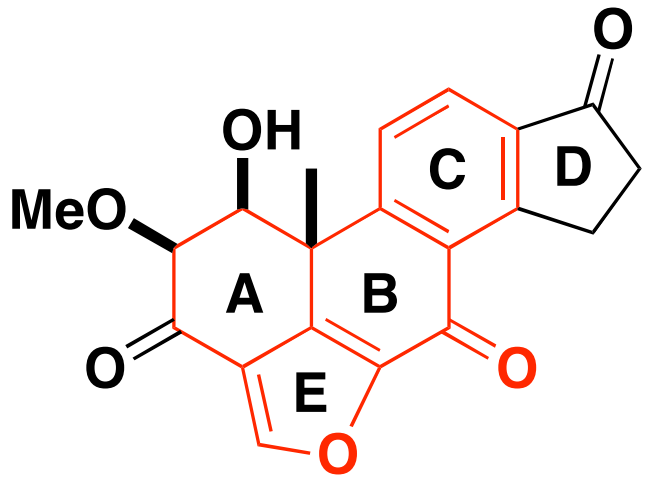
Progress Toward the Synthesis of the Tetracyclic Core of the Viridin Family



Kalyani J. Patil

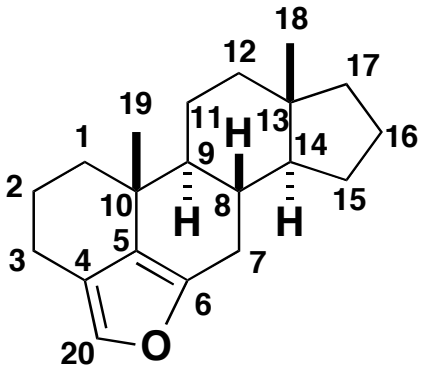
Research Topic Seminar

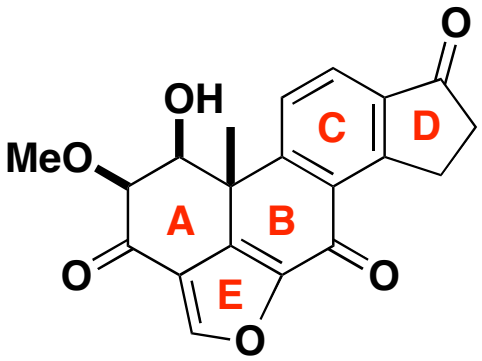
June 3 rd 2006

Outline

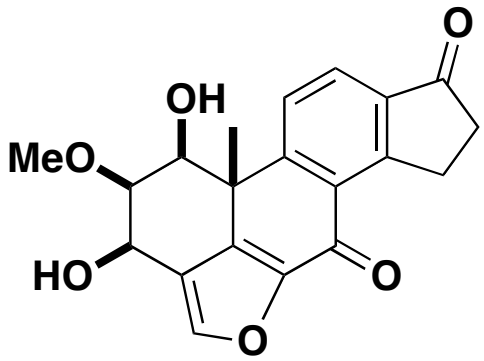
- **Isolation and Structure**
- **Biological Activity**
- **Synthetic Approaches Toward Furanosteroids**
- **Tetracyclic Core of Viridin - Wipf Group**
- **Future Work**

Structure of Furanosteroids

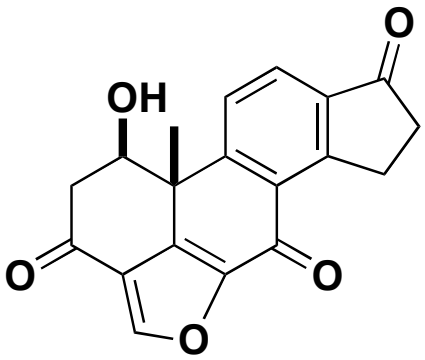




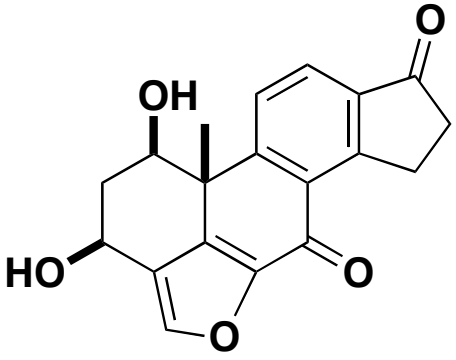
Viridin (2 nM)



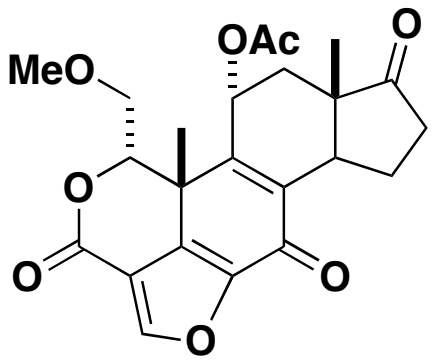
Viridiol



Demethoxyviridin (0.1 nM)



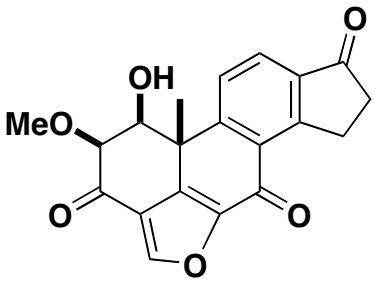
Demethoxyviridiol



Wortmannin (4.2 nM)

- Isolated from fungi
- Possess antifungal, antibiotic, and anti-inflammatory activity
- Potent inhibitors of phosphatidylinositol 3-kinase (PI3-K)

Isolation of Furanosteroids

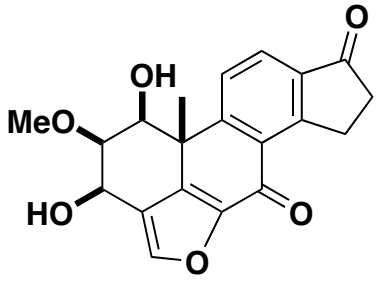


Viridin

Isolated in 1945 from *Gliocladium virens*

Structure Determined in 1966 by X-Ray Crystallography

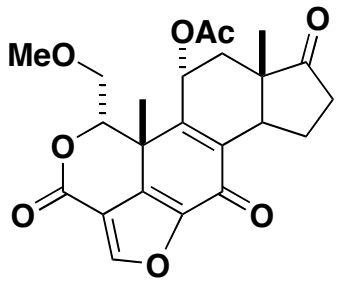
Originally Isolated as Antifungal Agent



Viridiol

Isolated from *Gliocladium deliquescens* and *G. virens*

Antifungal and Phytotoxic Metabolite

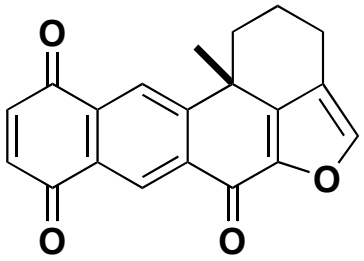


Wortmannin

Isolated in 1957 from *Penicillium wortmannii* and in 1972 from *Myrothecium roridium*

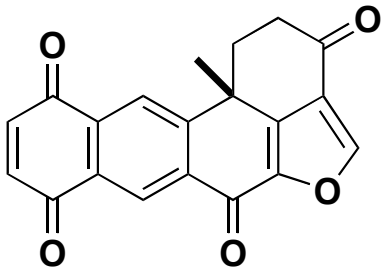
Structure Determined in 1972

Planar Polycyclics from Marine Sponge *Xestospongia*

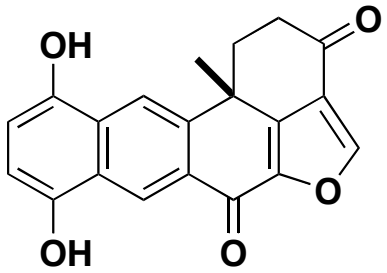


(+)-Xestoquinone

Isolated from *Xestospongia Sapre* in 1960



(+)-Halenaquinone



(+)-Halenaquinol

Isolated from *Xestospongia Exigue* in 1983

- **Antibacterial Activity**
- **Cardiotonic Properties**
- **Inhibition of pp60 Kinase**
- **Inhibition of EGF Kinase**
- **Inhibition of the Dual Specificity Phosphatase Cdc25**

Phosphatidylinositol-3-Kinase (PI-3-Kinase)

- **Important Enzyme for Intracellular Signaling**
- **Phosphorylation of Inositol Lipids at the 3-Position: Primary Enzymatic Activity of the PI-3-Kinases**
- **Different Members of the PI-3-Kinase Family Generate Different Lipid Products**

Signaling Through PI-3K Lipid Products and their Targets

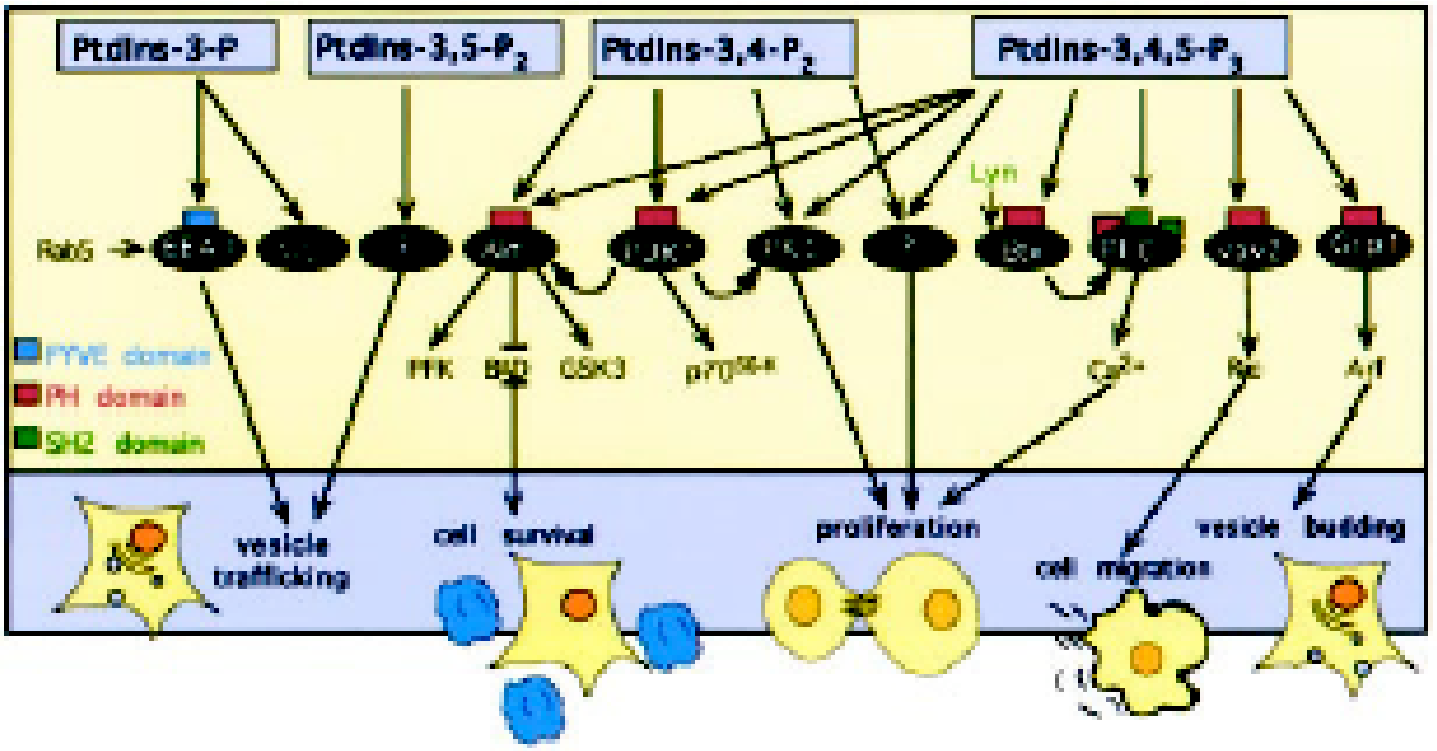


FIG. 2. Signaling through PI 3-K lipid products and their targets. The lipid products of PI 3-K are indicated at the *top* of the figure, and the cellular processes affected by these lipids are indicated at the *bottom*. The *black ovals* indicate the direct targets of each lipid, and the *small boxes* indicate the protein domains that directly bind to them.

Rameh, L. E.; Cantley, L. C. *J. Biol. Chem.* **1999**, *274*, 8347.

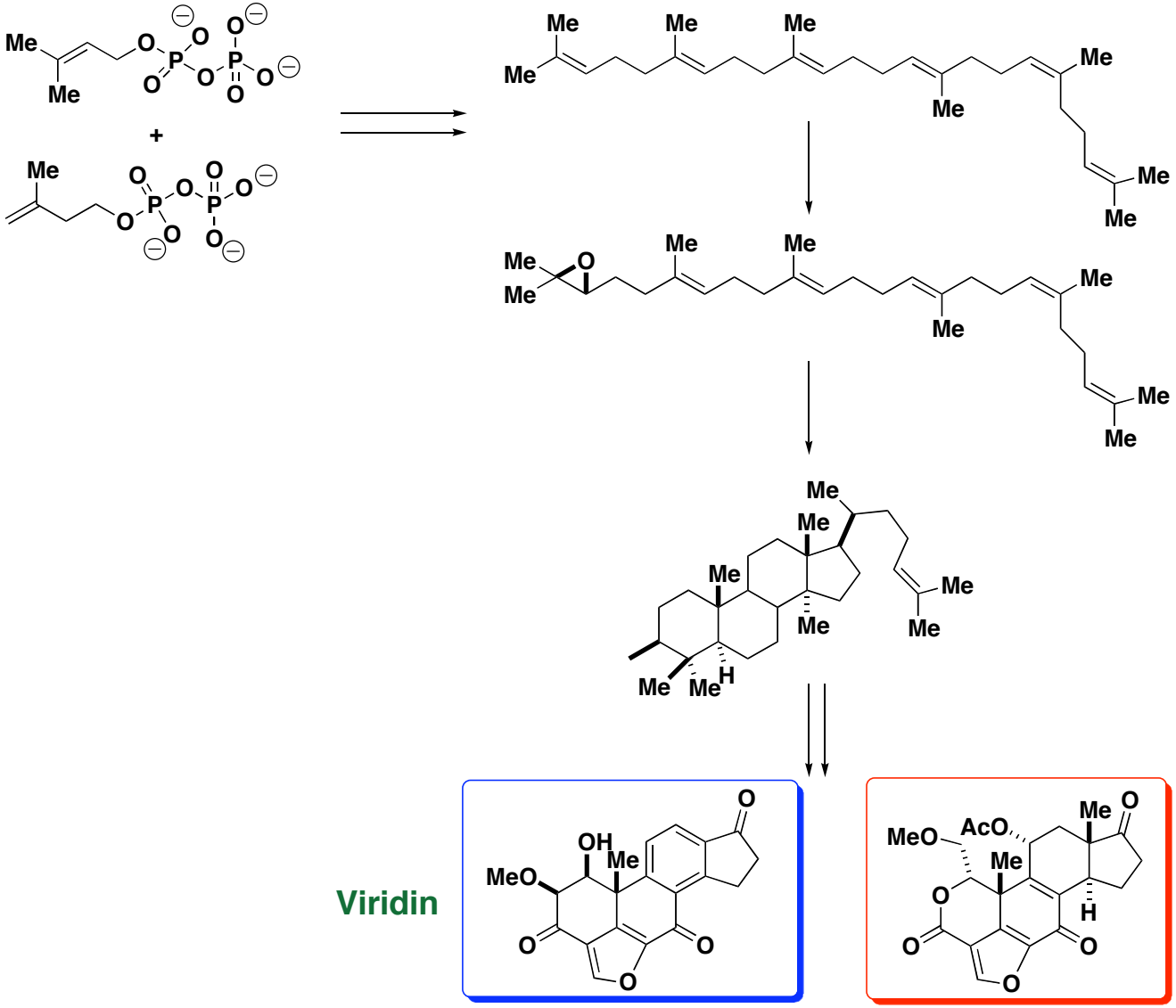
Phosphatidylinositol-3-Kinase (PI-3-Kinase)

- **PI-3-Kinase was initially purified and cloned as a heterodimeric complex consisting of**
  - **110 kDa catalytic subunit p110 α**
  - **85 kDa regulatory/adaptor subunit p85 α**

- **9 mammalian PI-3-Kinases have been identified**

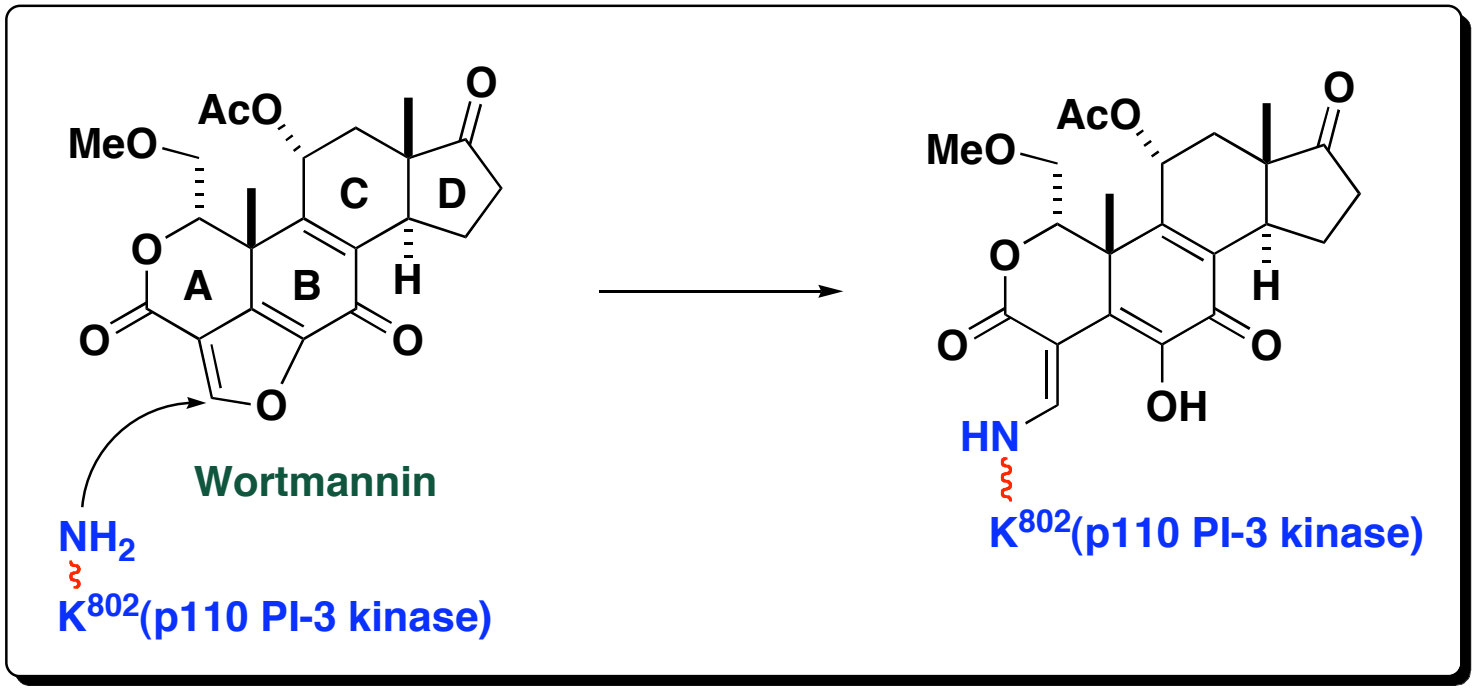
- **Divided into 3 classes based on sequence homology and substrate preference *in vitro***

Furanosteroids: Proposed Biosynthesis



Hanson, J. R. *Nat. Prod. Rep.* **1995**, *12*, 381.

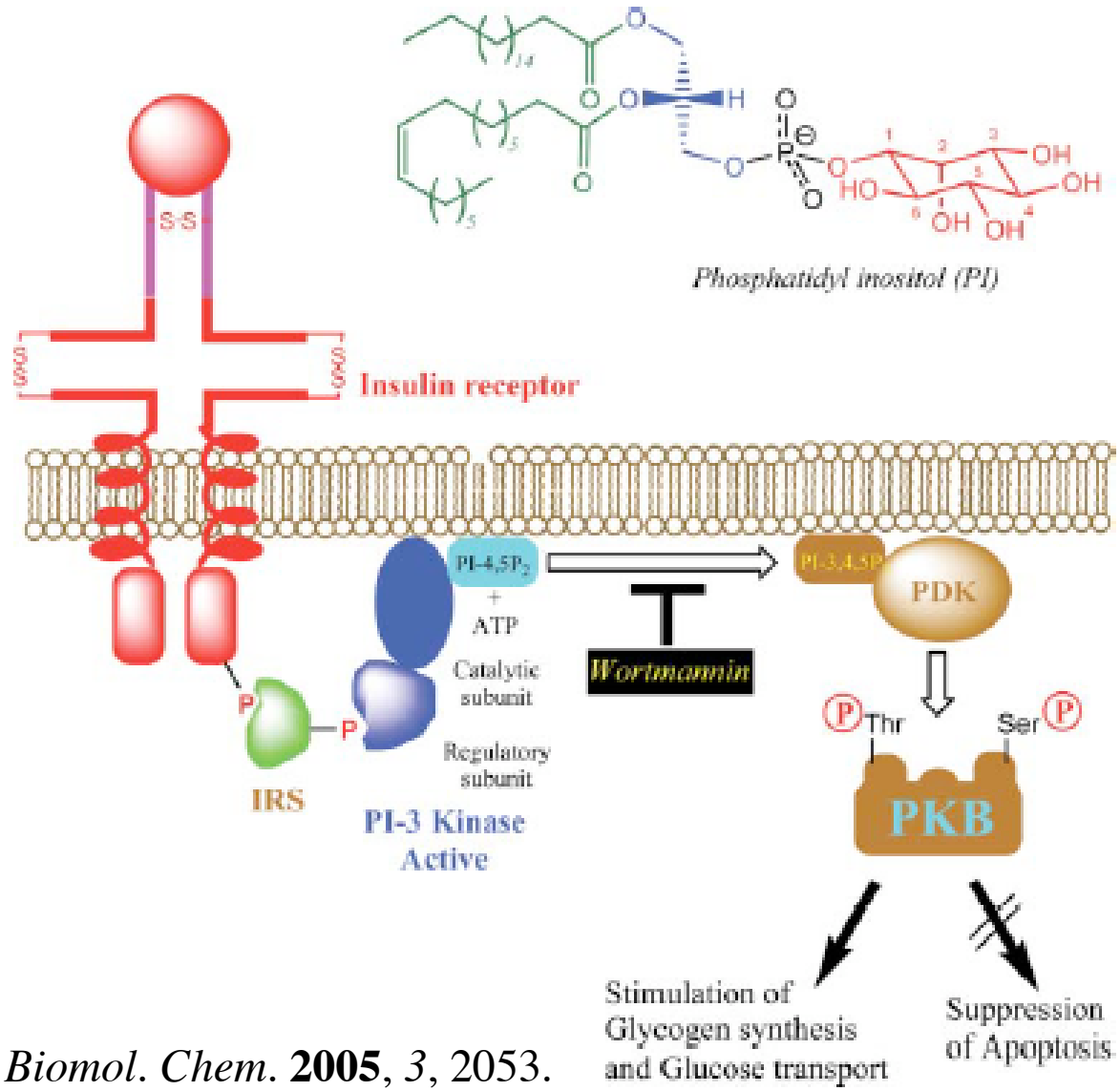
Wortmannin: Mechanism-Based Inhibitor of PI-3-Kinase



- **An Irreversible Inhibitor of PI-3-Kinase**

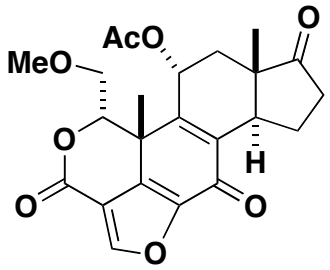
- **Nucleophilic Attack at the Electrophilic C-20 Position of the Furan Ring by Lys^{802} of p110 PI-3-Kinase**

PKB Regulation Through Inhibition of the Phophorylation at the 3-Position of Inositol Lipids



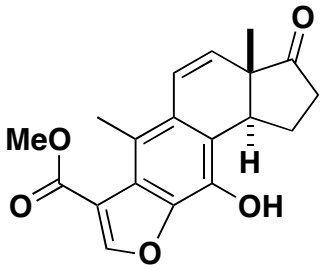
Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053.

Structural Analogs and IC_{50} Values for in vitro PI-3 Kinase Inhibition

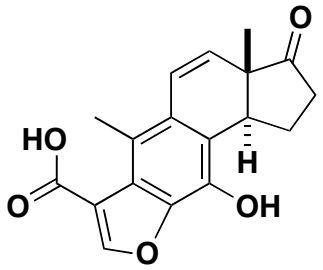


Wortmannin

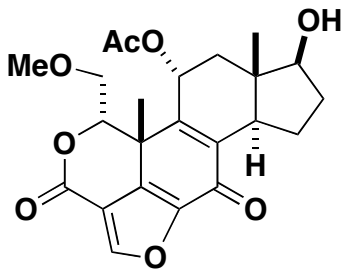
IC_{50} = 4.2 nM



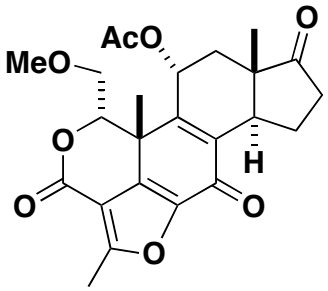
IC_{50} = 4600 nM



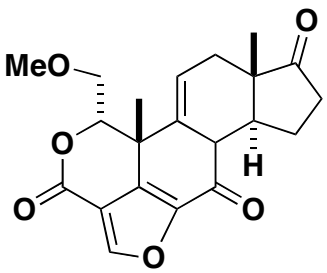
IC_{50} = > 32,000 nM



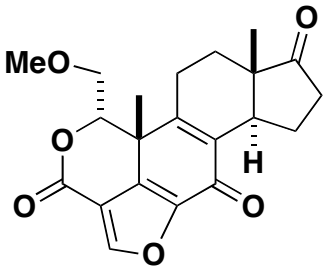
IC_{50} = 0.4 nM



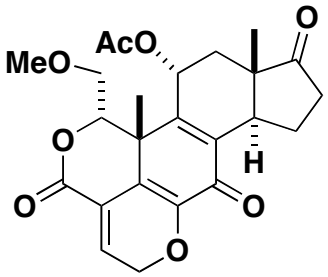
IC_{50} = >500 nM



IC_{50} = 6 nM



IC_{50} = 16.7 nM



IC_{50} = 271 nM

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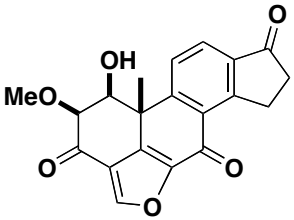
Synthesis of Furanosteroids

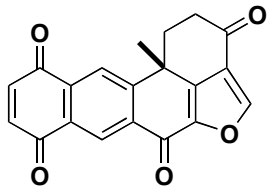
Viridin



RODRIGO - *o*-Benzoquinone Monoketals Cascade Reactions

SORENSEN - Alkyne Trimerization and Electrocyclic Rearrangement

Halenaquinone

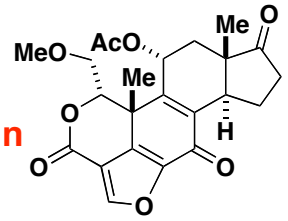


HARADA - Chiral Building Block

RODRIGO - *o*-Benzoquinone Monoketals Cascade Reactions

SHIBASAKI - Asymmetric Intramolecular Cascade Heck-Suzuki Couplings

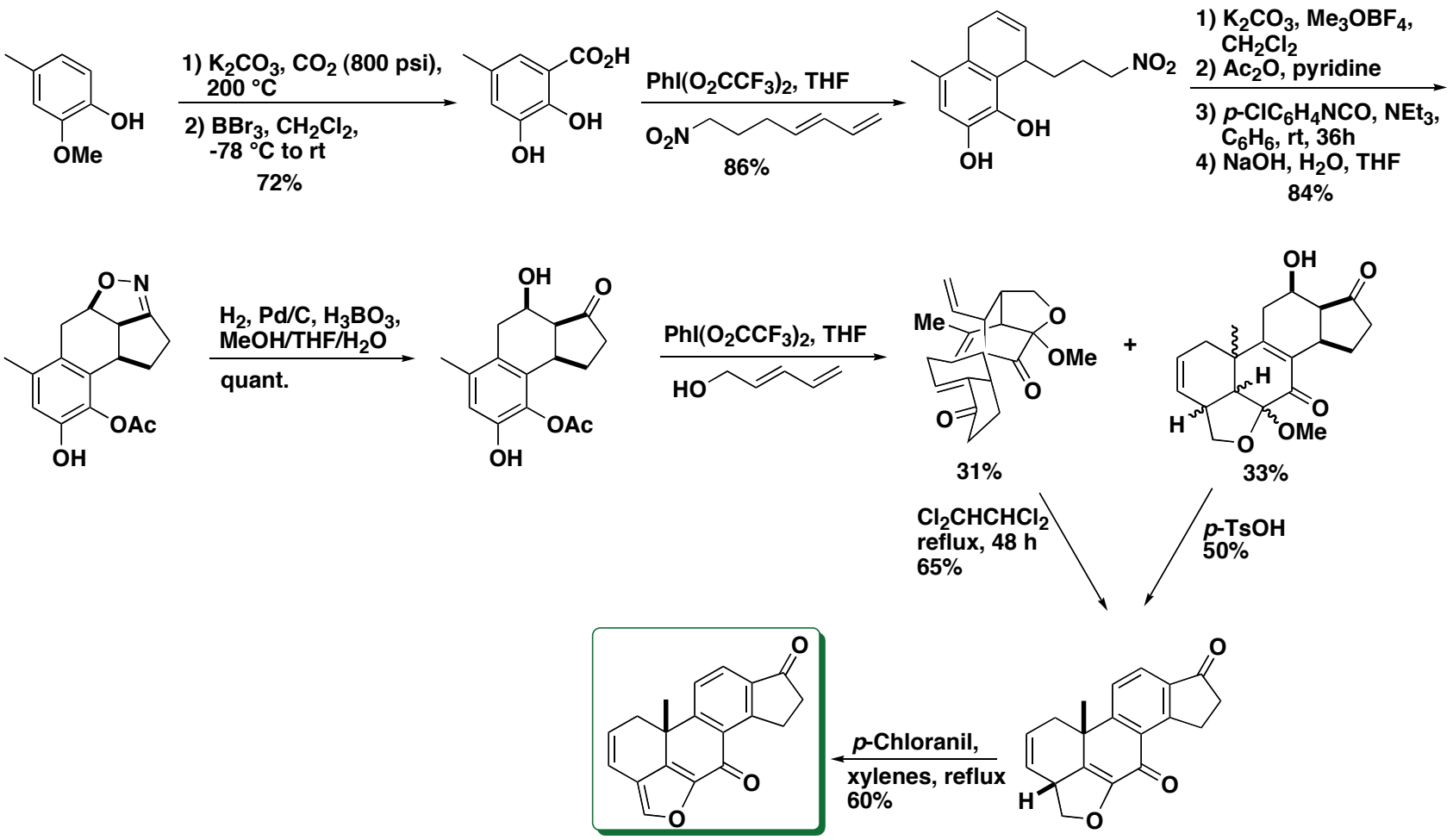
Wortmannin



SHIBASAKI - *C*hiral Building Block

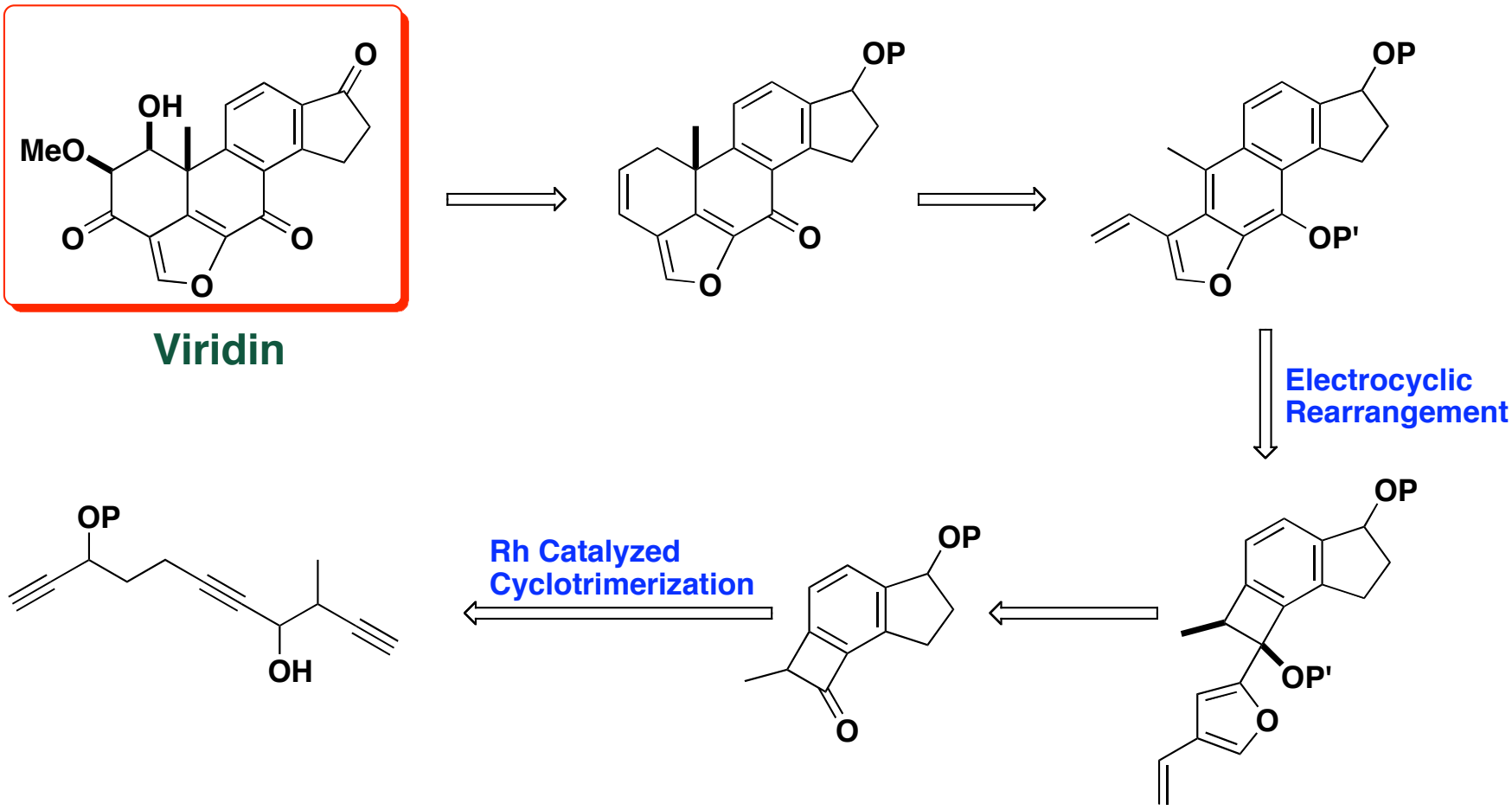
SHIBASAKI - Diastereoselective Intramolecular Heck Coupling and Diosphenol Claisen

Synthesis of Pentacyclic Core of Viridin - Rodrigo

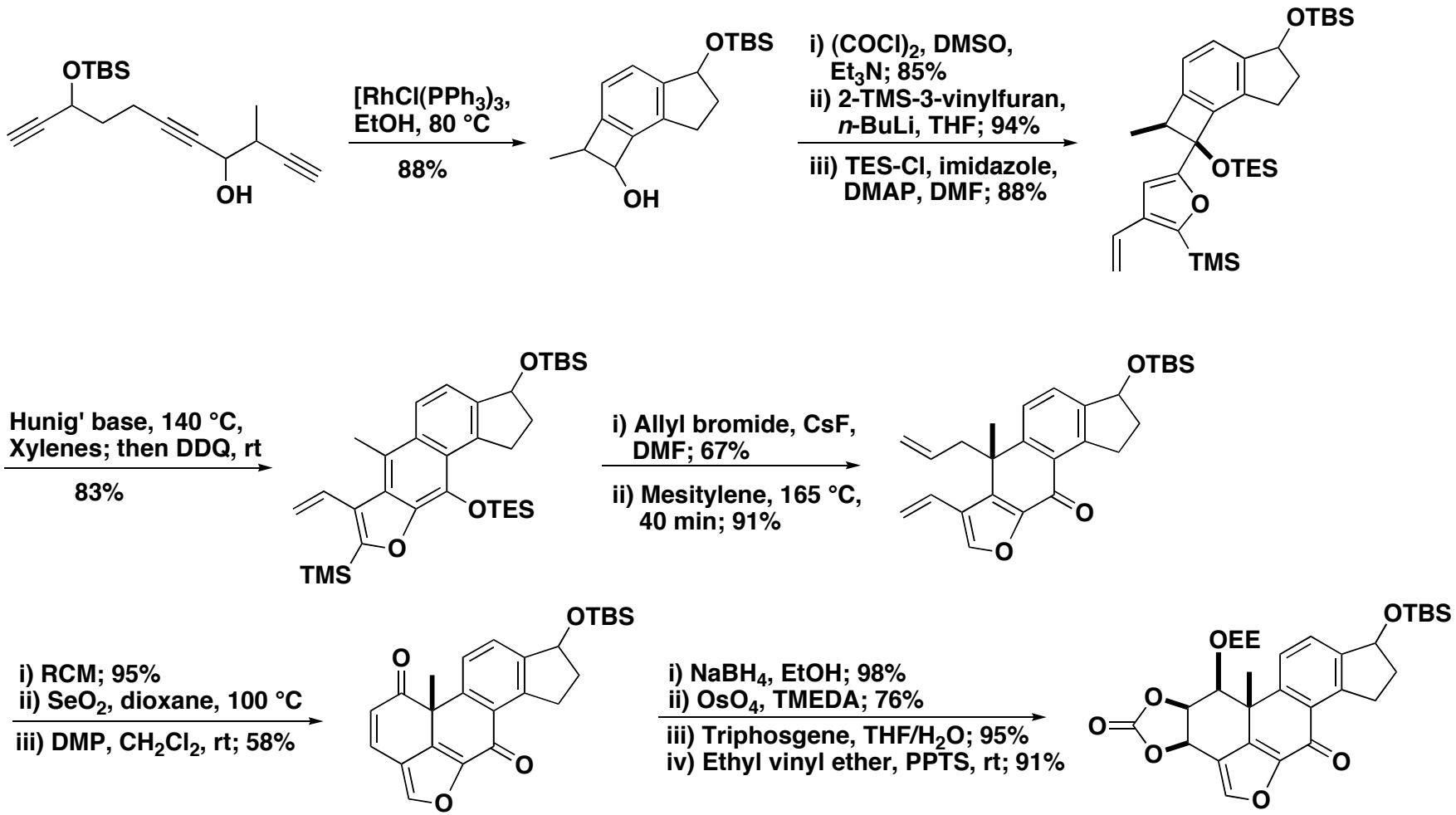


Souza, F. E. S.; Rodrigo, R. *Chem. Commun.* **1999**, 1947.

Retrosynthetic Analysis of (±)-Viridin - Sorensen

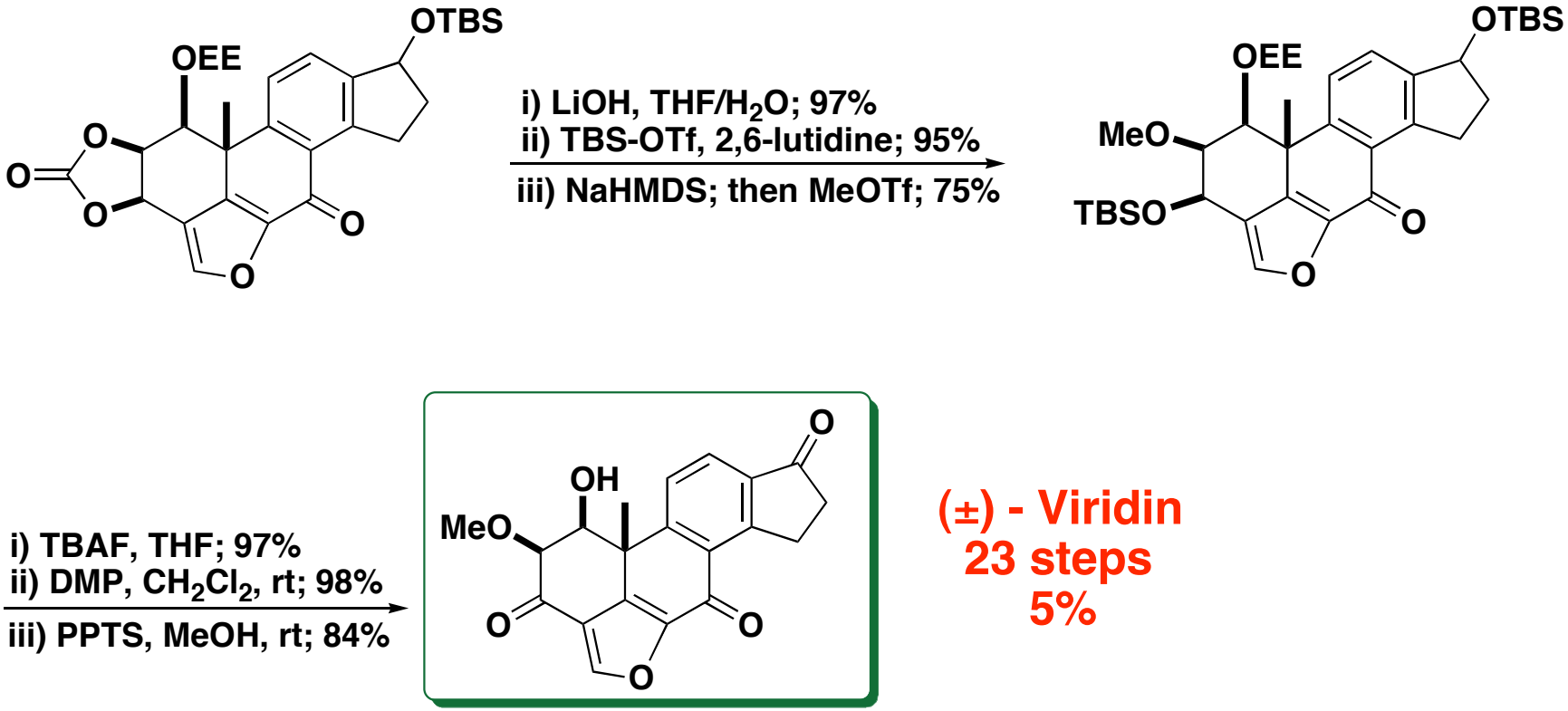


Synthesis of (±)-Viridin - Sorensen



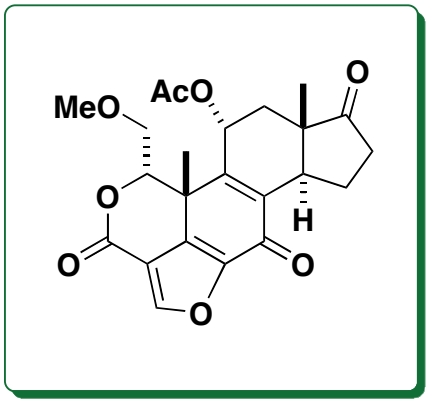
Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1947.

Synthesis of (±)-Viridin - Sorensen

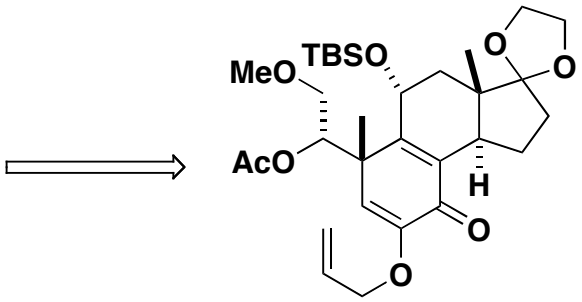


Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1947.

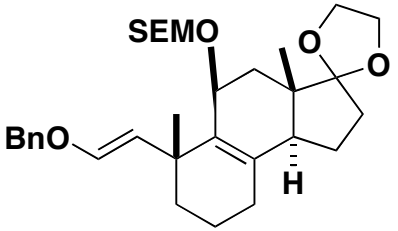
Retrosynthetic Analysis of Wortmannin - Shibasaki



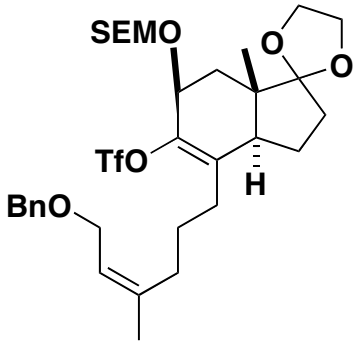
Wortmannin

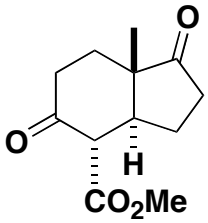


Diosphenol-Claisen Rearrangement

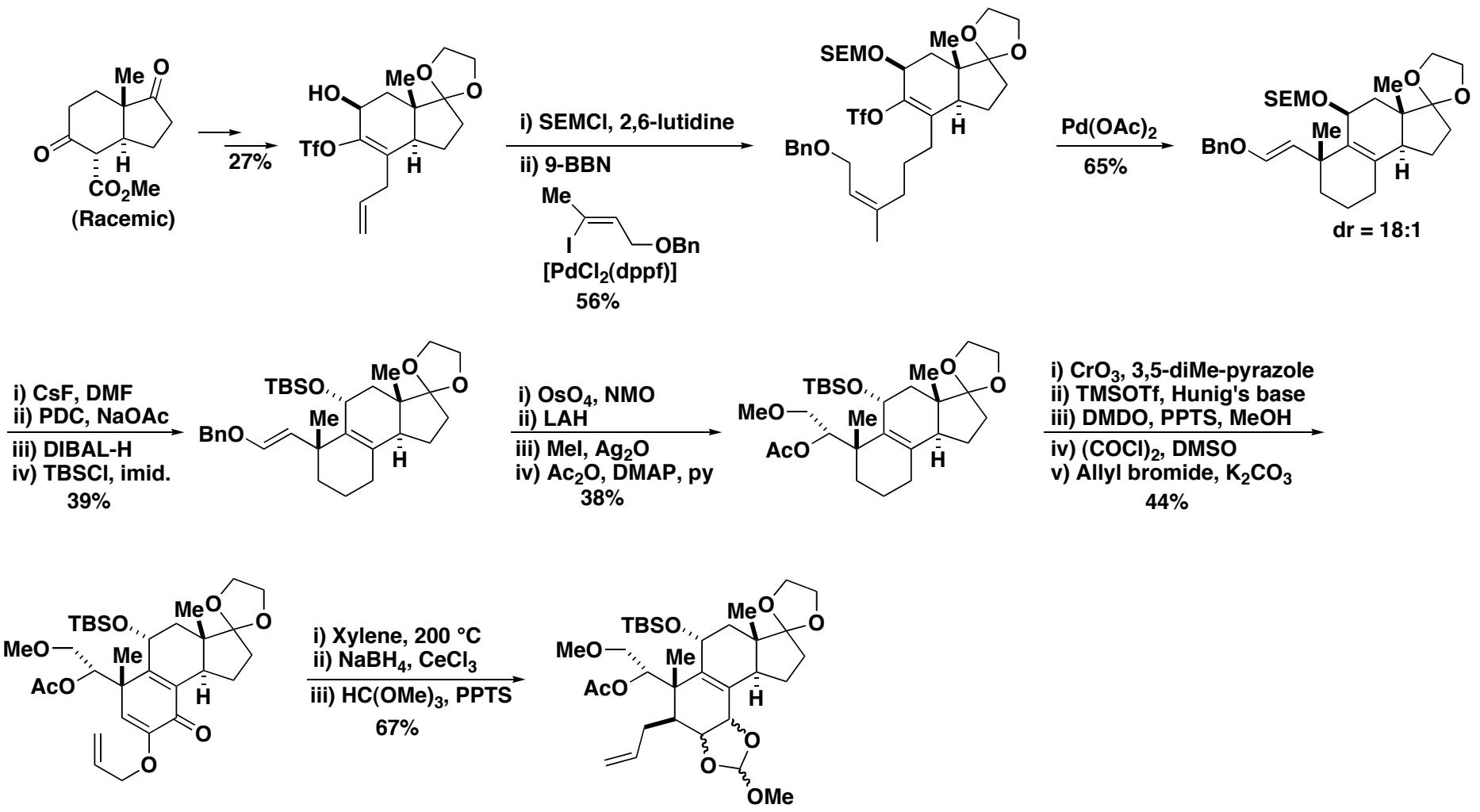


Intramolecular Heck



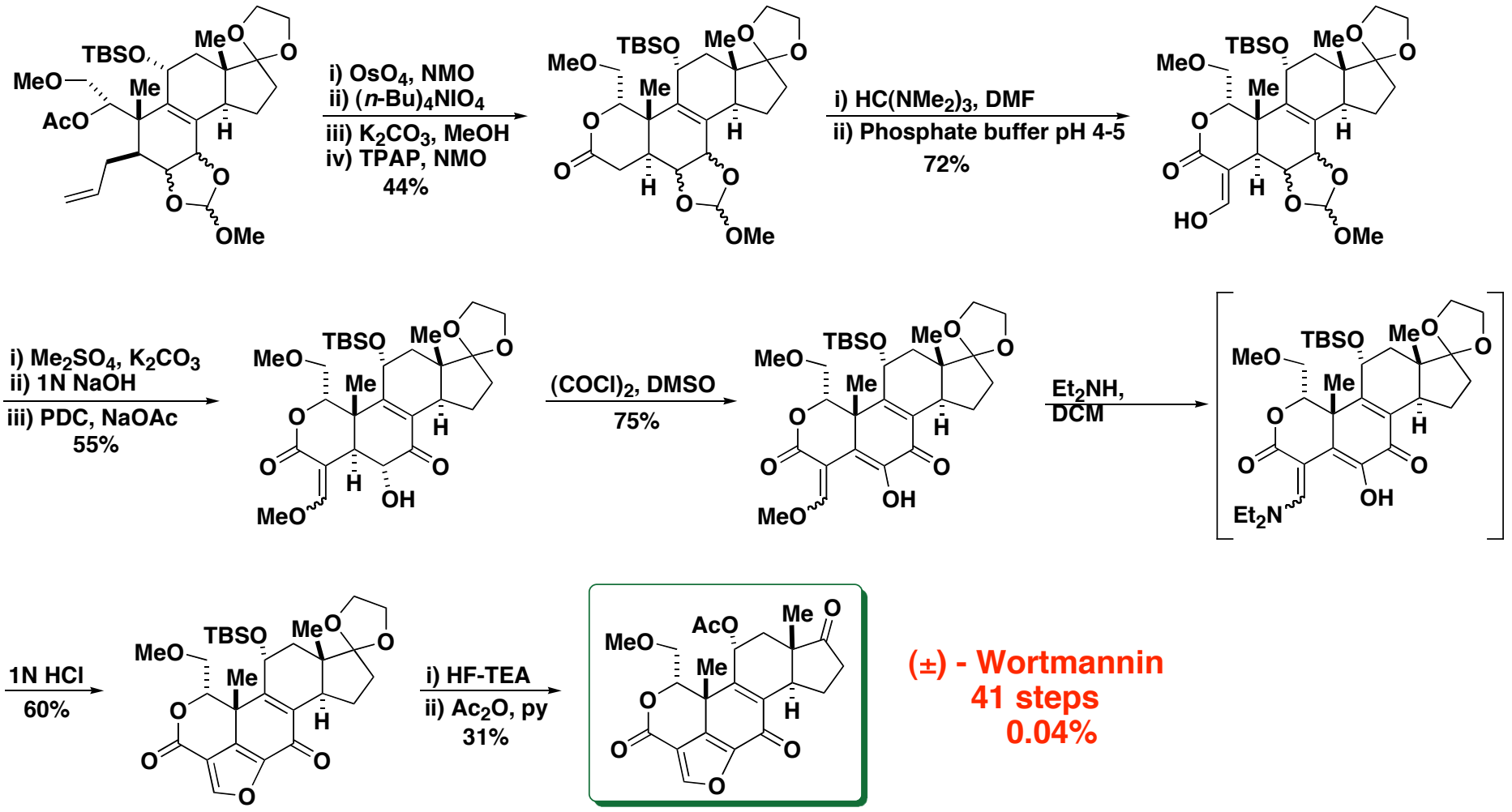


Synthesis of (±)-Wortmannin - Shibasaki



Mizutani, T.; Honzawa, S.; Tosaki, S-y.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4680.

Synthesis of (±)-Wortmannin - Shibasaki



Mizutani, T.; Honzawa, S.; Tosaki, S-y.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4680.

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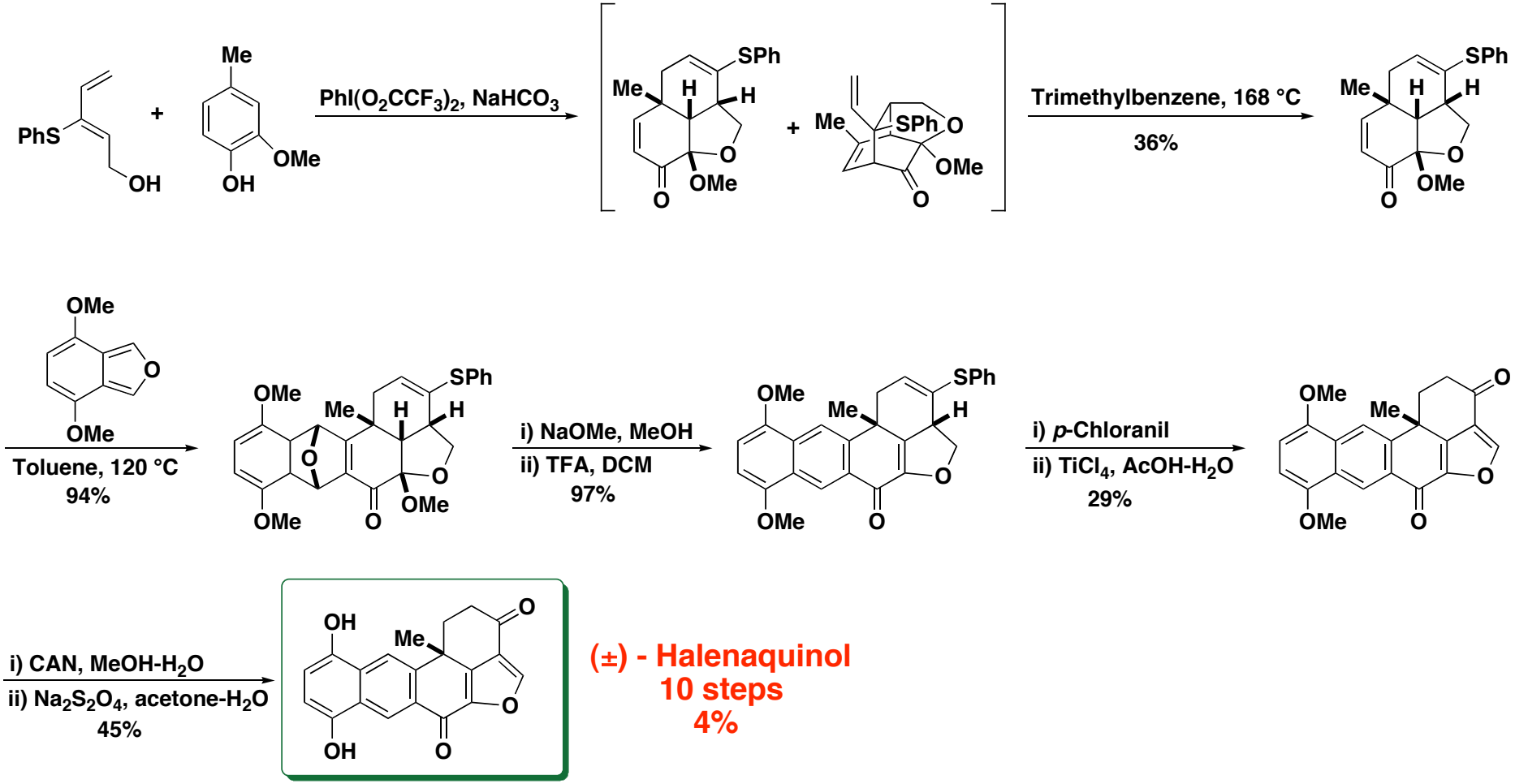
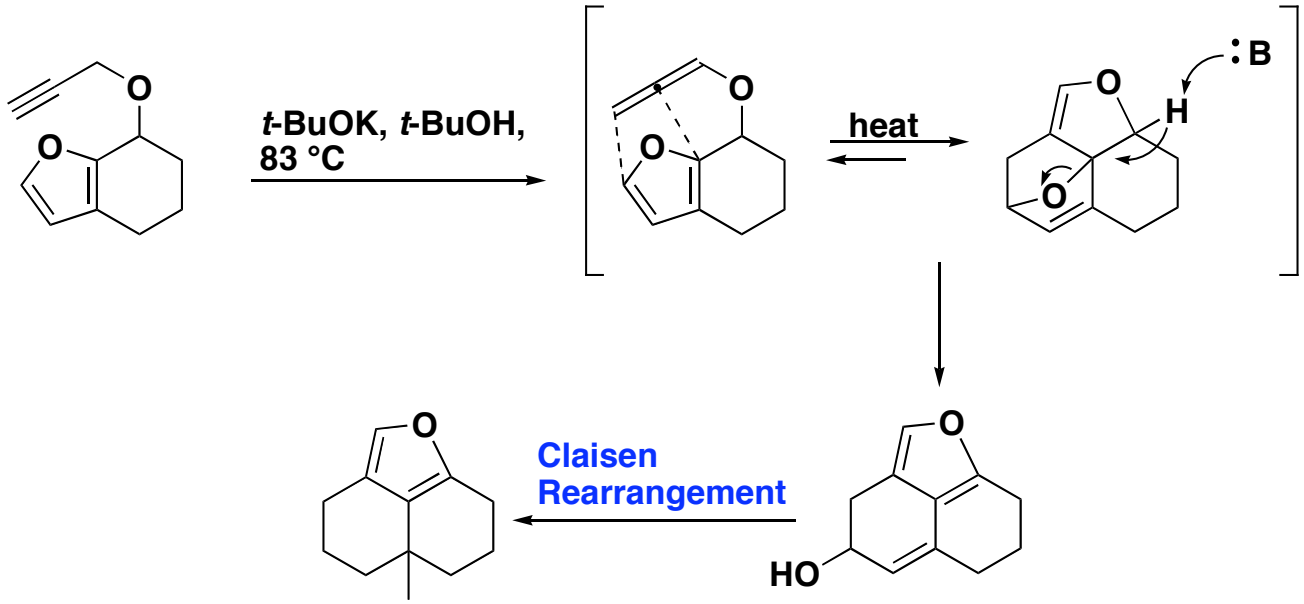
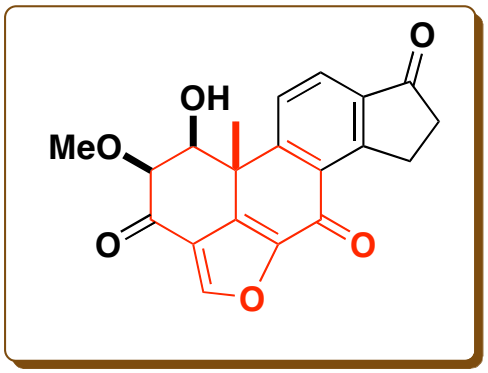
Synthesis of (±)-Halenaquinol - Rodrigo



Sutherland, H. S.; Souza, F. E. S.; Rodrigo, R. G. A. *J. Org. Chem.* **2001**, *66*, 3639.

Furan Ring Transfer Reaction

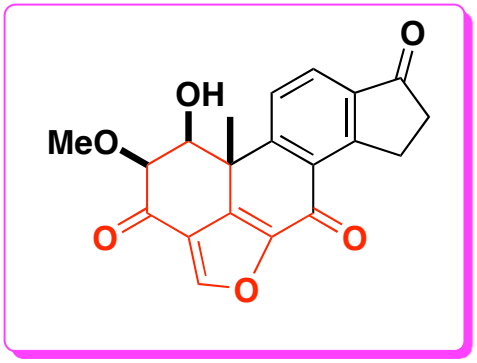




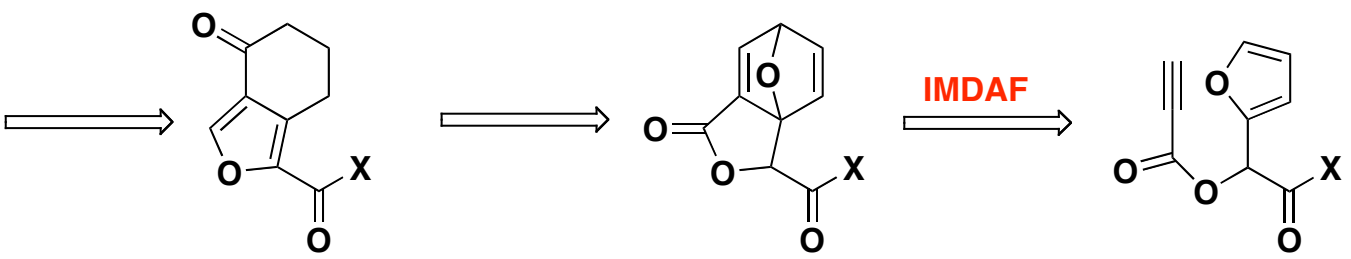
Viridin

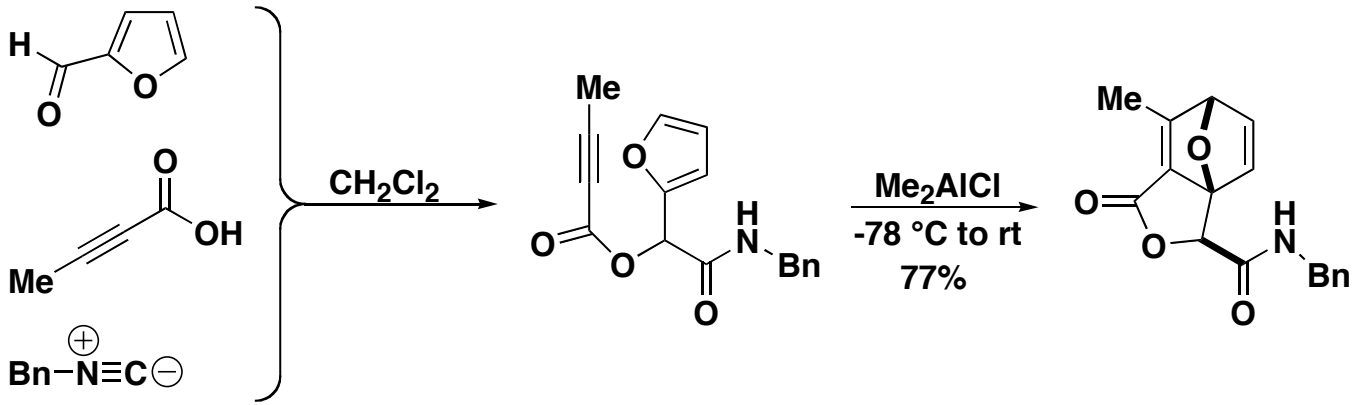
Yamaguchi, Y.; Hayakawa, K.; Kanematsu, K. *Chem. Commun.* **1987**, 515.

Sequential Passerini/Diels-Alder Reaction



Viridin





Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett*. **2002**, *43*, 943.