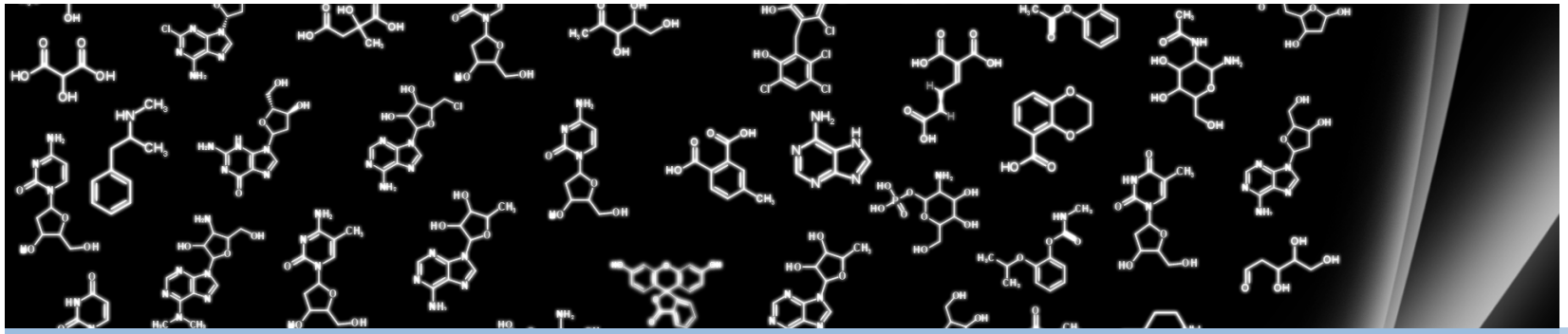

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# A Concise Synthesis of (+)-Artemisinin

Zhu, C.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 13577-13579

Manuel Gnägi
Department of Chemistry and Biochemistry
University of Bern
Journal Club Group Renaud

# **Silas P. Cook** (Indiana University)

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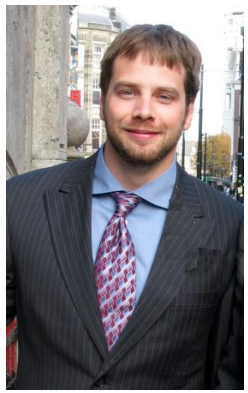
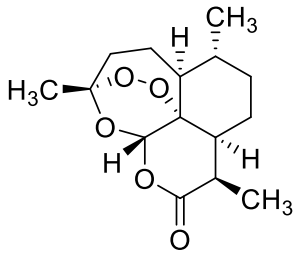


- B.A at Reed College, Portland OR (1999)
- PhD at Prof. S. J. Danishefsky
  (Columbia University, New York, 2001-2006)
- Postdoc at Prof E. Jacobsen
  (Harvard University, 2006-2009)
- Professor at the Indiana University, 2009 – present

- Research:
  - Total synthesis of molecules with biological activity in oncology, anti-infectives, neurological disorders and Third World Ailments
  - Catalysis: Wide range, focus on “green catalysis” e.g. iron

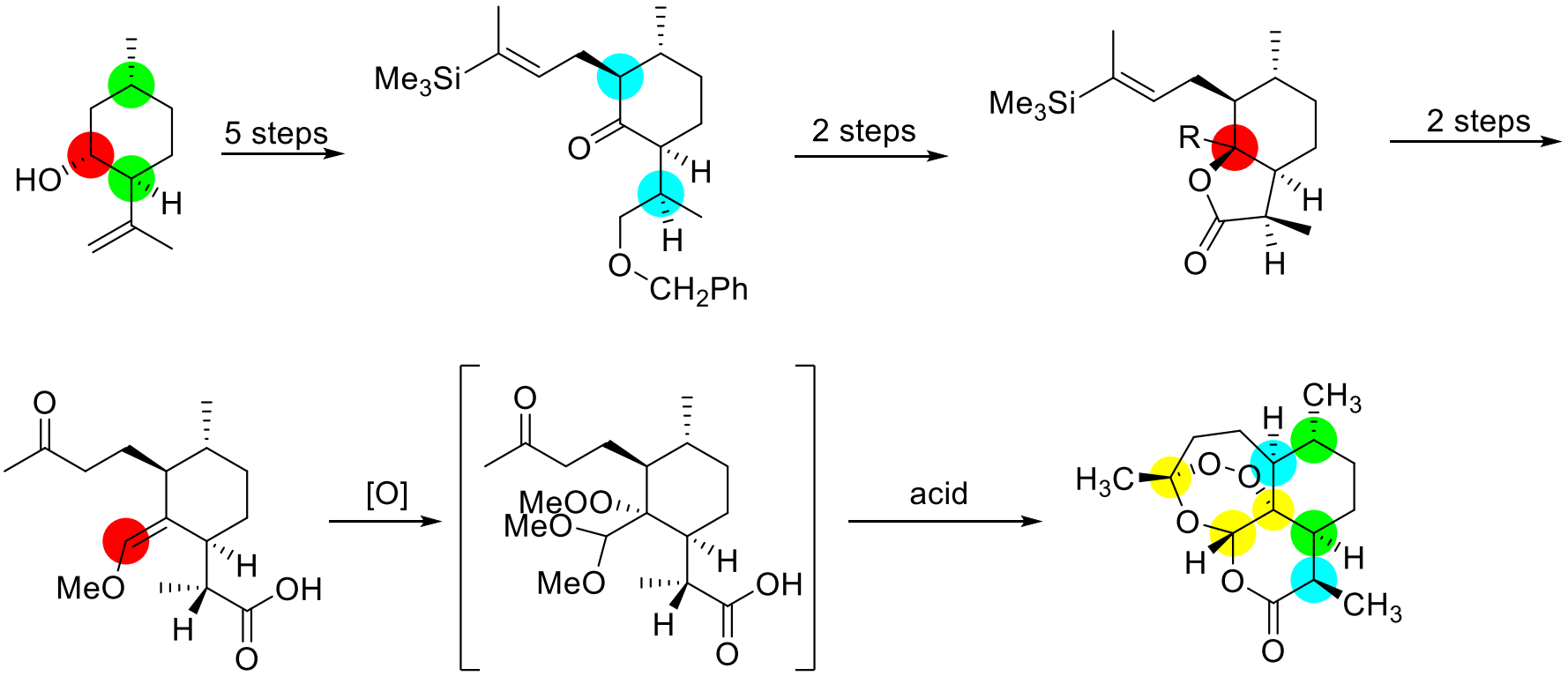
# (+) - Artemisinin




- Currently, the most effective treatment against Malaria-causing *Plasmodium* parasites is an artemisinin-based combination therapy
- Malaria affects over 200 million people each year, around one million dies
- Artemisinin is currently obtained by extraction or semi-synthesis, but too expensive
- Previous total-syntheses start from expensive terpene-based materials.

*World Malaria Report 2011;* World Health Organization, Geneva, **2011**

# La-Roche synthesis

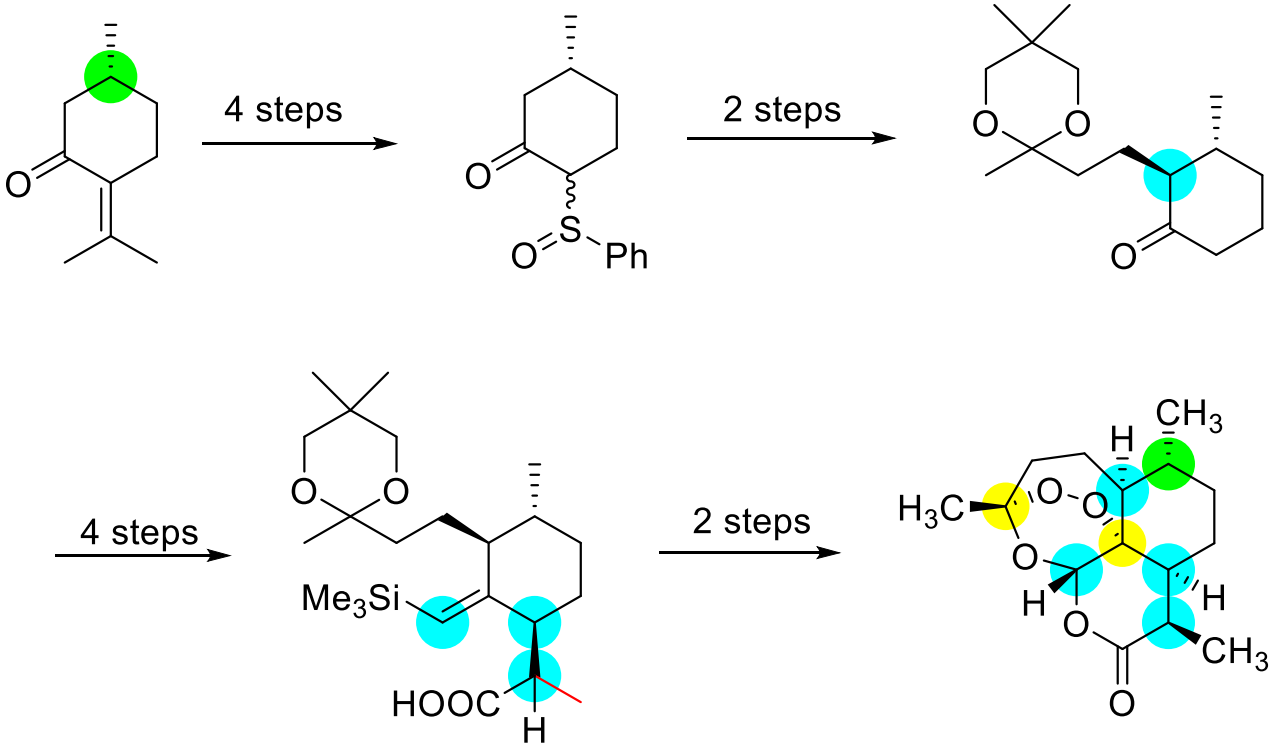



source of stereocenter

bought during the synthesis destroyed afterwards last two steps

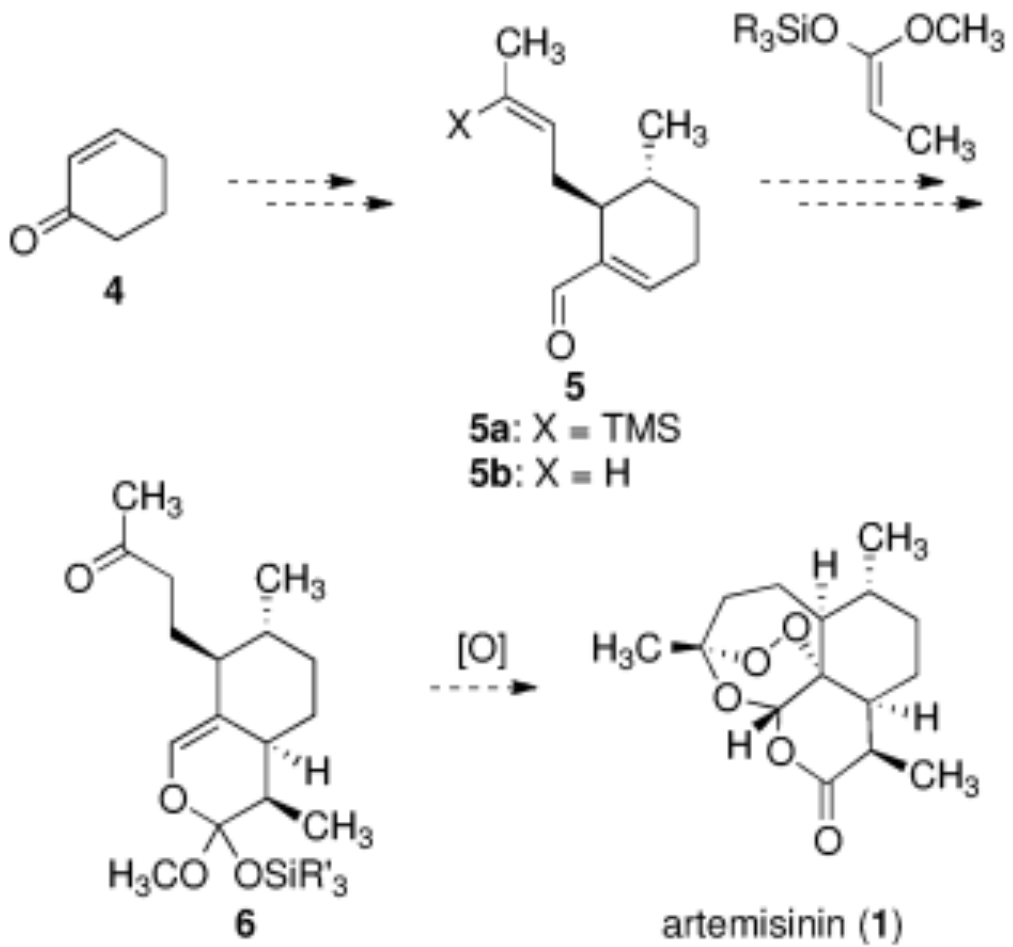
Schmid, G., Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105,* 624-625

# Jennings-White synthesis

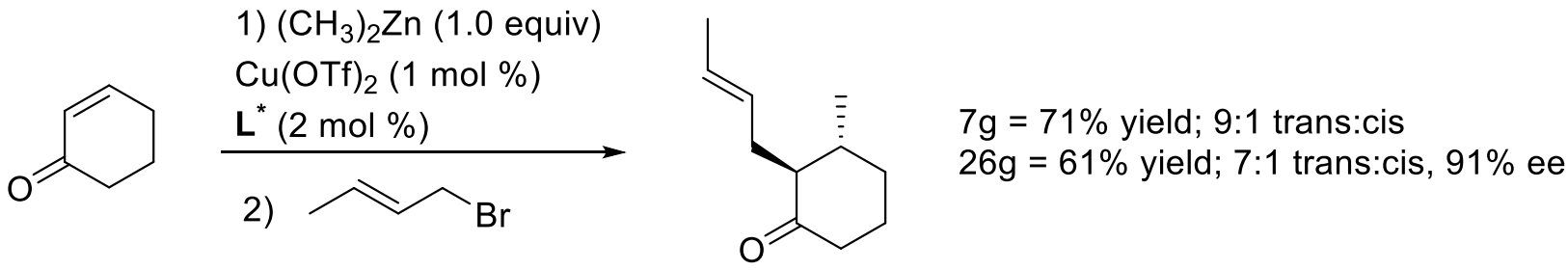



Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114,* 974-979

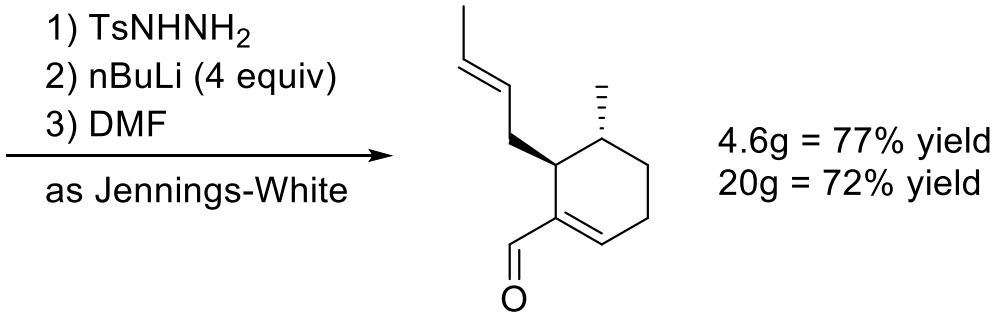
# Retrosynthetic plan



# Forward synthesis I

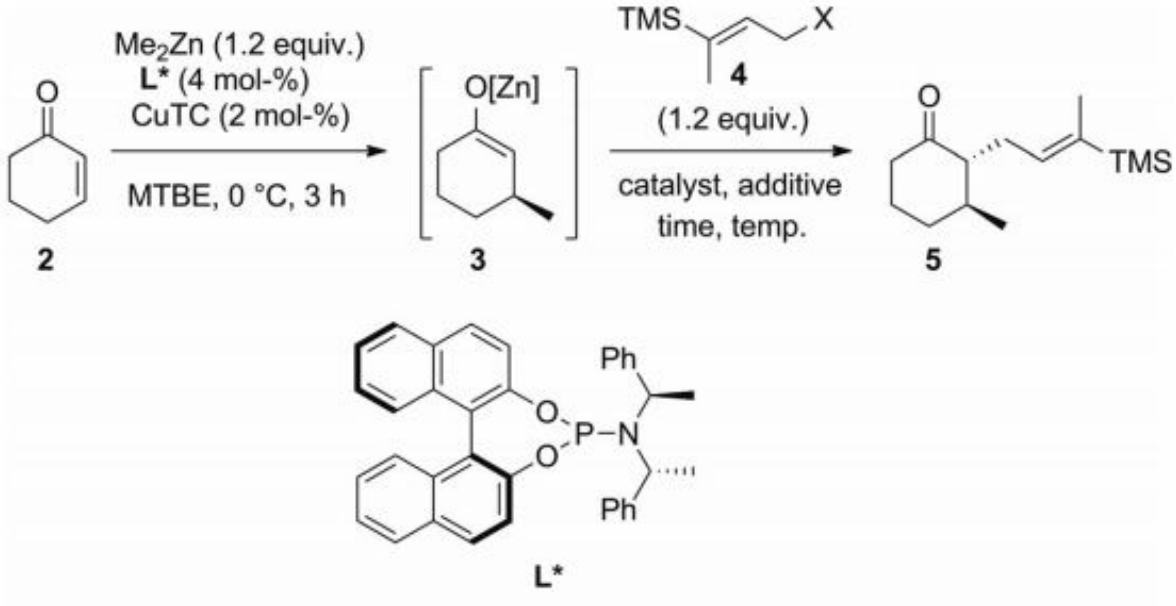



7g = 71% yield; 9:1 trans:cis
26g = 61% yield; 7:1 trans:cis, 91% ee




4.6g = 77% yield
20g = 72% yield

# Mechanism of cyclohexanone functionalization




The yield was improved from 26% to 80% by switching to toluene, bringing zinc-enolates back in the game

Jarugumilli, G. K.; Zhu, C.; Cook, S. P. *Eur. J. Org. Chem.* **2012**, 1712-1715

# Forward synthesis II

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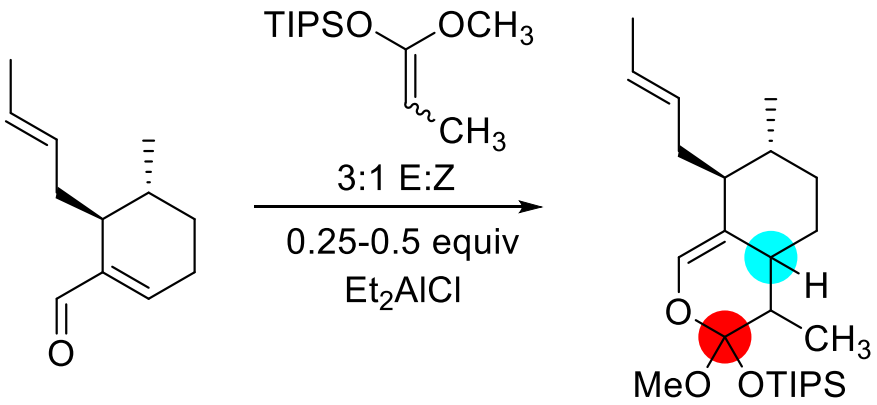
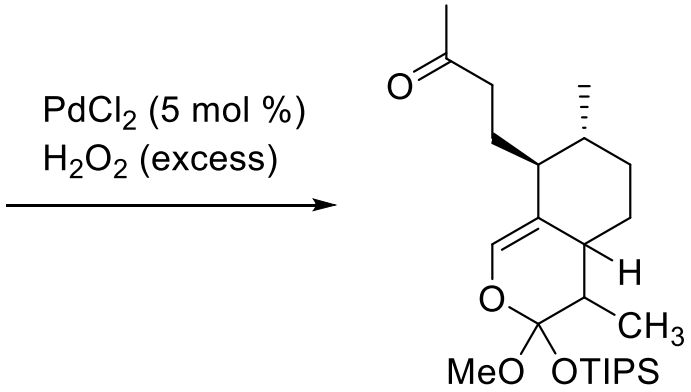
- Unusual [4+2] reaction for the installation of the lactone ring




1.8g = 95% yield; 6/2/1/1 dr
47g = >98% yield; 10/4/1/1 dr

"2 of 3 centers are irrelevant for the synthesis"
The center with the proton is probably fully controlled




9.4g = 61% yield
(31% ethyl ketone)

# Mechanism of the [4+2] - I

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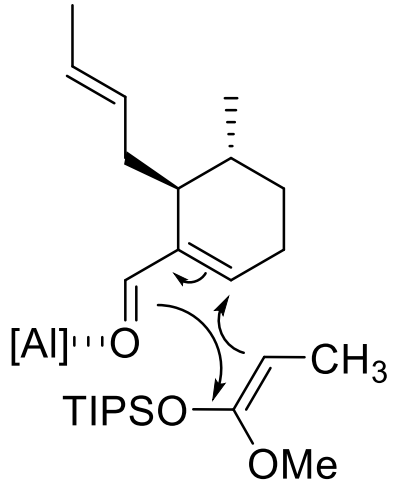
- Looks like a simple [4+2] mechanism, what could go wrong?



# Mechanism of the [4+2] - II

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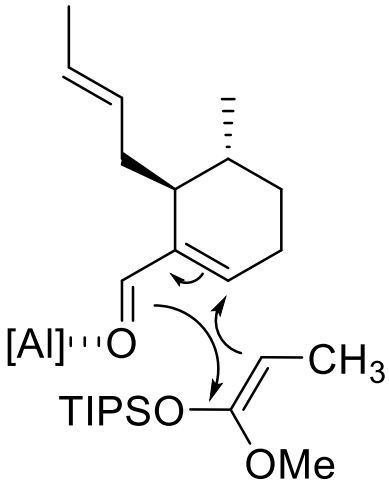
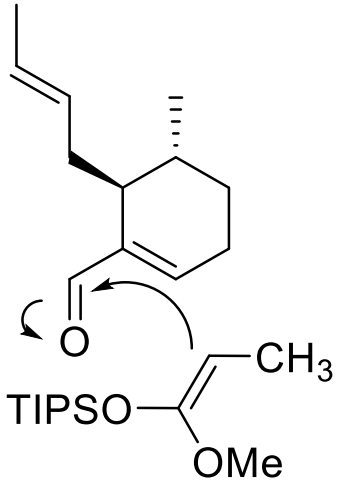
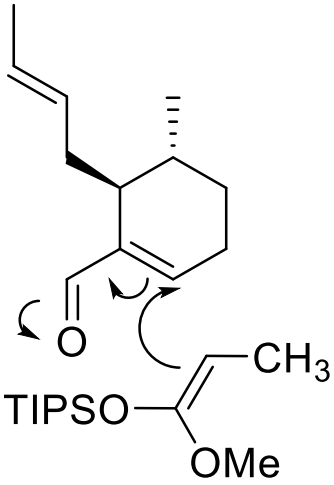
- Possible side reactions



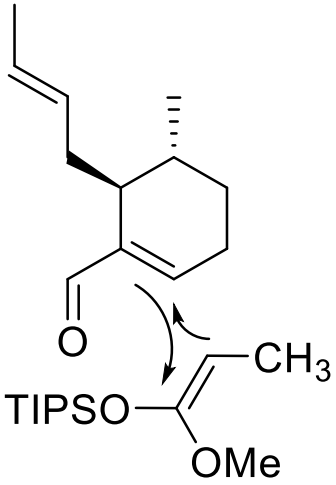

[4+2]




Mukaiyama Aldol




Mukaiyama Michael




[2+2]

# Forward synthesis III

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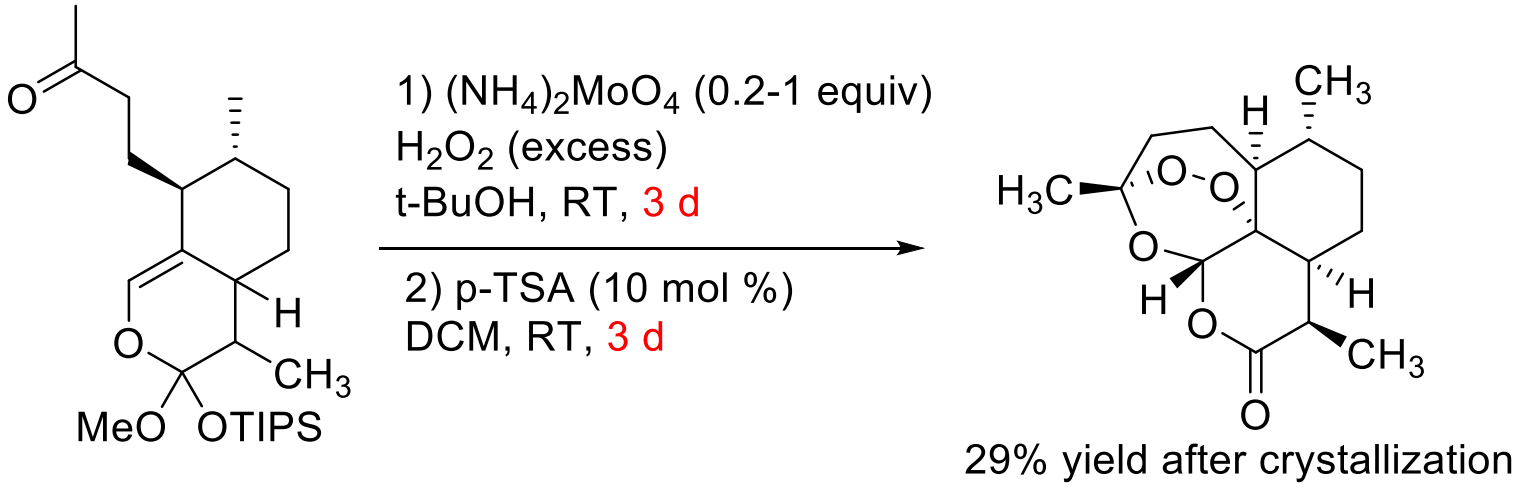
- The usual steps to complete the molecule




$$2H_2O_2 \xrightarrow{MoO_4^{2-}} 2H_2O + {}^1O_2$$

Nardello, V.; Marki, J.; Vermeersch, G.; Aubry, J. M . *Inorg. Chem.* **1995**, *34,* 4950-4957

# Mechanism/ Intermediates in the oxidation

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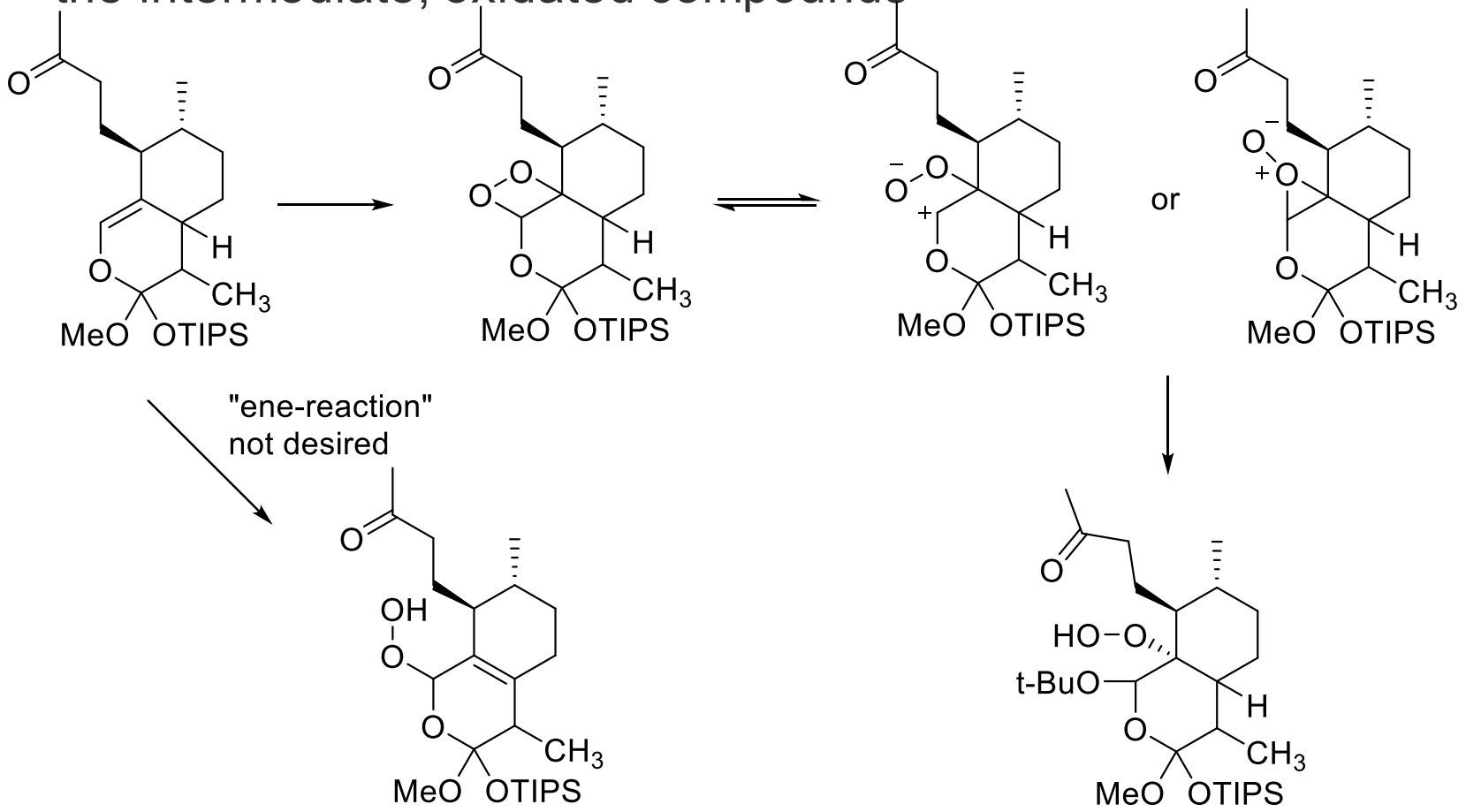
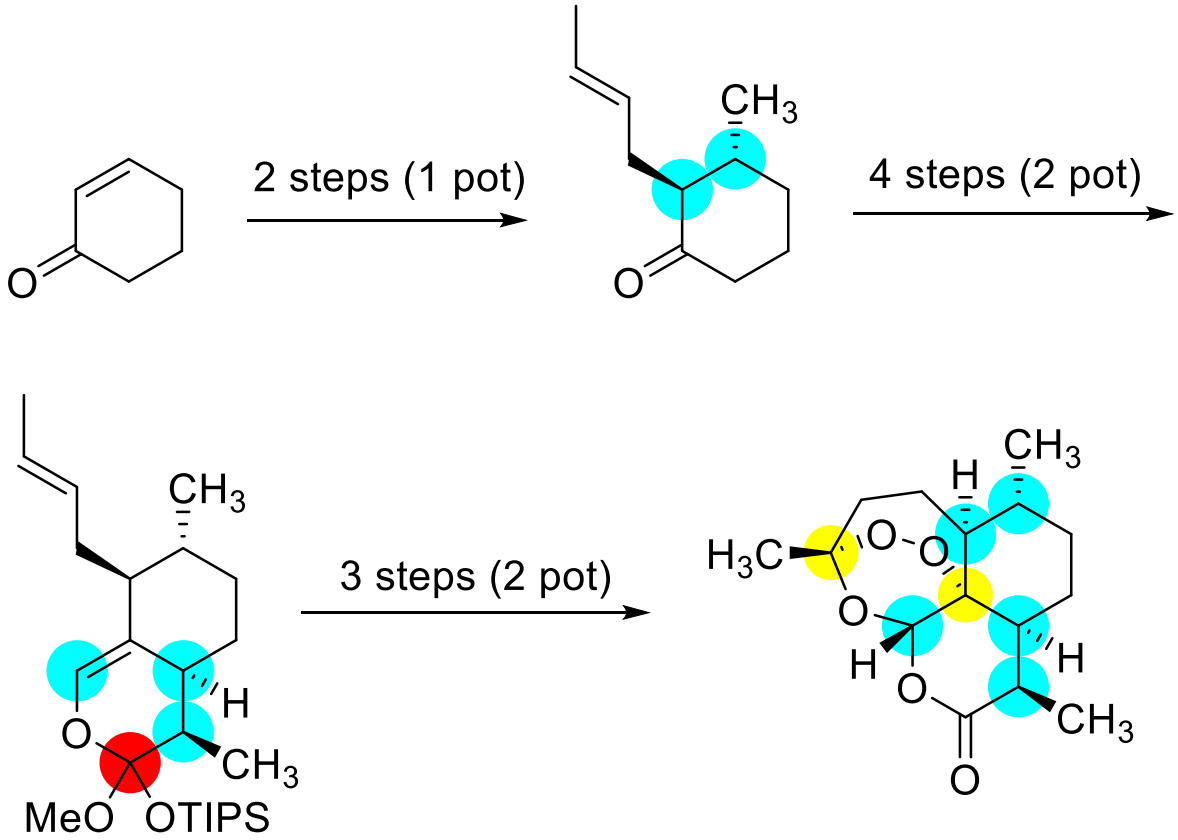
- None of the three papers mentioned could determine the nature of the intermediate, oxidated compounds




Asveld, E. W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1980**, *102,* 3644-3646

# Strategy overview



# The conclusion

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- The synthesis solves the problem of expensive starting materials
- The synthesis is somewhat shorter (less steps) than the previous ones
- Key steps: Zinc enolate alkylation, [4+2] annulation and high-yielding oxidation of internal olefin

# The conclusion

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- The synthesis does not solve the problem of the late peroxide formation with bad selectivity (all the syntheses have only 30-40% yield for the last steps)
- The last two steps take 3 days each
- The paper provides little information about the stereochemistry of some intermediates and the mechanism of the last steps