

Studies Toward the Total Synthesis of (±)-Noelaquinone



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The Role of Natural Products in Drug Discovery

For thousands of years medicine and natural products have been closely linked through the use of traditional medicines and natural poisons.

Which is the STATUS of NATURAL PRODUCTS in DRUG DISCOVERY today ?

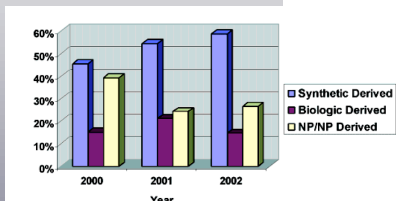


Table 1. Top 35 Worldwide Ethical Drug Sales for 2000, 2001, and 2002^a with Natural Product-Derived Drugs in Blue,^b Biologically Derived Drugs in Magenta,^c and Synthetically Derived Drugs in Black^d

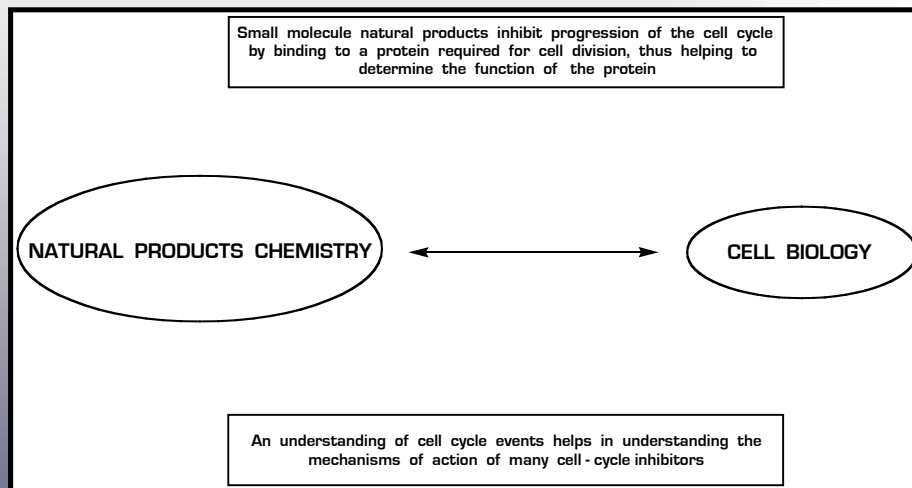
Rank	2000	2001	2002
1	Omeprazole	Atorvastatin	Atorvastatin
2	Atorvastatin	Omeprazole	Simvastatin
3	Simvastatin	Simvastatin	Omeprazole
4	Amlodipine	Lansoprazole	Erythropoietin (J&J)
5	Lansoprazole	Amlodipine	Amlodipine
6	Lorazepam	Erythropoietin (J&J)	Lansoprazole
7	Erythropoietin (J&J)	Lorazepam	Olanzapine
8	Celecoxib	Celecoxib	Paroxetine
9	Fluoxetine	Olanzapine	Celecoxib
10	Olanzapine	Paroxetine	Sertraline
11	Paroxetine	Sertraline	Interferon α -2b+Ribavirin
12	Sertraline	Metformin/Metformin+Glyburide	Rofecoxib
13	Rofecoxib	Rofecoxib	Salmeterol+Fluticasone propionate
14	Erythropoietin (Amgen)	Erythropoietin (Amgen)	Gabapentin
15	Metformin/Metformin+Glyburide	Pravastatin (BMS)	Pravastatin (BMS)
16	Estrone	Estrone	Erythropoietin (Amgen)
17	Amoxicillin + Clavulanic acid	Amoxicillin + Clavulanic acid	Alendronate Sodium
18	Enalapril	Fluoxetine	Losartan/Losartan+Hydrothiazide
19	Pravastatin (BMS)	Risperidone	Risperidone
20	Insulin	Losartan/Losartan+Hydrothiazide	Venlafaxine
21	Ciprofloxacin	Insulin	Esomeprazole magnesium
22	Losartan/Losartan+Hydrothiazide	Ciprofloxacin	Fexofenadine
23	Pravastatin (Sankyo)	Gabapentin	Clopidogrel bisulfate
24	Risperidone	Alendronate sodium	Insulin
25	Paclitaxel	Leuprolide acetate	Estrone
26	Leuprolide Acetate	Fexofenadine	Lorazepam
27	Azithromycin	Venlafaxine	Amoxicillin+Clavulanic acid
28	Interferon α -2b+Ribavirin	Sildenafil	Sildenafil
29	Sildenafil	Azithromycin	Valisartan
30	Gabapentin	Interferon α -2b+Ribavirin	Citalopram hydrobromide
31	Fluticasone propionate	Pravastatin (Sankyo)	Leuprolide Acetate
32	Clarithromycin	Filgrastim	Oxycodone HCl
33	Filgrastim	Fluticasone propionate	Azithromycin
34	Cyclosporin	Enoxaparin	Montelukast sodium
35	Lisinopril	Vaccines (Aventis)	Rituximab

^a Top 35 worldwide ethical drug sales data supplied by Wood Mackenzie, Boston, MA. ^b NP-derived indicates that the drug is either a NP, a semisynthetic derivative of a NP, or a synthetic drug that is modeled on a NP pharmacophore. ^c Biologically derived indicates that the drug is hormone or protein derived. ^d Erythropoietin is sold by both Johnston & Johnston (J&J) and Amgen, while pravastatin is marketed in Japan by Sankyo and the United States by Bristol-Myers Squibb (BMS).

Understanding the Cell-Cycle with Natural Products

Understanding Protein Function in Cells

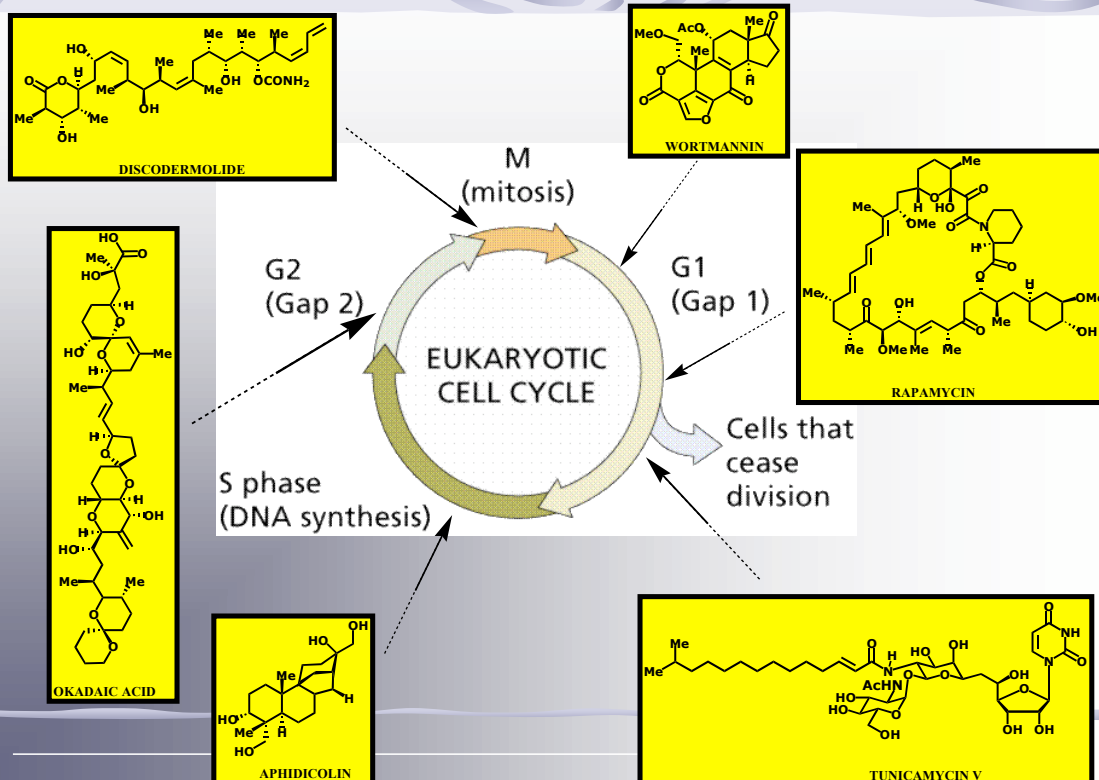
- **Genetic Approach:** making mutations in genes that alter the function of the encoded protein
- **Chemical Approach:** to alter the function of the protein directly by using a cell-permeable ligand that binds to the protein in its intracellular environment



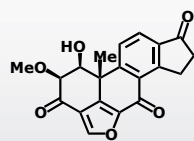
Currently the most valuable collection of ligands for use in the study of protein function are **NATURAL PRODUCTS** or compounds that are closely related to a **NATURAL PRODUCT**

Schreiber, S. L. *et al. Chem. Biol.* 1996 3 623.

Relative Timing of Arrest by Different Cell-Cycle Arrest Agents

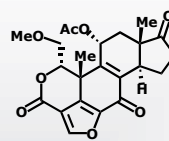


The Viridin Family of Steroidal Antibiotic: The Furanosteroids



Viridin

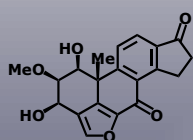
Isolated in 1945 from *Gliocadium Virens*
structure determined in 1966



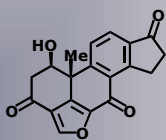
Wortmannin

Isolated in 1957 from *Penicillium Wortmannii* and in 1972
from *Myrothecium Floridium*, structure determined in 1972

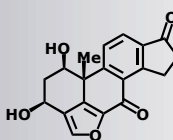
- Anti - Inflammatory Activity
- Antibiotic Activity
- Potent and Specific Phosphoinositide 3 - kinase (PI 3K) Inhibitors



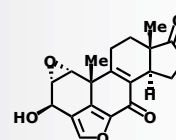
Viridol



Demethoxyviridin



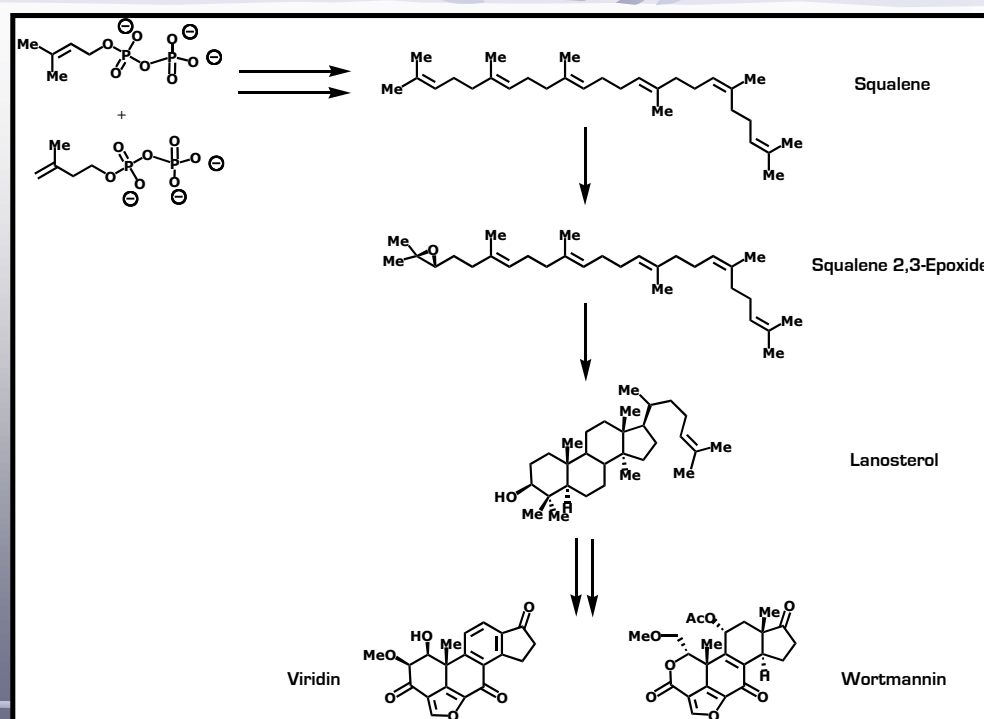
Demethoxyviridol



Wortmannolone

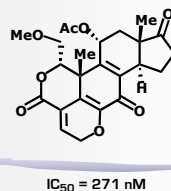
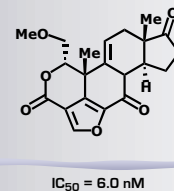
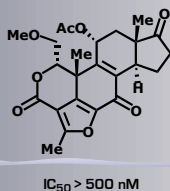
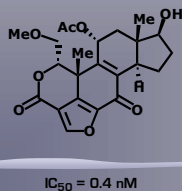
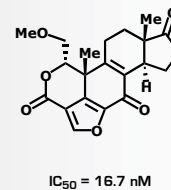
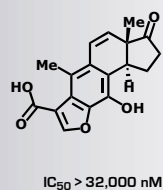
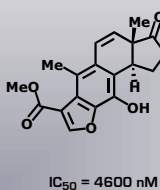
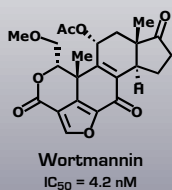
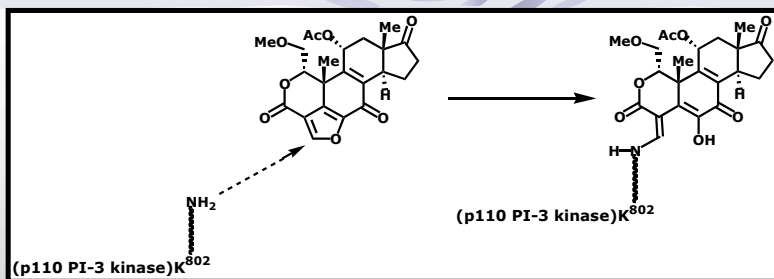
Wipf, P. and Halter, R. J. *Org. Biomol. Chem.* **2005** *3* 2053.

Furanosteroids: Proposed Biosynthesis



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

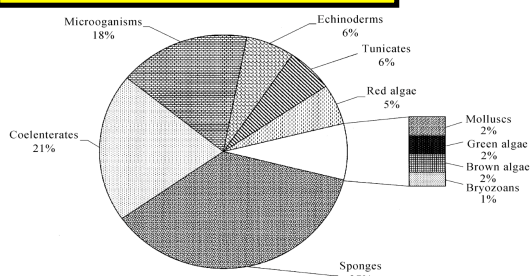
Wortmannin Irreversible Inhibition of PI-3 Kinase



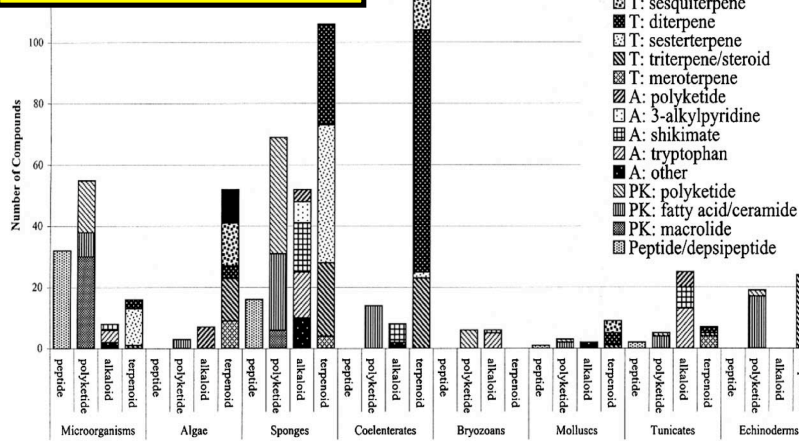
Norman, C. S. *J. Med. Chem.* 1996 39 1106.

Planar Polycyclics from the Marine Sponge *Xestospongia*

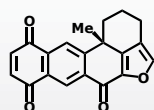
Distribution of Marine Natural Products by Phylum



Biogenetic Origins of Marine Natural Products

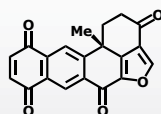


Planar Polycyclics from the Marine Sponge *Xestospongia*



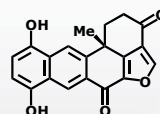
(+)-Xestoquinone

Isolated from *Xestospongia Sagra* in 1960



(+)-Halenaquinone

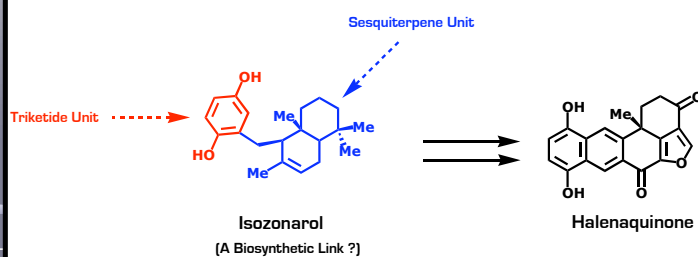
Isolated from *Xestospongia Exigua* in 1983



(+)-Halenaquinol

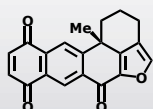
- Antibacterial Activity
- Cardiotoxic Properties
- Inhibition of pp60 Kinase
- Inhibition of EGF Kinase
- Inhibition of the Dual Specificity Phosphatase Cdc25

Are These Compounds Triketides - Sesquiterpenes Hybrids?



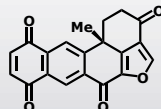
Protein Tyrosine Kinase (PTK) Inhibition

IC₅₀ values against pp₆₀



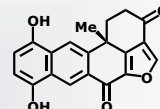
(+)-Xestoquinone

IC₅₀ = 60 μM



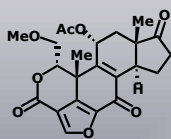
(+)-Halenaquinone

IC₅₀ = 1.5 μM



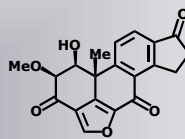
(+)-Halenaquinol

IC₅₀ = 0.6 μM



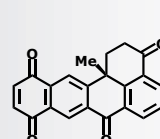
Wortmannin

IC₅₀ >> 200 μM



Viridin

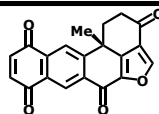
IC₅₀ = 30 μM



IC₅₀ = 27 μM

Synthetic Efforts Outline

Halenaquinone

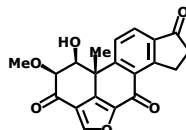


HARADA [Chiral building block]

RODRIGO [*o*-Benzoquinone monoketals Cascade Reactions]

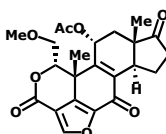
SHIBASAKI [Catalytic Asymmetric Intramolecular Cascade Heck-Suzuki Couplings]

Viridin



SORENSEN [Alkyne Trimerization and *p*-Claisen Rearr.]

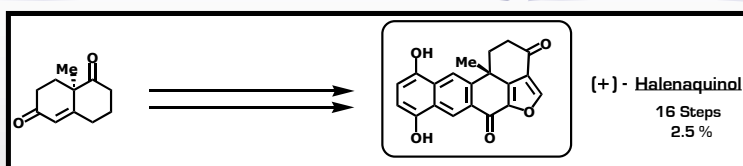
Wortmannin



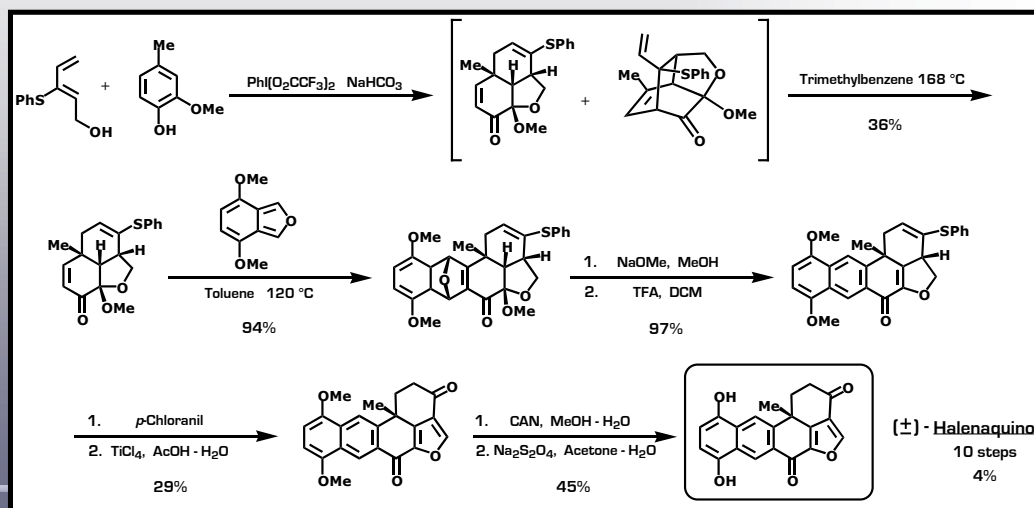
SHIBASAKI [Chiral building block]

SHIBASAKI [Diastereoselective Intramolecular Heck Couplings and Diosphenol Claisen]

Synthesis of (±) - Halenaquinol [Rodrigo]

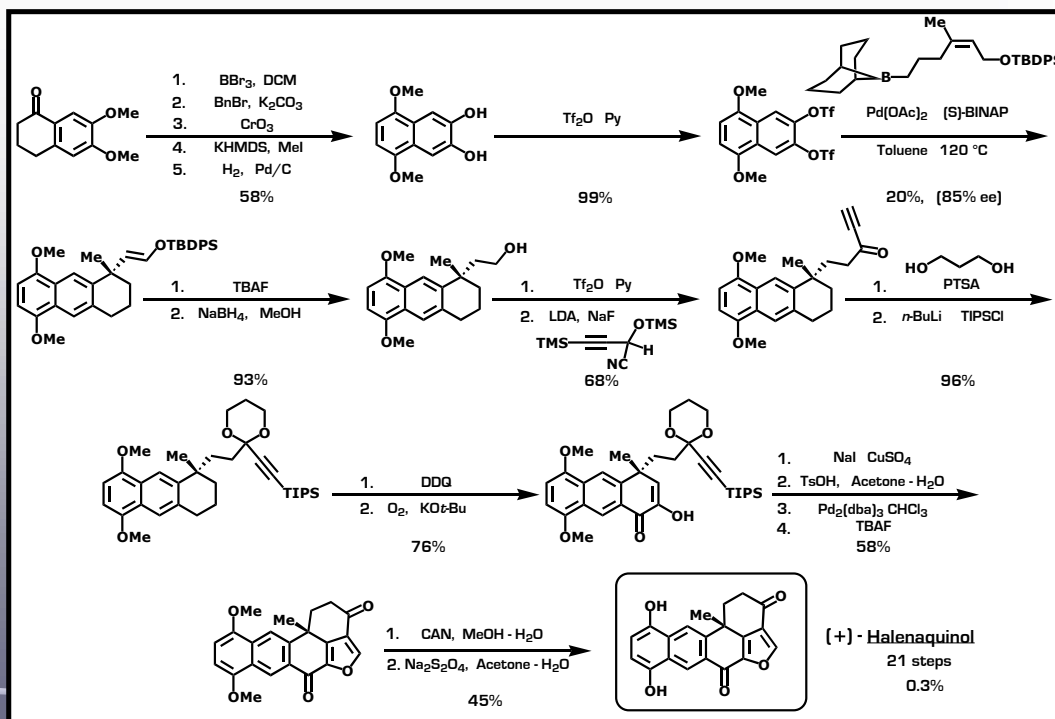


Harada, N. *et al* *J. Am. Chem. Soc* **1988** 110 8483.



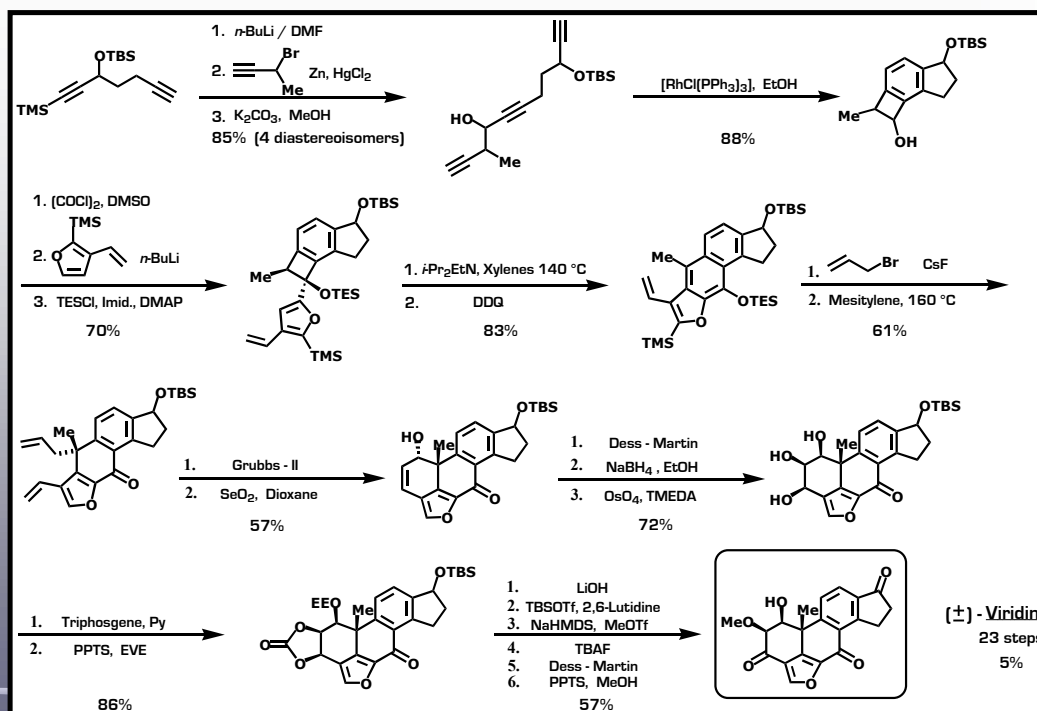
Rodrigo, R. G. A. *et al* *J. Org. Chem.* **2001** 66 3639.

Synthesis of (+) - Halenaquinol [Shibasaki]



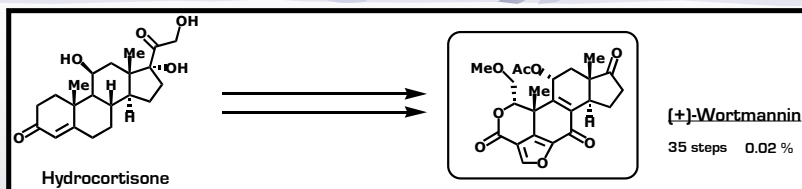
Shibasaki, M. *et al* *J. Org. Chem.* **1996** 61 4876.

Synthesis of (±) - Viridin [Sorensen]

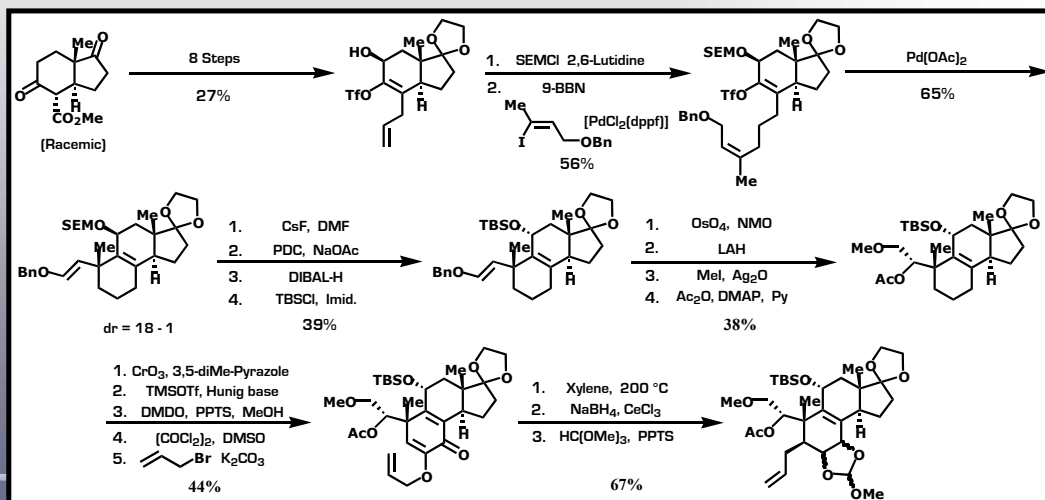


Sorensen, E. J. *et al* *Angew. Chem. Int. ed.* **2004** 43 1998.

[1] Synthesis of (±) - Wortmannin [Shibasaki]

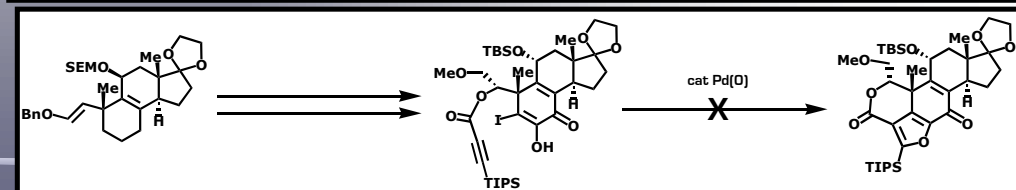
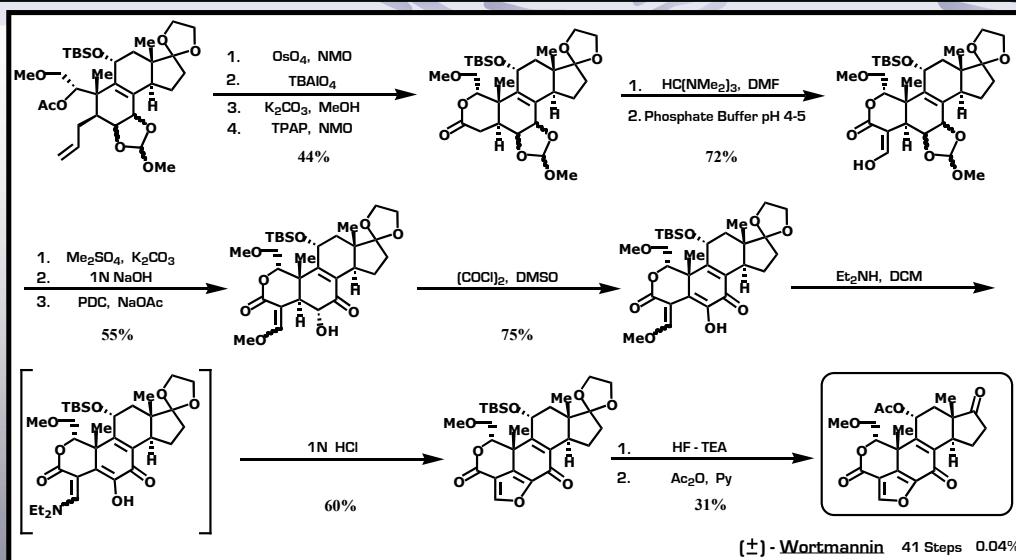


Shibasaki, M. et al *Tetrahedron. Lett.* 1996 37 6141.



Shibasaki, M. et al *Angew. Chem. Int. Ed.* 2002 41 4680.

[2] Synthesis of (±) - Wortmannin [Shibasaki]



Shibasaki, M. et al *Angew. Chem. Int. Ed.* 2002 41 4680.