

# **NF $\kappa$ B and Natural Product**

**Guojun Pan  
Group Meeting  
April 26, 2012**

# Outline

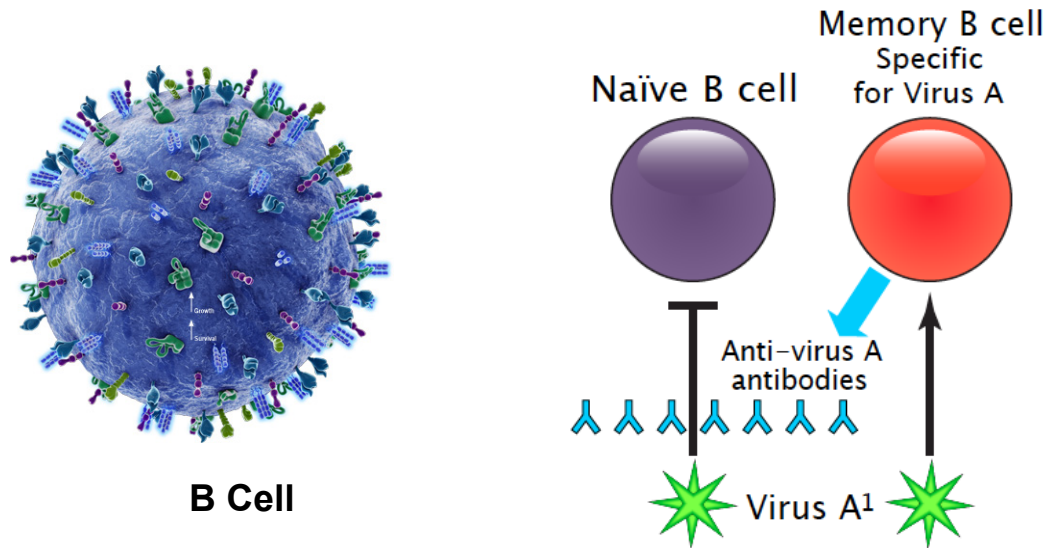
## I. B cells and NF $\kappa$ B

- B Cells, immunoglobulin
- NF $\kappa$ B and its mechanism of action
- NF $\kappa$ B activation and inhibition
- Natural products as NF $\kappa$ B inhibitors

## II. Syntheses of some NF $\kappa$ B inhibitors

- Lupeol
- Cycloepoxydone

# B Cells



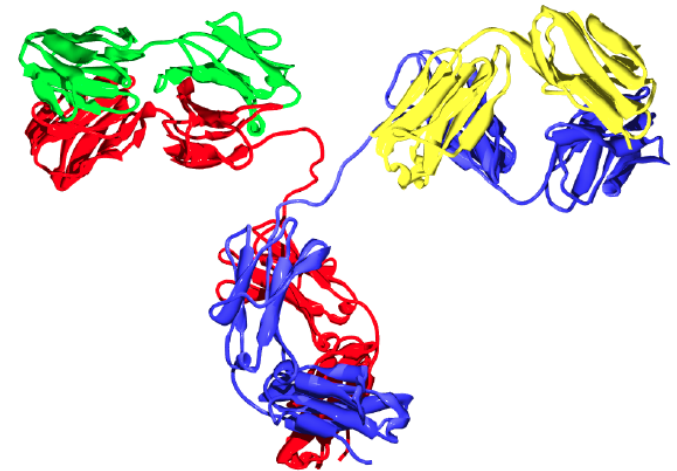
- B cells are lymphocytes that play a large role in the humoral immune response.
- The principal functions of B cells are to make antibodies against antigen, perform the role of antigen-presenting cells (APCs) and eventually develop into memory B cells.
- Essential component of the adaptive immune system.

[http://en.wikipedia.org/wiki/B\\_cells](http://en.wikipedia.org/wiki/B_cells)

<http://www.biooncology.com/images/therapeutic-targets/b-cell-ig.jpg&imgrefurl>

# Immunoglobulin (Antibody)

- A typical antibody is composed of two immunoglobulin (Ig) heavy chains and two Ig light chains.
- The immunoglobulin (antibody) light chain is the small polypeptide subunit of an antibody.
- Two types of light chain in humans and other mammals:
  - kappa ( $\kappa$ ) chain, encoded by the immunoglobulin  $\kappa$  locus (IGK@) on chromosome 2.
  - lambda ( $\lambda$ ) chain, encoded by the immunoglobulin  $\lambda$  locus (IGL@) on Chromosome 22.



**An antibody molecule:**  
**Heavy chains: red, blue**  
**Light chains: green, yellow**

# NF $\kappa$ B

- NF $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of DNA.
- NF $\kappa$ B was first discovered in the lab of Nobel Prize (1975) laureate David Baltimore in 1986.
- NF $\kappa$ B family members share structural homology with the retroviral oncoprotein v-Rel, resulting in their classification as NF $\kappa$ B/Rel proteins.
- There are 5 proteins in the mammalian NF $\kappa$ B family:

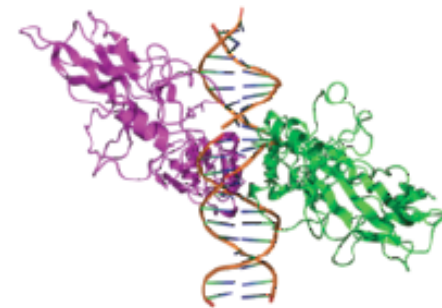
Class	Protein	Aliases	Gene
I	NF- $\kappa$ B1	p105 $\rightarrow$ p50	NFKB1
	NF- $\kappa$ B2	p100 $\rightarrow$ p52	NFKB2
II	RelA	p65	RELA
	RelB		RELB
	c-Rel		REL

[http://en.wikipedia.org/wiki/NF- \$\kappa\$ B](http://en.wikipedia.org/wiki/NF-<math>\kappa</math>B).



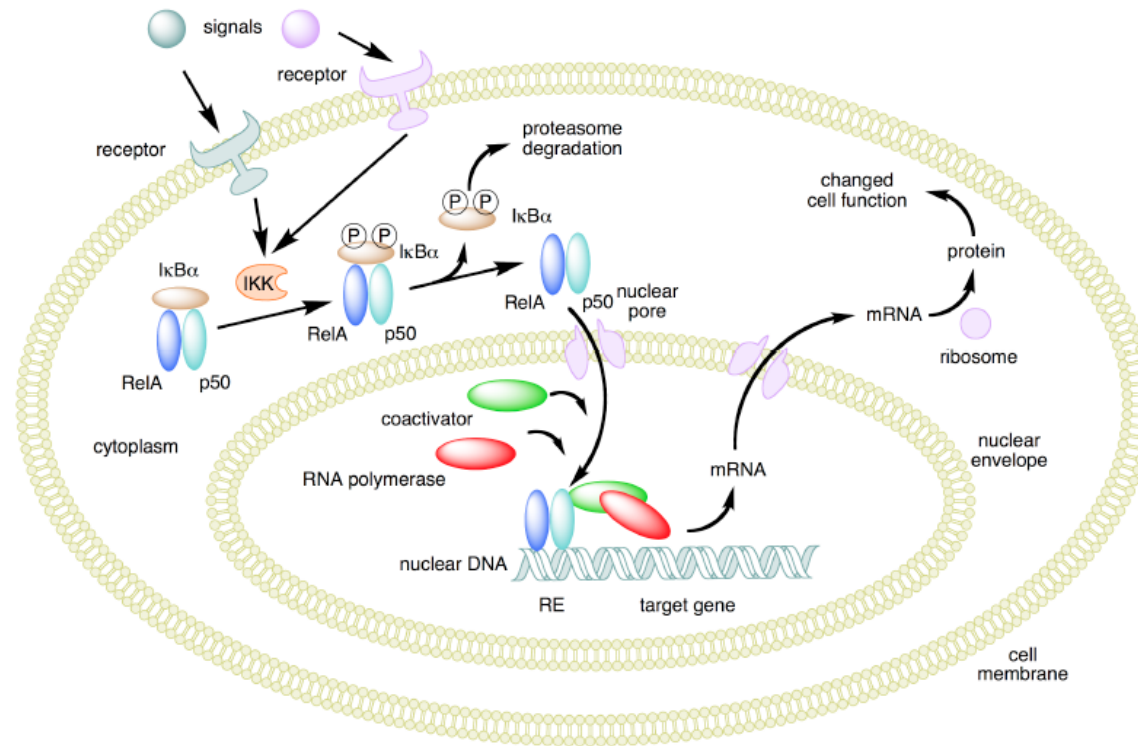
Baltimore in 2008

## RELA



Side view of the crystallographic structure (PDB 2RAM (<http://www.rcsb.org/pdb/explore/explore.do?structureId=2RAM>) ) of a homodimer of the RELA protein (green and magenta) bound to DNA (brown).

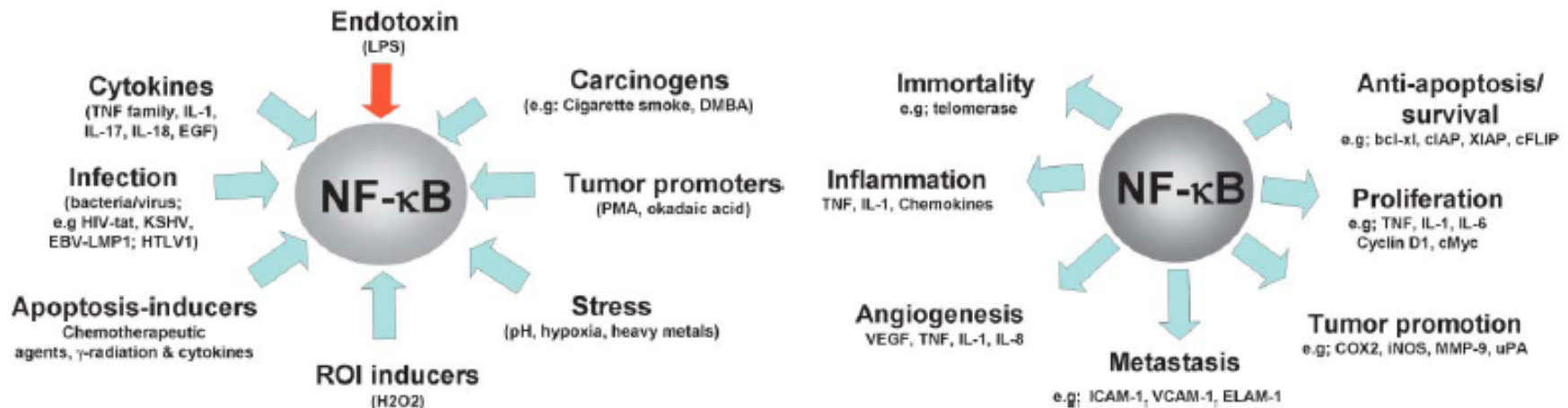
# Mechanism of NF $\kappa$ B Action



- NF $\kappa$ B is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, uv, oxidized LDL, bacterial or viral antigens.
- NF $\kappa$ B is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival.
- NF $\kappa$ B belongs to the category of “rapid-acting” primary transcription factor.

[http://en.wikipedia.org/wiki/Immunoglobulin\\_light\\_chain](http://en.wikipedia.org/wiki/Immunoglobulin_light_chain)  
[http://en.wikipedia.org/wiki/File:Antibody\\_IgG2.png](http://en.wikipedia.org/wiki/File:Antibody_IgG2.png)

# Aberrant NF $\kappa$ B Activation



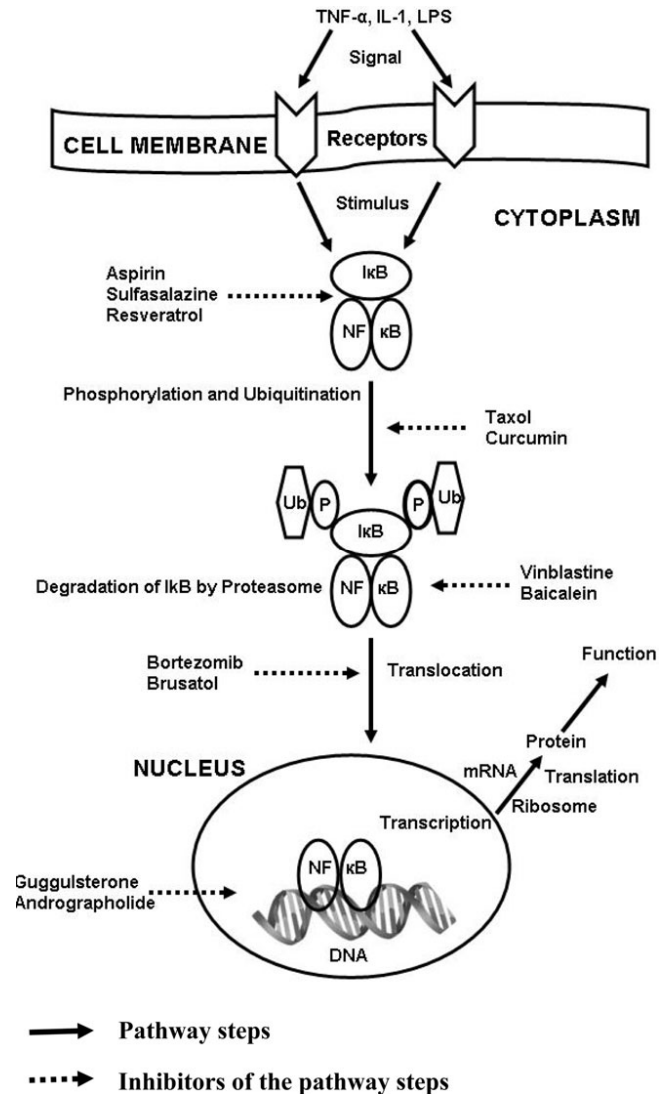
Activation of NF $\kappa$ B by inflammatory agents, carcinogens, Tumor promoters, viral proteins, stress, chemotherapeutic Agents, and  $\gamma$  radiation.

Expression of numerous genes is regulated by Activation of NF $\kappa$ B

- Incorrect regulation of NF $\kappa$ B has been linked to cancer, inflammatory and autoimmune disease, septic shock, viral infection, and improper immune development.
- In many tumors and inflammatory disease, such as inflammatory bowel disease, arthritis, sepsis, gastritis, asthma, atherosclerosis, NF $\kappa$ B was found to be constitutively active.

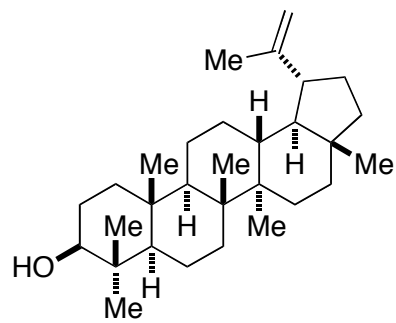
# Inhibition of NFκB

- Methods of inhibiting NFκB has potential therapeutic application in cancer and inflammatory diseases.
- NFκB serves an important immune function, its absence can result in severe immunodeficiency.
- NFκB inhibitors are most likely to be used as adjuvants along with other cancer therapies.

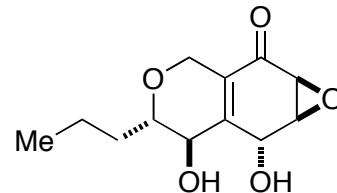




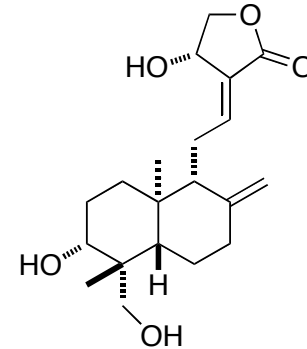
# Natural Inhibitors of NF $\kappa$ B



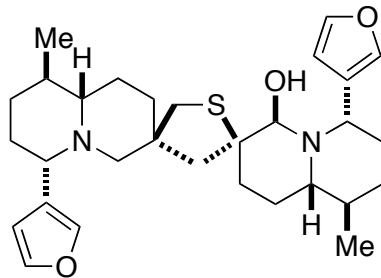
Lupeol



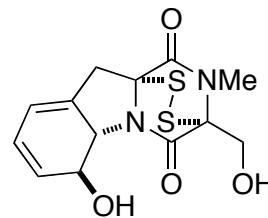
Cycloepoxydon



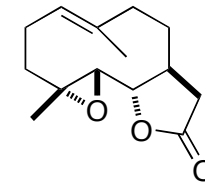
Andrographolide



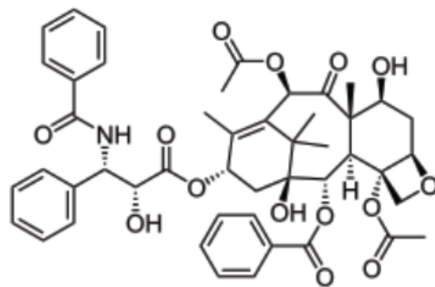
6-Hydroxythionupharidine



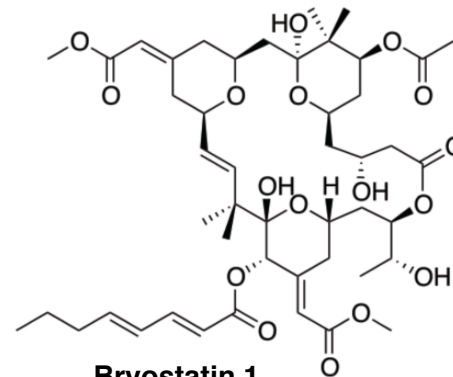
Gliotoxin



Parthenolide

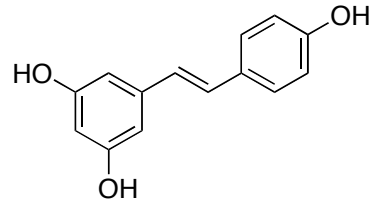


Paclitaxel



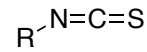
Bryostatin 1

# Food and Cancer Chemoprevention



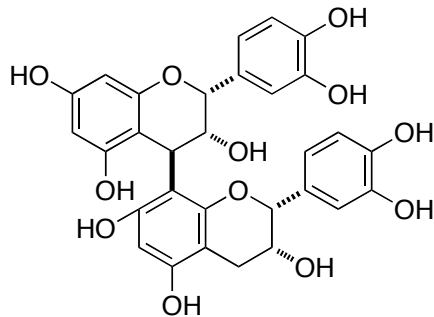
**Resveratrol**

(wines, grape juice, peanut, mulberry, blueberry, cocoa powder, dark chocolate)



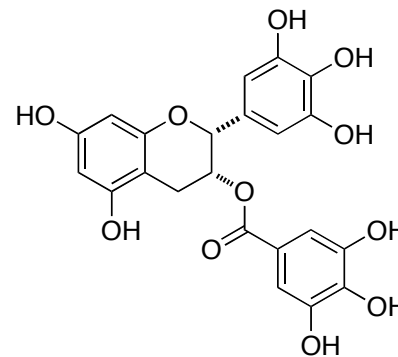
**Isothiocyanates**

(wasabi, horseradish, mustard, radish, brussels sprout, watercress, nasturtiums)



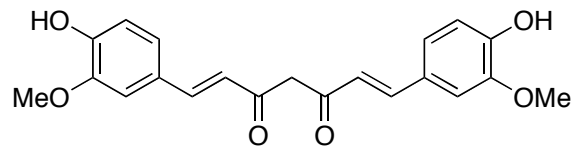
**Procyanidins**

(apple, cinnamon, cocoa beans, grape seed, grape skin, wines, bilberry, cranberry, black currant, green tea, black tea)



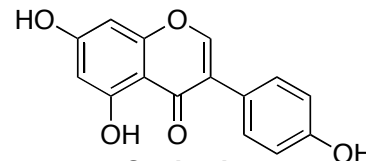
**Epigallocatechin gallate**

(green tea)



**Curcumin**

(turmeric, ginger)



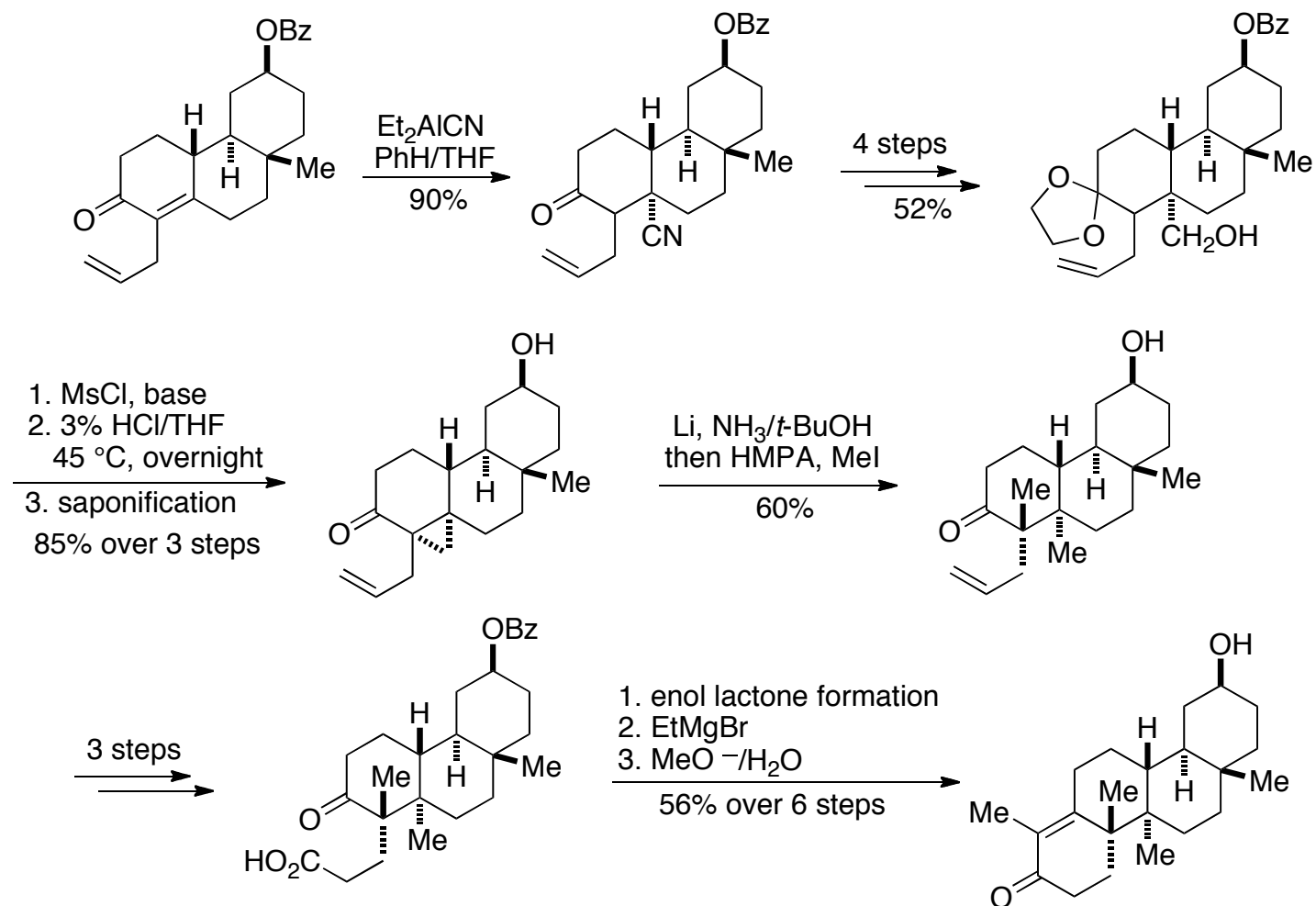
**Genistein**

(fava beans, soy beans, kudzu, psoralea, coffee)

# Syntheses of some NF $\kappa$ B inhibitors

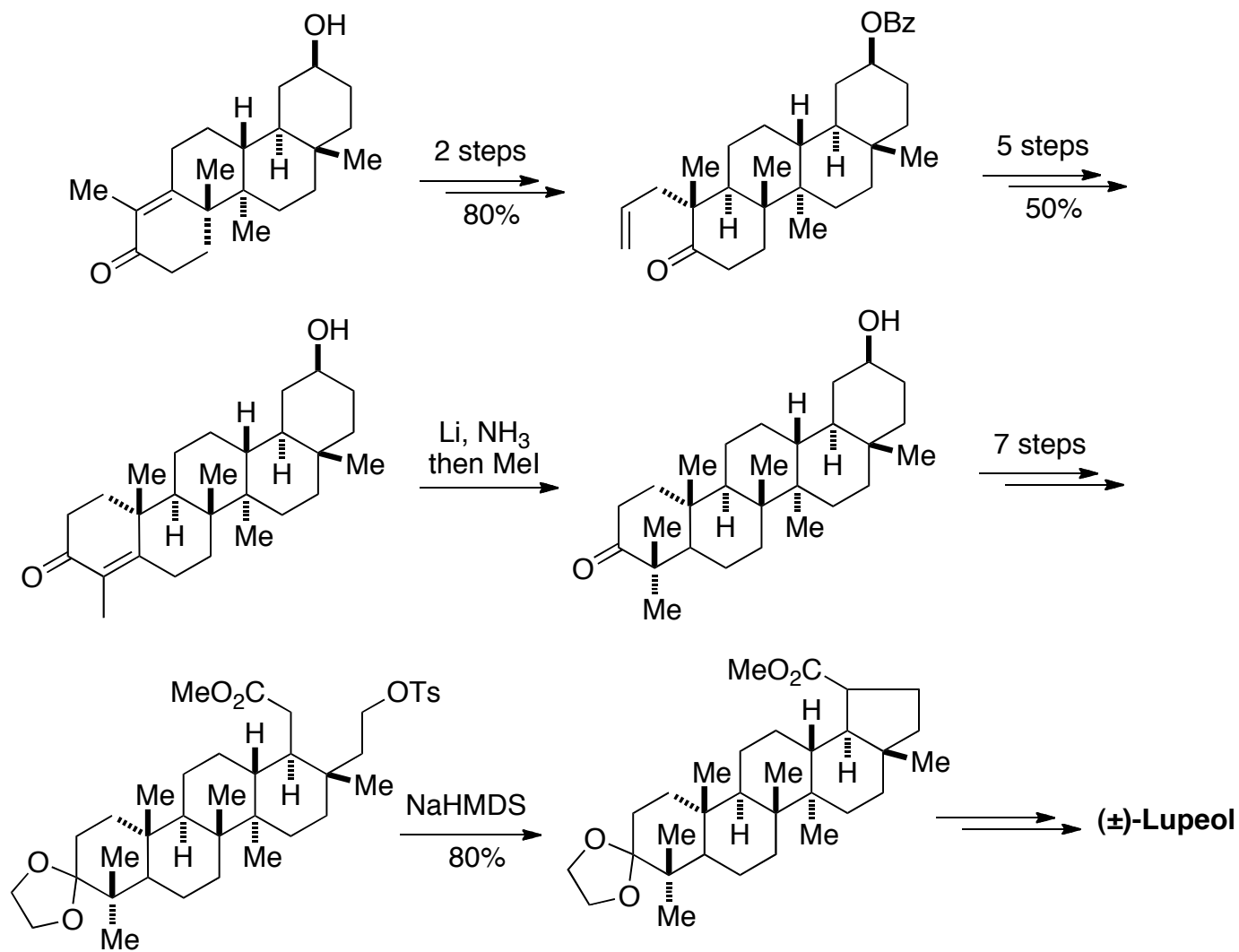
- Lupeol  
Stock's synthesis  
Corey's synthesis
- Cycloepoxydone  
Porco, Jr's synthesis  
Mehta's synthesis

# Stock's Synthesis of Lupeol



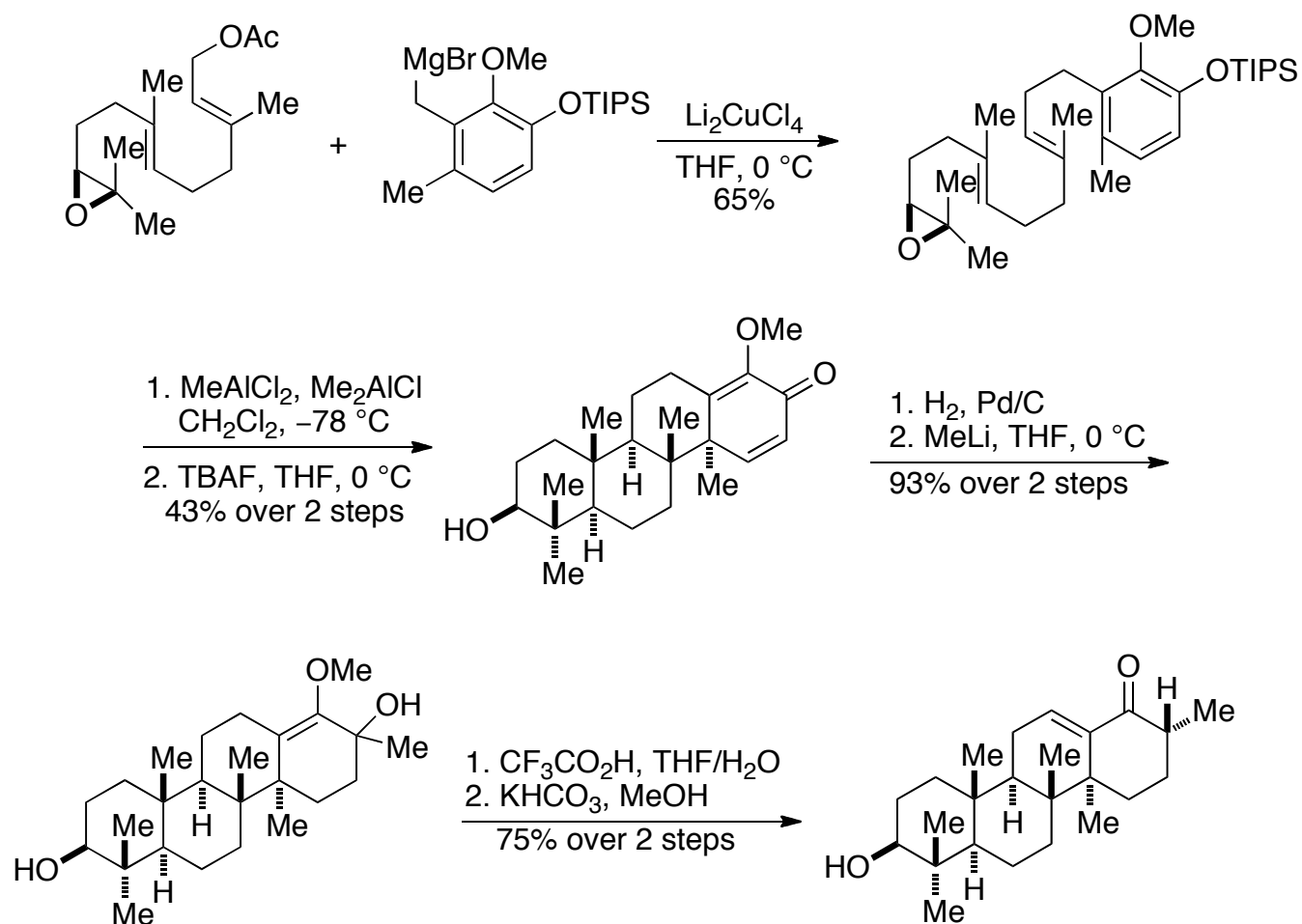
Stock, G. et al. *J. Am. Chem. Soc.* **1971**, 93, 4945.

# Stock's Synthesis of Lupeol



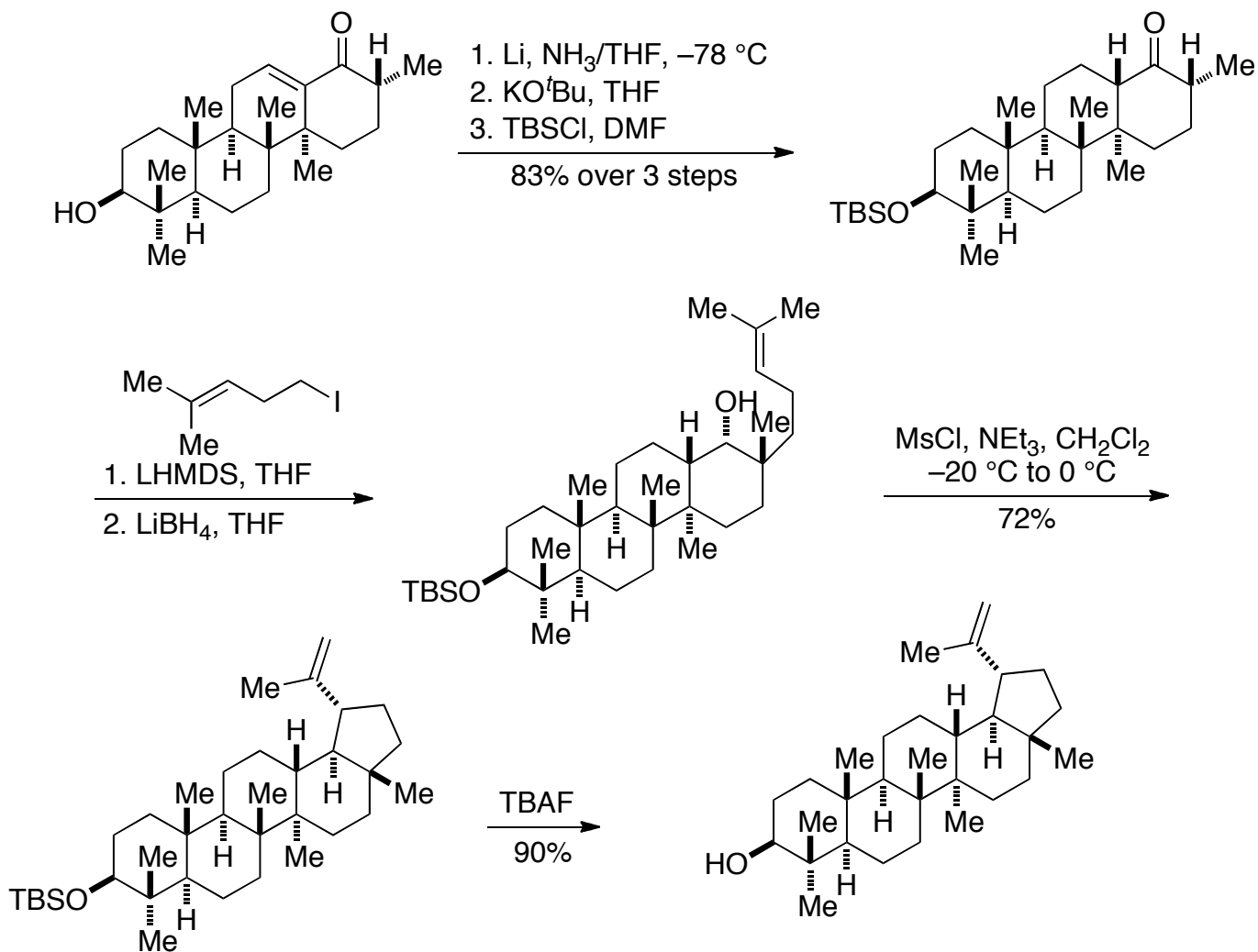
Stock, G. et al. *J. Am. Chem. Soc.* **1971**, 93, 4945.

# Corey's Synthesis of Lupeol



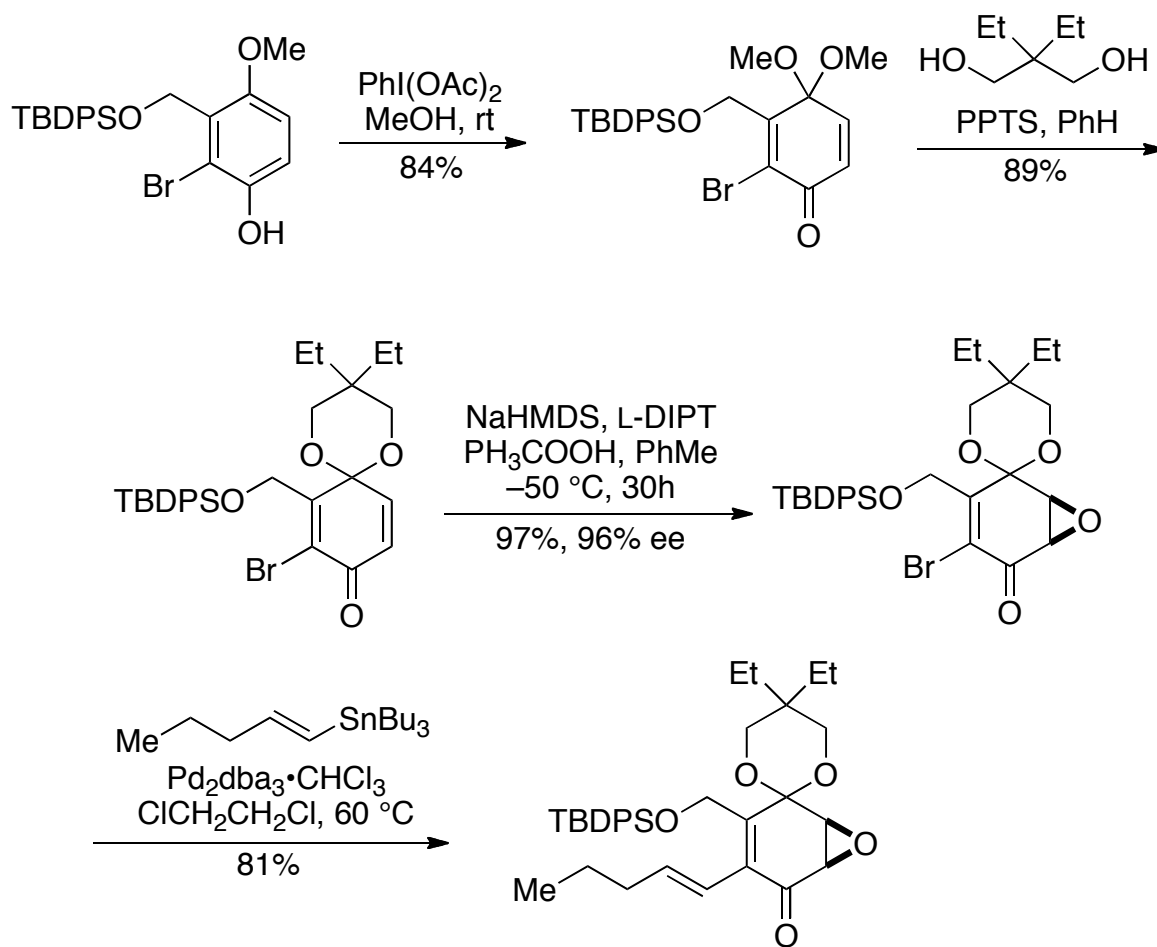
Corey, E. J. et al. *J. Am. Chem. Soc.* **2009**, 131, 13928.

# Corey's Synthesis of Lupeol



Corey, E. J. et al. *J. Am. Chem. Soc.* **2009**, 131, 13928.

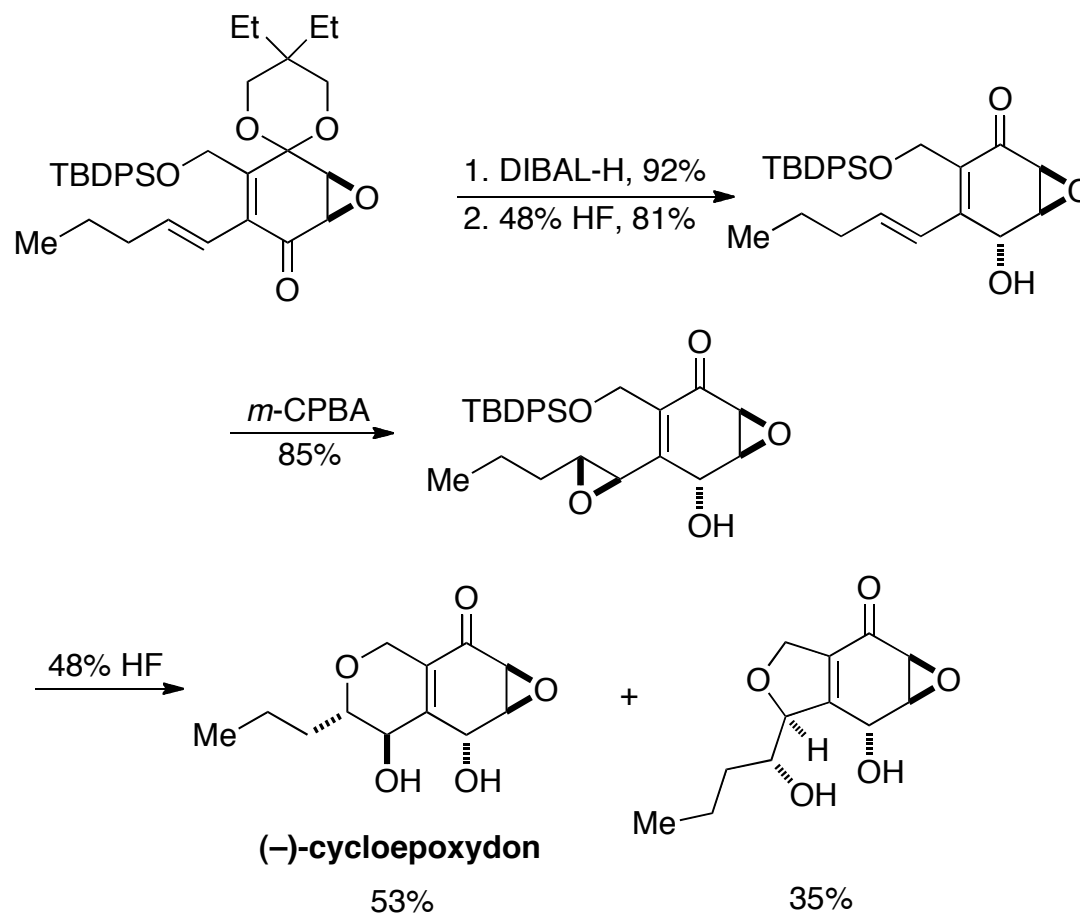
# Porco, Jr's Synthesis of cycloepoxydon



Porco, Jr, J. A. et al. *J. Am. Chem. Soc.* **2001**, 123, 11308.

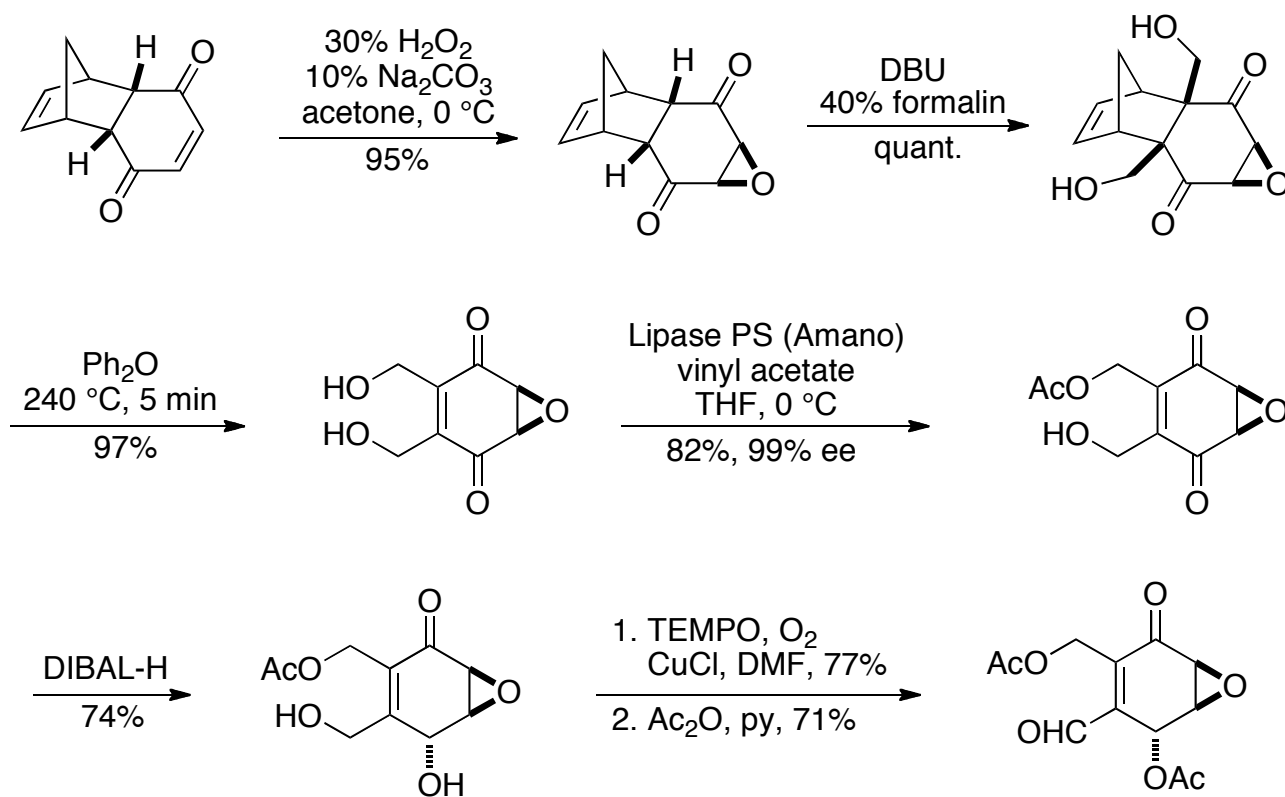


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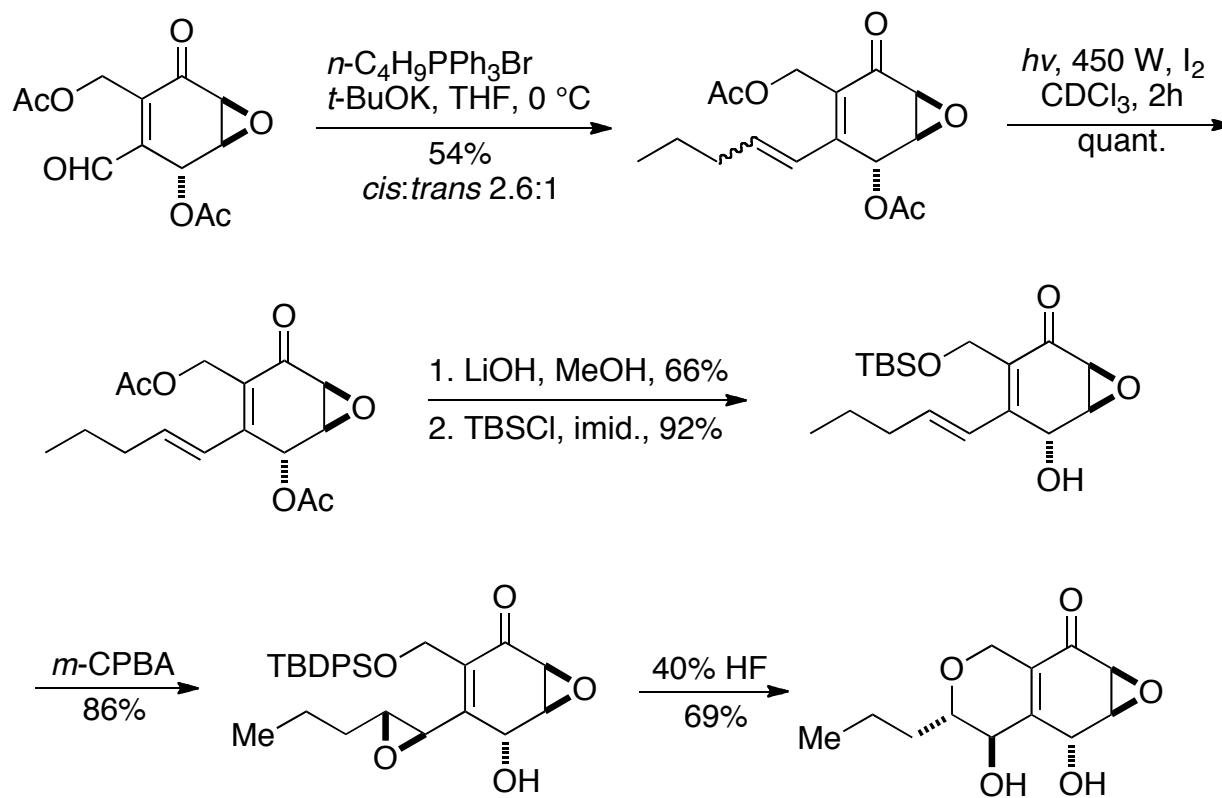


Porco, Jr, J. A. et al. *J. Am. Chem. Soc.* **2001**, 123, 11308.

# Mehta's Synthesis of cycloepoxydon



# Mehta's Synthesis of cycloepoxydon



# Summary

- NF $\kappa$ B is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival. It is essential component of the adaptive immune system.
- Improper regulation of NF $\kappa$ B has been linked to cancer, inflammatory and autoimmune disease, septic shock, viral infection, and improper immune development.
- Methods of inhibiting NF $\kappa$ B has potential therapeutic application in cancer and inflammatory diseases.