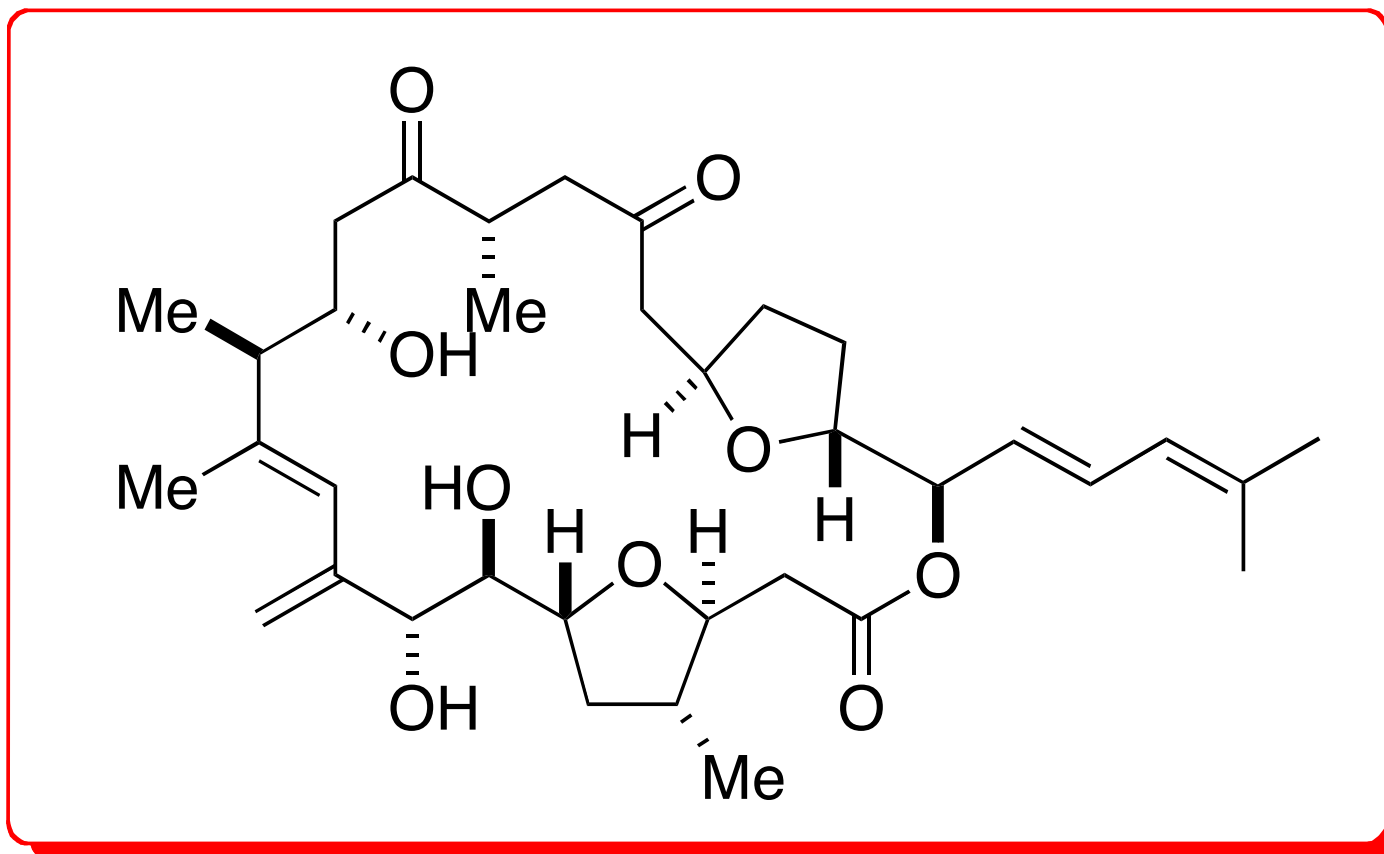


Enantioselective Total Synthesis of Amphidinolide F



Mahapatra, S.; Carter, R. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7948

Dimas José da Paz Lima
Wipf group - Current Literature
August 25, 2012

A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

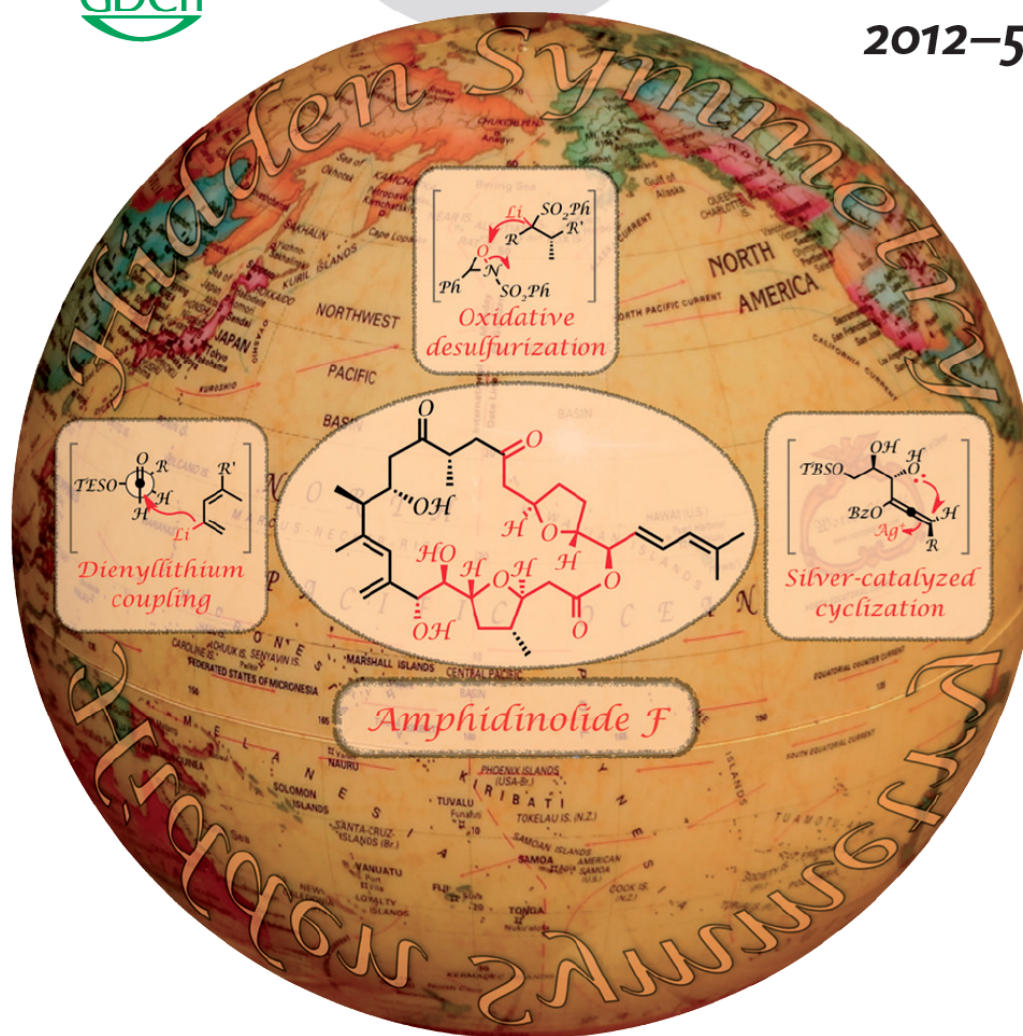
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2012–51/32



Amphidinolide F - Isolation, Structure and Biological Active

Amphidinolides are secondary metabolites from *Amphidinium* sp. collected from Okinawa Island by Kobayashi et al.

The family of amphidinolides contains more than 30 members that possess a highly oxygenated macrolactone core

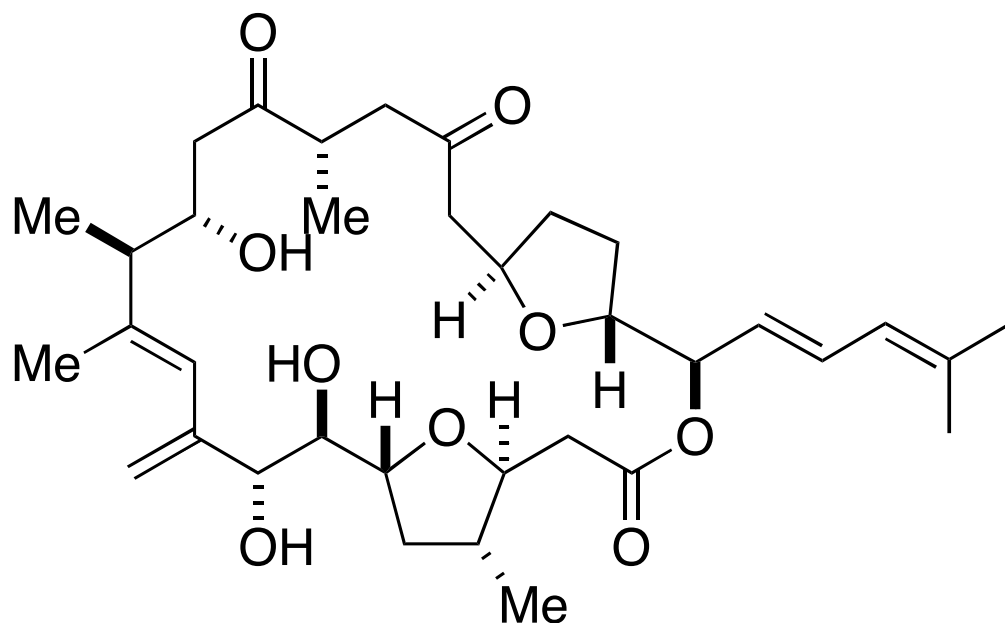
Amphidinolide F exhibited cytotoxic activity against L1210 ($IC_{50} = 1.5 \mu\text{g/mL}$) and KB cell ($IC_{50} = 3.2 \mu\text{g/mL}$)

11 stereogenic centers

Two THF rings

1,4-diketone moiety

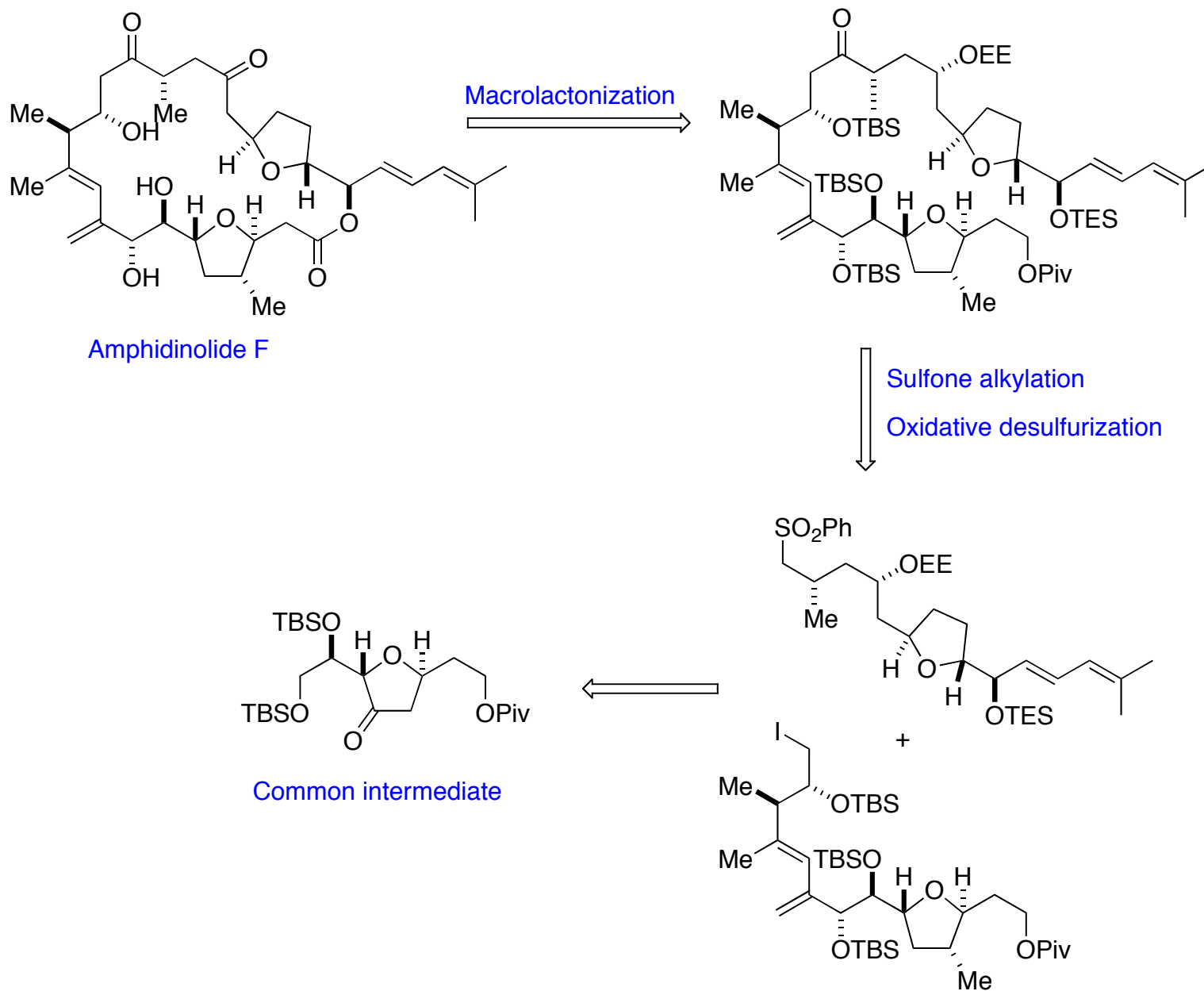
Highly substituted diene moiety



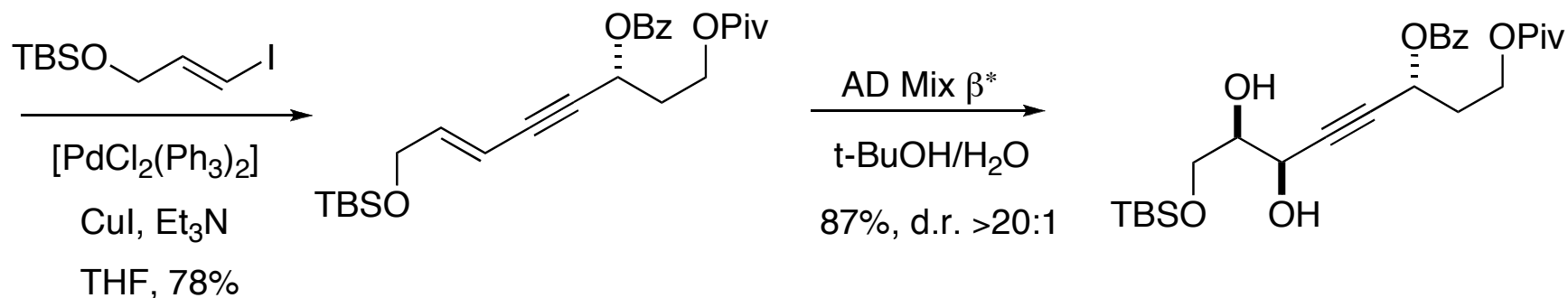
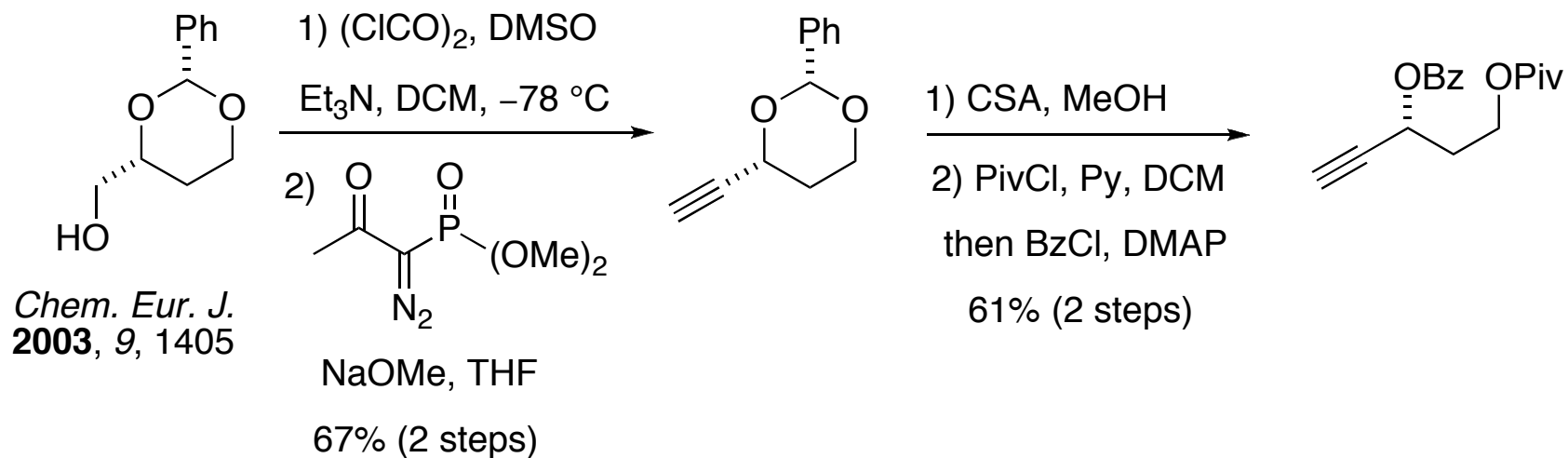
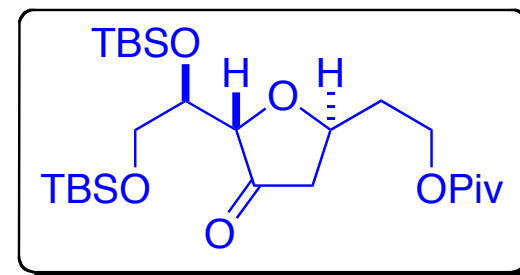
Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271

Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77

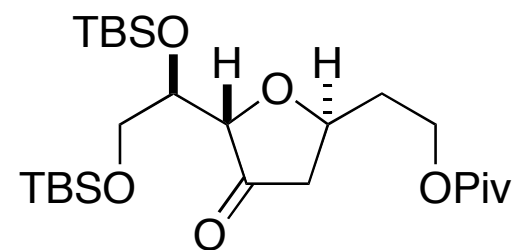
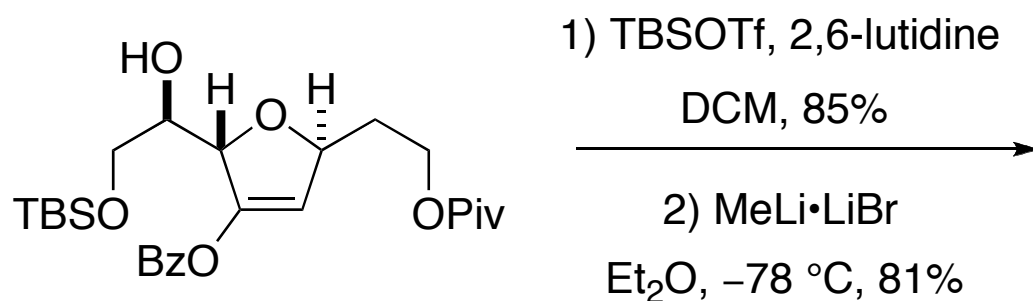
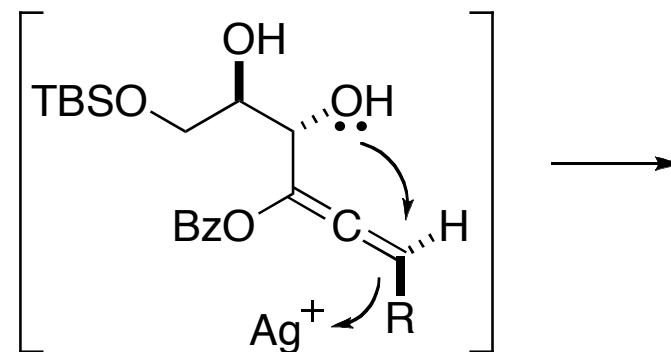
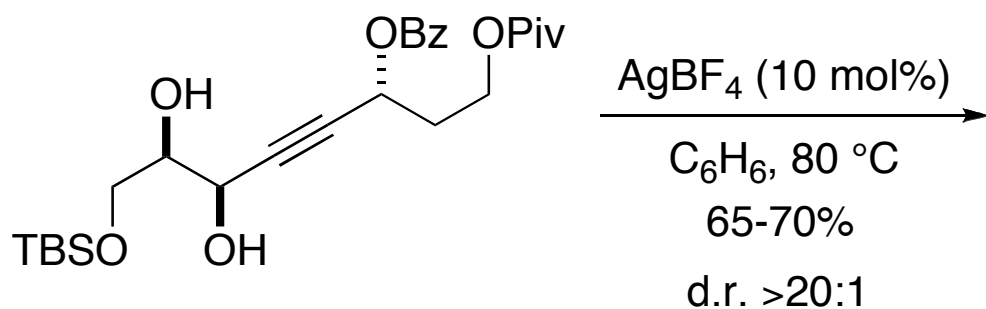
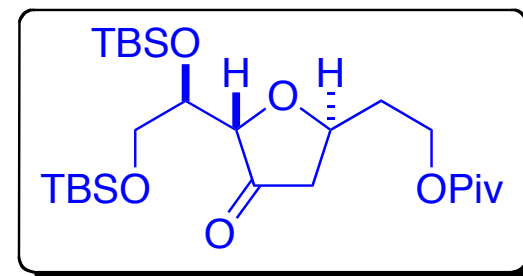
Retrosynthesis



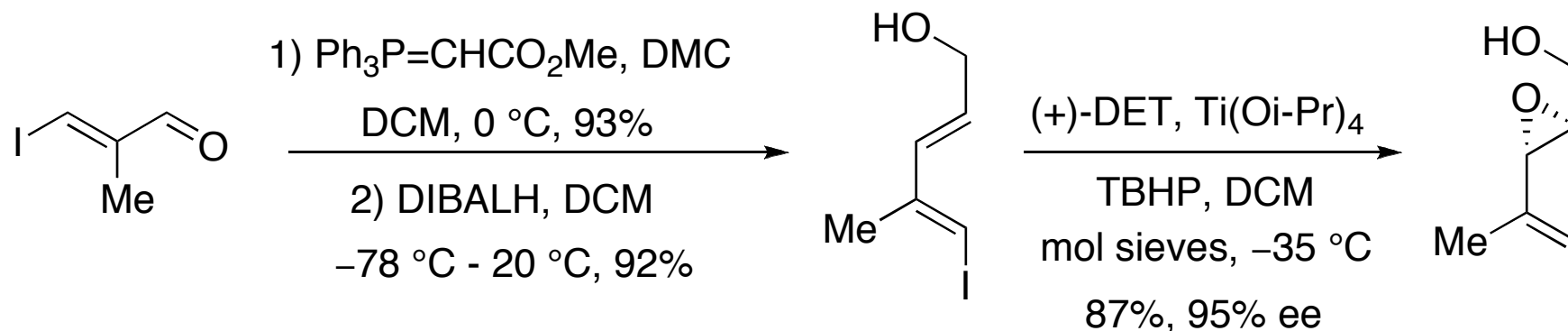
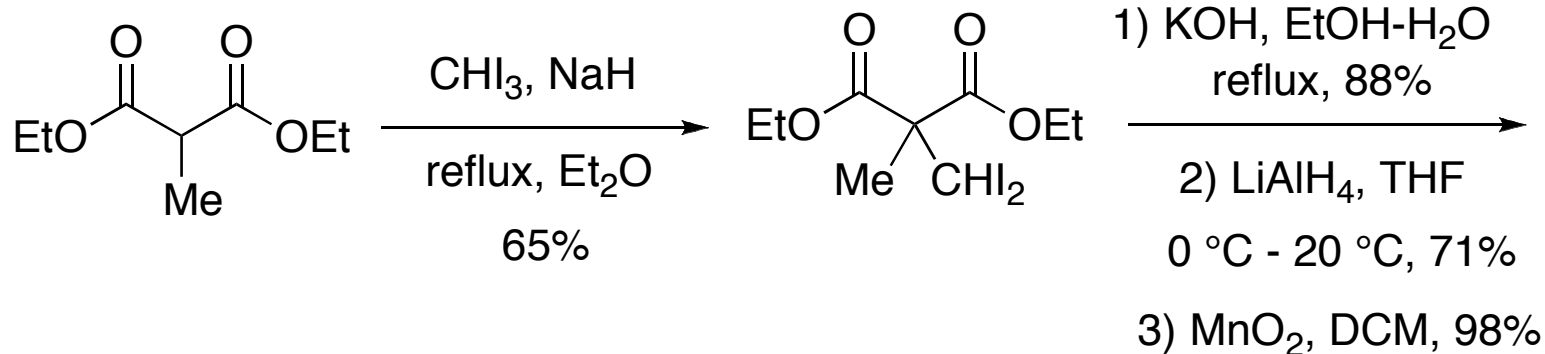
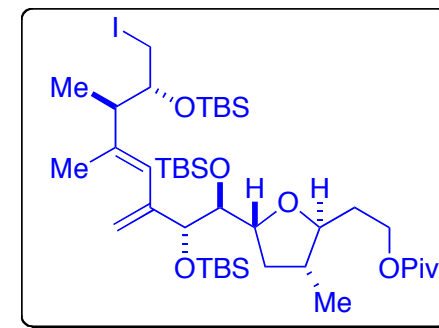
Synthesis of Common intermediate



Synthesis of Common intermediate

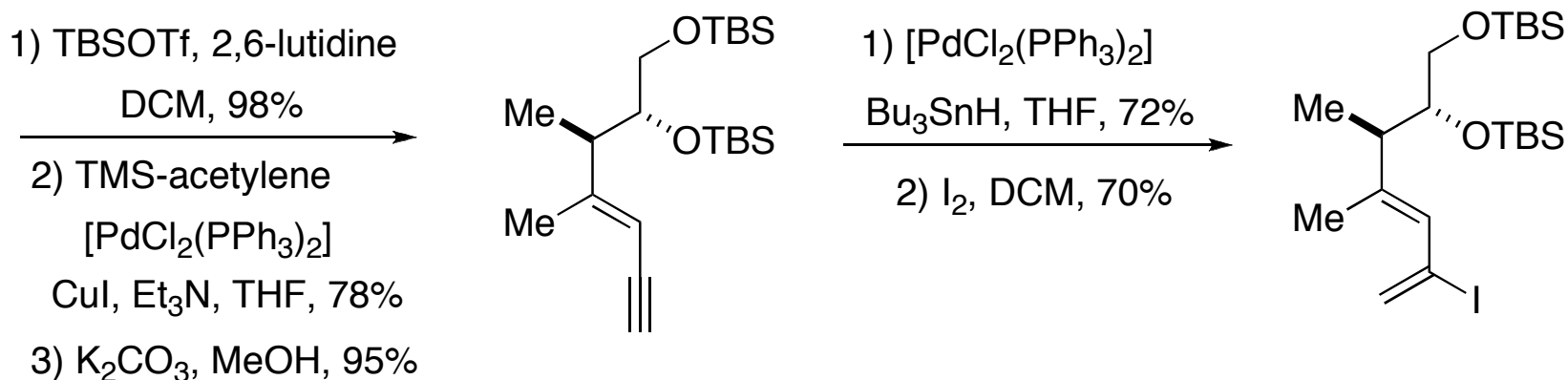
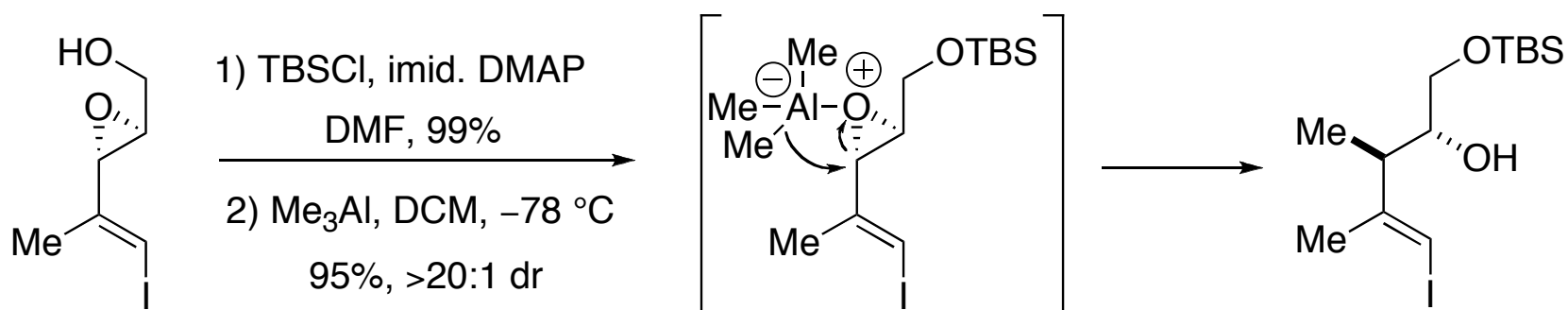
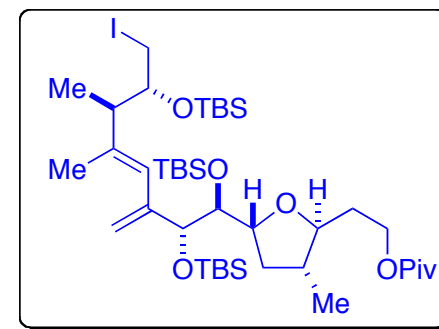


Synthesis of the left-hand segment

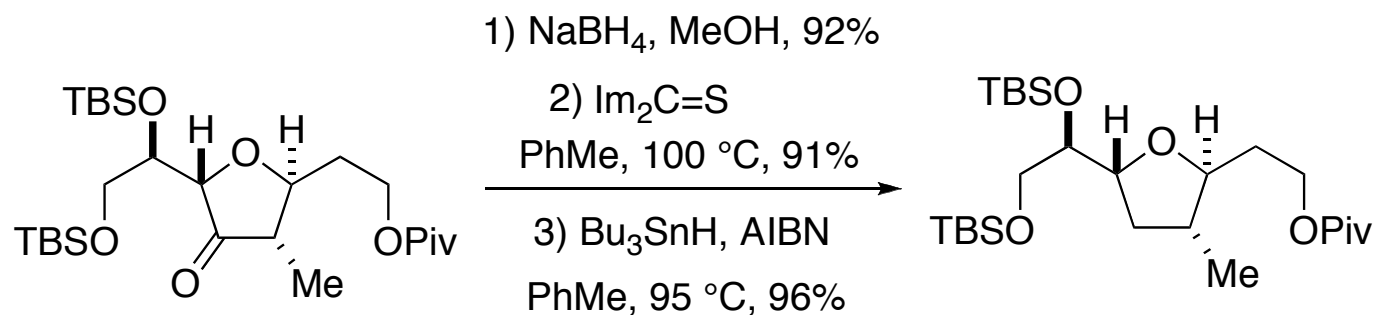
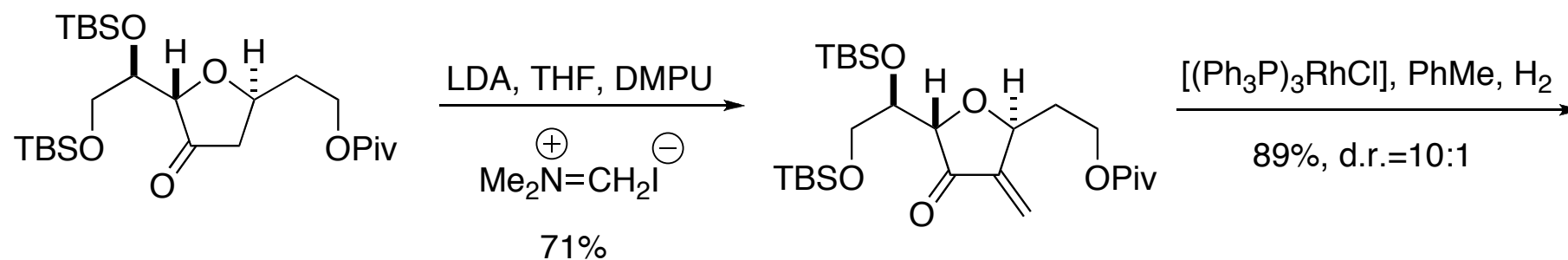
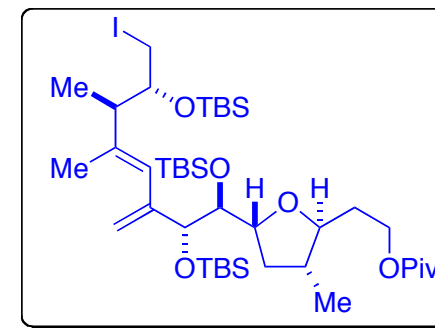


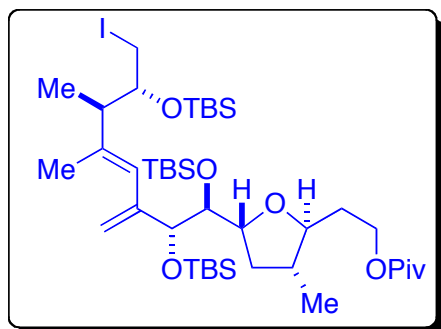
Mahapatra, S.; Carter, R. G. *Org. Biomol. Chem.* **2009**, *7*, 4582

Synthesis of the left-hand segment

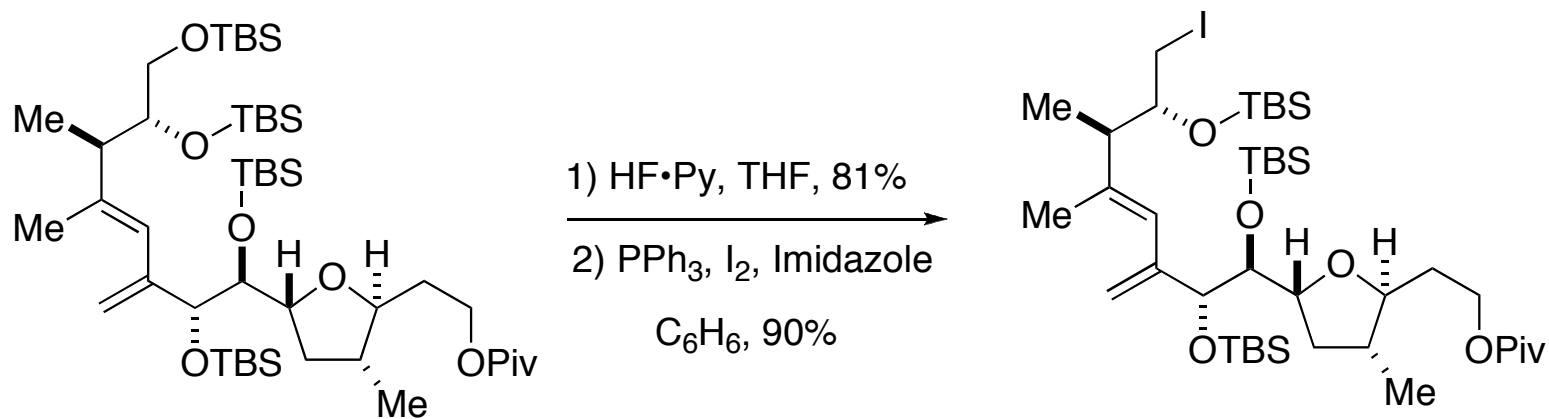
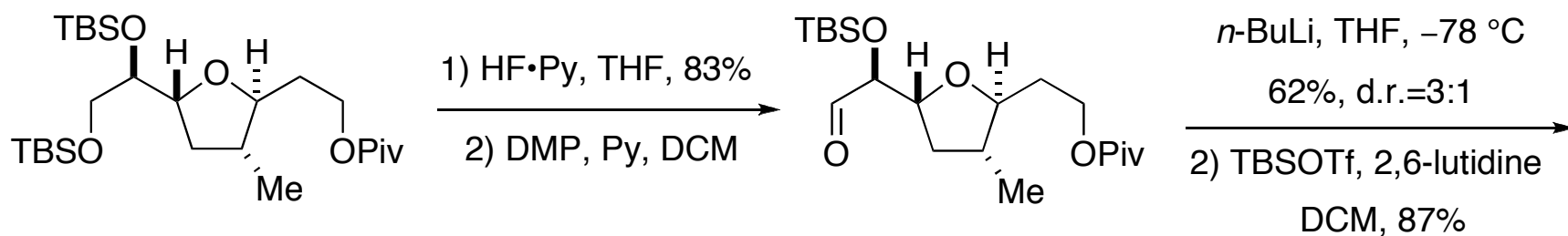


Synthesis of the left-hand segment

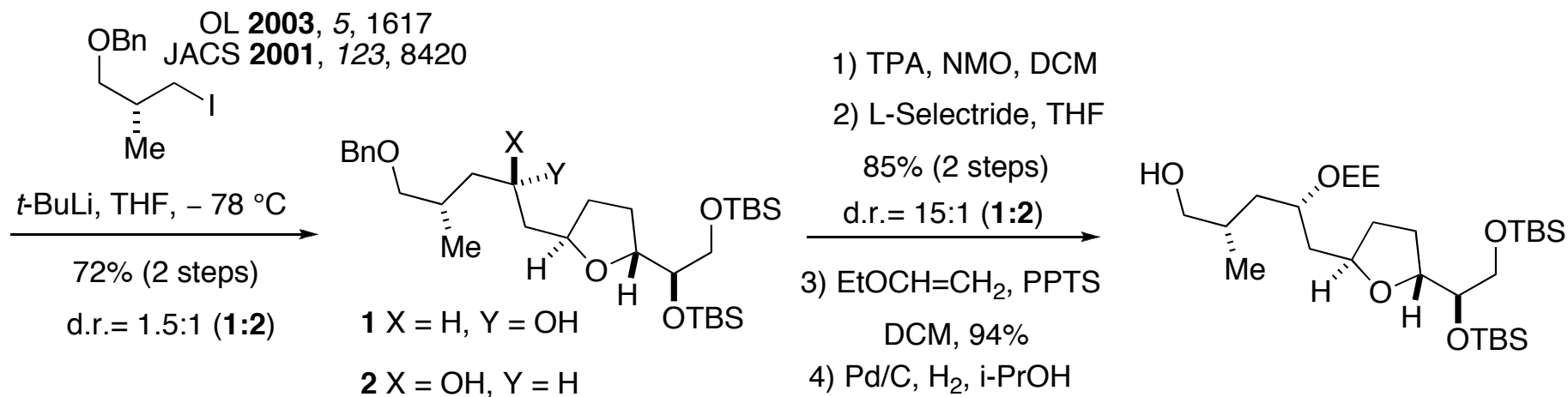
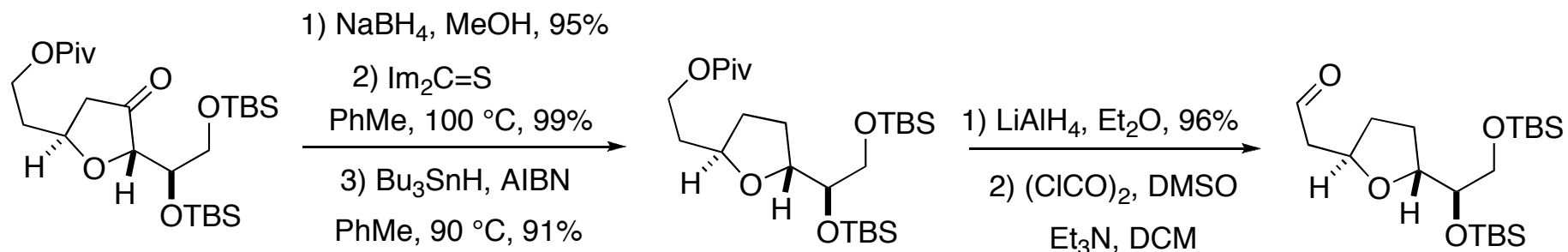
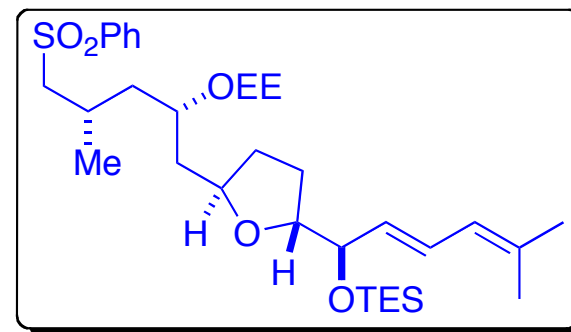




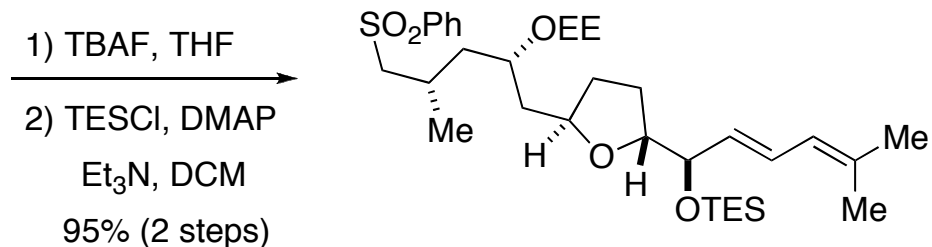
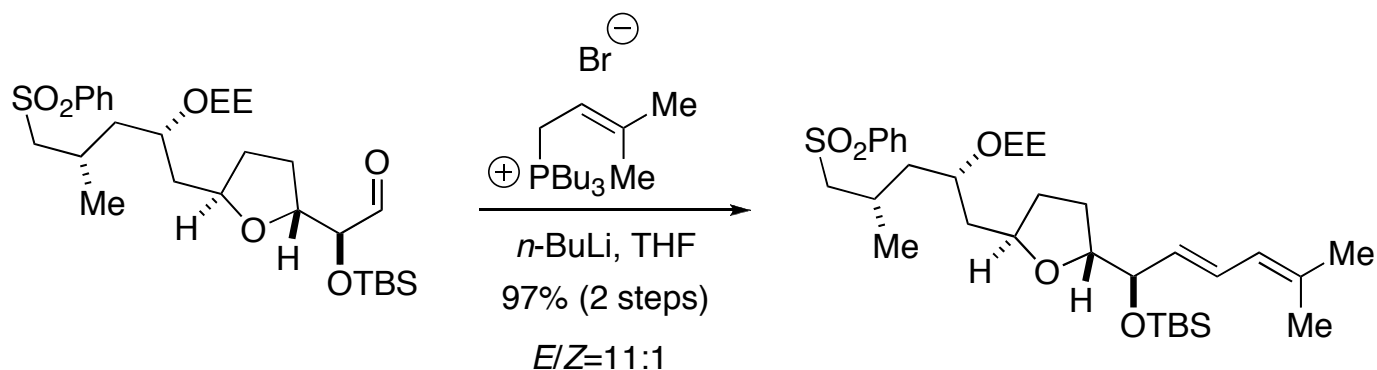
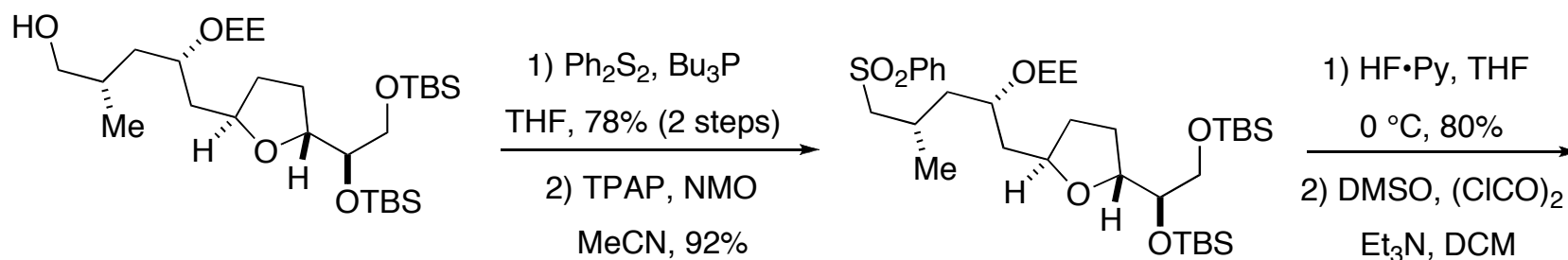
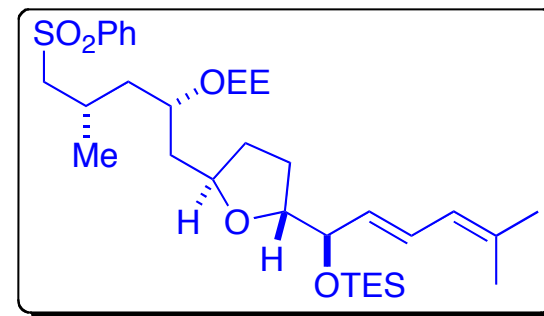
Synthesis of the left-hand segment



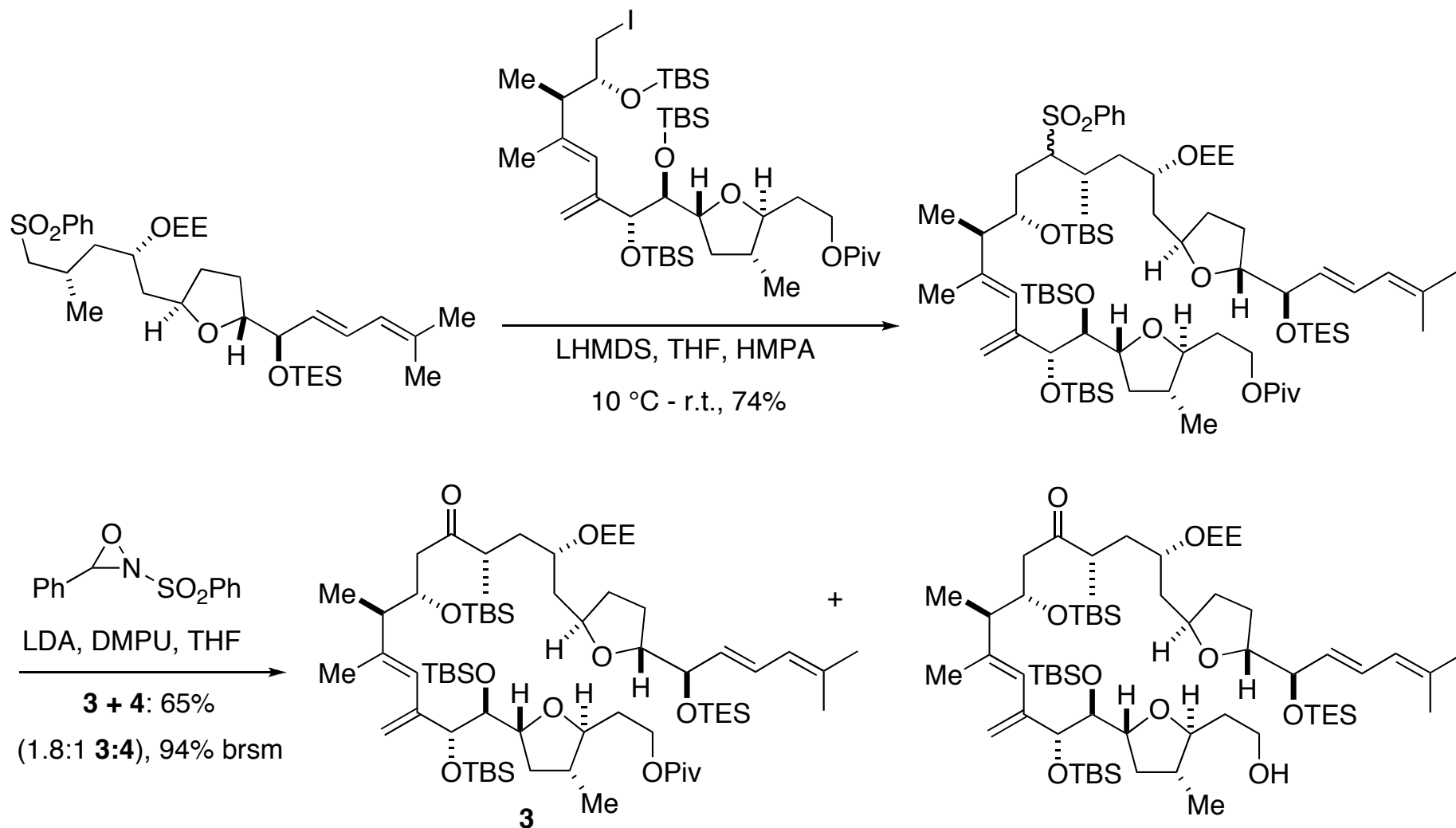
Synthesis of the right-hand segment



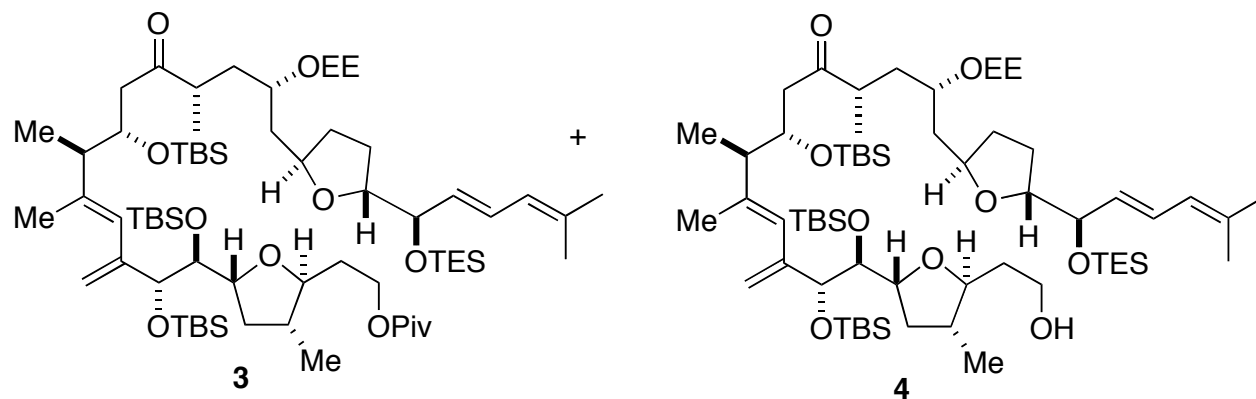
Synthesis of the right-hand segment



Completion of the Synthesis



Completion of the Synthesis



1) LiAlH_4 , Et_2O

2) $(\text{ClCO})_2$, Et_3N , DCM

83% (2 steps)

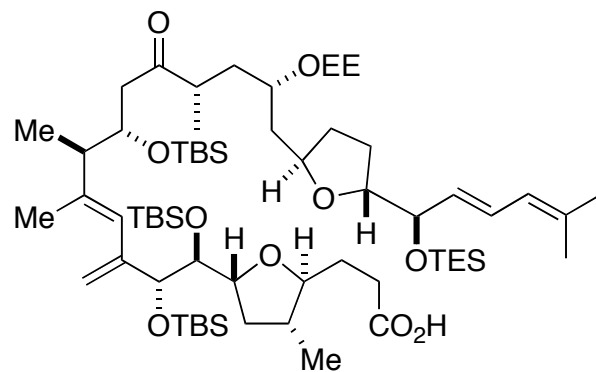
$(\text{ClCO})_2$, Et_3N , DCM , 83%

Aldehyde

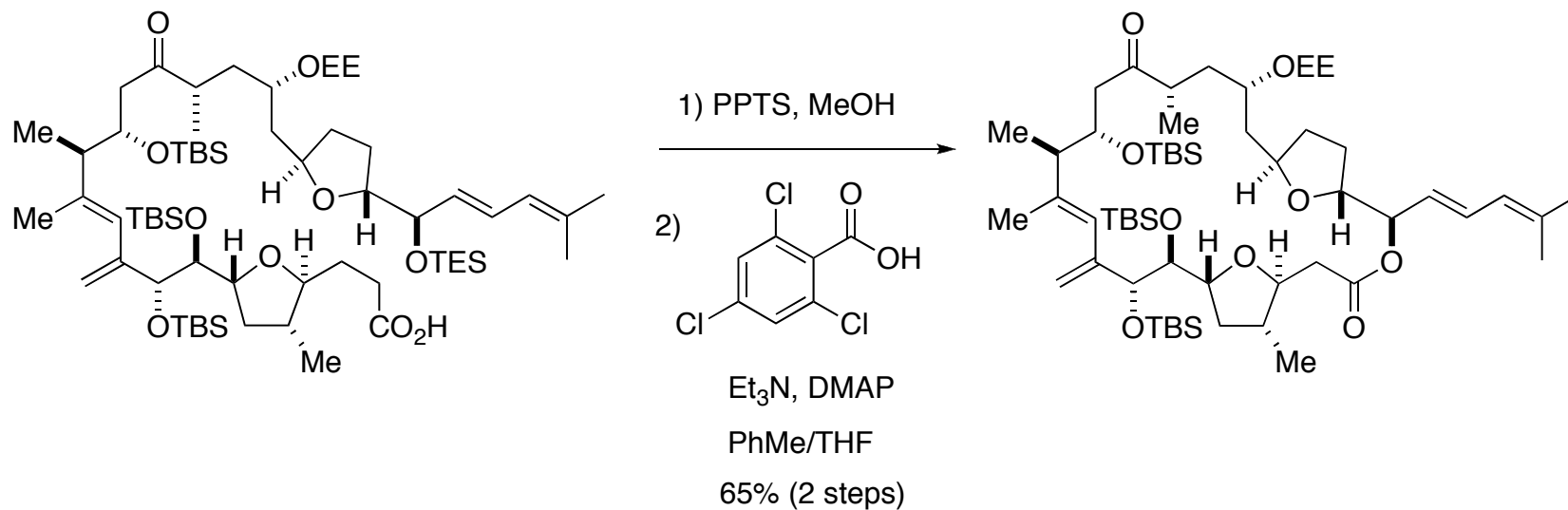
NaClO_2 , 2-Me-2-butene

$\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$

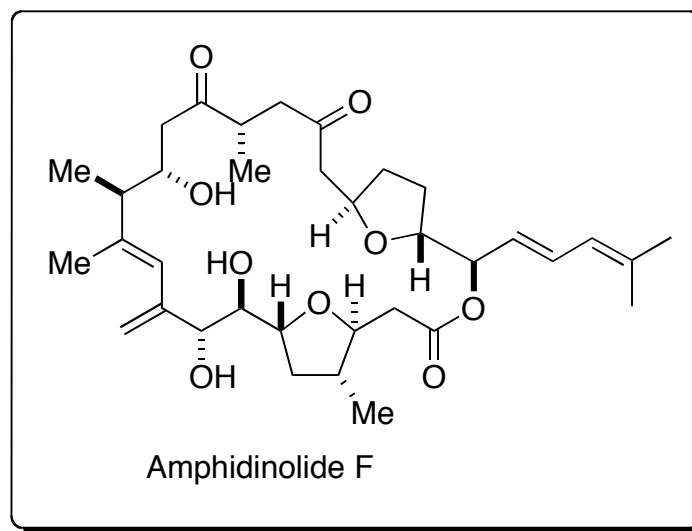
t-BuOH/ H_2O , 85%



Completion of the Synthesis



- 1) AcOH, THF, H₂O
2) DMP, Pyr
62% (2 steps)
- 3) Et₃N·HF
Et₃N/MeCN, 56%



Summary and Outlook

*Amphidinolide F was synthesized in 34 steps (longest linear Sequence)

*Key transformations include:

- Silver-catalyzed dihydrofuran formation
- Diastereoselective ring opening of vinyl iodide/allylic epoxide
- Regioselective hydrostannylation of enyne
- Diastereoselective addition of 2-lithio-1,3-diene to aldehyde
- Sulfone alkylation/Oxidative desulfurization sequence