SYNTHETIC ORGANIC CHEMISTRY

Francesco Nicotra
Department of Biotechnology and Biosciences, University of Milano Bicocca, Milano, Italy

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Summary

Synthetic organic chemistry is the art of building-up organic compounds from smaller entities. This science has found application in the production of organic compounds of commercial interest, in the construction of new, potentially bioactive molecules derived from rational design, in the challenge to synthesize very complex natural products, in finding new methods and strategies to render this science more efficient.

The synthesis of a complex organic compound requires a synthetic analysis and planning; the most efficient method consists in the retrosynthetic analysis which is based on proper disconnections that virtually generate smaller fragments that are in turn disconnected till commercially available compounds are reached. Each reaction in the synthetic scheme must affect only the required functional group leaving intact the others, which therefore must be protected. The protection-deprotection strategy is of fundamental importance in a synthetic plan. Stereoselectivity is also fundamental in the synthetic strategy, as most target molecules are chiral. Different approaches have been developed to perform stereoselective syntheses: chiral substrates of natural origin (the chiral pool) have been used as starting materials; chiral auxiliaries or chiral catalysts have been exploited to induce stereoselectivity; the chiral resolution of a stereoisomeric mixture has also been performed. In order to simplify and fasten the synthetic procedures, a solid phase approach has been developed. This method allows automation of some repetitive synthetic procedures, such as peptide or oligonucleotide synthesis, and shortens the others by simplifying the purification steps. The solid phase technique allowed the development of combinatorial synthesis, an approach that generates a high number of organic compounds, based on the combinatorial disposition of different building blocks in the construction of the products. Finally, nowadays there is an effort to render synthetic chemistry more environmentally friendly. This effort is mainly based on the use of reaction media such as water or fluorous recyclable biphasic systems. All these studies make organic synthesis more and more efficient, economic and safe.

1. Introduction

1.1 Definition and Story of Synthetic Organic Chemistry

The term *synthesis* means in Greek “put together”. Synthetic organic chemistry is the “art” of building-up complex molecular structures of organic compounds putting

together smaller, easily accessible (commercially available) compounds. This art has a relatively recent story. Among the very first examples of organic synthesis we can mention the synthesis of urea performed by Wöhler in 1828 and that of acetic acid performed by Kolbe in 1845. From around 1900, a great number of synthetic efforts have been made, and more complex structures such as camphor (Komppa, 1903 and Perkin, 1904) or the complex structure of haemin (Fisher, 1929) have been produced (Figure 1).

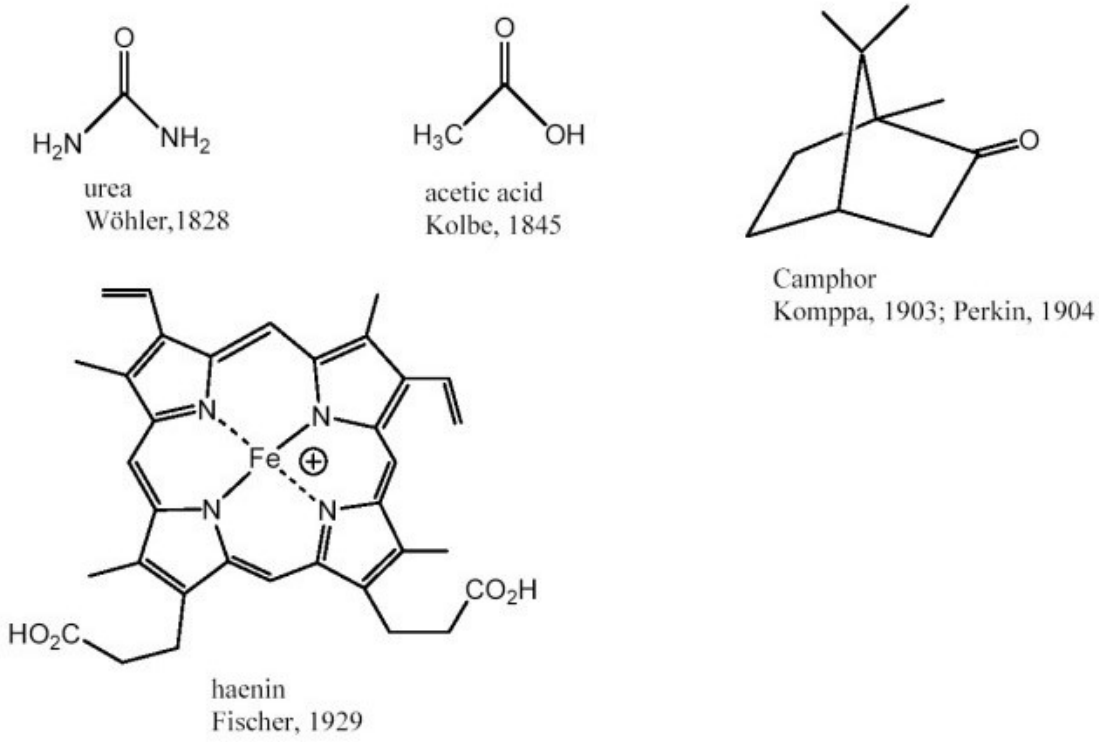
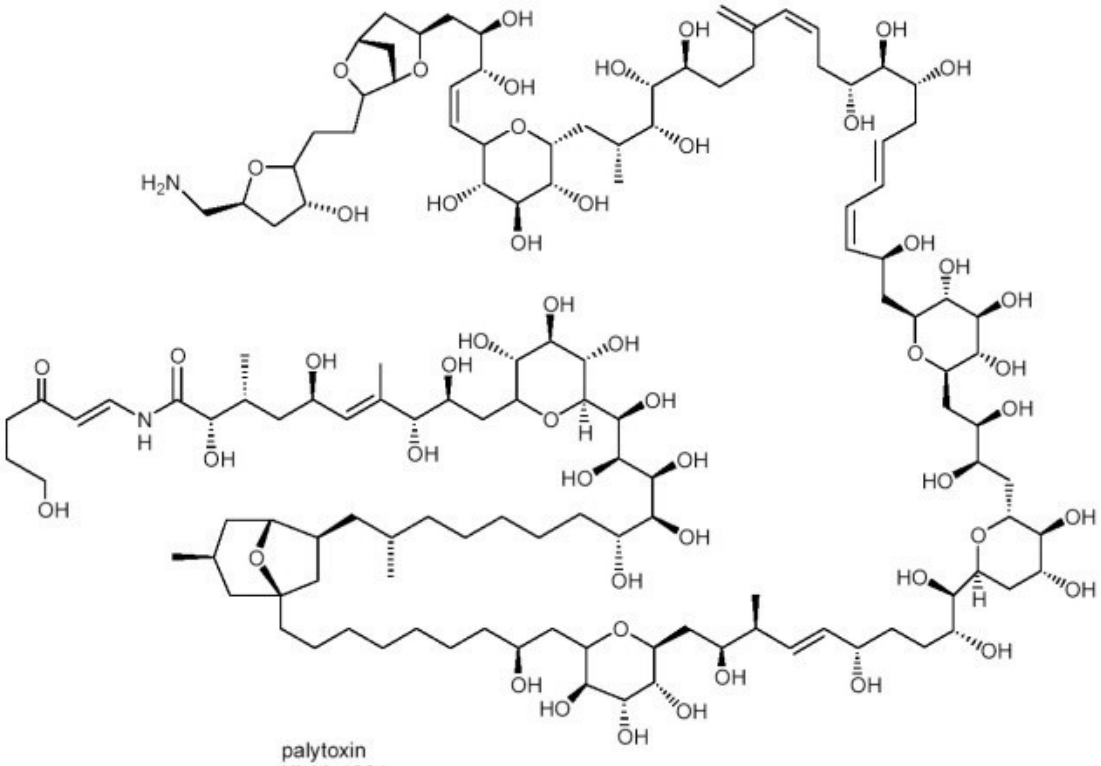


Figure 1: Examples of natural products synthesized in ancient times

Synthetic organic chemists have reached a high level of specialization, and nowadays extremely complicated and attractive compounds of natural origin, such as palytoxin or taxol (Figure 2), just to make a couple of examples, have been synthesized. The development of complex multistep syntheses not only does make accessible a variety of biologically active compounds, but also allows the discovery of new reagents or reaction strategies (activation, protection, deprotection, stereo control, see below). As a matter of fact, despite it is possible that, given time and expertise, any even very complex organic compound could be synthesized in a small scale, the time and the cost required for the synthesis of very complex structures render the process unpractical for commercial purposes. Therefore there is an increasing effort in training to simplify and "automate" as much as possible the synthetic processes. In particular the solid phase methodology shortens the tedious and time consuming work-up procedures required at each synthetic step.



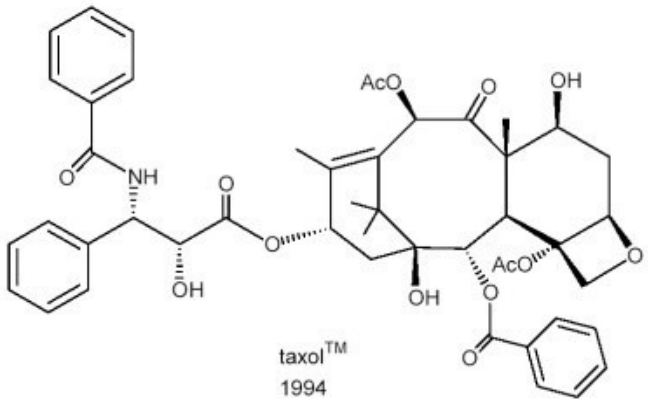


Figure 2: Two complex synthetic targets that have been synthesized: palytoxin and taxol

The efforts of synthetic organic chemists therefore are devoted not only to the total synthesis of complex organic compounds (target oriented synthesis)**,** but also to the development of new synthetic methods (method oriented synthesis).

1.2. Target Oriented Synthesis

The goal of target oriented synthesis is the obtainment of a more or less complex organic molecule. It can be a natural bioactive compound, or a compound derived from rational design as potentially bioactive, or a compound of commercial relevance, or even a compound of theoretical interest. Drugs, flavors, nutraceuticals, new materials are examples of the most common and interesting targets.

A target oriented synthesis must be as much efficient as possible in terms of yield, cost and time. The target can be a new molecule, the properties of which must be tested, or a known molecule that already found industrial application. In this last case it is interesting to note that the new synthetic procedure make sense only if it is more efficient than the previously reported.

1.3. Method Oriented Synthesis

The methods oriented synthesis is devoted to the development of new reagents, new catalysts, new reaction and work-up procedures, in general to any innovation that can improve a synthetic procedure. Particular attention is devoted to the yields, the stereochemical outcome, the atomic economy of the reactions (in terms of atoms of the reagents that are not inserted in the products, and therefore lost), and more generally to the environmental impact of the process. In order to improve the synthetic methods (and to show their ability) synthetic chemists have chosen very often quite complex synthetic targets such as palytoxin and taxol (Figure 2). Despite the synthesis of these targets will require several years and will never be industrially applicable, the efforts to solve the synthetic problems encountered during the synthesis are a fantastic "practice field" for the methodological innovation.

Synthetic organic chemistry also concerns polymerization processes, which are treated in *Polymer Chemistry and Environmentally Degradable Polymers*, and structural modifications which require only one reaction, which can be deduced from the topic devoted to the organic chemical reactions (see *Organic Chemical Reactions*). This topic is mainly devoted to multi-step syntheses of complex molecular architectures. In this context, two main categories must be considered:

(a) syntheses that require the reiterative junction of bifunctional monomers, such as aminoacids, carbohydrates and nucleotides.
(b) syntheses that require the construction of a complex skeleton made mainly by carbon atoms.

In both cases a synthetic strategy is required.

2. Synthetic Strategy

The construction of a complex organic structure, defined ***target molecule***, requires first of all the identification of the smaller fragments that can be used to build-up the final target. In the case of oligomers such as peptides, oligosaccharides or oligonucleotides, the choice is obvious: the constituent monomers are the building blocks, and the synthesis requires the junction of those monomers by condensation. Two functional groups, one for each monomer, are involved in the reaction, whereas the other functional groups of the molecule, which can interfere in the reaction, must be **protected**. In order to perform the condensation, it is then required to activate one of the two functional groups that must react together. Nowadays peptide and oligonucleotide

synthesis can be performed in an automated manner due to the repeatable procedure. In the case of oligosaccharides, one additional problem must be solved, when a sugar links another sugar or an aglycon, a stereogenic center (the anomeric center) is involved in the reaction, and therefore two possible stereoisomers (defined α- and β- anomers) can be formed. Therefore the stereochemical outcome of the reaction must be controlled in order to obtain the desired stereoisomer. This problem, together with the fact that carbohydrates present more than one hydroxyl group, and only one must react with the second sugar, makes oligosaccharide synthesis not trivial.

When the target molecule present a complex skeleton mainly made by carbon atoms chains, no constituent monomers or building blocks can be immediately envisaged. In this case the identification of the starting materials for the synthesis requires much more fantasy and some rules: in other words a retrosynthetic analysis.

2.1. Retrosynthetic Analysis

The concept of retrosynthetic analysis has been developed by E. J. Corey who received for this reason the Nobel Prize in chemistry in 1990. In Corey's words "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 retrosynthetic analysis is based on a sequence of ***disconnections***. Each disconnection is a mental process in which a molecule is fragmented into two pieces that in the mind of the synthetic organic chemist can generate the molecule under examination by known reactions. To make a simple example, Figure 3 shows the possible disconnections of a simple target molecule. The cleavage of the linkage between the carbon atom bearing the oxygen and the ethyl (a) or the methyl (b) group makes two possible disconnections. The carbon atom bearing a hydroxyl group can be generated from a carbonyl function (electrophile), by reaction with a carbanion (nucleophile). In Figure 3 the electrophile is the carbonyl group of acetone (disconnection a) or propanone (disconnection b) and the nucleophile an organometallic reagent such as ethyl magnesium bromide (disconnection a) or methyl lithium (disconnection b). The carbanion is defined ***synthon*** whereas the organometallic reagent from which it is generated is defined ***synthetic equivalent***.

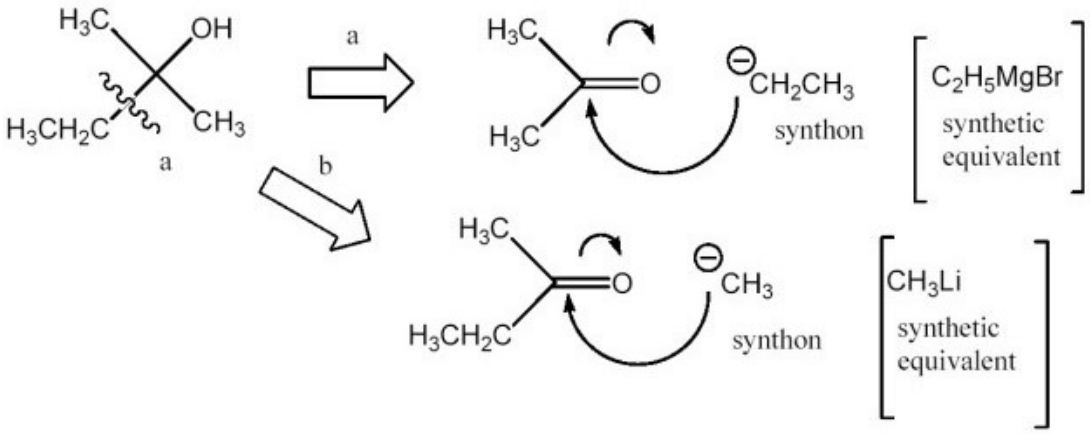


Figure 3: The retrosynthetic analysis: a simple disconnection that presents two possibilities.

Often, the target molecule is formed by a skeleton made not only by carbon atoms, but also involving some heteroatoms. The heteroatom represents and/or is part of functional groups. The carbon-heteroatom bonds of the functional group are ideal position for a disconnection. To make an example, esters and lactones, or amides and lactams, can be easily disconnected into the fragments that can generate those bonds, one containing the carboxylic group and the other containing the hydroxyl or the amino group. The presence of functional group in the skeleton of a target molecule will direct the choice of the disconnection (Figure 4)

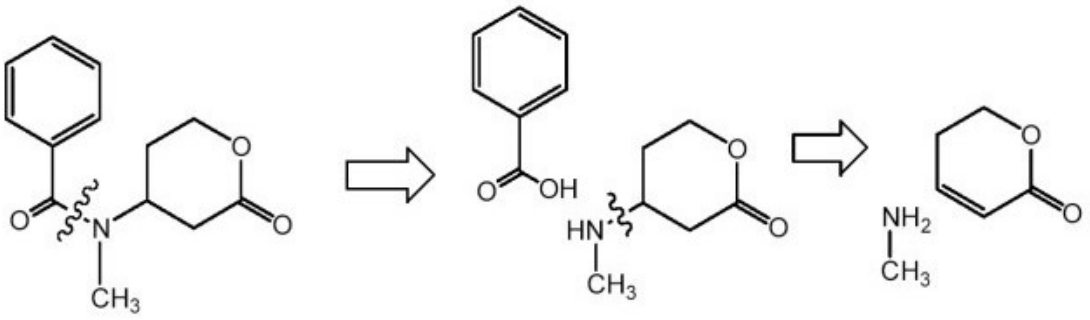


Figure 4: Disconnection of a molecule containing an amidic bond.

In the example reported in Figure 4 the amide is generated from benzoic acid and a secondary amine, which in turn can be obtained by Michael addition to an α,β-unsaturated ester. In both cases, a carbon-heteroatom linkage is involved.

Another important instrument in the retrosynthetic strategy is the ***functional group interconversion***. To understand the meaning of this term, consider the retrosynthetic strategy shown in Figure 5.

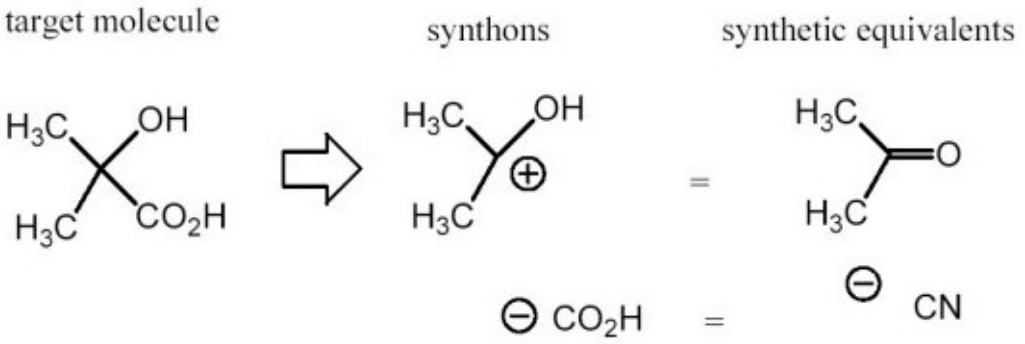


Figure 5: A simple disconnection: the cyanide ion is the synthetic equivalent of the $^{-}$COOH synthon.

The retrosynthetic scheme requires a synthon in which the carbon atom with a hydroxyl group is the electrophile, the synthetic equivalent being the ketone. The other synthon therefore must be a nucleophile, the carboxylic fragment in fact is represented as a carbanion, and the synthetic equivalent is the cyanide ion, which is stable. Through a functional group interconversion it is possible to convert the nitrile into a carboxylic acid.

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Biographical Sketch

Francesco Nicotra was born in Catania in 1950. He graduated in Chemistry at the University of Catania in 1973; then he moved to the University of Milano where he became permanent researcher in 1981 and associated professor in 1987. In 1985 he spent a post-doc period at the University of Orleans, under the supervision of Pierre Sinay. Actually he is full professor of organic chemistry at the University of Milano Bicocca and Director of the Department of Biotechnology and Biosciences. He is member of the IUPAC Committee of Organic and Biomolecular Chemistry and chairman of the subcommittee of Biotechnology. He is also the Italian representative in the International Carbohydrate Organisation. The research interests ranges across the synthesis of various biologically active compounds, in particular carbohydrates and structural analogs, the development of new synthetic methods and the use of biocatalysis.