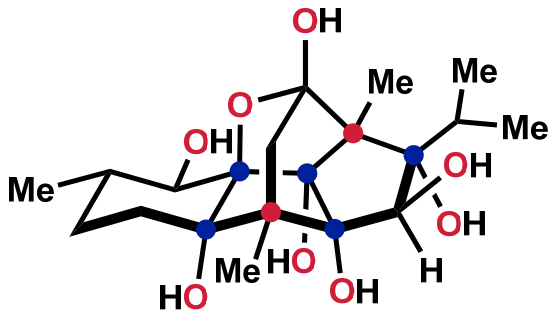
Total Synthesis of Ryanodol and Perseanol



Reporter: Zhimao Zhang

Supervisor: Prof. Quan Cai

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- **Introduction**
- **Total Synthesis of Ryanodol**
  - ✓ P. Deslongchamps
  - ✓ M. Inoue
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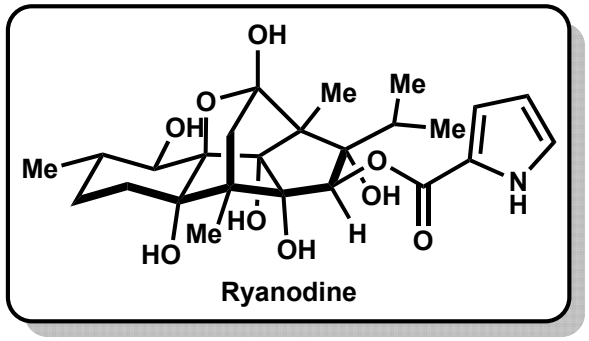
- **Total Synthesis of Perseanol**
  - ✓ S. E. Reisman
- **Summary**

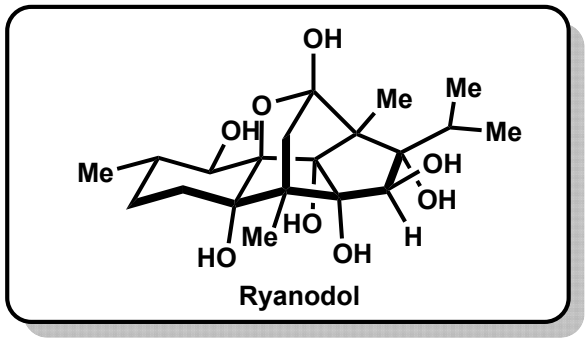
Introduction

1. Isolation and identification



Ryanodine


Ryania speciosa Vahl.



Ryanodol


Persea indica

CHARACTER

High-affinity ligand of ryanodine receptors (RyR)

⇩

RyR regulate Ca^{2+} release in organisms

⇩

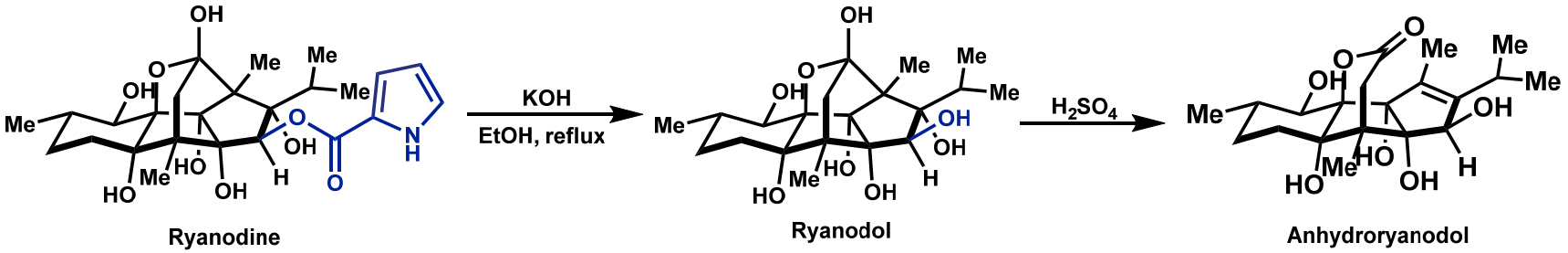
Insecticidal activities

Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 3086;
González-Coloma, A. *J. Chem. Ecol.* **1990**, *16*, 2723.
González-Coloma, A. *Phytochemistry* **1993**, *34*, 397.

Introduction

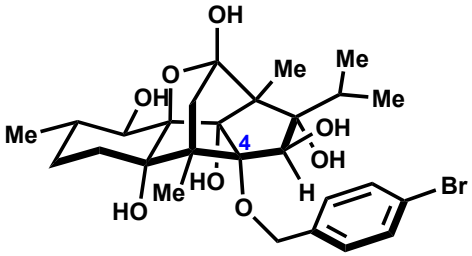
1. Isolation and identification

Chemical degradation

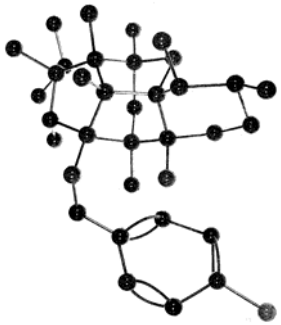


Ryanodine → Ryanodol → Anhydroryanodol

X-ray analysis



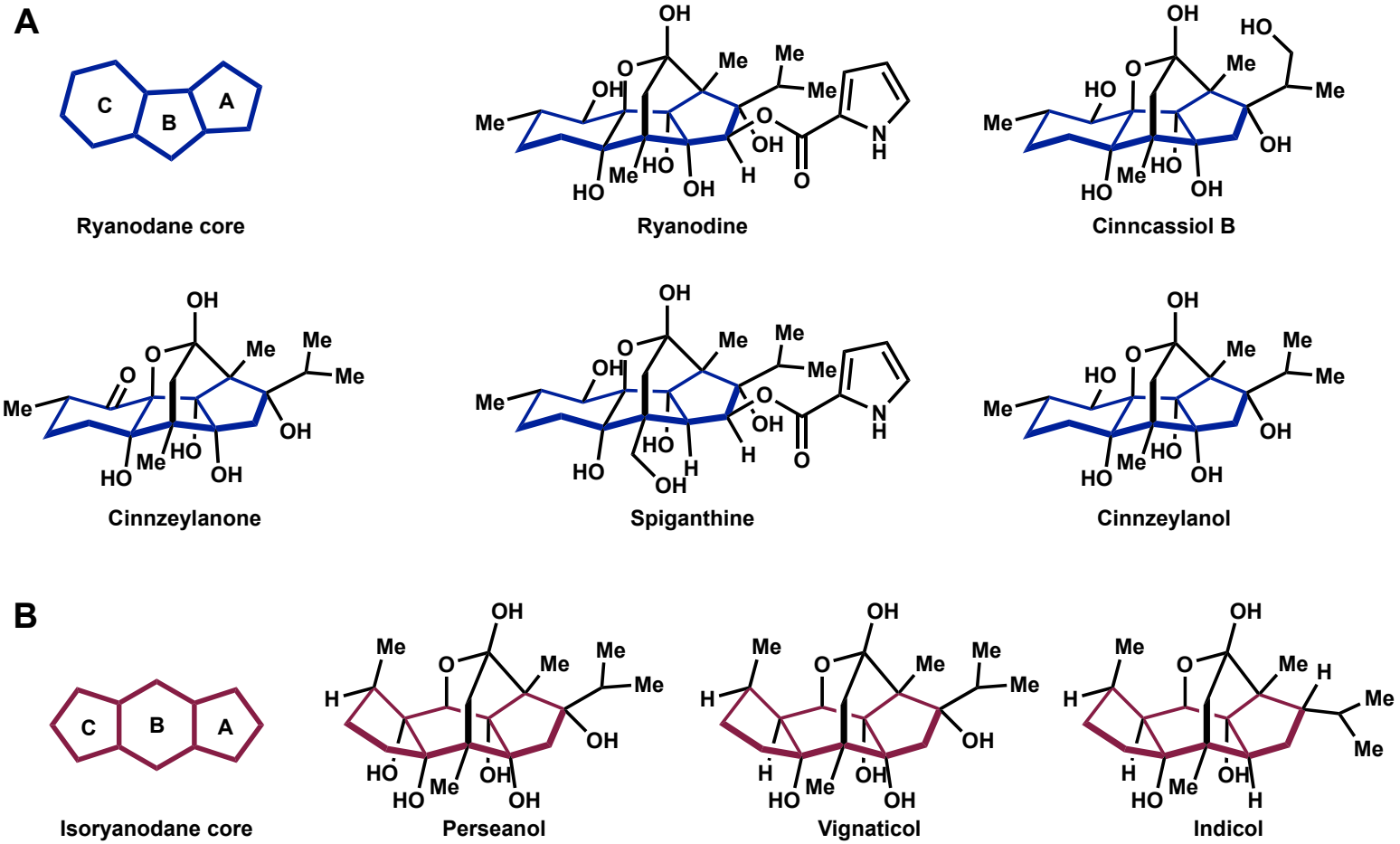
Ryanodol-*p*-bromo benzyl ether



Wiesner, K. *Can. J. Chem.* **1951**, *29*, 905;
Wiesner, K. *Tetrahedron Lett.* **1967**, *8*, 221;
Przybylska, M. Can. J. Chem. **1968**, *46*, 795.

Introduction

2. Ryanodane diterpenoids

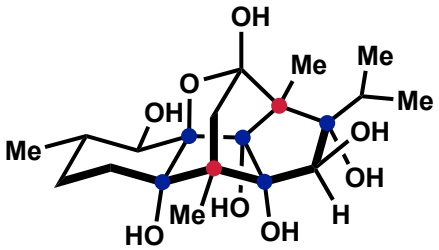


Murakoshi, S. *Agr. Biol. Chem.* **1976**, *40*, 2305;
Nohara, T. *Chem. Pharm. Bull.* **1980**, *28*, 2682.
Fraga, B. M. *J. Agric. Food Chem.* **1996**, *44*, 296;
Fraga, B. M. *J. Nat. Prod.* **1997,** *60*, 880;

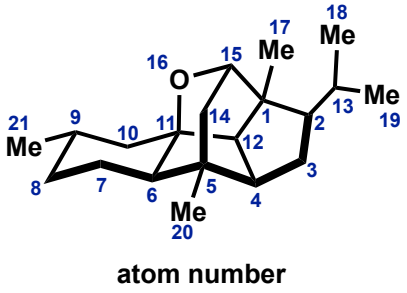
.

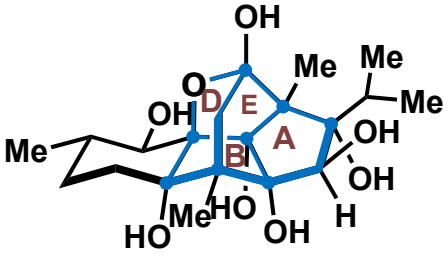
Introduction

3. Structural features of Ryanodol



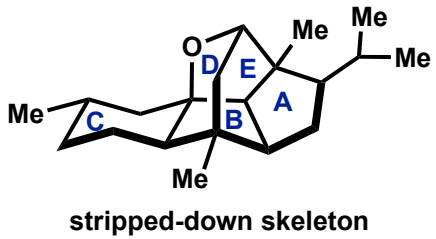
- 5 rings system (6-5-5)
- 11 contiguous stereogenic centers
- 2 all-carbon quaternary carbons
- 8 oxygenated carbons





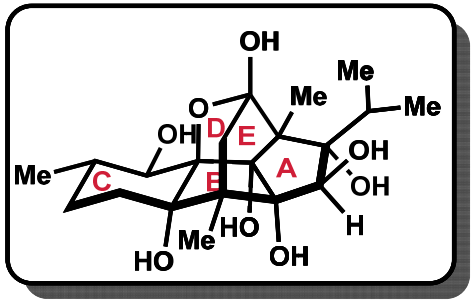
ABDE-ring moiety

- 10-carbon framework
- 8 tetrasubstituted



Total Synthesis of Ryanodol — *Deslongchamps*

P. Deslongchamps

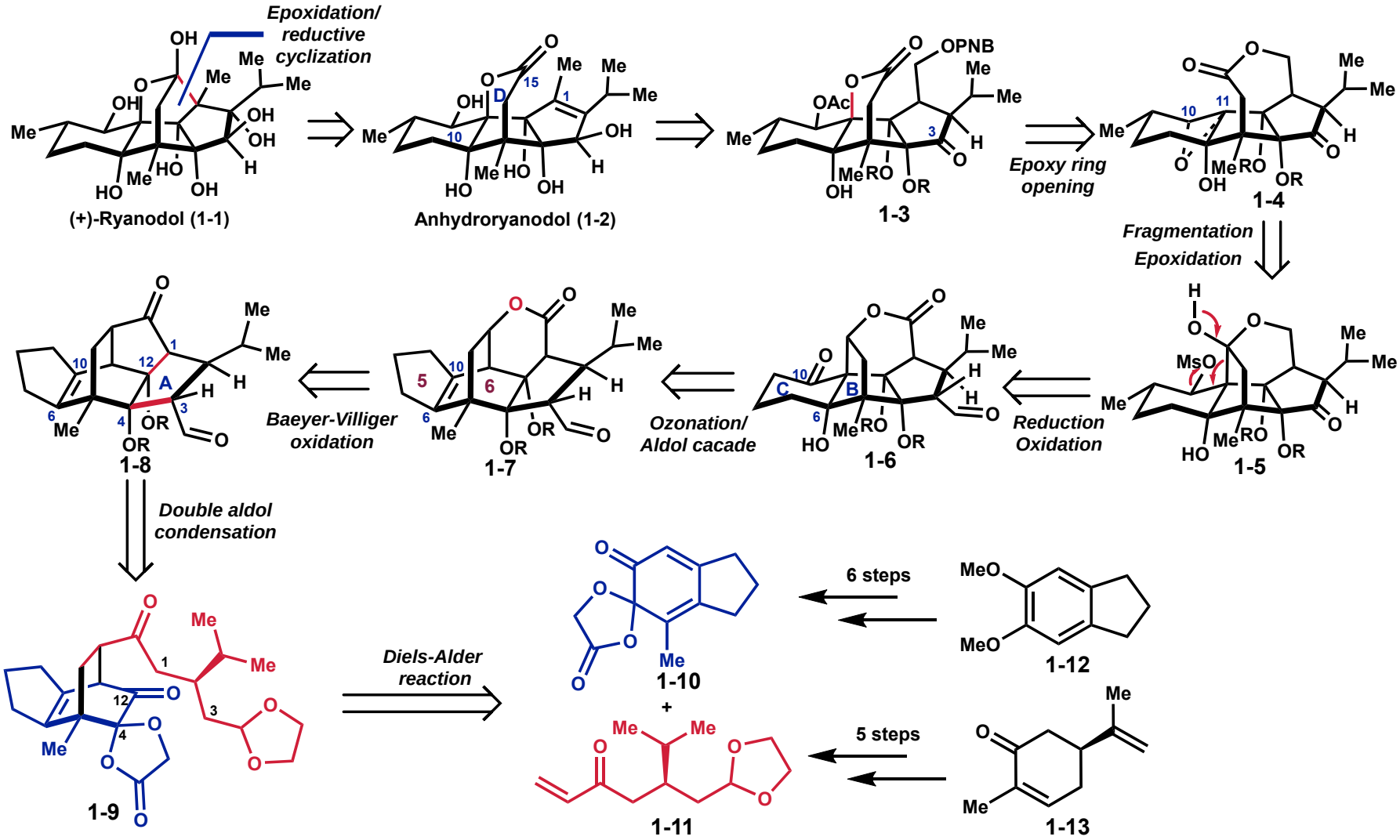


The construction order: A→(B, C)→D→E

Deslongchamps, P. *Can. J. Chem.* **1979**, *57*, 3348.

Total Synthesis of Ryanodol — *Deslongchamps*

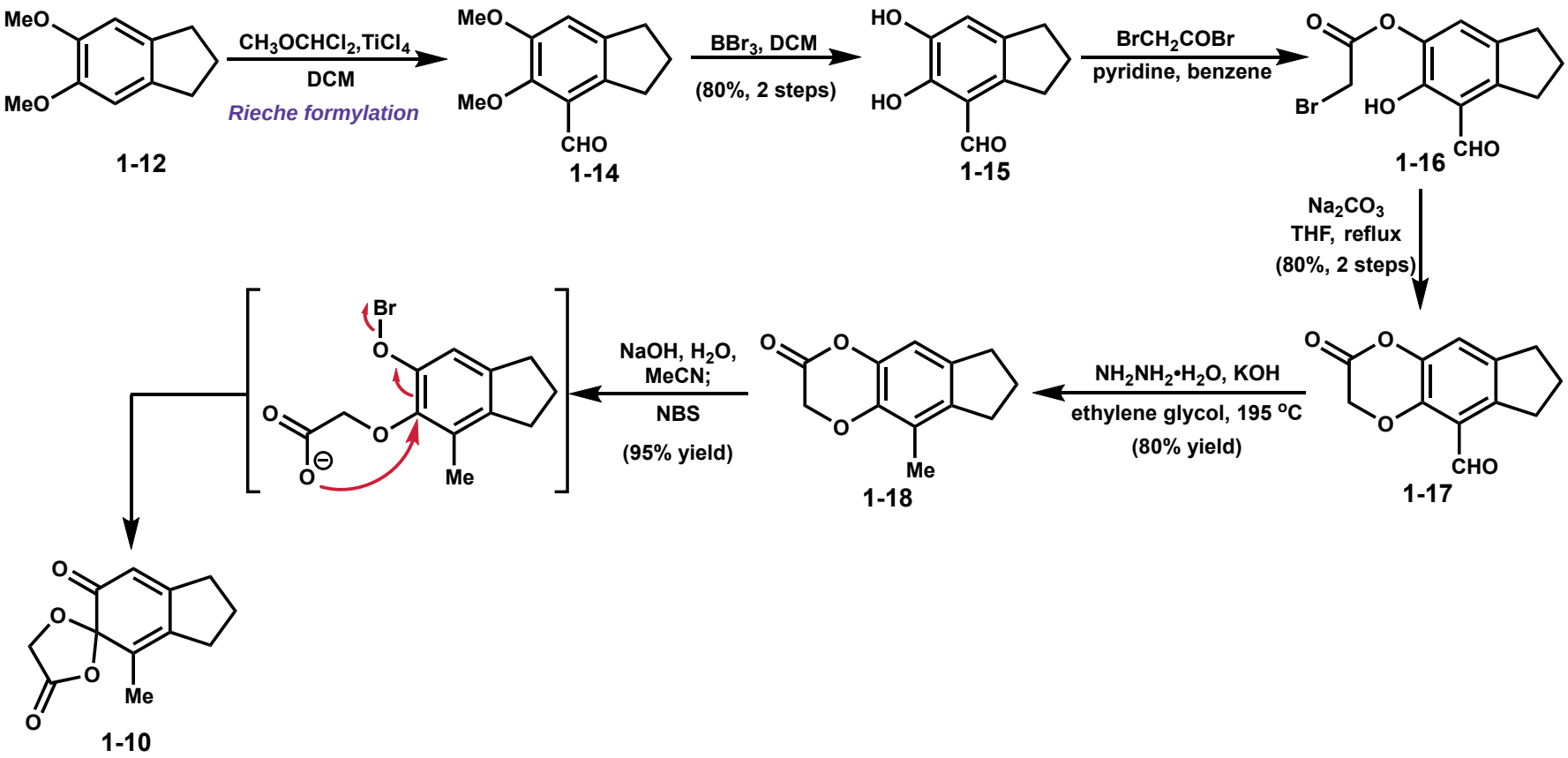
1. Retrosynthetic Analysis



Total Synthesis of Ryanodol — *Deslongchamps*

2. The synthesis of the Diels-Alder reactants

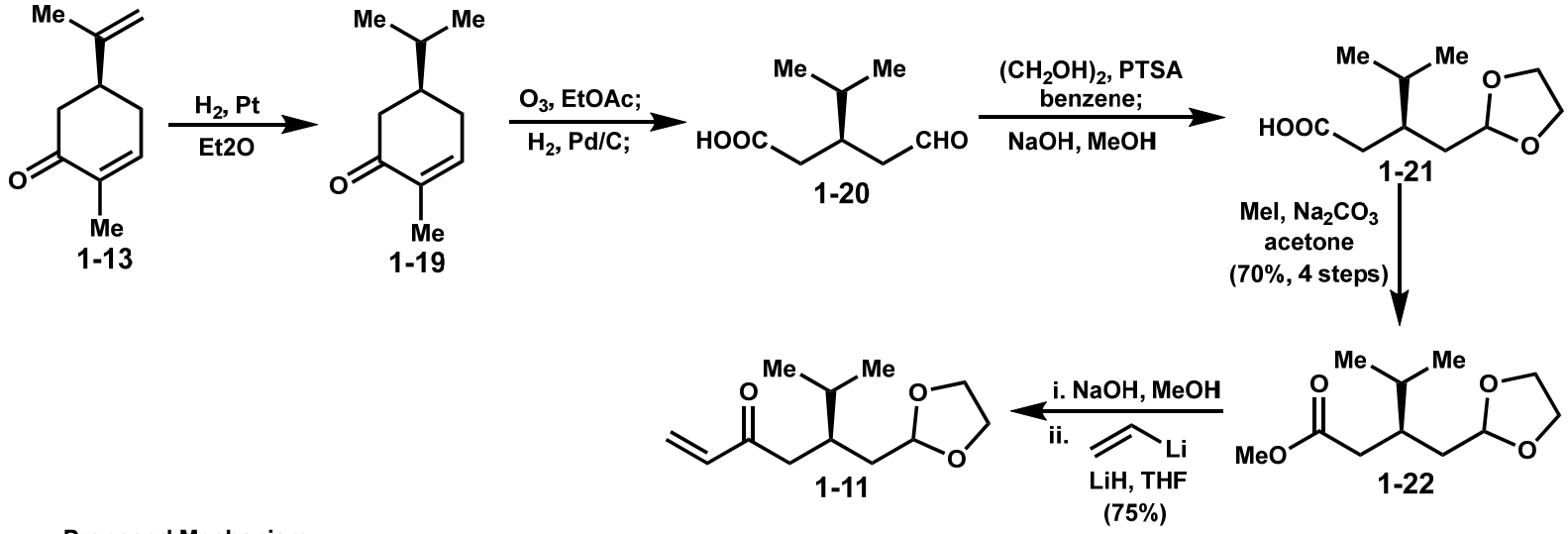
The Synthesis of diene



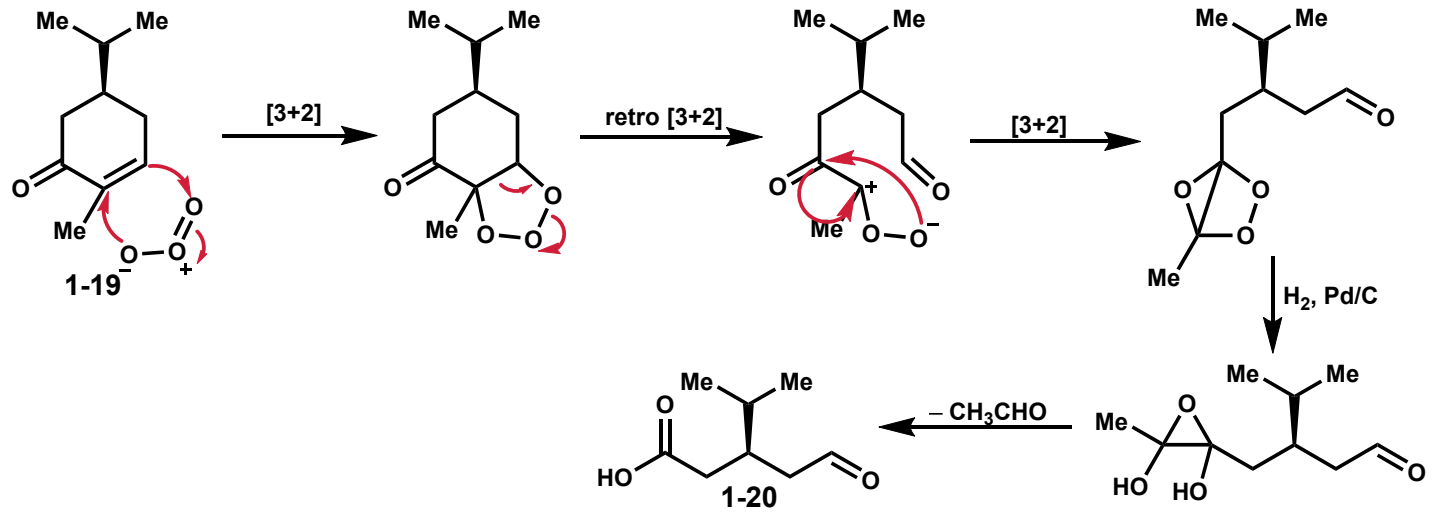
Total Synthesis of Ryanodol — *Deslongchamps*

2. The synthesis of the Diels-Alder reactants

The Synthesis of Dienophile

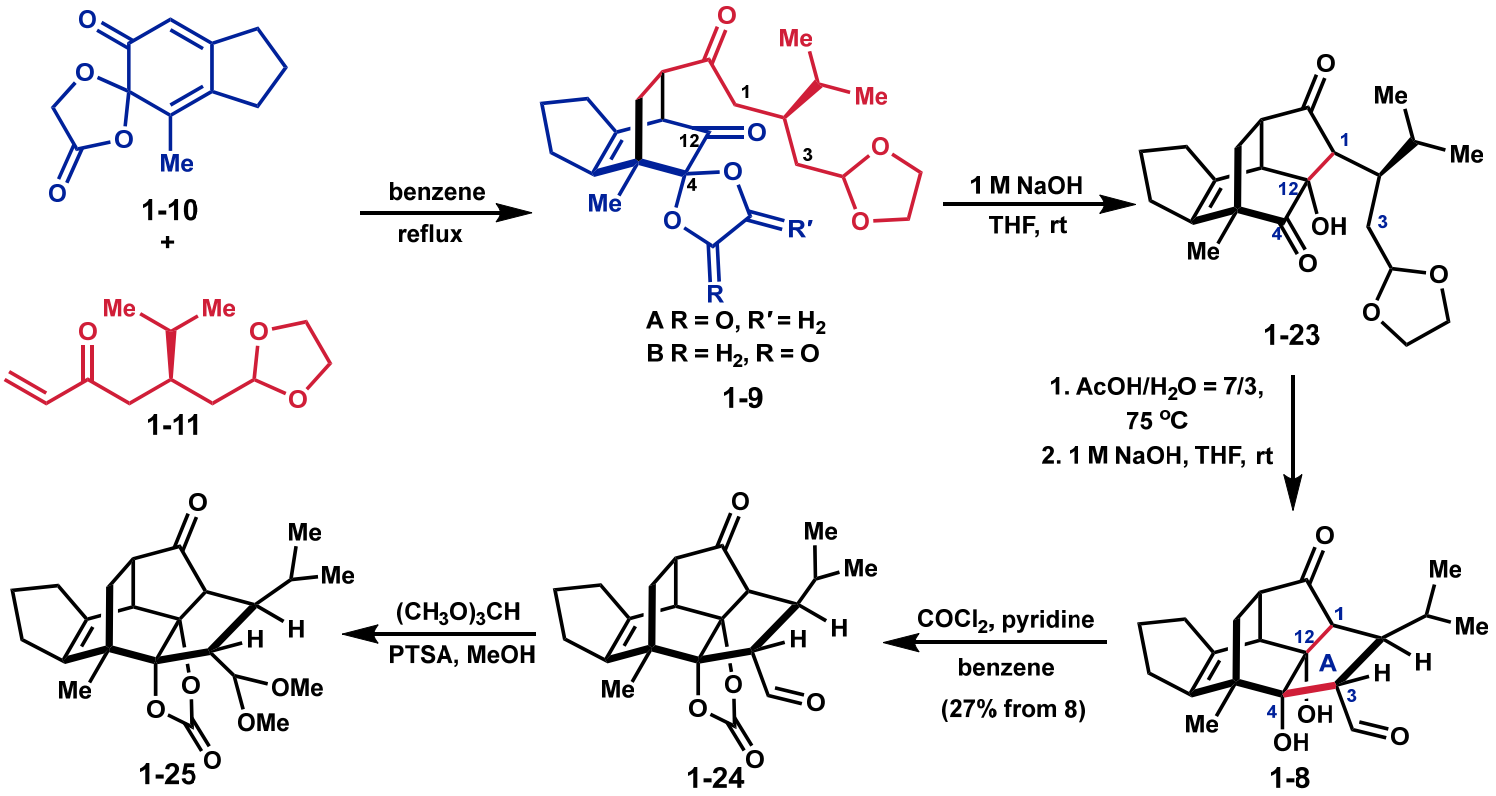


Proposed Mechanism



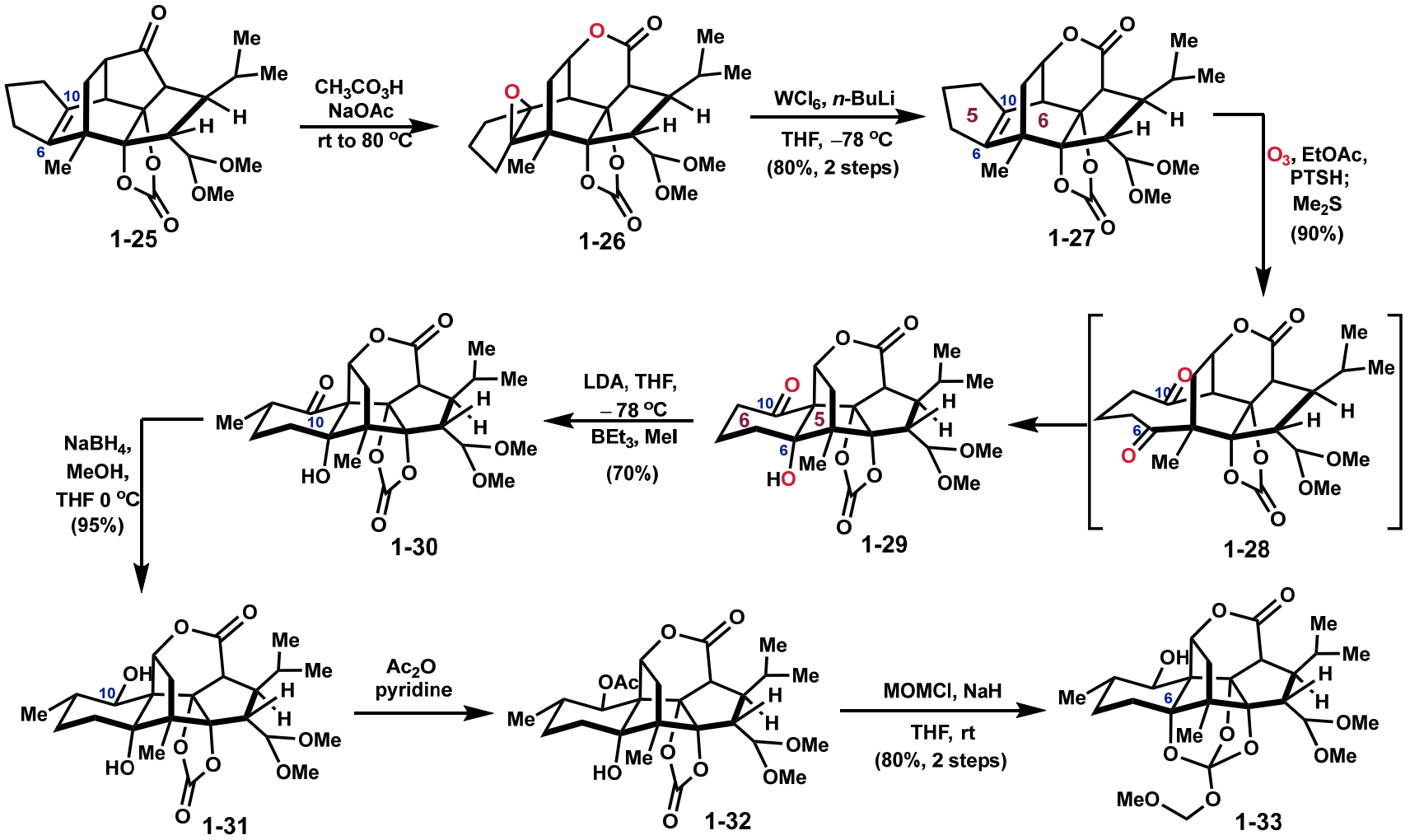
Total Synthesis of Ryanodol — *Deslongchamps*

3. The construction of A ring



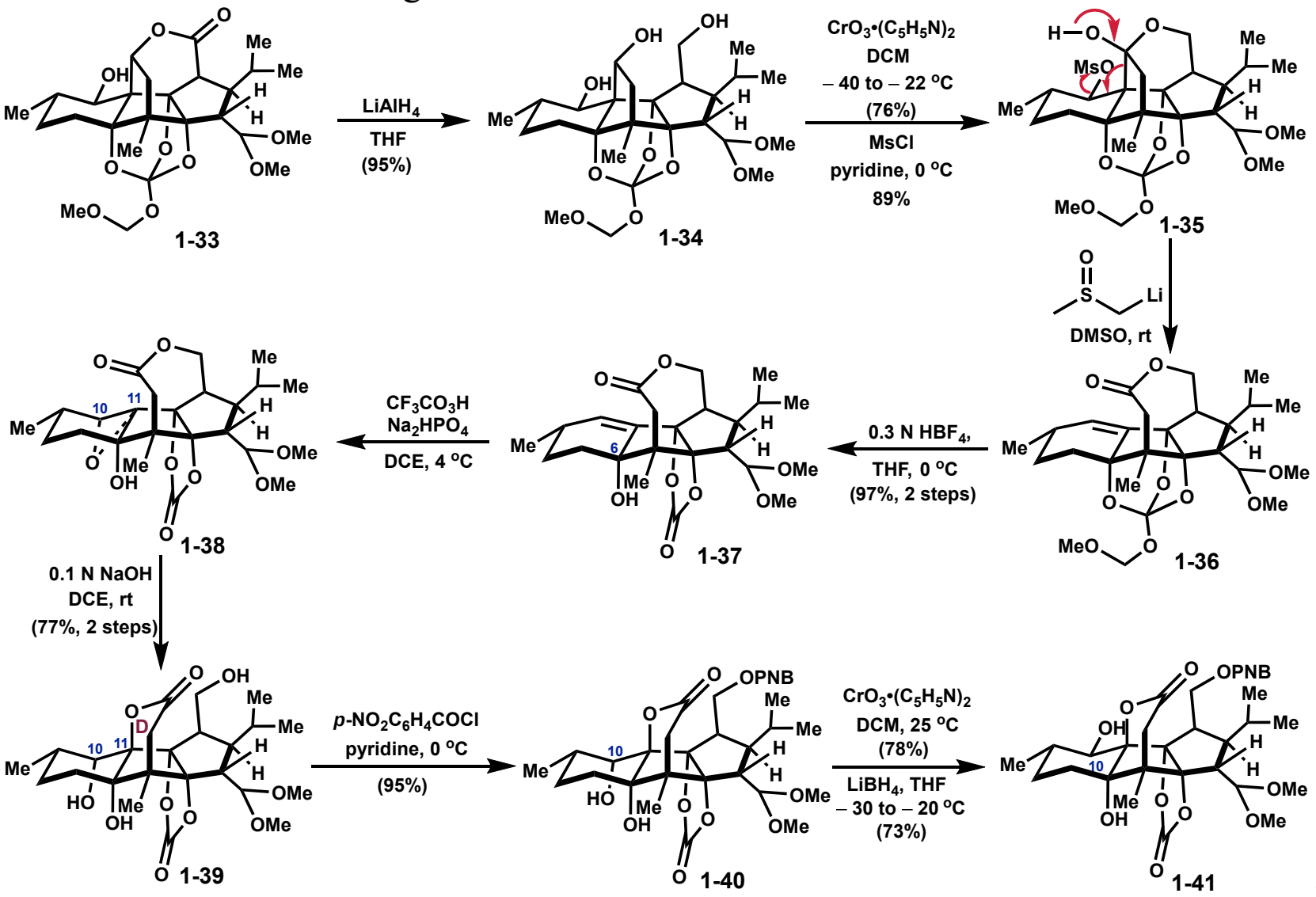
Total Synthesis of Ryanodol — *Deslongchamps*

4. The construction of B&C ring



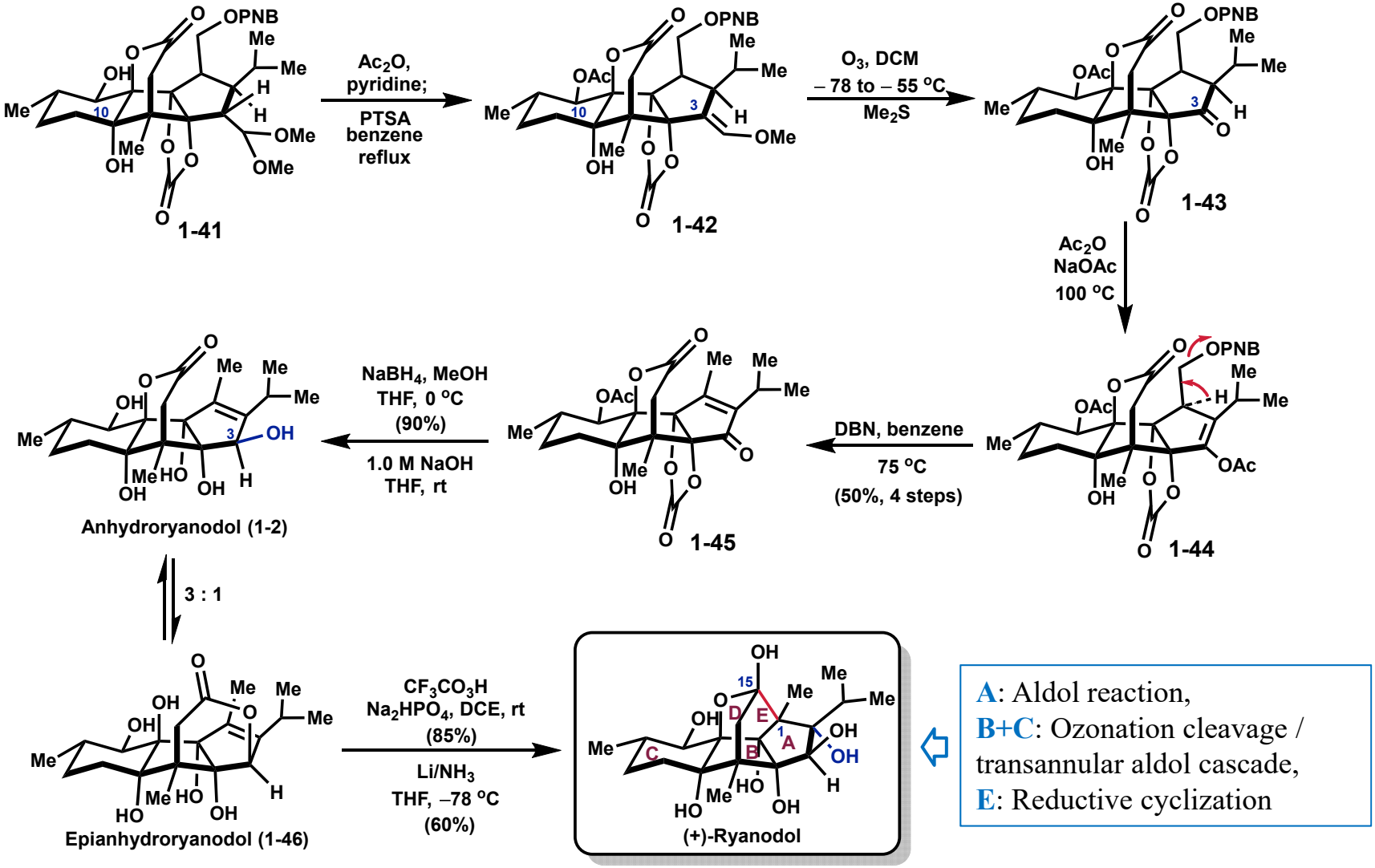
Total Synthesis of Ryanodol — *Deslongchamps*

5. The construction of D ring



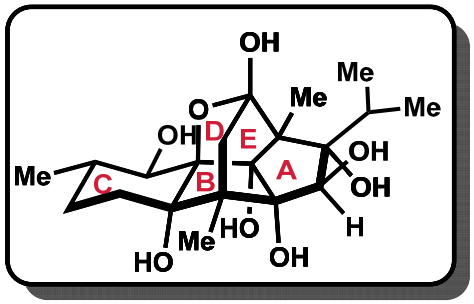
Total Synthesis of Ryanodol — *Deslongchamps*

6. The construction of Final ring



Total Synthesis of Ryanodol — *Inoue*

M. Inoue

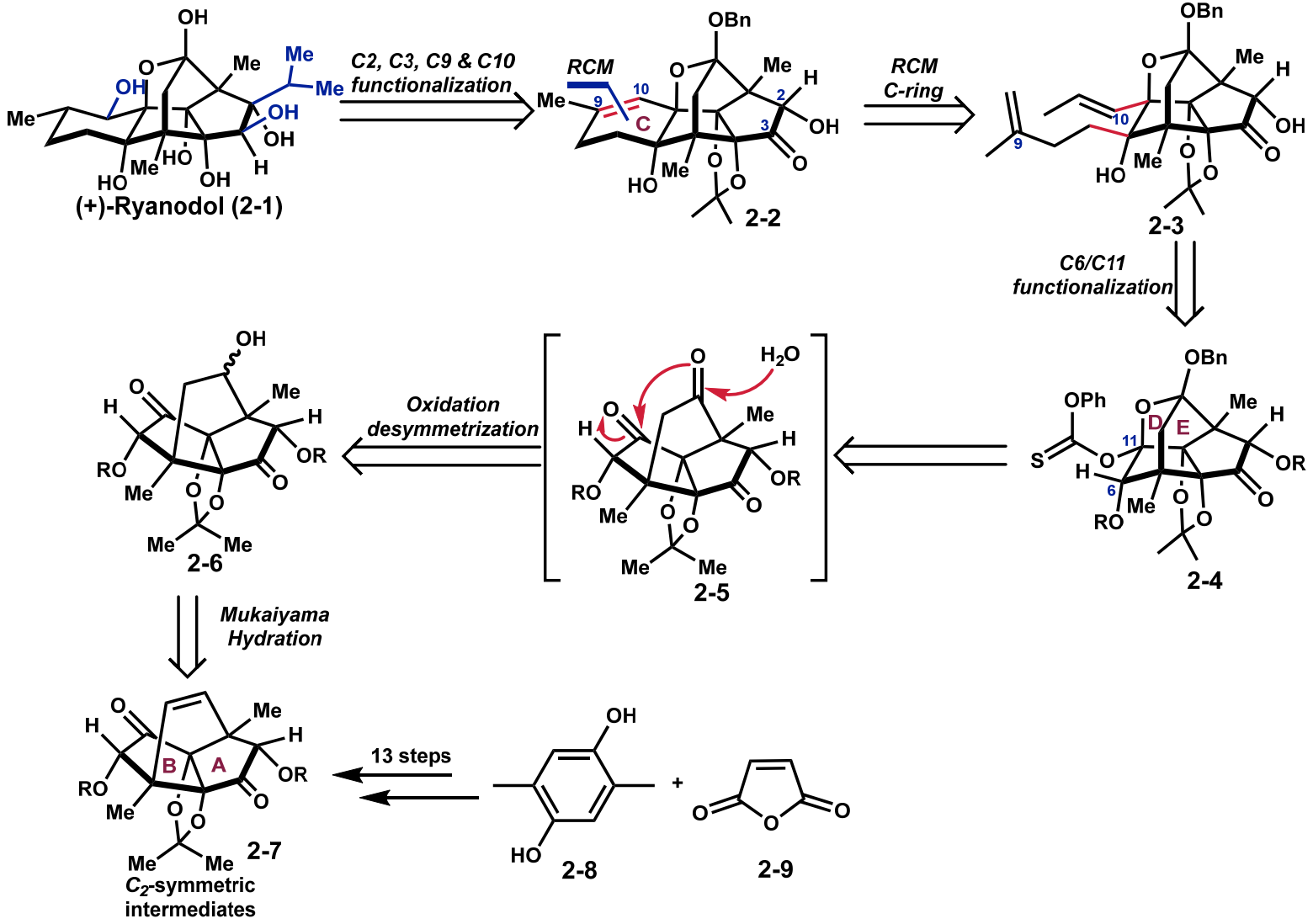


The construction order: (A, B)→(D, E)→ C

Inoue, M. *J. Am. Chem. Soc*. **2014**, *136*, 5916.

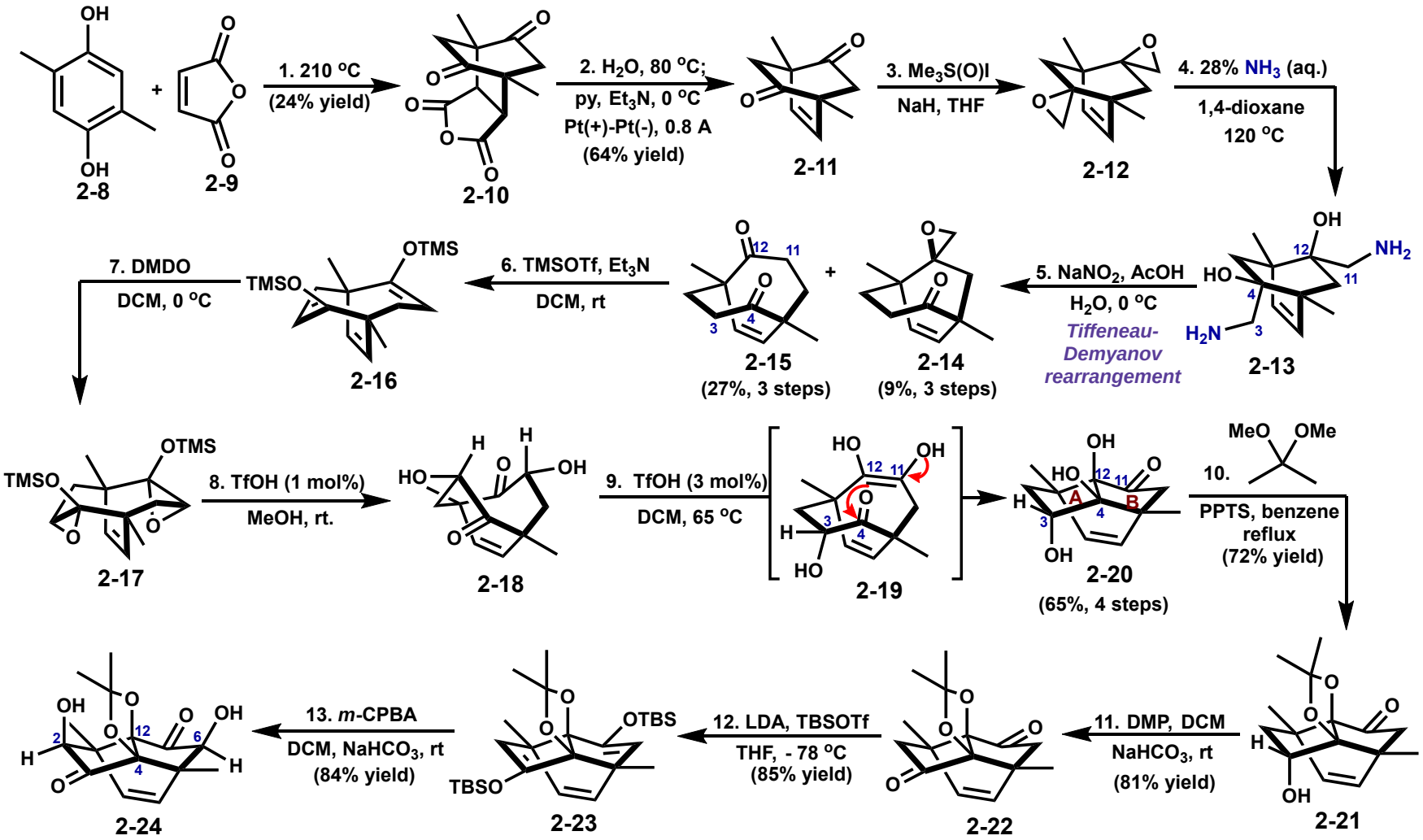
Total Synthesis of Ryanodol — *Inoue*

1. Retrosynthetic Analysis



Total Synthesis of Ryanodol — *Inoue*

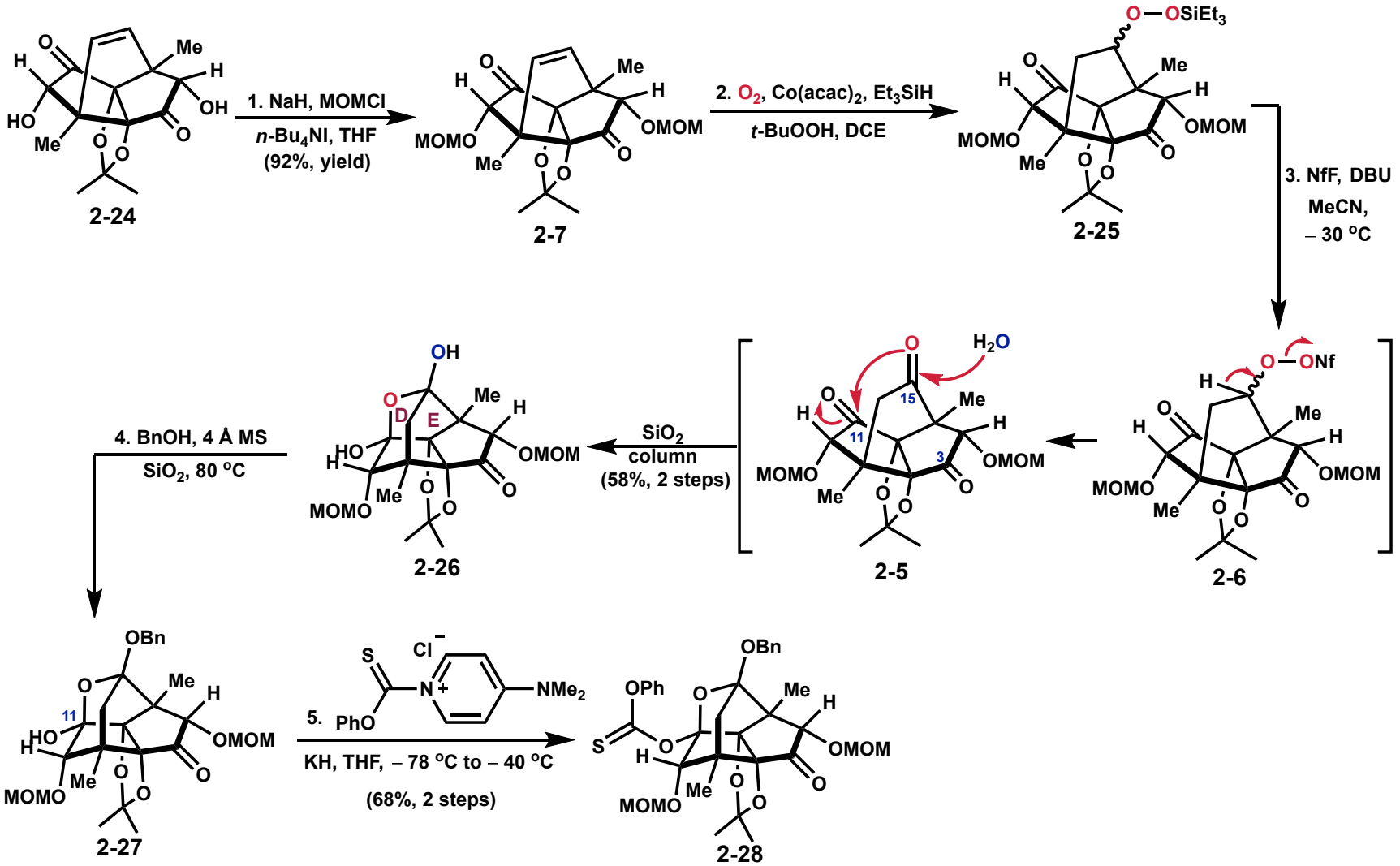
2. The construction of C_2-symmetric intermediates



Inoue, M. *Tetrahedron Lett*. **2009**, *50*, 1035;
Inoue, M. *Chem. Sci*. **2013**, *4*, 1615.

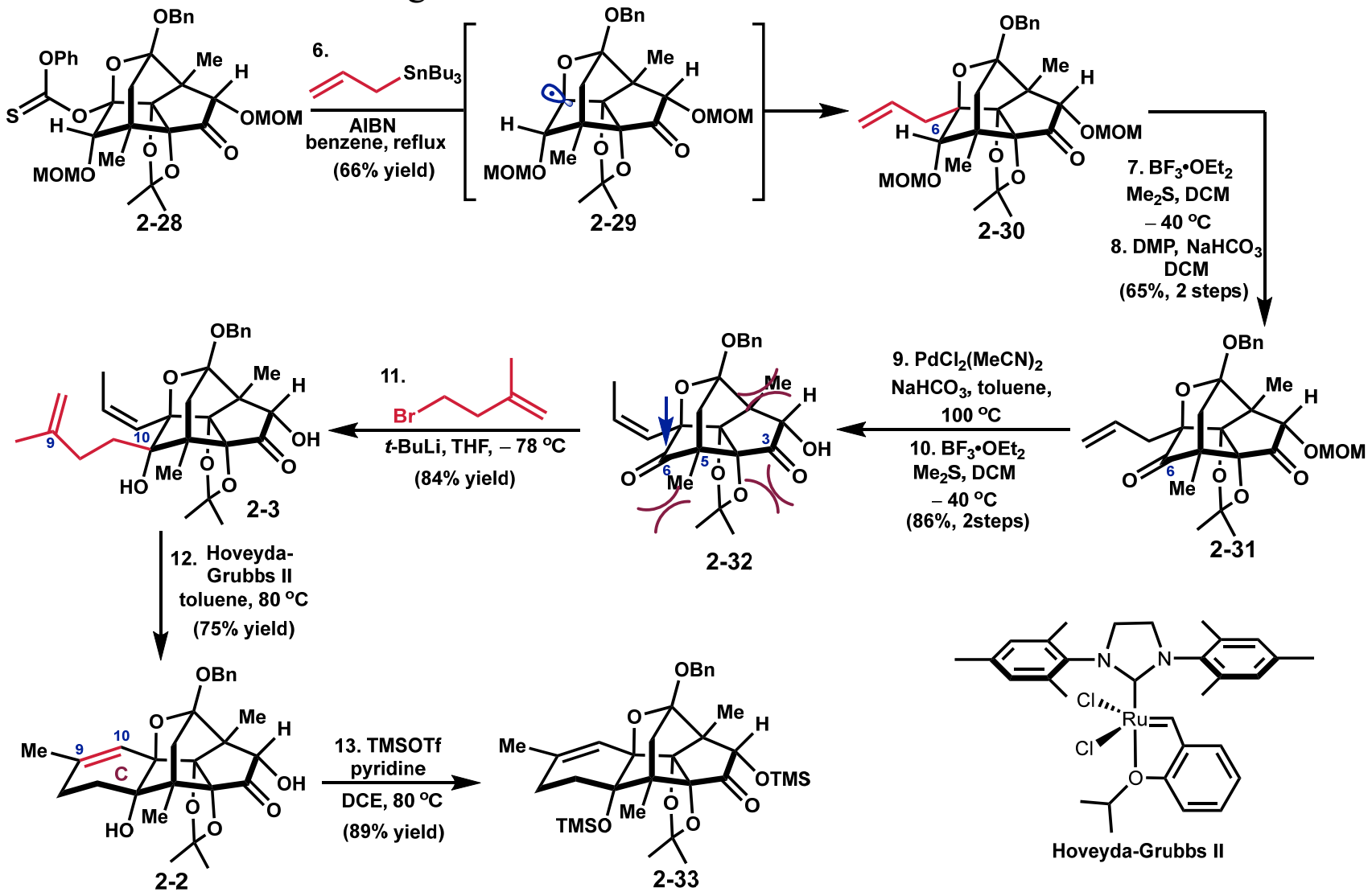
Total Synthesis of Ryanodol — *Inoue*

3. The construction of D&E rings



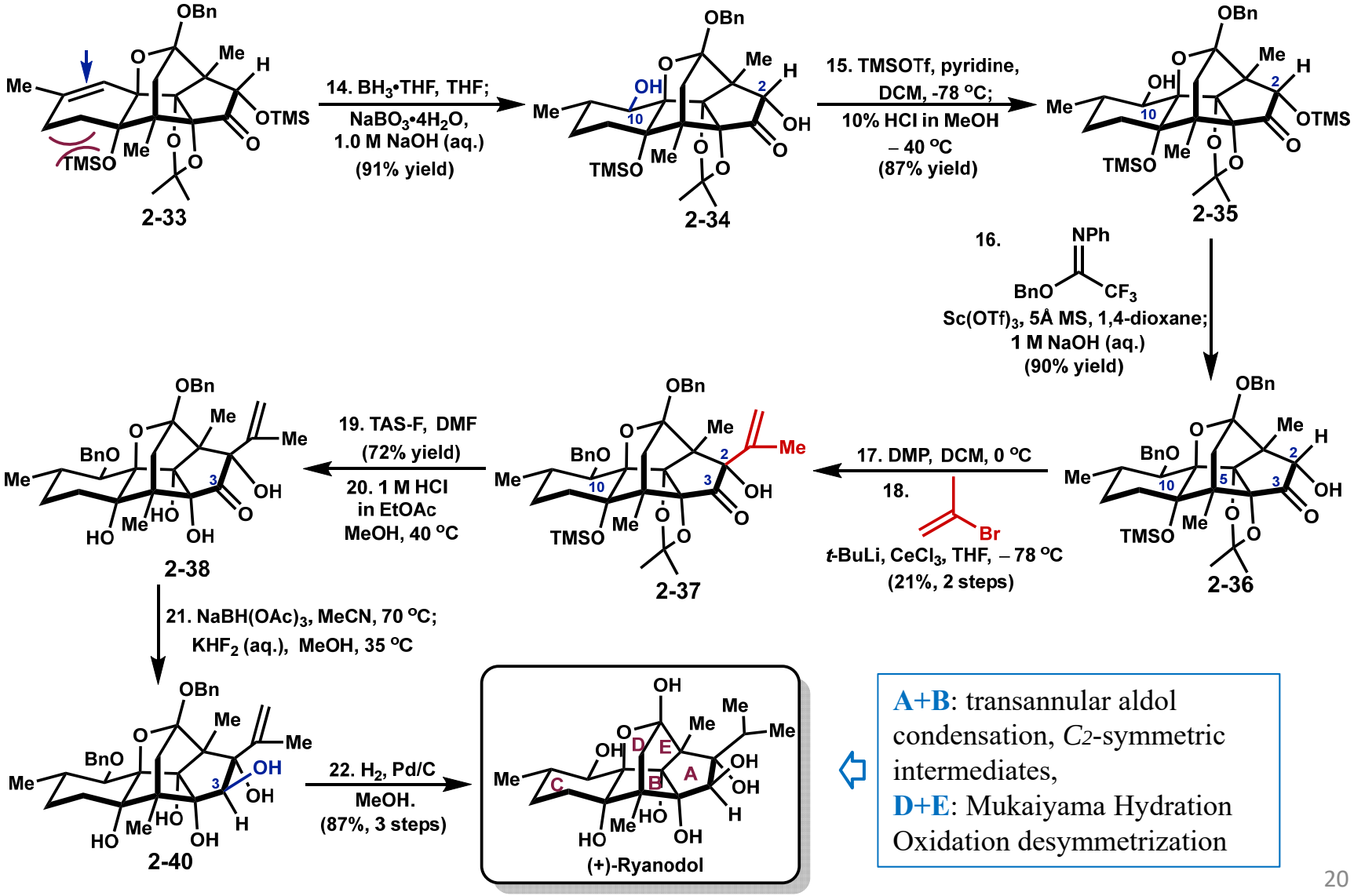
Total Synthesis of Ryanodol — *Inoue*

4. The construction of C ring



Total Synthesis of Ryanodol — *Inoue*

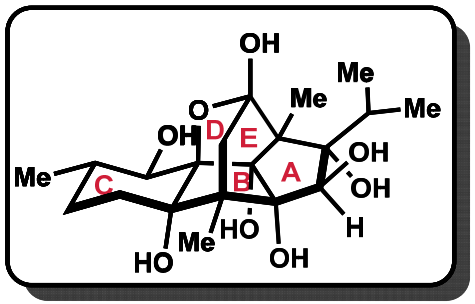
5. Functionalization of C2, C3, C9&C10



A+B: transannular aldol condensation, *C2*-symmetric intermediates,
D+E: Mukaiyama Hydration Oxidation desymmetrization

A 15-step Synthesis of (+)-Ryanodol — *Reisman*

S. E. Reisman

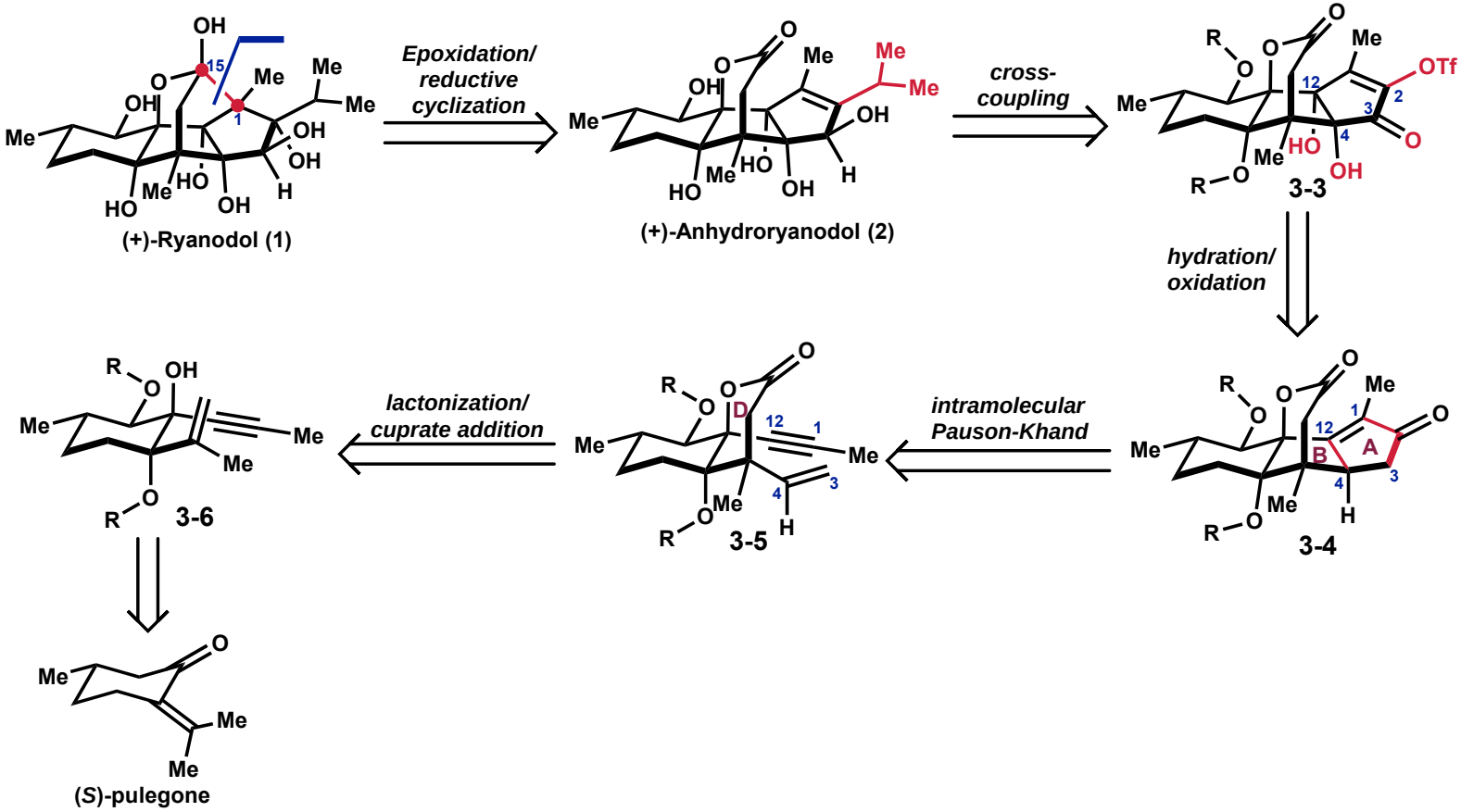


The construction order: C→D→(A, B)→E

Reisman, S. E. *Science* **2016**, *353*, 912.

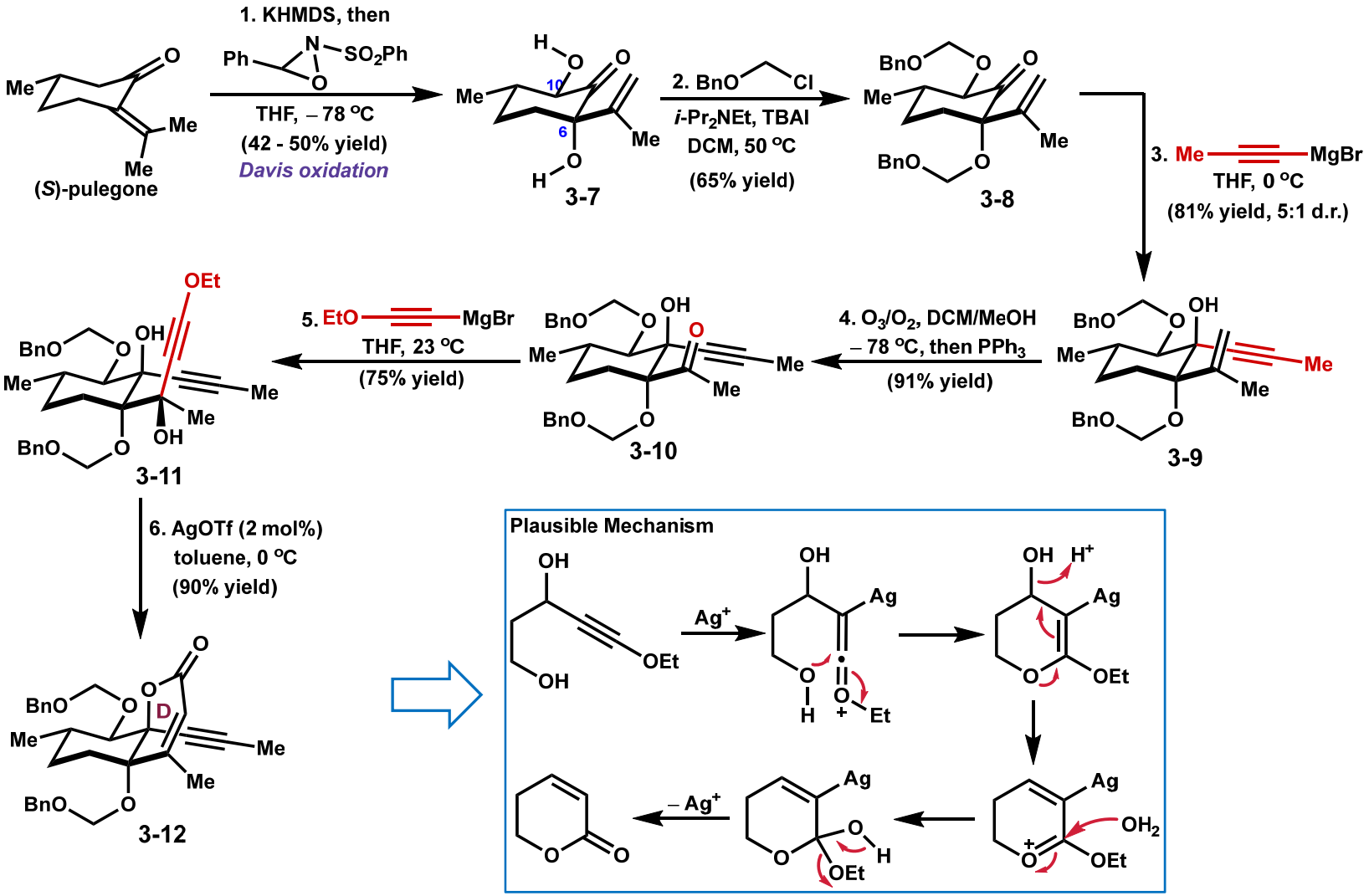
A 15-step Synthesis of (+)-Ryanodol — *Reisman*

1. Retrosynthetic Analysis



A 15-step Synthesis of (+)-Ryanodol — *Reisman*

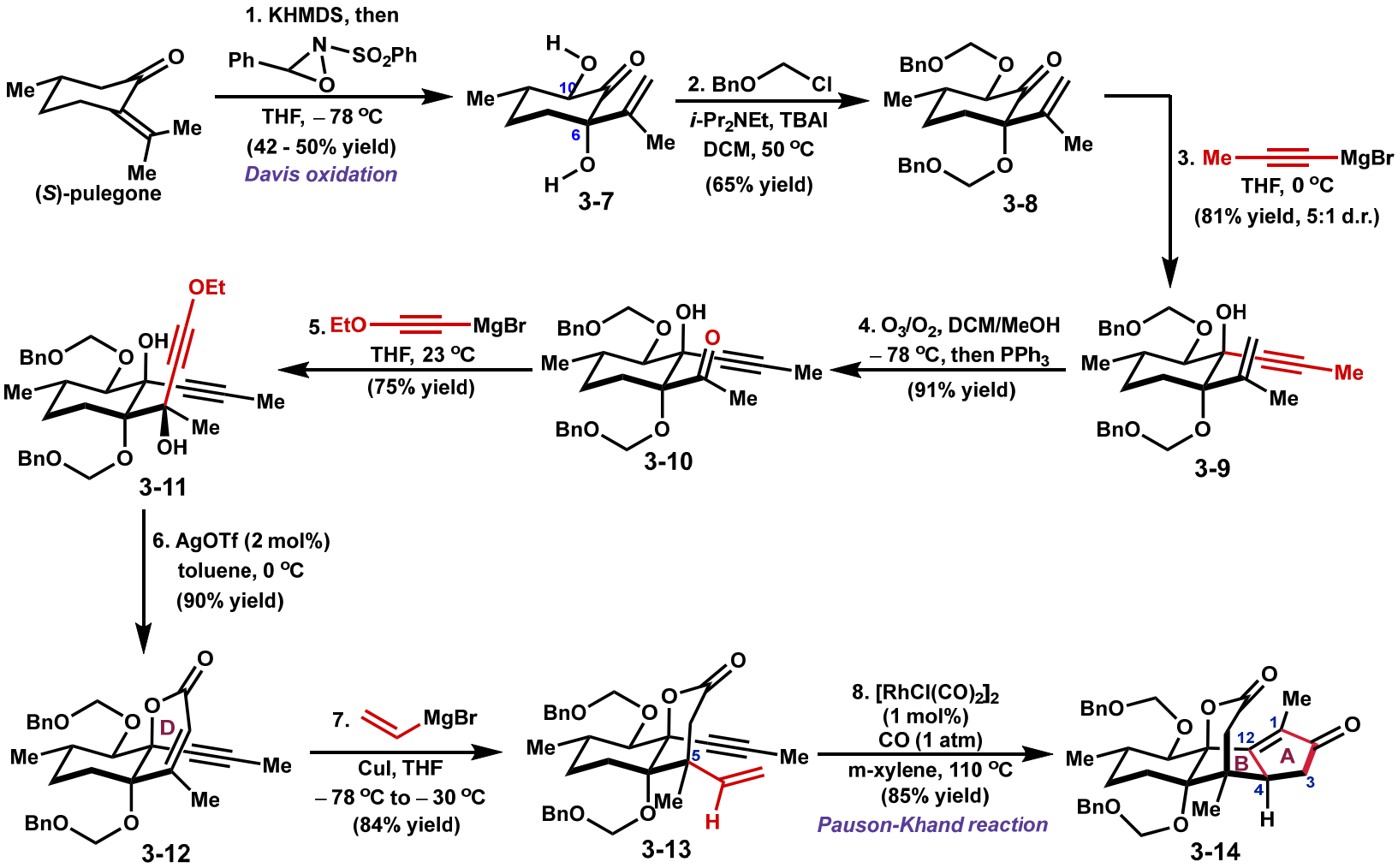
2. The construction of Anhydroryanodol skeleton



Akai, S. *Org. Lett.* **2013**, *15*, 4150.

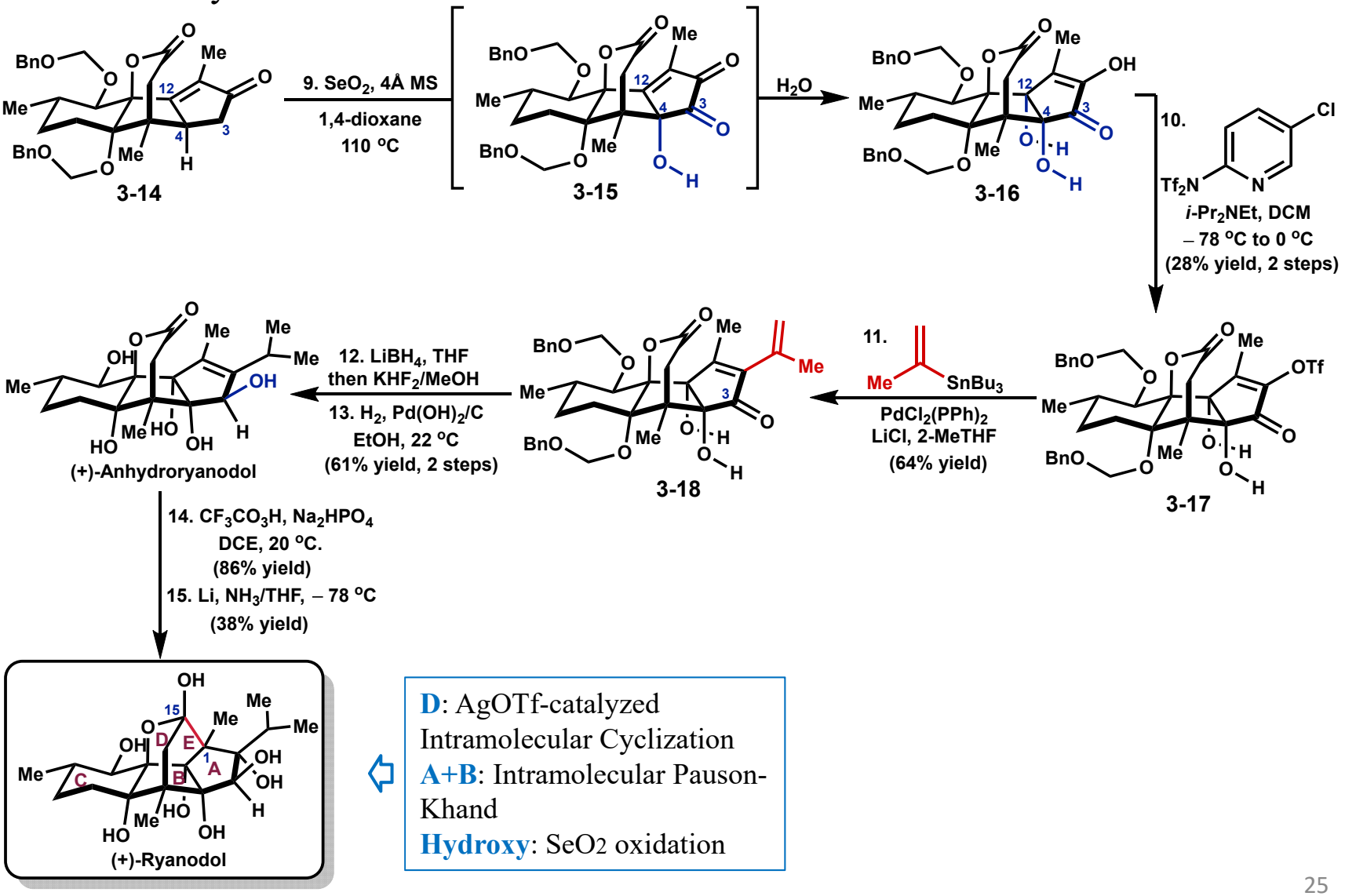
A 15-step Synthesis of (+)-Ryanodol — *Reisman*

2. The construction of Anhydroryanodol skeleton



A 15-step Synthesis of (+)-Ryanodol — *Reisman*

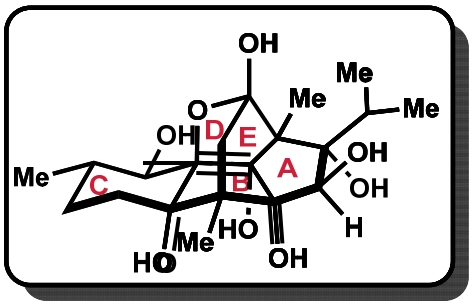
3. Oxidation/hydration



D: AgOTf-catalyzed Intramolecular Cyclization
A+B: Intramolecular Pauson-Khand
Hydroxy: SeO_2 oxidation

Synthesis of Anhydroryanodol — *Micalizio*

G. C. Micalizio

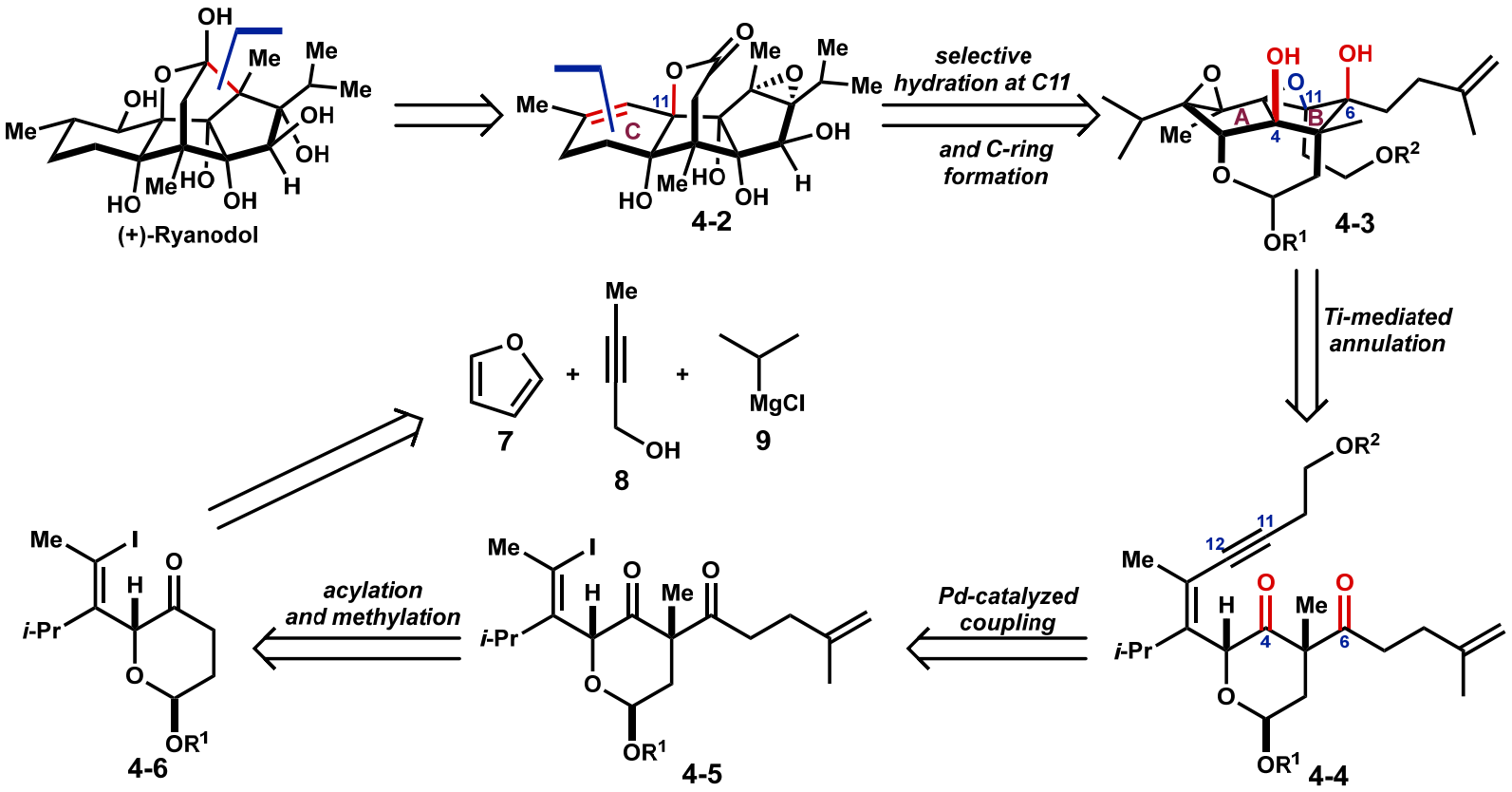


The construction order: (A, B)→D→C→E

Micalizio, G. C. *J. Am. Chem. Soc.* **2020**, *142*, 12937.

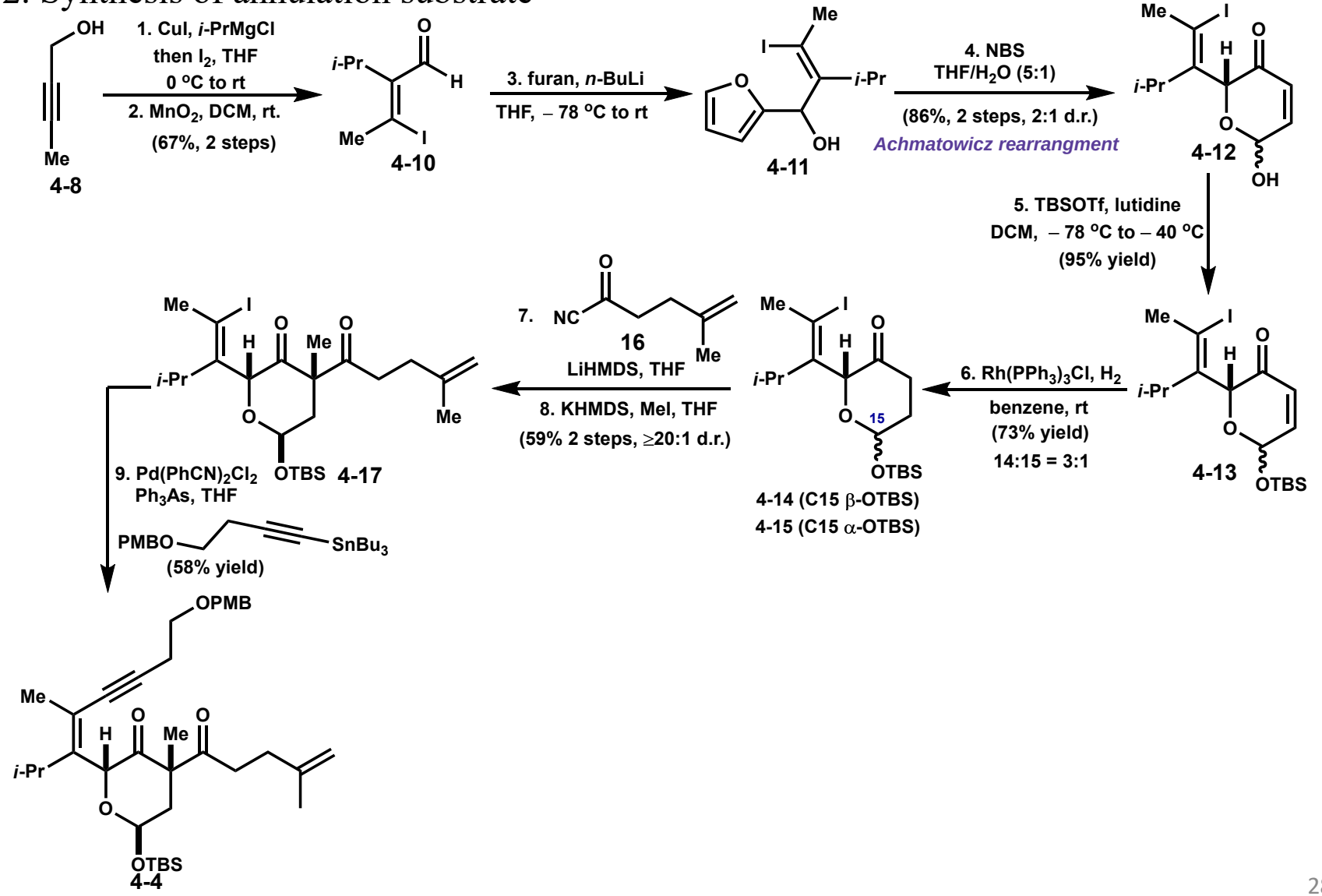
Synthesis of Anhydroryanodol — *Micalizio*

1. Retrosynthetic Analysis



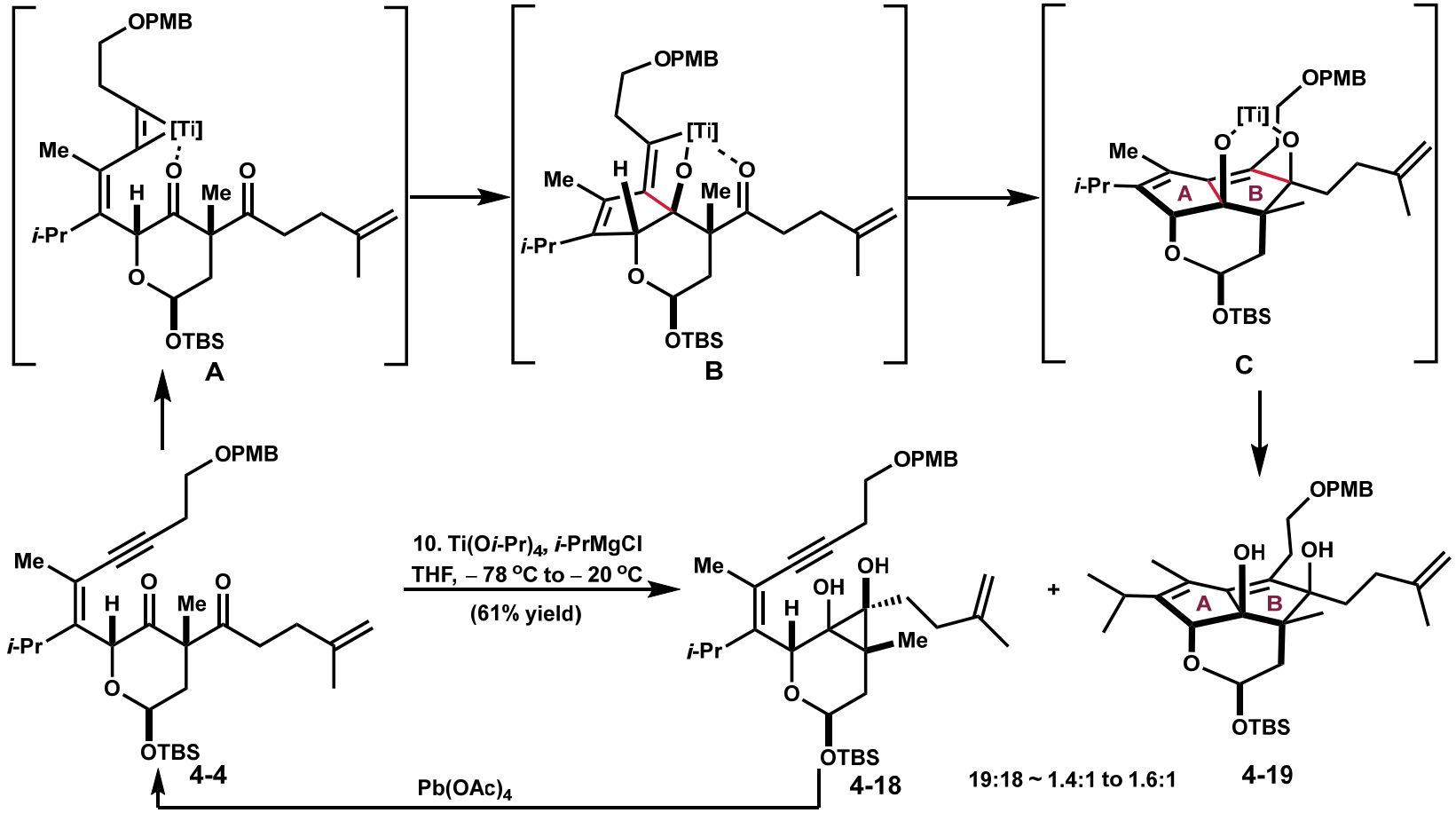
Synthesis of Anhydroryanodol — *Micalizio*

2. Synthesis of annulation substrate



Synthesis of Anhydroryanodol — *Micalizio*

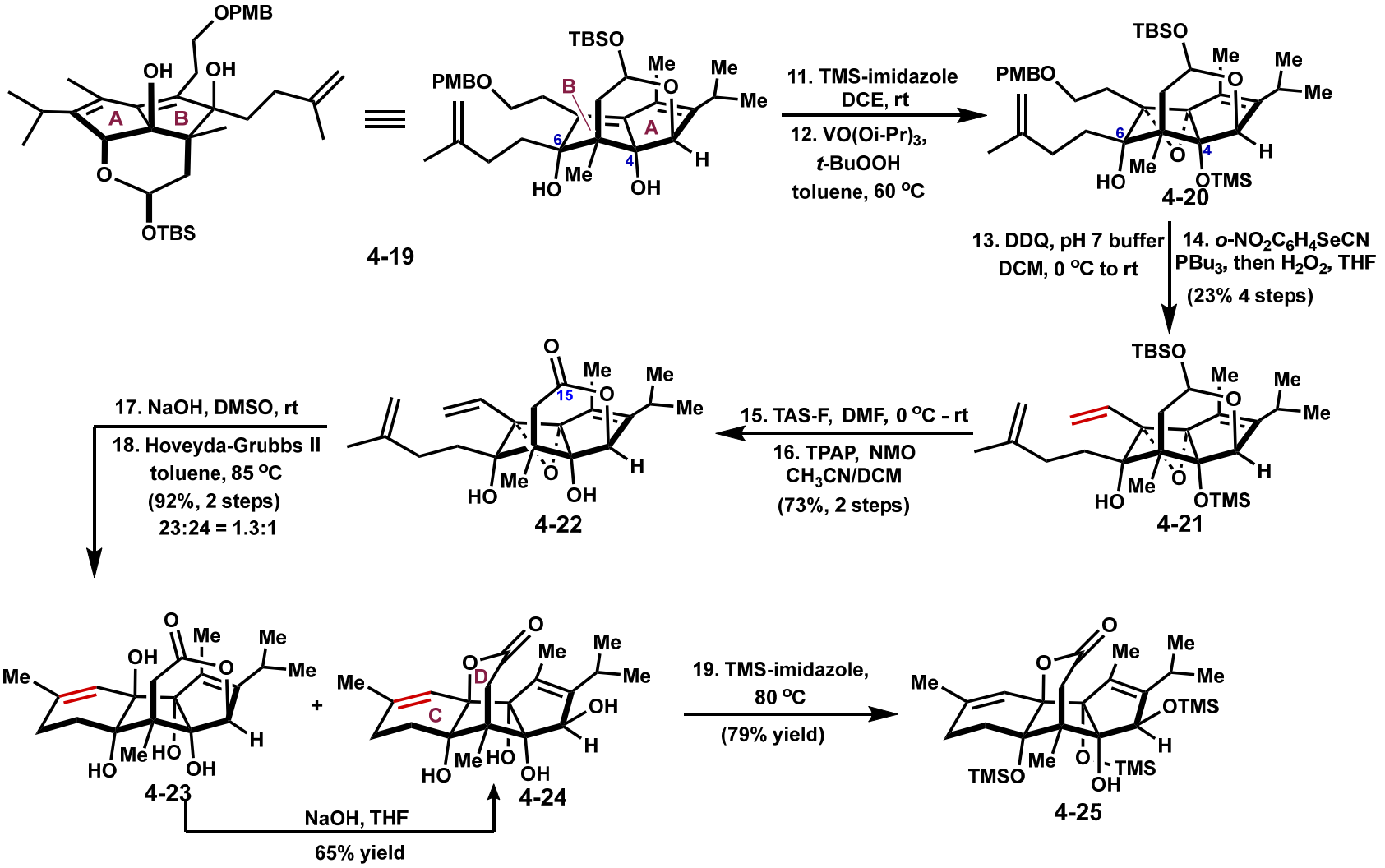
3. Oxidative metallacycle-mediated annulation



Micalizio, P. *J. Am. Chem. Soc*. **2017**, *139*, 12374;
Micalizio, P. *Org. Lett*. **2019**, *21*, 6126.

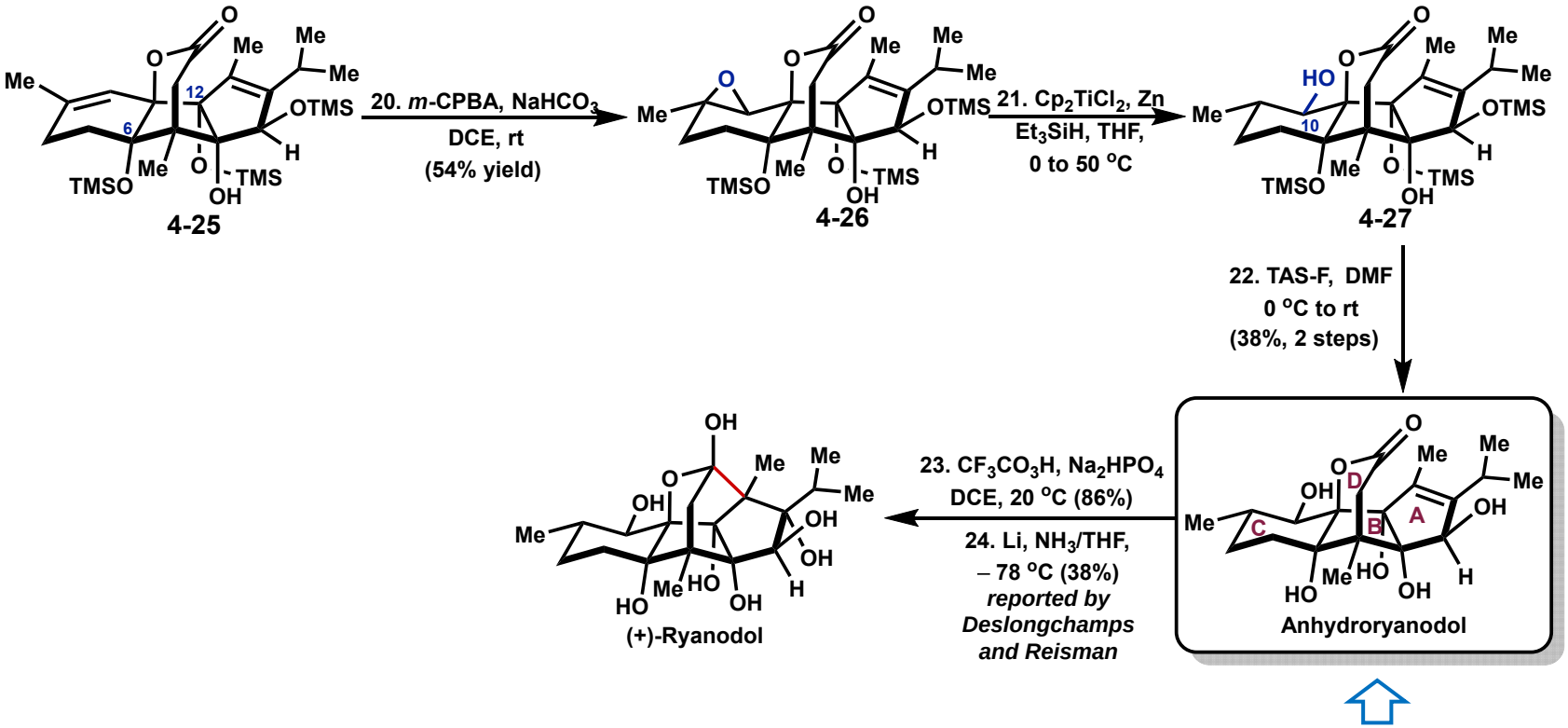
Synthesis of Anhydroryanodol — *Micalizio*

4. The construction of Anhydroryanodol skeleton



Synthesis of Anhydroryanodol — *Micalizio*

5. Convert to Anhydroryanodol



A+B: Ti-mediated annulation
D: selective epoxide opening