Proto-Daphniphylline

Clayton H. Heathcock

"Organic synthesis is the utilization of laboratory skill to bring to fruition the product of our imagination."

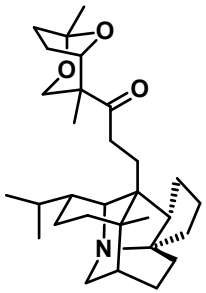
"The goal was to use sound mechanistic reasoning to invent multistep syntheses that were sufficiently non-obvious that they would serve as object lessons for other scientists, and thereby contribute to a general elevation of the level of sophistication of the science of large molecule synthesis."

Daphniphyllum macropodum, Japan

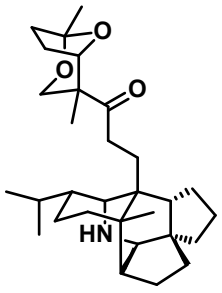
Daphniphyllum is a genus of dioecious evergreen trees and shrubs native to central and southern Japan

Over 214 Daphniphyllum alkaloids have been reported since 1966.

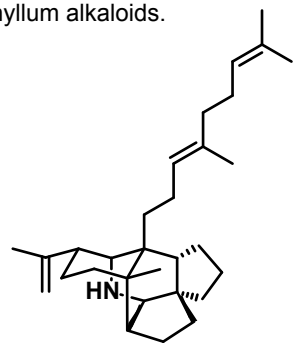
Heathcock and co-workers have proposed a biogenetic pathway for Daphniphyllum alkaloids and demonstrated biomimetic total syntheses of several Daphniphyllum alkaloids.



daphniphylline



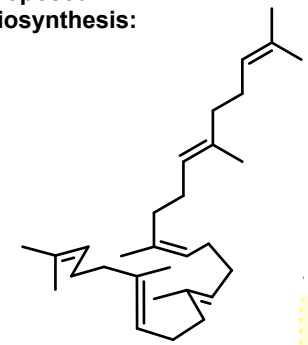
secodaphniphylline



proto-daphniphylline

Proposed Biosynthesis:

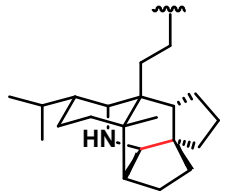
"We think that the molecular frameworks of most natural products arise by intrinsically favorable chemical pathways - favorable enough that the skeleton could have arisen by a nonenzymic reaction in the primitive organism."



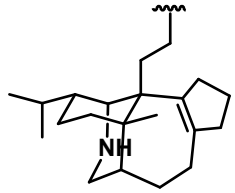
squalene

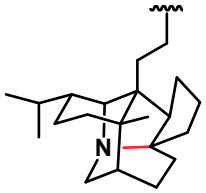
[oxidation + cyclization]

key biomimetic step



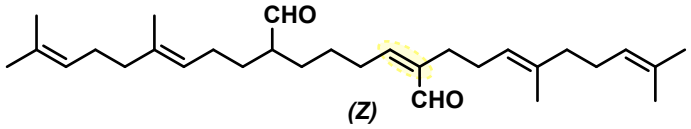
secodaphniphylline skeleton



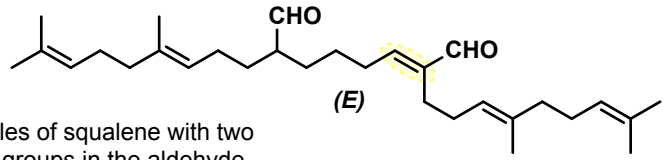


daphniphylline skeleton

Key Intermediates:



(Z)



(E)

Examples of squalene with two methyl groups in the aldehyde oxidation state are precedented.

Nat. Prod. Rep., **2009**, *26,* 936; *Science,* **1990,** *248,* 1532; *Proc. Natl. Acad. Sci.,* **1996,** *93,* 14323

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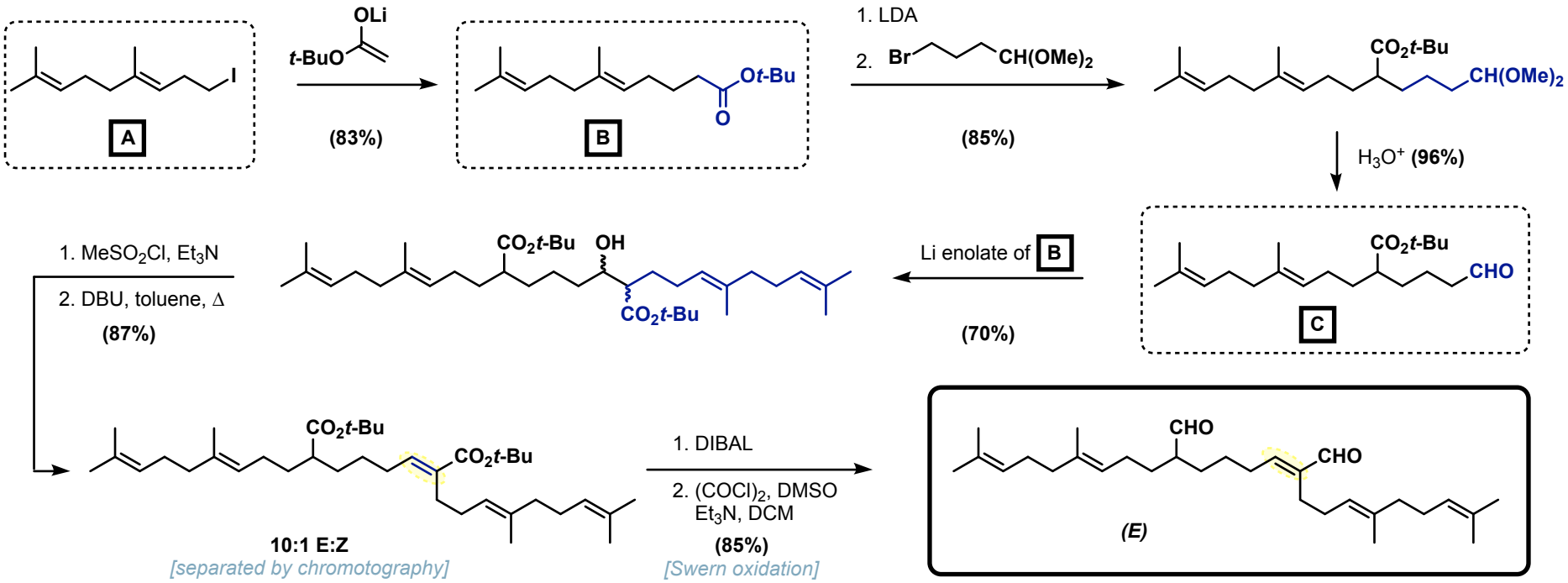

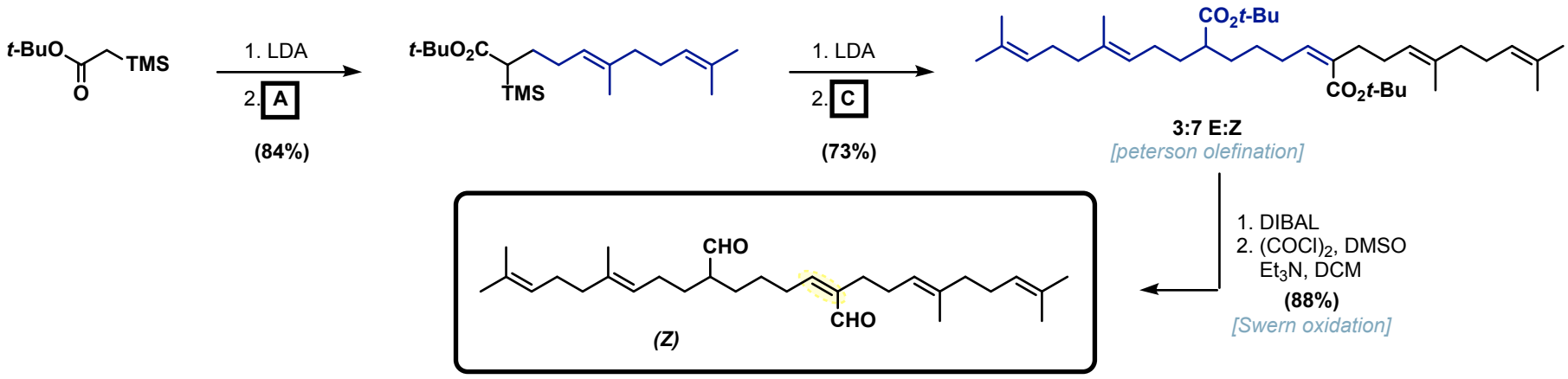

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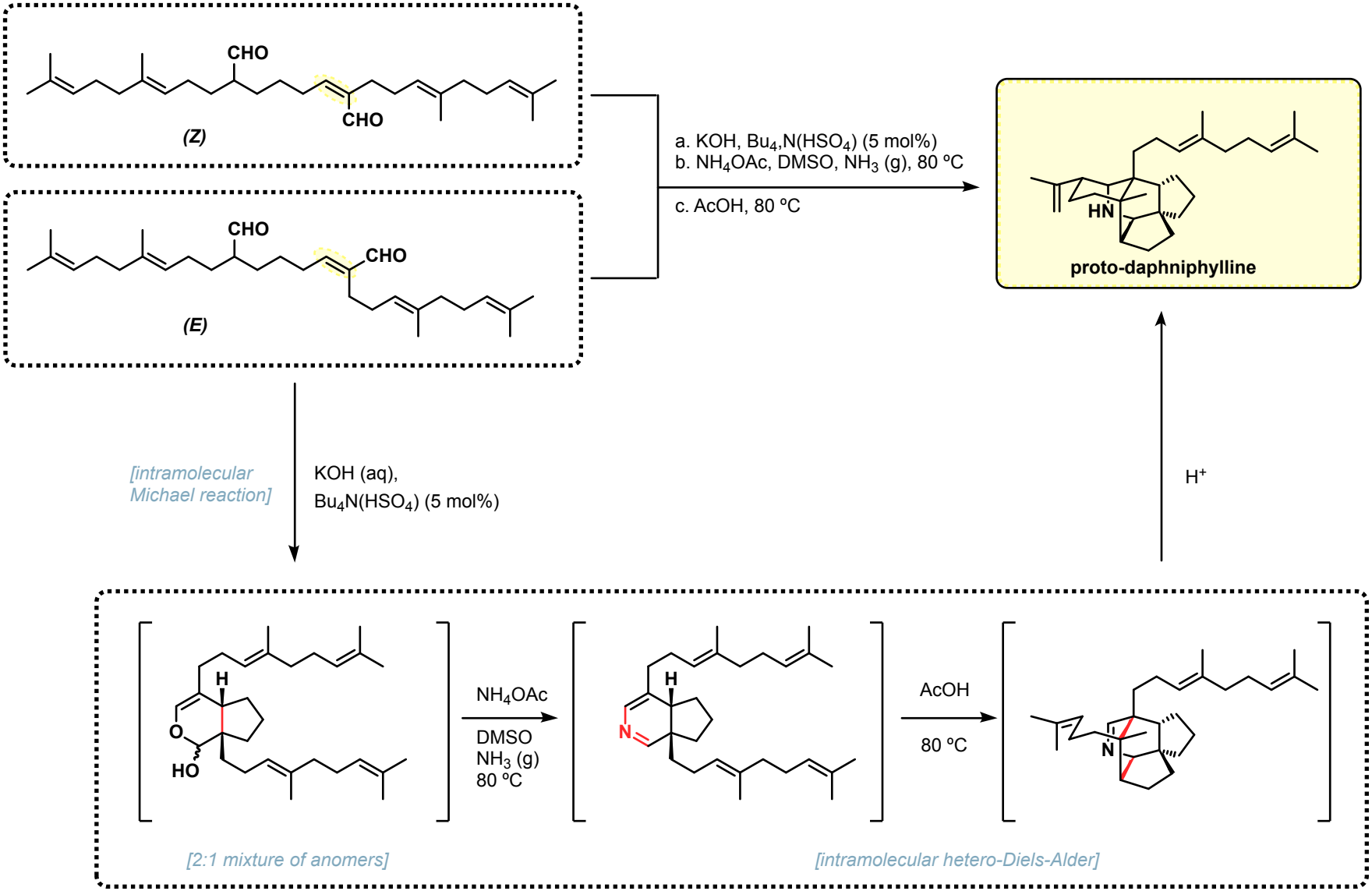

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