Total Synthesis of (+)-Daphmanidin E

Matthias E. Weiss and Erick M. Carreira

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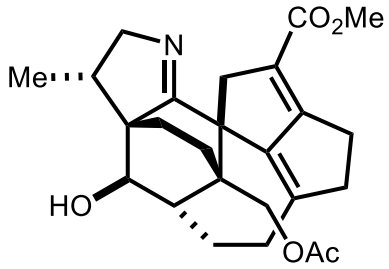
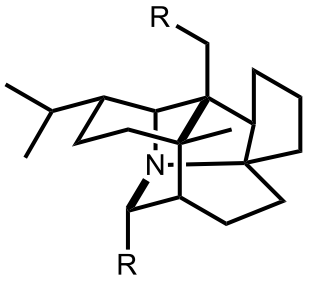


(+)-daphmanidine E

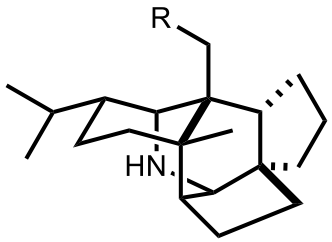
Ki Bum Hong
Current Literature
November 12, 2011

Isolation, Background

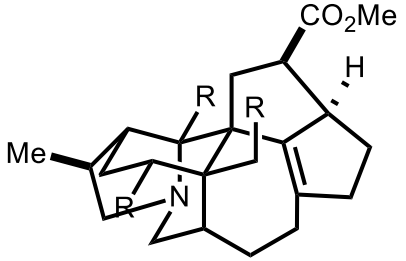
- About two hundred Daphniphyllum alkaloids - from thirteen species of the genus *Daphniphyllum*
- Daphniphyllum alkaloids are classified based on six Daphniphyllum alkaloids (daphniphylline, secodaphniphylline, yuzurimine, daphnilactone A, daphnilactone B and yuzurine)



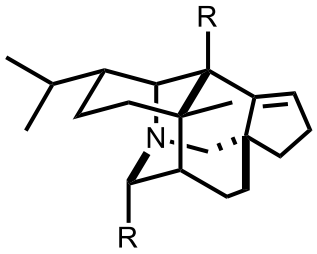
daphniphylline-type



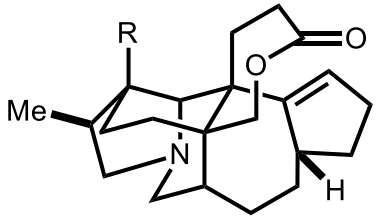
secodaphniphylline-type



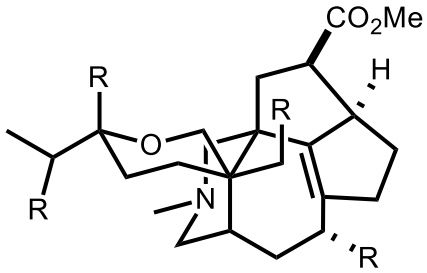
yuzurimine-type



daphnilactone A-type



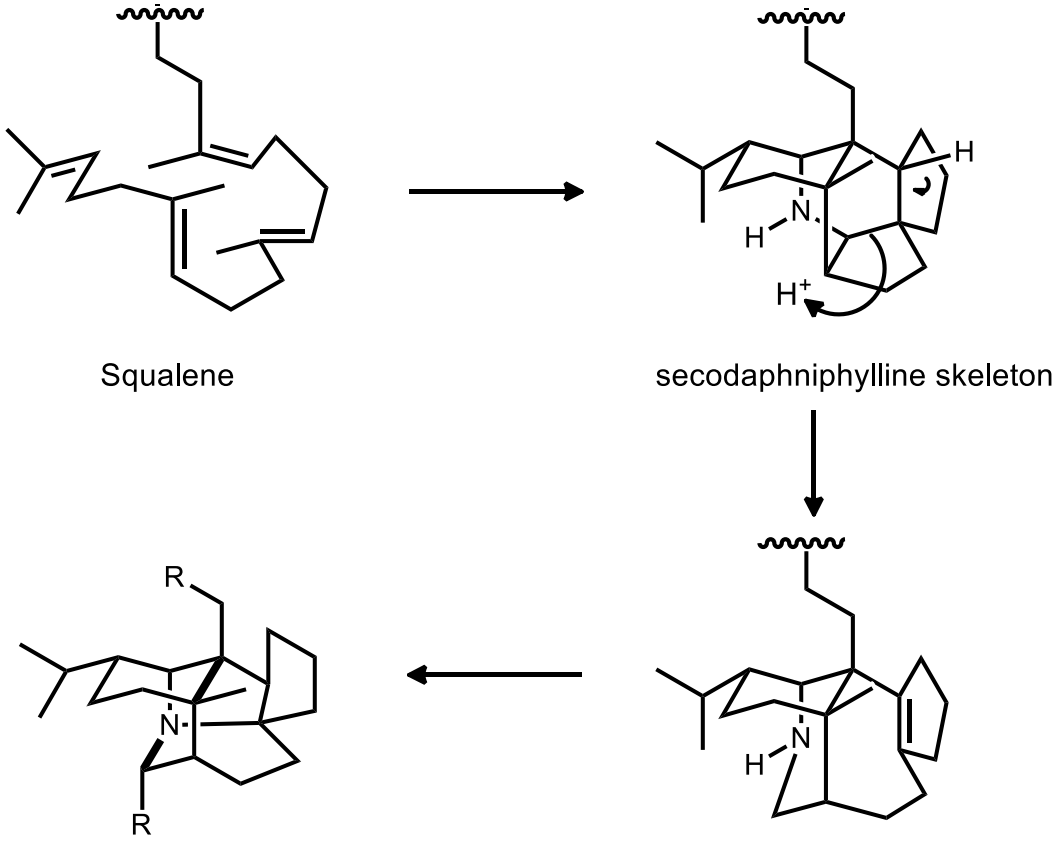
daphnilactone B-type



yuzurine-type

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

Proposed Biosynthesis



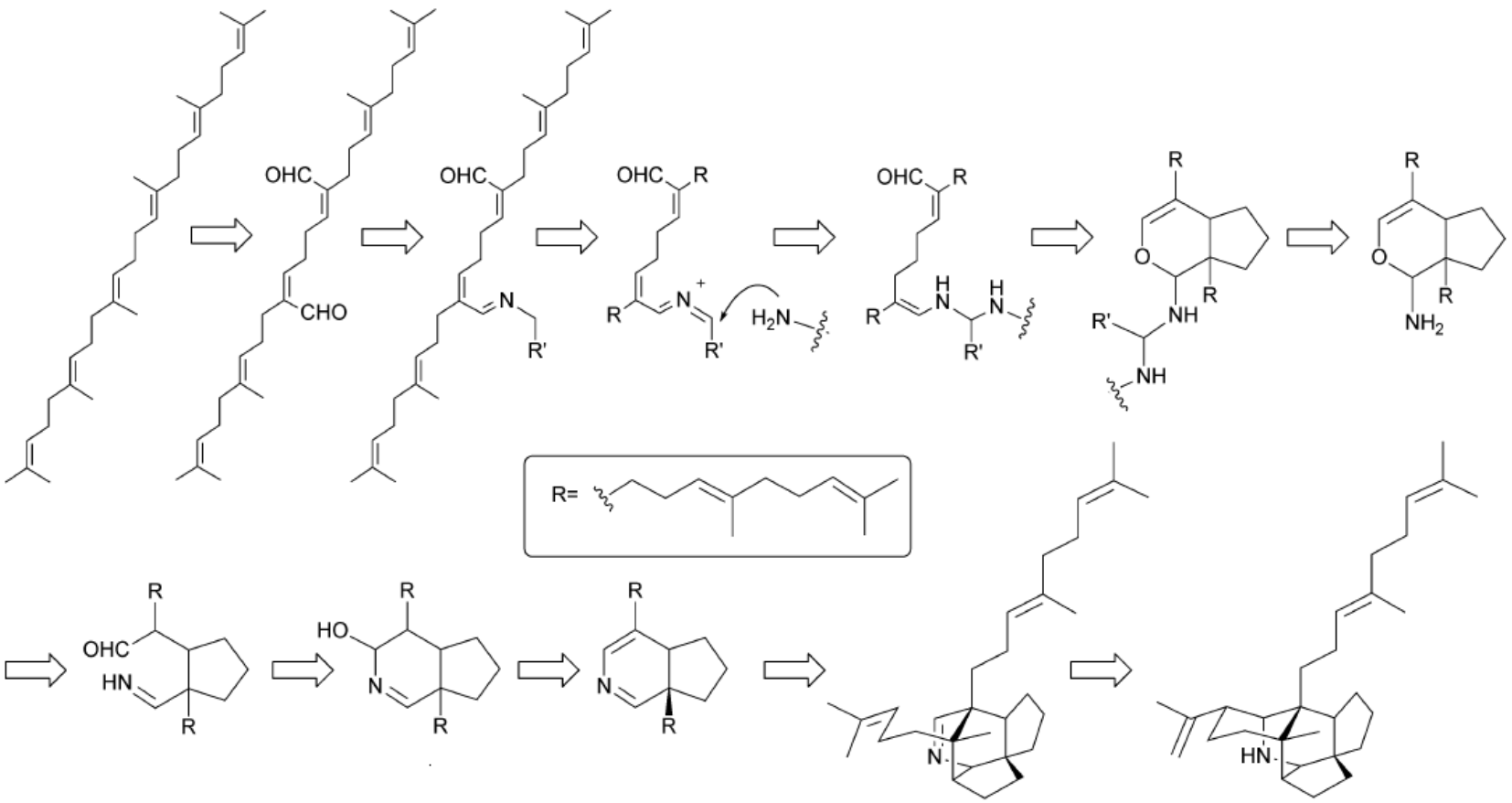
Squalene

secodaphniphylline skeleton

daphniphylline skeleton

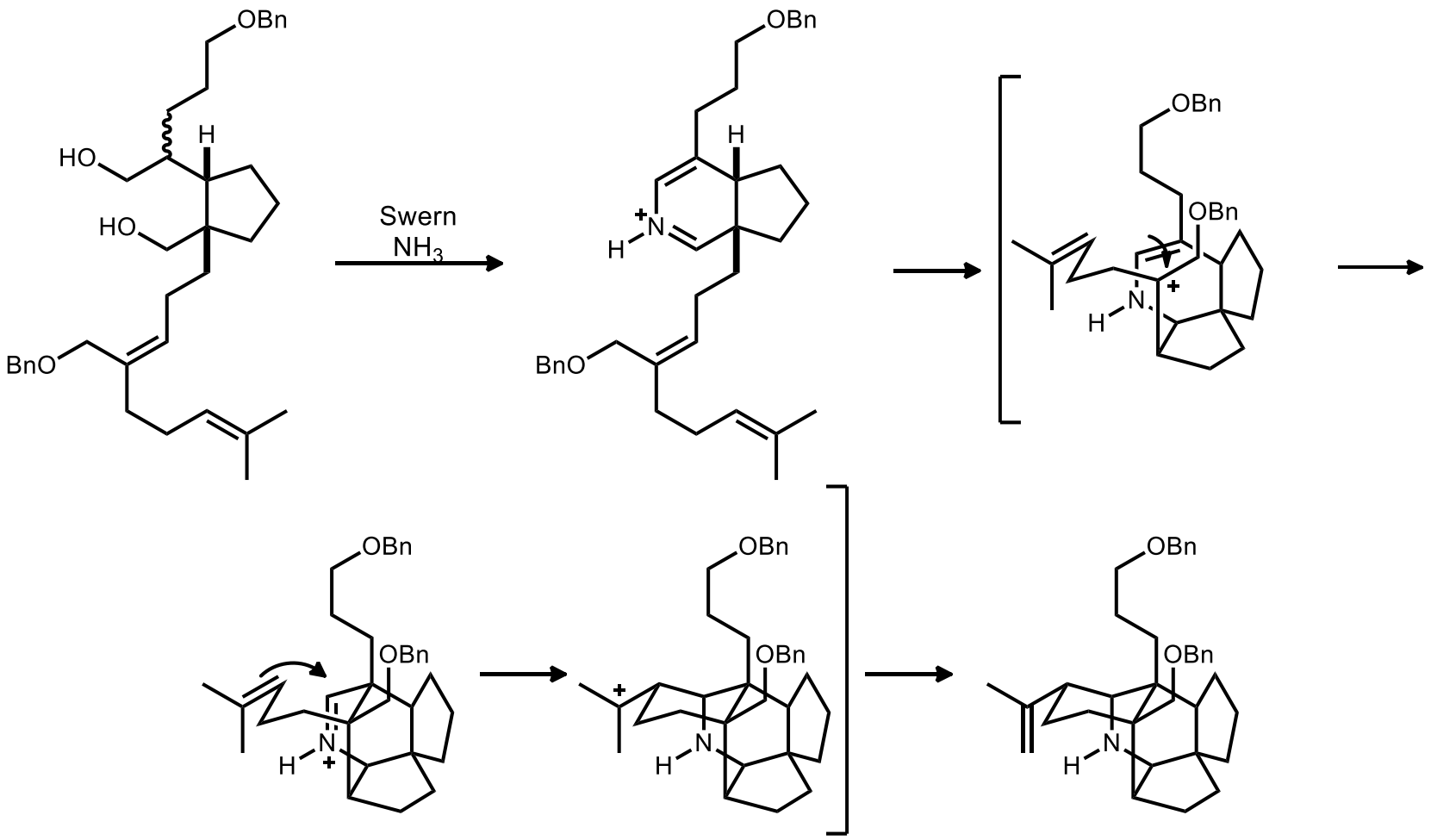
Yamamura. S. *Tetrahedron Lett.* **1973**, *14*, 2129

Proposed Biosynthesis



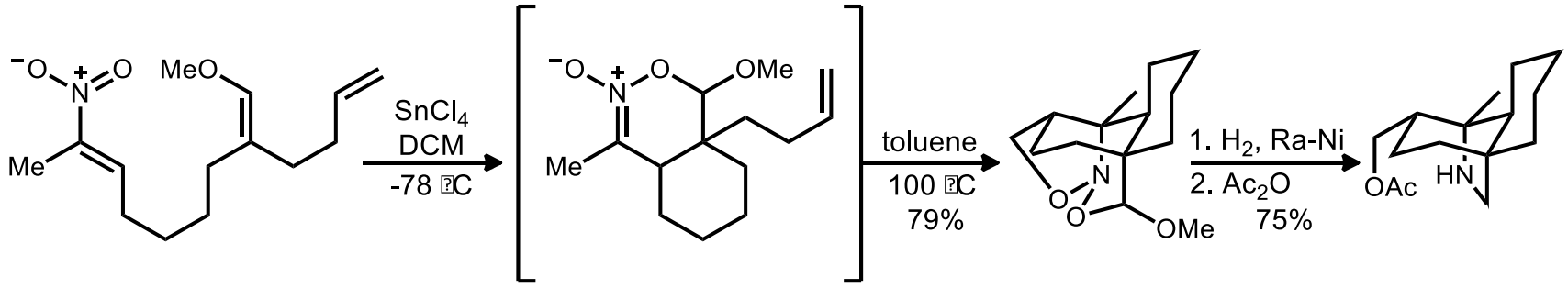
Heathcock, C. H. *Proc. Natl. Acad. Sci.* **1996**, *93*, 14323

Daphniphyllum Alkaloids; Heathcock's Approach

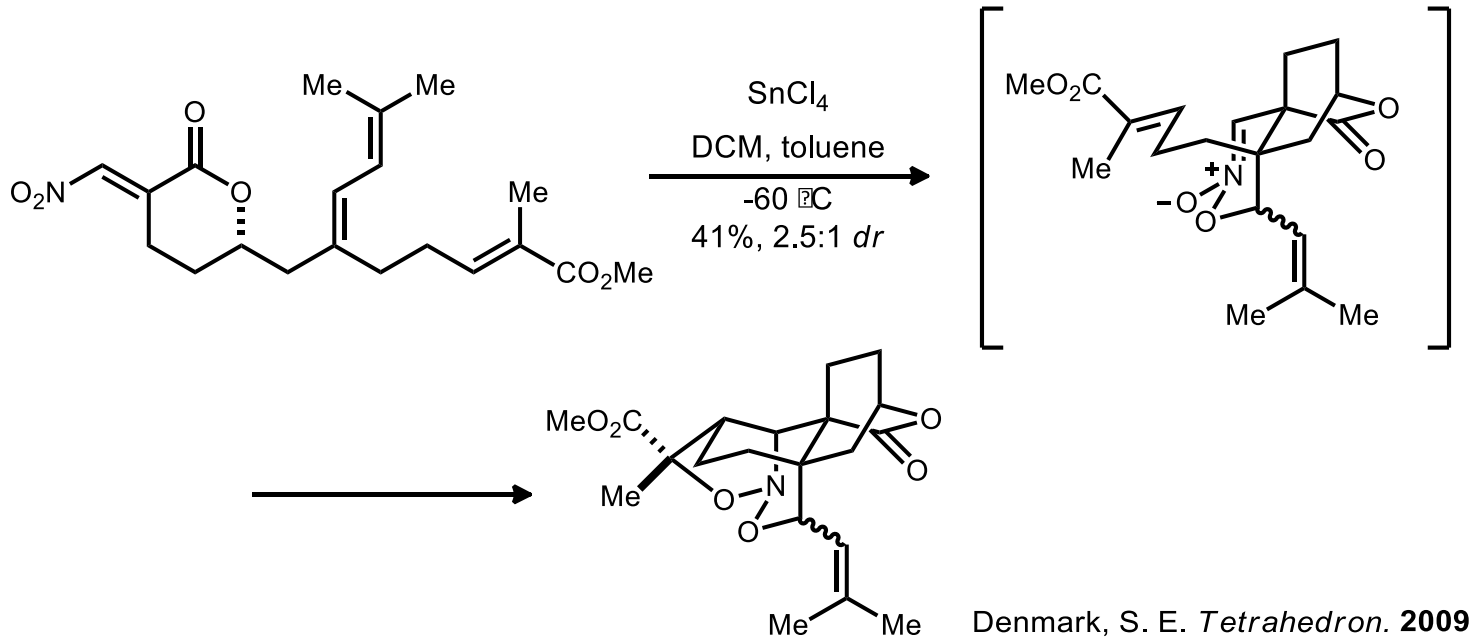


Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 2544
Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 2566
Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 2575
Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 2585

Denmark's Double Cycloadditions of Nitroalkene



Denmark, S. E. *Org. Lett.* **2001**, *3*, 2907

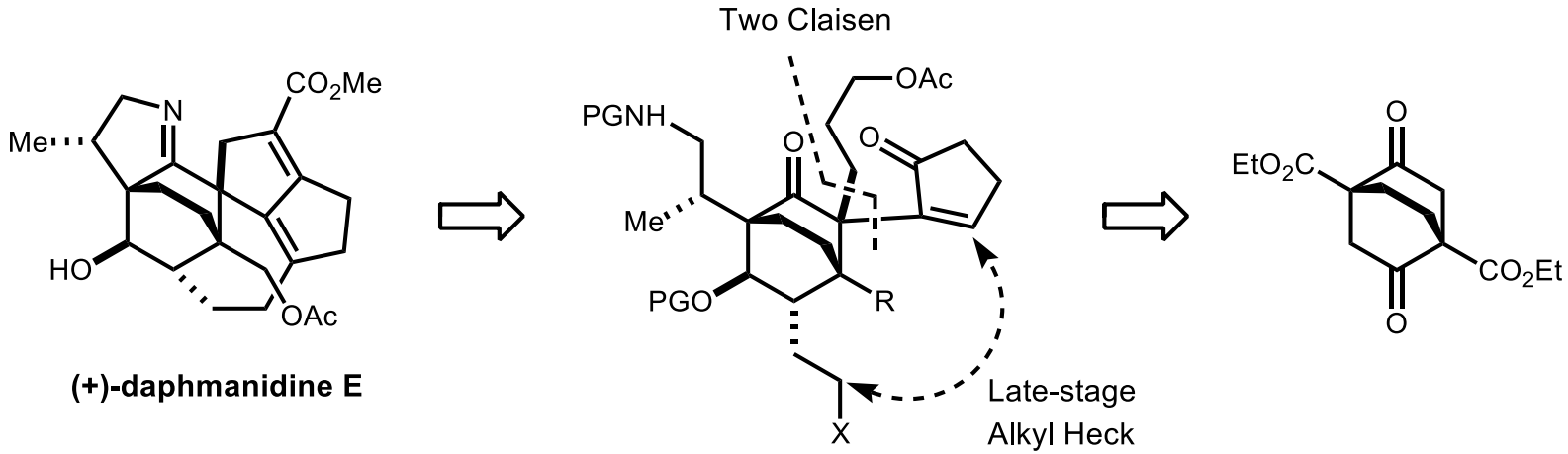


Denmark, S. E. *Tetrahedron.* **2009**, *65*, 6535

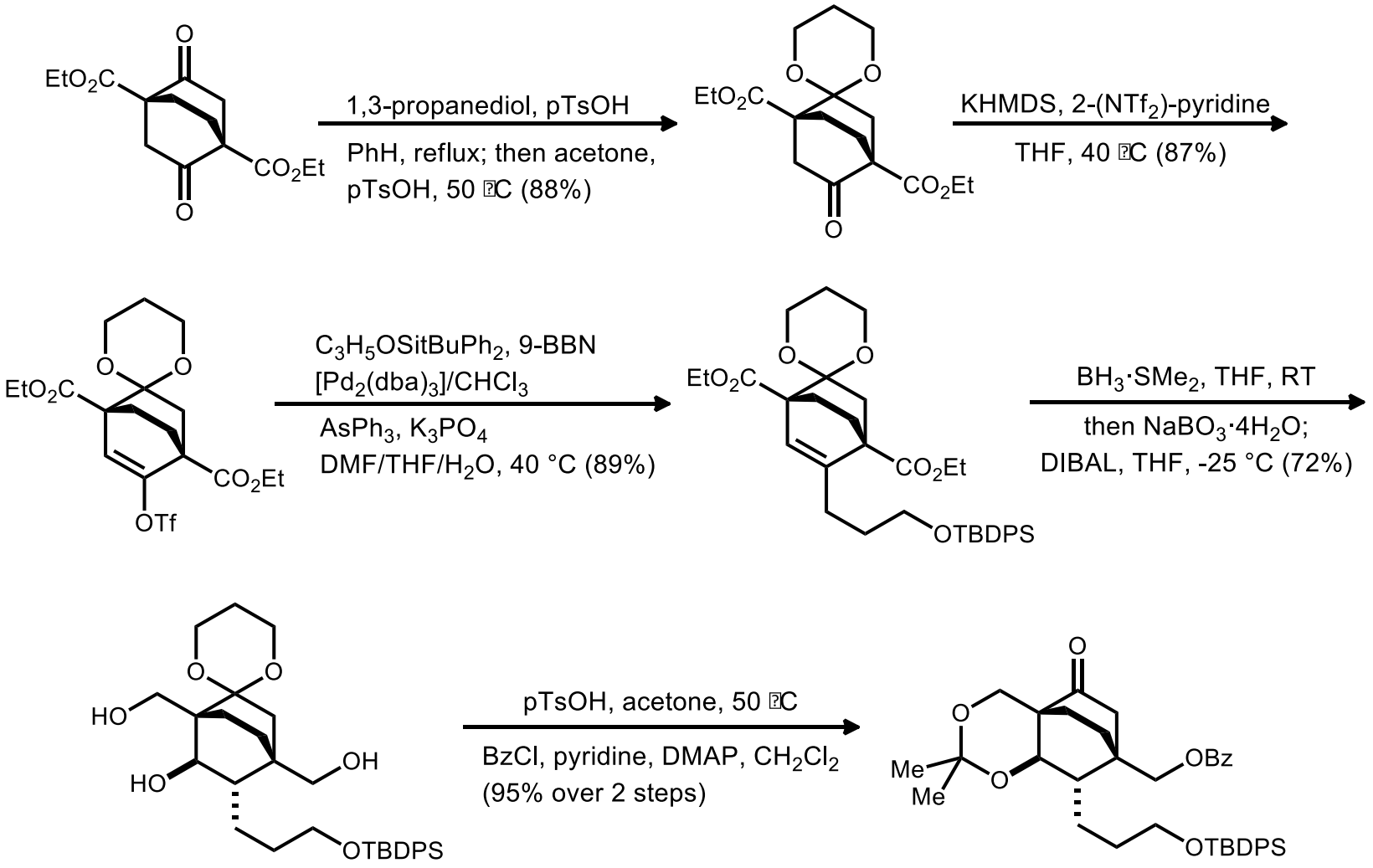
Background and Retrosynthetic Analysis

- Highly complex polycyclic structure
  - bicyclo[2.2.0]octane, decahydrocyclopenta[*cd*]azulene
- Vasorelaxant activity
- ^{1}H and ^{13}C and 2D NMR analysis

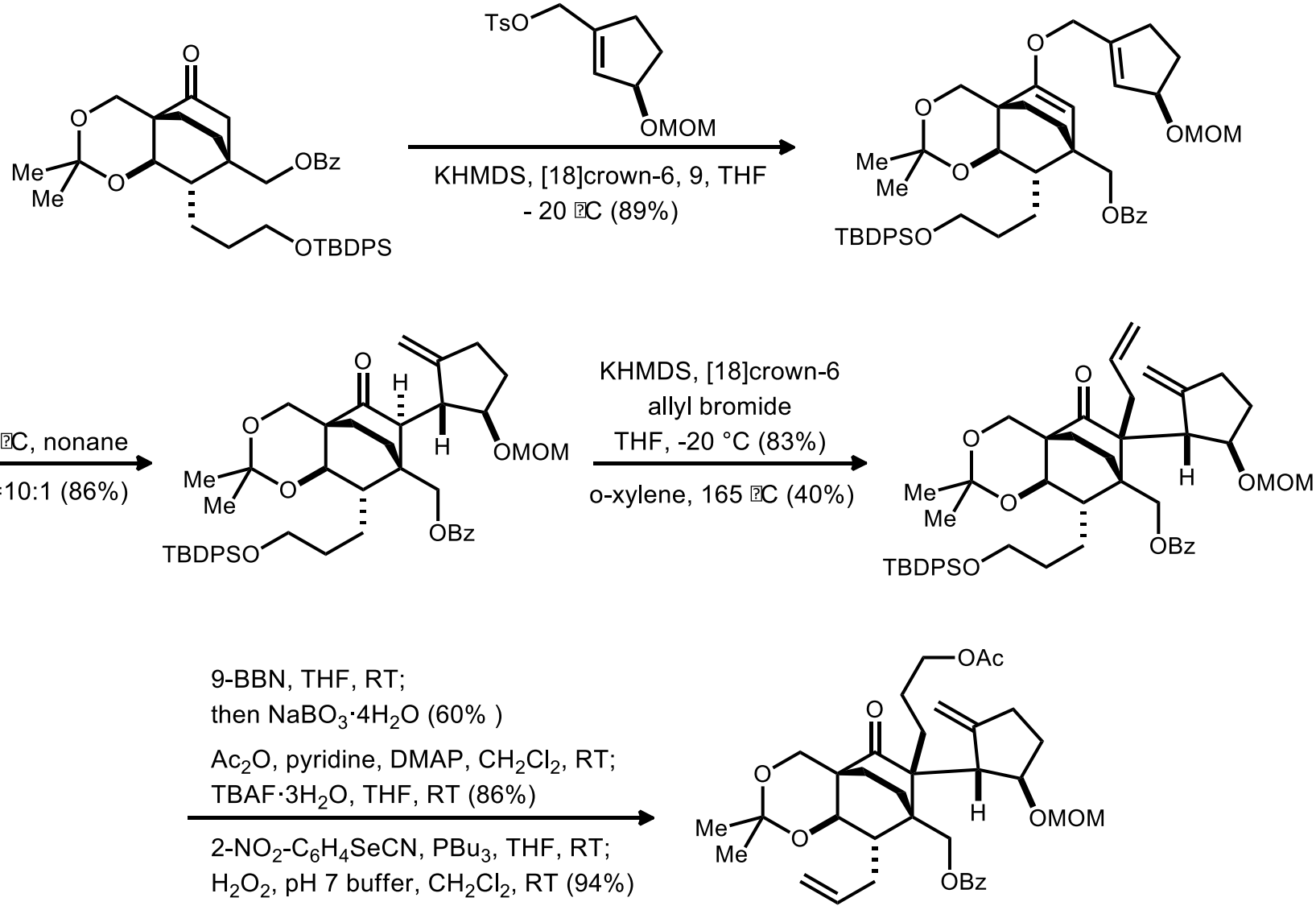
Kobayashi, J. *J. Nat. Prod.* **2006**, *69*, 418



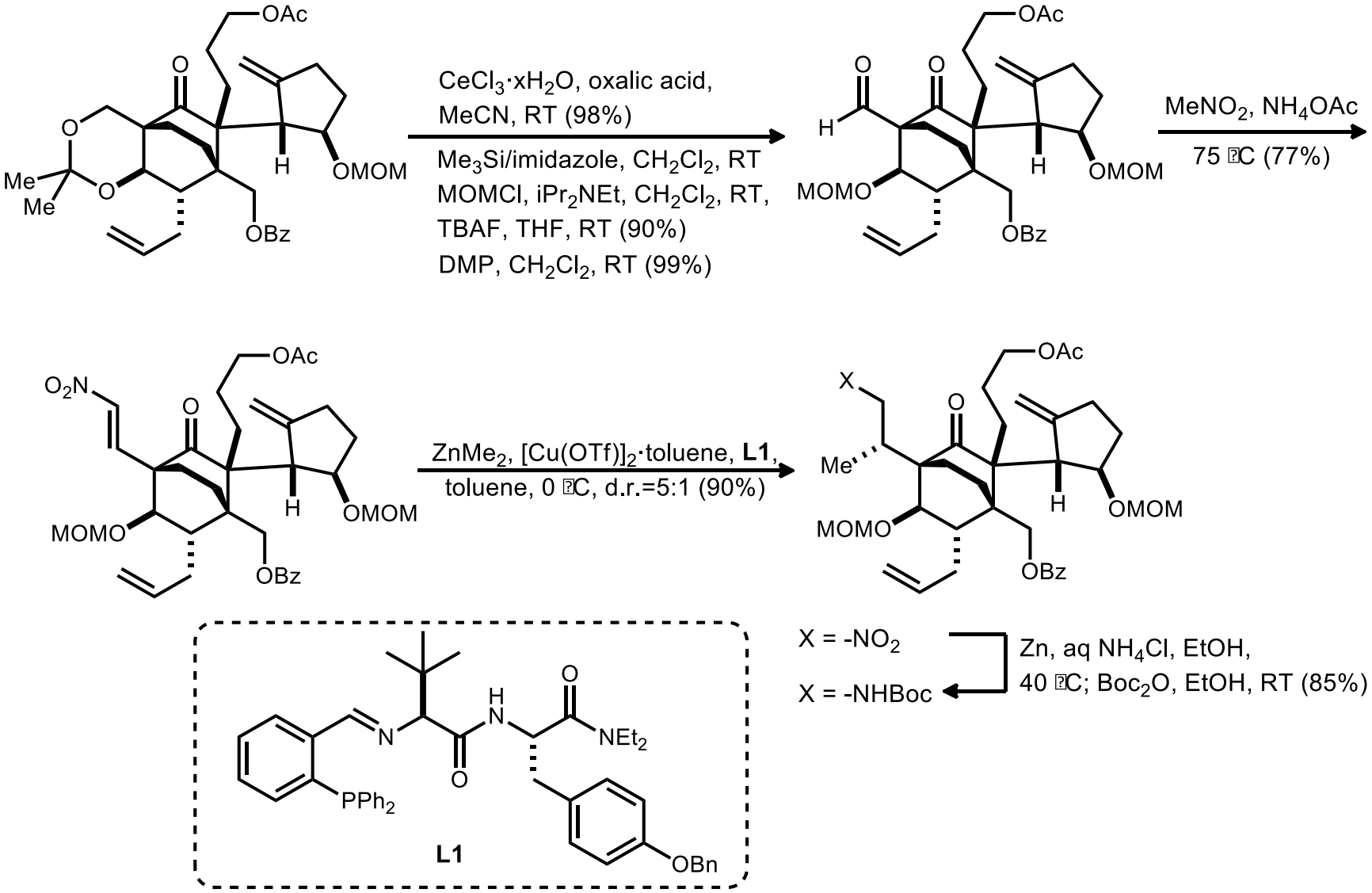
Elaboration of Bicyclo[2.2.2]octadione



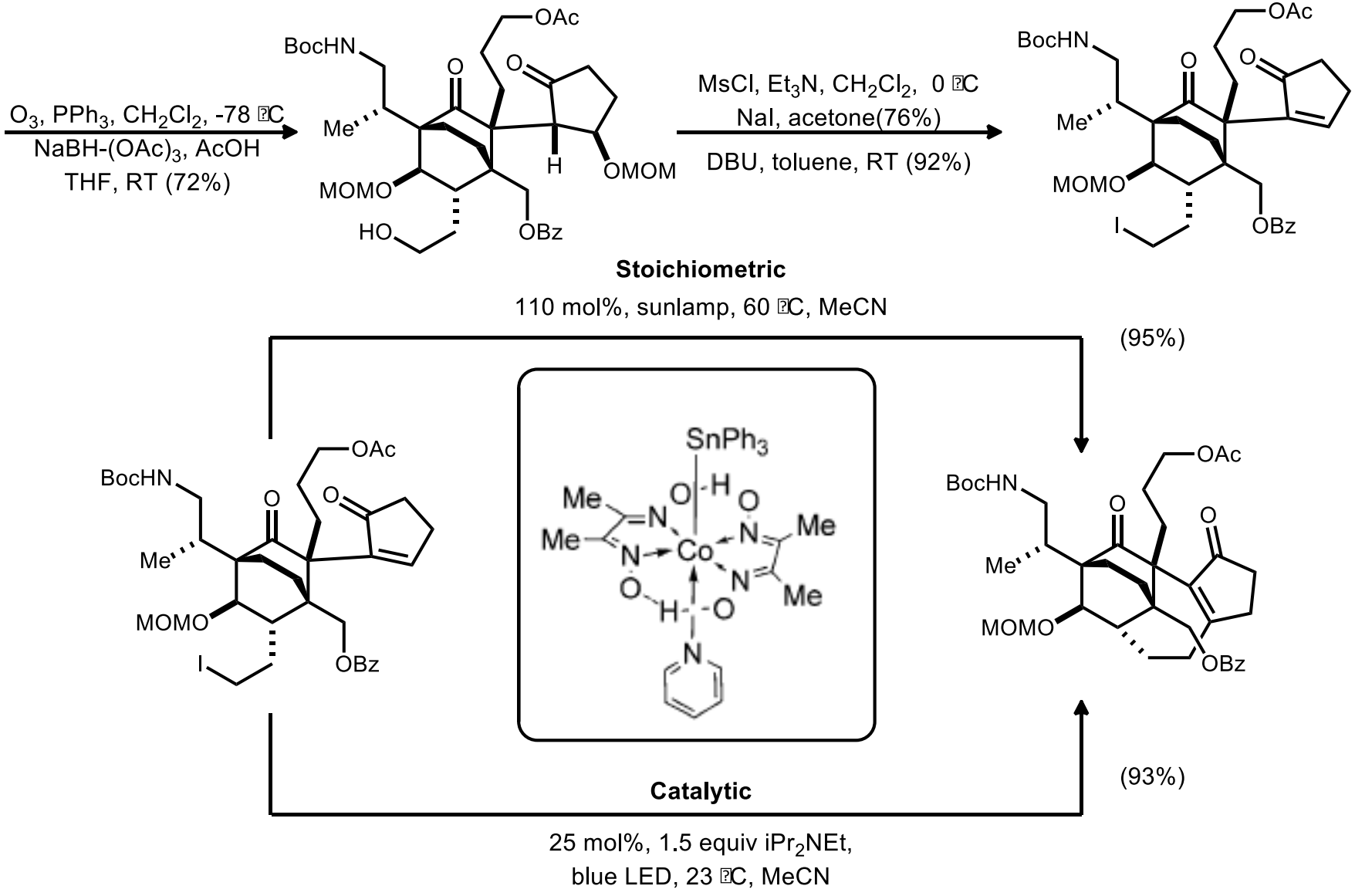
Two-Consecutive Claisen Rearrangements



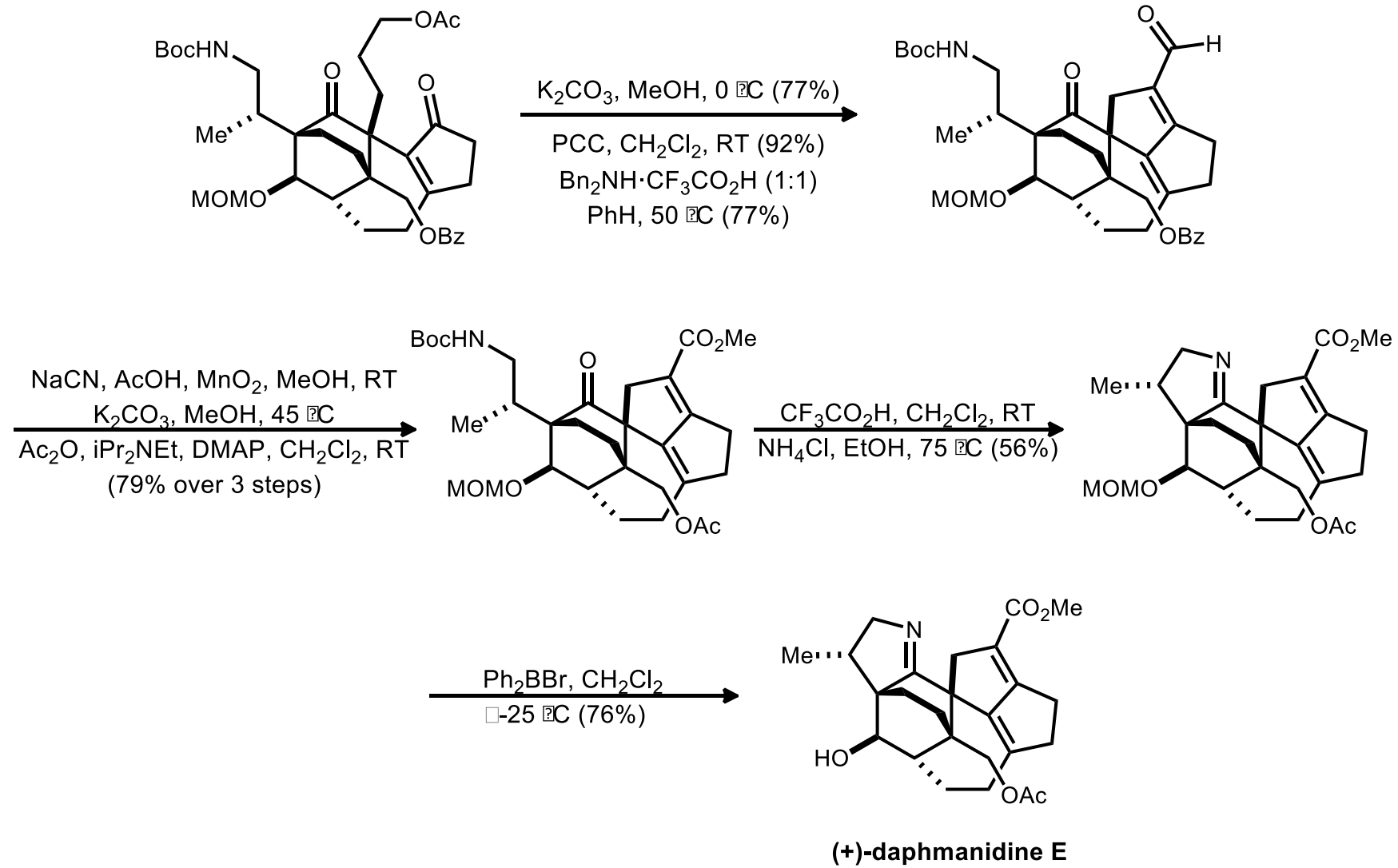
Henry and Conjugated Addition of Alkylzinc



Cobaloxime-Mediated Heck Cyclization



End Game



(+)-daphmanidine E

Conclusions

- the first total synthesis of a member of the daphmanidin alkaloids, namely (+)-daphmanidin E
- C_2-symmetric building block, two Claisen rearrangements to install a hindered quaternary stereogenic center
- copper/peptide complex as a catalyst for a reagent controlled stereoselective conjugate addition
- the late-stage ring closure of an alkyl iodide onto an enone to form the seven-membered carbocycle - a cobalt-catalyzed Heck coupling reaction