Synthetic Developments Towards the Preparation of Erythromycin and Erythronolide Derivatives

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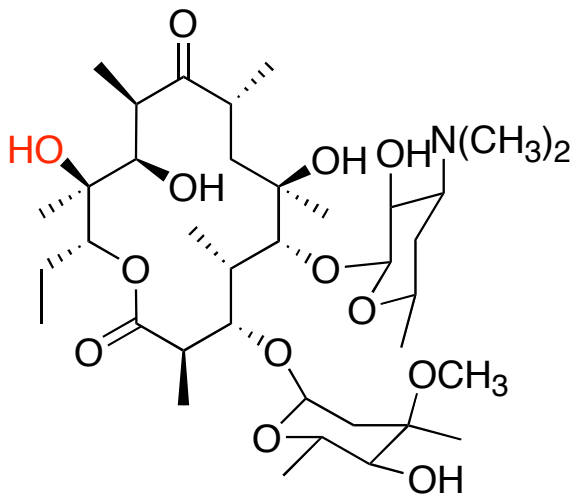
Denmark Group Meeting

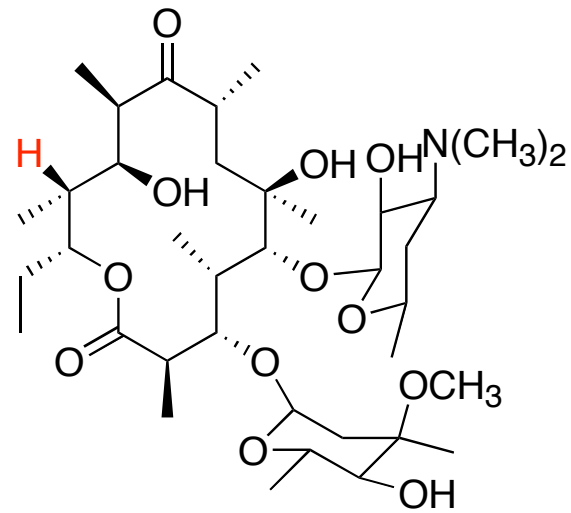
8-9-2005

"…most extensive project in organic synthesis…this phenomenon is not rational" --J. Mulzer

Erythromycin A/B



A

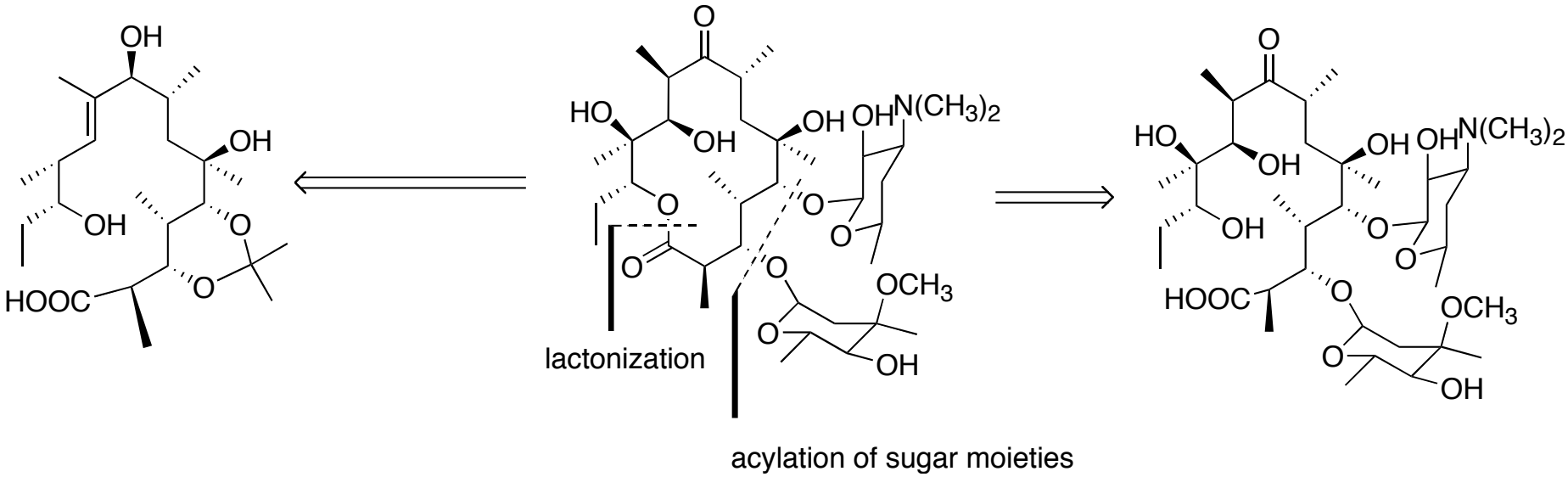


B

- Produced from the fungus *Streptomyces erythreus*
- Used as widespread antibiotic

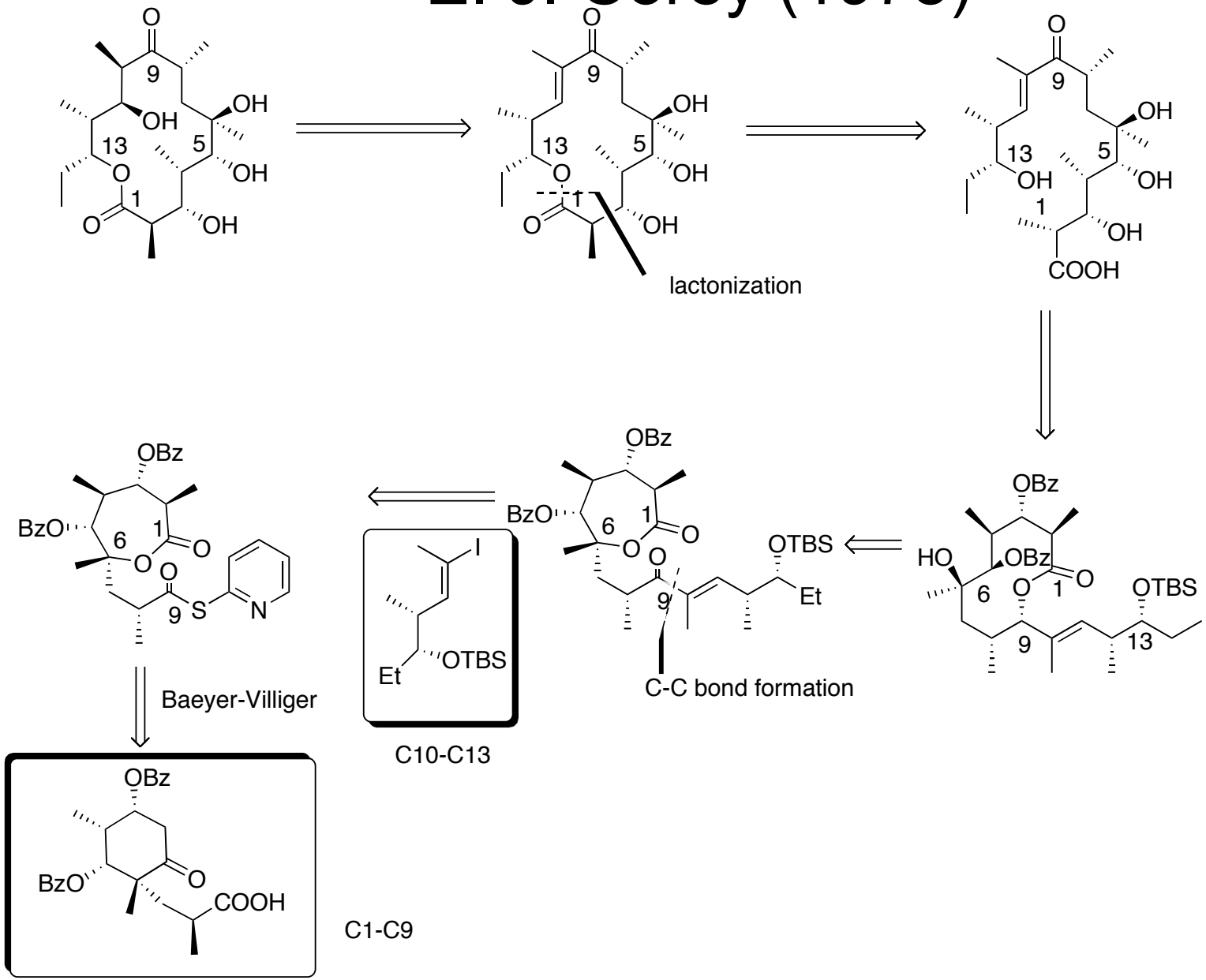
- Synthetic Challenges
  - 10 defined stereogenic centers
  - 14 membered macrocyclic lactone
  - Two hemi-acetal sugar moieties

Initial Retrosynthetic Analysis

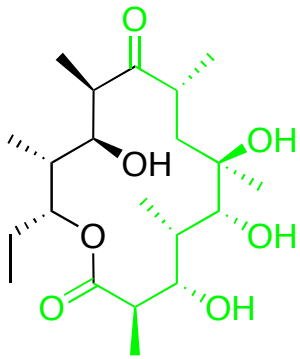


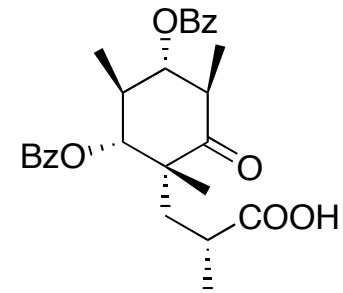
1. Form macro-lactone and append sugar moieties
2. Attempt lactonization with sugar moieties appended

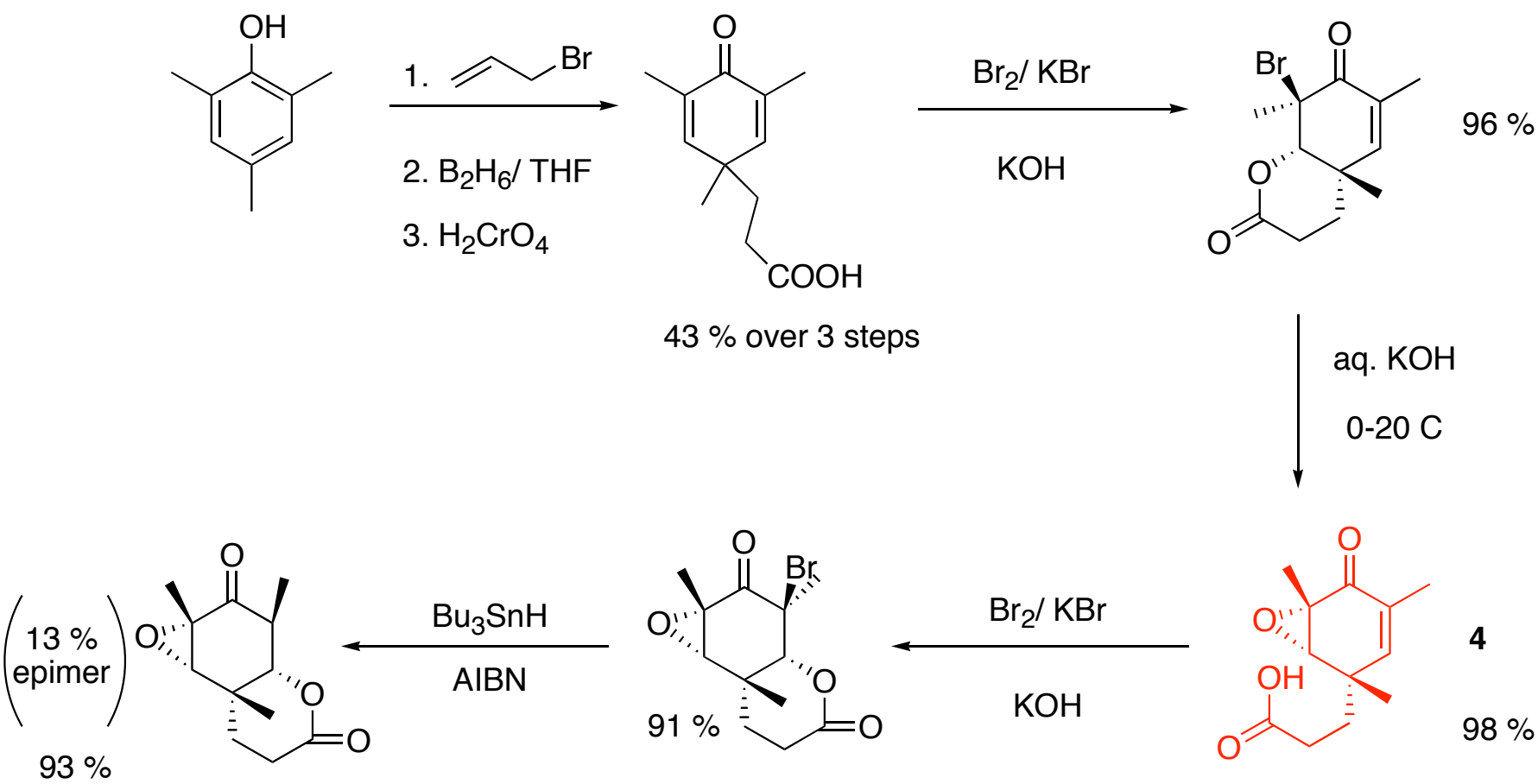
Total Synthesis of Erythronolide B-
E. J. Corey (1978)



Preparation of Cyclic Intermediate

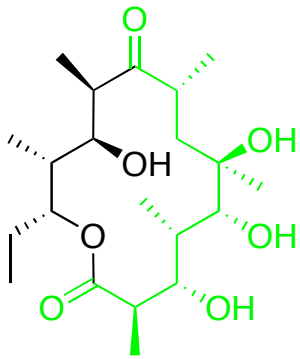


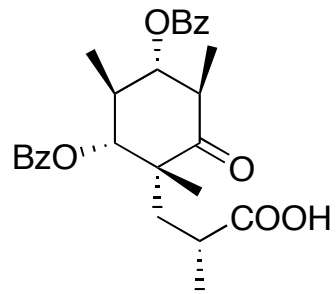


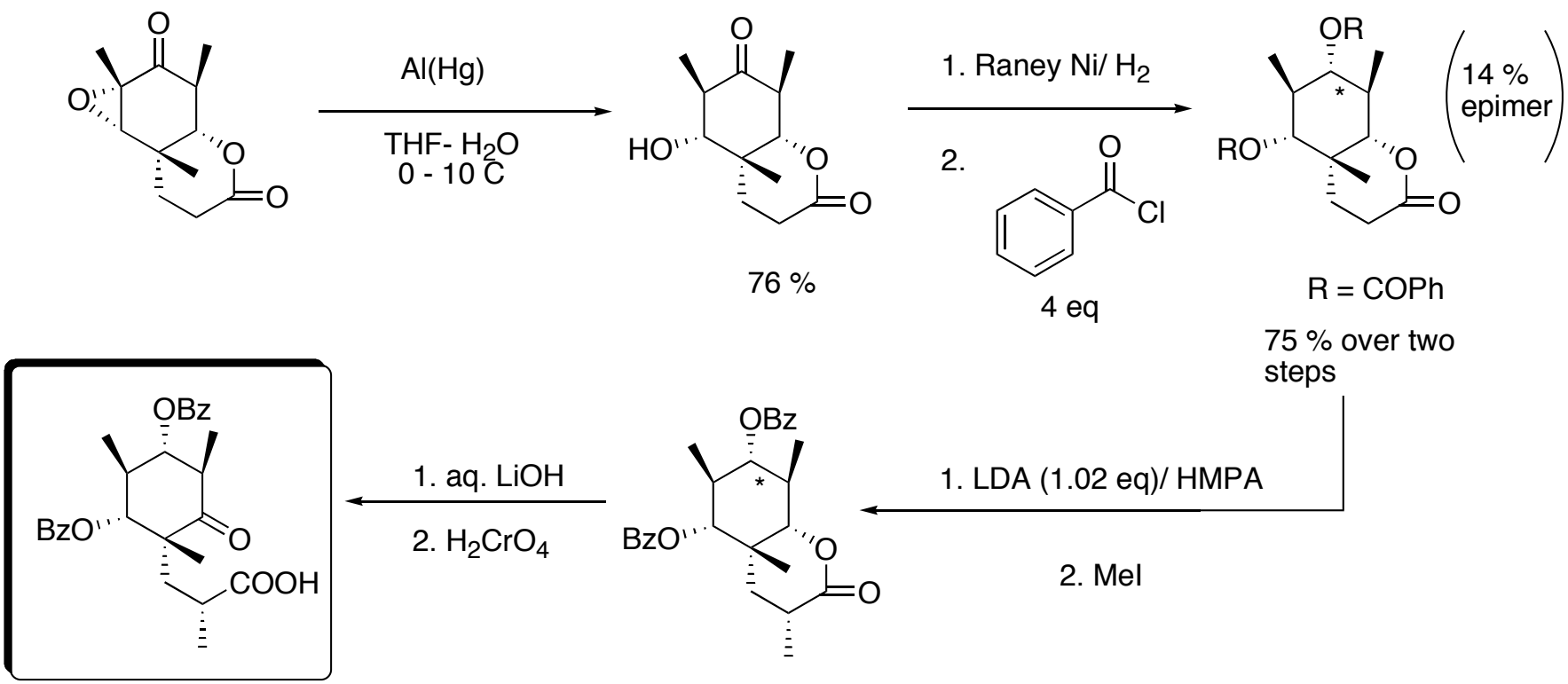


J. Am. Chem. Soc, **1978**, *100*, 4618.

Completion of Cyclic Intermediate

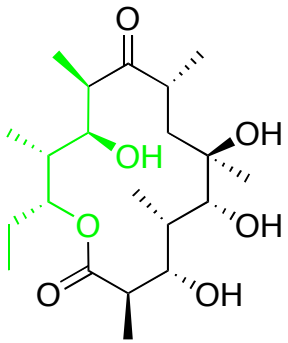


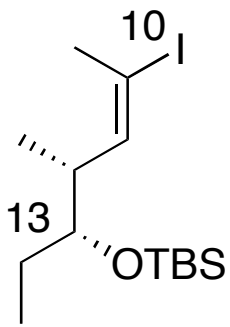


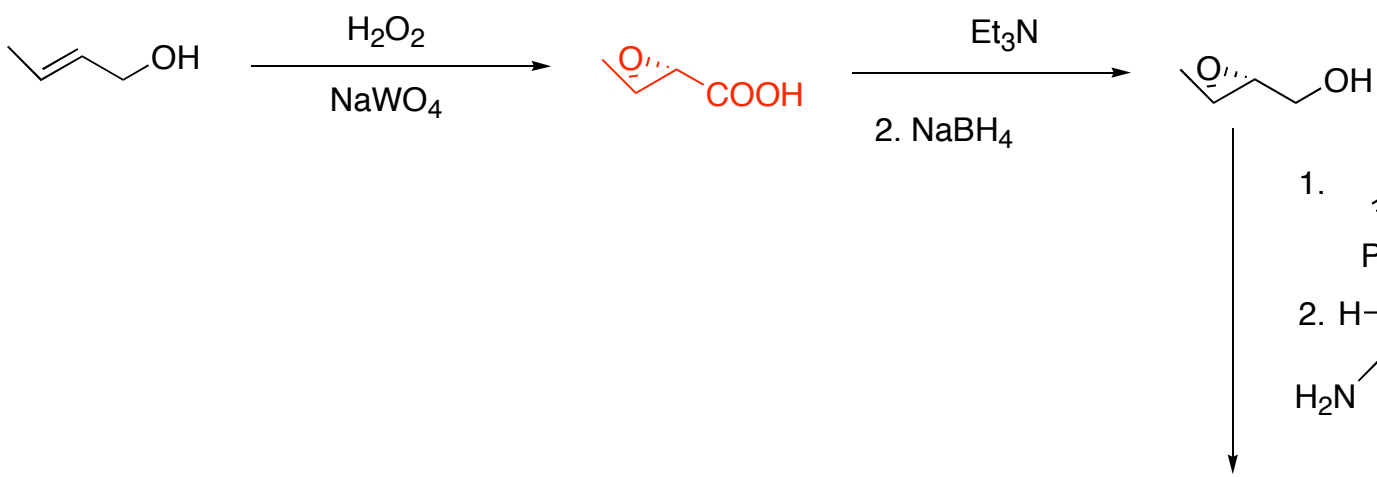


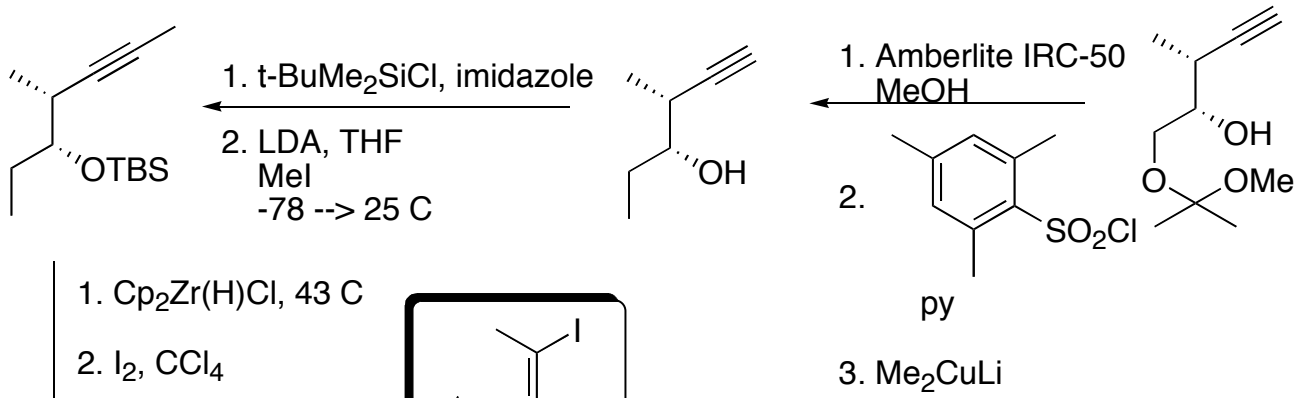
J. Am. Chem. Soc, **1978**, *100*, 4618.

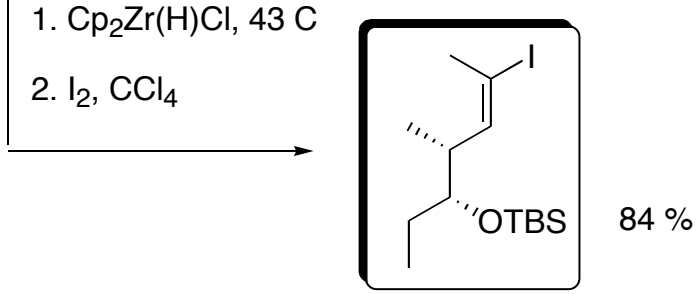
C10-C13 Fragment





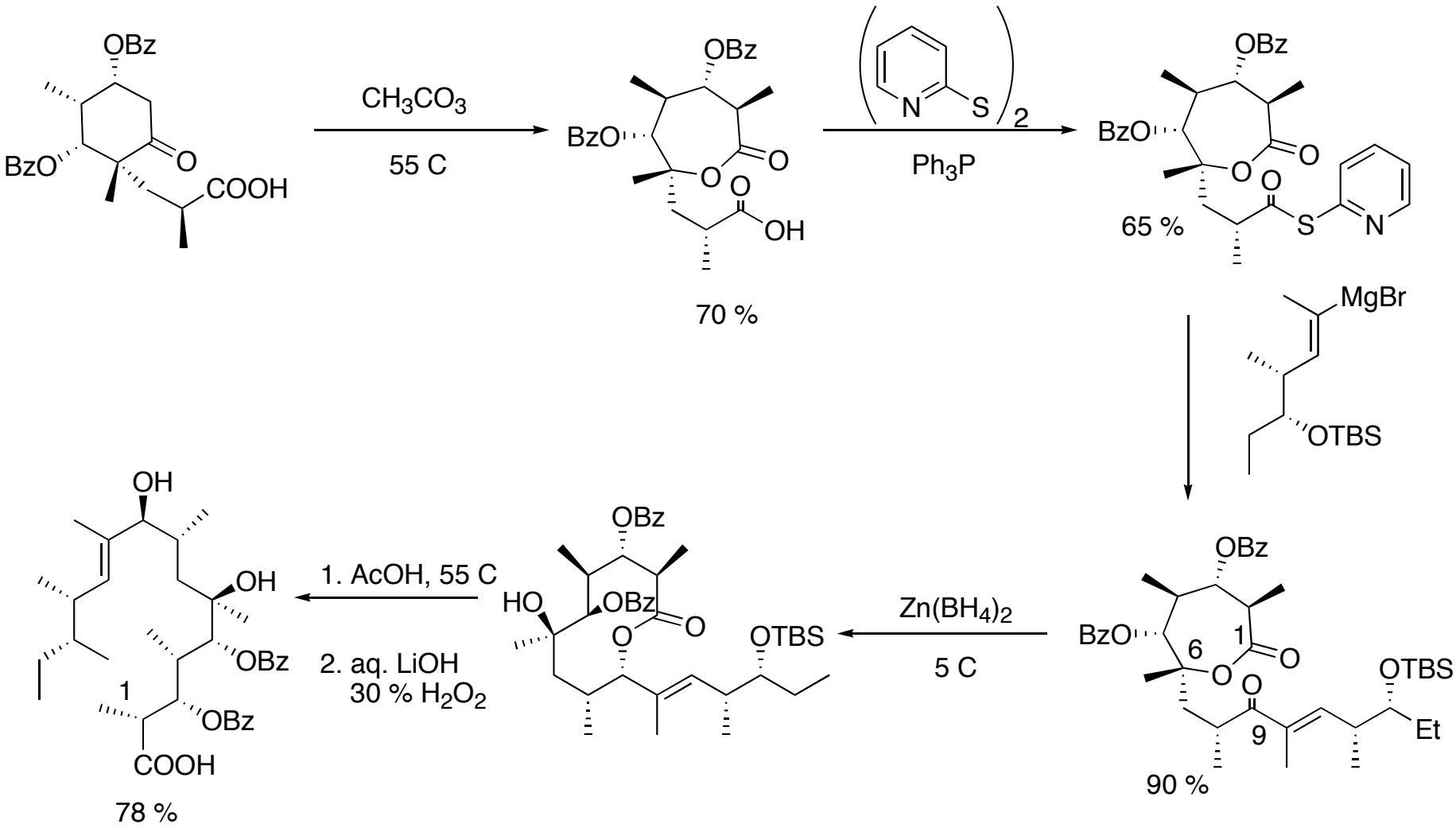






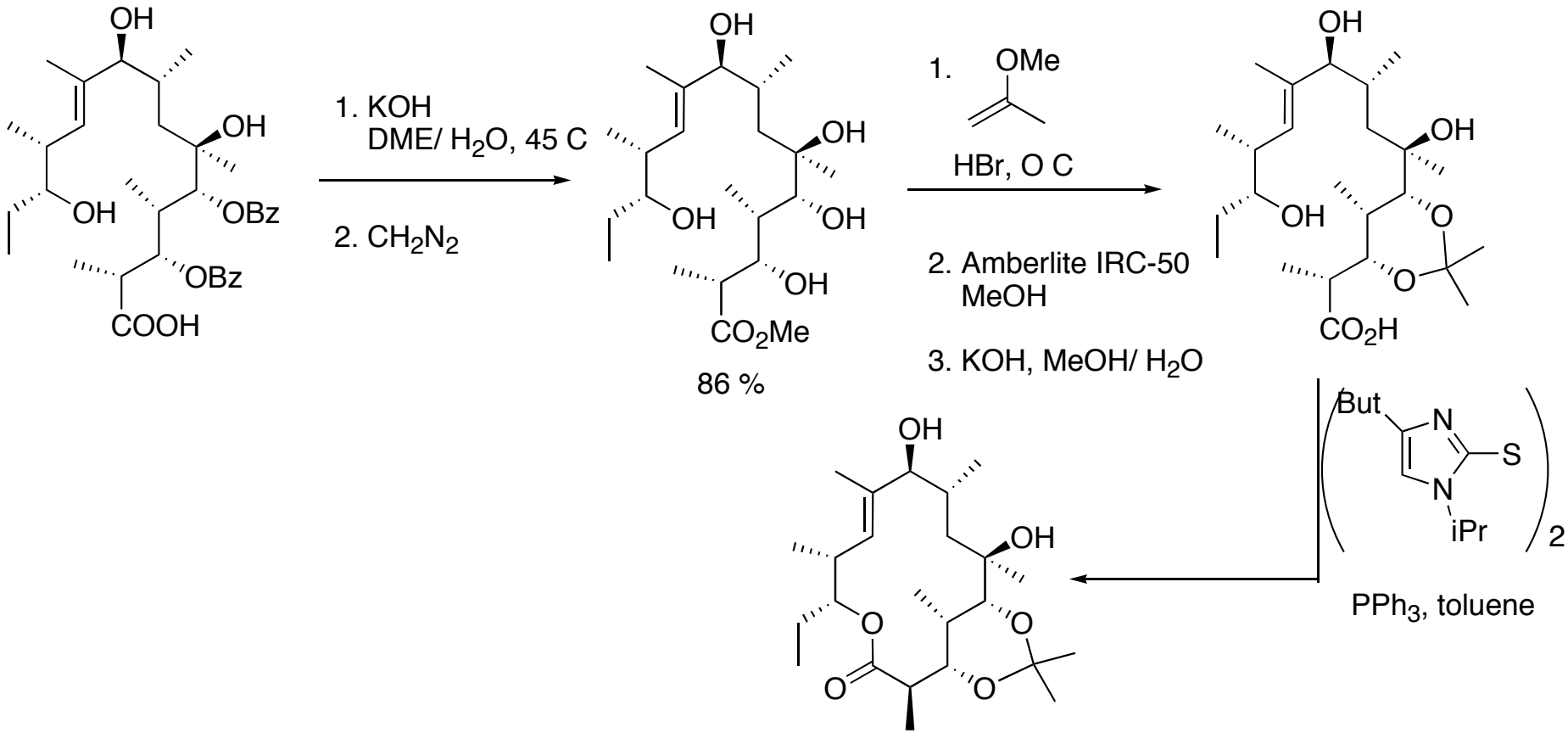
J. Am. Chem. Soc, **1978**, *100*, 4618.

Total Synthesis of Erythronolide B: Fusion of two key intermediates



J. Am. Chem. Soc, **1978**, *100*, 4620.

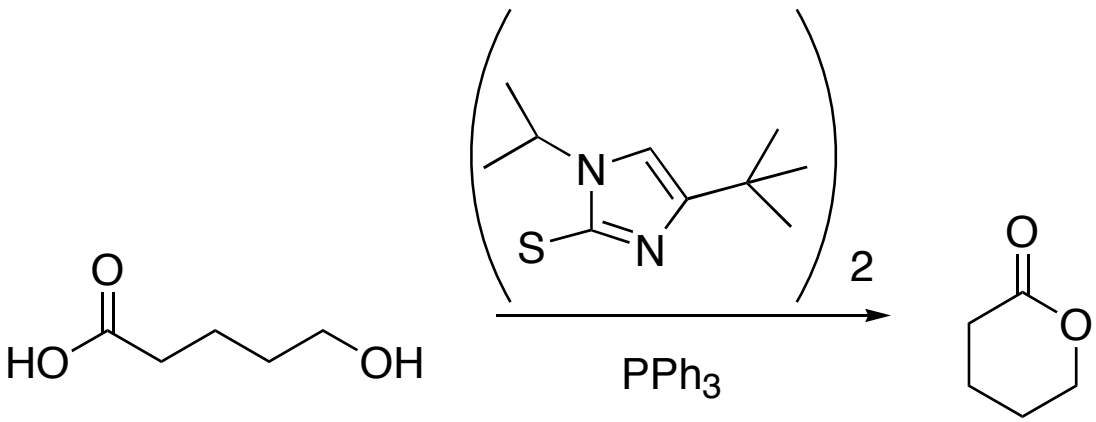
Preparation of macrocyclic core



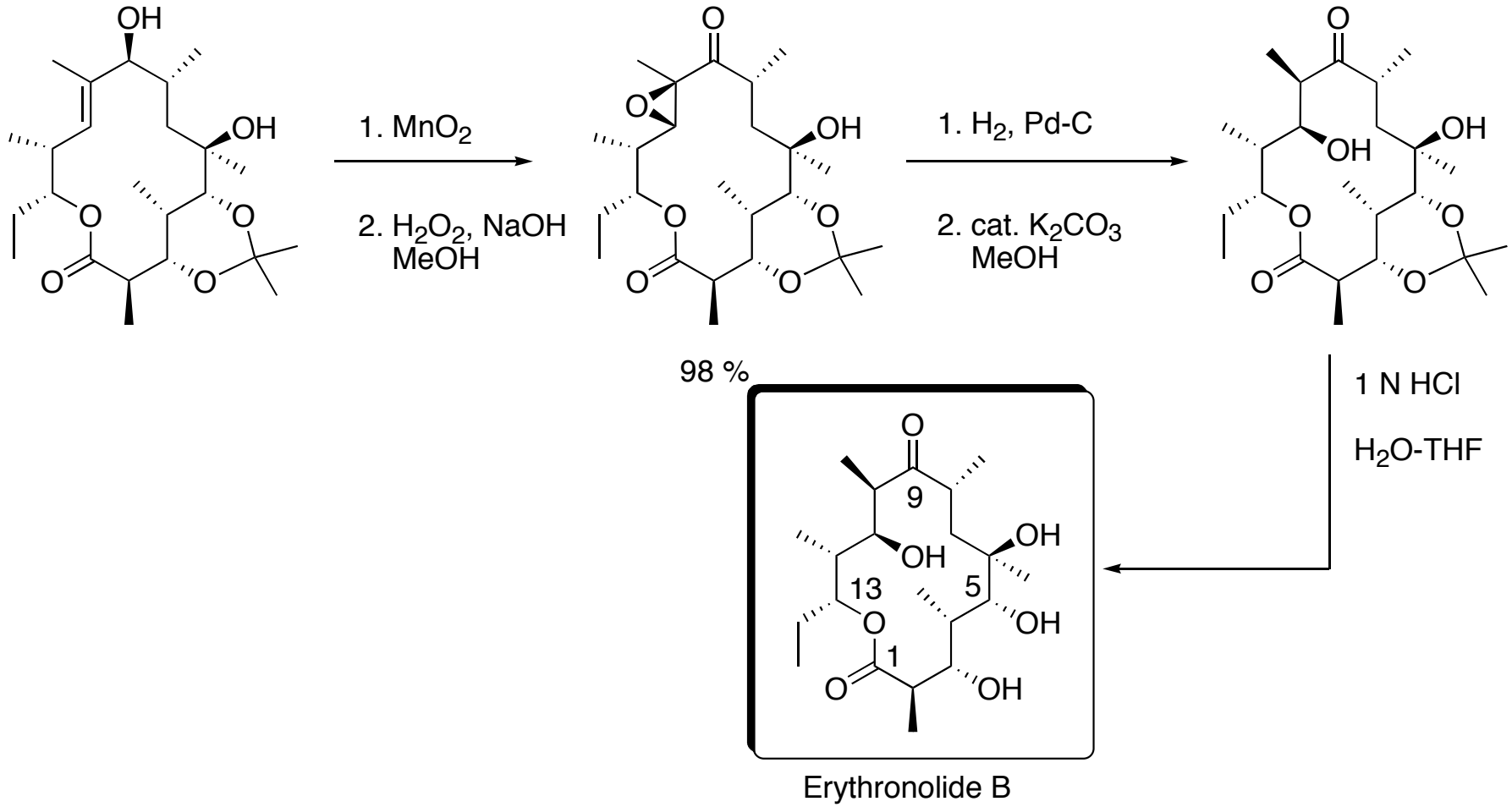
J. Am. Chem. Soc, **1978**, *100*, 4620.

Pop Quiz

- What is the mechanism for activation?
- Provide an experiment to provide support for proposal!
- What are the side products?



Final Steps- Erythronolide B



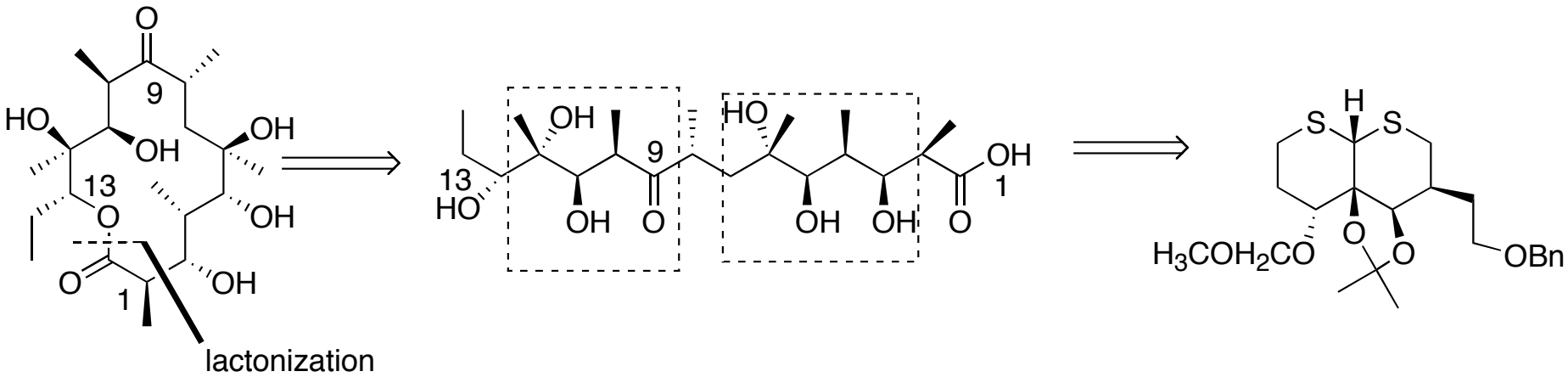
J. Am. Chem. Soc. **1975**, *97*, 654.

Summary- Erythronolide B Synthesis

- Themes
  - Use of cyclic intermediates to set desired stereocenters
  - Use of key resolutions to separate racemic products

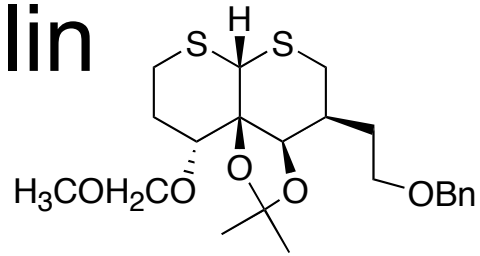
- Conclusions
  - Macrolactonization can be accomplished with use of activated acid/ alcohol sequence to form large ring lactones
  - Bromo-lactonization can be used as a powerful tool to set stereocenters

Total Synthesis of Erythromycin A
R. B. Woodward (1981)

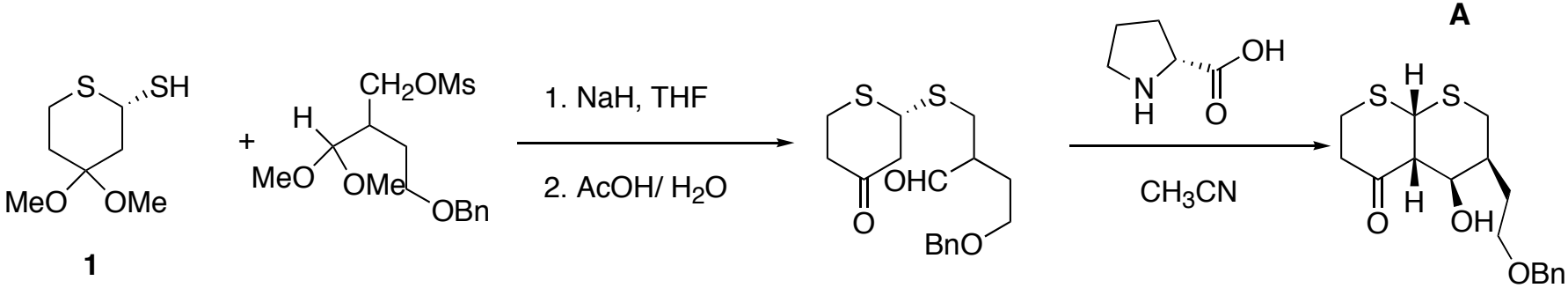


"Erythromycin…looks hopelessly complex, particularly in the view of its plethora of asymmetric centers" --Woodward (1956)

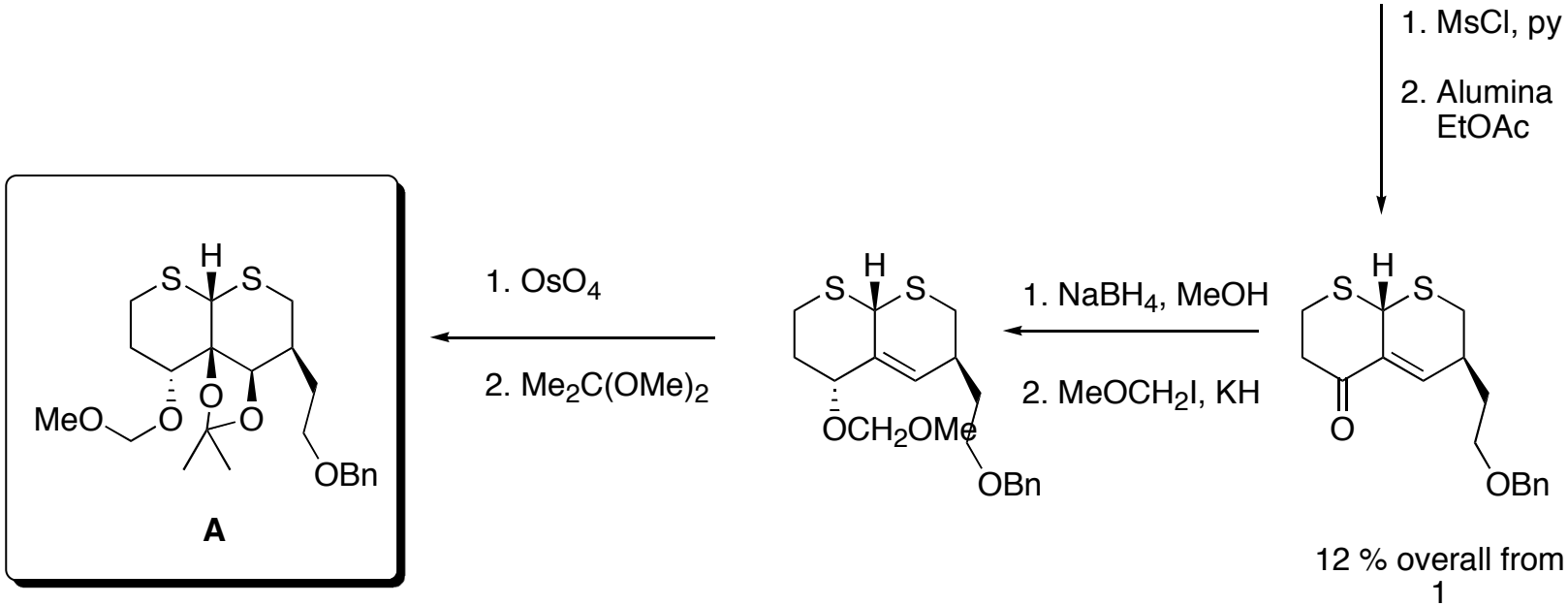
Preparation of key dithiadecalin intermediate



A



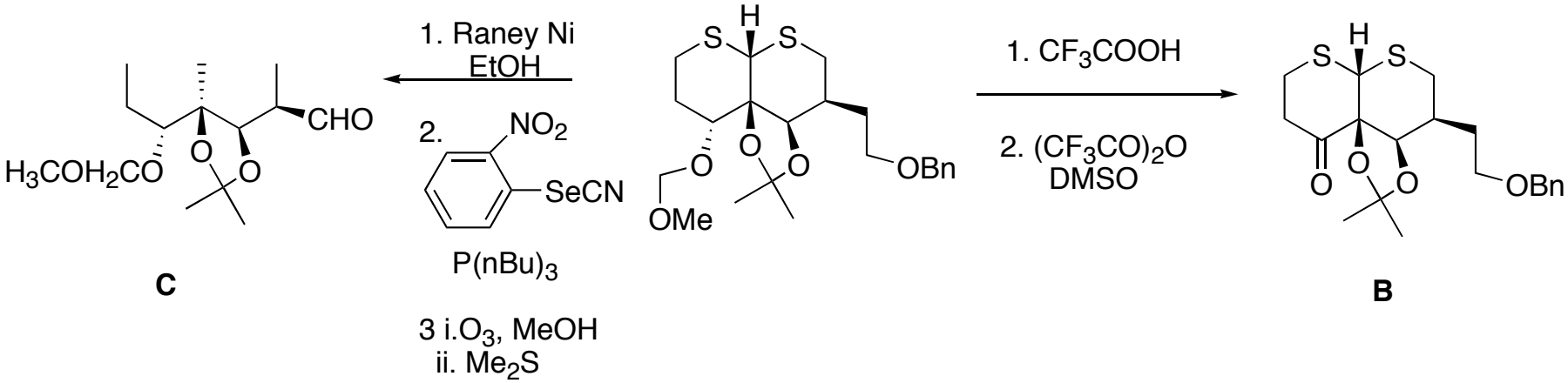
(70 %, 82 % ee)



12 % overall from 1

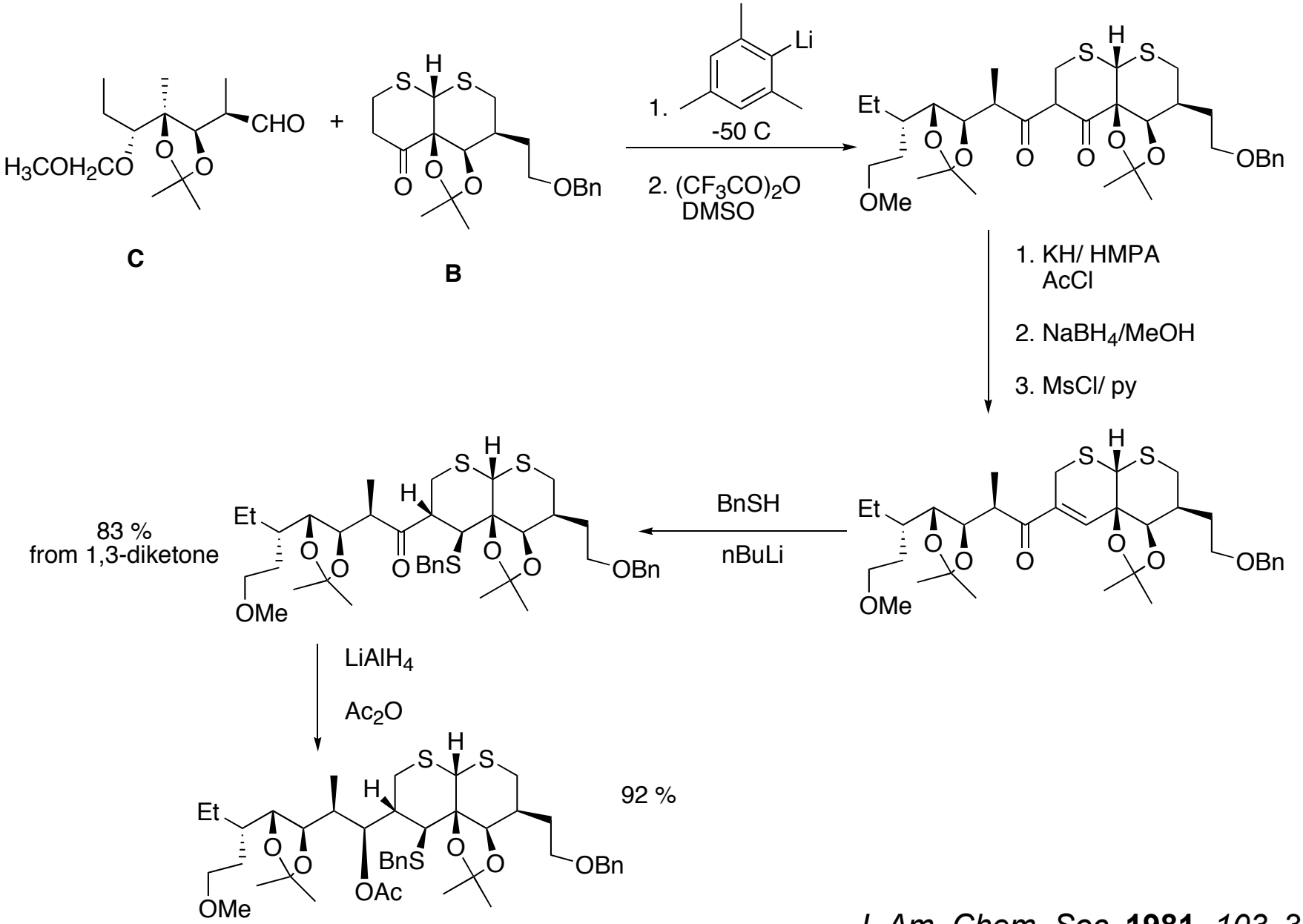
J. Am. Chem. Soc. **1981**, *103*, 3211

Synthesis of two intermediates from the same reagent



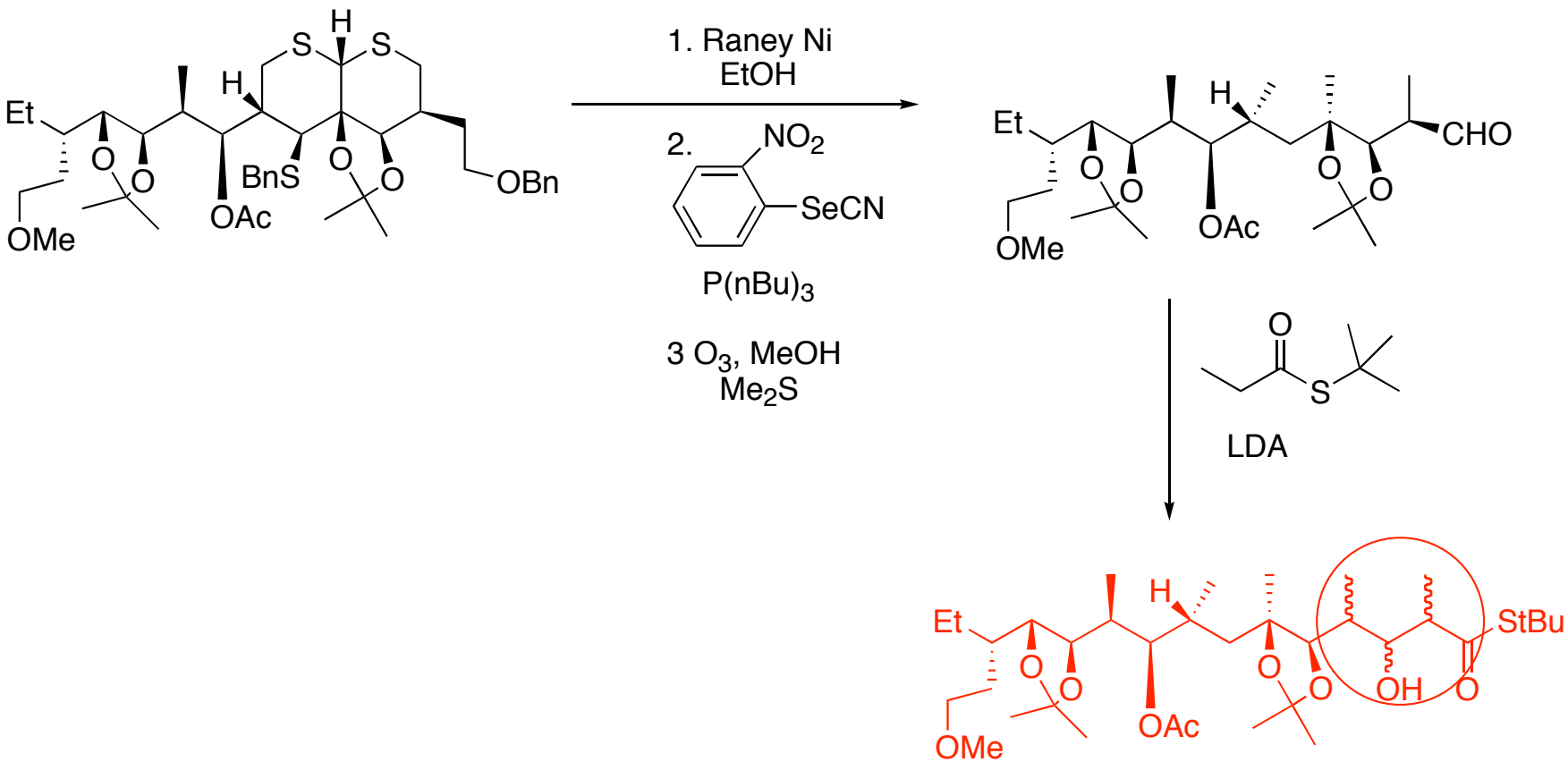
J. Am. Chem. Soc. **1981**, *103*, 3211

Two intermediates merge together



J. Am. Chem. Soc. **1981**, *103*, 3211

Completion of seco acid chain



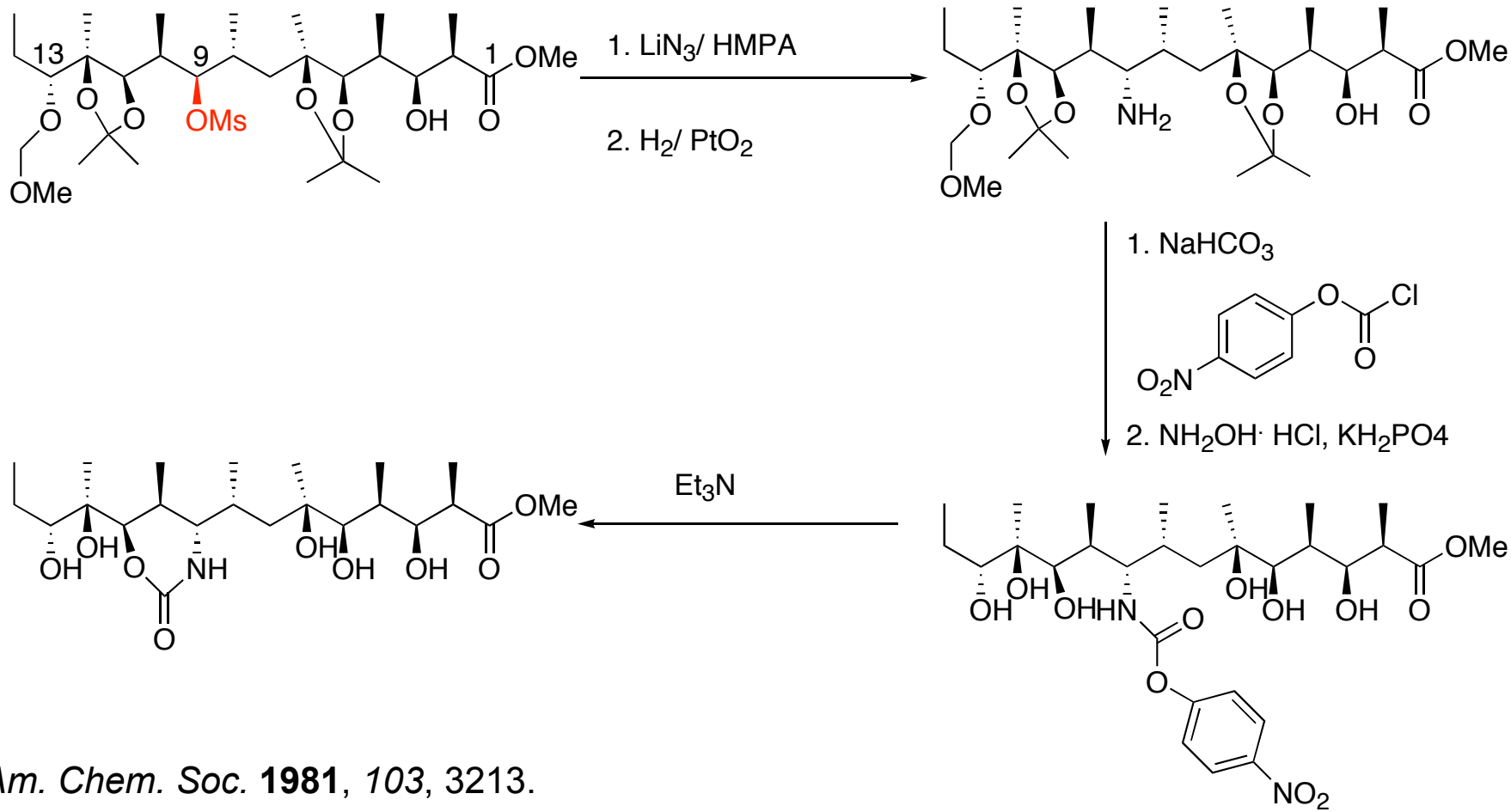
What is the configuration??

Provide a model (hint..hint)

J. Am. Chem. Soc. **1981**, *103*, 3211

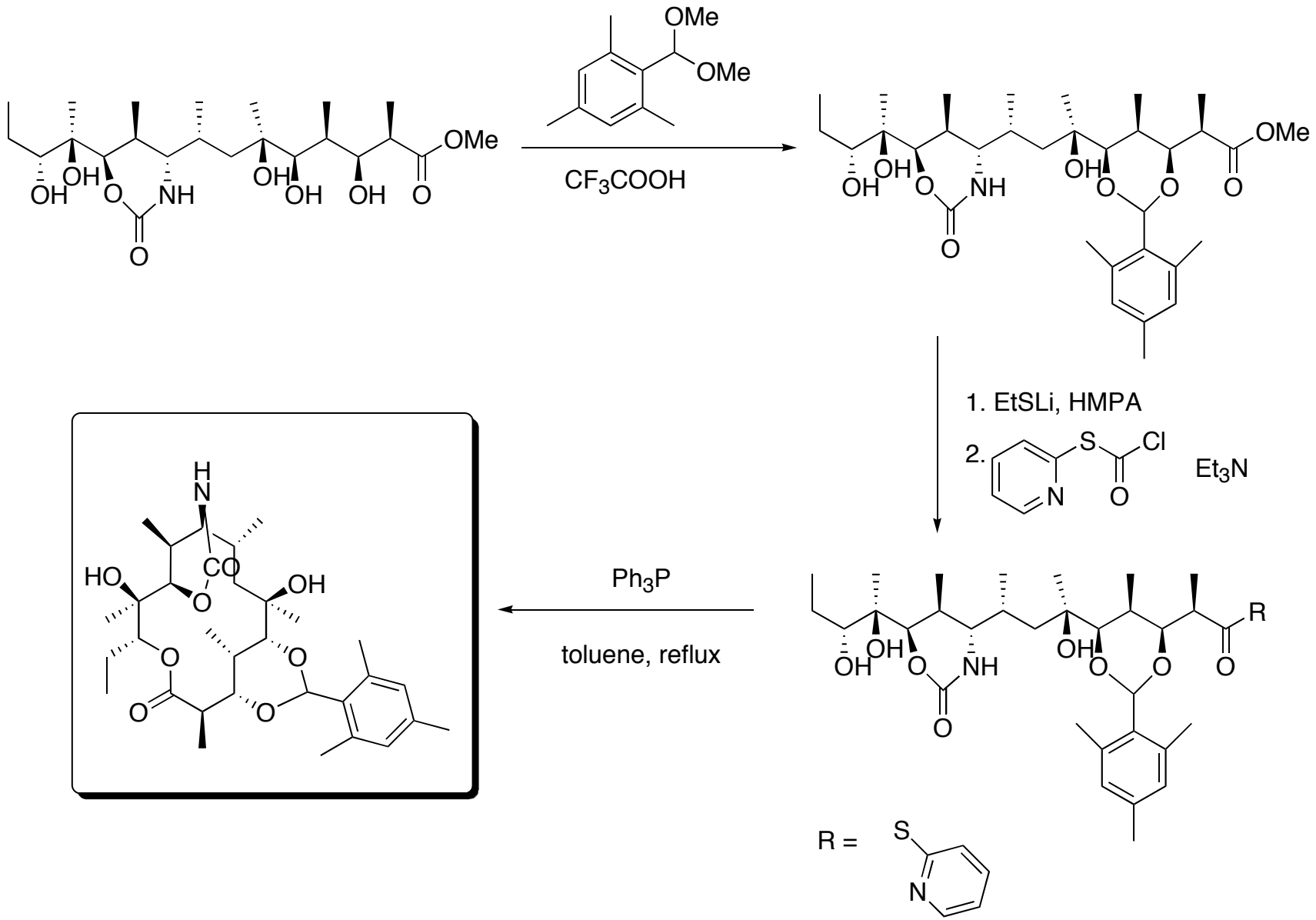
Lactonization: How hard can it be??

- There are 2 crucial aspects that Woodward discovered during his studies
  1) The configuration at C9 MUST BE (S)
  2) Cyclic protecting groups at C3-C5 AND C9-C11



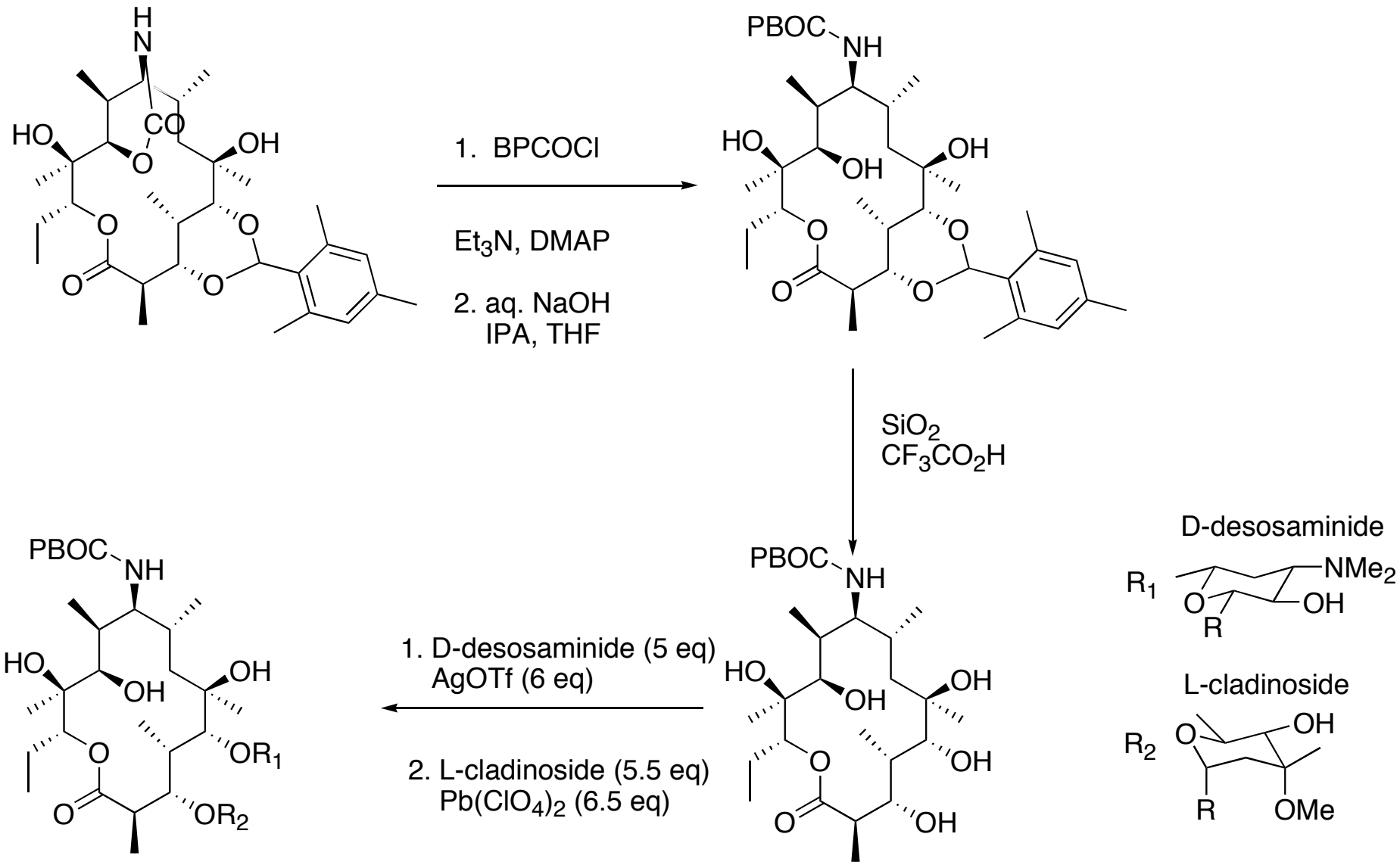
J. Am. Chem. Soc. **1981**, *103*, 3213.

Completion of Erythronolide A core



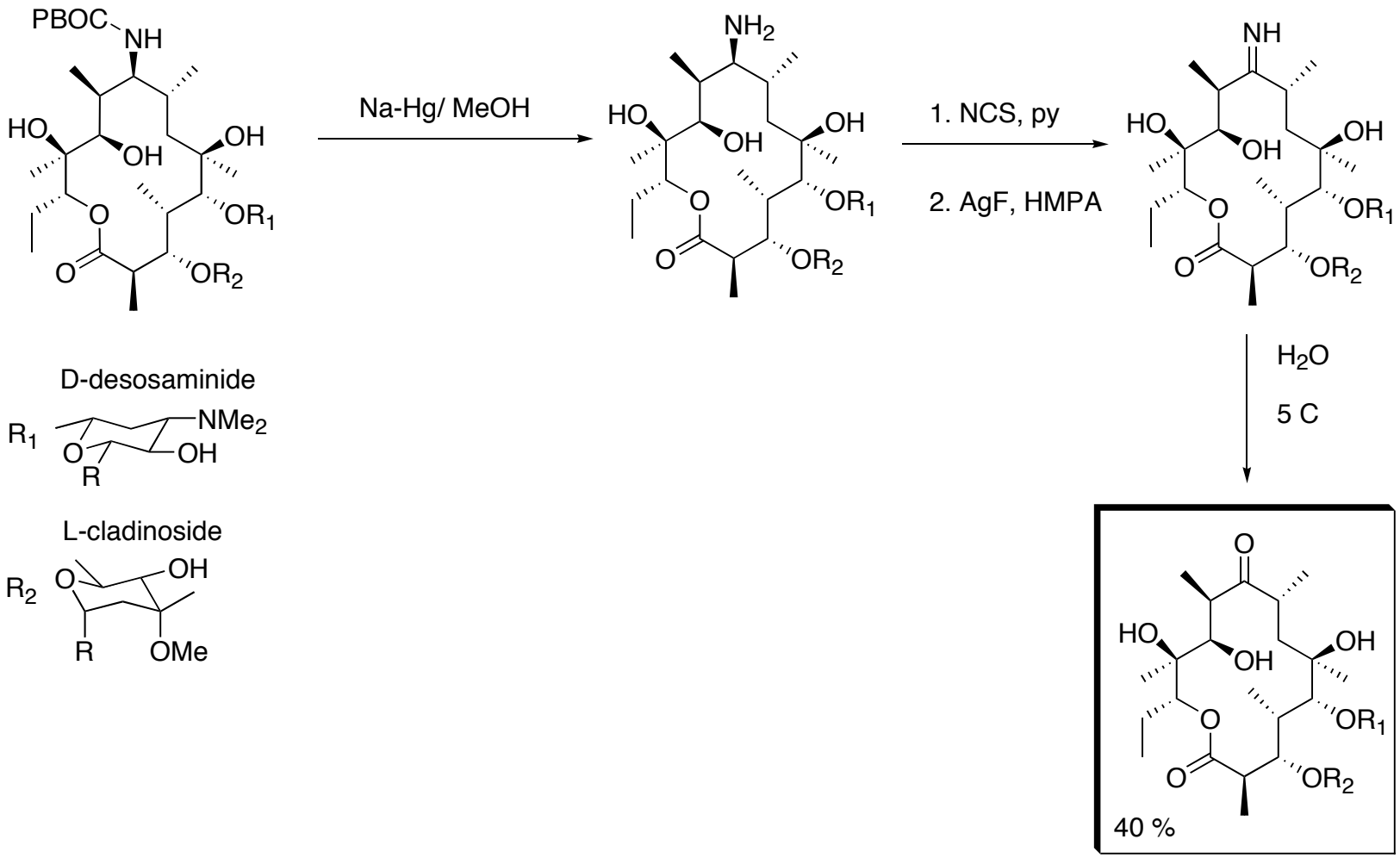
J. Am. Chem. Soc. **1981**, *103*, 3213.

Attachment of sugar moieties



J. Am. Chem. Soc. **1981**, *103*, 3217.

Synthesis of Erythromycin A



Erythromycin A

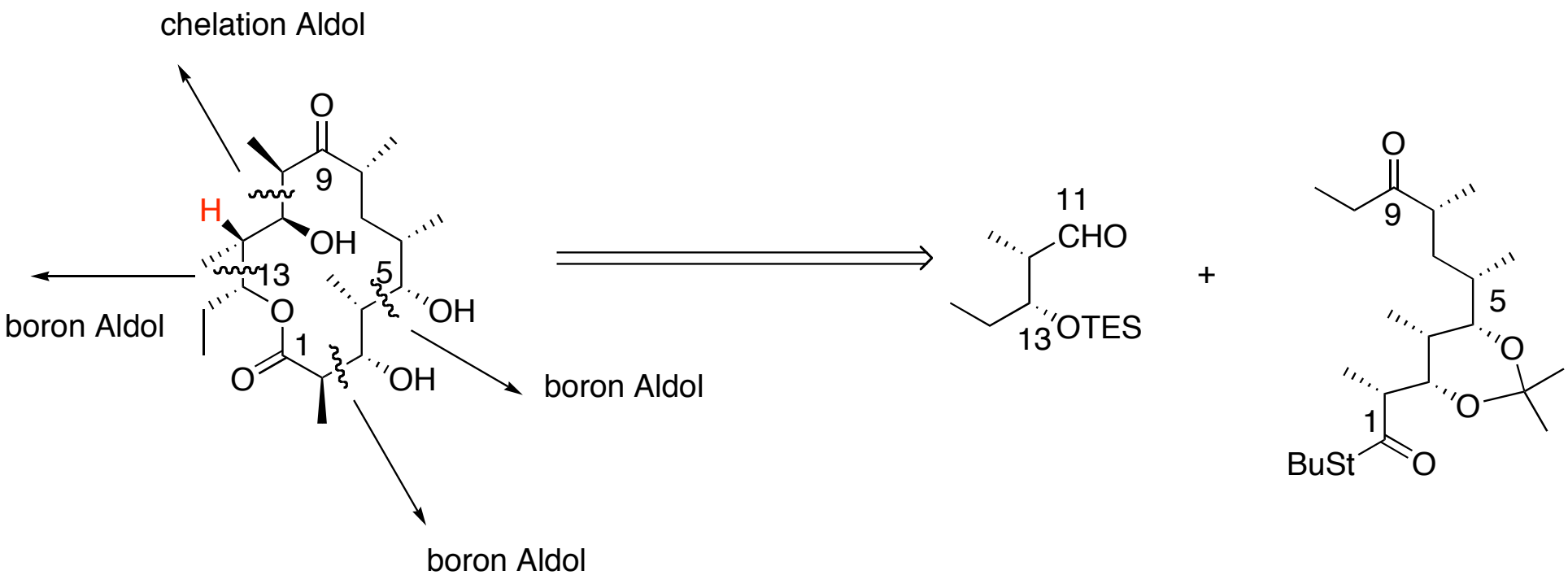
J. Am. Chem. Soc. **1981**, *103*, 3213.

Conclusions- Total Synthesis of Erythromycin A

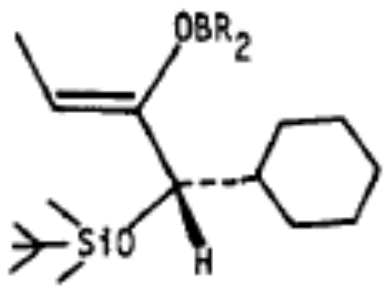
- Themes
  - Recognition of 2 repeating subunits
  - Use of one key intermediate to set 7 stereocenters
  - Use of decalin (cyclic) system for stereocontrol

- Conclusions
  - The use of inherent chirality of molecule to set adjacent centers (Aldol/ Cram model)
  - The necessary protection of key positional hydroxyl groups
  - The ability to attach sugar moieties easily

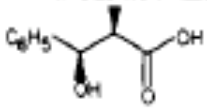
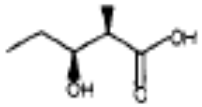
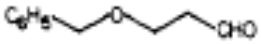
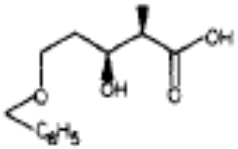
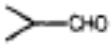
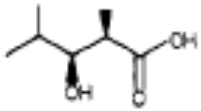
Total Synthesis of 6-deoxyerythronolide B-
S. Masamune (1981)



Stereoselective Aldol Condensation: Chiral Boron Enolates

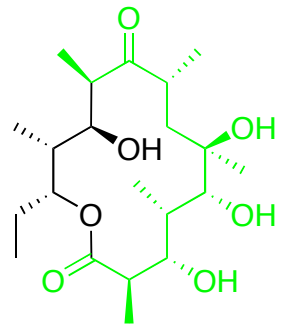


12a: BR_2=9-BBN
12b: R=n-C_4H_9
12c: R=c-C_5H_{11}

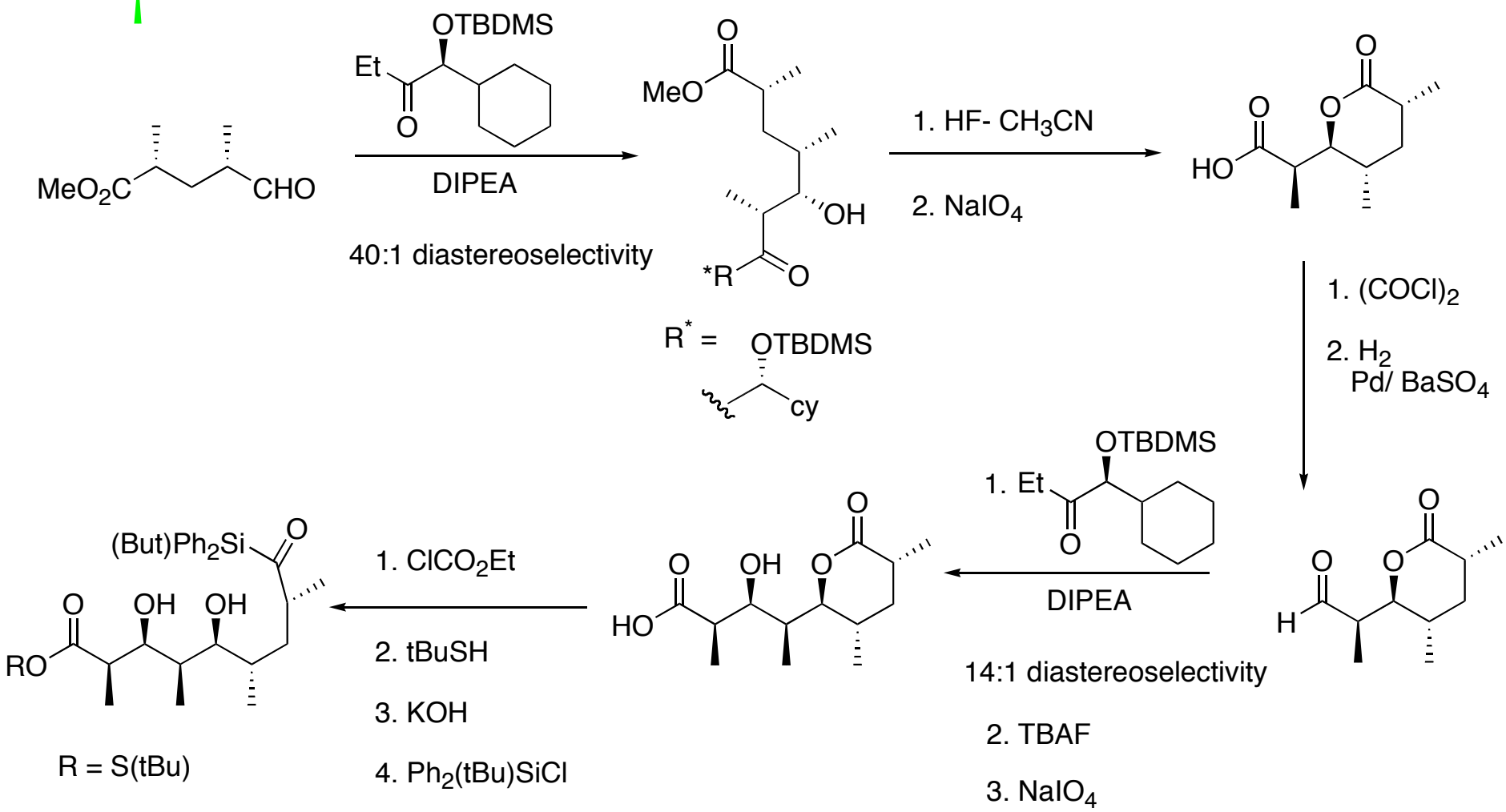
aldehyde (14)	boron enolate	ratio of[a] 16 to 17	major β-hydroxy acid (18)
C_6H_5–CHO 14a	12a 12b 12c	14:1 40:1 75:1	 18a
 14b	12a 12b 12c	17:1 50:1 >100:1	 18b
 14c	12a 12b 12c	16:1 28:1 100:1	 18c
 14d	12a 12b 12c	>100:1 >100:1 no reaction	 18d

- Exclusive formation of Z-enolate
- Selectivity increases with larger substituents on boron (B)
- Presence of □□substitution proves problematic with large groups on B

J. Am. Chem. Soc., **1981**, *103*, 1566

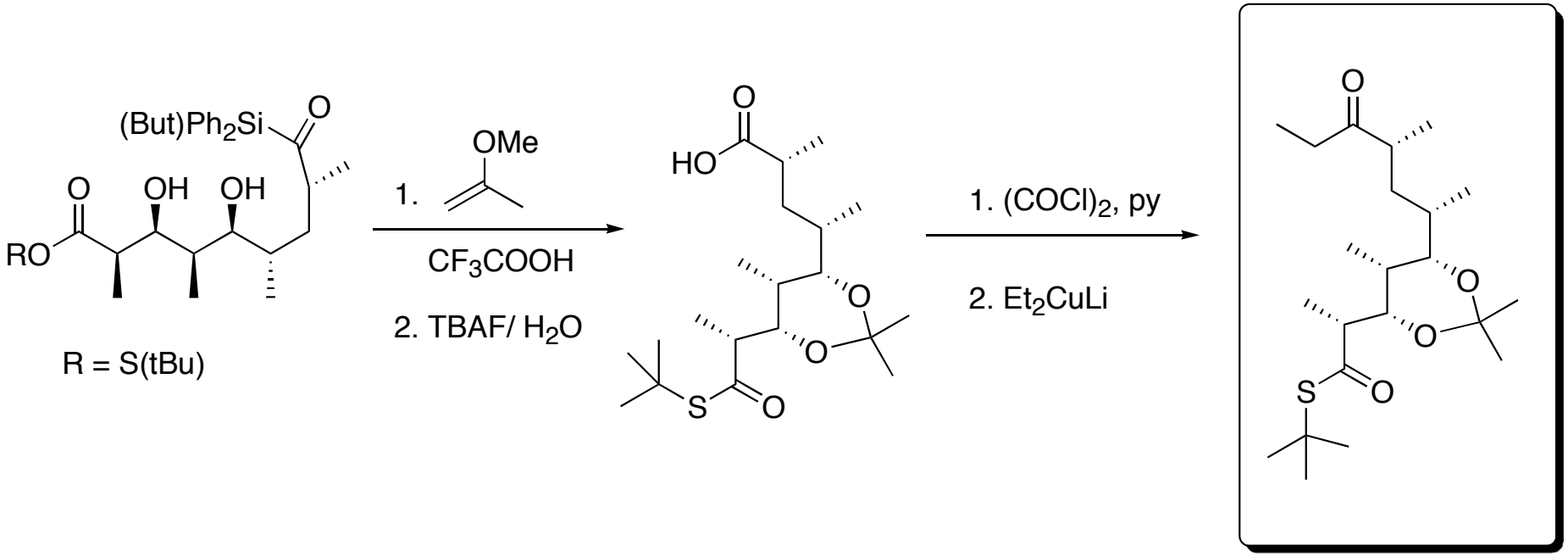


Synthesis of C1-C10 fragment



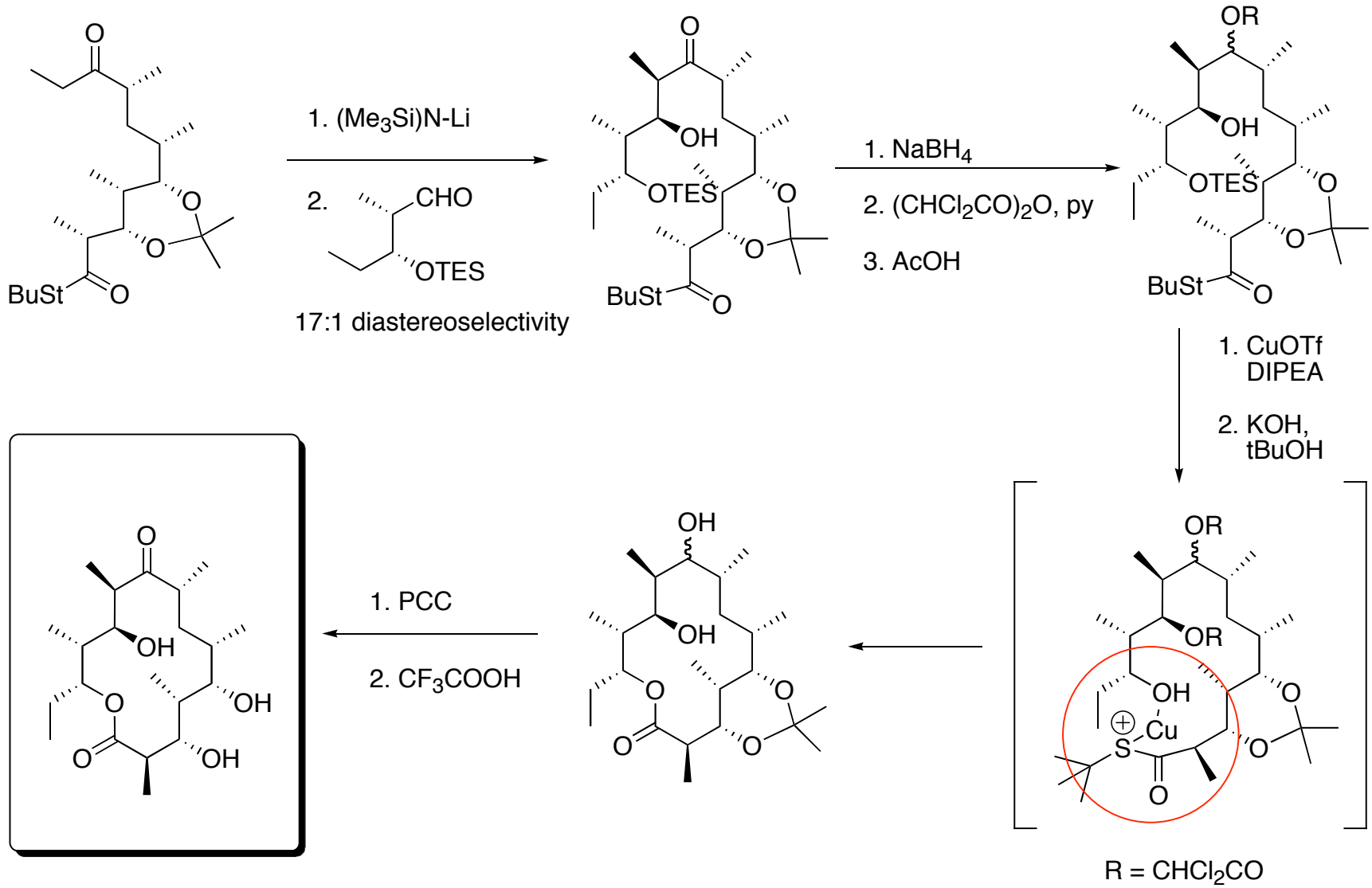
J. Am. Chem. Soc., **1981**, *103*, 1568

Completion of C1-C10 fragment



J. Am. Chem. Soc., **1981**, *103*, 1568

Left and Right Halves Brought Together



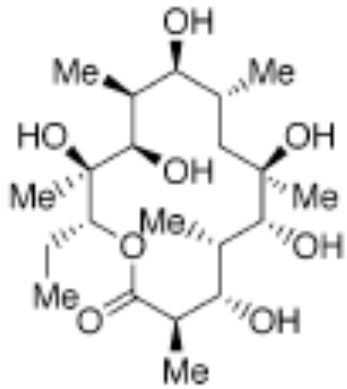
J. Am. Chem. Soc., **1981**, *103*, 1568

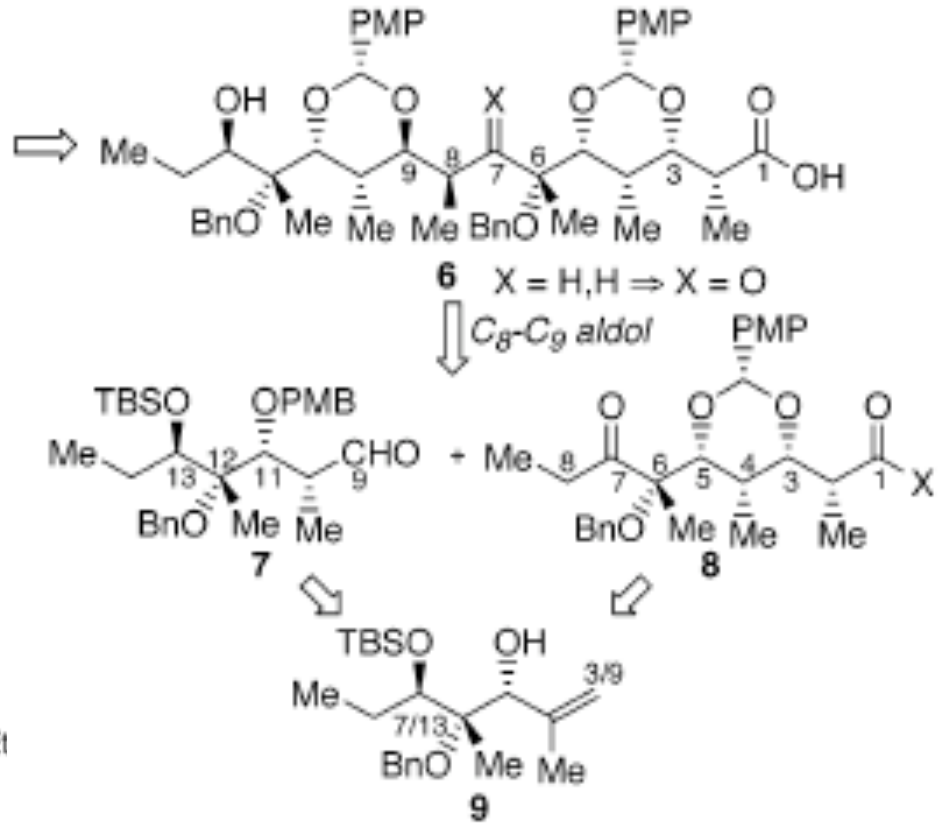
Conclusions- Total Synthesis of 6-deoxyerythronolide B

- Themes
  - Use of aldol disconnects to form 8 out of 10 stereocenters
  - Development of stereoselective aldol chemistry using boron enolates
  - Improvement upon lactonization method using metal/sulfur activation

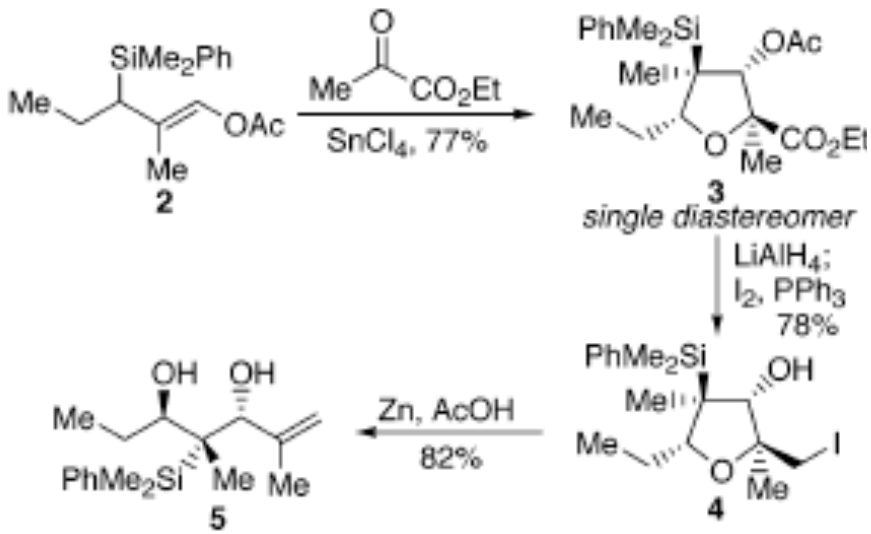
- Conclusions
  - The power of aldol chemistry to form contiguous stereogenic centers (simplification)
  - The ability for stereoselective formation of two chiral centers with 1 reaction

(9S)-Dihydroerythronolide A-
[3+2] Annulation of Allylic Silanes (K. A. Woerpel)



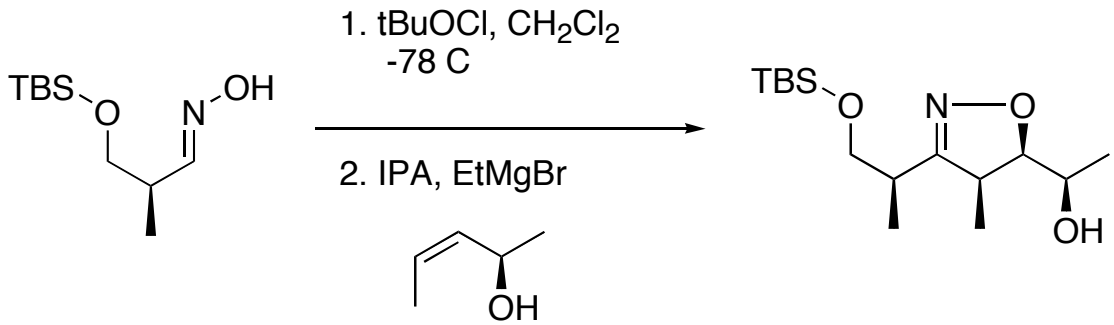


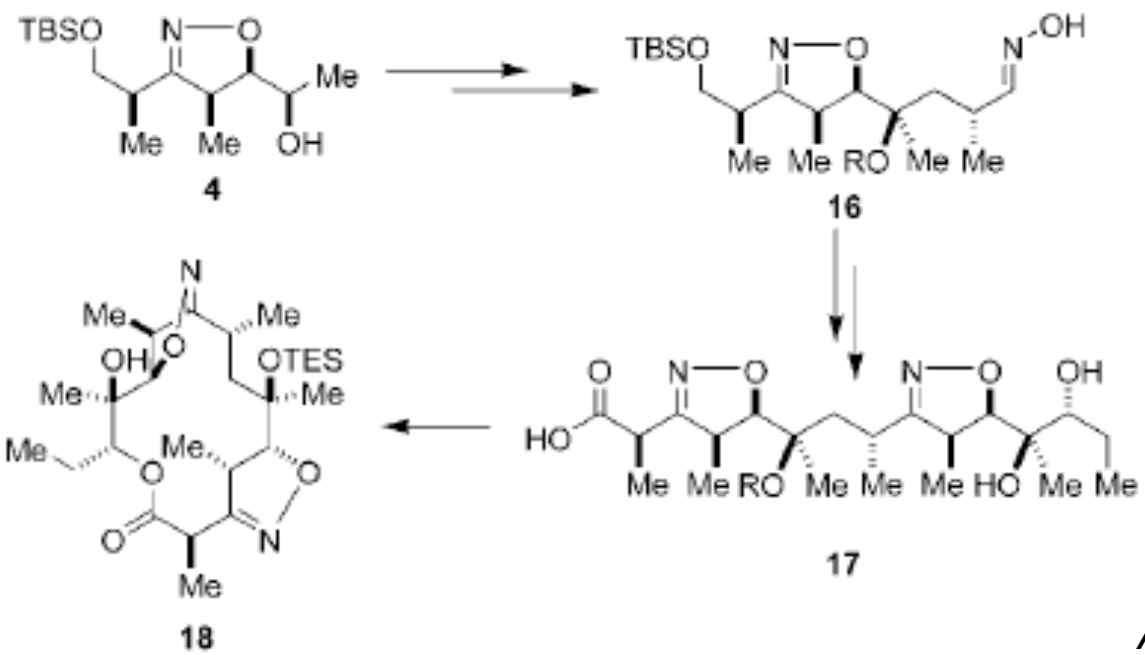
[3+2] annulation



J. Am. Chem. Soc., **2003**, *125*, 6018.

Use of Mg mediated cycloaddition- Synthesis of Erythronolide A (E. M. Carriera)





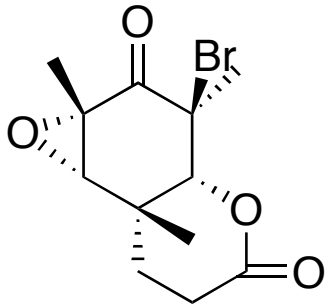
ACIEE, **2005**, *44*, 4036.

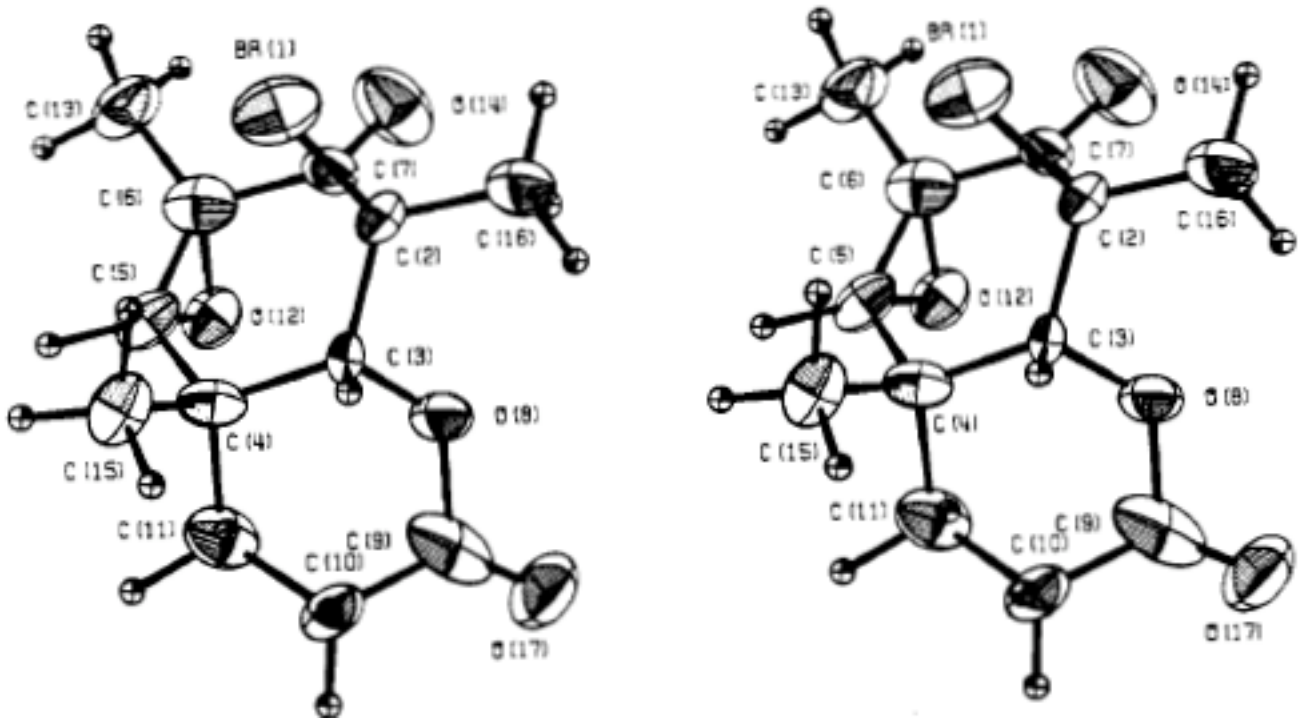
Conclusions- Erythromycin/ Erythronolide Syntheses

- Macrolactonization has been improved to easily access large ring lactones
- Formation of contiguous stereogenic centers has evolved to today's asymmetric protocols
- Erythromycin will continue to be a tool used to test developments in the area of asymmetric organic synthesis

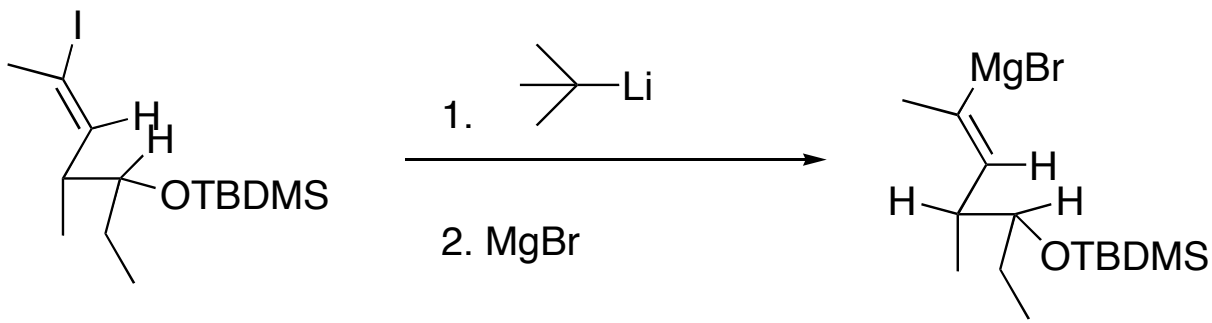
- Overview
  - Corey- traditional organic chemistry to set contiguous stereocenters
  - Woodward- recognition of key structural aspects for macrolactonization
  - Masamune- development of asymmetric aldol chemistry to set chiral centers

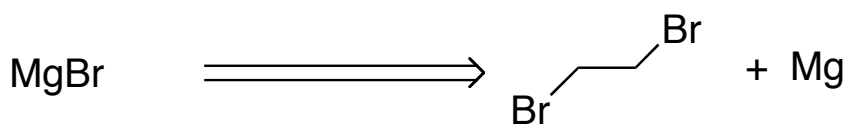
X-Ray of levorotatory bromo lactone





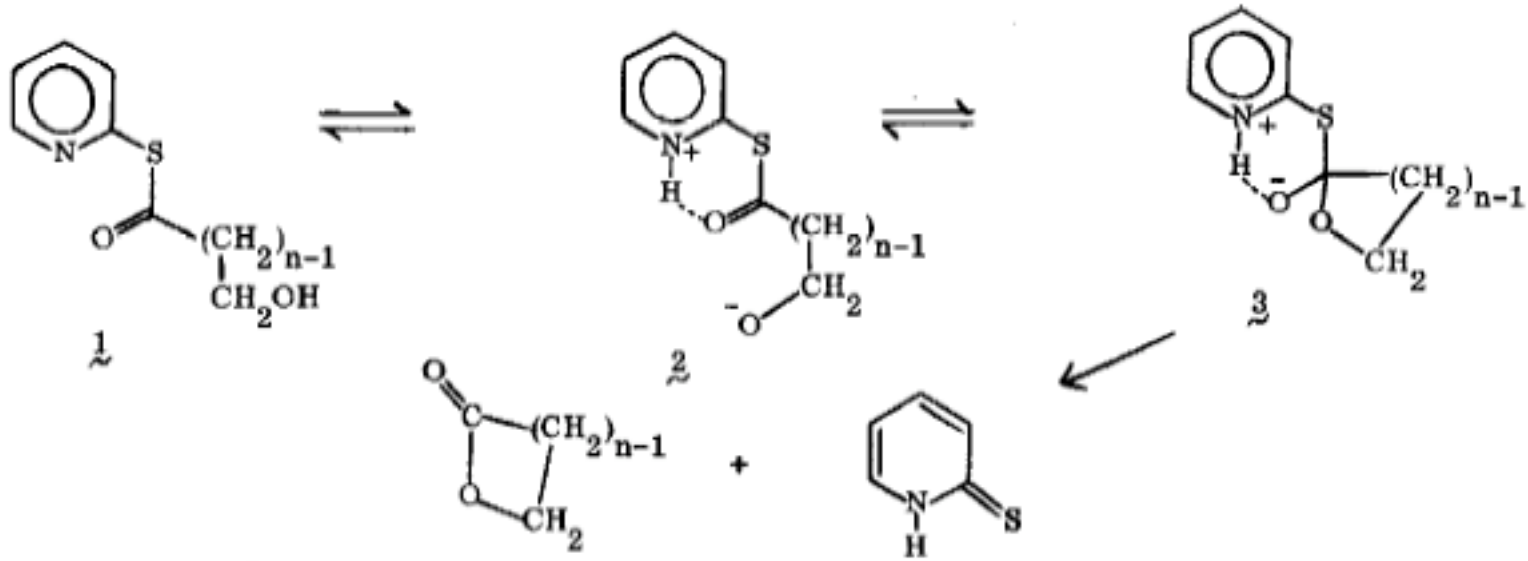
Preparation of C10-C13 Grignard





Mechanism: Double Activation

1.



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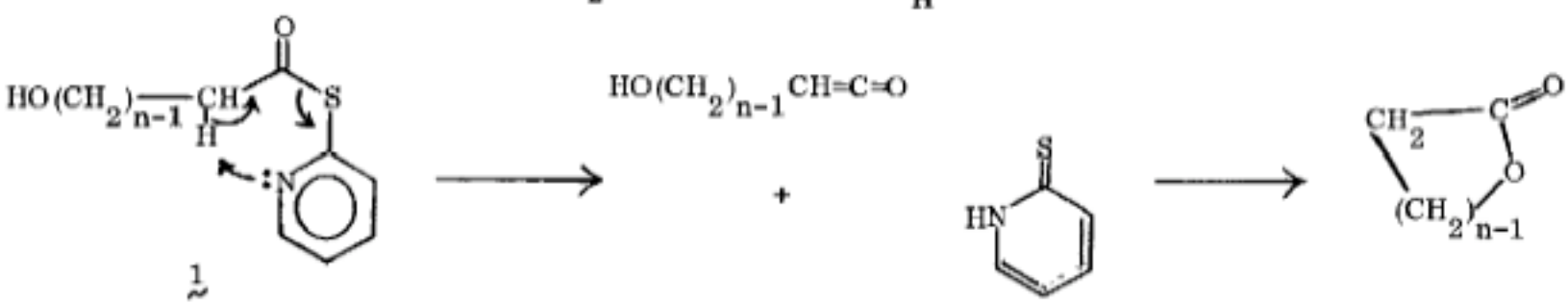
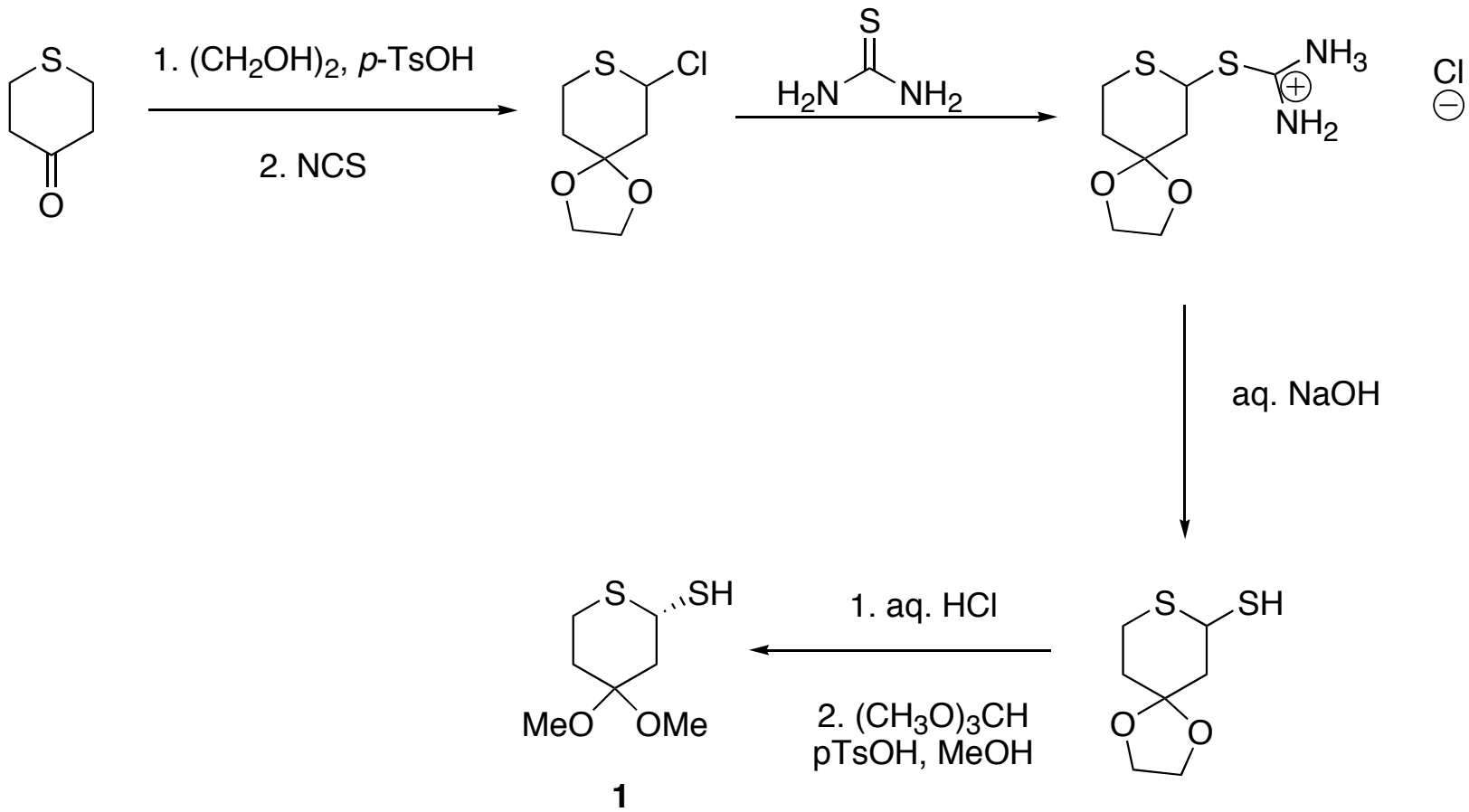


Evidence for 1:

1. O-deuterated (1) afforded lactone with NO deuteride incorporation
2. Lactonization occurs with no α-H for ketene formation

Tetrahedron Lett. **1976**, *38*, 3405.

Preparation of hemi thio-acetal (1)

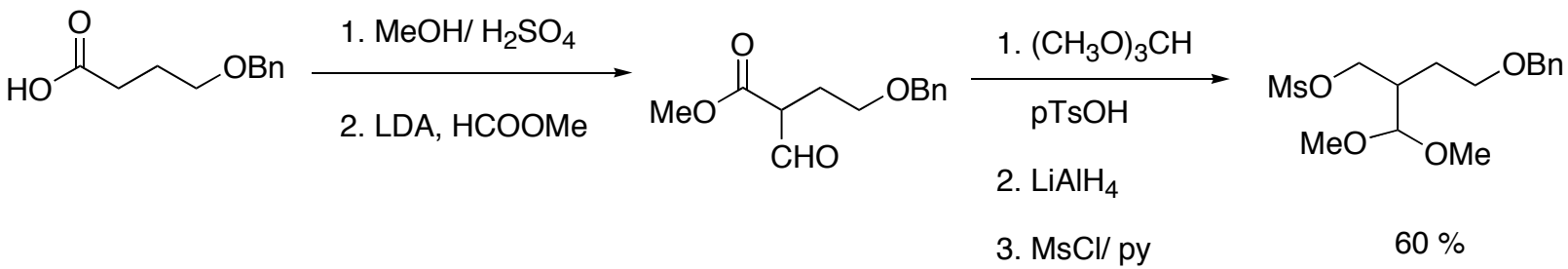


1

65 %

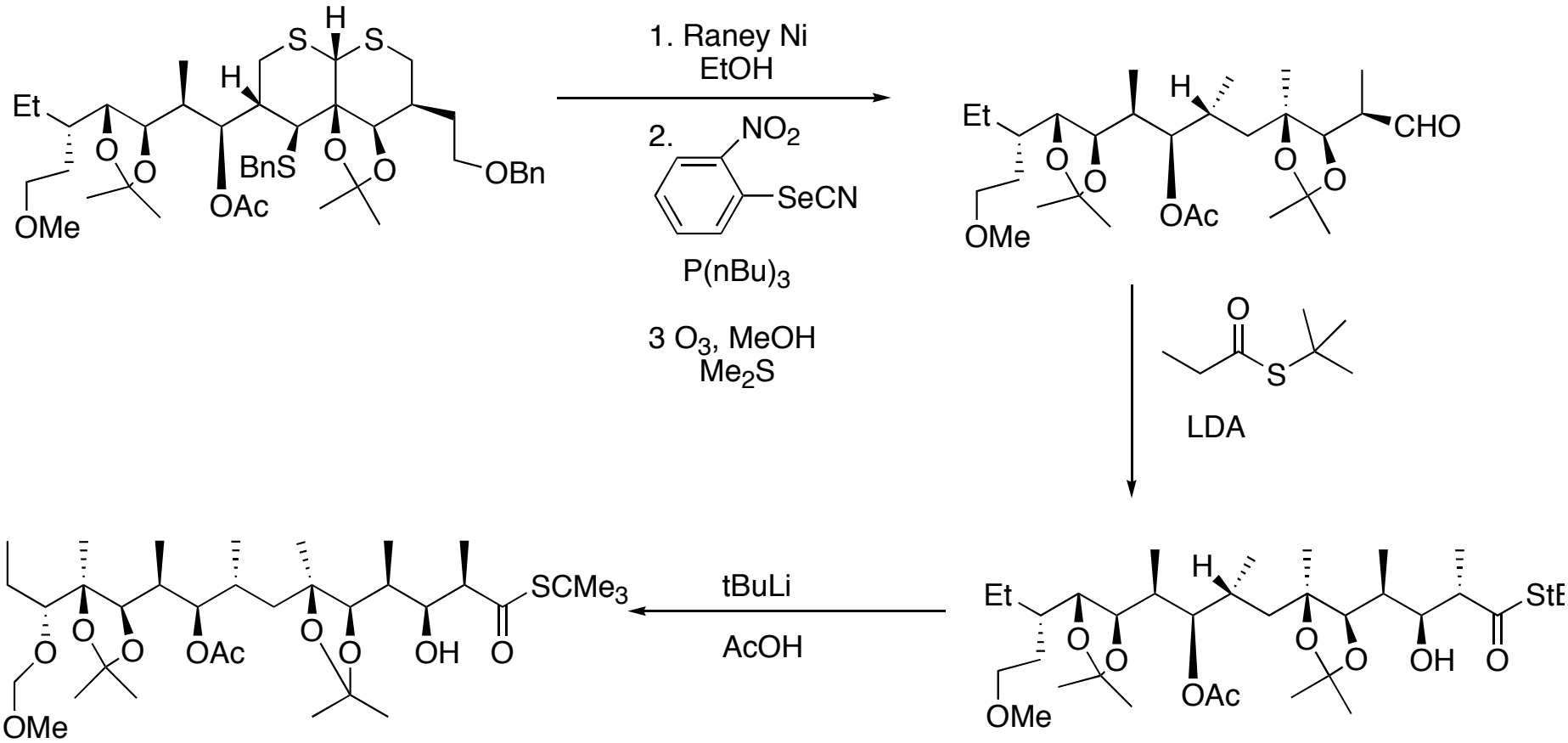
ACIEE, **1977**, *16*, 196.

Preparation of protected □,□□hydroxy butanal



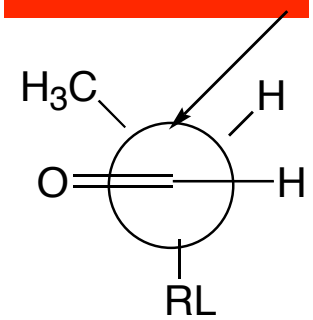
J. Org. Chem. **1967**, 32, 1844
Tetrahedron Lett. **1971**, 2953

Completion of seco-acid



Seco acid A intermediate

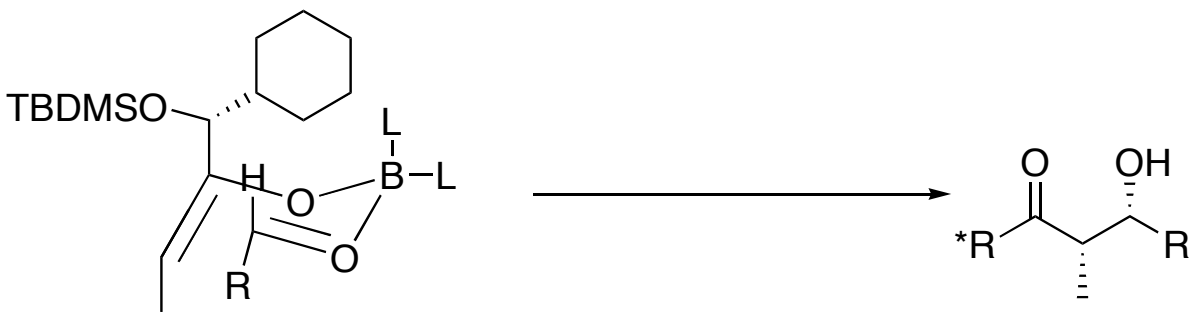
Model: CRAM enolate



J. Am. Chem. Soc. **1981**, *103*, 3211

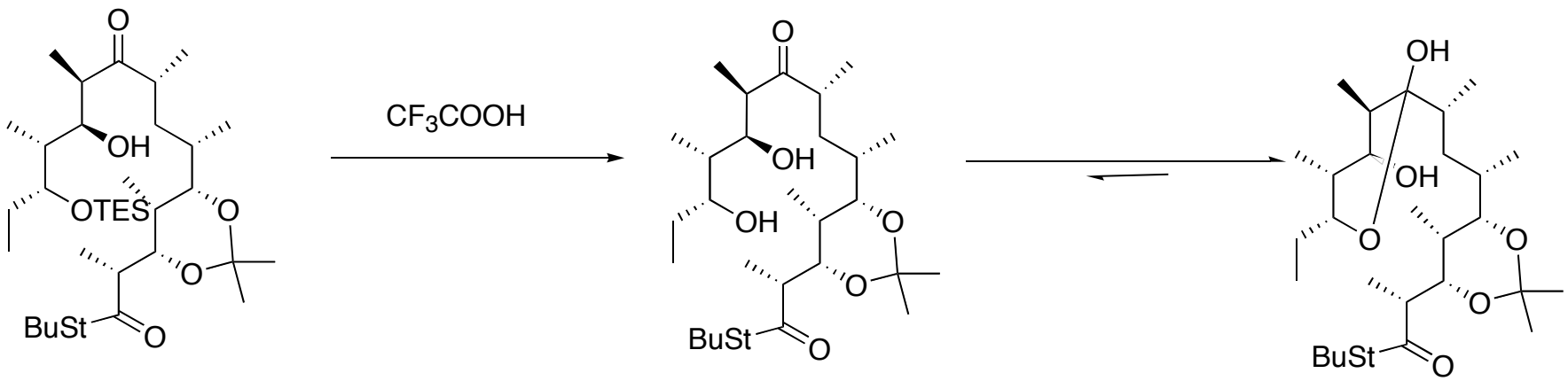
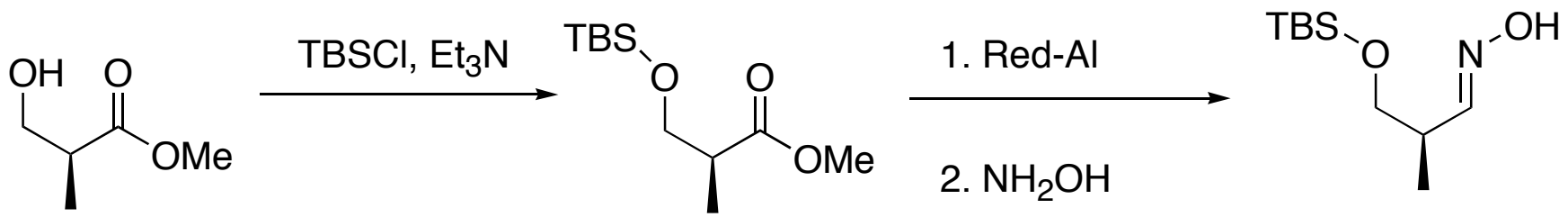
Proposed transition state for boron enolate

(S) configuration



(R) configuration

Problems with lactonization…again!!



Preparation of (S)-3-hydroxylisobutyrate oxime