

Pestalotiopsis A

Jan. 28, 2009

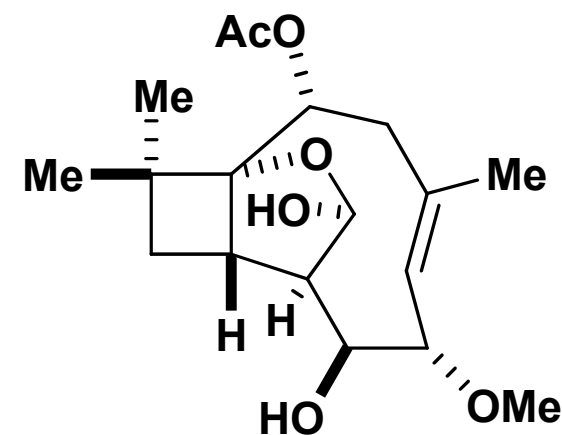
Anne-Marie Dechert

Background

- Isolated in 1996 from an endophytic fungus associated with the Pacific Yew tree
- Has shown cytotoxicity and immunosuppressant activity in preliminary assays
- Has an unprecedented oxatricyclic system
- Structural features include:
 - a γ -lactol
 - a highly oxygenated (E)- cyclononene ring
 - a geminally methylated cyclobutane
 - 7 stereocenters

3 groups are currently working on this natural product

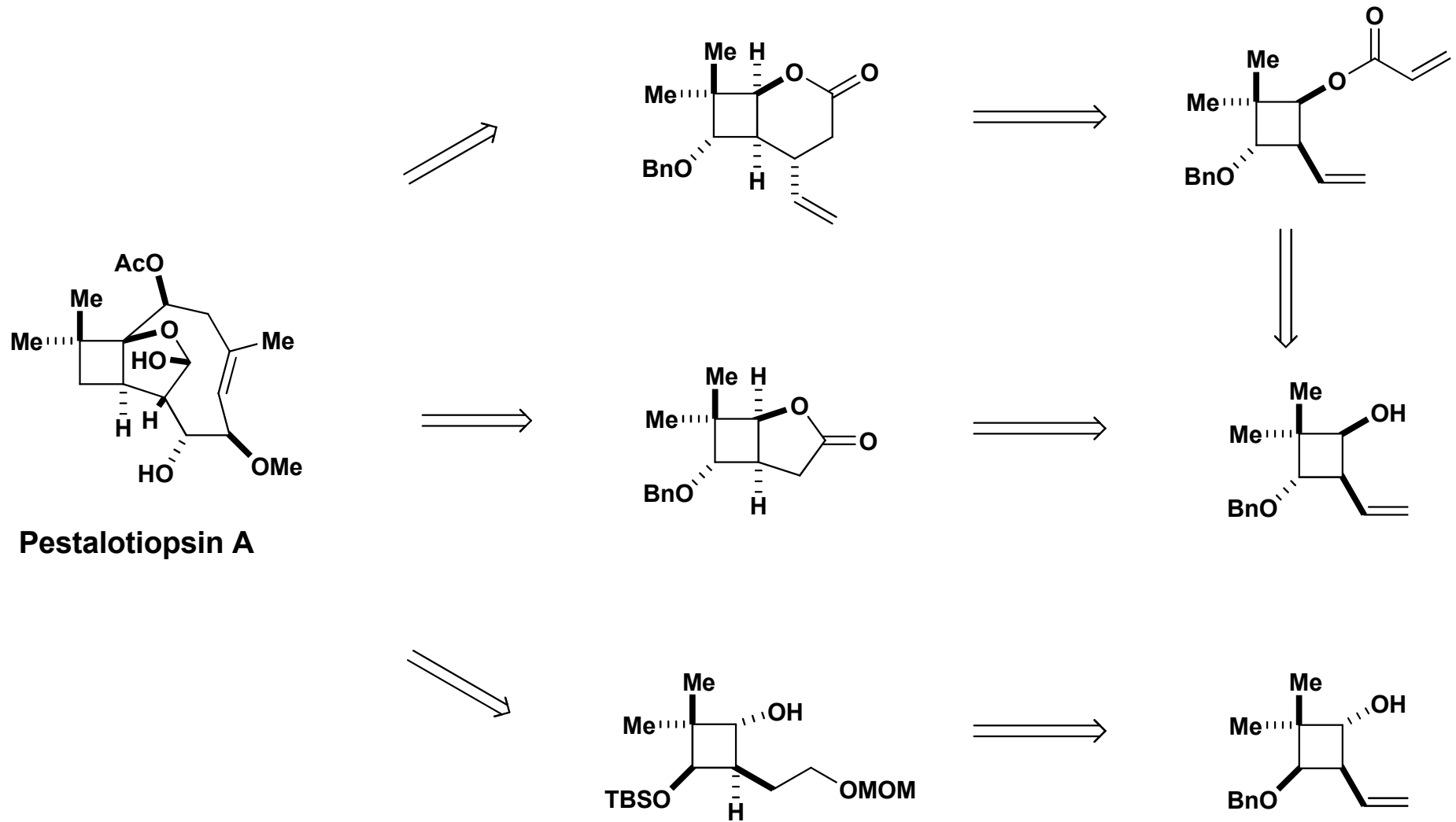
1 total synthesis to date, the opposite enantiomer of the natural product



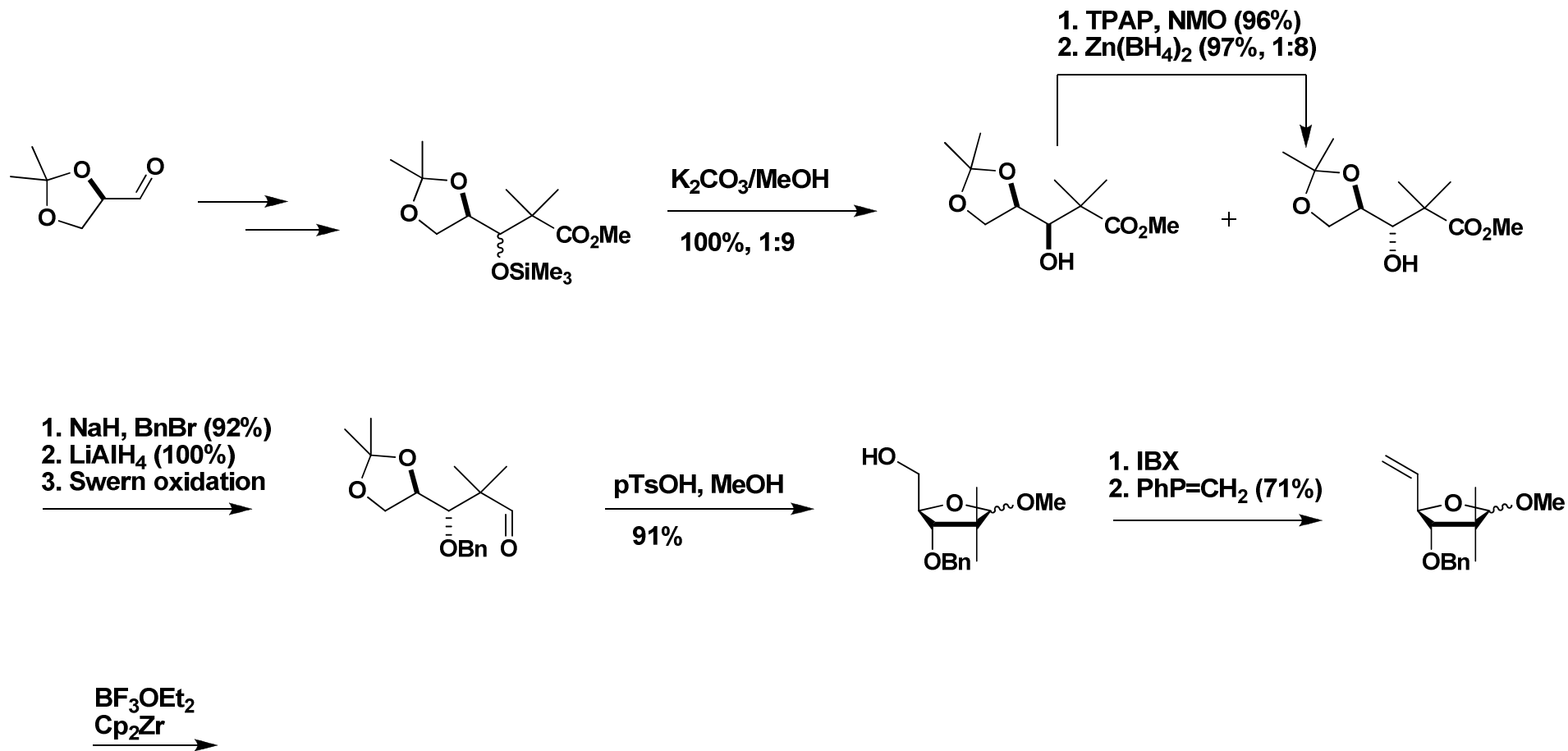
(-)-Pestalotiopsin A



Paquette's Retrosynthesis



Paquette's Approach

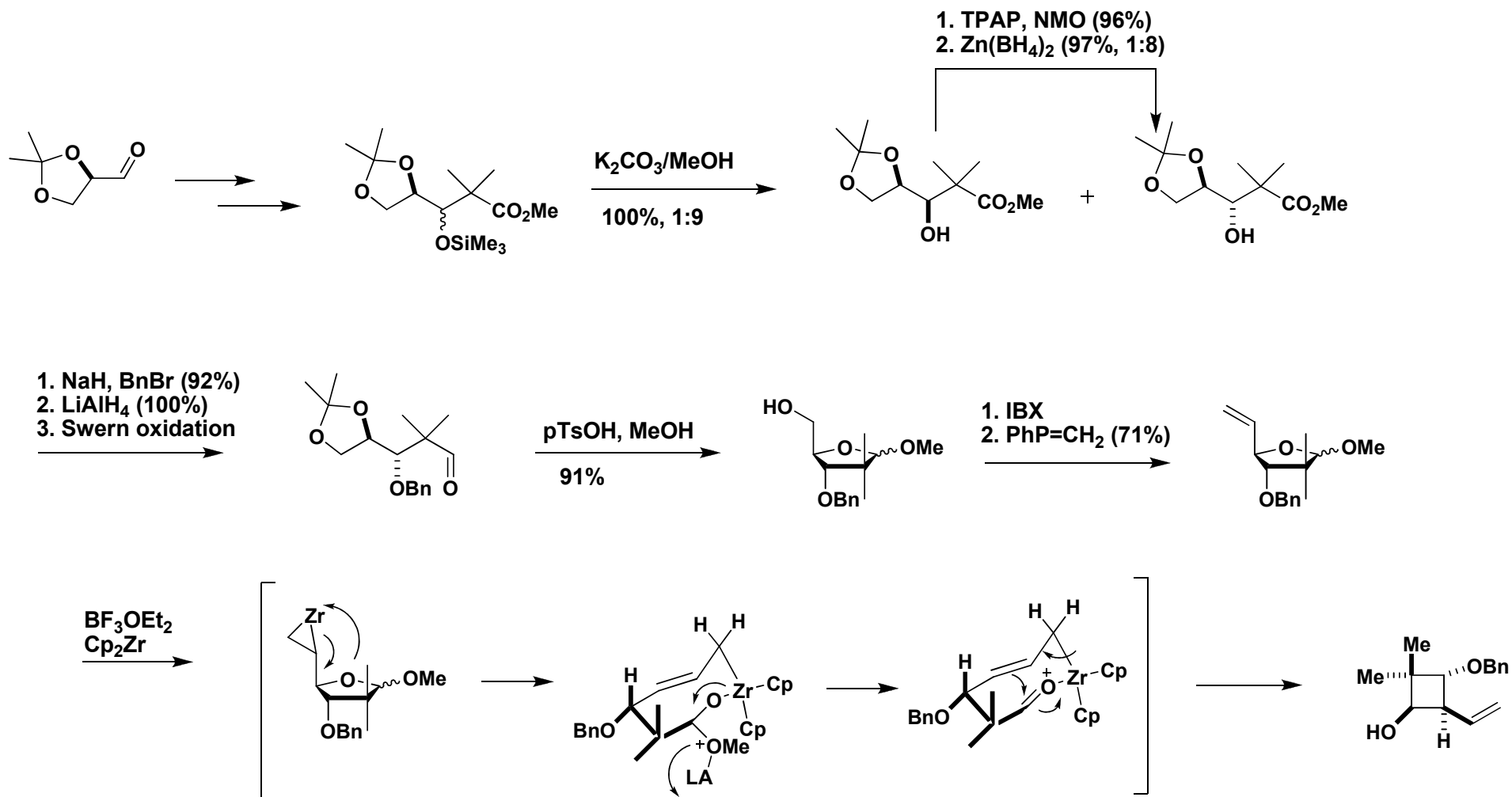


Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, 8, 2429.

Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, 72, 7135.

Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, 72, 7125.

Synthesis of the Common Precursor

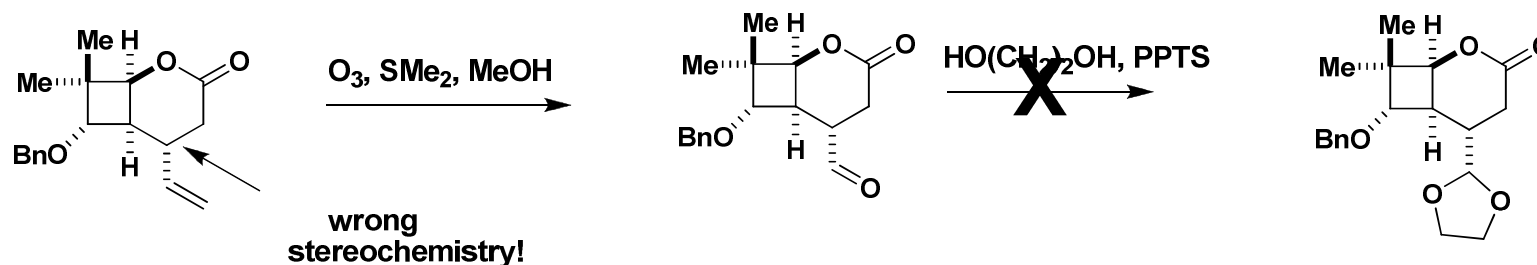
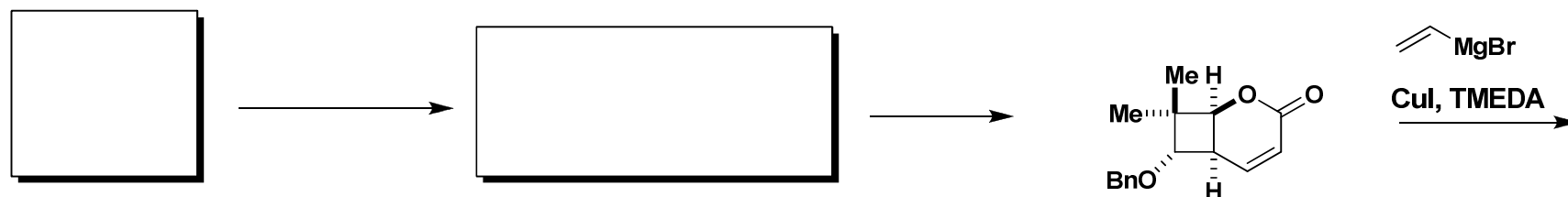


Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, 8, 2429.

Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, 72, 7135.

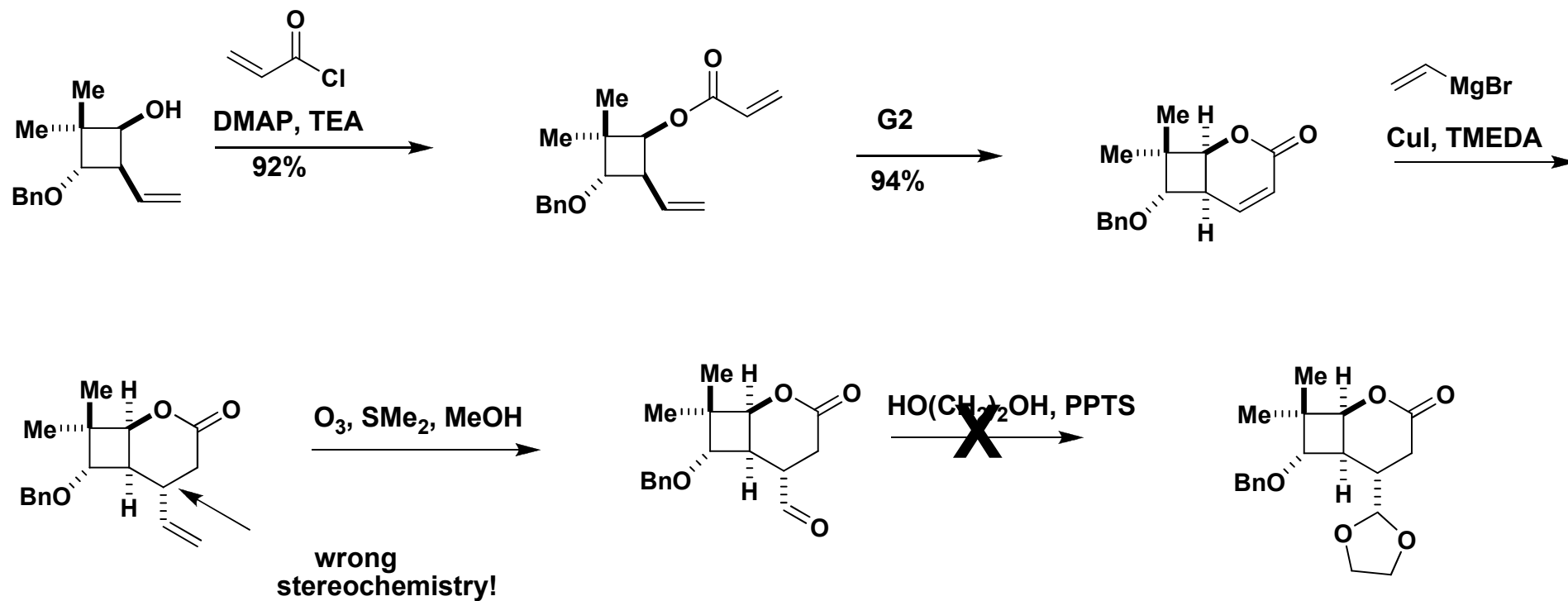
Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, 72, 7125.

4.2.0 Lactone Approach

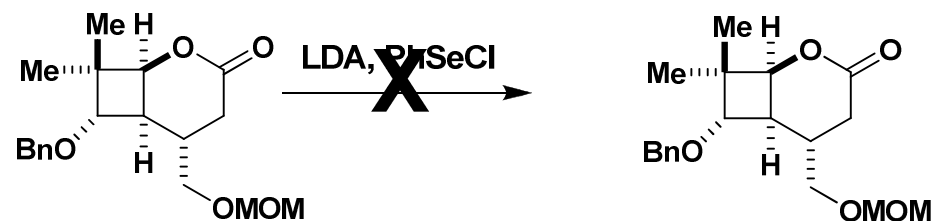
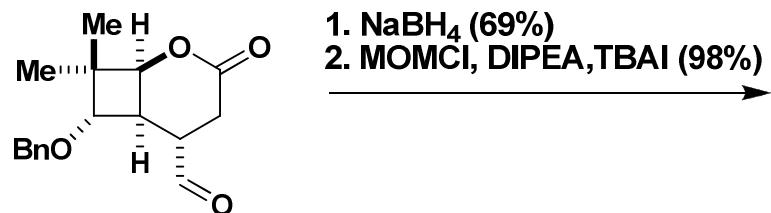
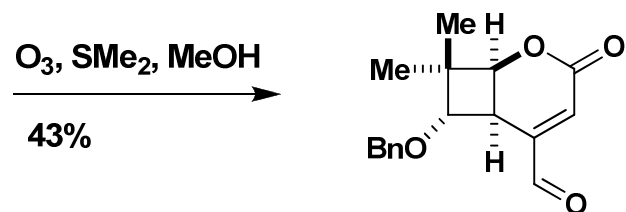
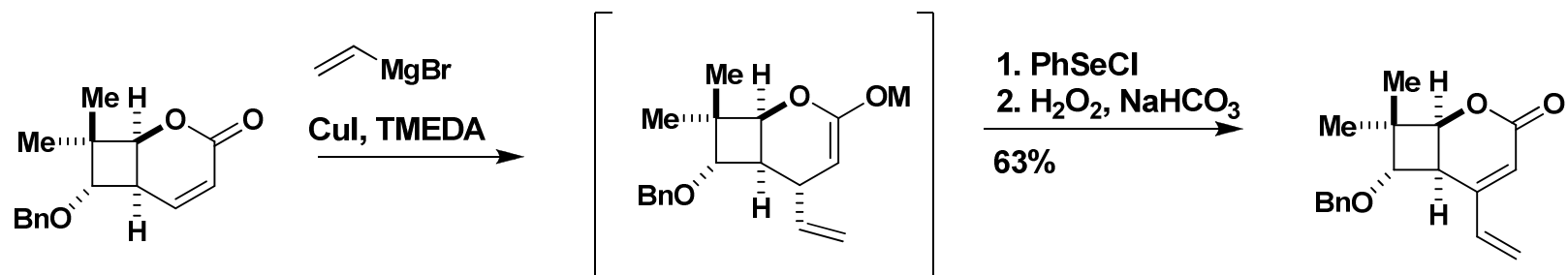


Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429.
Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135.
Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125.

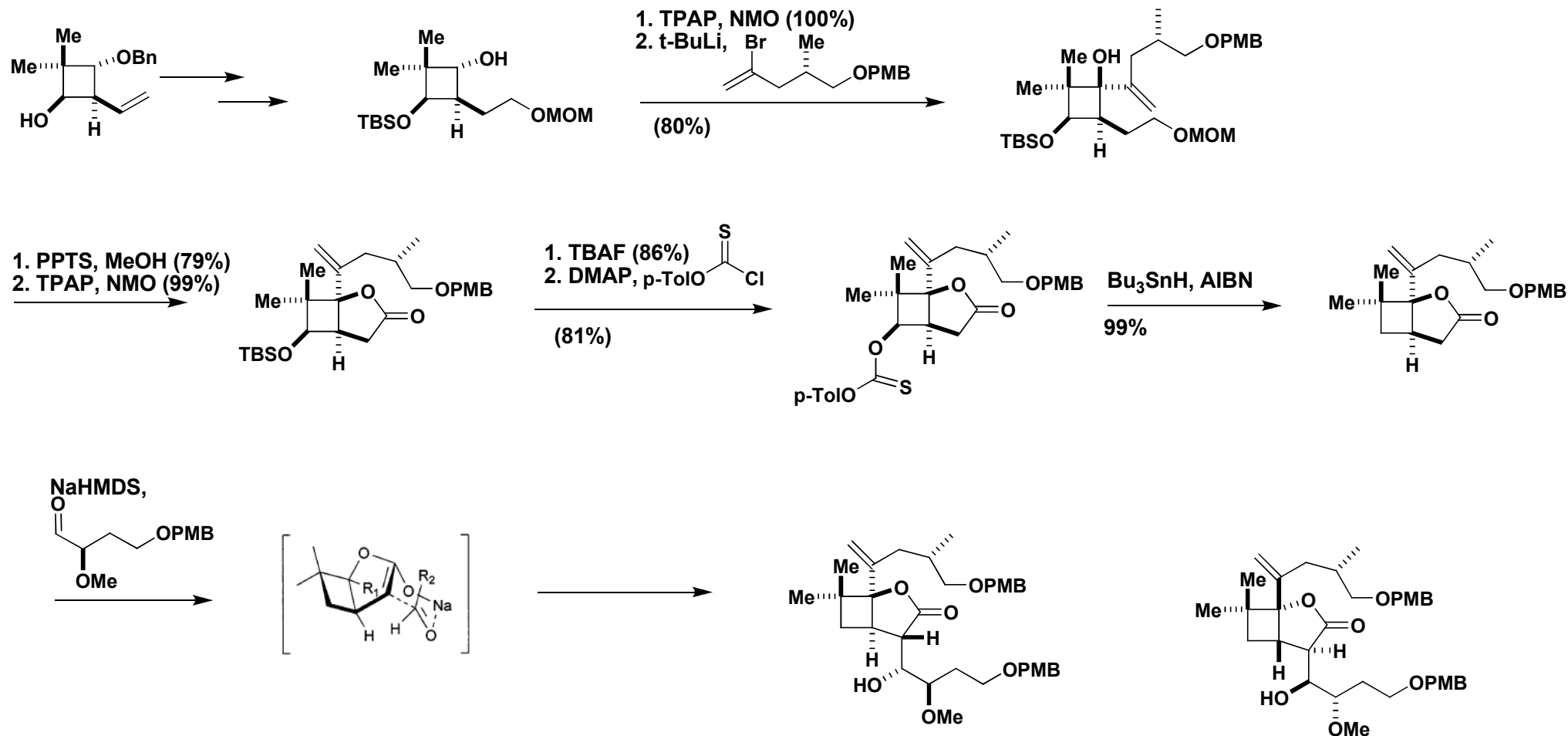
4.2.0 Lactone Approach



4.2.0 lactone Approach Continued



Installation of the side chains

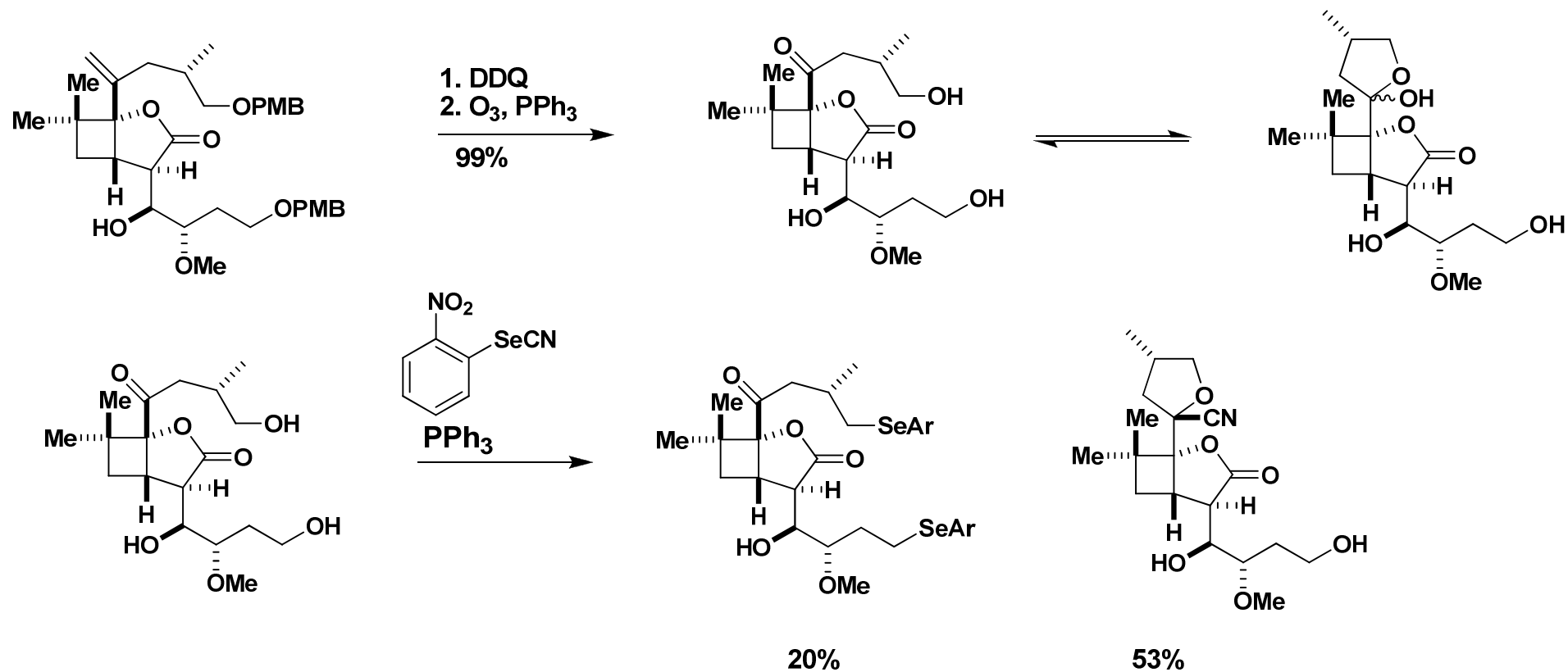


Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429.

Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135.

Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125.

Progress Toward the Synthesis of the Diene

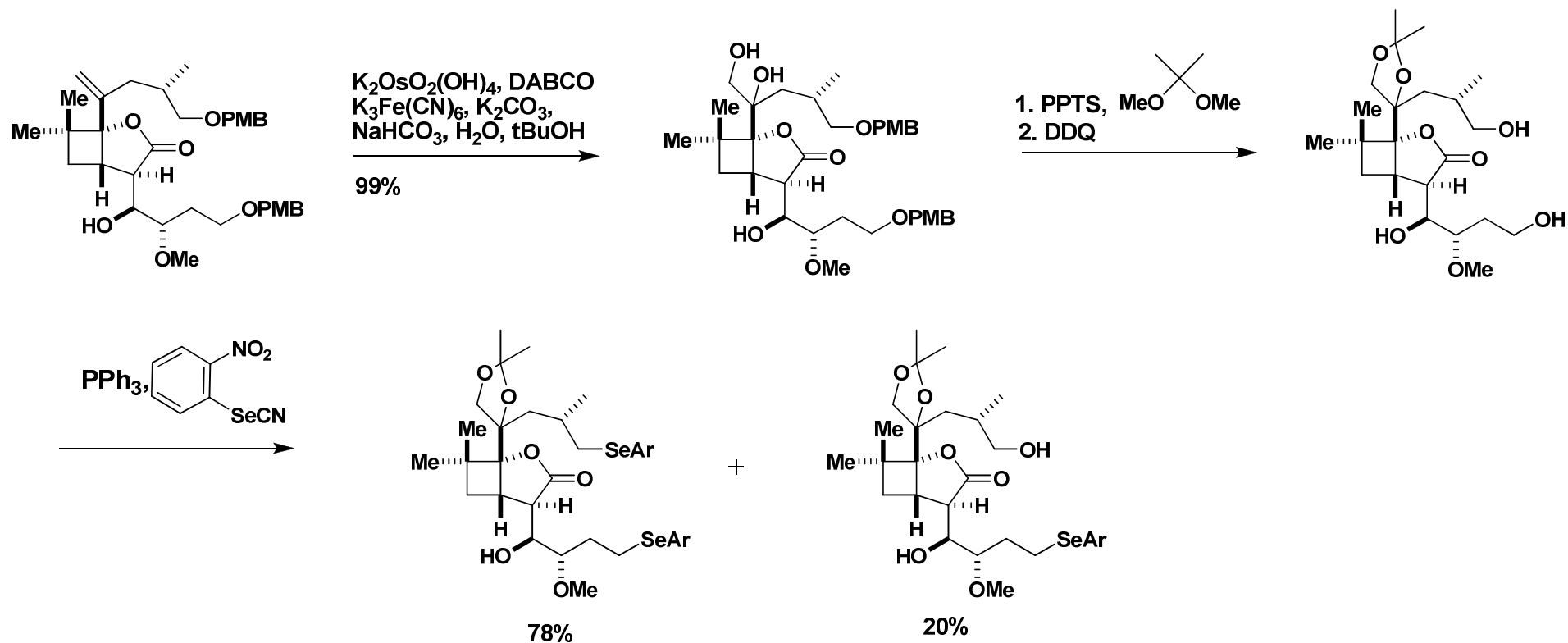


Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429.

Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135.

Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125

Other Attempts to Form the Diene for RCM

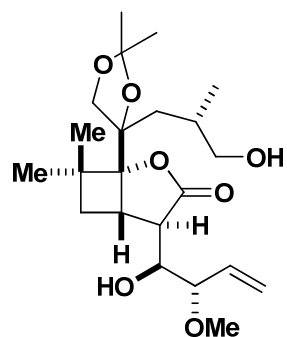
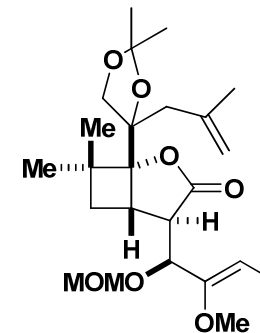
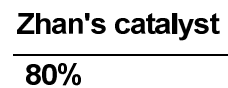
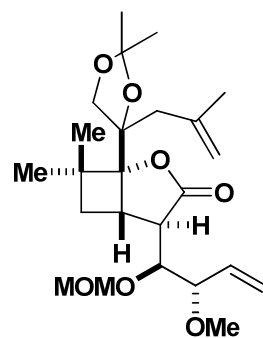
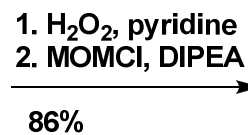
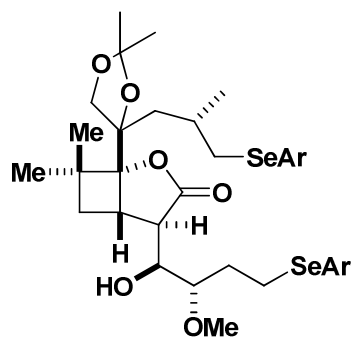


Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429.

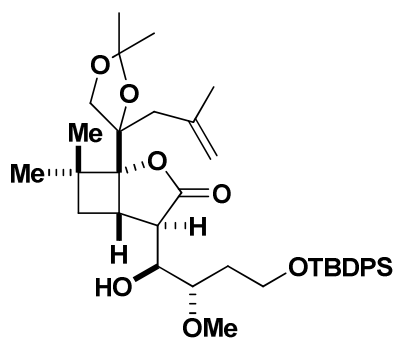
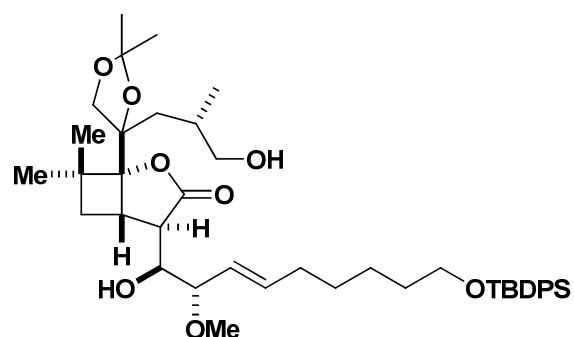
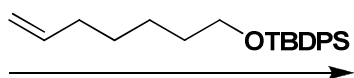
Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135.

Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125

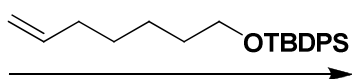
Ring Closing Metathesis Attempts



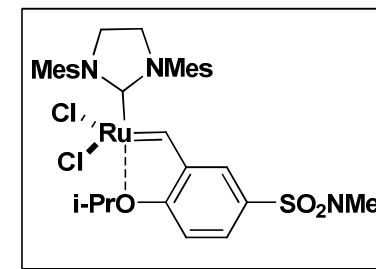
Zhan's catalyst



Zhan's catalyst



no reaction



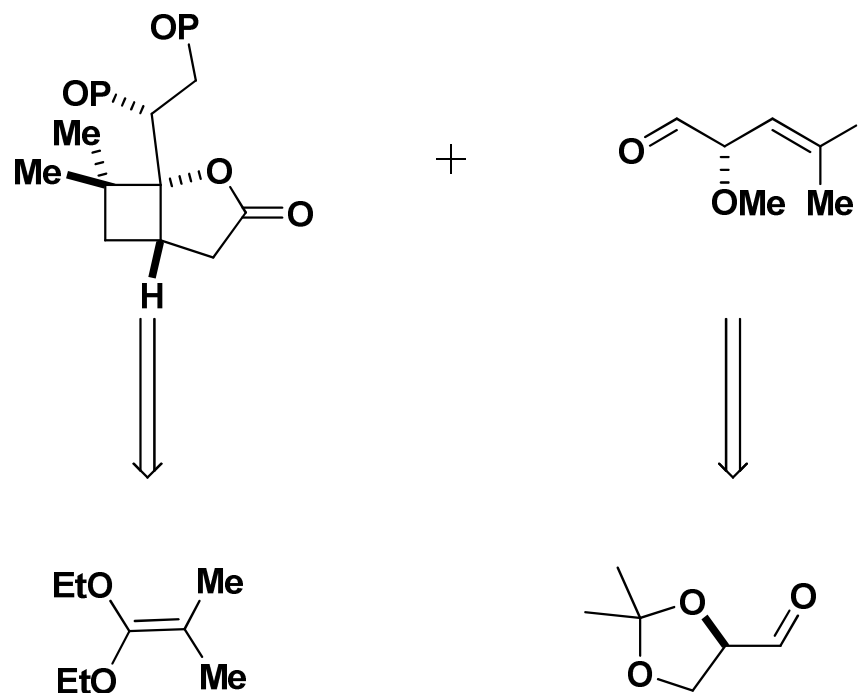
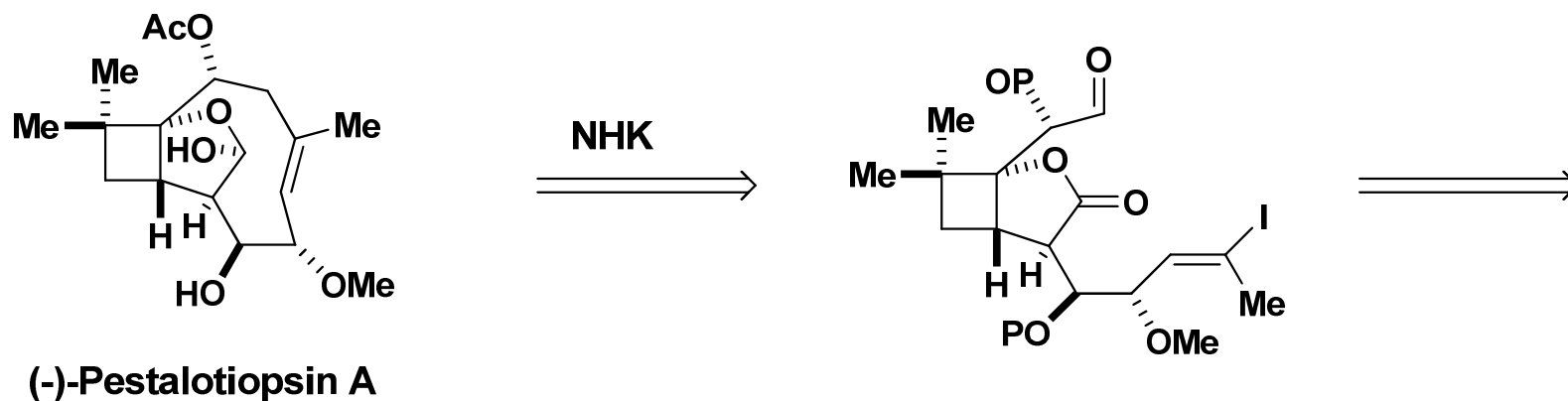
Zhan's catalyst

Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429.

Paquette, L. A.; Dong, S.; Parker, G. D. *J. Org. Chem.* **2007**, *72*, 7135.

Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125

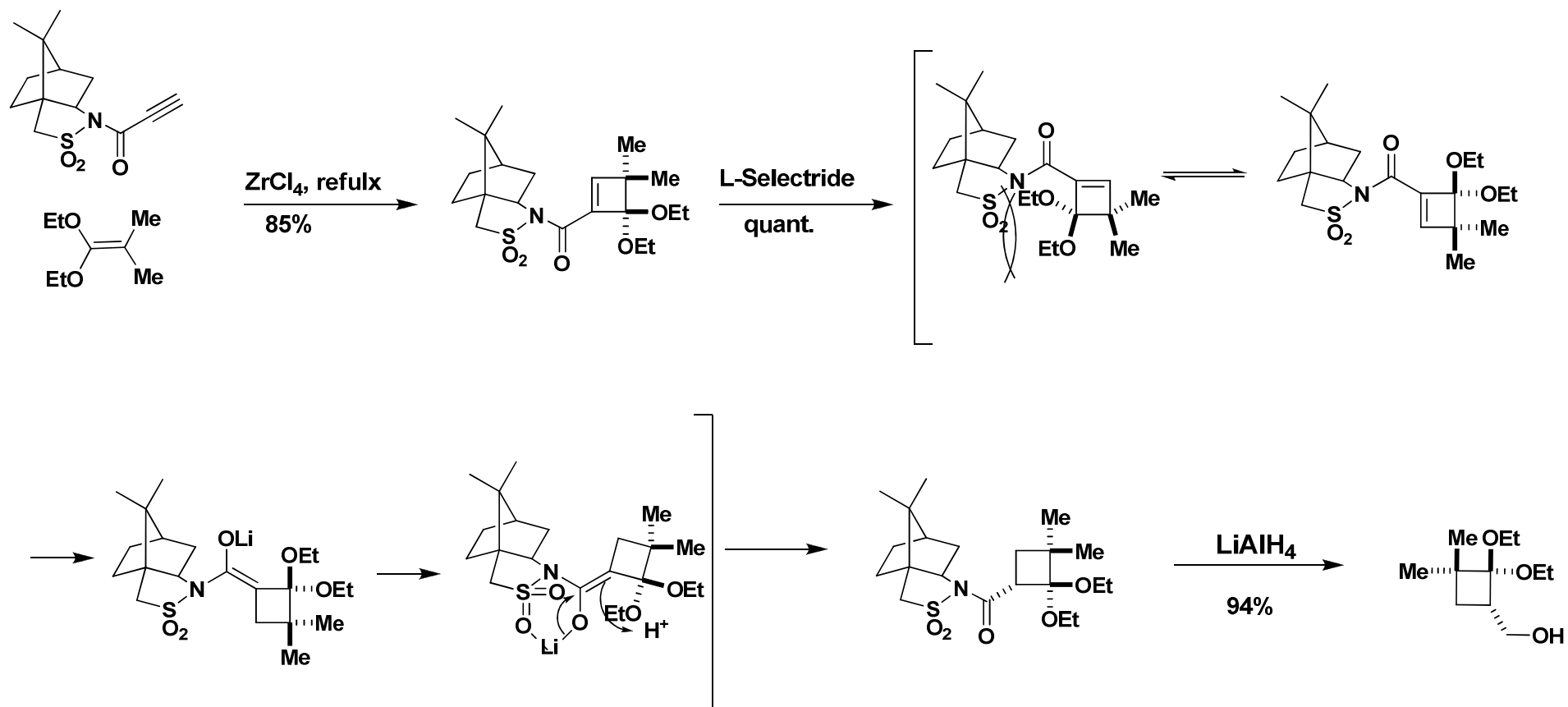
Tadano Retrosynthesis



Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron. Lett.* **2005**, *46*, 5815.

Takao, K.; Hayakawa, N.; Yamaa, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3426.

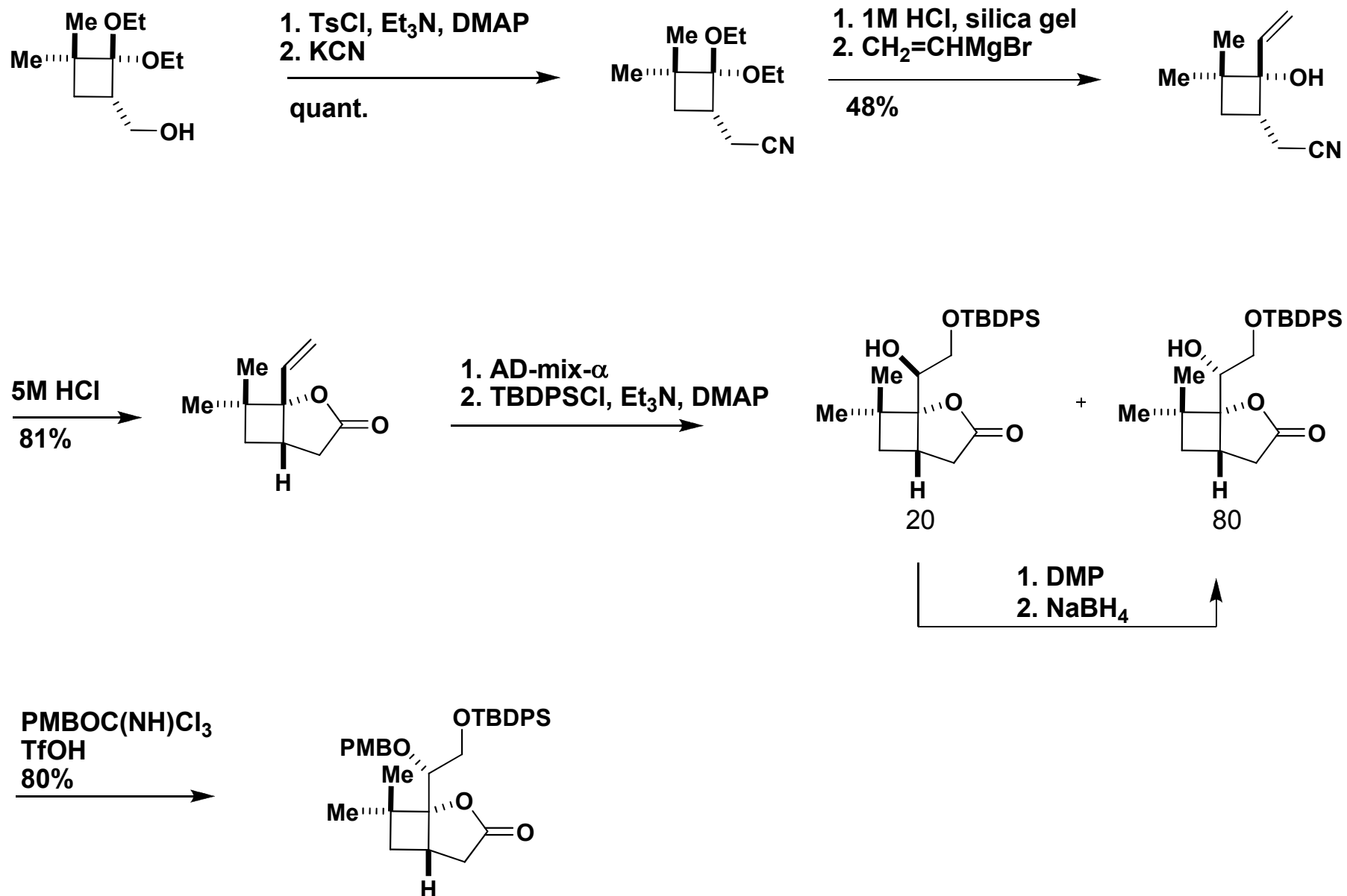
Synthesis of Bicyclic Lactone



Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron. Lett.* **2005**, *46*, 5815.

Takao, K.; Hayakawa, N.; Yamaa, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3426.

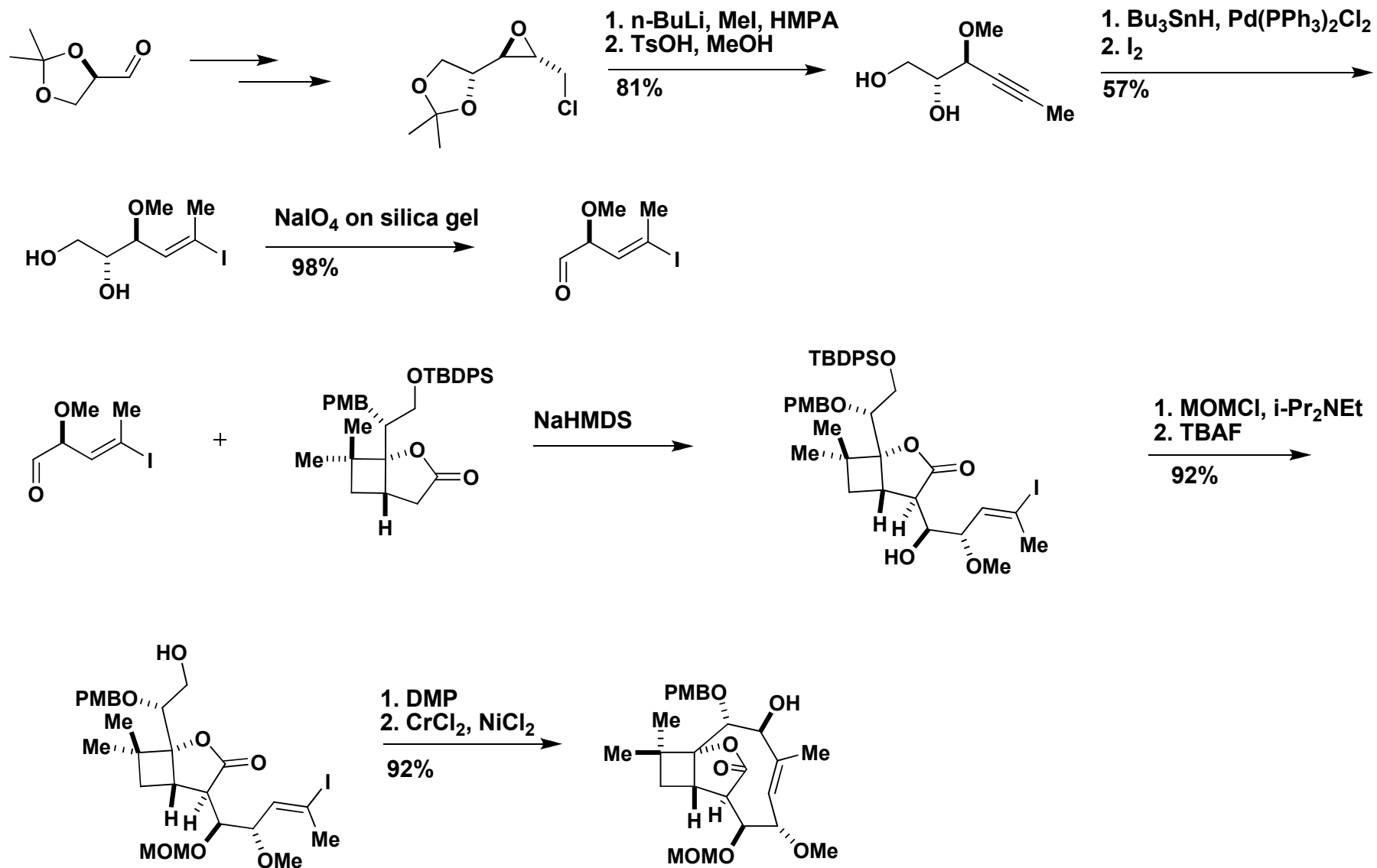
Synthesis of Bicyclic Lactone



Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron. Lett.* **2005**, *46*, 5815.

Takao, K.; Hayakawa, N.; Yamaa, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3426.

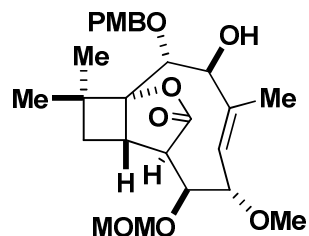
Preparation of the Chiral Aldehyde



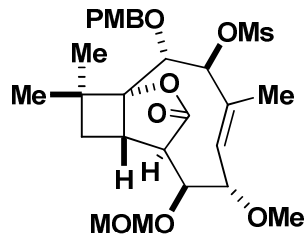
Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron. Lett.* **2005**, *46*, 5815.

Takao, K.; Hayakawa, N.; Yamaa, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3426.

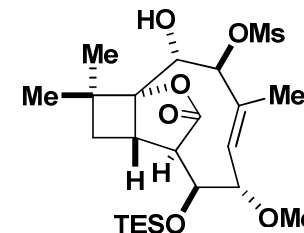
End Game



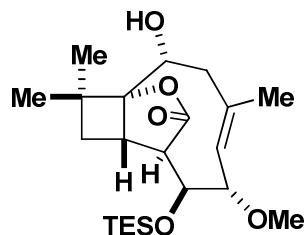
MsO₂, pyridine, DMAP
(93%)



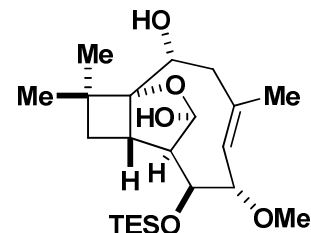
1. 4M HCl
2. TESOTf, pyridine (72%)
3. DDQ (89%)



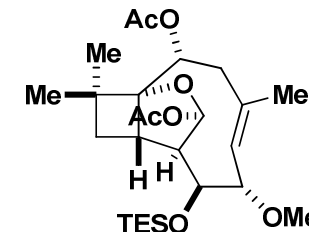
Pd₂(dba)₃, nBu₃P, NaBH₄
(87%)



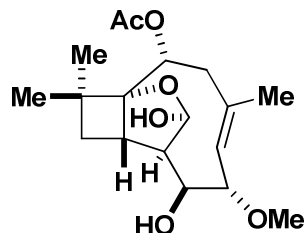
DIBAL (78%)



Ac₂O, pyridine
(82%)



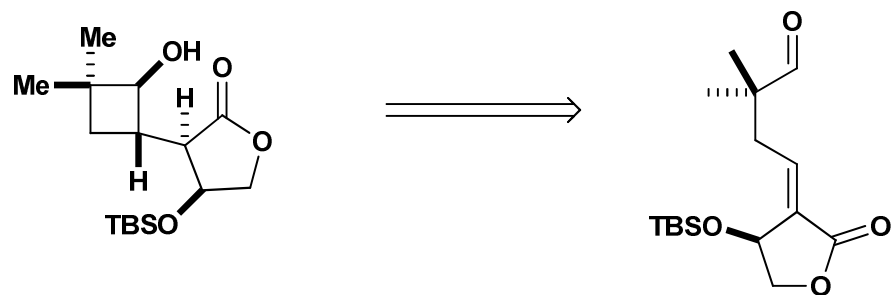
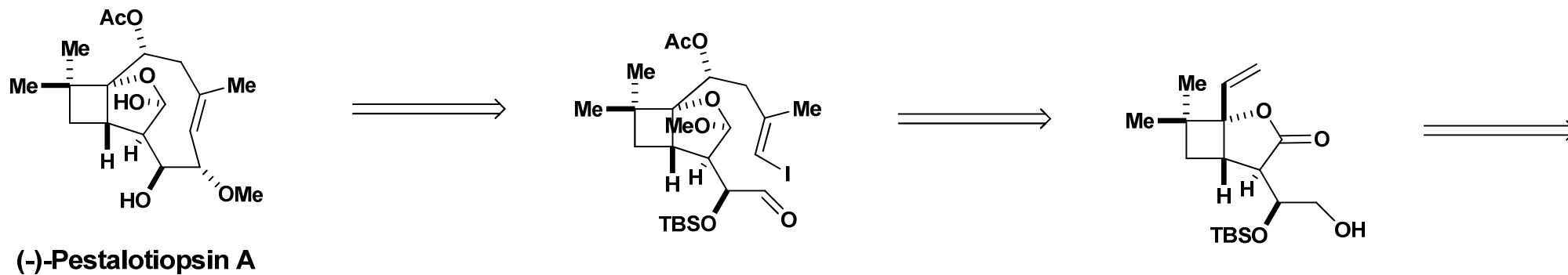
AcOH, H₂O, THF
(96%)



Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron. Lett.* **2005**, 46, 5815.

Takao, K.; Hayakawa, N.; Yamaa, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem. Int. Ed.* **2008**, 47, 3426.

Procter's retrosynthesis



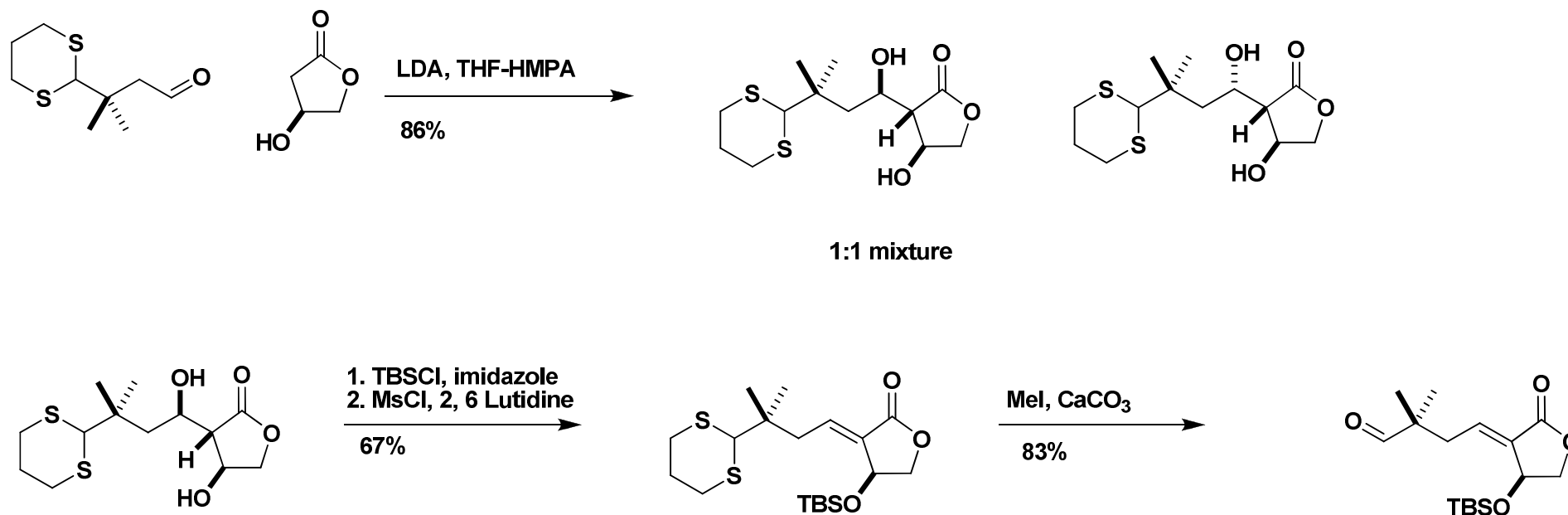
Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 3, 2001.

Johnston, D.; Couche, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2002**, 1, 328.

Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, 68, 3190.

Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 5631.

Synthesis of the Unsaturated Aldehyde



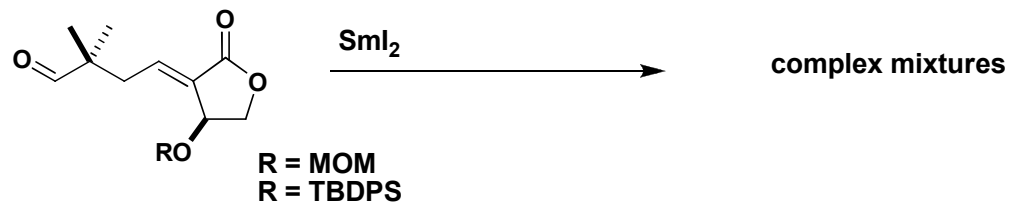
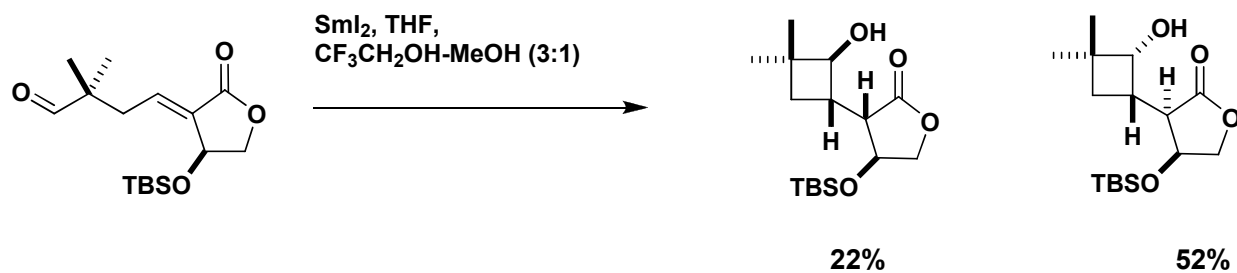
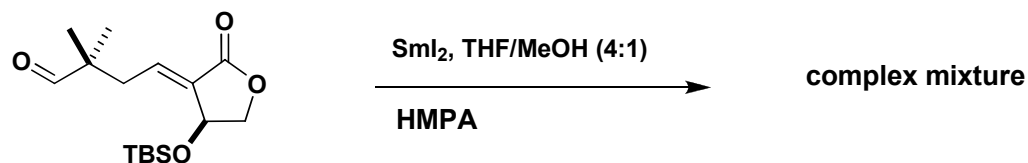
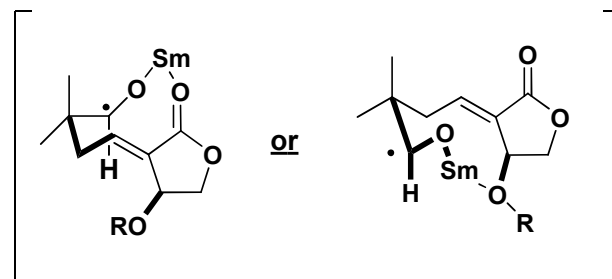
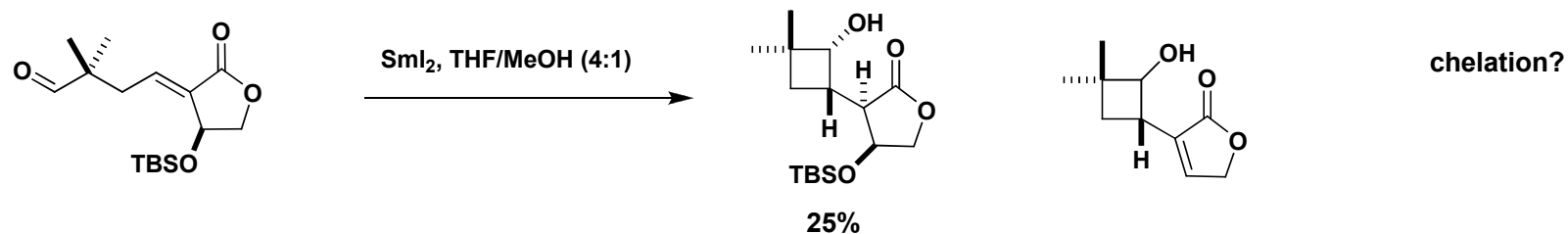
Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 3, 2001.

Johnston, D.; Couche, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2002**, 1, 328.

Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, 68, 3190.

Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 5631.

Sm(II) cyclization studies



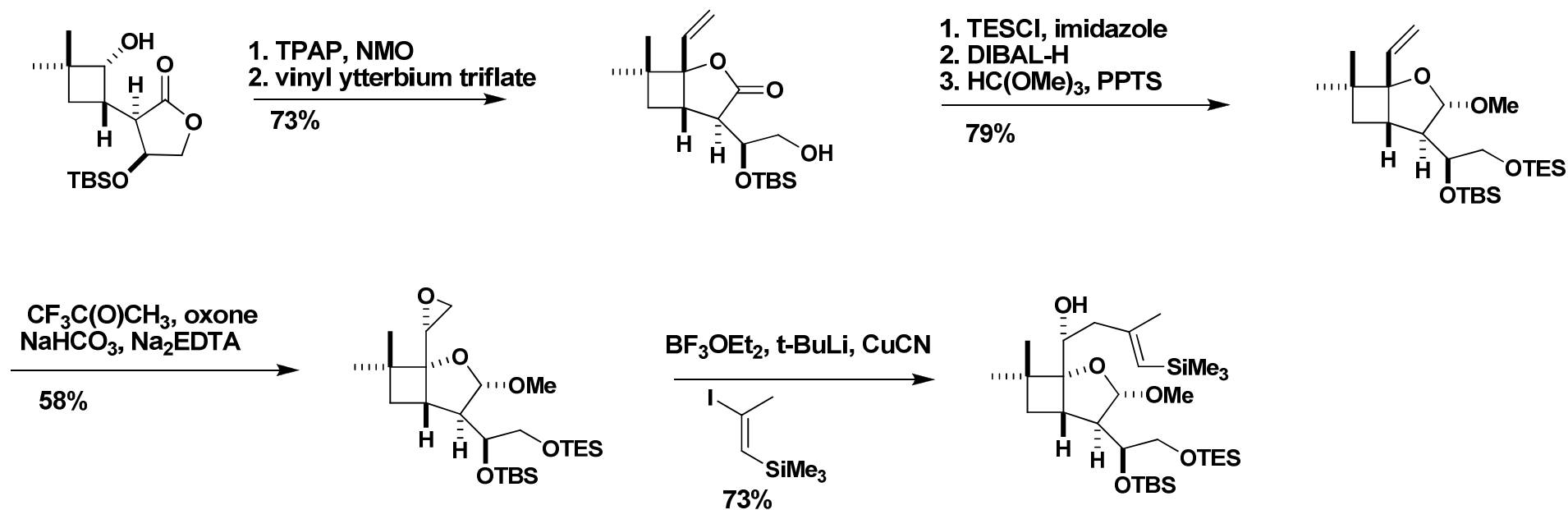
Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 3, 2001.

Johnston, D.; Couche, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2002**, 1, 328.

Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, 68, 3190.

Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 5631.

Synthesis of the NHK Precursor



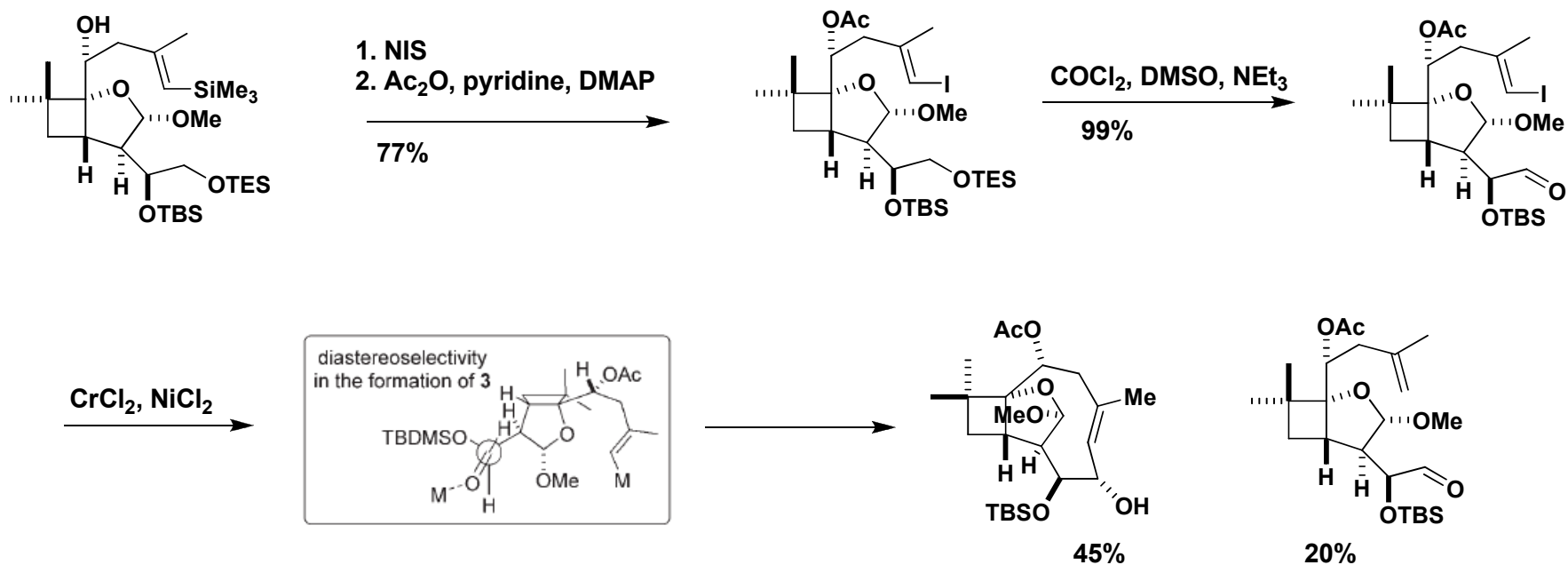
Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 3, 2001.

Johnston, D.; Couche, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2002**, 1, 328.

Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, 68, 3190.

Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 5631.

An Intramolecular NHK Reaction



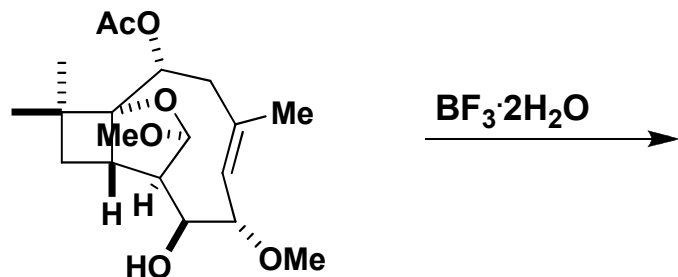
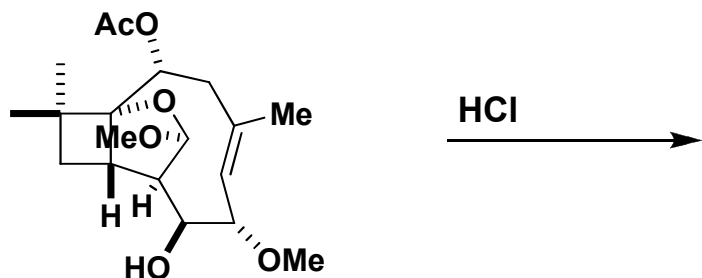
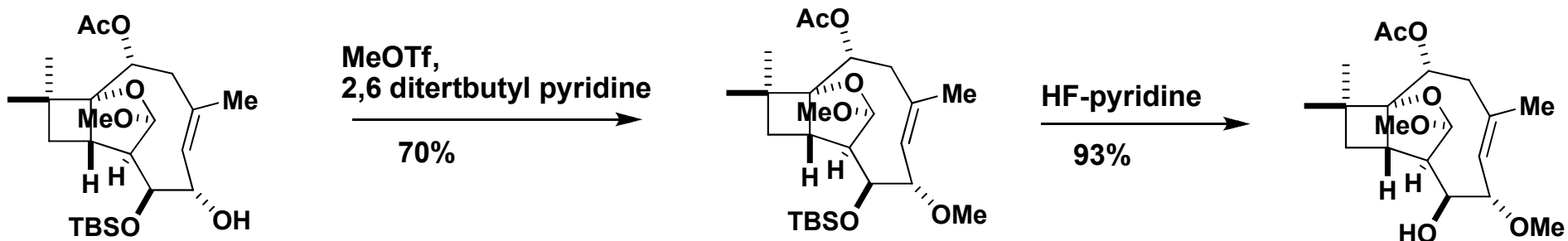
Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 3, 2001.

Johnston, D.; Couche, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2002**, 1, 328.

Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, 68, 3190.

Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 5631.

End Game Strategy



Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 3, 2001.

Johnston, D.; Couche, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2002**, 1, 328.

Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, 68, 3190.

Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem. Int. Ed.* **2008**, 47, 5631.

