Protecting-group-free synthesis

Synthetic chemists would dearly like to be able to work without protecting groups, but they are very glad that they exist.

Koert, U. Angew.

Chem. Int. Ed. Engl. 1995, 34, p. 1370

Hoffman R. W.*;*Synthesis **2006***, 21,* p. 3531-41

Introduction

Precise control of the individual reactivity of functional groups within a complex molecular architecture remains a largely unanswered challenge

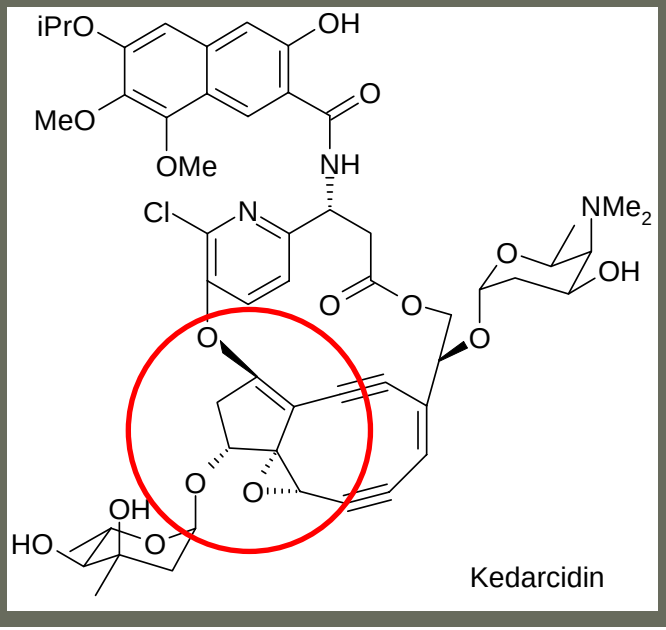
⇨ Protecting groups are a standard solution to this challenge.

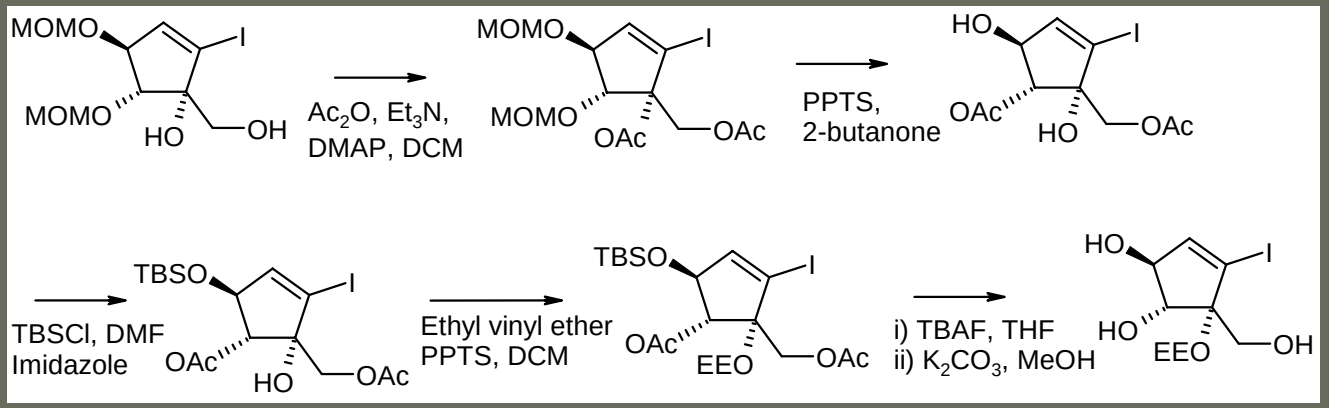
Protecting groups are easily appended : - allow smooth individual transformation

-Are then easily removed

⇨ Protecting groups use has became a routine even on molecules of low complexity.

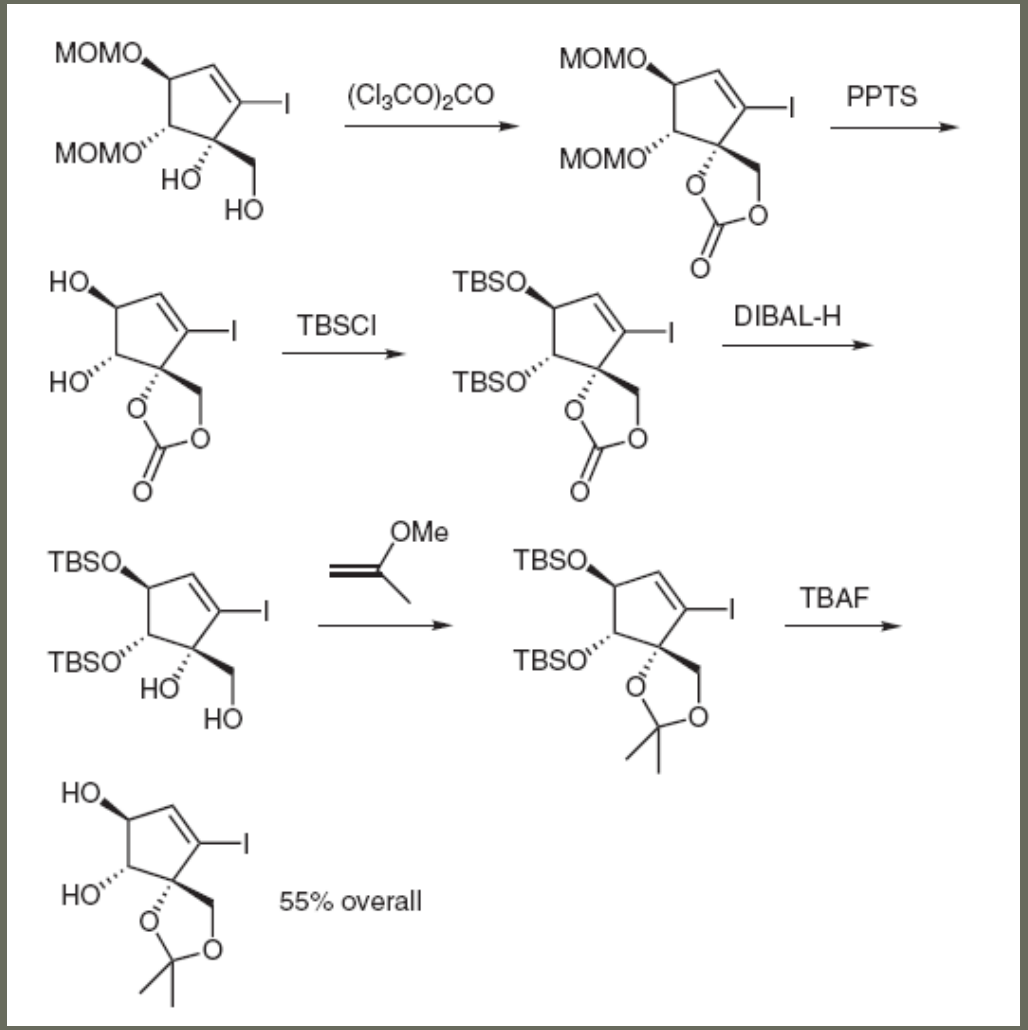
Abusing of protecting group





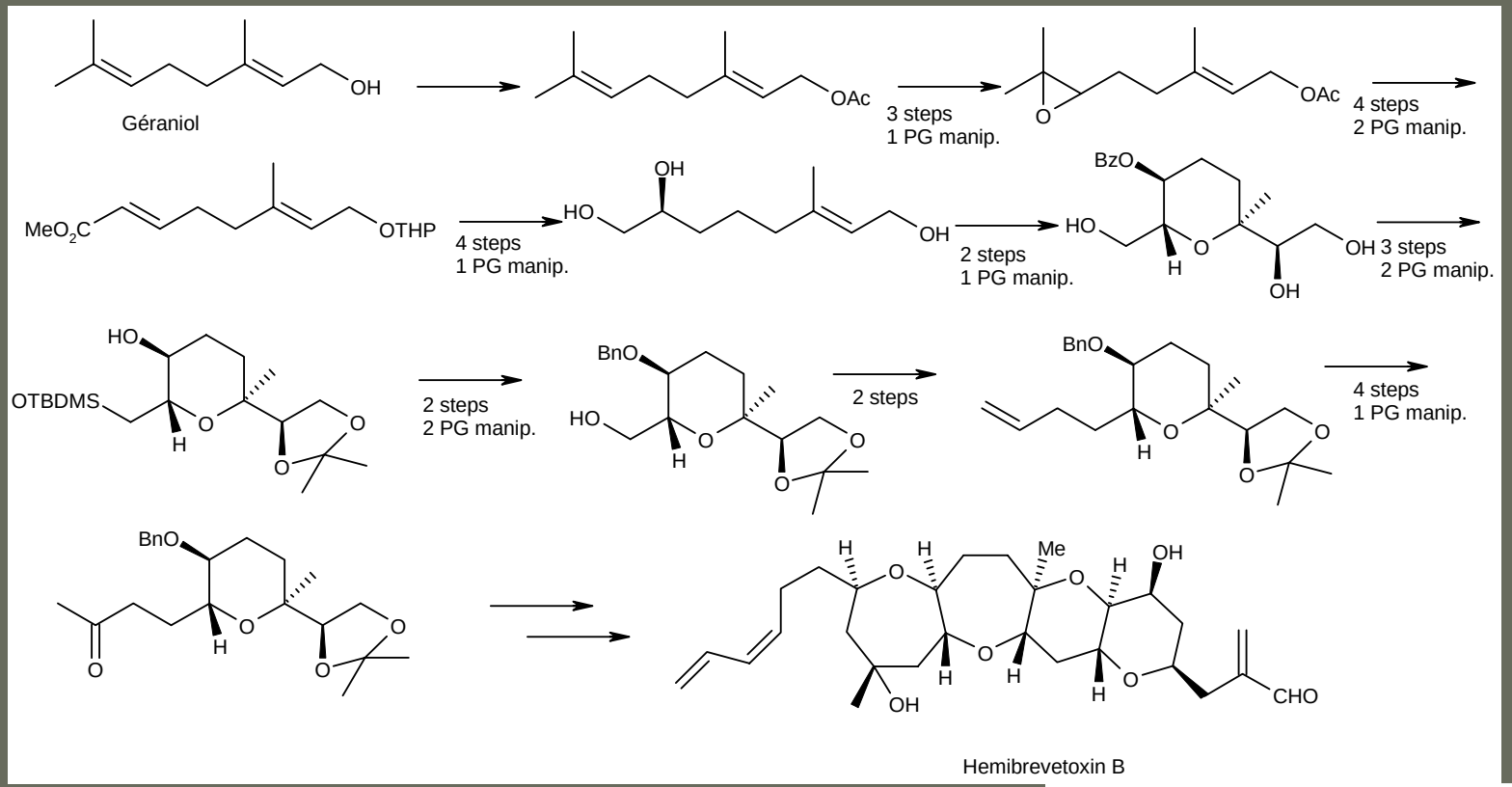
Yoshimura F.; Kawata S.; Hirama M. *Tetrahedron. Lett.* **1999**, *40*, 8281

Abusing of protecting group



Koyama, Y.; Lear, M. J.; Yoshimura, F.; Ohashi, I.; Mashimo, T.; Hirama, M. *Org. Lett.* **2005**, *7*, 267.

Abusing of protecting group



Hemibrevetoxin B

Tetrahedron Lett. **1996,** 217
27 steps
11 protecting group manipulations

Introduction

Hendrickson[1] : “An ideal synthesis should consist of only skeleton-building reaction”

⇨ Protecting group are absolutely contrary to the principles of an ideal synthesis.

- Addition of at least two steps

- Can lower efficiency of a synthesis in case of unforeseen difficulties encountered during their removal or side reaction due to their presence.

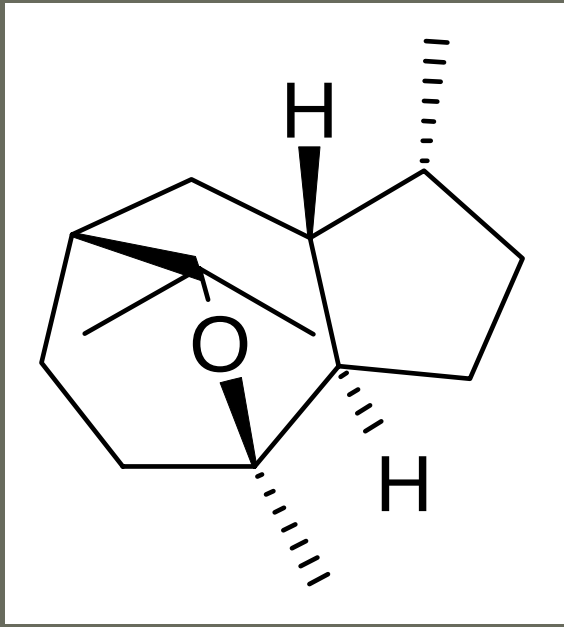
⇨ Multi-step industrial syntheses of drugs candidates avoided the use of protecting groups, 35% are protection-free synthesis

Org. Biomol. Chem. **2006**, *4, p. 2337*

(1) Hendrickson J. B.*; JACS* **1975**, *97, 5784*

Introduction

Example of an industrial synthesis : Kessane



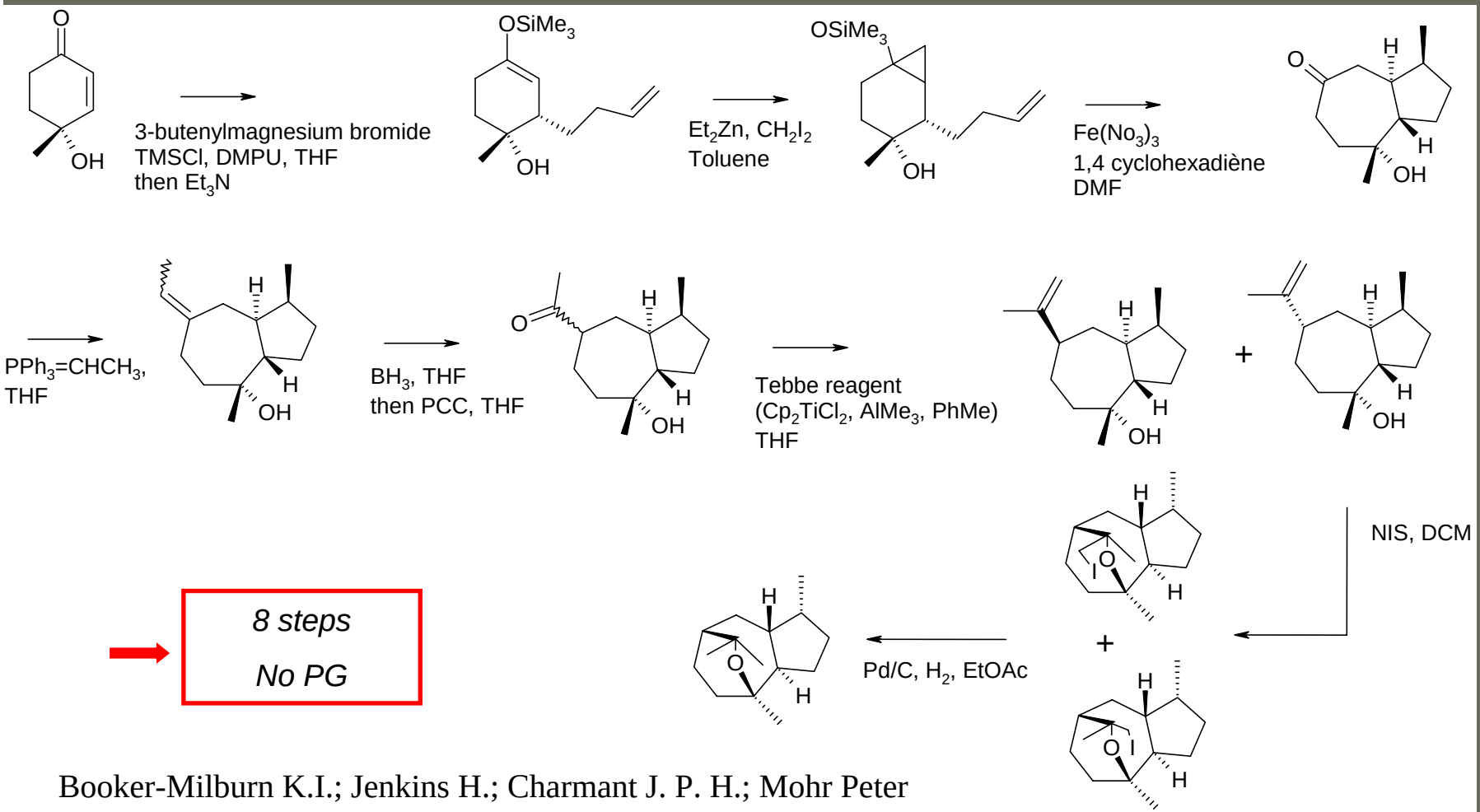
Constituent of Japanese Valarian root

Sedative and anxiolitic effects

Booker-Milburn K.I.; Jenkins H.; Charmant J. P. H.; Mohr Peter *Org. Lett.* **2003**, *5*, 3309

Introduction

Example of an industrial synthesis : Kessane



Booker-Milburn K.I.; Jenkins H.; Charmant J. P. H.; Mohr Peter
Org. Lett. **2003**, *5*, 3309

Introduction

Why do we want to avoid protecting groups?

⇨ Advantages :

Mask competitive reactivity

Allows the increase of synthetic targets complexity

(increase of the molecular weight)

⇨ Disadvantages :

Increase of the number of steps

Loss of material and time

Atom economy? green chemistry ?

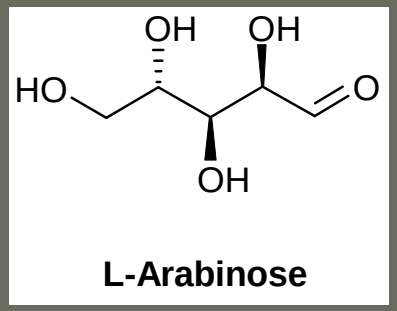
Loss of the generality of the method.

Early examples

⇨ Early PG free synthesis : Muscarine

Isolated from "*Amanita muscaria*" in 1869

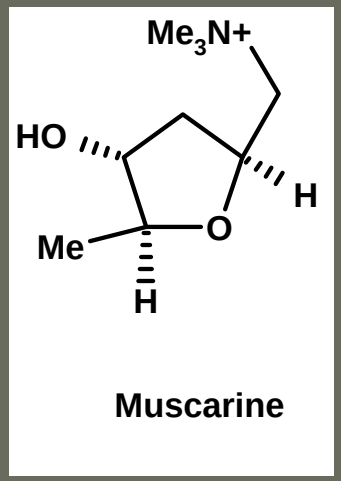
Mimics the action of neurotransmitter acetylcholine



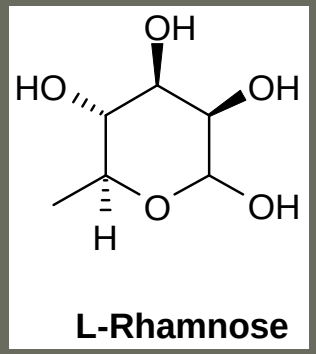
L-Arabinose

Hardegger, 1957

9 steps



Muscarine



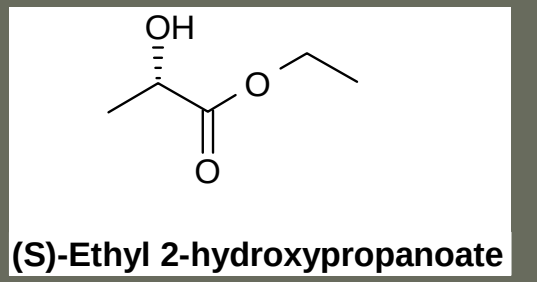
L-Rhamnose

Fleet, 1992

9 steps

Chan, 1992

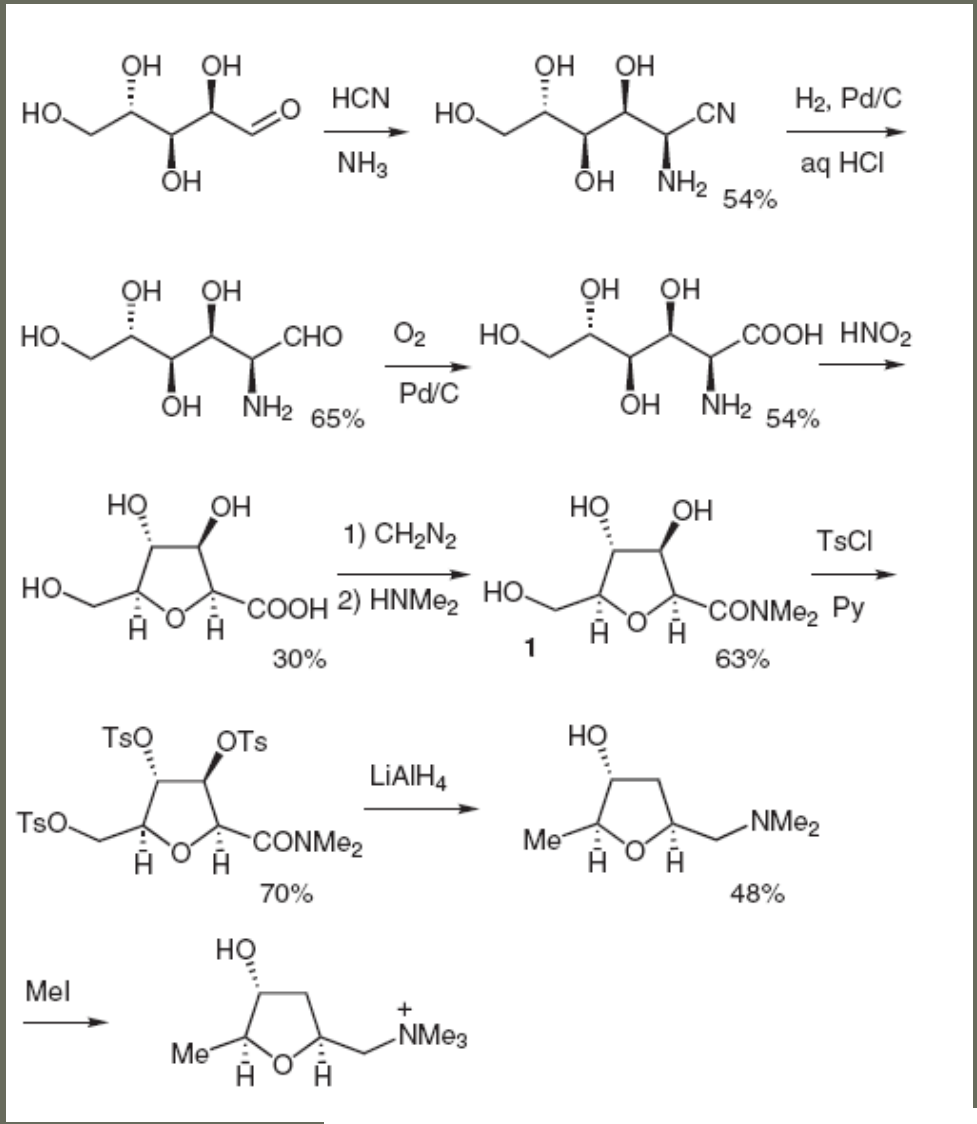
5 steps



(S)-Ethyl 2-hydroxypropanoate

Early examples

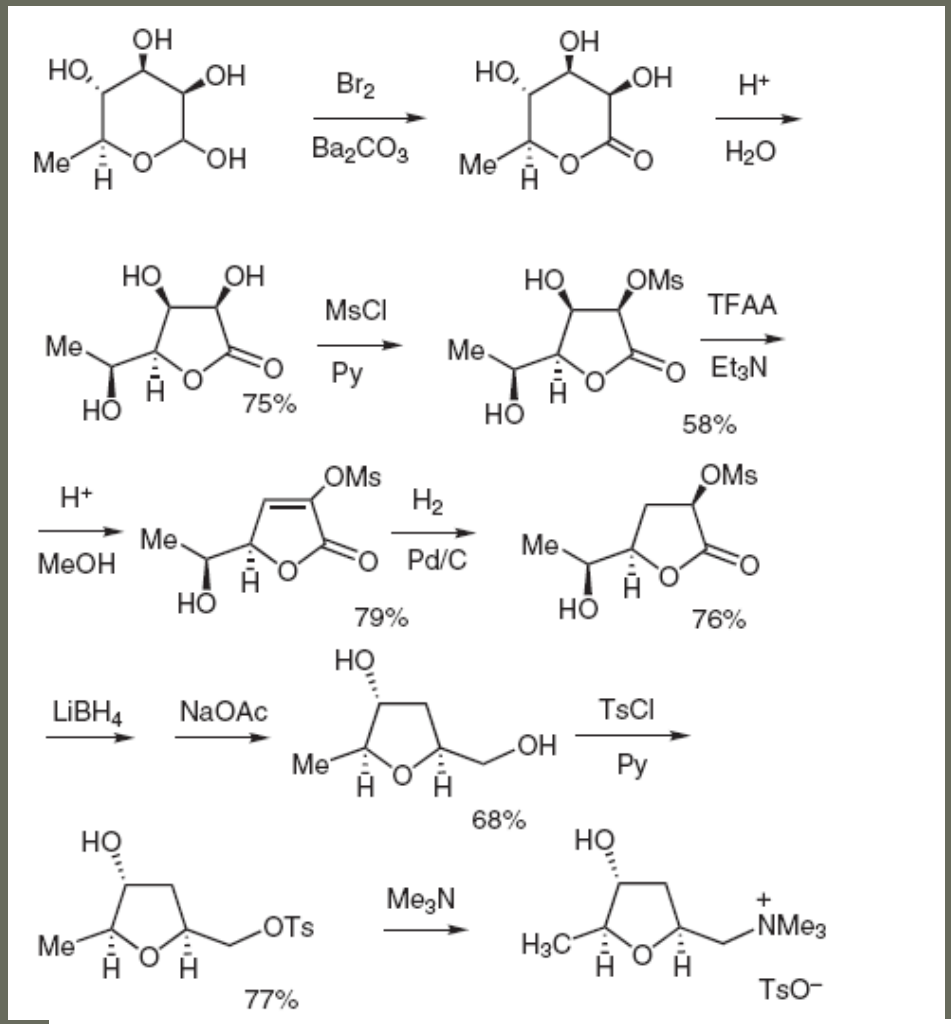
⇨ Muscarine synthesis



Hardegger, E.; Lohse, F. *Helv. Chim. Acta* **1957**, *40*, 2383.

Early examples

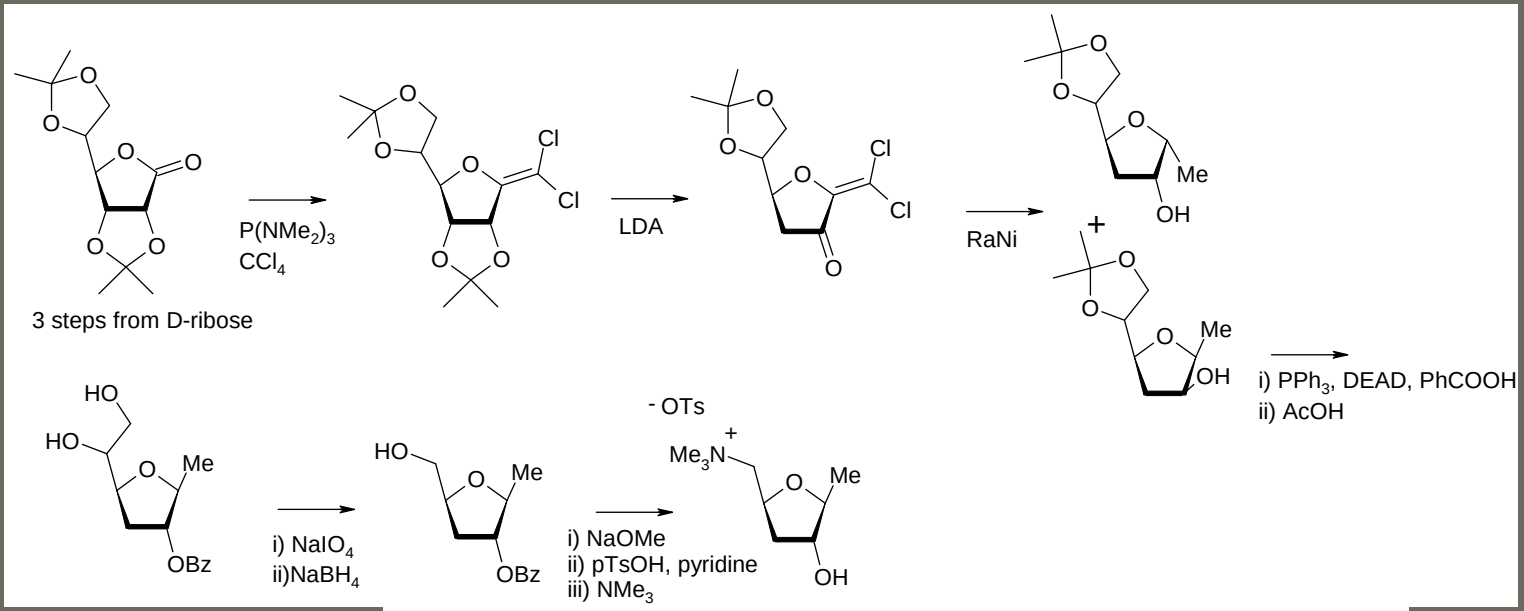
⇨ Muscarine synthesis



Mantell, S. J.; Fleet, G. W.; Brown, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3023.

Early examples

⇨ Muscarine synthesis

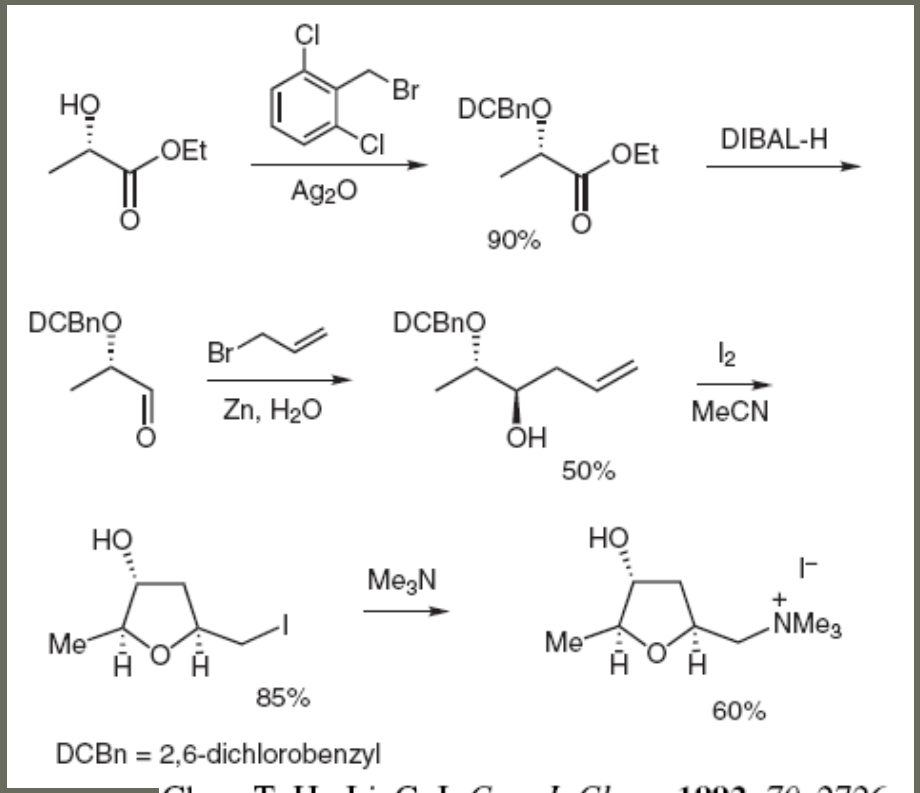


Bandzouzi A.; Chapleur Y. *J. Carbohydr. Res.* **1987**, *171*, 13

⇨ 13 steps, 4 PG manip.

Early examples

⇨ Muscarine synthesis



Chan, T. H.; Li, C. J. *Can. J. Chem.* **1992**, *70*, 2726.

How to avoid Protecting Groups ?

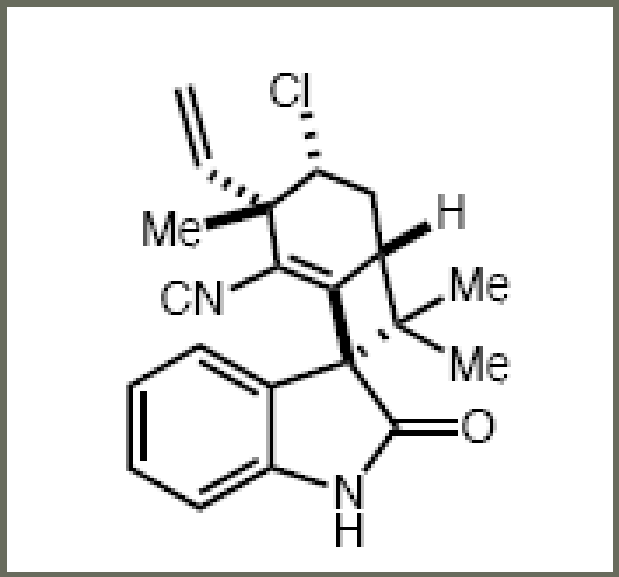
- Use of protection-deprotection in situ schemes
- Use of biogenesis-oriented syntheses
- Use of Transition-metal-catalysed skeleton formation
- Changing the order of introduction of functional groups

Use of in-situ processes

Welwitindolinone A synthesis

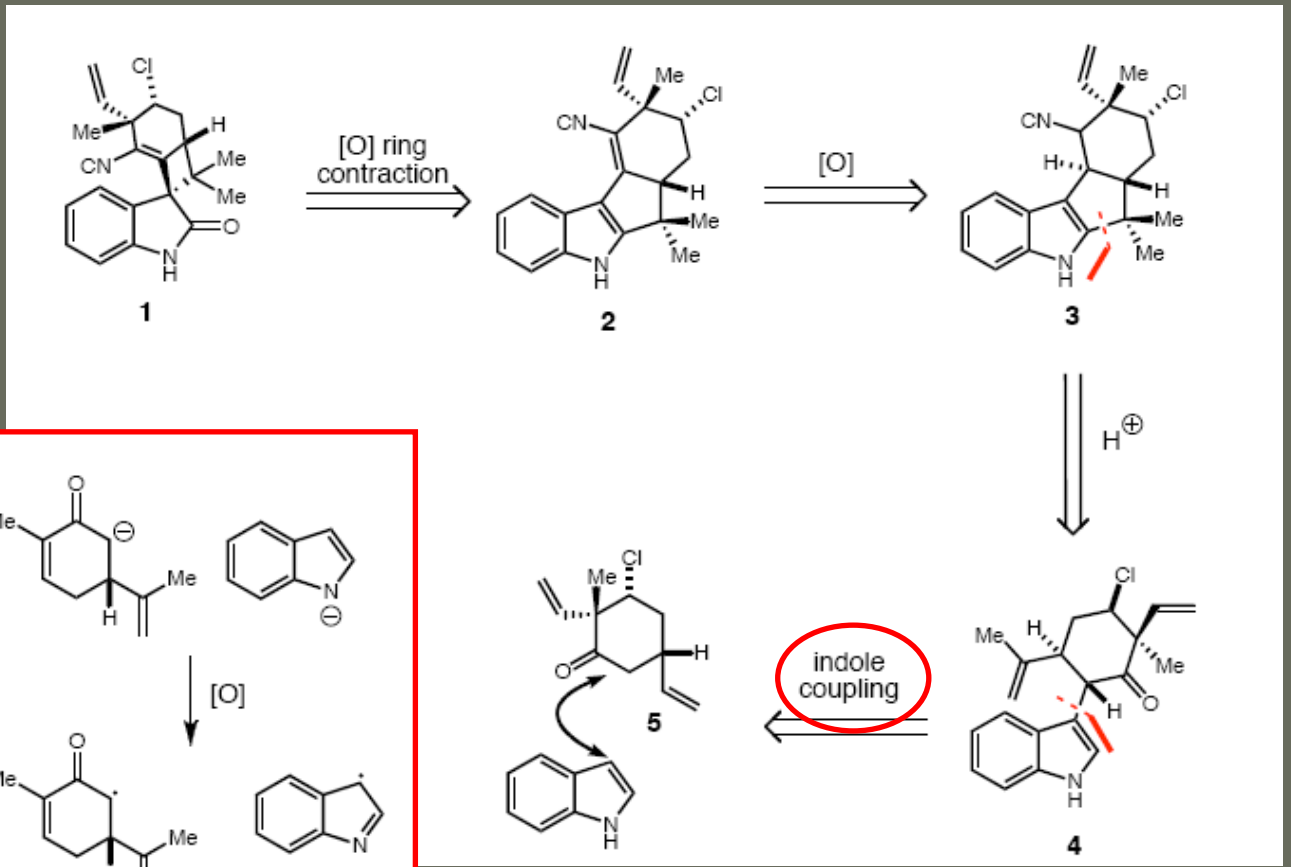
Isolated from "*Blue Green Algae*" in 1994
Activity for reversing multiple drug resistance

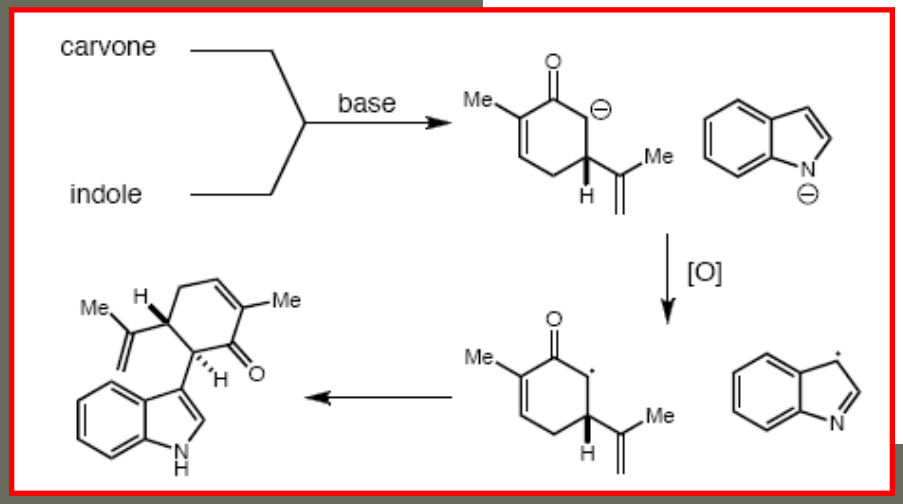
Blue Green Algae (BGA) production unit at Bhawanipatna, Kalahandi (Under Construction)



Use of in-situ processes

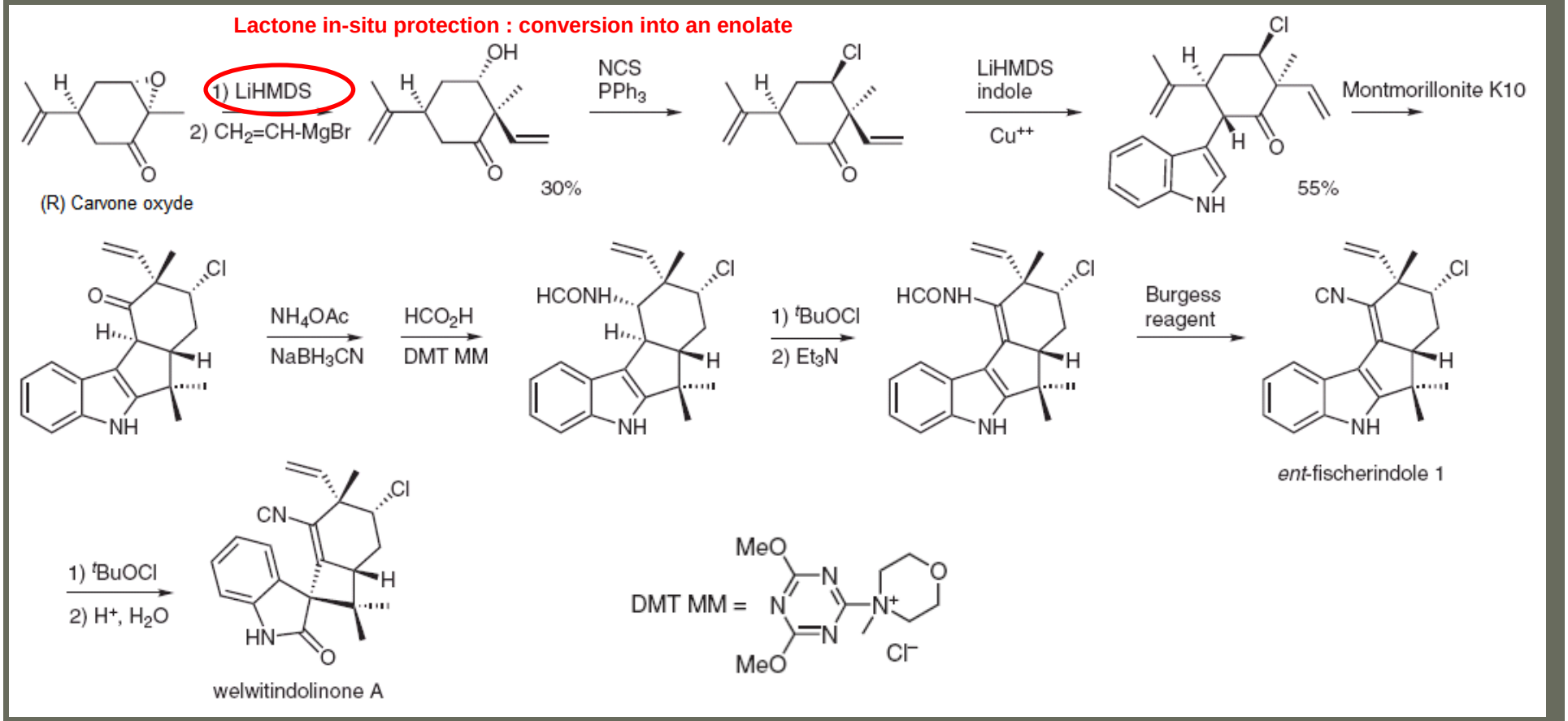
Welwitindolinone A Baran's synthesis : retrosynthetic analysis





Use of in-situ processes

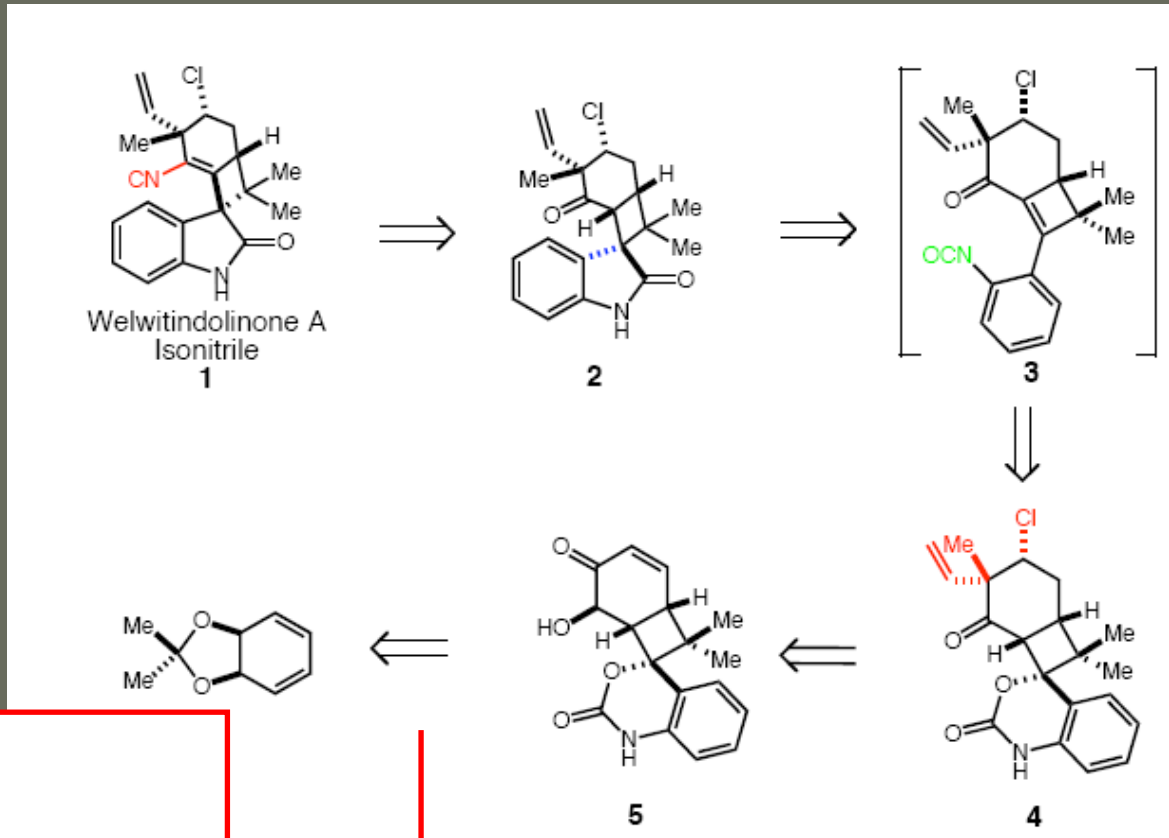
Welwitindolinone A Baran's synthesis : without PG



Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394.

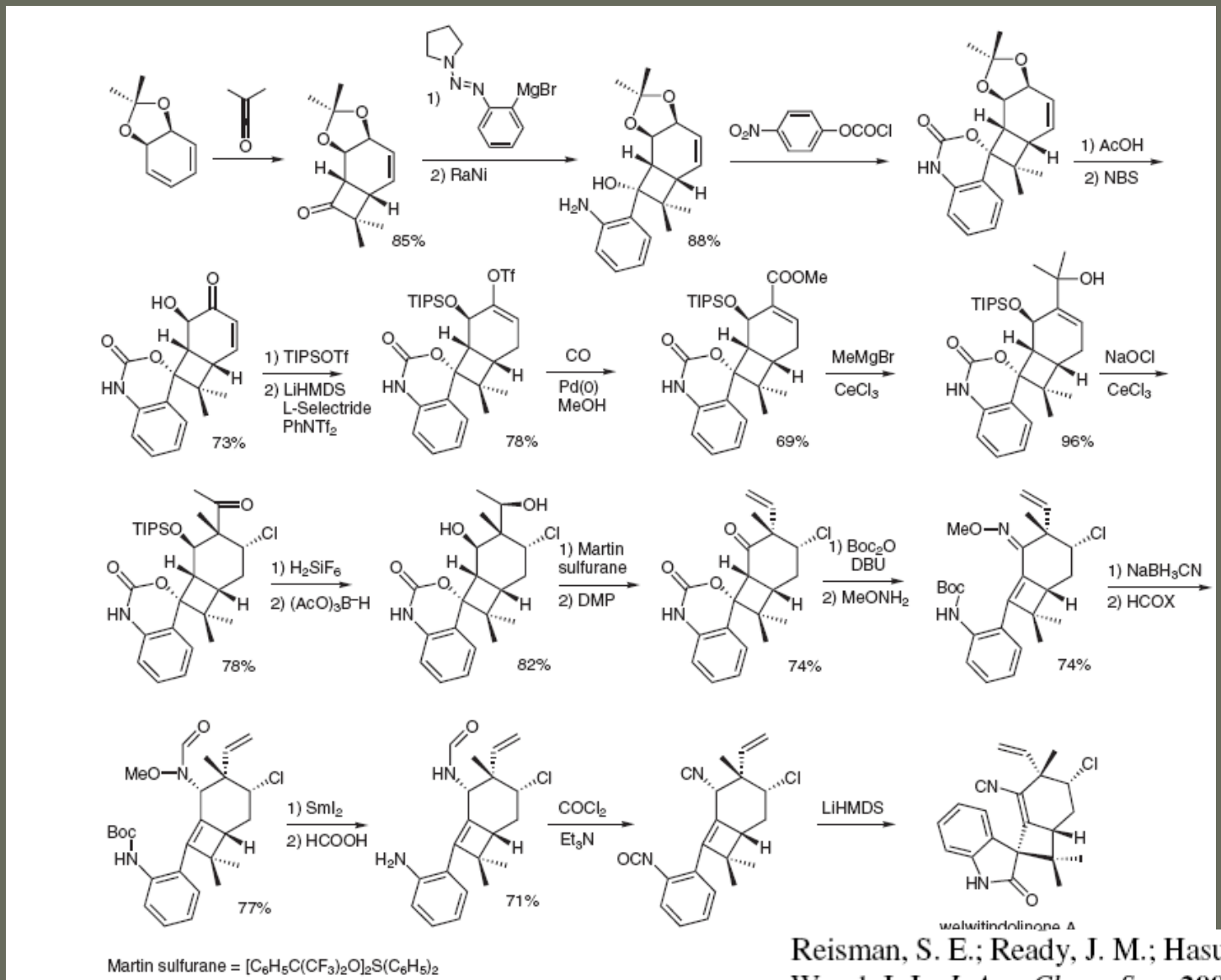
Use of in-situ processes

Welwitindolinone A Wood's synthesis : retrosynthetic analysis



Use of in-situ processes

Welwitindolinone A Wood's synthesis : with PG

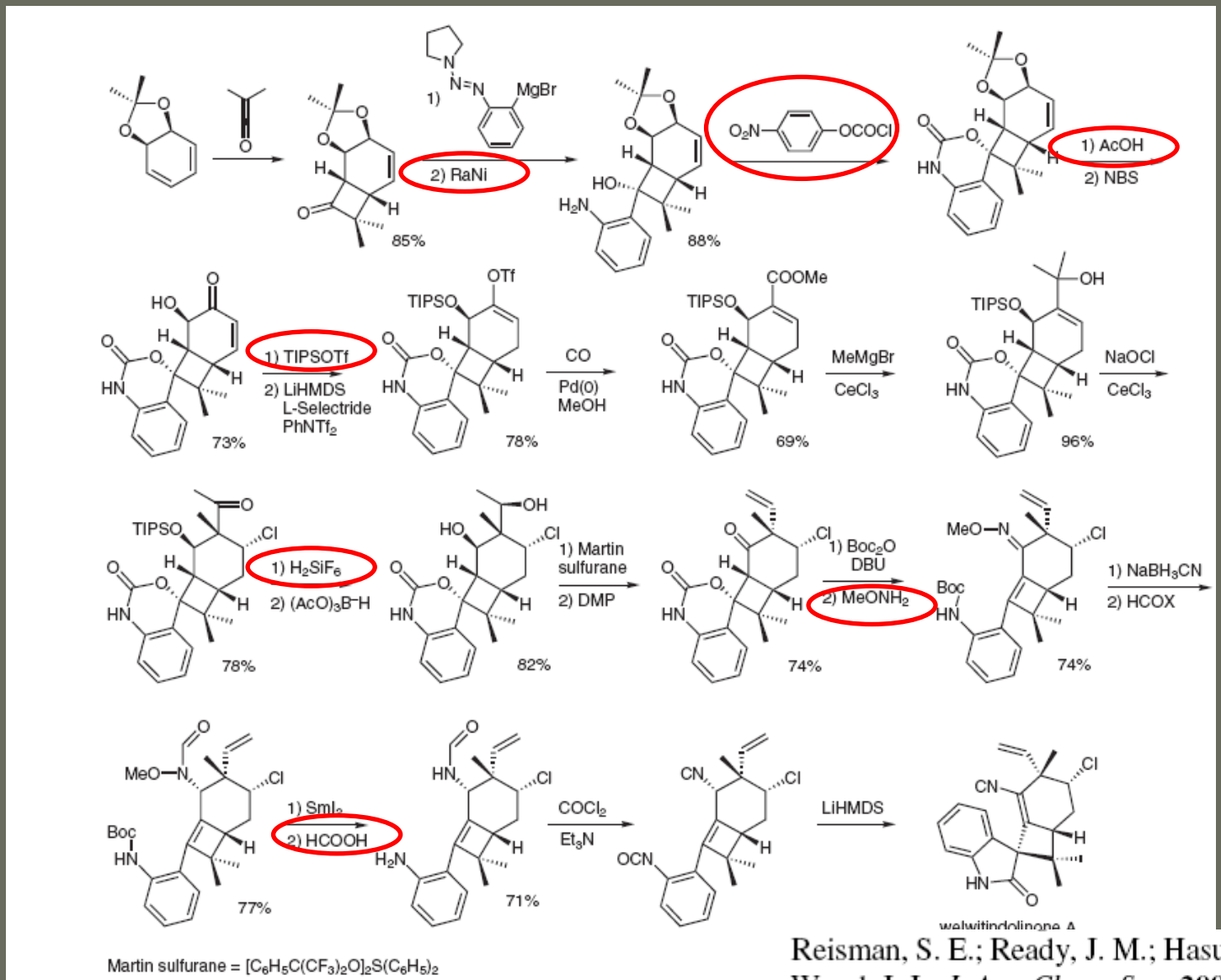


Martin sulfurane = $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$

Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448.

Use of in-situ processes

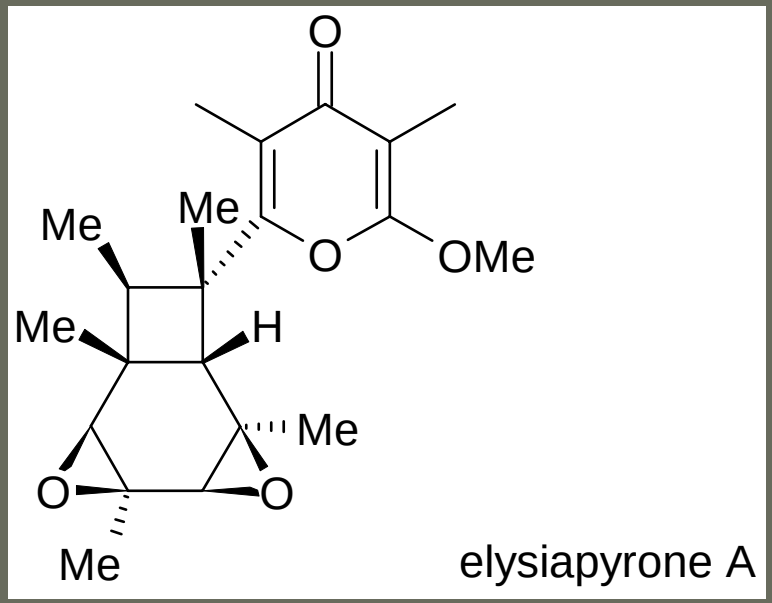
Welwitindolinone A Wood's synthesis : with PG



Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448.

Use biogenesis-oriented syntheses

Elysiapyrone A synthesis



elysiapyrone A

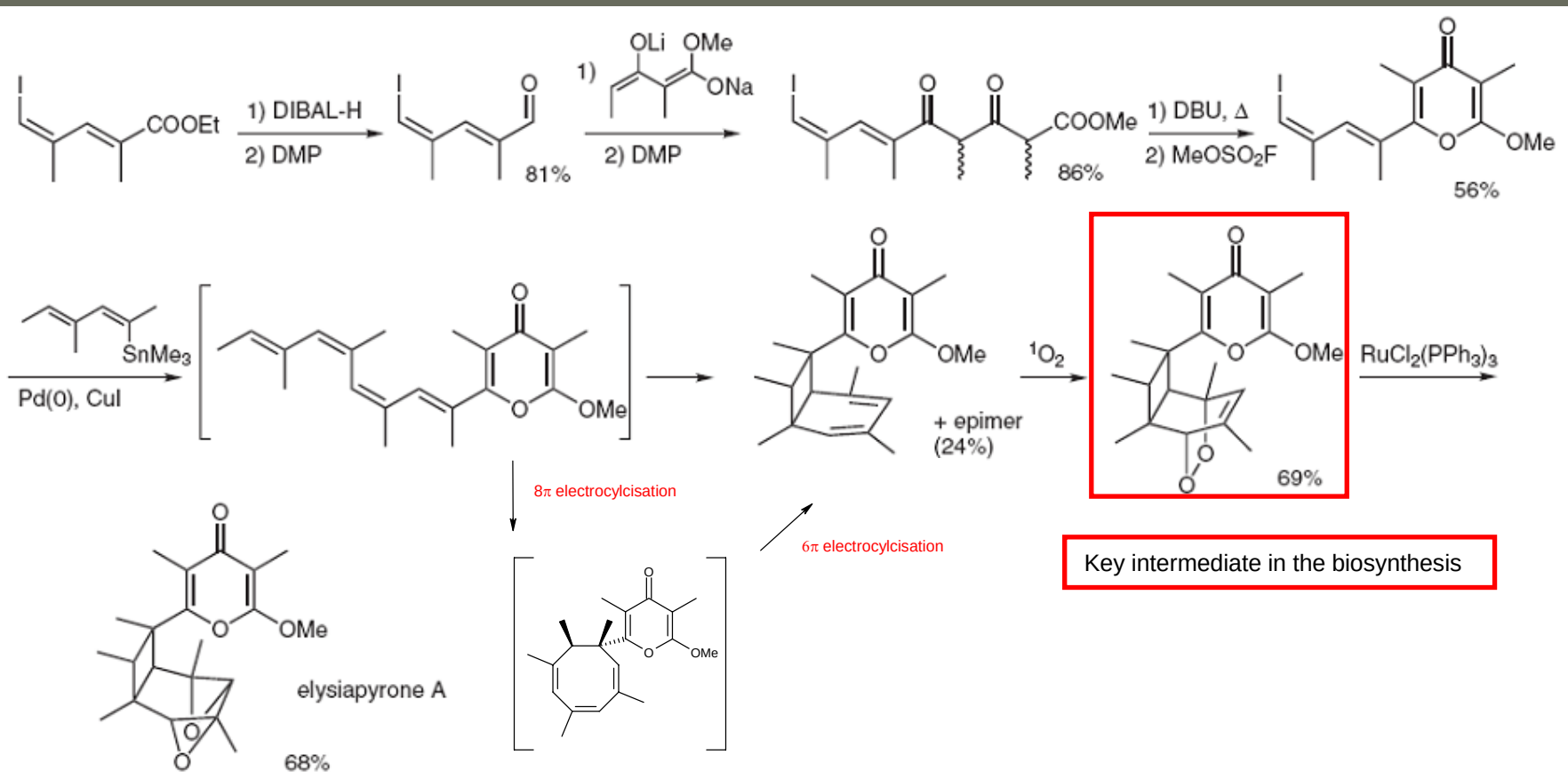
Isolated from sea slug “Elysia Diomedea”

Activity for reversing multiple drug resistance

Barbarow J. E.; Miller A. K.; Trauner D. *Org. Lett.* **2005**, *7*, 2901

Use biogenesis-oriented syntheses

Elysiapyrone A synthesis



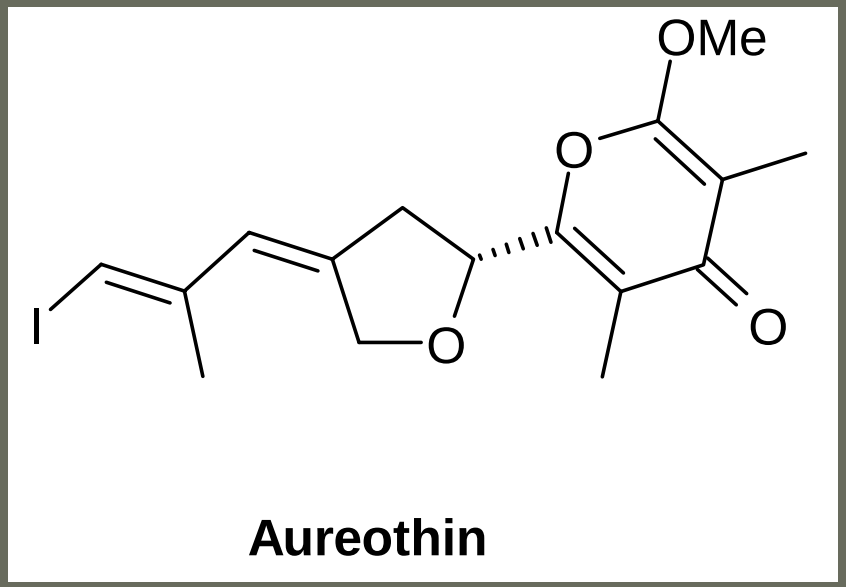
Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901.

Use of transition-metal-catalysed skeleton formation

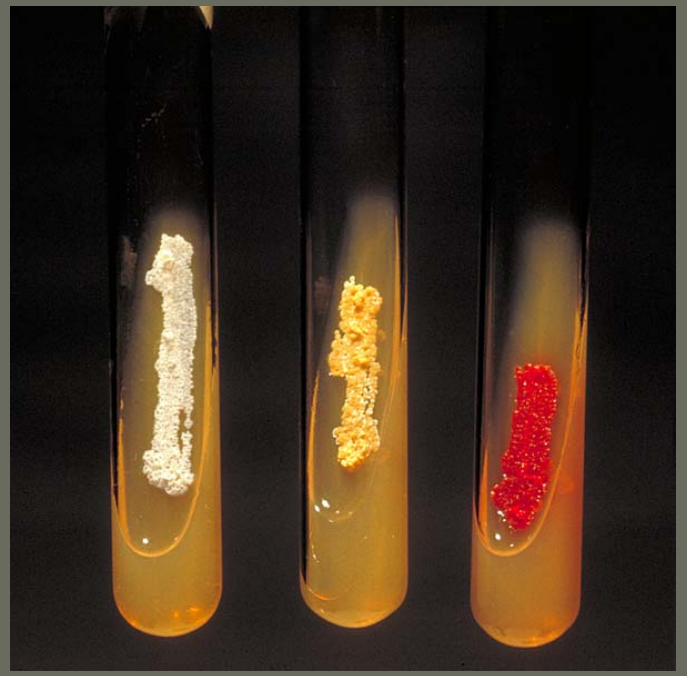
Aureothin synthesis

Found in the mycelia of several actinomycetes

Antitumor, antifungal and pesticide activities

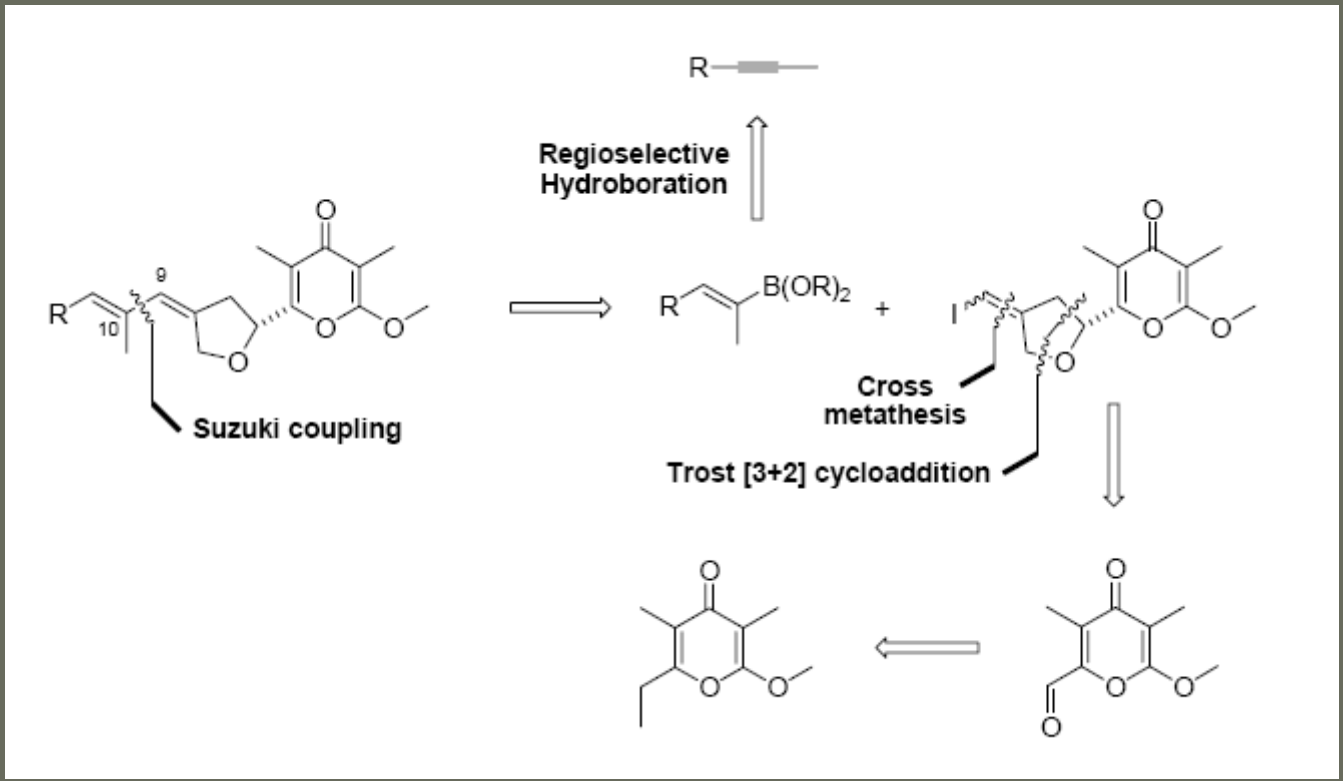


Aureothin



Use of transition-metal-catalysed skeleton formation

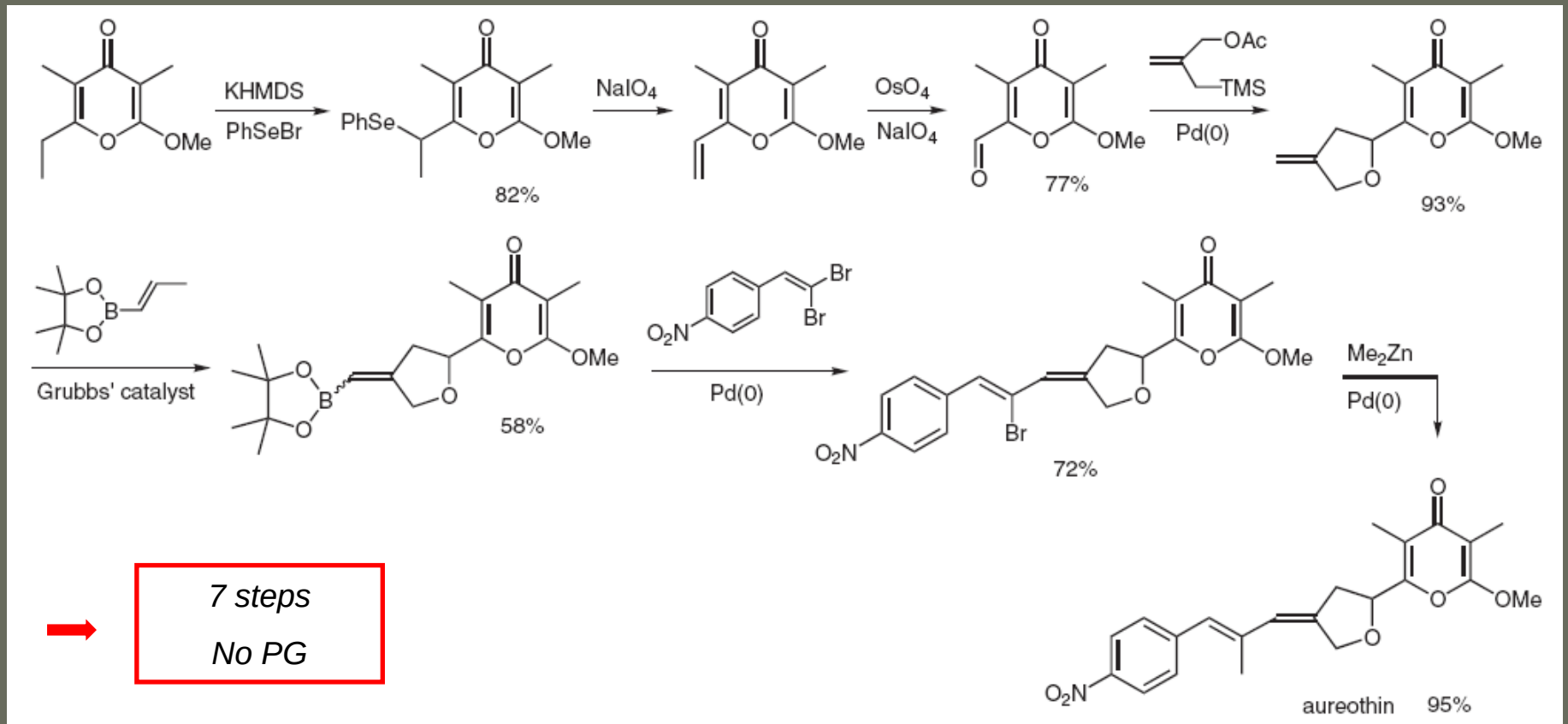
Aureothin Baldwin's synthesis : retrosynthetic scheme



Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675.

Use of transition-metal-catalysed skeleton formation

Aureothin Baldwin's synthesis : without PG



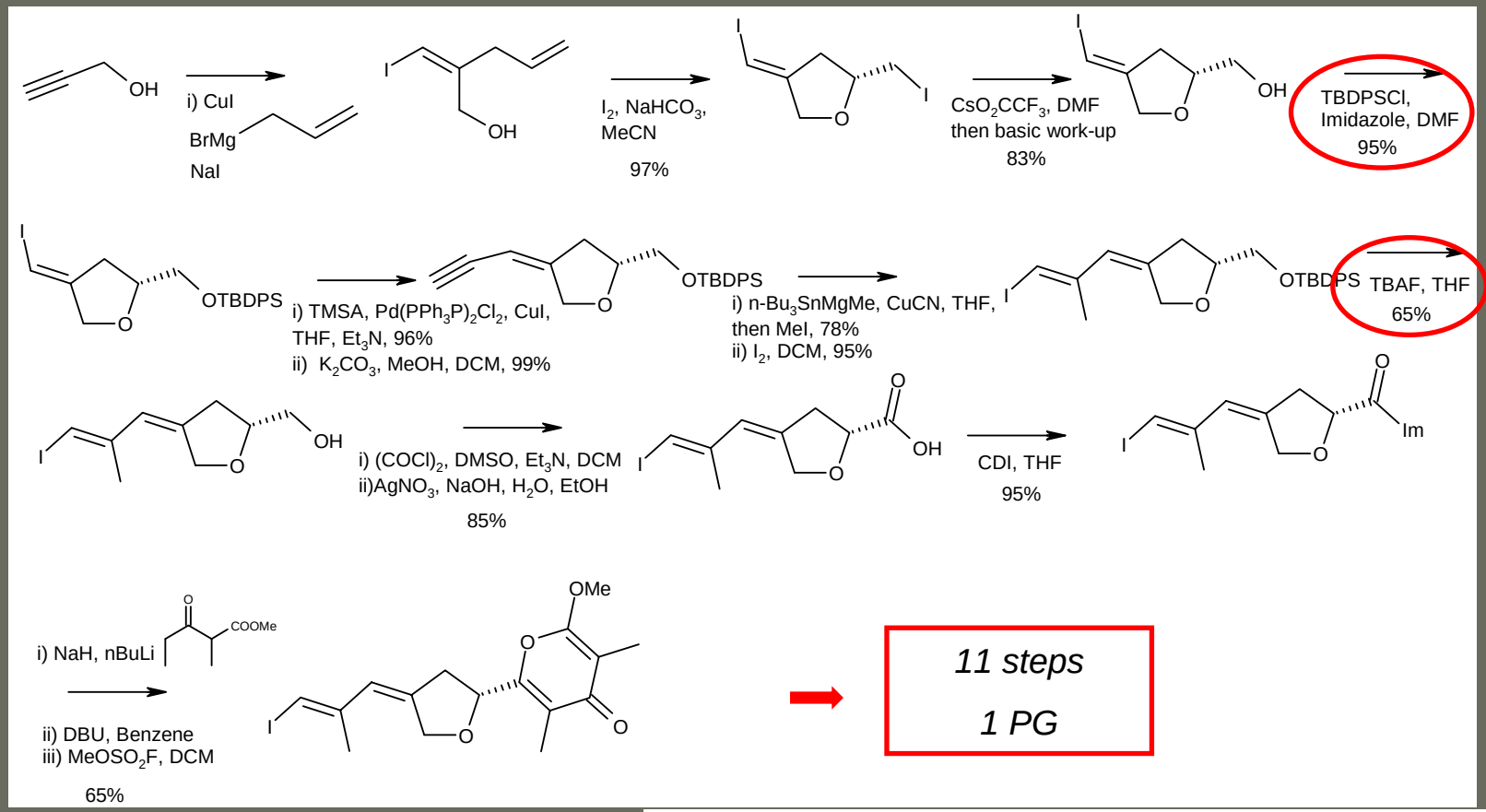
7 steps

No PG

Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675.

Use of transition-metal-catalysed skeleton formation

Aureothin Trauner's synthesis : with PG

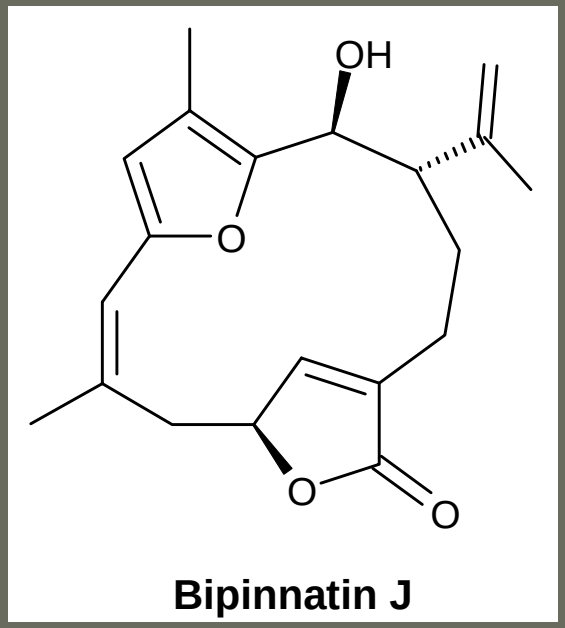


Liang G.; Seiple I. B.; Trauner D. *Org. Lett.* **2005**, *7*, 2837

Use of transition-metal-catalysed skeleton formation

Bipinnatin J synthesis

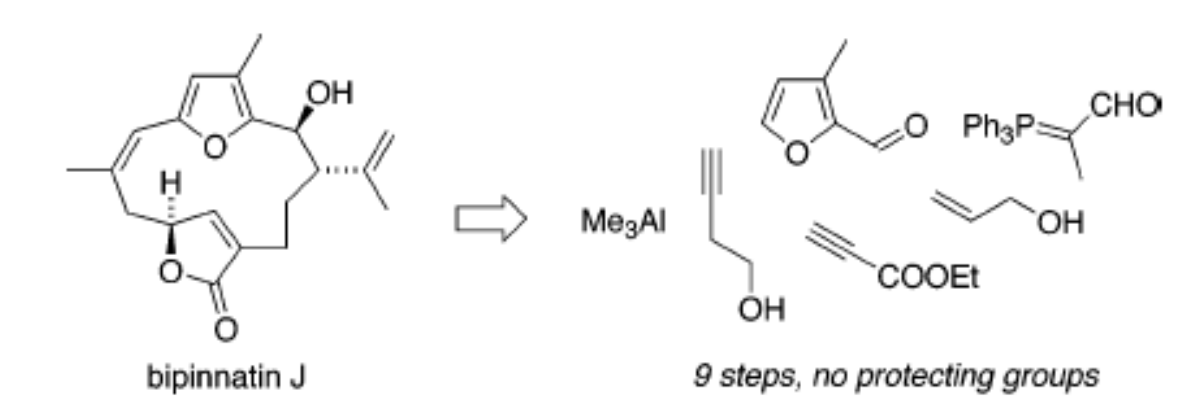
Isolated from "*Pseudopterogorgia bipinnata*" in 1998



Bipinnatin J

Use of transition-metal-catalysed skeleton formation

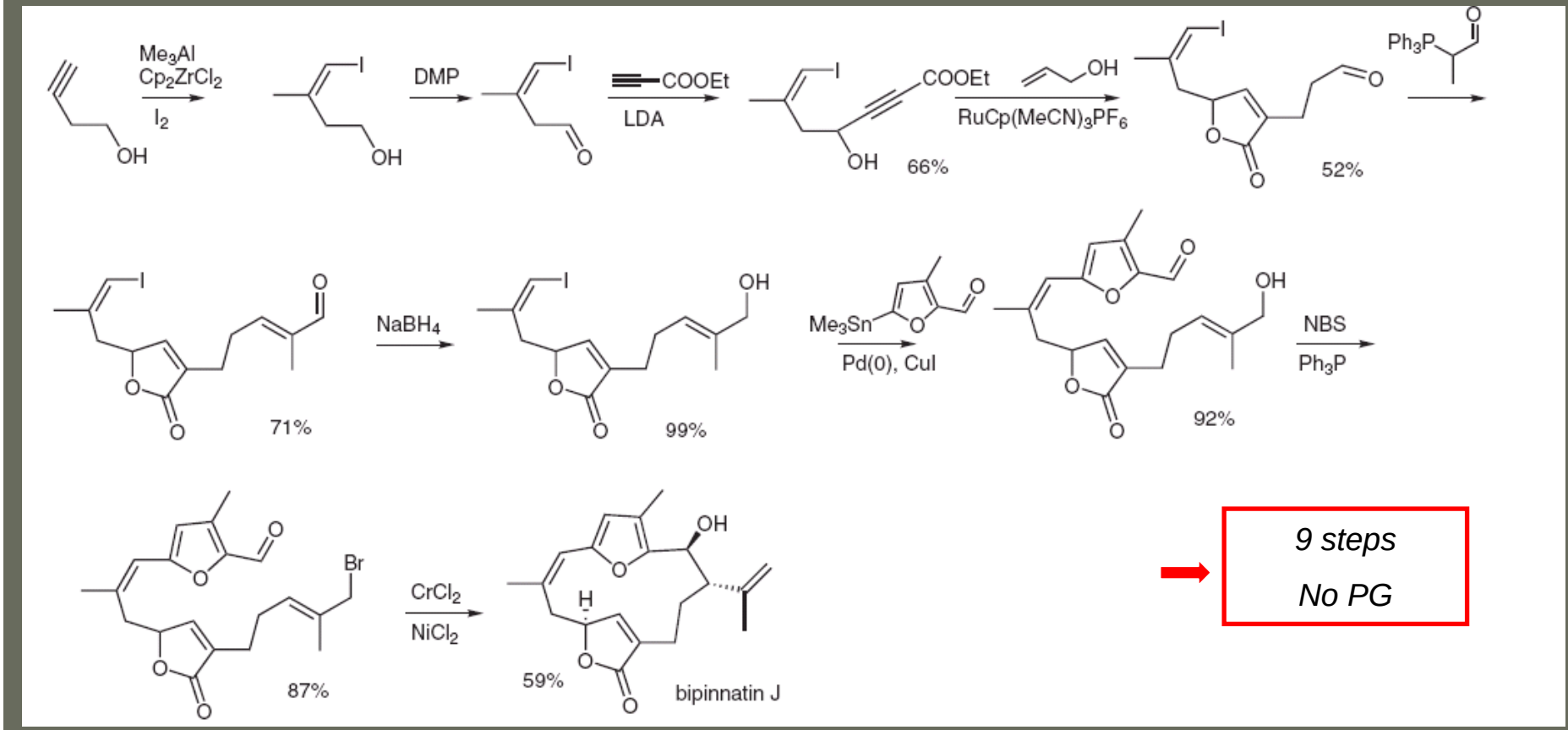
Bipinnatin J first synthesis : without PG
Retrosynthetic scheme :



Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345.

Use of transition-metal-catalysed skeleton formation

Bipinnatin J first synthesis : without PG
Ruthenium-catalysed Alder-ene, Stille, Nozaki-Hiyama-Kishi reaction



9 steps

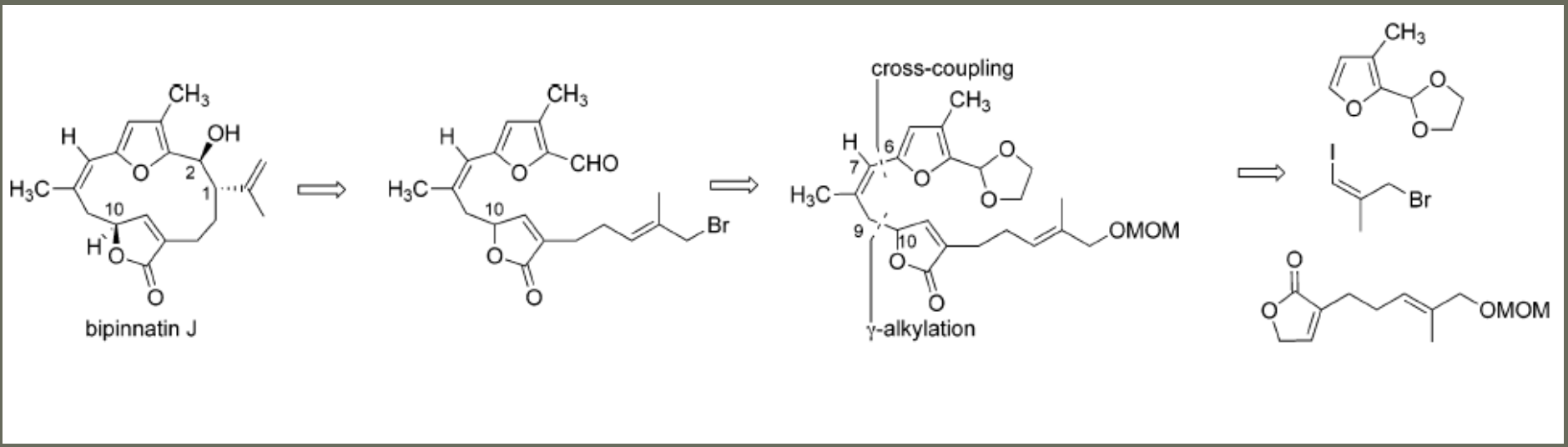
No PG

Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345.

Use of transition-metal-catalysed skeleton formation

Bipinnatin J second synthesis : with PG

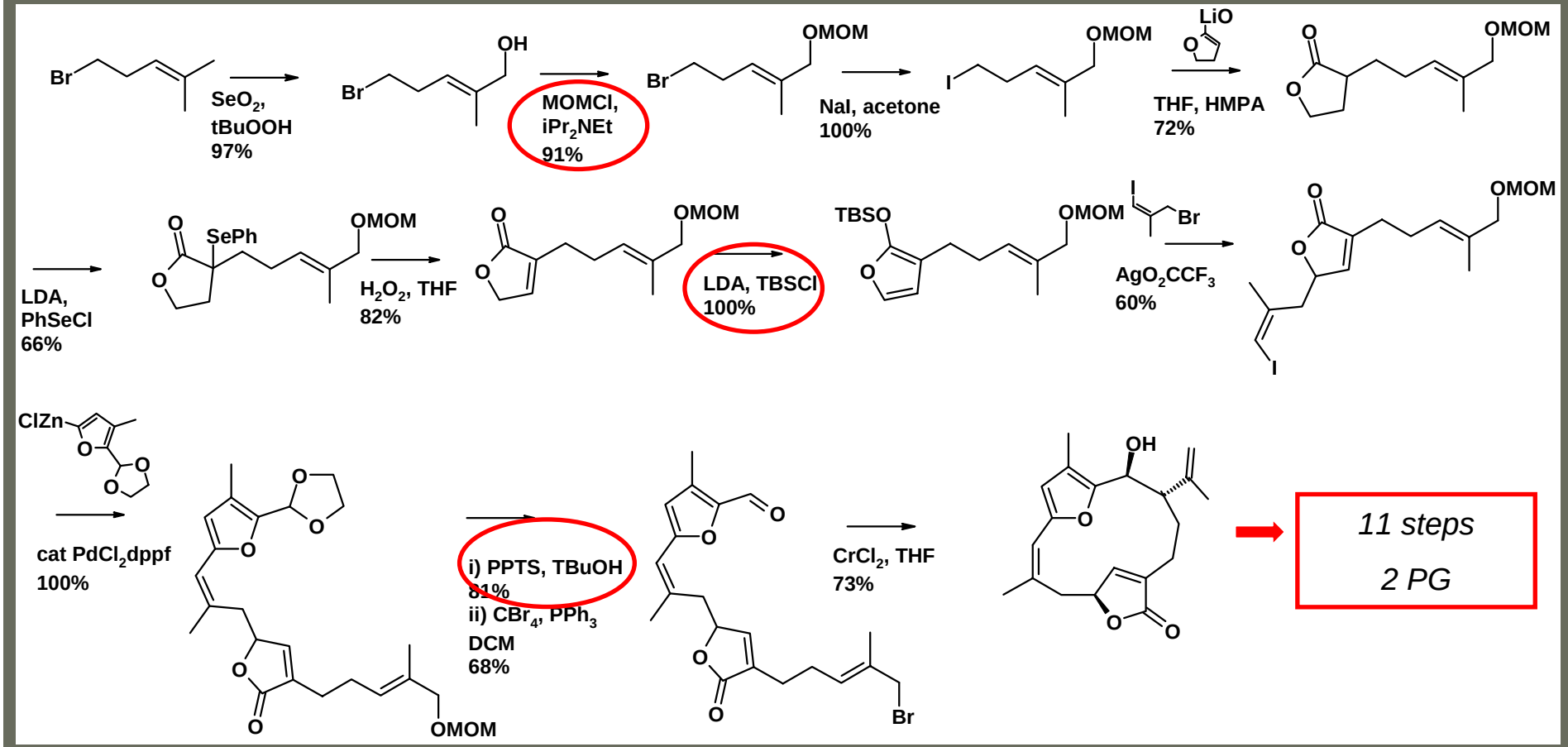
Retrosynthetic scheme



Huang Q.; Rawal V. H.; *Org. Lett.* **2006**, *8*, 543

Use of transition-metal-catalysed skeleton formation

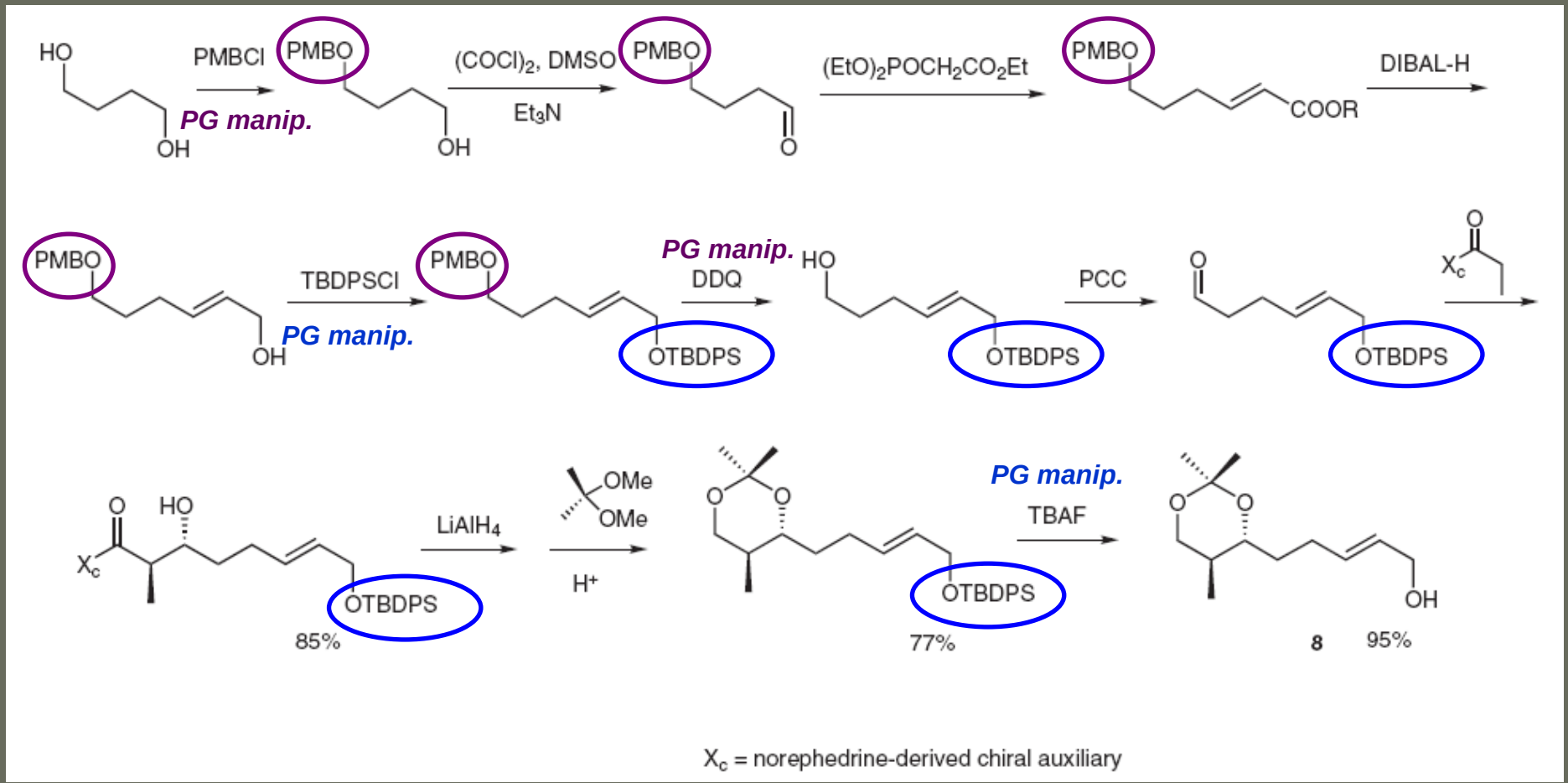
Bipinnatin J second synthesis : with PG



Huang Q.; Rawal V. H.; *Org. Lett.* **2006**, *8*, 543

Order of functional groups introduction

With protecting group : 11 steps, 4 PG manipulation steps

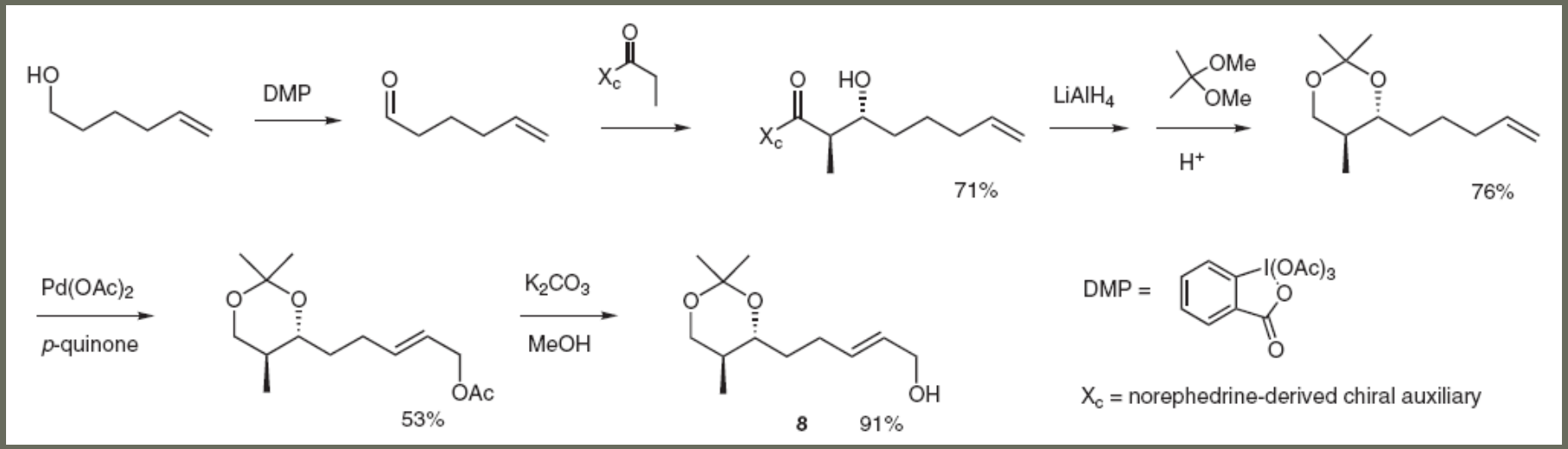


X_c = norephedrine-derived chiral auxiliary

Yohimizu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978.

Order of functional groups introduction

Without protecting group : 6 steps



Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223.

Conclusion

The advent of PG and the logic underpinning their use revolutionized and empowered chemical synthesis but now the bar has to be raised on “economies” of complex molecules total syntheses. and PG free syntheses constitute a promising area .

Major challenge of today’s syntheses :

Minimum number of steps, atom economy, minimize waste production…

⇨ Avoidance of PG is a major aspect to streamline the synthesis of complex target molecules.

Conclusion

Limitations:

- PG free synthesis involved a certain amount of risk and speculation owing to the unpredictable reactivity that is inevitably encountered at the late stages of a total synthesis.

- In some case, the use of PG may offer a more efficient or even sole solution.

Ex : certain classes of molecules will perhaps always require some level of protection for practical issues of purification and characterization.

“With regards to the issue of protecting groups, we would submit that these artificial agents, while often enabling in the certain classes of molecules, are the direct offspring of chemists inability to control chemoselectivity”

P. S. Baran et al. *Acc. Chem. Rev.* **2009**, *42*, 530

Conclusion
some tips if you can’t avoid them…

Good protecting groups :
Are small compared to the mass of you are trying to make.
Can be applied and remove in great yield
Allow the functionality to survive the reaction conditions required.
Allow selective deprotection under mild conditions.

Do not introduce stereocenters. Uncontrolled stereocenters in protecting groups complicate the manipulation and handling of the material by increasing the number of diastereoisomers.

To avoid them :
Remember adjustment of oxidation state is often easy.
Ex: never carry an aldehyde through multiple steps (undergo facile aldol condensation, is easily air-oxidised.

Thank you for your attention…