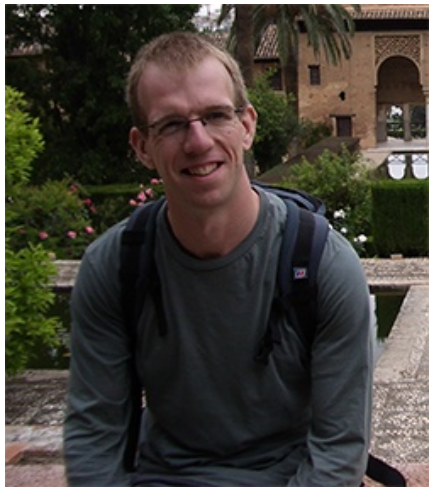
Total Synthesis of (+)-Rubriflordilactone A

Reporter: Hong-Qiang Shen

Checker: Bo Wu

Date: 2015/11/17



Edward A. Anderson
University of Oxford

Anderson, E. A. *et al.*
Angew. Chem. Int. Ed. **2015**, *54*, 12618.

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Introduction

Prof. Edward A. Anderson

Position: Advanced Research Fellow in University of Oxford

Education:

1993–1997 B.A. University of Oxford

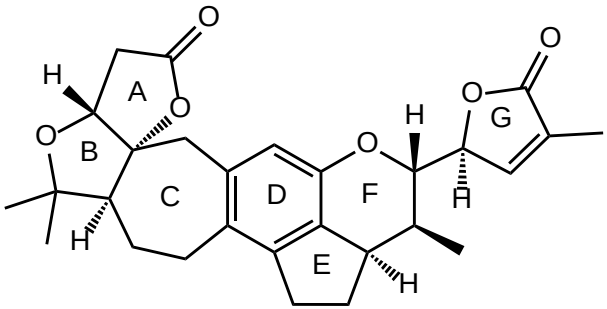
1997–2001 Ph.D. University of Cambridge

2001–2003 Postdocral Position Scripps Research Institute

2003–2007 Junior Research Fellowship at Homerton College, University of Cambridge

2007– Advanced Research Fellow in University of Oxford

Introduction



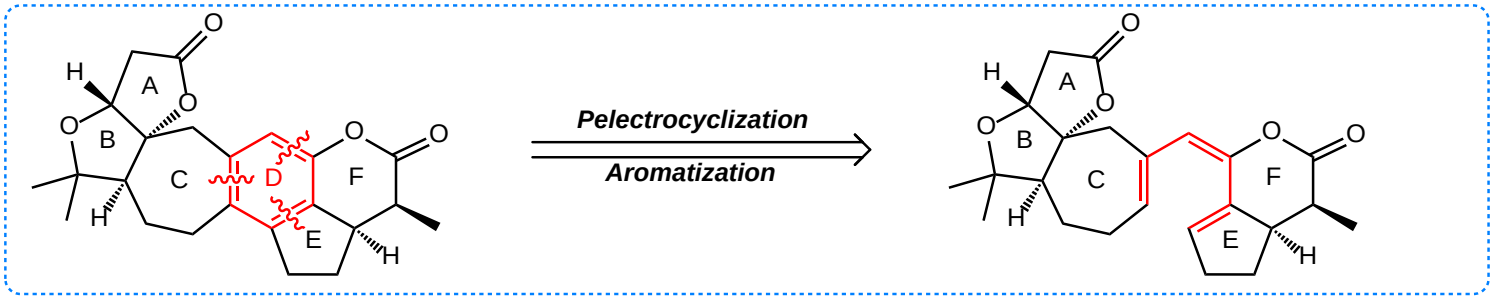
(+)-Rubriflordilactone A

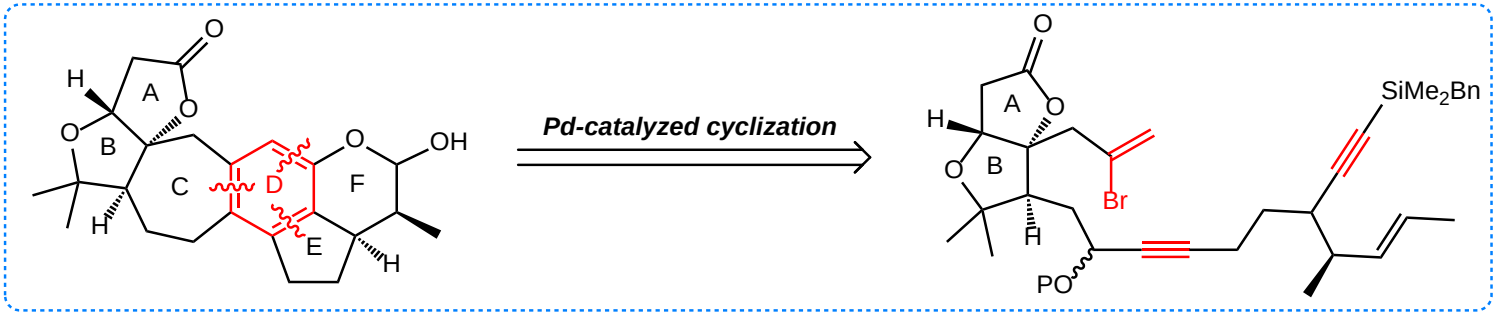
Schisandra rubriflora
红花五味子

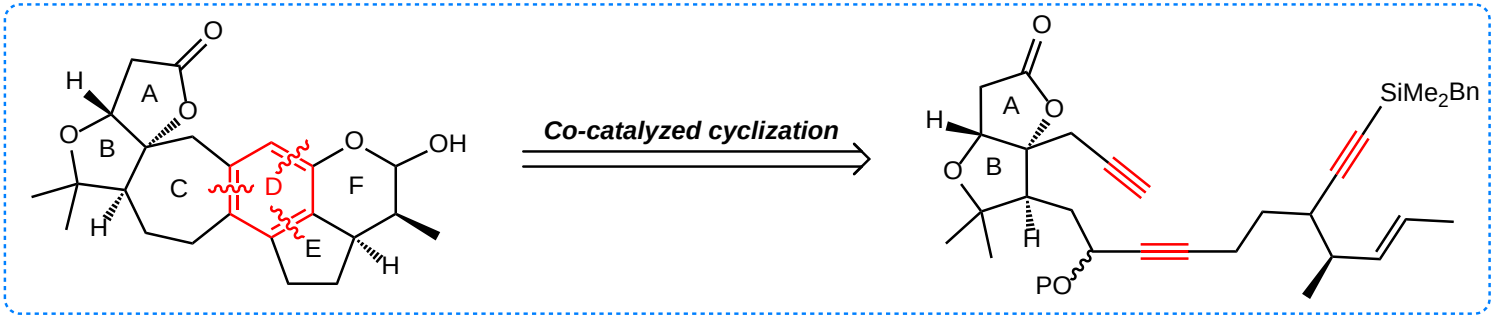
- Isolated from *Schisandra rubriflora* in 2006
- Exhibit promising anti-HIV activity
- Seven stereocenters, complex fused ring systems and multisubstituted arene motif in heptacyclic framework

Sun, H.-D. *et al. Org. Lett.* **2006**, *8*, 991.

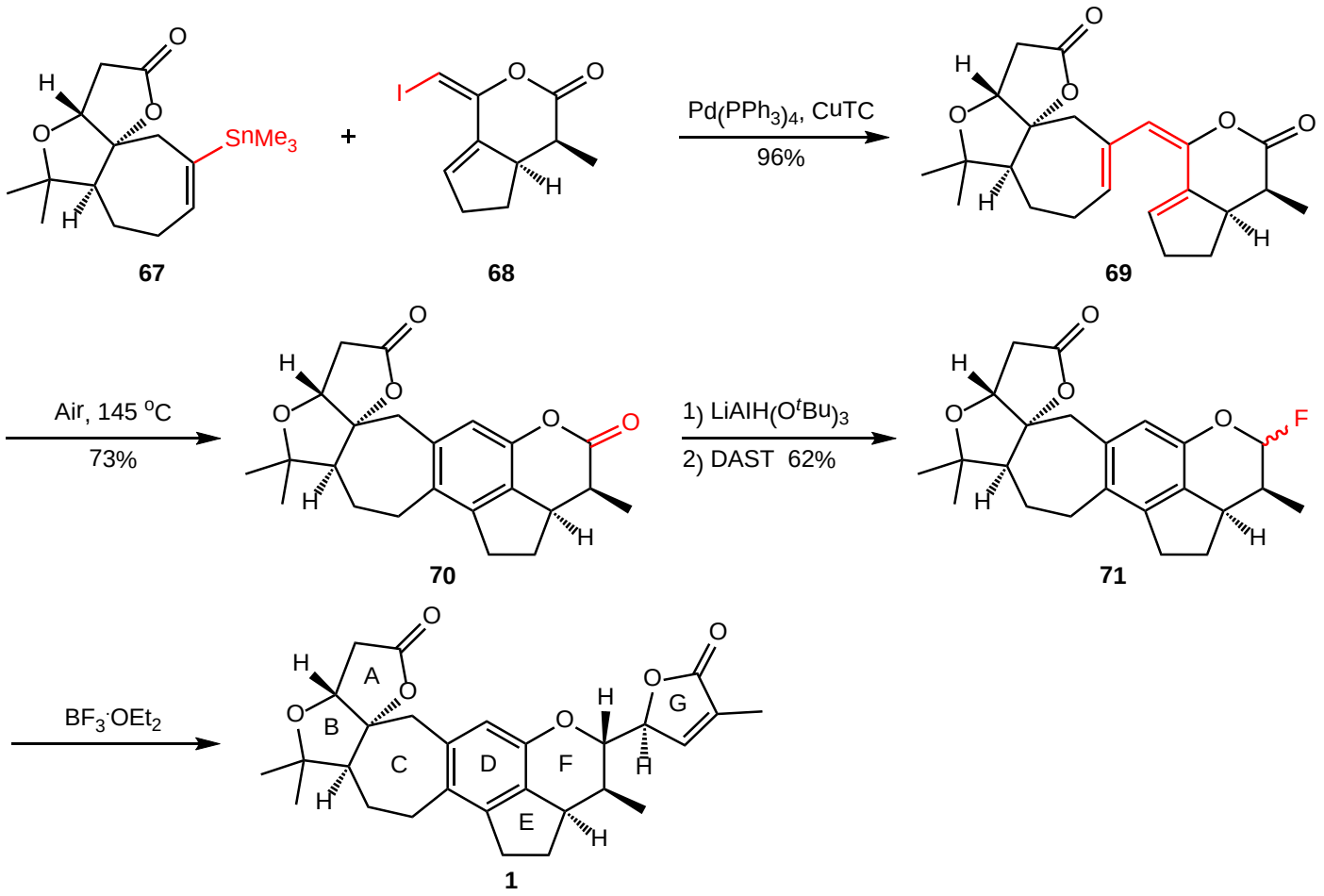
Proposed Retrosynthesis







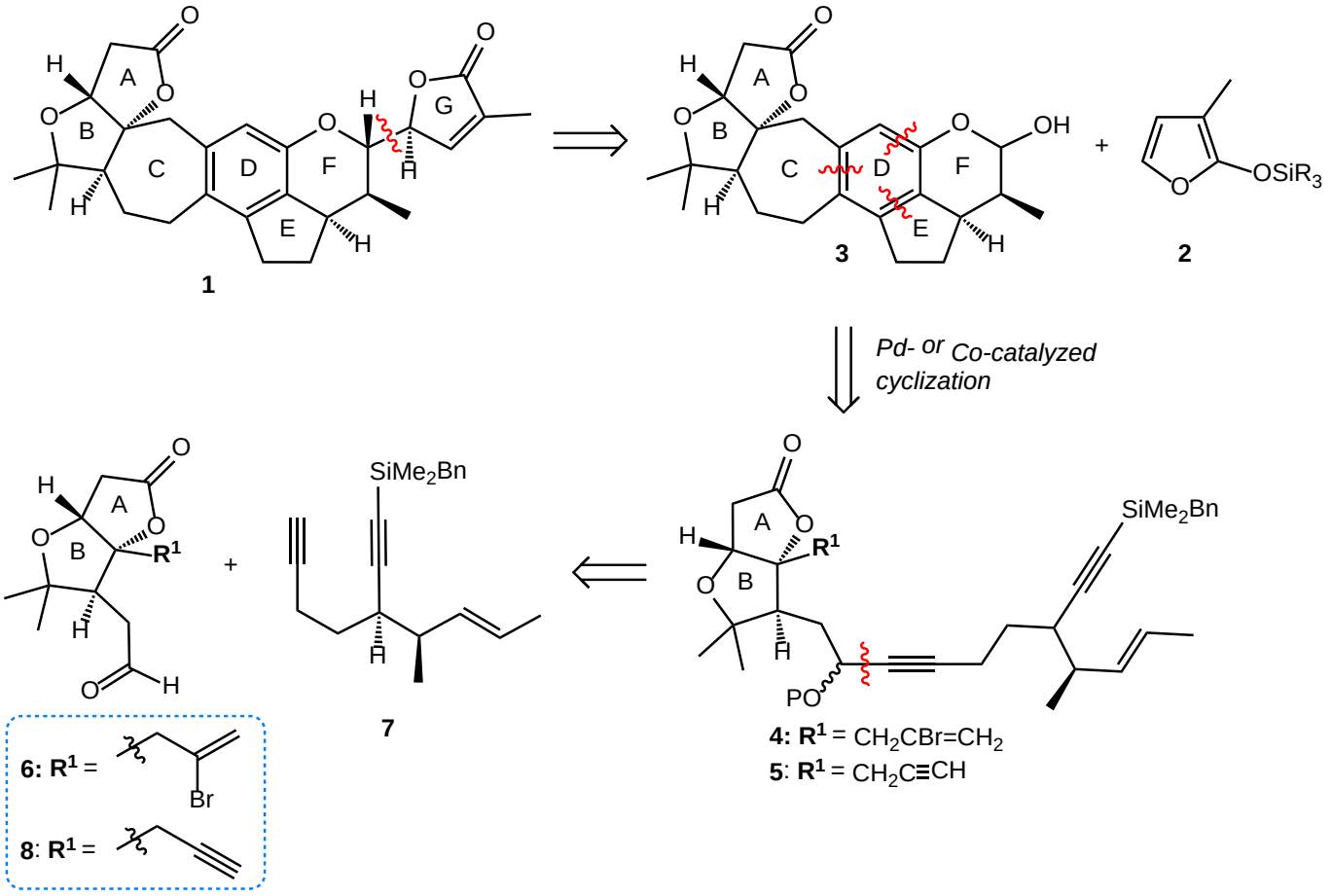
Li's Method



Li, A. *et al. J. Am. Chem. Soc*. **2014**, *136*, 16477.

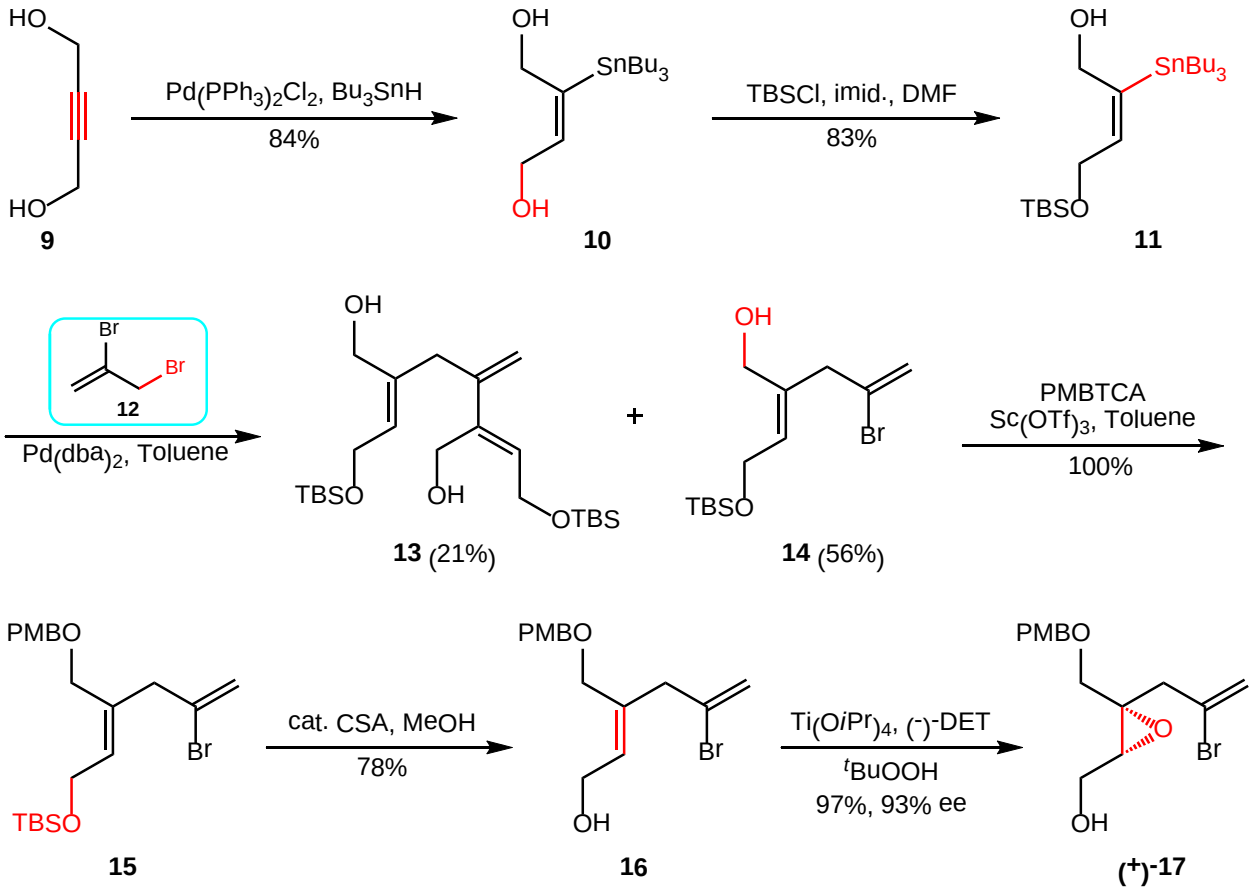
Anderson's Method

Proposed Retrosynthesis:



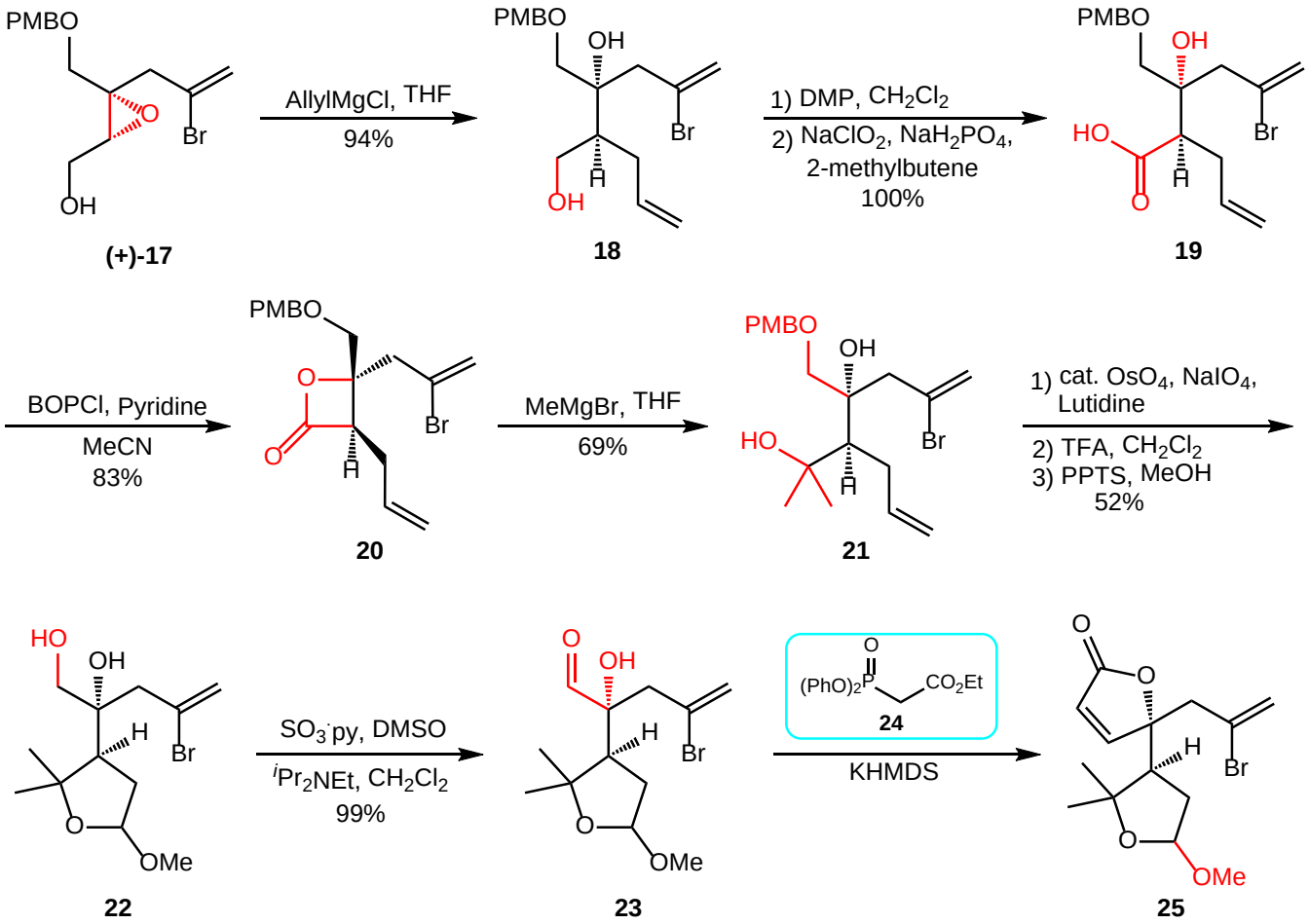
Anderson, E. A. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 12618.

Synthesis of Key Intermediate 6

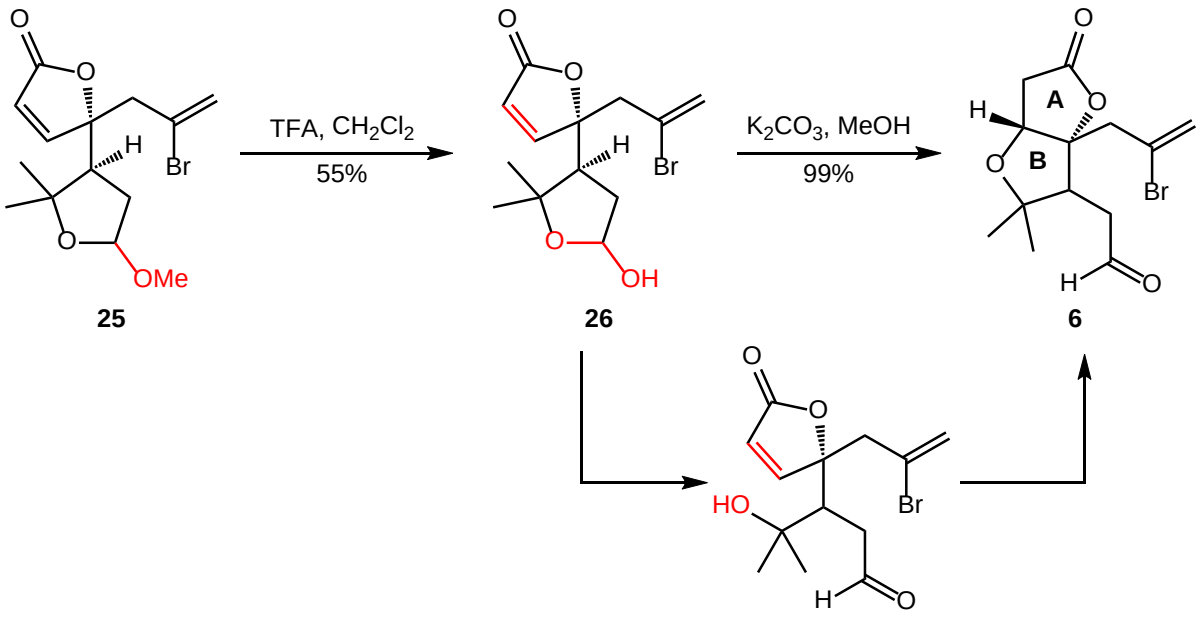


Anderson, E. A. *et al. Org. Lett*. **2014**, *16*, 4480.

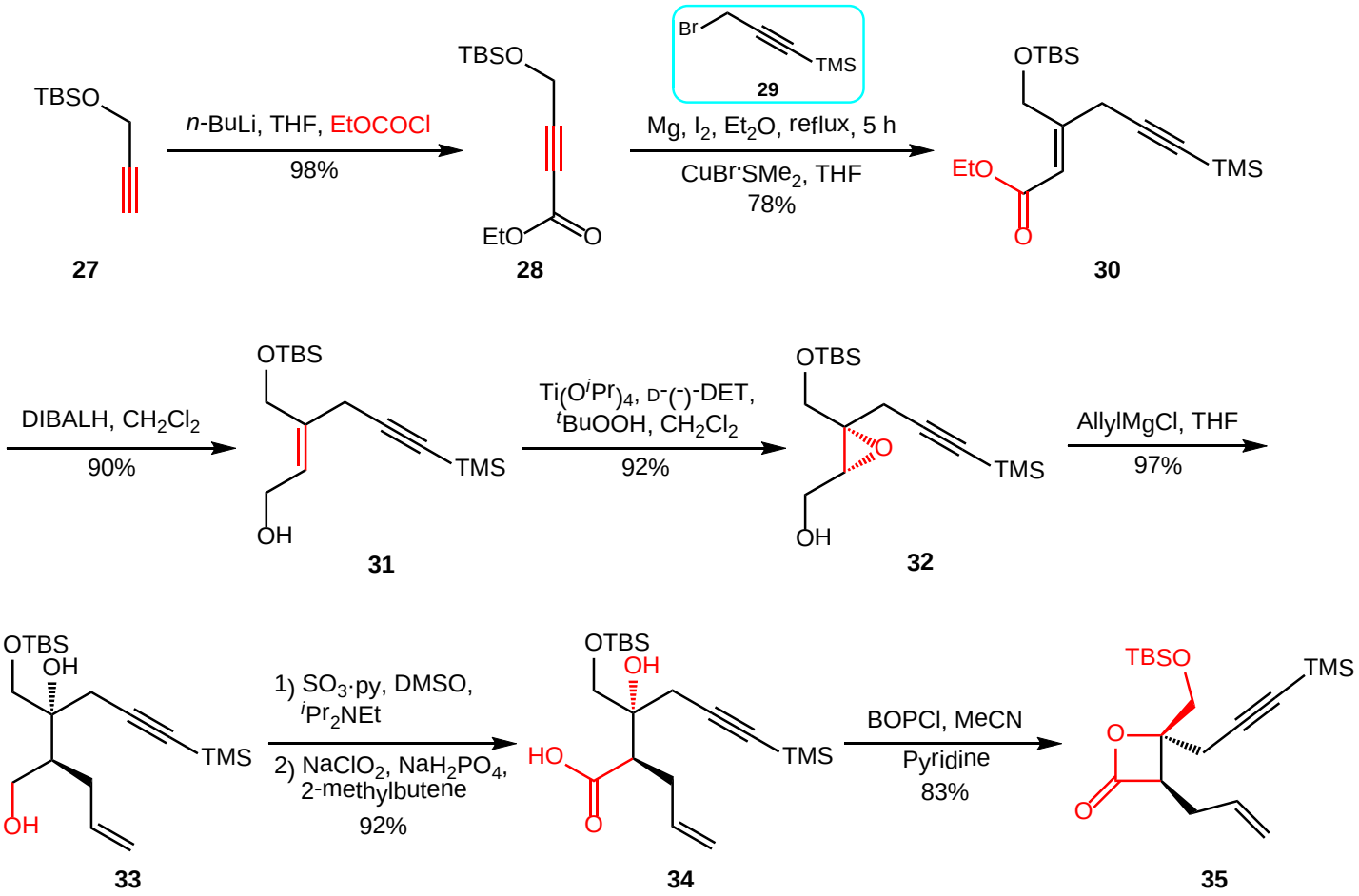
Synthesis of Key Intermediate 6



Synthesis of Key Intermediate 6

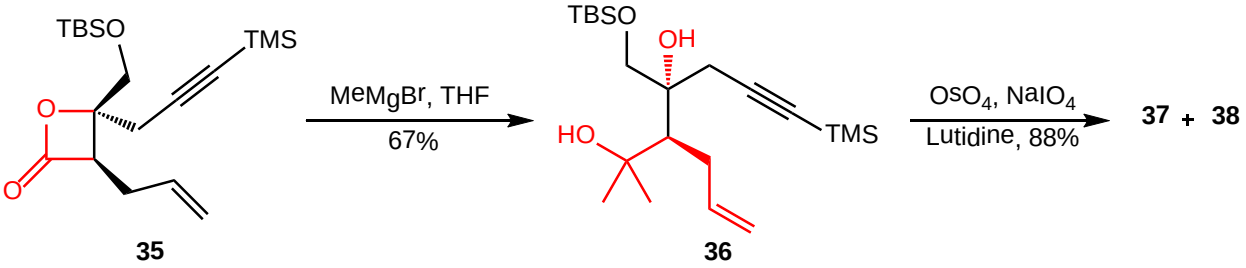


Synthesis of Key Intermediate 8



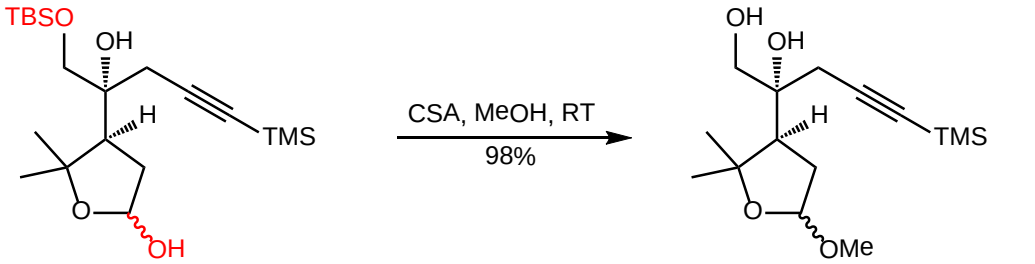
Anderson, E. A. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 12618.

Synthesis of Key Intermediate 8



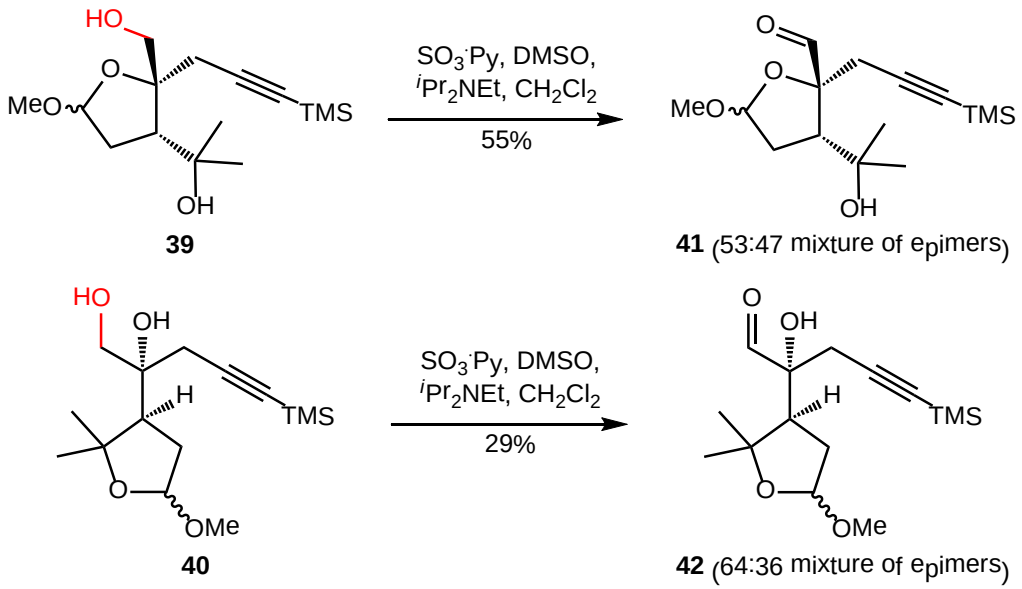
35 **36**

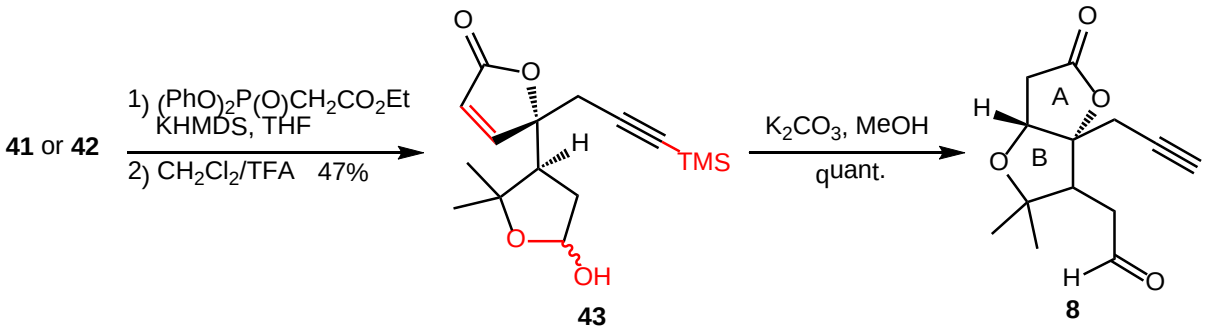
37 (mixture of epimers) **39** (53:47 mixture of epimers)



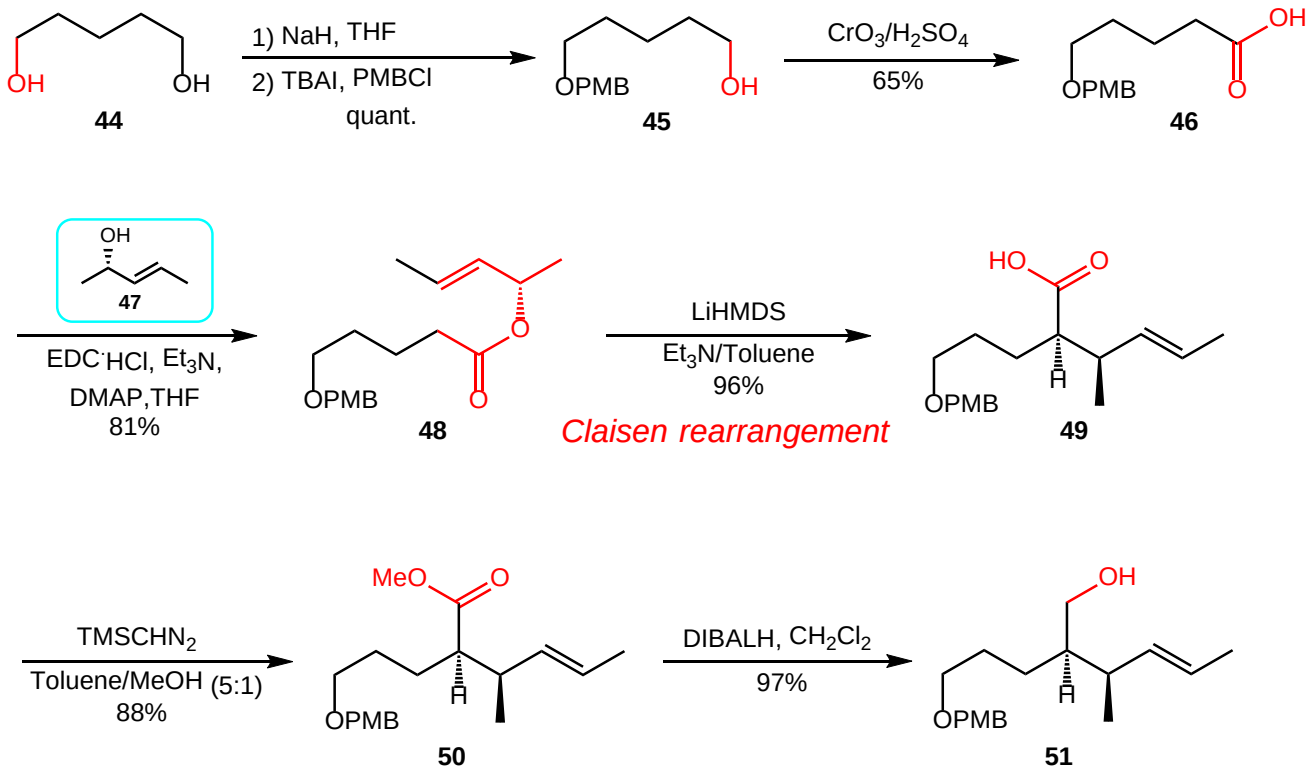
38 (mixture of epimers) **40** (64:36 mixture of epimers)

Synthesis of Key Intermediate 8

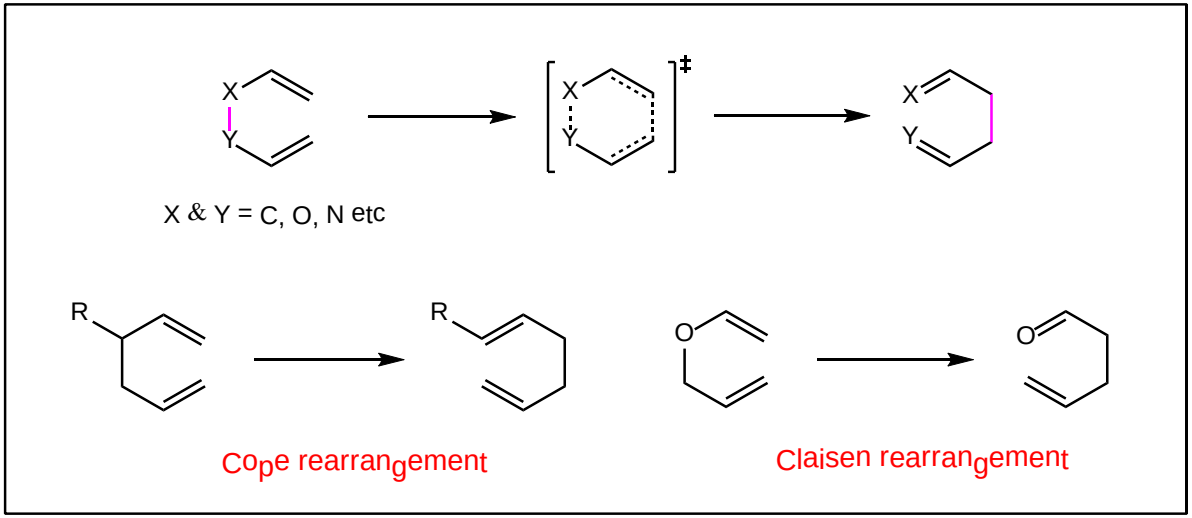


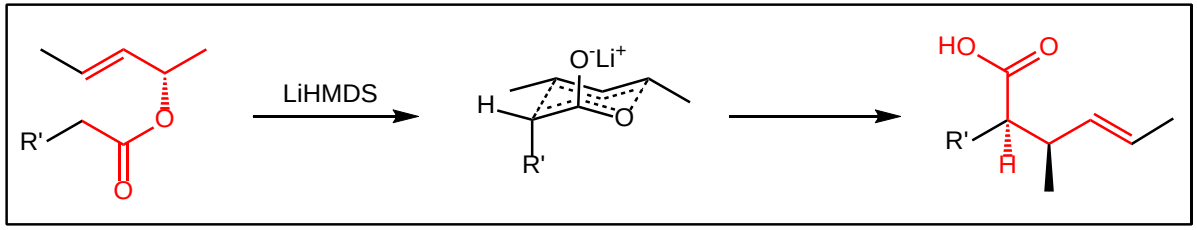


Synthesis of Key Intermediate 7

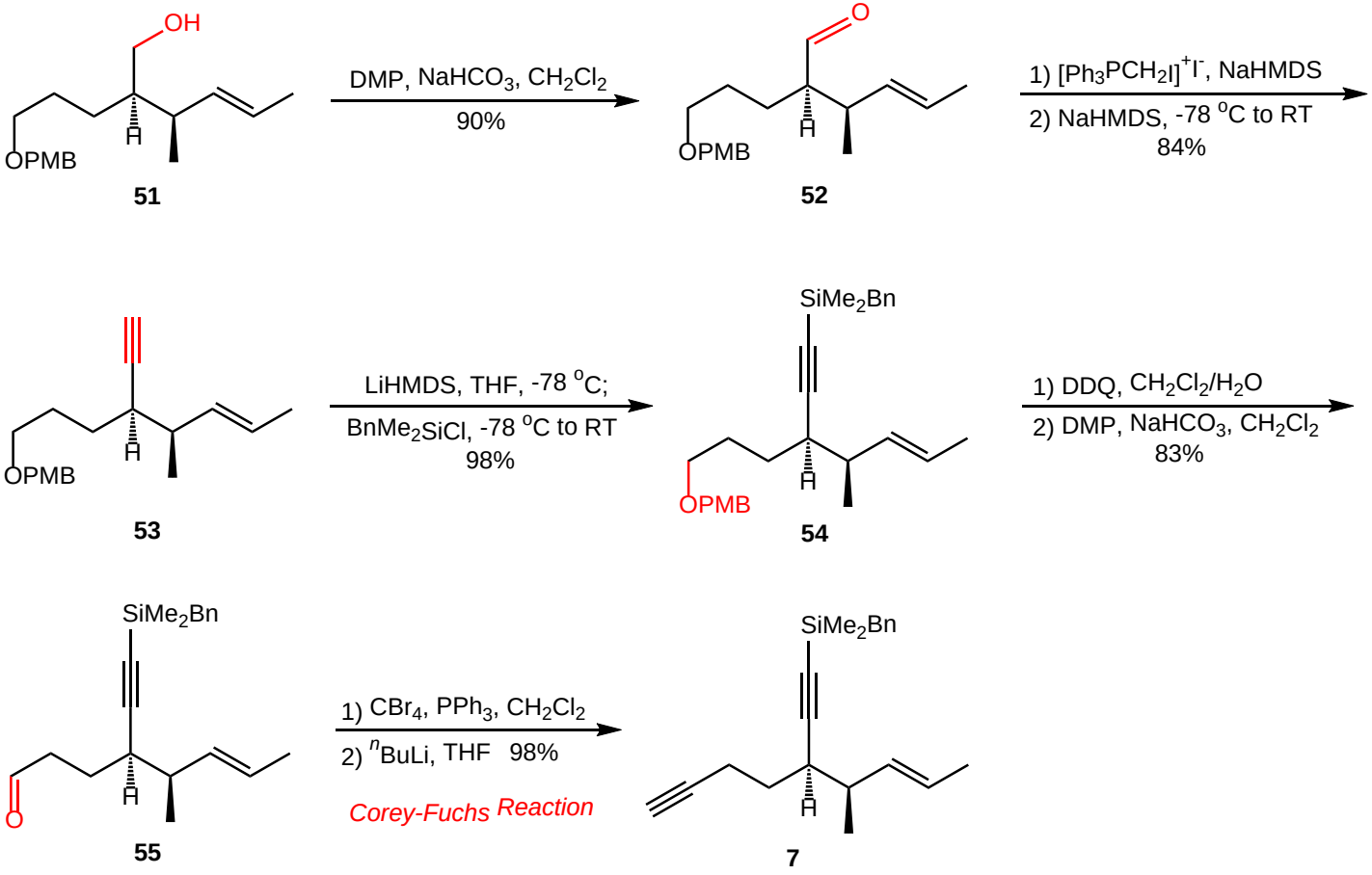


[3,3]-Sigmatropic Rearrangement

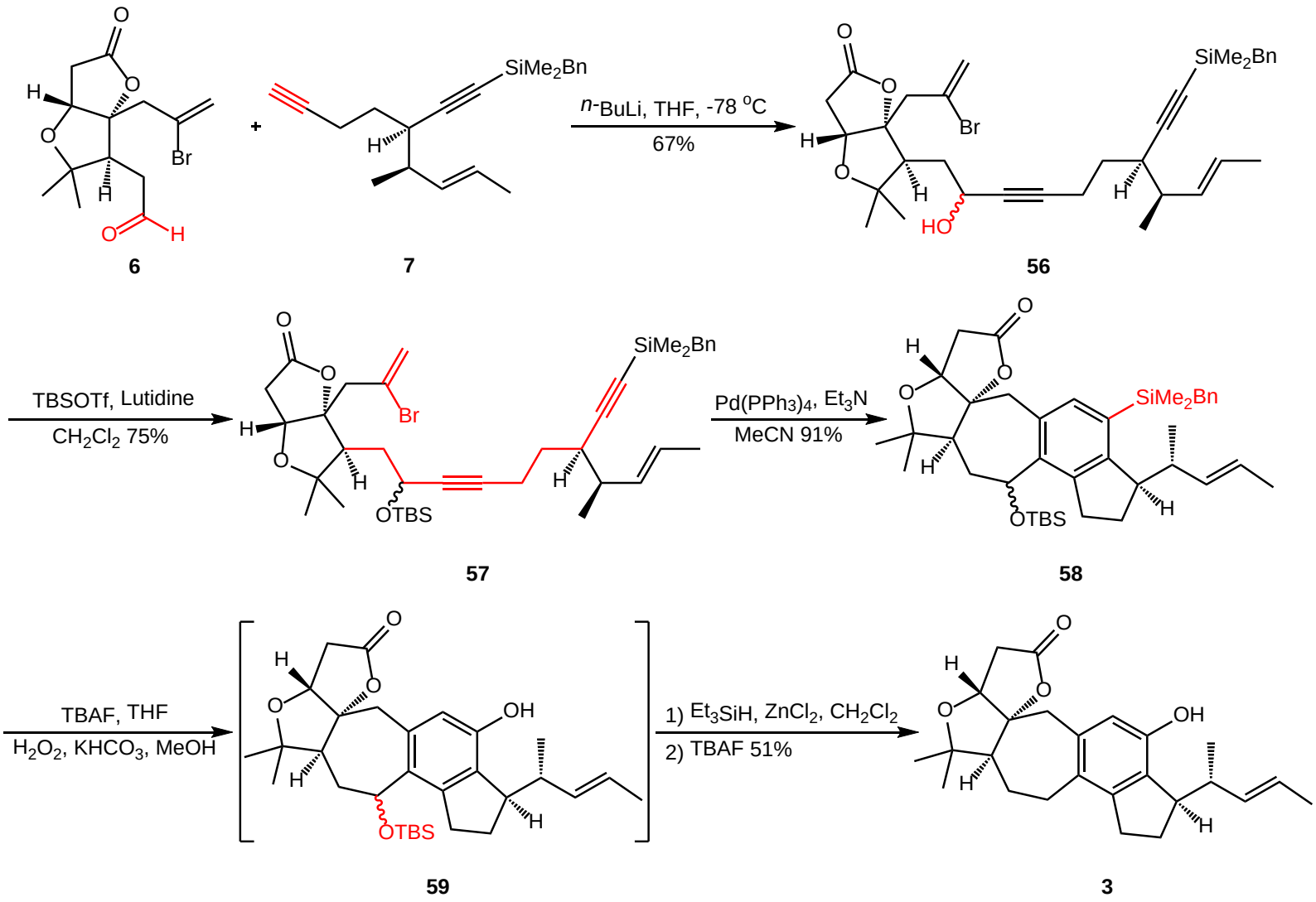




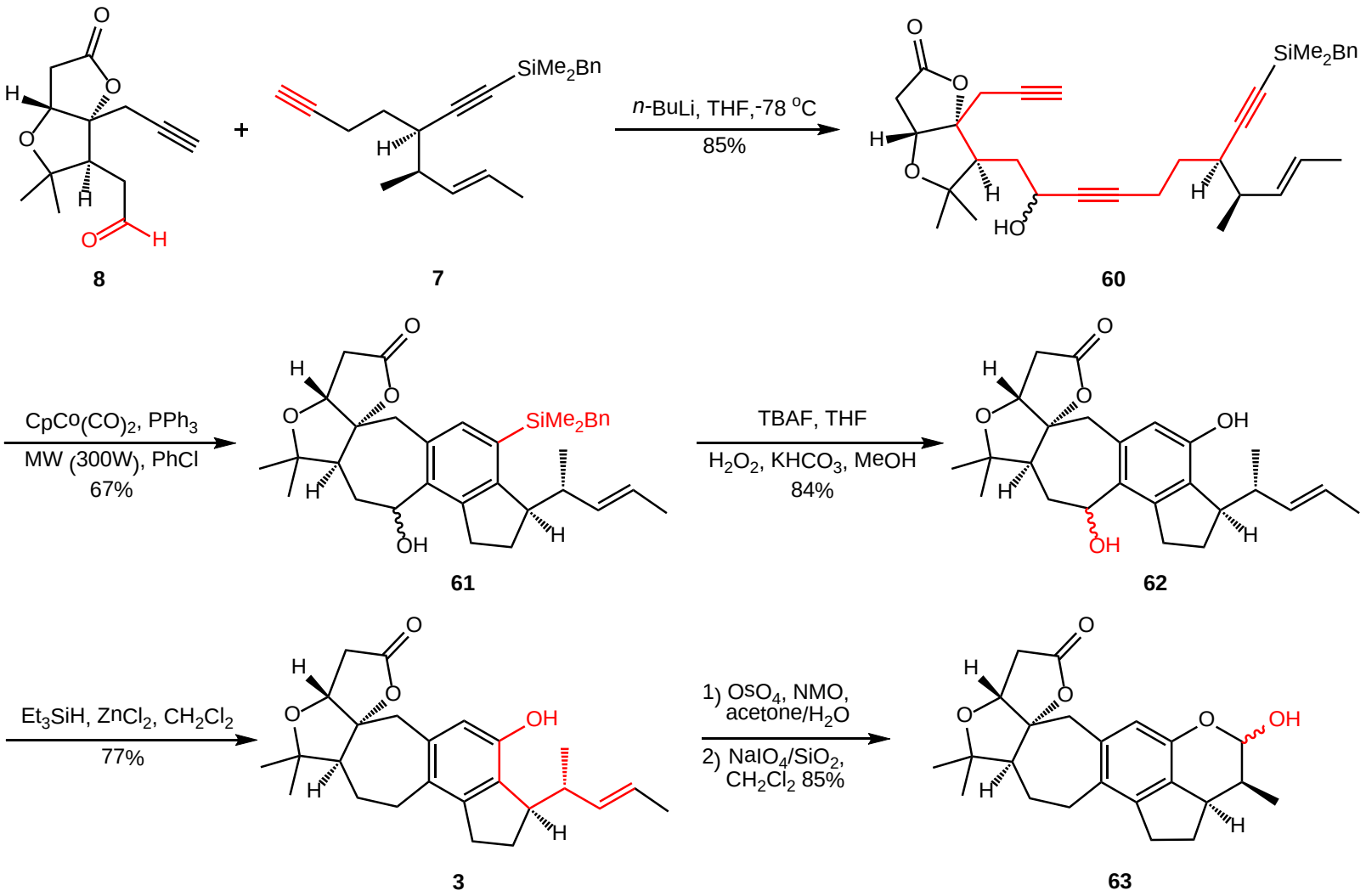
Synthesis of Key Intermediate 7



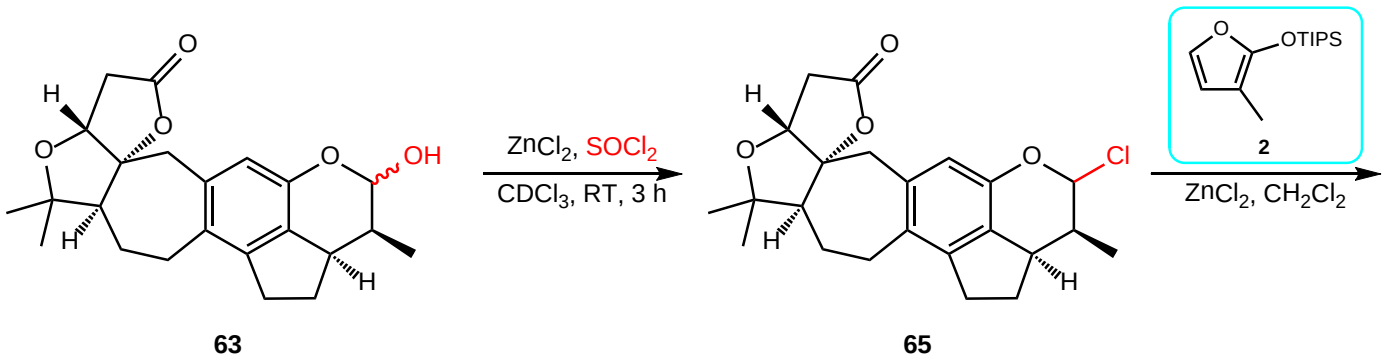
Synthesis of Key Intermediate 3



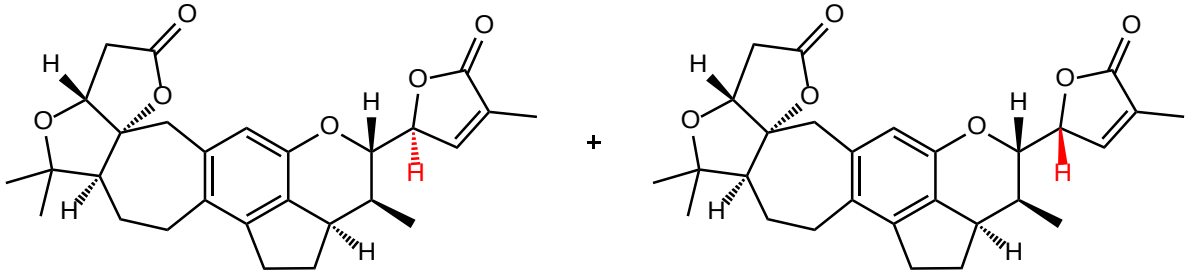
Synthesis of Key Intermediate 3



Completion of the Synthesis



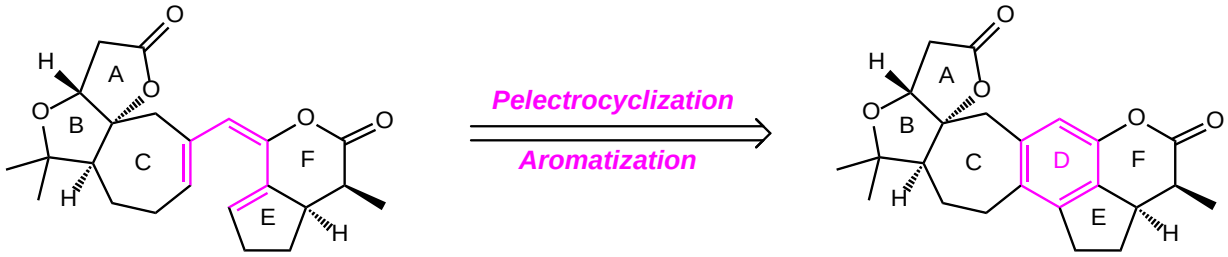
63 **65**



1: **rubriflordilactone A** (38%) + **66** (33%)

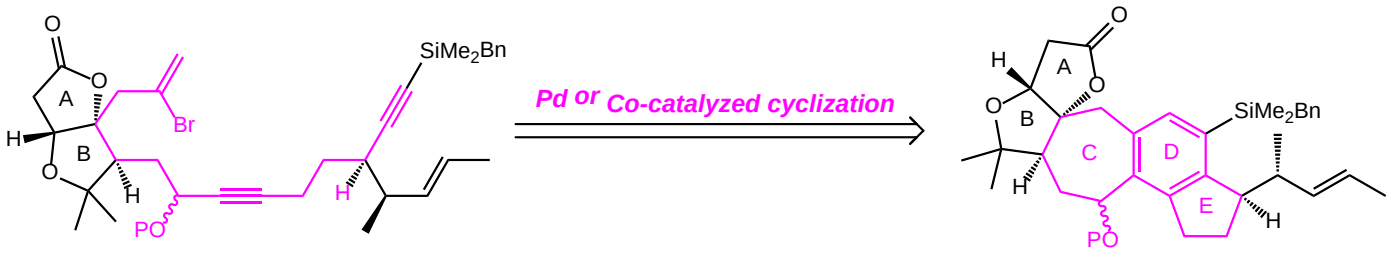
Summary

Li's Method:



- 18 steps, 2.4% overall yield
- Key step: a one-pot 6π-electrocyclolization aromatization

Anderson's Method:



- 20 steps, 3.3% overall yield
- Key step: palladium or cobalt-catalyzed cyclization

Chinese herbal plants of the Schisandra and Kadsura genera have afforded a rich diversity of structurally related nortriterpenoid natural products, which are characterized by complex fused ring systems, a high degree of oxygenation, and densely arrayed stereochemistry. Many of these have been found to exhibit bioactive properties, including promising levels of anti-HIV activity. Their attractive architectures also represent a formidable synthetic challenge, first met in 2011 by Yang and co-workers in their synthesis of schindilactone A. This landmark achievement has recently been complemented by an elegant asymmetric synthesis of rubriflordilactone A by Li et al., where a pelectrocyclization was used to assemble the challenging pentasubstituted D-ring arene; and syntheses of the related family members schilancitrilactones B and C, and propindilactone G.

Herein, we describe two convergent enantioselective total syntheses of rubriflordilactone A, which are distinct from previous work in that the CDE ring system at the heart of the natural product framework is formed in a single tricyclization step. The two syntheses differ in the method used to construct this CDE framework, which is achieved under either palladium or cobalt catalysis; the products of these key cyclizations converge on a common late-stage intermediate.

In conclusion, we have developed two synthetic strategies that achieve enantioselective syntheses of rubriflordilactone A. These employ palladium or cobalt catalysis to assemble the ABCDE ring system as the key framework construction step. The routes are strategically highly convergent because their common late-stage intermediate is just four steps from the end of the synthesis. The modular nature of the coupling between a functionalized diyne and AB-ring aldehydes to assemble the cyclization substrates enables a unified approach to other members of this fascinating family of natural products, and offers a high degree of flexibility for the synthesis of rubriflordilactone analogues.