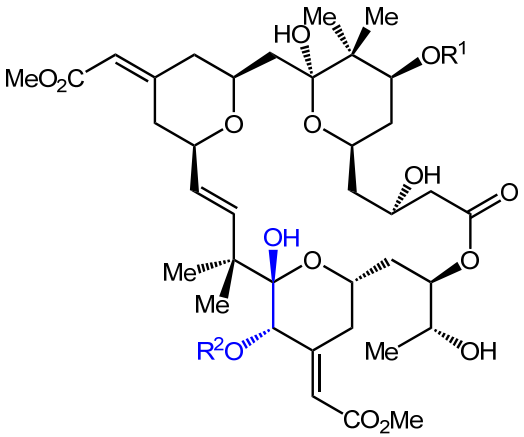
2010-12-21 Report: Duo-Sheng Wang
Checker: Qing-An Chen

Total Synthesis of Bryostatin 16 Using a Pd-Catalyzed Diyne Coupling as Macrocyclization Method and Synthesis of C20-*epi*-Bryostatin 7 as a Potent Anticancer Agent

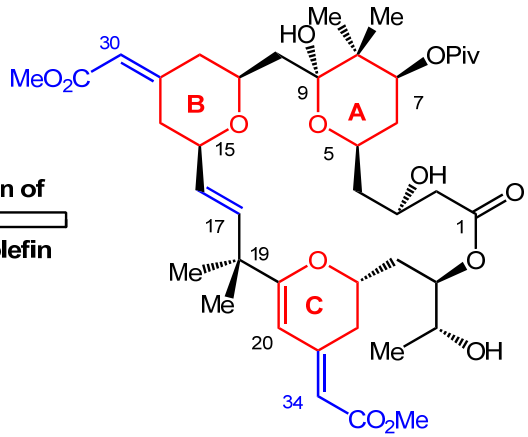
Trost, B. M.* *et al* *J. Am. Chem. Soc.* **2010**, *132*, 16403-16416.
Nature **2008**, *456*, 485-488.

Bryostatins



Bryostatin 1, 2, 4-9, 12, 14, 15

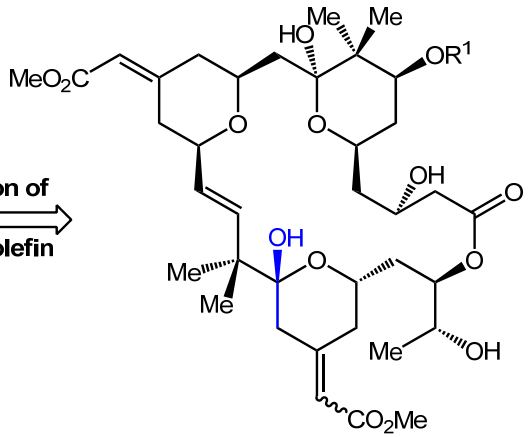
oxidation of C19-20 olefin



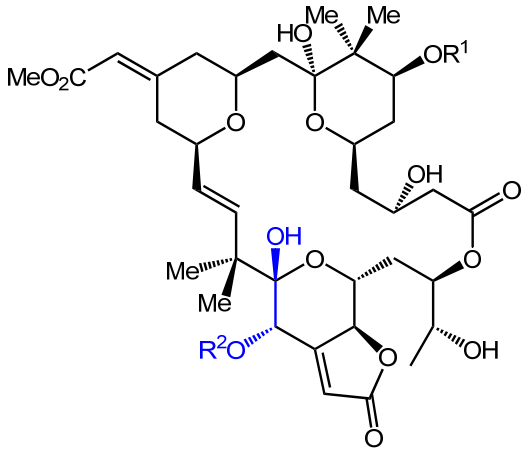
Bryostatin 16 (**1**)

Bryostatin 17 (C21-34 isomer)

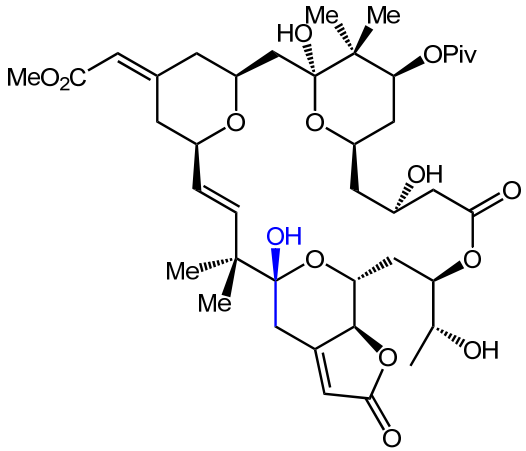
hydration of C19-20 olefin



Bryostatin 10, 11, 13, 18

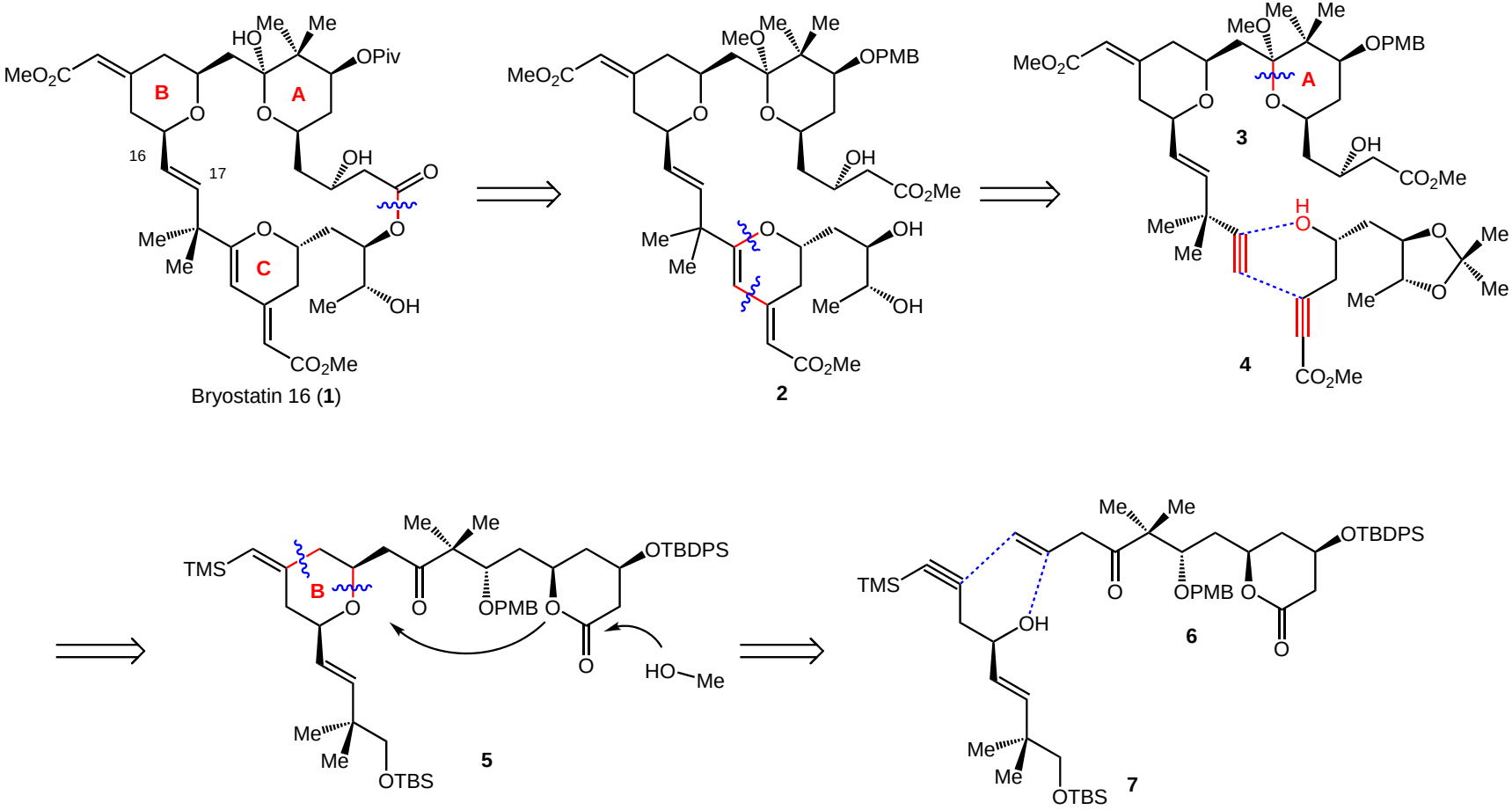


Bryostatin 3, 19



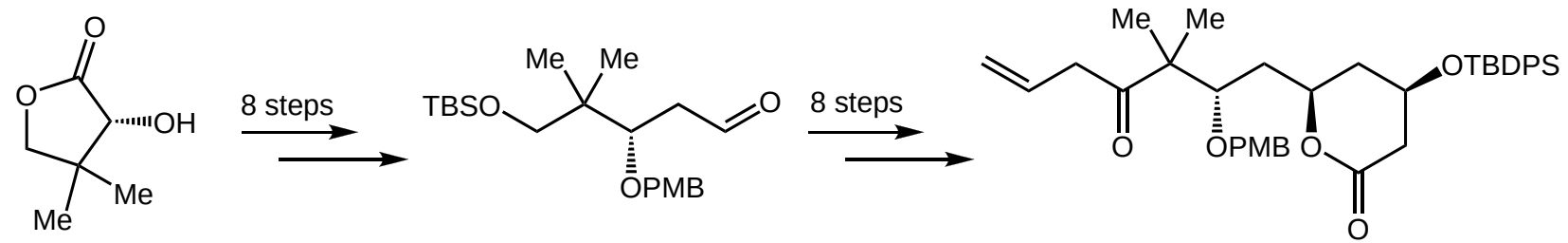
Bryostatin 20

First-Generation Strategy



Synthesis of Alkene 6

Previous Synthesis of Alkene **6**

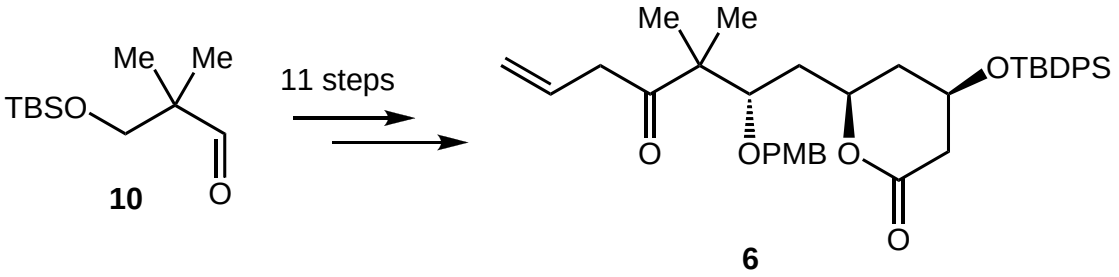


(*R*)-Pantolactone (**8**) **9** **6**

16 overall steps

Trost, B. M.* *et al* *J. Am. Chem. Soc.* **2007**, *129*, 2206-2207.

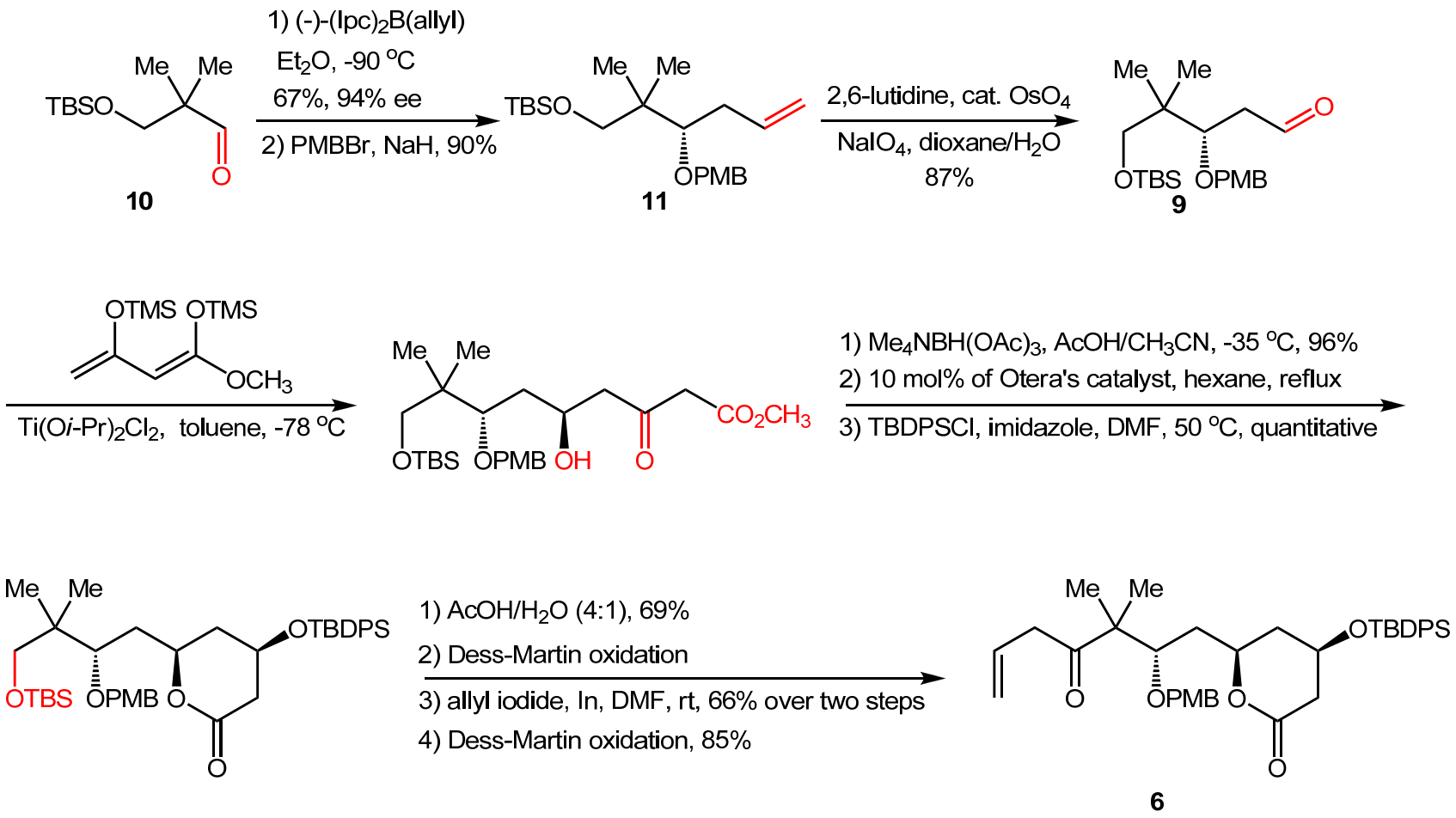
Improved Synthesis of Alkene **6**



10 **6**

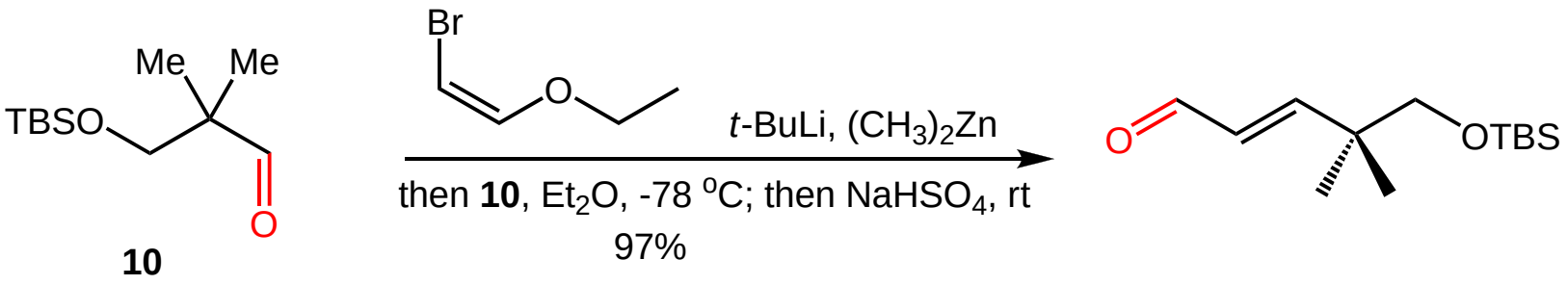
Trost, B. M.* *et al* *Nature* **2008**, *456*, 485-488.

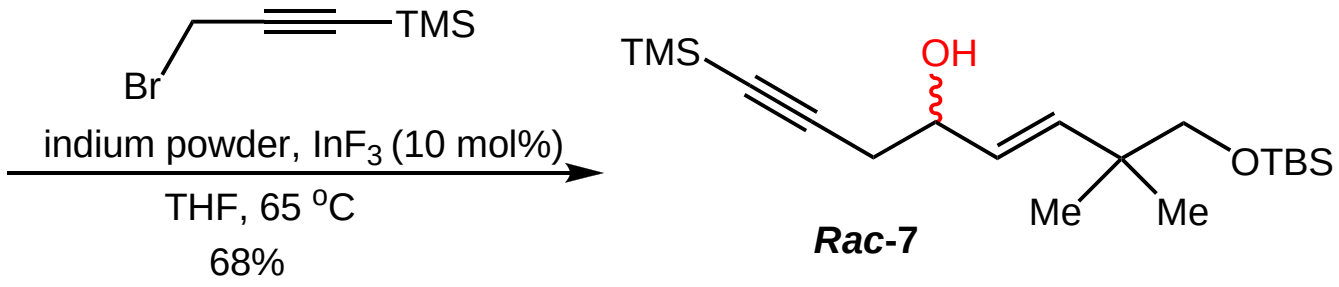
Synthesis of Alkene 6

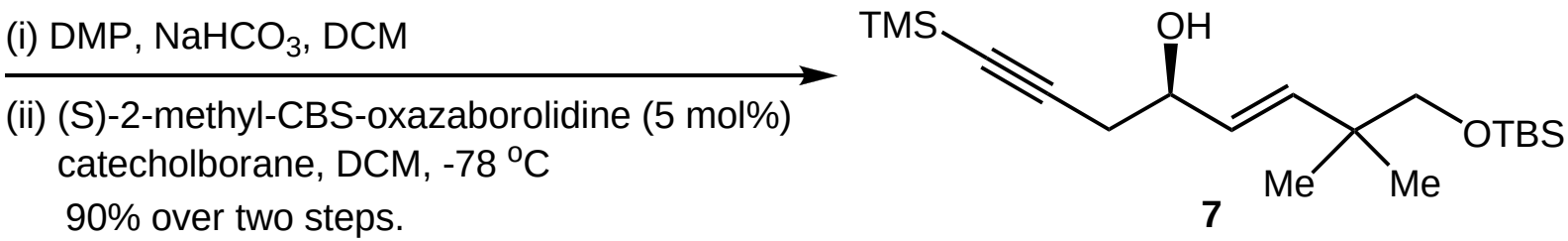


Trost, B. M.* *et al* *Nature* **2008**, *456*, 485-488.

Synthesis of 7

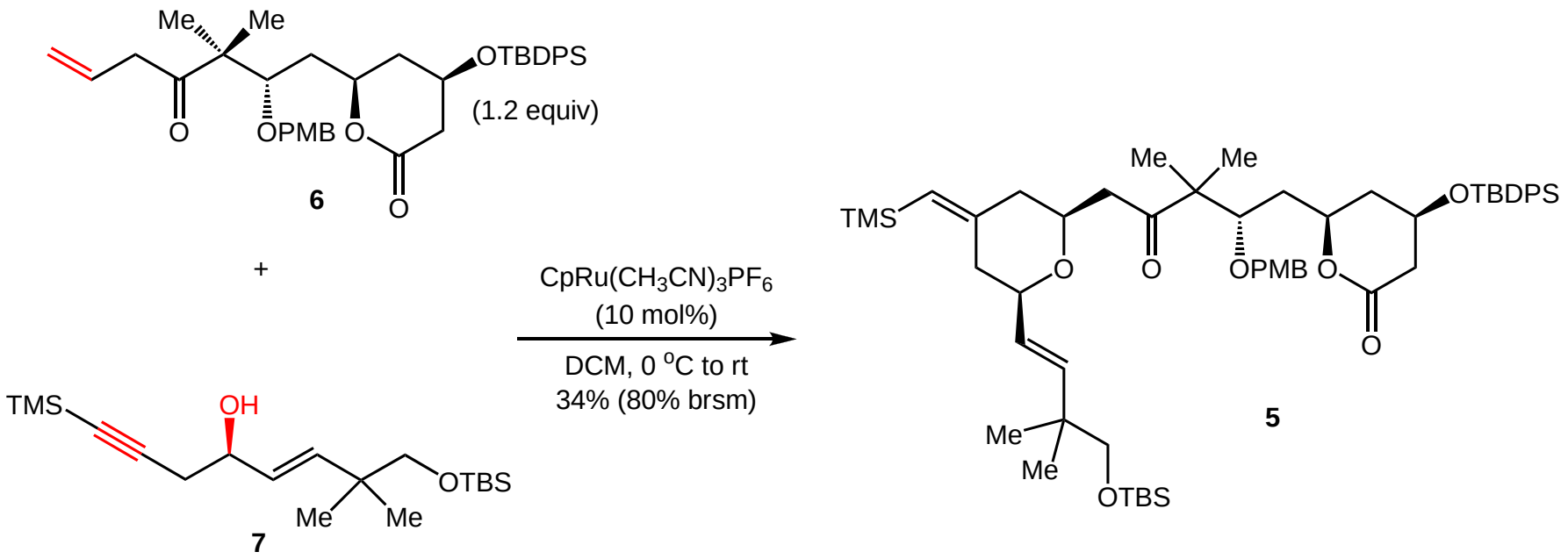




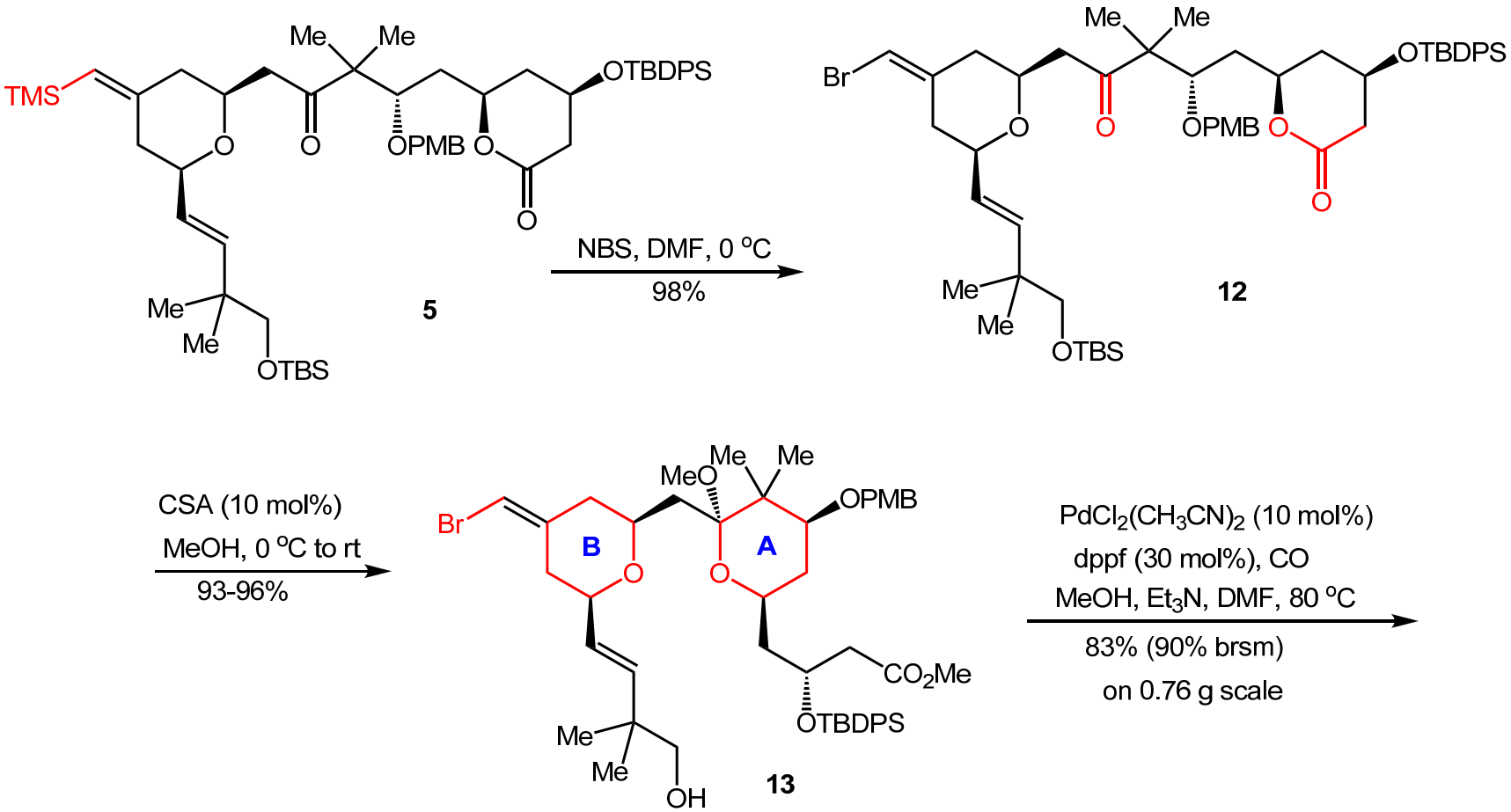


Trost, B. M.* *et al* *Nature* **2008**, *456*, 485-488.

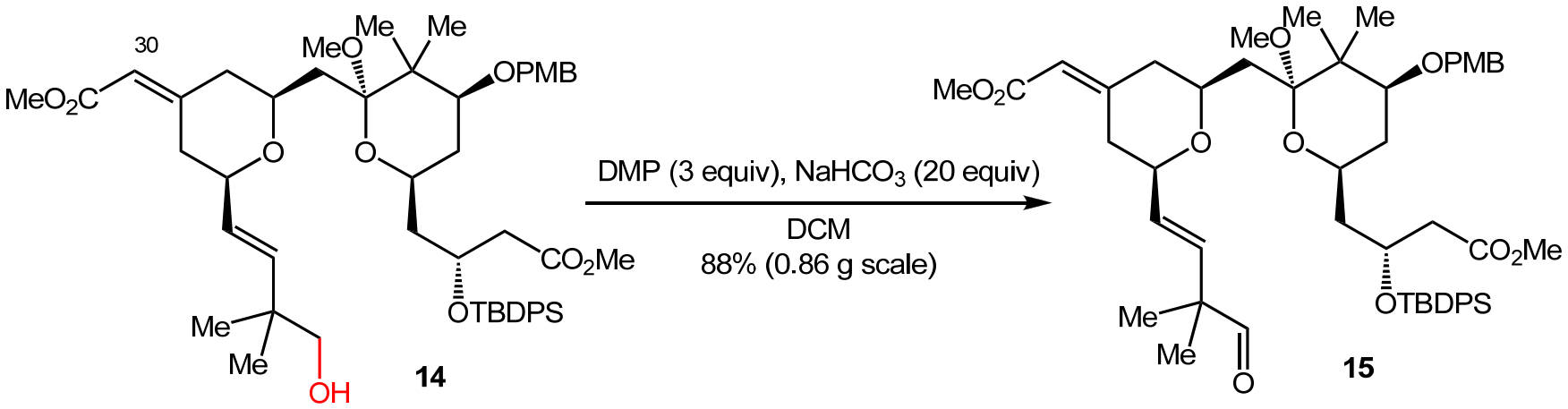
Synthesis of *cis*-Tetrahydropyran **5**



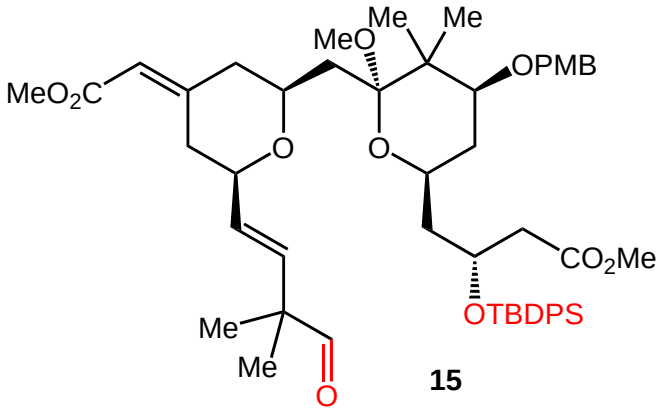
Synthesis of Aldehyde **15**



Synthesis of Aldehyde **15**



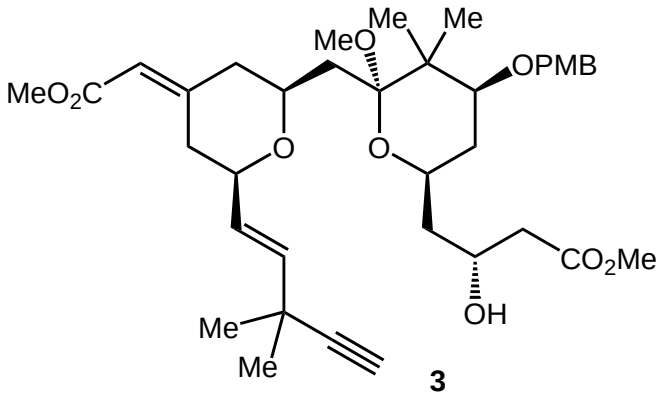
Synthesis of the Key Coupling Partner **3**



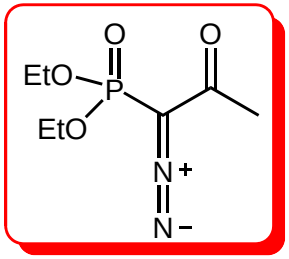
15

1) Ohira-Bestmann reagent, 100%

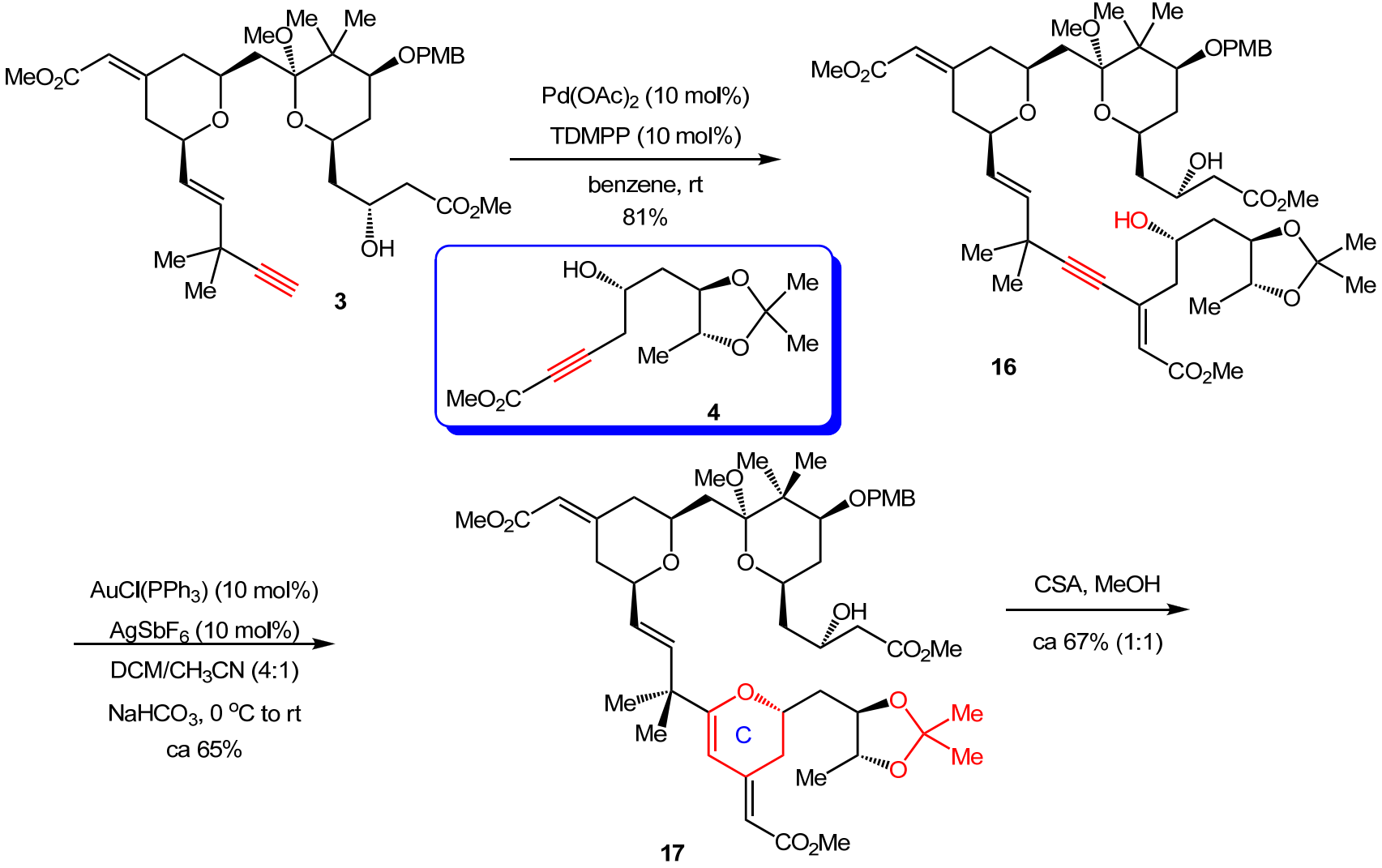
2) TBAF (1.1 equiv)
20 mol% HOAc
0.06 M, THF, rt
90% (96% brsm)



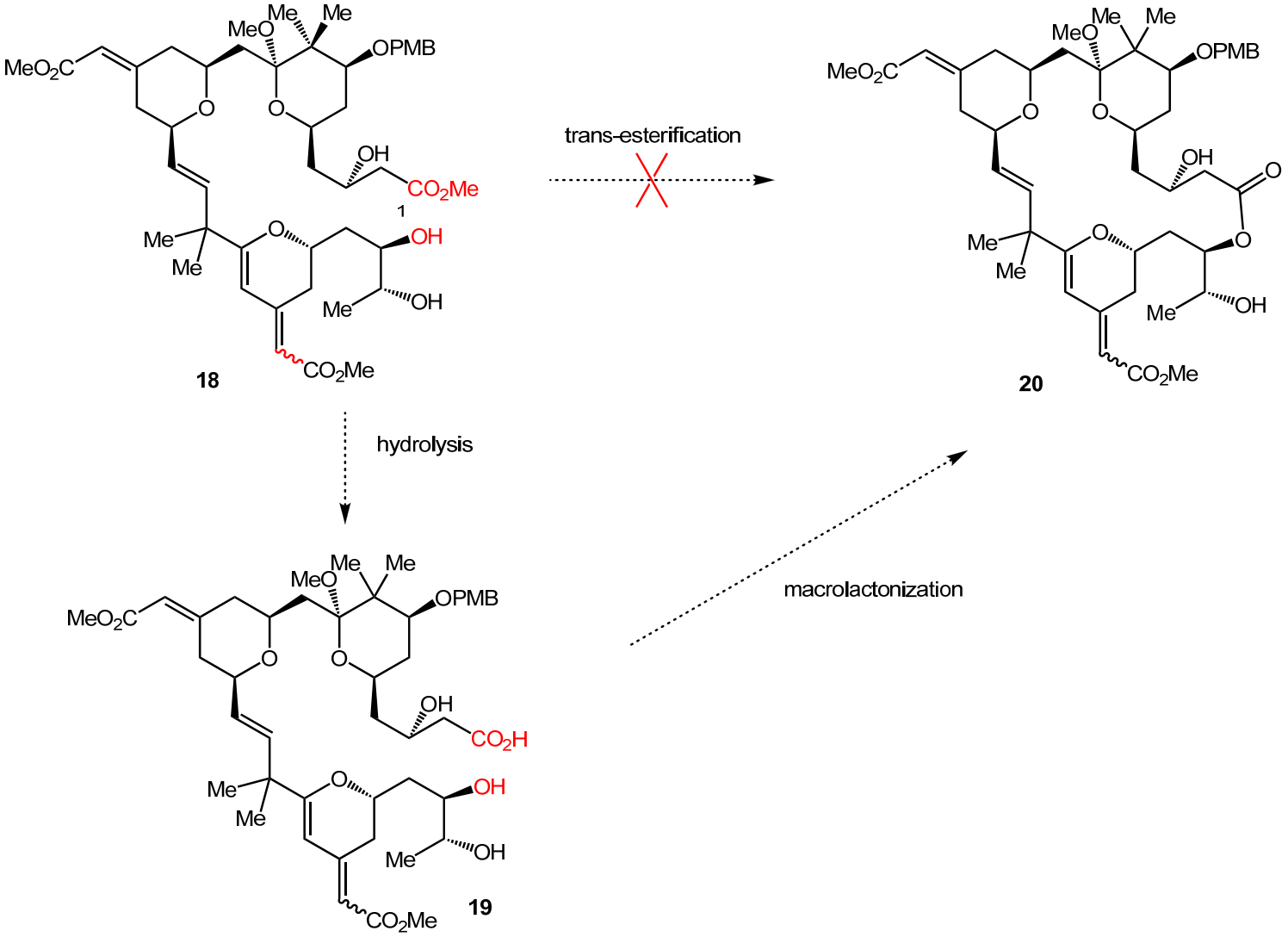
3



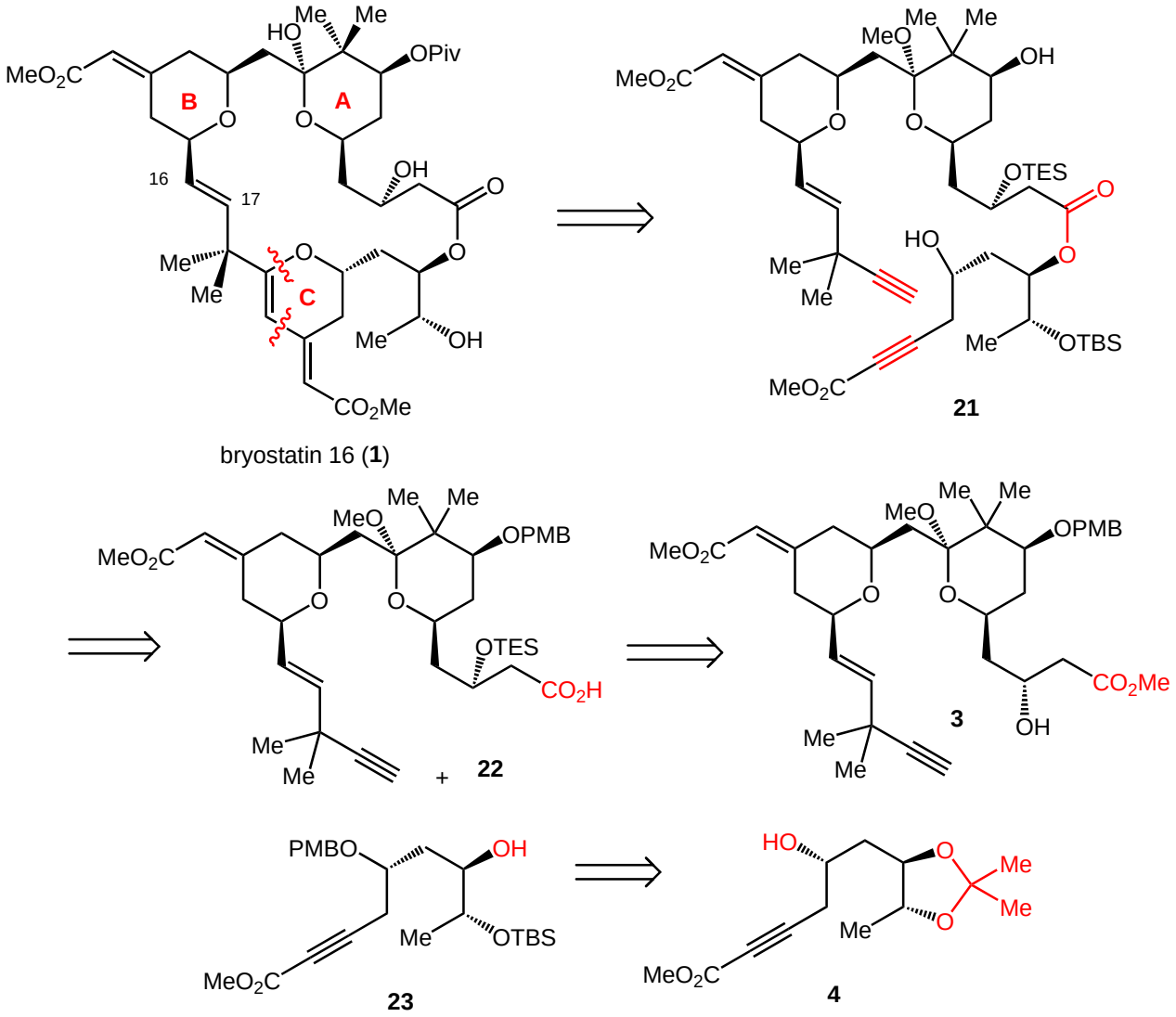
End Game of the First-Generation Strategy



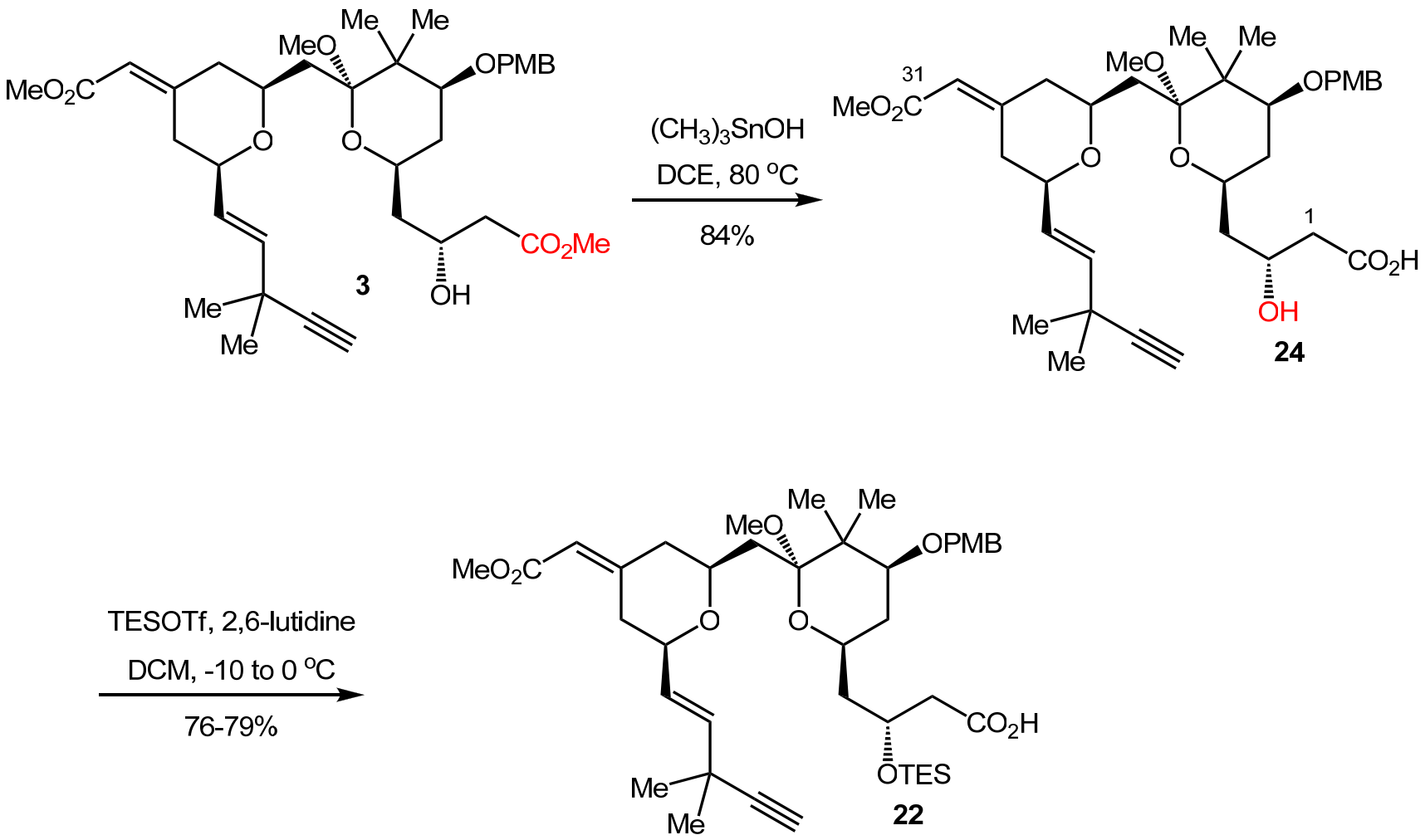
End Game of the First-Generation Strategy



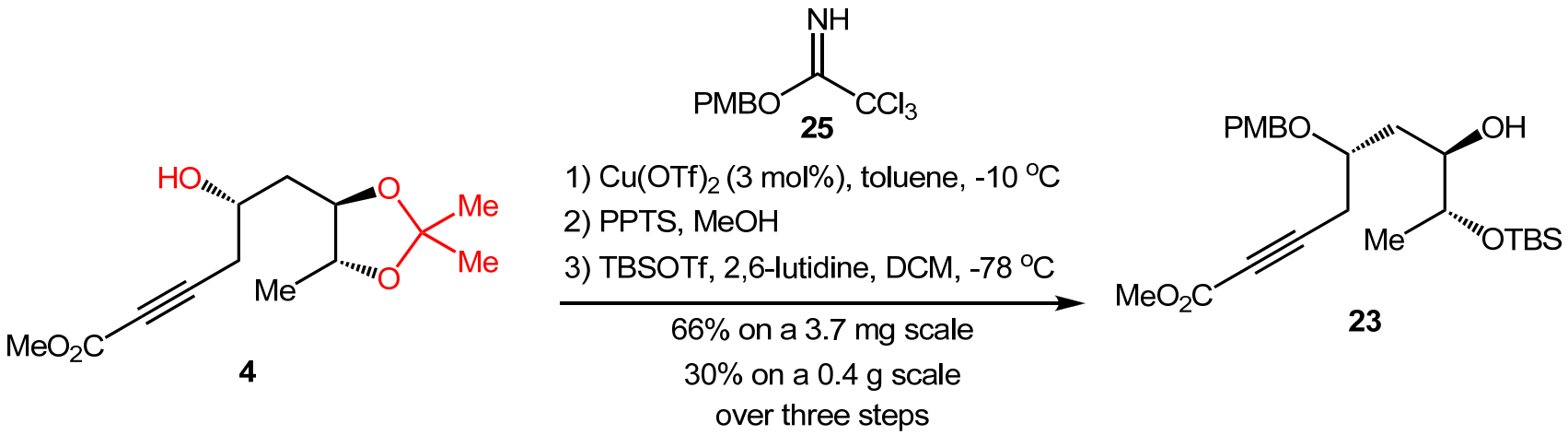
Synthetic Plan of the Second-Generation Strategy



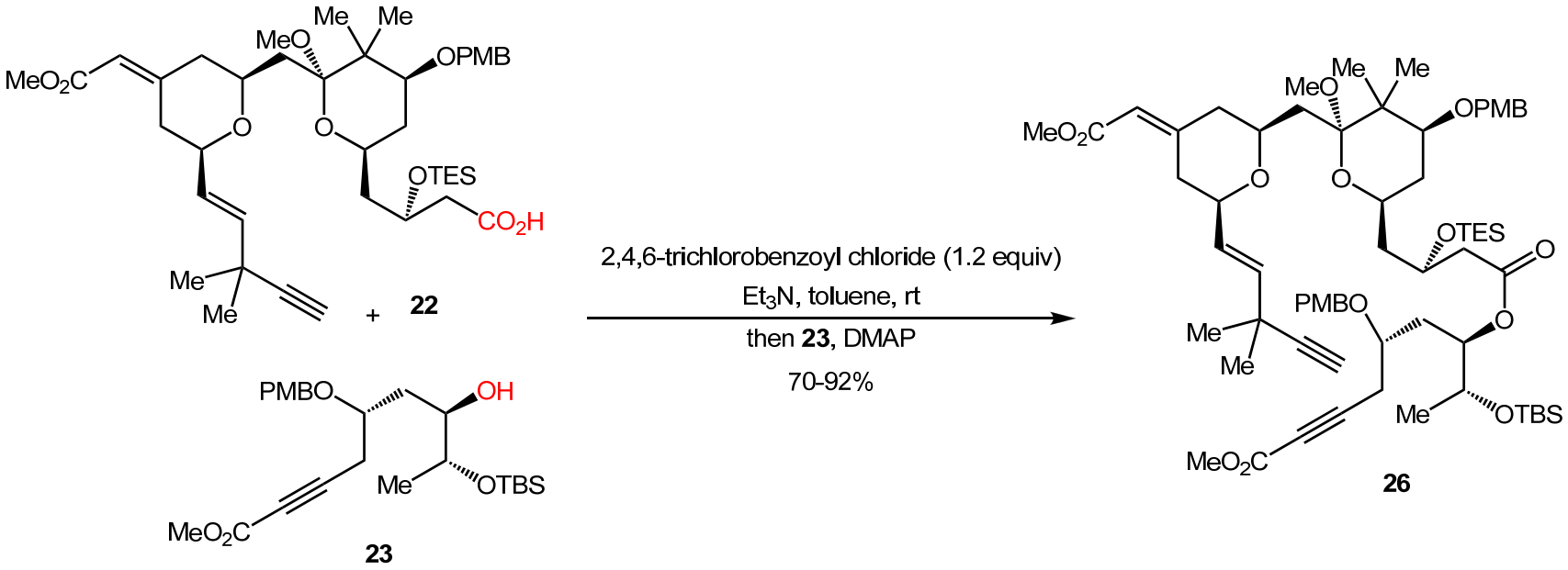
Synthesis of Acid Fragment **22**



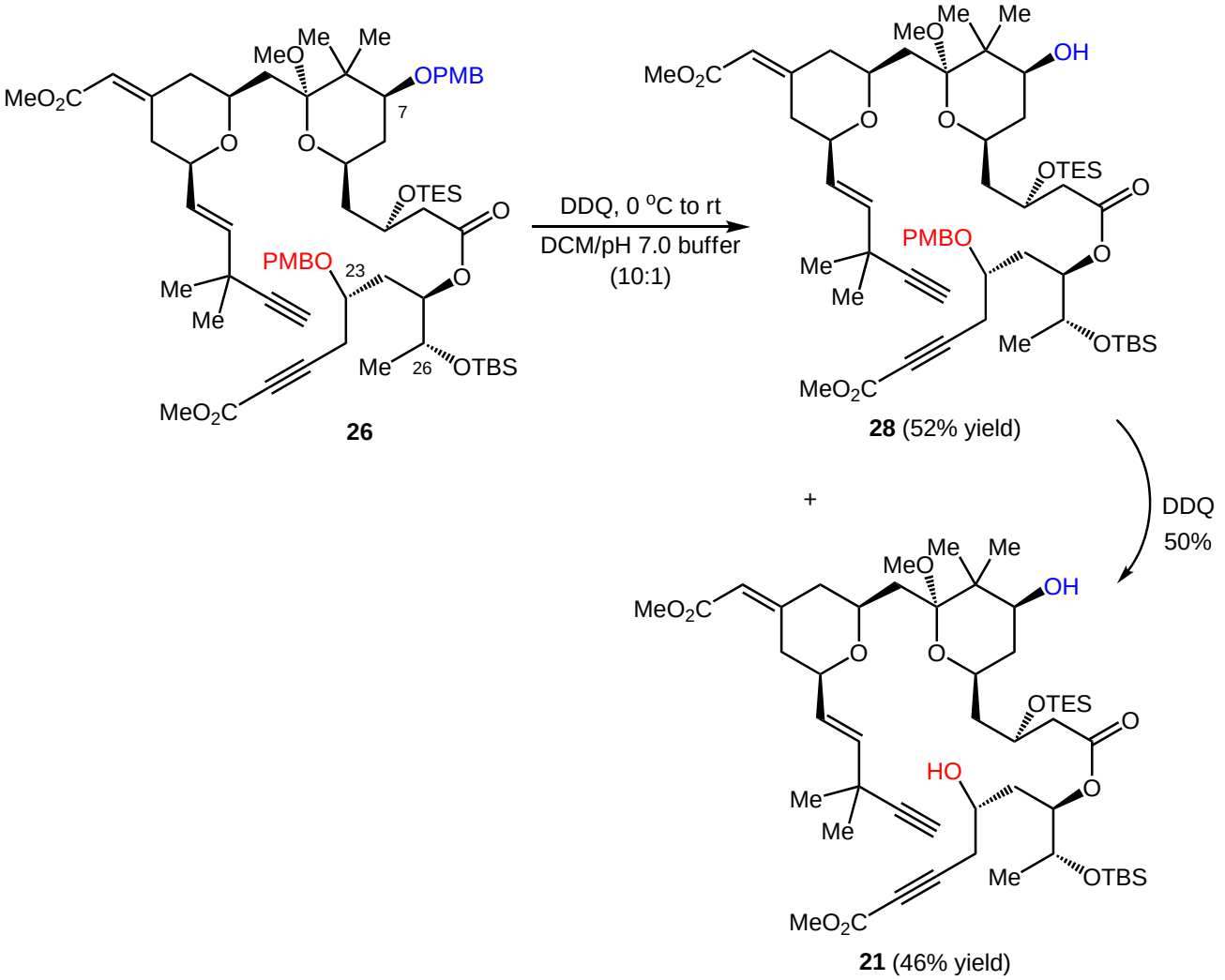
Synthesis of **23**



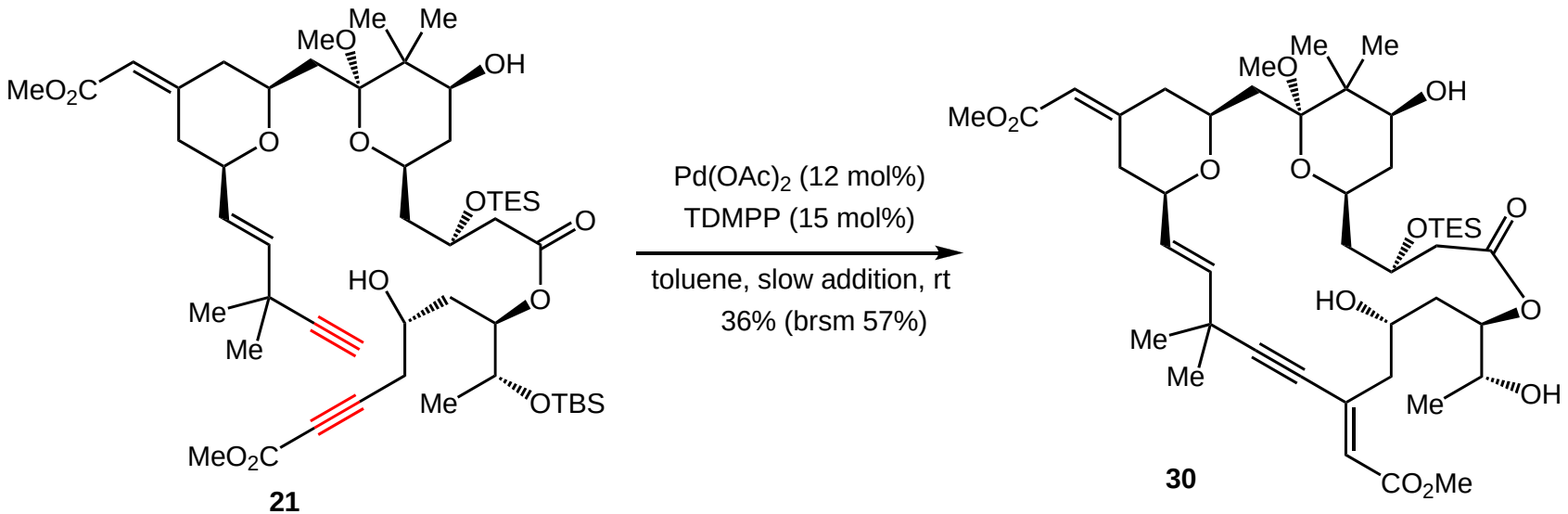
Esterification between Acid **22** and Alcohol **23**



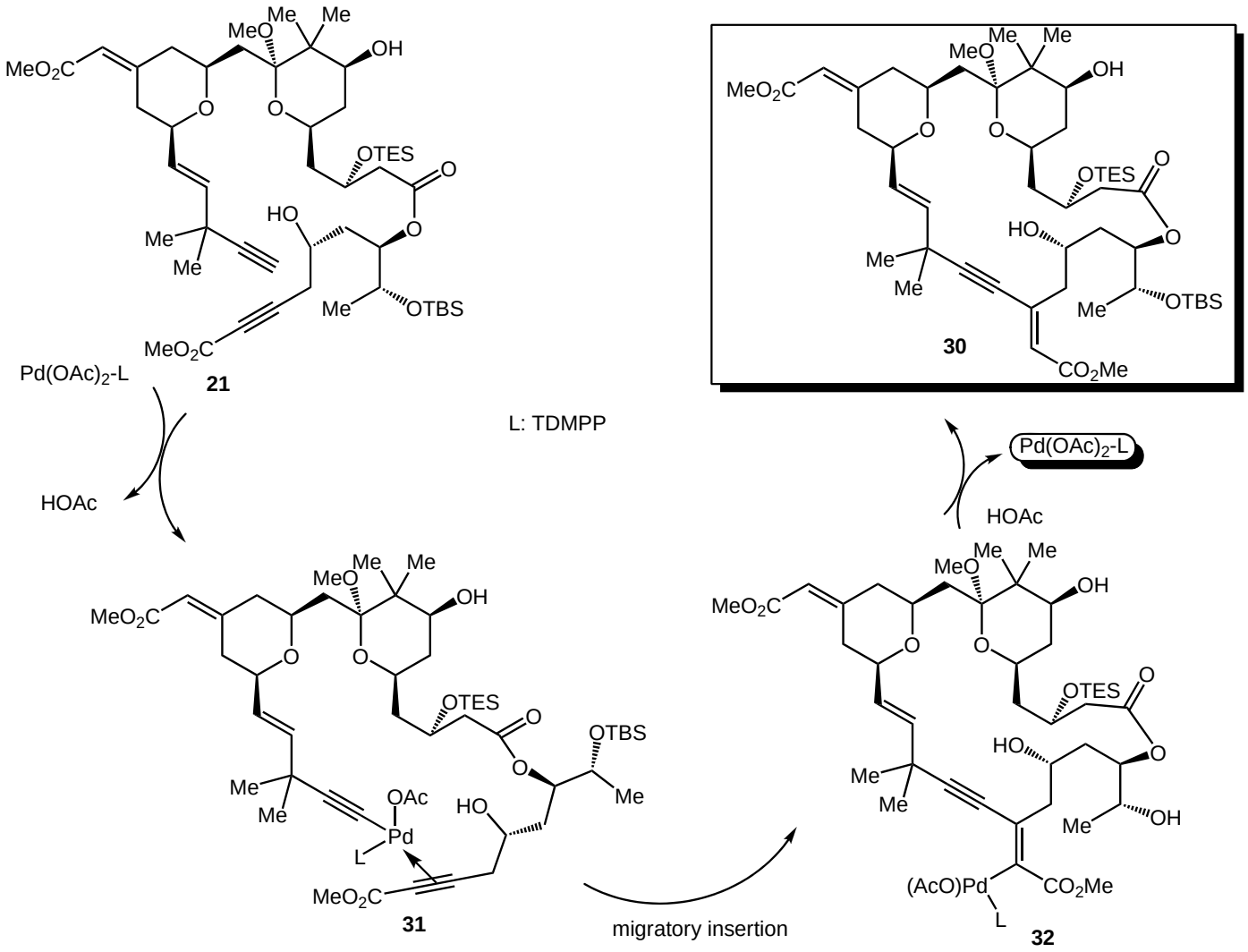
PMB Deprotection



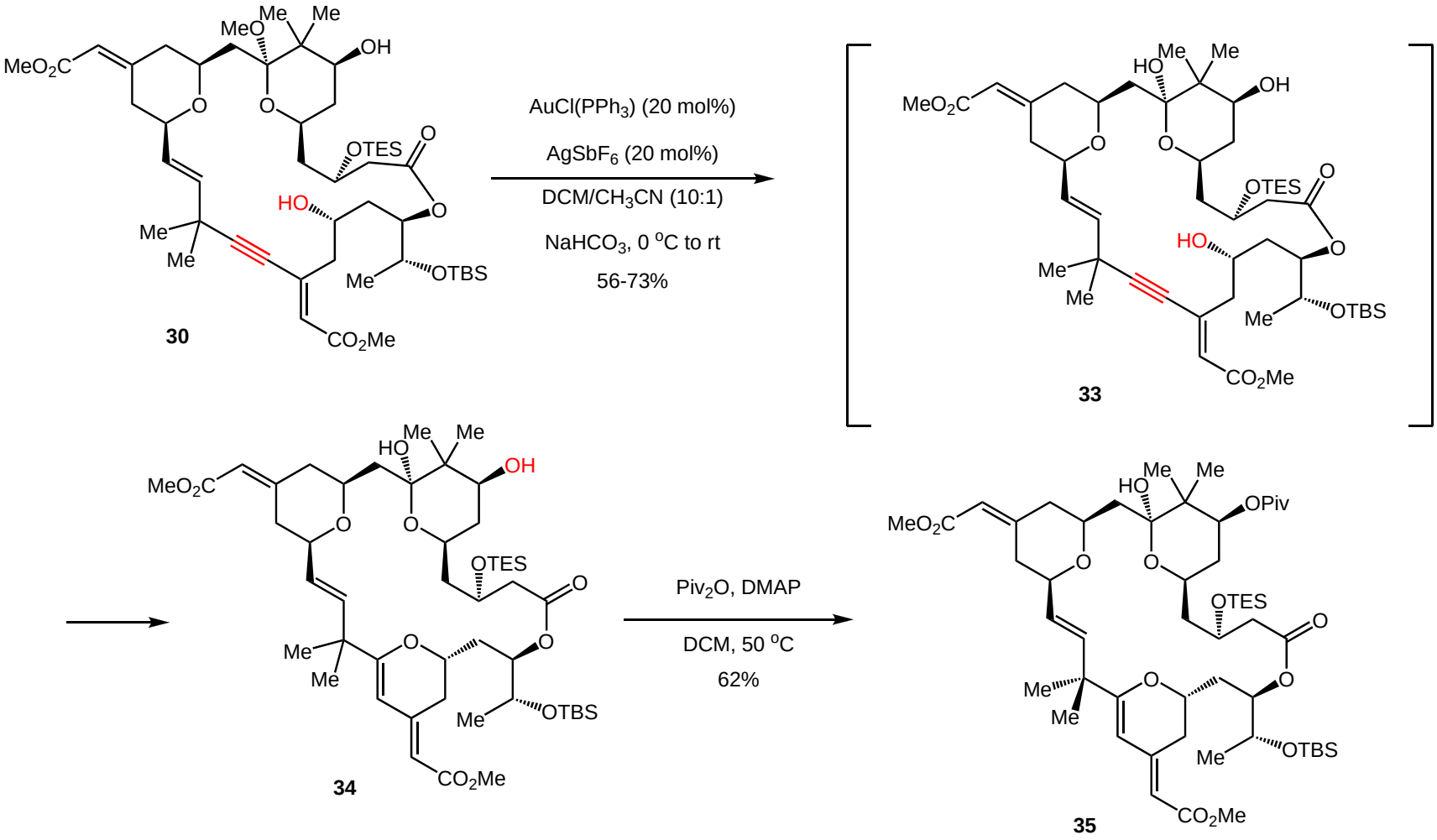
Macrocyclization via Alkyne-Alkyne Coupling



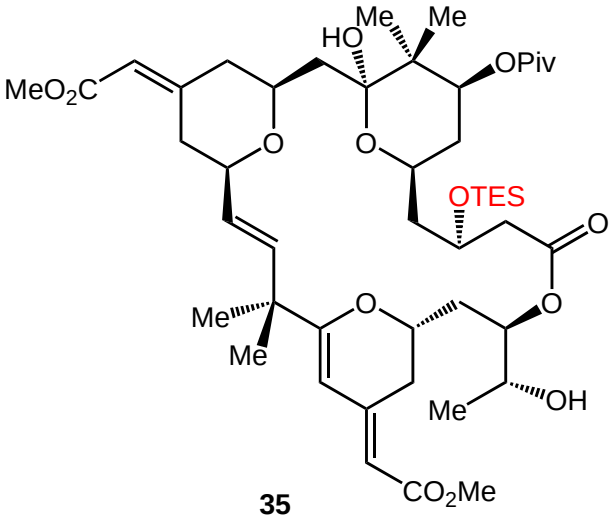
Plausible Mechanism



Synthesis of THP **35**



Synthesis of Bryostatin **16**

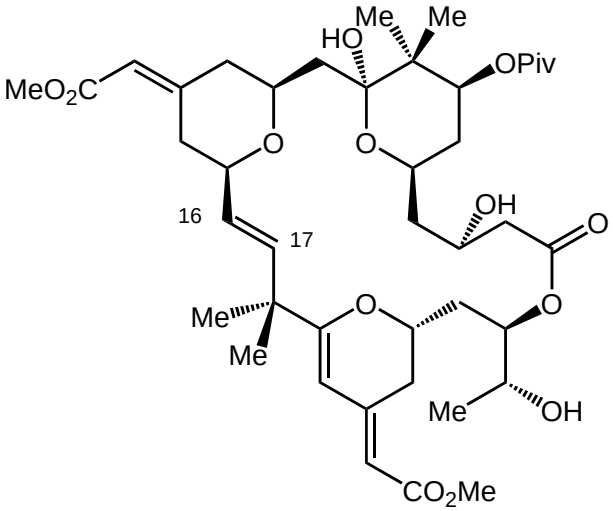


35

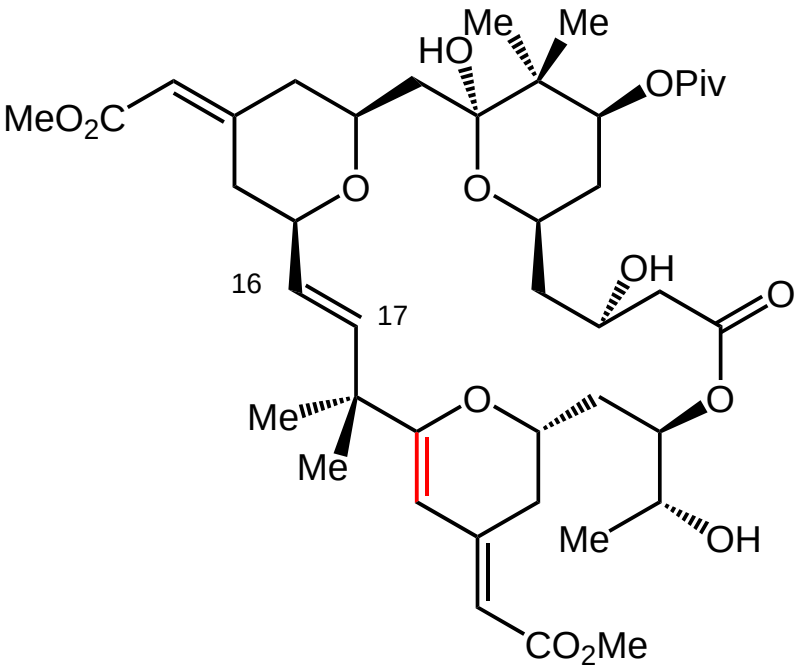
TBAF (5 equiv)

0 °C to rt

52%



bryostatin **16** (**1**)



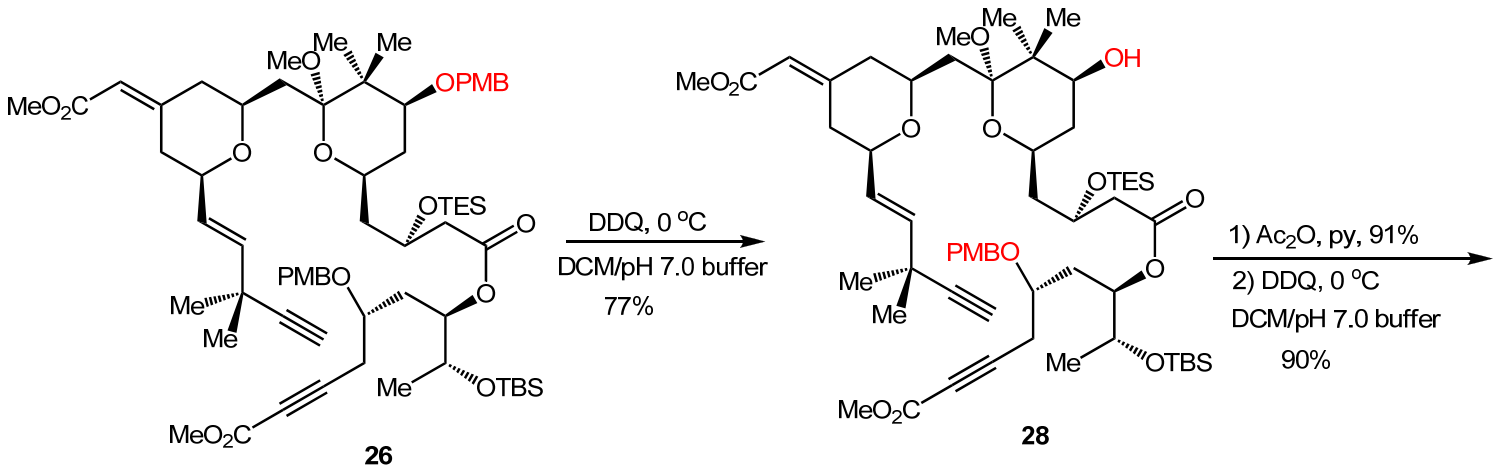
bryostatin 16 (**1**)

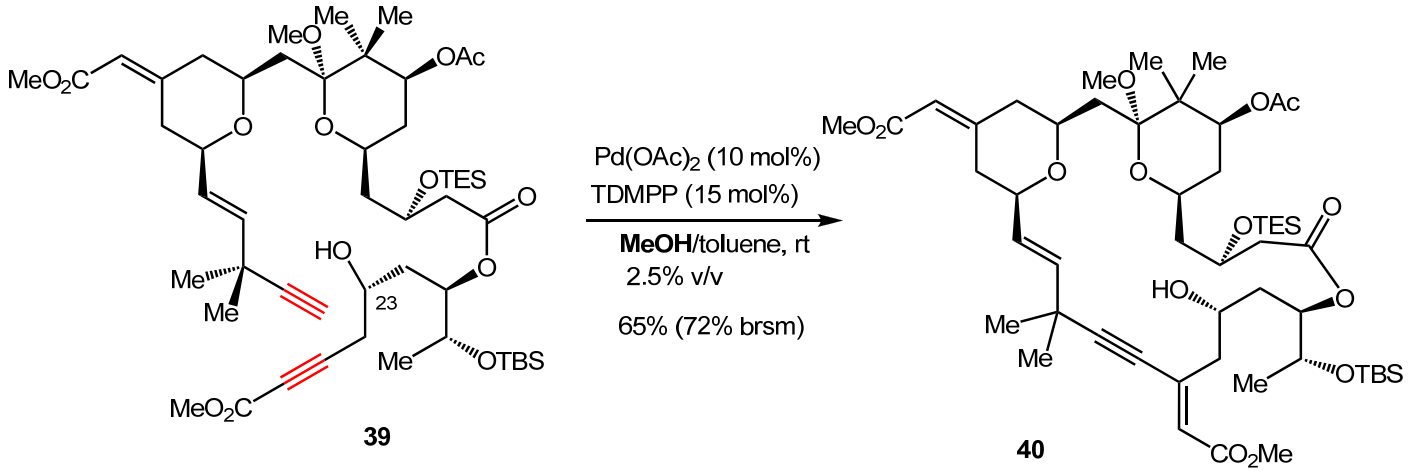
?

other bryostatins

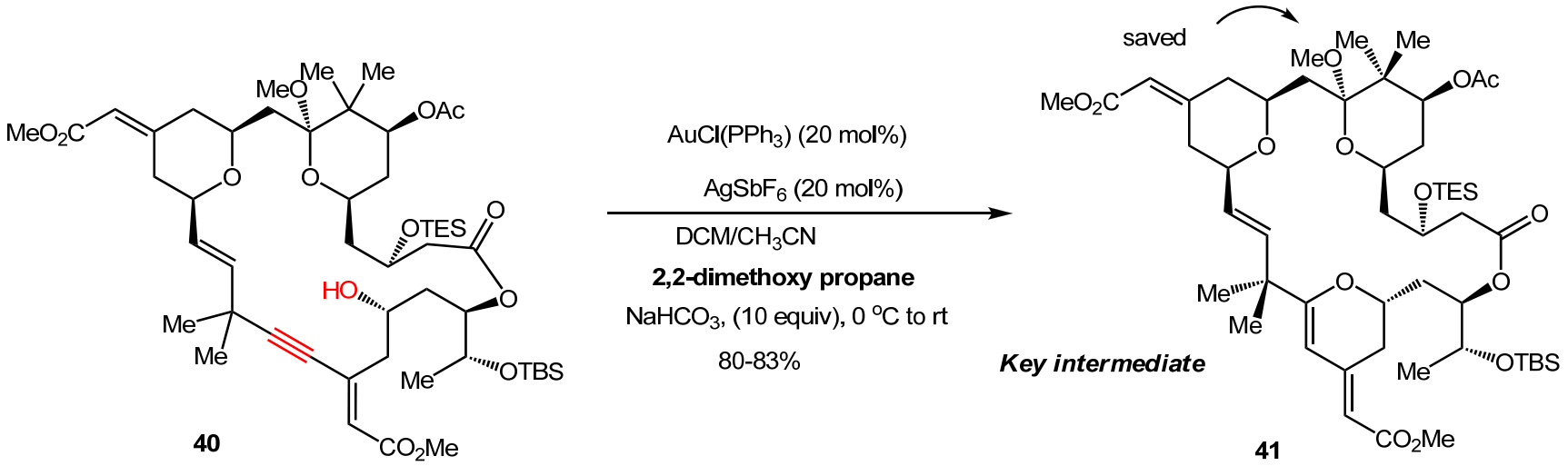
or their analogues

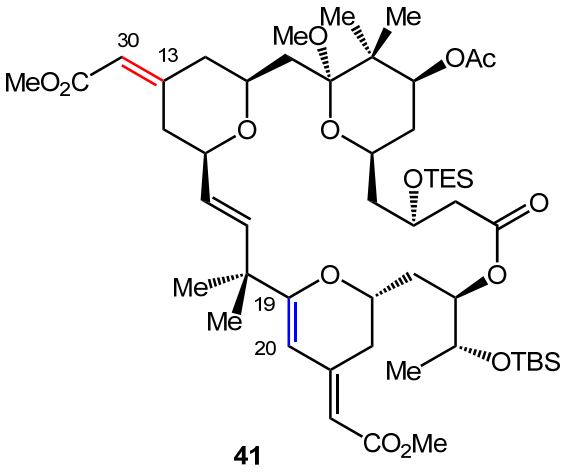
Synthesis of Key Intermediate **41**





Synthesis of Key Intermediate **41**





41

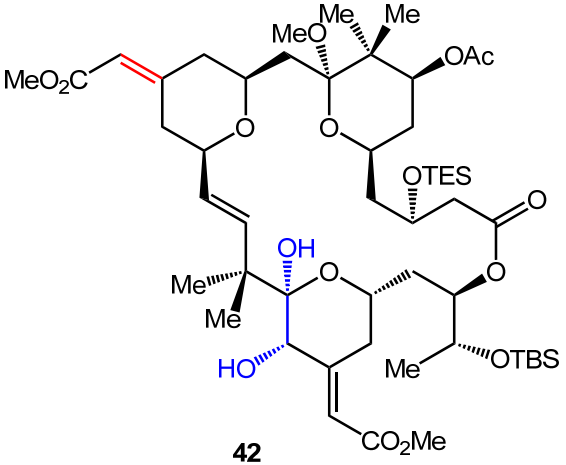
$K_2OsO_4(OH)_4$ (2 mol%)

$(DHQ)_2PHAL$ (10 mol%)

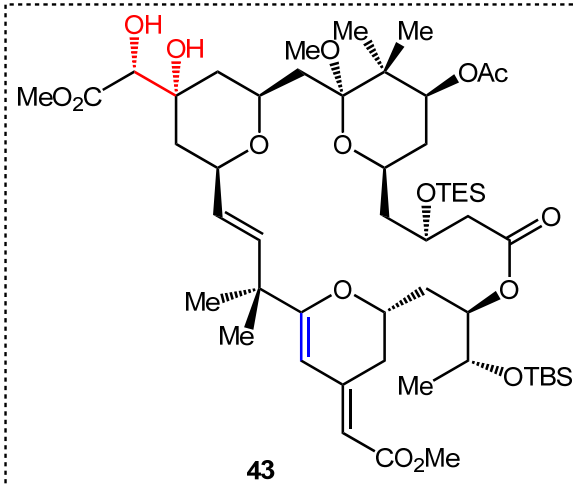
$K_3Fe(CN)_6$, $KHCO_3$

$CH_3SO_2NH_2$, $KHCO_3$

$^tBuOH/H_2O$, 0 °C



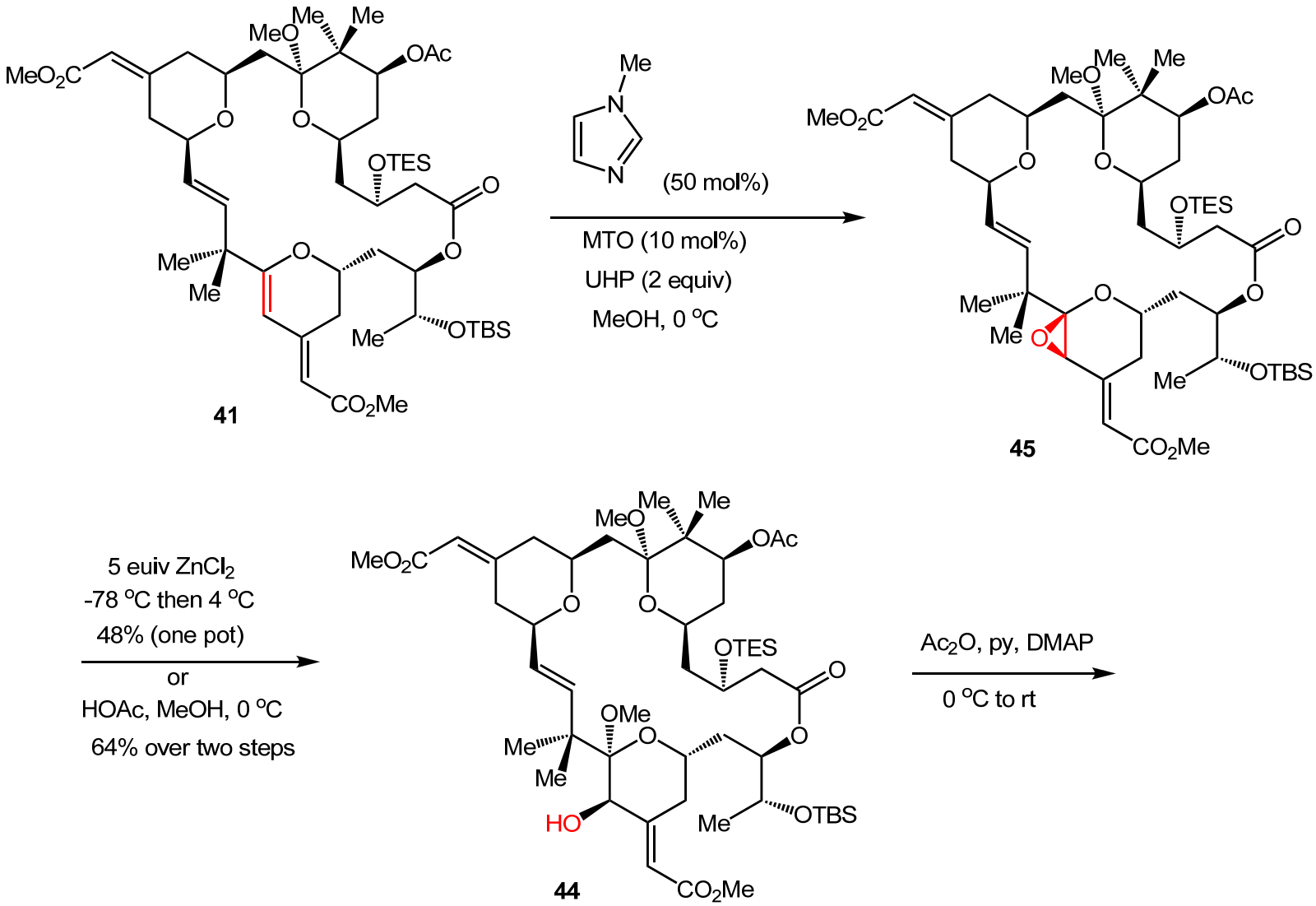
42



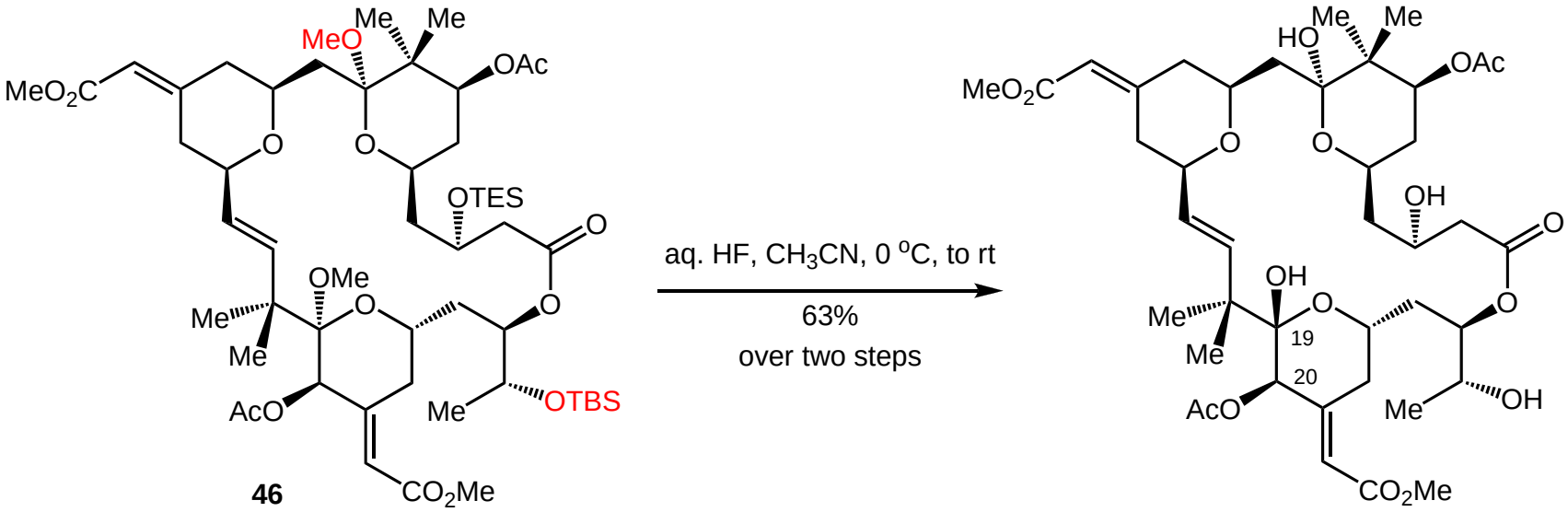
43

70% yield

Synthesis of Alcohol **44**



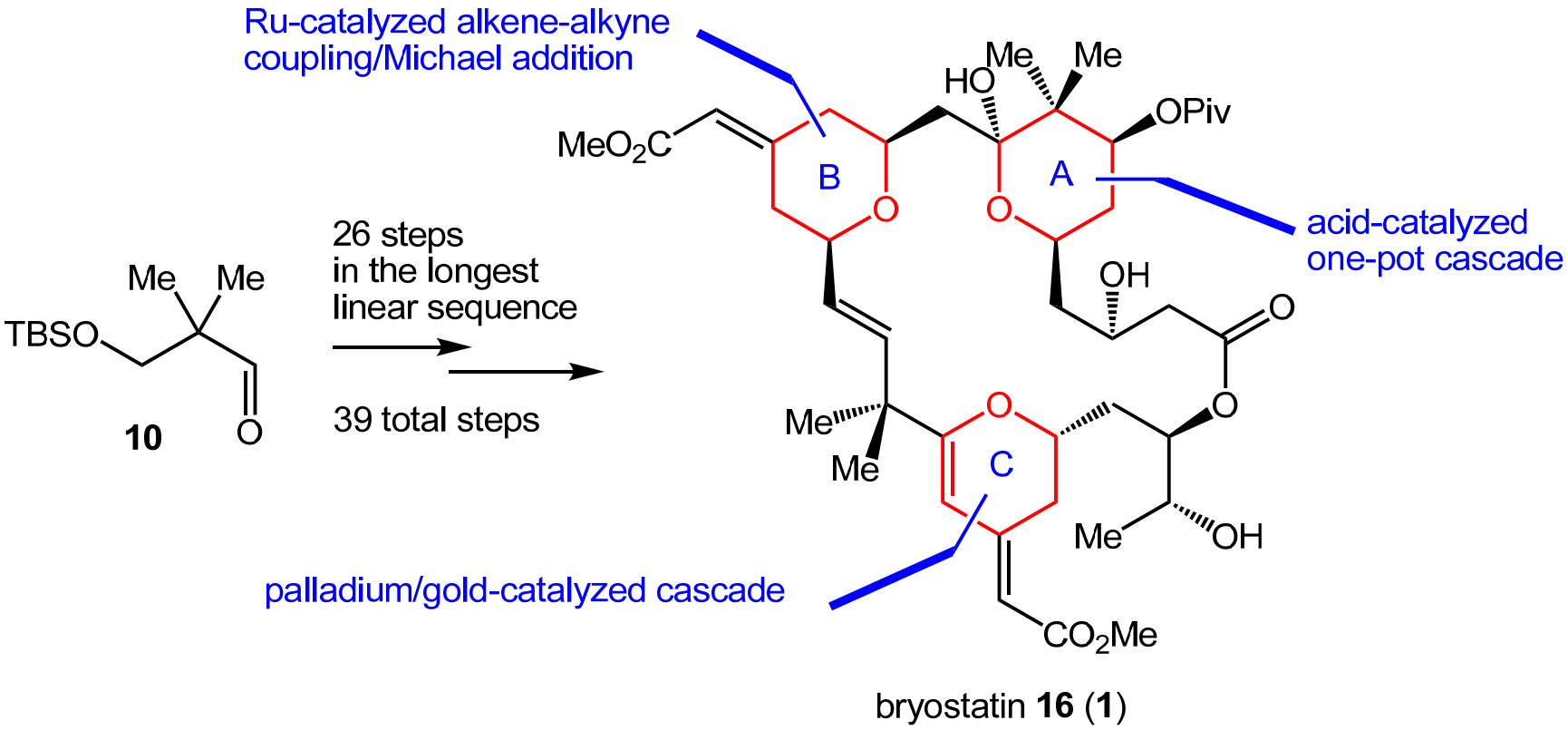
End Game of the Synthesis of 20-*epi*-Bryostatin **7** (**47**)



46

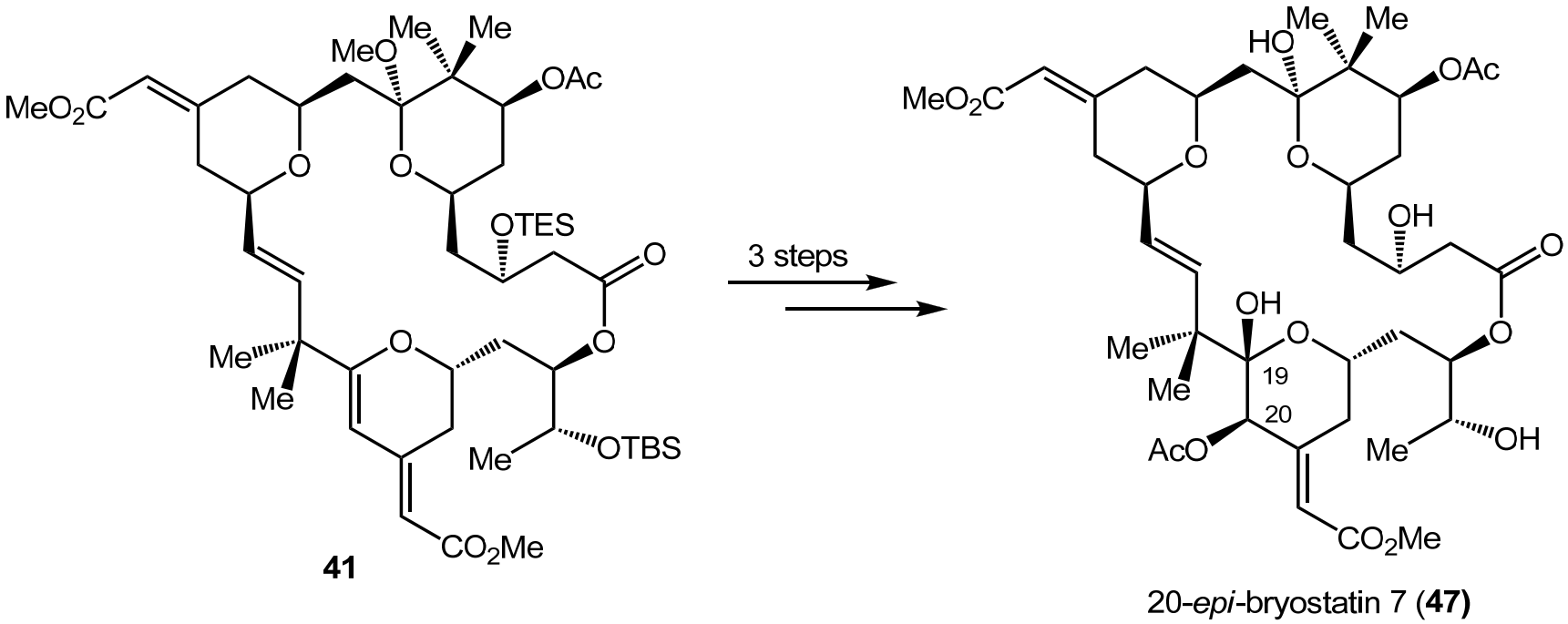
20-*epi*-bryostatin 7 (**47)**

Summary



bryostatin **16** (**1**)

Summary



41

20-*epi*-bryostatin 7 (**47**)

Introduction

Bryostatins 1-20 were first isolated in 1968 by Pettit and co-workers from the marine bryozoan *Bugula neritina*. These structurally complex macrolides exhibit a remarkable range of biological activities, including antineoplastic activity, synergistic chemotheoreputic activity, cognition and memory enhancement, recovery of brain damage, etc.

Conclusion

In summary, we have developed a unique and highly concise strategy (26 steps in the longest linear sequence, 39 total steps from aldehyde **10**) for the asymmetric total synthesis of bryostatin 16. A Pd-catalyzed alkyne-alkyne coupling was employed for the first-time as a macrocyclization method in natural product synthesis. The efficiency of our synthesis can also be attributed to a tandem Ru-catalyzed alkene-alkyne coupling/Michael addition to form the B-ring, an acid-catalyzed one-pot cascade to form the A-ring, a directed chemoselective ester hydrolysis, and a palladium/gold-catalyzed cascade to form the C-ring of bryostatin 16. These atom-economical and/or chemoselective approaches not only are useful in bryostatin syntheses, but should also be indicative for the synthesis of numerous other polyacetate-polypropionate-derived natural products.