Oxidative Dearomatization of phenols

2011. 8. 23.

Hyung Min Chi

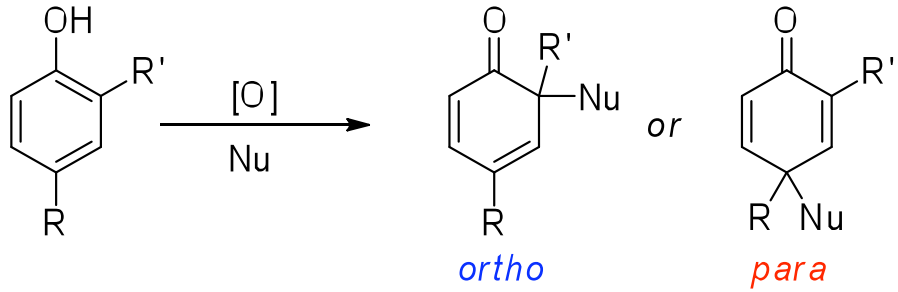
Group Meeting Presentation

Outline

- Oxidative Dearomatization
  - Directionality / types
  - Breaking aromaticity
  - Common strategies used
  - Applications in synthesis of natural product compounds

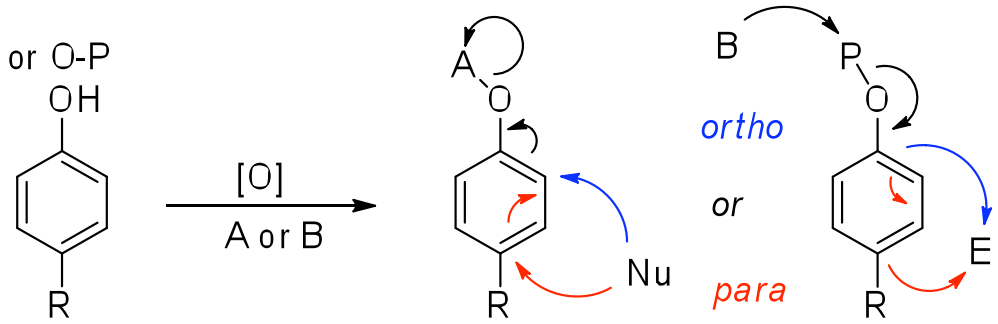
Oxidative Dearomatization

- Oxidative dearomatization



- Directionality of electron flow
  - Oxidative vs Oxidative/alkylative (Nucleophilic/Electrophilic)

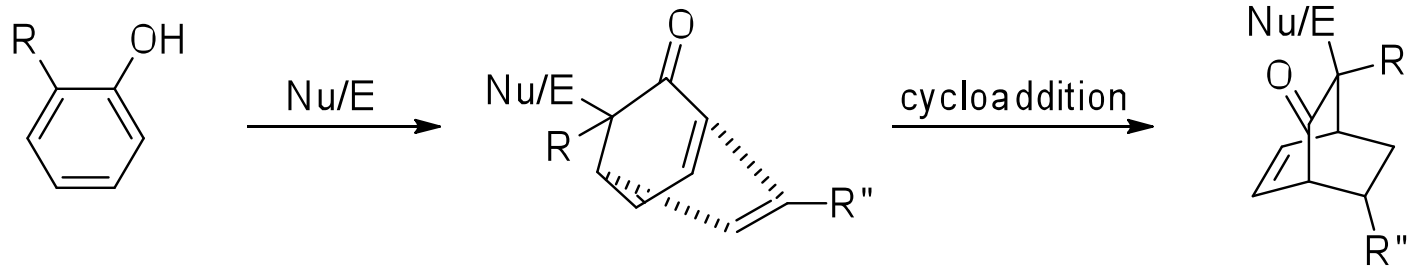
Nu = nucleophilic oxygen/carbon E = electrophilic carbon
A = activating reagent P = protective groups



Rappoport, *The Chemistry of Phenols*, **2003**, John Wiley & Sons.

Commonly used Strategies

- Efficiently converting the cyclohexadienone structure into complex 3D organic structures
  - Tandem [4+2] cycloaddition — Danishefsky, *JACS* **2006**, *128*, 16440.
  - Triggering Diels-Alder cycloaddition (IMDA) — Liao, *Org. Lett.* **2007**, *9*, 4563.
  - Michael addition (MEM) — Porco, Jr., *JACS* **2007**, *129*, 12682.
  - Retro Diels-Alder / Diels-Alder sequence — Snyder, *JACS* **2009**, *131*, 1745.
  - Claisen dearomatization / Diels-Alder cycloaddition — Theodorakis, *PNAS* **2004**, *101*, 12030.

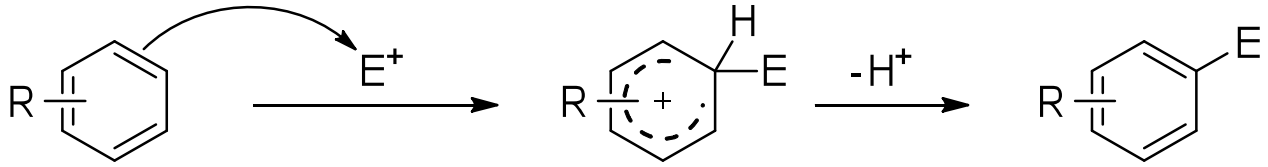


Barriers for dearomatization

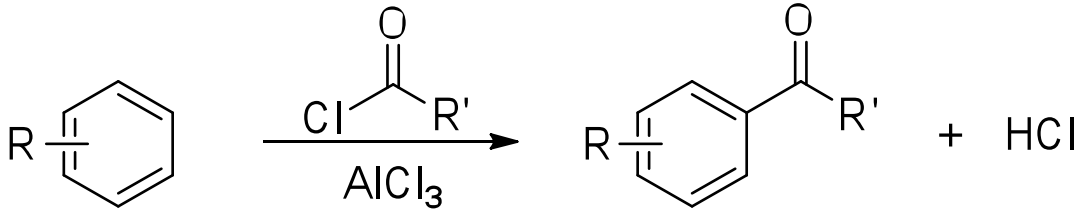
- Aromaticity of benzene ring 35.5 kcal/mol

Franklin, *JACS* **1950**,*72*,9,4278.

- Driving force
  - Activating reagents
  - Structural feasibility
  - Cascade reactions sequence
- S_EAr



- Friedel-Crafts reaction

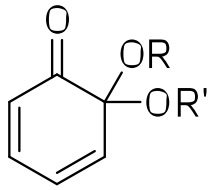


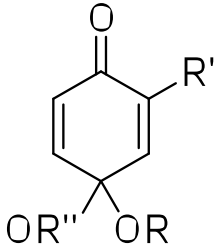
Strategic applications of named reactions in organic synthesis, **2005**, Elsevier.

Classification by product type

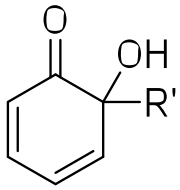
- Dearomatization of phenols with oxygen-centered nucleophiles

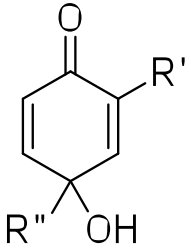
Benzoquinones





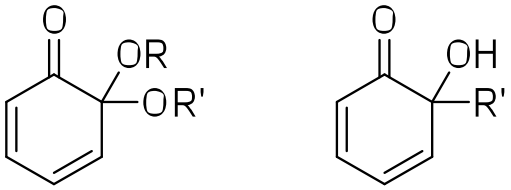
Quinols





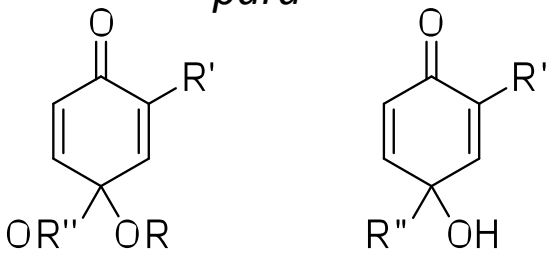
Classification by product type

- Dearomatization of phenols with oxygen-centered nucleophiles



Benzoquinones *ortho* Quinols

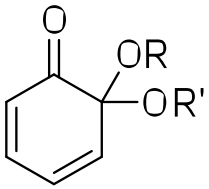
para

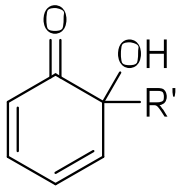


Classification by product type

- Dearomatization of phenols with oxygen-centered nucleophiles

$Pb(OAc)_4$
PIFA
mCPBA



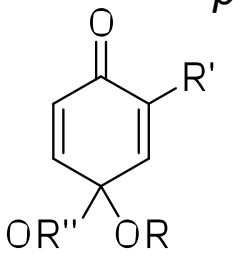


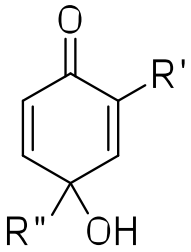
$Pb(OAc)_4$
PIDA/PIFA
Cu(sparteine)

Benzoquinones — *ortho* — Quinols

para

$Pb(OAc)_4$
oxone





PIDA/PIFA

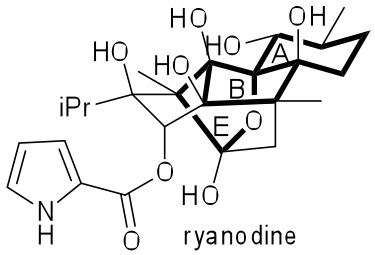
Enantioselective process

- Starting with chiral (tether/auxiliary attached) phenol for stereoselectivity

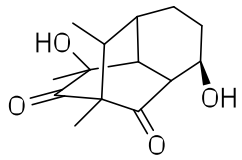
- Use of chiral reagents to achieve enantioselectivity after formation of meso compound via dearomatization
  - Usually applies for the *para*-dearomatization

- Direct oxidation that discriminates two enantiotopic faces

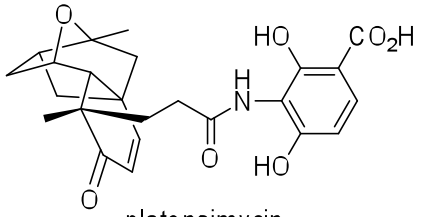
Natural products synthesized using oxidative dearomatization method



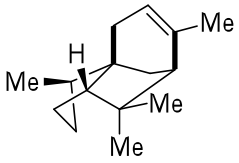
ryanodine



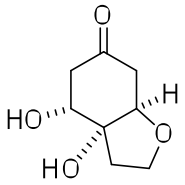
penicillone B



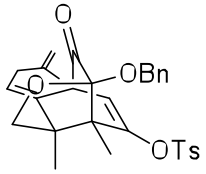
platensimycin



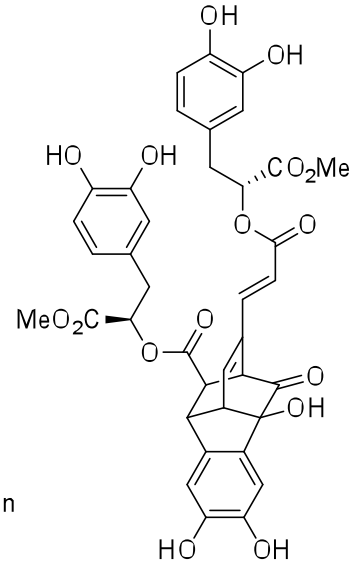
cedrene



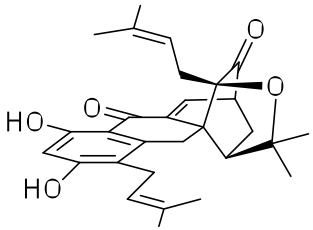
cleroindicin D



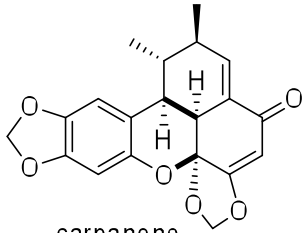
11-O-debenzoyltashironin



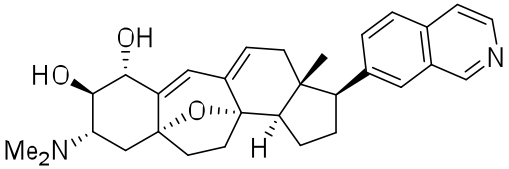
helisorin



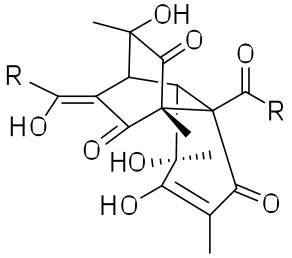
forbesione



carpanone

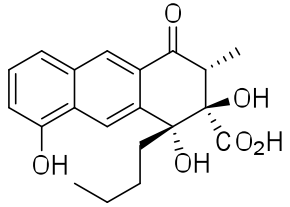


(+)-cortistatin A

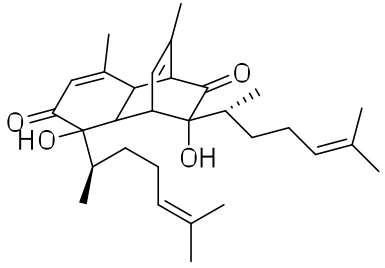


bisorbicillinoids

vinigrol



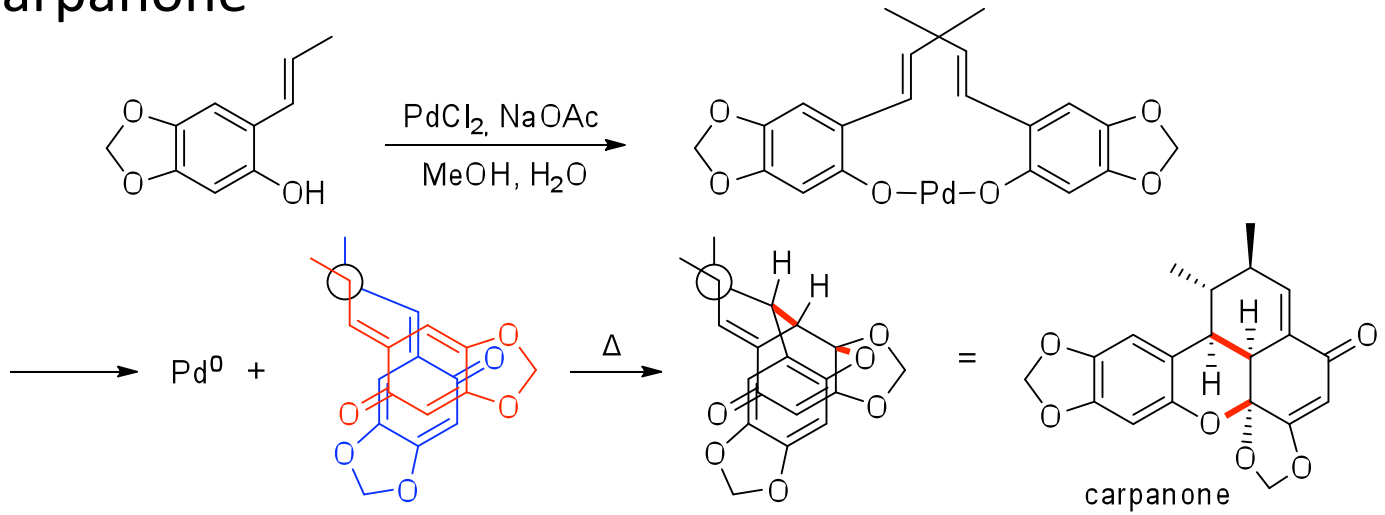
(+)-rishirilide B



bacchopetiolone

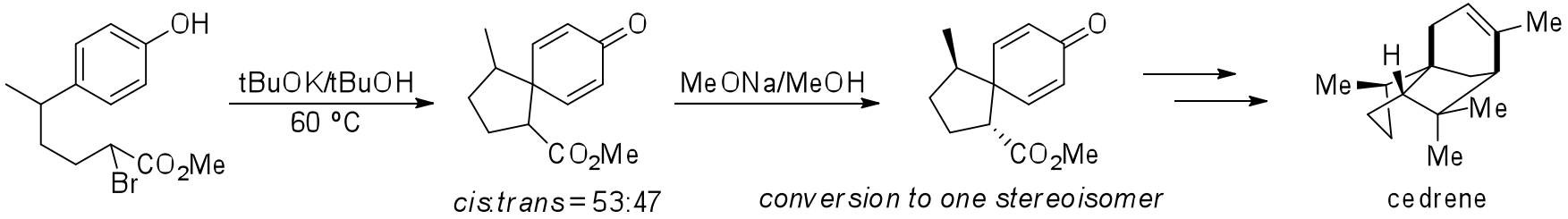
Earlier works

- Carpanone



- Cedrene

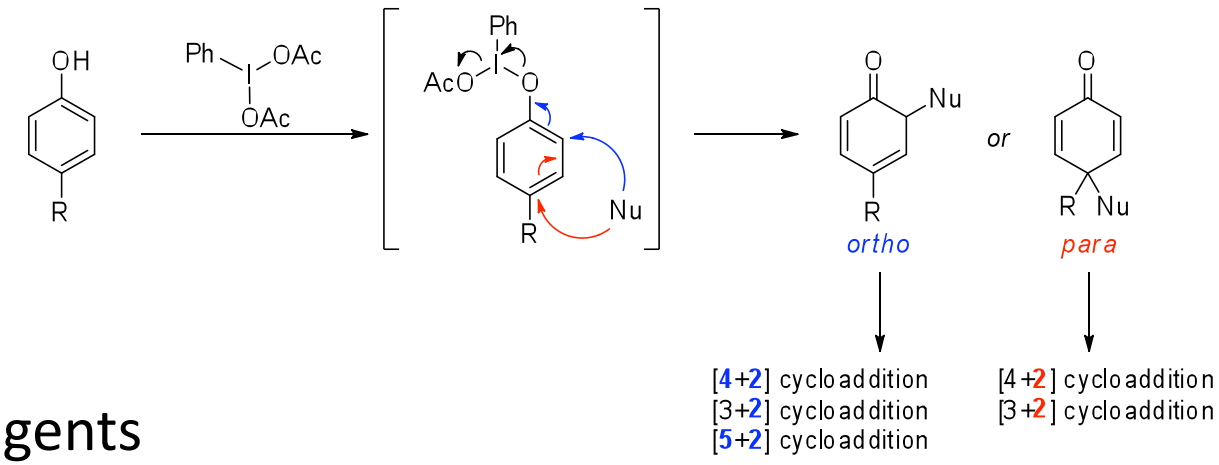
Chapman, *JACS* **1971**, *93*, 6696.



Corey, *JACS* **1969**, *91*, 1557.

Iodine III reagent

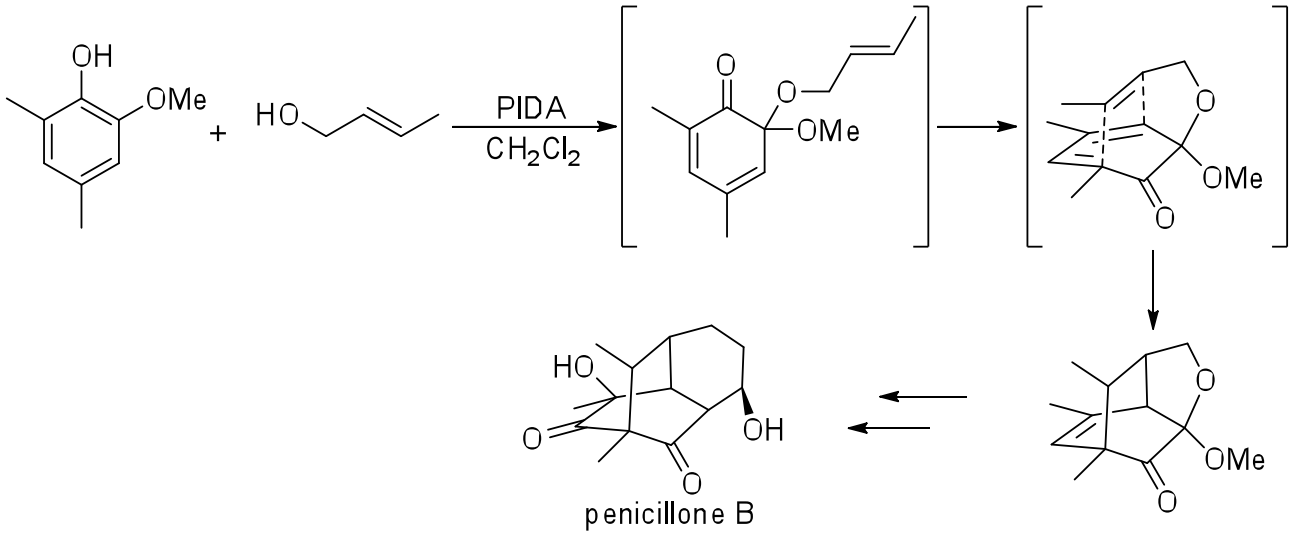
- Hypervalent iodine III reagents (PIDA, PIFA, etc)



- Reagents
  - $PhI(OAc)_2$, $PhI(TFA)_2$, F-$PhI(TFA)_2$,…

Iodine III reagent

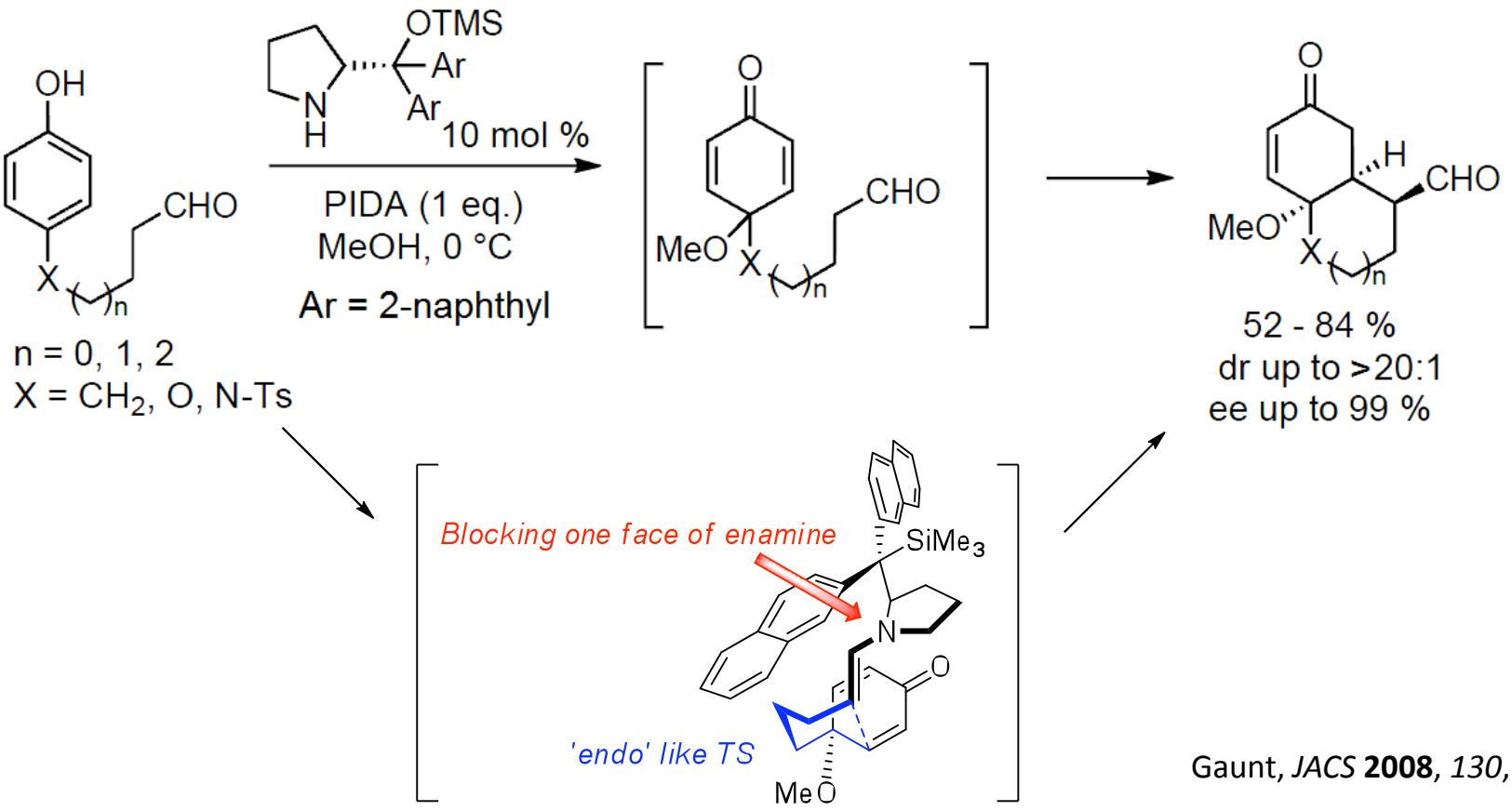
- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - penicillone, IMDA cascade, ortho



Liao, *Org. Lett.* **2007**, *9*, 4563.

Iodine III reagent

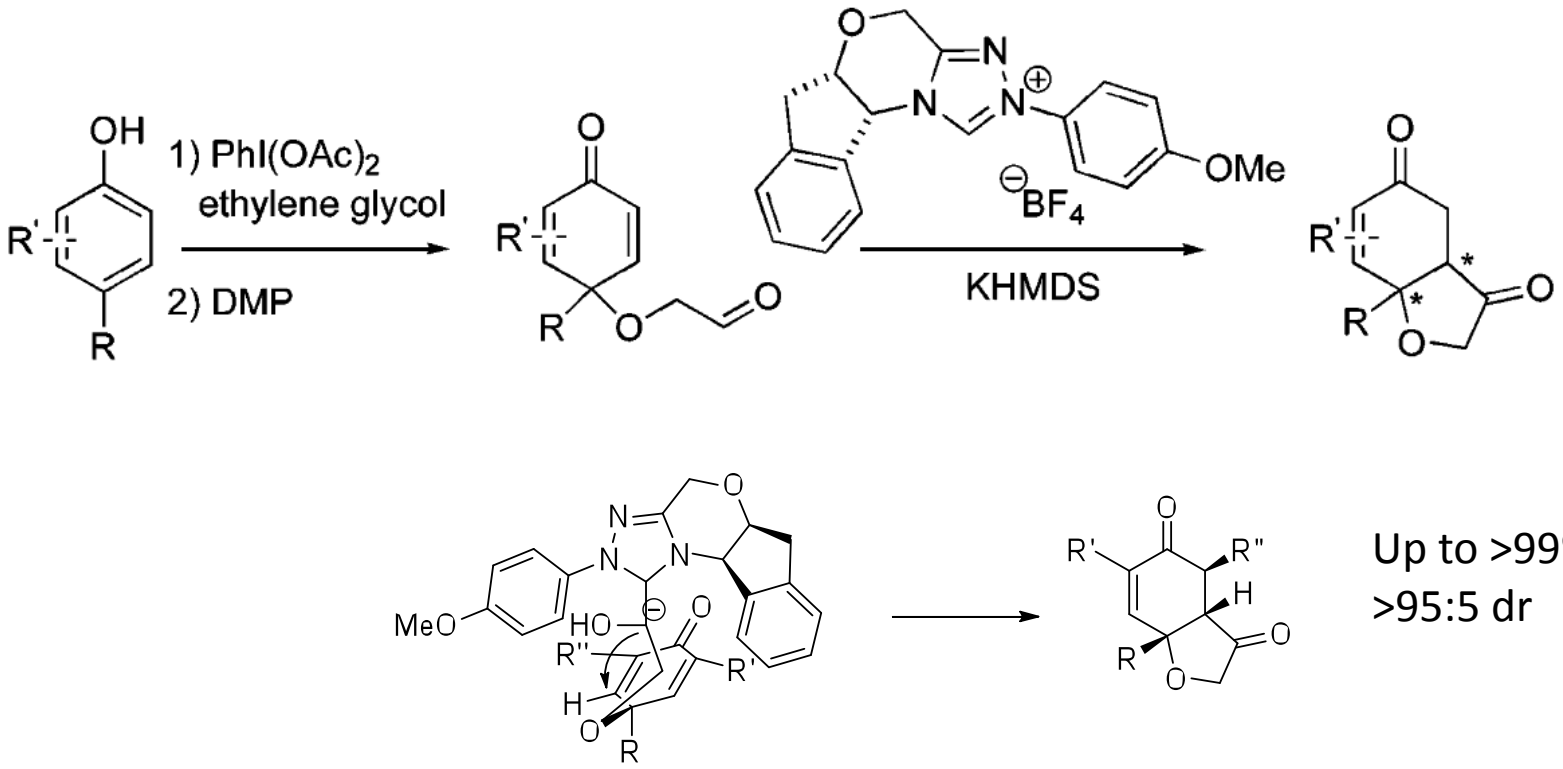
- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - enantioselective proline catalyzed



Gaunt, *JACS* **2008**, *130*, 404.

Iodine III reagent

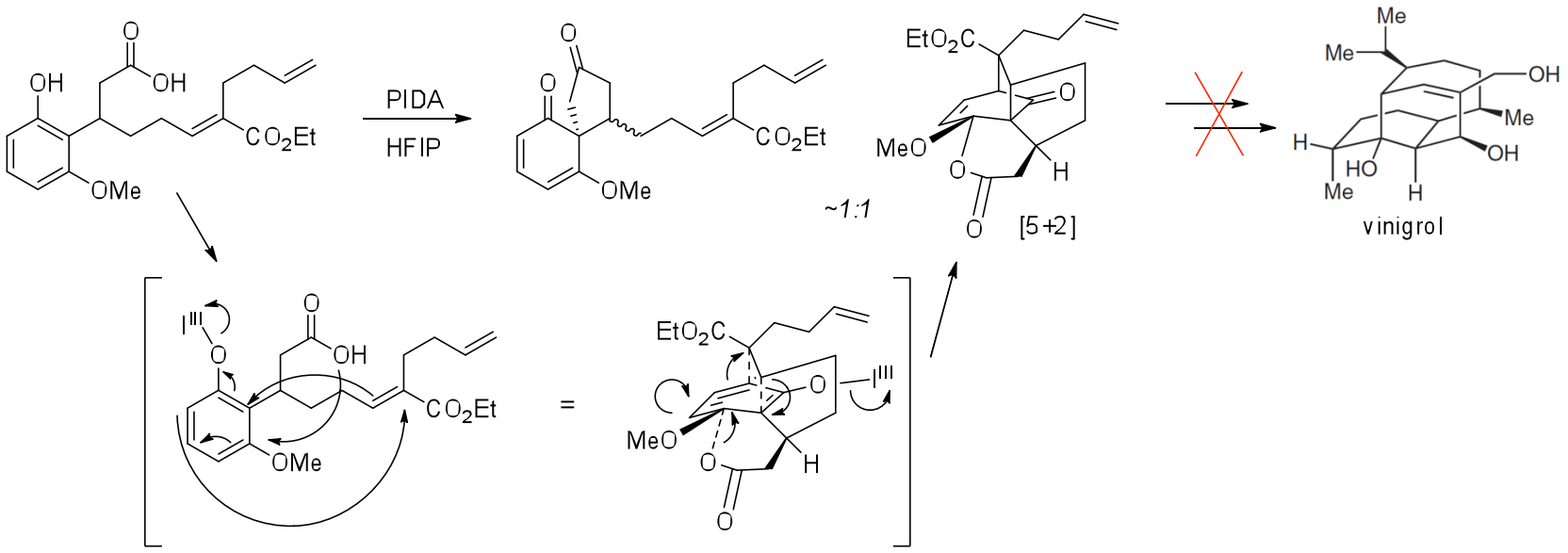
- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - enantioselective aminoindanol-derived triazolium catalyst



Rovis, *JACS* **2006**, *128*, 2552.

Iodine III reagent

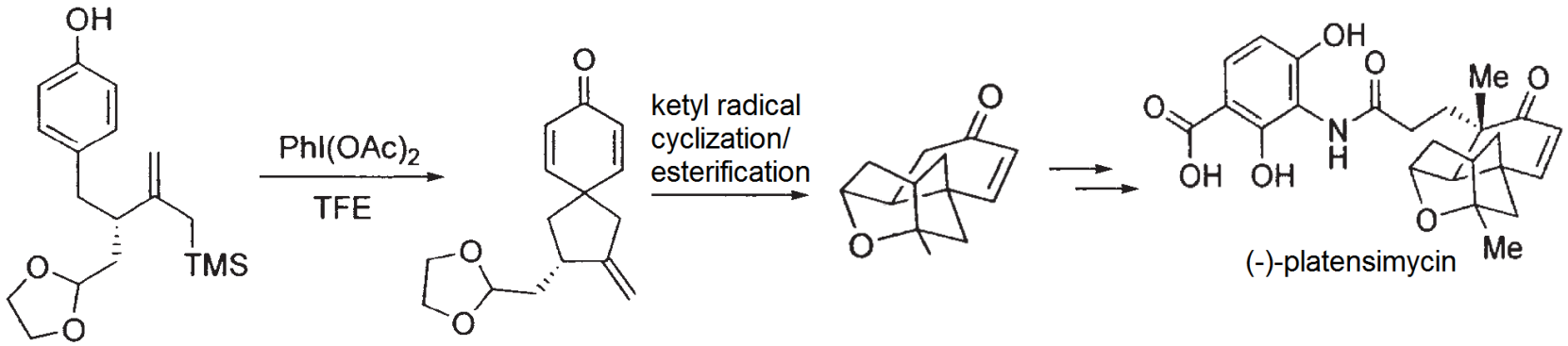
- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - Synthesis approach to vinigrol
  - Polar cationic [5+2] intramolecular cascade



Njardarson, *Synlett* **2009**, 23-27.

Iodine III reagent

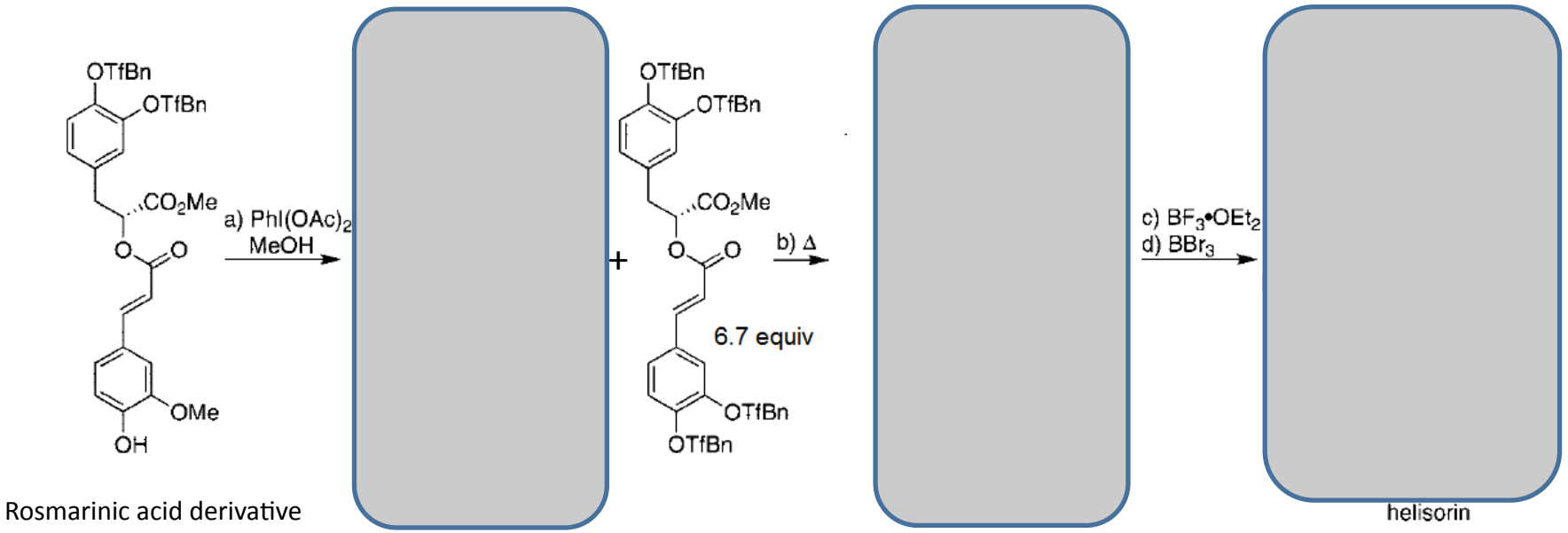
- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - (-)-platensimysin
  - 2 syntheses; enantioselective cycloisomerization approach using [{Rh(cod)Cl}$_2$] with *S*-BINAP
  - Myers' asymmetric alkylation followed by dearomatization



Nicolau, *ACIE* **2007**, *46*, 3942.

Group Question!!!

- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - helisorin



Rosmarinic acid derivative

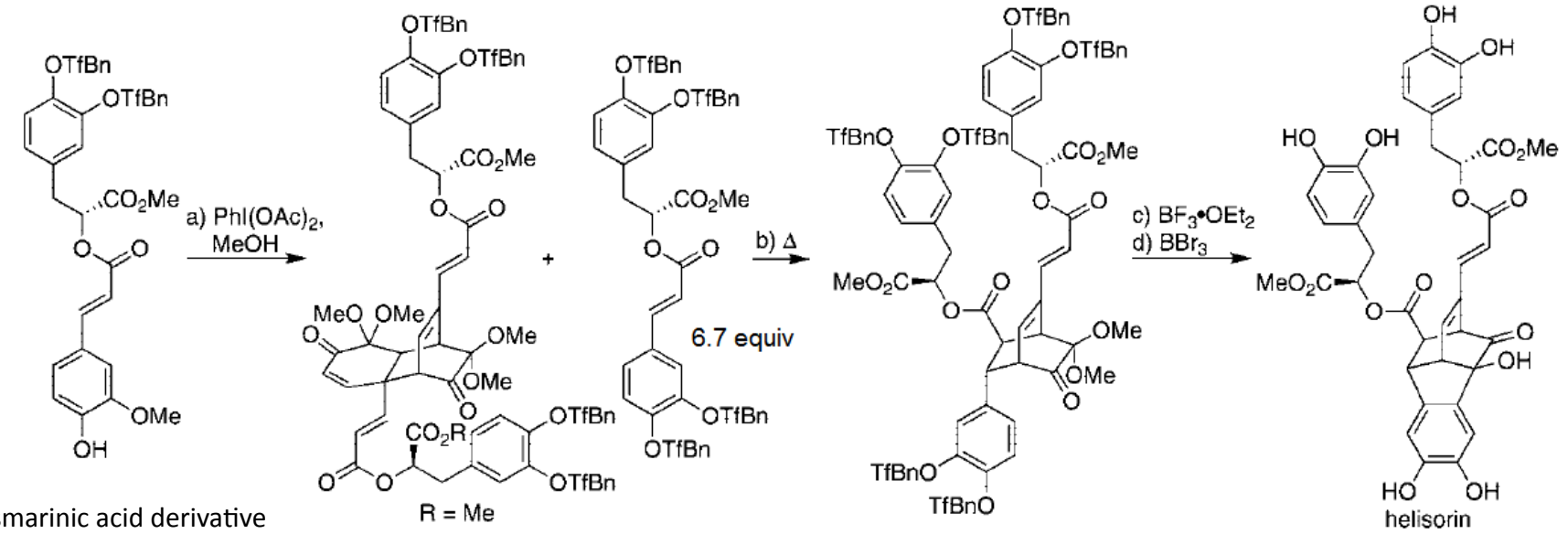
C41H38O11

C39H38O16

Snyder, *JACS* **2009**, *131*, 1745.

Iodine III reagent

- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - helisorin
  - Spontaneous dimerization / Retro Diels-Alder / Diels-Alder sequence

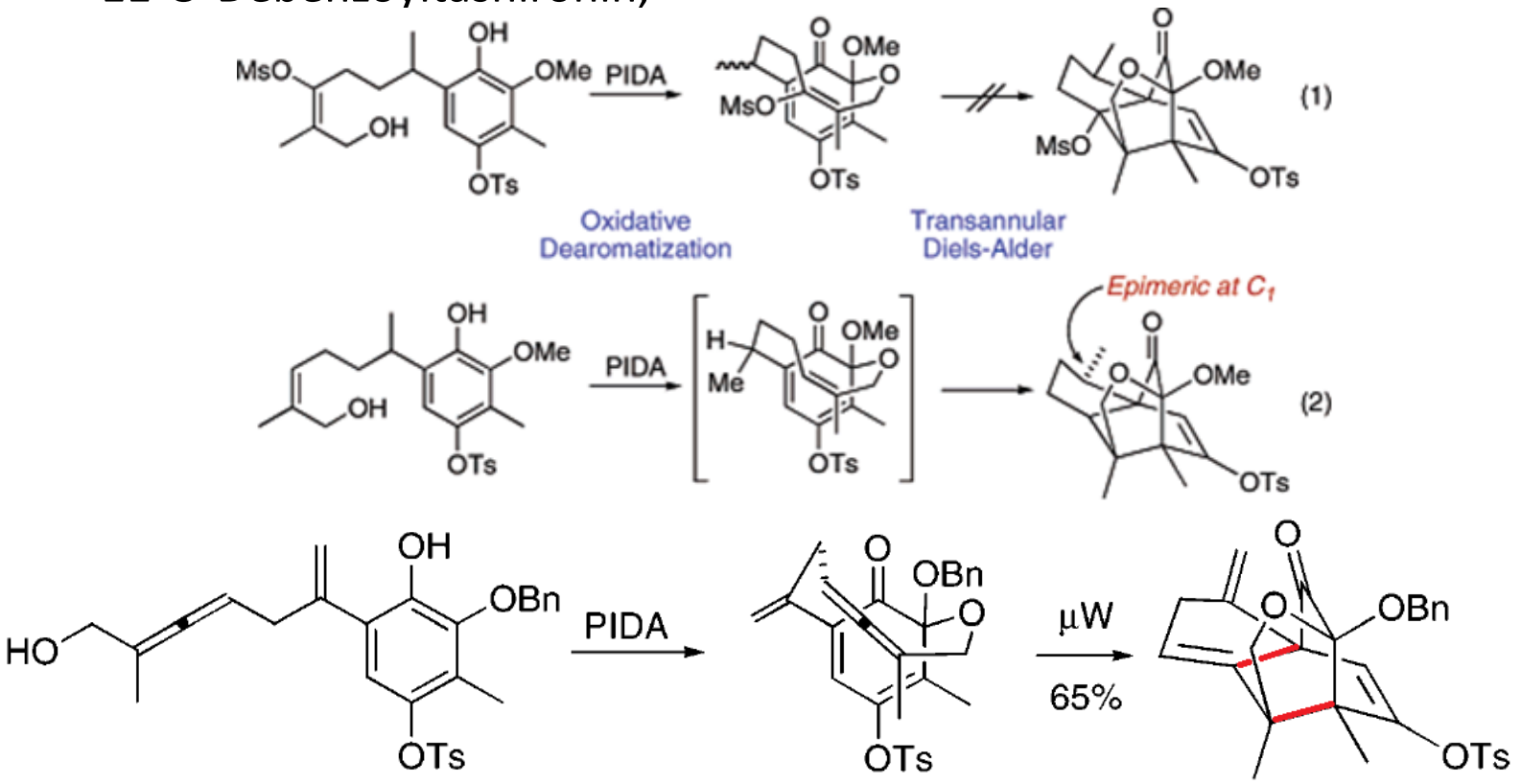


Rosmarinic acid derivative

Snyder, *JACS* **2009**, *131*, 1745.

Iodine III reagent

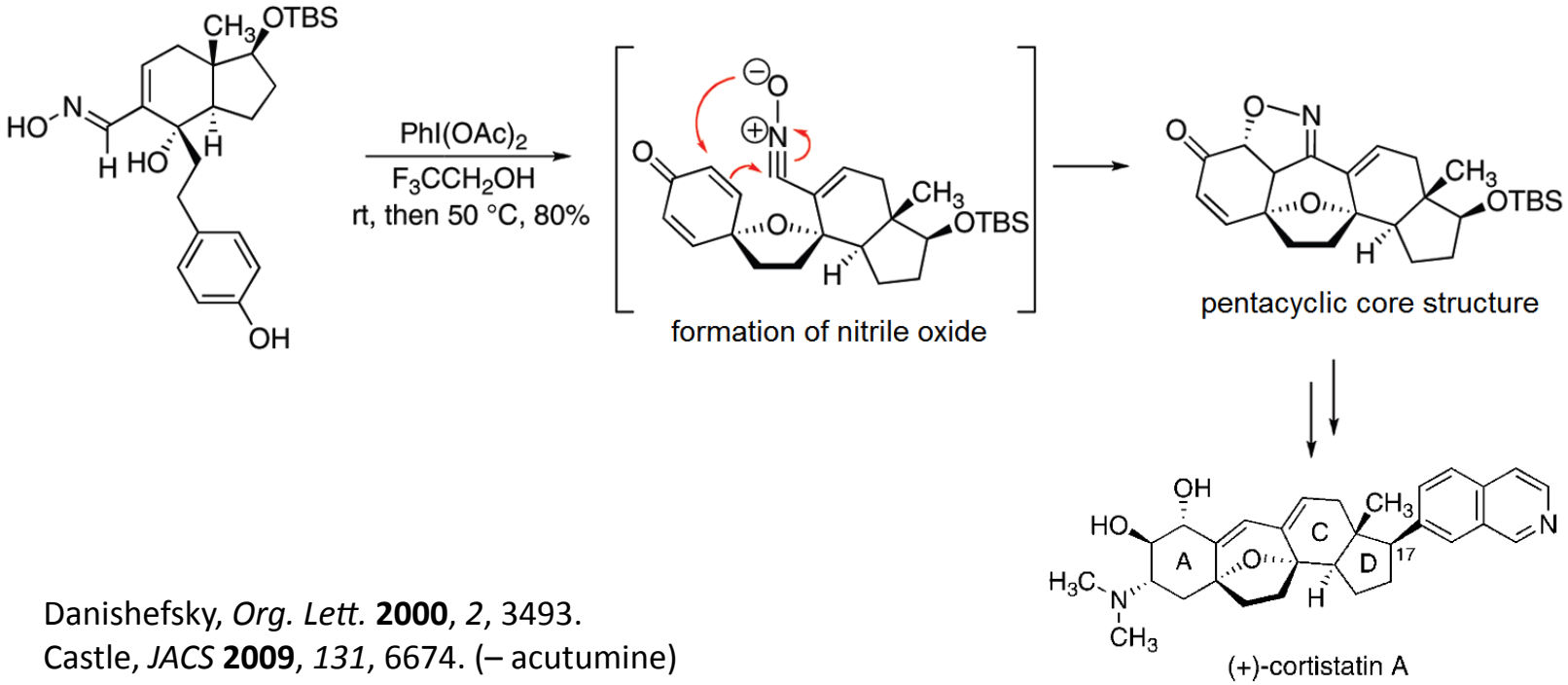
- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - 11-O-Debenzoyltashironin,



Danishefsky, *JACS* **2006**, *128*, 16440.

Iodine III reagent

- PIDA (= $PhI(OAc)_2$, bis(acetoxy)iodobenzene)
  - cortistatin A

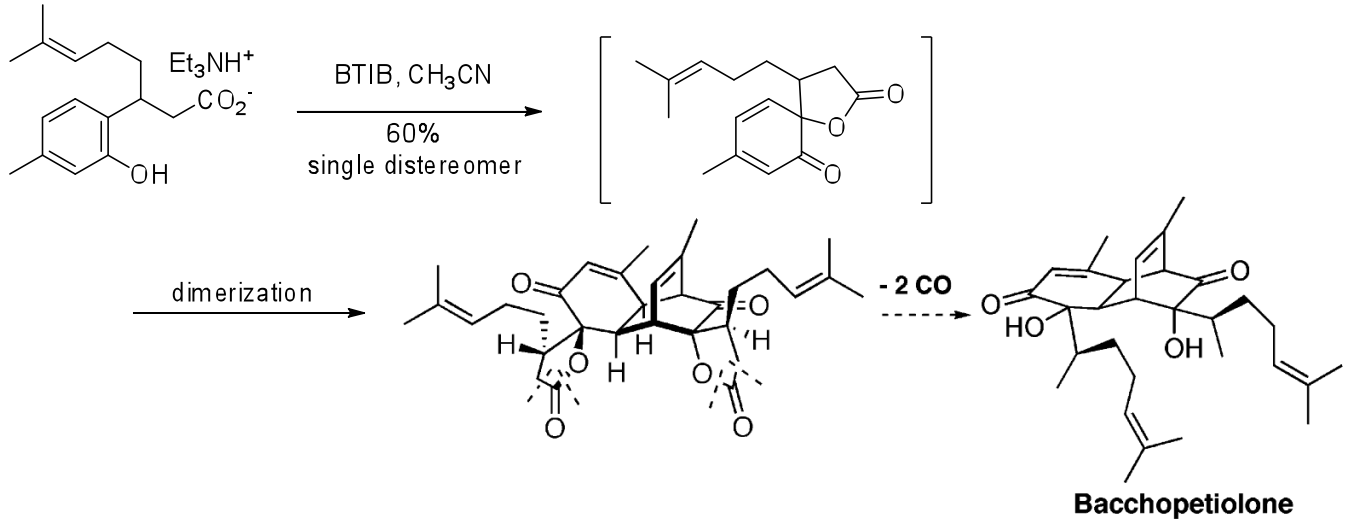


Danishefsky, *Org. Lett.* **2000**, *2*, 3493.
Castle, *JACS* **2009**, *131*, 6674. (– acutumine)
Quideau, *Org. Lett.* **2002**, *4*, 3975. (+ puupehenone)
Quideau, *ACIE* **2008**, *47*, 3552. (+ biscarvacrol)
Snyder, *ACIE* **2010**, *49*, 5146. (dalesconol B)

Sorensen, *Org. Lett.* **2009**, *11*, 5394.

Iodine III reagent

- PIFA or BTIB, (= $PhI(TFA)_2$, bis(trifluoroacetoxy)-iodobenzene)
  - bacchopetiolone *(dimeric sequiterpene isolated from Chilean shrub Baccaris petiolata)*
    - Oxidative spirolactonization, ortho dearomatization
    - Undergoes dimerization via endo transition state
    - Two stereoselective steps: Lactone formation then DA reaction

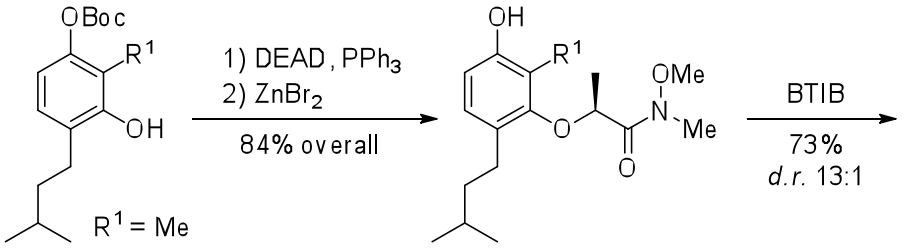


Bacchopetiolone

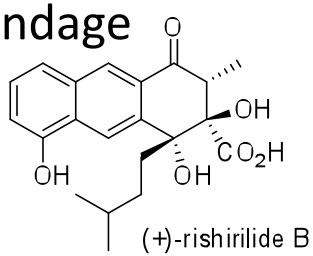
Wood, *Org. Lett.* **2006**, *8*, 5421.

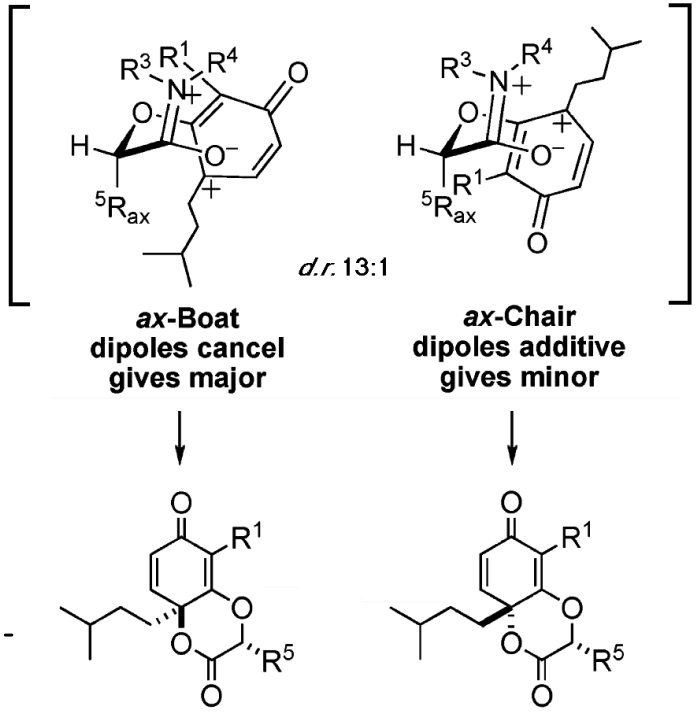
Iodine III reagent

- PIFA or BTIB, (= bis(trifluoroacetoxy)-iodobenzene)
  - (+)-rishirilide B



  - First enantioselective synthesis of (+)-rishirilide B (28 steps, 2.5% yield)
  - Danishefsky: rac -> (-)
  - Weinreb amide appendage
  - Lactic amide chiral auxiliary

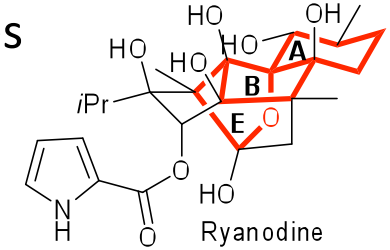


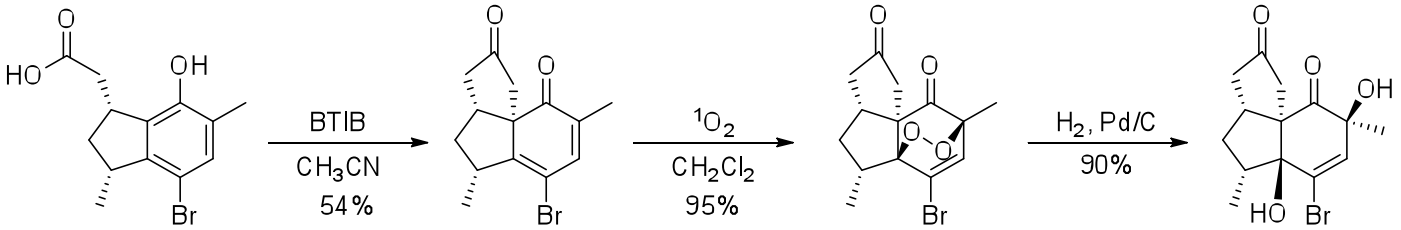


Pettus, *JACS* **2006**, *128*, 15625.

Iodine III reagent

- PIFA or BTIB, (= bis(trifluoroacetoxy)-iodobenzene)
  - BCE ring system of ryanodine
  - phenolic oxidation/intramolecular trapping/singlet oxygen
  - trans-fused bridgehead-oxygenated [4.3.0]-bicycles

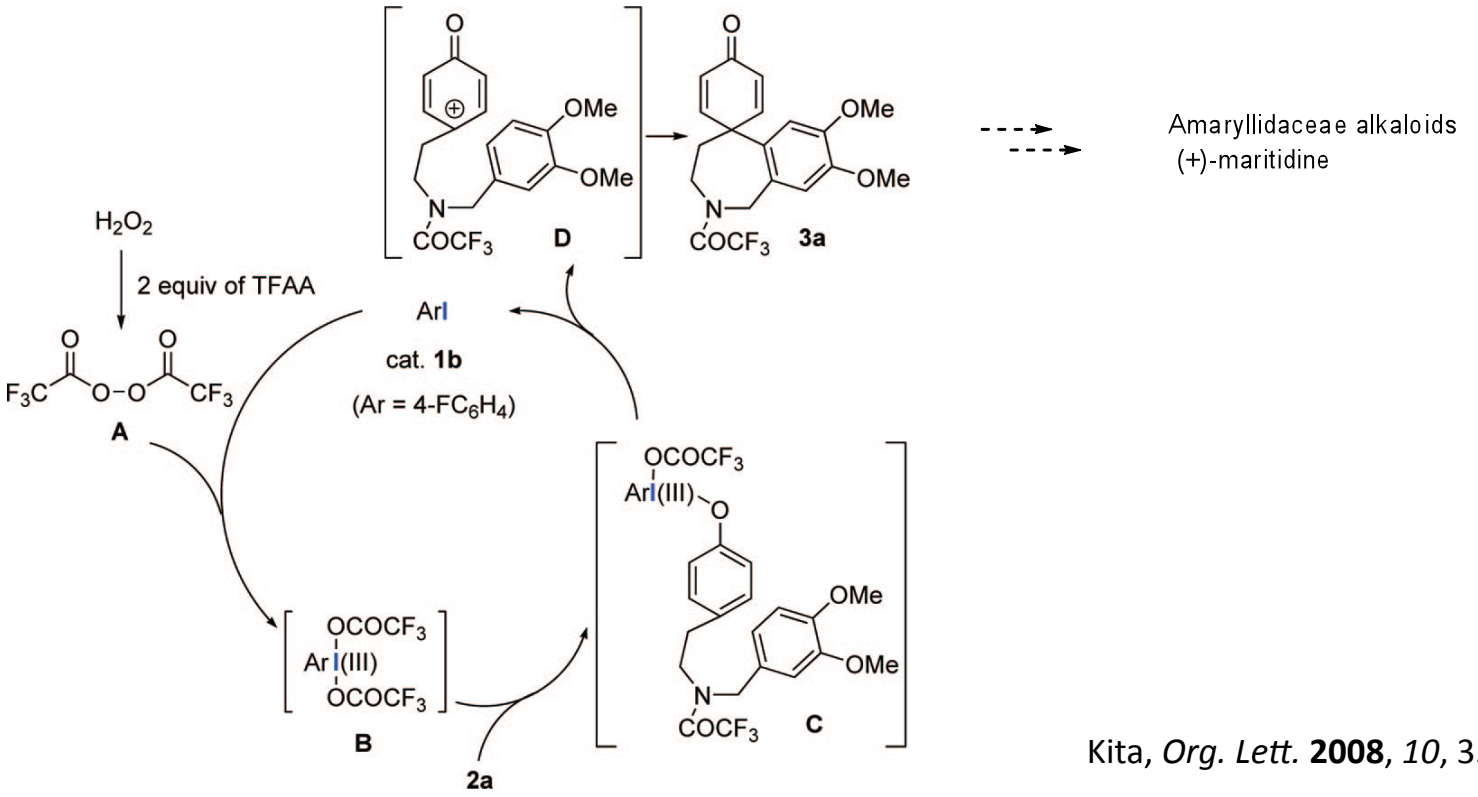




Wood, *Tetrahedron* **2003**, *59*, 8855.

Iodine III reagent

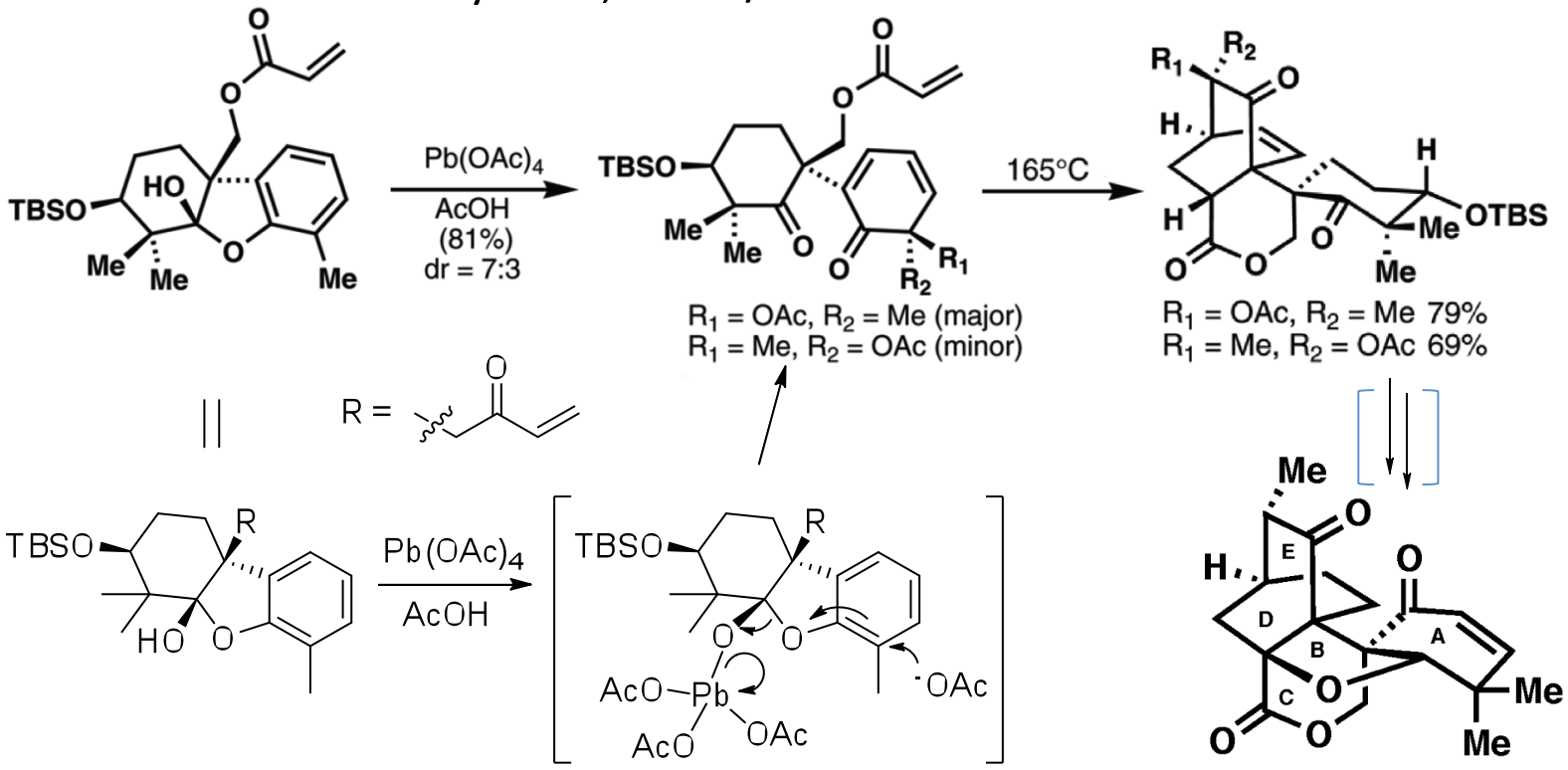
- bis(trifluoroacetoxy)iodo(4-fluoro)benzene w/ TFAA
  - (+)-maritidine.
    - Catalytic iodine III species



Kita, *Org. Lett.* **2008**, *10*, 3559.

Pb(OAc)$_4$

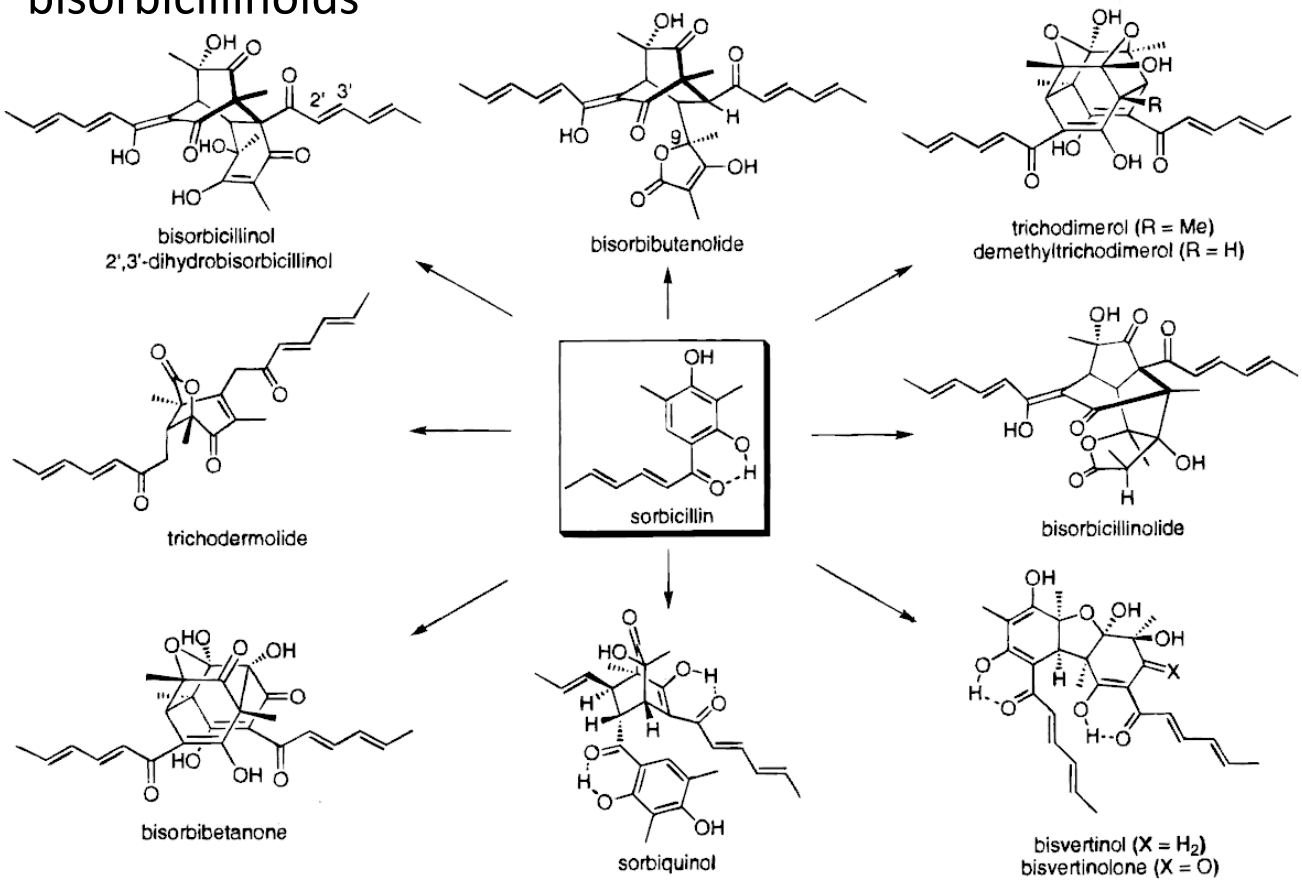
- PTA (= Pb(OAc)$_4$, lead tetraacetate)
  - core of Maoecrystal V, ortho/IMDA



Baran, *Org. Lett*. **2009**, *11*, 4774.

$Pb(OAc)_4$

- PTA (= $Pb(OAc)_4$, lead tetraacetate)
  - bisorbicillinoids



Nicolau, *JACS* **2000**, *122*, 3071.

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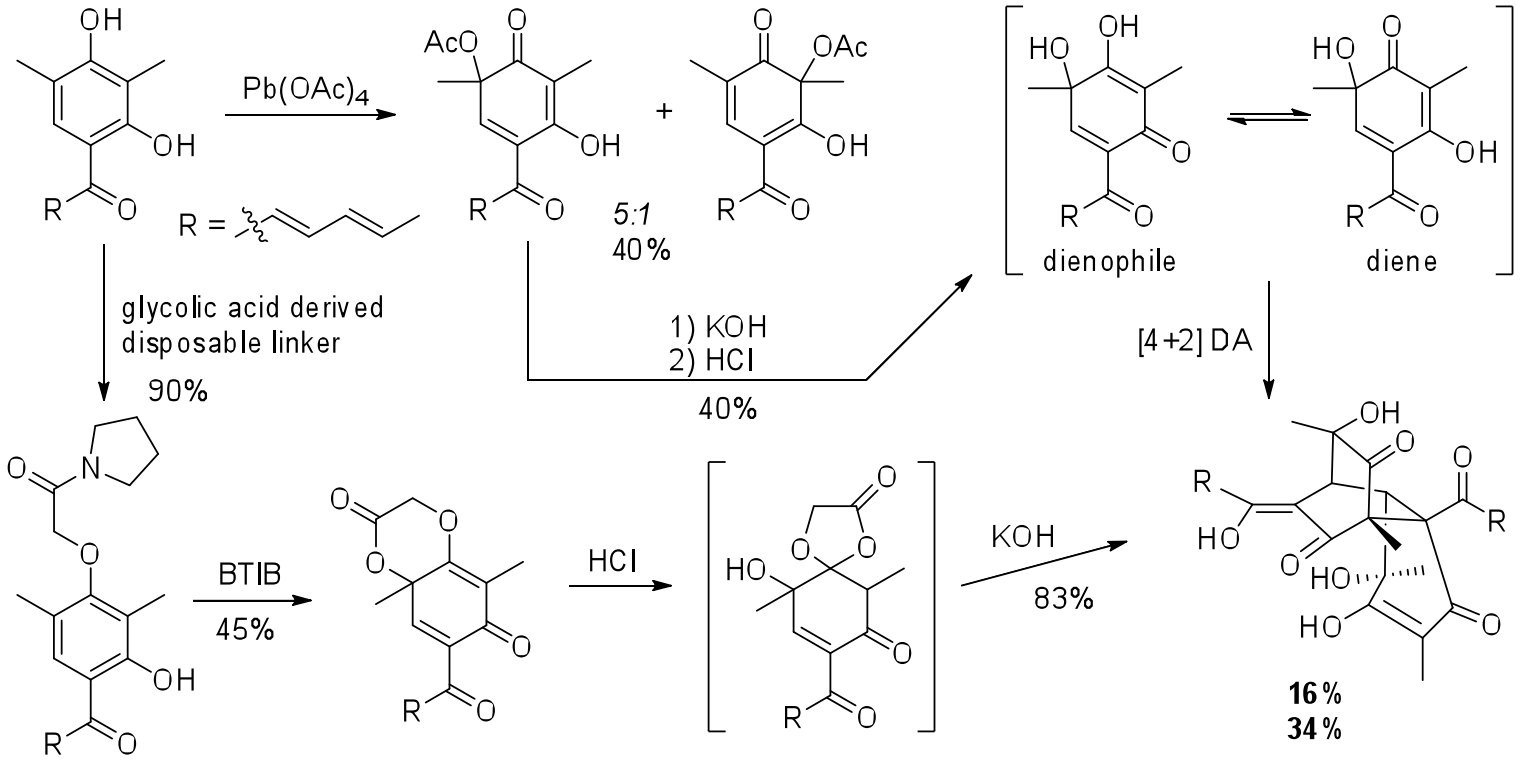
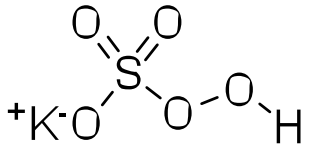
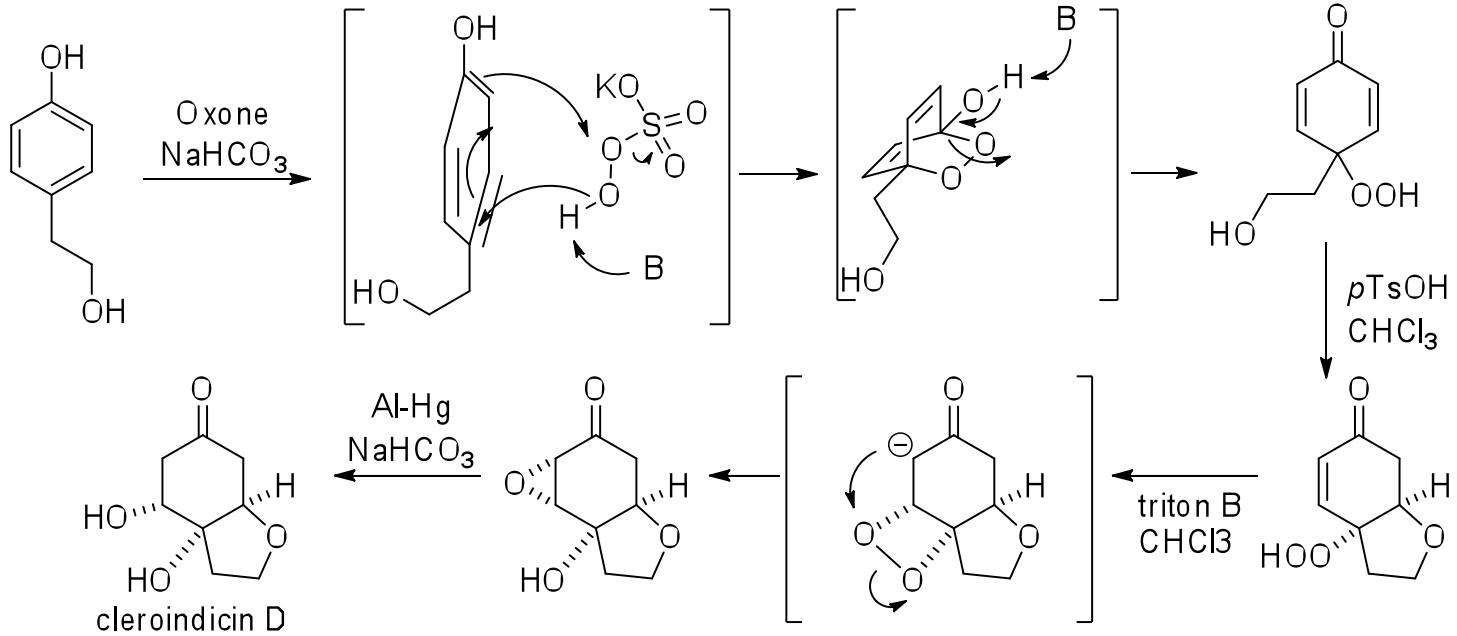


Nicolau, *JACS* **2000**, *122*, 3071.
Pettus, *Org. Lett.* **2001**, *3*, 905.

Oxone

- Oxone as the source of singlet oxygen
  - Potassium peroxymonosulfate

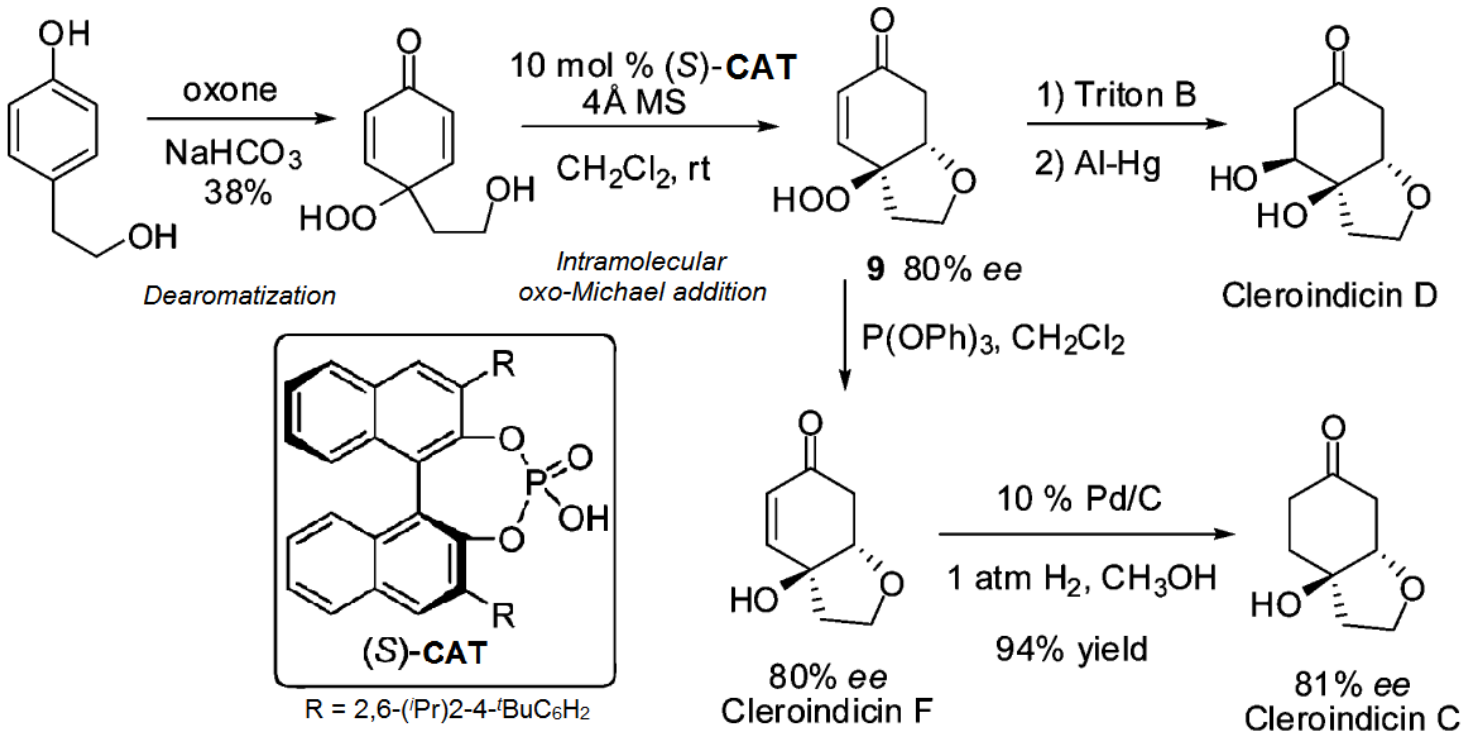




Carreno, Urbano, *Org. Lett.* **2007**, *9*, 5019.

Oxone

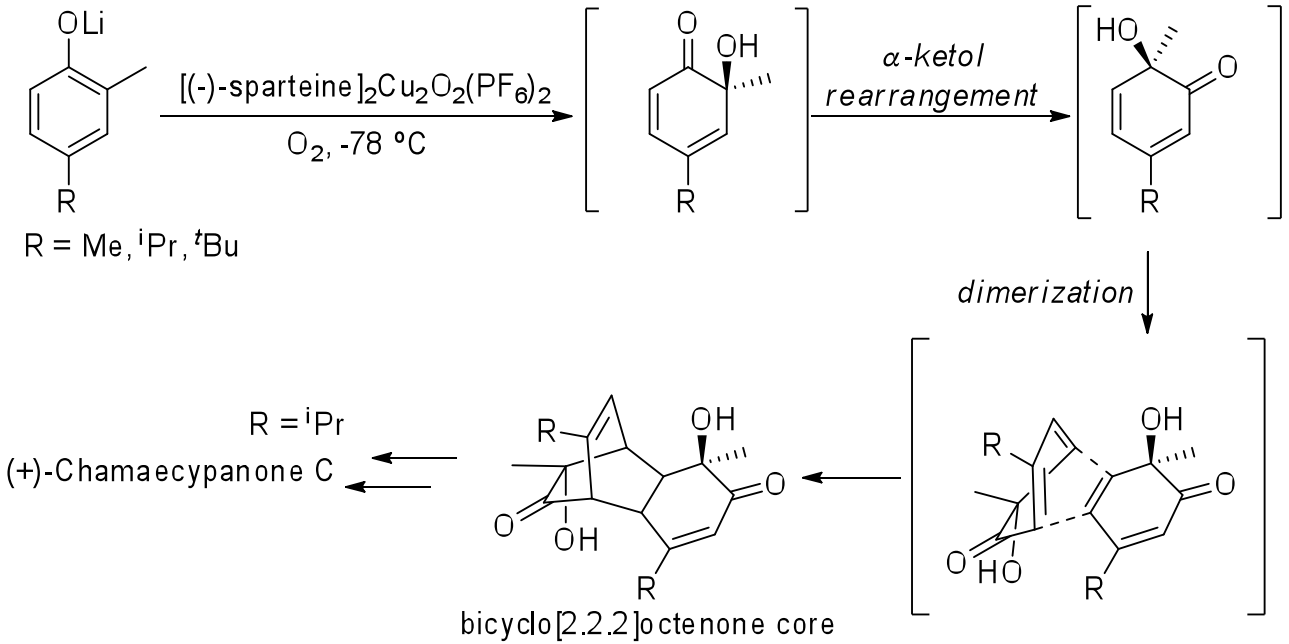
- Oxone as the source of singlet oxygen
  - Followed by Bronsted acid-catalyzed enantioselective oxo-Michael reaction



You, *JACS* **2010**, *132*, 4056.

[{(-)-sparteine}$_2$Cu$_2$O$_2$] complex

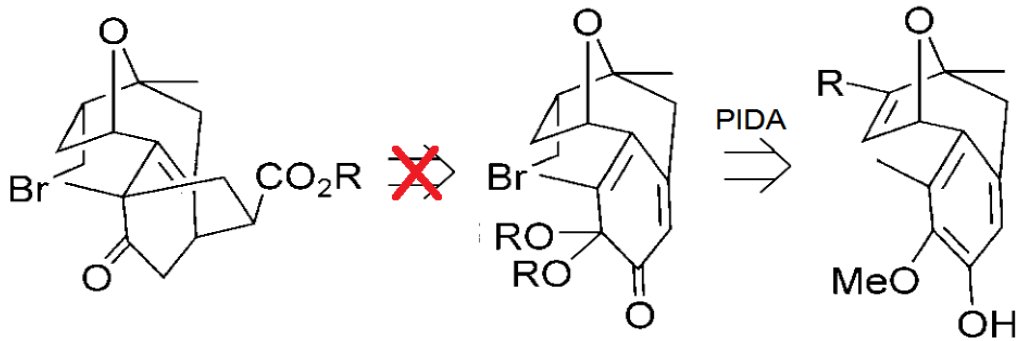
- [Cu(MeCN)$_4$]PF$_6$, sparteine, O$_2$.
- High enantioselectivity
  - (+)-Chamaecypanone

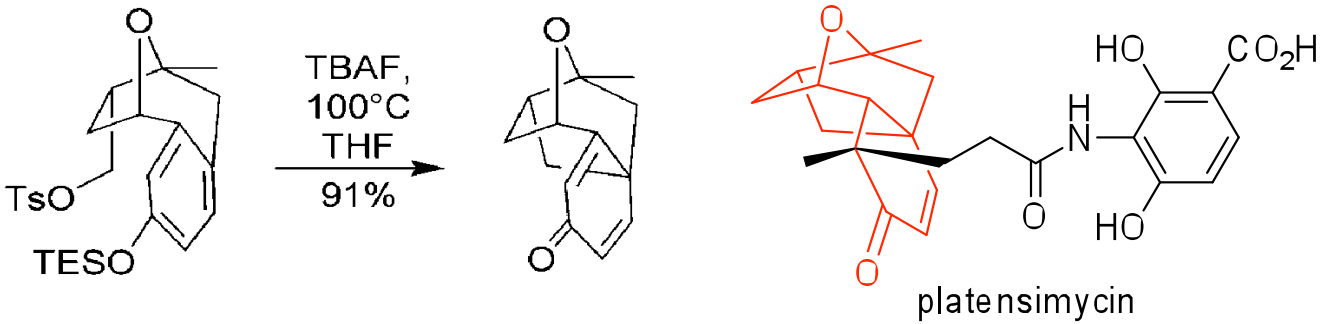


Porco, Jr., *ACIE* **2009**, *48*, 1494.
Porco, Jr., *JACS* **2008**, *130*, *9*, 2738.

Fluoride (TBAF)

- Promoting dearomatization by formation of strong Si-F (135 kcal/mol) bond at elevated temperature
- TBAF
  - platensimycin

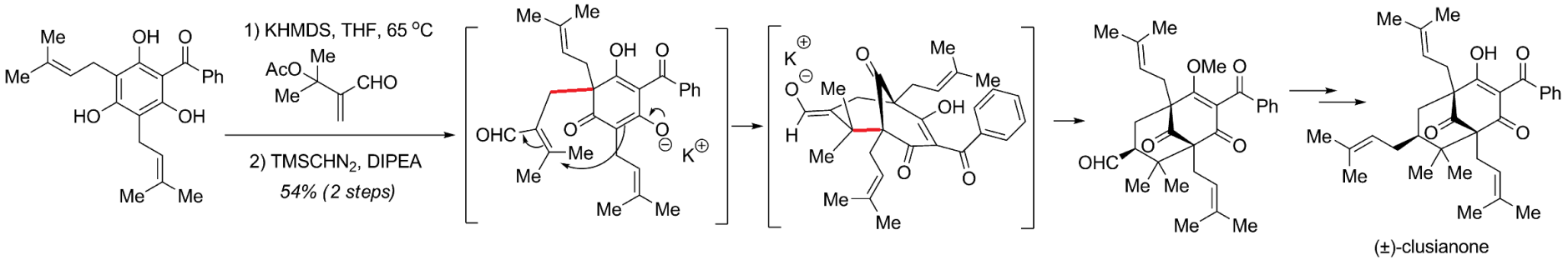




Njardarson, *ACIE* **2009**, *48*, 8543.

KHMDS

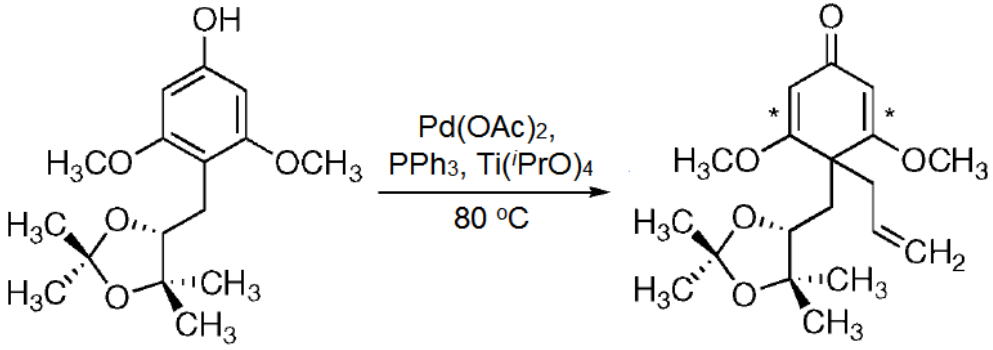
- MEM (michael addition/elimination/michael addition)
  - Formation of bicyclo[3.3.1] framework, clusianone

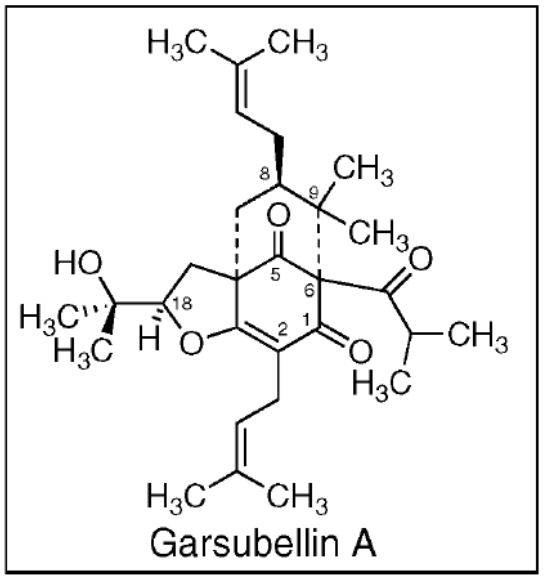


Porco, Jr., *JACS* **2007**, *129*, 12682.

Transition metals

- Direct para C-alkylation or O-alkylation followed by tandem Claisen-Cope rearrangement.
- Application
  - garsubellin A

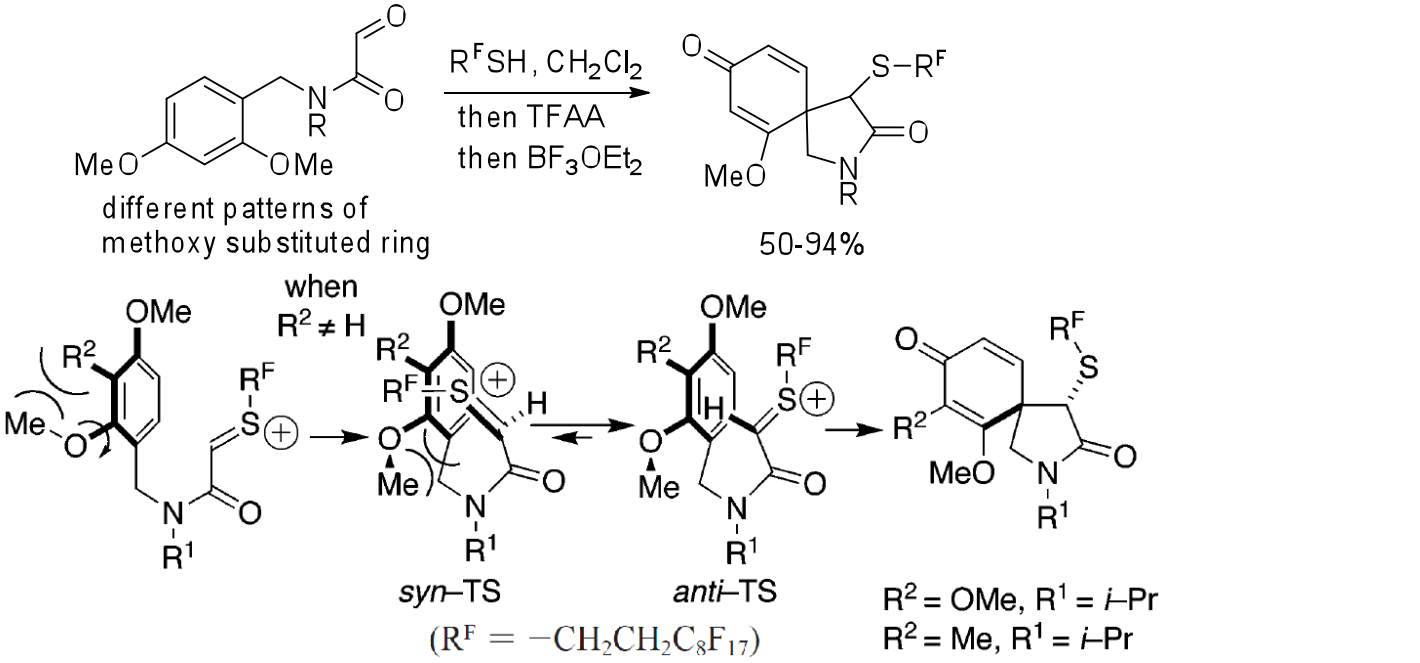




Danishefsky, *JACS* **2006**, *128*, 1048.

R^FSH

- Generation of highly activated thionium ion by addition of Fluorinated thiols to aldehyde
- Spirocyclization, forming 2-azaspiro[4.5]decane core
  - spirostaphylotrichin, diastereoselectivity

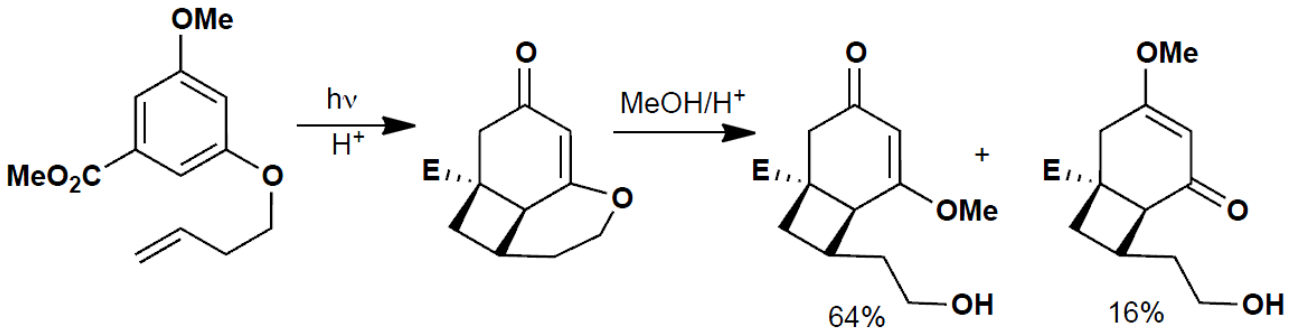


R^2 = OMe, R^1 = *i*–Pr
R^2 = Me, R^1 = *i*–Pr

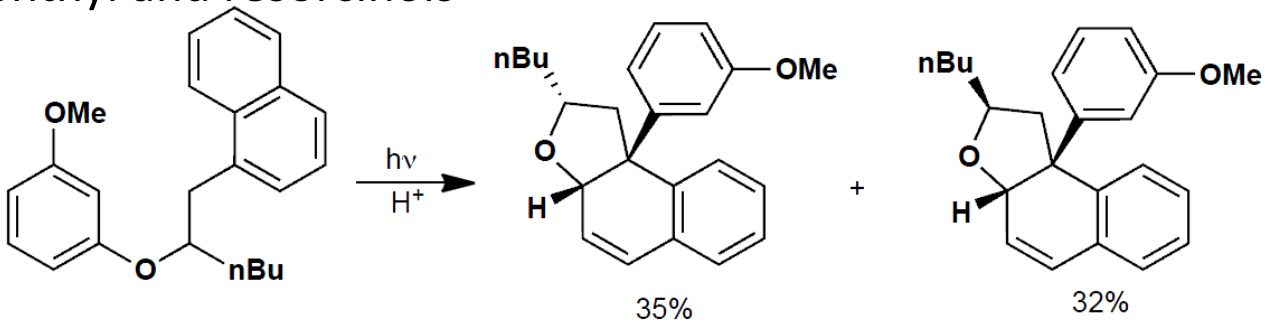
Procter, *Org. Lett.* **2008**, *10*, 1441.

Photochemical dearomatization

- [2+2] photocycloadditions
  - Bichromophoric derivatives



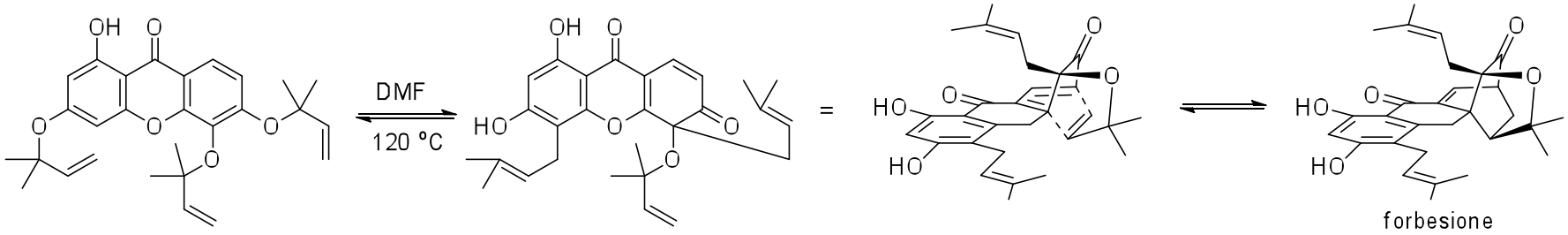
  - Naphthyl and resorcinols



Hoffmann, *Synthesis* **2001**, *8*, 1236.
Hoffmann, *Tetrahedron* **2002**, *58*, 7933.

Thermal dearomatization

- Thermal conditions in polar aprotic solvents (DMF) led to Claisen dearomatization/DA cascade (CDDA)
  - Gambogin



Theodorakis, *PNAS* **2004**, *101*, 12030.

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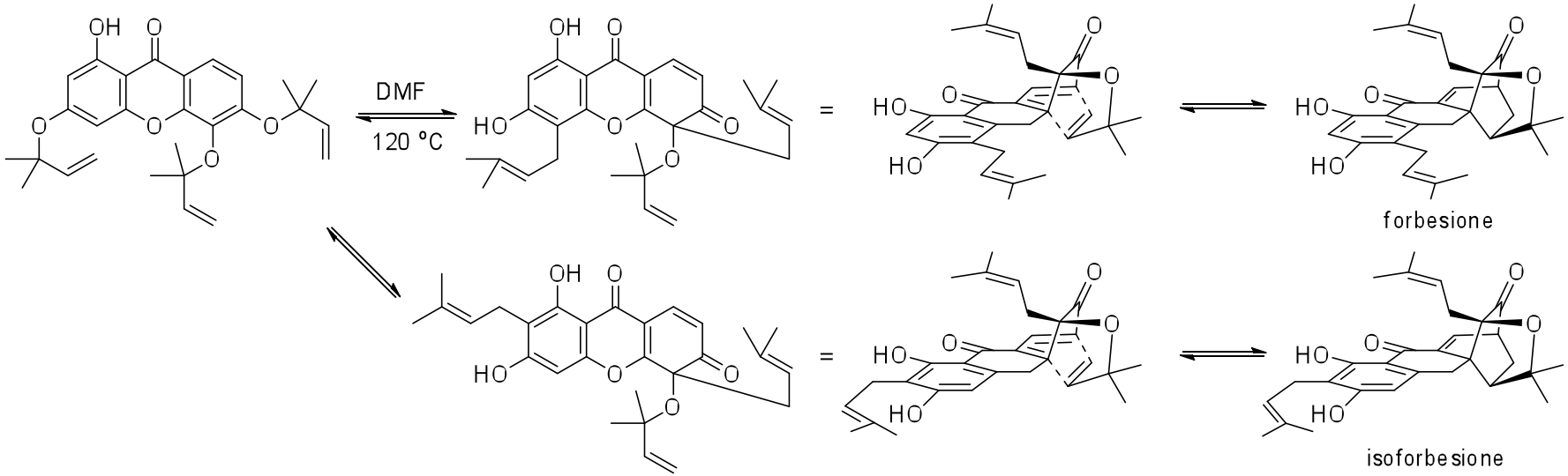

Theodorakis, *PNAS* **2004**, *101*, 12030.

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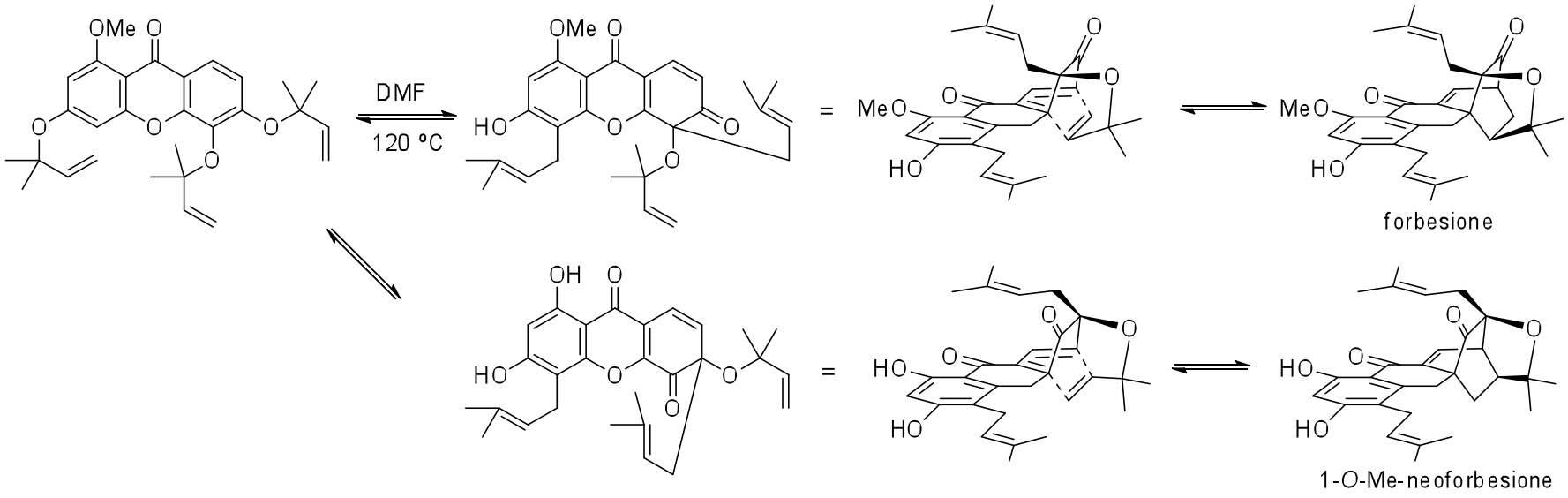

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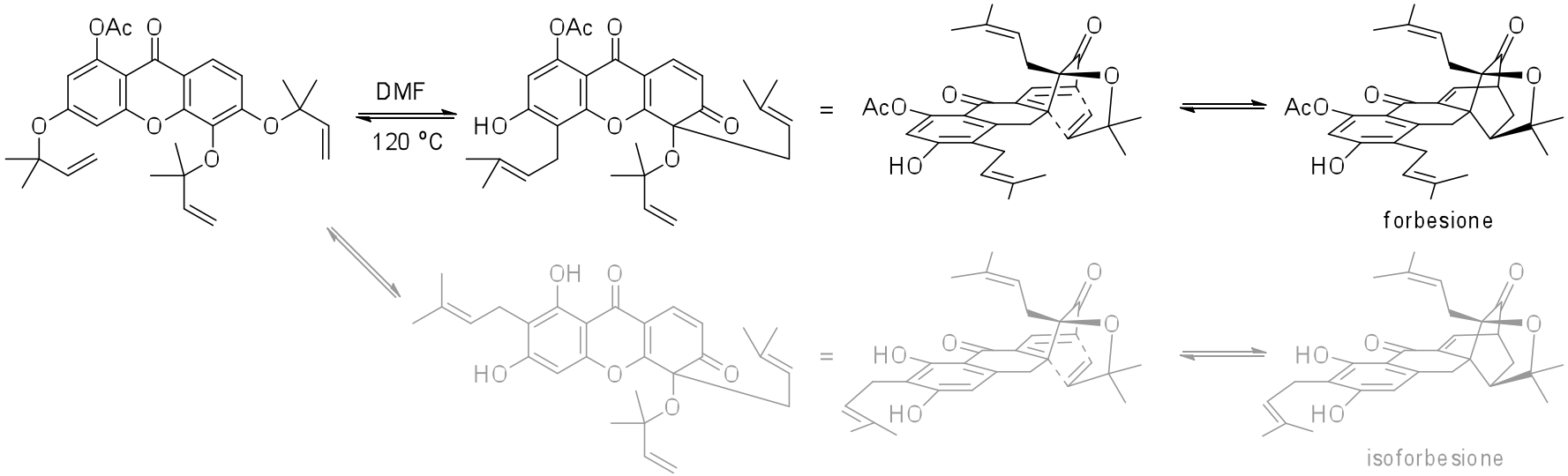

Theodorakis, *PNAS* **2004**, *101*, 12030.

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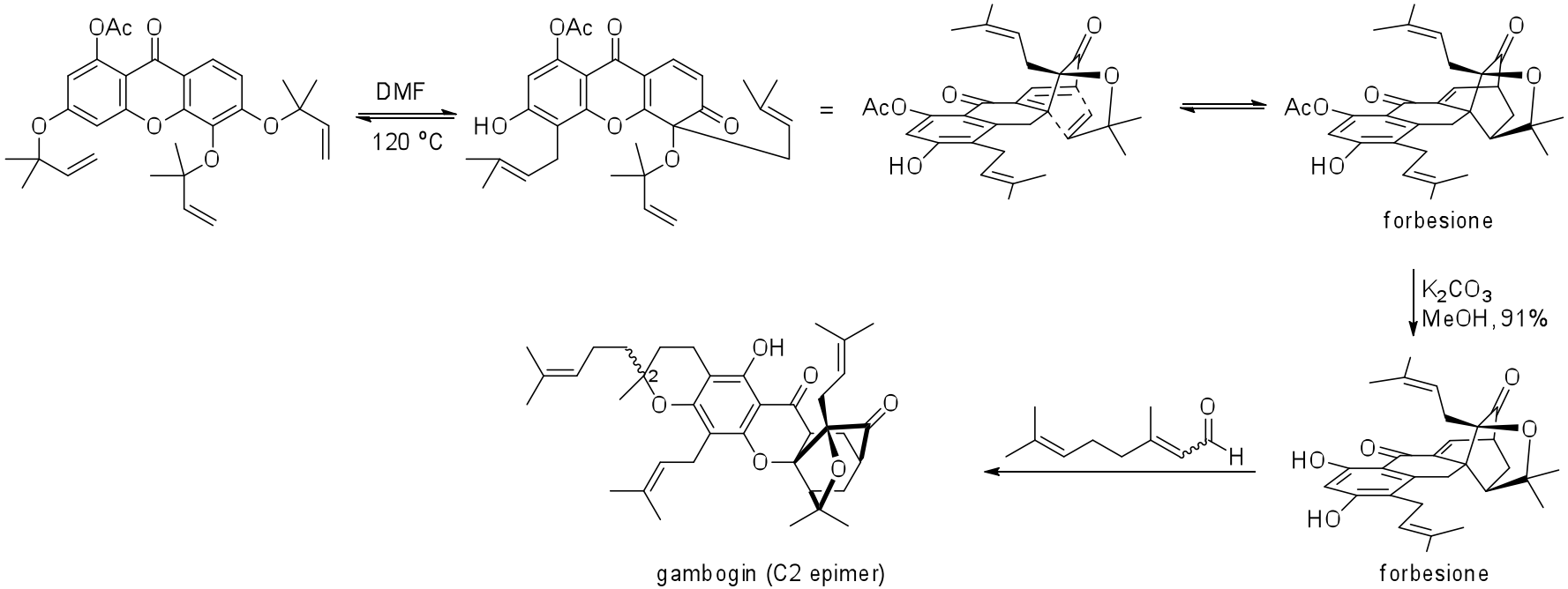
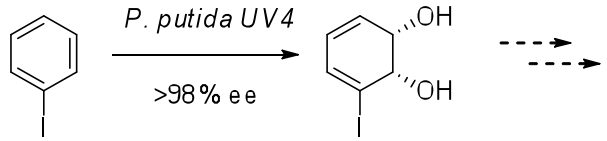
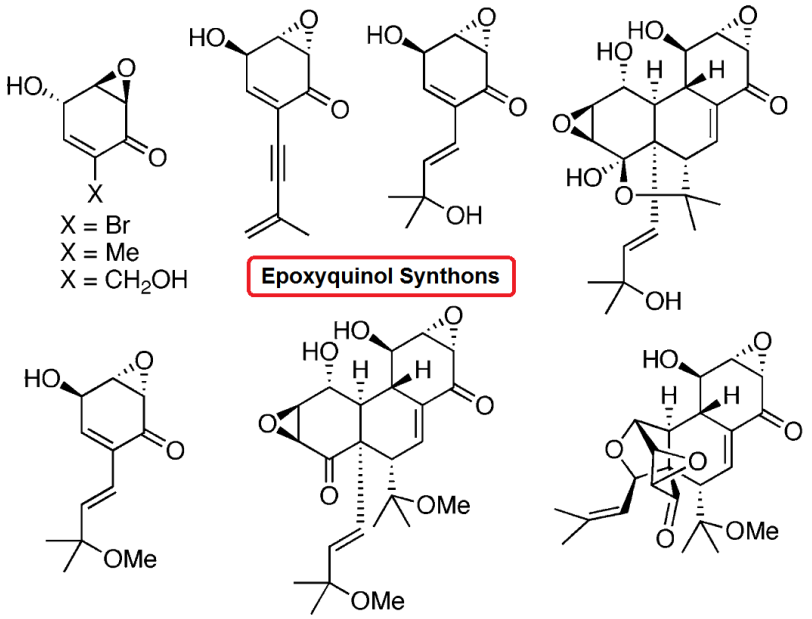


Theodorakis, *PNAS* **2004**, *101*, 12030.

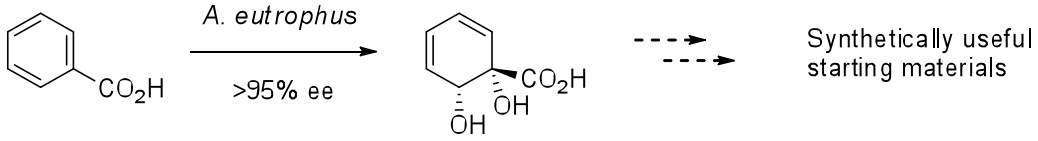
Enzymatic / Microbial Process

- *Pseudomonas putida UV4*





- *Alcaligenes eutrophus B9*
  - Preparation of the useful building blocks for biologically active compounds



Banwell, *Org. Lett.* **2009**, *11*, 4290.
Myers, *Org. Lett.* **2011**, *3*, 2923.

Conclusions

- A number of reagents and strategies for oxidative dearomatization and its sequential cascades has been developed to achieve the complex structures of naturally occurring compounds.

- Thank you!