# Total Synthesis of and Studies Surrounding Batrachotoxinin A

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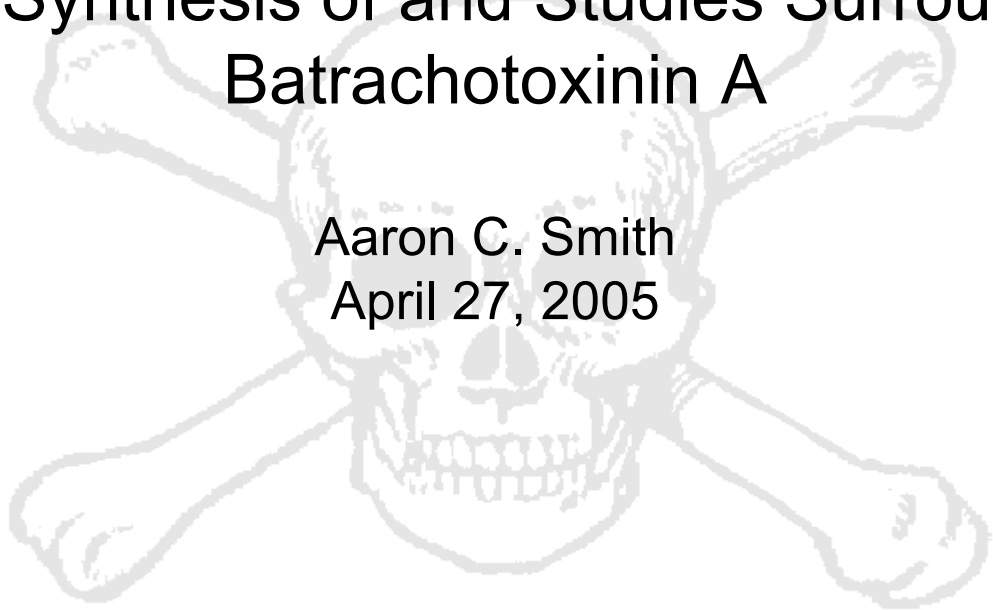


Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998,** *120,* 6627.
Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994,** *35,* 8333.
Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994,** *35,* 8337.

# Structure and Biological Activity

- Isolated from skins of the green-banded poison dart frog, *phyllobates aurotaenia,* as well as from feathers of a New Guinea bird, *Pitohui*

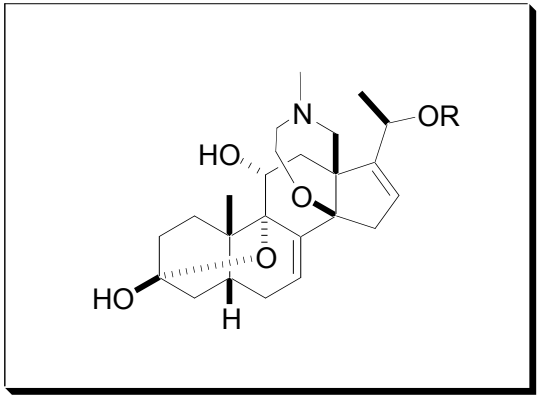
- Recent data proposes source of the batrachotoxins is a melyrid beetle that is a dietary source for the birds

- Among the most toxic natural substances, 250 times more potent than strychnine

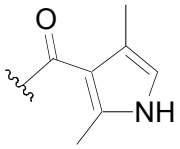
- Bind with high affinity to voltage-gated sodium channels in nerve and muscle membranes, locking them in an open state

- Structures of bachratoxinin A and bachratoxin determined through X-ray analysis and chemical correlation, respectively

- Structural features include steroid-based pentacyclic core, a seven-membered oxazapane ring, and a hemiketal moiety

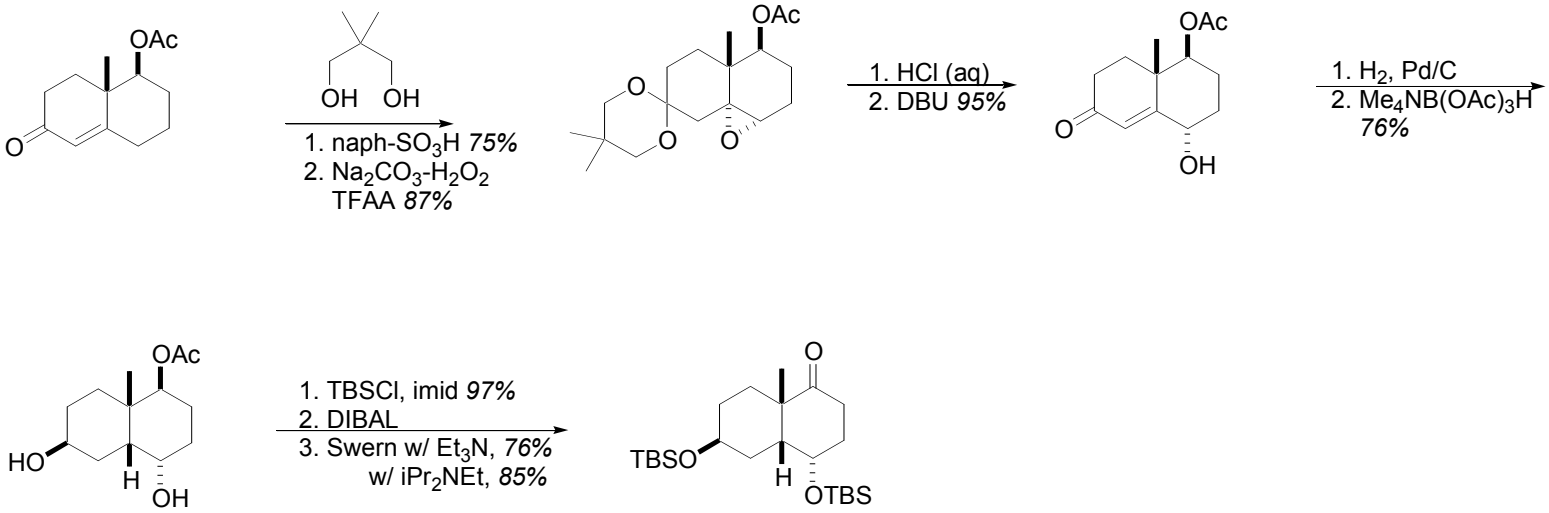



**Batrachotoxinin A**: R = H

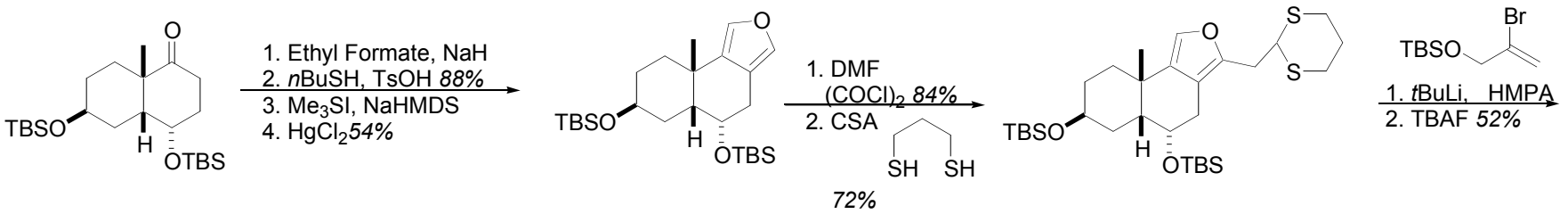
**Batrachotoxin**: R = 

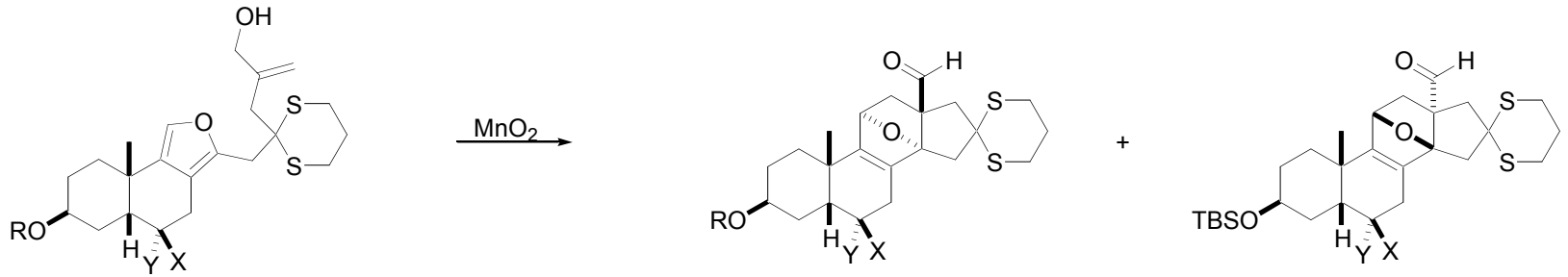
# Retrosynthetic Analysis

# Synthesis of Ketone



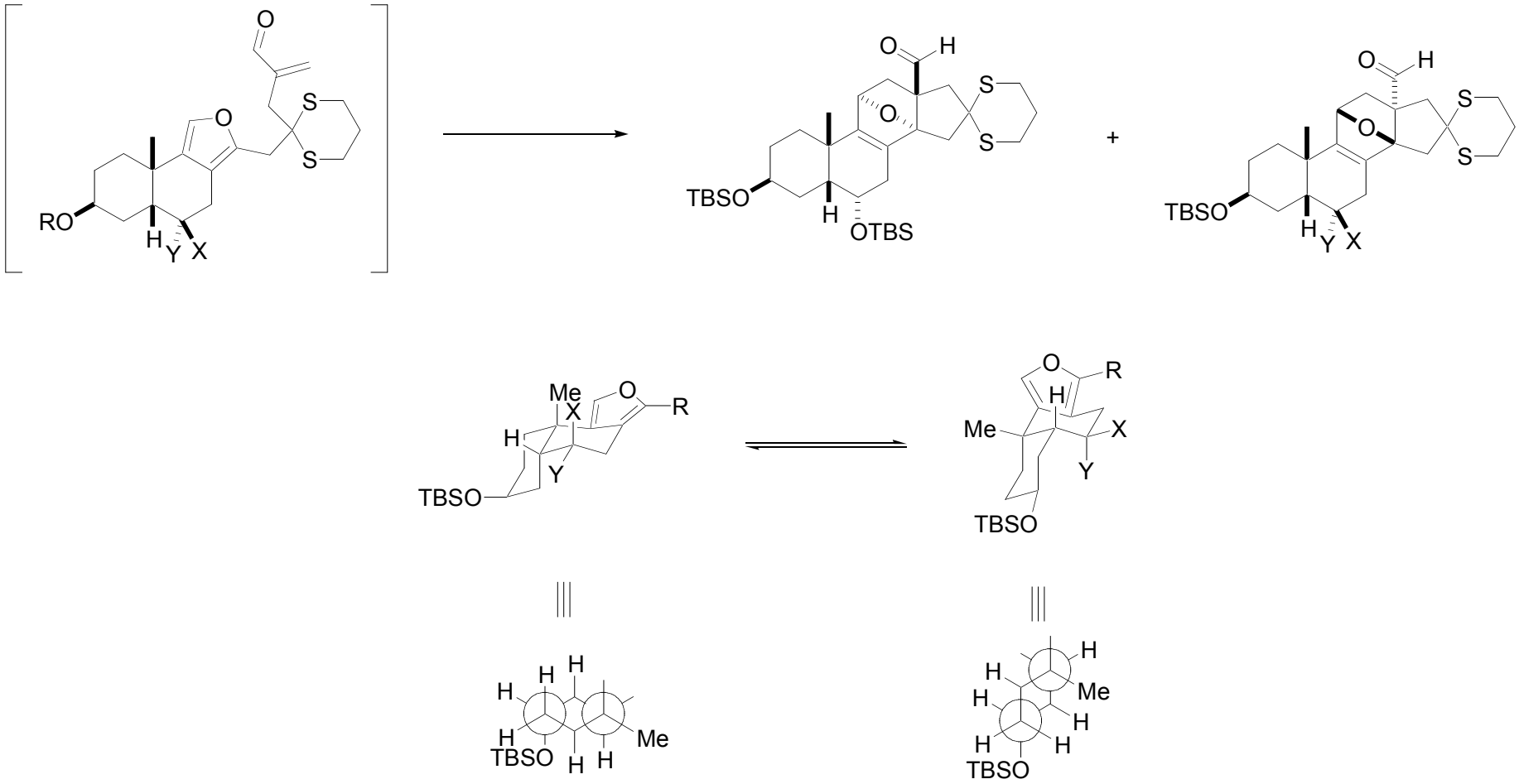
# Synthesis of Diels-Alder Precursor



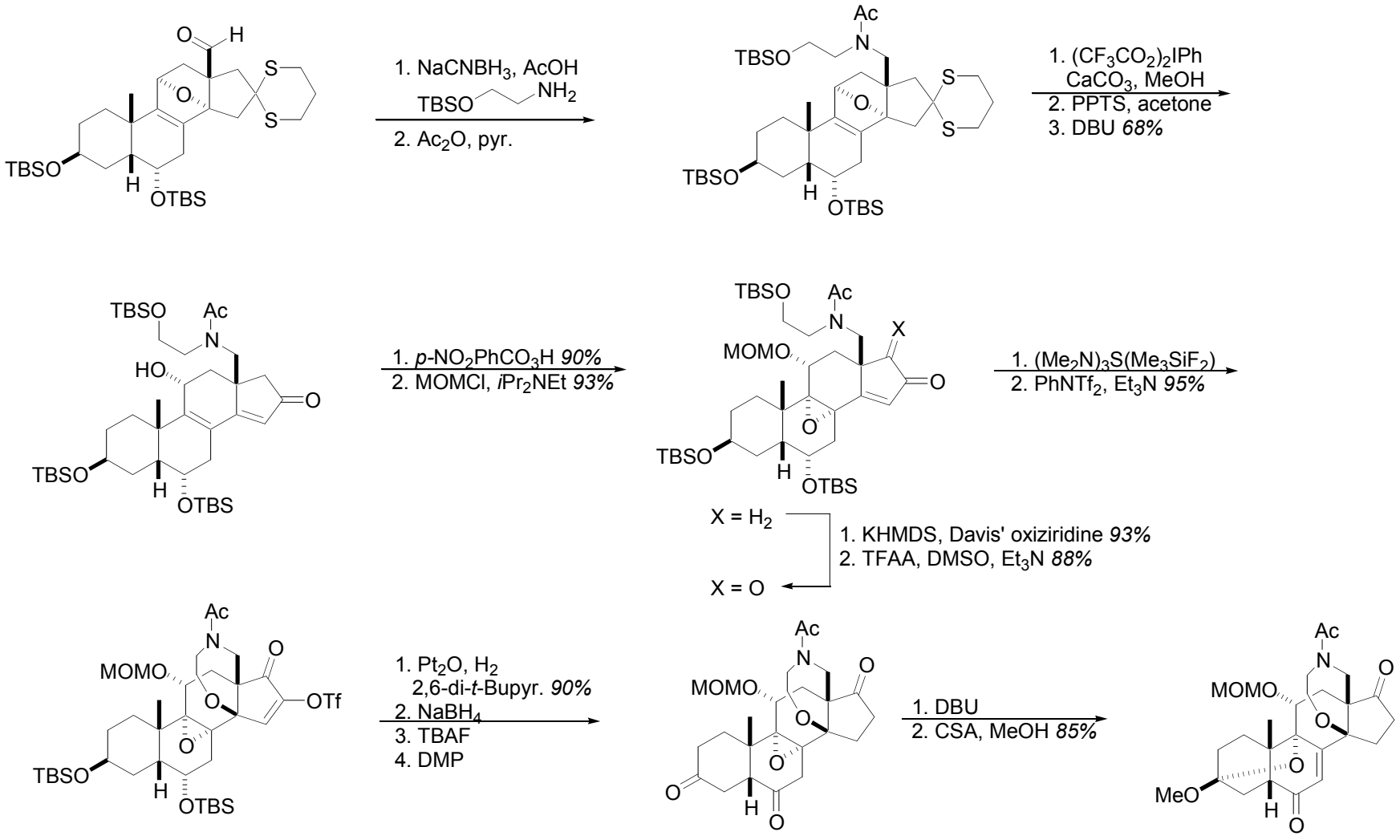




| entry | R | X | Y | yield, % | ratio (X:X) |
|---|---|---|---|---|---|
| **a** | TBS | H | OTBS | 70-75 | >25:1 |
| **b** | TBDPS | H | H | 75-80 | >3:1 |
| **c** | TBDPS | OPMB | H | 40-50 | 1.4:1 |

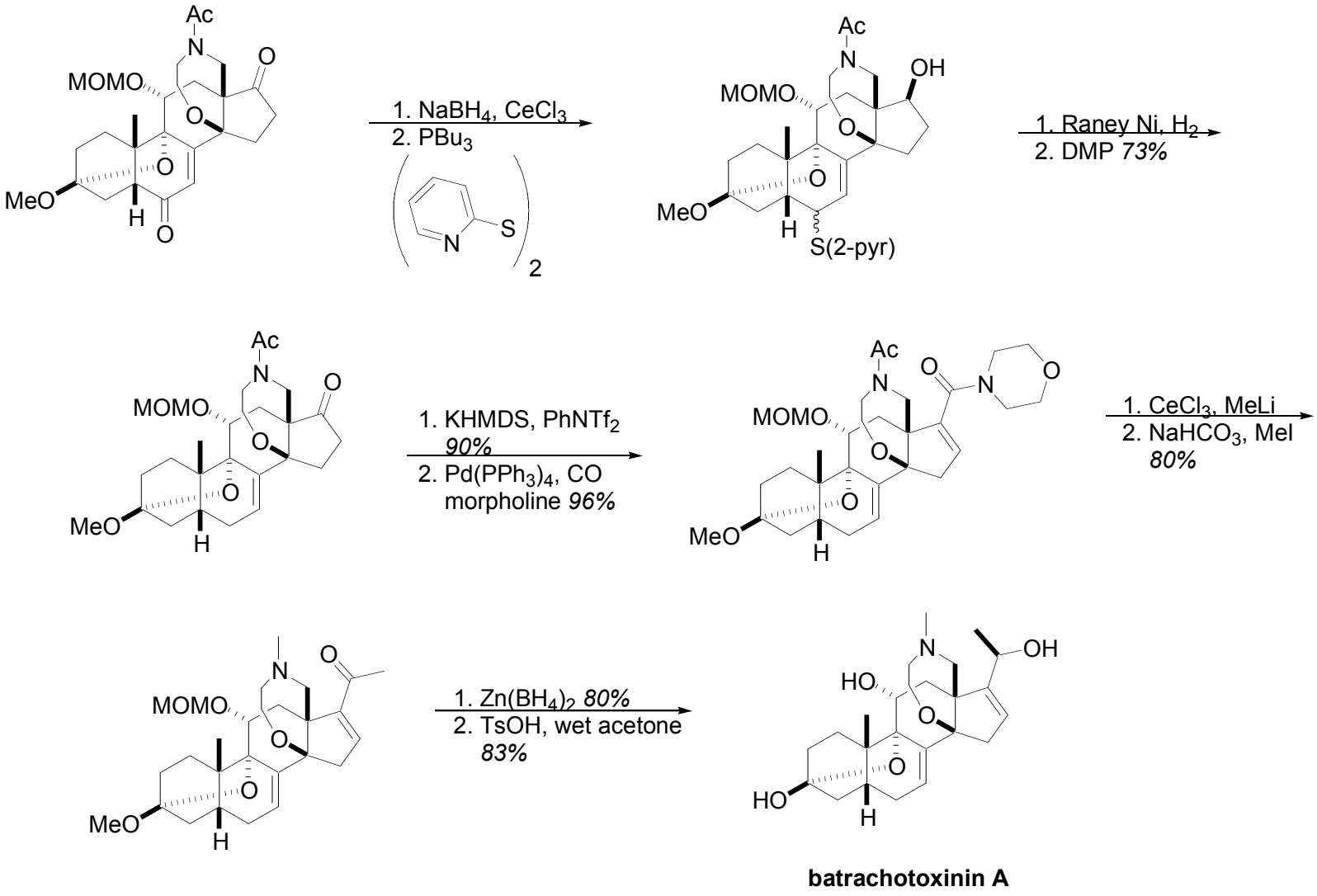
# Stereoselectivity of the Diels-Alder



# Synthesis of Methyl Ketal

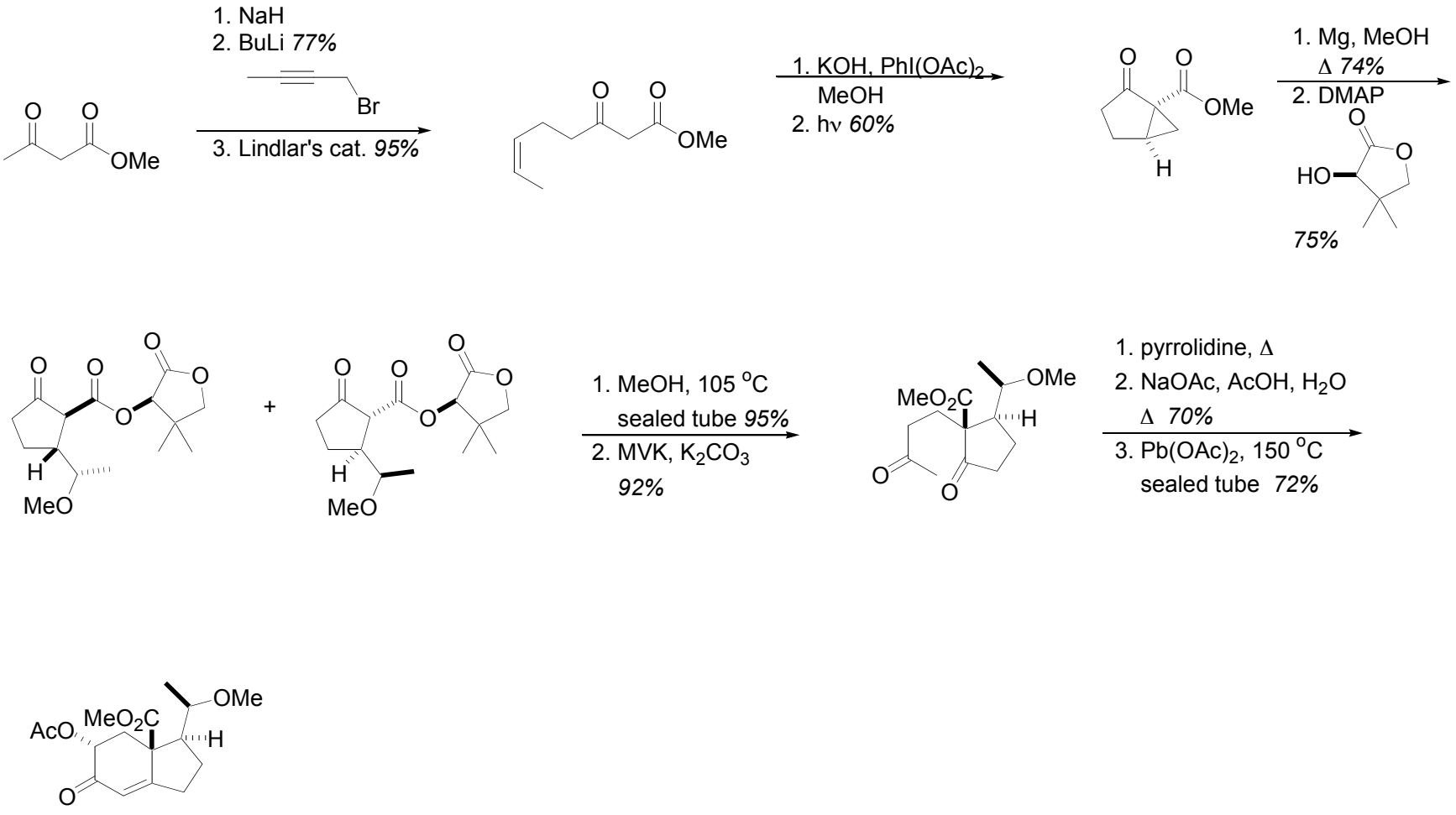


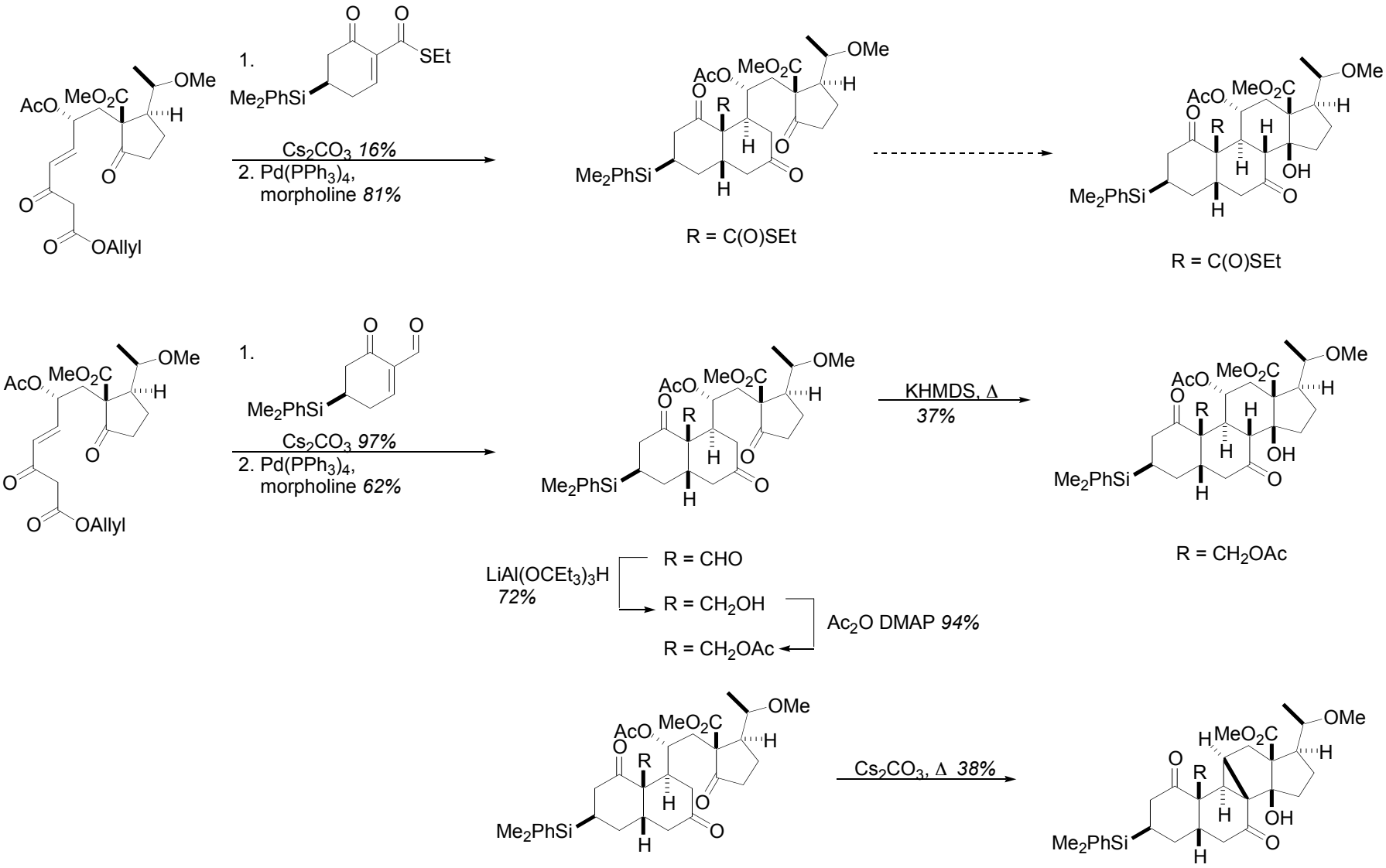
# Completion of Synthesis




**batrachotoxinin A**

# Synthesis of an Advanced Intermediate




1.
Me2PhSi
SEt
Cs2CO3 16%
2. Pd(PPh3)4,
morpholine 81%
AcO
MeO2C
OMe
H
OAllyl
R = C(O)SEt
Cs2CO3 97%
2. Pd(PPh3)4,
morpholine 62%
KHMDS, Δ
37%
R = CH2OAc
LiAl(OCEt3)3H
72%
R = CHO
R = CH2OH
Ac2O DMAP 94%
R = CH2OAc
Cs2CO3, Δ 38%
OH