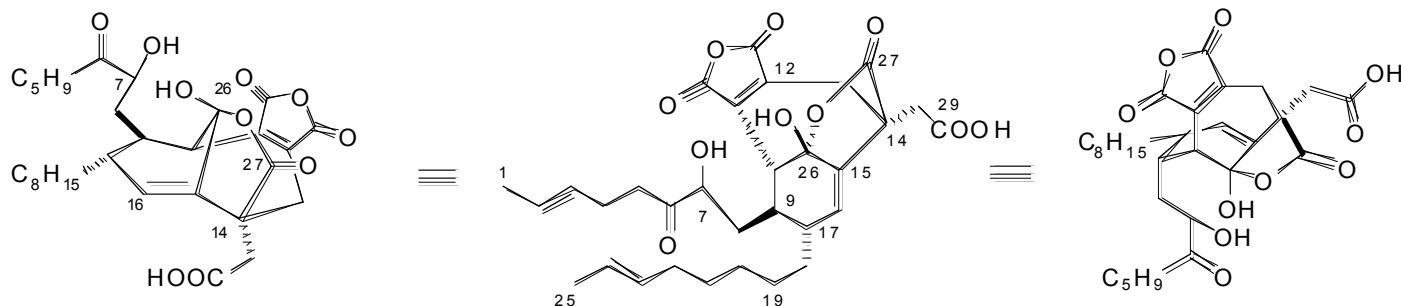


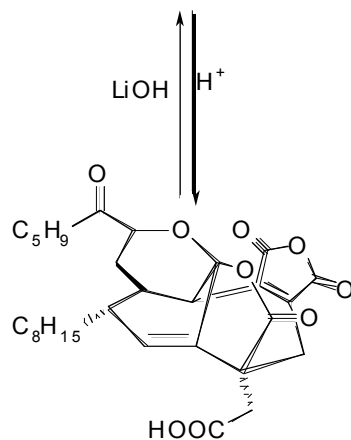
Synthesis of the Phomoidrides (CP 225,917 & CP 263,114)

Chem. Rev. **2003**, *103*, 2691.



(+)-Phomoidride A; C7 = S (CP-225,917)

(+)-Phomoidride C; C7 = R



(-)-Phomoidride B; C7 = S (CP-263,114)

(-)-Phomoidride D; C7 = R

Isolated from a fungus found on the twigs of a juniper tree in Texas (Pfizer, 1997)

Found to inhibit Ras farnesyl transferase and squalene synthase

- In studies as cholesterol lowering and anti-cancer drugs

Relative configuration determined by NMR analysis

Absolute configuration determined by synthesis (Nicolaou, 2000)

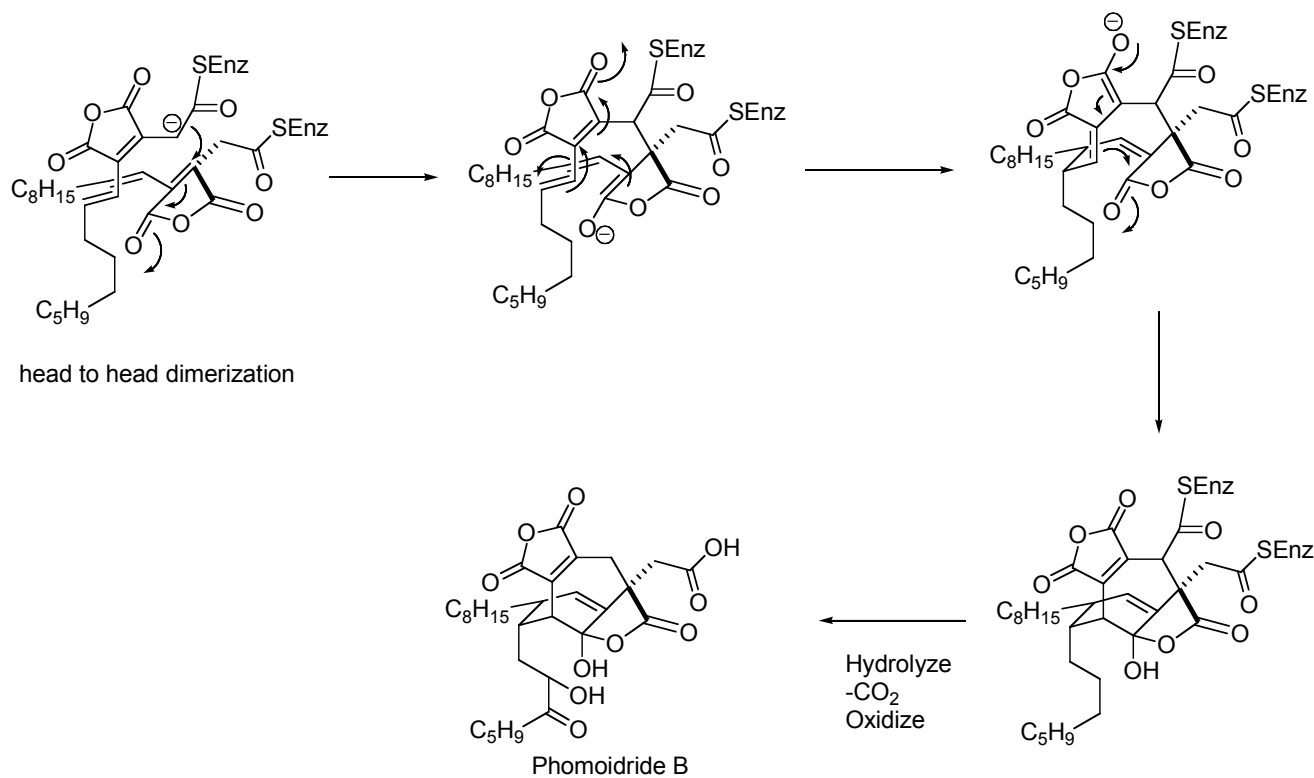
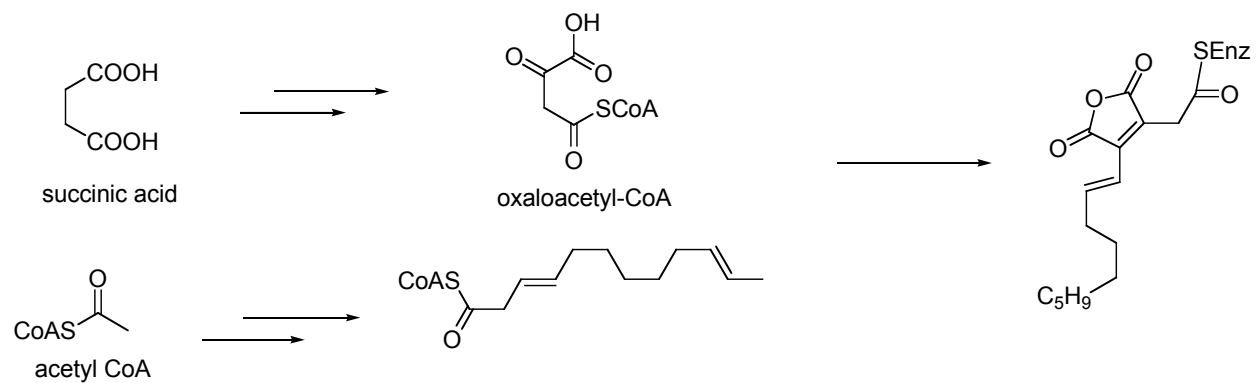
4 total syntheses and >18 partial syntheses

Key features are a [4.3.1] bicyclo system containing a bridgehead double bond; quat center (C14); and maleic anhydride moiety

All four compounds have been isolated from natural sources

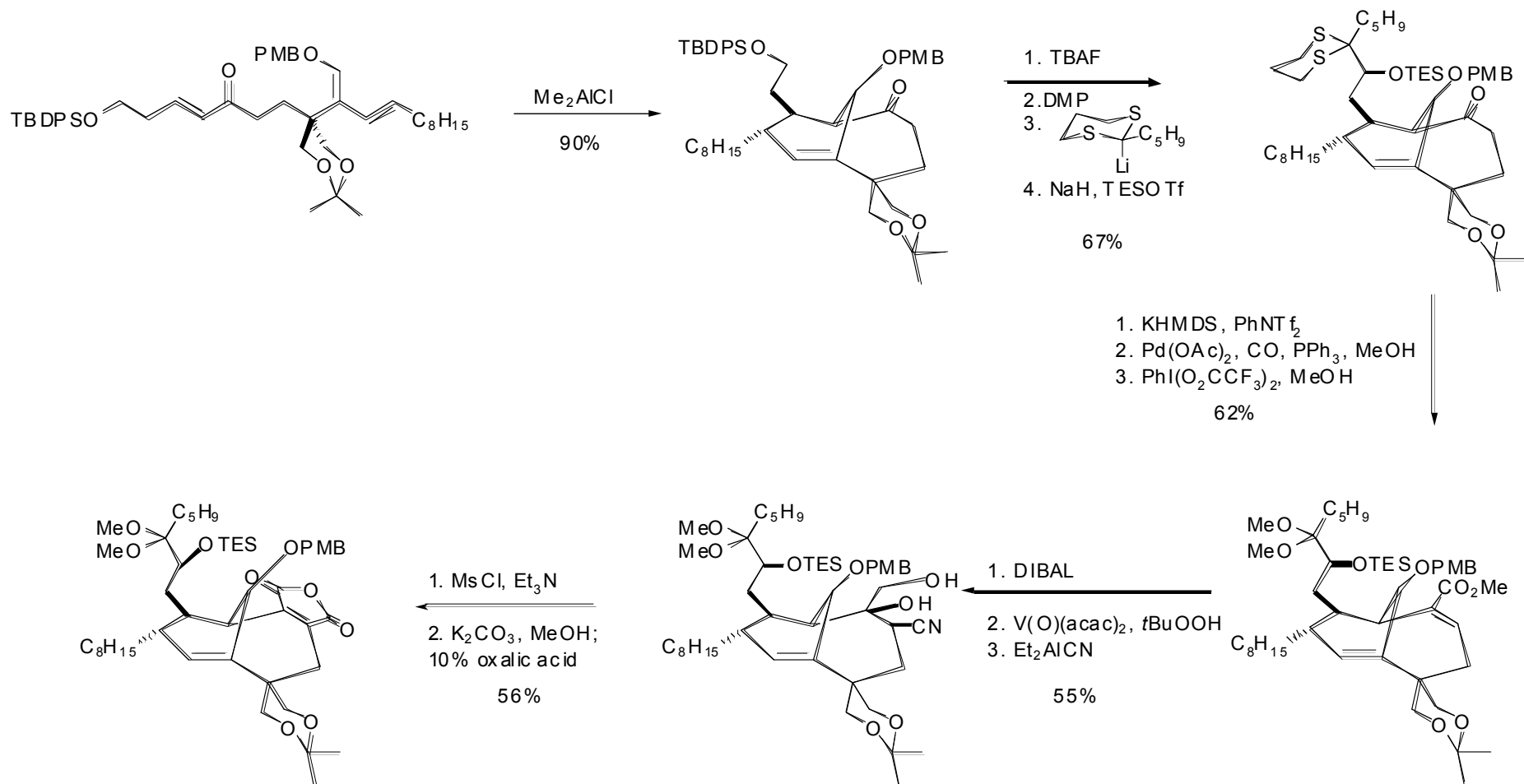
Proposed Biosynthesis

Sulikowski; *JACS*, **2000**, 122, 420.

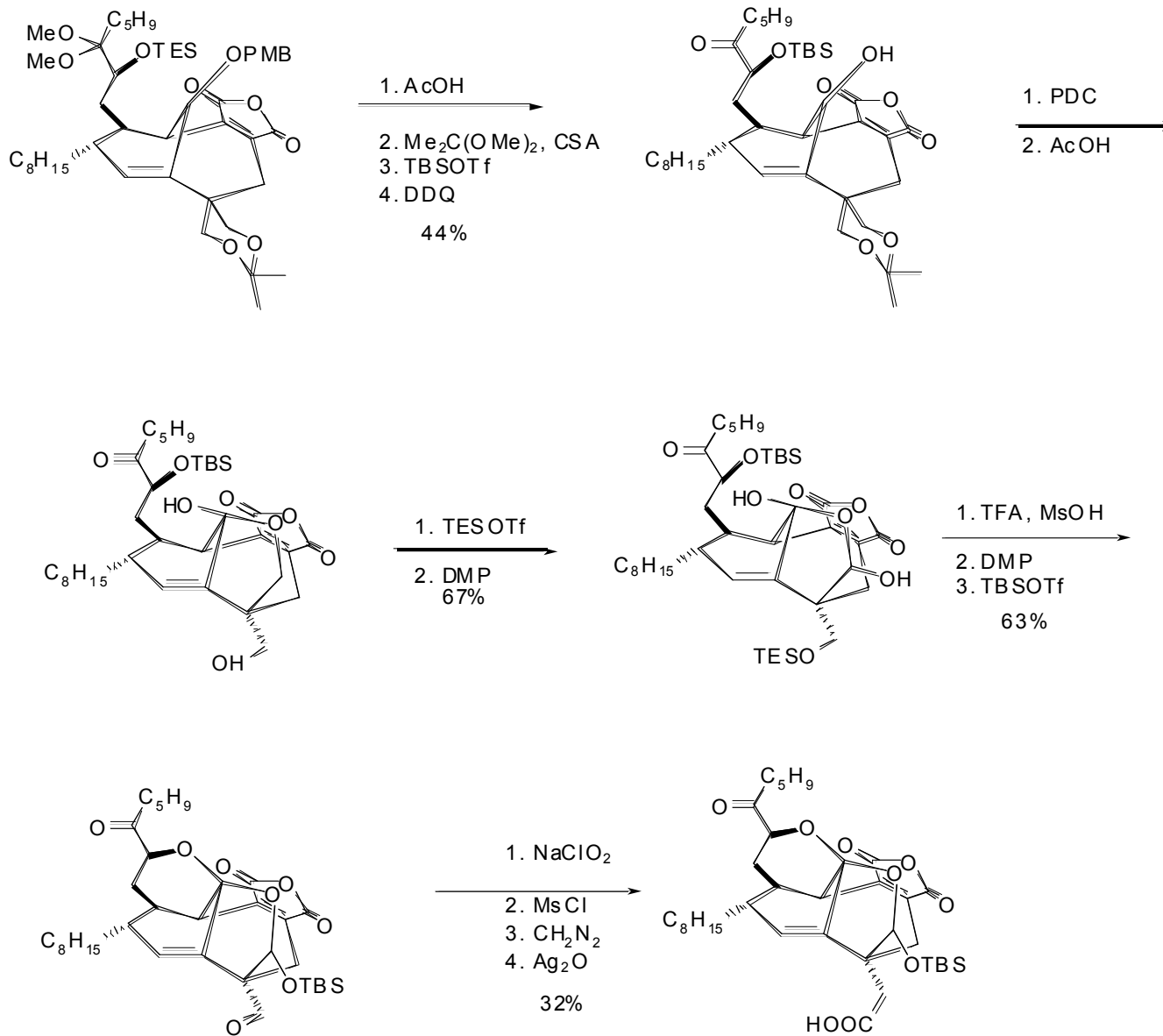


Nicolaou's Total Synthesis

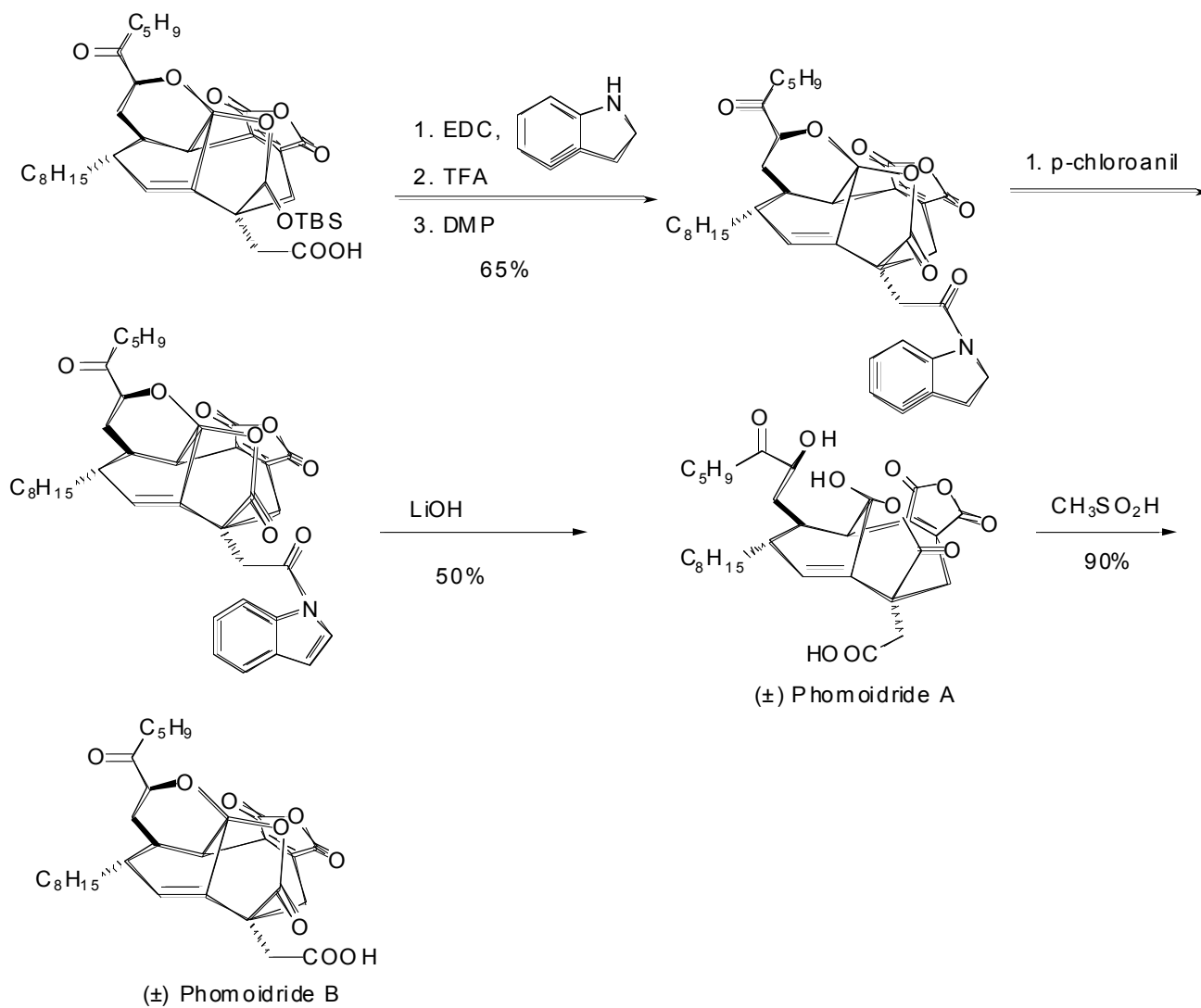
Angew. Chem. Int. Ed. **1999**, *38*, 1669; 1676



Nicolaou cont.

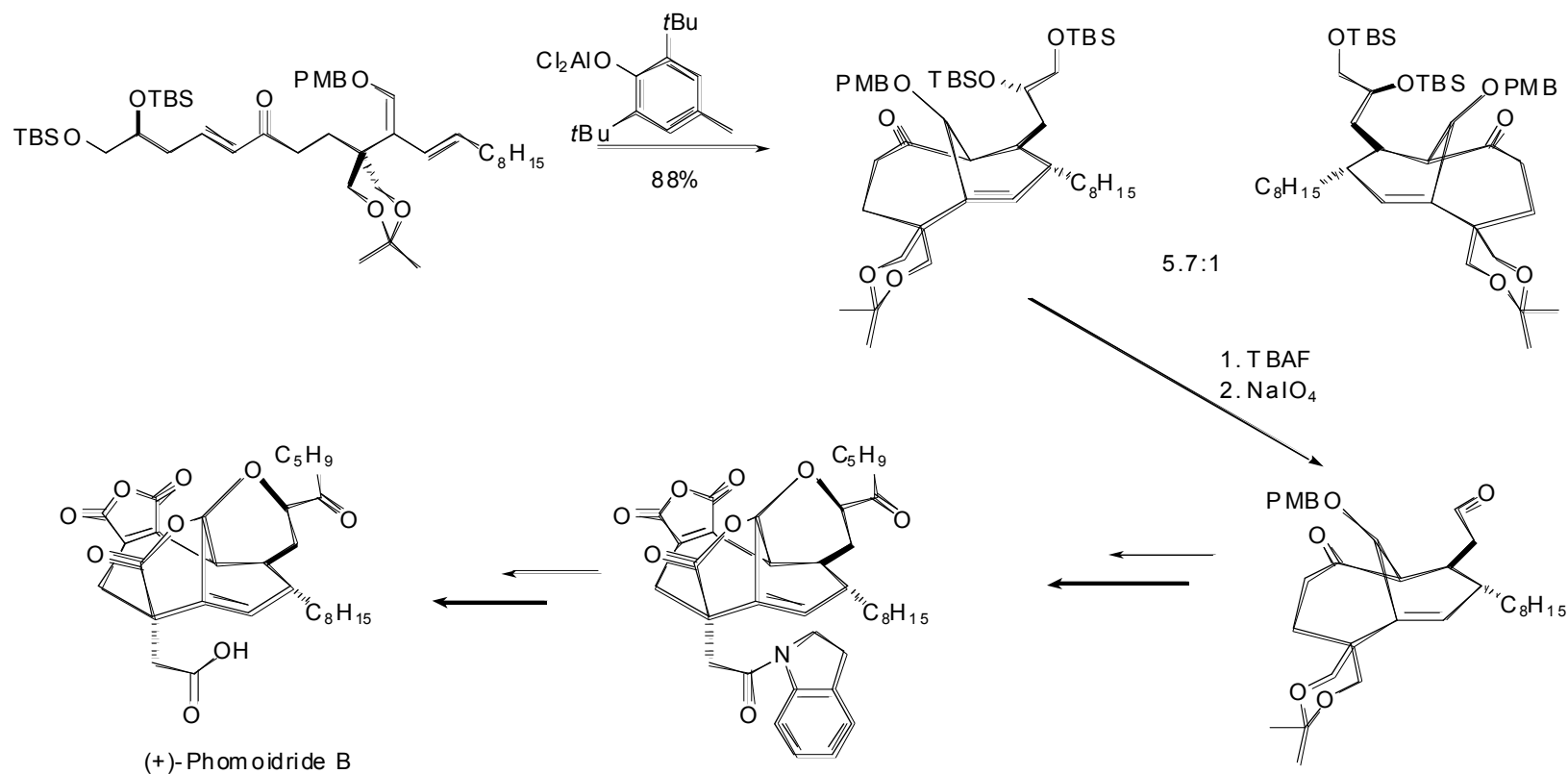


Completion of Nicolaou's Synthesis



Nicolaou's Asymmetric Synthesis-Determination of Absolute Configuration

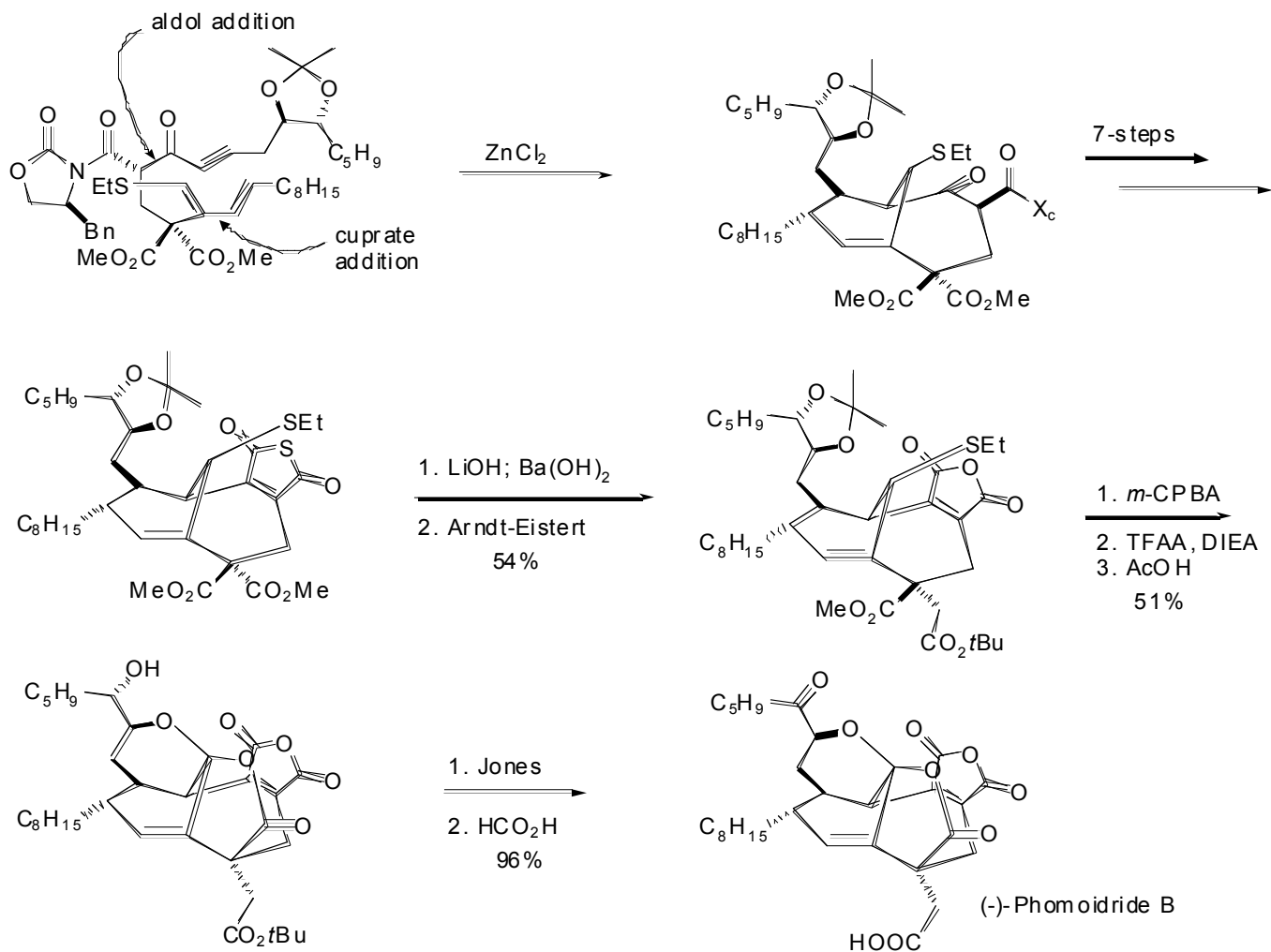
Angew. Chem. Int. Ed. **2000**, *39*, 1829



Compared with compound obtained from natural source: opposite rotation

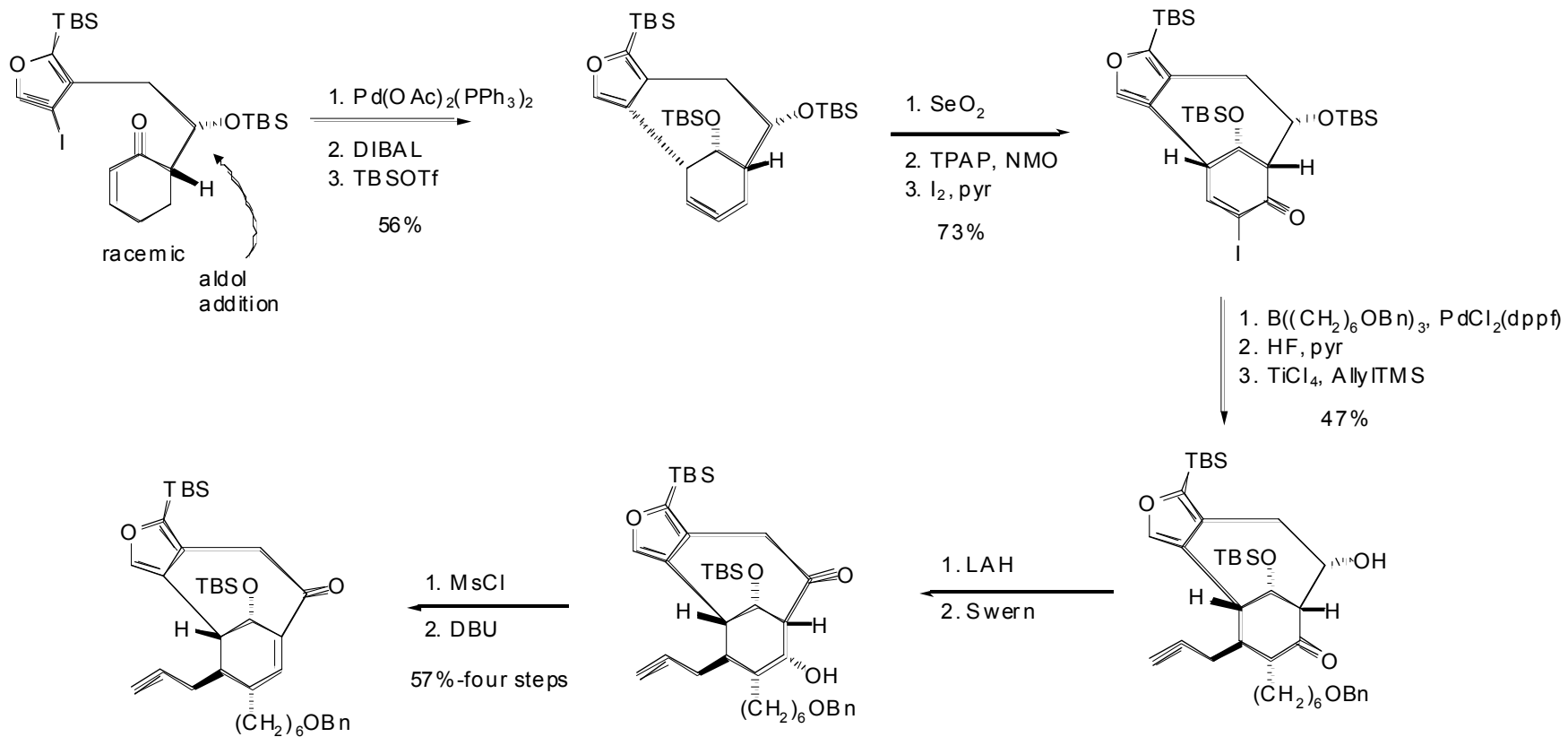
Fukuyama's Synthesis- 1st Asymmetric Synthesis of Natural Enantiomer

JACS 2000, 122, 7825

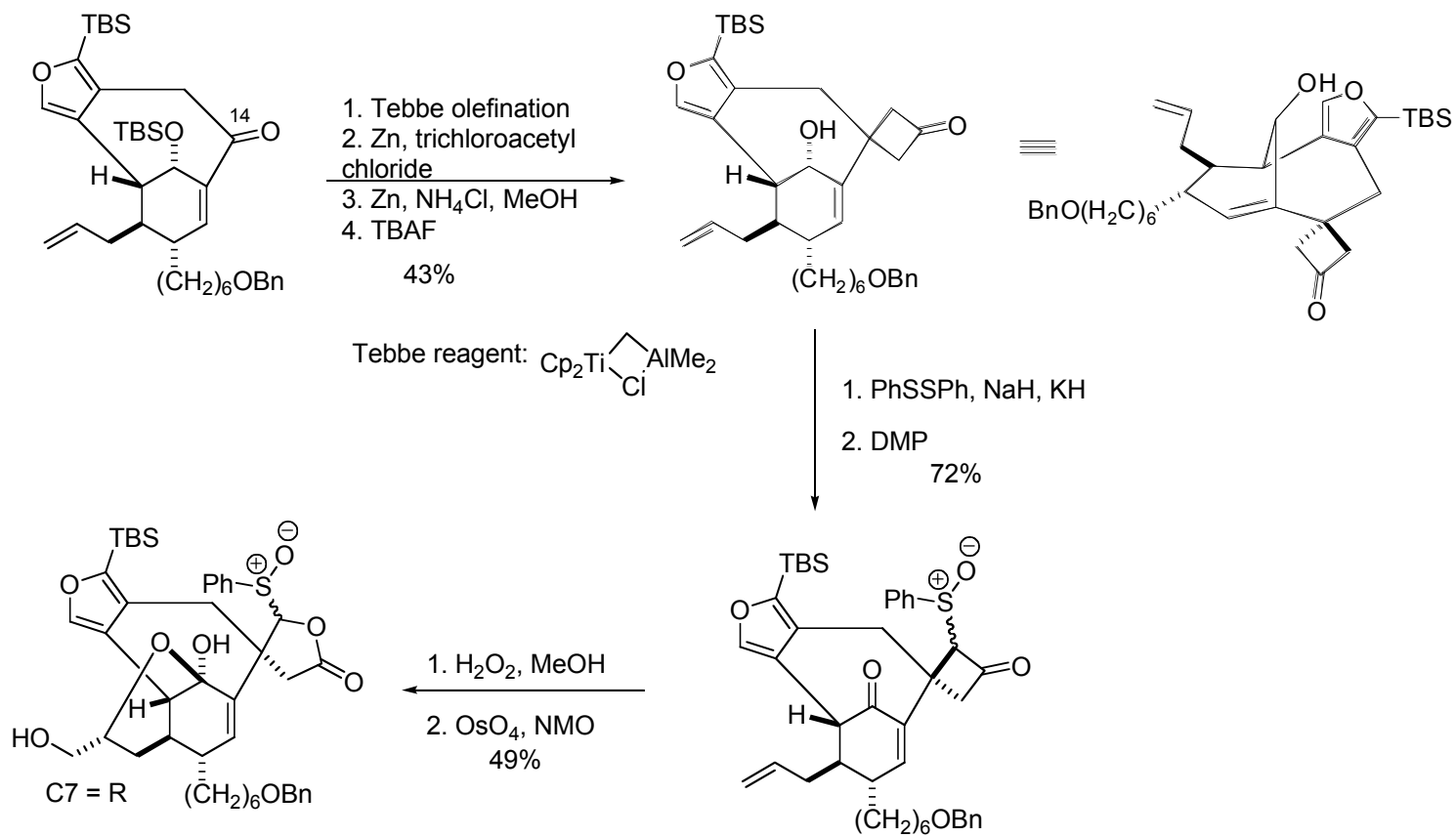


Danishefsky's Total Synthesis: Insight into C7 Configuration

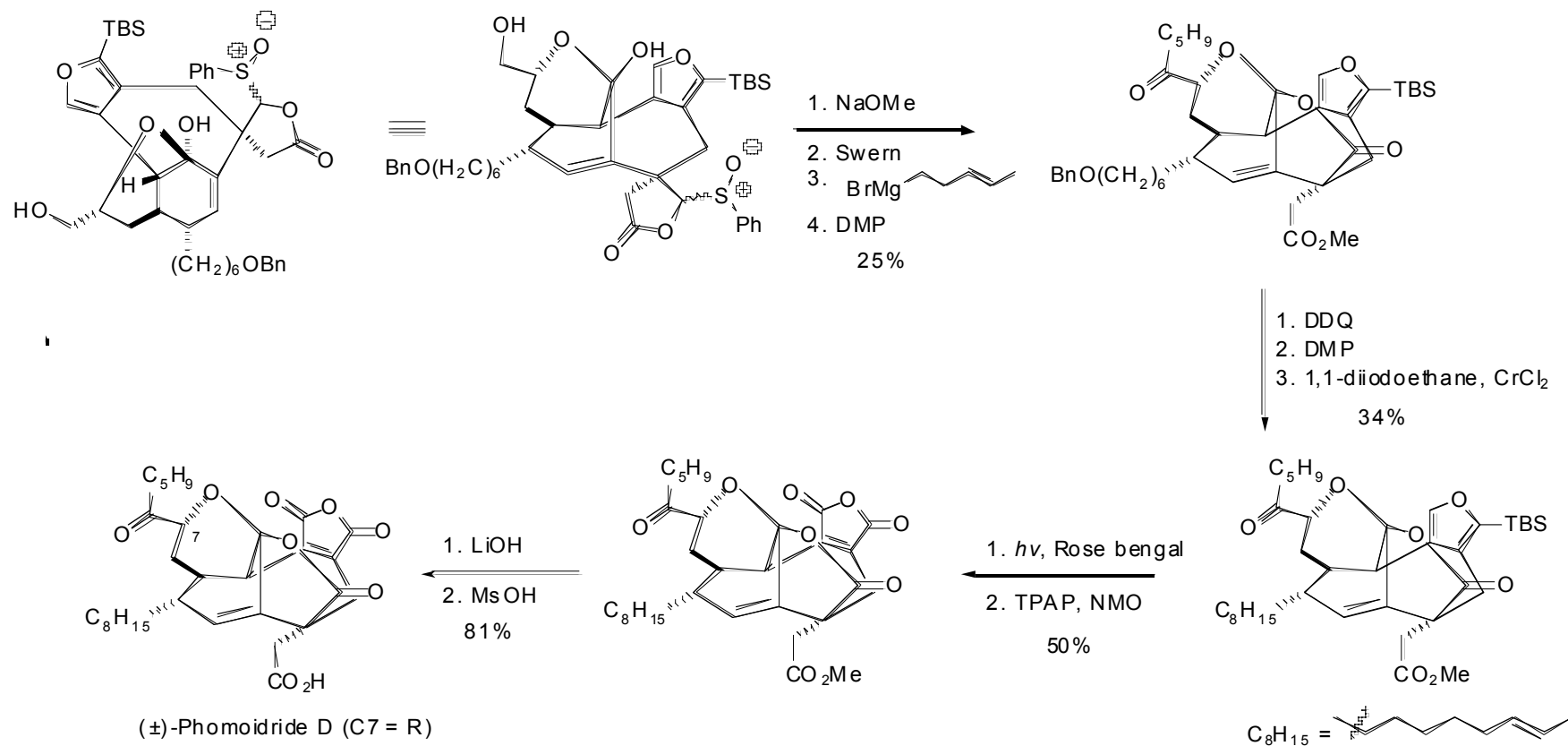
Angew. Chem. Int. Ed. **1999**, *38*, 1485; **1999**, *38*, 3197



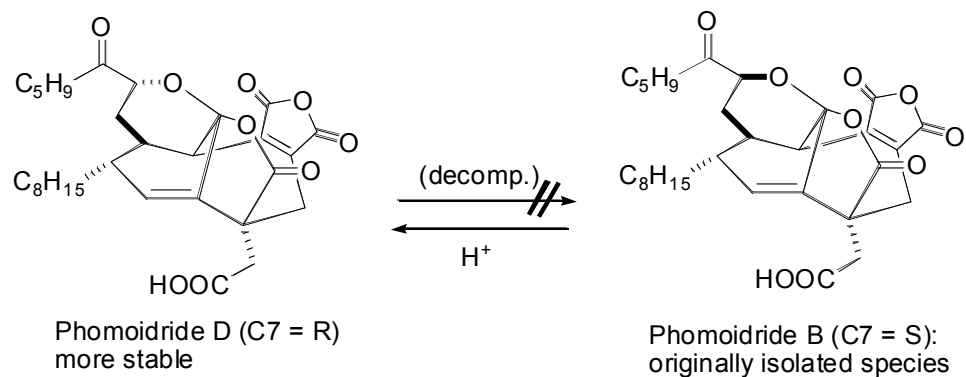
Danishefsky cont.



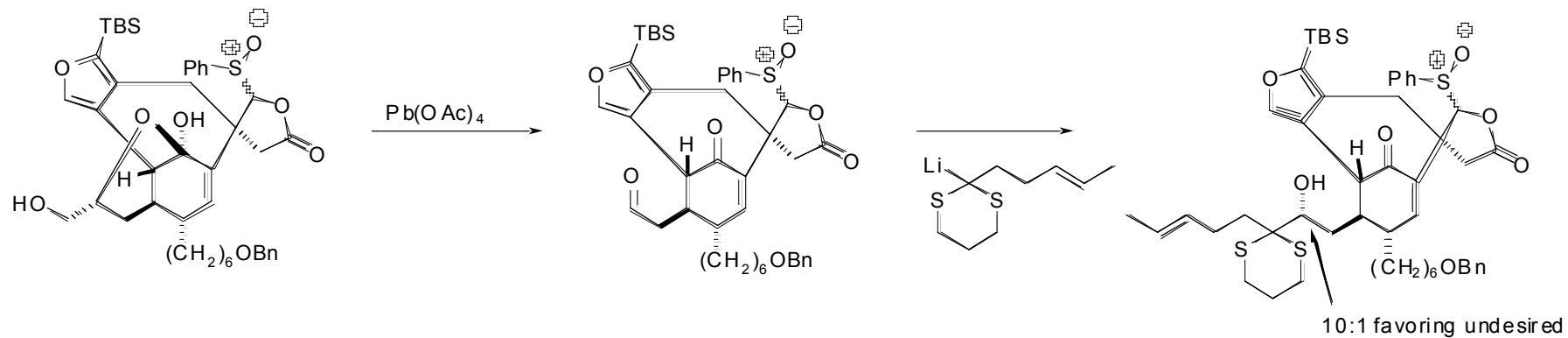
Completion of 7-*epi* Phomoidride B



The C7 Configuration

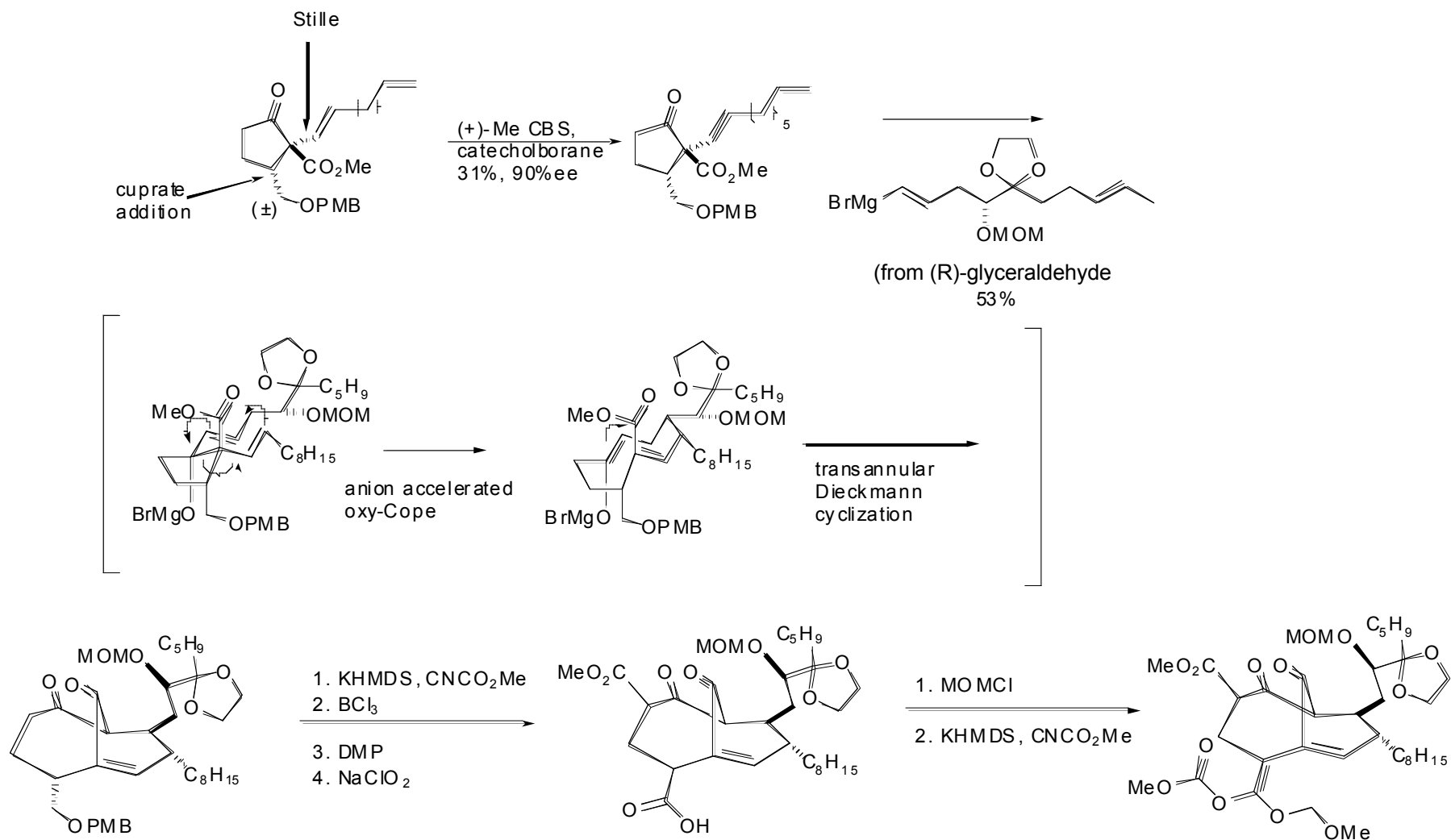


7 step sequence

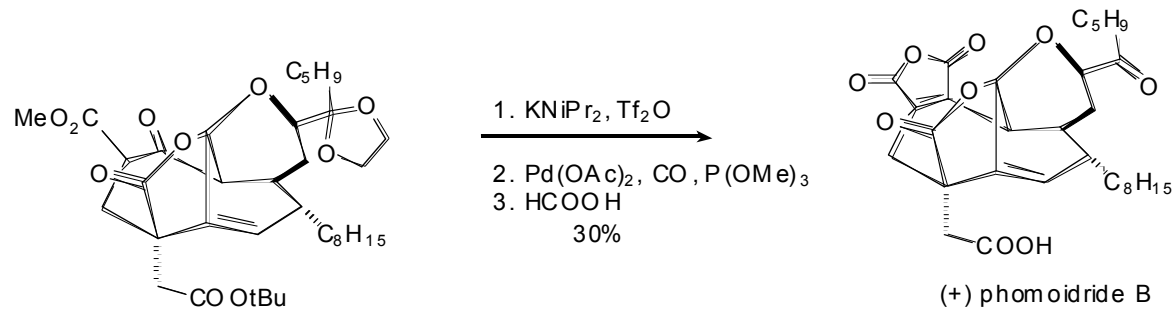
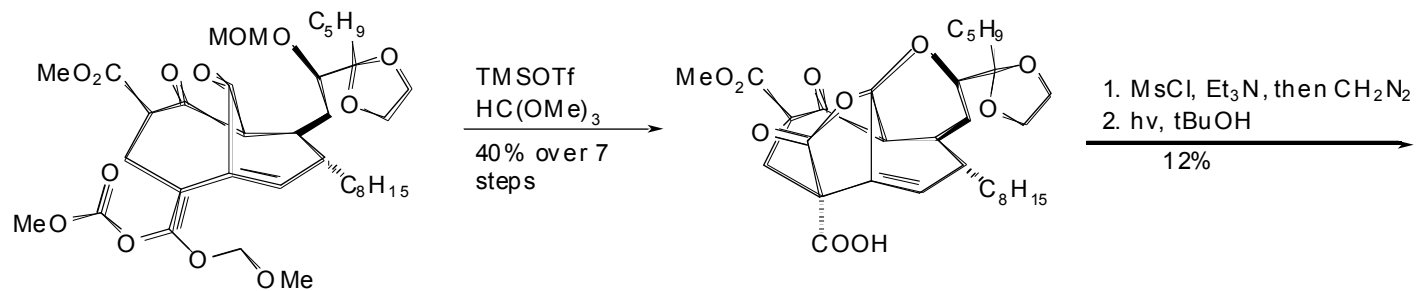


Shair's Total Synthesis of *ent*-Phomoidride B

JACS, 2000, 122, 7424.

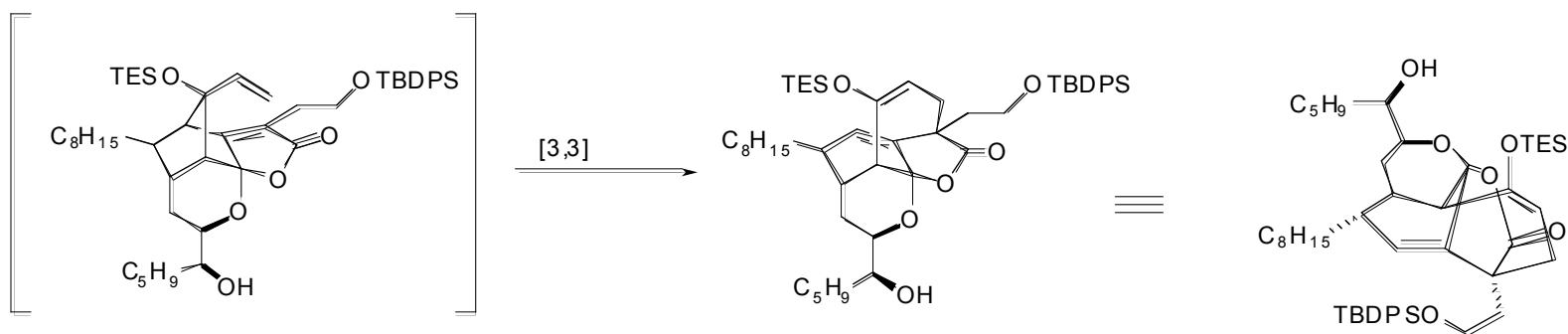
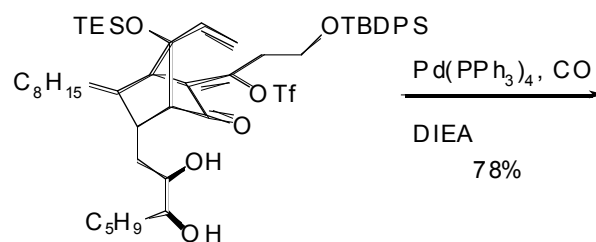
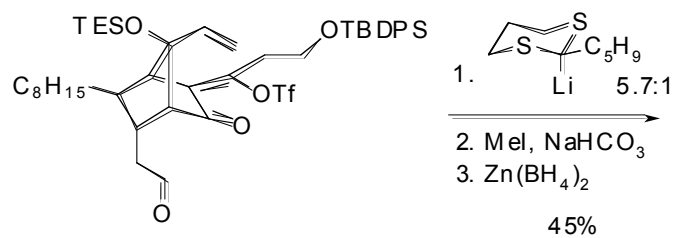
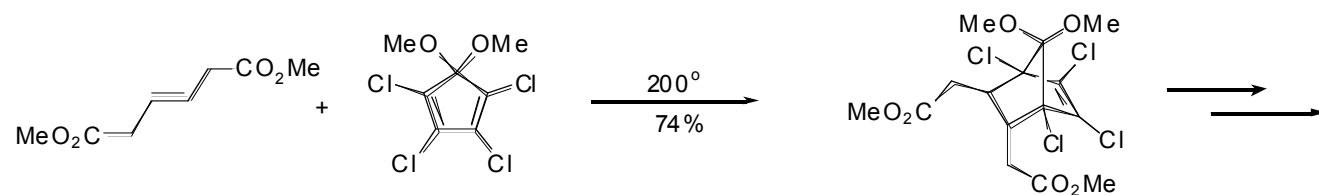


Completion of Shair's Synthesis



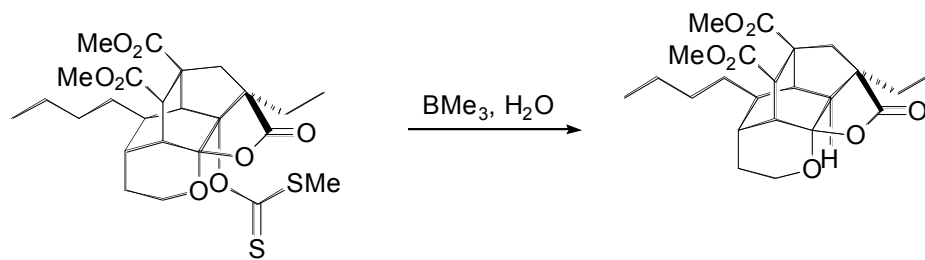
Leighton's Approach

JOC, 2003, 68, 1693



Tin-Free Deoxygenation

JACS, ASAP



Proposed Mechanism

