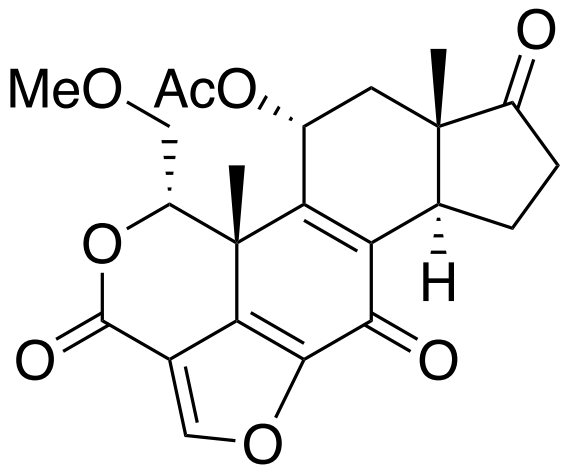
Enantioselective Total Synthesis of (+)-Wortmannin



(+)-wortmannin

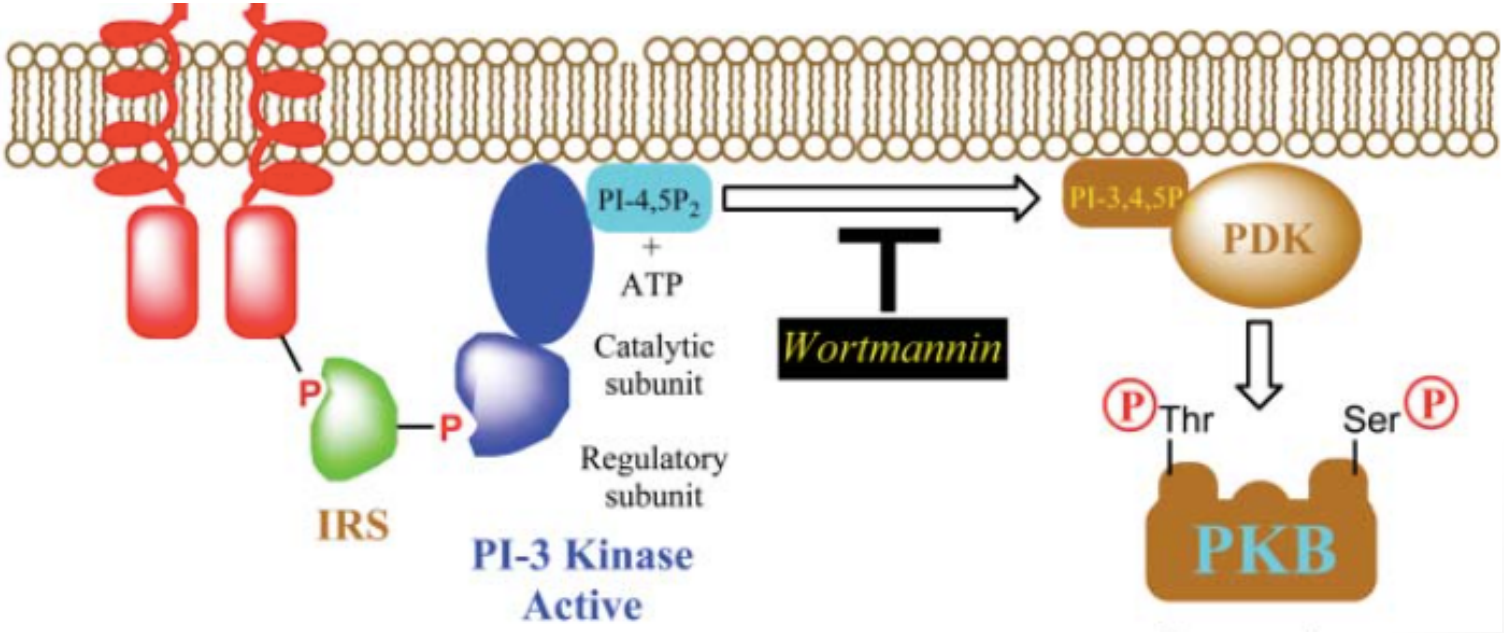
Guo, Y.; Quan, T. Lu, Y.; Luo, T. *J. Am Chem. Soc.* **2017**, *139*, 6815-6818

John Milligan
Wipf Group Meeting

Current Literature
June 10, 2017

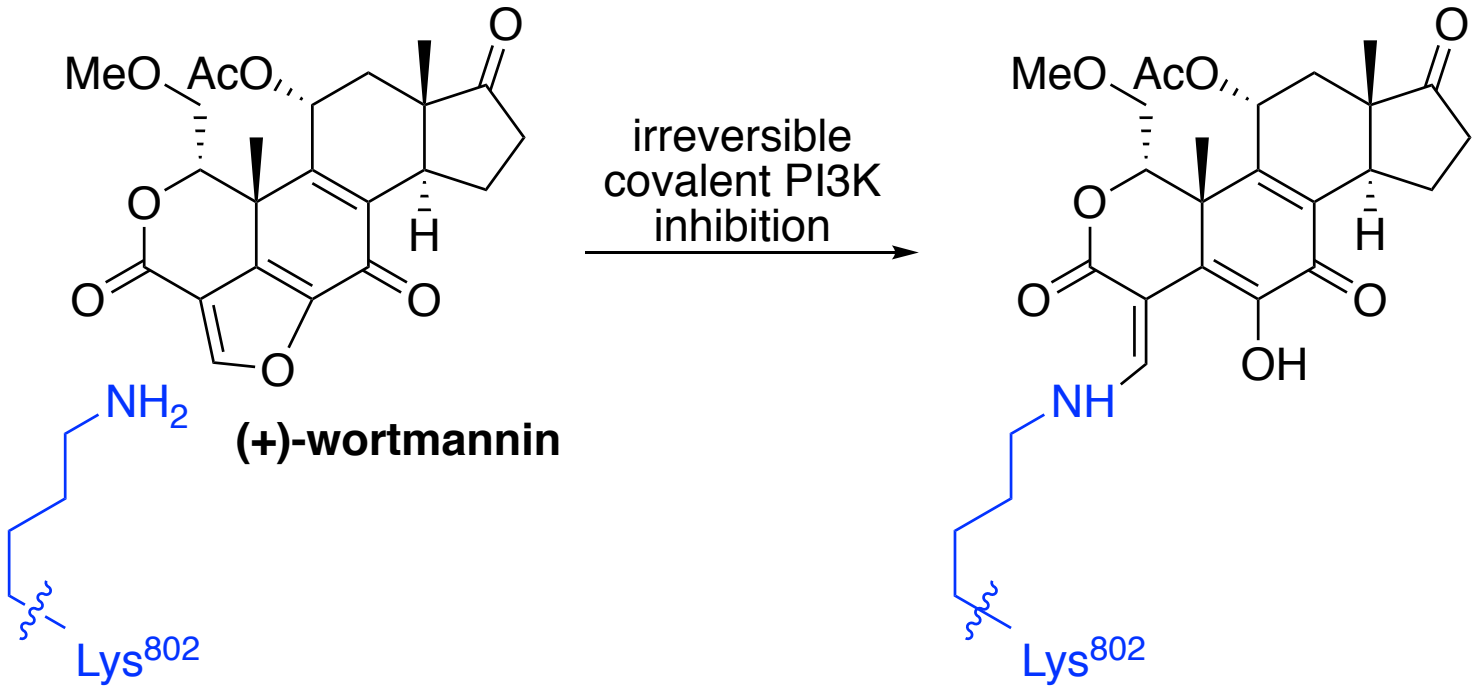
Wortmannin

- First isolated in 1957, but structure not confirmed until the early 1970's
- Potent (IC_{50} = 5 nM) inhibitor of phosphatidylinositol 3-kinase (PI-3K), which is part of a signaling cascade for cell growth and differentiation



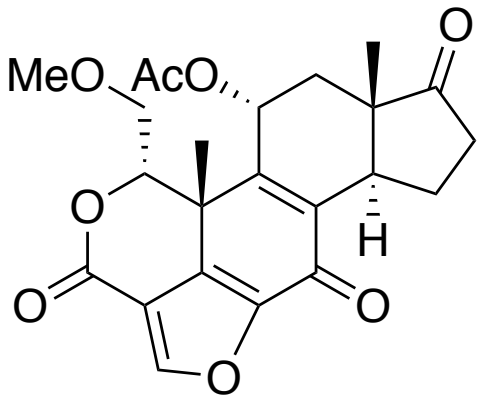
Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053-2061.

Mechanism of action



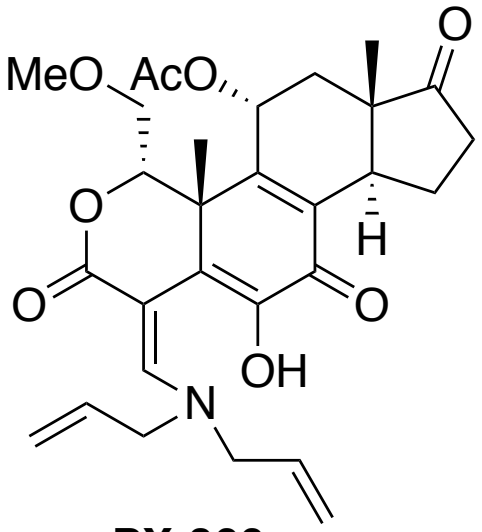
- Strained (12 kcal/mol) and electrophilic furan motif allows for covalent attachment of Lys-802 on PI-3K

Wipf group contributions



(+)-wortmannin

furan cleavage



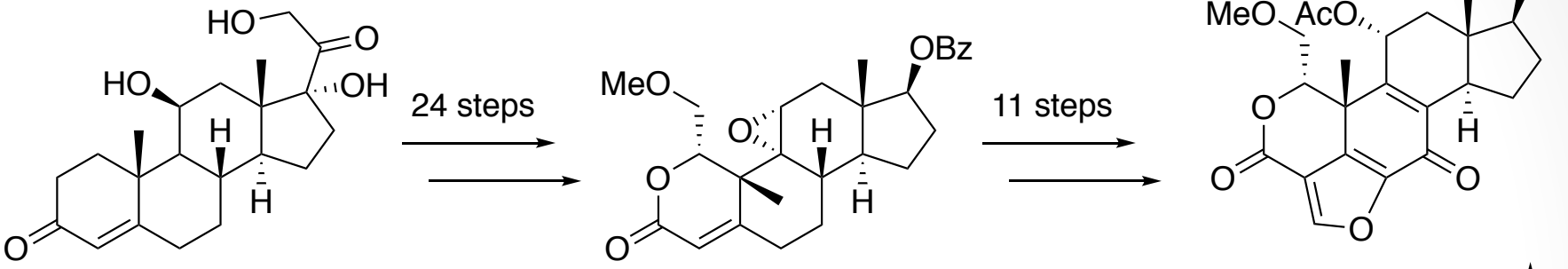
PX-866

- IC_{50} of against purified PI3K: 0.1 nM
- more stable *in vivo*
- decreased toxicity

Ihle, N. T.; Paine-Murrieta, G.; Berggren, M. I.; Baker, A.; Tate, W. R.; Wipf, P.; Abraham, R. T.; Kirkpatrick, D. L.; Powis, G. *Mol. Cancer Therap.* **2005**, *4* (9), 1349-1357.

Previous Total Syntheses

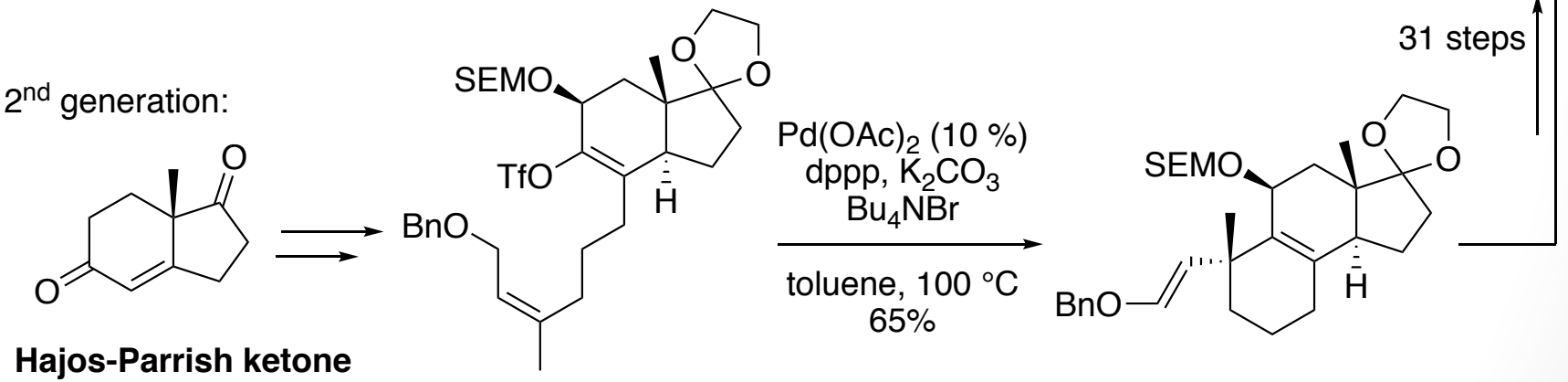
1st generation:



hydrocortisone

(+)-wortmannin

2nd generation:

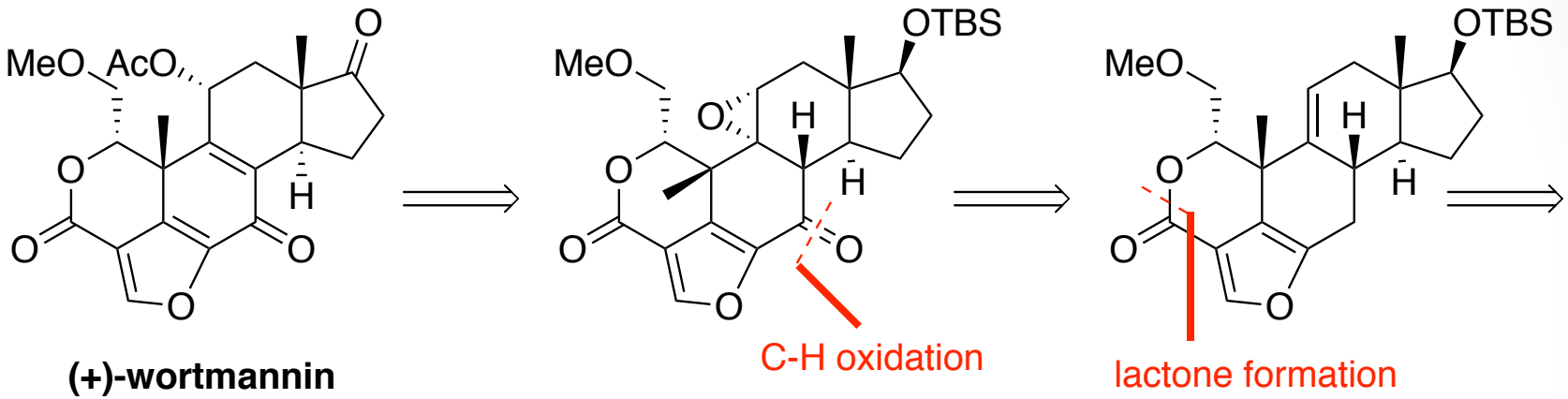


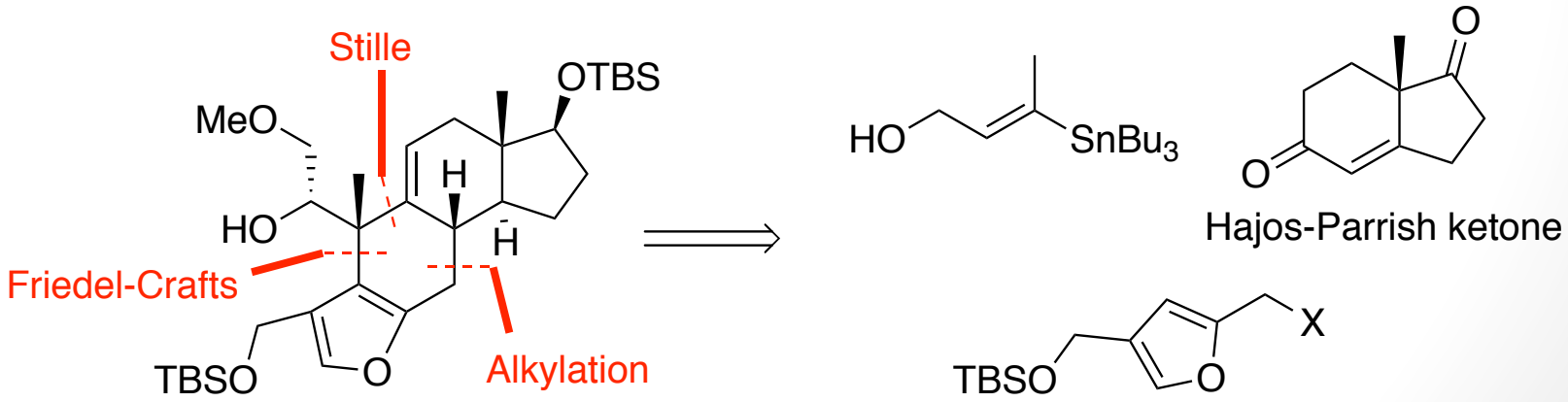
Hajos-Parrish ketone

Sato, S.; Nakada, M.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 6141-6144.

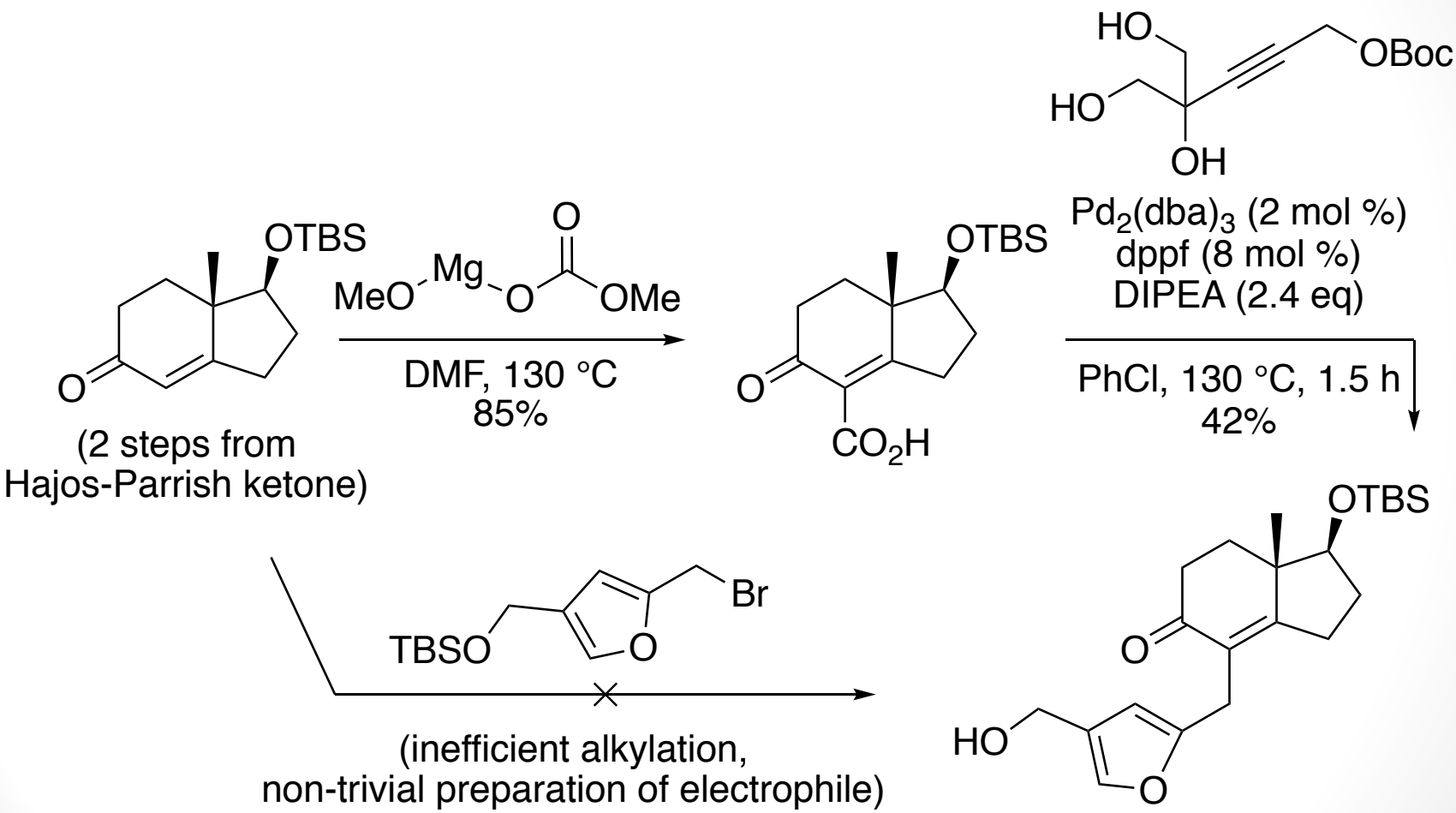
Mizutani, T.; Honzawa, S., Tosaki, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4680-4682

Title paper: retrosynthesis



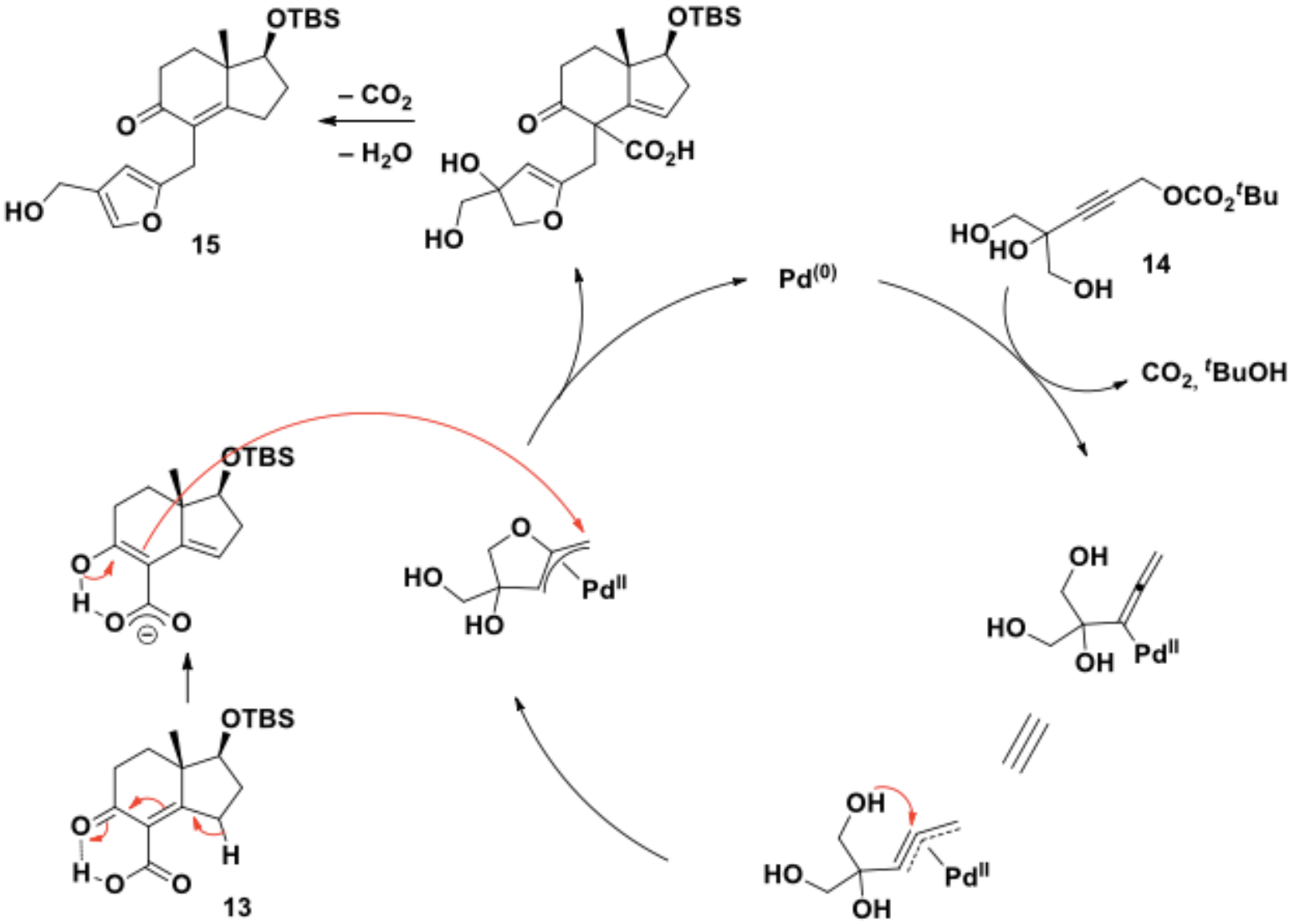


Furan Synthesis

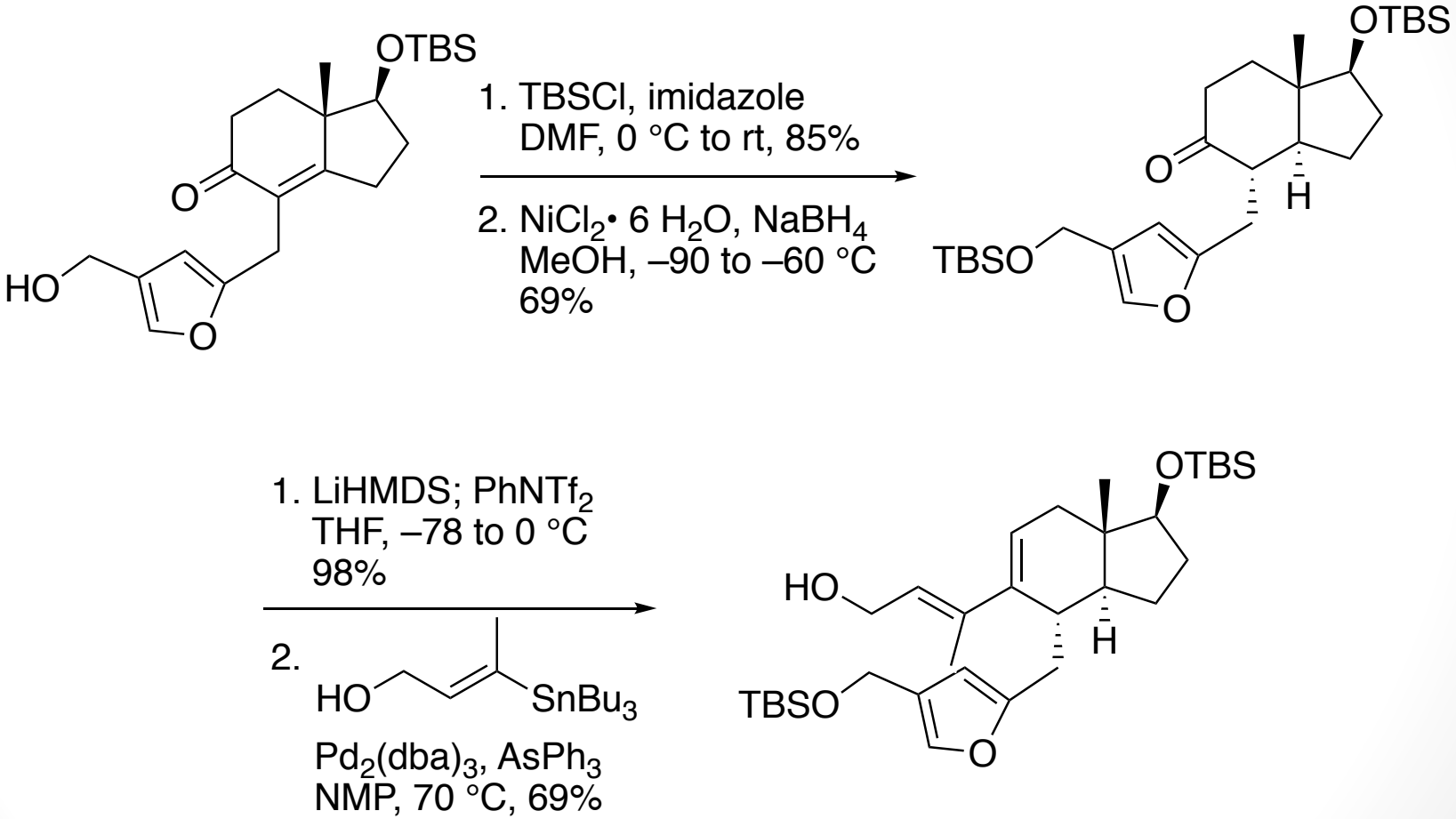


Carboxylation with MMC: Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.

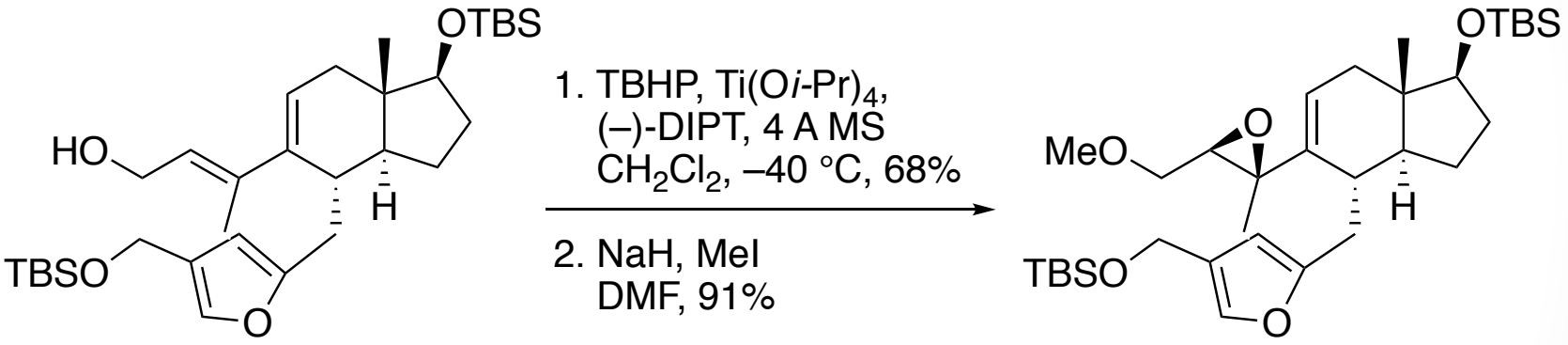
Furan Synthesis Mechanism



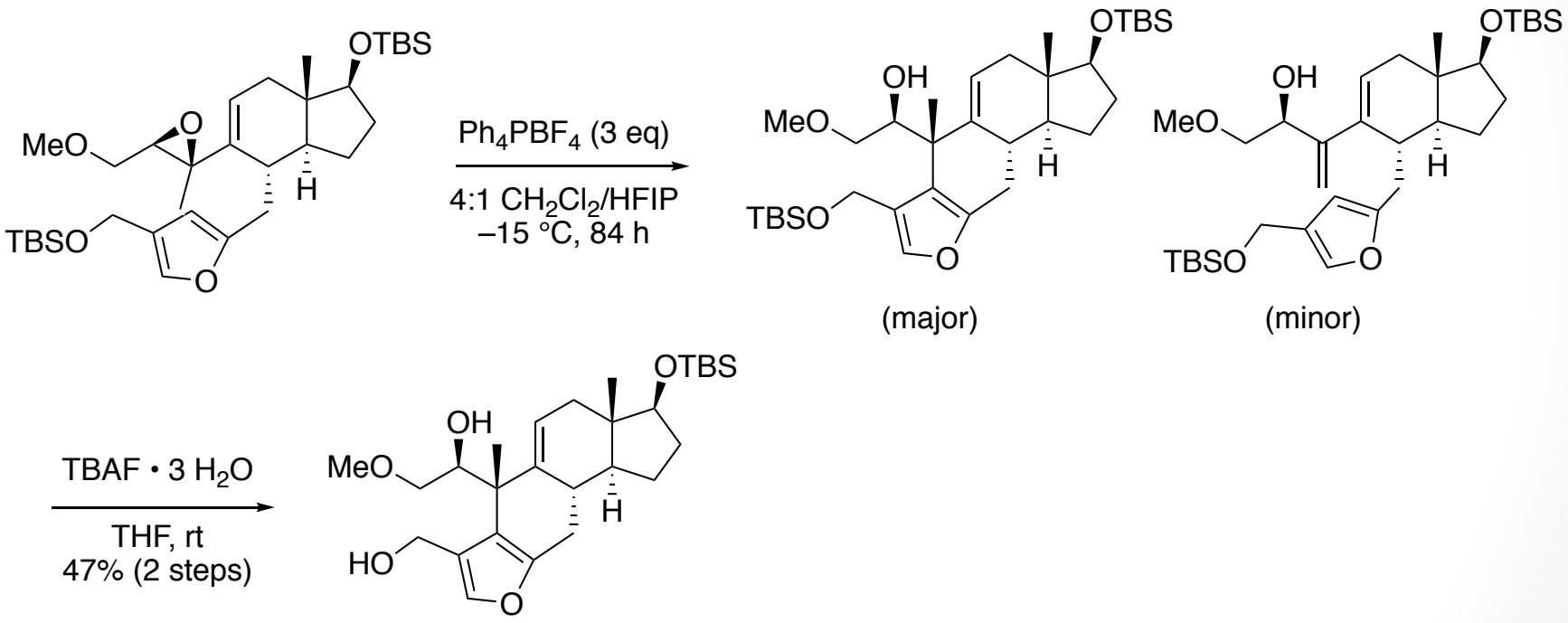
Reduction/Coupling



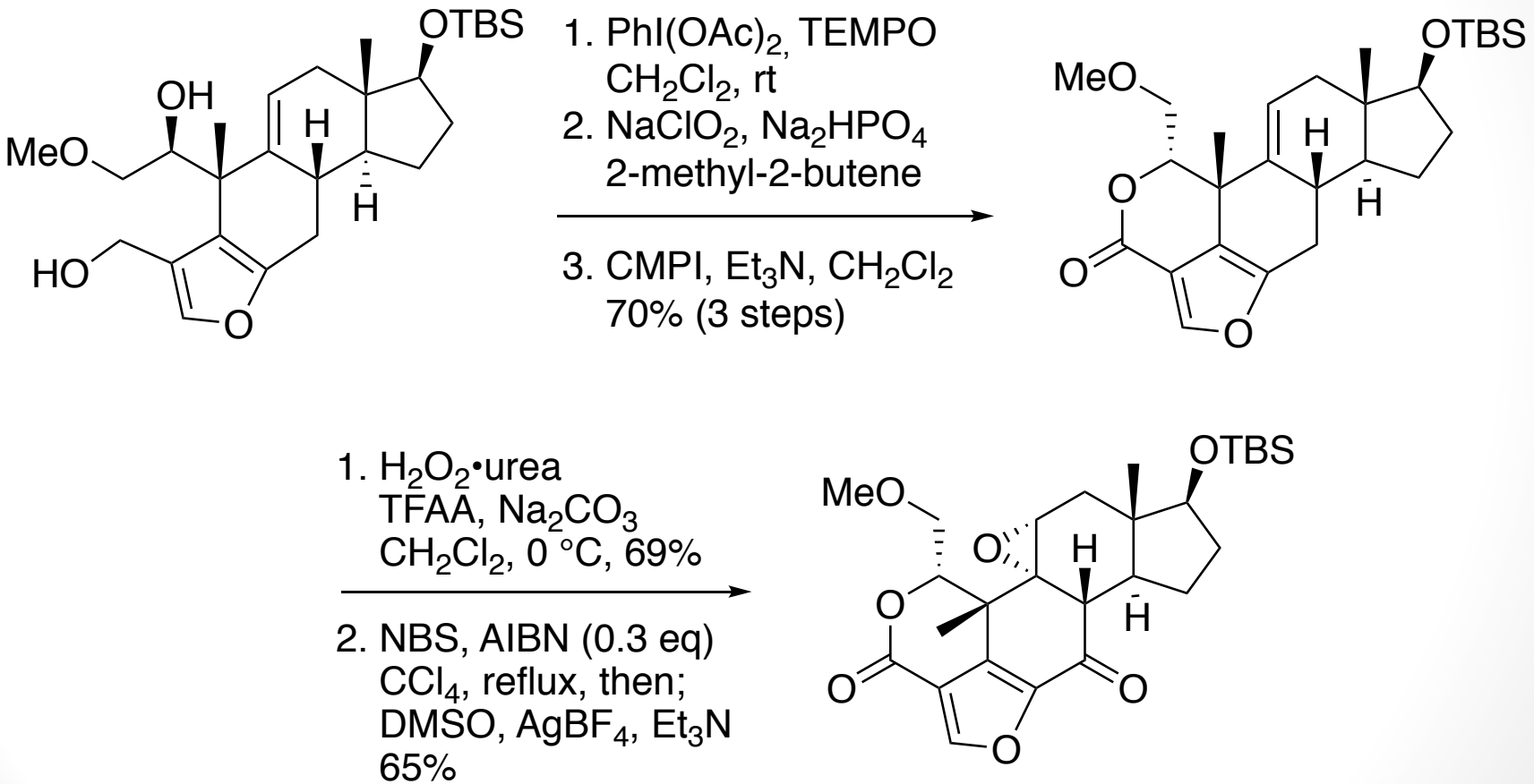
Epoxidation



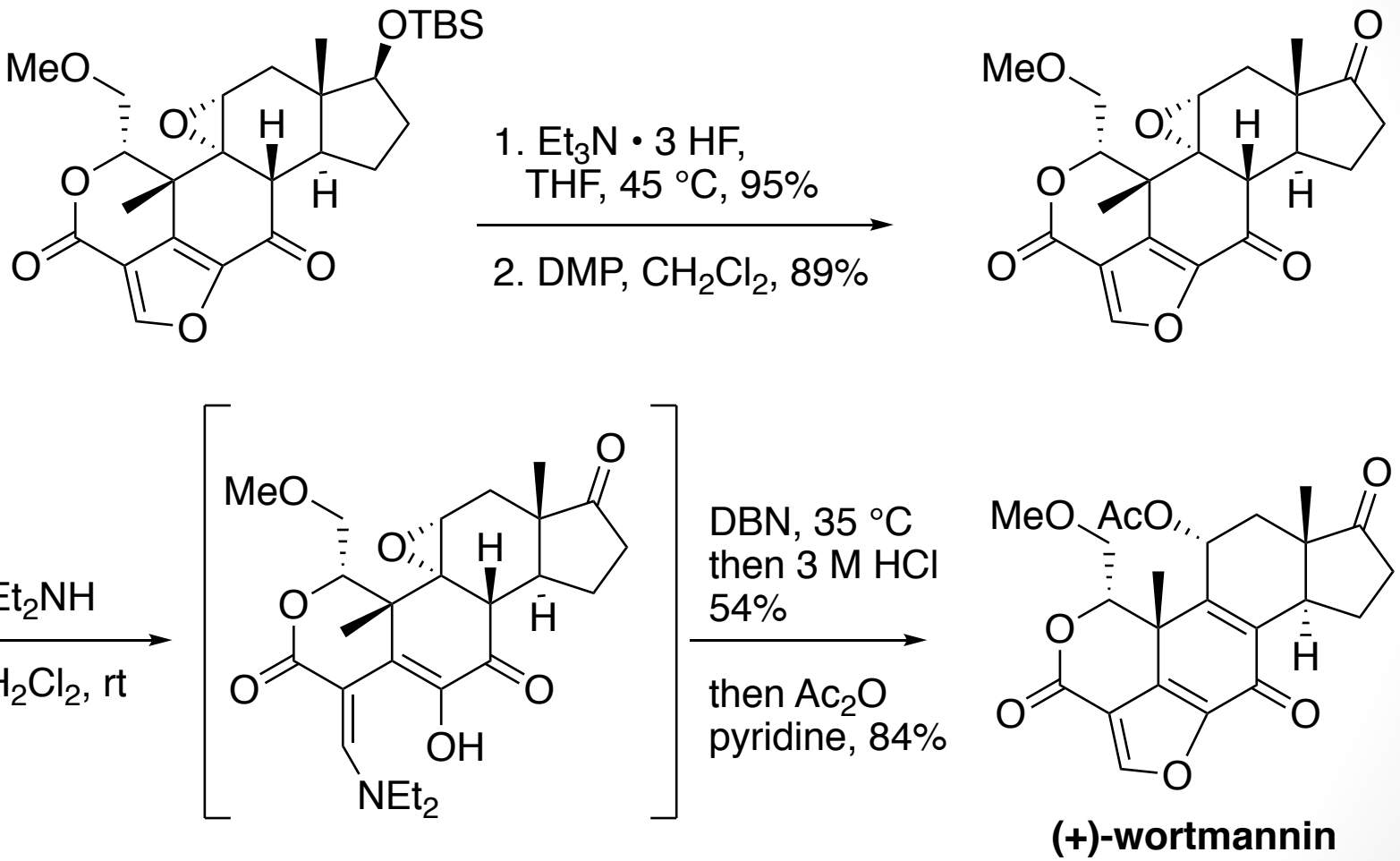
Intramolecular Friedel-Crafts



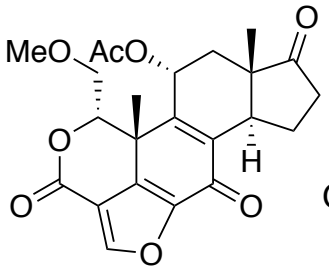
Oxidation Sequence



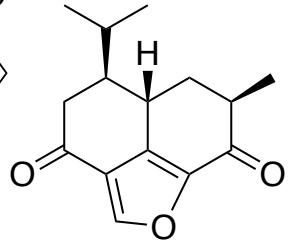
End Game



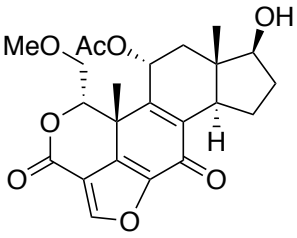
(+)-wortmannin

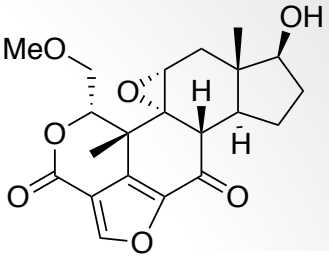


(+)-Wortmannin



(–)-Hibiscone C



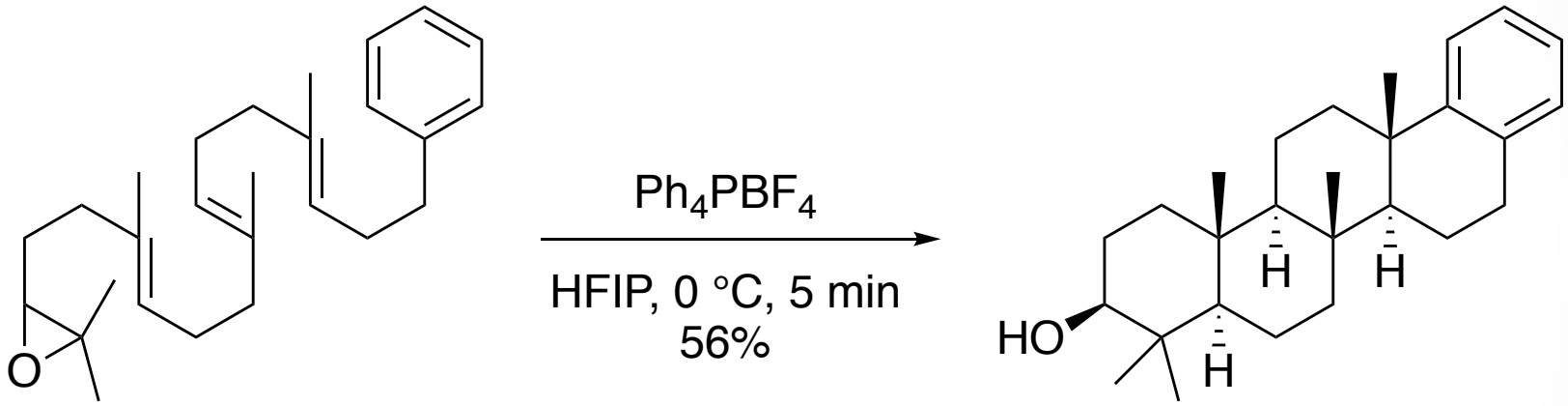


Kinases	(+)-**1**	(–)-**4**	(+)-**24**	(–)-**25**
p110α	8.0 ± 2.2	>100000	2.8 ± 0.6	420 ± 127
p110β	12.2 ± 1.7	N.D.	2.8 ± 0.5	74 ± 19
p110δ	21 ± 6.0	N.D.	10.1 ± 5.0	495 ± 173
p110γ	10.2 ± 2.1	N.D.	10.8 ± 5.7	215 ± 35
VPS34	14.2 ± 3.3	N.D.	7.7 ± 1.1	87 ± 12
p110α (E545K)	N.D.	N.D.	2.4 ± 0.6	384 ± 121
p110α (H1047L)	N.D.	N.D.	3.6 ± 0.5	172 ± 43
PI3K-C2β	N.D.	N.D.	39 ± 11	429 ± 194
PI4Kβ	N.D.	N.D.	99 ± 15	>10000
PLK1	N.D.	N.D.	74 ± 35	N.D.
PIP5K1A	N.D.	N.D.	>10000	>10000
CLK1	N.D.	N.D.	>10000	N.D.
CSNK1E	N.D.	N.D.	>10000	N.D.
CSNK1G3	N.D.	N.D.	>10000	N.D.
EGFR (G719C)	N.D.	N.D.	>10000	>10000
EGFR (L861Q)	N.D.	N.D.	N.D.	>10000
MST1	N.D.	N.D.	>10000	N.D.

[a] K_d ± SEM (nM) values were measured using KdELECT (DiscoverX).

Conclusions

- The total synthesis of (+)-wortmannin was completed in 21 steps and 0.4% overall yeild from the Hajos-Perrish ketone
- Key features include a novel Pd-mediated furan synthesis, intramolecular Friedel-Crafts alkylation, and late stage formal C-H oxidation
- Kinase profiling of synthetic wortmannin and related analogs was conducted



Tian, Y.; Xu, X.; Zhang, L.; Qu, J. *Org. Lett.* **2016**, *18*, 268-271.