

Literature Report III

Total Synthesis of (+)-Daphmanidin E and (-)-Calyciphylline N

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Checker: Zhang-Pei Chen

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Carreira, E. M. *et al. Angew. Chem., Int. Ed.* **2011**, *50*, 11501.

Smith, A. B. *et al. J. Am. Chem. Soc.* **2015**, *137*, 3510.

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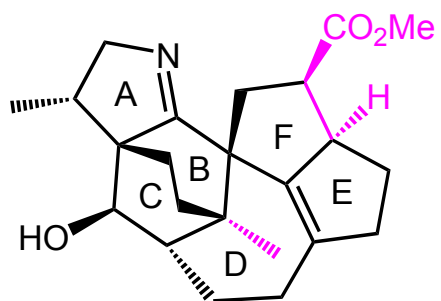
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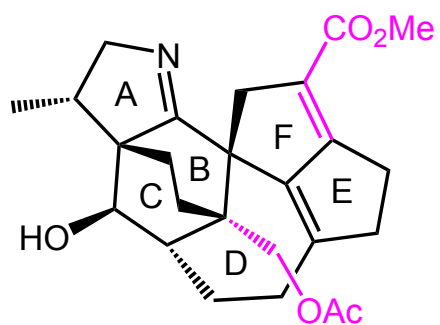
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Introduction



(-)-Calyciphylline N

Isolated from the leaves and stems of *Daphniphyllum calycinum* in 2008

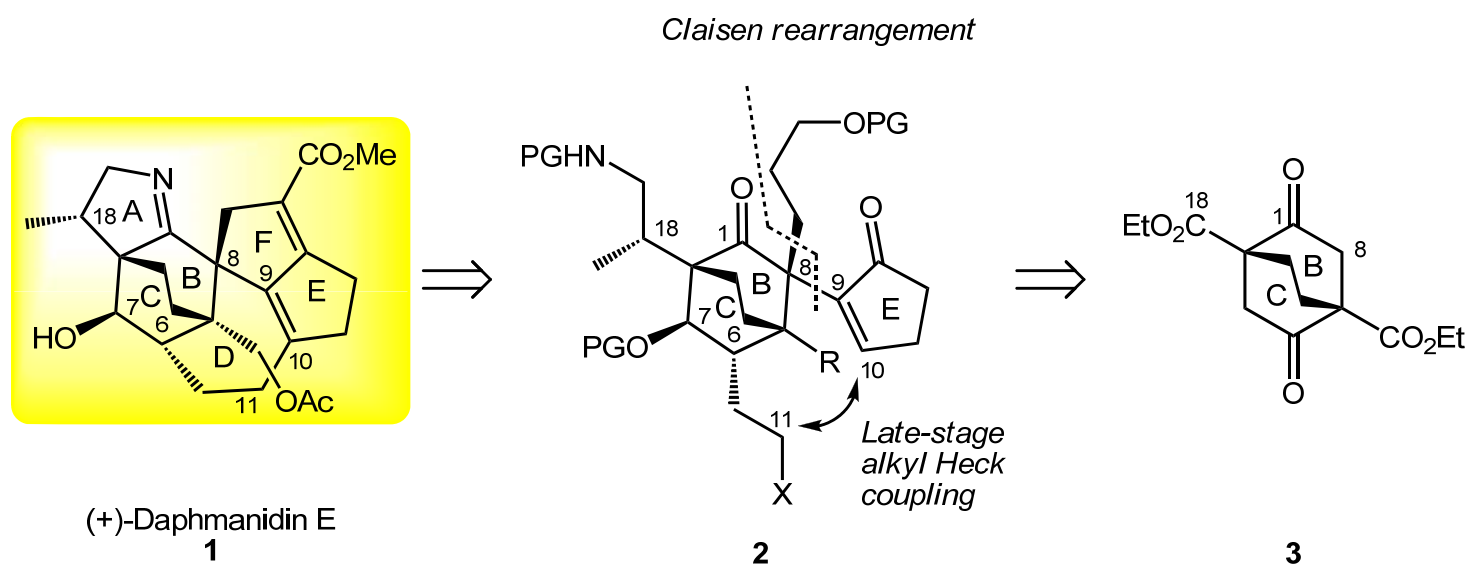


(+)-Daphmanidin E

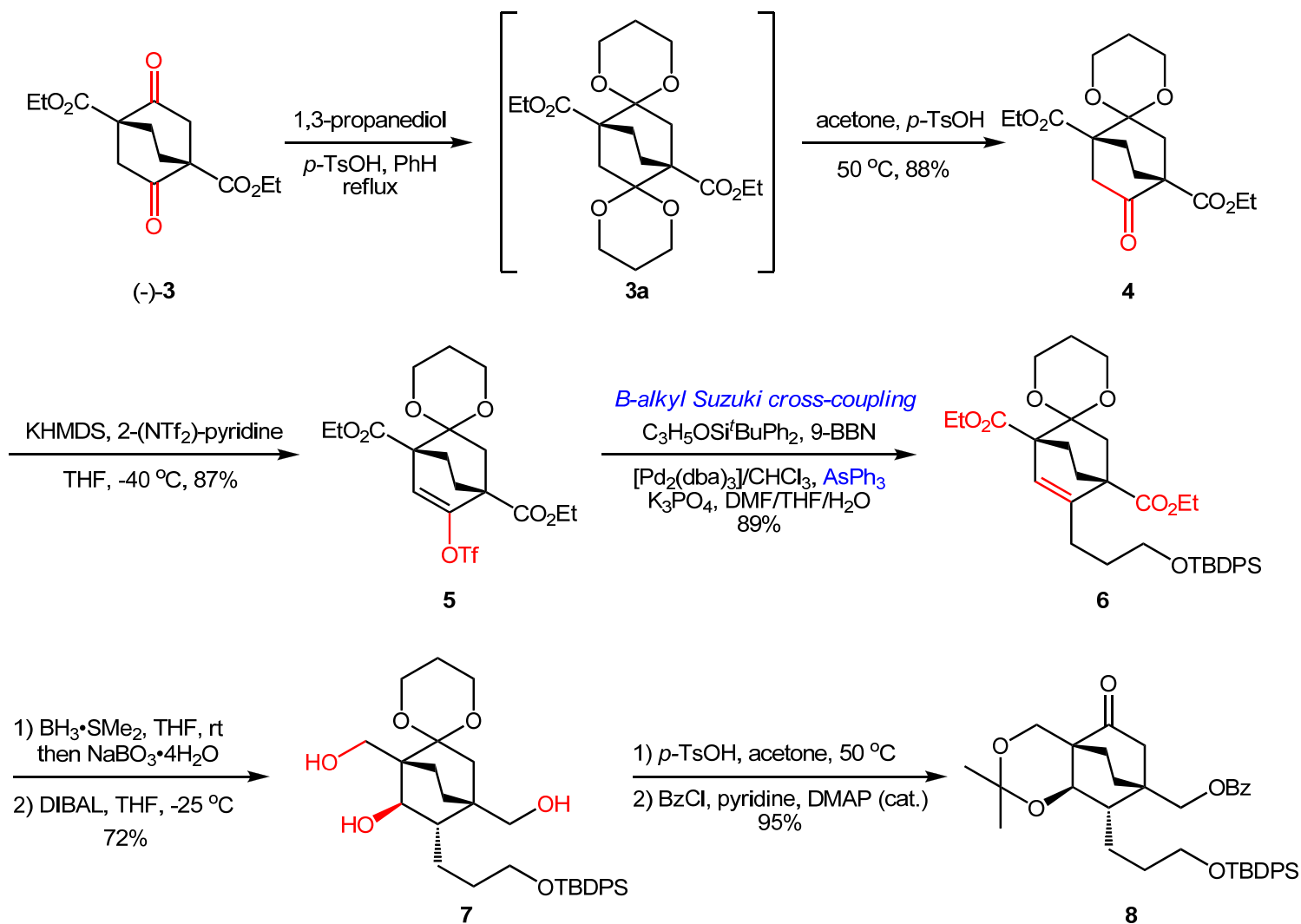
Isolated from leaves of *Daphniphyllum teijsmannii* in 2006
Exhibit moderate vasorelaxant activity on rat aorta



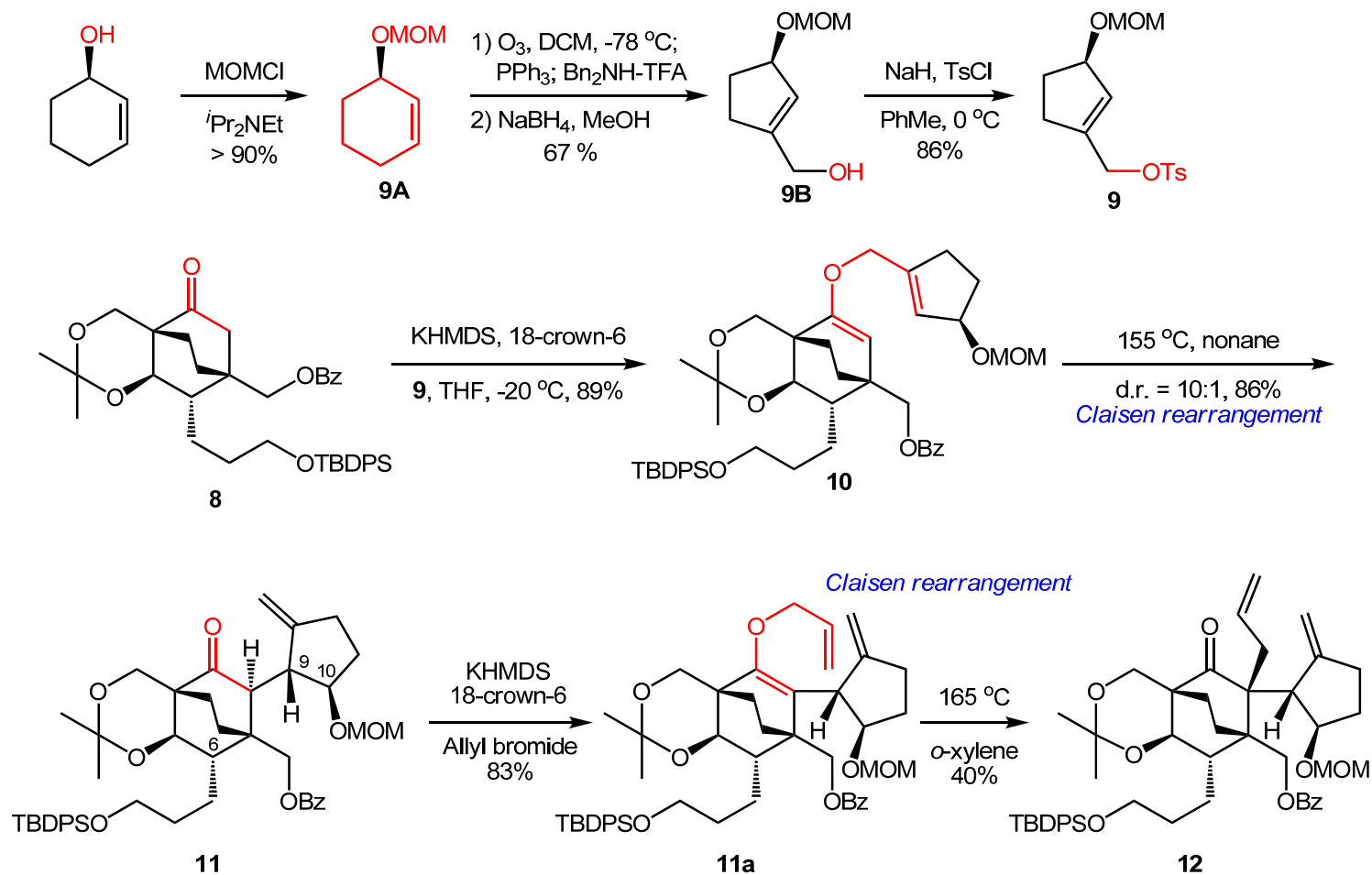
Retrosynthetic analysis of (+)-Daphmanidin E



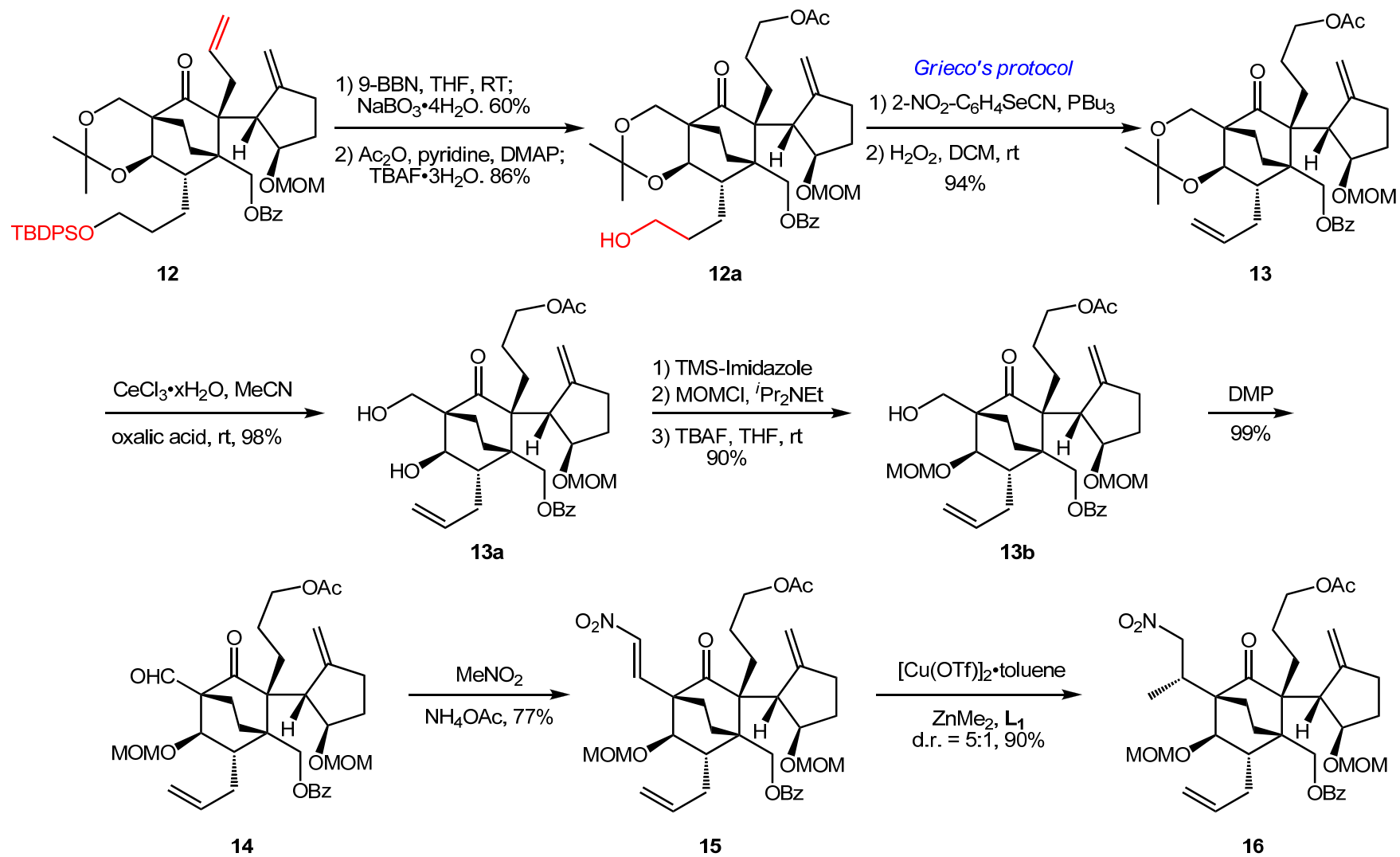
Total synthesis of (+)-Daphmanidin E



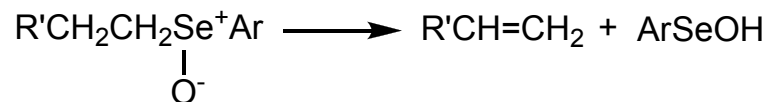
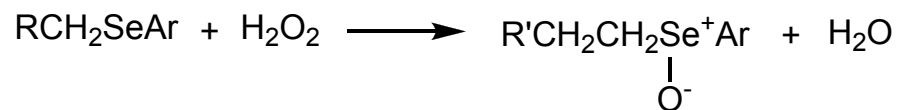
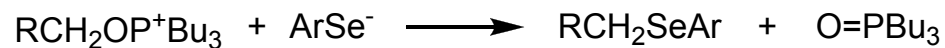
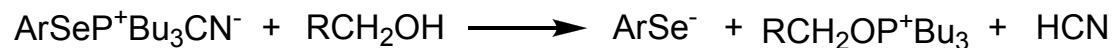
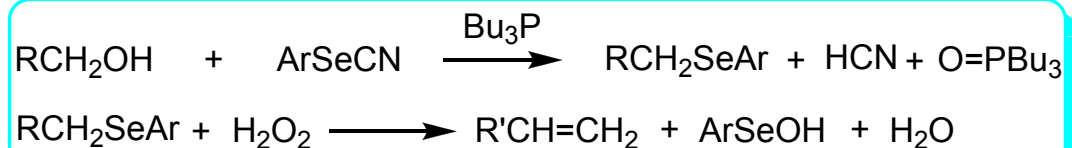
Total synthesis of (+)-Daphmanidin E



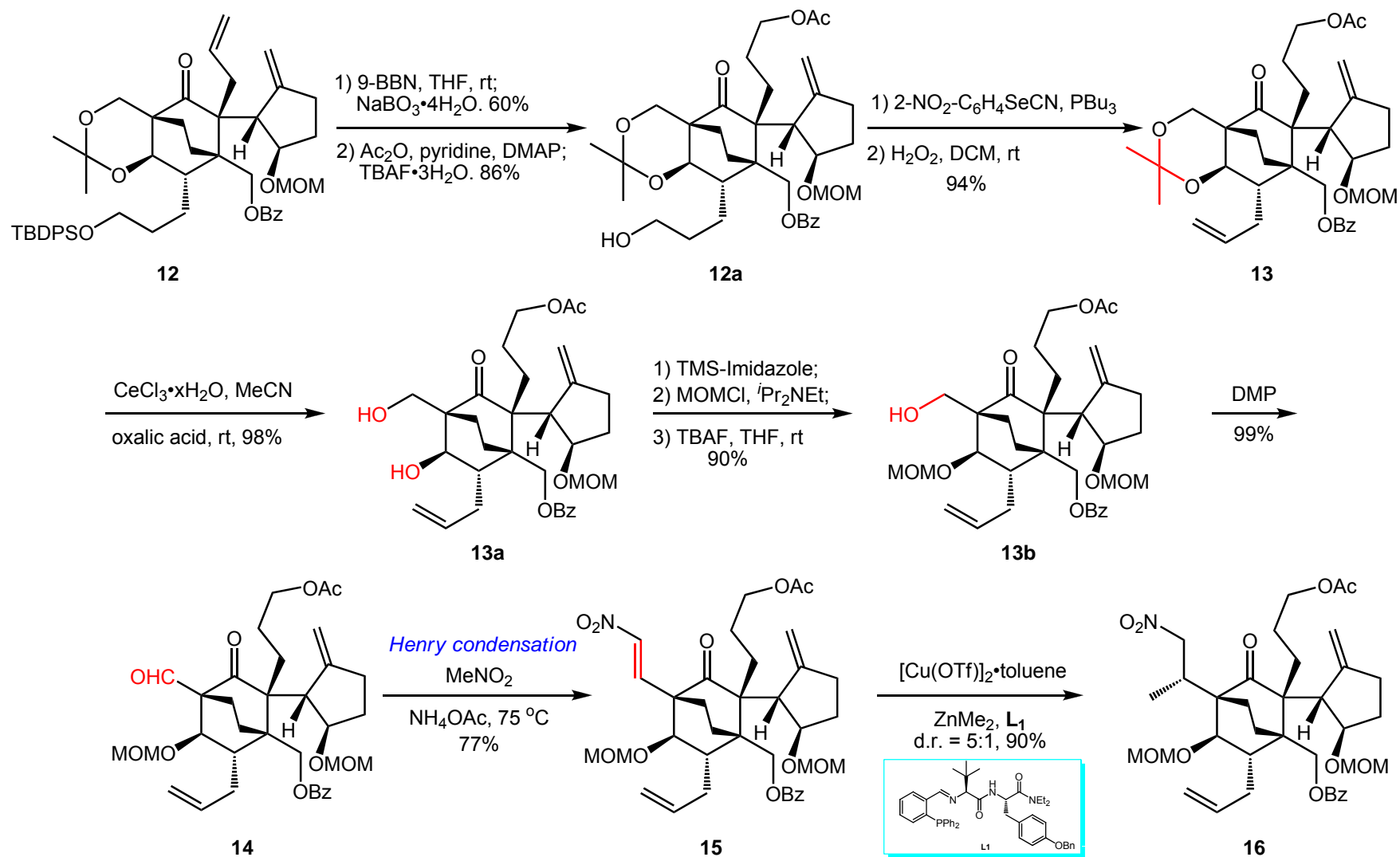
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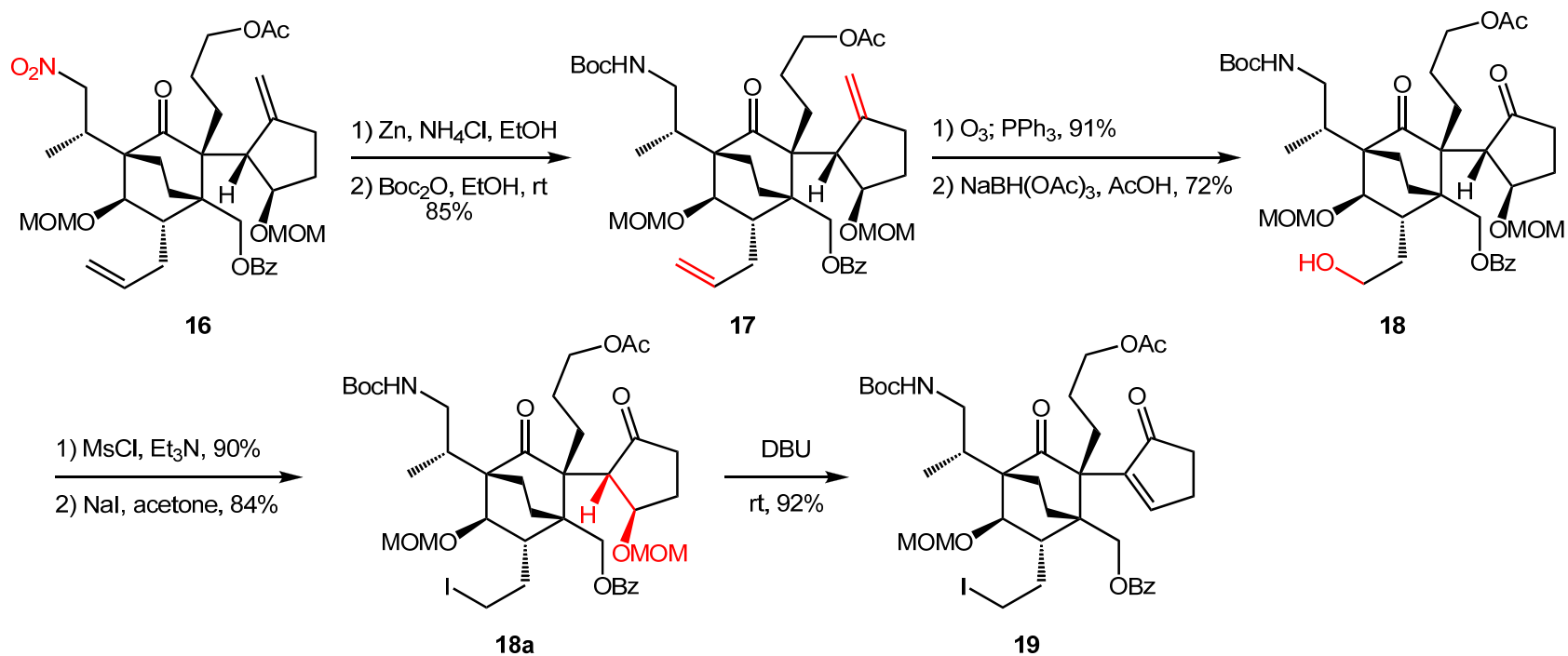
Grieco's protocol



Total synthesis of (+)-Daphmanidin E

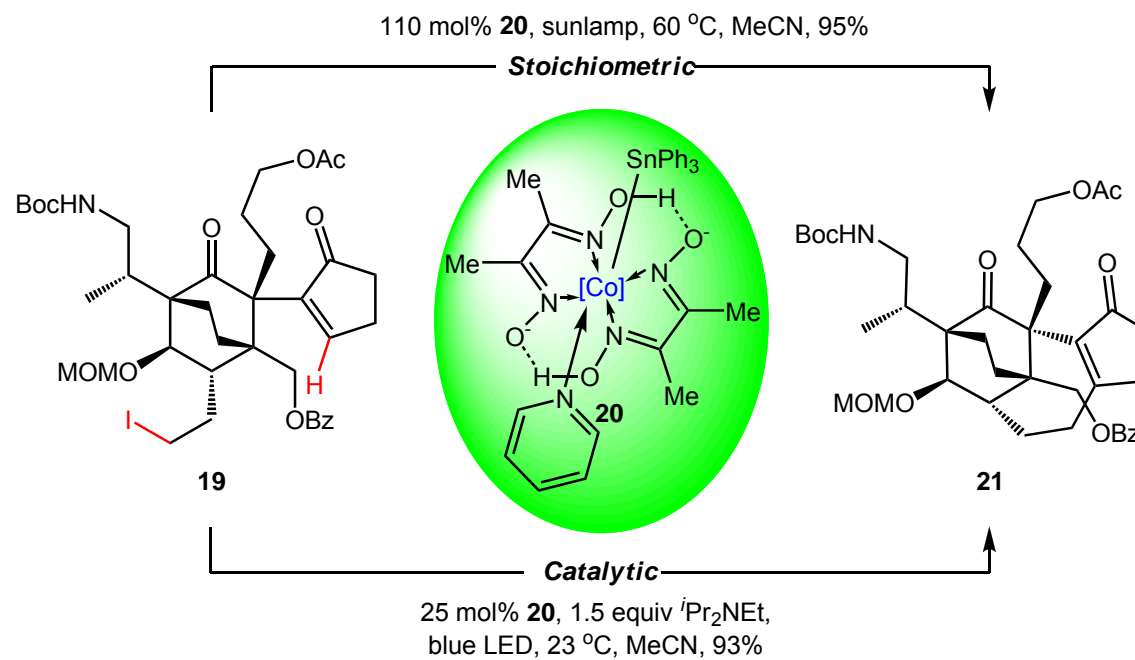


Total synthesis of (+)-Daphmanidin E

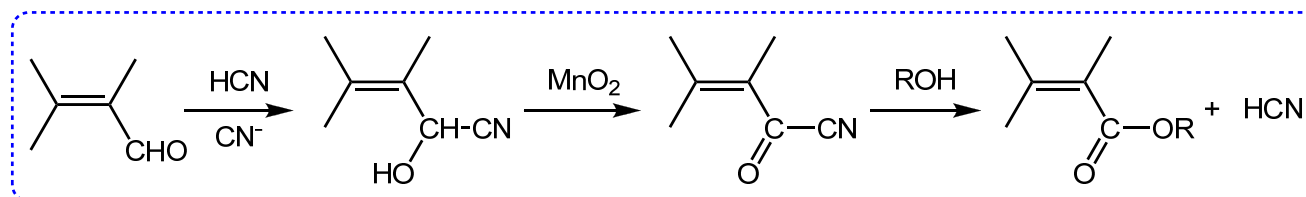
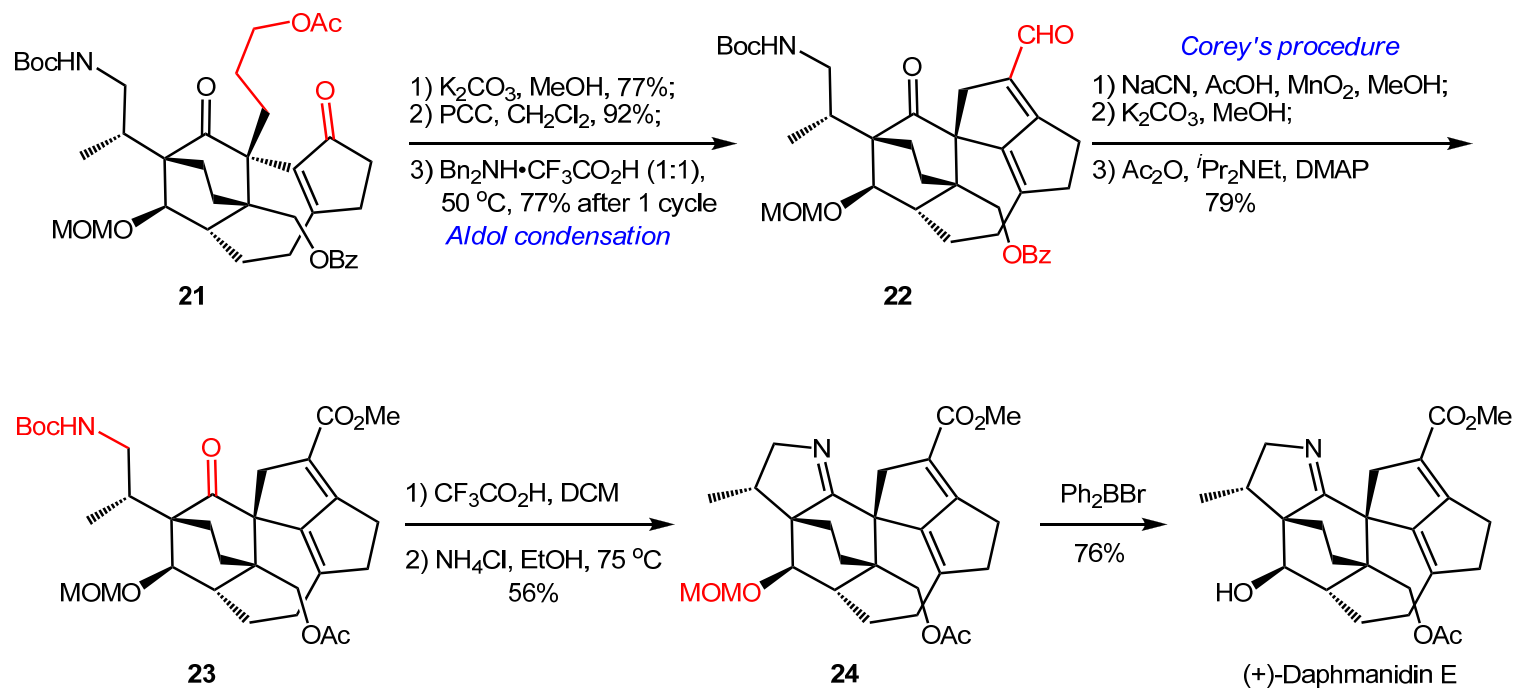


Total synthesis of (+)-Daphmanidin E

Alkyl-Heck coupling reaction

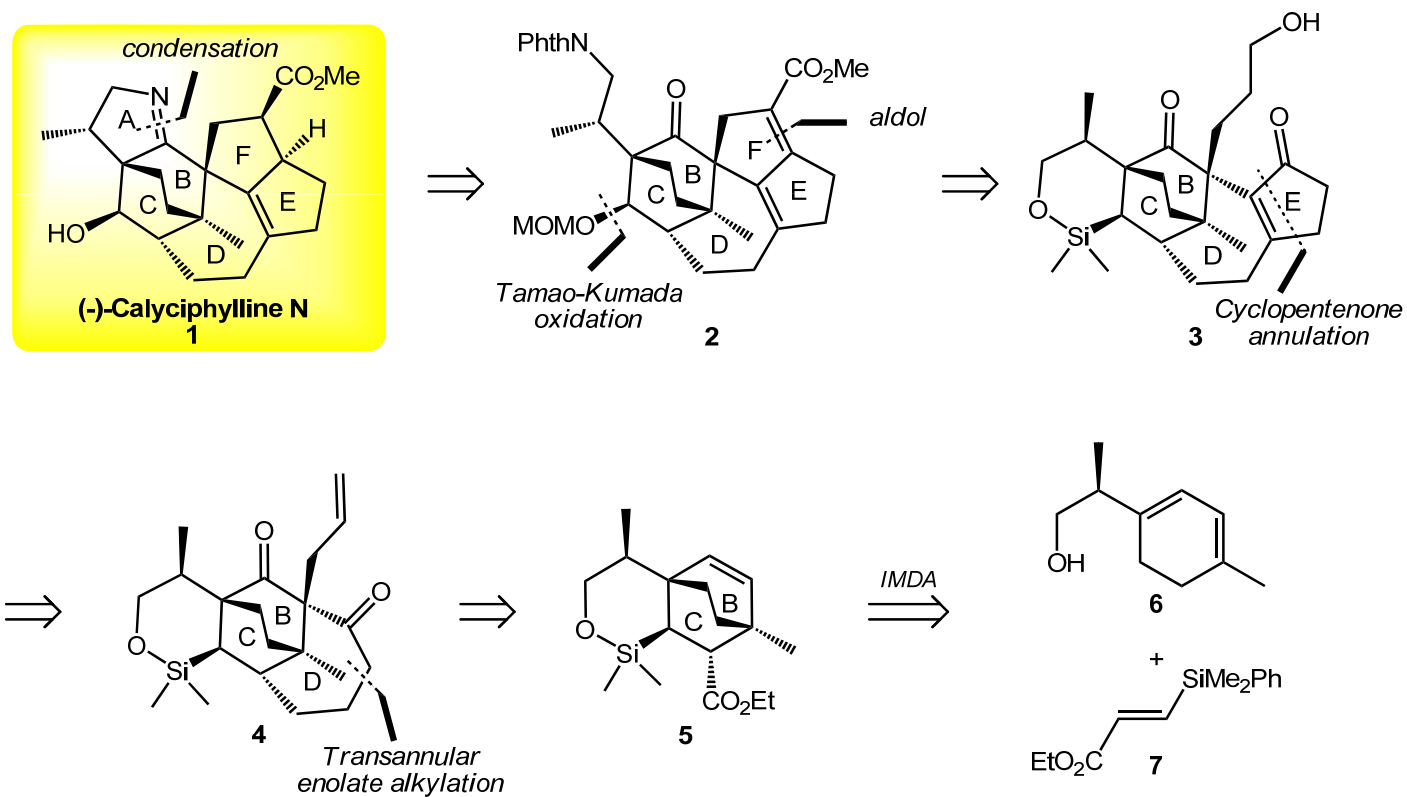


Total synthesis of (+)-Daphmanidin E

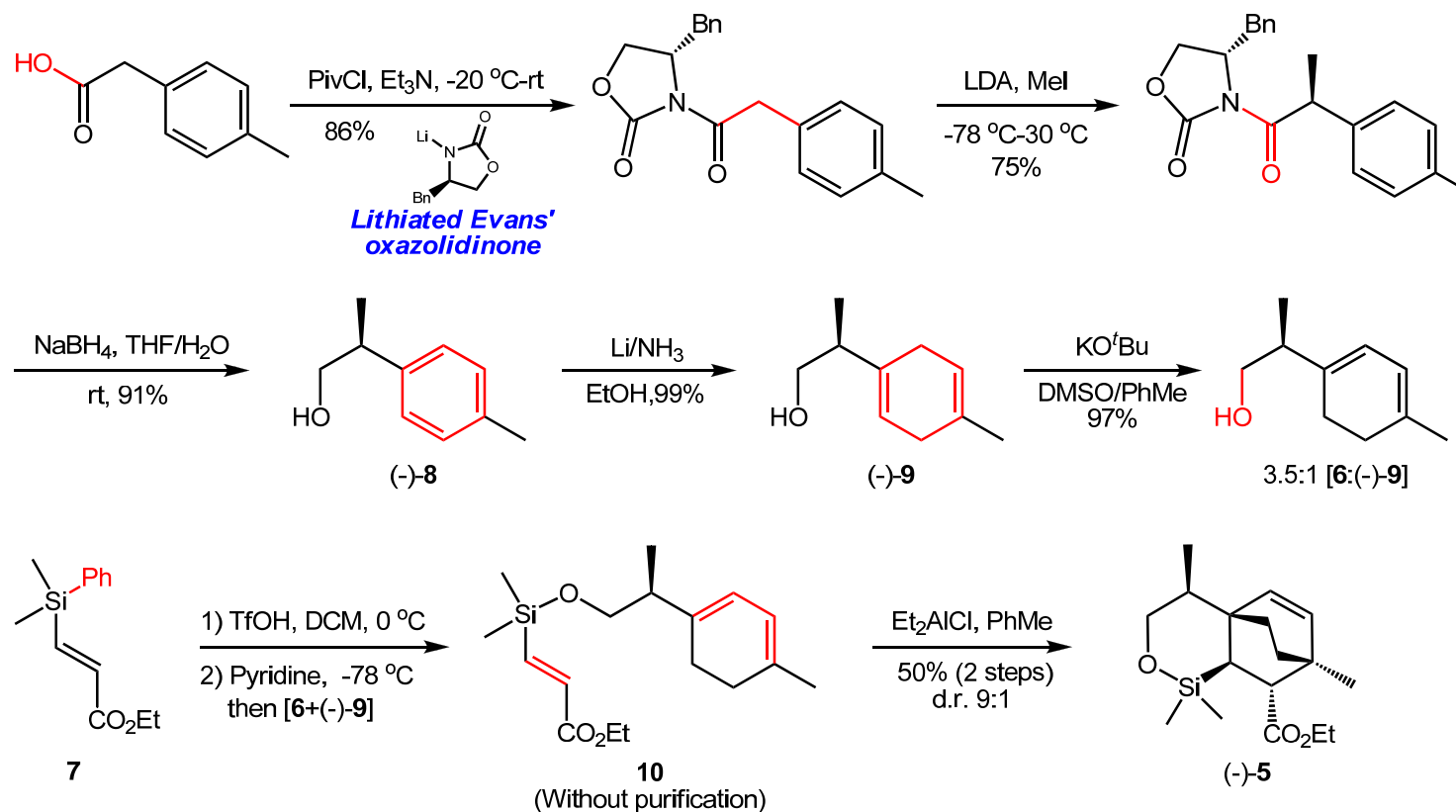


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 Corey, E. J. *et al. J. Am. Chem. Soc.* **1968**, *90*, 5616.

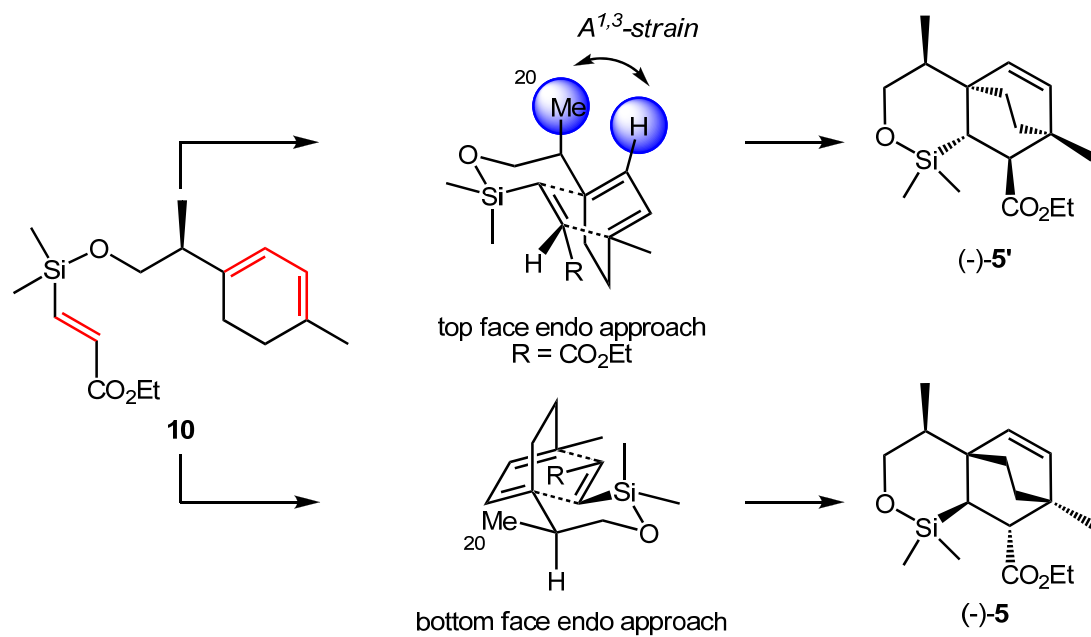
Retrosynthetic analysis of (-)-Calyciphylline N



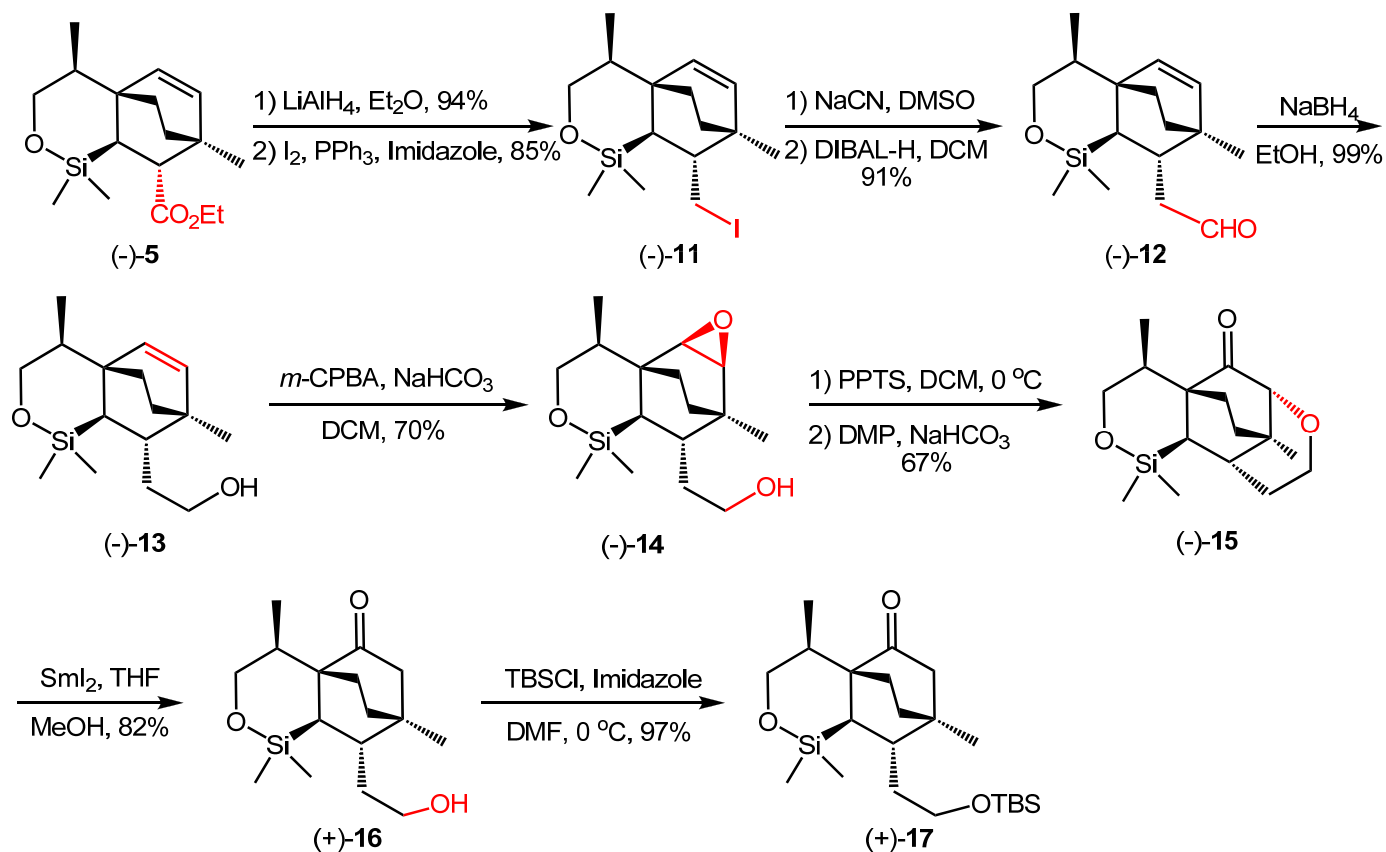
Total synthesis of (-)-Calyciphylline N



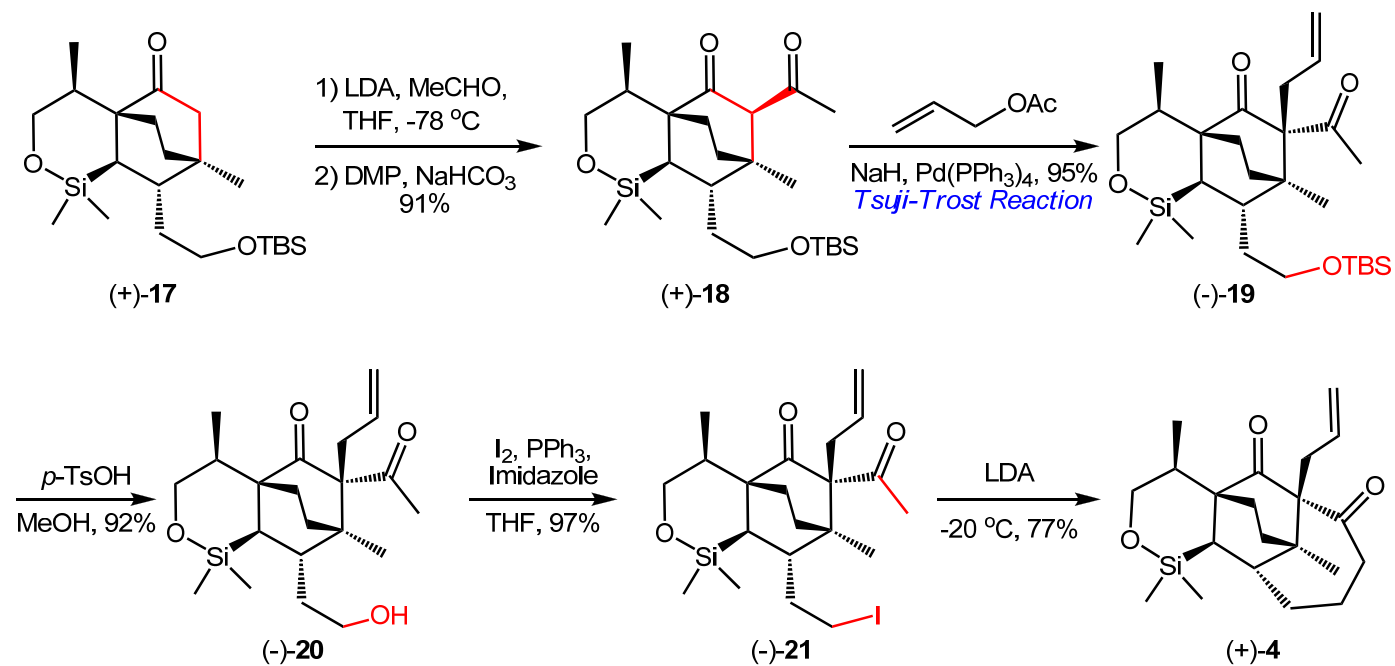
Intramolecular Diels-Alder reaction



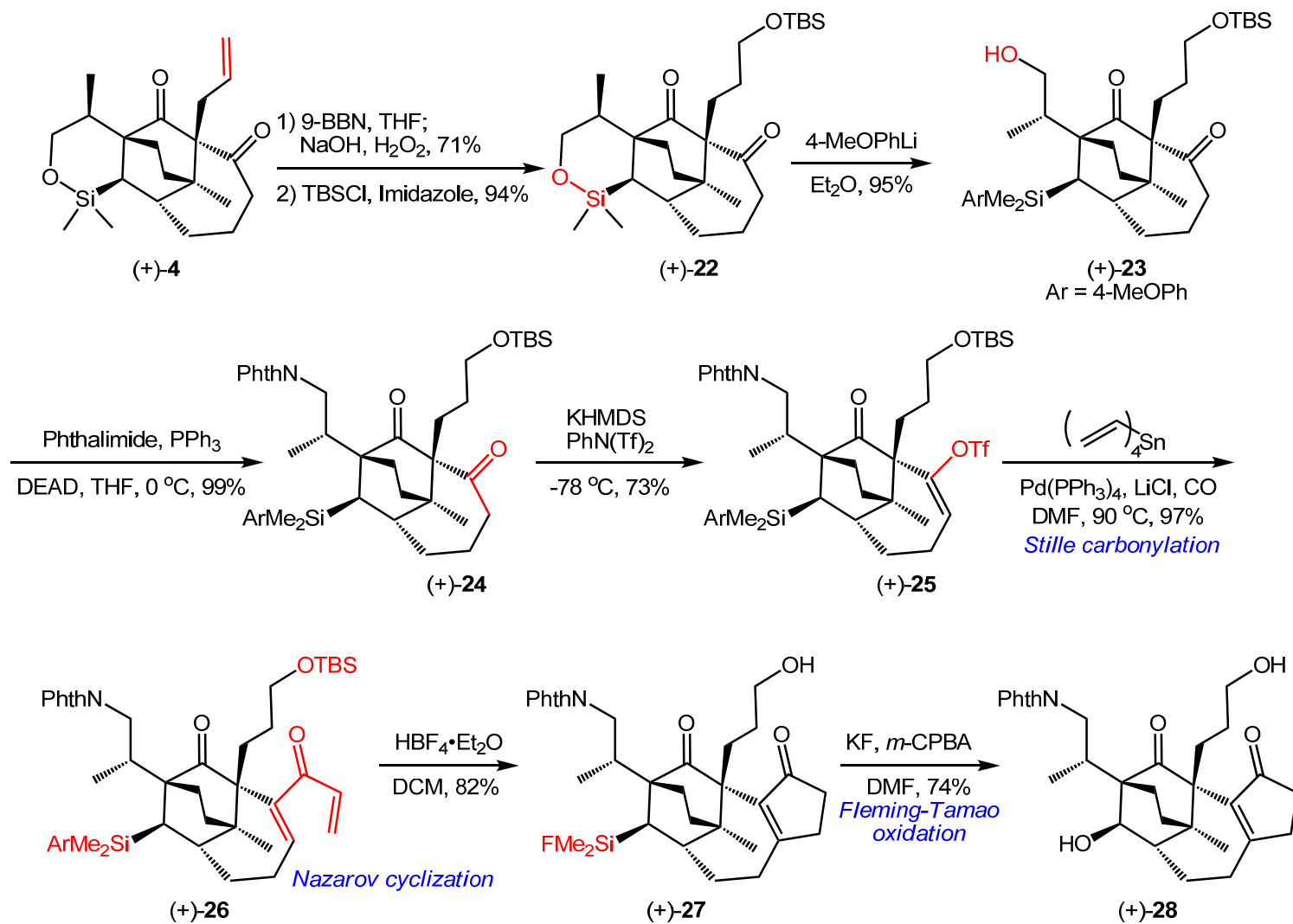
Total synthesis of (-)-Calyciphylline N



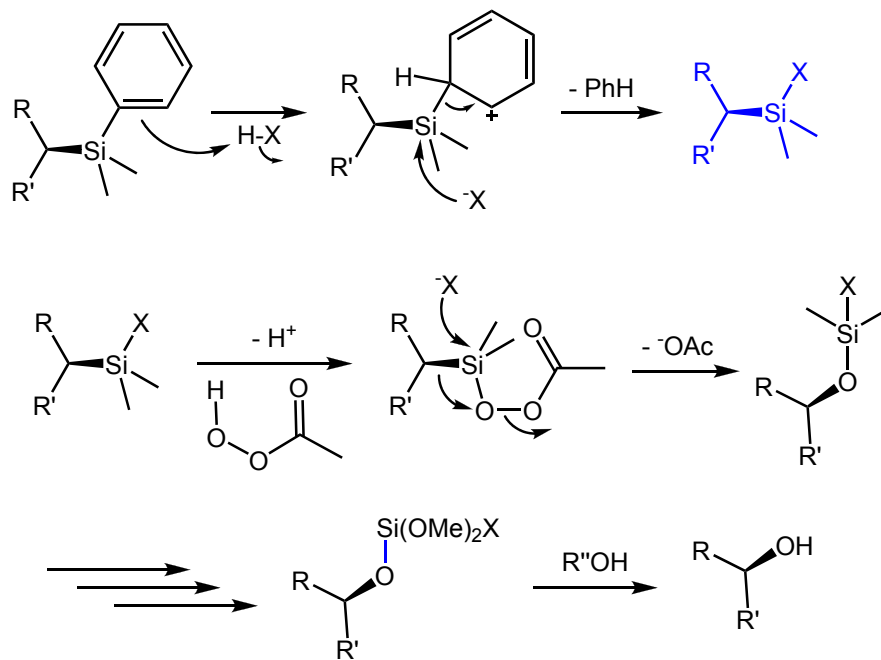
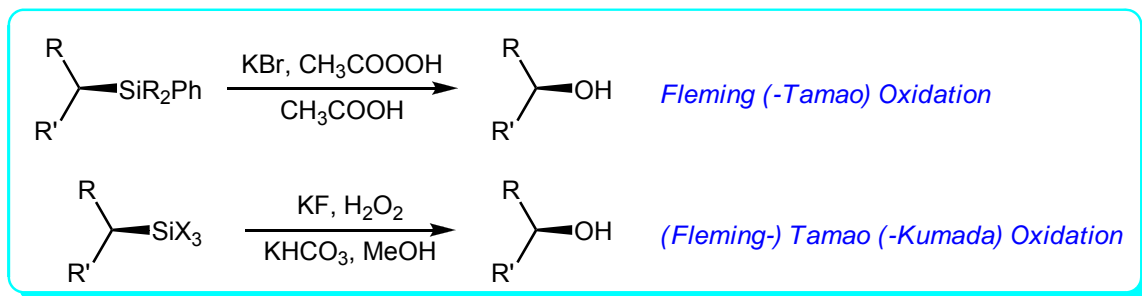
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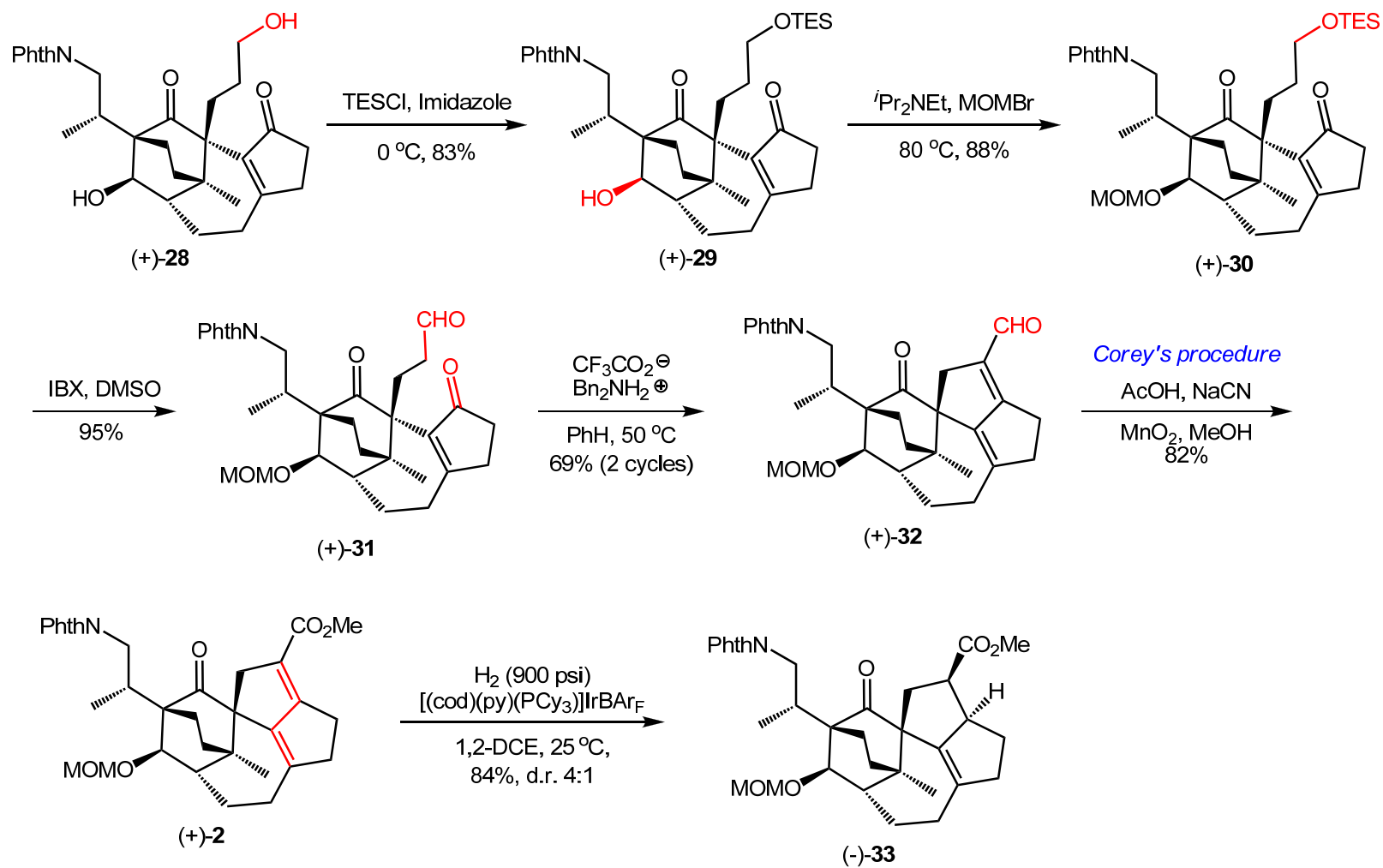
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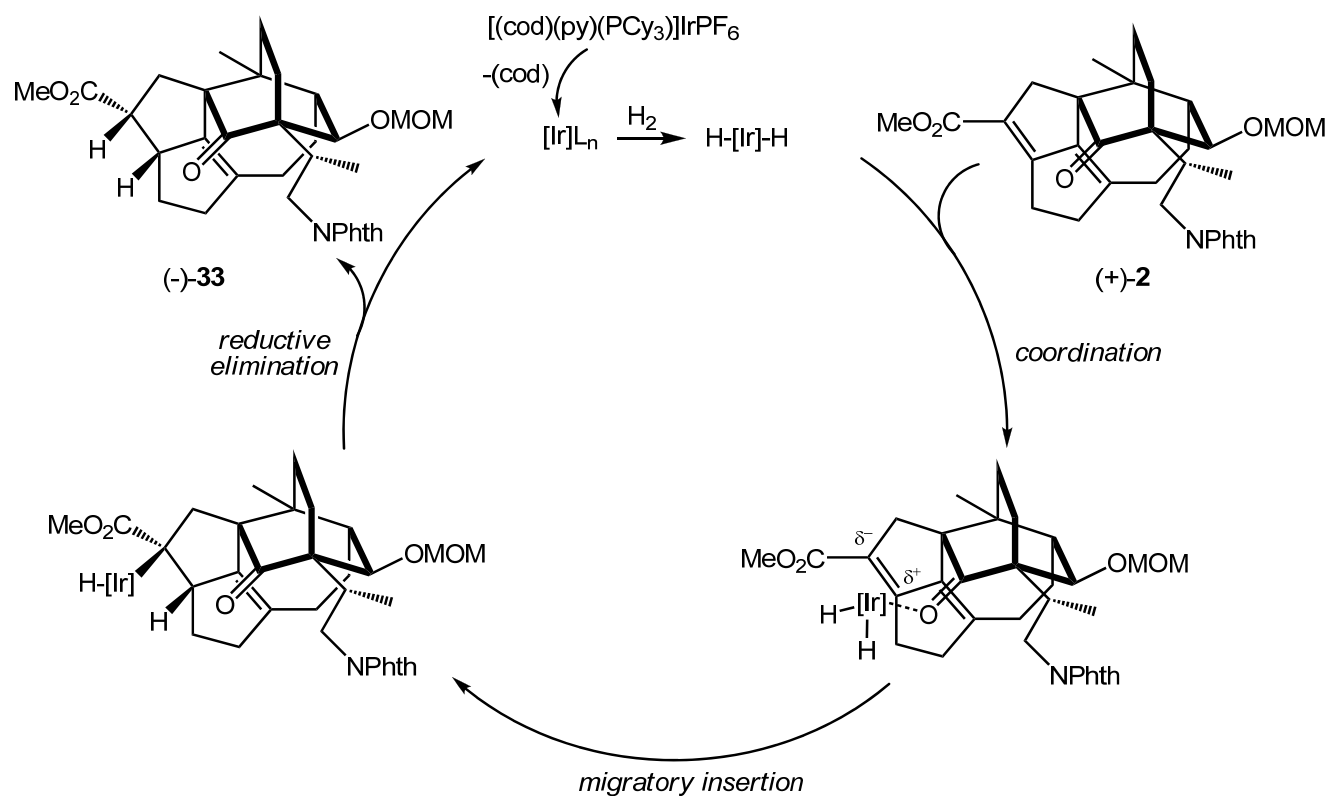
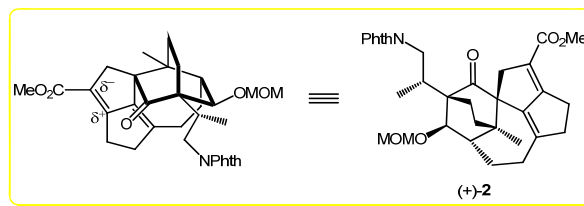
Fleming -Tamao Oxidation



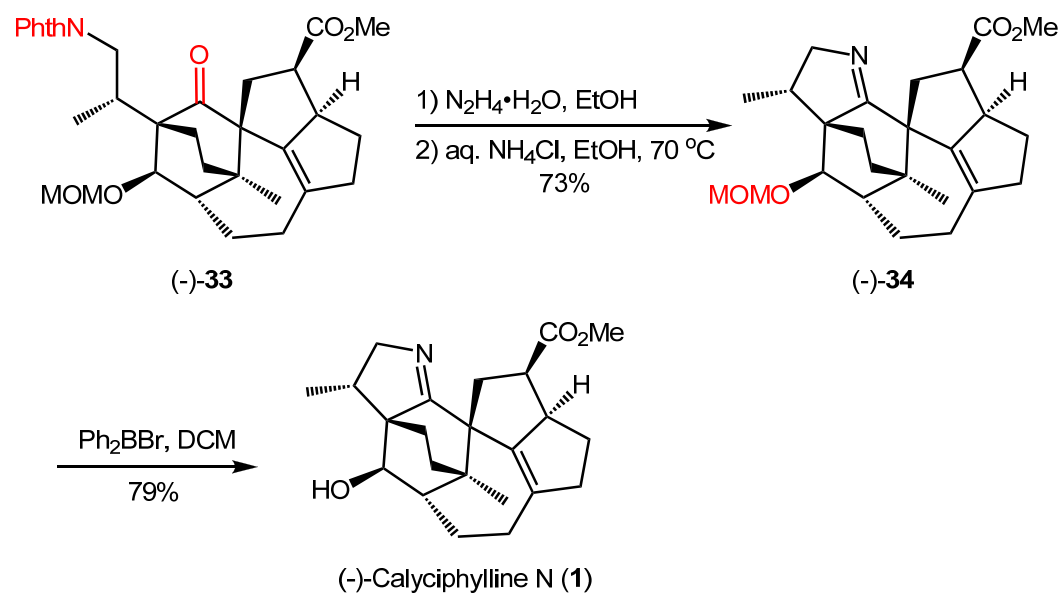
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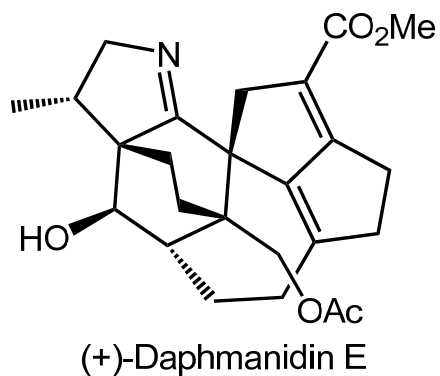
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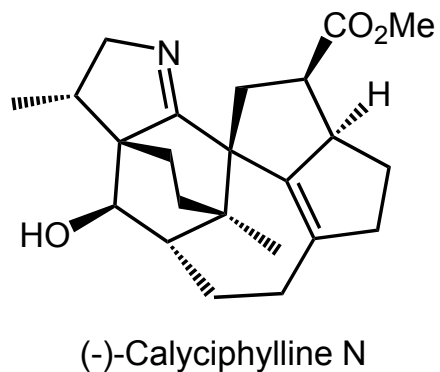


Summary



- Two consecutive Claisen rearrangements
- Henry condensation
- Strategy of Heck cyclization
- Intramolecular Diels-Alder reaction
- Unsaturated aldehyde to methyl ester

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- Transannular enolate alkylation
- Stille carbonylation/Nazarov cyclization
- Hydrogenation of conjugated diene ester
- Intramolecular Diels-Alder reaction

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The daphniphyllum alkaloids, a family of natural products numbering more than 200 members, have attracted considerable attention due to both their diverse biological activities and structural complexities. For example, in the late 1980s, Heathcock and co-workers proposed an innovative biosynthetic pathway for these alkaloids, which led to several elegant biomimetic syntheses. More recently, impressive total syntheses of (+)-daphmanidin E and daphenylline have been achieved by Carreira and Li, respectively.

The first total synthesis of a calyciphylline alkaloid, (–)-calyciphylline N (**1**), has been achieved with a longest linear sequence of 37 steps from known alcohol (–)-**8**. Highlights of the successful synthesis include a substrate-controlled, intramolecular Diels–Alder reaction to construct the bicyclic core and set four contiguous stereocenters; a highly efficient one-pot Nazarov cyclization/proto-desilylation sequence, which in one flask completes ring E and activates the silicon moiety toward Fleming–Tamao oxidation, demonstrating the use of the 4-methoxyphenyl substituent as a readily introduced and easily replaced aryl group for the activation of otherwise unreactive hindered siloxanes; and finally, exploitation of a subtle structural change permitting chemo- and diastereoselective hydrogenation of an extremely hindered diene ester that installed the C14 and C15 stereogenic centers. In all, the strategies delineated herein should prove useful for the future synthesis of related members of this alkaloid class.
