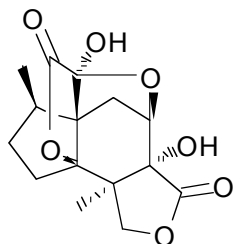


Enantioselective Total Synthesis of (-) Jiadifenolide

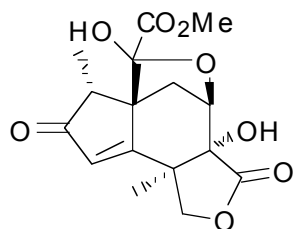
Xu, J; Trzoss, L; Chang, W. K; Theodorakis, E. A
Angew. Chem. Int. Ed. **2011**, *50*, 3672-3676

Jiadifenolide and Related Natural Products



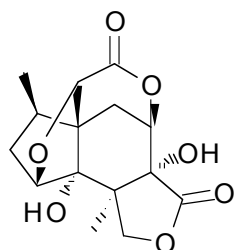
(-)-Jiadifenolide

- Isolated from the pericarps of *Illicium jiadifengpi* by Fukuyama and co-workers in 2009
- Highly oxygenated pentacyclic cage structure
- Promoter of neurite growth
- Potential therapeutic value for neurodegenerative diseases

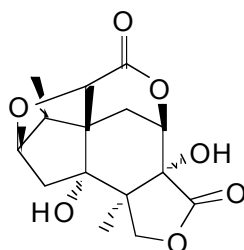


Jiadifenin

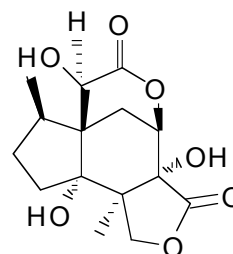
- Isolated from the pericarps of *Illicium jiadifengpi* by Fukuyama and co-workers in 2002
- First total synthesis by Danishefsky and co-workers
- Biological studies showed Jiadifenin upregulates the action of NGF (Nerve growth factor)



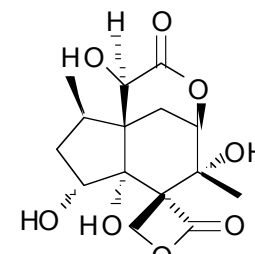
Jiadifenoxolane A



Jiadifenoxolane B



Noemajucin



Anisatin

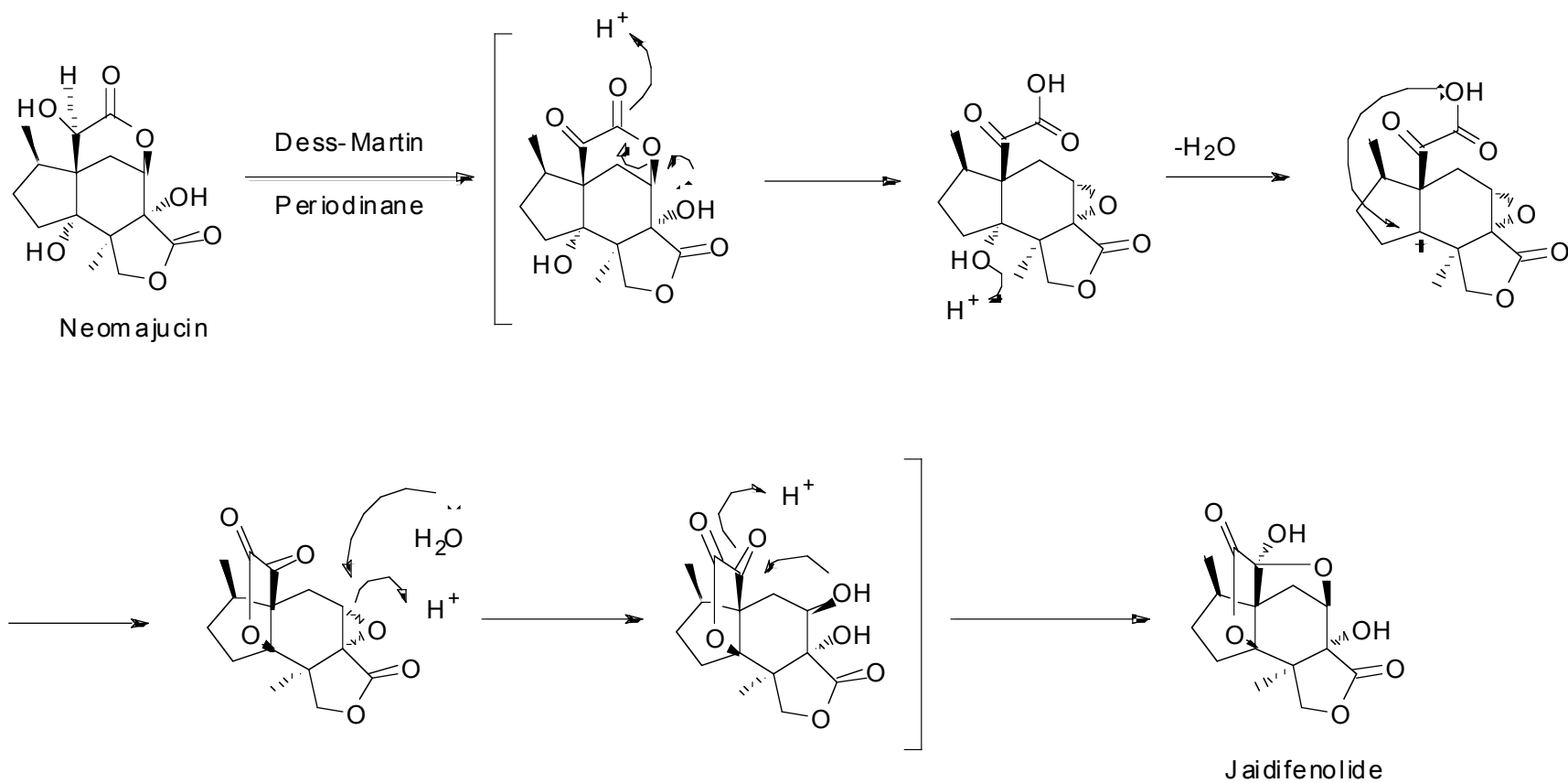
Kubo, M.; Okada, C.; Huang, J-M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Org. Lett.* **2009**, *11*, 5190

Yokoyama, R.; Huang, J-M.; Yang, C.S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65*, 527

Cho, Y. S.; Carcache, D. A.; Tian, Y.; Li, Y. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358

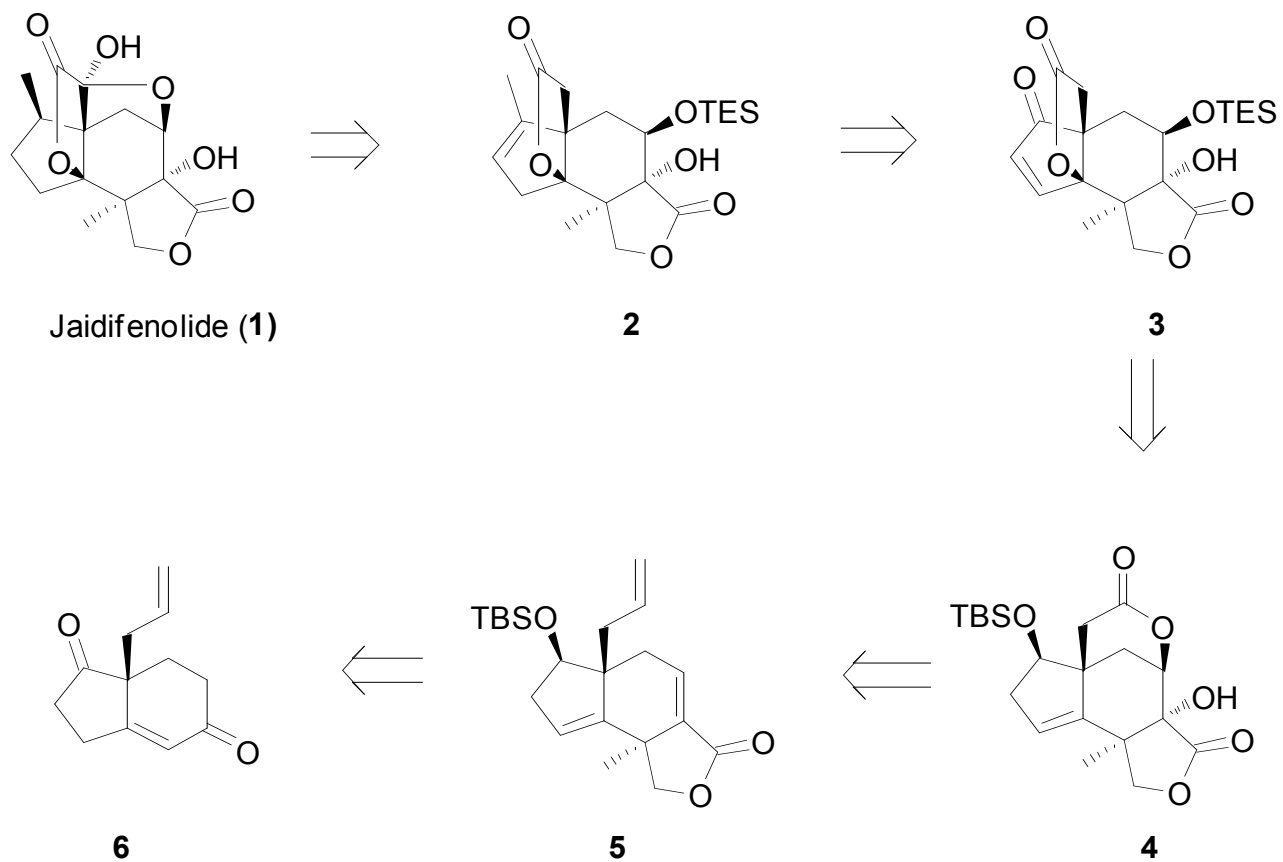
Carcache, D. A.; Cho, Y. S.; Hua Z.; Tian, Y.; Li, Y. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1016

Oxidative Conversion of Neomajucin to Jaidifenolide



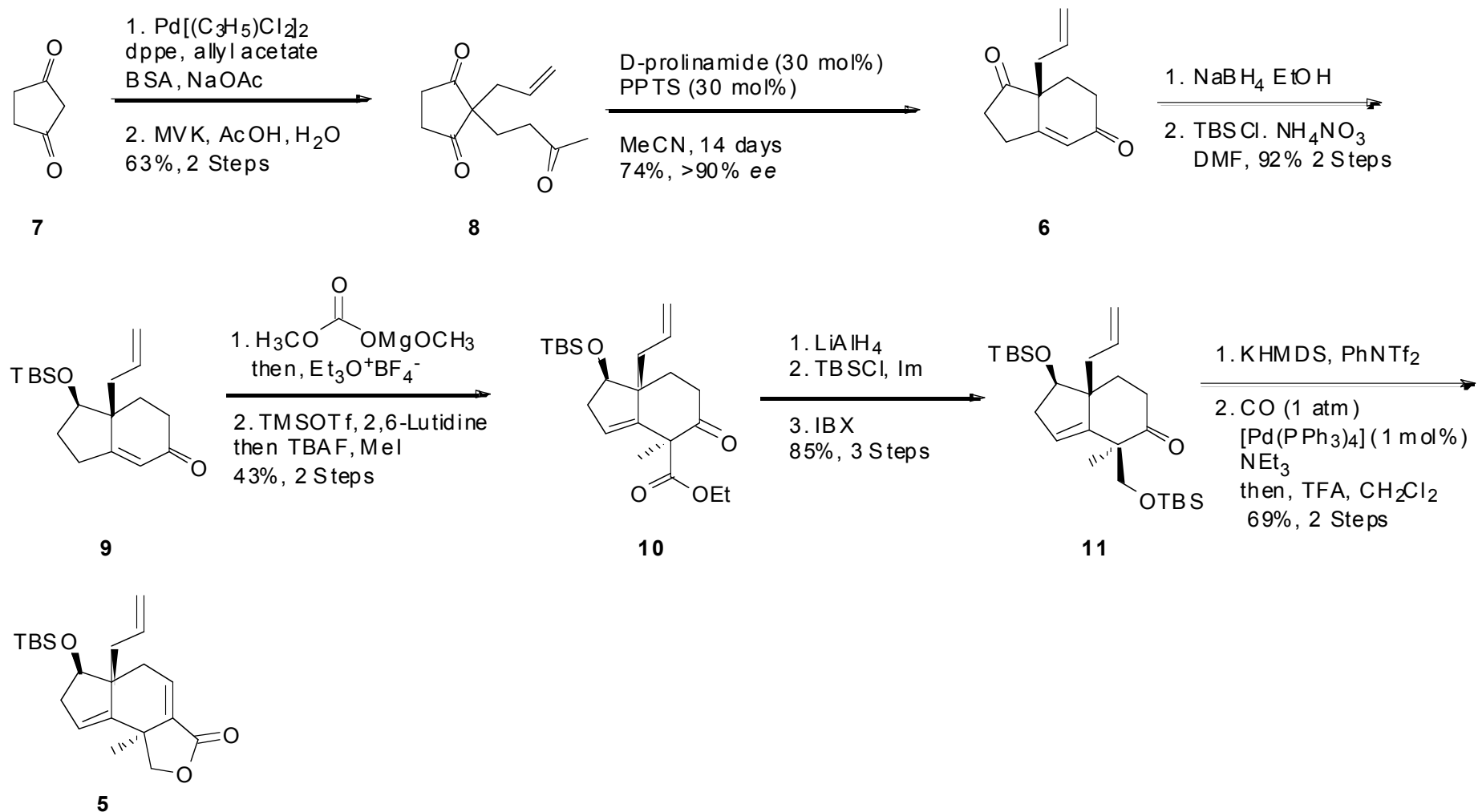
Kubo, M.; Okada, C.; Huang, J-M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Org. Lett.* **2009**, *11*, 5190

Retrosynthesis

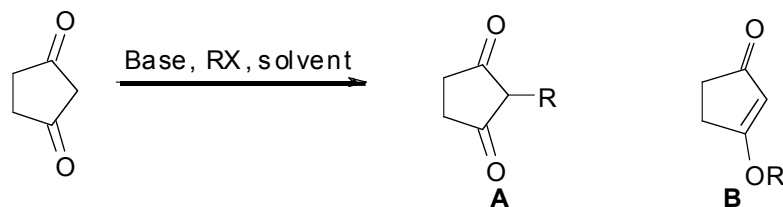


Xu, J; Trzoss, L; Chang, W. K; Theodorakis, E. A *Angew. Chem. Int. Ed.* **2011**, *50*, 3672

Synthesis of tricyclic lactone 5

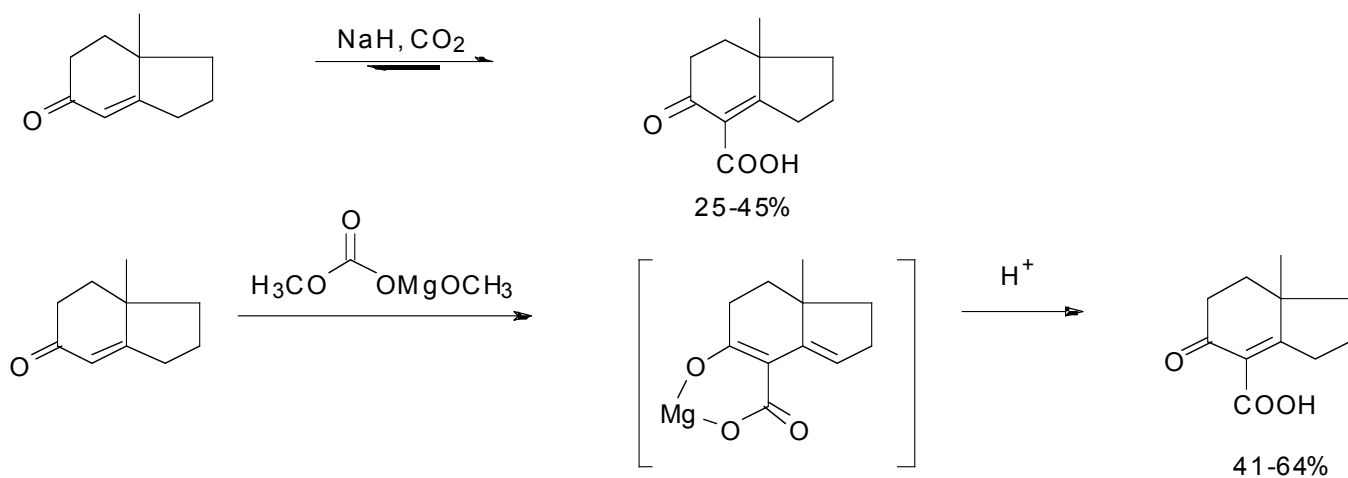


Ruprah, P. K.; Cros, J-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org Chem.* **2002**, 3145-3152
 Zhang, X-M.; Wang, M.; Tu, Y-Q.; Fan, C-A.; Jaing, Y-J.; Zhang, S-Y; Zhang, F-M. *Synlett*, **2008**, 18, 2831-2835



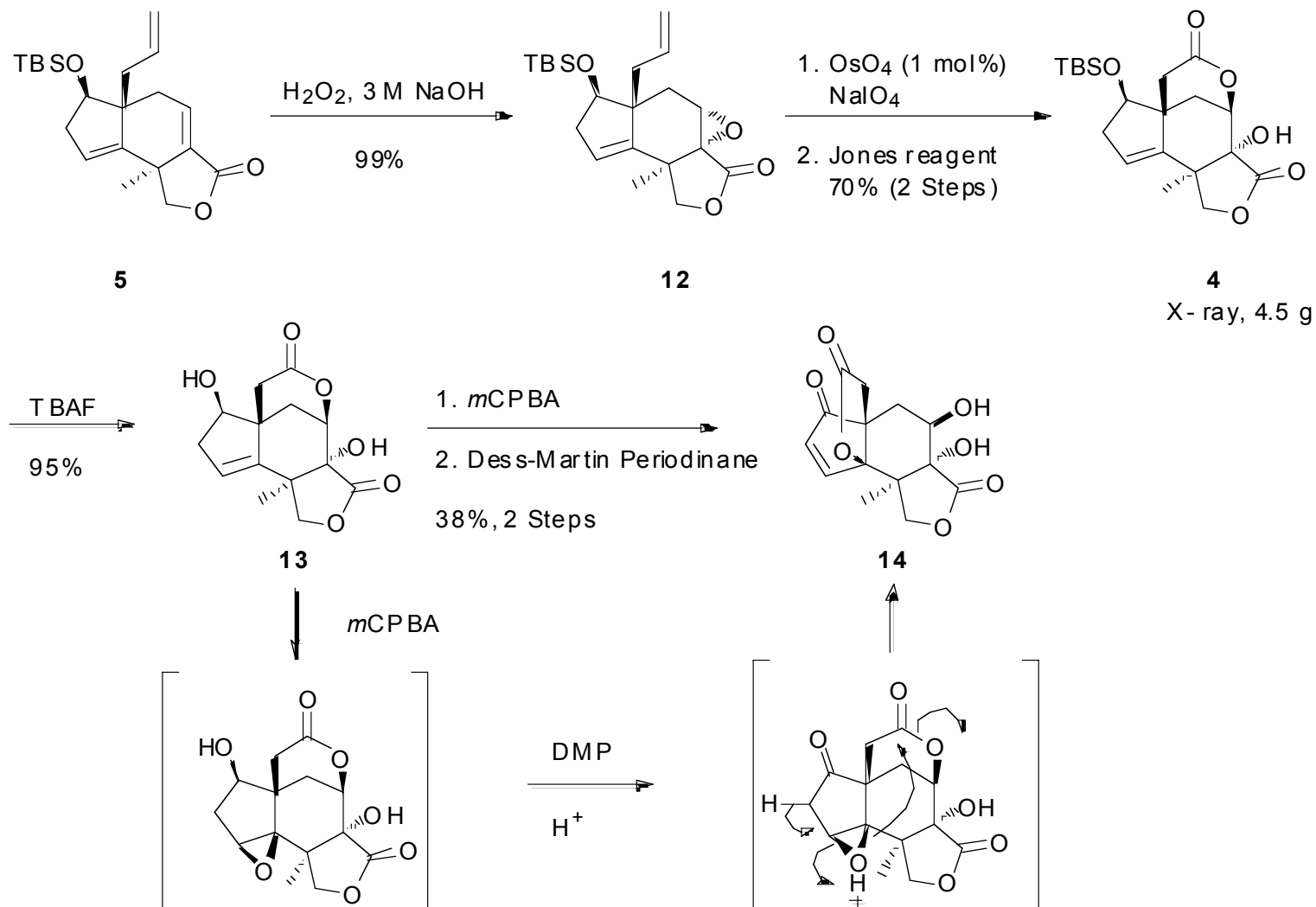
R	X	Conditions	Yield % (A)
Me	I	NaOH/H ₂ O/dioxane reflux	35
	I	TIOEt/MeI, 41 C	5
CH ₂ CH=CHC ₂ H ₅	Cl	KOH/H ₂ O	41
CH ₂ C≡CC ₂ H ₅	Br	Na ₂ CO ₃ /H ₂ O/PTC	65

Schick, H.; Eichhorn, I. *Synthesis*, **1989**, 477-492

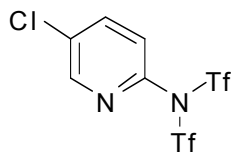
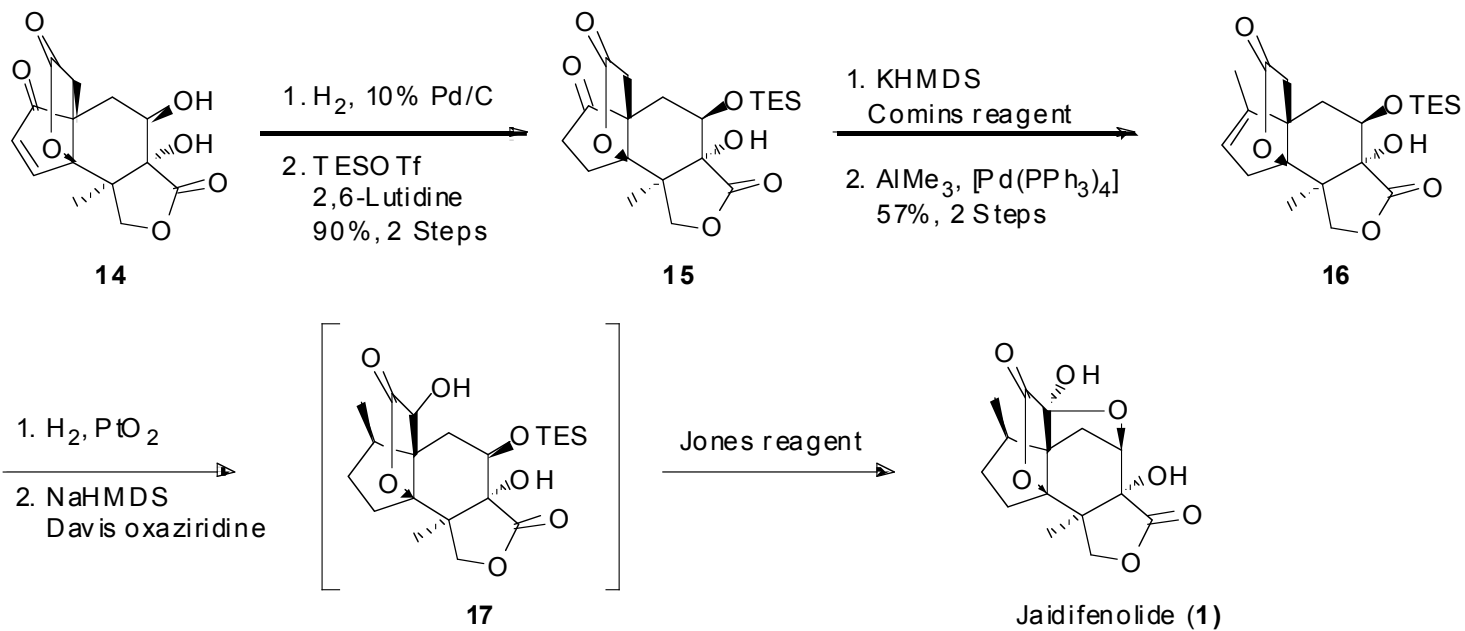


Mecheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675-681

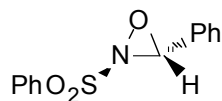
Synthesis of Lactone 14



Completion of the Synthesis



Comins Reagent



Davis Oxaziridine

Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc. Perkin Trans 1*, **1989**, 2513

Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087

Conclusions

- First total synthesis of (-)-jiadifenolide, in 1.5% overall yield and 25 total steps
- Acid-induced cascade reaction to setup desired lactone
- Gram scale synthesis of tetracyclic lactone **4**, can be used in synthesis of related natural products and analogs