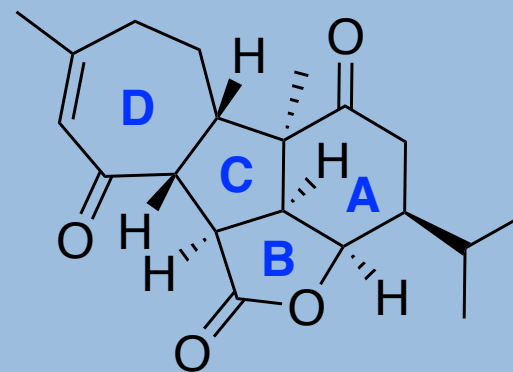


Enantioselective Total Synthesis of (-)-Pavidolide B

J. Am. Chem. Soc. **2017**, 139, 13989–13992

Zhang, Yan, Li, Gong and Yang



Pavidolide B

Journal Club, 25 January 2018

Lars Gnägi, Group Prof. Renaud

Zhang Yang

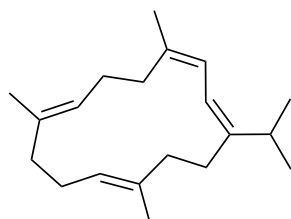
- > **1989-1992, Ph.D.**
The Chinese University of Hong Kong
(Henry N. C. Wong)
- > **1992-1995, PostDoc**
The Scripps Research Institute (K. C. Nicolaou)
- > **1995-1998, assistant professor**
The Scripps Institute, dept. chemistry
- > **1998-2001**
Harvard Med, dept. of cell biology
- > **Since 2002, Changjiang Professor of Chemistry**
Dept. of Chemistry, Peking University



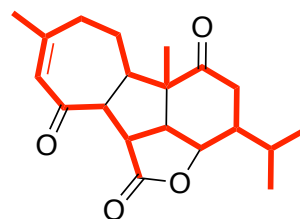
From: <http://www.chem.pku.edu.cn/zyang/>

(-)-Pavidolide B

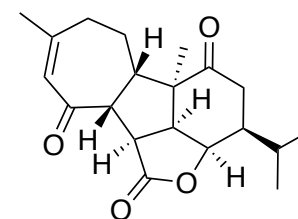
- > Pavidolide B is a marine cembranoid (diterpenoid with 14-C macrocycle)



basic structure of
a cembranoid



cembranoid structure
in Pavidolide B

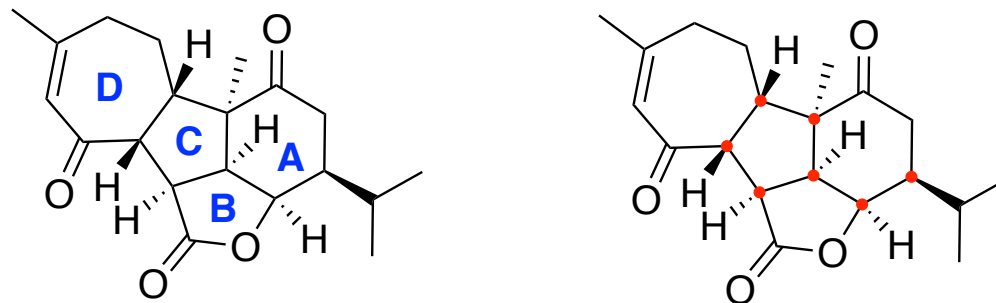


Pavidolide B

- > First isolated in a small quantity from the soft coral *sinularia pavida*.
- > High selective inhibitory activity against a number of human promyelocytic leukemia cell lines.

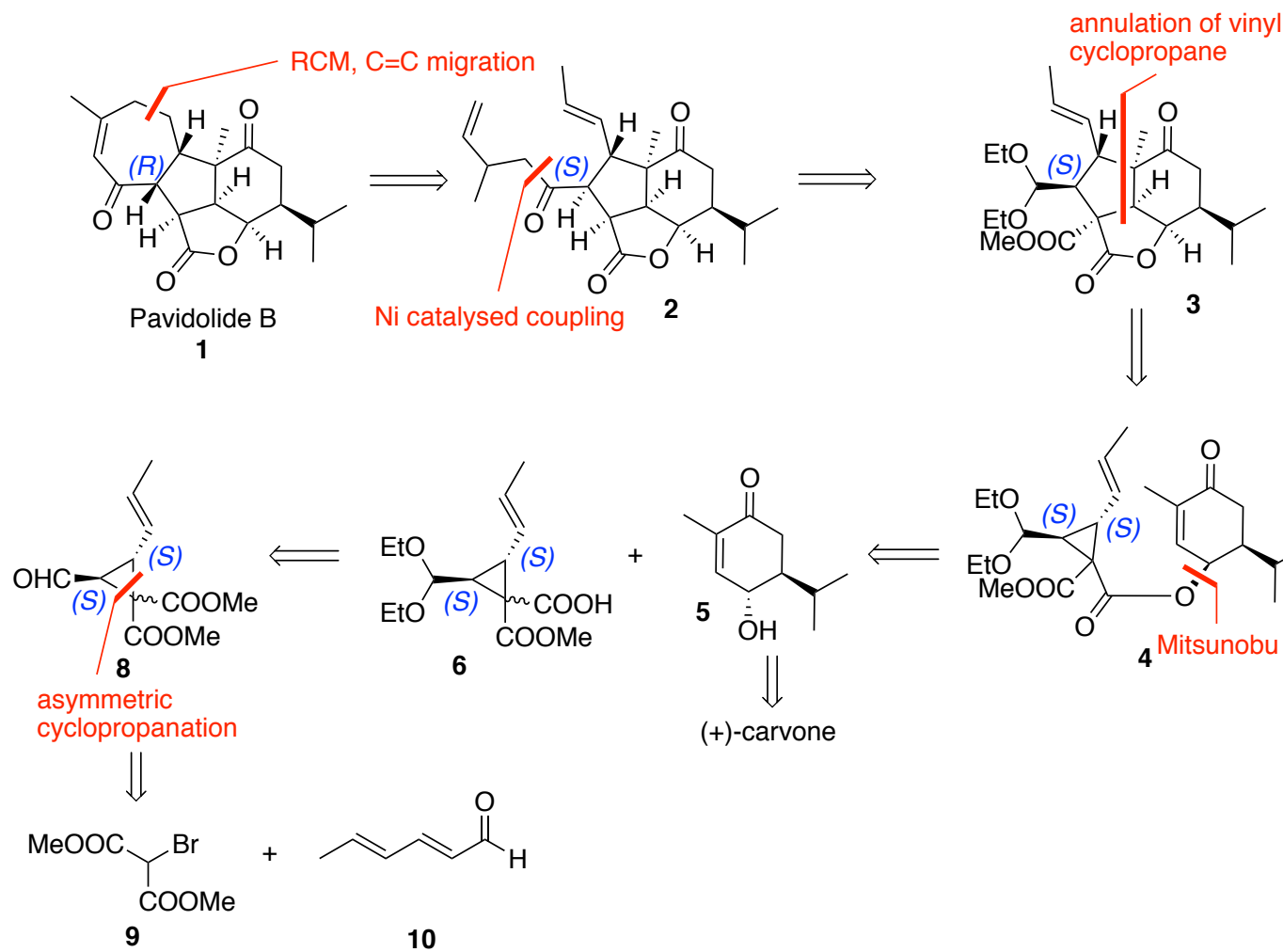
(-)-Pavidolide B

- > Pavidolide B has dome-shaped structure of the fused A-B-C-ring system – the C-ring is fully functionalised

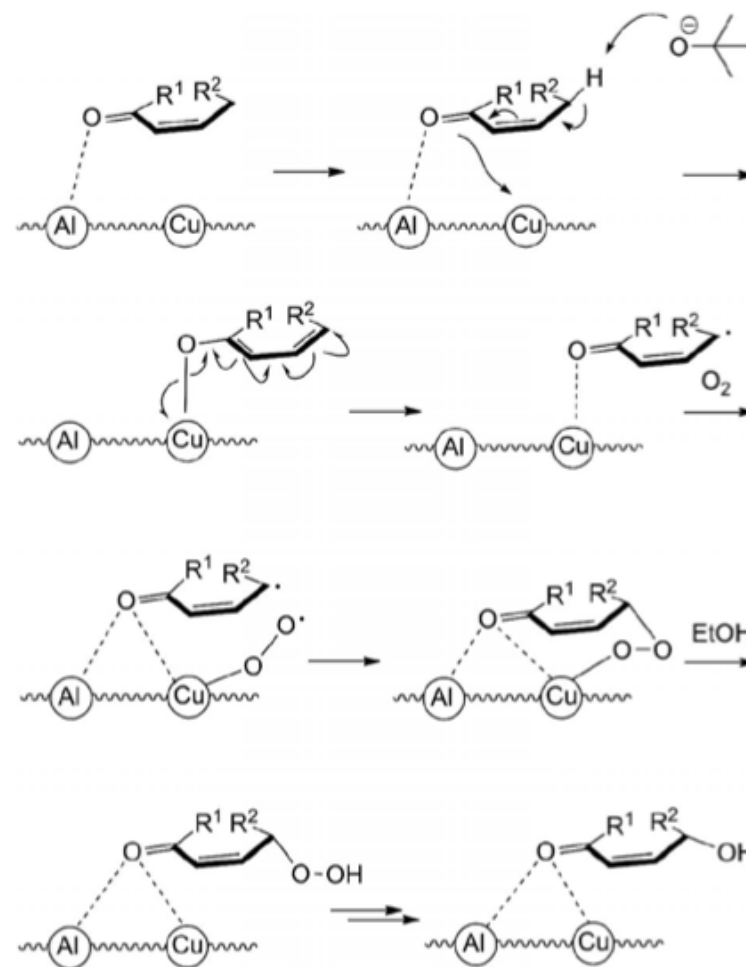
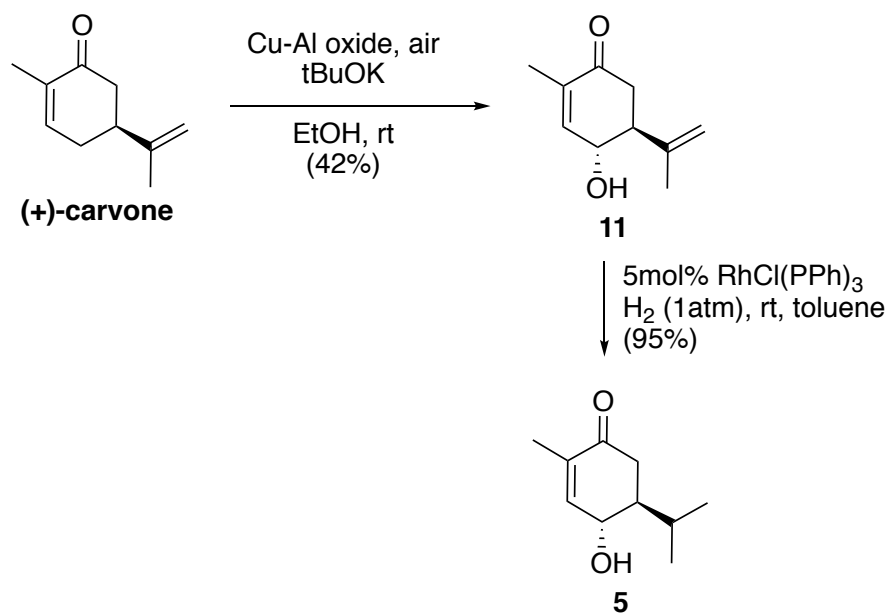


- > 7 contiguous stereocenters are found, 5 of which are located in the C-ring (one of them quaternary)

Retrosynthesis

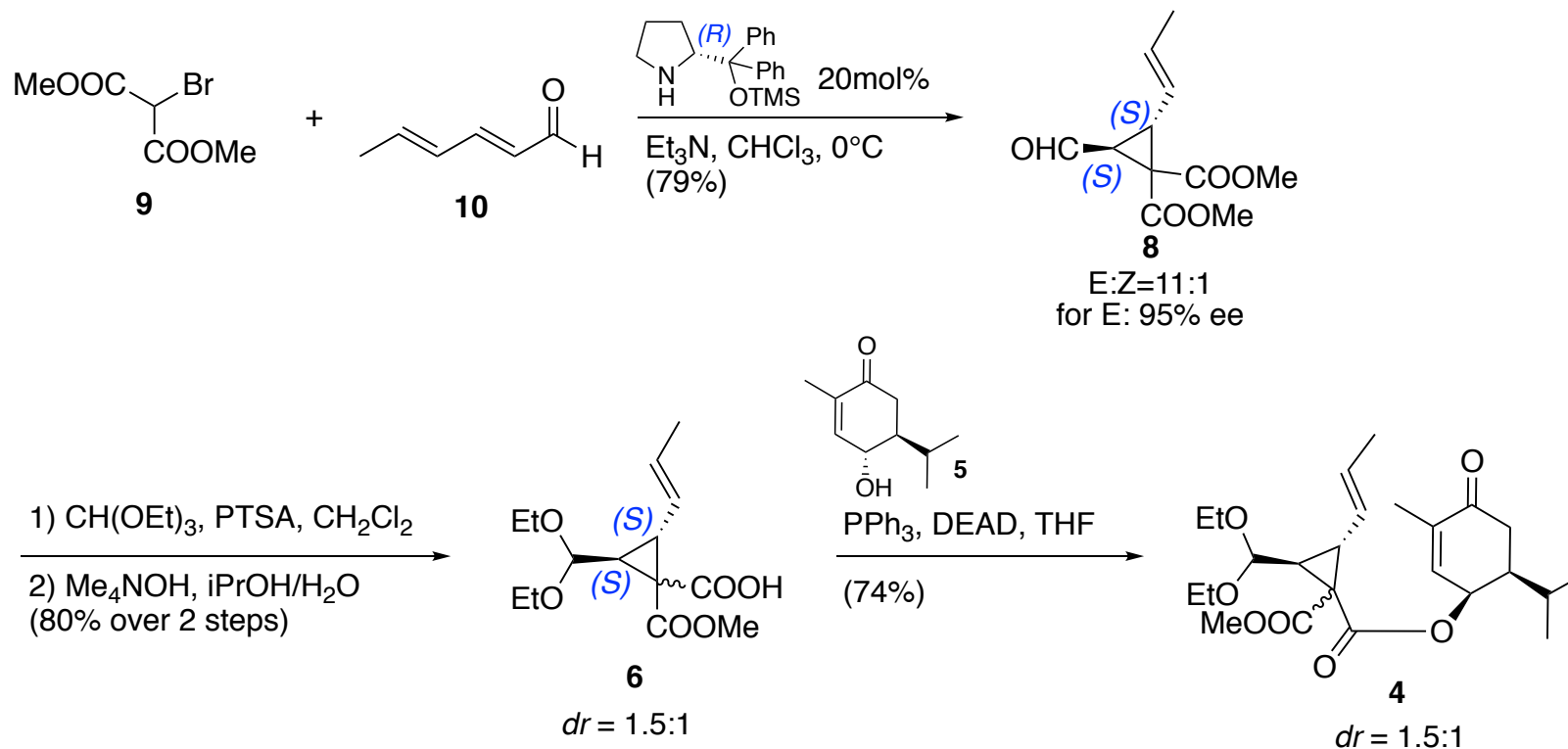


Synthesis of building block 5



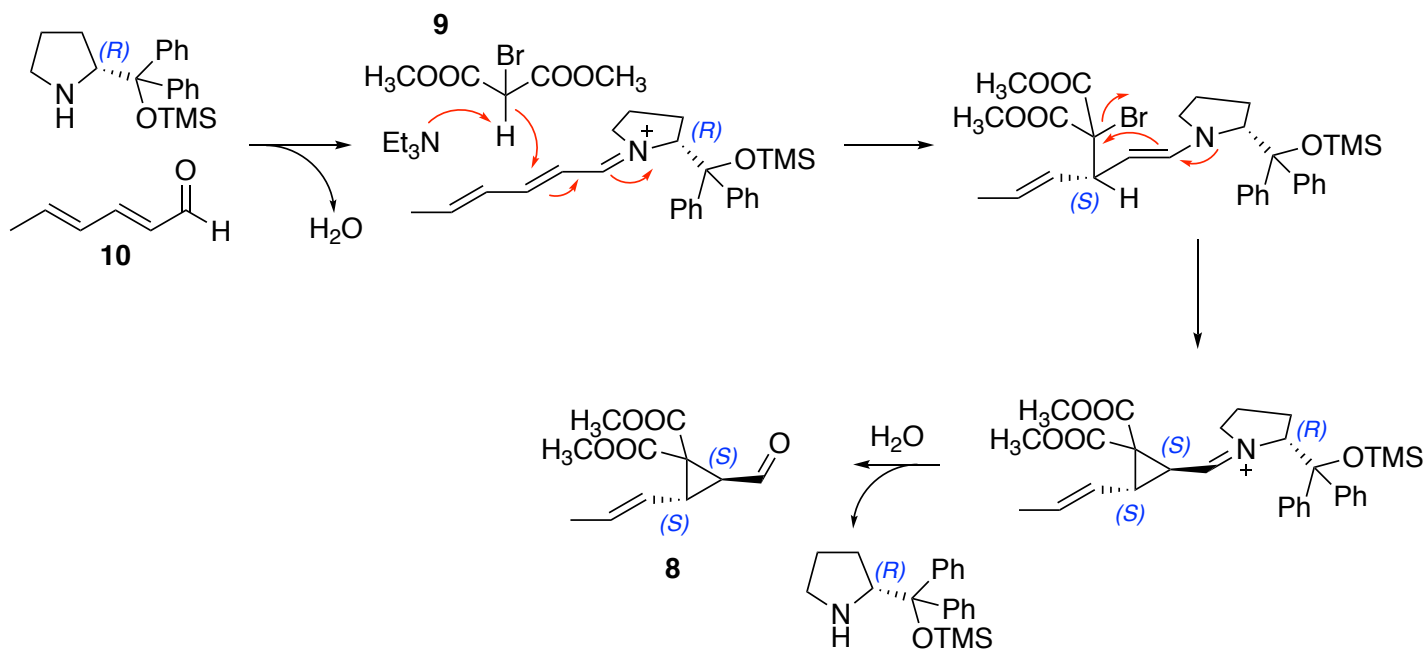
Eur. J. Org. Chem. **2013**, 8307–8314

Synthesis of building block 4



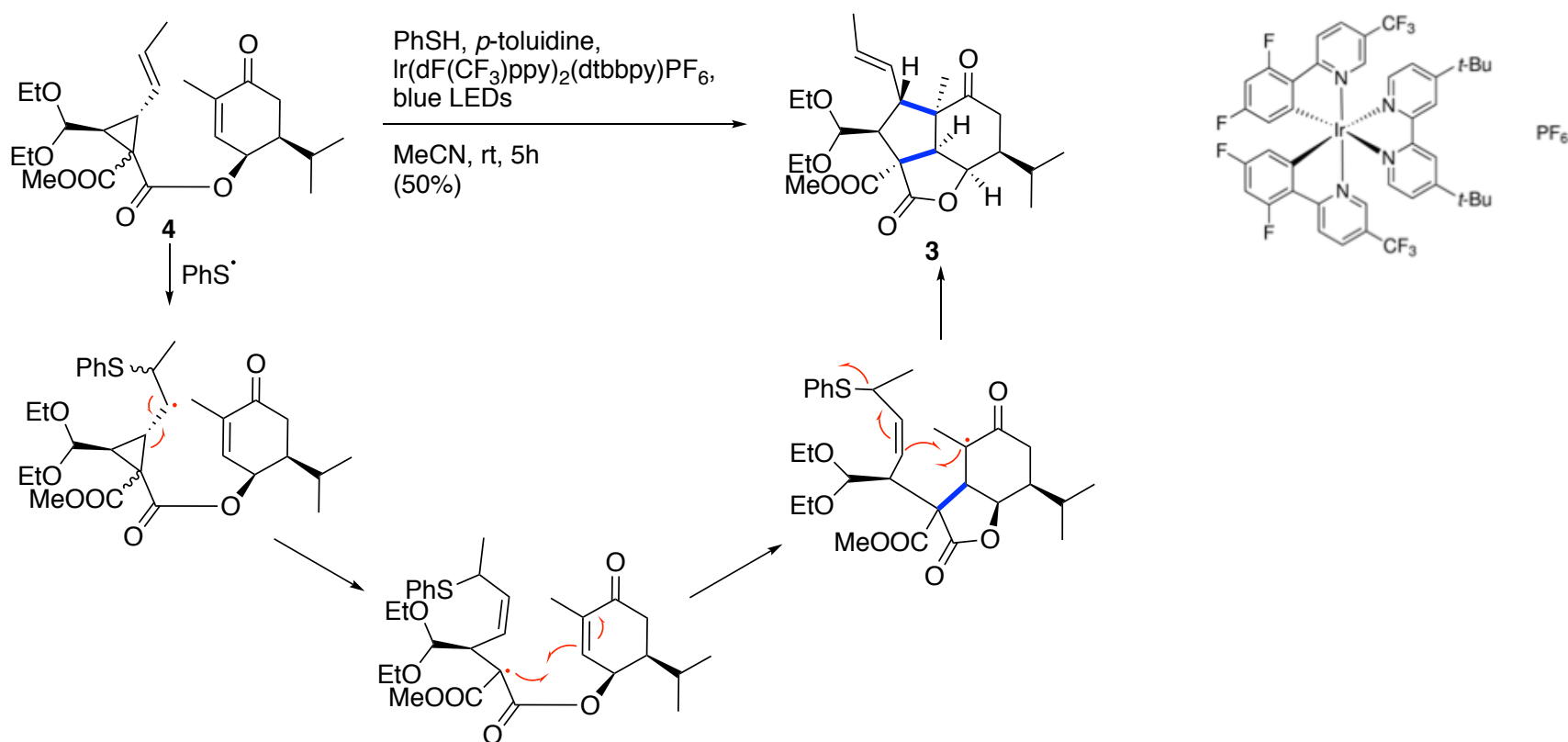
Explanation

> enantioselective cyclopropanation

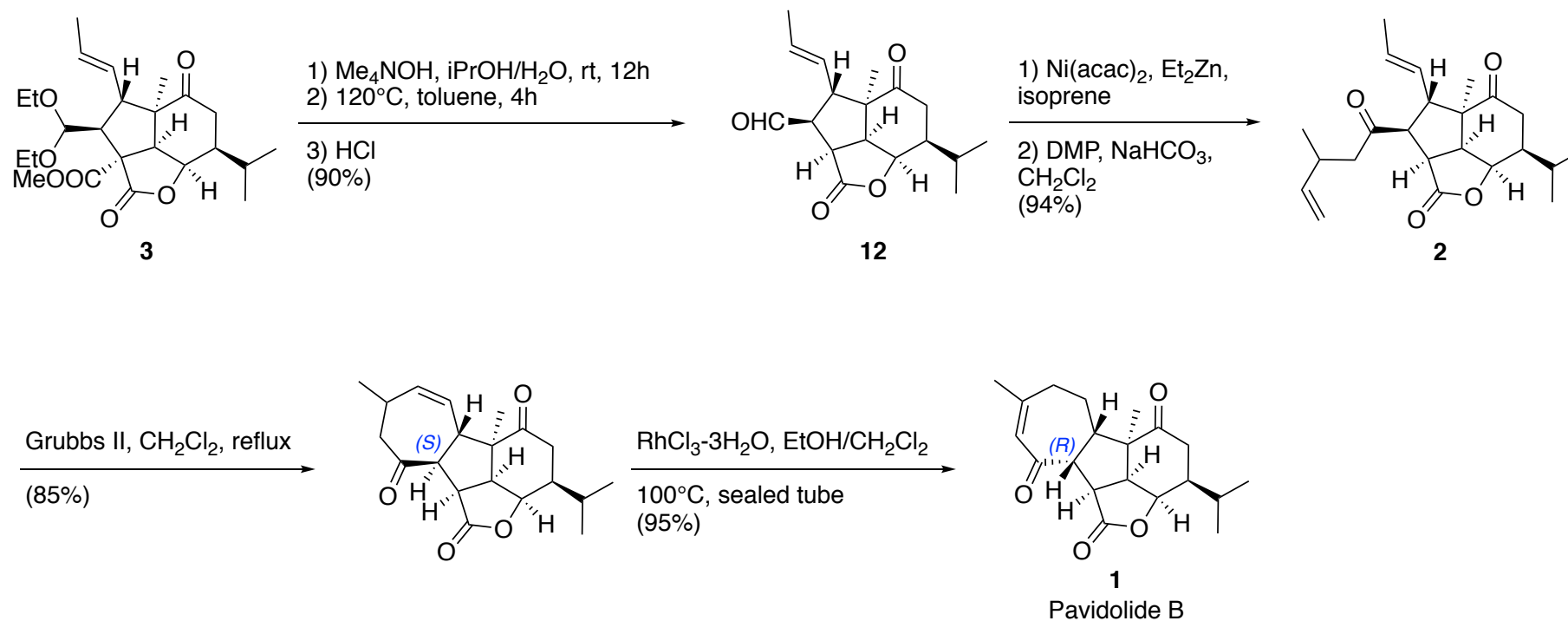


The key step

> annulation of vinylcyclopropane

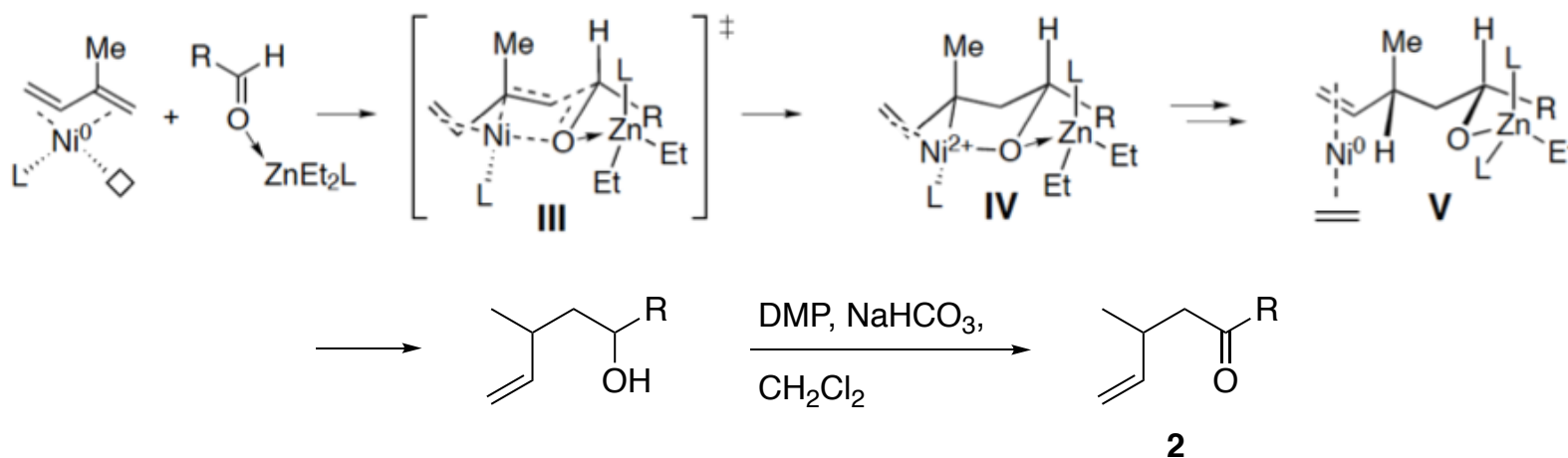


Completing the synthesis



Explanation

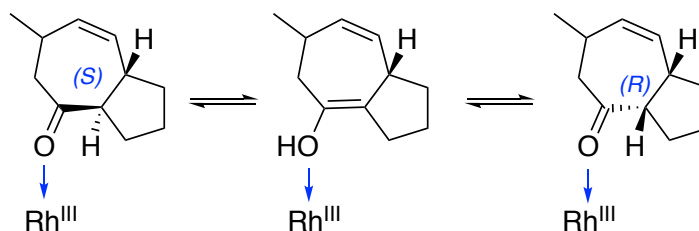
- > homoallylation from saturated dienes using Et₂Zn
- > Hydroxylation takes place at the more substituted side of the diene (more e⁻-rich).



- > No control of stereochemistry needed in the total synthesis

Explanation

- > Rh catalysed isomerisation (cis is more stable)



- > Mechanism of isomerisation to the more stable olefine is complex: migration about the ring with exchange of protons.
- > Migration only takes place in cyclic systems without quaternary carbon in between.

To sum up...

- > First enantioselective total synthesis of Pavidolide B
- > No new reactivity/method but efficient route
- > 10 linear steps with overall yield of 16%
- > In the key step, 2 C-C bonds were formed to build a system of 3 fused rings and 4 stereocenters (one of them quaternary)
- > All steps were multi-gram scaleable with reproducible & high yields.