Design Constraints in Practical Syntheses of Complex Molecules: Current Status, Case Studies with Carbohydrates and Alkaloids, and Future Perspectives

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Contents

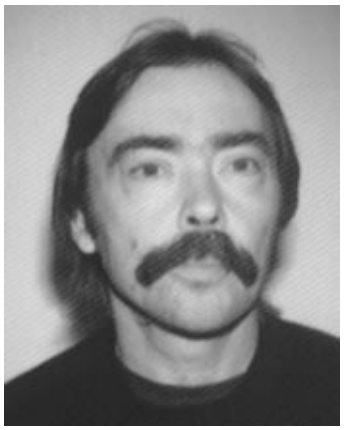
"What have you lost, Mulla?"
"My key," said Nasrudin.
"Where did you drop it?"
"At home."
"Then why, for heaven's sake, are you looking for it here?"
"There is more light here."

a Sufi Parable

I. Introduction

I chose this quotation as an epigraph to a survey that critically examines issues pertinent to the efficient preparation of pharmaceuticals, agrochemicals, and other materials. This parable, when considered in context with current trends in both science and society, illustrates exceedingly well the popular drive to pursue those ventures that are easy to accomplish yet give an appearance of a high degree of sophistication and thus tend to elicit disproportionate levels of praise and recognition.

I have been invited to write an article that focuses on brevity in organic synthesis and emerging technologies and processes that improve the overall practicality of synthesis. These are indeed timely issues for a discipline the ultimate purpose of which is to provide to society those compounds that improve or sustain life. If organic chemistry were as well understood as, for example, mechanical engineering, fulfilling such a task would not be so formidable.



Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, and, following his arrival in the United States in 1968, he received his B.S. in chemistry at Virginia Tech in 1973. He studied with Professor E. Wenkert at Rice University, where he received his Ph.D. in 1977. After a postdoctoral fellowship with Professor W. Oppolzer at the University of Geneva, he joined the faculty at Illinois Institute of Technology in Chicago. In 1982 he moved to Virginia Tech, where he was promoted to Professor of Chemistry in 1988, a position he held until moving to the University of Florida as Professor of Chemistry in January 1995. Among the awards he has received are the A.P. Sloan Fellowship (1981), the NIH Research Career Development Award (1984), a Fulbright Fellowship at the University of Montevideo, Uruguay, for a lectureship (1984–1985) and for research (1985–1986), and the American Cyanamid Faculty Research Award (1992). The research interests of the Hudlicky group include the development of enantioselective synthetic methodologies, the design of practical syntheses of natural products, enzymatic methods of synthesis, and microbial degradation of aromatic hydrocarbons with procaryotic dioxygenases. The group has devoted a considerable effort to the implementation of general synthetic methodology for triquinane sesquiterpenes (1978–1988) and, more recently, for carbohydrates and derivatives.

Unfortunately, or perhaps fortuitously for those of us that enjoy the element of artistic expression in chemistry, this is not the case—the field of synthesis is not in any danger of being reduced to engineering in the foreseeable future. More than a few statements announcing the maturity of synthesis have been committed to paper, and many such pronouncements are cited verbatim in an excellent treatise, written by Seebach in 1990,[1] entitled "Organic Synthesis—Where Now?" In this article the field of synthesis, with many of its accomplishments, is summarized and projected, quite optimistically, into a very successful and expansive, multidisciplinary future. No one, having carefully read the above review, could continue to insist that organic chemistry is a mature science. The discipline of synthesis, as a composite of technique, craft, and art, has not quite succeeded in delivering the terms of its primary

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covenant: the provision a timely manner of reasonable amounts of needed materials.

The mission of this article is not to analyze various societal factors that are responsible for the apparent lack of progress in the practicality of organic synthesis. Rather this essay provides a guide to differential modes of analysis that may aid in the overall efficacy of execution of multistep syntheses. It will highlight the connection between the brevity of a synthetic sequence and the use of new technologies and the combined effect of these two parameters on the overall impact of such sequence. When a synthetic task has been executed to a certain level of perfection, it is not important whether the beholder is a referee of a journal article, an examiner of a research proposal, an evaluator of a procedure for *Organic Synthesis*, or a process chemist. All levels of appreciation, from the spark of imagination to the expression of art will be instantly apparent. Those synthetic ventures that are simple yet do not sacrifice either craft or artistic expression will have the highest impact. Indeed, to achieve maximum simplicity and brevity, a synthetic sequence requires an efficient combination of inspiration and new technology.

Ideally, in either the pursuit or the evaluation of synthetic ventures, none of the aforementioned qualities should be sacrificed or overemphasized at the expense of another. Overall brevity of a sequence need not compromise the element of art. The technology need not be complex, yet it can adequately fulfill a purpose. The effect of an elegant synthetic scheme on the observer is comparable to that of a beautiful painting, a photograph, or a musical composition. The examples chosen for this article meet this criterion, though none approach the "ideal synthesis" as defined by Wender,[2] that is, a synthesis of one step in 100% yield from readily available, inexpensive starting materials in a resource-effective and environmentally responsible process.

Central to the overall success of a synthesis is the researcher's ability to make intellectual connections in a multidimensional matrix or "space" of synthetic design. (Throughout this review the definition of space implies the mathematical concept as defined by *n* dimensions coupled with certain specific qualities that pertain to imagery of targets, substructures, and reagents and their energetics and symmetry in a time-dependent process.) Beyond the three-dimensional molecular shapes lie the other dimensions required for the process of assembly: the order of operations, the conditions of the reactions, the identity of reagents and solvents, the environment of isolation, the symmetry of reagents and of reactions, the nature and the reason for the formation of any byproducts, the incorporation of new techniques, and so forth. A multistep synthesis must therefore be considered as a dynamic continuum in which every event depends on all others.

The first and most important step is recognition of the pattern that connects starting material to product. This can involve an obvious, simple disconnection or a major jump across several disconnections—the greater the jump, the greater the artistic impression. The connection between a target and new technology, or between a target and existing technology, represents the first level of successful design and must therefore be foremost of all of the considerations made by the researcher. The technology domain may comprise not only new developments in procedures or physical handling of materials but also any advances in data handling, information retrieval, data-base analyses and comparisons, new analytical methods, and finally the introduction of new concepts, views, or paradigms, as defined by Thomas Kuhn in *The Structure of Scientific Revolutions*.[3]

The survey begins with the premise, admittedly somewhat subjective, that even today adequate technology exists within the synthetic community to achieve most tasks; therefore, emphasis should be placed on brevity of operations and simplicity of design, unless of course a new technology offers unprecedented advantages over existing methods. It is likely that this new technology will be adopted from another discipline, as in the recent union of microbiology or molecular biology with preparative organic chemistry in the emerging field of biocatalysis. The future direction of synthesis will almost certainly be dictated by multidisciplinary efforts; several examples will be presented to support this paradigm.

Finally, it is important to remember that the late R. B. Woodward's contribution to the philosophy of synthesis was in the arena of *design*, not in the development of new technology, although he did use or inspire the development of new technology to satisfy a particular need. His synthesis of reserpine did not contain any "new chemistry" yet its design is still admired 40 years later. In the future more credit should be given to those researchers who focus on clever connections in the design of synthetic sequences. Focus on clever design does not in any way diminish the need to discover new reactions and to study their mechanistic intricacies for eventual optimization. It simply charts the most efficient way to a target. This is, and will certainly remain, the purpose of our guild.

II. Issues Impacting Synthesis

This review attempts to summarize concepts that most synthetic practitioners use intuitively but for which no precise language exists. As synthetic chemistry continues its evolution as an empirical discipline, there is a great need for a more adequate language. I have found that verbalization of intuitive thought pertaining to synthetic chemistry is extremely difficult and is probably inadequate to describe in a comprehensible fashion the mechanism of mental processes responsible for creation of synthetic plans. Nevertheless I am making an attempt with the hope that it will inspire others to improve it further.

Honorable attempts have been made recently to place synthetic planning at a higher level of cognitive predictability. An excellent review has appeared on the topic of disconnective strategy,[2] and several monographs are available that link topology-based arguments and graph theory to synthetic planning.[4–6] Equally excellent is a book published on the more

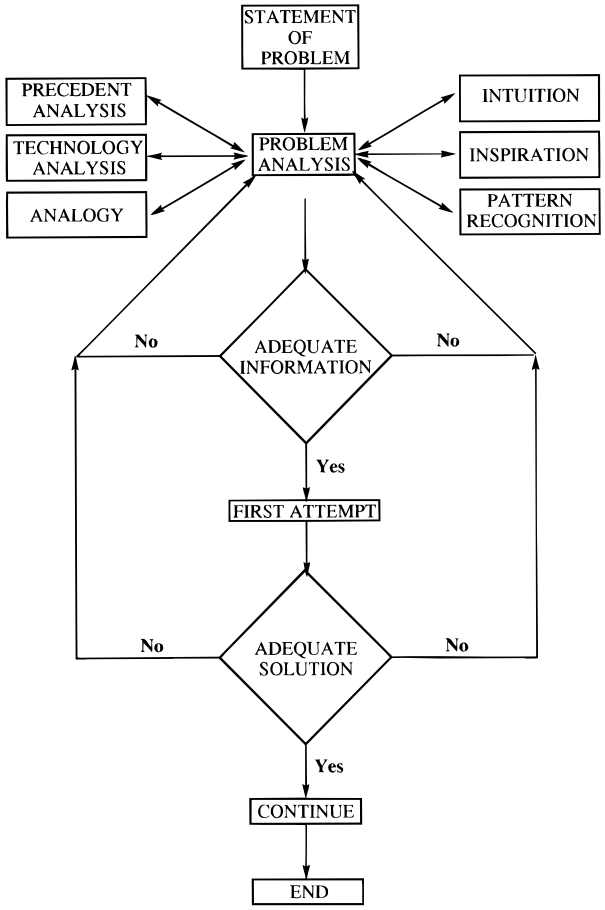


Figure 1. Flowchart representation of problem analysis.

quantitative aspects of design and optimization of organic synthesis that are important in process design.[7] In section III.1 is a brief overview of computer-assisted design (CAD) methodology and its impact on the future direction of synthesis.

Portrayed in Figure 1 is a flowchart of an ideal time coordinate for a problem in synthetic chemistry. Of course, such a representation assumes that the initial decisions linking the target to the starting material will be correct—a low practical probability at best.

Nevertheless the contents of this diagram are valid for an evolving or a multigeneration approach to a practical synthesis and are supported by examples presented in this review. The following sections attempt to dissect the intuitive thought that precedes the formulation of a design protocol and to "quantify" such a design. Some aspects of the existing theoretical foundation for synthetic design will also be presented in section III. In the spirit of the theme of this review, the issues of brevity and technology will be examined first.

1. Brevity of Execution

The covenant set forth in the Introduction states that the ultimate purpose of synthetic ventures is the provision of realistic amounts of needed materials. Thus, brevity will be considered as the most important issue in the initial analysis of any synthetic problem. The overall yield of a sequence is, of course, affected by the total number of physical operations. For this reason, it is advantageous to combine multiple bond-forming sequences into "one-pot" reactions, eliminate duplication of steps, reduce protection and deprotection, reduce the use of those functional groups that must later be removed, use tandem reaction sequences, and so on. Such adjustments in the overall strategy will tend to diminish the total number of steps and therefore provide the simplest way to improve brevity. Excellent examples of these strategies have recently appeared in the literature and have been reviewed.[8−10] Some of the more recent examples of these strategies are presented in this review.

It is important to look first at a numerical analysis of reaction yields and their effect on overall yield as a function of number of steps in a sequence. Second, enrichment of isomeric ratios as a function of the number of distinct operations will be analyzed. Third, several examples of brief syntheses will be presented.

The Question of Chemical Yield

This simplest of parameters is almost always overlooked in academic pursuits, and perhaps this oversight might be justified if the pursuit is concerned with the validation of new technology or a first attempt at a particularly difficult target. However, a chemist should always return to the problem in an iterative fashion to improve weak points once the first-generation effort has proven reasonably successful. All too often this attitude is absent in academic pursuits, and we would all do well to attend to a multigenerational approach to solving synthetic problems, as exemplified in the life-long efforts of the late Karel Wiesner.

Despite the high probability that a first-generation total synthesis will not be efficient, the community of chemists somehow expects it to be so anyway, and statements about practicality appear in academic presentations of syntheses of 50 or more steps.[11] Sometimes publications (or research proposals) even offer to solve the "supply problem" of a particular compound by first-generation synthetic efforts of more than 50 steps in length. My criticism of such reports focuses on the concept of "false advertising" or "deceptive or otherwise inaccurate" reporting of yields and the calculations of the number of steps for the sake of some quantitative comparison. Only one synthesis can be declared as the first. On the other hand, it is no more possible to declare any one preparation the best than to compare the musical talents of, say, Dvorak, Beethoven, and Mozart. My criticism is never aimed at the noble efforts to attain a particularly difficult target that proved elusive for a number of years. One need only compare recent synthetic accomplishments such as taxol,[12,13] brevetoxin B,[14] or palytoxin[15] with the attainment of vernolepin 20 years ago[16] to appreciate the degree of complexity associated with today's targets and the expectations of the synthetic audience awaiting the next achievement. Nevertheless, even taxol and other targets of even greater complexity will eventually be viewed as attainable in a practical manner; it is only a question of time and effort. In cases where syntheses are evaluated by practicality, any preparation over 25 steps simply cannot be considered viable. It is relatively easy to convince skeptics

Table 1. Overall Yield of a Sequence as a Function of Number of Steps

no. of steps	50%	70%	75%	90%	maximum product mass (g)[a]
1	50	70	75	90	
2	25	49	56	81	
3	12.5	34	42	73	
4	6.25	24	32	66	
5	3.12	17	24	59	15.6, 120, 295
6	1.56	12	18	53	
7	0.78	8	13	48	
8	0.39	6	10	43	
9	0.19	4	7.5	38	
10	0.09	3	5.6	35	0.45, 28, 175
15	**0.003**	**0.5**	**1.3**	**20.6**	0.015, 6.5, 103
20	0.0001	0.08	0.28	12.2	0.0005, 1.4, 61
25	0.0000025	0.02	0.07	7.2	—, 0.35, 36

[a] The weights refer to the amount of material having a molecular weight of 500 and being obtained by a sequence of the stated length from one more of starting material having molecular weight of 100. The theoretical yield for this sequence is therefore 500 g of material.

Table 2. Enrichment of Isomeric Mixtures as a Function of Manipulation

		ratio			
enrichment (E)	X_o/Y_o	at n=1	at n=2	at n=3	at n=4
2	2/1 (67/33)	4/1	8/1	16/1	32/1
	9/1 (90/10)	18/1	36/1	72/1	144/1
	19/1 (95/5)	**38/1**	**76/1**	**158/1**	**316/1**
	49/1 (98/2)	98/1	196/1	392/1	
	110/1 (99.1/.9)	220/1	440/1	880/1	
10	2/1 (67/33)	20/1	200/1	400/1	
	9/1 (90/10)	90/1	900/1		
	19/1 (95/5)	**190/1**	**380/1**		
	49/1 (98/2)	490/1			
	110/1 (99.1/.9)	1100/1			
100	2/1 (67/33)	200/1	400/1		
	9/1 (90/10)	900/1			
	19/1 (95/5)	**1900/1**			
	49/1 (98/2)	4900/1			
	110/1 (99.1/.9)	11000/1			

that such statements are valid on the basis of numerical analysis.

Similarly open to criticism, or at least to debate, is the effort, quite in the spirit of the Sufi parable that opened this essay, to strive for perfection in control of diastereo- or enantioselectivities beyond acceptable levels of practicality. Table 1 presents the harsh realities of yield calculations for syntheses up to 25 steps in length; Table 2 indicates similar realities for the fate of ratios of isomeric mixtures as a function of the number of transformations performed with such mixtures, provided enrichment factors for the transformations have been defined or are possible. Following the formulation of two basic rules for pursuit of brevity along the available laws of algebra, we will then look at various chemical or procedural factors affecting the overall efficiency of synthesis.

There is no evidence to indicate that a reaction that proceeds quantitatively assures a quantitative yield of product upon physical isolation. In fact any handling of "quantitative" mixtures will always diminish the true yield significantly. The loss in yield will be a function of the scale of the reaction, the method of isolation and analysis, and weighing accuracy. Despite this common-sense fact, many authors insist on reporting quantitative yields or isolated yields in excess of 95%, and some publications in the area of preparative organic synthesis report yields evaluated by means of GC, HPLC, NMR, or recovered starting material. Such scenarios are simply judged impossible in principle, and it would be elementary to discern the truth upon careful repetition. (Of course, no one will repeat a 45-step synthesis only to prove that the reported yields were based on weighing wet samples!) At least these reports simply lack any value to a practical application or eventual scale-up.[11]

To appreciate the effect of the number of steps on the overall yield of a sequence let us look at Table 1 in which a process with assumed yields of 50%, 70%, 75%, and 90%, respectively, is examined. A rational limit of 25 steps is placed on any synthesis.

From this table several deductions can be made upon inspection of the values. First, for a process where the starting material had a molecular weight of 100 and the product 500, the total mass available by a sequence 15 steps in length (indicated in bold face type in Table 1) for 50, 75, and 90% scenarios would be 15 mg, 6.5 g, and 103 g, respectively. Second, it is far more important to pursue yield improvements for the individual steps in the range 50−75% than in the higher range of 75−90% because the overall improvement factor does not increase sufficiently at the higher individual yield to warrant the extra effort. This parameter is apparently little known to those chemists who insist on either attaining, or at least reporting, yields higher then 90% whenever possible. Notice, for example, that improving the individual yields for each step from *50% to 70% leads to a 167-fold increase* in the overall yield for a 15-step sequence, but improvement of each step from *70% to 90% accords only a 41-fold increase* for the same. On the basis of the above analysis we can formulate the first generalization of practicality of synthetic ventures:

> Generalization 1. Yield optimization should be first attended to in the range 50−80%, rather than in the range 80−95%, because of the lower value of the improvement-to-effort ratio in the latter case.

It is clear that a chemist should concentrate on developing a concise route to the target within the guidelines of the above generalization and submit the semioptimized, multigeneration solution to the problem to the appropriate process scale-up authorities for final streamlining. To be realistic we will not consider the possibility of synthetic sequences greater then 25 steps because of the astronomical diminishment of weights of product in comparison to the required weight of starting material.

The Question of Isomeric Ratios

Table 2 contains ratio enhancements for the major product of a binary mixture of isomers. The ratio is given by the formula

$$X/_nY_n = E^n (X_o/Y_o)$$

where n is the number of operations that the mixture

is subjected to, X_n/Y_n is the ratio after n operations, *E* is the enrichment factor (differences in solubility, vapor pressure, rates of a reaction, etc., for the two isomers), and X_o/Y_o is the initial ratio of isomers. It is reasonable to assume that almost any physical operation performed on a mixture of isomers will provide some enrichment of composition. A simple filtration of a mixture through alumina or silica may allow for enrichment on the basis of the difference in the free energy of adsorption for the two materials. The same may be true for handling certain scalemic mixtures, although the generalization will not apply as readily as in the case of diastereomeric compositions. Caution must therefore be exercised in extrapolations of this premise to enrichments of enantiomeric purity. Enrichments in the range of 5−10-fold are common for crystallizations, whereas enrichments greater than 100-fold are available from rate differences of chemical and especially enzymatic reactions.

It follows from the improved ratios of isomers presented in Table 2 that any mixture better than 9/1 requires minimal handling or treatment to eliminate the minor isomer. It is therefore difficult to understand the current trend in synthetic chemistry of "perfecting" the diastereoselectivity of a reaction from, say, 95/5 to 200/1 and then further to 400/1. Furthermore it is operationally difficult, if not impossible, to distinguish between a 200:1 and a 400:1 mixture by instrumental methods available to most synthetic chemists. Such an exercise is completely unnecessary when one observes the enrichment of such mixtures under circumstances of a 10-fold differential. In practice, enrichments of this magnitude are common; therefore, the need for greater selectivity control is obviated. Such efforts should be directed to more important issues, at least during first-generation attempts. On the other hand, the presence of 0.1% of an undesired isomer in a mixture weighing 1 000 000 kg (a projected scale for the preparation of Merck's HIV drug) translates into 1000 kg of unwanted waste material. Nevertheless, the concerns with isomeric ratio control should be left out of first- and second-generation research phase efforts, provided the operator has attained at least 95/5 control. With the technology available today such control is attainable for many reactions. The data in Tables 1 and 2 provide common-sense-based advice for the reporting of yields and ratios in current literature.

> Generalization 2. Isomer ratio control in excess of 99.9 to 0.1 (corresponding to $\Delta G = 4$ kcal/mol) constitutes superfluous effort in first-generation attempts. Almost any physical operation performed on such a mixture will render the major isomer sufficiently pure for subsequent use.

Brevity in Reaction Design

There are some rather obvious design features that reduce of the number of physical transforms during synthesis. Several of these already enjoy the focus of the community under the general heading of "tandem reaction sequences", "cascade reaction sequences", or "domino reactions". Described in a recent review,[8] these processes involve two or more consecutive reactions, each dependent on the formation of a reactive functionality in the step before. On the other hand, the term "consecutive reactions" or "one-pot sequence" refers to a sequence of consecutive reactions independent of one another; each reaction begins by the addition of a reagent or substrate. We can define the term *redundant* or *degenerate operations* to mean that several mechanistically diverse pathways are available to the reacting system that leads to the formation of the product and therefore the exact experimental definition of each is unimportant. The reactions that lead to a large number of carbon−carbon bond formations per step also increase the brevity of the overall sequence. Connectivity analysis for complex molecules is usually required. This strategy is clearly presented in a recent review by Wender[2] and in the adjoining treatise by Bertz.[5] For clarity we divide the discussion into several groups with attendant examples in each.

Domino and Consecutive Reactions

This topic has been recently summarized in review[8] and monograph[10] forms. Because of the relatively narrow distinction between the two as defined by Tietze,[8] we will discuss these modes together. From the point of view of an operator, the only difference between the two lies in the point along the sequence at which one or more catalysts or reagents need to be added to effect either the initiation of a sequence (i.e., domino reaction) or propagation to the next step (i.e., consecutive reaction). From a practical perspective, it is far more important to look at the quality of the sequence as a whole rather than to distinguish between the two types of reactions.

Powerful examples of this methodology illustrate the importance of carefully designing sequences of mutually dependent reactions. For example, intramolecular cyclopropanation of a diene with an appropriate carbenoid generates molecular assemblies that are suited for more than one product topology. Figure 2 shows a situation in which either five- or seven-membered ring annulation is possible;

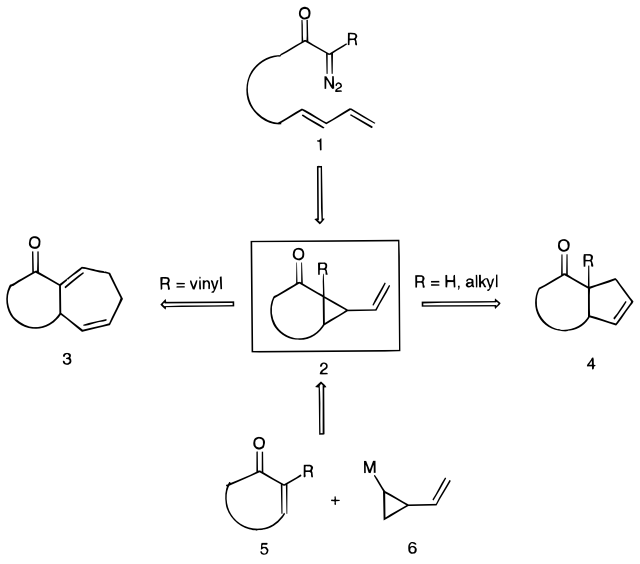


Figure 2. Domino reactions in design of terpene topology.

only the identity of function R defines which one. If the carbenoid is substituted with either hydrogen or an alkyl group, the resulting vinylcyclopropane is set up to undergo a vinylcyclopropane−cyclopentene rearrangement,[4,17−19] whereas a functionalization of the same carbenoid with a vinyl group leads to a precursor for the divinylcyclopropane rearrangement and the annulation of a seven-membered ring.[20,21] Both of these strategies have been used extensively in efficient syntheses of natural products.[4,17−22] The key intermediate **2** can also be attained by an intermolecular process involving the addition of a nucleophilic vinylcyclopropane (e.g., cuprate) to an appropriate enone, a process indeed used by Wender, Piers, Moreno, Davies, and others as an efficient entry to various sesquiterpene skeletons.[23] These are good examples of internally dependent tandem sequences or domino reactions. There are several reviews on both the divinylcyclopropane (Cope) rearrangement[20,21] and the cyclopentene rearrangement[17−19] that address aspects of methodology as well as the exploitation of these rearrangements in the total synthesis of terpenoid natural products.

An elegant example of multiple bond-forming sequences is the recent synthesis of racemic perovskone **(7)** by Majetich.[24] The recognition of the availability of multiple bond-forming sequences led first to a stepwise execution of the pathway **8** through **7** and eventually to a one-pot sequence, as shown in Figure 3. A fascinating number of transformations takes place under the conditions of Lewis acid catalysis of the initial Diels−Alder reaction of **8** and **9**: isomerization of the exocyclic methylene followed by an ene reaction, capture of the tertiary cation by the enol, and finally formation of the ether bridge upon addition of acidic resin.

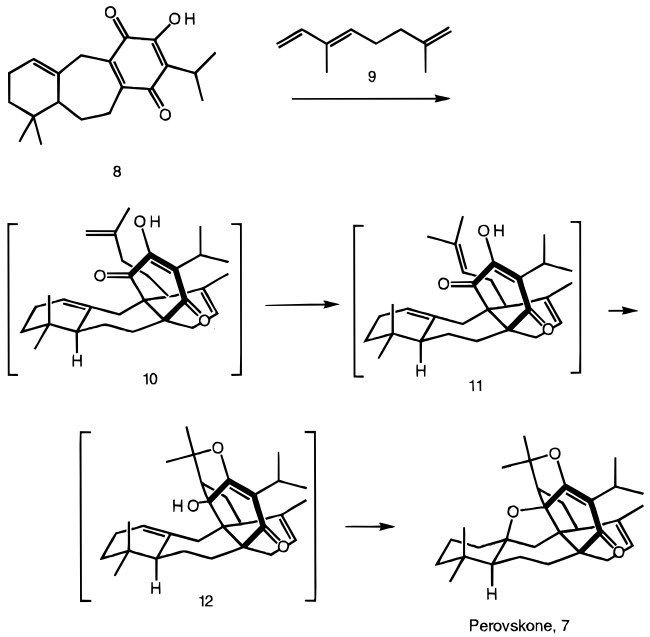


Figure 3. Perovskone synthetic cascade.

In the synthesis of aphidicolin by Holton,[25] several steps of a sequence were combined into a one-pot operation (but only after the individual steps had been worked out!), as shown in Figure 4. Michael addition of lithium enolate **13** to vinyl sulfoxide **14**

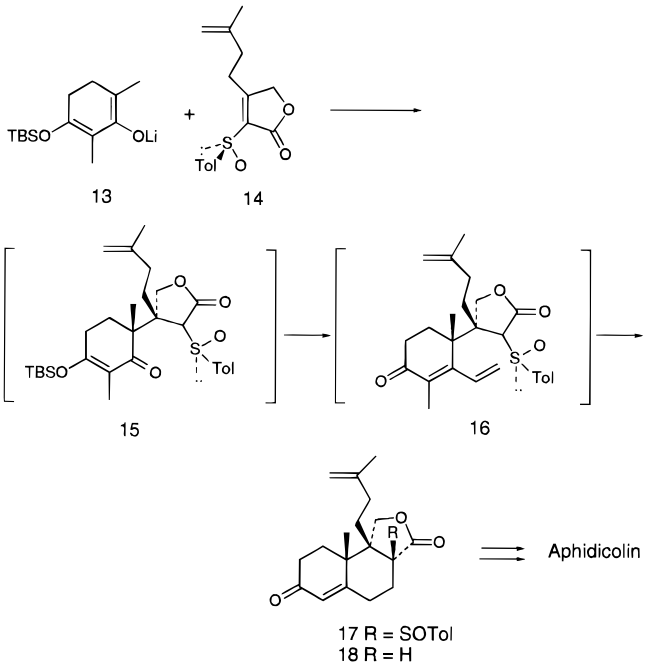


Figure 4. One-pot synthesis of the aphidicolin precursor.

furnished **15**, which was treated with vinyllithium followed by methanolic HF to effect the formation of dienone **16**. Further addition of methanolic sodium methoxide led to the 1,6-conjugate addition to **17**, which was isolated in 45% overall yield. Several of the chiral centers and much of the total carbon mass present in the desired target were effectively installed in the first operation of the synthesis.

The pursuit of a second-generation design of the [4+1] annulation technology developed in our own laboratory led us to consider an anionic variant to cyclopropanation of dienes with diazo ketones as a route to vinylcyclopropanes containing carboxylate functionalities.[4,18,19] A new and more efficient protocol, [2+3] annulation of enones, was ultimately expressed in the total synthesis of retigeranic acid **22**.[26,27] The tandem sequence consists of Michael addition of the ester dienolate derived from **19** to enone **20**, followed by internal S_N2 displacement of the halide to afford cyclopropane **21**, which contains all of the carbons of the target and which is set up to undergo the vinylcyclopropane−cyclopentene rearrangement (Figure 5). The convergent design of this

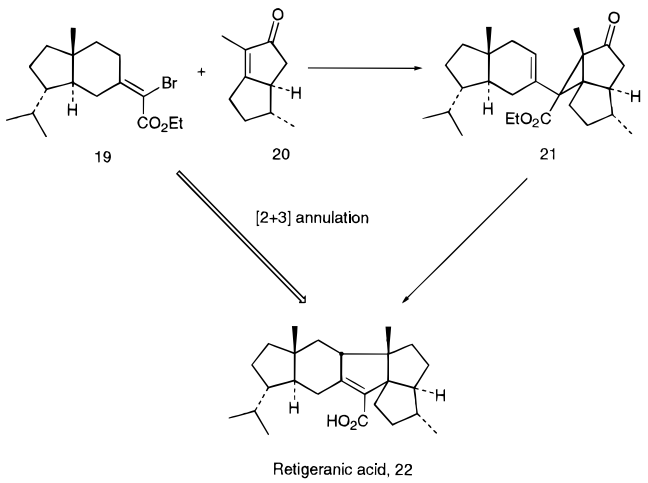


Figure 5. Convergent synthesis of retigeranic acid.

particular synthesis focused on the proper choice and placement of functionality, i.e., the acrylic acid unit directly generated by the rearrangement. The principal disadvantage of this route is the carbonyl functionality necessary for control of regiochemistry in the rearrangement that must be later removed. Nevertheless, the 14-step synthesis of this sesterterpene remains the shortest to date.

A truly exceptional example of sophistication in the design of a tandem sequence is Heathcock's synthesis of the pentacyclic daphniphylline skeleton (Figure 6).[28,29] The skeleton is assembled in nine operations with an overall yield of 44% and in a reasonable amount (3 g). Such a design demonstrates the feasibility of total synthesis as a route to therapeutically important compounds. (The title alkaloids are usually isolated in gram amounts from 1000 kg of leaves of *D. macropodum*.)[29] The cyclization of **27**, viewed as either a Diels–Alder reaction or sequential acid-catalyzed cyclizations, followed by final adjustments (three steps: hydrogenation, Jones oxidation, and esterification) of the cyclization product, leads to **28**. The precursor of the acetic acid-catalyzed cyclization is assembled *in situ* by the action of ammonia on dialdehyde **26**, obtained by a reduction–oxidation sequence from the product of the triply convergent dialkylation of cyclopentene carboxylate **24**. At the time of synthesis of **28**, the details of its biogenesis were not known, other that it originated from squalene, but the synthetic design took advantage of biomimetic thinking as evidenced by the anticipated folding and cyclization of precursors such as **26** and **27**. A later application of this methodology led to a concise (11 steps, 9% overall yield) preparation of daphnilactone.[30]

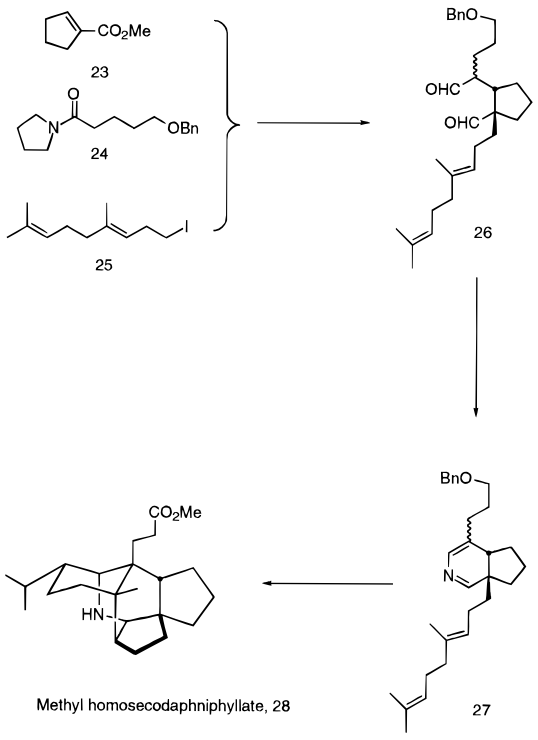


Figure 6. Daphniphyllate synthesis by Heathcock.

Generalization 3. Whenever possible, individual reaction sequences should be combined into an intramolecular cascade of maximum length.

Redundant or Degenerate Operations

This term describes those operations that follow multiple mechanistic pathways or involve intermediates of differing chemical or stereomeric composition yet lead to the same product regardless of the number of combinatorial possibilities. The first example to illustrate this principle is the degenerate transformation of two vinylcyclopropanes, **29a** and **29b**, in Wender's cedrene synthesis.[31] Their bromination and subsequent unraveling of the vinylcyclopropane system leads to allylic bromides **30** and **31**. These isomers either equilibrate under the reaction conditions or undergo their own independent reduction pathways to allylic radical **32**, which provides only the more substituted olefin in cedrene **33**.[31] The degeneracy of such a scheme, as depicted in Figure 7, automatically increases the simplicity and, therefore, the brevity and overall efficiency of the entire synthesis. As described in more detail in a previously published analysis of Wender's approach, the degeneracy of a sequence may be considered as an additional dimension of a synthesis.[32] If such a degeneracy forms an integral part of the synthetic plan, it might even be unnecessary to isolate the intermediate mixtures unless there is a special need to do so. Such a sequence is conducive to large-scale process because there are steps that involve physical manipulation of intermediates.

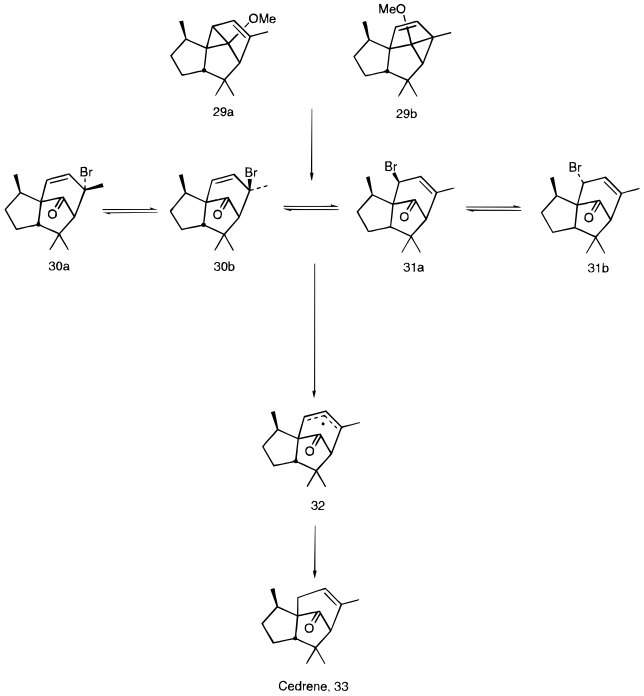


Figure 7. Degenerate rearrangements in Wender's cedrene synthesis.

A similar degenerate operation in Heathcock's second-generation design for lycopodine (**35**) (Figure

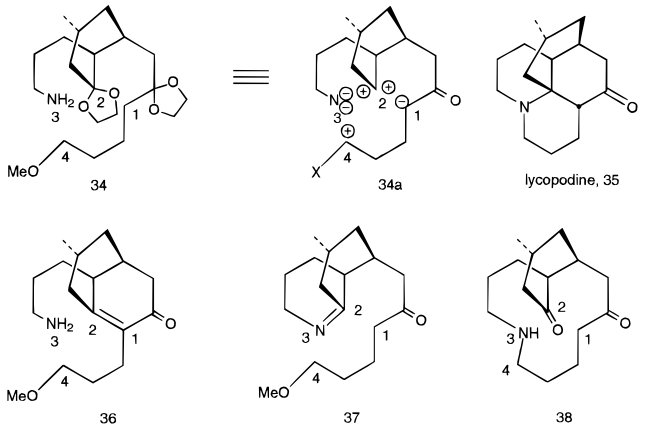


Figure 8. Redundant or degenerate condensation themes in lycopodine synthesis.

8)[33] is equally impressive. The precursor to the acid-catalyzed cyclization has a number of pathways available to it. Schematically represented in **34a** is the ionic parity (or functional consonance)[34] of precursor **34**. Although it seems likely that the first step of the acid-catalyzed condensation is the formation of the imine of type **37** (i.e., connectivity from atoms 2 to 3), the pathways through enone **36** (1,2 connectivity), or even macrocyclic amine **38** under certain conditions, cannot readily be excluded. Furthermore the condensation cascade need not proceed through fully hydrolyzed ketal moieties. A protonated enol ether (from a partially opened ketal) can serve the function of an electrophile, and the enolized tautomer of such species can fulfill the role of a nucleophile in the subsequent condensation reaction. This sequence is one of the most striking examples of a mechanistically redundant process—whatever the precise sequence, the final outcome is the assembly of the lycopodine skeleton through a combination (there are a total of 48 options) of reactions at sites 1, 2, 3, and 4. A more detailed analysis of the lycopodine synthesis has been published.[32]

A final example is the redundant hydrolytic opening of stereoisomeric epoxides in which only one pathway can be executed in accordance with the stereoelectronic demands for such an opening, as demonstrated in the recently completed synthesis of pancratistatin[35] (discussed later in this review). The initial design called for the hydrolysis of the α-isomer **39** as shown in Figure 9. Unanticipated problems with the generation of that particular stereoisomer forced the preparation of the *β*-isomer **40**, which is subject to anti−diaxial opening to furnish the same diol that would have been formed from the regioisomeric opening of the α-isomer. As long as the nucleophile is water, the product of either sequence must be the *trans*-diol **41**. When such redundancy can be incorporated into an overall synthetic plan, it can obviate the need for concern with detailed stereocontrol of individual synthetic steps.

These examples illustrate the importance of considerations that lead to the most efficient synthetic procedure. Such considerations may be anticipated or completely serendipitous. Because the incorporation of redundant operations can eliminate concerns over the control of outcome at individual stages, it is an important dimension of synthesis and contributes greatly to the brevity and the simplicity of the entire operation. The ultimate philosophical ambiguity (or redundancy) of synthetic ventures is the issue whether or not a synthetic operation has been executed in accordance with the original, planned design or whether it was committed to practice by an exploitation of a serendipitous discovery. In the final evaluation of an accomplished project it matters not.

> Generalization 4. Mechanistically redundant steps simplify the overall sequence and frequently remove regio- or stereochemical problems. Every effort should be made to incorporate such steps into the final synthetic design.

2. Incorporation of New Technology

In this section the second important issue that impacts organic synthesis, that of new or emerging technology, will be considered. Historical analysis of the methods used in synthetic organic chemistry over the past 50 years is revealing. This period brought about some milestone accomplishments in the area of reagent chemistry. The ultimate measure of acceptance of a procedure by the chemical community is their appearance in articles with no citation to the original inventor. Examples include the Wittig reaction and other well-established "name" reactions, the use of the *tert*-butyldimethylsilyl protecting group (few organic chemists trained after the mid-1970s actually know of the original report on the use of this group by Corey and Venkateswarlu in 1972[36]), and many others.

One of the most fascinating developments in the postwar era was undoubtedly the development of the Sharpless epoxidation and, even more significantly, related developments that ensued from the original disclosure, pursued by Sharpless and others.[37,38] Frequently, an original disclosure serves as a pivotal

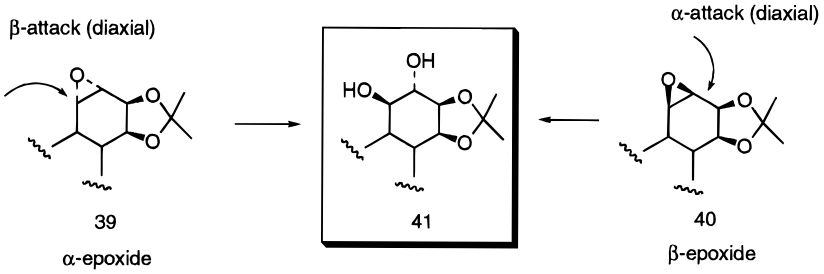


Figure 9. Degenerate opening of α- and *β*-isomers in cyclic oxiranes.

idea from which extrapolations may arise. Certainly the inspiration that a disclosure of new technology provides to others in the field is of equal or greater value than the actual contents of the disclosure itself. Witness, for example, the overwhelming amount of knowledge amassed in the area of asymmetric induction with chiral auxiliary groups, catalytic processes for introduction of chirality, chiral-synthon-based approaches to asymmetric synthesis, and many other methods.[39] It does not serve the purpose of this review to cover exhaustively all the excellent accomplishments in organic synthesis as this is comprehensively done in a recent compilation.[39] Rather, a few selected methods will be discussed that highlight efficiency in construction of specific targets. Each method discussed here has a rich history and a large following among a diverse group of investigators and has therefore become accepted on a permanent basis.

Umpolung Reagents

A major advance in reagent chemistry was the introduction of "umpolung" or reversed polarity reagents. This concept, referred to by R. B. Woodward as "polarity reversal", has been summarized[40,41] and is widely accepted as a permanent tool. Nevertheless, it is important to remember that little of this chemistry was used prior to the 1970s and, as in the case of the *tert*-butyldimethylsilyl protecting group, almost no one references the seminal paper by Seebach and Corey[42] (published as a full paper in the *Journal of Organic Chemistry* in 1975) when using dithiane-based acyl anion equivalents as synthons.[43]

Catalytic Oxidation

The Sharpless−Katsuki epoxidation[37] of allylic alcohols is undoubtedly one of the most visible contributions to reagent methodology in the latter part of this century.[37,38] The disclosure of this method has provided inspiration for the future direction within the Sharpless group[44,45] and to others in related disciplines.[46,47] The catalyst development has undergone continuous streamlining and extension of its use to other functional groups. Research activity in this area continues.

Catalytic Hydrogenation and Cyclopropanation

Accomplishments in catalyst design for homogeneous hydrogenation and cyclopropanation of olefins have been impressive. The Noyori hydrogenation of β-dicarbonyl compounds[48] has been developed to a fine level of understanding and predictability; catalysts are available for the selective production of either enantiomer of hydroxy esters. The hydrogenation of acrylic acids (Ru-Binap)[49] is useful in the production of naproxen, and the Monsanto process for the hydrogenation of acylaminoacrylic acids (Rh-diphos)[50] yields L-dopa. The formation of optically active cyclopropanes by rhodium-based catalysts[51] has also attained important status in carbon−carbon

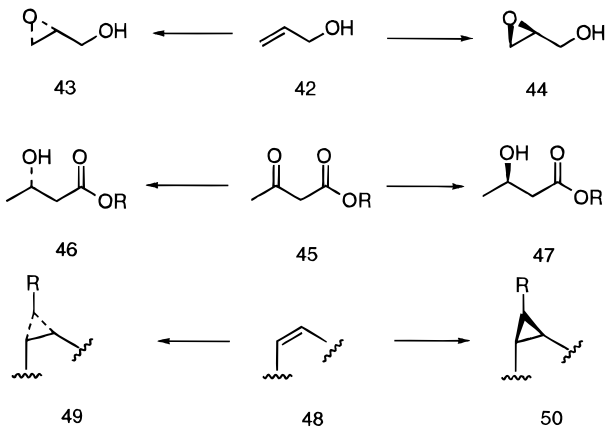


Figure 10. Control of enantiodivergence via catalytic methods.

bond-forming methodology and, more importantly, has inspired others to develop analogous processes for the aziridination of olefins.[52] Being able to produce either enantiomer by changing only the catalyst in an otherwise identical reaction setup is, of course, a highly desirable property, common to the methods portrayed in Figure 10. Ideally, the chemical route to the two enantiomers (epoxides **43** and **44** from allylic alcohol **42**, hydroxy esters **46** and **47** from keto ester **45**, and enantiomeric cyclopropanes **49** and **50** from disubstituted olefin **48**) is identical in energy expenditure in all respects except for symmetry, which is accounted for by the design of the catalyst.

Oxidation of Unactivated C–H Bonds

Perhaps one of the most challenging problems in reagent design, this topic has been addressed from the vantage point of transition-metal processes, oxygenation processes, remote functionalization methods, and enzymatic means. The remote functionalization of carbon atoms by means of proximal radicals generated from nitrite esters (Barton reaction) is a good example.[53] Recent reviews are available on this topic;[54] therefore, only one elegant example of this process will be illustrated here. Shown in Figure 11 is a solution to a regio- and stereochemically defined

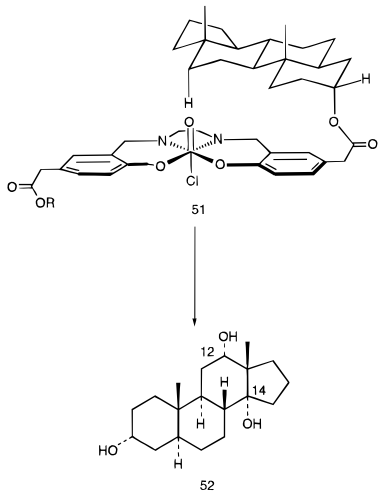


Figure 11. Tethered oxidation of a steroid nucleus.

oxidation which mimics the enzymatic catalytic process where the major premise is the forced proximity of the reacting centers. Thus exposure of the manganese salen complex to iodosylbenzene generated the active species **51** and led to the oxidation of the steroid nucleus at position 12 and 14, albeit in modest yields, suggesting an intramolecular process.[55]

Directed ortho-Metalation of Aromatic Compounds

In the introduction to this review, I made a suggestion that major advances in the field of synthesis would arrive from outside the discipline. The analysis of some of the catalytic processes mentioned in the previous section certainly lends credence to such a statement as all of these developments rely heavily on expertise in transition-metal chemistry. That such expertise found expression in organic synthesis is due to the curiosity of the creators of these methods and to their willingness to depart from the conventional methods that were available at the time.

Gilman[56a] and Wittig[56b] disclosed the metalation of anisole some 55 years ago. Since then this particular technique has grown into a discipline of its own with many independent developments.[57,58] In the synthesis of ochratoxin, Snieckus[59] demonstrated a solution to a long-standing problem: the preparation of tetra- and pentasubstituted aromatic rings in a controlled manner. The *ortho*-metalation protocol developed over the years by Snieckus and Beak[60] is used to functionalize the first site (E_1) in the *O*-arylcarbamate **53**, followed by a second metalation at the ortho position. The aryl anion undergoes a rearrangement to *o*-hydroxybenzamide, which then directs, following the protection of the phenol, the third and final metalation (E_3), as indicated in Figure 12. Ochratoxins **54** and **55** have been attained by this method in four steps.[59] In the thirteen years since the publication of the review by Beak and Snieckus,[60] this methodology has been extrapolated to many uses. It is now a permanent mainstay in aromatic functionalization as it accords both efficiency and full regiocontrol over the introduction of multiple functional groups. An updated summary of this field is forthcoming in the near future.[61]

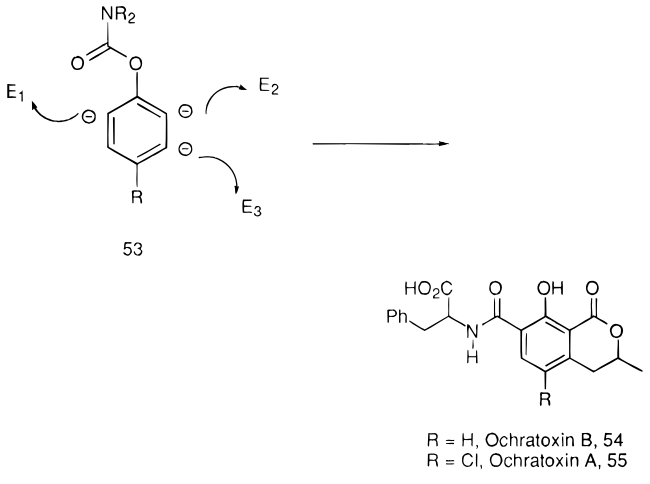


Figure 12. *ortho*-Metalation approach to ochratoxin.

Tandem Radical Cyclization Reactions

Since Buchi's β-agarofuran[62] and Stork's seychellene[63] syntheses, research in the area of radical cyclizations has provided a number of examples that demonstrate efficient carbon−carbon bond-forming technology. Several recent reviews[64,65] offer a summary of accomplishments in this area and indicate the tremendous generality of this method.

Two examples of efficient carbocyclic construction are shown in Figure 13. The anti-substituted precursor **56** is cyclized directly to hirsutene **57** in 53% yield, establishing the linearly fused triquinane skeleton in one step.[66] Topographical adjustments in the functional substitution of the precursor led to the application of the same technique to the synthesis of coriolin via cyclization of **58** to **59** in 54% yield.[67] The radical cyclization protocol has been applied to the synthesis of both linear and angular triquinanes (here represented by silphiperpfol-6-ene,[68] which was obtained along with its epimer) and constitutes therefore a general method of synthesis.

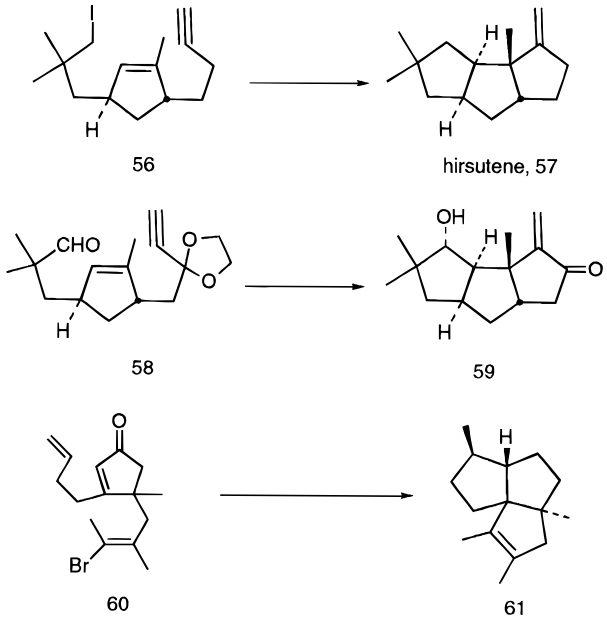


Figure 13. Radical cascade design of triquinanes.

Multiple C–C Bond-Forming Methods

The now classic steroid cyclization of a linear precursor to a steroid nucleus reported by W. S. Johnson certainly belongs in the category of efficient methods.[69] Progesterone is obtained from **62** in approximately 56% yield, as shown in Figure 14.

Conceptually similar in that multiple bond formation takes place in a tandem fashion is Vollhardt's enyne cyclization approach to steroids with an aromatic ring B.[70] The cyclization is mediated by $CpCO(CO)_2$ and is followed by a tandem cycloreversion/Diels−Alder sequence as shown in Figure 14.

An exceedingly efficient bond-forming methodology has been realized in the 1,3-photoaddition of olefins to arenes. This method has been exploited by Wender in the general design of triquinane terpenes, as exemplified by his approach to cedrene (**33**) (Figure

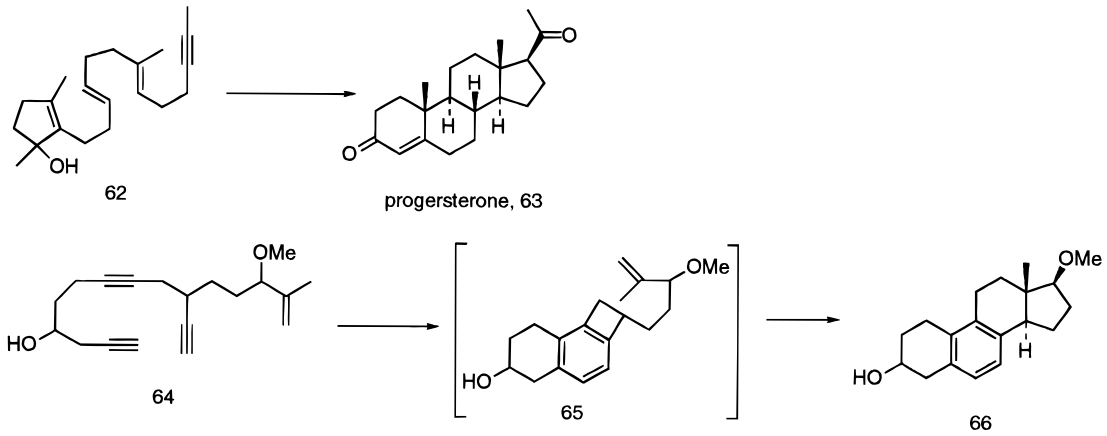


Figure 14. Tandem cyclization themes in steroid synthesis.

15).[31] The above methods are related by their efficiency in constructing multiple stereocenters with excellent selectivity.

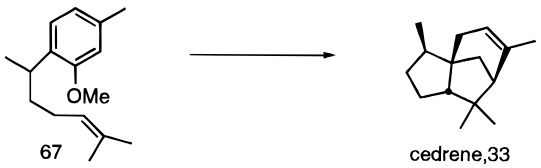


Figure 15. *meta*-Photocycloaddition methodology in sesquiterpene design.

Aldolase-Mediated Carbohydrate Synthesis

Wong has prepared unnatural azasugars,[71] previously shown to be inhibitors of β-*N*-acetylglucosaminase and other glycosidases,[72] by FDP (fructose 1,6-diphosphate) aldolase condensation of dihydroxyacetone phosphate with two stereoisomeric azidoaldehydes, **69** and **70**. Enzymatic aldol condensation followed by cleavage with acid phosphatase and hydrogenation gave the hydroxylated pyrrolidine derivatives **71** and **72**. Deoxynojirimycin **74** was made similarly from aldehyde **73**.[73,74]

This approach to highly functionalized materials in an enantioselective manner indicates the power of the biocatalytic approach to synthesis. The combination of synthetic chemistry with enzyme-mediated transformations has many advantages over traditional synthetic methods.

Enzymatic Differentiation of Meso Compounds

A very useful method in enantioselective synthesis is the enzymatic differentiation of meso compounds. This is easily accomplished either by hydrolysis of meso diesters or by monoesterification of diols. Cyclitols of type **75** are rendered optically pure by this protocol,[75] and the method is general for other cycloalkanediols such as cycloheptenediols **77**, the enzymatic desymmetrization of which led to an enantiodivergent synthesis of calystegine.[56] Similarly, oxidation of meso diols of type **80** by horse liver alcohol dehydrogenase (HLADH) has been shown by Jones[77] to lead predominantly to selective desymme-

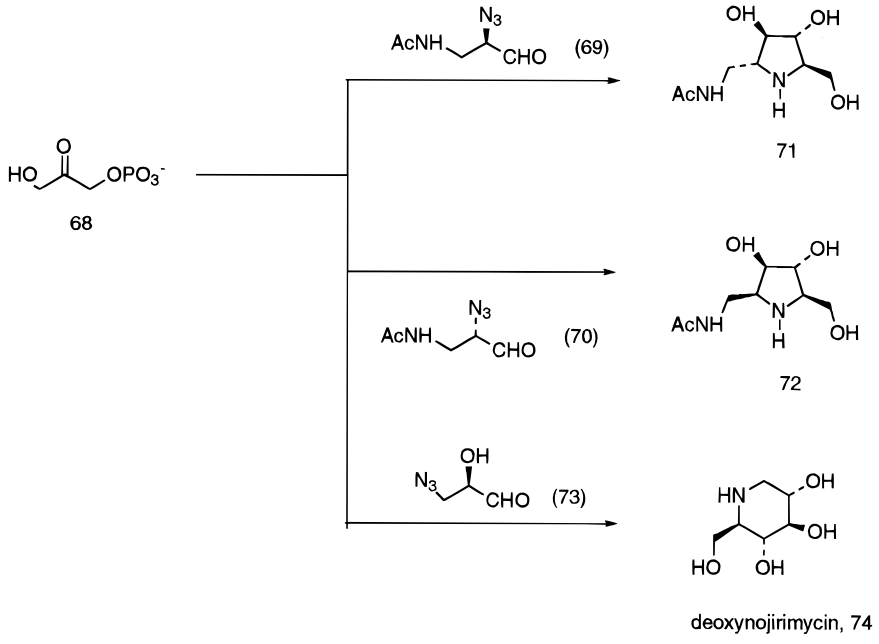


Figure 16. Biocatalytic synthesis of glycosidase inhibitors.

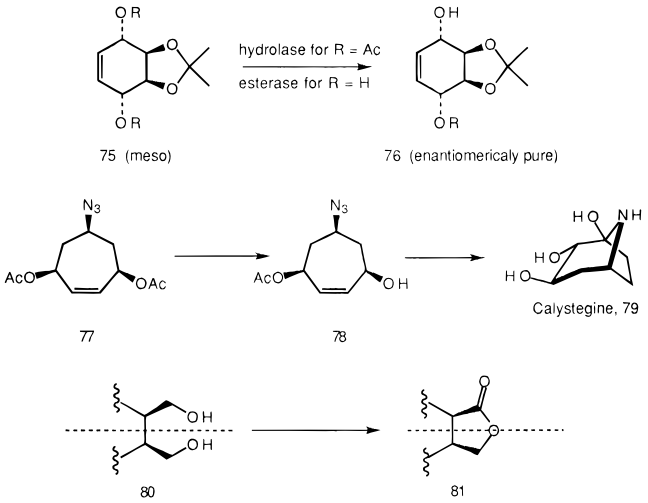


Figure 17. Enzymatic desymmetrization of meso compounds.

trization of the *pro-S* alcohol group, which undergoes further oxidation with concomitant lactonization as shown in Figure 17. These examples further underscore the power of biocatalytic transformations. The most popular aspect of this methodology, the lipase-mediated desymmetrizations, has been reviewed.[78,79]

Use of Oxidoreductase Enzymes in Synthesis

Unlike lipases, hydrolases, or simple alcohol dehydrogenases (such as those obtained from yeast), most oxidoreductases are unstable in purified form and difficult to work with. In addition, cofactor regeneration has to be considered for all such enzymes. For these reasons their use is far less common than that of hydrolytic enzymes. When oxidoreductases are used in preparative biotransformations, it is usually in whole-cell fermentations where cofactor regeneration is undertaken by the living organism. A notable exception is cyclohexanone monooxygenase, which is stable in pure form and can therefore be used with cofactor regeneration. Walsh's report on the enzymatic Baeyer−Villiger reaction[80] (Figure 18) revived interest among organic chemists in a transformation known from microbial degradation of ketones.[81] Expression of this methodology in enantioselective synthesis has been advanced by Taschner,[82] Furstoss,[83] and others in many applications.[84]

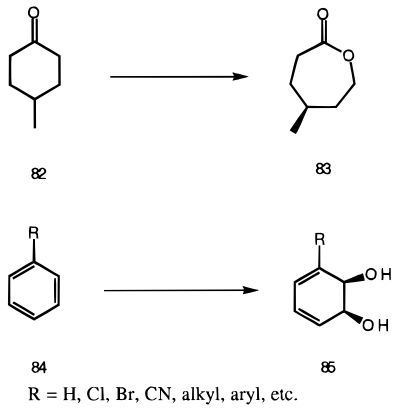


Figure 18. Enzymatic Baeyer−Villiger reaction and aromatic dioxygenation.

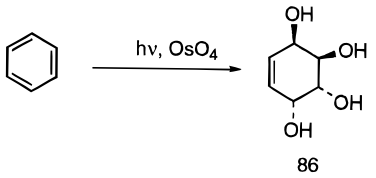


Figure 19. Motherwell's oxygenation of benzene.

The growth in application of the arene dioxygenase enzymes to enantioselective synthesis has been tremendous. Until very recently, the reaction, formalized by the transformation of **84** to **85**, had no equivalent in organic reagent chemistry. Finally, in 1995, Motherwell reported the racemic synthesis of conduritols and inositols by photochemical osmium tetroxide oxidation of benzene (Figure 19).[85] This represents the first reported chemical equivalent to the enzymatic process. The enzymatic version was discovered by Gibson[86,87] in the late 1960s and thoroughly investigated in relation to the microbial degradation of xenobiotic aromatic compounds. Gibson furnished the scientific community with both the blocked mutant *Pseudomonas putida* 39D and the recombinant organism *Escherichia coli* JM109. More than 200 diol metabolites produced by the action of these two organisms had been identified by the early 1990s.[88,89] The diffusion of this fascinating transformation into the realm of synthetic chemistry has been rather slow and arduous. To this day this technology has not been blessed with full acceptance of the American synthetic community, despite more than 100 papers describing the efficient use of such transforms in synthesis and the complete acceptance in European and Japanese communities.[90,91] The resistance to the use of enzymatic transformations is puzzling,[92] especially in view of the incredible simplification of issues such as enantioselectivity, efficiency, environmentally friendly protocols, and so on. It is interesting to note that almost 20 years elapsed from Gibson's initial report to the first paper on the use of cyclohexadiene *cis*-diol in synthesis, by Ley in 1987.[93] It is fitting to conclude the section on new technology with the introduction of this particular transformation because much of the discussion that follows will highlight syntheses that use toluene dioxygenase-derived diene−diols.

The examples presented so far demonstrate concisely the incorporation of new and emerging technologies into the growing synthetic repertoire. All of these technologies have, once incorporated, greatly improved the process of molecular assembly. The list is not exhaustive, but it contains those classes of transformations that, in the author's opinion, had a major impact on preparative chemistry. The reader should have noticed that the major advances have come from the outside of the traditional synthetic domain. Sharpless and others have been heavily influenced by transition-metal chemistry, and the research of Wong, Jones, and Sih, as well as that in our own group, has relied on advances made in the fields of microbiology and molecular biology.

Thus, at the conclusion of this section, I reaffirm the validity of the paradigm stated in the introduction and insist on the multidisciplinary nature of further advances in the field. The discourse in the next section further dissects the elements essential

to adequate performance in synthesis to reaffirm that new technology cannot be expressed in a reinvestigation or optimization of established reactions (this parameter is indeed reduced to engineering and process control) beyond a reasonable level as defined in generalizations 1 and 2. New technology can, however, manifest itself in a new type of design strategy that may or may not require development of new technique to be successful.

> Generalization 5. The greatest improvement of any technique becomes available via multidisciplinary or collaborative efforts. Ventures into seemingly unrelated areas in search of a solution to a synthetic problem are to be encouraged for these provide the most important advances.

III. Strategy in Synthetic Design: Dimensional Analysis and Examples

From time to time attempts have been made to describe the process by which synthetic chemists arrive at a pleasing solution to a synthetic problem. Some excellent ideas have resulted from this effort, for example disconnective strategy as an analytical tool in design, as well as in the *post facto* rationalization advanced by Warren.[94] The concept of synthons[43] and network analysis[95] proposed by Corey ultimately led to computer-assisted design (CAD).[96−106] Connectivity analysis as an exhaustive tool in design has been described by Wender;[2] Bertz has successfully coupled it with graph theory[5] to predict and explain the issues of complexity, reflexivity (or symmetry),[5,107] and vulnerability[5] in terms that may seem somewhat esoteric for the average organic chemist. An excellent text for a student of synthetic design at any level is *The Logic of Chemical Synthesis* by Corey and Cheng[108] and, of course, the equally enjoyable reading on selected syntheses by Fleming[109a] and Lindberg,[109b] among others.

We have made a very primitive attempt to rationalize and to verbalize design elements used in our pursuit of triquinane syntheses[4] and later in a similarly general design arising from the use of *cis*-arene diols.[91] But, even after all this, it is painfully obvious that a language of molecular design that adequately expresses insight and pattern connection is yet to be invented. Such a language would greatly simplify the attainment of practicality in organic synthesis because it would address the issues of generality and exhaustive synthesis of entire classes of molecules by using the same method or even the same material; such language must relate synthetic planning to topology, a task again not reduced to everyday quantitative practice by organic chemists as of this writing.[4,91,110] Again the idea of a journey outside the borders of our kingdom applies. I will do my utmost to verbalize some of the concepts and to support their "real-world" applications with examples.

1. Computer-Assisted Design

The most serious problem in verbalizing synthetic strategy or retrosynthetic reasoning is the lack of simple language by which to accomplish the task. The spectrum of attempts ranges from the application of graph theory and set topology, as done for example by Ugi,[111] Bertz,[5] and others,[6] on one hand, to the relatively simple connectivity analysis by Corey,[108,112] Wender,[2] Hendrickson,[101] and Hanessian[98,100] on the other. In the middle of the spectrum lie Jorgensen's CAMEO programs,[104,105] which aid in the analysis of actual mechanistic pathways, and some of the databases and planning programs advanced by Hanessian.[100] The former group of applications is not readily accessible to the usually impatient synthetic chemist who is either unwilling or unable to make the time investment required to learn these special techniques. The language of retrosynthesis, synthons, and transforms, originally used by Corey,[108] allows a qualitative approach, and, therefore, it is appreciated more easily by organic chemists as "user friendly." However, most of the applications in the middle of the above spectrum, as well as the use of the LHASA program[113] and any of the currently popular substructure databases, require knowledge of computer software and hardware. As pointed out by Hendrickson[101] at the conclusion of his paper on the SYNGEN program, organic chemists will have to become comfortable with the everyday use of computers in the future.

The first attempt at a computer-aided design was disclosed by Corey and Wipke almost 25 years ago.[102] The logic in this and subsequent programs[103] was understandable to most synthetic chemists because it is based on the reverse of a synthetic scheme. All possible "retrosynthetic" transforms could be analyzed against a database of known transformations. Of course, the number of all possible transformations is astronomical—in an example worked out by Hendrickson,[101] a bondset analysis for the assembly of the estrone skeleton from one-carbon units yielded 6×10^{23} assembly routes, implying that every molecule in a mole of cortisone could be made by a different path![101] Hendrickson's SYNGEN program[96,101,106] is based on the analysis of convergent routes to a target, emphasizing skeletal rather than functional disconnection. This strategy allows the program to be highly interactive within defined expert systems of reaction or structure databases for retrieval of "real" starting materials. The program contains several useful internal limits (e.g., no more than six bonds may be disconnected from the target to avoid the situation described above for the assembly of a steroid from one-carbon fragments) and avoids refunctionalization or alteration of noncrucial functional groups. The analysis produced by SYNGEN for an estrone derivative **87** is shown in Figure 20.

The strategically important bonds (labeled 1, 2, and 3) are disconnected in sequence to eventually afford the simplest convergent set of available starting units, A, B, and D. Note that no refunctionalization is necessary in the forward direction of the synthesis once the starting materials have been identified. Interface with REACCS and SYNLIB allows access to over 25 000 distinct reactions during the forward analysis of the design.[101]

Operational differences between the logical approach of a computer and the intuitive approach of a

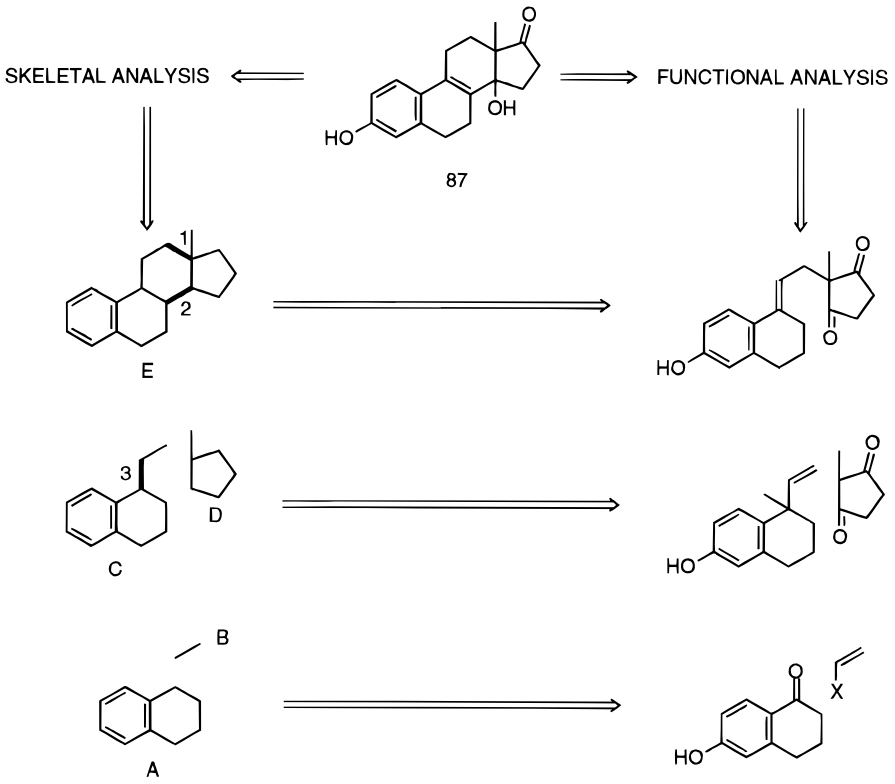


Figure 20. Retrosynthetic analysis for a steroid derivative by SYNGEN.

Table 3. Advantages and Disadvantages of CAD

advantage	disadvantage
speed of processing	no intuitive judgment
multievent analysis	inability to connect unrelated events
expert system assembly	lack of personality
absence of ego	absence of ego
no particular bias	no particular bias

human mind are responsible for a void in the effective use of computers for synthesis. The more mechanical aspects of graph manipulation are, of course, more easily done with a computer, as evidenced by the standard applications of structure processing programs, molecular mechanics calculations, ab initio calculations, and structure or substructure databases. However, the more intuitive aspects of expression are, as yet, inaccessible to the computer. Table 3 lists some of the advantages and disadvantages of computer-driven design of synthesis. Unquestionably, any comparison of a technical nature of a computerized performance and human performance will favor the computer. On the other hand, the lack of human qualities and both positive and negative traits in today's expert systems make the comparison more favorable toward human achievement. Most authors who have written summaries of synthetic accomplishments allow for some level of judgment, using strictly human terms, in their description of syntheses.

A recent essay by Hanessian[99] reflects on art versus logic in the context of recognition of "chirons" in the targets and their eventual use in the final assembly. Man and machine have been compared in their ability to recognize and connect events or objects of varying degree of sophistication in another essay devoted to the rational "chiron" design of syntheses.[98] Initial heuristic considerations of chiral, nonracemic building blocks for total synthesis led to the development of the CHIRON program, based primarily on pattern recognition of defined structural features.[100] The program operates on simple 2-D structural input and then conversion to 3-D. Several features of this program make it attractive to those chemists not versed in programming skills. The input can be viewed in a number of modes, including Fischer and Newman projections. Chiral substructure search and isomer or duplicate structure search modes are augmented by analysis of overlapping or similar segments common to one or more molecules. This feature of the program is unique in that it begins to resemble the human memory process in comparing abstract shapes in search of similarities. Thus it is possible to view and relate the structures of, for example, morphine and gibberelic acid and to compare common structural features. (There are two five-carbon and 19 four-carbon segments containing convergent structural features common to these two molecules).[100] The computer-assisted precursor selection (CAPS) routine of the program compares stereochemical and functional convergences on the basis of pattern recognition drawing on a large database of precursory materials.

Henessian attempted to make the workings of the CHIRON program resemble the human process closely. Yet the verbalization of what really occurs during the creative process is difficult. Because the scientific literature is not the medium to express philosophical thoughts or insights, the only way to learn of the process that various practitioners use is through lectures or monographs, which offer more freedom to depart from the presentation of facts. It is unclear whether the current CAD technology offers such freedom. Nevertheless, the CHIRON program seems to offer a valuable "playing" mode in that

structures of latent relevance may be dissected and compared without a specific purpose in mind. This type of activity, a childlike freedom in letting the mind wander, almost certainly occurs in the chemist's mind when reading and viewing synthetic literature. It is this seemingly random mixing and overlay of information that provides a fertile ground for serendipitous discovery.

2. Pattern Recognition

Pattern recognition is probably the most important parameter in the overall success of synthesis because it links the target to either a substructure goal or to the very origin of the synthesis. It is difficult at best to explain how original connections are made. Obviously, several independent sets of data must be visualized in the context of a desired goal. The precise mechanism of this process is unknown, but what is certain is that without adequate background information the linking process cannot work.

In 1974 the late Robert V. Stevens taught strategy to my own graduate synthesis class in a very simple and effective manner: he urged us not to confine our thoughts to any single representation of a molecule. First, we should view the target from all possible angles to avoid being limited by the view most often presented in the literature. (To make a point: how many of us would draw indole with the nitrogen in the "north" and the benzene portion in the "east"?) Second, he asked that the problem be clearly defined in the context of available technology—only if it could not be solved by means of existing technology should a new method be considered. At the time, Professor Stevens's favorite example of a synthetic problem that required new methodology was the preparation of unsymmetrical biphenyls, a problem solved adequately many years later by Suzuki[114] and related coupling protocols[115] that augmented greatly the Ullman method.[116] It was not until I began work on this review that I grasped the true brilliance of his approach.

The nonobvious, yet successful, disconnections that chemists sometimes make must be the result of simultaneous imagery evoked by superimposition of singular data entries. The first of two examples discussed here is Wender's model synthesis of the taxol ring system **92**.[117] An interpretation of the strategy employed in this synthesis should yield those elements of analysis that support the above statements. In order for the pinene strategy to have been conceived, knowledge of two key transformations had to be available to the designer. The fragmentation of epoxy alcohol **88** to the unsaturated carbonyl system **89** had to be "superimposed" on the image of the conceptually similar cleavage of the bicyclo[4.2.0]octane ring system **90** to **91** in order that their combination lead to the model application directed toward taxol, as illustrated in Figure 21. Note that the olefinic and carbonyl units in both **89** and **91** are found in taxol and in the model system, albeit with different connectivity. It goes without saying that the image of the ring system of taxol also had to be in mind for this strategy to be formulated. A connectivity analysis of taxol, approached with the idea of "target relevant complexity" as defined by

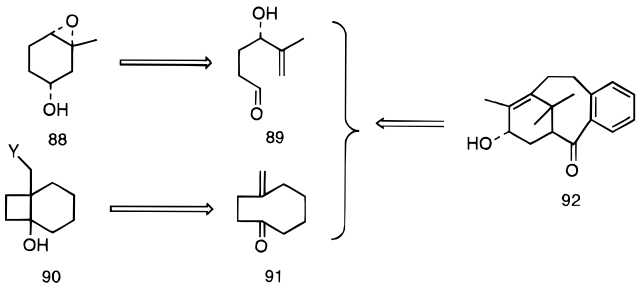


Figure 21. Data elements required for fragmentation approach to taxol.

Wender,[2] should in principle arrive at the same formulation after performing all disconnections, but it could not produce this outcome by processing just three "images." Similarly, graph theory treatment of these two transforms would yield identical results because these events contain parallel connectivity patterns and are mechanistically related. The ability of a chemist to connect previously stored three-dimensional images simultaneously with a current problem is thus far unmatched in the world of computer-assisted design.

The second example presented here is our own approach to sugars, which relied on the exploitation of enzymatic transformations (i.e., new technology) in a design of a general method based on arguments in molecular topology (i.e., three-dimensional and simultaneous imagery of targets and substructures). Shown in Figure 22 is a two-directional retro synthetic analysis connecting aromatics to sugars. What must be visualized are two different dimensions, one pertaining to the "symmetry space" and the other dealing with the actual forward or retrograde transforms. What I mean by symmetry space throughout this article is that set of dimensions in the overall synthetic plan that play a role in defining the absolute stereochemistry of any given set of transformations. Thus facial selectivity in reactions of arenes or olefins and the preference of an enzyme for the oxidation of one alcohol over another in a meso diol are events that are symmetry-driven and can be separated from those that are connected to functional manipulations independent of enantiomeric or diastereomeric considerations. The key transformation that must be "retroimaged" in the sugar−arene graph in Figure 22 is the Ferrier rearrangement because it provides the abstract connection between the hexose nucleus **93** and conduritol **95**, via inosose **96**, which would be the primary product of a "forward" Ferrier rearrangement. Here it is very important to use the R. V. Stevens rule mentioned above: the operator must be able to temporarily ignore the issue of stereochemistry in order to recognize (by mentally rotating the molecule) that inosose **96** can also result from the hydrolysis of an enol ether or a vinyl halide present in **95**. Proceeding backwards, the successive elimination of one water molecule and the reduction of one hydroxyl in **95** furnishes **85**, where a reduction of a diol to an olefin gives arene **84**. It is this imagery that triggers the visualization of an inositol, for example, as a triply hydroxylated, triply oxidized benzene nucleus. In the forward direction it is assumed that adequate technology exists (chemical or enzymatic) that can be utilized to selectively

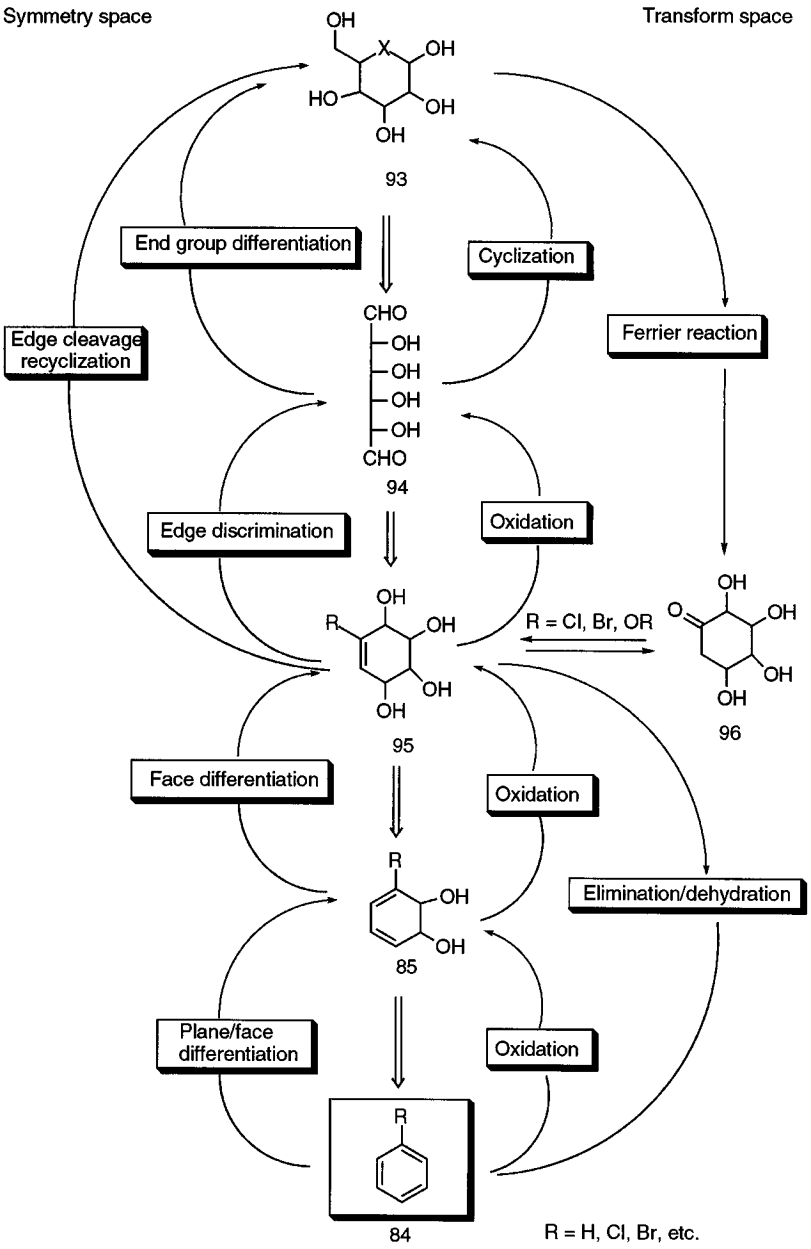


Figure 22. Design imagery for carbohydrate synthesis from aromatic compounds.

cyclize the product of the cleavage of **95**, the dialdehyde **94**, to the corresponding hexose with reduction of the nonparticipating aldehyde group. In the actual execution of this design, the identity of aldehyde **94** remained "latent", that is another selective protocol was found to bypass such a functionally symmetrical intermediate in preference to a more direct route to hexose **93**.

These images all occur in the transform dimension of synthetic analysis. The symmetry dimension is concerned with imagery of the operations necessary to bring about the face-selective hydroxylation of the aromatic ring. If the product is meso, as it would be for benzene, there must be another desymmetrizing image, either at the stage of achiral arene **85** the symmetrical image of **95** or the end group differentiation in dialdehyde **94**. All this can proceed simultaneously in the imaging process provided two conditions have been met: the contemplator must have the knowledge of Gibson's protocol for aromatic dihydroxylation, and also be aware of the chemical connection between a hexose and an inosose (i.e., the Ferrier reaction). Amusingly, it actually required much more time to type this sort of a rationalization than it took the original inspiration to form by the joint processing of the isolated key pieces of data. Once the image of the forward pathway was formulated, the details of the additional dimensions required for execution appeared trivial. As in the taxol problem, analysis of this type would not be expected from a computational approach because it is not strictly logical. Nevertheless, the results of our research in carbohydrate synthesis force us to return quite often to this picture because it is exhaustive and accounts for all stereochemical possibilities in the target, hexose **93**, as will be demonstrated in the accompanying examples. A more in-depth analysis of the general protocol for the synthesis of all classes of carbohydrates has been published.[91]

As another proof that previously acquired information must be considered in the context of the targeted goal, consider the problem of constructing four equiva-

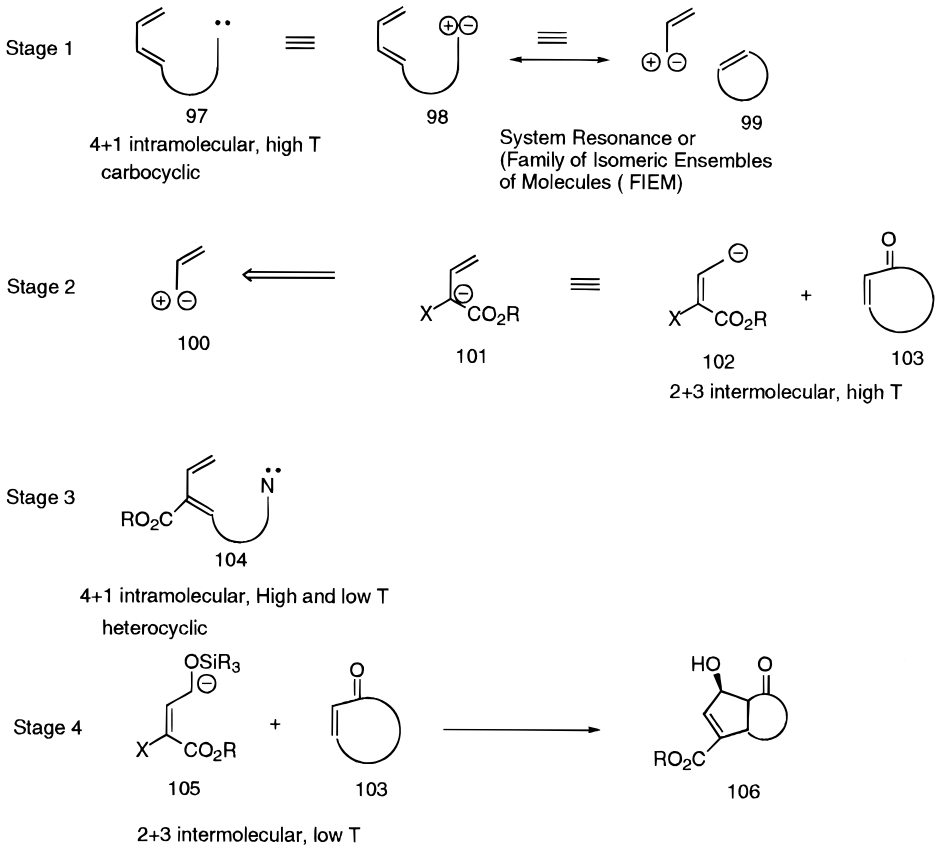


Figure 23. Evolution of carbo- and heterocyclic annulations.[4]

lent triangles from six matches of equal length. Graphically there are several solutions but none in which the matches do not cross. When this problem is presented to chemists they usually construct a tetrahedron (the only valid solution) almost immediately. Nonchemists will arrive at the same correct solution, but only after they begin to think in the third dimension and usually after a considerable length of time. Why? Because the tetrahedral shape has not been "internalized" in their imaging process (as a learned reflex, akin to those that result from constant repetition of certain tasks: musicians, martial artists, professional drivers all have internal reflexes for certain situations.) Again, a computer solution to this problem would proceed *without preference or priority* through all permutations.

From imagery in three dimensions, it is not difficult to proceed to the multidimensional nature of synthesis once the dimensions are defined and taken into account during the planning stages of the project. In order to visualize of the various synthetic dimensions, consider the following analogy. If a professional were compared with a number of other professionals on the basis of his personality, experience, and education as the three major parameters that may make him suitable for a specific task, the definition of the task itself would not lead to the selection of the best person for the job unless these were connected to the history of each of the candidates and the likely future requirements of the task. A multidimensional matrix of each candidate's other qualities can be compared to a similar matrix of expectations for the task itself and a subtractive overlap of these two "spaces" in their entirety would yield those qualifications unique in the best candidate. For example, the ability to speak a local language (one of many "dimensions" in the candidate's profile and a subset of education) in a place of a new business venture (a "dimension" of the task) could easily influence the selection in favor of that person. A dimension is therefore one (or more) parameters that are required for a completion of a time-dependent process.

In analyzing a forward synthetic plan, one must simultaneously consider all consequences of conditions that were previously imagined in the reverse mode and construct and analyze a matrix of all those aspects that will be likely to dictate the outcome. These "dimensions" then may include identities of reagents; conditions of reactions in the individual steps; symmetry of all compounds, viewed separately and in light of the overall goal; the number and the order of individual steps; and so on. Successful achievement of a target will be the natural outcome of the correct combination of all events that have been ordered into a sequence as a result of the analysis.

3. Analysis of Precedent and Extrapolations

Once an initial plan is formulated, it is again compared to known data in a more focused fashion. The evaluation of analogies is useful in extending an idea in another direction. Some good examples are the extrapolation of the Diels−Alder reaction to its heterocyclic variants, the extension of sigmatropic processes to their heterocyclic permutations, and extrapolation of the diazoketone-based annulation to a more advanced anionic variant (see, for example, Figure 23). Such analyses usually broaden the use of existing methodology by expanding the field of

applications but, more importantly, lead to further improvements in the actual execution. Although small extrapolations based on precedents are valuable, I caution against relying too much on established precedent because a method reported to have failed in one case may well succeed in a new context.

The development of cyclopentene annulation, shown in Figure 23, illustrates the dimension of precedent and at the same time illustrates the evolution of topological issues connected to exhaustive design of molecules belonging to a similar class. Conceptually this design represents a more refined version of the previously tested [4+1] annulation shown in Figure 2. The [2+3] version is convergent and therefore shorter in execution; it also tolerates the presence of more functionalities than the technology relying on the use of sensitive diazoketones. The presence of the carboxylate on the vinylcyclopropane allows the use of milder methods. It was this feature that ultimately led to the development of low-temperature conditions for the vinylcyclopropane−cyclopentene rearrangement.[118]

The evolution of that particular technology follows the flowchart diagram of synthesis shown in Figure 1 perfectly. The initial version—[4+1]—evolved into a more efficient one—[2+3]—which in turn led, in a third-generation design, to incorporation of elements necessary for low-temperature rearrangement.[118] At that point only one item remained to perfect this technique, the incorporation of asymmetry (a "dimension" of the development of this technology). It proved unnecessary because there was already an adequate solution to this problem. Enantiomerically pure cyclopropanes are already available via either catalytic cyclopropanation or asymmetric Michael addition. Because only one chiral center in a vinylcyclopropane is unaffected by the rearrangement and because the resulting cyclopentene will be *cis*-fused, it follows that an optically pure vinylcyclopropane would furnish an optically pure cyclopentene. The only remaining aspect (dimension) of this technique to pursue was its general applicability to nitrogenous compounds. The method was naturally extrapolated to the azide−diene cycloaddition method or [4+1] pyrroline annulation,[119] reactions that also proved amenable to low-temperature conditions.

The representation in Figure 23 shows reaction development as a function of permutations in valence and atom replacement along a time coordinate. It is described in more detail in a previously published work on the application of this annulation methodology to concise synthetic design of terpenes and alkaloids.[4] The initially formulated [4+1] annulation of diazoketones resulted from considerations of the Diels−Alder reaction as precedent.[4] The carbenoid **97** can be expressed ionically as **98**, which transposes to **99**, a system having identical valences and atoms yet differing in overall topology. We have termed this phenomenon *system resonance* or *retrosynthetic resonance*[27] to indicate that, during a disconnective assembly of either hybrid, there is a point, much like a reaction transition state, where no physical distinction between the two entities can be made. In other words, system resonance implies a "transition-state" identity of two or more disconnective approaches to the same target.[4,27] This concept is not substantially different from that describing constitutional isomerism or *family of isomeric ensembles of molecules* (FIEM), coined by Gasteiger and Ugi,[111] but may be more easily visualized without relying on the principles of graph theory.

By expressing fully the functionality necessary to describe **100**, we arrived at the ester dienolate anion of 2-bromocrotonate **102** as the three-carbon partner in the [2+3] annulation. Although more efficient than the first stage effort, this procedure still required high temperatures for the vinylcyclopropane−cyclopentene rearrangement. When the aspects of stages 1 and 2 were combined and a carbenoid "replaced" with a nitrene, the [4+1] pyrroline annulation emerged.[4,19,119] The presence of the ester allowed the use of low temperature, and soon after, the final form—stage 4—was developed to the point where the addition of the silicon-terminated unit and the cyclopentene rearrangement all took place below −78 °C.[118] It was immediately applied in a synthesis of (−)-specionin.[120] This development took a little over 10 years and was applied to the concise preparation of many natural products containing carbocyclic and heterocyclic five-membered rings. Several detailed reviews addressing methodology development and extrapolations as well as applications have been published.[4,19,119]

These examples illustrate precedent analysis and subsequent extrapolations of methodology that lead to improvements and refinements of the particular technique. It is evident that brevity is well served when one compares a first-generation effort with a final version.

4. Connectivity and Topology

This topic has received recent attention in reviews by Wender[2] and Bertz.[5] The analysis of disconnective operations by permutations has been shown to lead to well-executed design as evidenced, for example, by the pinene−verbenone rearrangement route to the taxol ring system. Connectivity analysis is a valuable tool even when it is not used in strict adherence to the principles of graph theory.[5] The analysis can sometimes be undertaken intuitively, coupled with considerations of topography and topology, as defined recently.[110]

To illustrate this kind of analysis, I have chosen an example in carbohydrate design. The retrograde connectivity parameters of the alternative view of the Ferrier rearrangement (shown in Figure 22) around which our carbohydrate design was structured are shown in Figure 24. The cleavage of the hexose yields the open form **107**, the rotation of which to **108** allows the hypothetical metathesis of the aldehyde and the CH bond directly to an inositol nucleus **109**. Note that the elimination of one molecule of water from **109** would yield the inosose product of the Ferrier reaction, which would normally be achieved by the formal loss of water from **107** and recyclization. This type of divergent analysis is helpful in connecting the target topologies to the appropriate starting materials. Both explanations are related by the manipulation of a single molecule of water and the necessary bond reorientation transforms. The

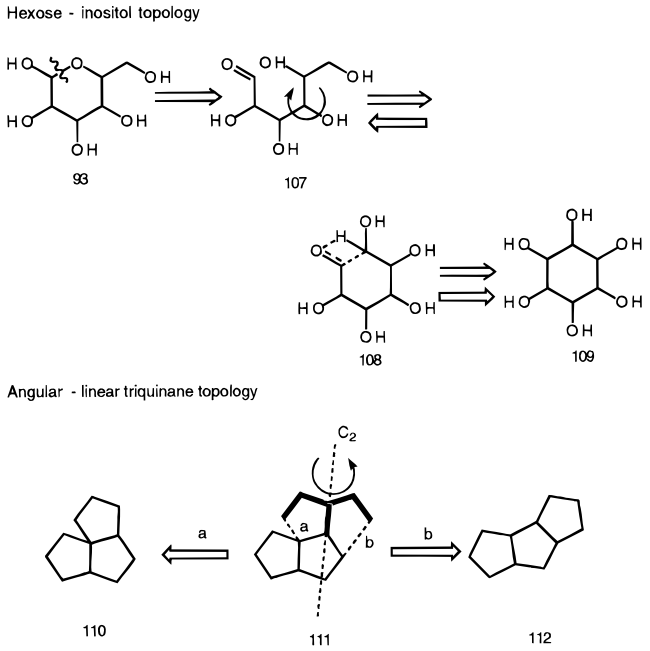


Figure 24. Connectivity relationships in carbohydrate[91] and terpene[4] topology.

CHIRON program should actually pick this possibility out by comparing the convergence of structural segments of the two compounds, **93** and **109**. An intermediate such as **108** lends itself to synthesis of both hexoses and inositols, the only operation required being the rotation of a single bond. While the nature of stereochemical configuration in either class of compounds constitutes a topographical relationship, **93** and **109** are clearly representatives of two distinct topologies. Similar rotational disconnections have led to the conception of a topologically distinct design of linear versus angular triquinanes,[4] shown below for comparison.

Figure 25 shows the relationship between hexoses, inositols, and the arene *cis*-diols. The type of topology and topography found in the product is dictated by selection of one of the six edges of the diene−diol for oxidative cleavage and recyclization or further oxidation. In inositol design, this selection dictates also the order of further peripheral functionalization. If the precursor is enantiomerically pure, only diastereomeric issues need to be addressed in such functionalizations, and this task simply becomes a function of *syn* versus *anti* placement of subsequent

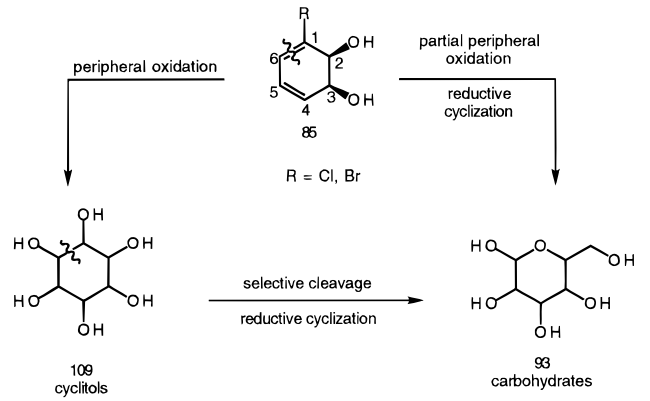


Figure 25. Selective design of hexoses and inositols from arene diols.

groups with respect to the diol unit. In carbohydrate design, the choice of a particular edge of the cyclohexane for cleavage will dictate the mode of recyclization and therefore the final topograhy of the hexose. In turn, more attention must be paid to the introduction of substituents because the properly functionalized inositol nucleus is the penultimate precursor of the hexose target. The planning of protection and deprotection of oxygens and the liberation of the edge selected for cleavage can also be viewed as a "dimension" of the planning process. It is clear that exhaustive design of molecular classes is dependent on the analysis of combinatorial possibilities in molecular topology. This type of analysis also qualifies as a "dimension" of a synthetic design, and in the next section it will be related to symmetry concepts for enantiodivergent design.

Consider for a moment the task of preparation of 64 stereoisomers of inositols (fully protected with different groups) and the 16 isomers of hexoses from a common intermediate and by similar experimental protocols. The above reasoning would be essential in order for a systematic execution of such a task (the reduction of which to practice has been demonstrated on a number of examples).[91] Thus the overall brevity of generalized design greatly depends on exhaustive analysis of connective permutations.

5. Symmetry Issues

A recent review analyzes in detail symmetry issues in enantiodivergent design.[91] The most important concept requiring illustration for those who plan to use enzymatic differentiation is the enantiomeric "switch", which allows energetically equivalent pathways to proceed to two enantiomers. Let us look at the case of the face-selective functionalization of arene **113**, as shown in Figure 26. An enzyme such as toluene dioxygenase will select only one site, let us say the one leading to **114**. Because the enantiomer of the enzyme is unlikely to be available, the operator must use **114** in the preparation of both enantiomers of the target. The geometrical operation that relates **114** and **115** is the interchange of groups X and Y. Such an interchange is not possible in practice without passing through a symmetrical intermediate at some point. It is impossible in principle to perform the interchange of these two groups simultaneously without the introduction of an additional element of asymmetry. (For example, an exchange of X for Y by using the adjacent hydroxyl as a tether, covalently connected to Y through a removable functionality such as a sulfide, silane, or

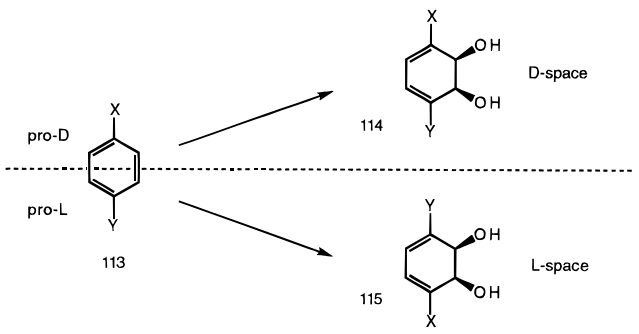


Figure 26. Principle of proenantiotopic differentiation.

thioester, would retain asymmetry throughout the process.) Such a design would undoubtedly lengthen the overall synthesis. However, the interchange is only important at the stage of target because it, and it alone, defines the enantiomeric constitution of the product. It is nevertheless possible to evaluate the steps of the synthetic sequence so that only one would be assigned the function of an enantiomeric switch. It can sometimes be accomplished by changing the actual order of chemical operations at a strategically crucial point.

In the meso differentiation of diols, for example, this switch is accomplished by choosing a chemically different transform (that is, a transformation defined in reagent space and not in symmetry space). Thus one of the two hydroxyls is *esterified with one particular enzyme*, but an acetate of either hydroxyl can be hydrolyzed *with a different enzyme*. Thus the sequence shown is valid in either direction as a function of different reagents (in this case enzymes). Experimental control of these variables is shown in Figure 17 for the transformation of **75** to **76**, where both enantiomers of the target are available. These are not chemical considerations but rather mathematical ones in which the reacting species, reagents, the ordering of events, types of reactions, and the outcomes are all equal variables or dimensions of the particular sequence.

An illustration of "latent" symmetry is shown in Figure 27. To invert the enantiomeric space of diol **85a** would require a 1,4-transform of the chlorine atom across the plane of "latent" symmetry. ("Latent" is used here to denote at the same time the chemical removability of the halogen and the possibility of symmetrization.) A similar situation exists in the two enantiomers of pinitol (**116**), where a 1,2-transform and an interchange of methoxy and hydroxy substituents is required. Because the rest of the molecule is not involved in this operation and because (if one "removes" or renders "latent" the chlorine atom for the purpose of this analysis) it maintains a plane of symmetry, such a switch can be accomplished by reordering reaction sequences and transformations. Only the chlorine atom makes the molecule both dissymmetric and assymetric; it will later be removed. The synthetic plan takes into account this "incipient" or "latent" transform (see section III.6), and the path to a particular enantiomer is defined by the precise point at which either the differentiating element (e.g., the chlorine atom) is removed or a functionality is introduced to define part of the particular enantiomer (e.g., the installation of either the *cis*- or the *trans*-diol unit in pinitol enantiomers).

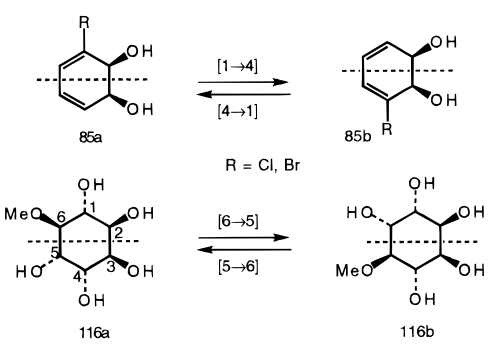


Figure 27. Enantiomeric switch in inositol design.

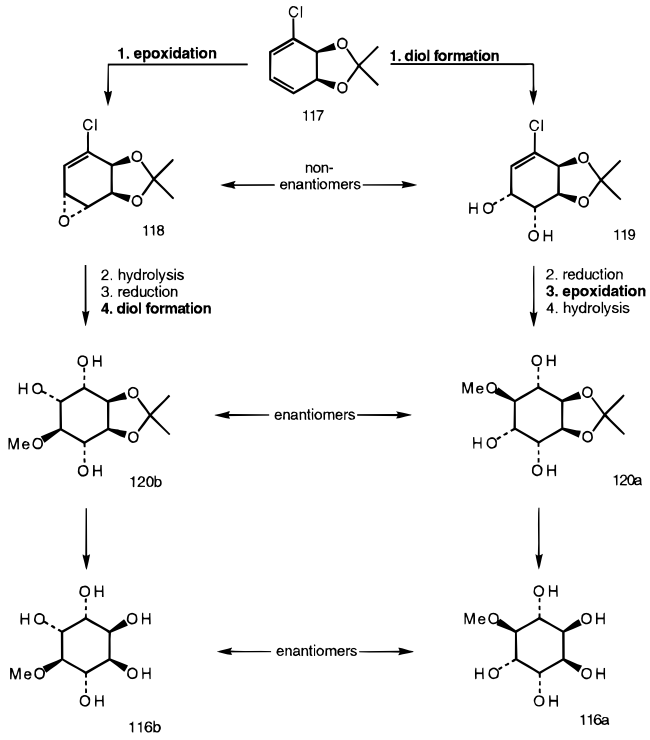


Figure 28. Enantiodivergent design of pinitol enantiomers.

A classic example of these principles is illustrated in the synthesis of the enantiomers of pinitol, shown in Figure 28.[121,122] The two pathways are identical in effort; they use the same reagents, transformations, and conditions. The only difference is the relative order of reaction, which dictates which functionality is set at which stage of synthesis, according to predicted reactive tendencies of the two olefins in **117**. Enantiomers differ geometrically, but not energetically, only in "symmetry space" and not in "reaction space" in reactions with achiral reagents. This principle can be applied to all compounds that contain a plane of latent symmetry (determined by manipulating functionalities present in a molecule to create the opposite enantiomer by a symmetrical transposition, as was shown for the arene *cis*-diols **85a** and **85b** in the case of symmetry analysis of pinitol design in Figure 27).

A similar example from the alkaloid realm is the synthesis of trihydroxyheliotridanes from erythruronolactone by a symmetry-controlled, enantiodivergent protocol, as portrayed in Figure 29.[119,123] In this example, a chemical operation at site a or b will automatically lead to a reflection of symmetry. The lactone and the lactol are similar in reactivity, differing only in their relative rates of reaction with nucleophilic reagents. Thus rate difference can be used as a dimension in the synthetic plan; the decision to make the first functionalization at either a or b can be made based on such a difference. That **121** is not meso is due to the relatively fragile difference in oxidation states of sites a and b.

The above analysis leads to concise execution of an enantiodivergent synthesis and is also amenable to exhaustive design of classes of molecules such as

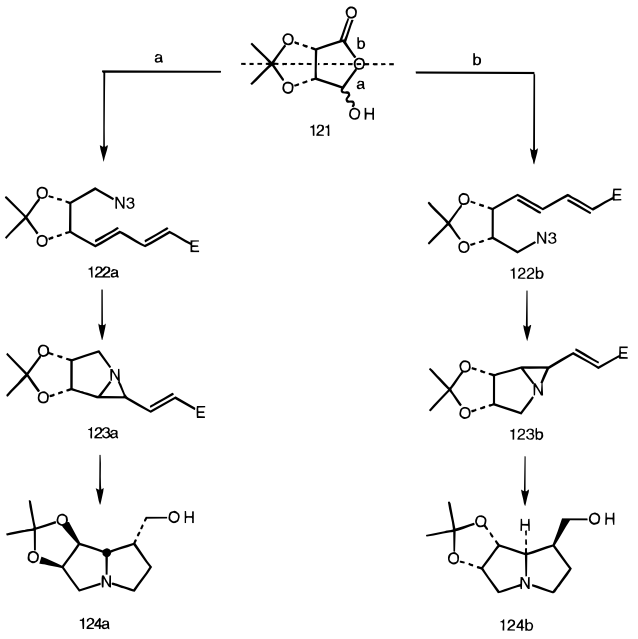


Figure 29. Enantiodivergent design of trihydroxyheliotridanes.

carbohydrates and alkaloids. The general applicability of this type of design will be addressed in the final section of this review.

The concept of latent symmetry used here is not to be confused with the concept of reflexivity described by Bertz[5] and useful in evaluations of molecular graphs for either symmetrical or C_2 symmetrical molecules. Bertz states that if either a molecule or its synthesis graph are symmetrical, the execution of the synthesis simplifies. Such syntheses are called "reflexive" and the status of "reflexivity" is sometimes attained even in unsymmetrical molecules by performing one or more operations. In a recent article Alvarez and Serratosa have extended this analysis to dissection of symmetrical molecules and point group analysis in designing convergent syntheses.[107] The concept of two-directional synthesis, or functionalization of identical termini of a chain in both directions, is also related to these principles. A two-directional strategy can greatly increase the efficiency of the sequence.[124]

6. Commutative Principles and Latent or Incipient Transforms

The logic of the enantiodivergent synthesis of the two enantiomers of pinitol by identical routes resembles the commutative principle in algebra. If a synthetic sequence is viewed as a dimensional sum of operations, then the order of these operations should have no influence on the final outcome in that dimension of synthesis not relevant to the formation of bonds. The entry into and the exit from the symmetry space is independent of the events taking place in the reagent space unless such events lead to removal of dissymmetry or asymmetry in any synthetic intermediates. Examples of this principle would be the reduction of the chlorine atom in chlorobenzene *prior to* the enzymatic dioxygenation (removal of dissymmetry in an achiral molecule) or the removal of chlorine from **85a** *after* the dioxygenation (removal of asymmetry). Similarly, either oxidation or reduction of **121** would render the molecule meso. Avoiding potentially symmetrizing steps in a synthesis must also be viewed as a parameter or a dimension of the sequence. When reaction steps and reagent application are ordered in two different ways to lead separately to the two enantiomers of the target, the synthesis is said to be enantiodivergent. The two routes, while perfectly identical in reagent applications, lead to two different symmetry outcomes because the order of application has been changed in the symmetry dimension (for example, by reflection or transposition of functionality across the plane of proenantiotopic symmetry in Figure 27).

> Generalization 6. Synthetic pathways to two enantiomers of a target should be chemically and physically identical except for the symmetry of the sequence and the order of reagent application.

Commutative principles also relate to incipient transformations along the synthetic sequence. Thus the *anticipated* reduction of a halogen atom in the diene−diol derived from chlorobenzene represents an incipient transform. Such transform allows the functional group to occupy a latent position in the synthesis—in other words, it serves a defined function in symmetry or as a directing group but not for the purpose of unique chemical reactivity. An incipient or latent transform can be, for example, a planned scission of a specific bond in the functionalized cyclitol. A double bond assumes the latent identity of a diol if its introduction is planned later in the synthetic sequence. Conversely, a diol is a synthon for an olefin, by means of the Corey−Winter reaction.

The above reasoning obviates the need for the introduction of such steps as inversions of stereogenic centers into a synthetic plan because these operations can be considered symmetry-dependent and could be accounted for by symmetry operations. The brevity of a sequence can be greatly affected and so can the general methodology design. Figure 30 shows the distinction between the design of azasugars (where the nitrogen is a part of the six-membered ring) and aminocyclitols (where the nitrogen functionality is a substituent on the ring). In both cases the nitrogen

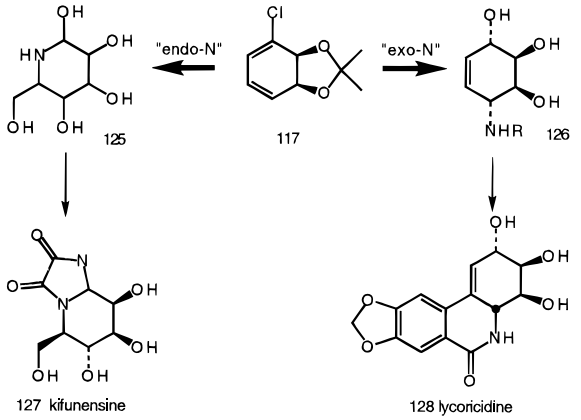


Figure 30. Design of exo- and endonitrogenous cyclitols and azasugars.

must first be introduced on the periphery of the cyclohexadiene diol **117**. (Thus the olefin can be viewed as a latent amino alcohol.) In the case of azasugar design, a selected edge of the cyclohexene is oxidatively cleaved, and the nitrogen cyclizes onto one of the electrophilic termini. There are six edges that can undergo oxidative cleavage; therefore, there are twelve possible cyclization modes, some of which can be excluded on the basis of strain. Aminocyclitol **126** and azasugar **125** are related according to the same disconnective logic as hexose **92** and cyclitol **94** (Figure 21). In the example shown here, these compounds, generated efficiently from diene−diol **117**, have been used in the total syntheses of the glycosidase inhibitor kifunensine (**127**)[125] and the antitumor Amaryllidaceae alkaloid lycoricidine (**128**).[126]

IV. Selected Examples

In this last section of the survey are several examples of successful synthetic design. Our own group has expended considerable effort over the years to think in terms of classes of molecules rather than isolated targets. In this I am forever grateful to my three mentors: the late R. V. Stevens, E. Wenkert, and W. Oppolzer. All three insisted on designing general methods of synthesis for alkaloids, terpenes, and other natural products. None used the same strategy—Professor Stevens built his methodology around a successful reaction, Professor Wenkert was guided by biogenesis where known and intuition where not, and Professor Oppolzer fitted the ene reaction into possible permutations of terpene skeletons. All have been eminently successful in their effort. We have had a good deal of fortune in the design of triquinanes and later pyrrolizidine alkaloids through the application of a unique annulation methodology.[4] Our emphasis has always been on multigenerational approaches because of the potential ameliorations.

The applications of biocatalytically derived diene−diols to enantioselective synthesis were performed at an even higher level and in complete accord with the covenant of this survey regarding brevity and new technology. Microbiology provided us with a new technique, which furnished us with a single enantiomer equipped with rich functionality. The brevity became evident upon implementation of the general design features for carbohydrates and later for alkaloids along precisely defined principles. We formulated several rules that were to become inviolate. The first and most important of these:

> Generalization 7. If a synthesis of a target, regardless of its complexity, cannot be successfully executed in 15 steps or less, then either the proposed plan or the applied technique must be replaced.

We have managed so far to keep within these guidelines and intend to do so in the future.

The second rule, which contrasts with the desire to develop fully general methods emanating from single precursors, states:

> Generalization 8. The outcome of a successful and brief synthesis depends on the most effective combination of the best available technique with efficient design. Restraint should be exercised in the overuse of any one method at the expense of brevity.

With these two rules in mind, let us examine how the carbohydrate and alkaloid design complies.

1. Carbohydrate Synthesis

In Figure 31, the logic of our strategy aimed at the synthesis of carbohydrates is delineated. The single enantiomer of a diene−diol such as **96a** contains two *cis*-hydroxyls, and these are used to direct the construction of the next chiral center either *syn* or, as acetonide **117**, *anti*. Thus the diastereoselectivity of mannose-type sugar units is addressed. A method has been developed to invert either the C2 or C3 hydroxyl; this allows access to glucose-type sugars.[127] Thus regio- and stereochemical concerns are resolved, and what remains is the precise definition of topology (e.g., inositol vs hexose, aminocyclitol vs azasugar, mannose vs glucose configuration), functional disposition of target, and the D- or L- constitution of the product. The cyclitol manifold involves simply functionalizing the remaining olefins with appropriate groups, whereas the azasugars and hexoses require cleavage and recyclization. To extend this logic to pseudosugars, we take advantage of the vinyl halide in **117** and functionalize, via Stille coupling,[128] this terminus with the carboxylate required for the eventual hydroxymethylene unit. Recent work from our laboratories demonstrates that all of these targets are available in short sequences, as portrayed in the summary (Figure 36). The final aspect of the general method, that of enantiodivergence, is solved in a manner illustrated for the synthesis of pinitol or of both enantiomers of erythrose,[123,129] by taking advantage of the proenantiotopic plane of symmetry in starting diols as illustrated above for pinitol synthesis. (A proenantiotopic plane of symmetry is one that would exist only after a removal or transposition of a key functionality or the reflection across which generates the enantiomer of the molecule. For definition of this term, see refs 121 and 122.)

In the spirit of general application, all of the sugar types portrayed in Figure 30 have been prepared by short sequences and their attainment stands as a

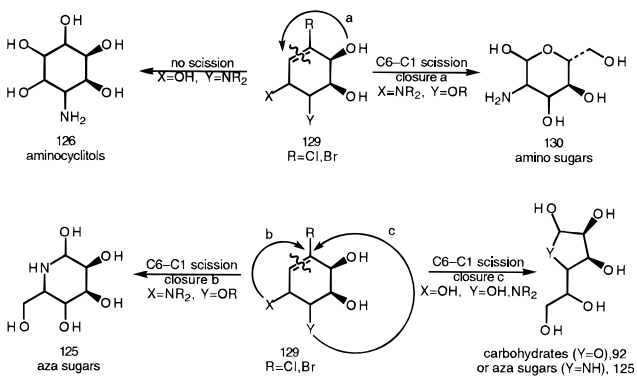


Figure 31. Exhaustive design of hexose carbohydrates.

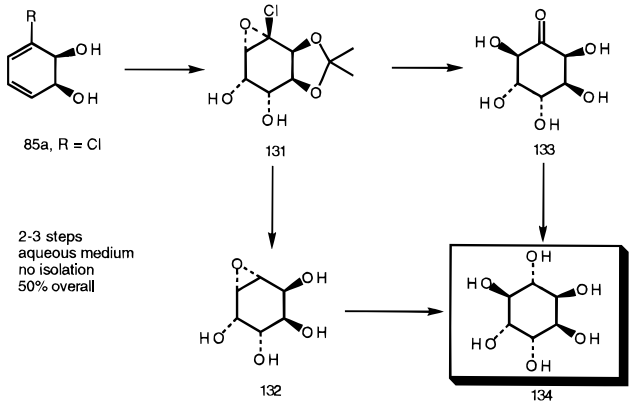


Figure 32. Efficient third-generation synthesis of D-*chiro*-inositol.

validation of biocatalysis as a new technology. The showcase of the method in terms of practicality is undoubtedly the third generation synthesis of D-*chiro*-inositol (**134**) (Figure 32). The unique conversion of diol **96a** to the chloroepoxy diol **131** is accomplished with aqueous $KMnO_4$ in acetone, the latter being left over from the in situ protection of the diol.[130] Initially, the halide is reduced with R_3SnH, and the reaction mixture is extracted into an aqueous layer. Addition of sodium benzoate and reflux of the water layer leads to hydrolysis of the epoxide in **132** and deprotection of the diol to afford the inositol in approximately 50% overall yield from **96a**. Even more efficient is the final version, which involves initial oxidation followed by hydrolysis to D-*chiro*-inosose **133**, all in one operation. The inosose is reduced with triacetoxyborohydride via chelation to the title compound.[130−132] This effort has proven important in view of the potential of this compound as a possible remedy for type II diabetes.

A glance at the final figure of this survey reveals some accomplishments in the area of sugar design: conduritols,[133] aminocyclitols[126,134,135] inositols,[131,132] erythrose,[129] mannose,[132] various azasugars,[125,136,137] pseudosugars,[128] aminosugars,[138] and, most recently, the perdeutero derivative of mannose (Figure 35).[139] Compounds such as mannose-d_7 could not conceivably be prepared efficiently by standard carbohydrate-based methods. Its attainment in only a few steps stands as a classic example of the proper matching of technology (i.e., the enzymatic dioxygenation) with design (i.e., a general method of synthesis). With the demonstration that all or most classes of carbohydrates are accessible, we can exit this field of applications and look at similar accomplishments in the field of oxygenated alkaloid synthesis.

2. Alkaloid Synthesis

The recognition of the oxygenation patterns of the alkaloids pictured in Figure 33 connects the design of their preparation to the cyclohexadiene diols obtained by fermentation. The identity of the diol unit from the starting material **117** in each of the targets is easily discerned. What is more important from a design perspective is the impact this unit will have on the fate of subsequent stereocenters. The design of trihydroxyheliotridanes[123] and kifunensine[125,136] follows the strategy of the [4+1] intramo-

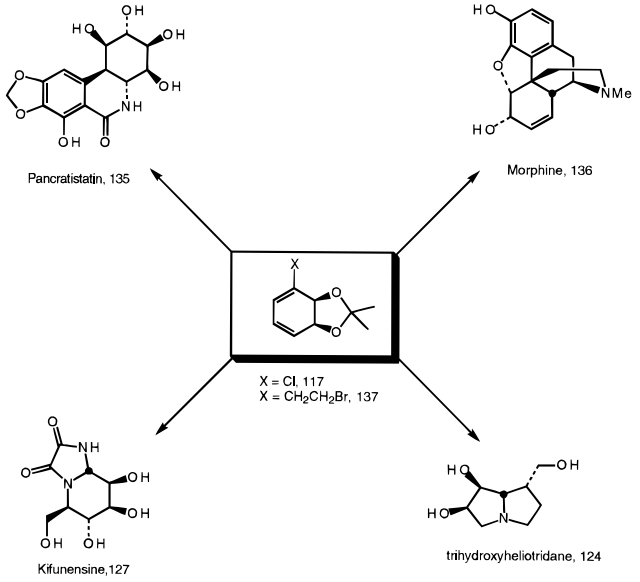


Figure 33. Biocatalytic design for oxygenated alkaloids.

lecular pyrroline annulation[4] connected with the use of enantimericaly pure diols in the former and the design in the azasugar domain in the later. Similarly, the design of lycoricidine[126,135] followed the execution of syntheses of simple aminocyclitols.[134] Our approach to morphine is now in its third generation and employs biocatalytic substrates, such as **137** and its *ortho*-bromo analog, having greater complexity than the diol derived from chlorobenzene (Figure 33).[140] I selected the synthesis of pancratistatin and its 7-deoxy isomer to demonstrate the merits of a multigenerational approach to an efficient solution of a problem.

Like taxol, pancratistatin represents another truly controversial situation that places synthesis in a critical light. The compound is needed for completion of clinical trials for treatment of several types of cancer, but it is unavailable in the required quantities by isolation methods. (Six grams can be extracted from 44 kg of plant material.) Synthesis, if competitive with isolation, would therefore be the way to supply this important material. Pancratistatin does not have the tremendous complexity of taxol, but is still quite difficult to synthesize, as evidenced by the number of approaches in the literature and by some of the difficulties encountered in the synthesis.[35] An efficient preparation of this material and the solution to its supply for testing would therefore benefit the societal appreciation of organic synthesis, which at the moment is not enjoying a positive view.

We approached this problem by connecting the known aromatic unit **139** with the vinylaziridine **138**, which was derived from bromobenzene in four steps, (Figure 34).[35] The coupling proved efficient, but the manipulation of benzamide and tosylamide in **140** required extra effort. Nevertheless, the first-generation resulted in a brief synthesis (13 steps), which remains the shortest to date.[141] The last transformation certainly merits mention in the spirit of this review, because it takes place in refluxing water and a total of five mechanistically distinct events take place: hydrolysis of the epoxide, loss of the BOC group, loss of the acetonide, hydrolysis of the ben-

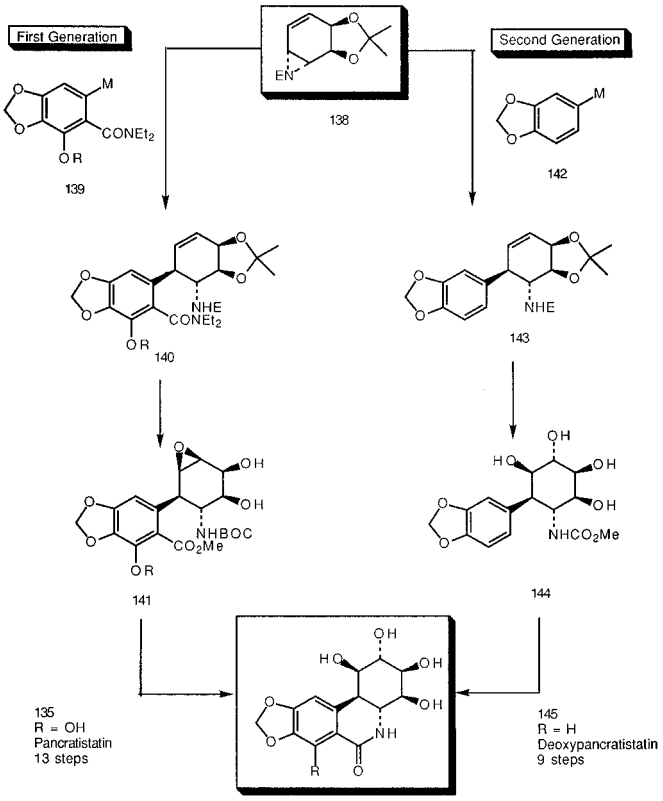


Figure 34. Two generations of pancratistatin synthesis.

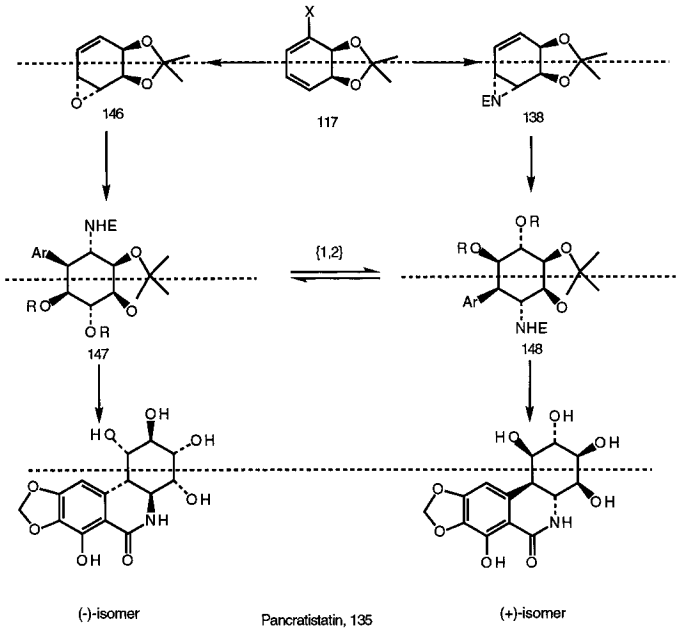


Figure 35. Enantiodivergent approach to (+)- and (−)-pancratistatin.

zoate ester, and, remarkably, an anchimeric debenzylation of the phenol.

To eliminate the functional manipulations encountered in the first attempt, we modified the approach as shown in Figure 34. Elimination of the benzamide and the tosylamide reduced the sequence to nine steps.[142] To indicate what must be accomplished in the third-generation effort now ongoing in our laboratories, let us look at the projected design shown in Figure 34. With the knowledge of previously encountered problems in the preceding two generations, we will once more take advantage of the latent symmetry of halogenated diols. Conversion of the diene−diol **117** to either the vinyl epoxide **146** or the vinyl aziridine **138** allows the establishment of those functionalities, the reflection of which across the plane of proenantiotopic symmetry (dashed lines in Figure 34) eventually generates both enantiomers of pancratistatin. Notice that **147** and **148** are reflexively identical except for the {1,2} shift of aryl and hydroxyl functionalities in the same way as the intermediates in the synthesis of pinitols. The decision as to which enantiomer is synthesized in the forward direction (a consideration not involving

reagents) is made at that stage of synthesis that employs either the oxirane or the aziridine as an electrophile. It is therefore important to search for and to locate those elements of latent or incipient symmetry (indicated by reflection of functionalities across dashed lines in Figure 35) that reduce the experimental manipulation of intermediates to a minimum. A description of this particular design is a fitting conclusion because it brings together all of the principles discussed in this review. Structured in a manner identical to that used in the synthesis of pinitols, this preparation is projected to yield the two enantiomers of the alkaloid in less than seven steps, and may, after appropriate optimization, help in the supply of the compound at least for testing purposes. Moreover, with this design it is possible to prepare the perdeutero analog of either enantiomer by starting with perdeuterobromobenzene. Such compounds, and other unnatural derivatives, may be useful in determining the mode of action of this alkaloid.

V. Summary

The agenda that we undertook some time ago is beginning to pay off in the brief design and execution of synthetic targets. It was stated that the goal of a synthetic craftsman is the provision of realistic amounts of material, and I hope that the examples given in this review conform to that principle. An attempt was made to quantify "somewhat" the type of thought that guides us in designing short and general pathways to various targets, mindful at all times not to overextend the use of any one given method or technique but rather to utilize always the best combination of what is best suited for a particular purpose. The judgment of these accomplishments will be left to future generations.

For now, there are new challenges facing the organic community. These, for the most part, deal with the perceived value of the art in a constantly changing society. We may begin to recover some respect if we abide by the covenant set forth in the Introduction and continue to solve the problems placed before us in a practical manner. In conclusion, I direct the reader to Figure 36, which offers an abbreviated list of compounds we prepared that are relevant to the title of this review. The reader should appreciate the fact that all were made from chlorobenzene by a combination of biocatalytic and synthetic techniques. Given the vast number of existing metabolites of aromatic and other compounds and the equally vast repertoire of enzymes, the future possibilities for the use of biocatalysis as a synthetic tool seem without limits.[143]

It would also seem appropriate to point out a new beginning of the chemoenzymatic transformations of chlorobenzene in a venture that is completely unrelated to any of our past pursuits but one that evolved naturally as a consequence of spatial imagery of inositols. The oligomers of L-*chiro*-inositol,[144] tetramer **159** and octamer **160**, portrayed in Figure 37, have been made in two steps from epoxide **146**, which is available in three steps from bromobenzene. Thus

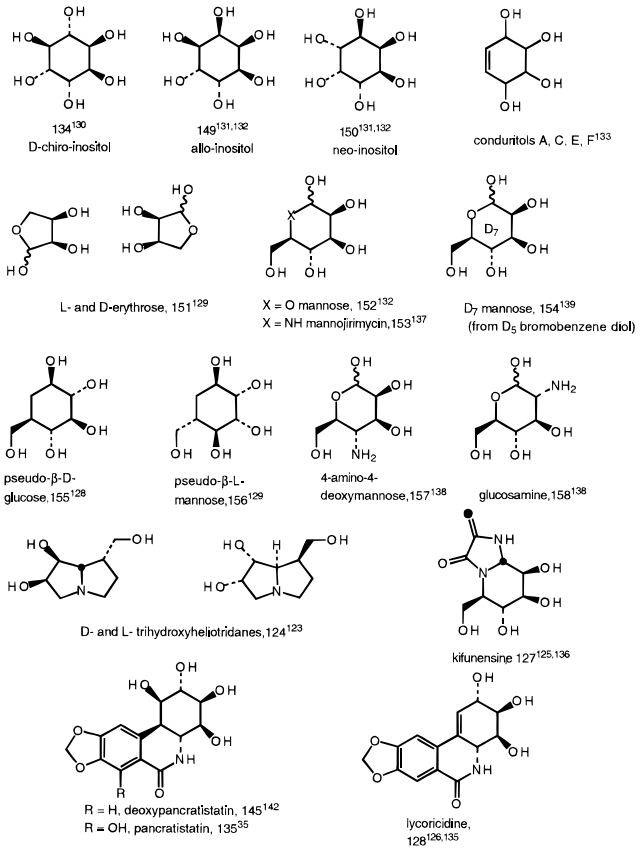
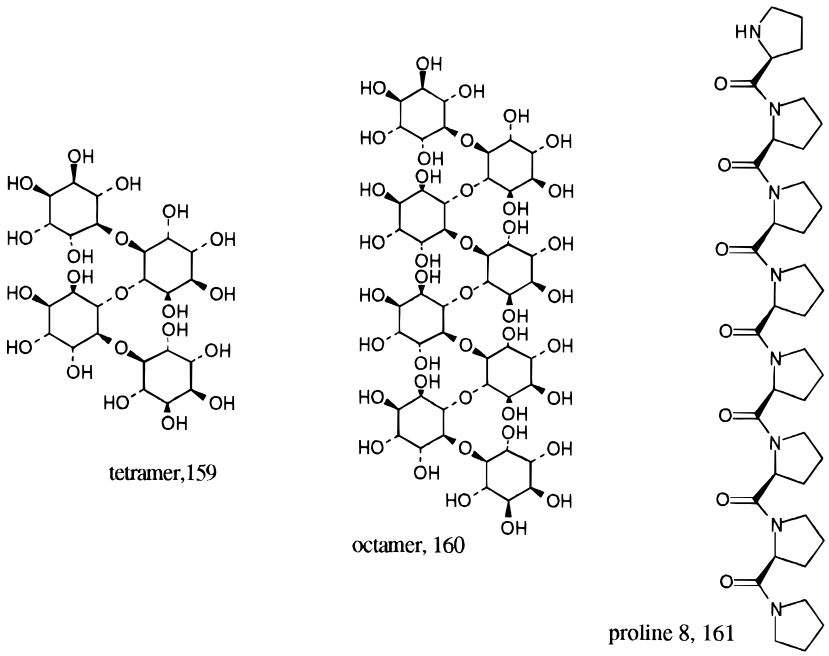


Figure 36. Carbohydrates and alkaloids synthesized from chlorobenzene by biocatalysis.

complex structures of hitherto completely unknown compounds can be prepared by the correct combination of planning, dreaming, and perseverance. The secondary structure (β-turn) displayed by these oligomers in comparison to an octamer of proline promises a new and exciting field of research on the physical, chemical, and biological properties of these compounds. In the spirit of the theme of this review it would be interesting to speculate on how these compounds could be attained in five steps or less from an achiral material by employing traditional methods of synthesis.

During my reading of various publications that I would classify as being on the edge of or slightly beyond standard organic synthetic literature (but certainly enjoyable and instructive), I happened to notice a most appropriate quotation with which to close this review. It appeared in an article by Hanessian,[98] describing also the various "dimensions" of creative design and comparing these to computerized processes.

> ...a synthesis plan should consider all possible approaches regardless of their seemingly 'far-off' nature.
>
> *He who sits at the bottom of a well to contemplate the sky will find it small.*
>
> Han-Yu (768−824 A.D.)
>
> Organic synthesis is the crossroad of several other subdisciplines. It can be viewed as the means, the end, or the beginning, depending on the type of objective, viewpoint, and project....



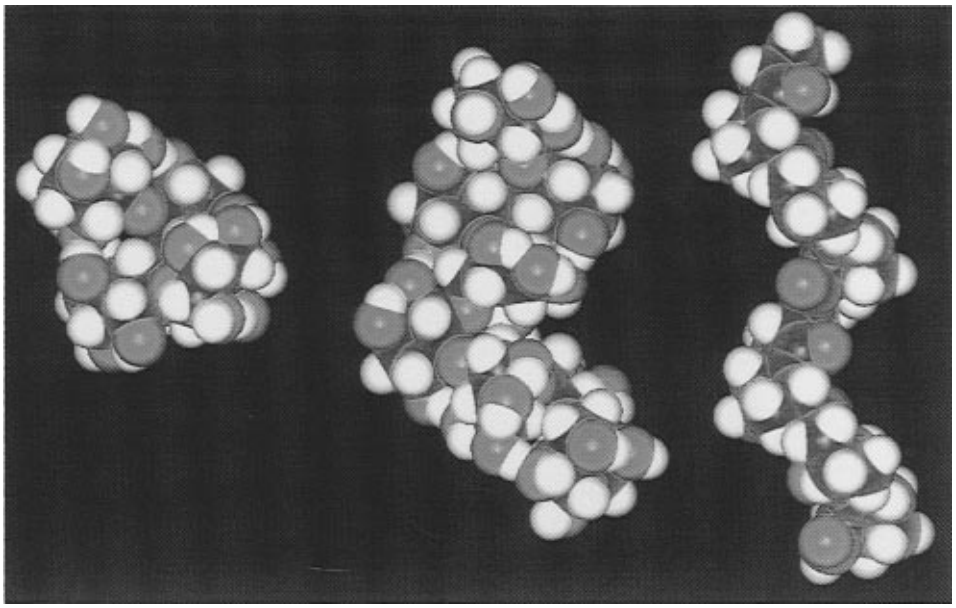


Figure 37. Secondary structure characteristics of some inositol oligomers and comparison of the structures to an octamer of proline.

It will be interesting to come back to this review in 10 years time and see what has been further improved in the practice of organic synthesis.

Acknowledgments

The author is grateful to all of his coworkers (some 120 postdoctoral fellows and students) for their able execution of projects mentioned in this review and to the sources that funded our work over the last 18 years. The names of co-authors appear in the literature references cited in this review. Special thanks are extended to Dr. Joel Bolonick, San Leandro, CA, for his contributions in molecular modeling. I am also grateful to the reviewers of this article, who made a number of constructive suggestions. Last but not least, I thank Dr. Josie Reed for severly editing the text.

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(11) One of the unfortunate trends that is noticable in the literature over the last 15 years or so is the misrepresentation of reaction yields, overall yields, and the total number of steps reported for a given sequence. Although I have never met anyone in the synthetic community who did not insist on honest and realistic reporting of results, the above practice continues at an unabated pace and is apparantly tolerated by referees to a large extent. The count of steps for a total synthesis, for example, frequently begins at the stage of a "readily available" known compound, which is referenced. Thus cursory reading of such a report may give the impression that a synthesis is 12 steps long when in fact the starting material, known but not commercially available, requires eight steps to prepare. Such a practice constitutes a deliberate effort to deceive the reader. A similar argument can be made over the reporting of maximum reaction yields, a practice that is driven by competition for numbers so prevalent in our society. A random comparison of yields in the articles from the 1960s and 1970s with those in the current publications illustrates the inflation of reported yields and supports this observation. The practice of false advertising will lead to low reproducibility of results and, in the long run, to a lack of credibility for the science reported during the current period. In my opinion, it also contributes to the underappreciated standing that the chemists enjoy in the society at large. (See also section 1.2 of Seebach's essay, ref 1.) It is extremely important to provide credible information, not fast results, as part of permanent record, because the entire period will be judged by it.
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(92) As incredible as this may seem, there are some in the synthetic community that openly reject the idea of enzymatic transformations as "cheating" or the "inability to design a catalyst properly" that will accomplish turnover rates similar to those of enzymes. Some views and discourse on the possible reasons for this resistance have been published: See ref 32; Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113; and the preface to the latter volume. Preparative biocatalysis, or the combination of enzymatic and chemical methods, has been accepted in the industrial world and in the academic communities of Europe and Japan. By comparison, very few research groups in the United States actively pursue research in this area. The resistance to accept this field is also reflected in the reluctant funding of such programs. In spite of the demonstrated superiority that biocatalytic design has over traditional methods of synthesis of enantiomerically pure compounds, research proposals dealing with preparation of medicinally viable targets by such methods have not been well received by the NIH system (in the author's experience). On the other hand, when the review of such proposals was conducted in the format used by the NSF, or by industrial pannels, the same proposals rejected by the former system were recommended by the latter. I do not believe that our case is unique in this regard, but I accept the premise that any new technology requires a transition period before it is accorded a permanent status.
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