THE LOGIC OF CHEMICAL SYNTHESIS: MULTISTEP SYNTHESIS OF COMPLEX CARBOGENIC MOLECULES

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by

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Carbogens, members of the family of carbon-containing compounds, can exist in an infinite variety of compositions, forms and sizes. The naturally occurring carbogens, or organic substances as they are known more traditionally, constitute the matter of all life on earth, and their science at the molecular level defines a fundamental language of that life. The chemical synthesis of these naturally occurring carbogens and many millions of unnatural carbogenic substances has been one of the major enterprises of science in this century. That fact is affirmed by the award of the Nobel Prize in Chemistry for 1990 for the "development of the theory and methodology of organic synthesis". Chemical synthesis is uniquely positioned at the heart of chemistry, the central science, and its impact on our lives and society is all pervasive. For instance, many of today's medicines are synthetic and many of tomorrow's will be conceived and produced by synthetic chemists. To the field of synthetic chemistry belongs an array of responsibilities which are crucial for the future of mankind, not only with regard to the health, material and economic needs of our society, but also for the attainment of an understanding of matter, chemical change and life at the highest level of which the human mind is capable.

The post World War II period encompassed remarkable achievement in chemical synthesis. In the first two decades of this period chemical syntheses were developed which could not have been anticipated in the earlier part of this century. For the first time, several very complex molecules were assembled by elaborately conceived multistep processes, for example vitamin A (O. Isler, 1949), cortisone (R. B. Woodward, R. Robinson, 1951), morphine (M. Gates, 1956), penicillin (J. C. Sheehan, 1957), and chlorophyll (R. B. Woodward, 1960).[1] This striking leap forward, which was recognized by the award of the Nobel Prize in Chemistry to R. B. Woodward in 1965,[2] was followed by an equally dramatic scientific advance during the past three decades, in which chemical synthesis has been raised to a qualitatively higher level of sophistication. Today, in many laboratories around the world chemists are synthesizing at an astonishing rate complex carbogenic structures which could not have been made effectively in the 1950's or early

1960's. This advance has been propelled by the availability of more powerful conceptual processes for the planning of chemical syntheses, the use of new chemical methods, in the form of reactions and reagents, and the advent of improved methods for analysis, separation and determination of structure. Many talented investigators all over the world have contributed to the latest surge of chemical synthesis. Their efforts constitute a collective undertaking of vast dimensions, even though made independently, and their ideas and discoveries interact synergistically to the benefit of all. I am happy to have been selected by the Nobel Committee for contributions to the science of chemical synthesis, but I am even more pleased that this important field of science has again received high recognition.

Genesis

In the fall of 1947, as an undergraduate at the Massachusetts Institute, I took a course in Advanced Synthetic Organic Chemistry, taught by the distinguished chemist A. C. Cope, in which the major reactions of synthesis were surveyed. It was explained that very few new synthetic methods remained to be found, since only five important reactions had been discovered in the preceding fifty years; and we students were advised to learn how to devise chemical syntheses using the available portfolio of known constructions. We were given numerous molecular structures as synthetic problems. After doing a few of the problem sets, I had developed sufficient skill and experience to handle all of the remaining assignments with ease, much as I had learned to use the English language, to prove mathematical theorems, or to play chess. My new found competence in chemical problem solving seemed to result from an automatic "know how" rather than from the conscious application of well-defined procedures. Nonetheless, even though I had mastered the classical reactions, designing syntheses of molecules beyond the modest level of complexity of these instructional problems still eluded me. Molecules such as morphine, cholesterol, penicillin, or sucrose were so forbidding that they defined the frontiers of 1947; each seemed to be unique and to require a very high level of creativity and invention. Much of my research over the years has been devoted to probing those frontiers and advancing the level of synthetic science by an approach consisting of three integral components: the development of more general and powerful ways of thinking about synthetic problems, the invention of new general reactions and reagents for synthesis, and the design and execution of efficient multistep syntheses of complex molecules at the limits of contemporary synthetic science.

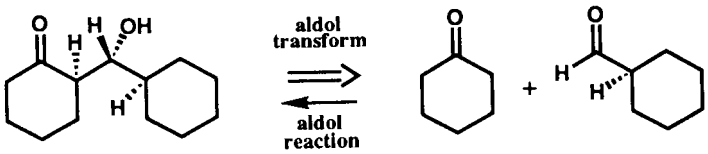
Retrosynthtic Analysis

During the first half of this century most syntheses were developed by selecting an appropriate starting material, after a trial and error search for commercially available compounds having a structural resemblance to the target of synthesis. Suitable reactions were then sought for elaboration of the chosen starting material to the desired product. Synthetic planning in

most instances was strongly dependent on an assumed starting point. In the fall of 1957 I came upon a simple idea which led to an entirely different way of designing a chemical synthesis. In this approach the target structure is subjected to a deconstruction process which corresponds to the reverse of a synthetic reaction, *so as to convert that target structure to simpler pecursor structures, without any assumptions with regard to starting materials.* Each of the precursors so generated is then examined in the same way, and the process is repeated until simple or commercially available structures result. This "retrosynthetic" or "antithetic" procedure constitutes the basis of a general logic of synthetic planning which was developed and demonstrated in practice over the ensuing decade.[3, 4, 5] In an early example, retrosynthetic planning for the tricyclic sesquiterpene longifolene (1) (Chart I) produced several attractive pathways for synthesis, one of which was selected and validated by experimental execution.[6] The basic ideas of retrosynthetic analysis were used to design many other syntheses and to develop a computer program for generating possible synthetic routes to a complex target structure without any input of potential starting materials or intermediates for the synthesis.[4, 5] The principles of retrosynthetic analysis have been summarized most recently in the textbook, "The Logic of Chemical Synthesis"[7] which was written for advanced undergraduate and graduate students of chemistry. The retrosynthetic way of thinking about chemical synthesis also provided a logical and efficient way to teach synthetic planning to intermediate and advanced students, a good example of the intimate link between teaching and research in an academic setting. A brief synopsis of the retrosynthetic planning of syntheses will now be given.

Retrosynthetic[8] (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. Such trees, called EXTGT trees since they grow out from the TGT, can be quite complex since a high degree of branching is possible at each node and since the vertical pathways can include many steps. This central fact implies the need for strategies which control or guide the generation of EXTGT trees so as to avoid explosive branching and the proliferation of useless pathways.

Each retrosynthetic step requires the presence of a target structure of a keying structural subunit or *retron* which allows the application of a particular transform. For example, the retron for the aldol transform consists of the subunit HO-C-C-C=O, and it is the presence of this subunit which permits transform function, e.g. as follows:



Transforms vary in terms of their power to simplify a target structure. The most powerful of simplifying transforms, which reduce molecular complexity in the retrosynthetic direction, occupy a special position in the hierarchy of all transforms. Their application, even when the appropriate retron is absent, may justify the use of a number of non-simplifying transforms to generate that retron. In general, simplifying transforms function to modify structural elements which contribute to molecular complexity: molecular size, cyclic connectivity (topology), stereocenter content, element and functional group content, chemical reactivity, structural instability, and density of complicating elements.

Molecular complexity is important to strategy selection. For each type of molecular complexity there is a collection of general strategies for dealing with that complexity. For instance, in the case of a complex polycyclic structure, strategies for the simplification of the molecular network, i.e. topological strategies, must play an important part in transform selection. However, the most efficient mode of retrosynthetic analysis lies not in the separate application of individual strategies, but in the concurrent application of as many different independent strategies as possible.

The major types of strategies[7] which are of value in retrosynthetic analysis may be summarized briefly as follows.[8]

1. Transform-based strategies - long range search or look-ahead to apply a powerfully simplifying transform (or a tactical combination of simplifying transforms) to a TGT with certain appropriate keying features. The retron required for application of a powerful transform may not be present in a complex TGT and a number of antithetic steps (subgoals) may be needed to establish it.
2. Structure-goal strategies - directed at the structure of a potential intermediate or potential starting material. Such a goal greatly narrows a retrosynthetic search and allows the application of bidirectional search techniques.
3. Topological strategies - the identification of one or more individual bond disconnections or correlated bond-pair disconnections as strategic. Topological strategies may also lead to the recognition of a key substructure for disassembly or to the use of rearrangement transforms.
4. Stereochemical strategies - general strategies which clear, *i.e.* remove, stereocenters and stereorelationships under stereocontrol. Such stereocontrol can arise from transform-mechanism control or substrate-structure control. In the case of the former the retron for a particular transform contains critical stereochemical information (ab-

solute or relative) on one or more stereocenters. Stereochemical strategies may also dictate the retention of certain stereocenter during retrosynthetic processing or the joining of atoms in three-dimensional proximity. A major function of stereochemical strategies is the achievement of an experimentally valid clearance of stereocenters, including clearance of molecular chirality.

5. Functional group-based strategies. The retrosynthetic reduction of molecular complexity involving functional groups (FG's) takes various forms. Single FG's or pairs of FG's (and the interconnecting atom path) can key directly the disconnection of a TGT skeleton to form simpler molecules or signal the application of transforms which replace functional groups by hydrogen. Functional group interchange (FGI) is a commonly used tactic for generating the retrons of simplifying transforms from a TGT. FG's may key transforms which stereoselectively remove stereocenters, break topologically strategic bonds or join proximate atoms to form rings.
6. "Other" types of strategies. The recognition of substructural units within a TGT which represent major obstacles to synthesis often provides major strategic input. Certain other strategies result from the requirements of a particular problem, for example a requirement that several related target structures be synthesized from a common intermediate. A TGT which resists retrosynthetic simplification may require the invention of new chemical methodology. The recognition of obstacles to synthesis provides a stimulus for the discovery of such novel processes. The application of a chain of hypotheses to guide the search for an effective line of retrosynthetic analysis is important.

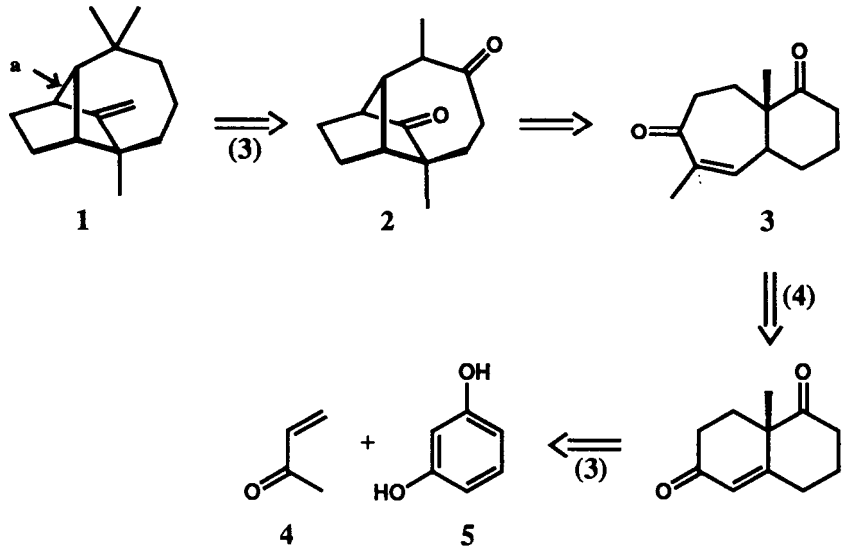
Other strategies deal with optimization of a synthetic design after a set of pathways has been generated antithetically, specifically for the ordering of synthetic steps, the use of protection or activation steps, or the determination of alternate paths.

Systematic and rigorous retrosynthetic analysis is the *broad principle* of synthetic problem solving under which the individual strategies take their place. Another overarching idea is the use *concurrently* of as many independent strategies as possible to guide the search for retrosynthetic pathways. *The greater the number of strategies which are used in parallel to develop a line of analysis, the easier the analysis and the simpler the emerging synthetic plan is likely to be.*[10]

An abbreviated form of the 1957 retrosynthetic plan for the synthesis of longifolene (1) is shown in Chart I. Changes in the retrosynthetic direction are indicated by a double arrow (⟹) to distinguish them from the synthetic direction of chemical reactions (→) and the number below indicates the number of transforms required for the retrosynthetic change if greater than one. The selection of transforms was initially guided by a topological strategy (disconnection of bond *a* in 1). The Michael transform, which simplifies structure 2 to precursor 3, can be found by general transform selection procedures.[5,9] The starting materials for the synthesis which

emerge from retrosynthetic analysis, 4 and 5, have little resemblance to the target structure 1.

A detailed explanation of this example of retrosynthetic analysis has been given. [6b, 10] During the past 20 years systematic retrosynthetic thinking has permeated all areas of carbogenic synthesis. It is no longer possible to teach the subject of carbogenic synthesis effectively without the extensive use of retrosynthetic concepts and thinking.



Retrosynthetic Analysis For Longifolene (1957)

Chart I

Computer-Assisted Retrosynthtic Analysis

The use of computers to generate possible pathways for chemical synthesis, which was first demonstrated in the 1960's, [4,5,9,11] was made possible by the development of the retrosynthetic methods outlined above and the required computer methodology. Graphical input of structures by hand drawing using an electrostatic tablet and stylus, in the natural manner of a chemist, and output to a video terminal[4,12] provided an extraordinarily simple and effective interface between chemist and machine. Chemical structures were represented in the machine by means of atom and bond tables, and manipulated by appropriate instructions. Algorithms were devised for perception by machine of structural features, patterns, and subunits which are needed for synthetic analysis. Techniques were developed for storage and retrieval of information on chemical transforms (including retron recognition and keying) using a higher level "chemical English" language. The program (LHASA) was designed to be interactive, with any level of control or input desired by the user, and to emulate the problem-

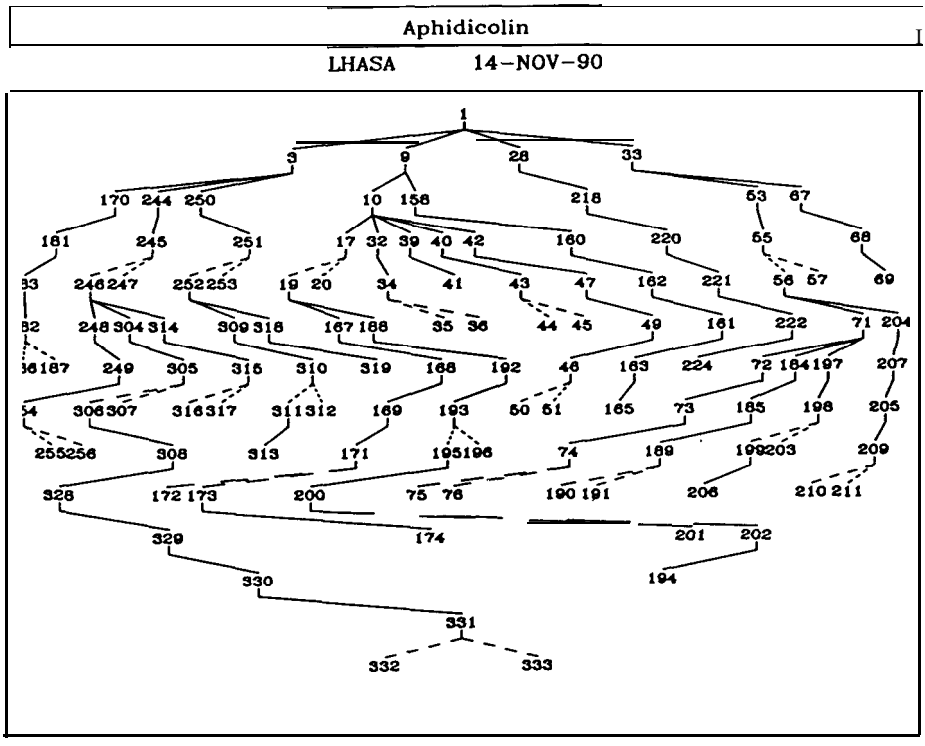


Chart II

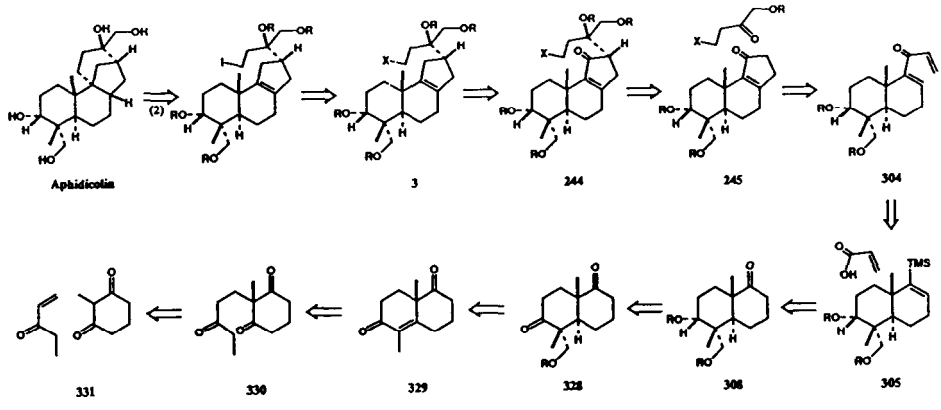


Chart III

solving approaches of synthetic chemists. The chemical knowledge base, written so as to be intelligible to a practicing chemist, contains all the types of information required for generation and evaluation of retrosynthetic changes, for example, data on individual transforms and their mechanisms, scope, and limitations. The performance of the program is below that which should eventually be possible because of the immensity of the task and the modest size of our research effort. However, despite present limitations, including a modest knowledge base of about 2000 transforms, LHASA is capable of providing interesting suggestions of synthetic pathways for challenging targets. The present level of capability of LHASA can best be appreciated by its performance on specific problems. Shown in Chart II is the EXTGT tree generated by LHASA for the antiviral agent aphidicolin, using just one particular line of analysis. The pathway in this tree from intermediates 332 and 333 to aphidicolin consists of the structures shown in Chart III.[13] The suggestion by LHASA of such non-obvious pathways is both stimulating and valuable to a chemist.

The field of computer assisted synthetic analysis is fascinating in its own right, and surely one of the most interesting problems in the area of machine intelligence. Because of the enormous memory and speed of modern machines and the probability of continuing advances, it seems clear that computers can play an important role in synthetic design. However, before that potential can be realized, many difficult computing problems must be solved. Multistep retrosynthetic look-ahead, even under strategic guidance, requires complex and powerful software. Vast amounts of information - structural, stereochemical, and chemical - must be generated and analyzed using all available chemical knowledge. A massive undertaking will be required.

New Synthetic Methodology and Multistep Synthesis of Complex Molecules

The invention of new reactions and reagents has revolutionized the field of carbogenic synthesis, literally placing an extraordinarily powerful new chemistry alongside the classical reactions of the pre-1950 period. Without this methodology, the achievements of modern chemical synthesis would not have been possible. Two early landmarks in this advance, the discovery of the Wittig synthesis of olefins and the hydroboration of olefins, were highlighted by the award of the Nobel Prize in Chemistry for 1979 to G. Wittig and H. C. Brown. More recent developments have provided many methods which are noteworthy for their great chemical selectivity and stereochemical control and for their suitability in the construction of complex molecules. Indeed, many new synthetic processes have been discovered as a result of a perceived need in connection with specific problems involving novel or complicated structures and a deliberate search for suitable methodology. The rational design of such methods depends on the use of mechanistic reaction theory, stereochemical principles, and a wide range of chemistry involving many elements and ephemeral reactive intermediates.

A key to the success of many of the multistep chemical syntheses which

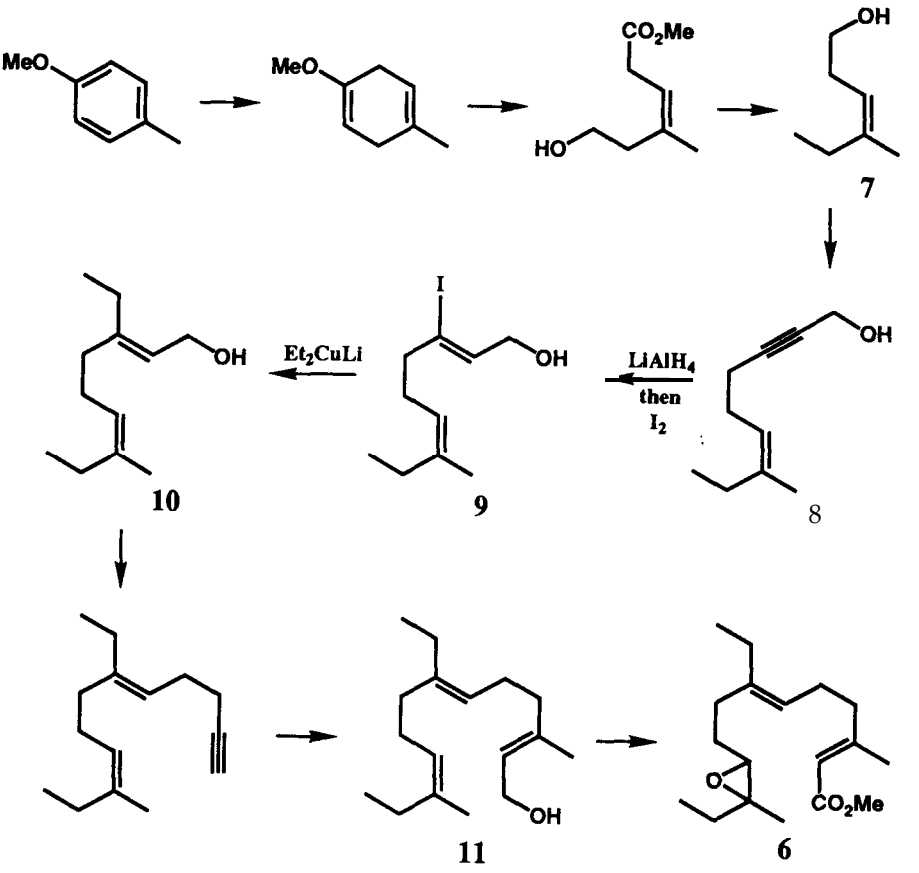


Chart IV

have been demonstrated in our laboratories over the years has been the invention of new methodology. Since more than fifty such methods have been developed in our laboratory, it is impossible to summarize this aspect of synthetic research in a brief article. However, a few examples may serve to illustrate the effectiveness of these new methods in providing access to rare and valuable carbogenic compounds and their impact on the whole field of chemical synthesis.

The discovery and identification of the insect juvenile hormone of *Cecropia,* now known as JH-I)[14] in 1967 generated immense interest because of the potential of such nontoxic compounds for insect control." Chemical synthesis was essential because of the extreme paucity of material from natural sources. Despite the apparent simplicity of structure 6, a stereospecific route for the synthesis was not obvious, because no general methods existed in 1967 for the stereocontrolled generation of the trisubstituted olefinic units which it contains. The first stereospecific synthesis of 6[16] was possible using new methodology which was specifically devised for this

application. An abbreviated version of the synthesis is shown in Chart IV. The first olefinic intermediate (**7**) was synthesized **from *p*-methoxytoluene** in a way which guarantees the Z-configuration of the stereocenter. Reaction of **8** with $LiAlH_4$ (*trans* hydroalumination) followed by iodine (replacement of Al by I) produced **9** stereospecifically by a novel sequence.[16] The replacement of iodine in **9** by ethyl was effected by another new process, cross coupling of a vinylic iodide with an organocopper reagent, which provided **10** stereospecifically. A completely analogous series of reactions converted **10** to triene **11**, from which JH-I (6) was obtained by a novel selective oxidation sequence. Thus, the synthesis outlined in Chart IV depended on no less than four new synthetic methods. Three of these methods have come into very general use. The coupling of carbon groups using organocopper chemistry is now a major method of chemical synthesis.[17] The related carbometallation of acetylenes, also developed in connection with the synthesis of **6**,[16b,18] has been extended in many directions, and this approach has become commonplace for the stereospecific construction of trisubstituted double bonds, a frequently occurring type of structural unit in biologically active natural substances.

The ready availability of the insect juvenile hormone **6** permitted a wide range of biological studies and an understanding of the best ways of using such "third generation" agents for insect control. Inexpensive synthetic mimics of insect juvenile hormone are now produced commercially as environmentally safe insect control products.

Numerous naturally occurring microbial substances, especially antibiotics, are members of the "macrolide" structural family and contain a lactone functional group as part of a many membered ring. The key to the successful synthesis of complex macrolides such as erythronolide B (**12**), the precursor of the erythromycin antibiotics, was the development of new methodology for macrolactone ring formation (Chart V). Our group developed a very mild, effective and general method for this synthetic operation, the double-activation method, [19] which subsequently has been widely used. Thio-ester **13**, produced by total synthesis,[20] was converted to macrolactone **15** simply by heating in toluene solution. Internal proton transfer in **13** generates the internal ion pair **14**, which is doubly activated for the internal carbonyl addition required for ring closure to **15**. Erythronolide B was obtained from **15** by a simple reaction sequence.[20] The double-activation method has been used effectively for the synthesis of a number of other remarkable natural macrocyclic lactones (Chart V) including brefeldin A (**16**), an inhibitor of protein transport and processing in mammalian cells,[21] the microbial iron transporter enterobactin (**17**),[22] and the marine eicosanoid, hybridalactone (**18**).[23]

Bilobalide (**19**) is a complex and unusual molecule produced by the ginkgo tree, *Ginkgo biloba.* An effective synthesis of **19** was made possible by the development of a remarkable reaction for the formation of five-membered rings (Chart VI).[24] The readily available chiral diester **20** was converted by Claisen acylation to the acetylenic keto diester **21**. Treatment of **21**

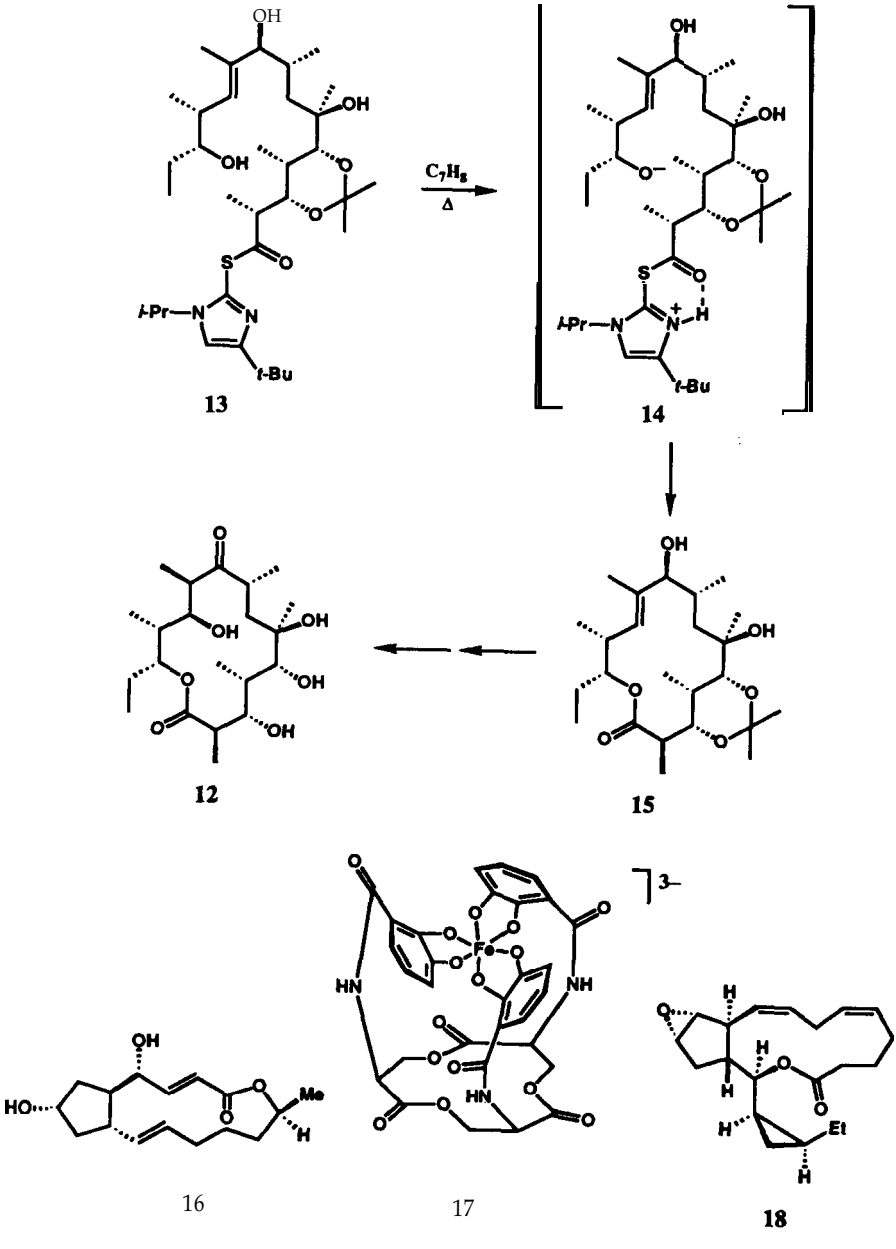


Chart V

with base effected a novel ring closure to give the bicyclic ketone 22, which was then transformed into bilobalide (19) by a multistep sequence. There are several variants on this cyclization methodology which demonstrate considerable scope.[25]

A wide range of reagents and reactants have played a role in the new methodology developed in our group: transition metals; metal-ion complexes; and silico, sulfo, boro, alumino, phospho, and stanno carbogens. The new general methods which have resulted include processes for ring formation, chain extension, oxidation, reduction, functional group transformation, activation, protection, and stereochemical control.

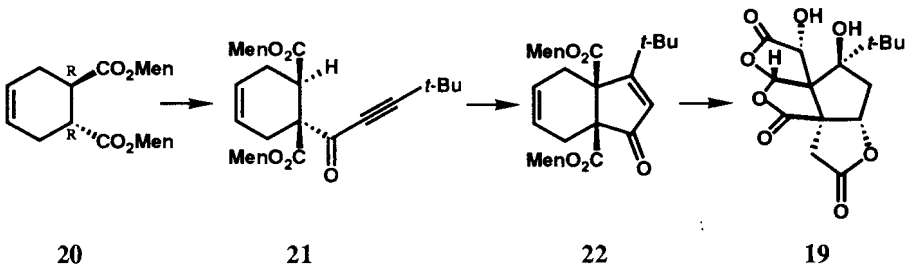


Chart VI

Multistep Synthesis - General

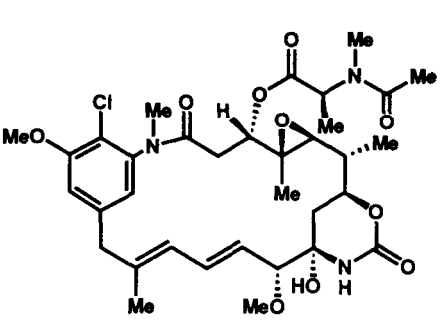
To a synthetic chemist, the complex molecules of nature are as beautiful as any of her other creations. The perception of that beauty depends on the understanding of chemical structures and their transformations, and, as with a treasured work of art, deepens as the subject is studied, perhaps even to a level approaching romance. It is no wonder that the synthetic chemist of today is filled with joy by the discovery of a new naturally occurring structure and the appearance of yet another challenge to synthesis. It makes no difference that the realization of a difficult synthesis entails long hours of study, thought and physical effort, since a complex chemical synthesis is an exciting adventure which leads to a beautiful creation. I believe that the case for molecular synthesis, as a high intellectual endeavor and as a scientific art form, can stand on these merits. The chemist who designs and completes an original and esthetically pleasing multistep synthesis is like the composer, artist or poet who, with great individuality, fashions new forms of beauty from the interplay of mind and spirit.

It is fortunate that molecular synthesis also serves the utilitarian function of producing quantities of rare or novel substances which satisfy human needs, especially with regard to health, and the scientific function of stimulating research and education throughout the whole discipline of chemistry.

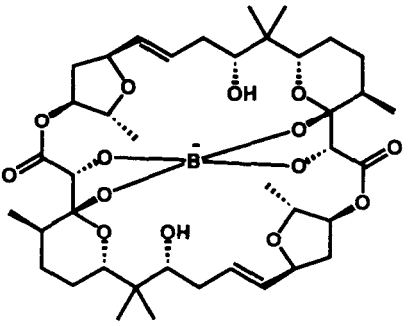
Our research group has been responsible for the creation of more than one hundred new multistep syntheses of interesting molecules, our sonatas and string quartets. The step-by-step construction of most of these targets of synthesis is outlined in the *"Logic of Chemical Synthesis"*[7] and is discussed in detail in the original research papers referred to therein. The structures of a small, and somewhat random, selection of these synthetic targets are shown in Charts VII a and VII b. A few comments will be given here on the syntheses of each of these to provide an overview of this aspect of our research.

Maytansine [26a] and aplasmomycin,[26b] each scarce and therapeutically interesting, were synthesized enantioselectively and with control of stereochemistry using novel methodology for assembling the molecular skeleton and for forming the macrocyclic unit. These syntheses and that of erythronolide B [19 26c] provided early demonstrations that such complex, macrocyclic molecules can be made efficiently by multistep total synthesis.

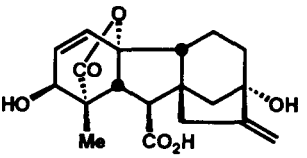
Gibberellic acid resisted total synthesis, despite studies in several leading laboratories, for more than two decades because of an unusually forbidding arrangement of structural subunits. The first successful synthesis, and subsequent improved versions, [26d] required a deep and complex retrosynthetic analysis[26e] and a number of new concepts and methods. An entirely different strategic approach was utilized for the first synthesis of the biosynthetically related plant regulator antheridic acid[26f] which confirmed the proposed gross structure and clarified the stereochemistry. The availability of synthetic antheridic acid is essential to the further study of this rare and potent plant hormone.



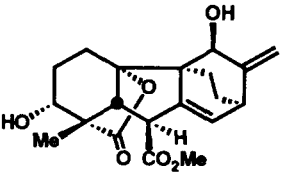
Maytansine



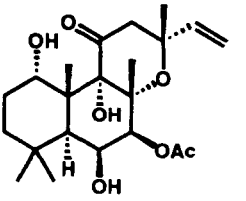
Aplasmomycin



Gibberellic Acid



Antheridic Acid



Forskolin

Chart VII a

Forskolin, the first known activator of the enzyme adenylate cyclase, is a promising therapeutic agent which is available only in limited quantity from plant sources. An efficient multistep synthesis of forskolin, which is both enantio- and stereocontrolled, has been developed[26g] based on several new synthetic methods. The synthesis of picrotoxinin, known since 1811 and a potent inhibitor of the neurotransmitter **γ-aminobutyric** acid, would not have been possible without retrosynthetic analysis and new methodology.[26h] Perhydrohistrionicotoxin, a rare and highly bioactive alkaloid from poison-

ous frogs, is a useful tool in neuroscience which was easily produced by total synthesis. [26i]

Pseudopterosin E,[26j] a powerful antiinflammatory agent, and venustatriol,[26k] an antiviral agent, are biosynthesized by marine organisms in only trace amounts. Both are available in chiral form by efficient enantiocontrolled multistep syntheses.

Last, but no means least, in this brief summary of our studies on the total synthesis of complex molecules, is the case of ginkgolide B, an unusual substance for several reasons. Ginkgolide B is biosynthesized in the roots of the unique and ancient ginkgo tree, *Ginkgo biloba,* by an extraordinarily complex biosynthetic process, for reasons that are unknown. It is an active

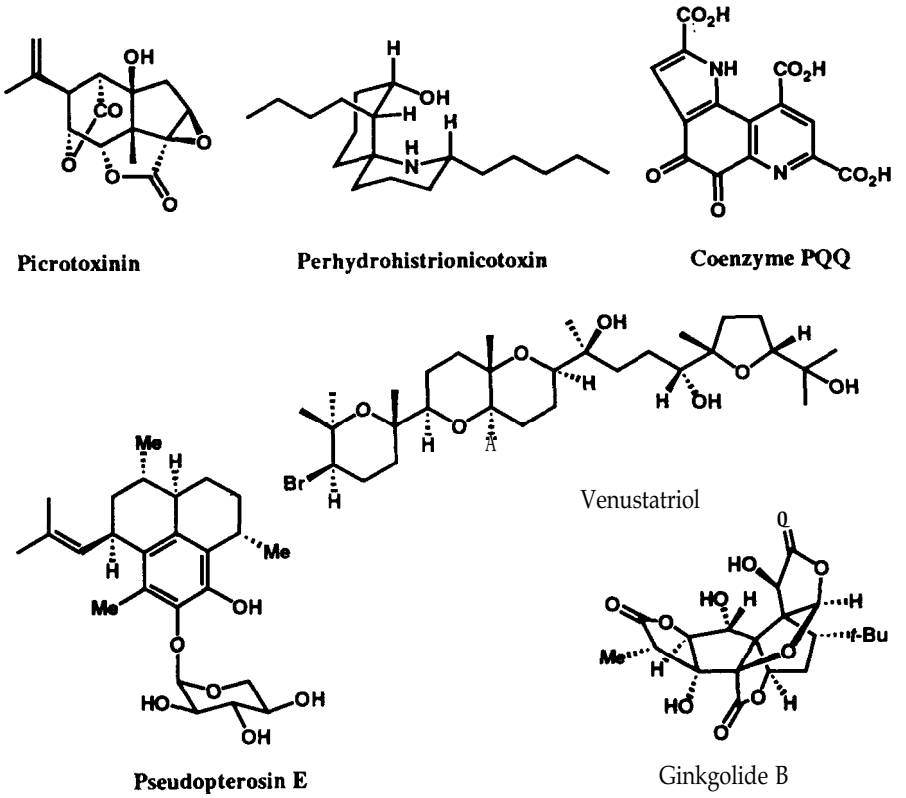


Chart VII b

ingredient in the medicinal extract of ginkgo which is now widely used in oriental and western medicine. The total synthesis of ginkgolide B posed a challenge for synthesis in the 1980's which was comparable to the most difficult problems of earlier eras, for example, steroids in the 1950's or vitamin B-12 and gibberellic acid in the 1970's. That challenge was met in just three years of research, thanks again to the power of modern retrosynthetic planning and to the invention of new tools for this particular synthesis.[26l,27]

Multistep Synthesis Exemplified - The Prostaglandins

The prostaglandins, the first of the known eicosanoids, were detected as bioactive substances more than fifty years ago. However, it was not until the pioneering work of K. Sune Bergström and his group in Sweden in the 1950's and 1960's that the structures of the various members of the prostaglandin family were determined.[28] For that research Bergström and Bengt Samuelsson received (together with John Vane) the Nobel Prize in Medicine for 1982, and deservedly so since, as has been written of the prostaglandins: "Their actions and the pharmacologic agents that influence their formation affect almost every aspect of medical practice."[29] The occurrence of only trace amounts of prostaglandins (PC's) in mammalian sources and the potent effect of these twenty-carbon carboxylic compounds on muscle and blood vessels indicated the need for an effective synthesis that would make available all of the PG's in ample amounts for the study of their physiologic effects and therapeutic uses. The problem of chemical synthesis was complicated by uncertainties regarding the stability and chemistry of PG's, and the existence of three different families (**PG_1's, PG_2's** and **PG_3's**) each consisting of several members. The first total synthesis of the principal PG's, demonstrated by 1967,[30,31] made available the important members of the first family (PGA_1, PGE_1 and **$PGF_{1\alpha}$**) and allowed an evaluation of their chemical properties which facilitated the design of a general synthetic route to all of the prostaglandins. This general synthesis of prostaglandins provided access to all PG's from a single intermediate, commonly known as the Corey lactone aldehyde.[32,33] In various forms this flexible synthesis has been used by laboratories all over the world to prepare not only naturally occurring PG's but also countless structural analogs on any scale.[34]

The original version of the 1969 general synthesis of PG's is summarized briefly in Chart VIII. The bicycloheptenone **23** was synthesized stereospecifically by a novel Cu(II) catalyzed Diels-Alder reaction followed by alkaline hydrolysis of the resulting adduct. Alkaline peroxide converted **23** to the hydroxy acid **24** which was readily resolved using (+)-ephedrine. Lactonization and functional group interchange operations transformed **24** into the Corey lactone aldehyde **25,** a versatile precursor of all of the PG's and analogs thereof. Enone **26** (Am = C_5H_{11}), produced stereospecilically from **25** by Horner-Emmons coupling, upon reduction with zinc borohydride generated the required 15-*(S)-alcohol* along with the 15-(*R*)-diastereomer which was separated and recycled via **26** to the 15-(*S*)-alcohol. Protection of the hydroxyl groups at C(11) and C(15) afforded the corresponding bistetrahydropyranyl (bis THP) ether, 27. Reduction of the lactone function of **27** to lactol (R_2AlH) and Wittig coupling produced **28** stereospecifically. Acidic hydrolysis of **28** afforded **$PGF_{2\alpha}$** (**30**), whereas oxidation of **28** followed by hydrolysis gave PGE_2(**29**). Hydrogenation of the 5,6-double bond in **28** followed by these same final steps produced **$PGF_{1\alpha}$** and PGE_1. A parallel series of transformations was used to convert **25** to **$PGE_{3\alpha}$** and PGE_3.

Although the 1969 bicycloheptenone route to PG's was highly effective

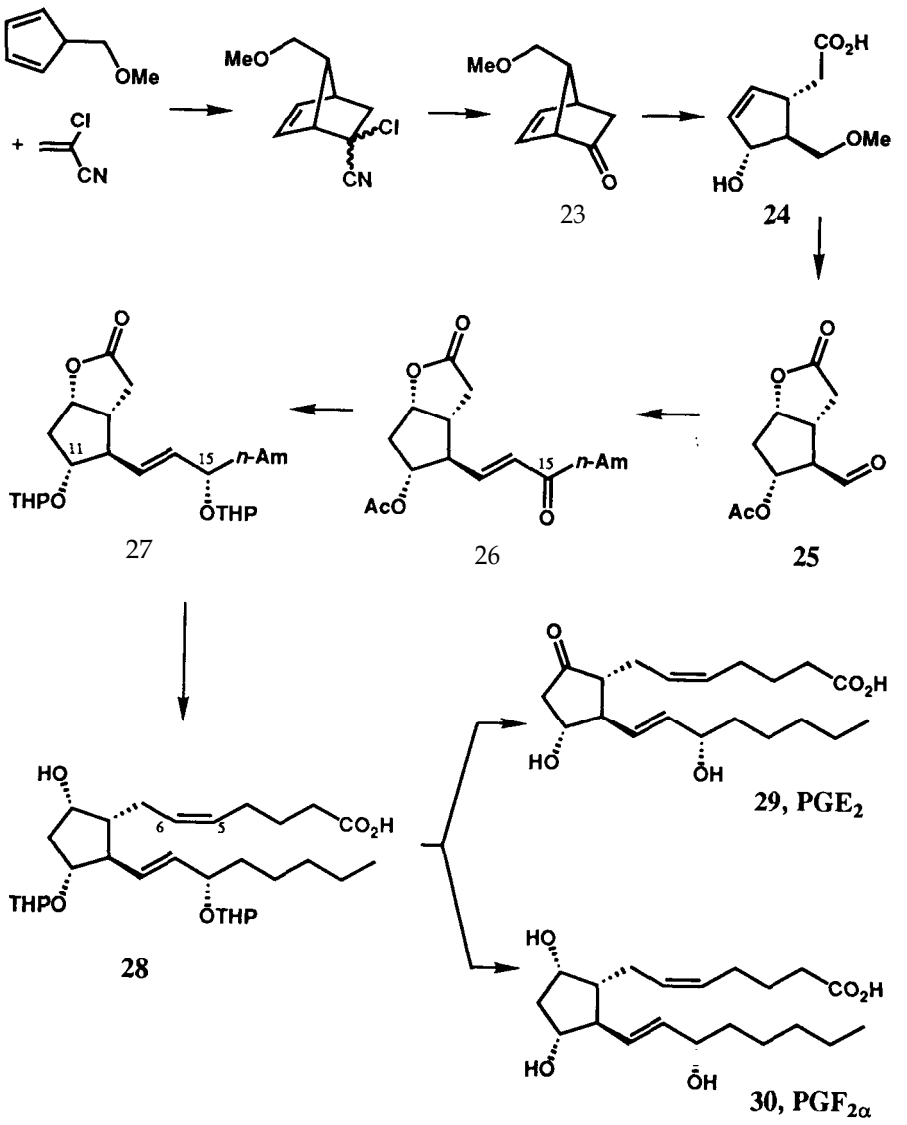


Chart VIII

for the synthesis on a large scale, it was not the ultimate. The Diels-Alder route to **23** produced racemic material which in turn necessitated the resolution of hydroxy acid **24**. Another problem was the lack of stereospecificity in the reduction of the C(15) keto group of **26**. Both of these limitations were overcome by the invention of novel methodology which has simultaneously opened up large new areas of synthetic endeavor.

The problem of controlling the stereochemistry of reduction of the 15-keto group in **26** was solved in a number of different ways (Chart IX). First, the use of a bulky trialkylborohydride reagent with a suitably chosen "controller" group at the C(11) oxygen, for example phenylcarbamoyl, resulted

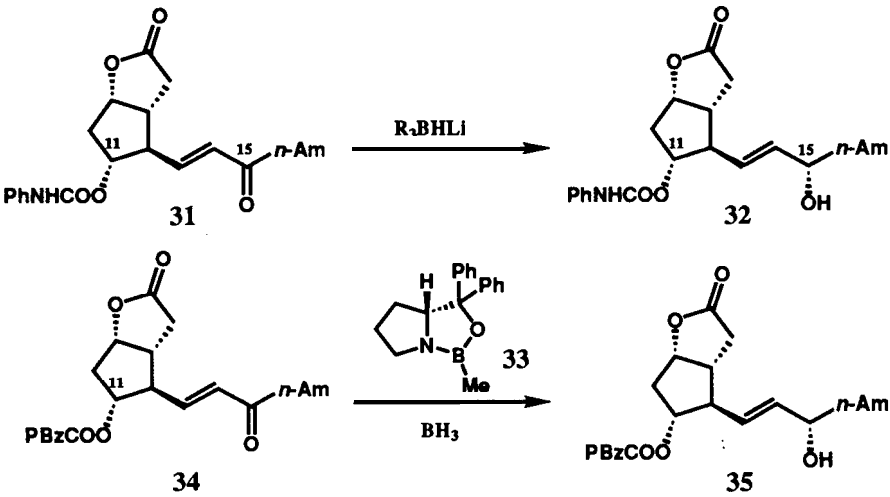


Chart IX

in reduction of C(15) to give the required 15-(*S*) product with greater than 10:1 diastereoselectivity.[33,35] Further, the small amount of 15-(*R*) by-product was easily separated for recycling. Second, using the chiral catalyst **33** (10 mole %) and borane (0.6 mole equivalent) in tetrahydrofuran as solvent at ambient temperature, the 15-ketone **34** was reduced to the 15-(*S*) alcohol **35** with 9: 1 diastereoselectivity.[33,36]

Oxazaborolidine **33** is a remarkable catalytic reagent. It controls the absolute stereochemistry of reduction of a large variety of ketones in addition to accelerating the rate of reduction by borane. The absolute stereochemistry of the reduction product of an achiral ketone R_SCOR_L, where R_S is smaller than R_L, is predictable.[37,38] The observed catalysis and enantioselectivity are in accord with the mechanism outlined in Chart X. The catalyst **33** has been shown to complex with borane stereospecifically to give a species which is activated for binding to the ketonic substrate. Complexation at the sterically more available lone pair of the carbonyl oxygen and internal hydride transfer then leads to the observed enantiomerit secondary alcohol. In this mechanism the reagent **33** literally acts like a *molecular robot:* It first picks up and holds one of the reactants, BH_3, and becomes activated toward the other. It attaches to the ketone in a precise three dimensional assembly that facilitates a transfer of hydrogen between the two reactants to form a *specific* enantiomer of the reduction product. The molecular robot finally discharges these products and repeats the reaction cycle. Such action by the small molecule **33** resembles catalysis by enzymes, which can also be regarded as molecular robots. Of course, **33** lacks the substrate-shape and size discrimination of enzymes because it is too small to possess a binding pocket or distal multicontact recognition sites.

The action of the molecular robot **33** represents a new direction for chemical synthesis. In the past, most synthetic constructions have depended

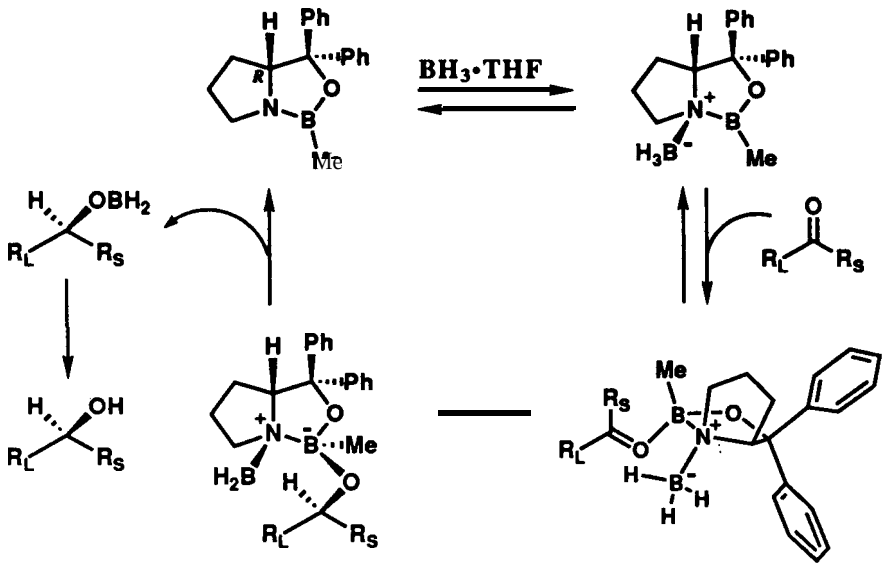


Chart X

on pairwise collisions between reactants without the help of a robot-like assembler. It is likely that synthetic chemistry will produce many new molecular robots in the future as a part of its advance to greater heights.

Two solutions were developed for the enantioselective synthesis of bicycloheptenone 23 (Chart VIII) of the correct chirality for the production of natural prostaglandins. In the first of these, a stereocontrolled aluminium chloride-catalyzed Diels-Alder reaction between benzyloxymethylcyclopentadiene (37) (Chart XI) and the acrylate ester of S-phenylmenthol (36) was used with the result that the required adduct 38 was formed with very high (32: 1) enantioselectivity.[39] Adduct 38 was converted via ketone 23 to iodo lactone 39 which was obtained in enantiomerically pure form in high yield by a single recrystallization and converted to the standard PG intermediate 40. In addition, 8-phenylmenthol was recovered efficiently. The enantioselective formation of 38 can be understood from the geometry shown for the complex **36●A**1 C 1 $_3$ and the steric screening by phenyl of the *si* (rear) face of the acrylate **α,β-double** bond. The efficiency of the S-phenylmenthol controller stimulated the development of other controllers (chiral auxiliaries) for use in enantioselective synthesis.[40]

More recently, this achievement has been surpassed by the development of a *molecular robot* which assembles the achiral components, as shown in Chart XII, to give the required Diels-Alder adduct in 94 % yield and almost 50: 1 enantioselectivity.[38,41] Conversion to enantiomerically pure iodolactone 39 was accomplished using standard procedures.[42]

The general synthesis of prostaglandins by the 1969 pathway can now be carried out efficiently and with total stereochemical control, in a way that could not have been foreseen twenty years ago. Such progress augurs well

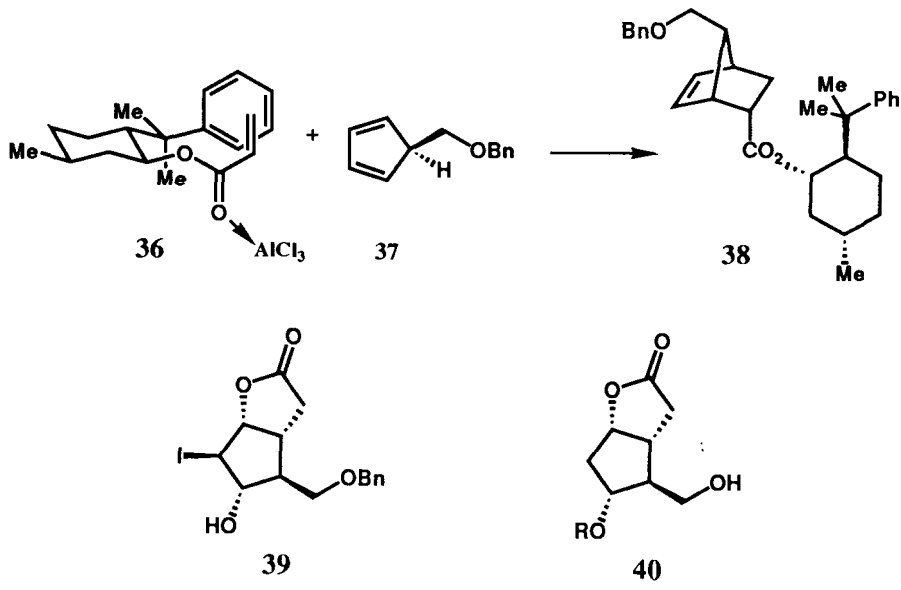


Chart XI

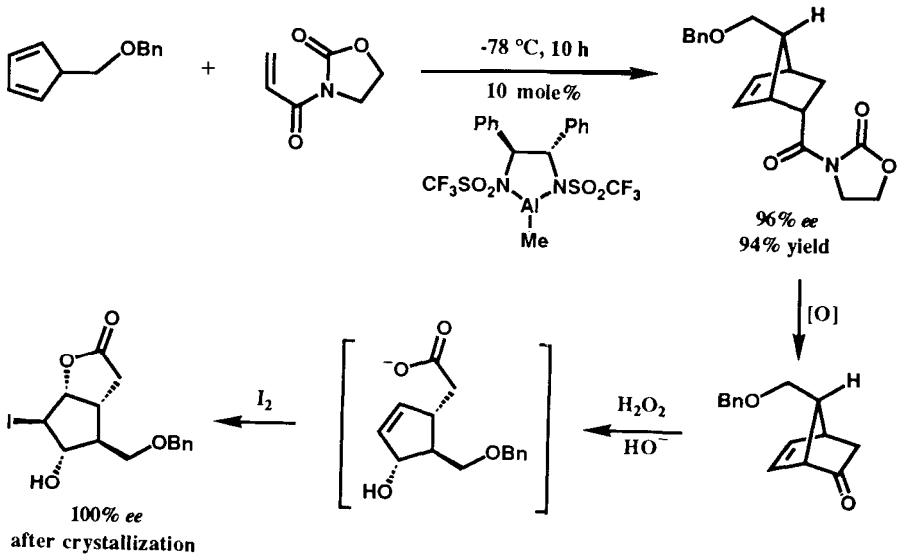
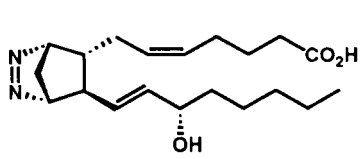


Chart XII

for the future of chemical synthesis. It is not unlikely that today's chemical synthesis, magnificent as it may now appear, will prove to be rudimentary as compared to that of the next century.

The trail of research which originated with the synthesis of prostaglandins was followed for more than two decades, eventually including the synthesis



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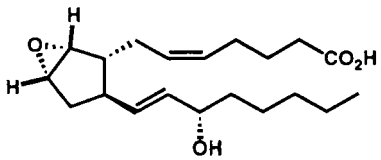
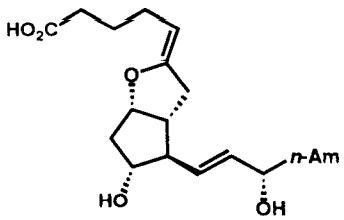
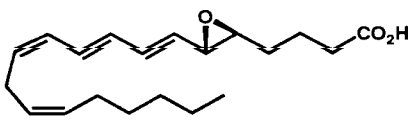


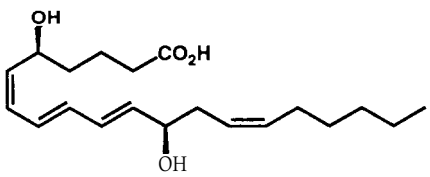
42



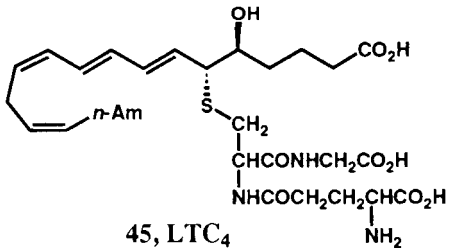
43, PGI_2



44, LTA_4



46, LTB_4



45, LTC_4

Chart XIII

of many other members of the eicosanoid (twenty-carbon) class of mammalian cell regulators. A few of the highlights of this program deserve mention. The biosynthesis of prostaglandins occurs by the oxidative conversion of the C_{20} unsaturated acid arachidonic acid to the bicyclic endoperoxide PGH_2, which serves as a precursor not only of PGE_2 and $PGF_{2\alpha}$, but also of PGI_2 and thromboxane A_2.[43] We were able to synthesize a stable, active azo analog (**41**) of the unstable PGH_2[44] (Chart XIII) and stable, active analogs (e.g. **42**) of the unstable thromboxane A_2,[45] as well as PGI_2 itself (**43**).[46] In 1977 we suggested the structure of the unstable eicosanoid which is known as leukotriene A_4 (LTA_4) (**44**) and, by early 1979, had synthesized that structure in advance of isolation from natural sources.[47] Collaborative research between our group and the Karolinska team headed by Bengt Samuelsson established that LTA_4 combines with glutathione to form the primary "slow reacting substance," now known as LTC_4 (**45**).[47] The detailed stereochemistry of the chemotactic leukotriene LTB_4 (**46**) was first established by synthesis.[47,48] The chemical syntheses of these leukotrienes made these compounds available in quantity for the many hundreds of biological

studies which ensued. Useful new compounds which are active as antagonists of $PGF_{2\alpha}$,[49] thromboxane A_2,[50] and LTB_4,[51] and as inhibitors of leukotriene biosynthesis[52] have also emerged from our synthetic program.

It is my hope that our studies in the eicosanoid field[34] will prove to be a harbinger of future programs in academic synthetic research, since there is an unparalleled opportunity for the application of chemical synthesis to biological and medical problems at a fundamental level.

Acknowledgement

It gives me great pleasure to express my indebtedness to many individuals who deserve credit for the accomplishments summarized herein: my teachers at the Lawrence High School and the Massachusetts Institute of Technology, my colleagues at the University of Illinois and Harvard University, my wonderful collaborators in research, and my very dear family. Research grants from the National Science Foundation, the National Institutes of Health, Pfizer Inc. and numerous other donors have provided the necessary financial support.

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