

Master Course
in Organic Chemistry

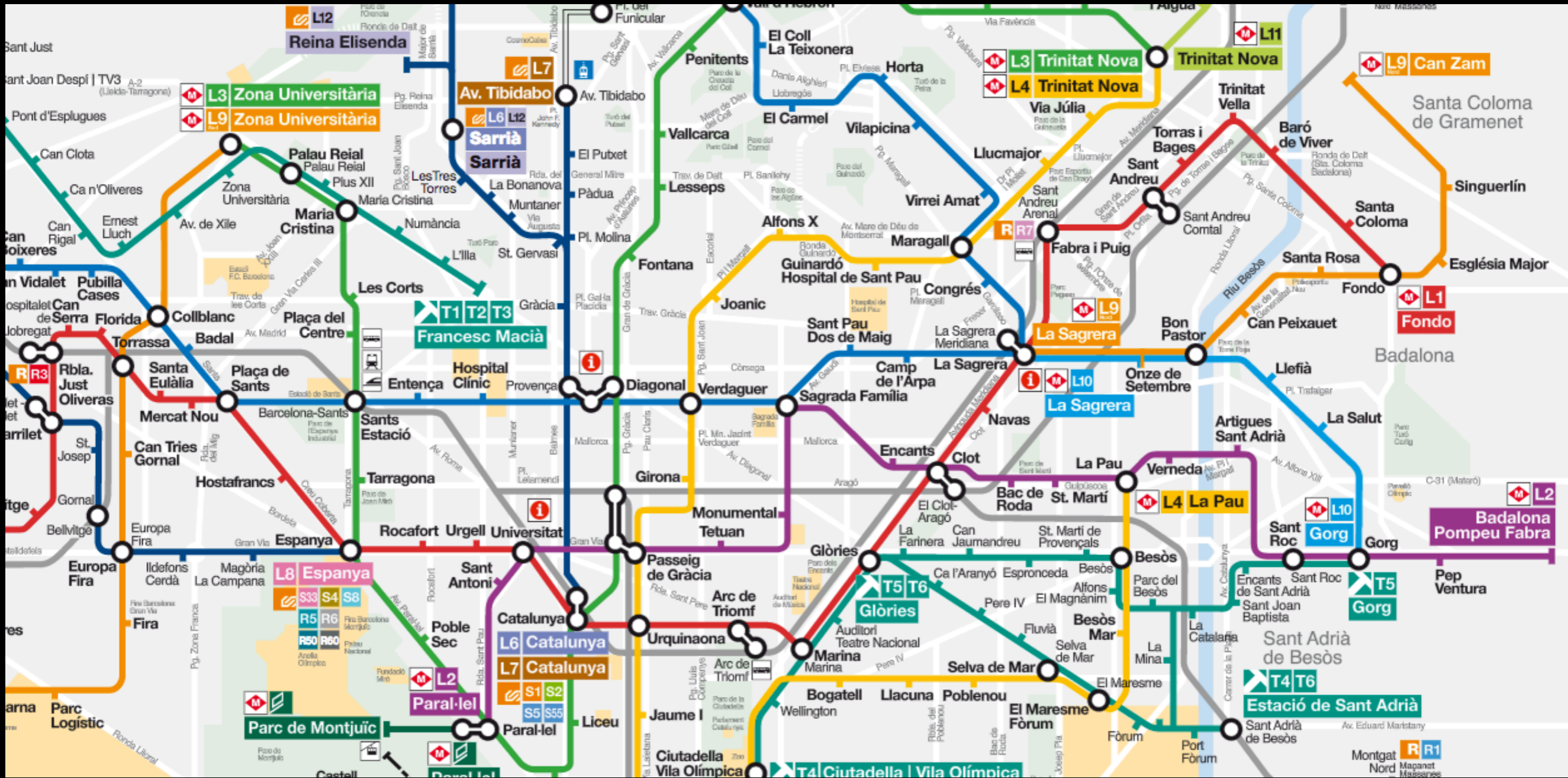
2018-19

methods and design
in organic synthesis



Pere Romea

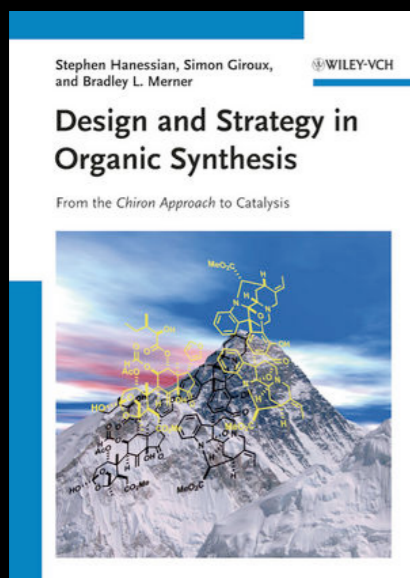
Barcelona Metro&Tramway map



3. Guidelines (a few)

Asking a chemist how he came upon precisely the starting materials and reactions that so elegantly led to the desired results would probably be as meaningless as asking Picasso why he painted as he did

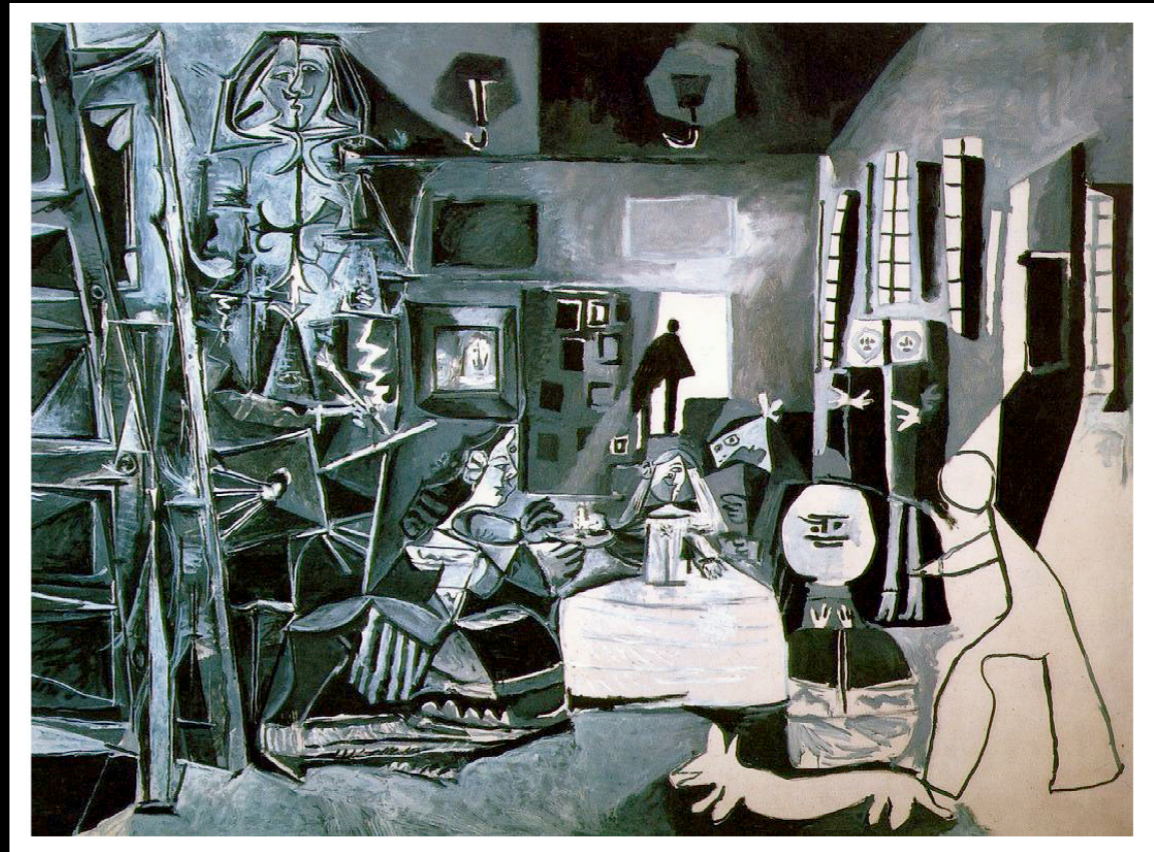
Elias J. Corey



For an approach to the similarities between synthesis and art, see Chapter 1



Las Meninas
Diego Velázquez, 1656



Las Meninas
Pablo Picasso, 1957

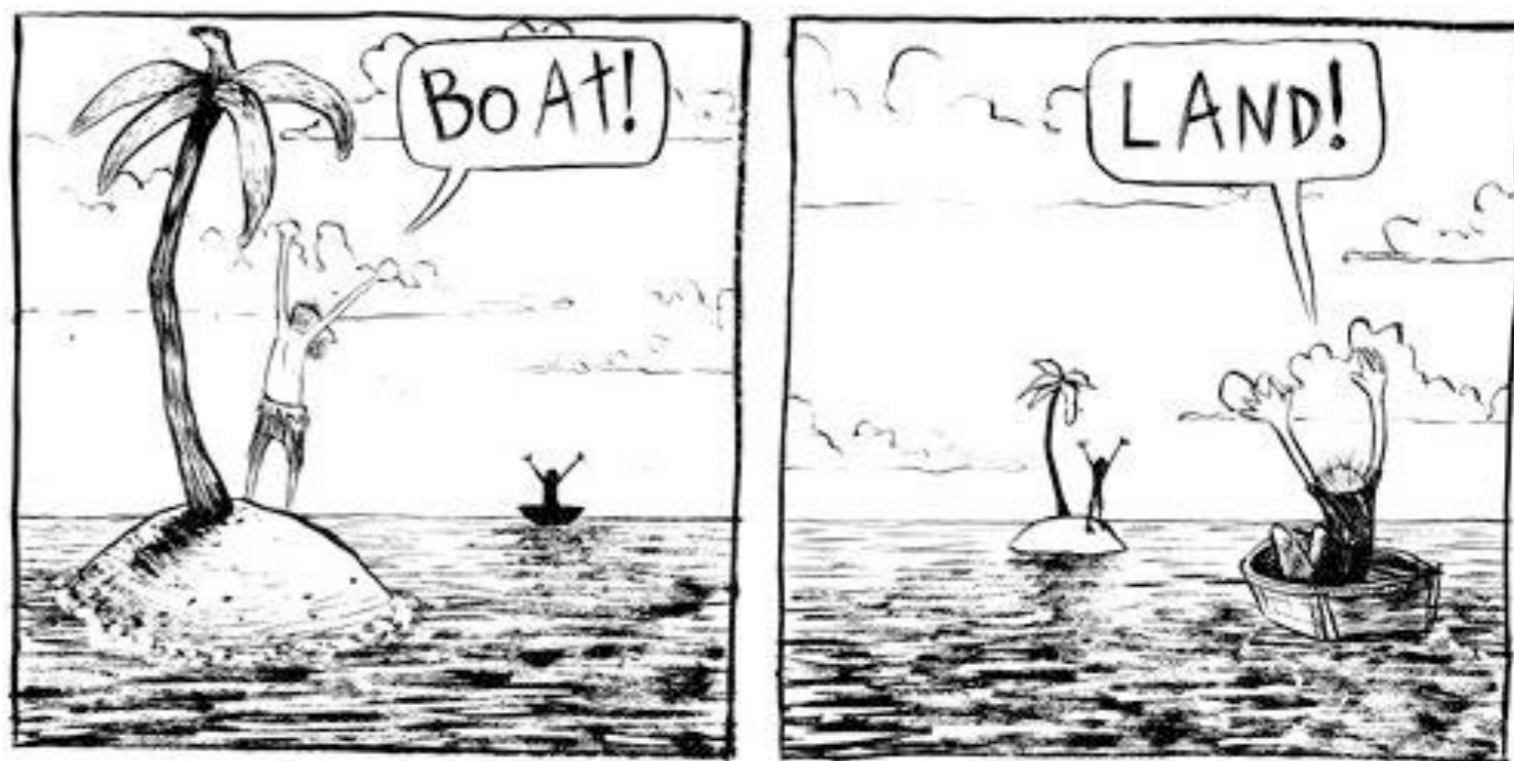


Las Meninas
Salvador Dalí, 1960

1

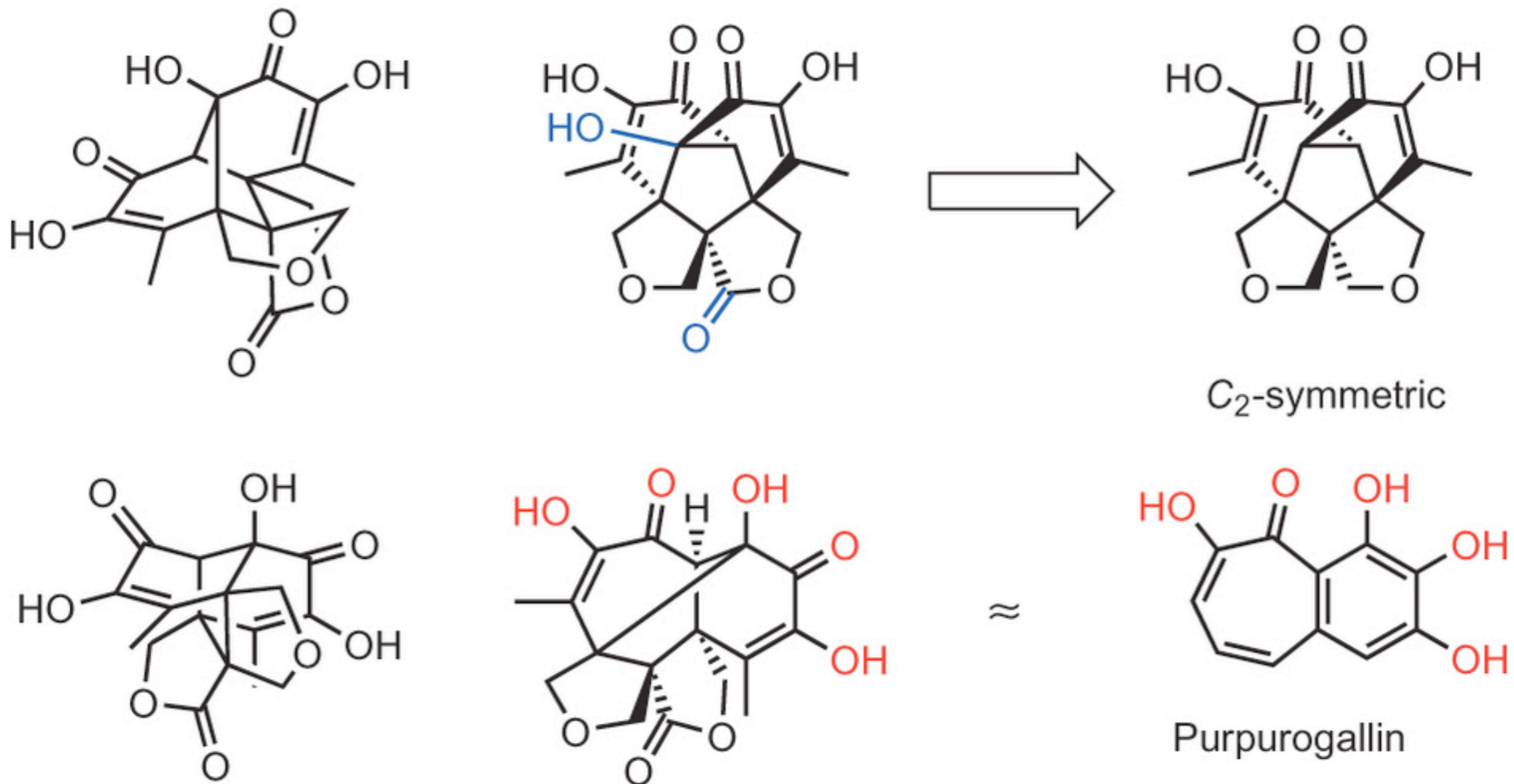
drawing
a source of inspiration

different points of view
different feelings



draw a target molecule from different
points of view to catch a **pattern**

Epicolactone



Trauner, D. *Nature Chem.* **2015**, *7*, 879

If drawn in a certain way, *epicolactone* reveals a **pattern** that resembles *purpurogallin*
Based on this insight, a biomimetic synthesis was designed with a great success



*Lunch atop RCA skyscraper
New York, 1932*

2

reactivity
a source of risks

don't disconnect building blocks

**disconnections should correspond
to known, reliable reactions**

for compounds consisting of two parts,
joined by a heteroatom
disconnect next to heteroatom

reliable reactions?

1. Truly general reactions whose success rests on thousands of reliable examples

2. Reactions reliable for simple substrates but tend to fail with compounds having more complex arrays

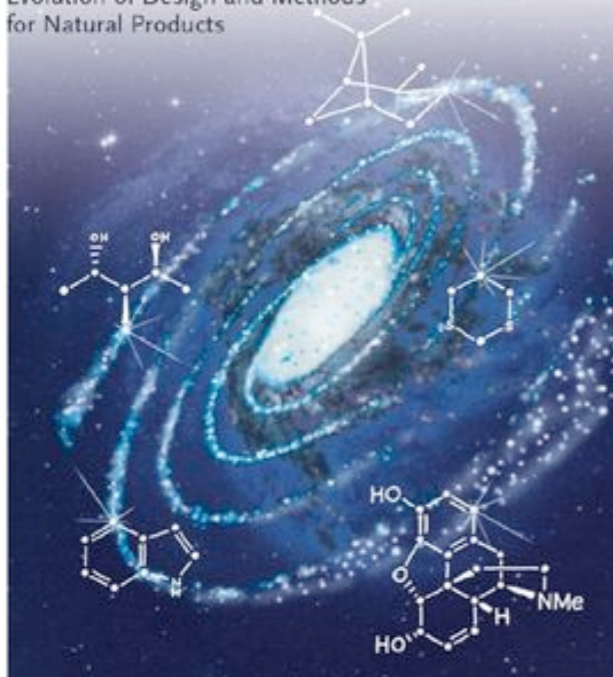
3. Selective procedures invented or adapted as solutions to unique and isolated problems

Tomáš Hudlický
and Josephine W. Reed

WILEY-VCH

The Way of Synthesis

Evolution of Design and Methods
for Natural Products



Chapter 1.3

reliable reactions?



Has it been reported in OS?

Has it been widely used in the literature?



Does it look like mechanistically simple?

Has a colleague of you tried it before?

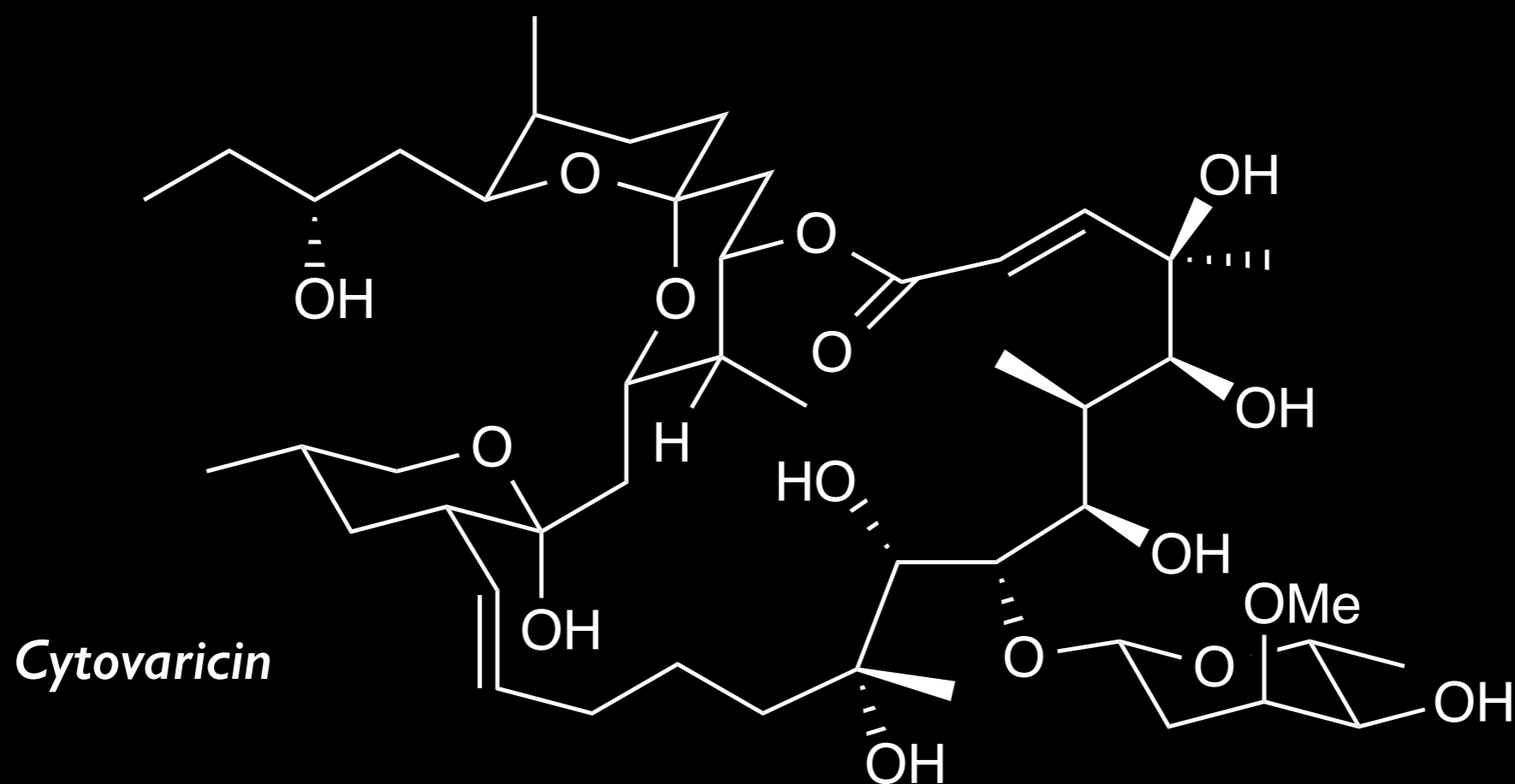
sensitive functional groups reactivity

3



The Dance Classe
Edgar Degas, 1873–1876

The stability of cytovaricin was evaluated under a variety of reaction conditions. The overriding constraint was the sensitivity of the molecule to acid

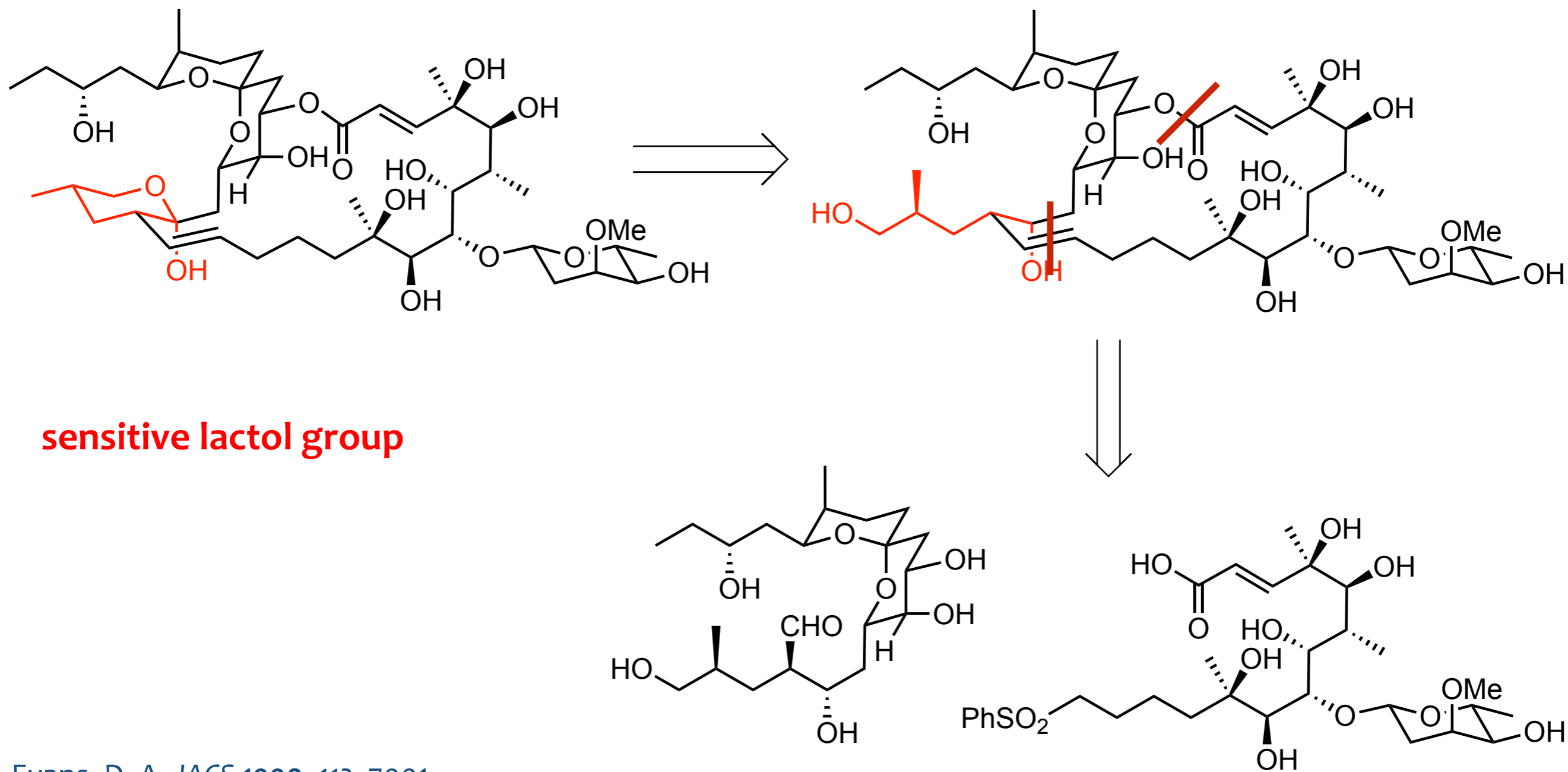


“Not surprisingly, our first disconnection involved the cytovaricin lactol”

Evans, D. A. *JACS* 1990, 112, 7001

The **MOST REACTIVE FUNCTIONAL GROUPS** must be disconnected at the beginning of the retrosynthetic analysis, which would then constitute the final synthetic operation, thus diminishing its exposure to potentially unsuitable reaction conditions

Cytovaricin

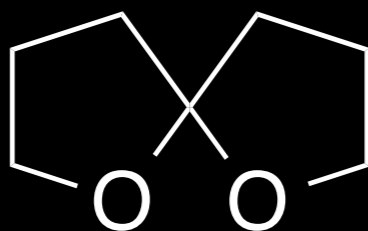


Evans, D. A. *JACS* **1990**, *112*, 7001

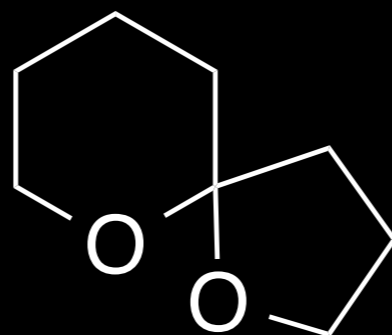
“We elected to carry this portion of the molecule in reduced oxidation state until late in the synthesis, hoping to effect oxidation to the C17 ketone only in the penultimate step”

Spiroketal

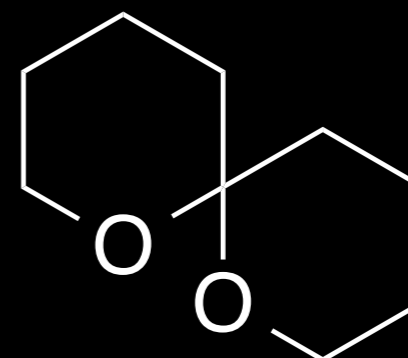
embedded in the structure of many natural products,
are a clear example of labile functional group



[5,5]



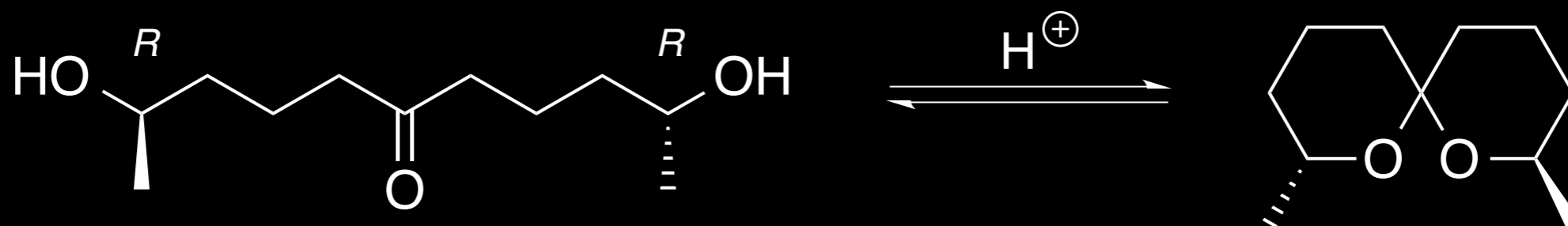
[6,5]



[6,6]

Pihko, P. M. *CR* 2005, 105, 4406; Paterson, I. *CR* 2005, 105, 4237
Carter, R. G.; Kuiper, D. L. *Science of Synthesis* 2014, Section 2.18, pp 863–868

Spiroketal contain a challenging structure.
How many spiroketals could be obtained from
this dihydroxy ketone?
Which is the most stable?

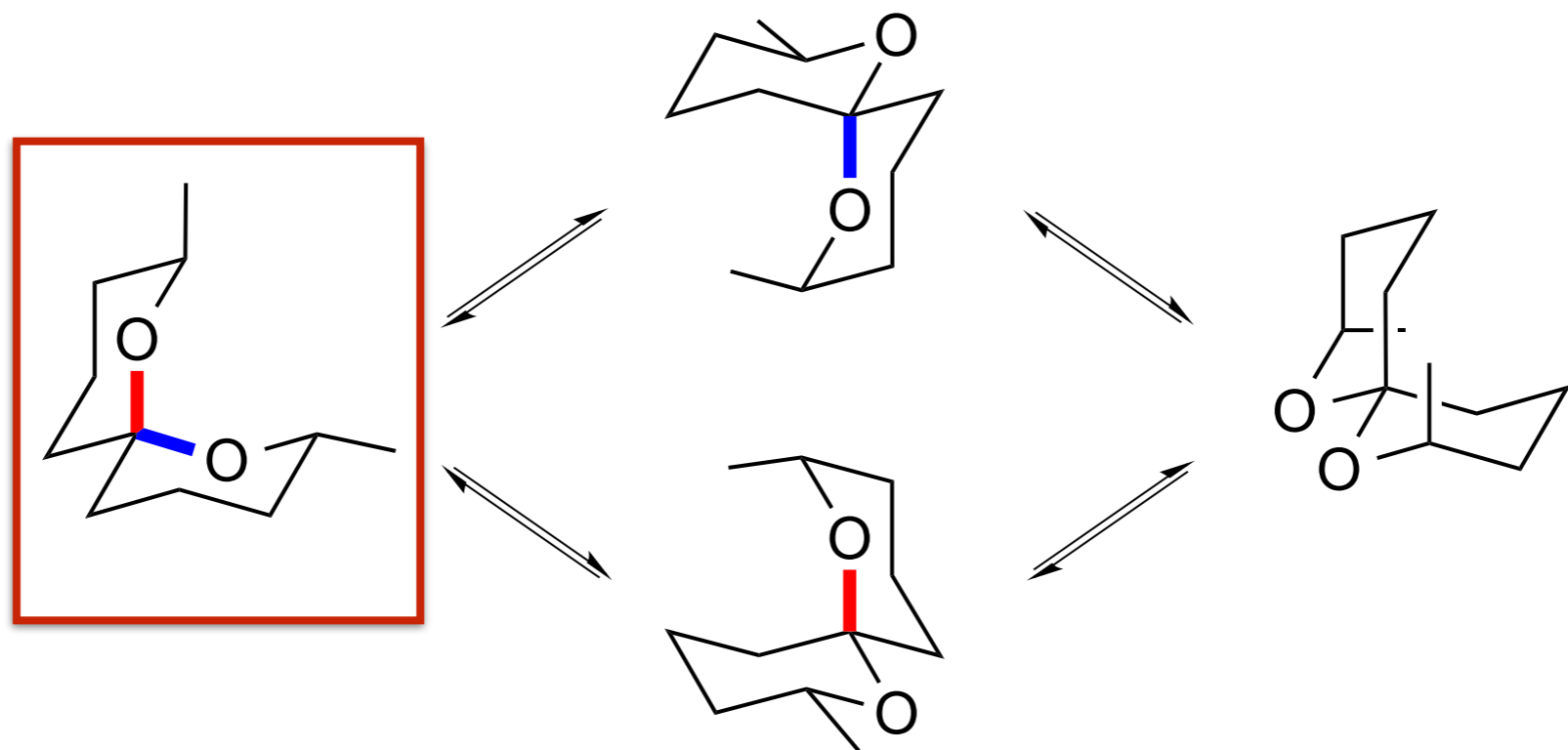


Assumptions:

1. Both six-membered rings adopt a chair-like conformation
2. The conformational equilibrium is slow

Remember!

ANOMERIC EFFECT
preference for the synclinal (gauche) conformation
of a fragment $CY-C-XC$
 g^+g^+

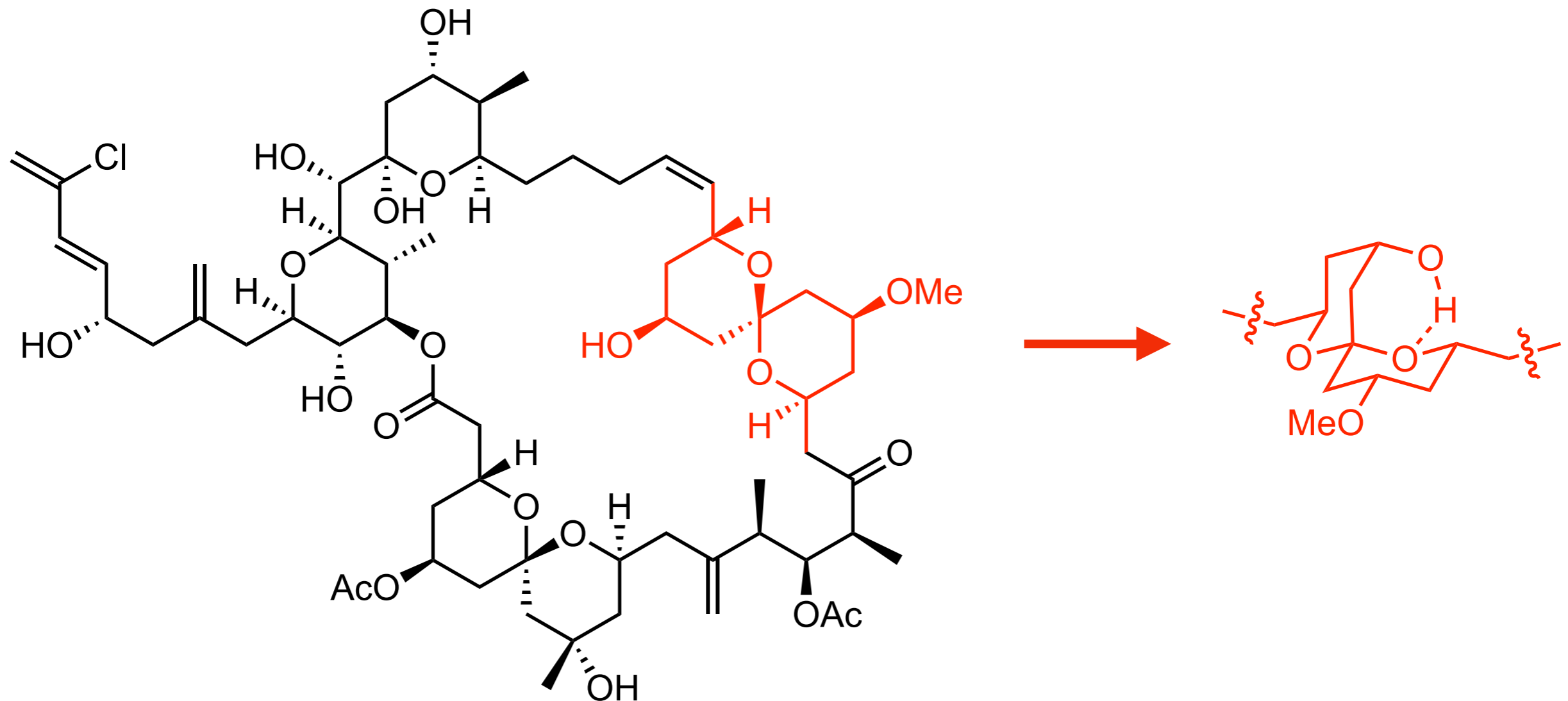


THERMODYNAMIC CONTROL vs KINETIC CONTROL



... but other effects can also play a crucial role,
as **hydrogen bonding**

Spongistatin I



Paterson, I. CR **2005**, 105, 4237

It has been proposed that the nonanomeric configuration of the CD spiroketal unit is stabilized by intramolecular hydrogen bonding. In addition, conformational constraints imposed by the macrocyclic structure most likely favor the nonanomeric configuration.

a source of inspiration:
symmetry



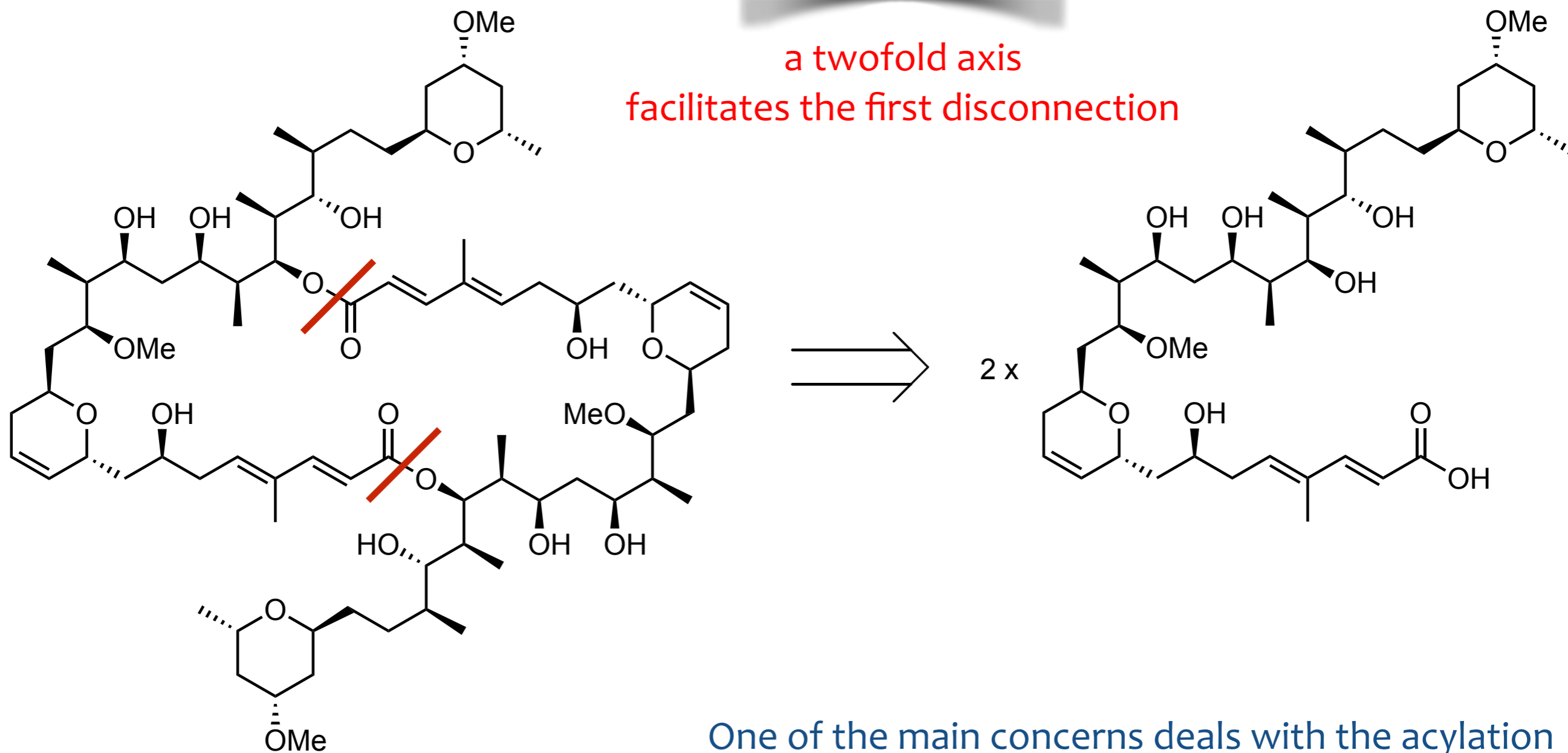
The recognition and exploitation of the
SYMMETRY

is one of the most powerful ways
to simplify complexity
and synthesize a molecule

Swinholide A

C₂ symmetry

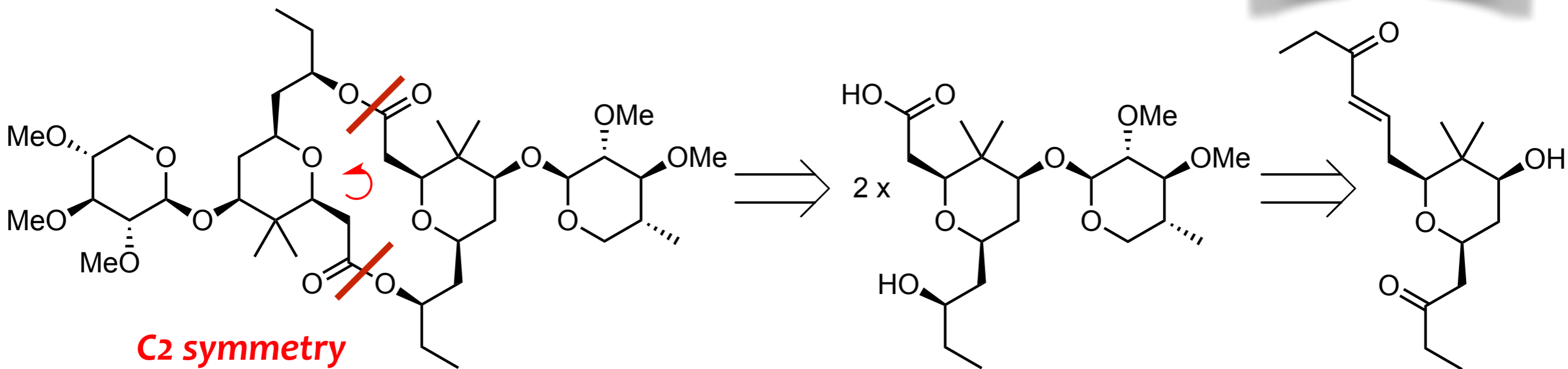
a twofold axis
facilitates the first disconnection



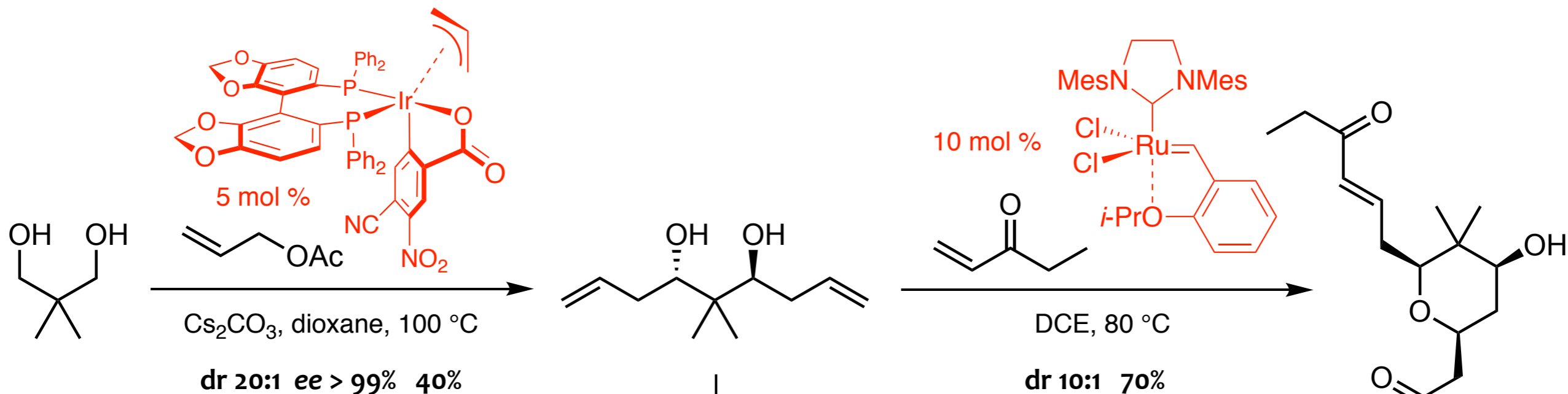
One of the main concerns deals with the acylation
of the appropriate OH groups
TACTIC ISSUE

Cyanolide A

Symmetrical?



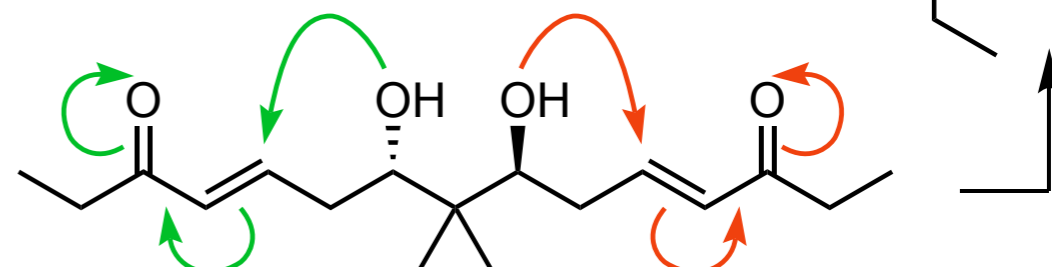
C2 symmetry



Krische, M. J. *ACIE* 2013, 52, 4470

LATENT SYMMETRY

Homotopic groups



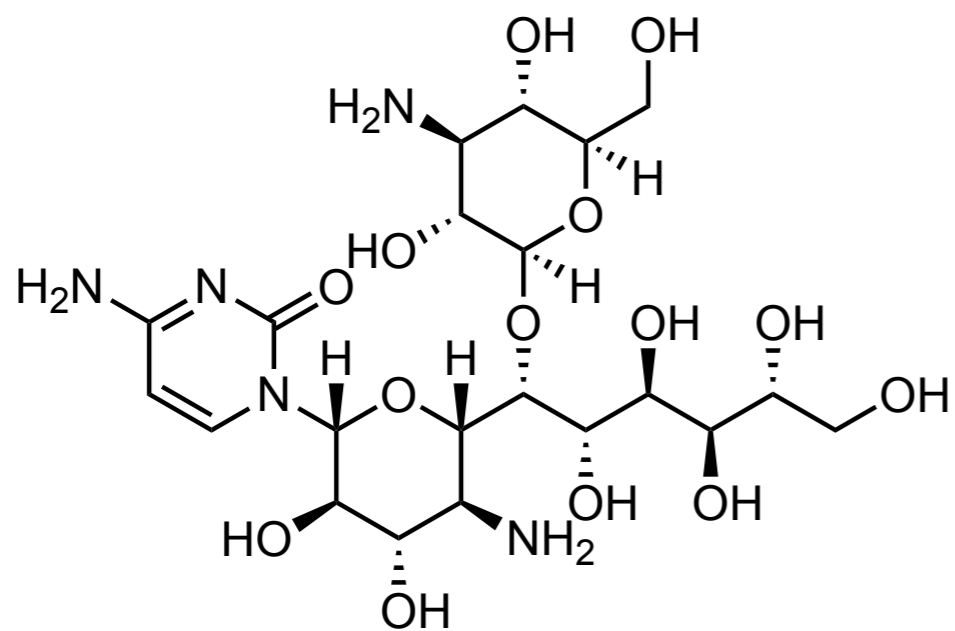


The identification of a **symmetric intermediate**, from which a **desymmetrization-step** can be applied, is a powerful strategy to complete the total synthesis of a wide array of compounds

ANALYSIS OF TOPICITY IS REQUIRED TO DESIGN SYNTHESIS

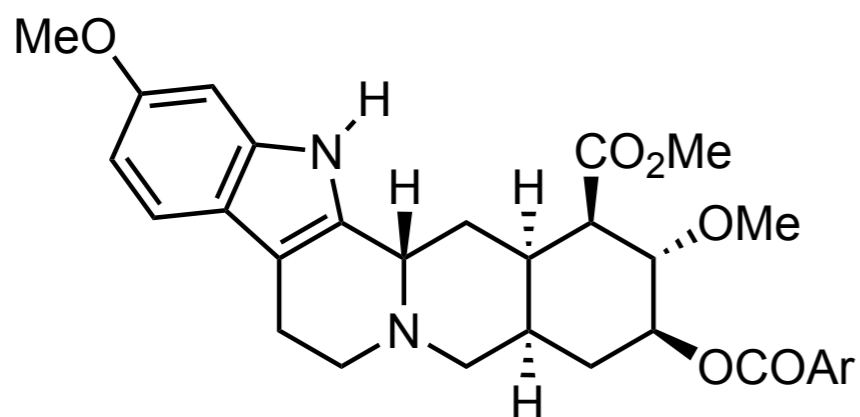
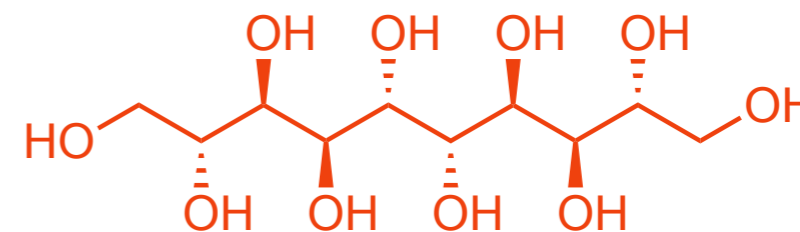
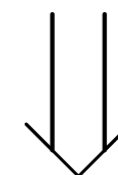
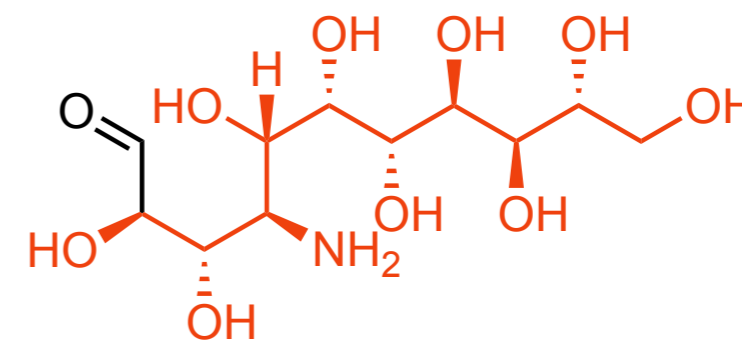
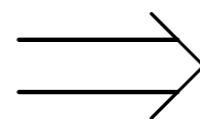
See Supporting Information (Topicity)



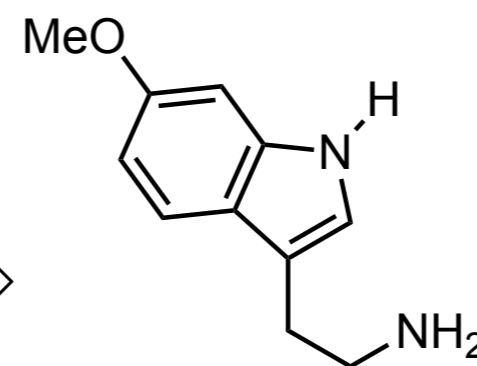
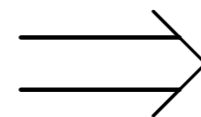


Hikizimycin

Schreiber, S. L. *JACS* 1992, 114, 2524



Reserpine



Chen, D. Y.-K. *ACIE* 2018, 57, 16152

What is the **topicity** of the reacting groups or π -faces?

Homotopic?

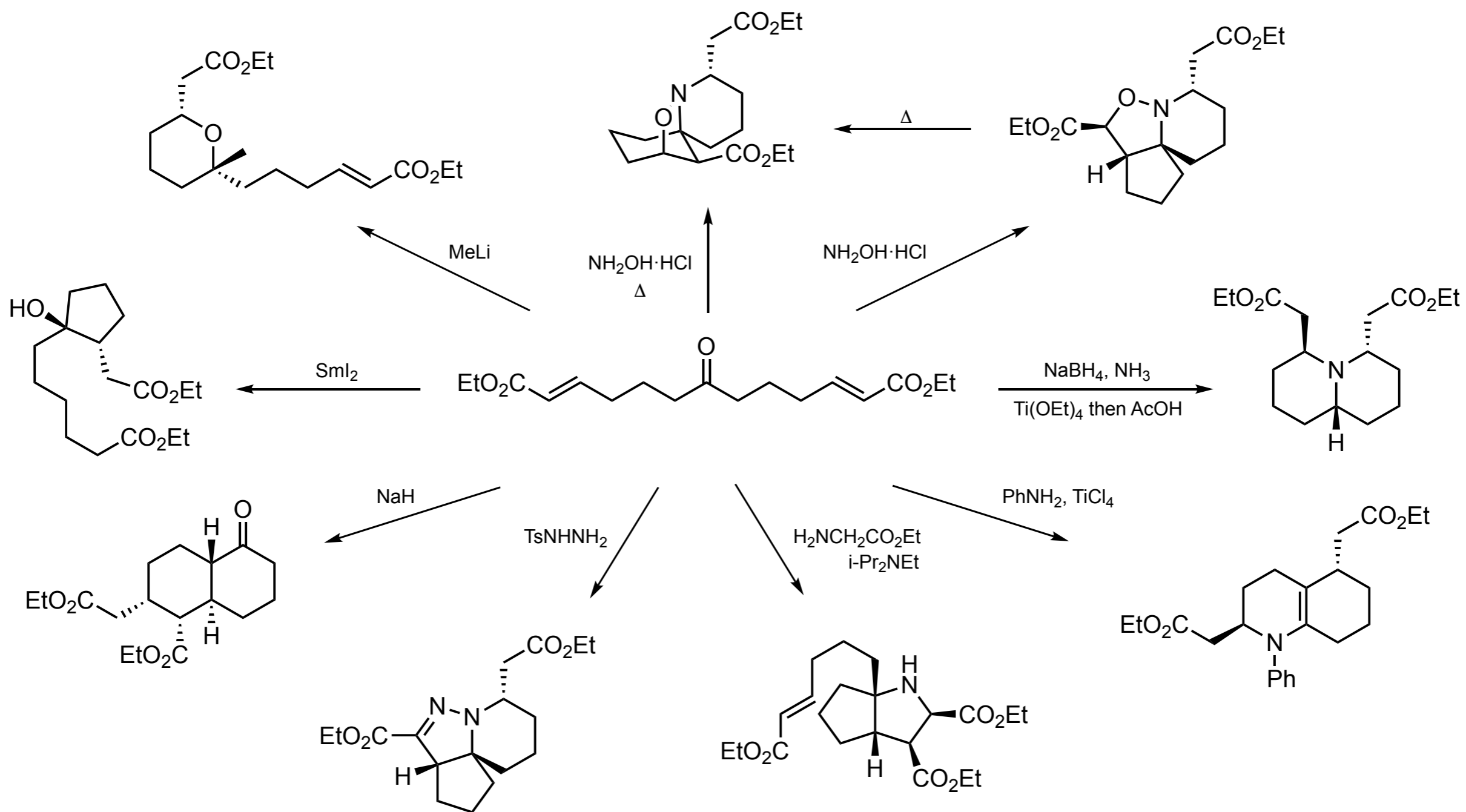
Enantiotopic?

Diastereotopic?



Depending on the answer, chiral or achiral reagents **can** or **must** be used

Differentiation of enantiotopic groups using achiral reagents





From a **tactical** point of view, the identification of a **symmetric intermediate** may suggest a particular synthetic sequence. Then, **simultaneous two-directional syntheses** lead the way to implement highly efficient retrosynthetic analyses

ANALYSIS OF TOPICITY IS REQUIRED TO DESIGN SYNTHESIS

See Supporting Information (Topicity)



One-Directional Synthesis



Sequential Two-Directional Synthesis

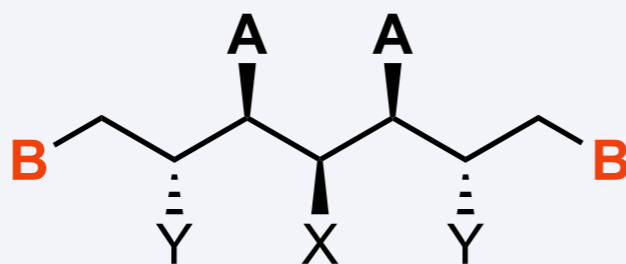
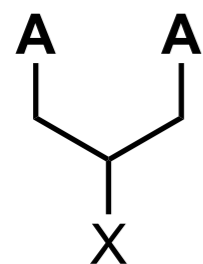


Simultaneous Two-Directional Synthesis



The structure grows faster and more pure

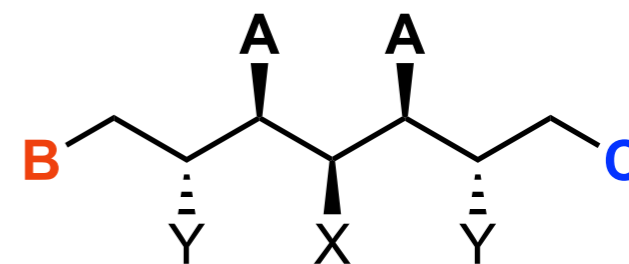
Achiral and Meso Chains



Enantiotopic groups

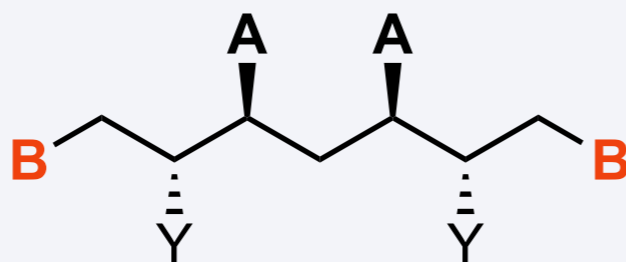
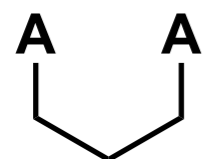
“symmetric” intermediates

Schreiber, S. L. *ACR* 1994, 27, 9
Magnuson, S. R. *Tet* 1995, 51, 2167

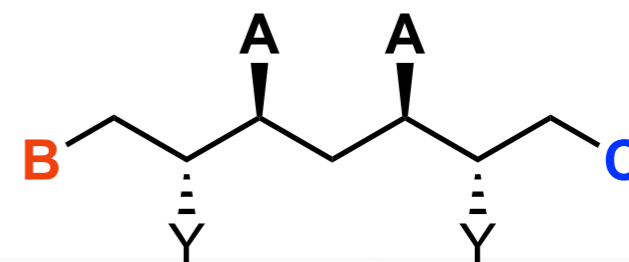


Differentiation by chiral reagents

C₂-Symmetric Chains

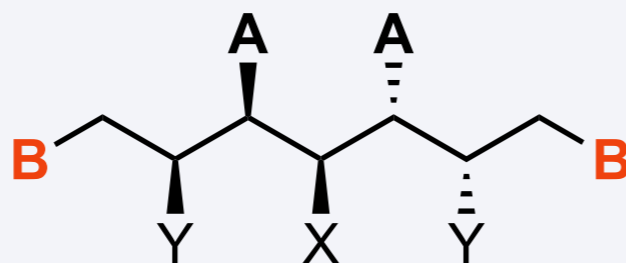
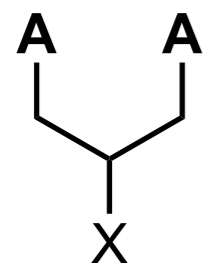


Homotopic groups

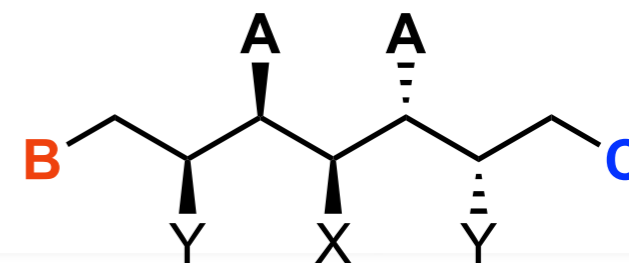


Differentiation by achiral reagents

Pseudo C₂-Symmetric Chains



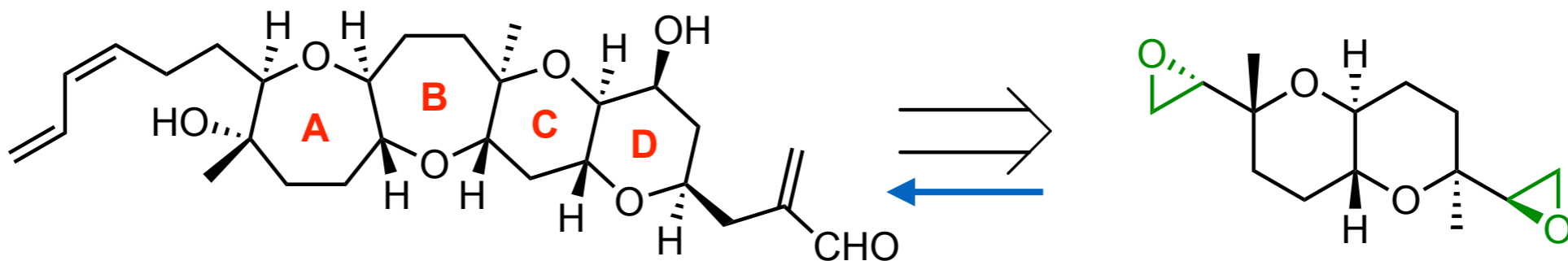
Diastereotopic groups



Differentiation by achiral reagents

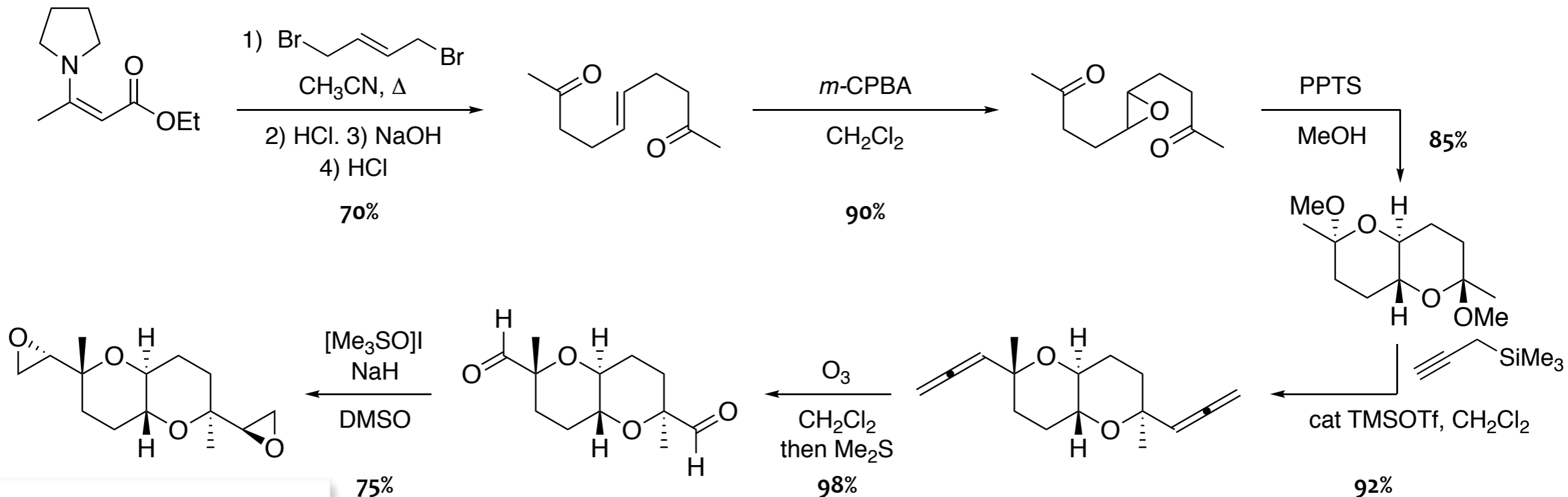
Methods of Two-Directional Chain Syntheses

Differentiation of enantiotopic groups? **Chiral** reagents are required



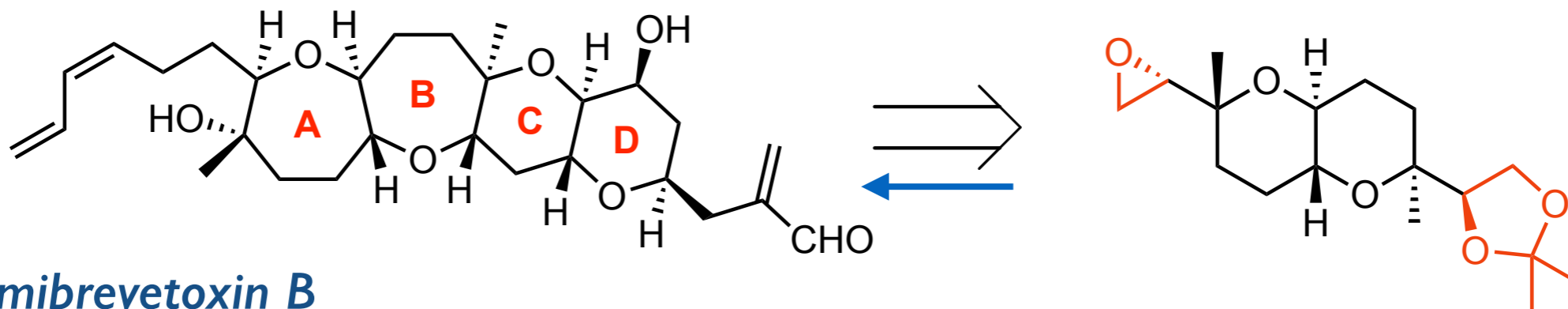
Hemibrevetoxin B

Nakata, T. *TL* 1996, 37, 213, 6365



Symmetric intermediate
Achiral compound

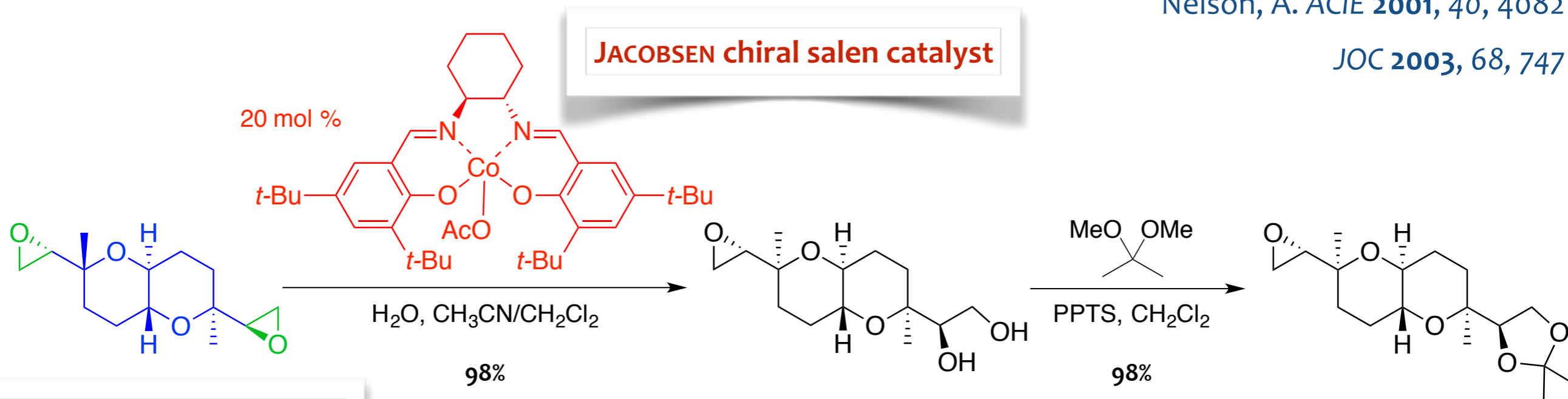
Differentiation of enantiotopic groups? **Chiral** reagents are required



Nakata, T. *TL* **1996**, 37, 213, 6365

Nelson, A. *ACIE* **2001**, 40, 4082

JOC **2003**, 68, 747



centrosymmetric molecule
enantiotopic groups

For a review on meso compounds, see Hoffmann, R. W. *ACIE* **2003**, 42, 1096

brief **summary**

draw the target molecule

1

2

simple, **reliable, selective** reactions
crucial role of **heteroatoms**

disconnect **reactive** groups first

3

4

take advantage of **symmetry**

looking at **further**

In addition to centers of high chemical reactivity
or kinetic (thermal) instability,

molecular complexity involves

molecular size, cyclic connectivity,
functional group & stereo center content

looking at **further**



Keeping in mind these ideas,
**the quest for
the wise choice of**

appropriate simplifying transforms remains

Structure-Based Strategy ■

Recognition of a potential intermediate or starting material
(see Chapter 2)

Functional Group-Based Strategy ■

Analysis of the relationships among the functional groups of a TGT
leading to the identification of suitable transforms
(Next Chapter 4)

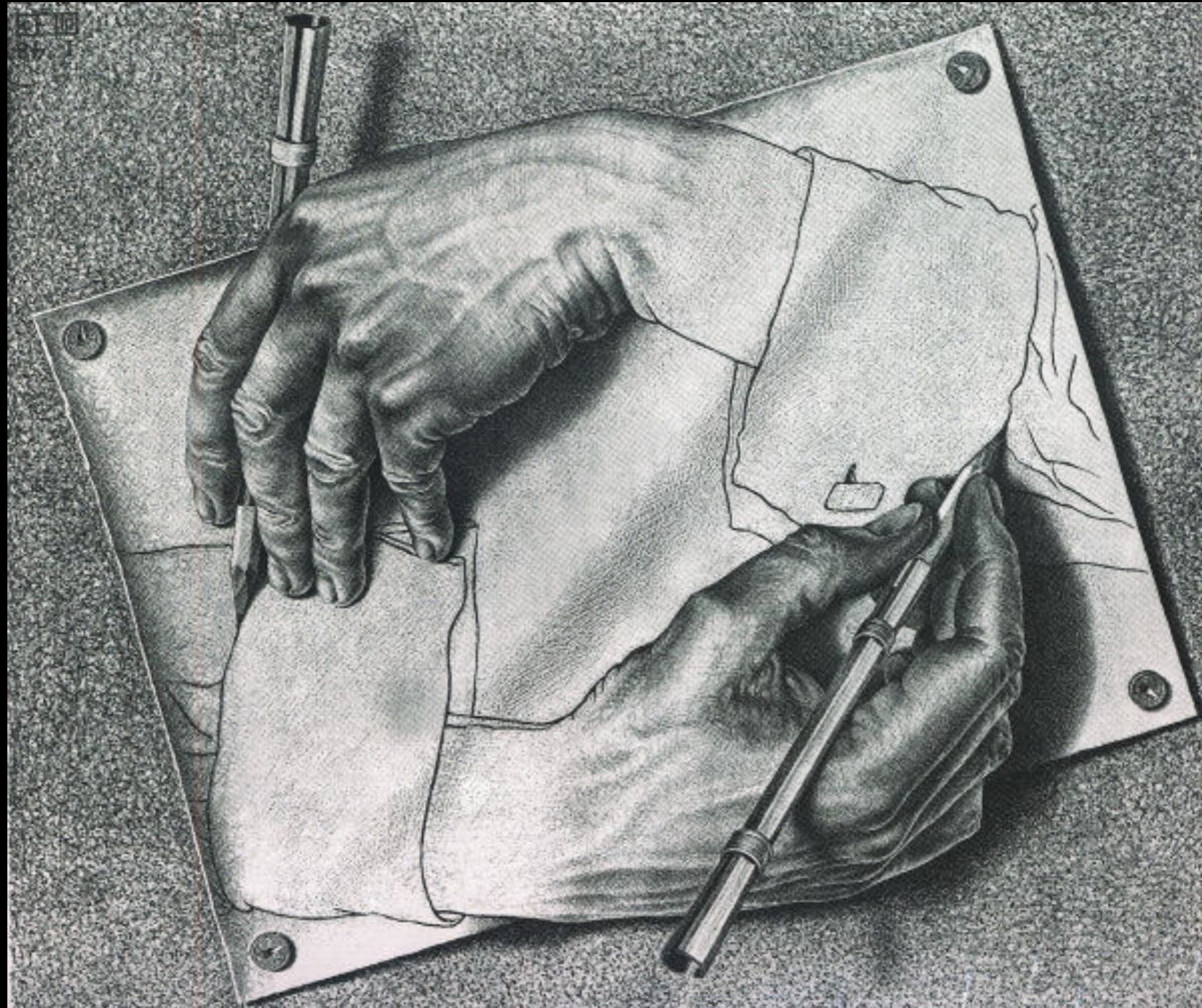
Transform-Based Strategy ■

Identification of a retron required for application of
a powerful simplifying transform
(Chapter 5)

supporting information



Pere Romea



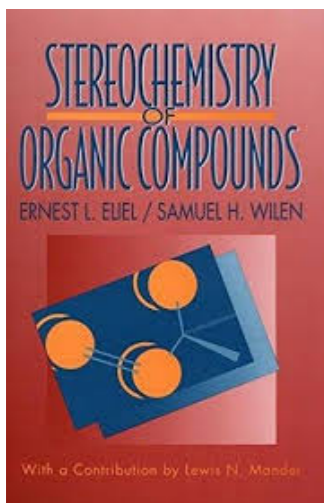
Drawing Hands
Mauritius Cornelis Escher
1948

3. SI : Topicity

Topicity

*a very powerful tool
to analyze the structural relationships
of **atoms, groups, or faces** of a π bond*

*From the Greek **topos** (place)*



Stereochemistry of Organic Compounds
E. L. Eliel, S. H. Wilen
Chapter 8

Two atoms, constitutionally identical groups, or π faces can be

Homotopic

identical, indistinguishable

Heterotopic

different, distinguishable



**Constitutionally
Heterotopic**

placed in different positions

**Stereo
Heterotopic**

the stereochemical environment is different

Enantiotopic

*the difference can only be observed
in a chiral environment*

Diastereotopic

*the difference may be observed
both in a chiral or achiral environment*

Two atoms, constitutionally identical groups, or π faces can be

Homotopic

identical, indistinguishable

Heterotopic

different, distinguishable



**Constitutionally
Heterotopic**

placed in different positions

**Stereo
Heterotopic**

the stereochemical environment is different

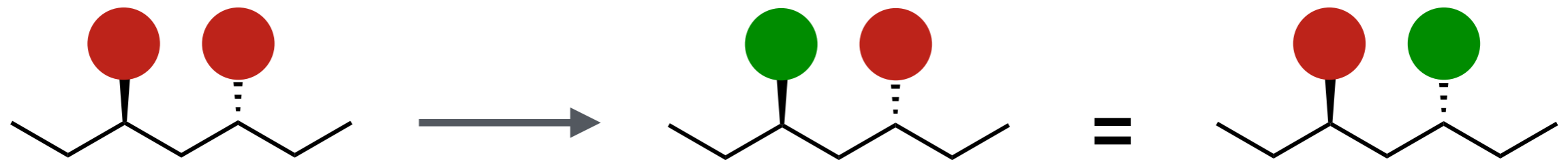
Enantiotopic

*the difference can only be observed
in a chiral environment*

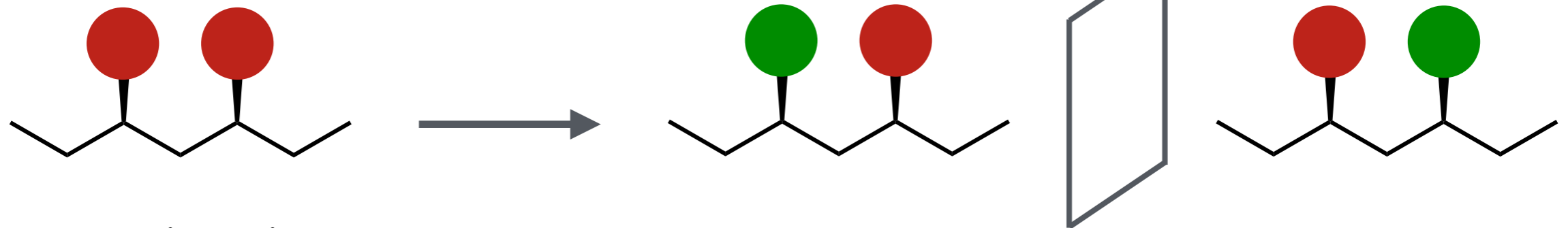
Diastereotopic

*the difference may be observed
both in a chiral or achiral environment*

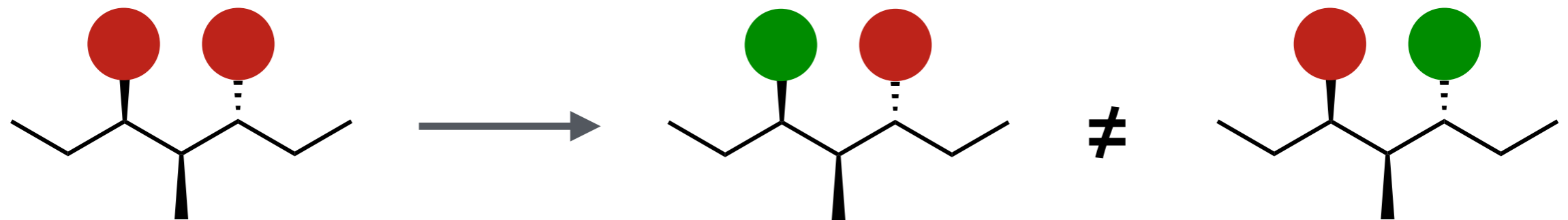
Substitution and Addition Criteria



Homotopic

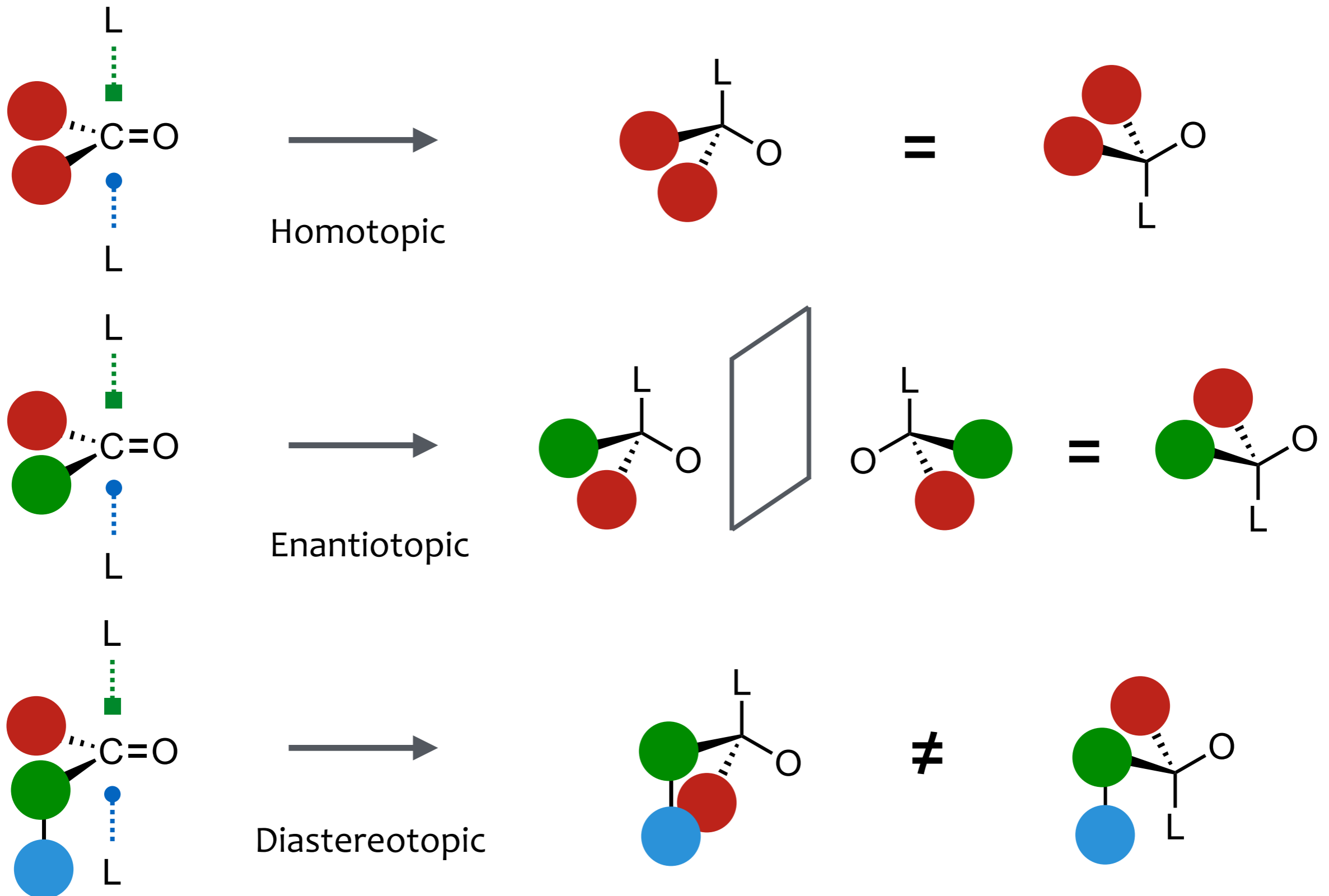


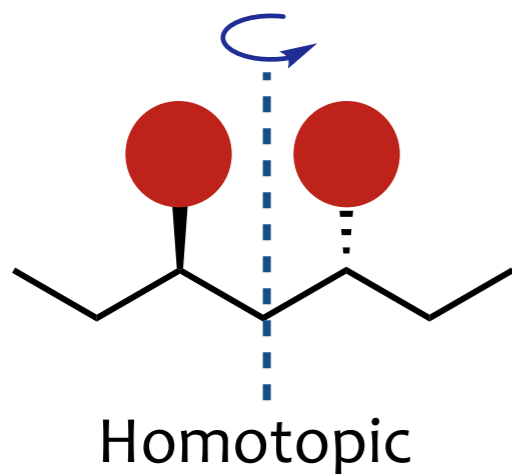
Enantiotopic



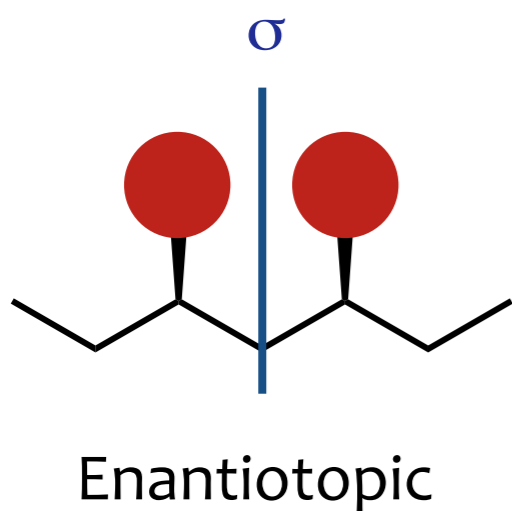
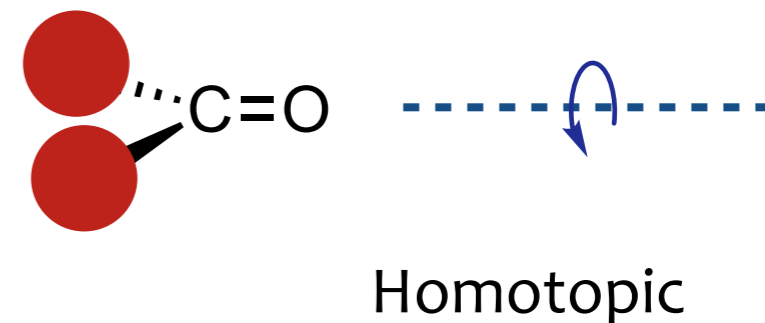
Diastereotopic

Substitution and Addition Criteria

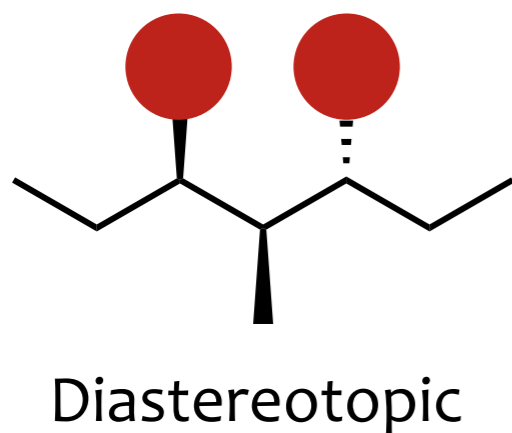
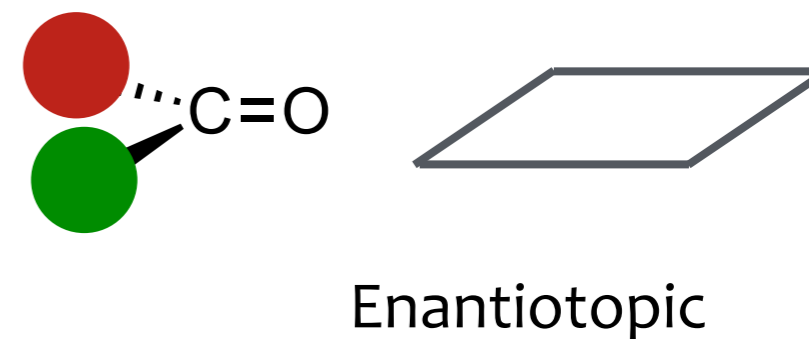




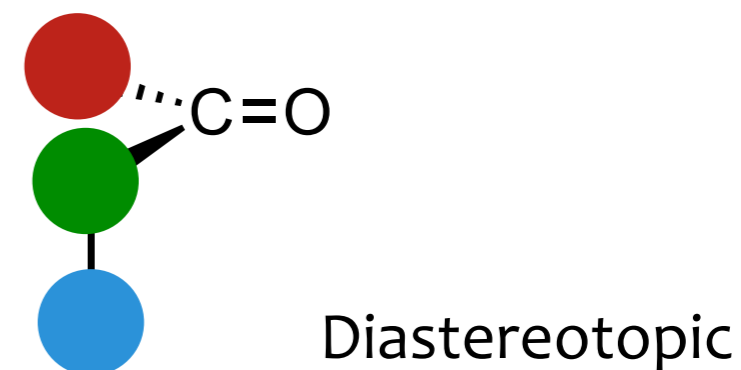
Simmetry axis



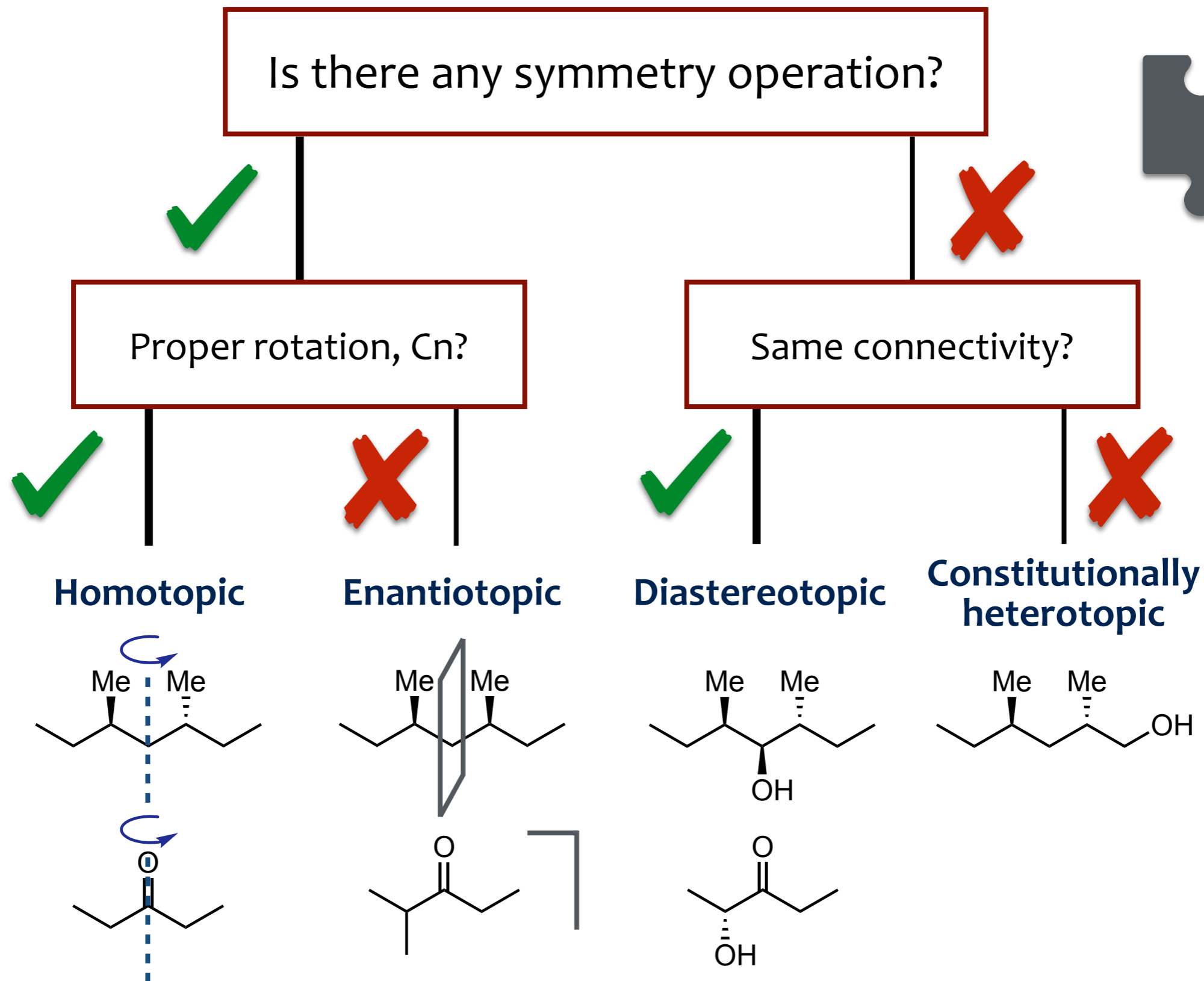
Simmetry plane

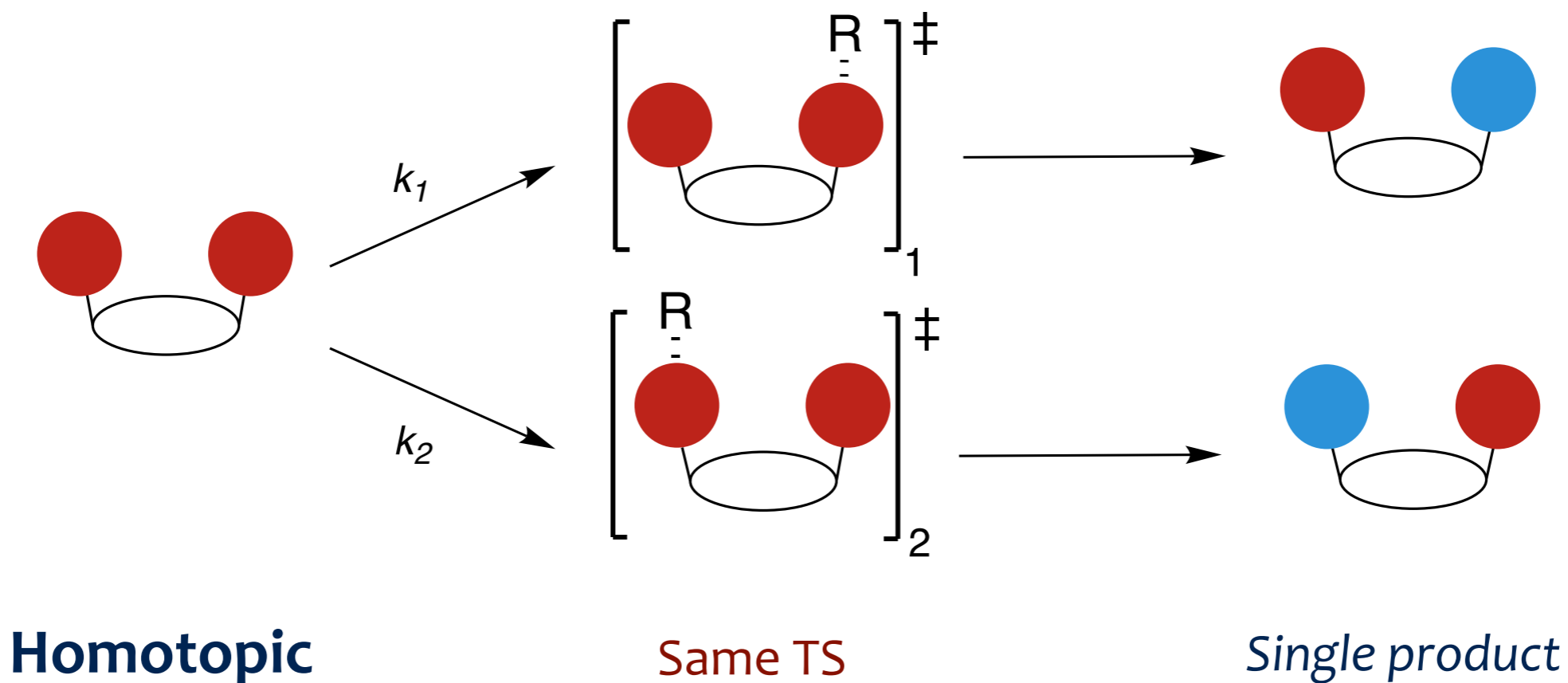


No simmetry element



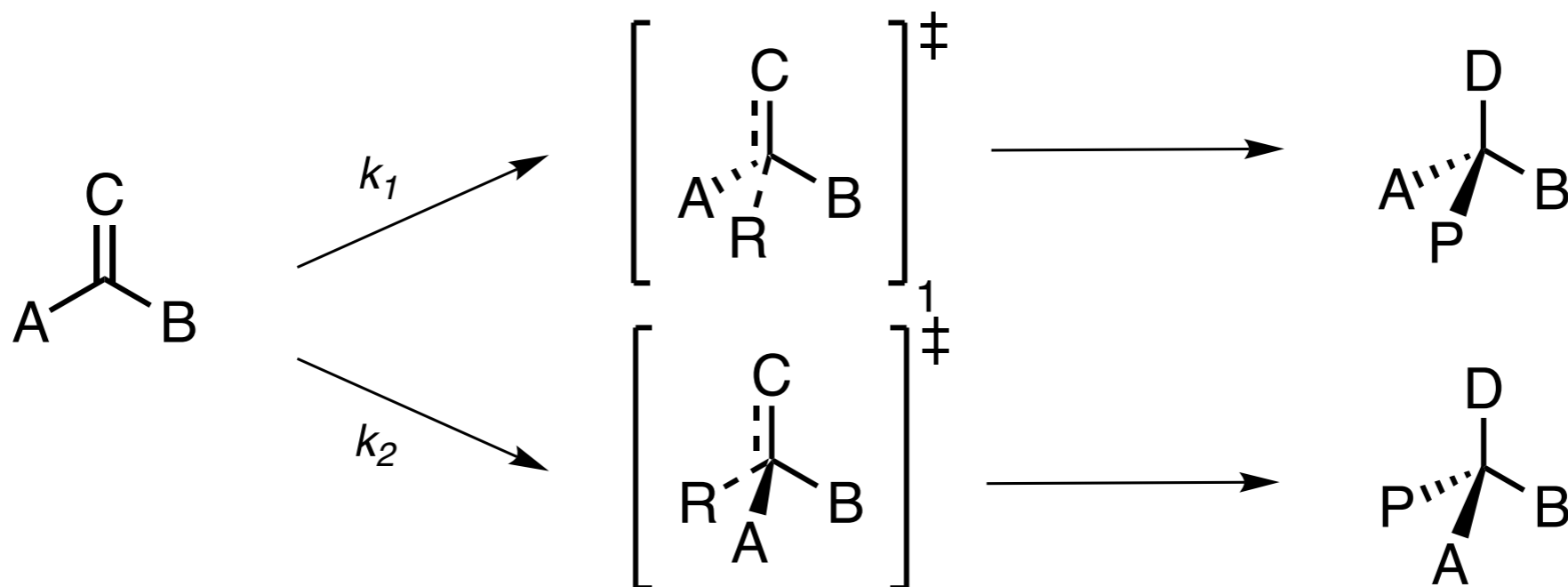
Symmetry Criterion: A Chart for Topicity





Enantiotopic	R achiral	Same energy TS <i>Enantiomers</i>	Racemic mixture
	R chiral	Different energy TS <i>Diastereomers</i>	Non racemic mixture or diastereomers

Diastereotopic **Different energy TS**
Diastereomers **Diastereomers**



Homotopic

Same TS

Single product

Enantiotopic

R achiral

Same energy TS
Enantiomers

Racemic mixture

R chiral

Different energy TS
Diastereomers

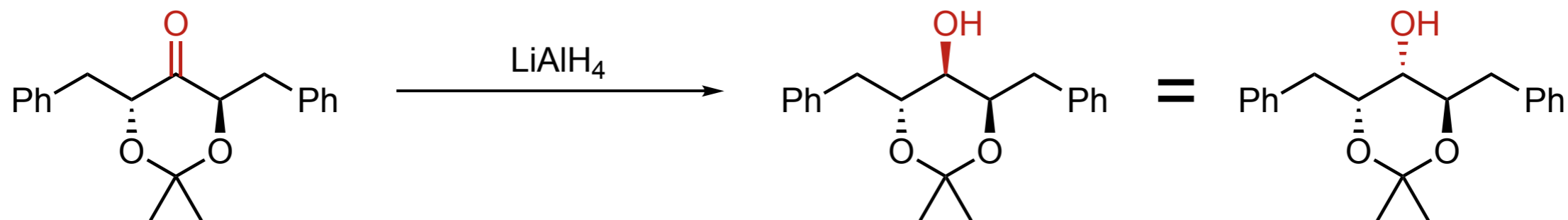
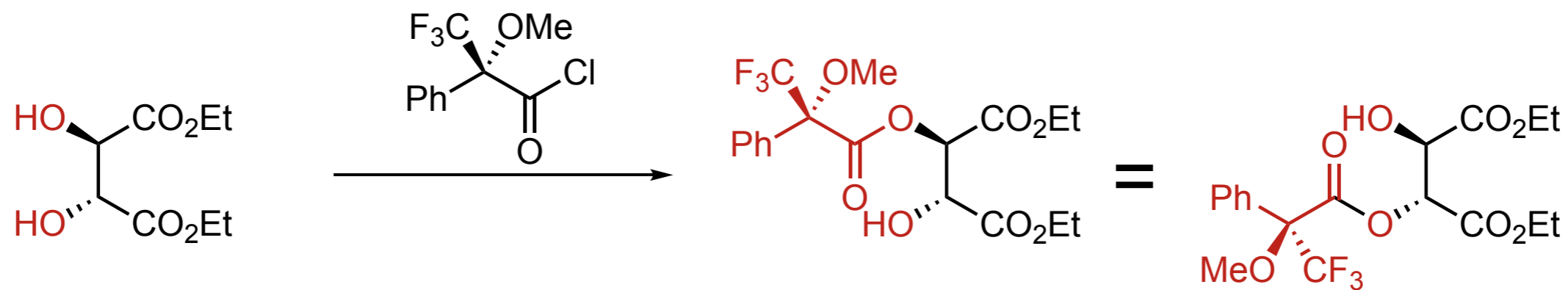
Non racemic mixture
or diastereomers

Diastereotopic

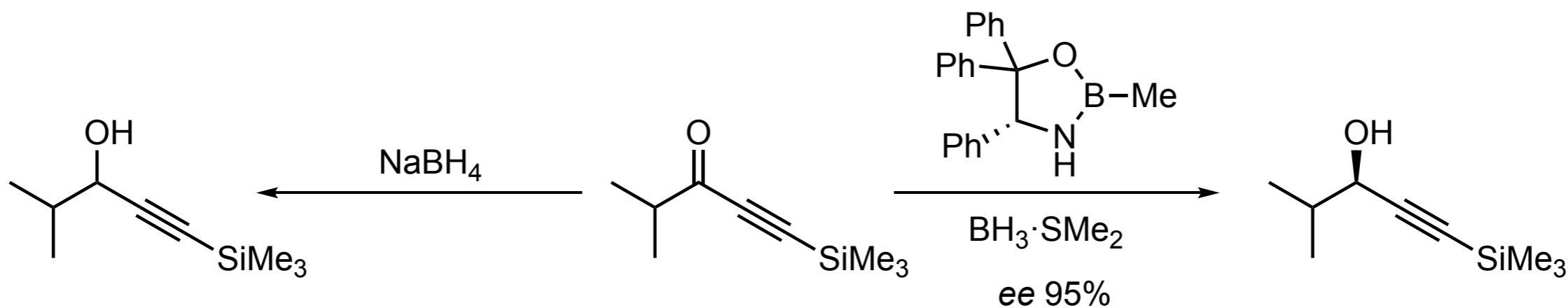
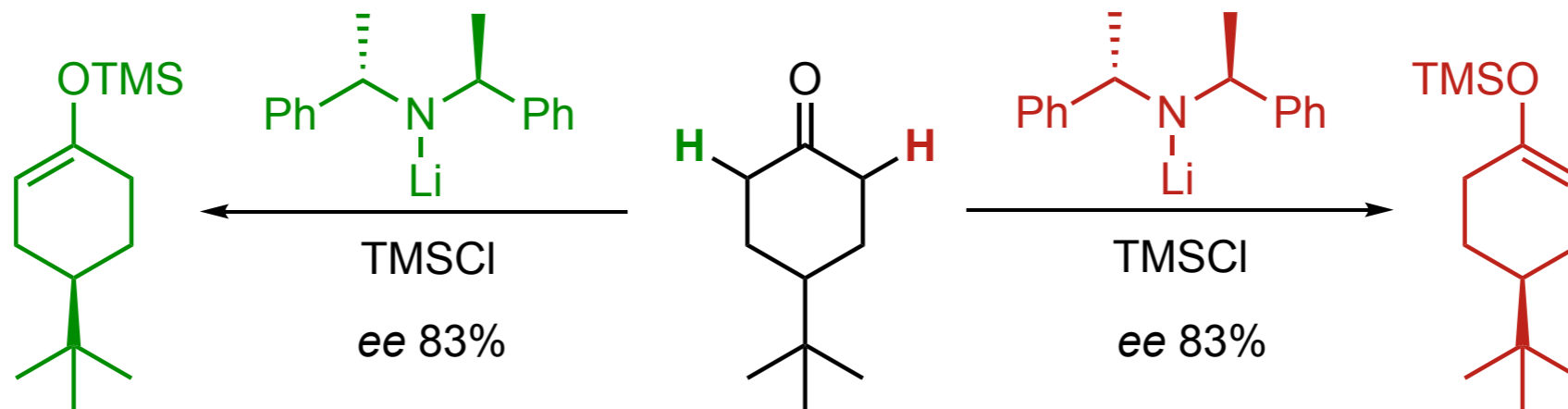
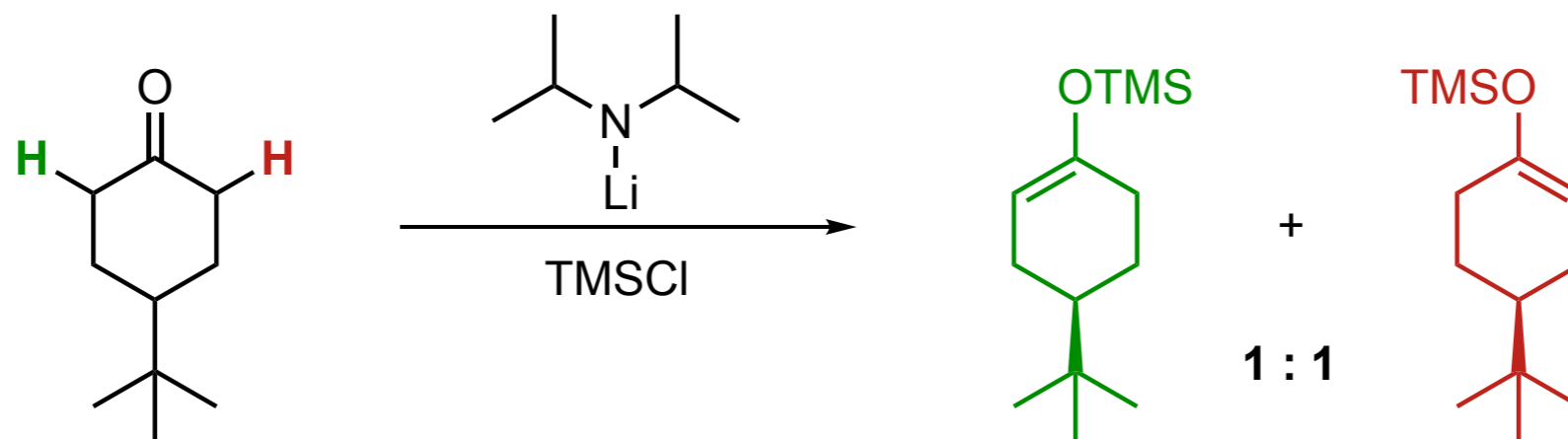
Different energy TS
Diastereomers

Diastereomers

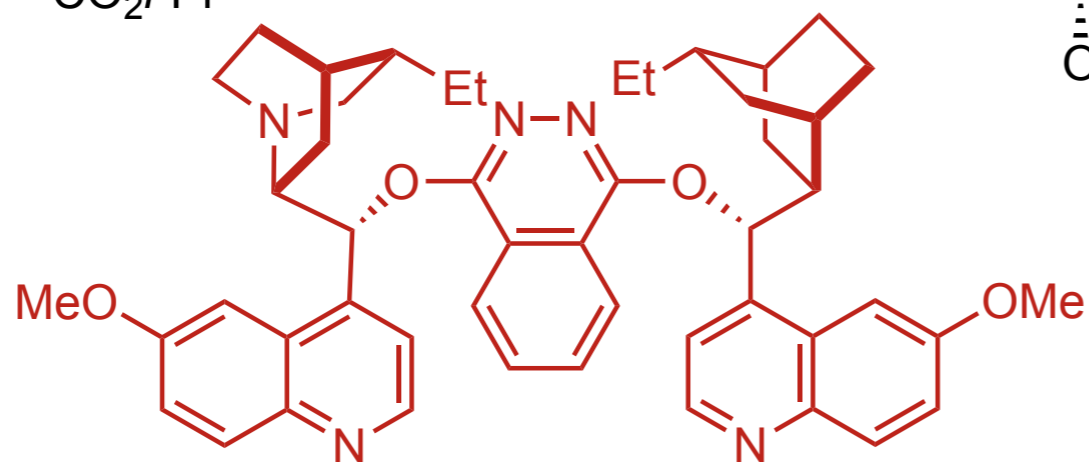
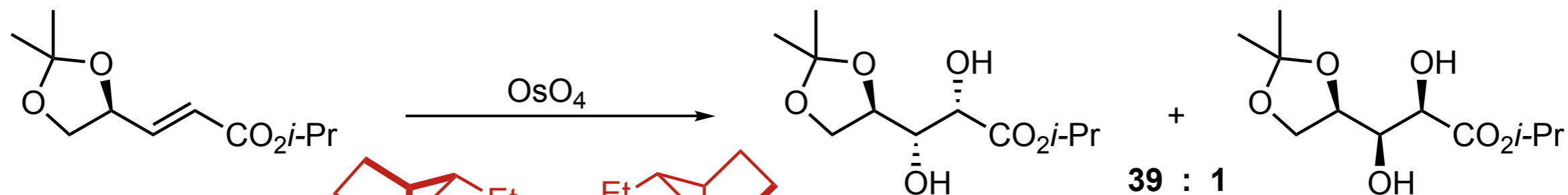
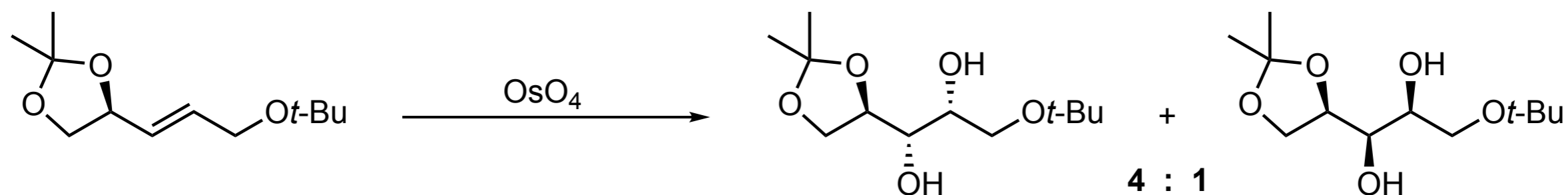
➤ **Homotopic atoms, groups, or π -faces cannot be differentiated by any reagent**



➤ *Enantiotopic atoms, groups, or π -faces can only be differentiated by a chiral reagent*

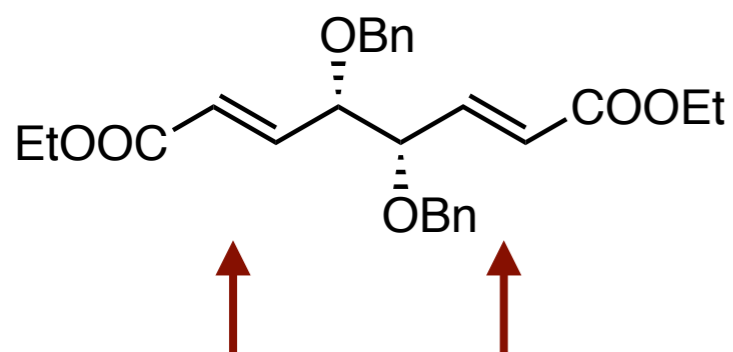


➤ **Diastereotopic atoms, groups, or π -faces can be differentiated by any reagent**

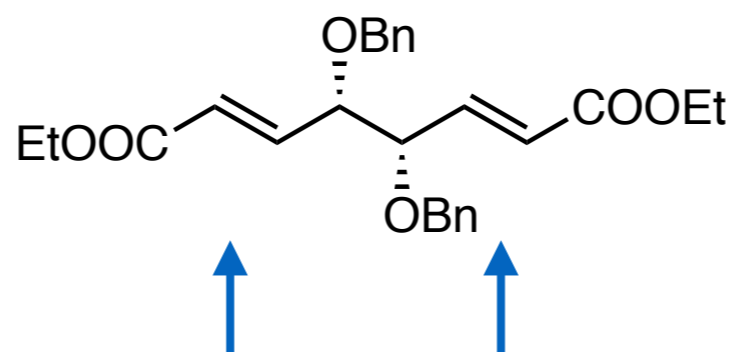


1 mol% $(\text{DHQD})_2\text{-PHAL}$

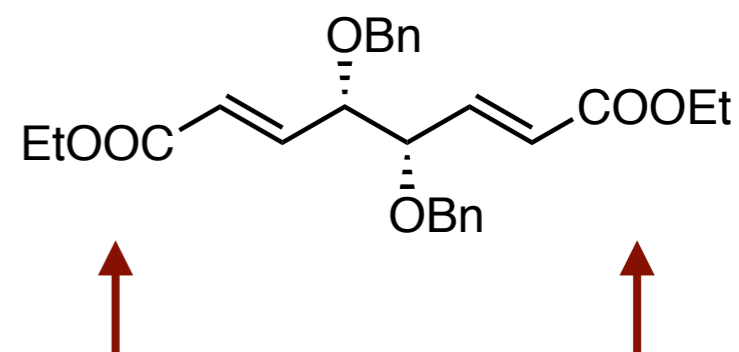
Hikizimycin Synthesis. Schreiber, S. L. *JACS* **1990**, 112, 9657; **1992**, 114, 2524



both olefins are homotopic



up & down of both olefins are diastereotopic



both esters are homotopic

