Total Syntheses of Heimiol A, Hopeahainol D, and Constrained Analogues

Scott A. Snyder, Nathan E. Wright, Jason J. Pflueger, and Steve P. Breazzano

ACIE Early View

Presented by: Jared Hammill

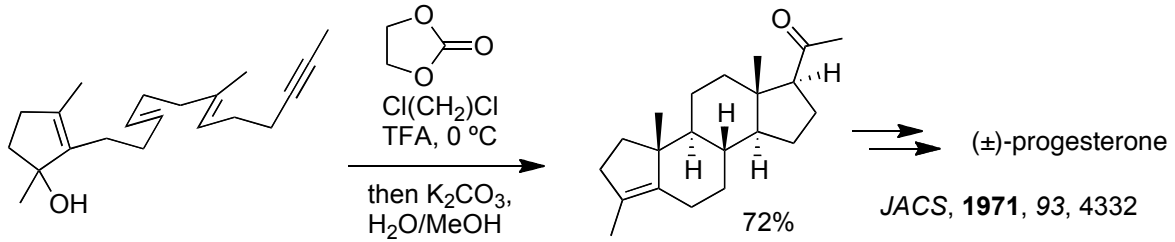
The Synder Group

- Scott A. Snyder
  - Undergrad @ Williams college
  - Grad school @ Scripps under K.C. Nicolaou
    - 18 papers, 2 book chapters, 1 Book: Classics II
  - Post-doc @ Harvard under E.J. Corey
  - Currently @ Columbia as an Associate Professor of chemistry, without tenure
- Research Focus: Target-Driven Discovery
  - Halonium-Induced polyene cyclization

http://www.columbia.edu/cu/chemistry/groups/snyder/index2.htm

Halonium Induced Cyclizations

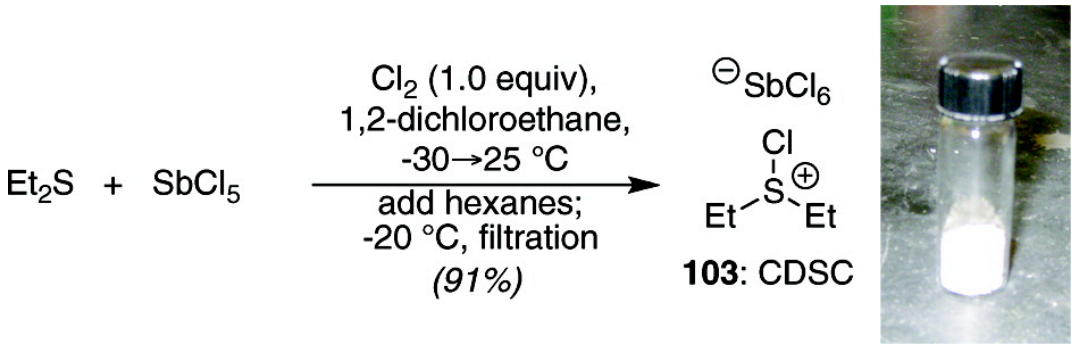
- Goal
  - Expand polyene cation-π cascades to include halogen initiators

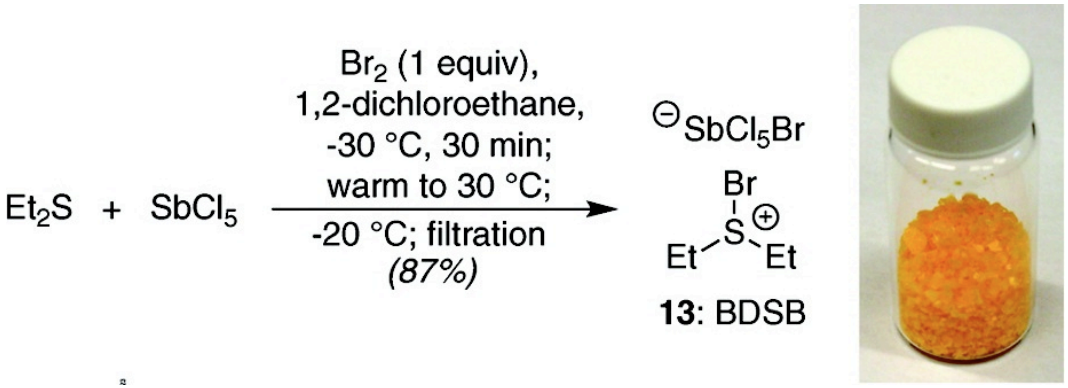


  - Need better synthetic variant of haloperoxidases
  - Current problems:
    - Olefin selectivity
    - Poor reactivity with unactivated aromatic systems
    - Aromatic halogenation

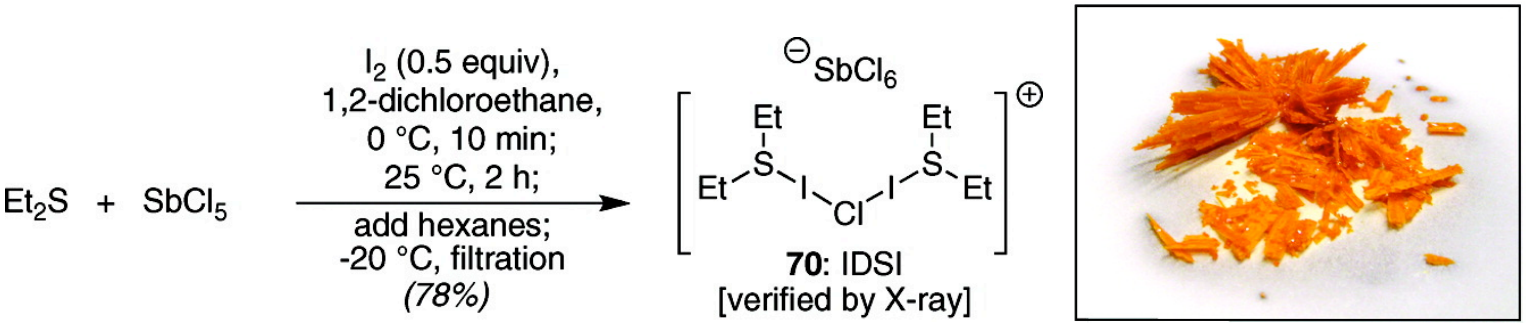
Review of pi-cation cascades: *Chem. Rev.* **2005**, *105*, 4730

New & Simple Reagents



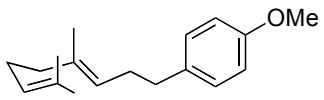
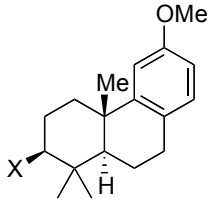
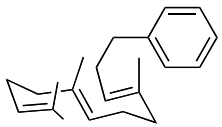
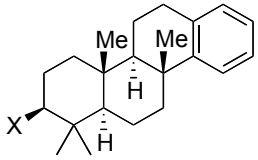
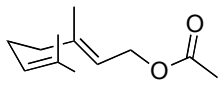
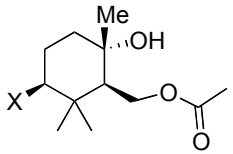
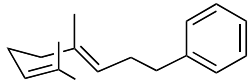
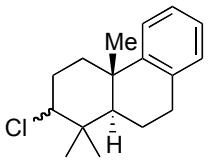
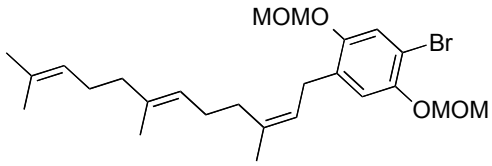
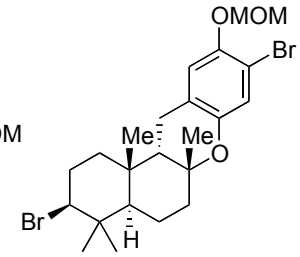


- Stable >1 yr @ -20 ºC
- Air stable for weighing
- Scalable >100 g



JACS, **2010**, *132*, 14303

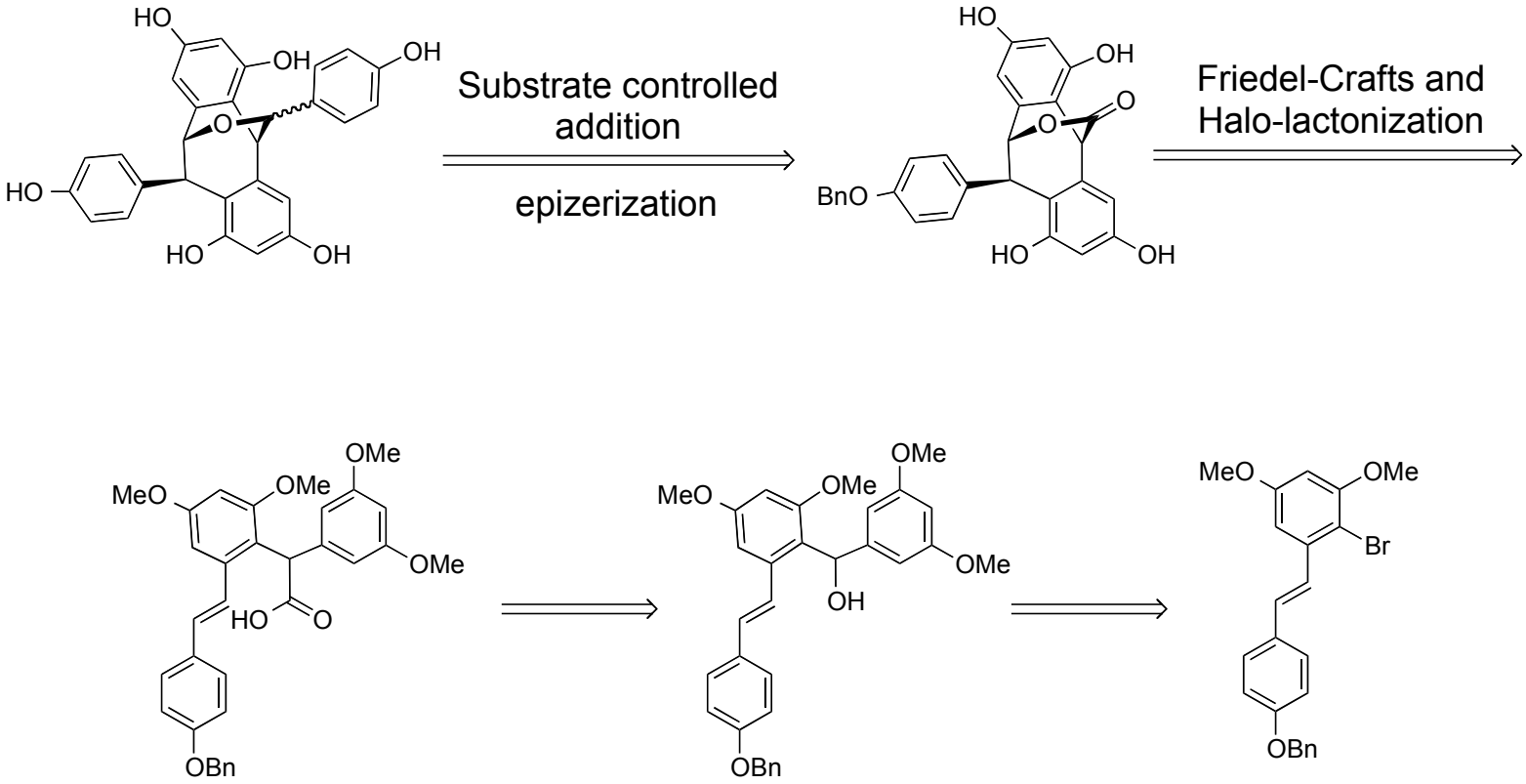
Applications

Starting Material	Product	Temp (ºC)	Time (min)	yield
		25	5	X= Br (73%) X=I (90%)
		-25	5	X= Br (76%) X= I (60%)
		0	1	X= Br (80%) X= I (45%) X= Cl (18%)
		-25	5	46% (1:1 mix)
		-25	5	42%

precursor to peyssonic acid A

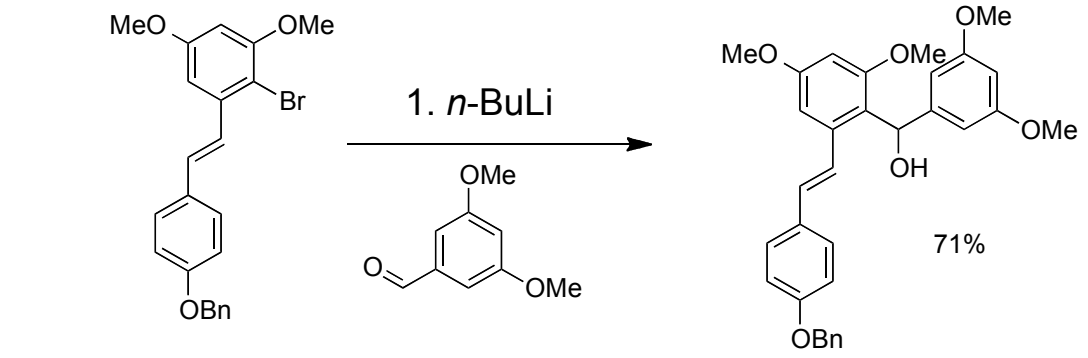
ACIE, **2009**, *121*, 7899 *JACS*, **2010**, *132*, 14303
Tet, **2010**, *66*, 4796 *ACIE*, **2010**, *49*, 5146

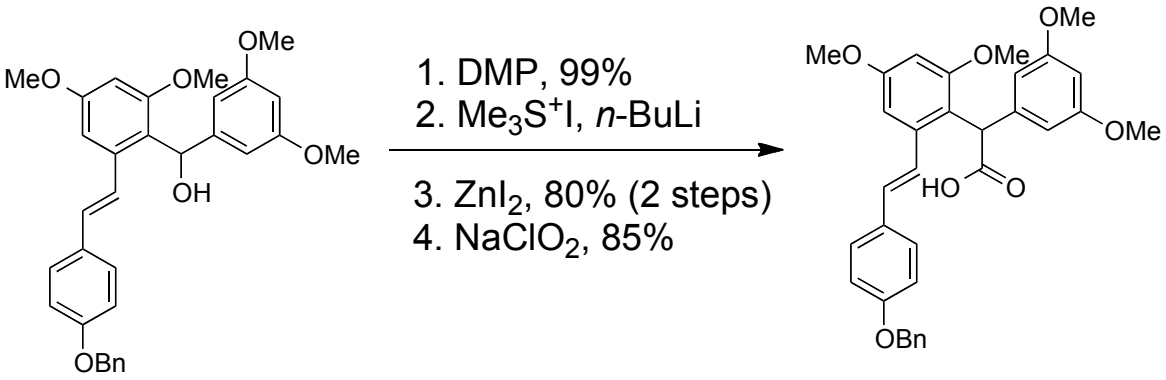
Title Paper



ACIE, **2011**, *50*, early view

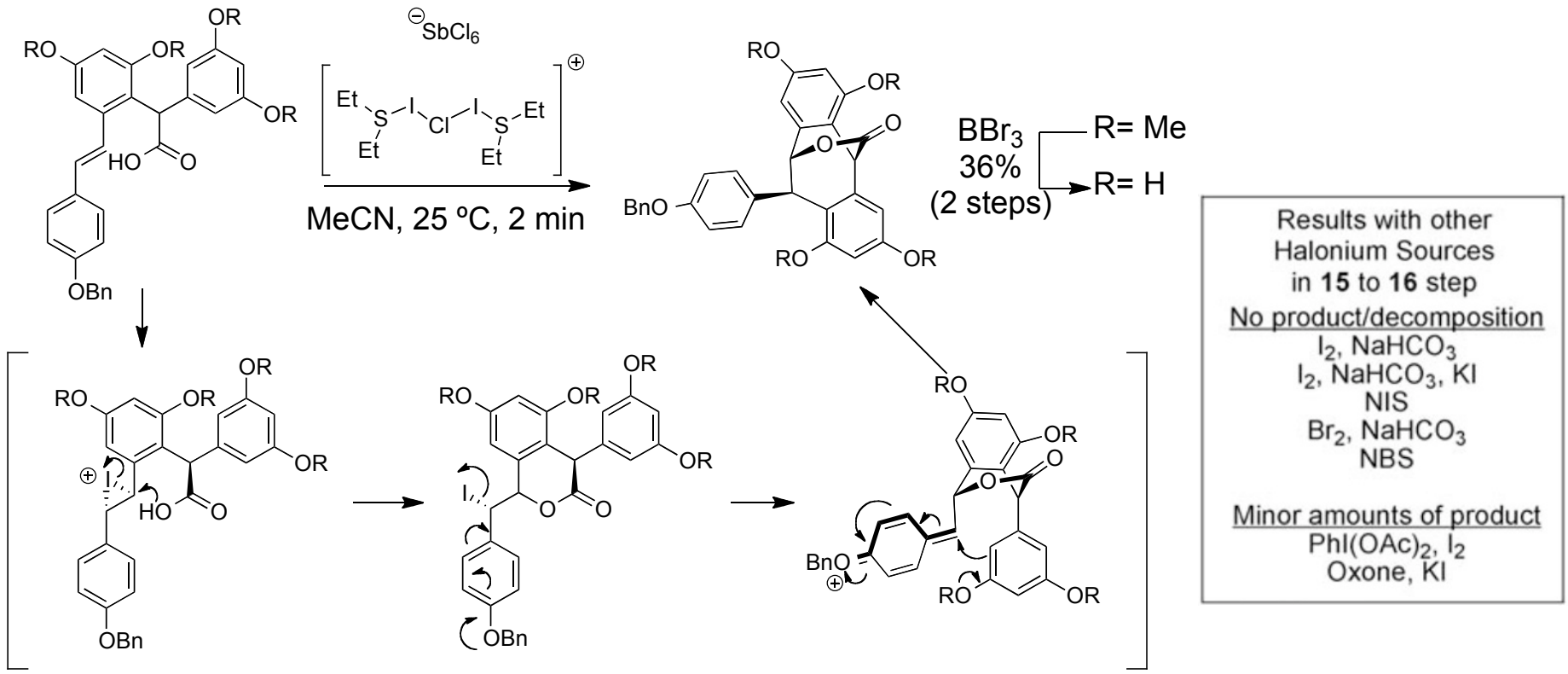
Synthesis of Precursor





ACIE, **2011**, *50*, early view *ACIE*, **2007**, 46*, 8186*

Key Cascade



Results with other Halonium Sources in **15** to **16** step

No product/decomposition

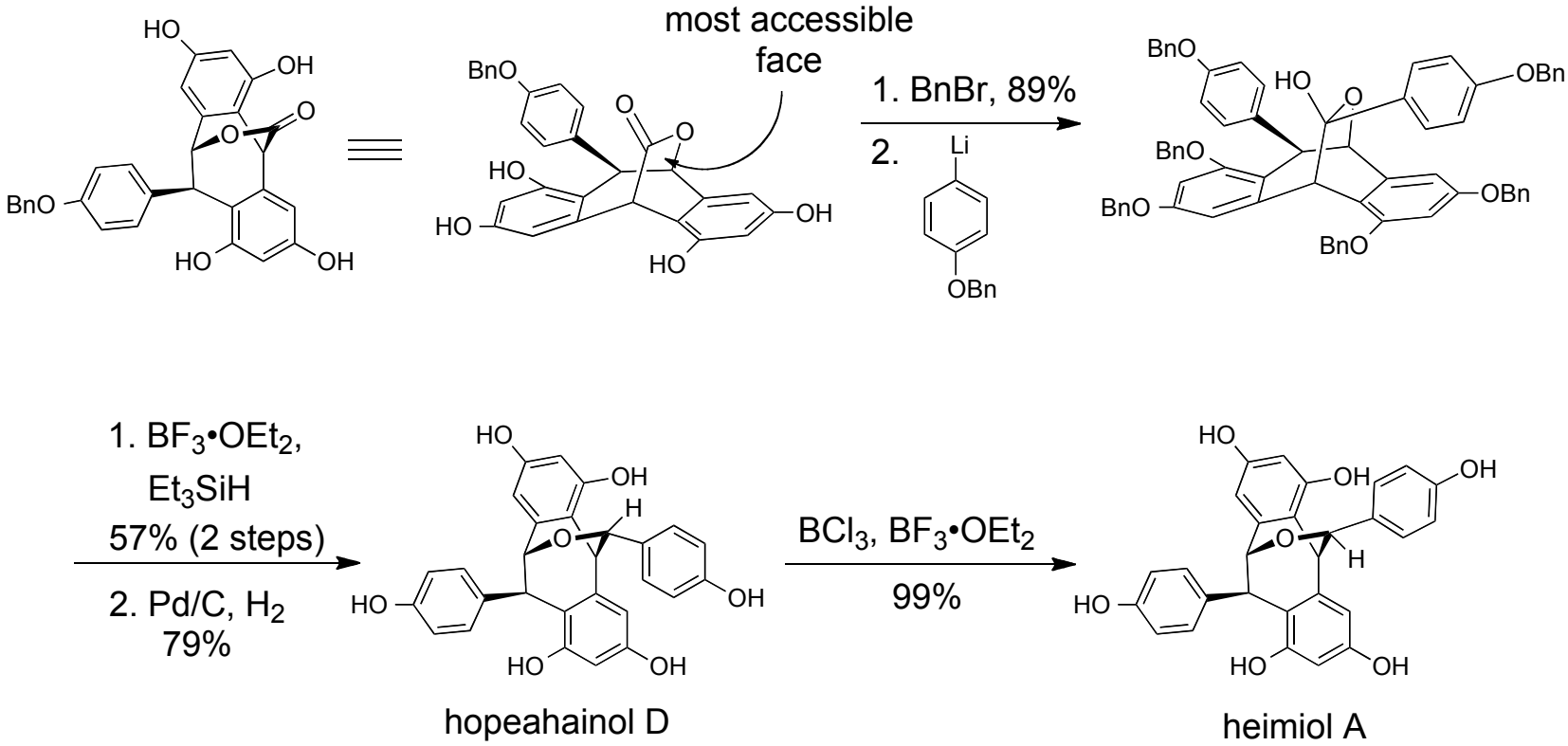
I_2, $NaHCO_3$
I_2, $NaHCO_3$, KI
NIS
Br_2, $NaHCO_3$
NBS

Minor amounts of product

$PhI(OAc)_2$, I_2
Oxone, KI

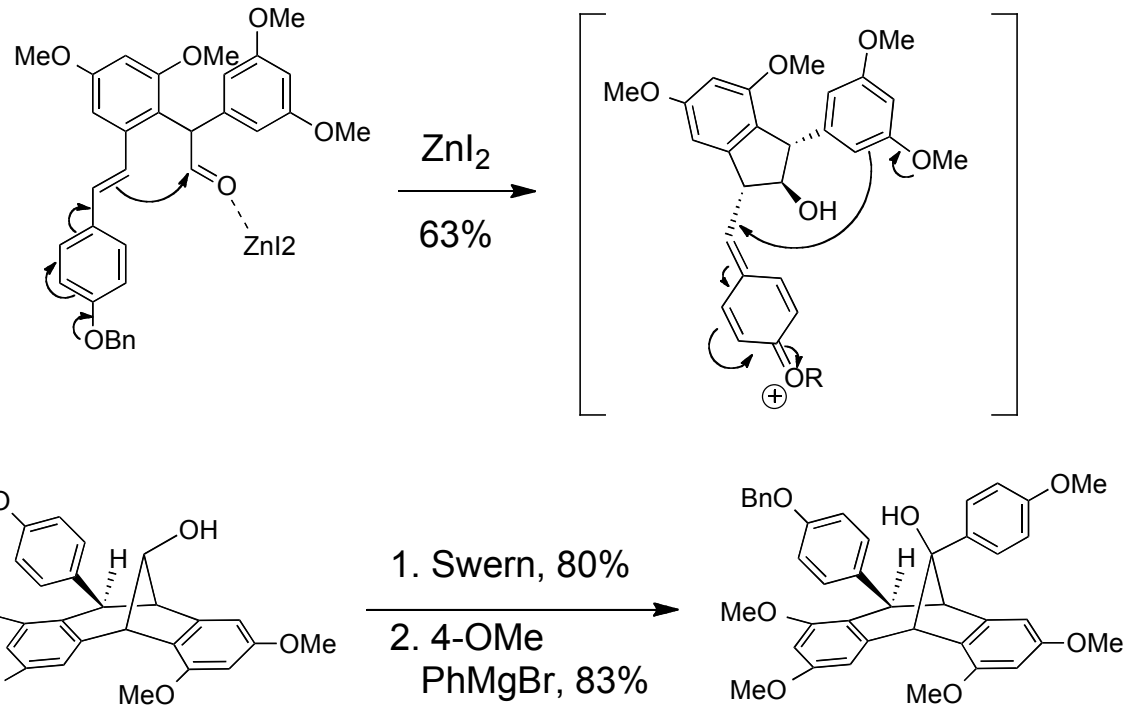
ACIE, **2011**, *50*, early view

Substrate Controlled End Game



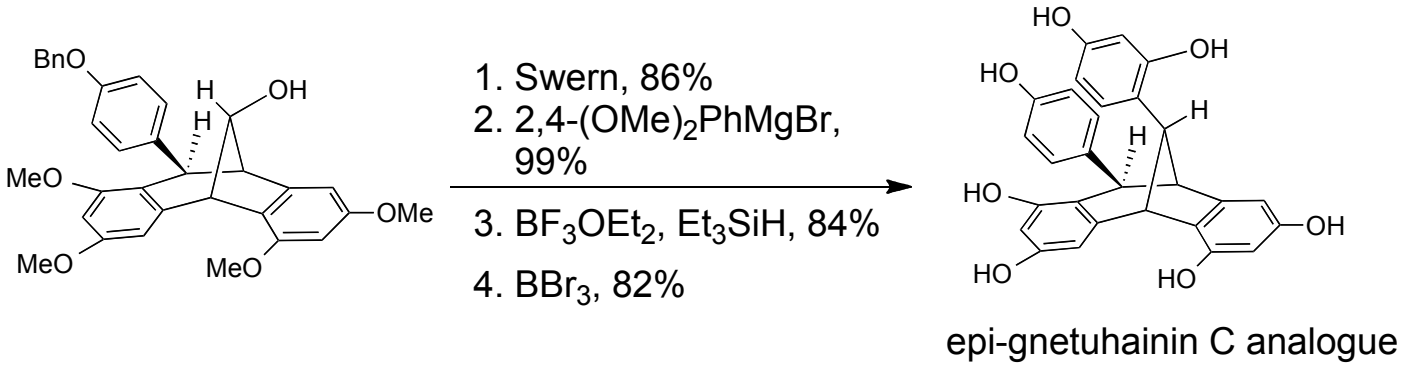
ACIE, **2011**, *50*, early view

5-membered Cascade



ACIE, **2011**, *50*, early view

End Game



epi-gnetuhainin C analogue

ACIE, **2011**, *50*, early view

Conclusions

- First total racemic synthesis of heimiol A and hopeinol D
  - heimiol A (11 steps, 8.6%, 0.5 mg)
  - hopeinol D(11 steps, 6.9%, 3.3 mg)

- Key iodolactonization/intramolecular Friedel-Crafts cascade utilizing their new reagent IDSI

- Successfully applied their Friedel-Crafts reaction to a 5-membered ring