蘭州大學 | LANZHOU UNIVERSITY

Synthetic Organic Chemistry (有机合成化学)

– 研究生基础课程系列

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Syllabus

1. Introduction
2. Chemistry of C=C bonds
3. Chemistry of C=O bonds
4. Metal-Catalyzed cross coupling (C-C bond) reactions
5. Multiple bonds formation
6. Pericyclic reactions
7. Radical reactions
8. Chemistry of carbenes (carbeniods)
9. Oxidaton and reductions
10. Protecting groups
11. Synthetic analysis and design

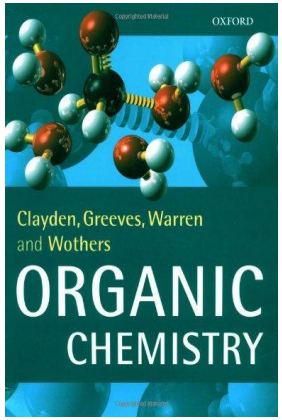
Recommended stuff

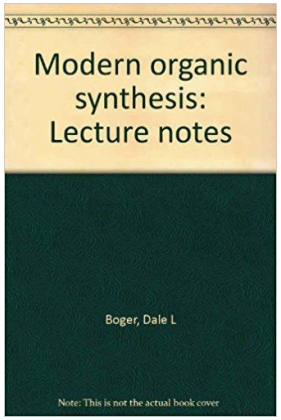
BOOKS:

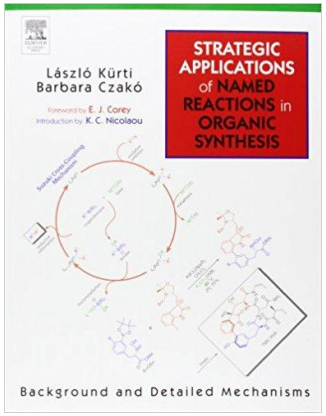
- Clayden et al, *Organic Chemistry*, Oxford
- D. Boger, *Modern organic synthesis: lecture notes*, TSRI Press
- Kurti et al, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier
- 胡跃飞，林国强，现代有机反应，**Vol I-V**，化学工业出版社，**2008**

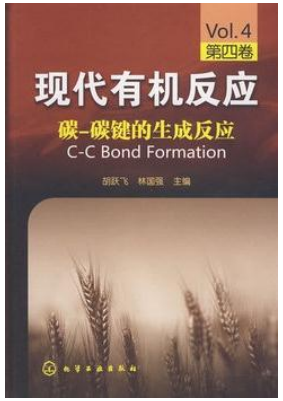
Online resources

- Evans online handouts (Harvard University)
- Meyers online handouts (Harvard University)
- Jeffrey W. Bode, OC IV: *Advanced Methods and Strategies in Synthesis* (ETH-Zürich)









Organic Synthesis Definition

Chemical synthesis is the intentional construction of molecules by means of chemical reactions.

Sir John W. Cornforth

J. W. Cornforth
The Nobel Prize
in Chemistry 1975

Organic synthesis is a special branch of **chemical synthesis** and is concerned with the construction of organic compounds via organic reactions.

Total synthesis is the chemical synthesis of a molecule, usually a natural product, from relatively simple starting materials.

By K. C. Nicolaou

K. C. Nicolaou
@ Scripps

introduction

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.

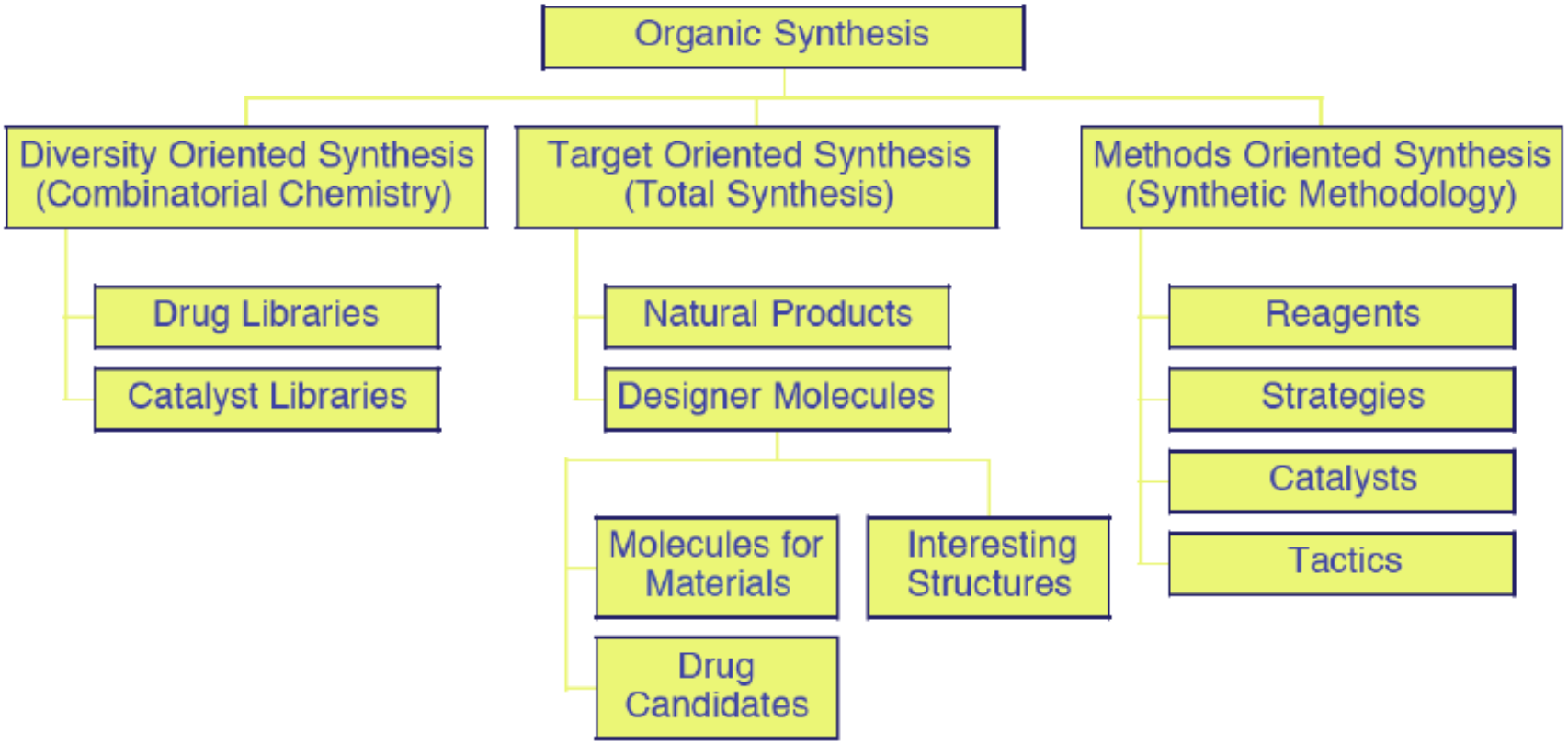
This process usually begins with the **design of a synthetic plan (strategy)**

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 synthesis of a target molecule

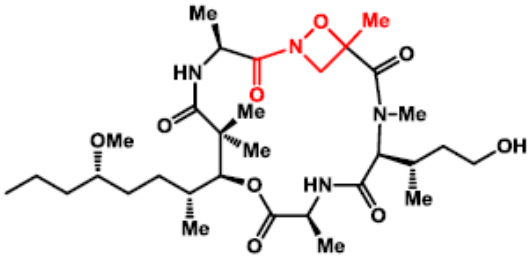
Nicolaou, K. C. Classics in Total Synthesis

Organic Synthesis Classification

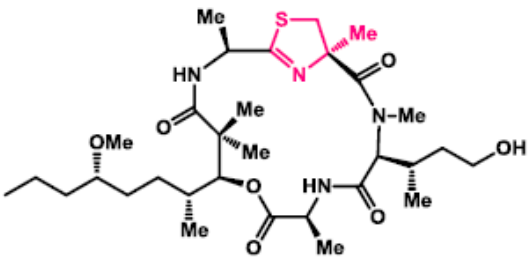


Why we synthesize organic molecules?

- **To prove molecular structures of natural products**



presumed Halipeptin A



revised Halipeptin A

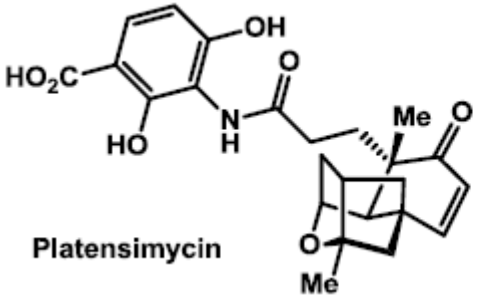
- **To discover new reactions, strategies**

E. J. Corey

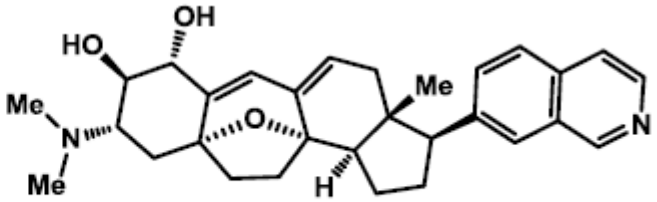
PCC, Protecting Groups (TBS, MOM…….)
Corey-Bakshi-Shibata Reduction, Corey-Fuchs Alkyne Synthesis,
Corey-Chaykovsky Epoxidation and Cyclopropanation,
Corey-Kim Oxidation, Corey-Nicolaou Macrolactonization,
Corey-Winter Olefination…….

Why we synthesize organic molecules?

- To make molecules for biological and SAR studies

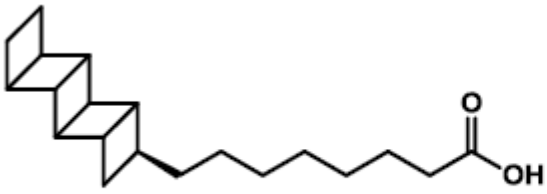


Platensimycin



Cortistatin A

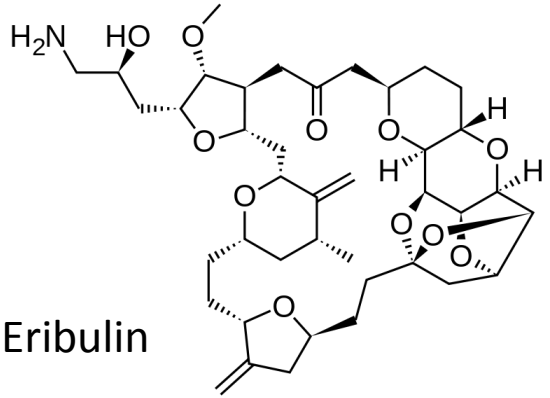
- To understand their structure/function



pentacycloanammoxic acid

Why we synthesize organic molecules?

- **To develop a process for useful compound in large-scale**



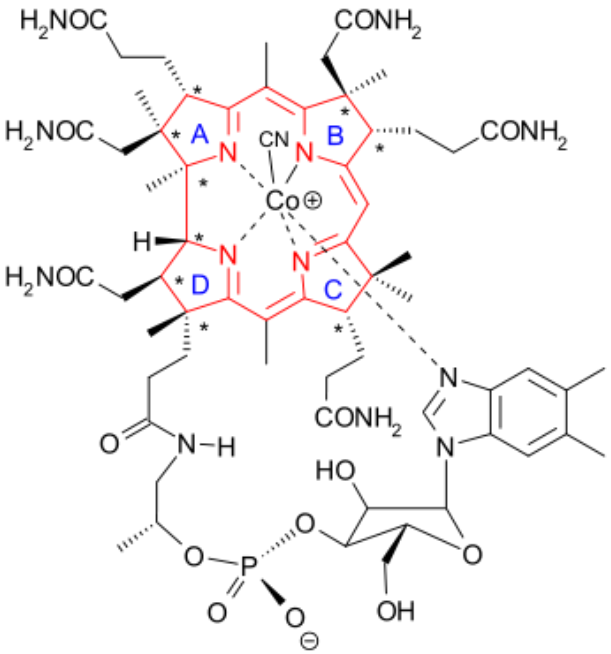
Eribulin

Eribulin is a fully **synthetic macrocyclic** ketone analogue of the marine natural product halichondrin B, to treat patients with metastatic **breast cancer.**

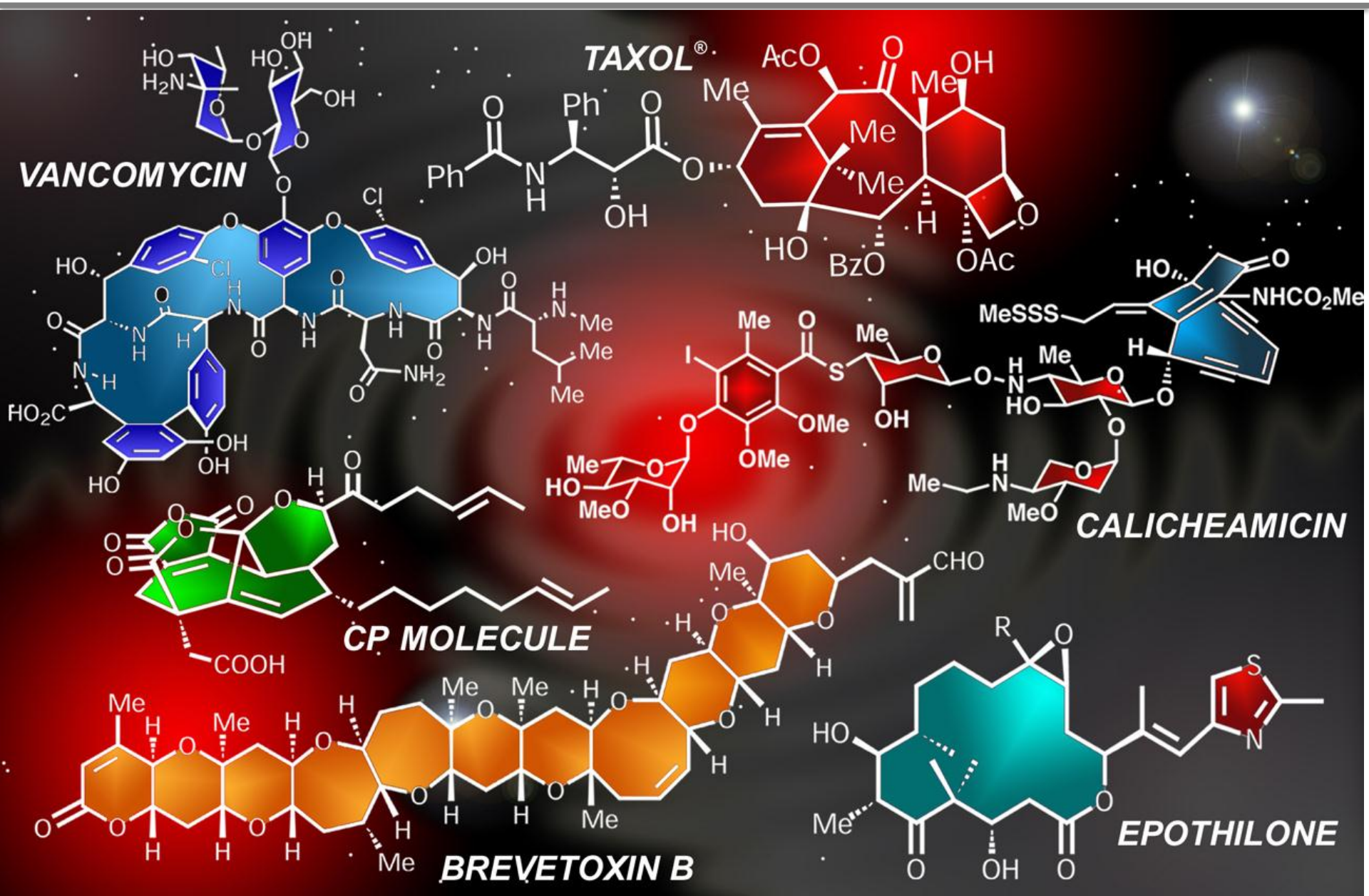
- **Because they are there!**

  for challenge,

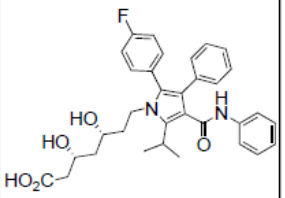
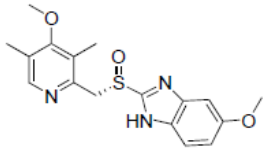
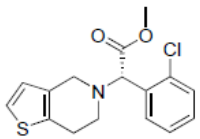
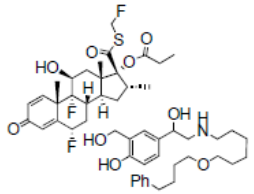
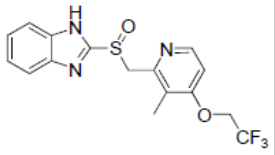
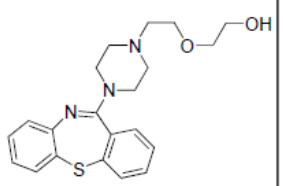
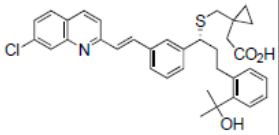
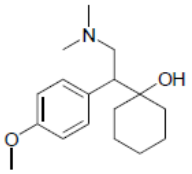
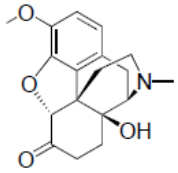
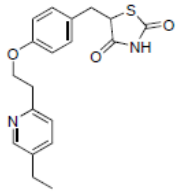
  for excitement also



The targets can be Natural Products ...



The targets can be biologically active compounds

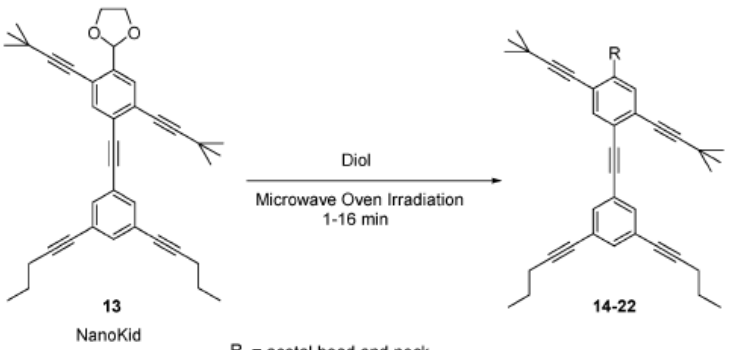
1 Lipitor	**2** Nexium	**3** Plavix	**4** Advair Diskus	**5** Prevacid
				
2007 Rank: 1 Company: Pfizer 2008 Sales: $5.88 Billion	2007 Rank: 2 Company: AstraZeneca 2008 Sales: $4.79 Billion	2007 Rank: 5 Company: Bristol-Myers Squibb 2008 Sales: $3.80 Billion	2007 Rank: 3 Company: GlaxoSmithKline 2008 Sales: $3.57 Billion	2007 Rank: 4 Company: TAP 2008 Sales: $3.30 Billion
Profile: An HMG-CoA reductase inhibitor used to lower LDL cholesterol levels.	**Profile:** A proton pump inhibitor used to treat heartburn and esophagitis.	**Profile:** A platelet aggregation inhibitor used to reduce stroke and heart attack risk.	**Profile:** A corticosteroid and a bronchodilator used to treat and prevent asthma.	**Profile:** A proton pump inhibitor used to treat gastric reflux disease.
6 Seroquel	**7** Singulair	**8** Effexor XR	**9** OxyContin	**10** Actos
				
2007 Rank: 7 Company: AstraZeneca 2008 Sales: $2.91 Billion	2007 Rank: 6 Company: MERCK 2008 Sales: $2.90 Billion	2007 Rank: 8 Company: Wyeth 2008 Sales: $2.66 Billion	2007 Rank: 33 Company: PURDUE 2008 Sales: $2.50 Billion	2007 Rank: 10 Company: Lilly 2008 Sales: $2.45 Billion
Profile: An antipsychotic used to treat schizophrenia and bipolar mania.	**Profile:** A leukotriene receptor antagonist used to treat asthma and allergies.	**Profile:** A serotonin and norepinephrine reuptake inhibitor used to treat depression.	**Profile:** An opioid analgesic used to treat moderate to severe pain.	**Profile:** A thiazolidinedione used to treat type 2 diabetes.

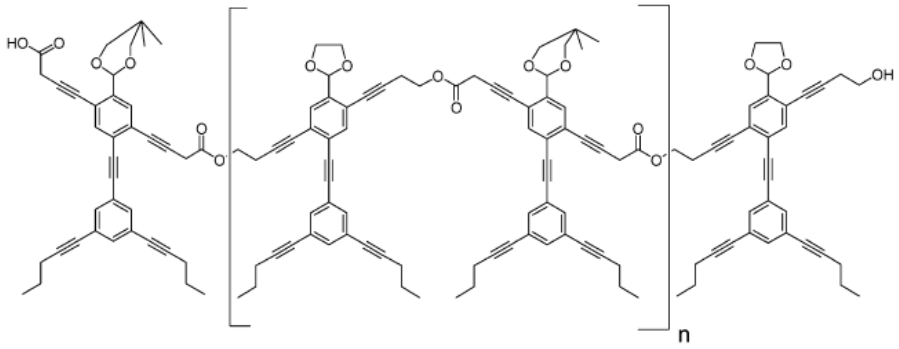
Top 10 Brand-Name drugs in 2008

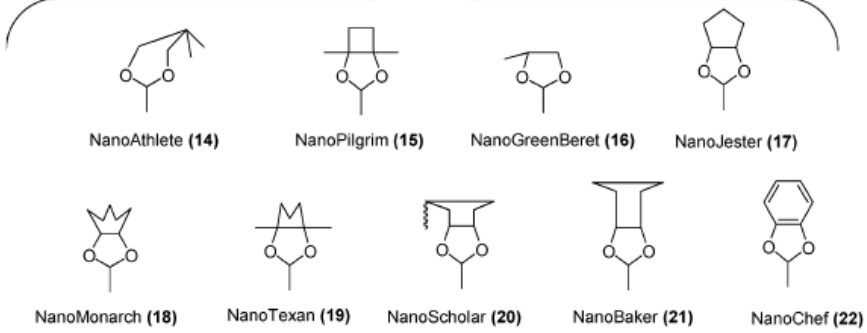
Compiled and Produced by the Njardarson Group (Cornell University) Jón T. Njarðarson

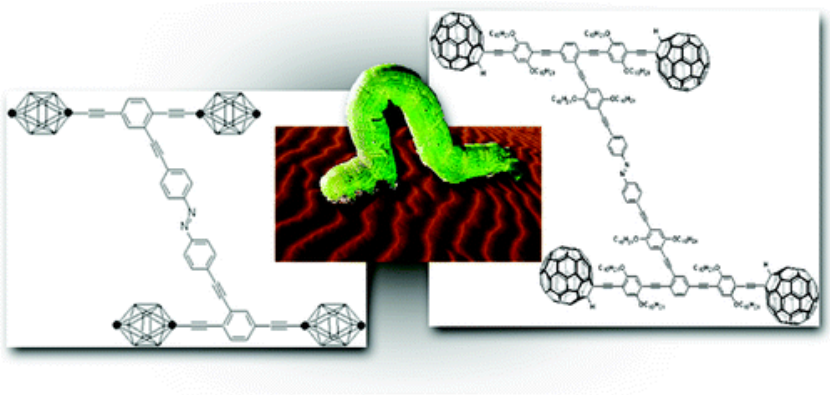
The targets can be…

… or artistic or anthropomorphic attributes









The NanoPutians: *JOC*, **2003**, *68*, 8750; ***Nanoworm:*** *Org. Lett.*, **2008**, *10*897

NanoPutians, following the lead of the Lilliputians in Jonathan Swift's classic, *Gulliver's Travels*

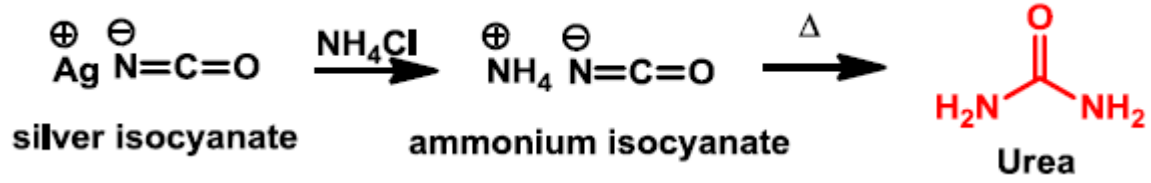
Some concepts ...

- **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.

History: 19th Century

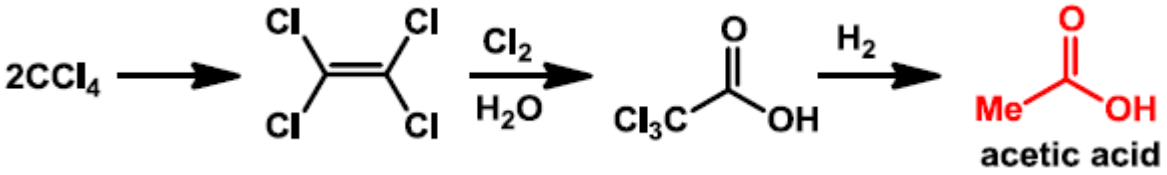
1828, urea (Wöhler)

- marks the beginning of organic synthesis
- Inorganic substance was converted into an organic substance.



1845, acetic acid (Kolbe)

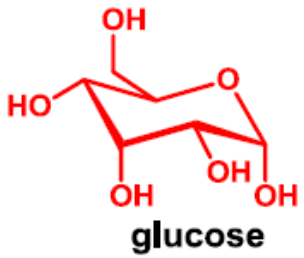
♣ The word "synthesis" was used for the first time



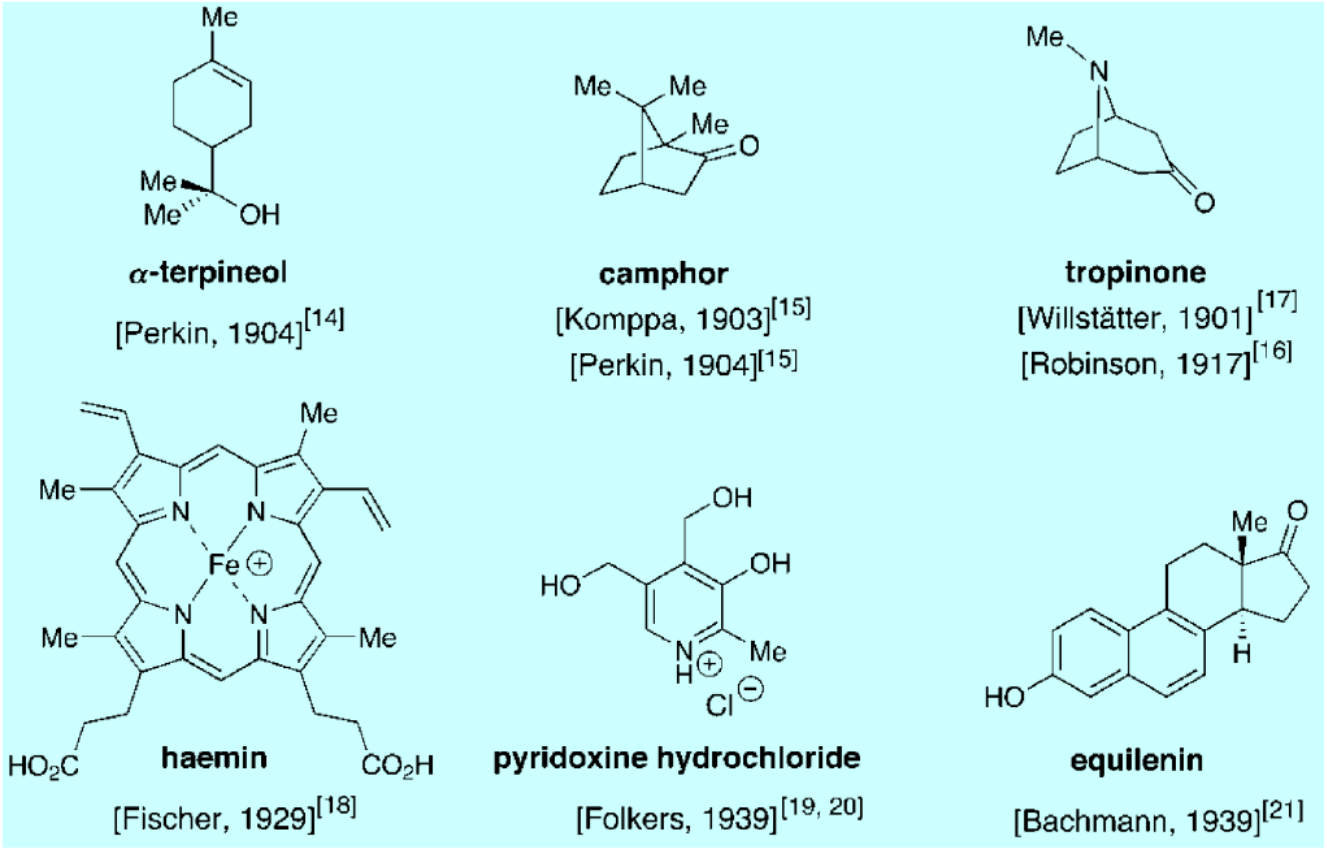
1890, glucose (H. E. Fischer)

♣ the Nobel Prize for chemistry in 1902

♣ stereochemical control



History: Pre-WW II Era

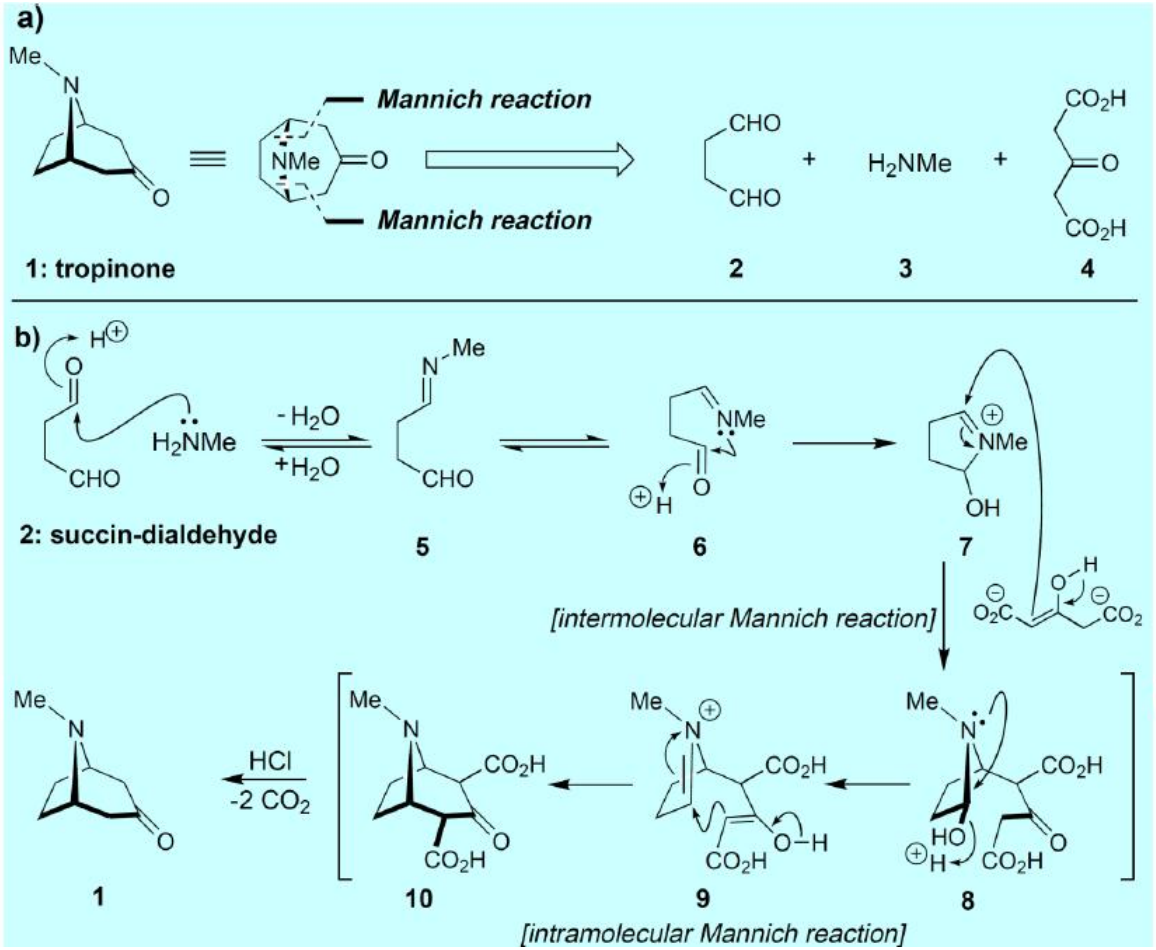


In contrast to the former syntheses,

which were based on the availability of starting materials that contained a major portion of the final atomic framework. Depended on the knowledge of reactions suitable for forming polycyclic molecules.

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

History: Pre-WW II Era



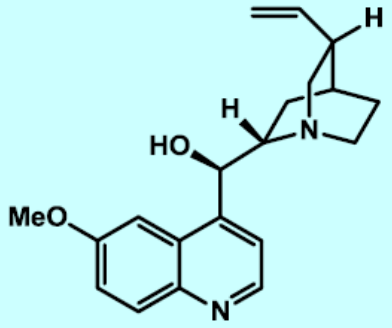
R. Robinson
The Nobel Prize
in Chemistry 1947

- **1917, tropinone (Robinson)**
  - ♣ Biomimetic synthesis
  - ♣ Cascade sequence

R. Robinson, *J. Chem. Soc.* **1917,** *111,* 762

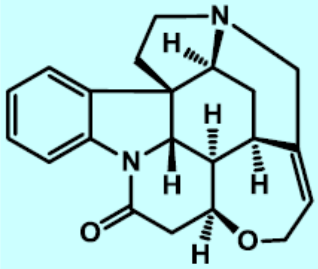
Post-World War II Era: the Woodward Era

"for his outstanding achievements in the art of organic synthesis." **(RBW, Nobel Prize, 1965)**



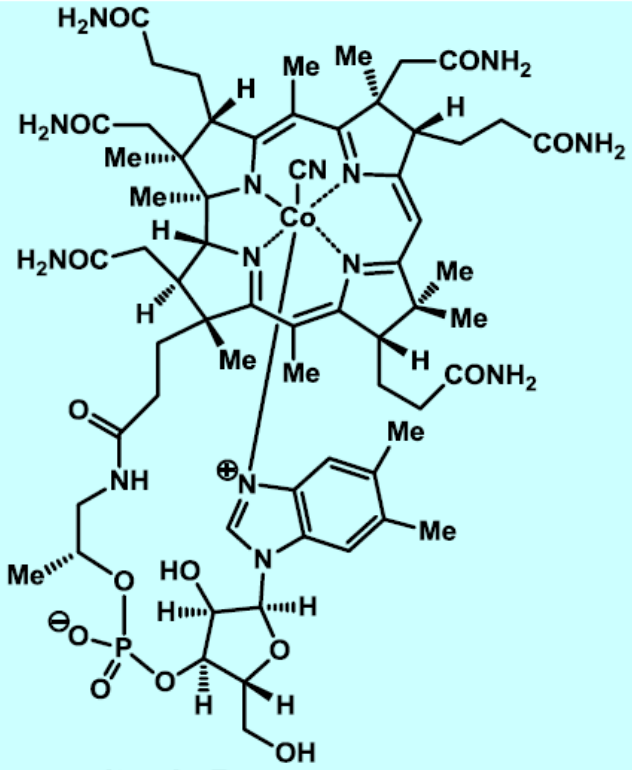
quinine

Woodward & Doering, 1944



strychnine

Woodward, 1954



vitamin B_{12}

Woodward & Eschenmoser, 1973

R. B. Woodward

A. Eschenmoser

Post-World War II Era: the Woodward Era

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 ...

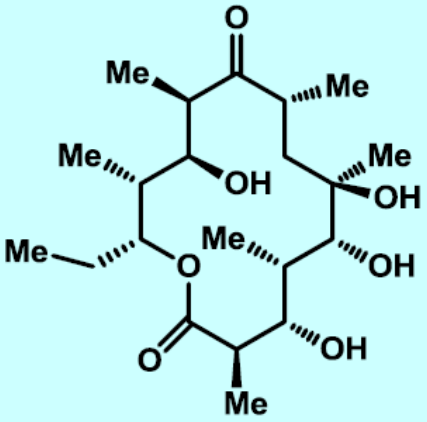
The great master of reasoning by mechanistic analogy and the unrivaled protagonist of the field's transition from an advanced level of "synthesis by directed chemical thinkering" to the level of "synthesis by design" was Robert Burns Woodward.

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

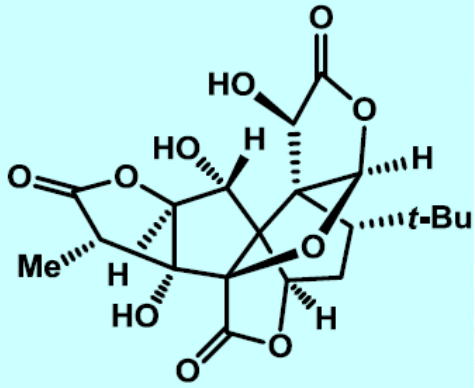
History: Corey Era

"for his development of the theory and methodology of organic synthesis" **(EJC, Nobel Prize, 1990)**

longifolene
Corey, 1961



erythronolide B
Corey, 1975



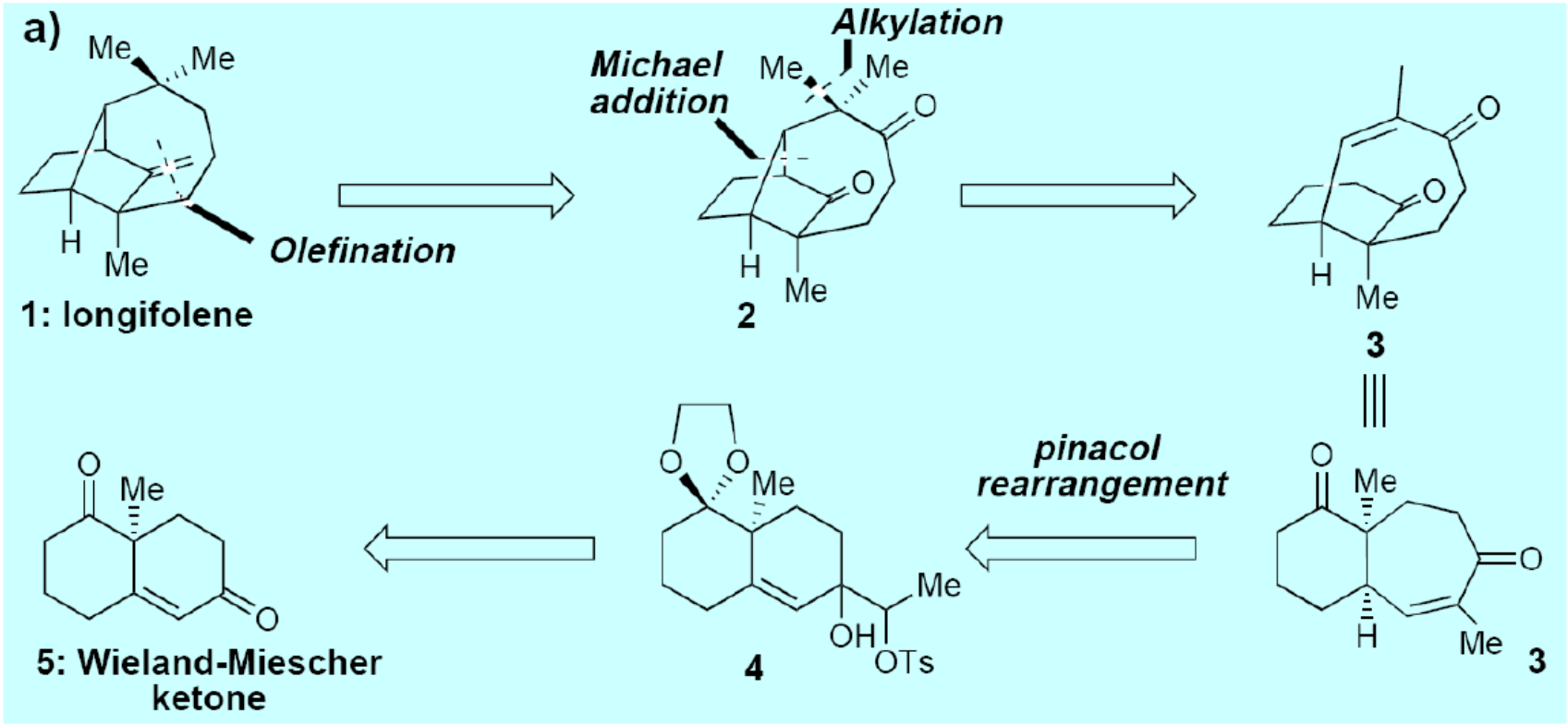
ginkgolide B
Corey, 1988

E. J. Corey

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 (consciously or unconsciously) must be engaged in such practices.*

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

History: Corey Era



Retrosynthetic Analysis

E. J. Corey made organic synthesis into the precise science.

History: Corey Era

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.

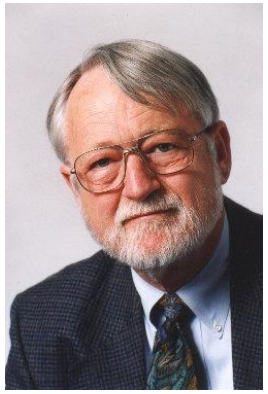
Through retrosynthetic analysis and introduction of new synthetic reactions, he has succeeded in preparing biologically important natural products, previously thought impossible to achieve.

Corey's contributions have turned the art of synthesis into a science“

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

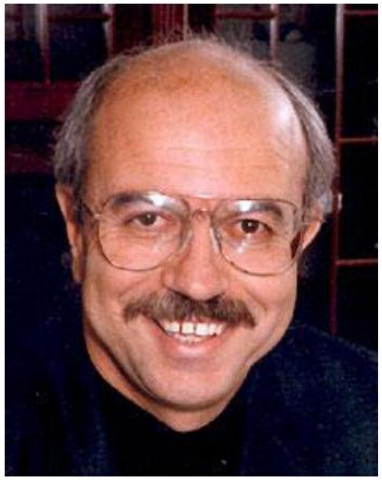
History: Modern Era

Key players in total synthesis



Clayton H. Heathcock
@ UC Berkeley

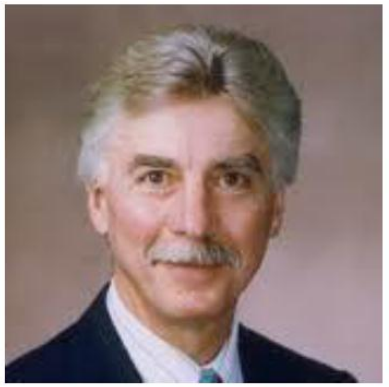
L. E. Overmann
@ UCI



K. C. Nicolaou
@ Scripps

And Evans, Boger,
Ley, Trost,
Curran……

S. J. Danishefsky
@ Columbia



P. A. Wender
@ Stanford

Search term: total synthesis

SciFinder A CAS SOLUTION — *Full list* → Microsoft Excel 97-2003 工作表

	Sample Analysis - Author Name	*Sep 11, 2017*
	0 Selected terms of 36,983	Sorted by Frequency
Rank	Analysis Value	Count
1	Nicolaou K C	≥ 218
2	Danishefsky Samuel J	≥ 144
3	Kametani Tetsuji	≥ 100
4	Boger Dale L	≥ 94
5	Overman Larry E	≥ 90
6	Corey E J	≥ 85
7	Trost Barry M	≥ 84
8	Fukuyama Tohru	≥ 75
9	Fukumoto Keiichiro	≥ 74
10	Paterson Ian	≥ 67
11	Ley Steven V	≥ 66
12	Mori Kenji	≥ 66
13	Yadav J S	≥ 64
14	Baran Phil S	≥ 60
15	Tatsuta Kuniaki	≥ 58
16	Yang Zhen	≥ 58
17	Martin Stephen F	≥ 57
18	Smith Amos B III	≥ 56
19	Anon	≥ 55
20	Cook James M	≥ 55

Tetsuji Kametani
@ Tohoku University

Dale L. Boger
@ Scripps institute

Barry M. Trost
@ Stanford U

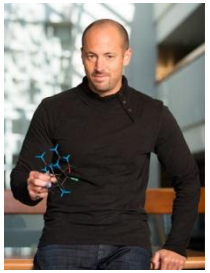
Tohru Fukuyama
@ Nagoya University

Keiichiro Fukumoto
@ Tohoku University

Ian Paterson
@ U Cambridge

Steven V. Ley
@ U Cambridge

Kenji Mori
@ Sci. U of Tokyo



Phil S. Baran
@ Scripps Institute

Zheng Yang
@ PKUSZ

Stephen F. Martin
@ U Texas

Amos B. Smith III
@ U Pennsylvania

Other key players

Brian M. Stoltz
@ Caltech

Mohammad Movassaghi
@ MIT

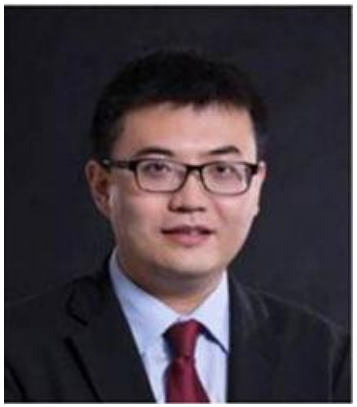
Scott A. Snyder
@ U Chicago

马大为
@ 上海有机所（SIOC）

Richmond Sarpong
@ UC Berkeley

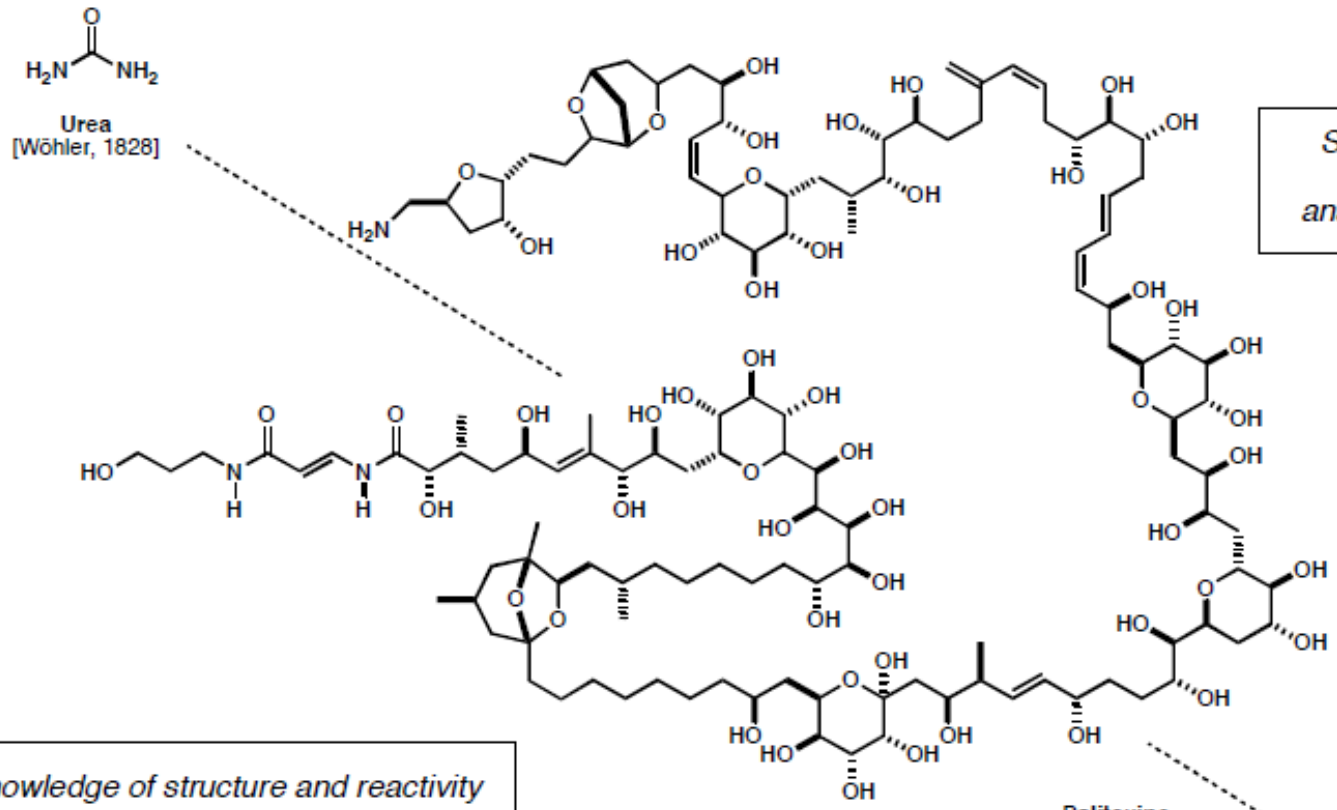
Ryan A. Shenvi
@ Scripps Institute

Sarah E. Reisman
@ Caltech



李昂
@ 上海有机所（SIOC）

Organic synthesis: where to go?



Spectroscopic & analytic techniques

Knowledge of structure and reactivity

Sophisticated reagents & selective processes

Stereochemical control

XXI Century

Where now?

How to Evaluate Organic Synthesis

- **Yield**

$$\%\ Yield = \frac{Mass\ of\ product\ actually\ made}{Maximum\ mass\ of\ product\ that\ could\ be\ made} \times 100$$

- **Selectivity: the key to synthetic efficiency**
  - ♣ Chemoselectivity
  - ♣ Regioselectivity
  - ♣ Diastereoselectivity and Enantioselectivity

- **Economy: the green criterion**
  - ♣ Atom Economy

$$\%\ Atom\ economy = \frac{Mass\ of\ wanted\ product(s)}{Total\ mass\ of\ products} \times 100$$

  - ♣ Step Economy
  - ♣ Redox Economy

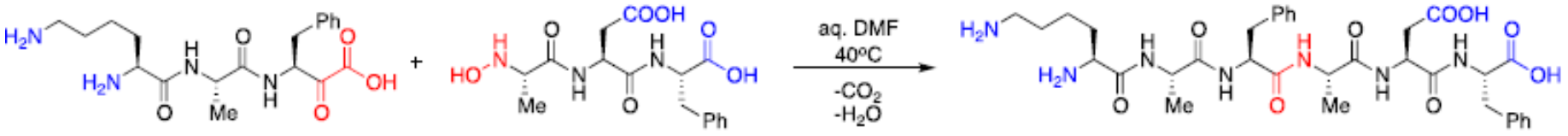
P. S. Baran, *Chem. Soc. Rev.* **2009,** *38,* 3010.

Selectivity

Chemoselectivity（化学选择性）

“Chemoselectivity is the preferential reaction of a chemical reagent with one of two or more different functional groups.”

the reaction of one functional group in preference to others

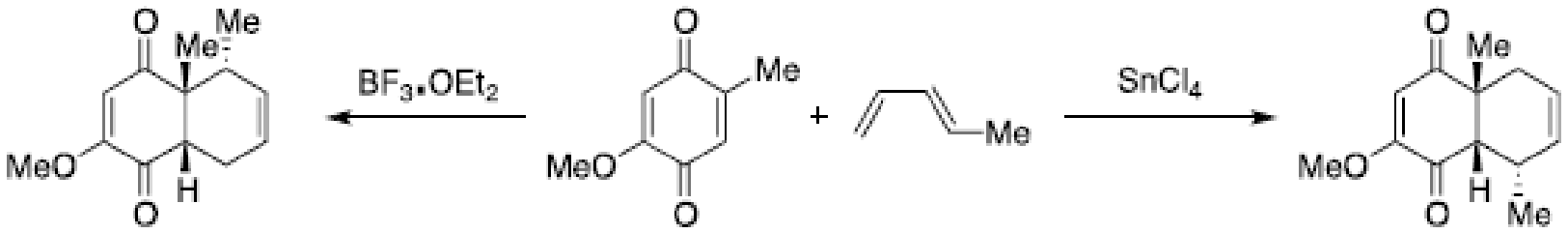


Bode *ACIE* **2006**, *45*, 1248

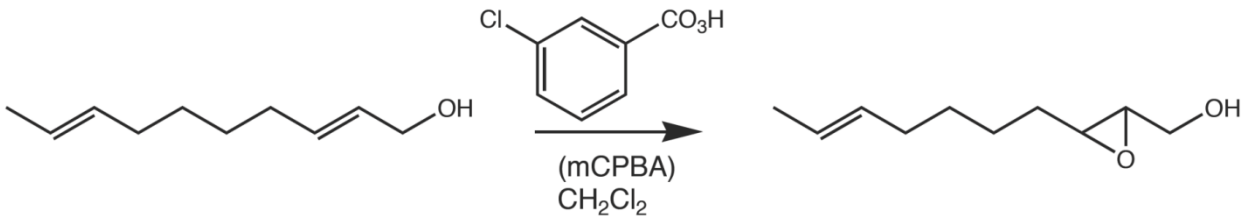
Selectivity

Regioselectivity (区域选择性)

A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over all other possible directions."



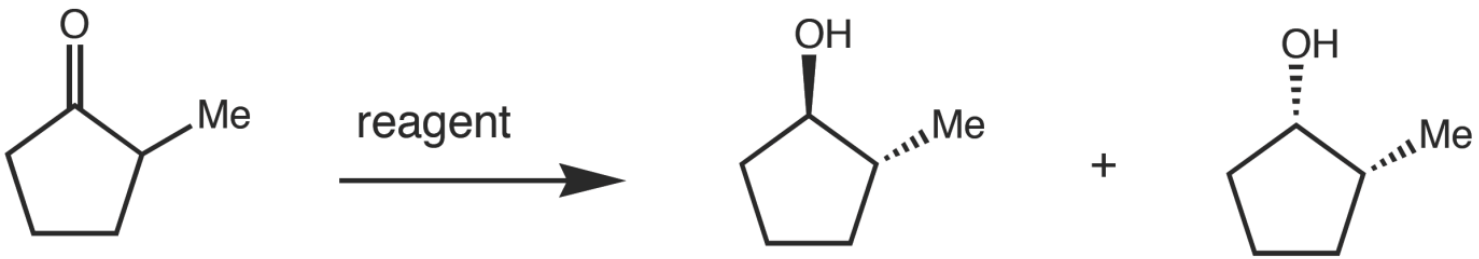
Reusch *JOC* **1980**, *45*, 5012



Selectivity

Stereoselectivity (立体选择性)

A reaction in which only one stereoisomer among a mixture of stereoisomers reacts.

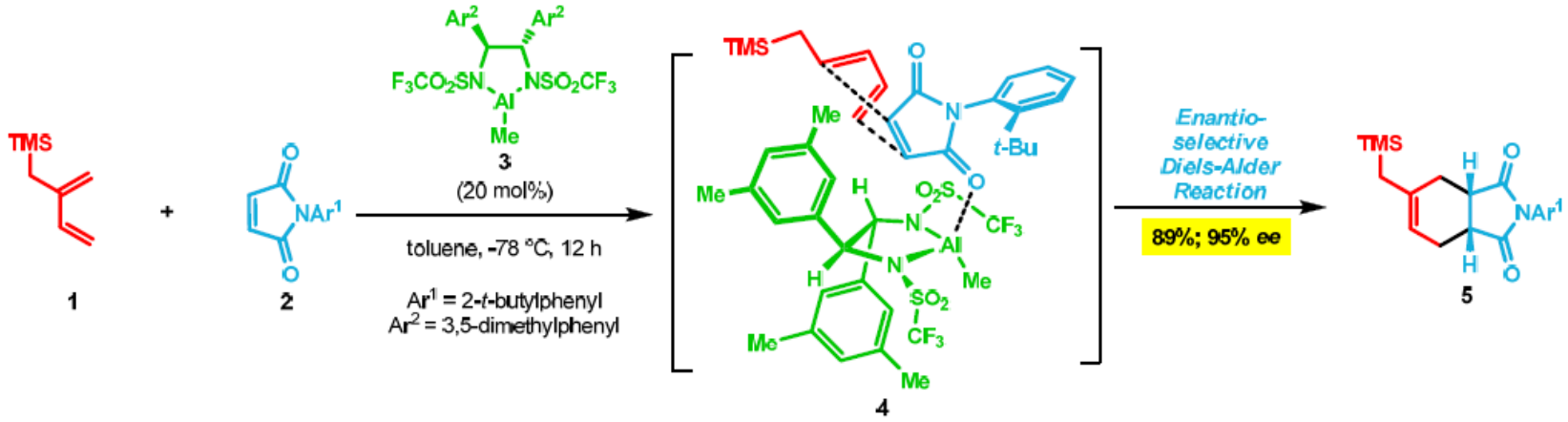


$LiEt_3BH$ is called L-Selectride

reagent	*trans/cis*
$NaBH_4$	74/26
$LiEt_3BH$	2/98

Selectivity

Enantioselectivity（对映选择性）



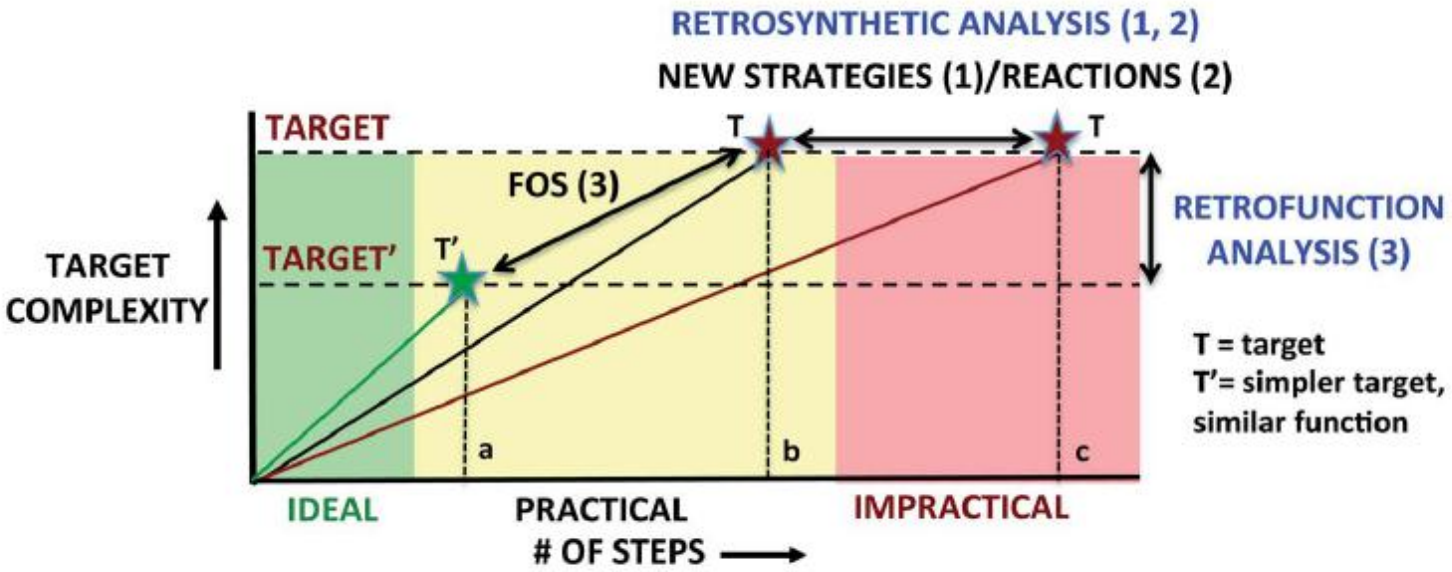
Corey, E. J. *J. Am. Chem. Soc.* **1995**, 117, 9616-9617.

e.e.% = enantiomeric excess:

$$ee = [(R-S)/(R+S)]*\%$$

Green Criterions: Step Economy

"Minimising the number of steps leads to an efficient multistep synthesis in terms of cost and time expended to obtain the desired target" **(P. A. Wender)**



THE IDEAL SYNTHESIS

- ONE STEP • 100% YIELD
- SIMPLE AND SAFE
- ECONOMICAL (STEP, TIME, ATOM/WASTE)
- ENVIRONMENTALLY ACCEPTABLE

TOWARD THE IDEAL

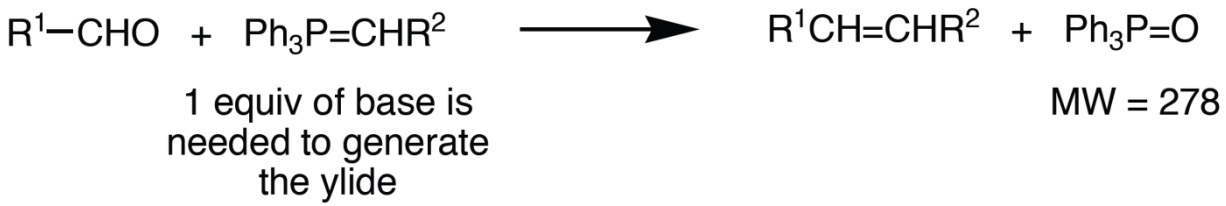
- OPTIMIZE STRATEGIES (HOLISTIC)
- NEW REACTIONS/REACTIVITIES
- FUNCTION-ORIENTED SYNTHESIS (FOS)
  (function 1st, design simpler target)

P. A. Wender, *Tetrahedron* **2013**, 69, 7529-7550

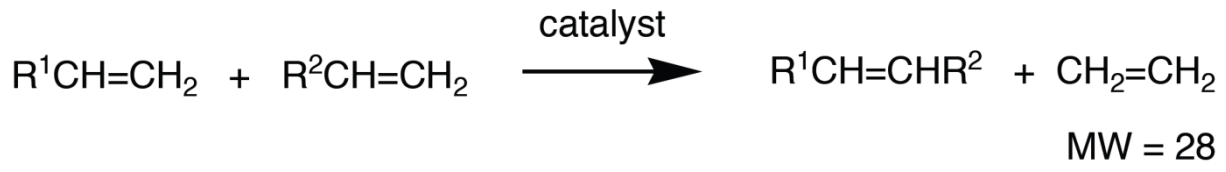
Green Criterions: Atom Economy

"To maximise the mass efficiency of a reaction with respect to all of the reactants."
(B. M. Trost)

- The Wittig reaction has a broad scope and is often stereoselective, but it ranks low in atom economy

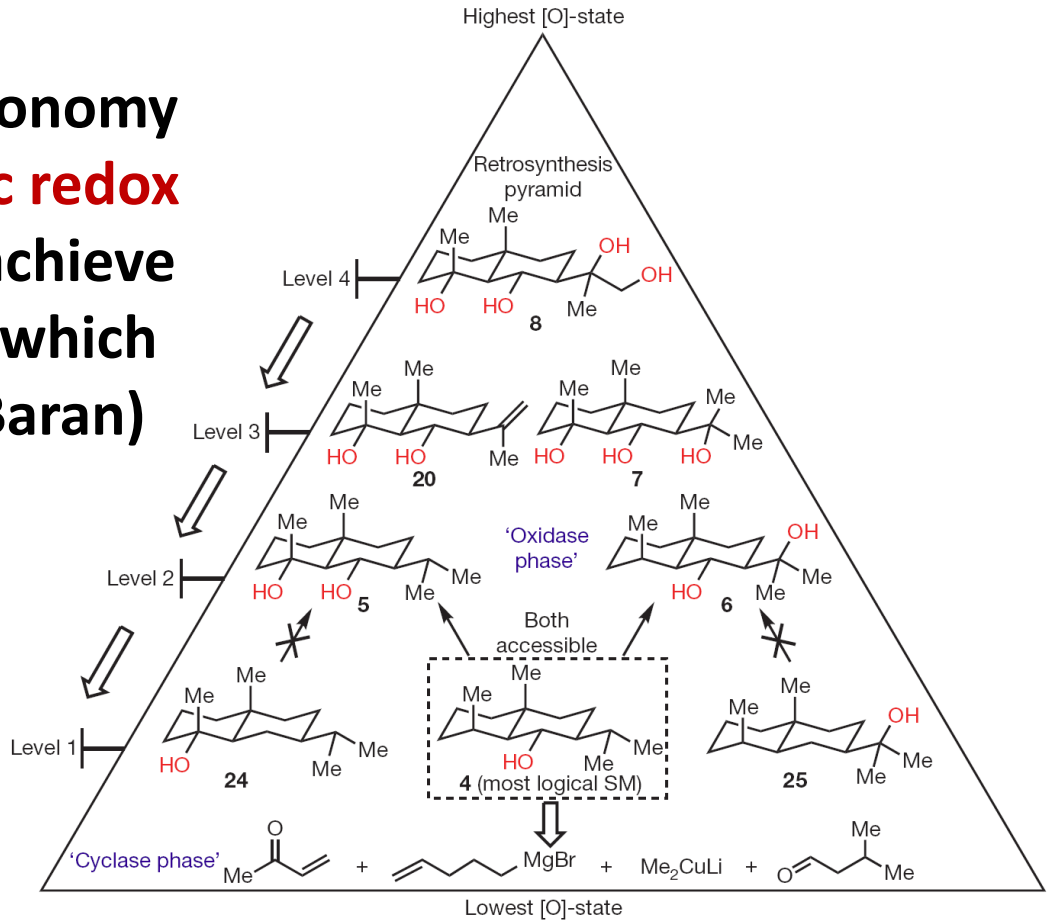


- The alkene metathesis reaction has a narrow scope and gives isomeric mixtures, but ranks high in atom economy



Green Criterions: Redox Economy

"The basic goal of redox economy is to minimize non-strategic redox manipulations in order to achieve an isohypsic synthesis-one which has no redox steps." (P. S. Baran)



P. S. Baran, *Angew. Chem. Int. Ed.* **2009,** *48,* 2854.

Ideal Synthesis

$$\%\text{ideality} = \frac{[(\text{no. of construction rxns}) + (\text{no. of strategic redox rxns})]}{(\text{total no. of steps})} \times 100$$

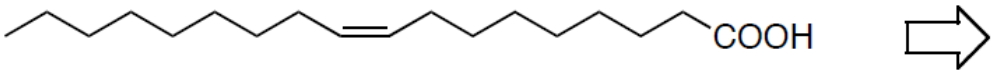
Construction reactions are those which form skeletal bonds (C-C and C-heteroatom). **Strategic redox reactions** (another form of construction reaction) have been previously defined as those that directly establish the correct functionality found in the final product, such as asymmetric oxidations and reductions or C-H oxidations. All other types of reactions fall into the category of a **concession step**:

(1) **Nonstrategic redox manipulations** (i.e., reduction of ester to alcohol), (2) **functional group interconversions** (i.e., alcohol to mesylate to azide), and (3) **protecting group manipulations**.

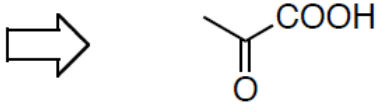
P. S. Baran, *J. Org. Chem.* **2010,** *75,* 4657.

Nature is usually not atom and redox economic...

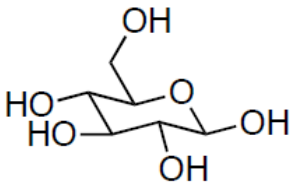
However, ...



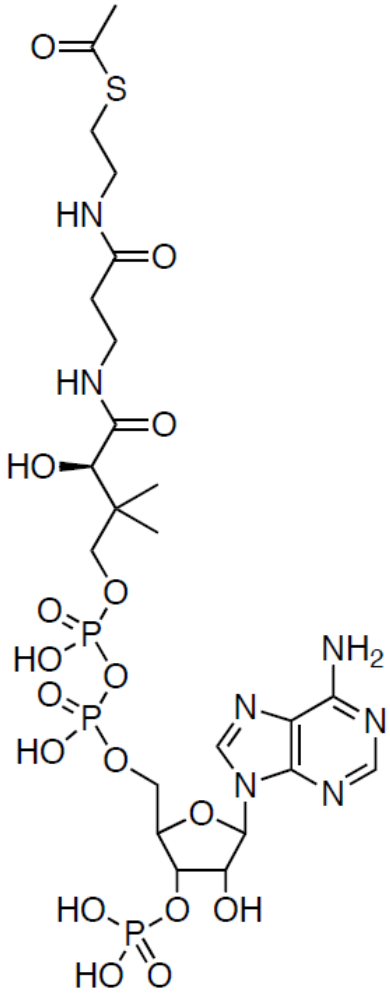
oleic acid



pyruvate



glucose



acetyl CoA

Future of Organic Synthesis

If we judge the state of our science by these strict criteria and compare its present power with that of Nature, then we will understand that, despite its glorious past and proud lineage, the art and science of chemical synthesis is still in its youth and in need of much improvement and advancement for its own sake.

如果用大自然的能力来评判有机合成的状态的话，我们就不难理解，虽然它有着辉煌的过去和高贵的血统，但它尚年轻，还需要更大的提高和发展。

K. C. Nicolaou, *Tetrahedron* **2003,** *59,* 6683