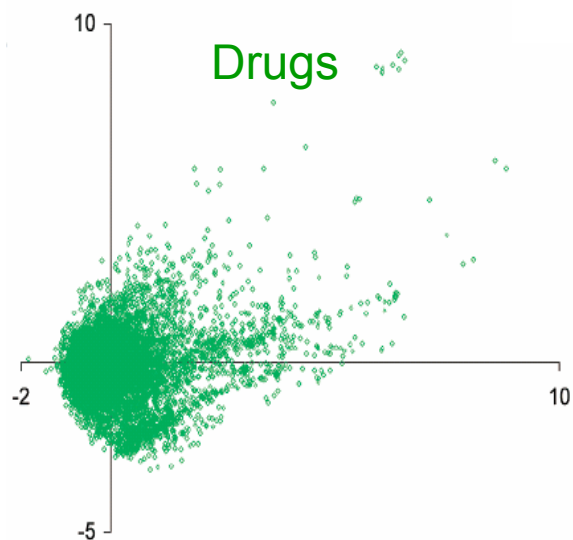
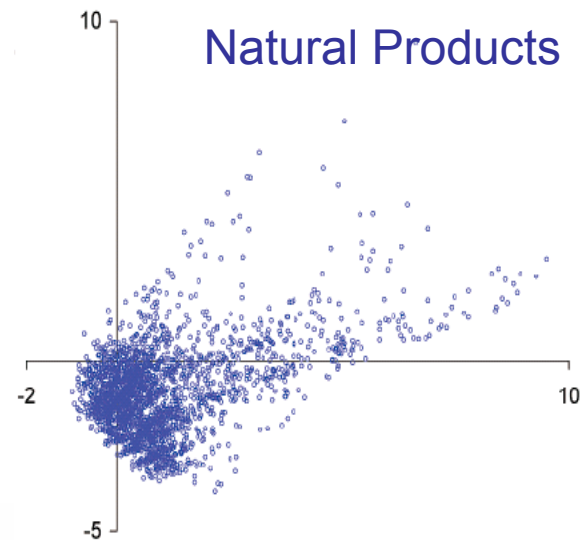
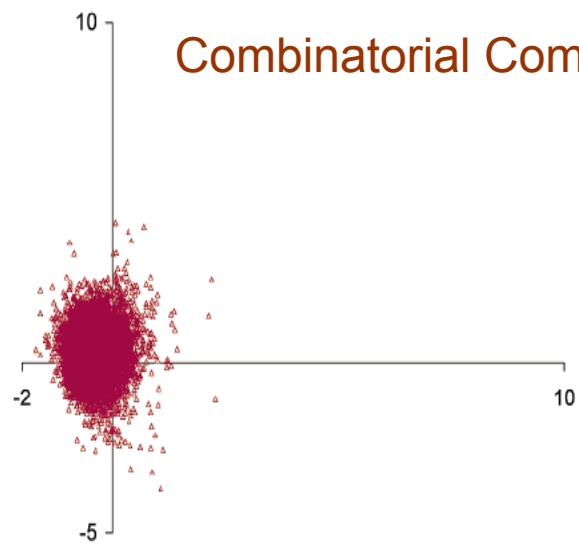


# Steroid Spiroketal Peptide: Triple Hybrid Constructs

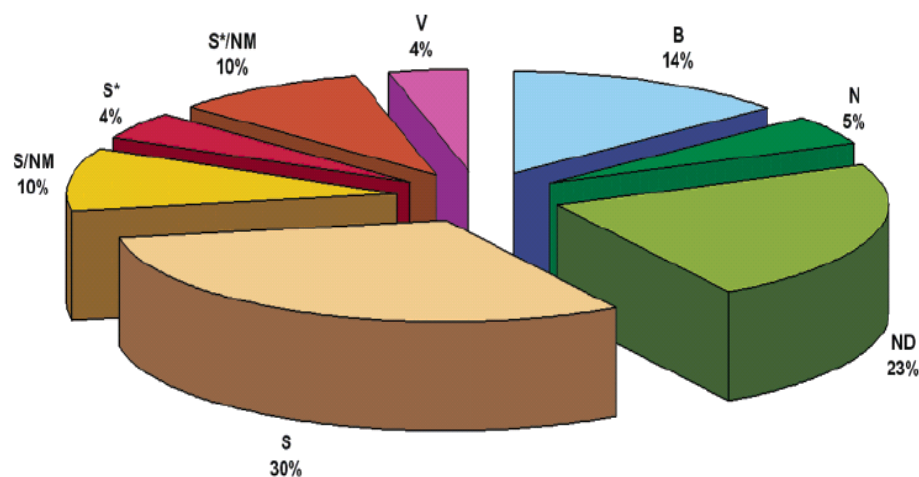
Abhisek Banerjee  
Research Topic Seminar  
19-Feb-2008

# Where Do We Stand.....

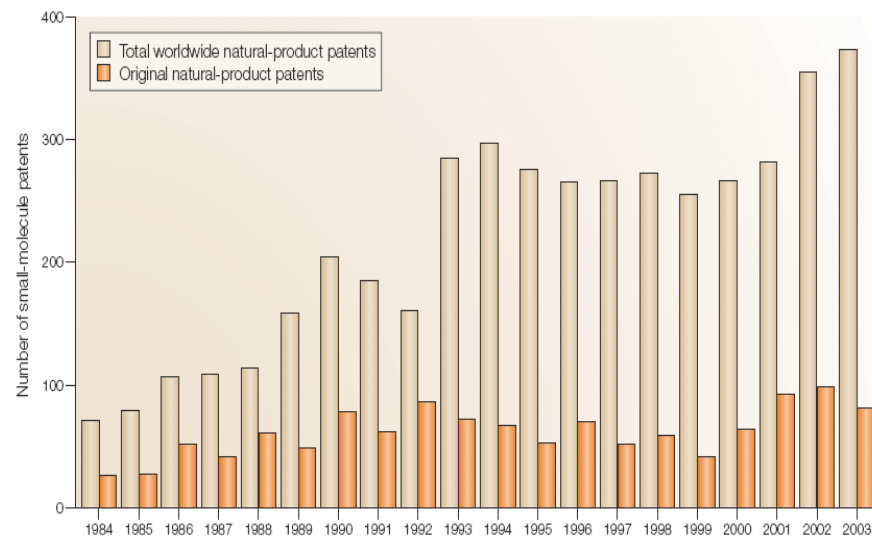


# Natural Products in Drug Discovery

## All New Chemical Entities (NCEs) 1981-2006



B: Biological; N: Natural Product; ND: Derived from N;  
 S: Totally synthetic drug; V: Vaccine; NM: N Mimic  
 S\*: Synthetic but Pharmacophore is/was from N;



## Worldwide Pharmaceutical Natural Product Patents

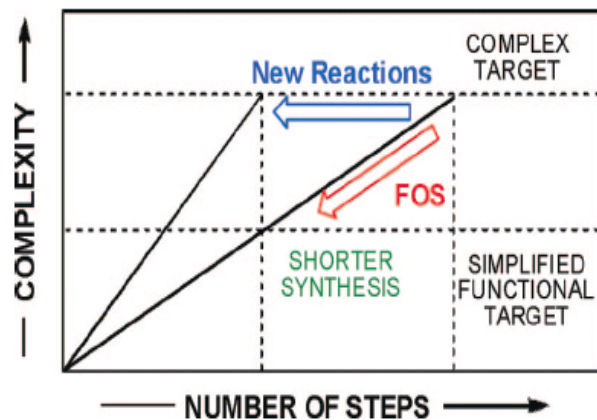
More Natural Product Like.....

Newman D. J. et al. *J. Nat. Prod.* **2007**, 70, 461

Abhisek Banerjee @ Wipf Group; Kuehn F. E. et al. *Nat. Rev. Drug Discovery* **2005**, 4, 206

2/16/2008

# Function-Oriented Synthesis

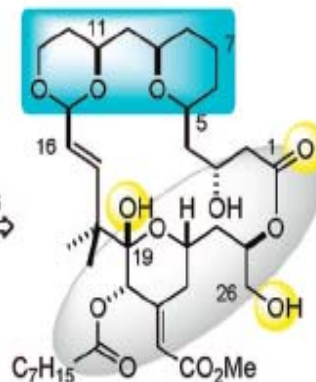


## Designing One's Own Target:

Bryostatin  $K_i = 1.4 \text{ nM}$   
 $> 70$  steps

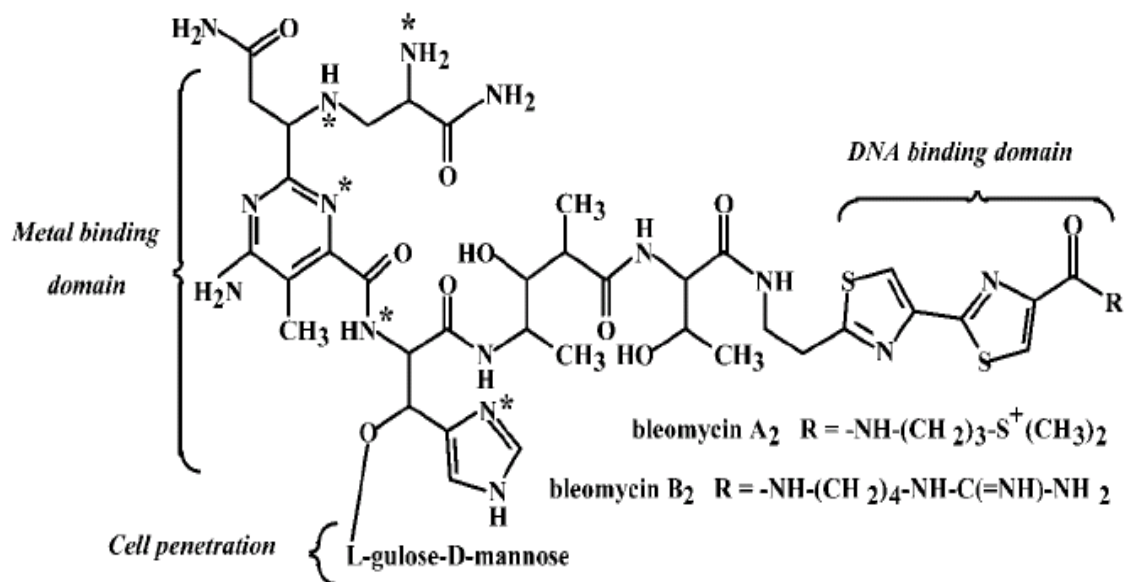


Function Oriented Synthesis



Lead Analog  $K_i = 0.3 \text{ nM}$   
 $29$  steps

# Hybrid Molecules: Dream or Reality?



Bleomycin: Three structural entities  
with three different biological roles

Meunier B. *Acc. Chem. Res.* **2008**, *41*, 69

# Steroid-Spiroketal Nucleus in Natural Products

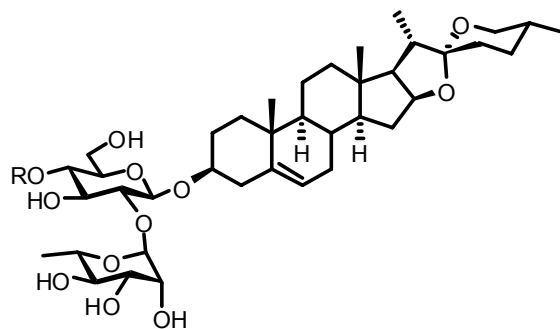
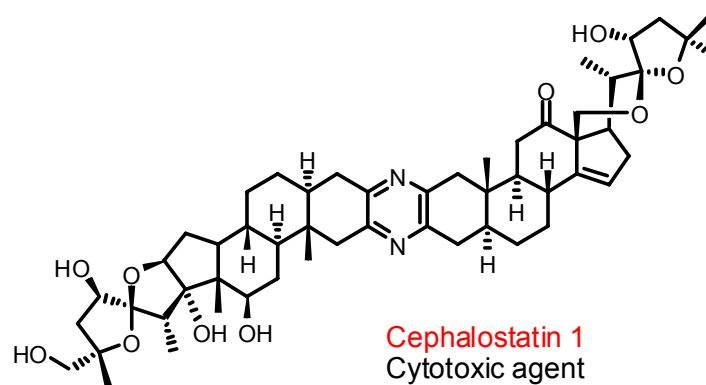
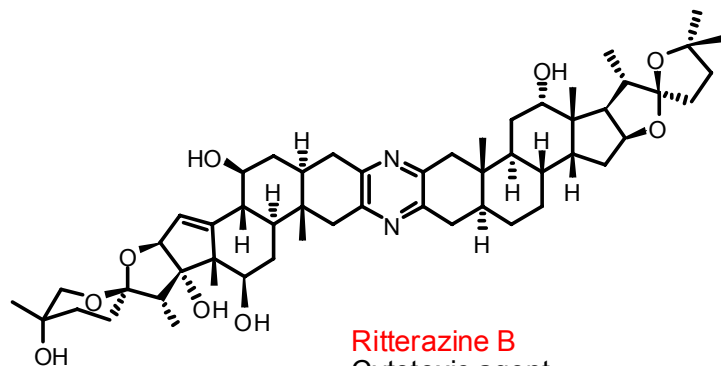
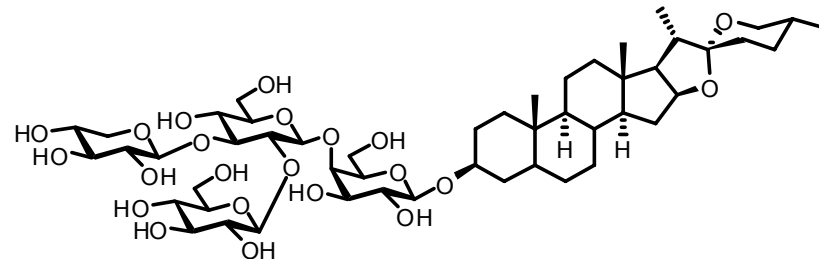


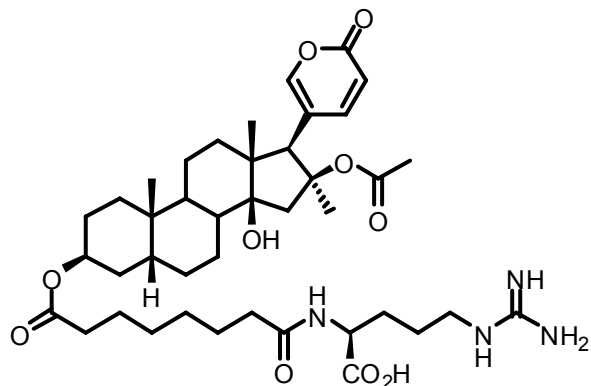
Exhibit Cardiovascular, Cytotoxic, Antifungal, Antitumor, Hemostatic activity

IC<sub>50</sub> (HeLa Cell): 3.8 and 1.1 μM



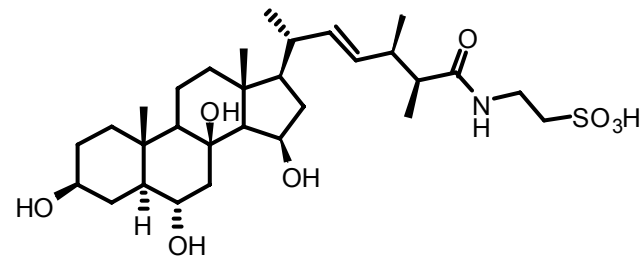
Shair M. D. et al. *J. Am. Chem. Soc.* **2007**, 129, 6589  
Fuchs P. L. et al. *Bioorg. Med. Chem. Lett.* **1999**, 9, 419  
Hui Y. et al. *Org. Lett.* **2005**, 7, 669

# Steroid Peptide Natural Conjugates



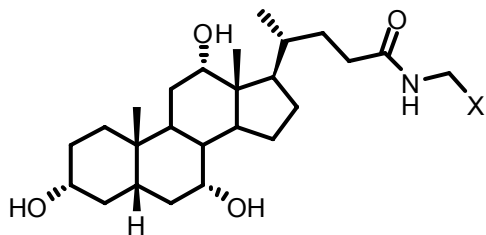
**Bufetoxin**

Isolated from Chinese Hoptoad



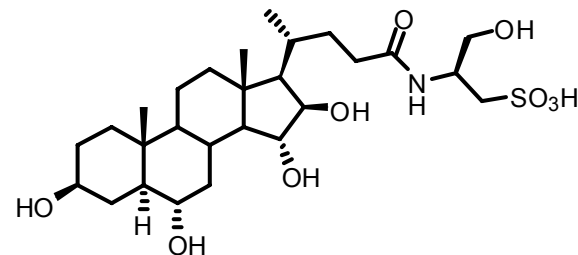
**Triseramide**

Isolated from Starfish



X: CO<sub>2</sub>H, Choyl glycine

X: SO<sub>3</sub>H, Choyl taurine

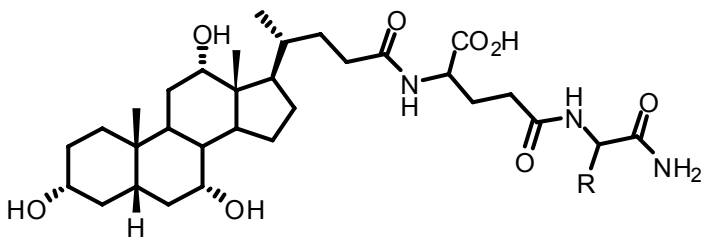


**Carolisterol C**

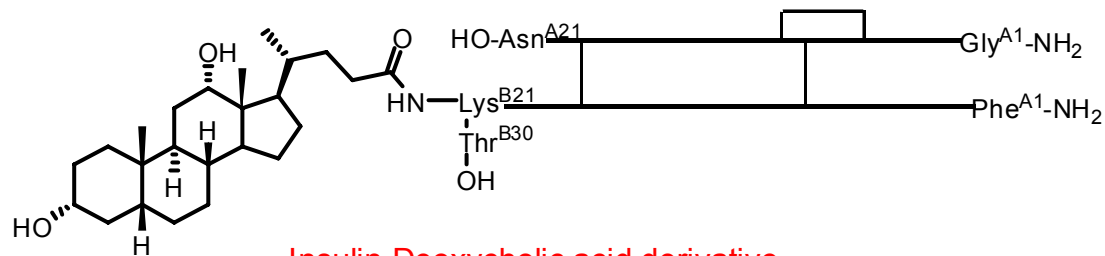
Isolated from Starfish

Pore V. S. et al. *Curr. Med. Chem.* **2006**, 13, 813

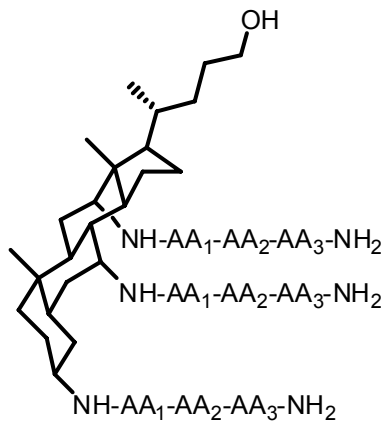
# Steroid Peptide Conjugates



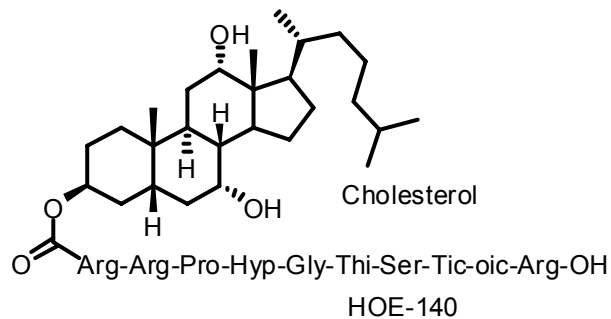
Cholic acid conjugate  
HIV Protease Inhibitor



Insulin-Deoxycholic acid derivative



Cationic Steroid Antibiotics



HOE-140

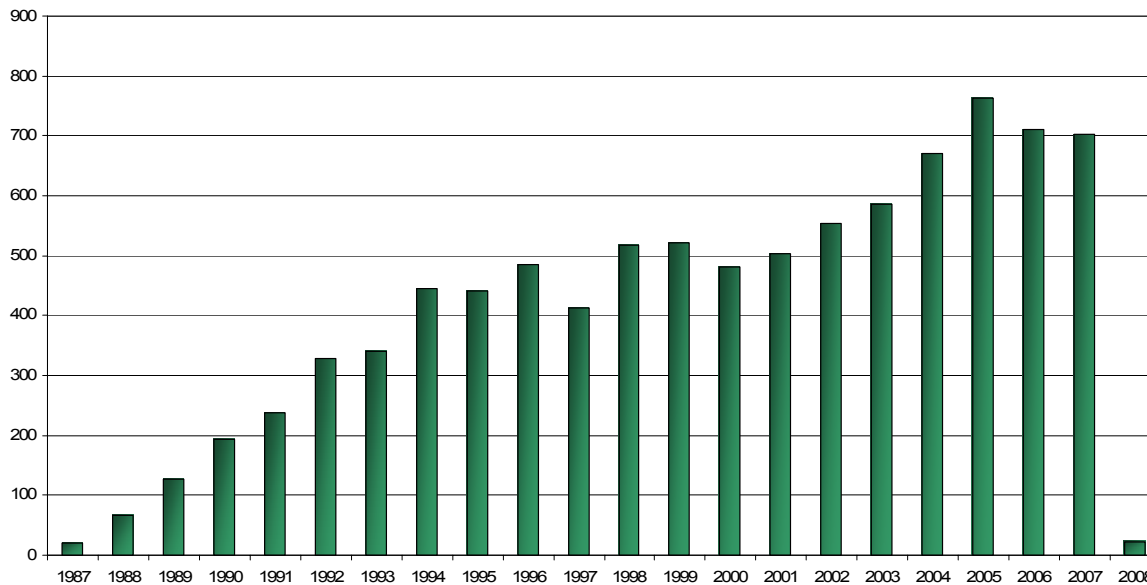
Pore V. S. et al. *Curr. Med. Chem.* **2006**, *13*, 813



# Arginine-Glycine-Aspartic Acid (RGD) Tripeptide

Most of the integrin superfamily members especially  $\alpha_v\beta_3$  and  $\alpha_{IIb}\beta_3$ , recognize Arg-Gly-Asp (RGD) sequence, an epitope shared by a variety of extracellular ligands including vitronectin, fibronectin, osteopontin, bone sialoprotein and fibrinogen.

Patents & Publications in 20 years

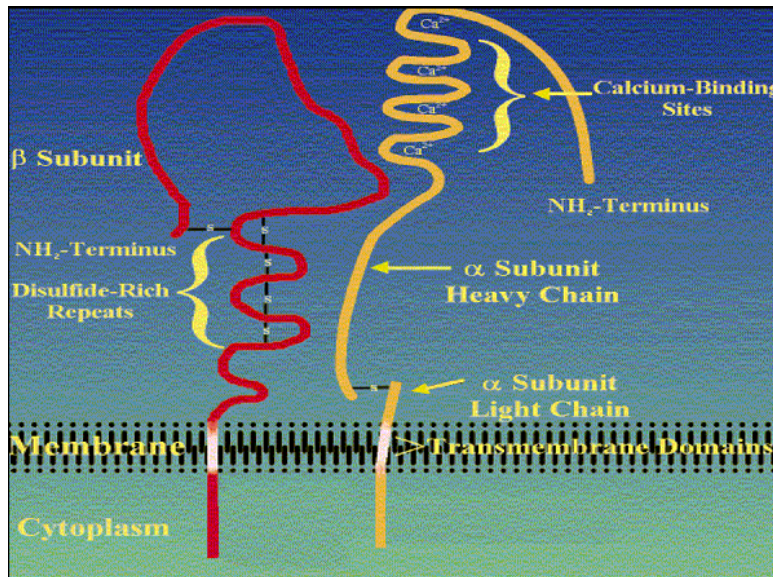


Pioneer: Erkki Ruoslahti, Burnham Institute of Medical Research  
*Nature* 1984, 309, 30 and *Science* 1987, 238, 491

A Generic Field of Research

# Integrins

Integrins are a large family of heterodimeric non-covalent proteins expressed on cell surface.



- ✓ Consists of two different chains  $\alpha$  and  $\beta$  which associates to provide  $\alpha_x\beta_y$  receptors
- ✓ 18  $\alpha$  and 8  $\beta$  subunits are known which produces 26 different heterodimers
- ✓ Large N-terminal extracellular domain  
Transmembrane domain  
Short C-terminal intracellular tail

Therapeutic targets due to cell adhesion

Kessler H. et al. *J. Med. Chem.* **2003**, 46, 4393

Abhisek Banerjee @ Wipac Group  
Cheng Y. et al. *Mini Reviews in Medicinal Chemistry* **2002**, 2, 531

2/16/2008

## $\alpha_v\beta_3$ Integrin

- ✓ Expressed on the cell surface of a variety of cell types such as Platelets, Endothelial cells, Vascular muscle cells, Osteoclasts and Tumor cells.
- ✓ Plays key role in Physiological processes such as angiogenesis, apoptosis.
- ✓ Expected to have major impact on the treatment of Osteoporosis, Rheumatoid arthritis, and Cancer.
- ✓ For drug development it is desirable to obtain antagonists selective to  $\alpha_v\beta_3$ .

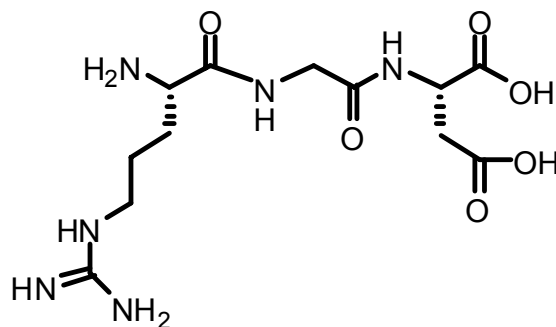
Kessler H. et al. *J. Med. Chem.* **2003**, 46, 4393

Chapleur Y. et al. *Mini Reviews in Medicinal Chemistry* **2002**, 2, 531

# Towards More Active and Selective RGD Mimetics

## Essential Parts of Pharmacophore

- Carboxylate Group
- Guanidinium moiety
- Hydrophobic group

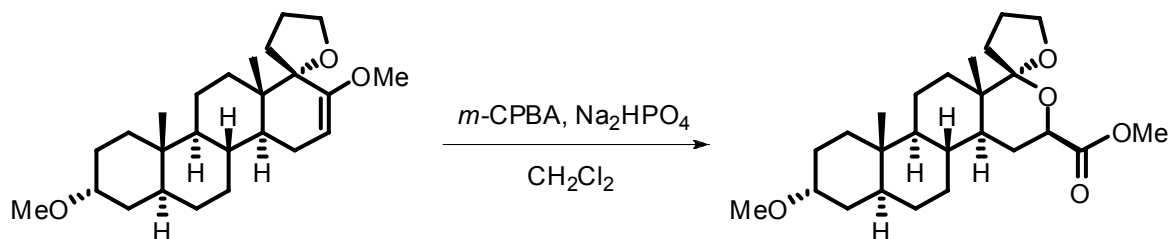
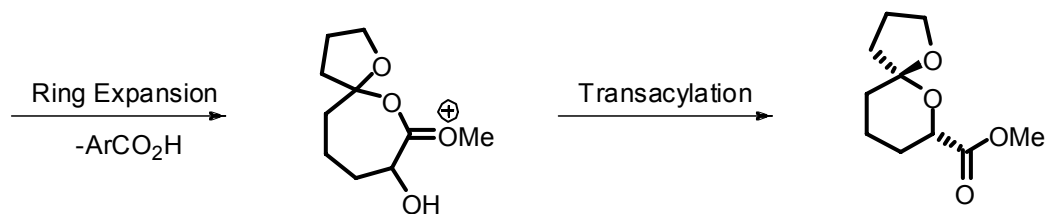
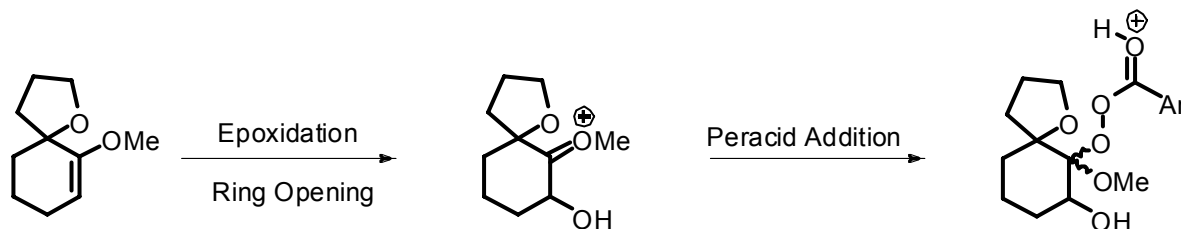
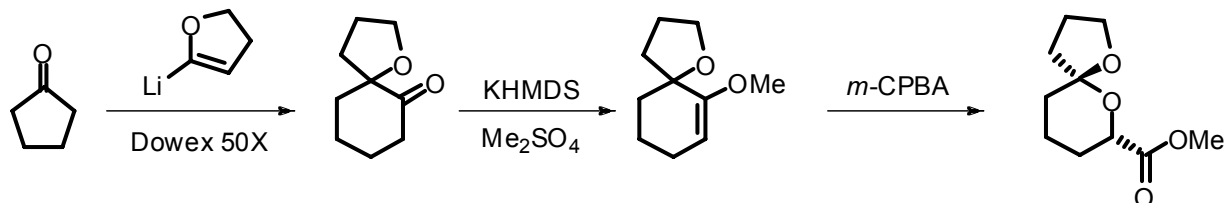


## Some Key Features

- Shorter distance between guanidinium and carboxylate group (< 6.7Å).
- Conformational constraints with rigid cores, cyclic structures, turn inducers.

Chapleur Y. et al. *Mini Reviews in Medicinal Chemistry* **2002**, 2, 531

# Spiroketal via Oxidative Enol Ether Rearrangement



# Acknowledgments

Prof. Peter Wipf

David Waller

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Shuli Mao

Amol Kulkarni

Wipf Group Members