In organic synthesis research: never give up, keep trying!

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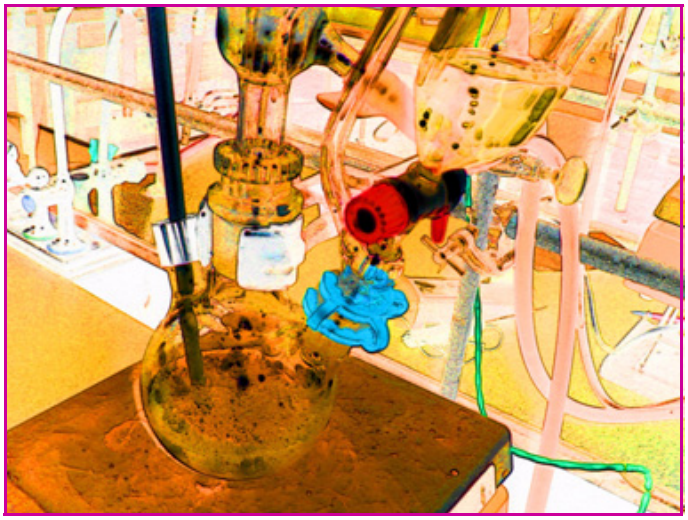
Résumé **Dans la recherche en synthèse organique : ne jamais désespérer, toujours essayer !**
Les chercheurs débutants en synthèse organique doivent être mis en garde contre les nombreux obstacles qui peuvent survenir tout au long de leur recherche, dont les chercheurs aguerris sont parfaitement conscients. Les exemples développés dans cet article, choisis parmi tant d'autres dans la littérature, pourront éclairer les jeunes chercheurs sur les énormes efforts déployés par leurs prédécesseurs pour résoudre les problèmes, notamment lors de la synthèse multi-étape. En voyant la nature et la taille des difficultés rencontrées par leurs aînés, ils comprendront la nécessité de s'armer scientifiquement et psychologiquement : patience, espoir, ambition, créativité, connaissance et rationalité sont indispensables pour surmonter l'échec. Ces efforts engagés dans la synthèse de molécules d'architecture complexe telles que les molécules naturelles finissent parfois par aboutir à des nouveautés sans précédent.
Mots-clés **CP-molécules, cyclooctatétraène, fullerène, quinine, taxol, vitamine B_{12}.**

Abstract Beginners in organic synthesis research should be warned of the possibly serious hurdles along the road; yet, the deeply delved ones are already well-aware of. The herein-cited examples, culled from the wealthy literature, may enlighten researchers on the endeavors of their predecessors. By understanding the huge difficulties the forerunners have experienced in multistep synthesis undertakings, new engaging researchers will understand the need of being armed psychologically and scientifically: patience, hope, ambition, creativity, knowledge, and rational thought are required to surmount the failures in synthesis sequences. The synthetic challenges of structure-complicated natural molecules make the endeavors sufficiently ripen their reasoning to produce novelties and unprecedented findings.
Keywords **CP-molecules, cyclooctatetraene, fullerene, quinine, taxol, vitamin B_{12}.**

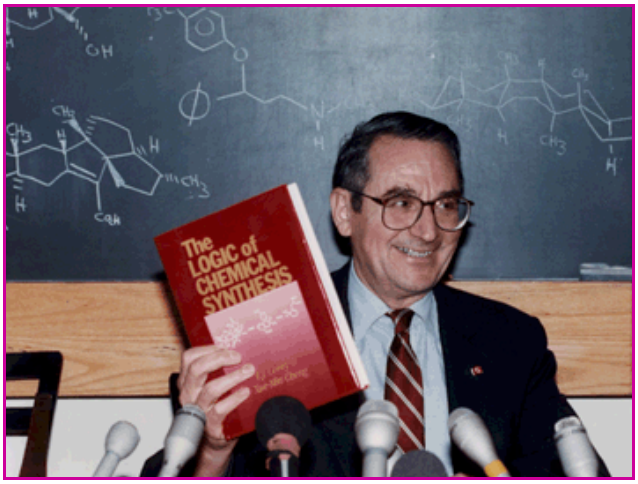
Complex molecules and chemists commitments

In performing research, hope, courage, endurance, resourcefulness, creativity, and stamina of daring are considered, among others, basic requisites. In many occasions, an unabated hope positively contributes to the success of a planned work. Pessimism and despair would negatively discourage the synthetic worker to go along with his commitment, but hope would rather raise his spirits, enlarge his sight field, and consequently, thrust him to envision the next steps for a successful ongoing project. Rare were those with a culminating hope who failed. *Grasping a hope* in any endeavor remains probably the best and last advice and recommendation that may be given to a frustrated researcher; a positive word is undoubtedly more powerful than a negative one.



By courtesy of Xavier Bataille (ENCPB, Paris).

Synthetic chemists are usually interested in either making far-reaching or brand new molecules or streamlining the conditions for already-existing reactions. Such research can be either "mission-driven" or "curiosity-driven". In the history of chemistry, the syntheses of natural molecules with increasingly complicated and frightening architectures have been coveted in order to collapse the defiant force of the nature; yet, the latter mightily, arrogantly and outstandingly makes them using other routes while expending rather lower energies *via* complicated biosyntheses. A confession from many eminent scientists consists of the omnipresent vitalism of the nature, no matter how epic the scientists' achievements. For instance, Sir John Warcup Cornforth, the Nobel Prize laureate in chemistry in 1975, expressed his view on this issue as [1]: "*The doctrine of vitalism, with its idea of a mysterious force pervading living matter and differentiating it from the non-living, is still alive and vocal; even among scientists it died hard.*"



Elias James Corey, Nobel Prize in chemistry in 1990.
Courtesy AP/World Wide Photos.

Although the hurdles in research are commonly viewed negatively, they should rather be considered landmarks to new discoveries, to unveil the secrecy in a synthesis issue, and to nurture further the research endeavor. In this line, Professor Kyriakos Costas Nicolaou mentioned in his concluding remarks in one of his papers [2]: "*For nature, in her designs, is* ***the supreme master****, and thriving to mimic her efficiency and elegance is a most rewarding endeavor.*"

To embark on the preparation of a new molecule and based on his own knowledge and the available literature, the chemist customarily mapped out the reactions, devised the sorting-out of the method and the apparatus. Thus, his first attempt leads to an outcome, which can be either the expected or unexpected. The latter results may be unprecedented ones or only a failure of the attempt as planned. Hence, the chemist will be either stunned by the unexpected results or smitten with the failure. Shrewd and deft as he might be, he should value the unprecedented findings, as they may pave new avenues in the research. For this point, Nicolaou's advice is quite enlightening [2]: "*... The moral of the story is that one should not be too quick to sweep unexpected observations under the carpet when they do not serve one's immediate purposes*."

On the other hand, he will retrospectively looked at his failed reaction work-up and scrutinize it to find the flaws and, accordingly, ponder new conditions or skillfully designed other alternatives. Again, this next attempt may hopefully afford the expected results or the expectation is rather distorted, calling for other or amended conditions. Likewise, the chemist resumes making changes until he shrieks "*Eureka*". In doing so, he triumphs over the challenge. Had he desperately quit his synthesis task, he would have unfortunately lost the bet.

Elias James Corey, the recipient of Nobel Prize in chemistry in 1990, confessed regarding the complexity of the synthesis research task [3]: "*It makes no difference that the realization of a difficult synthesis entails long hours of study, thought and physical effort,* ***since a complex chemical synthesis is an exciting adventure which leads to a beautiful creation***." Also, he admiringly heightens the chemist and beautifies further his holy task [3]: "*The chemist who designs and completes an original and esthetically pleasing multistep synthesis is like the composer, artist or poet who, with great individuality, fashions new forms of beauty from the interplay of mind and spirit.*"

Yet it is an obvious human gesture that the experimentalist scientist would stop halfway his project as long as he could not attain his initially planned objective. But to be triumphant, a tireless pursuit in elaborating experiments until the first glance of hope is imperative. Had he refrained from resuming his work, he would have disappointingly buried his idea, and the project would fade into oblivion or, in a better case, permitted the forthcoming researchers to resuscitate his launched project, and probably succeed and harvest thereafter. In the history of the experimental chemistry, there are numerous examples dealing with patience and stubbornness-adorning research tasks that were finally crowned with victory and prizes. Fairly saying, this victory should not selfishly be considered an intrinsic emotional feeling for the victorious person, but it is a victory for the entire research community, as the latter would necessarily benefit from it.

With an ardent curiosity, Louis Pasteur did not desperately stop at his following remarks on the behavior of racemates: "*The hemihedral faces which in the tartrates were all turned the same way were in the racemates inclined sometimes to the right and sometimes to the left*." He was stunned by the behavior of the racemates and rationally concluded that they may be a mixture of right and left-handed forms, unlike the single handedness of tartrate salts. In 1848 he, as a shrewd researcher, decided to go further, that is to separate the two forms. Using tweezers, he painstakingly separated them by hand: two piles of the right and the left-handed forms. With this gesture, he made a tremendous advancement for humanity; without his laboring effort to clear up the racemate puzzle, the thalomide-related problem, as many others, could have not be resolved.

To persuade chemists of recognizing the macromolecule entity was not an evident and a straightforward task. That polymer science is what it is nowadays owes to the **fifteen-year** struggle of Hermann Staudinger for the macromolecule concept and his firm concern and conviction about its existence. His theory was that rubber, cotton and other natural substances exist in the form of macromolecules and not as aggregates, as has been commonly believed. Even though the attacks by his detractors were so numerous [4] that he once exclaimed in frustration saying "*Here I stand and can do no other*", he tirelessly performed experiments to demonstrate the existence of the macromolecule. Heinrich Otto Wieland, one of his opponents, even advised him to reject bluntly the idea of a giant molecule [5]: "*My dear friend, drop the idea of your macromolecules; organic molecules with a molecular weight higher than 5000 do no exist… purify your rubber, then it will crystallize.*" X-ray crystal structure studies and ultracentrifugation experiments supported clearly his theory. Staudinger did not surrender to the critics but kept trying to convince the scientific community and finally succeeded.

Besides, beginners in organic synthesis research must be aware of the nature of the on-going organic syntheses. It is by far no longer confined to make molecules of simple structures, but it concerns those having a great number of atoms and organic functional groups, as the nature presents them to us. The ways these molecules are made let us think of their real complexity, which can stem from the existence of several chiral centers (2^n enantiomers for n asymmetric centers present in a molecule) and the unusual architecture. Thus, researcher background is expected to include the art in the chemical synthesis: for example, the asymmetric synthesis for preparing preferentially one enantiomer,

masterly developed by William S. Knowles, Ryoji Noyori and K. Barry Sharpless, and the retrosynthesis technique cleverly founded by E.J. Corey.

There are too many organic molecules of ever-increasing structural complexity which were made and whose syntheses called for rational thought although, at times, proper methods and analytical techniques were scarce. Hereafter and for illustrative purposes, our choice, yet non-exhaustive, picked up the historic timeline of the synthesis of some of these molecules: cyclooctatetraene, vitamin B_{12}, taxol, CP-molecules, and fullerene C_{60}. In addition, *table I* gathers a few of the many synthesized complex molecules. Their syntheses generally were motivated by their unique properties, for example pharmaceutical. The paradigm of taxol is that it can be extracted in a pitifully minute amount; it would take almost six 100-year old yew trees to provide enough taxol to treat just one cancer patient. Isn't that a reasonable motive for its chemical synthesis in a sufficient quantity?

A compendium of myriad of natural molecules, which have been the endeavors of many eminent organic synthetic chemists, is indubitably the elegant twentieth century review of Nicolaou *et al.* [6]. This well penned paper brings back the total syntheses of these fearsome molecules, showing the great number of steps and the wealthy chemistry involved.

Table I - **Some synthetically endeavored molecules**.

Molecule name	Chemical formula	Special properties	Involved synthetic chemists	Year	Number of steps
Haemin (Hemin)	$C_{34}H_{32}O_4N_4FeCl$ Porphrin family	Red pigment of blood; oxygen carrier	H. Fischer	1929	14
Morphine	$C_{17}H_{18}O_3N$ 5 chiral centers	Analgesic	M.D. Gates	1956	14
Penicillin V	$C_{15}H_{18}O_5N_2S$ β-lactam 4 chiral centers	Antibacterial properties	J.C. Sheehan K.R. Henery-Logan	1957	12
Progesterone	$C_{20}H_{30}O$ Steroid 6 chiral centers	Preparation of the lining of uterus for the implantation of an ovum; ovulation suppressor	W.S. Johnson	1971	12
Erythronolide B	$C_{24}H_{31}O_7$ Macrolide 10 chiral centers	Antibiotic	E.J. Corey	1978	21
Monensin	$C_{13}H_{57}O_{11}$ Polyether 17 chiral centers	Antibiotic	Y. Kishi W.E. Still	1979 1980	39 30
Efrotomycin	$C_{58}H_{88}O_{20}N_2$ 19 chiral centers	Antibiotic, elfamycin family	K.C. Nicolaou	1985	19
Okadaic acid	$C_{44}H_{66}O_{13}$ 17 chiral centers	Phosphatases inhibitor, tumor promoter	M. Isobe	1986	26
Amphotericin	$C_{48}H_{70}O_{17}N$ Polyene macrolide 19 chiral centers	Antifungal agent	K.C. Nicolaou	1987	40
Palytoxin	$C_{124}H_{213}O_{50}N_2$ 63 chiral centers	Toxic properties	Y. Kishi	1989	7
Cytovaricin	$C_{47}H_{27}O_{15}$ Macrolide 17 chiral centers	Antineoplastic activity	D.A. Evans	1990	21
Calicheamcin	$C_{54}H_{28}O_{21}N_3S_4I$ 18 chiral centers	Potent anticancer Antibiotic activity	K.C. Nicolaou	1992	35
Rapamycin	$C_{51}H_{78}O_{13}N$ 15 chiral centers	Immunosuppresive potency	K.C. Nicolaou	1993	22
Asidophtine	$C_{22}H_{26}O_4N_2$ 4 chiral centers	Anticocktoach/ insecticidal powder	E.J. Corey	1999	10

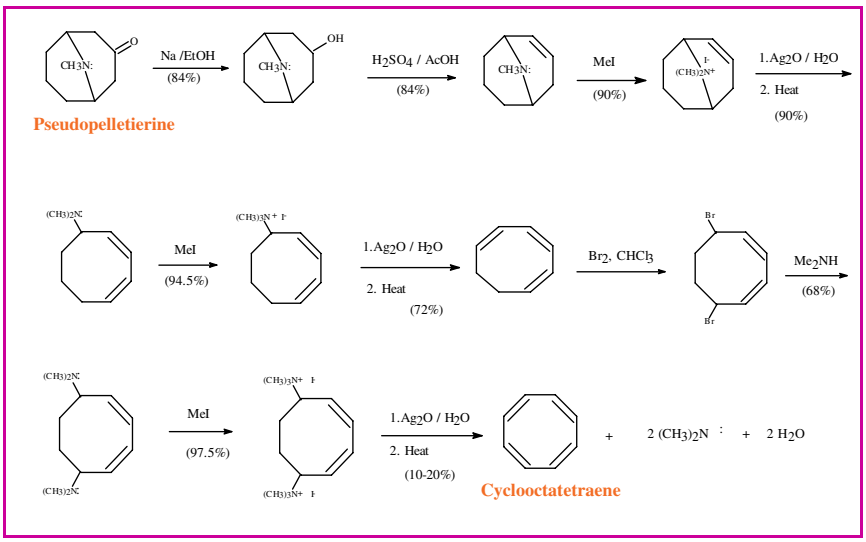


Figure 1 - **Synthesis of cyclooctatetraene** (Willstätter, 1911; Overberger, 1947).

One could easily be in a daze and fall into a trance on seeing the numerous reactions and reagents, realizing how daring and ingenious the practitioners were.

Worrying cyclooctatetraene, successfully remade (1911, 1948)

The German chemist Richard Martin Willstätter, the recipient of Nobel Prize in chemistry in 1915, wanted to make cyclooctatetraene in order to elucidate its aromatic property and compare its chemistry with that of benzene. At the time, this motive was a novelty and to make such a molecule was a genuinely valuable exercise. The long-run synthesis of the cyclooctatetraene (from 1905 to 1911) demonstrates how stubborn and patient Willstätter was. The synthesis was completed starting from pseudopelletierine, an alkaloid from the bark of the pomegranate tree (see *figure 1*). Although the yield was miserable (≈ 3%), he was able to compare its properties with those of benzene and found a substantial difference. The later attempts by other chemists to replicate the Willstätter's synthesis failed, although the chemistry behind this is straightforward, involving mainly three Hoffmann elimination sequences. As a consequence, some chemists outright cast some doubt on the real product Willstätter came by, and their lingering doubt lasted for more than **30 years** although he reported the reduction of the cyclooctatetraene to cyclooctane and its oxidation to suberic acid, strong evidence of the authenticity of his product. In 1947, Charles Overberger, under the supervision of the eminent Arthur Clay Cope, reproduced it and thus confirmed it [7]. It is enlightening to recall that Walter Reppe in 1940 prepared cyclooctatetraene by polymerizing acetylene over a nickel cyanide catalyst and in the presence of calcium carbide; surprisingly, Reppe published his results only eight years later [8]. Being aware that this compound can be produced in a large scale by the Reppe's process, I intend to point out again how synthetic chemists did not give up trying and their unabated efforts were finally crowned with success.

Nowadays, several workers are interested in cyclooctatetraene derivatives due to their display of electronic properties in organic light emitting.

Corey's retrosynthesis: a rational thought at the right time (1957)

Customarily, the synthetic chemist has at hand readily available starting materials and a set of known reactions, methods and rules. To tackle the synthesis of a relatively complicated organic molecule, the chemist tries to build it from these starting materials without a soundly rational strategy, that is, in a groping way. In some cases, it works but after going astray many times. An ingenious innovation for rational multistep synthesis would be to break down the target molecule into more accessible and less tantalizing molecular species. This strategy is coined "*retrosynthesis*" or "*antithesis*" as advanced and pioneered by E.J. Corey in 1957, amazingly only seven years after his PhD degree and at the age of 29; he even termed this strategy as "*the logic of chemical synthesis*", defined as [3]: "*… to convert that target structure to simpler precursor structures without any assumptions with regard to starting materials.*" The retrosynthetic analysis was not merely the result of a theoretical work but an imaginative upshot of the synthesis hurdles.

One of the first molecules made with the aid of the retrosynthetic analysis was *longifolene*, starting with resorcinol and buten-1-one as pictured in *figure 2*. The retrosynthesis was used as the basis of a computer program for drawing a possible synthesis outline of an organic molecule. The idea of retrosynthesis had been used earlier by Rabe, Prelog, and Woodward to prepare quinine by converting it into quinotoxin and homomeroquinene which were in turn target molecules.

With the retrosynthesis approach, the synthesis of complex molecules was no longer forbidden and time-consuming, providing the availability of suitable methods and reagents. Literature is ablaze with numerous examples of such molecules. For instance, the synthesis of *ginkgolide*, which was as troublesome as vitamin B_{12}, was achieved expeditiously within **only three years** in the 1980s by Corey's research group.

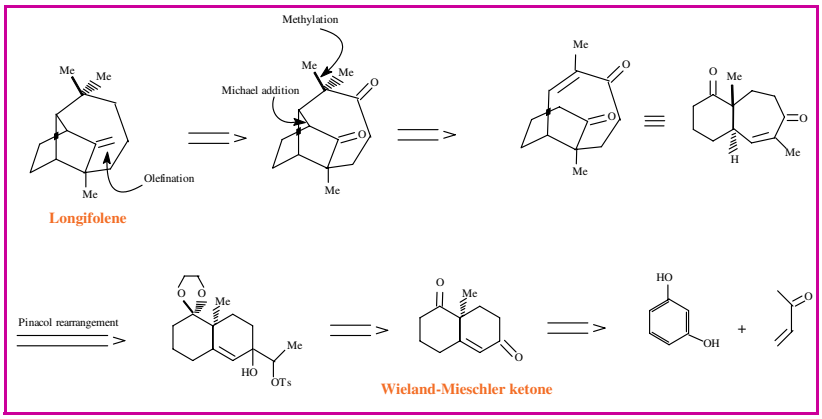
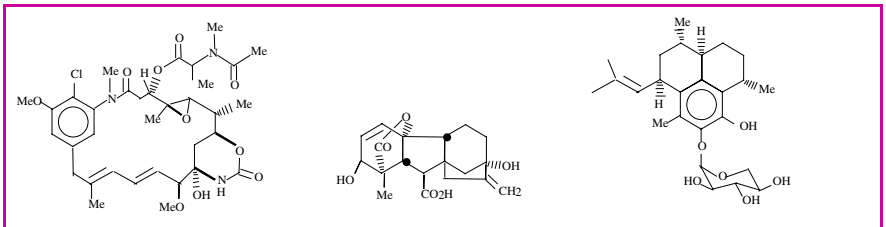


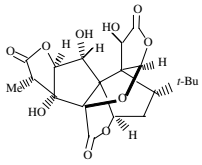
Figure 2 - **Retrosynthetic analysis of longifolene** (Corey, 1957).



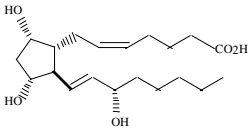
Maytansine (1980)

Gibberellic acid (1978)

Pseudopterosin E (1989)



Ginkgolide B (1988)



Prostaglandin F2alpha (1969)

Figure 3 - **Some synthetic molecules of Corey's era**.

The total synthesis of *gibberelic acid* proved to be difficult because it contains an unusually complicated arrangement of structural units; indeed many synthetic chemists vainly attempted this for more than two decades. Only with the help of the retrosynthetic analysis did Corey finally accomplish its synthesis. *Figure 3* compiles some of the myriad of molecules prepared by Corey's group.

Vitamin B_{12}: the Mount Everest climbed (1972)

Mount Everest, the world highest mountain (29 035 ft: 8 856 m) seemingly defied man to reach its summit. The first attempt to ascend the mount was in 1924 by George H.L. Mallory, who died during this arduous adventure. Not only is its height forbidding but also the massive snow and ice avalanches. Despite these seemingly insuperable obstacles, however, Sir Edmund Hillary and Tenzing Norgay finally reached its summit on May 28, 1953. The vitamin B_{12} *via* its exotic structure stood in the eyes of the synthetic chemists as the Mount Everest (*figure 4*) [9]. As expected, the difficulties in dealing with this molecule were apparent right at the start. The first tedious task was to establish its molecular structure, and propitiously the X-ray technique came along. It took almost **eight years** (1948-56) of persistent work for Dorothy Crowfoot-Hodgkin (Nobel Prize in chemistry in 1964) at Oxford University to reveal its real structure. Afterwards, its chemical synthesis remained an unmet challenge and a tantalizing task to synthetic chemists: the molecule contains the corrin ring having four small rings of five atoms, a cobalt atom sitting inside the corrin, and no fewer than **15 chiral centers**. The tremendous consistency and the robustness of its chemical structure unsurprisingly require commensurate devotees. So, it is not unusual that the synthesis of this molecule necessitated an organic chemist whose synthetic robustness and stamina was commensurate with its intricacy. That chemist with the requisite qualification and acumen existed at the right time, a time period of flourishing synthesis, and was Robert Burns Woodward. Not exaggerating his qualifications, chemists have frequently witnessed his scientific ability and ambitions, sharp wit and aspirations to take on the synthesis challenges. Albert Eschensmoser, his Swiss collaborator in the B_{12} synthesis, described the Woodward's chlorophyll synthesis as "*Woodward's extraordinary insight into the reactivity of complex organic molecules*". As for the complexity of the molecular structure of B_{12}, Woodward, who succeeded in making other complicated molecules, confessed that it is "*a monster*". Among the **99 scientists from 19 countries** embarked on making B_{12} was Sir John Warcup Cornforth who unfortunately gave up, confessing that he had only "*some nice clay from*

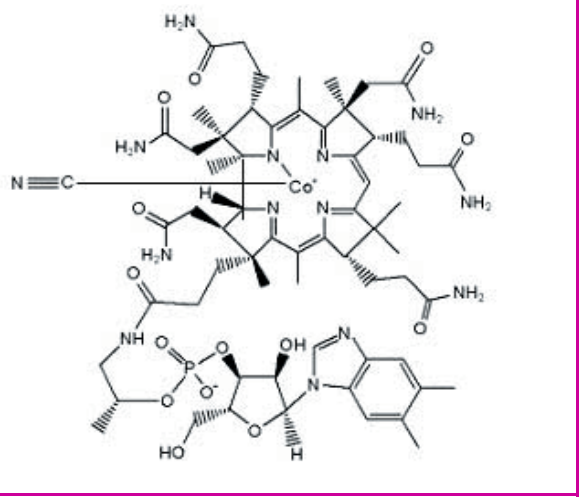
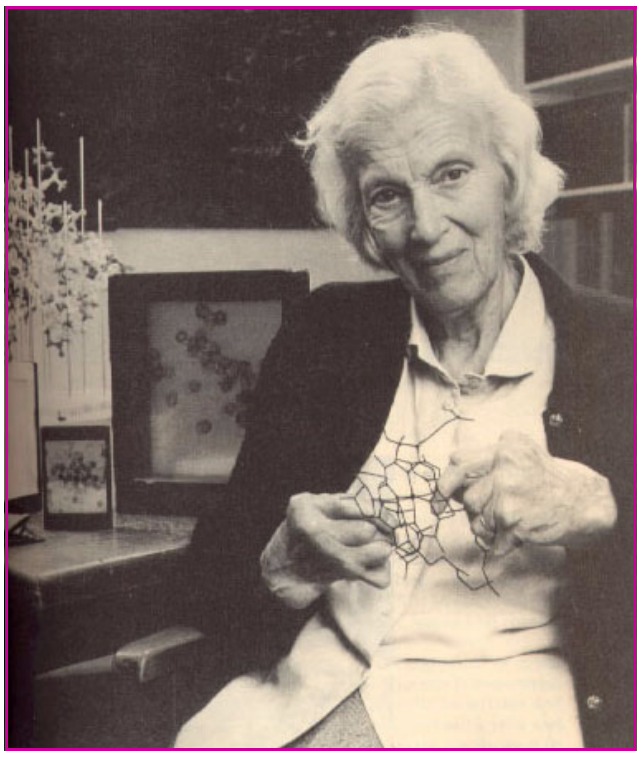


Figure 4 - **Vitamin B_{12}**: the Mount Everest!



Dorothy Crowfoot-Hodgkin, Nobel Prize in chemistry in 1964.

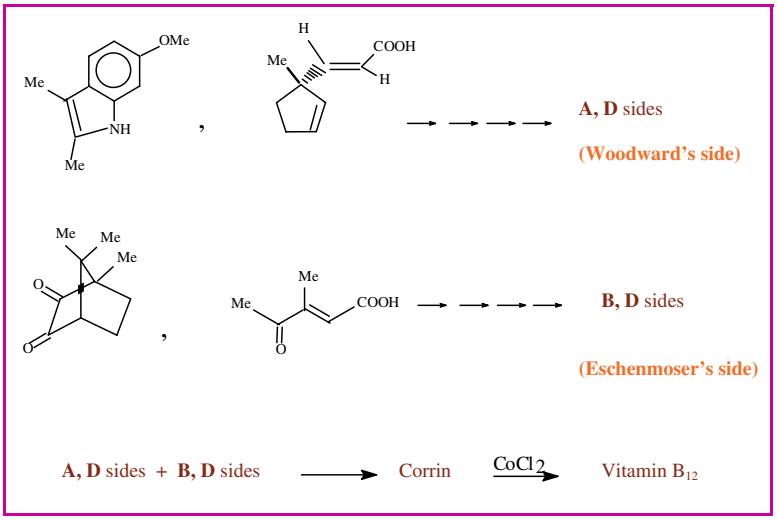


Figure 5 - **Synthesis of vitamin B_{12}** (Woodward, Eschenmoser, 1972).

which he hoped to make bricks." The impetus for the synthesis was not only academic but also to make B_{12} on an industrial scale because it was used to treat pernicious anemia; patients were relieved by consuming large quantities of liver which turns out to contain B_{12} in an amount of about 2-5 mg.

Until 1965, Albert Eschenmoser at the Eidgenössiche Technische Hochschule (ETH) in Zürich and Robert Burns Woodward at Harvard University in USA worked independently on the synthesis of B_{12}. While the former started his synthetic work on vitamin B_{12} in 1960, the latter began one year later. Realizing the difficulty of their task, they decided to consolidate their efforts. They split the synthetic work into two parts: Eschenmoser took over the construction of the two east-sided rings (**B** and **C**), Woodward was charged with the two west-sided rings (**A** and **D**) (*figure 5*) [9-10]. Woodward's group found out that they could make their assigned rings from a molecule called β-corrnorsterone. In making the latter molecule, Woodward applied the Diels-Alder reaction to construct carbon-made rings of steroid-like molecules (amazingly, Woodward was only ten years old when he first became interested in the Diels-Alder's report). In his attempt, and to his surprise, he found that the reaction gave him exclusively one of the two possible chiral products. He wanted to understand this stereoselectivity and shrewdly pondered the possible clockwise and anti-clockwise rotations of the orbitals. His next wonder was how to put this flair of a possible explanation into a proper theory; he said: "*I very soon realized that I needed more help*." As might be understood, Woodward did not give up or put the whole thing aside, but asked for help. Fortunately and fatefully, a young insightful theorist named Roald Hoffmann was next door as one of the staff of the chemistry department at Harvard. Woodward approached him, outlined his ideas and then said: "*Can you make this respectable in more sophisticated terms?*"

In the ensuing years (1965-69), the Woodward-Hoffmann rules were brought forth and set in terms of "orbital symmetry". These rules are based on the following hypothesis: "*in concerted reactions molecular orbitals of the reactant are continuously converted into molecular orbitals*." According to these rules, there are chemical pathways that are "*symmetry allowed*" and others "*symmetry forbidden*". Also, a new terminology was introduced including *disrotatory* and *conrotatory*. Eschenmoser soon made use of this rule in making corrin ring from its four components; the rule allowed him to obtain the product with the right chiral geometry. He praised this rule and pointed out its serendipitous side saying [9]: "*Would hardly exist today, had the efforts at Harvard to synthesize the **A**-**D** half of **the B_{12} molecule not stimulated the discovery of the Woodward-Hoffmann rules**. If the term "beauty" of a reaction is ever justified in such a context, it is in this one.*"

Although Woodward had announced the total synthesis of B_{12} at a meeting in New Delhi in February 1972, a tidier description of it was disclosed in November 1972 at a chemistry symposium at Wesleyan University in Middletown (Connecticut, USA). The **11-year** synthesis of vitamin B_{12} took about **100 steps**, an unconceivable number for a total synthesis. Within these strides, there was a great need for immense imagination and invention. Was not it a colossal task meriting a reward?

At the end of this glimpse of vitamin B_{12} synthesis story, the concluding remark can be the one given by Eschenmoser: "*Many chemists were led to believe that Woodward had shown in principle that any natural product, be it ever so complex, would be amenable to synthesis, given only a great enough investment of time and resources.*"

Woodward's synthesis endeavor did not stop at the vitamin B_{12}, and the last statement of Eschenmoser rang true. In fact, Woodward dauntlessly assaulted the syntheses of many complicated natural products within a short period of time; some of the reputed ones are depicted in *figure 6*: cholesterol (1953), one of the components of cell membrane; reserpine (1956), a medication for high blood pressure and

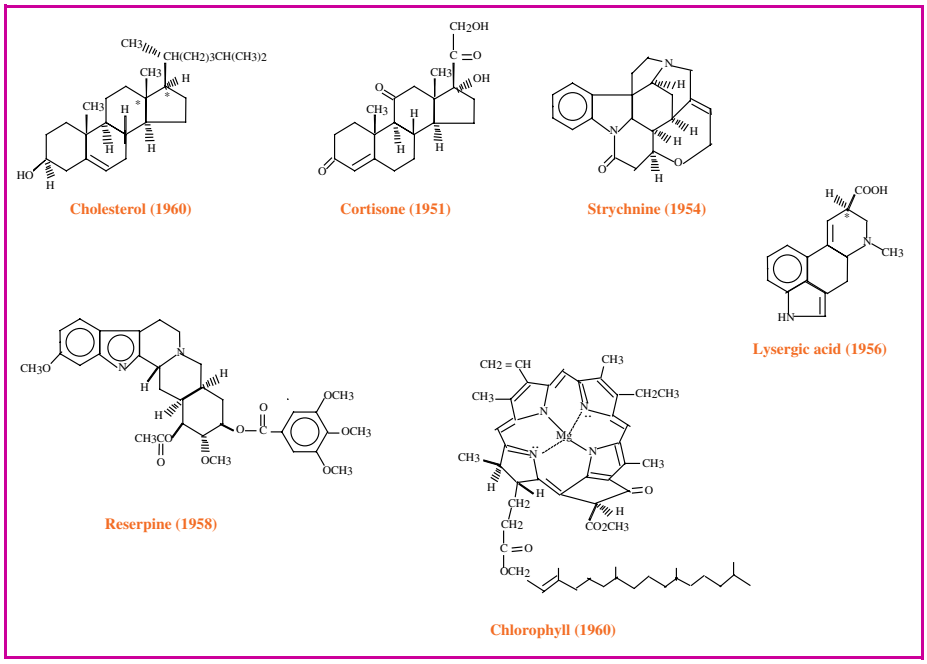


Figure 6 - **Some synthetic molecules of Woodwardian's era**.

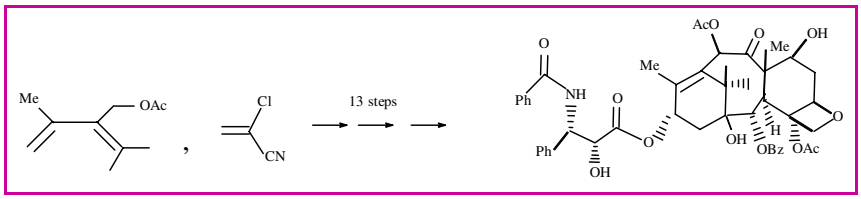


Figure 7 - **Synthesis of taxol** (Nicolaou, 1994).

nervous disorders; lysergic acid (1956), a pharmaceutical for circulatory, obstetric and physiological disorders; strychnine (1954), a deadly poison; chlorophyll (1960), the green pigment of the plants. Indeed, this period of time of synthesis has been coined the Woodwardian era. In 1950s, the structure of terramycin, a valuable antiobiotic, had been a serious puzzle because of its industrial importance; many chemists had taken the challenge but with no real success. It was the ingenuity of Woodward that clarified the problem forever. Sir Derek Barton (Nobel Prize in chemistry in 1969) said about this solution: "*The most brilliant analysis ever done on a structural puzzle was surely the solution (1953) of the terramycin problem* [...] *Woodward took a large piece of cardboard, wrote on it all the facts and,* ***by thought alone****, deduced the correct structure for terramycin. Nobody else could have done that at the time*."

Taxol synthesis: a harsh labor for a wonder drug (1994)

Of the wonder drugs, taxol has been a central occupation of many scientists because it displays a totally unique mode of action in cancer treatment. A glance at its story is worthy. In the 1960s, the National Cancer Institute in USA started a program of screening of extracts from a wide variety of plant tissues for anti-tumor activity. In 1962, clinical trials showed that the extract from the bark of the Pacific yew tree revealed a cytotoxicity activity against human cancer cells [11]. In 1967, Wani and Wall of the Research Triangle Institute (USA) isolated the active material, and in 1971 they reported its chemical structure [12]. In the late 1970s, research was devoted to show how taxol worked and to what extent it was effective in cancer patients. In the 1980s, clinical assays proved that taxol displays promising activity against many types of advanced cancer: ovarian, breast, lung, head, neck, and esophageal [13]. In 1994, taxol was approved for breast cancer and considered a better alternative to radiotherapy and surgery. Unfortunately, its concentration in the yew tree is miserably low: 0.5 g for 12 kg of bark; six 100-year old trees are needed to provide enough taxol to treat one patient. Thus, a chemical synthesis of it was conceived as an ultimate alternative and a must. And, indeed, in 1980-1990s, over a hundred academic synthetic organic chemistry laboratories disclosed various approaches to its synthesis. Of these concerted efforts, the main ones credited were K.C. Nicolaou (1994), R.A. Holton (1994), S. Danishefsky (1996), P.A. Wender (1997), T. Mukaiyama (1998), and I. Kuwajima (1998). *Figure 7* traces the synthesis of taxol by Nicolaou in a very shortened form [2].

Quinine synthesis: a final chapter (2001)

The anti-malarial effect of quinine has been credited to a serendipitous legend starring an Indian from South America who was suffering from malaria [14]. The use of the cinchona bark was introduced in Europe in 1639 after the dramatically successful treatment of the Countess de Chinchón, the wife of Spanish Viceroy of Peru, from a tertian fever. Since then prepared bark powder has been coined the "Countess's powder". This bark contains more than twenty-five alkaloids, including quinine, which was extracted and separated in 1820 by the French chemists, Pierre Joseph Pelletier and Joseph Bienaimé Caventou. In 1852, Louis Pasteur undertook its first stereochemical investigation, identifying quinine as *levo-rotatory* substance. In 1854, Adolph Strecker established the quinine formula as $C_{20}H_{24}N_2O_2$ which was later confirmed by Skraup. However, the correct atoms connections in the quinine molecule were set primarily by Paul Rabe in 1907. Because of its four existing chiral centers meaning **16 stereoisomers**, its synthesis has been an unparalleled challenge. In fact, **it took more than hundred years** to determine finally the authentic structure. Nonetheless, it is worth citing some of the many organic synthetic chemists who have been influential in the synthesis of quinine throughout the many years: August Wilhelm Hoffmann, William Henry Perkin, Paul Rabe, Vladimir Prelog, Robert Burns Woodward, William Doering, Milan R. Uskokovic, Marshal Demotte Gates, and Gilbert Stork. Amazingly, it was only in 2001 that the latter worker succeeded in making quinine in its real shape [15] (*figure 8*); Stork used (*S*)-4-vinylbutyrolactone which was prepared by Taniguchi [16]. Aside from the Stork results, the real compounds found by the others actually lacked stereochemical control, and all the synthetic ways (including Stork's) required **no less than 13 steps**. To show how optimistic and resistant Stork was towards the quinine synthesis is to recall that he reported the first stereoselective quinine synthesis in 1946, **55 years** before his final success. In their attempt, Robert Burns Woodward and von Doering in 1944 synthesized quinine in a lower yield (0.075%), involving **15 steps**; and with stereoselectivity lacking, only three of the four asymmetric carbons were reached. Thus, it has been the devotion of the chemists who restlessly took over in row the far-reaching synthesis of quinine; it took more than one and a half century of chemists' endeavors to respond positively to the nature's challenge.

Eric N. Jacobsen reported in 2004 the first catalytic asymmetric total synthesis of quinine and quinidine using (*S*,*S*)-salen(Al) complex through **16 steps** with overall yield of 5% [17]. In the same year Kobayashi published the quinine and quinidine synthesis through a stereocontrolled epoxy intermediate starting with a disubstituted cyclopentene that was transformed into disubstituted piperidine [18]; the synthesis involved more than **10 steps**.

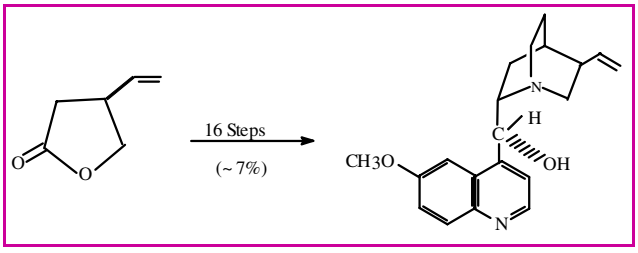


Figure 8 - **Synthesis of quinine** (Stork, 2001).

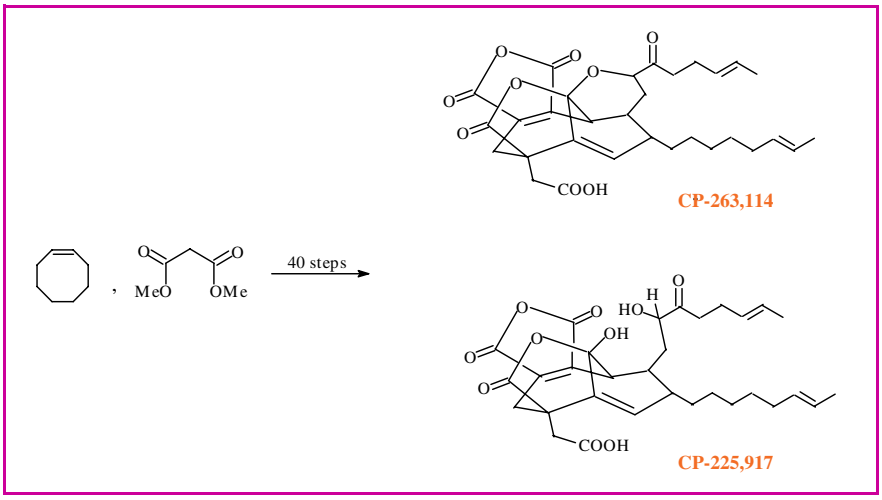


Figure 9 - **Synthesis of CP-molecules** (Nicolaou, 2002).

Sturdy CP-molecules collapsed (2002)

In 1990s, Takushi Kaneko at Pfizer's research laboratories disclosed the discovery of substances which they called "*CP-molecules*" coded as CP-225,917 and CP-263,114, the phomoidrides **A** and **B** (see *figure 9*). These compounds are endowed with anticancer and cholesterol-lowering properties. They intrigued synthetic chemists not because of their size but by the bond connectivity they display in addition to the existence of two five-membered rings, two six-membered rings, one seven-membered ring, one nine-membered ring and some vulnerable functionalities, enclosing five stereogenic centers, all of which pose a real challenge. Moreover, these compounds are among a few that violate the Bredt's rule which states that no double bond can be formed within the bridgehead of a bicyclic structure.

The assault on its synthesis was undertaken mainly by four research groups: Tohrn Fukuyama's, Samuel J. Danishefsy's, Mathew D. Shair's, and K.C. Nicolaou's. Professor Nicolaou of the Scripps Research Institute and University of California accepted the challenge and embarked on work in 1996. In a review [2], Nicolaou pictured his CP-molecules synthesis endeavor like the legendary battle between Theseus and Minotaur, demonstrating the huge challenge. Truly, this review is a masterly paper because not only many attempted reactions and about 300 compounds and intermediates are delineated, but also the course of reaction sequences is elegantly narrated with turning events and switchovers. The project faced many failures and frustrations along the road, but with the diligence of his research group, successive and succinct successes have ensued. To show how persistent the group was, Nicolaou recounts: "*Early one morning, **after another failure**, I* [Nicolaou] *called Phil* [one of his PhD students] *to my office, sat him down and said: "This project is always in shambles, and it is very painful to everyone. **I think we should cut our losses and just forget about the CP molecules**. I would not think any less of you if you stop now." Phil's eyes widened and he immediately declared: "**Impossible, I will never stop until CP has fallen and I know Zhong** [the other PhD student] **feels the same way. This is what a PhD is all about, isn't it**?" "OK, good, you passed the test. Now you can go back to work…*"

May I bona fide say to the failing synthetic chemist who strives for reaching his desired molecule: "*Take a rest, you deserve it, and come back later to resume your synthetic project with a novel strategy, a better endeavor, and full of hope*."

Fortunately, the effort will be resumed with more endurance and hope, and finally will be adorned with a great success. The two-year total synthesis required **40 steps** involving many grams of starting materials, cyclooctene and dimethylmalonate, to make milligrams of the targeted CP-molecules [19-21] (*figure 9*). Phil S. Baran, a dedicated researcher, was relieved by coming to the end of the scene; as he put it: "*Atop the mountain, it feels like a 200-ton anvil has lifted off my back.*" It was the profound commitment of Phil and his unshakable determination that these "monster" molecules finally have fallen down. Professor Samuel Danishefsky, a towering figure in chemical synthesis, who was also tempted to perform the synthesis of the CP-molecules, said about the Nicolaou's group success: "*It's an extremely impressive accomplishment.*"

Not only did this endeavor entail the synthetic approach of the target molecules, but it also came up with new and unexpected chemical reactions.

Bending flat molecules towards fullerene C_{60} (2002)

To bend a stable flat molecule, effort is needed. The fullerene C_{60} or buckminsterfullerene, an allotropic form of the carbon in form of a perfect soccerball, was accidentally discovered in 1985 by Sir Harold W. Kroto, Richard E. Smalley, and Robert F. Curl while trying to make the polynylcyanides, and for which they were awarded the Nobel Prize in 1996.

The beauty of fullerene C_{60} has nurtured a sustained interest in its synthesis. Its perfectly symmetric shape (I_h group symmetry, 120 symmetry operations) makes the synthesis of this carbon molecule a weighty challenge, which thwarted the interests of at least two research groups: Professor Peter W. Rabideau (Ames Laboratory, Iowa State University) and Professor Lawrence T. Scott (Boston College). It is also worth noting more the magnitude of the challenge: besides the 50 π bonds, C_{60} has 90 C-C bonds and an enormous strain as quantified by its heat of combustion, about 600 kcal/mole. Scott, aware of this serious problem, stated: "*Building a 60-carbon cage with 32 rings will be no trivial task, of course, even with strain problem reduced, and we are unaware of anyone who has taken on the challenge.*"

Indeed, in both laboratories, the assault on the synthesis of fullerene was incepted in the 1990s. Their plans were to build up, a brick at a time, bowl-shaped hydrocarbons to reach finally the projected molecule. Their continuous efforts brought forth to other intriguing molecules: the buckybowls or semibuckminsterfullerenes. To reach these molecules, Rabideau started by making corannulene, a C_{20} carbon network representing the polar cap of the fullerene C_{60}. The synthesis of corannulene, a geodesic polyarene, was first made by Barth and Lawton in 1966 at the University of Michigan, but the yield was so low (few mg) and necessitated a long and difficult **17-step process**. All subsequent attempts to amend the process **failed for about 25 years**. Scott, however, tried the flash vacuum pyrolysis technique (FVP) to

make it and succeeded; the corannulene was obtained in a high purity [22]. On the other hand, Rabideau made a distinct improvement with respect to the yield; he, with a serendipity involvement, found a practical way to produce corannulene in large scale, 25 grams, that is two orders of magnitude greater [23]. Rabideau employed the FVP technique introduced by Scott to form the buckybowl or the semifullerene.

After tedious and restless work, Scott, in 2002, finally and extraordinarily succeeded in synthesizing C_{60} in **12 steps** from ordinary chemicals (*figure 10*), using the FVP technique [24]. He won the multistep synthesis bet!!! Yet the overall yield was minute, no higher than 1%. This success may be less surprising because Scott is a Robert Burns Woodward's student. He met many challenging obstacles and failures before reaching the molecule. But these unwanted obstacles were circumvented by rational thought and aspiration and led to novel principles which were not previously known. Scott's rational thought lies in his use of the FVP technique to promote the Roger Brown rearrangement. I quote these principles as [25]:

- Curvature can be temporarily induced in polyarenes by FVP;
- Radical-initiated C(aryl)-C(aryl) coupling reactions can be used to catch the distorted conformations;
- Hydrogen atom 1,2-shifts can be exploited to circumvent onerous synthetic challenges;
- Cyclodehydrogenation cascades can be relied on to stitch together adjacent arms of a π system, once the curvature has already been induced.

The other lesson from Scott's work is that FVP, which had previously served only for destructive objectives, is now considered a powerful constructive tool for making complex molecules from simpler ones.

Benefits and spin-offs

Successful synthesis not only provides a self-satisfaction to the worker but also entails many pivotal points for a general benefit. The best lessons that can be drawn from the syntheses of the complex molecules and the involved endeavors are but not exhaustively summarized as follows:

1. To reach one's goal in organic synthesis, one cannot be discouraged and disappointingly surrender to the obstacles and failures; but instead, with hope and audacity, one can circumvent and tide over the difficulties and the frustrations.

2. Do not blindly and outright put aside the negative results, but keep trying to understand the origins of the failures and to search a better remedy.

3. The course of the long-route synthesis may profitably pave novel avenues: new reaction, new methodology, new rules, new principles, new products, and new mechanisms. For example, Robert Robinson, a leading figure in organic synthesis, would not have invented his annulation (or annellation) if he had not been working on the synthesis of steroids (complex molecules), and Robert Burns Woodward and Roald Hoffmann would not have invented the symmetry rules if Woodward had not been working on the synthesis of vitamin B_{12}.

4. Serendipity has been omnipresent along the research and many amazing instances appear in the literature. A remarkable example is that of Clayton H. Heathcock [26] who, while working on the synthesis of the *Daphniphyllum* alkaloids, stumbled on an accidental occurrence that led to a great improvement in his undertaken synthesis; that is methylamine was inadvertently used instead of ammonia because of a mislabeled bottle, and the yields of the products were unexpectedly and significantly enhanced. Probably serendipitous results, I would say, impress more than the expected ones. On Commencement Day 50 years ago at Harvard University, the honorary speaker, Sir Alexander Fleming, the discoverer of penicillin by accident, advised the young graduates in his address: "*Never neglect an extraordinary appearance or happening. It may be a false alarm and lead to nothing. But it may, on the other hand, be the clue provided by fate to lead to some important advance*."

5. Rational reasoning and logic in the synthesis are fundamental.

6. Friendly competition in the synthetic work of complex molecule nurtures the creativeness of the involved competitors. A harsh controversy and a friendly rivalry on any chemistry-related issue would positively and certainly enrich chemistry.

7. Cooperative inter-laboratories work on a research project would indubitably be more fruitful and profitable.

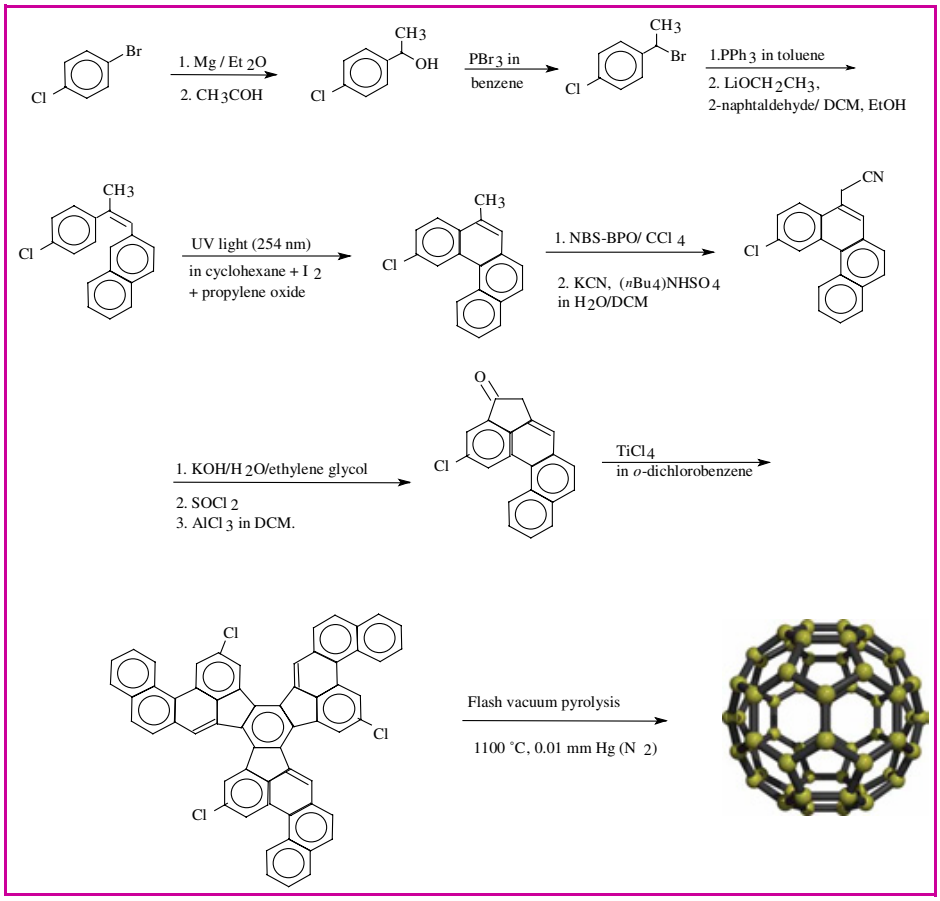


Figure 10 - The 12-step **synthesis of fullerene C_{60}** (Scott, 2002).

8. Dedicated workers in organic synthesis generally triumph at the end.

9. Rewards of fastidious synthetic work will be of great merits.

Finally, the words of Professor Teruadi Mukaiyama in his terse paper "From a synthetic organic chemist" are worth quoting [27]: "*It is our task to dig out further effective synthetic methods hidden in the mines of wisdom. They may be unseen but are inexhaustible. Exploration of excellent methods (reactions) will eventually help to accomplish the total synthesis of complex molecules. Therefore, cooperation between what is "predictable" and "unpredictable" will be the key to our future.*"

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