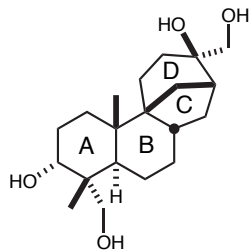


# An Analysis of the Total Syntheses of Aphidicolin

An Evans Group Afternoon Seminar

Krista Beaver

March 20, 1998

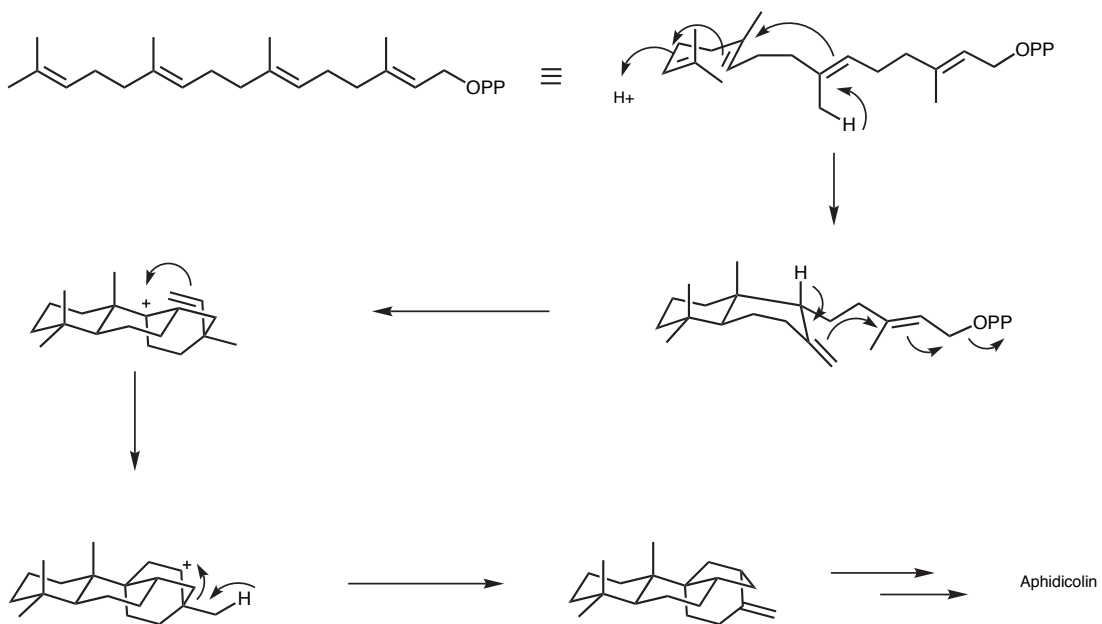


Aphidicolin

- Isolated from the fungus *Cephalosporium aphidicola* (Hesp, *Chem. Comm.* **1972**, 1027)
- Structure determined by X-ray crystallography and chemical degradation
- Demonstrated activity against DNA viruses and human and murine neoplastic cell lines; acts via inhibition of DNA polymerase  $\alpha$  (*Cell* **1981**, 23, 647)

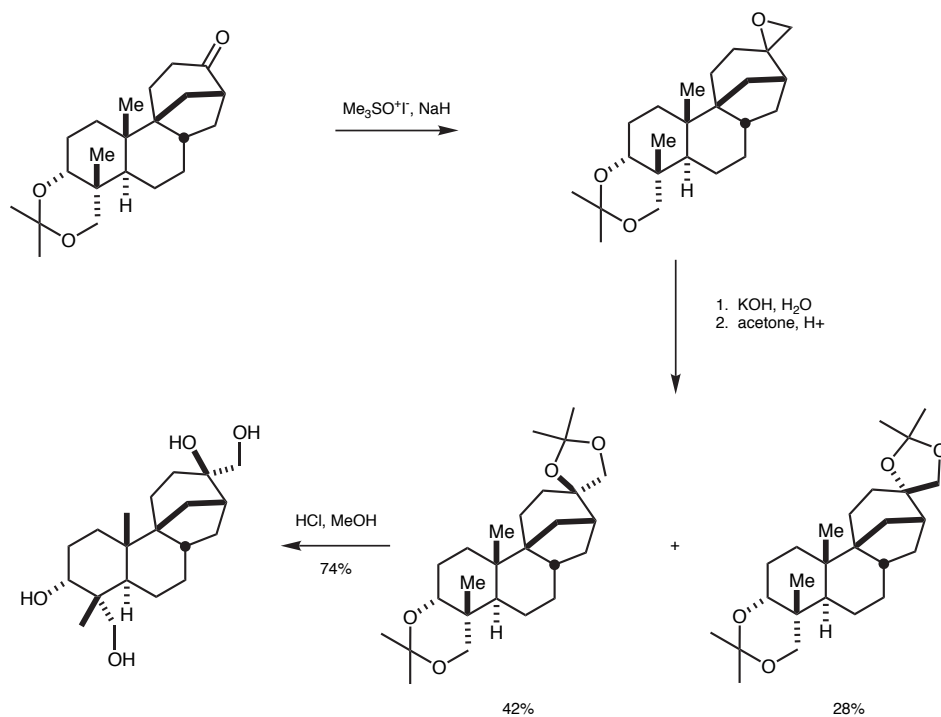
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## Proposed Biosynthesis



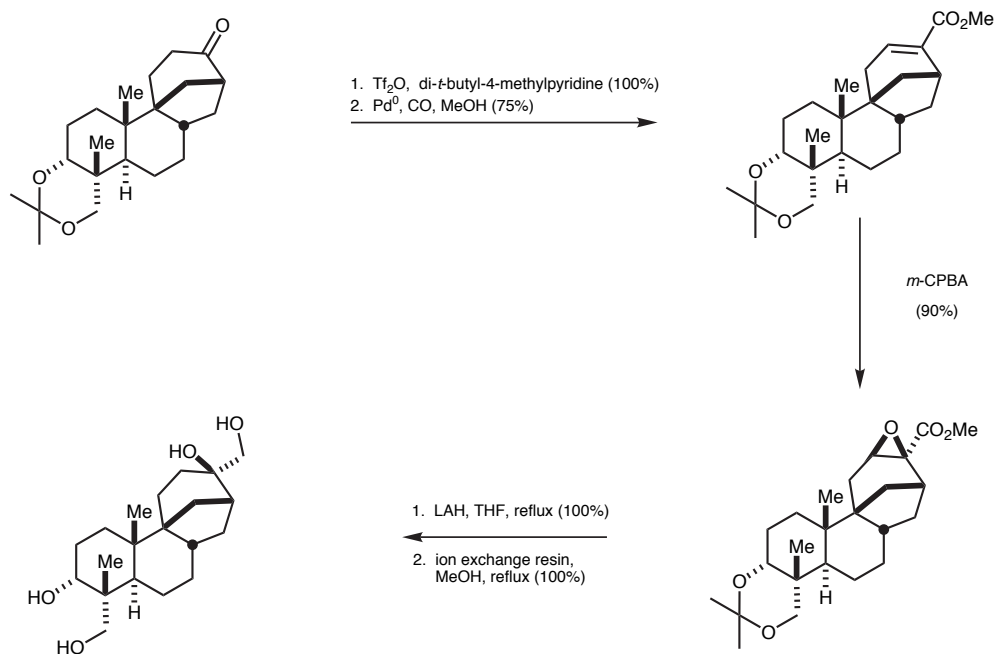
Hanson, *JCS Perkins* **1988**, 1477

Endgame Strategies - An Early Approach



Hesp, *JCS Perkins I* 1973, 284

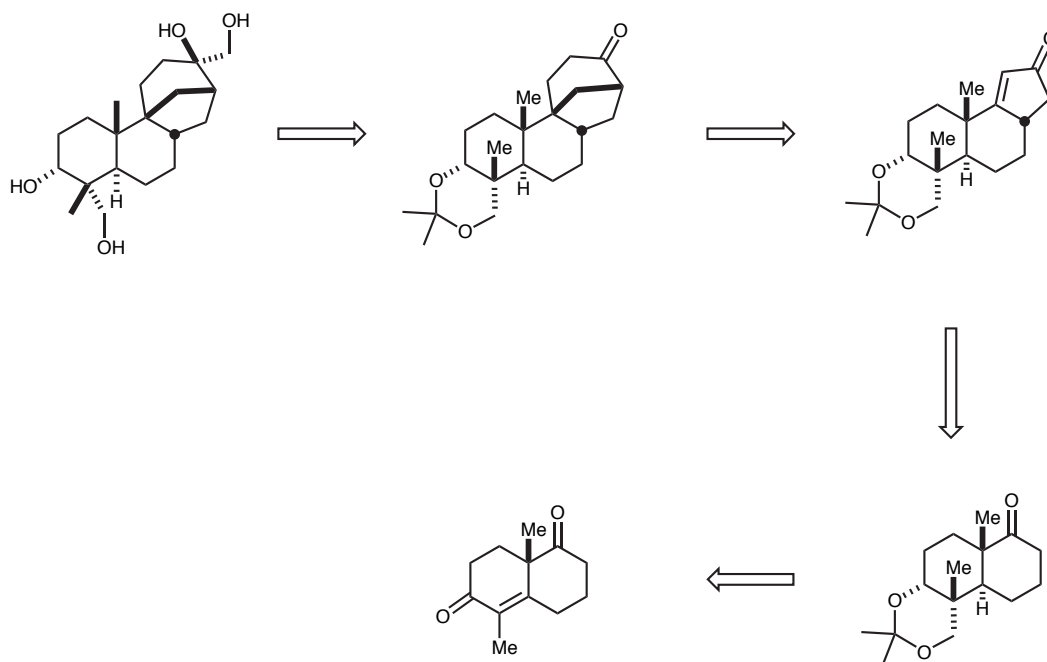
Endgame Strategies - An Improvement



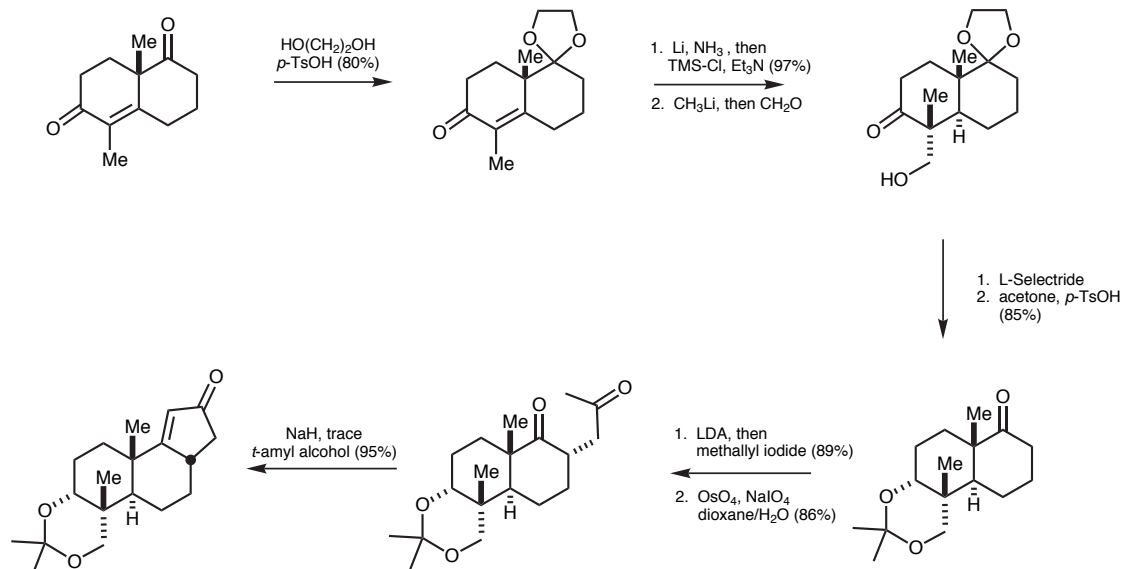
• Overall yield was improved to 67% from 31%

A. B. Smith III, *JCS Perkins I* 1991, 969

McMurry - Retrosynthetic Analysis

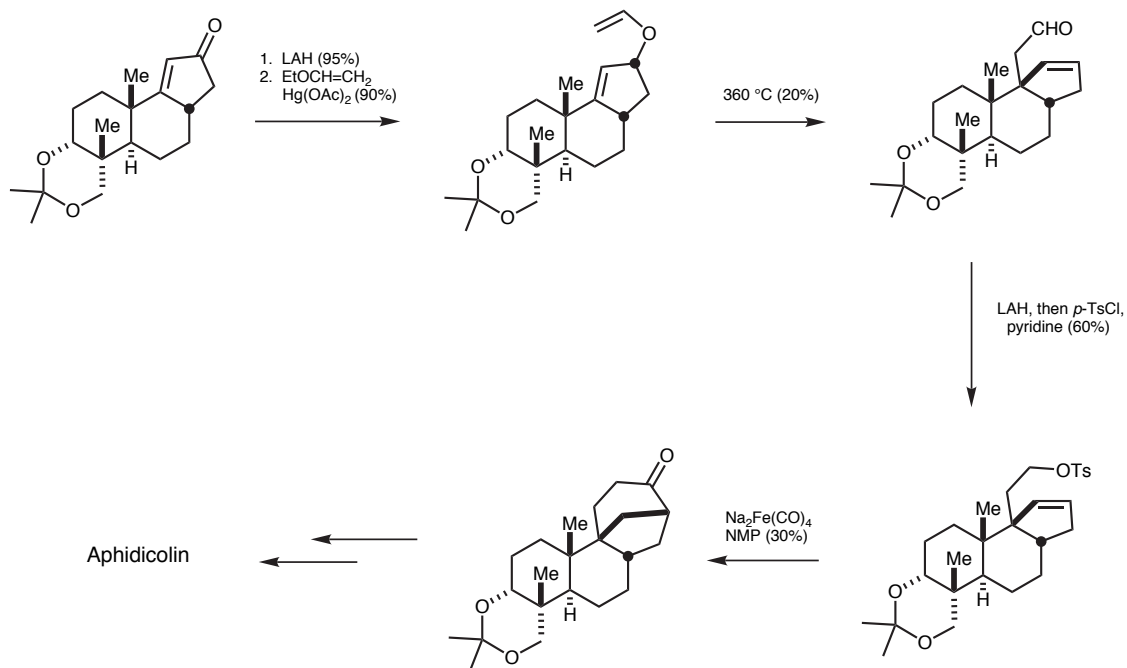


McMurry Synthesis - A Robinson Annulation



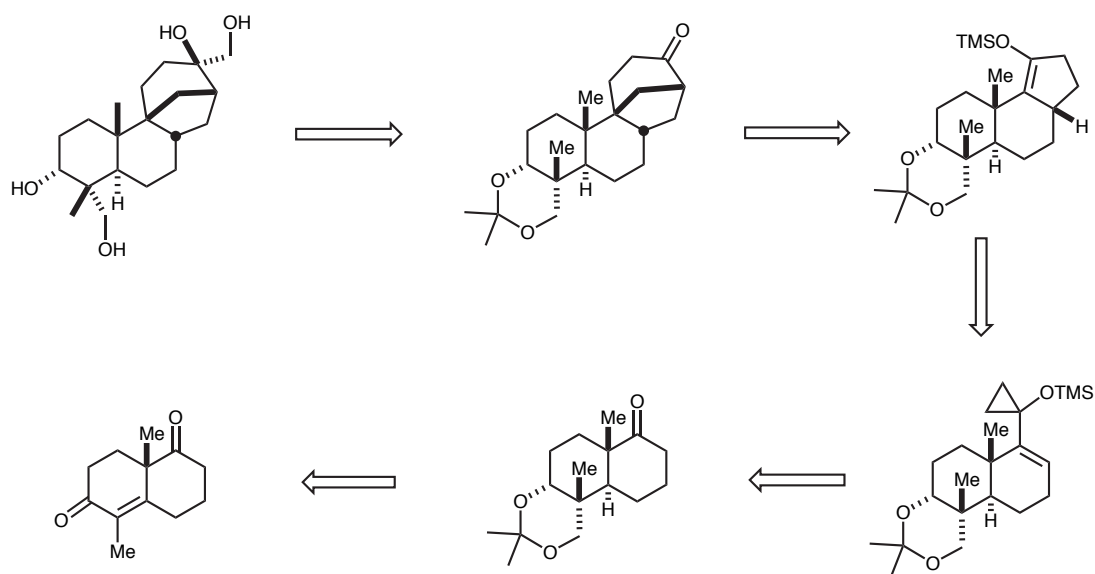
J. E. McMurry JACS 1979, 1330

McMurry - Completion of the Synthesis

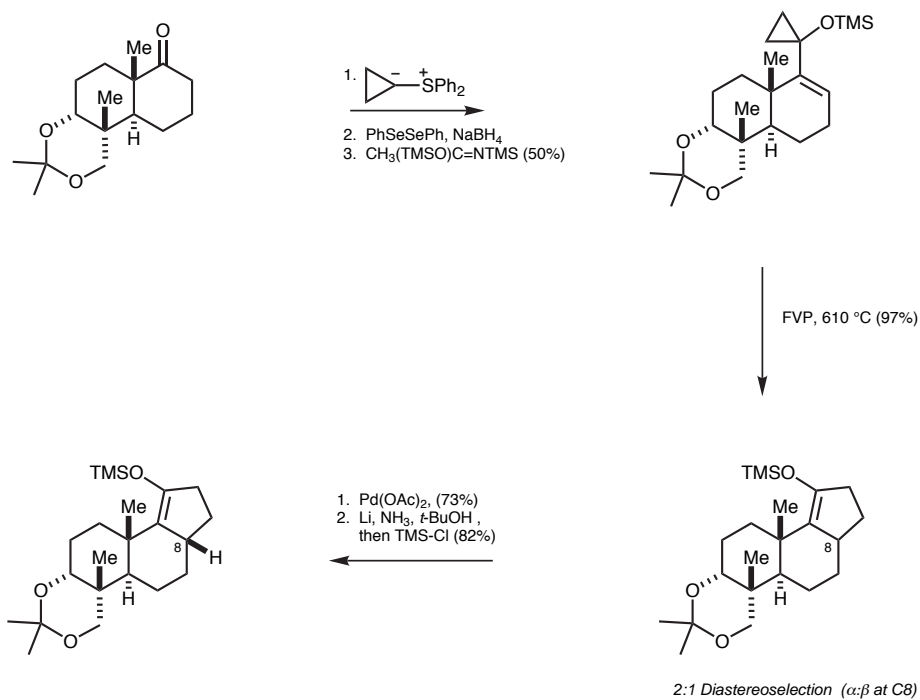


J. E. McMurry JACS 1979, 1330

Trost - Retrosynthetic Analysis

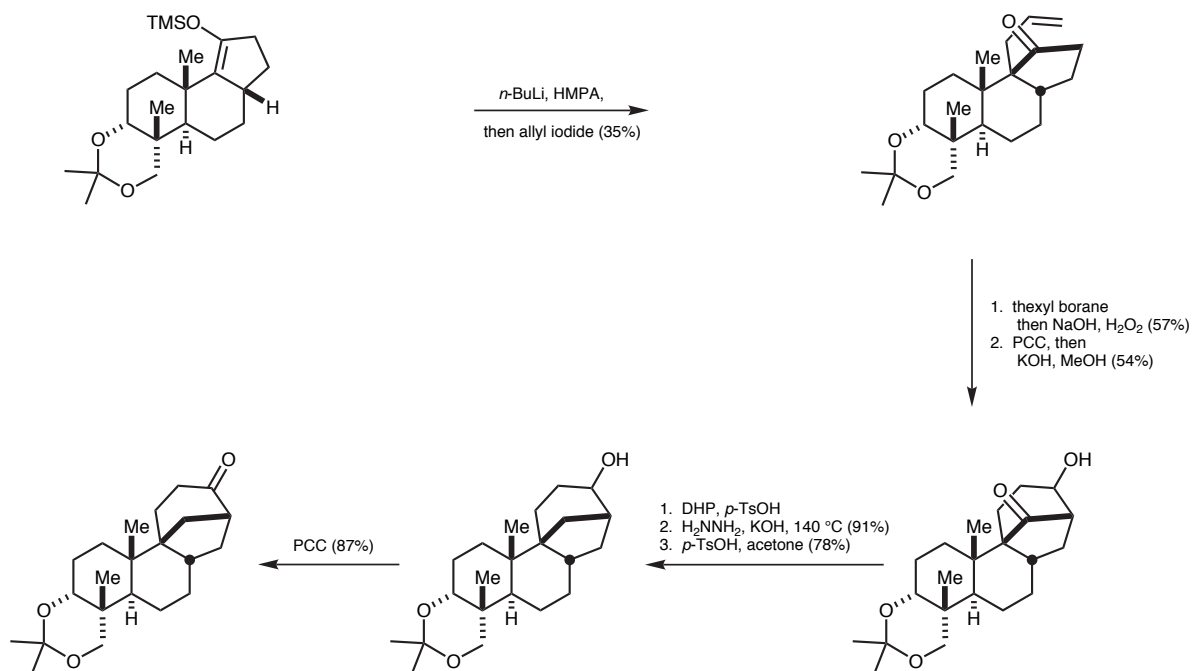


Trost - A Vinyl Cyclopropane Rearrangement



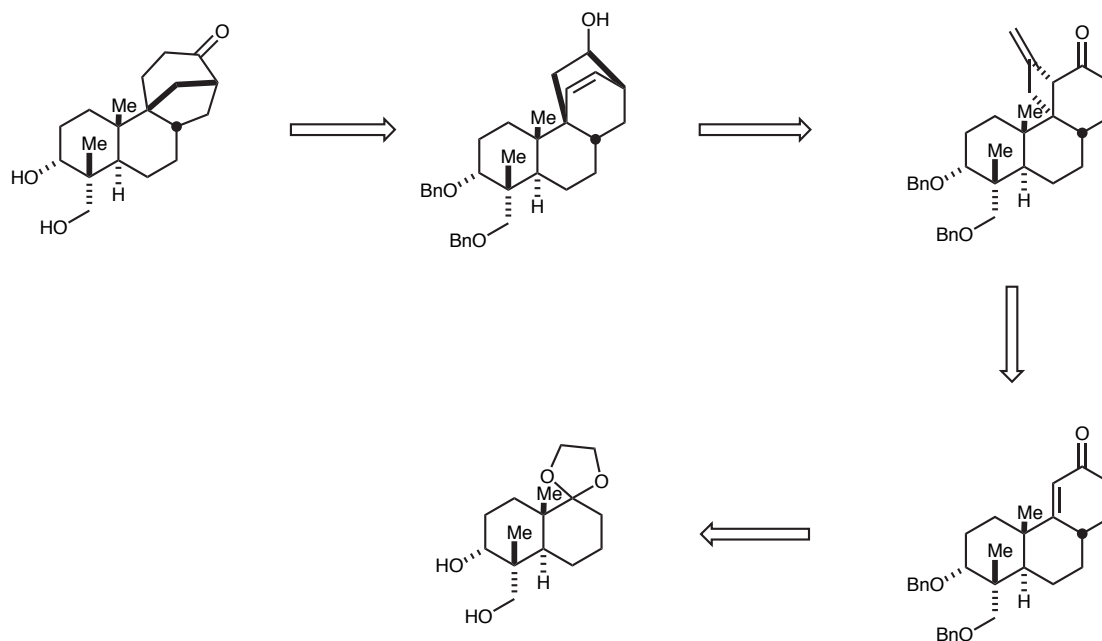
Trost, JACS 1979, 1328

Trost - Completion of the Synthesis

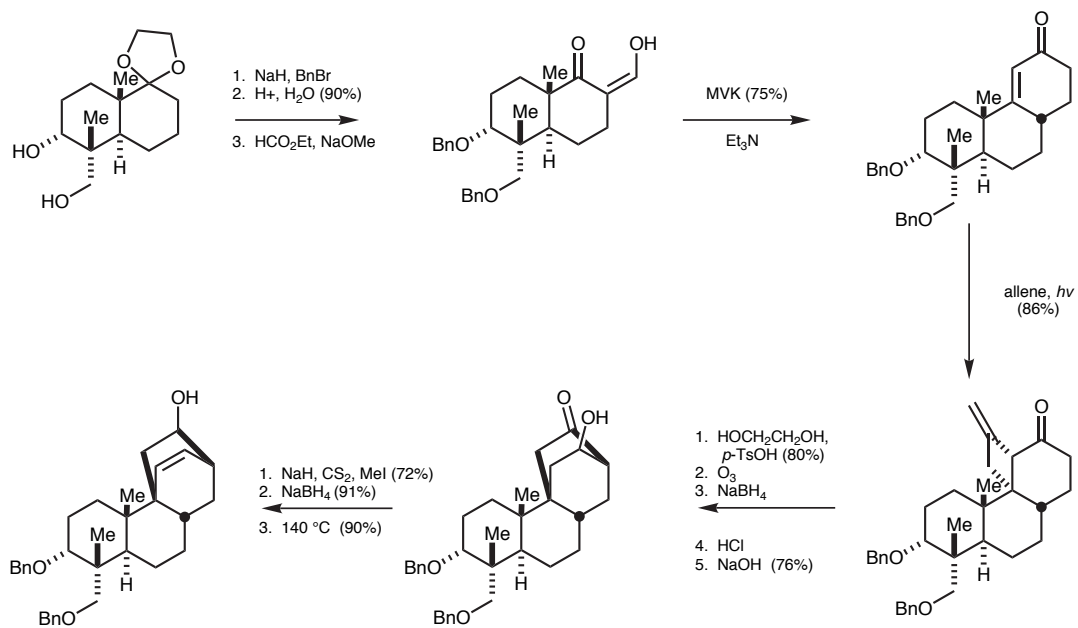


Trost, JACS 1979, 1328

Bettolo and Lupi - Retrosynthetic Analysis



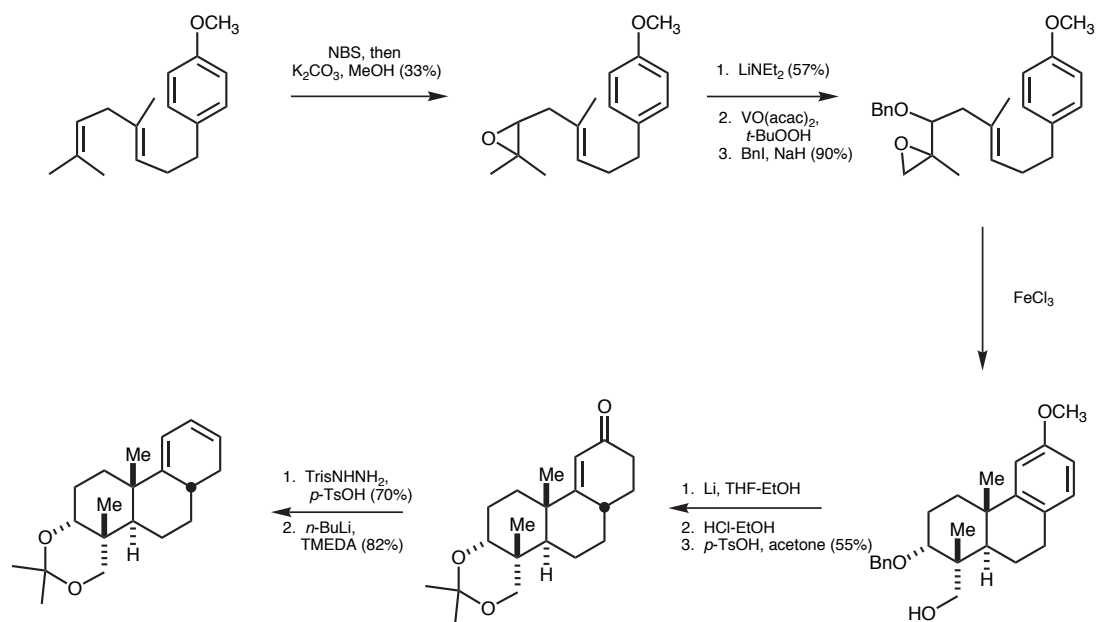
Bettolo and Lupi - [2+2] Cycloaddition



Bettolo, Lupi, *HCA* 1982, 371  
Bettolo, Lupi, *HCA* 1983, 1922  
Bettolo, Lupi, *HCA* 1988, 872

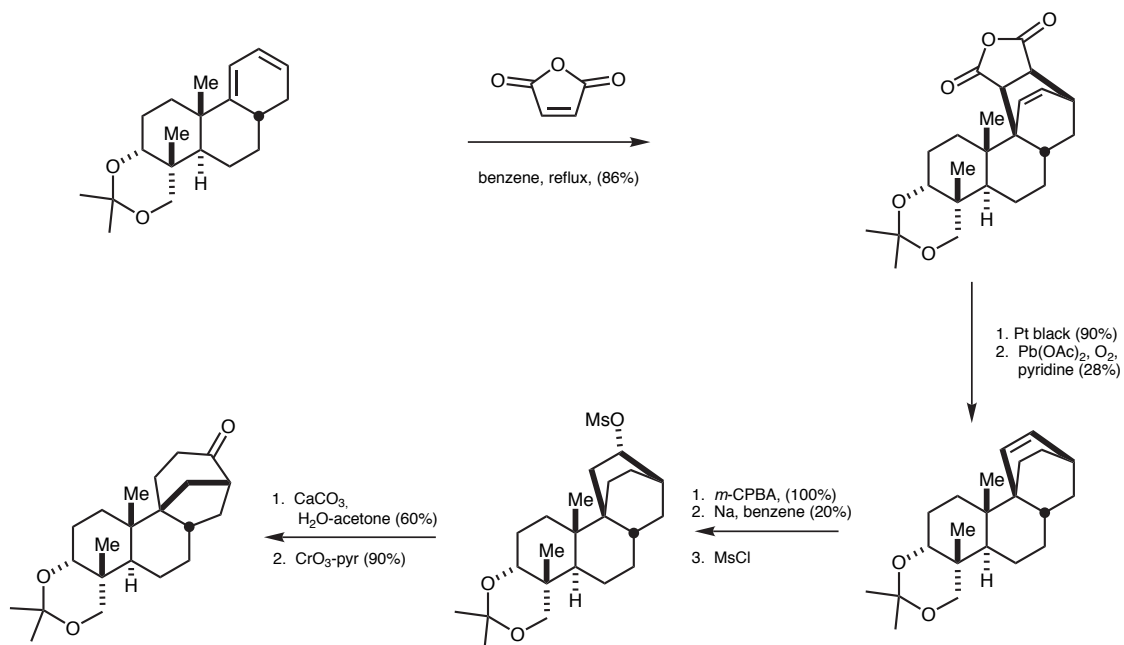


van Tamelen - A Biogenetic Approach



van Tamelen, *JACS* **1983**, 142

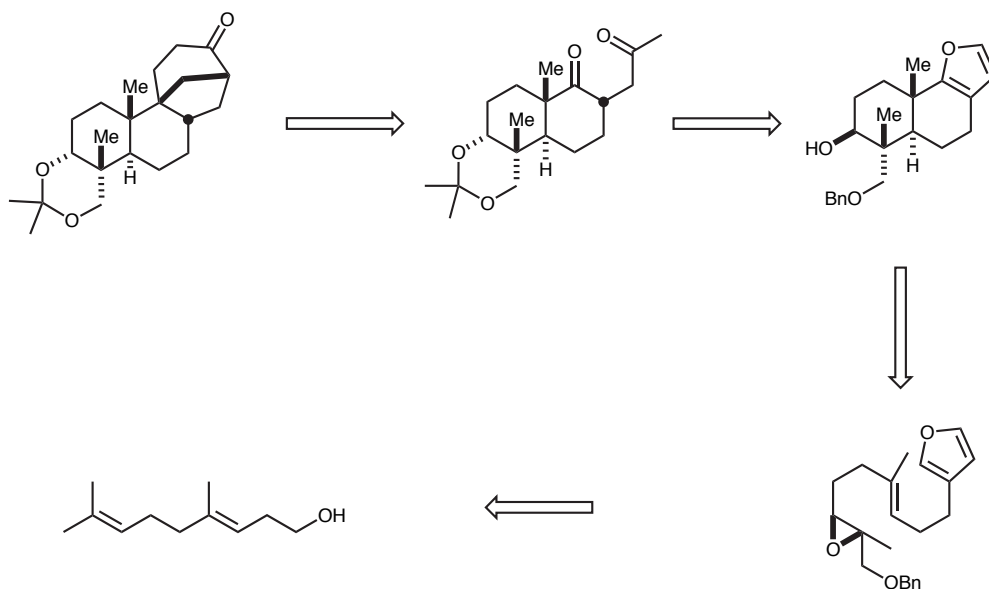
Van Tamelen - Completion of the Synthesis



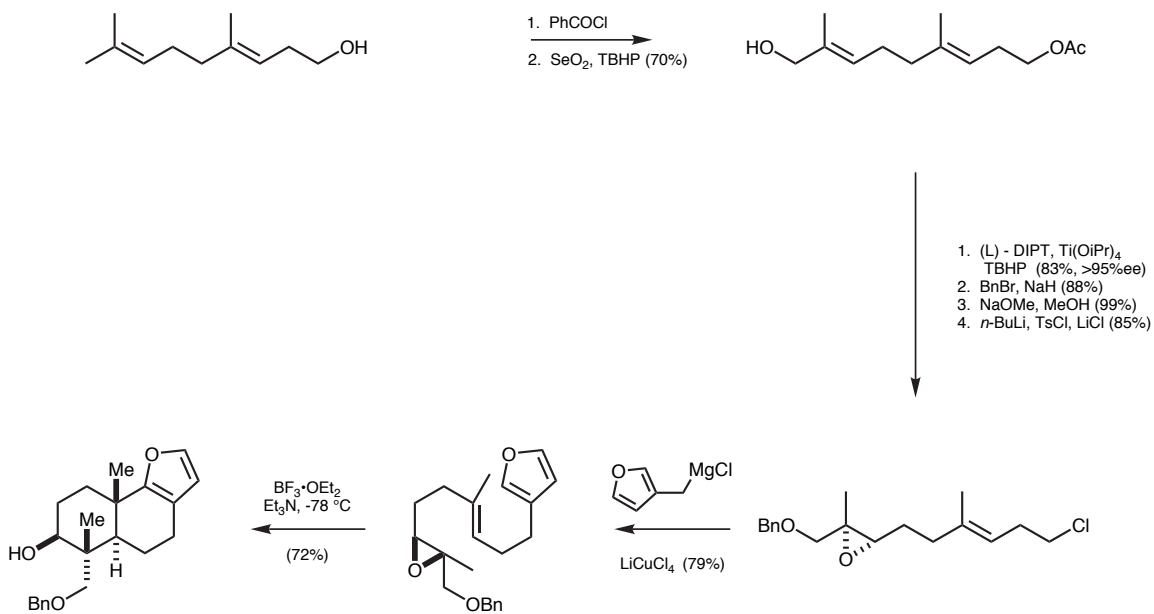
van Tamelen, *JACS* **1983**, 142



Tanis - Retrosynthetic Analysis

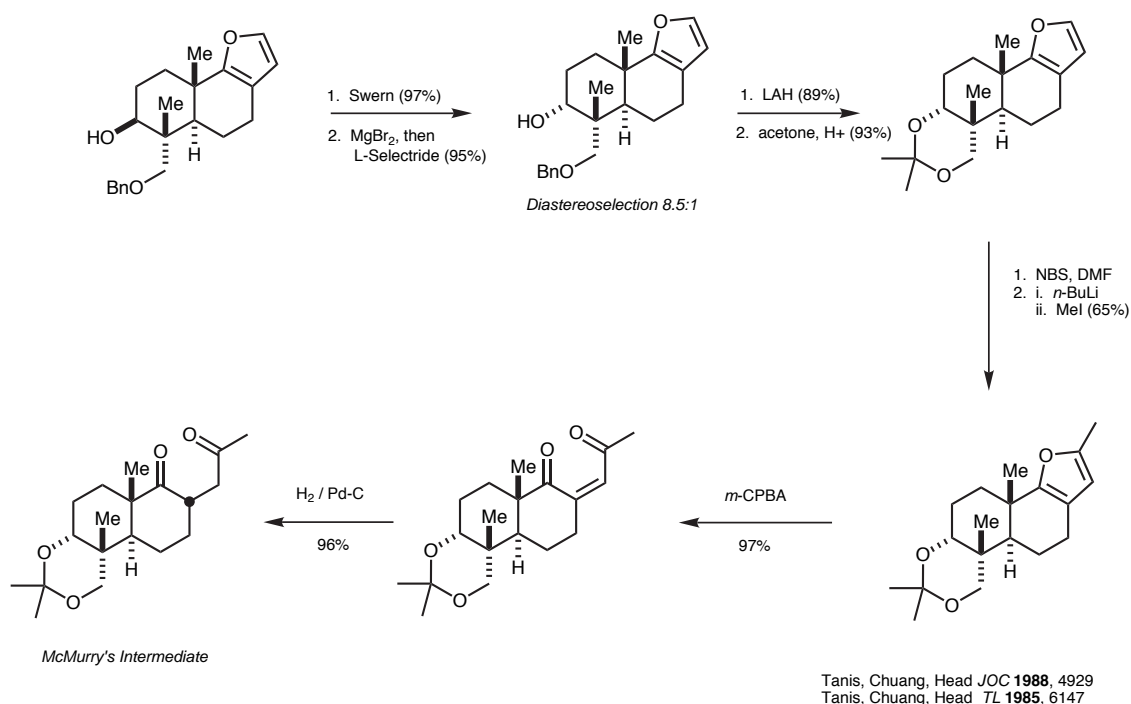


Tanis - Cationic Cyclization

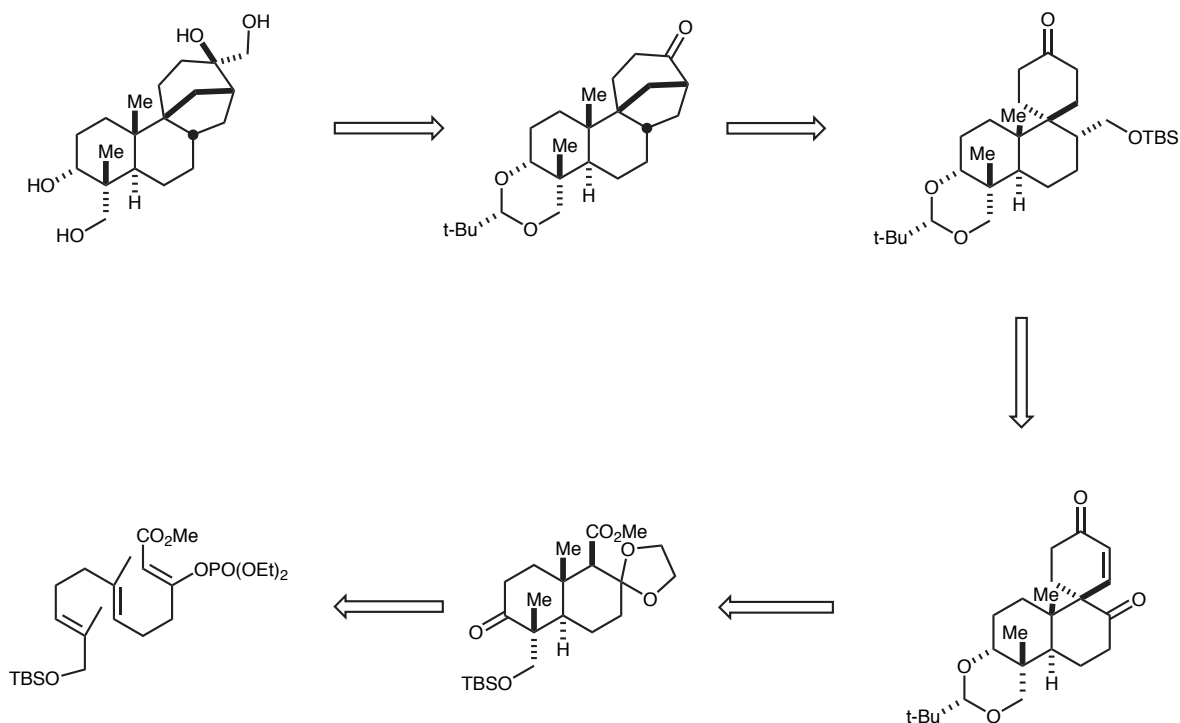


Tanis, Chuang, *Head JOC* **1988**, 4929  
Tanis, Chuang, *Head TL* **1985**, 6147

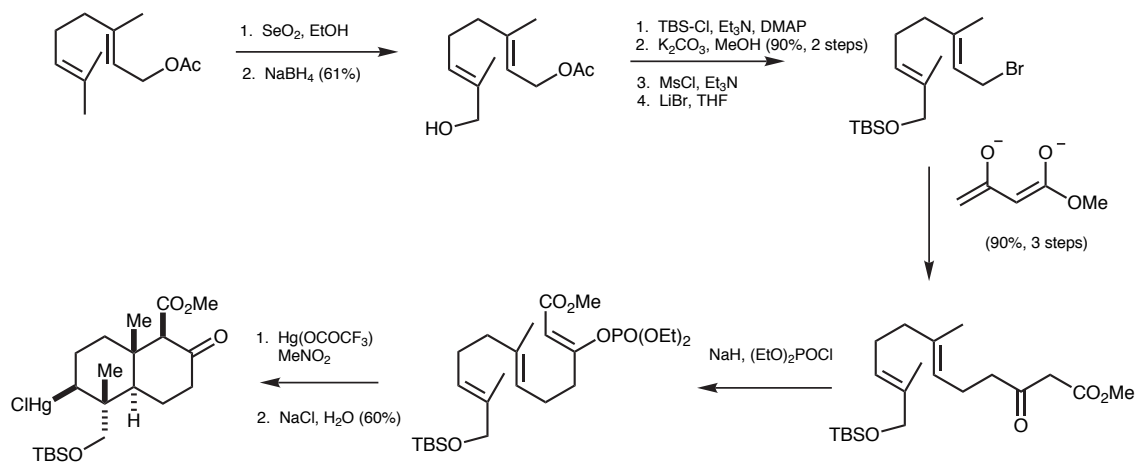
Tanis - Completion of the Synthesis



Corey - Retrosynthetic Analysis

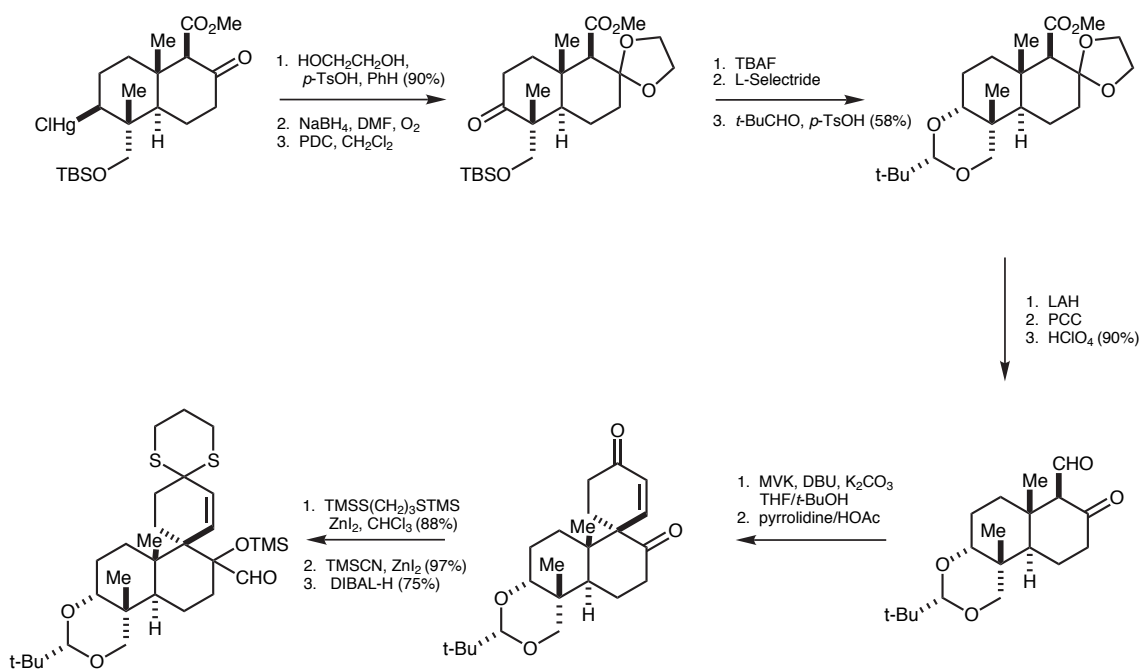


Corey - Total Synthesis



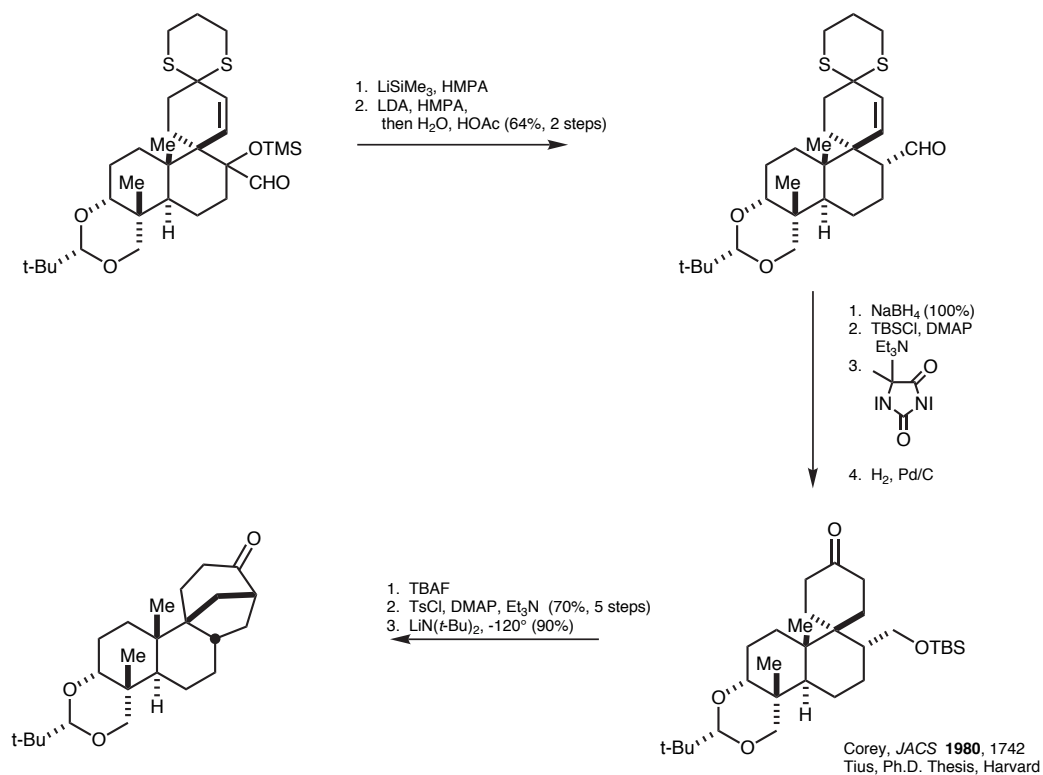
Corey, JACS **1980**, 1742  
Tius, Ph.D. Thesis, Harvard

Corey - Elaboration of the Bicycle

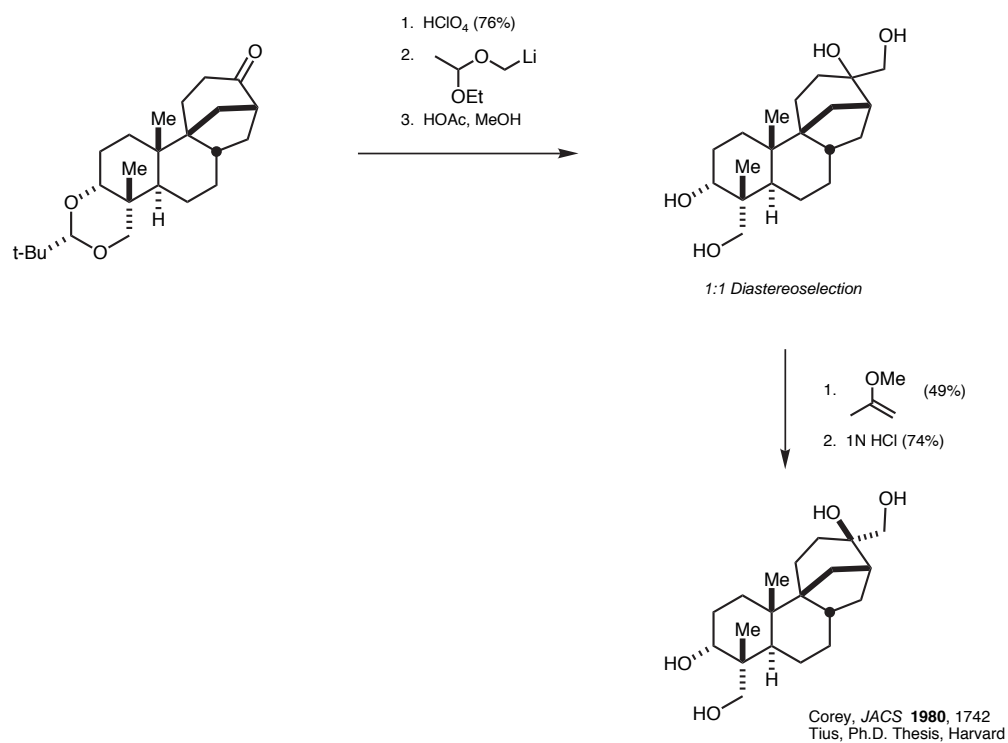


Corey, JACS **1980**, 1742  
Tius, Ph.D. Thesis, Harvard

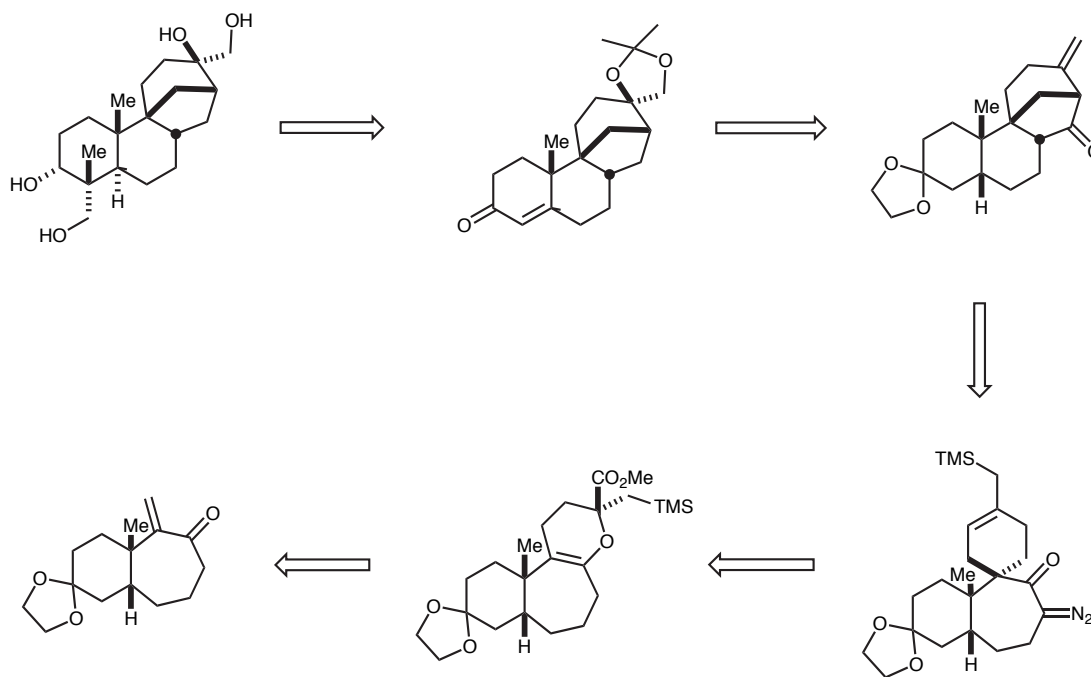
Corey - Construction of the C/D Ring System



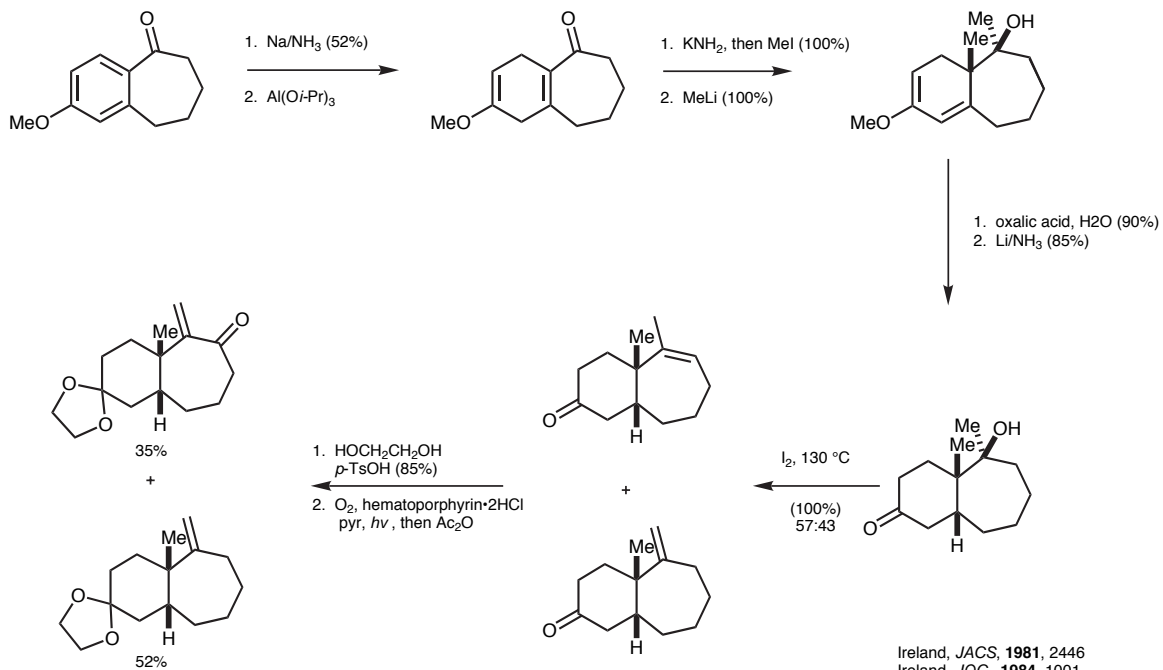
Corey - Completion of the Synthesis



Ireland - Retrosynthetic Analysis

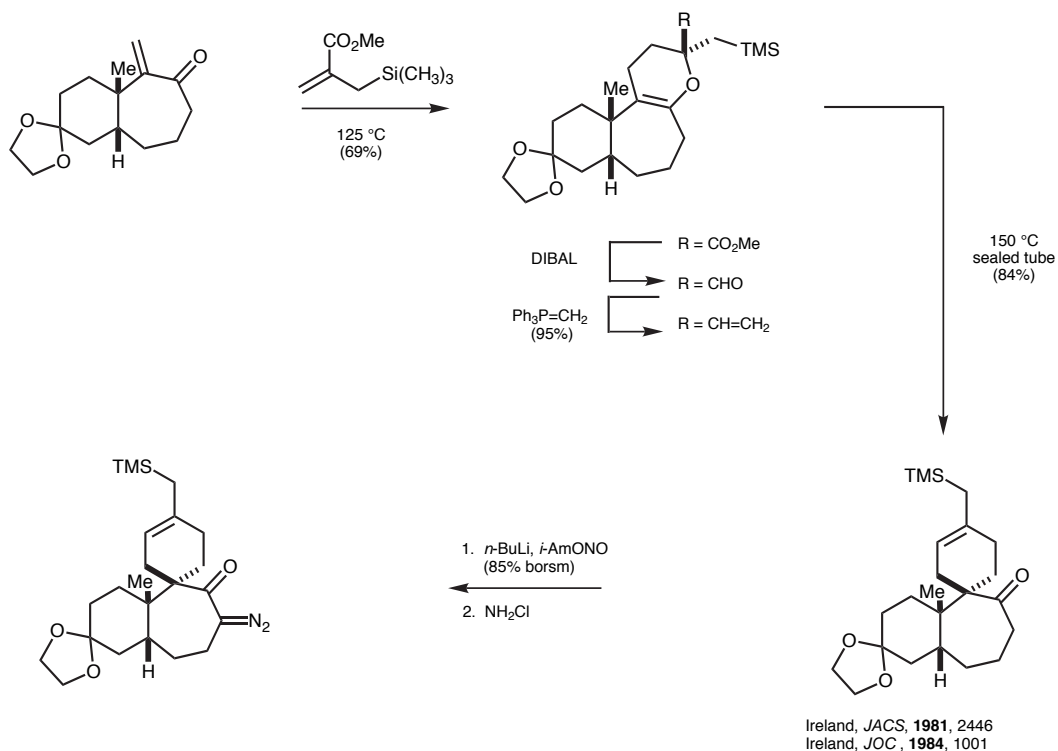


Ireland - Synthesis of 'Homo-Wieland Mischer Ketone'

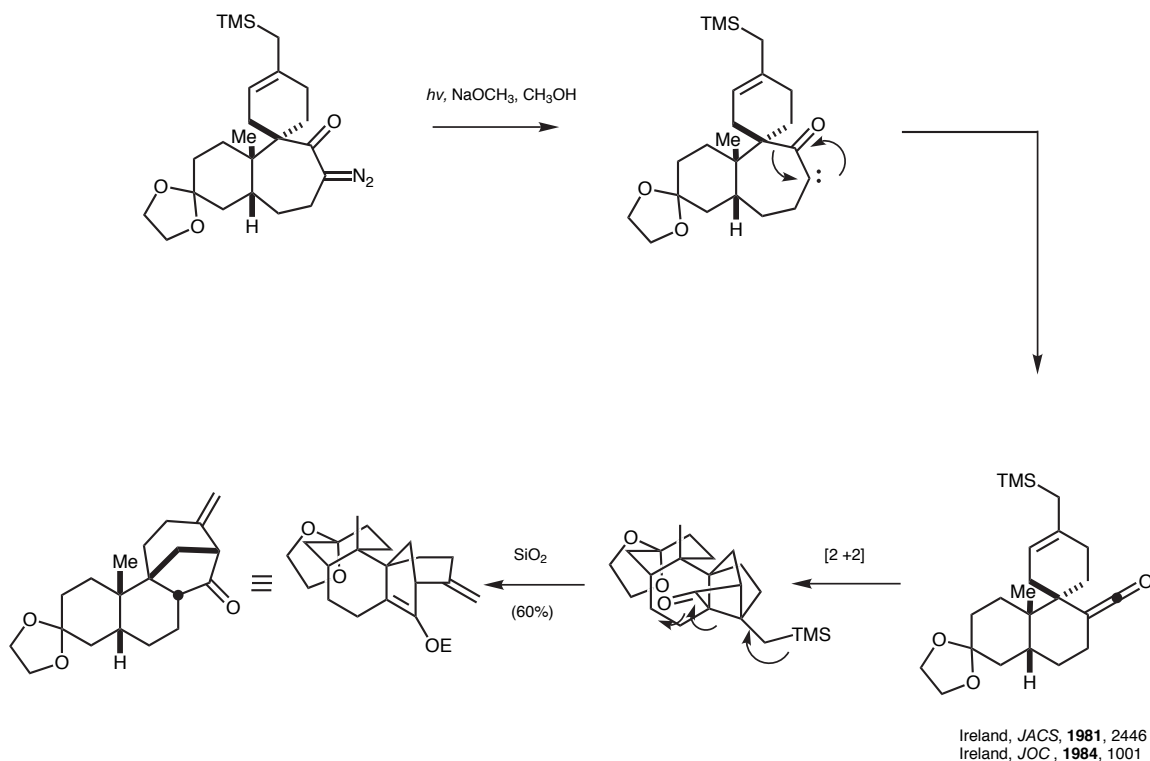


Ireland, JACS, 1981, 2446  
Ireland, JOC, 1984, 1001  
Ireland, JOC, 1979, 4323  
Ireland, JOC, 1979, 4318

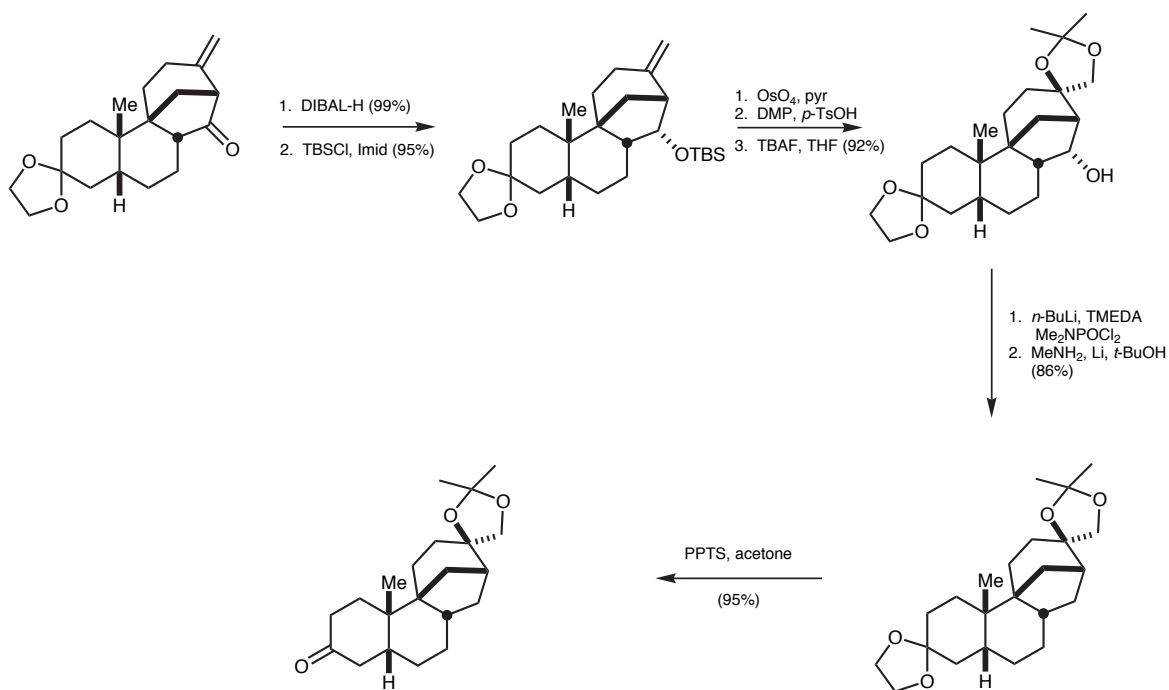
Ireland - Hetero-Diels Alder Reaction



Ireland - the Rearrangement

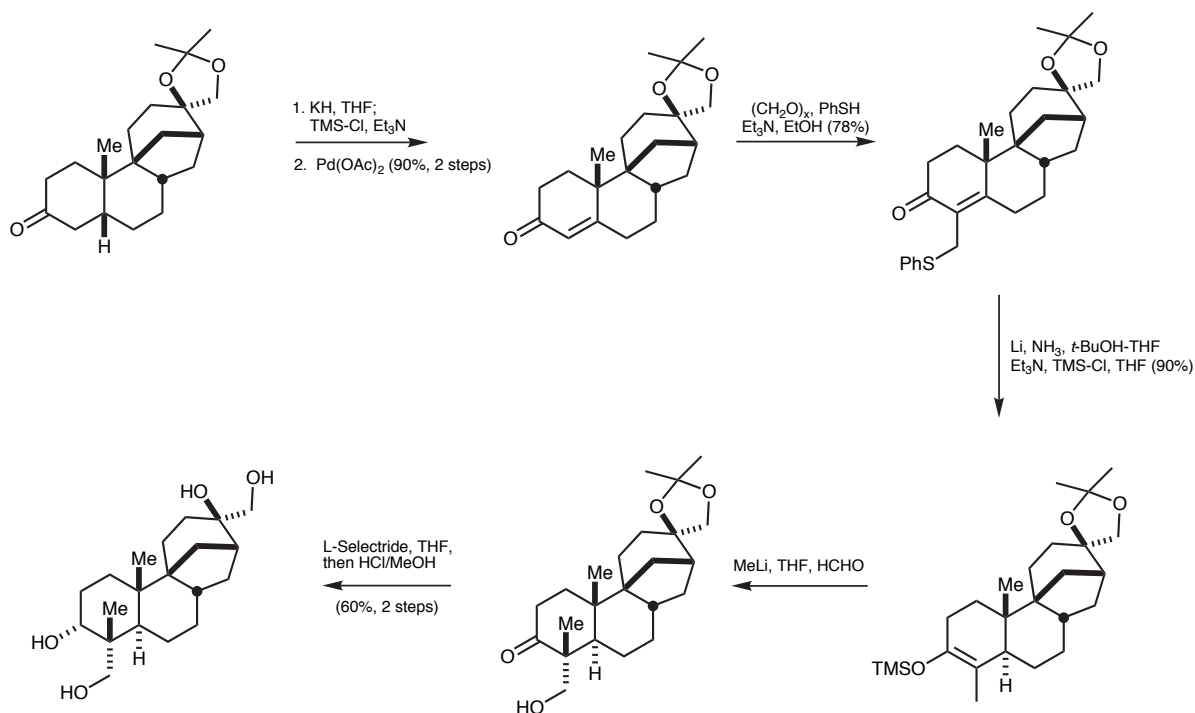


Ireland - Further Elaboration



Ireland, *JACS*, **1981**, 2446  
Ireland, *JOC*, **1984**, 1001

Ireland - Completion of the Synthesis

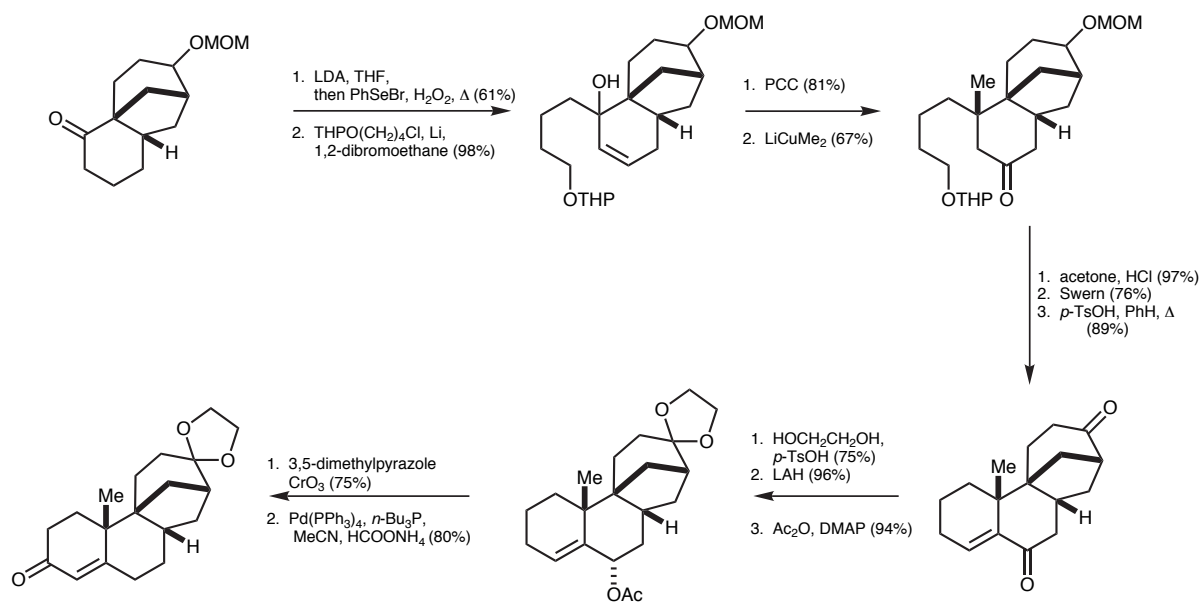


Ireland, *JACS*, **1981**, 2446  
Ireland, *JOC*, **1984**, 1001





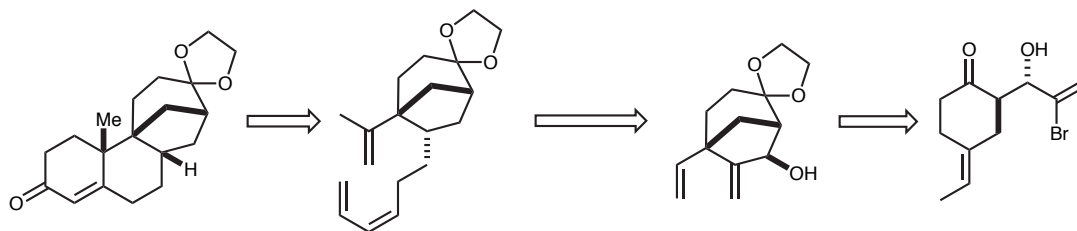
Iwata - Completion of the Synthesis



• elaborated to Aphidicolin by the methods of Ireland and Smith

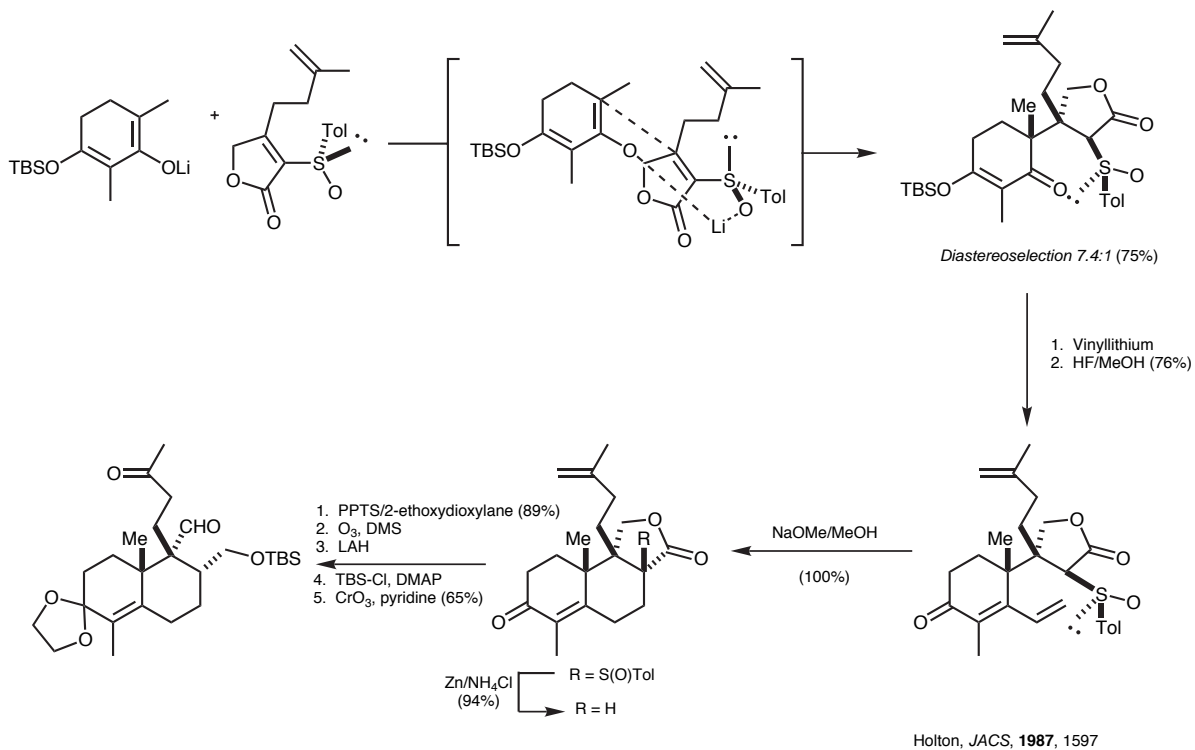
Iwata, *Chem. Pharm. Bull.*, **1994**, 1756  
Iwata, *Chem. Pharm. Bull.*, **1995**, 193  
Iwata, *Chem. Pharm. Bull.*, **1985**, 944  
Iwata, *Chem. Pharm. Bull.*, **1993**, 1900

Fukumoto - Retrosynthetic Analysis

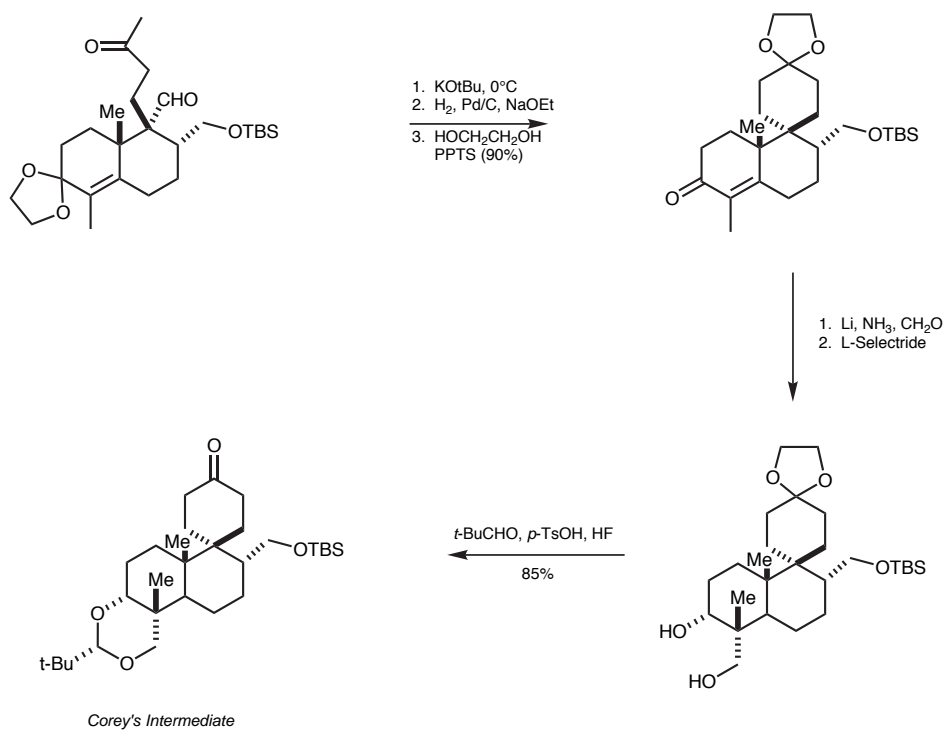




Holton - Enantioselective Total Synthesis



Holton - Completion of the Synthesis



*The Final Tally*

	<i>Longest Linear Sequence</i>	<i>Overall Yield</i>
McMurry	18 steps	0.9% yield
Trost	23 steps	0.6% yield
van Tamelen	25 steps	0.03% yield
Bettolo/Lupi	24 steps	2.9% yield
Ireland	28 steps	0.93% yield
Corey	37 steps	0.96% yield
Tanis	27 steps	2% yield
Iwata	40 steps	0.19% yield
Fukumoto	25 steps	2.3% yield
Holton	28 steps	1.65% yield