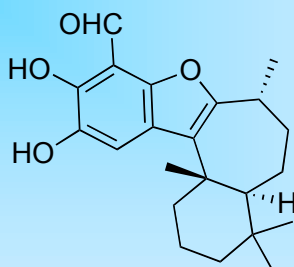


Progress Towards the Total Synthesis of Liphagal



Julia Vargas

Research Topic Seminar

April 14, 2007

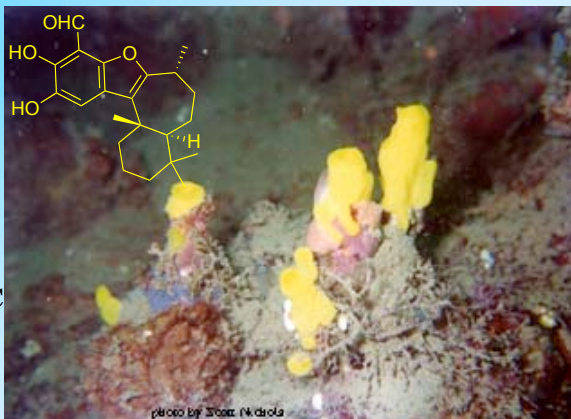
Outline

- Liphagal: Structural Elucidation and Biology
 - Proposed Biosynthesis of Liphagal
 - The Frondosins; structural similarity
 - Future Work
-

Liphagal

- Isolated from marine sponge:
Aka coralliphaga

- Collected off Coast of Dominican Republic
- Meroterpenoid with unprecedented carbon skeleton
- Structure elucidated by HREIMS, ^1H and ^{13}C NMR, HMQC, HMBC 1-D NOESY and optical rotation

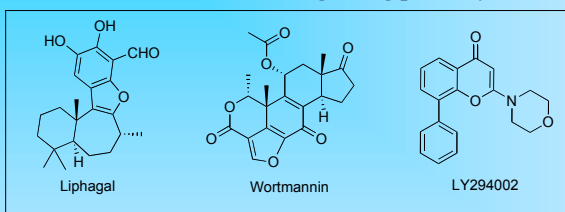


http://striweb.si.edu/bocas_database/details.php?id=3401

Marion, F. et al, *Org Lett.*, **2006**, 8, 321

Biological Activity

- Inhibitors of the PI3K signaling pathway



- Small molecules capable of attenuating PI3k signaling should have therapeutic potential for cancer, cardiovascular disease, and inflammatory and autoimmune disorders

PI3k plays central role in regulation of cell proliferation, cell survival, adhesion, movement, membrane trafficking, glucose transport and neurite growth

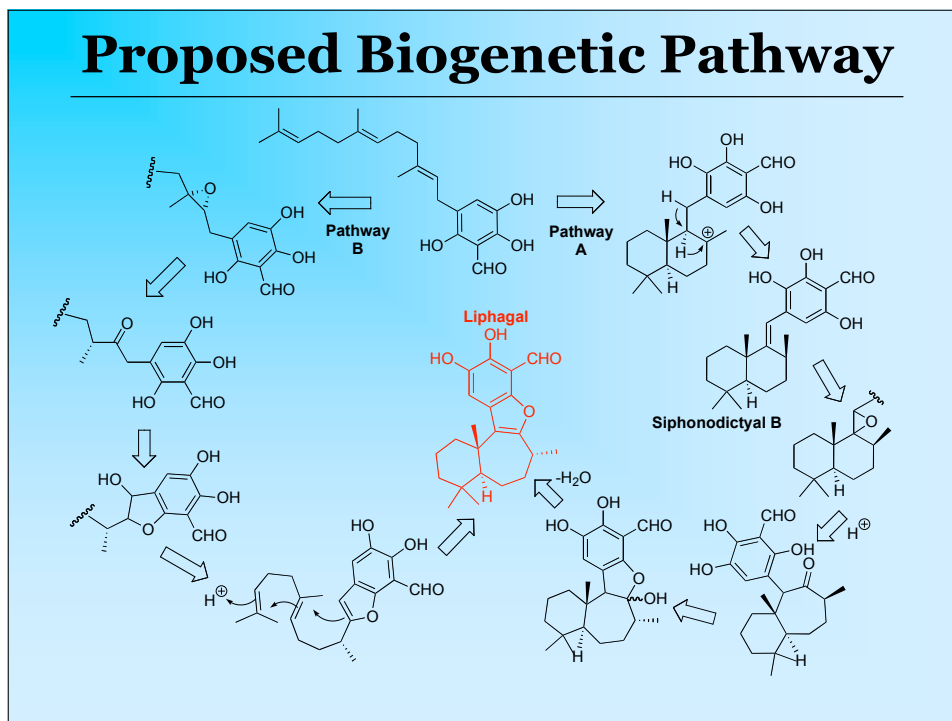
Fluorescent polarization enzyme assay against PI3K α :

Compound	IC ₅₀ (nM)
Liphagal	100
Wortmannin	12
LY294002	550

- Liphagal was ~10-fold more potent against PI3K α than against PI3K γ

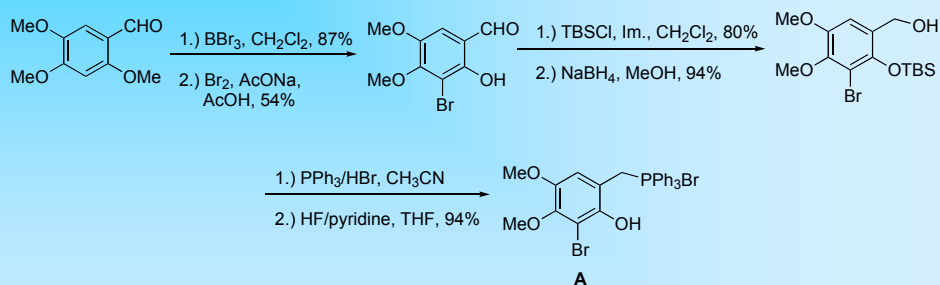
Marion, F. et al, *Org Lett.*, **2006**, 8, 321

Proposed Biogenetic Pathway



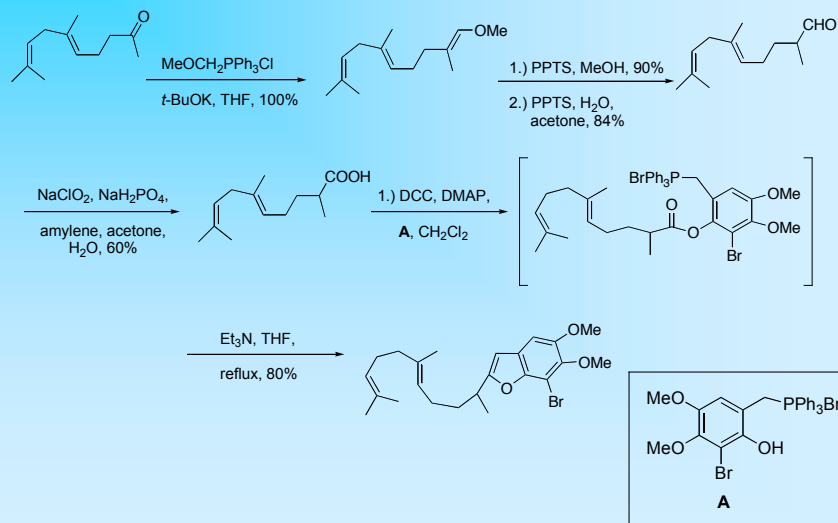
Biomimetic Synthesis of Liphagal

Biomimetic Cyclization Precursor:

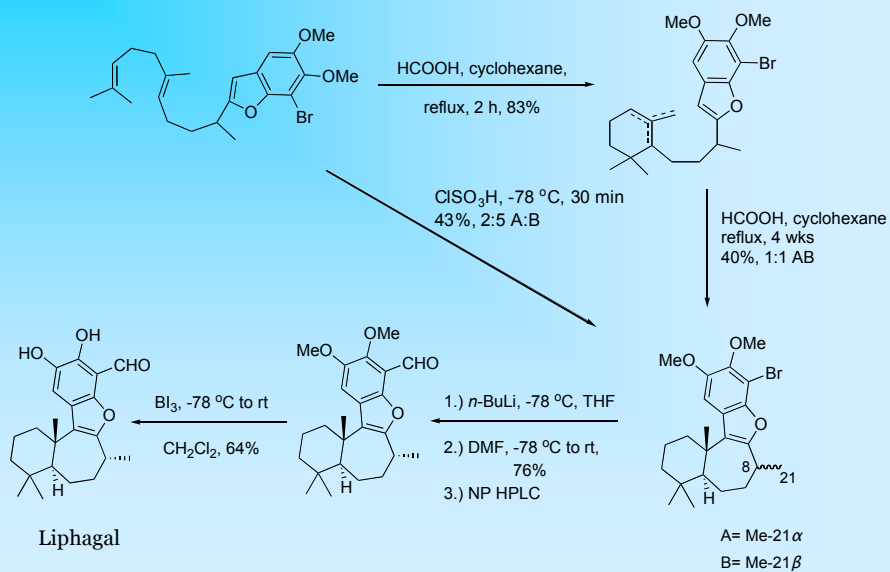


Biomimetic Synthesis of Liphagal

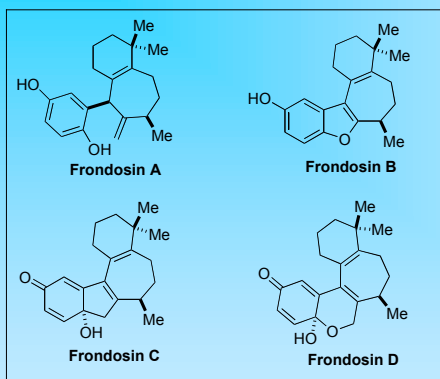
Biomimetic Cyclization Precursor:



Biomimetic Synthesis of Liphagal



Frondosins

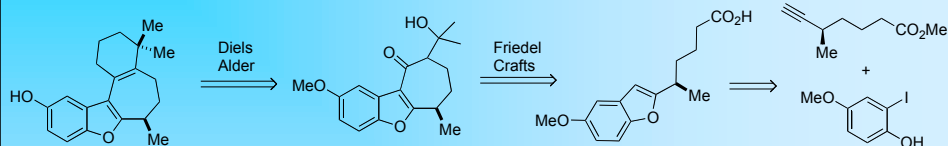


- Sesquiterpene hydroquinone derivatives
- Isolated from micronesian marine sponge *Dysidea frondosa*
- Agonists of interleukin-8 (IL-8) and inhibitors of protein kinase C in low μM range
- anti-inflammatory, antiviral, recently reported ability to inhibit HIV-1 replication

Danishefsky, S. J. *JACS*, **2001**, 123, 1878

Frondosin B

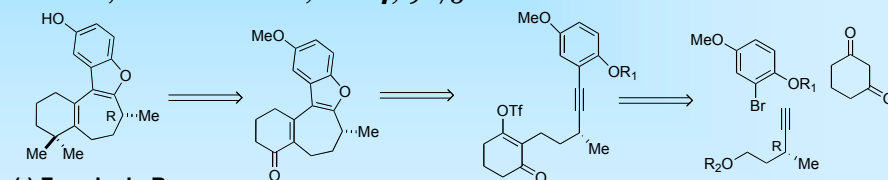
Danishefsky, S. J. *JACS*, **2001**, 123, 1878



(+) Frondosin B

18 steps, 0.08% overall yield

Trauner, D. *Tetrahedron*, **2004**, 9675

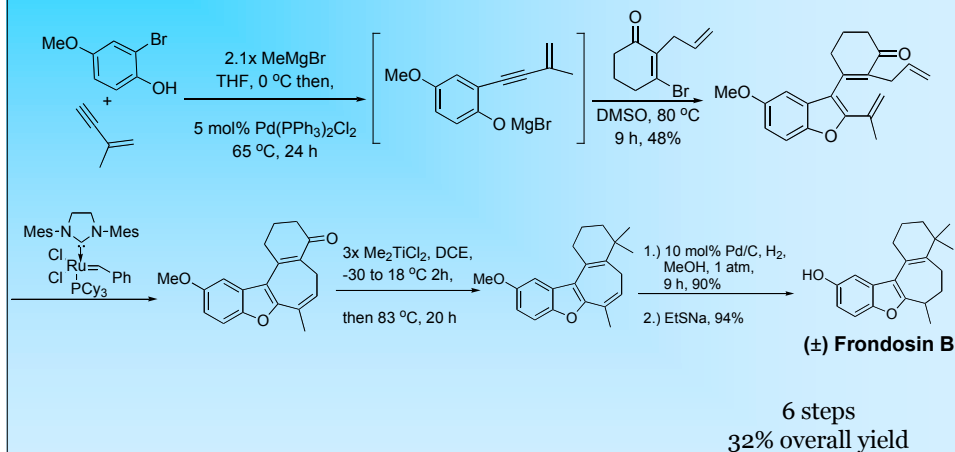


(-) Frondosin B

20 steps, 7.3% overall yield

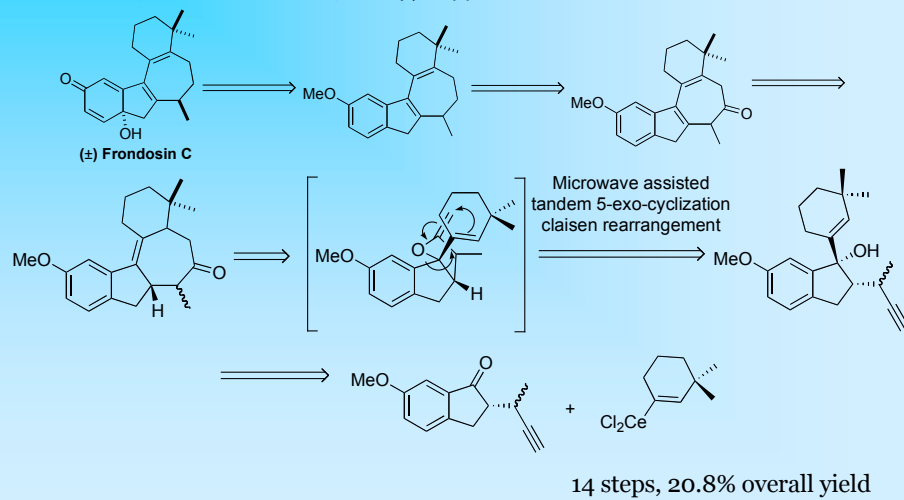
Frondosin B

Flynn, B. L. *Org. Lett.*, **2004**, *6*, 457



Frondosin C

Ovaska, T.V. *Tetrahedron*, **2007**, 1899



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