Survey of Tetrodotoxin Syntheses

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SuperGroup Meeting

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Outline

- Introduction and trivia
- Kishi synthesis (1972, racemic)
- Isobe synthesis (2003, asymmetric)
- Du Bois synthesis (2003, asymmetric)
- References

“Certain varieties of puffer fish, especially the *tora fugu,* or tiger puffer *(S. rubripes),* and the closely related *ma fugu*, or common puffer (*S. porphyreus*), are highly prized as comestibles in Japan. The indulgence of the taste is fraught with some peril, since the livers and ovaries of the fish contain a powerful poison.”

R. B. Woodward [“The Structure of Tetrodotoxin” *Pure & Appl*. *Chem*. **1964**, *9*, 49]

Introduction

- First isolated from the ovaries of the puffer fish (Fugu) in 1909.
- Named after the puffer fish family "Tetraodontidae."
- Responsible for 10-200 deaths per year.

Tetrodotoxin Trivia

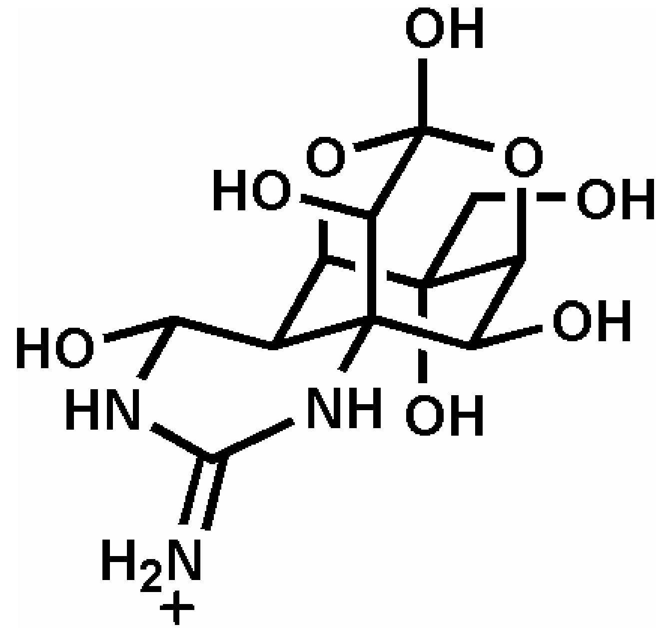
- 1200 times deadlier than cyanide. One fish contains enough poison to kill 30 adults.
- Must be licensed to prepare fugu. Typical meal is $100-200. Some chefs add a small amount of toxin to the meal for a “tingly” effect.
- Supposedly the only delicacy not served the Japanese emperor.

Trivia Continued

- Toxin is actually generated by the bacteria *Pseudomonas* which the fish consumes
- A potent neurotoxin, it binds to pores of Na-channel proteins in nerve-cell membranes.
- It does not cross the blood-brain barrier, rendering the victim fully conscious but paralyzed. Death is typically from asphyxiation.
- No antidote. Treatment is emptying of the stomach, consumption of activated charcoal, and hoping for the best.

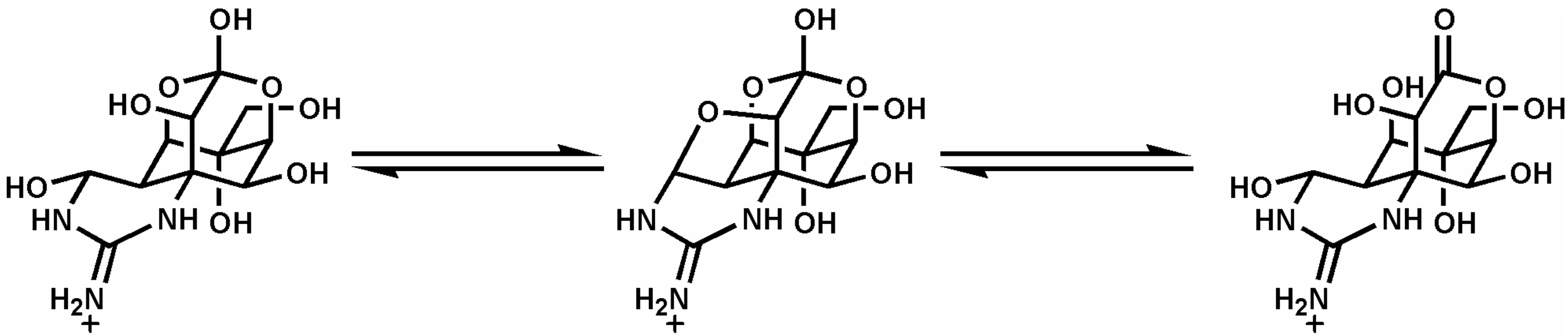
Tetrodotoxin

- Independent structure elucidation by the Hirata-Goto[1], Tsuda[2], and Woodward[3] groups.
- Absolute stereochemistry confirmed by X-Ray in 1970.[4]
- Contains an unprecedented dioxa-adamantane skeleton functionalized by hydroxyl groups, an ortho ester, and a cyclic guanidine with hemiaminal.



(-)-tetrodotoxin

Tetrodotoxin Equilibria

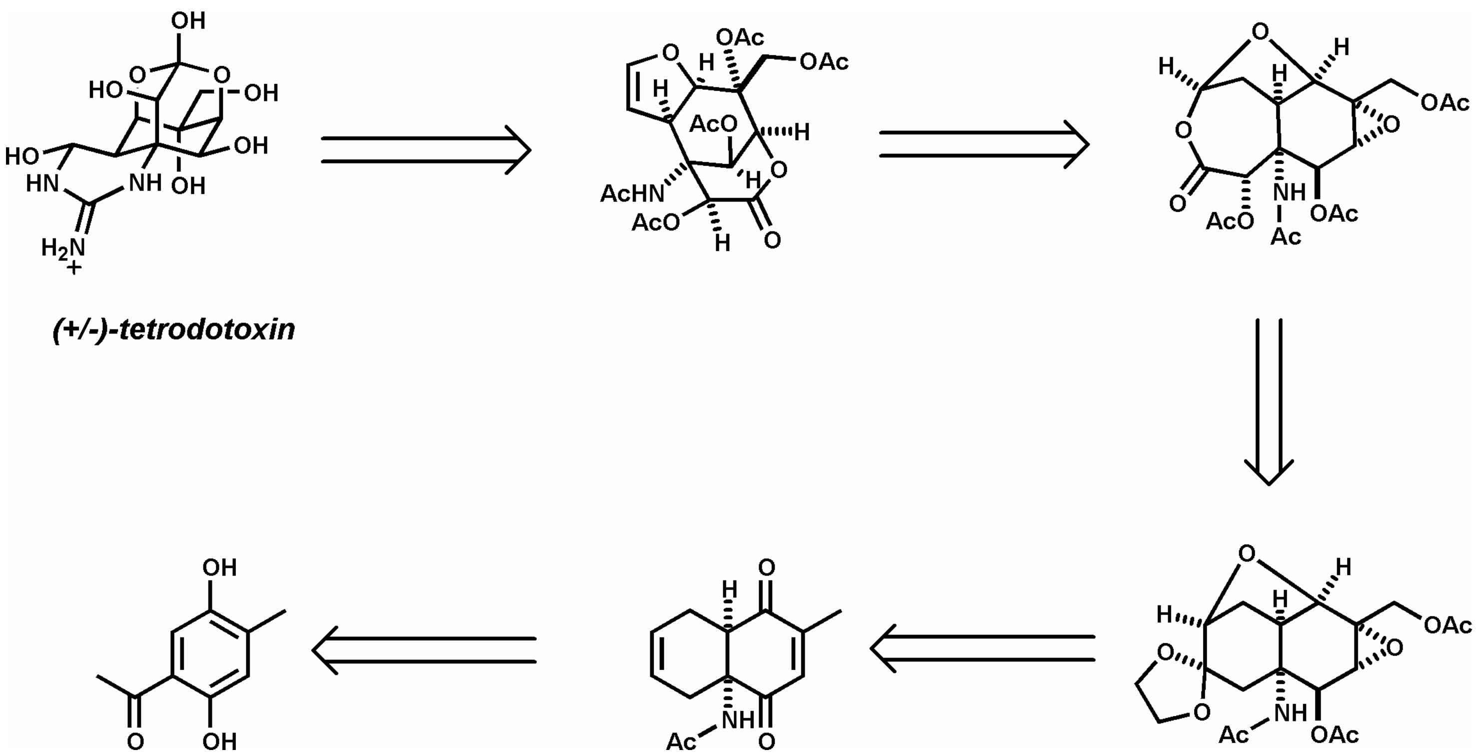


(-)-tetrodotoxin
ortho ester form

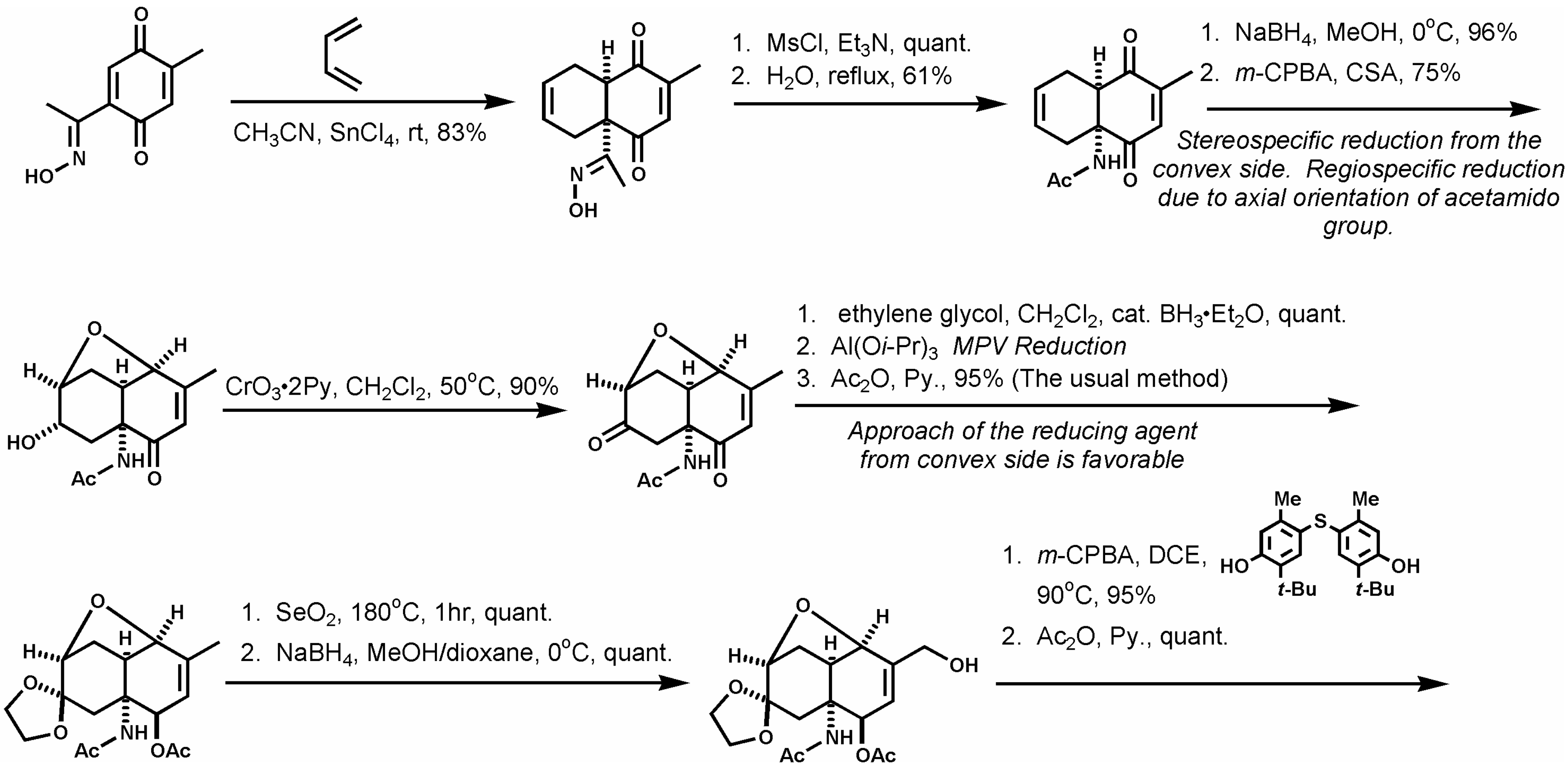
anhydride form

lactone form

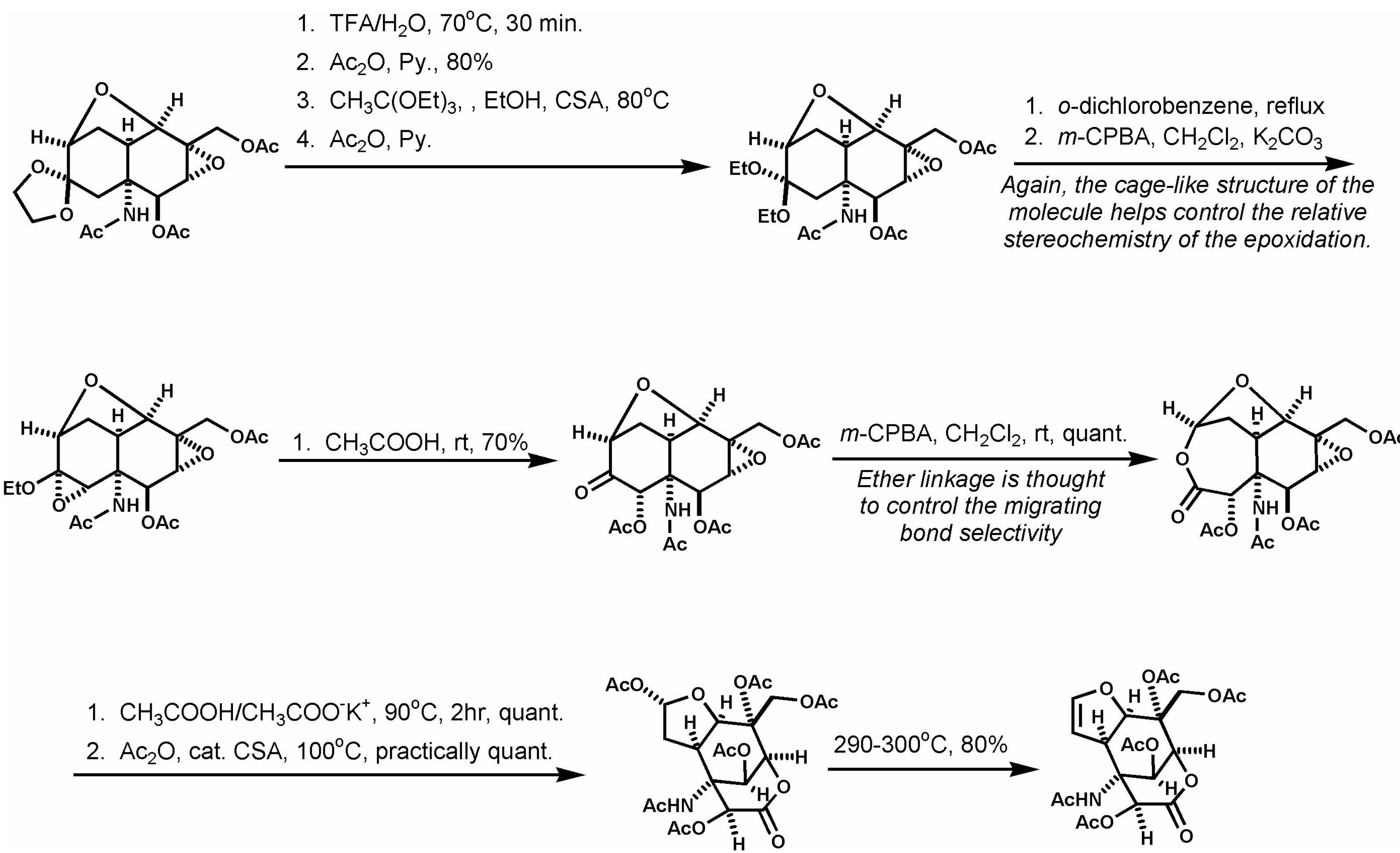
Kishi Retrosynthesis[5]



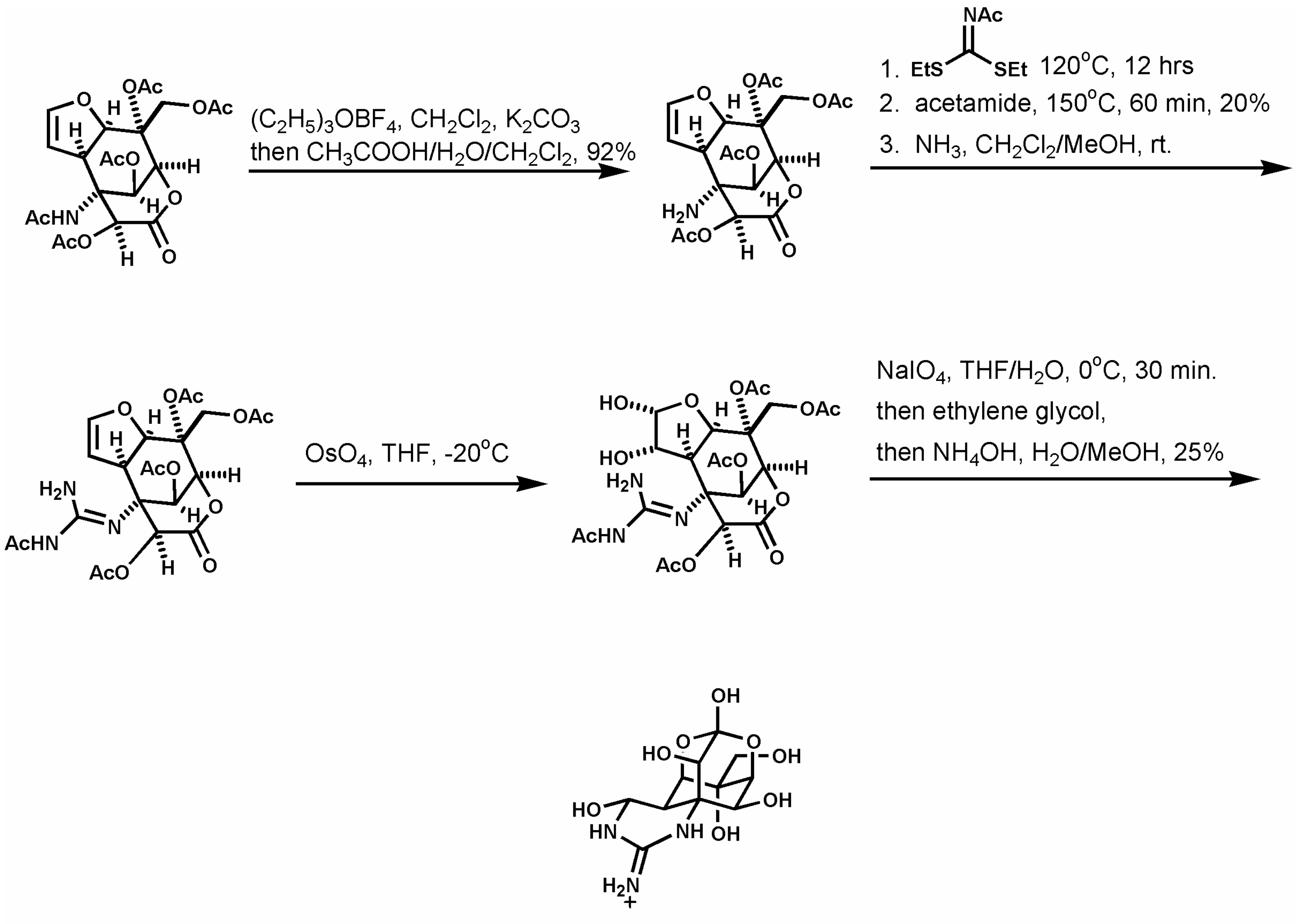
Kishi Synthesis[5]



Kishi Synthesis[5]

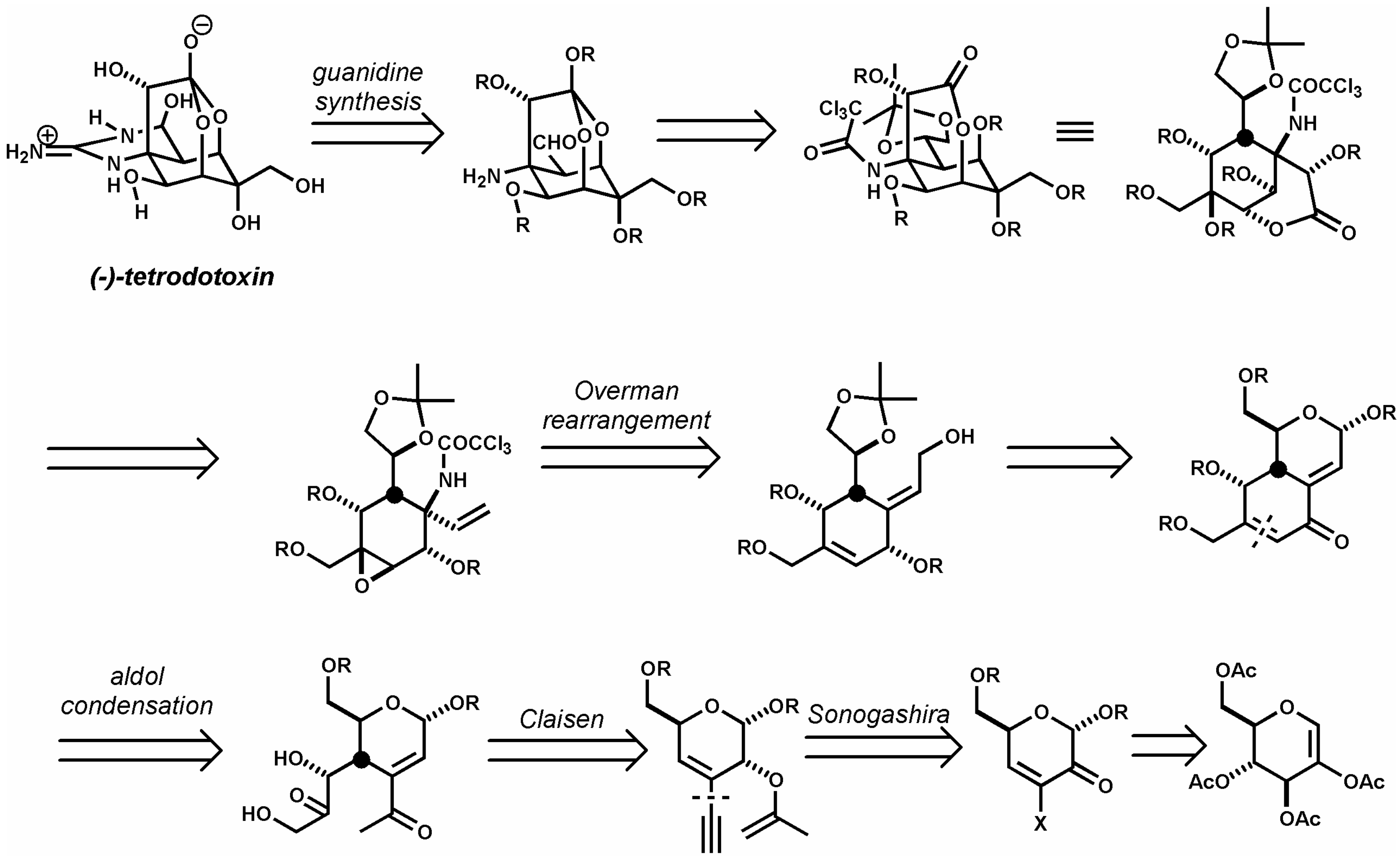


Kishi Synthesis[5]

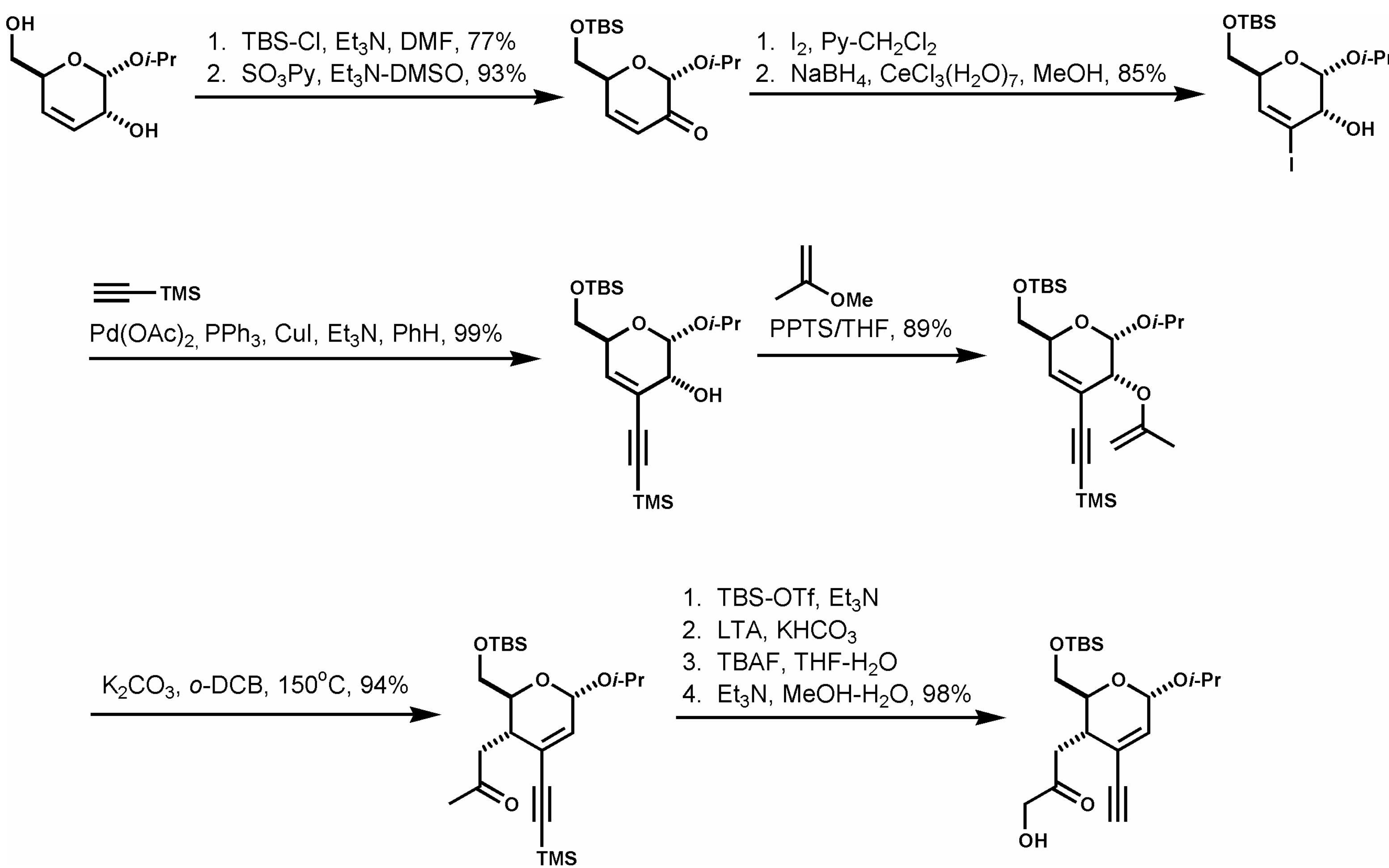


(+/-)-tetrodotoxin

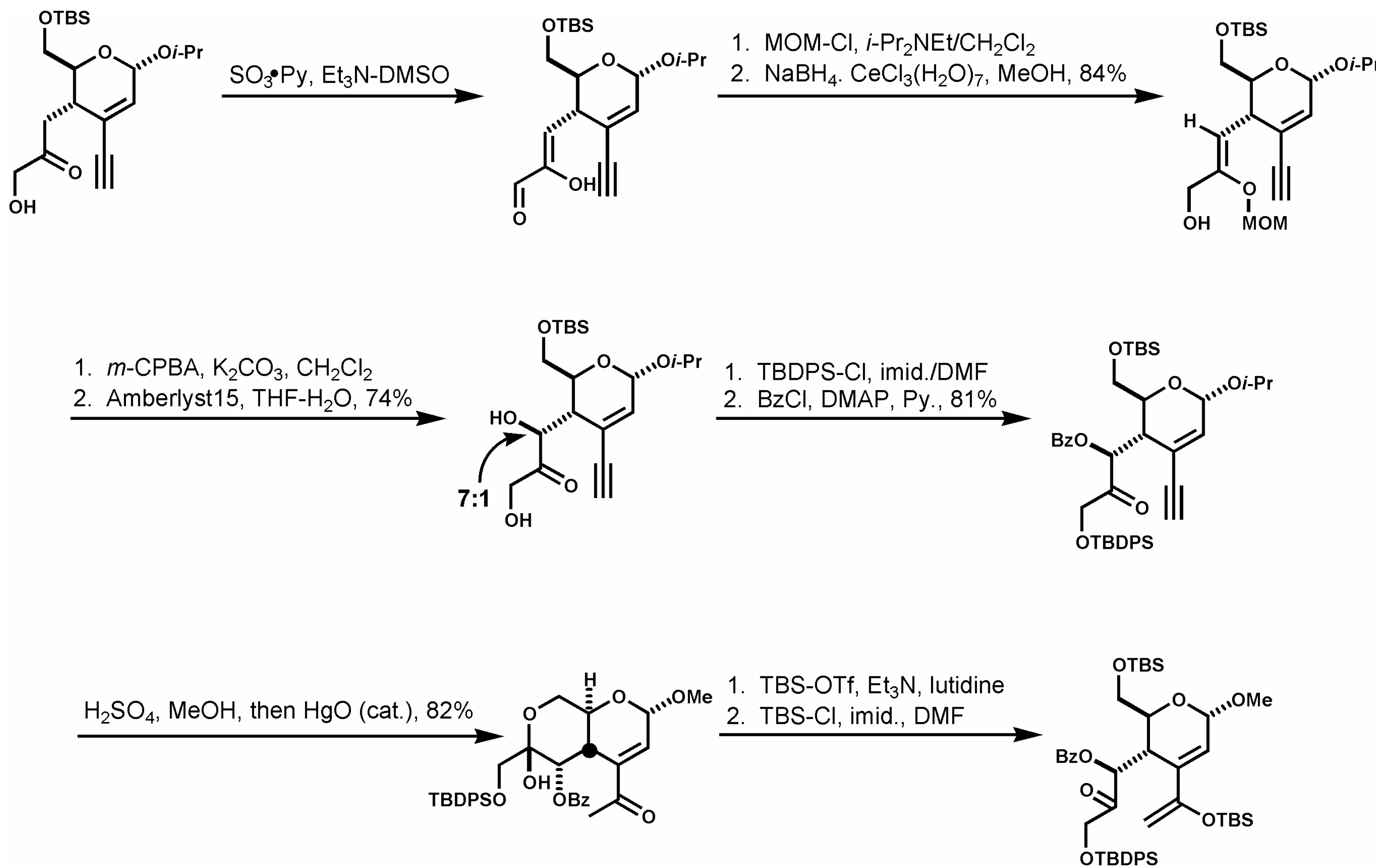
Isobe Retrosynthesis[6]



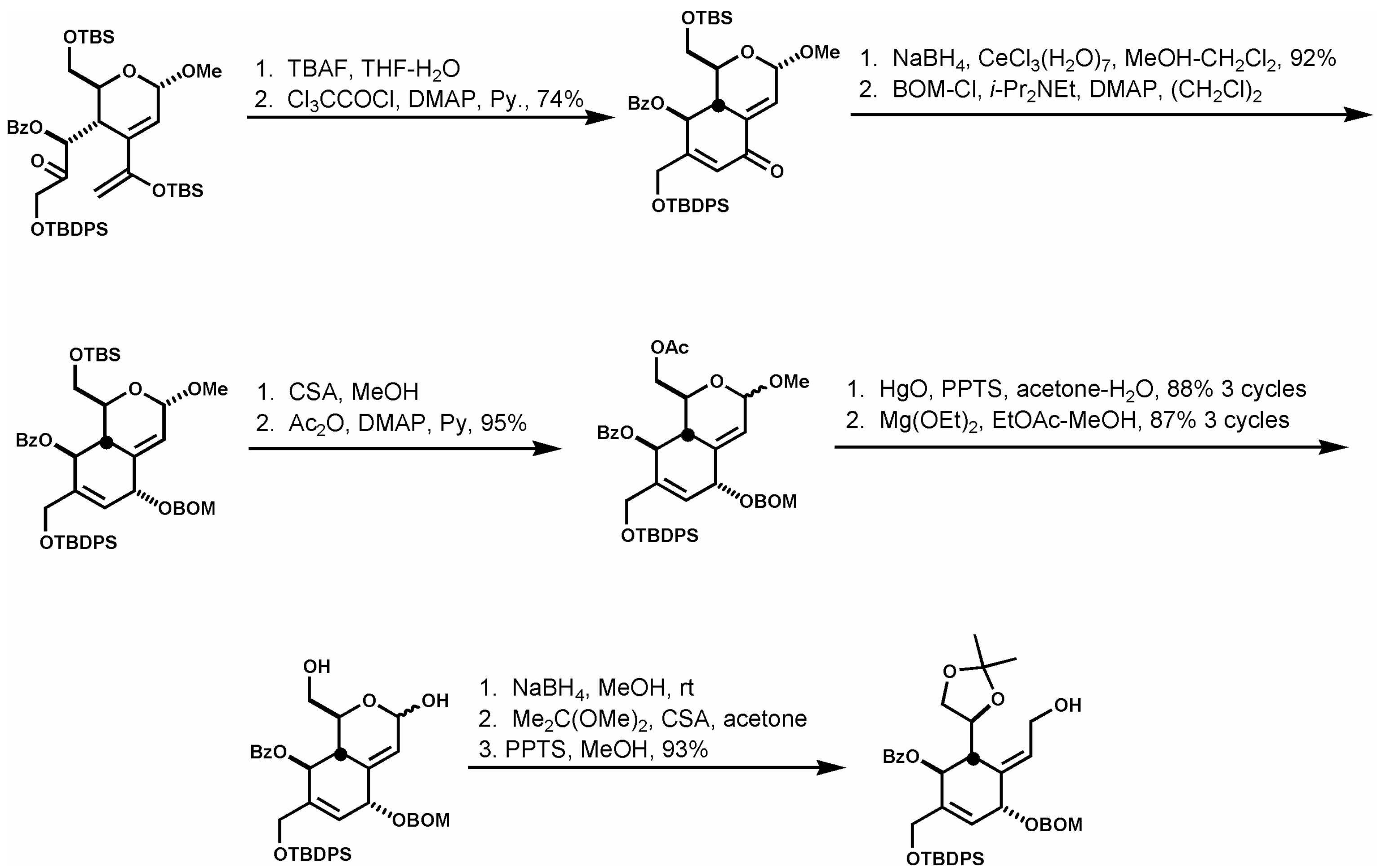
Isobe Synthesis[6]



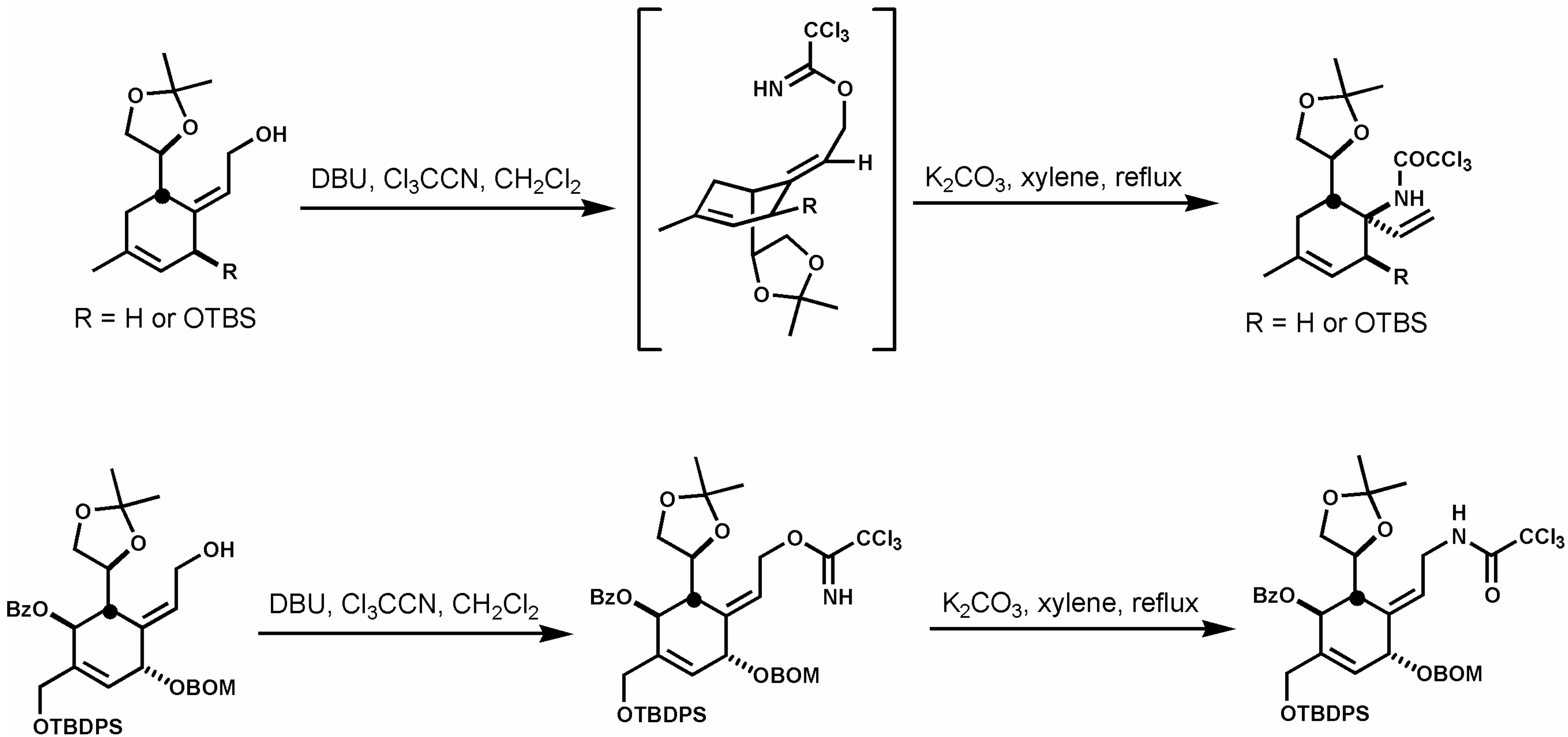
Isobe Synthesis[6]



Isobe Synthesis[6]



Isobe Synthesis[6]



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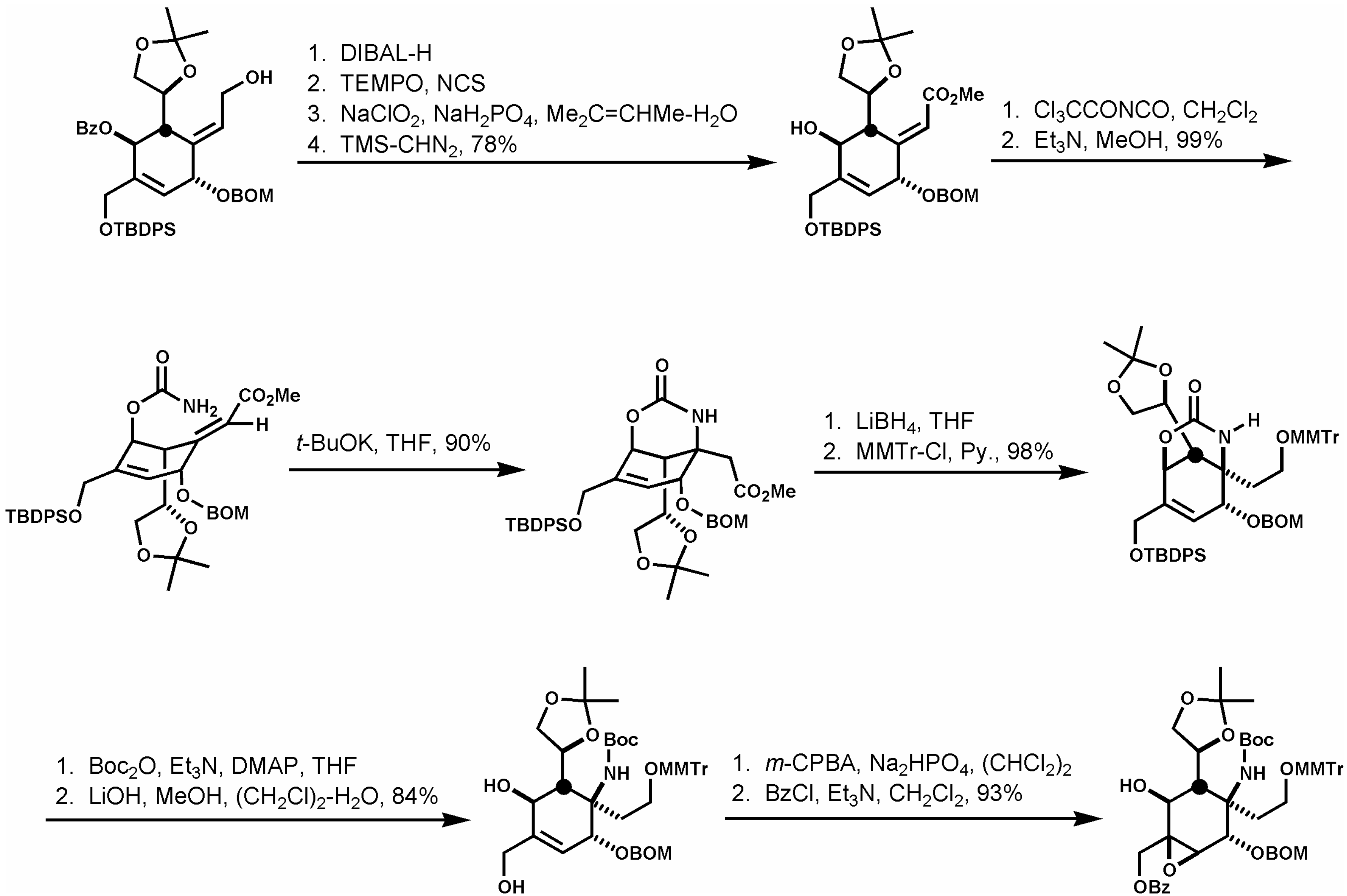

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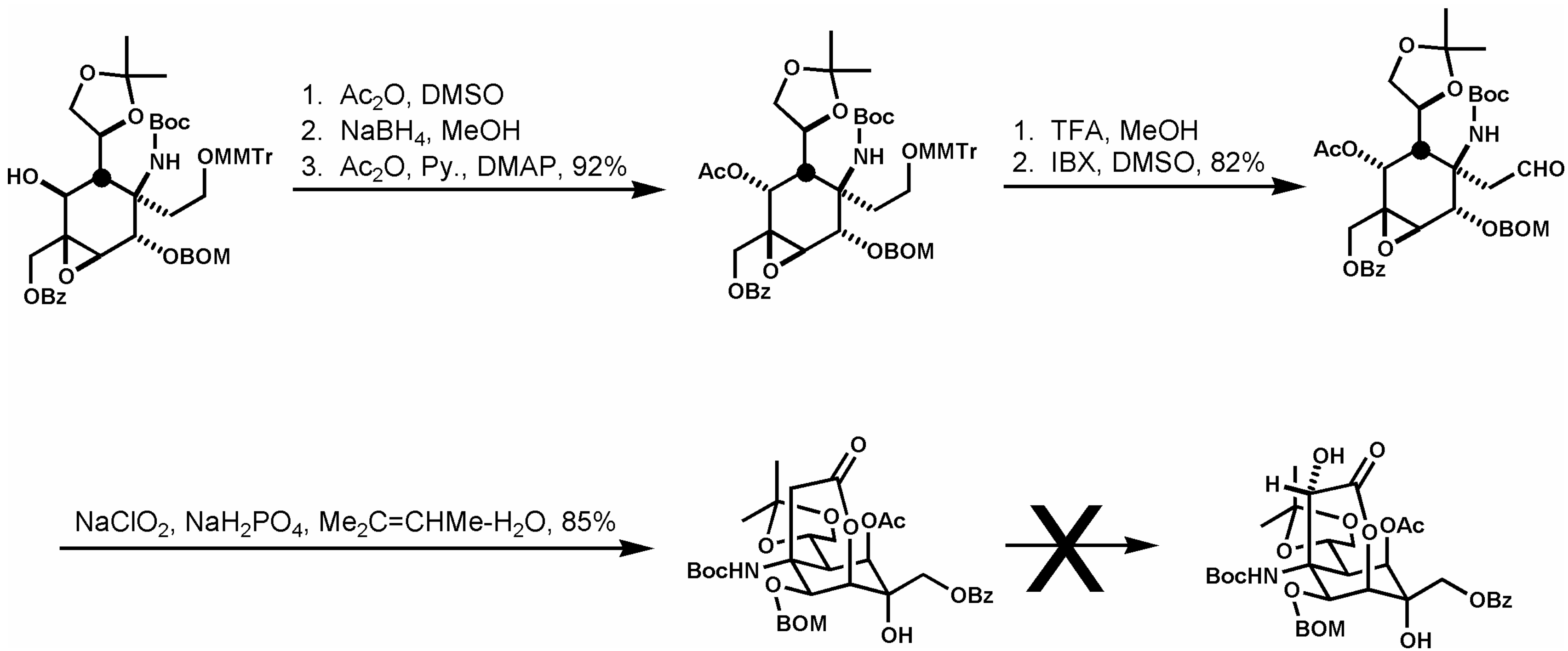

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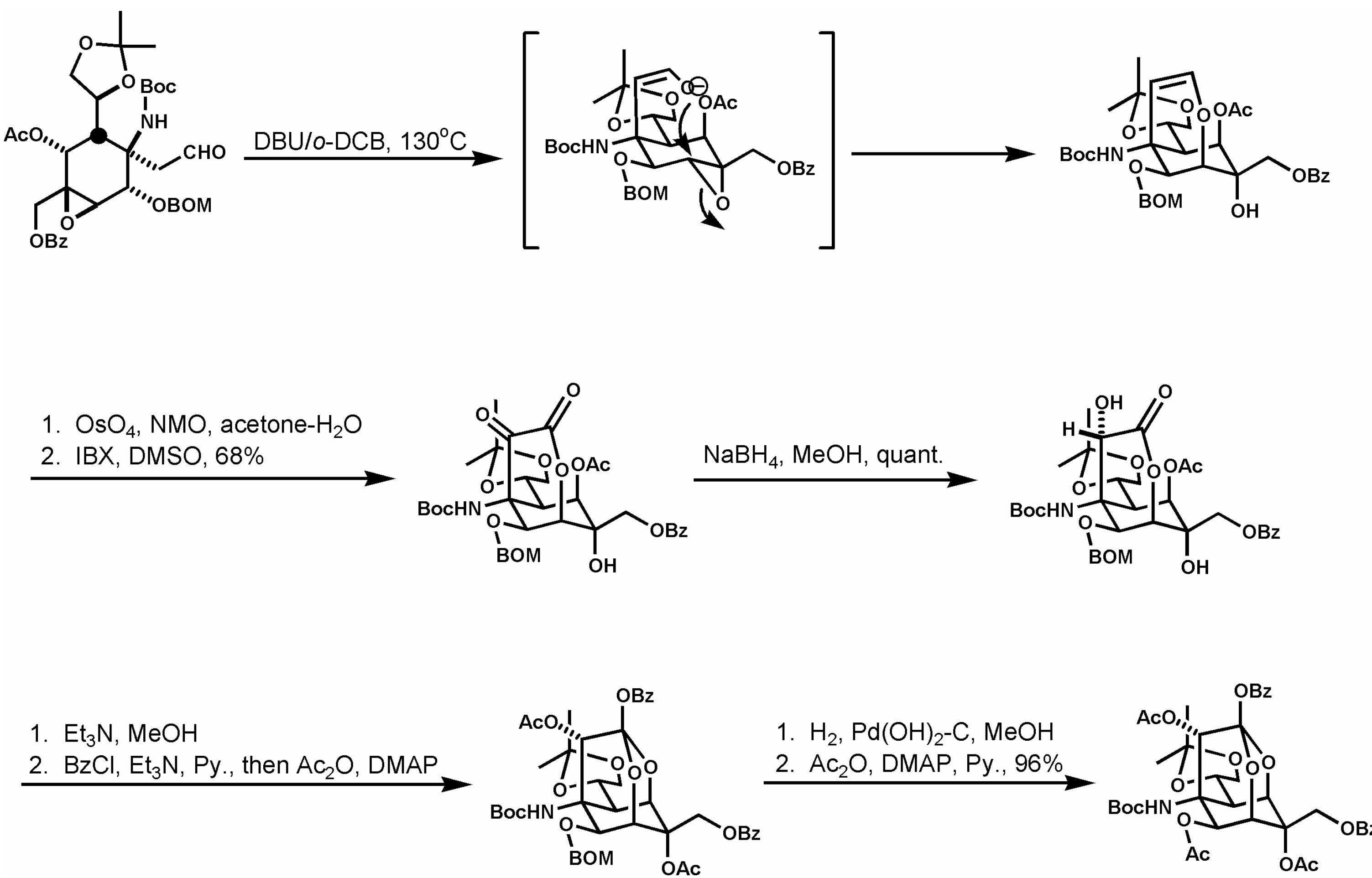
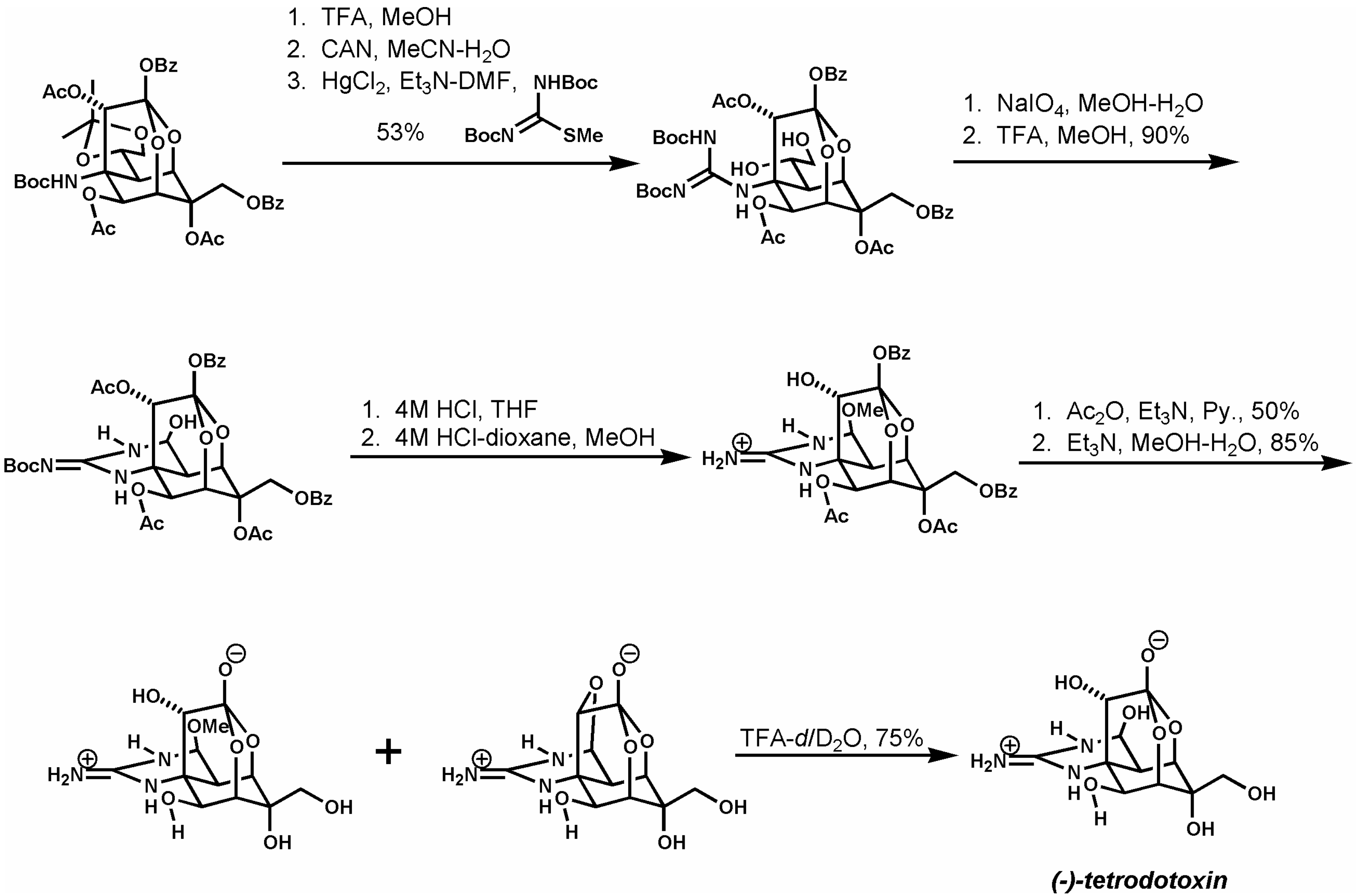
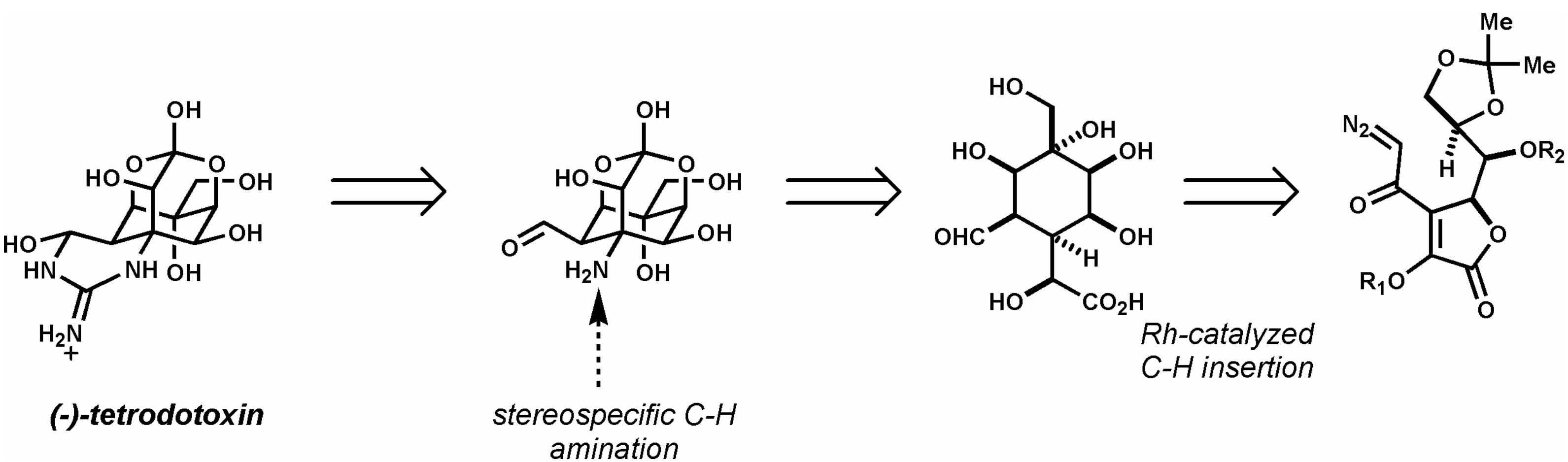


Isobe Synthesis[6]



Du Bois Retrosynthesis[7]



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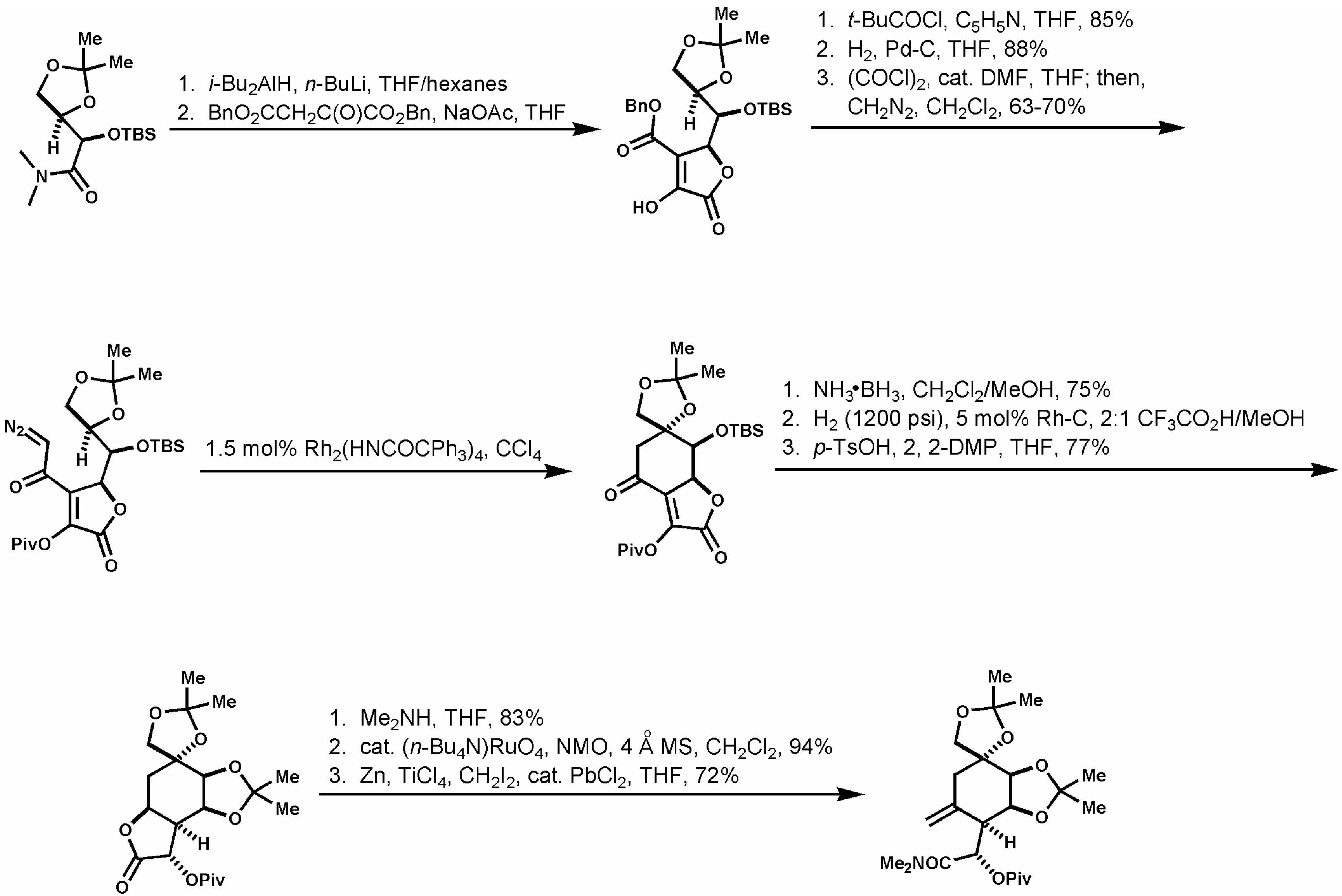

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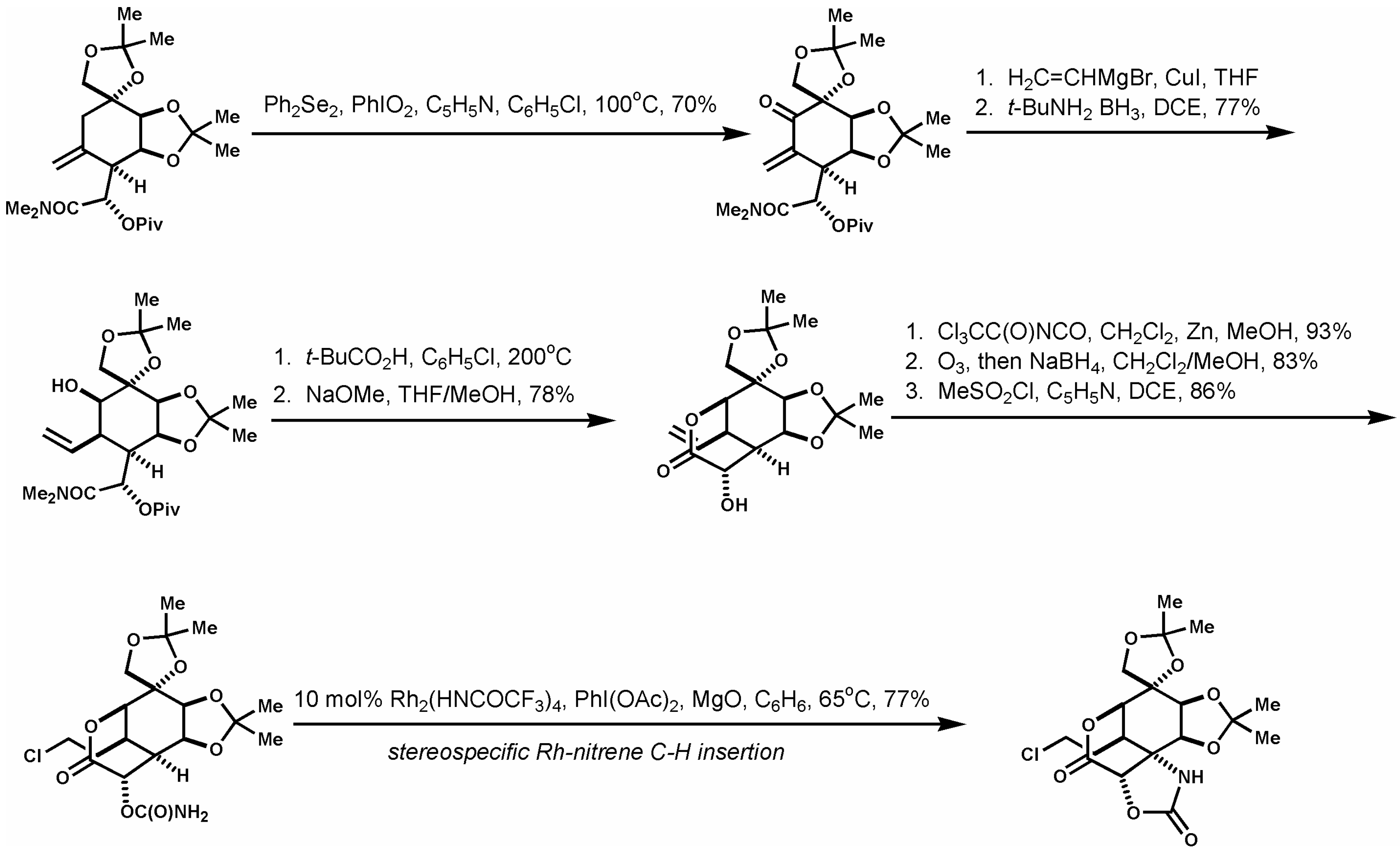

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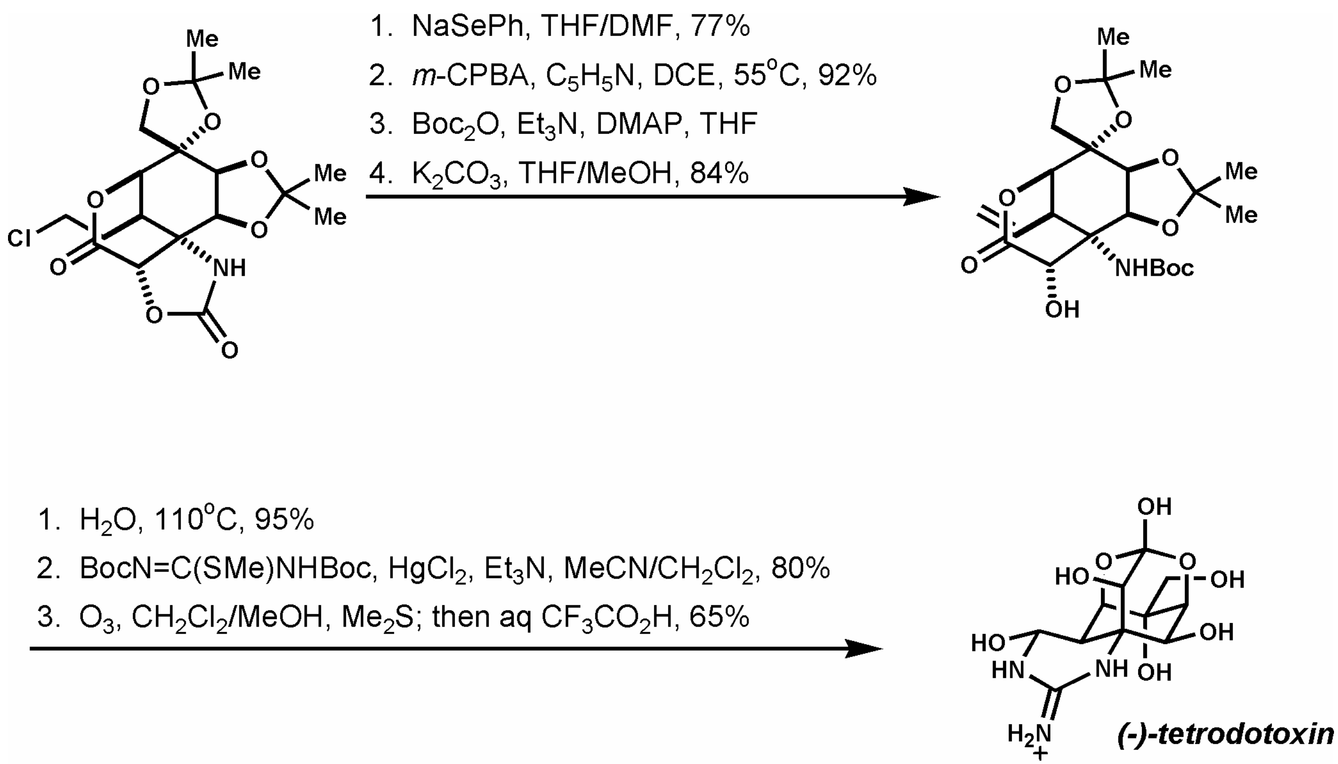

References

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5. (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217-9219.
   (b) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219-9221.

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