

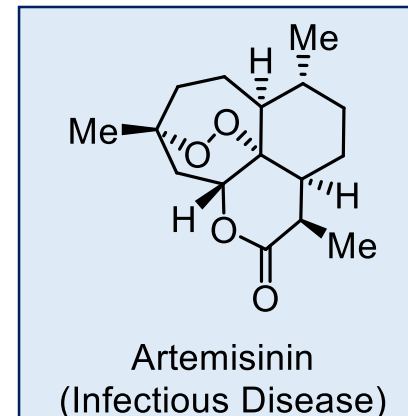
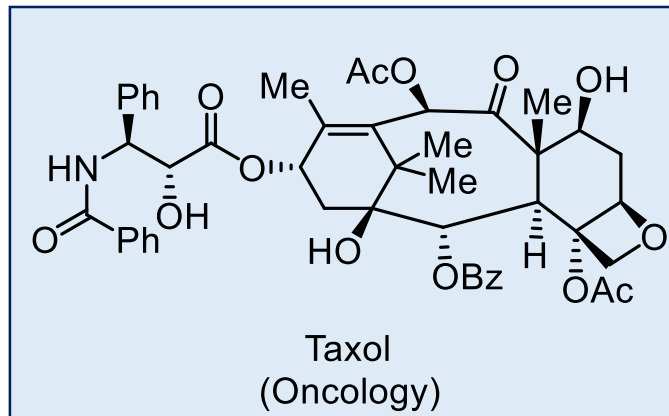
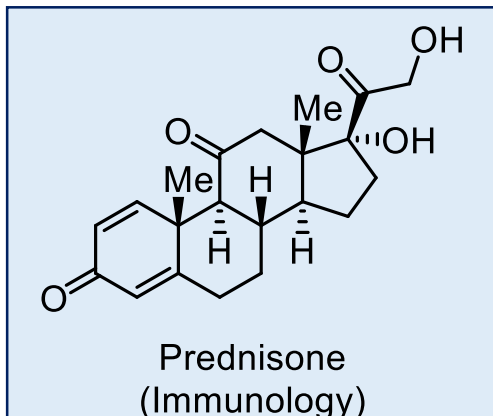


Utilizing 'Chiral Pool' Towards Synthesis of Complex Terpene Natural Products

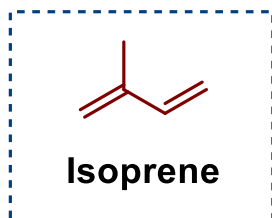
Harsh Patel
Literature Meeting
3/27/17

Terpenes

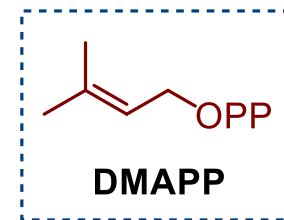
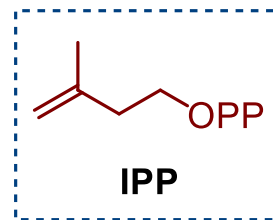
- > 30,000 members
- Perfume, Flavoring and Medicine



- Isoprene Fragment – Building Block?

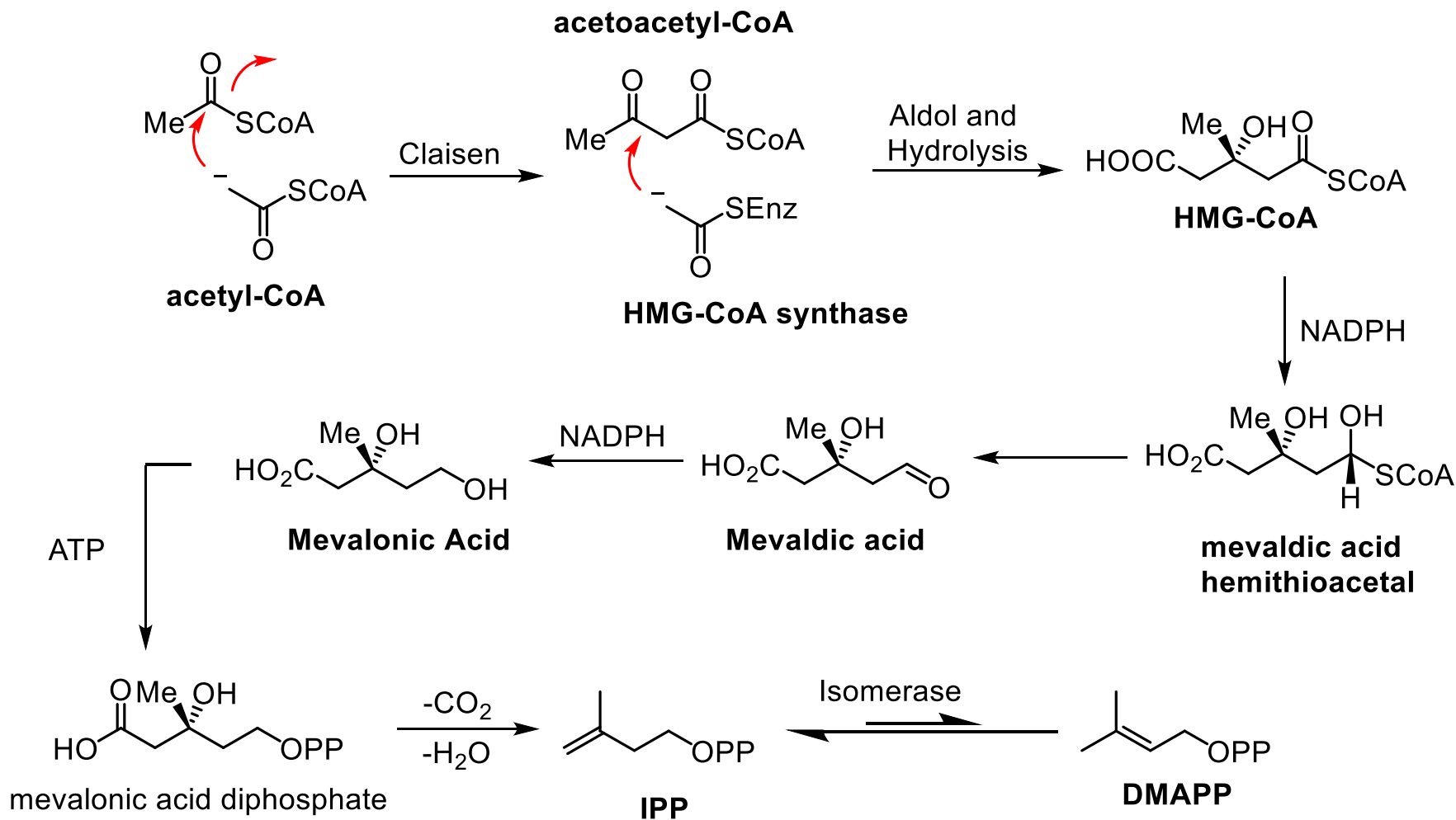


- isopentenyl pyrophosphate (IPP) &
- dimethyl allyl pyrophosphate (DMAPP)
– Actual Building Blocks

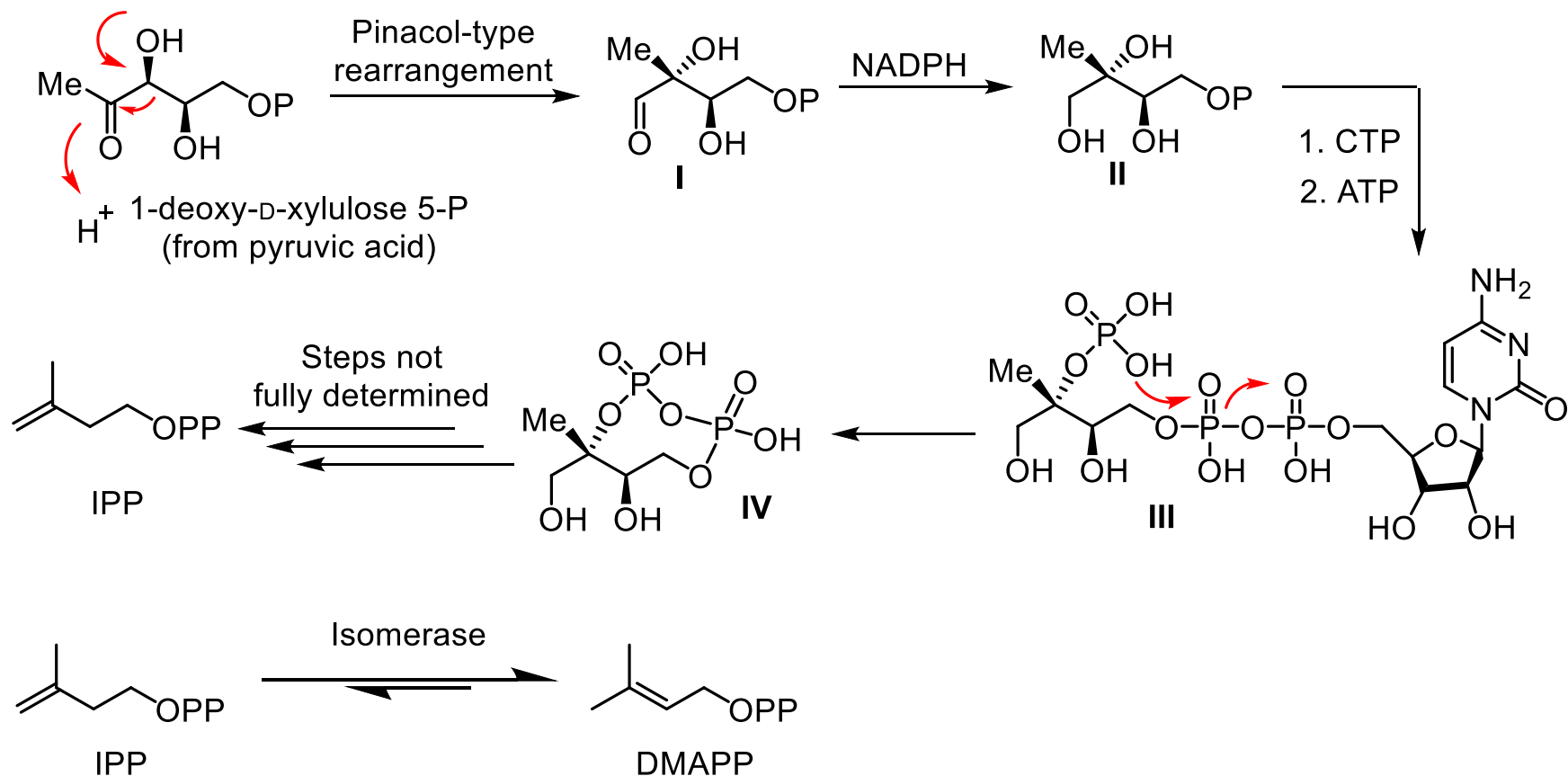


Mevalonate Pathway & Deoxyxylulose Pathway

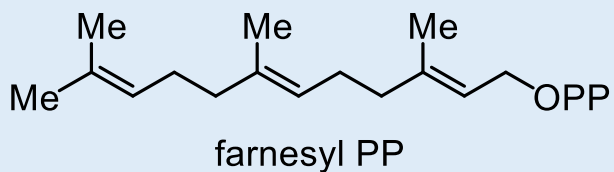
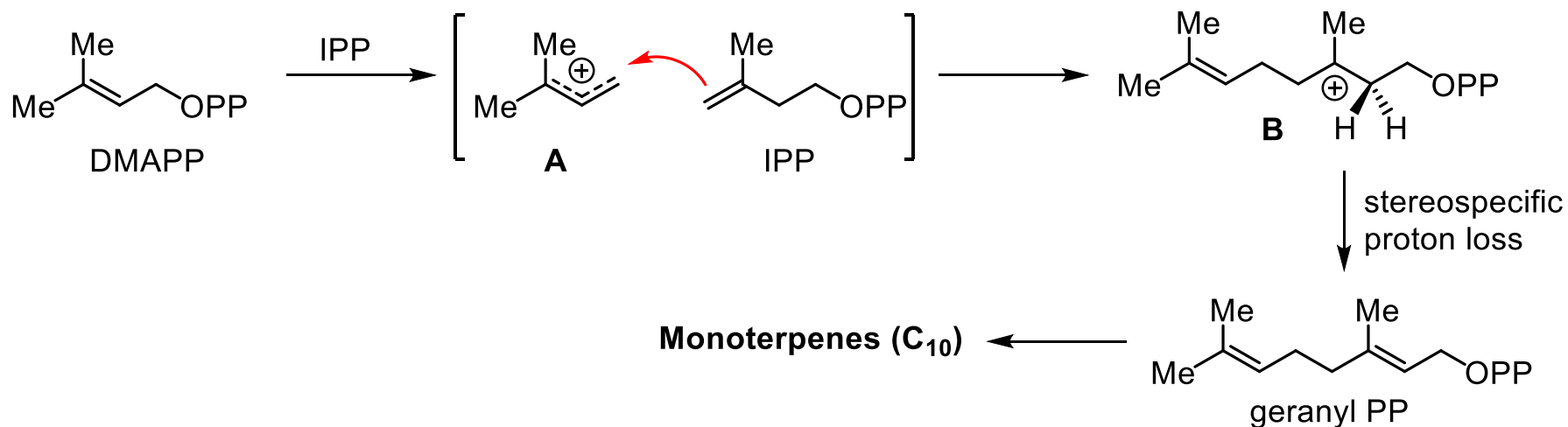
Mevalonate Pathway



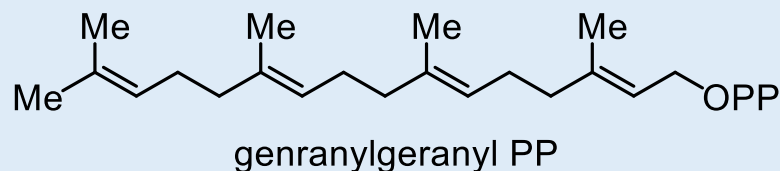
Deoxyxylulose Pathway



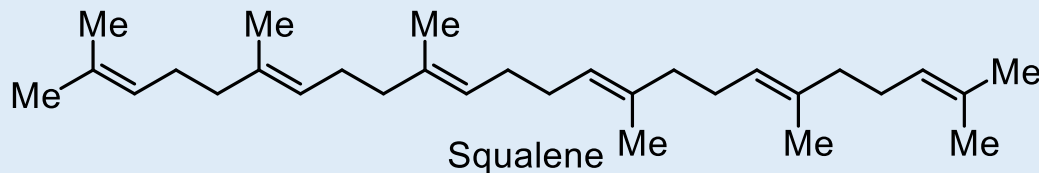
Condensation of Building Units



Sesquiterpenes (C₁₅)

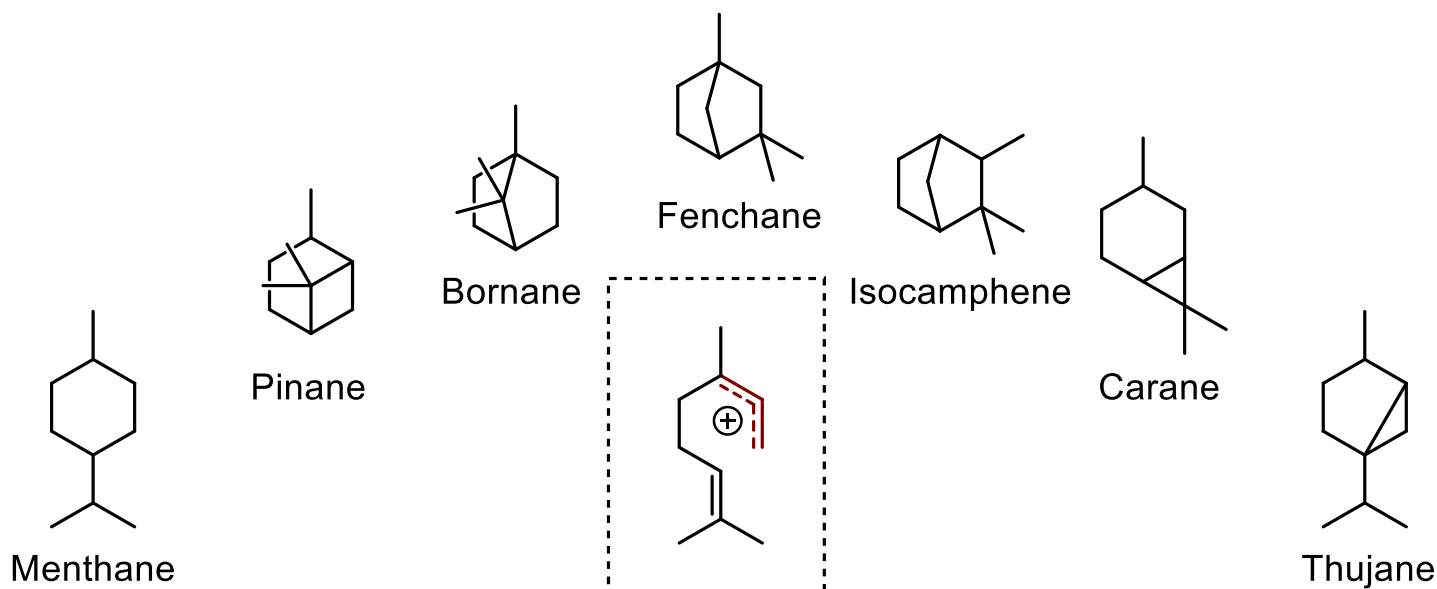
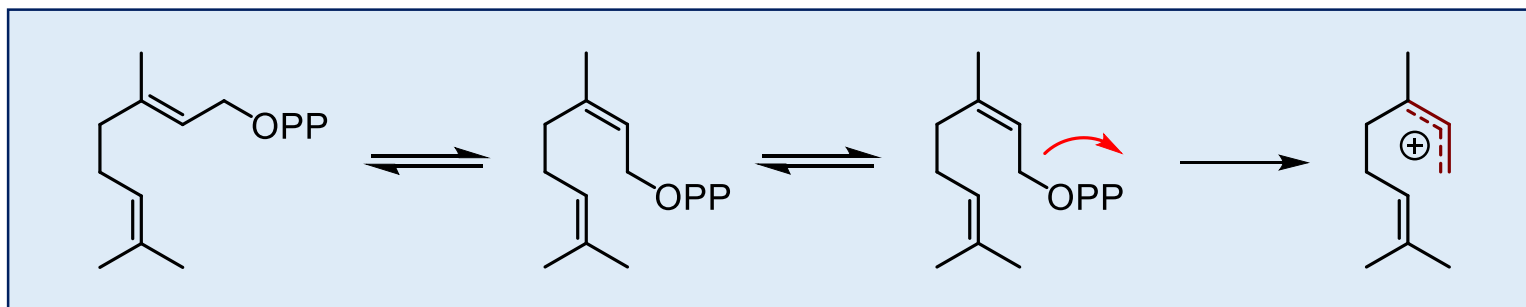


Diterpenes (C₂₀)



Triterpenes (C₃₀)

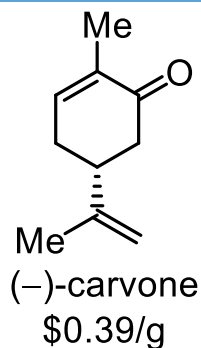
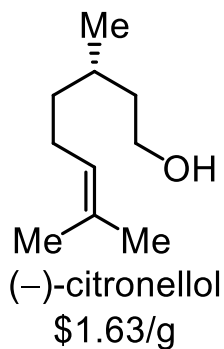
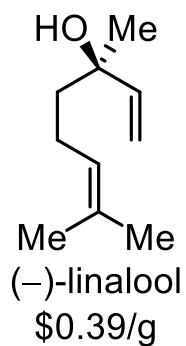
Fate of the Pyrophosphate Building Blocks



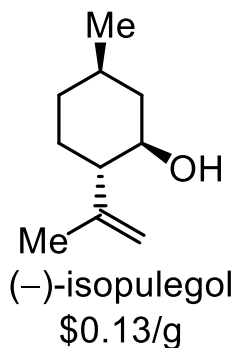
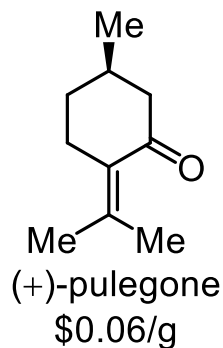
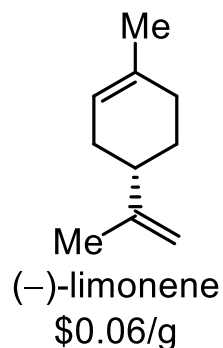
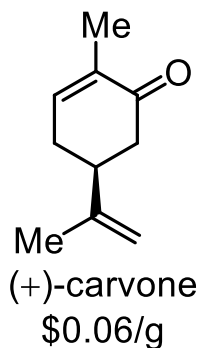
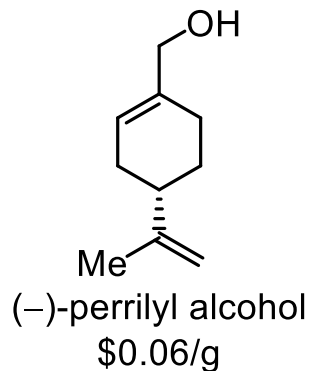
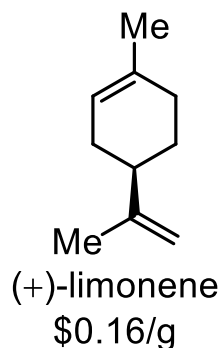
- 7 different carbon skeleton
- Several sites of hydration and elimination to terminate carbocation
- Complexity increases rapidly

Chiral Pool

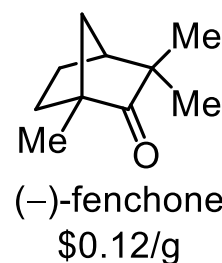
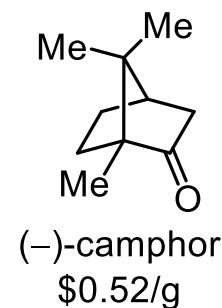
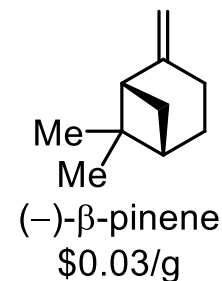
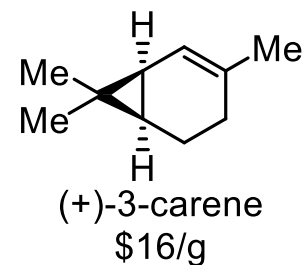
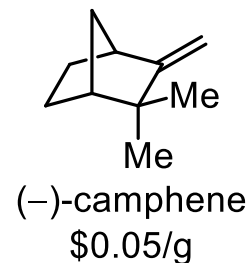
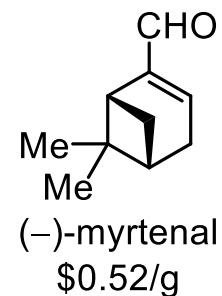
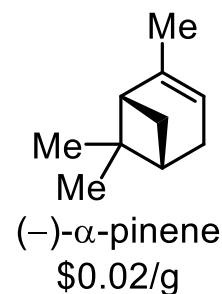
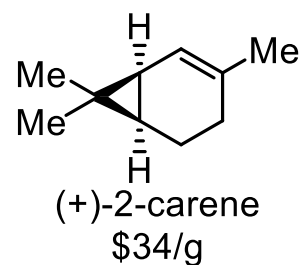
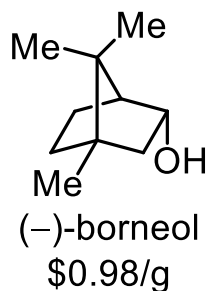
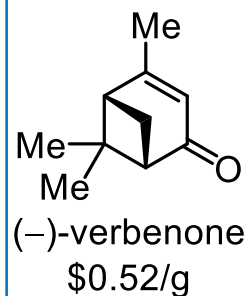
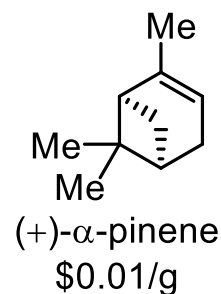
Acyclic



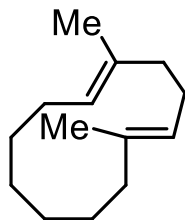
Cyclic



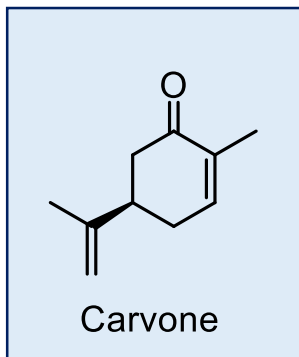
Bicyclic



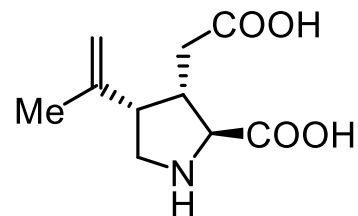
Carvone



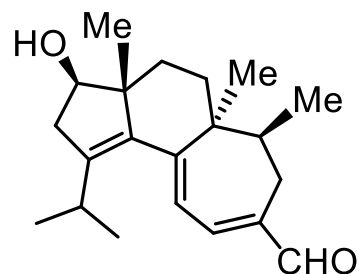
Cubitene
Lindel, 2012



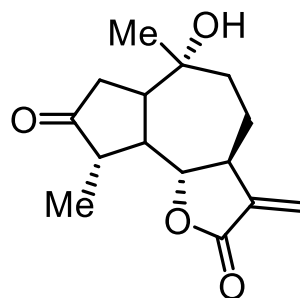
Carvone



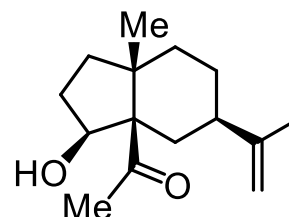
Kainic Acid
Fukuyama, 2011



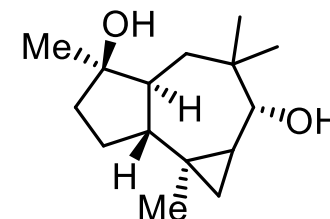
Cyrneine A
Gadermann, 2012



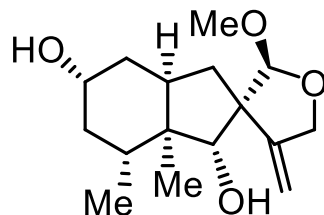
Chinensiolide B
Hall, 2010



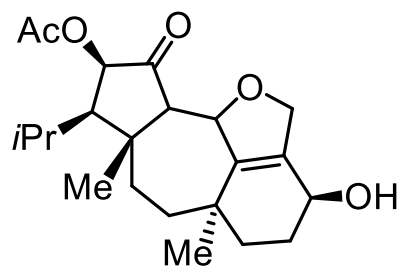
Cyperolone
Kirsch, 2012



Omphadiol
Romo, 2011

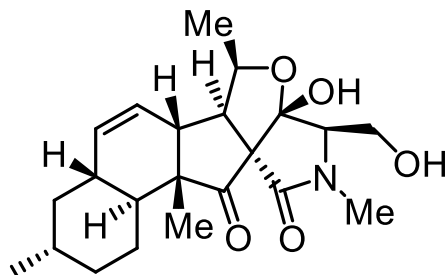


Peribysin E
Danishefsky, 2008

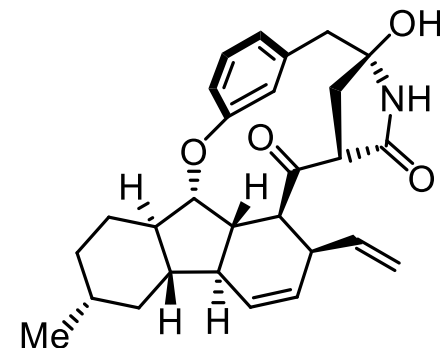
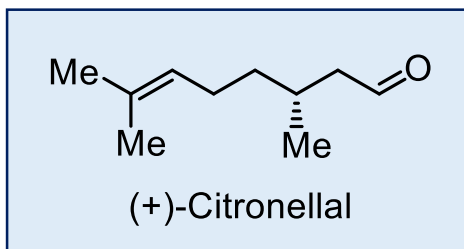


Guanacastepen E
Sorensen, 2006

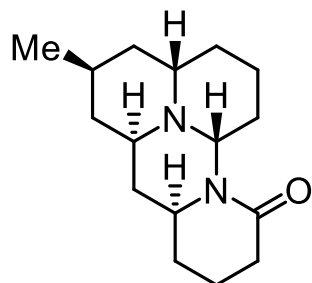
Citronellal



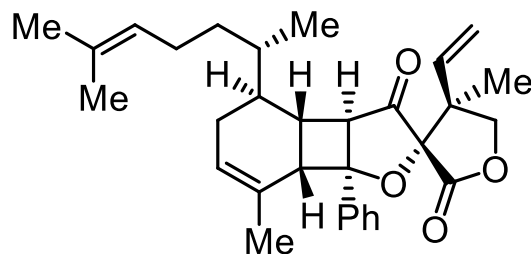
(-)-Fusarisetin A
Theodorakis, 2012



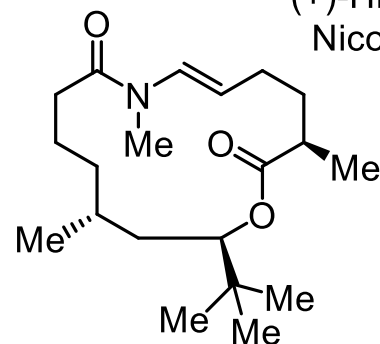
(+)-Hirsutellone B
Nicolaou, 2009



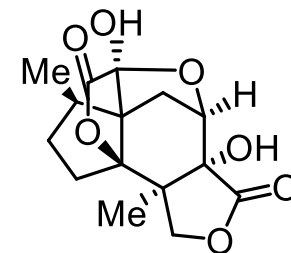
Cernuine
Takayama, 2008



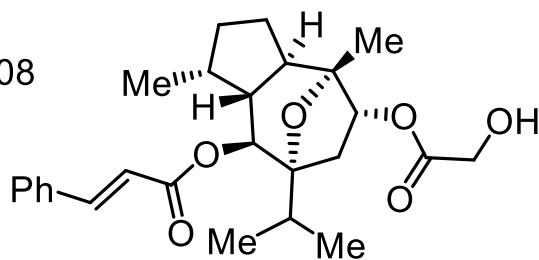
Biyouyanagin A
Nicolaou, 2008



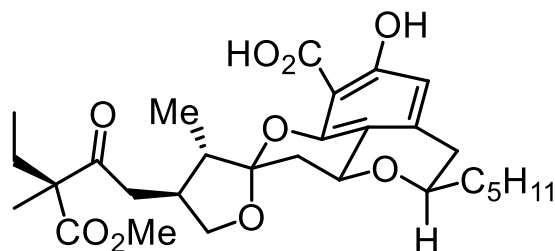
(-)-Palmyrolide
Reddy, 2013



(-)-Jiadefenolide
Shenvi, 2015

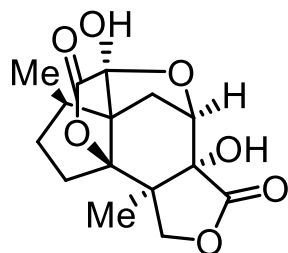


(-)-Englerin A
Ma, 2010
Chain, 2011



Berkelic Acid
Snider, 2009

Jiadenfenolide



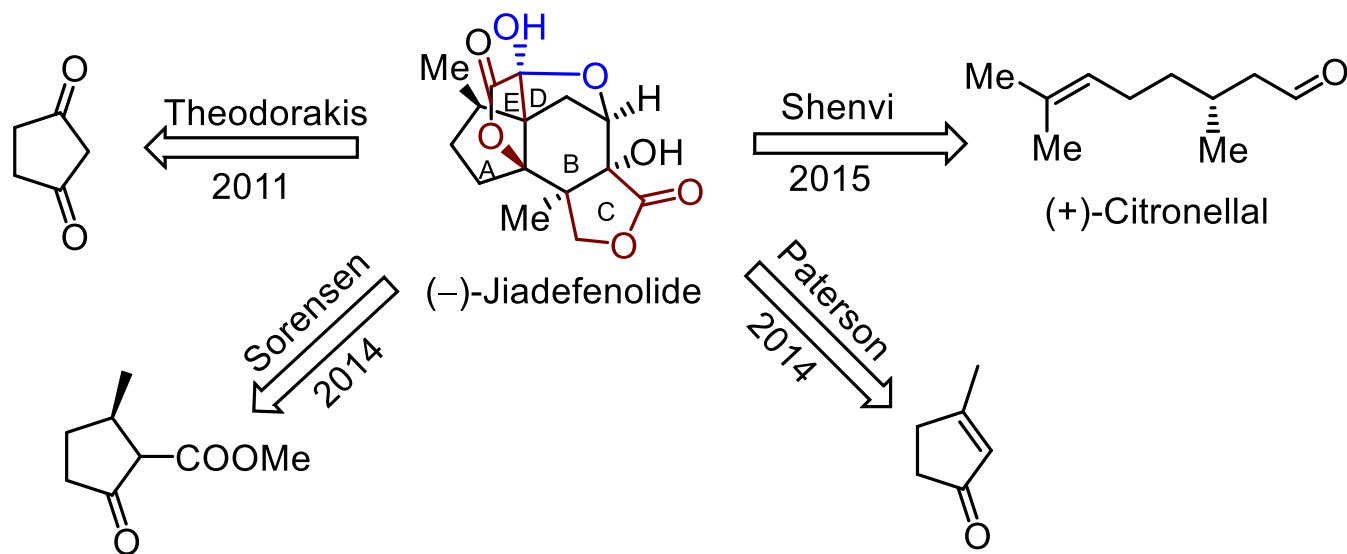
(-)-Jiadenfenolide

Significance

Isolated from the pericarp of *Illicium jiadifengpi*

Promotes Neurite outgrowth

Potential in treatment of neurodegenerative disorders



Siler, D. A.; Mighion, J. D.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2014**, 53, 5332.

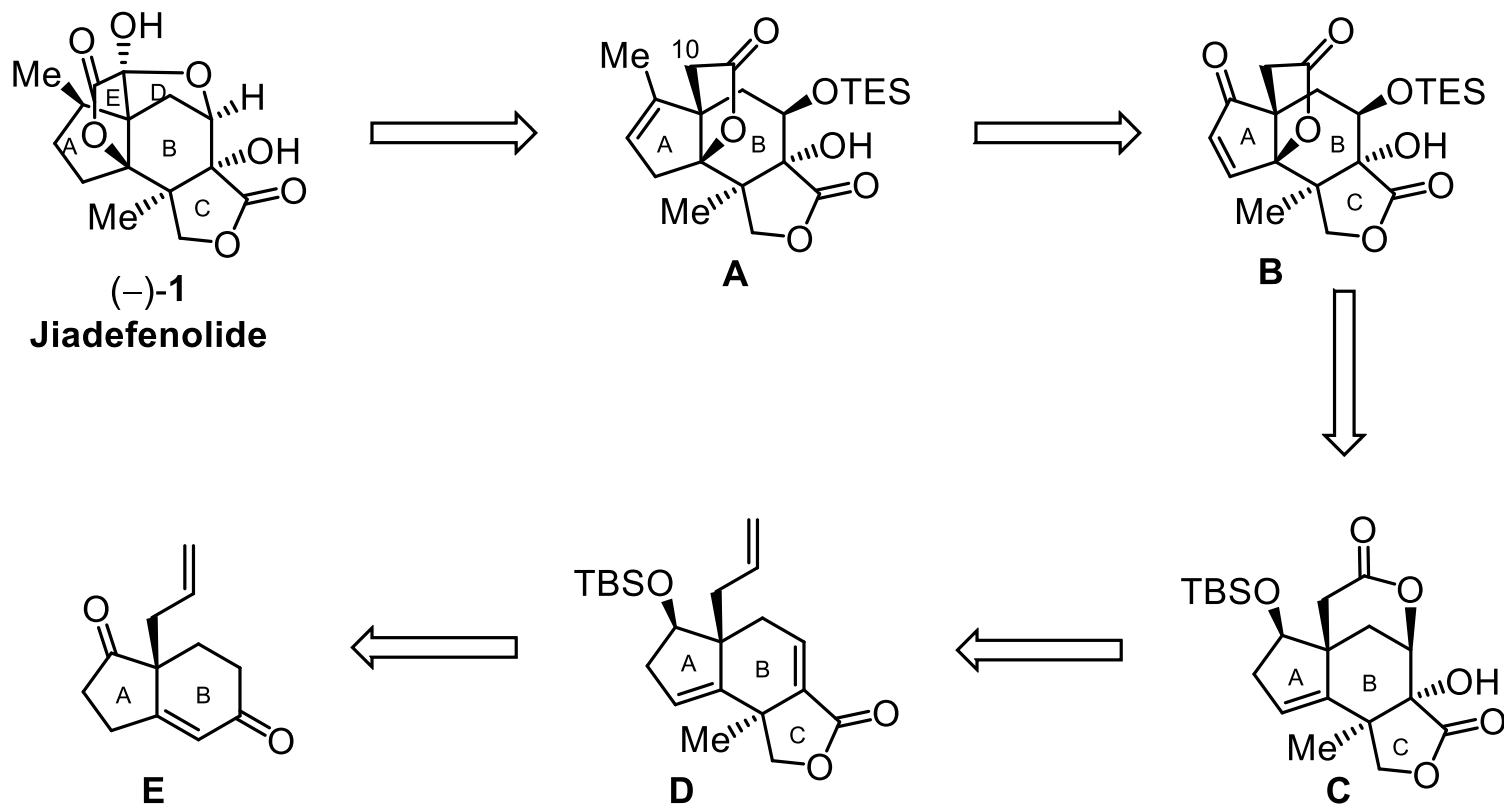
Lu, H. H.; Martinez, D. M.; Shenvi, R. A. *Nature Chem.* **2015**, 7, 604.

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

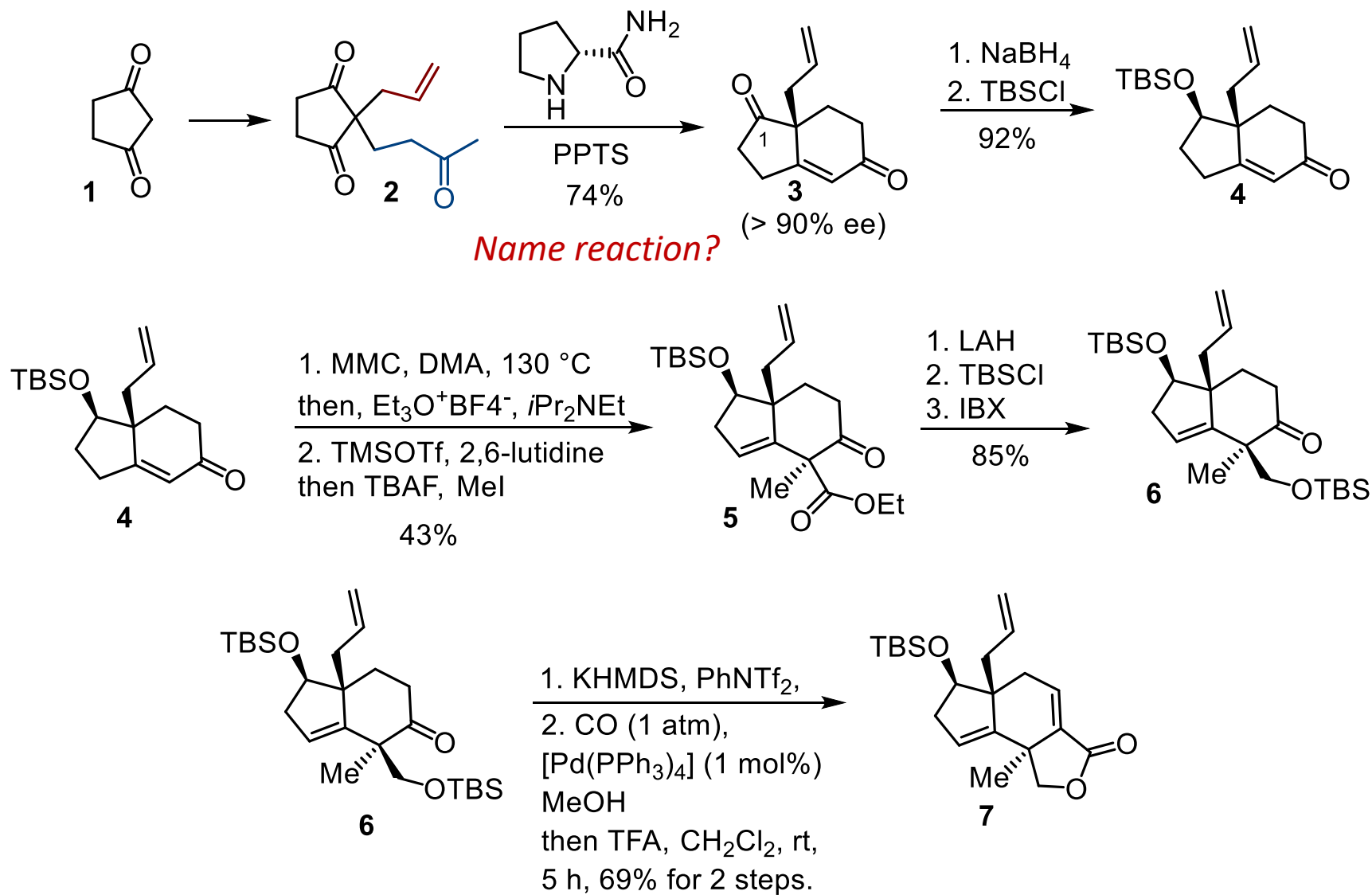
Paterson, I.; Xuan, M.; Dalby, S. M. *Angew. Chem. Int. Ed.* **2014**, 53, 7286.

Jiadenfenolide – Theodarkis 2011

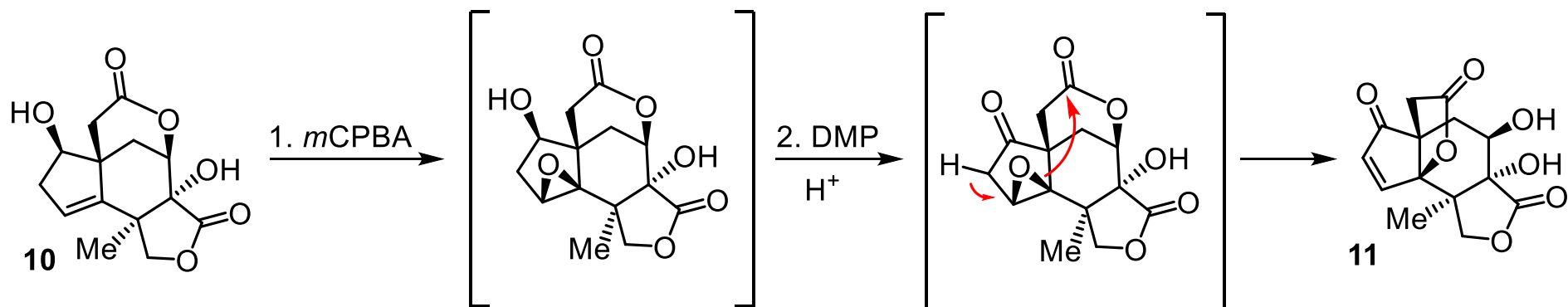
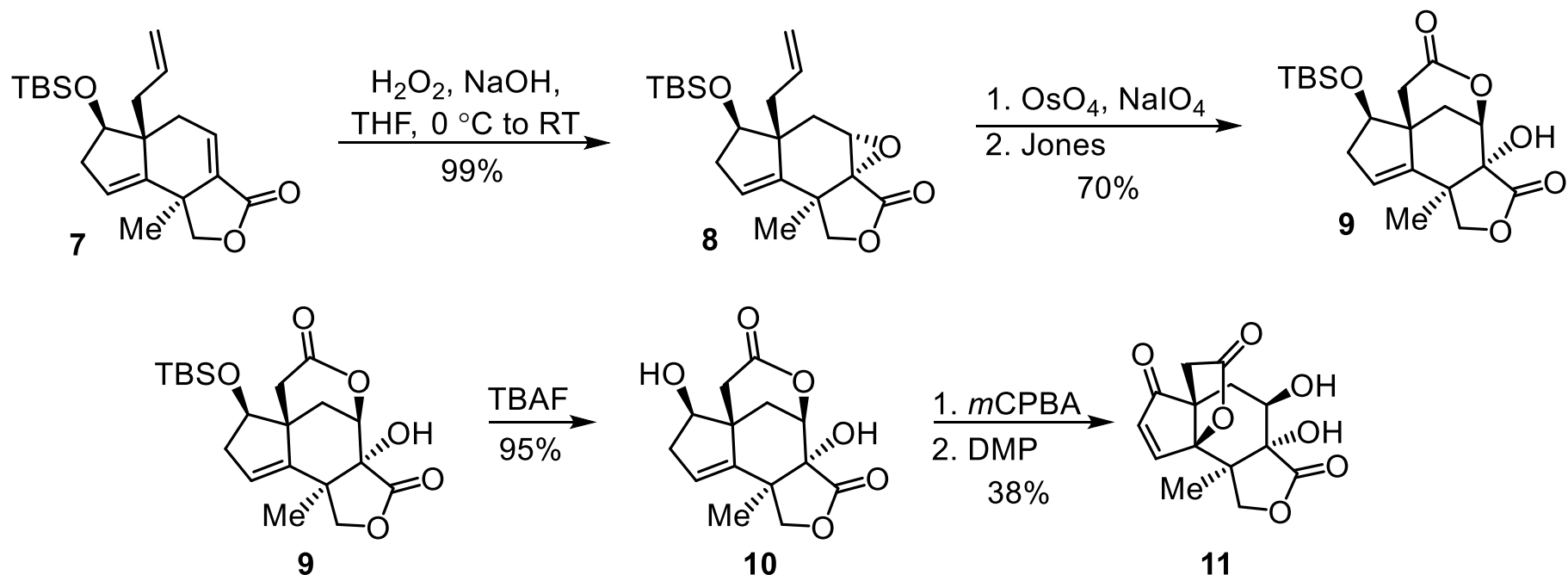
Retrosynthesis - Theodarkis 2011



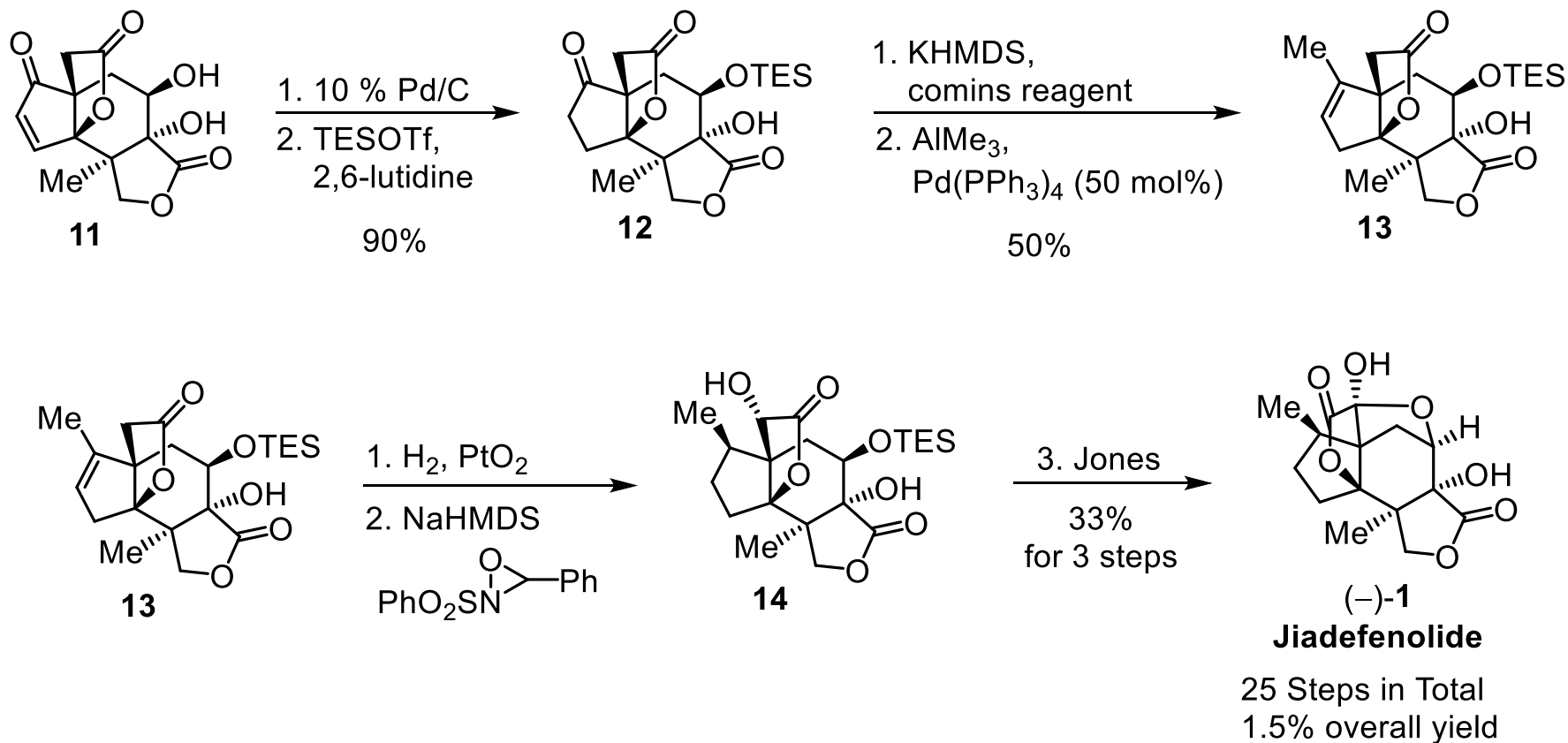
Jiadenfenolide – Theodorakis 2011



Jiadenfenolide – Theodorakis 2011

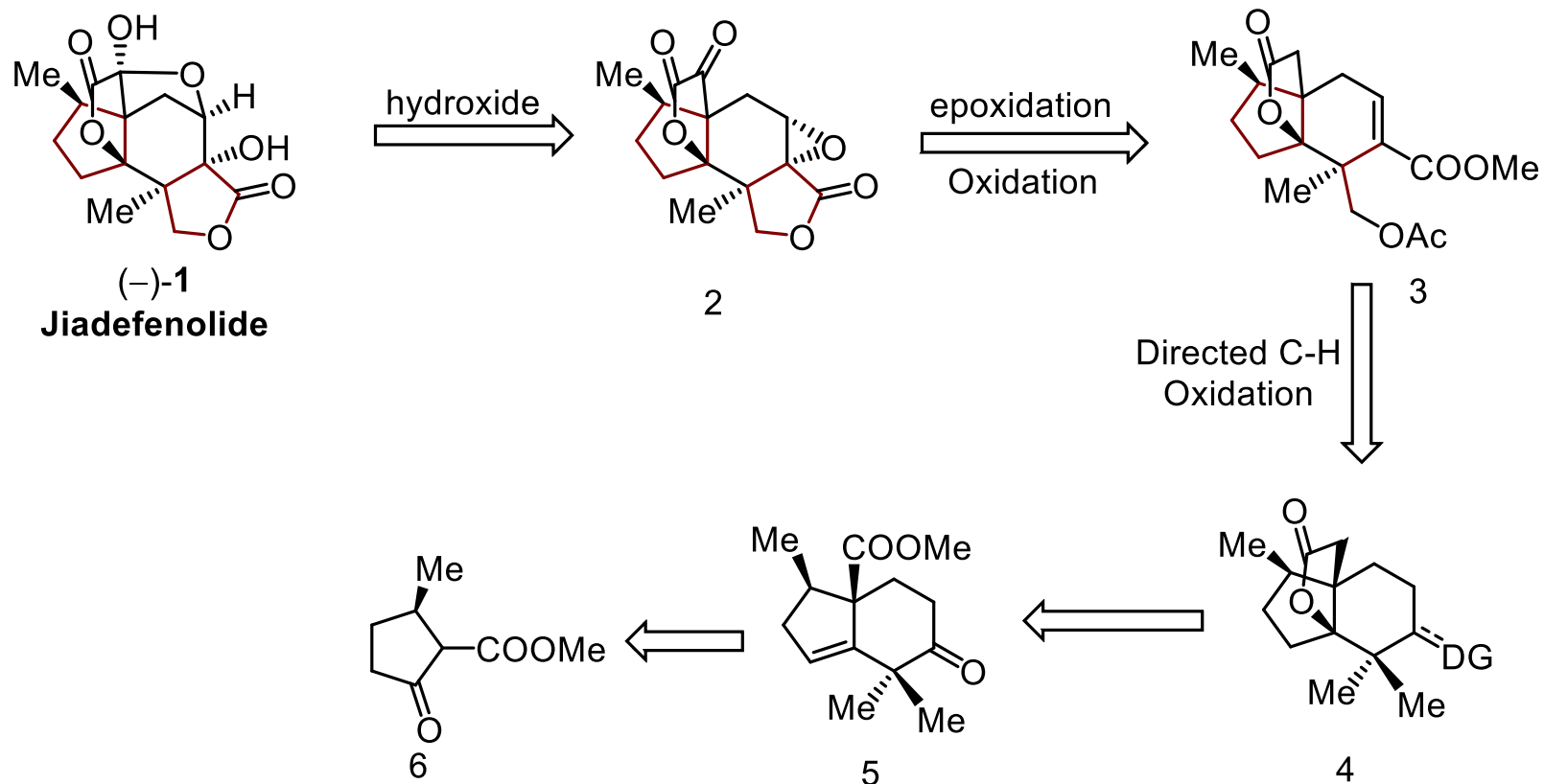


Jiadenfenolide – Theodorakis 2011



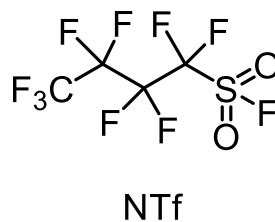
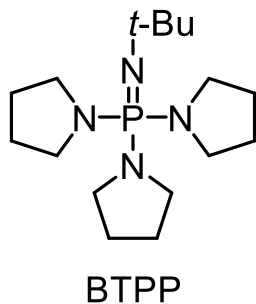
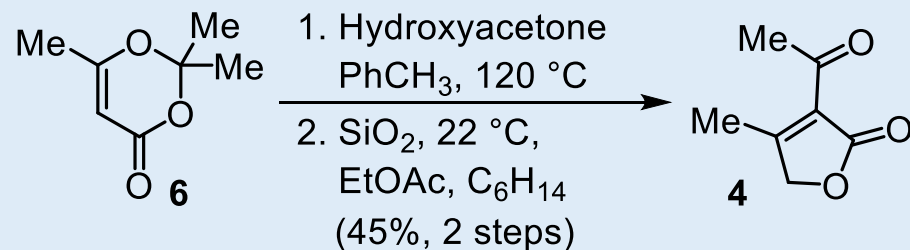
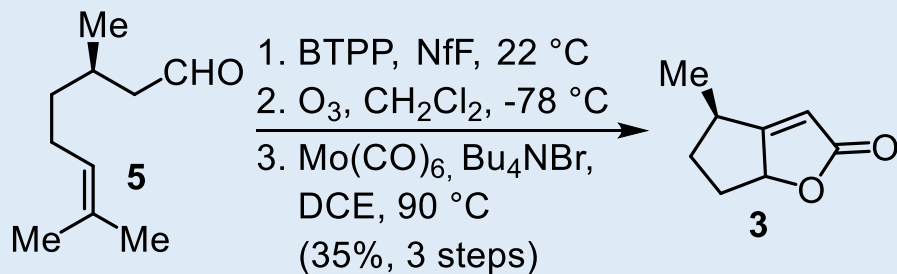
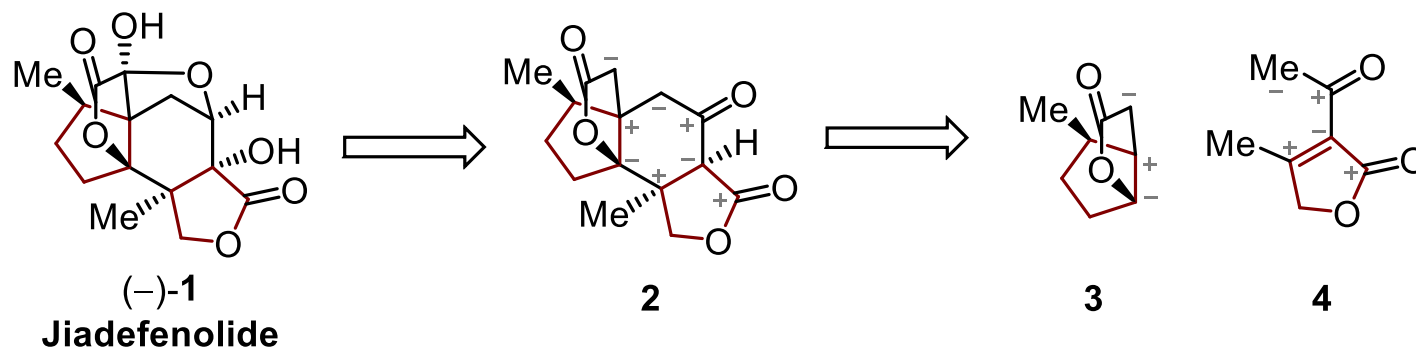
Jiadenfenolide – Sorensen 2014

SORENSONS 2014



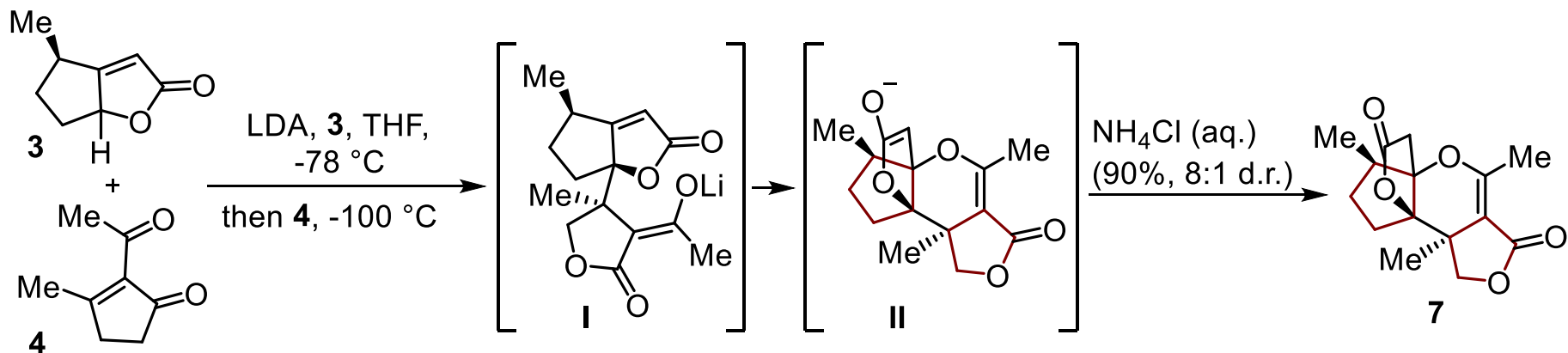
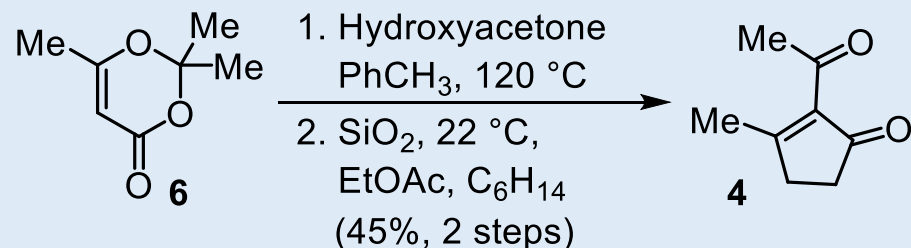
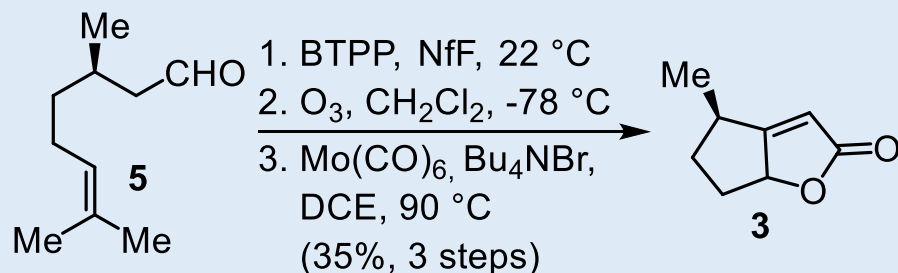
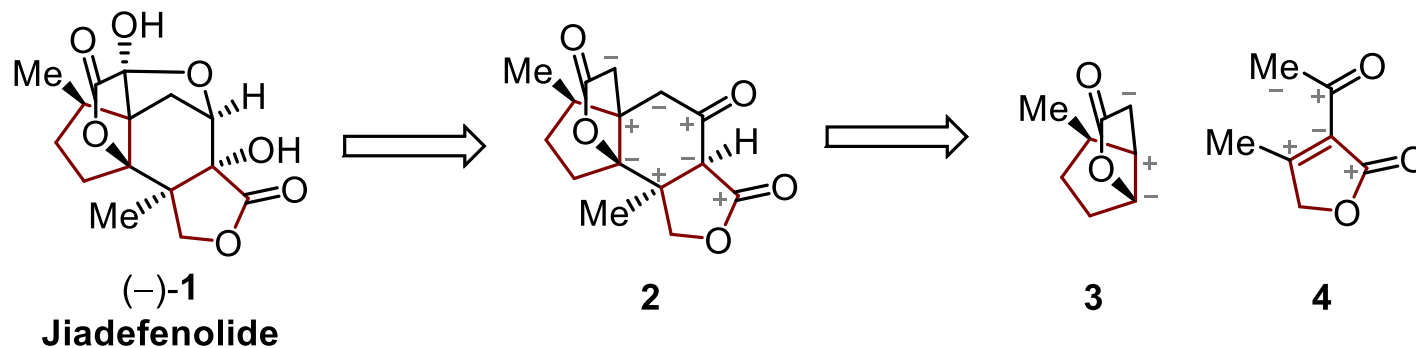
18 Steps to (-)-1 **Jiadenfenolide** from 6
(Overall yield not reported)

Jiadenfenolide – Shenvi 2015

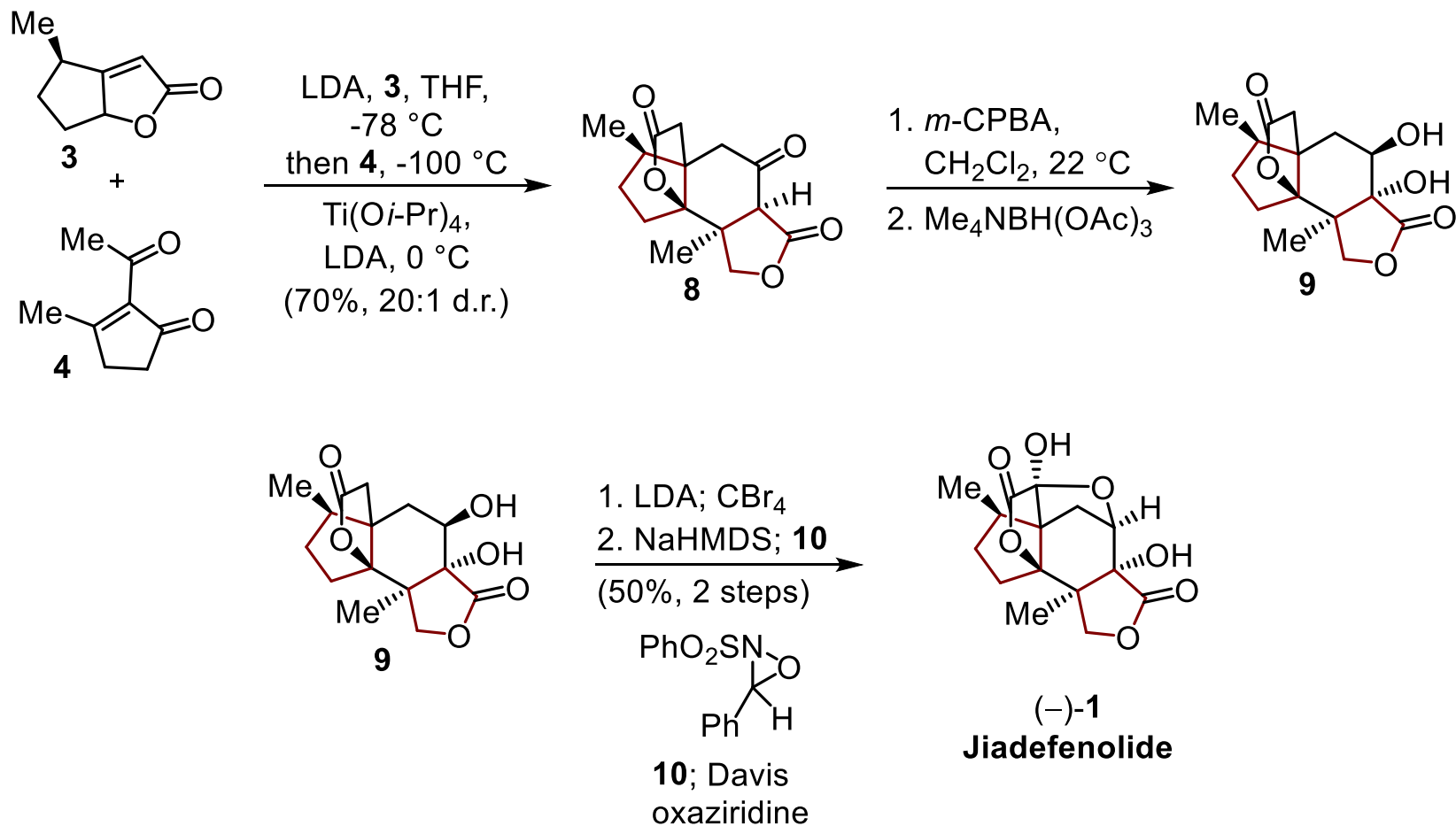


tert-butyl-imino-tri(pyrrolidino)phosphorane)

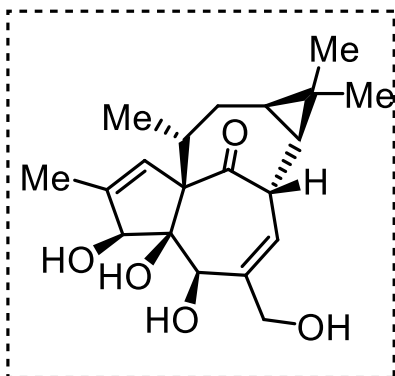
Jiadenfenolide – Shenvi 2015



Jiadenfenolide – Shenvi 2015



Ingenol



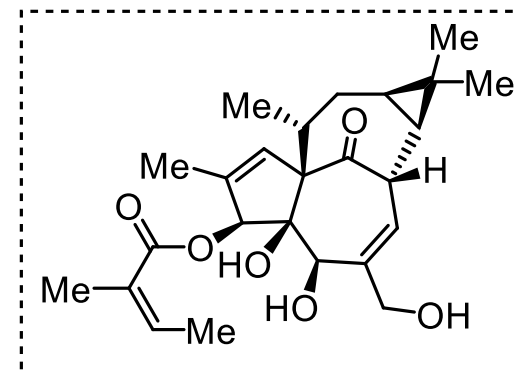
Ingenol

Significance

Isolated from *Euphorbia ingens*

anticancer and anti-HIV activity

Ingenol mebutate (FDA approved)



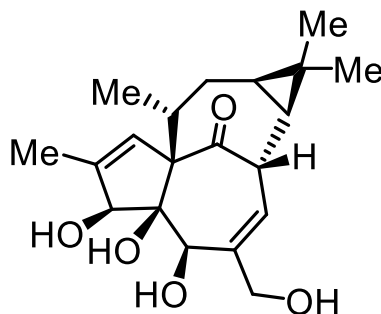
Ingenol mebutate

Jeon, 2002

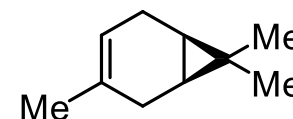
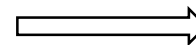
Tanino et al, 2003

Wood, 2004

Watanabe, 2004



Ingenol



Baran, 2013
(14 steps)

Mostly racemic synthesis
32-48 steps

Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726.

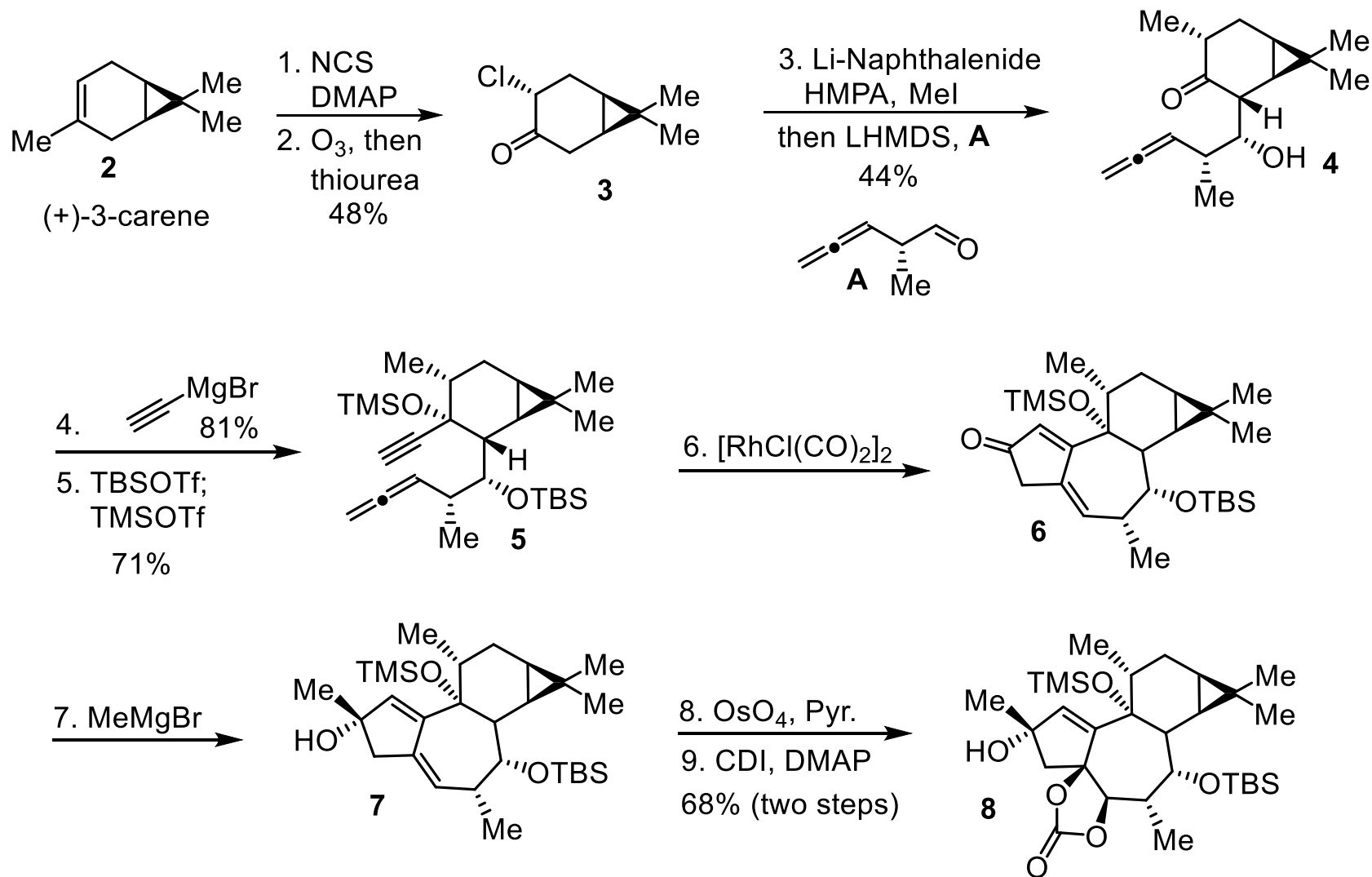
Tanino K. et al., *J. Am. Chem. Soc.* **2003**, *125*, 1498.

Nickel, A. et al., *J. Am. Chem. Soc.* **2004**, *126*, 16300.

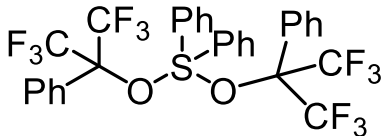
Watanabe, K. et al., *J. Org. Chem.* **2004**, *69*, 7802.

Jorgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878.

Ingenol



Ingenol



THANK YOU