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Design and Implementation of Tactically Novel Strategies for Stereochemical Control Using the Chiron Approach

Johann Josef Loschmidt (1821-1895): a Forgotten Genius

chemists helping chemists in research & industry

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About Our Cover:

Fig. 1

When our chemist collector bought this painting (oil on canvas, 19 x 22 inches) some years ago, it was a 'wreck' (Fig. 1). Luckily, an art-historian friend had a photograph of this *Presentation in the Temple* as it looked some 100 years ago. Some time since that photograph was taken, the painting was cut down, perhaps because of water or fire damage, the figures of Simon and the baby Jesus were scraped off right down to the canvas, and that area was then overpainted. During restoration of the 'wreck', the figures of Simon and the baby had to be reconstructed. You can read more about this in the *Detective's Eye* described below.

The artist, Jan Lievens, also painted the "St. Paul" on the cover of our current Catalog-Handbook, which contains a brief discussion of the artist in the "About Our Cover". Lievens produced his best works around 1630, when this "Presentation" was painted. It is a beautiful work, and so seems a fitting cover for Professor Hanessian's paper which is also great art, of a different kind.

Jan Lievens has long been very much in the shadow of Rembrandt, even though their early works are comparable in quality. In fact many works by Lievens, such as our *St. Paul,* were long attributed to Rembrandt. Hence this painting is also a fitting cover for Dr. Wiswesser's historical eye-opener which rediscovers the brilliant work of Josef Loschmidt.

NEW

The Detective's Eye: Investigating the Old Masters

Twenty paintings (including the still life on this cover) that have been reproduced on our *Acta* covers and five that have been on our catalog covers were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 - March 19, 1989) for which Isabel and Alfred Bader were guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist-collector's interest in art and connoisseurship as well.

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among the thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historian information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Lab Notes

A common problem when preparing samples for thin-layer chromatography is to find a handy piece of apparatus in which to hold the vials or durum tubes in which the sample is being prepared.

We have recently discovered that Aldrich Suba•Seal septa caps, when inverted, are exactly the correct shape to support tubes of this type. Particularly useful are the 4- and 8-mm septa.

Neil S. Ringan
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Department of Molecular and Life Sciences
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Editor's note: Aldrich carries Suba•Seal septa in both white and red rubber. Please consult the Equipment Section of our Catalog/Handbook.

For some experiments, we have required a supply of air saturated with various different organic vapors at ambient temperature. When the organic liquids were fairly nonvolatile, we experienced difficulty in achieving reproducible concentrations of saturated vapor (as evidenced by glc analysis).

The traditional method of producing saturated vapors involves a gas line in which air is pumped through a series of glass vessels containing organic liquid. We were looking for a simple, rapid and effective method somewhat less cumbersome and easily organized at any point in our laboratories. The solution proved to be very simple.

A Drechsel tube was used to disperse air into an organic liquid contained in a flask immersed in a common ultrasonic laboratory cleaning bath. Sonication provided very efficient vapor production in the flask from which the vapors were passed through a second bubbler held at room temperature outside the ultrasonic bath. This second bubbler serves two purposes: (a) it helps prevent atomized liquid from being carried over and (b) it ensures saturation at ambient temperatures since ultrasonic baths normally operate a few degrees above ambient.

The method is clearly adaptable for the generation of saturated vapors at temperatures other than ambient.

Timothy J. Mason
Paul Sephton
The Sonochemistry Group
Coventry Lanchester Polytechnic
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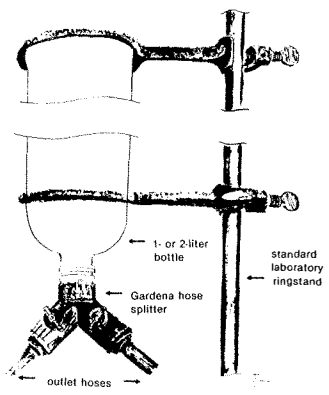
Editor's note: Aldrich lists Bransonic ultrasonic baths. Please check the Equipment Section of our Catalog/Handbook.

If you are tired of the lines at the counter when students are obtaining reagents, or of spills and the inconvenience of reagent bottles and dispensers, or of washing and storing glassware, you may wish to try this teaching tip.

Your local hardware/garden store carries a two-outlet "Y" adapter for outside faucets equipped with two, lever-type, continuous turning control valves. A suitable type of adapter is made by Gardena. The input end just fits on plastic soda (pop) bottles. Prepare your non-caustic solutions, deionized water, dilute acids (or anything that is safe when stored in a plastic container right in the soda bottle), attach the Gardena Y fitting, place a large ringstand ring over the bottle neck, up-end the entire apparatus and suspend on a ringstand with another ring at the top for security (see diagram). Two lines of students can dispense their solutions accurately and easily *without* spillage while controlling the outflow from a dribble to the full flow. If you need a larger volume-flow output, simply poke an air hole in the bottom of the soda bottle. When you are finished with the solution, simply rinse the soda bottle and recycle it. No more washing glassware!



The Gardena Y fits most plastic soda bottles, so you have .5-, 1-, 2- and even 3-liter containers. An extra hose washer has been added to the fittings to prevent leaks, and a 5-cm piece of Tygon® tubing has been connected to each end of the Y to make access easier for the students.

Bob Zafran
Abraham Lincoln High School
555 Dana Avenue
San Jose, CA 95126

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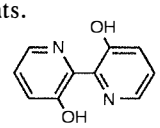
Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Aldrich Boys.

Professor Randy Ruchti of the Department of Physics at the University of Notre Dame suggested that we offer 2,2′-bipyridine-3,3′-diol, a fluorescent dye with a large Stokes shift,[1,2] of interest as a scintillator for the superconducting super collider. Among the advantages of this dye are its photochemical stability and its solubility in many organic solvents.



Naturally, we made it.

(1) Langhals, H.; Pust, S. *Chem. Ber.* **1986,** *118,* 4674.
(2) Sepiol, J.; Bulska, H.; Grabowska, A. *Chem. Phys. Lett.* **1987,** *140,* 607.

It was no bother at all, just a pleasure to be able to help.

Design and Implementation of Tactically Novel Strategies for Stereochemical Control Using the Chiron Approach

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I. INTRODUCTION

As we approach the twenty-first century, the present generation of organic chemists will reflect upon this decade as the turning point in the art of stereocontrolled synthesis. While present-day accomplishments may be regarded as modest in the year 2001, those who will work in the field at that time will have the onus of doing much better. Stereochemical control is not just a requirement nowadays, but a way of life in the laboratory as we strive for the highest optical purity for those targets we choose to synthesize. Biological response is intimately related to enantiomeric purity, a situation which is well appreciated in medicinal chemistry. Stereochemistry is therefore an important link between biology and chemistry. Challenged by this need, and armed with a rapidly expanding wealth in synthetic methodology, numerous research programs dealing with "asymmetric synthesis" were initiated over the past 10 to 15 years.[1] The fruits of these intensive efforts have been in continuing harvest since then, and innovations on many fronts are steadily forthcoming. Today, enantiomeric and diastereomeric excesses for a given transformation of less than 90% are frowned upon, when only a decade ago, attaining such levels was regarded as the sought-for exception. An optical purity of *ca.* 100% is only a relative measure of the true state of affairs, depending on what standard we adopt or what method we use to reach this revered figure. Practically, an optical purity of 90% corresponds to a 95:5 ratio of isomers which may be good enough for a single reaction. A multi-step sequence, however, with each proceeding in 90% optical efficiency, will rapidly lead to a much diminished purity for the final product, unless the "other isomer" can be separated *en route.* Chemists therefore strive to get as close to 100% purity as their methods will allow. Since the dividing line between a 90%-plus optical purity and the expected "maximum" level is tenuous beyond a certain point, other factors such as practicality, efficiency, generality, and overall appeal must be considered.

II. STEREOCHEMICAL CONTROL AND OPTICALLY PURE TARGETS

Controlling the stereochemical outcome of a chemical transformation has always been a major goal for synthetic organic chemists. Nowhere are such needs more manifest than in the synthesis of natural products and molecules of biological interest. Different eras have brought forth increasingly novel targets with correspondingly challenging solutions. While the goals have not changed over the years, the criteria for innovation have. New and often misused terms (*e.g.,* chiral this or that) have become a part of our spoken and oftentimes written lexicon. Bond formation is invariably considered in terms of site and stereochemical selection. While we may never beat nature at her own game of producing a plethora of products, we are becoming increasingly adept in producing what nature normally does not need, or possibly cannot make. This in itself is a major triumph of modern-day organic synthesis, and much of it is due to innovations in stereochemical control. When we consider stereochemical control, we generally focus on a given reaction at a time. However, it is the collection of several such transformations that constitutes a synthetic scheme culminating with the production of an optically pure (or enriched) compound. General synthetic approaches and global strategies to a given target may change depending on the investigator. This shows the individuality, creativity and personal philosophies of the synthetic chemist, and it enriches the subdiscipline of total synthesis enormously. Faced with a given transformation involving stereochemical control, however, opinions and ultimate

Professor Stephen Hanessian (left) receiving the first Canadian Alfred Bader Award in Organic Chemistry from Dr. Alfred Bader.

choices may not be as divergent as in the planning of the overall blueprint. Our common ground is the repertoire of "methods" that we are taught, and will, in turn, continue to teach. However, a blueprint for a synthesis is not an unrelated set of reactions, but a chain of interdependent events.

Stereochemical control in a given reaction relies on the application or exploration of notions and concepts well known in organic chemistry (Figure 1). Depending on the type of bond to be formed, we may exploit certain "effects" that are inherent in or imposed upon the substrate, in order to gain maximum stereochemical control. Coupled with these notions and effects is the proper choice of reaction conditions and an astute power of observation. The combination of all these factors may lead to the design of new reagents, catalysts, etc., hence to what we sometimes loosely refer as "innovation". Truly genuine innovation is rare, even if at first sight it appears to be unprecedented. We are all each other's intellectual feeders, reluctantly interdependent, learning still, yet rebelling for our identities and our place in the system.

At the present time, the main strategies for stereocontrolled synthesis are reagent- or substrate-based and involve either acyclic or cyclic molecules, or combinations thereof.[2] Such templates can be interconverted either before or after the chemical event and the effects listed in Figure 1 are operative here. Thus, with the aid of an "imposed" chiral auxiliary, and implicating notions of chelation, for example, it may be possible to functionalize an acyclic molecule in order to produce a stereochemically pure or enriched product as exemplified by the aldol condensation (Figure 2).[3] Asymmetric induction may also be brought about using external reagents or catalysts as in the Sharpless epoxidation, for example.[4] Cyclic molecules may be manipulated to benefit from a privileged conformation, from steric bias and topological effects. Bond formation in such systems will usually occur with a high level of stereochemical control. Enzymatic and microbial processes, as well as modern biotechnological methods, will play increasingly important roles in the synthetic chemist's repertoire of reagents and methods. A synthetic blueprint may draw upon one or more of these strategies in order to generate optically pure products. It is the judicious choice of such methods, coupled with good "timing" in the sequence, that will determine the optical purity of the final product. As previously mentioned, such issues as efficiency, practicality and overall appeal must be factored

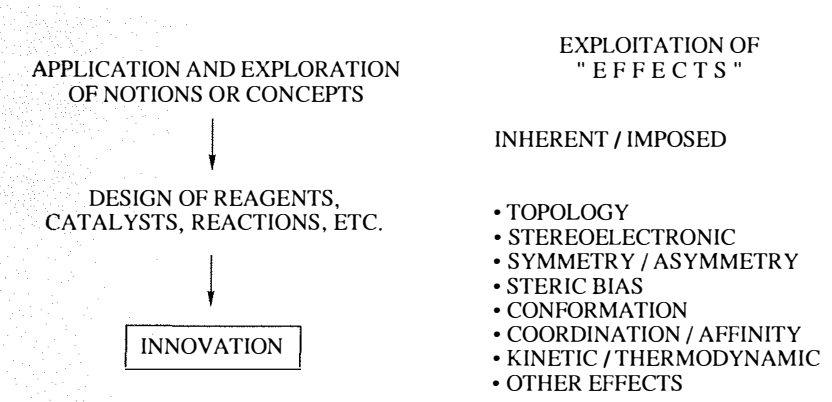


Fig. 1. Stereochemical control in bond formation.

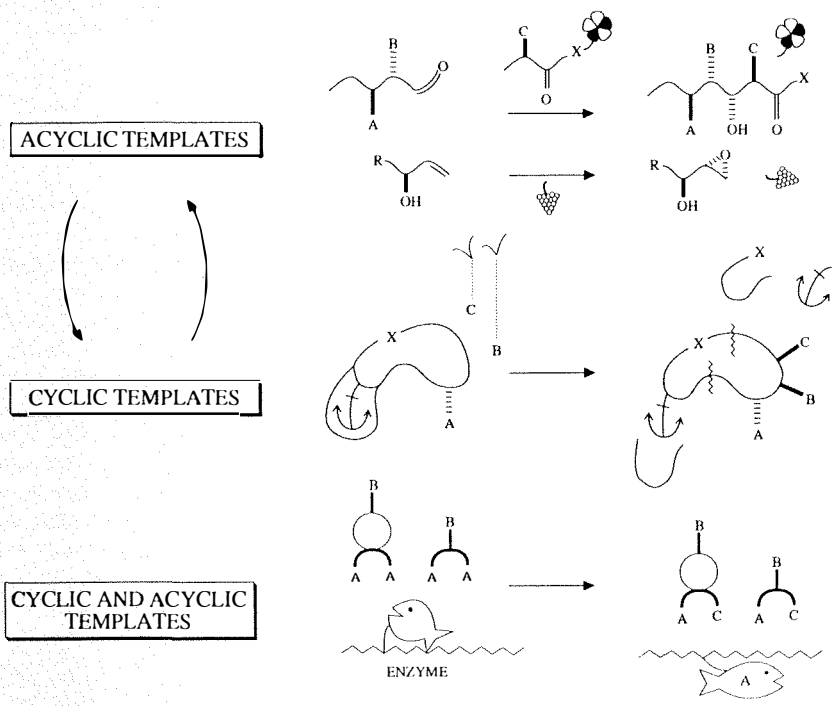


Fig. 2. Strategies for stereochemical control. Homochiral, racemic and achiral substrates.

CHIRON = CHIRal synthON

DEFINITION : AN ENANTIOMERICALLY PURE INTERMEDIATE OR MOLECULE THAT CONTAINS A HIGH LEVEL OF FUNCTIONAL AND STEREOCHEMICAL OVERLAP WITH A SUBSTRUCTURE IN THE TARGET.

TWO BASIC PHILOSOPHIES :

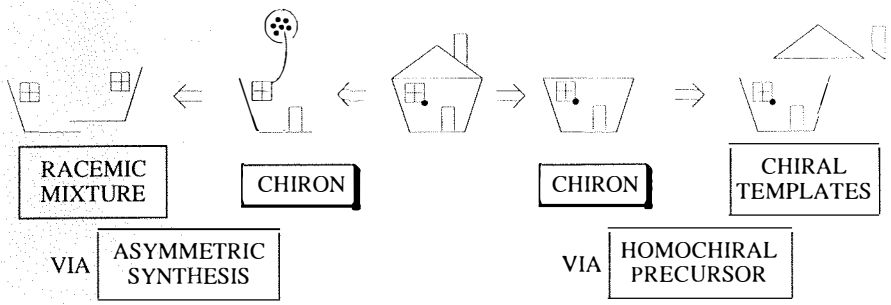


Fig. 3. Access to optically pure targets: the chiron approach.

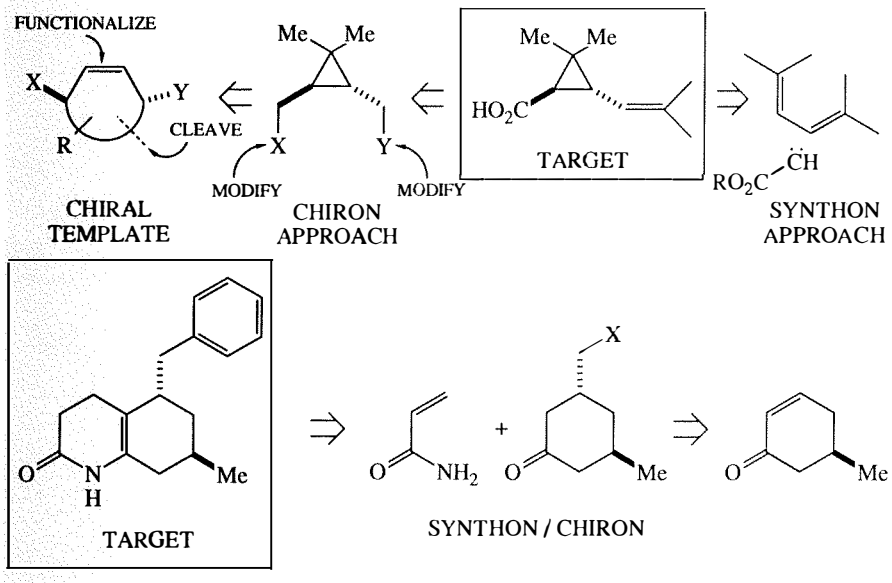


Fig. 4. Chirons and Synthons.

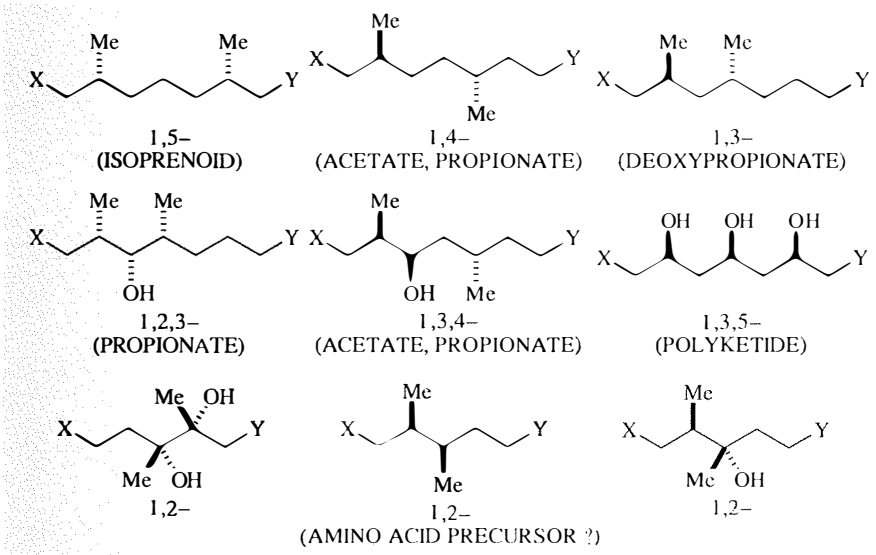


Fig. 5. Vicinal, alternating and remote substitution: toward a general strategy from a single chiral progenitor.

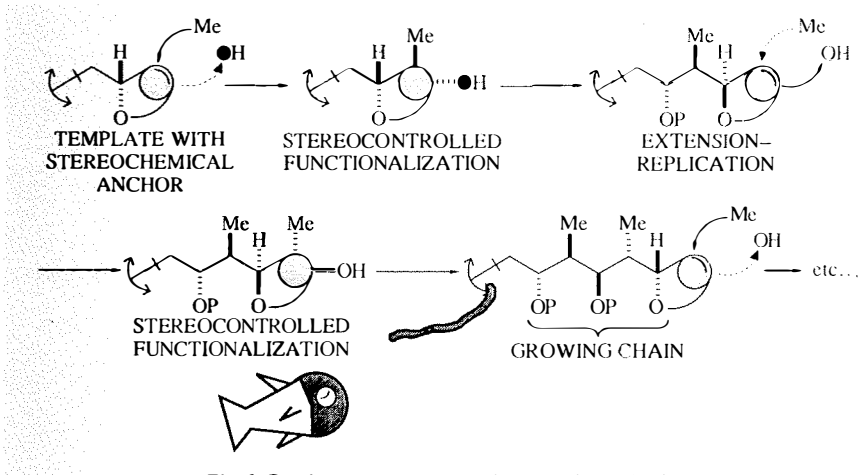


Fig. 6. Propionate- and deoxypropionate-derived subunits.

into a "successful" synthesis. One should not overlook the need, or fail to appreciate the importance of eventually scaling up a given process. It is in such cases that a fundamental contribution to synthesis may be tested against the rigors of process chemistry and the reality of economics in the plant.

III. THE CHIRON AND SYNTHON APPROACHES

A number of years ago, we suggested the term *"chiron"* to describe a *chir*al synth*on*.[5] We define a *chiron* as an enantiomerically pure molecule that contains a good level of functional and stereochemical overlap with a substructure in the target. Although chirons can be obtained from a number of sources, in general they are accessible *via* asymmetric synthesis or preexisting optically pure chiral molecules (templates) (Figure 3).

The *chiron approach* to synthesis involves disconnections of strategic bonds in a target structure with minimum perturbation of chiral centers. A maximum overlap of functional, stereochemical and carbon framework between target (or substructure) and the *chiron* is ideally sought. A *chiron* may lose its resemblance to its progenitor with increasing manipulation to approach the target structure.

The *synthon approach,* first proposed by E.J. Corey[6] and widely used in synthetic operations, involves the generation of idealized fragments, intermediates, *etc.,* by bond disconnections in a retrosynthetic (antithetic) fashion. In the *synthon approach,* disconnections are generally made at logical sites which facilitate bond formation in the forward sense. It is mostly the type of functional group(s) present, and the chemical feasibility or precedent that dictate the strategy. Thus, the presence of a β-hydroxy ketone subunit in the target molecule may indicate an opportunity for an aldol reaction, hence the generation of an aldehyde and an enolate equivalent as synthons. Stereochemical control is expected to be achieved *via* an asymmetric version of the aldol reaction in such a case. The generation of a cyclopropane ring may rely on a classical reaction between a diene and an appropriate carbene. Again, stereochemical issues are not a prime concern, but can be adjusted to control relative, but not absolute stereochemistry (Figure 4).

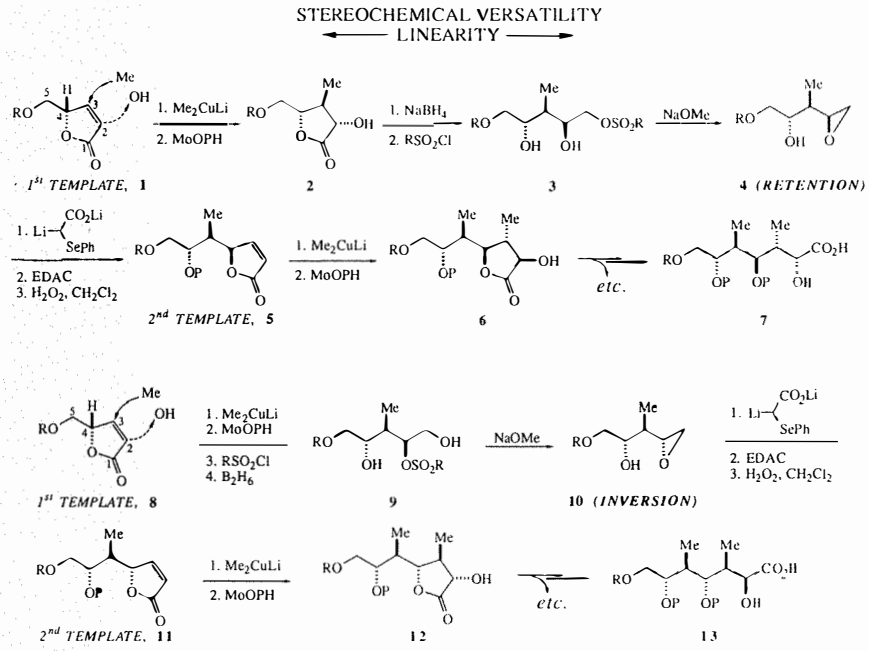
The *chiron approach* also capitalizes on retrosynthetic analysis, except that conservation of stereochemistry during bond disconnection is at a premium. Chiral substructures derived from target molecules

become the primary goals. Here, it is the type of chiral substructure and its possible chiral progenitor that dictate the strategy and the chemistry to be carried out. By relating such substructures to specific chiral starting materials at the onset, the scenario for a strategy is established, the synthetic routes are truncated to a select few, and the main issue becomes one of *how best to proceed in the forward direction from precursor to subtarget.* The *synthon approach,* on the other hand, can lead to a synthesis "tree" with each branch leading to a different starting material, hence a number of possible routes. Philosophically, the differences may appear to be subtle, but operationally they are significant. In some instances, both approaches may converge as shown in Figure 4.

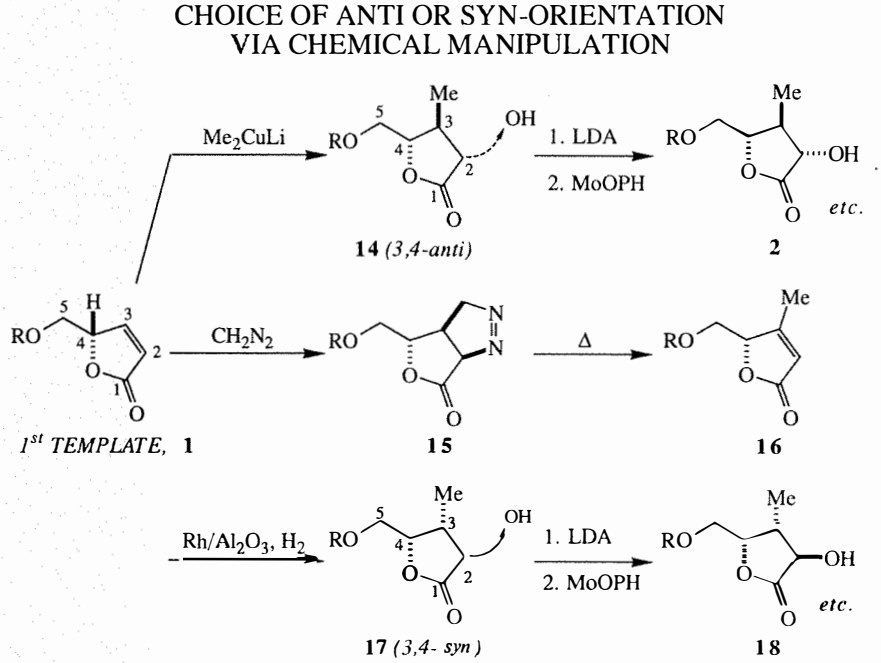
IV. VARIANTS AND ALTERNATIVES TO NATURE'S BIOSYNTHETIC PATHWAYS THROUGH SYNTHESIS

Nature builds her molecules through a set of unique and ingenious biochemical pathways. The mechanisms of these complex reactions have been the object of extensive studies, and a number of pathways to important classes of natural products are well understood. For example, carbon chains containing alternating sequences of C-methyl groups with or without intervening hydroxy groups are produced *via* the so-called polypropionate pathway. The carbon frameworks of a large number of natural products, including therapeutically important antibiotics (*e.g.,* erythromycin) are produced by this pathway. It is also this pattern of substitution that has intrigued synthetic chemists in recent years, particularly with the realization that the aldol condensation is ideally suited for addressing this problem.[3,7] Indeed, important advances in this domain brought forth an exceedingly powerful method for stereochemical control in acyclic carbon chains bearing a set of sequential methyl-hydroxyl-methyl subunits. Other approaches to propionate-derived substructures are also possible using acyclic and cyclic templates.[8] As a consequence, a number of previously unattainable synthetic targets in the macrolide antibiotic area, for example, have gradually succumbed to the might of the modern aldol era and to other powerful methods as well. The C-methyl group can also arise *via* other pathways, and it can be found in different patterns of substitution as shown in Figure 5. Carbon chains containing alternate hydroxy groups arise from the so-called polyketide

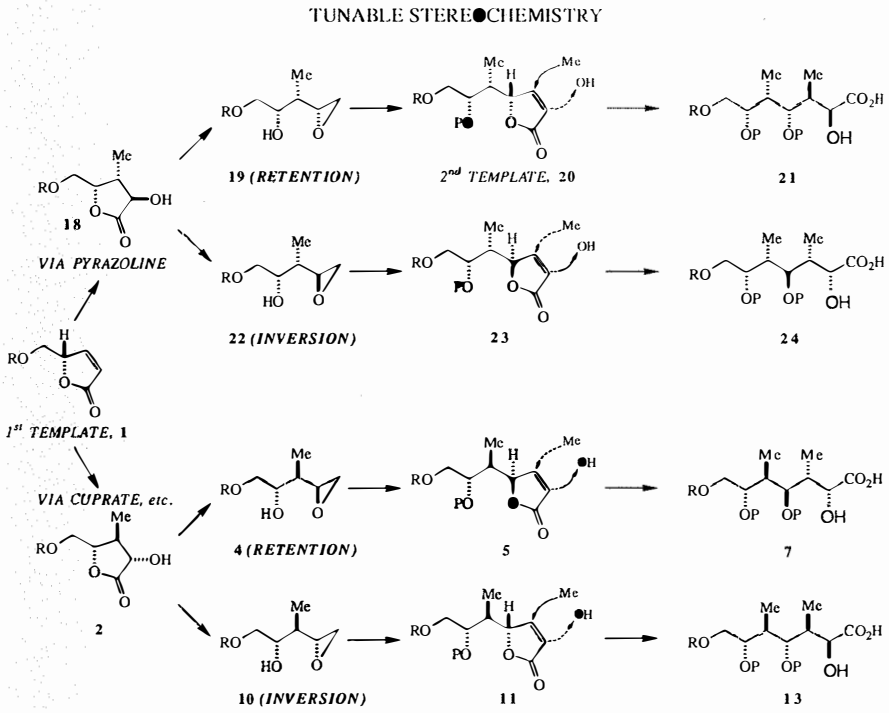
Scheme 1



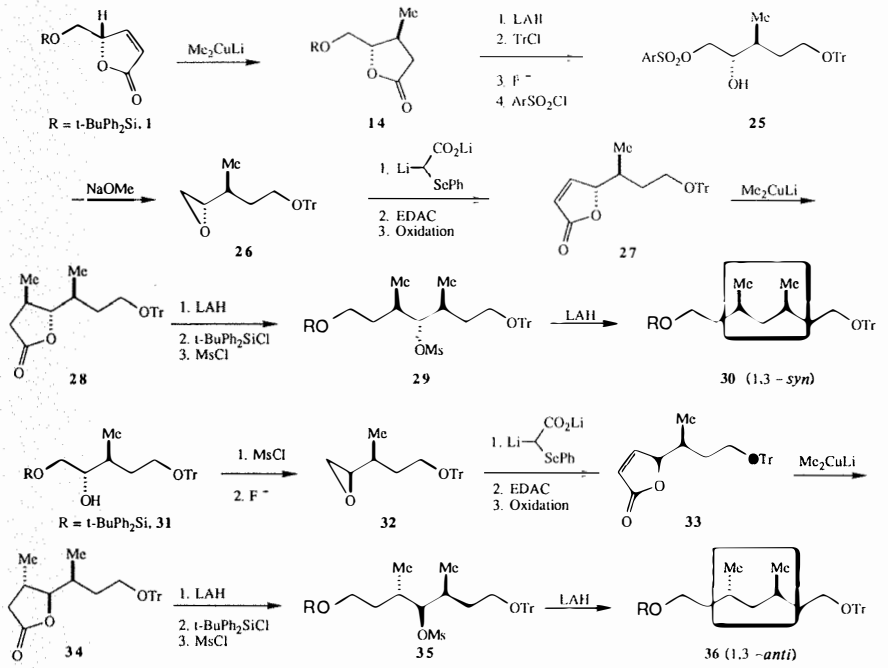
Scheme 2



Scheme 3



Scheme 4



pathway involving reduction of β-dicarbonyl systems.

Ingenious approaches to the stereocontrolled assembly of subunits containing the above-mentioned patterns of substitution have emerged over the past decade. Although very few methods provide *general* applications in this area, most types of polypropionate-derived intermediates can be synthesized with a high level of optical purity *via* the aldol condensation or one of its variants, provided the proper chiral auxiliary is used.[3] Carbohydrates have also been particularly useful in this and related areas, since bond-forming processes have predictable site- and stereoselectivity.[5,9] Several other strategies are also available that address the assembly of carbon chains with multiple stereogenic centers.[7]

Our intention was to find a strategy that would provide a tactically novel alternative to acyclic stereoselection, where virtually *any* combination of C-methyl or hydroxy substitution patterns can be addressed.

V. THE LACTONE REPLICATION STRATEGY FOR ALTERNATE, REMOTE AND VICINAL C-METHYL SUBSTITUTION

1. Alternate C-Methyl Substitution (Propionates and Deoxypropionates)

Our strategy exploits the merits of a γ-lactone template with inherent electrophilic as well as nucleophilic reactivity. Stereochemical control is governed by a bulky substituent present in a position capable of influencing the approach of incoming functional groups as illustrated in Figure 6. Consider a butenolide template with a bulky protective group directly attached to a resident stereogenic center (stereochemical anchor). Consider next the site-selective attack of a "nucleophilic methyl" α to the stereogenic center, and trapping a reactive intermediate with an "electrophilic hydroxyl group". By virtue of the presence of the stereochemical anchor and vicinal steric effects, each incoming group will tend to adopt an *anti* orientation to the existing group on the template. It should now be possible to extend this template chemically and replicate it to recreate the initial scenario. Now that the stereochemical anchor is even bulkier, sequential stereocontrolled introduction of methyl and hydroxy groups should again proceed in the *anti* mode, thus producing another propionate-type subunit. In principle, the process can be reiterated and the result should be a growing polypropionate chain.[10,11]

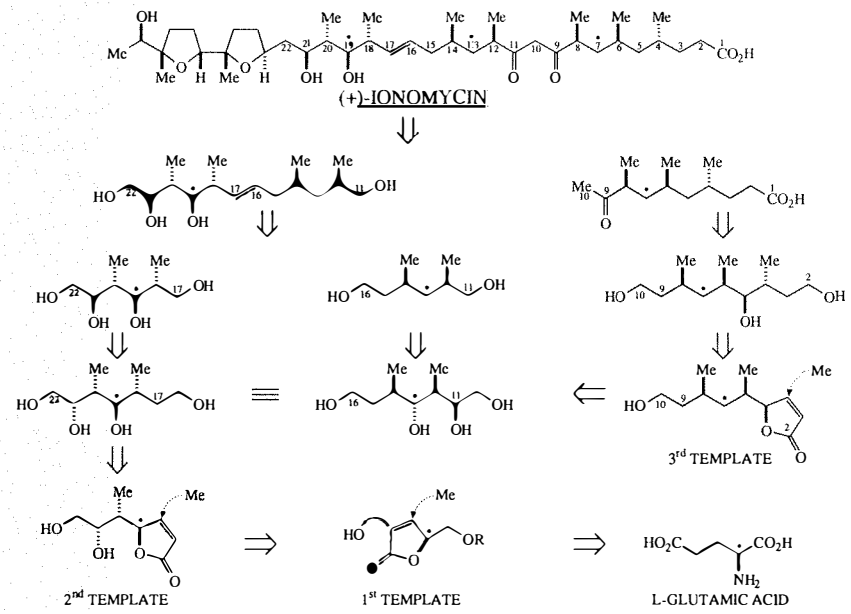
The readily available *(R)*- and *(S)*-4-

hydroxymethyl-2-buten-4olides[12] offer an ideal template for such a strategy. Starting with the crystalline *tert*-butyldiphenylsilyl *(R)*-4-hydroxymethylbutenolide[9] **(1)** as the first template, it is possible to add lithium dimethylcuprate and subsequently treat the resulting enolate with oxodiperoxomolybdenum pyridine-HMPA complex (MoOPH)[13] to give a fully substituted lactone **2** with an all-*anti* pattern of substitution. Reduction and epoxide formation *via* the primary sulfonate, followed by a 2-carbon extension[14] with dilithio-(phenylseleno)acetate, lactonization, and elimination gives a new butenolide **5**, which is the replicated template. Reiteration of the sequence leads to the second lactone **6** with a full complement of alternating methyl and hydroxy groups and a definitive pattern of substitution as shown in the acyclic counterpart **7** (Scheme 1). By applying the same extension-replication sequence to the *inverted* epoxide **10**, which is readily obtained from the same common intermediate, it is possible to obtain a *different* pattern of substitution hence another diastereomer as shown in the lactone **12** and its acyclic equivalent **13.**

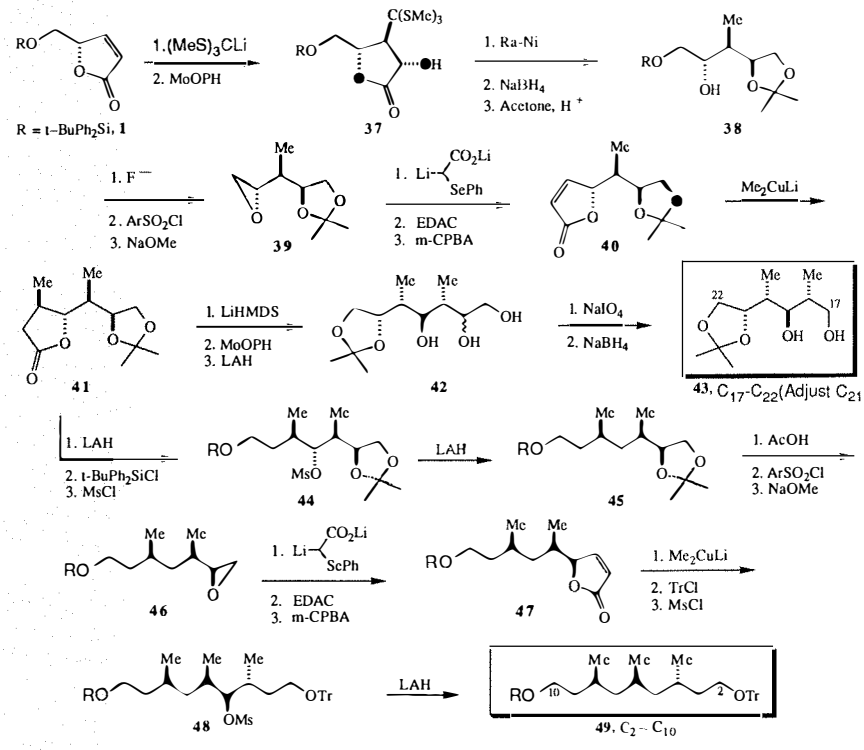
Since the conjugate addition protocol introduces the methyl group predominantly from the side *opposite* to the bulky sidechain (as in **14,** Scheme 2), a method was sought to provide the alternative *syn* disposition. Thus, treatment of the butenolide **1** with diazomethane provides a Δ^2-pyrazoline derivative **15** which, upon heating, loses dinitrogen and gives the corresponding methyl butenolide **16.**[15,16] Catalytic hydrogenation is predictably selective to provide the desired *syn* relationship at C_3/C_4 in the resulting product **17.** Enolate formation and hydroxylation furnishes the *anti-syn* lactone **18,** thus giving access to a new α-hydroxylactone which is poised for a second cycle of functionalization, extension and replication.

By virtue of the difference in the nature of the terminal groups, and the possibility to extend in either direction, and/or to adjust stereochemistry in the process, each reiteration can produce several diastereomeric structural units with predetermined patterns of substitution. It should thus be possible to write down a particular combination of a propionate-derived molecule or subunit, and to select the best synthetic protocol simply by working backwards and choosing the appropriate pathway. These possibilities are summarized in Scheme 3, where a linear sequence is shown for each case. It should be emphasized, however, that after each reiteration, the butenolide template can be subjected to a conjugate

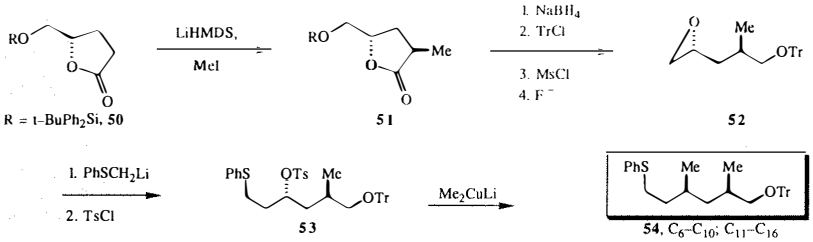
Scheme 5



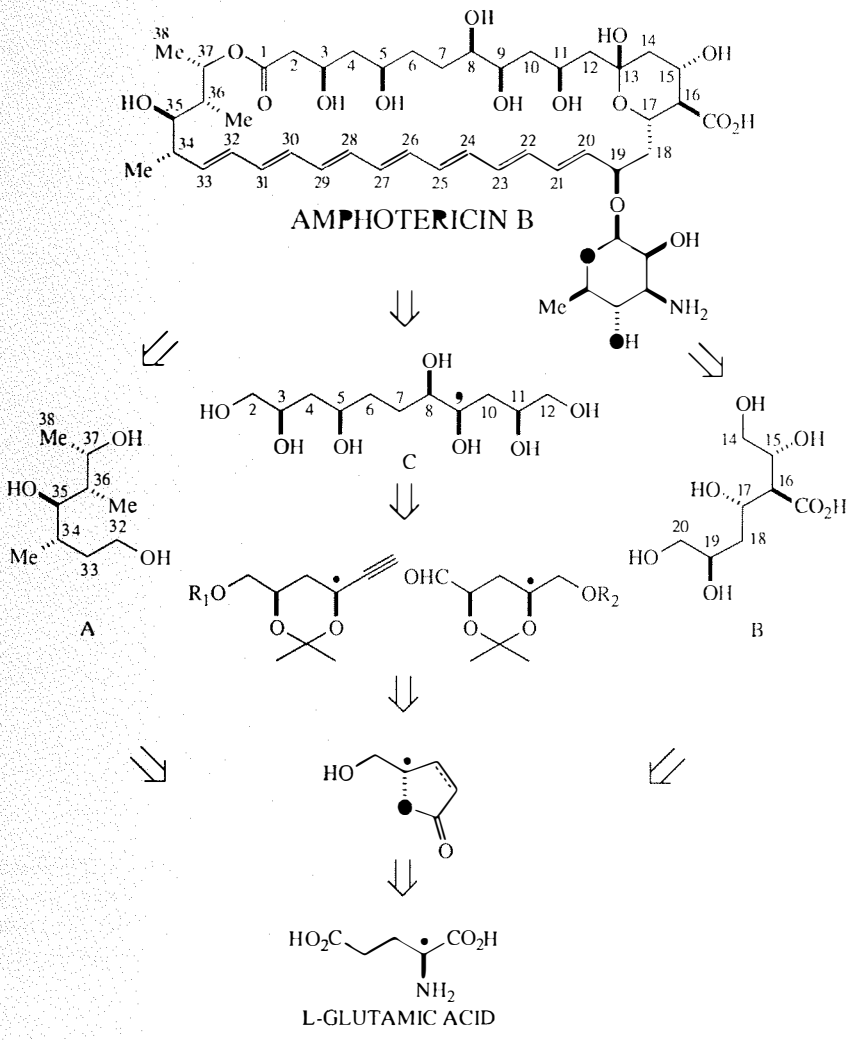
Scheme 6



Scheme 7



Scheme 8



addition or Δ^2-pyrazoline protocol at will, with the options for retention and inversion at the epoxide level.

In our opinion, the butenolide replication strategy for polypropionates offers the following advantages:

- general approach for *any* combination of subunits
- stereochemical flexibility and functional diversity
- linear or convergent operation
- high predictive power
- single chiral progenitor

2. 1,3-C-Methyl Substitution—Chirons for Ionomycin and Amphotericin B

Scheme 4 illustrates in detail the application of this strategy for the construction of seven-carbon diols and triols containing various arrangements of C-methyl and hydroxy groups.[10] Here chain extension and lactone replication are done from the hydroxymethyl end, *via* epoxide **26.** Conjugate addition of lithium dimethylcuprate affords **28,** which is reduced and preferentially silylated to give an intermediate with a predisposed pattern of methyl-hydroxymethyl substitution. Deoxygenation can be done *via* reductive desulfonyloxylation of the mesylate **29** to give the seven-carbon diol **30** having a 1,3-*syn* arrangement of C-methyl groups. This corresponds to two repeating subunits in ionomycin as shown in Scheme 5. Adopting the same protocol, but proceeding with the inverted epoxide **32,** the latter leads eventually to a 1,3-*anti* arrangement as in the triol **35** or the diol **36.**

The ionophore antibiotic ionomycin has an interesting array of C-methyl substitution patterns with and without intervening hydroxy groups. It has been the subject of synthetic studies in a number of laboratories[17] including our own.[10,18] The anatomy of ionomycin is shown in Scheme 5, where it can be seen that the various subunits can be derived from a single progenitor utilizing the butenolide replication protocol. Thus, the original stereogenic carbon of L-glutamic acid (see solid circle) and the entire five-carbon framework can be found hidden in the C_5-C_9, C_{11}-C_{15}, and C_{18}-C_{22} subunits of ionomycin. The synthesis of the C_2-C_{10} and C_{17}-C_{22} subunits of ionomycin was accomplished using this strategy and a common intermediate as shown in Scheme 6. In order to maximize stereochemical control, conjugate addition to the butenolide **1** is done with tris(methylthio)methyllithium, followed by quenching the enolate with MoOPH. The desired C-methyl group is obtained by reductive desulfurization of **37** and the selectively protected product **38** is taken through an epoxide formation, extension and butenolide replication to give **40.** Conjugate addition leads to a common intermediate **41** which is elaborated to the tetrol **43.** The latter needs stereochemical adjustment at C_{21} which is readily achieved *via* formation of an epoxide with concomitant inversion of configuration. The common intermediate **41** is now deoxygenated *via* the mesylate **44** and the resulting triol is taken through the extension-replication protocol to produce the third butenolide template **47** in this sequence. Introduction of the C-methyl group and further manipulation lead to the C_2-C_{10} subunit of ionomycin **49.**

Although the butenolide replication strategy nicely leads to predetermined patterns of substitution of C-methyl and hydroxy groups, deoxygenation is necessary to access deoxypropionate subunits (*e.g.,* C_2-C_{10} and C_{11}-C_{16} of ionomycin). We have developed an expedient route to such deoxygenated subunits by a direct C-methyl displacement reaction of tosyloxy groups.[19]

We take advantage of the stereocontrolled C-methylation of *O-tert*-butyldiphenylsilyl *(R)*-4-hydroxymethylbutyrolactone **50** which affords the crystalline lactone **51**[10,20] (Scheme 7). Reduction, mesylation and treatment with fluoride ion affords the inverted epoxide **52** which is subjected to a one-carbon homologation to give the phenyl thioether derivative **53.** Our strategy was to effect a sulfur-assisted C-methylation reaction of the corresponding tosylate. Indeed, this plan was highly successful, affording the expected 1,3-*syn* dimethyl compound **54** in over 90% yield. This chiron is a precursor to the C_6-C_{10} and C_{11}-C_{16} subunits of ionomycin. Except for simple substrates, reaction of sulfonates with a variety of cuprates normally leads to low or modest

yields of substitution. Thus, not only does this protocol provide the desired subunits expediently, but it also sets the stage for subsequent coupling reactions at the C_{10}-C_{11} and C_{16}-C_{17} junctions.[22]

The development of this novel sulfur-assisted cuprate displacement reaction was the result of a need to optimize our butenolide-based strategy for the synthesis of ionomycin without the necessity to deoxygenate. Total synthesis can thus greatly stimulate the development of novel transformations in organic chemistry. *If we must climb the mountain,*[23] *we might as well discover a shorter and a more daring route to the summit!*

The antibiotic amphotericin B has a "western" subunit that is derived from a propionate pathway.[24] Our retrosynthetic analysis is shown in Scheme 8, where three chiral subunits—**A**, B and C—are identified. Once again, a single chiral progenitor emerges for these three subunits. The propionate-derived C_{32}-C_{38} subunit can be synthesized from the butenolide precursor as shown in Scheme 9.[25] Here, we proceed *via* an already established protocol to the butenolide **33.** The tris(methylthio)methyl group was used as a C-methyl substitute in order to ensure complete stereocontrol in the *anti*-hydroxylation step to give **56** after reductive desulfurization. The final functional and stereochemical adjustments are inherent to the linear synthetic strategy. Thus, configurational inversion of **57** with subsequent introduction of a terminal C-methyl group can be maneuvered *via* epoxide formation and reductive opening without unnecessary steps leading to the intended subunit **59.**

Examples of conjugate addition to butenolides have been reported by other groups also,[11,26] and the products have been utilized as chirons in the total synthesis of a variety of natural products.

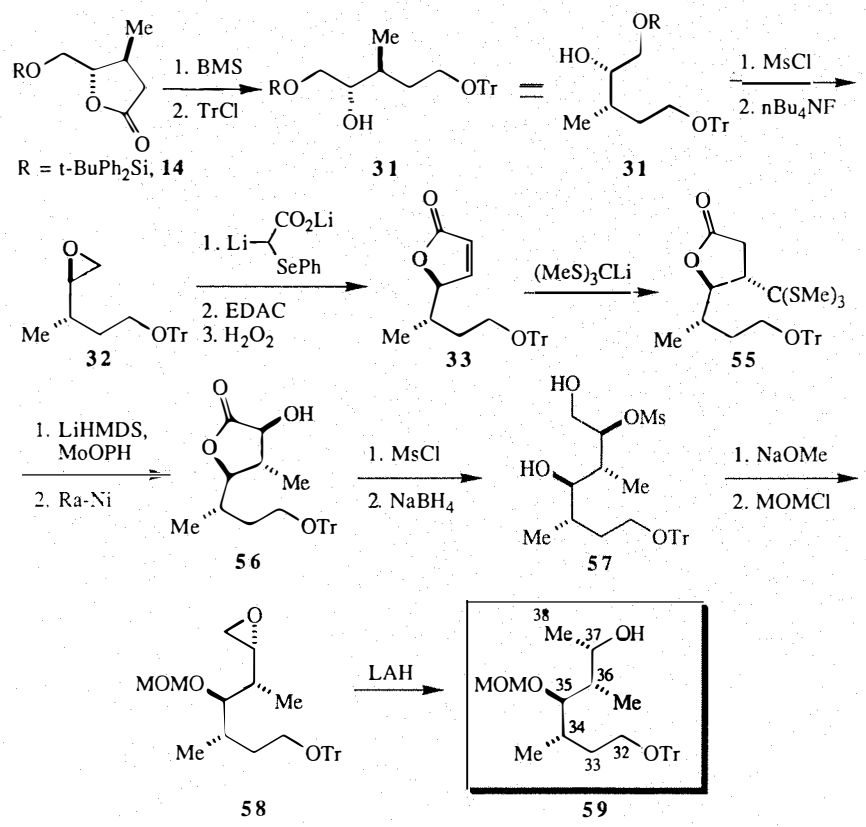
3. 1,5-C-Methyl Substitution

Remotely situated 1,5-C-methyl groups on acyclic carbon chains are found in a variety of natural products such as vitamin E,[27] and they arise *via* isoprenoid intermediates. Their access in optically pure form has relied mainly on the coupling of two chiral subunits that already contain the C-methyl groups, and on other strategies. The lactone replication technology developed in our laboratory offers a novel and practical solution to such systems as illustrated in Scheme 10.[20]

The readily available *(R)*-4-hydroxymethylbutyrolactone can be transformed into the corresponding naphthylsulfonate **60,** and the latter can be C-methylated with a selection of >11:1.[20] The crystalline product **61** is transformed into the epoxide **62,** which is extended and lactonized to give **63.** This replicated lactone can once again be subjected to a stereocontrolled C-methylation *via* the enolate (>11:1 selectivity) to afford the lactone **64.** Having served its useful purpose, the lactone template is converted to the acyclic triol **65** with two differentiable protective groups. Deoxygenation then provides the seven-carbon diol **66** with a *syn*-1,5-C-methyl substitution pattern as found in Vitamin E. The *anti* arrangement can be easily obtained from the common epoxide intermediate **62** by a different strategy. Thus, acetate extension leads to the lactone **67,** which is subjected to oxidative elimination of the phenyl thioether group to give the 2-methylbutenolide **68.** Catalytic reduction affords the triol **69** with the expected orientation of C-methyl groups. Finally, reductive desulfonylation proceeds smoothly to give the selectively protected triol **70** having a 1,5-*anti* pattern of substitution.

The seven-carbon units so produced are endowed with functional duality by virtue of the inherent symmetry and substitution pattern. All optical isomers of 2,6-dimethyl-1,4,7-heptanetriol and 2,6-dimethyl-1,7-heptanediol, as well as other related derivatives, can be obtained from a common intermediate. It is also obvious that alkylation of such butyrolactone enolates can be done with other electrophilic reagents, thus giving the opportunity to diversify the functionality.[28]

Scheme 9

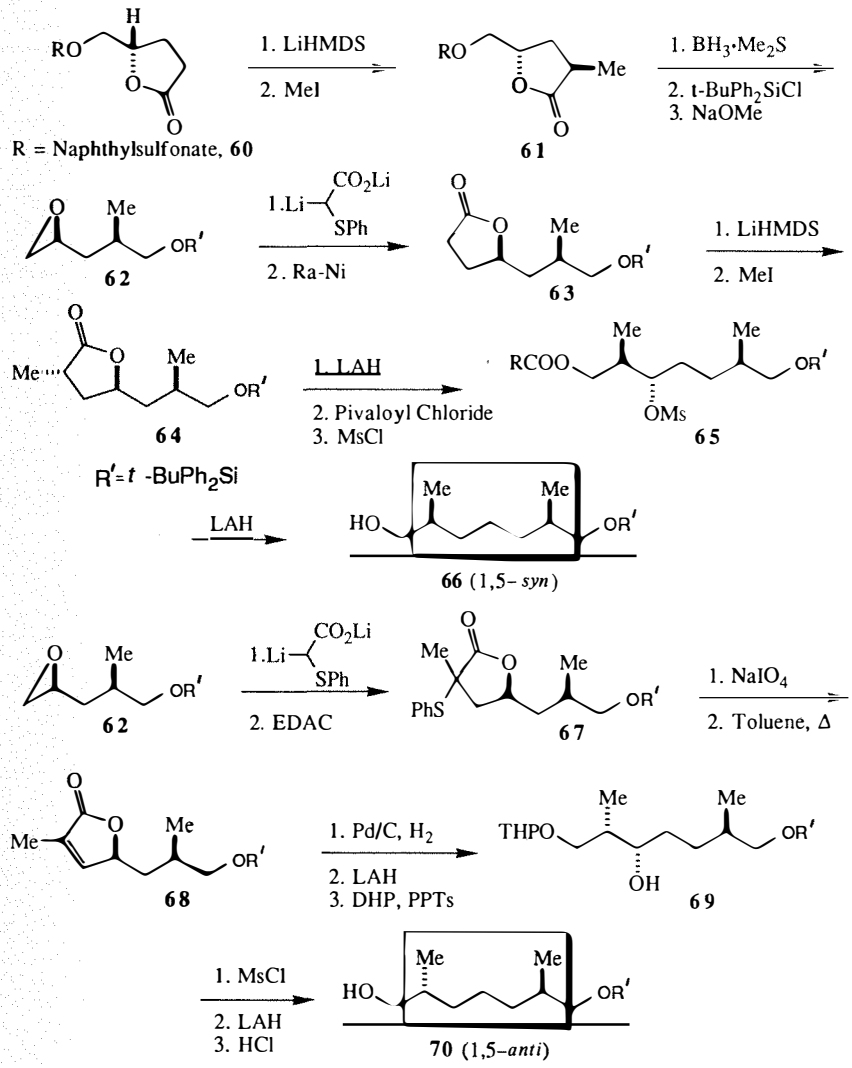


4. 1,4-C-Methyl Substitution

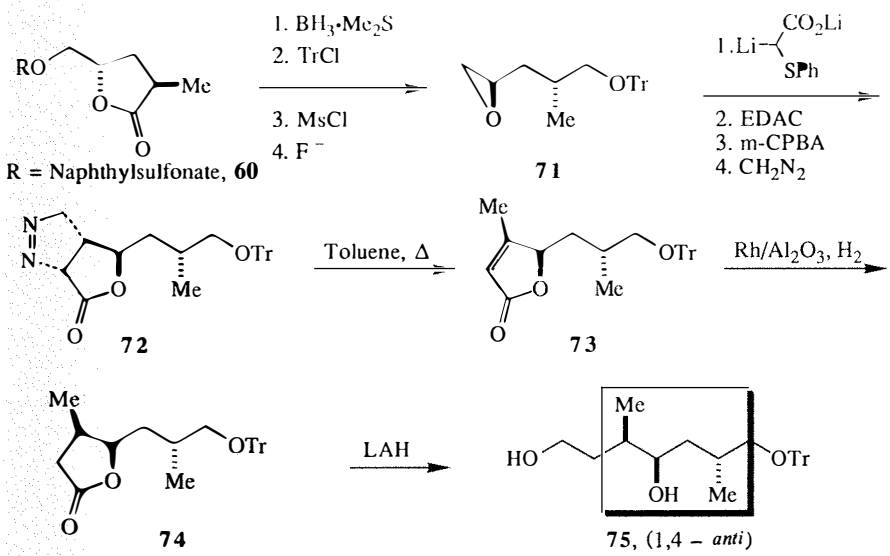
By combining the butenolide and butyrolactone replication strategies, it is possible to assemble acyclic chains having a 1,4-C-methyl substitution pattern as shown in Scheme 11.[10] The butenolide obtained from the extension-replication protocol applied to epoxide **71** is treated with diazomethane to give the Δ^2-pyrazoline derivative **72.** Thermolysis leads to the methylbutenolide **73,** which, upon sequential catalytic and hydride reduction, affords the lactone **74** and eventually the triol **75.**

It is obvious that virtually all other diastereomers of **75** or related derivatives can be obtained by the proper choice of epoxide (retention or inversion), and by adopting a conjugate addition or Δ^2-pyrazoline protocol. As in the previous cases, the acyclic intermediates have stereochemical and functional plurality by virtue of the different protection of the terminal hydroxy groups.

Scheme 10



Scheme 11



5. 1,3-Polyols

The lactone replication strategy can also be utilized to generate 1,3-diol subunits with predetermined stereochemistry.[29,30] Although the tactical part is the same as in the preceding cases involving electrophilic capture by an enolate, the opportunities for stereochemical control are even greater. This is due to the inherent functional disposition of the 1,3-polyols initially produced, and the possibility to extend at either end (Scheme 12). The option for inversion of configuration at the epoxide formation step prior to extension and replication adds another dimension for stereochemical control in accessing any 1,3-polyol arrangement. By virtue of the possibility to generate an α-hydroxy lactol from the lactones (hence, a hydroxy aldehyde), it is possible to introduce an acetate subunit *via* a Wittig reaction. Reduction and lactonization provide yet another mode of replication at the lactone end of the original template.

Schemes 13 and 14 illustrate two protocols for the construction of stereoregular 5 + 2[n] 1,3,5-polyol units.[30] Once again, by virtue of the end-group differentiation, highly symmetrical units can be effectively elaborated while maintaining their chiral character. Stereocontrolled hydroxylation of the enolate derived from **50** with MoOPH affords a 7:1 mixture of the 2-hydroxylactones **76** and **77**, respectively. The crystalline **76** can be extended to **78** and the corresponding lactone subjected to hydroxylation to give **80** and its C_2 epimer (6:1). The all-*syn* polyol **81** is obtained after reduction with borohydride. Scheme 14 illustrates a strategy that utilizes the acetate extension-lactonization method for lactone replication. Thus, reduction of **76** and subsequent functional group manipulation lead to the inverted epoxide **83**, then the lactone **84**. Formation of the enolate and hydroxylation afford a 2.5:1 ratio of C_2 epimeric lactones. The major isomer **85** is then transformed into the *syn-anti* polyol **87** in which one of the primary hydroxy groups is preferentially protected.

An expedient synthesis of the C_2-C_{12} polyol subunit which constitutes the polyketide-derived portion of amphotericin B was possible as shown in Scheme 15.[31] Due to the inherent partial symmetry properties in the desired product, it was possible to use a common intermediate by manipulating the extremities prior to coupling. The aldehyde **89** is easily obtained from the hydroxylactone **76** in three high-yield steps. The common precursor **88** is then transformed into an aldehyde **90**, enantiomeric with **89** (except for the difference in protective groups). Introduction of the acetylenic function by established methodology[32] affords **91**, ready

for coupling with **89.** This reaction affords a major product **92** in which the newly introduced alcohol group has the incorrect sense of chirality. Adjustment *via* a Mitsunobu reaction affords **93** in high yield, and subsequent catalytic hydrogenation furnishes the C_2-C_{12} polyol subunit of amphotericin B in over 30% overall yield from **76.**

The C_{14}-C_{20} subunit of amphotericin B was also constructed from the precursor utilized for the polyol subunit.[25] The pattern of substitution needed in the subtarget dictates the type of epoxide and butenolide to be produced. Extension and replication of the epoxide **95** produces the butenolide **96** which is treated sequentially with tris(methylthio)methyllithium, then MoOPH to produce the desired *anti* substitution pattern (Scheme 16). The bulk of the tris(methylthio)methyl group ensures the very high degree of stereocontrol observed in the two steps. Moreover, it provides an excellent source of the intended carboxyl group at C_{16}.

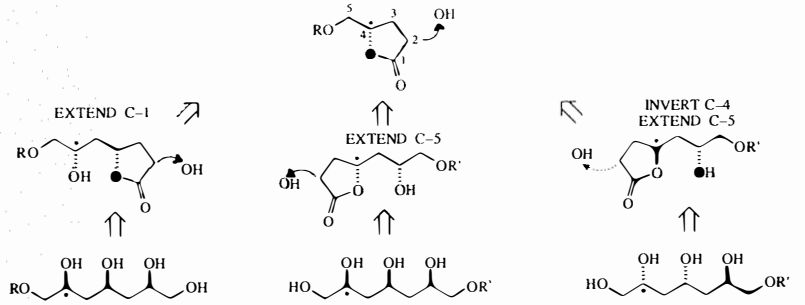
6. Vicinal Substitution

Figure 5 shows a number of vicinally substituted subunits with secondary and tertiary C-methyl groups. In general, such patterns of substitution are not easy to prepare in stereocontrolled fashion, particularly if optically pure molecules are required. For example, a number of pyrrolizidine alkaloids contain such subunits as shown in Scheme 17 where stereochemical decoding and appropriate disconnections lead to five-carbon hydroxy acids which have substitution patterns that are difficult to access. A number of synthetic studies have addressed this problem, but general strategies are still in high demand.[33]

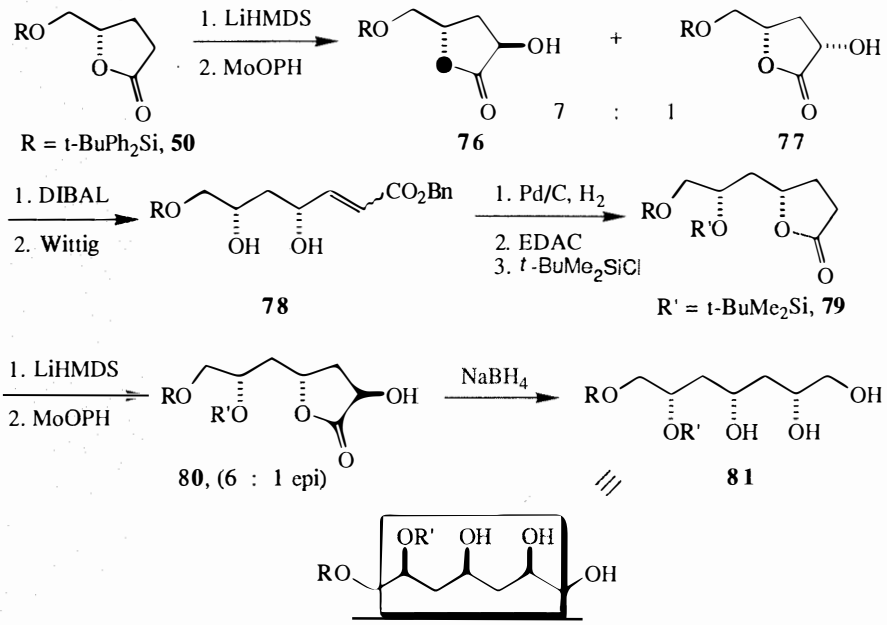
The butenolide template is ideally suited to furnish directly a variety of five-carbon chirons with predisposed vicinal substitution.[15] Thus, conjugate addition of tris(methylthio)methyllithium to **1** and trapping the resulting enolate with methyl iodide predictably furnish the *anti* substitution pattern seen in **100.** Desulfurization with Raney nickel gives the crystalline lactone derivative **101** which is also depicted as its open-chain hydroxy acid form **102.** Treatment of **100** with base followed by MoOPH, then desulfurization, leads to a tertiary alcohol derivative **103.** Stereocontrolled hydroxylation takes place from a side *opposite* to the bulky tris(methylthio)methyl group (Scheme 18).

The lactone derivative **17,** readily available *via* the Δ^2-pyrazoline route, can be C-methylated to give the lactone derivative **105** which is diastereomeric with **102** (Scheme 19). The vicinal C-dimethyl-substitution pattern in **106** corresponds to that found in sceleratine, and is easily available from butenolide **1** in four high-yield

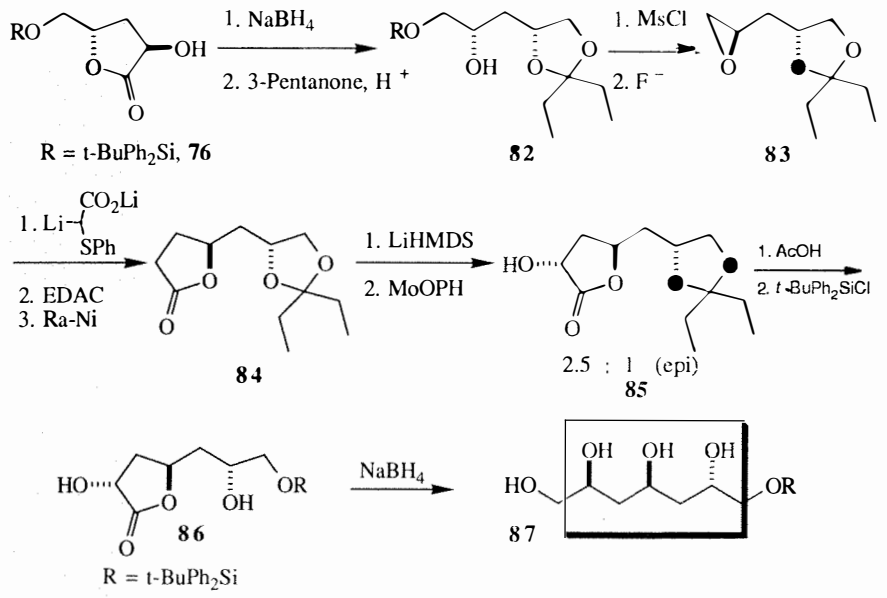
Scheme 12



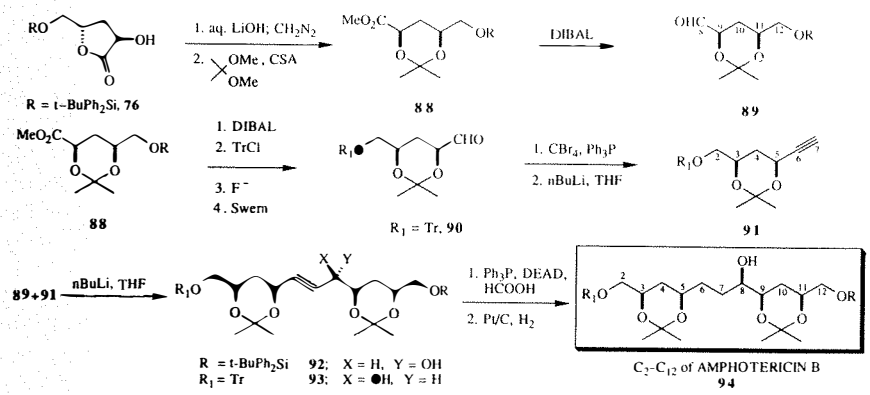
Scheme 13



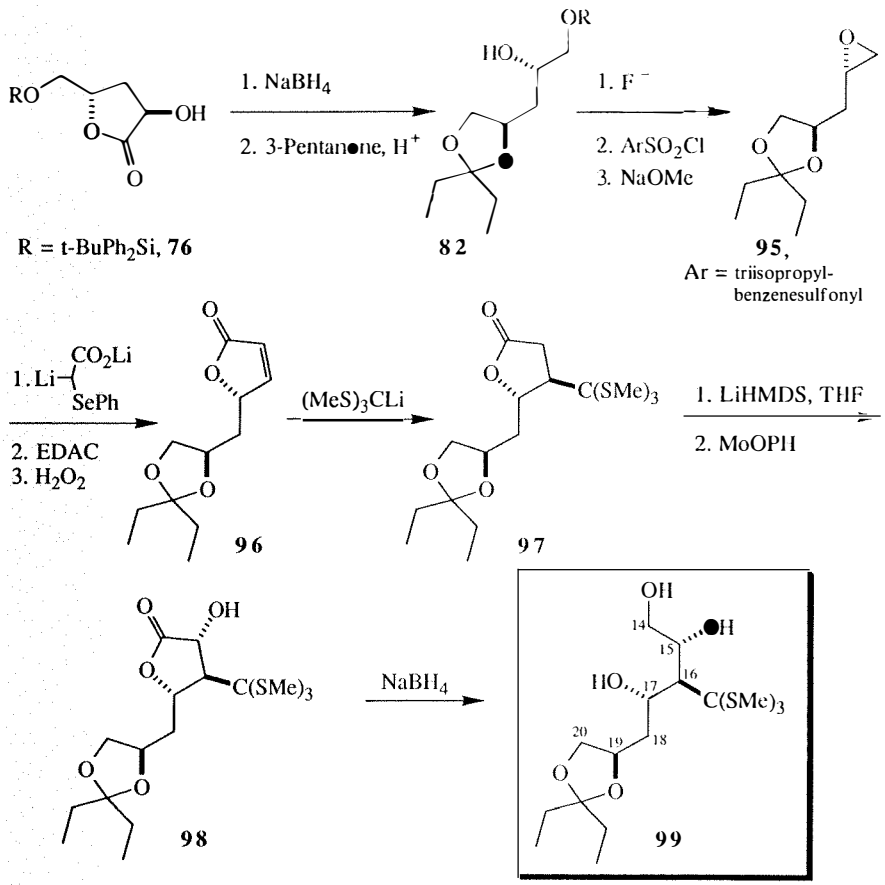
Scheme 14



Scheme 15



Scheme 16



steps. Hydroxylation of the enolate derived from **105** furnishes the tertiary alcohol derivative **107** (diastereomeric with **104** in Scheme 18). Finally, it is possible to C-methylate the pyrazoline derivative **15** to give **109,** albeit in modest yield (44%). Thermolysis then gives the vicinally dimethylated butenolide **110** which, when subjected to hydroxylation with osmium tetroxide, affords a high yield of the corresponding diol **111** in which two vicinal tertiary alcohols are situated. This is precisely the stereochemical arrangement found in the diacid portion of monocrotaline. Since epimerizations at tertiary alcohol centers are not practical, the technology shown in Schemes 18 and 19 offers a highly stereocontrolled and predictable access to vicinally substituted subunits containing such functionality.

Acknowledgments

It has been my good fortune and privilege to be associated with a large number of dedicated collaborators, who over the past twenty years, have contributed in a significant way to the progress of our chemistry. The majority of these talented individuals are presently involved in various aspects of innovative research work in many parts of the world. Some have risen to great heights in their chosen fields which is a reflection of their brilliance, versatility and vision. This is also an immense source of pride and satisfaction for me. The work described in this article was made possible through the efforts of a small group of excellent coworkers who are cited in the references. To them as well as all past members of my group I offer my heartiest thanks and best wishes. To the various Canadian granting agencies as well as industrial contributions world-wide I express my deepest appreciation.

References and notes:

1) See, for example, *Asymmetric Synthesis;* Morrison, J.D., Ed.; Academic: New York, 1983-1985.
2) Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem., Int. Ed.Engl.* **1985,** *24,* 1.
3) For recent reviews, see Heathcock, C.H. In *Asymmetric Synthesis;* Morrison, J.D., Ed.; Academic: New York, 1984; Vol. 3, p 111. Evans, D.A.; Nelson, J.V.; Taber, T.R. In *Topics in Stereochemistry;* Eliel, E.; Allinger, N.L.; Wilen, S.H., Eds. Wiley: New York, 1982; Vol. 13, p 1. Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 555. Masamune, S.; Choy, W. *Aldrichim. Acta* **1982,** *15*(3), 47. Mukaiyama, T. *Org. React.* **1982,***28,* 103. Evans, D.A. *Aldrichim. Acta* **1982,** *15*(2), 23.
4) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981,** *103,* 464. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *ibid.* **1987,** *109,* 5765.
5) Hanessian, S. *The Total Synthesis of Natural Products: The Chiron Approach;* Pergamon Press: Oxford, 1983.
6) Corey, E.J. *Pure Appl. Chem.* **1967,** *14,* 19; see also Warren, S. *Designing Organic Syntheses;* John Wiley & Sons: New York, 1977.
7) For a recent review, see Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1987,** *26,* 489.
8) For selected recent non-aldol examples, see Stork, G.; Rychnovsky, S. *J. Am. Chem. Soc.* **1987,** *109,* 1564. Burke, S.D.; Schoenen, F.J.; Murtiashaw, C.W. *Tetrahedron Lett.* **1986,** *27,* 449. Collum, D.B.; Still, W.C.; Mohamadi, J. *J. Am. Chem. Soc.* **1985,***107,* 6647. Woodward, R.B. *et al. ibid.* **1981,** *103,* 3210, 3213, 3215. Heathcock, C.H.; Jarvi, E.J.; Rosen, T. *Tetrahedron Lett.* **1983,***24,* 2661. Stork, G.; Paterson, I.; Lee, H.T. *J. Am. Chem. Soc.* **1982,** *104,* 4686. Ziegler, F.; Keisley, A.; Thottahil, J.K.; Wester, R.T. *ibid.* **1988,** *110,* 5434 and references cited therein.
9) For some reviews, see also Inch, T.D. *Tetrahedron* **1984,** *40,* 3161. Fraser-Reid, B.; Anderson, R.C. *Fortschr. Chem. Org. Naturst.* **1980,** *39,* 1. Vasella, A. In *Modern Synthetic Methods;* Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt am Main, 1980; p 173.
10) Hanessian, S.; Murray, P.J. *Tetrahedron* **1987,** *43,* 5072. Hanessian, S.; Murray, P.J.; Sahoo, S.P. *Tetrahedron Lett.* **1985,** *26,* 5627.
11) For another approach, see Stork, G.; Rychnovsky, S. *Pure Appl. Chem.* **1987,** *59,* 345. *Idem ibid.* **1986,** *58,* 767.

12) The butenolide can also be named as *(S)*-5-(hydroxymethyl)furan-2(5*H*)-one or 2,3-dideoxy-D-glycero-pent-2-eno-1,4-lactone. For several preparations, see ref. 10.
13) Vedejs, E.; Larsen, S. *Org. Synth.* **1985,** *64,* 127.
14) Hanessian, S.; Hodges, P.J.; Murray, P.J.; Sahoo, S.P. *Chem. Commun.* **1986,** 734.
15) Hanessian, S.; Murray, P.J. *J. Org. Chem.* **1987,** *52,* 1170. Hanessian, S.; Wallach, D.; Murray, P.J., unpublished results.
16) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982,** *17,* 311.
17) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987,** *28,* 731. Evans, D.A.; Morrissey, M.M.; Dow, R.L. *ibid.* **1986,** *27,* 1007. Schreiber, S.L.; Wang, Z. *J. Am. Chem. Soc.* **1985,** *107,* 5303. Nicoll-Griffith, D.; Weiler, L. *Chem. Commun.* **1984,** 659. Wutts, P.G.M.; Costa, R.D.; Butler, W. *J. Org. Chem.* **1984,** *49,* 2582.
18) Hanessian, S.; Murray, P.J. *Can. J. Chem.* **1986,** *64,* 2231.
19) Hanessian, S.; DeHoff, B.; Thavonekham, B., unpublished results.
20) Hanessian, S.; Murray, P.J.; Sahoo, S.P. *Tetrahedron Lett.* **1985,** *26,* 5623.
21) See, for example, Still, W.C.; Galynker, I. *J. Am. Chem. Soc.* **1982,** *104,* 1774. Trost, B.M.; Klum, T.P. *ibid.* **1981,** *103,* 1864.
22) Hanessian, S. *Alfred Bader Award Address,* 3rd Chemical Congress of North America, Toronto, Ontario, **1988**; Org. 256.
23) Danishefsky, S. *Aldrichim. Acta* **1986,** *19*(3), 59.
24) For an account of the total synthesis of amphotericin B and pertinent recent references, see Nicolaou, K.C.; Daines, R.A.; Ogawa, Y.; Carborty, T.K. *J. Am. Chem. Soc.* **1988,** *110,* 4696 and previous papers.
25) Hanessian, S.; Sahoo, S.; Botta, M. *Tetrahedron Lett.* **1987,** *28,* 1147.
26) See, for example, Damon, R.E.; Schlessinger, R.H. *Tetrahedron Lett.* **1976,** 1561. Tomioka, K.; Isiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984,** *40,* 1303.
27) For selected syntheses, see Cohen, N.; Eichel, W.F.; Lopresti, R.J.; Newkom, C.; Saucy, G. *J. Org. Chem.* **1976,** *41,* 3512. Fuganti, C.; Grasselli, P. *Chem. Commun.* **1979,** 995. Trost, B.M.; Klum, T.P. *J. Am. Chem. Soc.* **1979,** *101,* 6756. Still, W.C.; Darst, K.P. *ibid.* **1980,** *102,* 7387. Heathcock, C.H.; Jarvi, E.T. *Tetrahedron Lett.* **1982,** *23,* 2825. Koreeda, M.; Brown, L. *J. Org. Chem* **1983,** *48,* 2122. Bérubé, G.; Deslongchamps, P. *Can. J. Chem.* **1984,** *62,* 1558 and references cited therein.
28) See, for example, Tomioka, K.; Cho, Y.S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988,** *53,* 4094, and references cited therein. See also Takano, S. *Pure Appl. Chem.* **1987,** *59,* 353.
29) For a recent review, see Masamune, S.; Choy, W. *Aldrichim. Acta* **1982,** *15,* 47.
30) Hanessian, S.; Sahoo, S.P.; Murray, P.J. *Tetrahedron Lett.* **1985,** *26,* 5631; see references cited therein for polyol methodology.
31) Hanessian, S.; Sahoo, S.P.; Botta, M. *ibid.* **1987,** *28,* 1143.
32) Corey, E.J.; Fuchs, P.L. *ibid.* **1972,** 3769.
33) See, for example, Niwa, H.; Okamoto, O.; Yamada, K. *ibid.* **1988,** *29,* 5139. Vedejs, E.; Ahmad, S.; Larsen, S.D.; Westwood, S. *J. Org. Chem.* **1987,** *52,* 3937 and references cited therein.

About the Author

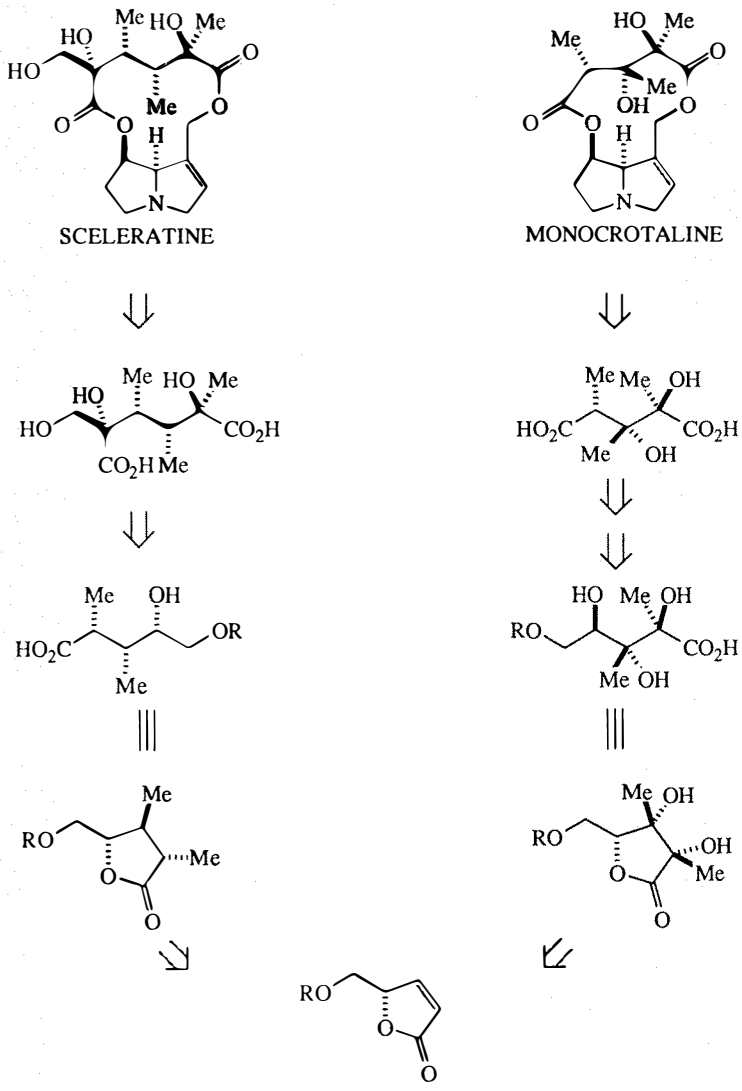
Stephen Hanessian obtained his Ph.D. degree with the late Professor M.L. Wolfrom at Ohio State University in 1960. He then joined the Parke-Davis research laboratories in Ann Arbor, Michigan, where he was involved in various aspects of natural-product chemistry. In the fall of 1968, Dr. Hanessian moved to Canada and joined the faculty at the Université de Montréal as Associate Professor. A year later, he was promoted to full professor. He has been McConnell Professor since 1979.

Dr. Hanessian's scientific accomplishments over the past two decades have had a major impact on organic, bio-organic and medicinal chemistry. His contributions to synthetic organic chemistry have covered a diverse cross-section of activities. He has been one of the most successful practitioners of natural-product synthesis from chiral precursors (the Chiron approach), having devised pathways to complex molecules such as thromboxane$_2$, spectinomycin, several macrolide and β-lactam antibiotics, the octosyl acids and the avermectins, to mention a few. Recently he has developed computer programs that analyze and perceive stereochemical features in complex molecules, thus greatly facilitating synthesis planning.

Dr. Hanessian's research in the area of protective groups and reactive functionalities is widely used today. He has devised tactically and conceptually novel approaches to the asymmetric synthesis of molecules with multiple stereogenic centers. His recent work on the "replicating lactone strategy" provides a general approach to the construction of polypropionate and related subunits from a single chiral progenitor with a high level of predictability. Over the years, Dr. Hanessian has made important contributions in the area of synthetic carbohydrate chemistry, particularly with regard to stereocontrolled methods of glycoside synthesis. He was able to bring this important subdiscipline into the mainstream of modern organic chemistry.

Dr. Hanessian's scientific accomplishments have been characterized by a combination of elegance, creativity and practical utility.

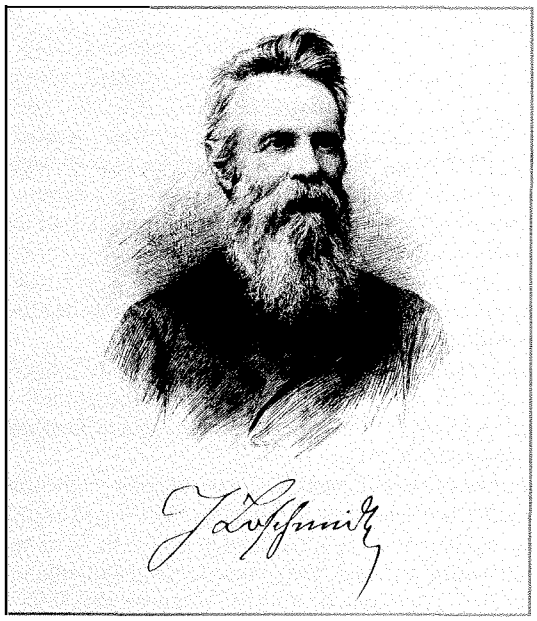
Scheme 17



Johann Josef Loschmidt (1821-1895): a forgotten genius

Benzene rings and much more in 1861

William J. Wiswesser



One of the most puzzling problems facing chemists in the middle of the last century was the structure of benzene and its derivatives. Ask chemists anywhere in the world who was the first person to present the structure of benzene correctly, and the answer will be August Kekulé, probably followed by a reference to his dream about a snake biting its tail. Much has been written about this dream, yet it is really quite irrelevant, because Kekulé was not the first chemist to propose the structure of benzene. It was, in fact, Johann Josef Loschmidt who first published the correct structure in 1861.

Johann Josef Loschmidt was so far ahead of his contemporaries, and so shy and self-effacing, that they may be forgiven for overlooking his monumental contributions to the structural representation of molecules. Today, however, it is a shameful neglect of our chemical heritage to continue to disregard his famous firsts:

1. The first correct cyclic structure of benzene and of many aromatic chemicals, 121 in all.
2. The first representation of the allyl moiety.
3. The first representation of the vinyl moiety and of many others.
4. The first representation of cyclopropane, 21 years before it was made by Freund.
5. The first picture book of molecules, containing graphic displays with atomic domains, rather than abstract bond lines.
6. The first double- and triple-bond marks (within the overlaps).
7. The first realistic displays of atomic sizes and bond distances (largest overlap with triple bonds).
8. The first set of diagrams with correct C = 12, N = 14, O = 16 formulas.
9. The first textbook use of atomic-group symbols.
10. The first use of valence prime marks on these and atomic symbols ("Valenz" was introduced by Wichelhaus in 1868, 7 years later).
11. The first LINE-FORMULA NOTATIONS ("rational formulas").
12. The first revelations of hexavalent and tetravalent sulfur.

It was Richard Anschütz, a Kekulé student, who first recognized Loschmidt's importance. In 1913, he republished Loschmidt's work and graphic representation of molecules, added a brief biography of Loschmidt, and made many comments about the work.[1]

Loschmidt was born to a poor peasant family in a village near Carlsbad, Bohemia, in 1821. In Loschmidt's obituary in 1895, his good friend, Ludwig Boltzmann, related that Loschmidt so hated farm work that his parents considered him useless for anything but studies. Encouraged by his village priest and teacher, he went to high school, and eventually attended Prague University. At the age of 21, he went to the University and the Polytechnic Institute (now the Technical University) in Vienna, first studying philosophy and mathematics, and then the natural sciences, physics and chemistry.

Loschmidt then became involved in several industrial ventures in Lower Austria, Styria, Bohemia and Moravia, making potassium nitrate and oxalic acid, among other products. These ventures were technical successes but financial failures. In the early 1850's, he returned to Vienna penniless, took a job as a concièrge, and then qualified as a school teacher.

Loschmidt was always attracted to the major theoretical problems in the natural sciences, and today he is best remembered for the "Loschmidt Number", his 1865 calculation of the number of molecules in one milliliter of an ideal gas.

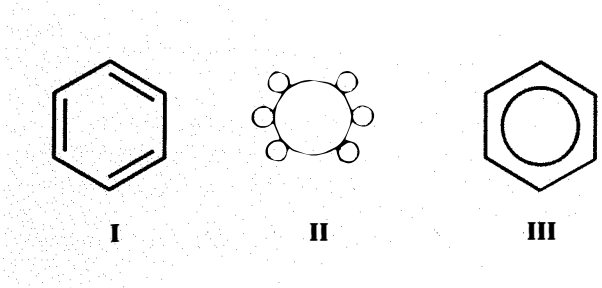
Four years earlier, however, he had published privately what can be called the monograph of the century. This was a modest octavo booklet containing a 47-page essay entitled *Constitutions-Formeln der organischen Chemie in geographischer Darstellung*.[2]

In each generation since, someone has recognized and written about Loschmidt's greatness. It was a brief reference to Loschmidt's work in Kekulé's famous paper presented in Paris in 1865 and published in *Bull. Soc. Chim. Fr.* **1865**, *3*(2), 100 that kindled Richard Anschütz's interest. Intrigued, he tried to find out more. At first, all he could discover was a brief description in a reference by Hermann Kopp, a German crystallographer, the teacher and friend of Kekulé. Eventually he obtained a copy of Loschmidt's pamphlet from an antiquarian book dealer in Vienna. In the comments which he added to his 1913 reprint, Anschütz expressed the amazement with which he read this little work. He immediately wondered whether Kekulé had also read it, and, if not, where he had heard about Loschmidt's work. He came to the conclusion that Kekulé had definitely not read the book but believed that he must have heard of it from Hermann Kopp who

had written the abstract for *Liebigs Jahresbericht* **1861,** *1,* 335. Unfortunately, Kopp was not well versed in organic chemistry and probably did not realize the full significance of the work he was reviewing.

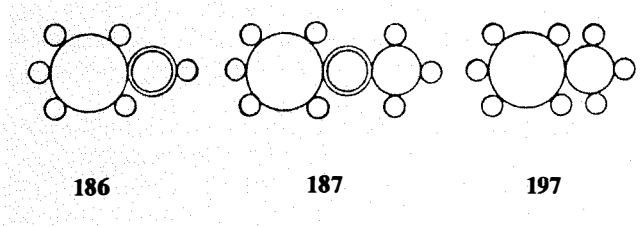
August Kekulé's lone reference to Loschmidt's work is in a single sentence in that French paper of 1865 *"Elle me parait préférable aux modifications proposées par M.M. Loschmidt et Crum-Brown."*

Kekulé proposed the hexagonal structure (I) of benzene.



I **II** **III**

Four years earlier, Loschmidt had proposed the circular (II) structure 18 5, in the work of 1861. Few chemists now using III realize how close this is to Loschmidt's formulation. Phenol was shown as 186, anisole as 187, toluene as 197, 121 aromatic compounds in all, many of these correct.



186 **187** **197**

In 1945 Moritz Kohn wrote an article about Loschmidt based on Anschütz's biography, and published it in the *Journal of Chemical Education.*[3] Three years later, Hubert de Martin wrote a dissertation[4] at the University of Vienna.

Dr. de Martin's well written thesis refers to many original documents and gives a number of details of Loschmidt's personal life, few of which were mentioned by Anschütz. At the age of 66 Loschmidt married his housekeeper Karoline Mayr, 25 years his junior. Their only son, Josef Karl, died of scarlet fever in 1898, at age ten, three years after his father's death. Karoline Loschmidt lived until 1930, when she died of cancer.

Dr. de Martin also discusses Loschmidt's chemical essay of 1861 in detail (pp 58–64 in the thesis), and concludes that it was almost unknown because it was privately printed and was not read by chemists who understood it—until Anschütz read it some 50 years later. Thus it is clear that, although Loschmidt is well known among physicists for the Loschmidt/Avogadro number, he remains virtually unknown among chemists.

In order to make his work more widely available, Aldrich is offering copies of Anschütz's republished work of 1913, including his comments on Loschmidt's work. This is much easier to use than the 1861 book, because the original fold-out plates, which are clumsy to handle and which can be torn easily, have been reduced in size. Also, Anschütz has made some minor corrections to the structures. But for the serious chemical historian, Aldrich also offers copies of the small book of 1861 together with the seven fold-out plates. In that book of 54 pages, the first 47 deal with 368 chemical structures, including 121 of aromatic compounds. The remaining six pages deal with studies in physics, gas kinetics, unrelated to chemical structures.

Two important questions arise: why has Loschmidt not been recognized as the first person to depict correctly the structures of benzene and many other compounds, and why was his genius as a chemist not recognized by scientists in Vienna?

The answers to both questions lie in the personality of Loschmidt himself. He was a shy and self-effacing man who never travelled outside the Austro-Hungarian Empire, who never pushed himself to publish in the major chemical journals or to give lectures at important international meetings. His small book was a masterpiece, but who knew about it? In contrast, August Kekulé was a world-famous professor, a great lecturer and teacher, and author of the most widely read textbooks of his time.

In 1890, the 25th anniversary of 'his' formulation of the structure of benzene, Kekulé spoke of his dream. Perhaps he really did have that dream, based on what he had heard of Loschmidt's work. It is not of great importance; Loschmidt had published his simple and brilliant work four years earlier.

Anschütz began his comments about Loschmidt (page 99) with the words: "The Austrian physicist, Joseph Loschmidt ... was originally a chemist." Clearly, Anschütz thought of Loschmidt first and foremost as a physicist.

It must have been unusual for a man to come to Vienna penniless, to start as a caretaker, a "Hausbesorger", and eventually to qualify as a university professor. That he finally became a close personal friend of Josef Stefan and Ludwig Boltzmann (much younger men who were the greatest Viennese physicists of their time) is evidence that he was appreciated but, again, almost entirely as a physicist and physical chemist.

In 1866, he became Privatdozent at the University of Vienna, and, two years later, Associate Professor. He was elected to the Royal Academy of Sciences (Kaiserliche Akademie der Wissenschaften) in 1867, and the following year the University gave him the honorary degree of Doctor of Philosophy. The next year he founded the "Chemisch-Physikalische Gesellschaft", a society of chemists and physicists in Vienna, and in 1875 became the chairman of the Physical Chemistry Institute. He became Dean of the Faculty of Philosophy in 1877, and in 1885 was elected to the Senate of that faculty. Despite these honors, all his contemporaries failed to realize that that tiny book of 1861 was really the masterpiece of the century in organic chemistry.

Acknowledgements:

I would like to thank Dr. Christian Noe and Dr. Alfred and Isabel Bader for their exceptional help with this essay.

References:

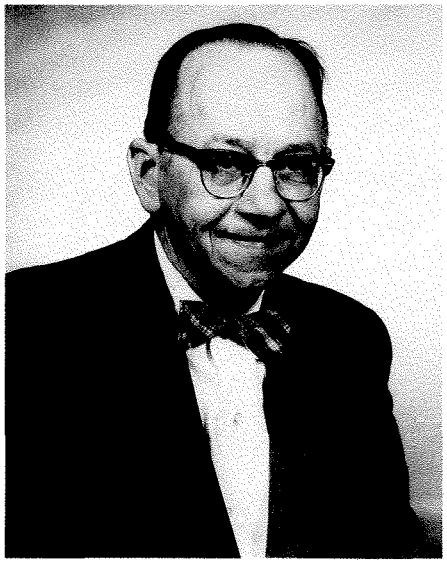
1) Anschütz, R. *Konstitutions-Formeln der organischen Chemie in graphischer Darstellung,* Loschmidt, J., republished in Ostwald's *Klassiker der exakten Wissenschaften,* Leipzig, 1913.

2) Loschmidt, J. *Chemische Studien, A. Constitutions-Formeln der organischen Chemie in geographischer Darstellung, B. Das Mariotte'sche Gesetz,* Vienna, 1861.

3) Kohn, M. *J. Chem. Educ.* **1945,** 381.

4) Loschmidt, J. *Sein Leben und Wirken.* Ph.D. thesis of Hubert de Martin, submitted to the faculty of philosophy of the University of Vienna in November, 1948. 235 typewritten pages, with documents.

About the Author



William J. Wiswesser graduated with a B.S. from Lehigh University in 1936 and received an honorary D.Sc. from Lehigh in 1974. He has worked for the Hercules Research Center, Trojan Powder Co., Picatinny Arsenal, Cooper Union, Willson Products, and the U.S. Army at Fort Detrick and is presently working in the Weed Science Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture. His interest in simplifying chemical structure descriptions began in college when he developed a chemical shorthand based on valence-line diagrams. Today, some 50 different research organizations have more than three million Wiswesser Line Notation (WLN) records in their computers. He has written or coauthored over 50 papers, and is editor of *CWIK List News* (Chemical World Index Key) as well as the *Pesticide Index.* He is past chairman of the Lehigh Valley Section and of the History of Chemistry Division of ACS. His honors include the U.S. Army Exceptional Civilian Service award, the first "Reading Chemist of the Year" award, the Austin M. Patterson award, the Herman Skolnik award of the ACS Division of Chemical Information, the Chemical Notation Association award, and the 1981 award of the Institute of Information Scientists.

Award-Winning Chemistry

1988 - Professor Stephen Hanessian

Stephen Hanessian, McConnell Professor of Chemistry at the University of Montreal, is the recipient of the first Canadian Alfred Bader Award in Organic Chemistry given by the Canadian Society for Chemistry in 1988.

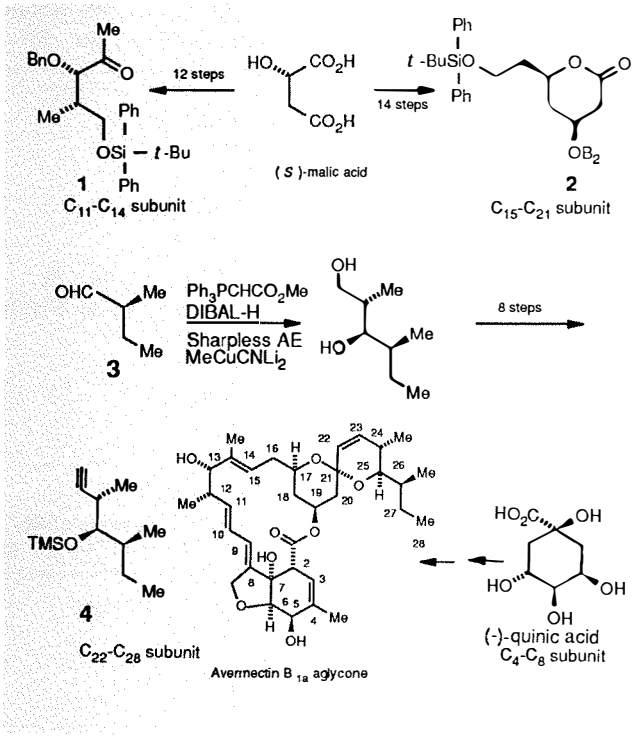
Professor Hanessian's interests range from synthetic endeavors in the fields of natural-product, carbohydrate, asymmetric synthesis, and antibiotic chemistry to computer analysis and design for the synthesis of enantiomerically pure compounds, *e.g.*, the *CHIRON* approach.* His recent advances in stereochemically controlled addition to butenolides have furnished a valuable synthetic alternative to acyclic stereoselection. A recurrent theme in his research is the utilization of nature's storehouse of optically active compounds as readily available, versatile starting materials. Thus, with (*S*)-5-(hydroxymethyl)-2(5*H*)-furanone derived from glutamic acid as the single chiral progenitor, and a replicating lactone sequence mimetic of the polypropionate and polyketide pathways, it is possible to construct acyclic chains of any combination of methyl and/or hydroxy groups with complete stereocontrol.*

His contributions are not only exciting from the perspective of total synthesis of specific targets, but have often resulted in the development of general synthetic methods applicable to a broad spectrum of products. Target molecules have included ionomycin,[1] amphotericin B,[2] avermectin B_{1a}[3], octosyl acid A,[4] some penems[5] and carbapenems,[6] to name a few.

We congratulate Professor Hanessian on his continued success and describe below some contributions exemplifying the versatile methodology developed in his laboratories.

Avermectin B_{1a} Synthesis

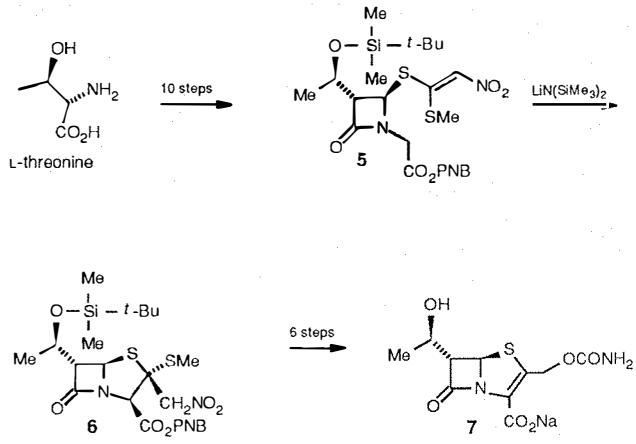
In the preparation of this potent anthelmintic, the Hanessian group took advantage of both acyclic and cyclic naturally occurring chiral templates. Thus, one approach[3a] utilized (*S*)-malic acid as the source for both enantiomerically pure ketone **1**, the C_{11}-C_{14} subunit, and seven-carbon lactone **2**, the C_{15}-C_{21} subunit. A previous sequence converted D-glucose to these two segments. L-Isoleucine-derived **3** provided the necessary chirality for the C_{22}-C_{28} segment. In this transformation, a combination Wittig reaction, Sharpless AE,[7] and organocuprate strategy afforded



pure **4** containing an additional asymmetric center. Finally, a precursor for subunit C_1-C_8 was developed from the readily available (-)-quinic acid. Assembly of these segments and attachment of a glycoside afforded the title compound.

Penem Synthesis

(5*R*,6*S*,8*R*)-6-(α-Hydroxyethyl)-2-(hydroxymethyl)penem-3-carboxylic acid,[5] and hence its highly bioactive 2-*O*-carbamoyl derivative **7**, was constructed utilizing L-threonine as the initial chiral template. This was transformed into the optically active



azetidinone **5** in preparation for a unique stereocontrolled intramolecular Michael addition to form the bicyclic system **6** and thus the final product **7**. In this preparation, Hanessian's synthetic elegance combines inexpensive starting materials with *mild* ring closure.

References:

* See page 3 for a review by Professor Hanessian.

(1) Hanessian, S.; Murray, P.J. *Can. J. Chem.* **1986,** *64,* 2231. (2) Hanessian, S.; Sahoo, S.; Botta, M. *Tetrahedron Lett.* **1987,** *28,* 1147. (3) a) Hanessian, S. *et al. Pure Appl. Chem.* **1987,** *59,* 299. b) Hanessian, S. *et al. J. Am. Chem. Soc.* **1987,** *109,* 7063. (4) Hanessian, S.; Kloss, J.; Sugawara, T. *ibid.* **1986,** *108,* 2758. (5) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *ibid.* **1985,** *107,* 1438. (6) Hanessian, S.; Desileis, D.; Bennani, Y., unpublished results. (7) Sharpless, K.B. *et al. J. Am. Chem. Soc.* **1987,** *109,* 5765.

For a list of Aldrich products utilized in this chemistry, see page 12 of this issue of Aldrichimica Acta.

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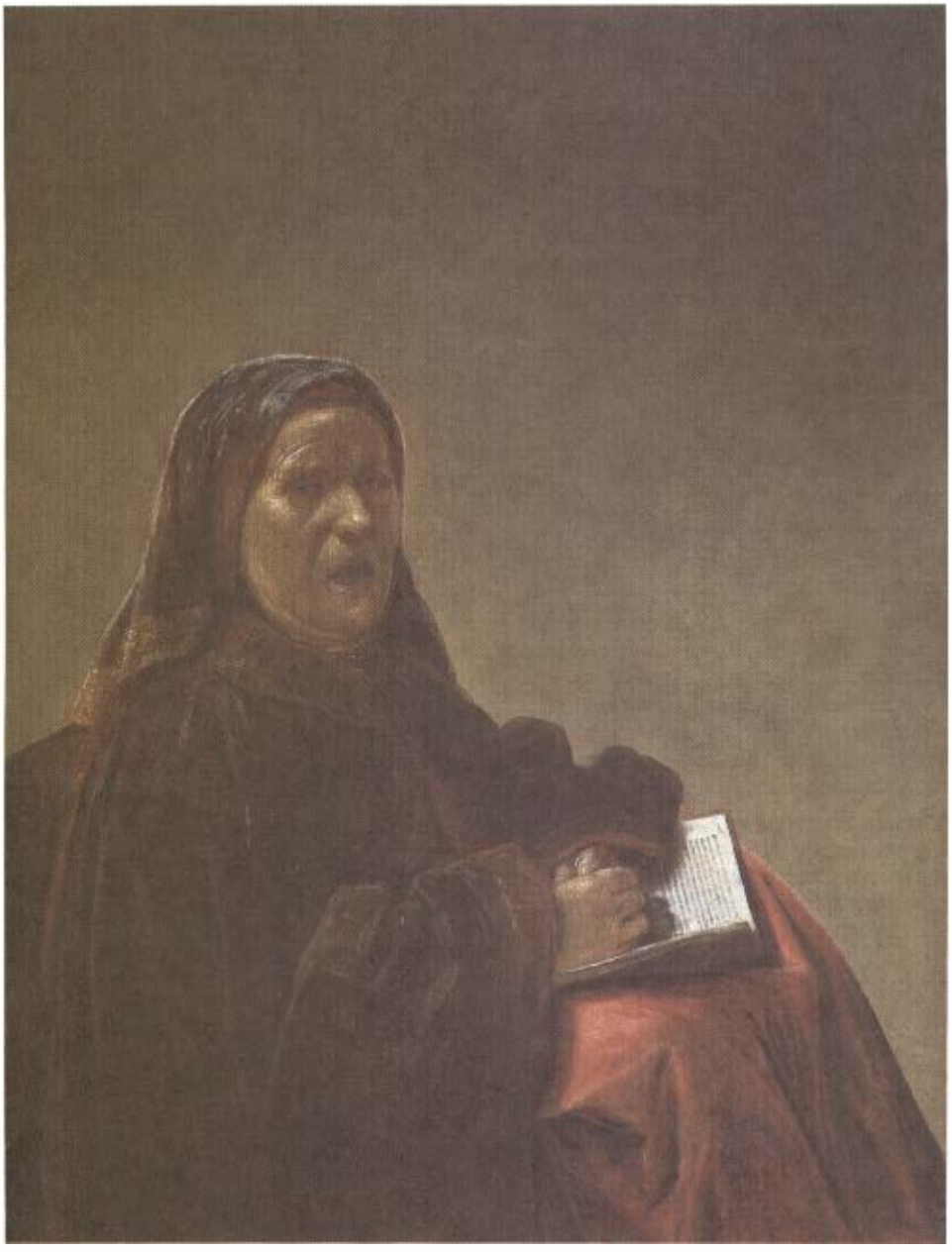

The Direct Synthesis of Non-Transition-Metal Organo Derivatives

Teaching Organic Synthesis: Why, How, What?

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About Our Cover:

Fig. 1

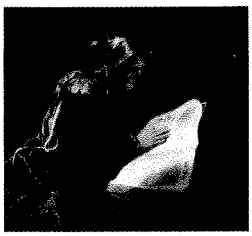

Fig. 2

Readers of our *Acta* know how our chemist-collector loves puzzles. One of the greatest puzzles in Dutch 17th-century art is the identity of the Master IS, an artist active in the middle of the century, influenced by Rembrandt. Only about a dozen of his works are known, and these are usually dated about 1650. One of his masterpieces, dated 1649, graced the cover of our *Acta,* Vol. 16, No. 1.

His best known work is a moving portrait of an old woman (Fig. 1) in the Kunsthistorisches Museum in Vienna. Recently, our chemist-collector acquired the painting on our cover (oil on wood, 18½ x 14 inches), monogrammed but undated, of a woman looking up from her book—perhaps a biblical subject—possibly Hannah in the Temple (Luke 2). Did the artist depict his mother as Rembrandt depicted his in 1631, in the painting (Fig. 2) now in the Rijksmuseum in Amsterdam?

As discussed in *The Detective's Eye* described below, the artist's figures look Eastern European. Did an eastern or perhaps a Scandinavian artist come to Amsterdam to study with Rembrandt?

The Master IS: a monogram in search of a name.

NEW

The Detective's Eye: Investigating the Old Masters

Twenty-one paintings that have been reproduced on our *Acta* covers and five that have been on our catalog covers were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 - March 19, 1989) for which Isabel and Alfred Bader were guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist-collector's interest in art and connoisseurship as well.

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among the thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historian information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Lab Notes

I wish to direct this suggestion to chemists who do some glassblowing or to those involved in a user-friendly glassblowing shop.

There is no common, ready source of screw-thread connections for use as building blocks for glassblowing. The most common screw-thread size is 13-425. The Wheaton Micro Kit® (Z10,372-1), which has many useful applications, is a very good example of screw-thread connection utility. The 5-ml Wheaton round-bottom micro flask (Z10,667-4) has a 13-425 screw-thread, but there is another option. The 4-ml Wheaton sample vial (Z18,870-0) offers an inexpensive source of 13-425 screw-thread. These vials are borosilicate glass and can be easily connected to Pyrex® glass or other glass of similar quality.

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Editor's note: We are pleased to offer the Wheaton sample vial with 13-425 screw-thread suggested by Pavel Drasar.

Aldrich also carries other screw-thread Wheaton glassware, as well as caps and septa to fit screw-thread size 13-425. Please check the Equipment Section of our Catalog/Handbook or contact us for more information.

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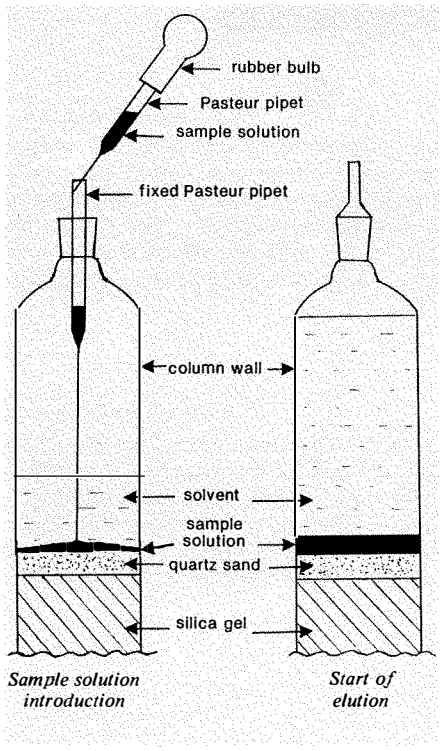
Introduction of a sample on a chromatographic column is the most critical part of widely used procedures such as "flash", "filtering-column" and "vacuum" chromatography. Most often, it is recommended that the sample solution be introduced *via* a Pasteur pipet on a wet silica gel bed from which the solvent has been eluted. This method is prone to the risks of bed surface disturbance and uneven sample application with resulting decrease in column efficiency. For several years our lab has used a simple method which does not carry these risks.

Fix a Pasteur pipet with a long capillary with narrow end (to reduce flow) above the prepared chromatographic column. The column must contain a 2-10cm layer of solvent on top of the silica gel bed, preferably covered with a 1-2cm layer of quartz sand (see Figure). The pipet tip should end just above (1-2mm) the surface of the column bed. Dissolve the sample in a solvent (mixture) of high specific gravity but low elution power. CCl_4, $CHCl_3$, benzene and cyclohexane are recommended. The specific gravity of the solvent for sample dissolution should exceed that of the eluting solvent system by at least 0.1. Rapidly transfer the sample solution using a short-ended Pasteur pipet, into the one fixed on the column. In several seconds the sample solution will form an even layer between the top of the column bed and the solvent layer. Remove the Pasteur pipet, add (if necessary) additional solvent and start chromatography (vacuum, gravity, low-pressure). The sample will automatically and very efficiently load onto the chromatographic sorbent at the beginning of elution. According to measurements, the procedure results in approximate doubling of the effectiveness of flash chromatography in terms of theoretical plate number.



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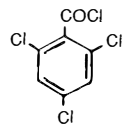
Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by

Professor K.C. Nicolaou of the University of Pennsylvania suggested that we offer ***2,4,6-trichlorobenzoyl chloride*** used in Yamaguchi's efficient method of converting long-chain hydroxy acids to large-ring lactones.[1] This macrolactonization procedure involves initial formation of a mixed anhydride between the substrate hydroxy acid and ***2,4,6-trichlorobenzoyl chloride***, followed by ring closure (lactonization) on treatment with DMAP in toluene solution. Yamaguchi's method has been used in the syntheses of macrocyclic lactones such as elaiophylin,[2] (-)-cladospolide A,[3] neomethynolide,[4] (+)-conglobatin,[5] and 6-*epi*-colletodiol.[6]



Naturally, we made it.

(1) Yamaguchi, M. *et al. Bull. Chem. Soc. Jpn.* **1979,** *52,* 1989. (2) Kinoshita, M. *et al. ibid.* **1988,** *61,* 2369. (3) Mori, K.; Maemoto, S. *Liebigs Ann. Chem.* **1987,** 863. (4) Inanaga, J.; Kawanami, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986,** *59,* 1521. (5) Schregenberger, C.; Seebach, D. *Liebigs Ann. Chem.* **1986,** 2081. (6) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984,** *25,* 2163.

It was no bother at all, just a pleasure to be able to help.

The Direct Synthesis of Non-Transition-Metal Organo Derivatives

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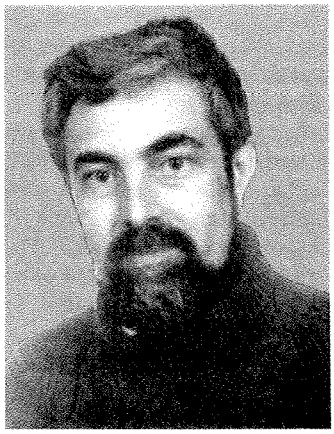


INTRODUCTION

The direct synthetic approach to the formation of organo-element derivatives has a long and distinguished history which stretches back to Frankland's isolation of the first metal alkyls in 1849 (eq. 1).

Although somewhat neglected of late, this invaluable method captured a Nobel Prize for Victor Grignard in 1912 and has since been used in many industrial processes often involving huge quantities of products.[1] In this review, the term "direct synthesis" is used to cover those reactions in which the free element is treated with hydrocarbons or alkyl/aryl halides; sometimes it is beneficial to add a halogen "getter", such as sodium or copper, to the system.

In an earlier review,[2] that champion of direct synthesis, Eugene Rochow, suggested that the greatest advantage of using the free element is its stored chemical free energy obtained by the expenditure of much thermal or electrical energy — as he states, "the hard work has already been done by the metallurgist, and the chemist can make use of all the stored energy to let his reactions run themselves." The beauty of the technique lies in its very simplicity, the high yields often obtained and the unexpectedly novel structures which can arise. Recent research suggests that many syntheses which proved to be unsuccessful or sluggish in the past may be more amenable if the reaction vessel is bathed with ultrasound.[3]

To help those readers who wish to quickly scan the review for relevant information, the elements are discussed group by group as they appear in the periodic table. Although the halogens react with many alkyl/aryl halides, this relatively trivial halogen-exchange reaction will not be discussed here.

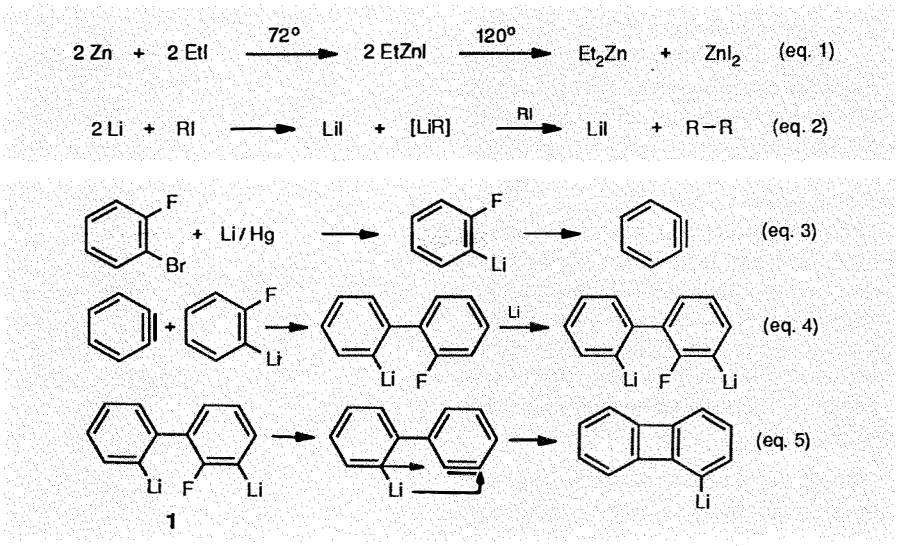
GROUP I, THE ALKALI METALS

Li, Na, K

Since all the alkali organo-derivatives are both oxygen- and moisture-sensitive, their synthesis must be carried out under dry nitrogen or argon. Organolithium reagents are conveniently prepared from alkyl/aryl chlorides and bromides in ether, THF or hydrocarbon solvents; the metal is employed as chips, wire or sand, as determined by the reactivity of the organic substrate[4] (Table 1). (The traces of sodium usually present in commercial lithium appear to be highly beneficial[5] since sodium-free lithium is often found to be inactive.) Whereas organic fluorides are normally inert, alkyl iodides tend to be too reactive and give rise to Wurtz-coupling products (eq. 2).

Although lithium does not react readily with fluorides, Wittig[6] has used lithium amalgam to metallate aryl fluorides in the ortho position (eqs. 3 and 4). Work-up of the products, which involved hydrolysis, gave biphenylene in about 30% yield; thus, it would appear that the reaction in equation 4 could be a ready source of 1-lithiobiphenylenes which are probably formed from **1** *via* an intramolecular addition to an aryne (eq. 5).

Curious products have been found



during the attempted formation of intermediate lithium species from some perchlorinated organic compounds[7-10] (eqs. 6-8). Several other reactions which probably involve the prior formation of lithium reagents are found to be accelerated in the presence of ultrasound and, in one case, will actually occur in *damp* tetrahydrofuran.[3]

The X-ray crystal structures of organolithiums have been reviewed by Setzer and Schleyer[11] who include data on aromatic anionic species, such as dilithium naphthalide, which are not considered to be within the scope of this discussion.

Synthetic work with the finely divided heavier alkali metals is altogether more difficult than that employing lithium. Due to the pyrophoric nature of the reagents, it is recommended that the entire, flame-dried apparatus be placed in a nitrogen-filled glovebox and continuously flushed with purified, dry nitrogen. The organometallic products are also extremely reactive and care must be taken to choose a solvent which cannot be metallated; their ease of decomposition (*via* α or, more commonly, β elimination) is K > Na > Li.

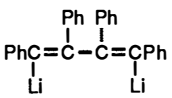
GROUP II ELEMENTS
Beryllium and magnesium

Direct synthesis appears not to be the method of choice for preparing organoberyllium compounds, although alkyl and arylberyllium halides can be isolated by heating the metal and RX to about 100-130° in sealed tubes.[12] In contrast, the literature describing the interaction of magnesium with organic halides to produce the well-known Grignard reagents is vast. The constitution of Grignard reagents in solution is complex and depends, among other things, on the solvent, the halogen, concentration and temperature.[13] Normally, the reaction (eq. 9) is carried out under dry nitrogen in aprotic, polar solvents such as ethers or tertiary amines, but occasionally hydrocarbons have been employed. Although the order of reactivity of the organic halide is I > Br > Cl > F, it is often found that the reaction has an induction period, probably associated with the layer of oxide which tends to coat magnesium; a tiny crystal of iodine is usually sufficient to activate the metal surface and cause the reaction to start. Full synthetic details are available,[13,14] including those for large-scale reactions.[1,15]

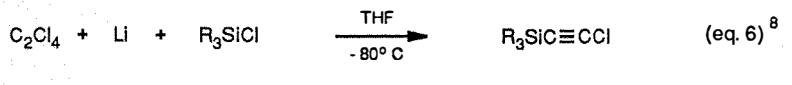
Among the more specialized Grignard reagents prepared by direct synthesis are

Table I

Direct Synthesis of Organo Derivatives of the Alkali Metals[a]

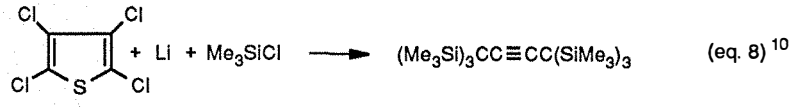
Organic Substrate	Metal	Solvent/Temp.	Product	Reference
BuBr	Li chips	ether; reflux	BuLi	b, c
	Li dispersion	pentane; reflux		d
C_3F_7I	Li/2% Na	ether; -40° C	C_3F_7Li	e
$H_2C{=}CHCl$	Li/2% Na dispersion	THF / argon	$H_2C{=}CHLi$	f
$Br(CH_2)_4Br$	Li powder	ether; -10° C	$Li(CH_2)_4Li$	g
PhBr	Li chips	ether; reflux	PhLi	h
CCl_4	Li vapor	800° C	CLi_4; C_2Li_4; C_2Li_2	i
PhC≡CPh	Li			j
Ph_3CH	Li	DME	Ph_3CLi	k
Ph_3CCl	Na/Hg	hydrocarbon	Ph_3CNa	l
n-$C_5H_{11}Cl$	K sand	pentane	n-$C_5H_{11}K$	m
PhCl	Na sand	benzene	PhNa	n
PhMe	Cs	THF	$PhCH_2Cs$	o
$PhCH_2CH_2Ph$	Cs-Na-K	THF	$PhCH_2Cs$	p
$PhOCH_2CH{=}CH_2$	Li	THF	$LiCH_2CH{=}CH_2$	q
t-RCl	Li/2% Na	pentane or Et_2O	*t*-RLi	r

(a) For the simple derivatives of lithium, see ref. 4. (b) Butyllithium is a convenient intermediate for the formation of other lithium reagents *via* Li-halogen or Li-hydrogen exchange reactions; made industrially in tonnage quantities. Argon is the preferred inert gas. (c) Gilman, H.; Zoellner, E.A.; Selby, W.M. *J. Am. Chem. Soc.* **1933,** *55,* 1252. (d) Hart, H.; Sandri, J.M. *Chem. Ind.* **1956,** 1014. (e) Beel, J.A.; Clark, H.C.; Whyman, D. *J. Chem. Soc.* **1962,** 4423. (f) West, R.; Glaze, W.H. *J. Org. Chem.* **1961,** *26,* 2096. (g) West, R.; Rochow, E.G. *ibid.* **1953,** *18,* 1793. (h) Evans, J.C.W.; Allen, C.F.H. *Organic Syntheses;* Blatt, A.H., Ed.; Wiley: New York, 1943; Coll. Vol. 2, p 517. (i) Chung, C.; Lagow, R.J. *Chem. Commun.* **1972,** 1078; Landro, F.J.; Gurak, J.A.; Chinn, J.W.; Lagow, R.J. *J. Organomet. Chem.* **1983,** *249,* 1. (j) Braye, E.H.; Hübel, W.; Caplier, I. *J. Am. Chem. Soc.* **1961,** *83,* 4406. (k) Truce, W.E.; Amos, M.F. *ibid.* **1951,** *73,* 3013. (l) Renfrow, B.; Hauser, C.R. *Organic Syntheses;* Blatt, A.H., Ed.; Wiley: New York, 1943; Coll. Vol. 2, p 607; similarly for K, Rb, Cs. (m) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1964,** *3,* 287, 362. (n) Ruschig, H.; Fugmann, R.; Meixner, W. *Angew. Chem.* **1958,** *70,* 71. (o) Collignon, N. *J. Organomet. Chem.* **1975,** *96,* 139. (p) Grovenstein, E.; Quest, D.E.; Sengupta, D. *Organomet. Synth.* **1986,** *3,* 384; many substituted derivatives can be made in this way. (q) Eisch, J.J.; Jacobs, A.M. *J. Org. Chem.* **1963,** *28,* 2145. (r) *tert*-R = adamantyl, diamantyl, noradamantyl, twistyl, triptycyl, homoadamantyl. Molle, G.; Bauer, P.; DuBois, J.E. *J. Org. Chem.* **1983,** *48,* 2975.



(eq. 6)[8]

(eq. 7)[9]



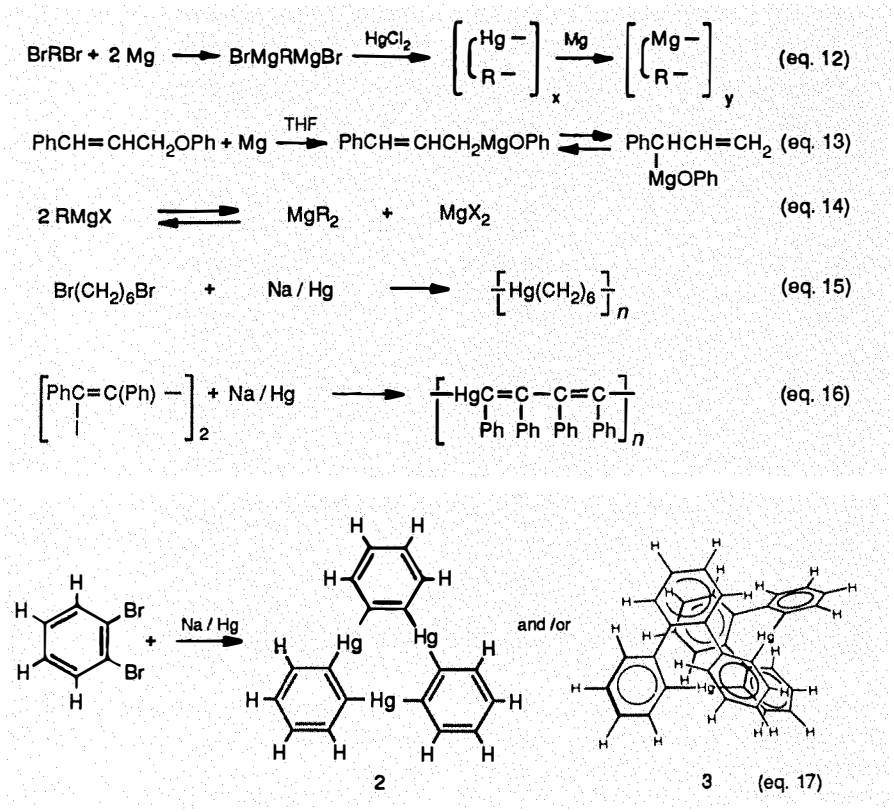
(eq. 8)[10]

$$RX + Mg \longrightarrow \text{"}RMgX\text{"} \quad \text{(eq. 9)}$$
R = alkyl or aryl, X = halogen

$$R_FX + Mg \longrightarrow R_FMgX \quad \text{(eq. 10)}$$
$R_F = CF_3, C_3F_7$

$$C_6X_5Y + Mg \longrightarrow C_6X_5MgY \quad \text{(eq. 11)}$$
X = F; Y = F, Cl, Br, I
X = Cl; Y = Cl

The classical method of preparing R_2Mg derivatives is to add dioxane to the corresponding Grignard and force the "equilibrium" in equation 14 to the right by removing the dihalide as a dioxane complex. However, this procedure leaves the dialkyl magnesium containing traces of ether solvent. Ether-free diamylmagnesium has been obtained[26] by treating amyl chloride with powdered magnesium at 85°.



those containing perfluoroalkyl[16] (eq. 10) and perhaloaryl (eq. 11; I,[17] Cl[18]) groups, the latter perhaloarylmagnesium halides being useful precursors of tetrahaloarynes. Di-Grignard reagents of α,ω-dihaloalkanes, $X(CH_2)_nX$, with n varying from 4 to 12, can also be prepared[19,20] and have been used to synthesize magnesacycloalkanes *via* the mercurials[20] (eq. 12). Wurtz coupling is a problem with some organohalides and, in such cases, "ether-splitting" reactions can be used to give the related magnesium aryl oxides[21,22] (or aryl sulfides in a few cases[23]) (eq. 13).[22] The corresponding alkoxides result when 1:1 mixtures of RCl and R'OH are treated with magnesium.[24] Recent innovations include the activation of magnesium by either condensation of the vapor to -196° (liquid nitrogen) with a solvent and warming the slurry to room temperature or reducing $MgCl_2$ with potassium in refluxing THF; such an activated metal will even form Grignard reagents with aryl fluorides.[13,14]

Although magnesium does not react with *sec*-butyl chloride either alone or in hydrocarbon solvent, addition of limited amounts of ether to these systems gives di-*sec*-butylmagnesium which can be made ether-free by co-distillation with hydrocarbon.[27] Dicyclopentadienylmagnesium is the product formed by heating magnesium to about 500° and passing cyclopentadiene vapor over it;[28] a recent innovation is the use of cyclopentadienyltitanium trichloride as a catalyst which allows the reaction to proceed at 0° in THF.[29] It is also possible to make unsolvated amine complexes of dibutylmagnesium directly *via* the reaction of *n*-butyl chloride, magnesium and tetramethylethylenediamine in hexane.[30]

Calcium, strontium and barium

Earlier problems associated with the syntheses of calcium, strontium and barium organo-derivatives appear to have stemmed from impurities in the metals; certainly removal of virtually all the sodium from calcium allows the smooth formation of RCaX in ethers[31] or even hydrocarbons.[32] Contrary to previous reports, organic chlorides and bromides, as well as the iodides, can be employed. Co-condensation of Ca, Sr and Ba vapors with alkyl halides at low temperature gives solvent-free alkylhalogenometal products; under the same conditions cyclopentadiene and indene form $M(C_5H_5)_2$ and $M(C_9H_7)_2$ respectively, in high yield.[33] Liquid ammonia is sometimes a convenient solvent for metallation reactions of the alkaline earths. $Ca(C_5H_5)_2$,[34] $Ca(C_9H_7)_2$[34] and $M(C{\equiv}CPh)_2$ (M = Ca; Sr; **Ba**[35]) have been synthesized in good yields in this medium.

Zinc, cadmium and mercury

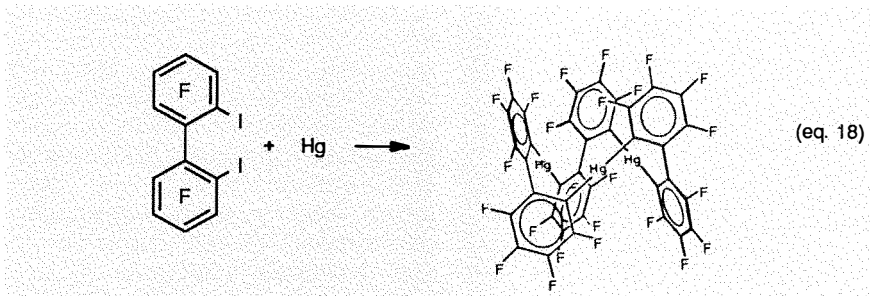
Modifications to Frankland's original method for the production of organozinc derivatives have included the use of Zn-Cu couples and Zn-Na alloys,[25a] but the best method is to form active zinc *via* either the reduction of $ZnCl_2$ with potassium in THF[25a] or to produce slurries by condensation of zinc vapor in various solvents.[25b] These powders will react with alkyl/aryl bromides or iodides giving, after distillation, R_2Zn.[25] Similarly, cadmium slurries form alkylcadmium iodides with RI.[25b] Active zinc also produces higher yields when used in the Reformatsky reaction.[25a] Details are available[36] for the preparation of highly active zinc-copper couples used to make cyclopropanes from a mixture of dihalomethane, olefin and Zn-Cu (the Simmons-Smith reaction).

Zinc treated with alkyl,[37] perfluoroalkyl[38] or perfluoroaryl[39] halides in coordinating solvents forms RZnX, whereas heating Zn, Cd or Hg directly in a sealed tube with iodopentafluorobenzene produces the bis(pentafluorophenyls), $M(C_6F_5)_2$,[17,40] in a reaction similar to Emeleus' classic preparation of the perfluoroalkyls from CF_3I. Perfluoroalkyl derivatives can now be prepared in high yield from metal atoms and either R_FI[25b] or CF_3 radicals made in a radiofrequency discharge.[41]

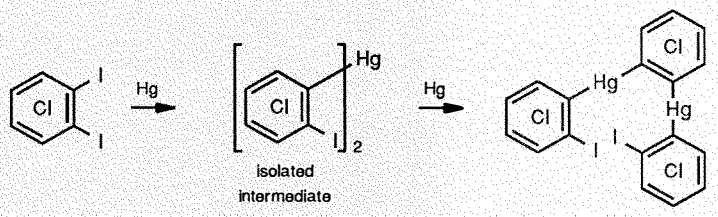
Although not strictly within the scope of this review, mention ought to be made of the fact that electrochemical oxidation of metals is a convenient route to many organometallic species.[42] Typical syntheses, including diagrams of apparatuses, have been described in detail for MeCdI, EtCdI and $C_6F_5CdBr{\cdot}2,2'$-bipyridyl.[43]

Alkali metal amalgams, on shaking with organic halides, give R_2Hg,[40] usually in very good yield; when a dihalide is used, mercury heterocycles result (eqs. 15,[44] 16[45] and 17[46]). With methyl- or methoxy-substituted dihalobenzenes in equation 17,

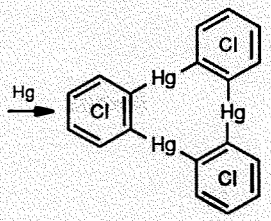
no substituted derivatives of terphenylenemercury dimer **3** were detected.[47] Macrocycles, including the perfluoro-[48] and perchloro-[47b] analogs of **2** also result when mercury is heated in sealed tubes with the corresponding diiodides (eqs. 18[49] and 19).

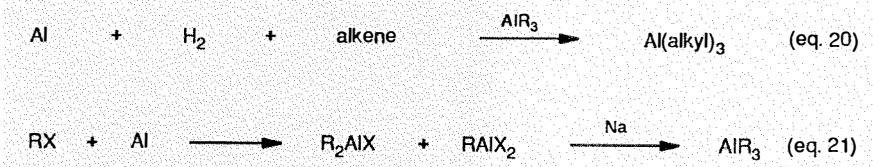


(eq. 18)



(eq. 19)





GROUP III ELEMENTS
B, Al, Ga, In, Tl

Elemental boron is apparently too inert to undergo direct syntheses.[2] Although the other Group III elements have been used since the turn of the century, recent work has concentrated on the activated metals.[25] As pointed out by Klabunde and Murdock,[25b] the commercial-scale evaporation of aluminum is now so commonplace that their metal vapor-solvent vapor cocondensation technique for activation of aluminum has a high industrial potential; the powders can be stored for months under nitrogen without losing their activity.

Typical of these activated elements, aluminum and indium react readily with alkyl or aryl halides to give organometal halides;[25,50] in lieu of activation, magnesium alloys of Al,[2] Ga[51] and In[52] have been used to speed up the reactions with alkyl halides. Bulk indium will attack alkyl bromides and iodides at room temperature[53] but the formation of $RInX_2$ and R_2InX takes days rather than hours. Tris(pentafluorophenyl)indium results when an excess of indium is heated in a sealed tube to 160° with C_6F_5I; with less indium, some $(C_6F_5)_2InI$ is also produced.[54] ***Caution:*** *It is not recommended that aluminum be heated with polyfluoroaromatic compounds because some Al-C_6F_5 compounds have been known to detonate; indeed, any direct syntheses in autoclaves or glass tubes which involve aluminum should be considered extremely hazardous.*

Electrochemically-assisted syntheses of $RInX_2$ and $RInX_2$•2,2′-bipyridyl (R = Me, Et, Ph, $PhCH_2$, C_6F_5; X = Cl, Br, I) occur in cells of the type $Pt^-[RX + MeCN]In^+$; when R'_4NX replaces the 2,2′-bipyridyl, anionic species $[RInX_3]^-$ result.[55] Cyanoethyl derivatives of thallium are formed in electrolysis cells containing β-iodopropionitrile.[42b]

Aluminum alkyls are made industrially in huge quantities by two "direct" processes which are difficult to adapt safely to a smaller scale (eqs. 20 and 21).

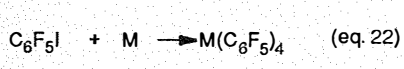
GROUP IV ELEMENTS
Si, Ge, Sn, Pb

Direct synthesis is particularly important for the the Group IV elements[2,56,57] and is used to make available huge quantities of dimethylsilicon dichloride for the silicone industry (the Rochow process). Methyl chloride (or, in general, a variety of alkyl or aryl halides[56]) is passed over heated silicon which is usually mixed with copper to keep the operating temperature lower (280-400°). The main products, in order of abundance, are Me_2SiCl_2, $MeSiCl_3$ and Me_3SiCl of which the first, being most important commercially, can be made to account for over 85% of the total products. Even with a simple halide like methyl chloride, over 40 products have been identified; also, β-hydrogen loss to form alkenes can be troublesome with the higher alkyls;[56] similar reactions occur with germanium[57] and tin.[38,58] Lead,[25b] usually alloyed with sodium,[2] will react with organic halides, but the products are normally PbR_4 because organolead halides are often unstable to heat and tend to disproportionate into PbR_4, PbX_2 and R_2; however, activated lead slurries in ethers such as diglyme and dioxane give Me_3PbI when treated with methyl iodide.[25b] Electrochemical syntheses of the tetrapropyls and tetrabutyls of lead and tin can be accomplished in an undivided cell provided with a zinc cathode and a lead (or tin) anode; dimethylformamide and dimethyl sulfoxide were the solvents of choice.[59]

Polyfluoroaromatic derivatives of germanium and tin are very stable thermally and hence make good candidates for high-temperature syntheses not involving activation of the elements (eqs. 22,[49a] 23[49a] and 24[49a]).

GROUP V ELEMENTS
P, As, Sb, Bi

Red phosphorus reacts on heating with a wide variety of alkyl iodides (in the presence of iodine as a catalyst) to give



(eq. 22)

M = Ge (325° C), Sn (240°)

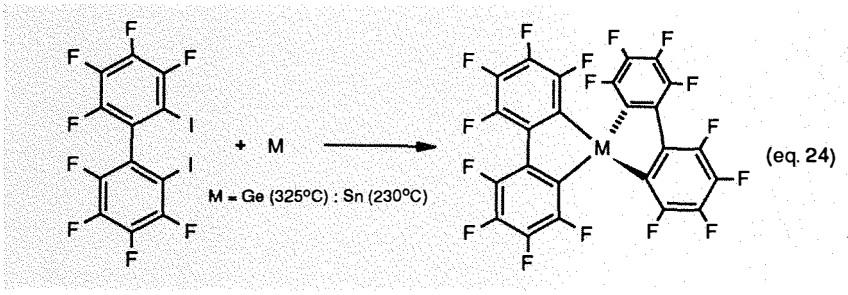
(eq. 23)

alkylphosphorus iodides which, on hydrolysis, yield the oxides, R_3PO.[60] The more reactive white allotrope,[60] or red phosphorus activated with copper,[61] will even attack methyl chloride under pressure at temperatures between 200° and 350°, the products in this case being tetramethylphosphonium chloride, $MePCl_2$, Me_2PCl and PCl_3. Alcohols ($>C_5$) also react with red phosphorus at 200° (eq. 25).[60] Organic halides are attacked by copper-activated arsenic, antimony and bismuth under flow conditions at elevated temperatures to yield RMX_2 and R_2MX.[62] Perfluoroalkyl iodides, in autoclaves or sealed tubes, combine with phosphorus,[63] arsenic[64] and antimony[65] forming mainly $M(CF_3)_3$ together with varying amounts of CF_3MI_2 and $(CF_3)_2MI$; iodopentafluorobenzene reacts similarly giving $M(C_6F_5)_3$.[49a]

When the organic halide employed in the synthesis possesses a halogen on two neighboring carbon atoms, the products can include some novel heterocycles [(eqs. 26[66] and 27 (X = H; M = P,[67] As;[48] X = F; M = P,[48] As,[48,68], Sb,[48,68,69] Bi;[70] X = Cl; M = As,[71] Sb,[69,71] Bi[71])]. By using a mixture of tetrafluoroethylene and iodine in the presence of phosphorus, the required (but unstable) diiodide is formed *in situ* (eq. 28).[66] These reactions should be capable of extension to a wide variety of other heterocycles and deserve further study. The old Paneth technique,[72] in which heated metallic mirrors were etched away by alkyl radicals to give volatile organometallics, has been extended to CF_3 radicals. These are produced by pyrolysis of hexafluoroacetone and, when passed over a heated bismuth film, give small quantities of $Bi(CF_3)_3$.[73] Bismuth organometallics have also been synthesized *via* electrolysis using a Bi cathode in the presence of RI.[74]

GROUP VI ELEMENTS
S, Se, Te

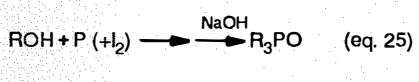
The use of free chalcogens, especially sulfur,[75] in organic synthesis is very extensive and only partial coverage will be attempted here. Many alkyl/aryl halides react on heating with S, Se and Te; the method has also been extended to include the perfluoroalkyls[76] and perfluoroaryls[49a] (see eqs. 29-32). By suitable choice of reagents, it is possible to perform some of these direct syntheses in aqueous media[2] (eqs. 33 and 34). As found in Group V, when the organic substrate possesses two reactive halogen atoms (or if $C_2F_4 + I_2$ is used), heterocyclic products result, some examples of which are shown in equations 35,[77] 36,[78] 37,[49a] 38,[79,81] 39,[82] 40,[66,76b] 41[76b,83] and 42[76b]).



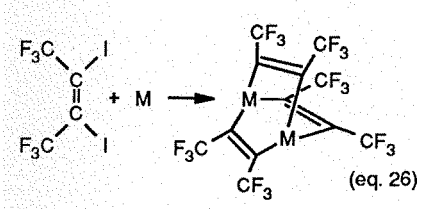
(eq. 24)

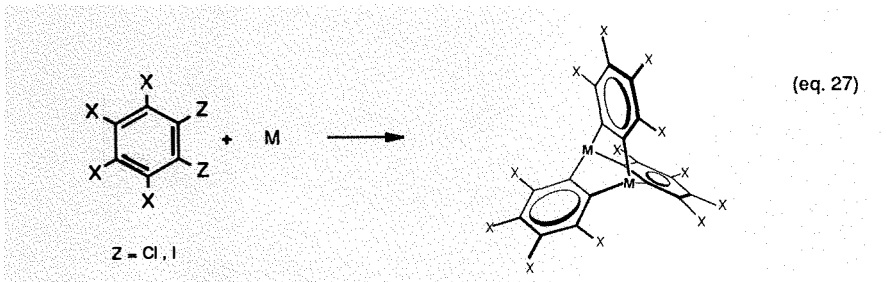
On passing either tetrafluoroethylene or polyfluorinated acetylenes through refluxing sulfur at atmospheric pressure, different types of heterocycles result (eqs. 43[66] and 44[76b]).

A variety of substituted thiophenes and selenophenes have been obtained from hydrocarbons but the reactions can be complex. For example, selenium and acetylene produce no less than 33 products;[84] sulfur and acetylene[85] give, among others, compounds 4, 5 and 6. The commercial synthesis of thiophene, 4, is achieved[85] by direct interaction of sulfur with C_4 hydrocarbons at 565 °; dibenzothiophene is also made on a large scale by heating sulfur with biphenyl in the presence of $AlCl_3$ as a catalyst,[85,86]



(eq. 25)


(eq. 26)



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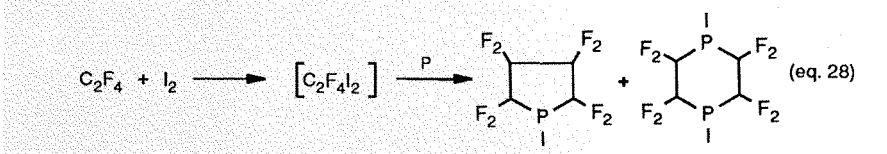
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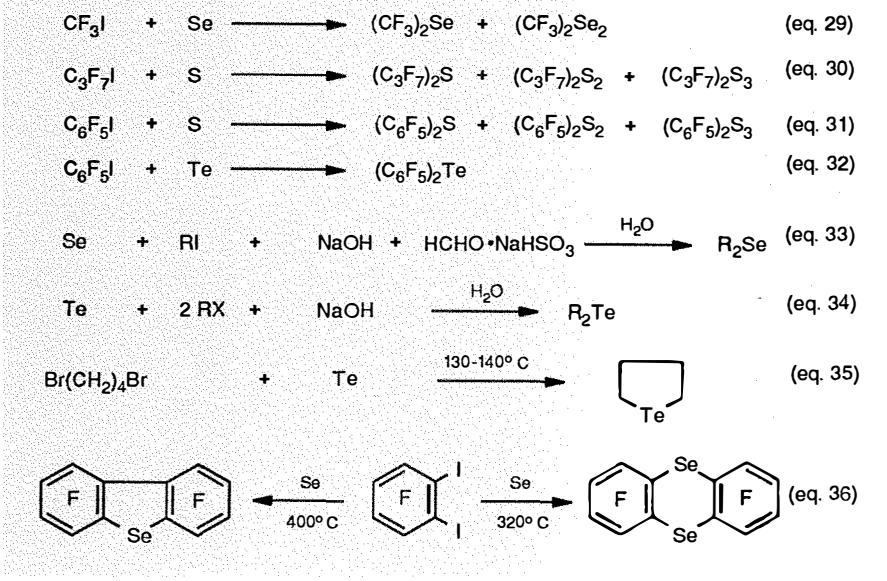

(eq. 29)
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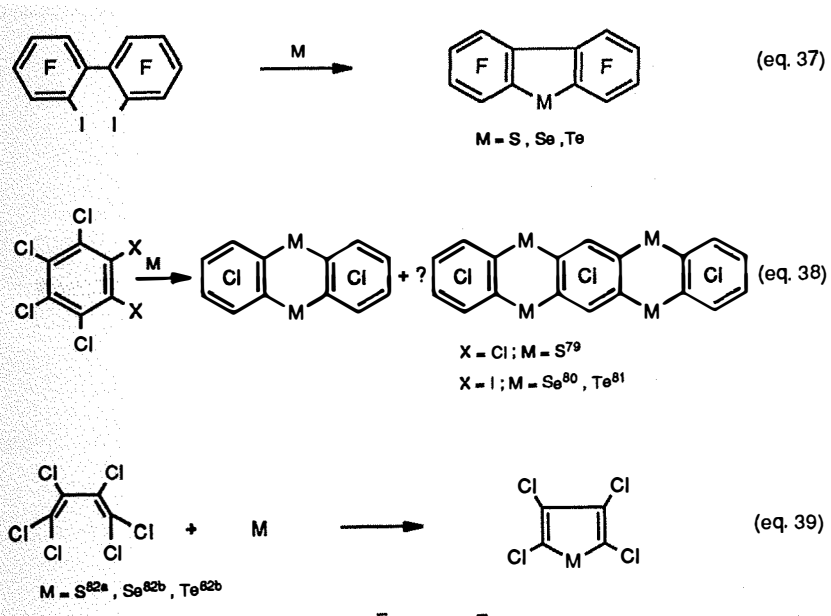
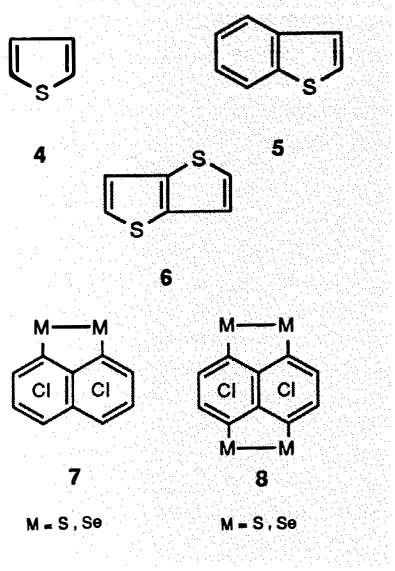
(eq. 36)





up to 80% conversion being possible. Somewhat surprisingly, other similar hydrocarbons[85] tend only to evolve hydrogen sulfide. (Dibenzoselenophene results from the insertion of selenium into biphenylene.[87]) Other reactions between sulfur and hydrocarbons include equations 45,[88] 46[88] and 47[89] (but see also references 75a and 75b, the latter containing a discussion of the reactions of atomic sulfur).

There is much current interest in compounds containing aromatic rings with polychalcogenide bridges because of their possible use in the formation of electrically conducting complexes. Towards this end, Klingsberg has achieved the syntheses of compounds **7** and **8** simply by heating sulfur or selenium with octachloronaphthalene.[90] Russian work[91] has shown that high yields of bis(pentafluorophenyl) sulfide can be obtained by treating C_6F_5H with sulfur in the presence of antimony pentafluoride; $(C_6F_5)_2S_2$ is also isolated in 10% yield as a by-product. If 1,2,4,5-tetrafluorobenzene is used, a polymer, $[-S\text{-}C_6F_4-]_n$, results. Trifluoromethyl radicals, generated by the pyrolysis of hexafluoroacetone, attack a tellurium mirror to give $CF_3Te\text{-}TeCF_3$.[72]

CONCLUSION

As can be seen from this short review, the simple technique of direct synthesis gives rise to a very wide spectrum of organometallic compounds, some of which have remarkably complex structures. Often the two reactants can be taken "off the shelf" and turned, within an hour or two, into a desired product; in some cases, there is no other available synthesis. It is because of this simplicity that industry has been quick to exploit the method wherever possible. Apart from Grignard production,

direct synthesis is now relatively little used by academic research groups, which is surprising since it would appear to be the best available way to make thermally stable heterocycles such as the 1,6-disubstituted triptycenes; undoubtedly, many new heterocycles await discovery by this technique. Perhaps the biggest stimulus to further research will eventually prove to be the potential profitability of compounds related to Klingsberg's chalcogen-bridged naphthalenes.[90]

References:

1) Birmingham, J.M. *et al.* "Industrial Synthesis and Applications of Organometallics." In *Conference Proceedings;* Whipple, H.E., Ed.; *Ann. N.Y. Acad. Sci.* **1965,** *125,* 1.
2) Rochow, E.G. *J. Chem. Ed.* **1966,** *43,* 58.
3) Bremner, D. *Chem. Brit.* **1986,** 633.
4) Wakefield, B.J. *The Chemistry of Organolithium Compounds;* Pergamon Press: Oxford, 1974.
5) Kamienski, C.W.; Esmay, D.L. *J. Org. Chem.* **1960,** *25,* 1807; see, however, *Chem. Brit.* **1987,** *27* for a warning.
6) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956,** *89,* 1334.
7) Ballard, D.H. *et al. Pure Appl. Chem.* **1969,** *19,* 449.
8) West, R.; Quass, L.C. *J. Organomet. Chem.* **1969,** *18,* 55.
9) Shiina, K.; Gilman, H. *J. Am. Chem. Soc.* **1966,** *88,* 5367.
10) Ballard, D.H.; Gilman, H. *J. Organomet. Chem.* **1968,** *12,* 237.
11) Setzer, W.; Schleyer, P.v.R. *Adv. Organomet. Chem.* **1985,** *24,* 353.
12) Gilman, H.; Schulze, F. *J. Am. Chem. Soc.* **1927,** *49,* 2904. Zakharkin, L.I.; Okhlobystin, O.Y.; Strunin, B.N. *Isv. Akad. Nauk. S.S.S.R.* **1961,** 2254; *Chem. Abstr.* **1962,** *57,* 13785h.
13) Lindsell, W.E. *Comprehensive Organometallic Chemistry;* Pergamon Press: Oxford, 1982; Vol. I, Chapter 4. Ashby, E.C. *Quart. Rev. (London)* **1967,** *21,* 259.
14) Kharasch, M.S.; Reinmuth, O. *Grignard Reagents of Non-Metallic Substances;* Prentice Hall: Englewood Cliffs, 1954. Ioffe, S.T.; Nesmeyanov, A. *The Organic Compounds of Magnesium, Beryllium, Calcium, Strontium and Barium,* North Holland: Amsterdam, 1967.
15) Bott, L.L. *Hydrocarbon Process. Pet. Refiner* **1965,** *44,* 115.
16) McBee, E.T.; Battershell, R.D.; Braendlin, H.P. *J. Org. Chem.* **1963,** *28,* 1131. Treichel, P.M.; Stone, F.G.A. *Adv. Organomet. Chem.* **1964,** *1,* 143.
17) Cohen, S.C.; Massey, A.G. *Adv. Fluorine Chem.* **1970,** *6,* 83.
18) Pearson, D.; Cowan, D. *Org. Synth.* **1964,** *44,* 78. See also Chivers, T. *The Chemistry of the Carbon-Halogen Bond;* Patai, S., Ed.; Wiley: New York, 1973; p 917.
19) Normant, H. *Bull. Soc. Chim. Fr.* **1972,** 2161. Whitesides, G.M.; Gutowski, F.D. *J. Org. Chem.* **1976,** *41,* 2882.
20) Bickelhaupt, F.; Akkermann, O.S. *Organomet. Synth.* **1986,** *3,* 403.
21) Maercker, A. *J. Organomet. Chem.* **1969,** *18,* 249. Maercker, A.; Jaroschek, H.-J. *ibid.* **1976,** *108,* 145.
22) Maercker, A. *Organomet. Synth.* **1986,** *3,* 398.
23) Maercker, A.; Jaroschek, H.-J. *J. Organomet. Chem.* **1976,** *116,* 21.
24) Bryce-Smith, D.; Graham, I.F. *Chem. Commun.* **1966,** 559.
25) a) Rieke, R.D. *Acc. Chem. Res.* **1977,** *10,* 301. b) Klabunde, K.J.; Murdock, T.O. *J. Org. Chem.* **1979,** *44,* 3901.
26) Glaze, W.H.; Selamn, C.M. *J. Organomet. Chem.* **1966,** *5,* 480.
27) Kamienski, C.W.; Eastham, J. F. *J. Org. Chem.* **1969,** *34,* 1116.
28) Barber, W.A. *Inorg. Synth.* **1960,** *6,* 11.
29) Saito, T. *Chem. Commun.* **1971,** 1422.
30) Gitlitz, M.H.; Considine, W.J. *J. Organomet. Chem.* **1970,** *23,* 291.
31) Bryce-Smith, D.; Skinner, A.C. *J. Chem. Soc.* **1963,** 577. Kawabata, N.; Matsumura, A.; Yamashita, S. *Tetrahedron* **1973,** *29,* 1069.
32) Kawabata, N.; Matsumura, A.; Yamashita, S. *J. Org. Chem.* **1973,** *38,* 4268, 3403.
33) Gowenlock, B.G.; Lindsell, W.E.; Singh, B. *J. Chem. Soc., Dalton Trans.* **1978,** 657.
34) Kirilov, M.; Petrov, G.; Angelov, C. *J. Organomet. Chem.* **1976,** *113,* 225.
35) Coles, M.A.; Hart, F.A. *ibid.* **1971,** *32,* 279.
36) LeGoff, E. *J. Org. Chem.* **1964,** *29,* 2048.
37) Gaudemar, M. *Organomet. Synth.* **1986,** *3,* 407, 409, 411.
38) Miller, W.T.; Bergman, E.; Fainberg, A.H. *J. Am. Chem. Soc.* **1957,** *79,* 4159.
39) Evans, D.F.; Phillips, R.F. *J. Chem. Soc., Dalton Trans.* **1973,** 978.
40) Larock, R.C. *Organomercury Compounds in Organic Synthesis;* Springer-Verlag: New York, 1985; Chapter 2.
41) Bierschenk, T.R.; Bailey, W.I.; Lagow, R.J. *Organomet. Synth.* **1986,** *3,* 426. Morrison, J.A. *Adv. Inorg. Chem. Radiochem.* **1983,** *27,* 293.
42) a) Tuck, D.G. *Pure Appl. Chem.* **1979,** *51,* 2005. b) Tedoradze, G.A. *J. Organomet. Chem.* **1975,** *88,* 1.
43) Habeeb, J.J.; Osman, A.; Tuck, D.G. *Organomet. Synth.* **1986,** *3,* 417
44) Sawatsky, H.; Wright, G.F. *Can. J. Chem.* **1958,** *36,* 1555.
45) Braye, E.H.; Hübel, W.; Caplier, I. *J. Am. Chem. Soc.* **1961,** *83,* 4406.
46) Awad, S.B.; Brown, D.S.; Cohen, S.C.; Humphries, R.E.; Massey, A.G. *J. Organomet. Chem.* **1977,** *127,* 127.
47) a) Wittig, G.; Härle, H. *Annalen* **1959,** *623,* 17. b) Al-Jabar, N.A.A.; Massey, A.G. *J. Organomet. Chem.* **1984,** *275,* 9.
48) Woodard, C.M.; Hughes, G.; Massey, A.G. *ibid.* **1976,** *112,* 9.
49) a) Cohen, S.C.; Reddy, M.L.N.; Massey, A.G. *Chem. Commun.* **1967,** 451. *Idem J. Organomet. Chem.* **1968,** *11,* 563. Massey, A.G.; Reddy, M.L.N. *Organomet. Synth.* **1986,** *3,* 591. b) Weidenbruch, M.; Wessal, N. *Chem. Ber.* **1972,** *105,* 173.
50) Rieke, R.D.; Chao, L. *Synth. React. Inorg. Met.-Org. Chem.* **1974,** *4,* 101. *Idem ibid.* **1975,** *5,* 165. *Idem J. Org. Chem.* **1975,** *40,* 2253.
51) Fedorov, V.A.; Makarenko, V.G. *Tr. Khim. Khim. Tekhnol.* **1975,** 19; *Chem. Abstr.* **1976,** *85,* 143170w.
52) Todt, E.; Dötzer, R. *Z. Anorg. Chem.* **1963,** *321,* 120.
53) Gynane, M.J.S.; Worrall, I.J. *J. Organomet. Chem.* **1974,** *81,* 329.
54) Deacon, G.B.; Parrott, J.C. *Aust. J. Chem.* **1971,** *24,* 1771.
55) Habeeb, J.J.; Said, F.F.; Tuck, D.G. *J. Organomet. Chem.* **1980,** *190,* 325.
56) Petrov, A.D. *Synthesis of Organosilicon Monomers,* Consultants Bureau: New York, 1964. Zuckerman, J.J. *Adv. Inorg. Chem. Radiochem.* **1964,** *6,* 383. Voohoeve, R.J.H. *Organohalosilanes — Precursors to Silicones;* Elsevier: New York, 1967. Rochow, E.G. *J. Am. Chem. Soc.* **1945,** *67,* 963, 1772.
57) Rochow, E.G. *et al. J. Am. Chem. Soc.* **1947,** *69,* 1729. *Idem ibid.* **1950,** *72,* 198. *Idem ibid.* **1951,** *73,* 5486. Quane, D.; Bottei, R.S. *Chem. Rev.* **1963,** *63,* 403. Moedritzer, K. *J. Organomet. Chem.* **1966,** *6,* 284.
58) Luijten, J.G.A.; van der Kerk, G.J.M. *Organometallic Compounds of the Group IV Elements;* MacDiarmid, A.G., Ed.; Edward Arnold: London, 1968; Neumann, W.P. *Angew. Chem., Int. Ed. Engl.* **1963,** *2,* 165.
59) Mengoli, G. *et al. J. Electrochem. Soc.* **1972,** *124,* 364. *Idem Electrochim. Acta* **1976,** *21,* 889. *Idem J. Appl. Electrochem.* **1976,** *6,* 521.
60) Hays, H.R.; Peterson, D.J. *Organophosphorus Compounds;* Kosolapoff, G.M.; Maier, L., Eds.; Wiley-Interscience: New York, 1972; Vol. 3, p 341.
61) Maier, L. *Angew. Chem.* **1959,** *71,* 574, 575.
62) Maier, L.; Rochow, E.G.; Fernelius, W.C. *J. Inorg. Nucl. Chem.* **1961,** *16,* 213; Maier, L. *Inorg. Synth.* **1963,** *7,* 82.
63) Bennett, F.W.; Emeleus, H.J.; Haszeldine, R.N. *J. Chem. Soc.* **1953,** 1565. *Idem ibid.* **1954,** 3598, 3896.
64) Brandt, G.R.A.; Emeleus, H.J.; Haszeldine, R.N. *J. Chem. Soc.* **1952,** 2552. Emeleus, H.J.; Haszeldine, R.N.; Walaschewski, E.G. *ibid.* **1953,** 1552. Ayscough, P.B.; Emeleus, H.J. *ibid.* **1954,** 3381.
65) Dale, J.W.; Emeleus, H.J.; Haszeldine, R.N.; Moss, J.H. *ibid.* **1957,** 3708.
66) Krespan, C.G. In *The Chemistry of Sulfides;* Tobolsky, A.V., Ed.; Wiley Interscience: New York, 1968; p 211. Krespan, C.G. *J. Am. Chem. Soc.* **1961,** *83,* 3432. Krespan, C.G.; Langkammerer, C.M. *J. Org Chem.* **1962,** *27,* 3584.
67) Weinberg, K.G.; Whipple, E.B. *J. Am. Chem. Soc.* **1971,** *93,* 1801. Weinberg, K.G. *J. Org. Chem.* **1975,** *40,* 3856. Weinberg, K.G. U.S. Patent 3 557 204, 1972; *Chem. Abstr.* **1972,** *76,* 153927b. Weinberg, K.G. U.S. Patent 3 651 147, 1971; *Chem. Abstr.* **1971,** *75,* 6088e.
68) Mistry, T.K.; Massey, A.G. *J. Organomet. Chem.* **1981,** *209,* 45.
69) Al-Jabar, N.A.A.; Massey, A.G.; Mistry, T.K. *Organomet. Synth.* **1986,** *3,* 630. Al-Jabar, N.A.A.; Massey, A.G. *J. Organomet. Chem.* **1984,** *276,* 331.
70) Massey, A.G., unpublished results.
71) Humphries, R.E.; Al-Jabar, N.A.A.; Bowen, D.; Massey, A.G.; Deacon, G.B. *J. Organomet. Chem.* **1987,** *319,* 59.
72) Paneth, F.A. *Trans. Faraday Soc.* **1934,** *30,* 179. *Idem J. Chem. Soc.* **1935,** 366.
73) Bell, T.N.; Pullman, B.J.; West, B.O. *Aust. J. Chem.* **1963,** *16,* 722.
74) Chernykh, I.N.; Tomilov, A.P. *Elektrokhimiya* **1974,** *10,* 1424; *Chem. Abstr.* **1975,** *82,* 91701m.
75) a) Oae, S. *Organic Chemistry of Sulfur;* Plenum Press: New York, 1977. *The Chemistry of Organic Sulfur Compounds;* Kharasch, N.; Meyers, C.Y., Eds.; Pergamon Press: New York, 1966; Vol. 2. b) Strauz, O.P. In *Organosulfur Chemistry;* Janssen, M.J.; Ed.; Wiley Interscience: New York, 1967; p 11.
76) a) Hauptschein, M.; Grosse, A.V. *J. Am. Chem. Soc.* **1951,** *73,* 5461; Brandt, G.A.R.; Emeleus, H.J.; Haszeldine, R.N. *J. Chem. Soc.* **1952,** 2198. *Idem Science,* **1953,** *117,* 311. $Te(CF_3)_2$ is too unstable to make by this method. b) Banks, R.E.; Haszeldine, R.N. In *The Chemistry of Organic Sulfur Compounds;* Kharasch, N.; Meyers, C.Y., Eds.; Pergamon Press: New York; Vol. 2, p 137.
77) Duffield, A.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1965,** *87,* 2920.
78) Cohen, S.C.; Massey, A.G.; Woodard, C.M. *Organomet. Synth.* **1986,** *3,* 642.
79) Beck, G.; Holtschmidt, H. Ger. Offen. 2 229 162, 1974; *Chem. Abstr.* **1974,** *80,* 83004e.
80) Humphries, R.E.; Massey, A.G., unpublished results.
81) Humphries, R.E.; Al-Jabar, N.A.A.; Massey, A.G., unpublished results.
82) a) Geering, E.J. *J. Org. Chem.* **1959,** *24,* 1128. b) Mack, W. *Angew. Chem., Int. Ed. Engl.* **1965,** *4,* 245.
83) Tiers, G.V.D. *J. Org. Chem.* **1961,** *26,* 2538.
84) Gronowitz, S. *et al. Chem. Scr.* **1974,** *5,* 236. *Idem ibid.* **1976,** *10,* 159.
85) Klemm, L.H.; Karchesy, J.J.; McCoy, D.R. *Phosphorus Sulfur* **1979,** *7,* 9.
86) Voronkov, M.G.; Faitel'son, F.D. *Khim. Geterotsikl. Soedin.* **1967,** 245; *Chem. Abstr.* **1967,** *67,* 90744f.
87) Gaidis, J. *J. Org. Chem.* **1970,** *35,* 2811.
88) Horton, A.W. *ibid.* **1949,** *14,* 761.
89) Dayagi, S.; Goldberg, I.; Shmueli, V. *Tetrahedron* **1970,** *26,* 411.
90) Klingsberg, E. *ibid.* **1972,** *28,* 963.
91) Yakobson, G.G.; Furin, G.G.; Terent'eva, T.V. *J. Org. Chem. U.S.S.R.* **1974,** *10,* 802 (English pagination).

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Teaching Organic Synthesis: Why, How, What?

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When there is much desire to learn, there of necessity will be much arguing, much writing, many opinions; for opinion, in good men, is but knowledge in the making.
John Milton (1608-1674)

1. WHY

One of the great organic chemists of the last century, Marcelin Berthelot,[a] wrote:

Chemistry creates its subject. This creative ability, similar to that of art, essentially distinguishes Chemistry among the natural sciences.

One of the great organic chemists of this century, Jack E. Baldwin, wrote:

It is foolish to give the impression that Chemistry is some sort of sub-branch of Physics. It is not. Chemistry has a totally different philosophy and has a strongly creative potential. It can create substances and materials never dreamt of before.

One further step to the purely observational science, the preparation of substances has been the great achievement of Chemistry since its birth. Synthesis is the name of the game and particularly so in Organic Chemistry.

Organic Synthesis must be an important topic in Organic Chemistry curricula at the upper level. It is a complex subject and it is up to the teacher to make it clear, comprehensive, and attractive:

Science can be mastered from books alone only at the most elementary level. For the journey to the frontiers of knowledge, an experienced and willing master is needed as a guide.

E. Borek

2. HOW

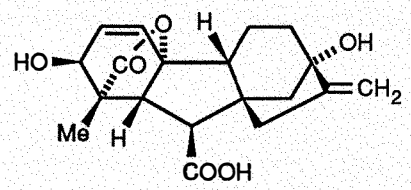
When teaching Organic Synthesis, we tend to focus mainly on planning the synthesis of rather complex molecules, prompted by their greater intellectual elegance.

This is, however, only one part, albeit an important one, of Organic Synthesis. We should also offer a wider perspective: industrial *versus* laboratory synthesis, time limitations, technical and economic considerations and the different nature of the criteria to be used in the selection of a synthetic method. Three examples are paradigmatic: *cyclobutadiene, gibberellic acid* and *acrylonitrile.*

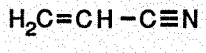
The synthesis of a highly reactive molecule, such as *cyclobutadiene,* demands esoteric reaction conditions and temperatures down to -260 °C. It involves the photochemical elimination of carbon dioxide from a precursor bicyclic lactone in a solid argon matrix.[1] Economic considerations are irrelevant. The only aim is to obtain the compound, whatever the cost and effort.

Gibberellic acid is an example of the contest of the synthetic chemist with nature, a titanic exercise in perseverance which required 41 steps for the total synthesis.[2] It constitutes a brilliant intellectual achievement providing a measure of the power

cyclobutadiene



gibberellic acid



acrylonitrile

[a] Berthelot (1827-1907) was one of the more important and influential chemists of his time. He was a professor at the Collège de France and a member of the Académie Française. He even served twice as a minister to the French government. No man is perfect, however. A great step towards the rationalization of organic reactions and synthesis was the introduction of the atomic notation during Berthelot's time. Unfortunately, Berthelot did not understand it and threw all the weight of his authority against the atomic notation.

of Organic Synthesis.[b] The academic synthetic chemist can be motivated by the sheer beauty of the synthesis he or she is pursuing[c] and it is easy to lose contact with the real world of useful Chemistry. In E.J. Corey's own words:[4]

> *The appeal of a problem in synthesis and its attractiveness can be expected to reach a level out of all proportion to practical considerations, whenever it presents a clear challenge to the creativity, originality, and imagination of the expert in synthesis.*

Finally, economic considerations bear the decisive weight in the preparation of an industrial product on a large scale: brief, simple, cheap synthesis, preferably in a single step. These, however, can involve drastic reaction conditions, often inapplicable in the laboratory, such as continuous-flow methods,[d] reaction times of a fraction of a second and temperatures up to 500-700 °C for *acrylonitrile*.[3]

These examples show the wide variety of situations faced in organic synthesis.[e]

3. WHAT

Although General Organic Chemistry courses include the preparative methods for each functional group, Organic Synthesis at an upper level aims to teach the synthetic philosophy and methodology: How to confront the design of an organic molecule, plus which methodology and general criteria are involved.

Building upon Basic Organic Chemistry, we must use a multitude of reactions and transformations. Some of them will be known already. Others will be the subject of explanation, extension or systematization. The construction of carbon frameworks, oxidation and reduction processes and the use of organometallic reagents are the relevant topics to be discussed, together with the interconversion of functional groups and the activation and protection of functionality.

3.1. Synthetic Reactions

The possibilities open to the synthetic chemist are notably expanded by the availability of as large a selection of synthetic reactions as possible. Woodward[5] used to say that the organic chemist, facing the need of a synthetic transformation, should attempt a reaction which is, in this order:

a) known
b) predictable
c) desirable, whether or not known or predictable.

Usually, courses in Organic Synthesis tend to put the emphasis on synthetic reactions, as collected and systematized in classical Organic Synthesis textbooks,[6] such as House's and Carruthers'. There is no shortage of sources in this area.[7]

In the last two decades, this field has undergone an explosive expansion, particularly in some areas. First, in connection with the growing use of reagents derived from less common elements, it is important to mention the increasing synthetic potential of silicon,[8] boron[9] and phosphorus reagents, which are far beyond the classsical Wittig reaction.[10] The synthetic use of organometallic reagents, already firmly established,[11] has been greatly expanded with the use of heavy- and transition-metal organometallic reagents.[12,13] In this connection, the synthetic applications of precious-metal complexes are also growing fast and allow the development of synthetically useful organic transformations.[14] Finally, the use of heterocycles in Organic Synthesis, first systematized by Meyers,[15] continues to progress,[16] but further research is needed on new systematization.

3.2. Synthetic Techniques

The introduction of new synthetic reactions is, of course, very important. But no less so is the development of new synthetic techniques. They have led to vast improvements in the synthetic capability of Organic Chemistry, solving otherwise insurmountable synthetic problems.

Phase-transfer catalysis is the first of these techniques,[17] with its two main versions: the use of quaternary ammonium salts and the use of macrocyclic catalysts, such as crown ethers and macrocyclic polyamines.[18] However, the classical phase-transfer reactions must be already considered a case of the so-called interfacial synthesis. It includes, besides liquid-liquid phase-transfer catalysis, reactions taking place at gas-liquid, solid-liquid or gas-solid interfaces, reactions in colloidal phases and topochemical reactions in multilayers.[19]

An important milestone in the field of synthetic techniques was the introduction of polymer-supported reactions. Its origin was the Merrifield peptide synthesis,[20] but it now has a much larger scope[21] and can be applied to a wide variety of synthetic reactions.[22] The ease of elimination of excess reagent, side products and solvent, which are easily washed away, leads to fast operation and high yields.

The intervention of external physical factors has also been felt in synthesis. The role of electric current in promoting organic reactions has been known for a long time, but was restricted to a few examples, such as the Kolbe electrolysis. However, the number and variety of synthetic transformations promoted by electricity is now enormous, often with much better results than the corresponding chemical reaction, if it exists at all. This, of course, must be borne in mind when teaching Organic Synthesis, and two systematic and didactic reviews[23,24] are most useful in this respect. The book edited by Baizer and Lund provides a comprehensive introduction to the topic.[25] It is worth noting that "electrosynthesis", as it is often called, has also found its own niche within industrial organic synthesis.[26]

Light, as a physical factor, gives rise to photochemical reactions. It is hard to exaggerate the role of such reactions in modern Organic Synthesis. They accomplish very useful synthetic transformations, many of them only possible by photochemical routes.[27]

Less well known, and as yet more limited, is the use of ultrasound[28] and microwaves[29] in Organic Synthesis, as well as the use of very high temperatures for a very short time (flow

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[b] R.B. Woodward put it brilliantly:
It can scarcely be gainsaid that the successful outcome of a synthesis of more than thirty stages provides a test of unparalleled rigor of the predictive capacity of the science and of the degree of its understanding of its part of the environment. Since Organic Chemistry has produced synthesis of this magnitude, we can, by this yardstick, pronounce its condition good.

[c] We are not alone. The physicist Hermann Weyl wrote:
In my work, I have always tried to conjugate truth and beauty. But when I was forced to choose, I usually chose beauty.

[d] Tundo discusses this topic and some attention is paid to the prospects and applications of continuous-flow synthesis in research: Tundo, P. *Continuous Flow Methods in Organic Synthesis;* Wiley: New York, 1989.

[e] If we agree with Lord Alexander Todd:
I am inclined to think that the development of polymerization is perhaps the biggest thing Chemistry has done,
the preparation of polymers should also be included in a general presentation of Organic Synthesis. Although the special approach for the preparation of macromolecules constitutes a separate topic, the mere mention of it must suffice in this overview.

thermolysis) to promote synthetic transformations otherwise difficult or impossible to achieve.[30]

A final, very rapidly expanding field, which carries us to the frontiers of Biochemistry, is the use of enzymes in Organic Synthesis. A comprehensive review[31] and a book[32] provide a good survey of this topic. Reactions promoted by enzymes as "biocatalysts" have enormous advantages over purely "organic" reactions: very mild conditions (physiological pH and temperature), total elimination of rearrangements and racemizations, reaction rates up to 10^{12} times as fast and total chemo-, regio- and stereoselectivity—in a word: selective catalysis of only one reaction route. Today, it is clear that there is an enzymatic equivalent for most organic reactions,[f] perhaps with the exception of Diels-Alder reactions and other concerted processes.[g] Only the high cost of enzymes curtails their full-scale introduction in Organic Synthesis, but the possibilities are exciting.[h]

3.3. The Third Dimension in Organic Synthesis

An essential point when teaching Organic Synthesis is the consideration of the third dimension. Any explanation of Organic Synthesis must include its stereochemical aspects. Stereoselective synthesis is an ever-growing field[33] and its present situation has recently been reviewed in a special issue of *Chemistry in Britain*.[34]

The stereochemical implications of classical synthetic reactions and the advances in new reagents and methods for inducing stereoselectivity must be explained. Among the more relevant, we include the development, mainly by Brown's group, of a great variety of reactions with chiral organoboranes, which allow an excellent stereoselectivity in many asymmetric syntheses.[35] A particularly interesting approach is to combine the chirality of a carbohydrate with a boron moiety.[36] Oppolzer has reviewed the use of camphor derivatives as chiral reagents[37] and Meyers[38] has focused on the use of formamidines. Amino acids and oxathianes are also good reagents for inducing stereoselectivity. The role of amino acids in asymmetric synthesis had been systematized in 1982 by Drauz *et al.*[39] and their increasing importance is clearly apparent in the comprehensive book by Coppola and Schuster.[40] As for oxathianes, the method developed by Eliel[41] is interesting from a didactic standpoint, because of its clear, simple approach. It makes use of the asymmetric induction effect of a chiral oxathiane ring, by selective coordination of the ring oxygen to a reagent such as a Grignard compound. The easy elimination of the oxathiane moiety by hydrolysis and the very high enantiomeric excesses fulfill the requirements of the ideal asymmetric synthesis.

Another approach to stereoselective synthesis is the use of chiral catalysts rather than reagents. Chiral phase-transfer catalysts, in particular, give very good enantiomeric excesses, whether with quaternary ammonium salts[42a] or chiral crown ethers.[42b] Ghosh[43] has even proposed possible examination questions on this topic. The ultimate in stereoselective synthesis is reached with the use of enzymes, the stereoselective catalysts *par excellence*. A simple, attractive presentation of this topic can be found in two recent reviews.[44] A highly imaginative approach is the chiral template concept.[45a] Hanessian's *chiron* methodology leads to stereoselectivities approaching that of enzymes.[45b]

Still less conventional (if the previous methods could be so called) is the induction of stereoselectivity by external physical factors. First, electromagnetic fields can induce an enantiomeric excess which can turn a "normal" reaction at least partially into an enantioselective synthesis.[46] Greater attention must be paid to induction of stereoselectivity by sound or light irradiation,[47] even up to total enantiomeric purity.[i] This kind of phenomenon could be responsible for the generation of chirality in prebiotic chemical evolution,[48] which led to life on Earth.[j]

3.4. Synthesis Design

The main knowledge to be transmitted when teaching synthesis involves planning and strategy: the design methodology by means of retrosynthetic analysis.[49] The pioneering textbook by Warren[50] set the path to the teaching of this concept in a logical and systematic way.[51,52] However, a degree of freedom is most necessary to allow room for creative intuition:

> *The synthetic chemist is more than a logician and a strategist; he is an explorer strongly influenced to speculate, to imagine and even to create. These added elements provide the touch of artistry*[k] *which can hardly be included in a cataloguing of the basic principles of synthesis, but they are very real and extremely important.*
>
> *E. J. Corey*

3.4.1. Retrosynthetic Analysis

Two concepts have contributed greatly to the contemporary progress of synthetic strategy. First is the *synthon* concept as defined by Corey[4]—a structural unit in a molecule related to possible synthetic operations: a unit which can be formed or assembled by known or conceivable synthetic reactions, but is different from the reactant itself and independent of the particular reaction type to be used. This allows a high degree of abstraction in the retrosynthetic reasoning.

The second is the concept of polarity inversion or, to use the original German word, *Umpolung*. Thus, the design of a synthesis is greatly rationalized and simplified by the distinction between reactants with normal and inverse reactivity. Many organic molecules contain functional groups with heteroatoms such as nitrogen or oxygen. These atoms impose on the chain an alternating sequence of polar reactivity, with donor and acceptor centers on the carbon atoms.[l] Any process inverting the donor-acceptor nature in the chain positions or violating the alternating pattern is *Umpolung*. It is obvious that procedures leading to this inversion[53,54] will result in an extraordinary increase in the synthetic possibilities of a molecule. On the other hand, the concept offers an heuristic principle, a classification scheme for the key task of identifying strategic bonds in retrosynthetic analysis by the disconnection approach.[51]

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[f] Sometimes with such common "catalysts" as baker's yeast: Tsuboi, S. *Tetrahedron Lett.* **1986,** *27,* 1951. Lipkowitz, K. B.; Mooney, J.L. *J. Chem. Educ.* **1987,** *64,* 985.

[g] However, certain sigmatropic processes, such as the Claisen rearrangement, can be promoted enzymatically. See ref. 31.

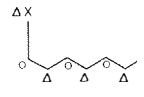
[h] The ever-increasing number of commercially available enzymes, particularly the impressive collection offered by Sigma-Aldrich, will surely make an important contribution to it.

[i] A linguistic annotation: Can we talk here of asymmetric induction? Where is the frontier between *induced* and *non-induced* stereoselectivity in a terminology which is coming to resemble the legendary Tower of Babel?: Tietze, L.F.; Beifuss, U. "Non-Induced Highly Diastereoselective Intramolecular..." *Angew. Chem., Int. Ed. Engl.* **1985,** *24,* 1042.

[j] The end reason for the generation of chirality is a most puzzling question. S. Mason has calculated that a protein formed by L amino acids has an energy which is 10^{-4} kJ/mol lower than the alternative protein made of D amino acids. This difference seems to arise from the electroweak force discovered by physicists Lee and Yang.

[k] The hundred or so examples collected in the second edition of *Art in Organic Synthesis* are most enlightening on this "touch of artistry": Anand, N.; Bindra, J.S.; Ranganathan, S. *Art in Organic Synthesis,* 2nd ed.; Wiley: New York, 1988 (Aldrich Cat. No. **Z18,470-5 $39.95**).

[l] A useful notation indicates the donor character by the symbol Δ and the acceptor character by o. Thus, in a chain as depicted below, the heteroatom (N,O) and the carbons 2,4,6... are donors, whereas carbons 1,3,5... behave as acceptors in polar reactions:



These developments have helped to rationalize the more intuitive and often faltering approach to Organic Synthesis. Even so, many students experience great difficulty in retrosynthetic reasoning, because it represents a major departure from problem-solving techniques with which they are familiar. Levy has recently proposed a trick for introducing the principle of retrosynthesis by using examples outside the realm of Organic Chemistry.[55]

3.4.2. Retro Mass Spectral Synthesis

Synthesis design involves an elaborate intellectual process. Its success depends on the mind using retrosynthetic reasoning, its knowledge and its experience in Organic Chemistry. It is significant that great chemists who excelled in purely intellectual synthesis design have investigated ways to assist their minds in this endeavor.

The first of these is the methodology developed by Kametani, which he called "Retro Mass Spectral Synthesis".[56] It is derived from a clever and simple basic idea: since fragmentation of a molecule in the mass spectrometer is a bond-breaking process, a parallelism can be found with a molecular degradation. Therefore, Kametani proposed that an analogy would exist with the opposite process of bond construction in synthesis. Thus, examining the fragmentation scheme of a molecule on its mass spectrum allows the design of a synthetic route for it. As a simple example, a cyclohexene breaks in the mass spectrometer to give ethylene and butadiene fragments. Conversely, the synthesis of a cyclohexene involves the opposite process: Diels-Alder cycloaddition. When applied to complex molecules, this simple idea led to brilliant natural-product syntheses.[56b] The mass spectral fragments of a molecule were successfully used as synthons in its synthesis, modified, when necessary, to be able to use tractable reactants in the laboratory.

3.4.3. Computer-Aided Design

A totally different, but no less successful, approach is to enlist the help of computers. It was only natural. When planning synthetic routes, the organic chemist must remember large numbers of organic reactions, must know which of these reactions work for which kind of molecules, and must extrapolate from previous knowledge. Computers are very suited to this job and during the past twenty years or so programs have been developed to help the synthetic chemist.

Corey's name must again be mentioned as a pioneer and active protagonist.[57] His program, OCSS (Organic Chemical Simulation for Synthesis), was revolutionary in its approach, allowing the use of computer graphics for communicating with the machine in the chemist's language. Its heir is the important LHASA (Logic and Heuristics Applied to Synthetic Analysis).[58] Using the same graphic language, LHASA and other synthesis programs,[m] generate an interactive process. The synthetic chemist draws in as a target structure the molecule to be synthesized and the program makes suggestions, also graphically, for possible synthetic precursors to that target using the large collection of reactions in the database.[n] When a precursor is selected, the program returns suggestions for synthesizing that precursor. If the precursors are not of immediate access, the process is repeated until easily available starting materials are reached. Entire synthetic routes can be devised in this fashion.

However, a serious problem, a limiting factor in computer-aided design, is the database—the reaction arsenal from which the program can choose the proposed transformations, as the chemist draws from his memory and his library. Constantly updated, the database can grow out of all proportion. There are many general reactions for each functional group, but some classes of compounds have their own rather specific reactions. Some processes apply to one compound only and every week new reactions are being discovered in an apparently exponential growth. Are all these reactions to be stored in the database? Systems have been developed with thousands of transformations but the number is infinite. Furthermore, and more importantly, a program designed around a database will give access only to *known* reactions since, obviously, only these can be introduced.

What a huge leap forward could come from the development of a computer system capable of "reasoning" without the limitations of a reaction file? Such is the aim of the EROS program (Elaboration of Reactions for Organic Synthesis).[59] The concept of EROS was devised in order to avoid a database of reactions[o] and also to avoid the treatment of Chemistry from the limiting standpoint of functional groups. Central to the approach is a *formal* handling of organic reactions, where they are treated as bond-breaking and -making, taking consideration of electron shifting. This principle is applied to *all* atoms and bonds in a molecule, regardless of any preconception of functional groups. The computer can now generate synthetic transformations, in principle *all* conceivable reactions: a method to deal freely with molecular architecture which results in the proposals made by the machine. On examining them, we will find that some are known reactions. Others, however, will be new, as yet undiscovered reactions, which can eventually be incorporated into the body of knowledge we call Organic Chemistry.

But a price has to be paid. The number of reactions which could be obtained by applying a formal reaction generator scheme could be very high indeed. We could, therefore, find ourselves in the awkward position of examining a very high number of reactions, many of them chemically meaningless.

It is not like that, and this is the second huge achievement of EROS. The major task undertaken by its authors is to develop what they named "an automatic evaluation package" that allows the selection of *chemically feasible* reactions, *i.e.*, to endow the program with criteria which amount to *basic chemical knowledge*, capable of rejecting chemically absurd processes. Thus, the machine will propose to the chemist, together with known reactions, only those that, although novel, are possible.[p]

[m] There are several computer programs devoted to assisting chemists in choosing synthetic routes. SECS (Simulation and Evaluation of Chemical Synthesis), its offshoot CASP, and SOS (Simulation of Organic Synthesis) should be mentioned, as well as SYNCHEM, which evaluates each stage to suggest the best precursor: Haggin, J. *Chem. Eng. News* **1983**, *61*(19), 7.

All of these programs work backwards, in the sense that they perform a retrosynthetic analysis. The opposite approach is used in the program CAMEO, which works in the synthetic, rather than retrosynthetic, direction. Whereas the former programs help the chemist decide: "What precursors and reagents should I use to make compound X?", CAMEO answers the question, "If I subject compound Y to reaction Z, will I get X or something else?" (see ref. 57).

[n] In fact, the program offers several, sometimes a great many, alternative possibilities. The synthetic chemist must examine them and choose the alternative he finds to be most reasonable, most realistic or simply most graceful. There is no obvious automatism and, at least in the field of Organic Synthesis, a beautiful sentence by Albert Camus is still valid: *In an obvious world, art would not exist.*

[o] Although perhaps the more developed program, EROS, is not totally alone. Another program, from Hendrickson's group (Hendrickson, J.B.; Braun-Keller, E. *J. Comp. Chem.* **1980**, *1*, 323; *idem Tetrahedron* **1981**, *37(Supp. 1)*, 359), takes a similar theoretical approach. These are logic-based (expert) systems, *versus* information-oriented programs and are capable of suggesting new chemistry to the user.

[p] At this point, the chemist feels sentimentally inclined to read footnote *n* again.

What about teaching computer-assisted Organic Synthesis at a lower level? Some of the authors involved in program development have made attempts to adapt them for teaching purposes.[60] However, the big programs discussed are complex and their use requires, together with experience, at least a mid-size machine and complex computer languages. It is, therefore, didactically important to publish simpler programs which can be run on microcomputers and are written in BASIC, such as Turner's CYNTHIA,[61] Pollet's SYNDES[62] or the SOS-based program used by Bertrand *et al.*[63] A useful source for the interested teacher is the compilation of references published by Wood.[64]

4. CONCLUSION

Organic Synthesis is the field in which the chemist fully realizes the relevance of differences, however subtle, between molecules.[65]

To a physicist, all molecules are the same: simple manifestations of the Schroedinger equation. But a chemist appreciates the differences.

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References

1) Maier, G. *Angew. Chem., Int. Ed. Engl.* **1974,** *13,* 425. For a general survey on cyclobutadiene synthesis, see Garratt, P.J. In *Comprehensive Organic Chemistry;* Barton, D.H.; Ollis, W.D., Eds.; Pergamon: Oxford, 1979; Vol. 1, p 381.
2) Corey, E.J. *et al. J. Am. Chem. Soc.* **1978,** *100,* 8031. See also ref. 59.
3) Weissermel, K.; Arper, H.J. *Industrielle Organische Chemie. Bedeutende Vor und Zwischen Producte,* 2nd ed.; Verlag Chemie: Weinheim, 1978; Chapter 11. Jubb, A.H. In *Basic Organic Chemistry;* Tedder, J.M.; Nechvatal, A.; Jubb, A.H., Eds.; Wiley: London, 1975; Vol. 5, Chapter 7.
4) Corey, E.J. *Pure Appl. Chem.* **1967,** *14,* 19.
5) Woodward, R.B. *Plenary Lecture on the Occasion of the 75th Anniversary of the Spanish Royal Society of Chemistry,* Madrid, Spain, 1978.
6) House, H.O. *Modern Synthetic Reactions,* 2nd ed.; W.A. Benjamin: Menlo Park, 1972. Carruthers, W. *Some Modern Methods of Organic Synthesis,* 3rd ed.; Cambridge University Press: Cambridge, 1986.
7) As an encyclopedic reference book, "The Houben-Weyl" provides exhaustive information: *Houben-Weyl Methoden der Organischen Chemie,* 4th ed.; Koster, R., Ed.; Georg Thieme-Verlag: Stuttgart, 1982-1984.
8) Fleming, I. *Some Uses of Silicon Compounds in Organic Synthesis;* In *Organic Synthesis Today and Tomorrow*; Trost, B.M.; Hutchinson, C.R., Eds.; Pergamon: Oxford, 1981. Weber, W.P. *Silicon Reagents for Organic Synthesis;* Springer Verlag: New York, 1983. Although the use of organosilicon compounds has been intense in the last decade, only recently is the mechanistic interpretation of their reactions being studied: Apeloig, Y. "Mechanistic Organosilicon Chemistry: Cationic Reactive Intermediates"; *Commun. to ESOC V* Jerusalem (Israel), 1987.
9) Brown, H.C. *Organic Synthesis via Boranes*; Wiley: New York, 1975. Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*; Academic Press: New York, 1988. Brown, H.C. *Tetrahedron,* **1986,** *42,* 5497. An important improvement results from the use of borane-amine complexes, which are stable to air, highly selective and can be used in protic solvents: Hutchings, R.O. *Org. Prep. Proced. Int.* **1984,** *16,* 335.
10) *Organophosphorus Reagents in Organic Synthesis;* Cadogan, J.I., Ed.; Academic: New York, 1980.
11) Negishi, E. *Organometallics in Organic Synthesis;* Wiley: New York, 1980. Kauffman, T. *Top. Curr. Chem.* **1980,** *92,* 111.
12) Kauffman, T. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 410.
13) Colquhoun, H.M. *New Pathways for Organic Synthesis: Practical Applications of Transition Metals*; Plenum: New York, 1984.
14) Tsuji, T. *Tetrahedron* **1986,** *42,* 4361.
15) Meyers, A.I. *Heterocycles in Organic Synthesis;* Wiley: New York, 1974.
16) For a recent example, see Padwa, A. *Tetrahedron Lett.* **1987,** *28,* 913.
17) Dehmlov, E.; Dehmlov, S. *Phase Transfer Catalysis,* 2nd ed.; Verlag Chemie: Weinheim, 1983. For a primer on this topic, see Sjöberg, K. *Aldrichim. Acta* **1980,** *13*(3), 55. See also the survey by Dehmlov in the Merck publication cited in ref. 18. Difficult to read, but extremely useful as a reference work, is the recent book by Keller: Keller, W. *Phase Transfer Reactions;* G. Thieme-Verlag: Stuttgart; 2 vols., 1986-1987.
18) Izatt, R.M.; Christensen, J.J. *Synthetic Multidentate Macrocyclic Compounds;* Academic Press: New York, 1978. See also, Bradshaw, J.S. *et al. Chem. Rev.* **1979,** *79,* 37. C.J. Pedersen, the discoverer of crown ethers, published the story of his momentous discovery: Pedersen, C.J. *Aldrichim. Acta* **1971,** *4*(1), 1. Also useful for the teacher is the review authored by Weber and published by Merck: Weber, E. In *Phase Transfer Catalysis;* Merck-Schuchardt: Darmstadt, 1987; p33. A recent general overview: Izatt, R.M.; Christensen, J.J. *Synthesis of Macrocycles. The Design of Selective Complexing Agents;* Wiley: New York, 1987.
19) Carraher, C.E. *Interfacial Synthesis;* Marcel Dekker: New York, 1982.
20) Merrifield, R.B. *J. Am. Chem. Soc.* **1963,** *85,* 2149. For a review, see Barany, A.; Merrifield, R.B. In *The Peptides;* Gross, E.; Meienhofer, J., Eds.; Academic: New York, 1979-1981; Vol 2.
21) For a review, see Akelah, A.; Sherrington, D.C. *Chem. Rev.* **1981,** *81,* 557.
22) Hodge, P.; Sherrington, D.C. *Polymer Supported Reactions in Organic Synthesis;* Wiley: New York, 1980. Sherrington, D.C.; Hodge, P. *Synthesis and Separations Using Functional Polymers;* Wiley: New York, 1988. *Preparative Chemistry Using Supported Reagents;* Laszlo, P., Ed.; Academic: San Diego, 1987.
23) Shono, T. *Tetrahedron* **1984,** *40,* 811.
24) Baizer, M. *ibid.* **1984,** *40,* 935.
25) *Organic Electrochemistry: An Introduction and a Guide,* 2nd ed.; Baizer, M.; Lund, H., Eds.; Marcel Dekker: New York, 1983.
26) Janson, R. *Chem. Eng. News* **1984,** *62*(47), 43.
27) Two excellent books provide a comprehensive overview of the topic: *Synthetic Organic Photochemistry;* Horspool, W., Ed.; Plenum: New York, 1984. *Photochemistry in Organic Synthesis;* Coyle, J., Ed.; The Royal Society of Chemistry: London, 1986.
28) Boudjouk, P. *J. Chem. Educ.* **1986,** *63,* 427. Abdulla, R.F. *Aldrichim. Acta* **1988,** *21*(2), 31; For a comprehensive review, see Mason, T.J.; Lorimer, J.P. *Chem. Soc. Rev.* **1987,** *16,* 239. *Idem ibid.* **1987,** *16,* 275. The use of cheap ultrasound cleaning baths allows the easy introduction of sonochemistry into the teaching laboratory: Mason, T.J.; Lorimer, J.P.; Moorhouse, J.P. *Educ. Chem.* **1989,** *21,* 13.
29) Giguere, R.; Majetich, G. *Tetrahedron Lett.* **1986,** *27,* 4945.
30) Karpf, M. *Angew. Chem., Int. Ed. Engl.* **1986,** *25,* 414.
31) Bryan-Jones, J. *Tetrahedron* **1986,** *42,* 3351.
32) *Biocatalysts in Organic Synthesis;* Tramper, J.; van der Plas, H.C.; Linko, P., Eds.; Elsevier: New York, 1986.
33) ApSimon, J.W.; Collier, T.L. *Tetrahedron* **1986,** *42,* 5157. For a wider survey, see Nogradi, M. *Stereoselective Synthesis;* Verlag-Chemie: Weinheim, 1987.
34) Davies, S.G.; Brown, J.M.; Pratt, A.J.; Fleet, G. *Chem. Brit.* **1989,** 259 (a special issue devoted to this subject).
35) Such reactions have been reviewed some time ago: Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *Tetrahedron* **1981,** *37,* 3547 and more recently in the issue of *Aldrichimica Acta* dedicated to Prof. Brown: Srebnik, M.; Ramachandran, P. V. *Aldrichim. Acta* **1987,** *20*(1), 9. See also, Matteson, D.S. *Synthesis* **1986,** 973.
36) Brown, H.C.; Park, W.; Cho, B. *J. Org. Chem.* **1986,** *51,* 1934. Allenylboronic esters seem to be very effective for enantioselective synthesis: Yamamoto, H.; Haruta, R.; Ishiguro, M.; Ikeda, N. *J. Am. Chem. Soc.* **1982,** *104,* 7667.
37) Oppolzer, W. *Tetrahedron* **1987,** *43,* 1969.
38) Meyers, A.I. *Aldrichim. Acta* **1985,** *18*(3), 59.
39) Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 584.
40) Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids;* Wiley-Interscience: New York, 1987.
41) For a clear, didactic survey, see Eliel, E.L. "Asymmetric Reactions and Processes in Chemistry"; *Am. Chem. Soc. Symp. Ser.* 1982, No. 185, p 37; *Phosphorus and Sulfur,* **1985,** *24,* 73.
42) a) *N,N*-Dimethylephedrine is a good example: Hijame, T. *J. Am. Chem. Soc.* **1974,** *97,* 1627. Fiaud, J.C. *Tetrahedron Lett.* **1975,** 3495. b) For two representative cases, see Cram, D.J.; Sogah, G.D.Y. *Chem. Commun.* **1981,** 625. Dehmlov, E.V.; Sanerbier, C. *Liebigs Ann. Chem.* **1989,** 181.
43) Ghosh, A. *J. Chem. Educ.* **1987,** *64,* 1015.
44) Battersby, A.R. *Chem. Brit.* **1984,** 611. Pratt, A.J. *ibid.* **1989,** 282. See also ref. 31.
45) a) Hanessian, S. *Aldrichim. Acta* **1989,** *22*(1), 3. b) Hanessian, S. *The Total Synthesis of Natural Products: The Chiron Approach;* Pergamon: Oxford, 1983.
46) Among the pioneering work are Gerike, P. *Naturwissenschaften* **1975,** *62,* 38. Mead, C.A.; Moscowitz, A.; Wynberg, H.; Meuweise, F. *Tetrahedron Lett.* **1977,** 1063. More recently, Turro's group has made a bold foray in this area—organic reactions in colloidal aggregates and porous solids can be controlled even by the weak magnetic fields of a magnetic stirrer: *Chem. Eng. News* **1986,** *64,*(44), 44.
47) Scheffold, R. *Sound and Light in Synthesis of Enantiomerically Pure Compounds;* Springer-Verlag: New York, 1986.
48) For reviews on prebiotic synthesis, see Lemon, R.M. *Chem. Rev.* **1970,** *70,* 95. Ferris, J.P.; Hagan, W.J. *Tetrahedron* **1984,** *40,* 1093.

49) Fuhrhop, J.; Penzlin, G. *Organic Synthesis. Concepts, Methods, Starting Materials;* Verlag-Chemie: Weinheim, 1983; Chapter 3. For a very recent book by an authority, see Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis;* Wiley: New York, 1989.
50) Warren, S. *Designing Organic Synthesis. A Programmed Introduction to the Synthon Approach;* Wiley: New York, 1978.
51) Warren, S. *Organic Synthesis: The Disconnection Approach;* Wiley: New York, 1983.
52) Lindberg, T. *Strategies and Tactics in Organic Synthesis;* Academic: New York, 1984.
53) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979,** *18,* 239.
54) Hase, T.A. *Umpoled Synthons. A Survey of Sources and Uses in Synthesis;* Wiley: New York, 1987.
55) A shocking culinary example, in fact, is shown in Levy, I.J. *J. Chem. Educ.* **1988,** *65,* 853.
56) a) For a general description of the idea, see Kametani, T. *Acc. Chem. Res.* **1976,** *9,* 319. b) A clear survey has been published by Fukumoto within Kametani's scientific biography, Fukumoto, K. *Heterocycles* **1981,** *15,* 6.
57) Corey, E.J. *Quart. Rev.* **1971,** *25,* 455. Bersohn, M.; Esack, A. *Chem. Rev.* **1976,** *76,* 269. Gasteiger, J. "Syntheseplanung" in *Computer in der Chemie;* Ziegler, E., Ed.; Springer-Verlag: Heidelberg, 1984; p 207.
58) Several members of the LHASA group have published a most interesting, clear survey, which is delightful to read: Long, A.K.; Rubenstein, S.D.; Joncas, L.J. *Chem. Eng. News* **1983,** *61*(9), 22.
59) The large international group developing EROS has published a most enlightening review, on the very frontier of Chemistry: Gasteiger, J.; Hutchings, M.; Christoph, B.; Gann, L.; Hiller, C.; Low, P.; Marsilli, M.; Saller, H.; Yuki, K. *Top. Curr. Chem.* **1987,** *137,* 18. The fact that several of the authors involved belong to important chemical companies shows that the computer treatment of Organic Synthesis goes far beyond the huge intellectual achievement it represents.
60) Orf, H.W. *J. Chem. Educ.* **1975,** *52,* 464. Stolow, R.D.; Joncas, L.J. *ibid.* **1980,** *57,* 868. Xicant, J.; Serratosa, F. *Wheels for the Mind* (Spanish edition) **1989,** *4,* 17.
61) Turner, S. *Educ. Chem.* **1986,** 107.
62) This program is derived from the Hendrickson protocol (see footnote *o*) for systematic synthesis design: Pollet, R. *J. Chem. Educ.* **1986,** *63,* 624.
63) Bertrand, M.P.; Monti, H.; Barone, R. *ibid.* **1986,** *63,* 624.
64) Wood, J.A. *ibid.* **1987,** *64,* 501.
65) *Chem. Eng. News* June 5th, 1978, p 20.

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Professor Carlos Seoane was born in La Coruña, Spain, in 1951. He graduated in Chemistry from the University of Santiago de Compostela in 1973 and obtained his doctorate in Organic Chemistry under Professor J.L. Soto in 1975 with an Excellence Award. While at Santiago, he held a research fellowship, acting also as a teaching assistant. He then moved to the University in Alcalá de Henares and, in 1976, to the Universidad Complutense in Madrid, as an Assistant Professor, reaching tenure in 1978. In 1988 he became a full Professor and was appointed to the chair of Organic Chemistry at the Universidad de Castilla-La Mancha.

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Besides Chemistry, Professor Seoane enjoys soaring in a glider—not a bad hobby for picking up research inspiration from "Above".

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About Our Cover:

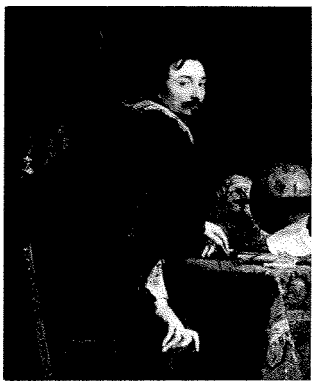


Fig. 1

Our chemist-collector loves puzzles, and so he purchased this painting not only because he liked it but because he hoped to be able to identify the artist and the sitter.

A great deal has been written about the painting—for instance, by Professor David McTavish in the *Age of Rembrandt*, offered below, and we cite his description here.

This elegant portrait (oil on canvas, 96½ x 78cm) is greatly influenced by Anthony van Dyck's *Portrait of Lucas van Uffeln*, now in the Metropolitan Museum of Art, New York (Fig.1). No doubt van Dyck painted the merchant and shipowner from Antwerp in Venice in 1622, some 20 years earlier than this portrait. Van Uffeln died in Amsterdam in 1637, and his possessions were auctioned there in 1637 and 1639, and it seems likely that our artist saw the van Dyck portrait at that time.

Our portrait shows an intelligent and refined man who, having just been interrupted at his studies, turns in ¾-profile to look at the spectator. The table holds what, in the seventeenth century, was thought to be a bust of Seneca, a portrait engraving and a book of music. Together, these objects suggest the sitter's interest in the arts and learning. Although the portrait furnishes us much information about the sitter, he has not yet been identified.

Nor has the name of the painter been established unequivocally. While the portrait clearly relies on van Dyck's precedent, the components have been rearranged in a more classical way. The handling of paint is also more restrained.

In time we hope that both identities—of artist and sitter—will be determined. Don't hold your breath, however, it may take a long time.

The beauty of this work makes it a fitting cover for the elegant papers by Professor Jeremy Knowles and Dr. Keith Ingold.

NEW *Telling Images—Images Révélatrices*

Large, 150-page catalog of thirty-six Old Master paintings now in a travelling exhibition touring Canada. All were given by the Baders to Queen's University.

The catalog illustrates all thirty-six paintings, thirteen of them in color (none of these were in the Age of Rembrandt exhibition described below). The extensive, scholarly text, written by Professor David McTavish, is in English and French.

The Detective's Eye: Investigating the Old Masters

Twenty-two paintings that have been reproduced on our *Acta* covers (including the one here) and five that have been on our catalog covers were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 - March 19, 1989) for which Isabel and Alfred Bader were guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist-collector's interest in art and connoisseurship as well.

Pictures from the Age of Rembrandt

Twenty-eight paintings that have been reproduced on our *Acta* covers, and seven that have been on our catalog covers were among the thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information—enough for several evenings of relaxed enjoyment—probably the best value in art-history anywhere.

Lab Notes

Disposable polyethylene gloves only come in one size which is far from form-fitting, resulting in a loss of dexterity to the wearer. I have found a simple solution to the problem. If rubber bands, approximately 1.5cm in diameter, are placed over each gloved finger and thumb much like rings, the excessive material can be concentrated at the base of the fingers and thumb leaving the fingertips unencumbered, greatly increasing dexterity and thus reducing the risk of dropping objects or knocking them over when reaching to grasp them.

Bliss S. Phillips, Chemist
NRRC, ARS, USDA
3417 W.. Capitol Dr.
Peoria, IL 61614

On reading the note on a small-scale filtration device from Messrs. Muir and Johnson [*Aldrichim. Acta* **1987,** *20*(3), 62], I was sorry to find that they had spent time perfecting something described by the late Louis F. Fieser in *Experiments in Organic Chemistry,* 2nd ed., 1941, p 322.

As a recently retired organic chemist who spent most of his working life at the bench, I have to recommend this book and the subsequent *Organic Experiments,* 1964, with a third edition in 1975, as absolutely essential reading for every organic preparative chemist. Further reading I commend includes *Morton's Laboratory Technique in Organic Chemistry,* 1938, and all the volumes of *Organic Syntheses.*

F.E. Smith
16 Broomleaf Road
Farnham, Surrey GU9 8DG
England

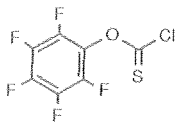
Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Derek Barton.

Sir Derek H.R. Barton, Distinguished Professor of Chemistry at Texas A&M University, kindly suggested that we offer **pentafluorophenyl chlorothionoformate,** a novel reagent for the Bu_3SnH-promoted deoxygenation of secondary alcohols. This reagent was found to be clearly superior to other thiocarbonyl reagents (*e.g.*, phenyl-, 2,4,6-trichlorophenyl- and pentachlorophenyl chlorothionoformate) with regard to reaction time and yield.

Naturally, we made it.



Barton, D.H.R.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1989,** *30,* 2619.

It was no bother at all, just a pleasure to be able to help.

Mechanistic Ingenuity in Enzyme Catalysis: Dehydroquinate Synthase

Jeremy R. Knowles
Department of Chemistry
Harvard University
12 Oxford Street
Cambridge, MA 02138

At first sight, enzymes are formidable catalysts. The specificity that enzymes show in substrate recognition and binding is exquisite, and the rate at which the subsequent chemical transformations are performed is extraordinary. An enzyme selects its substrate out of the thousands of metabolites in the cell, or finds its particular recognition site out of millions of more-or-less similar places on a DNA molecule, with unerring fidelity. Then, having formed the enzyme:substrate complex, a sequence of chemical steps follows at rates still unmatched by man's efforts. Yet as we learn more, and as we understand better, enzyme catalysts seem more ingenious than awesome. This shift in attitude of mechanistic enzymologists is nicely illustrated by the consideration of one enzyme, dehydroquinate synthase, which is responsible for the formation of the first six-membered carbocycle in the metabolic pathway that leads to the three aromatic amino acids.

The shikimate pathway, as illustrated in Figure 1, is the sequence of reactions that, in plants and microorganisms, produces phenylalanine, tyrosine and tryptophan, along with a host of other primary and secondary metabolites from ubiquinone to morphine.[1] The pathway begins with the condensation of phosphoenolpyruvate and erythrose 4-phosphate to give the seven-carbon keto acid, 3-deoxy-D-*arabino*-heptulosonate 7-phosphate (DAHP). This material is then converted into the carbocycle dehydroquinate (DHQ) by dehydroquinate synthase.[2,3] The pathway continues with the elaboration of the appropriate substituents and the generation of unsaturation to produce chorismate, which is the point at which the routes to the three aromatic amino acids diverge. The shikimate pathway is full of interesting and unusual enzymology, but we focus here on the second enzyme of the sequence, dehydroquinate synthase.

Dehydroquinate synthase is a monomeric protein of 362 amino acids[4] that requires, for catalytic activity, the presence of both a divalent metal cation [cobalt(II) has often been used in mechanistic studies on the enzyme, though zinc(II) is the more likely cation for the enzyme *in vivo*] and nicotinamide adenine dinucleotide (NAD^+).[2-4] The enzyme binds one metal ion and one NAD^+.[5] The need for NAD^+, a redox cofactor, is not immediately obvious since the

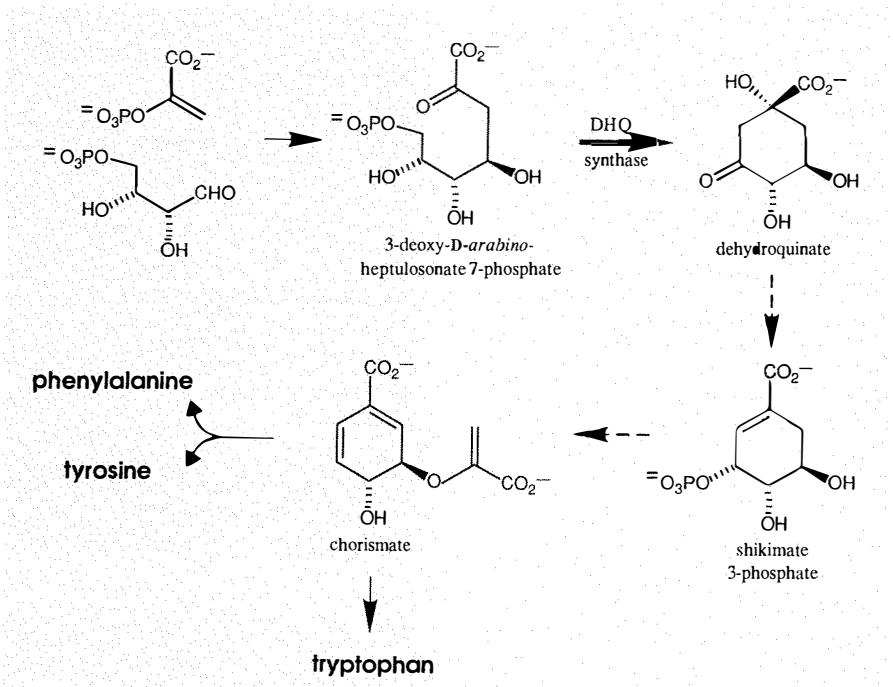


Fig. 1. ***The shikimate pathway.*** *In plants and in microorganisms, this metabolic sequence leads to the production of, among other things, the three aromatic amino acids: phenylalanine, tyrosine and tryptophan.*

Professor Jeremy Knowles (left) receiving the Alfred Bader Award in Bioorganic Chemistry from Dr. Alfred Bader.

overall conversion of DAHP to DHQ and inorganic phosphate (P_i) is redox neutral. In 1963, however, Sprinson neatly explained the NAD^+ requirement of the synthase by proposing the pathway shown in Figure 2.[2,6] In this proposal, the substrate DAHP (**1**) binds to the active site, and is oxidized at C-5 by enzyme-bound NAD^+ to produce the C-5 ketone (**I**) and NADH. The second step of the reaction then involves β-elimination of inorganic phosphate across C-6 and C-7 to yield the enone **II**. According to this pathway, the function of NAD^+ is to effect the oxidative activation of the substrate, which acidifies the C-6 proton and facilitates the phosphate elimination step. Phosphate having been lost, the enzyme-bound NADH now reduces the ketone at C-5 (regenerating the same configuration as in DAHP, **1**) to give the enol pyranose **III**. Ring opening of this species to **IV**, and then reclosure by attack of the enolate carbon (C-7) on the carbonyl group at C-2 in an intramolecular aldol reaction, produces DHQ (**2**) and completes the reaction. Chemically and logically this pathway is very attractive, and has many features that would surely have been included had an organic chemist been responsible for the design of dehydroquinate synthase.

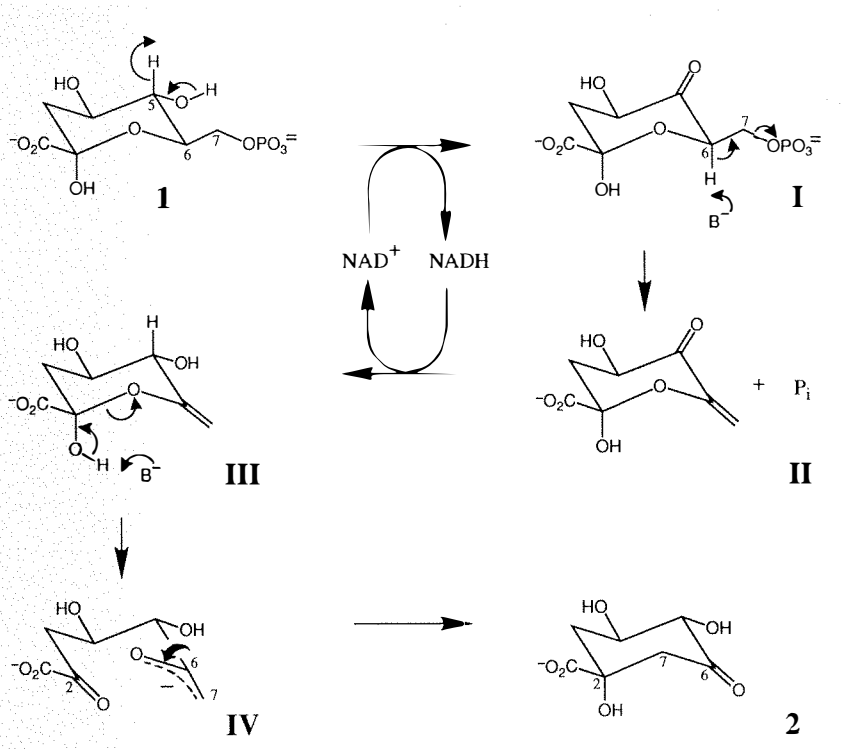
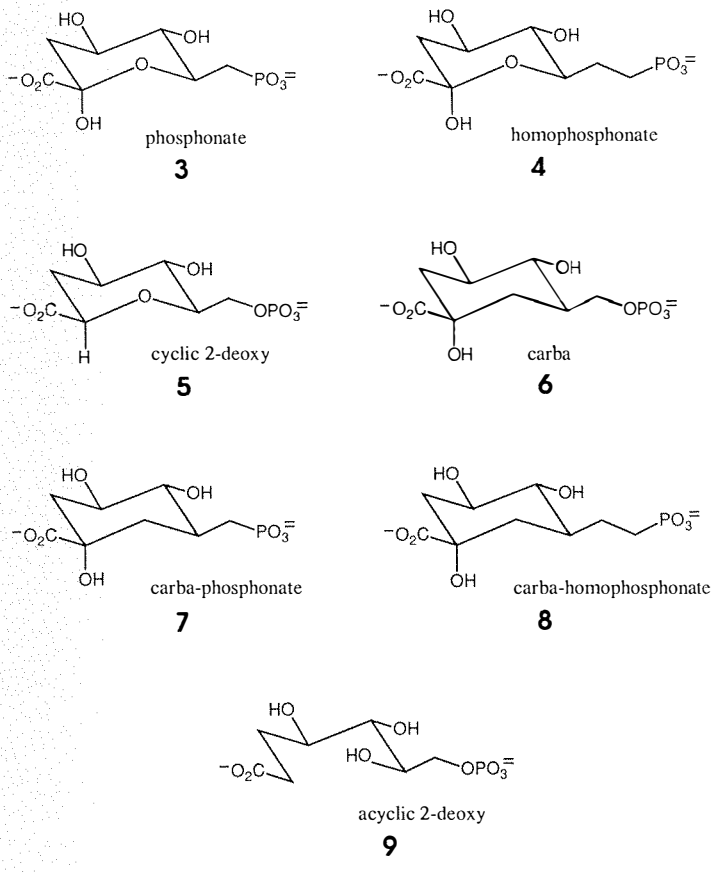


Fig. 2. The proposed mechanistic pathway followed by dehydroquinate synthase. *The substrate, 3-deoxy-D-arabino-heptulosonate 7-phosphate **(1)** is transformed in five steps to dehydroquinate **(2)**.*

Yet there are some troubling features for the enzymologist, not the least of which is the problem of how a monomeric enzyme, presumably having a single active site, can contain enough precisely placed catalytic groups to catalyze four different chemical processes. For the pathway of Figure 2 makes dehydroquinate synthase into a dehydrogenase, a phospho-lyase, a pyranose-opening enzyme, and an internal aldolase. Elsewhere in nature, enzymes exist whose sole function is to perform just one of these tasks, and we may reasonably ask whether dehydroquinate synthase represents what an enzyme can achieve (with the implication that most other enzymes are relatively pathetic), or whether the mechanism proposed for dehydroquinate synthase is somehow overambitious.

To attack the problems posed by the mechanism outlined in Figure 2, we have chosen to evaluate the behavior of a series of substrate analogs that, by virtue of minor structural alterations, cannot complete the reaction sequence. Thus the phosphonate analog **3** and homophosphonate analog **4** can only suffer the first catalytic step (as far as **I**, Figure 2), since the loss of P_i in the second step is (for **3** and **4**) impossible. The cyclic 2-deoxy analog **5** and the carba analog **6** can both, in principle at least, undergo the first three steps of the proposed pathway as far as **III** (Fig. 2), but can go no further because the ring-opening reaction of the fourth step is precluded.



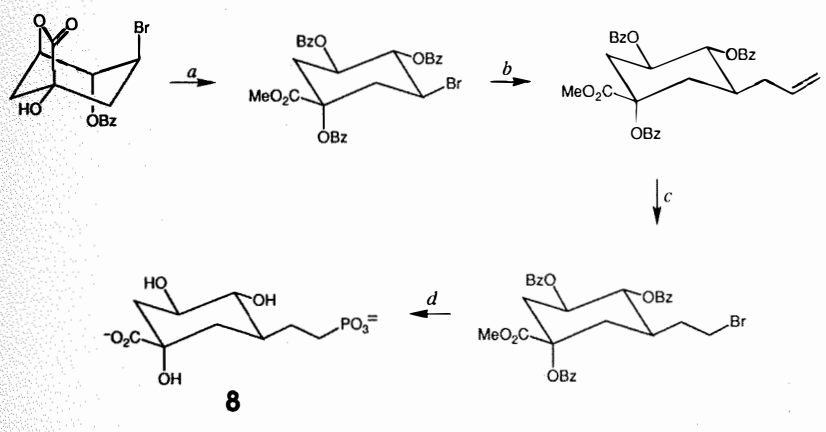


Fig. 3. ***Synthetic route to the ring carba-bomopbospbonate analog (8) of tbe natural substrate (1). In this analog, the pyranose ring oxygen and the bridging phosphoryl group oxygen have been replaced by methylene groups. a: MeOH-TsOH, then PhCOCl-pyridine; b: allyltributyltin-α,α'-azobisisobutyronitrile-benzene; c: O_3, then $NaBH_4$, then CBr_4-Ph_3P-THF; d: NaI-acetonitrile, then trimethyl phosphite, then trimethylsilyl bromide, then NaOH.***

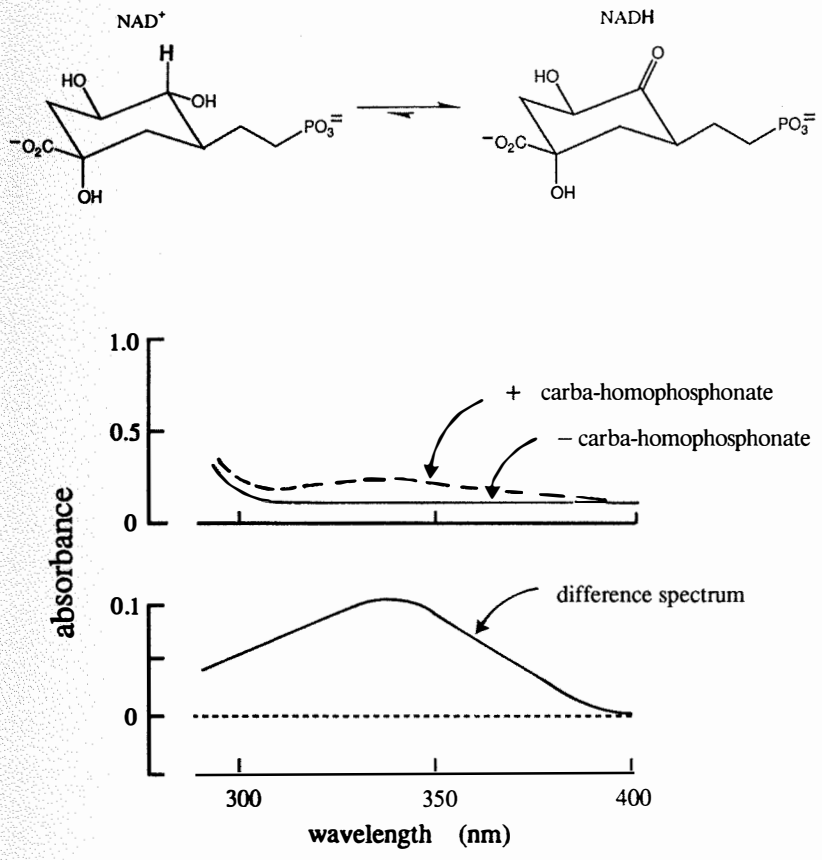


Fig. 4. ***Direct observation of enzyme-bound NADH.*** *The enzyme was treated with saturating levels of the carba-homophosphonate substrate analog* ***8****.*

Although it had been clearly established[2-5] that the catalytic activity of dehydroquinate synthase depends upon the presence of NAD^+, the chemical involvement of this cofactor in the reaction pathway was only presumptive. Rather than rely on arguments based on enzymological precedent[7] or on chemical reasonableness, we sought direct evidence for the dehydrogenase activity of the enzyme. The failure to detect any absorbance at 340nm (symptomatic of the formation of enzyme-bound NADH) during the steady-state reaction of the natural substrate **1**, prompted us to use substrate analogs that are structurally unable to undergo the second (elimination) step of Figure 2. These analogs, the phosphonate **3** and the homophosphonate **4**, were further modified so as to favor substrate oxidation (and, therefore, cofactor reduction) on the enzyme. The redox potential of a secondary alcohol-ketone couple is less negative if the α-carbon carries an oxygen heteroatom. For example, lactate is more readily oxidized by NAD^+ than is glycerate, and propane-1,2-diol is more readily oxidized by NAD^+ than is glycerol, by about 2 kcal/mol. We therefore reasoned that replacement of the α-heteroatom in the phosphonate **3** or in the homophosphonate **4** by a methylene group, giving the carbocyclic analogs **7** and **8**, would maximize our chances of tipping the redox equilibrium towards the oxidized substrate analog and NADH. The carbocyclic homophosphonate analog **8** was synthesized according to the scheme outlined in Figure 3. The bicyclic bromolactone monobenzoate[8] from quinic acid was converted first to the monocyclic bromotribenzoate, which was then subjected to free-radical alkylation with allyltri-*n*-butylstannane. The resulting allylic tribenzoate ester was then ozonolyzed and reduced to the 2-hydroxyethyl derivative, which was smoothly converted into the bromo compound with triphenylphosphine and carbon tetrabromide. Transformation to the iodo compound and treatment of this with boiling trimethyl phosphite in the Arbusov transformation gave, after deprotection and hydrolysis, the carbocyclic homophosphonate **8**.[9,10]

When the carbocyclic homophosphonate **8** was added to dehydroquinate synthase, a new absorbance at 340nm appeared (see Figure 4). The hope that use of the carbocyclic substrate analogs would favor the formation of oxidized analog and NADH was thus realized. If we assume that the extinction coefficient of enzyme-bound NADH is the same as NADH in free solution, then 85% of the enzyme-bound NAD^+ is converted to NADH in the presence of a saturating concentration of **8**. When different substrate analogs are used, the levels of NADH observed are in the order expected on the basis of the redox potential for oxidation at C-5 of the analog.[9] The

chemical involvement of the nicotinamide cofactor in the reaction catalyzed by dehydroquinate synthase seems assured by these experiments.

We next focused on the nature of the second step of the reaction outlined in Figure 2, for which we required the cyclic 2-deoxy substrate analog **5**. This material was conveniently synthesized from 2-deoxy-D-glucose as shown in Figure 5. Treatment of the tetraacetate of 2-deoxy-D-glucose with trimethylsilyl cyanide yielded both anomeric nitrilotriacetates. Hydrolysis of the two nitriles was followed by esterification and acetylation, and the β-ester triacetate was isolated. Deprotection and selective phosphorylation of the primary hydroxyl group gave, after further deprotection, the desired analog **5** (Fig. 5).[10] When **5** was incubated with the enzyme, we were encouraged to observe the catalytic production of P_i and of the 2-deoxy analog of the enol pyranose **III**, exactly as expected if **5** had suffered the first three steps of the sequence outlined in Figure 2: oxidation at C-5 with concomitant formation of NADH, β-elimination of P_i, and reduction at C-5 by the bound NADH. The identity of the product (the 2-deoxy analog of **III**) was established first by ^{1}H NMR (a part of which is illustrated in Figure 6A) and then by comparison with an authentic synthetic sample. In passing, we should note that the rate of processing of **5** by the enzyme is about 2% that of the natural substrate **1**, which suggests that the form of **1** that is handled by the enzyme probably is the cyclic pyranose, as drawn. This view is reinforced by the finding that the acyclic 2-deoxy substrate analog **9** does not react with the enzyme.[10] Indeed, **9** does not even bind detectably to the synthase.

The finding that the enzyme catalyzes the elimination of P_i from **5** prompted us then to investigate the stereochemical course of the elimination reaction (the second step of Figure 2). That is, does the loss of P_i follow a *syn* or an *anti* course? To answer this question, a sample of the 2-deoxy analog **5** stereospecifically deuterated at C-7 was required. This material was made from pentaacetyl-[6(*S*)-*d*]-D-glucose, **10**, to which a convenient route has been charted by Ohrui and his collaborators.[11] Compound **10** was first converted into stereospecifically labeled 2-deoxy-D-glucose by tin hydride reduction of the labeled bromoacetyl-D-glucose according to the method of Giese[12] (Fig. 7). This product was then transformed (following the route summarized in Figure 5 for the unlabeled molecule) into the [7(*S*)-*d*]-labeled analog of 2-deoxy-DAHP, **11**. This material is also shown in Figure 8, along with the two possible products of P_i loss (by *syn* elimination to **12**, or by *anti* elimination to **13**) that could result if **11** were processed through the first three steps of the proposed mechanism.

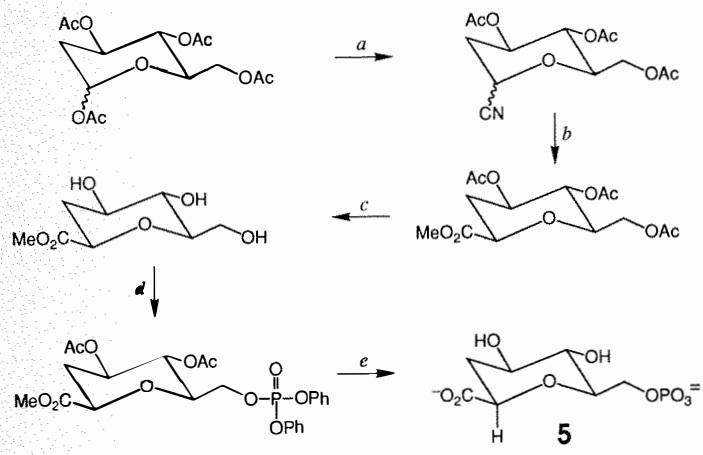


Fig. 5. ***Synthetic route to the cyclic 2-deoxy analog (5) of the natural substrate (1).*** *In this analog, the anomeric oxygen has been removed.* ***a:*** *Trimethylsilyl cyanide-BF_3 etherate-nitromethane;* ***b:*** *KOH-THF, then diazomethane, then acetic anhydride-pyridine;* ***c:*** *KOH-THF, then diazomethane;* ***d:*** *diphenyl phosphorochloridate-pyridine, then acetic anhydride-pyridine;* ***e:*** *H_2-Pt, then KOH.*

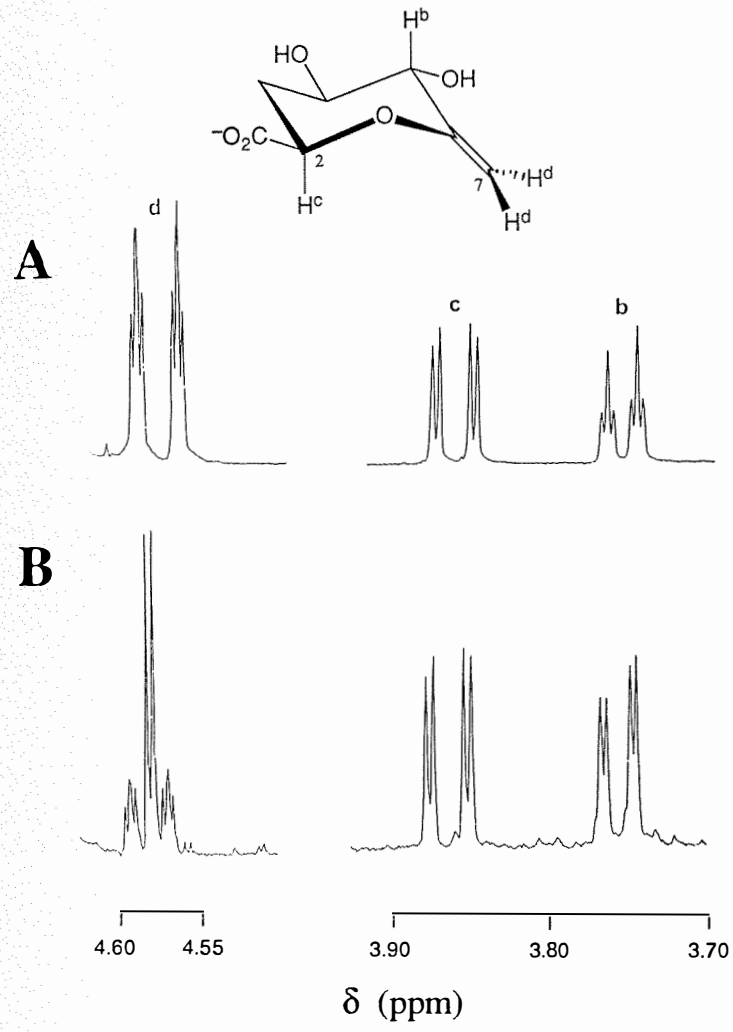


Fig. 6. ***Partial ^{1}H NMR spectra of the enol ether produced by the action of dehydroquinate synthase on the 2-deoxy substrate analog.*** ***A:*** *product from incubation with the unlabeled 2-deoxy substrate analog* ***5.*** ***B:*** *product from incubation with the [7S-d]-labeled 2-deoxy substrate analog* ***11.***

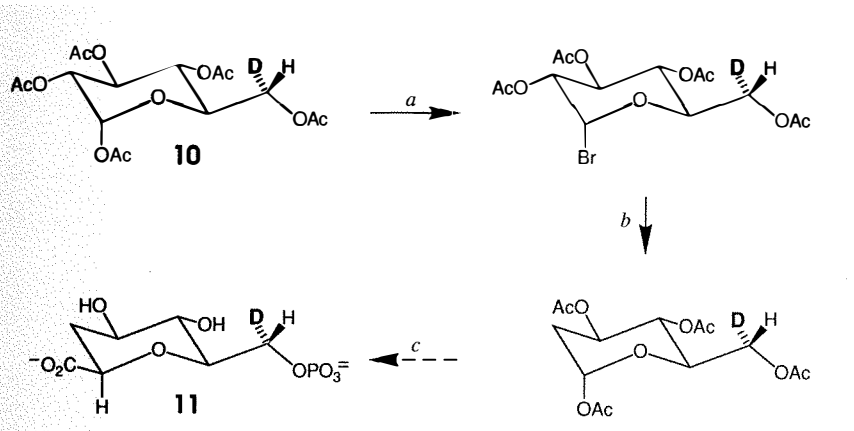


Fig. 7. ***Synthetic route to the stereospecifically labeled [7S-d] 2-deoxy substrate analog 11. a: HBr-HOAc; b: tri-n-butyltin hydride; c: the ten synthetic steps outlined in Figure 5.***

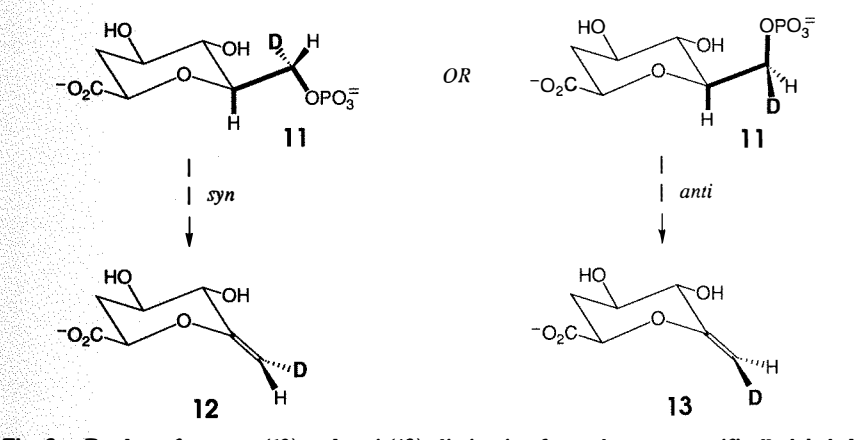


Fig. 8. ***Products from syn (12) and anti (13) elimination from the stereospecifically labeled [7S-d] 2-deoxy substrate analog 11.***

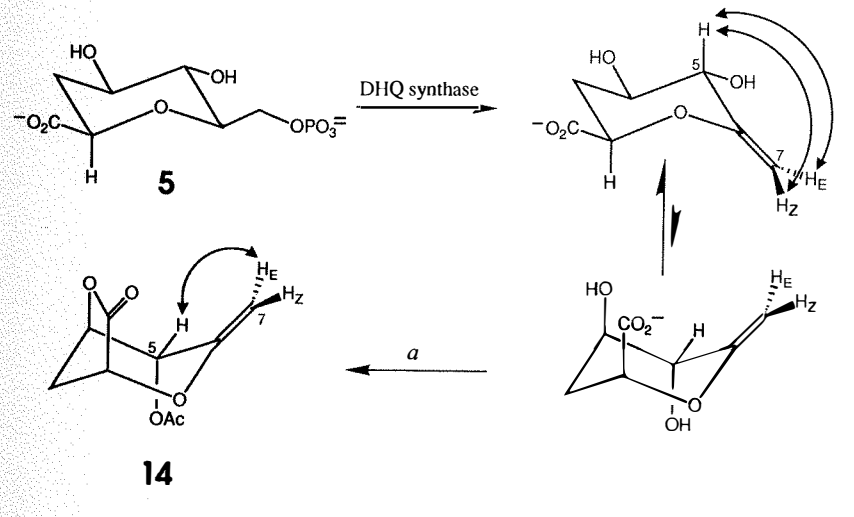
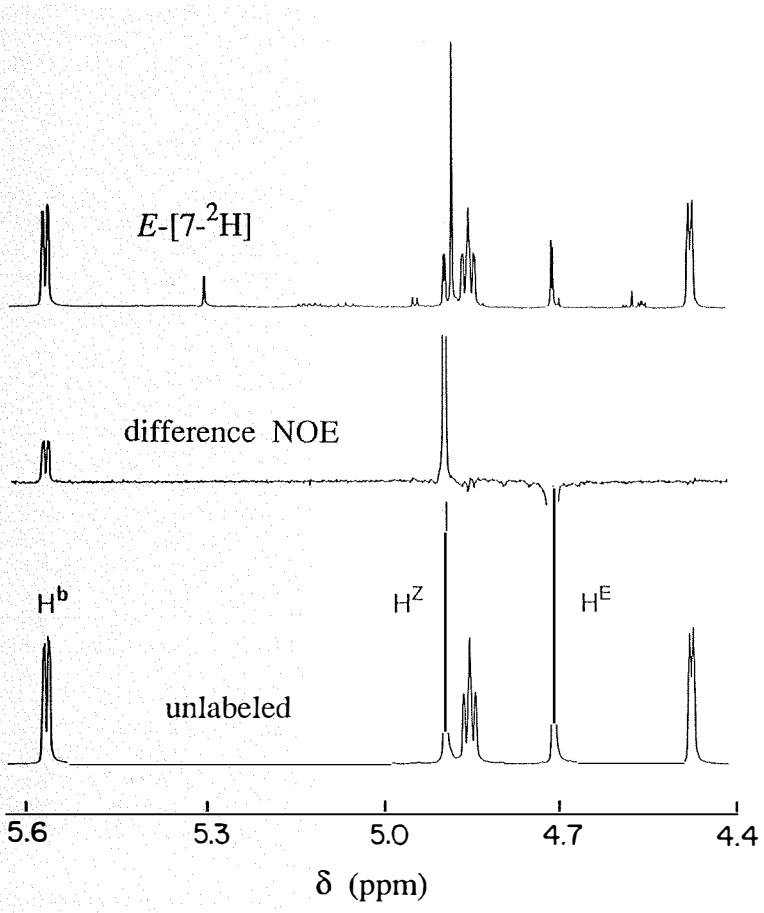


Fig. 9. ***Illustrating the fact that the C-5 proton is too far from the vinylic protons H_E and H_Z in the product from reaction of the enzyme with the 2-deoxy substrate 5.*** *After ring inversion and lactonization to the bicyclic lactone* ***14****, a nuclear Overhauser enhancement between the C-5 proton and H_E but not H_Z, is observed.* ***a:*** *Acetic anhydride-pyridine.*

When the [7(*S*)-*d*] analog **11** was incubated with the enzyme, the isolated product had the partial ^{1}H NMR spectrum shown in Figure 6B. It is clear that **11** is processed stereospecifically by the enzyme. The resonance of the upfield vinylic proton has largely disappeared (and thus carries the deuterium label), and the resonance of the downfield proton, simplified to a doublet, is isotopically shifted slightly upfield by the geminal vinylic deuterium. To discover whether the elimination is a *syn* or an *anti* process, we now had to establish whether the product from **11**, the ^{1}H NMR of which is shown in Figure 6B, is **12** or **13** (Fig. 8). The distances from the C-5 proton to H_E and H_Z (see Figure 9) in **12** and **13** are too large for assignment by nuclear Overhauser enhancement experiments, and the configurational assignment was therefore made by 'flipping' the conformation and locking the structure as the bicyclic lactone, **14** (Fig. 9). The partial ^{1}H NMR of this molecule is shown in Figure 10, and nuclear Overhauser enhancement experiments on this system then allowed the assignment of the deuterium label to the *E* position. That is, the product from the reaction of dehydroquinate synthase with the labeled [7(*S*)-*d*]-2-deoxy substrate analog **11**, is **12** rather than **13**. The elimination of phosphate occurs with *syn* stereochemistry.

The finding that the elimination is a *syn* process fits nicely with the emerging pattern of enzyme-catalyzed elimination reactions.[10] Thus, all the enzymes that catalyze the elimination of water from substrates for which the abstracted proton lies α to a ketone or a thiol ester eliminate water in a *syn* sense. In contrast, all the enzymes that catalyze the loss of water from substrates where the abstracted proton lies α to a carboxylate group proceed with *anti* stereochemistry. While the mechanistic implications of this dichotomy are not yet clear, it is gratifying that dehydroquinate synthase, where the abstracted proton is α to the ketone carbonyl group at C-5, follows a *syn* pathway.[10]

There are several ramifications of the finding that the elimination of P_i is *syn*. First, it was demonstrated by Sprinson[13] and by Haslam[14] and their collaborators that the overall reaction from **1** to **2** involves inversion of the configuration at C-7, and our definition of the stereochemical course of the elimination process restricts the possible transition-state geometries for the subsequent aldol reaction. This is illustrated in Figure 11, from which we see that, following a *syn* elimination of P_i, the appropriate epimer of labeled dehydroquinate is most readily produced by an internal aldol reaction that has a *chair*-like transition state. This, too, is gratifyingly consistent with the organic chemists' view of the favored transition-state geometry for aldol reactions.



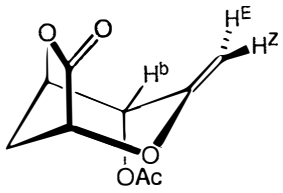


Fig. 10. ***Partial ^1H NMR spectrum of the bicyclic lactone 14.*** *Bottom spectrum: unlabeled bicyclic lactone derived from the product of incubating the enzyme with unlabeled 2-deoxy substrate analog* ***5****. Middle spectrum: difference nuclear Overhauser enhancement spectrum after irradiation of the resonance-labeled H_E. Top spectrum: labeled bicyclic lactone derived from the product of incubating the enzyme with [7S-d] 2-deoxy substrate analog* ***11****.*

A second implication of the finding of ***syn*** stereochemistry is that the mechanism of the elimination may be E1cB, and follow a stepwise pathway *via* the intermediacy of an enolate. To search for this enolate intermediate, we incubated the homophosphonate **4** with the enzyme in D_2O and looked for the time-dependent enzyme-catalyzed exchange of the C-6 proton with solvent deuterons. This exchange is illustrated in Figure 12, and, *pace* the fact that a substrate analog rather than the substrate itself was used, suggests that the second step of Figure 2 indeed follows an E1cB mechanism. Yet, when the C-6 proton exchange of other substrate analogs was investigated, we found an unexpected pattern. Thus, the phosphonate **3**, which binds to the enzyme much more tightly (K_i = 70 nM)[9] than the homophosphonate **4** (K_i = 60 μM)[9], suffers no exchange of the C-6 proton. The same pattern is seen for the corresponding carbocyclic analogs, **7** and **8**. This surprise led to the seductive suggestion that one of the substrate's peripheral phosphoryl oxygens might be responsible for the abstraction of the proton from C-6. To test this possibility, the carbocyclic *cis*- and *trans*-vinylhomophosphonates, **15** and **16**, were examined to see whether the enzyme can catalyze C-6 proton exchange in these molecules. Consis-

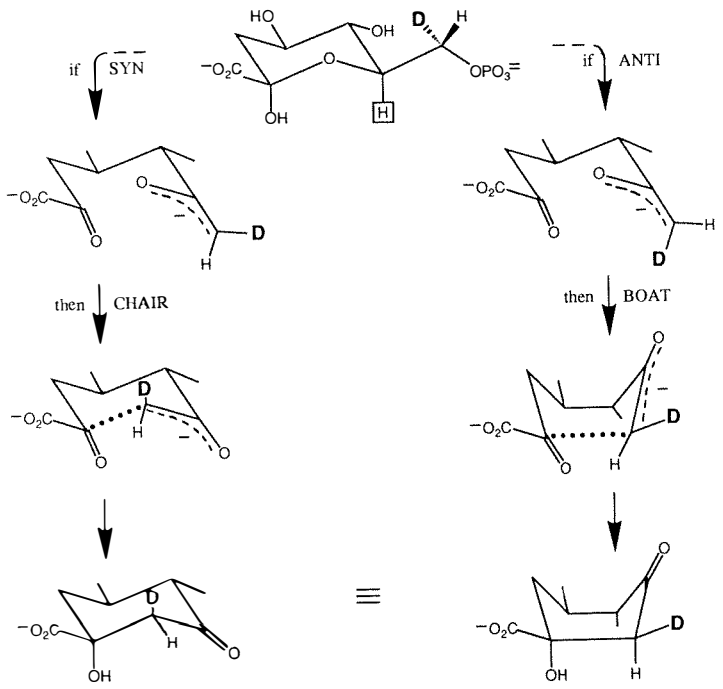


Fig. 11. ***Stereochemical relationships for the reaction catalyzed by dehydroquinate synthase.*** *Reacton of the [7S-d]-labeled substrate is illustrated. Since the overall reaction proceeds with inversion at C-7, the finding of a syn elimination suggests a chair-like transition state for the subsequent aldol reaction.*

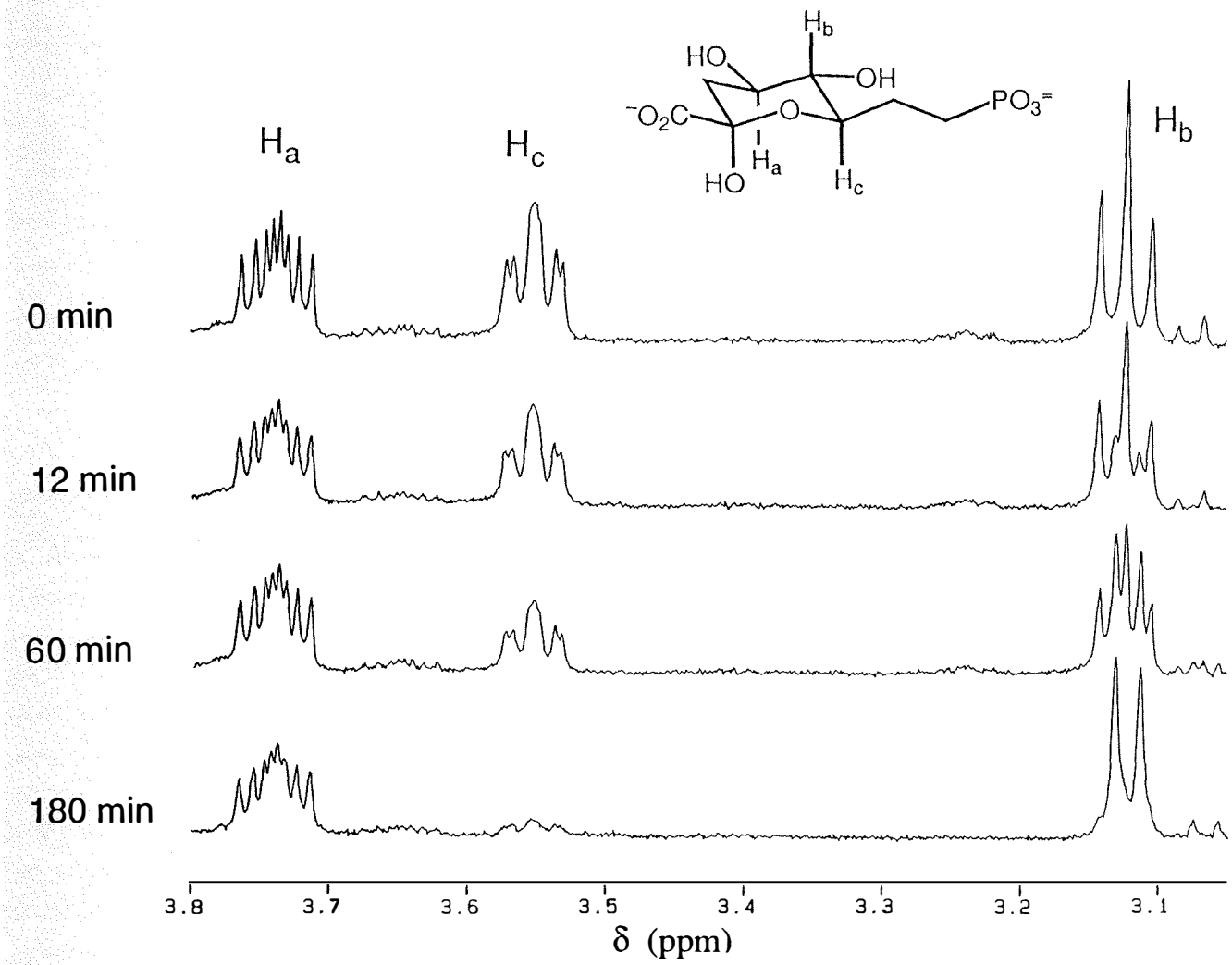


Fig. 12. Partial ^1H NMR spectrum of the homophosphonate substrate analog 4, after incubation with dehydroquinate synthase in D_2O for different times. *Enzyme-catalyzed exchange of the C-6 proton (H_c) is evident.*

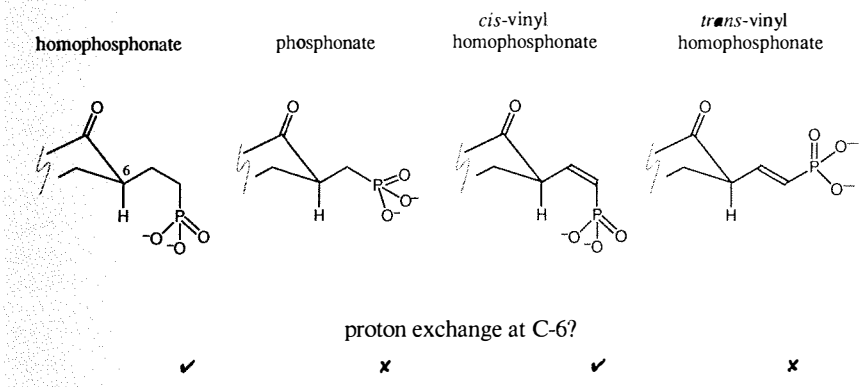
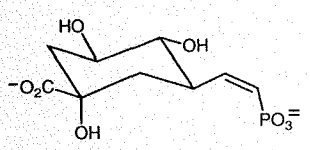


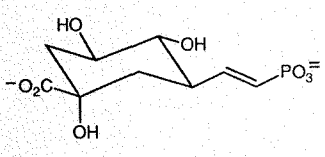
Fig. 13. Exchange of proton at C-6 of several substrate analogs with solvent D_2O, catalyzed by dehydroquinate synthase.

tent with the idea that the substrate acts as its own base, the *cis*-vinylhomophosphonate **15** was found to undergo C-6 proton exchange, whereas the *trans* compound **16** did not (Fig. 13). These data, involving analogs **3, 4, 7, 8, 15** and **16**, as well as (by implication) the natural substrate **1**, suggest that *the enzyme is not directly responsible for the E1cB elimination* of P_i from the substrate after oxidation at C-5. Provided that the substrate is bound to the enzyme in a conformation such that one of the peripheral phosphoryl group oxygens is appropriately positioned for C-6 proton abstraction, elimination of P_i from **I** (Fig. 2) may follow inexorably from the labilization of the C-6 proton by substrate oxidation at C-5 (see Fig. 13). There is good chemical precedent for such participation of a neighboring phosphoryl group in its own β-elimination,[15] and the involvement of enzyme functionality in catalysis of the elimination step in the dehydroquinate syn-



carba-*cis*-vinylhomophosphonate

15



carba-*trans*-vinylhomophosphonate

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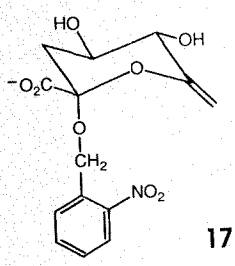

17

thase reaction may be minimal. Mere binding of substrate in an appropriate conformation may be enough to ensure the smooth conversion of **I** to **II** (Fig. 2).

The experiments described above provide a more detailed view of the first three steps of the pathway illustrated in Figure 2. What can be said of the last two steps, those that involve the ring-opening and internal aldol reaction of the enol pyranose intermediate, **III**? To examine this question, Bartlett and Satake[16] have recently synthesized intermediate **III**, using as the final deprotection step, the photochemical removal of the *o*-nitrobenzyl group from **17**. When **17** is subjected to photolysis in neutral aqueous solution, NMR analysis indicates the rapid and quantitative conversion to dehydroquinate, **2**! That is, the enol pyranose **III** spontaneously rearranges to **2**, and it is perhaps unnecessary for dehydroquinate synthase to catalyze this transformation at all. If **III** is lost from the enzyme (and, as we have seen, the 2-deoxy analog of **III** certainly is), **III** may smoothly and rapidly rearrange, without intervention or help from the enzyme, to the final product, **2**.

These results put the mechanistic pathway outlined in Figure 2 in a new light. It seems likely that dehydroquinate synthase is not, after all, an enzyme of unprecedented catalytic versatility and prowess. Perhaps it is merely a dehydrogenase, for the catalytic activity of which a divalent metal cation and enzyme-bound NAD^+ are both necessary and sufficient. The enzyme-catalyzed oxidation of C-5 of the substrate **1** may be followed by the (now facile) passive loss of P_i in an E1cB process to produce the enone **II**. Reduction of **II** to the enol pyranose **III** could complete the enzyme's catalytic involvement, for the loss of **III** from the active site would allow the rapid and stereoselective rearrangement of this species to the final product, dehydroquinate. While more experimental tests of these suggestions are needed before we can be confident of their validity, it seems possible that in the overall transformation that is mediated by dehydroquinate synthase, nature has neatly and ingeniously exploited several kinetically feasible and thermodynamically favorable processes. The superficially impressive enzyme that mediates the concatenation of catalytic steps outlined in Figure 2 may be no more, in reality, than a relatively banal dehydrogenase.

Acknowledgements

The work described herein was carried out by five splendid collaborators: John Frost, Judy Bender, Shujaath Mehdi, Ted Widlanski, and Stephen Bender, along with the financial support of the National Institutes of Health.

About the Author

Jeremy Knowles was educated at Magdalen College School, Oxford, and then served as a Pilot Officer in the Royal Air Force from 1953-1955, before graduating in the Final Honour School of Chemistry from Balliol College, Oxford, in 1959. He was awarded the D. Phil. in 1961, and came as a Postdoctoral Fellow to the California Institute of Technology. Returning to Oxford in 1962, he was elected Fellow and Tutor of Wadham College. In 1974, he joined the Harvard Faculty as Professor of Chemistry, and became the Amory Houghton Professor of Chemistry and Biochemistry in 1979. In 1983-1984 he was elected Newton-Abraham visiting Professor at Oxford University.

Professor Knowles was elected a Fellow of the Royal Society in 1977, and to the American Academy of Arts and Sciences in 1982. In 1984, he was elected to an Honorary Fellowship of Balliol College, Oxford. He became a Foreign Associate of the National Academy of Sciences, and a member of the American Philosophical Association, in 1988. He has been awarded the Charmian Medal of the Royal Society of Chemistry and the Alfred Bader Award in Bioorganic Chemistry, and an Arthur Cope Scholar Award from the American Chemical Society.

Professor Knowles' research is in the area of bioorganic chemistry, and involves the use of chemical methods and approaches to the solution of biochemical problems. He works on the physical-organic basis for the extraordinary specificity and rapid rates of enzyme-catalyzed reactions, on the evolution of enzyme function, the isolation and characterization of enzyme:substrate reaction intermediates, and on the stereochemical course of enzyme reactions. He has investigated the specificity and mechanism of serine and aspartyl proteases, his group introduced both aryl azides and diazirines for the photolabeling of biological receptors, and first evaluated the complete energetics of an enzymic reaction, developing the notion of 'catalytic perfection'. His research has also involved the mechanism and inhibition of β-lactamases, the stereochemical course of phosphotransferases, and features of enzymes in the shikimate pathway. Most recently, his group has focused on the pathways of evolutionary refinement of enzyme catalysts.

References:

1) Haslam, E. *The Shikimate Pathway;* Wiley: New York, 1974. Weiss, U.; Edwards, J.M. *The Biosynthesis of Aromatic Compounds;* Wiley: New York, 1980. Ganem, B. *Tetrahedron* **1978,** *34,* 3353.
2) Srinivasan, P.R.; Rothschild, J.; Sprinson, D.B. *J. Biol. Chem.* **1963,** *238,* 3176.
3) Frost, J.W.; Bender, J.L.; Kadonaga, J.T.; Knowles, J.R. *Biochemistry* **1984,** *23,* 4470.
4) Millar, G.; Coggins, J.R. *FEBS Lett.* **1986,** *200,* 11.
5) Bender, S.L.; Mehdi, S.; Knowles, J.R. *Biochemistry* **1989,** *28,* in press.
6) Rotenberg, S.L.; Sprinson, D.B. *J. Biol. Chem.* **1978,** *253,* 2210.
7) Frey, P. In *Pyridine Nucleotide Coenzymes, Part B;* Wiley: New York, 1987; p. 461.
8) Bartlett, P.A.; Maitra, V.; Chouinard, P.M. *J. Am. Chem. Soc.* **1986,** *108,* 8068.
9) Bender, S.L.; Widlanski, T.S.; Knowles, J.R. *Biochemistry* **1989,** *28,* in press.
10) Widlanski, T.S.; Bender, S.L.; Knowles, J.R. *ibid.* **1989,** *28,* in press.
11) Ohrui, H.; Horiki, H.; Kishi, H.; Meguro, H. *Agric. Biol. Chem.* **1983,** *47,* 1101.
12) Giese, B. *et al. Angew. Chem., Int. Ed. Engl.* **1987,** *26,* 233.
13) Rotenberg, S.L.; Sprinson, D.B. *Proc. Natl. Acad. Sci. U.S.A.* **1970,** *67,* 1669.
14) Turner, M.J.; Smith, B.W.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1975,** 52.
15) For example, Gallopo, A.R.; Cleland, W.W. *Arch. Biochem. Biophys.* **1979,** *195,* 152. Motui-DeGrood, R.; Hunt, W.; Hupe, D.J. *J. Am. Chem. Soc.* **1979,** *101,* 2182.
16) Bartlett, P.A.; Satake, K. *ibid.* **1988,** *110,* 1628.

Following are some Aldrich products related to Professor Knowles' article:

At the Organic Chemistry/Bioscience Interface: Rate Processes in Complex Systems

Keith U. Ingold
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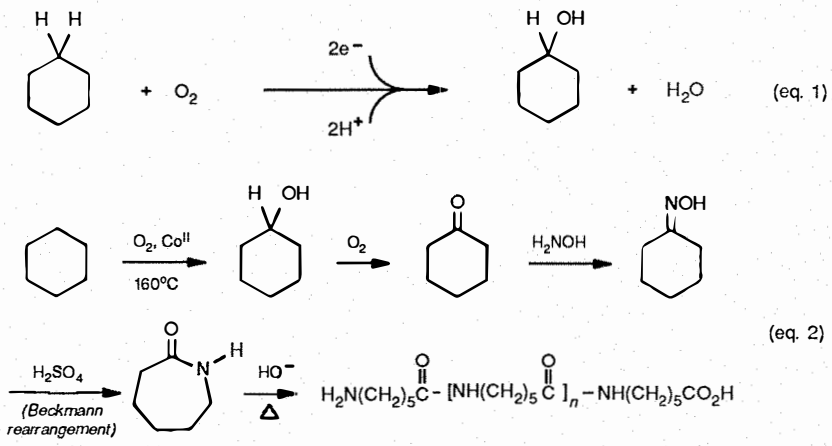
Canada

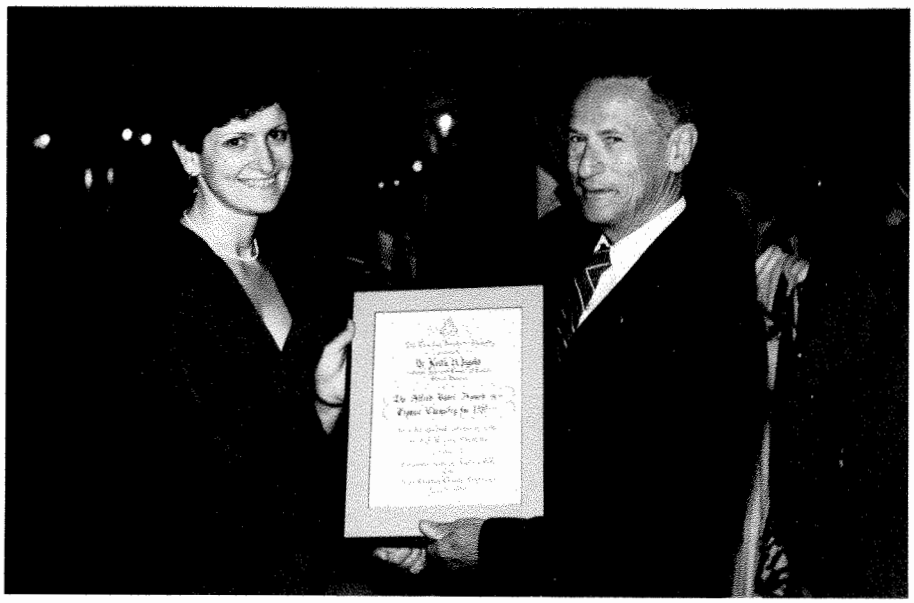
I am deeply honored to be this year's recipient of the Alfred Bader Award in Organic Chemistry. Since I spent the first six years of my research career working as a physical chemist on gas kinetics, this Award might seem to demonstrate a revolution in my research interests. This is not the case. It is more the 40-year evolution of a kineticist. This evolutionary process has been encouraged, aided and abetted by the most outstanding group of postdoctoral fellows, summer students, visiting scientists and external collaborators imaginable. The skills, dedication and insights of these many colleagues have ensured that the fundamental principles of physical and physical organic chemistry have been applied to ever more complex kinetic systems. I should like to take this opportunity to thank all my past and present colleagues for keeping me on my scientific toes and thereby ensuring that I have lived in interesting times.

Traditional chemical kinetic principles and techniques can provide new insights into the mechanisms of physiologically significant reactions and into the *in vivo* processes involved in the absorption and transport of lipophilic molecules. Today I shall talk about research in that vague, indefinable frontier region where organic chemistry fades away into the biosciences. I will apologize in advance for the fact that the stories I am going to tell are less complete and provide less definitive answers than is customary for an organic lecture. I could excuse myself with the truth that the research is still ongoing. However, a greater truth is that it is extremely difficult to ask the right questions at this foggy frontier, let alone come up with firm answers. Hence, the challenge and, if one makes any progress at all... the thrill and the excitement!

Cytochrome P-450 Hydroxylation of Alkanes

The oxidation of cyclohexane to cyclohexanol using molecular oxygen, two protons and two electrons is one of the simplest imaginable reactions (eq. 1). It is also an extremely important commercial reaction, since ~ 10^6 tons of cyclohexanol are made per year worldwide for conversion to caprolactam and hence to Nylon 6 (eq. 2). The commercial oxidation of cyclohexane must be the least efficient of all major industrial chemical processes. Typically, cyclohexane is air-oxidized at 160 °C (about 80 ° above its b.p.) in enormous pressurized tanks using Co^{II} as a catalyst. Because the desired oxidation products, cyclohexanol and cyclohexanone are both more susceptible to oxidation than cyclohexane under these conditions, the reaction is run only to 4% conversion, meaning that 96% of the cyclohexane must be separated from the products and recycled. However, even at this low conversion, the





Dr. Keith U. Ingold (right) receiving the Canadian Alfred Bader Award in Organic Chemistry from Miss Dorene Starrett, Manager, Customer and Order Services, Aldrich Chemical Co., Inc.

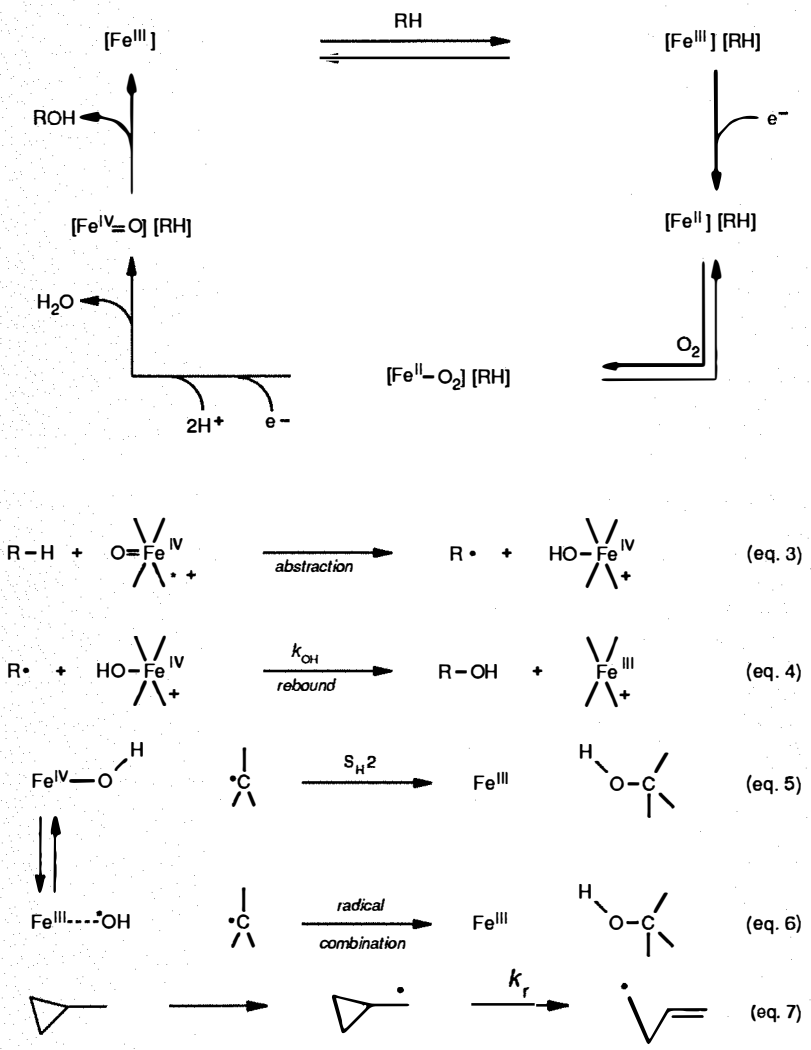
desired compounds constitute only 85% of the products.

In contrast to the commercial oxidation of cyclohexane, all of us can oxidize this compound to cyclohexanol with 100% efficiency. This oxidation occurs mainly in our livers and we use an iron, rather than a cobalt catalyst, cytochrome P-450. This is an iron protoporphyrin IX (Figure 1) embedded in a protein with the "back" of the iron atom (*i.e.*, the 5th coordination site) being protected by a thiolate ligand and the "front" being accessible *via* a hydrophobic pocket in the protein.[1] The catalytic cycle which converts an alkane, RH, to the alcohol, ROH, is shown in Scheme 1. Reading this cycle as a clock, our current concern lies between 9:00 and 10:30. The intermediates from 10:30, [Fe^{III}] the resting enzyme, to 6:00 can be observed, but the 9:00 species, [Fe^{IV}=O][RH], "inserts" an oxygen atom into RH too rapidly for this species to be observed. The mechanism by which the oxygen is "inserted" into a C-H bond was originally inferred to be just that, *i.e.*, an insertion. However, as Groves and coworkers[2] have demonstrated, with an appropriate choice of substrate the hydroxylation can occur with a loss of stereo- and regioselectivity. It has therefore been inferred that the hydroxylation of RH involves an initial hydrogen abstraction to form a carbon-centered radical, R• (eq. 3), followed by oxygen (hydroxyl) "rebound" from iron to carbon (eq. 4).

The interesting question relates to the nature of the "rebound" process. The two most obvious mechanisms are:

1. A bimolecular homolytic substitution (S_H2) by the carbon-centered radical at oxygen for iron (eq. 5).
2. Prior dissociation of the Fe-OH bond to form a "free" hydroxyl radical which combines with the adjacent carbon-centered radical (eq. 6).

Scheme 1



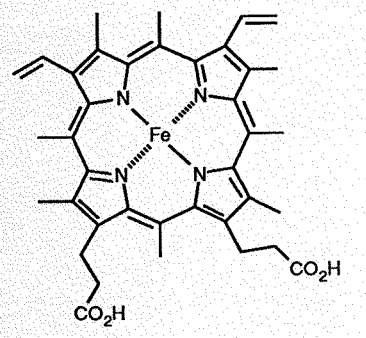
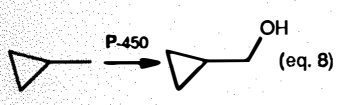


Fig. 1. The iron protoporphyrin IX of cytochrome P-450.

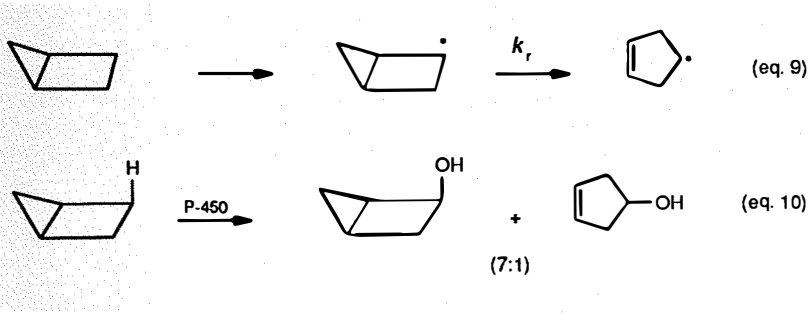
Mechanisms are deduced from product and kinetic studies. In a general sense the products are known, *viz.*, [Fe^{III}] and ROH. Kinetic studies must be concerned with *rate* rather than with *order*. That is, the hydroxylation of R is clearly a bimolecular reaction but it will obey first-order rather than second-order kinetics because there is strong evidence that the carbon-centered radical will be hydroxylated much more rapidly than it can escape from the hydrophobic pocket in the enzyme. The only reasonable way to measure the rate of hydroxylation of R• is to use an alkane which will yield a *calibrated free-radical clock*,[3] *i.e.*, R• must be an alkyl radical which undergoes an irreversible unimolecular rearrangement at a rate which has been measured[3] and which will compete with the hydroxylation process.

In 1987, Ortiz de Montellano and Stearns[4] applied the radical-clock method to alkane hydroxylations at 37 °C using rat-liver microsomes enriched in cytochrome P-450 by pretreatment of the rats with phenobarbital. The fastest calibrated clock was the ring-opening of the cyclopropylmethyl radical to yield the 3-butenyl radical[3] (eq. 7). This reaction has a rate constant of 1.2 x $10^8 s^{-1}$ at 37 °C but, despite its speed, methylcyclopropane yielded only cyclopropylmethanol[4] (eq. 8). Fortunately, a faster alkyl radical rearrangement was known[5] (eq. 9), but it had proved to be too fast to calibrate by the usual[3] electron spin resonance (ESR) spectroscopic method. That is, the cyclopropylmethyl clock was originally calibrated[6] by generating this radical photochemically in an ESR spectrometer in an inert solvent and measuring its absolute concentration at low temperatures where the 3-butenyl radical could also be observed and quantified. These two radicals were present at approx-

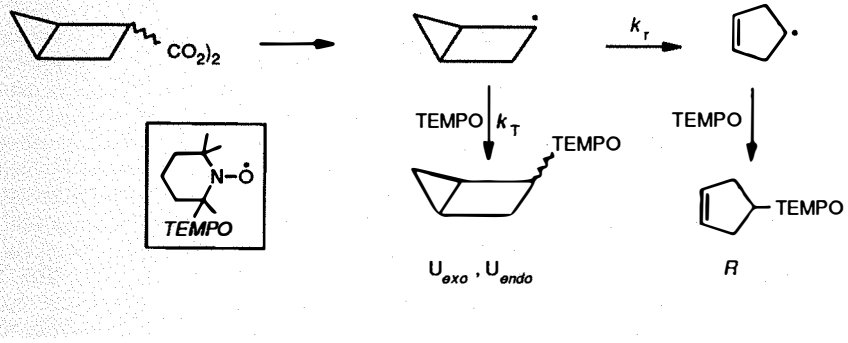


into a useful clock.

The simplest calibration procedure appeared to us to be to generate the bicyclopentyl radical in the presence of TEMPO and measure the relative yields of the TEMPO-trapped unrearranged and rearranged radicals at known TEMPO concentrations (Scheme 2). We chose TEMPO as the trap because we had previously determined the absolute rate constants for its reaction with a variety of alkyl radicals by laser flash photolysis (LFP) and found that these rate constants were all about $1 \times 10^9 M^{-1}s^{-1}$ at room temperature, showing little dependence on the nature of the carbon-centered radical.[7] Three TEMPO adduct radical products were detected which were identified as the *exo* and *endo* (2.4:1 ratio) adducts of the unrearranged radical and the adduct of the rearranged radical.[8] From the ratio of the two unrearranged adducts to the rearranged adducts, we determined that $k_r/k_T = 1.6M$ at 37 °C.[8] Taking $k_T = 1.4 \times 10^9 M^{-1}s^{-1}$ (the value found by LFP for trapping the cyclobutyl radical[9]) yielded $k_r = 2.4 \times 10^9 s^{-1}$. Combination with the P-450-derived alcohol product ratio found by Ortiz de Montellano and Stearns[4] gave the rate constant for oxygen rebound, $k_{OH} = 1.7 \times 10^{10} M^{-1}s^{-1}$.



Scheme 2



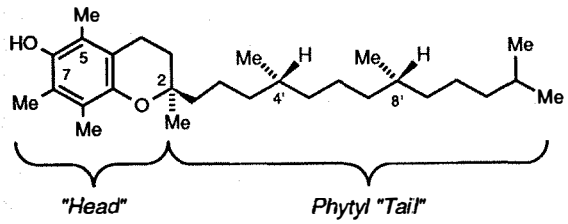


Fig. 2. Natural (2R,4'R,8'R)-α-tocopherol.

imately equal concentration at *ca.* 140K[6] with the unrearranged cyclopropylmethyl radical becoming the only species detectable at temperatures below ~120K. By way of contrast,[5] the bicyclo[2.1.0]pent-2-yl radical could not be detected by ESR spectroscopy even at temperatures as low as 110K; only the rearranged cyclopenten-4-yl radical was observed from which it was concluded that $k \geq 10^9 s^{-1}$ at ambient temperatures. The action of microsomal P-450 on bicyclopentane gave a 7:1 ratio of the unrearranged and rearranged alcohols[4] (eq. 10) which left us with the problem of calibrating this rearrangement to turn it

Of course, a single rate constant demonstrates nothing except that oxygen rebound is a very rapid process. We have therefore extended our studies to half-a-dozen polymethyl-substituted cyclopropanes. Rate constants have been measured by the TEMPO method for the ring opening of methyl-substituted cyclopropylmethyl radicals, and when two ring-opened radicals can be produced, their ratio has been determined.[9] The same compounds have been hydroxylated with P-450 using phenobarbital-induced rat-liver microsomes.[9] Most interestingly, *cis*- and *trans*-1,2-dimethylcyclopropane give the same secondary alcohol/primary alcohol ratio as found for the TEMPO alkyl radicals adducts, *viz.*, 3:1 and 1:1, respectively. That is, *cis*- and *trans*-2-methylcyclopropylmethyl radicals generated by P-450 oxidation of the parent hydrocarbons partition between the two ring-opening reactions to form the secondary and the primary alkyl radical in just the same ratio as when these radicals are formed in homogeneous solution. This demonstrates that the enzyme's hydrophobic pocket does not influence the ring-opening partitioning of either of these two 2-methylcyclopropylmethyl radicals but, nevertheless, the calculated rate constants for oxygen rebound are only about half as large as the value calculated from the bicyclopentane data. It seems improbable that k_{OH} would depend on the nature of the substrate if hydroxyl-ation involved combination of R• with a free HO• radical since the rate-controlling step would be fission of the iron-oxygen bond—a process which would be expected to be independent of the substrate. We therefore conclude that the most probable mechanism for the P-450 hydroxylation of alkanes involves the S_H2 reaction (eq. 5). Work is continuing to calibrate other rapid alkyl-radical rearrangements by the TEMPO method and to submit the parent hydrocarbons as substrates for hydroxylation by cytochrome P-450. The results obtained to date[9] remain consistent with hydroxylation *via* an S_H2 process but this "consistency" could be destroyed tomorrow.

Vitamin E: Which is Best, the Free Phenol or the Acetate?

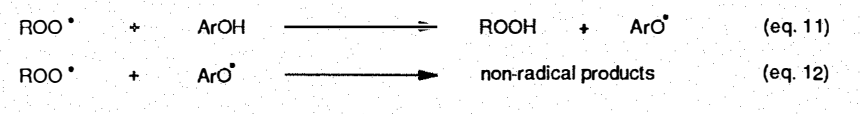
We have proved that natural vitamin E, 2*R*,4'*R*,8'*R*-α-tocopherol (Figure 2), is certainly the major and probably the sole lipid-soluble, radical-trapping antioxidant present in human blood.[10] That is, vitamin E (ArOH) inhibits lipid peroxidation *in*

vivo by trapping peroxyl radicals generated in biological membranes (eqs. 11 and 12) and it would be fair to say that we do not become rancid until it is our turn to become food, thanks to vitamin E.

Our extensive studies on this vitamin[11] began with an *in vitro* demonstration that α-tocopherol was the best peroxyl radical-trapping, phenolic antioxidant known at that time. In recent years, our research has moved increasingly to *in vivo* studies in animals and humans. One of the more intriguing *in vivo* questions we have answered is posed by the title of this section. In its natural form in food, vitamin E is present as α-tocopherol, *i.e.*, as the free phenol. However, commercial vitamin E is generally sold as α-tocopheryl acetate since this is much more air-stable than the phenol. The acetate is not a peroxyl radical trap nor is it absorbed from the intestine; instead it is first hydrolyzed to the phenol and it is the phenol which is absorbed.

To the companies that manufacture vitamin E it is naturally a matter of some concern whether the acetate is as effective a source of the vitamin as the free phenol. For 40 years they have dealt with this problem using the classical rat fetal-resorption bioassay.[12] The protocol for this bioassay involves placing a large number of female rats on a vitamin E-deficient diet for 2-3 months; the rats are then mated with vitamin E-sufficient males; impregnation and implantation proceed normally but, if the female does not receive vitamin E, the fetuses will die and be resorbed. The females are divided into six groups; three groups receive α-tocopherol at three different levels as a daily dose in corn oil for four days; the other three groups are similarly dosed with α-tocopheryl acetate at the same three levels. Sacrifice occurs on the fifth day and the "end-point" is determined by counting the number of live fetuses; for a given dose, the more live fetuses the greater the vitamin E activity of the dosed compound. Very surprisingly, this bioassay indicated that the phenol had only some 60%[12a] or 47%[12b] of the activity of the acetate—results which must have brought a sigh of relief to the companies which manufacture vitamin E!

Because "identical" rats are not identical, the fetal-resorption bioassay has a statistical nature and requires a large number of animals. We decided that in a properly designed, competitive biokinetic experiment, the relative bioactivities of phenol and acetate could be more reliably determined using even a single rat. In the event we actually used four rats, two were vitamin E-deficient (as in the bioassay) and two were E-sufficient.[13] These animals were dosed for four days with an equimolar mixture of d_6-2*R*,4′*R*,8′*R*-α-tocopherol and d_3-2*R*,4′*R*,8′*R*-α-tocopheryl acetate in corn oil, the deuterium labels having been placed in metabolically inactive positions. After sacrifice on the fifth day, the animals



(eq. 11)

(eq. 12)

were dissected, the lipids from blood and various tissues were extracted, and the ratio d_6-α-tocopherol/d_3-α-tocopherol was measured by GC/MS. The results were the same for all four rats, *i.e.*, the results were not affected by the animals' vitamin E status.[13] The mean d_6-/d_3-α-tocopherol ratio for the four rats was 0.49 ± 0.05,[13] in good agreement with the fetal-resorption bioassay.

We remained dubious that, under normal conditions, a chemically derivatized form of vitamin E (acetate) could provide more vitamin E than the natural vitamin (phenol). We therefore turned our attention to man. A single capsule containing 50mg of the deuterated phenol and 50mg of the deuterated acetate was swallowed with an evening meal by several volunteers. Blood was drawn on subsequent days and the ratio of α-tocopherol derived from the phenol and from the acetate in the plasma and red blood cells was found to be close to 1.0.[13] This provided the first scientific proof that "man was not a rat". However, certain important ladies rejected this conclusion saying with great vigor: "Nonsense, all men are rats". Clearly, further research was called for.

Rats are night feeders and in the N.R.C.'s animal facility, the rats are housed in a basement room with artificial illumination being provided from 6 a.m. to 6 p.m. At about 10 a.m. the technician doses the animals according to the bioassay protocol with the vitamin E preparation in corn oil. This is not dissimilar to a person swallowing half a pint of corn oil on an empty stomach (ugh!). Five rats were therefore treated rather more like our volunteers. They were fed an equimolar mixture of the deuterated phenol and the deuterated acetate in an aqueous bolus of laboratory food. Sacrifice occurred 24 hours later and was followed by dissection, lipid extraction and GC/MS analyses. The mean ratio of α-tocopherol derived from phenol to that derived from acetate was 1.06 ± 0.11.[13] Clearly, the ladies have a point; but perhaps more importantly, it is obvious that the long accepted measurement of vitamin E activity by the rat fetal-resorption bioassay is irrelevant to the animal under normal dietary conditions and, hence, is quite meaningless insofar as man is concerned.

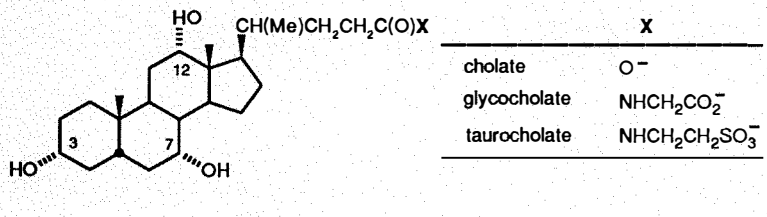
Is this relevant to you? Yes, if you dose yourself with commercial vitamin E. This can be bought as (natural) 2*R*,4′*R*,8′*R*-α-tocopheryl acetate or, at a lower price, as (synthetic) *all-racemic*-α-tocopheryl acetate. The "official" relative vitamin E activities of these two compounds is 1.36:1.00 — but this is based on the rat fetal-resorption bioassay! Our own studies (using deuterated natural and synthetic α-tocopherol on human volunteers as well as rats) show that natural α-tocopherol is retained about twice as well as the synthetic, *all-racemic* material.[14]

Stereochemical Discrimination

During the past 2-3 years, we have invested a lot of effort into trying to understand the absorption and transport of vitamin E in rats[15] and in man,[16] and in trying to identify the site(s) of chiral discrimination between α-tocopherol stereoisomers in rats[15] and man.[17] An early experiment involved rats fed a diet containing equimolar d_6-2*R*,4′*R*,8′*R*-α-tocopheryl acetate and d_3-2*S*,4′*R*,8′*R*-α-tocopheryl acetate.[15] Except for the liver, during the first three weeks of this experiment, all tissues favored natural 2*R*,4′*R*,8′*R*-α-tocopherol from day one. For some tissues, this chiral discrimination became quite dramatic, for example, a factor of 5.3 in the brain after 5 months. The liver is the main organ for chiral discrimination[17,18] which appears to occur during the manufacture of very low-density lipoprotein particles.[17] However, there are other sites of discrimination, for example, red blood cell membranes[19] and the intestine.[15]

Not unnaturally, our initial research[15] was concerned with the intestine because it is here that the two acetates are hydrolyzed to the corresponding phenols. Hydrolysis is achieved by a pancreatic enzyme, cholesterol esterase, which requires bile salts for activity. In the rats' large intestines we found 1.1 to 1.6 times as much 2*R*,4′*R*,8′*R*-α-tocopherol and 0.4 to 1.1 times as much 2*R*,4′*R*,8′*R*-α-tocopheryl acetate as for the corresponding 2*S*,4′*R*,8′*R* compounds,[15] which demonstrates that the acetate of natural α-tocopherol is hydrolyzed more rapidly than the acetate of the unnatural stereoisomer.

An attempt to model the hydrolysis of the two acetates *in vitro* using bovine cholesterol esterase, sodium cholate (40m*M*) as the obligatory bile salt and with the acetates dispersed in dimyristoylphosphatidyl choline "failed" in that the maximum rate of hydrolysis (V_{max}) for the 2*S*,4′*R*,8′*R*-α-tocopheryl acetate was



X	
cholate	O^-
glycocholate	$NHCH_2CO_2^-$
taurocholate	$NHCH_2CH_2SO_3^-$

Fig. 3. Cholate conjugates.

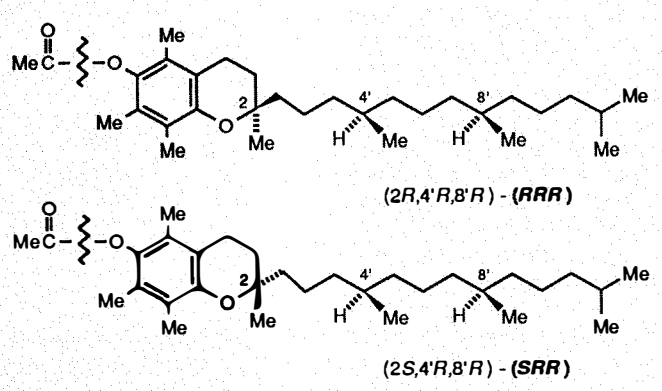


Fig. 4. α-Tocopheryl acetate stereoisomers.

about 7 times as great as V_{max} for the 2*R*,4′*R*,8′*R* acetate.[20] Subsequent work[18] proved that this "failure" was not due to the use of a bovine rather than a rat pancreatic esterase but rather to the choice of bile salt. In the same model system, except for the replacement of the cholate by its glycine and taurine conjugates (Figure 3), the values of V_{max} for the 2*R*,4′*R*,8′*R*-α-tocopheryl acetate were 8 and 25 times, respectively, as great as V_{max} for the other stereoisomer. These three bile salts can therefore modulate the stereoselectivity of the bovine esterase by a factor of ~200, despite the fact that the bond which is broken is separated by six bonds from the chiral center (Figure 4).

It is clear that each bile salt/substrate combination reacts with the enzyme in such a way that chiral information is conveyed to the active site. Since the 2*R*,4′*R*,8′*R*- and 2*S*,4′*R*,8′*R*-α-tocopheryl acetates could form different diastereoisomeric complexes with each of the different bile salts, we suggest that these are selected differently by the enzyme's active site. At **40m*M***, the bile salts will aggregate and the esterase-catalyzed reaction therefore probably involves hydrolysis of the acetates contained in micelles of different structures.

Whatever the precise mechanistic details, it is clear that we have stumbled upon a most interesting phenomenon. It would appear that any member of an endogenous family of chiral auxiliaries (the bile salts) can activate the enzyme and determine the stereoselectivity of the enzyme/(chiral) substrate reaction. *This stereochemical control mechanism would appear to be too valuable and versatile for Nature to use only once.*

Acknowledgement

This work was carried out by the individuals who are named in the list of references. To all of them I owe a deep and personal debt of thanks for the skill, determination and dedication they brought to their research. The work on vitamin E was made possible through the generosity of the Association for International Cancer Research; the National Foundation for Cancer Research; Eastman Chemical Products, Inc.; Eisai Co., Ltd.; and the Henkel Corporation.

References:

1) *Cytochrome P-450*; Ortiz de Montellano, P.R., Ed.; Plenum Press: New York, 1986.
2) Groves, J.T.; McClusky, G.A.; White, R.E.; Coon, M.J. *Biochem. Biophys. Res. Commun.* **1978,** *81,* 154. Groves, J.T.; Subramanian, D.V. *J. Am. Chem. Soc.* **1984,** *106,* 2177.
3) Griller, D.; Ingold, K.U. *Acc. Chem. Res.* **1980,** *13,* 317.
4) Ortiz de Montellano, P.R.; Stearns, R.A. *J. Am. Chem. Soc.* **1987,** *109,* 3415.
5) Jamieson, C.; Walton, J.C.; Ingold, K.U. *J. Chem. Soc., Perkin Trans. 2* **1980,** 1366.
6) Maillard, B.; Forrest, D.; Ingold, K.U. *J. Am. Chem. Soc.* **1976,** *98,* 7024.
7) Chateauneuf, J.; Lusztyk, J.; Ingold, K.U. *J. Org. Chem.* **1988,** *53,* 1629.
8) Bowry, V.W.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1989,** *111,* 1927.
9) Bowry, V.W., unpublished results.
10) Burton, G.W.; Joyce, A.; Ingold, K.U. *Lancet* **1982,** 327. *Idem Arch. Biochem. Biophys.* **1983,** *221,* 281. Ingold, K.U.; Webb, A.C.; Witter, D.A.; Burton, G.W.; Metcalfe, T.A.; Muller, D.P.R. *ibid.* **1987,** *259,* 224.
11) Burton, G.W.; Ingold, K.U. *Acc. Chem. Res.* **1986,** *19,* 194.
12) a) Harris, P.L.; Ludwig, M.I. *J. Biol. Chem.* **1949,** *180,* 611. b) Wieser, H.; Vecchi, M.; Schlachter, M. *Int. J. Vit. Nutr. Res.* **1986,** *56,* 45.
13) Burton, G.W.; Ingold, K.U.; Foster, D.O.; Cheng, S.C.; Webb, A.; Hughes, L.; Lusztyk, E. *Lipids* **1988,** *23,* 834.
14) Burton, G.W., unpublished results.
15) Ingold, K.U.; Burton, G.W.; Foster, D.O.; Hughes, L.; Lindsay, D.A.; Webb, A. *Lipids* **1987,** *22,* 163.
16) Traber, M.G.; Ingold, K.U.; Burton, G.W.; Kayden, H.J. *ibid.* **1988,** *23,* 791.
17) Traber, M.G., unpublished results.
18) Zahalka, H.A., unpublished results.
19) Cheng, S.C.; Burton, G.W.; Ingold, K.U.; Foster, D.O. *Lipids* **1987,** *22,* 469.
20) Zahalka, H.A.; Cheng, S.C.; Burton, G.W.; Ingold, K.U. *Biochim. Biophys. Acta* **1987,** *921,* 481.

About the Author

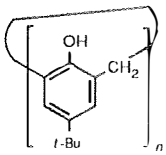
Keith U. Ingold was born in 1929 in Leeds, England. In 1949 he received his B.S. from University College London where his father, Sir Christopher, was head of the Chemistry Department. Dr. Ingold obtained his Ph.D. from the University of Oxford in 1951 working on hydrocarbon pyrolysis in the gas phase with Sir Cyril Hinshelwood, Nobel Laureate. He also emigrated to Canada in 1951 where he joined the National Research Council and was a Post-doctoral Fellow with F.P. Lossing working on the mass spectrometry of reactive intermediates. In 1953, he moved to the University of British Columbia for a second post-doc on mass spectrometry with W.A. Bryce. In 1955, he returned to Ottawa and the National Research Council to study, under I.E. Puddington in the Division of Applied Chemistry, the mechanism of the oxidative degradation of lubricating oils and to find improved methods for protecting them against such degradation.

The work on lubricating oils induced Dr. Ingold's lifetime interest in the chemistry of free-radical reactions in solution. It rapidly became apparent that an understanding of the inhibited autooxidation of lubricating oils required a great number of fundamental scientific facts that simply were not available. Dr. Ingold and J.A. Howard therefore launched into an extensive series of measurements of the kinetics and absolute rate constants for the elementary reaction involved in the inhibited and in the uninhibited autooxidation of pure hydrocarbons.

In 1967, Dr. Ingold acquired an electron spin resonance (ESR) spectrometer and, with D. Griller, pioneered the application of this instrument to studies on the kinetics of radical reactions in solution as well as the investigations of the structures of novel, long-lived (persistent) radicals.

About a decade later, Dr. Ingold began collaborating with J.C. Scaiano on the application of laser flash photolysis to the quantitative measurements of the rates of radical reactions that were too fast for investigation by ESR. Dr. Ingold maintains an active research program in this area, as demonstrated by the measurements with J. Lusztyk of the absolute rate constants for the trapping of carbon-centered radicals by nitroxides (*vide supra*). At about the same time, Dr. Ingold and G.W. Burton began their investigations into the chemistry of vitamin E. This work soon expanded into biology with interest focusing on the biokinetics of different forms of this vitamin (*vide supra*). The vitamin E work continues to provide more questions than answers—as has always been true of interesting and worthwhile scientific research.

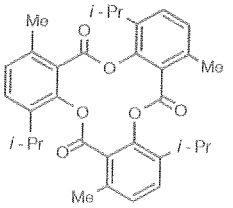
4-tert-Butylcalix(4)arene: Useful Host Molecule



Forms a stable complex with *tert*-butylamine in aqueous solution.[1] Excellent building block for a variety of derivatives employed as efficient ionophores for sodium[2] and rubidium[3] alkali cations, and as hosts for neutral organic molecules with selectivity.[4] Interesting potential enzyme mimic.[5]

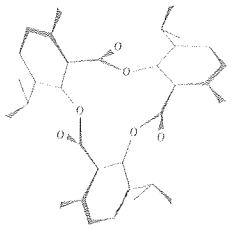
(1) Gutsche, C.D.; Iqbal, M.; Alam, I. *J. Am. Chem. Soc.* **1987,** *109,* 4314. (2) Diamond, D.; Svehla, G.; Seward, E.M.; McKervey, M.A. *Anal. Chim. Acta* **1988,** *204,* 223. (3) Reinhoudt, D.N. *et al. J. Am. Chem. Soc.* **1987,** *109,* 4761. (4) Shinkai, S.; Araki, K.; Manabe, O. *Chem. Commun.* **1988,** 187. (5) Bauer, L.J.; Gutsche, C.D. *J. Am. Chem. Soc.* **1985,** *107,* 6063.

Host-Guest Interactions: TOT Chemistry



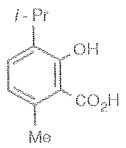
1

Clathrate inclusion complexes, *i.e.*, complexes formed by the encapsulation of guest molecules into cavities generated by the packing of crystalline hosts, are of great interest[1] because they provide useful models for studying biochemical phenomena[2] and "controlled" chemistry in the solid state.[3] ***Tri-o-thymotide*** **(1, TOT)** is a unique host molecule due to its many important characteristics (*e.g.*, the ability to complex with a greater number of guests of varying shapes and sizes) which allow complexation with over 100 guests bearing varied functional groups such as halogen, ether, ester, ketone and alcohol. While uncomplexed **TOT** crystallizes in an orthorhombic form, **TOT** complexes (or clathrates) crystallize in a variety of different forms such as trigonal cage and hexagonal-channel.



Although **TOT** can crystallize as a racemic compound in a nonsolvated form, it exists as an equilibrium of several chiral conformers [the most stable of which possesses a C_3 (propeller) symmetry] in solution and crystallizes with spontaneous resolution while forming an inclusion compound with the solvent. Thus, under appropriate conditions, a single enantiomer may crystallize selectively while the solution still remains racemic, due to rapid interconversion of conformers in solution.

In an era when solution-state asymmetric synthesis is making great strides, the potentially important solid-state asymmetric chemistry is also receiving increasingly greater attention from researchers.[5] For example, Gerdil and co-workers have demonstrated the presence of stereocontrol during the solid-state photooxygenation of a clathrate complex between *Z*-2-methoxy-2-butene and **TOT.**[6] The enhancement of guest enantiomeric purity by repeated crystallizations of the **TOT**-clathrate solutions,[7] as well as the possibility of applying this resolution method to relatively difficult-to-resolve compounds, such as halides, ethers and esters, has sparked interest in the use of **TOT** as a resolving agent.



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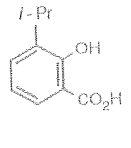

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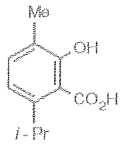

4

Investigation of the basis of the unique properties of **TOT** and the search for **TOT** analogs possessing similar or better properties are also areas of current interest.[8]

Aldrich now offers **TOT,** *o*-thymotic acid **(2,** the monomeric building unit of **TOT)** and two related salicylic acid derivatives **(3** and **4)** which serve as monomeric units for **TOT** analogs.

References:

(1) For recent reviews on host-guest complexation, see a) Cram, D.J. *Science* **1978,** *240,* 760 (Nobel Lecture). b) Tsoucanis, G. *Stud. Org. Chem.* **1987,** *32,* 207 (applications of clathrates). c) Cram, D.J. *Chem. Tech.* **1987,** *17,* 120. (2) a) Odashima, K.; Koga, R. *Cyclophanes;* Keehn, P.M.; Rosenfield, S.M., Eds.; Academic Press: New York, **1983;** Vol. II, Chapter 11. b) Sutherland, I. *Cyclophanes,* Keehn, P.M.; Rosenfield, S.M., Eds.; Academic Press: New York, **1983;** Vol. II, Chapter 12. (3) a) Popovitz-Biro, R. *et al. Pure Appl. Chem.* **1980,** *52,* 2693. b) Apple, W.R *et al. J. Am. Chem. Soc.* **1980,** *102,* 1158, 1160. (4) a) Keehn, P.M. *Cyclophanes,* Keehn, P.M.; Rosenfield, S.M., Eds.; Academic Press: New York **1983,** Vol. I, Chapter 3. b) Powell, H.M.; Lawton, D. *J. Chem. Soc.* **1958,** 2339. c) Downings, A.P.; Ollis, W.D.; Sutherland, I.O. *J. Chem. Soc. (B)* **1970,** 24. d) *Idem Chem. Commun.* **1968,** 329. e) Newman, A.C.D.; Powell, H.M. *J. Chem. Soc.* **1952,** 3747. f) Powell, H.M. *Nature* **1952,** *170,* 155. (5) Gerdil, R. *Top. Curr. Chem.* **1987,** *140,* 71 (review of TOT chemistry). (6) Gerdil, R.; Barchietto, J.; Jefford, C.W. *J. Am. Chem. Soc.* **1984,** *106,* 8004. (7) Arad-Yellin, R.; Green, B.S.; Knossow, M. *Origin of Life,* Wollam, Y., Ed.; D. Reidel: Holland, **1981;** 365. (8) Keehn, P.M. *et al. Tetrahedron* **1987,** *43,* 1519 and references cited therein.

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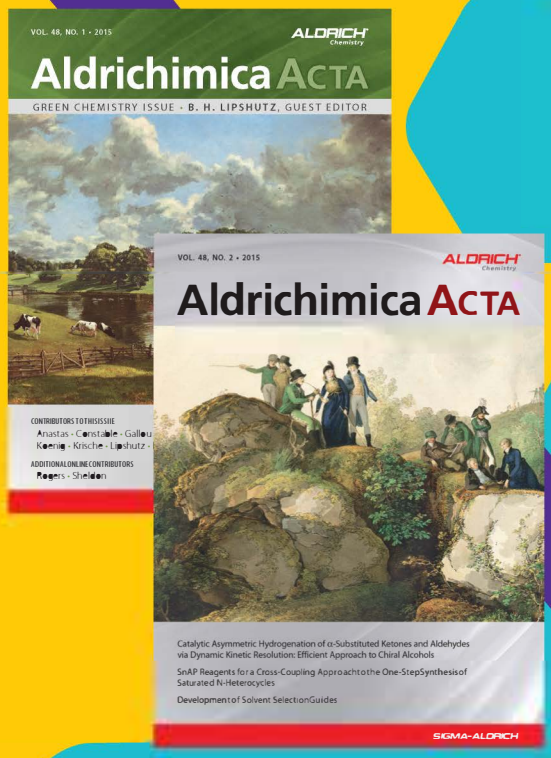

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