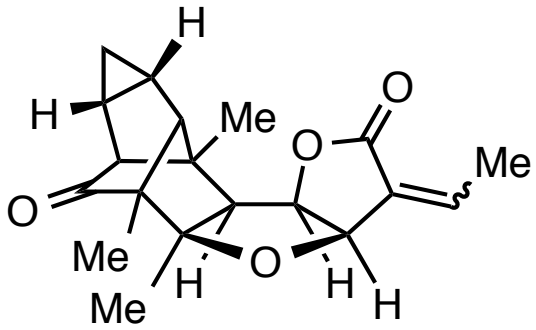
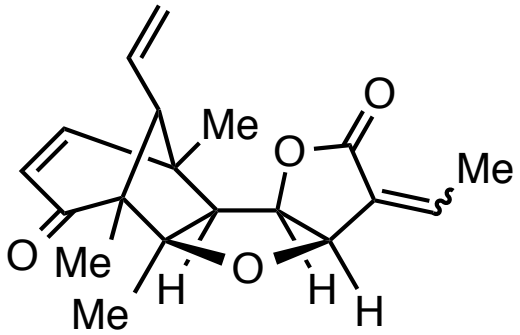
New Access to Pallambins



pallambin A : *(Z)*
pallambin B : *(E)*



pallambin C : *(Z)*
pallambin D : *(E)*

L. P. Martinez, S. Umemiya, S. E. Wengryniuk, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 7536–7539.

Valentin Soulard - Group Renaud
Journal Club – 29.06.17

UNIVERSITÄT BERN

Phil S. Baran

> B.S. with Honors in Chemistry, New York University (1997)

> Ph.D. with Prof. K.C. Nicolaou, The Scripps Research Institute (2001)

> Postdoctoral with Prof. E.J. Corey, Harvard University (2003)

> Associate professor, Scripps (2007)

> Full professor, Scripps (since 2008)

> More than 130 papers and several patents (39 years old)

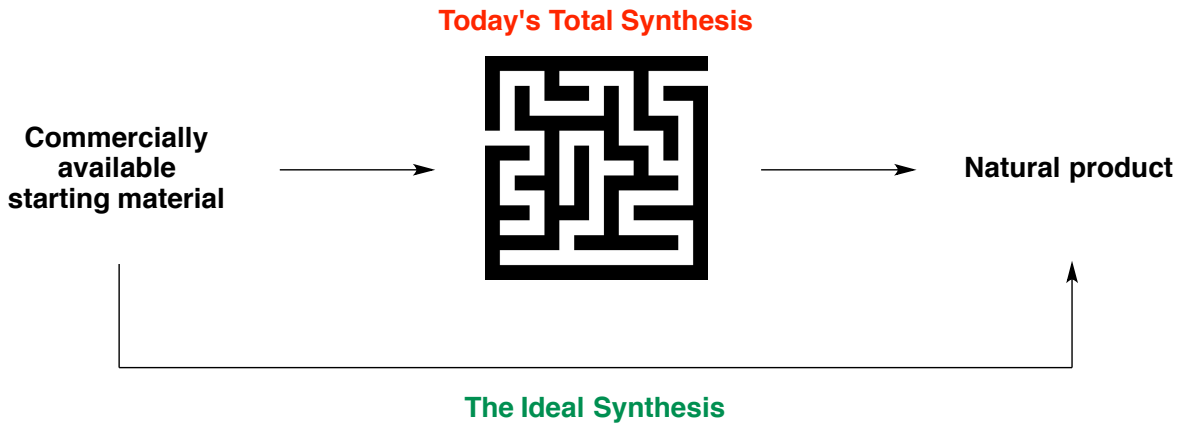
> Focus on synthesizing complex organic compounds, the development of new reactions, and the development of new reagents.

THE SCRIPPS RESEARCH INSTITUTE®

http://www.scripps.edu/baran/images/CV-PSB-07-07-16.pdf

Phil S. Baran

> Aiming for the Ideal Synthesis



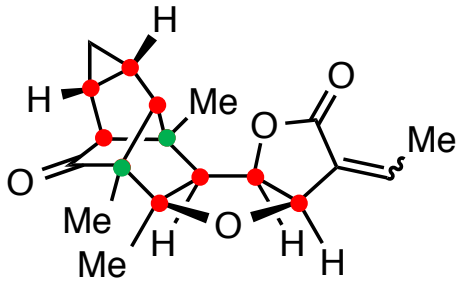
Ideal Synthesis : "...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality." - Hendrickson (1975)

T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657–4673.
J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**.

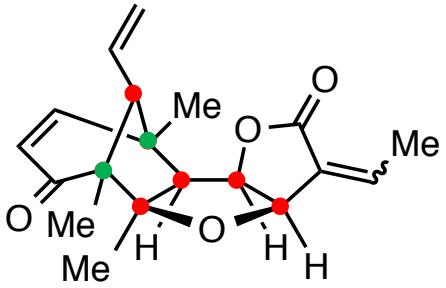
Pallambins C and D

> Pallambins A-D : isolated from the epilithic liverwort *Pallavicinia ambigua*

> No significant bioactivity but extraordinary chemical architectures



pallambin A : *(Z)*
pallambin B : *(E)*



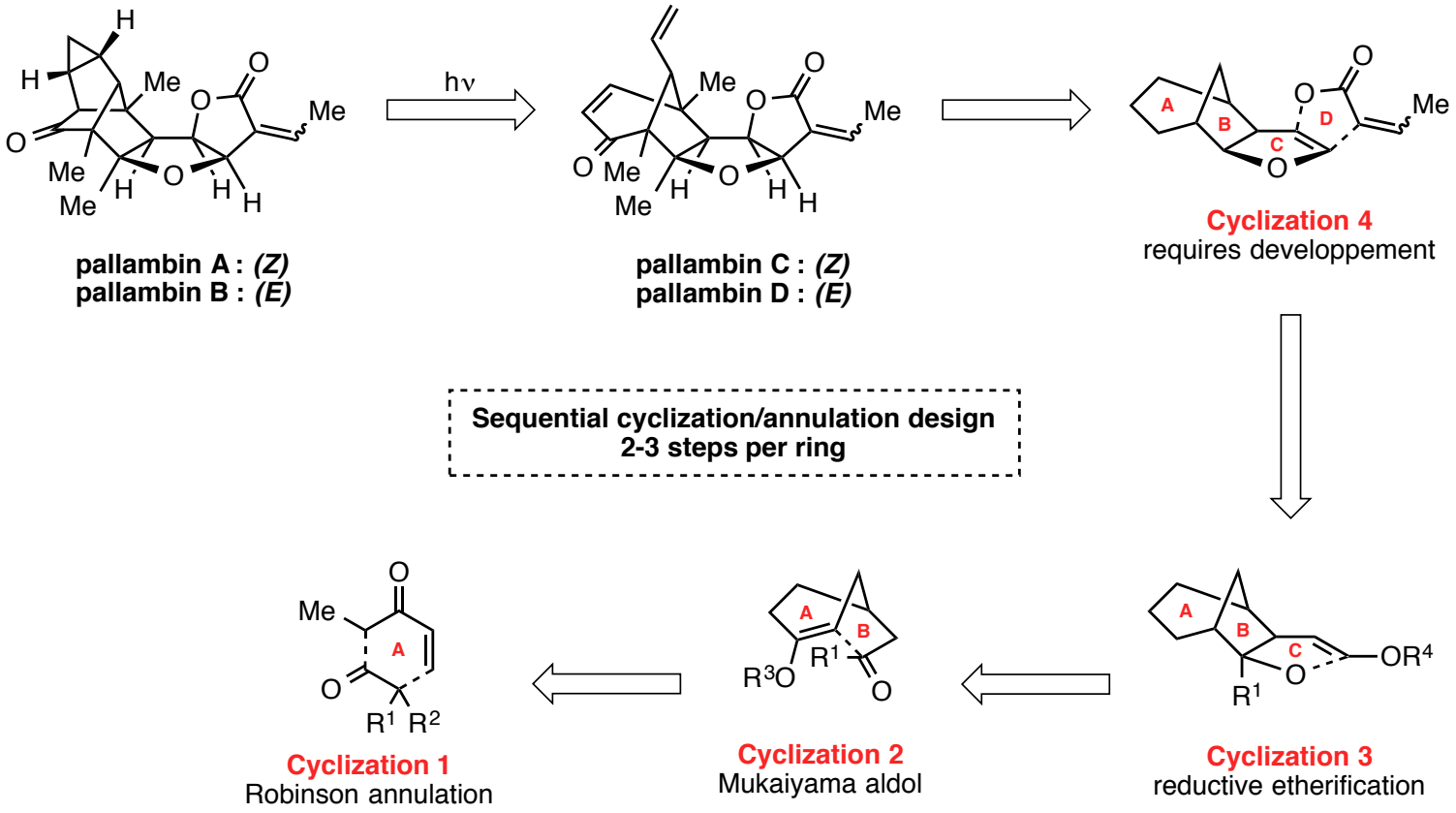
pallambin C : *(Z)*
pallambin D : *(E)*

> Two synthesis of Palambins have been developped :

- Carreira (ETHZ, 2015) – pallambins A and B in 23 steps
- Wong (Hong Kong, 2012)– pallambins C and D in 38 steps

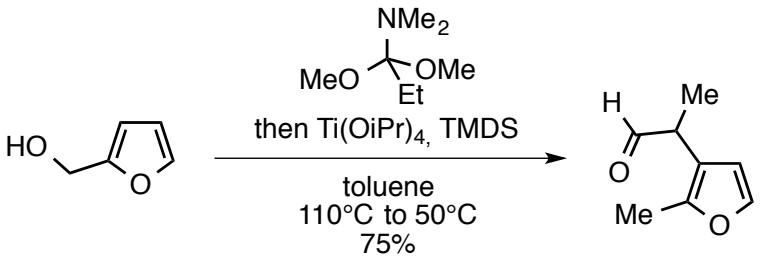
C. Ebner, E. M. Carreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 11227–11230.
X.-S. Xu, Z.-W. Li, Y.-J. Zhang, X.-S. Peng, H. N. C. Wong, *Chem. Commun* **2012**, *48*, 8517–3.

Retrosynthetic Analysis

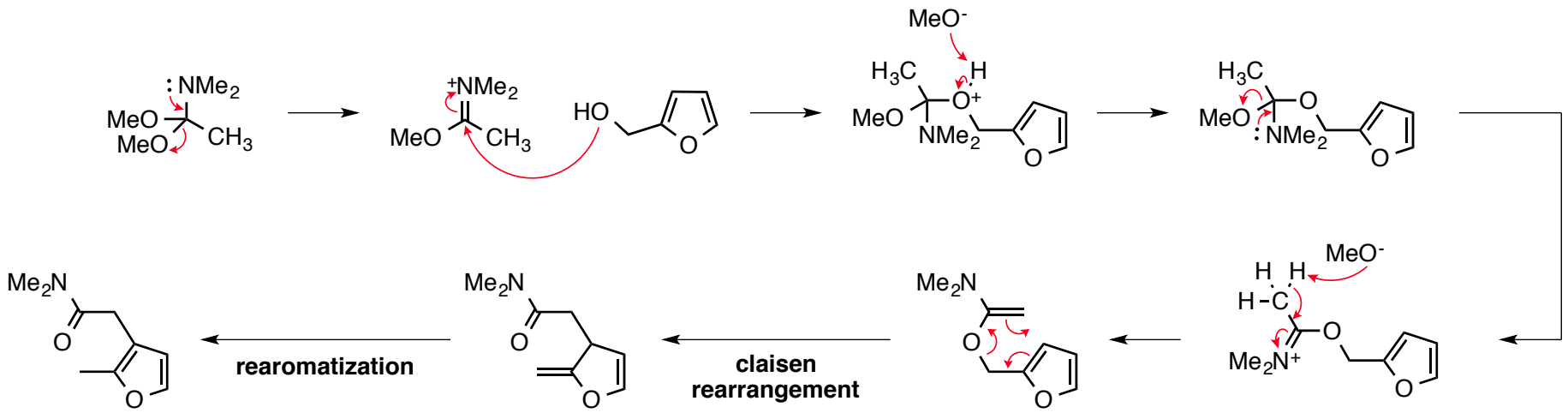


Zhang, J.-Z.; Zhu, R.-X.; Li, G.; Wang, L.-N.; Sun, B.; Chen, W.- F.; Liu, L.; Lou, H.-X. Org. Lett. 2012, 14, 5624.
Wang, L.-N.; Zhang, J.-Z.; Li, X.; Wang, X.-N.; Xie, C.-F.; Zhou, J.-C.; Lou, H.-X. Org. Lett. 2012, 14, 1102.

Total synthesis of Pallambins C and D

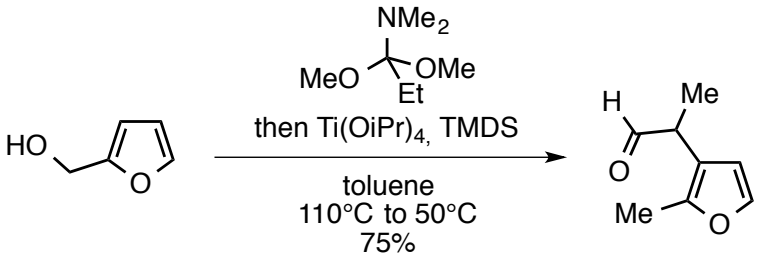


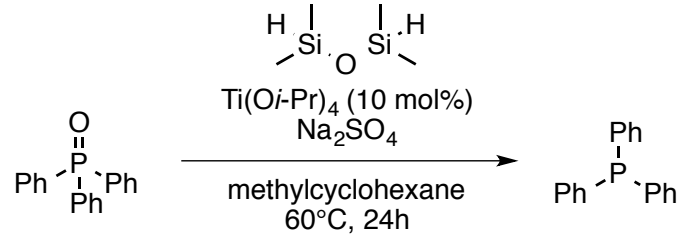
> Tandem Eschenmoser-Claisen Rearrangement



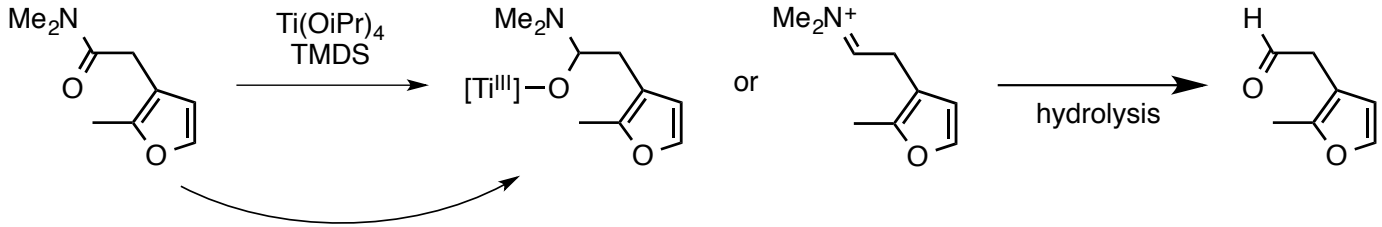
A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425–2429.

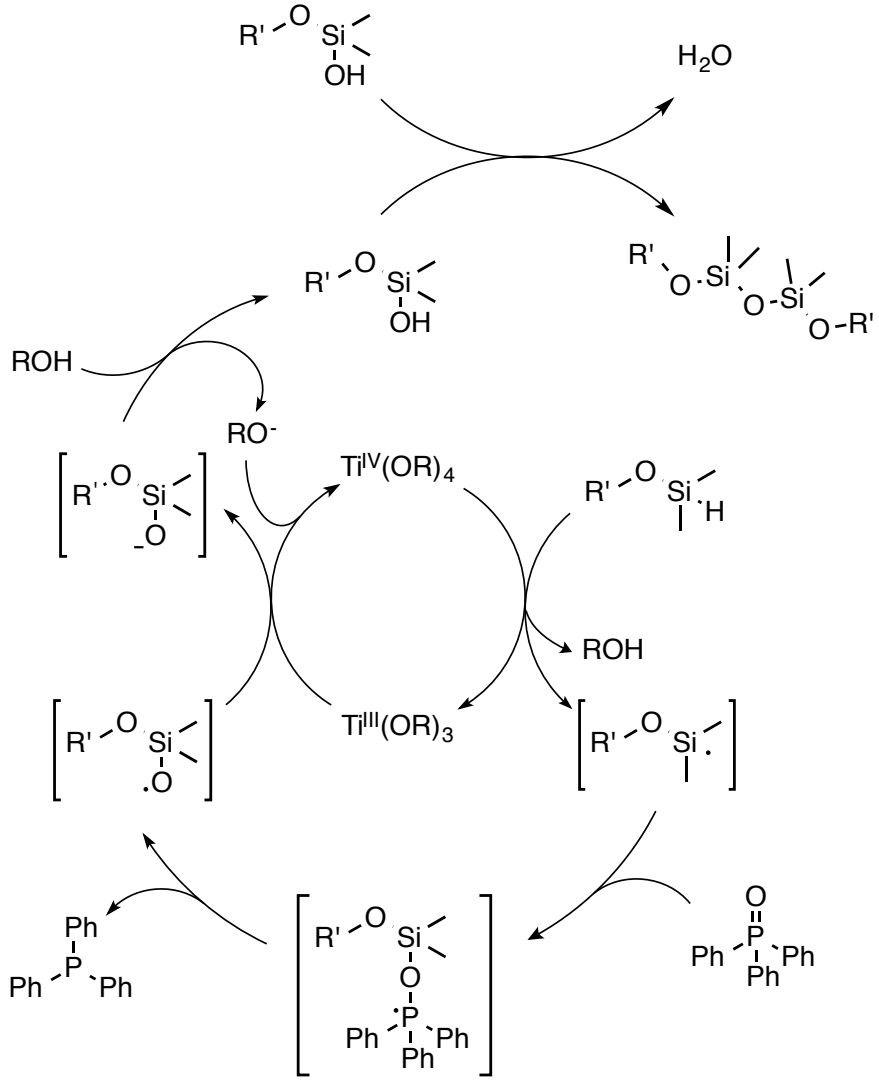
Total synthesis of Pallambins C and D





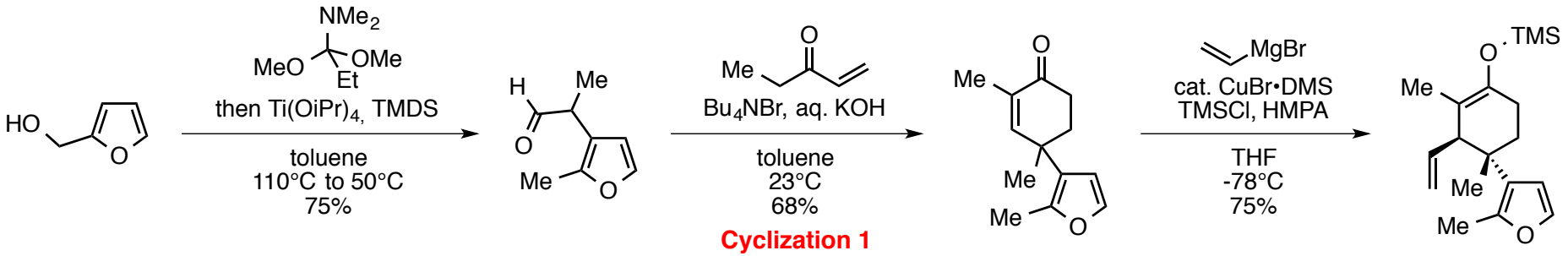
> Reduction of the Amide catalyzed by Titan



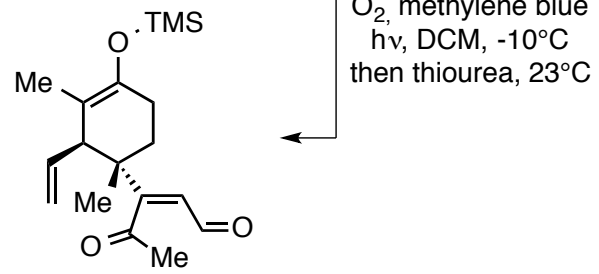


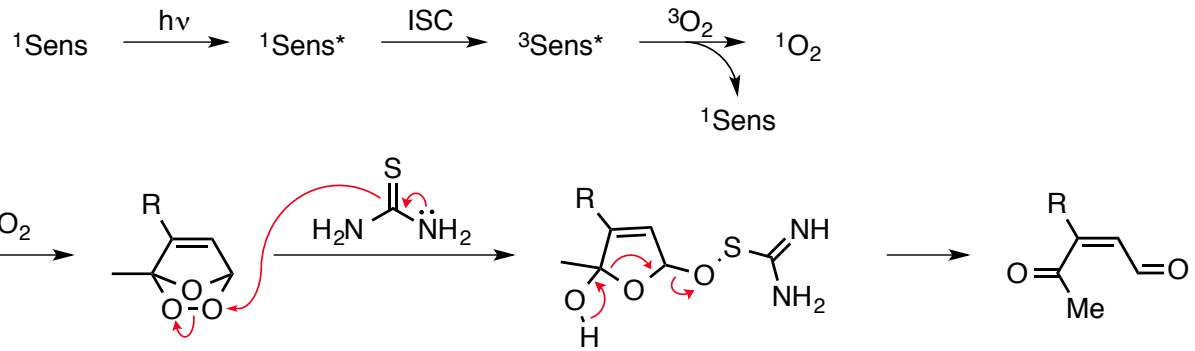
S. Laval, W. Dayoub, A. Favre-Réguillon, P. Demonchaux, G. Mignani, M. Lemaire, *Tetrahedron Letters* **2010**, *51*, 2092–2094.
C. Petit, A. Favre-Réguillon, B. L. Albela, L. Bonneviot, G. Mignani, M. Lemaire, *Organometallics* **2009**, *28*, 6379–6382.

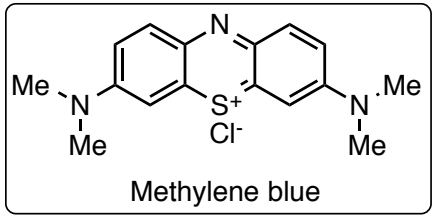
Total synthesis of Pallambins C and D



> Chemoselective Oxidative Scission of The Furan Heterocycle

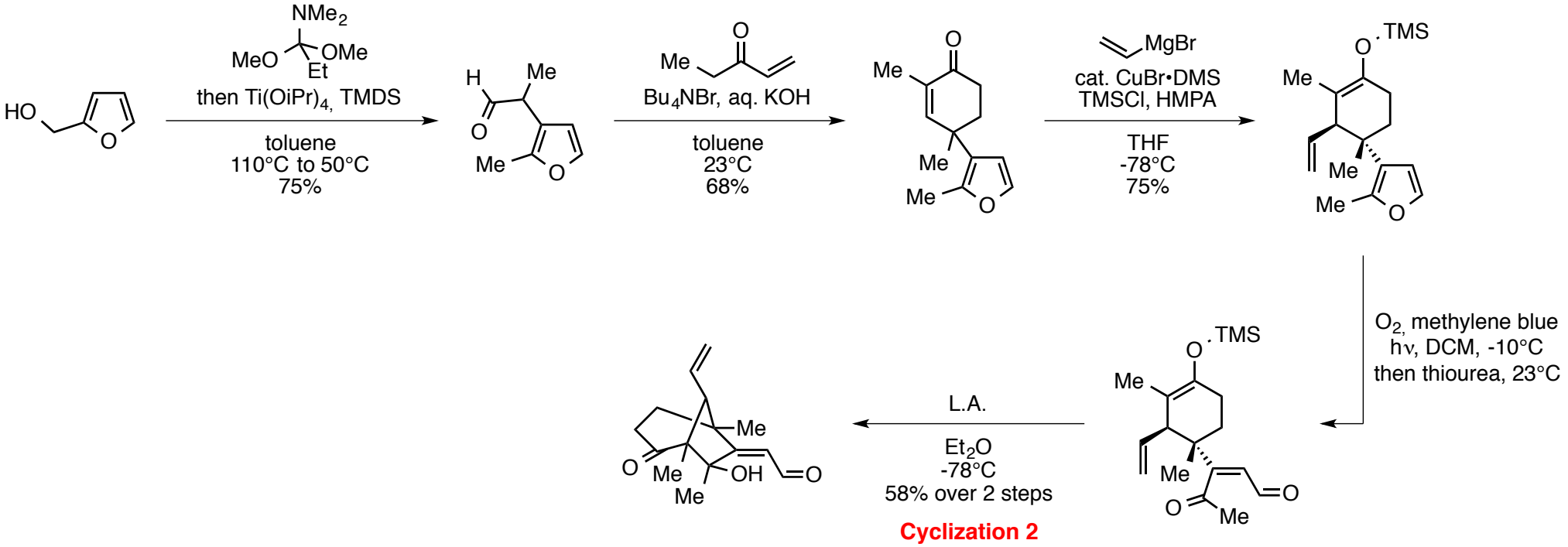




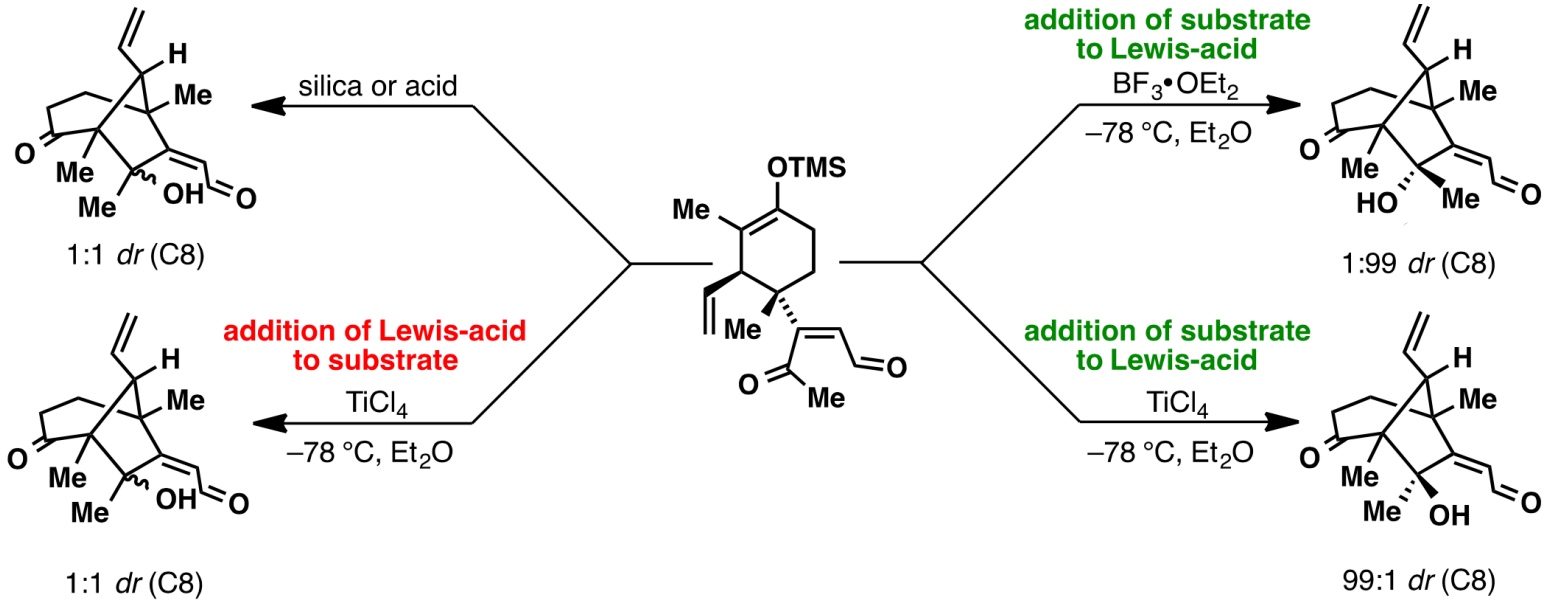


M. Iesce, F. Cermola, F. Temussi, *Current Organic Chemistry* **2005**, *9*, 109–139.

Total synthesis of Pallambins C and D

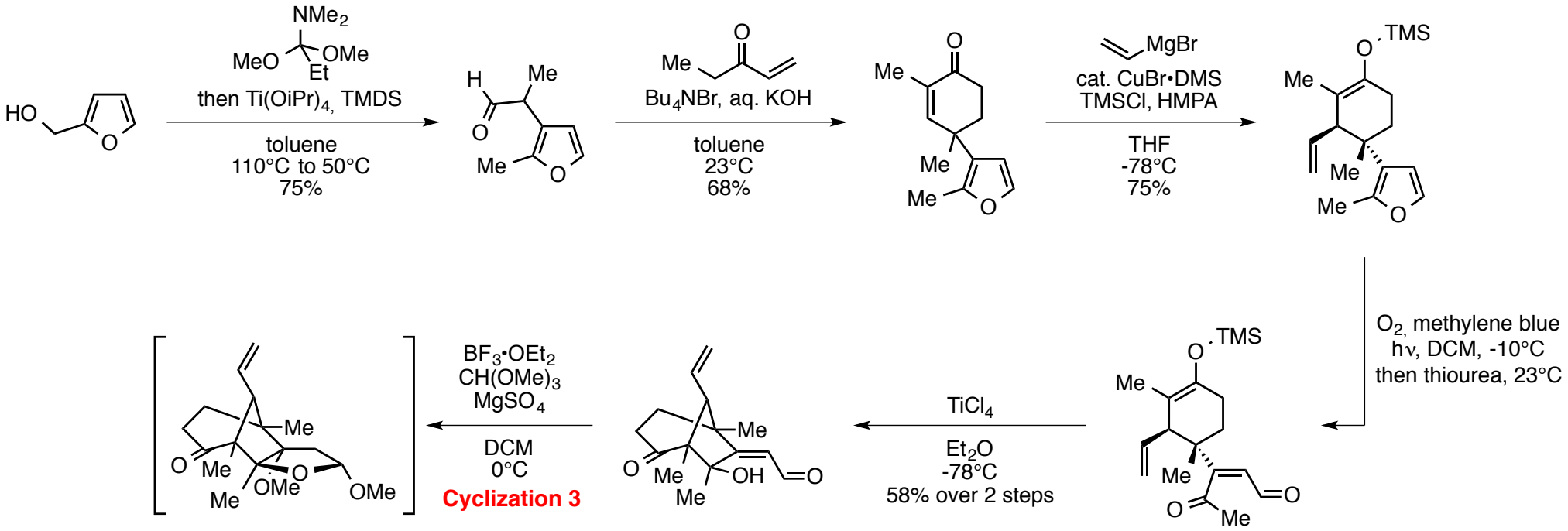


Mukayama-Aldol Reaction

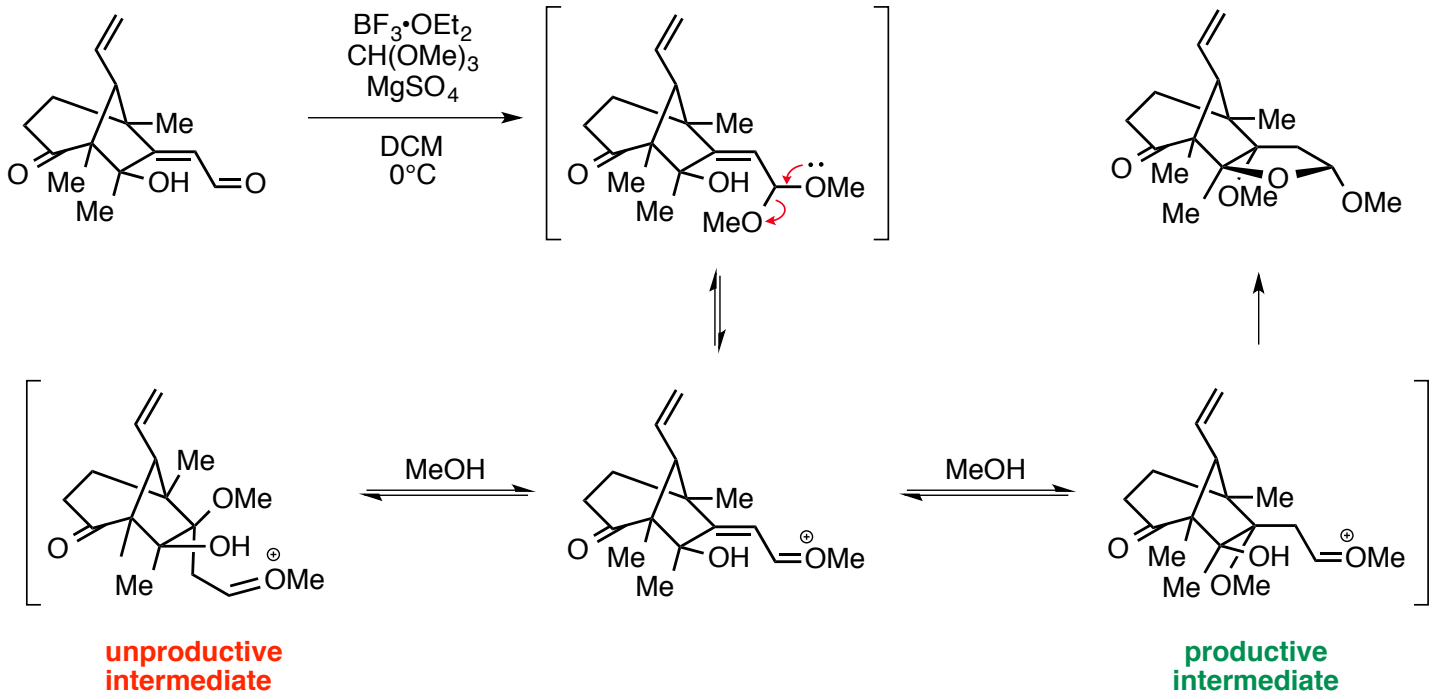


> Empirical discovery

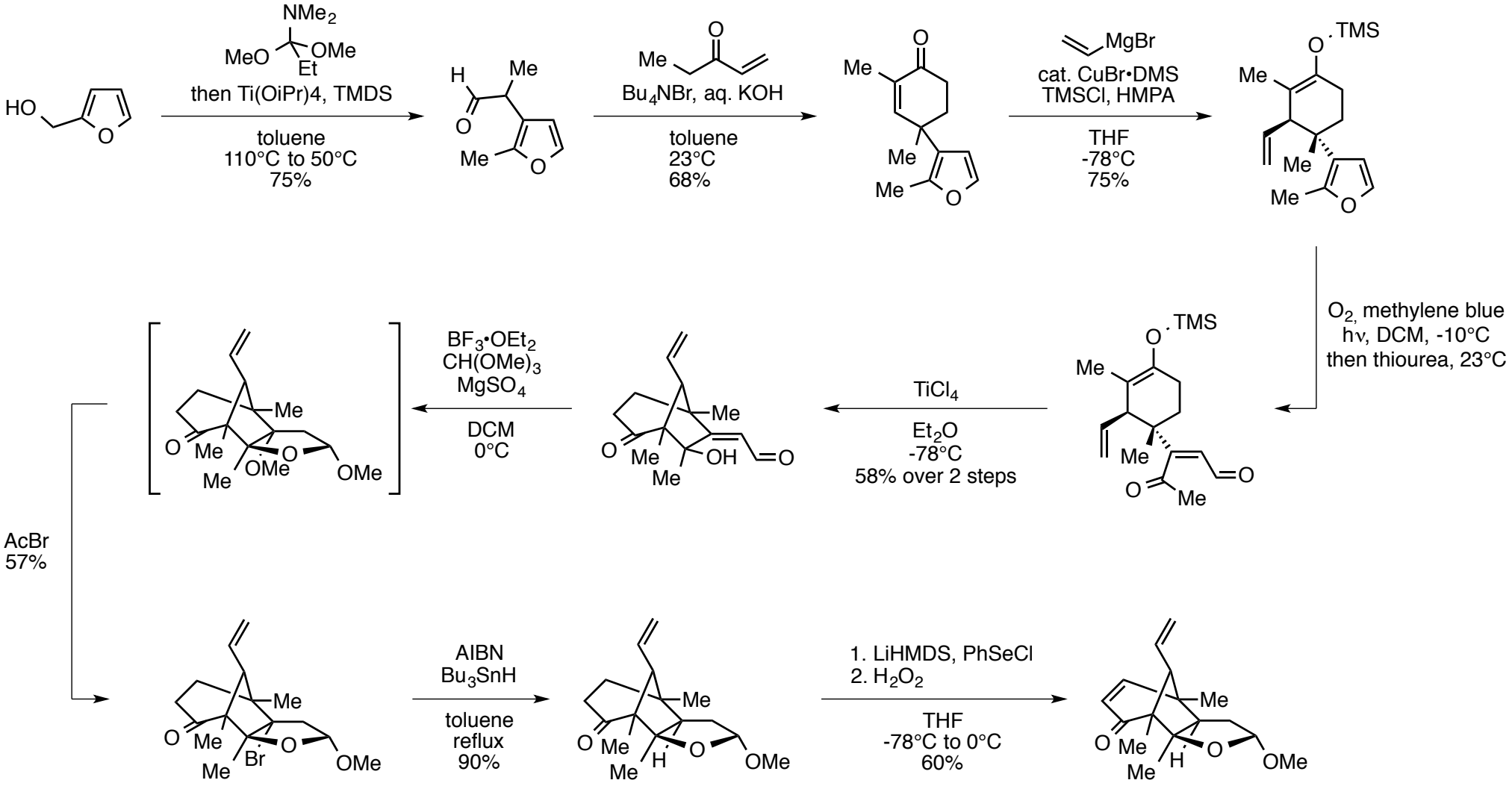
Total synthesis of Pallambins C and D



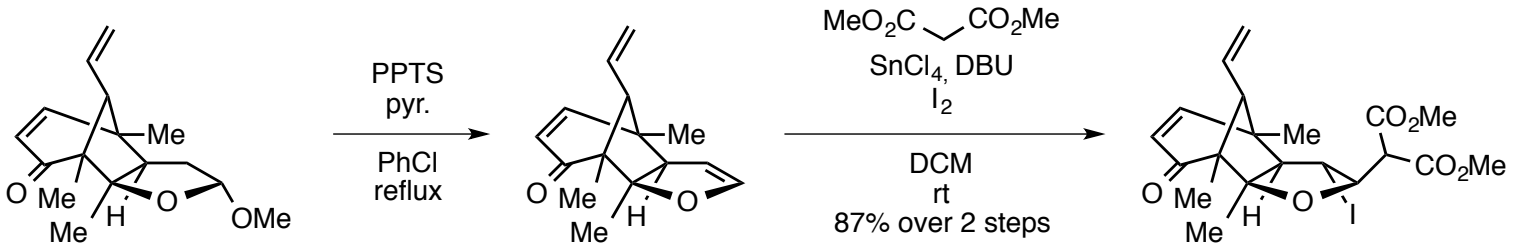
Mechanistic Model for C-ring Formation



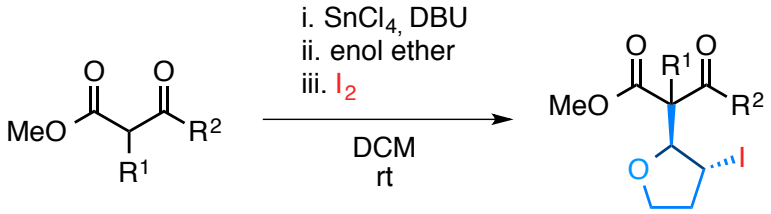
Total synthesis of Pallambins C and D

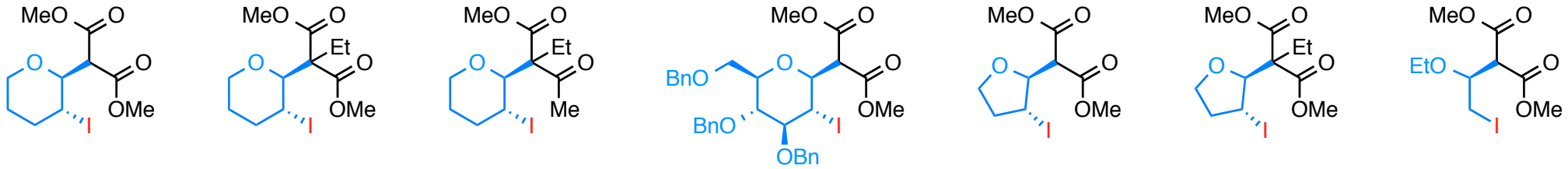


Total synthesis of Pallambins C and D



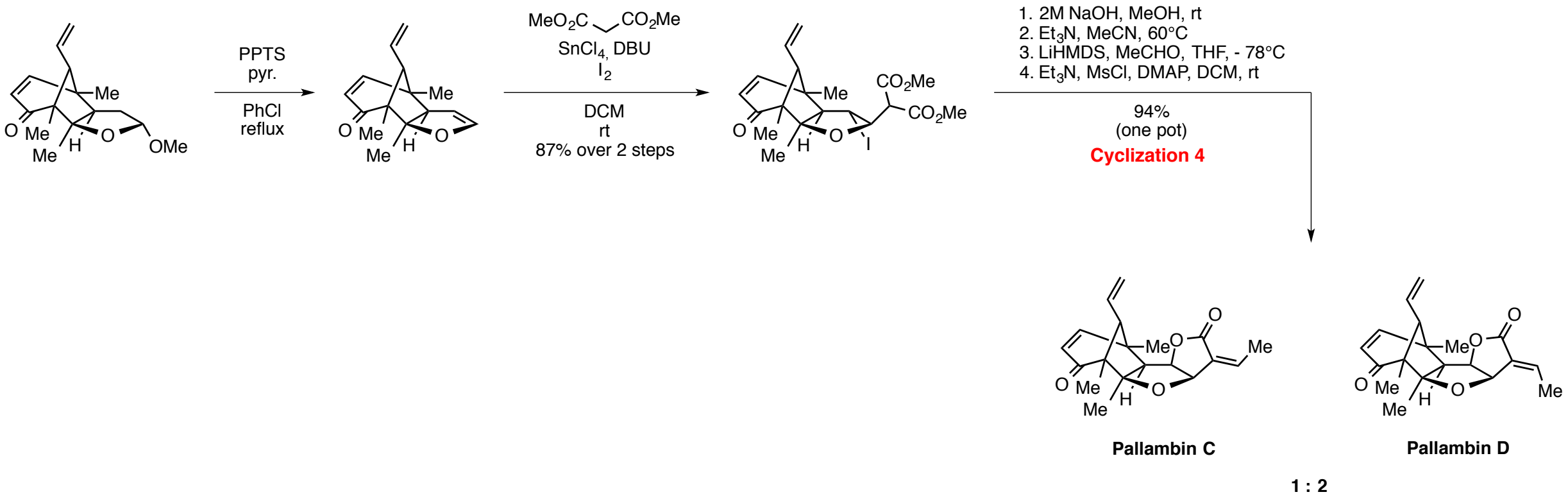
> Enol-Ether Difunctionalization Reaction



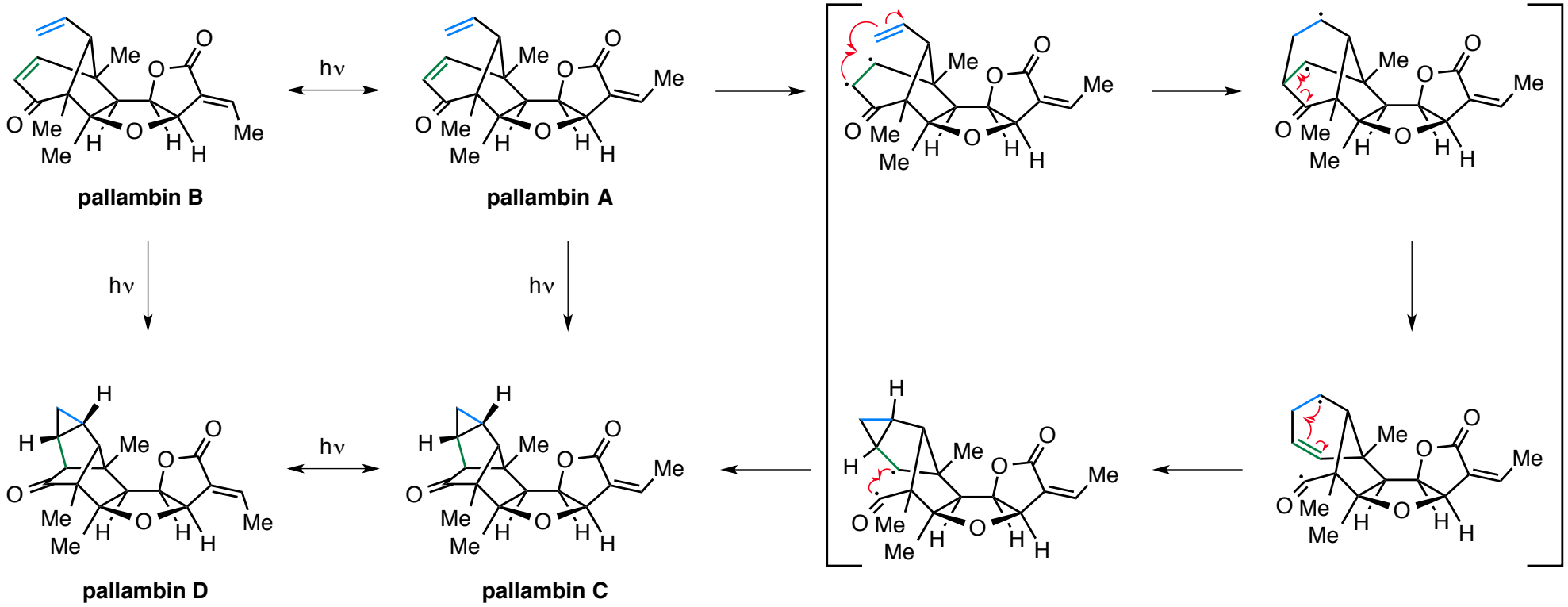


92% | 76% | 52% dr = 1 : 1 | 73% | 89% | 80% | 77%

Total synthesis of Pallambins C and D

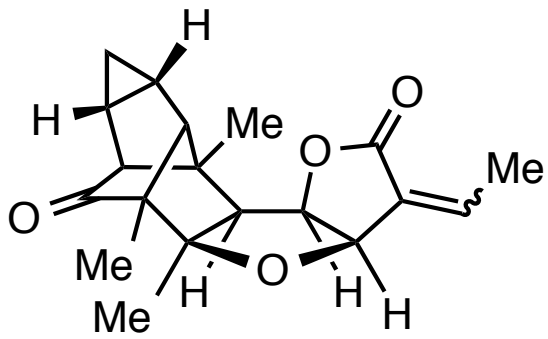


Interconversion of the Pallambins through Photoinduced Rearrangement

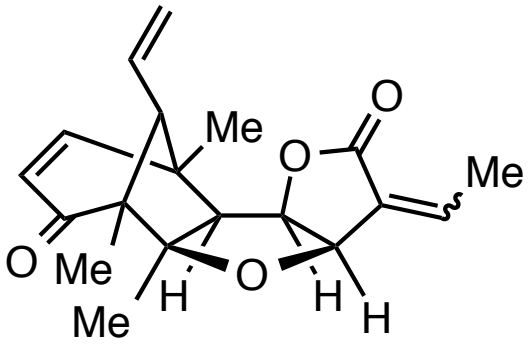


J.-Z. Zhang, R.-X. Zhu, G. Li, L.-N. Wang, B. Sun, W.-F. Chen, L. Liu, H.-X. Lou, *Org. Lett.* **2012**, *14*, 5624–5627.

Conclusion



pallambin A : *(Z)*
pallambin B : *(E)*



pallambin C : *(Z)*
pallambin D : *(E)*

> Concise synthesis

> 5.6% overall yield for 11 steps

> No protecting group manipulation

> « In fact, of the 11 discrete steps of this synthesis, only two are nonstrategic (steps 7 and 9), making it 81% ideal. » - Phil S. Baran

> Supporting information well detailed about the failed route and the evolution of the strategy.

> Access of to all the pallambins with an extra step.