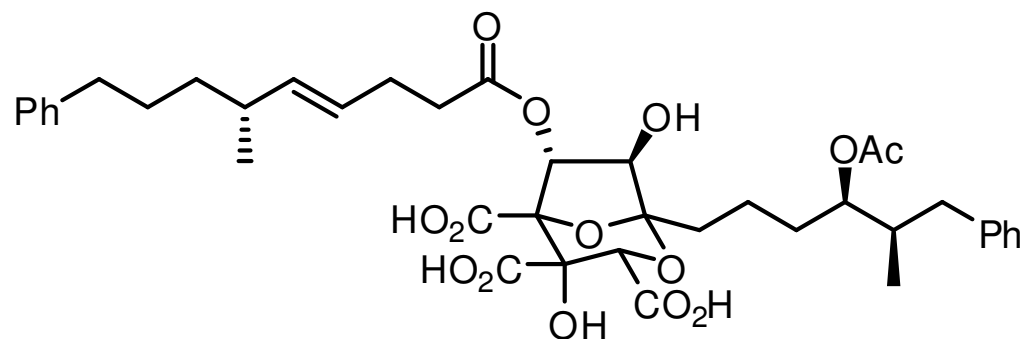


Zaragozic Acid C



Molecule in Review

Dan Griffith (Snyder Group)

July 10, 2009

Synthesis Literacy Group

Columbia University Chemistry

Key Literature

Total Syntheses Covered Here:

- Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.
- Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111.
- Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281.

Reviews:

- Nadin, A.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1622.
- Armstrong, A.; Blench, T. J. *Tetrahedron*, **2002**, *58*, 9321.

Griffith 2 - CU Synthesis Lit Group – Zaragozic Acid C

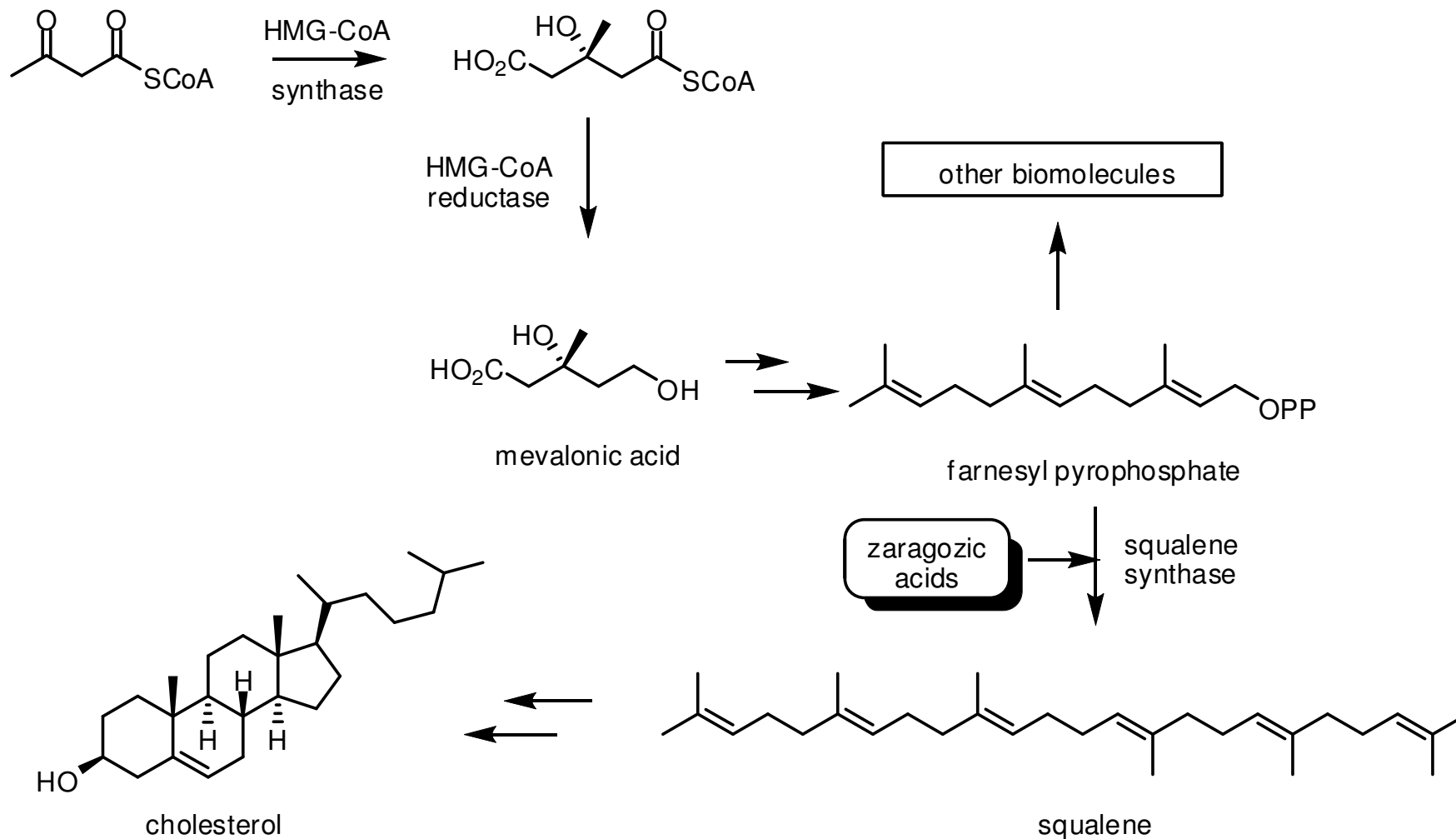
Isolation and biological activity

- Independently isolated in 1991-92 by three groups:
 - Merck
 - Glaxo
 - Mitsubishi Kasei Corporation

- Isolated from a variety of fungi
- Many family members containing different side chains
- Inhibitors of squalene synthase in cholesterol biosynthesis
- Zaragozic acid D also inhibits *ras*-farnesyl protein transferase

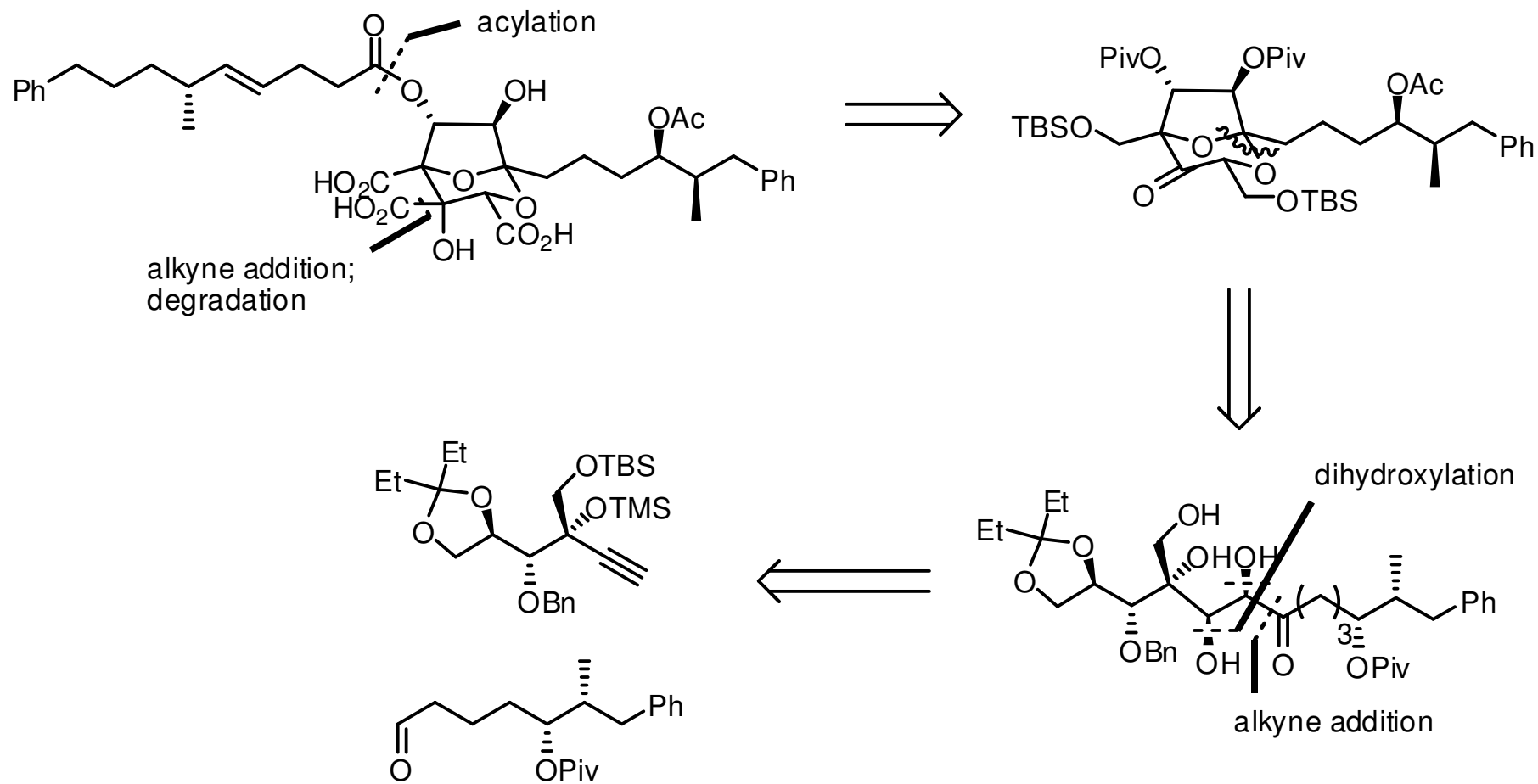
Griffith 3 - CU Synthesis Lit Group – Zaragozic Acid C

The Sterol Biosynthetic Pathway



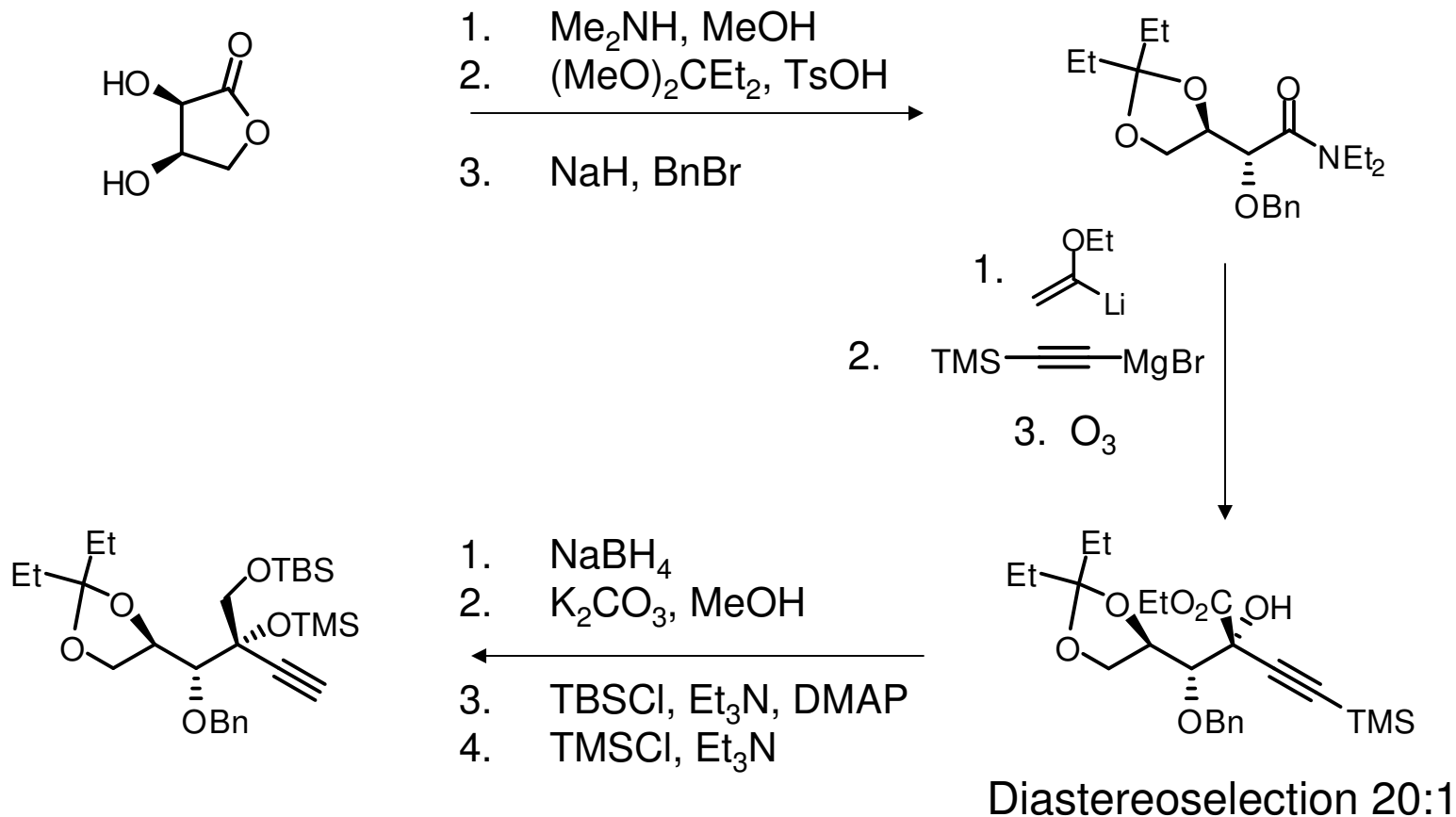
Griffith 4 - CU Synthesis Lit Group – Zaragozic Acid C

Carreira Retrosynthesis



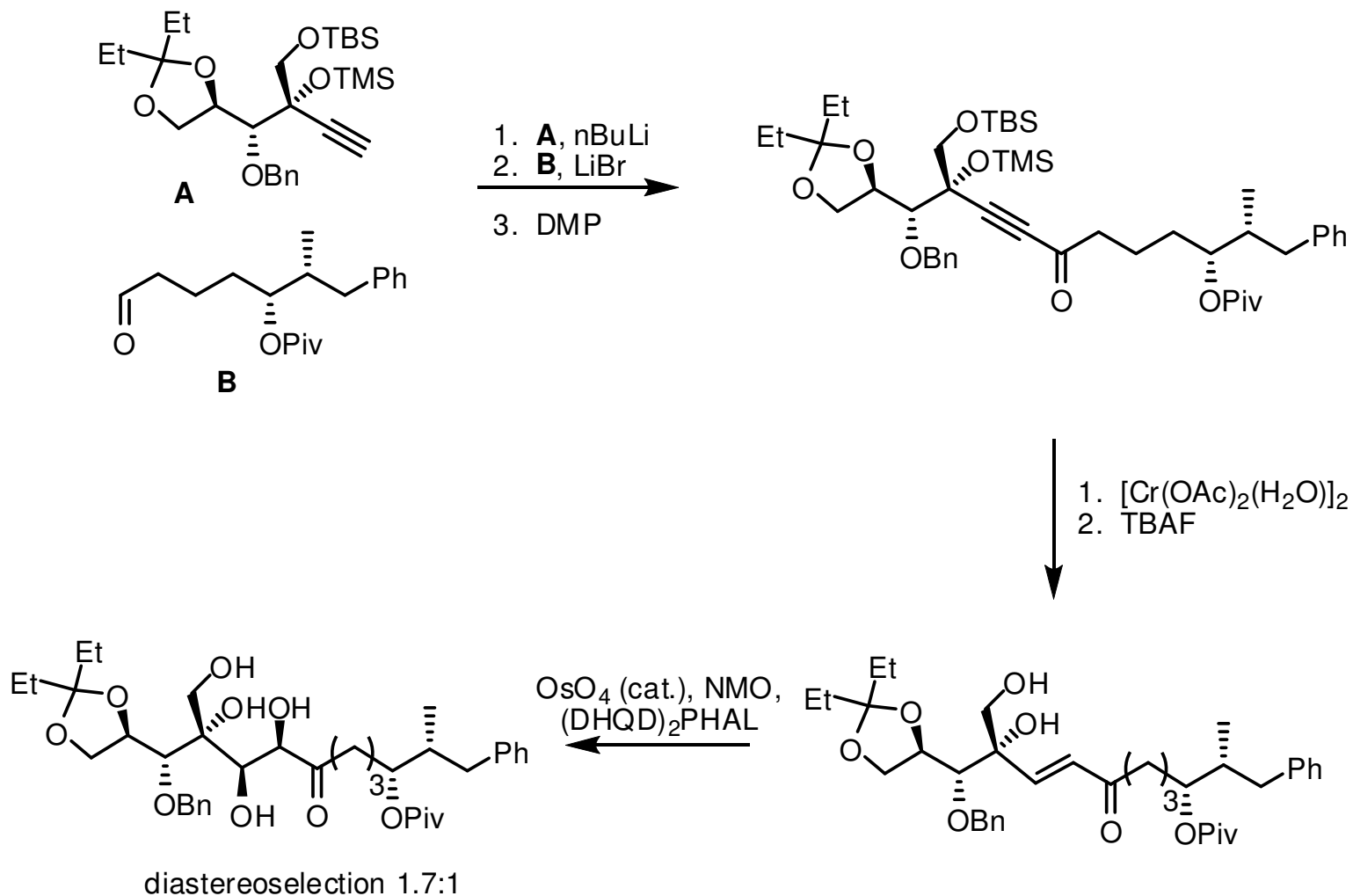
Griffith 5 - CU Synthesis Lit Group – Zaragozic Acid C

Carreira Synthesis



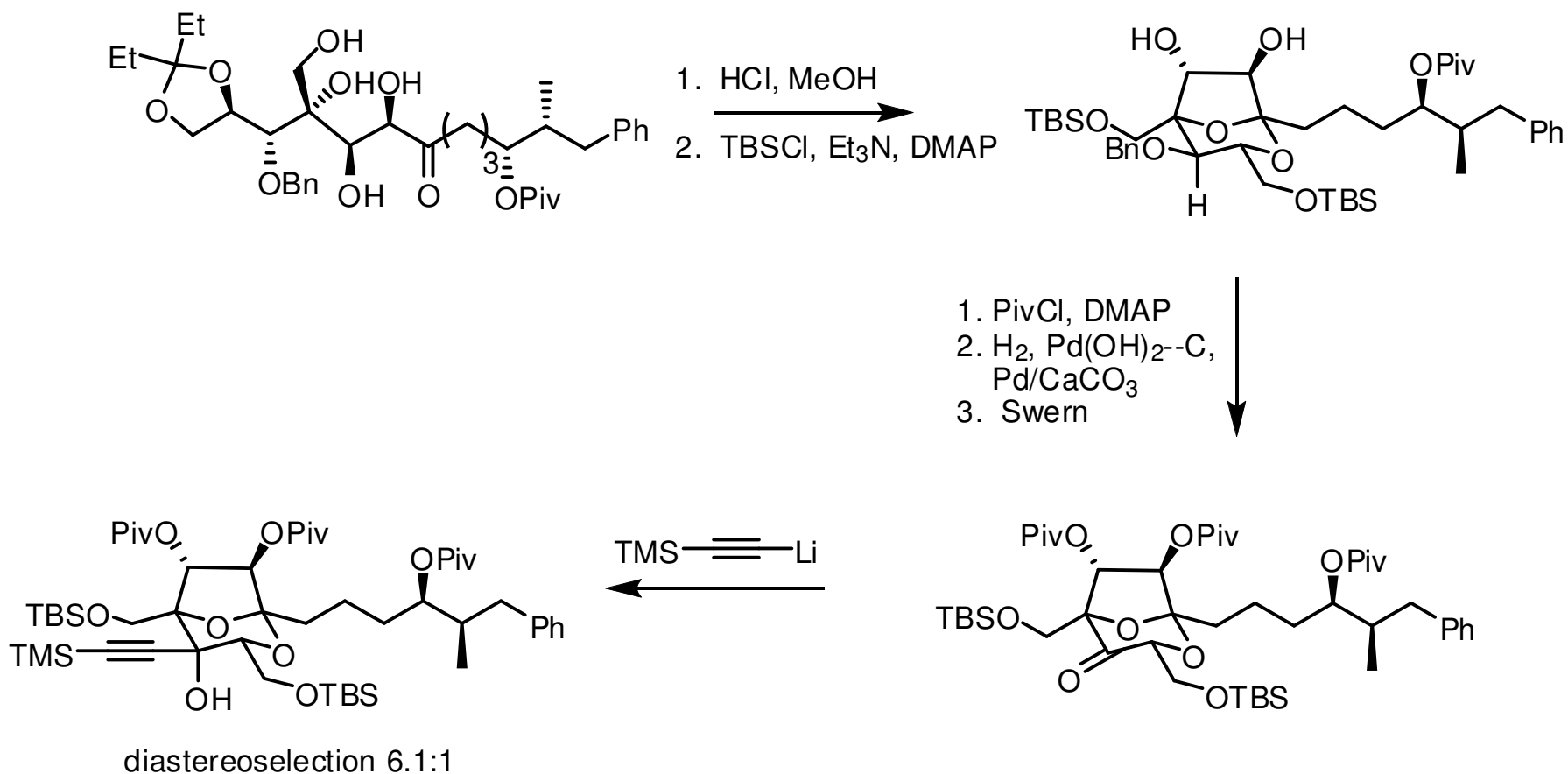
Griffith 6 - CU Synthesis Lit Group – Zaragozaic Acid C

Carreira Synthesis, continued



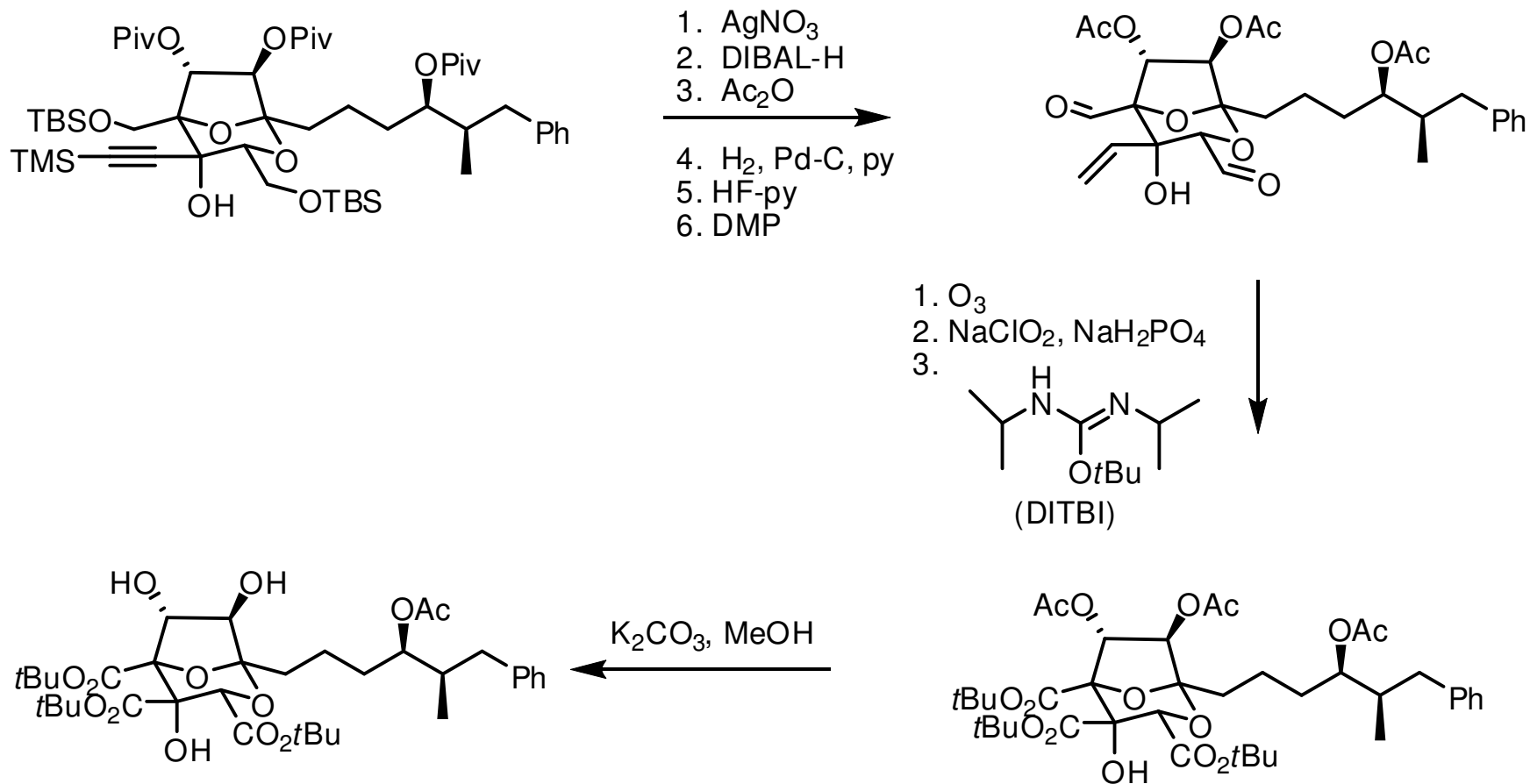
Griffith 7 - CU Synthesis Lit Group – Zaragozaic Acid C

Carreira Synthesis, continued



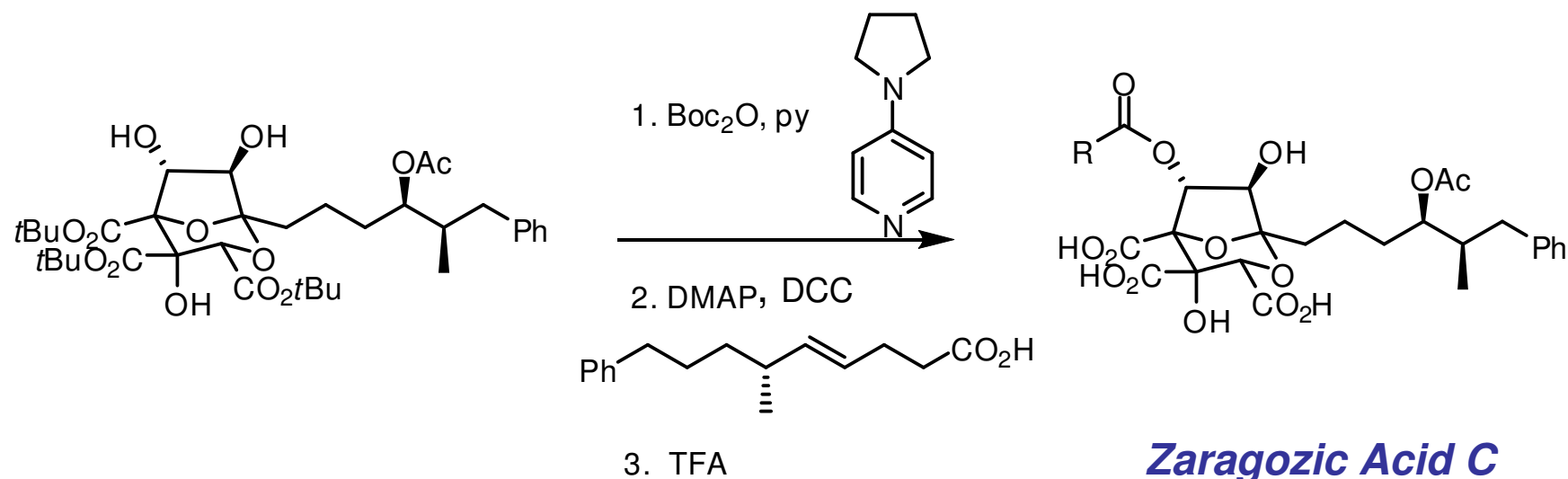
Griffith 8 - CU Synthesis Lit Group – Zaragozaic Acid C

Carreira Synthesis, continued



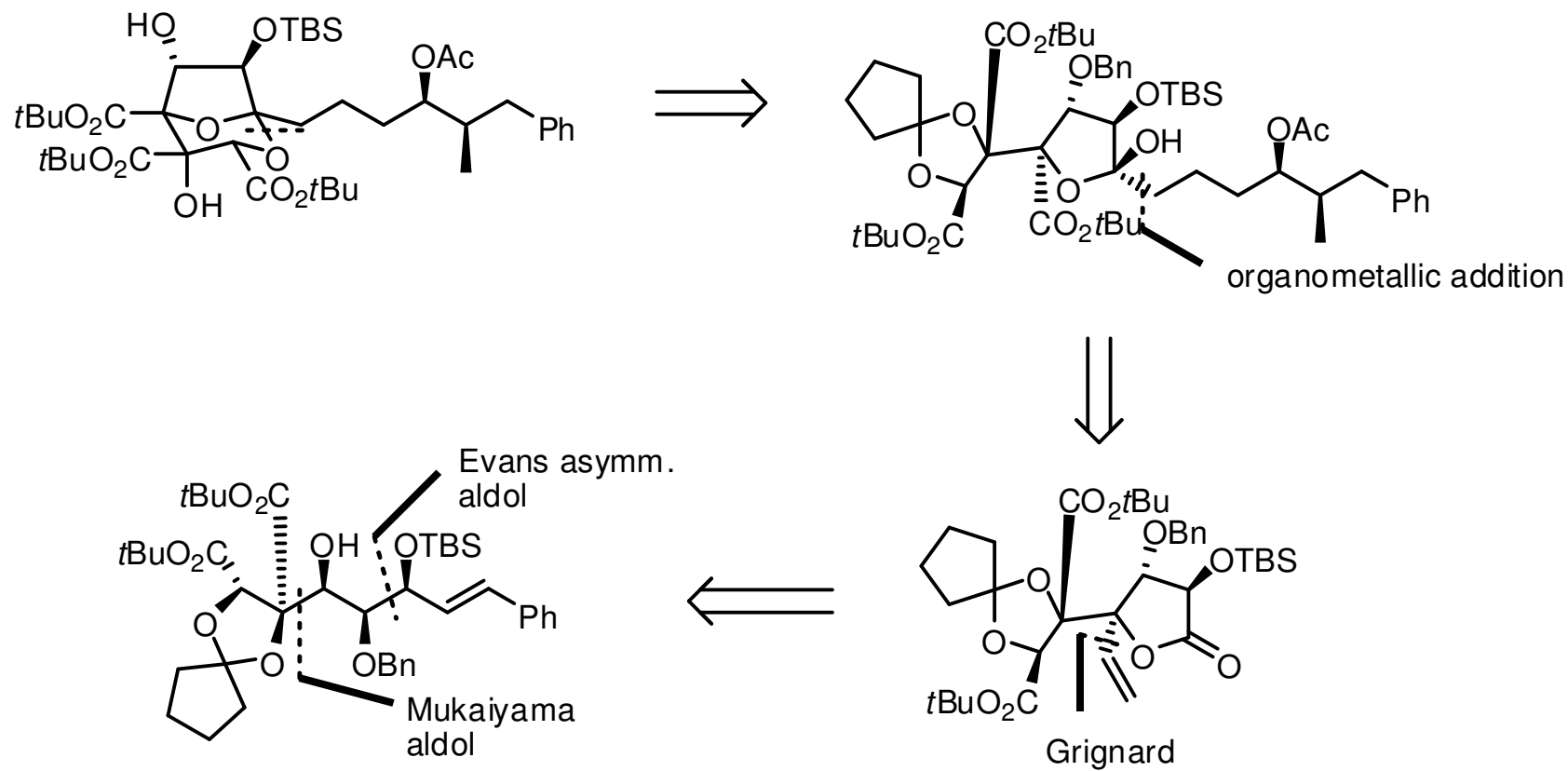
Griffith 9 - CU Synthesis Lit Group – Zaragozaic Acid C

Carreira Synthesis, concluded



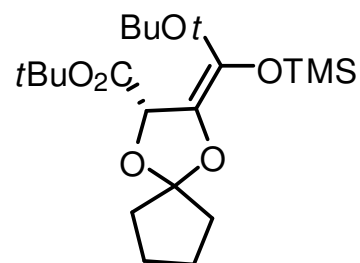
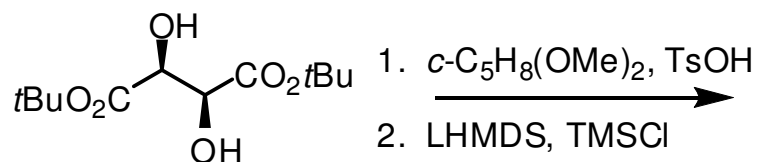
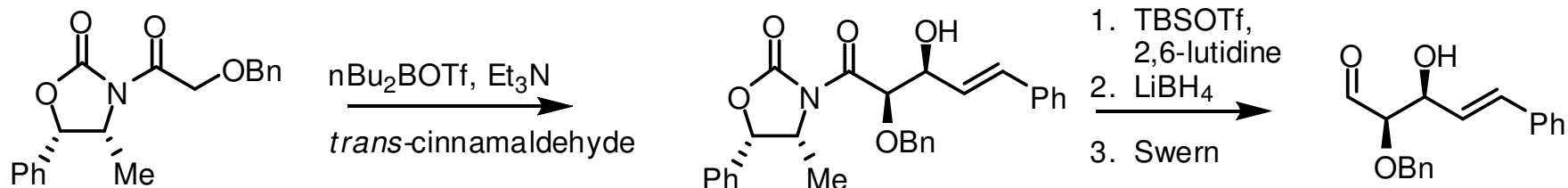
Griffith 10 - CU Synthesis Lit Group – Zaragozic Acid C

Evans Retrosynthesis

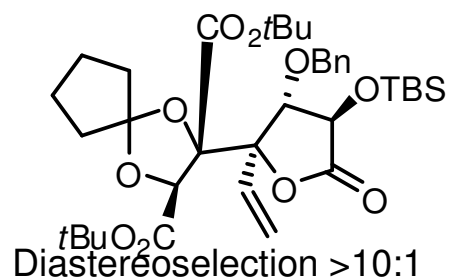


Griffith 11 - CU Synthesis Lit Group – Zaragozaic Acid C

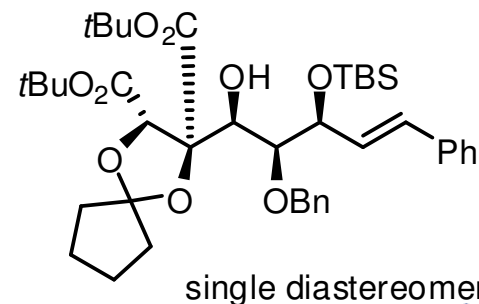
Evans Synthesis



$(iPrO)TiCl_3$

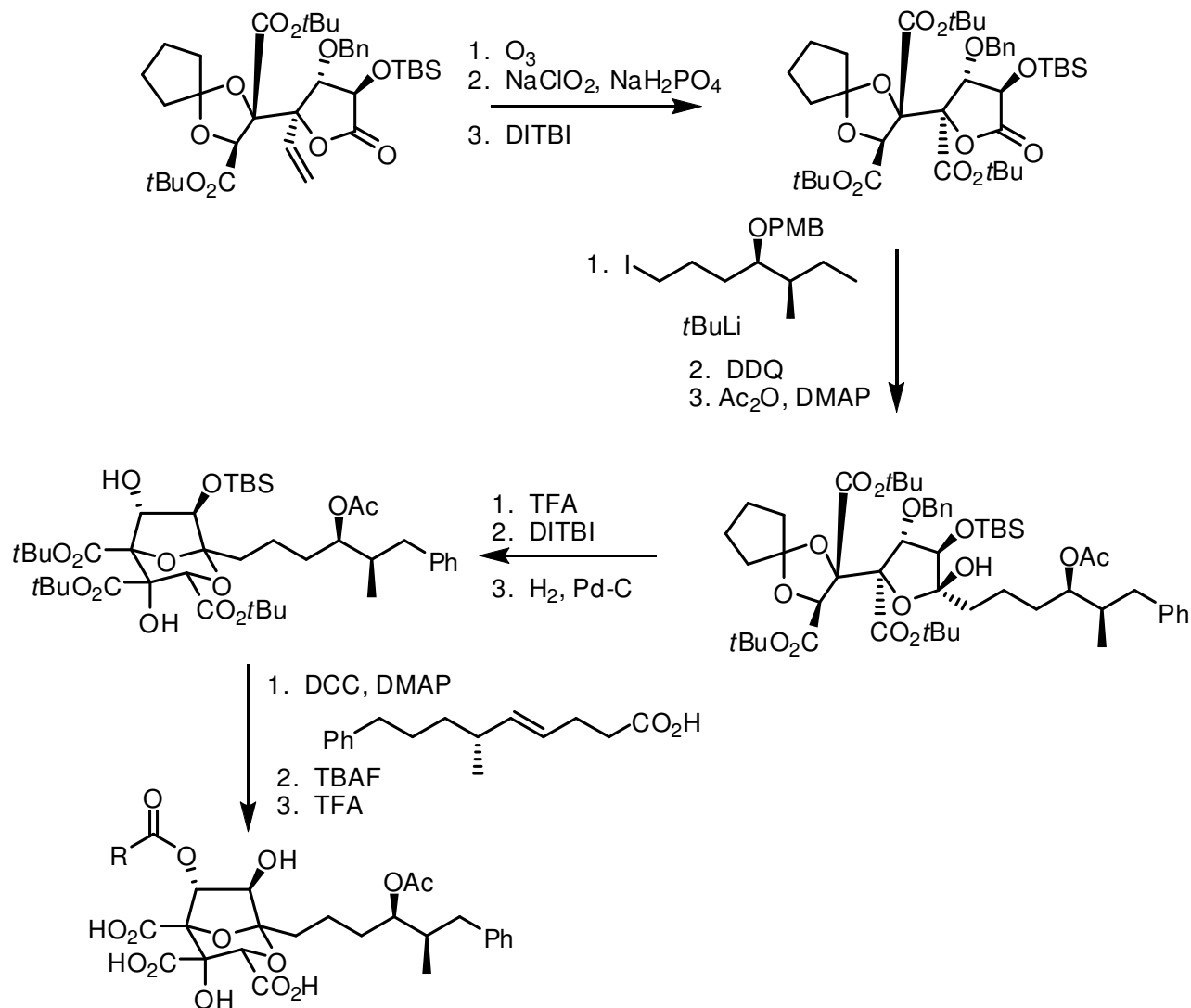


1. DMP
2. $CH_2=CHMgBr$
3. OsO_4, NMO
4. $Pb(OAc)_4$
5. TPAP, NMO



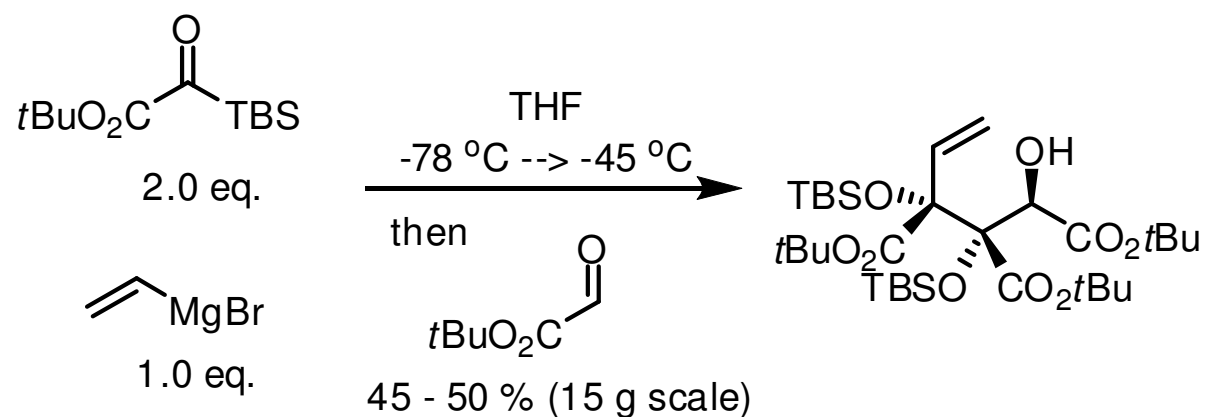
Griffith 12 - CU Synthesis Lit Group – Zaragozic Acid C

Evans Synthesis, concluded



Griffith 13 - CU Synthesis Lit Group – Zaragozic Acid C

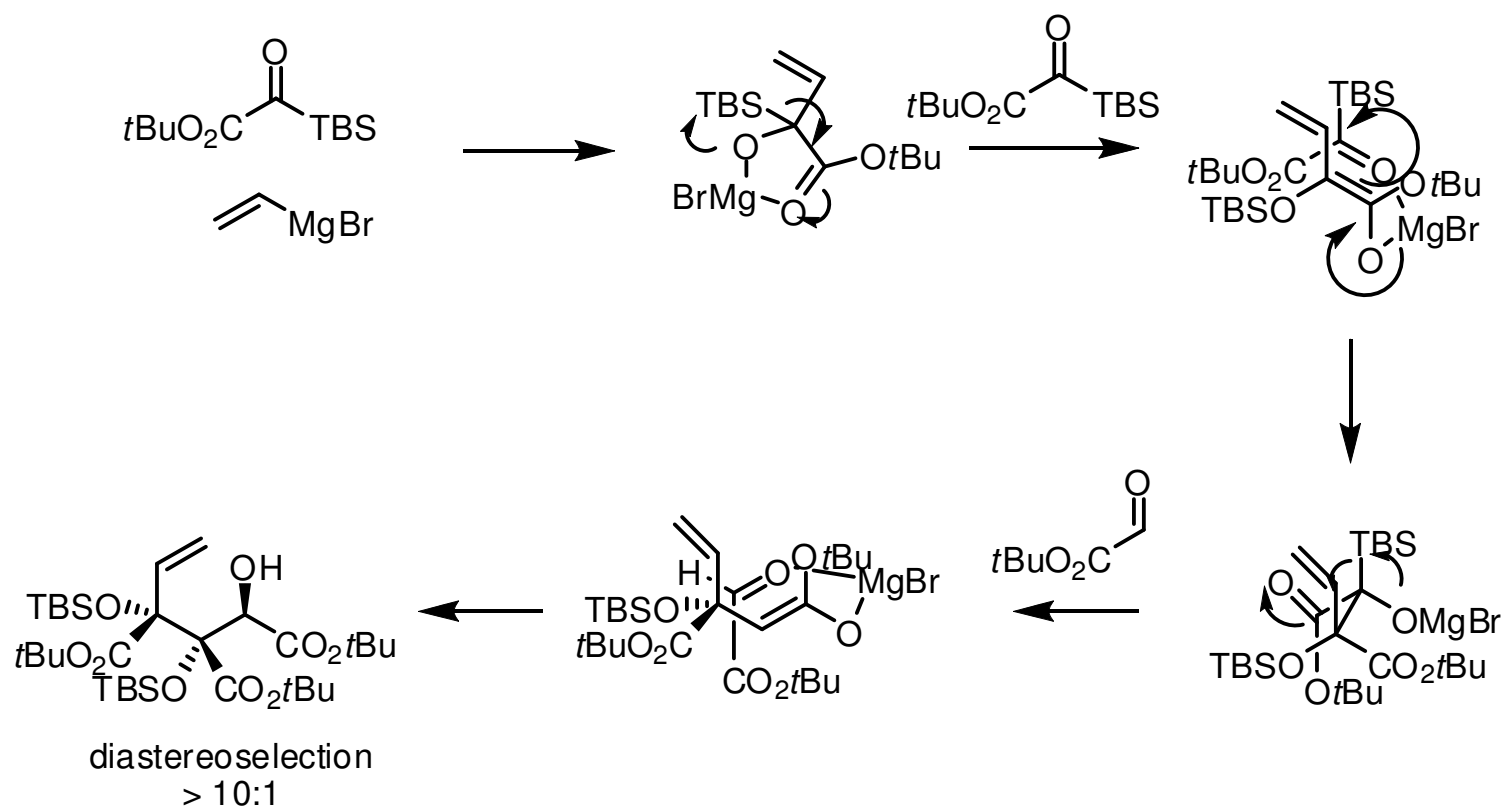
Johnson Synthesis



Mechanism?

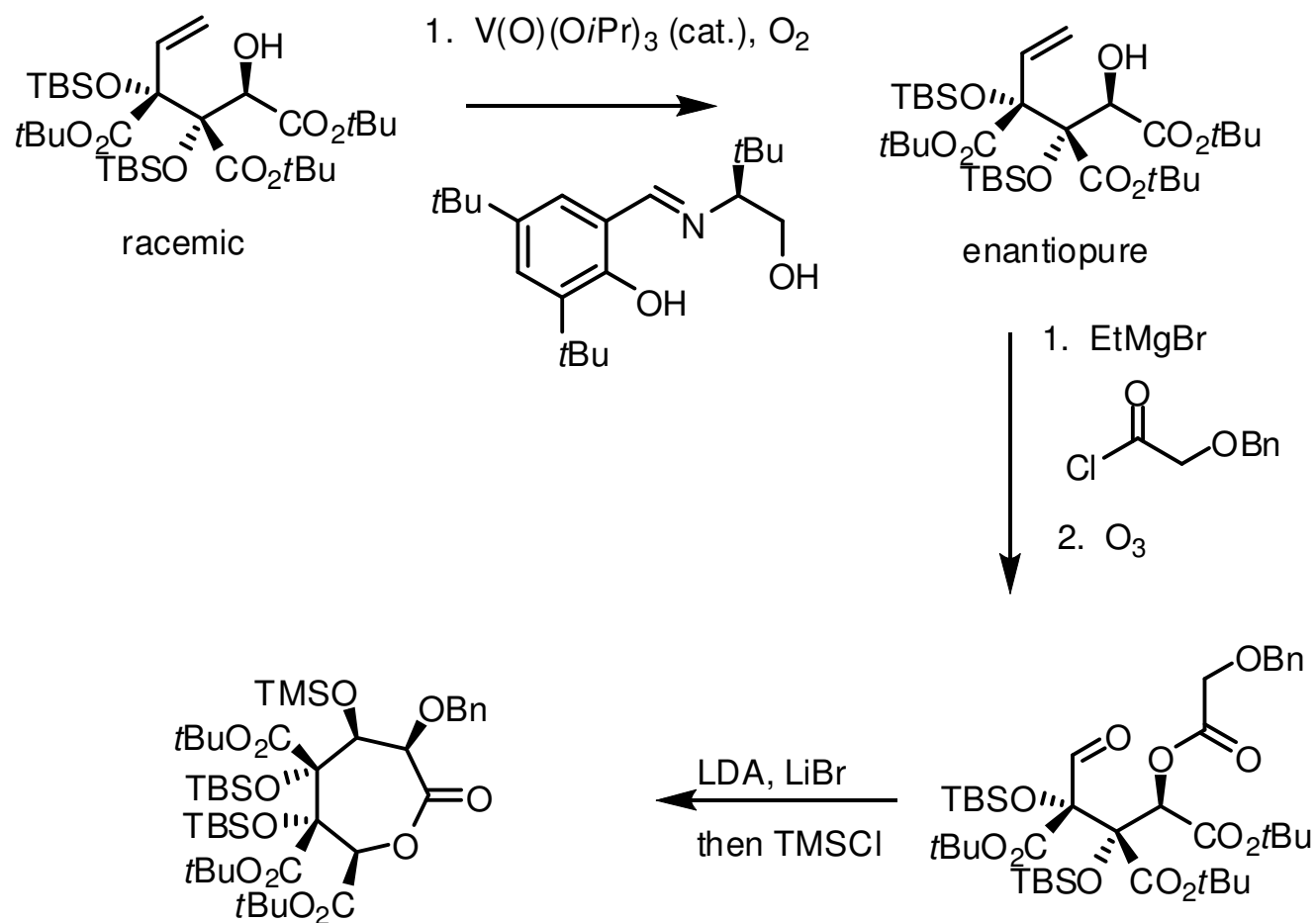
Griffith 15 - CU Synthesis Lit Group – Zaragozaic Acid C

Johnson Synthesis



Griffith 16 - CU Synthesis Lit Group – Zaragozaic Acid C

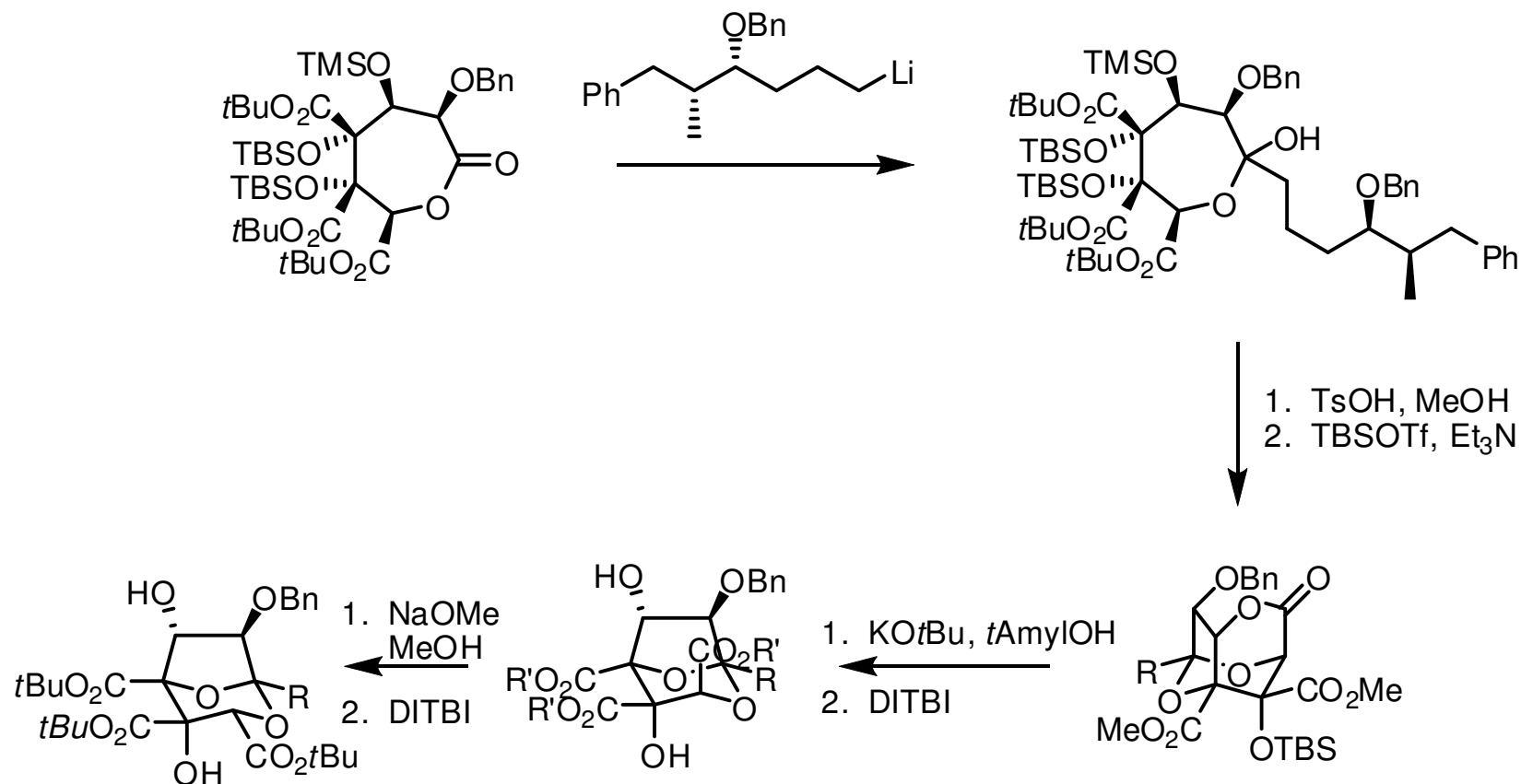
Johnson Synthesis, continued



Diastereoselection >20:1

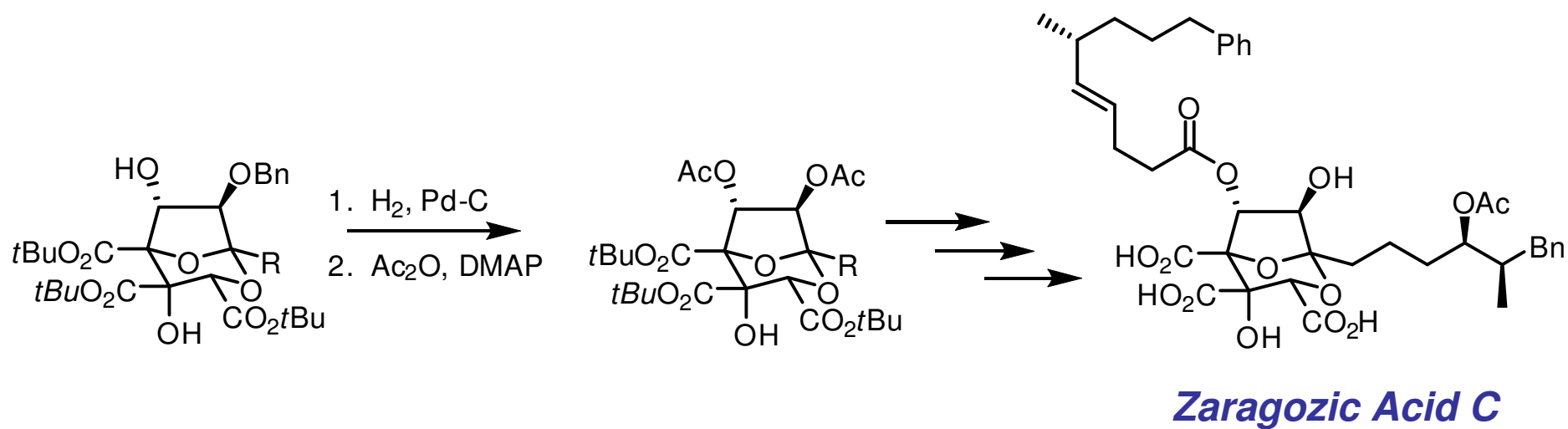
Griffith 17 - CU Synthesis Lit Group – Zaragozic Acid C

Johnson Synthesis, continued



Griffith 18 - CU Synthesis Lit Group – Zaragozaic Acid C

Johnson Synthesis, concluded



Griffith 19 - CU Synthesis Lit Group – Zaragozic Acid C

Comparison

Chemist	Step Count	Protections/ deprotections	Oxidations	Reductions
Carreira	33	17	7	3
Evans	22	7	7	1
Johnson	18	7	1	0

Griffith 20 - CU Synthesis Lit Group – Zaragozaic Acid C

END