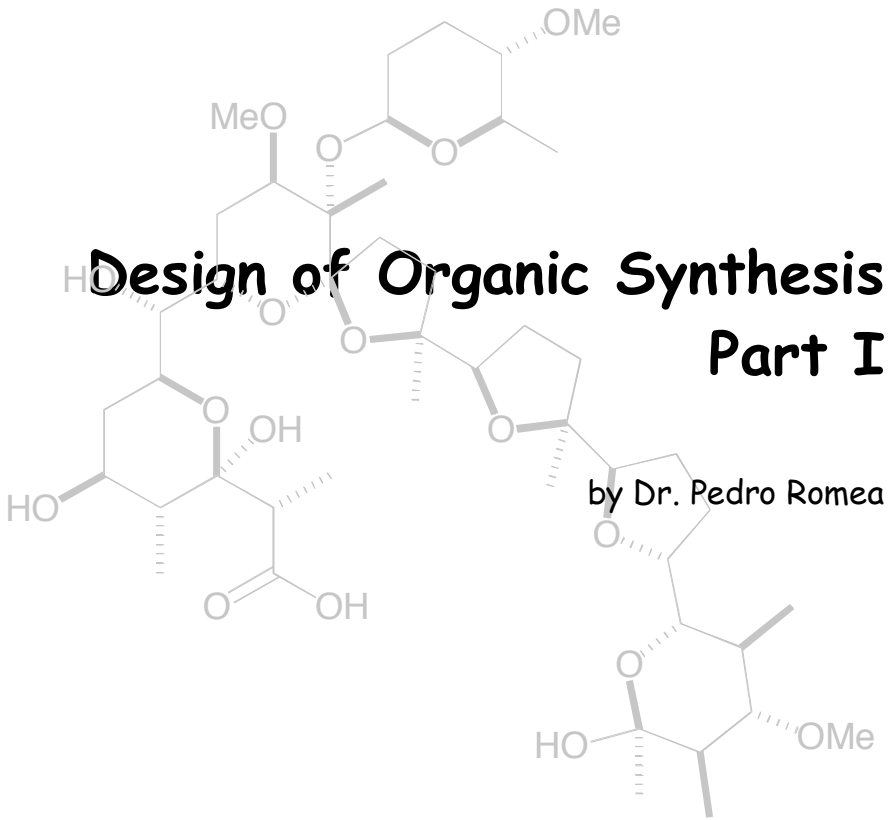
Postgraduate Programme in Organic Chemistry
2003-2004

Departament de Química Orgànica
Universitat de Barcelona



Design of Organic Synthesis
Part I

by Dr. Pedro Romea

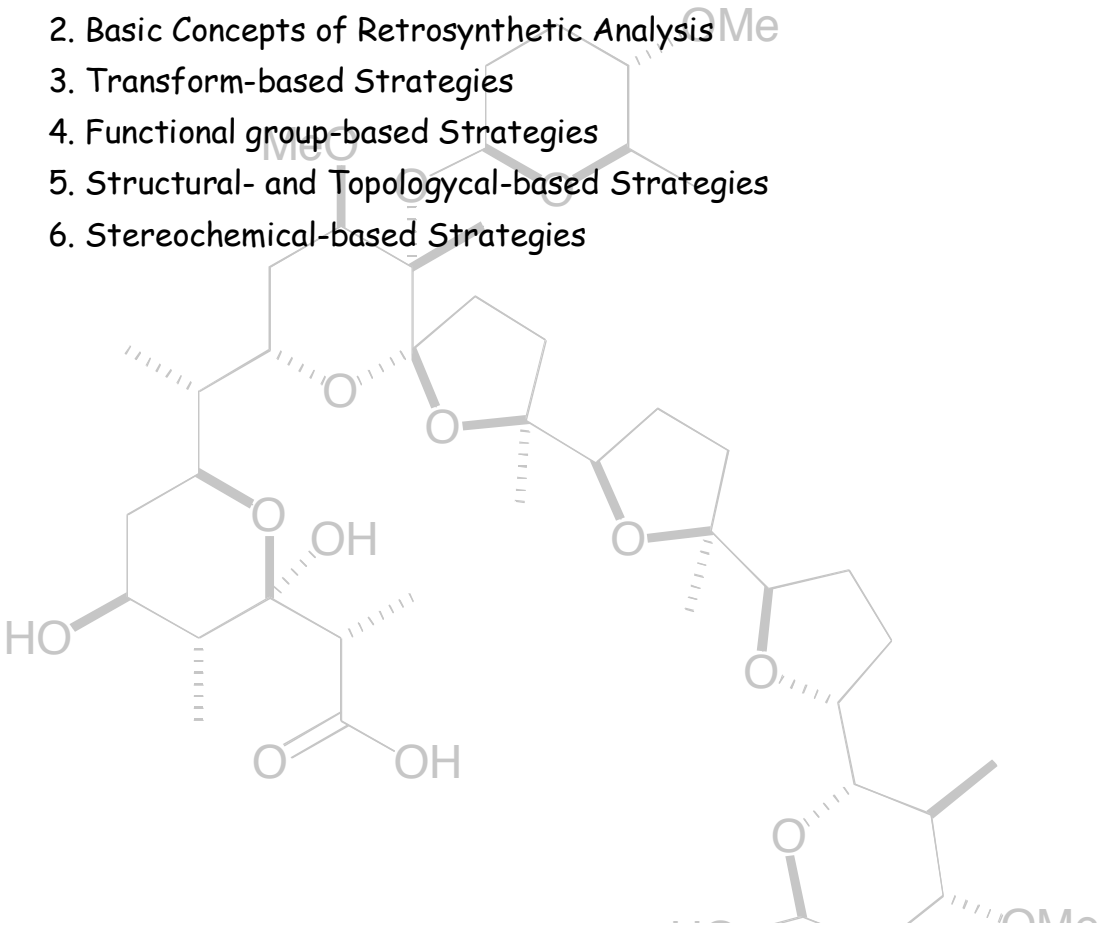
Design of Organic Synthesis. Part I

4 Credits

Wednesdays, from 15 to 17 h, Room 542

Part I

1. Introduction
2. Basic Concepts of Retrosynthetic Analysis
3. Transform-based Strategies
4. Functional group-based Strategies
5. Structural- and Topologycal-based Strategies
6. Stereochemical-based Strategies



Recommended Texts

Fleming, I. *Selected Organic Synthesis. A Guidebook for Organic Chemists.*
Wiley & Sons. New York, 1973

Serratosa, F. *Heurisko. Introducción a la sSíntesis Orgánica.*
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Hanessian, S. *Total Synthesis of Natural Products: the "Chiron" Approach.*
Pergamon Press. Oxford, 1985

Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis.*
Wiley & Sons. New York, 1989

Ho, T.-L. *Tactics of Organic Synthesis.*
Wiley & Sons. New York, 1994

Ho, T.-L. *Symmetry. A Basis for Synthesis Design.*
Wiley & Sons. New York, 1995

Lehn, J.-M. *Supramolecular Chemistry. Concepts and Perspectives*
VCH. Weinheim, 1995

Serratosa, F.; Xicart, J. *Organic Chemistry in Action. The Design of Organic Synthesis.*
Elsevier. Amsterdam, 1996

Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis. Targets, Strategies, Methods.*
VCH. Weinheim, 1996

Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry.*
Oxford University Press, 2001

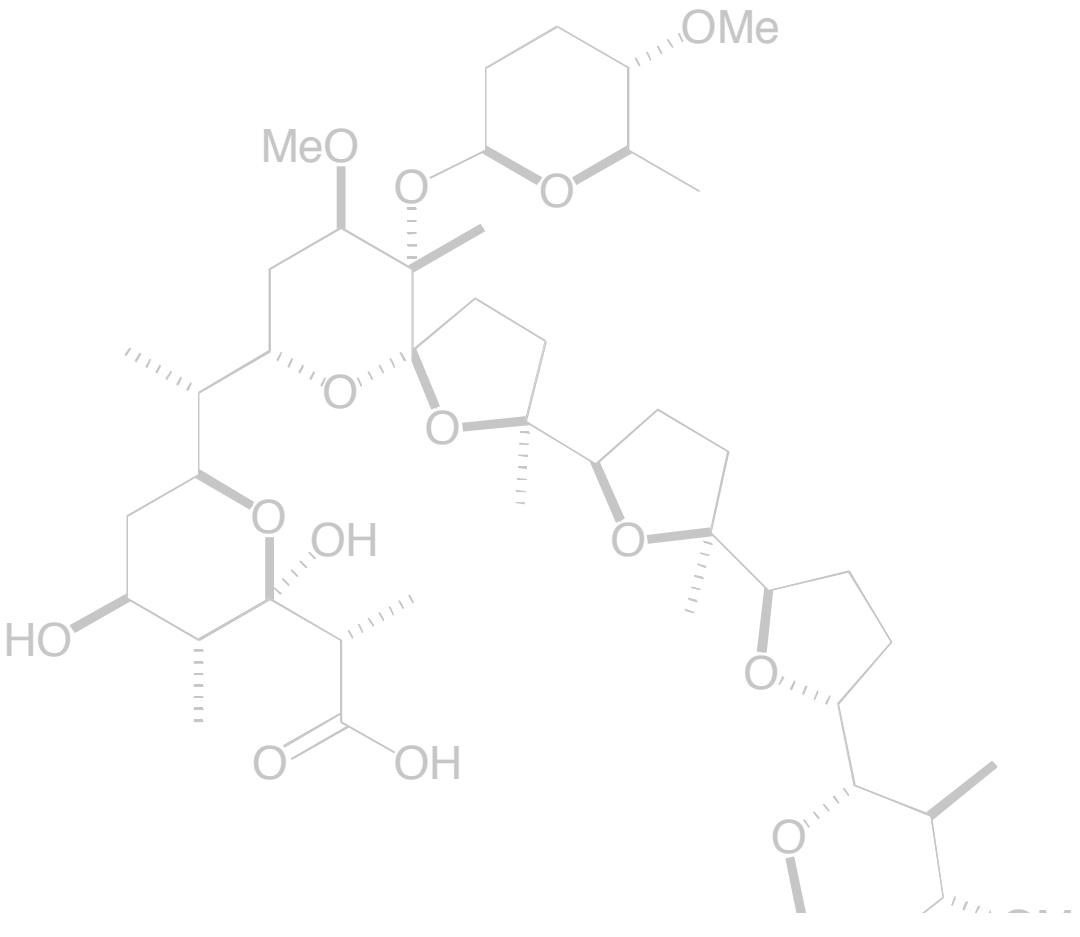
Fuhrhop, J.-H.; Li, G. *Organic Synthesis. Concepts and Methods.*
Wiley & VCH. Weinheim, 2003

Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II. More Targets, Strategies, Methods.*
Wiley & VCH. Weinheim, 2003

Recommended Texts (II)

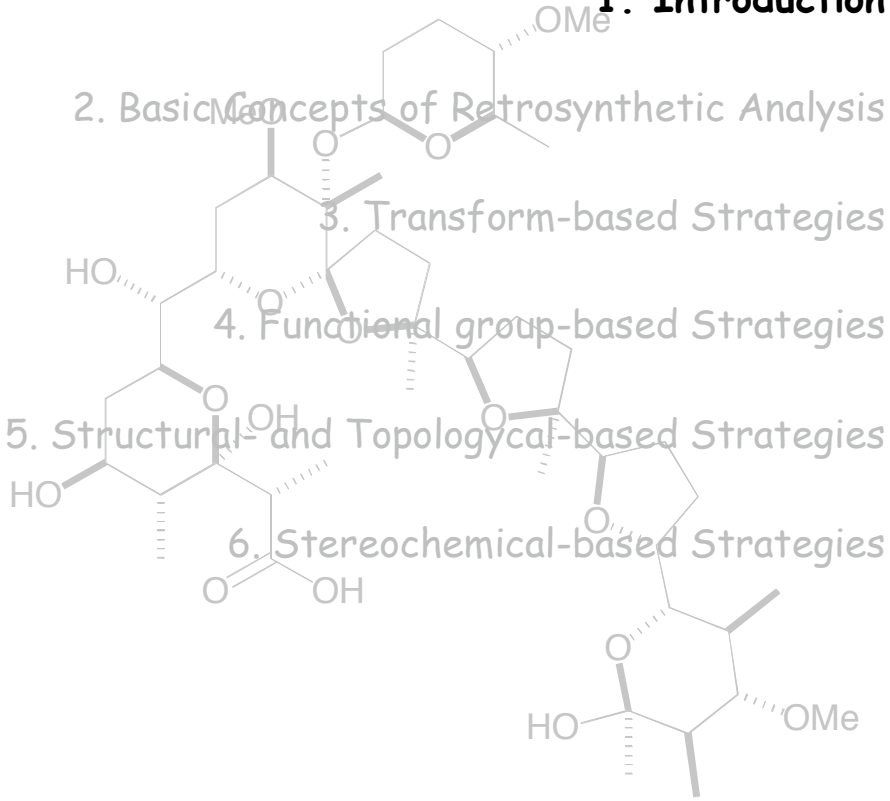
Warren, S. *Workbook for Organic Synthesis: the Disconnection Approach.*
Wiley & Sons. New York, 1982

Carda, M.; Rodríguez, S.; González, F.; Murga, J.; Falomir, E.; Castillo, E.
Síntesis Orgánica. Resolución de problemas por el método de desconexión.
Publicaciones Univ. Jaume I. Castellón, 1996



Part I

1. Introduction



What is Organic Synthesis?

If Chemistry is the science of matter and of its transformations

Synthetic chemistry is the science of constructing molecules from atoms and/or simpler molecules.

The discipline may be divided, according to the molecules involved, into

Synthetic Organic Chemistry and Synthetic Inorganic Chemistry.

The term Organic Synthesis is often used –may be incorrectly in strict terms– to mean the same

as Synthetic Organic Chemistry

Nicolaou, K. C. *Classics in Total Synthesis*

... the intentional construction of molecules by means of chemical reactions

Cornforth, J. W. 1994

Chemistry creates its subject.

This creative ability, similar to that of art, essentially distinguishes Chemistry among the natural sciences.

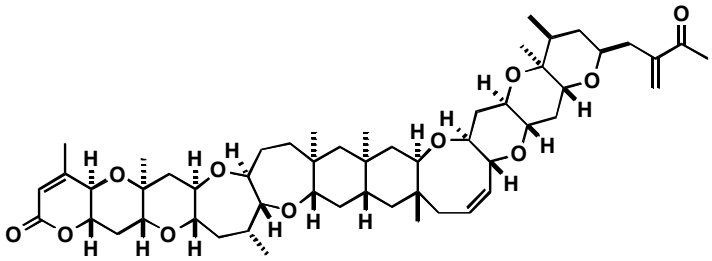
Berthelot, J. 1860

Then...

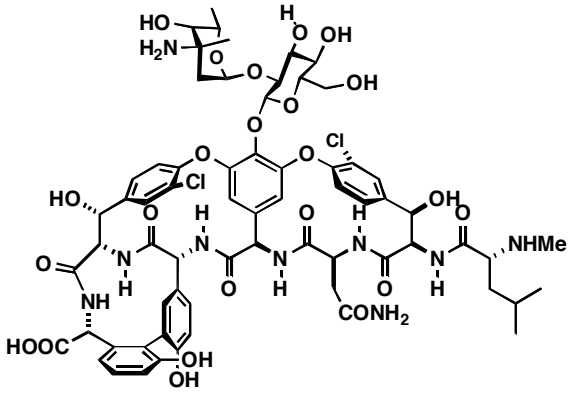
*The ultimate goal of Organic Synthesis is to assemble a given organic compound (**target molecule**)*
from readily available starting materials and reagents in the most efficient way.
*This process usually begins with the **design of a synthetic plan (strategy)***
which calls upon various synthetic reactions to address individual synthetic objectives in a certain sequence.
If a transformation or a strategic maneuver required by the synthetic plan has to be demonstrated before,
*the plan must rely on the development of a suitable **synthetic method** or **tactic***
to solve the particular problem at hand.
Thus, the science of organic synthesis is constantly enriched by new inventions and discoveries
pursued deliberately for their own sake or as subgoals within a program directed
towards the the synthesis of a target molecule.

Nicolaou, K. C. *Classics in Total Synthesis*

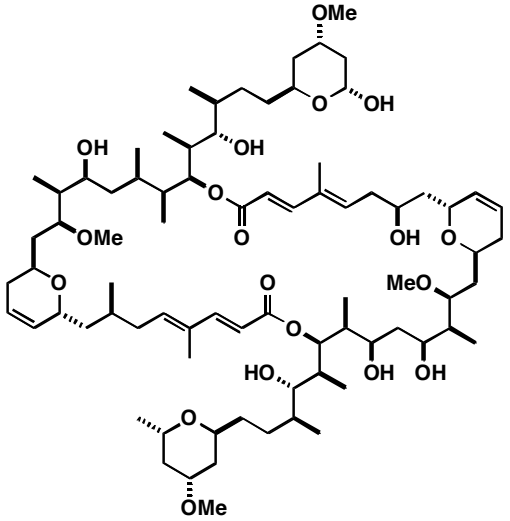
The targets can be Natural Products ...



Brevetoxin B
marine neurotoxin associated with the red tide catastrophes
[Nicolaou 1995]

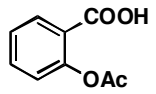


Vancomycin
antibiotic of last resort against anti-drug resistant bacteria
Evans 1995]

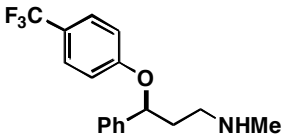


Swinholide A
cytotoxic potent activity against multi-drug-resistant (MDR) carcinoma cell lines
[Paterson 1994]

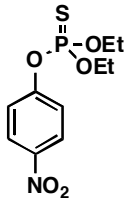
The targets can be compounds with interesting activities ...



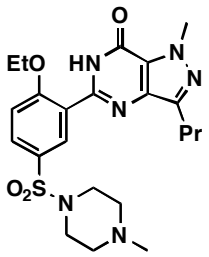
Acetylsalicilic acid (*Aspirin, Bayer*)



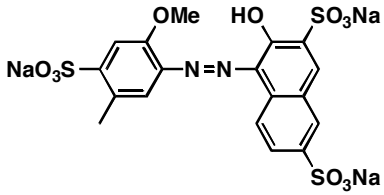
Fluoxetine (*Prozac, Eli Lilly*)
depressions



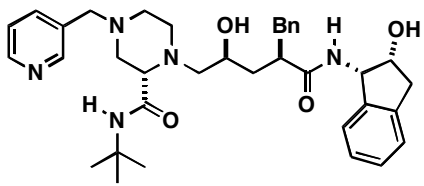
Parathion
insecticide



Sildenafil (*Viagra, Pfizer*)
male erection disfunction

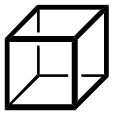


Allura red AC (Allied Chem)
red pigment



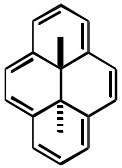
Crivixan (*Merck*)
anti AIDS

... or properties

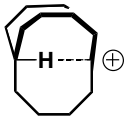


Cubane
a small and highly strained polyciclic compound
[Eaton, 1991]

Cyclobutadiene
an antiaromatic ring
[Maier, 1974]

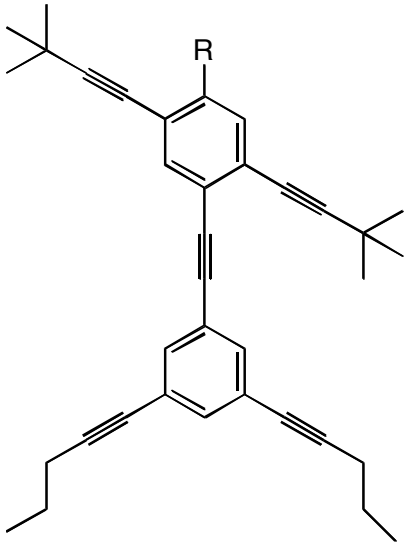


***trans*-15,16-Dihydropyrene**
an aromatic polyene
[Boekelheide, 1967]



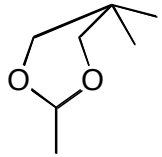
***in*-Bicyclo[4.4.1]tetradecyl cation**
stabilized by a hydrogen bond
[McMurry, 1989]

... or artistic or anthropomorphic attributes

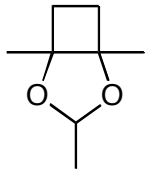


NanoPutians

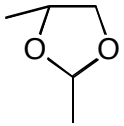
Tour, J. M. *JOC* **2003**, 8750



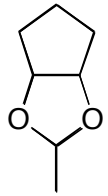
nanoathlete



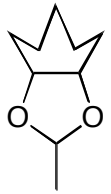
nanopilgrim



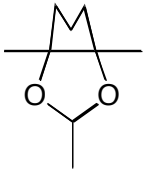
nanogreenberet



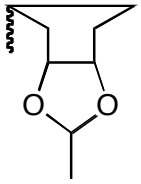
nanojester



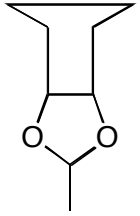
nanomonarch



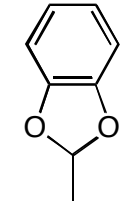
nanotexan



nanoscholar



nanobaker



nanochef

In summary, Organic synthesis deals with the construction of any organic structure.
Projects only must take into account industrial or lab scale
and time, technical or economical limitations.
In any case, the synthetic process should be simple, high yielding, cheap
and ...preferably in a single step.

Some concepts ...

Total synthesis *is the chemical synthesis of a target molecule from relatively simple starting materials*

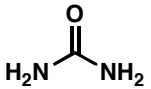
Formal total synthesis *is the chemical synthesis of an intermediate that has already been transformed into the desired target*

Partial synthesis or semisynthesis *designates the synthesis of a given molecule from an advanced precursor related to it*

Relay approach *defines the process in which a key intermediate previously synthetized is obtained by degradation from other product, including the final target molecule*

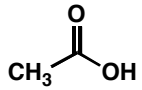
A brief glimpse of the History of Organic Synthesis

Nineteenth century



Urea
[Wöhler 1828]

The Organic Chemistry is born ...



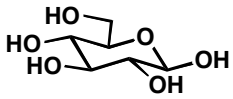
Acetic acid
[Kolbe 1845]

The word synthesis is introduced

Indigo
[Baeyer 1879]

German dye industry

Nobel Prize for Chemistry (1905)



D–Glucose
[Fischer 1890]

Stereochemical control is possible

Nobel Prize for Chemistry (1902)

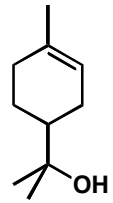
Very little planning was needed in this relatively simple synthesis ...

Deliberate syntheses could be developed using associative mental processes ...

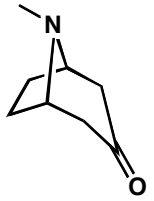
Associative thinking or thinking by analogy was sufficient ...

Corey, E. J. *The Logic of Chemical Synthesis*

Pre-World War II Era

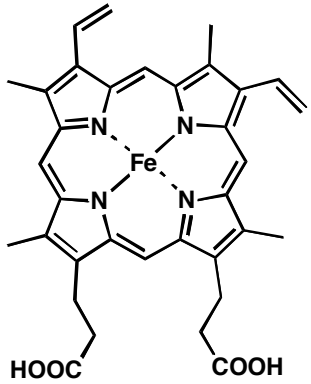


Terpineol
[Perkin 1904]



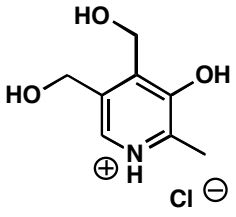
Tropinone
[Robinson 1917]

Nobel Prize for Chemistry (1947)



Haemin
[Fischer 1929]

Nobel Prize for Chemistry (1929)



Pyridoxine hydrochloride
[Folkers 1939]

In contrast to the former syntheses,

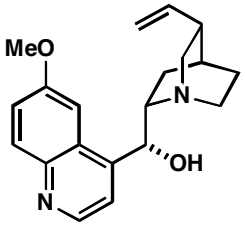
which were based on the availability of starting materials that contained a major portion of the final atomic framework,

these 20th century syntheses depended on the knowledge of reactions suitable for forming polycyclic molecules

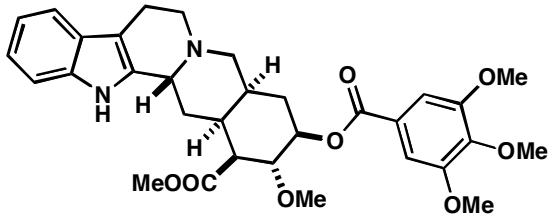
and on detailed planning to find a way to apply these methods.

Corey, E. J. *The Logic of Chemical Synthesis*

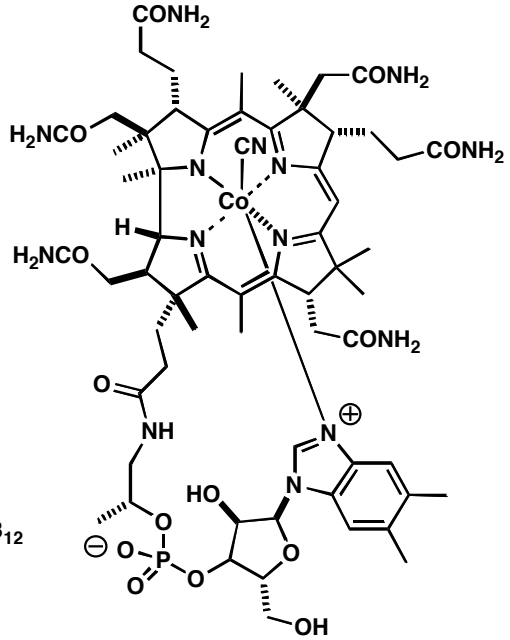
Post-World War II Era: the Woodward Era (1940–1970)



Quinine
[1944]



Reserpine
[1958]



Vitamin B_{12}
[1973]

Robert B. Woodward was probably the first to integrate mechanistic organic chemistry into his planning of syntheses in a consistent manner ...

Woodward's real achievements is that he intellectualized synthetic organic chemistry ...

The great master of reasoning by mechanistic analogy and the unrivaled protagonist of the field's transition from an advanced level of "synthesis by directed chemical tinkering" to the level of "synthesis by design" was Robert Burns Woodward

Robert Burns Woodward. Architect and Artist in the World of Molecules

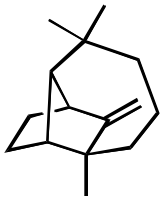
Post-World War II Era: the Woodward Era (1940–1970)

Robert B. Woodward was awarded the Nobel Prize for Chemistry in 1965
for his outstanding achievements in the art of Organic Synthesis

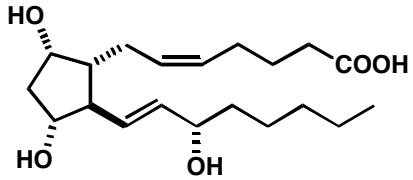
"... The synthesis of a complicated molecule is, however, a very difficult task;
every group, every atom must be placed in its proper position and this should be taken in its more literal sense.
It is sometimes said than organic synthesis is at the same time an exact science and a fine art.
Here, Nature is the uncontested master, but I dare say that the prize-winner of this year, Professor Woodward,
is a good second"

Professor A. Fredga.
Member of the Nobel Prize Committee for Chemistry1965

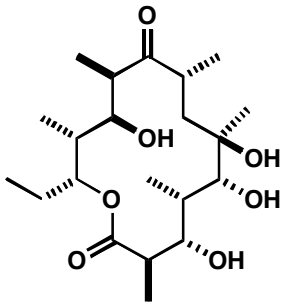
The Corey Era (1960–1990)



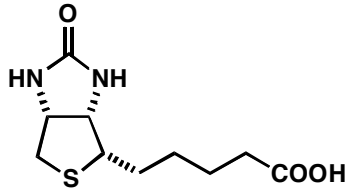
Longifolene
[1961]



Prostaglandin $F_{2\alpha}$
[1969]



Erythronolide B
[1975]



(+)-Biotin
[1988]

Corey's pursuit of total synthesis was marked by two distinctive elements,

retrosynthetic analysis *and the development of new synthetic methods as an integral part of the endeavor, even though Woodward (conciously or unconsciously) must be engaged in such practices*

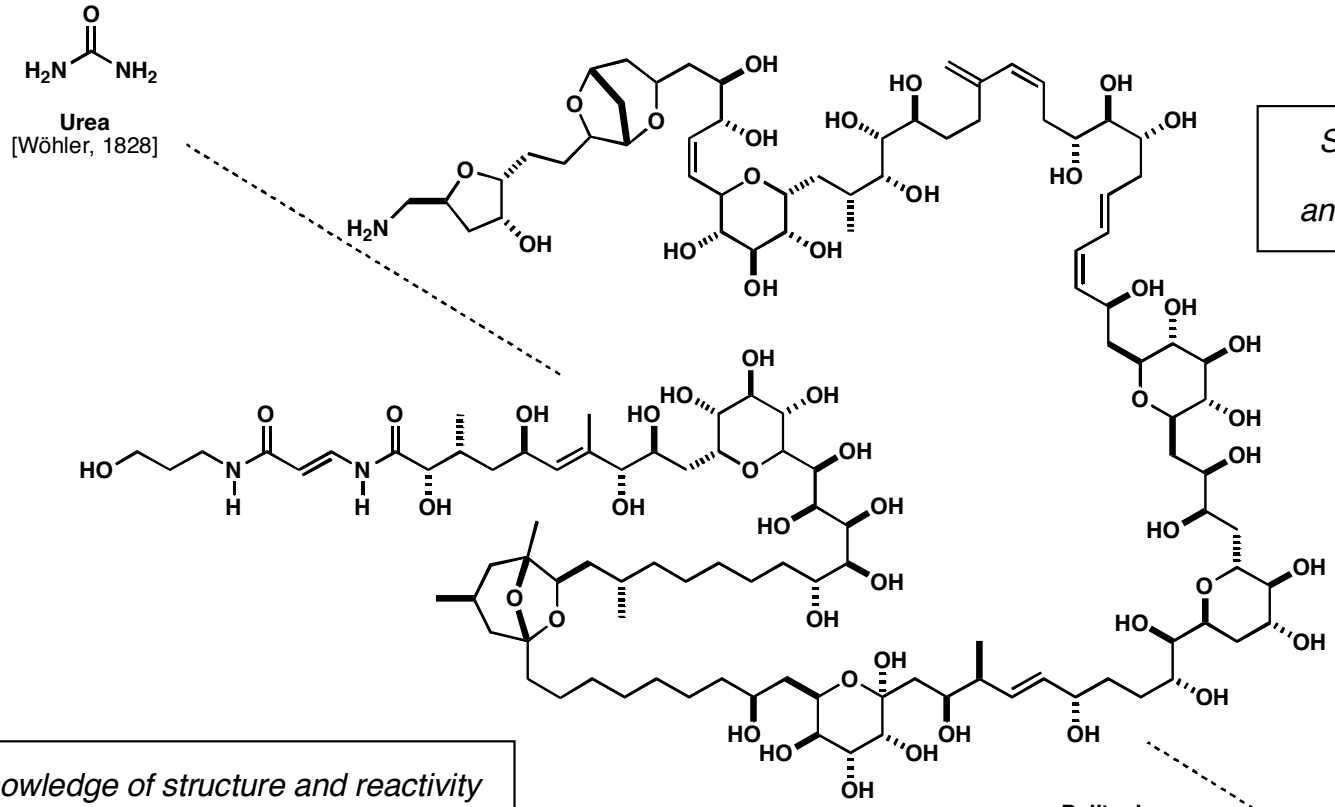
Nicolaou, K. C. *ACIE* **2000**

The Corey Era (1960–1990)

Elias J. Corey was awarded the Nobel Prize for Chemistry in 1990

"... Corey has thus awarded with the Prize for three intimately connected contributions, which form a whole.
Through retrosynthetic analysis and introduction of new synthetic reactions,
he has succeeded in preparing biologically important natural products, previously thought impossible to achieve.
Corey's contributions have turned the art of synthesis into a science"

Professor S. Gronowitz
Member of the Nobel Prize Committee for Chemistry
1990



Spectroscopic & analytic techniques

Knowledge of structure and reactivity

Sophisticated reagents & selective processes

Stereochemical control

XXI Century

Where now?

A more accurate diagnosis would focus on the fact that discrete boundaries no longer exist between the various natural sciences (mathematics, physics, chemistry,biology, medicine) and especially between related subdisciplines (in this case inorganic, biological, organic, and physical chemistry)...

..we have come to believe that virtually any molecule is amenable to synthesis...

...the exciting synthetic targets today are no longer molecules...; instead, they are systems associated with particular functions or properties...

Nevertheless, it will still be the chemists skilled in synthesis who will succeed in preparing the most interesting targets and exploring the most challenging themes...

I consider the most important message that organic synthesis continues to react forcefully and with vitality to new challenges, still ready to pursue old dreams"

Seebach, D. **Organic Syntheis–Where now?** *Angew. Chem. Int. Ed. Engl.***1990**, *29*, 1320-1367

Such accomplishments prompt comments such as "given enough manpower and money, synthetic chemists can make any complex molecule"; with such statements, attempts are made to criticize research in this field by declaring it mature and even dead! How unwise these statements are, for one only has to compare our synthetic power with that of nature in order to recognize the rather primitive state of the art. One message is clear: more expedient and economical processes are still needed to construct complex molecules, and this status will not change for some time to come. Asymmetric synthesis and catalysis are frontiers of enourmous potential. Natural products provide wonderful opportunities for the development of new synthetic methodologies and strategies for chemical synthesis

Nicolaou, K. C. **Classics in Total Synthesis**. VCH **1996**

Introduction

Chemical Synthesis is essentially entirely a creative activity, in which art, design, imagination, and inspiration play a predominant rôle...
The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand
ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both.

Woodward, R. B. *Art and Science in the Synthesis of Organic Compounds: Retrospect and Prospect*. **1963**

The organic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create.
These added elements provide the touch of artistry which can be included in a cataloging of the basic principles of synthesis
but they are very real and extremely important.

Corey, E. J. *Pure & Appl. Chem*. **1967**, *14*, 19

Like the artist, the chemist engraves into matter the products of creative imagination...
The essence of chemical science finds its full expression in the words of that epitome of the artist-scientist Leonardo da Vinci:
"...dove la nature finisce di produrre le sue spezie, l'uomo quivi comincia con le cose naturali,
con l'aiutorio di essa natura a creare infinite spezie"

Lehn, J. M. *Supramolecular Chemistry. Concepts and Perspectives*. VCH, **1995**

The Practice of Total Synthesis

With its share of glorious moments, setbacks, and frustrations Total Synthesis can be compared to the game of chess.
The object of this game is to capture the opponent's king by a series of allowed moves played out
in such a combination and order as outmaneuver the opponent.
Similarly, in total synthesis the object is to reach the target molecule
by a series of reactions which have to be carried out in the right sequence to outmaneuver natural barriers.
Studying and applying the moves (reactions) to capture the king (make the molecule) then becomes the object of total synthesis.
The practice and elegance of total synthesis involves and depends of the following stages:

1. Selection of the target: natural product or designed molecule

☞ ***2. DESIGN OF THE SYNTHETIC STRATEGY: RETROSYNTHETIC ANALYSIS***

3. Selection of the reagents and conditions

4. Experimental execution

Design *is a term that refers to a creative activity within the realm of technology, an activity that, to be sure, can ascend into the domain of great art. The* ***design*** *of a chemical synthesis is not science a priori: it is a fruit of science; its prerequisite is comprehensive matured, and approved scientific knowledge.*

Robert Burns Woodward. Architect and Artist in the World of Molecules

Further texts

Woodward, R. B. *Art and Science in the Synthesis of Organic Compounds: Retrospect and Prospect.* In Pointers and Pathways in Research, CIBA of India ,**1963**

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Corey, E. J.; Wipke, W. T. *Science* **1969**, *166*, 178.

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Hanessian, S.; Franco, J.; Larouche, B. *Pure&Appl.Chem.* **1990**, *62*, 1887.

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Diversos autors. *Frontiers in Organic Synthesis. Chem. Rev.* **1996**, *96*, Vol. 1.

Nicolaou, K. C.; Sorensen, E. J.; Winssinger, N. *J. Chem. Ed.* **1998**, *75*, 1226.

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Arya, P.; Chou, D. T. H.; Baek, M.-G- *Angew. Chem. Int. Ed.* **2001**, *40* , 339.

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Benfey, O. T.; Morris, P. J. T. *Robert Burns Woodward. Architect and Artist in the World of Molecules.* Chemical Heritage Foundation. Philadelphia, **2003**.

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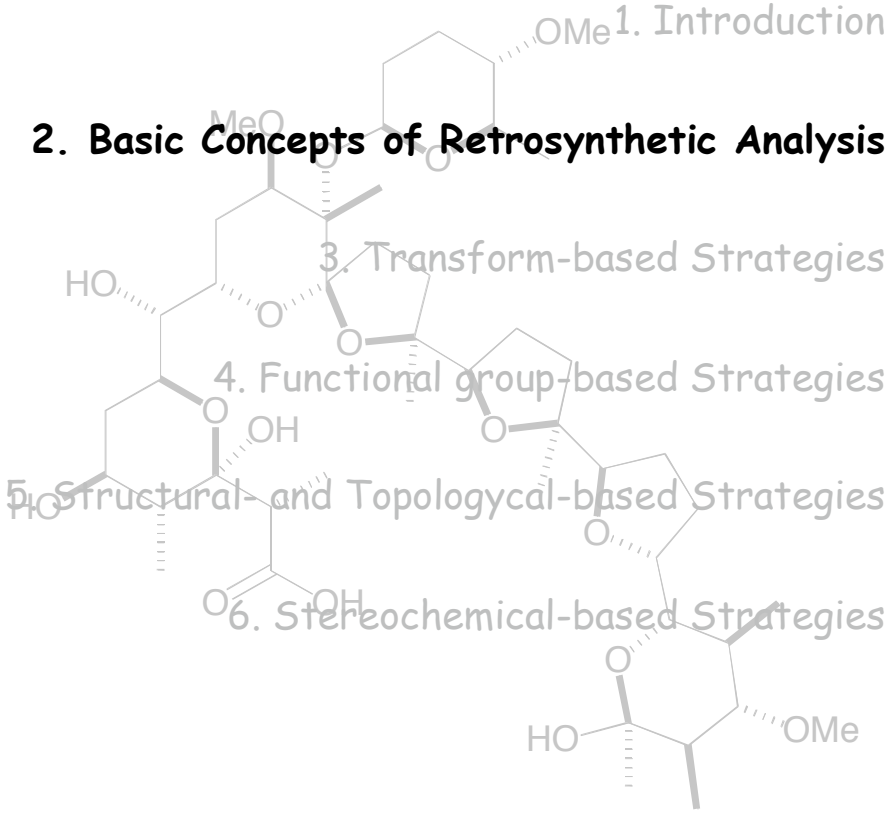
de la Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.* **2004**, *43* , 160.

Part I



In the beginning was ...
The Direct Associative Approach

Until Second World War

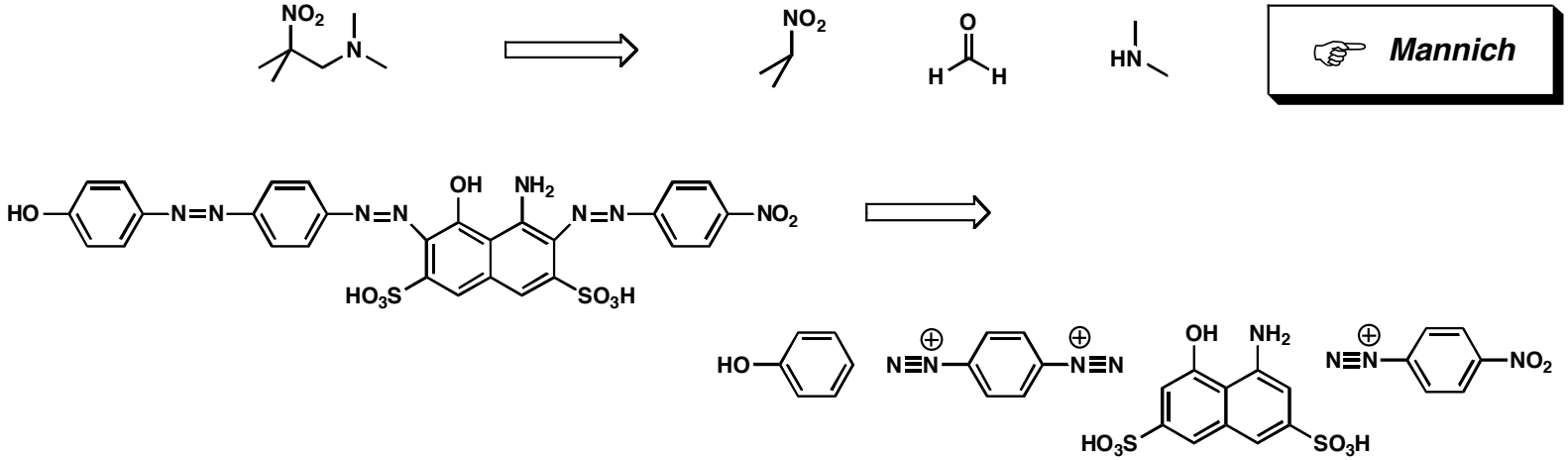
associative thinking or thinking by analogy was sufficient...

... with the exception of a minor proportion which
clearly depended on a more subtle way to thinking about and planning ...
syntheses were initially based
on the availability of starting materials that contained a major portion of the final atomic framework
and on the knowledge of reaction suitable for forming polycyclic molecules

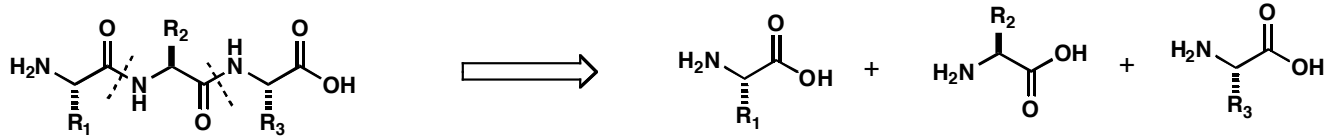
Corey, E. J. *The Logic of Chemical Synthesis*

In The Direct Associative Approach

the chemist directly recognises within the structure of the target molecule a number of readily available structural subunits, which can be properly joined by using standard reactions with which he is familiar



In the synthesis of peptides, recognition of the constituent aminoacids is almost immediate.
However, the realisation of the synthesis in the laboratory may be one of the most ardous tasks which the synthetic organic chemist faces



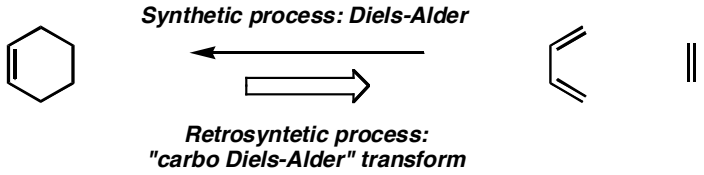
Serratosa, F. *Organic Chemistry in Action*

By the mid 1960's,
a different and more systematic approach was developed: ***Retrosynthetic Analysis***

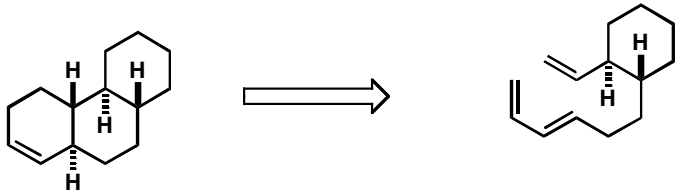
Retrosynthetic (or antithetic) analysis is a problem solving technique
for transforming the structure of a ***synthetic target (TGT) molecule***
to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis.
The transformation of a molecule to a synthetic precursor is accomplished
by the application of a ***transform, the exact reverse of a synthetic reaction****, to a target structure.*
Each structure derived antithetically from a TGT then itself becomes a TGT for a further analysis.
Repetition of this process eventually produces a ***tree of intermediates***
having chemical structures as nodes
and pathways from bottom to top corresponding to possible synthetic routes to the TGT.

Transform & Retron

The transformation of a molecule into a synthetic precursor is accomplished by application of ***a transform****,* ***the exact reverse of a synthetic reaction****, to a target structures.*



In order for a transform to operate on a target structure to generate a synthetic predecessor, the ***enabling structural subunit or retron*** *for that transform must be present in the target.*



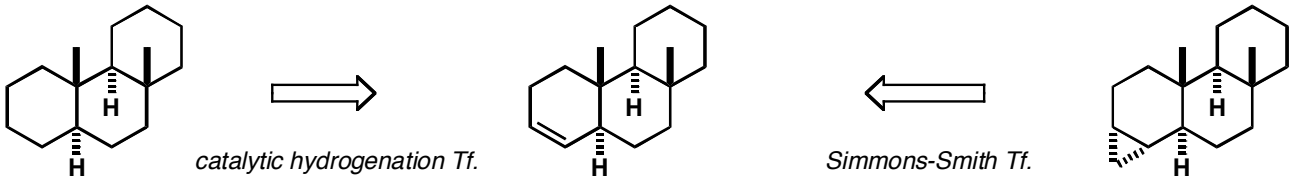
Diels–Alder Retron: a six–membered ring containing a π-bond

Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*.

It is possible, but not quite as easy, to find such retrosynthetic pathways

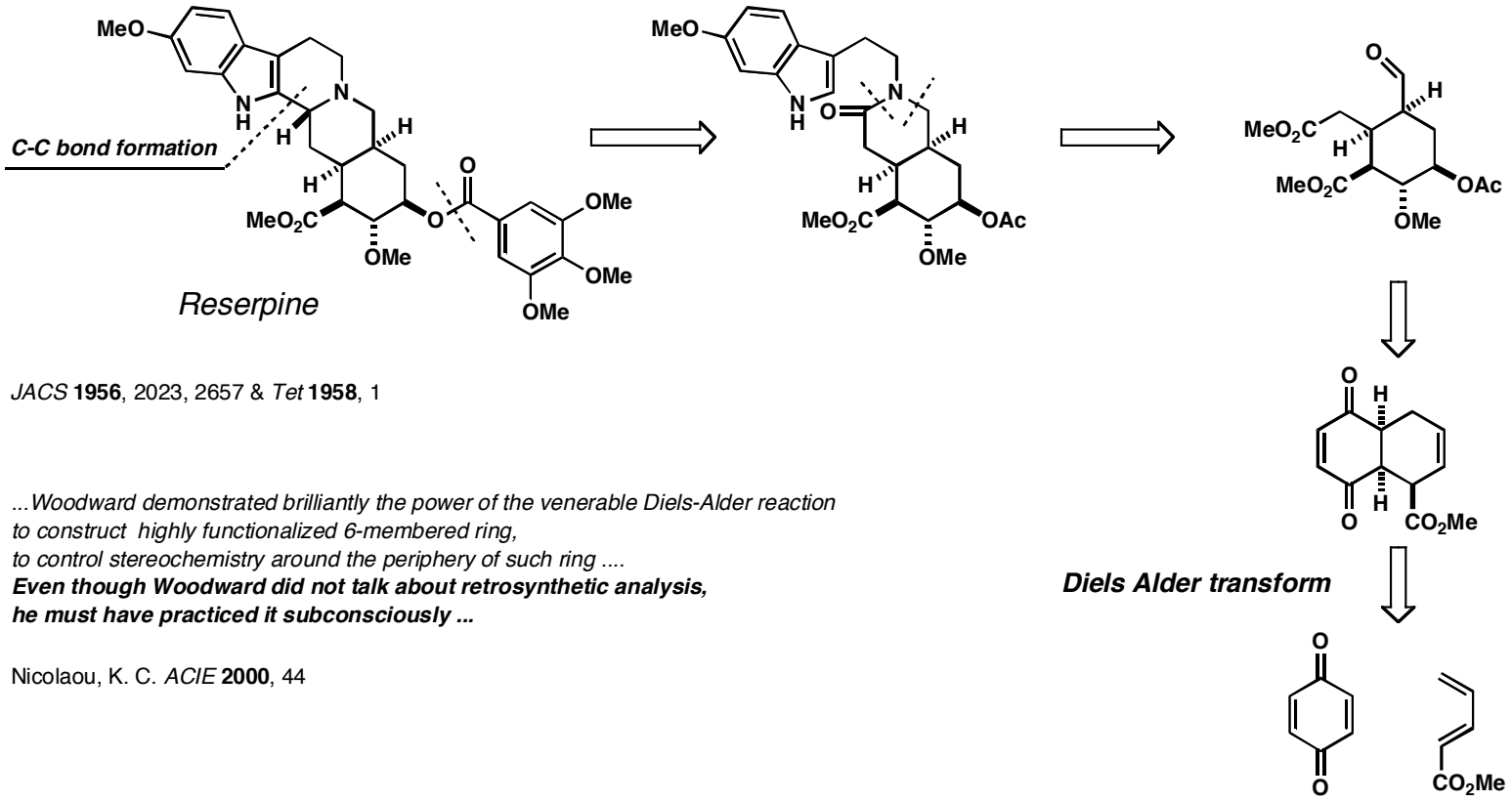
when only an incomplete or ***partial retron*** *is present.*

A 6-membered ring lacking a π*-bond can be regarded as a partial retron for the Diels-Alder transform*



☞ ***Diels Alder*** *is one of the most useful transforms*

A more complex case is found in reserpine synthesis by Woodward



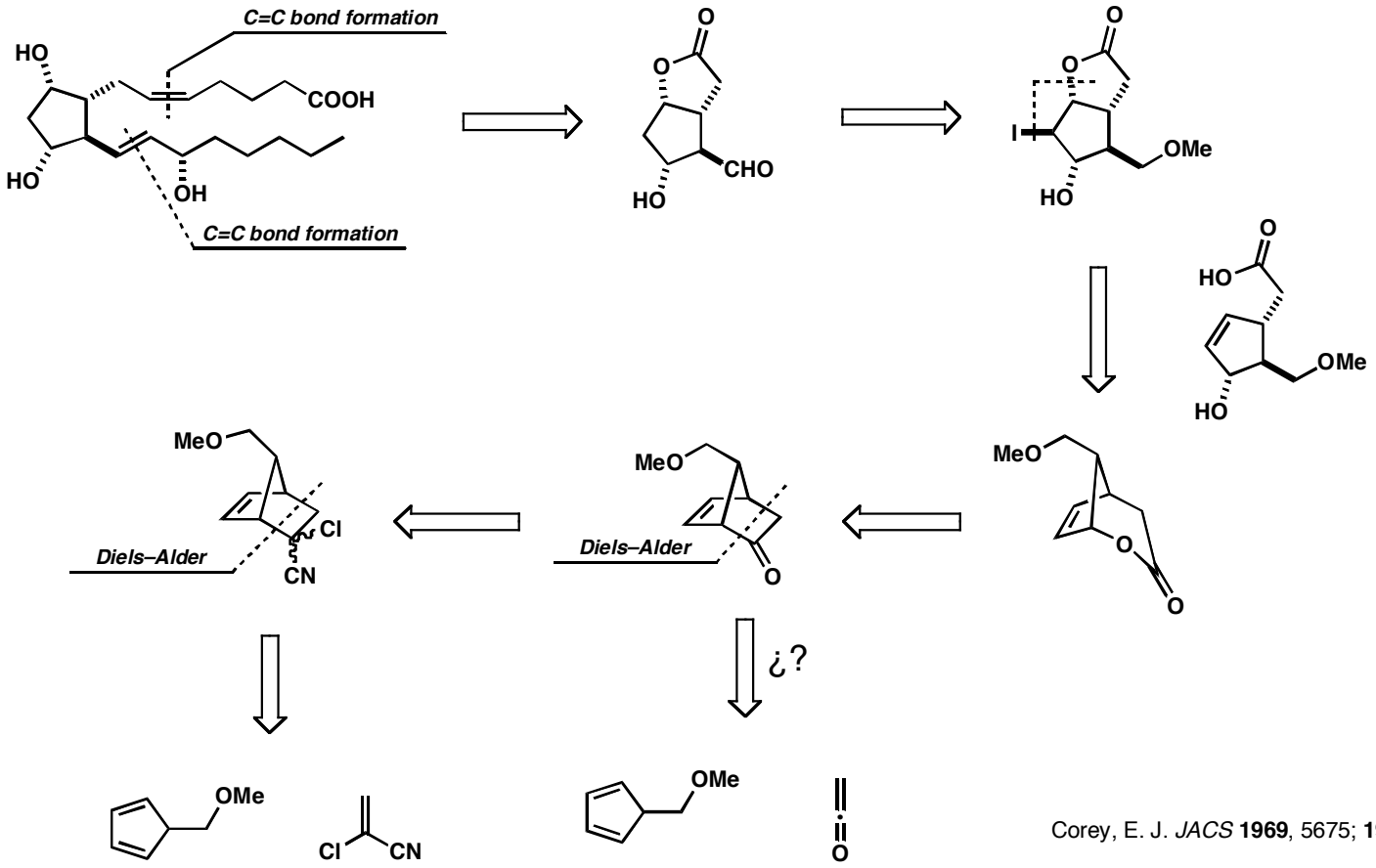
JACS **1956**, 2023, 2657 & *Tet* **1958**, 1

...Woodward demonstrated brilliantly the power of the venerable Diels-Alder reaction to construct highly functionalized 6-membered ring, to control stereochemistry around the periphery of such ring ....
Even though Woodward did not talk about retrosynthetic analysis, he must have practiced it subconsciously ...

Nicolaou, K. C. *ACIE* **2000**, 44

☞ *Pay attention to the stereochemistry*

... or in the PGF_{2a} synthesis by Corey



Corey, E. J. *JACS* **1969**, 5675; **1970**, 397, 2586

Transforms & Molecular Complexity

There are many thousands of transforms which are potentially useful in retrosynthetic analysis just as there are very many known and useful chemical reactions ...
One feature of major significance is the overall effect of transform application on ***molecular complexity.***

Molecular complexity *elements are*

(1) Molecular size
(2) Cyclic connectivity or topology
(3) Element or functional group content
(4) Stereocenter content/density
(5) Centers of high chemical reactivity
(6) Kinetic (thermal) stability

Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*.

Types of Transforms

1. Structurally simplifying transforms *effect molecular simplification by* ***disconnecting*** *molecular skeleton, and/or functional groups and/or stereocenters.*

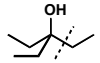
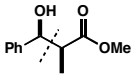
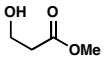
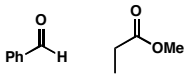
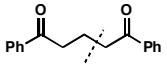
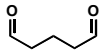
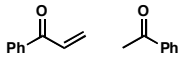
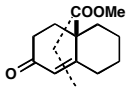
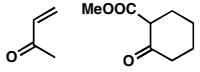
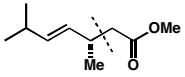
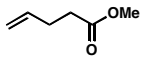
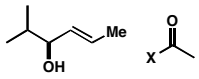
2. *There are transforms which bring about no essentially no change in molecular complexity, but which can be useful because they modify a TGT to allow the subsequent application of simplifying transforms.*
They include rearrangements of molecular skeleton, ***functional group interchange (FGI)****, and inversion/transfer of stereocenters.*

3. *Opposite to* ***1****,* ***structurally increasing complexity transforms*** *includes addition of rings,* ***functional groups (FGA)****, or stereocenters.*

Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*.

1. Structurally simplifying transforms ...

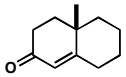
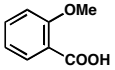
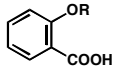
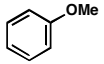
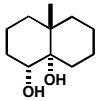
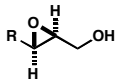
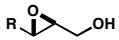
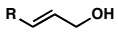
by disconnecting molecular skeleton.

TGT Structure	Retron	Transform	Precursors
		*Ionic addition to C=O*	 EtMet
		*Aldol reaction*	
		*Michael reaction*	
		*Robinson annulation*	
		*Claisen rearrangement*	

Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis.*

1. Structurally simplifying transforms ...

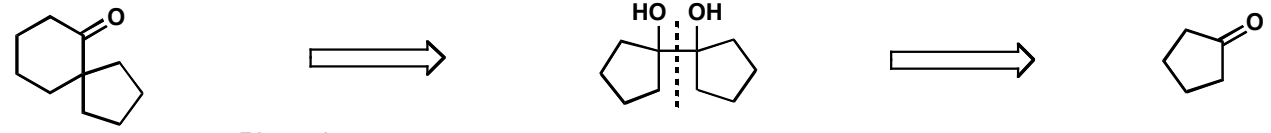
by disconnecting functional groups or stereocenters.

TGT Structure	Retron	Transform	Precursors
		*Allylic oxidation*	
		*o-Metallation & carboxylation*	
		*cis-Hydroxylation or Sharpless dihydroxilation*	
		*Sharpless epoxidation*	

Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis.*

2. Structurally "neutral" transforms ...by rearrangements of molecular skeleton,

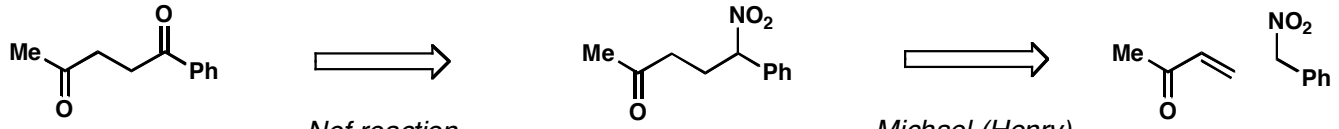
TGT Structure	Transform	Precursors



Pinacol rearrangement *Pinacol coupling*

... or functional group interchange (FGI)

TGT Structure	Transform	Precursors

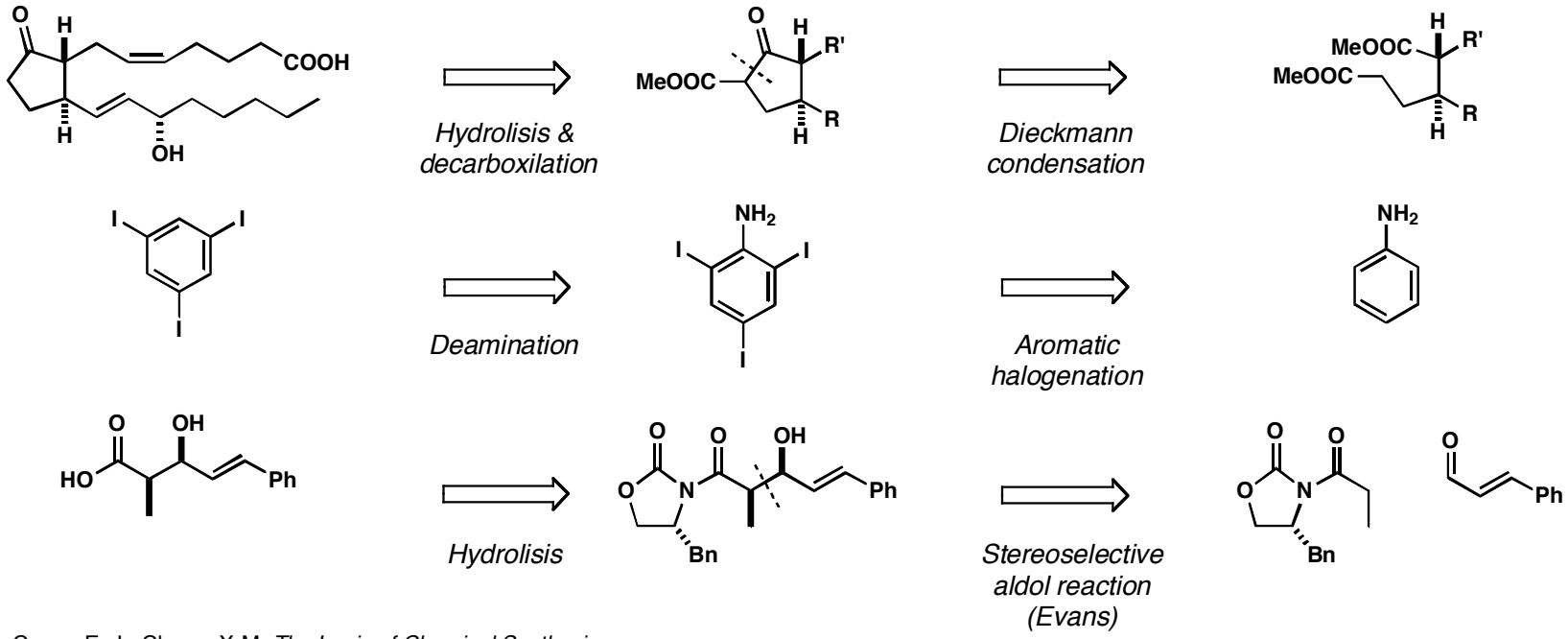


Nef reaction *Michael (Henry)*

Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*.

3. Structurally increasing complexity transforms includes addition of rings, functional groups (FGA), or stereocenters.

TGT Structure	Transform	Precursors



Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*.

Synthon

Corey defined synthon in 1967 as

***structural units within a molecule which are related to possible synthetic operations** or*

units which can be formed and/or assembled by known or conceivable synthetic operations"

Corey, E. J. *Pure&Appl. Chem***1967**, *14*, 19.

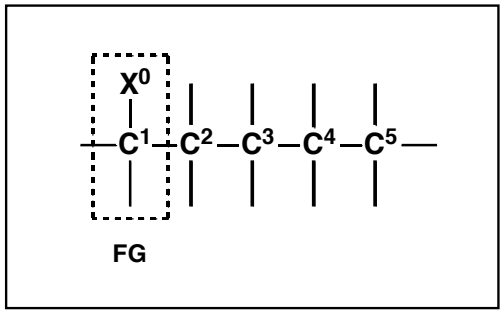
*... but later, he avoids this term and uses **synthetic precursor** instead.*

Corey, E. J. *The Logic ...*; *ACIEE* **1990**, 1320

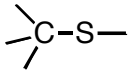
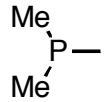
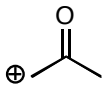
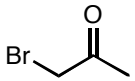
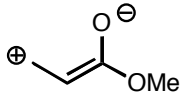
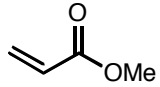
However, this concept easily rooted in the synthetic language and nowadays is commonly used.

Additionally, polar synthons have been classified...

Taking into account that the most common synthetic reactions are polar,
they can be viewed as combination of a negatively polarized (electronegative) carbon atom,
or ***electron donor, d,*** *of one synthon and*
a positively polarized (electropositive) carbon atom,
or ***electon acceptor, a,*** *of another synthon.*
Synthons are numbered (d^0, d^1, d^2,... or a^0, a^1, a^2, ...) with respect to
the relative positions of a functional group (FG) and the reacting site

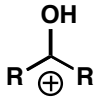


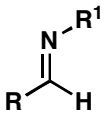
Fuhrhop, J.-H.; Li, G. *Organic Synthesis*

Synthons "d"				Synthons "a"			
Type	*Exemple*	*Reacting materials*	*Functional group*	*Type*	*Exemple*	*Reacting materials*	*Functional group*
d^0	$MeS^{\ominus}$	MeSH		a^0	$^{\oplus}PMe_2$	$ClPMe_2$	
d^1	$^{\ominus}C{\equiv}N$	$KC{\equiv}N$	—C≡N	a^1			—CO—
d^2	$^{\ominus}CH_2CHO$	CH_3CHO	—CHO	a^2			—CO—
d^3	$^{\ominus}C{\equiv}C–COOMe$	$HC{\equiv}C–COOMe$	$—CO_2Me$	a^3			—COOMe
Alkyl-d	$Me^{\ominus}$	MeLi		Alkyl-a	$Me^{\oplus}$	MeI	

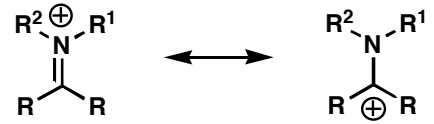
Synthons a[1]

Equivalent reacting species



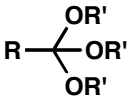


Imines are strongly related to aldehydes, although they show a poorer reactivity



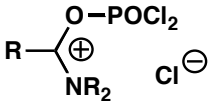
Imonium salts are easily prepared (i.e. Mannich) and are highly reactives

X = Cl, OAc, SR', OR'



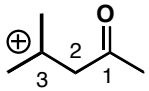
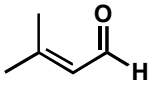
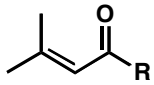
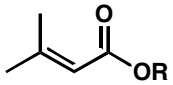
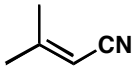
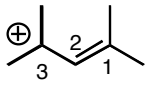
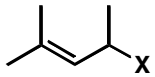
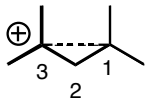
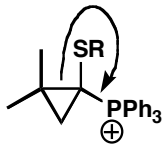
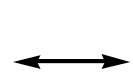
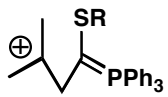
$[RCO]^+ [AlCl_4]^+$

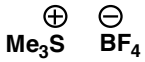
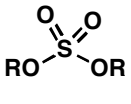
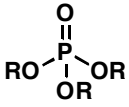
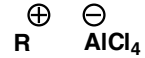
Friedel-Crafts



Vilsmeier-Haack

CO_2

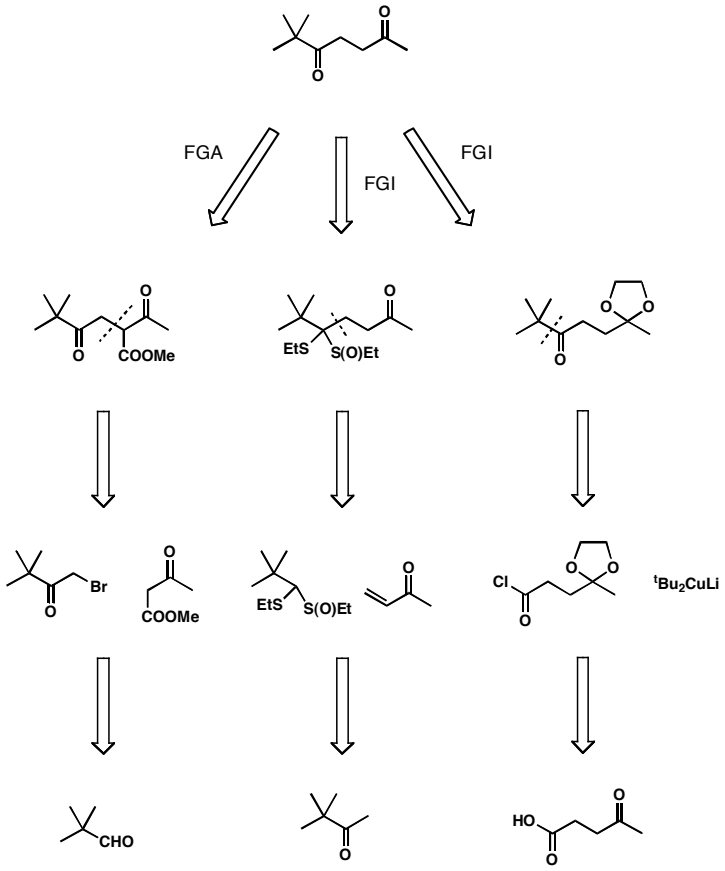
Synthons a[3]	*Equivalent reacting species*
	   
	 **X = Cl, Br, I, OTs, OMs, OTf, ...**
	  

Alkyl-a	*Equivalent reacting species*
	**R—X** **X = Cl, Br, I, OTs, OMs, OTf, ...**  *Meerwein*     *Friedel-Crafts*

Retrosynthetic analysis:
a Logic-centered methodology to the synthetis tree

The central point in this methodology is
***a rational and penetrating analysis** of the structure of TGT.*
Such analysis leads to a limited logical set of intermediate structures
which can be transformed into the original
in just one reaction or synthetic step.
Every structure generated is then carefully analysed as before
to give another set of structures,
which can be transformed into the preceding structures in one step.
*The process is repeated for every intermediate until a **"tree"***
of such intermediate structure is obtained.
By this process a set of possible alternative synthetic pathways is
generated which correspond to sequences of synthetic intermdiates
structures that go from possible starting materials to TGT:
it is the so-called "synthesis tree".

Serratosa, F. *Organic Chemistry in Action*
Fuhrhop & Li. *Organic Synthesis*



Serratosa, F. *Organic Chemistry in Action*

The design of synthesis is not a deductive activity:
the automatic application of a logic algorithm does not necessarily lead to a synthetic plan

Ihlenfeldt, W-D.; Gasteiger, J. *ACIEE* **1995**,2613.

Serratosa defined Synthesis as a ***heuristic activity***

"According to the Oxford Dictionary, the word ***heuristic*** *derives from the Greek* ***heurisko*** *("I find')*
and it is used as an adjective to describe activities directed towards
the act of discovering , including all those reasonings and arguments
that are ***persuasive and plausible without being logically rigorous****...*

The heuristic principles, in contrast with the mathematical theorems and the rules of proof,
do not pretend to be laws, an only suggest lines of activities*"*

Serratosa, F. *Organic Chemistry in Action.*

There is not a single approach to the synthesis of a TGT.
However, there are some guidelines that result really useful

Some Useful Guidelines

From Corey, E. J. *Pure&Appl. Chem.* **1967**, 19
Serratosa, F. *Organic Chemistry in Action.*
Warren, S & others. *Organic Chemistry*

***1**. There are many approaches to the synthesis of a TGT.*

***2.** All the synthetic routes can be derived through a*
***rational and penetrating analysis** of the structure of TGT,*
which should consider
i) symmetry, either real or potential,
ii) functional group relationships
(it is imperative to remove or modify the highly unstable groups)
iii) carbon skeleton: chains, rings and appendages
iv) stereochemistry

***3.** Then, the synthetic possibilities derive*
*from the identification of **retrons** and the application of **transforms**,*
*which permit the generation of **synthons**.*
*These **synthons** are next evaluated.*
*This repeating analysis produces the **synthesis tree**.*

***4.** The best route is the most simple, flexible, and efficient.*

***5.** It is desirable that disconnections correspond to known and reliable reactions. It is worth identifying the most difficult steps and to provide alternative routes (flexibility)*

***6.** Problems associated to the construction of the skeleton, the manipulation of functional groups, and the introduction of stereochemistry must be considered simultaneously.*
i) consider alternative disconnections and choose routes that avoid chemo- and regioselectivity problems
ii) use two-group disconnections wherever possible.

Some Useful Definitions

Target molecule
the molecule to be synthetized

Retrosynthetic analysis or retrosynthesis
the process of menthally breaking down a molecule into starting material

Transform
the exacte reverse of a synthetic reaction

Retron
structural subunit on the target that enables a transform to operate

Disconnection
an imaginary bond cleavage corresponding to the reverse of a real reaction

Synthon
idealized fragments resulting from a disconnection

Reagent
a real chemical compound used as the equivalent of a synthon

Synthesis tree
set of all the possible disconnections and synthons leading from the target to the starting materials of a synthesis

Guidelines in action: Simmetry

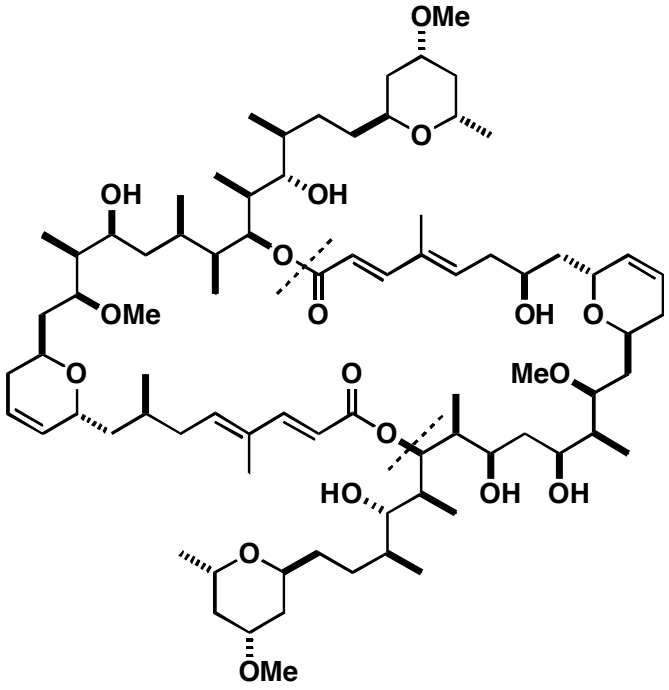
*A TGT molecule is said to have **real symmetry** if the structure possesses simmetry elements:*
***axis, plane or centre**.*
*Otherwise, it is said to have **potential symmetry** when, although asymmetrical molecule,*
may be disconnected to give either a symmetrical structure or two synthetically equivalent structures.

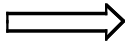
The recognition of symmetry in the structure of the TGT may be of paramount importance
in the choices of disconnections to simplify the molecular complexity

Ho, T.-L. *Symmetry. A Basis for Synthesis Design*
Serratosa, F. *Organic Chemistry in Action*

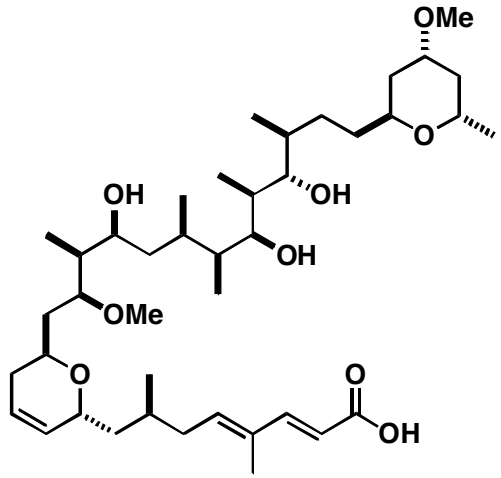
☞ *suggestion: have a look to **Two-directional Chain Synthesis***
Schreiber, S. L. *Chem. Scripta* **1987**, 563
& *Acc. Chem. Res.* **1994**, 9
Magnuson, S. R. *Tetrahedron* **1995**, 2167
Hoffmann, R. W. *ACIE* **2003**, 1096

Swinholide A





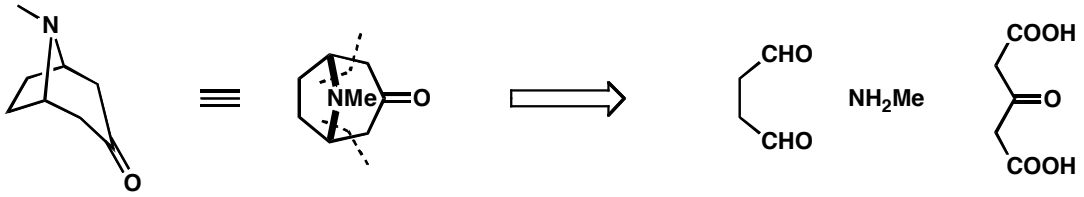
2 x



Paterson, I.
JACS **1994**, 2615, 9391
Tetrahedron **1995**, 9393–9437

☞ *regioselective esterification?*

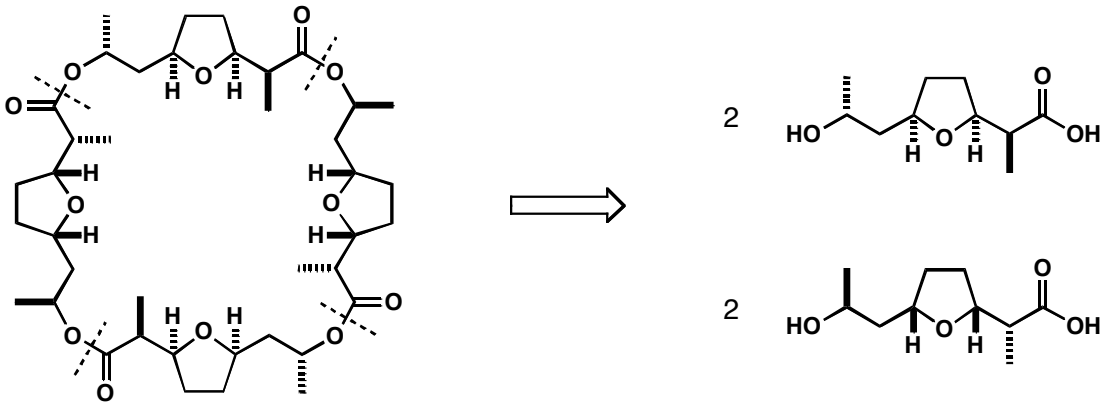
Tropinone



Robinson, R. *J. Chem. Soc.* **1917**, 762

See also, Fleming, I. *Selected Organic Synthesis*

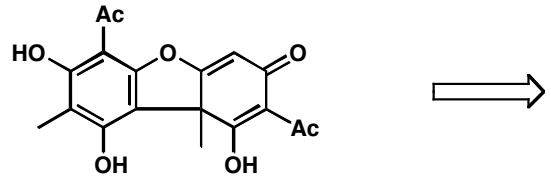
Nonactin



Bartlett, R. *JACS* **1984**, 5304

Fleming, I. *JCS Chem. Commun.* **1994**, 2285

Usnic acid

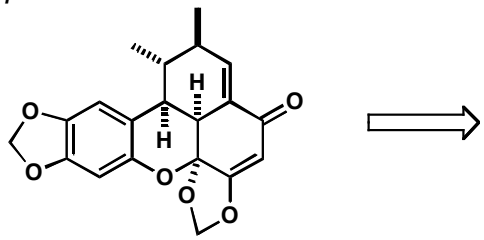


Barton, D. H. R.

Chem&Ind **1955**, 1039

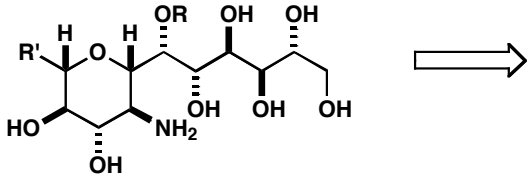
J. Chem. Soc. **1956**, 530

Carpanone



Chapman, O. L. *JACS* **1971**, 6696

Hikimycin



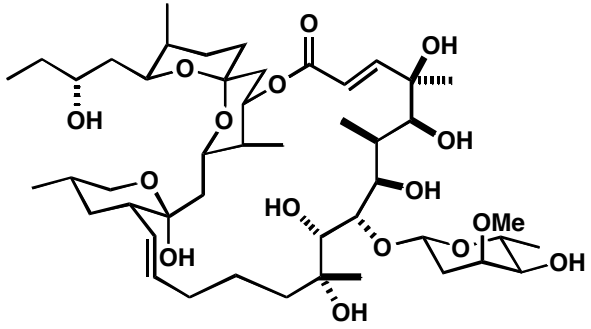
Schreiber, S.L. *JACS* **1992**, 2525

Guidelines in action: Unstable functional groups?

It is imperative to remove or modify the highly unstable groups:

Early strategic disconnections must address this type of problems.

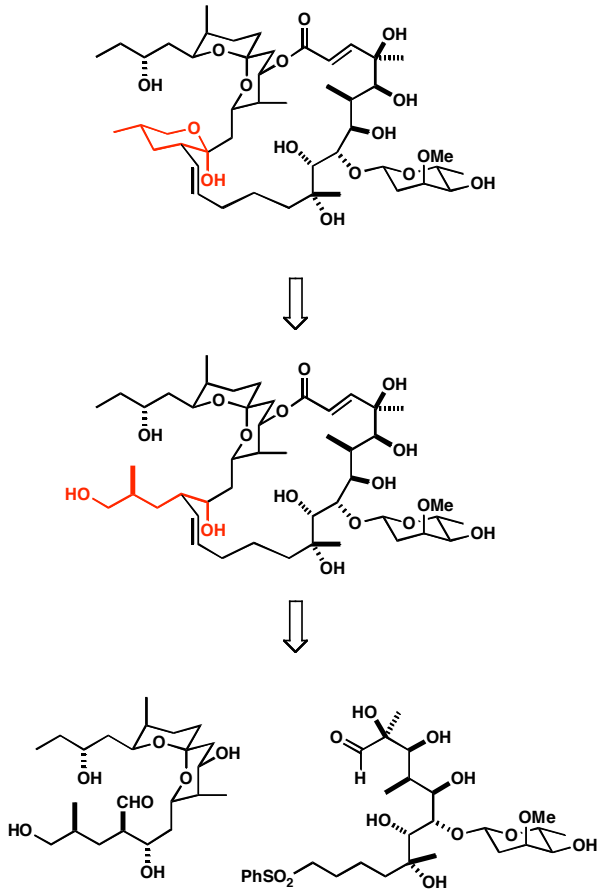
If this piece of information is not available, preliminary studies are often required ...



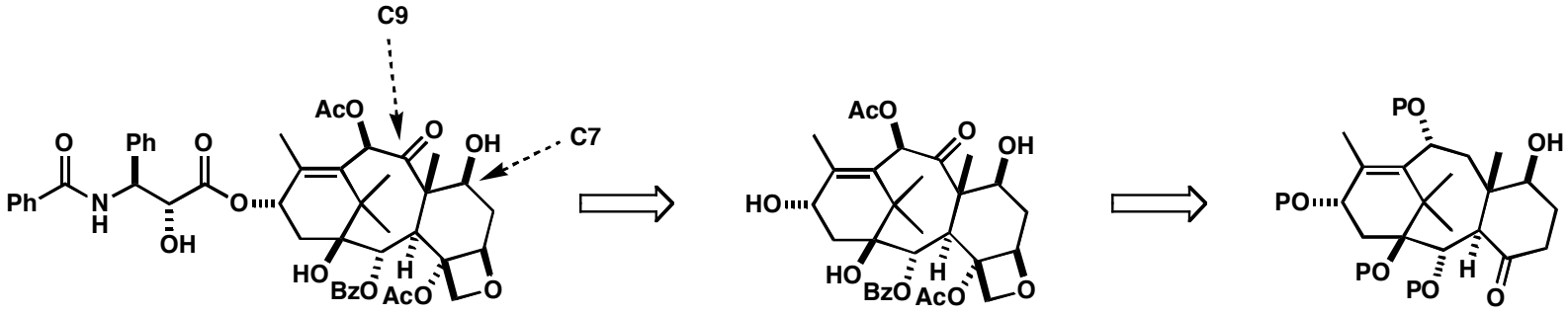
Citovaricin

At the outset of the project, no NMR spectroscopic or chemical stability data was available for the natural product.
Since such information is invaluable in the design stages of any complex synthesis plan, both spectroscopic and chemical studies were undertaken.
Evans, D. A. *JACS* **1990** 7001

Not surprisingly, our first disconnection involved the cytovaricin lactol



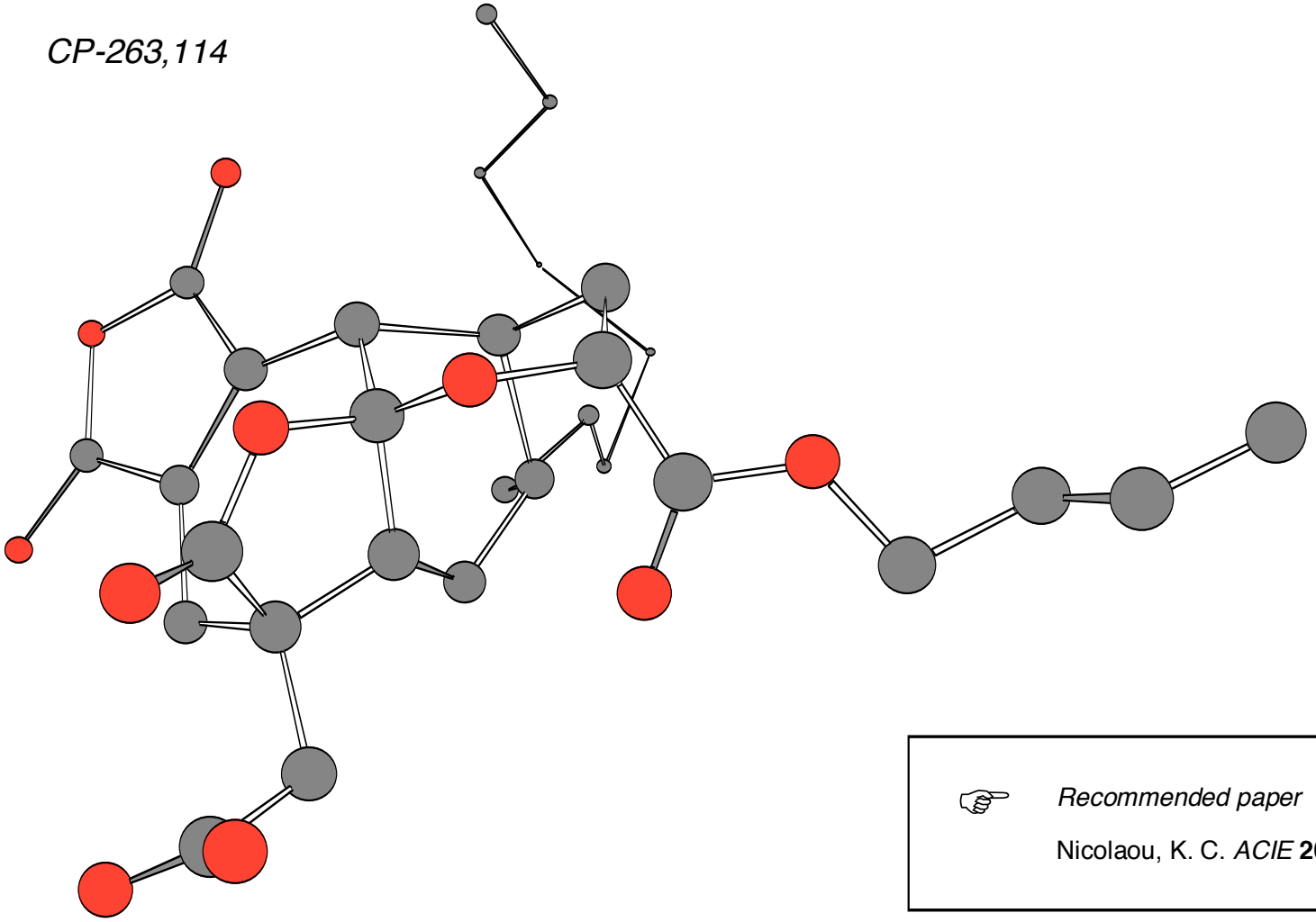
Taxol



The facile epimerization of taxol at C-7 is well documented,
and we chose to pursue a synthetic strategy in which this stereocenter would be introduced at an early stage
and carried throughout most of the synthesis ***in the absence of the C-9 carbonyl group***

Holton, R. A. *JACS* **1994**,1597

CP-263,114

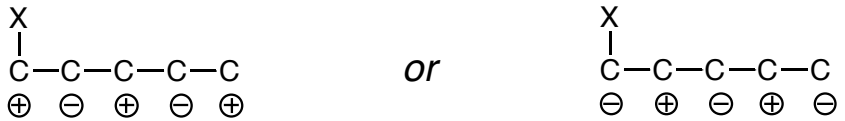


☞ *Recommended paper*

Nicolaou, K. C. *ACIE* **2002**, 2678

Guidelines in action: functional groups relationships?

Taking into account that most common synthetic reactions are polar,
*a bond forming process (and the corresponding transform) can be viewed as a combination of donor, **d**, and acceptor, **a**, synthons.*
Then, it might be useful to consider the carbon framework of any molecule as an ionic aggregate, whose origin relies on the presence of functional groups.



[*The symbol designations, + and –, simply denote potential electrophilic or nucleophilic site reactivity*]

Following this idea, Evans suggested an heuristic classification of functional groups
(Attention: only the heteroatom is considered as the functional group)

Type E: $C^{\oplus}-E$

$-OH \quad -OR$

$=O$

$-NR_2 \quad =NR$

$-X$ (halogen)

Type G: $C^{\ominus}-G$

Group I and II metals

$-AlR_2$

$-SiR_3$

Type A: $C^{\oplus/\ominus}-A$

$-NO_2 \quad =NOH \quad =NNHR \quad =N(O)R \quad -NR-NO \quad =N_2 \quad \equiv N \quad -NR_3^{\oplus}$

$-SR \quad -S(O)R \quad -SO_2R \quad -SR_2^{\oplus}$

$-PR_2 \quad -P(O)R_2 \quad -PR_3^{\oplus}$

$-BR_2$

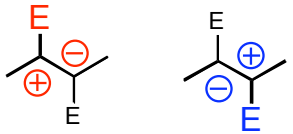
$=CR_2 \quad \equiv CR$

Transition metals

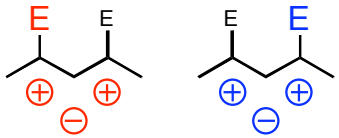
Evans, D. A. *Acc.Chem. Res.* **1974**, 147
Seebach, D. *ACIEE* **1979**, 239
Serratosa, F.*Organic Chemistry in Action*

*According to these ideas, it is possible to identify difunctional relationships (**consonant** or **dissonant**) among the functional groups in a TGT*

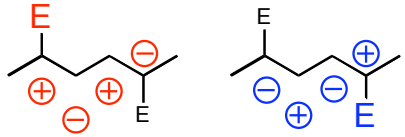
1,2-difunctional dissonant relationship



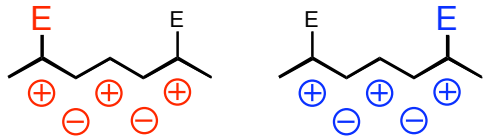
1,3-difunctional consonant relationship



1,4-difunctional dissonant relationship



1,5-difunctional consonant relationship



Consonant relationships usually permit to devise easy disconnections. However, dissonant relationships often require to introduce umpolung tactics, radical or perycyclic reactions

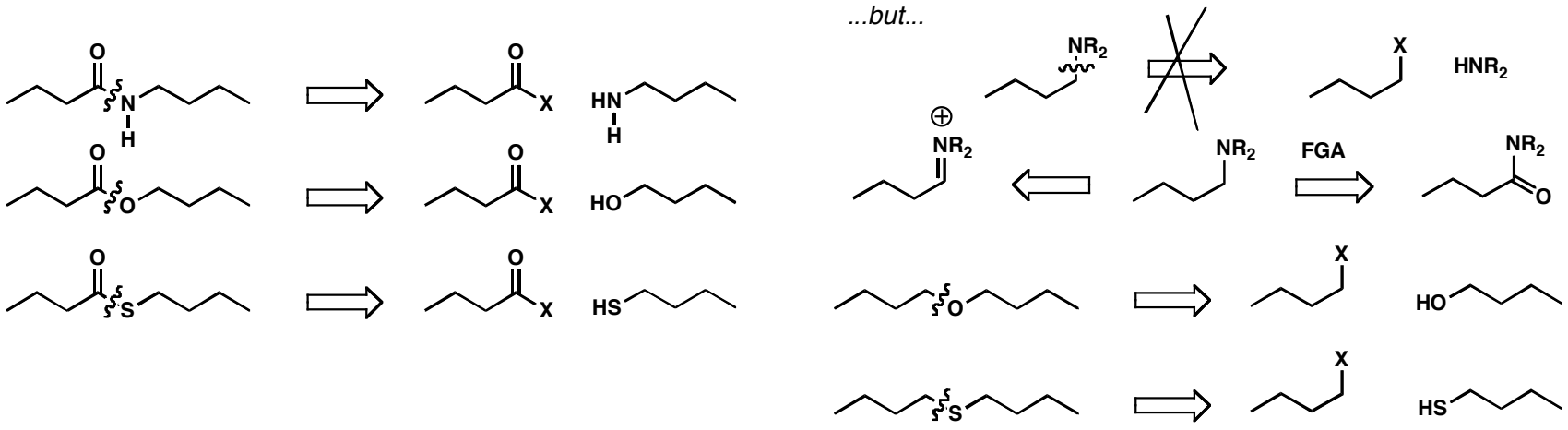
Guidelines in action: carbon–carbon disconnections

Those disconnections leading to two fragments of similar complexity are specially appealing.

Alkyl, aryl,... subunits may be considered as ***building blocks*** *and they should not be disconnected*

When an heteroatom (X = N, O, S), is embodied in the carbon framework,

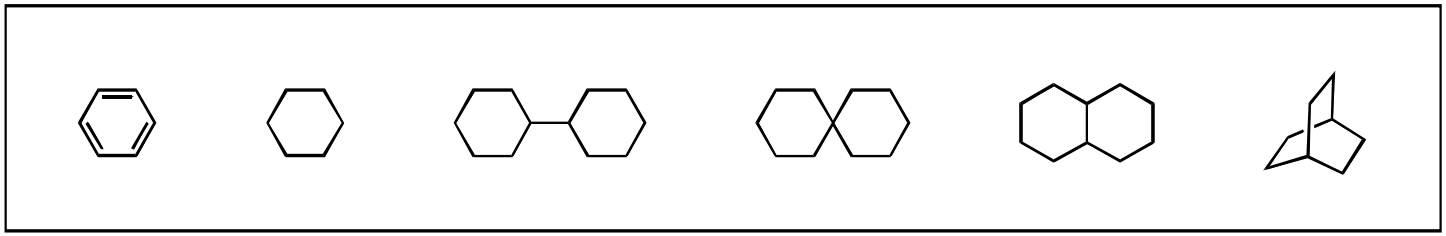
the C–X bond disconnection uses to be strategic



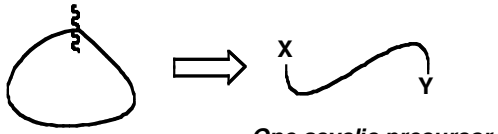
C–C disconnections far from functional groups or stereocentres are not favoured.

C=C disconnections are used to be strategic.

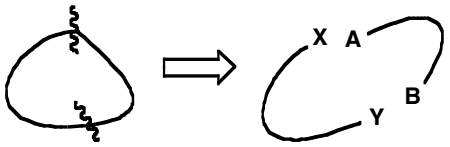
In the case of cyclic systems it is more difficult to elaborate general trends because of the different shapes present in these systems.



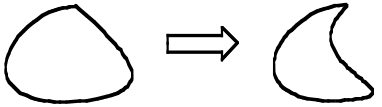
If it is a monocyclic system ...



One acyclic precursor



Two acyclic precursor



Another cylic precursor

☞ *pay attention to metathesis and radical chemistry*

☞ *pay attention to Diels-Alder*

Guidelines in action: stereochemical issues

The selective removal of stereocenters depends on the availability of stereosimplifying transforms, the establishment of the required retrons (complete with defined stereocenter relationships) and the presence of a favorable spatial environment in the precursor generated by application of such a transform...

The most powerful transforms produce an overall simplification on the stereochemistry, the functional group and the skeleton of the target molecules.

*Remember that stereocontrol can rely on the same molecule (**substrate control**) or on external reagents (**reacting control**) and that just one or several elements can play a crucial role (single or double asymmetric reactions, **matched** and **mismatched cases)***

Corey, E. J. *The Logic of Chemical Synthesis*
Masamune, S. *ACIEE* **1985**, 1
Evans, D. A.*Chem Rev.* **1993**,1307

Strategy and Tactic

In pursuit a total synthesis,
a chemist tries to foresee the key disconnections which will allow him to reach the target.
The set of these main disconnections defines and establishes the ***strategy.***
*However thoroughly proficient the strategy formulation (****the retrosynthetic analysis****) ...,*
still needs ***tactical*** *coordination to smooth the progression,*
otherwise the success will be ardous and unspectacular ...
although the demarcation between certain tactics and strategies is difficult to make.

Ho, T.-L. *Tactics of Organic Synthesis*

Strategies

Corey states that the technique of systematic and rigorous modification of structure in the retrosynthetic direction provides a foundation for deriving a number of different types of strategies to guide the selection of transforms and the discovery of hidden or subtle synthetic pathways ...

An overarching principle in retrosynthetic analysis is the concurrent use of as many of these independent strategies as possible

Corey, E. J. *The Logic of Chemical Synthesis*

In my opinion, these strategies may be helpful to understand retrosynthetic analysis, but not to put it in action. Moreover, it is sometimes difficult to differentiate them

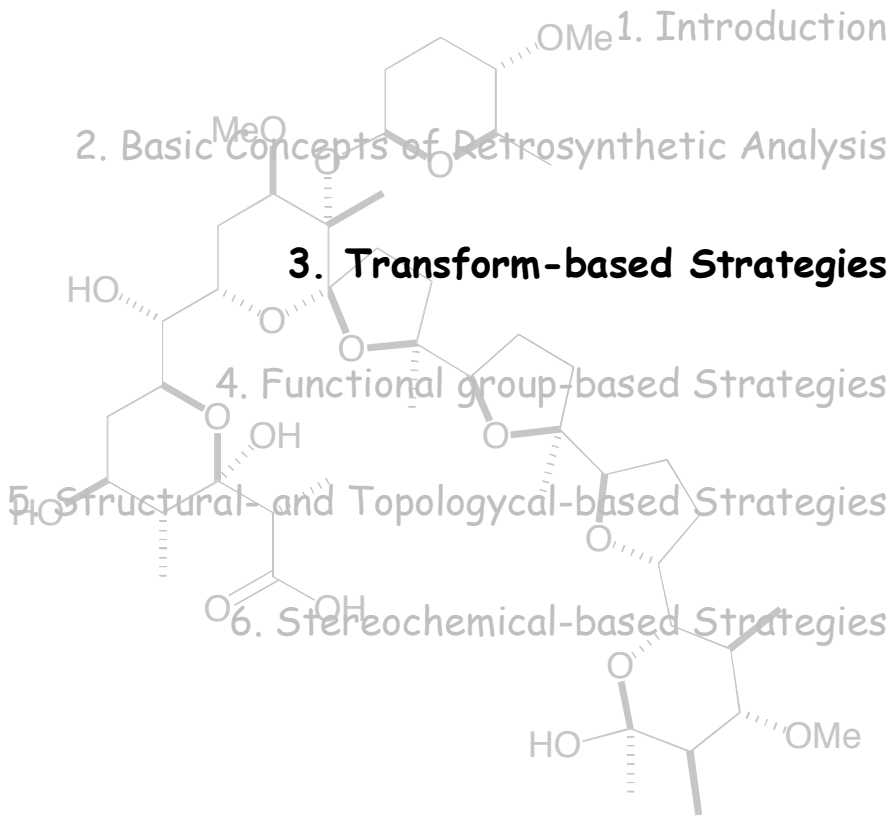
There are two types of useful general strategies which do not depend on molecular complexity:
transform-based strategy and structure-based strategy.
Additionally, three other general strategies can be indentified.

Transform-based strategies *rely on the application of powefully simplifying transforms.*
Structure-based strategies *rely on the recognition of possible strating materials*
or key intermediates for a synthesis.

Functional group-based strategies *identify functional groups as key structural subunits.*
Topological-based strategies *depend on the identification*
of one or more individual bond disconnections or
correlated bond-pair disconnections as strategic.
Stereochemical-based strategies *remove stereocenters and stereorelationships under control.*

Corey, E. J. *The Logic of Chemical Synthesis*

Part I

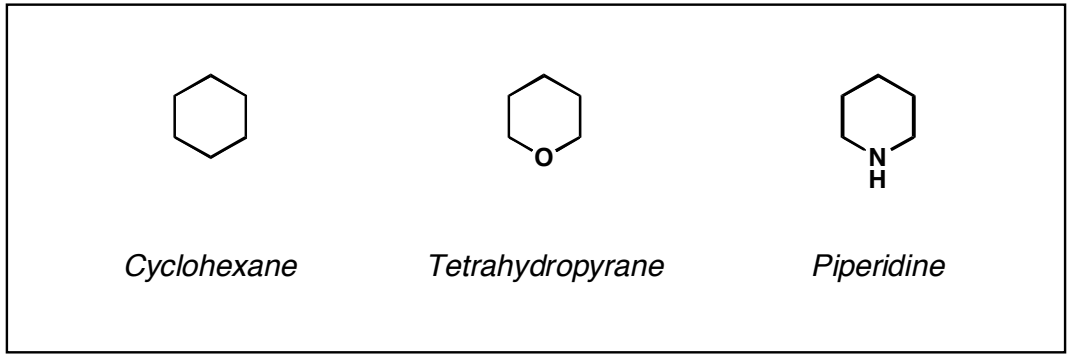


Transform-based strategies

Transform-based strategies consist on
the identification of a powerful simplifying transform leading to a TGT with certain keying features.
The required retron may be not present in a complex TGT
and a number of antithetic steps may be needed to establish it.

Such a strategy relies on synthetic and mechanistic knowledge,
*which can inspire the recognition of a hidden retron (**partial retron**)*

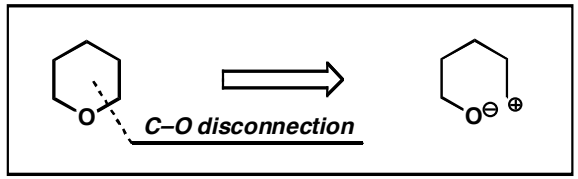
A case: six-membered cyclic motif

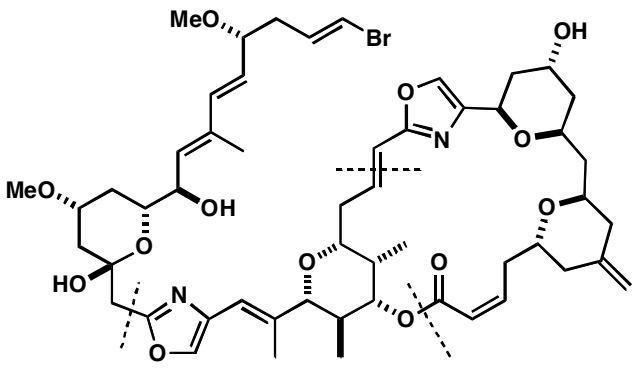


Is it possible to envisage any simple transform in these cyclic structures?

The answer could be ... yes, but

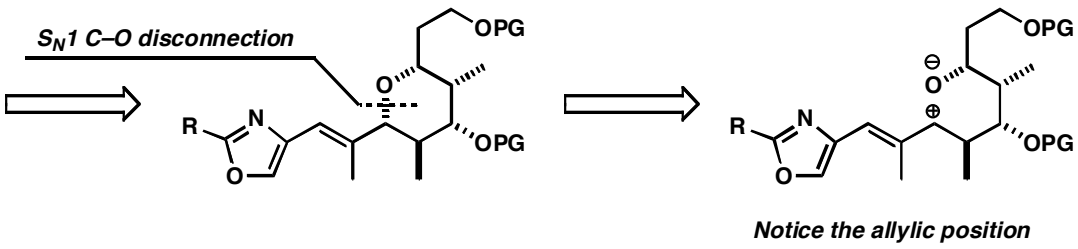
In the case of tetrahydropyran a straightforward disconnection, based on S_N2 or S_N1 processes, can be easily envisaged



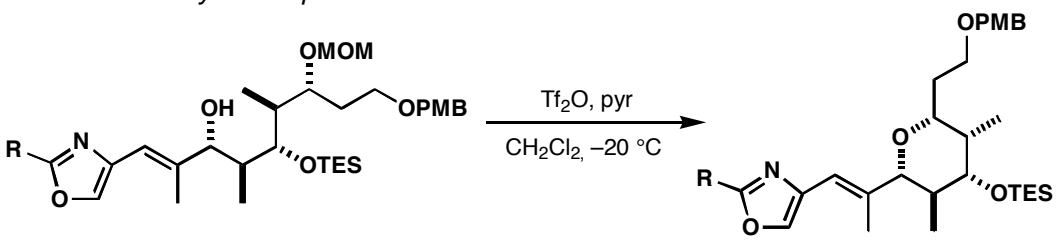


Phorboxazole A

Williams, D. R. *ACIE* **2003**, 1258



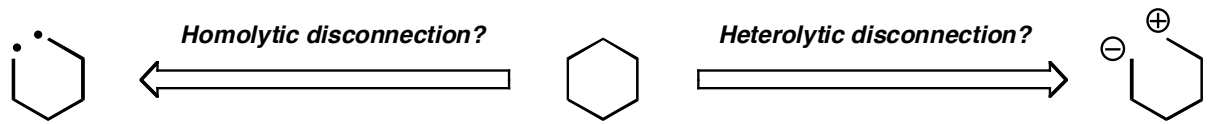
From a synthetic point of view



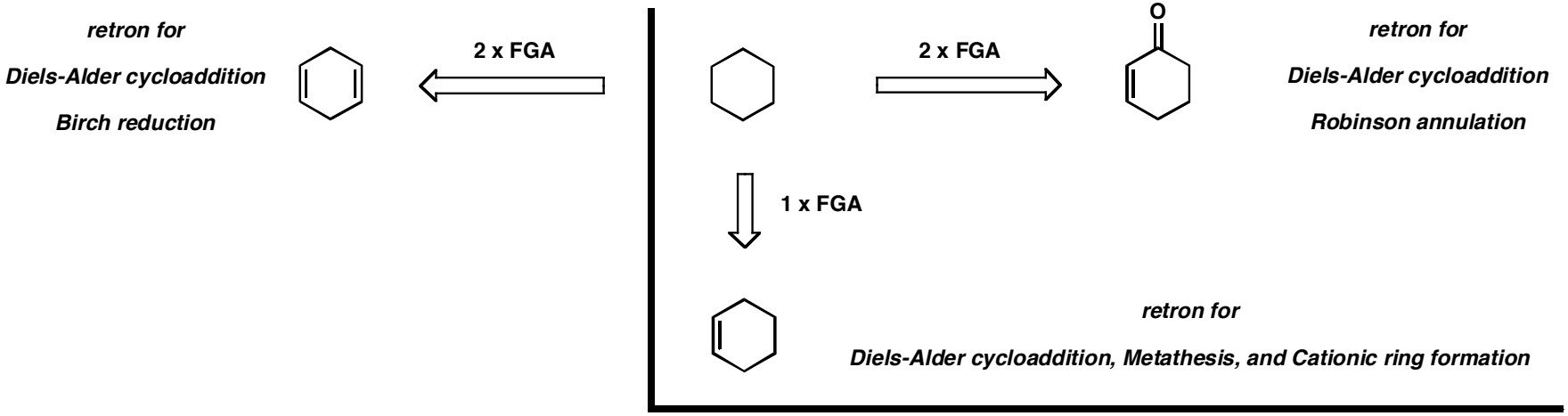
For a similar retrosynthetic analysis based on a S_N2 process, see

Forsyth, C. J. *JOC* **1997**, 5672 & Zhou, W.-S. *Synlett* **2003**, 1817

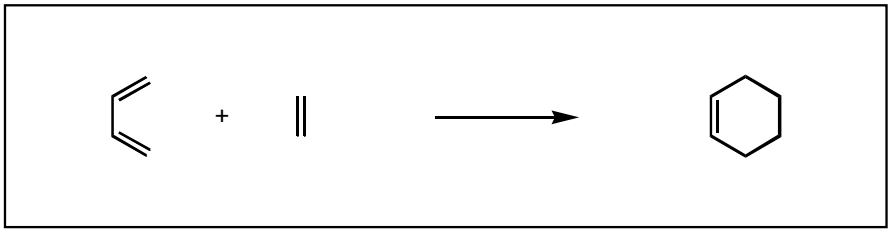
However, it becomes more difficult to identify a similar transform in the cyclohexane case ...

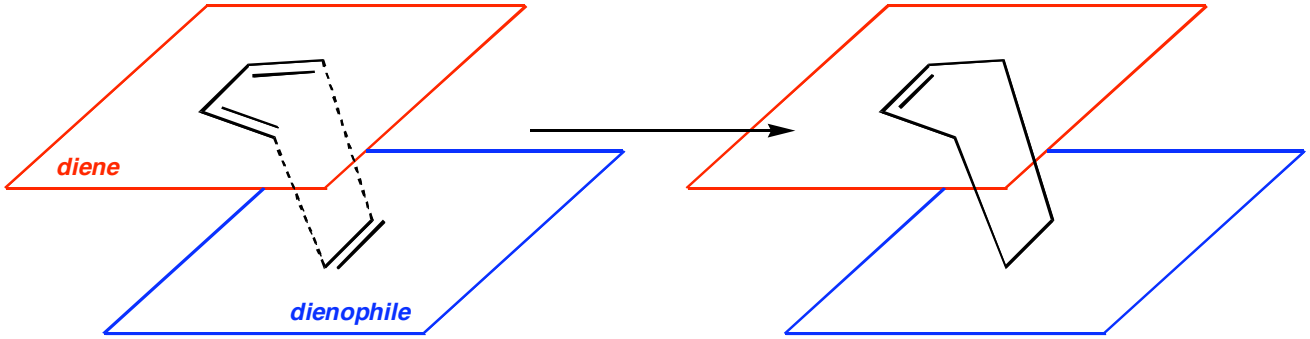


*... and **FGA transforms** are required*

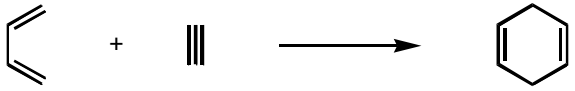


The venerable Diels-Alder reaction: a [4π_s + 2π_s] cycloaddition

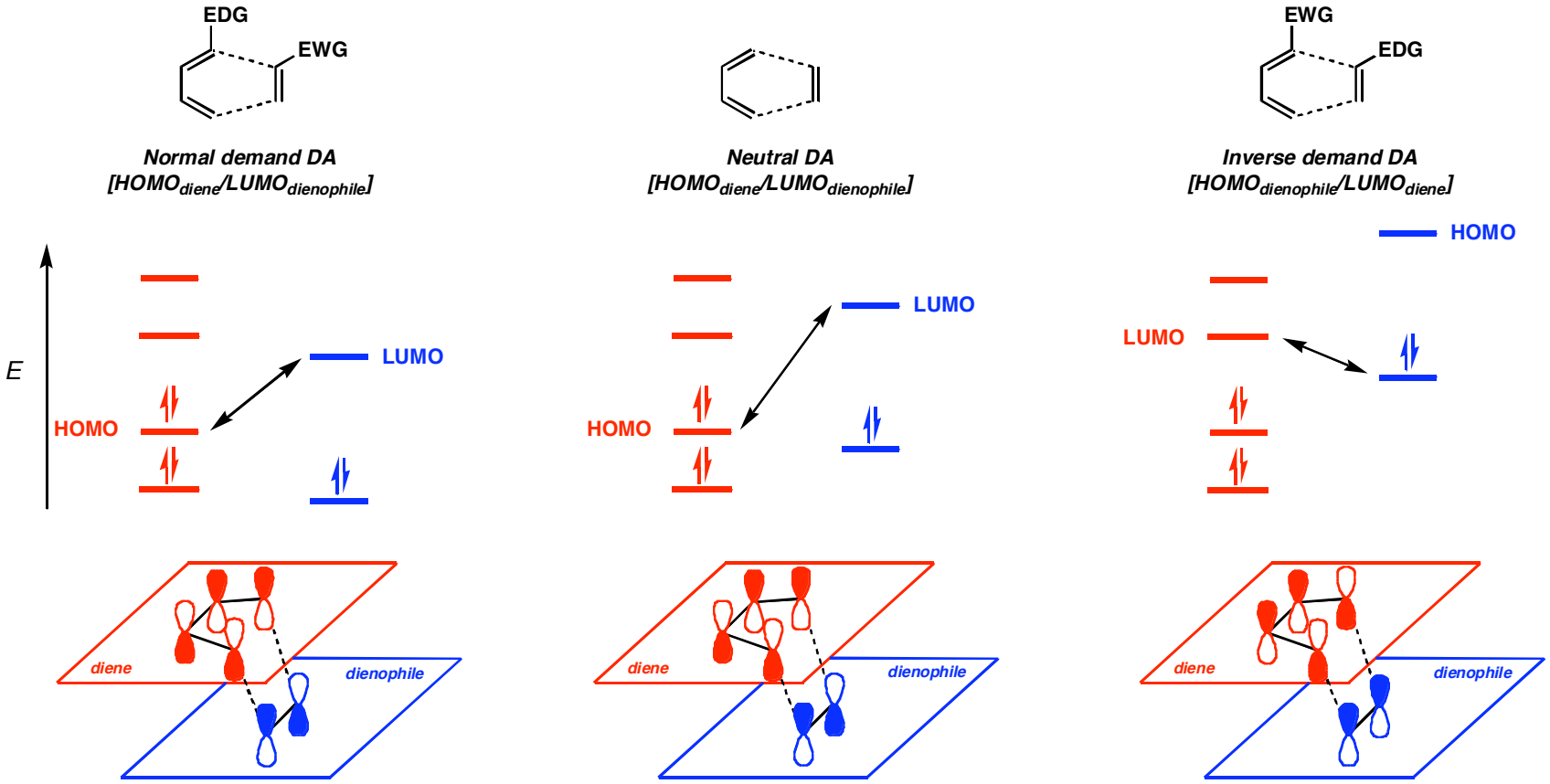




Remeber that an alkyne can also partcipate in the process

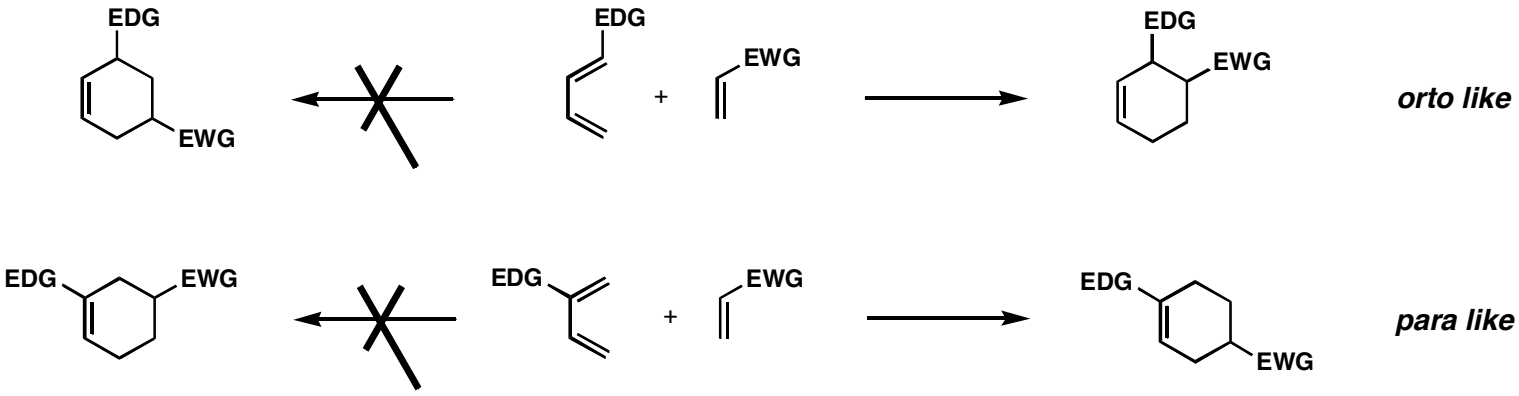


It can be rationalized through Frontier Orbital analysis ...

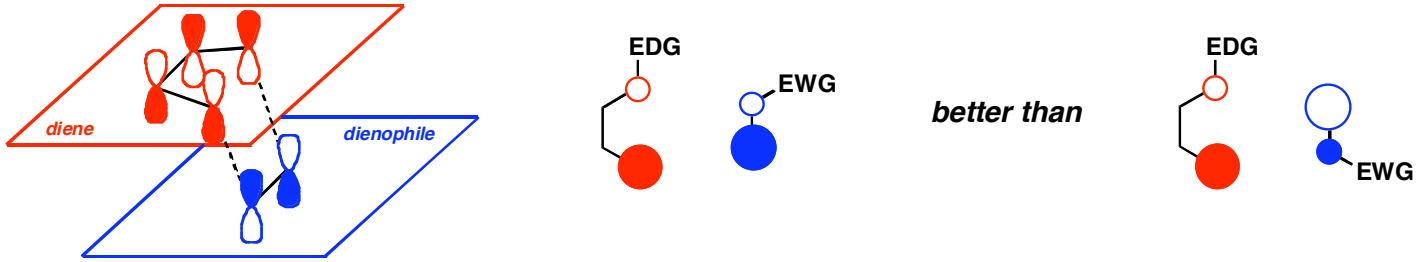


... which permits to predict the regio-, site- and the relative stereochemistry.

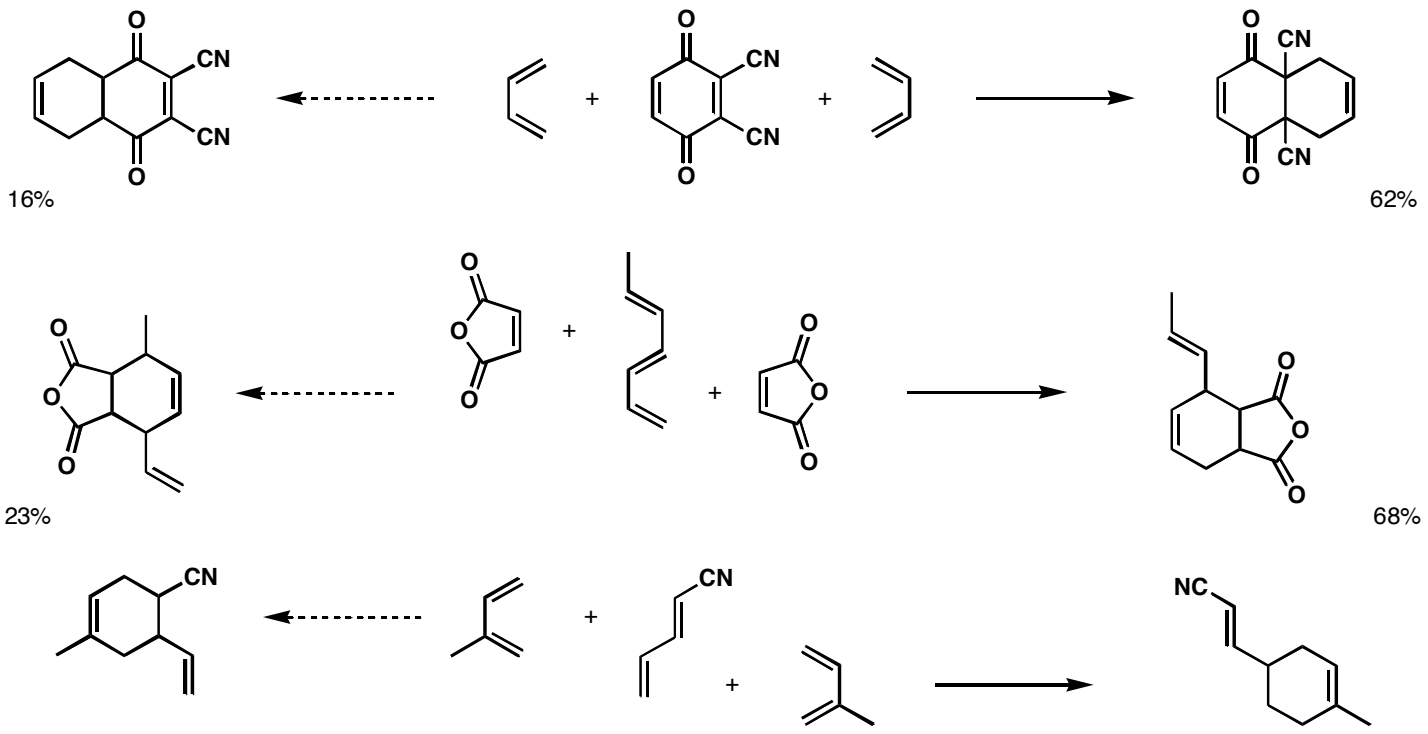
Regioselectivity: ***orto-para rule***



The coefficients of AO of the monosubstituted diene and of the mono-substituted dienophile are not equal at each end

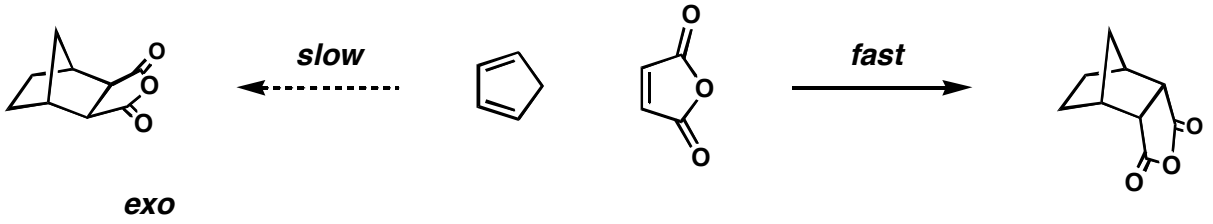


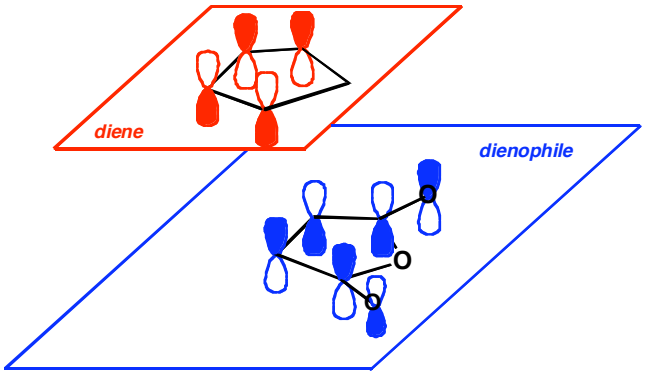
Siteselectivity

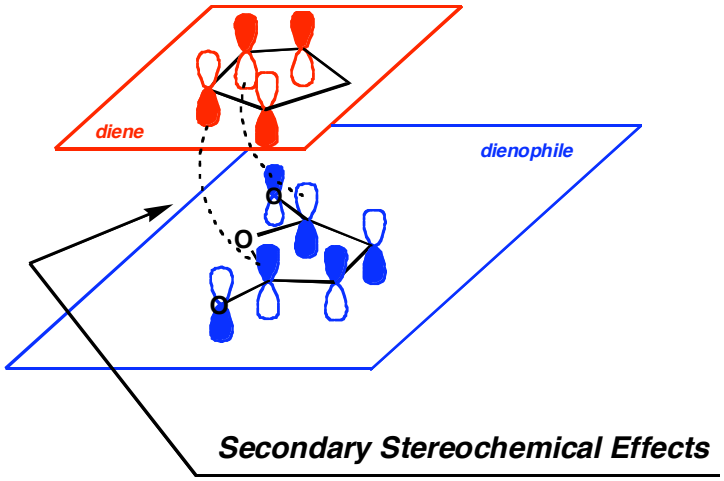


For a siteselectivity analysis in unsymmetrical quinones, see Corey, E. J. *JACS* **2004**, 4800

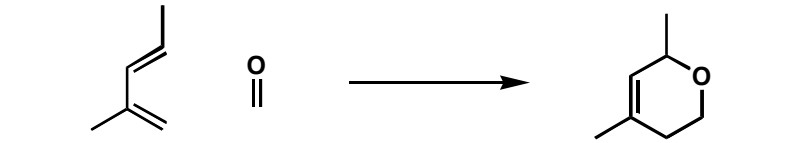
Relative stereochemistry: ***endo rule***



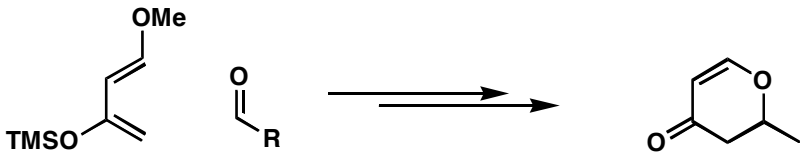


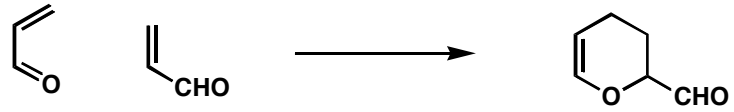


There are Diels Alder reactions in which an heteroatom is part of the dienophile (or the diene) systems, which gives access to heterocycles.
It is the called ***hetero Diels Alder***

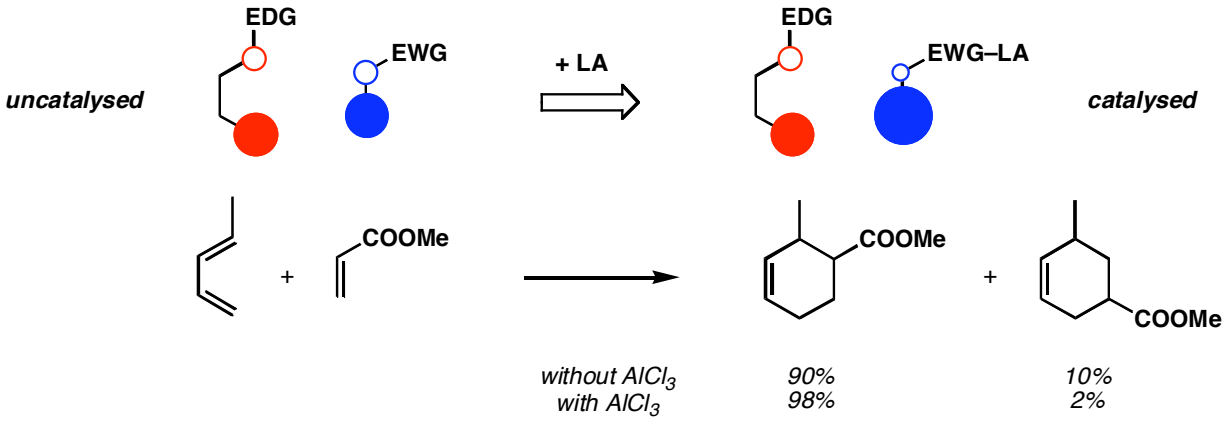


Danishefsky's diene



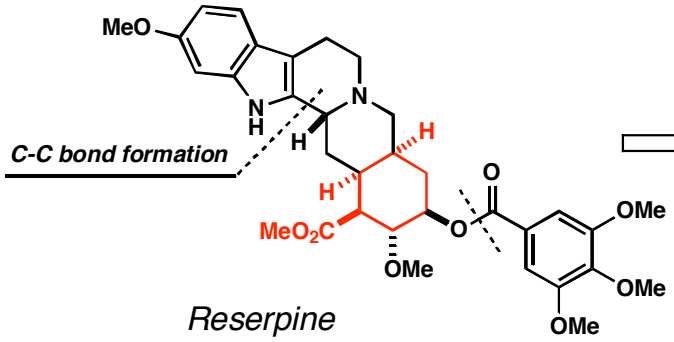


Finally, it is worth mentioning the crucial influence of Lewis acid on the process.
Lewis acid catalysed DA reactions are faster and more stereo and regioselective.
All these features can be explained by the effect the Lewis acid has on the LUMO of the dienophile.
The Lewis acid coordination with the dienophile
lowers the energy of the LUMO, which increases the rate,
modifies the LUMO coefficient, increasing the regioselectivity,
and makes the secondary interaction greater that in the uncatalysed case,
which accounts for the greater endo selectivity



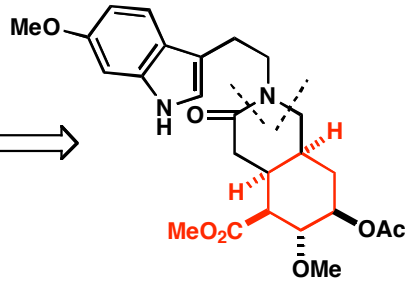
Suggestion: read Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*

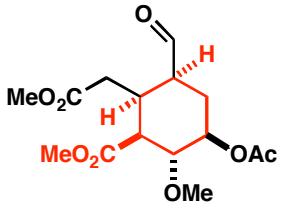
Just a classic: reserpine by Woodward



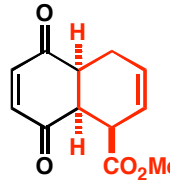
Reserpine

JACS **1956**, 2023, 2657 & *Tet* **1958**, 1

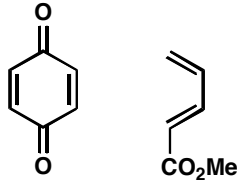




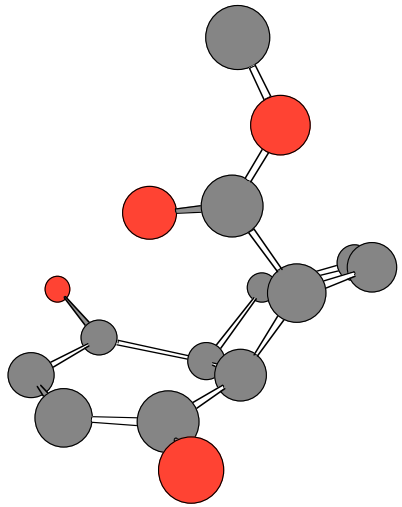
Six membered ring containing the required stereochemistry



Diels Alder transform

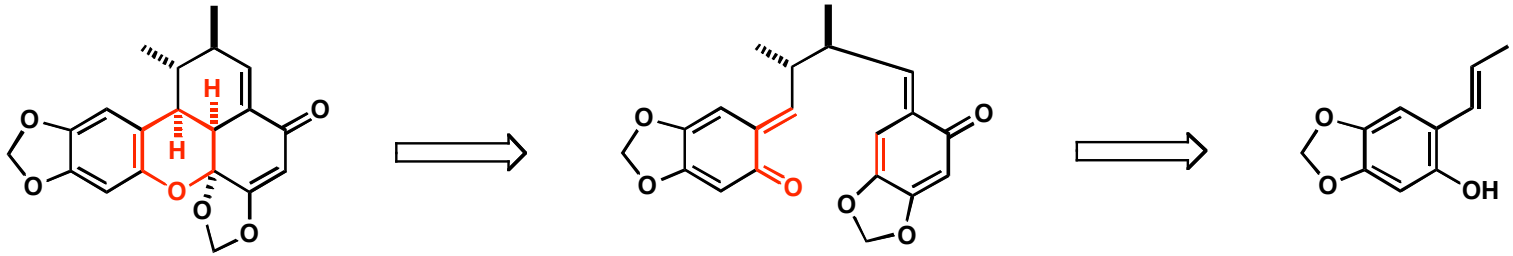


Concave face



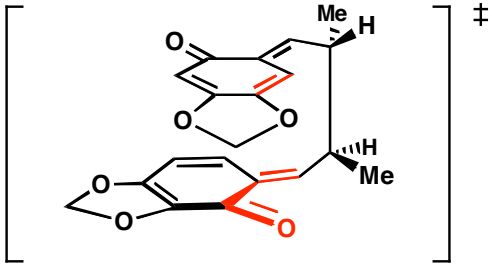
Convex face

An intramolecular hetero Diels-Alder exploiting symmetry: carpanone by Chapman



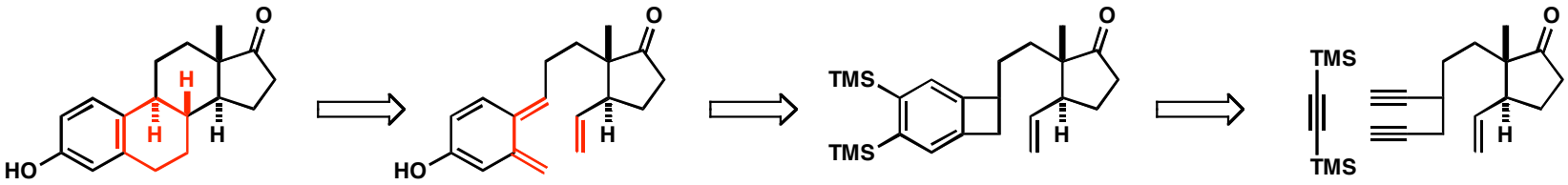
Carpanone

JACS **1971**, 6696



Transition state for this process?

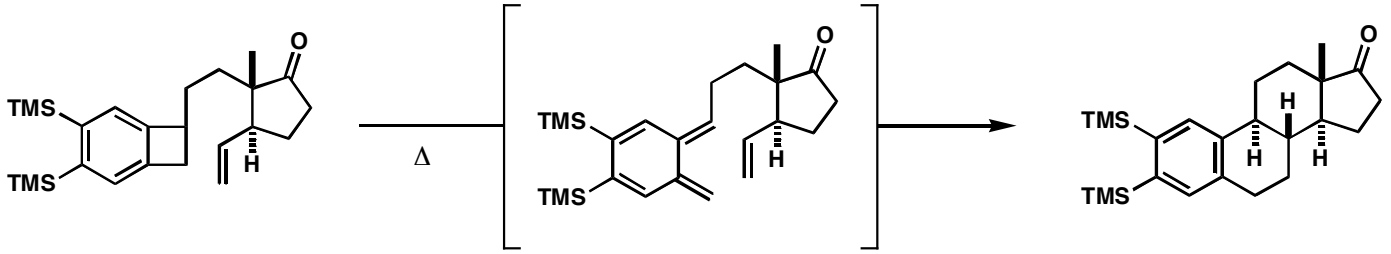
The power of tactic combinations: estrone by Vollhardt



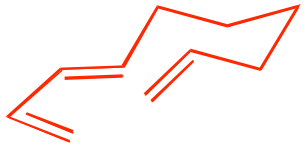
Estrone

Pay attention to the stereochemistry

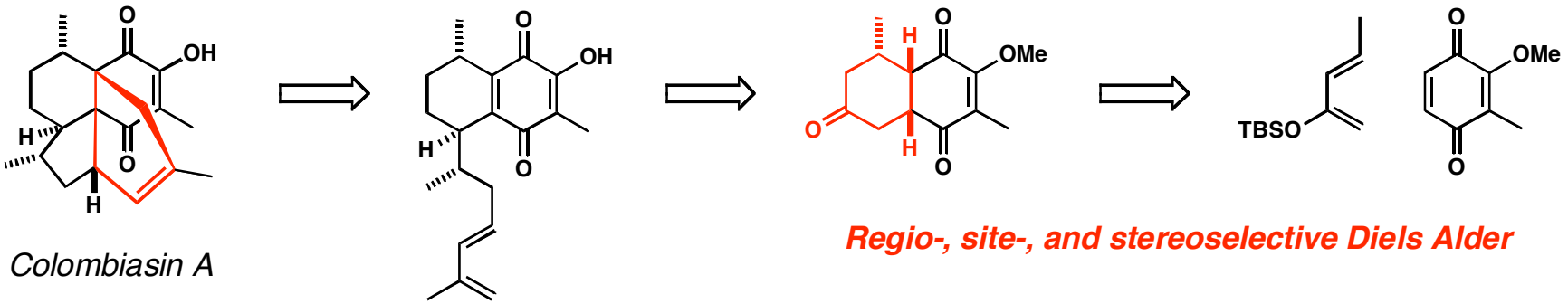
JACS **1980**, 5253



Notice that an exo-transition state is now required



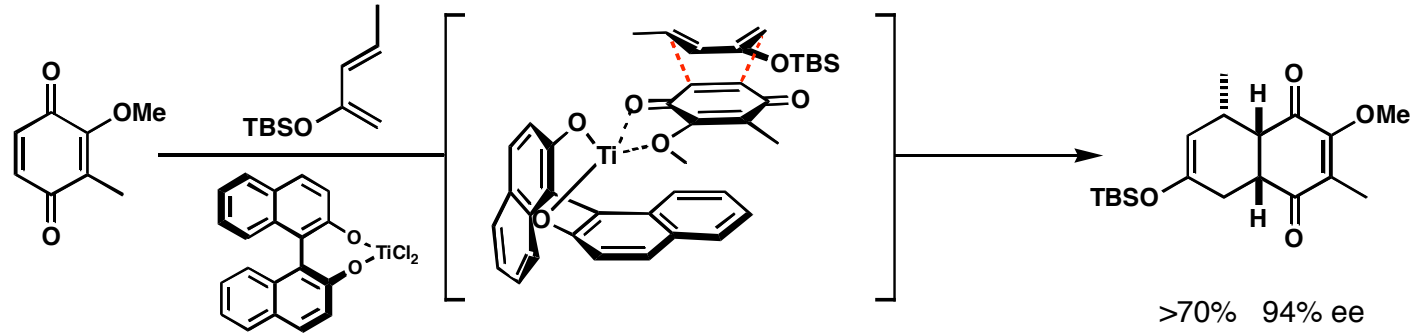
An asymmetric Diels Alder reaction: colombiasin A by Nicolaou



Colombiasin A

ACIE **2001**, 2482

Regio-, site-, and stereoselective Diels Alder



>70% 94% ee

Olefin Metathesis: the reaction of the 90s?

... olefin metathesis has come to the fore in recent years owing to the wide range of transformations that are possible with commercially available and easily handled catalysts.

Consequently, ***olefin metathesis is now widely considered as one of the most powerful synthetic tools in organic chemistry....***

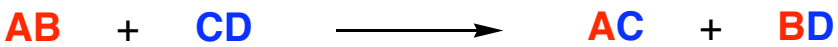
With the evolution of new catalysts, the selectivity, efficiency, and functional-group compatibility of this reaction have improved to a level that was unimaginable just a few years ago.

These advances together witha better understanding of the mechanism have brought us to a stage where ***more and more researchers are employing cross-metathesis reactions in multistep procedures and in the syntheis of natural products.***

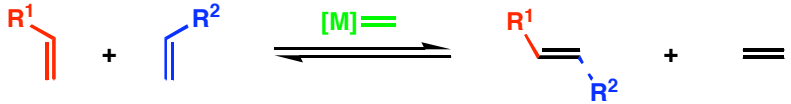
Blechert, S. *ACIE* **2003**, 1900 and references therein

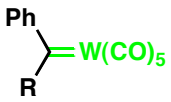
Schrock, R. R.; Hoveyda, A. H. *ACIE* **2004**, 4592.

Metathesis = ***Meta*** *(change)* & ***thesis*** *(position)*

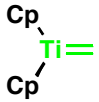


Olefin metathesis can be formally described as the intermolecular mutual exchange of alkylidene fragments between two olefins promoted by metal-carbene complexes

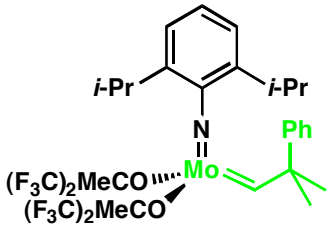




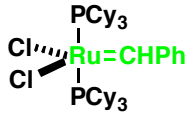
Katz 1976



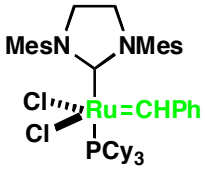
Tebbe 1978



Schrock 1990



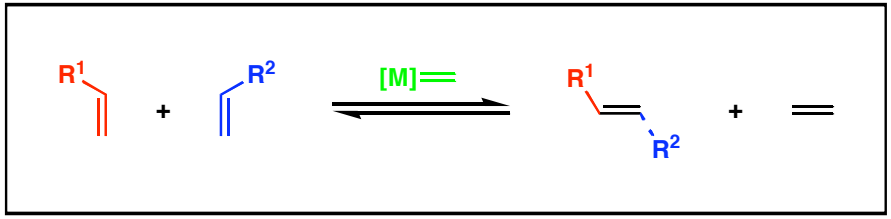
Grubbs 1995

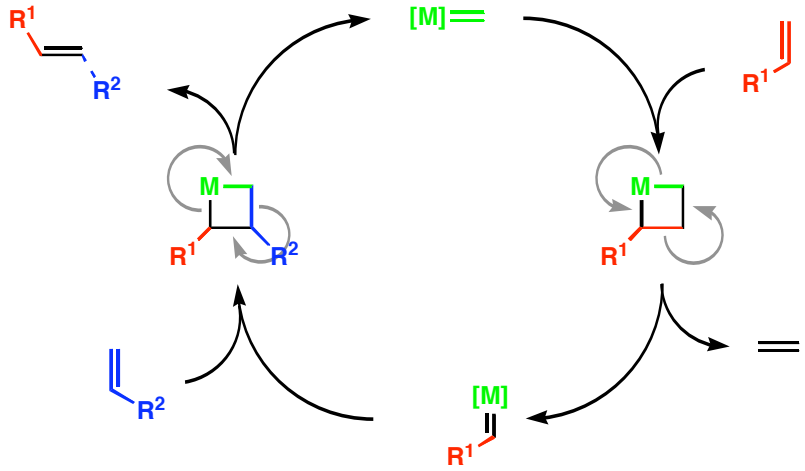


Grubbs 1999

The perfect reaction?

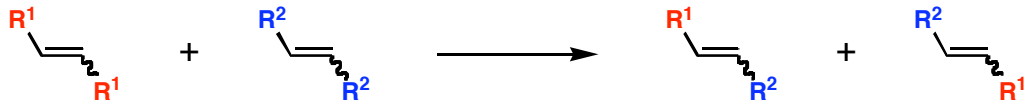
- *The process is catalytic (1–5 mol%)*
- *High yields under mild conditions*
- *High levels of chemo-, regio-, and stereoselectivity*
- *The reaction is reversible*
- *The starting materials are easily prepared*
- *The olefinic products are suitable for further structural elaboration*



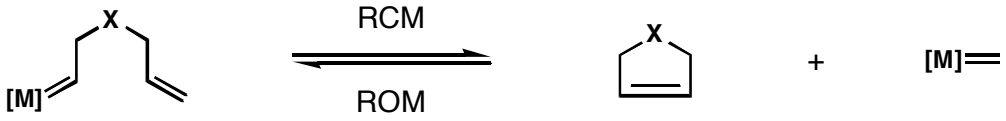


Three main variations on the metathesis theme ...

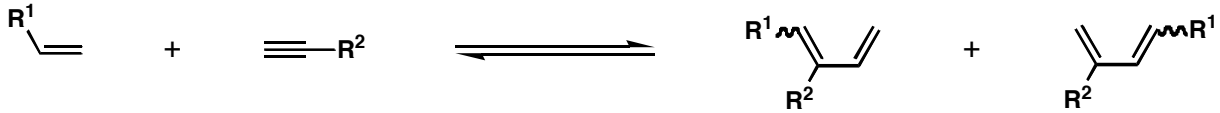
a) Cross–Metathesis



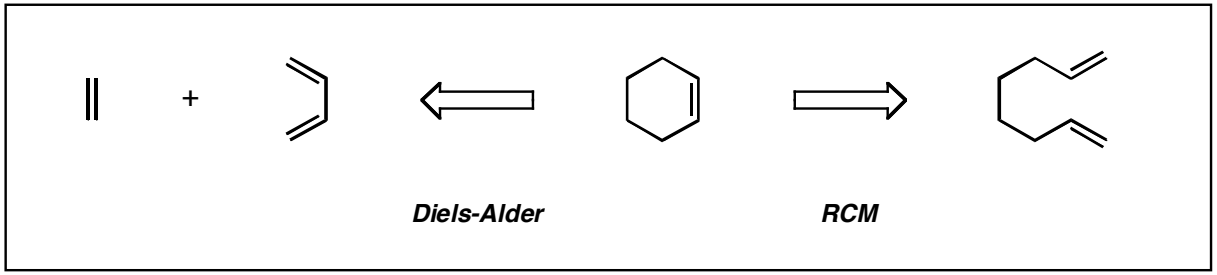
b) Ring-Closing & Ring-Opening Metathesis (RCM & ROM)



c) Enyne metathesis



Diels-Alder and Ring-Closing-Metathesis (RCM): two transforms for cyclohexene retron



+ 2 C–C & – 1 C=C

(Catalytic) process

Inter or intramolecular process

Reversible

Up to four new stereocenters

Carbon- and hetero-Diels-Alder are possible

0 C–C & 0 C=C

***Catalytic** process*

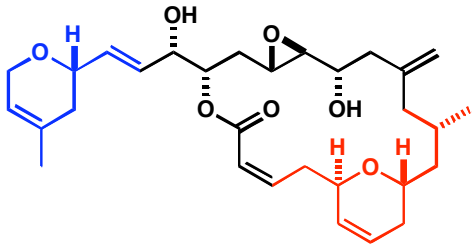
Intramolecular process

Reversible

No new stereocenters

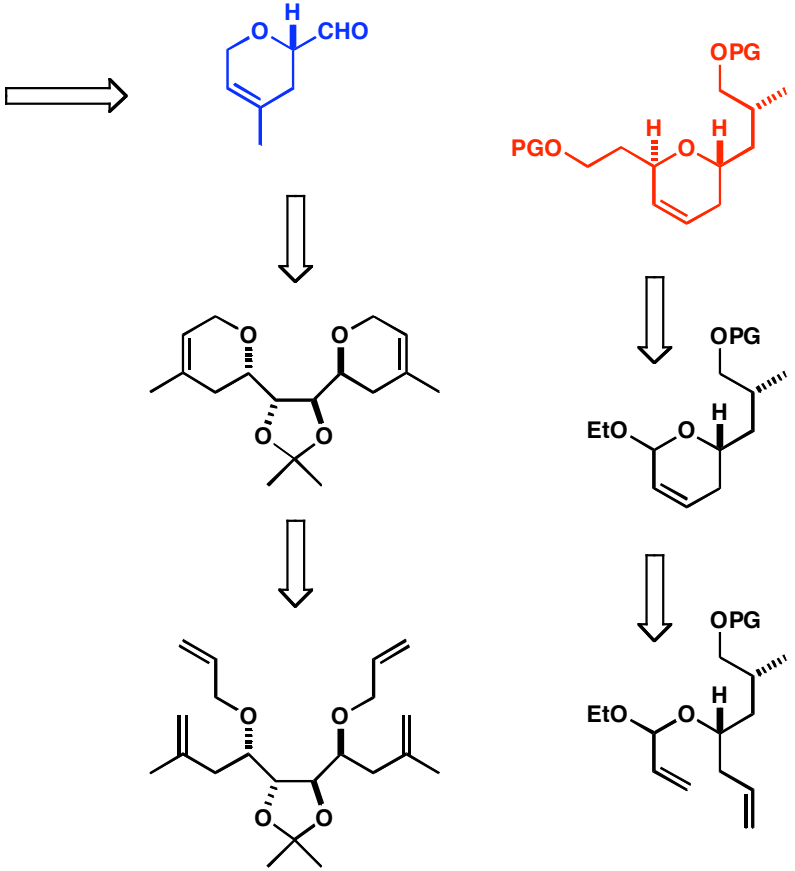
Carbon- and hetero-RCM are possible

The power of RCM: laulimalide by Ghosh and Mulzer

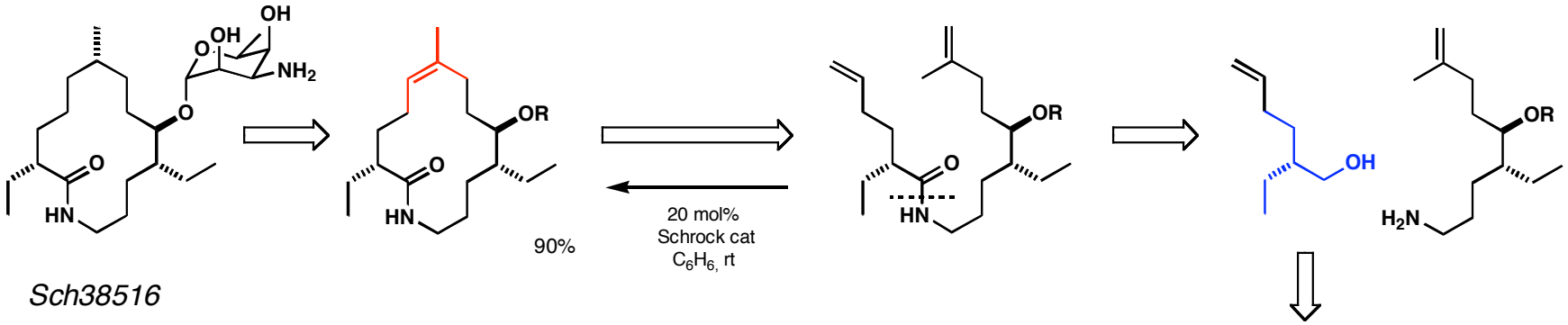


Laulimalide

See Ghosh, A. K. *JOC* **2001**, 8973
Mulzer, J. *Adv. Synth. Catal.* **2002**, 573

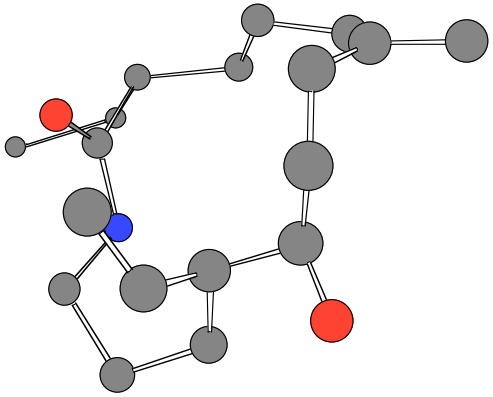


Pioneering catalytic transforms: Sch38516 by Hoveyda

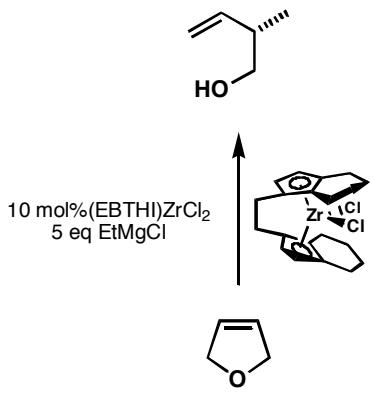


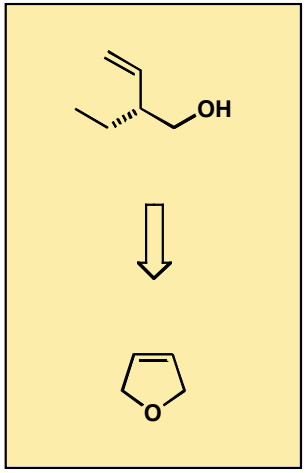
Sch38516

JACS **1997**, 10302



65% ee>97%

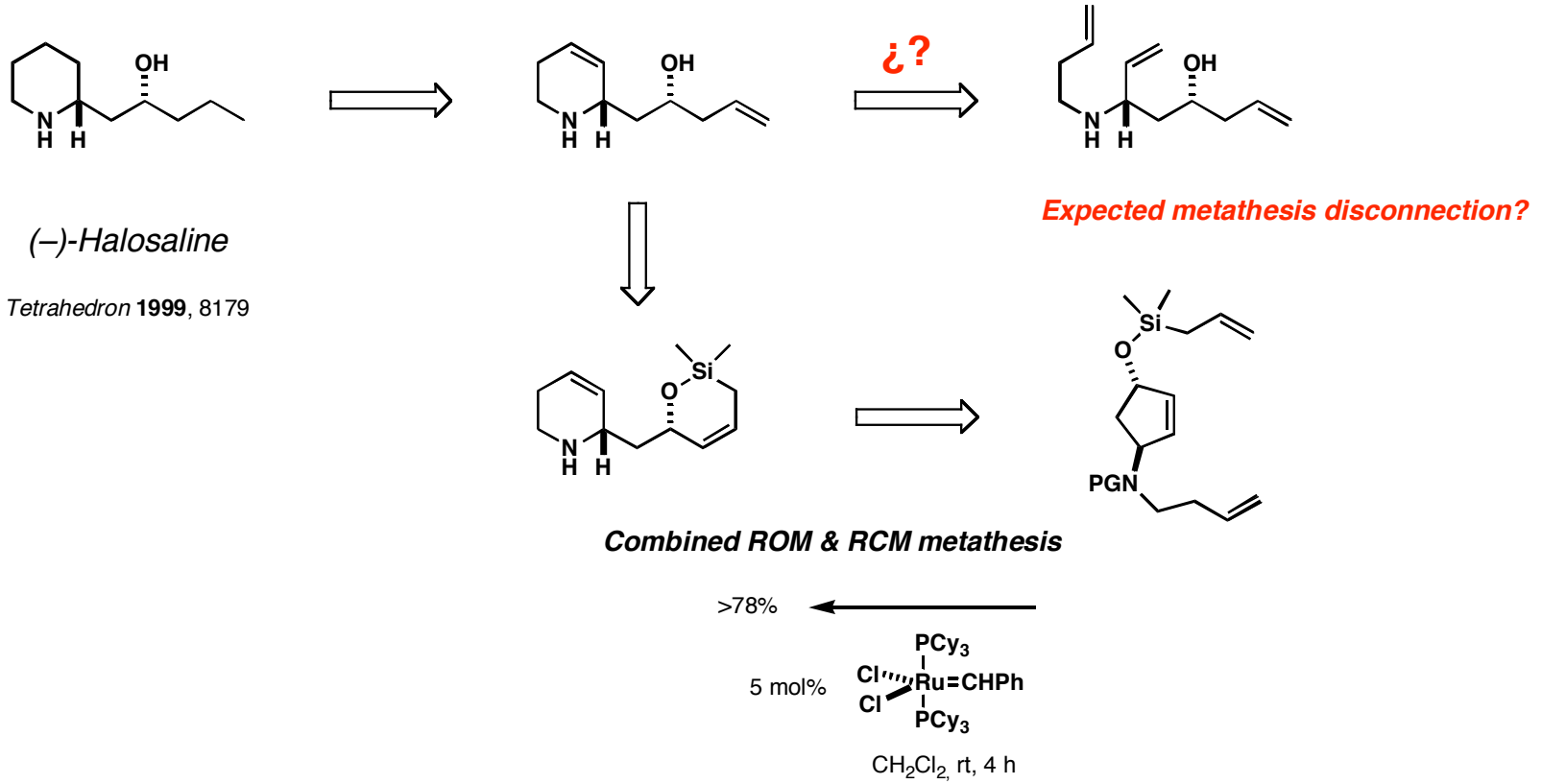




Zirconium-Catalyzed Asymmetric Carbomagnesation

Hoveyda, A. *JACS* **1993**, 6997

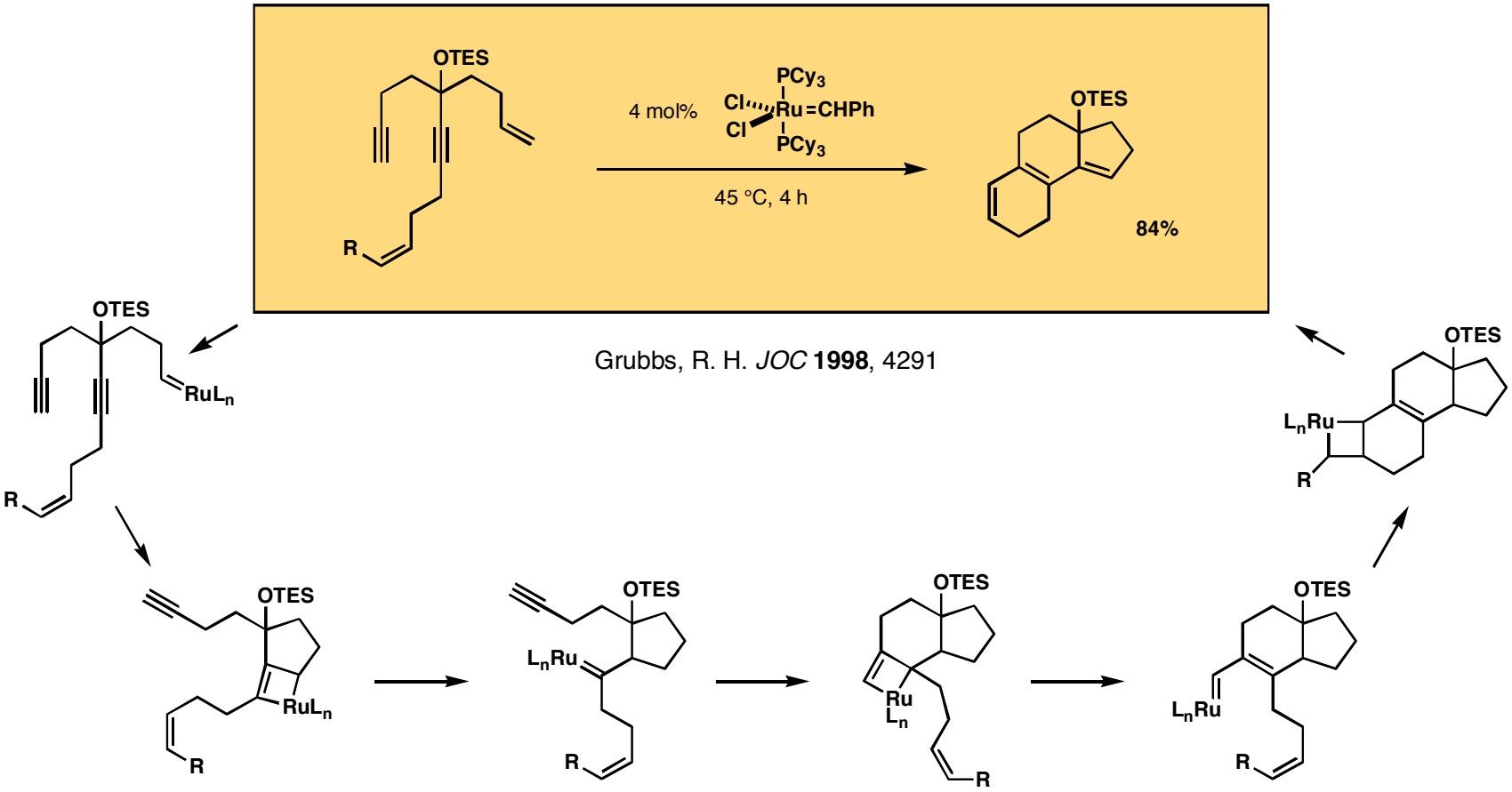
The hidden retron: halosaline by Blechert



(–)-Halosaline

Tetrahedron **1999**, 8179

Domino cyclization mediated by metathesis: Grubbs



Grubbs, R. H. *JOC* **1998**, 4291

Will domino transforms rule the waves?

*A **domino** reaction is a process involving two or more bond-forming transformations (usually C–C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.*

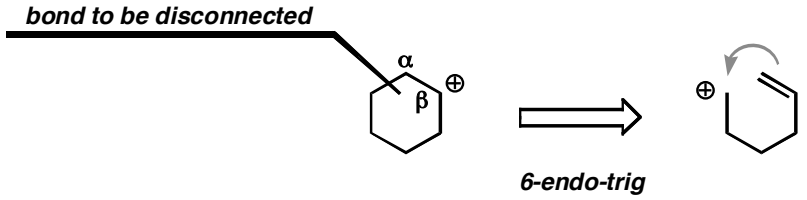
Tietze, L. *Chem. Rev.* **1996**, 115

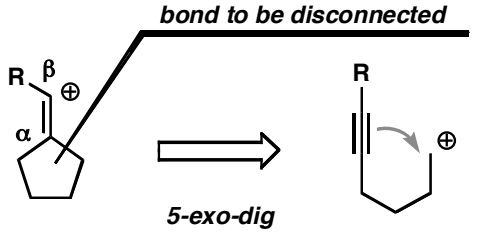
*With ever-increasing pressure to fashion diverse molecular architectures rapidly through efficient and atom-economical processes with high degrees of selectivity, **cascade reactions** are destined to become an integral design aspiration of most synthetic endeavors. In order to push the state-of the art of these sequences ...will require increasingly precise mechanistic and kinetic understanding of organic transformations combined with a large dose of intellectual flexibility and creativity.*

Nicolaou, K. C. *Classics in Total Synthesis II*

Cation π-cyclization

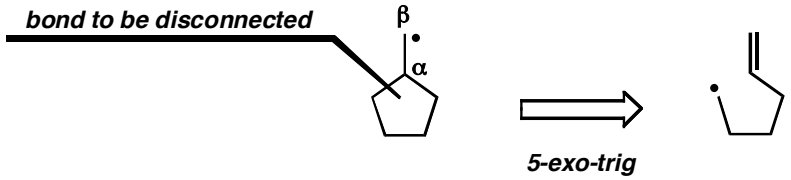
The retron for the cation π-cyclization transform can be defined as a carbocation with charge β to a ring bond which is to be cleaved.

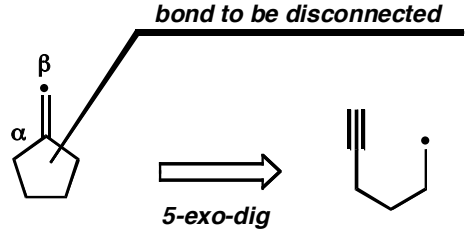




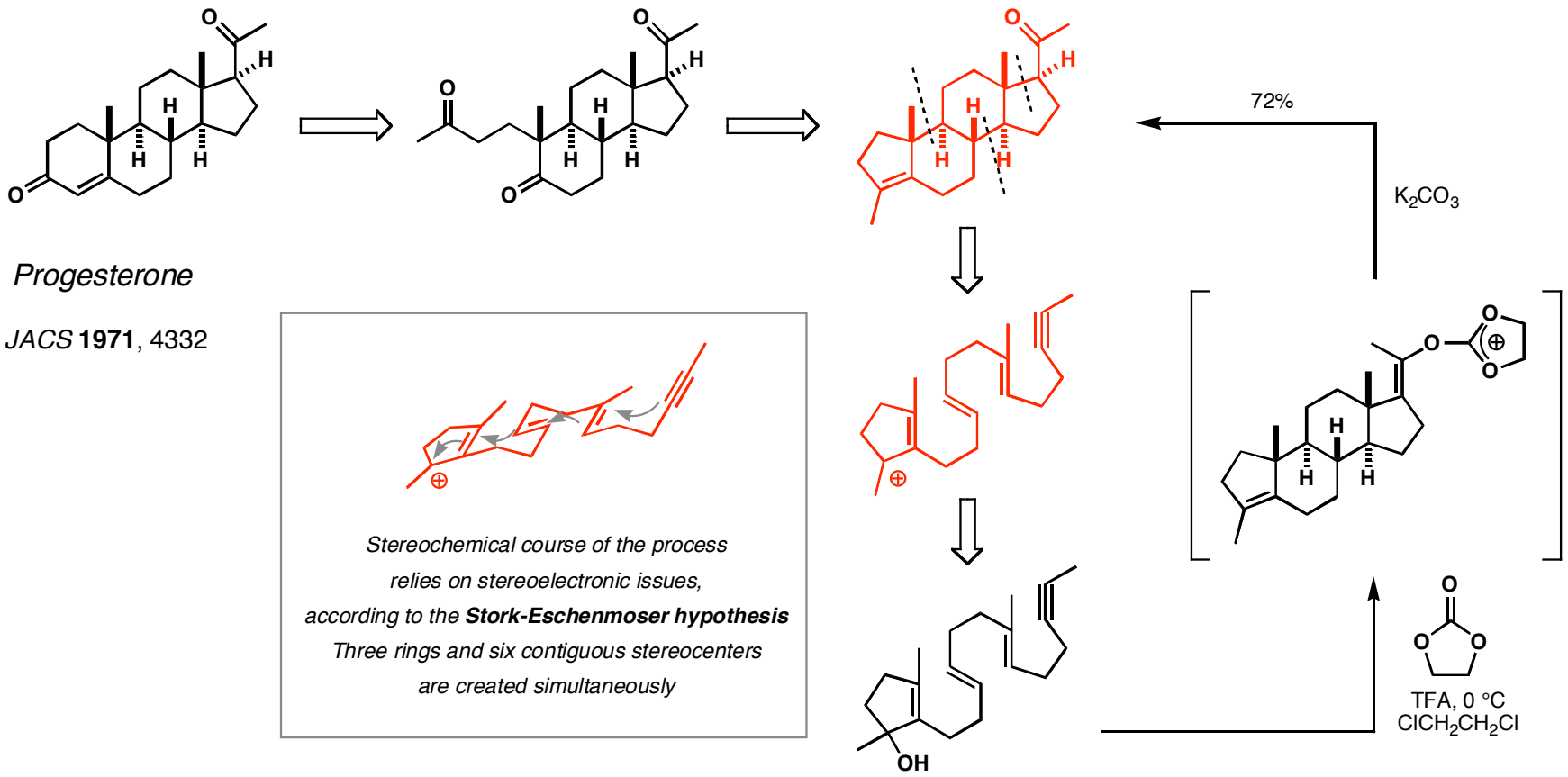
Radical π-cyclization

In a similar way, the retron for the radical π-cyclization transform can be defined as a radical with electron β to a ring bond which is to be cleaved, but ...





Just a classic of cation π-cyclization: progesterone by Johnson

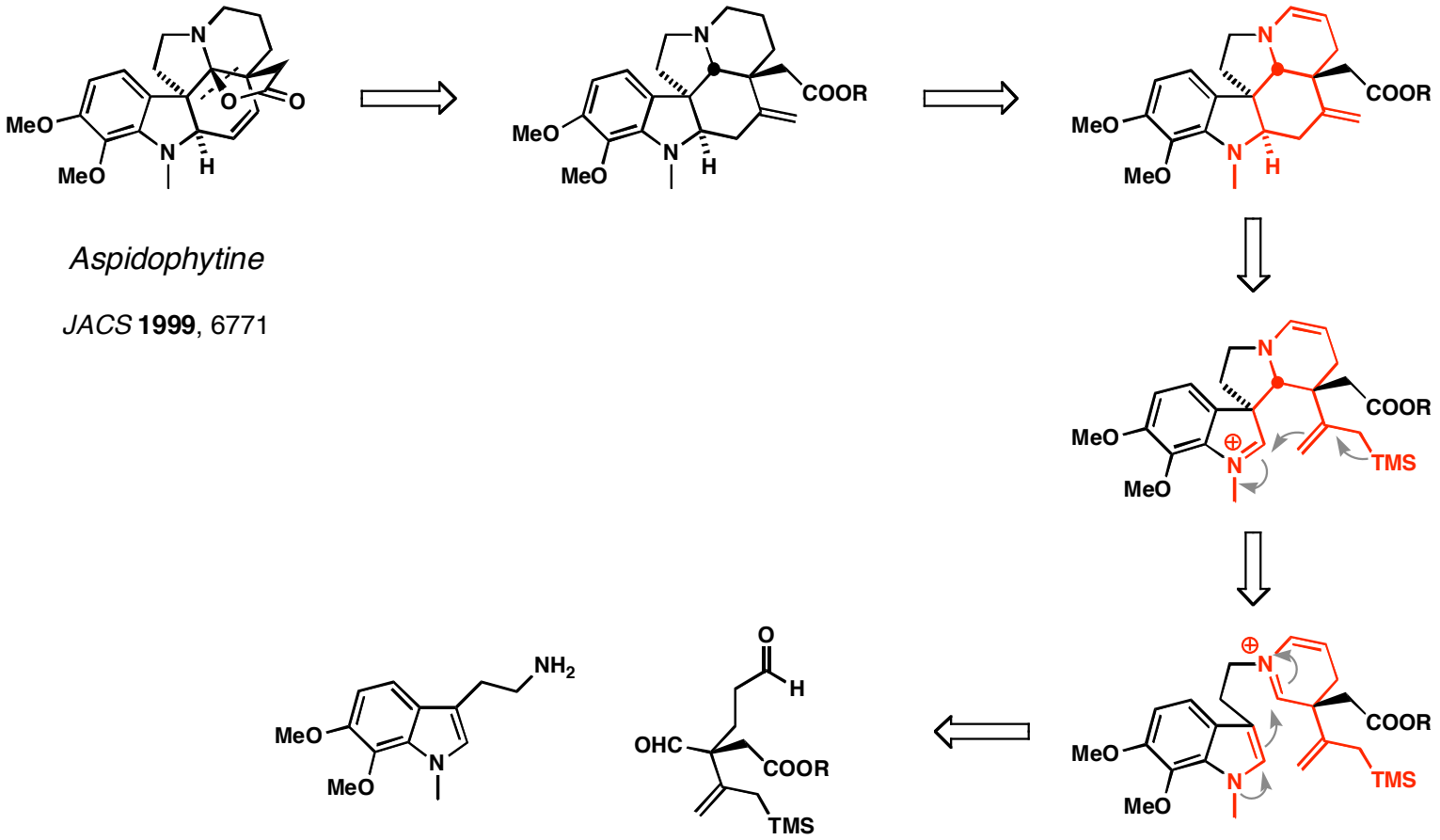


Progesterone

JACS **1971**, 4332

Stereochemical course of the process relies on stereoelectronic issues, according to the ***Stork-Eschenmoser hypothesis*** *Three rings and six contiguous stereocenters are created simultaneously*

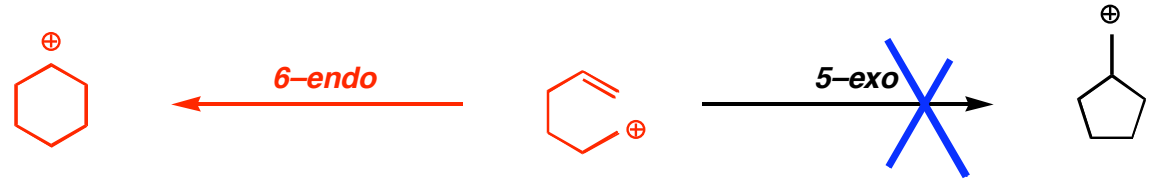
A nice solution to a daunting problem: aspidophytine by Corey

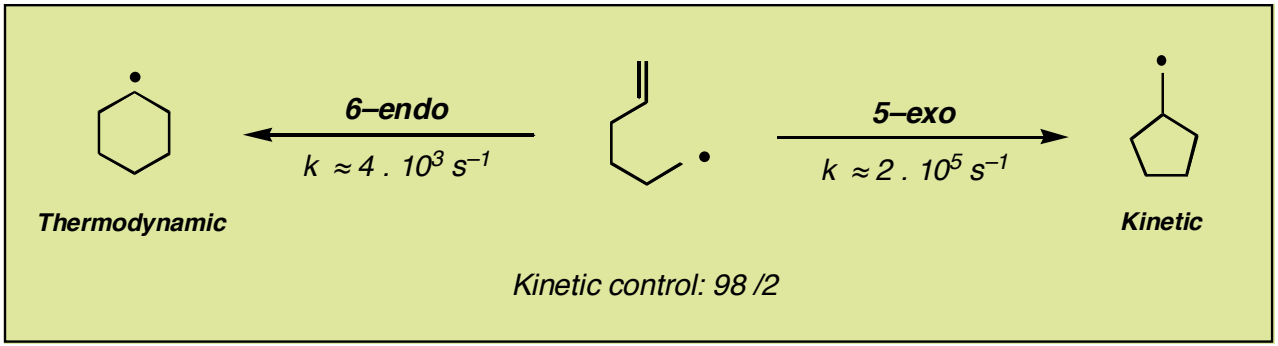


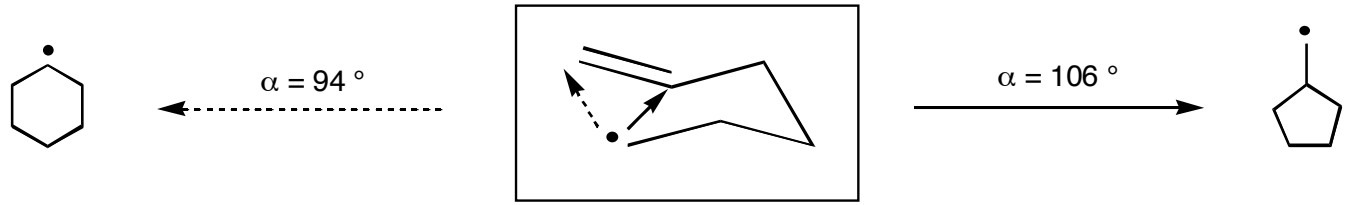
Aspidophytine

JACS **1999**, 6771

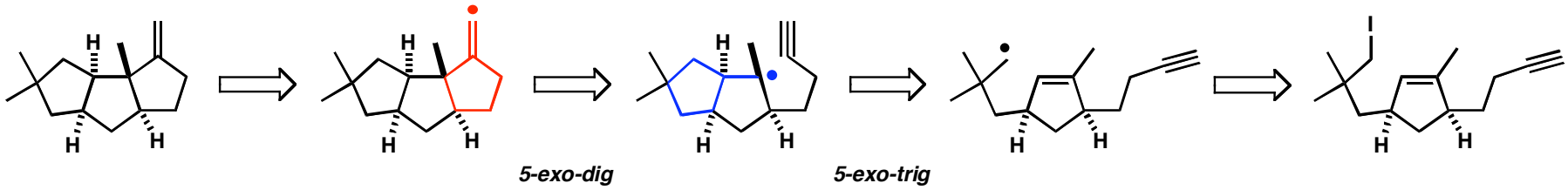
Apparently similar radical π-cyclization







Just two classics of radical π-cyclization: hirsutene and $\Delta^{9(12)}$-capnellene by Curran

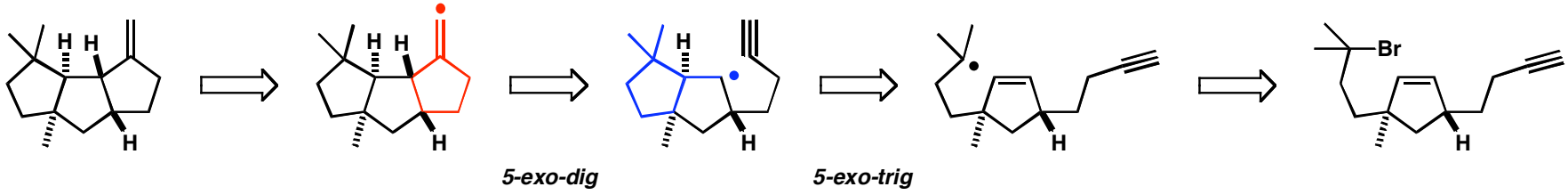


Hirsutene

JACS **1985**, 1448

n-Bu_3SnH, AIBN cat, PhH (0.02 M), Δ

80%



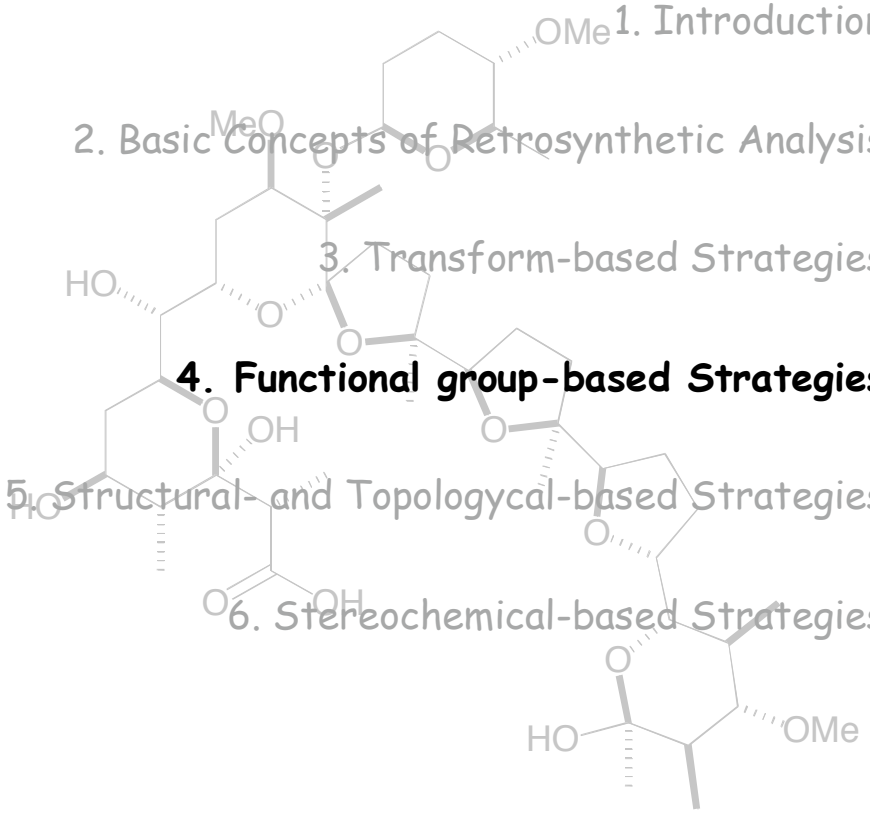
$\Delta^{9(12)}$-Capnellene

TL **1985**, 4991

n-Bu_3SnH, AIBN cat, PhH (0.02 M), Δ

80%

Part I



Functional groups?

Organic molecule ≡ *Carbon skeleton* + *Functional groups*

σ bonds: C_{sp3} – C_{sp3} & C_{sp3} – H bonds

atoms or set of atoms
that give rise to characteristic chemical behaviour

The concept of functional group provides a valuable framework for understanding reactivity
and
an useful tool to go deeply into retrosynthetic analysis

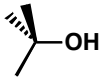
Corey classifies the functional groups, FG, in three families:

1st Level: *the most important FG*

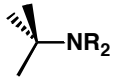
alkenes

arenes

alkynes



alcohols



amines

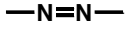
aldehydes, R = H, & ketones

acids, X = OH, esters, X = OR', & amides, X = NR_2

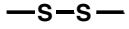
nitro

ciano

2nd Level: *less important FG*



diazo



disulfide

phosphine

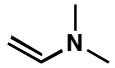
3rd Level: *<u>peripheral</u>, which are associated with useful reagents providing activation or control in chemical processes, or combination of more fundamental groups*

halides

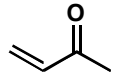
sulphones

boranes

phosphonium



enamine



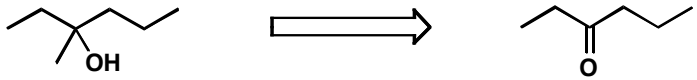
enone

They can also be associated into super-set or super-families depending on their electronic behaviour

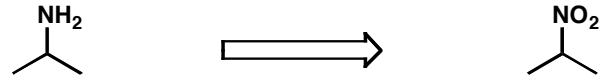
EWG*: CO, CN, SOR, NO_2 or* ***EDG:*** *OR, NR_2*

Furthermore, many retrons contain only a single FG, while others consist of a pair of FG's separated by a specific path

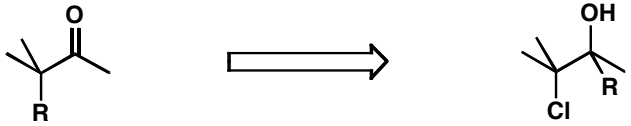
***I**. Transforms involving a single FG*



Removal of an appendage

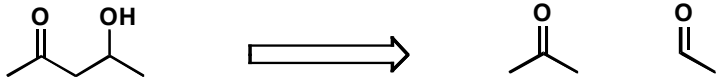


FG interconversion

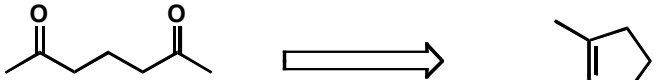


Rearrangement

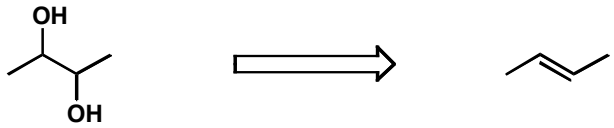
***II**. Transforms requiring a pair of FG*



Through C – C disconnection



Formation of a new path



Modification of functionality without altering carbon path

For a molecule contain ing n FG's ***there are n(n–1)/2 possible pairs*** *...*

Functional group-based strategies

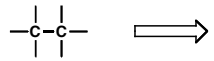
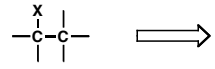
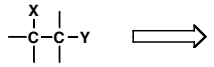
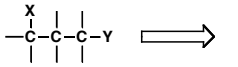
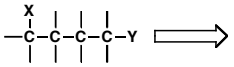
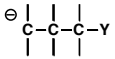
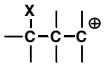
The use of functional group to guide retrosynthetic reduction of molecular complexity.

Single FG's or pairs of FG's, and the interconnecting atom path,
can key directly the disconnection of a TGT skeleton to form simpler molecules or
signal the application of transforms wich replace functional by hydrogen.
FGI is a commonly used tactic for generating from a TGT retrons which allow the application of simplifying transforms.
FG's may key transforms which stereoselectively remove stereocenters,
break strategic bonds or join proximate atoms to form rings.

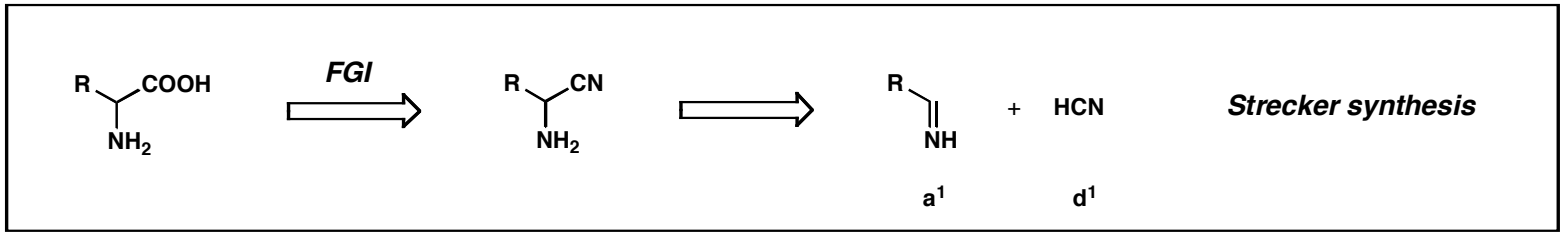
As mentioned early (see Chapter 2),
taking into account that most common synthetic reactions are polar,
a bond forming process (and the corresponding transform) can be viewed as a combination of donor, ***d****, and acceptor,* ***a****, synthons.*
Then,obvious rules can apply to arrangement of functionality in the product

alkyl a + ***alkyl d***	***non-functional product***
alkyl a + d^1 or ***alkyl d*** + a^1	***monofunctional product***
a^1 + d^1	***1,2-difunctional product***
a^1 + d^2 or a^2 + d^1	***1,3-difunctional product***
a^1 + d^3 or a^2 + d^2 or a^3 + d^1	***1,4-difunctional product***

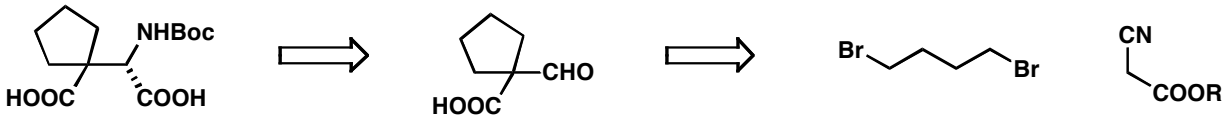
These disconnections correspond to ***consonant relationships***

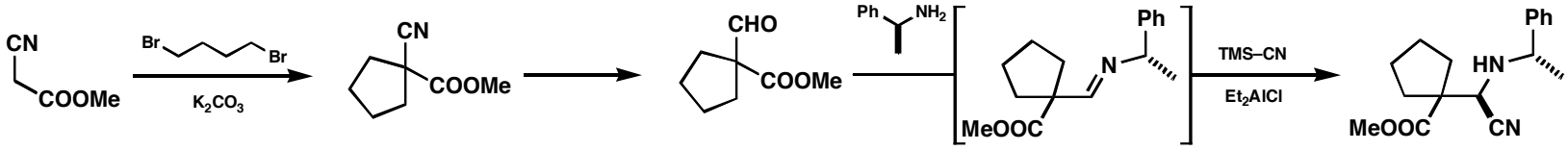
TGT		*Synthon combination*	
Non functional		 **alkyl a**	 **alkyl d**
Monofunctional		 **a^1**	 **alkyl d**
1,2-Difunctional		 **a^1**	 **d^1**
1,3-Difunctional		 **a^1**	 **d^2**
1,4-Difunctional		 **a^1**	 **d^3**
		 **a^2**	 **d^2**
		 **a^3**	 **d^1**

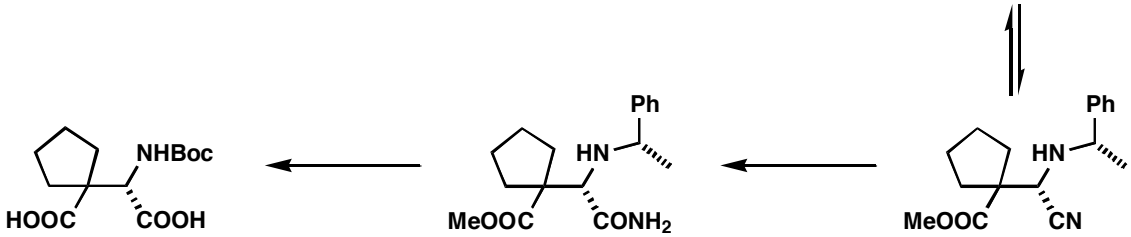
1,2-Difunctional systems: $a^1 + d^1$ combination



Cyclopentyl aspartic acid

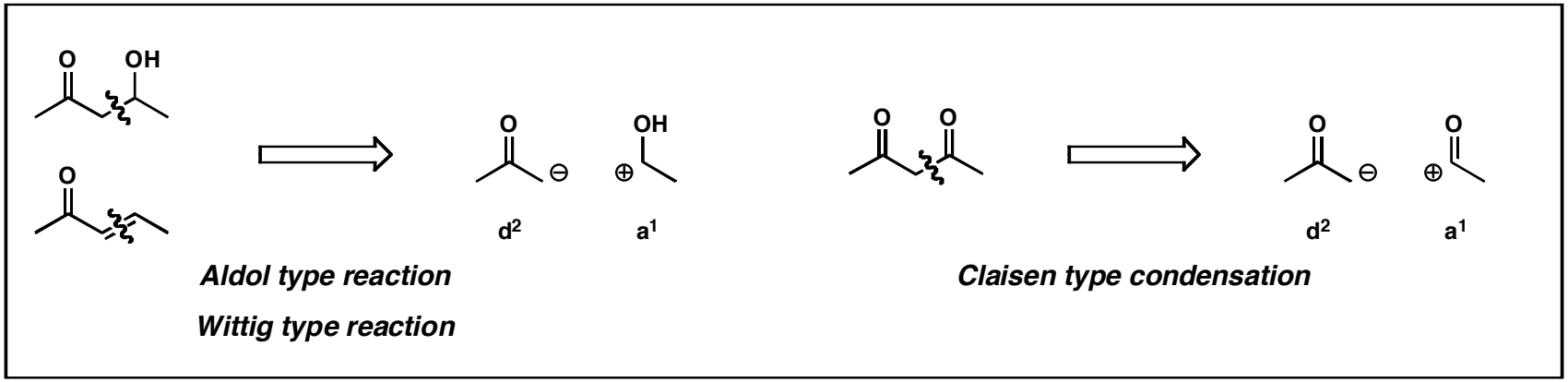






Moss, N. *Synthesis* **1997**, 32

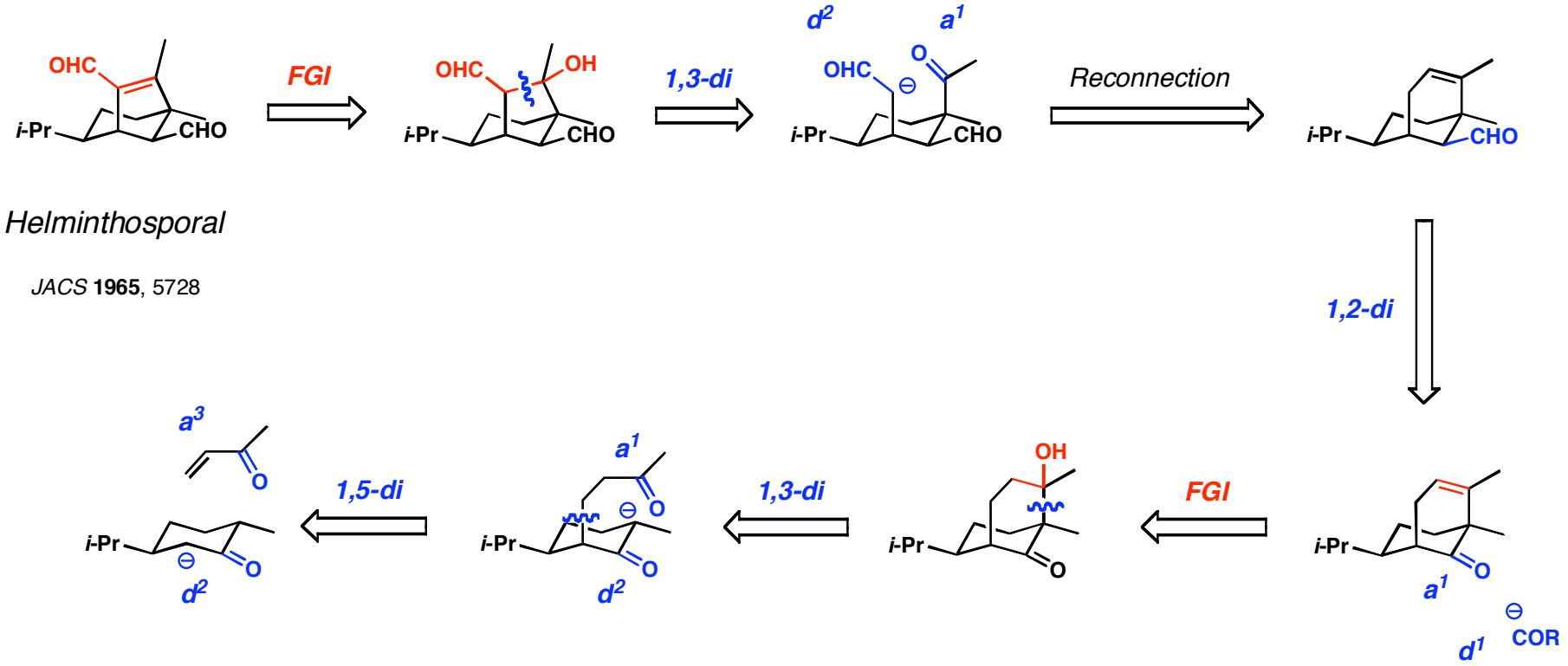
1,3-Difunctional systems: $a^1 + d^2$ combination



d^2 synthons: enol, enolate and synthetic equivalents

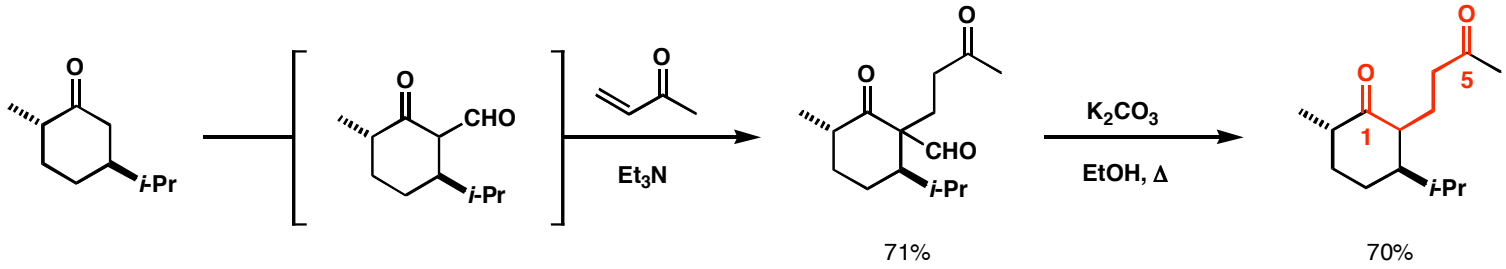
a^1 synthons: aldehydes, ketones and esters

A benchmark: helminthosporal by Corey

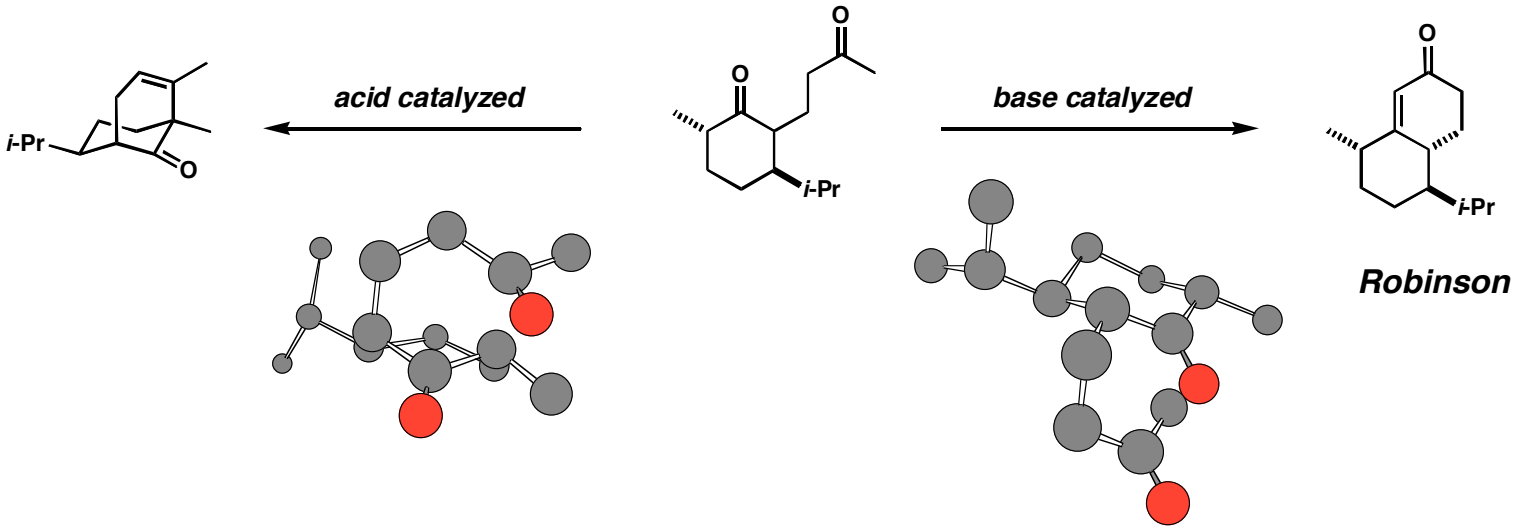


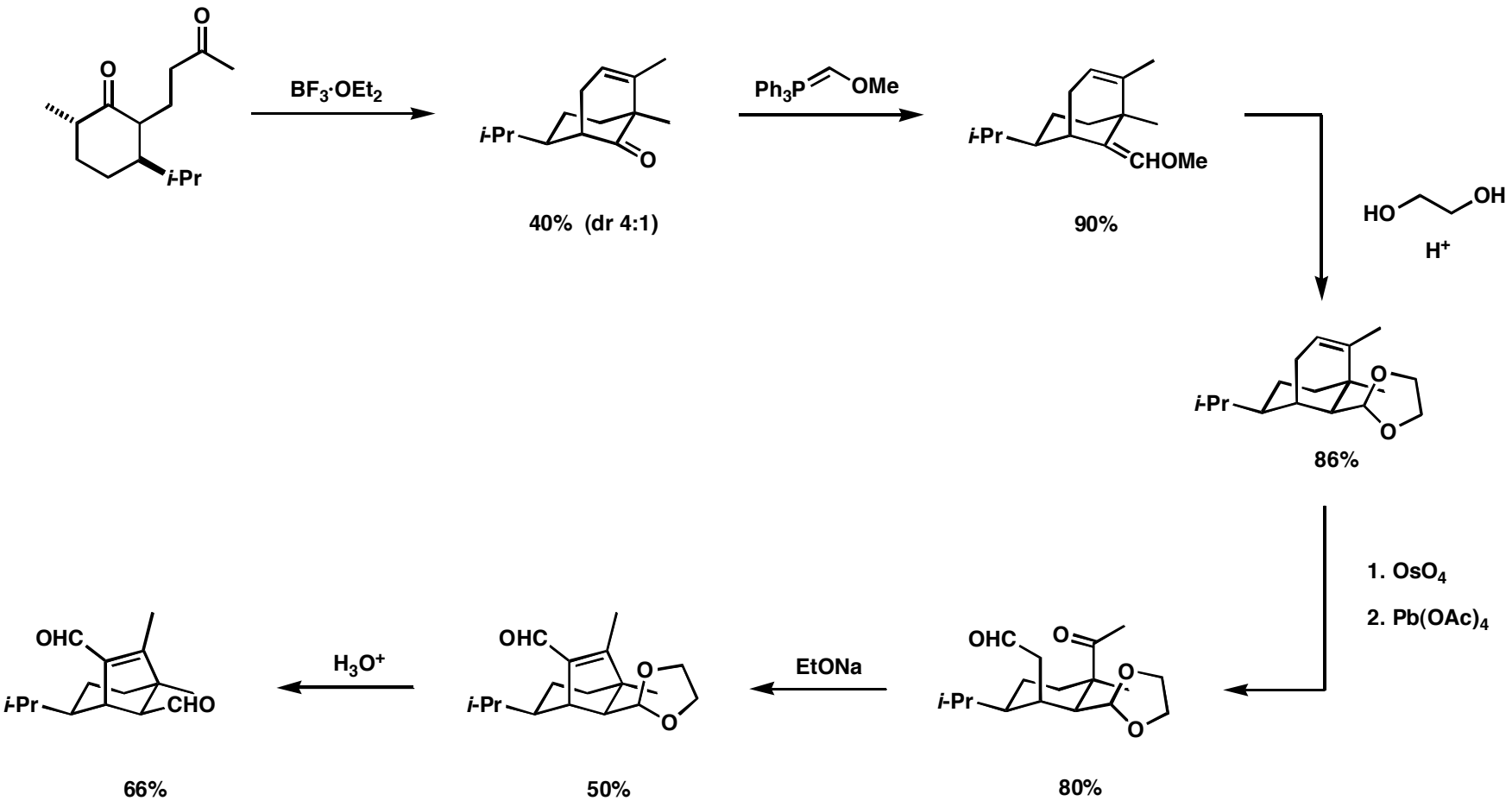
Helminthosporal

JACS **1965**, 5728

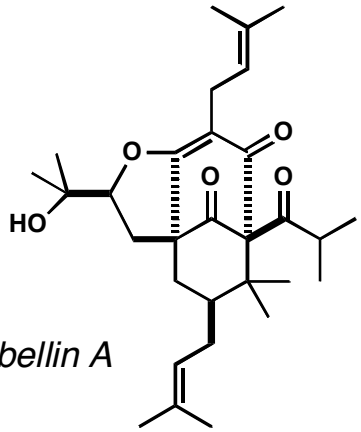


Attention:
this 1,5-difunctional relationship can evolve through two different pathways

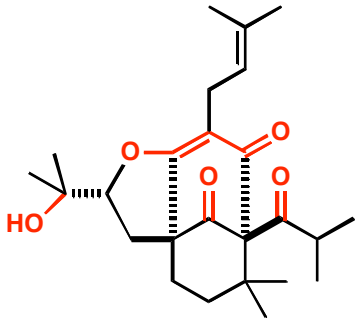



O
O
i-Pr
BF3·OEt2
i-Pr
O
40% (dr 4:1)
Ph3P
OMe
i-Pr
CHOMe
90%
HO
OH
H+
i-Pr
O
O
86%
1. OsO4
2. Pb(OAc)4
OHC
O
i-Pr
O
O
80%
EtONa
OHC
i-Pr
O
O
50%
H3O+
OHC
i-Pr
CHO
66%

A polifunctional target: 18-epi-tricyclic core of garsubellin A by Shibasaki



Garsubellin A



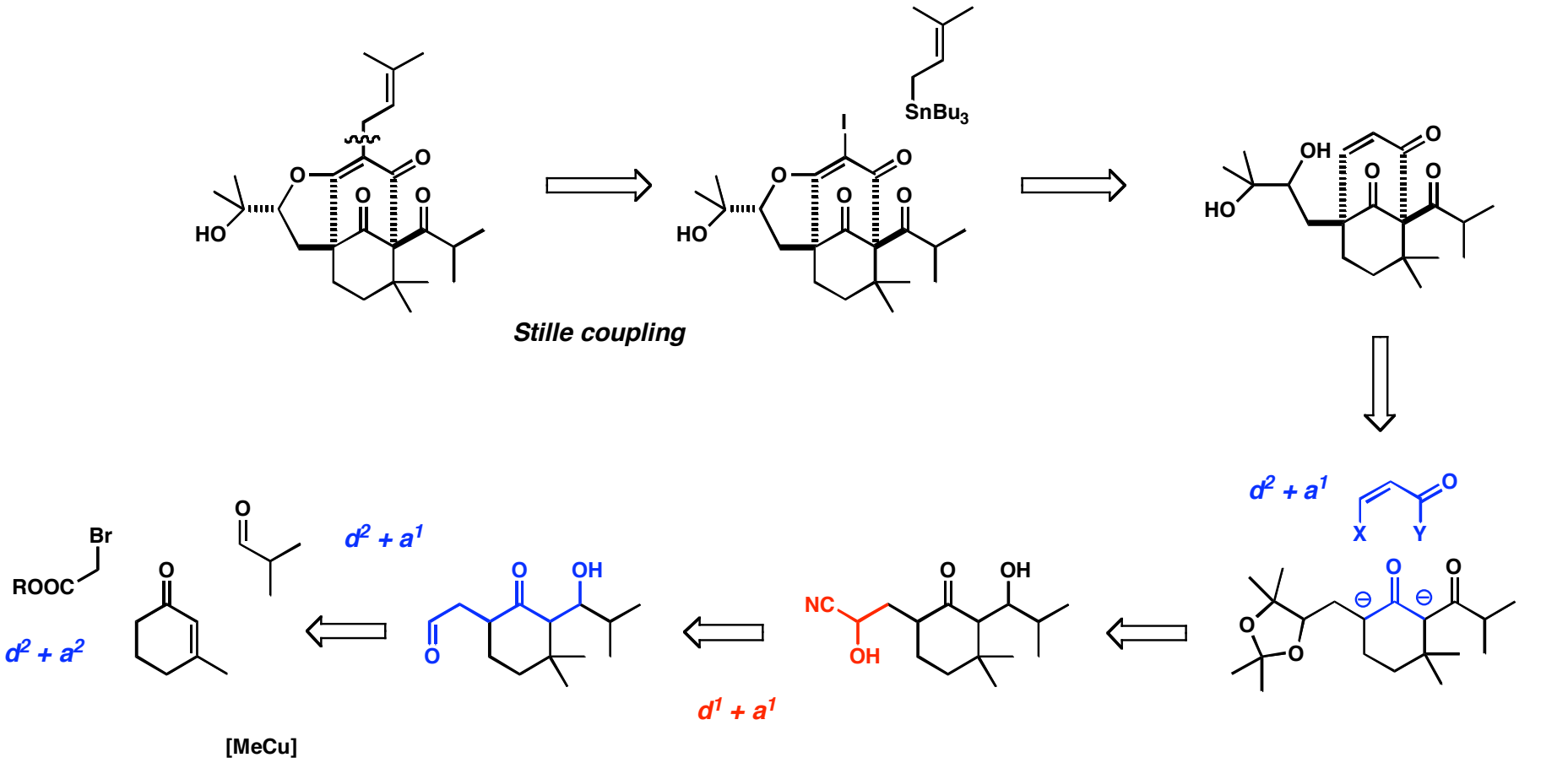
Model of Garsubellin A

OL **2002**, 859

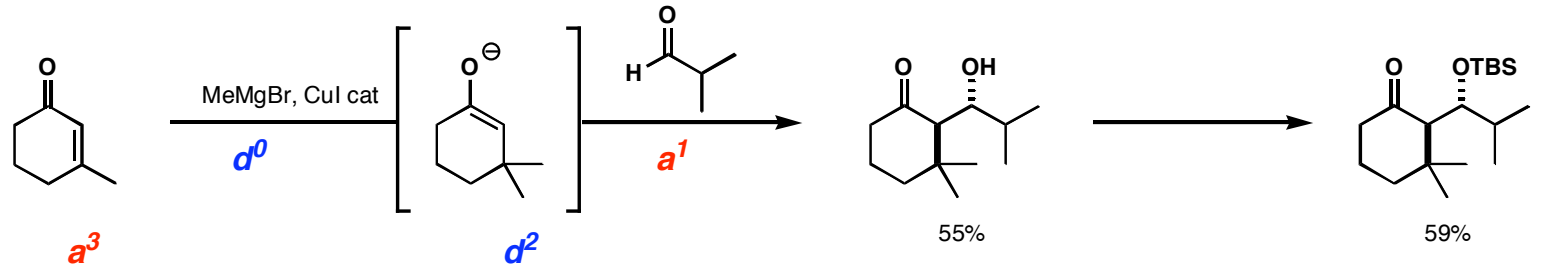
Six FG: 15 possible FG's pairs

1,3-difunctional relationships

play a crucial role

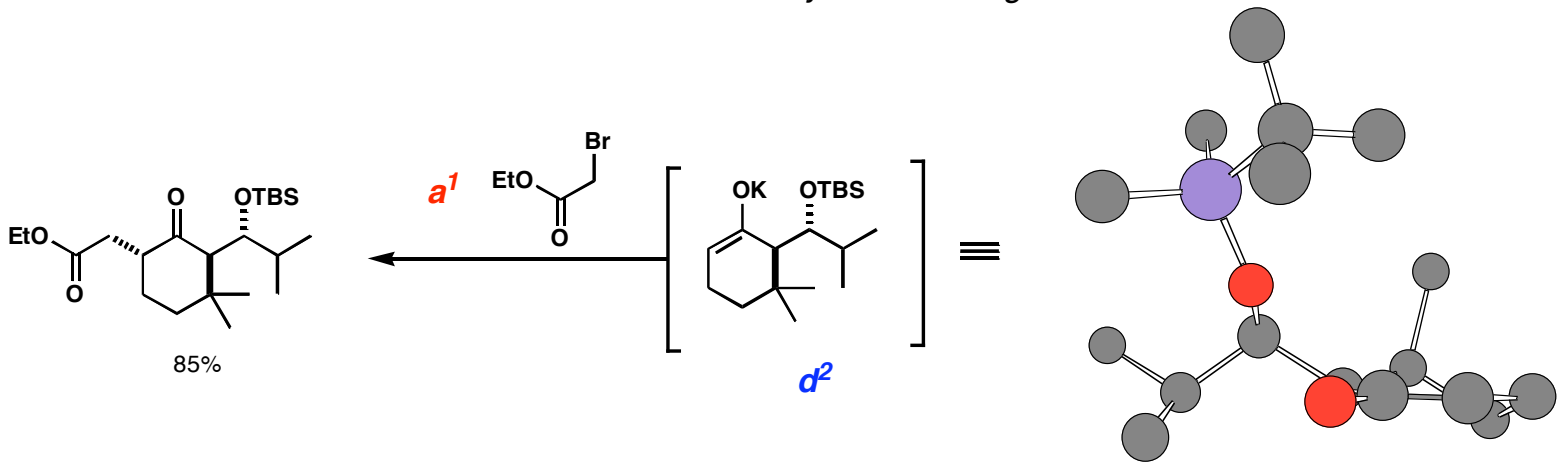

HO
O
O
O
O
I
SnBu3
Stille coupling
OH
d2 + a1
X
Y
NC
OH
d1 + a1
Br
ROOC
d2 + a2
[MeCu]

Strategy leads the way, but tactics accounts for the success

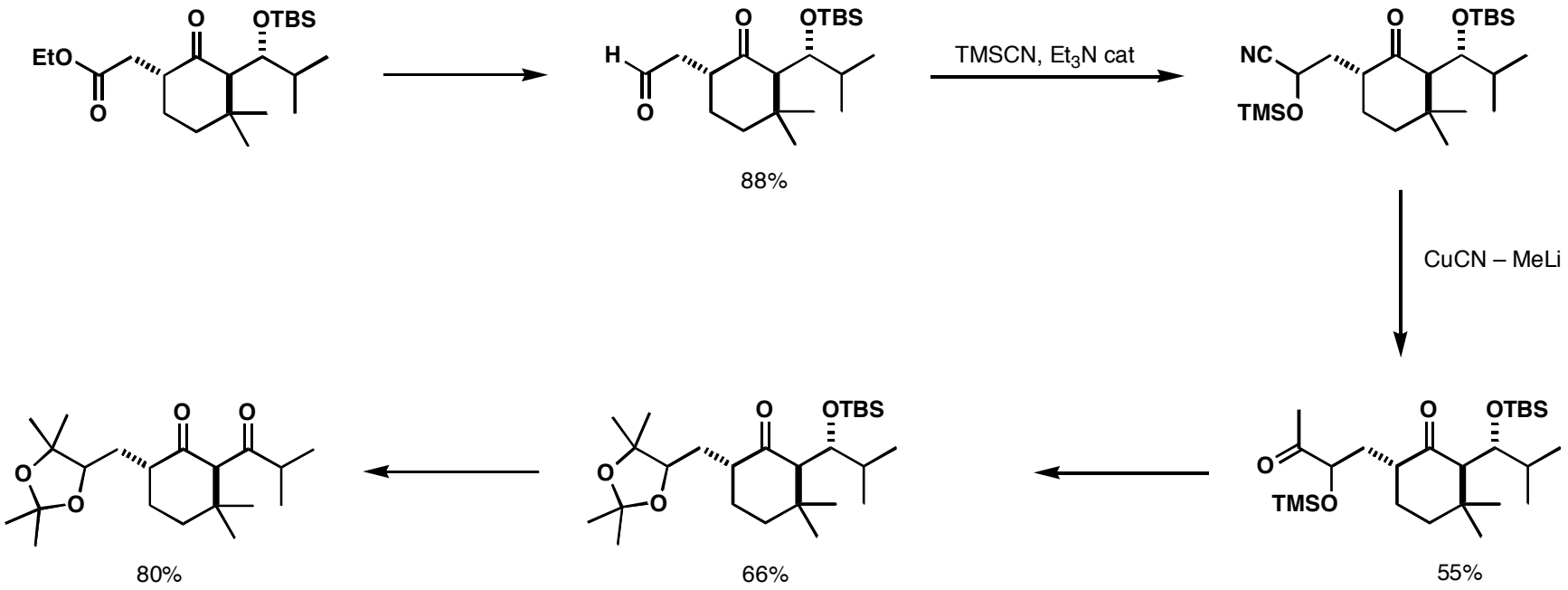


Kinetic trap of the resulting enolate avoids regioselective problems

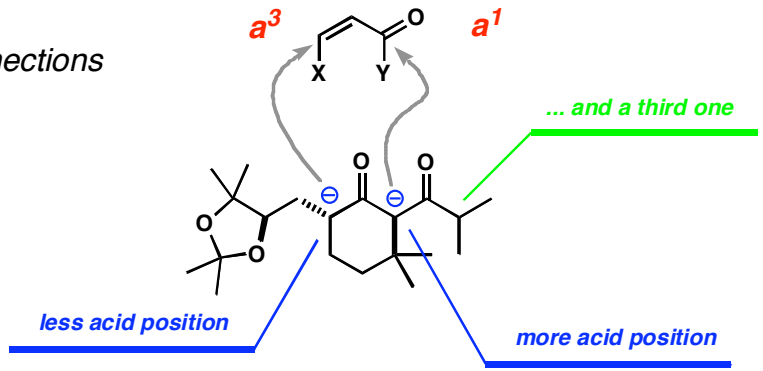
Now, this issue arises, ... but kinetic enolate is easily formed using KHMDS

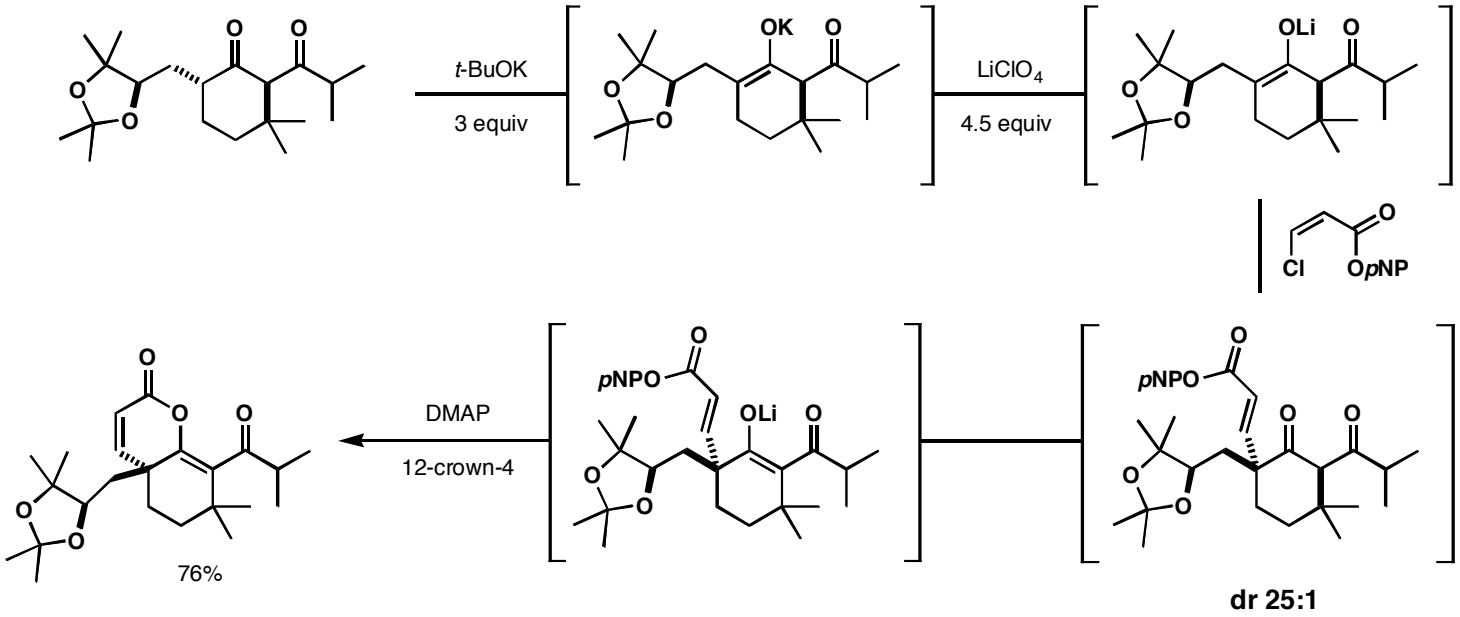


Functional group manipulation ....

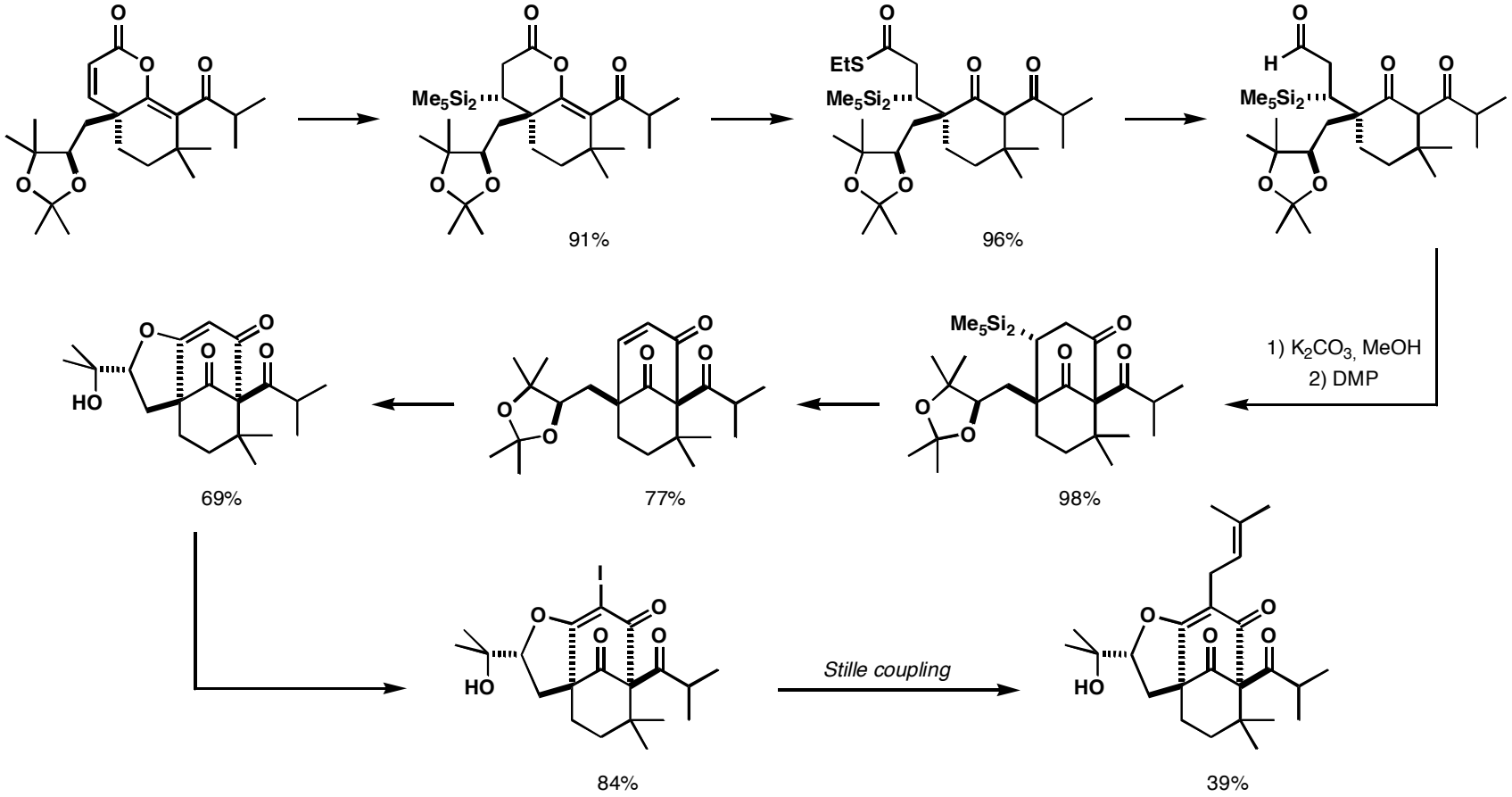


Retrosynthetic strategy is based on the following disconnections



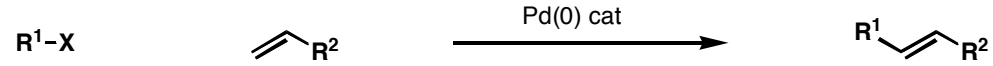


Getting the right connectivity goes through a long way ....



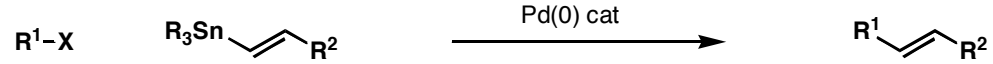
At this point, it is worth mentioning some useful C–C forming reactions

Heck reaction



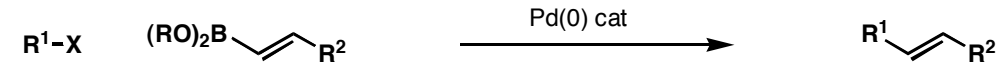
R^1: no β–H
X : halogen

Stille reaction



R^1: no β–H
X : halogen, OTf

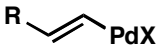
Suzuki reaction



R^1: no β–H
X : halogen, OTf

Fuhrhop & Li identifies the intermediate shown below as an ***a^1*** *synthon*

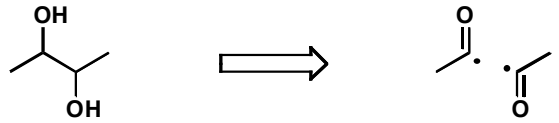
R^1–Pd–X *i.e.*



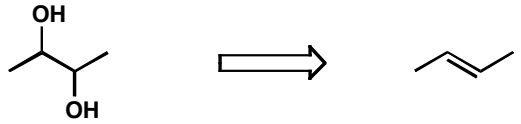
What should be the analysis in the case of dissonant relationships?

It should be considered the opportunity of ...

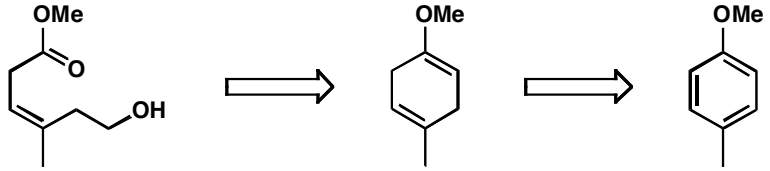
☞ *... radical desconnections*



☞ *... redox-based processes*



☞ *... reconnecting rings*



☞ *... altering the reactivity:* ***umpolung*** *or reversible reactivity inversion*

Seebach, D. *ACIEE* **1979**, 239

See also, Johnson, J. S. *ACIE* **2004**, 1326.

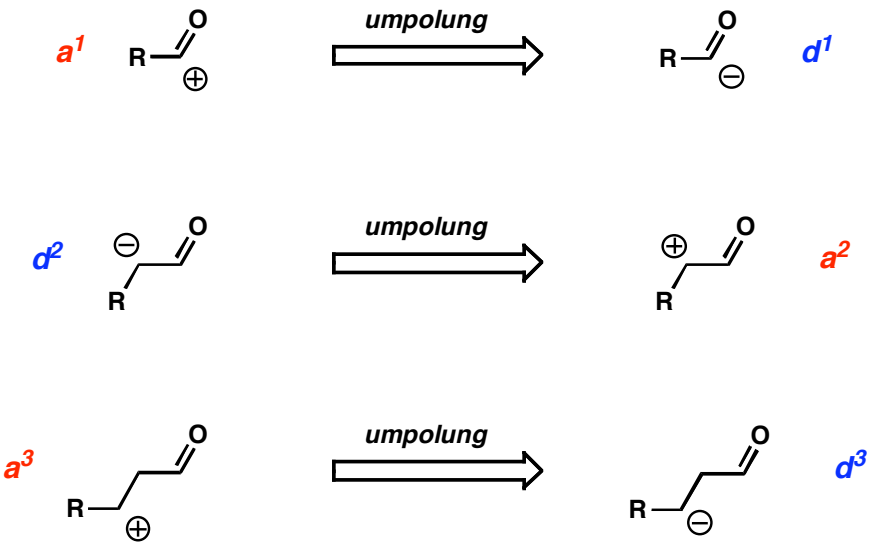
In a retrosynthetic sense,

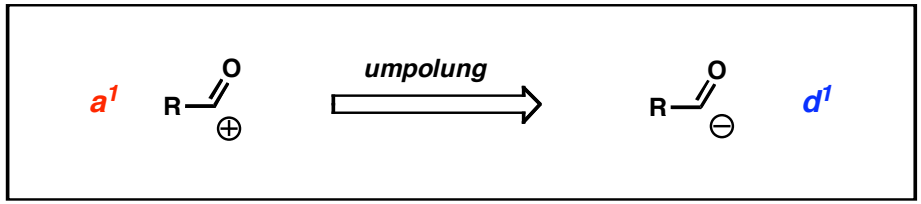
if a desconnection is identified as strategic but is not permitted by the particular core functional group present,

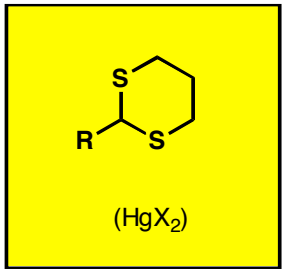
the replacement of that group by an equivalent which allows or actuates becomes a subgoal objective.

*Obviously, such an operation requires a synthetic step that permits to invert (**umpolung**) the type of synthon,*

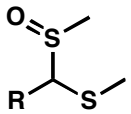
from acceptor to donor or from donor to acceptor



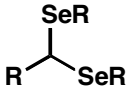




(HgX_2)



(H_3O^+)



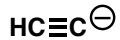
(CuX_2)

(*t*-BuLi)

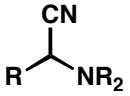
(H_3O^+)

(BuLi or LDA)

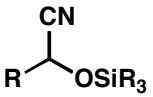
(Hg^{2+})



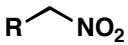
(TMSCN)



(H_3O^+ o Cu^{2+})

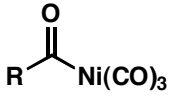


(H_3O^+)

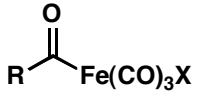


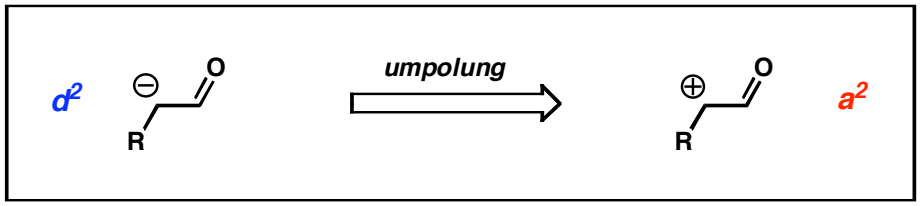
($TiCl_3$)

$Ni(CO)_4$ + RLi

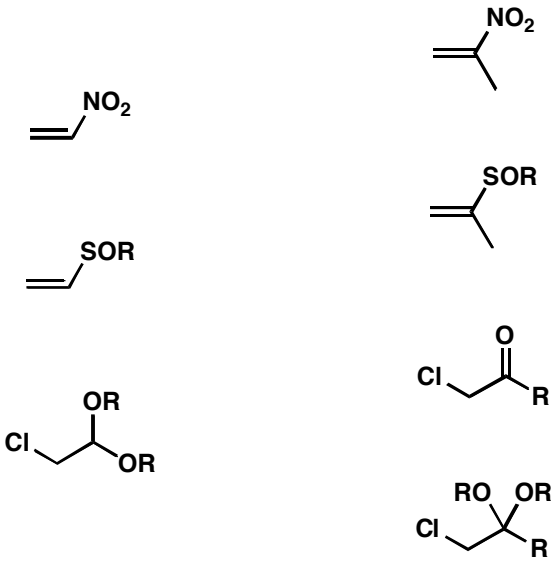


RCOX + $Fe(CO)_4^{2-}$

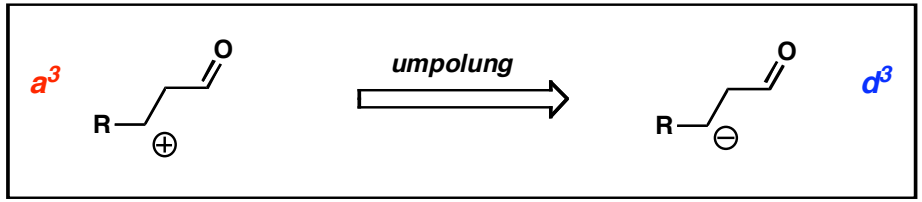




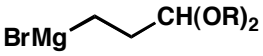
Formilmethyl *synthon*

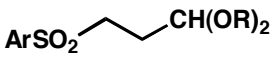


often undesired reactions

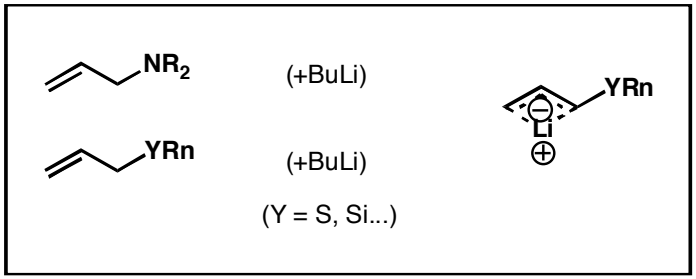


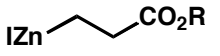
Formilethyl *synthon*

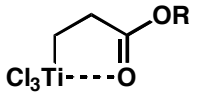




(+BuLi)

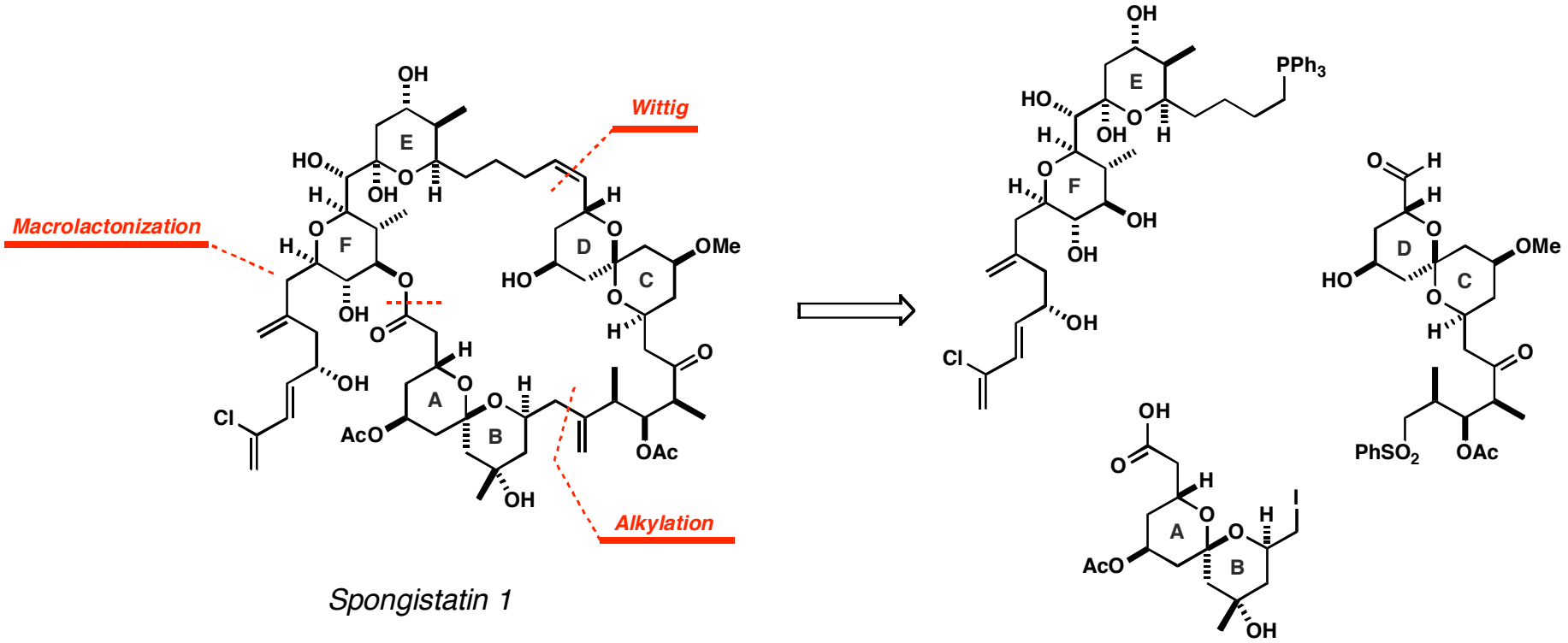






The Spongistatins: architecturally Complex Natural Products through umpolung concept

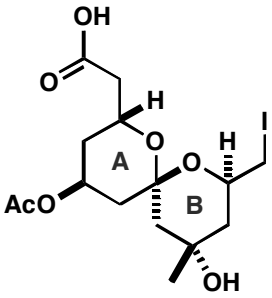
by A.B. Smith III

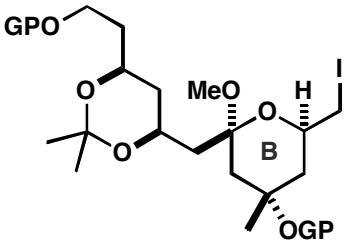


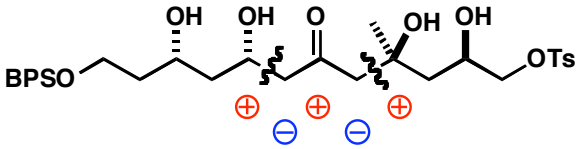
Spongistatin 1

ACIE **2001**, 191,195; *OL* **2002**, 783

Fragment A–B



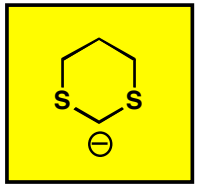


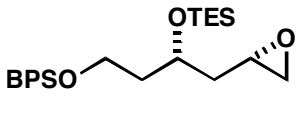


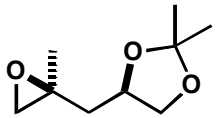
1,3-Consonant relationships

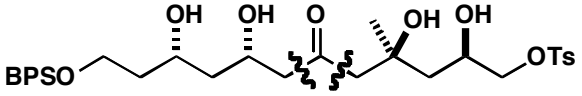
Aldol reaction could be the answer?

It could be, but it was envisioned another disconnection

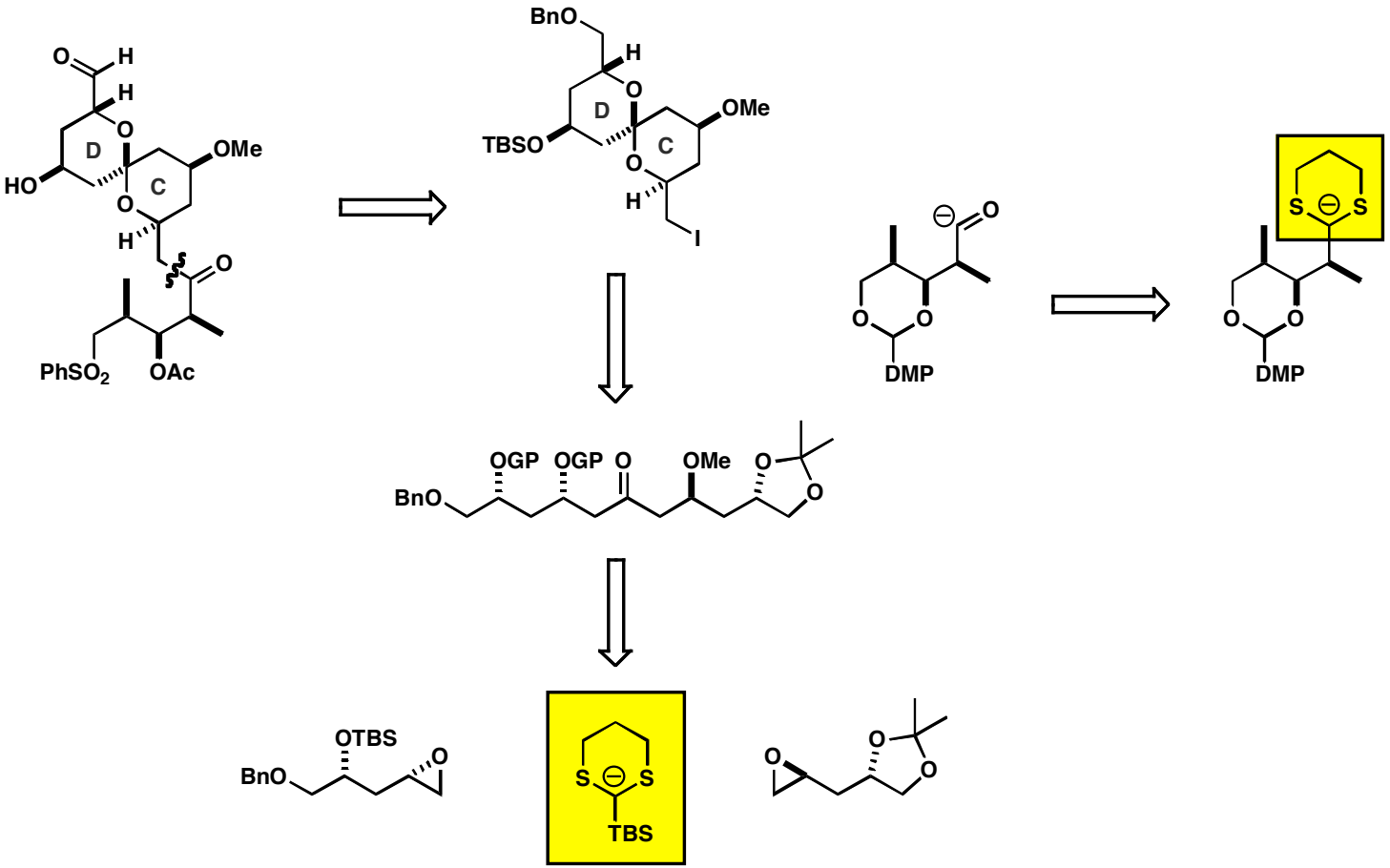




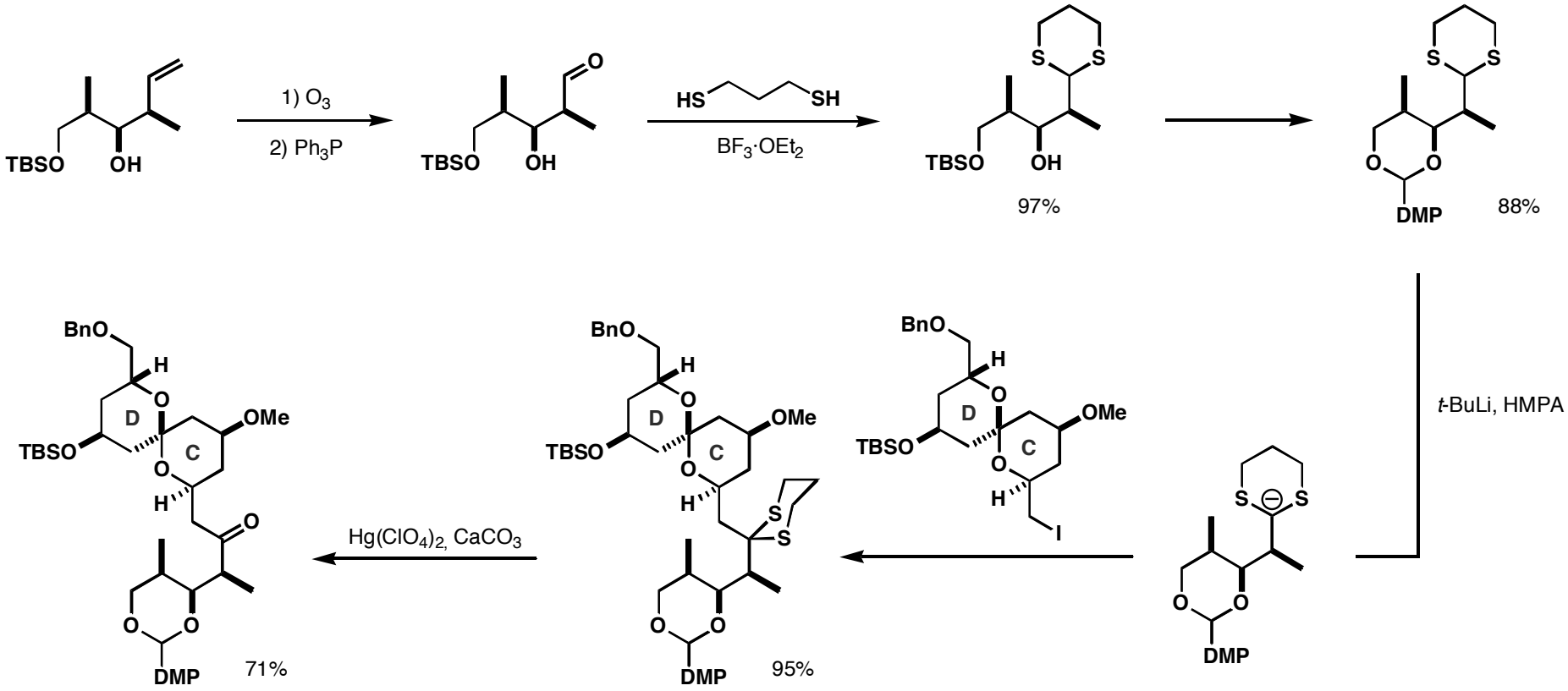




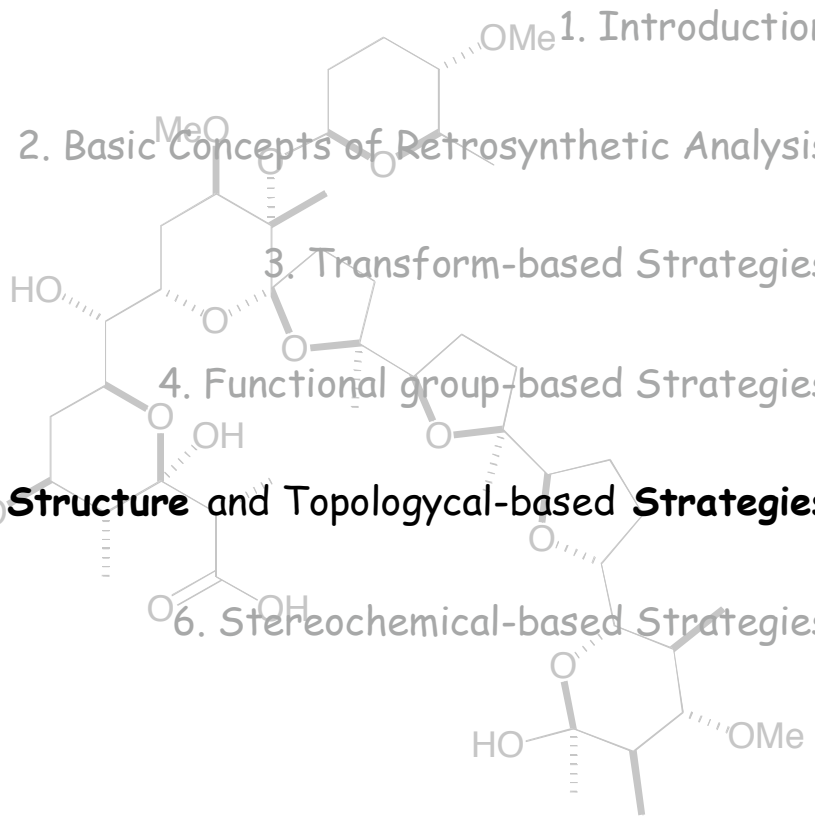
Fragment C–D


O
H
H
O
D
OMe
HO
C
O
H
O
PhSO2
OAc
BnO
H
O
D
OMe
TBSO
C
O
H
I
O
O
O
DMP
S
S
O
O
DMP
OGP
OGP
O
OMe
O
BnO
O
OTBS
BnO
O
S
S
TBS
O
O
O

Fragment C–D


1) O_3
2) Ph_3P
HS
SH
$BF_3{\cdot}OEt_2$
TBSO
OH
97%
DMP
88%
t-BuLi, HMPA
BnO
H
O
D
C
OMe
I
95%
$Hg(ClO_4)_2$, $CaCO_3$
71%

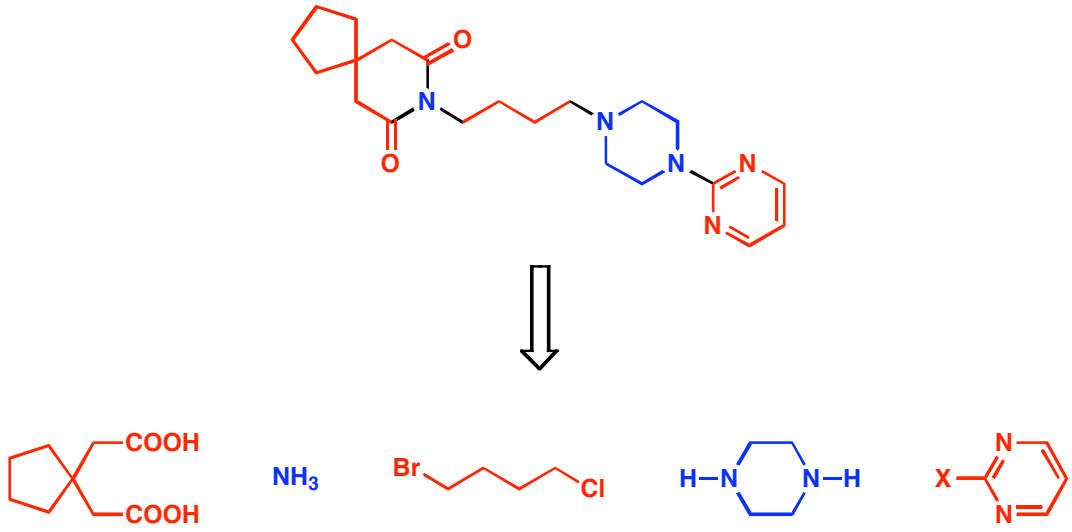
Part I



Structure-goal strategies

Structure-goal strategies are based on
the identification of a potential starting material, building block,
retron–containing element or initiating chiral element.
In other words, the retrosynthetic analysis is guided by the use of a particular structure corresponding to a potentially available starting material or synthetic intermediate.

In many synthetic problems the presence of a certain type of subunit in the target molecule coupled with information on the commercial availability of compounds containing that unit can suggest potential starting materials



building blocks

Chiron approach: synthesis of enantiomerically pure compounds

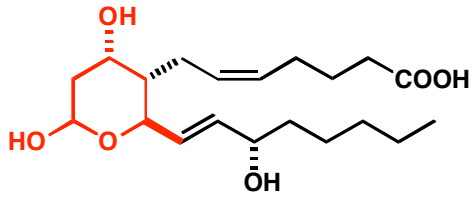
The chiron approach to synthesis involves disconnection of strategic bonds in a target molecule with minimum pertubation of existing stereogenic centers.
This generates chirons with a maximum overlap of functional groups, of stereochemical features, and of carbon framework with the target molecule (or a given substructure).
Such molecules normally contain one to five or six stereogenic centers and can originate from Nature (terpenes, carbohydrates, α-amino acids, α-hydroxy acids,...),
from asymmetric reactions on achiral substrates, from resolution of racemates,
and from enzymatic and related sources.
By relating a TGT to chiral starting materials as the outset, the scenario for a synthesis plan is established.
In the chiron approach,
***it is the type of chiral substructure present in the molecules that will dictate the strategy**.*
The main issue now deal with proceeding in the forward direction using the inherent or newly-created chirality and building from there.

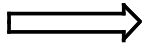
Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*
Pure & Appl. Chem. **1993**, 1189

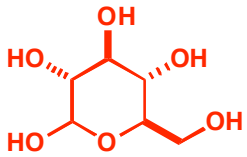
Sugars

carbon framework	asymmetric centres	sense of chirality	sequential functionality
acyclic	**1–5 (or 6)**	**2^n permutations**	**α-hydroxy aldehyde, ...**
cyclic	**(includes anomeric center)**	**generally D**	**α-amino aldehyde, ...**
combination			**polyols, amino alcohols, ...**
3–7 carbon atoms			

Thromboxane B_2

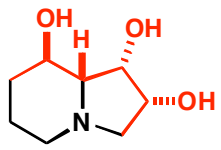


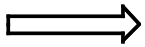


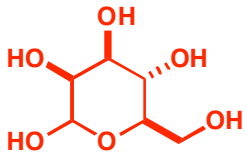


D-Glucose

Swainsonine

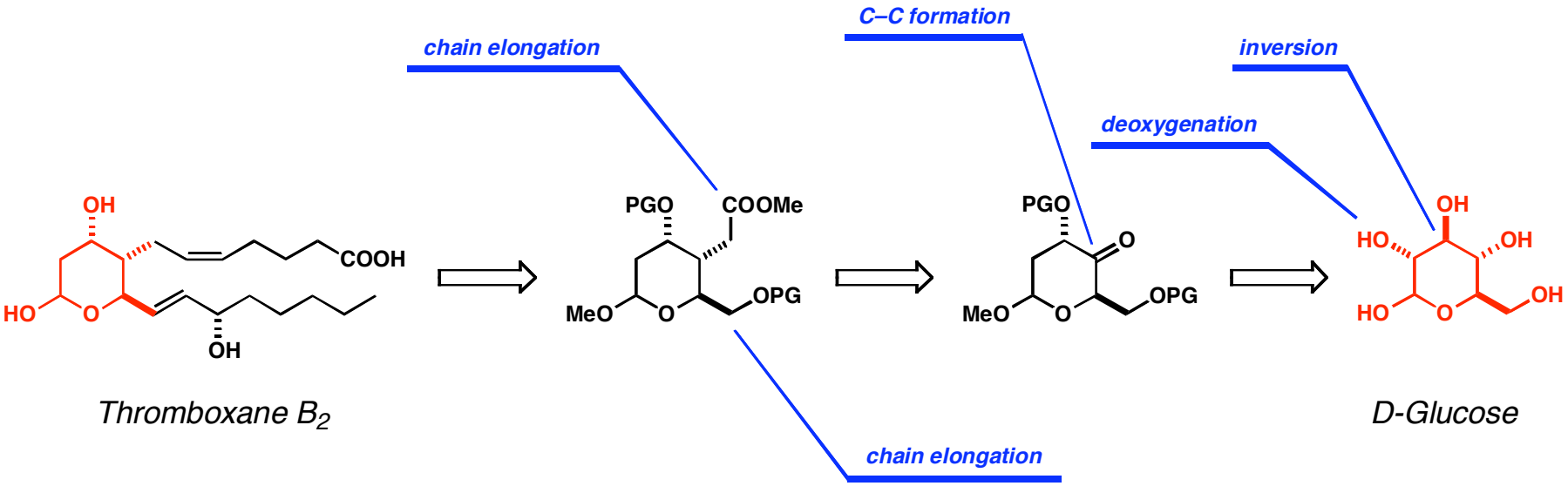






D-Manose

The power of sugars: thromboxane B_2 by Hanessian

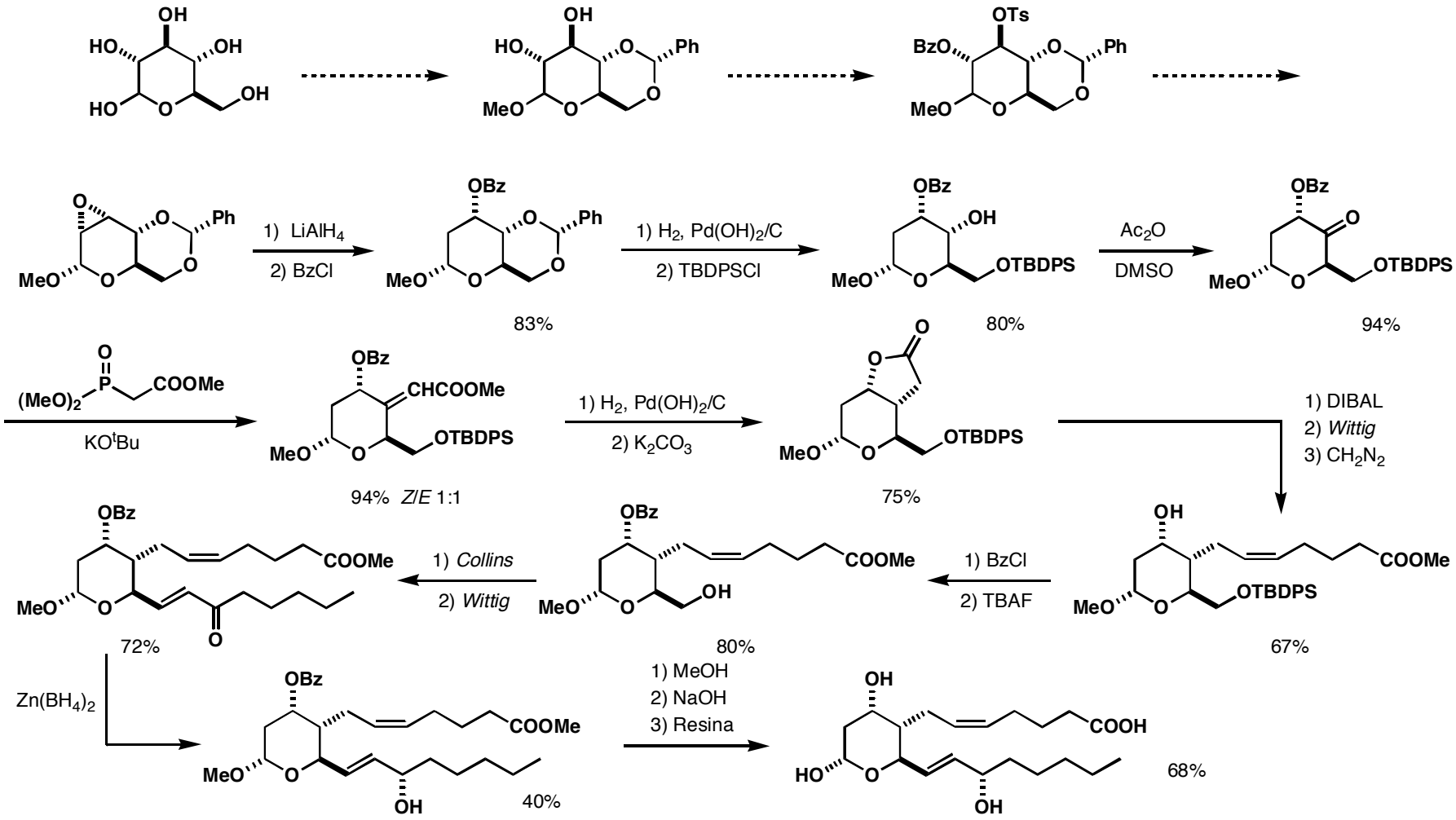


Thromboxane B_2

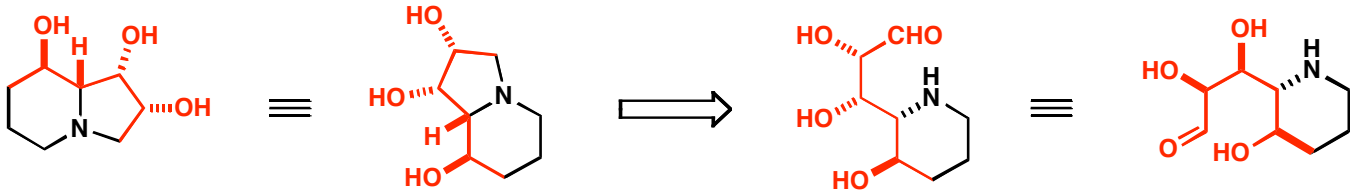
D-Glucose

Can. J. Chem. **1977**, 562

Can. J. Chem. **1981**, 870

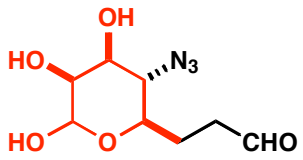

1) LiAlH4
2) BzCl
83%
1) H2, Pd(OH)2/C
2) TBDPSCl
80%
Ac2O
DMSO
94%
(MeO)2
COOMe
KOtBu
94% Z/E 1:1
1) H2, Pd(OH)2/C
2) K2CO3
75%
1) DIBAL
2) Wittig
3) CH2N2
67%
1) BzCl
2) TBAF
80%
1) Collins
2) Wittig
72%
Zn(BH4)2
40%
1) MeOH
2) NaOH
3) Resina
68%

Swainsonine by Fleet

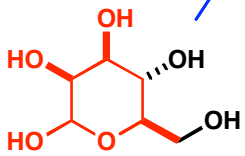


Swainsonine

Tetrahedron Lett. **1984**, 1853

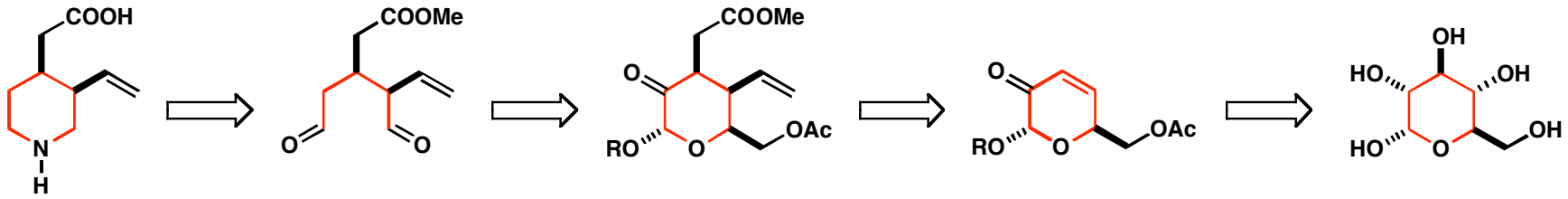


Attention:
two inversions are required



D-Mannose

(+)-Meroquinone by Hanessian



(+)-Meriquenone *D-Glucose*

Tetrahedron **1990**, 231

It is evident that

all the hydroxyl groups in D-glucose must be destroyed en route to the construction of the carbon skeleton

of (+)-meroquinone, which can be regarded as a stereochemically wasteful procedure.

However, the D-glucose framework is efficiently used to install the two vicinal C-substituents by

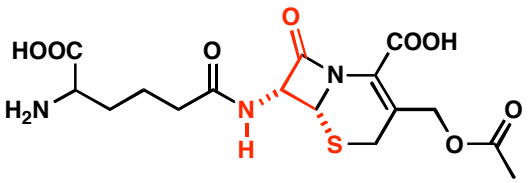
a sequential stereocontrolled one-step conjugate addition and enolate trapping protocol on a readily available enone

Pure & Appl. Chem. **1993**, 1189

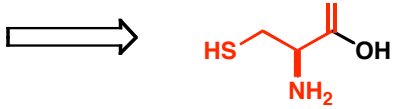
Amino acids, hydroxy acids, terpenes

	carbon framework	*asymmetric centres*	*sense of chirality*	*sequential functionality*
Amino acids	acyclic (except proline) 3–6 carbon atoms	1 or 2	generally L	α-amino acid α-amino or β-substituted acid
Hydroxy acids	acyclic 3–4 carbon atoms	1 or 2	*R* or *S* combinations	α-hydroxy acid α,β-dihydroxy acid
Terpenes	acyclic cyclic	generally 1 or 2	*R* or *S*	enone α-substituted ketone

Amino acids

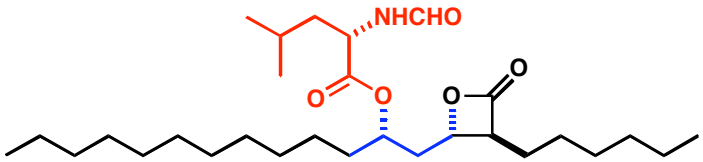


Cephalosporin C

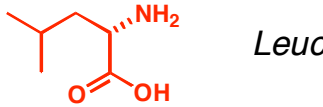


Cysteine

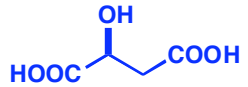
Hydroxy acids



Tetrahydrolipstatin



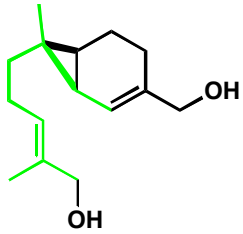
Leucine

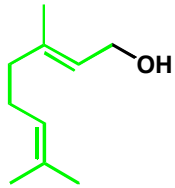


L-Malic acid

Terpenes

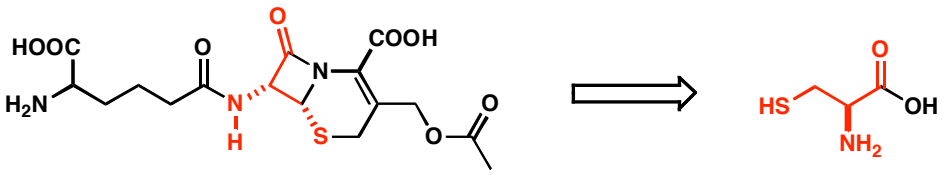
dl-Sirenin





Geraniol

A brilliant performance: cephalosporin C by Woodward



Cephalosporin C

Cysteine

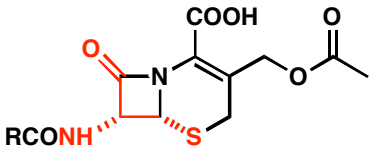
JACS **1966**, 852

Often in the course of synthetic work one or two key ideas set the style, development, and outcome of the investigation, while providing the flexibility essential for any long journey through unknown territory, beset with perils which at best can be only dimly foreseen.

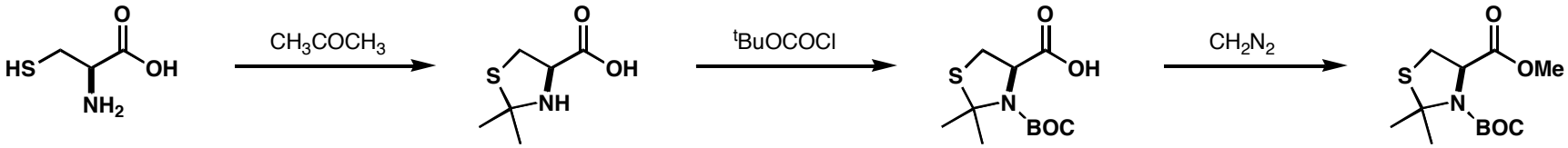
In planning our synthesis of cephalosporin the first of these definitive concepts was our choice of L(+)-cysteine as our starting material. This readily available substance possesses a two carbon backbone in which are attached a carboxyl group, an α nitrogen atom and a β sulfur atom

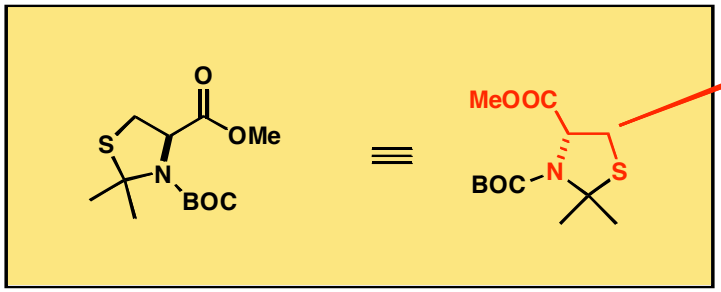
– in short, it presents in ready-made fashion a large portion of the crucial substituted β-lactam moiety of the cephalosporin.

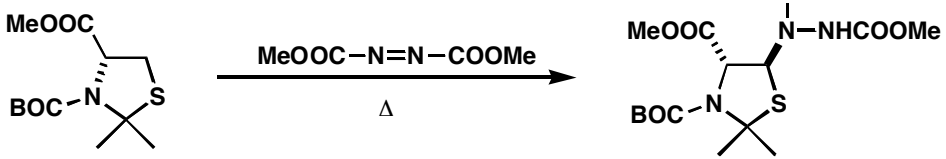
Nobel Lecture, 1965

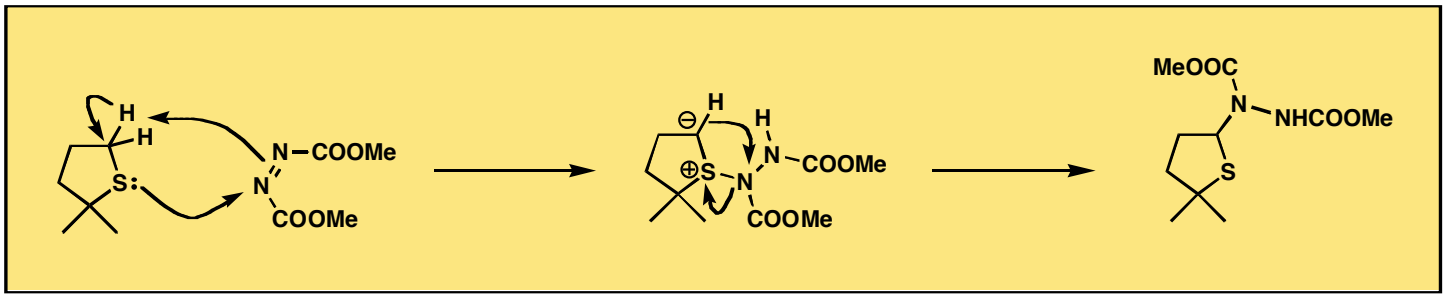


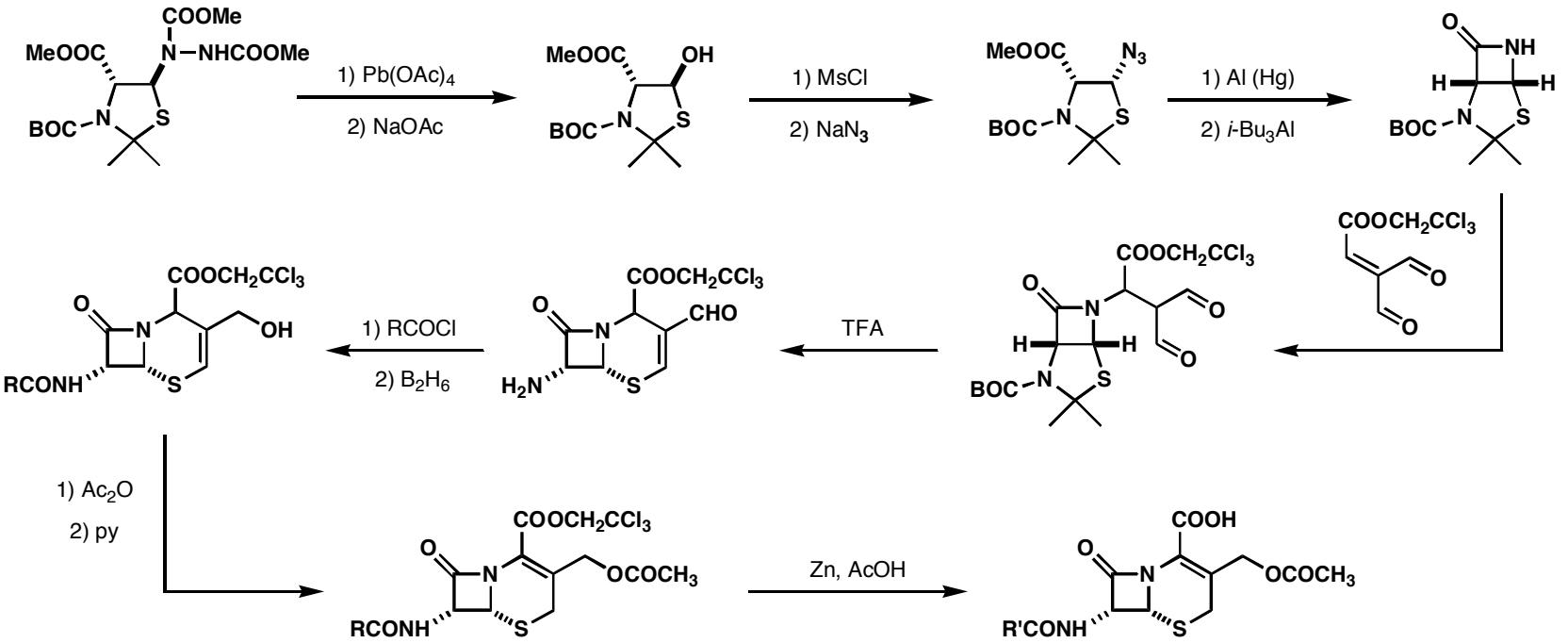
Cephalosporin C



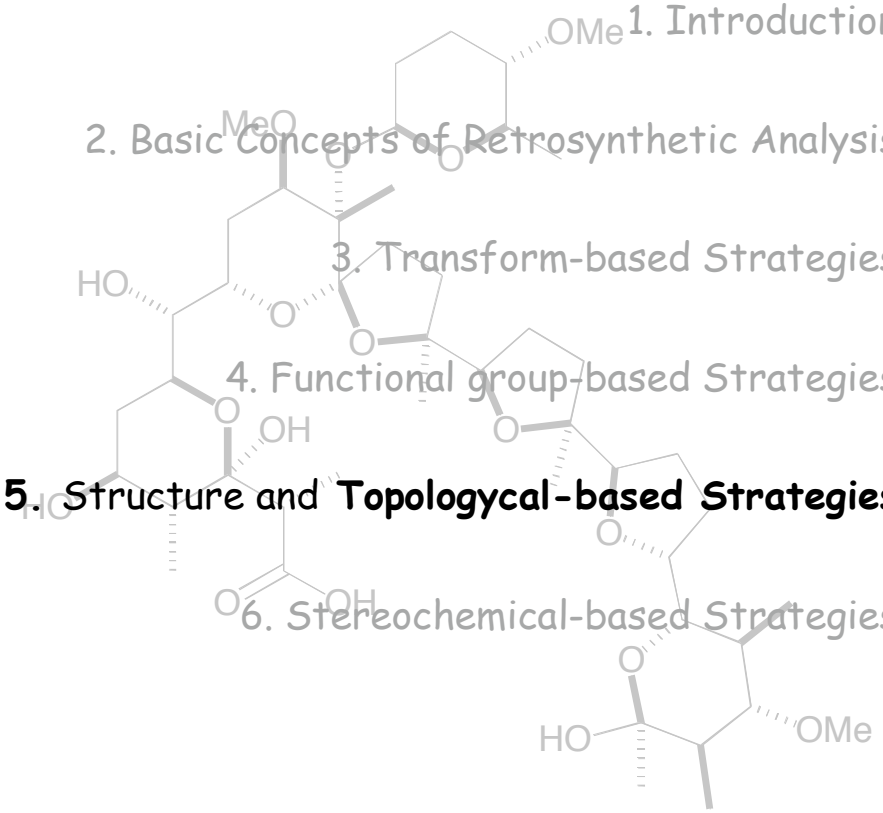





H
H
S
N–COOMe
N
COOMe
H
H
S
N
N–COOMe
COOMe
MeOOC
N
NHCOOMe
S


COOMe
MeOOC
N–NHCOOMe
BOC
N
S
1) Pb(OAc)4
2) NaOAc
MeOOC
OH
BOC
N
S
1) MsCl
2) NaN3
MeOOC
N3
BOC
N
S
1) Al (Hg)
2) i-Bu3Al
O
NH
H
H
BOC
N
S
COOCH2CCl3
O
O
O
COOCH2CCl3
O
N
O
H
H
O
BOC
N
S
TFA
COOCH2CCl3
O
N
CHO
H2N
S
1) RCOCl
2) B2H6
COOCH2CCl3
O
N
OH
RCONH
S
1) Ac2O
2) py
COOCH2CCl3
O
N
OCOCH3
RCONH
S
Zn, AcOH
COOH
O
N
OCOCH3
R'CONH
S

Part I



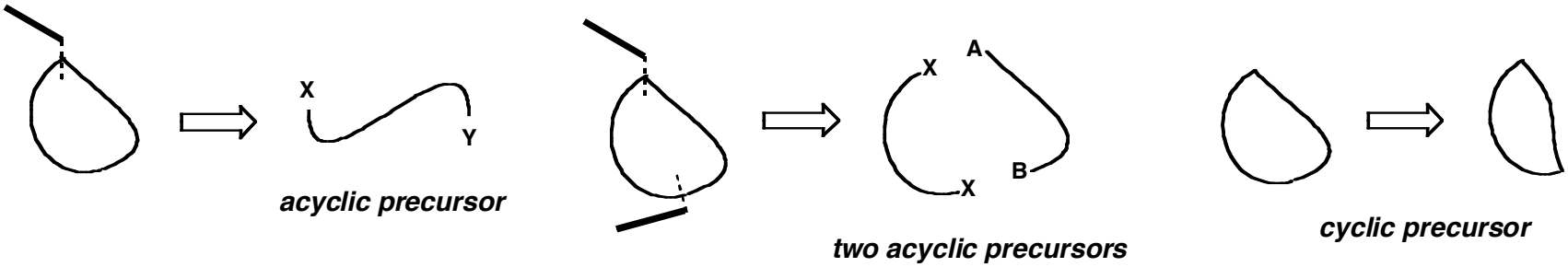
Topological-based strategies

The existence of alternative bond paths through a molecular skeleton as a consequence
of the presence of cyclic subunits gives rise to a topological complexity
which is proportional to the degree of internal connectivity.
Then, topological strategies are based on
the use of a particular bond, pair of bonds, set of bonds, or subunit as eligible for disconnection
to guide retrosynthetic analysis.
Conversely, the designation of bonds or cyclic subunits as ineligible for disconnection

The disconnection of a ***strategic bond*** *simplifies the topological complexity of a TGT*

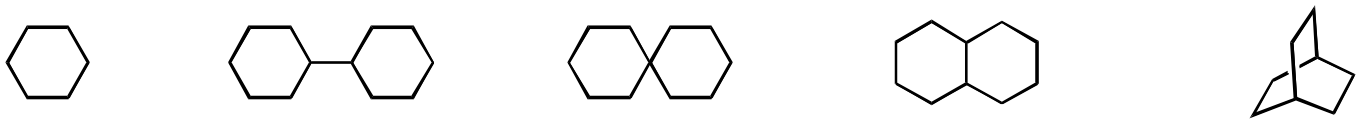
Guidelines

- *It is not worth disconnecting aromatic or heteroaromatic systems.*
- *Cycloalkyl subunits bound to the carbon skeleton should not be disconnected*
- *Several options should be considered.*



acyclic precursor ***two acyclic precursors*** ***cyclic precursor***

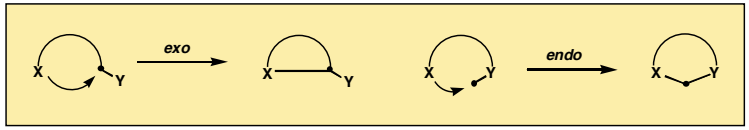
- *The kind of cyclic system has to be considered*

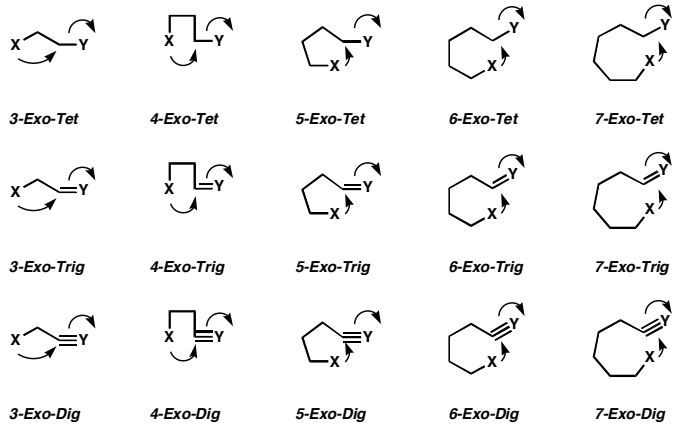


Isolated ***Directly joined*** ***Spiro system*** ***Fused system*** ***Bridged system***

Isolated rings

*The **Baldwin rules** often constitute a good starting point to analyze the synthetic possibilities un bon punt de partida .*



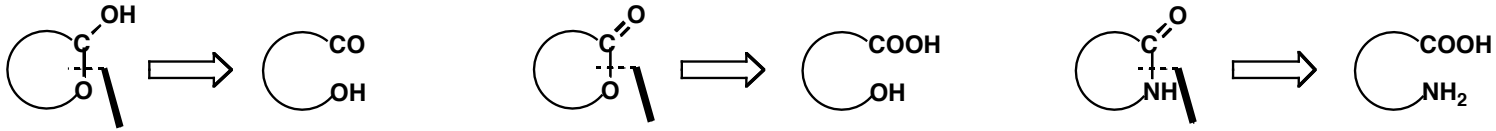


Rule 1. Tet	**Rule 2. Trig**	**Rule 2. Dig**
a) 3,4,5,6,7-Exo allowed	*a) 3,4,5,6,7- Exo allowed*	*a) 3-4- Exo forbidden*
b) 5 i 6-Endo forbidden	*b) 3,4,5-Endo forbidden*	*b) 5,6,7-Exo allowed*
	c) 6,7-Endo allowed	*c) 3,4,5,6,7-Endo allowed*

Baldwin, J. *JCS Chem. Commun.* **1976**, 734

Isolated rings

If any heteroatom, X, is a member of the ring, C–X bonds are often strategic

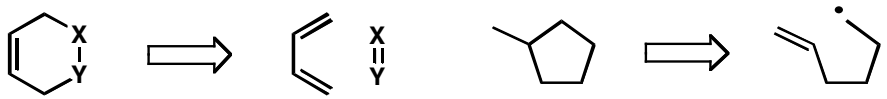


The success of such disconnections is highly dependent on the size of the ring

It is possible that several retrons are easily identified in a cyclic TGT.

Some of them are highly appealing

Diels-Alder (hetero Diels-Alder)

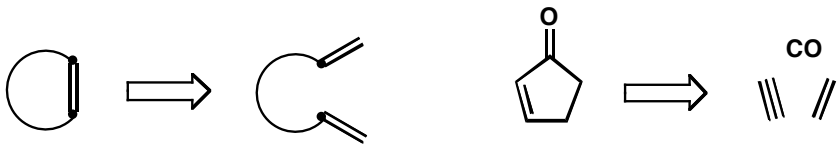


Radicals

Metathesis

Cannon & Blechert.

ACIE **2003**, 1900



Pauson-Khand

Gibson&Stevenazzi

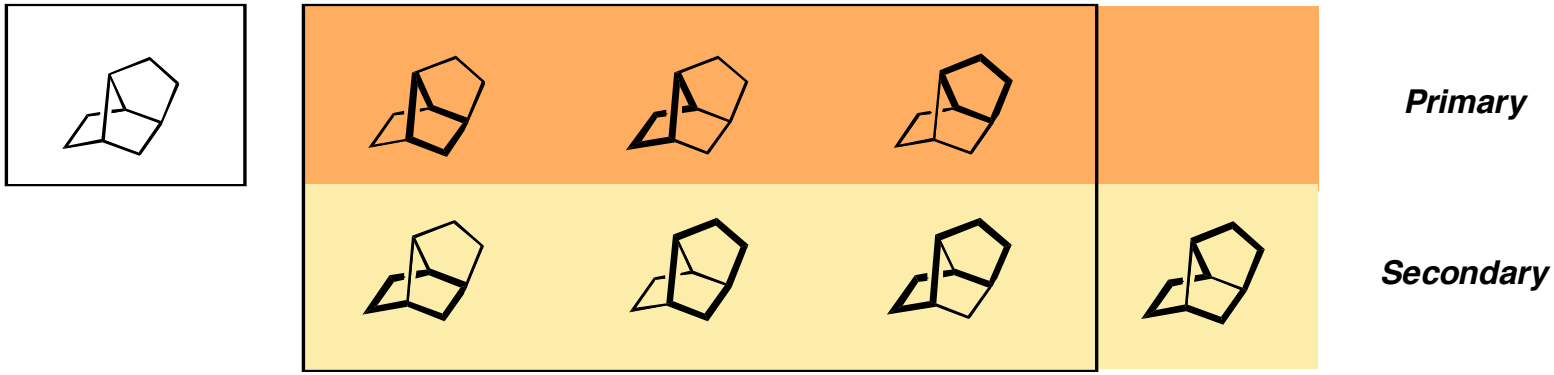
ACIE **2003**, 1800

Fused and Bridged systems

Primary rings *are those that can not be constructed by the sum of two or more smaller rings*

Secondary rings *are those that are not primary rings*

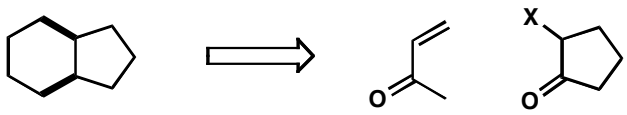
Synthetically significant rings *are 3-7 membered primary or secondary rings*



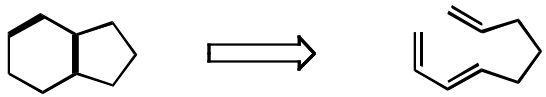
Bonds can also be classified depending on the cyclic system

Topological criteria for the disconnection of fused rings

1. Cleavage of two cocyclic bonds which are exendo to a fusion bond, especially bonds involving heteroatoms



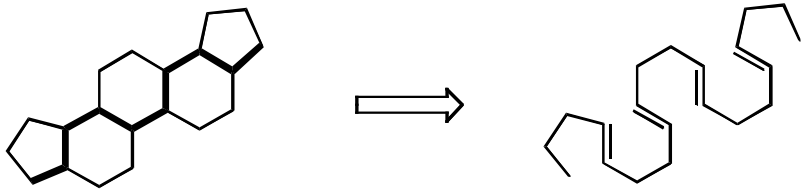
2. The disconnection of a cocylic pair may be strategic is there is a cycloaddition transform potentially aplicable to that pair. Such bond-pair disconnection generally involve a fusion bond



3. All possible [2+1] and [2+2] disconnections of fused 3- and 4-membered rings are strategic

4. Fusion bonds are no no candidates for strategic one-bond disconnection if it produces a ring > 7 members

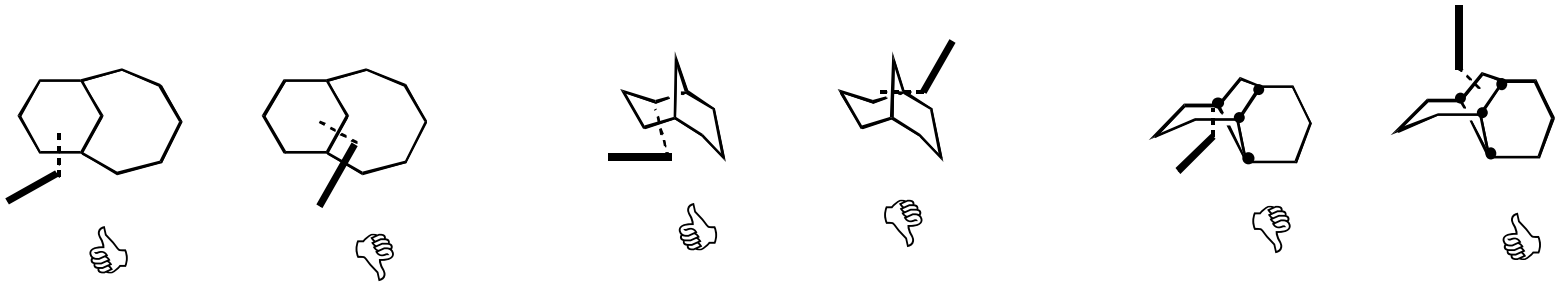
5. Fused ring structures with sequences of contigous exendo and fusion bonds in alternation may be strategic for disconnection



Topological criteria for the disconnection of bridged rings

1. A strategic bond must be exendo to a 4-7 primary ring and exo to a primary ring > 3.

2. A bond is not strategic if it is common to two bridged primary rings and its disconnection generates a > 7 new ring.



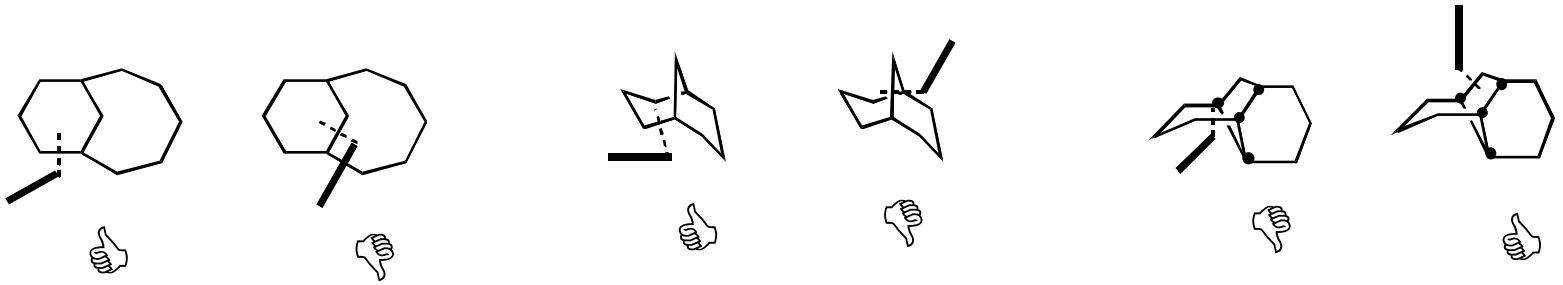
3.A strategic bond must be endo to a ring of maximum bridging. Within a bridged network, the ring of maximum bridging is usually that synthetically significant ring containing the greatest number of bridgehead atoms. Heterobonds involving O, N, and S do not necessarily follow this criterium.

4. The disconnection of a strategic bond can not generate an appendage bearing stereocenters

Topological criteria for the disconnection of bridged rings

1. A strategic bond must be exendo to a 4-7 primary ring and exo to a primary ring > 3.

2. A bond is not strategic if it is common to two bridged primary rings and its disconnection generates a > 7 new ring.



3.A strategic bond must be endo to a ring of maximum bridging. Within a bridged network, the ring of maximum bridging is usually that synthetically significant ring containing the greatest number of bridgehead atoms. Heterobonds involving O, N, and S do not necessarily follow this criterium.

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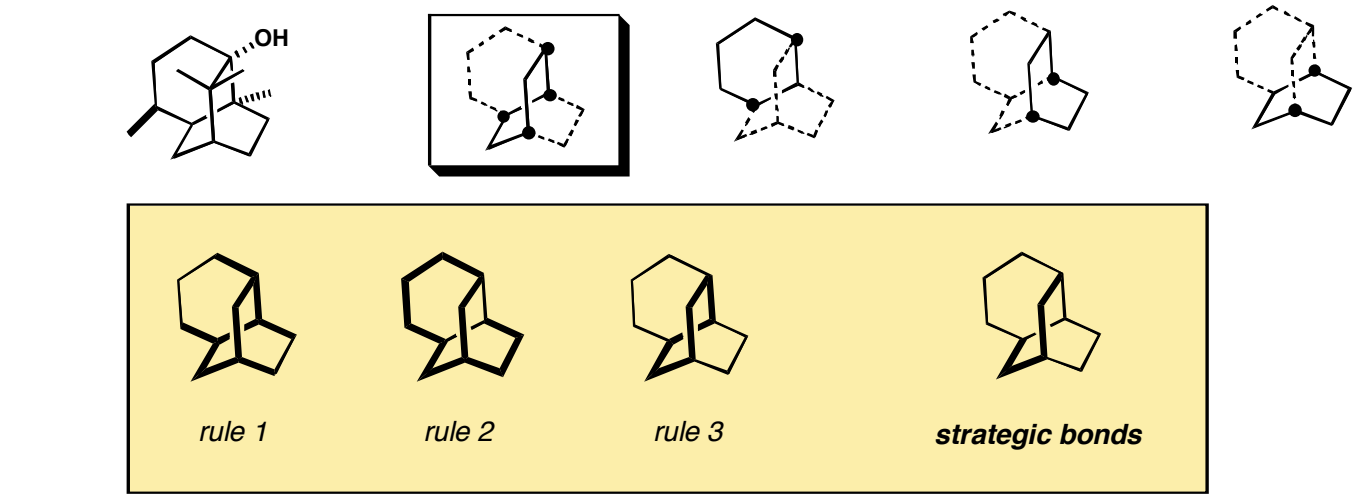
Patchouli alcohol

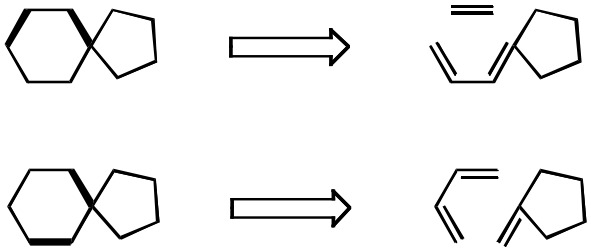


Serratosa, F. *Design of Organic Synthesis*

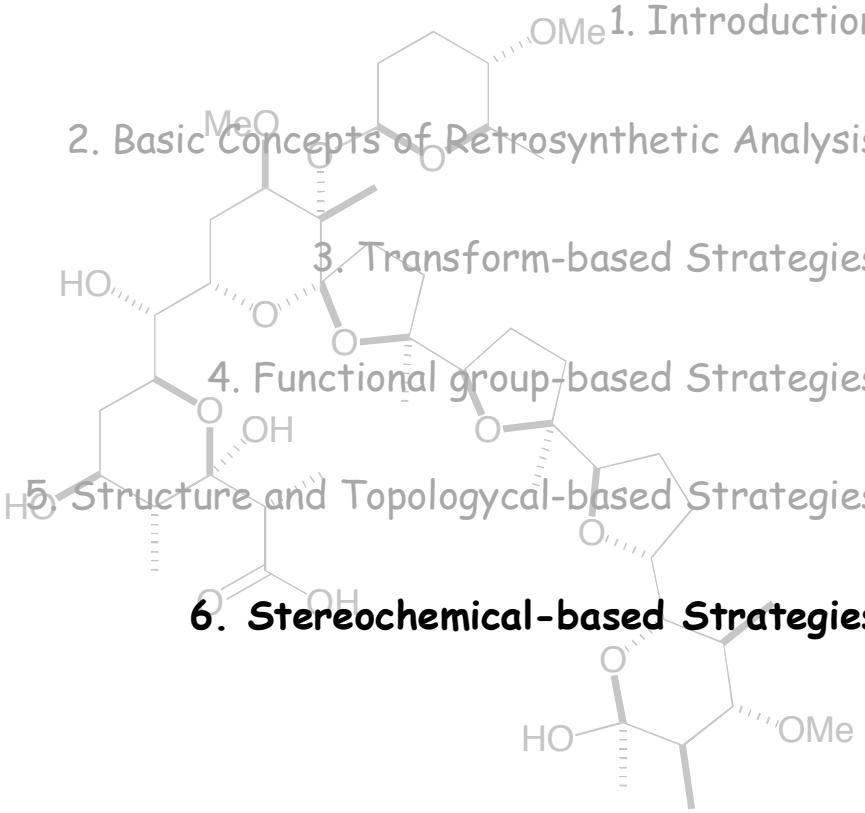
Topological criteria for the disconnection of spiro rings

1. Disconnection of exendo bonds

2. Disconnection of a pair of bonds: an exendo and a second one β in the same ring



Part I



Why should we consider stereochemistry?

For practical and aesthetic reasons, it is now common practice to plan synthesis in such a way so as to produce an enantiomerically pure (or enriched) TGT.
This has become a virtual necessity in pharmaceuthical research laboratories since stereochemistry is the common denominator between chemistry and biology.

Hanessian, S. *Pure & Appl. Chem.* **1993**, 1189

... About 80% of the active compounds that pharmaceutical companies have in the pipeline are chiral, and it is estimated that this fraction will increase, as the development of active compounds continues to be improved ...
The authorities responsible for the registration of new active compounds increasingly demand the targeted synthesis of one stereoisomer...
Enantiomerically pure compounds are also being used increasingly in the agrochemicals industry.
The targeted synthesis of the active enantiomer can improve the economics of the process and lead to reduced quantities applied and thus to reduced environmental impact.

Hauer, B. *ACIE* **2004**, 788

Where is stereochemistry from?

There are basically three main strategies to adopt when the synthesis of an enantiomerically pure molecule is considered:

1) resolution of a racemic final compound or an intermediate

2) use of an enantiomerically pure starting material,
which can be obtained by resolution, an asymmetric process or by relying on the "chiral pool"

3) through an asymmetric synthesis

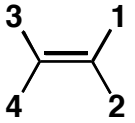
Stereochemical-based strategies

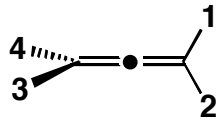
Stereochemical-based strategies consist on
the controlled removal of stereocenters and stereorelationships.
Such stereocontrol can arise from substrate-structure control or from transform-mechanism control.
In the case of the later, the retron from a particular transform contains
critical stereochemical information (absolute or relative) on one or more stereocenters.

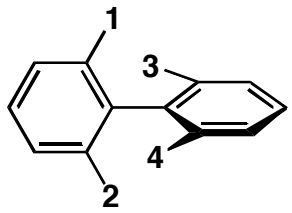
The direct goal of stereochemical strategies is the reduction of ***stereochemical complexity*** *by the retrosynthetic elimination of* ***stereogenic elements*** *in a TGT.*

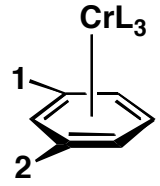
Stereocomplexity *depends on the number of stereogenic elements present in a molecule and their spatial and topological locations relative to one another.*

Stereogenic element *is a focus of stereoisomerism (stereogenic center, axis, or plane) in a molecule such that interchange of two ligands (i.e.* ***1*** *and* ***2****) attached to an atom in such a molecule leads to a stereisomer.*

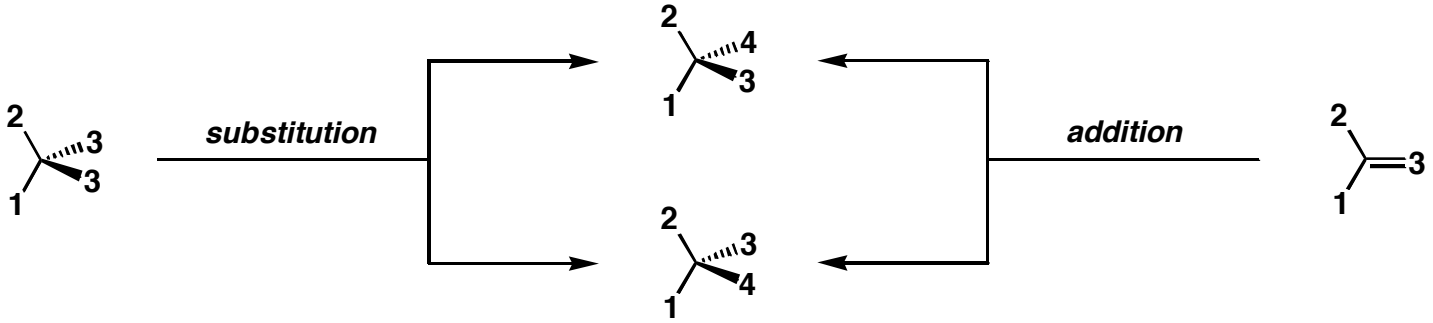








***From a synthetic point of view**, the introduction of **new** stereogenic centers into a TGT*
is normally achieved by means of two fundamentally distinct processes:
most commonly through addition to one or other stereoheterotopic (enantio- or diastereotopic) faces
of a double bond, but also by selective modification or replacement of stereoheterotopic ligands.



***From a retrosynthetic point of view**, the selective removal of stereogenic elements depends on the availability of **stereosimplifying transforms**, the establishment of the required retron and the presence of a favorable spatial environment in the precursor generated by the aplication of such transform.*

*The stereocontrol on **stereosimplifying transforms** can rely on*

1) mechanism

2) substrate or reagents structure bias (steric/stereoelectronic effects must be considered)

> ***Stereoelectronic effect***
>
> *is any effect determining the properties or reactivity of a species*
>
> *that depends on the orientation of filled or unfilled electron orbitals in space*

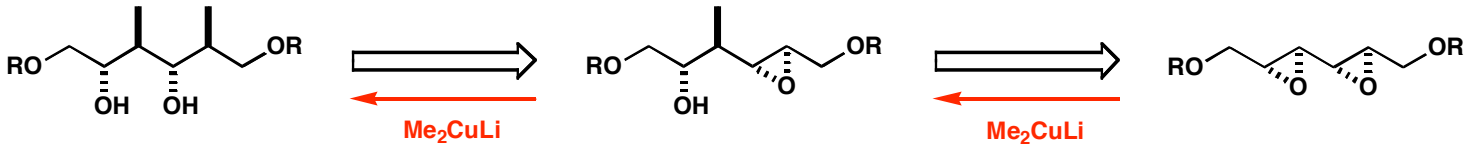
Mechanism: intrinsically stereocontrolled transforms

There are reactions which show stereoselectivity primarily because of mechanism:

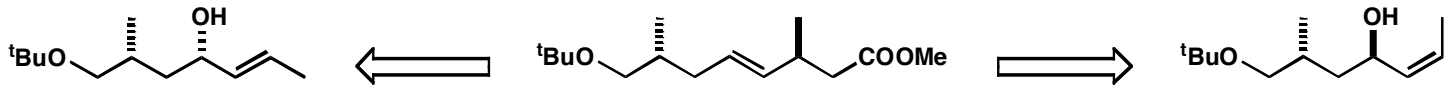
S_N2 processes,

hydroboration, epoxidation, OsO_4 oxidation of alkenes,...

Those disconnections involving C–C bonds are specially important



Mulzer, J. *ACIEE* **1990**, 1476



Ireland, R. E. *JOC* **1991**, 4031

Substrate: stereocontrol due to a stereochemical bias in the substrate

The stereochemical outcome of a wide range of reactions is not contolled by mechanistic issues.

Otherwise, ***it depends on the structure of the substrate or reagent****.*

The generation of a new stereocenter can be controlled by the steric bias of preexisting stereocenters.

This kind of stereocontrol is frequent in ***cyclic structures****, conformationally no flexibles.*

In ***acyclic systems****, the situation is much more complicated ...*

Given that the new stereocenters are usually created by addition to a sp^2 *carbon,*

high stereocontrol can be achieved if the molecule adopts a definite reactive conformation

in which one of the two diastereofaces is efficiently shielded by steric effects of the substituents.

Passively *by steric shielding of one or two diastereotopic faces on the reactive center.*

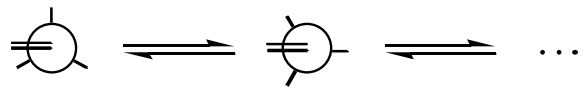
Actively *by binding the reagent in form of non-covalent interactions and*

directing it towards one of the diastereotopic faces

*Then, **steric** and **stereoelectronic effects** play a crucial role to devise powerful retrosynthetic analysis.*

***Conformational issues** must be considered*

Acyclic systems

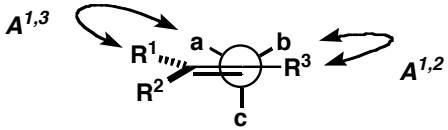


Cyclic systems

What conformation is the most stable? And the most reactive?

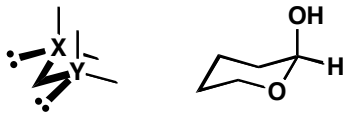
syn-pentane interactions

must be avoided



allylic strain

must be evaluated

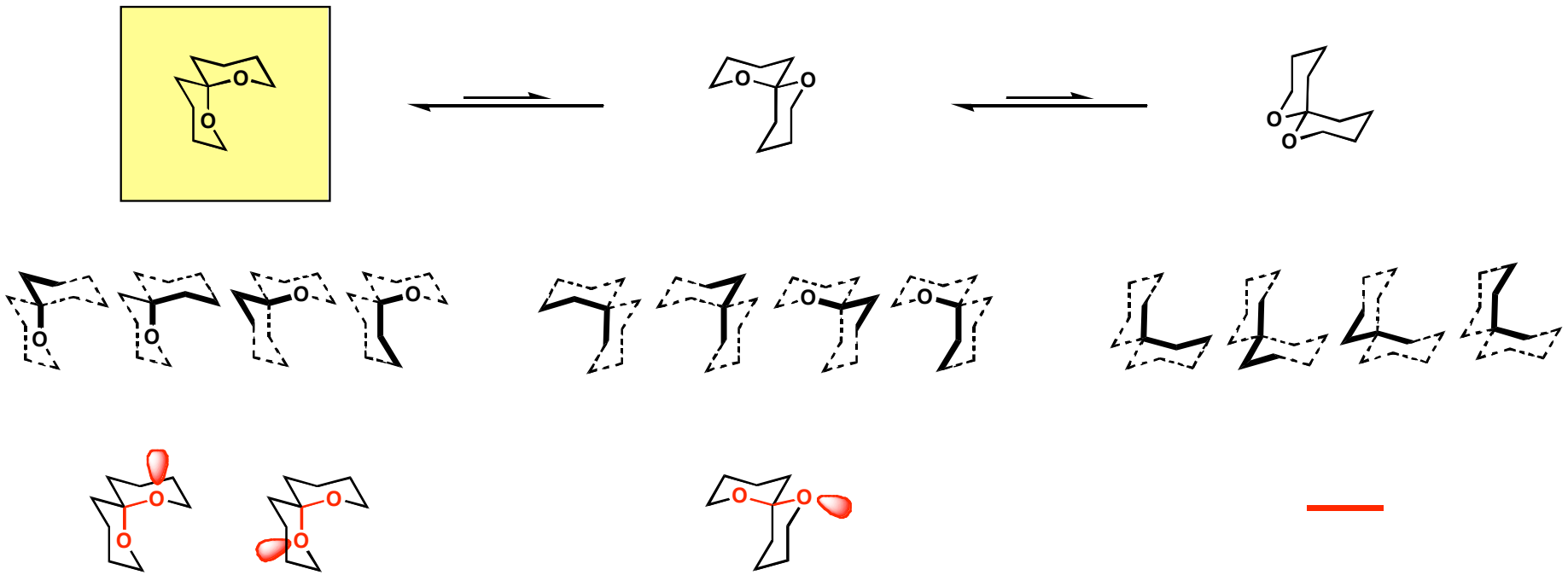


anomeric effects

are rewarded

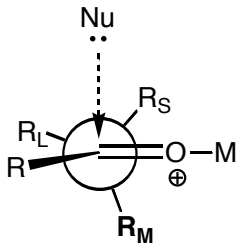
*Lewis acid – Lewis base considerations, coordination (**chelation**), hydrogen-bonding, ... must be also considered*

What is the most stable conformation of a 1,7-dioxaspiro[5.5] undecanespiro system?

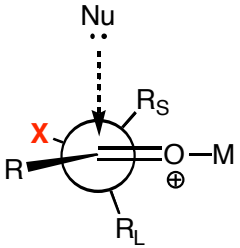


Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*

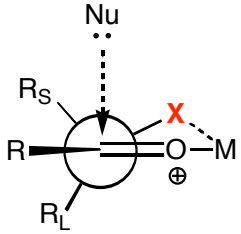
*Models proposed for 1,2–Asymmetric Induction **



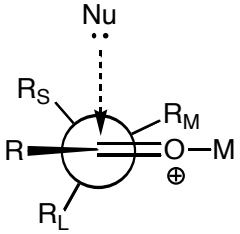
Cram acyclic model (1952)
Steric



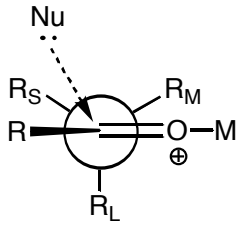
Cornforth acyclic model (1959)
Electrostatic



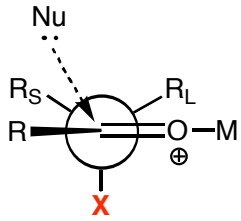
Cram rigid model (1959)
Chelation



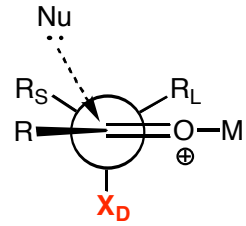
Karabatsos model (1967)
Ground-state, steric



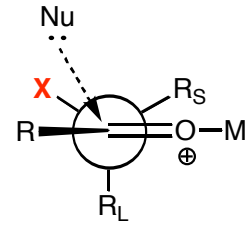
Felkin-Anh model (1977)
Steric, torsional, Bürgi-Dunitz



Felkin-Anh polar model (1977)
Electronic, torsional, Bürgi-Dunitz



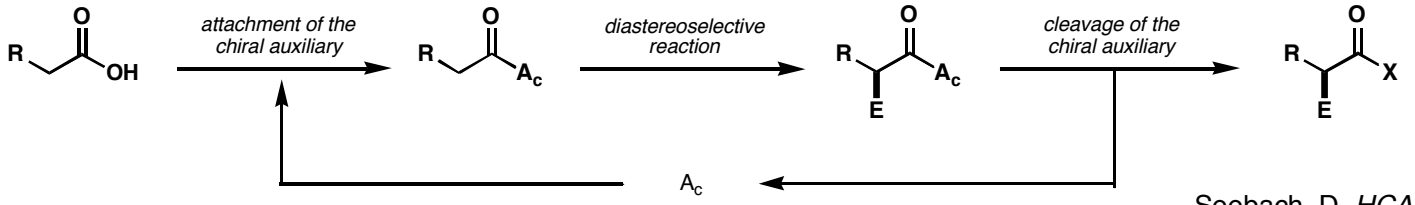
Cieplak model (1981)
Electronic, torsional, Bürgi-Dunitz



"Evans" model (2001)
Electrostatic, torsional, Bürgi-Dunitz

** Partially taken from a Evans, D. A. Seminar Group. 2001*

Chiral auxiliaries: stoichiometric asymmetric reactions



Seebach, D. *HCA* **1998**, 2093

An ideal chiral auxiliary has to fulfil several criteria:

i) it should be ***cheap, and both enantiomers should be readily available***

ii) ***attachment of the substrate to the auxiliary should proceed in high yield by simple methods****, applicable to a broad variety of substrates*

iii) there should be ***many different types of reactions to be carried out***

iv) the ***auxiliary must be stable under the conditions of the diastereoselective reaction***

v) there must be a ***high degree of diastereoselection***

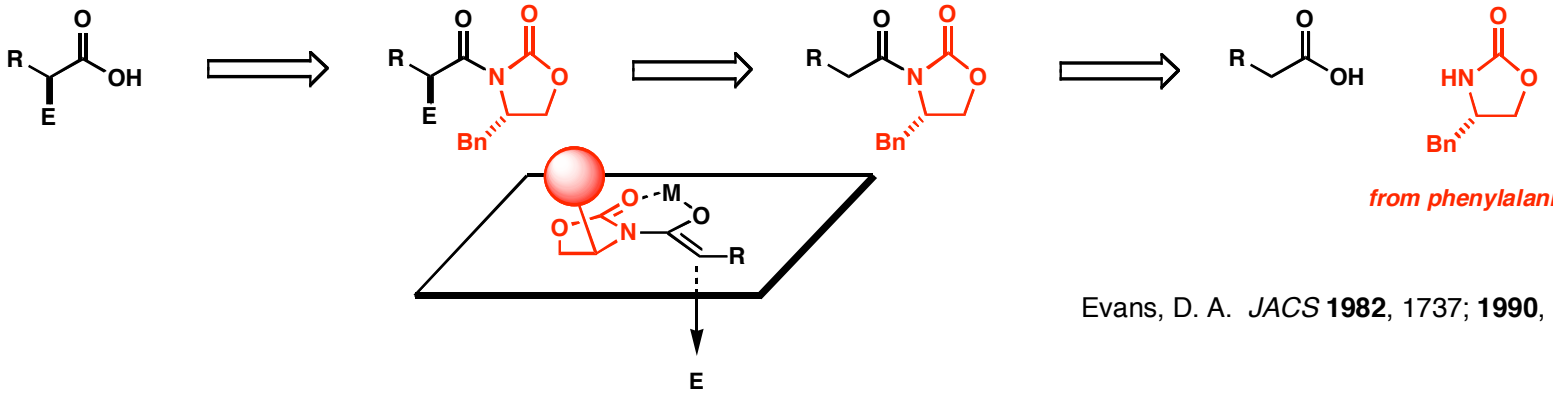
vi) the ***derivatives*** *of the chiral auxiliary* ***should preferably be crystalline,*** *allowing easier purification, and removal of diastereoisomeric ans other impurities by simple crystallization*

vii) ***the cleavage of the auxiliary must be possible with high yield under mild conditions****, and the procedures should be generally applicable*

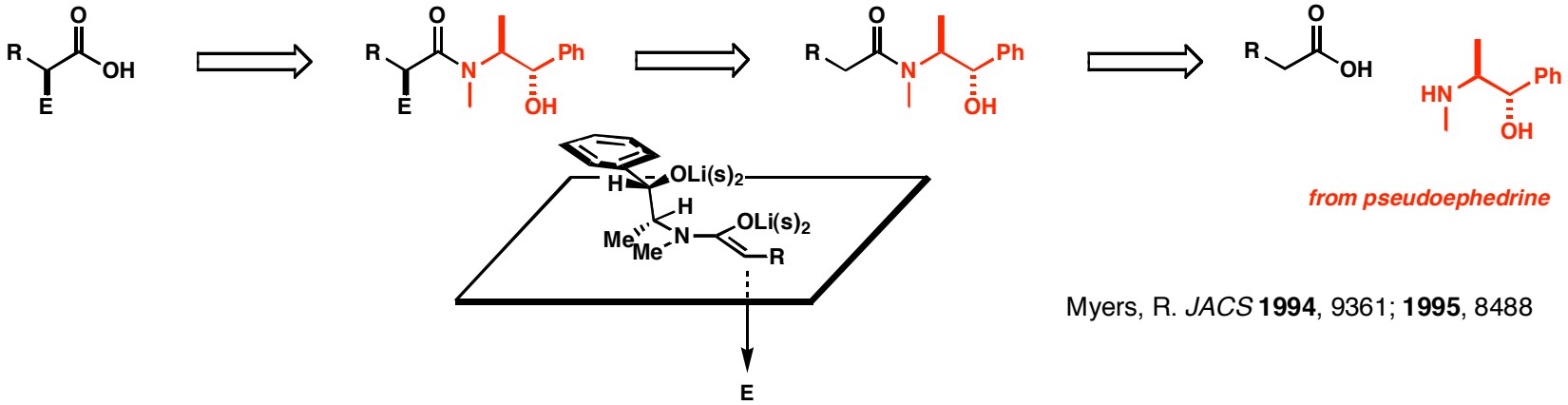
viii) ***the auxiliary should not be destroyed*** *under the conditions applied for cleavage****, thus allowing for recycling***

ix) isolation of the enantiomerically pure product and recovery of the auxiliary should be possible by simple methods.

Alkylation

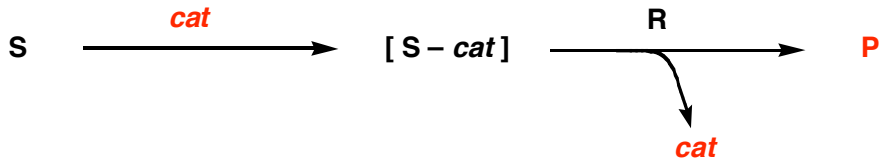


Evans, D. A. *JACS* **1982**, 1737; **1990**, 8215

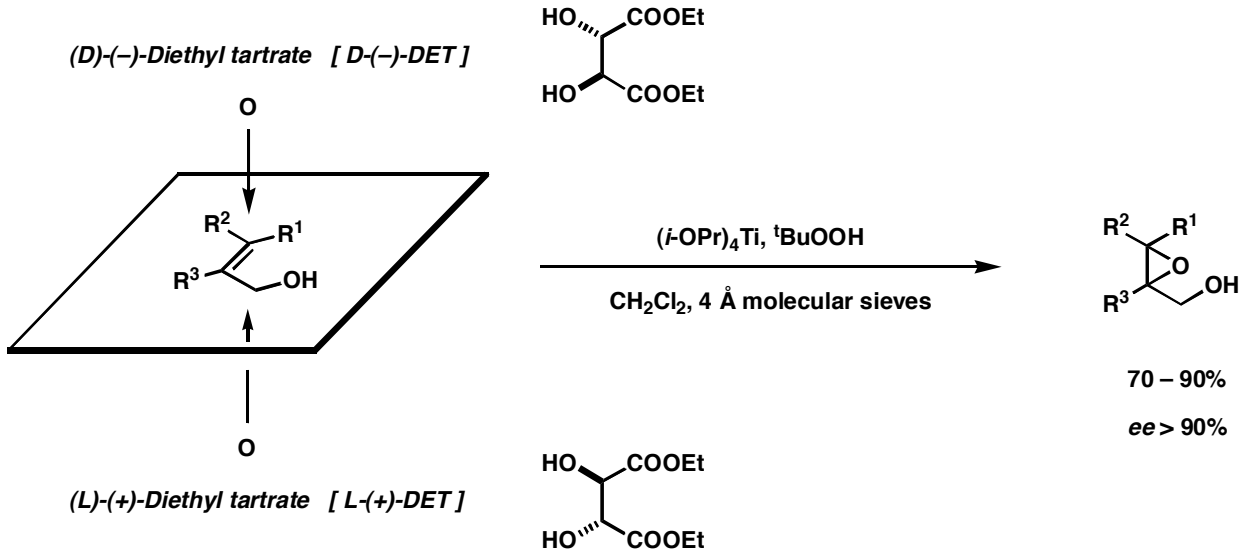


Myers, R. *JACS* **1994**, 9361; **1995**, 8488

Chiral catalysts: catalytic asymmetric reactions

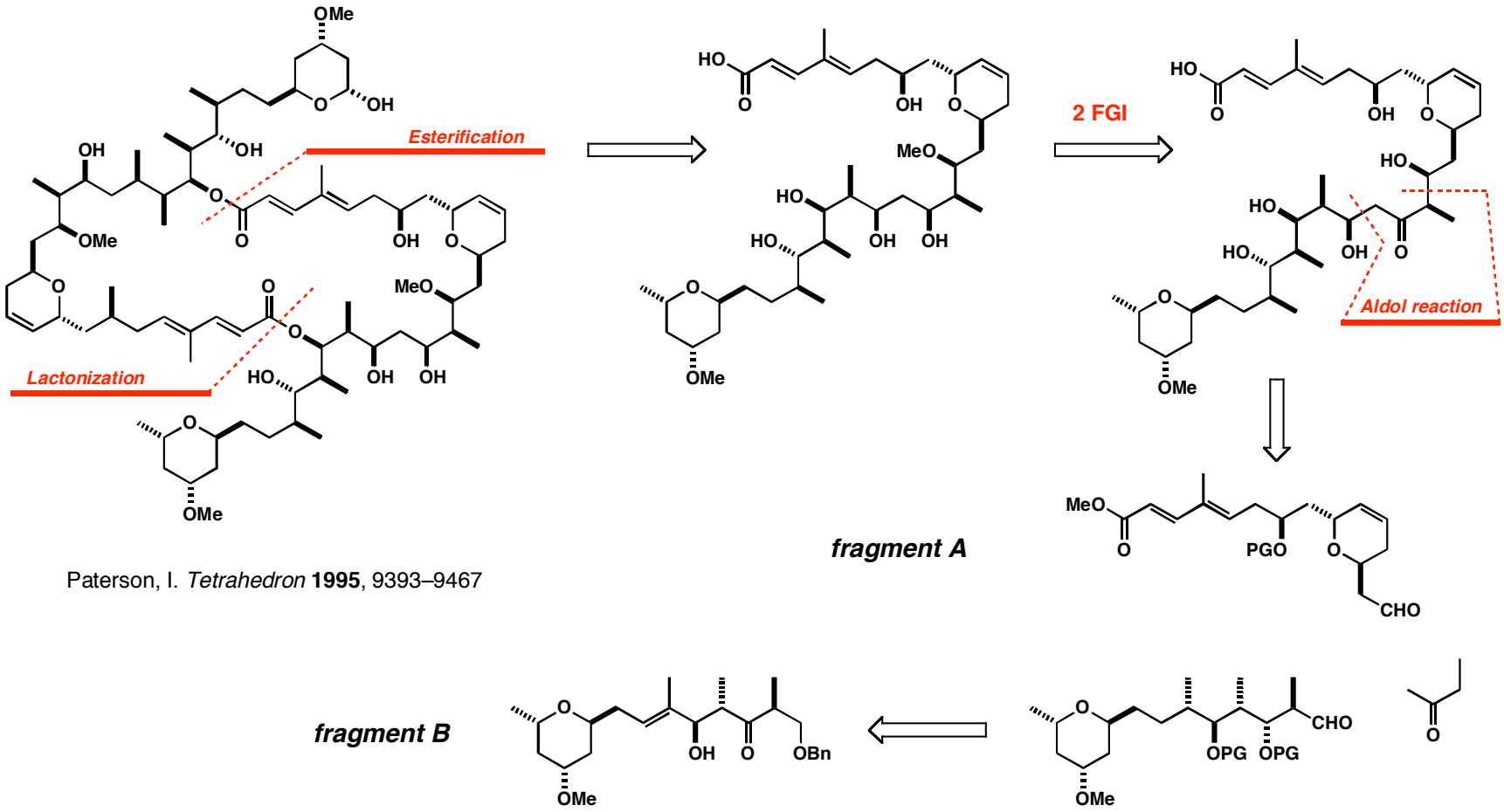


Sharpless asymmetric epoxidation



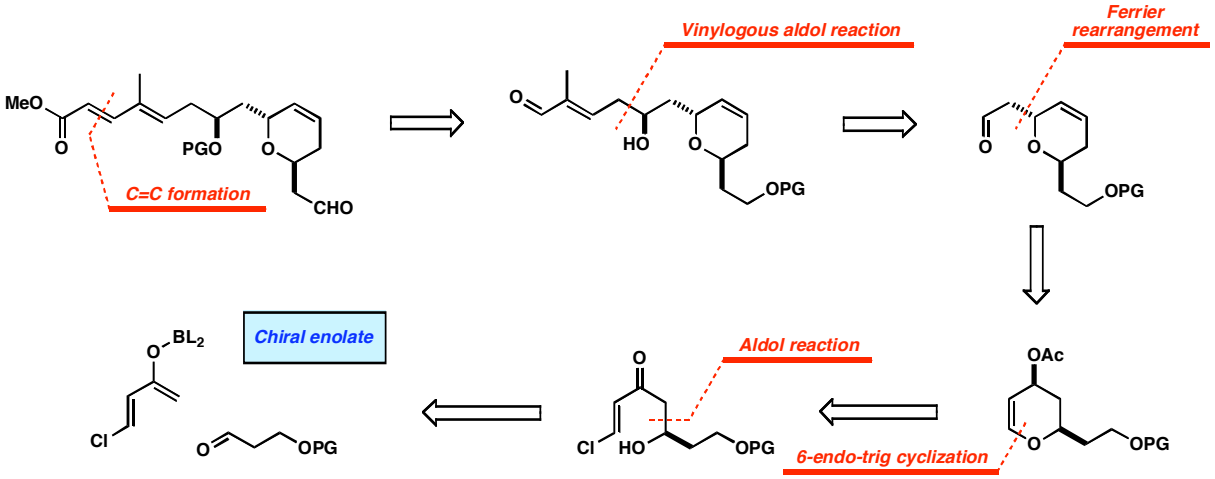
Sharpless, K. B. *JACS* **1980**, 5974

Mastering stereochemistry: swinholide A by Paterson

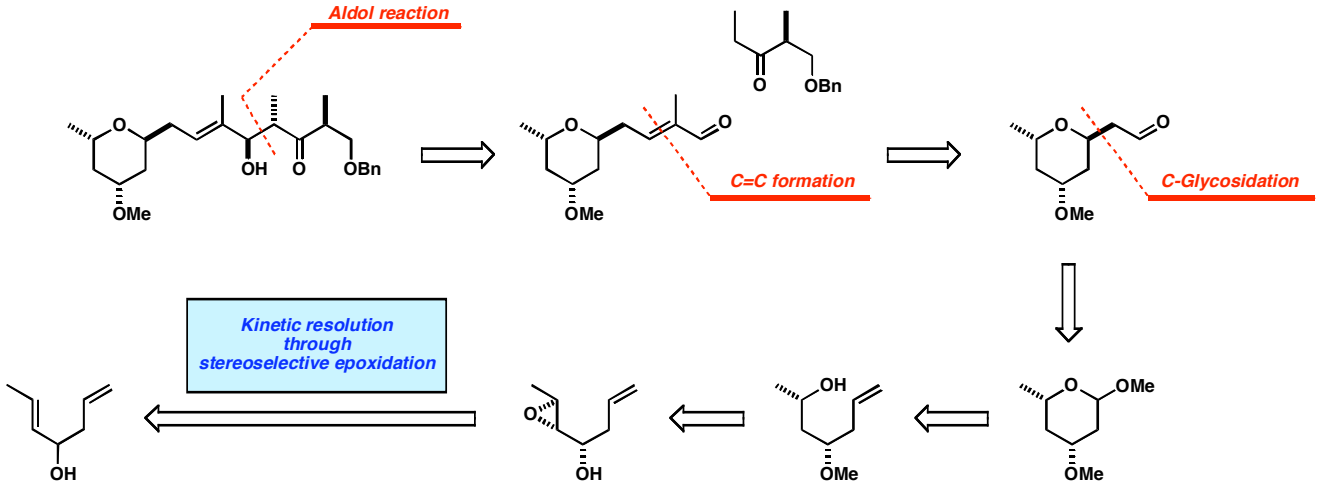


Paterson, I. *Tetrahedron* **1995**, 9393–9467

Fragment A



Fragment B



L'objectiu últim de l'anàlisi retrosintètica és el de dissenyar síntesis que permetin
assolir la molècula objectiu amb un mínim nombre d'etapes (idealment una),
el màxim rendiment possible (idealment 100%),
produint la mínima quantitat possible de subproductes (idealment cap)
d'acord amb un plan senzill, flexible i atractiu

Etapes individuals

*Cal prestar atenció a l'**eficàcia** de les etapes individuals,*
*la qual s'articula al voltant dels conceptes de **conversió, selectivitat** i **rendiment***

Per a una reacció $A \longrightarrow B$

Conversió, C: $\dfrac{(n_A)_{reaccionat}}{(n_A)_o}\ 100$

Selectivitat, S: $\dfrac{(n_B)}{(n_A)_{reaccionat}}\ 100$

RENDIMENT, R: $\dfrac{(n_B)}{(n_A)_o}\ 100$

$$\mathbf{R = (C \times S)\ \ 100}$$

*La selectivitat pot tenir diferents nivells: **quimioselectivitat**, **regioselectivitat** i **estereoselectivitat***

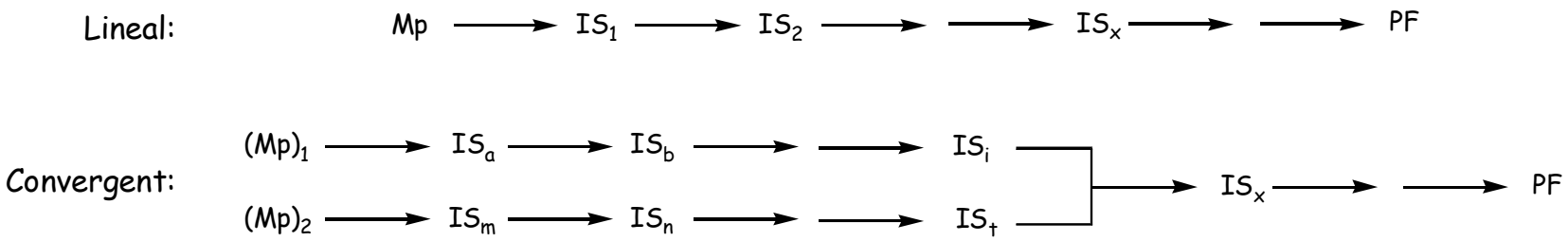
*Per aconseguir-la cal emprar reaccions el més selectives possibles i fer un ús racional dels **grups protectors***

Qüestions que cal considerar

- ***Com són les etapes individuals?***
  Quina informació es disposa sobre el mecanisme, l'abast del mètode, la selectivitat i el rendiment esperable?
  Quina informació sobre les necessitats experimentals es té?
  Escala? Reactius? Condicions tècniques? Purificació?

- ***Com s'organitzen les diferents etapes individuals?***
  Com, un cop acordada una determinada estratègia sintètica, puc dur-la a la pràctica amb un màxim d'eficàcia?
  Tàctica?
  Síntesis lineals i/o convergents?
  Es poden associar etapes individuals consecutives per tal d'assolir una millor eficàcia?

Síntesis Lineals i Convergents



En general, les síntesis convergents donen millor resultats que les lineals perquè solen donar rendiments superiors, posseeixen un grau superior de flexibilitat i es basen en anàlisis retrosintètiques més "simples".

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Hi ha, però, situacions en què pot resultar aconsellable dissenyar síntesis lineals... com per exemple en casos en què la síntesi pugui reduir-se a la repetició d'un mateix procediment sintètic, situació en la que un coneixement exhaustiu de les condicions experimentals i la possibilitat d'automatització poden resultar determinants