

Total Synthesis of Calicheamicin Type Eneidyne Natural Products

17/09/02 Yuki Fujimoto

Contents

Total synthesis of enediyne natural products

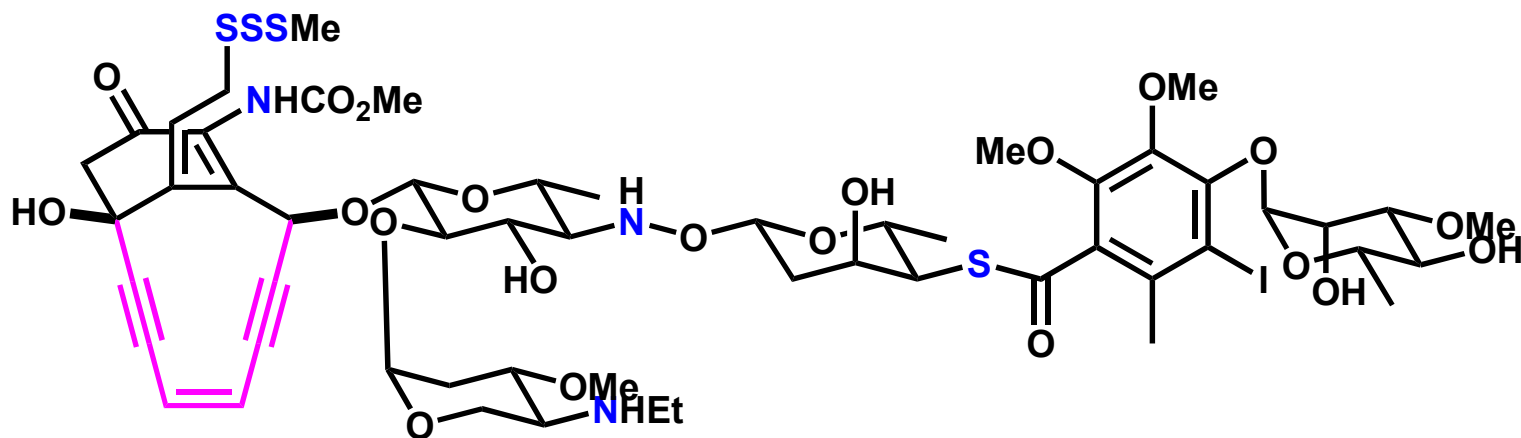
Introduction

calicheamicinone synthesis

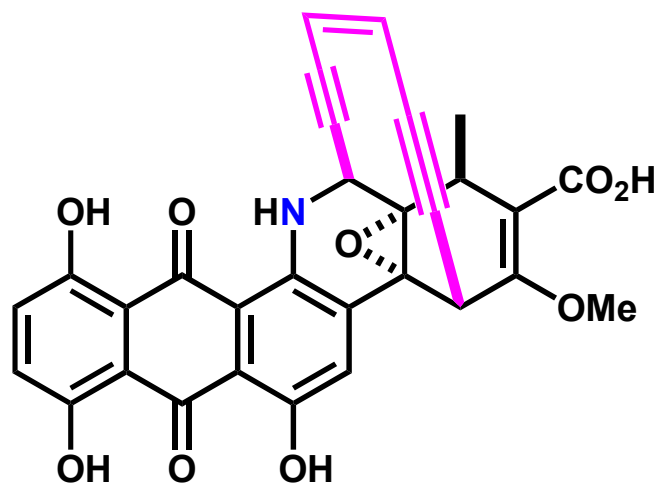
shishijimicin A synthesis (main paper)

Summary

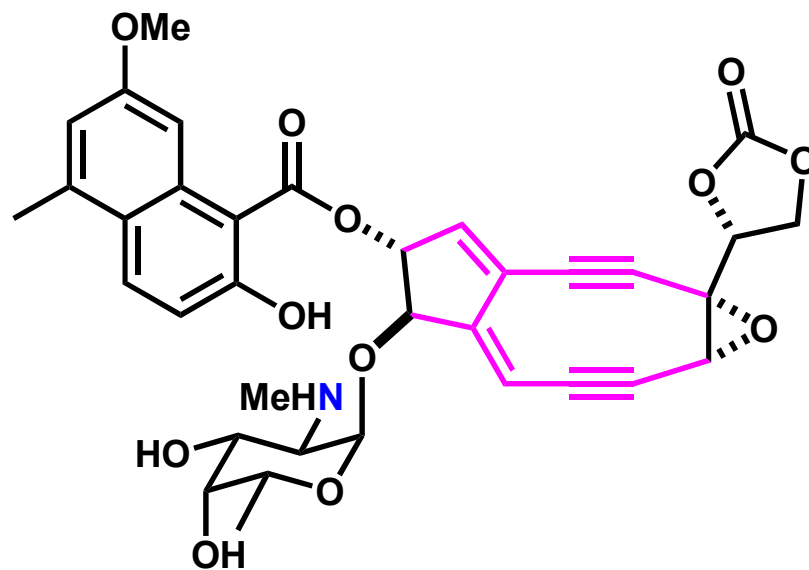
Eneidyne Natural Products



calicheamicin γ_1 (calicheamicin type)

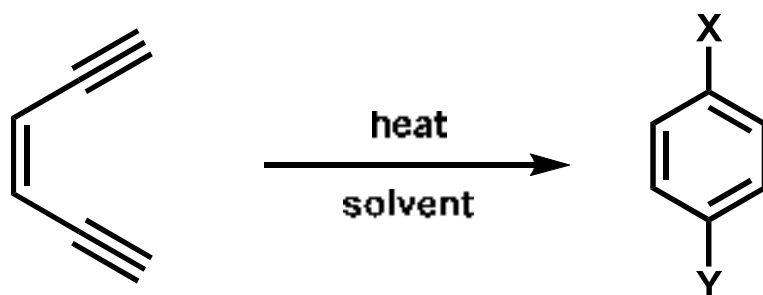
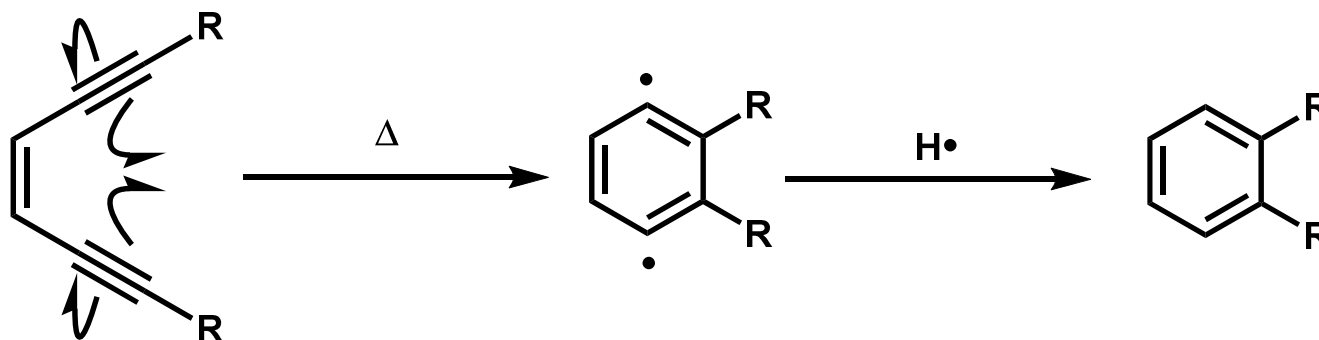


dynemicin A (dynemicin type)



neocarzinostatin chromophore
(chromoprotein type)

Bergman Cyclization



solvent	X	Y
1,4-cyclohexadiene	H	H
CCl_4	Cl	Cl
MeOH	CH_2OH	H

major: benzene

Distance of Diyne

Nicolaou's proposal
distance of diyne seem to be correlated to enediyne's stability.

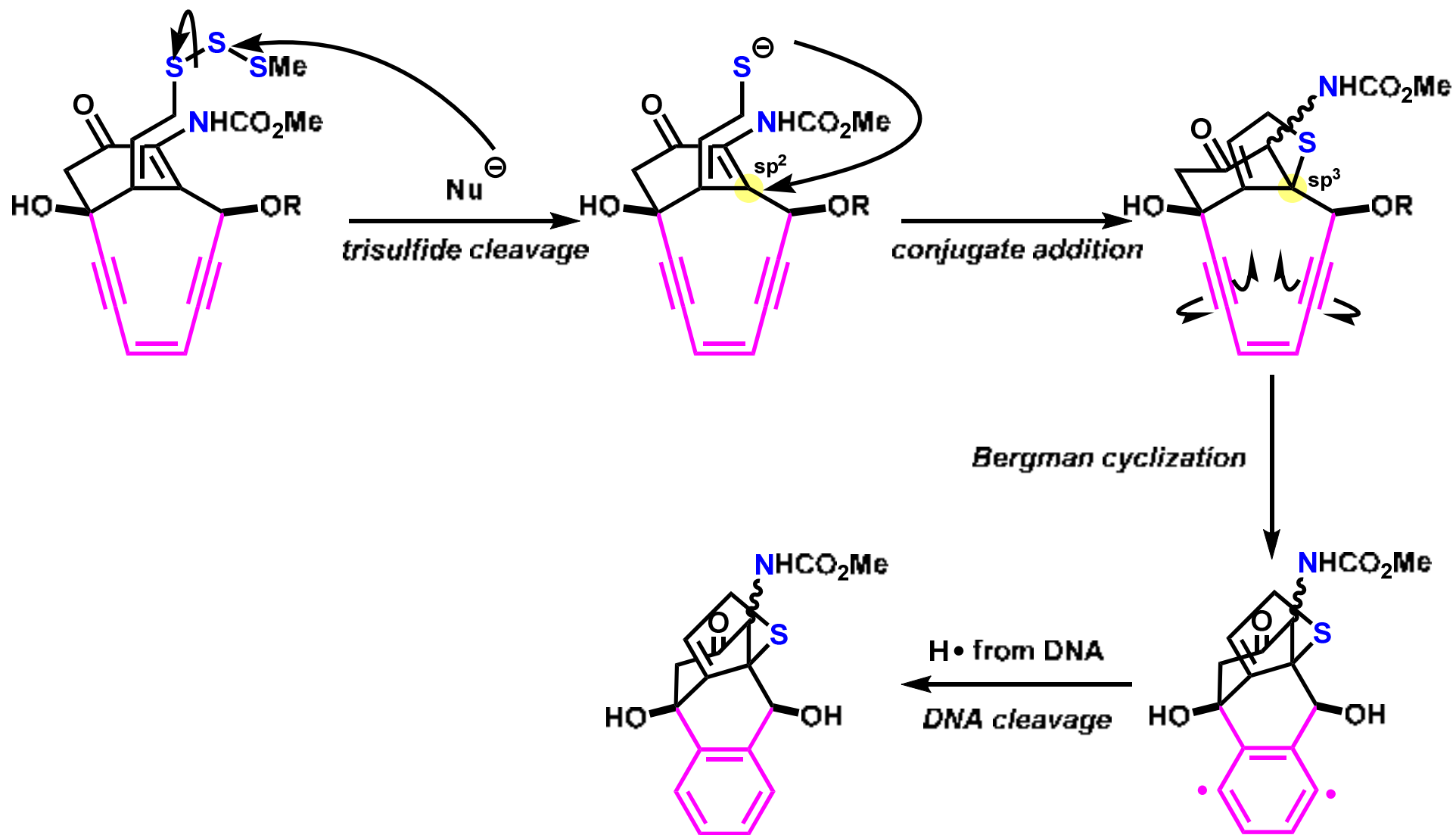


entry	compound	ring size	d [Å]	stability
1		10	3.25	$t_{1/2} = 18$ h at 37 °C
2		10	3.01	cyclized < 25 °C
3		10	3.40	$t_{1/2} = 52$ h at 37 °C
4		11	3.61	stable at 25 °C
5			4.12	stable at 25 °C $t_{1/2} = 30$ s at 200 °C

a) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

b) Nicolaou, K. C.; Dai, W. M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.

Calicheamicin Type Action Mechanism



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Total synthesis of enediyne natural products

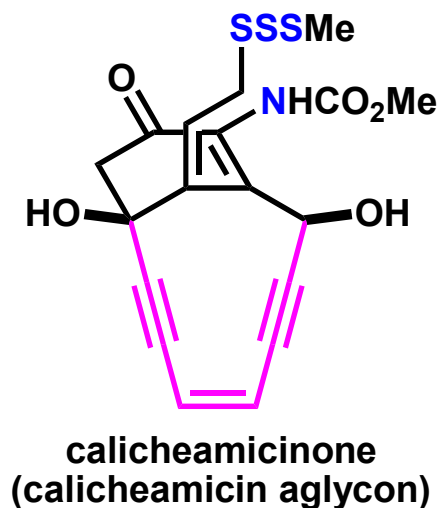
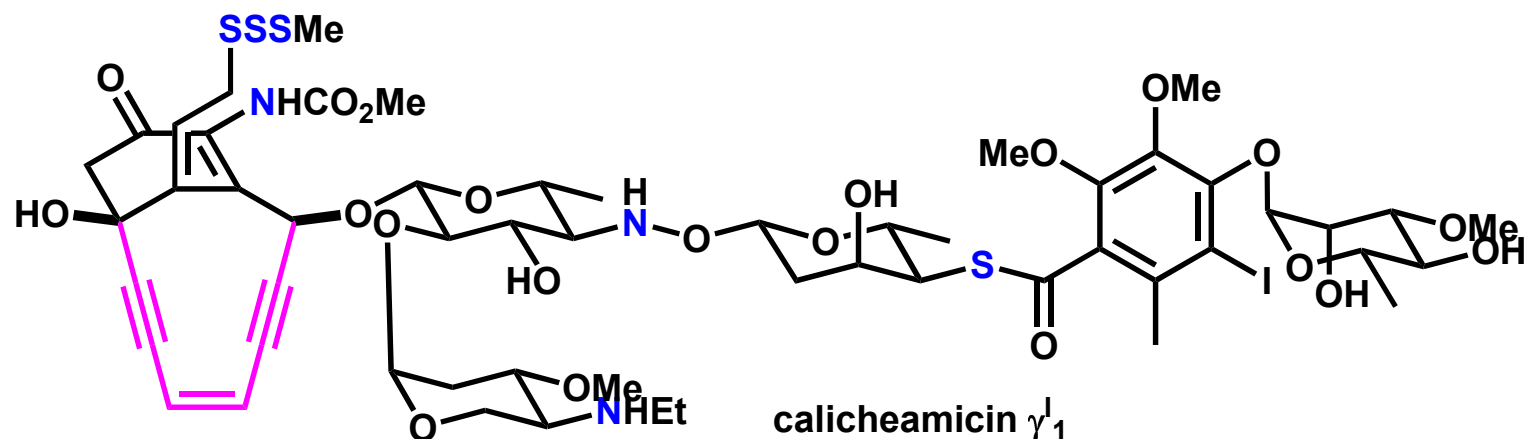
Introduction

calicheamicinone synthesis

shishijimicin A synthesis (main paper)

Summary

Introduction of Calicheamicin



Isolation

bacterial strain *Micromonospora echinospora ssp calichensis*¹⁾

Total synthesis of calicheamicin γ_1^I

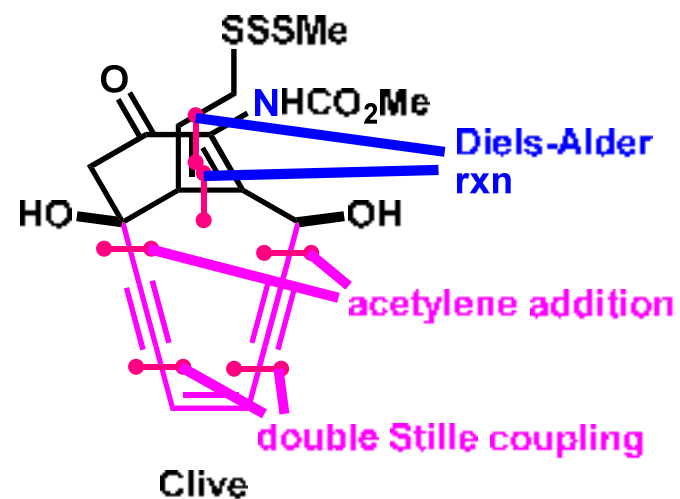
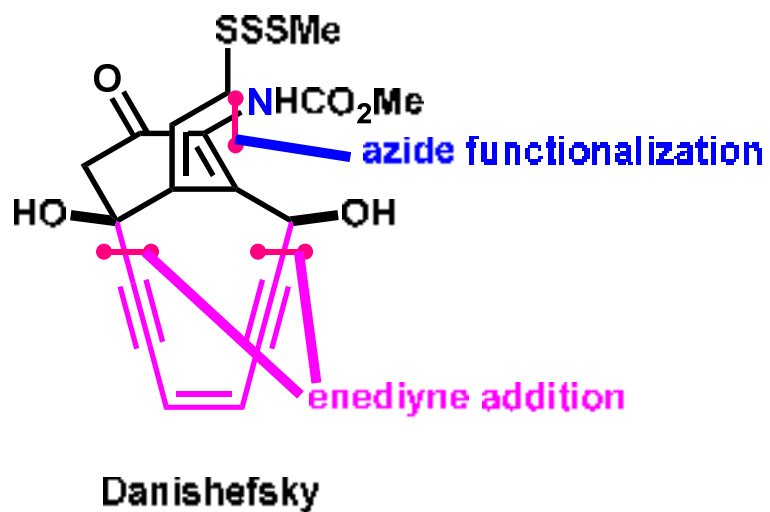
Nicolaou, K. C. (1992, enantiomeric)²⁾
Danishefsky (1994, enantiomeric)³⁾

Total synthesis of calicheamicinone

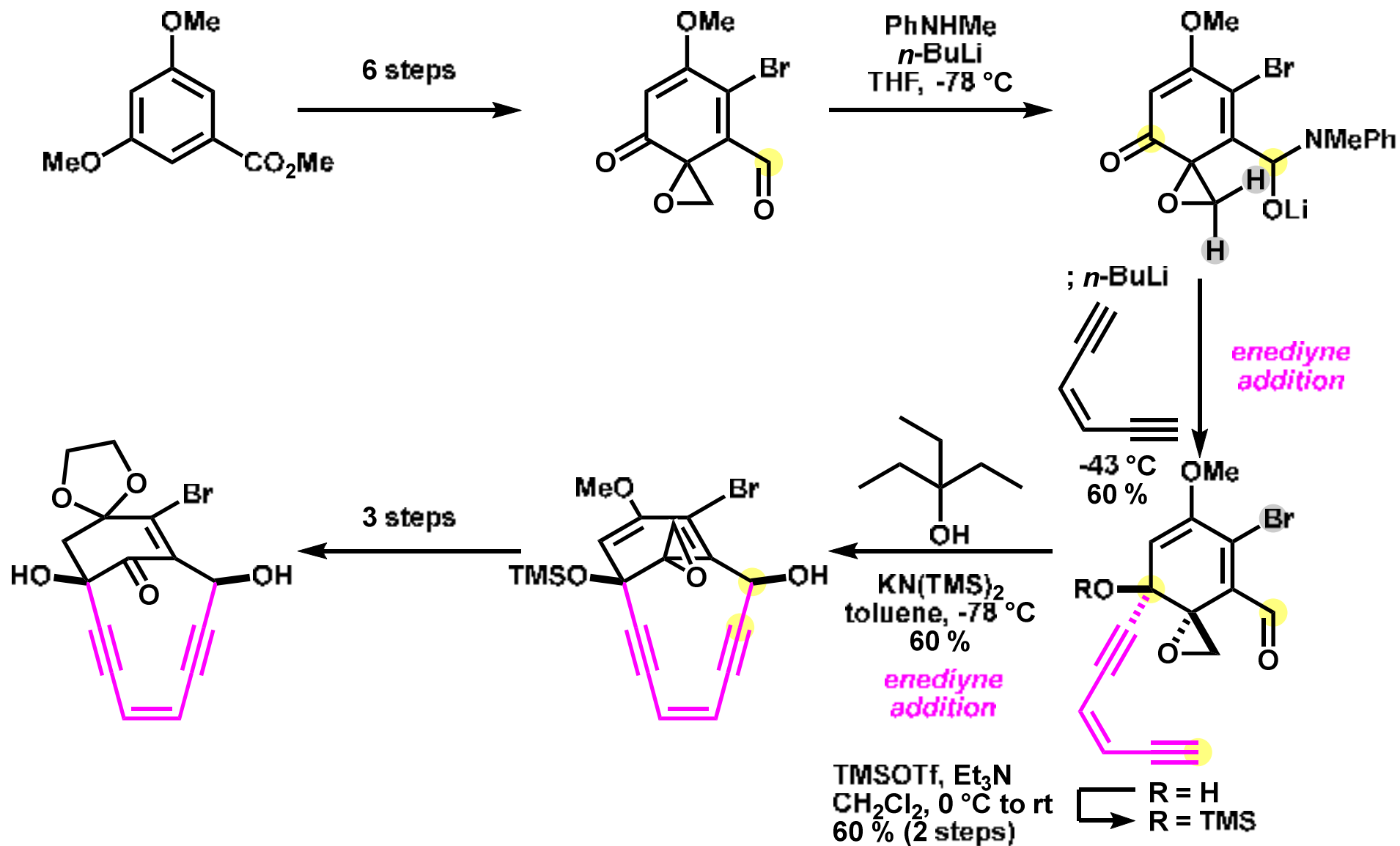
Danishefsky, S. J. (1990, racemic)⁴⁾
Nicolaou, K. C. (1993, enantiomeric)⁵⁾
Clive, D. L. J. (1996, racemic)⁶⁾
Magnus, P. (1998, racemic)⁷⁾

-
- 1) Borders, D. B. et al *J. Am. Chem. Soc.* **1987**, 109, 3464.
 - 2) Nicolaou, K. C. et al *J. Am. Chem. Soc.* **1992**, 114, 10082.
 - 3) Danishefsky, S. J.; et al *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 858.
 - 4) Danishefsky, S. J. et al *J. Am. Chem. Soc.* **1990**, 112, 3253.
 - 5) Nicolaou, K. C. et al *J. Am. Chem. Soc.* **1993**, 115, 7612.
 - 6) Clive, D. L. J. et al *J. Am. Chem. Soc.* **1996**, 118, 4904.
 - 7) Magnus, P. et al *J. Am. Chem. Soc.* **1998**, 120, 3518.

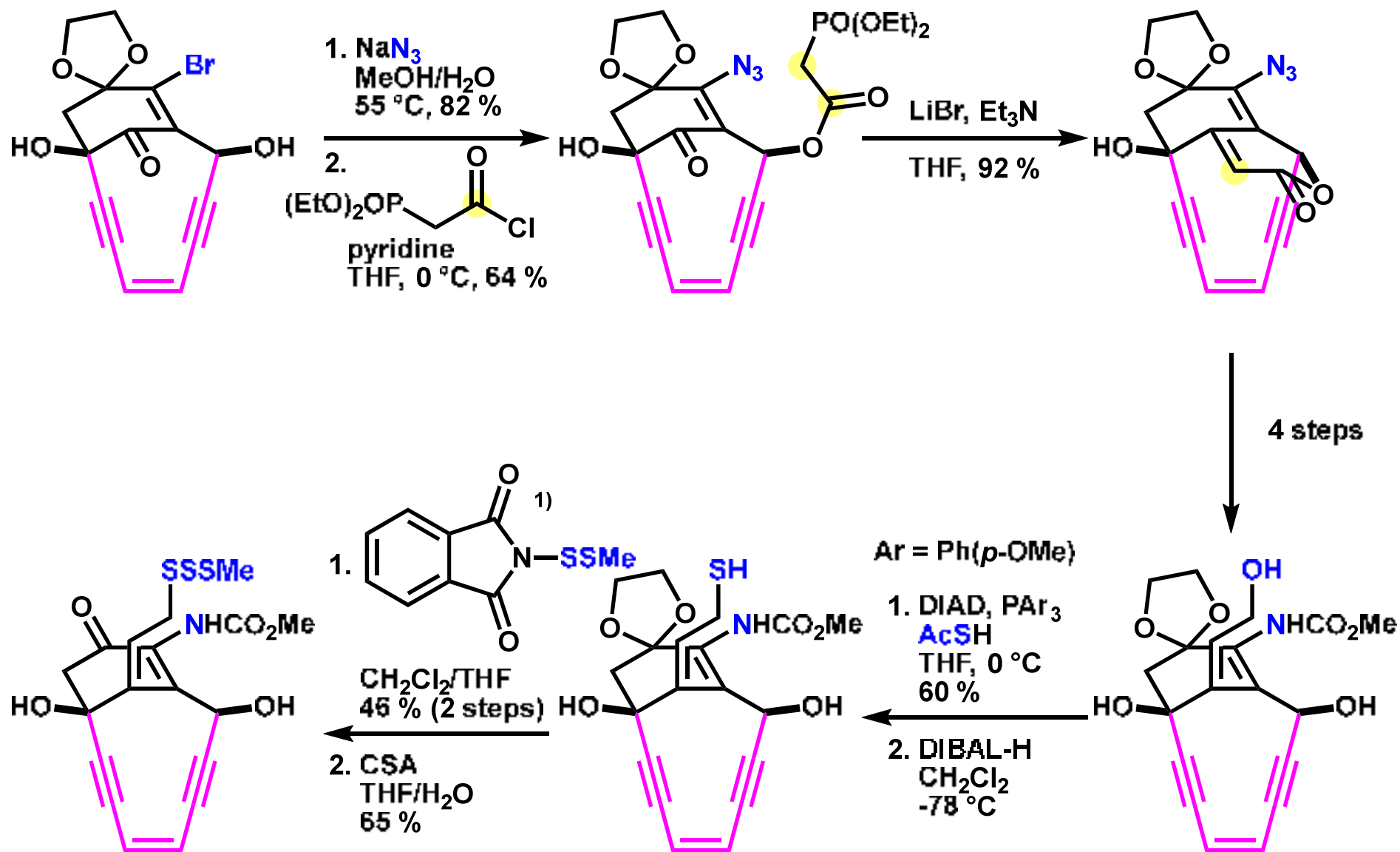
Strategy of Calicheamicin Synthesis



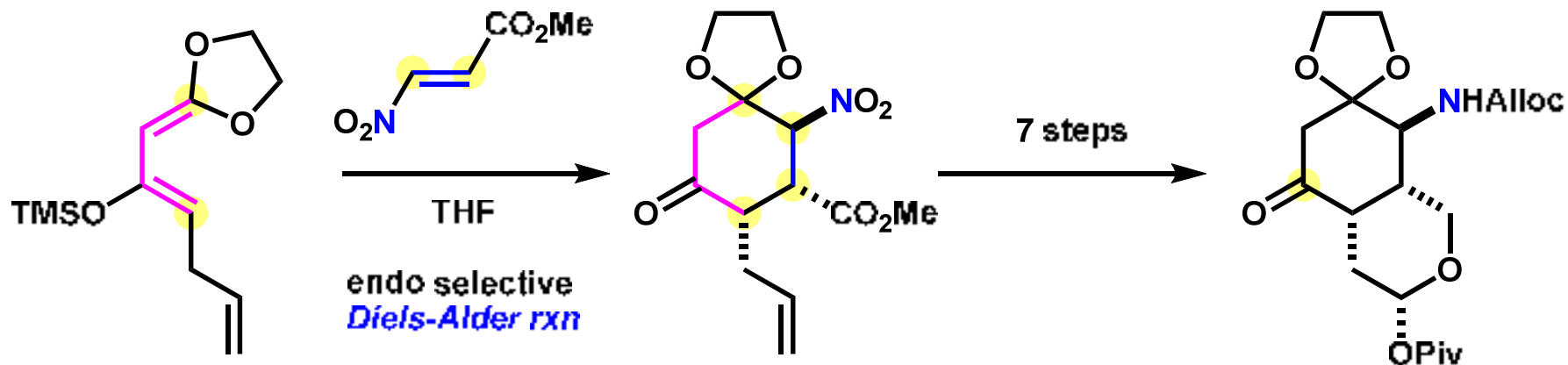
Danishefsky's Approach



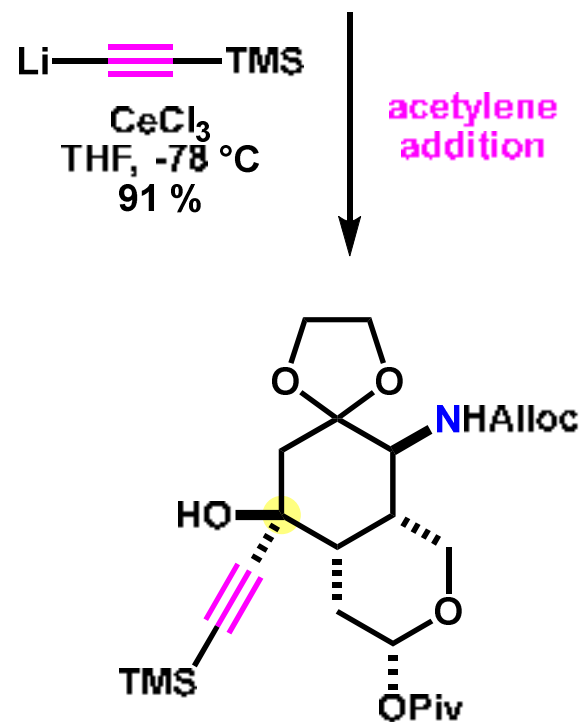
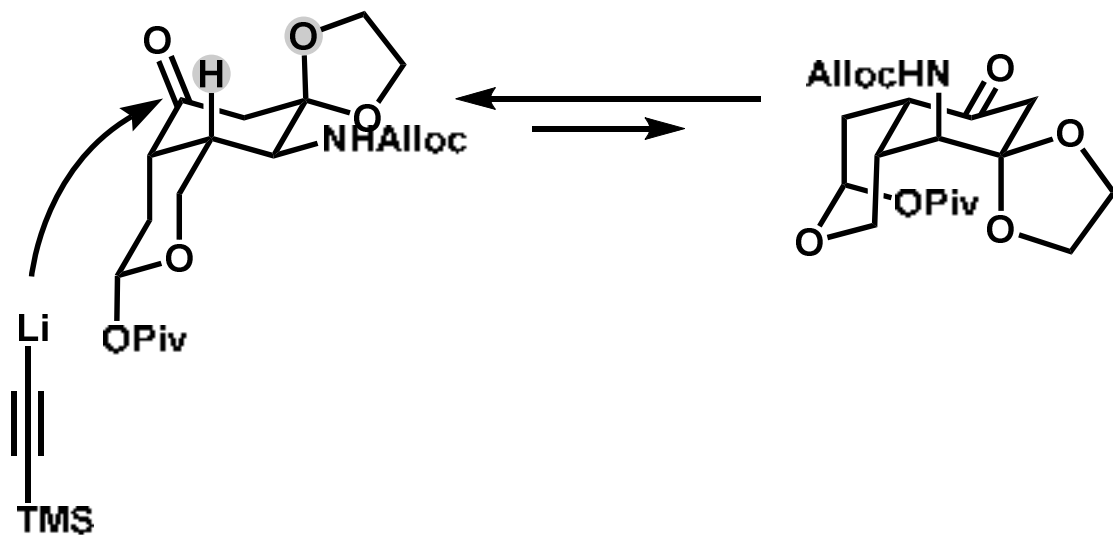
Danishefsky's Approach 2



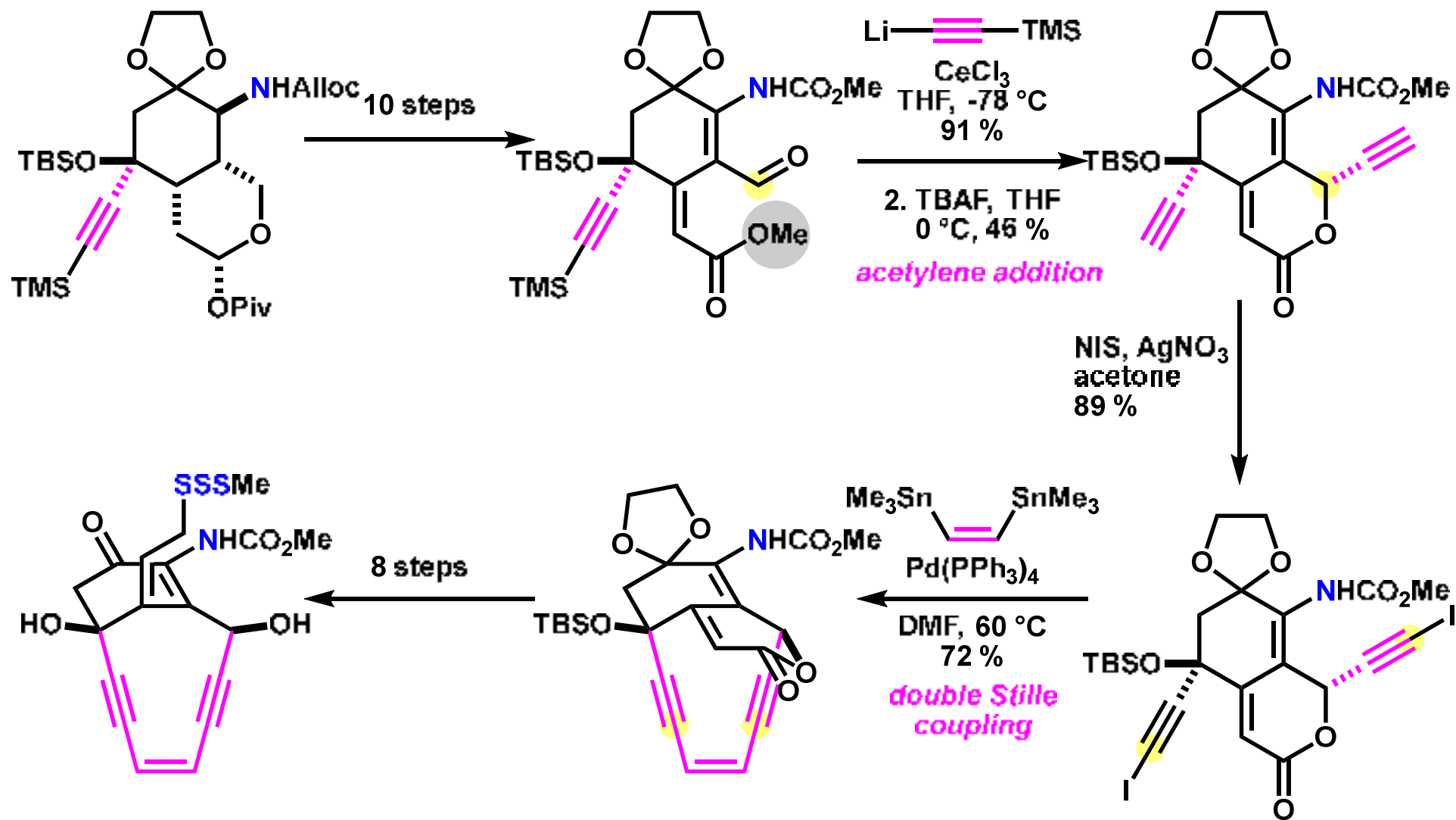
Clive's Approach



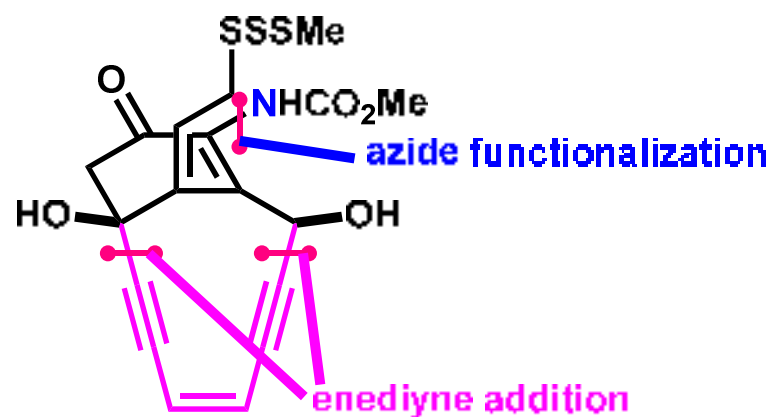
stereoselectivity of addition of TMS acetylene



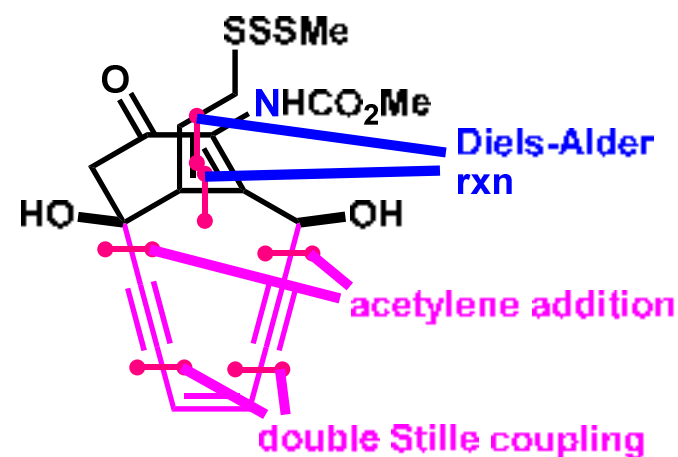
Clive's Approach 2



Summary of Calicheamicinone Synthesis



Danishefsky (22 steps, 0.2 % yield)



Clive (37 steps, 0.9 % yield)

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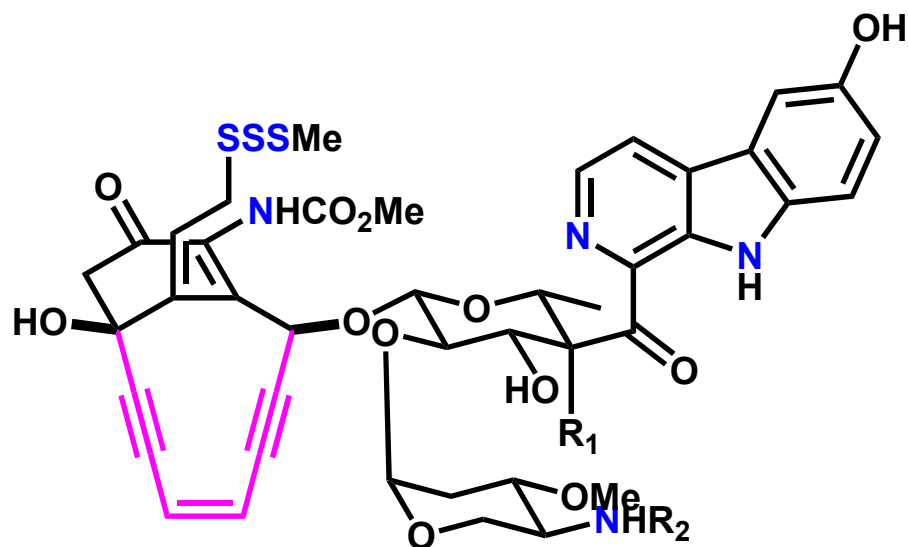
Introduction

calicheamicin synthesis

shishijimicin A synthesis (main paper)

Summary

Introduction of Shishijimicin



shishijimicin A ($R_1 = \text{SMe}$, $R_2 = i\text{-Pr}$)
shishijimicin B ($R_1 = \text{H}$, $R_2 = i\text{-Pr}$)
shishijimicin C ($R_1 = \text{SMe}$, $R_2 = \text{Et}$)

Isolation

lipophilic extract of the thin encrusting orange ¹⁾
ascidian *Didemnum proliferum* (2003)

Biological activity

antitumor
(IC₅₀ = 0.47 nM against P388 leukemia cells)

Structural features

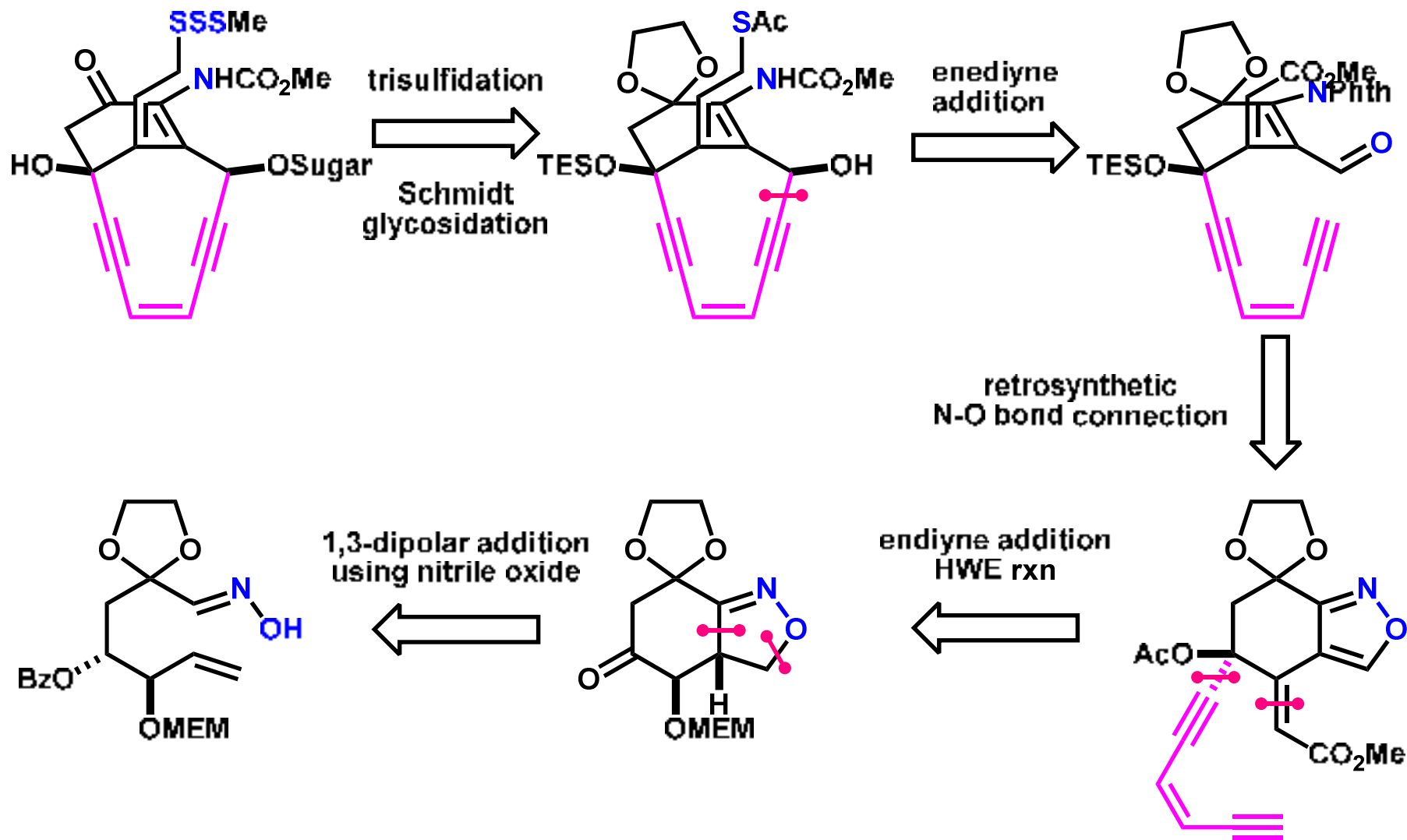
calicheamicinone
aminosugar and thiosugar
 β -carbolinyl

Total synthesis of shishijimicin A
Nicolaou K. C. (2015, enantiomeric) ²⁾

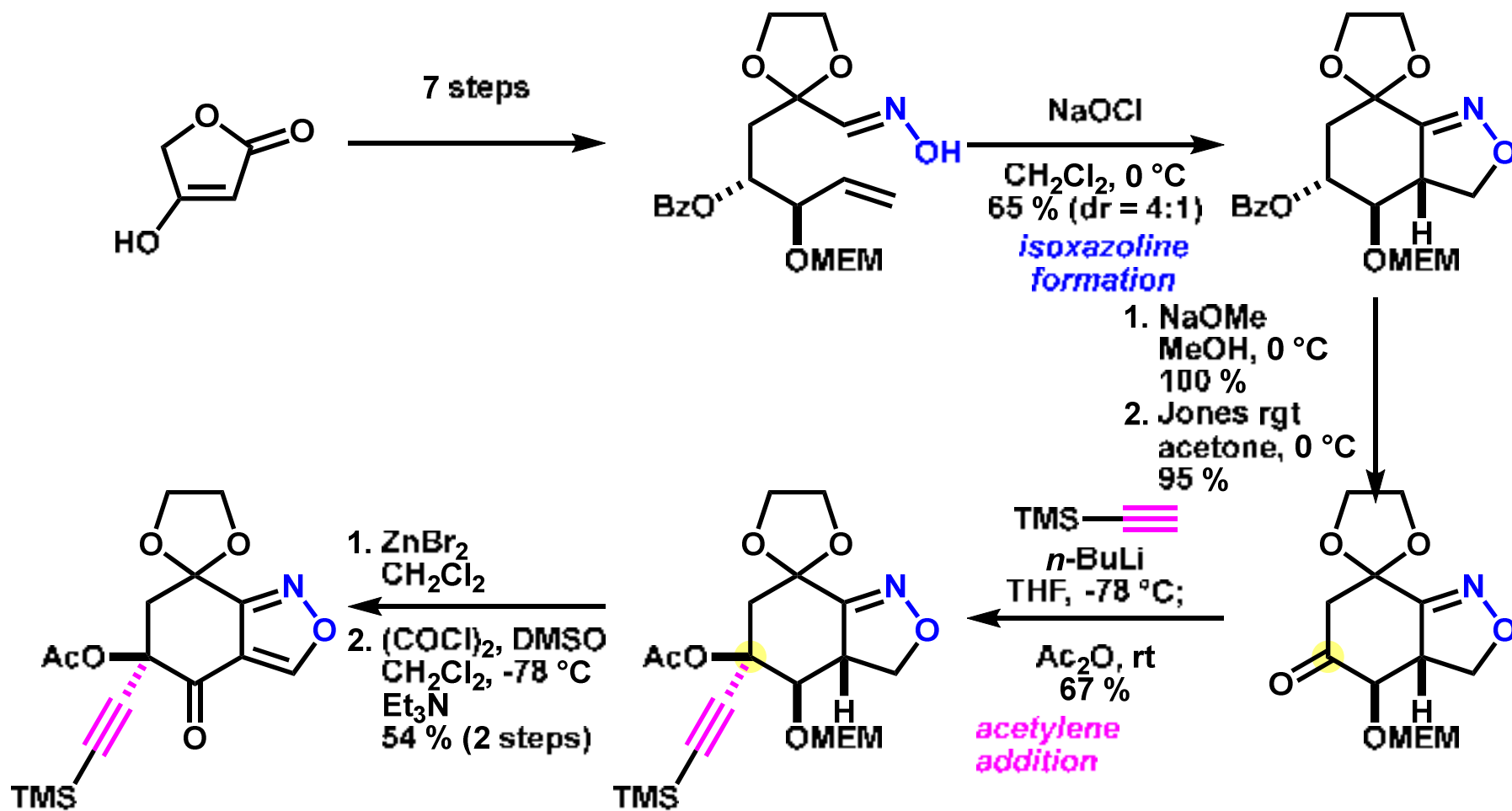
1) Oku, N.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **2003**, *125*, 2044.

2) Nicolaou, K. C.; Lu, Z.; Li, R.; Woods, J. R.; Sohn, T. *J. Am. Chem. Soc.* **2015**, *137*, 8716

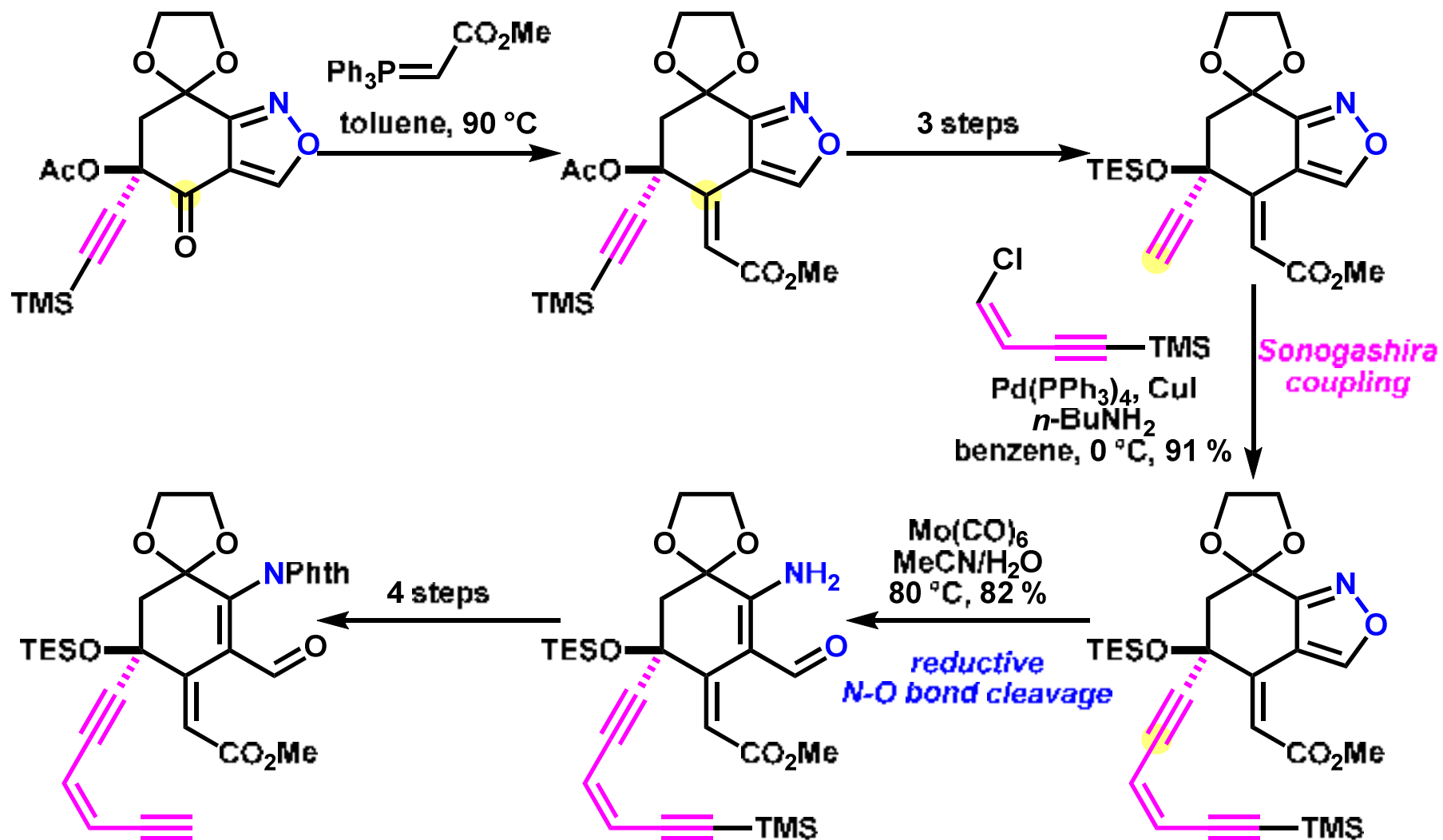
Retrosynthesis



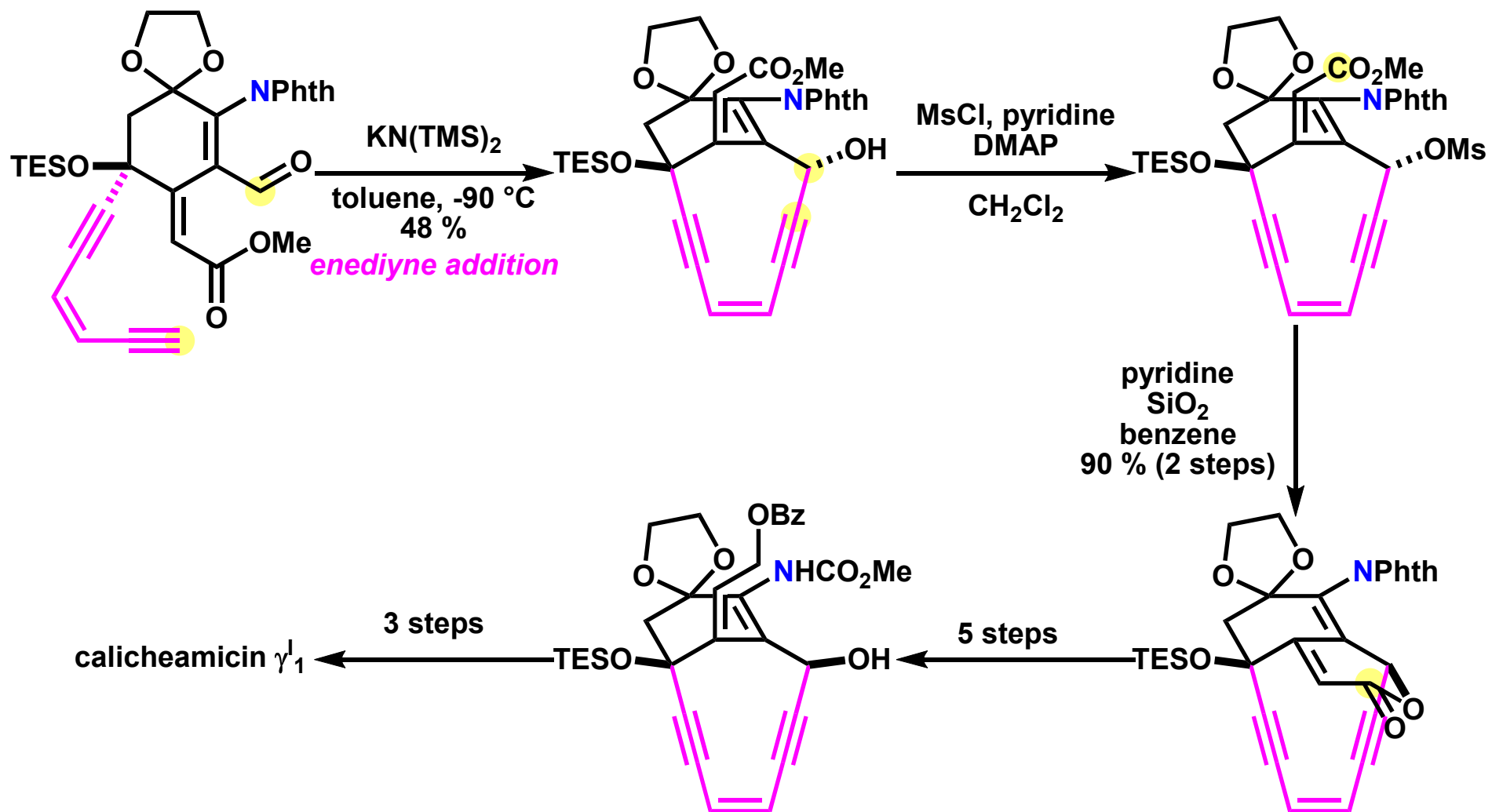
1st Route toward Calicheamicin 1



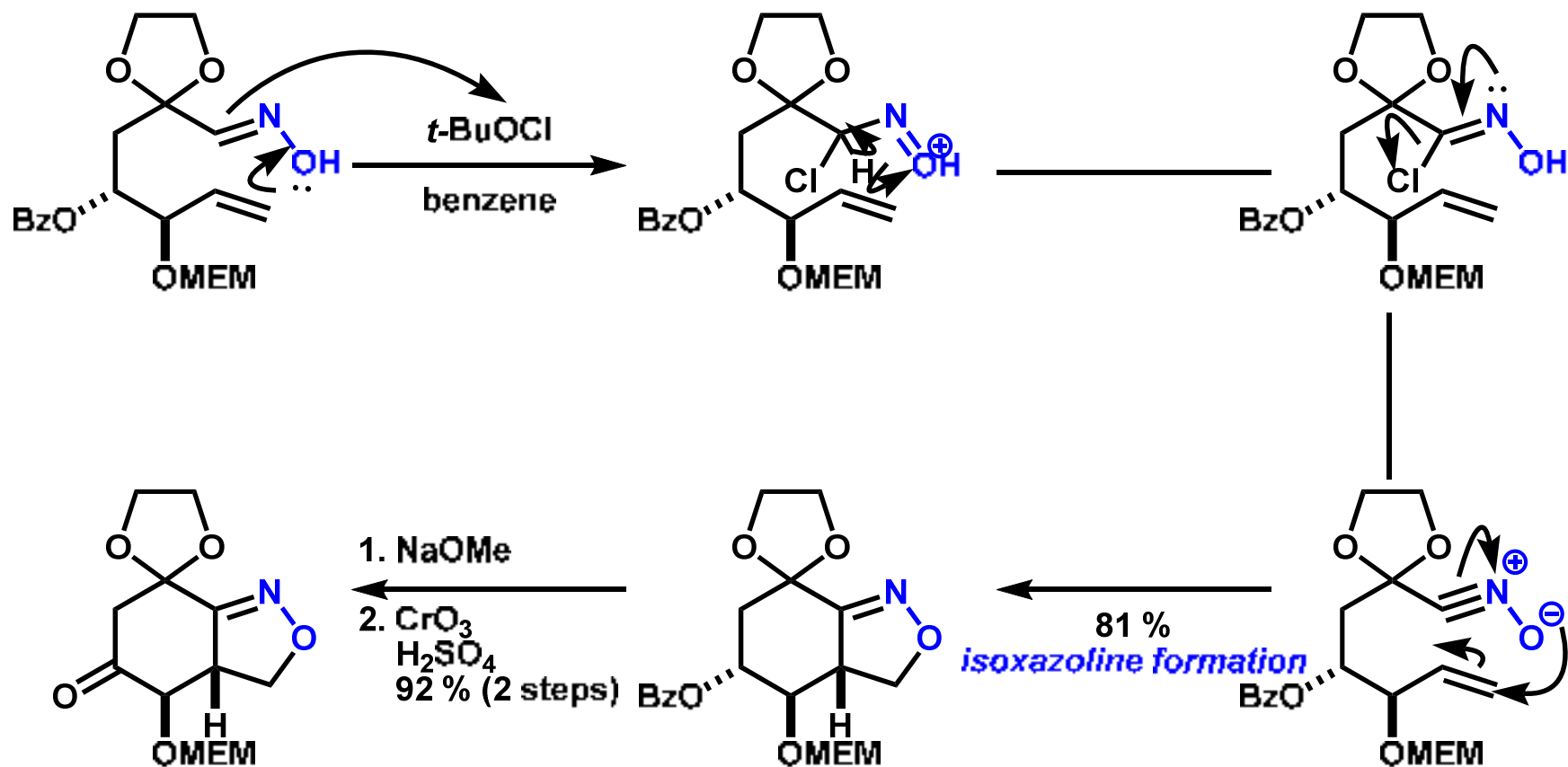
1st Route toward Calicheamicin 2



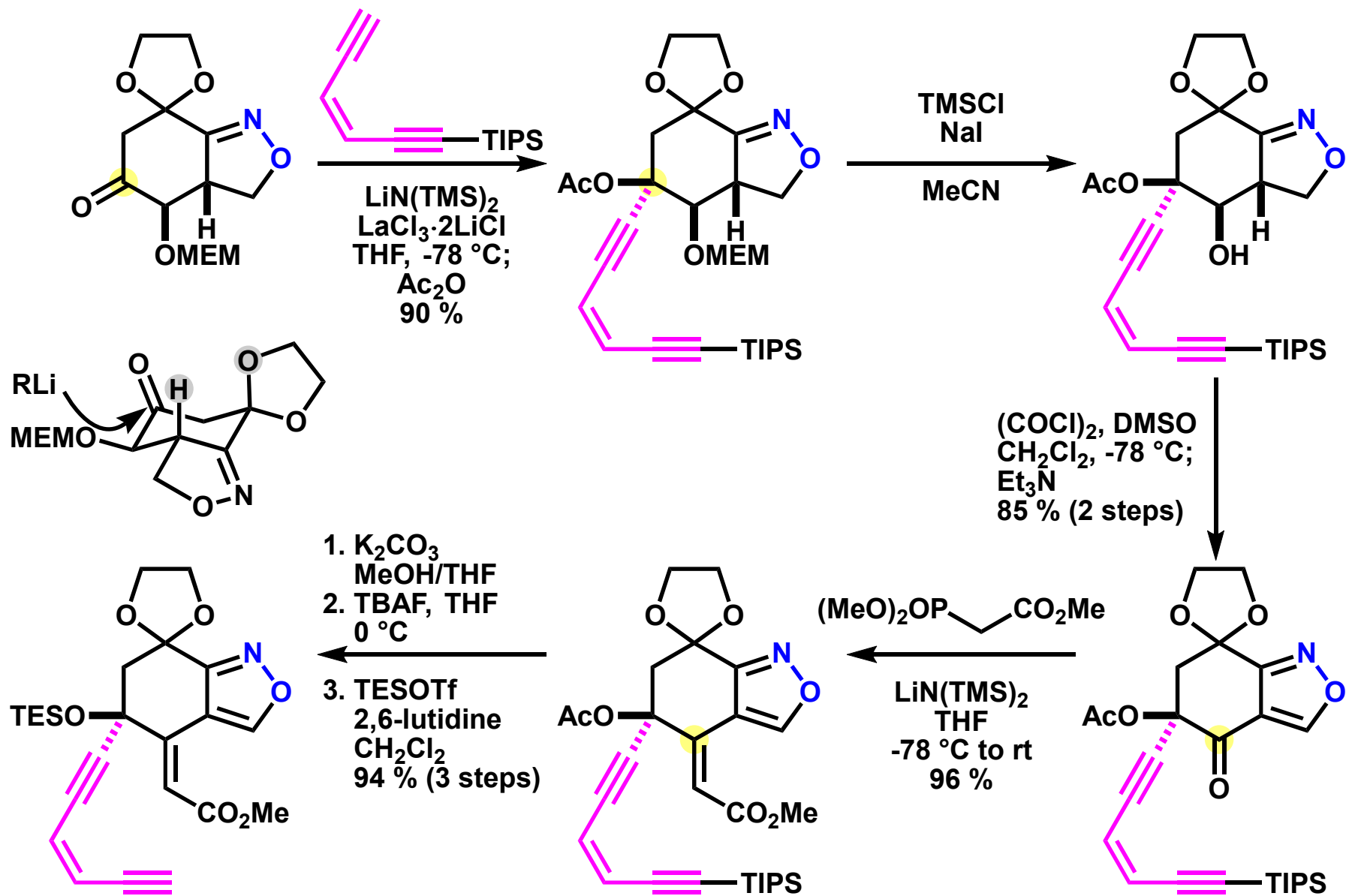
1st Route toward Calicheamicin 3



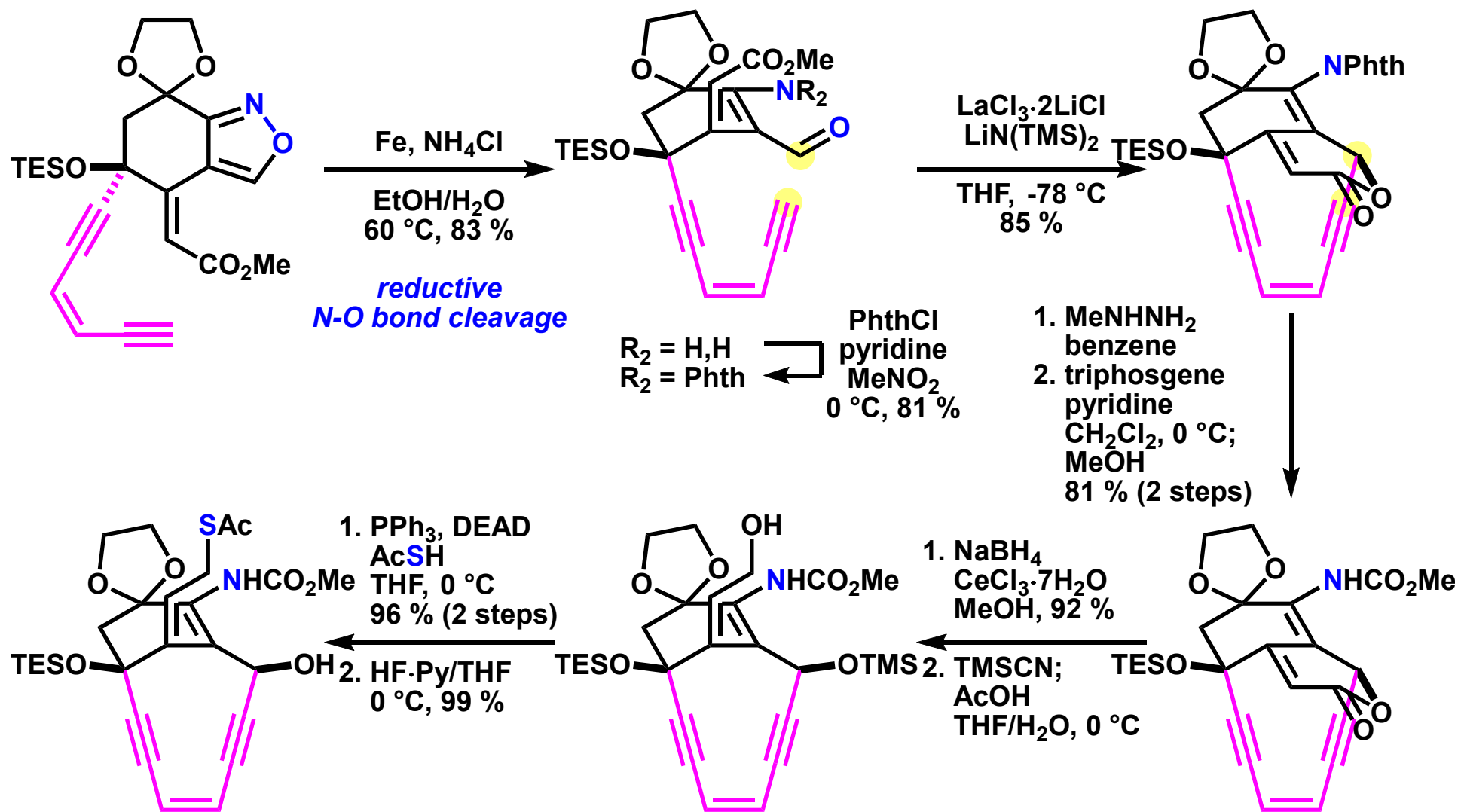
Isoxazoline Synthesis



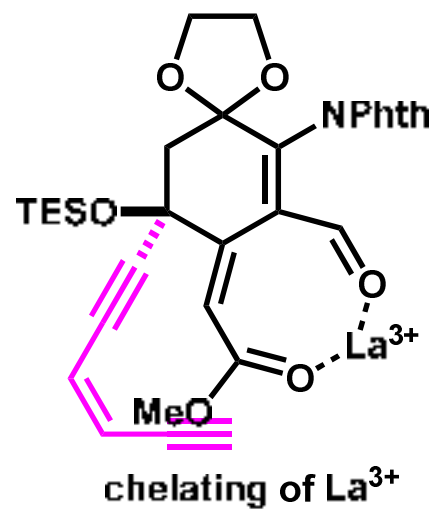
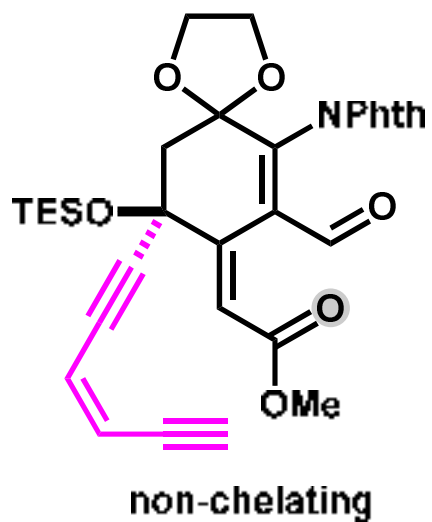
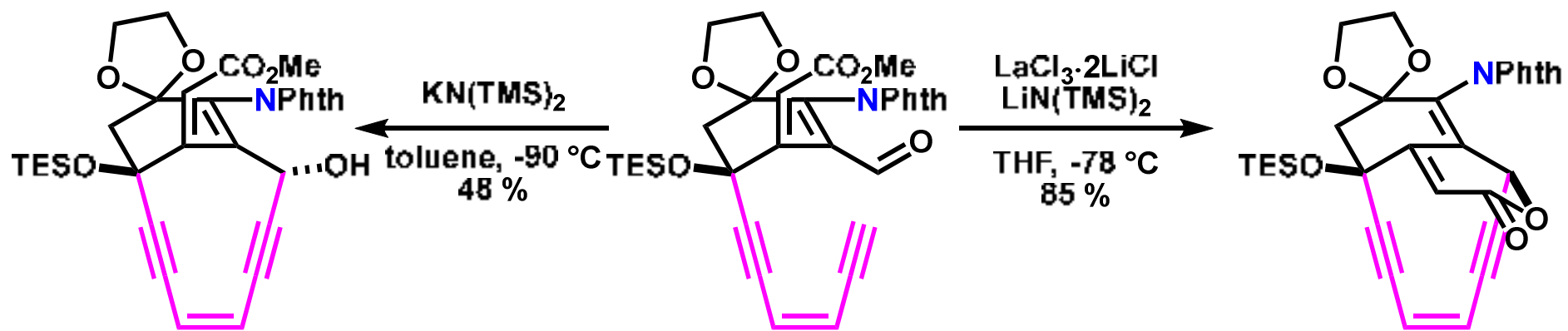
Introduction of Eneidyne Unit



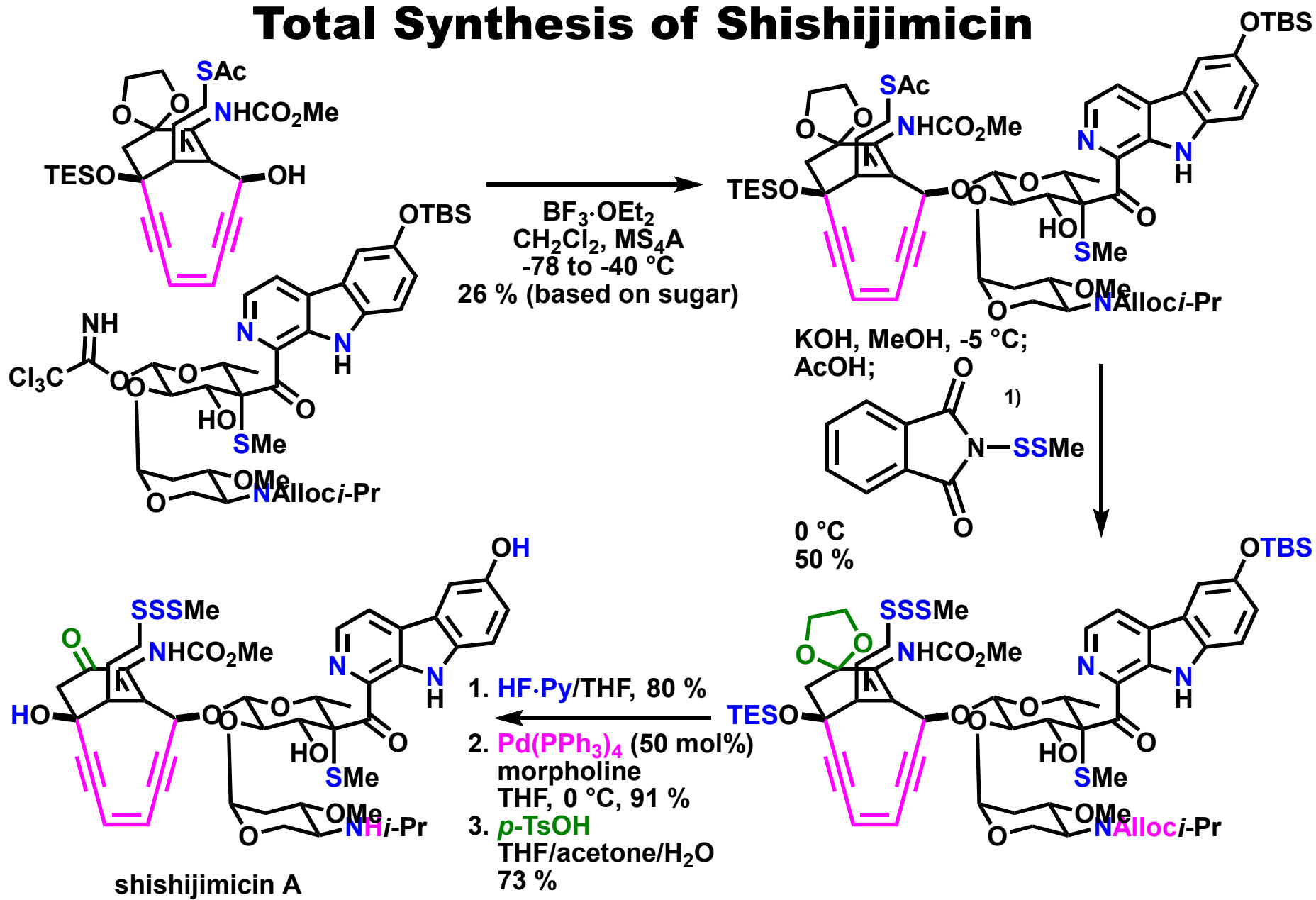
Synthesis of Shishijimicin Core



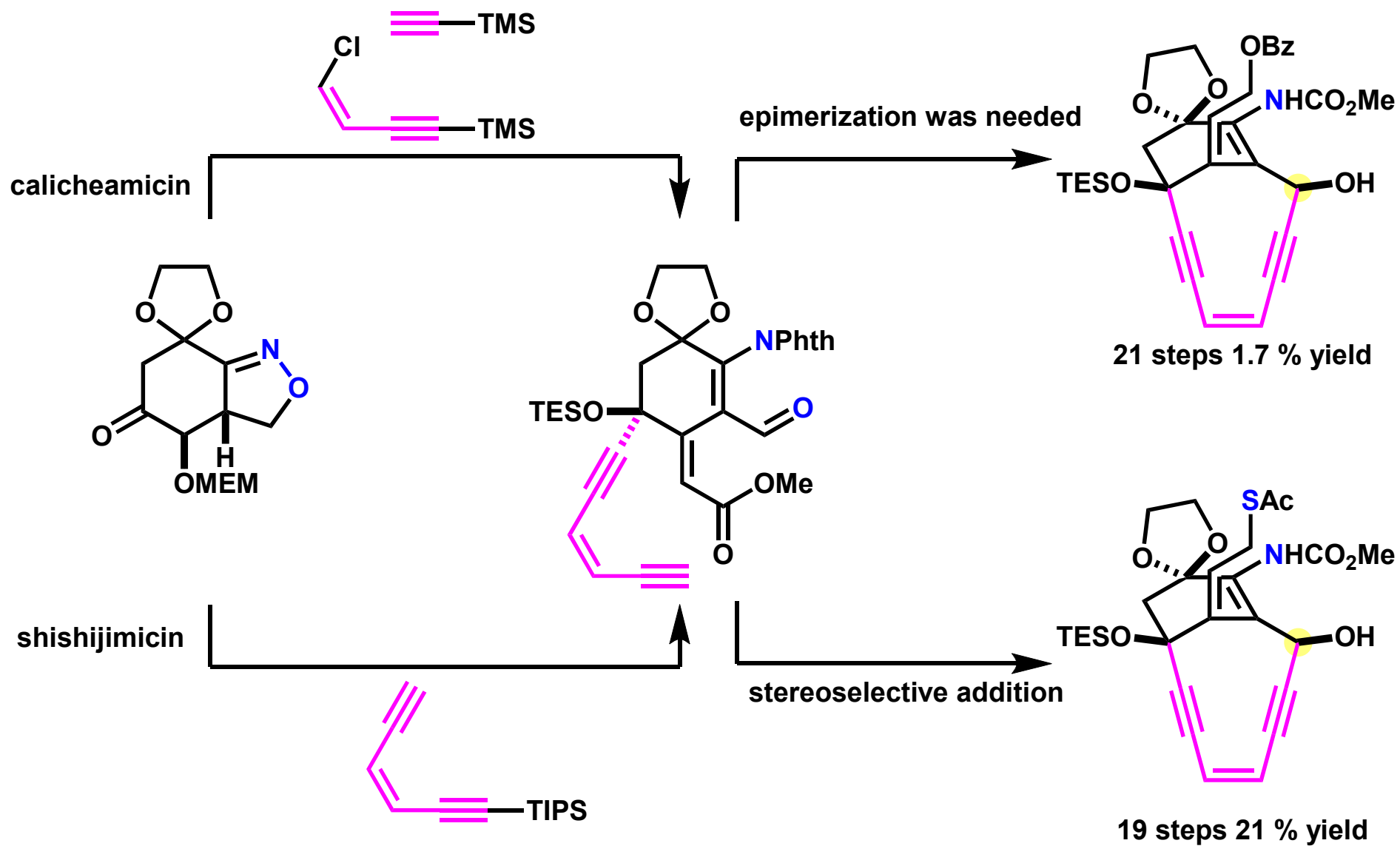
Inversion of Stereoselectivity



Total Synthesis of Shishijimicin



Summary



appendix

DNA Cleavage Main Mechanism

