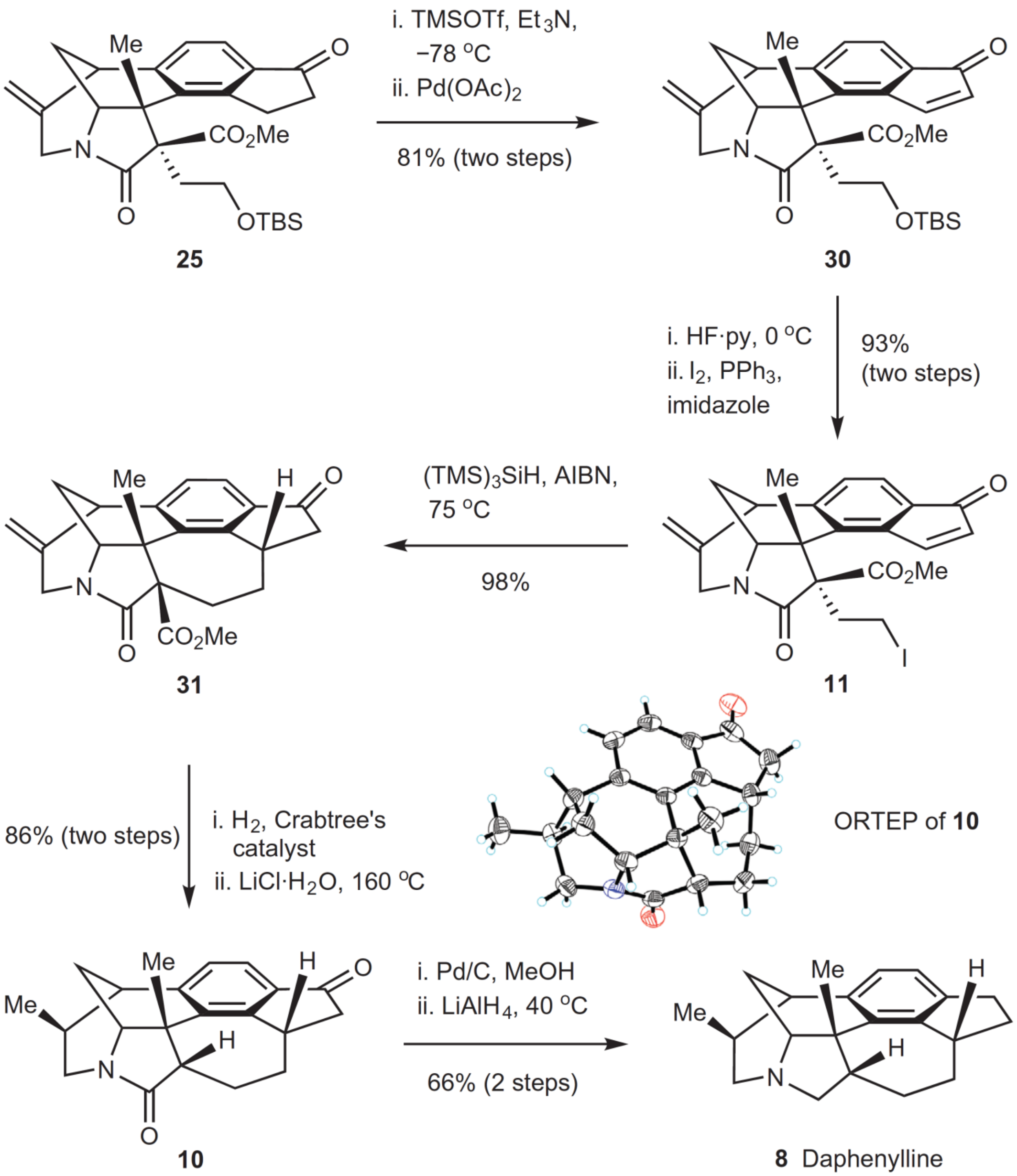
- Attempts to prepare cis-boronate/stannane reagents were not successful.

- Photoisomerization followed by photo induced eletrocyclization led to pentacyclic compound **24**.

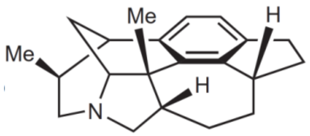


8 Daphenylline

Radical cyclization – 7 membered ring formation



- 7-exo-trig radical cyclization to consctruct the last ring and reduction gave the desired natural product.



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8 Daphenylline

Conclusions

- Daphenylline was prepared over 25 steps (19 by reported chiral alcohol **16**) with 1.28% of global yield (5.4% by alcohol **16**).

- The main strategy used to prepare this complex alkaloid was an Au induced 5-exo-dig cyclization, photoisomerization followed by photo induced eletrocycization and a radical induced intramolecular Michael addition.