Master Course
in Organic Chemistry

2018-19

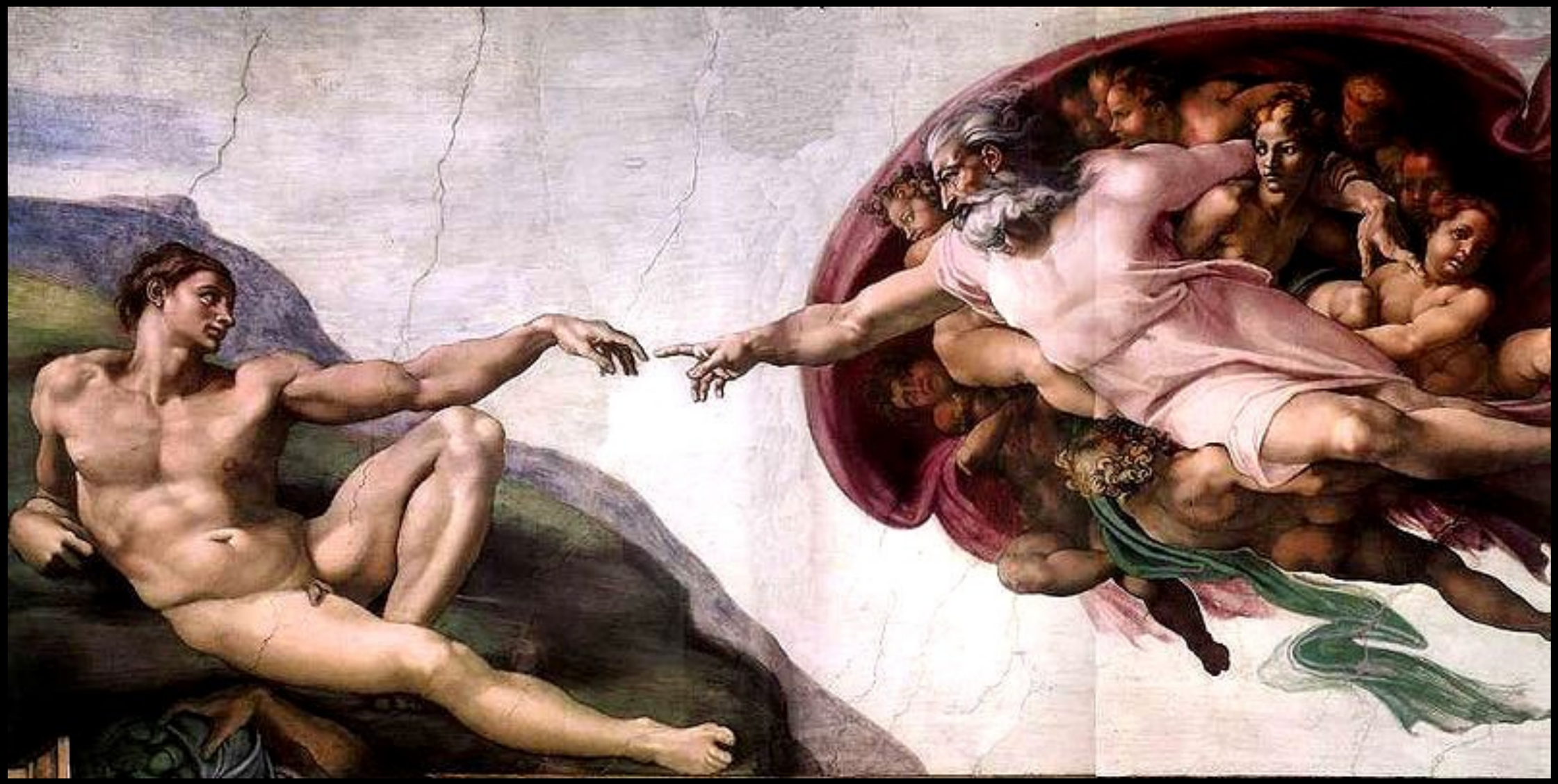
methods **and design** in organic synthesis

Pere Romea

Sistine Chapel, Michelangelo, 1508-1512

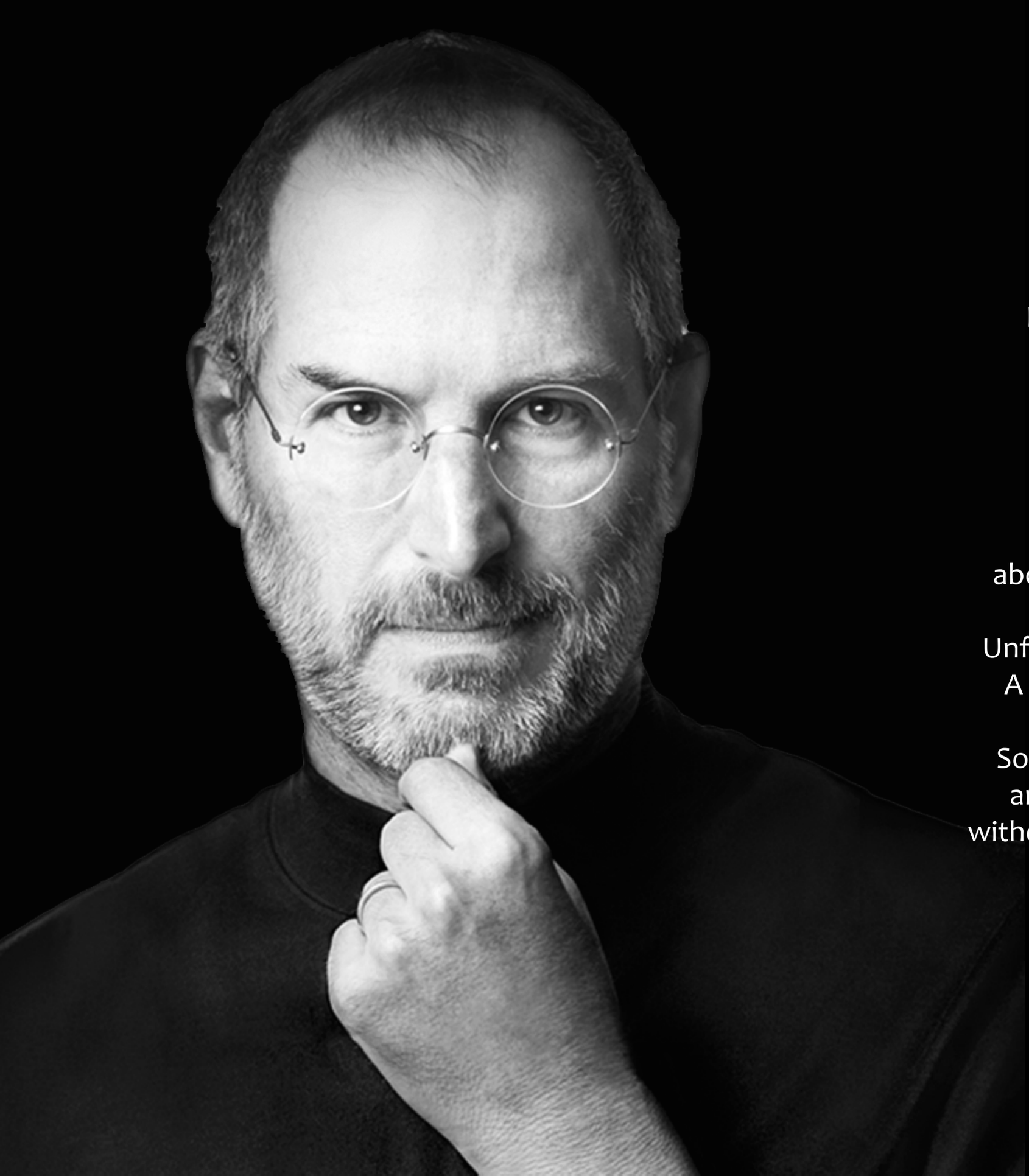
1. Introduction

Organic Synthesis …



Sistine Chapel
Michelangelo, 1508–1512

… deals with creation



Creativity is just connecting things.
When you ask creative people
how did they did something,
they feel a little guilty
because they didn't really do it,
they just saw something.

It seemed obvious to them after a while.
That's because they were able
to connect experiences
they've had and **synthesize** new things.
And the reason they were able to do
was that they 've had more experiences
or they have thought more
about their experiences than other people.

Unfortunately, that's too rare a commodity.
A lot of people in our industry haven't had
very diverse experiences.
So the don't have enough dots to connect,
and they end up with very linear solutions
without a broad perspective on the problem.
The broader one's understanding
of the human experience,
the better design we will have.

Steve Jobs, February 1995

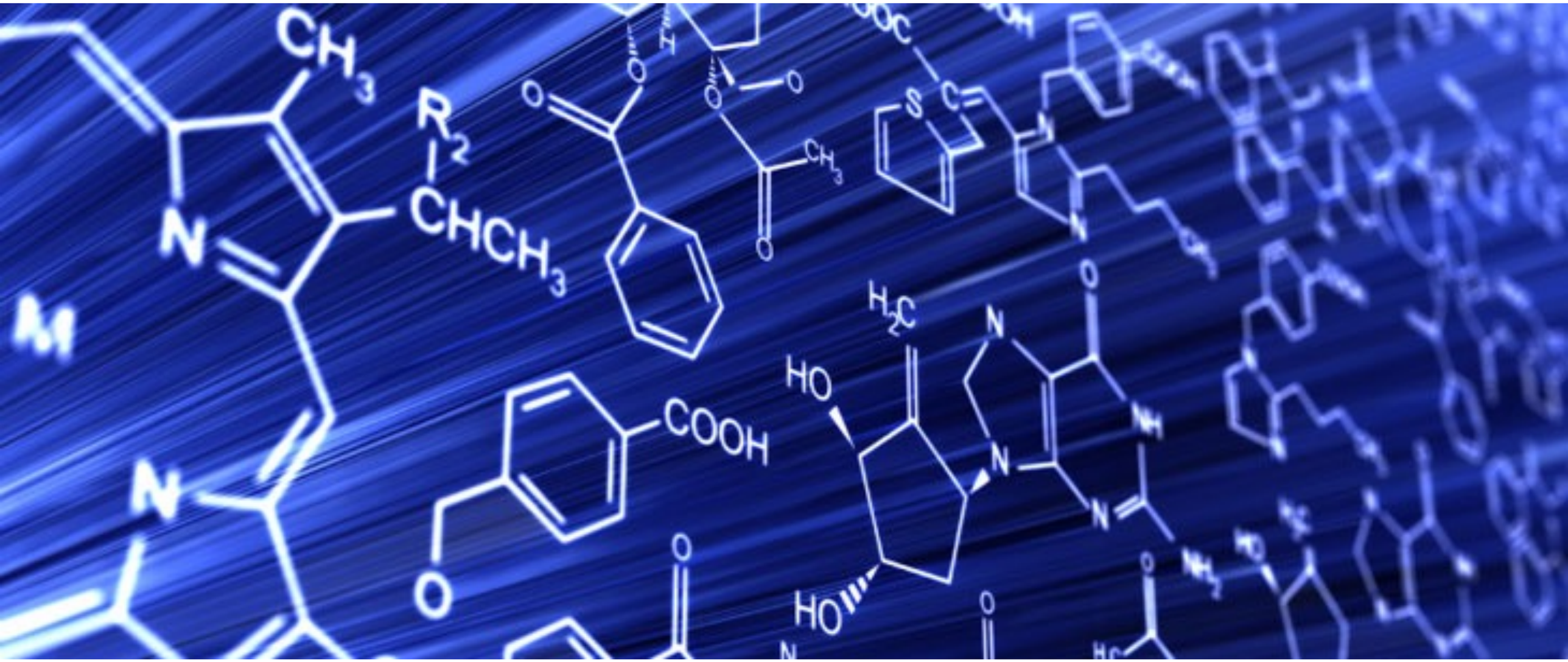
Creativity is just connecting things

What?

Why?

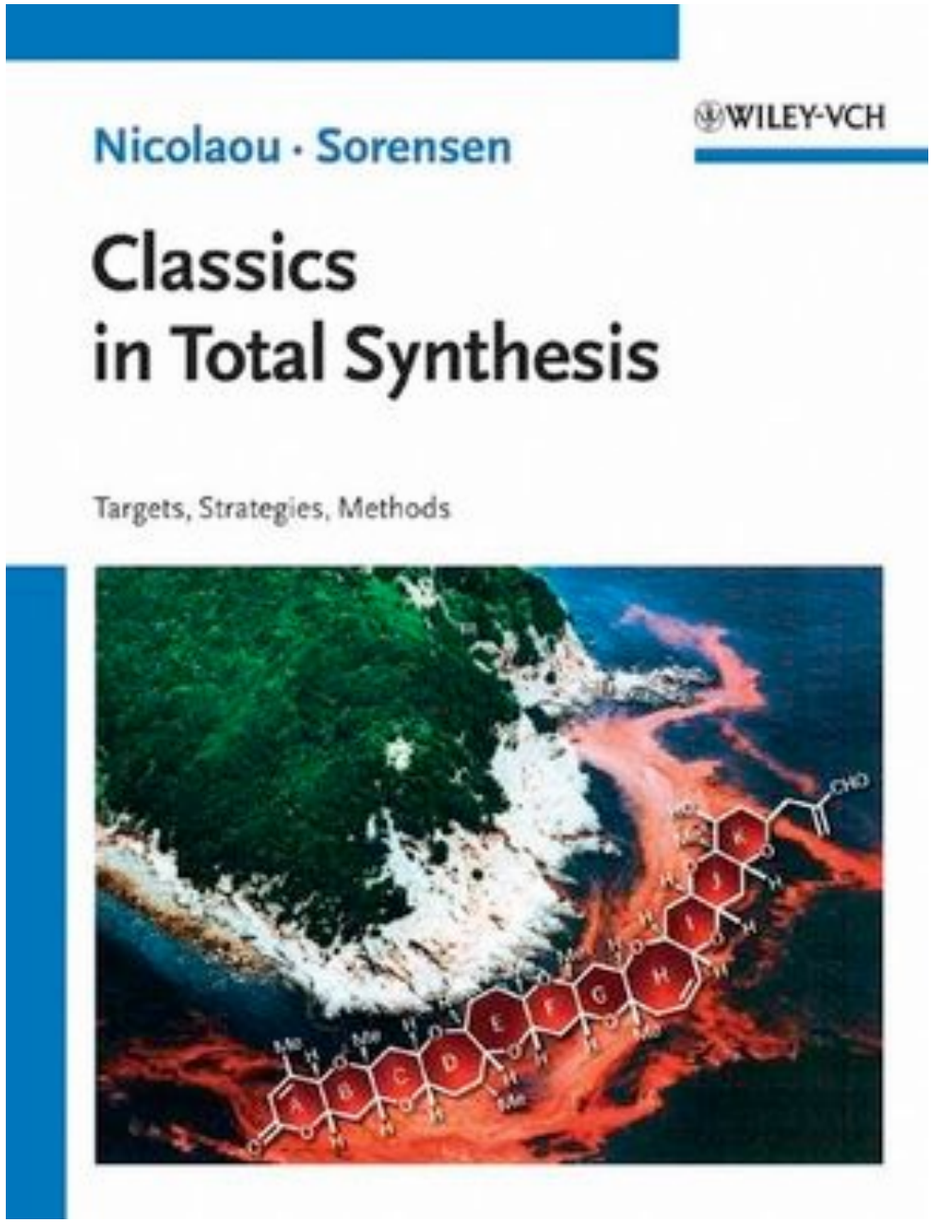
How?

Organic Synthesis



preparation of a natural or unnatural compound from simple precursors

What?

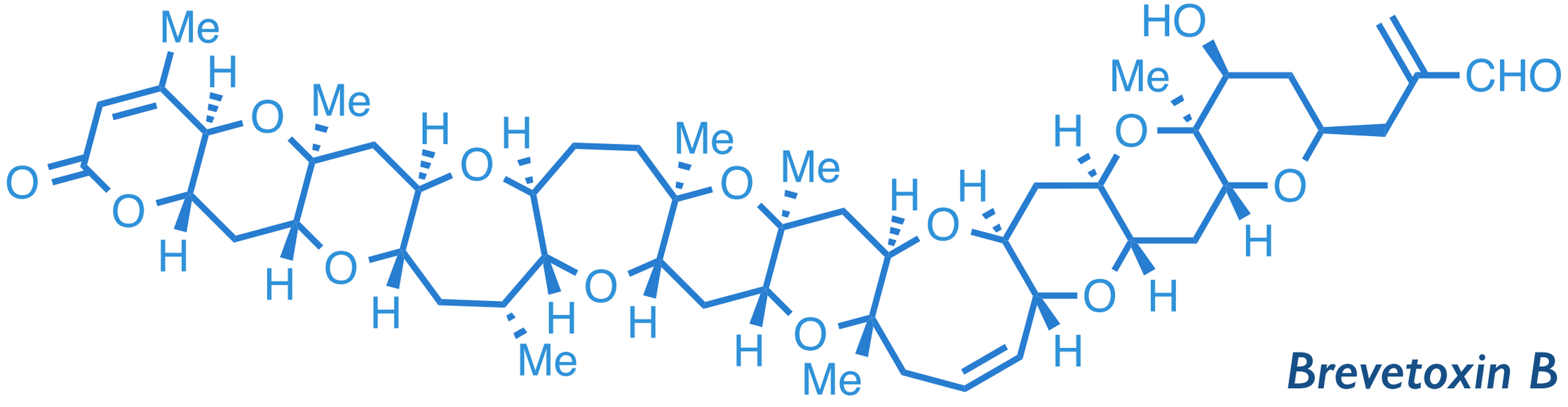


Natural products

One of the most potent neurotoxins produced by the red tide organism, *Gymnodium breve*

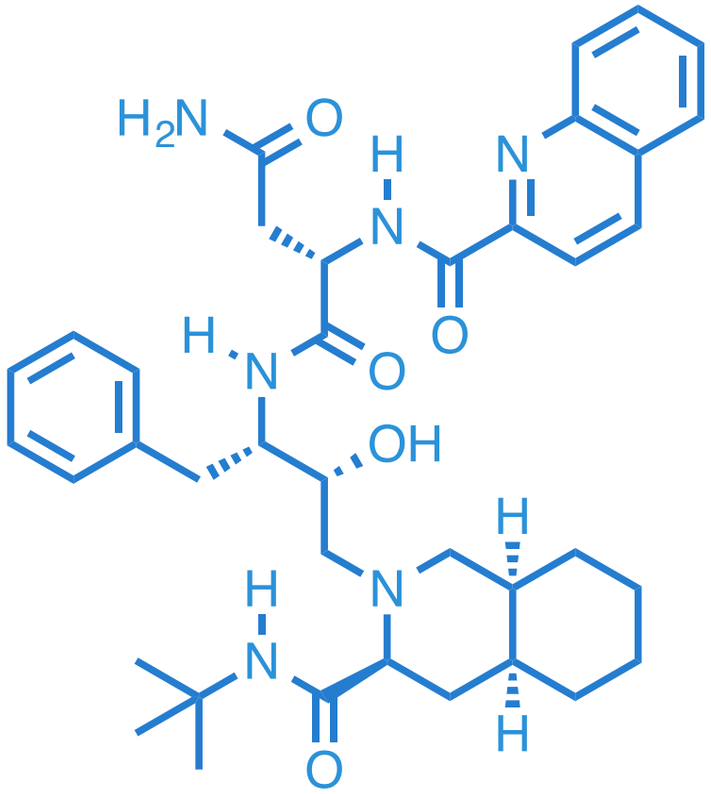
Nicolaou, K. C. *JACS* **1995**, *117*, 1173

Nakata, T. *JACS* **2004**, *126*, 14374

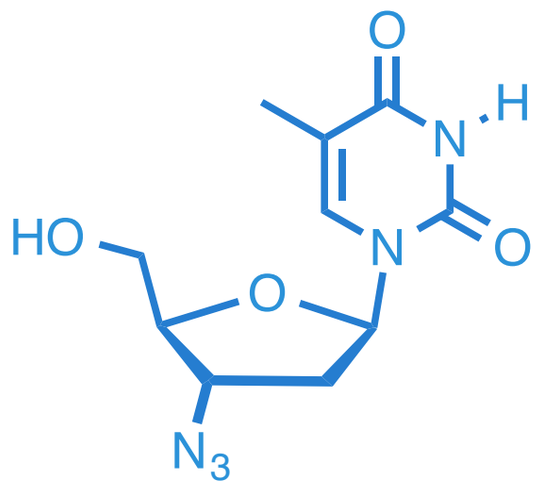


Brevetoxin B

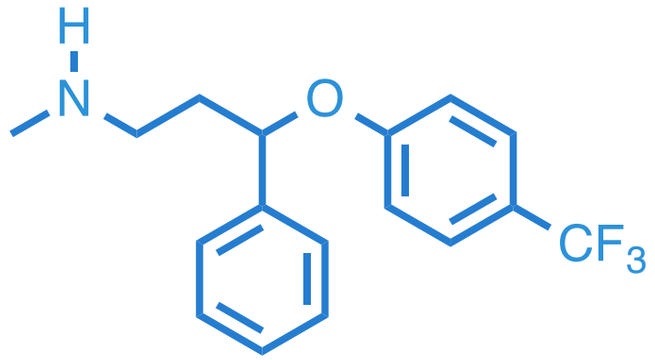
Unnatural products



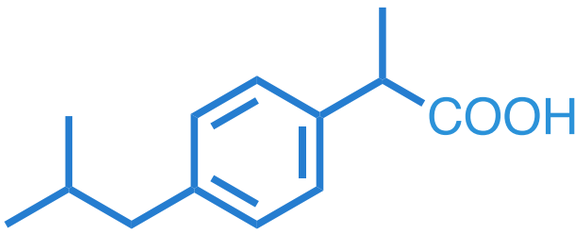
Saquinavir
Antiretroviral
Hoffmann-La Roche



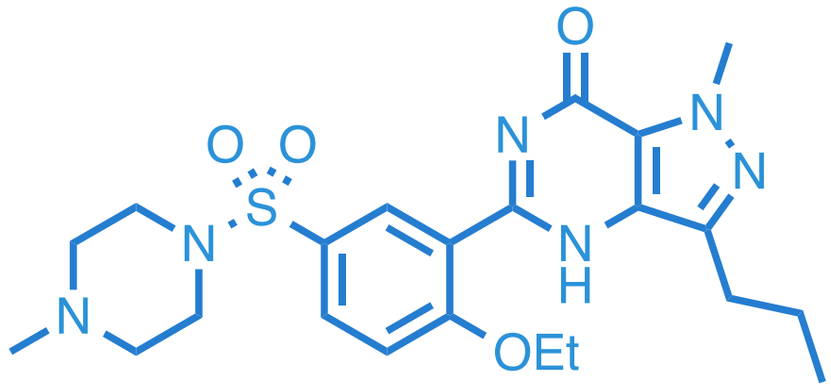
AZT
Antiretroviral



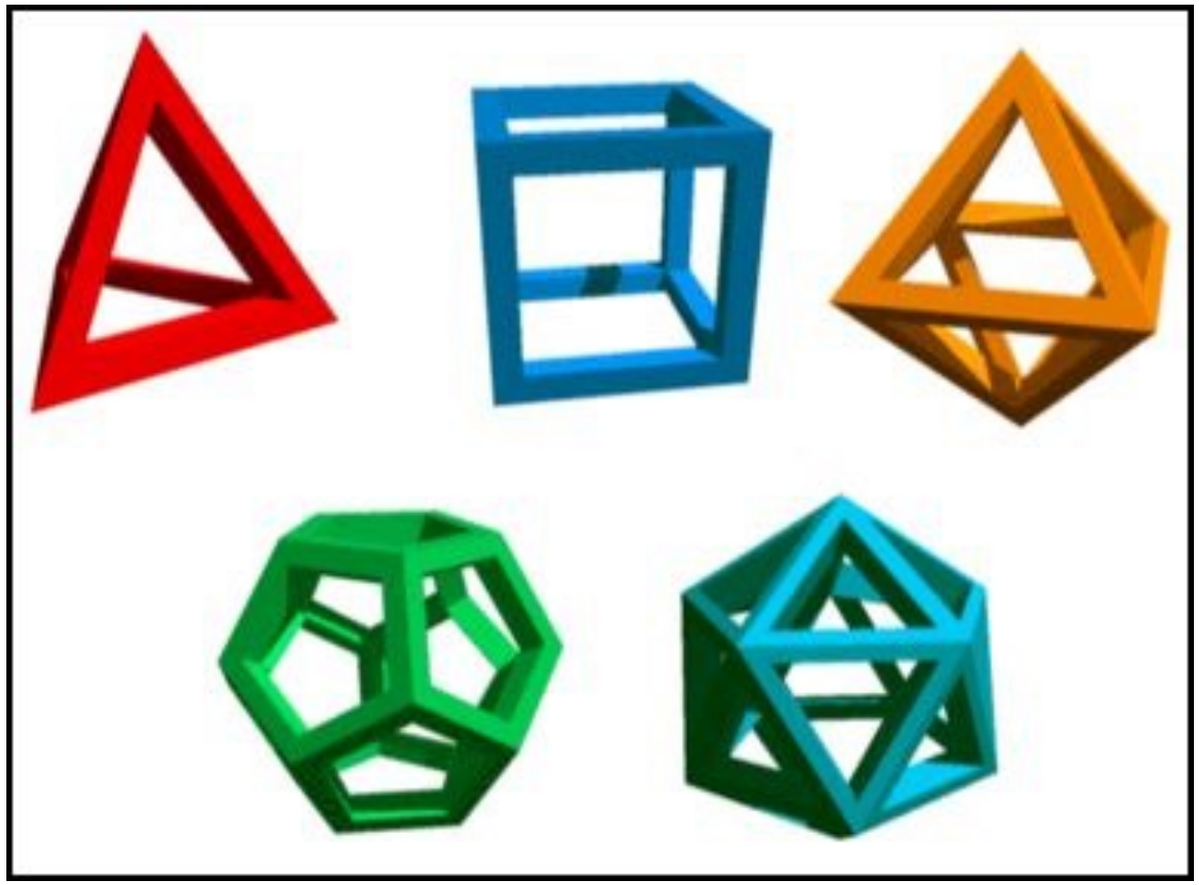
Prozac®
Antidepressant



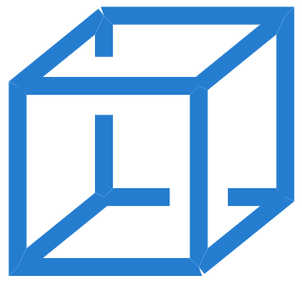
Ibuprofen
Antiinflammatory



Viagra®
Erectile dysfunction
Pfizer



Unnatural products

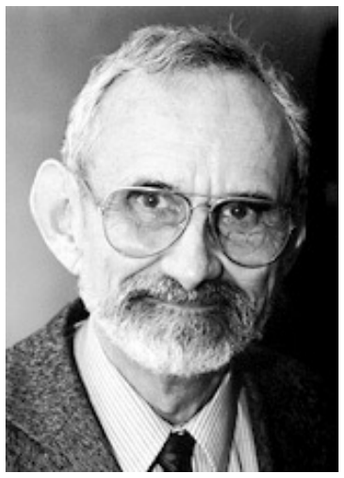


Cubane

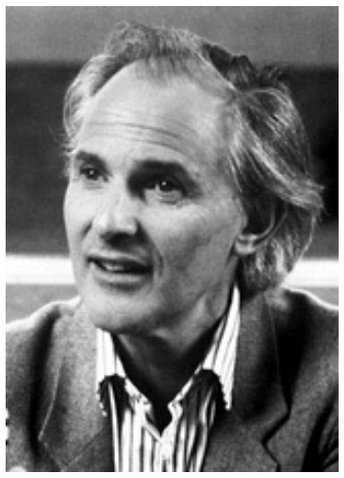
Eaton, P. E. *JACS* **1964**, *86*, 3157
ACIE **1992**, *31*, 1421

Platonic solids

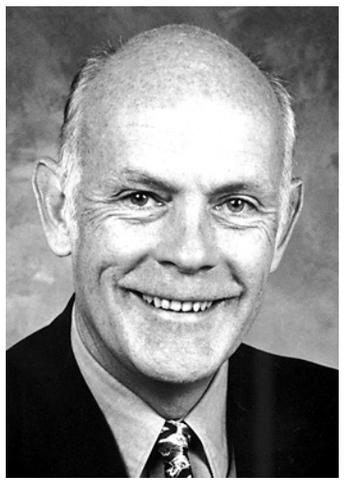
Fullerene



Robert F. Curl

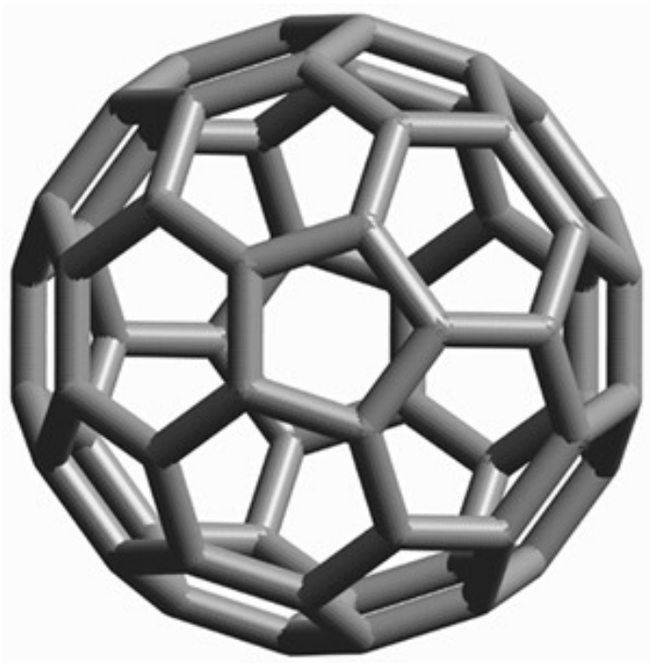


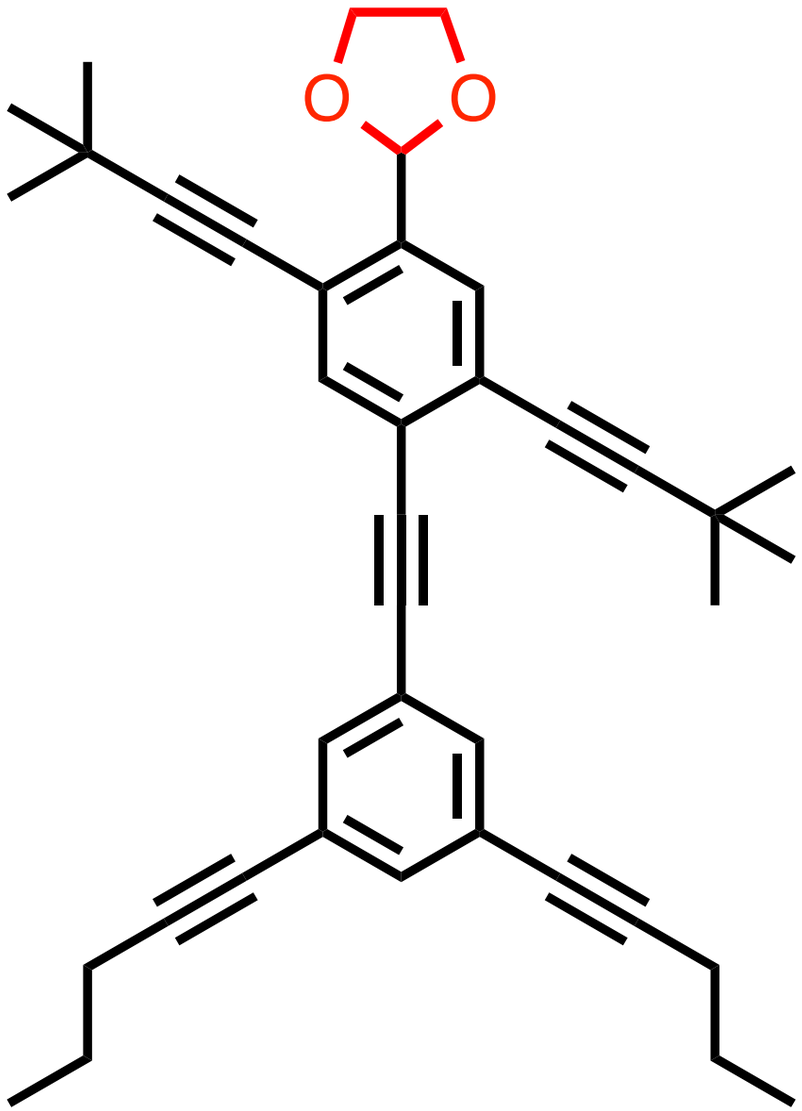
Harold Kroto



Richard E. Smalley

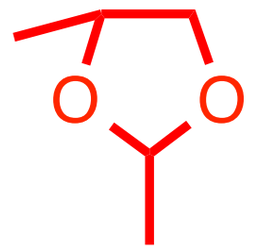
NOBEL PRIZE IN CHEMISTRY 1996



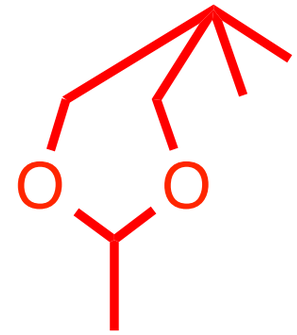


Nanoputians

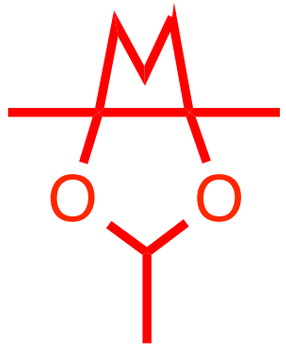
Tour, J. M. *JOC* **2003**, 68, 8750



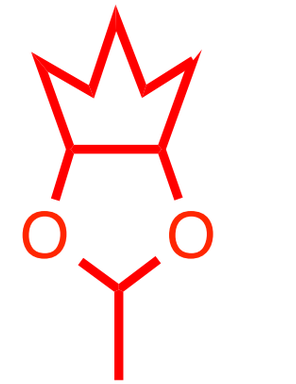
Nano Green Beret



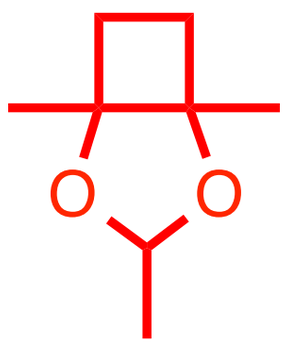
Nano Athlete



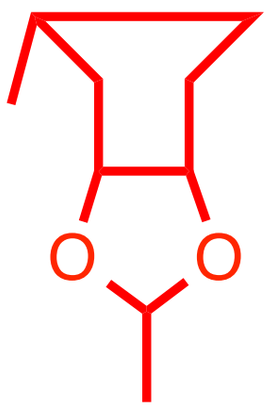
Nano Texan



Nano Monarch



Nano Pilgrim

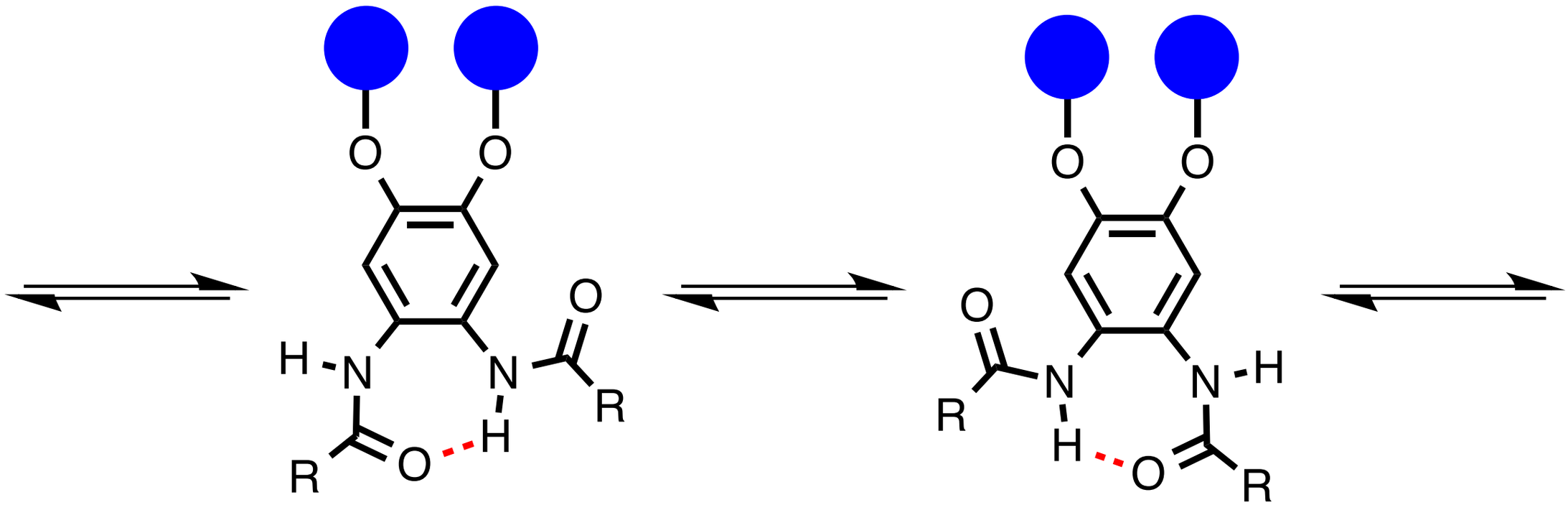


Nano Scholar

Functional molecules

Unnatural products

Rebek, J. M. *JACS* **1997**, *119*, 9911

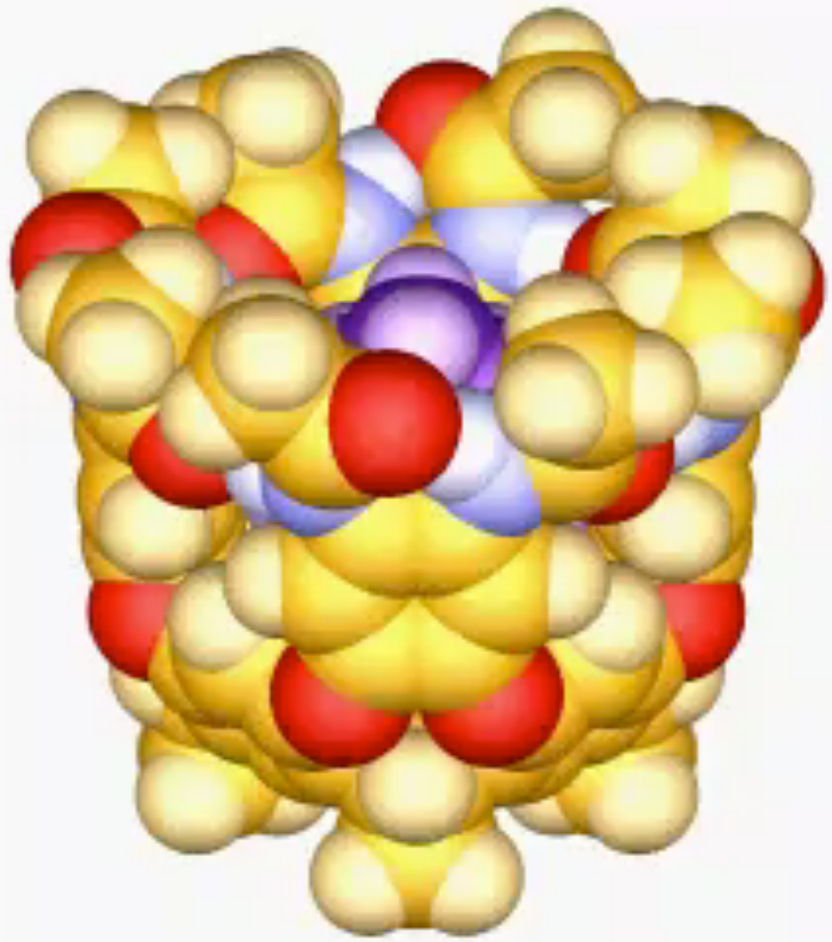


New **SYNTHETIC RECEPTORS**
have been designed to be used in molecular recognition studies.
The **volleyball** is an example of a system on the verge of assembly.
The bowl-shaped curvature of the resorcinarene features a rim rich in hydrogen bond donors and accepters and is poised to make a closed shell.

Functional molecules

Unnatural products

Rebek, J. M. *JACS* **1997**, *119*, 9911



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Nobel Prize in Chemistry 2016

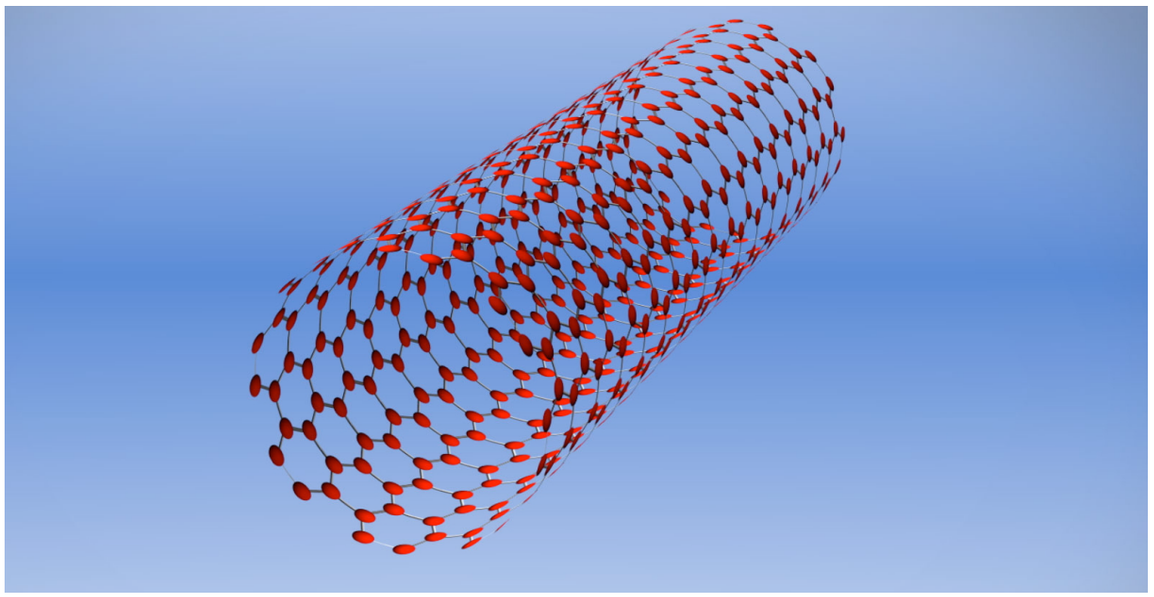
Jean-Pierre Sauvage

Sir J. Fraser Stoddart

Bernard L. Feringa

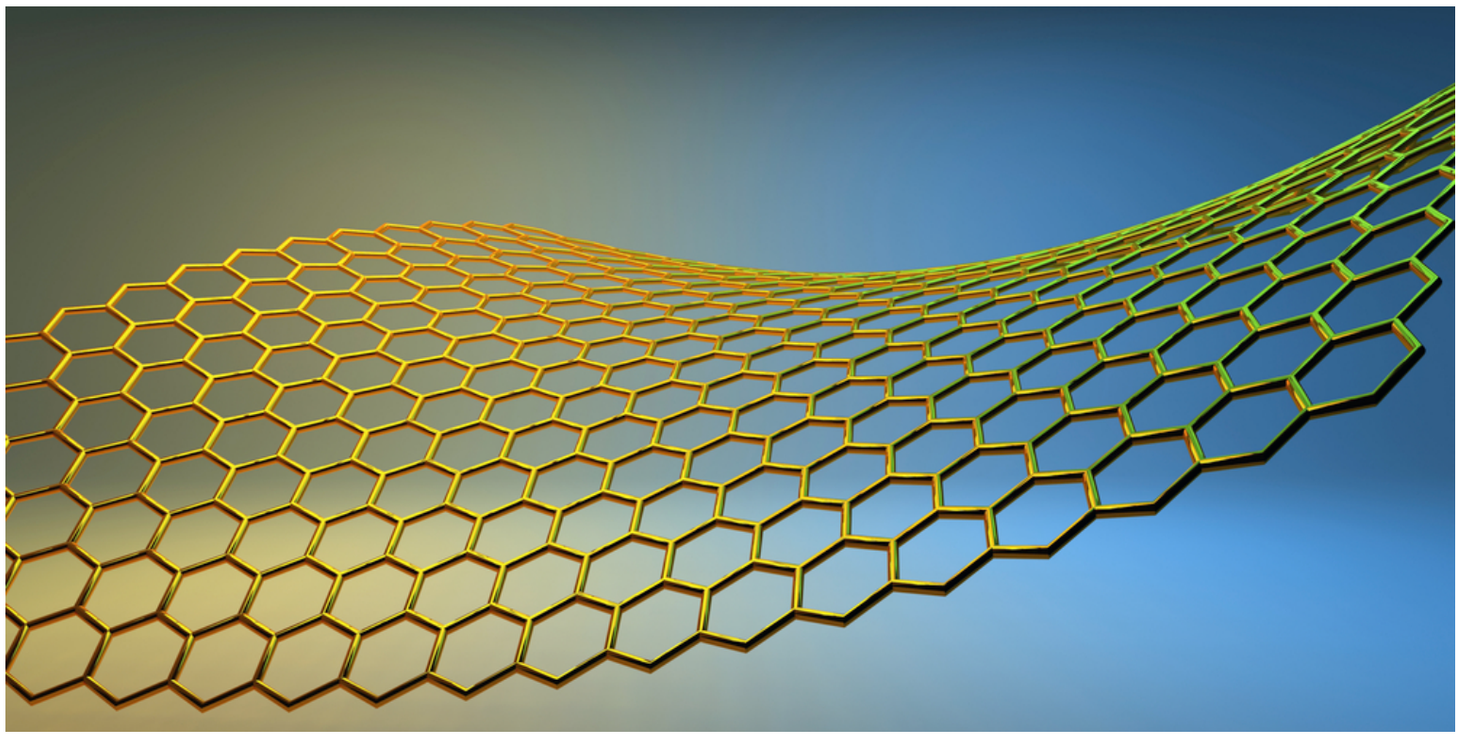
for the design and synthesis of molecular machines

New Materials



Nanotubes

Liquid crystals



Graphene

We can synthesize whatever we want

La chimie crée son objet

Cette faculté créatrice,
semblable à celle de l'art lui-même,
la distingue essentiellement
des sciences naturelles et historiques

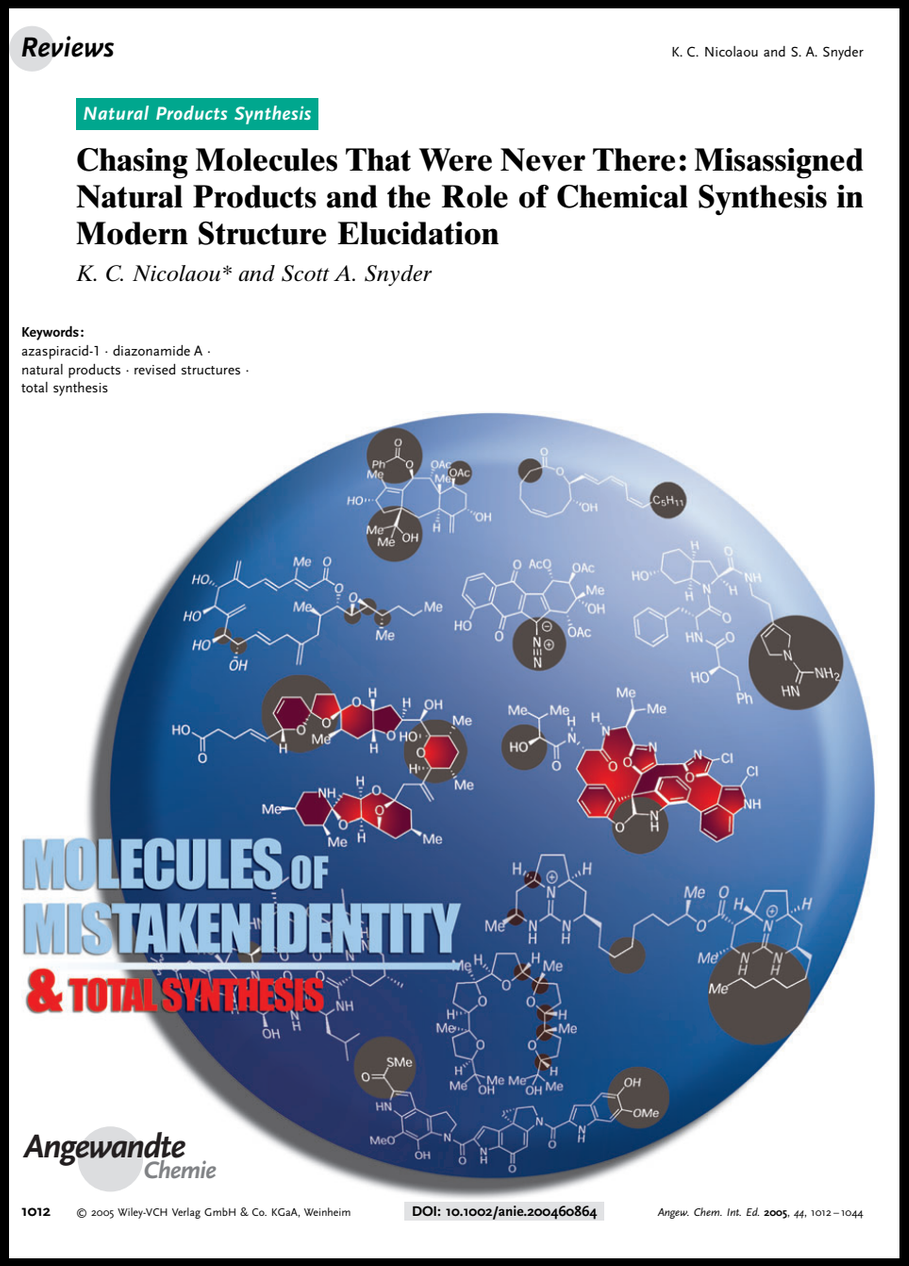
Marcellin Berthelot, 1860

Why?

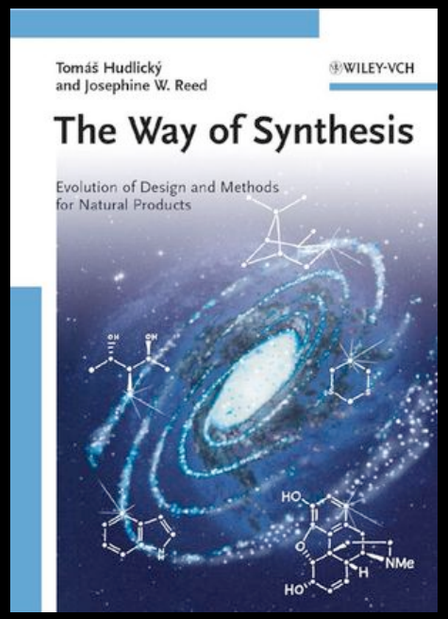
Chemistry: Why synthesize?

Ball, P. *Nature* **2015**, *528*, 327

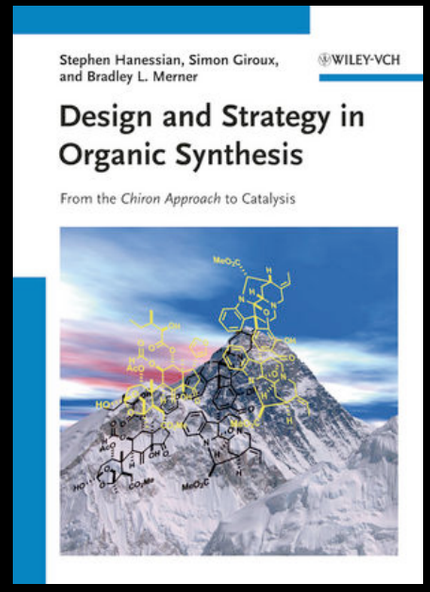
Total synthesis is the final proof for originally assigned structures …



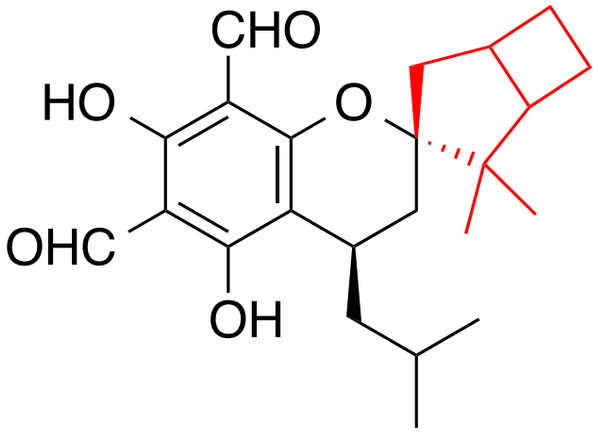
Nicolaou, K. C. *ACIE* **2005**, *44*, 1012



Chapter 1.2

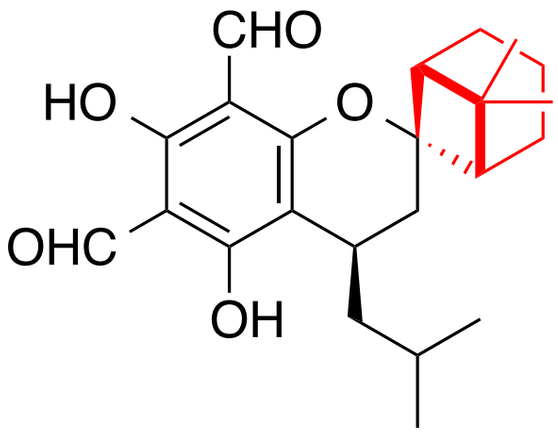


Chapter 2

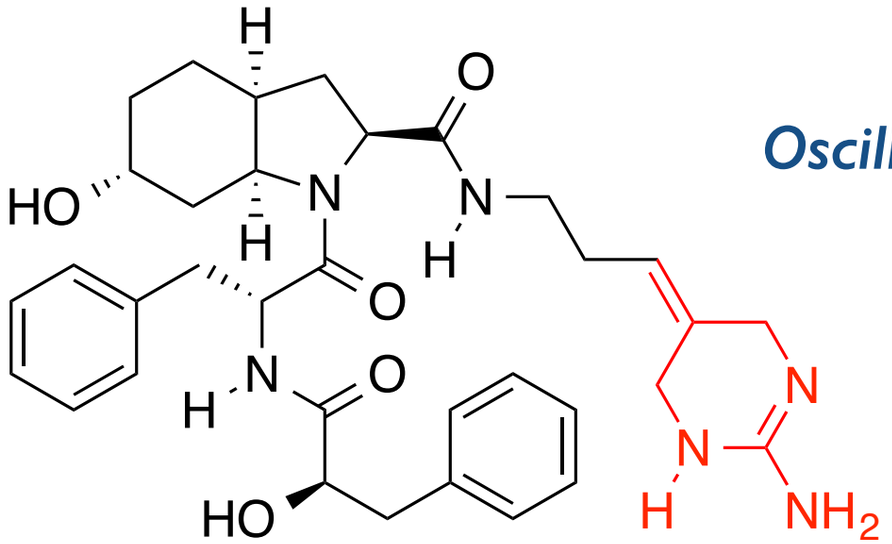


proposed

Robustadial A

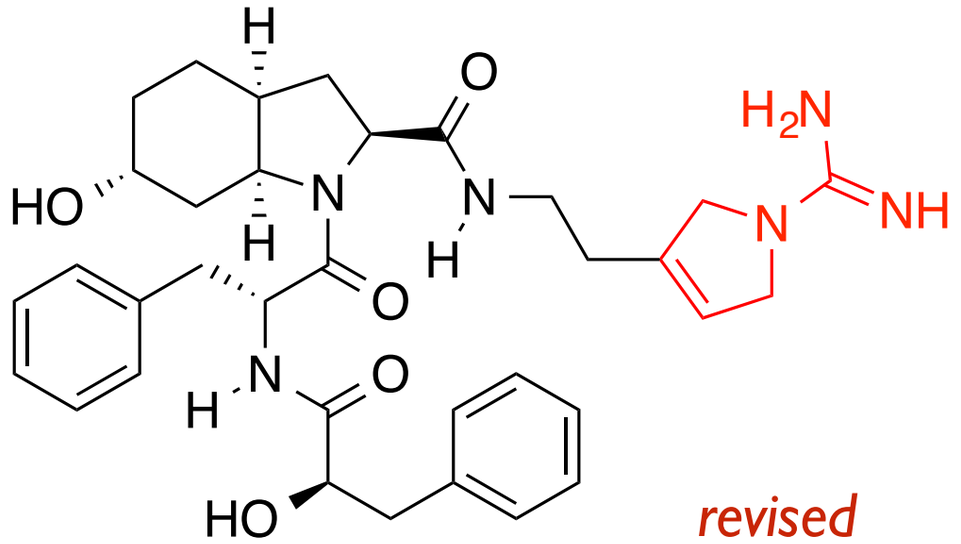


revised

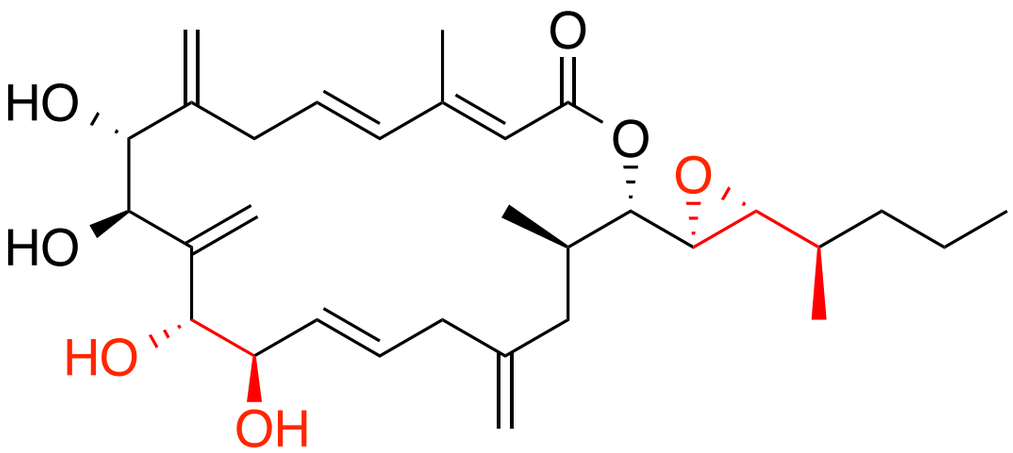


proposed

Oscillarin

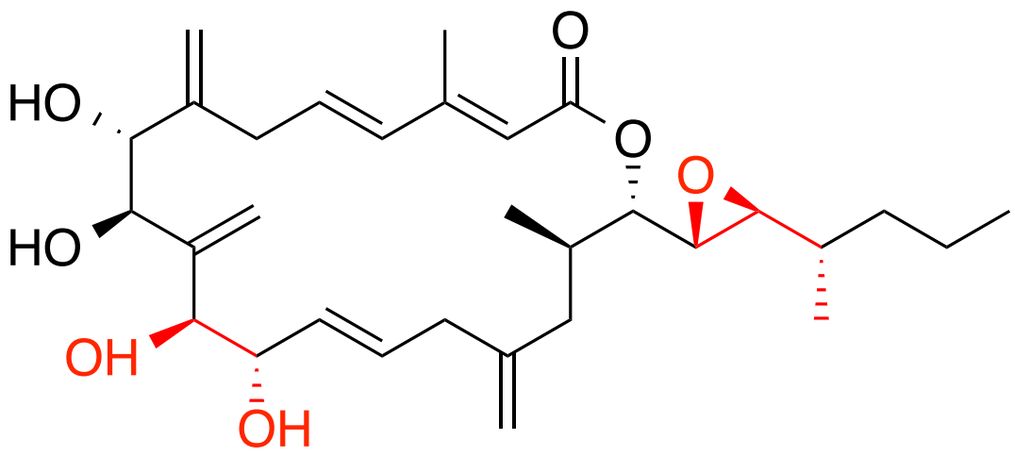


revised



proposed

Amphidinolide A



revised

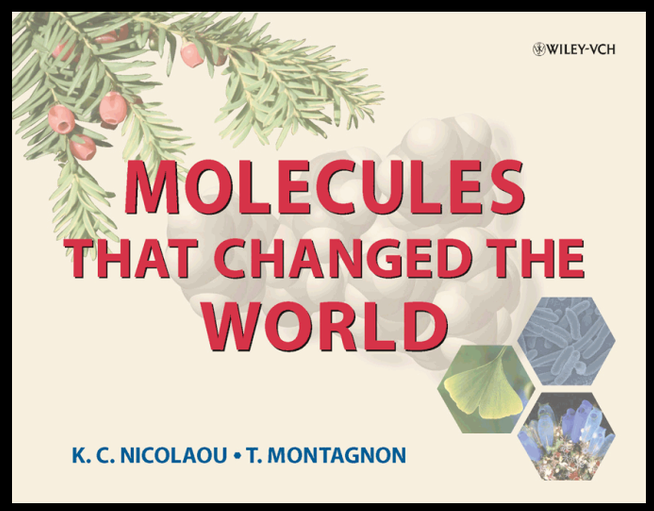
Total synthesis is the final proof
for originally assigned structures …

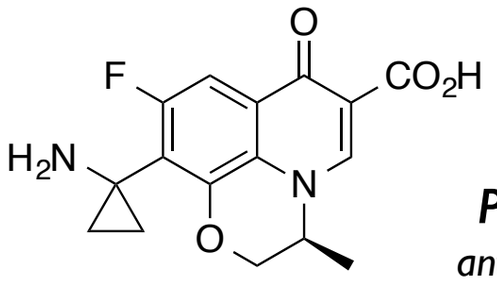
… and essential to prepare
pharmaceutical drugs, agrochemicals,
and new materials

recommended book

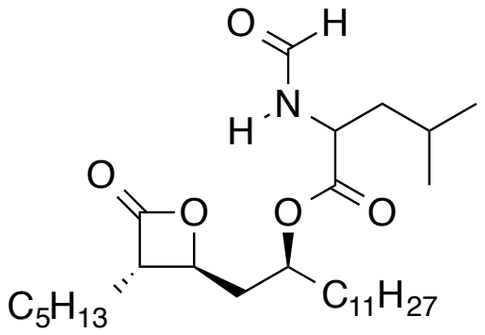
MOLECULES THAT CHANGED THE WORLD

Nicolaou, K. C.; Montagnon, T.

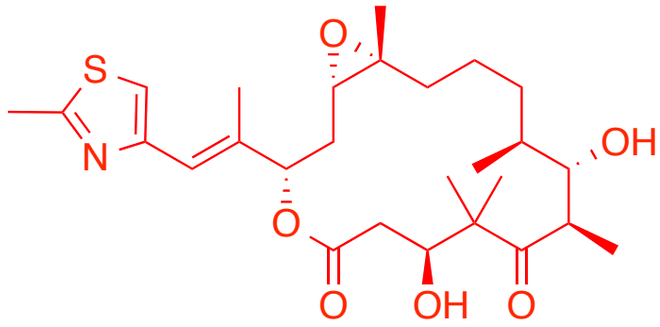




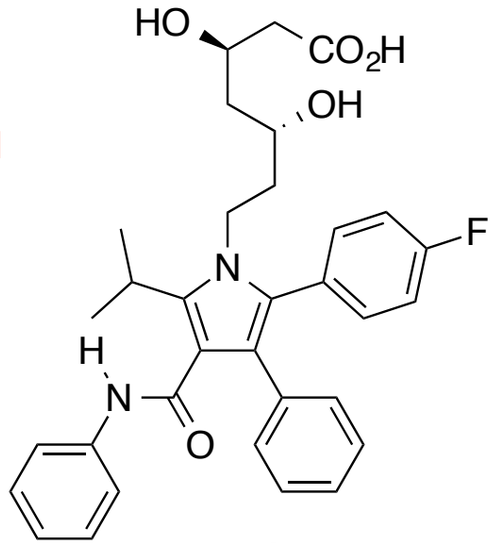
Palsil
antibiotic



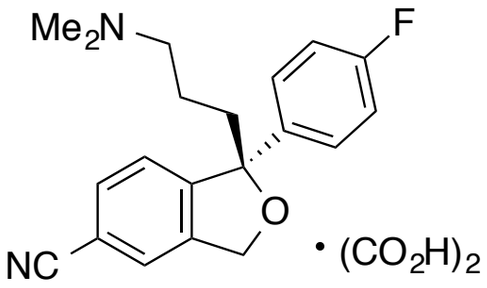
Xenical
antiobesity



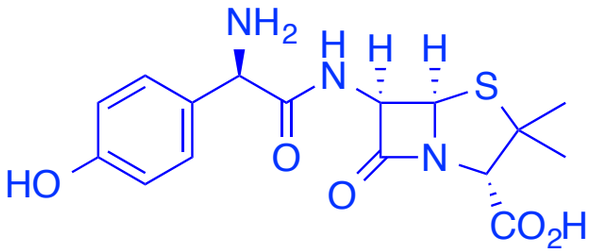
Epothilone B
anticancer



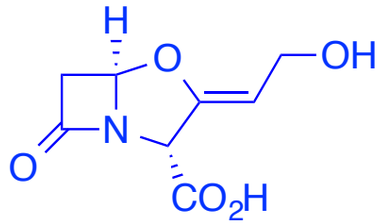
Lipitor
hypercholesterolemic



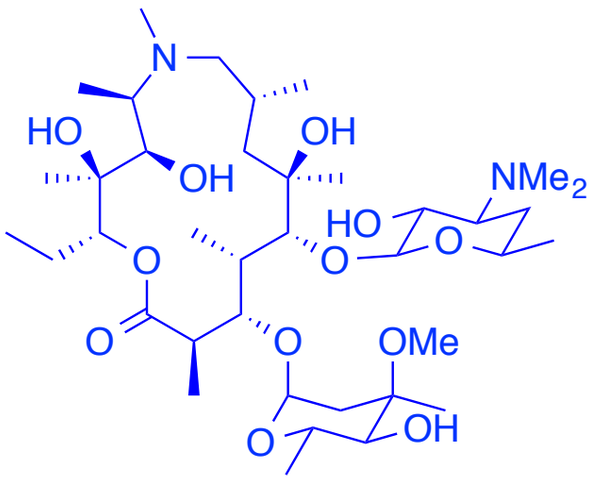
Cipralex
antidepressant



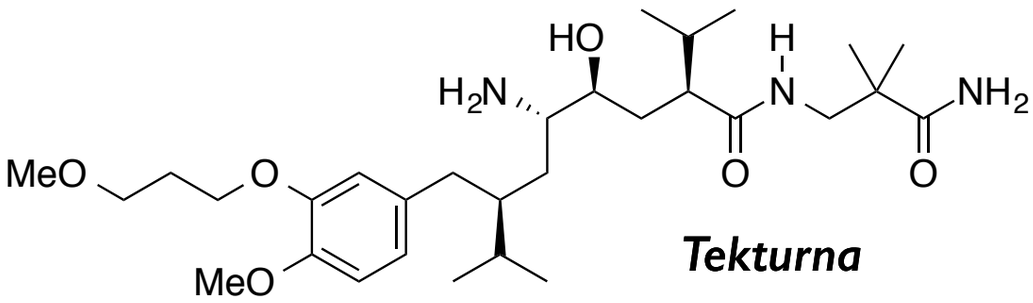
Augmentin
antibiotic



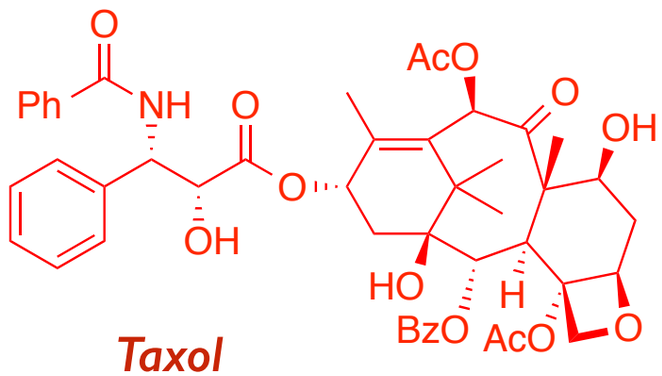
Clavulanic acid
antibiotic



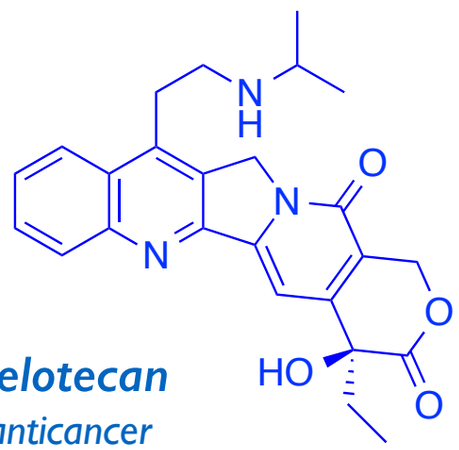
Zithromax
antibiotic



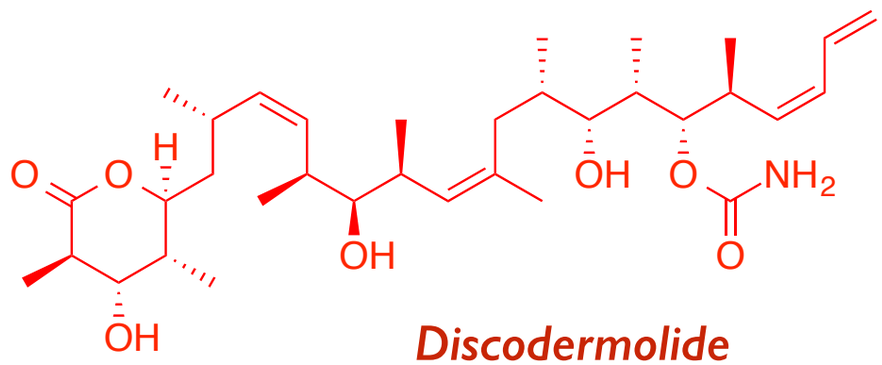
Tekturna
antihypertensive



Taxol
anticancer

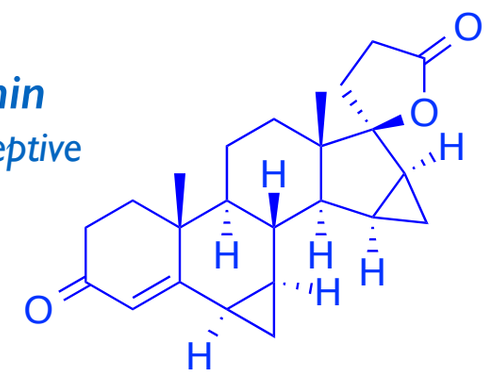


Belotecan
anticancer



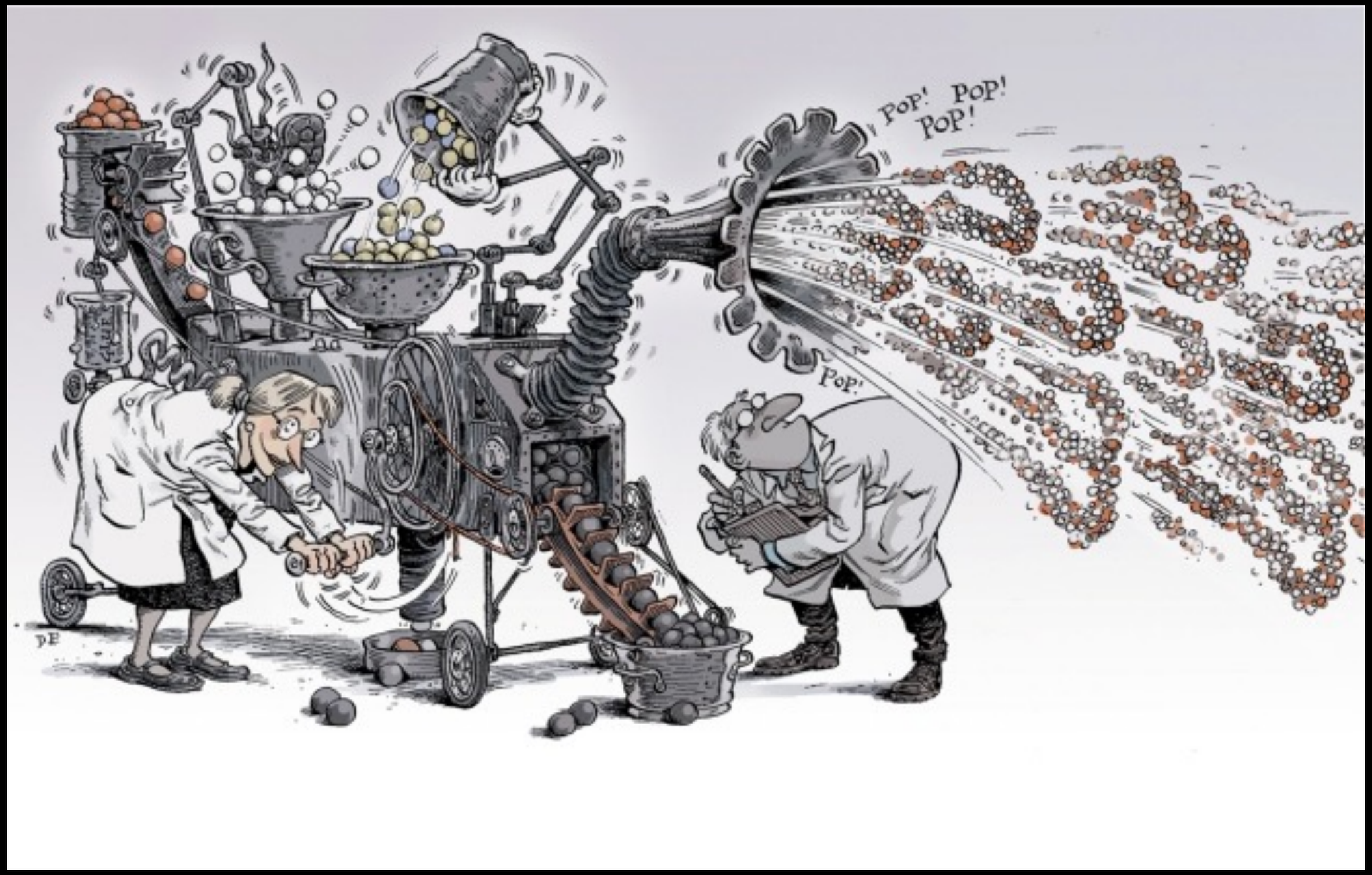
Discodermolide
anticancer

Yasmin
contraceptive



Chemistry: Why do chemists make molecules?

Ball, P. *Nature* **2015**, *528*, 327



... A lingering debate

Because **we need them**,

or we look for molecules with **useful properties**,

or to explore the **variety of shapes and structures**,

or we want to explore **theoretical questions**,

or because pedagogical reasons

Better than making molecules more complicated or larger is making them more useful, and making them in more useful ways.

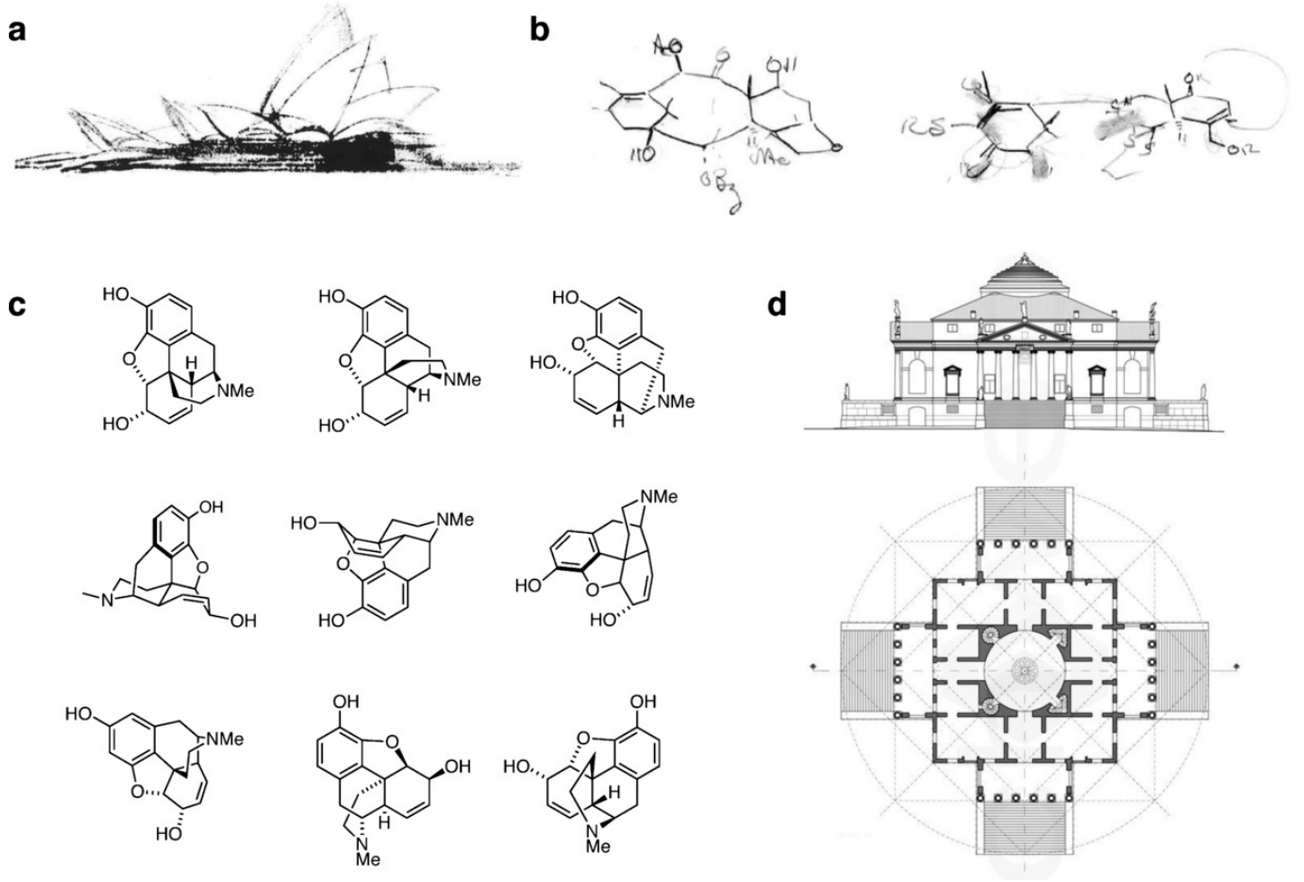
Like architecture,
chemistry deals in elegance in both design and execution.

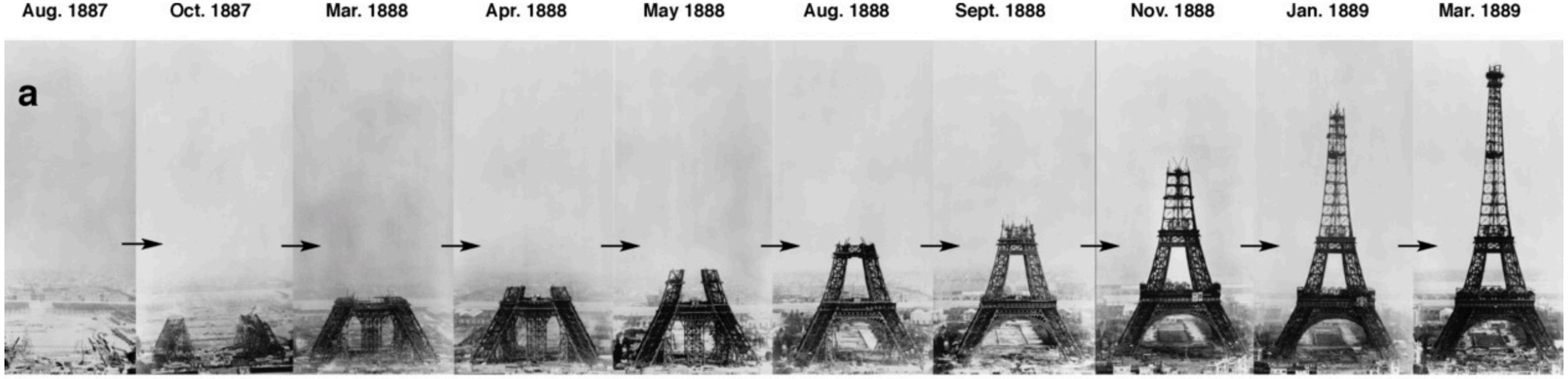
There has not been enough discussion of these aspects of the science:
how they are manifested, how they motivate,
how much they are worth conserving.

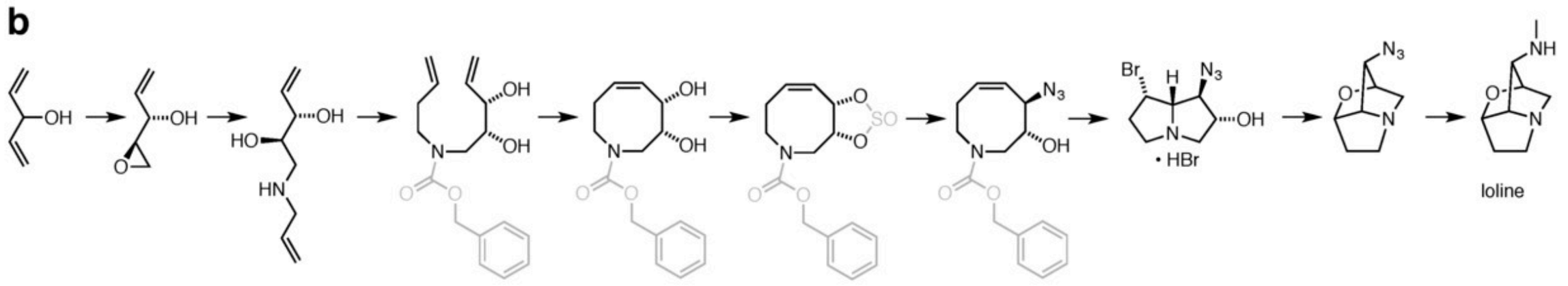
Trauner, D.

ACIE **2018**, 57, 4177

An inspiring essay on
the links between
architecture and **chemistry**







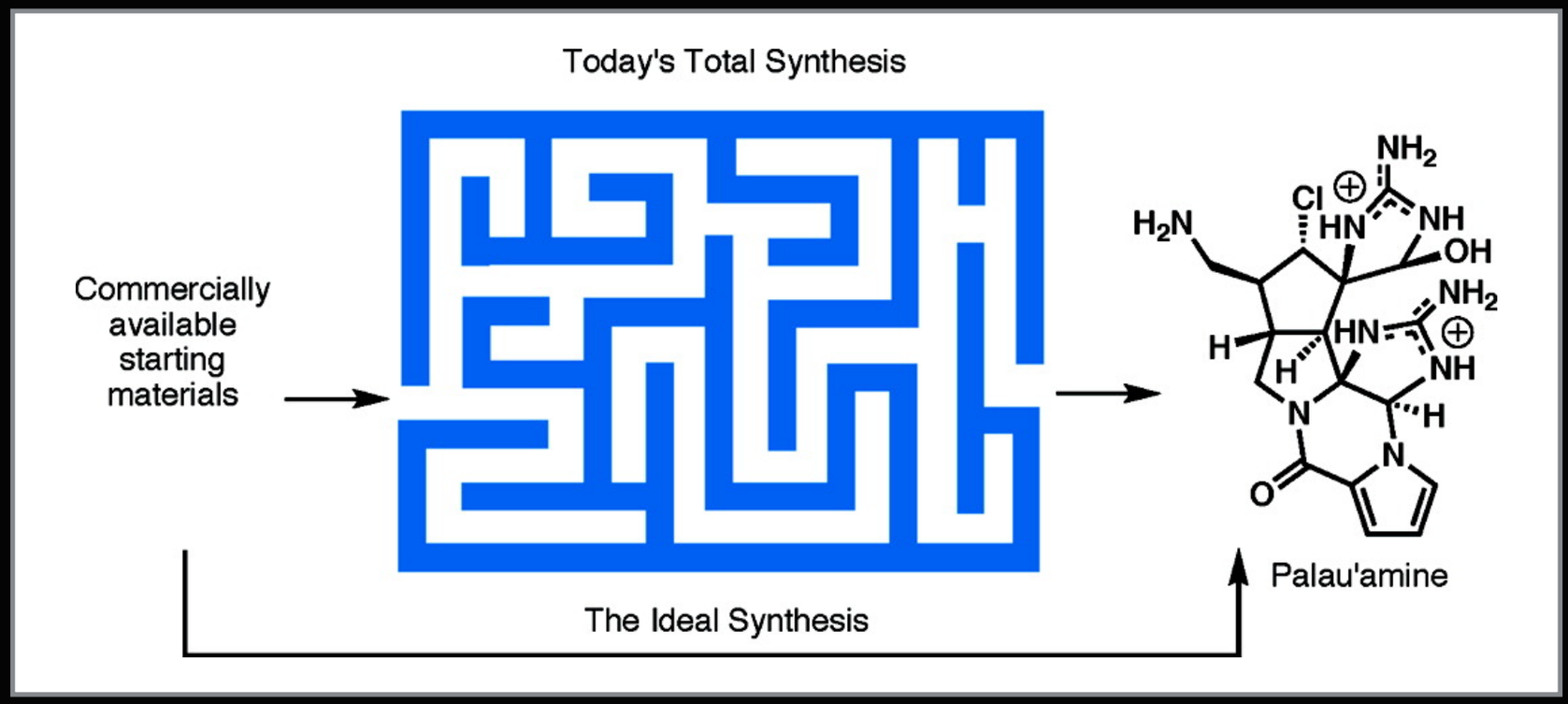
Grand Challenge

In 20–40 years,
scientists will be able to deliver
any desired molecule
within a timeframe
useful to the end–user,
using safe,
economically viable
and
sustainable processes

How to make molecules in days, not years!

How?

Irrespective of the target, there is an endless pursuit of the IDEAL SYNTHESIS



Baran, P. S. *JOC* 2010, *75*, 4657

IDEAL SYNTHESIS refers to the production of a target in a single synthetic operation from readily available starting materials, in 100% yield and without side-product formation.

The synthesis should be simple, safe, economically acceptable and environmentally friendly

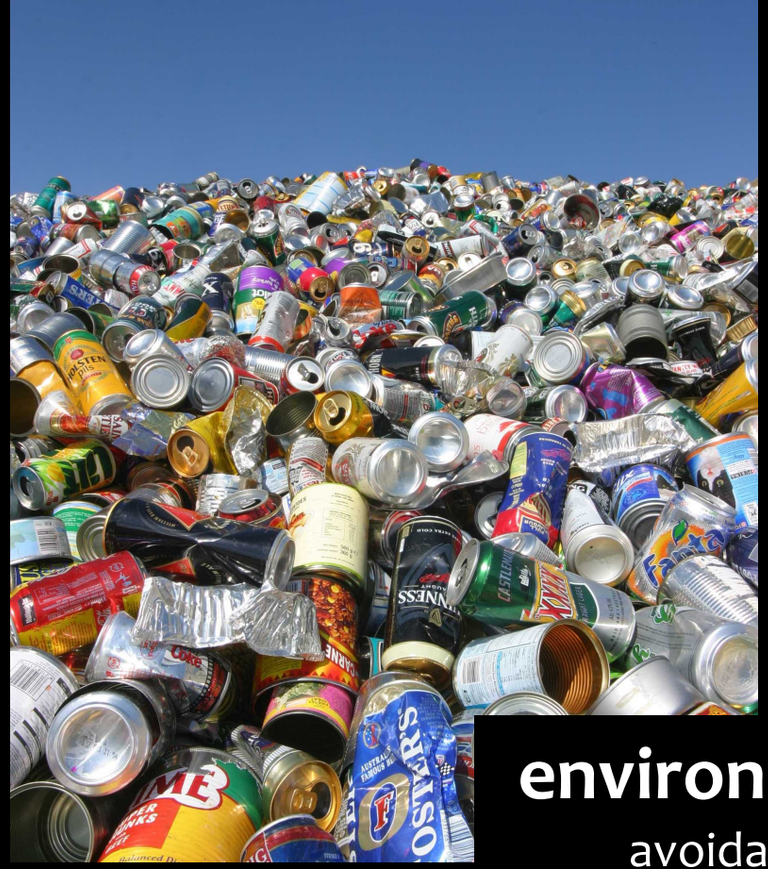
Wender, P. A. *Nature* **2009**, *460*, 197

economically acceptable

cost of materials (cheapest route)
novelty (patent route)

safety

avoidance of risky procedures



reproducibility

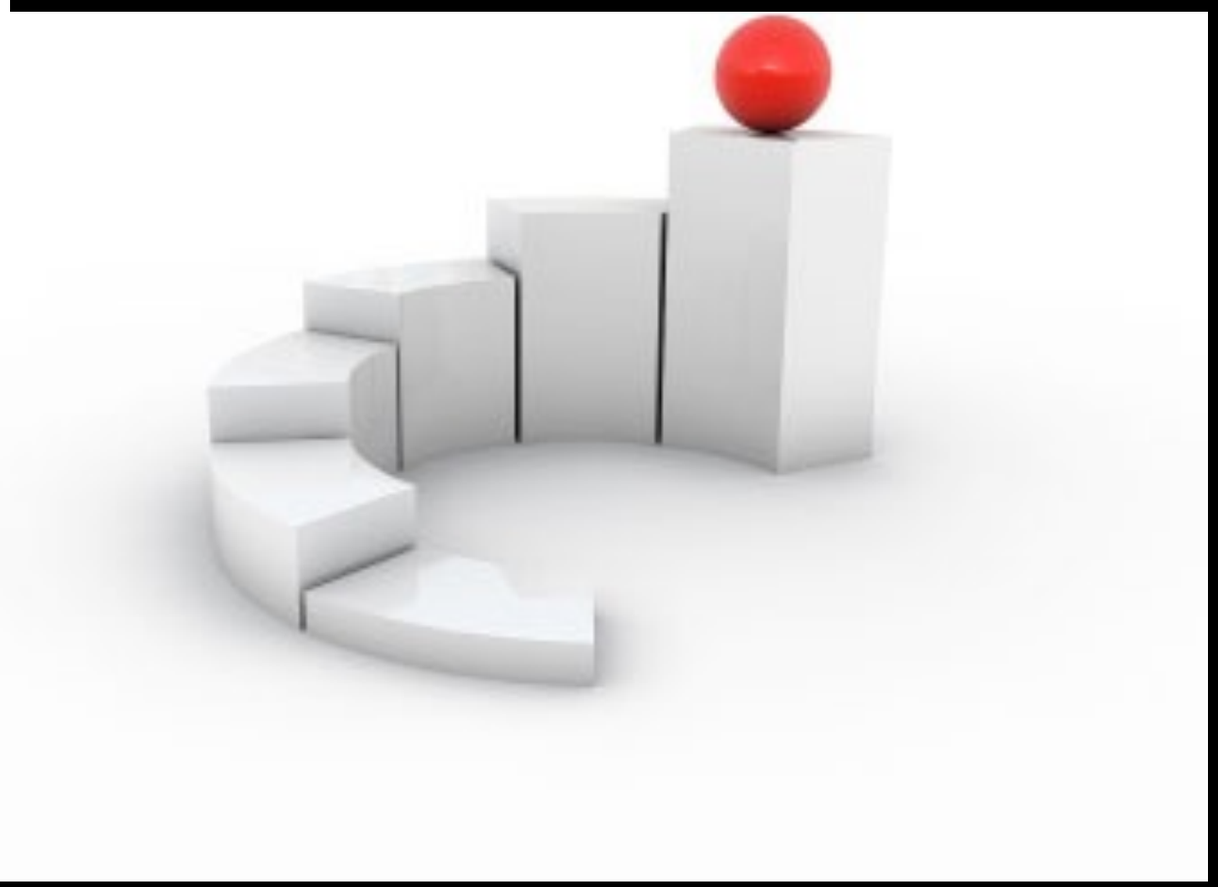
easily scaled-up

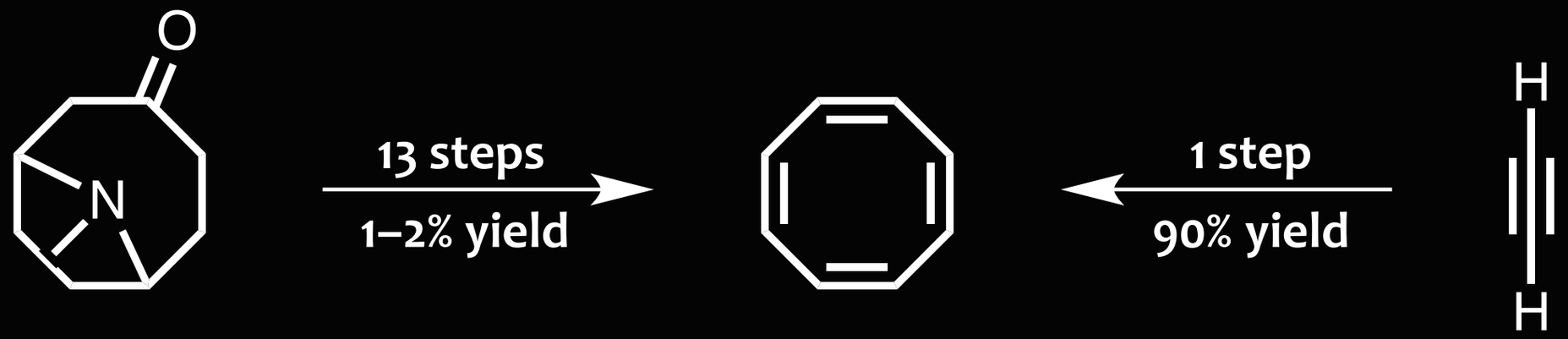
environmentally acceptable

avoidance of problematic waste
avoidance of toxic intermediates

highest yield

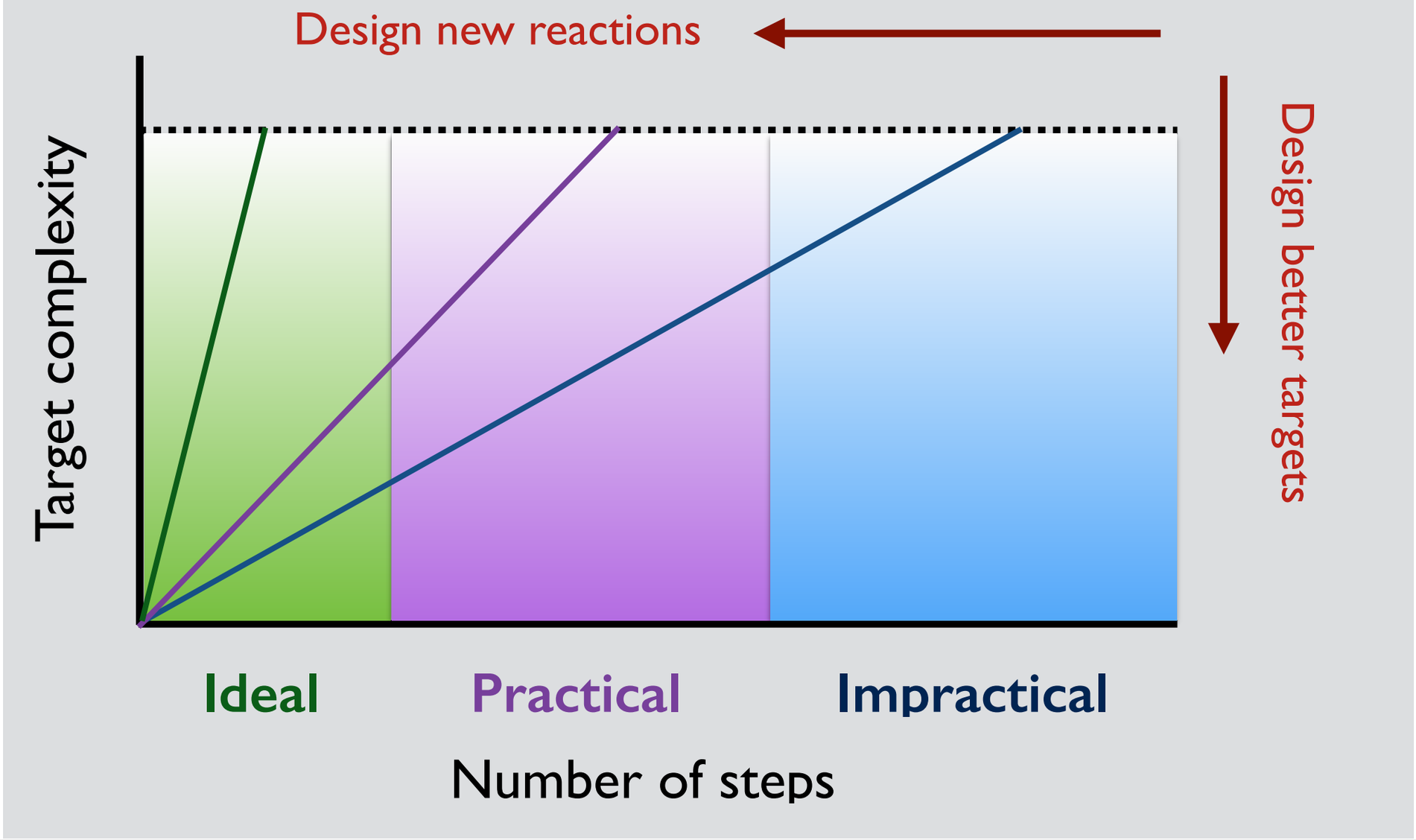
A Single Step?




O
N
13 steps
1–2% yield
1 step
90% yield
H
H

Unfortunately,
the vast majority of compounds
are synthesized through multistep routes.
Therefore, the NUMBER OF STEPS
of any synthetic sequence
is one the most important concerns

STEP ECONOMY

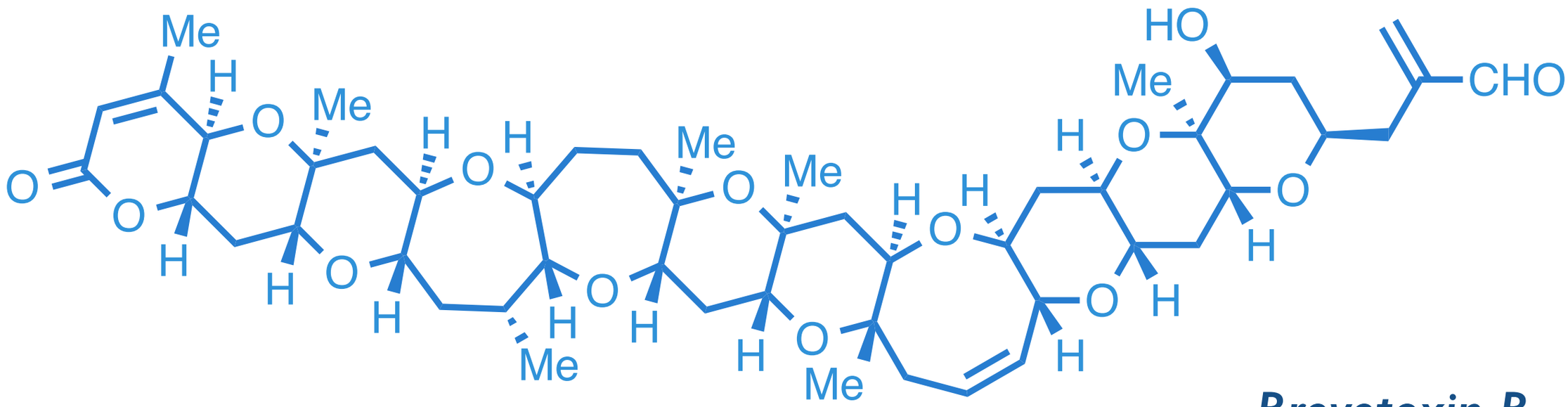


Toward the **ideal synthesis** and molecular function through synthesis-informed design

Wender, P. A. *Nat. Prod. Rep.* **2014**, *31*, 433

Synthesis at the molecular frontier

Wender, P. A. *Nature* **2009**, *460*, 197



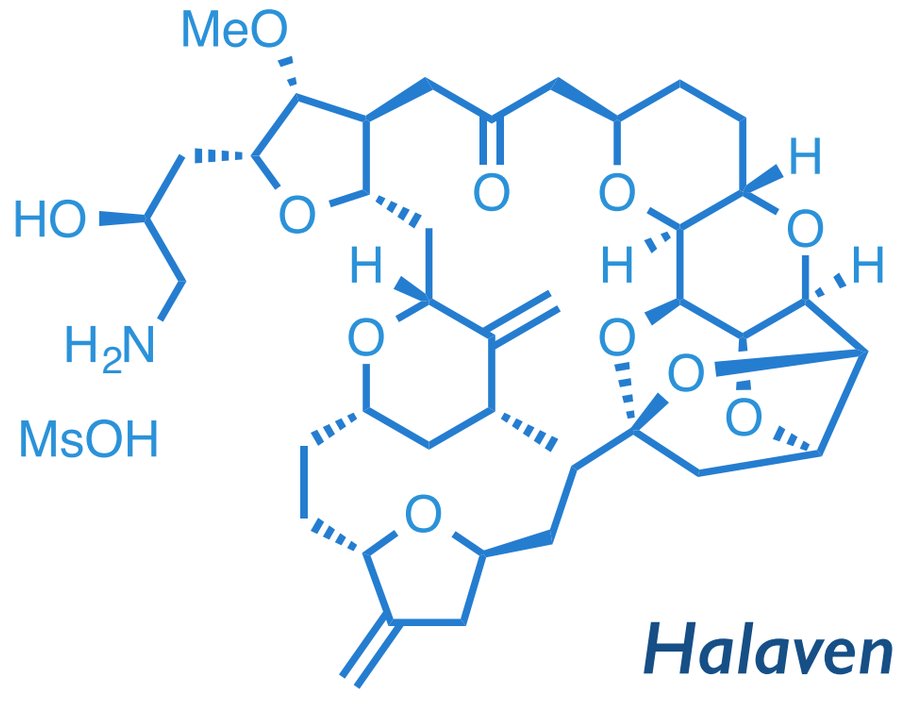
Brevetoxin B

Nicolaou, K. C. *JACS* **1995**, *117*, 1173

123 steps, 91% average ⟶ **0.0009% yield**

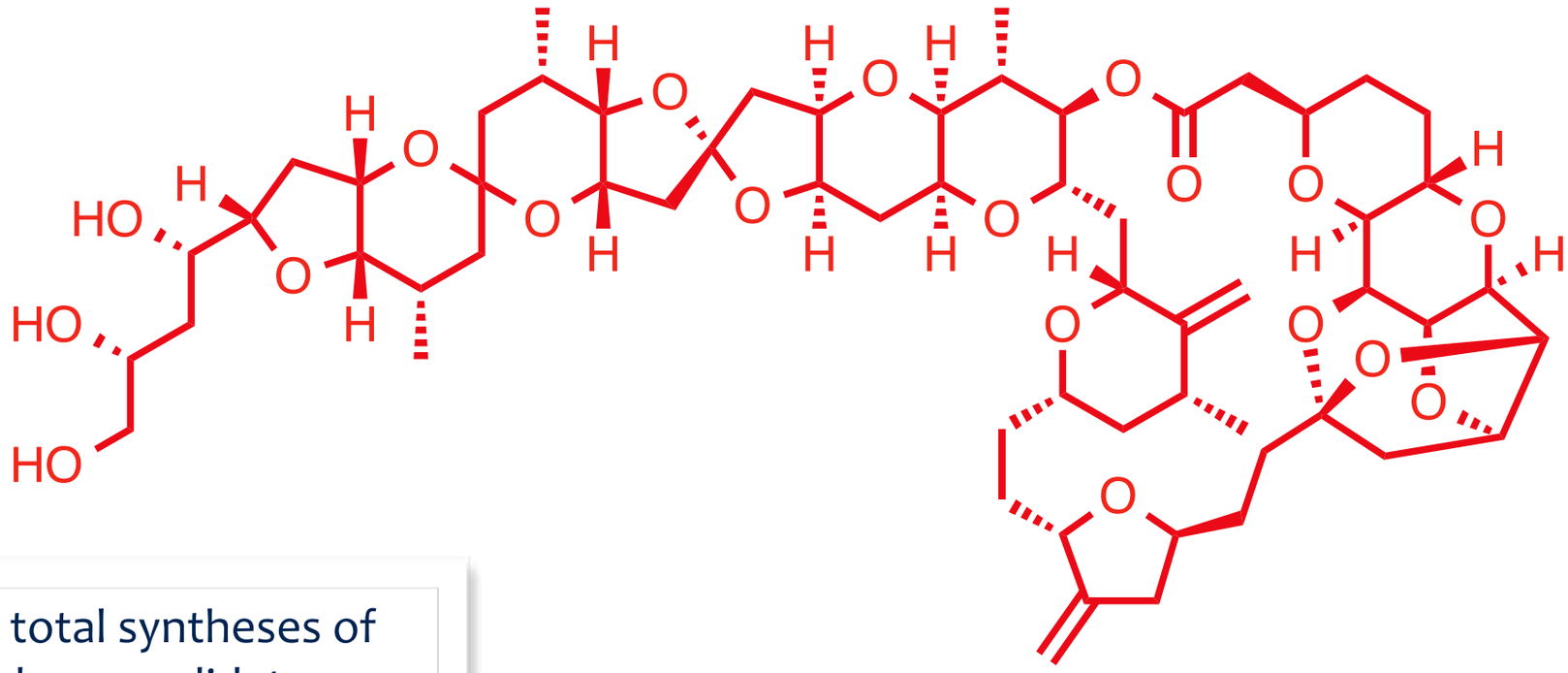
Nakata, T. *JACS* **2004**, *126*, 14374

90 steps, 93% average ⟶ **0.15% yield**



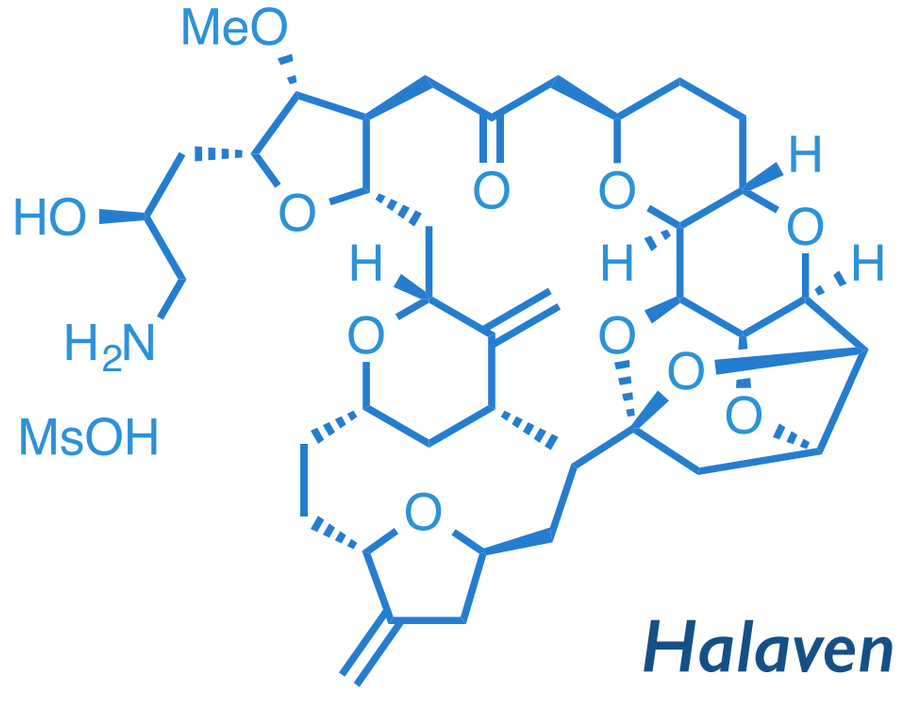
Halaven

One of the most active drugs to treat patients with metastatic breast cancer



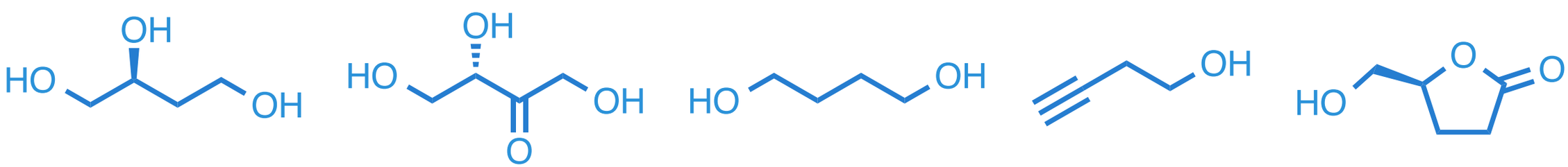
Halicondrin B

For an inspiring review on the total syntheses of complex natural product-based drug candidates, see Allred, T. K. *CR* **2017**, *117*, 11994



One of the most active drugs to treat patients with metastatic breast cancer

More than 35 steps



Starting materials

Yu, M. J. *Nat. Prod. Rep.* **2013**, *30*, 1158

IDEAL SYNTHESIS creates a complex molecule …

in a sequence of only construction reactions

involving no intermediary refunctionalizations,

and leading directly to the target,

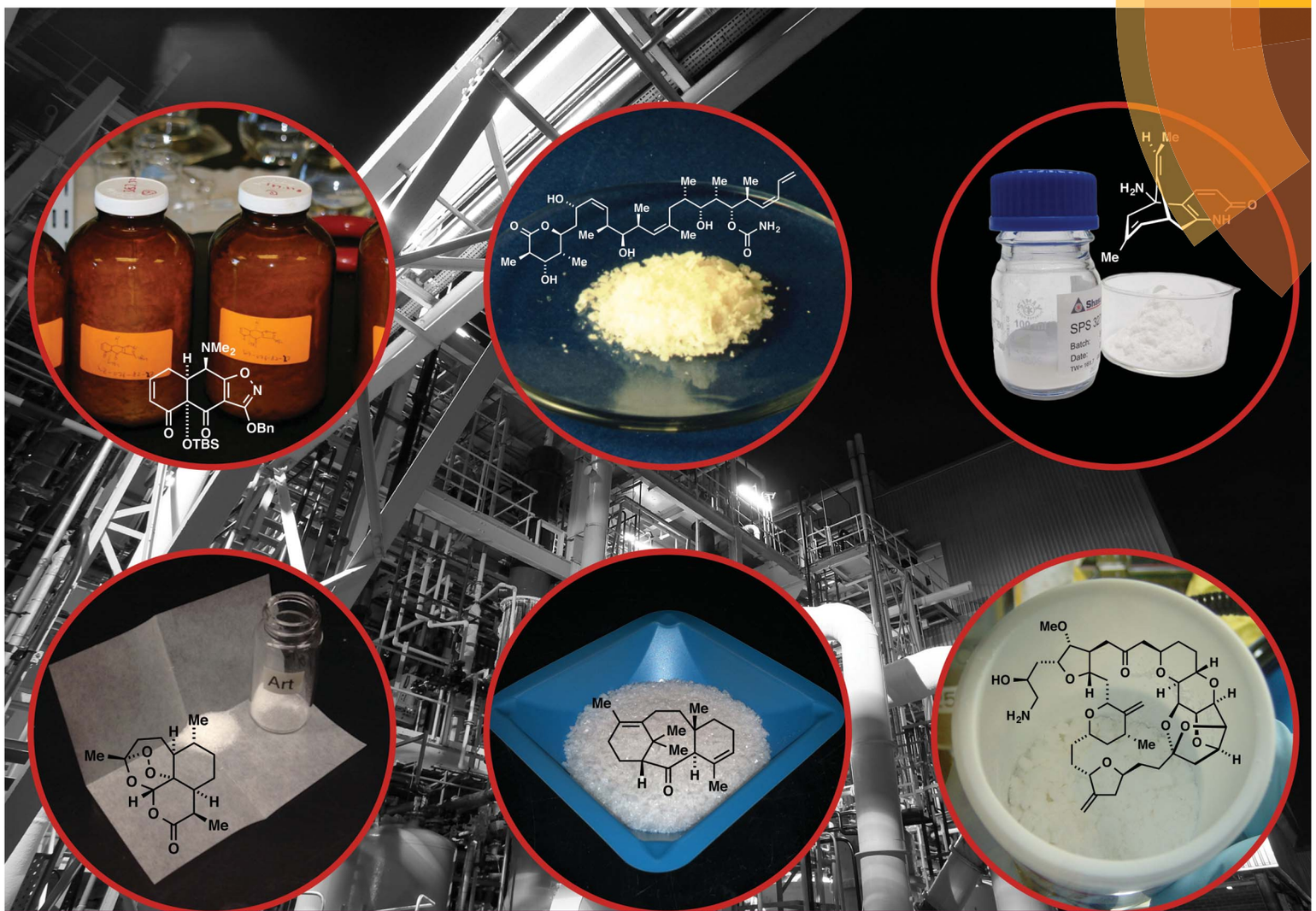
not only its skeleton but also its correctly placed functionality

Hendrickson, J. B. *JACS* **1975**, *97*, 5784

Volume 31 | Number 4 | April 2014 | Pages 403–606

NPR

Natural Product Reports
www.rsc.org/npr



Themed issue: Natural Product Synthesis

ISSN 0265-0568

ROYAL SOCIETY OF CHEMISTRY

HIGHLIGHT
Phil S. Baran *et al.*
Natural product synthesis in the age of scalability

Natural Product Reports

April **2014**, Issue 4

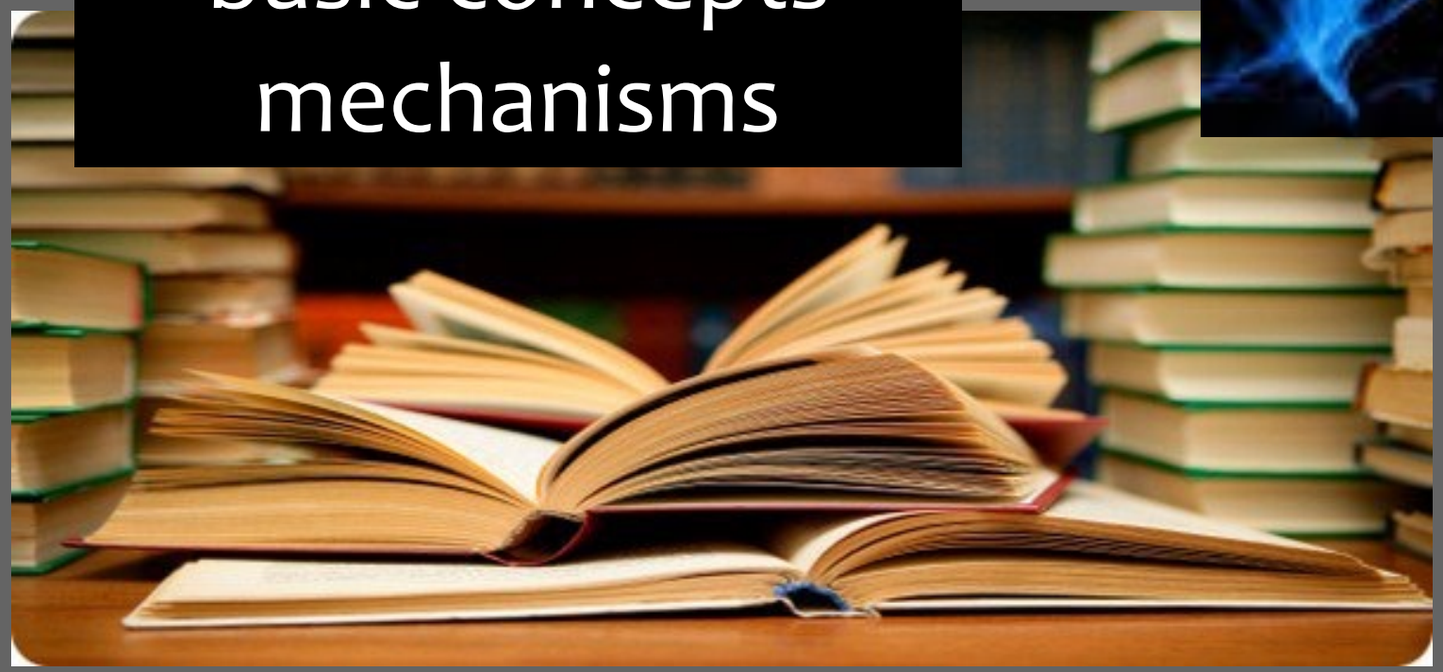
Chemical Reviews

September **2017**, Issue 18

What do we need?

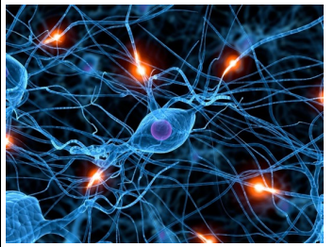
Strategy
structural analysis
retrosynthesis

Knowledge
basic concepts
mechanisms



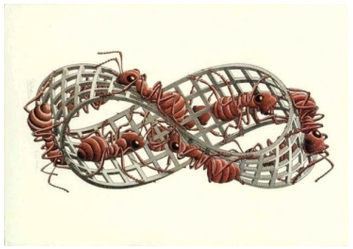
Reactivity
methods
protecting groups

http://diposit.ub.edu/dspace/handle/2445/61063



1. Introduction. Selectivity

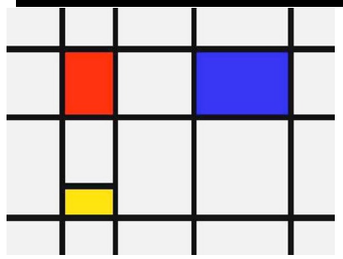
2014-2015 Autumn Ter



Moebius Strip
M. C. Escher, 1963

2. Pericyclic Reactions

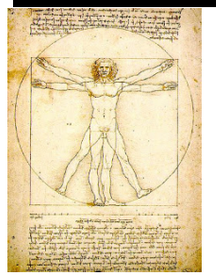
2014-2015 Autumn Term



Piet Mondrian

3. Synthesis of C=C Bonds

2014-2015 Autumn Term



The Vitruvian man or Canon for the human proportions
Leonardo da Vinci, 1492

4. Synthesis of C–C Bonds

2014-2015 Autumn Term

The great metaphysician
Giorgio de Chirico, s XX

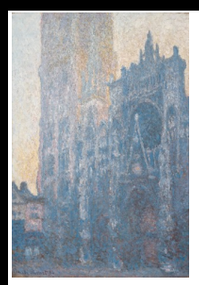
5. Intr. to Retrosynthetic Analys

2014-2015 Autum

Sky and Water I
Maurits Cornelis Escher, 1938

6. Functional Group Interconversion

2014-2015 Autumn Term



Rouen Cathedral
Claude Monet, 1892-94

7. Reductions

2014-

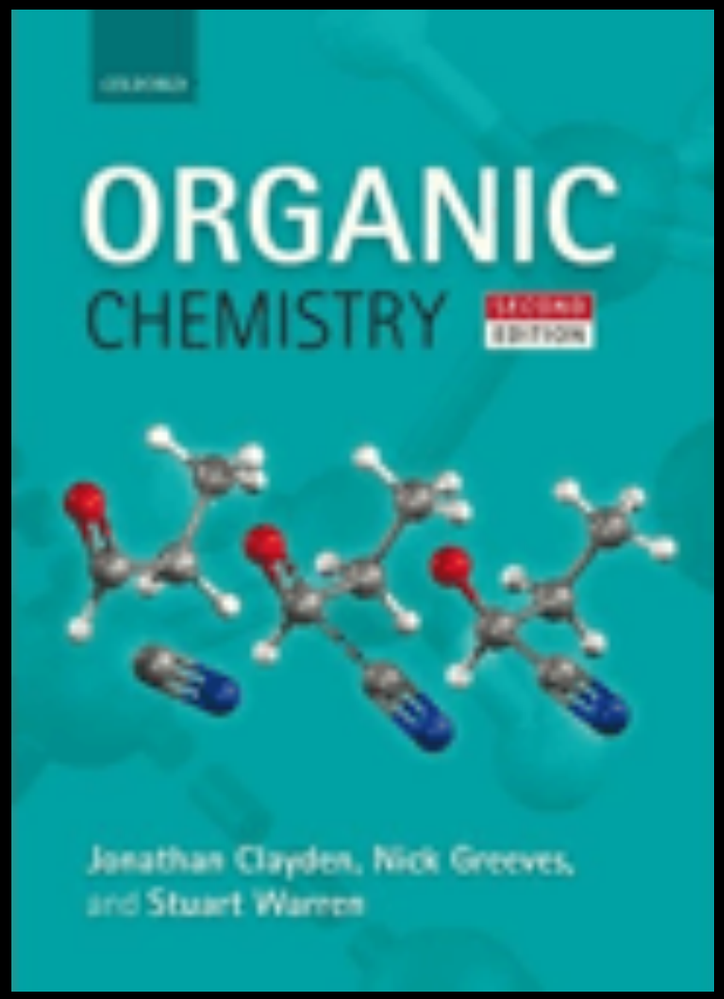
Rouen Cathedral
Claude Monet, 1892-94

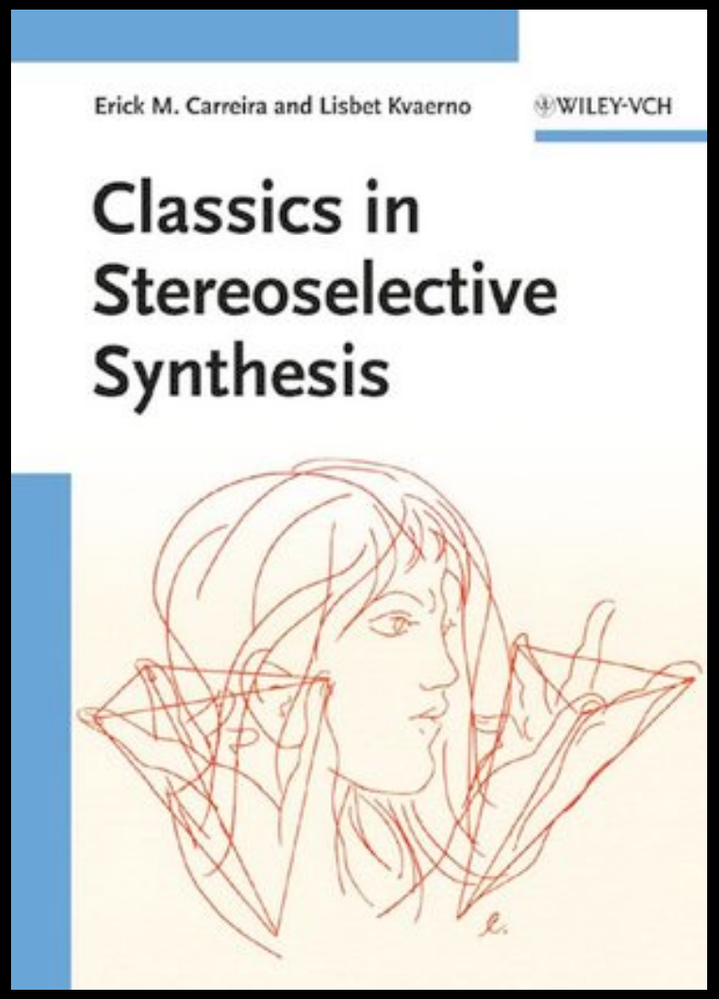
8. Oxidations

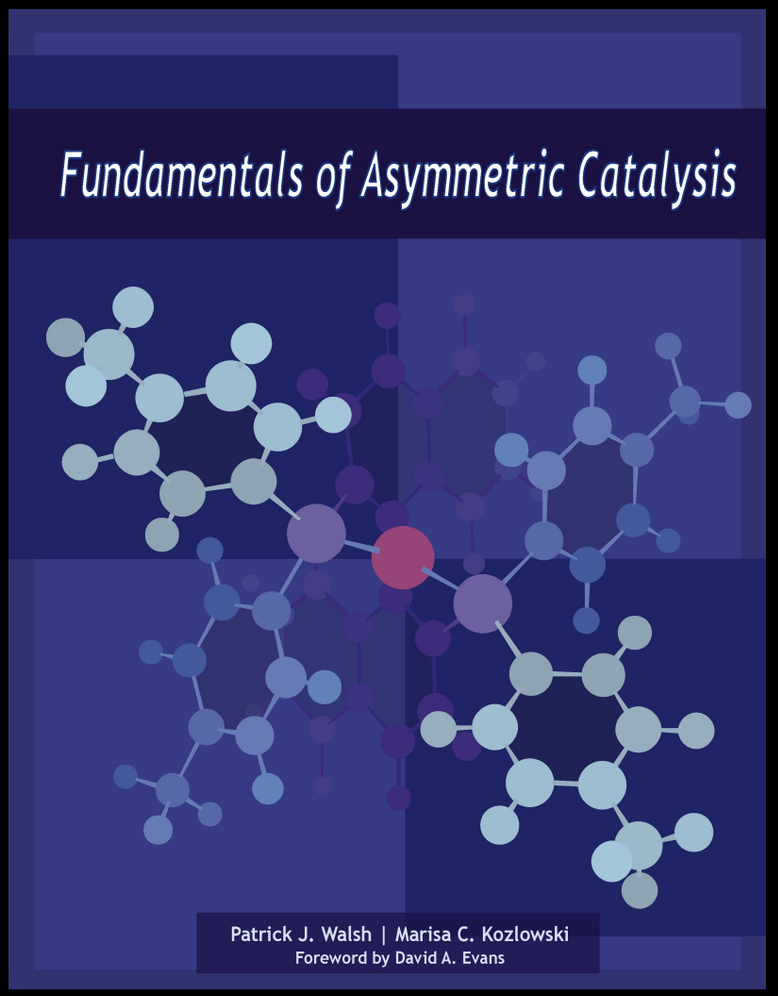
2014-2015 Autumn

Organic Synthesis
4th year chemistry

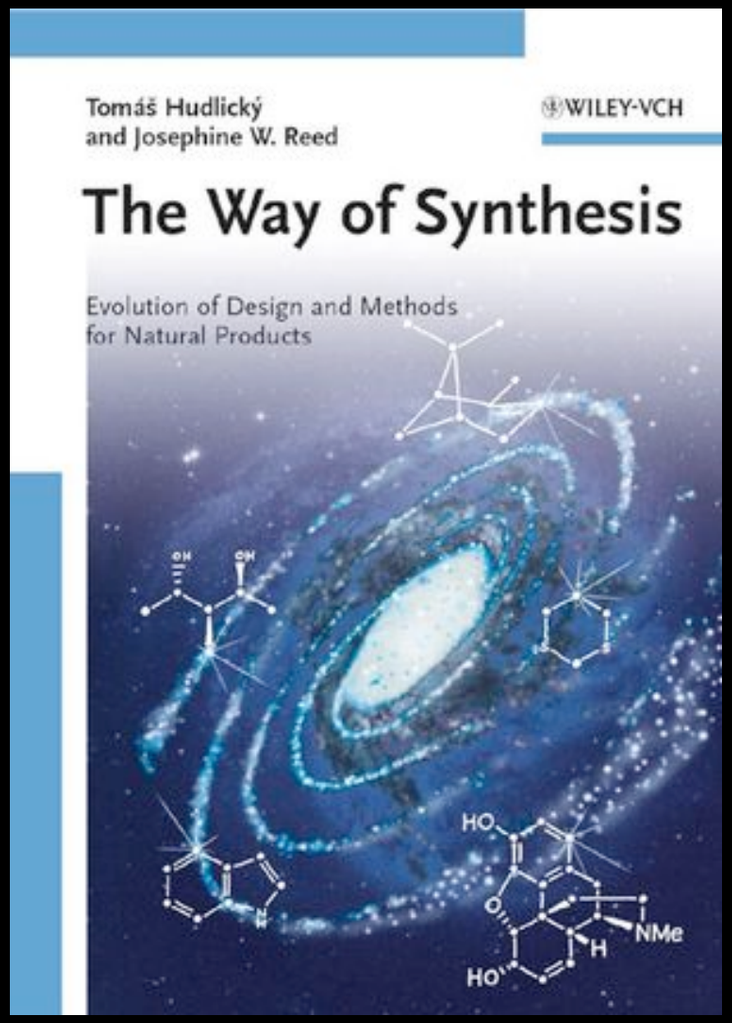
recommended **books**

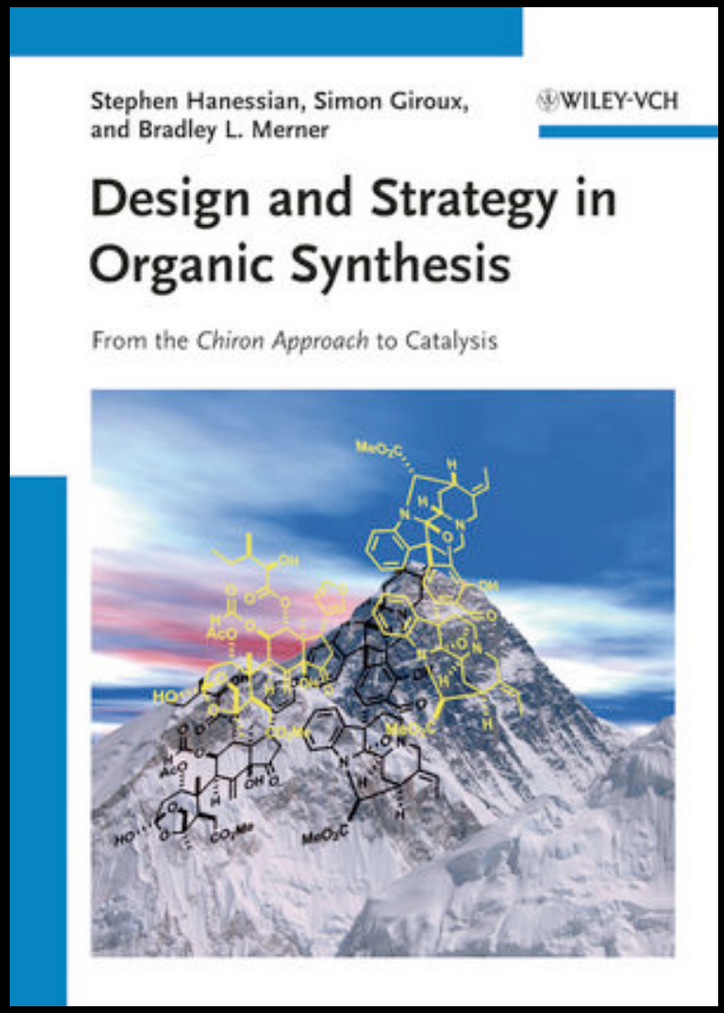


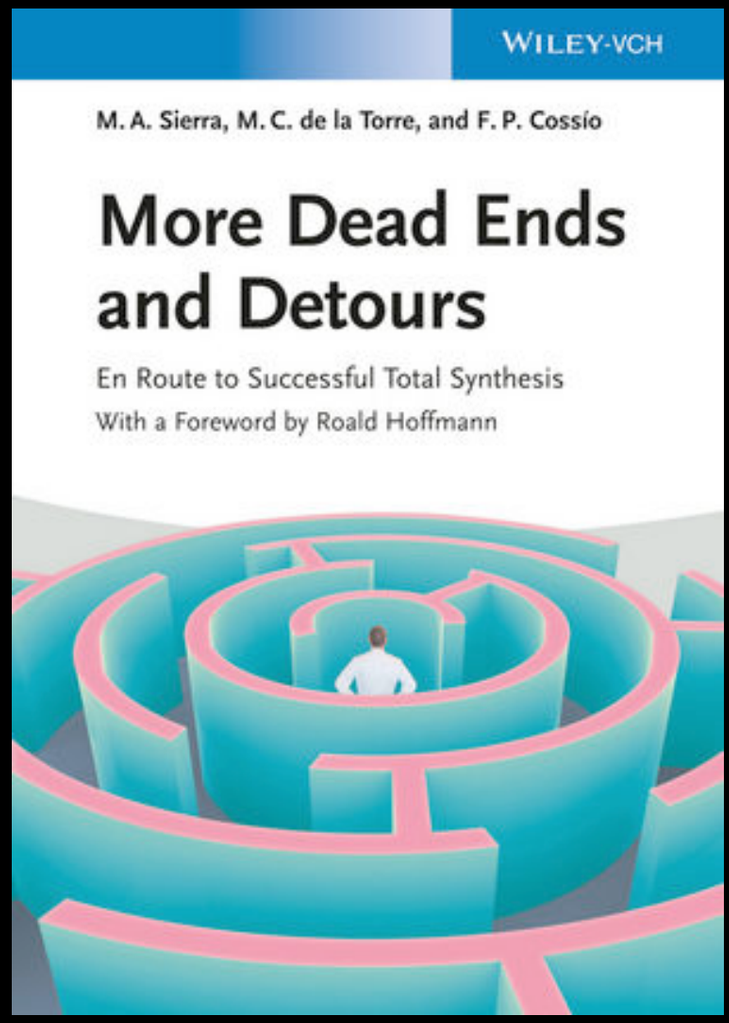




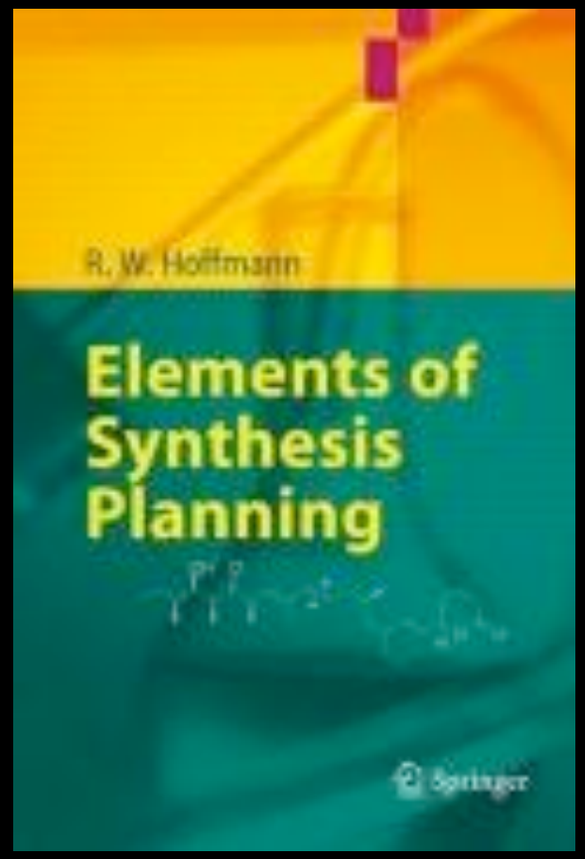
recommended **books**



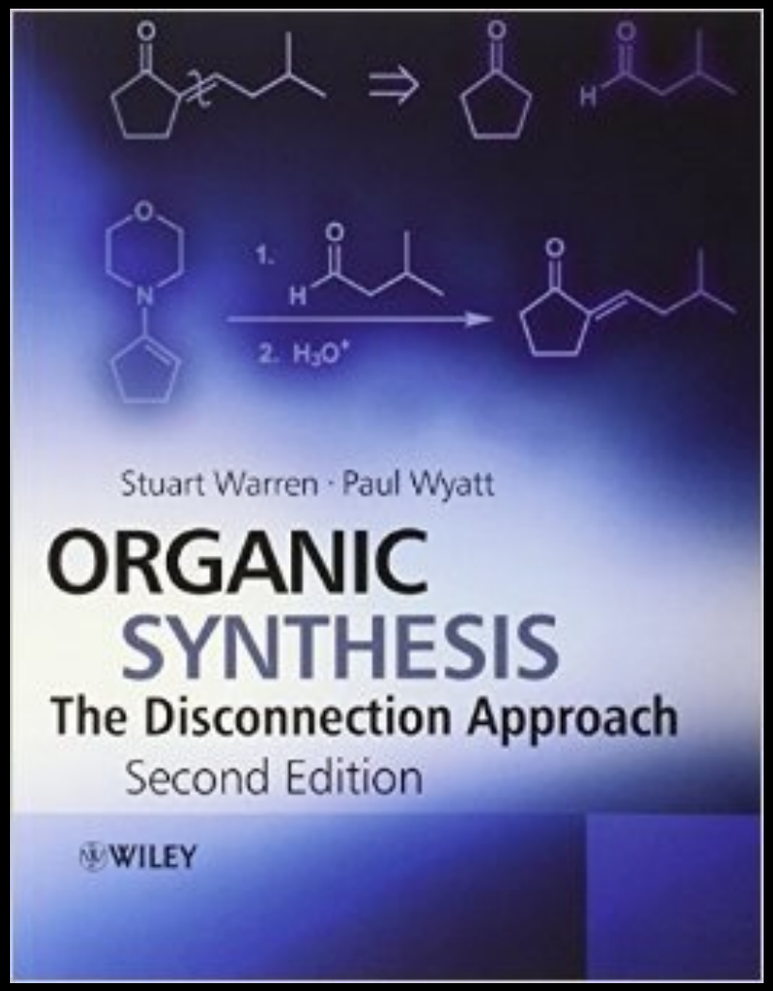


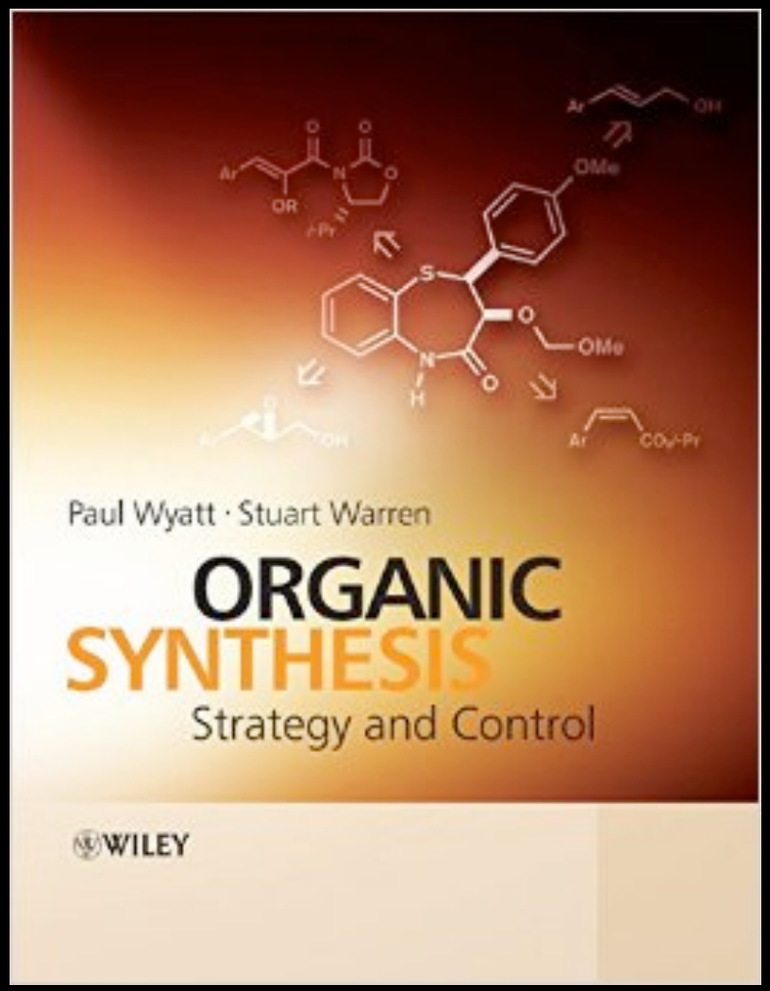


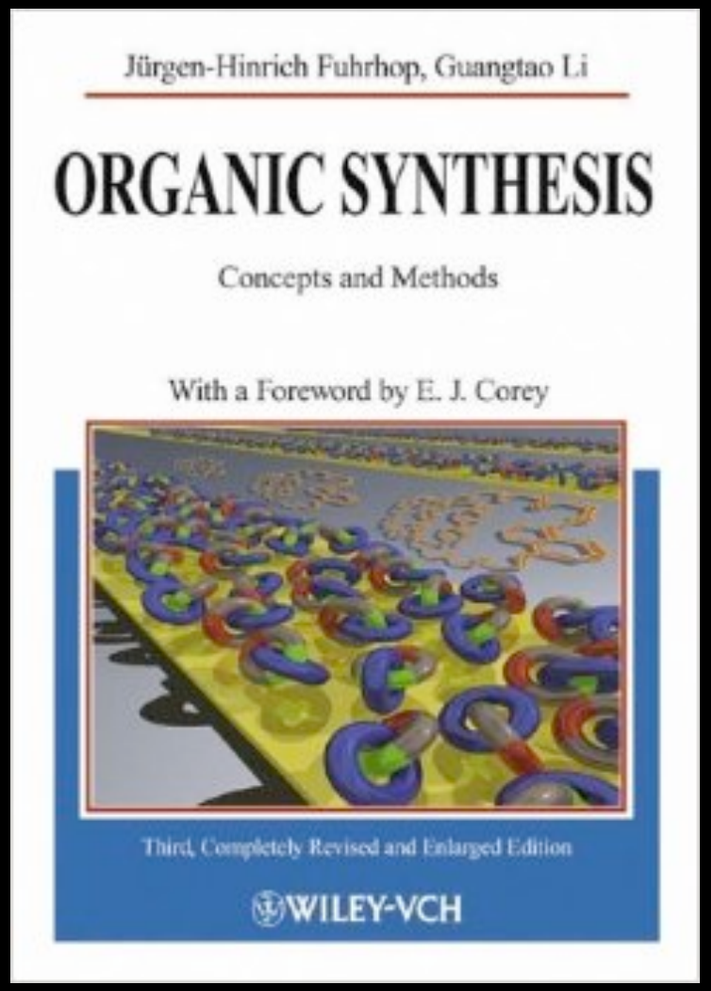
recommended **books**



recommended **books**







DOI: 10.1002/anie.201309315

What Matters?

*Alois Fürstner**

Alois Fürstner
Director, Max Planck Institute für Kohlenforschung

The inexorable force of chemical synthesis to create matter with entirely new properties has profoundly changed the world—and arguably so—largely for the better. Developed societies embrace the service that chemistry can provide, while otherwise cultivating a certain chemophobia (certainly in Europe). Many reasons are to be blamed for this somewhat schizophrenic attitude, including some severe mistakes on our own side. Another issue is the difficulty of conveying the beauty of our science to the general public. Organic chemistry uses a notation that only an adept scholar is able to understand. Mathematics and music face a similar challenge: as a result, the fruits of these disciplines are subject to mass consumption too, but real appreciation is scarce and, maybe, even declining as a consequence of changing priorities in the education system. One may complain about this situation, but we are well advised to keep touch with a broad audience. Neither ignorance nor skepticism form a sound basis for sustained public support for science in general and chemistry in particular. In fact, dwindling financial resources are an increasingly serious menace for basic research in many countries.

In times when money is tight, topics that do not promise any short-term revenues often have a hard time to get funded. The political expectations often take the form of top-down agendas that predetermine what scientists have to be interested in if they want to survive within their system. Neither can I convince myself that such "five-year plans" are the best response to the challenges that modern society is facing, nor do I believe that they correspond particularly well to the very nature of the chemical sciences. Let me give you a few examples that I consider reasonably representative.

It is fair to say that the organometallic chemistry of palladium, an exceedingly rare and expensive metal, has had a tremendous impact on our quality of life. Not only a panoply of important drugs, but also agrochemicals, liquid crystals, and even sun protecting agents, are made through palladium catalysis, with massive annual sales. Interestingly, this success story can be traced back to some pretty basic and curiosity-driven investigations. One of the key contributions was made by Tsuji and coworkers, who reacted malonate anions with stoichiometric(!) amounts of allylpalladium complexes to form mixtures(!) of products that can be made much more readily otherwise. Although definitely not practical, this result has fundamentally changed our understanding of organometallic chemistry because it proved that organopalladium species are electrophiles rather than nucleophiles (as essentially all other organometallic species known at the time). In similarly pioneering studies, Heck investigated the reactivity of organomercury(!) compounds in the presence of palladium salts. Incidentally, the author was working in industry at the time. Would any of these research projects get funded under today's circumstances? In a climate favoring investigations of practical relevance, such proposals might well cause Homeric laughter. Hence, everybody who has to take a drug compound made by cross-coupling partly owes his or her health the liberty of the funding agencies forty years ago—not to speak of the wealth that this chemistry has ultimately created in return to the start-up investment of money. "*This was sometime a paradox, but now the time gives it proof*" (*Hamlet*).

In this context, I also kindly ask you to re-read the original publication on biaryl formation through what later became famous as the Suzuki coupling. Would you have predicted then that this paper will change the world and finally lead its author to Stockholm? Olefin metathesis is yet another formidable case; only after a "lag period" of about three decades of pretty basic organometallic research was the avalanche set off. Finally, I can't help but reiterate the story of Karl Ziegler, former director of my own institute. As a young man he discovered that benzylpotassium reagents add to stilbene. This somewhat exotic result, however, actually denotes the first recorded case of a carbometalation reaction and, as such, Ziegler's first step on his path to polyethylene which took no less than three more decades from there on.

Of course, I appreciate that only very few innovations gain such relevance. At the meta-level however, these examples showcase that innovation eventually wins over trendiness, quality over political agendas, originality over mass production, curiosity over determinism, reliability over mannerism. Whereas glamour asks for immediate reward, innovation means sustained success.

If you ever tried to chase a complex natural product yourself, you may have experienced how challenging, labor intense, expensive, and even frustrating

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E-mail: fuerstner@kofo.mpg.de

recommended paper (I)

Fürstner, A.

ACIE **2014**, *53*, 8–9

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Editorial
Cite This: J. Am. Chem. Soc. 2018, 140, 4751−4755
pubs.acs.org/JACS

Natural Product Total Synthesis: As Exciting as Ever and Here To Stay

We have travelled far since 1828 and the interest attached to 'total synthesis' has disappeared

Sir Robert Robinson (1936)

The total synthesis of complex natural products still remains among the most exciting and dynamic areas of research, with representative publications in this area routinely ranking among the most-read in every chemistry-focused journal. Three excellent prior summaries of fantastic accomplishments in this area have appeared in 2008,[1] 2013,[2] and 2014,[3] with the creation of virtual issues highlighting many representative publications from those time periods. In all of the editorials accompanying those expertly curated virtual issues, strong cases were made for why total synthesis continues to be an important and topical area of investigation. In this editorial I'd like to address recent topical issues surrounding the future of this field.[4]

Total synthesis and synthetic organic chemistry as a whole provide society a fantastic return on investment with innumerable fundamental and applied tangible advancements. Historically, chemists educated in this area are some of the most sought after in industry, as the skills of making molecules can be utilized for designing an infinite array of translational applications in medicines, agrochemicals, and materials. But the justification for why this pursuit endures goes beyond the simple argument of supplying the demands of a particular labor market.[5] From a fundamental perspective, total synthesis is a barometer and proving ground for new methodologies and new strategies or ways of thinking.[6] Lessons from such endeavors can illuminate unique or underappreciated areas of chemical reactivity. Powerfully simplifying disconnections in the context of an obscure natural product family can have enormous downstream impacts as well. From an applied standpoint, having sustainable and reliable access to biologically active natural isolates can demystify new areas of biology or provide promising candidates for drug discovery.[7] In many cases such pursuits can serve as the only means for structural identification.[8] It is therefore puzzling that so frequently this area of inquiry is criticized or its motives questioned.[9] To be sure, the study of total synthesis does not consume inordinate taxpayer resources relative to other areas (quite the opposite, actually),[10] and among journal readership such studies are of extreme interest to the broad audience based on sheer download statistics. I would argue that based on this statistic alone it is self-evident that the field remains vibrant rather than stale and of little general appeal.

Among outsiders or those disconnected from the intricacies of the field, some may view total synthesis or synthetic organic chemistry as a whole as being a "mature" field,[11] perhaps even being immediately amenable to automation[12] or replacement with artificial intelligence algorithms.[13] In my view, those efforts are certainly worthwhile as long as they don't come at the expense of the very field they wish to simplify. In other words, such efforts do not intimidate, threaten, or provoke fear in the hearts of any practitioner of synthesis. Promises of computational chemistry and combinatorial chemistry displacing the field were made over the years, yet we are still here.[14] Thus, I would predict that our species will become capable of interplanetary colonization long before rooms of machines dramatically reduce the number of employable synthetic chemists or eliminate them all together.[12f]

The perception of synthesis "maturity" is probably due to the field being misunderstood rather than mature. This misunderstanding is partially self-inflicted, as with every large accomplishment in the area one can get the sense that an endpoint has been reached.[15] As a community, we have become quite adept at being able to make anything with enough resources, but we are still decades or perhaps even centuries away from making everything well.[16] The "age of feasibility" [17] did a great job to advertise the former capability and perhaps deemphasize the latter deficiency, thus setting the stage for critics to emerge.

The goals of sustainability and environmentally conscious science underlie the precepts of modern chemistry, and natural product synthesis is no different in that regard. Thus, the field is moving toward simplifying the way molecules can be made[18] so that perhaps one day even the most complex structures can be obtainable by engineers rather than basic scientists. It's not visionary to speculate that computer-designed, fully automated sequences are on the way—that is blatantly obvious. Despite hubristic promises otherwise, that day is still far away. Active practitioners in this area are fully cognizant of this fact but either are too busy doing science to write countless essays, blog posts, and opinion pieces on the subject or simply don't have a platform to do so. Well-designed retrosyntheses can fail even in simple settings, reproducibility is still an issue with precise experimental technique often essential for success,[19] selectivity (chemo, regio, stereo) is frequently hard to predict in complex settings, serendipity still abounds, visceral creativity and persistence determine success, and some of the most powerful disconnections and new reagents need to be invented from scratch—these facts bear repeating, especially to government officials that fund science and the Editors that publish it.[20] These very same bleak facts also underlie the charm and appeal of the area and are the reason that students are still magnetically attracted to it. Indeed, total synthesis programs still evoke an exciting sense of wonder and exploration of the unknown, not to mention the artistic aspects and inherent beauty of the final route. Thus, to state the obvious (to some), the "industry" of synthesis cannot be heroically "disrupted" with engineering advances and promises of utopian automation.[21] That's not to say that certain aspects of synthesis can't be made easier or accelerated with such advances.[22] And that's also not to say that folks like me in the synthesis community would not welcome such a day. Rather, it is still boring old human ingenuity, creativity, and curiosity[23] manifesting through the invention of new enabling methods, catalysts, reagents, and daringly different strategies that will push the field forward with the most "disruptive potential". In fact, many industries (such as drug discovery and development) are moving toward more and more complex targets,[24] and it is widely recognized that synthesis is often a rate-limiting step. For the reasons articulated above, advances in total synthesis and methodology can have a positive impact in making simple what was once

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DOI: 10.1021/jacs.8b02266
J. Am. Chem. Soc. 2018, 140, 4751−4755

recommended paper (II)

Baran, P. S.

JACS **2018**, *140*, 4751−4755

FORUM Synthesis

A constructive debate

Synthetic chemistry has long been used to prepare useful compounds — especially those that are hard to obtain from natural sources. But synthetic biology is coming of age as an alternative strategy. A biologist and two chemists debate the merits of their fields' synthetic prowess.

Building with biology

JAY D. KEASLING

Synthetic biology is essentially the assembly of well-characterized biological components into a system that performs a function, such as synthesizing a chemical. The field has advanced to the point that one can imagine producing nearly any organic molecule — even those that are not produced naturally — in an engineered microorganism. This has enormous implications for the production of speciality and bulk chemicals, drugs and fuels.

Structurally complex pharmaceutical ingredients based on natural products are particularly good targets for microbial production (Fig. 1a), because they can be difficult to produce by conventional chemical synthesis. Even when chemical syntheses for natural products are available, the routes used are often too long and/or low-yielding for large-scale preparation. For commercial production, such molecules are therefore typically harvested from organisms that produce them naturally, or from a mutant that generates higher yields. Alternatively, a semi-synthesis can be used in which a precursor to a desired compound is obtained from an organism and then converted to the final product using organic synthesis. However, these approaches tend to be time-consuming and expensive.

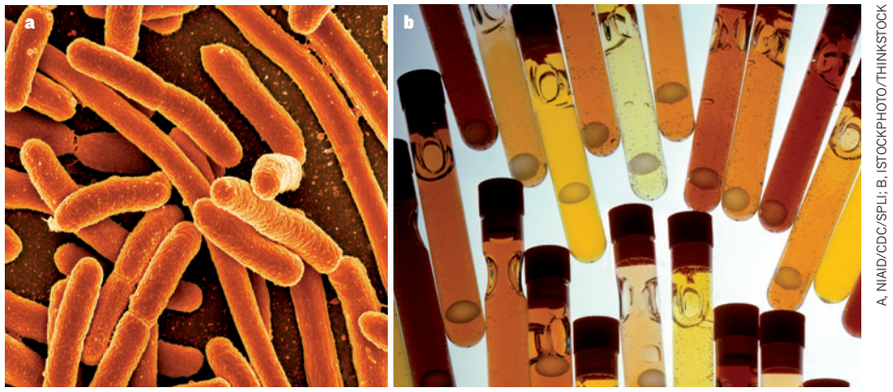
Naturally occurring compounds can be produced in microorganisms by transferring product-specific enzymes, or even whole metabolic pathways, from rare and/or genetically intractable organisms to those that can be readily engineered[1]. Similarly, fuels, bulk chemicals and speciality chemicals that are not produced naturally can be obtained by combining enzymes or metabolic pathways from different hosts into a single microorganism, or by engineering enzyme functions[2].

Synthetic biology has also been used for the large-scale semi-synthesis of natural products. For example, the antimalarial drug artemisinin is extracted from the plant *Artemisia annua*, but it is in short supply and is too expensive for most people with malaria[3]. By combining genes from *A. annua* and other organisms into a single strain of the yeast *Saccharomyces cerevisiae*, we have produced a fermentation process[4] to make artemisinic acid — which can easily be converted to artemisinin using chemical methods[5] — from simple sugars. The process is cost-effective, environmentally friendly and reliable, and is being developed for commercial production of the drug.

Synthetic biology has many advantages over chemical synthesis. First, the intermediates in a biosynthesis do not need to be purified before being used as substrates in the next reaction. Second, the many 'protection' and 'de-protection' steps typical of chemical synthesis — steps in which chemical groups are temporarily modified to stop them taking part in unwanted side reactions — can be avoided, because biosynthetic enzymes catalyse reactions only at the required positions in a substrate, avoiding side reactions at other groups. Third, most products of enzymatic reactions are racemically pure (the products form as just one of two possible mirror-image isomers), which is important for biologically active molecules. Fourth, cells can be engineered to secrete the final product, making it easier to purify. Finally, synthetic biology can use simple starting materials from renewable sources, helping to reduce our dependence on oil-derived feedstocks.

Even so, if synthetic biology is to match the power of synthetic chemistry, several problems must be addressed. For example, the biosynthetic enzymes responsible for producing important natural products need to be identified, so that they can be used in syntheses. We must also improve our ability to design enzymes that catalyse reactions not found in nature[6] if we are to expand the types of chemistry that can be engineered into cells. And we must learn how to reliably engineer biosynthetic pathways to achieve desired outcomes.

I envisage a day when customized cells will be built as catalysts for the biosynthesis of natural products, by designing chromosomes that harbour genes encoding the necessary biosynthetic pathways and also the minimal set of genes needed to construct the host organism from minimal nutrients. That day is fast approaching.



A, NIAID/CDC/SPL; B, ISTOCKPHOTO/THINKSTOCK

Figure 1 | Reaction vessels. **a**, Some biologists have argued that structurally complex molecules are best prepared in genetically engineered organisms, such as the bacterium *Escherichia coli* (pictured). **b**, Others think that chemical methods will endure as the most general option for synthesizing any desired compound.

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recommended **paper (III)**

for an interesting debate about the pros & cons of synthetic biology and synthetic chemistry

Keasling, J. D; Mendoza, A.; Baran, P. S.
Nature **2012**, *492*, 188–189

REVIEW SUMMARY

ORGANIC CHEMISTRY

The importance of synthetic chemistry in the pharmaceutical industry

Kevin R. Campos*, Paul J. Coleman*, Juan C. Alvarez, Spencer D. Dreher, Robert M. Garbaccio, Nicholas K. Terrett, Richard D. Tillyer, Matthew D. Truppo, Emma R. Parmee

BACKGROUND: Over the past century, innovations in synthetic chemistry have greatly enabled the discovery and development of important life-changing medicines, improving the health of patients worldwide. In recent years, many pharmaceutical companies have chosen to reduce their R&D investment in chemistry, viewing synthetic chemistry more as a mature technology and less as a driver of innovation in drug discovery. Contrary to this opinion, we believe that excellence and innovation in synthetic chemistry continue to be critical to success in all phases of drug discovery and development. Moreover, recent developments in new synthetic methods, biocatalysis, chemoinformatics, and reaction miniaturization have the power to accelerate the pace and improve the quality of products in pharmaceutical research. Indeed, the application of new synthetic methods is rapidly expanding the realm of accessible chemical matter for modulating a broader array of biological targets, and there is a growing recognition that innovations in synthetic chemistry are changing the practice of drug discovery. We identify some of the most enabling recent advances in synthetic chemistry as well as opportunities that we believe are poised to transform the practice of drug discovery and development in the coming years.

ADVANCES: Over the past century, innovations in synthetic methods have changed the way scientists think about designing and building molecules, enabling access to more expansive chemical space and to molecules possessing the essential biological activity needed in future investigational drugs. In order for the pharmaceutical industry to continue to produce breakthrough therapies that address global health needs, there remains a critical need for invention of synthetic transformations that can continue to drive new drug discovery. Toward this end, investment in research directed toward synthetic methods innovation, furthering the nexus of synthetic chemistry and biomolecules, and developing new technologies to accelerate methods discovery is essential. One powerful example of an emerging, transformative synthetic method is the recent discovery of photoredox catalysis, which allows one to harness the energy of visible light to accomplish synthetic transformations on drug-like molecules that were previously unachievable. Furthermore, recent breakthroughs in molecular biology, bioinformatics, and protein engineering are driving rapid identification of biocatalysts that possess desirable stability, unique activity, and exquisite selectivity needed to accelerate drug discovery. Recent developments in the merging fields of synthetic and biosynthetic chemistry have sought to harness these molecules in three distinct ways: as biocatalysts for novel and selective transformations, as conjugates through innovative bioorthogonal chemistry, and in the development of improved therapeutic modalities. The development of high-throughput experimentation and analytical tools for chemistry has made it possible to execute more than 1500 simultaneous experiments at microgram scale in 1 day, enabling the rapid identification of suitable reaction conditions to explore chemical space and accelerate drug discovery. Finally, advances in computational chemistry and machine learning in the past decade are delivering real impact in areas such as new catalyst design, reaction prediction, and even new reaction discovery.

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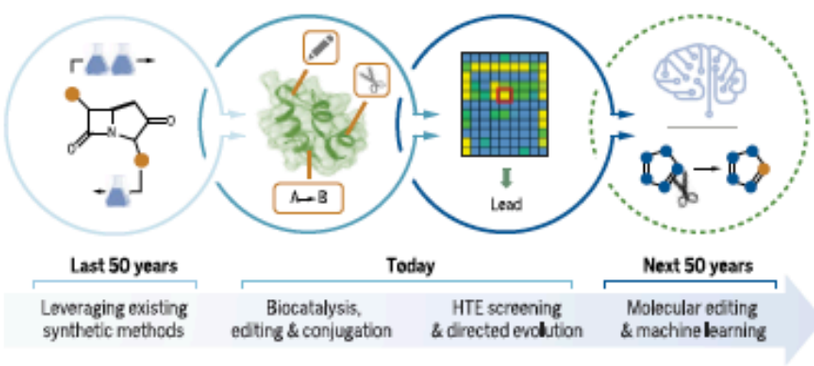
OUTLOOK: These advances position synthetic chemistry to continue to have an impact on the discovery and development of the next generation of medicines. Key unsolved problems in synthetic chemistry with potential implications for drug discovery include selective saturation and functionalization of heteroaromatics; concise synthesis of highly functionalized, constrained bicyclic amines; and C-H functionalization for the synthesis of α,α,α-trisubstituted amines. Other areas, such as site-selective modification of biomolecules and synthesis of noncanonical nucleosides, are emerging as opportunities of high potential impact. The concept of molecular editing, whereby one could selectively insert, delete, or exchange atoms in highly elaborated molecules, is an area of emerging interest. Continued investment in synthetic chemistry and chemical technologies through partnerships between the pharmaceutical industry and leading academic groups holds great promise to advance the field closer to a state where exploration of chemical space is unconstrained by synthetic complexity and only limited by the imagination of the chemist, enabling the discovery of the optimal chemical matter to treat disease faster than ever before. ■

Evolution of synthesis as a driver of innovation in drug discovery



Evolution of synthesis as a driver of innovation in drug discovery. Past, present, and future advances in synthetic chemistry are poised to transform the practice of drug discovery and development.

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recommended **paper (IV)**

an interesting outlook on the challenges facing organic synthesis in the context of pharmaceutical cindustry

Campos, K. R., Coleman, P. J.
Science **2019**, *363*, 244–251

See also
Blakemore, D. C.
Nat. Chem. **2018**, *10*, 383–394