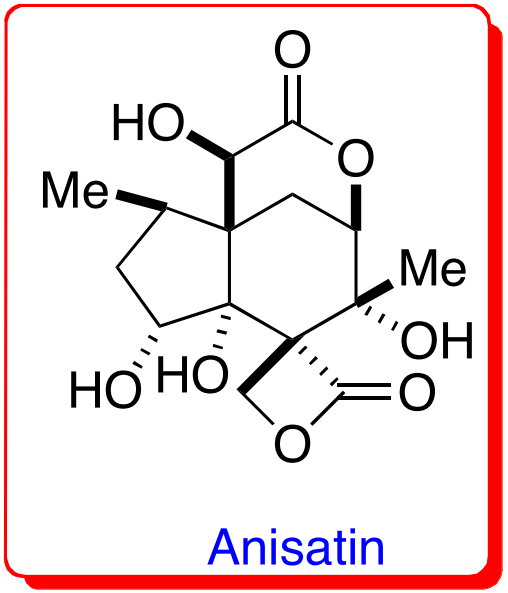
Total Synthesis of (-)-Anisatin

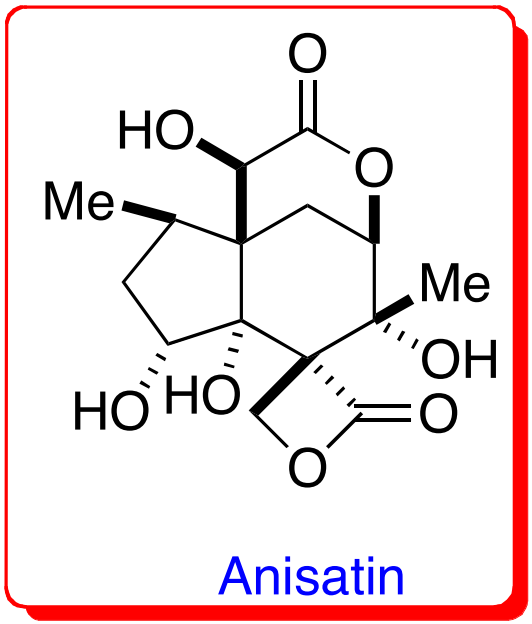


Ogura, A.; Yamada, K.; Yokoshima. S.; Fukuyama, T. *Org. Lett.* **2012**, *14*, 1632.

Dimas José da Paz Lima
Wipf's group - Current Literature
March 31, 2012

Anisatin - Isolation, Structure and Biological Active

*Anisatin was isolated as one of the toxic components of Japanese star anise (*Illicium anisatum*)

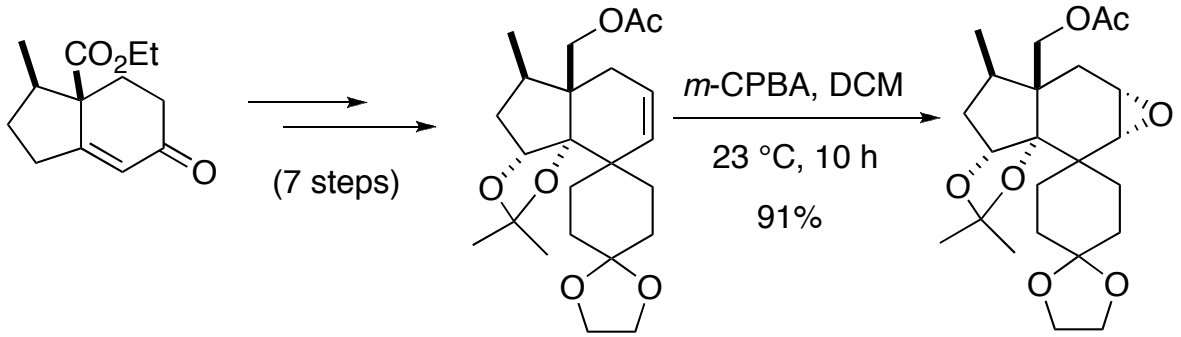


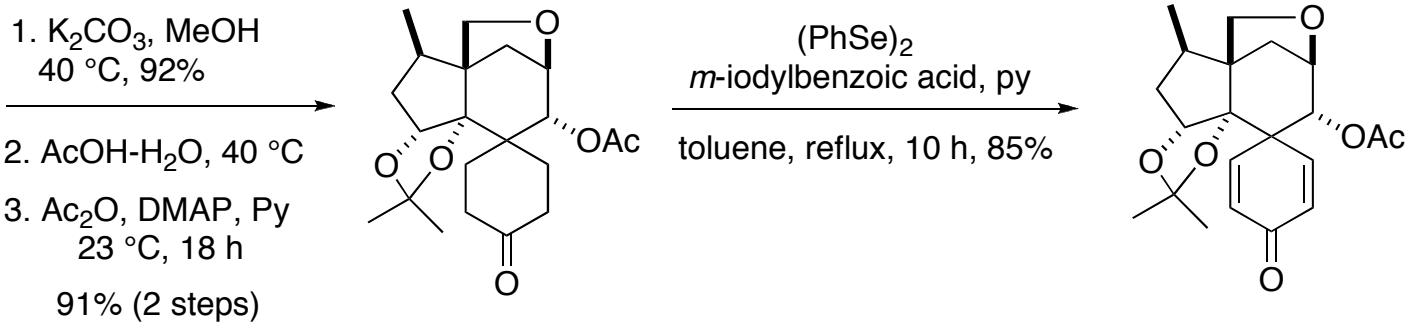
*8 Stereogenic centers
*Oxabicyclo[3.3.1]skeleton
*Spiro β-lactone

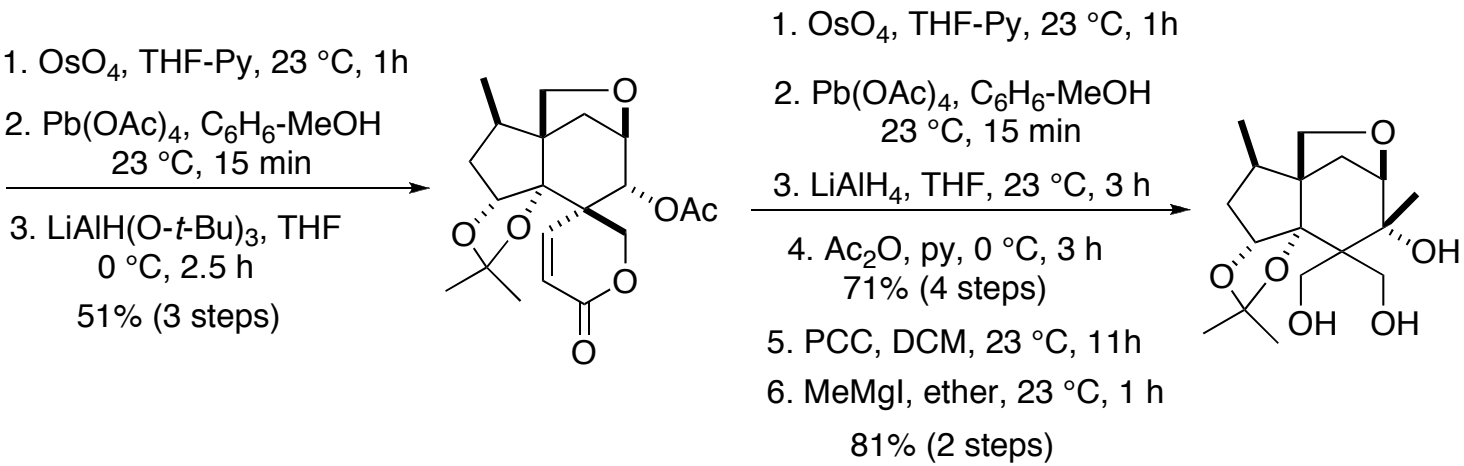
* Bioactivity as a strong GABA antagonist

1) Lane, J. F.; Koch, W. T.; Leeds, N. S.; Gorin, G. *J. Am. Chem. Soc.* **1952**, *74*, 3211.
2) Yamada, K.; Takeda, S.; Nakamura, S.; Hirata, Y. *Tetrahedron Lett.* **1952**, *74*, 3211.
3) Yamada, K.; Takeda, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199

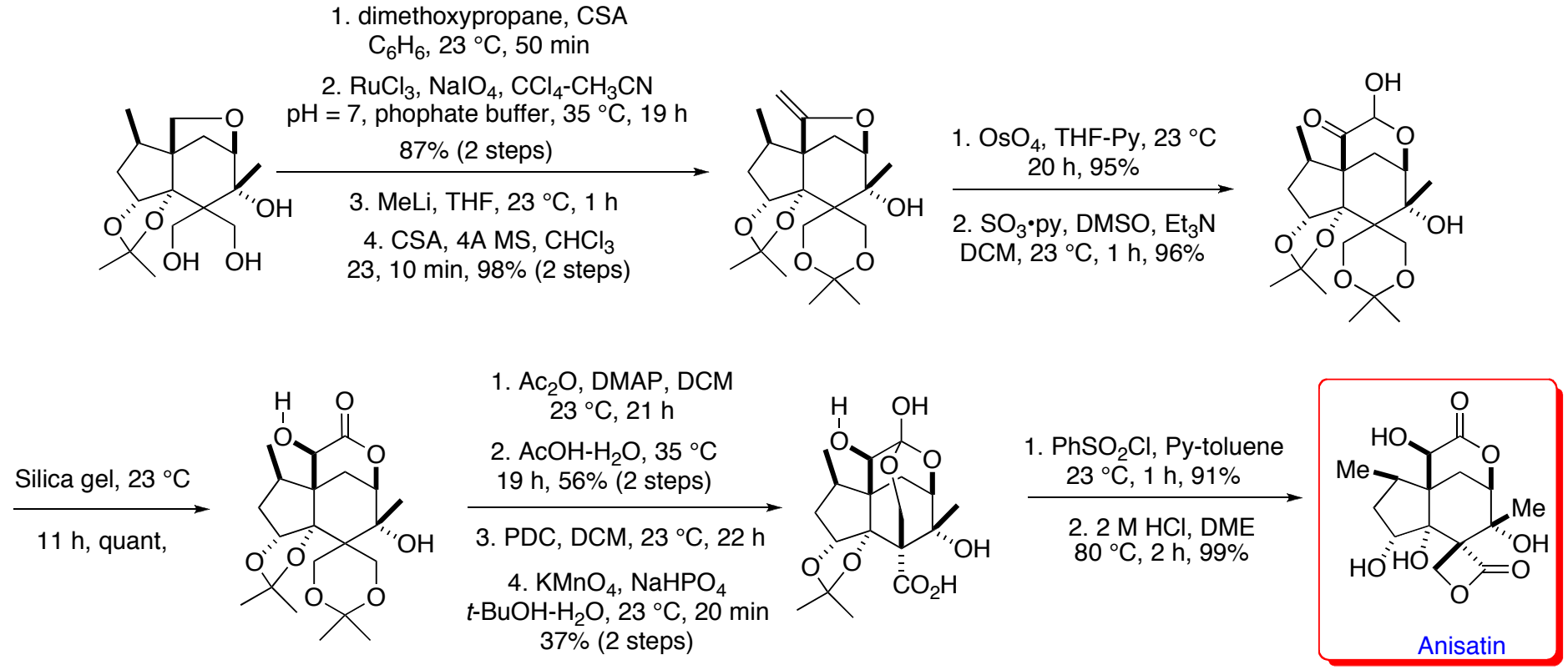
(-)-Anisatin: Niwa's Synthesis (1990)







(-)-Anisatin: Niwa's Synthesis (1990)

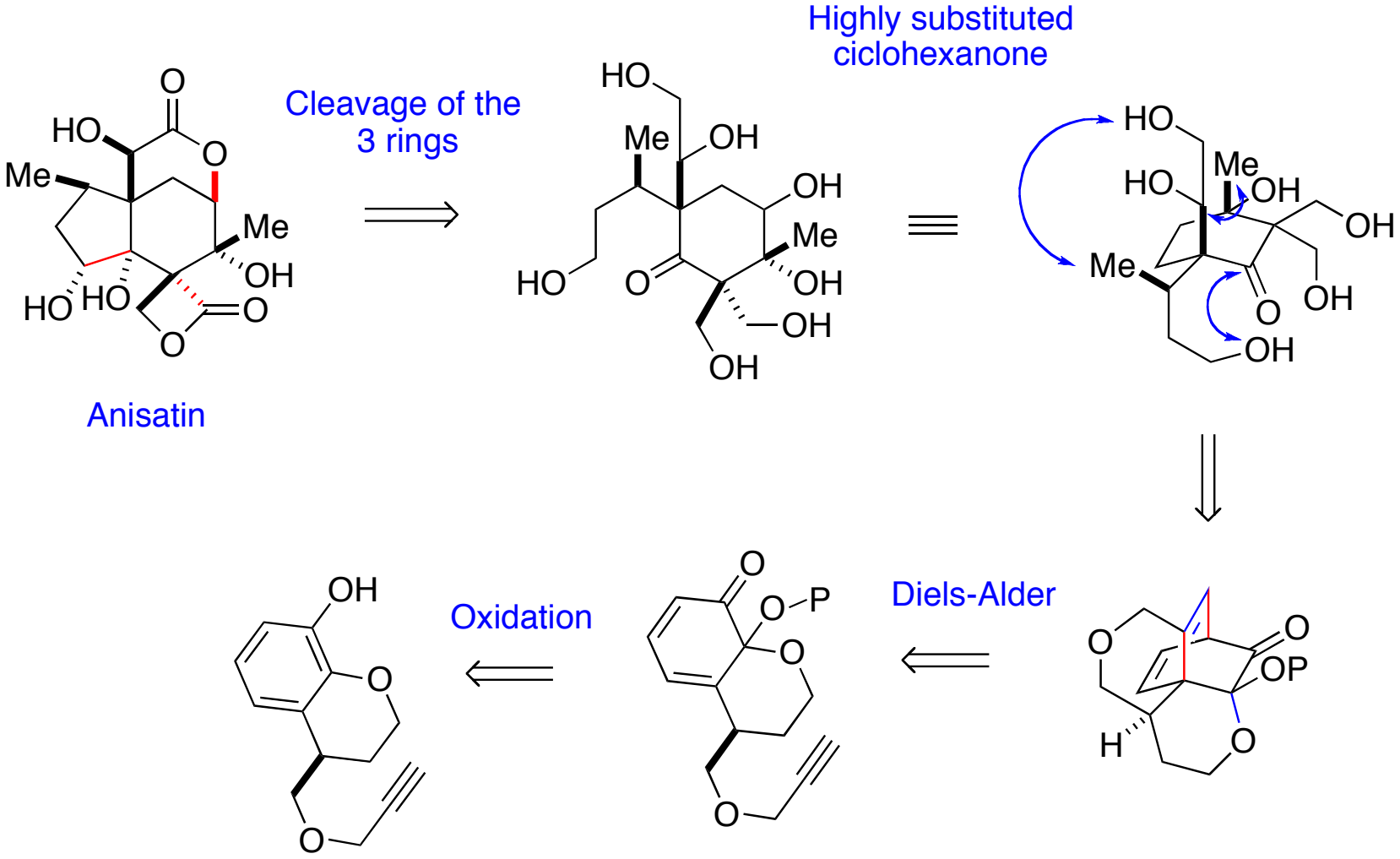


* 35 steps from commercially available material

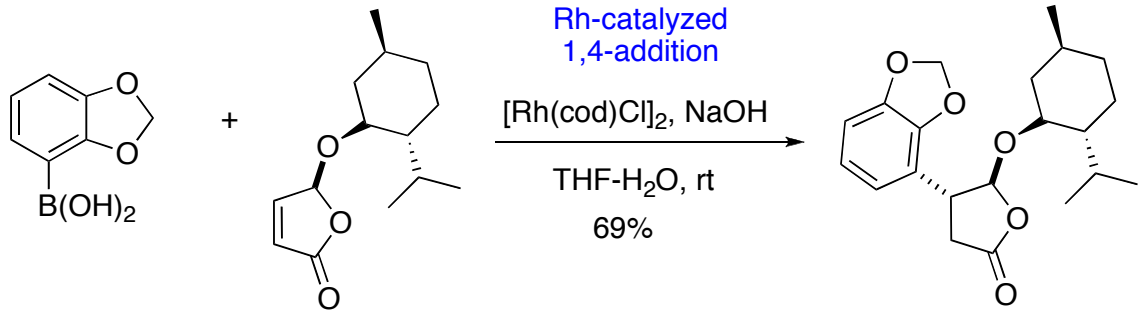
* 1.2% overall yield

Niwa, H.; Nisiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Mori, T.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001

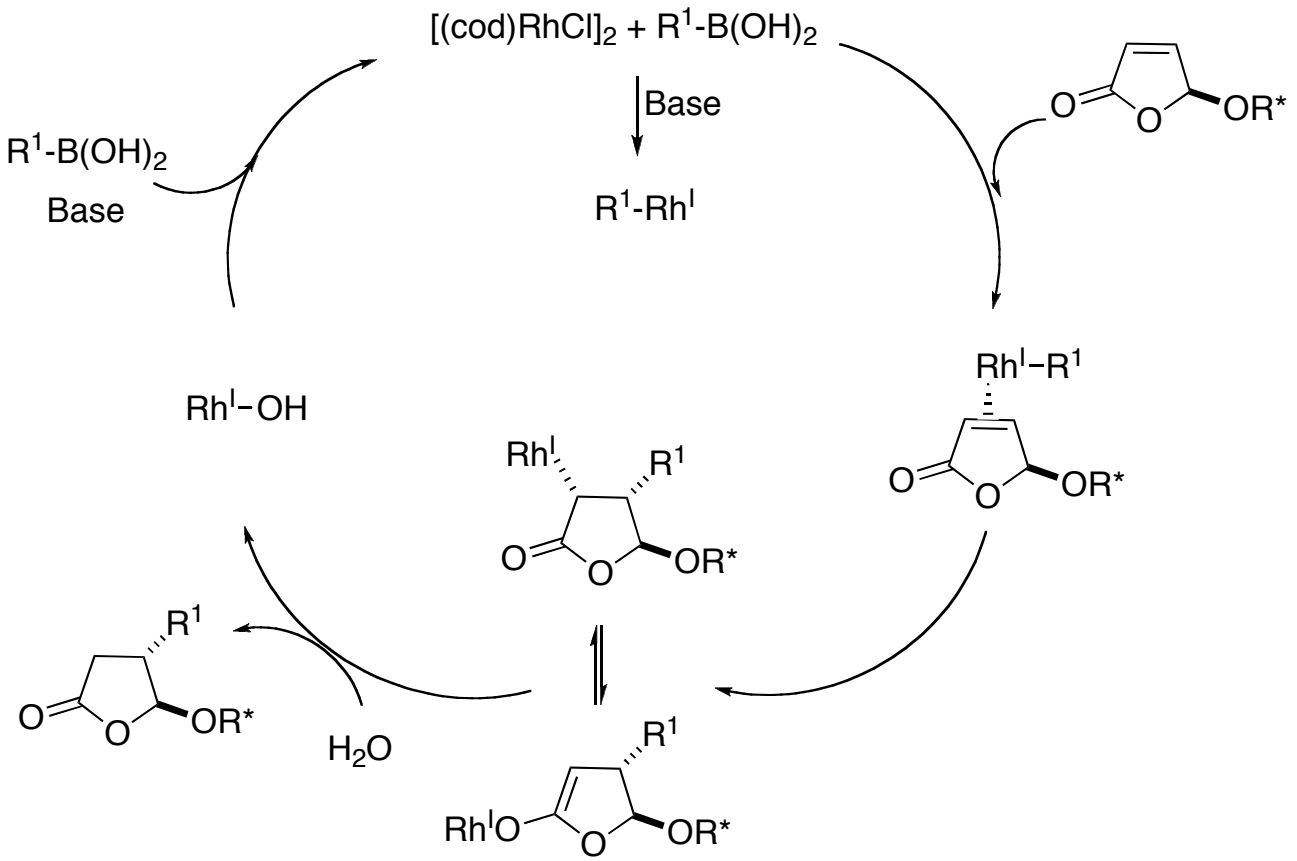
Title paper: Retrosynthesis



Synthesis of Phenol

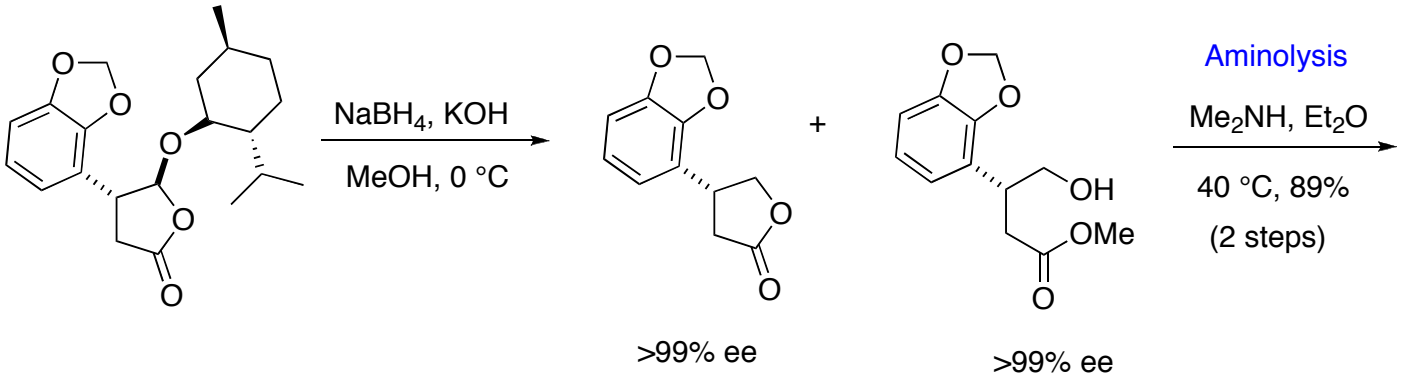


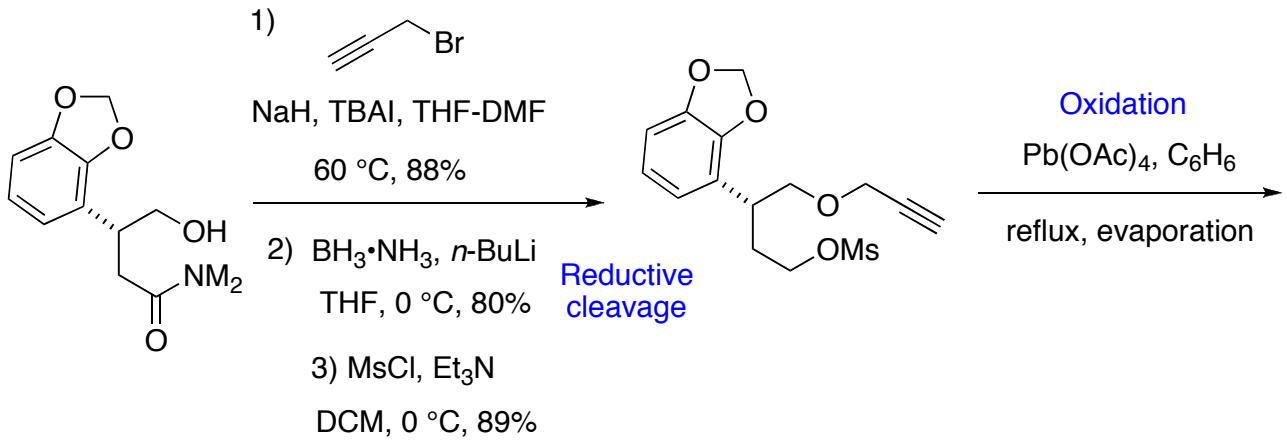
Proposed Mechanism

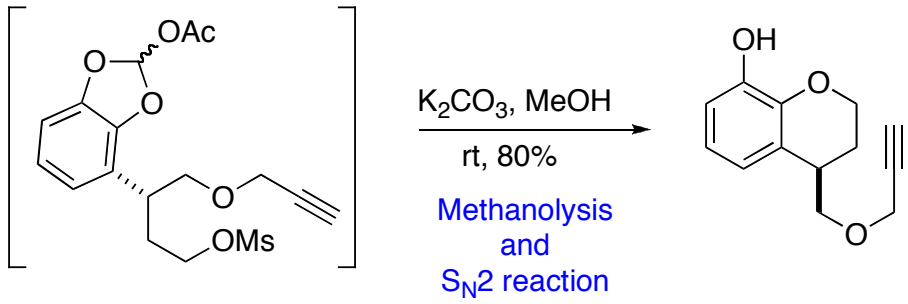


Navarro, C.; Moreno, A.; Csaky, A. G. *J. Org. Chem.* **2009**, *74*, 466

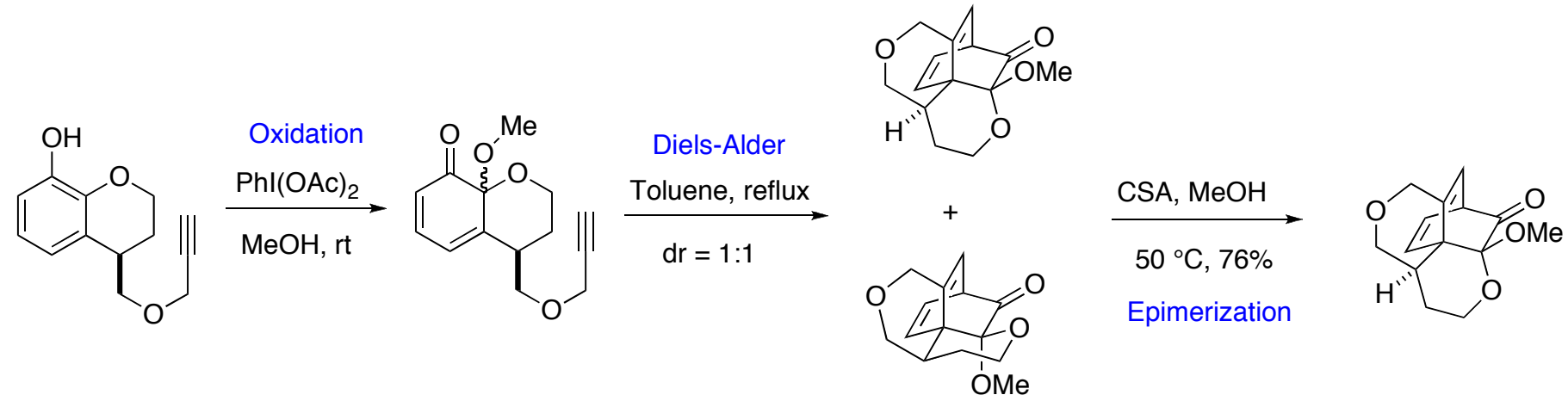
Synthesis of Phenol

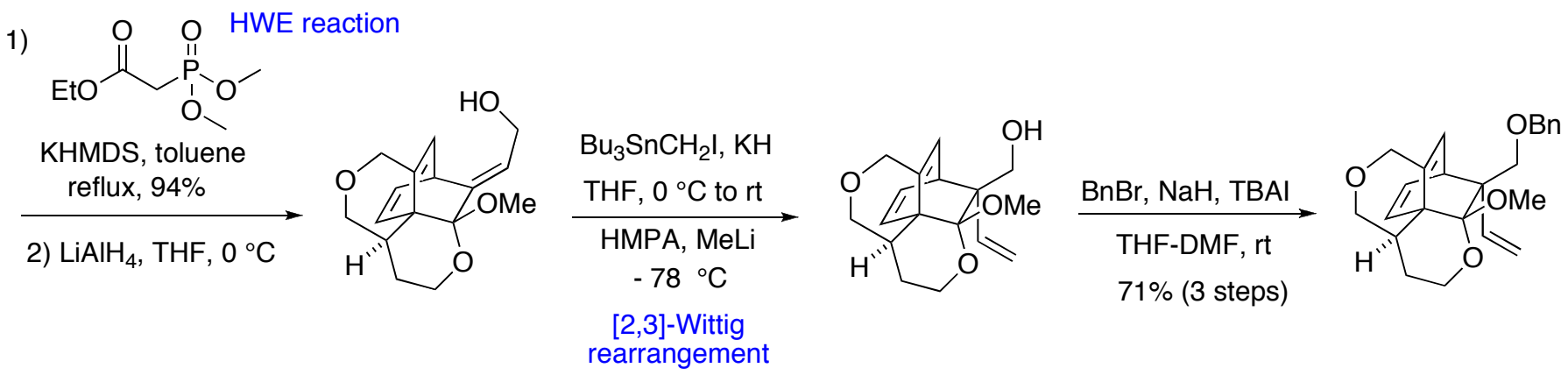




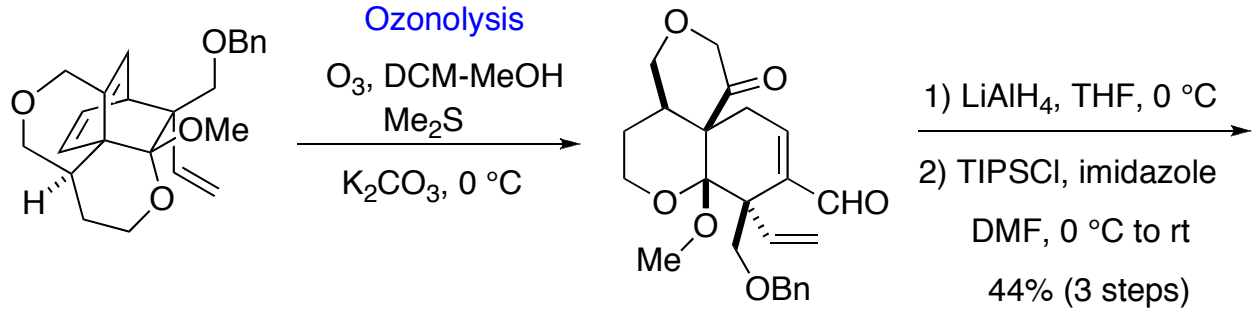


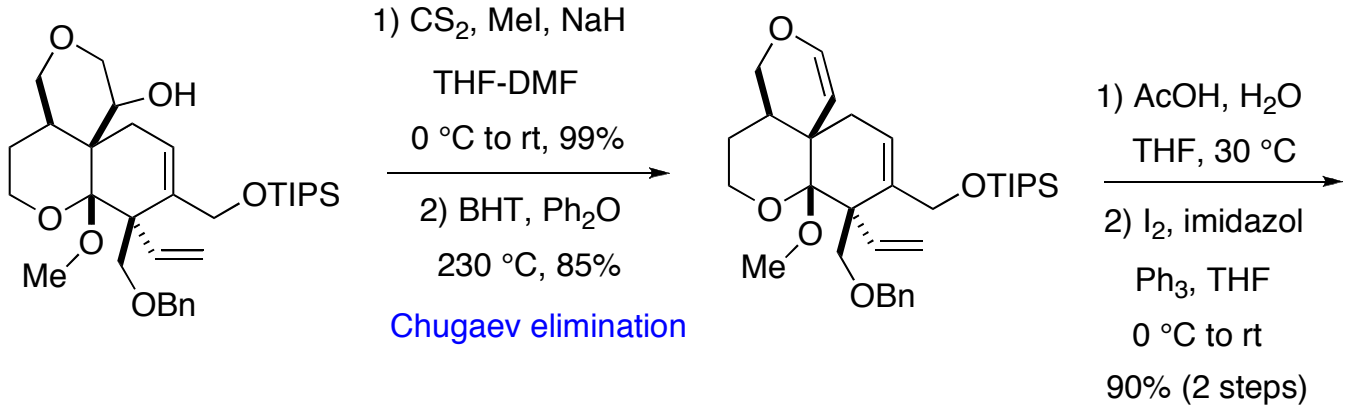
Construction of the Quaternary Stereogenic Centers

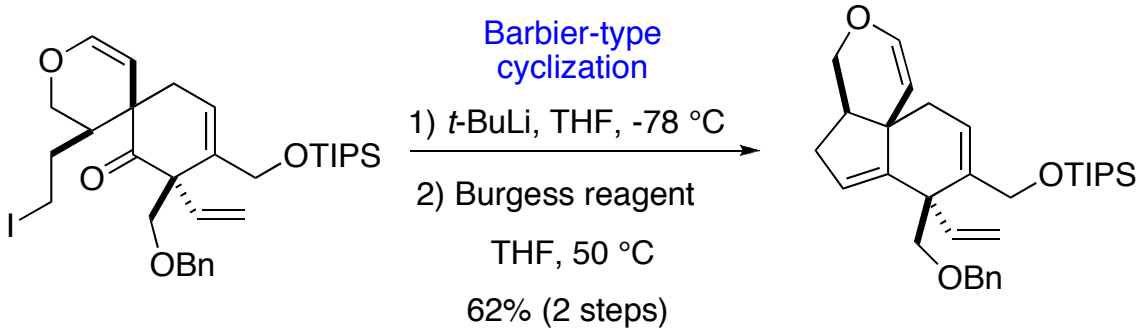




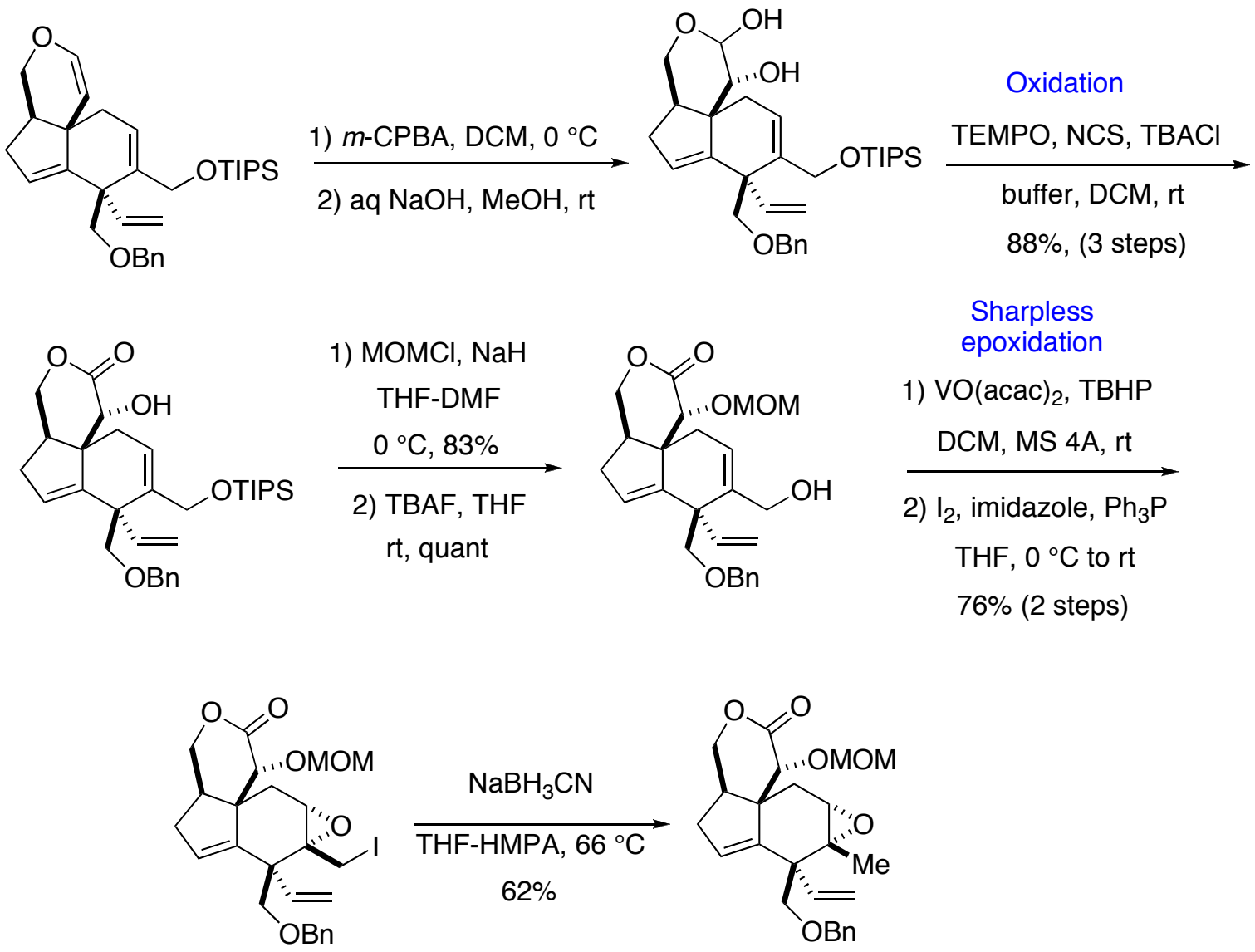
Construction of the Carbon Core of Anisatin



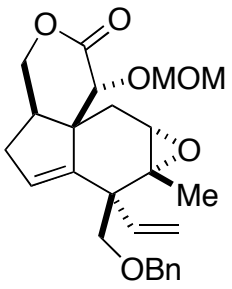




Introduction of the Oxygen Functionalities



Completion of the Synthesis

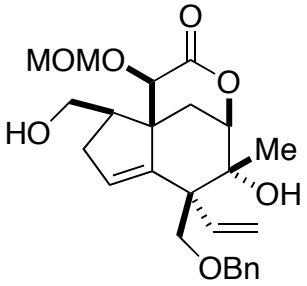


S_N2 reaction

aq NH_3, MeOH, 65 °C

aq HCl, EtOAc, 0 °C

85%



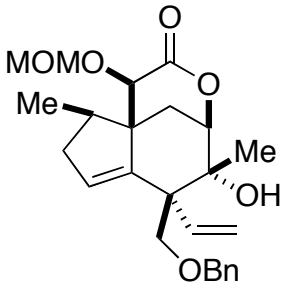
Radical-deoxiganation

1) ClC(S)OPh, Pyridine

MeCN, 0 °C, 89%

2) Bu_3SnH, AIBN

Toluene, 100 °C, quant.



1) MOMCl, NaI, *i*-Pr_2NEt

DME, reflux, 91%

2) O_3, Cl_2CHCH_3

-95 °C, Me_2S

Ozonolysis

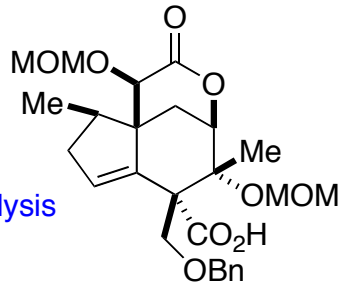
3) $NaClO_2$, NaH_2PO_4

2-methyl-2-butene

t-BuOH-H_2O, rt

73% (2 steps)

Pinnick oxidation



Hydrogenolysys

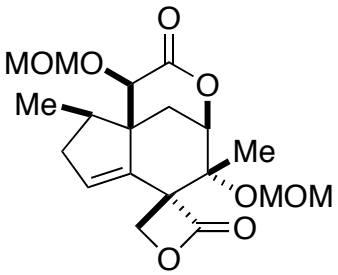
1) H_2, $Pd(OH)_2/C$

$NaHCO_3$, MeOH, rt, 97%

Lactonization

2) MNBA, DMAP

Toluene, rt, 90%

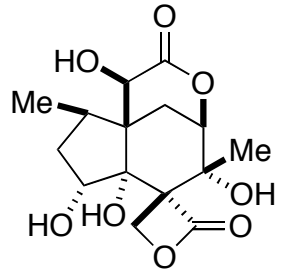


1) aq HCl, THF, 40 °C, 91%

Dihydroxylation

2) OsO_4, pyridine, rt, 58%

3) aq HCl, MeOH, 70 °C, 80%



Anisatin

Summary and Outlook

*Anisatin was synthesized in 40 steps in 0.23% overall yield

*Key transformations include:

-Intramolecular Diels-Alder reaction
-Stereosective [2,3]-Wittig rearragement
-Regioselective cleavage of the trisubstitued double bond
-Construction of the oxabicyclo[3.3.1] skeleton via cleavage by primary amide