

Literature Report

Synthesis of Cortistatins A, J, K and L

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Checker: Xin-Wei Wang

March 25, 2019

Dalian Institute of Chemical Physics



Flyer, A. N.; Myers, A. G. *et al. Nat. Chem.* **2019**, 2, 886.

CV of Prof. Myers, A. G.



Prof. Myers, A. G.

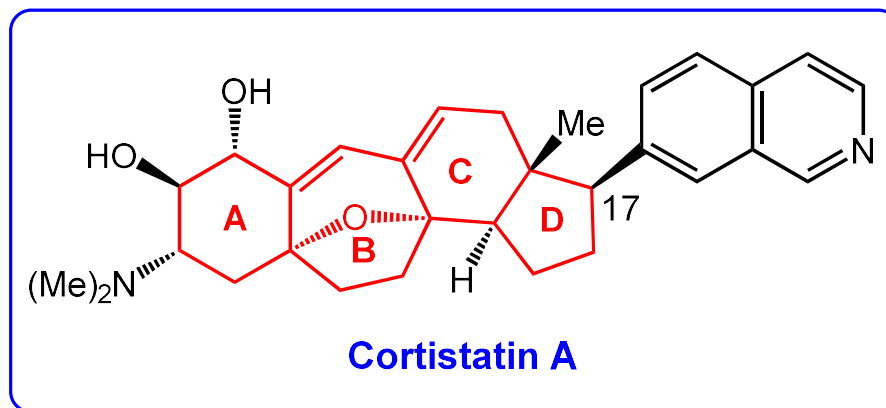
1978-1981	B.S. (MIT)
1981-1986	Ph.D. (Harvard University)
1986-1998	Prof. (Caltech)
1998-now	Prof. (Harvard University)

Research Fields: Total Synthesis of Complex Molecules

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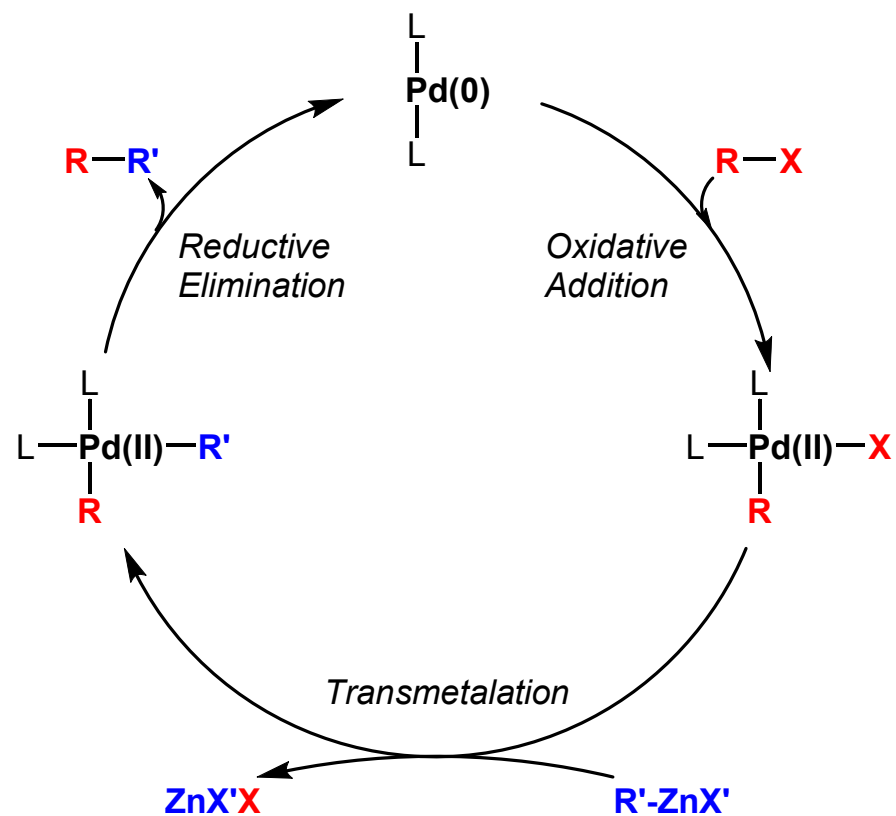
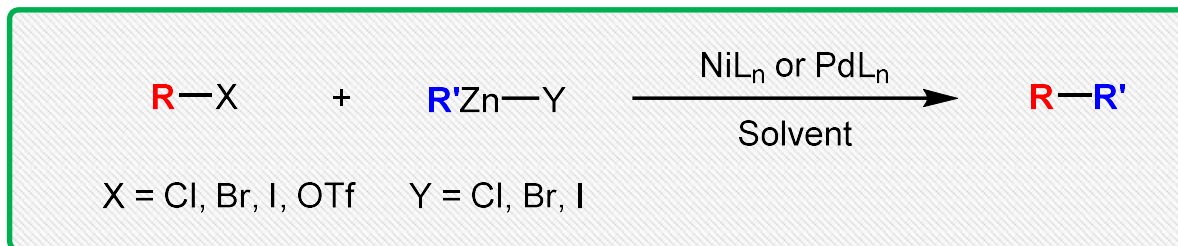
Introduction



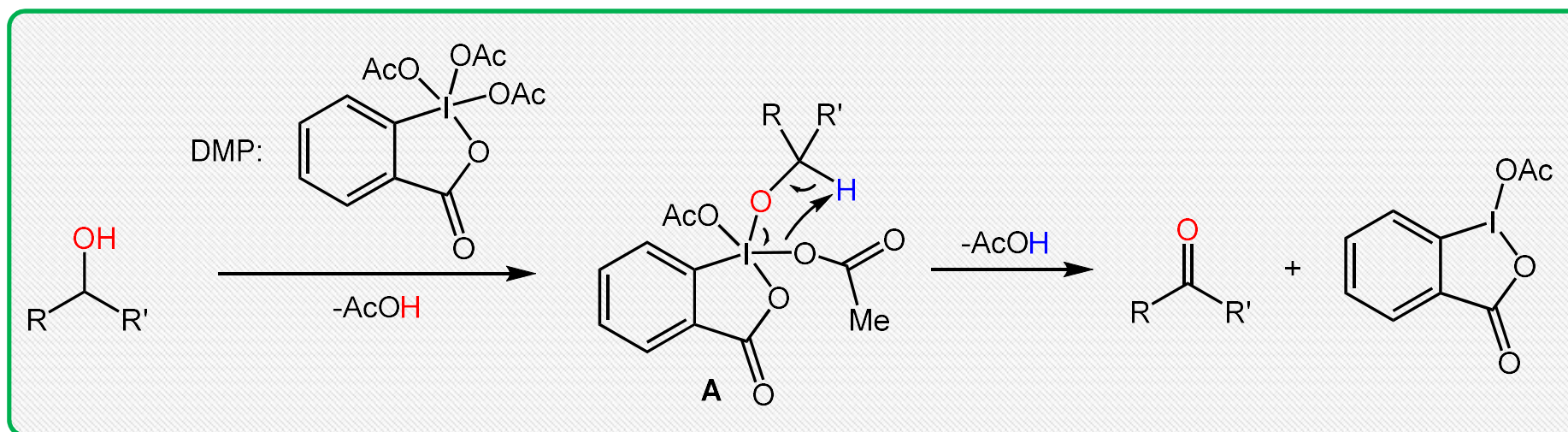
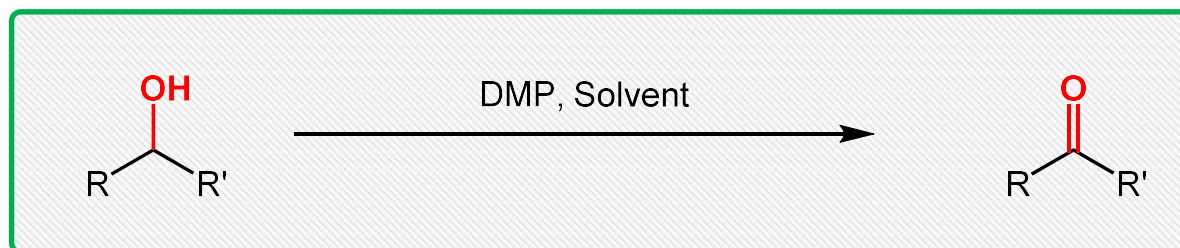
- ◆ Isolated in 2006 from *Corticium simplex*
- ◆ A heptacyclic skeleton
- ◆ An isoquinoline structural motif

Aoki, S. *et al.* *J. Am. Chem. Soc.* **2006**, 128, 3148.

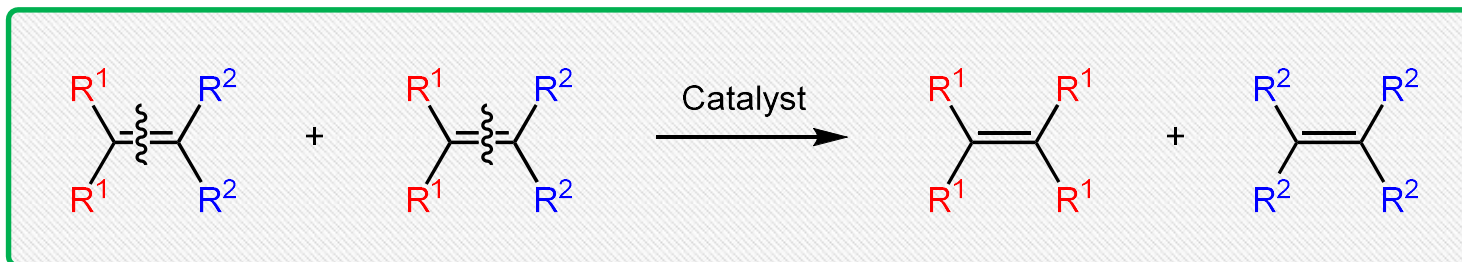
Negishi Coupling



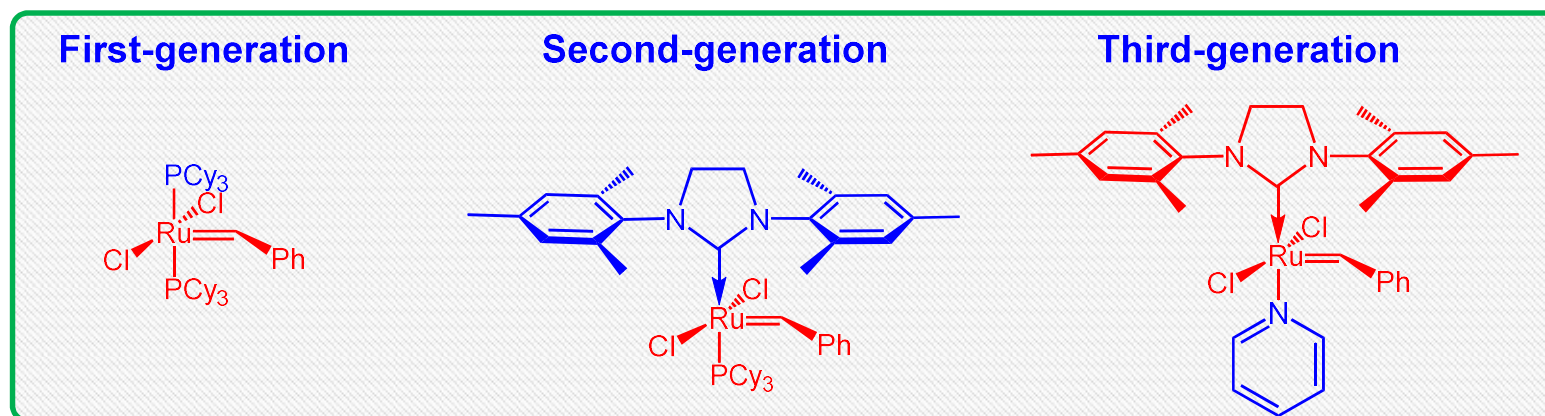
Dess-Martin Oxidation



Olefin Metathesis

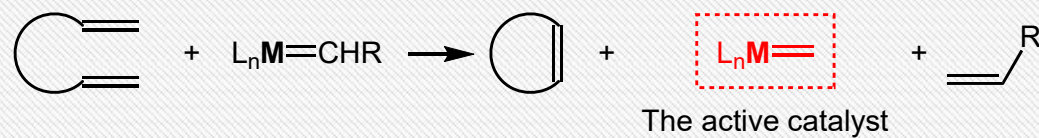


Grubbs Catalyst:

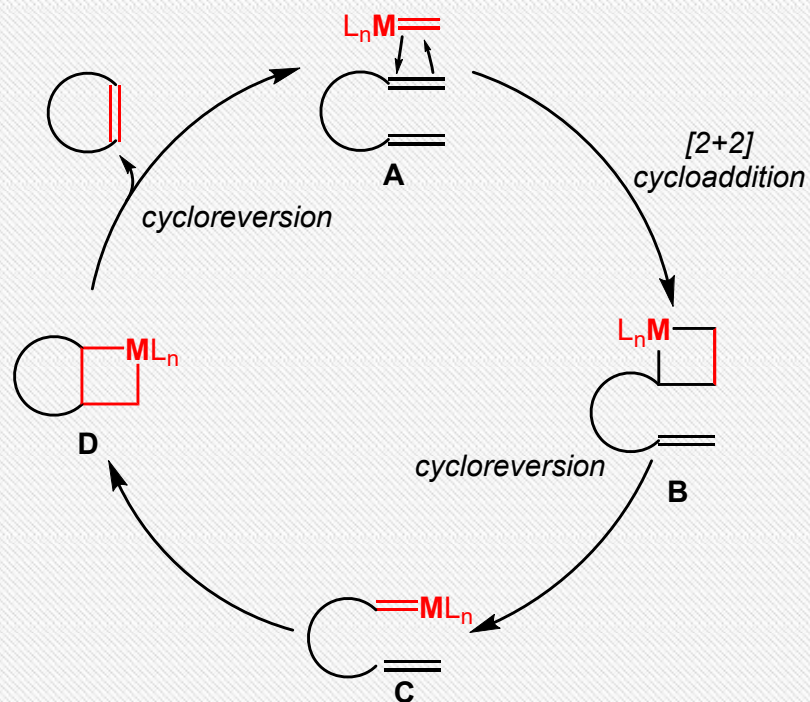


Olefin Metathesis

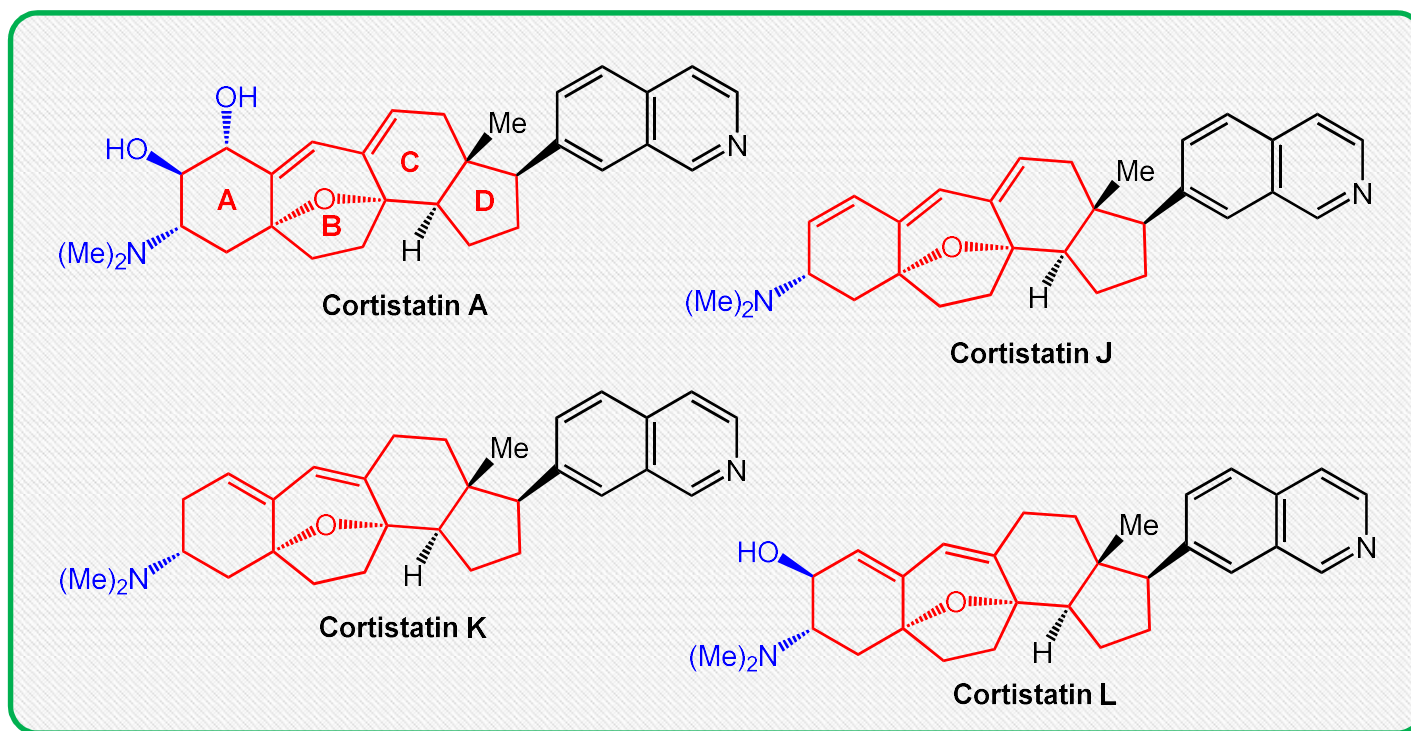
Generation of the real catalyst from the precatalysts:



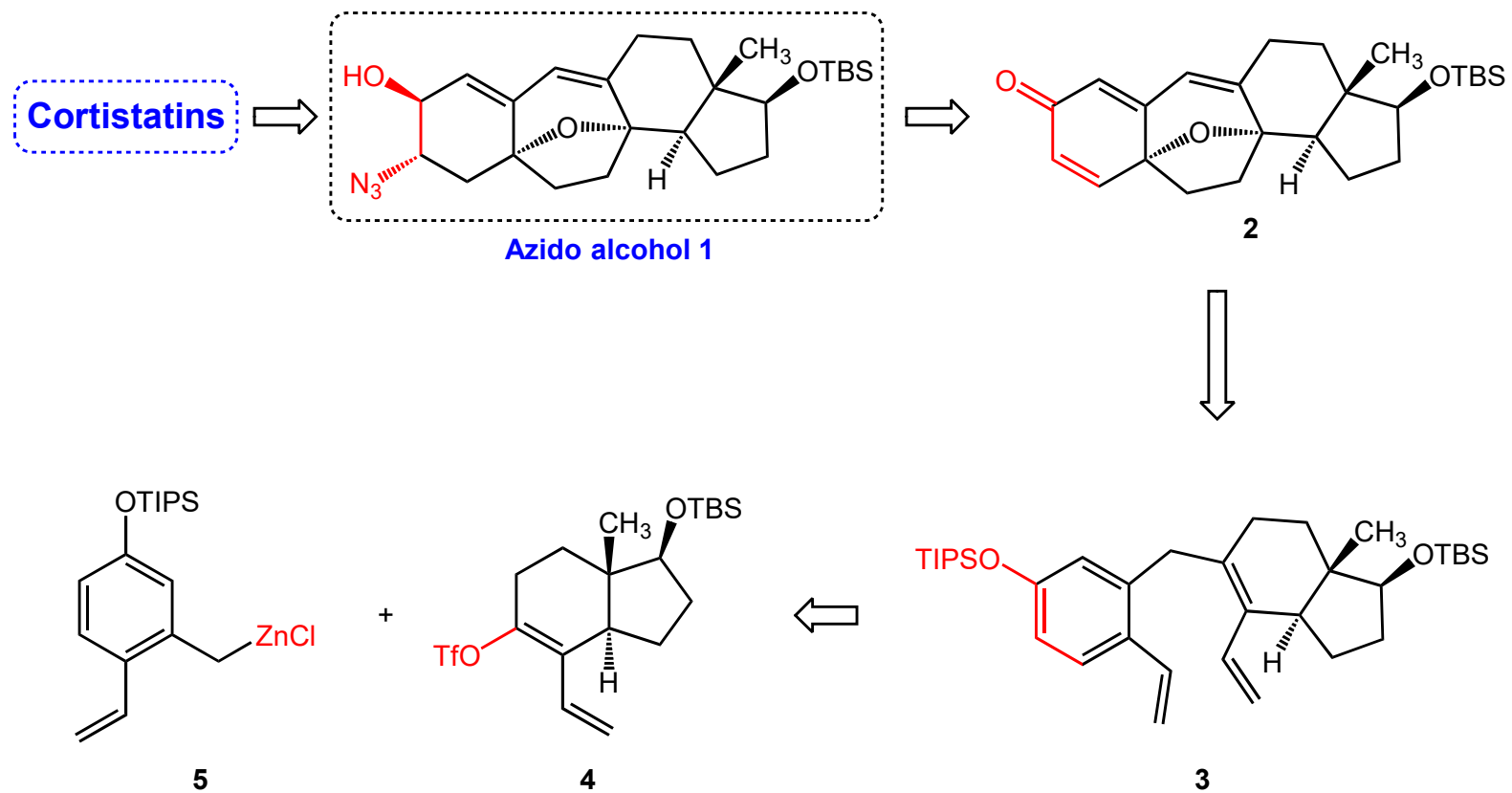
Catalytic cycle:



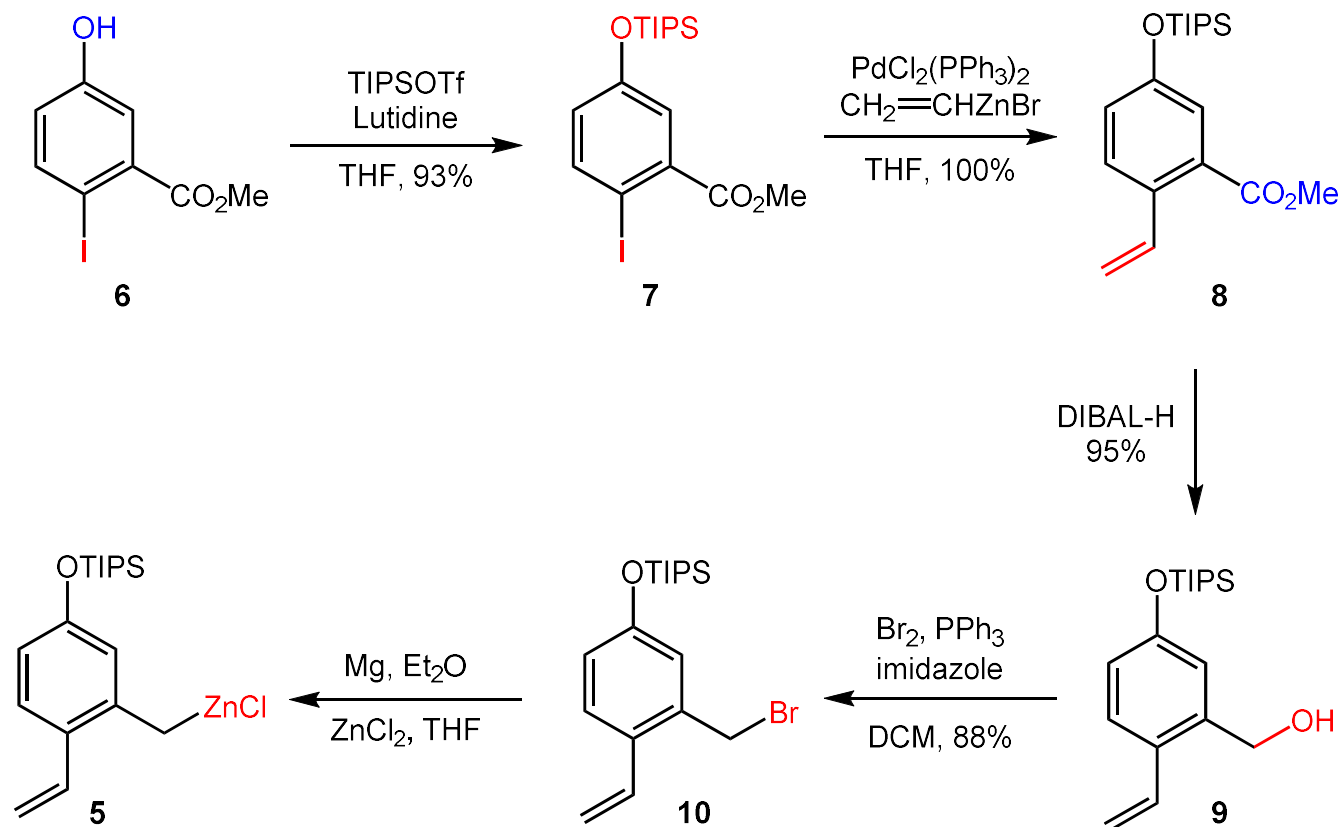
Introduction



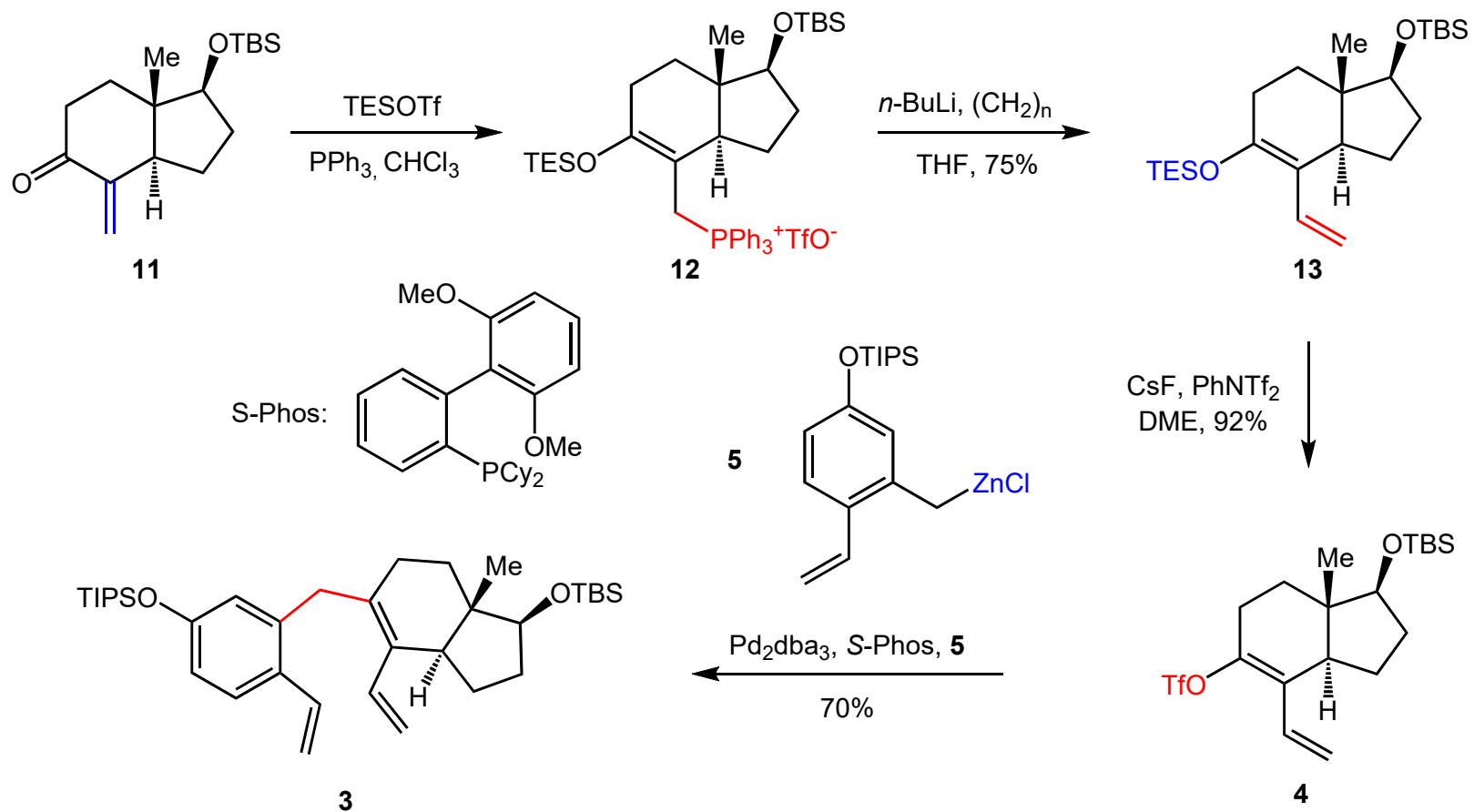
Retrosynthetic Analysis



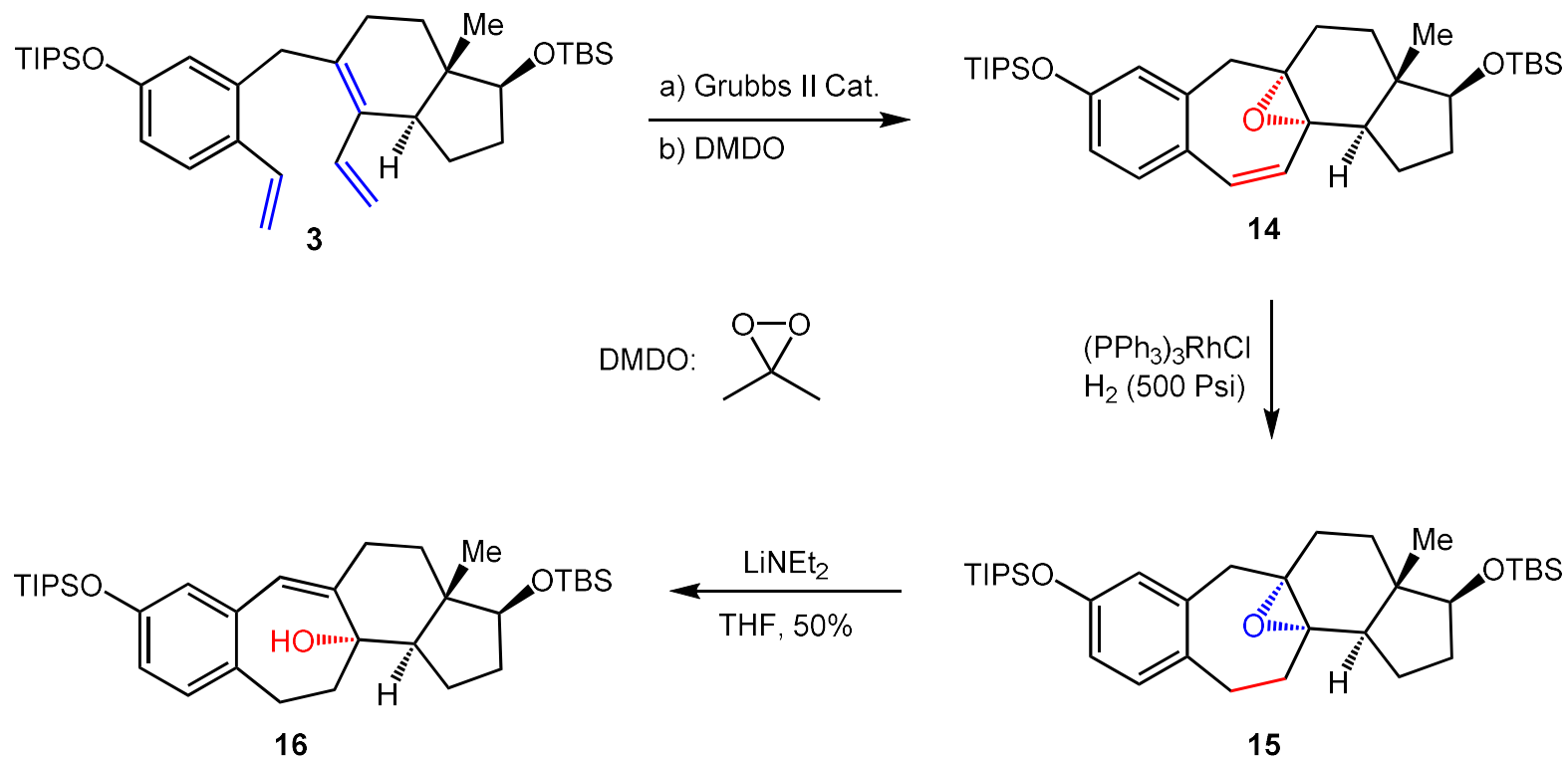
Synthesis of Intermediate 5



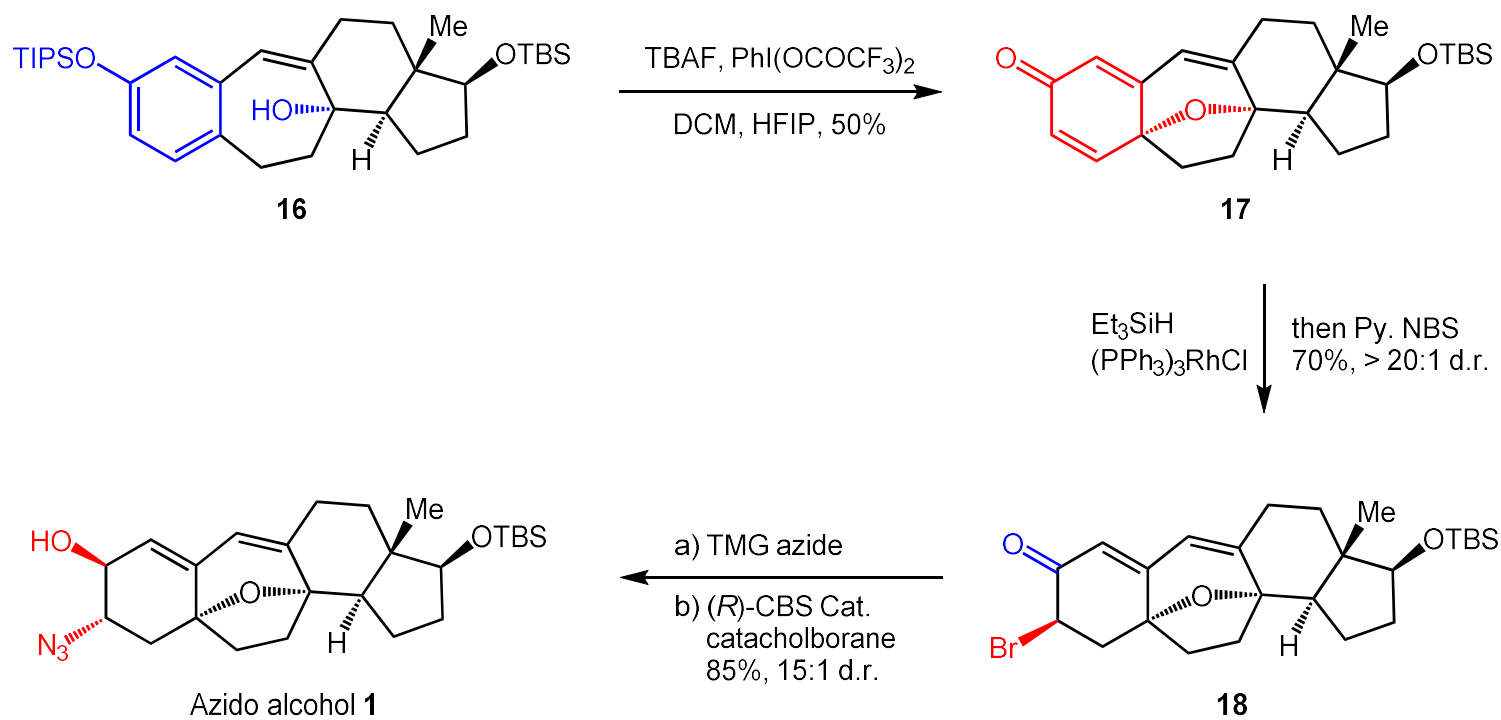
Synthesis of Intermediate 3



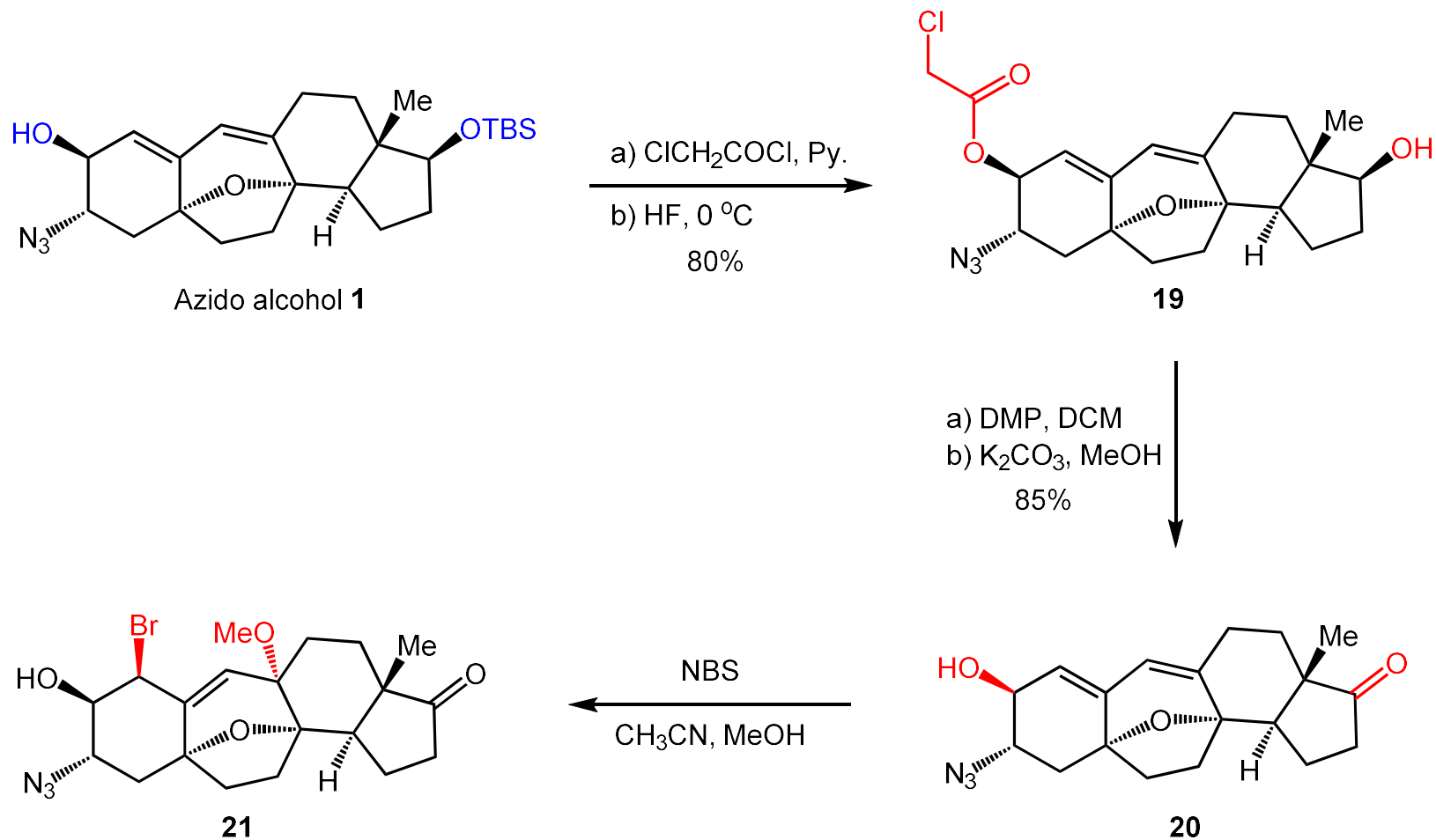
Synthesis of Intermediate 16



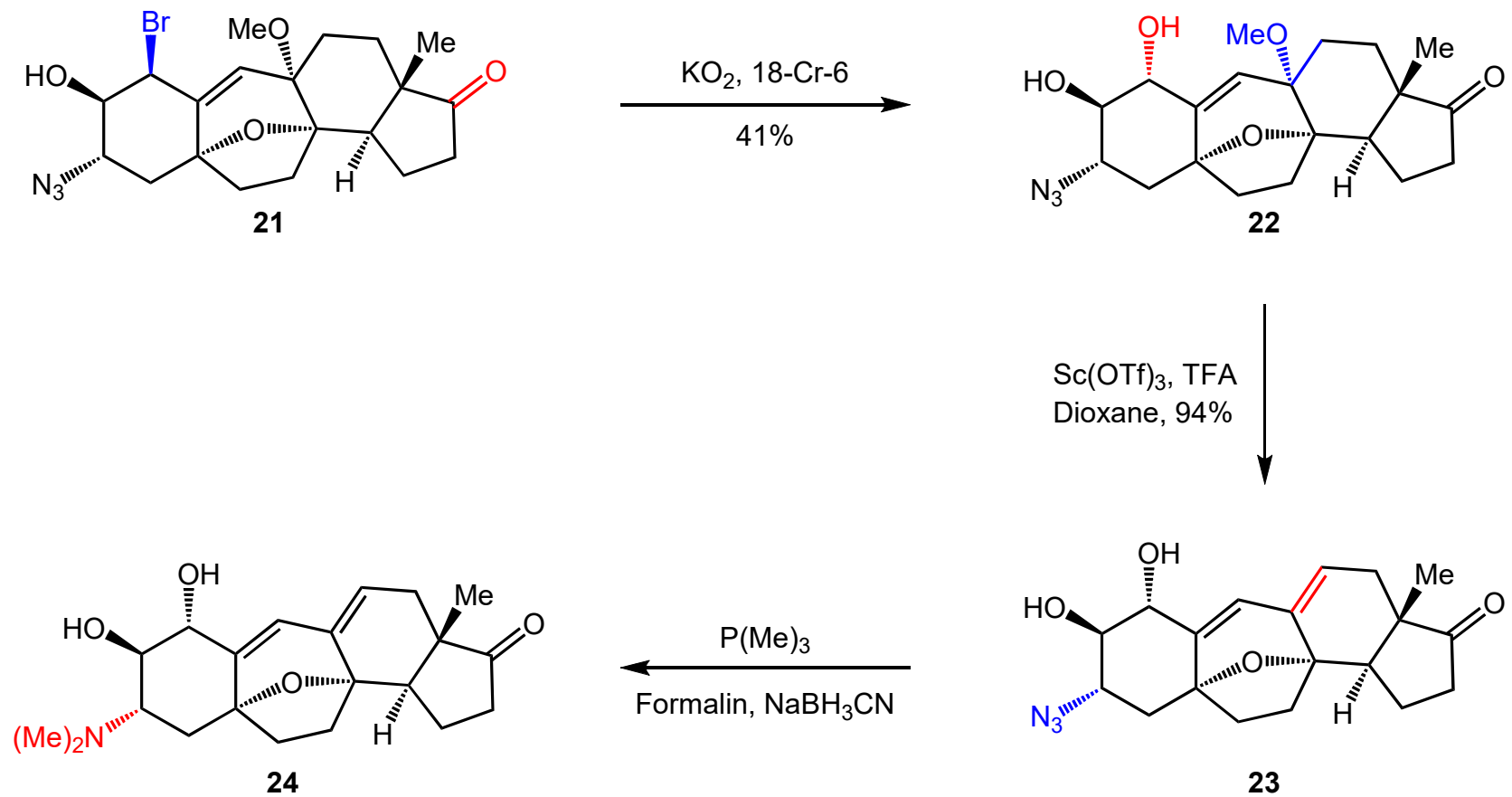
Synthesis of Key Intermediate 1



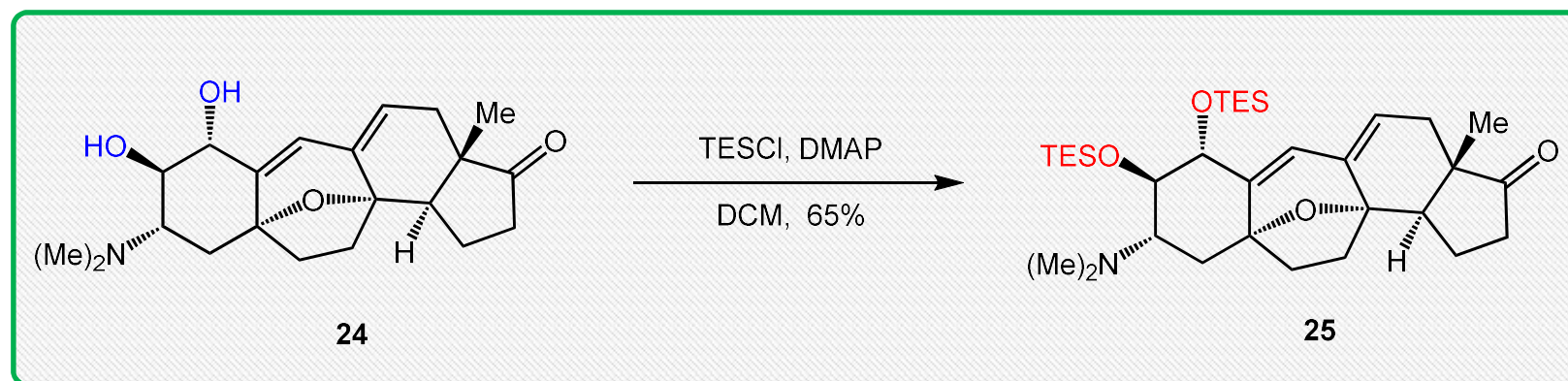
Synthesis of Cortistatin A Series



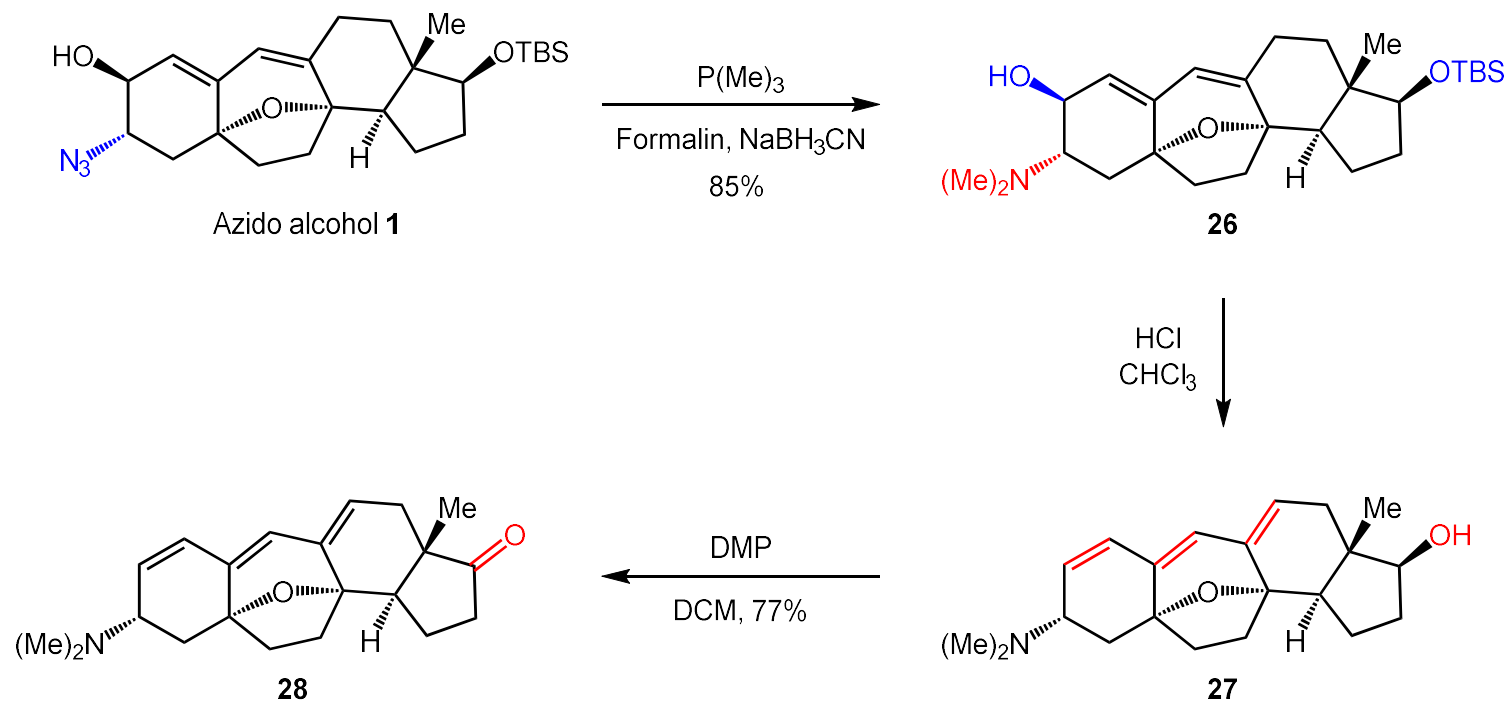
Synthesis of Cortistatin A Series



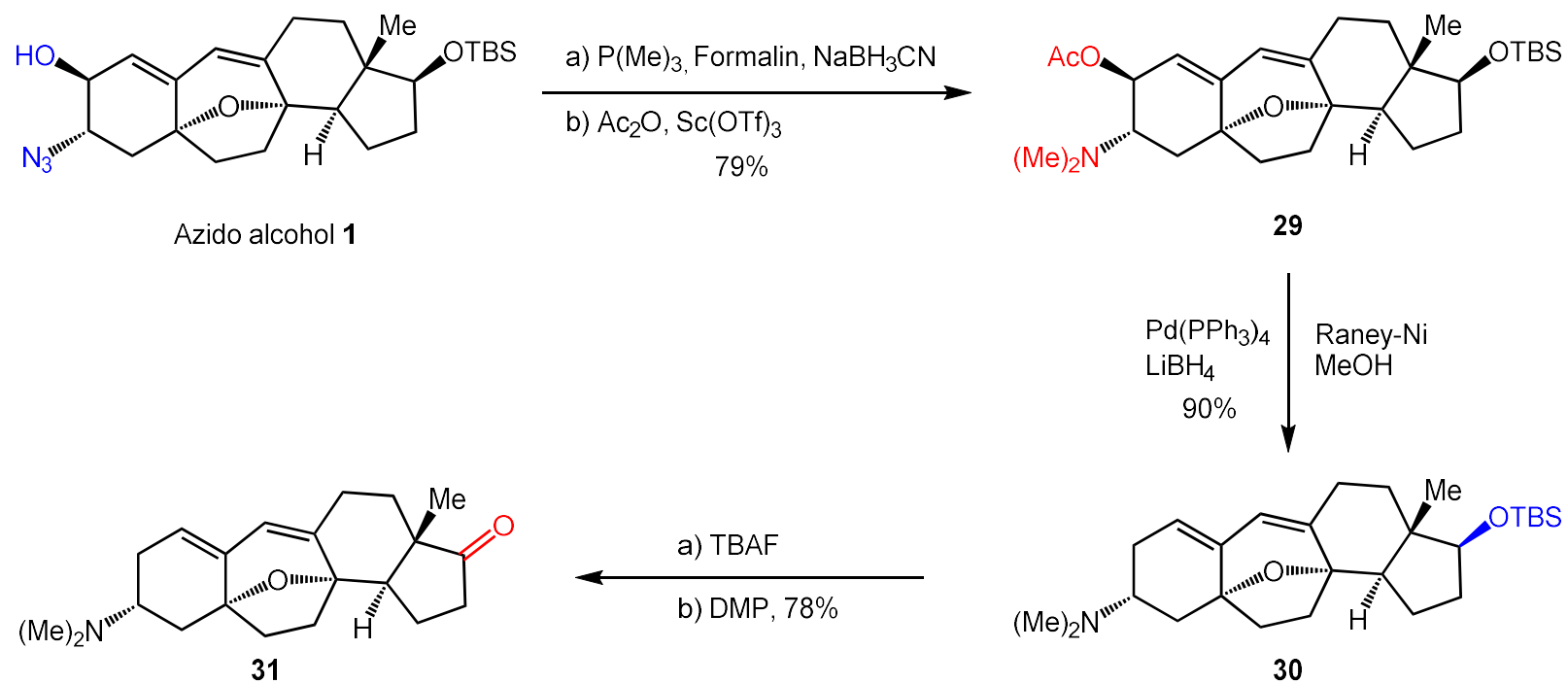
Synthesis of Cortistatin A Series



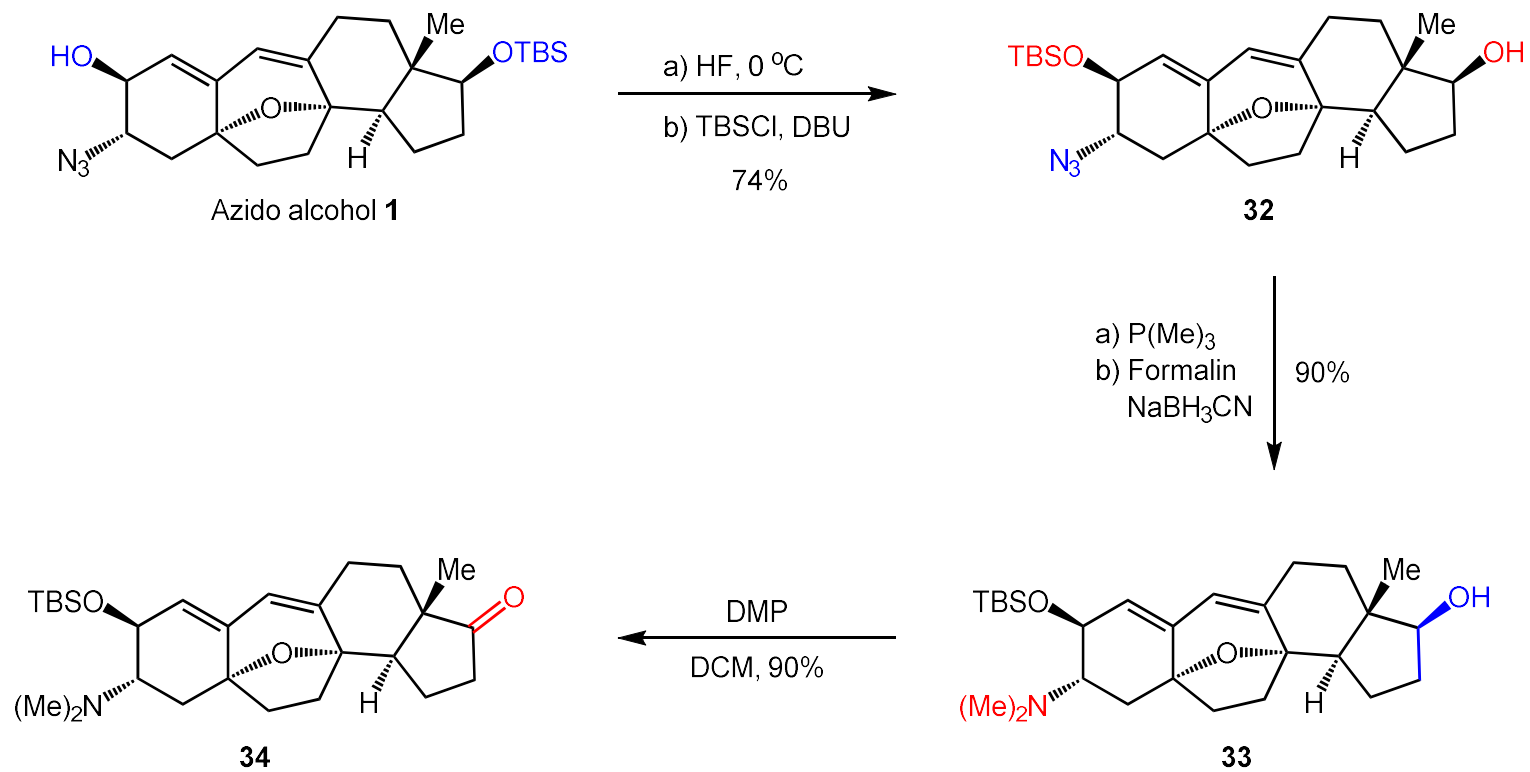
Synthesis of Cortistatin J Series



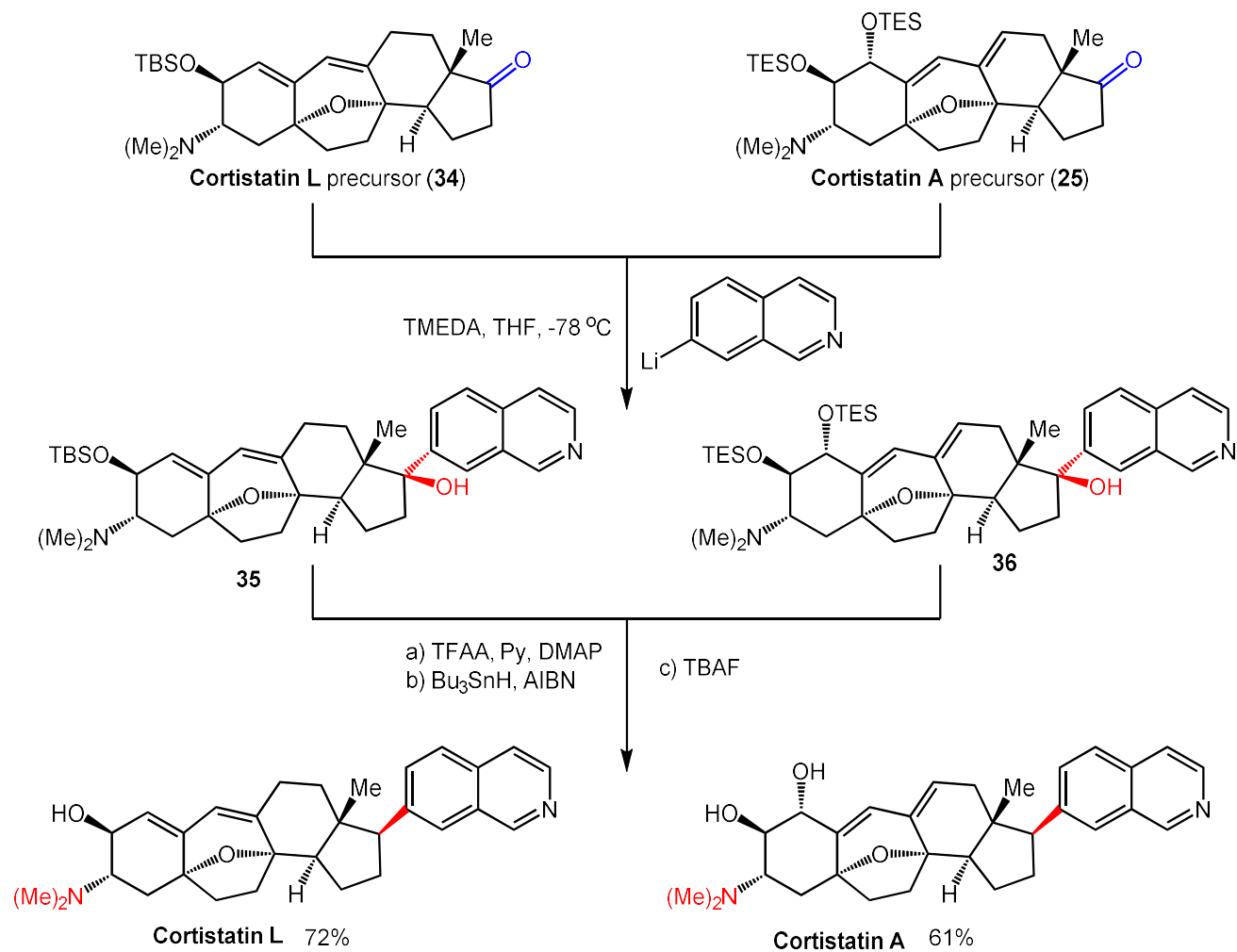
Synthesis of Cortistatin K Series



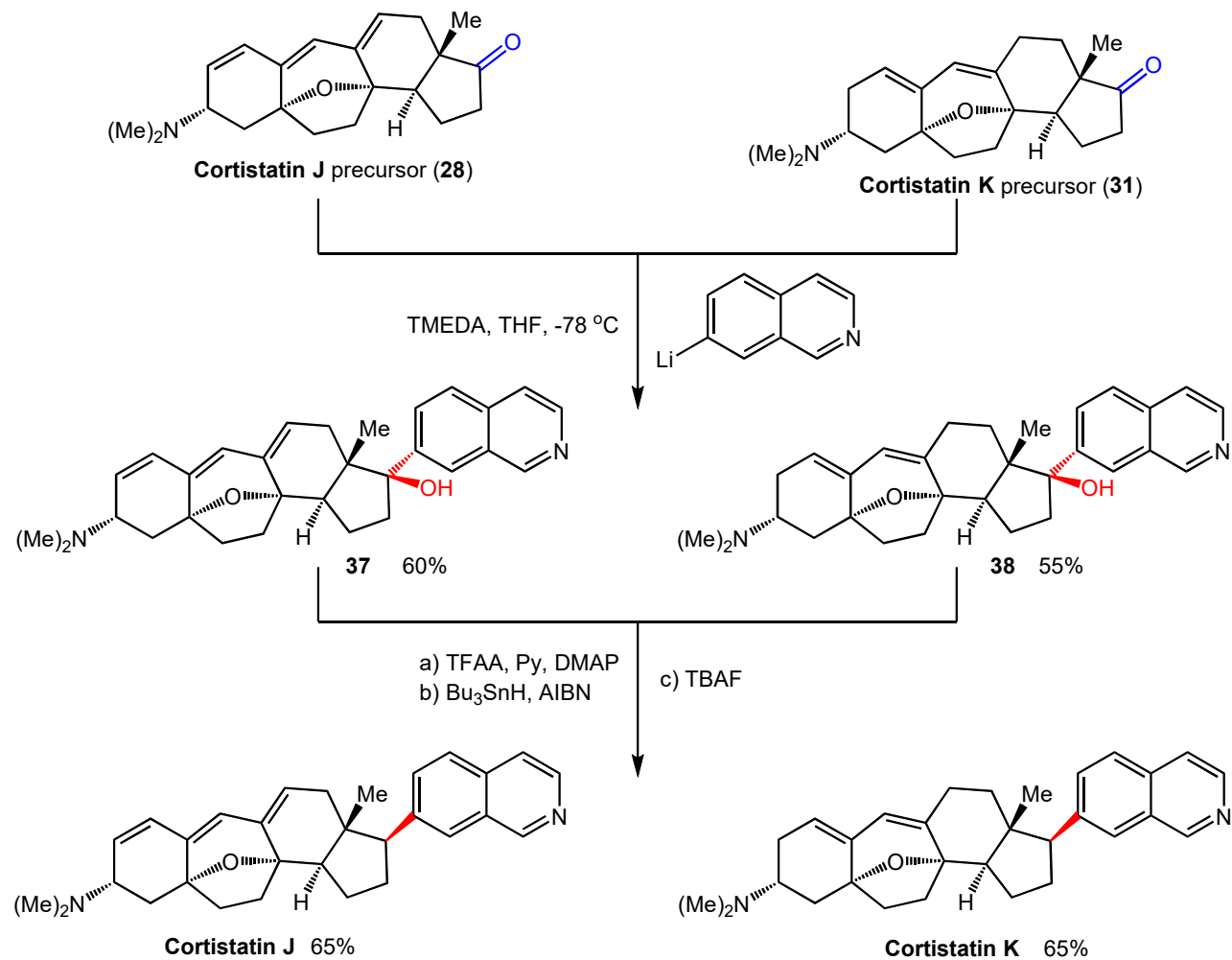
Synthesis of Cortistatin L Series



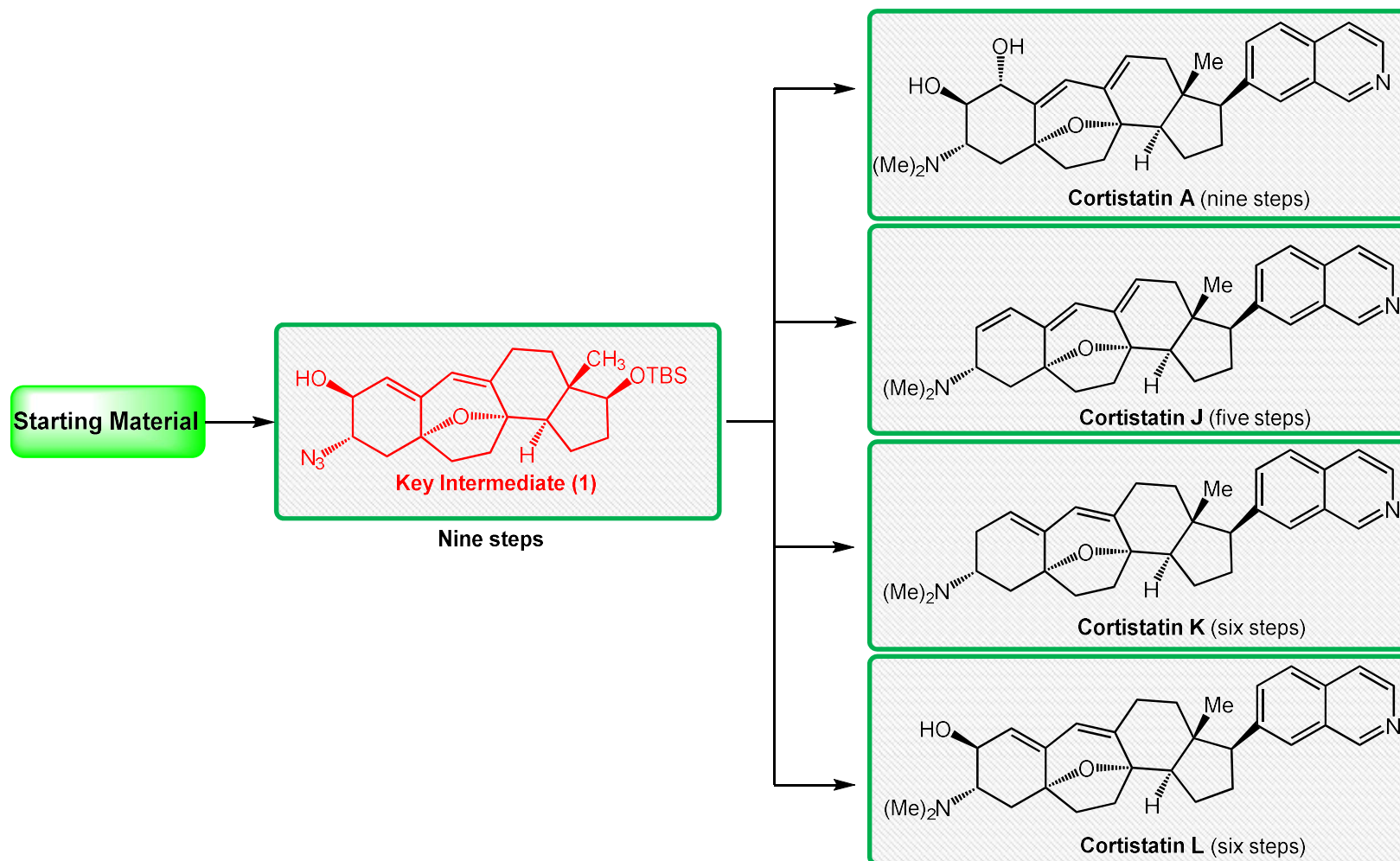
Synthesis of Cortistatin A, L



Synthesis of Cortistatina J, K



Summary



The First Paragraph

Since the structure of **cortistatin A** was elucidated by Kobayashi and colleagues in 2006, more than ten natural cortistatins have been described, which have a common modified steroidal skeleton with varying substitution of the A- and D-rings. **Many of these have profound effects on mammalian cells, and on human umbilical vein endothelial cells in particular.**

The First Paragraph

In 2008, Baran and colleagues reported the first laboratory synthetic route to cortistatin A, and subsequent to this a number of different approaches to the synthesis of cortistatins have been pursued, focused largely on the most highly functionalized member of the family, cortistatin A. **No fewer than three independent routes to cortistatin A have been reported to date, as well as a number of synthetic studies and formal routes.** In addition, the Nicolaou–Chen group has described a synthesis of cortistatin J.

The Last Paragraph

We have shown that the protected azido alcohol intermediate **1**, synthesized in a nine-step sequence beginning with the coupling of the benzylzinc reagent **5** and the enol triflate **4**, is readily transformed into advanced 17-keto precursors to cortistatins **A**, **J**, **K** and **L**. Each of these intermediates is in turn converted into the corresponding cortistatin final product by a three- or four-step sequence involving addition of a 7-isoquinolylorganometallic intermediate followed by deoxygenation.

The Last Paragraph

The latter sequence appears to be a general route to cortistatins with divergent substitutions of the **A**, **B** and **C** rings and it is anticipated that it will allow for late-stage introduction of diversely substituted isoquinoline groups and other heterocycles at position C17.

Acknowledgement

Thanks
for your kind attention !