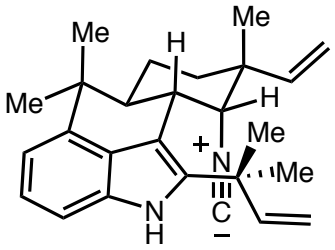
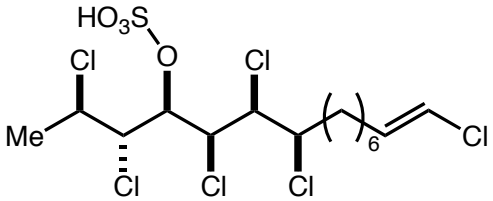
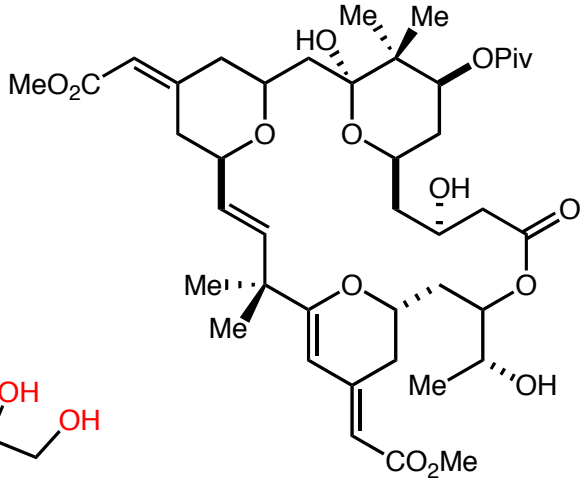
Organic Syntheses Published in Nature

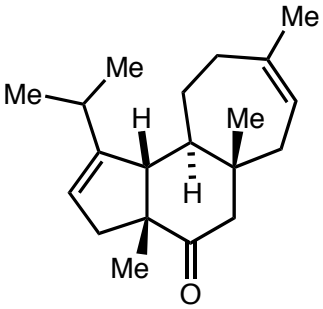
and Why

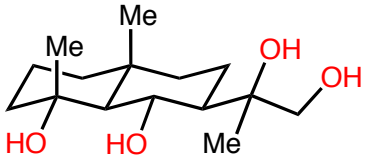
(2005-2010)











MacMillan Group Meeting
17 March 2011

Jeff Garber

Nature

- First published November 4, 1869
- Published by Alexander Macmillan
- Started by Joseph Norman Lockyer

Nature

- 2009 Impact factor: 34.48
- Comparable to *Science* in all statistics
- Far fewer chemistry articles *not* related to chemical biology or biochemistry

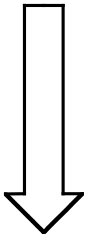
Nature

Criteria for publication (Articles and Letters)

Report original scientific research

Are of outstanding scientific importance

Reach a conclusion of interest to an *interdisciplinary* readership



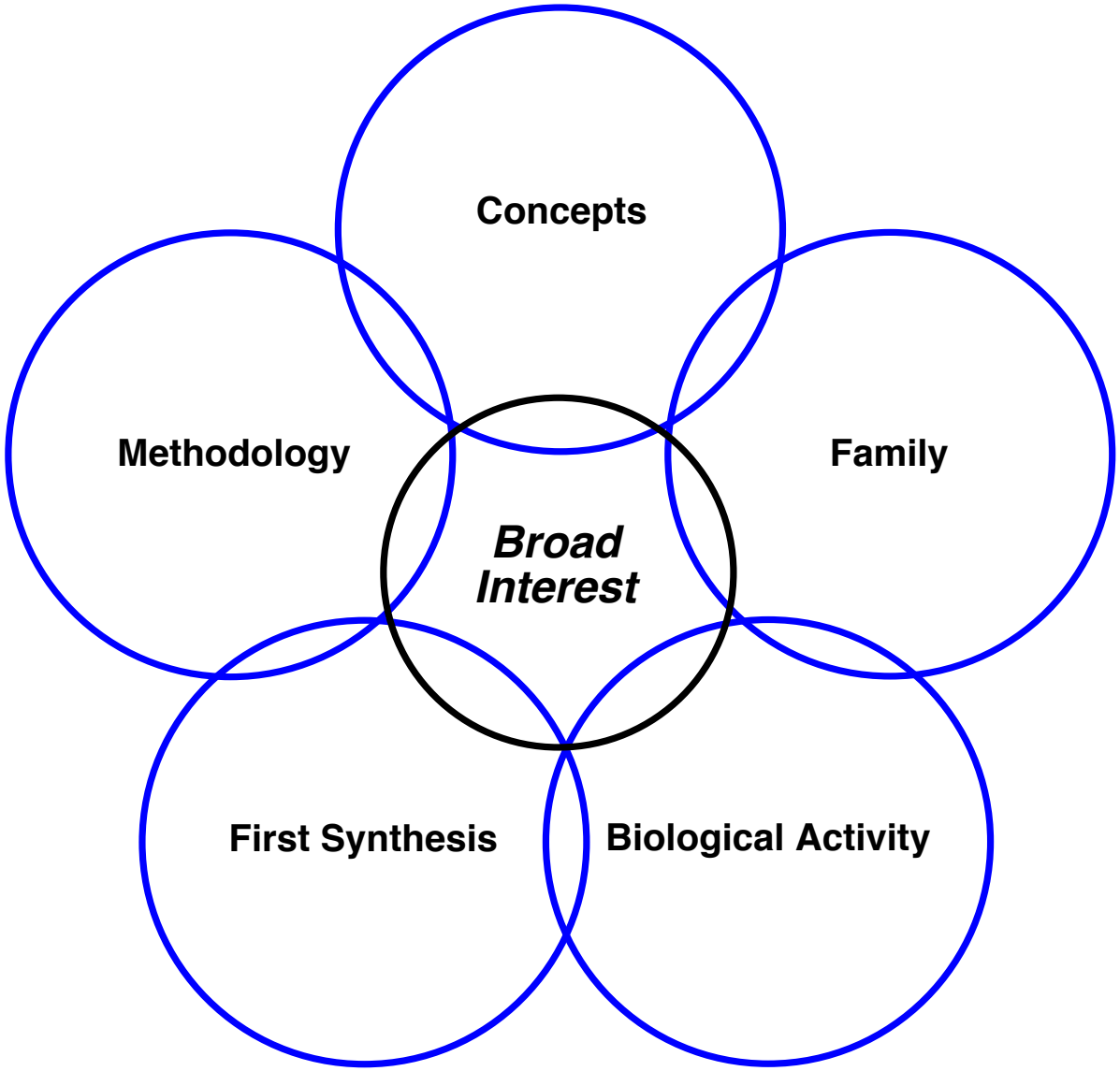
About 10,000 articles submitted/year

Only about 800 are accepted (8%)

Decision about broad interest made solely by *Nature* editors, not referees

www.nature.com

Why Nature *?*


Concepts
Methodology
Family
Broad Interest
First Synthesis
Biological Activity

Nature

Papers not covered in this talk

"Synthesis and structural analysis of 2-quinuclidonium tetrafluoroborate"
Tani, K., Stoltz, B. M. *Nature*, **2006**, *441*, 731-734.

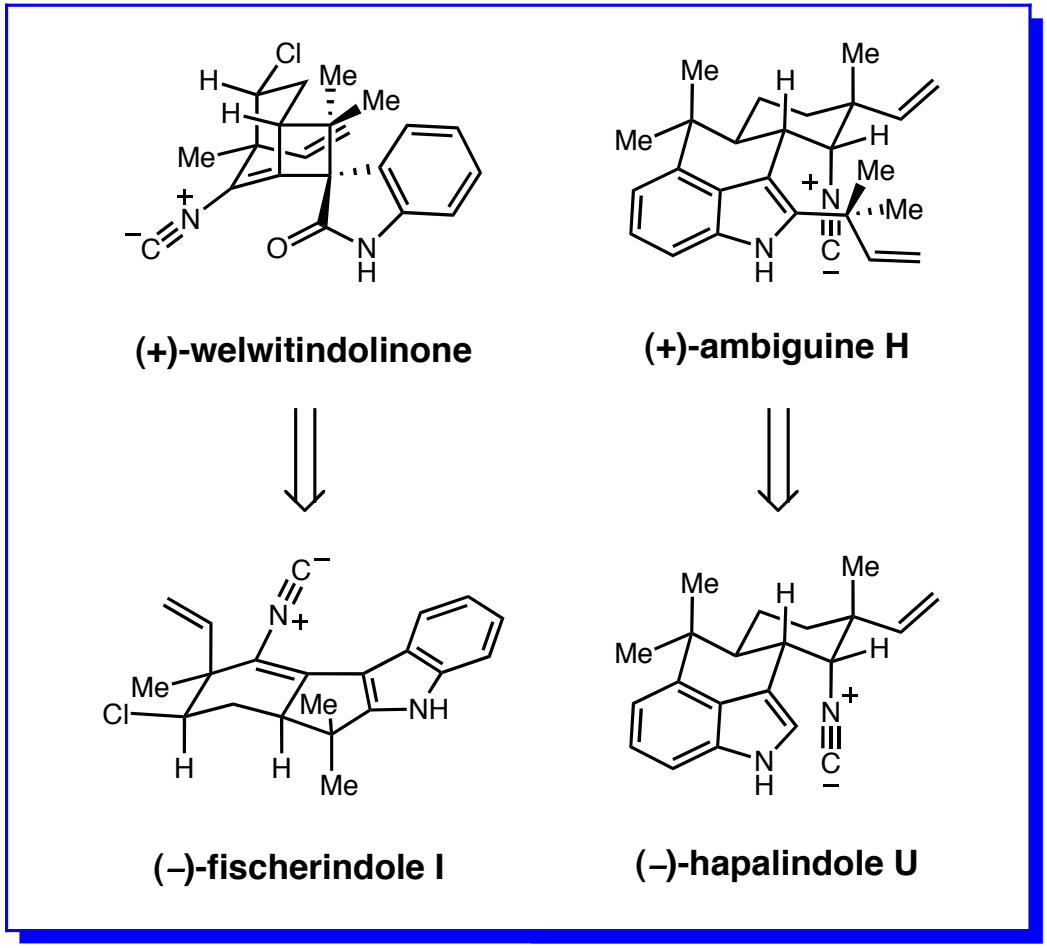
"Highly efficient molybdenum-based catalysts for enantioselective alkene metathesis"
Hoveyda *et al*. *Nature*, **2008**, *456*, 933-937.

"Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions"
Sutherland *et al*. *Nature*, **2009**, *459*, 239-242.

"Scaleable catalytic asymmetric Strecker syntheses of unnatural a-amino acids"
Jacobsen *et al*. *Nature*, **2009**, *461*, 968-971.

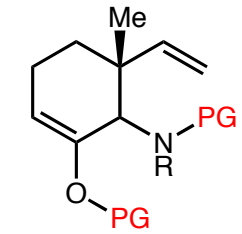
"*Umpolung* reactivity in amide and peptide synthesis"
Johnston *et al*. *Nature*, **2010**, *465*, 1027-1033.

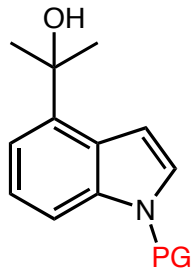
Total synthesis of marine natural products without using protecting groups



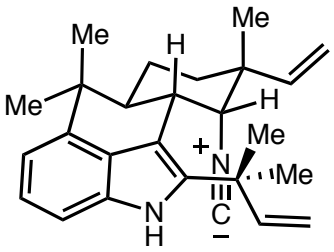
Baran, P.S., Maimone, T. J., Richter, J. M. *Nature*, **2007**, *446*, 404-408.

Protecting Group Free Syntheses: General Concept



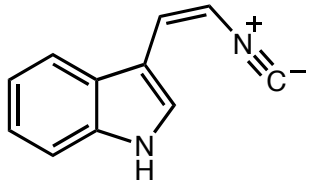


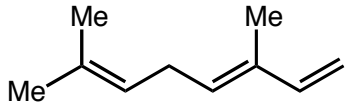
"Standard"

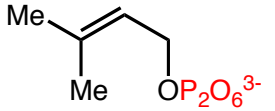


Ambiguine H

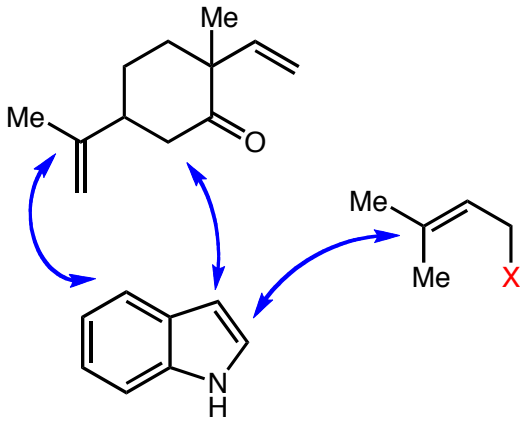
Biological







Baran



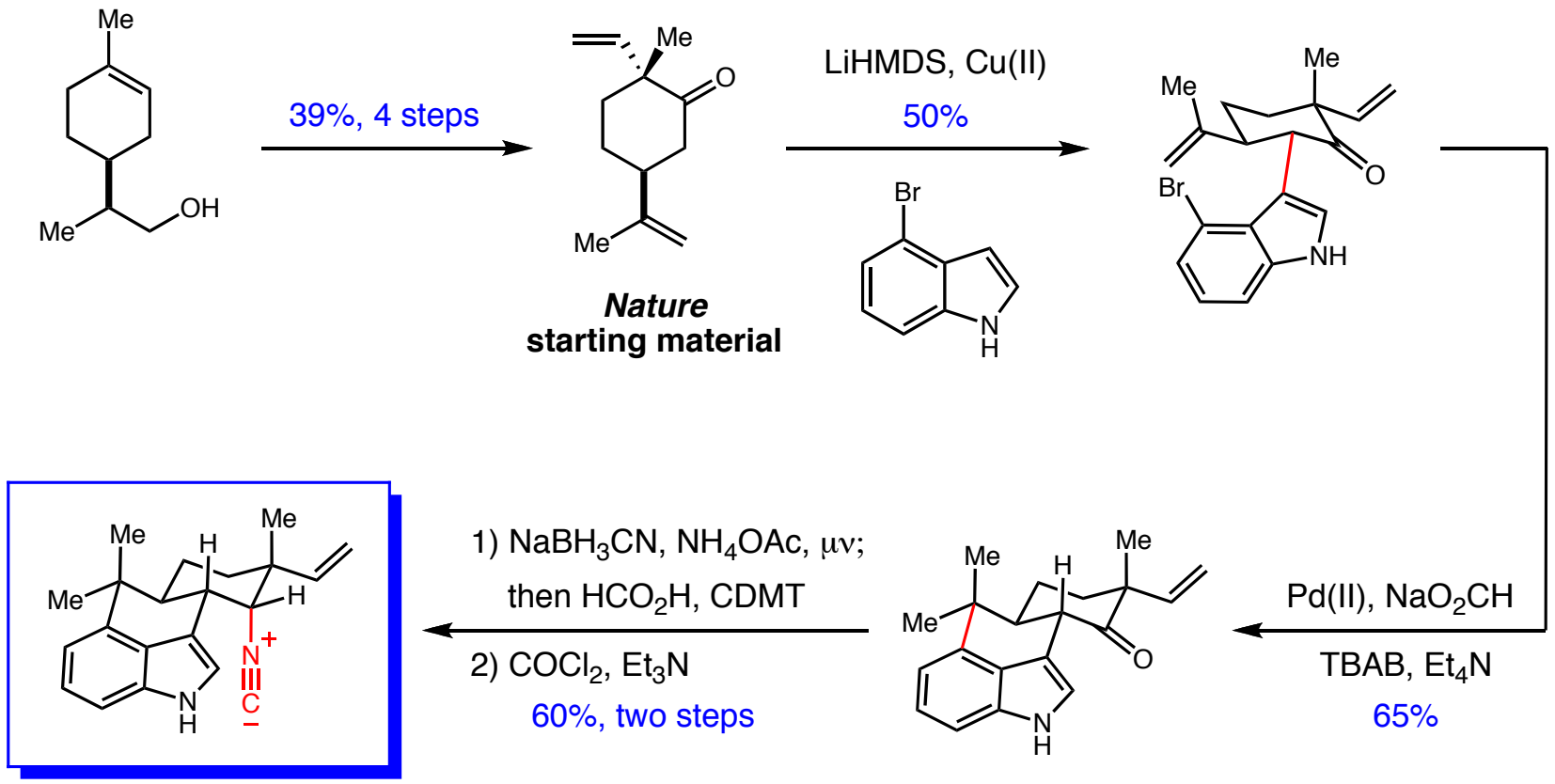
- Protecting groups needed
- "Caged reactivity"

- Enzymes necessary
- No protecting groups

- No enzymes

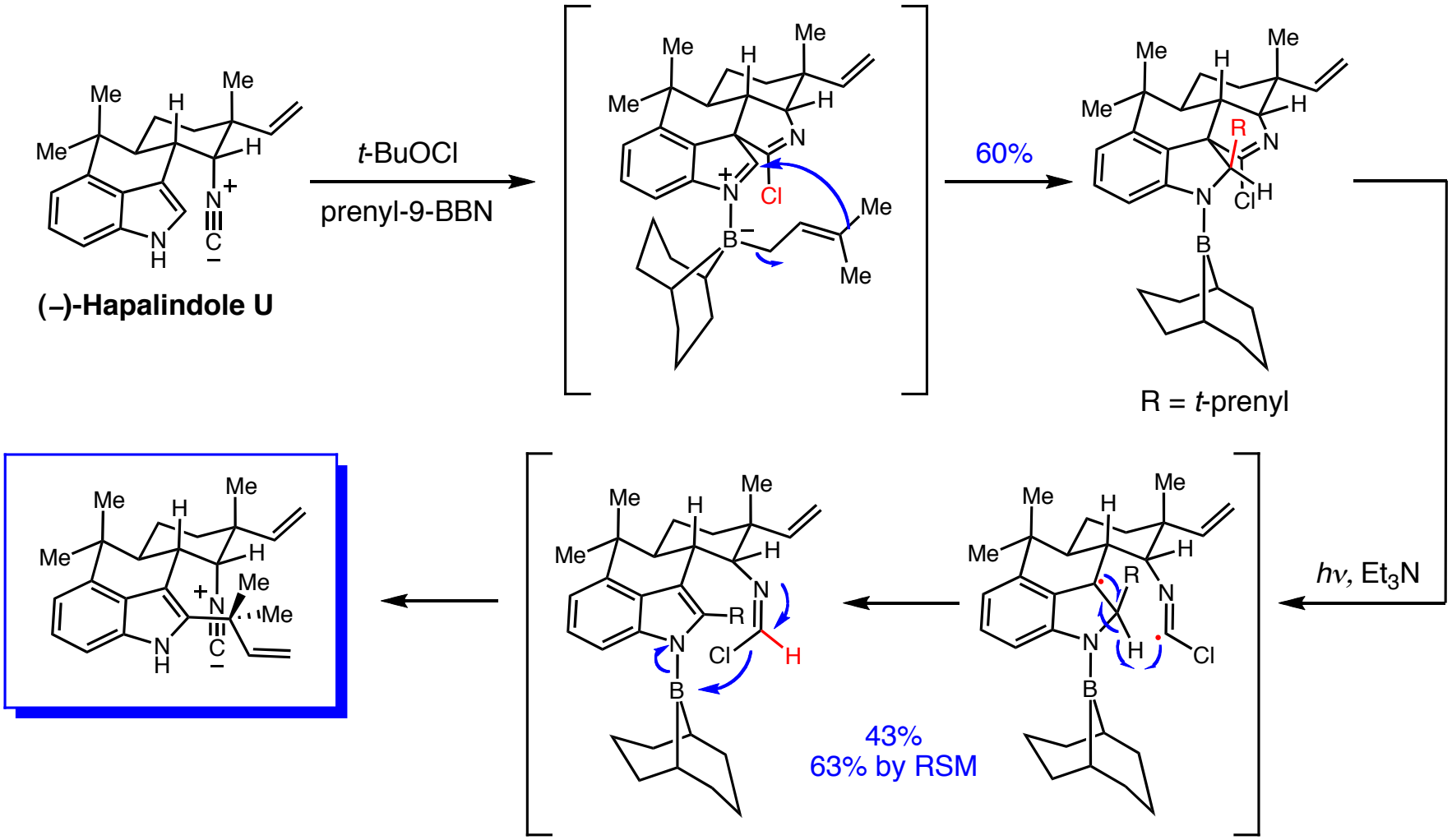
- No protecting groups

(–)-Hapalindole U



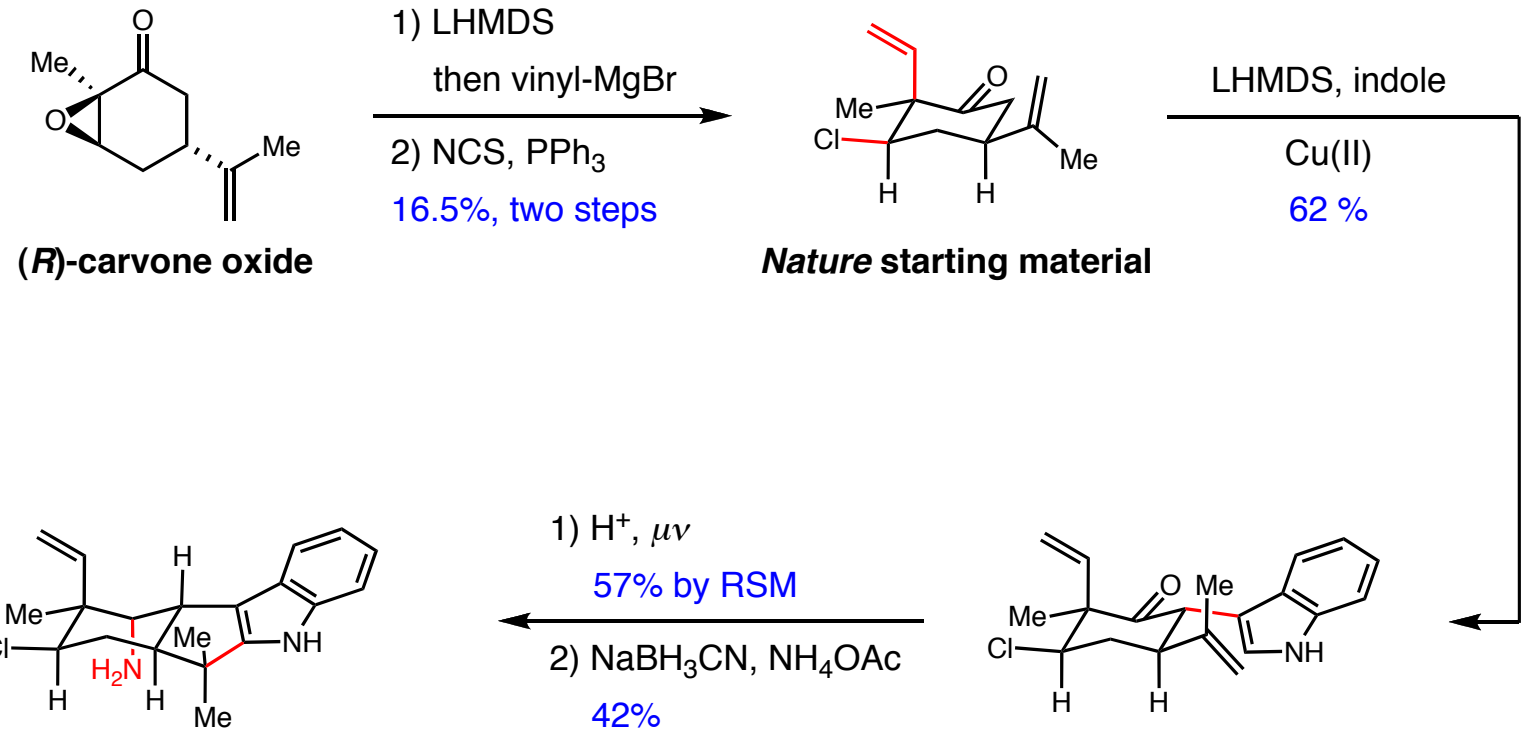
- 8 steps, 7.61% yield (from commercially available materials)
  - Previous: 20 steps, racemic (Natsume, 1990)

(+)-Ambiguine H

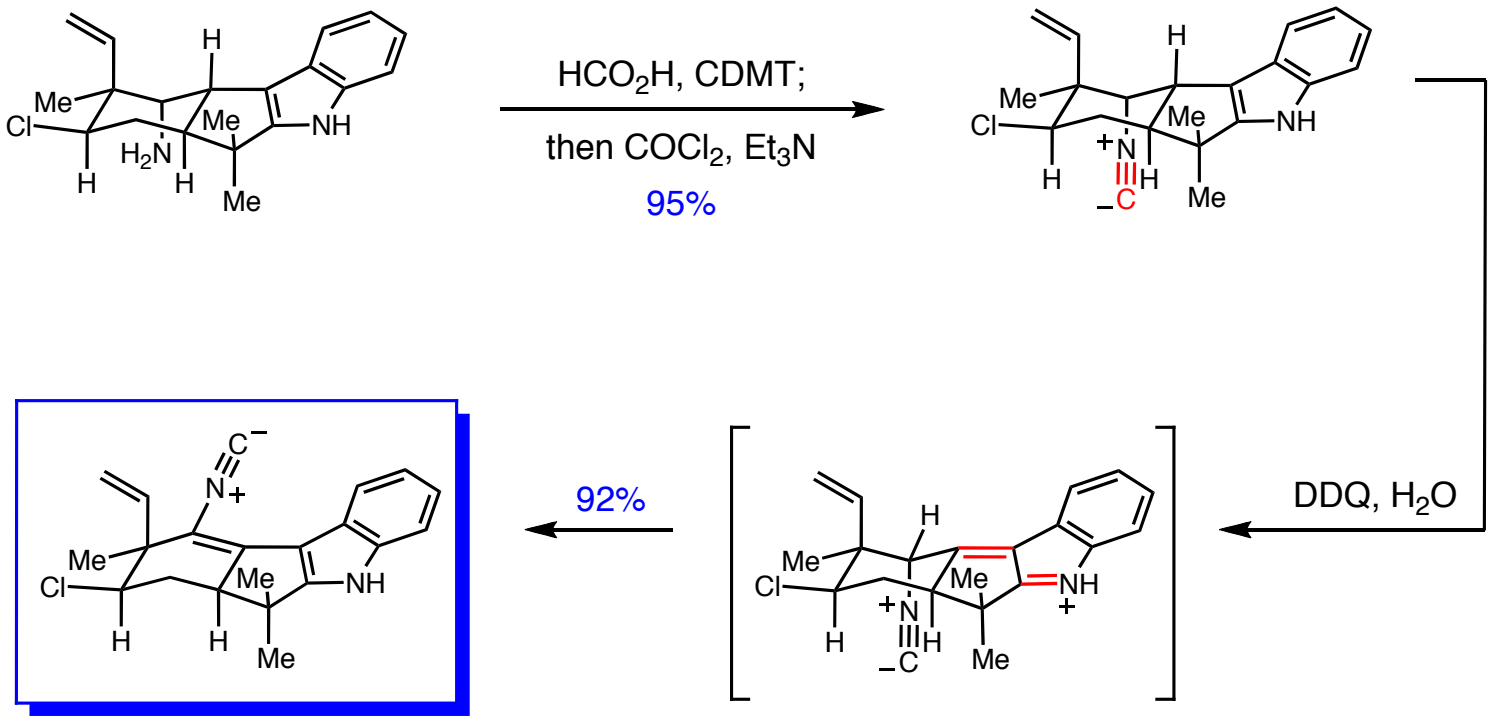


- 10 steps, 2.88% yield by RSM (from commercially available materials)
- No previous syntheses

(–)-Fischerindole I

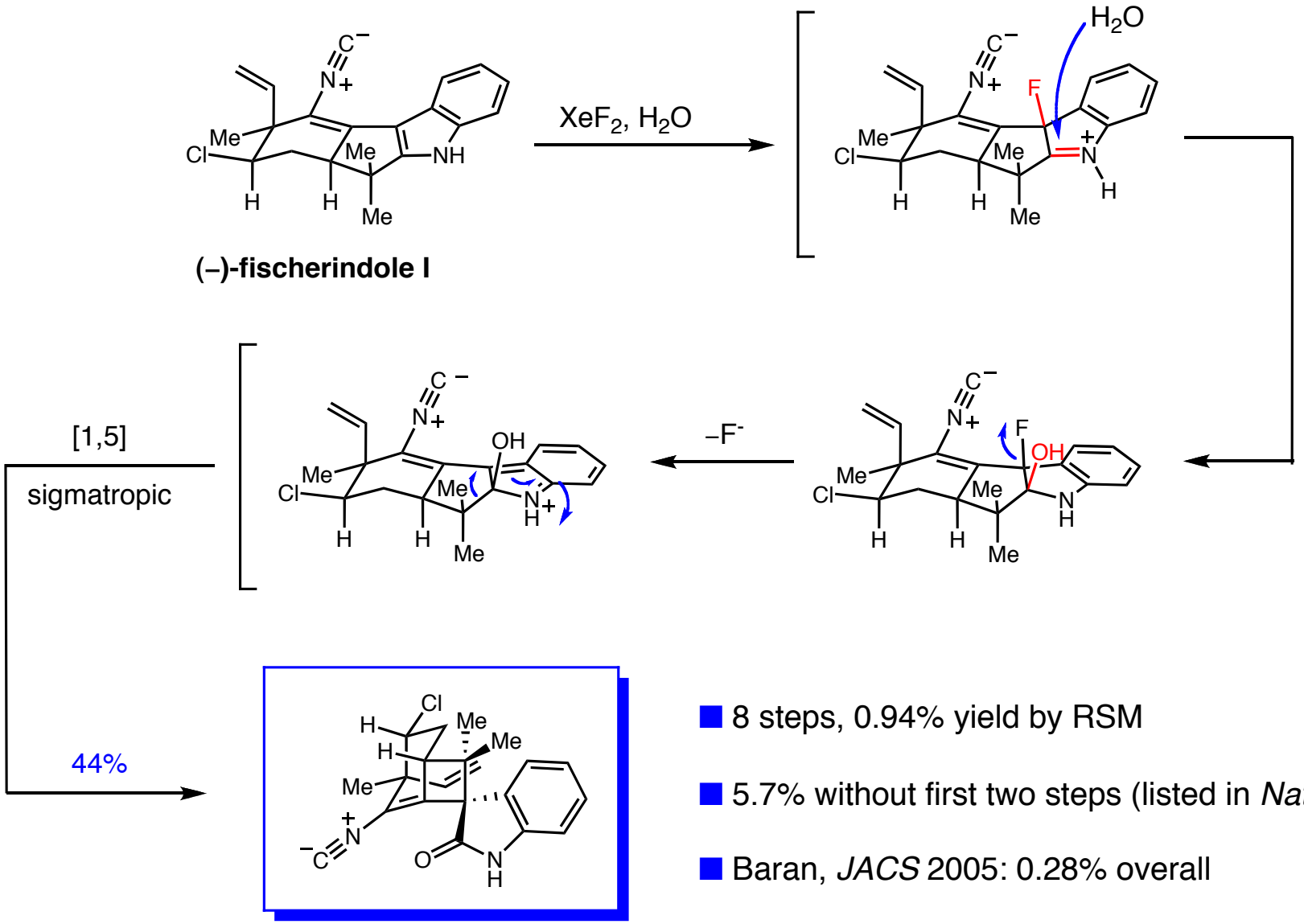


(–)-Fischerindole I



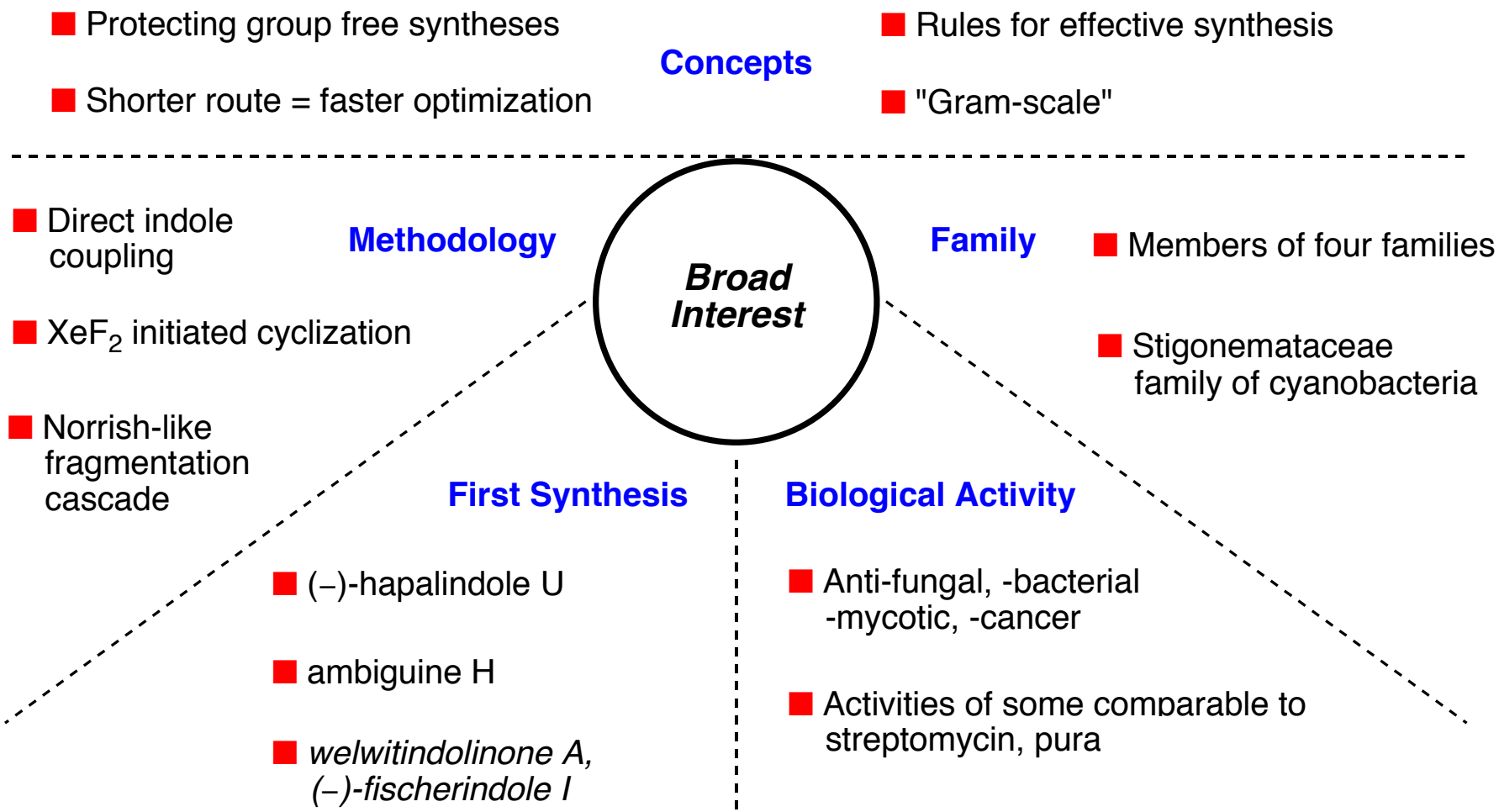
- 7 steps, 2.14% yield by RSM
- 13% without first two steps
- Previous: Baran, *JACS* 2005, 1.14%, 7 steps

(+)-Welwitindolinone

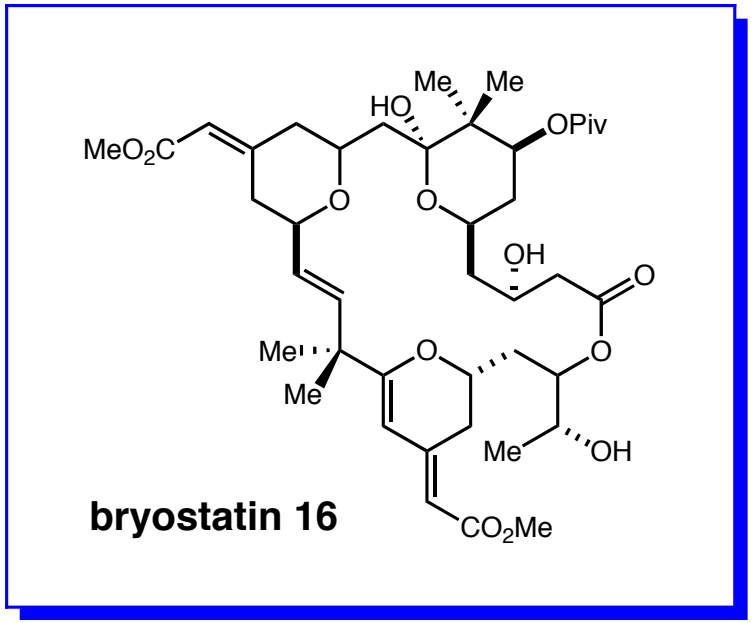


- 8 steps, 0.94% yield by RSM
- 5.7% without first two steps (listed in *Nature*)
- Baran, *JACS* 2005: 0.28% overall

Marine natural products overview



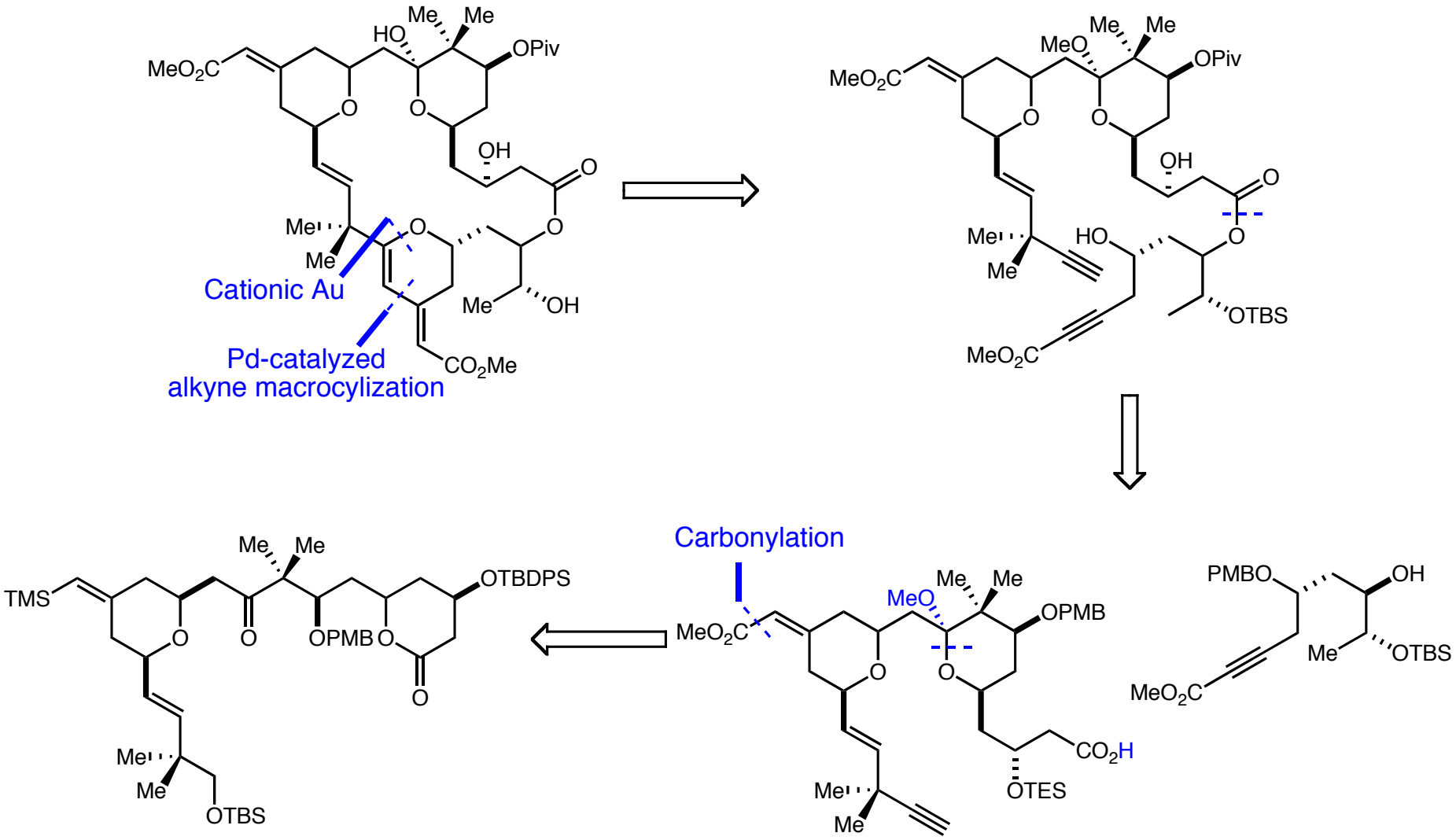
Total synthesis of bryostatin 16 using atom-economical and chemoselective approaches



bryostatin 16

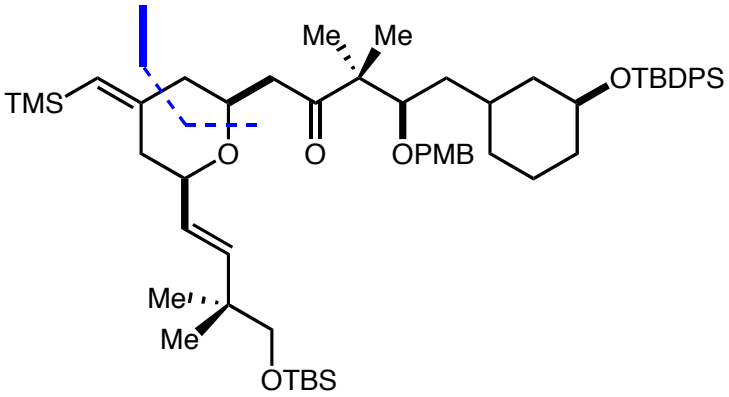
Trost, B. M., Dong, G. *Nature*, **2008**, *456*, 485-488.

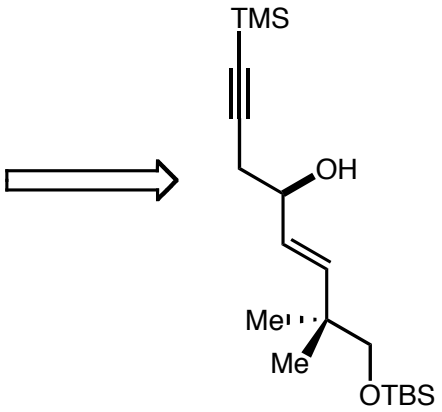
Bryostatin 16: Retrosynthetic Analysis

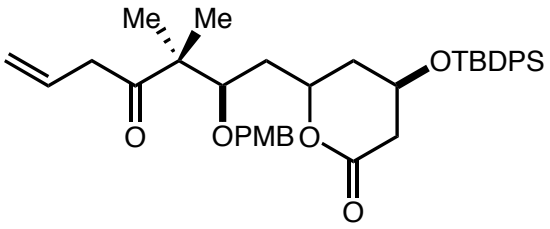


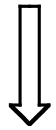
Bryostatin 16: Retrosynthetic Analysis

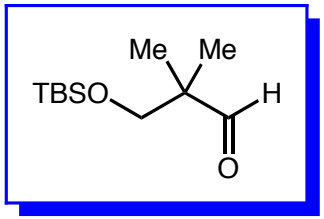
Tandem alkene-alkyne coupling/
Michael addition

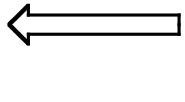


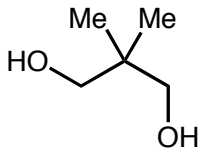








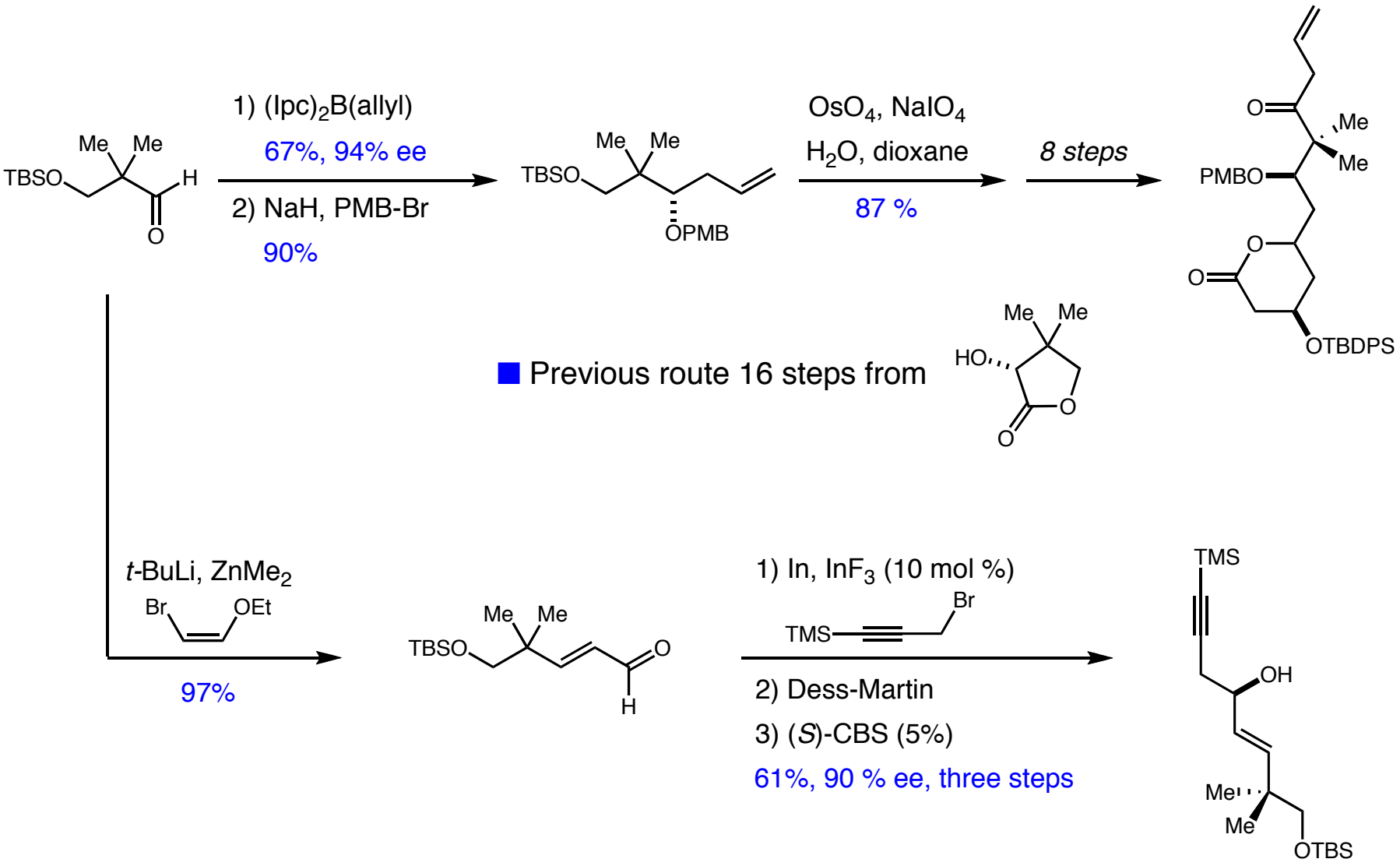




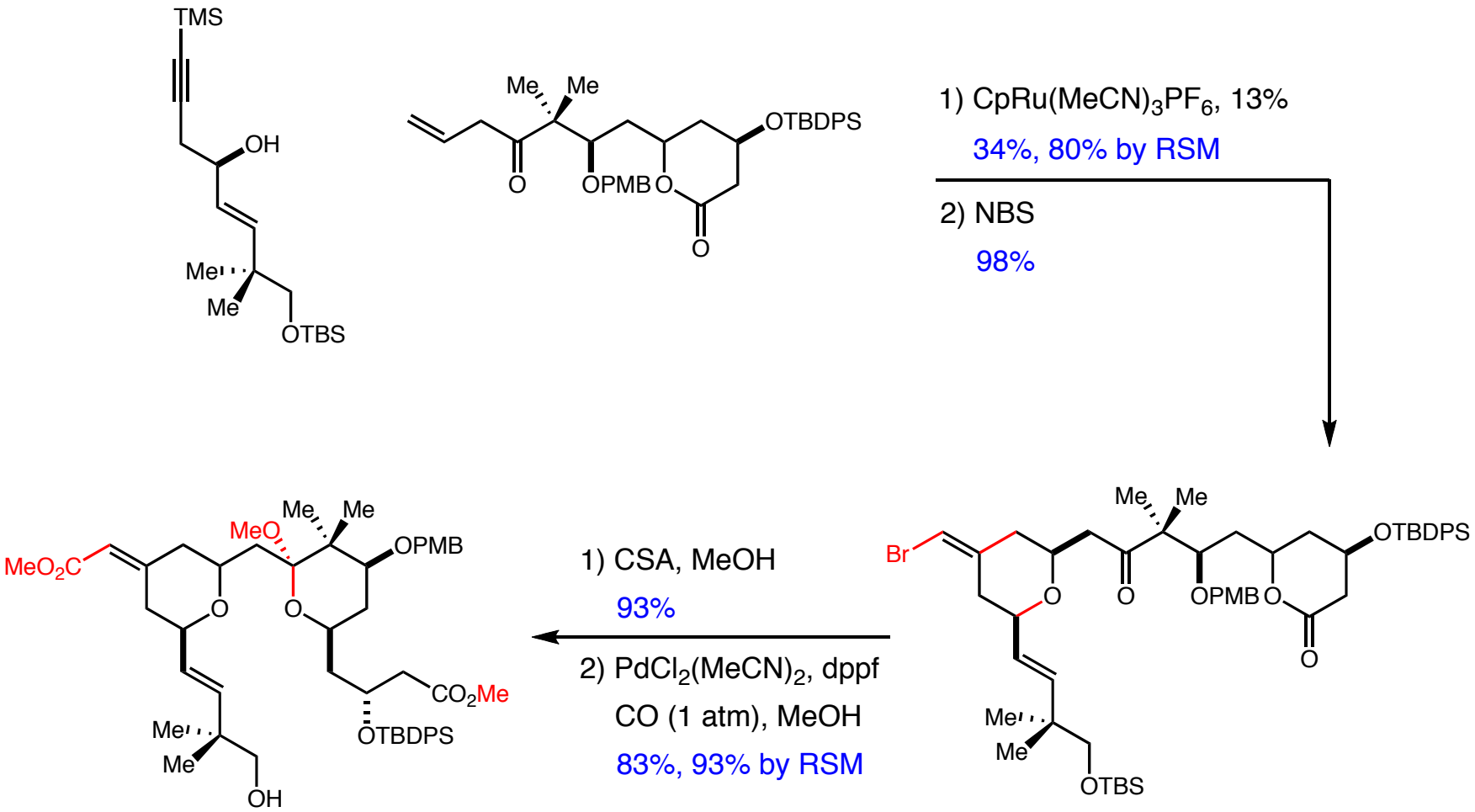
commercially available

- Convergent and "atom economical"
- Incorporates new methodologies
- Adaptable to analogue syntheses

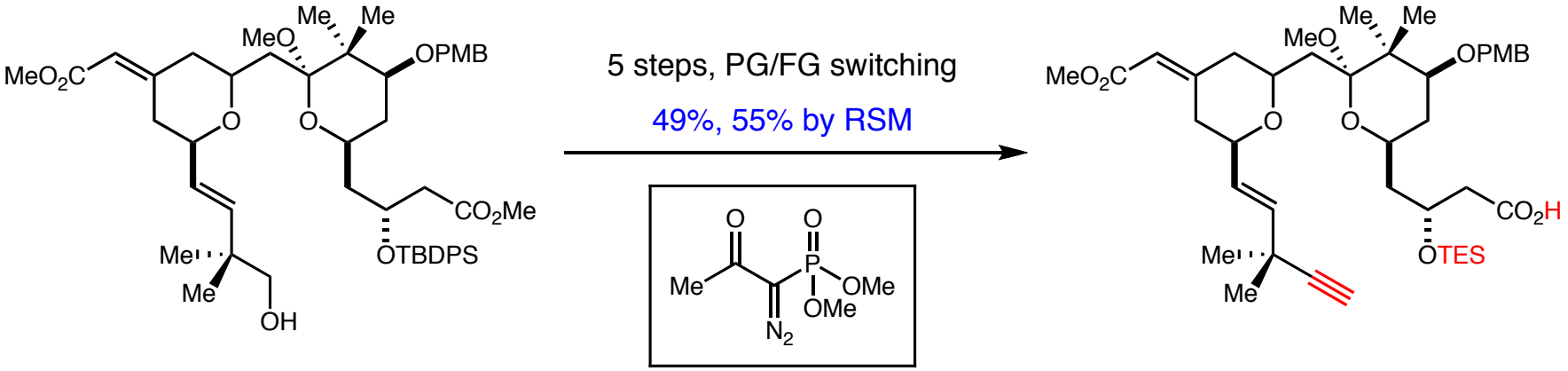
Bryostatin 16

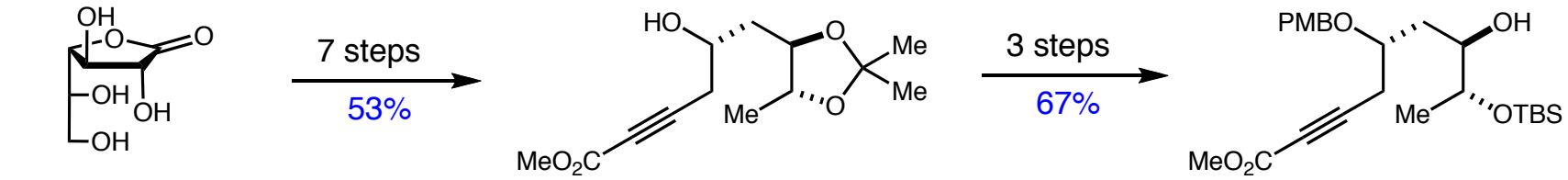


Bryostatin 16



Bryostatin 16

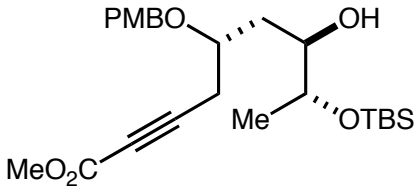


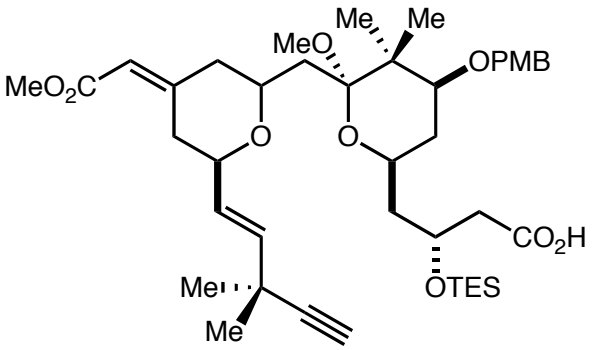


D-glactonic acid 1,4-lactone

***Nature* starting material**

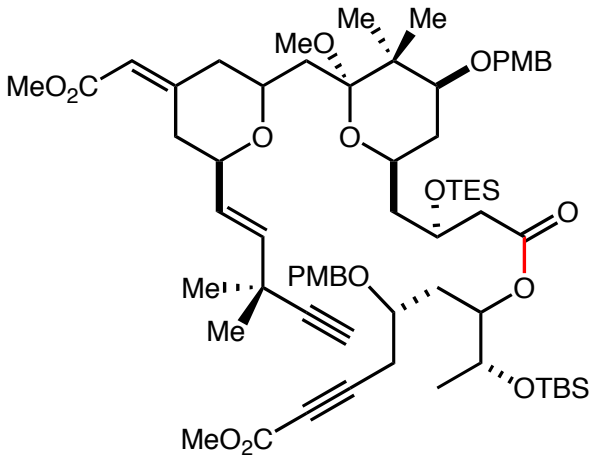
Bryostatin 16





(2,4,6-$Cl_3Ph)CH_2Cl$, Et_3N;
then acid, DMAP

92%

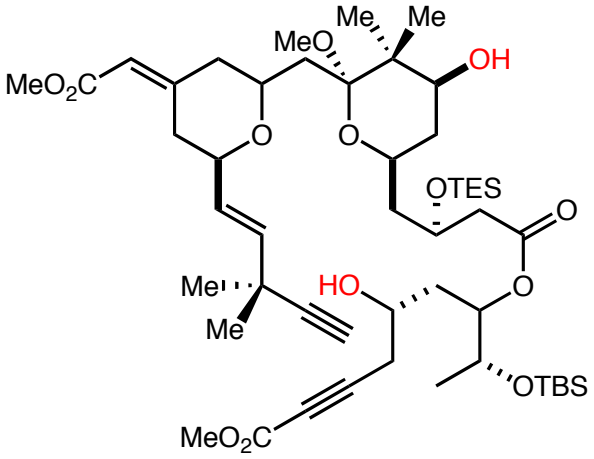


DDQ, pH 7.0 buffer

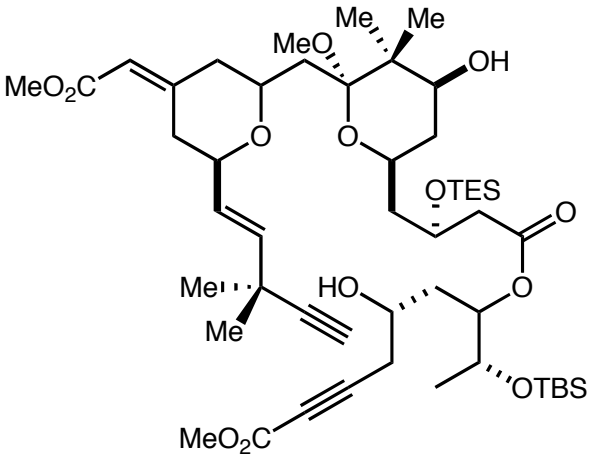
46% diol, 58% mono-PMB

Resubject mono-PMB

75% overall

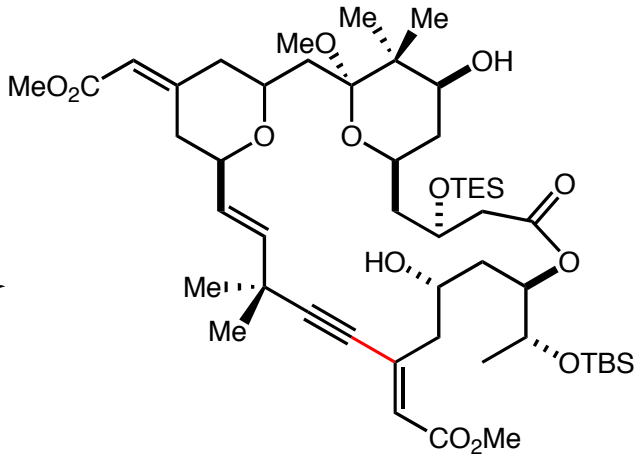


Bryostatin 16

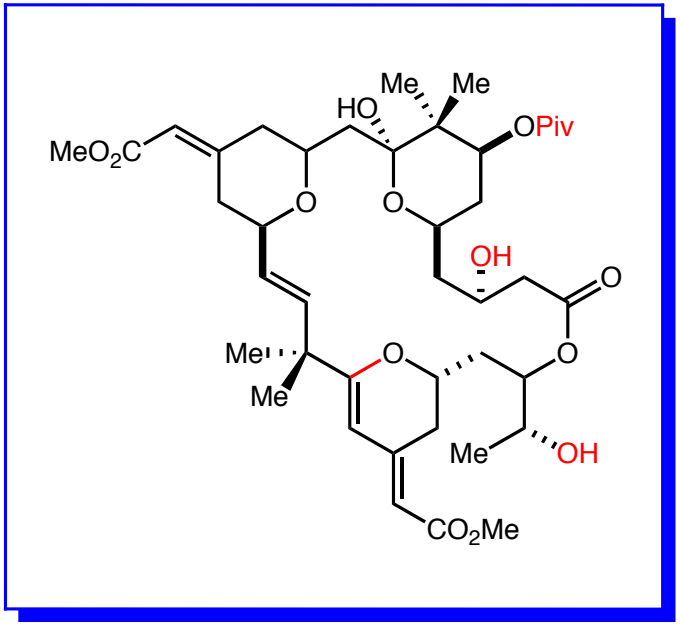


$Pd(OAc)_2$ (12 mol%)
$(2,6\text{-}(OMe)_2Ph)_3P$ (15 mol%)

56%



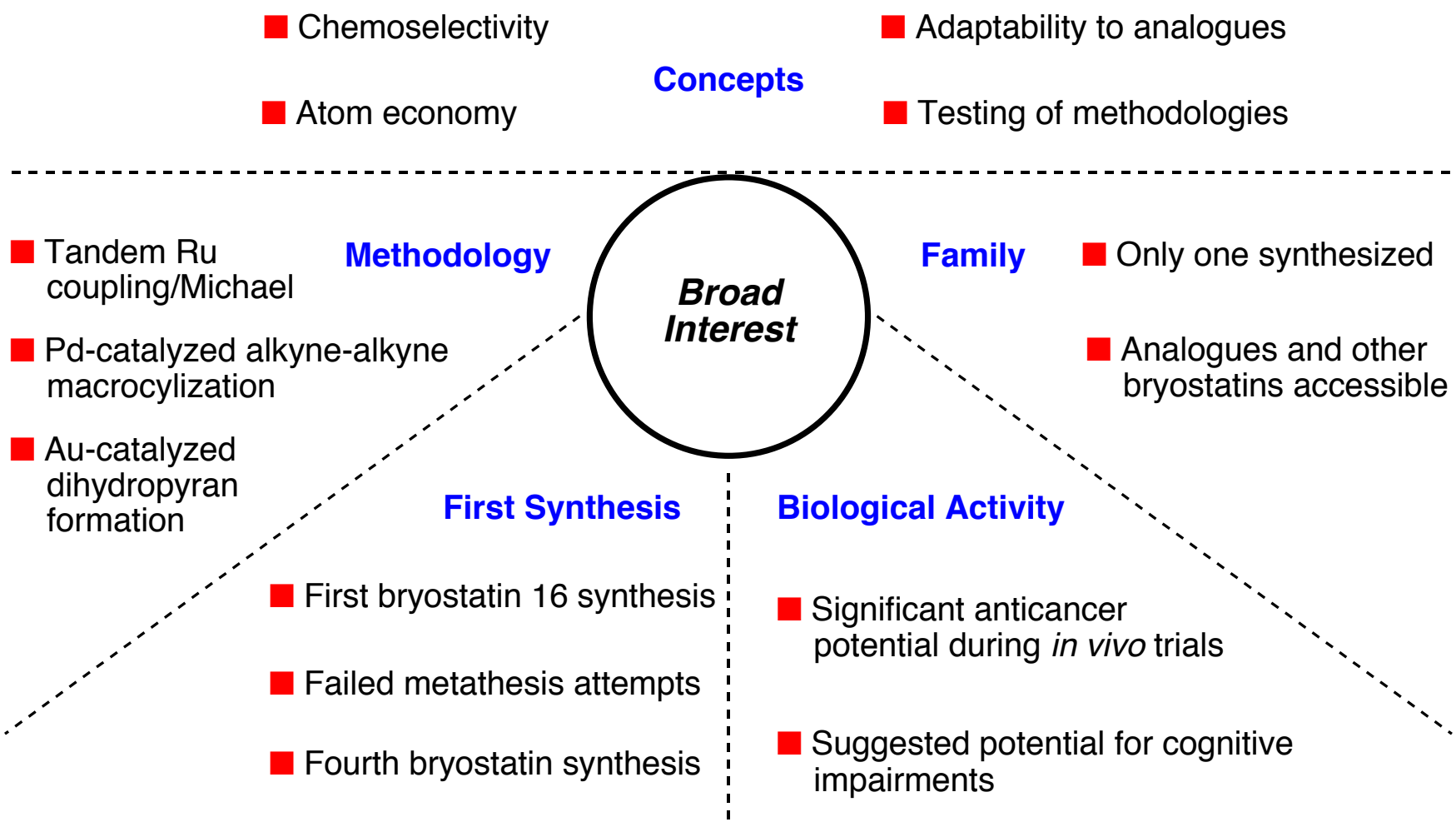
- Longest linear: 26 steps, 0.09%
  - By RSM: 0.27%
- 35 total steps
  - From commercial: 45 steps



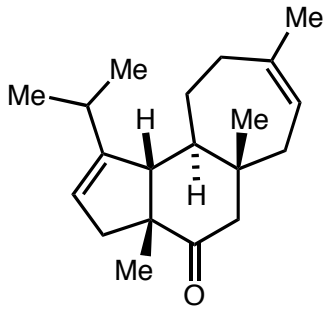
1) $AuCl(PPh_3)$ (20 mol%)
$AgSbF_6$ (20 mol%)
73%

2) Piv_2O, DMAP
3) TBAF
32%, last two steps

Bryostatin 16 overview



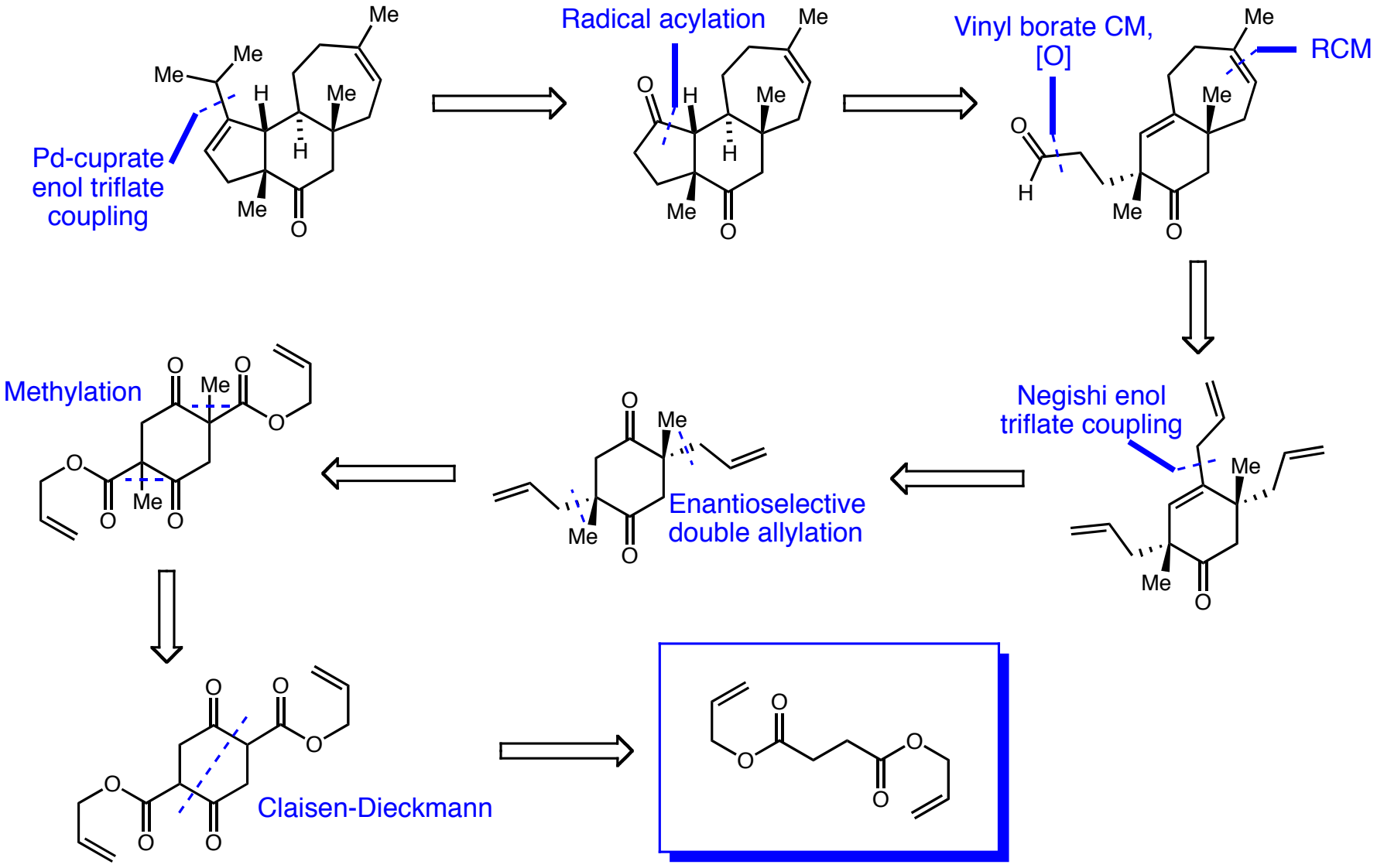
The total synthesis of (–)-cyanthiwigin F by means of catalytic enantioselective alkylation



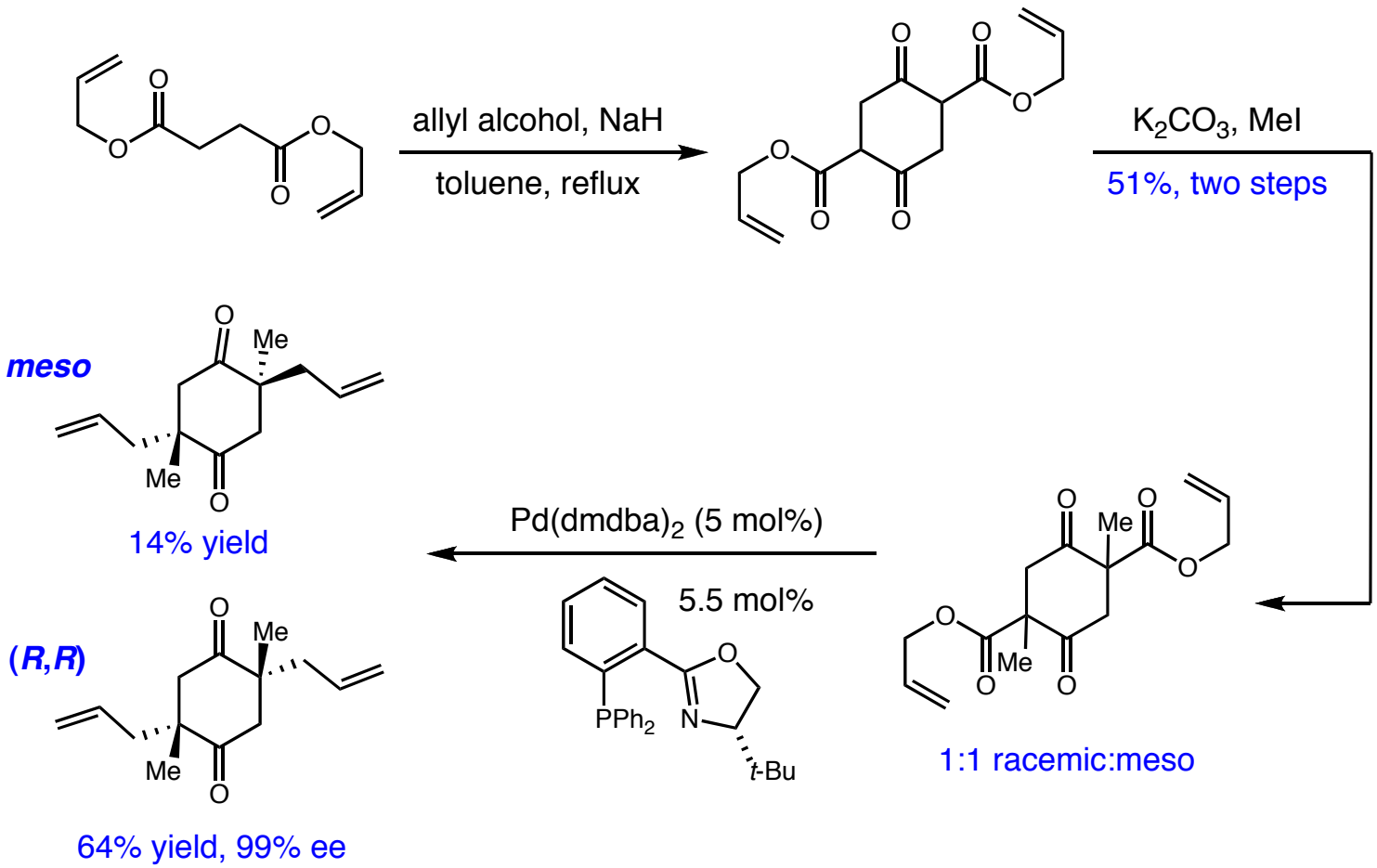
(–)-Cyanthiwigin F

Enquist, J. A., Stoltz, B. M. *Nature*, **2008**, *453*, 1228-1231.

(–)-Cyanthiwigin F: Retrosynthetic Analysis

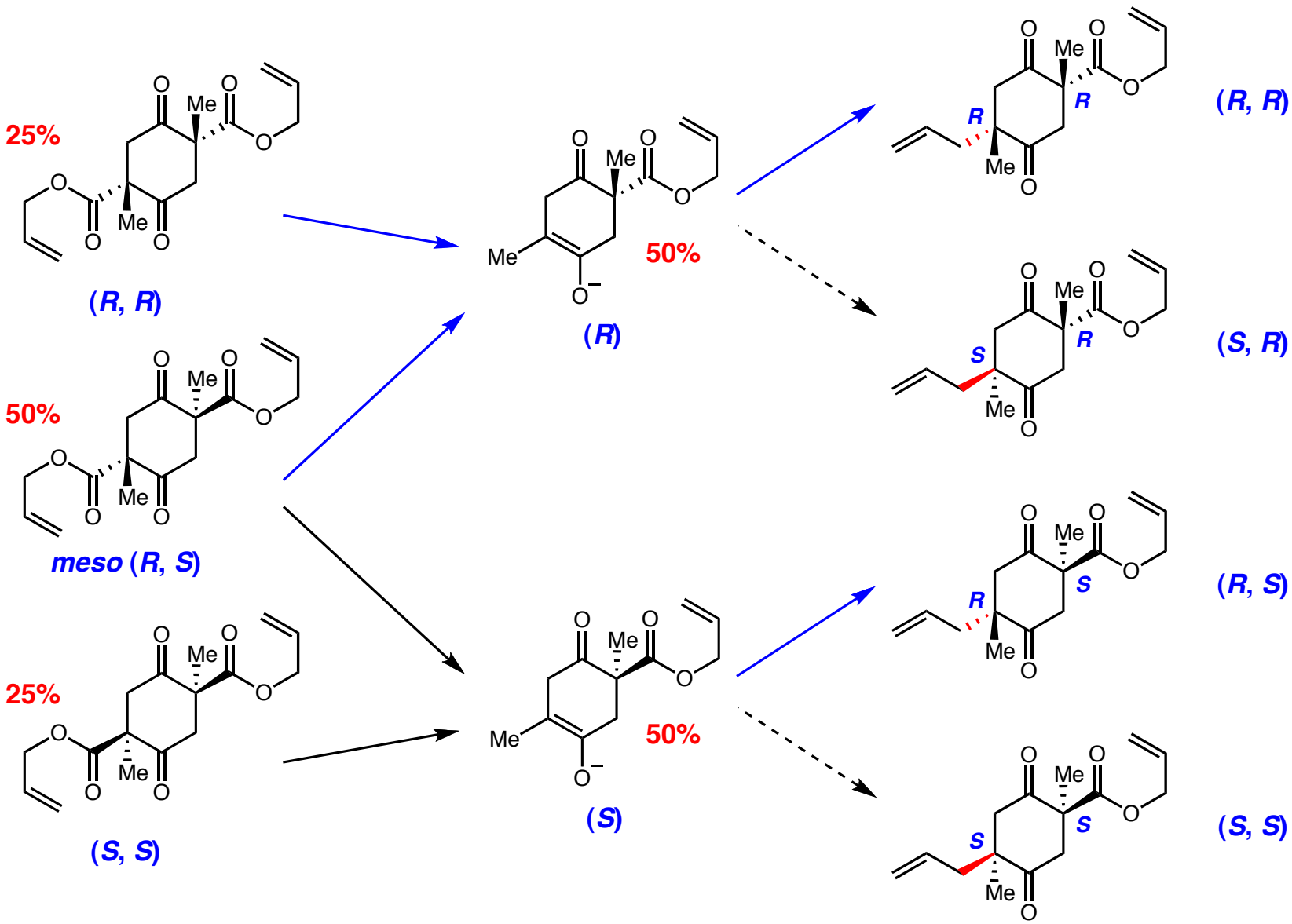


(–)-Cyanthiwigin F

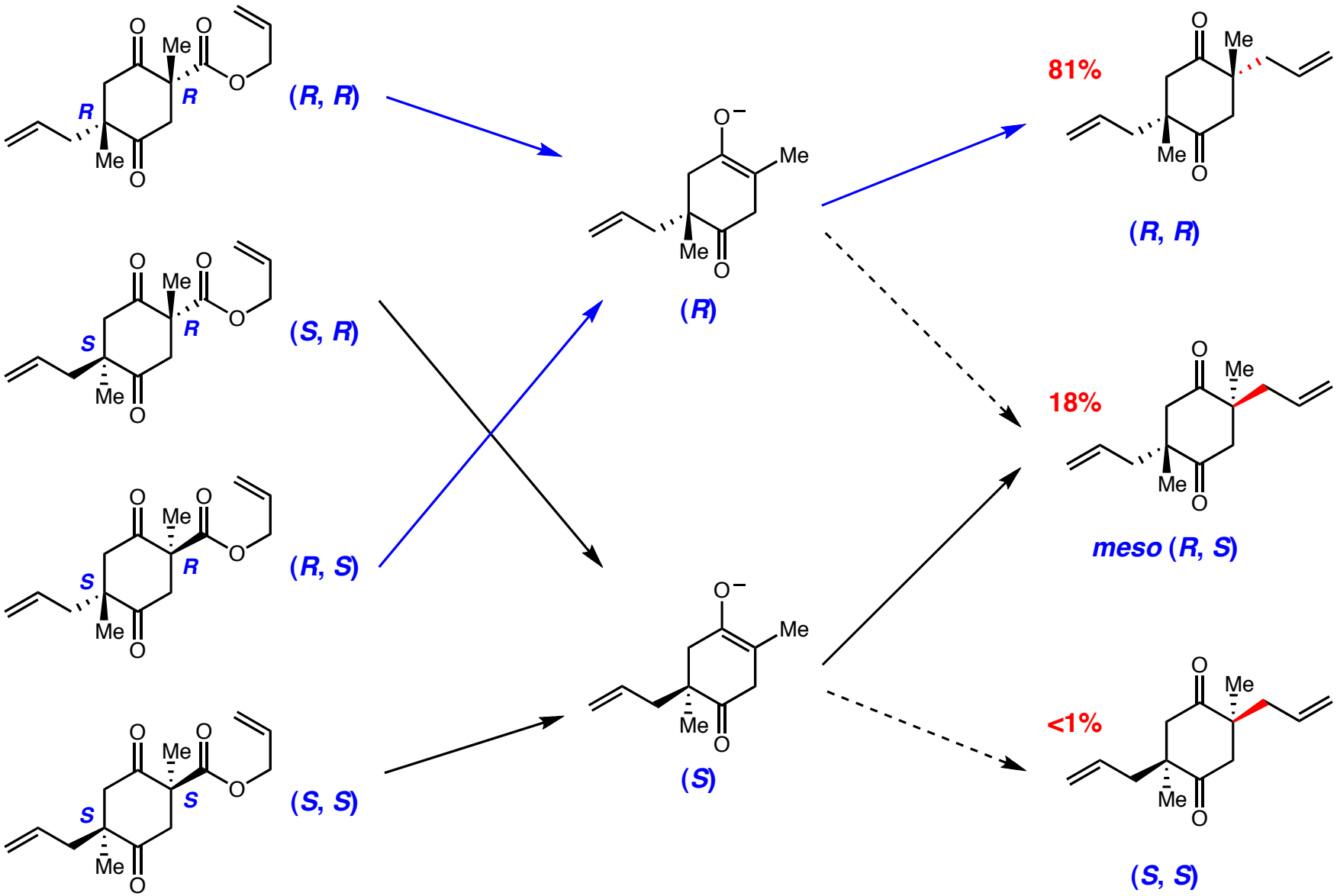


- Sets all key stereochemistry in one step
- Guides selective formation of other stereocenters

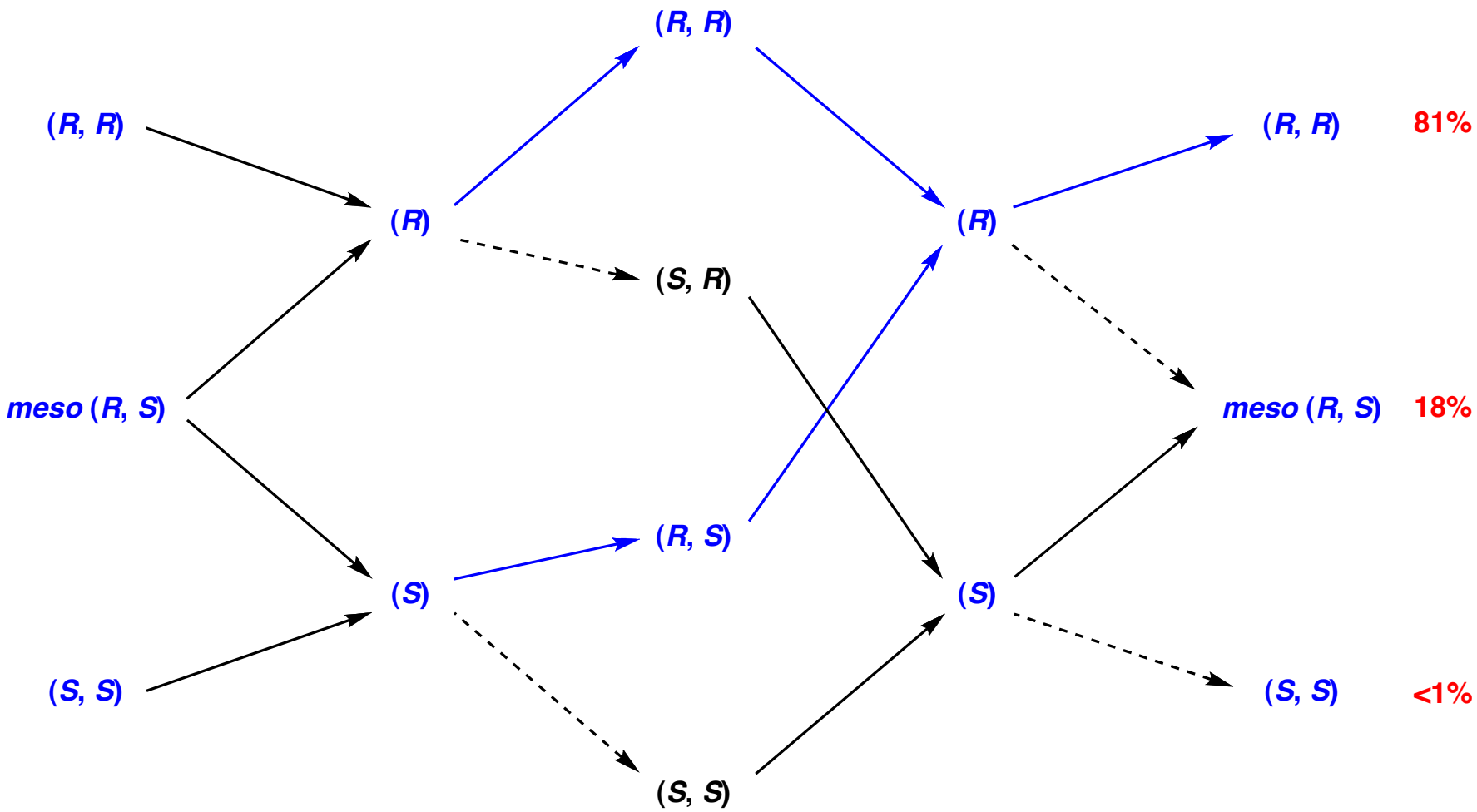
(–)-Cyanthiwigin F



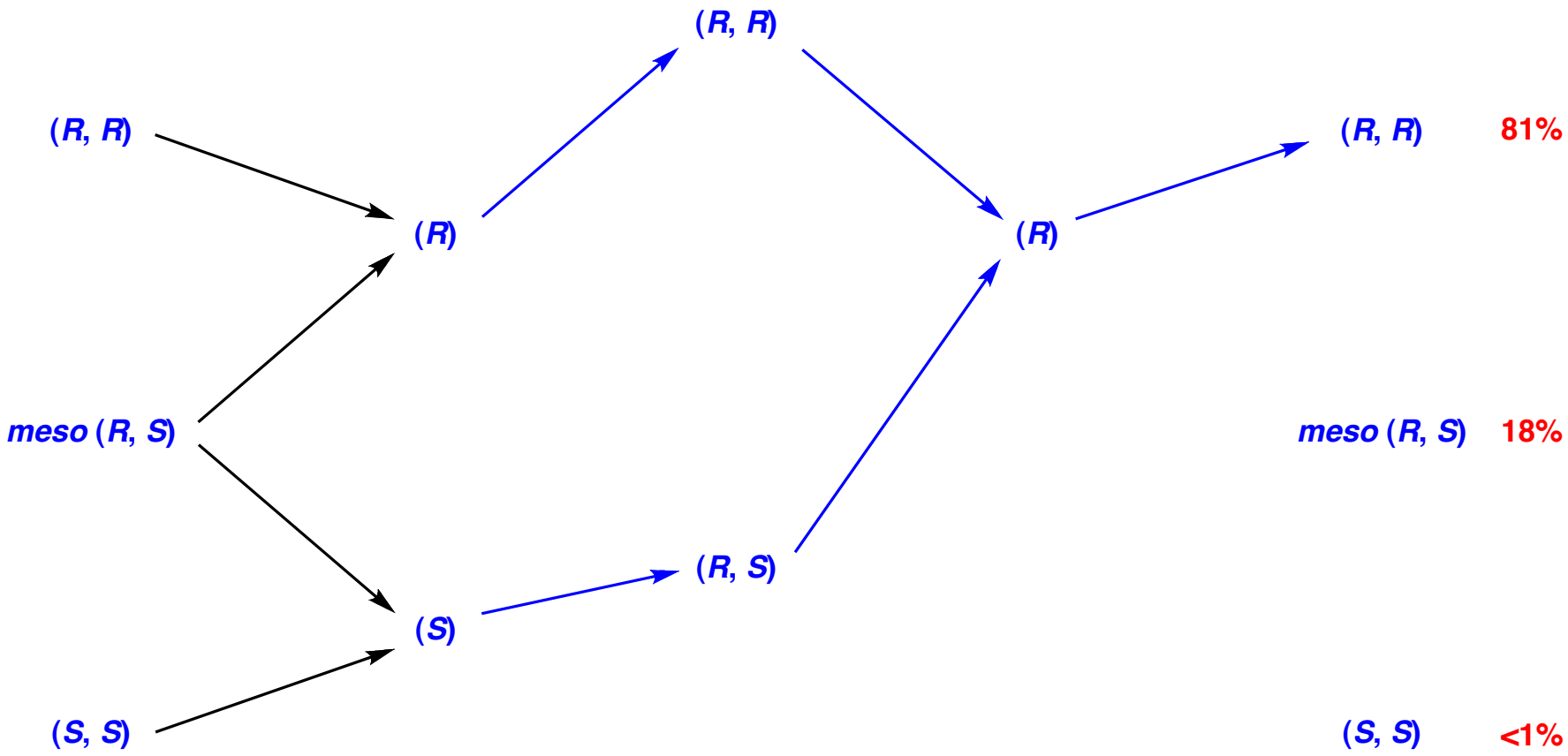
(–)-Cyanthiwigin F



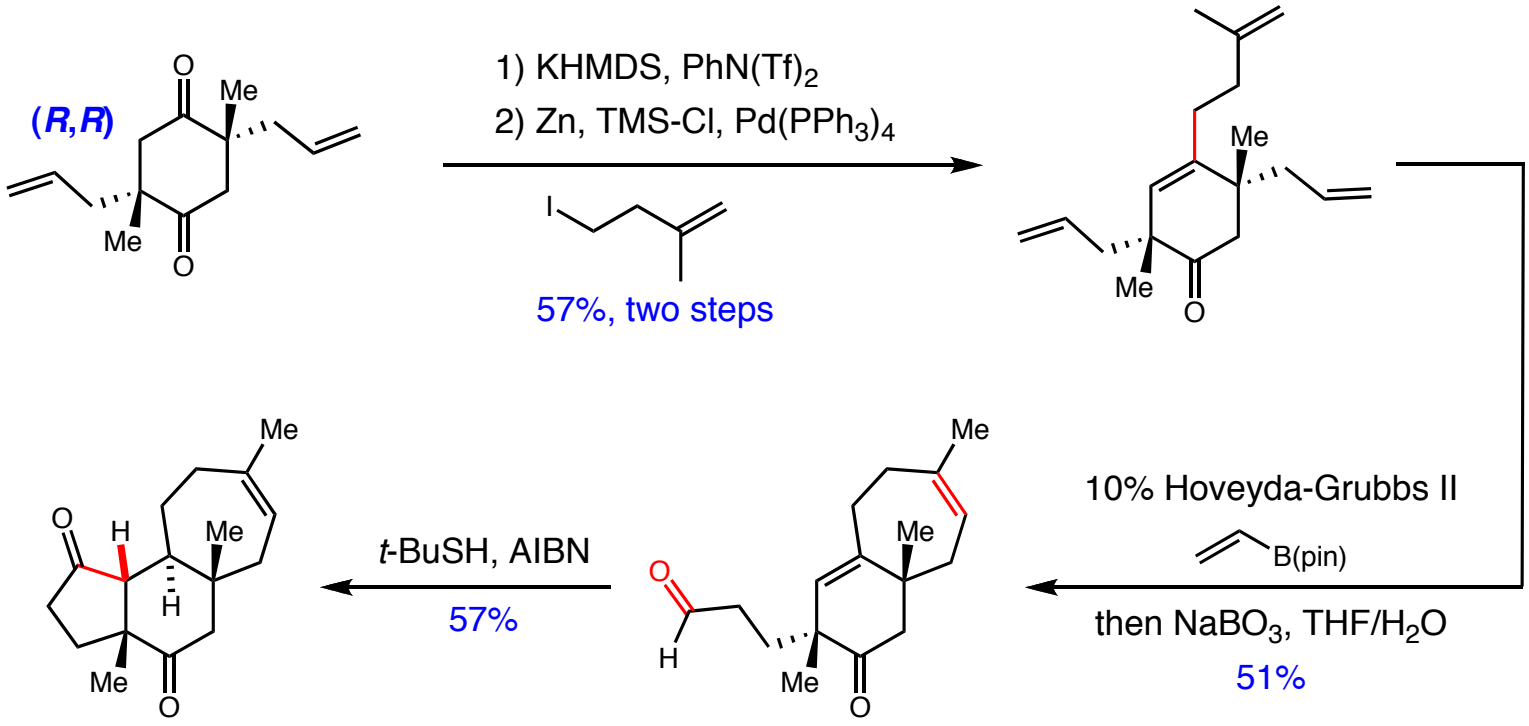
(–)-Cyanthiwigin F



(–)-Cyanthiwigin F

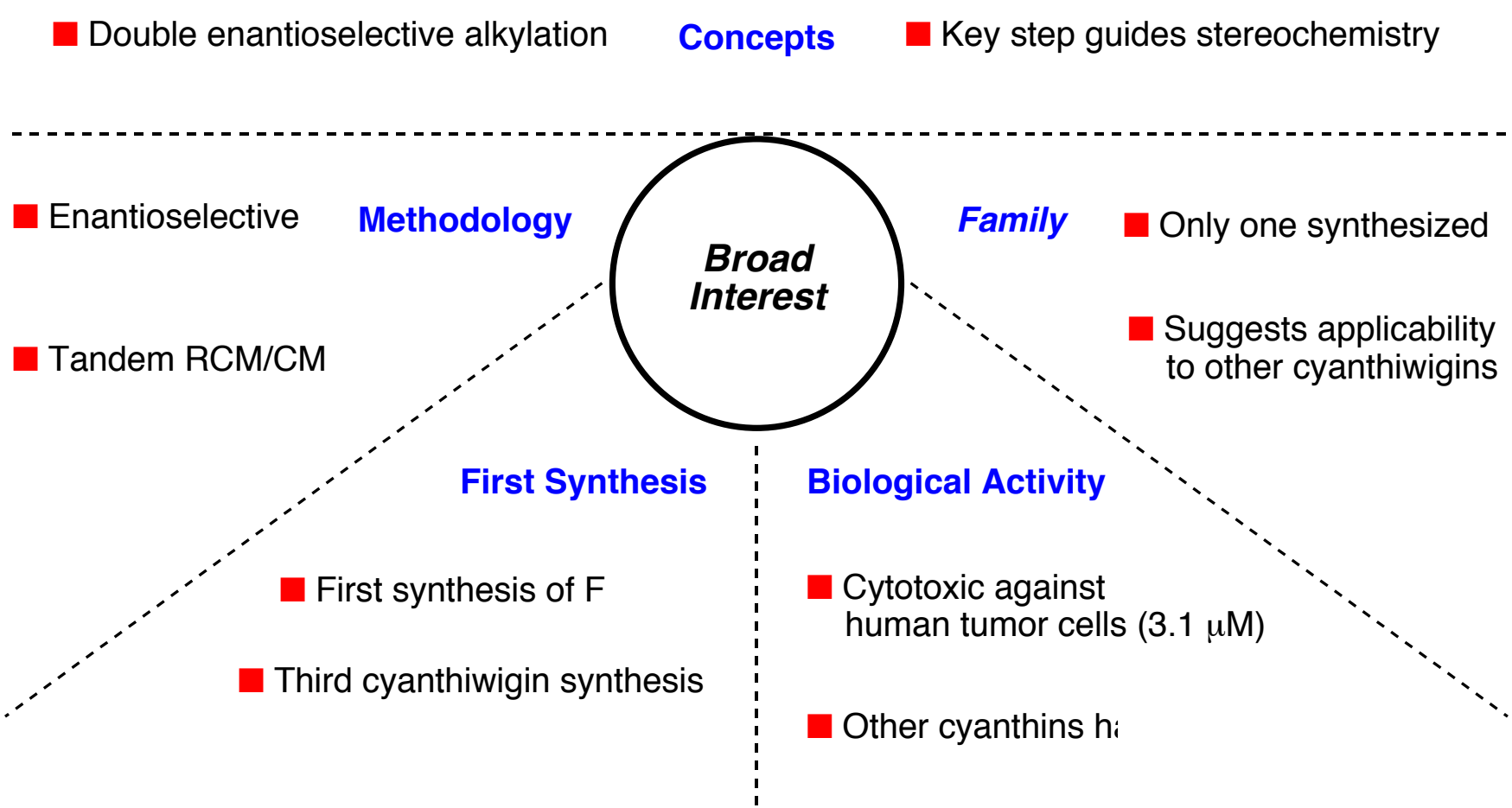


(–)-Cyanthiwigin F

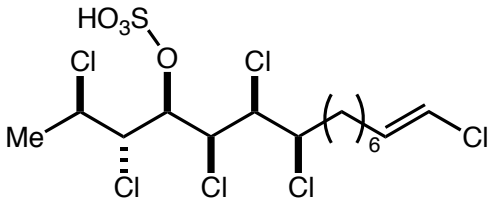


- 9 steps from diallyl succinate
- 2.06% yield, 99% ee, single diastereomer

Cyanthiwigin overview



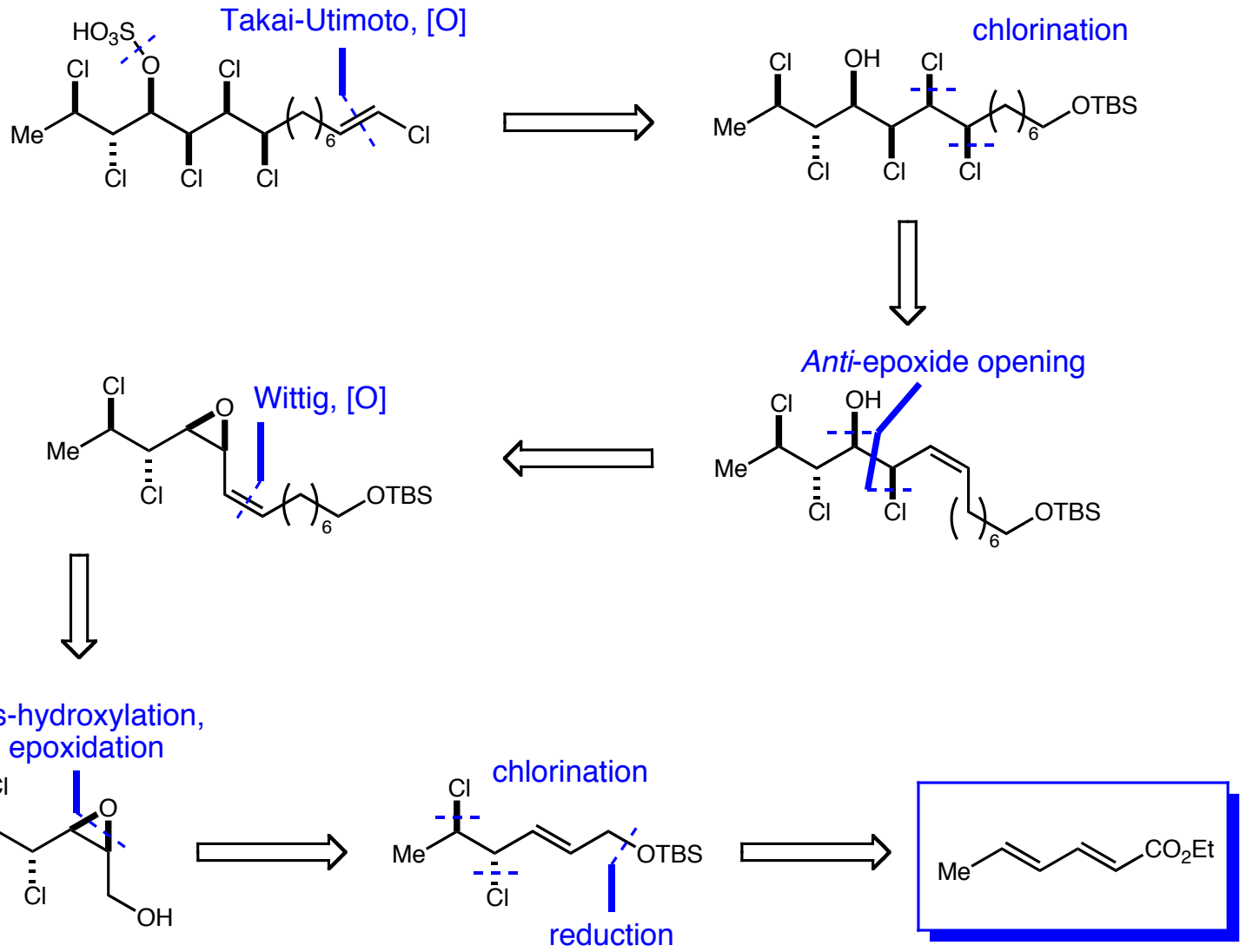
Total synthesis of a chlorosulpholipid cytotoxin associated with seafood poisoning



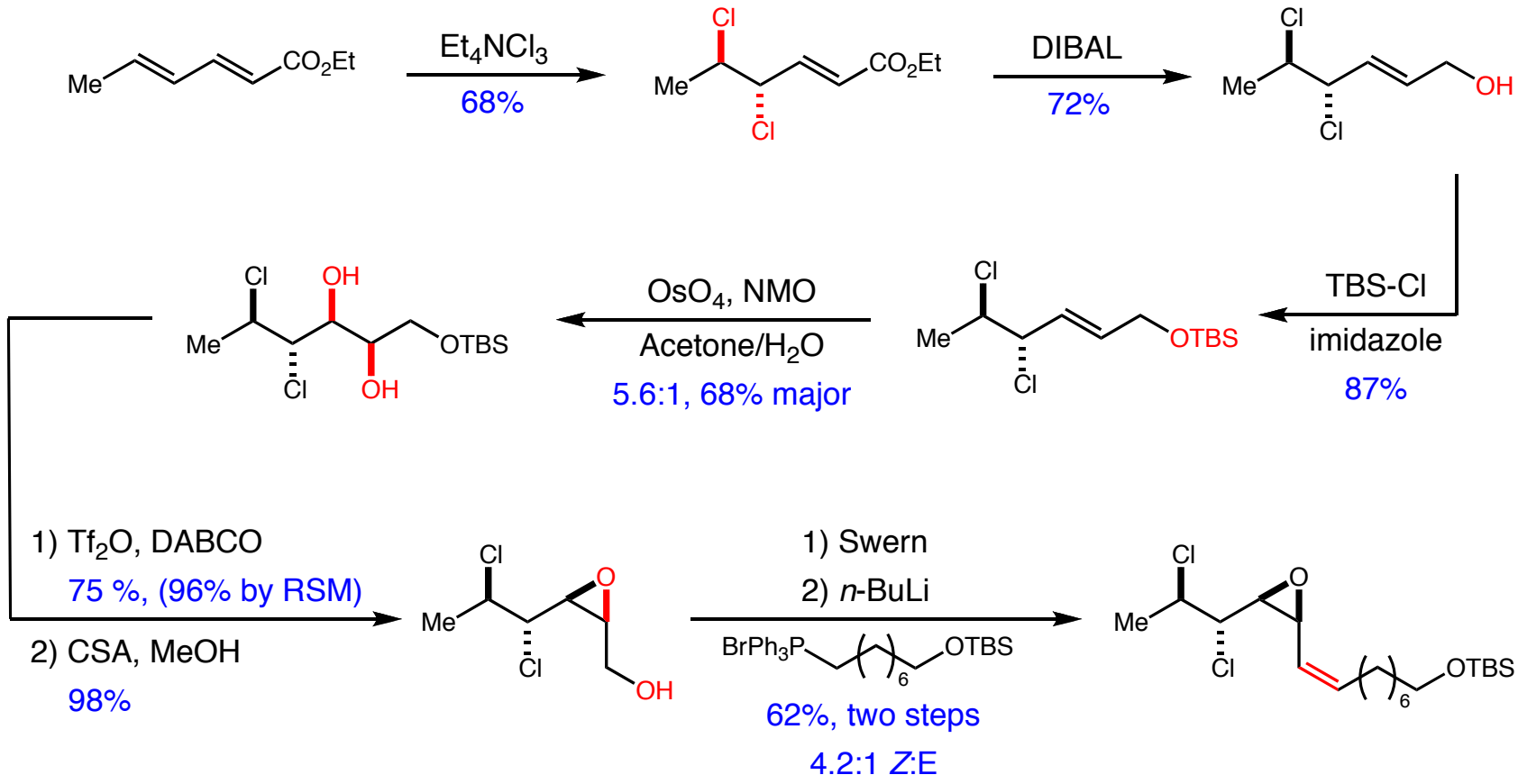
hexachlorosulpholipid

Nilewski, C., Geisser, R. W., Carriera, E. M. *Nature*, **2007**, *446*, 404-408.

Hexachlorosulpholipid: Retrosynthetic Analysis

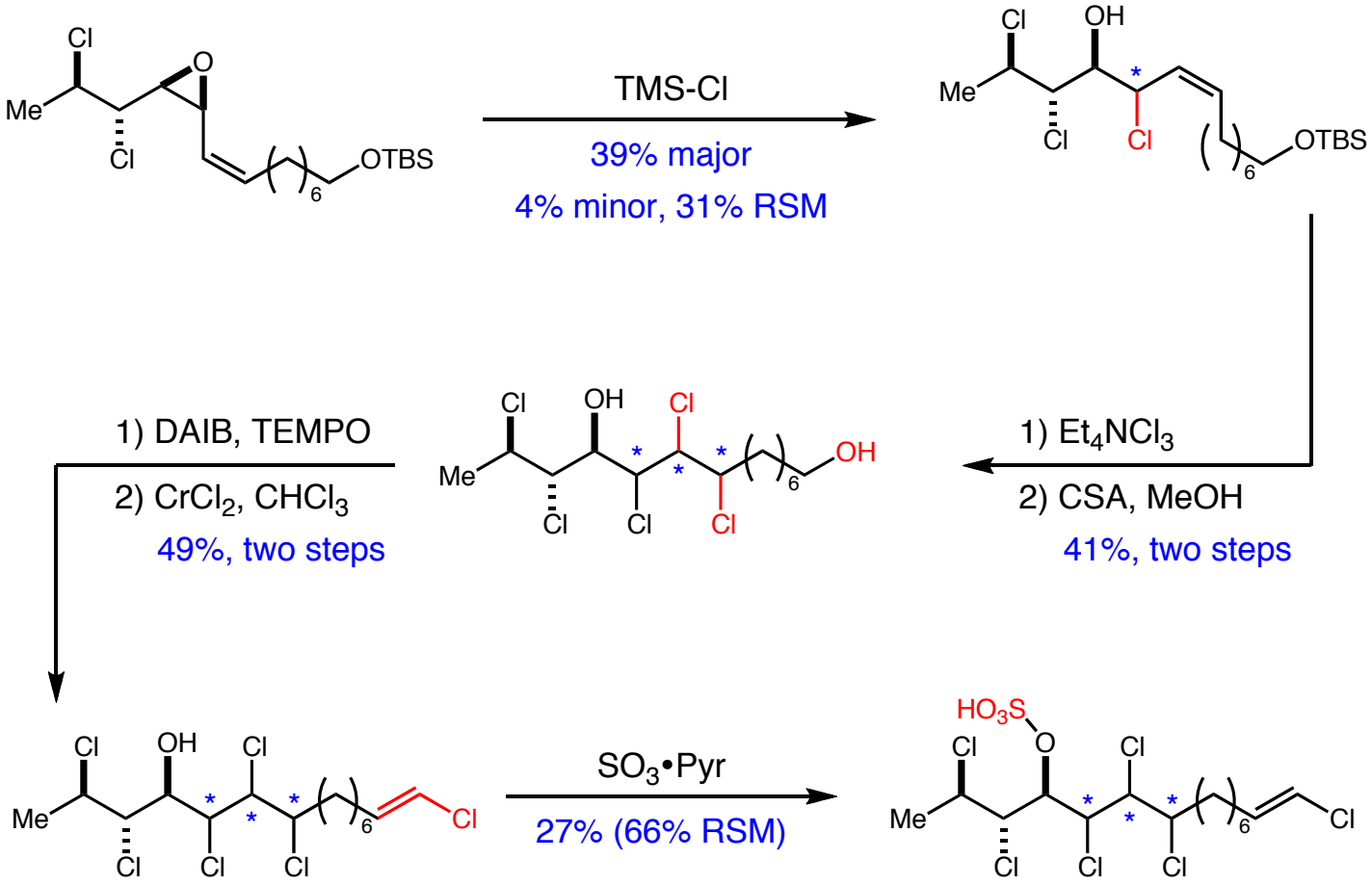


Hexachlorosulpholipid: First Route

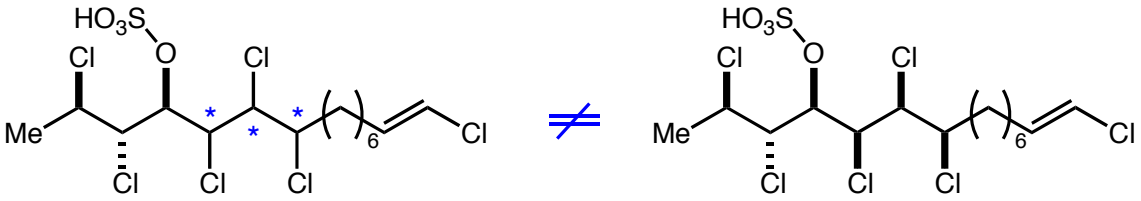


- Diastereoselective installation of chlorides
- Forms *cis* epoxide for chloride opening
- Wittig sets olefin geometry for chlorination

Hexachlorosulpholipid: First Route



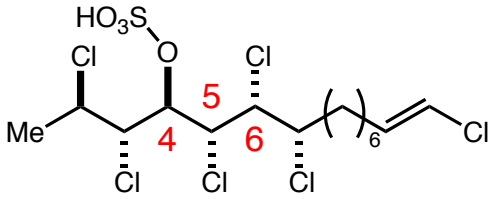
Hexachlorosulpholipid: First Route



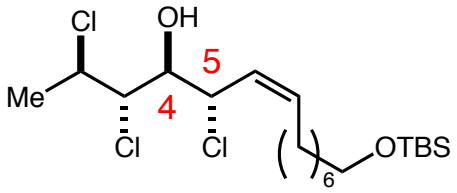
(±)-single diastereomer

natural product

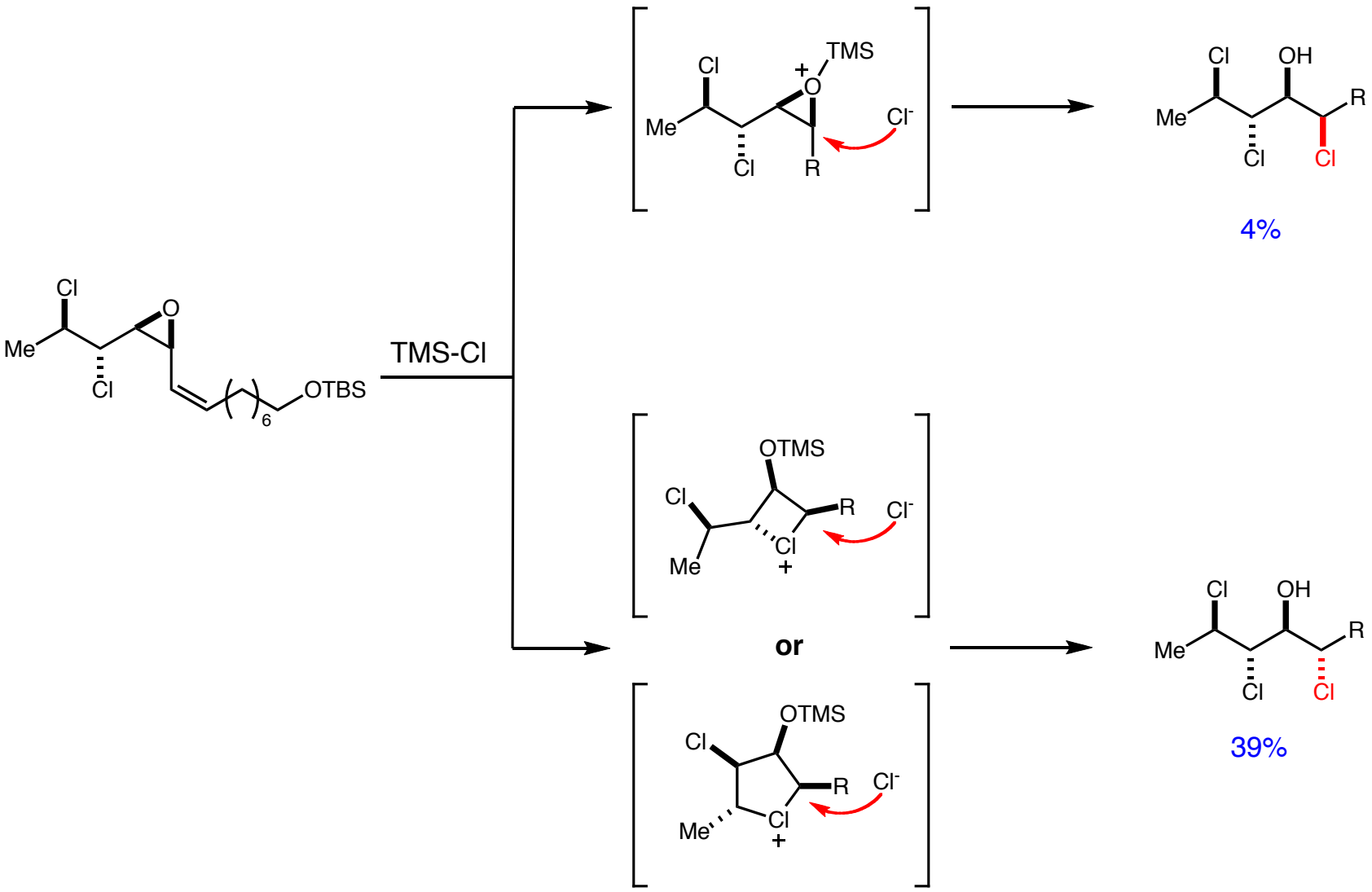
- 2D ^{1}H NMR and ^{1}H-heteronuclear coupling experiments determine relative configuration



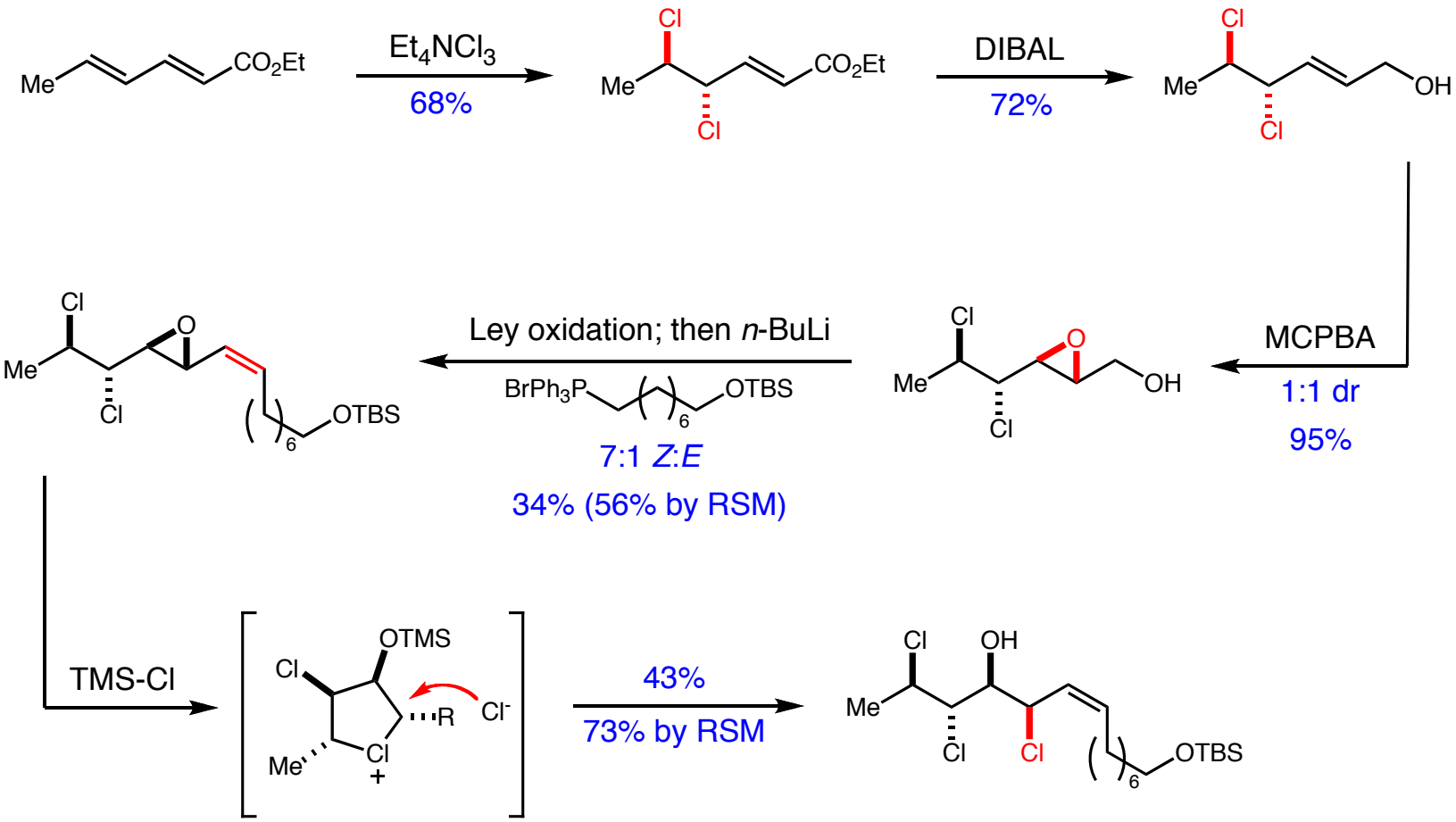
- Similar analysis of synthesized allylic chloride revealed 4,5-*anti* configuration



Hexachlorosulpholipid: Initial Route

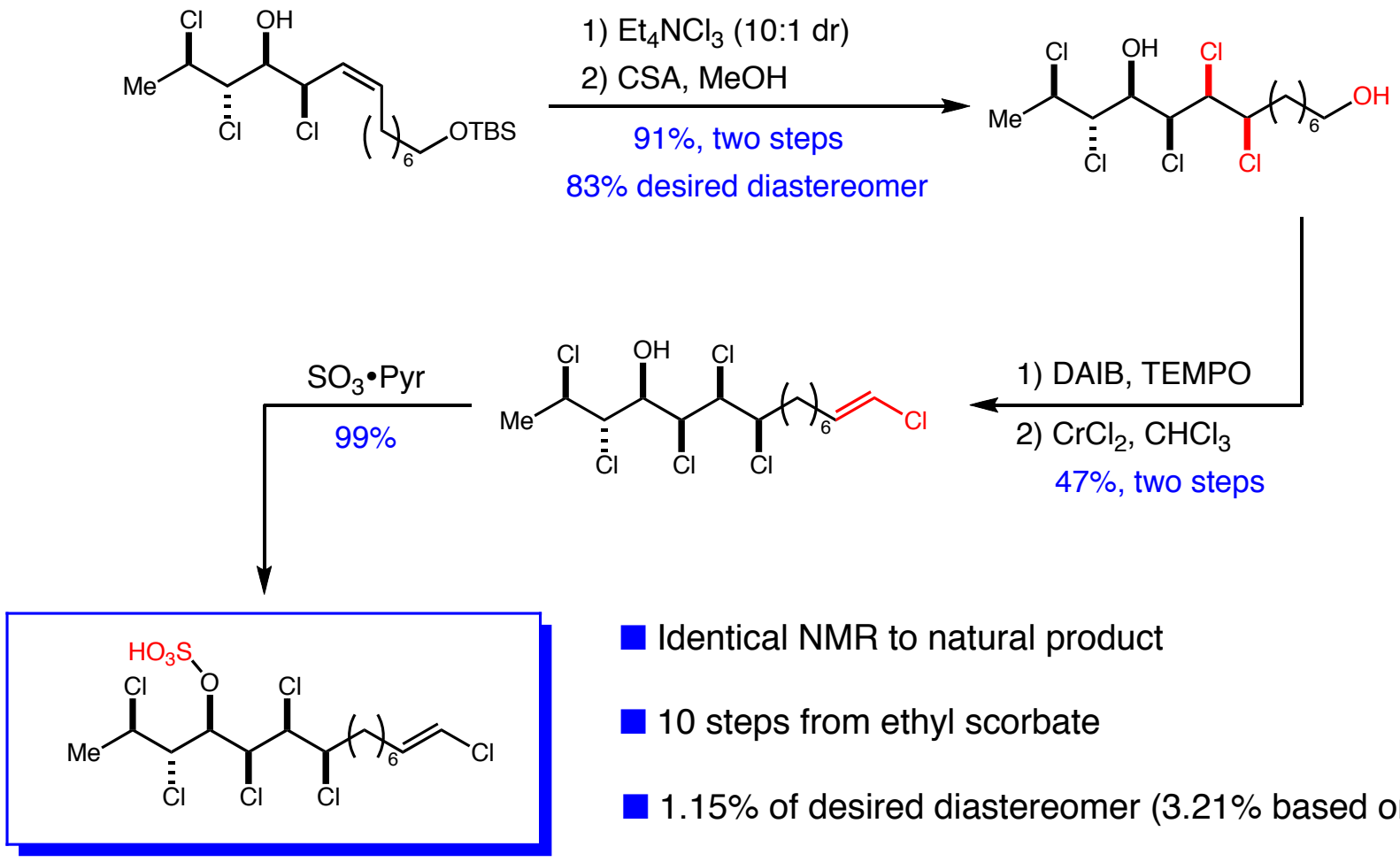


Hexachlorosulpholipid: Revised Route



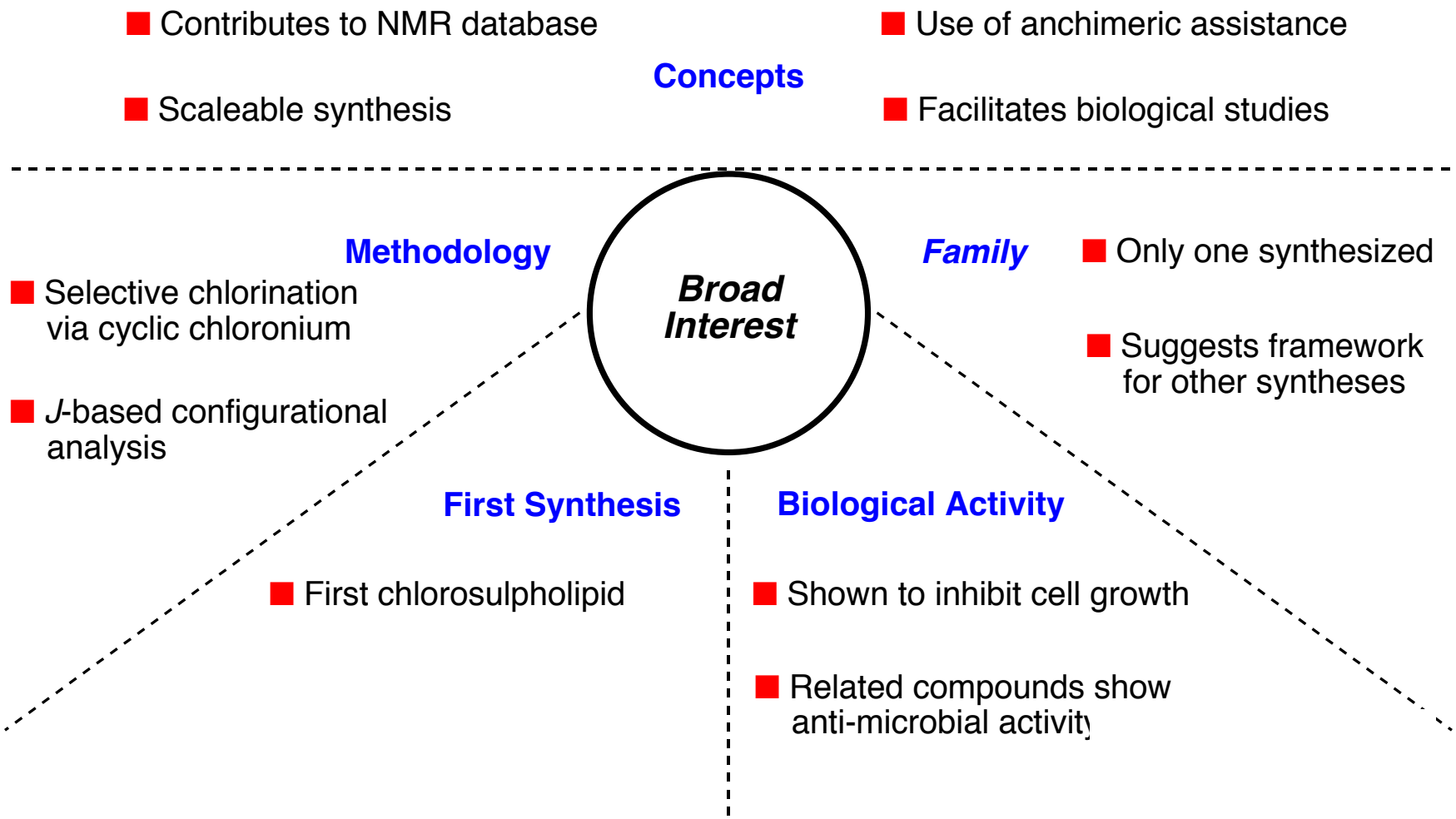
- Shortens previous route by 3 steps
- Improved *Z*-selectivity in Wittig
- Sets *trans* epoxide and utilizes anchimeric assistance to from chlorohydrin

Hexachlorosulpholipid: Revised Route

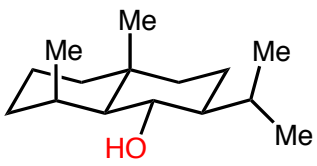


- Identical NMR to natural product
- 10 steps from ethyl scorbate
- 1.15% of desired diastereomer (3.21% based on RSM)

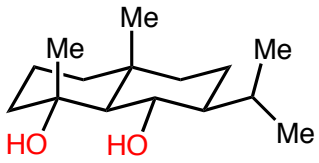
Hexachlorosulpholipid overview



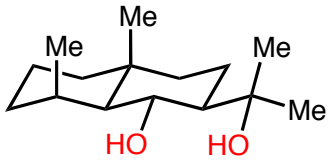
Total synthesis of eudesmane terpenes by site-selecitve C-H oxidations



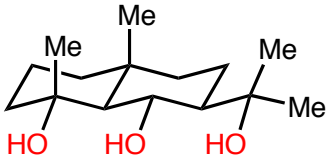
dihydrojunenol



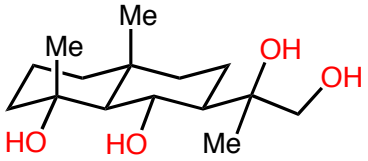
4-epiajanol



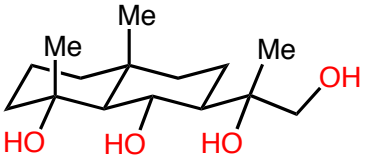
dihydroxyeudesmane



pygmol



eudesmantetraol



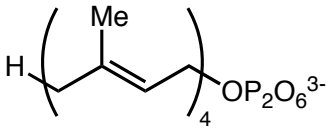
11-epieudesmantetraol

eudesmane terpenes

Chen, K., Baran, P. S. *Nature*, **2009**, *459*, 824-828.

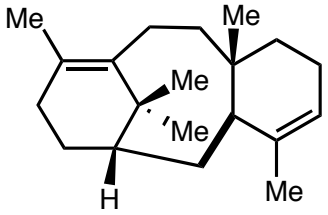
Terpene Syntheses: General Concept

■ Terpene biosynthesis



geranylgeranyl pyrophosphate

cyclase phase

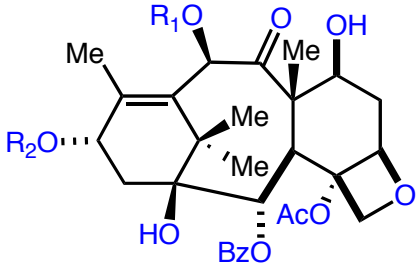


taxadiene

oxidation phase

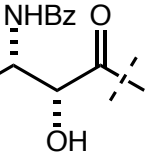
10-deactyl-baccatin III

R_1, R_2 = H



paclitaxel

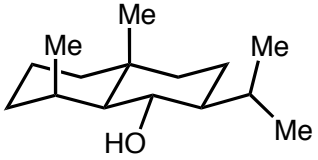
R_1 = Ac, R_2 =



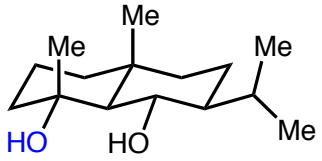
■ Two phase total synthesis approach

simple commercial starting materials

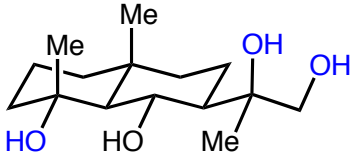
cyclase phase



oxidation phase

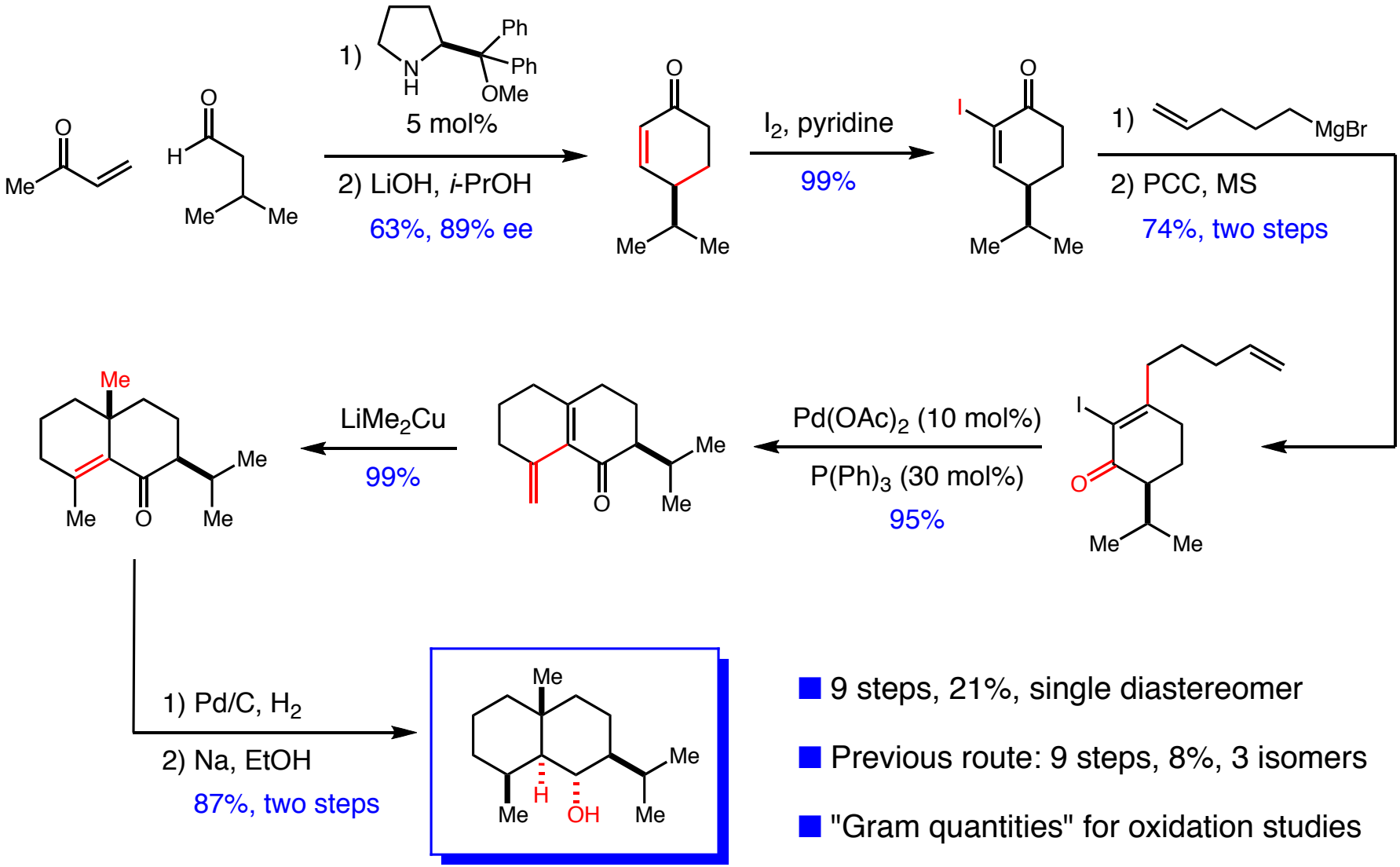


4-epiajanol



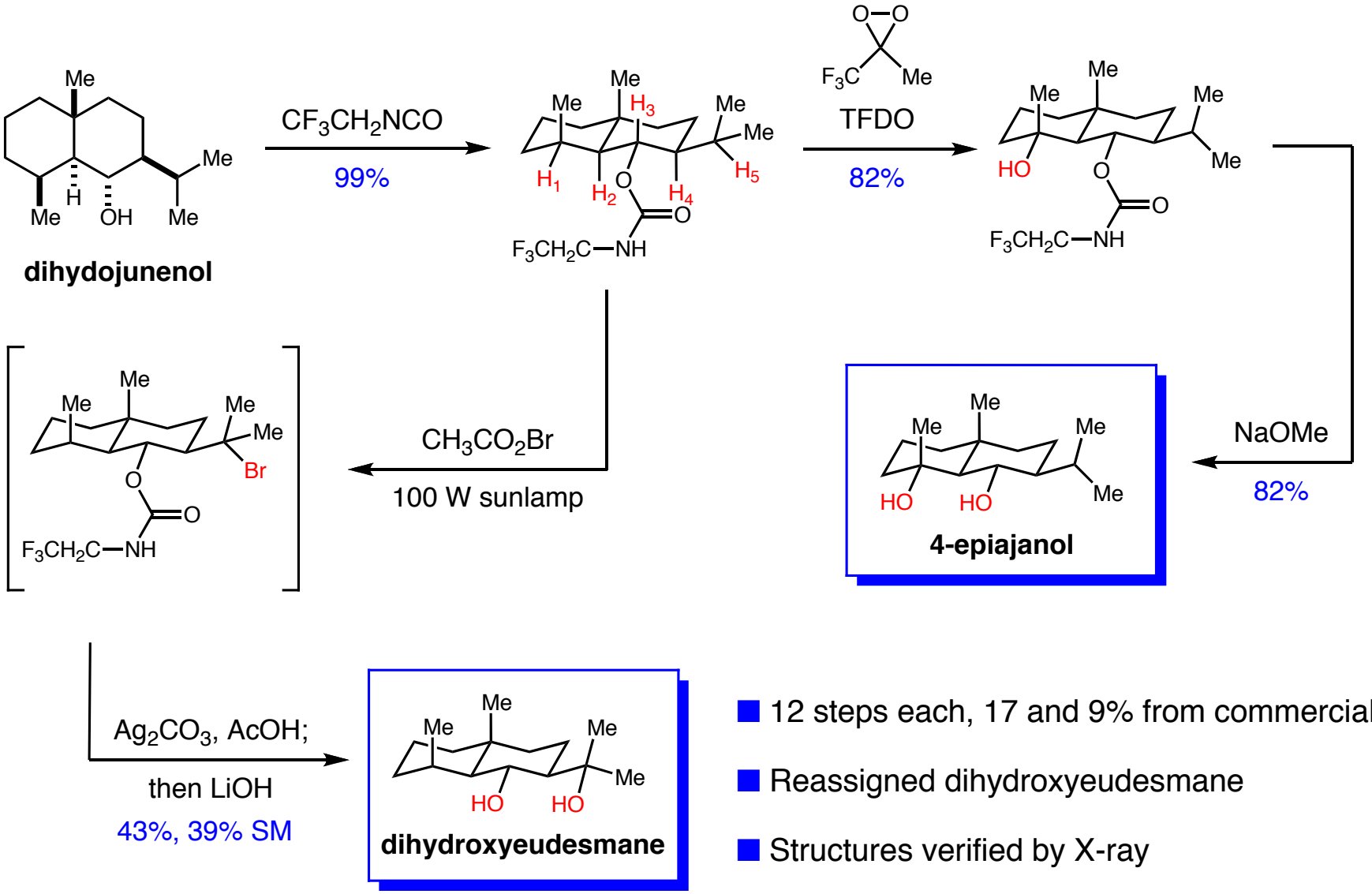
eudesmantetraol

Dihydrojunenol



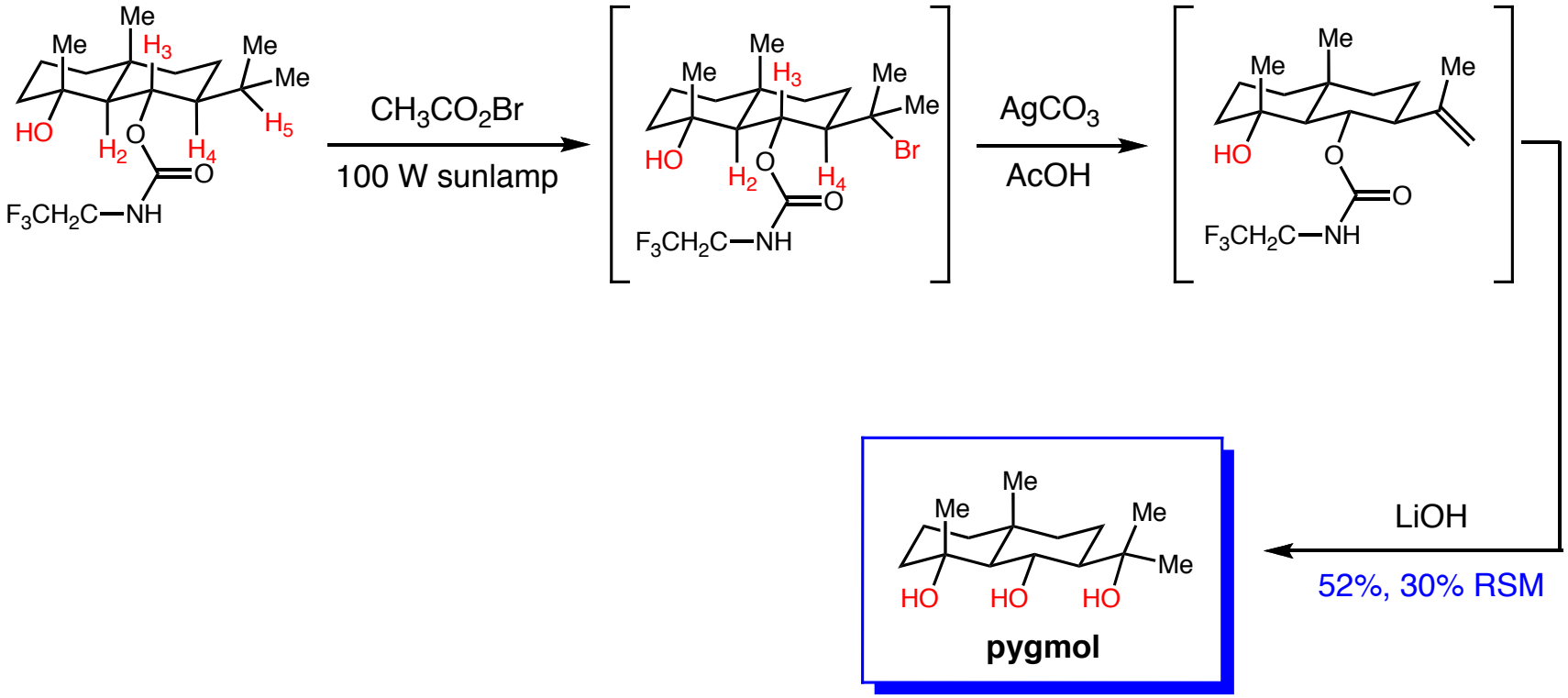
- 9 steps, 21%, single diastereomer
- Previous route: 9 steps, 8%, 3 isomers
- "Gram quantities" for oxidation studies

Eudesmane terpenes



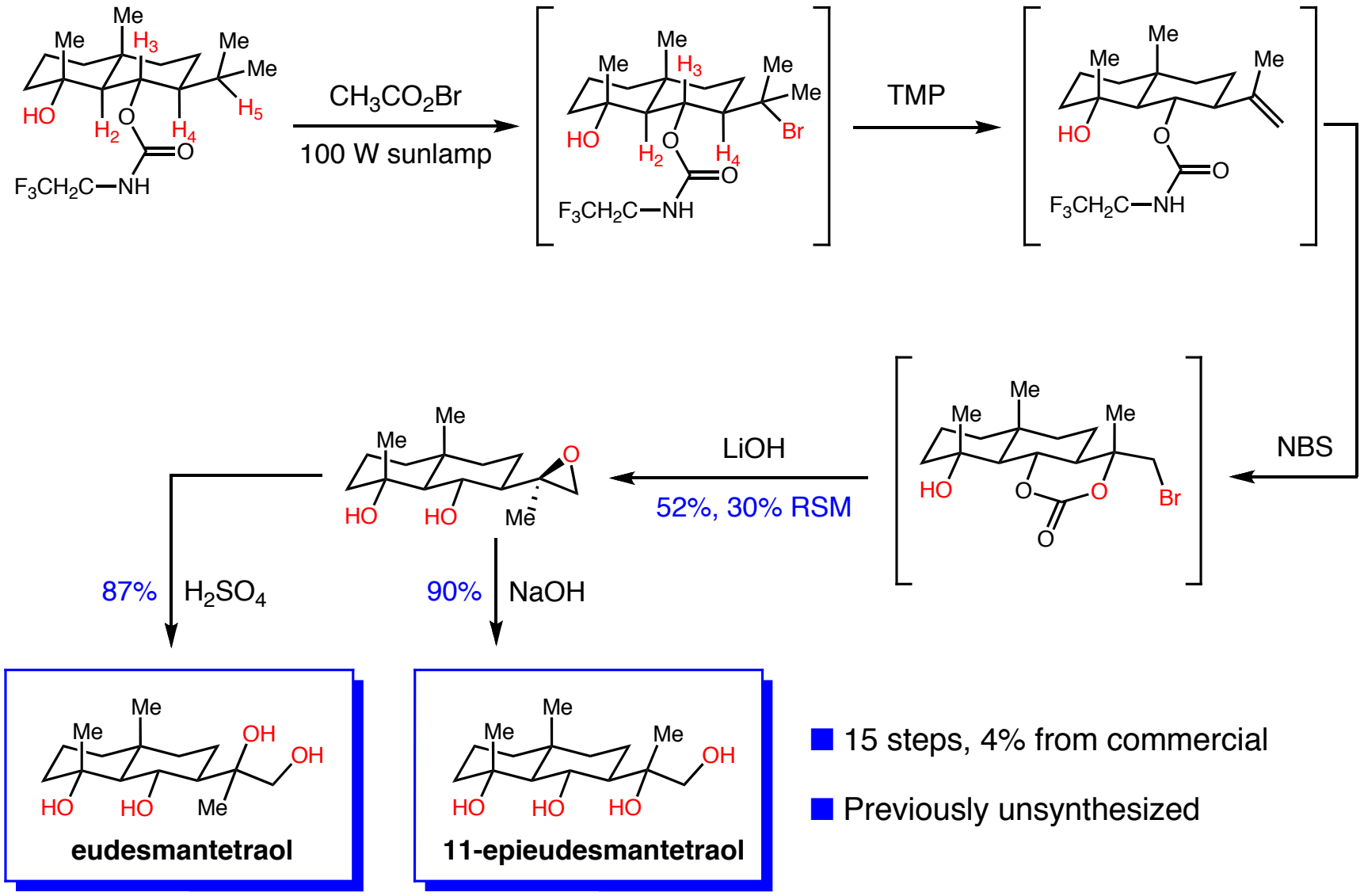
- 12 steps each, 17 and 9% from commercial
- Reassigned dihydroxyeudesmane
- Structures verified by X-ray

Eudesmane terpenes



- 13 steps, 9% from commercial
- Previously unsynthesized

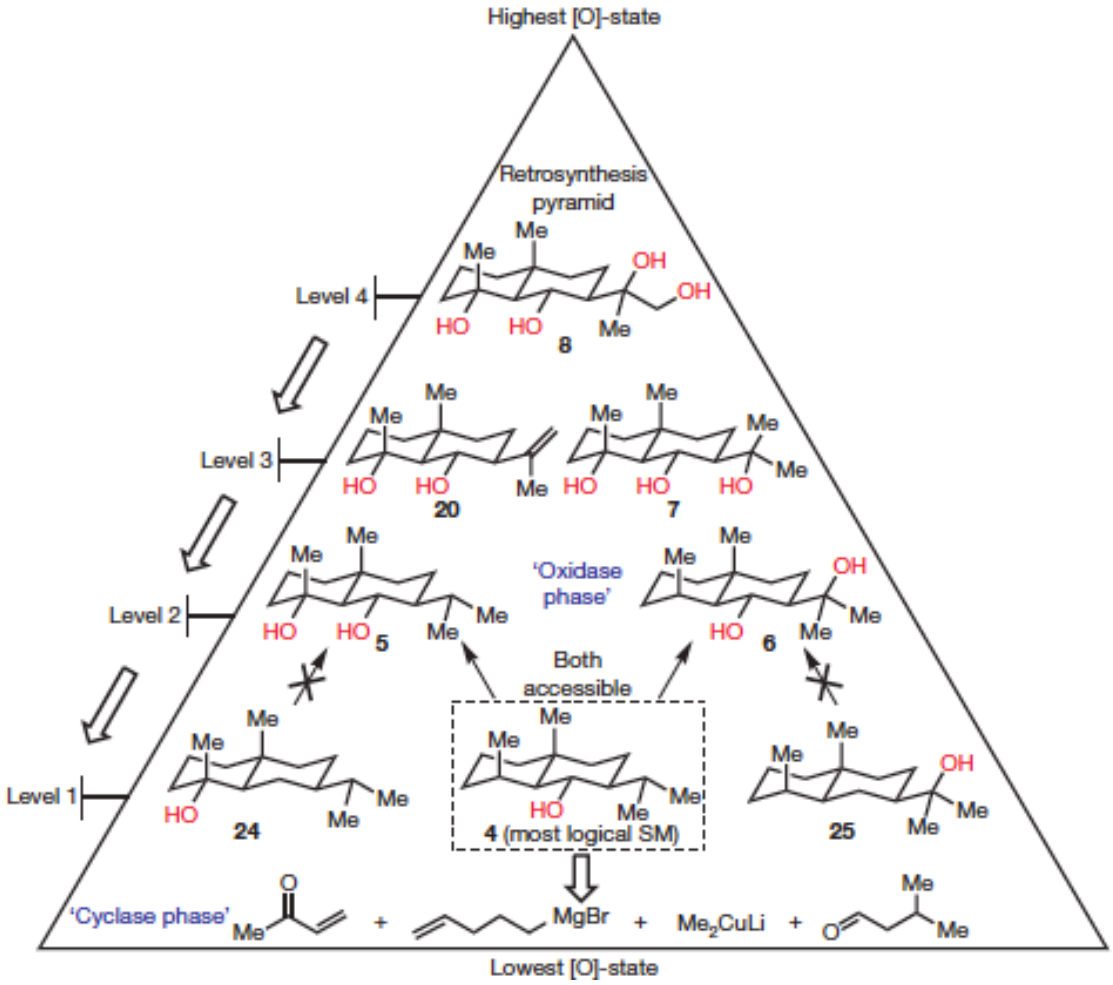
Eudesmane terpenes



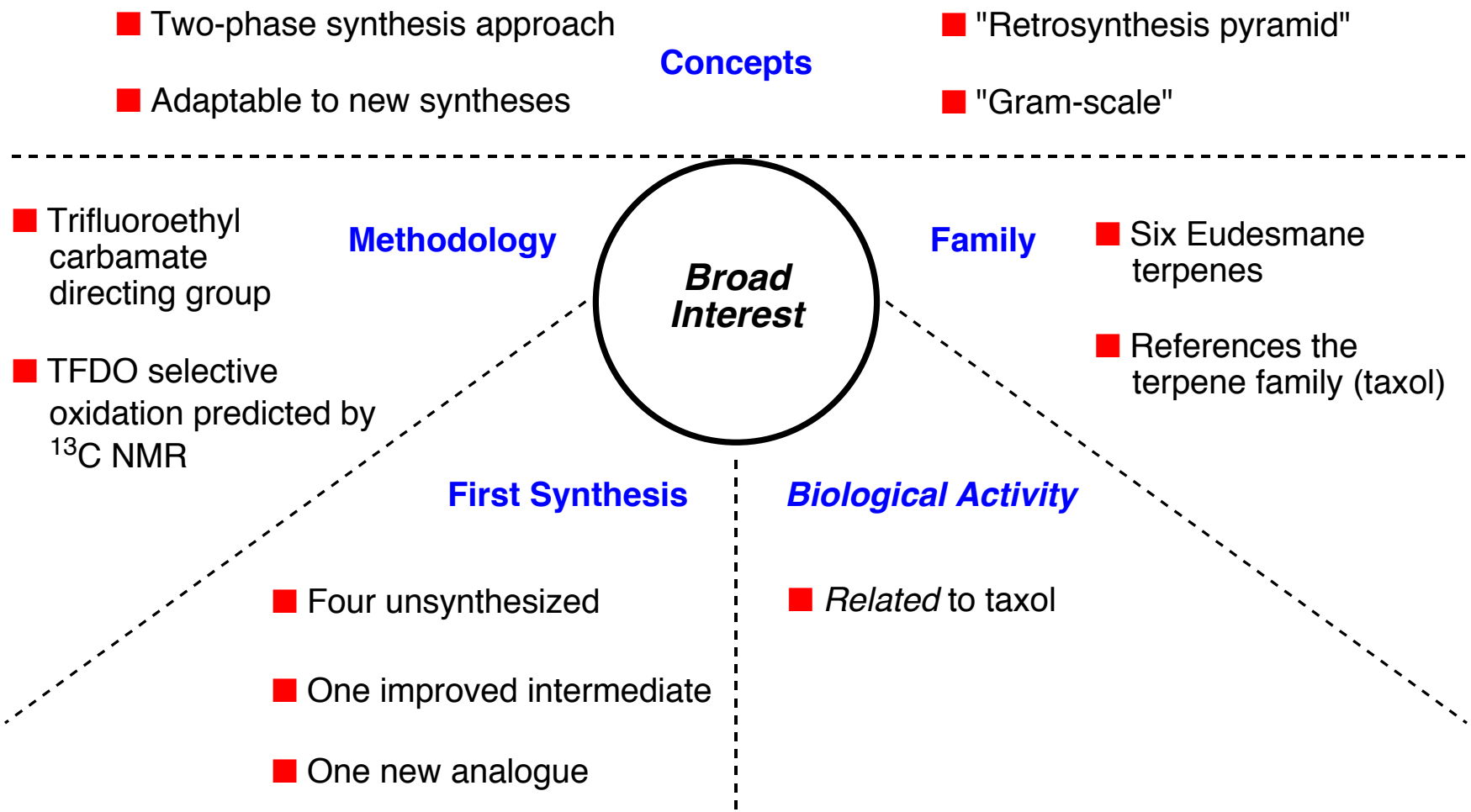
- 15 steps, 4% from commercial
- Previously unsynthesized

Linear Oxidation Concept

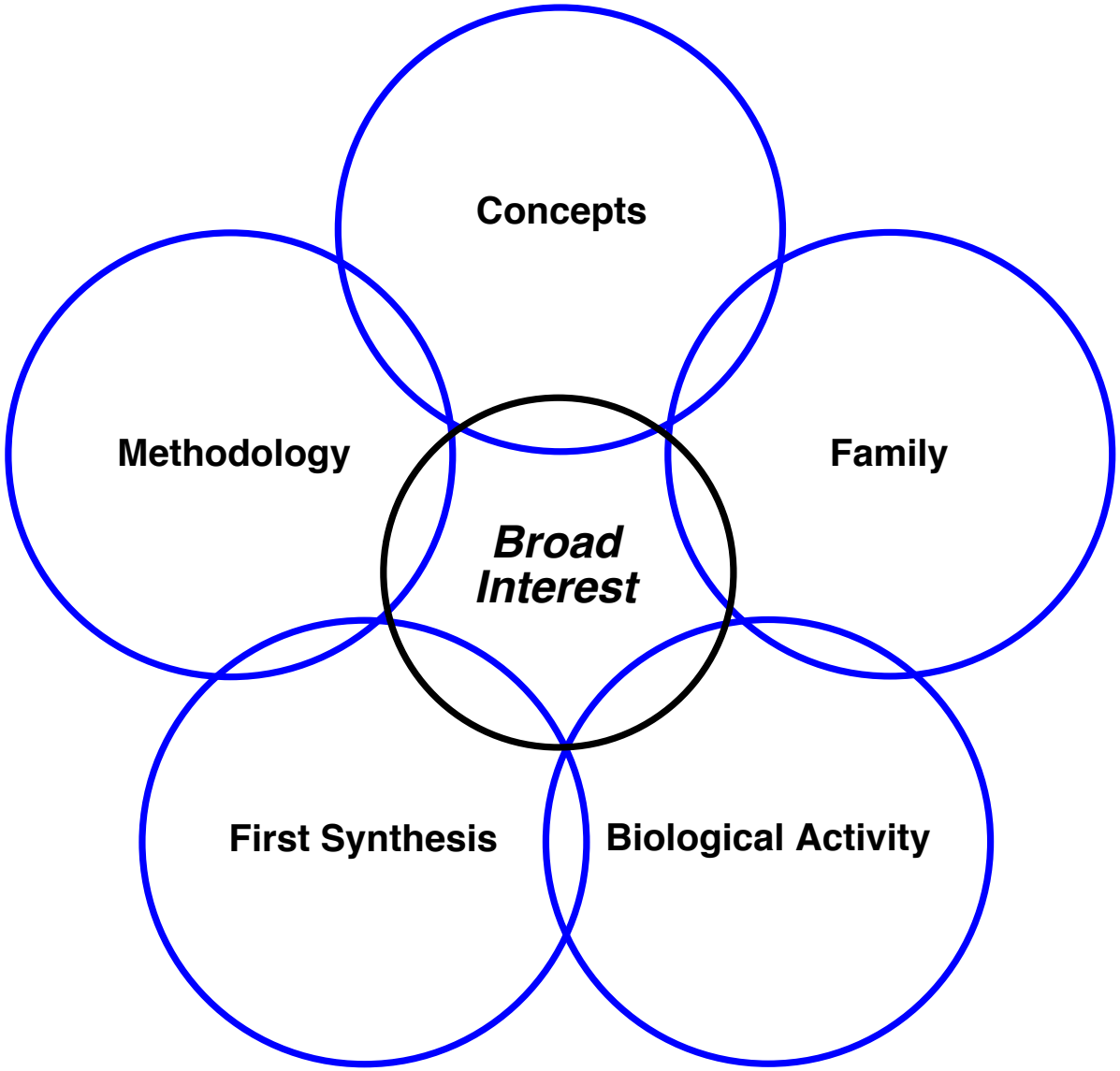
- "...linear C-H activation strategy featuring multiple site selective oxidations in total synthesis"



Eudesmane terpenes overview



Why Nature *?*


Concepts
Methodology
Family
Broad Interest
First Synthesis
Biological Activity