

Isolated from the fungus *Cephalosporium aphidicola*. Structure determined by X-ray crystallography and chemical degradation.

First shown to be active against DNA viruses, including Herpes simplex both *in vitro* and in the rabbit eye.

Also inhibits DNA replication and growth of several human and murine neoplastic cells, with no discernible toxicity, but both its insolubility in water and its deactivation *in vivo* by liver microsomal oxidase limited its clinical potential.

Enhanced tumor activity of the 17-glycinate HCl salt and the 16-fluoro-derivative have revived interest.

Synthetic challenges includes 8 stereocenters, especially the two adjacent chiral quaternary centers.

Isolation: Jarvis, J. A. J.; Neidle, S.; Brundet, K. M.; Dalziel, W.; Hesp, B. *J. Chem. Soc., Chem. Commun.* **1972**, 1027.

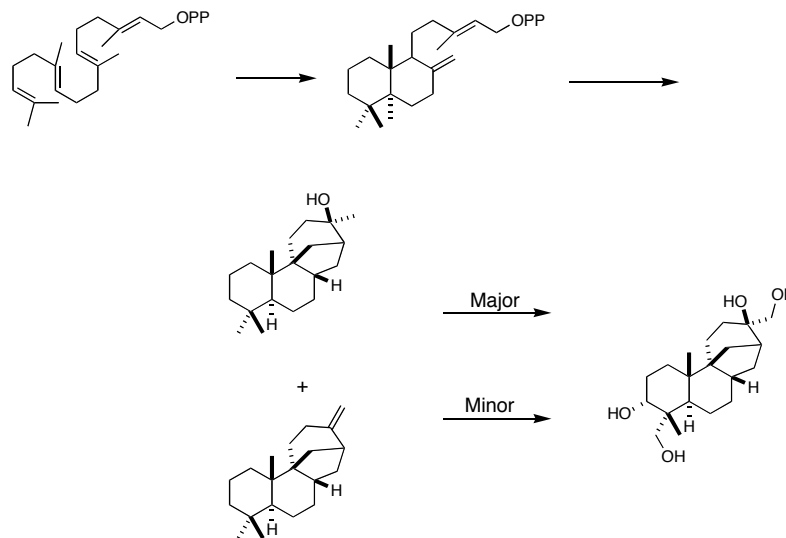
Bioactivity: (a) Bucknall, R. A.; Moores, J.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.* **1973**, 4, 294; (b) Spadari, S.; Focher, F.; Kuenzle, C.; Corey, E. J.; Meyers, A. G.; Hardt, N.; Rebuizzini, A.; Ciarrocchio, G.; Pedrali-Noy, G. *Antiviral Res.*, **1985**, 5, 93; (c) Pedrali-Noy, G.; Mazza, G.; Focher, F.; Spadari, S. *Biochem. Biophys. Res. Commun.*, **1980**, 93, 1094.

For a summary of total syntheses of aphidicolane and stemodane diterpenes from the late 1970s to 199: Toyota, M.; Masataka, I. *Tetrahedron* **1999**, 55, 5641-5679.

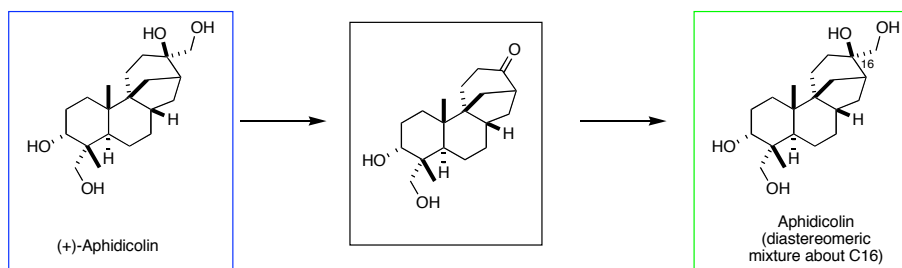
Some figures in this presentation were taken from: Beaver, K. *An Analysis of the total Syntheses of Aphidicolin*: An Evans Group Afternoon Seminar (March 20, 1998).

## Biosynthetic Pathway

Oikawa, et. al. *J. Am. Chem. Soc.* **2001**, 123, 5154-5155.



## Known degradation (during characterization) and reversion by the isolation group



## Smith

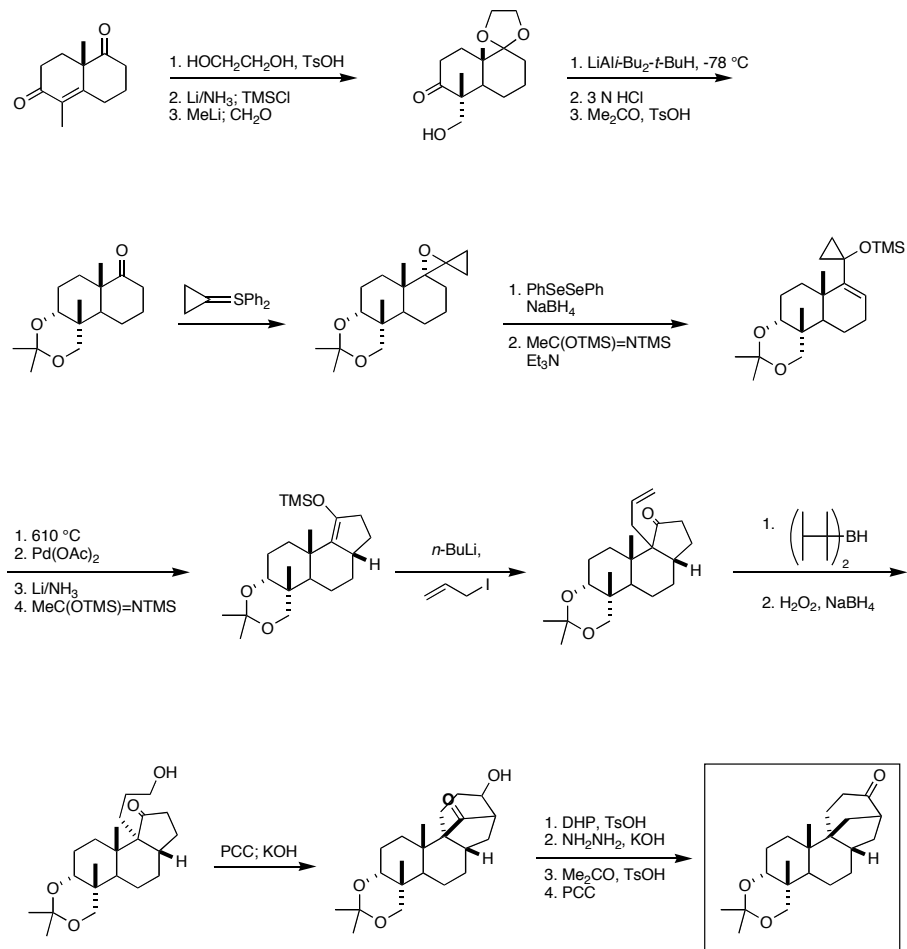
Rizzo, C. J.; Smith, A. B.; *Tet. Lett.* **1988**, 29, 2793-2796.

Rizzo, C. J.; Smith, A. B.; *J. Chem. Soc. Perkin Trans. 1* **1991**, 969-979.

Provides enantioselective synthetic routes from the ketone resulting from the degradation of (+)-Aphidicolin.

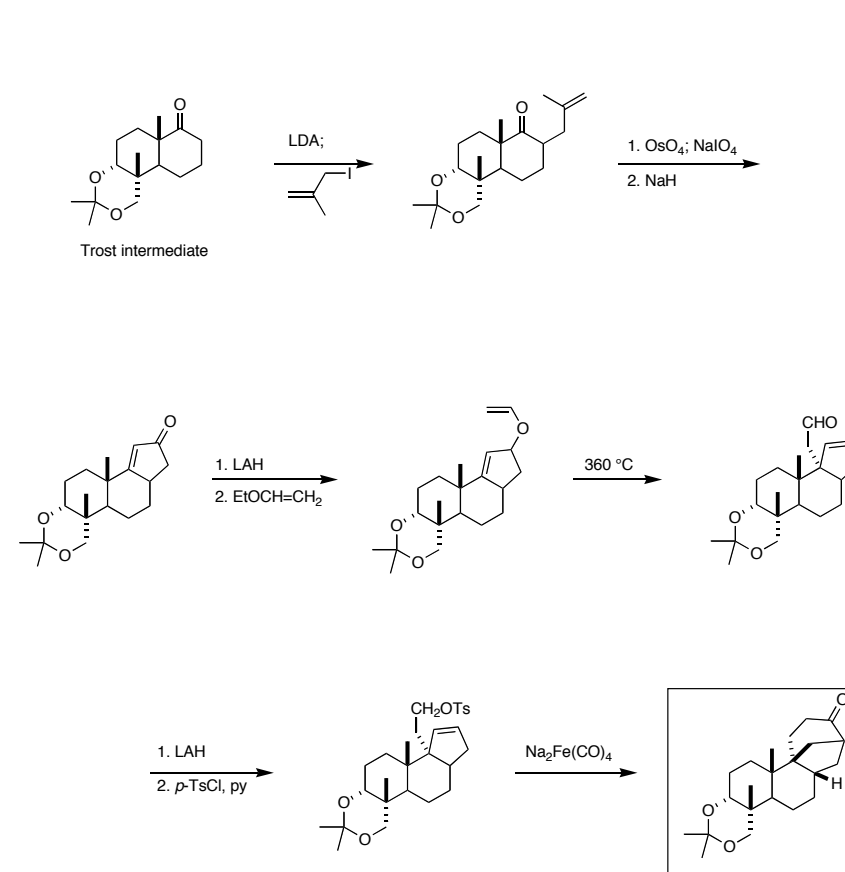
**Trost: A vinyl-cyclopropane rearrangement**

Trost, B. M.; Nishimura, Y.; Yamamoto, K.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1328-1330.



**McMurry: A Robinson Annulation**

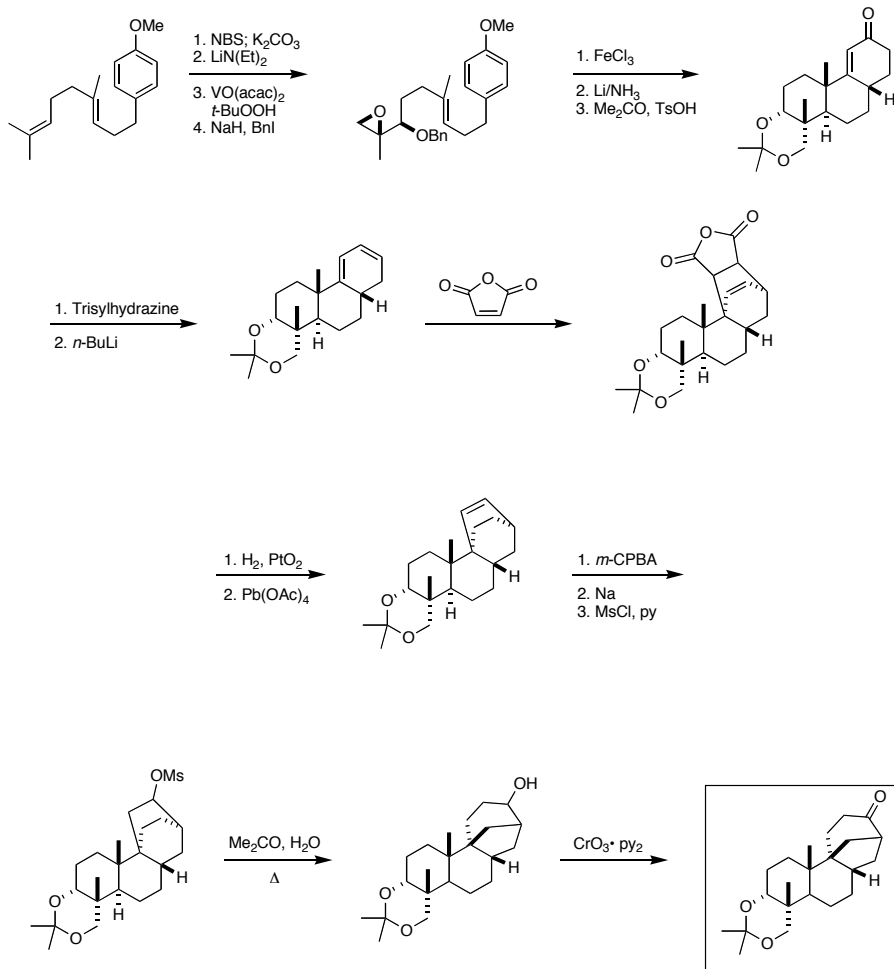
McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330-1332.





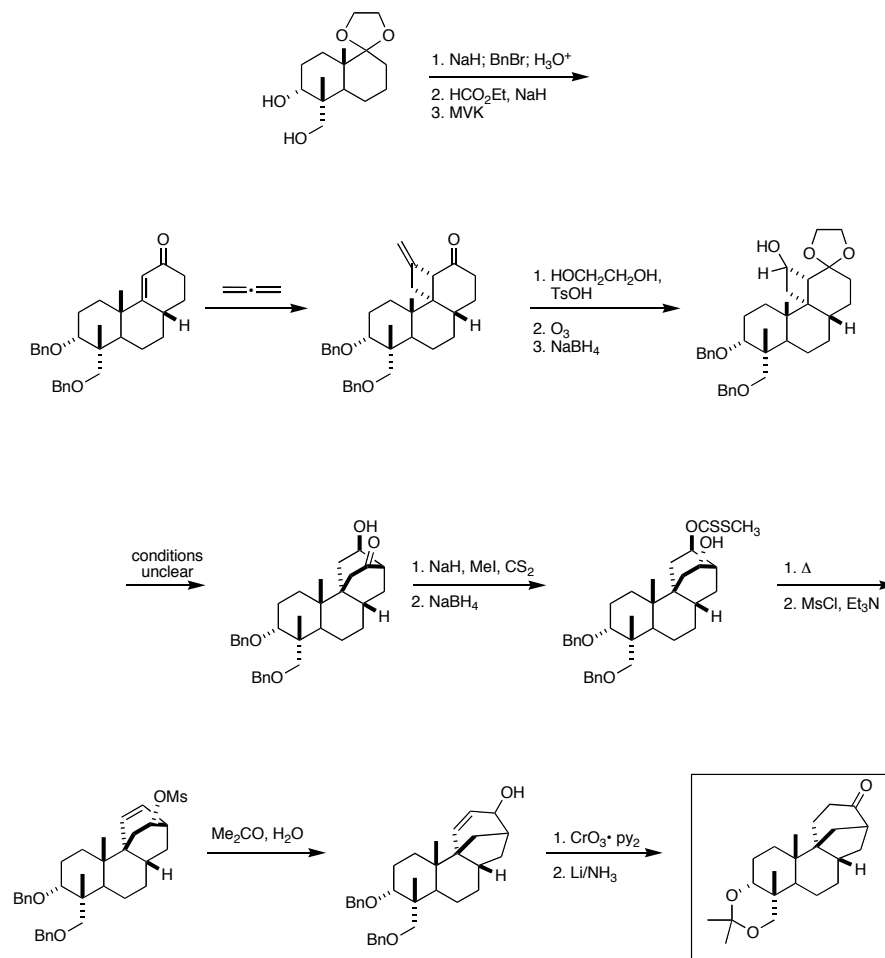
**Van Tamelen: A biogenetic approach**

van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142-143.



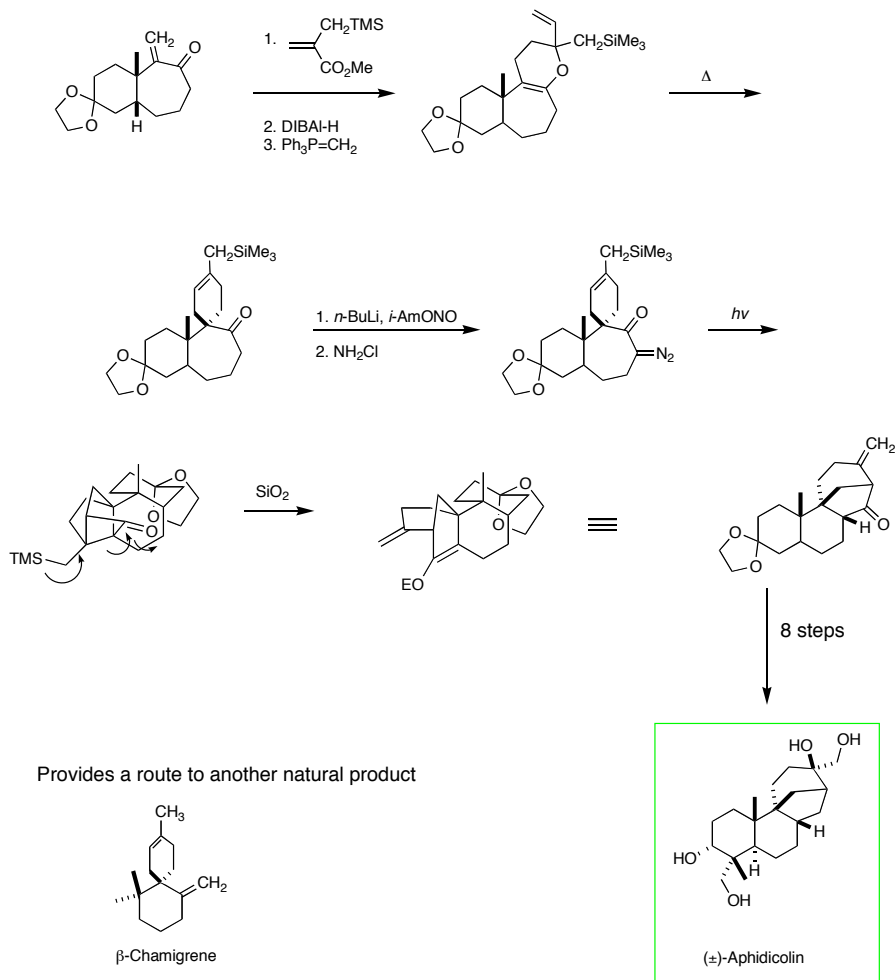
**Bettolo: [2+2] cycloaddition**

Bettolo, R. M.; Tagliatesta, P.; Lupi, A.; Bravetti, D. *Helv. Chim. Acta* **1983**, *66*, 1922-1928.



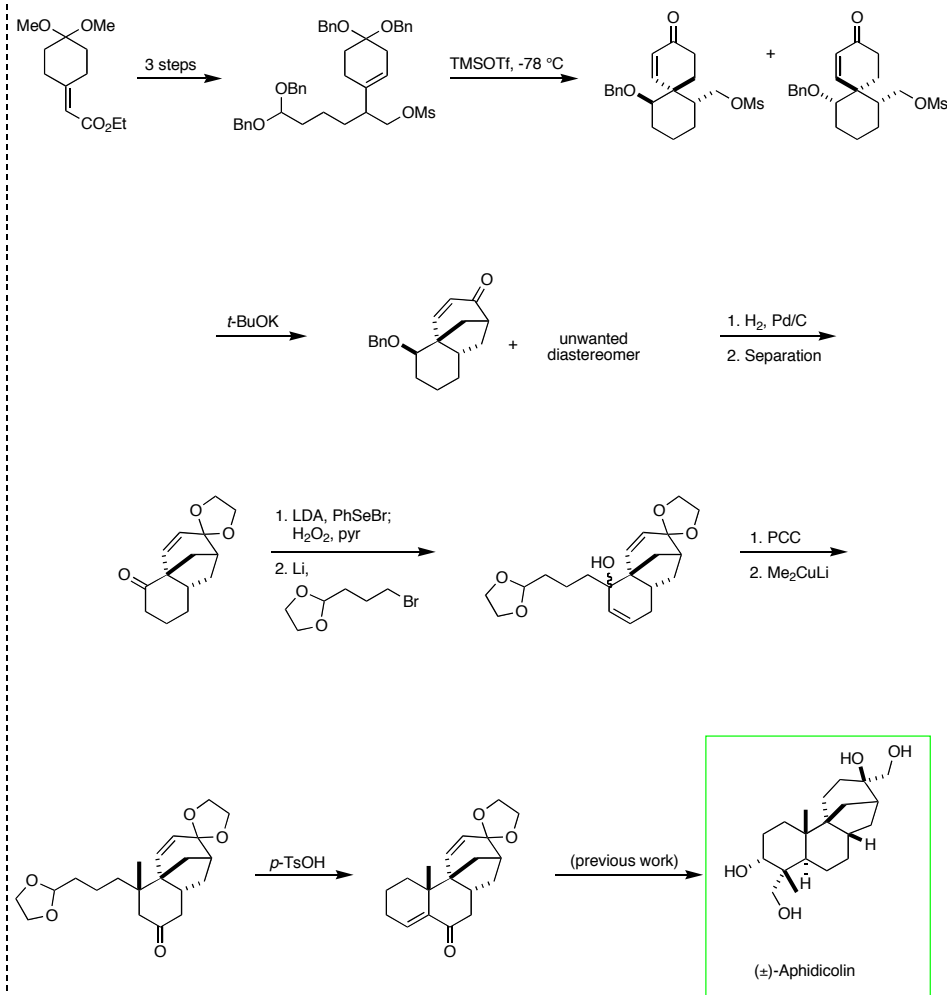
Ireland

Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001-1013.



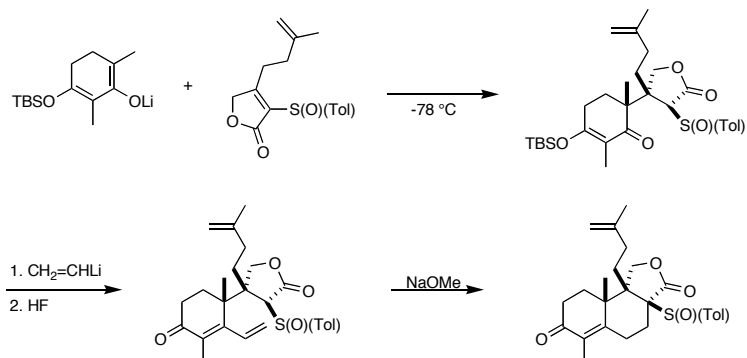
Iwata

Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Kim, S-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43* 1407-1411.

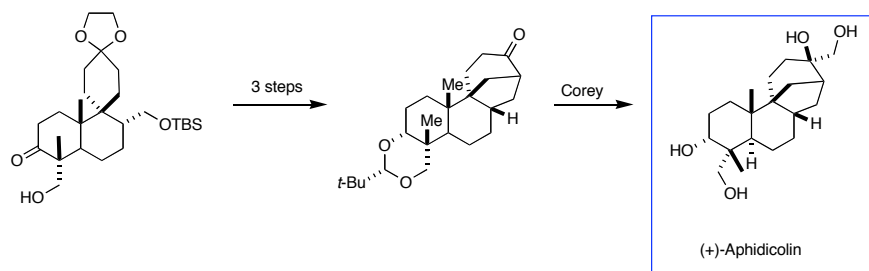
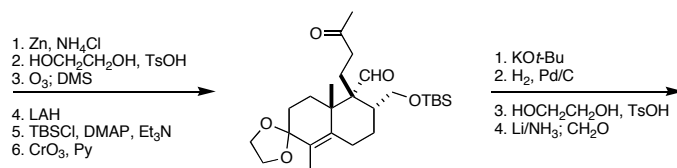


## Holton: First enantioselective synthesis

Holton, R. A.; Kennedy, R. M.; Kim, H.-B.; Krafft, M. E.; *J. Am. Chem. Soc.* **1987**, *109*, 1597-1600.

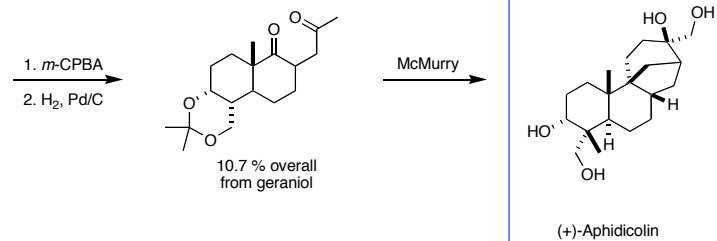
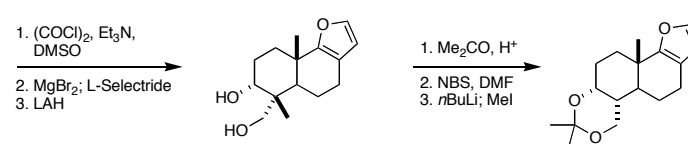
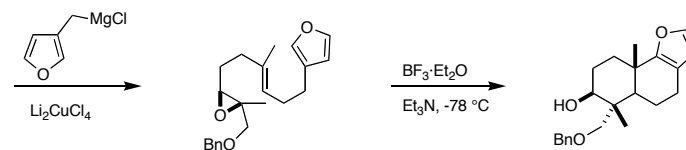
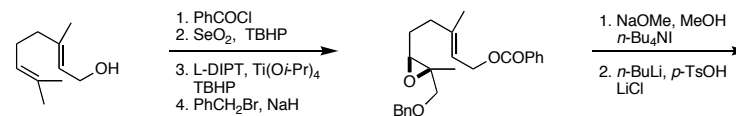


Note: These first three steps can be carried out in one pot in 45% overall yield.



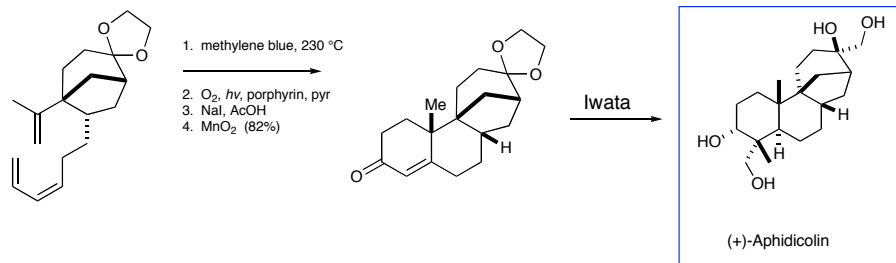
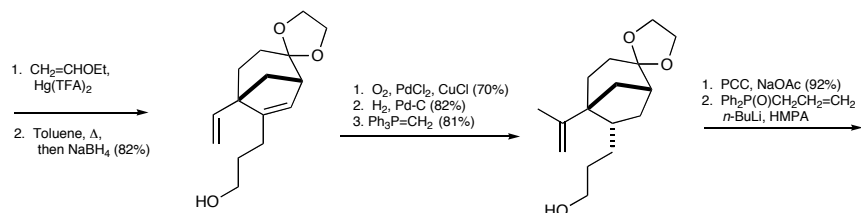
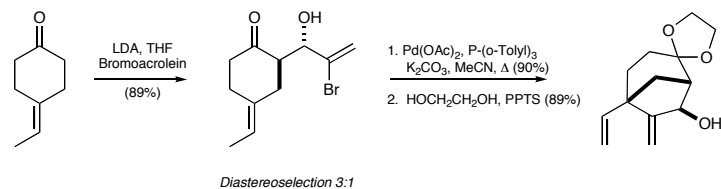
## Tanis: Cationic Cyclization

Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929-4938.



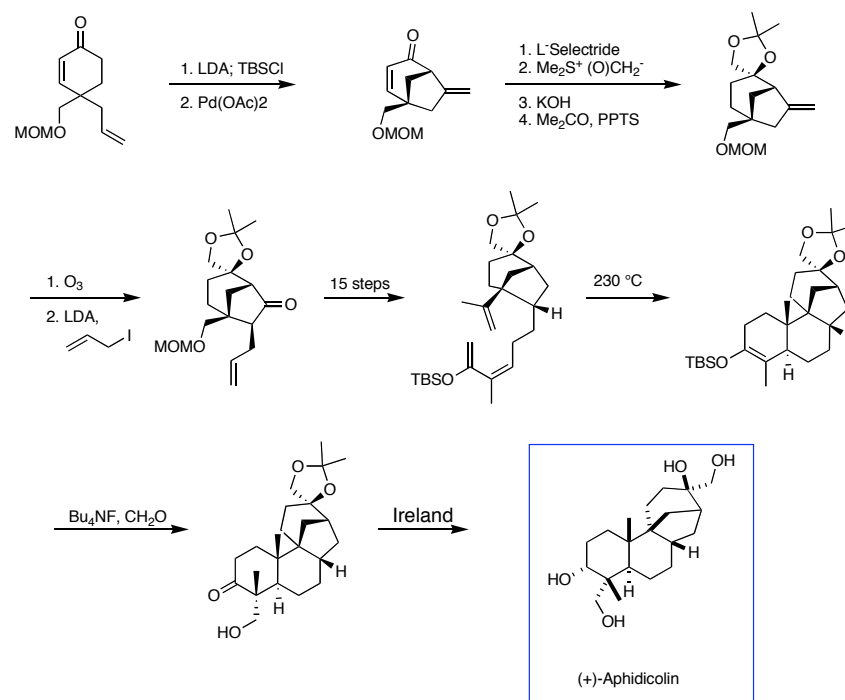
## Toyota/Fukumoto: The Heck Reaction

Fukumoto, et. al. *Tetrahedron* **1994**, 11153.  
Fukumoto, et. al. *Tetrahedron* **1994**, 10183.  
Fukumoto, et. al. *Tet. Lett.* **1994**, 6495.



## Toyota: Palladium-catalyzed cycloalkenylation

Toyota, M.; Sasaki, M.; Ihara, M. *Org. Lett.* **2003**, 5, 1193-1195.



## Summary

	Longest Linear Sequence	Overall Yield
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