Literature Report 4

Total Synthesis of Bryostatin 1

Reporter : Fan-Jie Meng
Checker : Lei Shi
Date : 2018-01-08

Maclaren, J. K.; Stevens, M. C.; Wender, P. A. *et al. Science* **2017**, *358*, 218

CV of Paul A. Wender

Education:

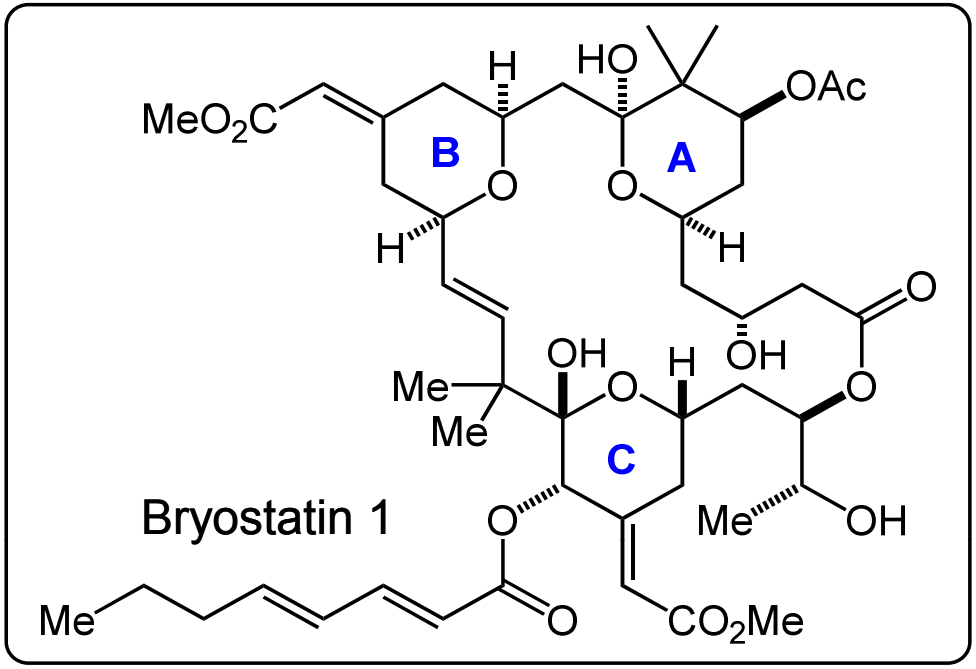
- **1965-1969** B.S., Wilkes College
- **1969-1973** Ph.D., Yale University
- **1973-1981** NIH Postdoc., Columbia University, Harvard University
- **1981-Now** Prof., Stanford University

Research:

- Bioinorganic Chemistry;
- Medicinal Chemistry;
- Organic Chemistry;
- Organometallic Chemistry.

Contents

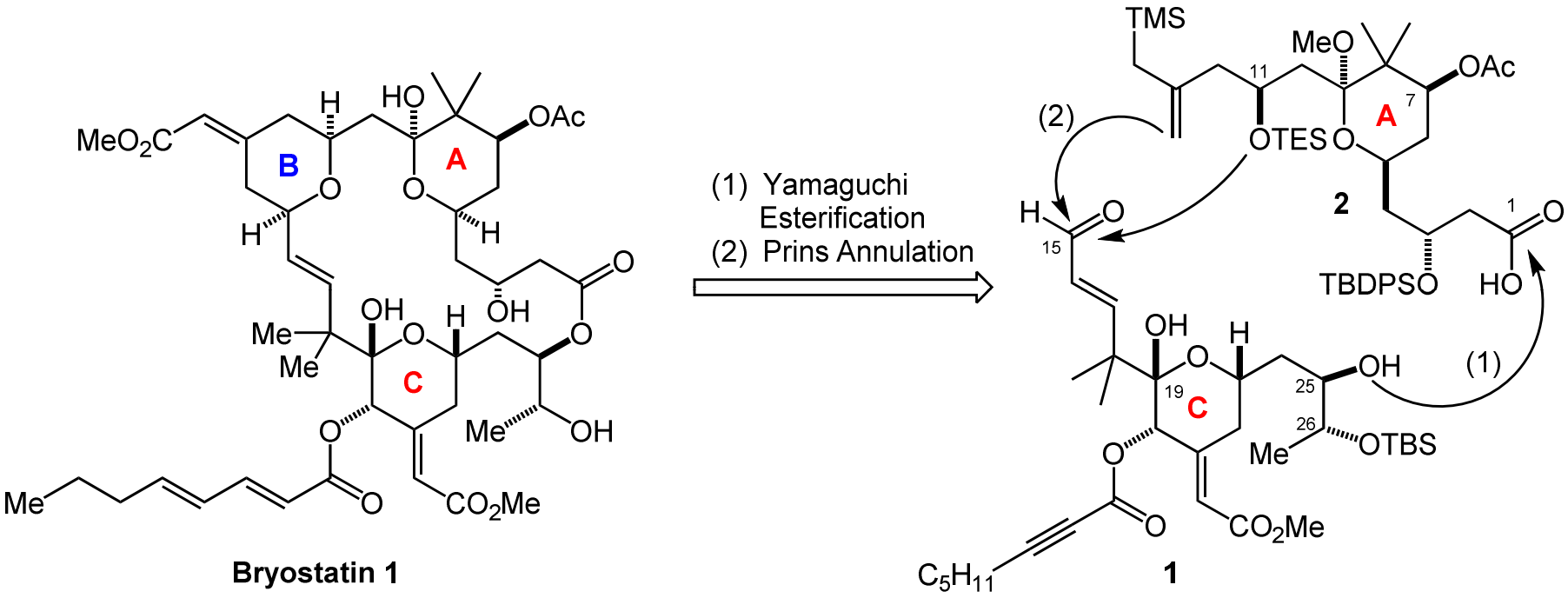
Introduction



Bugula neritina
草苔虫

- Bryostatin 1 is in clinical trials as a first-in-class latency reversal agent for the eradication of HIV;
- Several approaches to solving bryostatin's supply problem have been pursued since its first isolation in 1968;
- Three embedded hydropyran rings, 11 stereocenters, and a formidable array of multiple alkene, alcohol, ether, hemiketal, and ester functionalities.

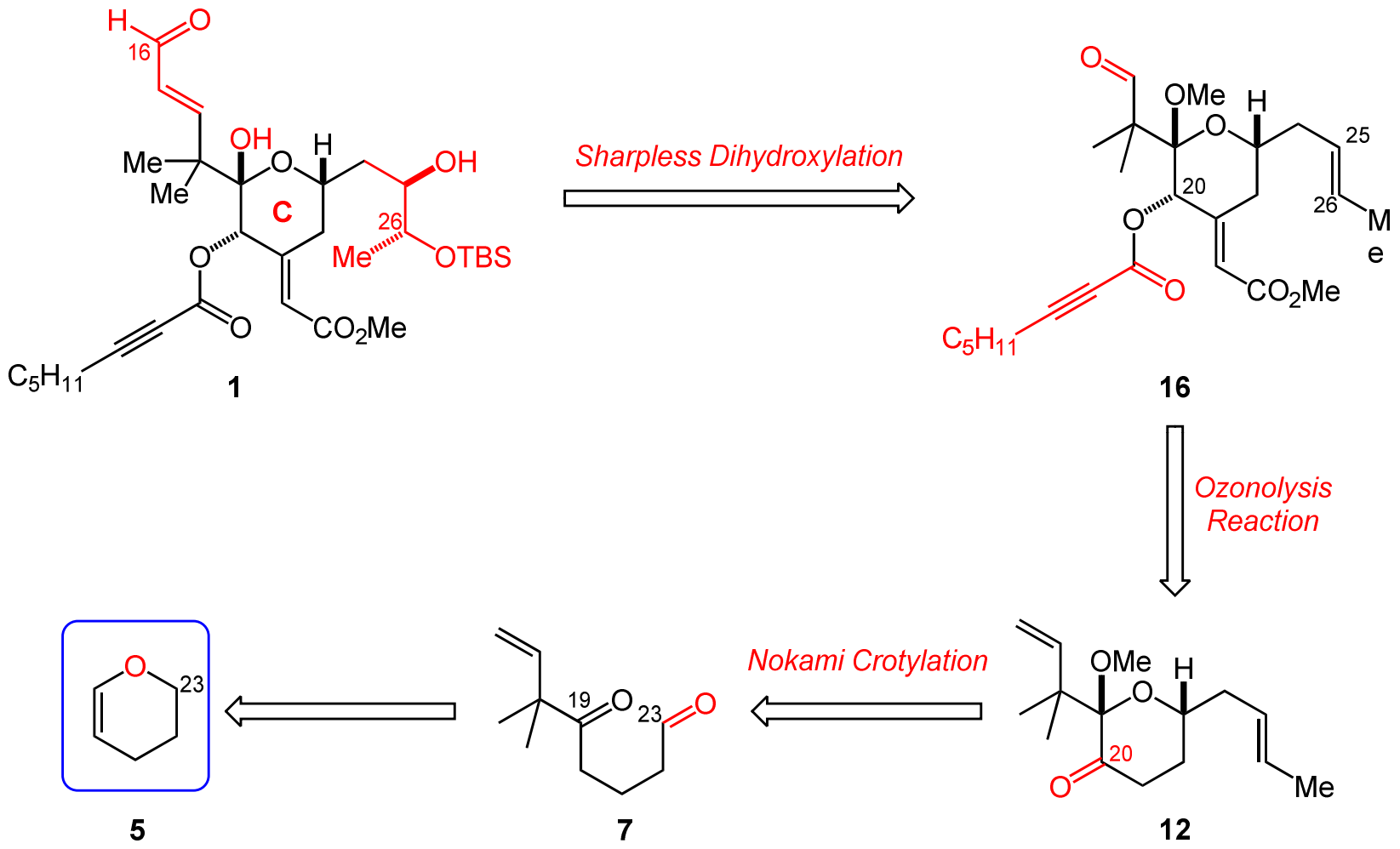
Retrosynthetic Analysis of Bryostatin 1



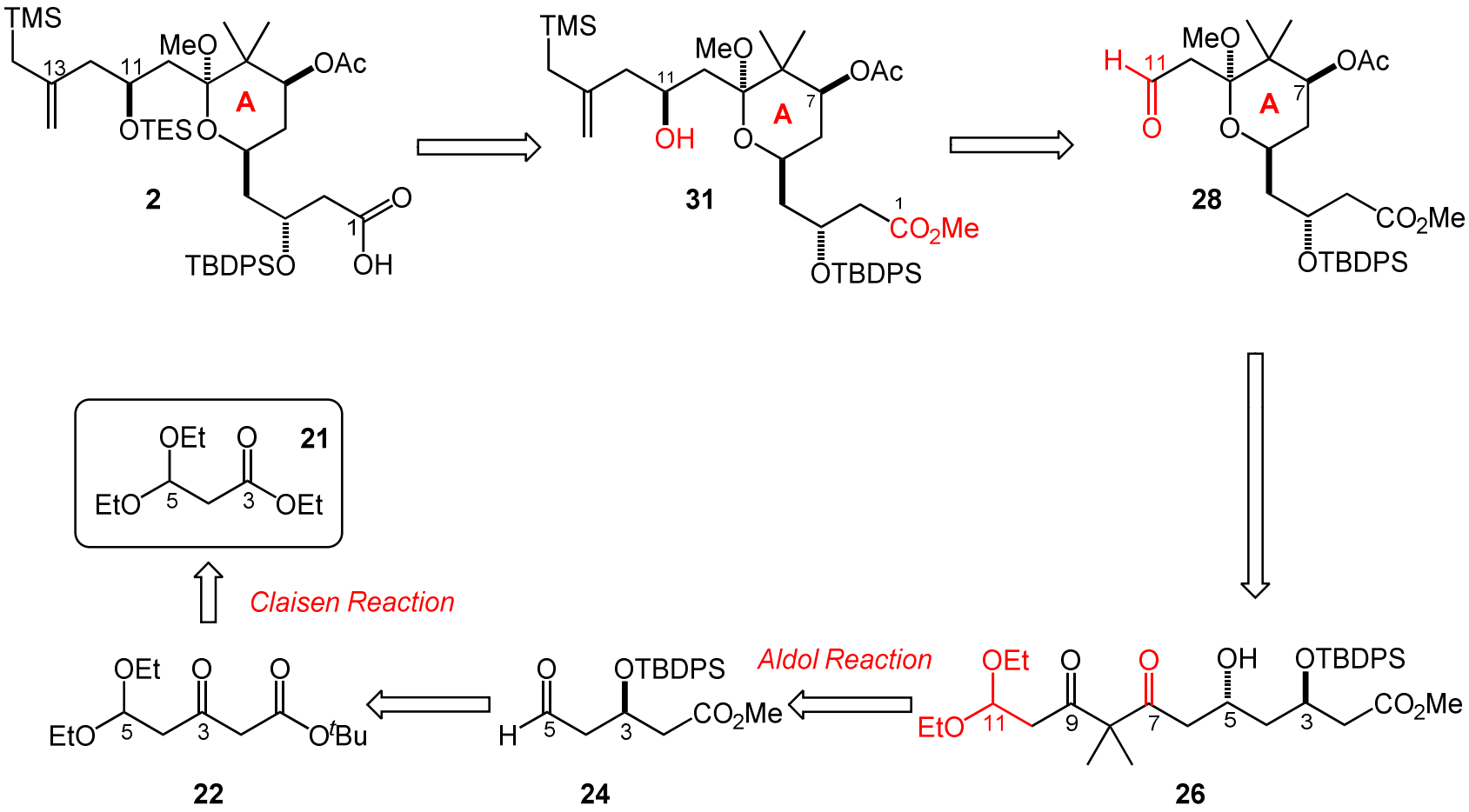
Bryostatin 1

Wender, P. A. *et al. Science* **2017**, *358*, 218

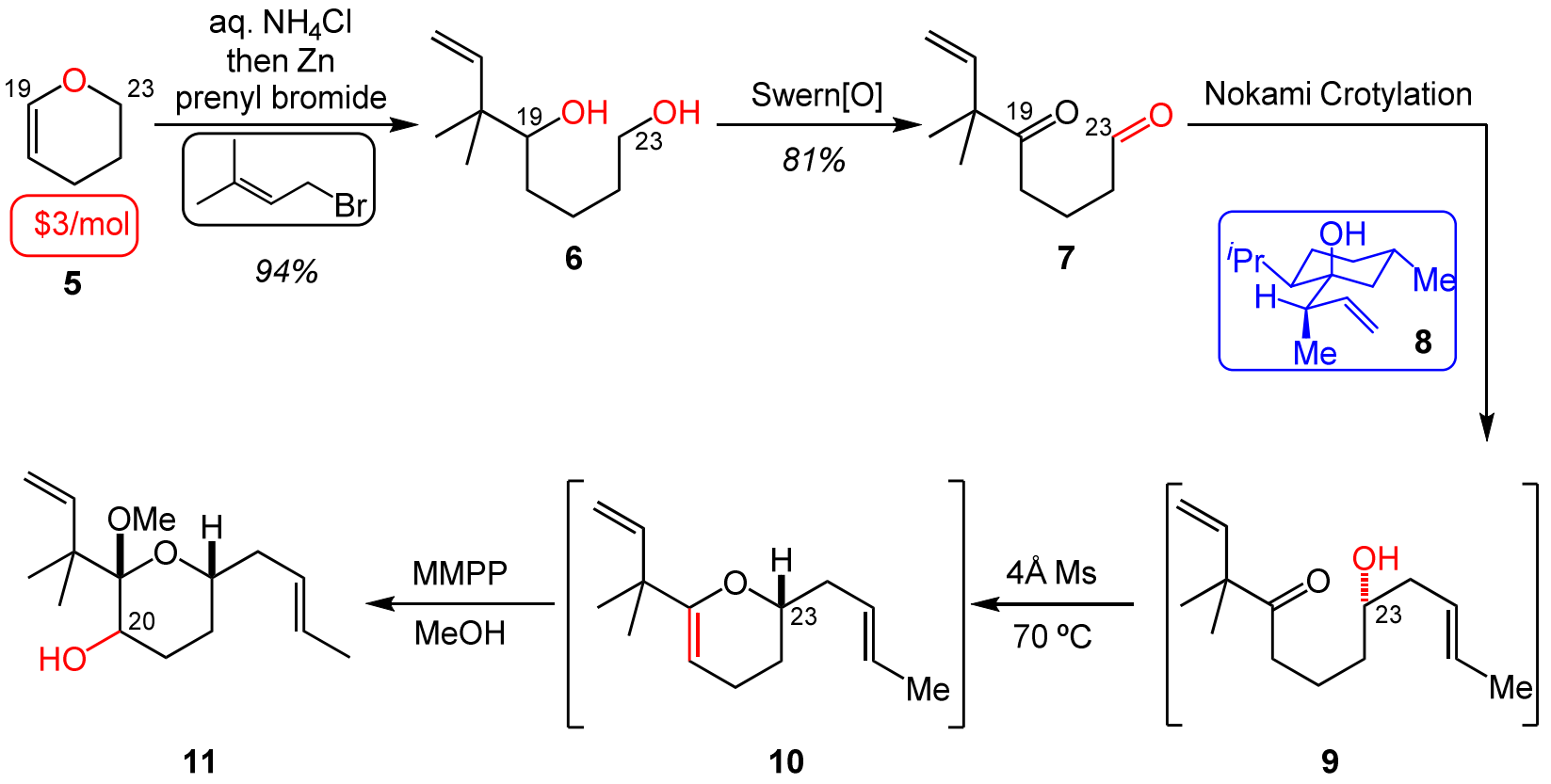
Retrosynthetic Analysis of Fragment 1



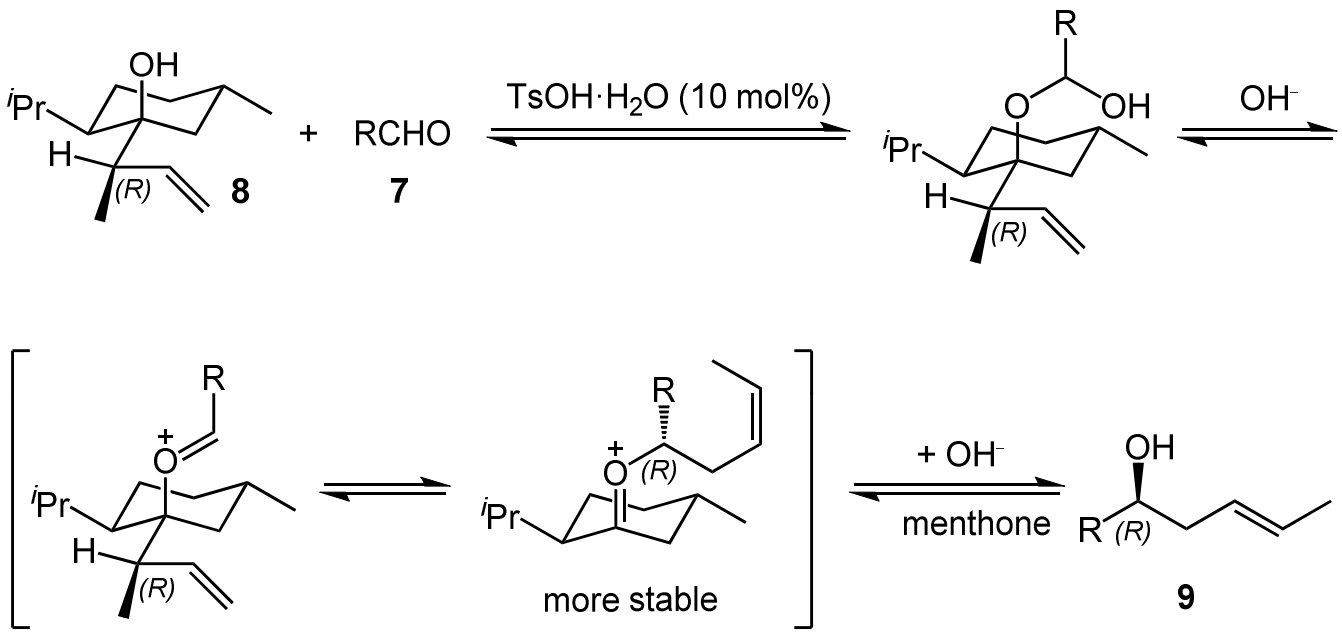
Retrosynthetic Analysis of Fragment 2



Synthesis of Fragment 1



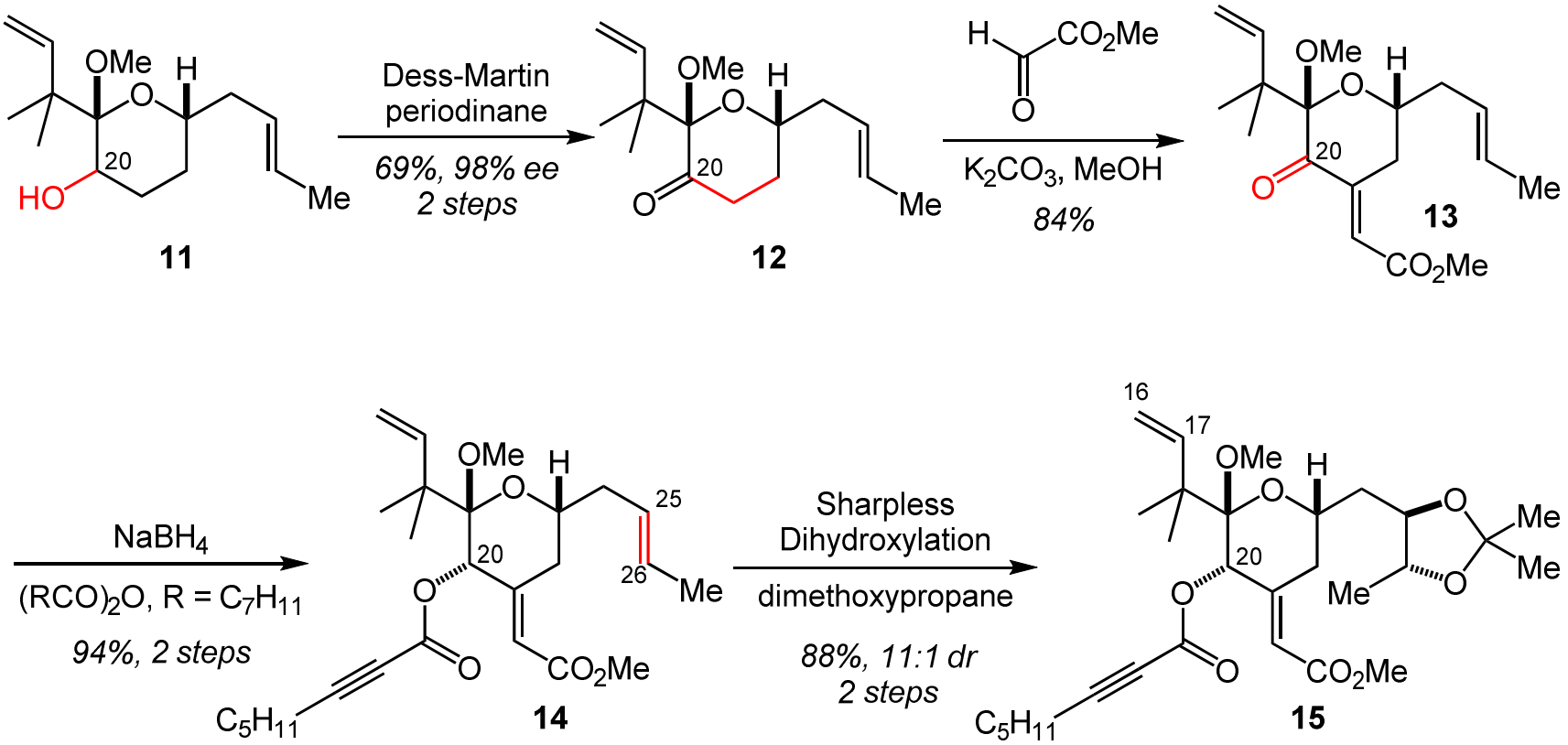
Nokami Crotylation



Asymmetric Crotylation of Aldehyde

Nokami, J. *et al. J. Am. Chem. Soc.* **2001**, *123*, 9168

Synthesis of Fragment 1



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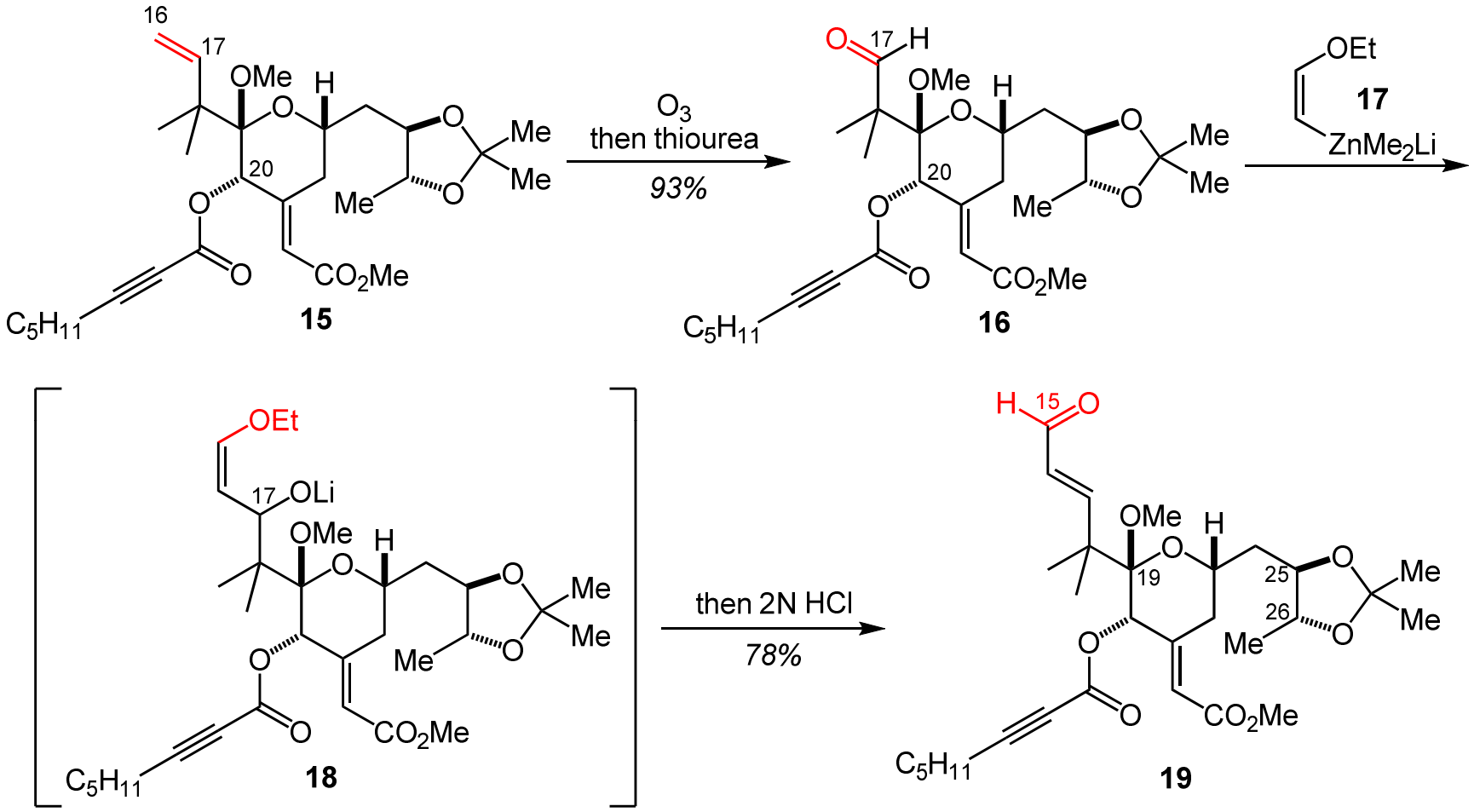
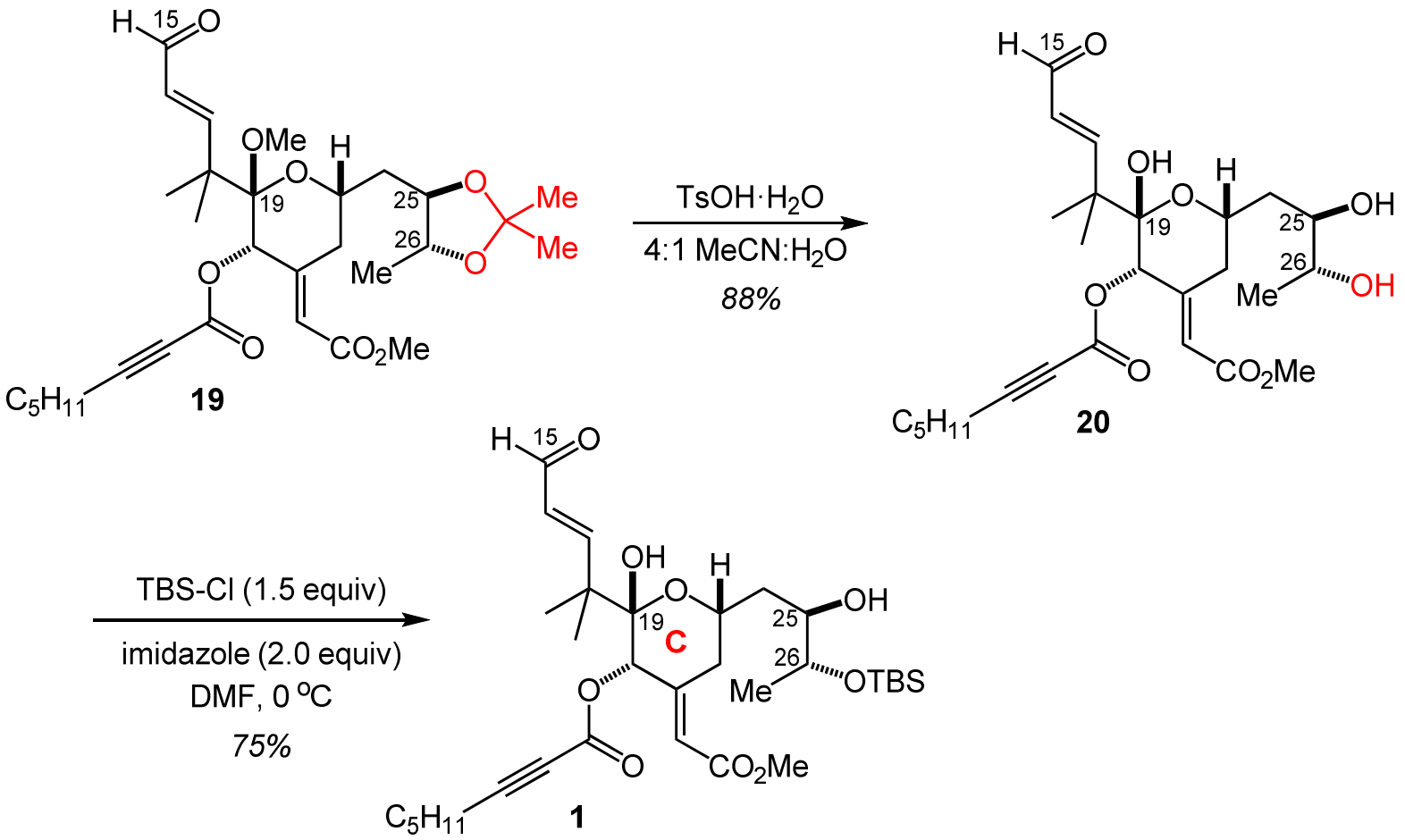
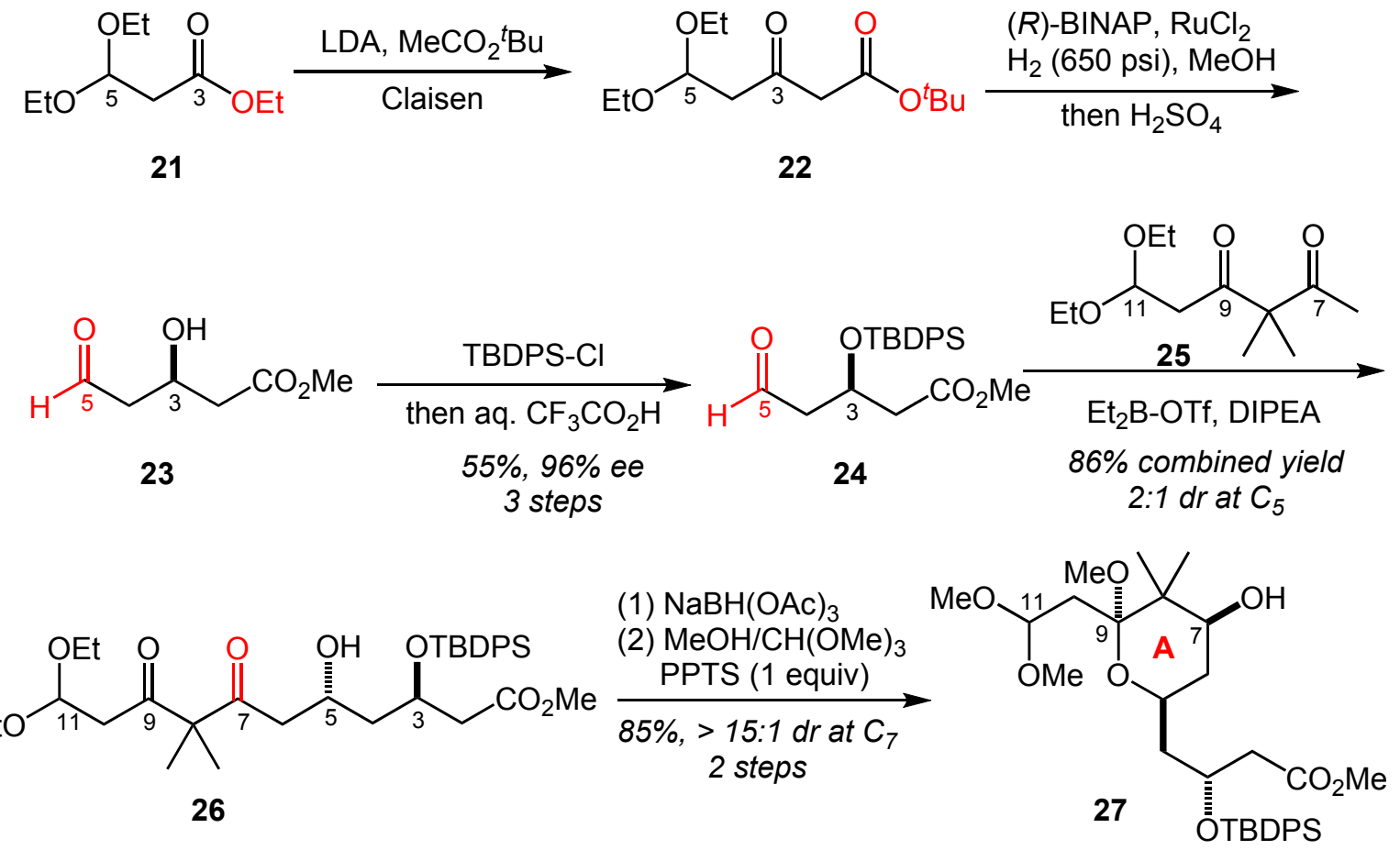


Synthesis of Fragment 1

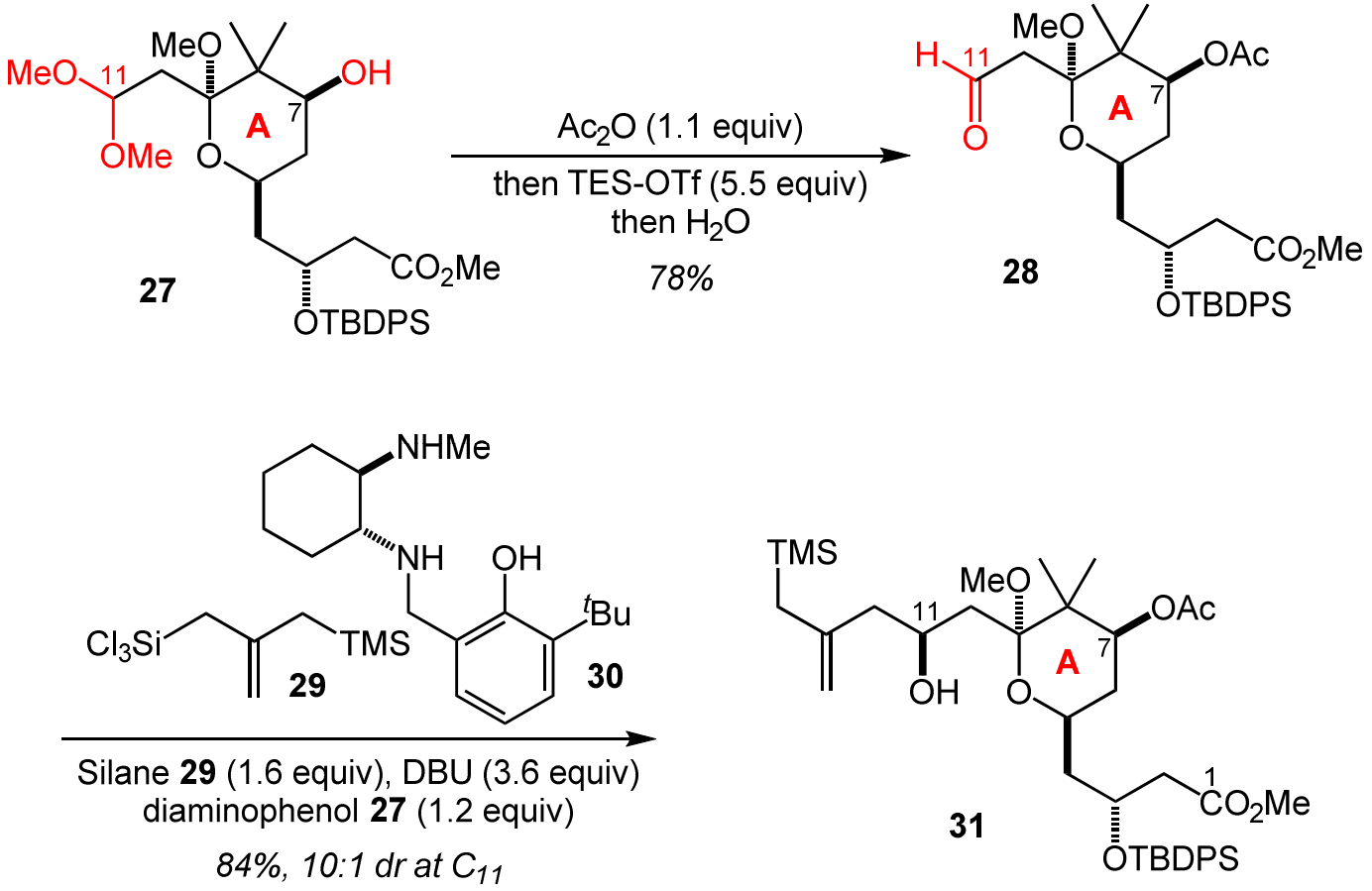


***Fragment 1**: 13 steps, 16% overall yield*

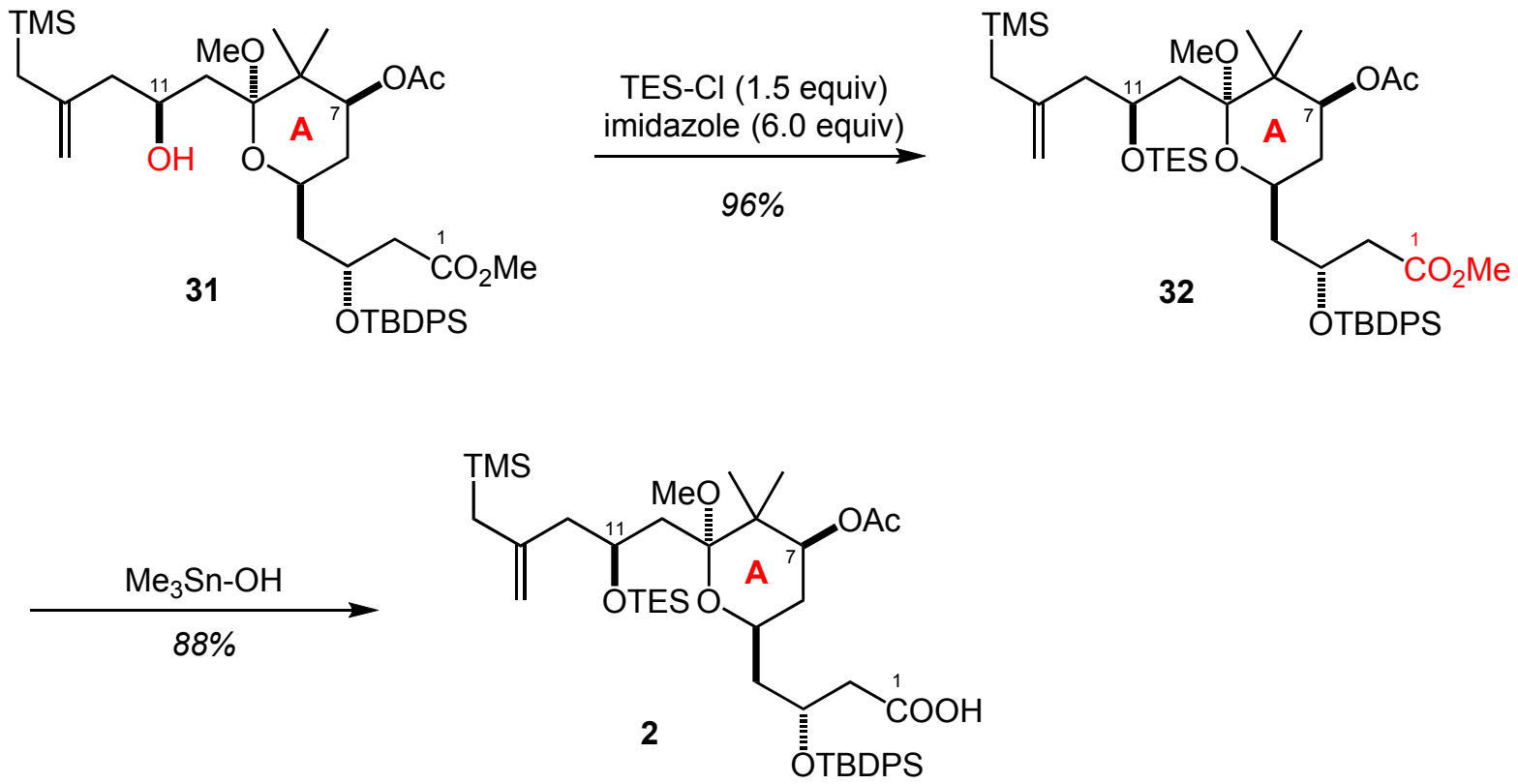
Synthesis of Fragment 2



Synthesis of Fragment 2

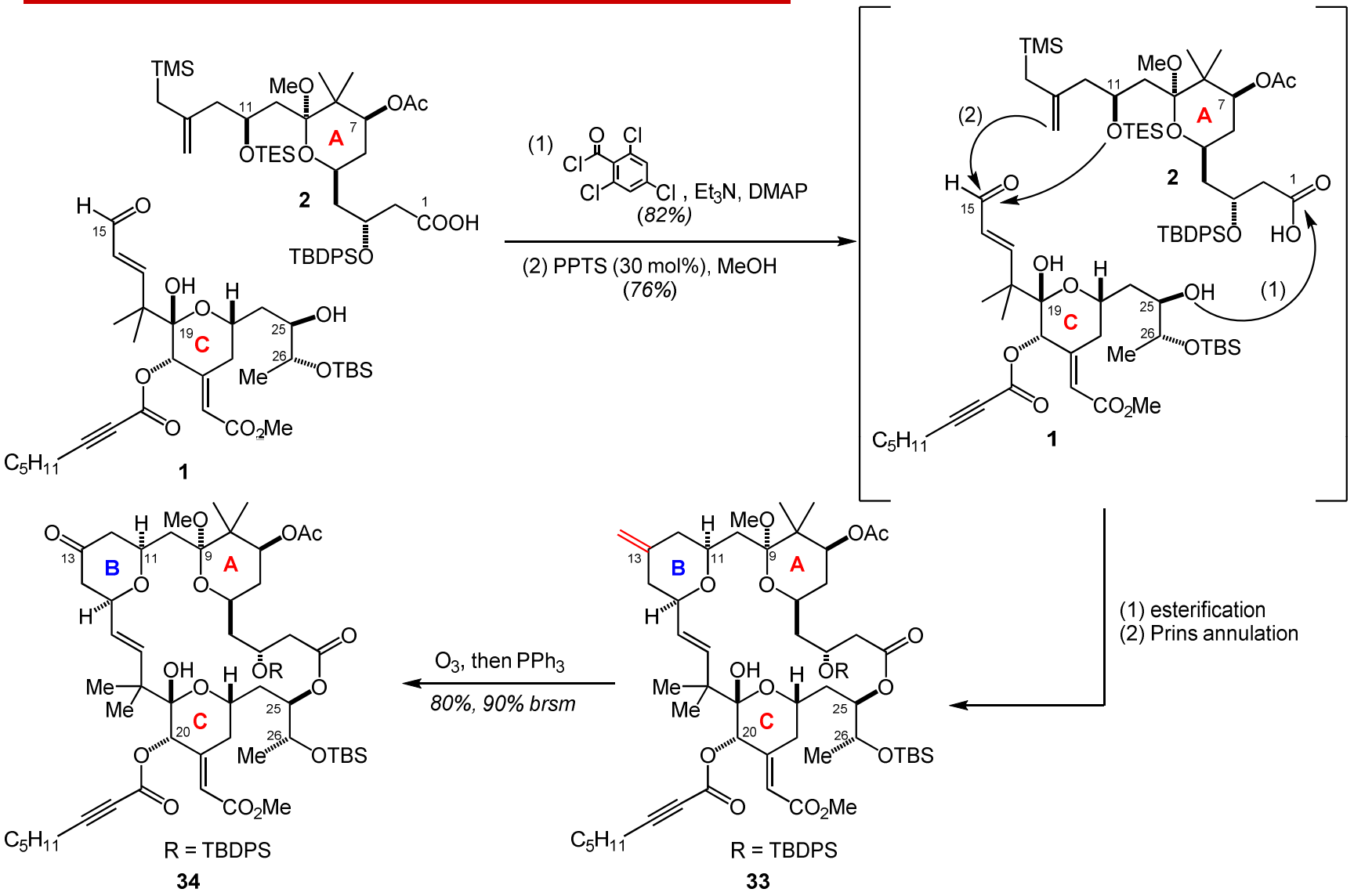


Synthesis of Fragment 2

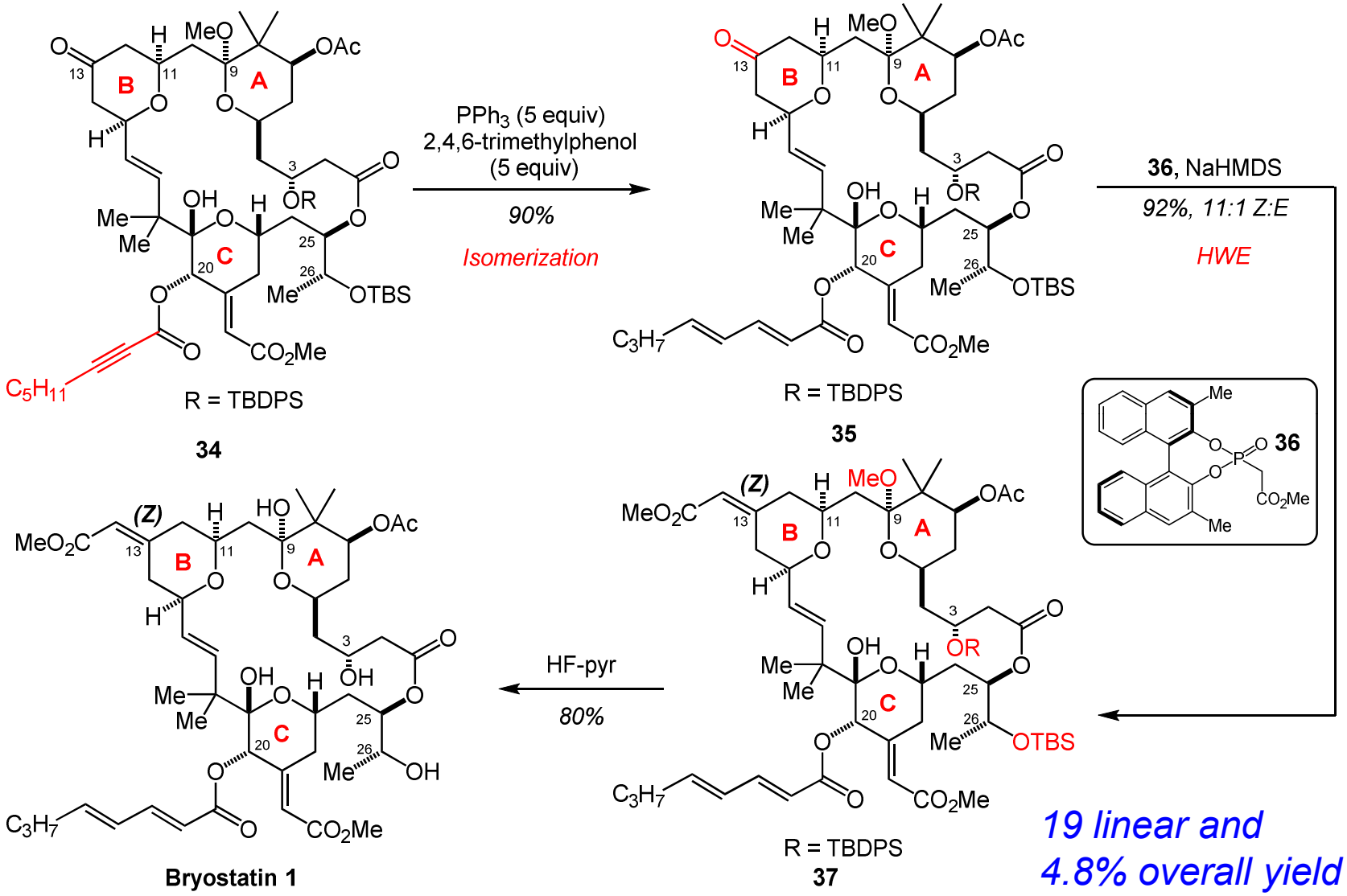


***Fragment 2**: 10 steps, 13% overall yield*

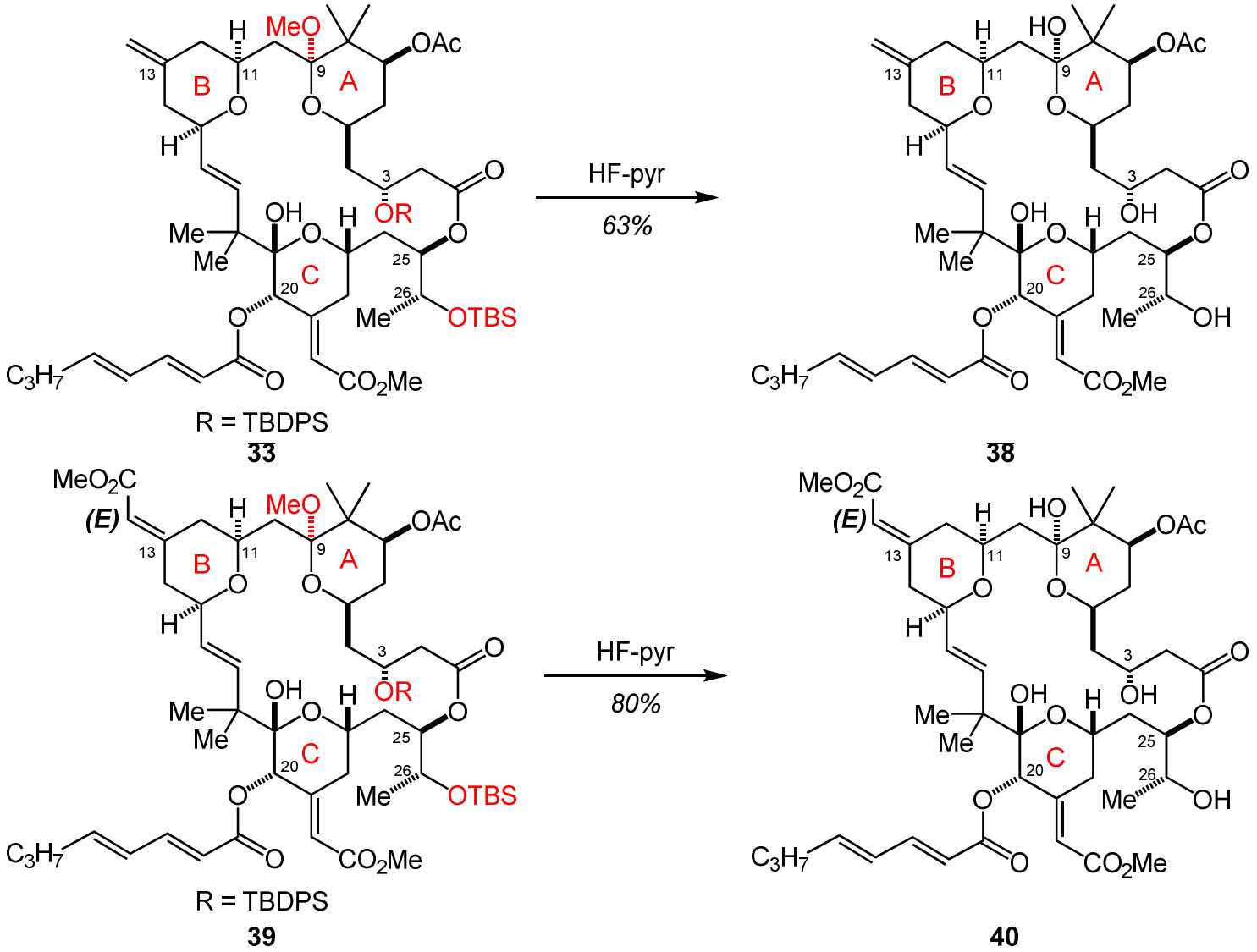
Total Synthesis of Bryostatin 1



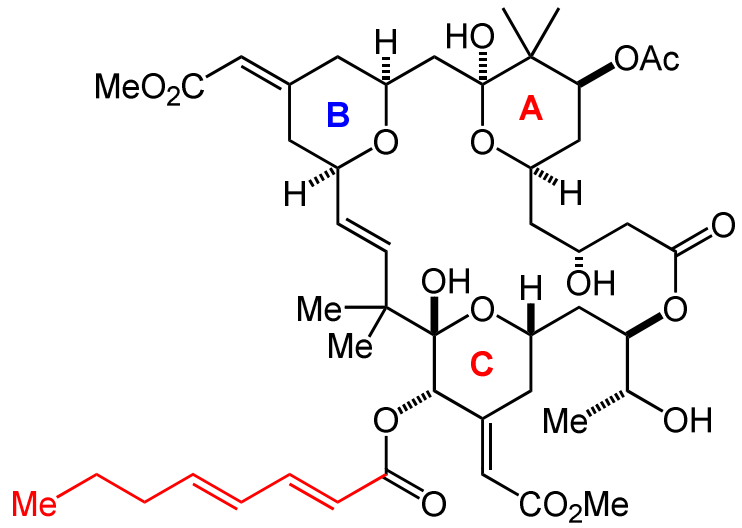
Total Synthesis of Bryostatin 1



Total Synthesis of Bryostatin 1



Summary



Bryostatin 1

- 19 linear and 29 total steps;
- 4.8% overall yield;
- Scalable synthesis of bryostatin **1** (> 2 grams);
- Prins-driven macrocyclization strategy;
- Asymmetric crotylation of aldehyde.

The First Paragraph

Bryostatin **1** is in clinical trials as a first-in-class latency reversal agent for the eradication of HIV/AIDS. It has also been advanced as a treatment for Alzheimer's disease and as an immunotherapeutic agent against cancer. These diseases represent leading causes of death, affecting hundreds of millions of patients and caregivers. Bryostatin **1**'s putative target, protein kinase C (PKC), has also been implicated in preclinical studies directed at the treatment of various unmet neurological and cardiovascular indications.

The Last Paragraph

This study opens practical, gram-scale access to bryostatin **1** and a wide range of analogs derivable from late-stage intermediates. For example, derivatives **35** and **37**, which feature structural variations of bryostatin's B-ring, were each accessed in one step from late-stage intermediates. Analogs **35** and **37** exhibited low nanomolar affinity to PKC-βI and PKC-δ, representative conventional and novel PKC isoforms, respectively. However, these compounds displayed different isoform selectivities relative to bryostatin **1**, which binds all conventional and novel PKC isoforms with single-digit nanomolar affinity.

The Last Paragraph

Because different isoforms are associated with different therapeutic indications, access to isoformselective PKC modulators enables the development of more therapeutically relevant, disease-specific leads. This work opens sustainable research access to bryostatin **1** as well as more synthetically accessible analogs that are proving to be more effective and better tolerated in comparative studies with cells, disease models in animals, and ex vivo samples taken from HIV-positive patients.

Acknowledgement

Thanks

for your attention