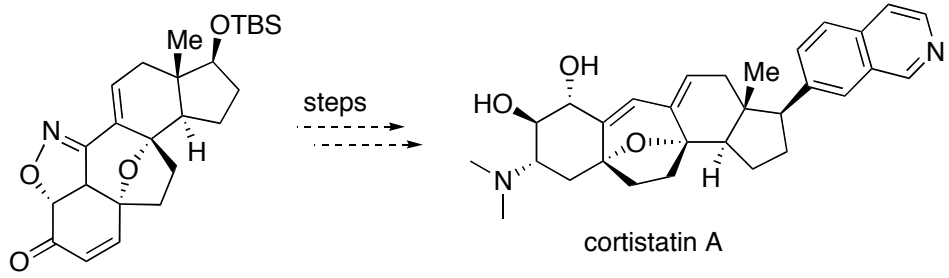
Approaches to the Core of Cortistatin A:

A Hypervalent Iodine-Induced Double Annulation Enables a Concise Synthesis of the Pentacyclic Core Structure of the Cortistatins

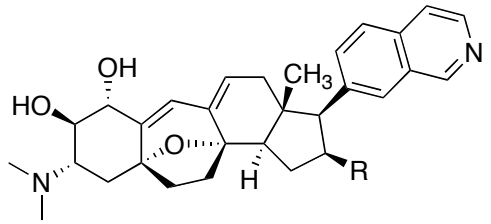


Frie, J. L.; Jeffery, C. S.; Sorensen, E. J. *Org. Lett.* **2009,** *ASAP*

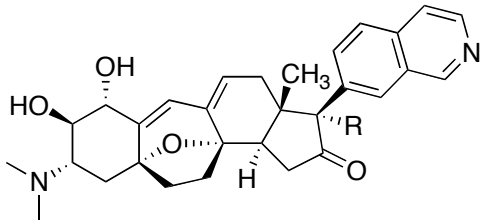
John Maciejewski
Wipf Group - Current Literature

14 November 2009

Isolation and Biological Activity



cortistatin A : R = H
cortistatin B : R = OH



cortistatin C : R = H
cortistatin D : R = OH

Cortistatin A

1 of 11 rearranged steroidal alkaloids isolated from marine sponge *Corticium simplex*

Inhibitor of angiogenesis - potential antitumor agent

Potent - IC_{50} of 1.8 nM for human umbilical vein endothelial (HUVEC) cells

Suppresses HUVEC cell growth - cytostatic; mechanism is unknown

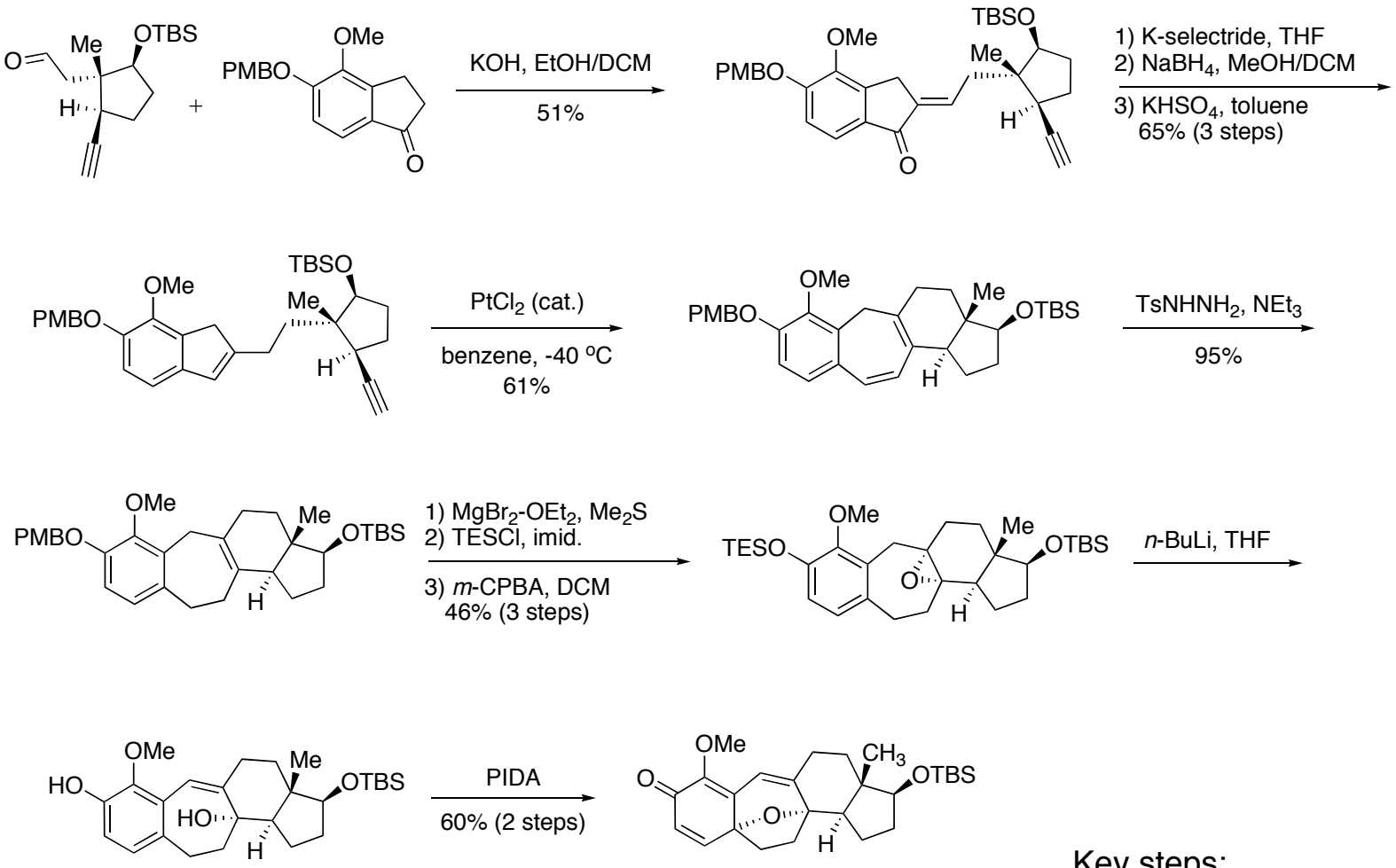
Structure determined by MS, 2D NMR (COSY, HMQC, HMBC) analysis, and X-ray

Three total syntheses of cortistatin A completed

Others focus on methodologies to prepare core of molecule

J. Am. Chem. Soc. **2006**, *128*, 3148

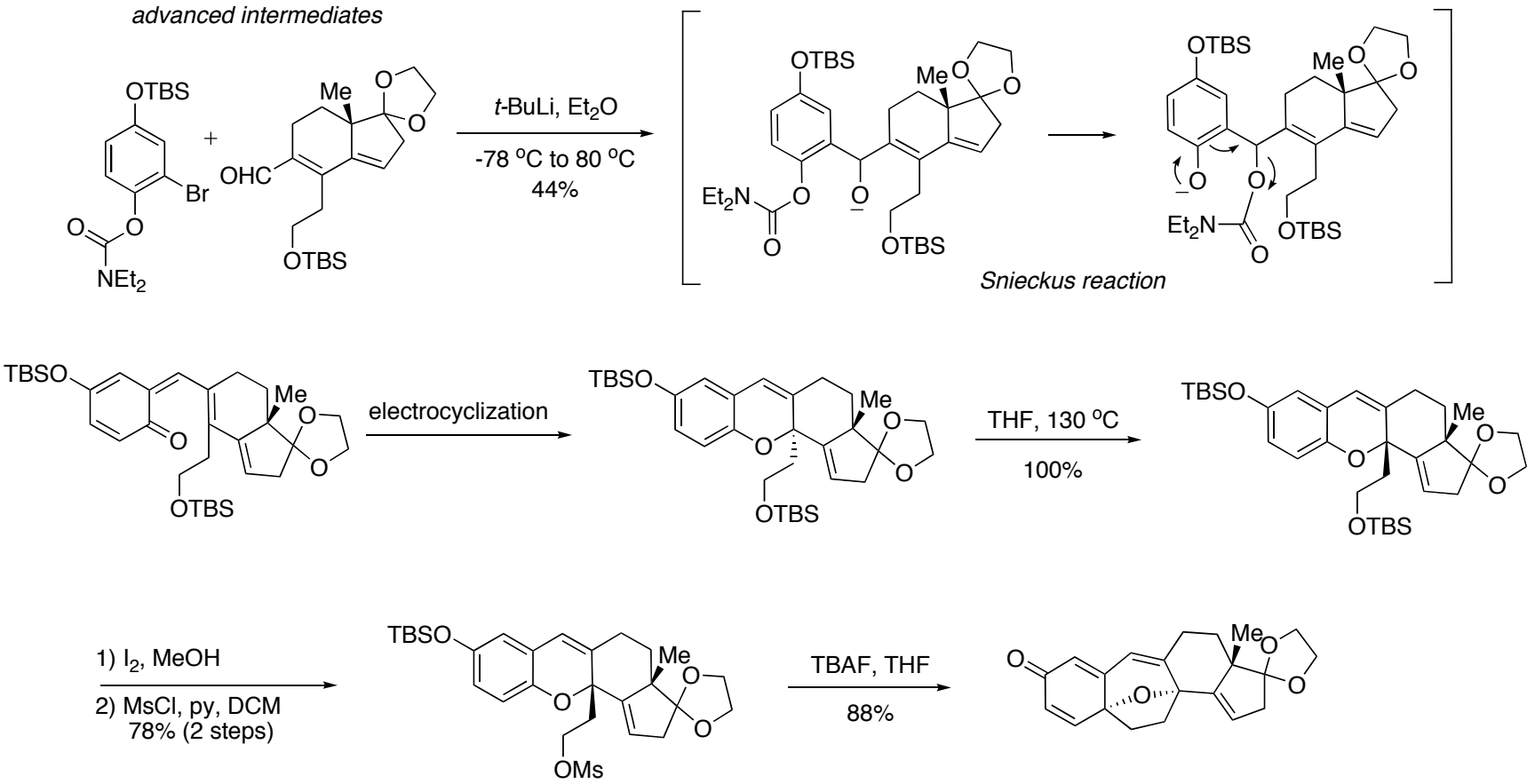
Sarpong Group - Core Approach



Key steps:
$PtCl_2$ catalyzed enyne cycloisomerization
oxidative dearomatization/ether formation

Angew. Chem. Int. Ed. **2008**, *47*, 6650

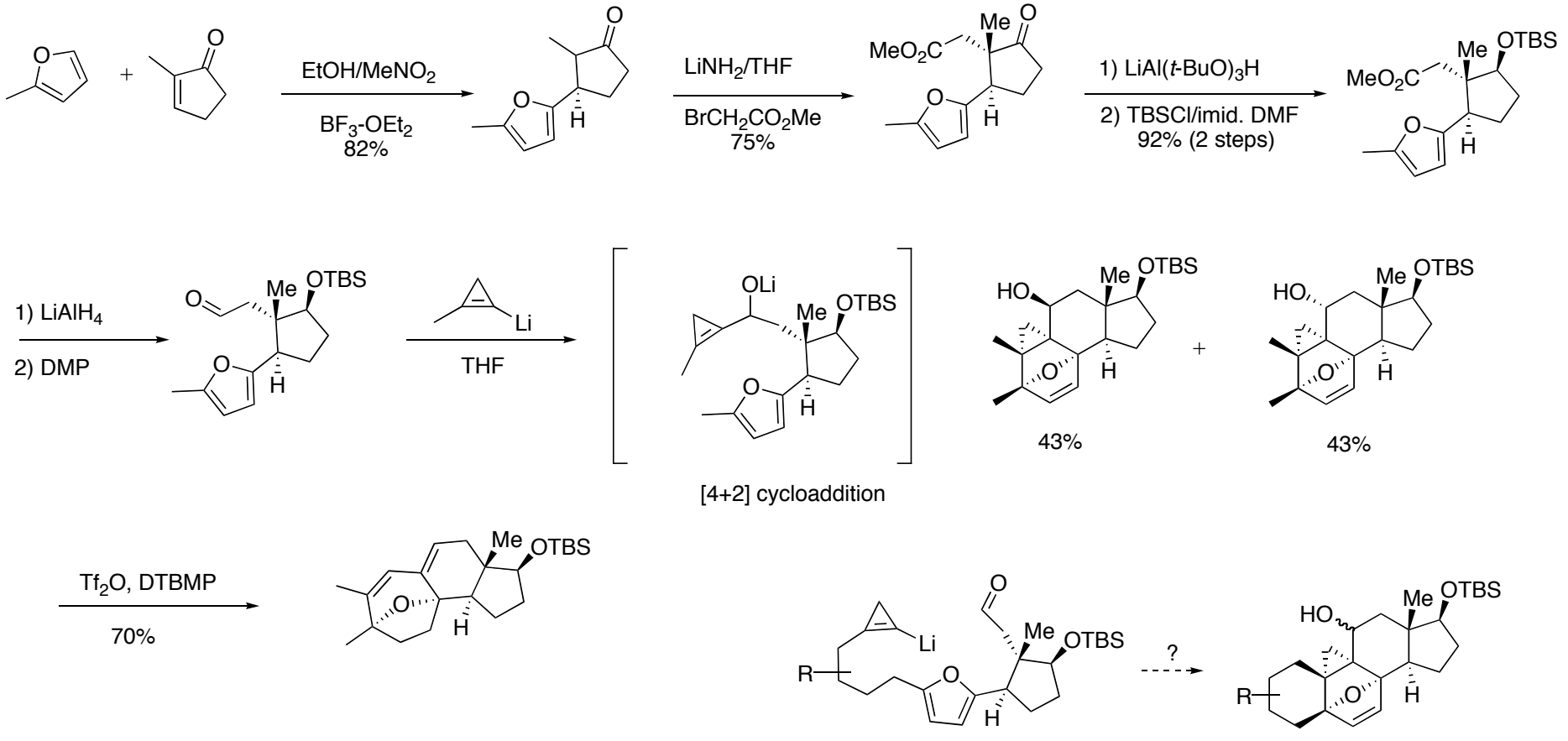
Danishefsky Group - Core Approach



Key steps:
retro-6π-electrocyclization/epimerization
alkylative de-aromatization

Tetrahedron Lett. **2008,** *49*, 6610

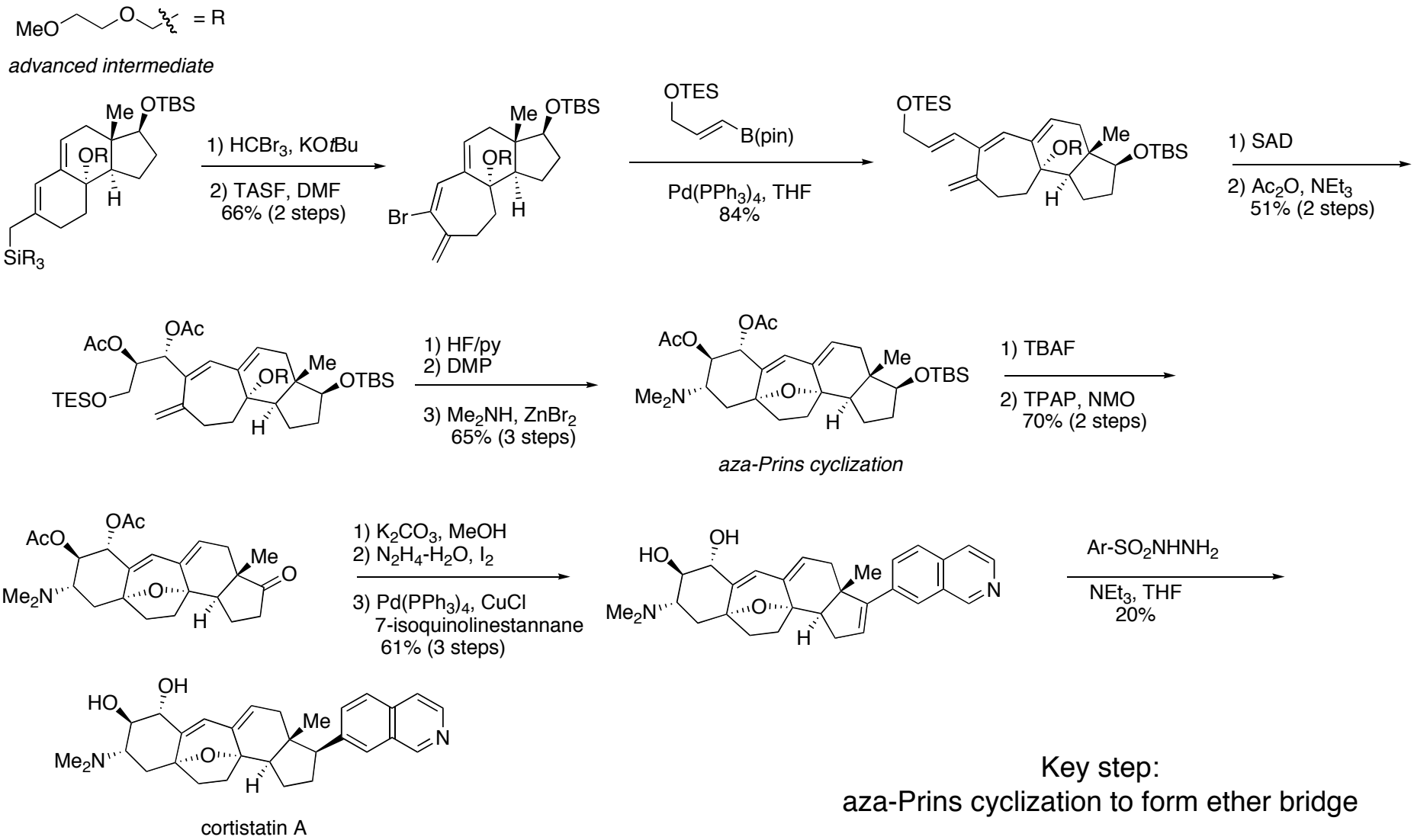
Magnus Group - Core approach



Org. Lett. **2009**, *11*, 3938

Key steps:
[4+2] cycloaddition
ionization/ring expansion

Shair Lab - *Enantioselective Total Synthesis*

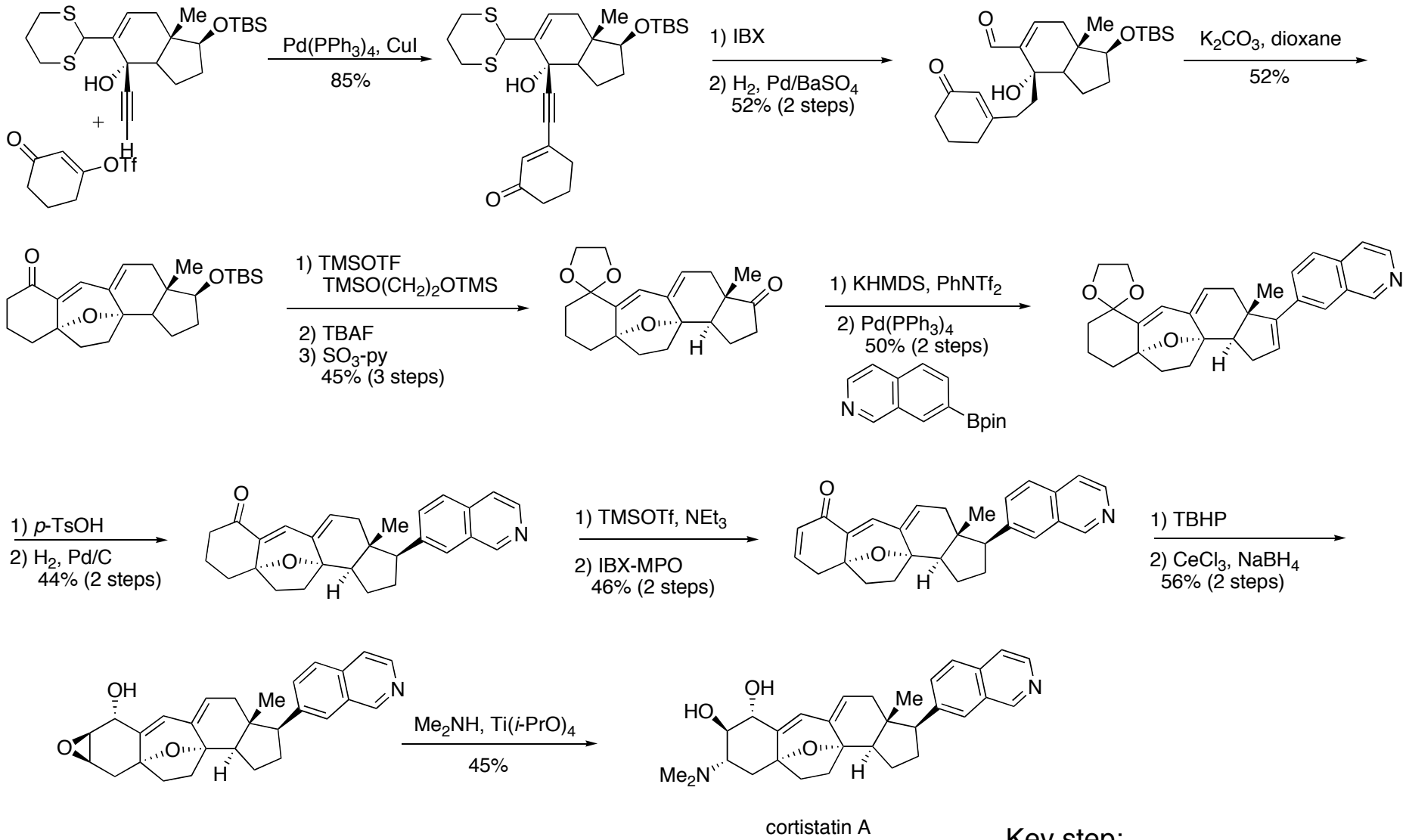


Key step:
aza-Prins cyclization to form ether bridge

J. Am. Chem. Soc. **2008**, *130*, 16864

Nicolaou Lab- *Enantioselective Total Synthesis*

advanced intermediate

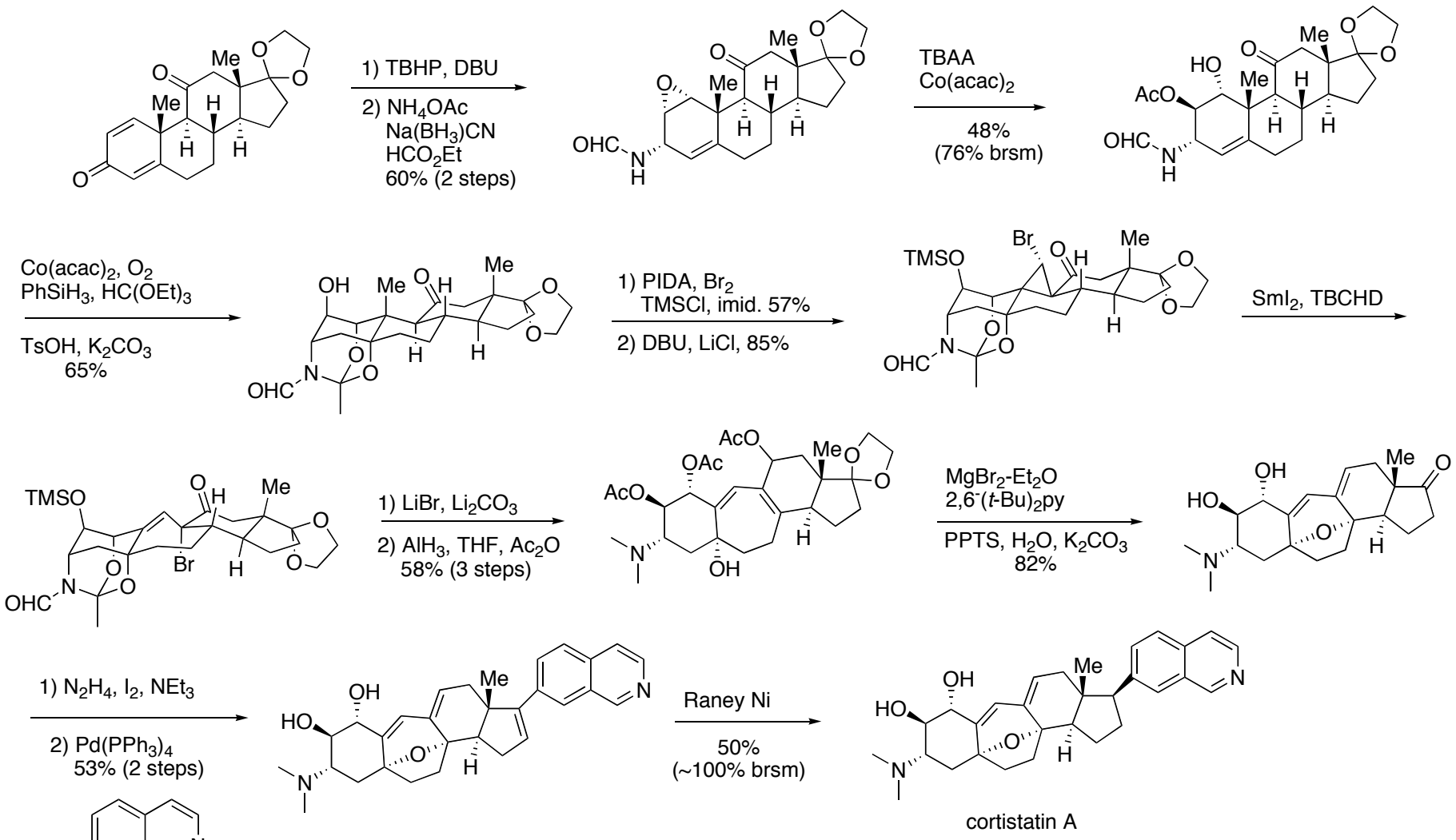


cortistatin A

Angew. Chem. Int. Ed. **2008**, *47*, 7310

Key step:
1,4-addition / aldol / dehydration cascade

Baran Lab - *Enantioselective Total Synthesis*



J. Am. Chem. Soc. **2008**, *130*, 7241

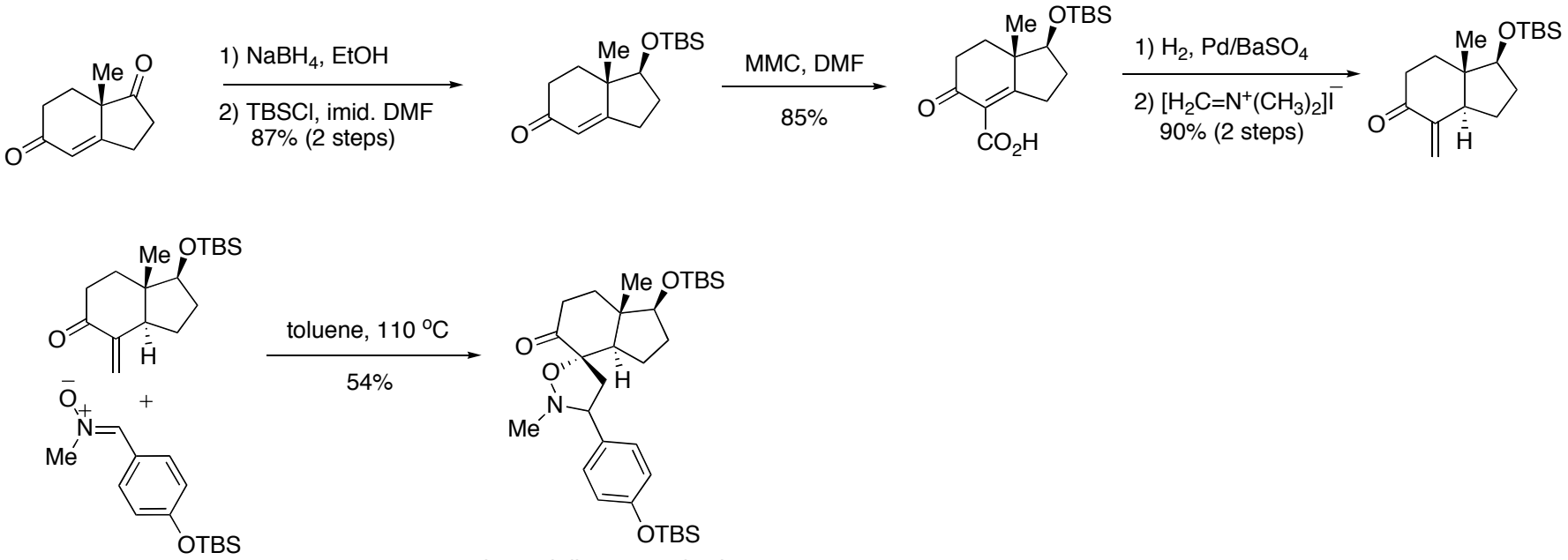
Key steps:

Steroid ($1.20/g) as starting material, contains 70% of carbon atoms

Geminal dihalogenation of unactivated hydrocarbon

Oxidative Cyclodearomatization/[3+2] Cycloaddition

Title Paper

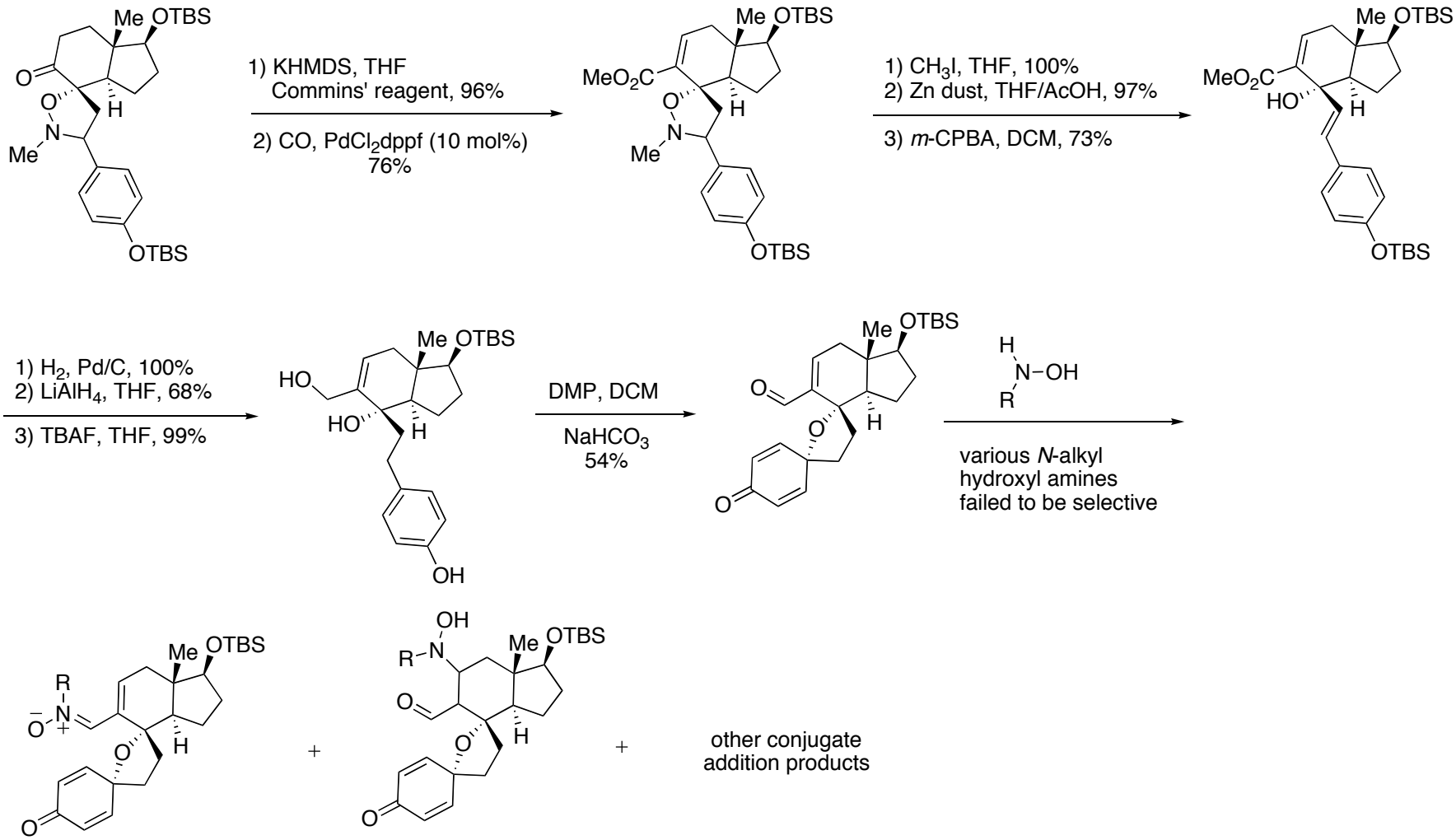


regio- and diastereoselective

Org. Lett. **2009,** *ASAP*

Oxidative Cyclodearomatization/[3+2] Cycloaddition

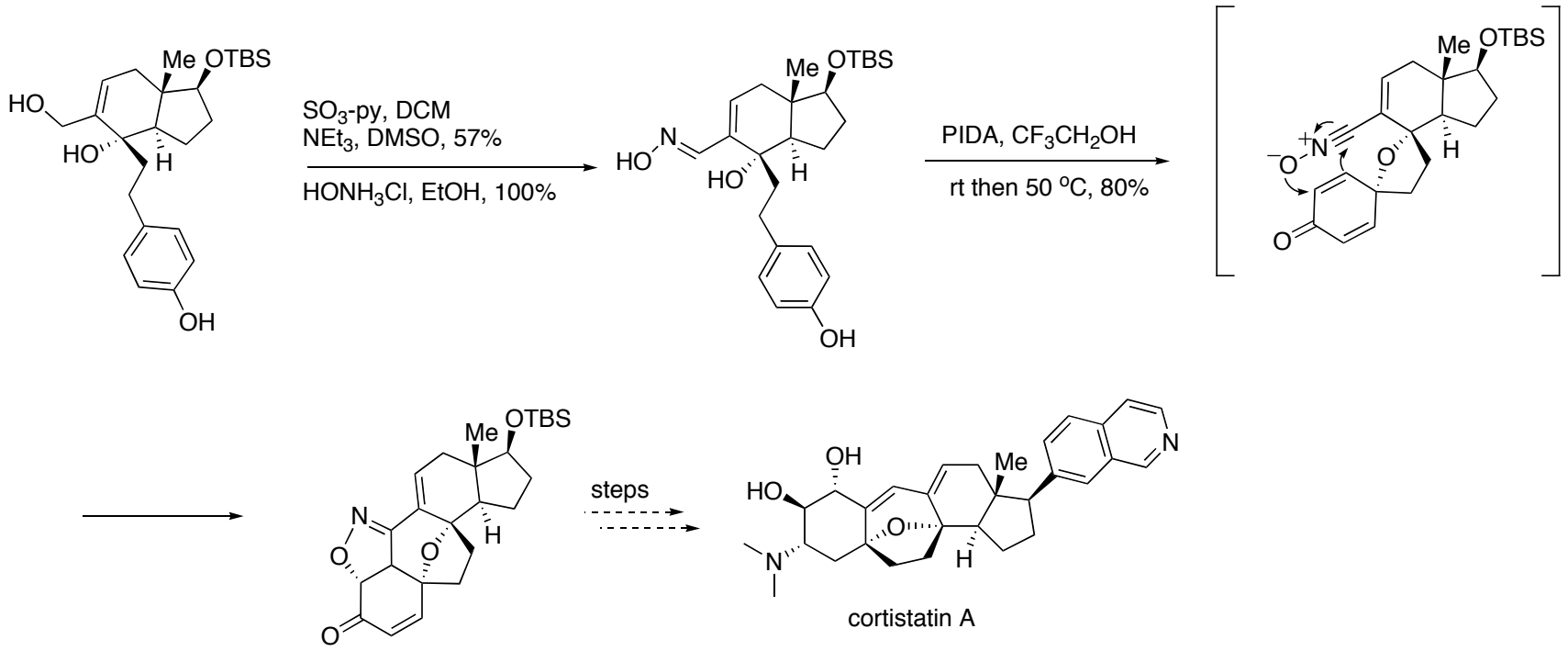
Title Paper



Org. Lett. **2009,** *ASAP*

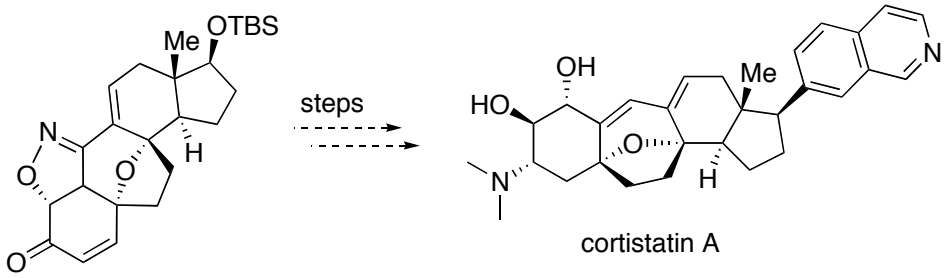
Oxidative Cyclodearomatization/[3+2] Cycloaddition

Title Paper



Org. Lett. **2009,** *ASAP*

Summary



Use of an oxidative cyclodearomatization/[3+2] cycloaddition to prepare cortistatin core

Baran, Nicolaou, and Shair have synthesized cortistatin A

Other laboratories continue to investigate methodologies to prepare cortistatin core