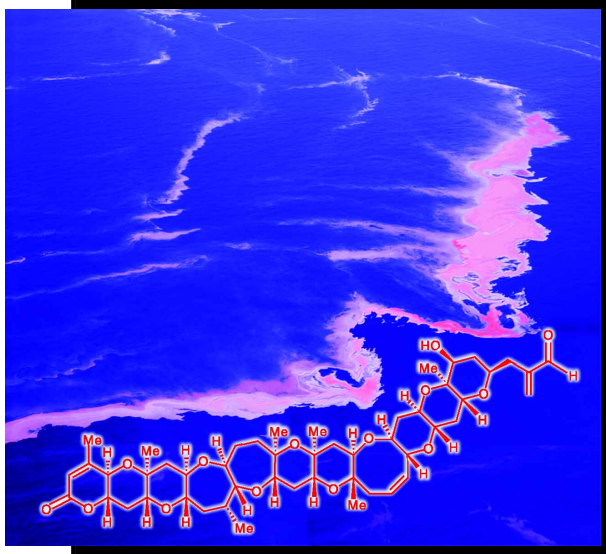
Viewpoints: Chemists on Chemistry

The Art and Science of Organic and Natural Products Synthesis

K. C. Nicolaou, E. J. Sorensen, and N. Winssinger

Outline

In this article, the history of the art and science of organic and natural products synthesis is briefly reviewed and the state of the art is discussed. The impact of this discipline on biology and medicine is amply demonstrated with examples, and projections for future developments in the field are made.



Other Material on Organic and Natural Products Synthesis in This Issue

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The Art and Science of Organic and Natural Products Synthesis

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Introduction

In contrast to "Silicon Valley", the term "Carbon Valley" has not yet been commonly applied to describe the many regions around the world where millions of carbon compounds are synthesized every year, some in multiton quantities in the name of basic research concerning materials science, biology, and medicine. It should! Such carbon valleys are found today in the northeastern United States, California, England, Central Europe, and Japan. They are dotted with universities and research institutes, pharmaceutical and biotechnology companies, and material science centers where scientists are hard at work effecting predesigned or random changes to the constitution and structure of matter and creating new substances. The practice of constructing molecules of carbon is called organic synthesis and it is, at the same time, an exact science and a fine art. When directed toward natural products, this endeavor is referred to as natural products synthesis.

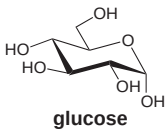
Organic and natural products synthesis is a relatively young science, having its beginnings in the 19th century. Since that time, synthetic chemists have perfected this science to the point where not only can genes and proteins be synthesized at will in the laboratory, but also an array of complex and fascinating molecular structures from the realm of natural products, commonly known as secondary metabolites, can be assembled by rational methods from simple starting materials. Furthermore, myriad designed and random molecular frameworks containing carbon atoms in combination with hydrogen, oxygen, nitrogen, sulfur, and halogens, as well as other atoms, can be synthesized on demand and tested for various applications. Such useful compounds range from biological tools and medicines to high-value materials for cosmetics, computers, sophisticated machines, and useful devices. In this article, we will examine the evolution of the art and science of organic and natural products synthesis (*1, 2*) to its present state, demonstrating its central role behind some of the most striking discoveries (*3*) of the 20th century and projecting well ahead into the next century (Fig. 1).

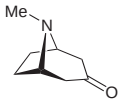
Figure 1. Organic and natural product synthesis as a driving force for discovery and invention in chemistry, biology, and medicine.

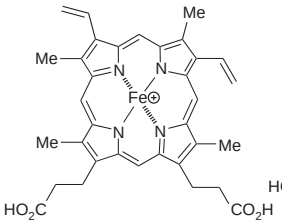
Historical Perspectives

When our ancestors were extracting the opium poppy or making wine, they had no idea what was going on at the molecular level, even after Demokritos proposed his atomic theory of matter in classical Greece (*4*). Later, in the Middle Ages, and despite their boasting, alchemists did not comprehend much of the changes they were effecting on matter. This state of affairs changed dramatically with the dawn of organic synthesis, which was marked by the preparation of urea, a naturally occurring organic compound, from ammonium cyanate, a substance regarded as inorganic (Fig. 2). (In early days, the term "organic" was reserved for compounds produced by living organisms; nowadays, the definition refers to all sorts of compounds of carbon, including both naturally occurring and man-made.) This revolutionary discovery was made in Germany by Wöhler in 1828.

Figure 2. Synthesis of urea by Wöhler (1828).







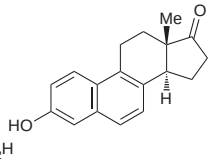


Figure 3. Some early landmark achievements in total synthesis.

*Corresponding author.

The recognition of man's ability not only to isolate and probe the properties of naturally occurring molecules but also to create new ones meant the dawn of a new era in science. Fueled by their newly acquired power and the excitement of creating the molecules of nature, chemists began to challenge the state of their art by targeting increasingly more complex substances. It should be noted that the principal aim of the early synthetic chemist was to unambiguously establish the structure of the natural product. Thus, the Wöhler synthesis of urea was followed by other milestone syntheses such as acetic acid (Kolbe, 1845), glucose (E. Fischer, 1890, Fig. 3), camphor (Komppa, 1903; Perkin, 1904), α-terpineol (Perkin, 1904), tropinone (Robinson, 1917, Fig. 3), hemin (H. Fischer, 1929, Fig. 3), equilenin (Bachmann, 1939, Fig. 3), pyridoxine hydrochloride (Folkers, 1939), and quinine (Woodward and Doering, 1944). E. Fischer received the Nobel Prize for Chemistry in 1902 for his pioneering work on the synthesis of purine and sugars, while H. Fischer received his Nobel Prize in 1930 for his total synthesis of hemin. However, it was not until after the Second World War that the science of organic and natural products synthesis experienced its most explosive period of growth. The second revolution in chemical synthesis was on. As discussed below, a number of factors synergistically contributed to this revolution, which continues today unabated, and to new and expanding frontiers.

The Art and Science of Organic and Natural Products Synthesis

During the first half of the 20th century came the understanding of the nature of the chemical bond (*5*) and the appreciation of organic reaction mechanisms. These were brought about by the insights of electronic theory and the appreciation of the significance of electron reorganization during the making and breaking of chemical bonds. These theories were pioneered by Robinson, Ingold, Pauling, and others and constituted a great leap forward in terms of explaining and, more importantly, predicting chemical reactivity. Then came the recognition of the importance of conformation of organic molecules as laid out systematically by Barton (*6*) in 1950, and the concepts of retrosynthetic analysis advanced by Corey in the early 1960s (*2*). These principles were of paramount importance in allowing the synthetic chemist to plan long reaction sequences for total synthesis with an unprecedented degree of confidence and predictability. Parallel advances in chromatographic and spectroscopic techniques made possible the analysis of reaction mixtures and the purification and characterization of organic compounds with unparalleled facility and speed. The accelerated discovery and invention of new synthetic reactions and reagents was stimulated by and contributed enormously to modern campaigns of total synthesis.

The scope and role of organic and natural product synthesis has also changed significantly in recent years, distancing itself from its original goal of confirming the structure of the targeted natural product. Even though chemical biology has been with us for some time, it was not until the 1990s that it became formalized as a frontier of chemistry with organic and natural products synthesis at its heart. We will discuss the state of the art in these subdisciplines and how they were shaped in the second half of the 20th century.

New Synthetic Methods

Organic synthesis derives its power from chemical reactions, reagents, and conditions, and synthetic strategies. Few such tools were available at the beginning of the 20th century. Fortunately, the science has witnessed an avalanche of new and powerful reactions and reagents such as the various organo-

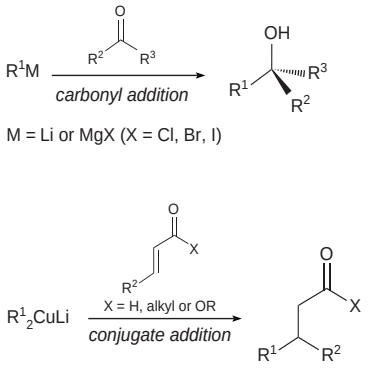


Figure 4. The Grignard and related organometallic reactions.

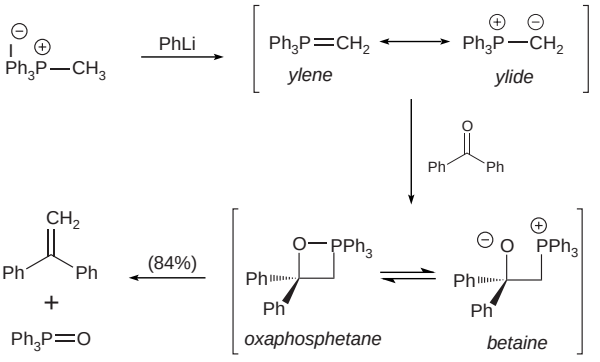


Figure 6. The first Wittig reaction (1953).

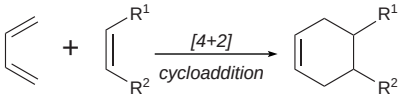


Figure 5. The Diels–Alder reaction (1928).

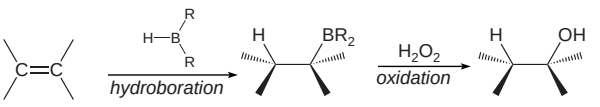


Figure 7. The hydroboration reaction (H. C. Brown, 1956).

metallic reagents (e.g., those of magnesium, lithium, and copper) opening up myriad carbon–carbon bond-forming reactions (Fig. 4) (*7*), the Diels–Alder reaction for combining dienes with dienophiles to construct two new carbon–carbon bonds and resulting in a cyclohexene ring (Fig. 5) (*8*), the Wittig reaction between phosphorus-stabilized anions and carbonyl compounds to form carbon–carbon double bonds (Fig. 6) (*9*), the hydroboration reaction by which many types of organic compounds can be made through addition of boranes to unsaturated systems (Fig. 7) (*10*), the palladium-catalyzed carbon–carbon bond-forming reactions through which complex carbon frameworks can be constructed with impressive ease and selectivity (Fig. 8) (*11*), and the introduction of the olefin metathesis reaction (Fig. 9) (*12*), as well as a plethora of powerful processes based on radical reactions (*13*). The spectacular advances made recently in the area of asymmetric catalysis deserve special discussion.

Catalytic Asymmetric Synthesis

A carbon atom with four different substituents can exist in two distinct stereochemical orientations, which are related to one another as any object is to its mirror image (*14*) (Fig. 10). This property of carbon gives rise to chirality and enantiomeric molecules, which are not identical in their behavior toward polarized light and toward the chiral and enantiomerically homogeneous molecules of life such as proteins and nucleic acids. A consequence of this phenomenon is that enantiomerically related molecules can have different biological and pharmacological properties, making enantiomeric purity an increasingly standard requirement for medicines.

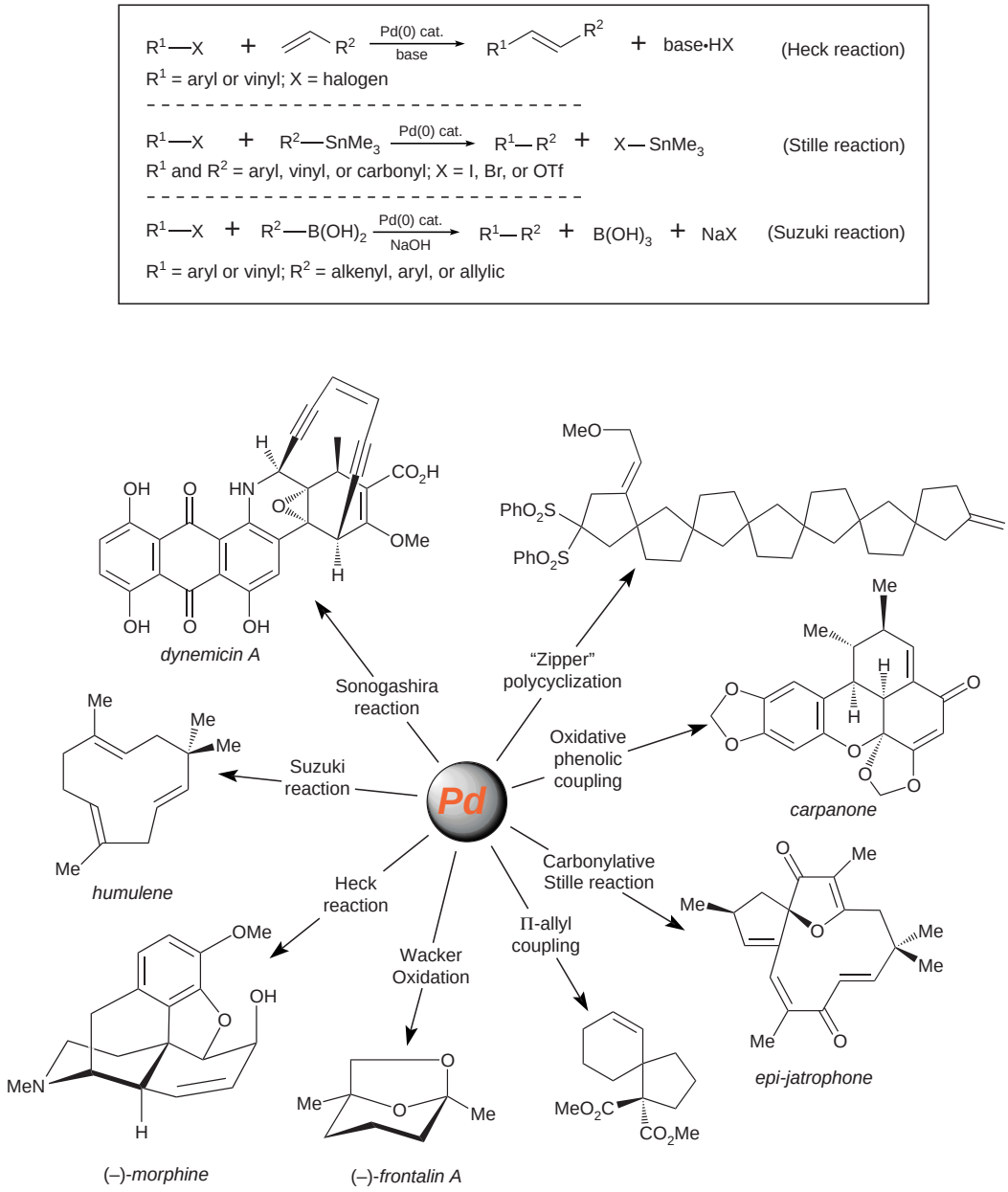


Figure 8. Palladium-catalyzed reactions (box) and syntheses of some complex molecules featuring palladium chemistry.

Even though the vast majority of natural products are enantiomerically pure, synthetic chemists have traditionally synthesized compounds in racemic form (equimolar mixtures of both enantiomers) and, whenever necessary, separated them into their components by resolution. This process commonly involves (i) combination with an enantiomerically pure compound, (ii) separation of the resulting diastereoisomers, and (iii) release of the desired enantiomer.

This process is wasteful in that at least half of the material is lost in the process. In the last two decades, however, increasing efforts have been devoted to the discovery and development of processes for the direct synthesis of individual enantiomers. Among these methods, the most elegant and promising are those utilizing optically active catalysts to effect asymmetric induction during synthetic operations with prochiral starting materials (*15, 16*). The total synthesis of complex natural products by catalytic asymmetric synthesis serves as a powerful driving force for the design of asymmetric catalysts and reactions and as an ideal testing ground for such discoveries. Once developed, such catalysts and processes can find their way into all kinds of applications in research laboratories and industrial settings for the synthesis of valuable enantiomerically pure products and intermediates.

Among the most powerful asymmetric catalysts and reactions discovered in the last few years and currently enjoying widespread applications are the intramolecular aldol reaction catalyzed by optically active amino acids (Fig. 11) (*17*), the enantioselective hydrogenation of α,β-unsaturated amino acid derivatives in the presence of soluble rhodium

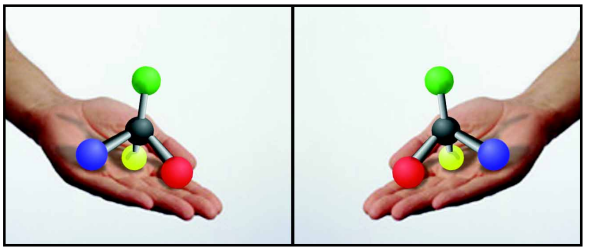


Figure 10. Enantiomers of a tetrahedral atom bearing four different substituents are not superimposable but rather are mirror images of each other in the same way as our two hands.

catalysts bearing chiral organic ligands used in the industrial production of L-DOPA, a drug clinically used against Parkinson's disease (Fig. 12) (*18*), the Takasago process for the production of L-menthol from a prochiral allylic amine (Fig. 13) (*1, 19*), the Katsuki–Sharpless asymmetric epoxidation (KSAE) of allylic alcohols (Fig. 14) (*1, 20*), the Noyori asymmetric hydrogenation of ketones with chiral ruthenium catalysts (Fig. 15) (*21*), and the Corey–Link catalytic asymmetric synthesis of α-amino acids via oxazaborolidine-catalyzed asymmetric reduction (Fig. 16) (*22*).

Given the major leaps forward in the field of catalytic asymmetric catalysis, this revolution within organic synthesis is certain to continue. It represents one of the most exciting and vigorous frontiers in organic chemistry and promises to impact profoundly on all of chemistry.

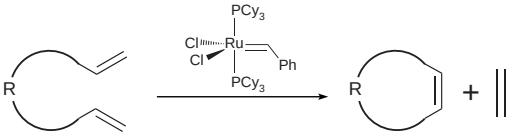


Figure 9. The intramolecular olefin metathesis reaction according to Grubbs.

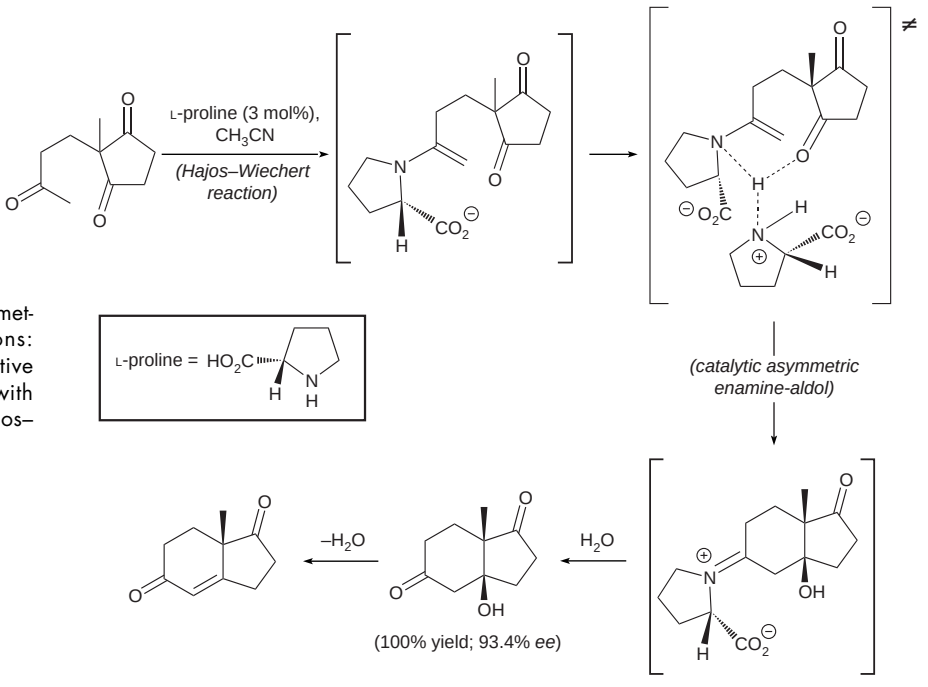


Figure 11. Catalytic asymmetric ring forming reactions: enantiotopic group selective aldol cyclodehydration with an L-amino acid (the Hajos–Weichert reaction, 1973).

Total Synthesis

The challenges posed by natural substances with complex and novel molecular structures are arguably among the most formidable faced by the synthetic chemist. The state of the art in total synthesis is therefore, more than any other endeavor in organic chemistry, an accurate reflection of the state of the science of organic synthesis. Relying on the arsenal of known reactions and reagents, but also through the invention and discovery of new ones, total synthesis aims at developing strategies to assemble a targeted molecule. Pushing the limits of total synthesis beyond its previous boundaries in terms of complexity, structural type, and efficiency almost always requires and results in new science and provides an instant test of its usefulness and applicability. It is this desire to reach higher levels of complexity, but also efficiency and selectivity, that drives organic synthesis to ever-increasing levels of sophistication.

The harvest of new synthetic technologies and strategies during a total synthesis program is frequently shared with other synthetic and medicinal chemists who apply the new discoveries and inventions to their own problems. In this sense the art and science of total synthesis becomes the engine that drives organic synthesis, and, in turn, both become the enabling technologies for biology and medicine. Simply stated, this is the science and technology that delivers "molecules in the bottle" for purposes of chemical biology and drug discovery and development, not to mention materials science and many other applications for the benefit of mankind.

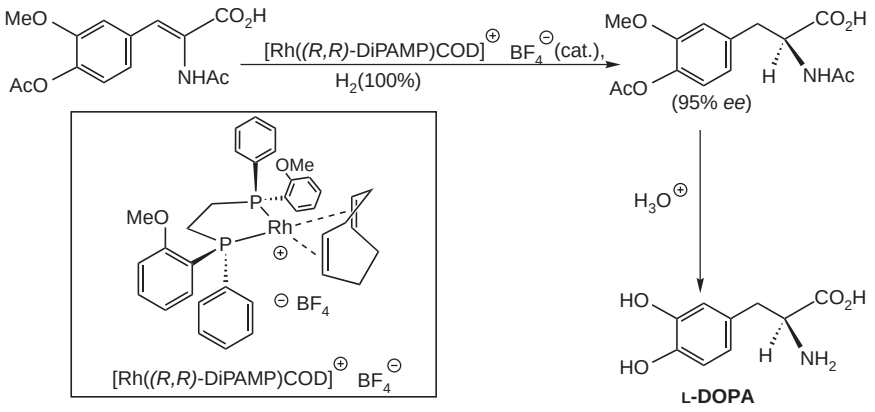


Figure 12. Industrial production of L-DOPA by catalytic asymmetric hydrogenation (Knowles, 1975).

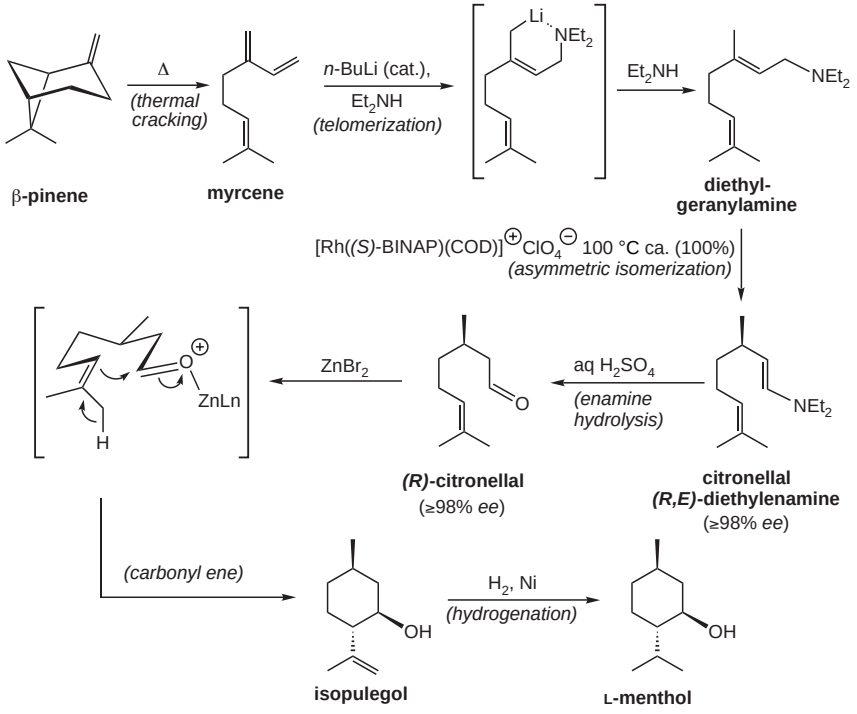


Figure 13. The Takasago process for the industrial production of L-menthol via catalytic asymmetric allylic amine → enamine isomerization.

A most remarkable revolution in total synthesis began in the 1950s with R. B. Woodward at the helm (*23*). Complex and biologically important natural products such as cholesterol, cortisone, lysergic acid, reserpine, strychnine, chlorophyll *a*, and cephalosporin C (see Fig. 17 for some of these structures) fell one after the other and the momentum continued into the 1970s and beyond. Brilliant strategies and tactics were the trademark of the Woodward era. R. B. Woodward was awarded the Nobel Prize for Chemistry in 1965 for his outstanding achievements in the art of organic synthesis (*24*).

Admired for both their intellectual and experimental aspects, these spectacular achievements were instrumental in gaining unprecedented respectability for the art of total synthesis. They made it clear that the science had moved away from its traditional role of proving the structure of the targeted natural product and into a golden age, demonstrating its power and creativity. A number of further significant advances brought the art to its current status of enviable power and prestige. Among these movements are the introduction of

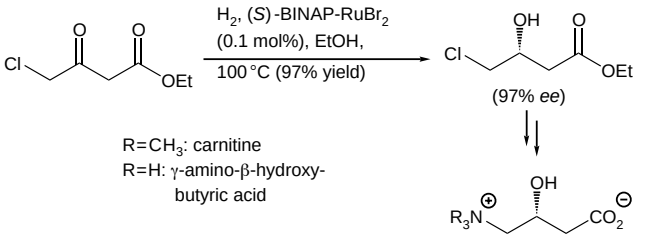
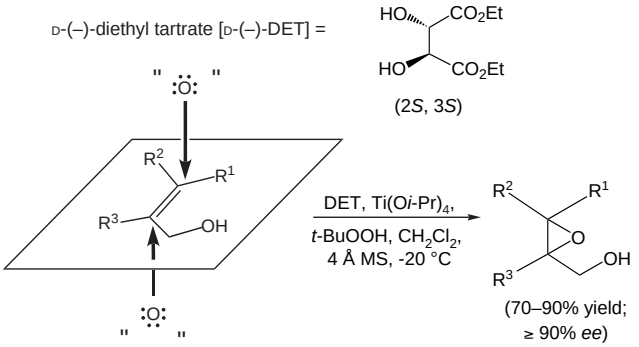


Figure 15. The Noyori catalytic asymmetric hydrogenation of ketones (1988).



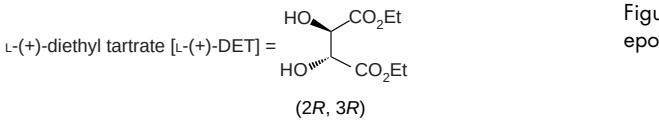
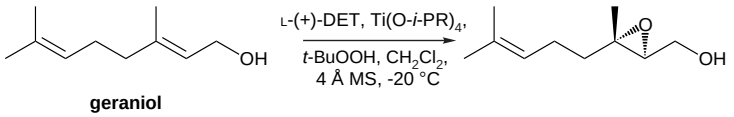


Figure 14. The Katsuki–Sharpless catalytic asymmetric epoxidation (1980).



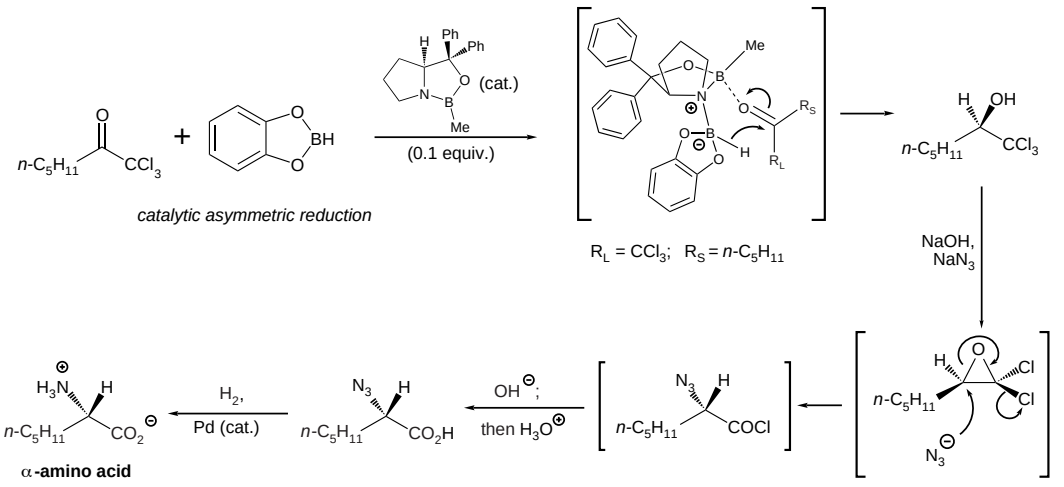


Figure 16. The Corey–Link asymmetric synthesis of α-amino acids (1992).

retrosynthetic analysis and the incorporation of new synthetic technology and chemical biology dimensions within the total synthesis programs.

Retrosynthetic Analysis and Strategy

Given a fascinating natural product with a complex and novel molecular architecture, how does the synthetic chemist devise a strategy for its total synthesis? In the early days of the science, when the structures involved were rather simple, this task was not so difficult. The chemist would compare the structure of the natural product with structures of known substances and choose the starting materials based on structural similarities. The few steps required to complete the synthesis would then be imagined without too much difficulty. But as the structures of the target molecules became more and more complex, this approach became archaic and ineffective, and a better way for designing and teaching strategy design had to be found. In 1961, E. J. Corey published a paper in which he laid out, for the first time, the principles of retrosynthetic analysis as a systematic approach to strategy design (Fig. 18) (*25*). Corey was destined to receive the Nobel Prize for Chemistry for his concepts of retrosynthetic analysis and brilliant contri-

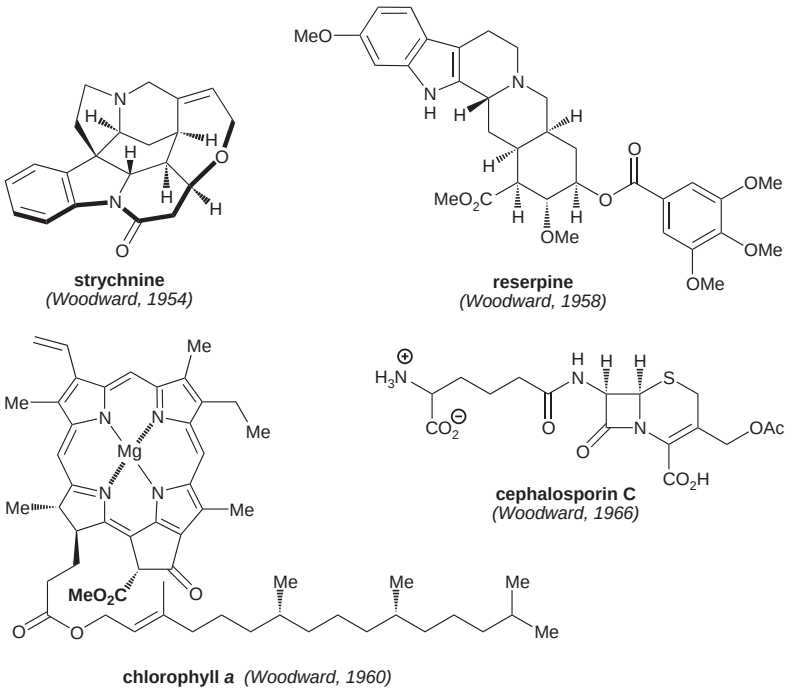


Figure 17. The Woodward era in total synthesis.

butions to organic synthesis (*26*). To convey the essence and spirit of retrosynthetic analysis in total synthesis, we quote a section from our recent book *Classics in Total Synthesis* (*1*), which includes quotations from Corey, Woodward, and Cavafy:

> **Section 1.9. Retrosynthetic Analysis**
>
> Retrosynthetic (or antithetic) analysis is a problem-solving technique for transforming the structure of a synthetic target (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a target structure. Each structure derived antithetically from a TGT then itself becomes a TGT for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the TGT.
>
> *E. J. Corey*

With these words E. J. Corey defines the concept of retrosynthetic analysis for which he received the Nobel Prize for Chemistry in 1990. Nowadays, it has become routine to think about a target molecule in terms of its retrosynthetic analysis. It is hard to imagine how chemists developed synthetic strategies prior to the formulation of these concepts in the 1960s without thinking, at least subconsciously, in these terms about complex organic structures.

Typically the synthetic strategist when faced with a new challenge focuses on the target, pondering and analyzing the proposed structure and identifying strategic bonds that may be advantageously disconnected in the retrosynthetic sense. Several such bonds and disconnections may become apparent either as a sequence to simplify the structure or as alternative approaches to such simplification. In a parallel mental process, the synthetic chemist also asks and attempts to answer the question of how to construct, in the synthetic direction, each bond broken by retrosynthesis, and how, if possible, to convert the simpler intermediates so generated to the more advanced targets in the retrosynthetic scheme. This can be an exhilarating experience, particularly at moments of brilliant flashes of inspiration, as perceived, of course, by the practitioner. The key to success at this stage is to be quite thorough and uncover subtle features of the structure under consideration that may lead to elegant and efficient synthetic schemes. Hastiness and compromise have no place in such planning and should be avoided. Instead, forcing oneself to upgrade and refine the retrosynthetic analysis, always aiming to apply novel disconnection and unprecedented maneuvers, frequently proves rewarding.

Having exhausted all retrosynthetic possibilities, the strategist is then in the position to evaluate the possible paths uncovered and devise the most attractive synthetic strategy for the construction of the targeted molecule. The strategy may dictate the invention of new reactions, reagents, and tactics, and may require model studies before synthesis on the real target can start. This is usually a good practice, for it is destined, more often than not, to result in new synthetic technology (a vital feature of a novel total synthesis) and to pave the way for a projected total synthesis. Other attractive features of a planned synthetic strategy are (i) efficient synthetic reactions; (ii) brevity; (iii) readily available and inexpensive starting materials; (iv) practical and convenient conditions; (v) flexibility of modification in case of pitfalls; (vi) adaptability to the synthesis of other members of the structural family, be they naturally occurring or designed molecules; and (vii) novelty, elegance, and artistry!

It is of paramount importance to recognize that in total synthesis the achievement itself is not always the prize or the most significant advance. Rather, it is the journey toward the target molecule that becomes the essence and significance of the exercise. The invention and development of new synthetic technology and strategies and the molecular design, chemical synthesis, and biological investigation of bioactive compounds

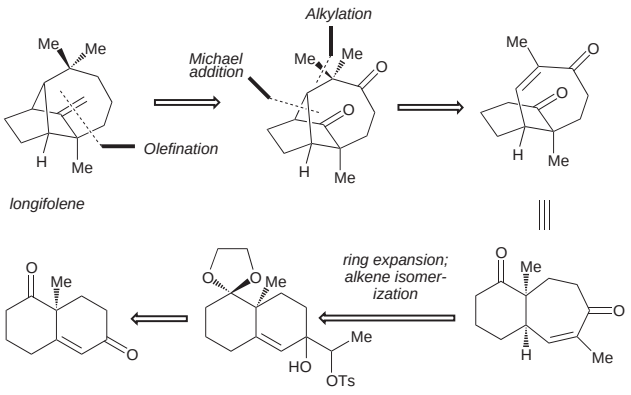
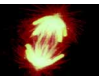


Figure 18. The concept of retrosynthetic analysis and the synthesis of longifolene by Corey (1961).



of the target's structural family are two emerging and important aspects of modern total synthesis. Chemists and biologists will no doubt be busy for a long time harvesting the benefits of this new field of investigation, which combines the best of chemistry and biology.

The following quotes from R. B. Woodward and C. P. Cavafy, a modern Greek poet, amplify the essence of total synthesis in a chemical and a more general sense, respectively (*1*).

> Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective.
>
> *R. B. Woodward*

Ithaca

When you start on your journey to Ithaca,
Then pray that the road is long,
Full of adventure, full of knowledge,
Do not fear the Lestrygonians
And the Cyclopes and the angry Poseidon.
You will never meet such as these on your path,
If your thoughts remain lofty, if a fine
Emotion touches your body and your spirit.
You will never meet the Lestrygonians,
The Cyclopes and the fierce Poseidon,
If you do not carry them within your soul,
If your soul does not raise them up before you.

Then pray the road is long.
That the summer mornings are many,
That you will enter ports seen for the first time
With such pleasure, with such joy!
Stop at Phoenician markets,
And purchase fine merchandise,
Mother-of-pearl and corals, amber and ebony,
And pleasurable perfumes of all kinds,
Buy as many pleasurable perfumes as you can;
Visit hosts of Egyptian cities,
To learn and learn from those who have knowledge.
Always keep Ithaca fixed in your mind.
To arrive there is your ultimate goal.
But do not hurry the voyage at all.
It is better to let it last for long years;
And even to anchor at the isle when you are old,
Rich withal that you have gained on the way,
Not expecting that Ithaca will offer you riches.

Ithaca has given you the beautiful voyage.

Without her you would never have taken the road.
But she has nothing more to give you.

And if you find her poor, Ithaca has not defrauded you.
With the Great Wisdom you have gained,
with so much experience,
You must surely have understood by then what Ithacas mean.

C. P. Cavafy

Chemical Synthesis and Chemical Biology

Chemical biology may be defined as the science of the interactions and effects of small molecules with biological systems such as proteins, nucleic acids, and other molecular receptors. While the field is still evolving and its definition is expanding to include newer areas of investigation at the interface of chemistry and biology, the discipline of organic and natural products synthesis is both central and vigorously flourishing. It is also certain that the art and science of organic and natural product synthesis will continue to drive and impact chemical biology research. For example, the isolation, structural elucidation, and total synthesis of biologically active natural substances and the investigation of their structure, reactivity, and interaction with biological systems constitute studies in chemical biology (*27*). The design, chemical synthesis, and biological evaluation of substances similar in structure to a natural product and the elucidation of the molecular mechanism by which such molecules interact and alter the function of biological systems are also examples of chemical biology studies. Such studies inevitably lead to a better understanding of the chemistry of life and provide the foundation for the drug discovery process. It is imperative to underscore the significance of each of these disciplines to biology and medicine and the importance of advancing them for their own sake.

Chemistry, Biology, and Medicine of Natural Products

Aspirin

In a letter to the Right Honorable George, Earl of Macclesfield and President of the Royal Society, the Reverend Edward Stone wrote on 25 April 1763: "There is a bark of an English tree, which I have found by experience to be a powerful astringent, and very efficacious in curing aguish and intermitting disorders" (*Philosophical Transactions of 1763*).

It was Edward Stone who carried out a systematic study of the medicinal properties of willow tree extracts and, although unaware of the nature of the active constituents, he observed the fever- and pain-reducing properties of the salicylates, the general term for derivatives of salicylic acid. However, it appears that the beneficial properties of willow tree extracts had already been known for centuries. The Greek physician Hypocrites recommended the use of willow bark extracts to alleviate the pain of childbirth and treat eye disease nearly 2500 years ago; and in his *Natural History*, the Roman Pliny the Elder noted that bark of the willow tree could relieve pain and remove warts.

Today, the most widely used salicylate derivative is acetylsalicylic acid, a substance universally known by its trade name aspirin (*28, 29*). It has been estimated that Americans consume approximately 80 billion tablets of aspirin per year and spend approximately 2 billion dollars a year on nonprescription pain medications, many of which contain salicylates. Aspirin is one of the most popular and widely used remedies for pain and fever in the world today (Fig. 19).

The etymology of the word aspirin is interesting. In 1860, Hermann Kolbe of Marburg University in Germany achieved a laboratory synthesis of salicylic acid and its sodium salt from phenol, carbon dioxide, and sodium. On the basis of this process, Friedrich von Heyden, one of Kolbe's students, established the first factory for the large-scale production of synthetic salicylates in Dresden, thus making large quantities available for clinical use at low cost. The widespread use of salicylic acid in the management of fever and pain would soon reveal its unpleasant side effect: gastric irritation. In 1898, the father of Felix Hofmann, a dye chemist at the Bayer division of I. G. Farben, was ingesting large quantities (6–8 grams per day) of sodium salicylate, the sodium salt of salicylic acid, to ameliorate the symptoms of rheumatoid arthritis and was, as a result, experiencing significant stomach irritation. In a search for a more easily tolerated (i.e., less acidic) derivative, Felix found a simple way to prepare acetylsalicylic acid and

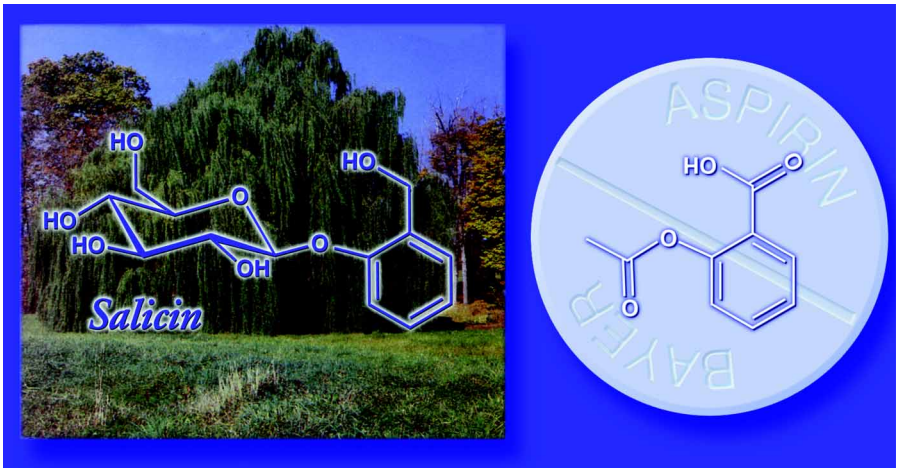


Figure 19. The discovery of aspirin. Salicin is the natural substance responsible for the pain relief effects of the willow tree (left), known from the times of Hippocrates. Aspirin (right) is a synthetic analog designed to avoid the undesired side effects of the natural product. Many other pain-relieving medications and antiinflammatory agents used today were inspired by this discovery.

observed that the new derivative was, in fact, more palatable and more effective at helping his father. The acetyl derivative proved to be an excellent candidate for development and was produced on a large scale in 1899. Heinrich Dreser, the director of research at Bayer, named the new compound "Aspirin", from the German Spirsäure (salicylic acid) with an initial "a" for acetyl.

More than 200 years have passed since Stone's recognition of the utility of willow tree extracts and we still have not fully elucidated the mechanisms by which aspirin elicits such a wide range of effects (*28b*). However, we do know that low doses of aspirin (less than one tablet a day) can stave off heart attacks and prevent cerebral thrombosis. Two to six tablets a day can alleviate pain and reduce fever, and, at higher doses, aspirin can reduce the inflammation and swelling of joints caused by gout, rheumatic fever, and rheumatoid arthritis. In the early 1970s, the hypothesis that aspirin and the salicylates act by blocking the biosynthesis of cellular hormones called prostaglandins was advanced (*30*). These hormones themselves elicit an unusually diverse array of physiological responses, including inflammation. More recent studies reveal that the antiinflammatory properties of aspirin accrue not only from its ability to inhibit prostaglandin biosynthesis, but also from its ability to prevent the activation of cells that mediate the initial phases of inflammation by disrupting molecular interactions within cell membranes (*31*).

Penicillin

In 1928, Sir Alexander Fleming's historic observation that a spot of mold, which had accidentally contaminated a culture of staphylococcus bacteria, caused the surrounding staphylococcal colonies to dissolve away, fostered one of the most spectacular contributions of basic science to medicine. Fleming cultivated the mold, discovered that the culture broth completely arrested the growth of staphylococci even when diluted 500–800-fold, and correctly deduced that the broth contained an active substance that was produced by the mold. The mold was later identified as *Penicillium notatum* and the powerful antibacterial agent that it produces was aptly named penicillin (Fig. 20) (*32*).

In retrospect, it is difficult to believe that a discovery as important as Fleming's could lie dormant in the literature of bacteriology for nearly a decade. In fact, the curative properties of penicillin were not appreciated until the collaborative research of Sir Howard Florey and Ernst Chain accomplished the isolation of penicillin and demonstrated that it could cure bacterial infections in human patients (*33, 34*). Penicillin would soon be regarded as a wonder drug, a miracle of modern medicine, owing to its ability to restore health to suffering patients who had been considered doomed.

As promising as the early clinical studies of penicillin were, extensive trials were hampered by a paucity of the antibiotic. Ironically, the event that radically altered this bleak situation was the onset of World War II (WWII). The great utility of penicillin as an antibiotic instigated a substantial cooperative British-American program during WWII, whose objectives were the elucidation of the molecular structure of penicillin, development of a practical pathway for its manufacture by chemical synthesis, and its large-scale production by fermentation methods (*35*). Nearly 1000 chemists from academic institutions and major pharmaceutical companies participated in this unprecedented British-American scientific venture. Although the goal of achieving a practical synthesis of penicillin before the end of the war was not achieved, large quantities of penicillin could be procured by fermentation

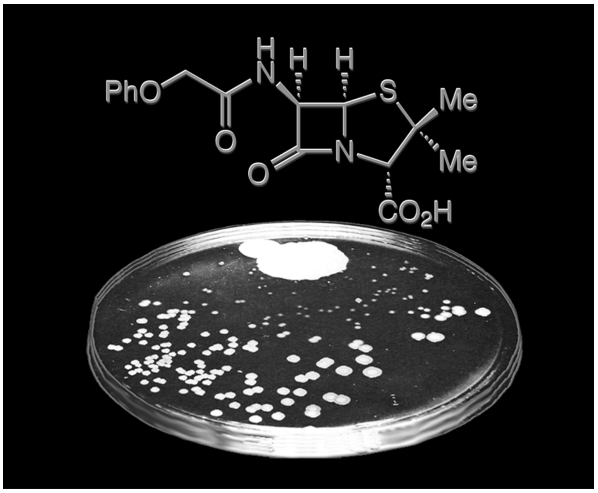


Figure 20. The discovery of penicillin. A mold landing accidentally on a Petri dish (large white spot) prevented bacterial growth (white spots) around it, arousing suspicion for an antibacterial compound secreted by the mold. Eventually, penicillin V (top) was isolated and a new era in medicine began.

methods and this permitted the practical use of the drug to combat bacterial infections. Many lives were saved, and penicillin would forever occupy a special place in medicine.

When addressing penicillin, it is sometimes more appropriate to use the plural term "penicillins", because nature provides a family of closely related substances that differ only with respect to the acyl grouping attached to the nitrogen atom adjacent to the β-lactam carbonyl group. Early in the British-American wartime penicillin project, it was recognized that the penicillins are assembled from a relatively small number of atoms, and this observation was the basis for believing that a practical chemical synthesis might be possible. However, there is not necessarily a correlation between the size of a molecule and the degree of difficulty associated with its synthesis. In spite of the best efforts of some of the most talented organic chemists of the 20th century, penicillin stubbornly resisted total synthesis. In fact, even when WWII came to a close in 1945, there was considerable controversy regarding the precise structure of the penicillins! However, this uncertainty was resolved in the same year when Dorothy Crowfoot-Hodgkin of the University of Oxford elucidated the structure of penicillin G (benzyl penicillin) by X-ray crystallography (*36*). This year also saw Sir Alexander Fleming, Sir Howard Florey, and Ernst Chain share the Nobel Prize in Medicine for the discovery of penicillin and its curative effect in various infectious diseases (*34*).

Twelve years after the end of WWII, the first rational total synthesis of a natural penicillin (penicillin V) was achieved by John Sheehan and his group at the Massachusetts Institute of Technology (*37*). This was a landmark achievement of organic synthesis. The daunting challenge that the penicillins presented to organic chemistry in the 1940s and 1950s is reflected in the following analogy made by Sheehan: "At the time of my successful synthesis of penicillin V in 1957, I compared the problem of trying to synthesize penicillin by classical methods to that of attempting to repair the mainspring of a fine watch with a blacksmith's anvil, hammer, and tongs" (*38*). To solve what was once regarded as the "impossible problem", new, mild methods of organic synthesis were required. The employment of readily cleavable phthalimide and *tert*-butyl ester protecting groups and the introduction and use of an aliphatic carbodiimide to close the recalcitrant penicillin β-lactam ring are noteworthy features of Sheehan's synthesis of penicillin V. Achievements in organic synthesis are particularly valuable when they are attended by the development of generally useful synthetic methods.

Vitamin B_{12}

The disclosure of the intricate structure of vitamin B_{12} (Fig. 21) in 1956 by Dorothy Crowfoot-Hodgkin and her collaborators at the University of Oxford (*39*) was appropriately characterized as one of the "finest contributions of British science to the chemistry of low molecular weight natural products" (*40*). Certainly the chemical synthesis of vitamin B_{12}, the culmination of a unique twelve-year collaboration between the late R. B. Woodward and his group at Harvard and Albert Eschenmoser and his group at ETH Zürich, is among the finest achievements of organic synthesis (*1, 41, 42*).

Vitamin B_{12} is a substance of great biochemical significance. Its structure resembles the structure of the blood pigment heme (Fig. 3) and the leaf pigment chlorophyll *a* (Fig. 17). In each molecule, a macrocyclic nucleus comprising four 5-membered heterocyclic rings is organized around a central metal atom. However, unlike its more modestly functionalized relatives, vitamin B_{12} is rich in stereochemical detail, with 9 stereocenters distinguishing the periphery of the macrocyclic nucleus.

When the Woodward–Eschenmoser synthesis began, it was known from the work of Bernhauer and coworkers that cobyric acid (Fig. 22), the simplest of the corrinoid natural products, could be converted to vitamin B_{12} in the laboratory (*43*). The problem of synthesizing vitamin B_{12} was thus reduced to the construction of cobyric acid, a substance that embodies the carbon framework of the vitamin itself. Like that of vitamin B_{12}, the macrocyclic framework of cobyric acid contains 9 stereocenters and supports 7 side-chains, 6 of which terminate in a primary amide group. The cobalt atom situated in the center of the corrin nucleus and the carbon–carbon bond joining rings A and D are other salient features of these molecules.

The efforts of the Woodward and Eschenmoser groups produced two distinct and elegant syntheses of cobyric acid. The principal difference between them is the manner in which the corrin nucleus is assembled. For years, the concept that guided the work of both groups involved the union of two advanced intermediates representing the A–D and B–C components of cobyric acid. The elaboration of precorrin cobalt complex **1** then set the stage for the establishment of a carbon–carbon bond between rings A and B during the course of ring closure (see **1** → **3**, Fig. 22). This strategy, the A–B variant, was designed to take full advantage of the tendency of uncyclized corrin precursors to organize themselves around a metal ion, an arrangement that brings the reactive carbon atoms in rings A and B into proximity.

The intimidating A–D sector of cobyric acid was synthesized stereospecifically by Woodward's group at Harvard. It is historically significant that Woodward's observations during the course of this work provided an empirical foundation for what would come to be known as the Woodward–Hoffmann rules (*44*). This major theoretical advance concerning the role of orbital symmetry in chemical reactions has profoundly influenced our understanding of pericyclic reactions. This example illustrates, even if in an extreme way, the powerful

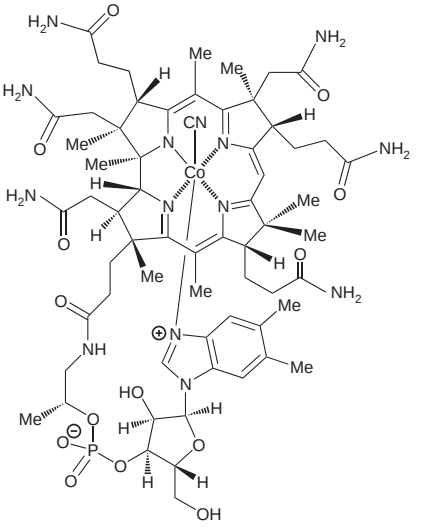


Figure 21. Molecular structure of vitamin B_{12}.

stimulus that research in organic synthesis has had on the development of the fundamental bases of organic chemistry.

Armed with a powerful new theory, the Eschenmoser group in Zürich conceived of a bold and brilliant strategy for creating the corrin framework of cobyric acid (*42*). The essence of this new approach, the A–D variant, is the establishment of the bond joining rings A and D during the course of a photoinduced ring closure of precorrin cadmium complex **2** (Fig. 22). As observed in model systems, uncyclized precorrin ligands arrange themselves helically around metal ions. Such an arrangement places the C-19 D-ring methylene and C-24 A-ring methylidene groups into neighboring regions of space, a prerequisite for any process leading to the union of these two atoms. Now, when precorrin metal complexes of type **2** are exposed to visible light, a rate-limiting shift of a hydrogen atom from the methylene group in ring D (C-19) to the exocyclic methylidene group of ring A occurs, giving rise to a high-energy π-system that subsequently undergoes a 1,15 $\pi \rightarrow \sigma$ cyclo-isomerization to an intact corrin chromophore (**3**, Fig. 22). In a crucial experiment, it was found that irradiation of precorrin cadmium complex **2** with visible light induces the desired ring closure and affords the corrin system (**3**) possessing the natural trans configuration at the A–D junction with 95% stereoselectivity. Owing to the helical arrangement of the precorrin ligand system about the cadmium ion, this elegant transformation is obliged to occur antarafacially and can only be conducted photochemically, an observation consistent with the Woodward–Hoffmann rules.

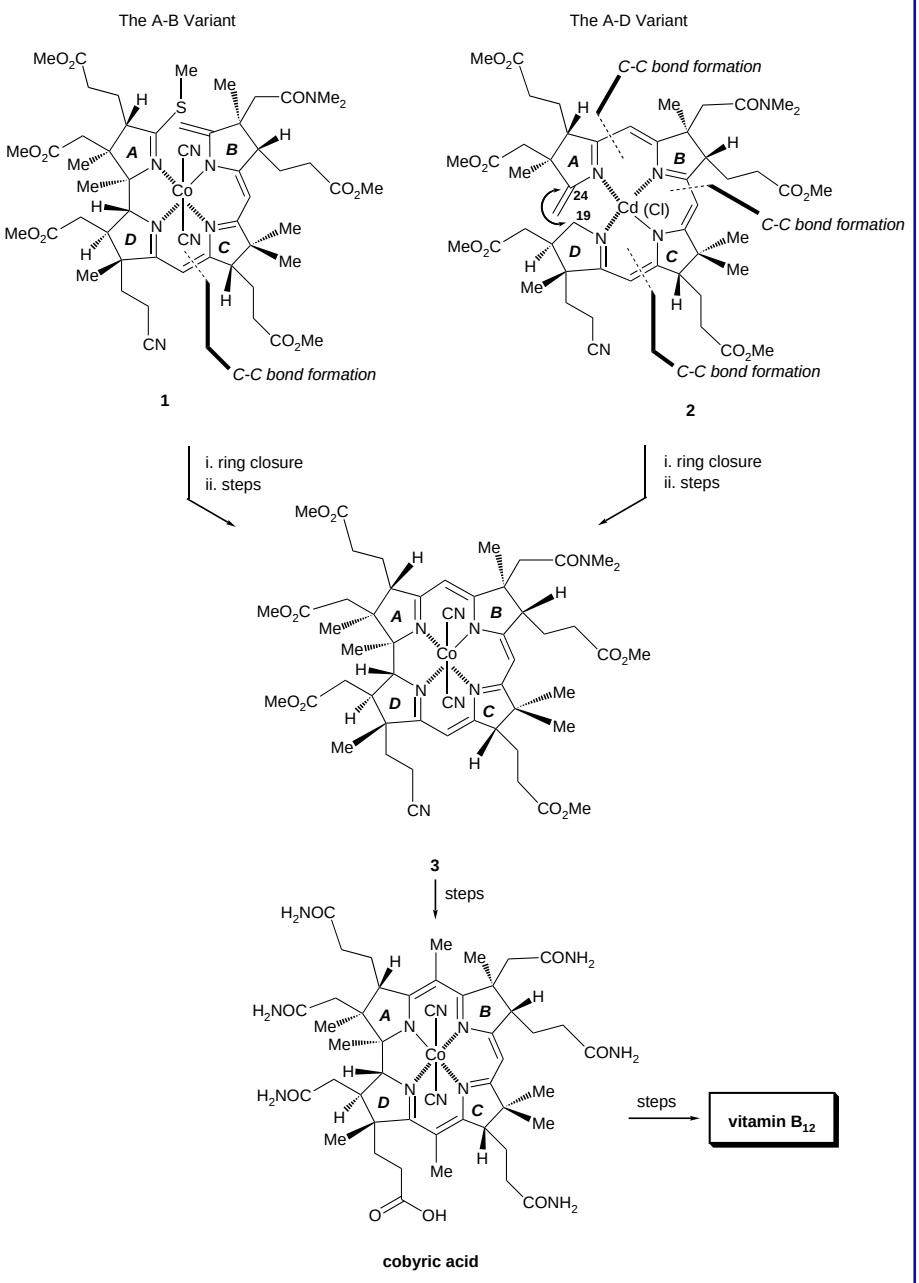


Figure 22. The final stages of the Woodward–Eschenmoser synthesis of cobyric acid and vitamin B_{12} (1973). The markers on structures **1** and **2** indicate retrosynthetic disconnections.

Both approaches to the synthesis of the corrin chromophore, the A–B and A–D variants, converged on a common corrin cobalt complex **3**. From compound **3**, the goal of synthesizing cobyric acid, and thus vitamin B_{12}, was accomplished collaboratively by the two groups. The numerous regional problems and the global challenge associated with the chemical synthesis of cobyric acid stimulated the development of much innovative and fascinating organic chemistry. The Woodward–Eschenmoser synthesis of vitamin B_{12} is one of synthetic organic chemistry's most inspirational achievements.

Ginkgolide B

The ginkgo tree, *Ginkgo biloba*, has probably existed on Earth longer than any other living tree (*45*). According to fossil records, *Ginkgo biloba* has existed since the Liassic period, 280 million years ago; its population density was greatest during the Jurassic period, 150 million years ago (*46*). An unusual gymnosperm with fan-shaped leaves, malodorous fleshy orange fruit, and edible seeds, the ginkgo is described as a "living fossil" because it apparently has not undergone any changes during the last million years (*46, 47*). Although the ginkgo was essentially unknown outside the

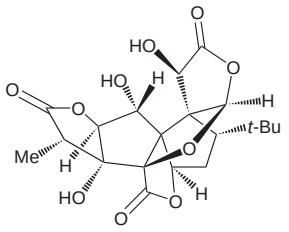


Figure 23. Molecular structure of ginkgolide B.

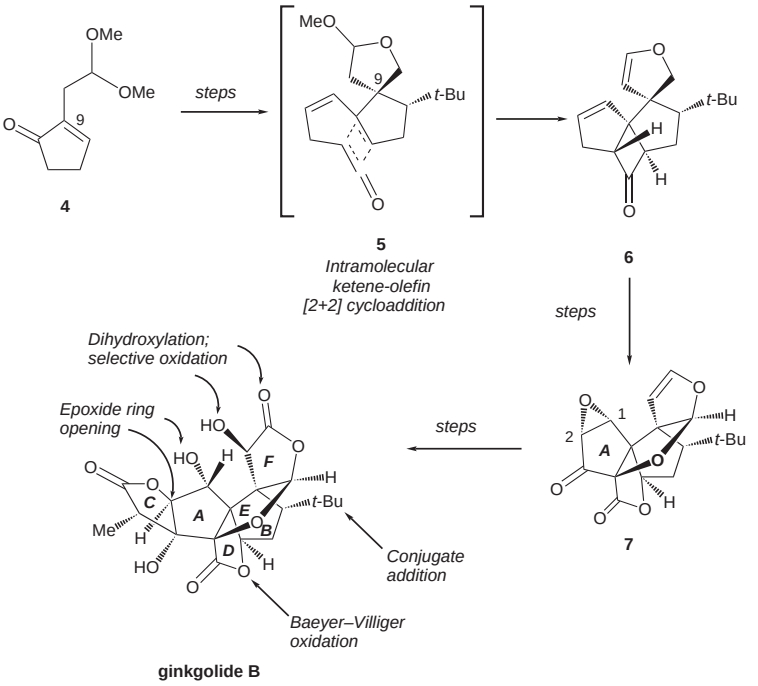


Figure 24. Highlights of Corey's total synthesis of ginkgolide B (1988).

Orient before the 18th century, it is now widely distributed throughout the world.

The beneficial properties of extracts from the ginkgo tree have been well known in China and India for centuries. Traditional Chinese medicine advocates the inhalation of a boiled-down extract of ginkgo leaves to alleviate asthma; in India, ginkgo extracts constitute an important ingredient of soma, a mystical liquid believed to increase life span (*47b*). In Japan, the edible seed of the ginkgo, the ginkgo nut, is used frequently in cooking.

A major milestone in the quest for the active constituents of ginkgo extracts was achieved in 1967, when K. Nakanishi and his group at Columbia University reported brilliant studies that established the elegant structures of four closely related substances known collectively as the ginkgolides (*48*). The novel cage structures of the ginkgolides comprise a central spiro[4.4]nonane carbon framework, 3 γ-lactone rings, one tetrahydrofuran ring, a *tert*-butyl group, and, in the case of ginkgolide B (Fig. 23), 11 stereocenters. These highly oxygenated, architecturally complex natural products are formidable. The total synthesis of ginkgolide B was achieved by E. J. Corey and his coworkers at Harvard in 1988 (*1, 49*). This beautiful work is exemplary of how sophisticated the science of creating complex molecules has become. Its general features are shown in Figure 24.

A conspicuous and unusual feature of ginkgolide B is the *tert*-butyl group attached to ring B. Before the structures of the ginkgolides were known, there was no precedent for the presence of a *tert*-butyl group in natural products (*48*). A distinguishing feature of Corey's synthetic strategy is the early introduction of this substituent and the deliberate reliance on its bulky nature for the purpose of guiding the stereochemical course of several crucial bond-forming reactions. A conjugate or 1,4-addition, a reliable reaction that is related to the venerable Michael addition, was used to attach the *tert*-butyl group to a suitably reactive cyclopentenone (**4**), which was destined to become ring B of ginkgolide B (Fig. 24).

Having served a valuable role in the creation of the quaternary stereocenter at C-9 (a quaternary stereocenter is one that bears four different carbon groups), the bulky *tert*-butyl group would again be called upon to influence the stereochemical course of an intramolecular ketene–olefin [2+2] cycloaddition (structure **5**, Fig. 24), perhaps the most elegant step of the total synthesis.

The single-step conversion of **5** to **6** accomplishes a substantial increase in molecular complexity. This transformation produces a valuable cyclobutanone ring that serves as a direct precursor to the D-ring γ-lactone of ginkgolide B. The required oxygen is introduced during the course of a regio- and stereospecific Baeyer–Villiger oxidation, an event attended by a one-atom ring expansion of the 4-membered cyclobutanone to the desired 5-membered γ-lactone. A cleverly designed sequence of reactions then furnishes compound 7 (Fig. 24).

At this late and critical stage of their synthesis, the Corey group was in a position to exploit the potential of the keto epoxide moiety (ring A, compound 7, Fig. 24). An appropriate appendage was introduced by nucleophilic attack on the carbonyl group, an event that was followed by opening of the epoxide ring with a liberated carboxyl group. A new carbon–oxygen bond was created at C-2 with complete inversion of stereochemistry, and the sixth and final ring of ginkgolide B was established in this crucial transformation. The task of oxidizing the F-ring enol ether was all that stood between the latter intermediate and ginkgolide B. The conversion of the former substance to the latter required only four steps, including dihydroxylation and selective oxidation. The first total synthesis of ginkgolide B by the Corey group is a magnificent achievement of contemporary organic synthesis.

Palytoxin

Certain soft corals of the genus *Palythoa* harbor a compound that is among the most poisonous nonpeptidic substances known and one of the largest marine-derived natural products yet isolated (*50*). This substance was given the name palytoxin (Fig. 25). The elucidation of its intimidating structure was the culmination of an effort that relied extensively on spectroscopic techniques and the methods of chemical degradation and synthetic organic chemistry (*51*). Palytoxin is particularly complex from a stereochemical point of view. With 64 stereocenters and 7 carbon–carbon double bonds that could exhibit geometrical isomerism, palytoxin could conceivably exist in 2^{71} different stereoisomeric forms. Nevertheless, it is produced in nature as a single stereoisomer.

The richly functionalized framework of palytoxin comprises 10 rings, each one containing an oxygen atom, six geometrically defined carbon–carbon double bonds, and a conspicuous *N*-acyl vinylogous urea. The constitutional and stereochemical complexity of palytoxin offered a mammoth challenge to the synthetic chemist. Clearly, such a structure would significantly burden the ability of organic synthesis to manage acyclic stereochemical relationships and would place a premium on the identification of efficient methods for the production of carbon–carbon bonds.

In spite of its size and complexity, palytoxin was synthesized in the laboratory by Yoshito Kishi, one of the grand masters of organic synthesis, and his group at Harvard (*1, 52*). This achievement was guided by a synthetic strategy that was highly convergent and was accompanied by the development of a number of important reactions. Figure 25 reveals the bond-forming processes that were utilized to achieve the construction of strategic carbon–carbon bonds. In addition to the venerable Wittig and related reactions, the $NiCl_2/CrCl_2$-catalyzed coupling of vinyl iodides and aldehydes and the construction of cis-trans conjugated dienes through Pd(0)-catalyzed unions of vinyl iodides with vinyl boronic acids (Suzuki reaction) proved valuable in the elaboration of the palytoxin molecule. In fact, Kishi's synthesis of palytoxin contributed significantly to the development and popularity of the Cr(II)/Ni(II)-mediated union of vinyl iodides and aldehydes, a process often referred to as the Nozaki–Takai–Hiyama–Kishi reaction (*53*). The total synthesis of palytoxin by the Kishi group is one of the most heroic achievements of contemporary organic synthesis.

Calicheamicin γ_1^I

It is instructive to recognize that a multifunctional and constitutionally unique natural product is itself a novel three-dimensional arrangement of organic functional groups, each of which individually is very familiar to organic chemists. But it is the confluence or interrelationships of a molecule's functionalities that gives that substance a particular reactivity or a potentially exploitable biological property. The secondary metabolite calicheamicin γ_1^I is a particularly beautiful example of how the chemistry of diverse functionality is harnessed collectively to produce powerful biological activity.

The story of calicheamicin γ_1^I began in the early 1980s (Fig. 26) (*54*). Contained within rocks collected by a Lederle scientist from a site near a highway in Texas were bacteria (*Micromonospora echinospora* ssp *calichensis*) that produced calicheamicin γ_1^I and several related compounds when grown in laboratory cultures. It was soon discovered that calicheamicin γ_1^I can strongly inhibit the division of cells from a number of tumors, a finding that motivated a substantial effort to uncover the structure of this promising substance. The revelation of calicheamicin's intimidating structure was the result of brilliant work by scientists from the Lederle Laboratories (*55*). Calicheamicin is a remarkable molecular assembly comprising two distinct domains. The larger of the two, the oligosaccharide sector, is composed of four monosaccharide units and an unusual hexasubstituted aromatic ring. The other domain is a rigid bicyclic framework that accommodates a unique

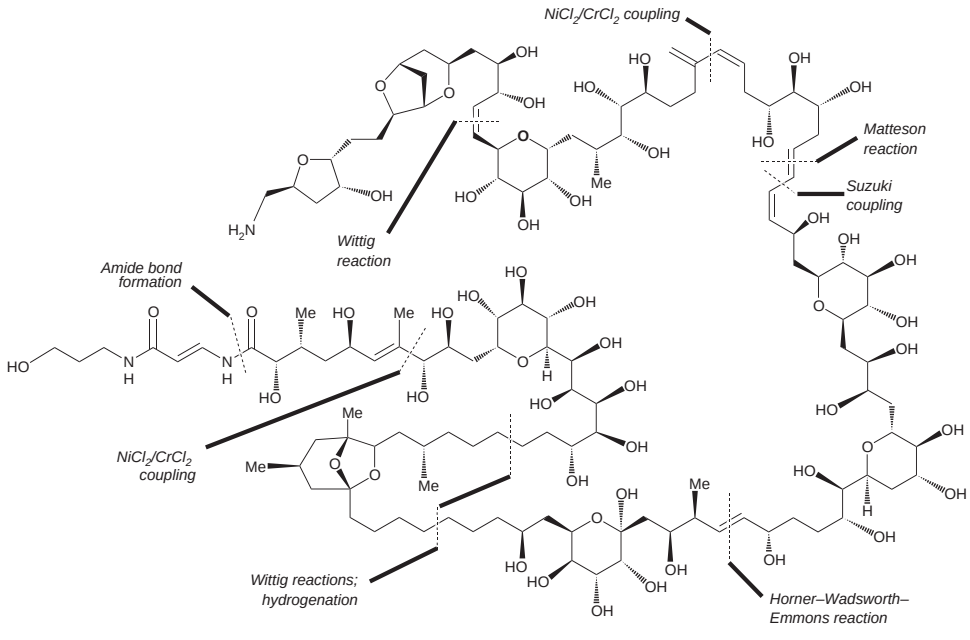


Figure 25. Molecular structure of palytoxin showing strategic bond disconnections utilized in its total synthesis (Kishi, 1994).

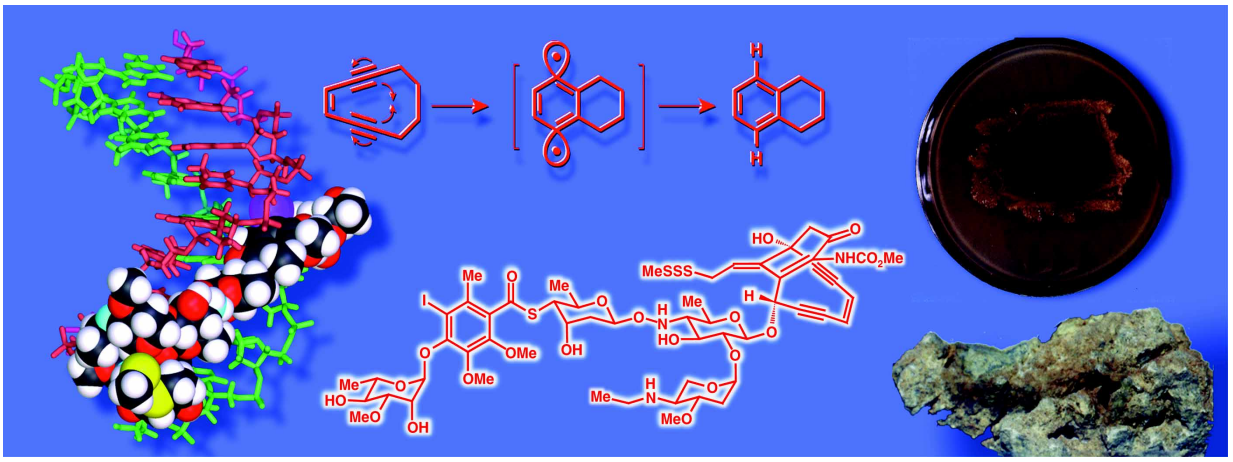


Figure 26. The discovery of calicheamicin γ_1^I. Within rocks (*caliche* in Greek, bottom right) collected in Texas lived bacteria (*Micromonospora calichensis*, top right, courtesy of George Ellestad, Lederle Laboratories) that produced calicheamicin γ_1^I (center bottom). This substance binds selectively in the minor groove of DNA (left) causing double-strand cuts to the genetic material via a Bergman-type cycloaromatization reaction (center top). These cuts are lethal to the cell, endowing calicheamicin γ_1^I with a phenomenally potent antitumor activity.

allylic methyl trisulfide and a novel pattern of unsaturation that had no precedent in the realm of natural products.

It was not surprising that calicheamicin's multifunctional character and unusual architecture would give rise to a novel biological mode of action. This molecule utilizes essentially all of its structural features to cause cleavage of the genetic material, deoxyribonucleic acid (DNA), with impressive sequence specificity. The oligosaccharide domain, the trans allylic trisulfide, the α,β-unsaturated ketone, and the conjugated 1,5-diyn-3-ene moiety participate in a cascade of reactions leading to the production of a highly reactive and short-lived species that proves destructive to the genetic material (Fig. 27). When calicheamicin γ_1^I encounters double-stranded DNA, the oligosaccharide domain, a sophisticated delivery system, anchors the molecule within the minor groove of DNA; even the unusual iodine atom attached to the hexasubstituted benzene ring plays an important role in this event by enhancing binding affinity. Either before or after binding to DNA (the precise sequence is not known), the allylic trisulfide moiety undergoes reduction to give an allylic thiolate ion (Fig. 27). By virtue of the (*E*) geometry of the C-13–C-14 double bond, this newly formed nucleophilic thiolate ion finds itself in proximity with the electrophilic β-carbon atom of the cyclohexenone. In such a favorable setting, a facile intramolecular Michael addition reaction occurs to give **9** as a transient intermediate. Evidently the C-9 $sp^2 \rightarrow$ C-9 sp^3 hybridization change that attends the intramolecular addition step causes a conformational change, which imposes a great deal of strain on the polyunsaturated 10-membered ring. To relieve this strain, the conjugated 1,5-diyn-3-ene moiety undergoes an interesting electrocyclic reaction known as the Bergman cycloaromatization (Figs. 26 and 27) (*56, 57*), thus generating the highly reactive benzenoid diradical **10**; it is this aggressive diradical that initiates double-strand cleavage of DNA by abstracting hydrogen atoms from the sugar–phosphate backbone.

The unprecedented molecular architecture of calicheamicin γ_1^I combined with its important biological activity and fascinating mechanism of action provided a unique opportunity for creative adventures in organic synthesis, molecular design, and biology. Calicheamicin is one of nature's most extraordinary nonpolymeric molecular assemblies and it offered a formidable challenge to synthetic organic chemists. In the late 1980s, several laboratories, including our own, put forth strong efforts to achieve a chemical synthesis of this natural product. At the outset, we were mindful of the very high likelihood that new, powerful chemical methodology and strategies would be needed to contend with the numerous regional problems presented by calicheamicin, not to mention the full scope of the total synthesis problem. In addition, our work drew inspiration from the hope that the powerful chemistry used by calicheamicin to cleave double-stranded DNA might be expressed in simplified settings where the problem of synthesis was sure to be more manageable (*58*). It is well to point out here that the targets of contemporary organic synthesis need not be restricted to substances existing in nature. Indeed, it is the science of organic synthesis, with its power to create new molecules, that is in a position to deliberately exploit useful reactivity arising from particular arrangements

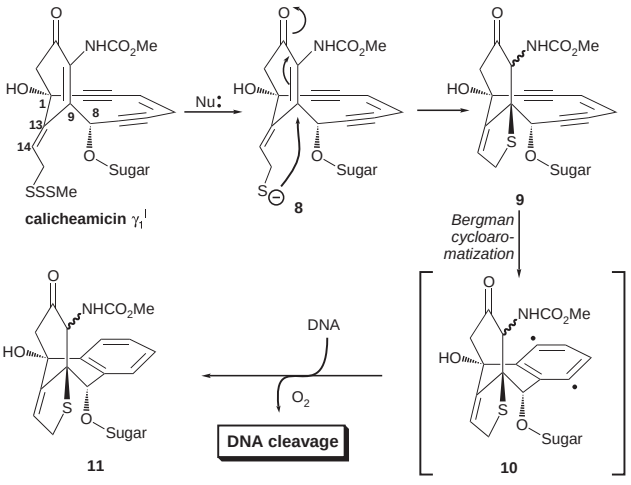


Figure 27. Proposed mechanism of action of calicheamicin γ_1^I (see also Fig. 26).

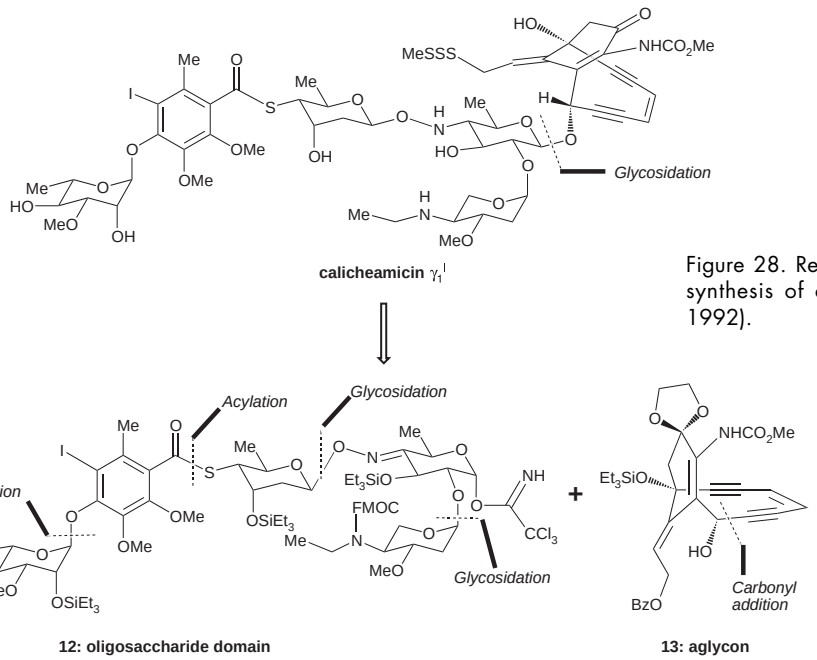


Figure 28. Retrosynthetic analysis and total synthesis of calicheamicin γ_1^I (Nicolaou, 1992).

of functional groups inspired by natural substances or by principles of organic chemistry.

As noted above, the calicheamicin γ_1^I molecule is composed of two distinct domains: an unusual oligosaccharide that serves as a "delivery system" and a sophisticated bicyclic framework containing a trisulfide "triggering device" and an enediyne "molecular warhead". Owing to its complex molecular architecture and multifunctional nature, calicheamicin stood tall and almost unapproachable from the chemical synthesis point of view. One of the more appealing aspects of synthetic work is that the synthesis of a complex molecule may be approached from many different vantage points. In his disclosure of the total synthesis of colchicine, R. B. Woodward acknowledged this when he stated that "although the specific objective in synthetic work is defined with unique precision, the manner of reaching it most emphatically is not. It would be possible to synthesize a molecule like colchicine in countless different ways, no one of which would resemble any other except in its outcome. Much of the charm and fascination of this kind of work lies in the free rein which the imagination may be permitted in planning the adventure, and as well in executing it" (*59*). Of course, myriad distinct pathways for synthesis could, in principle, converge on the calicheamicin molecule. But as we considered the problem of synthesizing this substance, it seemed most prudent to independently create the oligosaccharide domain and the rigid bicyclic core and

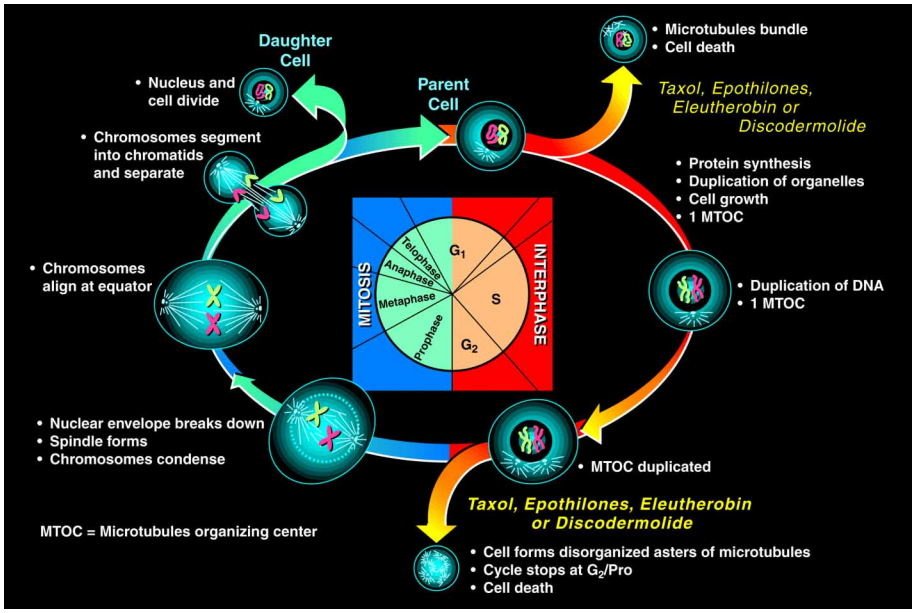


Figure 30a. The cell cycle and the cell-killing effects of taxol, epothilones, eleutherobin, and discodermolide via tubulin polymerization and microtubule stabilization.

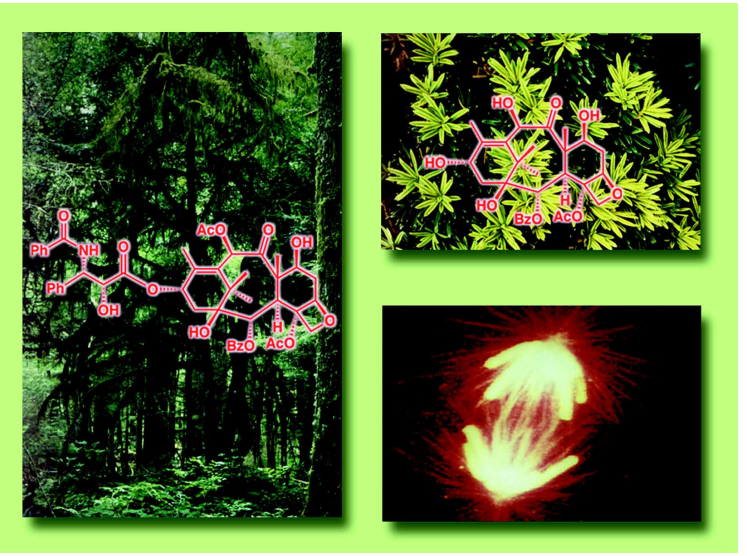


Figure 29. The discovery of taxol. Taxol was first isolated from the bark of the Pacific yew tree (left). It is produced today by semisynthesis from 10-deacetylbaccatin III, which is found in abundance in the needles and twigs of the European yew (top right). Taxol blocks the division of the mitotic spindle by polymerizing tubulin and stabilizing microtubules, resulting in arrest of cell replication and cell death (bottom right).

then seek to join them through a carbon–oxygen bond. This general idea is implied in the retrosynthetic disconnection shown in Figure 28. Eventually, we identified compounds **12** and **13** as suitable representatives of the oligosaccharide and aglycon sectors, respectively, and after extensive experimentation and persistence we effected their union via a stereoselective glycosidation reaction and completed the first total synthesis of calicheamicin γ_1^I (*1, 60*). A second total synthesis of this fascinating molecule was to follow shortly thereafter (*61*).

Taxol

Knowledge of the poisonous properties of extracts from the yew tree can be traced to ancient times. In book VI of his *Gallic Wars*, Julius Caesar mentions that Catuvolcus, a chieftain of the Eburones, committed suicide by taking an extract from the yew tree (*62*). For centuries, the yew was recognized as the tree of death and its extracts provided a common form of poisoning. However, the utility of the yew tree in the fight against cancer would remain unknown until the latter half of the 20th century.

In the early 1960s, the National Cancer Institute and the United States Department of Agriculture (USDA) initiated an ambitious program aimed at the discovery of new sources for anticancer drugs (*63–65*). Under the aegis of this program, A. Barclay, a botanist from the USDA, collected bark from the pacific yew, *Taxus brevifolia* Nutt. (Fig. 29), a slow-growing evergreen tree native to western North America. Roughly two years later, the National Cancer Institute sent 30 lb of this bark to M. Wall and M. Wani, chemists at the Research Triangle Institute in North Carolina, who found that a crude extract of the bark displayed cytotoxic activity against leukemia cells and significant inhibitory action against a variety of tumors. The active principle of the extract was eventually isolated in pure form by Wall and Wani and, after some preliminary structural studies, was given the name taxol (also known today as paclitaxel or Taxol). Studies were immediately undertaken

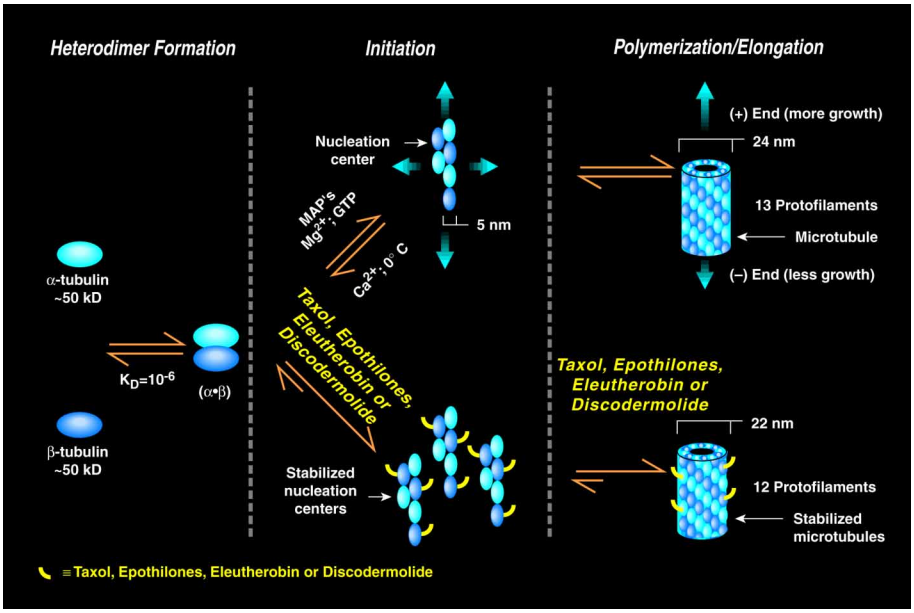


Figure 30b. Induction of tubulin polymerization and microtubule stabilization by taxol, epothilones, eleutherobin, and discodermolide.

to establish the structure of this promising natural product, and in 1971, Wall, Wani, and coworkers disclosed the molecular structure of taxol, including its absolute stereochemistry, on the basis of chemical, spectroscopic, and X-ray crystallographic data (*66*). Taxol was thus shown to possess the C_{20} carbon framework characteristic of the taxane diterpenes, albeit a highly oxygenated and functionalized one. The impressive structure of the compound whose effects had been known for centuries was finally revealed (Fig. 29).

Taxol's journey from the forest to the clinic was slow and arduous. In spite of its pronounced cytotoxicity, taxol was not seriously considered for development as an anticancer drug for several years owing principally to its low solubility in water (which made formulation difficult) and its scarcity in nature. The problem of supply was particularly serious. It has been estimated that the sacrifice of one 100-year-old yew tree affords approximately three kilograms of bark, from which approximately 300 milligrams of taxol can be obtained—a single dose for a cancer patient.

Interest in taxol as a potential anticancer drug was, however, rejuvenated when S. B. Horwitz and her collaborators disclosed taxol's unique activity as a promoter for tubulin polymerization (*67*). Tubulin is an important cellular protein that polymerizes reversibly to form microtubules, the building blocks of the mitotic spindle (Figs. 29 and 30a and b). Taxol binds to microtubules and stabilizes them, thereby altering the tubulin–microtubule equilibrium. In cells, this phenomenon results in the formation of discrete bundles of microtubules and the cell's inability to assemble a normal mitotic spindle. In the presence of taxol, cells cannot undergo mitosis and thus they die. The elucidation of this unique mechanism of action during the late 1970s and early 1980s accelerated the development of taxol as an antitumor drug. In recent years, taxol has been highly effective in the treatment of ovarian and breast cancer and is hailed as one of the most exciting new anticancer drugs to be developed in the later period of the 20th century.

The promising chemotherapeutic potential of taxol and the unprecedented mechanism by which it inhibits eukaryotic cell division stimulated substantial efforts to procure large quantities of this new drug. The bark of the Pacific yew tree harbors only minute quantities of the natural product. Moreover, the process by which taxol is isolated from the bark of *T. brevifolia* requires sacrifice of the tree. The collection of large amounts of bark for clinical trials (27,000 kilograms in 1989) caused serious concerns about the ecological impact of continued collection and about the survival of the Pacific yew. It was clear that this tree could not serve as a long-term source of the precious molecule; alternative sources had to be found.

The discovery that 10-deacetylbaccatin III (Fig. 29, top right), a precursor of taxol lacking both the C-10 acetyl group and the conspicuous C-13 ester side-chain, can be isolated in impressive yield (ca. 0.1%) from the leaves and needles of the European yew (*Taxus baccata*) and converted to taxol by semisynthesis (a process by which a naturally occurring substance is converted to another, usually more complex, substance) was a major advance in the quest for a sustainable source of the drug. The importance of this discovery is profound because the leaves and needles of *T. baccata* regenerate and thus provide a renewable source of 10-deacetylbaccatin III. Bristol-Myers Squibb employs a semisynthetic process in the commercial production of taxol from 10-deacetylbaccatin III, as does Rhône-Poulenc Rorer for the manufacture of Taxotere (a clinically used analog of taxol in which the PhCO group on the nitrogen atom has been replaced by a *t*-BuOCO group) (*65*).

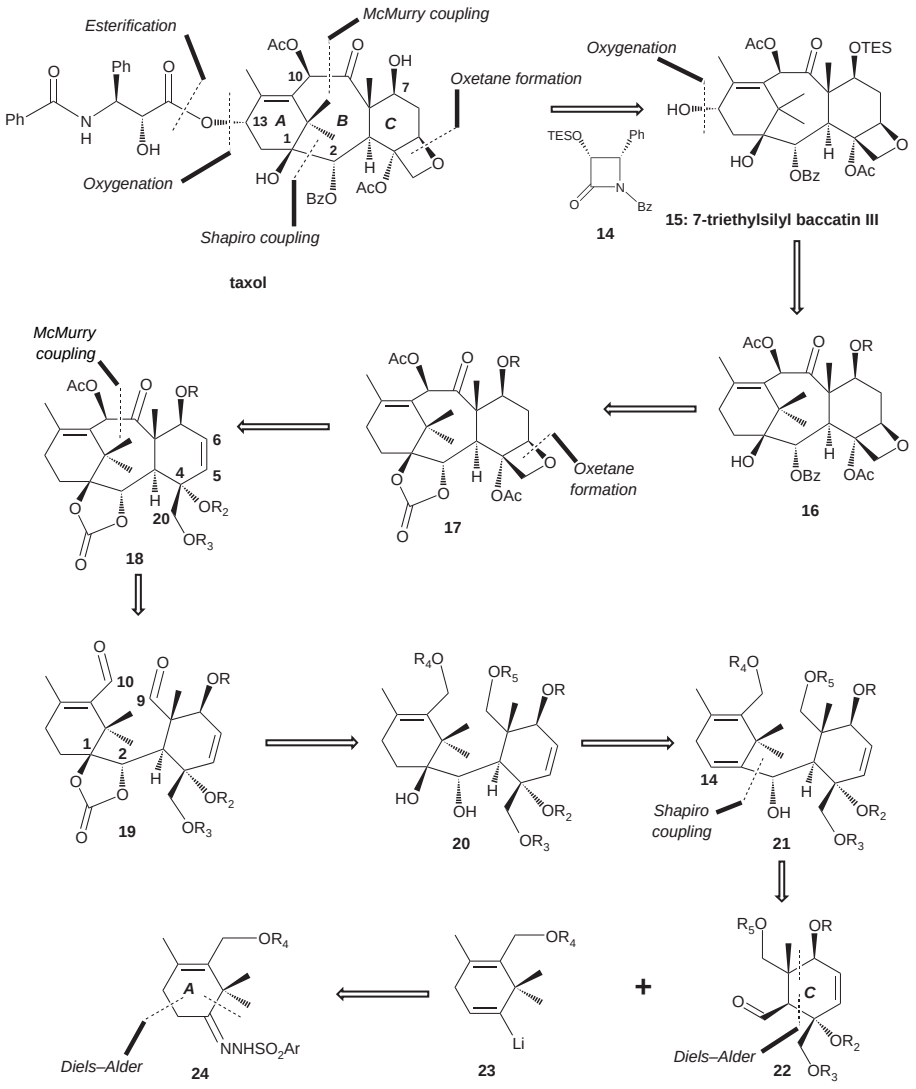


Figure 31. Strategic bond disconnections and retrosynthetic analysis of taxol (Nicolaou, 1994).

Owing to its powerful anticancer activity and novel structure, taxol attracted a strong interest from synthetic organic chemistry and advances in this area have been impressive. At the present time, five independent total syntheses of taxol have been achieved and a multitude of fascinating strategies have issued from undertakings in this area. For many studies, the complex molecular framework of this molecule offered a challenging testing ground for the development of new chemistry. Our efforts in this area were always guided by the goal of accomplishing a total synthesis of this celebrated diterpene (*1, 68, 69*). Figure 31 shows the strategic bonds that we identified for retrosynthetic disconnection.

Overall, our retrosynthetic analysis of taxol sought to simplify the structure by (i) stepwise disconnection of the side-chain (oxygenation, esterification); (ii) retro-opening of the oxetane ring; (iii) disassembly of the eight-membered ring using a McMurry coupling and a Shapiro reaction; and (iv) application of retro Diels–Alder reactions to address the construction of the two required cyclohexene rings A and C (Fig. 31). This analysis led to the formulation of an expedient and highly convergent strategy towards taxol, whose successful execution was favored by a number of factors.

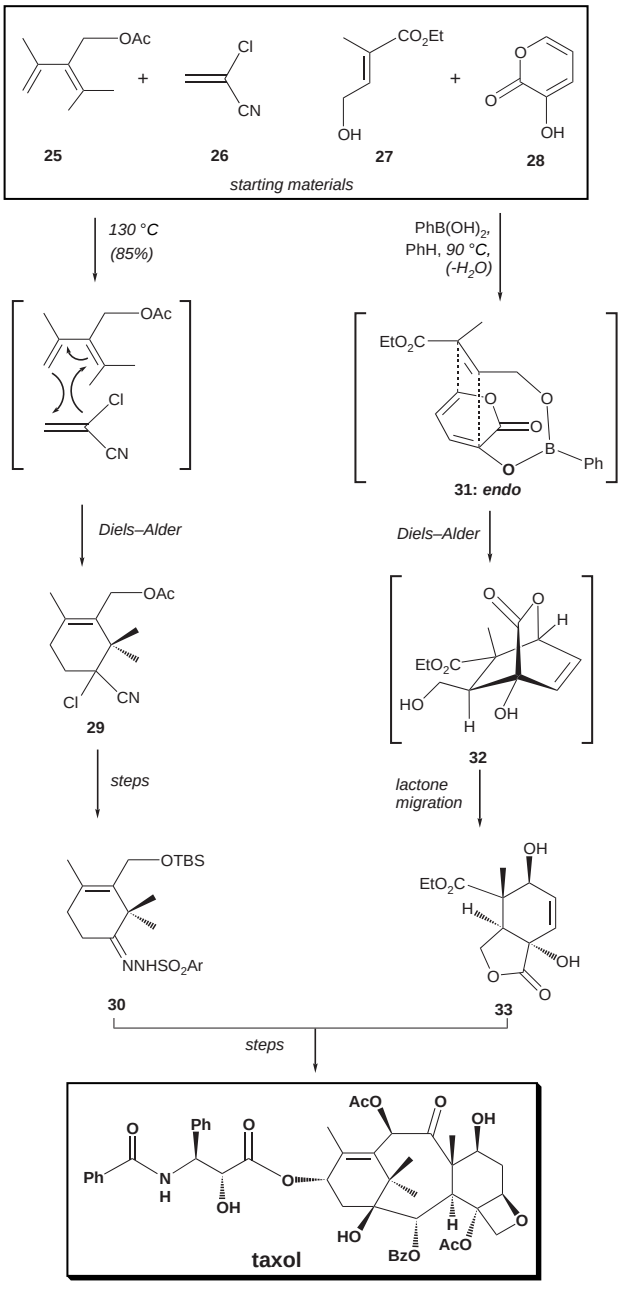


Figure 32. Assembly of the six-membered rings of taxol by Diels–Alder reactions and completion of the total synthesis (Nicolaou, 1994).

First, the attachment of the side-chain onto the taxol main framework was already reported in the literature (**14** + **15** → taxol, Fig. 31) (*70*). Second, employment of the cyclic carbonate engaging the adjacent oxygen atoms at C-1–C-2 in compound **19** was considered a valuable structural feature. In addition to its passive role as a protecting group for the C-1–C-2 diol system, the cyclic carbonate could conceivably provide the preorganization necessary to facilitate the projected pinacol ring closure to form taxol's 8-membered ring. We therefore assumed that the cyclic carbonate should have a very favorable effect on any process that brings about the union of carbons 9 and 10 by restricting rotational freedom of AC seco-taxane (**19**). The C-1–C-2 cyclic carbonate was thus envisioned to serve three important functions in this synthesis: it would provide protection for the adjacent hydroxyls attached to carbons 1 and 2; it could, by conferring rigidity to **19**, favorably influence the crucial pinacol cyclization; and it could serve as a convenient precursor to the C-1 hydroxy/C-2 benzoate system of taxol. Third, the retrosynthetic analysis led us to subtargets **22** and **24** (Fig. 31) as potential key intermediates.

Thus, the complex taxol molecule has been reduced to two cyclohexanoid sectors representing rings A and C of the natural product. In their most basic form, key intermediates **22** and **24** are simply cyclohexene rings and, therefore, it seemed prudent to devise a strategy for their construction based on the powerful and highly predictable Diels–Alder reaction. Noteworthy challenges with respect to compounds **22** and **24** were (i) the installation of four contiguous stereogenic centers in their correct configuration within the ring C sector **22** and (ii) the introduction of the functionality adjacent to the gem-dimethyl group in the ring A sector **24**. The powerful Diels–Alder reaction rose to both challenges, opening rapid entries to these intermediates starting from the simple intermediates **25**–**28** (Fig. 32). While the theory of the Diels–Alder reaction predicted the formation of the desired regioisomer **29** despite its steric congestion, a crucial tethering trick using boron guided the union of **27** and **28** to form the required building block **33** with its proper regio- and stereochemical features via intermediates **31** and **32** (Fig. 32). In addition to our total synthesis of taxol (*1, 68, 69*), there are currently four more syntheses in the literature (*71–74*).

The most prominent classes of secondary metabolites exhibiting potent antitumor activity by polymerizing tubulin and stabilizing cellular microtubules and thus disrupting the cell cycle (Fig. 30a and b) are Taxol and its close relative Taxotere (*65*); the fungal metabolites epothilones A and B (*75–77*); the scarce marine-derived natural product discodermolide (*78, 79*); and the recently discovered marine products sarcodictyins A and B (*80, 81*) and eleutherobin (*82, 83*) (Fig. 33). Organic synthesis has risen to the challenge provided by each one of these fascinating natural products. Emphasis is placed on the development of efficient pathways for the chemical synthesis of the particularly scarce marine-derived natural products discodermolide, the sarcodictyins, and eleutherobin.

Rapamycin

One of the most important contributions of natural products chemistry to modern medicine has been the discovery of molecules having the ability to suppress the immune system of organ transplant recipients, thereby preventing organ rejection. Figure 34 displays the impressive structures of cyclosporin A, FK506, rapamycin, and sangliferin A, four of the most promising immunosuppressants to come from nature so far. All four are produced by soil bacteria and exhibit powerful immunosuppressive activity by selectively inhibiting T lymphocyte activation (*84*). The concentrated search for immunosuppressant drugs with selective activity continues to be a major priority in transplant medicine.

Rapamycin is produced in nature by *Streptomyces hygroscopicus*, a bacterium indigenous to the soil of Rapa Nui (Easter Island) in the South Pacific (*85*). Although it was discovered more than 20 years ago, its therapeutic potential was not explored until the advent of the powerful immunosuppressant

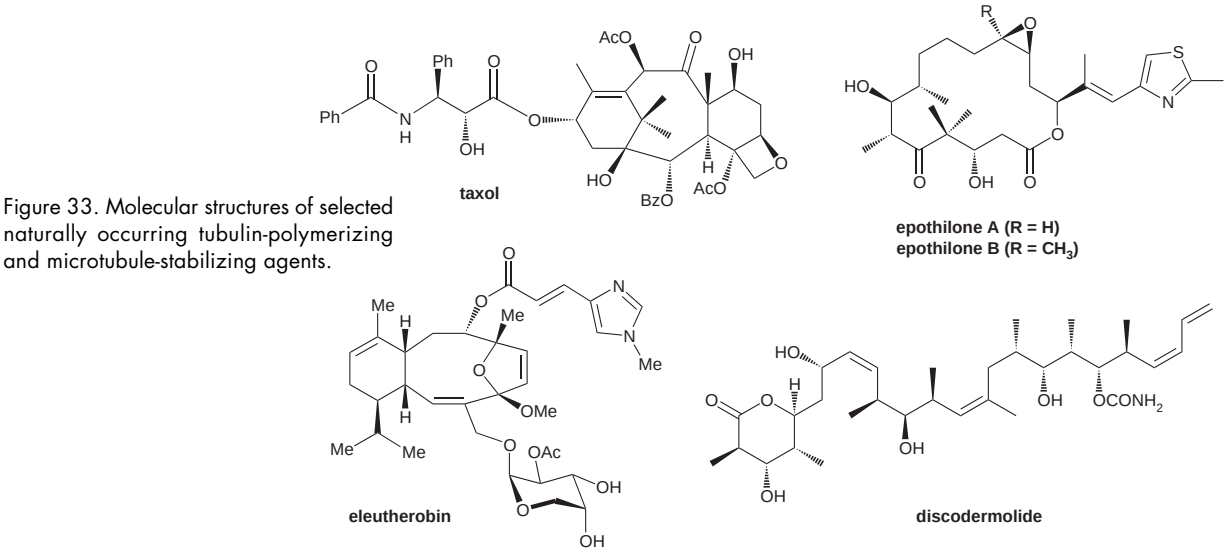


Figure 33. Molecular structures of selected naturally occurring tubulin-polymerizing and microtubule-stabilizing agents.

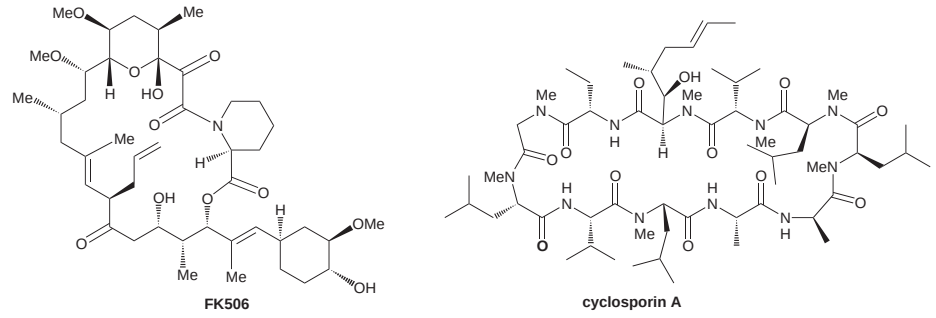
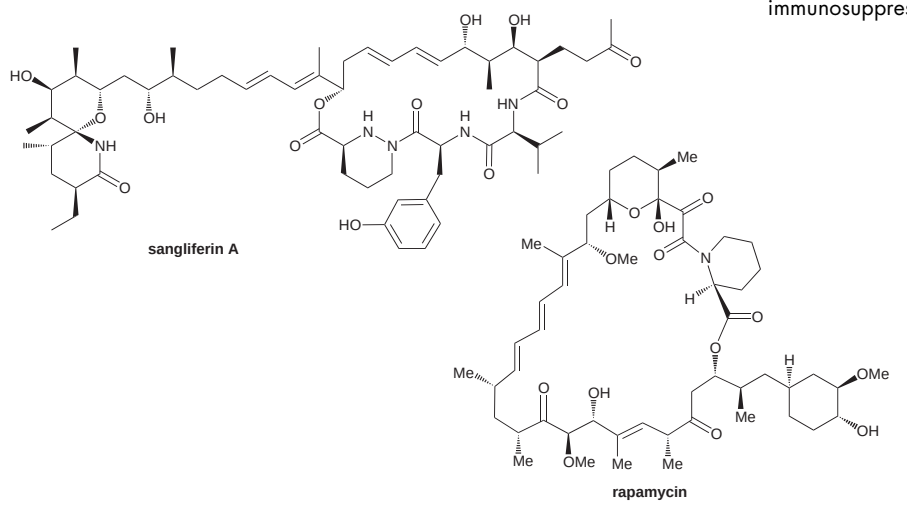


Figure 34. Molecular structures of selected immunosuppressive agents.



drugs cyclosporin A and FK506 in the 1980s. Rapamycin's obvious structural resemblance to FK506 and its potent immunosuppressive properties propelled it to the forefront of chemical and biomedical research as a target for total synthesis, a probe of immunological function, and a potential drug candidate in organ transplant therapy.

The rapamycin molecule is an impressive assembly of 51 carbons, 78 hydrogens, 13 oxygens, and one nitrogen atom. Its 31-membered macrocyclic structure conceals a vicinal tricarbonyl moiety and is further distinguished by 15 stereocenters, numerous electrophilic functional groups, and a salient all-trans conjugated triene. In a deliberate effort to challenge a new concept for the construction of polyene macrocycles, we pursued the daring ring-forming strategy shown in Figure 35. Owing to concerns regarding the stability of conjugated polyenic arrays, we decided to delay the construction of rapamycin's conjugated triene moiety to a very late stage in the synthesis. Eventually, we settled on the idea of building the triene moiety and the macrocycle of rapamycin in the same and final step. Gratifyingly, the bifunctional ethylene derivative **35** could indeed be joined with bis(vinyl iodide) **34** to give the rapamycin molecule. In this productive reaction (dubbed "stitching cyclization"), compound **35** is first coupled with compound **34** under the influence of a Pd(0) catalyst in an intermolecular fashion known as a Stille coupling reaction. This event is followed by an intramolecular Stille reaction that establishes the macrocyclic framework. It is noteworthy that this tandem reaction process can be conducted on a fully deprotected precursor and that its application in organic synthesis is finding increasing usage. Our first total synthesis of rapamycin (*1, 86*) was soon followed by a number of other syntheses of this compound (*87*).

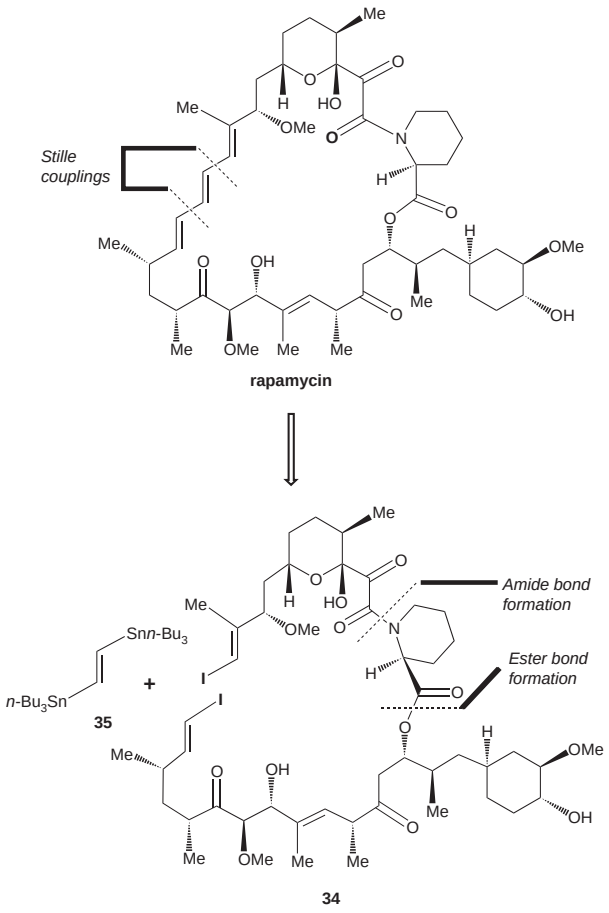


Figure 35. Retrosynthetic analysis of rapamycin: creation of the macrocycle through a double Stille coupling process ("stitching" cyclization) (Nicolaou, 1993).

Brevetoxin B

The harmful effects of algal blooms known as "red tides" (Figs. 36 and 37) may have been known as long ago as 1000

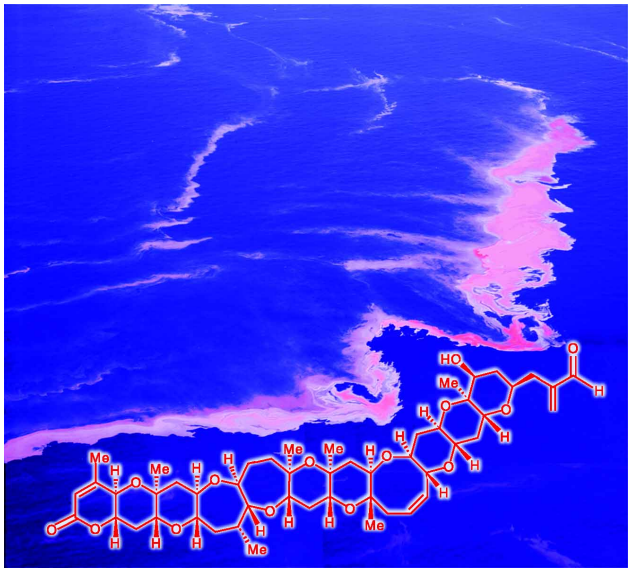


Figure 36. The discovery of brevetoxin B. "Red tides" caused by blooms of phytoplankton are responsible for massive marine-life kills and human poisonings. Among their active principles is brevetoxin B, a substance with unique molecular architecture and powerful neurotoxic properties.

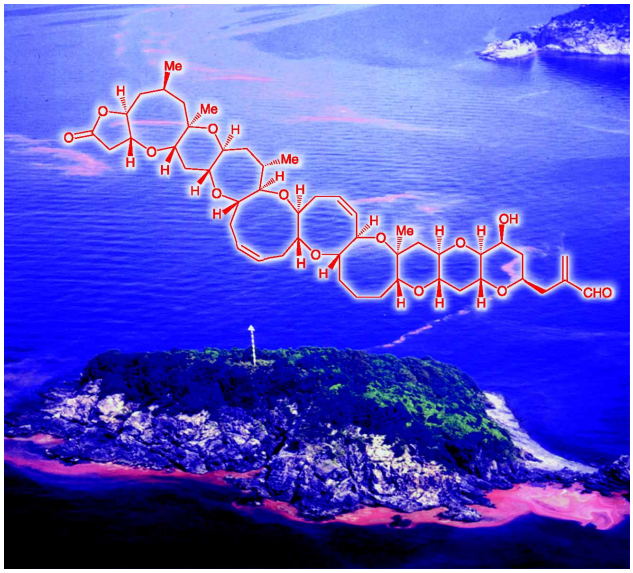


Figure 37. The discovery of brevetoxin A. Isolated from the same marine microorganism associated with the "red tides" (see Fig. 36), brevetoxin A is characterized by unprecedented molecular beauty and a 100-fold higher potency as a neurotoxin than its sister molecule brevetoxin B.

B.C.E., for a passage in the Bible acknowledges an event that some believe to be the first recorded incident of a red tide:

> and the waters that were in the river were turned to blood. And the fish that was in the river died; and the river stank and the Egyptians could not drink of the water of the river.
>
> *Exodus 7:20–21*

Red tide describes the discoloration of sea water caused by blooms of unicellular algae called phytoplankton, which constitute the base of the marine food chain. Dense growths of algae containing the carotenoid pigment peridinin appear red, although the term "red tide" also describes cases in which brown or green coloration is observed, or even cases without visible coloration. The occurrence of red tides is often accompanied by massive killings of fish and other marine life, as well as human poisonings (*88*). During a red tide episode in British Columbia in 1793, Captain George Vancouver and his crew suffered poisoning after consuming seafood from an area now known as Poison Cove. In more recent times, red tide episodes are recurring with an alarming increase in frequency, possibly due to an increase in the nutrient content of sea water caused by human pollution and shipping practices that spread algal growth. During one of several devastating red tide catastrophes in 1987–88, 740 bottlenose dolphins were found dead along the Atlantic coast of the United States from New Jersey to Florida. It was later determined that the dolphins were likely victims of the dinoflagellate *Gymnodinium breve*, a species of marine alga that produces and secretes the potent neurotoxins bearing the name brevetoxins.

Brevetoxin B (Fig. 36) and brevetoxin A (next section and Fig. 37) are hydrophobic molecules that penetrate cell membranes of neurons and bind selectively to the voltage-sensitive domains of sodium channels. This alters the conformation of the sodium channel protein and precipitates an influx of sodium ions, causing depolarization of the cell membrane. The brevetoxins pose a significant threat to the marine food chain and are believed to be responsible for many mass poisonings of humans who have eaten contaminated seafood.

Within the brevetoxin family, brevetoxin B occupies a position of historical significance because it was the first to be discovered. Its exquisite structure, which is distinguished by 11 trans-fused ether rings, 23 stereocenters, 3 carbon–

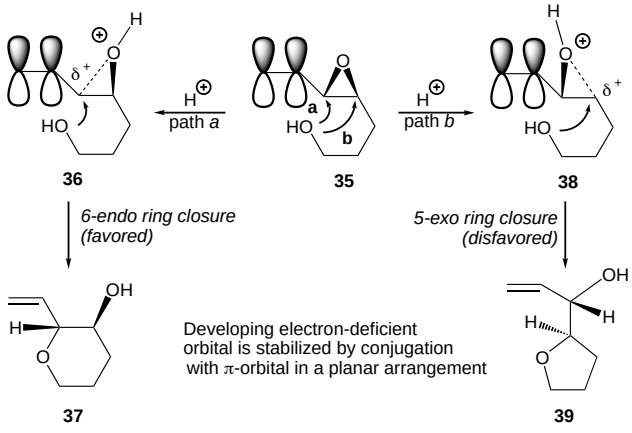


Figure 38. Methodology for the construction of cyclic ethers: 6-endo-activated hydroxy epoxide cyclization for the construction of tetrahydropyrans.

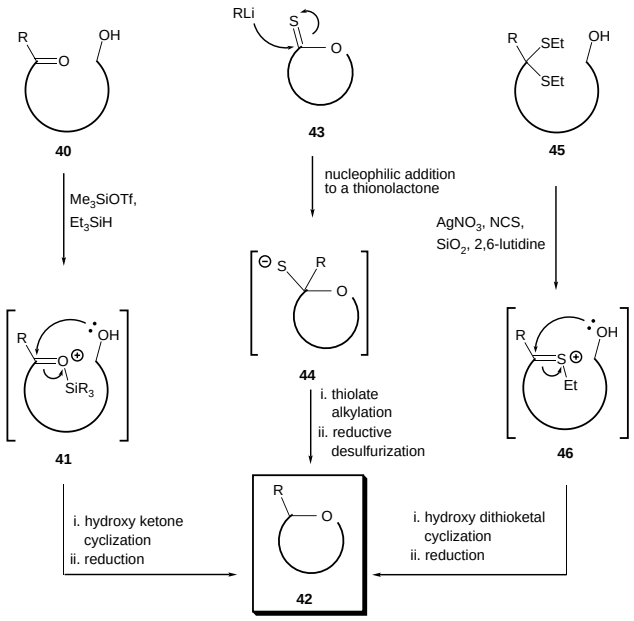


Figure 39. Methodology for the construction of cyclic ethers: the thionolactone, hydroxy ketone cyclization, and hydroxy dithioketal cyclization methods.

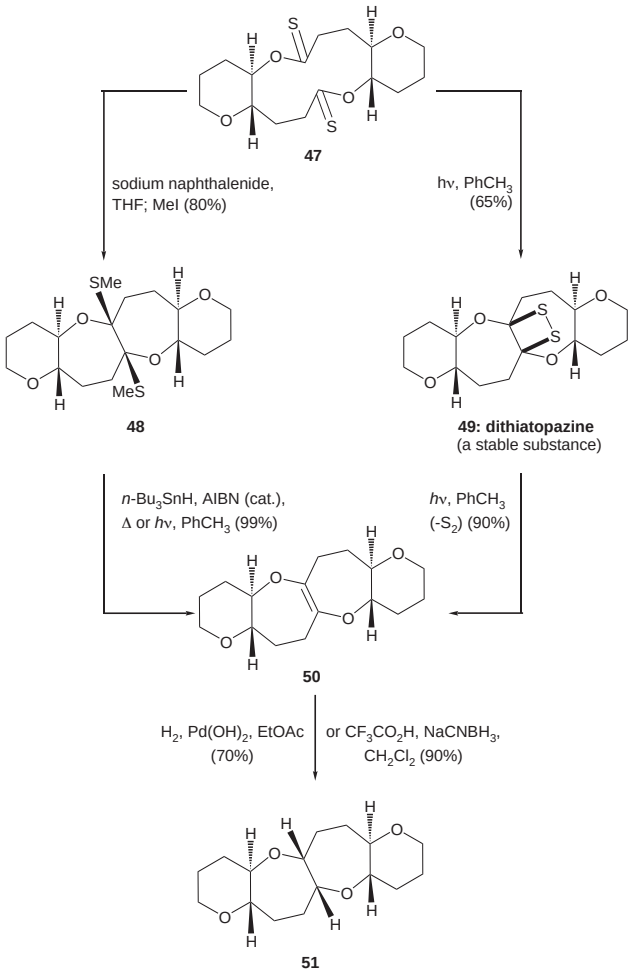


Figure 40. Methodology for the construction of cyclic ethers: bridging macrocyclic dithionolactones to form bi-cycles.

carbon double bonds, and 2 carbonyl groups, was uncovered by the spectroscopic and X-ray crystallographic work of the groups of Lin, Nakanishi, and Clardy (*89*). Brevetoxin B's striking molecular architecture (unprecedented at the time of its discovery in 1981), its association with the red tide catastrophes, its deadly biological activity, and the promise that it held for the development of innovative new chemistry all contributed to our decision to pursue its total synthesis.

As an objective for organic synthesis, brevetoxin B presented a formidable challenge and engaged the efforts of our group for 12 years. During this odyssey in organic synthesis (*88*), many new reactions were discovered and perfected for the purpose of addressing the unique challenges associated with constructing cyclic ethers of various sizes. Among the most useful and general methodologies were the 6-endo activated hydroxy epoxide cyclizations for the construction of tetrahydropyran systems (Fig. 38) (*1, 88*), the hydroxy dithioketal cyclization method for forming 8-membered-ring ethers, the hydroxy ketone reductive cyclization method for the construction of 7-membered-ring ethers, nucleophilic additions to thionolactones, and the bridging of macrocycles to bicycles (Figs. 39 and 40) (*1, 88*).

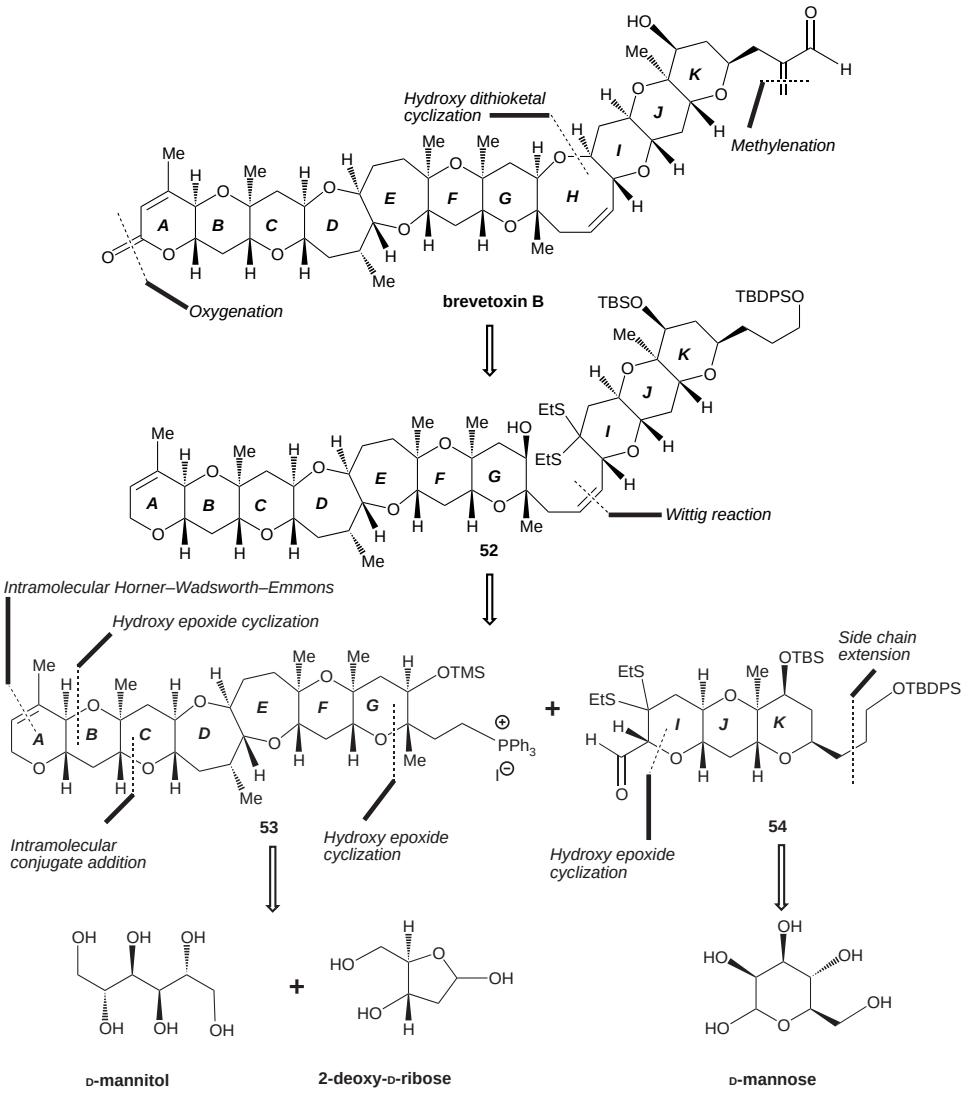


Figure 41. Retrosynthetic analysis and total synthesis of brevetoxin B (Nicolaou, 1994).

At the outset of our venture, we surmised that the complexity of the synthetic problem posed by brevetoxin B could be most effectively managed with a highly convergent strategy. What we did *not* appreciate for some time was the special difficulties inherent in the synthesis of the D–E substructure, the bis(oxepane) region, of brevetoxin B. The problem of constructing the contiguous 7-membered cyclic ethers of brevetoxin B proved recalcitrant and forced us to redesign our synthetic strategy twice. Nevertheless, the knowledge that we gained in pursuit of the first two unsuccessful campaigns was very valuable, for it shaped the development of the third, and ultimately successful, strategy (*1, 88, 90*).

A retrosynthetic analysis of our successful third-generation strategy is shown in Figure 41. On the basis of many prior experiences, we had much faith in the hydroxy dithioketal cyclization method for the construction of unsaturated 8-membered cyclic ethers (Fig. 39) and we decided to designate ring H as the final ring to be constructed. Compound **52** emerged as a plausible precursor of brevetoxin B, and its cis-disubstituted carbon–carbon double bond would, by restricting rotational freedom of the carbon chain, facilitate the crucial cyclization to give ring H. Of course, that particular double bond is also expressed in the natural product and could conceivably be established during a Wittig reaction between a phosphorus ylide derived from phosphonium salt **53** and aldehyde **54**. As one of the mildest and most reliable methods for the construction of bonds between carbon atoms, the Wittig reaction seemed ideally suited for the desired union. According to this plan, the challenging D–E substructure of brevetoxin B would be fashioned at a relatively early stage during the course of a synthesis of key intermediate **53**.

The problem of synthesizing the imposing brevetoxin B molecule was thus reduced to the synthesis of two advanced intermediates. Through a reliance on a menu of efficient and stereoselective reactions, it was possible to create compounds **53** and **54** in the desired stereochemical form from the indicated chiral pool building blocks. Thus, while D-mannitol and 2-deoxy-D-ribose would serve as starting materials for a synthesis of intermediate **53**, the stereochemistry and

functionality of D-mannose would be utilized in the creation of key intermediate **54** (Fig. 41). Following a path charted along these lines, the total synthesis of brevetoxin B was accomplished in 1994 (*1, 88, 90*).

Brevetoxin A

The wealth of information and experience gained during our synthesis of brevetoxin B fostered much confidence and induced us to undertake a chemical synthesis of brevetoxin A (Fig. 37), the most potent neurotoxin secreted by *G. breve*. Although the structure of brevetoxin A, elucidated in 1986 (*91*), bears a resemblance to brevetoxin B, the challenge posed by its molecular architecture is rather different. The juxtaposition of 7-, 9-, and two 8-membered cyclic ethers is a striking and most challenging feature of brevetoxin A. To cope with the problem posed by this diabolical sequence of rings, we developed powerful new chemistry based on the palladium-catalyzed cross-couplings of cyclic ketene acetal phosphates (Fig. 42) (*92*) to complement the methodology previously developed. This new chemistry performed admirably in our total synthesis of brevetoxin A (*93*) and could even be extended to the synthesis of variously substituted nitrogen-heterocycles as shown in Figure 42.

With an expanded armamentarium of methods for the construction of cyclic ethers, we embarked on a total synthesis of brevetoxin A. Figure 43 shows strategic bond disconnections and the retrosynthetic analysis that guided our effort. The synthesis of brevetoxin A was predicated on the intermolecular union of two advanced intermediates of comparable complexity, the BCDE (**57**) and GHIJ (**58**) ring systems, followed by the execution of a hydroxy dithioketal cyclization to establish the 8-

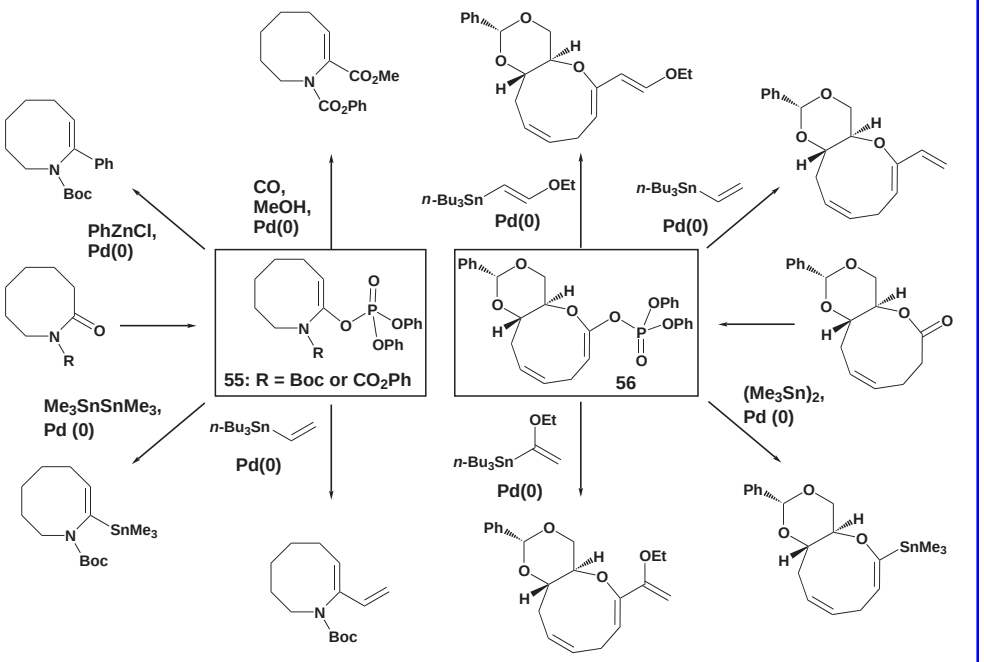


Figure 42. Selected new synthetic reactions of lactam- and lactone-derived enol phosphates.

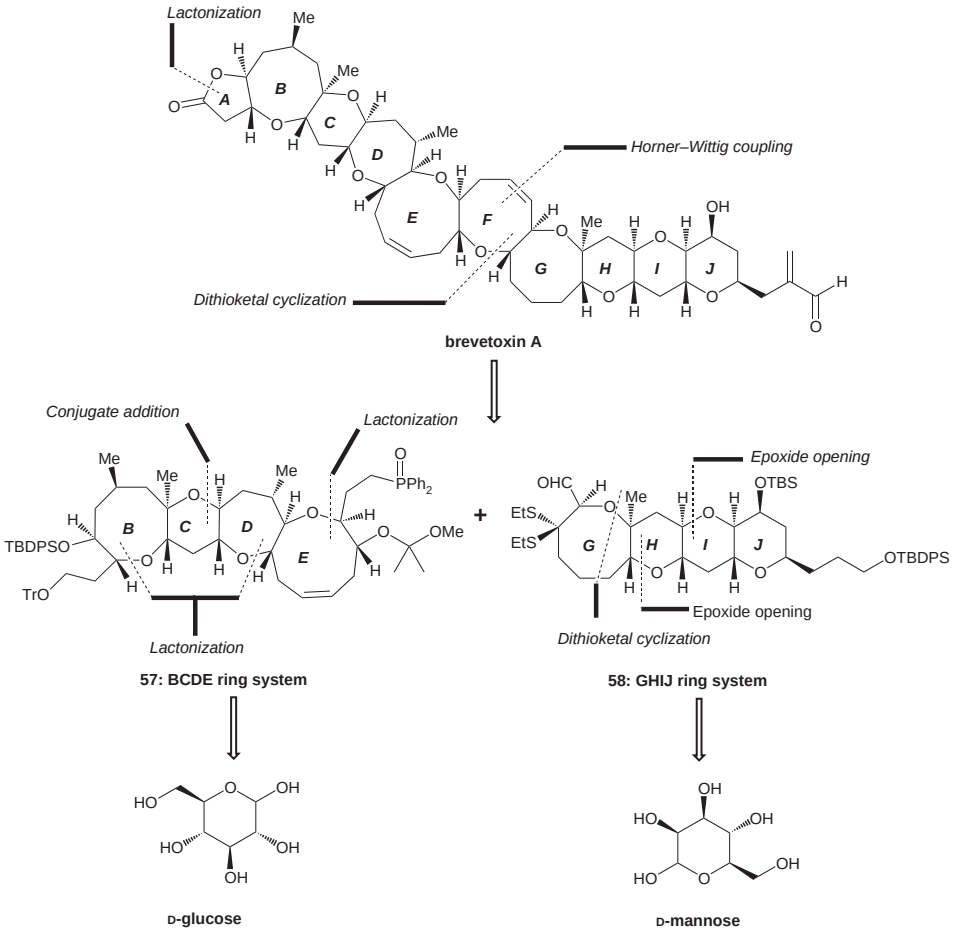


Figure 43. Retrosynthetic analysis and total synthesis of brevetoxin A (Nicolaou, 1997).

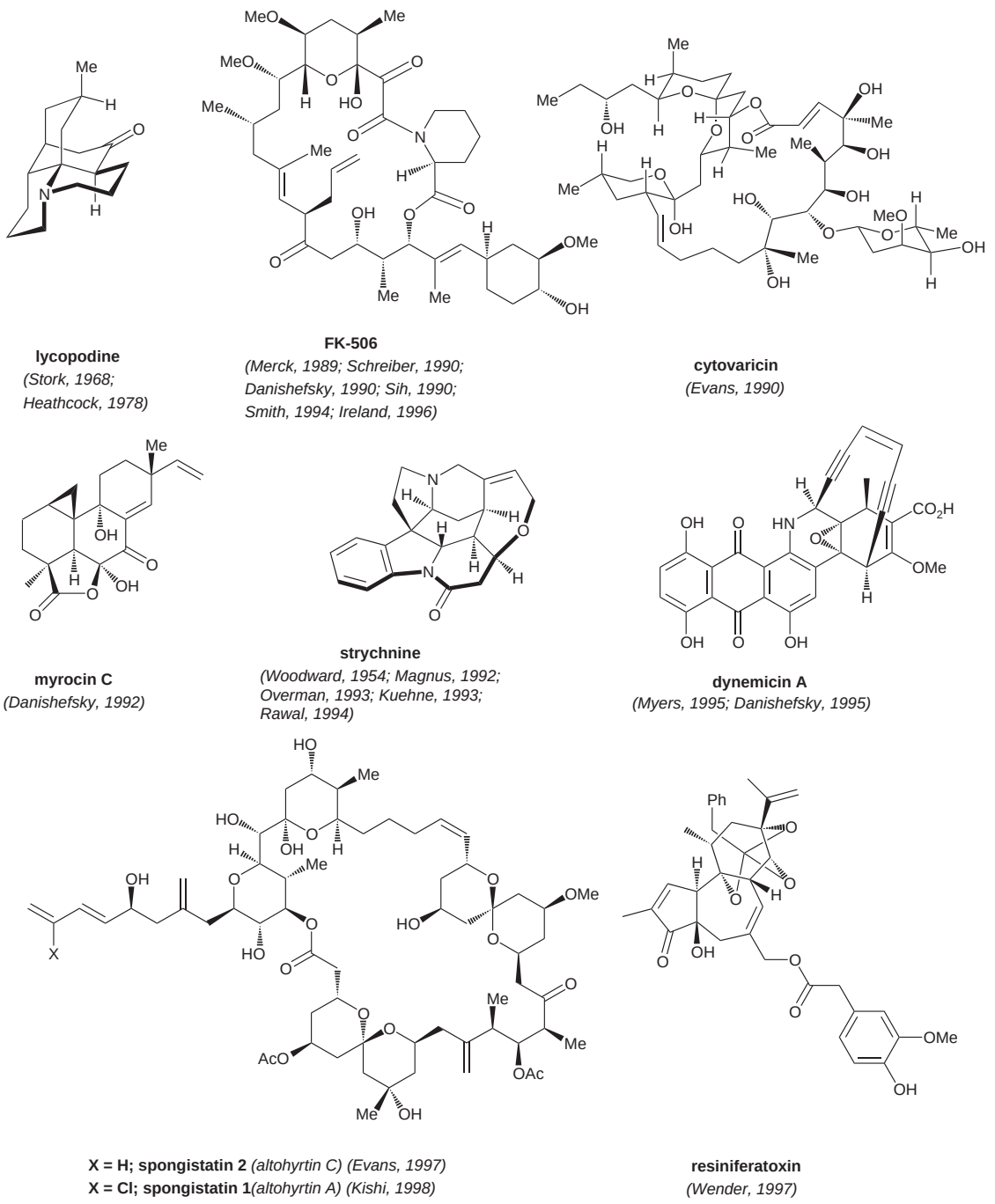


Figure 44. Selected landmarks in organic synthesis.

membered F-ring oxacycle. The final ascent to the natural product then required a few functional group manipulations and deprotections.

To achieve stereocontrolled syntheses of the two key intermediates **57** and **58**, we exploited the functionality and stereochemistry of two abundant and inexpensive chiral pool building blocks. Whereas the BCDE ring system was created from D-glucose, the GHIJ ring system was fashioned from D-mannose. As in our synthesis of brevetoxin B, the hydroxy epoxide and hydroxy dithioketal cyclization methods that performed so well in the construction of 6- and 8-membered cyclic ethers, respectively, also served admirably in our synthesis of brevetoxin A. But the challenge associated with the assembly of the functionalized 9-membered E-ring also inspired—indeed necessitated—the development of new chemistry. In this regard, the facility with which new carbon–carbon bonds are formed in palladium-mediated cross couplings of cyclic ketene acetal phosphates and vinylstannanes was gratifying and proved valuable in the elaboration of brevetoxin A's E-ring oxacycle, thus creating an opportunistic path toward the molecule. The total synthesis of brevetoxin A was completed in 1997 (*93*).

Other Landmarks in Total Synthesis

Space limitations do not allow a detailed inclusion of the many other landmark accomplishments in organic synthesis in general and total synthesis in particular. We do, however, wish to emphasize that there are many more brilliant accomplishments and that it is the collective contributions of those engaged in the field that make it so vibrant and exciting. Figure 44 exhibits some further landmarks in total synthesis from the laboratories of several masters of the art. The impressive total syntheses of lycopodine (*94*), FK-506 (*95*), cytovaricin (*96*), myrocin C (*97*), strychnine (*98*), dynemicin A (*99*), spongistatins 2 (*100*) and 1 (*101*), and resiniferatoxin (*102*) have enriched the conceptual framework of organic chemistry and extended considerably the power of the science.

Drug Discovery and Medicinal Chemistry

Even though the ancient practice of herbal medicine (*103*) continues to this day, society owes a great debt to chemistry and biology for generating an armory of awesome medicines (*104*). Today, the process of drug discovery and development is a highly sophisticated science based on principles of biology and chemistry (*105*). The discovery of the genetic code (*106*) and its consequences on one hand and the advent of chemical synthesis (*1, 2*) and analytical techniques on the other have contributed enormously to drug discovery and development. Traditionally, this multidisciplinary process, which thrives on synergistic collaborations of chemists and biologists, was practiced successfully from a number of perspectives, with chemistry often leading the way. Current approaches to drug discovery, however, have been more or less formalized to one rational recipe: biology defines and validates a biological target for intervention with a small molecule, which then becomes the responsibility of chemistry. The target, defined as the receptor, can be either an enzyme or an acceptor protein or even a gene. Compound libraries derived from natural sources (plants, bacteria, fungi, and marine organisms) or from organic synthesis are screened against biological targets for lead compounds and drug candidates.

Despite the wonderful record of natural products as drugs or leads for drug discovery, today most compound libraries for biological screening are derived from organic synthesis. Organic synthesis directed at the discovery and development of new medicines is called medicinal chemistry. Combinatorial synthesis, which will be discussed in more detail in the next section, is a technique by which large numbers of compounds

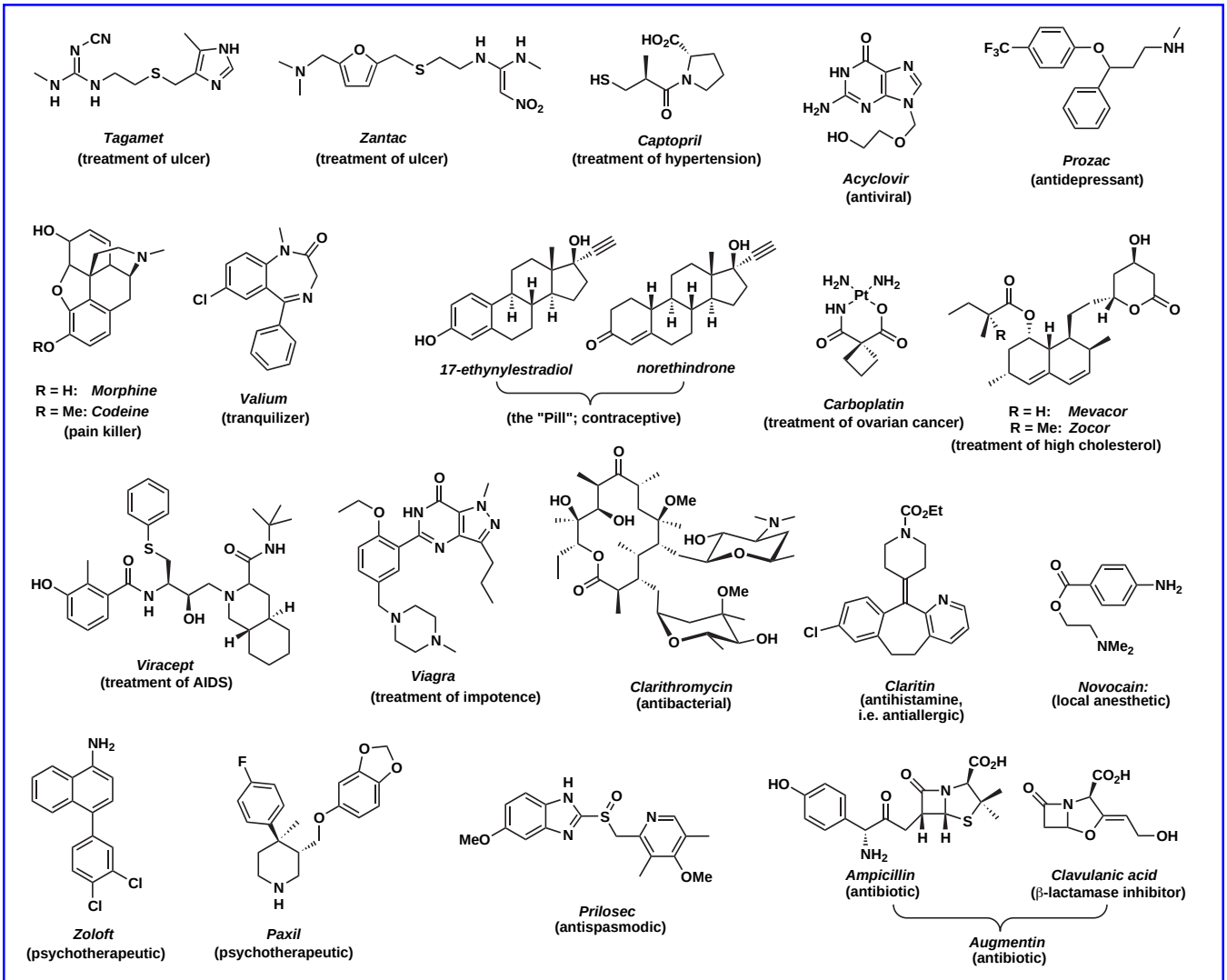
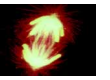


Figure 45. Selected medications of the 20th century.



can be synthesized simultaneously rather than one at a time, as was the case until recently. Both medicinal chemistry and combinatorial synthesis derive their power from organic and natural products synthesis, which therefore becomes the enabling technology for biology and medicine. For these reasons we must continue to sharpen this technology, for it is destined to play the most crucial role in accelerating the pace of drug discovery and development.

Today's medicinal chemist performs admirably in his or her quest for new drugs. Before success, however, enormous efforts have to be expended. This includes the identification of lead compounds and the refinement of their structures to translate into the proper pharmacological features such as potency, solubility, bioavailability, efficacy, and safety. Structural information about the receptor and receptor–ligand complexes often becomes crucial for the drug discovery process. With such data at hand, molecular modeling becomes a powerful tool in the hands of the medicinal chemist. This so-called rational drug design approach is today complemented by random screening strategies from natural product collections and libraries of synthetic compounds.

A number of milestones in drug discovery and design involving synthetic or semisynthetic molecules are shown in Figure 45 (*107*). They include Tagamet (*108*) and its sister drug Zantac, the histamine H_2-receptor antagonists used as antiulcer drugs; Captopril, the angiotensin-converting enzyme (ACE) inhibitor used against hypertension and congestive heart failure; Acyclovir, a reverse transcriptase inhibitor used to combat herpes and AIDS; the protease inhibitor Viracept, representing a group of compounds recently introduced as anti-AIDS drugs; Prozac, the highly successful antidepressant agent; "the Pill", a contraceptive formulation; Valium, a tranquilizer; Mevacor and Zocor, two cholesterol-lowering drugs; Carboplatin, an anticancer agent; Codeine, a pain killer; Clarithromycin, an antibacterial agent; Claritin, an antiallergic drug; Novocain, a local anesthetic; Zoloft and Paxil, two psychotherapeutic agents; Prilosec, an antispasmodic agent; Augmentin, an antibacterial formulation; and Viagra, an oral drug used to reverse impotence. In addition to these agents, the reader should be reminded of the many natural products such as erythromycin, amphotericin B, cyclosporin, and Taxol, which are used extensively as therapeutic agents today.

As we move into the next century and closer to characterizing the full sequence of the human genome, medicinal chemistry is poised for even greater successes and breakthroughs. Such breakthroughs are needed to combat the persistent menace of cancer, infection from drug-resistant pathogens, Alzheimer's disease, AIDS, arthritis, diabetes, heart disease, autoimmune disease, and many other ailments plaguing society, especially as the population ages. Medicinal chemistry will turn, as it always has, to organic and natural products synthesis for reagents and methods, theories and strategies, and for trained experts to enhance its power as it attempts to provide solutions to these problems.

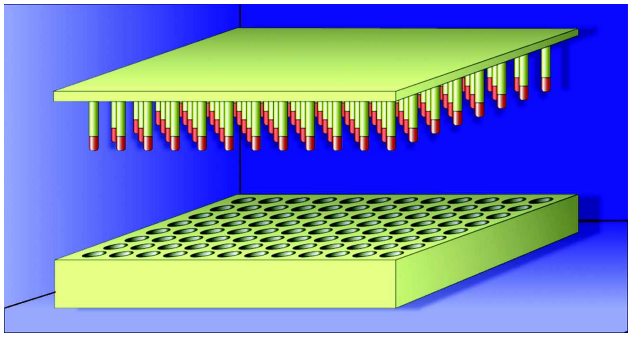


Figure 46. The multi-pin technology used by Geysen to synthesize a combinatorial peptide library.

Combinatorial Synthesis

Traditionally, synthetic chemists have devoted their efforts to constructing compounds one at a time. Medicinal chemists in particular designed and constructed potential drug candidates and lead compounds by targeting small organic compounds through stereospecific routes. In contrast to peptide and oligonucleotide chemistry, the required operations were carried out in solution, which demanded tedious workup and purification procedures. While this approach is still extremely valuable to the drug discovery and development process, the situation began to change in the 1990s as the revolution of solid-phase and combinatorial chemistry (*109*) spread throughout synthetic and medicinal chemistry laboratories. A number of factors are responsible for the advent of combinatorial synthesis. The ever-increasing pressure to produce larger and larger numbers of small organic molecules for biological screening purposes in the hope of speeding up the process of drug discovery and development is one. Another is the shining example of the way nature orchestrates evolution through the synthesis and selection of myriad compounds. But while nature produces its compound libraries in a random combinatorial fashion, we have the option of using logic to design ours. Finally, recent advances in molecular biology and ultra-high-speed screening techniques increased dramatically the number of biological targets and the demand for compounds that can be screened against them.

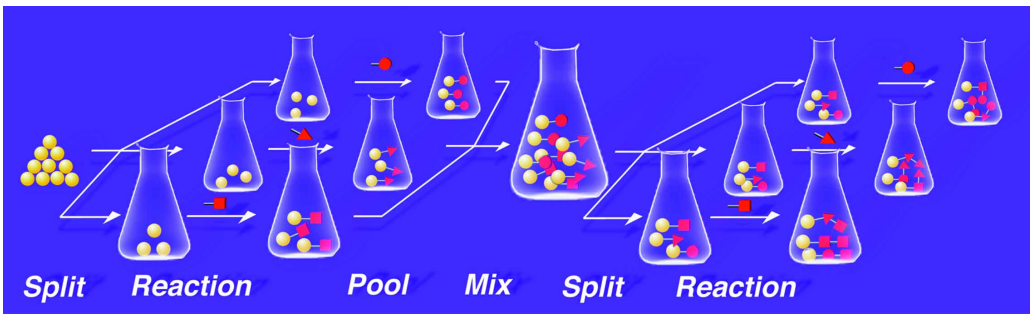


Figure 47. The "split-pool" strategy for combinatorial synthesis introduced by Furka.

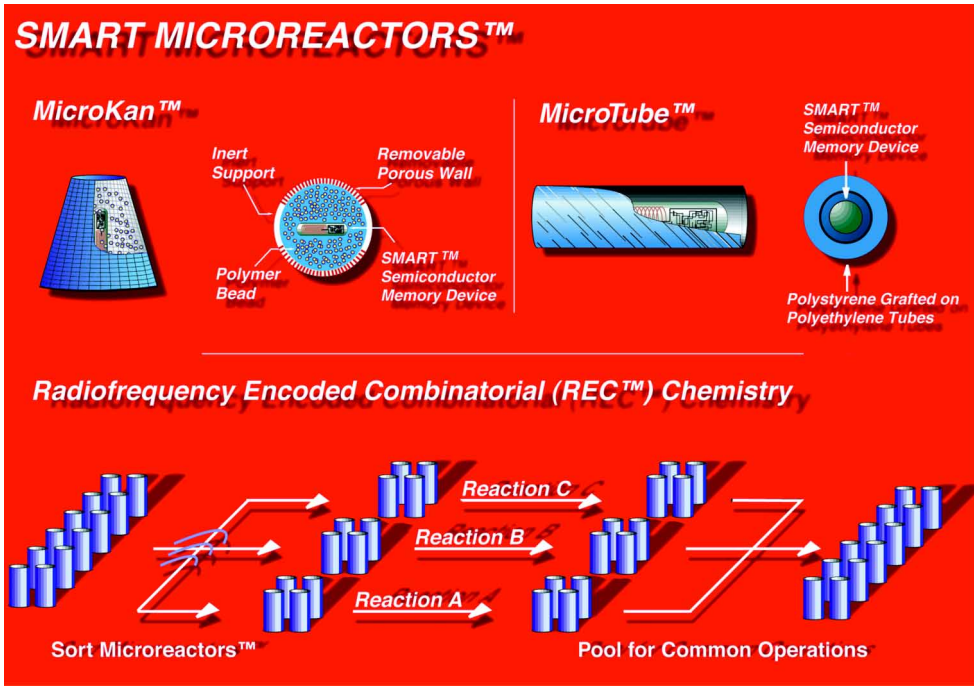


Figure 48. The radiofrequency-based encoding technology for combinatorial synthesis.

Challenged by these forces, synthetic chemists turned to ingenious methods to deliver the numbers and the molecular diversity of compounds required to feed the frenzy generated in biology and medicine. The solid-phase synthesis of peptides pioneered by Merrifield in the 1960s (*110*), for which he received the Nobel Prize for Chemistry in 1984, was an inspiring example of how compounds could be synthesized on solid supports by multistep sequences with relative ease and without purification at intermediate stages. It was no surprise, therefore, that the first example of combinatorial synthesis, reported by Geysen (*111*), involved peptides. Taking advantage of solid-phase peptide coupling reactions and the molecular diversity provided by the natural amino acids, Geysen simultaneously synthesized hundreds of hexapeptides using an array of pins grafted with a suitable solid support for chemical synthesis. Fixed on a platform, this multi-pin array is immersed in a microtiter plate with wells arranged in rows and columns containing appropriate building blocks and reagents in solution for the construction of all combinations of products. The fixed positions of the pins allow the structural identification of each library member (Fig. 46).

This paradigm of parallel synthesis is used extensively today, in both its solution and its solid-phase versions, to produce large libraries of small organic molecules for biological screening. An alternative and more elegant approach to combinatorial synthesis is the so-called "split-pool" strategy developed by Furka (Fig. 47) (*112*). According to this method, which requires solid-phase chemistry, a certain volume of resin beads is split into equal portions and the first synthetic step introduces a different building block to each portion of the resin. The resin beads are then pooled together for common operations (e.g., washings, deprotections, functional group manipulations). After thorough mixing, the resin is split again into the desired number of vessels and a second element of diversity is introduced by attaching a different building block to each portion. Iteration of this "split-pool" process is extremely powerful in terms of library size, since the number of different compounds that can be produced is exponentially related to the number of reactions performed. For example, if 20 building blocks are used in four cycles to synthesize combinatorially a tetramer library, the total number of compounds resulting will be 20^4, or 160,000. The practicability of this brilliant strategy (which relies on statistical distribution) is undermined, however, by the element of uncertainty in finding all possible structures (unless a large enough volume of resin is used) and the difficulties associated

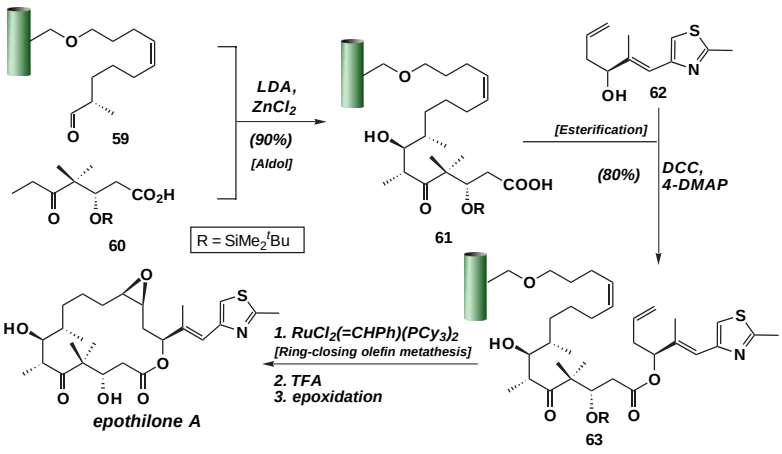


Figure 49. Solid-phase chemistry utilized in the synthesis epothilone A. A library of epothilones was constructed by varying the structures of building blocks **59**, **60**, and **62** (Nicolaou, 1997).

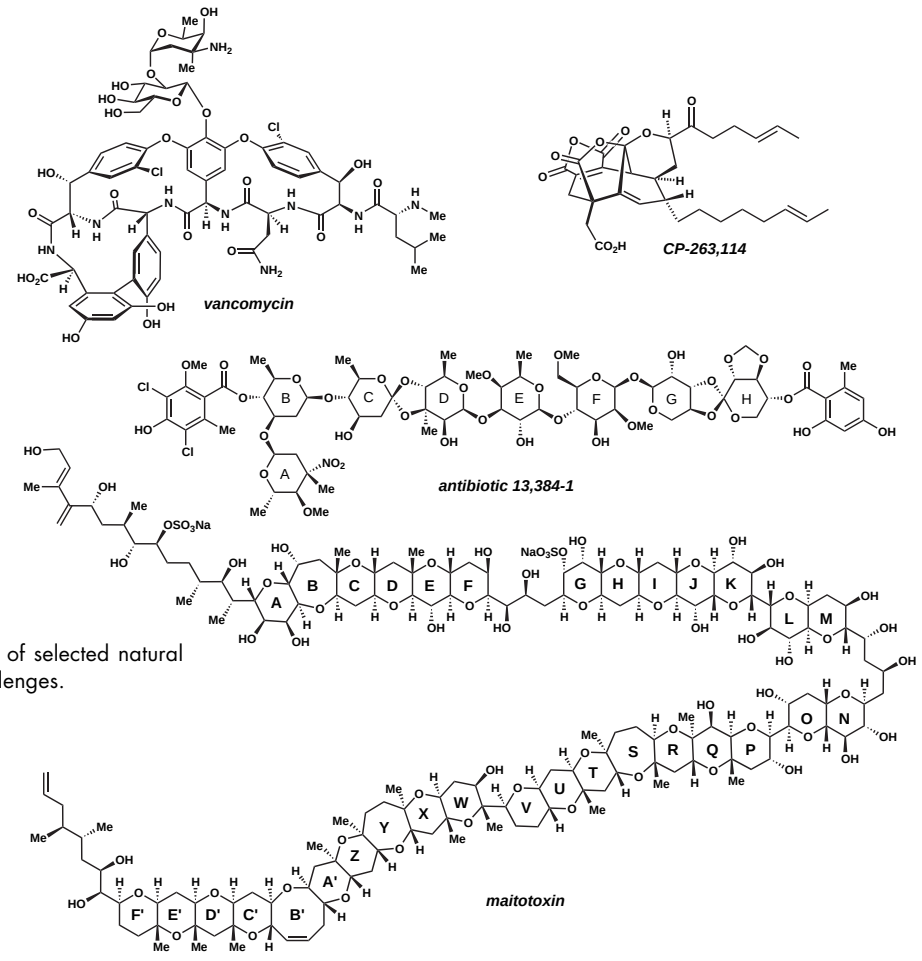


Figure 50. Molecular structures of selected natural products of future synthetic challenges.

with complete structural identification of each or of a particular library member, since only the last building block to be introduced is known.

These limitations of the "split-pool" combinatorial strategy stimulated the innovation of several novel encoding and microreactor technologies for the combinatorial synthesis and structural identification of single compounds as members of chemical libraries. One of the latest innovations in this area is the development of microreactors (MicroKans and Microtubes) equipped with electronic tagging devices (*113*). At the core of this technology is a microchip capable of receiving, storing, and emitting radiofrequency signals for the purposes of encoding and decoding the structure of individual compounds by simple sorting and reading using robotics and computer hardware and software (Fig. 48). Among the many applications of this technology, which is used routinely by many pharmaceutical and biotechnology companies today, is the synthesis of a combinatorial library of epothilones, which perhaps represents one of the frontiers of combinatorial synthesis in terms of structural complexity (Fig. 49) (*114*).

Although in its infancy, combinatorial synthesis promises to meet the challenge of molecular biology, which unravels the sequences of human genes at an unprecedented pace and begs for small organic molecules to bind and modulate their function. The dream is to have not only all 100,000 or so genes of the human genome sequenced, but also to identify specific compounds that will bind to the corresponding proteins and alter their function at will. Just as combinatorial chemistry played a role in the generation and evolution of these genes in nature, it appears almost certain that it will be combinatorial chemistry again, this time human-driven, that will produce the millions of molecules from which appropriate ligands will be selected. It is also evident that combinatorial synthesis demands, and will serve as the engine to drive, automation and standardization in synthesis. Robotics and informatics will play major roles in driving organic synthesis forward in its next phase of evolution.

Perspectives on the Future

Perhaps no other endeavor in chemistry can make a statement as strong as that made on behalf of organic and natural products synthesis in terms of stimulation and opportunity for discovery and invention. Such beneficial spin-offs and developments can take the form of experimental methods or theories. Conformational analysis (*6*), the Woodward and Hoffmann rules (*44*), and retrosynthetic analysis (*1, 2*) are prime examples of the latter category, whose impact on chemistry as a whole have been enormous.

It is abundantly clear that the state of organic and natural products synthesis is not only healthy, but vigorous and influential. Its power and impact is ever expanding into

materials science, physics, biology, and medicine. But most pleasing is the fact that there are still many practitioners of the art who appreciate it for what it is and derive enormous benefits and pleasure from advancing it for its own sake. These may not be the heroes of today to some, but they will certainly be recognized as such tomorrow, for their inventions and discoveries will make the present state of affairs in the field look, a century from now, as distant as the science of the last century looks to us today.

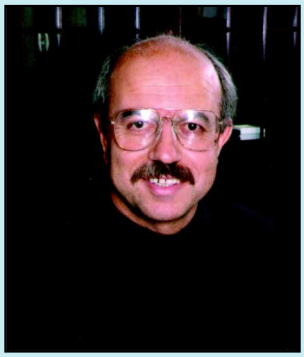
What should we expect in the next few decades? History always helps us understand the present and should allow us to make predictions for the future with some degree of certainty. But we must also remember that it is often the unexpected and serendipitous discoveries that have the greatest impact. Given that organic and natural products synthesis is fueled by the needs of the drug discovery and development process and biotechnology on one hand (*115*) and by the hunger of the synthetic chemist to apply creativity and imagination in conquering nature's most challenging and beautiful structures on the other, we should expect current trends in asymmetric catalysis, combinatorial synthesis, and total synthesis to continue. Solid-phase chemistry and automation will surely play increasing roles in the practices of synthetic chemists, as will computers and informatics.

Structures of unprecedented molecular architecture, complexity, and size such as vancomycin (*116*), CP-263,114 (*117*), antibiotic 13,384-1 (*118*), and maitotoxin (*119*) (Fig. 50) still stand tall, challenging and daring the synthetic chemist, while myriad others remain to be discovered. The search for new natural substances should continue with renewed vigor in the forests, soil, and oceans, particularly in view of the new advances in analytical and screening methods. It is logical to consider natural substances as biologically relevant—much more so than randomly synthesized compounds. Some may claim that synthetic chemists have reached the outer boundaries of their discipline and that given enough manpower and time they can make any structure, however complex it may be. While this is a welcome compliment, the issue is not *whether* anything can be made, but rather *how* it can be made. Efficiency, economy, environmental impact, and speed are key questions, not to mention elegance, creativity, and imagination. To bring home this point more emphatically, we should compare our ability to make molecules with that of nature: are we still in the Bronze Age? Or perhaps the Stone Age?

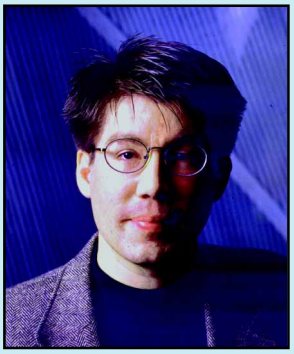
Despite logic and rationale, there will be the excitement of unexpected and serendipitous discoveries in our future. The Wittig reaction (*9*) and the discoveries of Teflon (*120*) and penicillin (*32–38*) were such serendipitous events that have

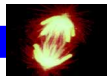
Viewpoints: Chemists on Chemistry

K. C. Nicolaou is one of the most influential practitioners of the art and science of organic and natural products synthesis in the world today. Born in Cyprus and educated in England and the U. S., he is currently Professor of Chemistry at the University of California, San Diego, and Chairman of the Department of Chemistry at The Scripps Research Institute, where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology. His impact on chemistry, biology, and medicine flows from his works in organic synthesis described in more than 400 publications and 50 patents, and from his dedication to chemical education as evidenced by his training of more than 250 graduate students and postdoctoral fellows. His recent book titled *Classics in Total Synthesis*, which he co-authored with his student Erik J. Sorensen, is used around the world as a teaching tool for students of organic synthesis. Nicolaou's research interests include the chemical synthesis, chemical biology, and medicine of novel natural and designed molecules. Among his most recent awards and honors are the Nichols Medal, the Linus Pauling Medal, and the Esselen Award.



Erik J. Sorensen graduated from Syracuse University with a B.A. in chemistry and received his Ph.D. degree in chemistry from the University of California, San Diego, in 1995 under the guidance of K. C. Nicolaou. As a student under Nicolaou's mentorship, he contributed to the total synthesis of the anticancer drug taxol and co-authored a book titled *Classics in Total Synthe-*





had enormous impact on our lives. It is also important to emphasize that moving forward in science is like walking on a curved surface, where new horizons come into view only as we approach them.

In our line of research, nature's beauty and wealth in terms of molecular architecture, biological activity, and medical value will continue to be the magnet and prime guiding force. One can hope for and easily envision, as well as look forward to, more fascinating molecules such as the penicillins and cephalosporins, taxol and calicheamicin, brevetoxin and eleutherobin. No doubt, nature has revealed only a small fraction of its vast store of molecular secrets. As we pursue their discovery and investigation we will learn from them and improve upon them for the benefit of humankind. Important roles in future research directions will also be played by ingenious molecular designs and our quest to enable and facilitate biology and medicine. Thus, the practitioner of organic and natural product synthesis will continue to be confronted by increasingly intriguing challenges and opportunities to invent and discover new science in the fields of chemistry, biology, and medicine. Appropriately faced and explored, such opportunities will surely deliver enormous rewards to society through advancements in chemical synthesis and chemical biology.

As a final word, we wish to reemphasize the importance of education and basic research for the benefit of humankind through innovation and discovery. Freedom of thought and fundamental research are prerequisites to any technology and application and must be fueled continuously with appropriate funding and encouragement to young people. We owe it to our children to ensure the continuance of the golden age of science that we have witnessed in the last 50 years or so. We hope that this article will contribute to attracting some of those young men and women to the science that is destined to shape the 21st century even more than it did the 20th century.

Acknowledgments

It is with enormous pride and pleasure that we wish to thank our collaborators whose names appear in the references and whose contributions made the described work possible and enjoyable. We gratefully acknowledge the National Institutes of Health USA, Merck Sharp & Dohme, DuPont Merck, Schering-Plough, Pfizer, Hoffmann-La Roche, GlaxoWellcome, Rhone-Poulenc Rorer, Amgen, Novartis, CaP CURE, the George E. Hewitt Foundation, and the Skaggs Institute for Chemical Biology for supporting our research programs.

The Art and Science of Organic and Natural Products Synthesis

sis. As a National Science Foundation Postdoctoral Fellow, he then pursued additional research in organic synthesis at the Memorial Sloan-Kettering Institute for Cancer Research in New York under the guidance of S. J. Danishefsky. In 1997, he returned to La Jolla, California, and assumed a position of Assistant Professor of Chemistry in The Skaggs Institute for Chemical Biology and the Department of Chemistry at The Scripps Research Institute. He immensely enjoys teaching organic chemistry. His research interests include the development of innovative strategies for total synthesis of bioactive natural products and the application of principles of organic chemistry to chemical biology.

Nicolas Winssinger was born in 1970 in Belgium, where he spent the first 15 years of his life. He then moved with his family to Rome, where he completed his high school education. He received his B.S. in chemistry from Tufts University conducting research in the laboratory of M. D'Alarcao on the synthesis 1,2 cyclic phosphate *myo*-inositol as part of a program aimed at the total synthesis of a secondary messenger in the insulin signal transduction pathway. Before joining The Scripps Research Institute in 1995 as a graduate student in chemistry, Nicolas worked for two years under the direction of M. P. Pavia at Sphinx Pharmaceuticals in the area of molecular diversity, focusing on combinatorial chemistry. At Scripps, he joined the laboratory of K. C. Nicolaou, where he has been working on methodologies for solid-phase chemistry and combinatorial synthesis. His research interests include natural products synthesis, molecular diversity, and molecular evolution, and their application to chemical biology.

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