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The psychobiological basis of heuristic synthesis planning—man, machine and the chiron approach

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Abstract - General strategies for the total synthesis of optically pure target molecules are reviewed with particular emphasis on the Chiron Approach which capitalizes on the use of chiral, non-racemic compounds as starting materials. The approach has been implemented in an interactive computer program which analyzes functional and stereochemical features in molecules and carries out a search of suitable starting materials and precursors for synthesis from a data base. The psychobiological basis of heuristic synthesis planning using notions of the human brain's bilateral asymmetry is discussed in the general context of the total synthesis of natural products.

ORGANIC SYNTHESIS IN PERSPECTIVE – THE LAST 35 YEARS

The annals of modern organic synthesis record a seminal volume on the subject under the title of "Perspectives in Organic Chemistry".[1] This frequently cited-monograph reflects in many ways the culmination of efforts in total synthesis covering a period of ten years after world war II. Already by 1956, complex molecules such as strychnine,[2] cedrol,[3] cortisone,[4] quinine[5] and reserpine[6] to name a few had been synthesized and obtained either in racemic form or in optically pure form via resolution. Each decade that followed brought forth a wealth of contributions towards total synthesis, culminating with the conquest in 1987, of palytoxin,[7] the largest organic molecule synthesized by man to date.

While the syntheses accomplished in the fifties and sixties were elegant in their design and deliberate in their execution, most were concerned with individual targets belonging to different classes of natural products. Since the structures differed substantially from one class to another, the strategies developed for one synthesis did not necessarily apply to other syntheses. The last decade or so has witnessed the emergence of a large number of extremely useful bond forming methodologies, and at an impressive pace. Consequently efforts in total synthesis have gained enormous momentum, and many molecules of increasingly complex nature have been synthesized.[8]

These elegant accomplishments have shared two common features that were inherent in the original design. Firstly, many syntheses have been based on a strategy that focuses on a reaction type as a key step. The feasibility of such reactions particularly in the context of a multistep synthesis has brought fourth general strategies, applicable to other types of target molecules, substructures of the same class, or of a totally different class. Secondly, in many instances, the products have been obtained in enantiomerically rich or even pure form.

The total synthesis of natural products has carried with it an aura of elegance and even romance over the years. In spite of its critics, certain aspects of synthesis will remain as a viable and active research endeavor, particularly if the targets are well chosen, and if the element of innovation is combined with practicality. For example, imipenem, a derivative of the potent β-lactam antibiotic thienamycin is manufactured by total synthesis today.[9] Thus, synthesis with its shortcomings, will always be the basic day-to-day task for the chemist. Recent advances in biotechnology and other processes inspired from nature have enriched our science enormously, broadened our horizons, and deepened our vision for the future. Synthesis must take into account such amenities and a synthesis plan should consider *all* possible approaches regardless of their seemingly "far off" nature.

"He (or she) who sits at the bottom of a well to contemplate the sky, will find it small"
Han-Yu (768-824)

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 1).

THE AGE OF OPTICALLY PURE PRODUCTS

With few exceptions, the biological activity of optically active organic molecules is invariably related to enantiomeric purity. Stereochemistry is therefore an important link between biology and chemistry, a situation which has been exploited by nature and imposed upon it by the process of natural selection. Recent initiatives related to the drug industry in particular have emphasized the acute need to test optically pure stereoisomers separately,[10] and to ultimately design stereoselective processes that produce the more active (and less toxic) component. Stereochemical control has therefore become an operational issue in everyday laboratory practice.

BIO-SCIENCES ⟷ ORGANIC SYNTHESIS ⟷ APPLIED SCIENCES

THE MEANS: EMERGENCE OF NEW STRATEGIES, APPROACHES, CONCEPTS, METHODOLOGY, ETC.

THE END: ACCESS TO BIOLOGICALLY IMPORTANT COMPOUNDS, PROCESSES, ETC.

THE BEGINNING: DISCOVERY OF A NEW BREED OF MAN-MADE MOLECULES, CATALYSTS, ETC.

Figure 1. Organic synthesis, the means, the end or the beginning?

One of the main differences in synthesis planning today compared to the accomplishments of the recent past is the necessity to produce optically pure molecules *avoiding resolution as the last step*. This "condition" has brought forward a tremendous burst of innovation in stereocontrolled processes particularly with regard to asymmetric synthesis[11] and other strategies,[12] and it has changed our outlook on synthesis planning. There are at present two general philosophies in the quest for optically pure products, (Figure 2). Each strives to create an enantiomerically or diastereomerically enriched (or pure) advanced intermediate with the highest possible level of functional and stereochemical overlap with the intended target or a given substructure. A number of years ago, the term chiron,[13] which is derived from chiral synthon, was suggested for such intermediates.

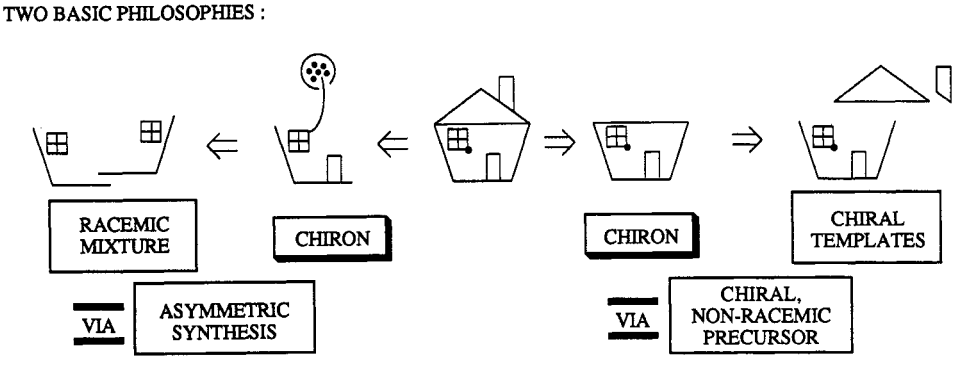

Figure 2. Access to optically pure molecules. Chirons (chiral synthons) generated via asymmetric processes or derived from nature (chiral templates)

Chirons are available through the elaboration of existing functionality in small naturally-occurring optically pure starting materials such as amino acids, carbohydrates, hydroxy acids, terpenes, etc... or from enzymatic, microbiological or biotechnologically derived sources. The chemical manipulation of such chiral templates to chirons by systematic functionalization normally relies on "resident" chirality for internal asymmetric induction. This approach has aesthetic appeal in addition to its predictive power and practicality (Figure 3). A large number of natural products belonging to different classes have been synthesized using this approach.

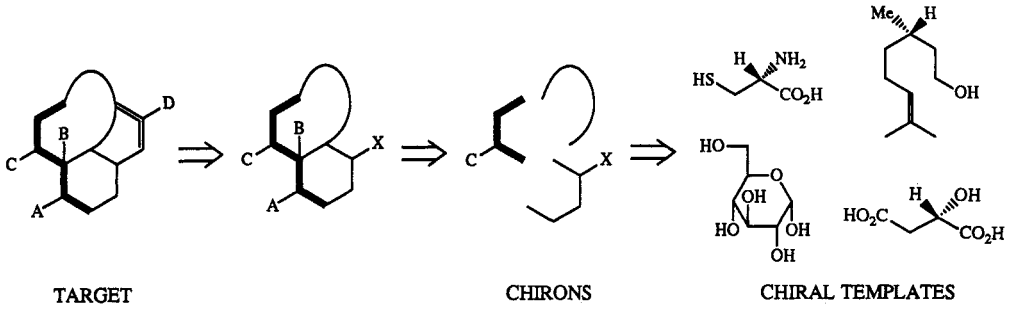

Figure 3. Total synthesis using the *Chiron Approach*

Asymmetric synthesis,[11] through a variety of techniques constitutes another source of chirons, particularly when one or two stereogenic centers are intended per reaction, with the exception of the asymmetric versions of the Diels-Alder reaction.[14] Asymmetric induction can be achieved generally via internal auxiliary-dependent processes, internal, resident chirality dependent processes (single of double stereodifferentiation) or through the influence of external reagents, catalysts, etc. (Figure 4). Asymmetric synthesis has a particularly creative aspect, and in many instances it too has the strong attributes of predictability and practicality.[15] The synthesis plan for a given target molecule may therefore draw upon one or more of these strategies in order to ultimately generate optically pure products.

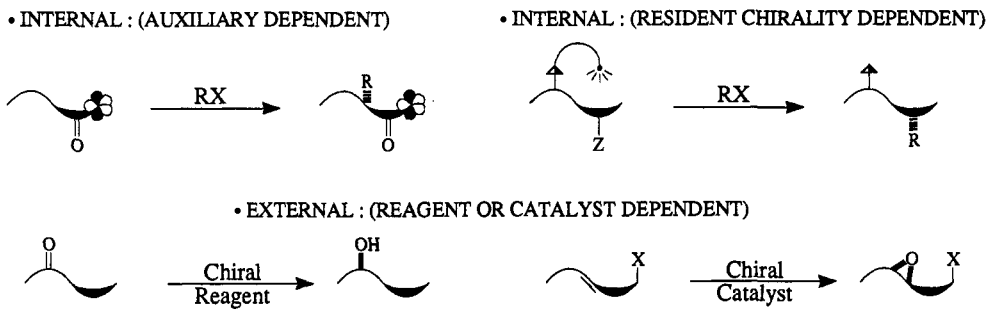

Figure 4. Types of asymmetric induction

STRATEGIES IN SYNTHESIS PLANNING – ANATOMY OF A SYNTHESIS

The thought process that leads to a synthesis plan (a blueprint) is a fascinating topic of discussion and conjecture. Figure 5 illustrates the anatomy of a synthesis and the various phases of operation be it visual, logistic or practical. For a given target molecule, there is an element of analysis and discovery from which a general strategy and a particular approach may emerge. The choice of one approach or another may ultimately dictate the outcome of the entire operation. There are at present two main approaches in total synthesis, namely the *Chiron* and *Synthon* approaches, that are applicable to a large variety of structurally diverse molecules. In addition, there are a number of other individual approaches that address the synthesis of specific classes of compounds or a particular type of substructure. The choice of a particular strategy or approach is the result of a careful analysis of several factors. Ultimately however, the final plan depends on the creativity, ingenuity and at times the preferences (biases?) of the investigator. It is this very feature that gives organic synthesis its unique character and creative flair.

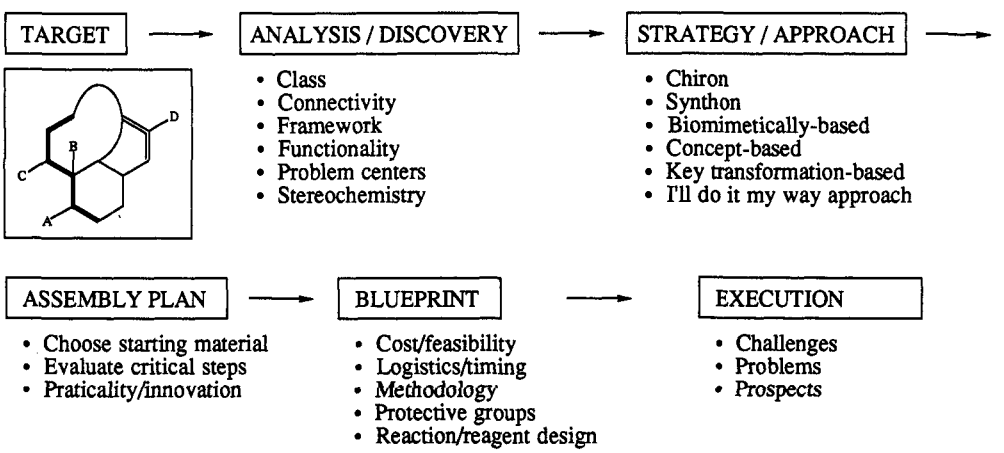

Figure 5. Anatomy of a synthesis

A. Precursor-based approaches

The ready availability of a starting material may lead to a viable strategy for the synthesis of a variety of structurally unrelated targets. This is usually the result of a prior successful experience and the realization of the potential of a given precursor. Grieco's use of the bicyclo[2:2:1]methylheptanone system as a key precursor to compactin,[16] thienamycin[17] and a substructure of tylonolide[18] is one example of such an approach. The butenolide replicating lactone strategy to polypropionates and deoxypropionates is another example.[19]

B. Transformation-based approaches

A key reaction may constitute not only a highlight in a synthetic sequence, but it may also be an inherent part of the strategy itself. Here we can cite the implementation of the asymmetric aldol reaction in the synthesis of polypropionate-derived natural products,[20] the hetero-Diels-Alder reaction[21] for the construction of the same type of molecules as well as carbohydrates, and the Ireland enolate Claisen rearrangement[22] for a variety of polyether-type antibiotics. In each case, the authors have demonstrated the viability of their respective methodologies in a number of challenging syntheses, hence the emergence of a general approach.

C. Biomimetically-inspired approaches

The polyene cyclization technology pioneered by W.S. Johnson[23] and applied to the total synthesis of steroidal structures represents a unique approach that addresses a specific class of natural product.

D. Concept-based approaches

Rigidity, conformational bias and stereoelectronic control can be the basis for key steps in a given synthesis. Woodward's synthesis of erythronolide A using a dithiadecalin template,[24] his synthesis of $PGF_{2\alpha}$[25] using a constrained 1,3,5-cyclohexane triol, and the Deslongchamps[26]-Ireland[27] independent approaches to macrolide antibiotics based on stereoelectronic control in dioxaspiro acetal templates, are some examples of concept-based approaches.

E. Other approaches

Several other elegant approaches have been reported over the years that address the synthesis of individual target molecules. Each offers its own key steps, highlights, particularities and oftentimes touches of genius.[8]

THE CHIRON AND SYNTHON APPROACHES

The *Synthon Approach* first proposed by E.J. Corey[28] and widely used in synthesis planning involves the generation of idealized fragments, intermediates,etc. by bond disconnection in a retrosynthetic sense.[8] In this approach, disconnections are generally made at logical sites which facilitate bond formation in the forward sense, based mostly on previous experience. *It is generally the type of functionality present in the target molecule and the chemical feasibility or precedent that dictate the strategy.* Thus the presence of a lactone or its equivalent in the target molecule may lead to a cycloalkanone precursor which itself could be derived from a cycloaddition of a diene and a ketene. The critical issues are concerned with selectivity in the cycloaddition as well as in the Baeyer-Villiger oxidation. But what if the oxidation involves the less substituted side of the cycloalkanone? Clearly another synthon strategy, or an altogether different approach must be sought. The generation of a cyclopropane ring may rely on a classical insertion reaction between a diene and an appropriate carbene in the synthon approach. The *Chiron Approach* may suggest a functionalized cyclopropane which in turn can be obtained from a chemoenzymatic approach involving a mesodiester using an esterase.[12] Stereochemical issues in the relative or absolute sense are usually not a prime concern in the synthon approach. However, disconnective analysis and the generation of synthons does not prevent us whenever possible to consider optically active intermediates. This can be achieved through the aegis of asymmetric processes, for example, or relying on an optically active natural product as starting material. These notions are illustrated in Figure 6.

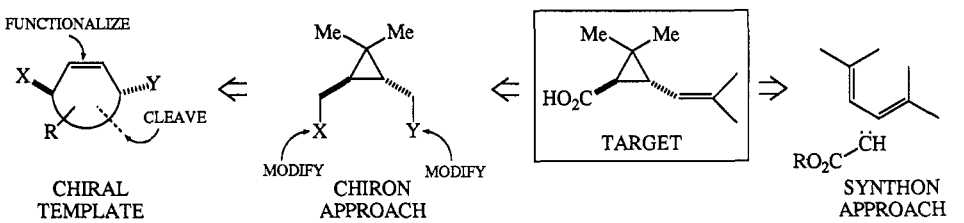

Figure 6. The Chiron and Synthon approaches

The *Chiron Approach* to synthesis involves disconnections of strategic bonds in a target molecule with minimum perturbation of stereogenic centers. A maximum overlap of functional, stereochemical and carbon framework between target (or substructure) and the chiron is ideally sought. Thus vicinal and alternating functionality, and ring systems for example are preferably maintained in the disconnective process en route to a chiron.The *Chiron Approach* capitalizes on the conservation of stereochemistry in going from target to chiron to the chiral template. Chiral substructures become the primary targets for synthesis. *It is the type of substructure and its possible chiral progenitor that dictate the strategy and chemistry to be carried out.* By relating such substructures to specific chiral starting materials at the onset, the scenario for a strategy is established, the synthetic routes are truncated to a select few, and the main issue becomes one of *how to best proceed in the forward direction from precursor to subtarget and target.* The synthon approach on the other hand generates a synthesis "tree" with each branch leading to a starting material, hence multiple routes to choose from . Although both approaches rely on a visual disconnection initially, the operational aspects can be quite different in view of the divergence of the philosophy of bond breaking steps. In some instances, both approaches may converge and a synthon may also be a chiron.

SYNTHESIS OF OPTICALLY PURE MOLECULES FROM CHIRAL TEMPLATES USING THE CHIRON APPROACH

As already discussed, the basic premise of the *Chiron Approach* is to relate some aspects of functional group and stereochemistry present in the target molecule to those present in a suitable optically pure starting material which is used as a chiral template, (Figure 3). This type of approach has been used for many years and recently formalized into a general approach.[11] Below we will demonstrate selected examples which involve a wide-cross-section of target structures that have been synthesized from various chiral precursors.

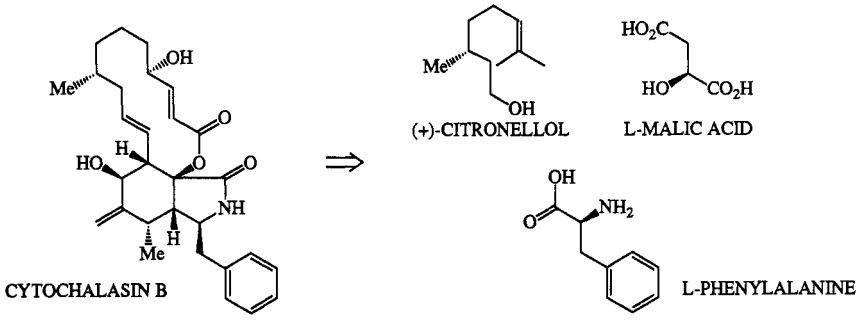

Figure 7. Apparent chiral templates in cytochalasin B

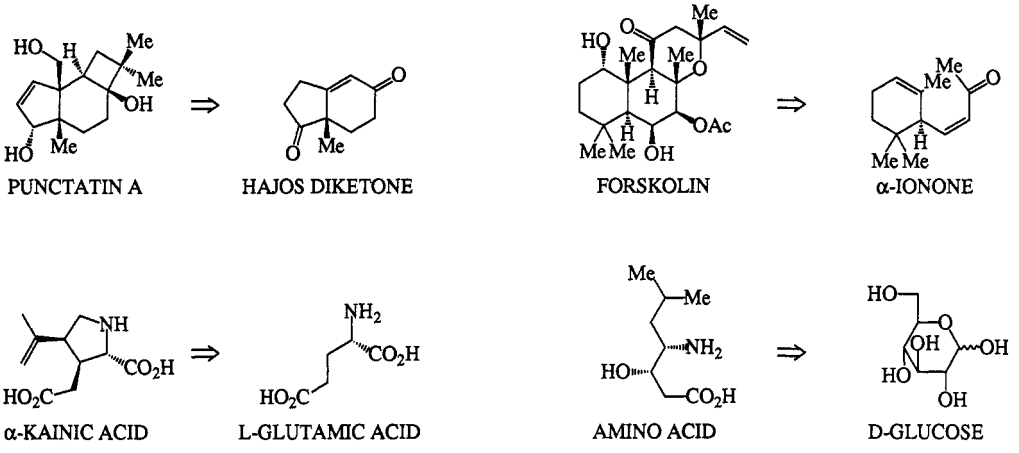

Figure 8. Partially hidden chiral templates in punctatin A, α-kainic acid, forskolin, and an amino acid from pepstatin.

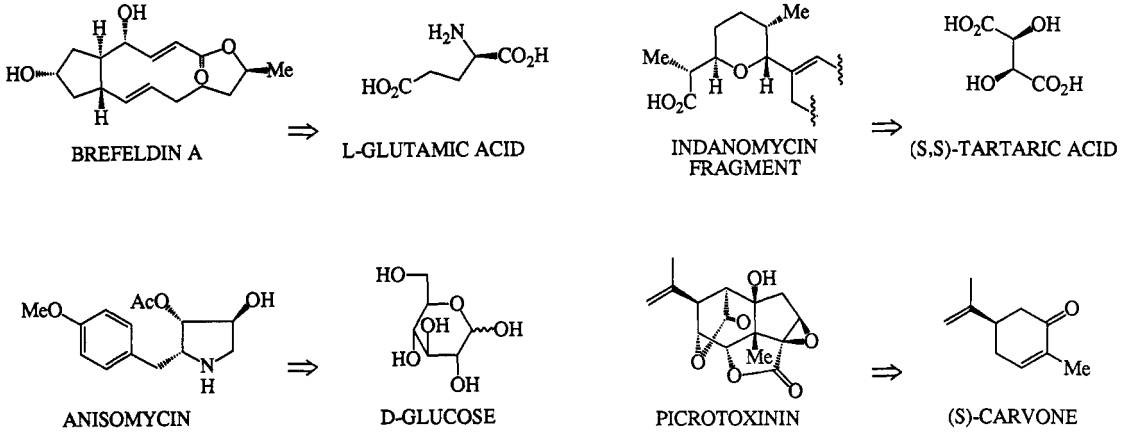

Figure 9. Hidden chiral templates of the amino acid, carbohydrate, hydroxy acid and terpene types.

In general the chiral templates are either *apparent, partially hidden, or hidden* in the carbon framework of the target structure. Selected examples are shown in Figures 7, 8 and 9 with greater emphasis on structures with partially hidden and hidden precursor frameworks. Figure 7 illustrates Stork's total synthesis of cyclochalasin B,[29] where the carbon frameworks of L-phenylalanine, L-malic acid and (+)-citronellol are clearly "seen" in the target structure. Examples of syntheses where the chiral templates are *partially hidden* in the target structure are shown in Figure 8. Thus, the frameworks of the Hajos diketone, L-glutamic acid, α-ionone and D-glucose can be recognized in the structures of the corresponding targets, punctatin A,[30] α-kainic acid,[31] forskolin[32] and an amino acid from pepstatin[33] respectively.

The *Chiron Approach* using chiral templates that have no immediate relationship to the target structures (*hidden templates*) is the most intriguing from the standpoint of design and discovery. The examples shown in Figure 9 illustrate the ingenious utilization of amino acids,[34] carbohydrates,[35] hydroxy acids[36] and terpenes[37] in the total synthesis of brefeldin A, anisomycin, indanomycin and picrotoxinin respectively.

THE PSYCHOBIOLOGY OF SYNTHESIS PLANNING

Aristotle is known to have said "Thought is impossible without an image". Indeed, much of the chemical "thinking" in synthetic organic chemistry is done through the imagery of structural formulae. Consider for example the process of synthesis planning for a given target molecule which invariably starts with a visual structural representation on paper. What follows in the mind's eye is a fascinating series of processing events that are controlled to a large degree by the right and left hemispheres of the brain. The psychobiological implications of the bilateral asymmetry of the human brain have been extensively studied in other areas.[38-40] It is well known that visual, spatial, intuitive, and relational processing is a characteristic of the right hemisphere of the brain, while the left hemisphere is concerned with verbal, rational, symbolic and analytic processing. Whereas the left hemisphere analyzes over time, the right hemisphere synthesizes over space. These quasi sub-conscious and instantaneous processes have a profound influence in synthesis planning. Figure 10 illustrates these notions in a flow-type diagram.

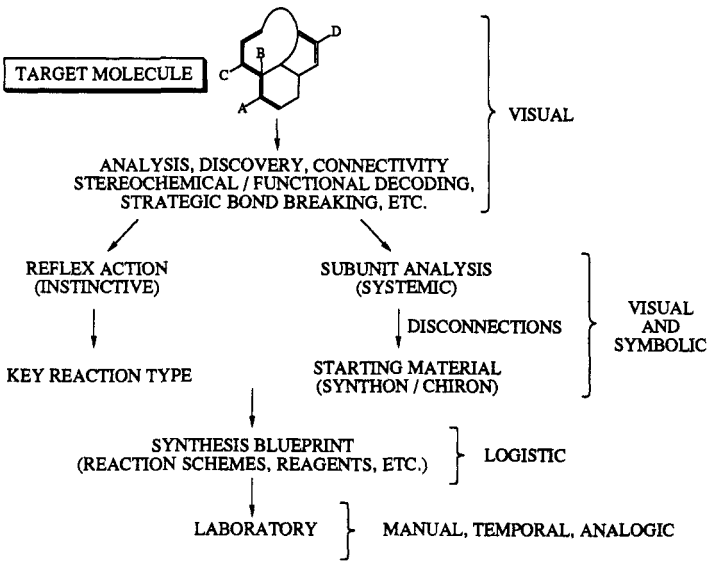

Figure 10. Visual and symbolic effects in synthesis planning.

We start by drawing a symbolic shape (as in the structure of a target molecule), which generates verbal instructions as a result of the eye-mind processing, culminating finally with a synthesis scheme. Our initial contact with the molecule in question is visual, where we analyze and discover functional, stereochemical, bond-breaking and bond-forming processes. What follows is a combination of visual and symbolic events which may involuntarily lead to a key name reaction through reflex action, or a key disconnection to a suitable precursor. A synthesis blueprint eventually results which is then tested out in the laboratory. Let us take the specific example of desacetyl forskolin and examine the psychobiological implications of the brain's bilateral asymmetry in the planning of a synthesis[41] (Figure 11). As in any analysis, be it chemical or not, there emerges a series of "signals" that are the result of visual and logical processing. For example, if the unbiased eye makes contact with the B ring, and if in addition one focuses on the cis-diol, reflex action may instantly suggest a Diels-Alder reaction as a key step followed by a cis-hydroxylation. A second reflex action may lead us to think in terms of an intramolecular Diels-Alder reaction. Thus, visual contact coupled with analogic and deductive reasoning make us "see" the synthesis in a certain way, (the "aha factor"). Another scenario may begin by focusing on the A ring harboring the gem-dimethyl group or catching a glimpse of it with the corner of the eye while looking at ring B. Reflex action, or a predisposed notion to use a chiral template as a building block may make us think of α-ionone. An altogether different approach will now emerge with the "discovery" of α-ionone, compared to the Diels-Alder approach (chiron vs synthon?). The feasibility of the two approaches is then tested on paper, simulating the entire synthesis with appropriate reagents including the use of protective groups, etc. It is at this junction in synthesis planning that biases and fixations resulting from the initial analysis enter into consideration, adding yet another mental barrier to cross in the long climb to the "top of the mountain". In such cases, new analyses, fresh outlooks and an unbiased approach could be beneficial.

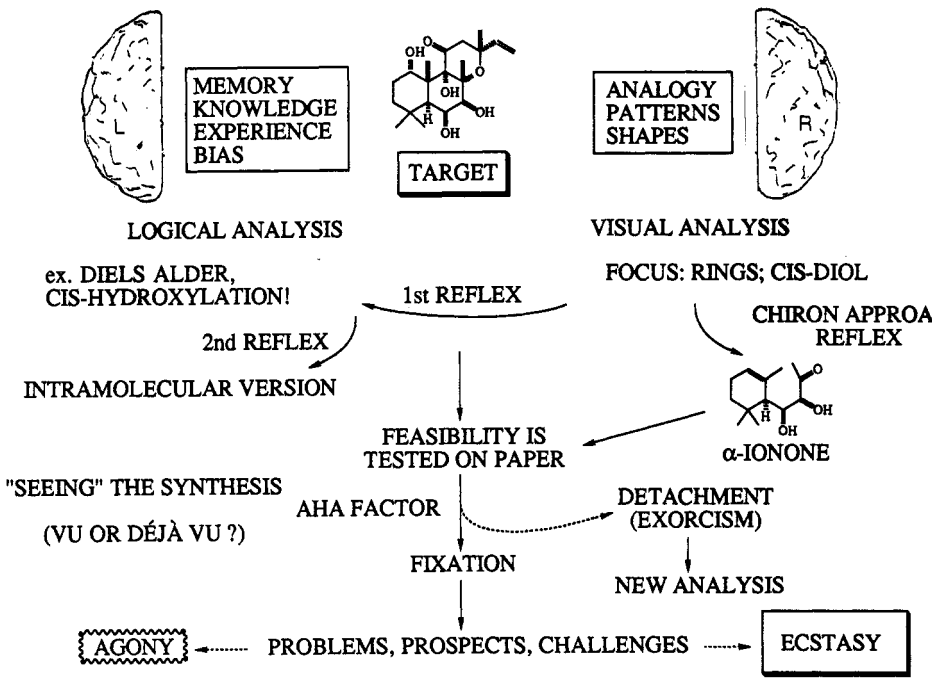

Figure 11. Psychobiology and organic synthesis

From the above analysis we can advance the hypothesis that retrosynthetic or disconnective analysis in synthesis planning is processed mainly by the right hemisphere of the brain. The sequential character of our thought process transforms the visual image of the target molecule into smaller subunits (chirons/synthons) or into fragments resulting from imaginary bond breaking. It follows that the synthesis proper (forward sense) is processed mainly by the left hemisphere of the brain. Memory, experience, logic and an acute sense of timing of the chemical events play a critical role in the choice of reagents, conditions, protective groups and other details involved in the elaboration of a synthesis scheme. Figure 12 depicts these notions and illustrates the key fragments in a recent total synthesis of dihydromevinolin.[42]

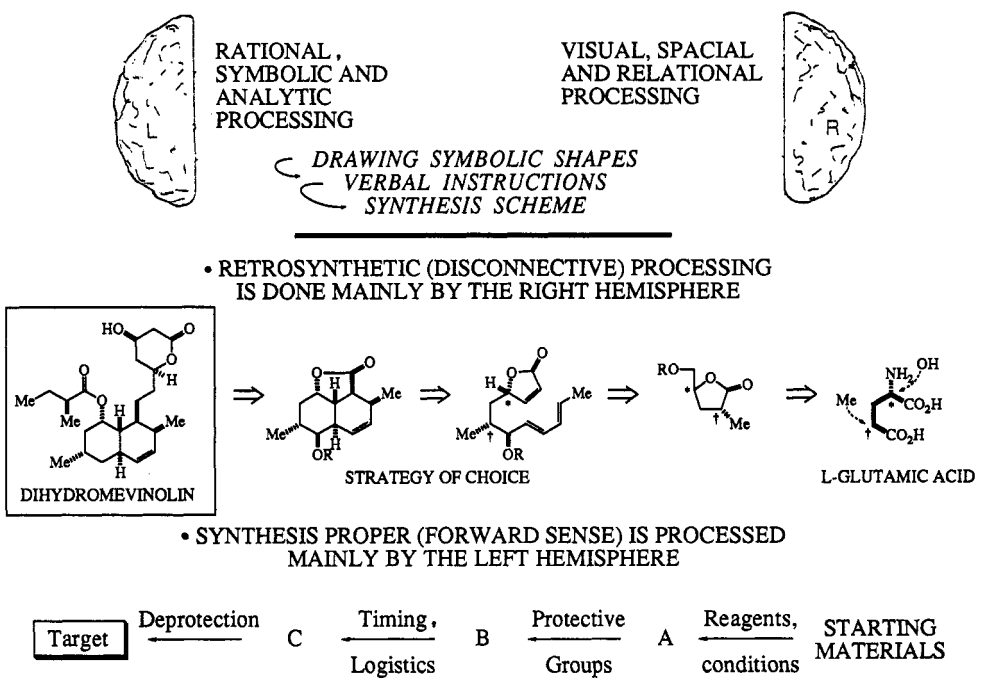

Figure 12. Retrosynthetic (disconnective) analysis and synthesis proper as processed by the brain

Having discussed our views of the psychobiological basis of chemical reasoning, particularly as it relates to synthesis planning, the question may be asked: "How does this make us better synthesis planners?" We are all somewhat biased in our thinking, mainly because of our different professional, sociological and psychological backgrounds. This in turn provides the individuality of thought and variety of approaches that characterizes organic synthesis. Although we are all dependent on literature precedents in the pursuit of our individual objectives, there is quite often an element of creativity associated with each and every synthetic approach to one and the same target.

Since visual contact is primordial in synthesis planning, perception skills and a knowledge of which bonds to break in a disconnective sense are important. In this regard, it would be interesting to be able to approach a synthesis design problem *with a totally unbiased view*, which is not an easy task. Imagery leads to instant flash thought which must be analyzed and weighted against "better" or "worse" ones, all with a clear vision of the consequences of each thought process. In order to extricate one's thoughts from precedents that are well encoded in our memory or subconscious regarding the same or a related structure, it might help to a. write the molecule upside down, b. *not* to name the molecule, c. to work with the mirror image, d. to work with a different or disguised structural representation (ex. Fischer or extended projection).

ON THE PROBLEM OF PERCEPTION

Since our first contact with a given target structure for synthesis is a visual one, it is inevitable that perception plays a critical role in our thought process and in the emergence of a viable strategy. Moreover, as discussed above, different individuals may have altogether different approaches based on what they "see" in a structure and how they choose to break bonds. Perception plays an important role in the *Chiron Approach* which seeks to relate chiral substructures in the target molecule to optically active starting materials. When the relationships are evident by simple visual overlap, the task of chemical manipulation becomes the major issue. However, the mere drawing of one of the structures in a different perspective or turned upside down, will momentarily throw us off and the relationship that was so obvious before will require a closer scrutiny. Figure 13 depicts the structure of acivicin, drawn in different perspectives by different authors who have described independently conceived and executed syntheses.[43] Only the last structure can be easily related to an amino acid precursor. Consider next, (S,S)-tartaric acid in three representations and its possible utilization in the synthesis of exo-brevicomin.[44]

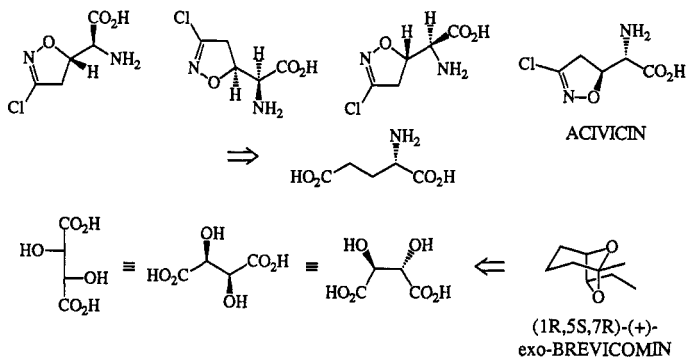

Figure 13. The many faces of acivicin (top) and of D- or (S,S)-tartaric acid

The more intriguing cases are those where substructures eventually find their synthetic origins in totally unrelated starting materials. How are those perceived? Is it through exceptional powers of vision and experience, or sheer genius? Consider for example the elegant synthesis eucannabinolide from (S)-carvone[45] where the entire carbon framework of this precursor was utilized (Figure 14)! The synthesis of the California red scale pheromone[46] from a known fragmentation product derived from (+)-camphor represents an example of the *Chiron Approach* where the target structure is *totally* unrelated to the precursor structure.

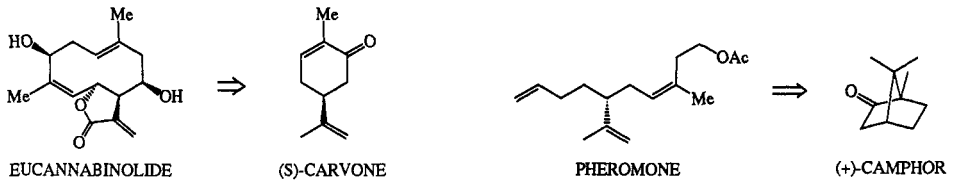

Figure 14. Very hidden chiral templates wherein the target is (S)-carvone?

Being cognizant of these problems of recognition, relations and difficulties arising from stereochemical features in general, both in teaching and in research, we turned to the computer for help. Specifically, we were interested in developing a computer program that could aid in certain aspects of stereochemical decoding an in helping us capture the "missing" information that results from dealing with flat 2-dimensional structures on paper.

THE CHIRON COMPUTER PROGRAM

This is an interactive computer program that was developed in our laboratories between 1984 and 1990, representing a 9 man/year effort. The Chiron Program offers the user some unique capabilities in the analysis and perception of structural, functional and stereochemical features in molecules, and in heuristic synthesis planning.[47,48] Its strongest attribute is the speed with which it can carry out such operations, since these would normally require a much longer period of time if done visually, even with the aid of molecular models. Thus, the program is able to "see" a molecule in a multitude of perspectives, and it will present the user with possibilities for relational analyses with other molecules that may have otherwise eluded the human eye.

The Chiron Program (68,000 lines of Pascal code) consists of several modules, each with a number of options. The CARS-2D menu (Computer Assisted Reaction Schemes and 2-D Drawing) offers the user several ways of rapidly drawing molecules and manipulating them. In addition to free-hand drawing, as well as with the use of specific templates, one can use the GRID option which allows chemical structures to be drawn uniformly by connecting the corners of a hexagonal grid. Imperfect structures drawn in the free-hand mode can be restored to correct relative dimensions and angles using the SHAPE option. A useful feature in CARS-2D is the PEPTIDE BUILD option, where user-designated amino acids are automatically linked as peptide bonds and displayed as a linear chain. It is also possible to REPLACE, INSERT, REVERSE and EXTEND with other amino acids (D- or L-), as well as with other molecules. This option greatly facilitates the drawing and conceptual planning of molecules intended as non-peptidic analogs of naturally occurring peptide-derived enzyme inhibitors for example.The program has provisions for storing molecules and for searching duplicate structures using the Morgan algorithm. Thus, diastereomeric and identical structures can be found using this option.

The Chiron Program has an automatic 2D→3D transfer capability using the CARS-3D menu, where the reflections of a molecule are simultaneously projected in horizontal (floor) and vertical (wall) planes. Rotating such molecules along a given axis gives the user a number of "hidden" perspectives, particularly since the reflections in the two planes are automatically changed also. The REAL-TIME option in CARS-3D offers a number of unique features, including stereoscopic viewing, simulated docking of two structures, ball and stick models, X-ray structural input and bond highlighting. An example of 2D→3D transfer of forskolin with highlighting is shown in the insert in Figure 15. Structures drawn in CARS-3D are not minimized to their most favorable conformations. The program provides the user an interface with MACROMODEL, MODEL, SYBYL, REACCS, X-ray data bases and other SMD-related systems.

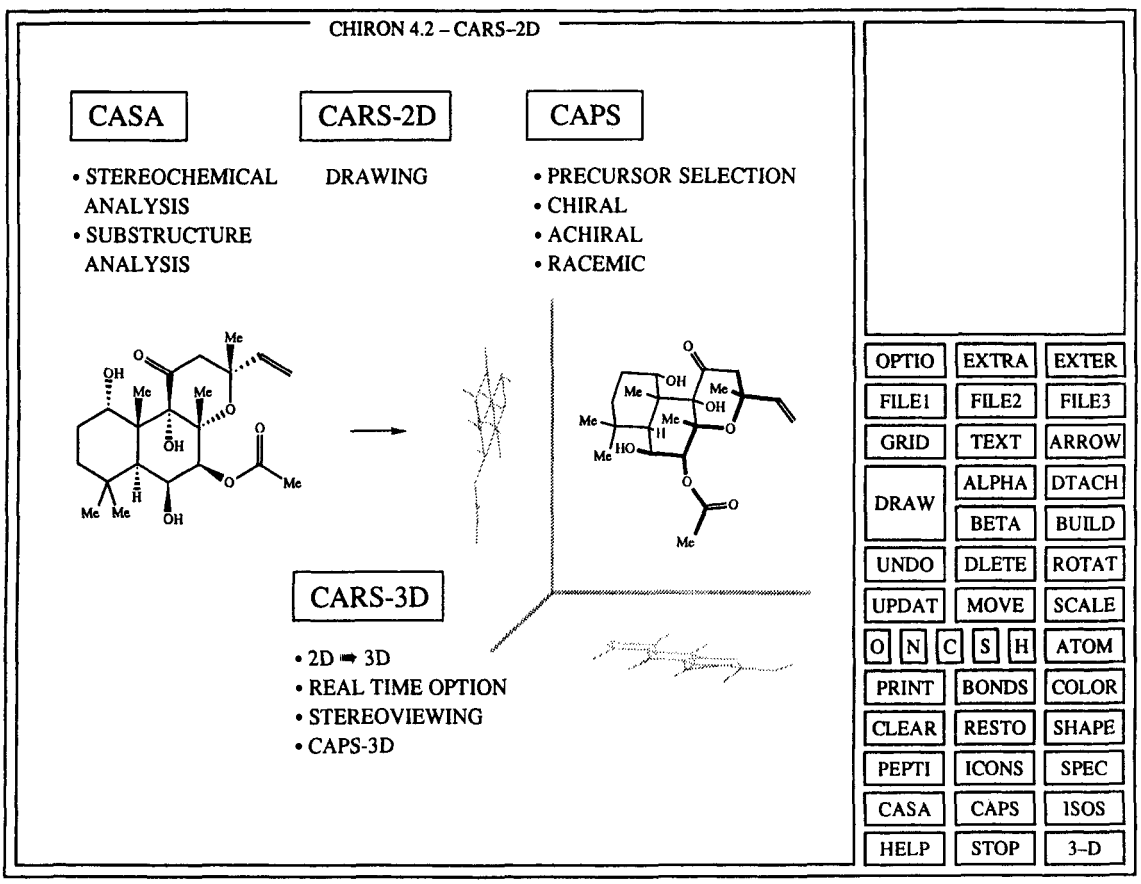

Figure 15. The CARS-2D menu and an insert from the 2D→3D transfer of forskolin, showing "wall" and "floor" reflections.

A. Stereochemical decoding

Figure 16 shows the output from CASA (Computer Assisted Stereochemical Analysis) for FK 506, where Fischer and extended projections are automatically generated by pointing to C_{12} and C_{27}. Figure 17 shows an example of the Chiral Substructure Search option where identical segments of four carbons or more are found by the program and highlighted in bold lines with an arrowhead showing the direction of overlap. This feature enables the user to find common precursors to structurally different molecules. For example, the biosynthetically equivalent C_{23}-C_{27}, C_2-C_6 and C_4-C_8 subunits in FK 506, erythronolide A and monensin A respectively are rapidly found by the program.

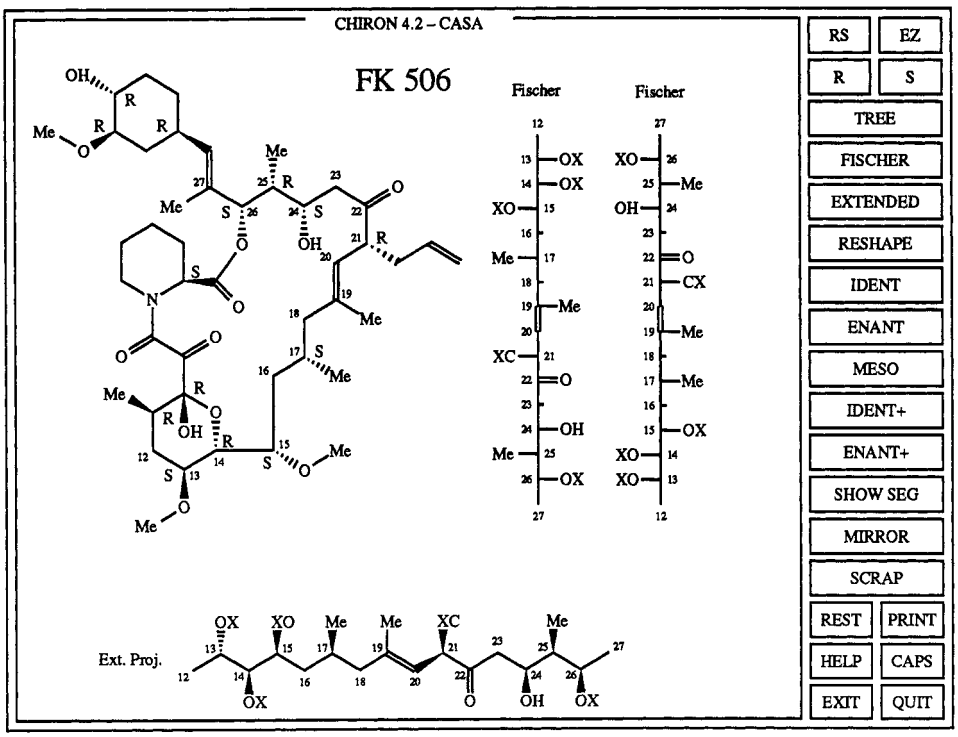

Figure 16. Assignment of R/S stereochemical notation and drawing of projections by the Chiron Program

B. Heuristic analysis and selection of precursors in synthesis

The main feature of the Chiron Program deals with a heuristic analysis of target molecules and the search for suitable starting materials for synthesis from a data base consisting of over 2000 chiral non-racemic, racemic and achiral precursors. The selection of precursors relies on a process of pattern recognition that involves a maximal overlap of carbon skeleton, functionality and stereochemistry with the target structure or a user-designated substructure.

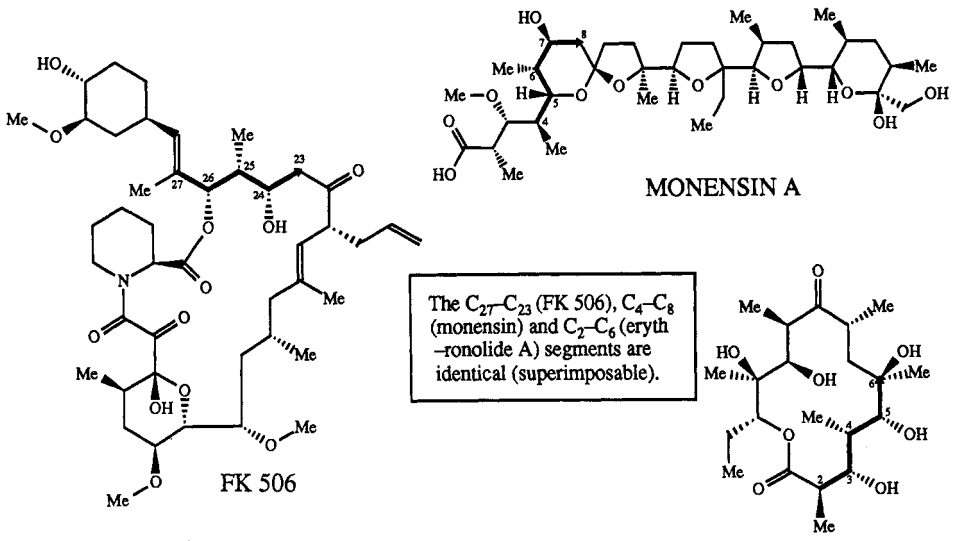

Figure 17. Chiral substructure searching

As in the *Chiron Approach* the program seeks initially to find precursors that have the best functional and stereochemical convergence with the target. Failing to find such precursors, the program will allow a series of standard transformations that convert a functional group into another (inversion, reduction, oxidation, etc.). The user can search for precursors based on one or more of the following parameters: a. type of carbon skeleton (acyclic, carbocyclic, aromatic, etc.), b. functional groups present or their equivalents (OH, terminal olefin, NH_2, etc.), c. number of stereogenic carbon atoms (3 or more), d. chiral non-racemic, achiral, and racemic precursors, and e. cleaved and reshaped precursors. Searches take a few minutes or less, with the number of hits appearing on the screen as the search progresses. The search can be interactive or in a batch mode. Precursors found in a given search can be displayed on the screen in four ways. a. RSP (rapid scanning of precursors), b. PLACE (where the precursor structure and its overlap characteristics appear on the screen), c. TRANSFORMATIONS (same as PLACE with additional key words pointing at sites to be chemically modified) and d. LIST (listing of the names, references and overlap features of precursors). A scoring system has been incorporated in the search process, that takes into account the degree of feasibility of the transformations, the overlap of carbon skeleton and best convergence of functional groups as well as stereochemistry. A flow chart of CAPS commands is shown in Figure 18.

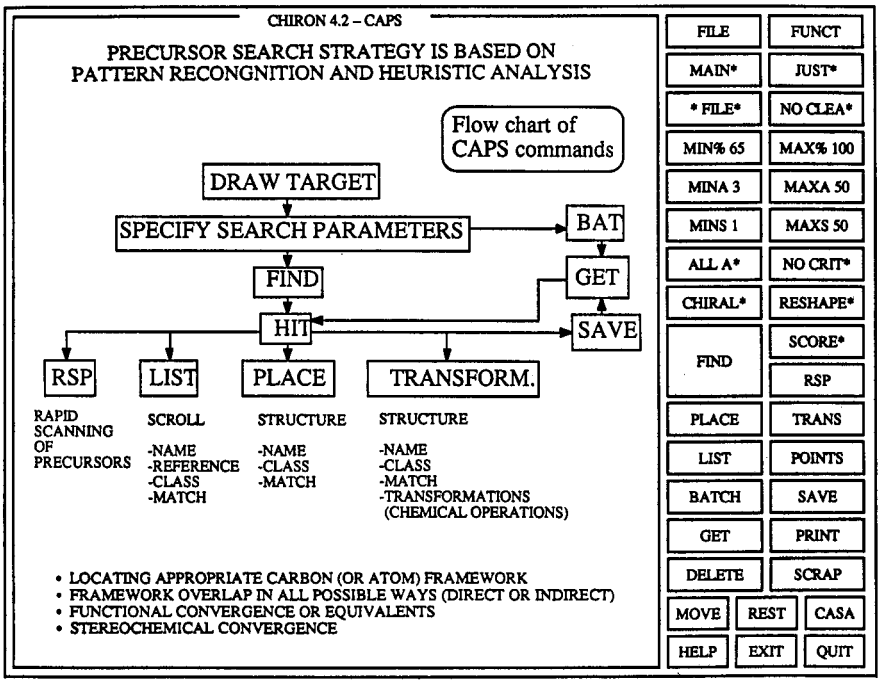

Figure 18. CAPS menu and flow chart of CAPS commands

C. Chiron analysis of selected target molecules – direct overlap with chiral templates

The Chiron Program will analyze the carbon framework of the target molecule, regardless of the perspective in which it is represented and it will relate its functional and stereochemical features to those found in the "best" precursor in the database. Preference is given to matching a larger span of carbon atoms and rings if applicable. Figure 19 shows the results of such searches for a few targets that have already been synthesized. The TRANSFORMATIONS option indicates a series of chemical events designated by descriptors or abbreviations. These simple "commands" give the user a sense of sequence and timing in the process of chemical manipulation of the particular precursor molecule. They also enhance the reflex factor that relates a key transformation to a name reaction, which has pedagogic value.

Thus, in the case of punctatin A, the program quickly found the Hajos diketone, also used by Paquette,[30] as a versatile chiral template, in addition to other candidates. A score of 71% was attributed by the program which reflects bonuses for the excellent cyclic overlap, the presence of the angular methyl group with the desired stereochemical orientation, and the anticipated feasibility of the transformations. In the second example B, the program proposed α-ionone as a precursor, once again based on an excellent match with the A ring, including the gem-dimethyl groups as well as the stereochemistry at the C_{12} junction, which is reflected in the score. One of the recently completed total syntheses of forskolin by Corey and coworkers[32] made use of α-ionone as a versatile chiral template. Oppolzer's synthesis of α-kainic acid from L-glutamic acid[31] used an intramolecular ene reaction to construct the trisubstituted pyrrolidine. The program readily recognized L-glutamic acid as a chiral template as seen in example C. Finally, the program chose a highly functionalized cyclopentane derivative, readily available from camphor,[49,50] as a precursor to ring C of ophiobolin C, which was also Kishi's choice.[51,52] In all of the above examples the program depicted the precursor structures on the screen in a manner which shows the best overlap. This facilitates the relational analysis between precursor and target structure (or substructure), and it allows one to conceive of different ways to complete the synthesis by systematic manipulation of functional groups. For example,

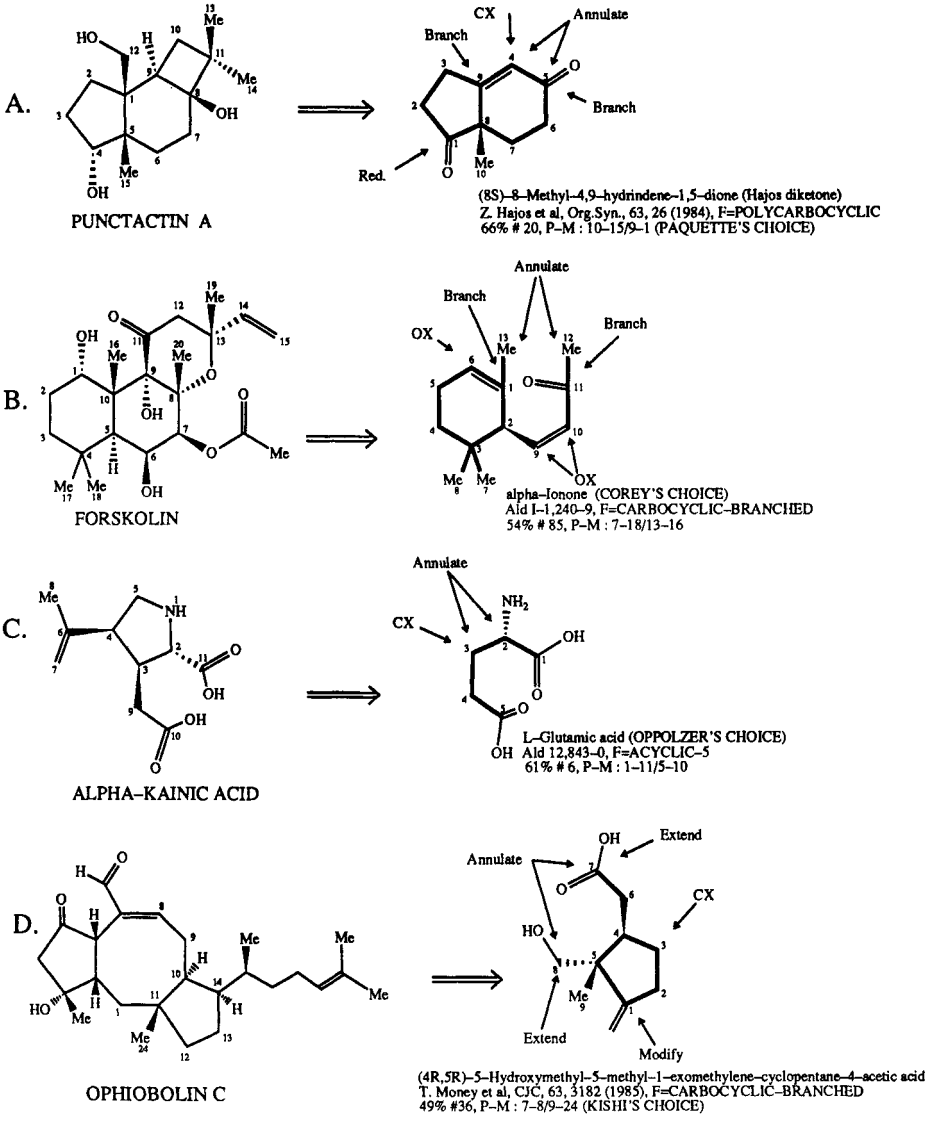

Figure 19. Chiron analyses of punctatin A, forskolin, α-kainic acid, and ophiobolin C showing selected precursors with excellent carbon framework, functional and stereochemical overlap.

the program recognizes the need to add another ring to the Hajos diketone in the synthesis of punctatin A. It also indicates the chemical transformations required to "complete" the convergence. The user is then prompted to conceive of an annulation method and to consider the correct sequence of reactions, before formulating an actual plan of attack. Thus, while the visual part is enhanced through the heuristic search method in the program, the intellectual exercise of logical thinking and devising bond forming processes remains the domain of the user.

In Figure 20, we demonstrate other examples of precursors selected by the program for the synthesis of gascardic acid,[53] hybridalactone[54] and eucannabinolide.[45] These natural products were each synthesized from precursors *different* than the ones shown here since the strategies and approaches differed. Hence a comparison of the precursors shown here with those actually used is not necessary. Thus in the case of gascardic acid, the camphor-derived precursor emerged once again since a good level of carbon substitution is evident, particularly with the presence of an angular methyl group. The cyclohexenone precursor also gives the quaternary center with the possibility of extension and annulation. Note however that the overall scoring evaluation of this precursor takes into account the potential difficulties associated with the functionalization of the vinylic methyl function, hence the comparatively lower score. Carbocyclic precursors were also selected by the program for hybridalactone, and in both instances maximum stereochemical convergence was found. The Corey synthesis[54] of hydridalactone utilized (+)-bicyclo[3.2.0] hept-4-ene-1-one as a chiral template, which was also found by the program (not shown here). In the Still synthesis[45] of eucannabinolide the three contiguous stereogenic centers were introduced by a sequence of ingenious transformations starting with (S)-carvone and proceeding through an anionic oxy-Cope ring expansion of an advanced intermediate. In one of many "acyclic" matches, the program found a branched-chain carbohydrate which contains the desired 1,3-diol and an acetic acid appendage that converge with C_4-C_9 substructure of the target. The C_1 and C_6 terminal atoms of the precursor coincide with sp^2 carbon atoms in the target, a feature which favors this precursor even more as reflected in the score. A specific search for 5-carbon precursors with a

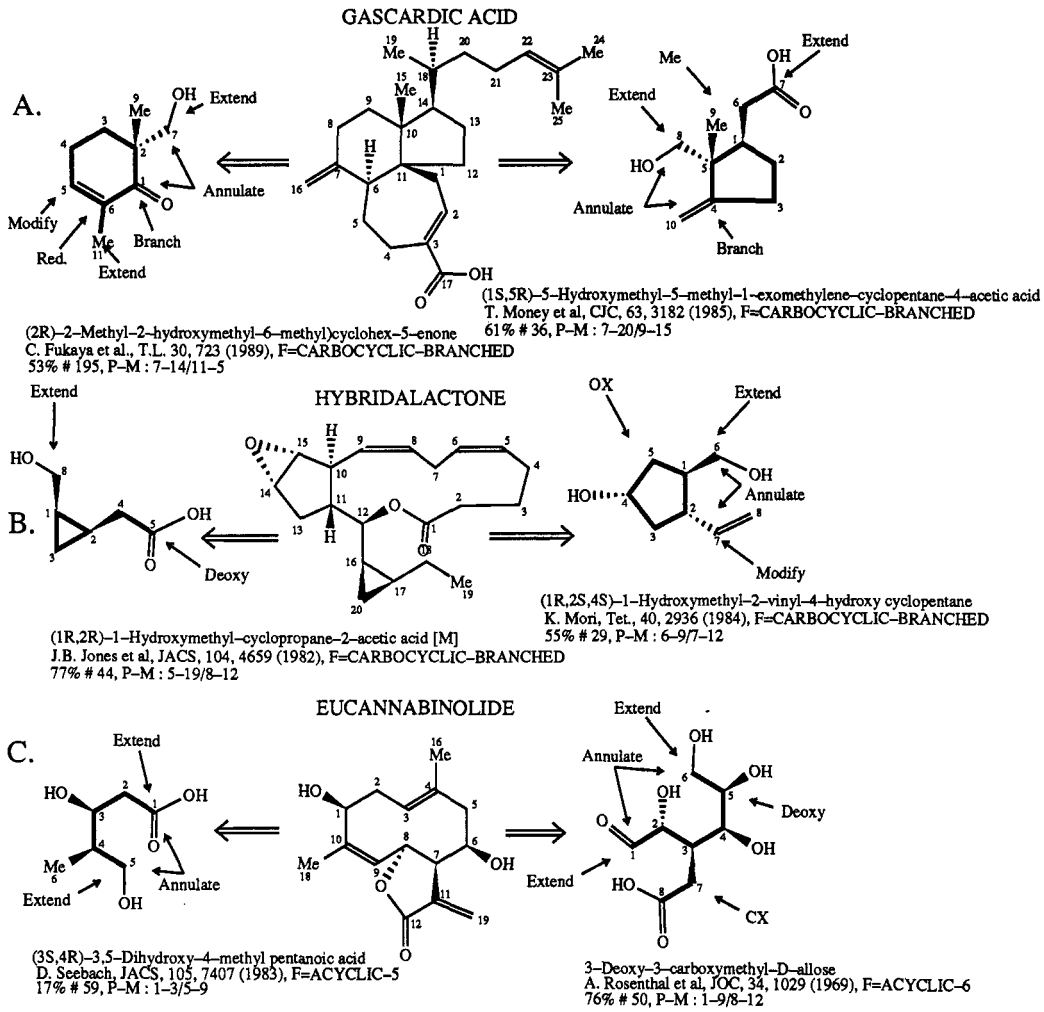

Figure 20. Chiron analysis and precursors for gascardic acid, hybridalactone and eucannabinolide showing direct template matching

secondary alcohol and a methyl group using the "functions" option led to (3S,4R)-3,5-dihydroxy 4-methylpentanoic acid. Although, the chirality at the C-methyl carbon will have to be destroyed en route to the vinylic system, there is good functional overlap otherwise. Other possibilities are shown in Figure 30.

The total synthesis of FK 506, a potent immunosuppressant was recently reported by Shinkai and coworkers at Merck.[55] The final assembly of FK 506 involved a number of enantiomerically pure fragments that were individually synthesized using different approaches. Figure 21 illustrates the output of the Chiron Program for FK 506, where quinic acid was found as a suitable precursor for the trisubstituted cyclohexane ring. This cyclitol was also used by the Merck group, who devised methods for the double deoxygenation of the C_2 and C_6 hydroxyl groups. Because of the nature of the substitution pattern in the carbohydrate and acyclic portions, the program tried to maximize convergence of the propionate and deoxypropionate-related subunits with appropriate precursors. Note the suggestion to use the dideoxy sugar as *a common precursor* to the C_{22}-C_{27} and C_9-C_{14} subunits in FK 506. In the first case, the convergence is quasi-perfect, but in the second case a hydroxylation-deoxygenation sequence is necessary. Since, a new stereogenic center must be created at C_{14}, a lower score is given to this precursor. Other more convergent precursors are also proposed for the carbohydrate subunit which maximize convergence with the existing functionality and stereochemistry (not shown here). The precursor suggested for the C_{18}-C_{22} subunit is shown in two perspectives by the program, where the terminal hydroxymethyl group can be considered as part of the macrolide chain (C_{18}) or as the vinylic methyl group.

The template approach to carbon framework matching instinctively leads us to make analogic juxtapositions. Consider for example, the target molecule shown in Figure 22, and (R)-5-hydroxy-2-piperidone as a possible starting material. The "normal" way to draw this precursor would be as shown to the left, with the lactam function coinciding with its counterpart in the target molecule. Indeed, the Chiron Program made the same assessment as shown in the retrosynthetic path A. Having made this choice, the program suggested the logical transformations seen in Figure 22 (A), which involve the introduction of unsaturation, and the formation of two carbon-carbon bonds. There remains an annulation-type process that accommodates the functionality and stereochemistry of the vicinal substituents in the cyclohexane ring. The hydroxyl group at C_5 could be the site of a C-C bond forming

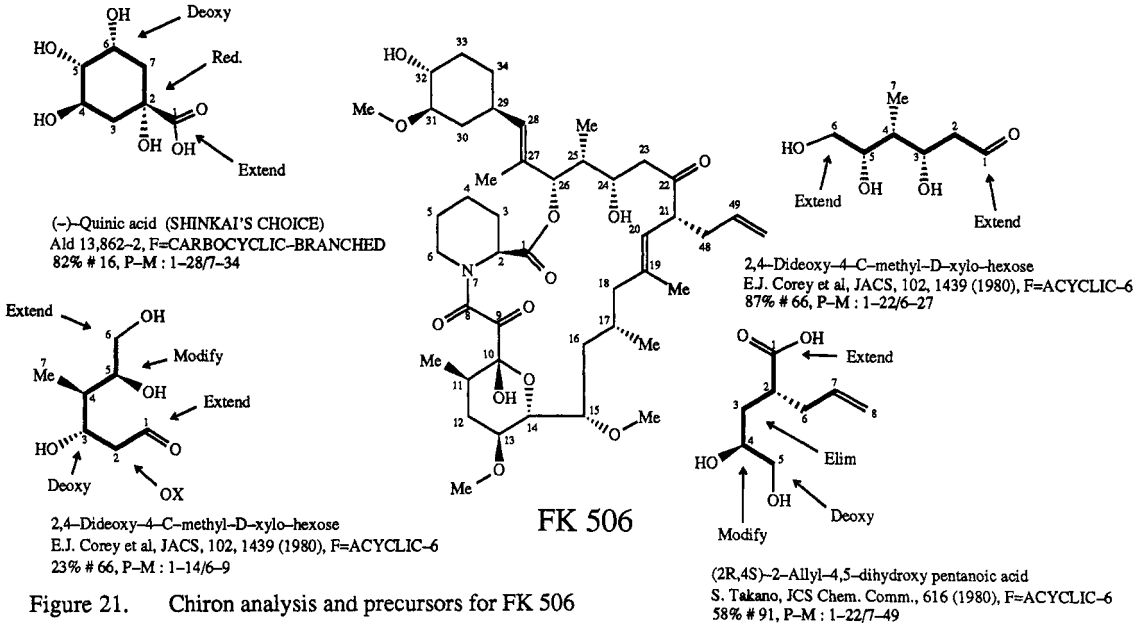

Figure 21. Chiron analysis and precursors for FK 506

reaction (CX) with inversion, but the elaboration of the ring via an annulation reaction poses a difficult problem. For this reason, this precursor may in fact be dismissed as a viable candidate. Only the persistent investigator will choose to look for the alternative perspective, shown on the right in Figure 22, possibly as a result of a flash thought or an image stored in the mind's eye as a déjà vu. The Chiron Program depicts this "flipped" perspective of the same precursor automatically, offering the user *another* sequence of reactions en route to the target. Thus, after appropriate protection of the hydroxyl group, the carbon-carbon appendages could be introduced via enolate chemistry followed by carbonyl branching, annulation, dehydration and oxidation in that sequence. Alternatively one could introduce unsaturation at C_3-C_4 and use the hydroxyl group as a handle for the C-C bond forming reaction at C_3 (ex. via a Claisen rearrangement). Clearly, if one were compelled to use this precursor the second perspective drawing (B) offers a more practical series of transformations compared to the first (A). This simple visual "flip", seldom done by man, but easily done by the computer program, demonstrates our limitations in perception, our vulnerability and our dependence on the "obvious". It is somewhat ironic that the success or failure of a synthesis may ultimately depend on how we draw the structures of the target molecule and precursor!

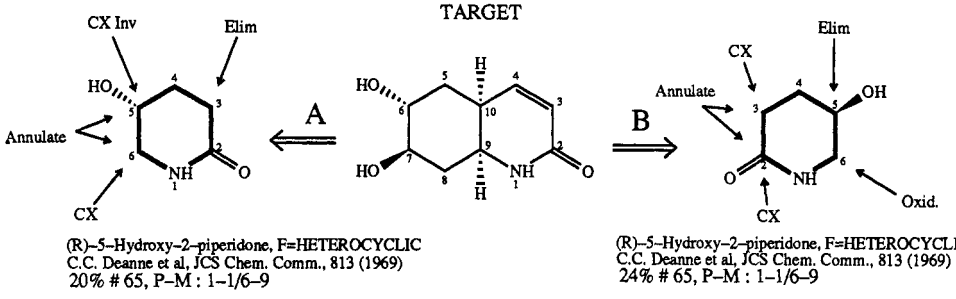

Figure 22. What a difference a "flip" makes!

D. Cleaved and reshaped precursors – a new dimension in heuristic analysis

In the previous examples of precursor searching, the program attempted to directly match the carbon framework of a given target molecule with those of acyclic or cyclic precursors depending on the best fit. Another feature in the program is the option to *cleave and reshape* acyclic and cyclic precursors. Thus diols and olefins are automatically cleaved and redrawn in a perspective that matches the shape of the corresponding substructure in the target molecule. Cleavage is also effected next to a carbonyl group such as a ketone or a carboxyl group as would be expected from a Baeyer-Villiger reaction on the more substituted carbon atom, from the oxidative decarboxylation of a carboxylic acid, and from the oxidative cleavage of an enolate or its equivalent. For the purpose of the efficient utilization of a chiral non-racemic precursor, the program will prefer *not* to cleave between adjacent stereogenic carbons in acyclic molecules and some cyclic molecules. Thus, certain cleavages are heavily penalized and the corresponding precursors will appear with much lower scores. Figures 23 and 24 illustrate examples of the CLEAVE and RESHAPE option with cyclic precursors *containing unsaturation*. In Figure 23 A, with PS-5 as a target, the program found (1R,2R)-2-amino-4-cyclohexene-1-carboxylic acid as a "cleavable" precursor. The "RESHAPE" option results in the automatic redrawing of the same precursor, after a hypothetical cleavage of the

double bond, and the attachment of functionality "X" at both ends (a given oxidation state), in a form that matches the C_2-C_9 framework of the target molecule. What emerges in the cleaved and reshaped structure is a nice match of the vicinal β-amino acid motif with perfect stereochemical overlap. Thus, the program was able to decode the structural, functional and stereochemical intricacies of the β-lactam antibiotic, and search for matching counterparts in the precursor data base (carbocyclic file). Moreover, it could further anticipate that cleavage of the double bond and reshaping would give a good overlap with the substructure carrying the stereochemical information. In the case of thienamycin, a hydroxylation is necessary at C_6 in the precursor, but for PS-5, this precursor seems ideal. Indeed, one of several syntheses of PS-5[56] was based on the utilization of the cyclic amino acid which originates from an enzymatic hydrolysis of a meso diacid. Interestingly this work was conceived independently, which demonstrates that man's visual powers[56] and the computer's heuristic search methods can coincide in some cases.

The second example shows the potential utility of (1R,5R)-5-hydroxy-2-cyclopentene-1-acetic acid as a precursor to the C_{20}-C_{24} substructure of FK 506. Note that after cleavage and reshaping, the pendant acetic acid chain overlaps with the C_{21} allyl side-chain and coincides with the correct stereochemistry at the site of branching.

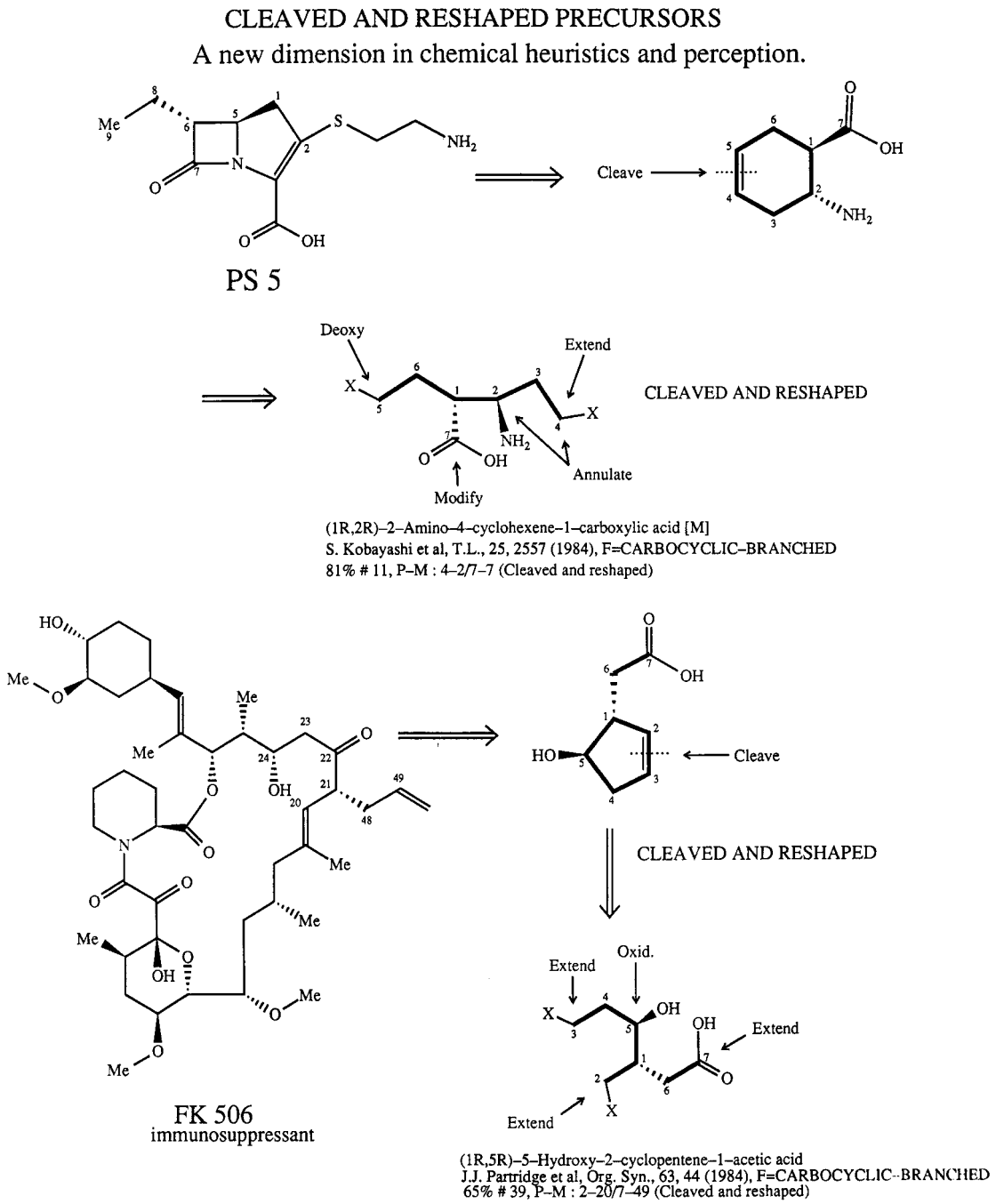

Figure 23. Cleaved and reshaped precursors for PS-5 and FK 506

Figure 24 A shows the results with thienamycin, using the same unsaturated precursor found for PS-5. Cleavage and reshaping by the program produced the same perspective overlap as for PS-5, except for the lower score. Clearly, this precursor was penalized for the absence of a hydroxyl group at C_6 which would overlap with C_8 in the target.

The second example B shows the CLEAVE and RESHAPE option for albolic acid. Here, the program recognizes the presence of the ring systems and the various appendages, including the "tough" angular methyl group at C_{11}. Accordingly, the bicyclic diketone, (R)-5-methyl bicyclo[3.3.0]oct-1-ene-3,6-dione was chosen by the program and cleaved at the olefinic site. The reshaped structure shown on the right in Figure 24 B is an excellent match for ring C of the target, as can be appreciated from the favorable disposition of functionality and the transformations that are suggested. It is of interest that the program shows a second structure (not shown in Figure 24), where the C_3-C_4

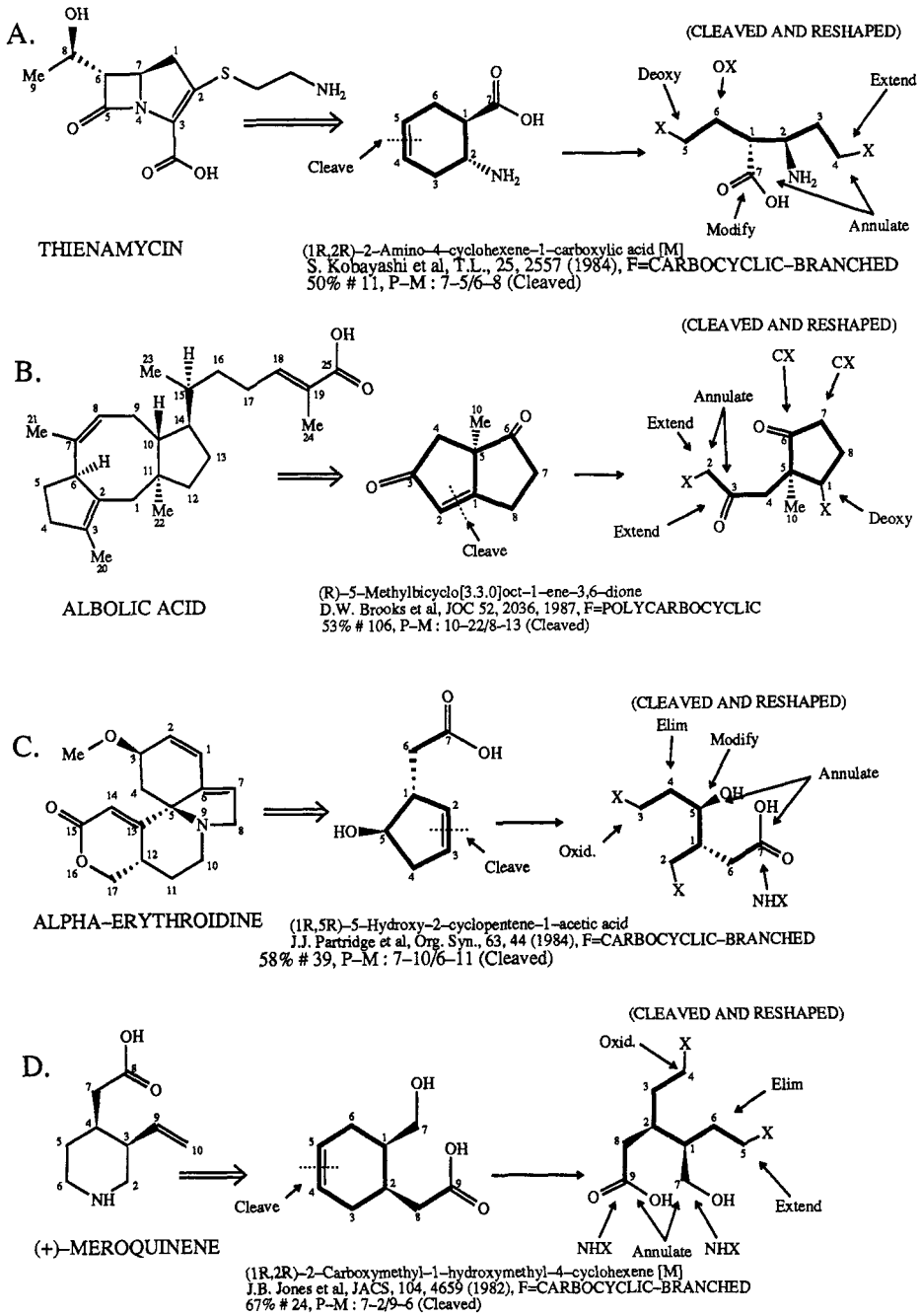

Figure 24. Cleaved and reshaped precursors for thienamycin, albolic acid, alpha-erythroidine and meroquinene.

bond resulting from the cleavage is "rotated" so that it overlaps with C_2-C_3 of the target, rather than C_2-C_6. The literature synthesis of albolic acid[57] involved the union of two cyclopentanoid iridoid chirons representing rings A and C which were not part of the precursor data base and differ in their substitution patterns from the one proposed by the program.

The third example shows the selection of a cyclopentene acetic acid derivative as a precursor to the lactone portion of alpha-erythroidine. Cleavage of the double bond and reshaping results in the open-chain hydroxy acid structure shown on the right in Figure 24 C. The carbon framework of the precursor overlaps with the lactone ring and the ethylamino appendage with the desired sense of chirality at the branch point. Once again, the key words provide a sequence of transformations to be effected with this precursor en route to an appropriate advanced intermediate.

The last example of the CYCLIC CLEAVE option shown in Figure 24 is the case of meroquinene as a target.[58] The *cis*-vicinally substituted vinylic and acetic acid appendages were "recognized" and a search initiated to find a match. The disubstituted cyclohexene shown in Figure 24 D, one of several precursors found by the program, harbors such a pattern of substitution. It may not be obvious to the viewer, that the desired appendages will emerge as a result of the cleavage. In order to efficiently utilize this precursor, one must now consider the construction of the piperidine ring (reductive amination?), and the differentiation of the oxidized appendages in such a way so as to introduce the desired oxidation states in the quasi symmetrical branches. A recently completed total synthesis of meroquinene[59] relied on a reductive amination protocol of a dialdehyde derived from a D-glucose derivative containing the acetic acid and vinyl groups, at C_3 and C_4 respectively.

The above is only a sampling of selected precursors containing unsaturation, and found in the CYCLIC CLEAVE and RESHAPE option. Naturally, the program cannot "invent" precursors, since it can only search in the existing data base, which is in constant expansion as new versions of the program are released.

Cleavage is also possible next to a carbonyl group as in a Baeyer-Villiger oxidation. Several total syntheses of hirsutic acid[60] utilize the chiral template approach that generates an advanced intermediate to rings B and C from a bicyclic ketone by an oxidation-ring expansion sequence. Figure 25 shows how the same precursor A was also found in the POLYCYCLIC file in conjunction with the CYCLIC CLEAVE option. Note that cleavage is favored on the more substituted side of the ketone. The CLEAVED and RESHAPED form of this precursor matches and overlaps as much functionality and carbon skeleton as possible. Interestingly, the ring expanded ketone B[60a] was also considered as a directly overlapping template by the program, since it offers excellent convergence with the B/C rings and allows further transformations based on carbonyl chemistry.

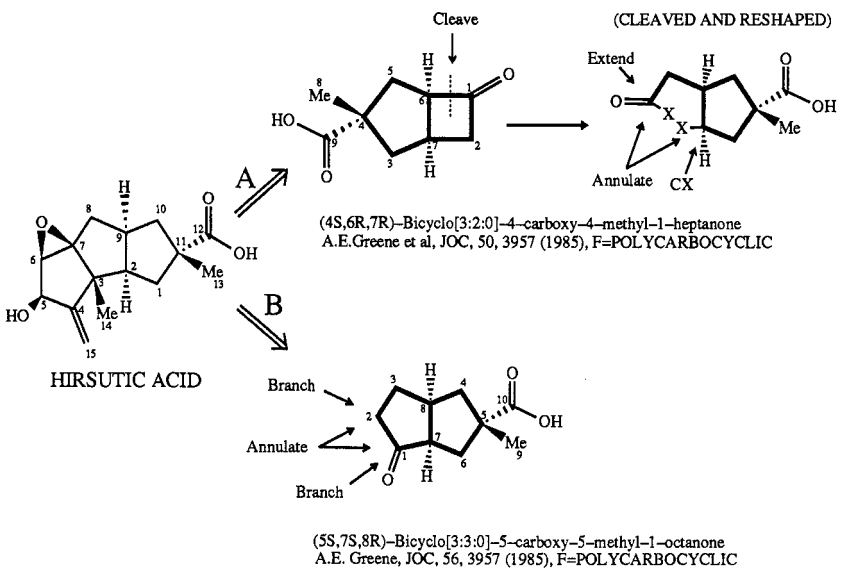

Figure 25. Chiron analysis of hirsutic acid showing the cleave and reshape option and a direct template match.

E. The MORE option – a second chance for rejected precursors

The Chiron Program chooses precursors by relying on a process of pattern recognition of carbon framework shapes either by a direct overlap or by an imaginary cleavage at selected sites followed by automatic reshaping. Since the search is done by individual comparisons of functional groups between target molecule and precursor, very often one "impossible" transformation (ex. oxidation of an unactivated methylene group) may abort the search,even if the remainder of the matches are quasi perfect. The MORE option in the CAPS module will catch some of these precursors and offer them to the user, indicating the site of the problem. By being made aware of such a precursor, the user may decide to modify it in such a way that it can now incorporate the desired functionality or its equivalent. A rejected precursor can therefore be reconsidered and the synthesis plan reexamined with the modified precursor which should be a much better match now.

A search for amino acid-type precursors for acivicin (Figure 26) would normally not find L-norvaline in spite of a seemingly perfect match of the framework and the presence of the α-amino acid functionality. The major hurdle of course is the difficulty to introduce the desired oxidation states without using elaborate schemes. These impractical transformations are taken into account by the program and a score of -1386% is given to L-norvaline! However, the user has the choice to be allowed to see such cases and make a decision accordingly. By searching in the MORE option, L-norvaline appears with a higher "bogus" score with the problem centers being identified. Now the user can perhaps search for a modified L-norvaline or even consider a synthesis of such an analog. Figure 26 also shows one of several outputs for the CYCLIC CLEAVE and RESHAPE option for the target molecule[61] indicated. It can be seen that after cleavage and reshaping, an excellent carbon skeleton overlap is found from a seemingly unrelated bicyclic precursor. The suggested transformations are also feasible with the notable exception of the

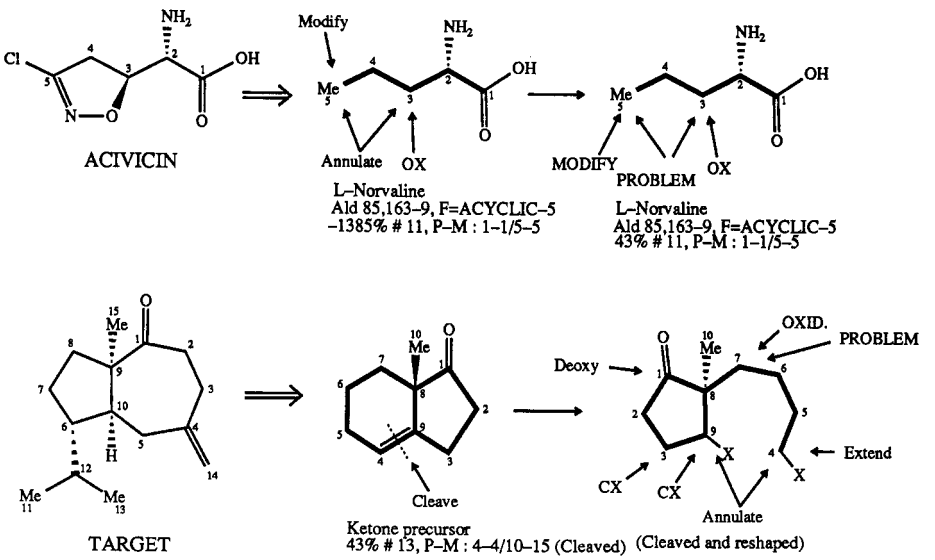

Figure 26. Almost "missed" precursors can be reconsidered using the MORE option in CAPS.

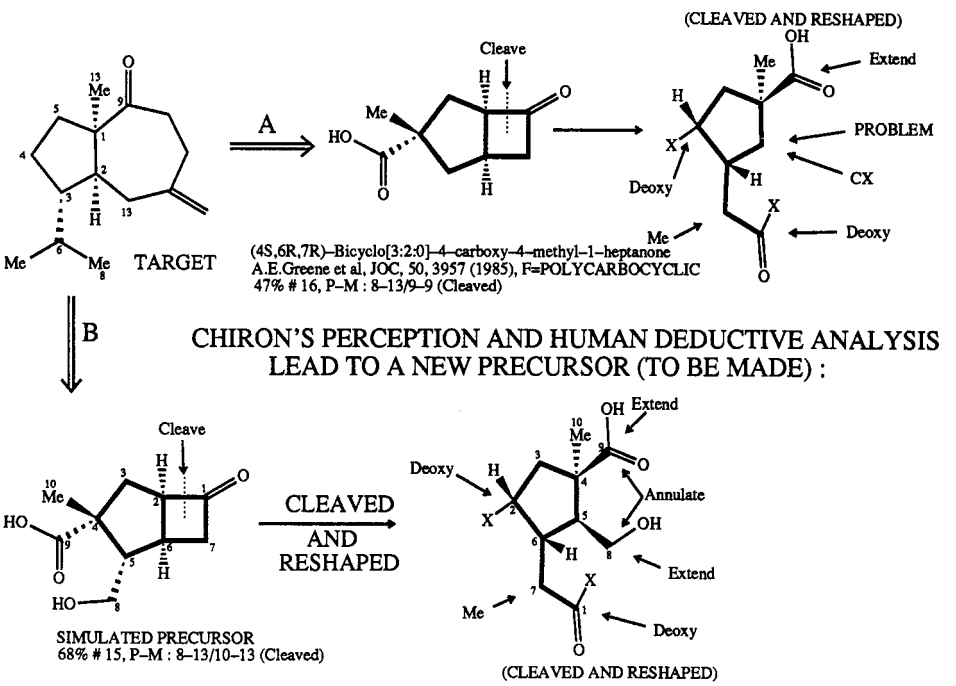

Figure 27. Man and machine working together

oxidation at C_7 of the precursor. The program indicates that there is a problem at that site, thus focusing the attention of the user for the desirability to have a useful functional group at C_7. Whether this is indeed possible is not an issue here, but the potential utility of the original ketonic precursor and a new version of it may be appreciated.

This proposal is illustrated in the case of another precursor found for the same target, where a Baeyer-Villiger oxidation was suggested (Figure 27 A). It is clear that while an excellent convergence emerges from the cleaved and reshaped precursor, functionalization at C_3 presents a major obstacle, hence the PROBLEM key word. If the same precursor were available with a usable substituent at C_5 (ex. hydroxymethyl, Figure 27 B), then the CLEAVE and RESHAPE option would lead to a much more versatile precursor which is also reflected in the score.

F. Selection of aromatic, heteroaromatic and achiral precursors

The precursor data base contains some 400 aromatic and heteroaromatic molecules selected mostly from commercial sources. As with the chiral precursors, direct template overlaps are effected in the search with provisions made for a certain number of aromatic-type chemical transformations. For example substitution ortho to a hetero atom is allowed and given priority over the meta and para positions. Figure 28 shows some of the precursors found for burchellin, previously synthesized by Büchi and coworkers[62] from 2-allyl-4,6-methylenedioxy-phenol. Chorismic acid (non-aromatic) and a dl-phenylbutyrolactone were suggested by the program for "maximum" convergence with the target substructures. The Büchi precursor was also found with a score of 68% (not shown here). Chorismic acid was also suggested as a precursor to the right-hand substructure of kadsurenone.[63] Once again, it should be noted that this precursor is depicted in a way so as to match as many functional groups or their synthetic equivalents as possible (compare with burchellin). An aromatic precursor containing a chiral appendage obtained from a Sharpless epoxidation[15] was one of the other choices for building kadsurenone from the aromatic end of the molecule. Finally, in this series, a heteroaromatic precursor with a chiral appendage, as well as an allylic dimethoxybenzene were selected as precursors to proemetine.[64]

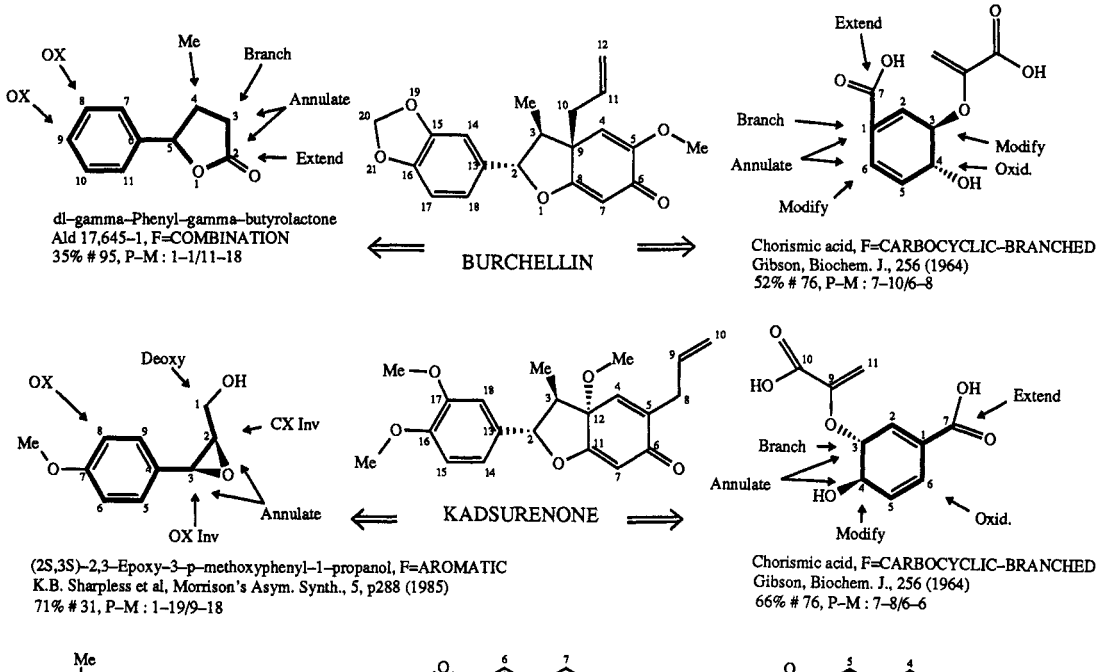

Figure 28. Chiron analyses of aromatic molecules

The program has a selection of small achiral precursors that can be used for the synthesis of racemic targets unless resolution or an asymmetric process is considered. For example, acetone dicarboxylic acid, an achiral precursor used in the commercial synthesis of thienamycin[9] was found by the program as a match for the C_2–C_7 substructure of the target. In addition, two other matches were suggested, one spanning "north-south" (C_5–C_{10}) and another covering "east-west" (C_2–C_8) as shown in Figure 29. One could therefore speculate if the "north-south" match may have not been a viable precursor which could still take advantage of the ingenious diazoinsertion reaction used for the critical ring closure reaction in the original synthesis.[9]

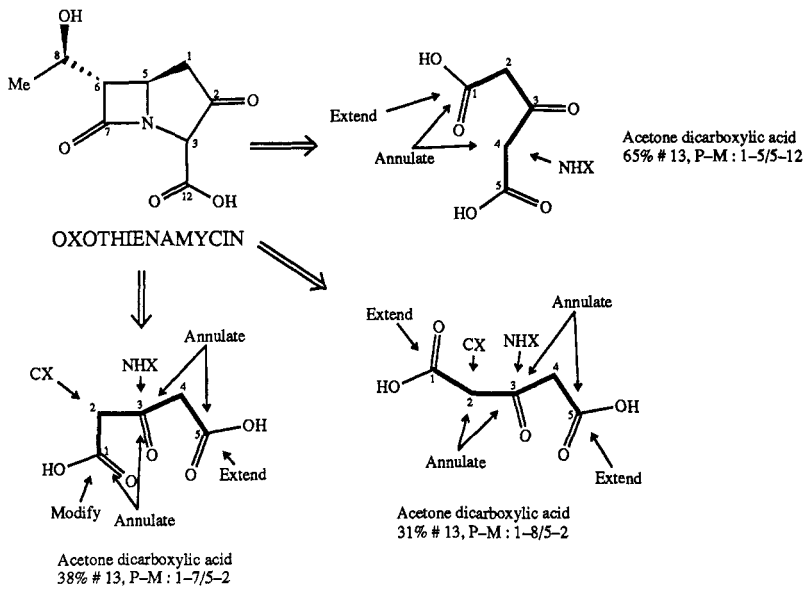

Figure 29. Suggested template matches of acetone dicarboxylic acid with oxothienamycin

THE "CHEMICAL TRANSFORMATIONS" IN THE CHIRON PROGRAM

As was amply demonstrated in the article, the main premise of the Chiron Program is to recognize skeletal, functional and stereochemical features in a target molecule and to select appropriate precursors from an available data base, by a process of intelligent pattern recognition aided by some "chemical rules". The functional group transformations are based on an A gives B (or not) concept, with the ease of execution being assigned a % score (ex. primary alcohol → acid, 80%, secondary halide → amine with inversion 80%; with retention, 30%, etc.).

Each score is normalized according to a ratio that represents the relative importance of that functional group. Penalties are given for a set of undesirable transformations, for imperfect matches, and for destroying asymmetric centers in a precursor for example. Bonuses are accorded for good overlap of carbon framework. The balanced scores which appear under the precursor name and reference are only meant to be a guideline. It is the user that must ultimately assess the suitability of the precursor and the practicality of the transformations.
Another level of transformations considers vicinal and reasonably remote reactivity resulting from the presence of an activating group (carbonyl, unsaturation, nitro, sulfone etc.). Thus, unsubstituted carbon atoms in α,β, and γ-positions to a carbonyl group for example are considered as potential sites for bond formation based on enolate chemistry, 1,4-conjugate addition after enone formation, etc. The ease of functionalizing such positions are considered by the program, and individual scores are attributed to each type of transformation (ex. substitution α- to a carbonyl group is more favored over the β-position, and much more than γ-). The program will perform a limited number of sequential hypothetical transformations in trying to relate a precursor to a substructure in a target. For example, a cleavage is possible next to a hydroxyl group in a cycloalkanol since in practice it is possible to oxidize the alcohol to a ketone and to do a Baeyer-Villiger oxidation to give the corresponding lactone. In such a case, the key words "oxid." and "cleave" will appear next to the hydroxyl group. In some instances, sequential operations are not recognized and the precursor will not be found. These cases are of interest since they allow for further refinements and modifications of the program.

An example of the potential cleavage at an unactivated site in an allylic position is shown in the choice of (S)-carvone as a synthetic precursor to eucannabinolide. Two of several cleavages and reshapings suggested by the program are shown in Figure 30. Cleavage of the C_4-C_5 bond was permitted because of its known reactivity via an allylic oxidation protocol.

In the Still elegant synthesis of eucannabinolide form (S)-carvone,[45] a number of chemical transformations (reduction, protection, oxidation and branching at C_4) were effected before performing a critical oxy-Cope fragmentation reaction at C_4-C_5 which led directly to the 10-membered ring system of the target. Although the program was not capable of suggesting these reactions specifically, it "jumped ahead" and indicated a possible cleavage at C_4-C_5. The hypothetical cleaved and reshaped product matched the target molecule by overlapping two substructures. Whether the indication to "cleave" (S)-carvone at C_4-C_5, or the suggested key words in the cleaved and reshaped structures, can actually trigger the required sequence of reaction in the user's mind to ultimately give the target molecule, is a matter of conjecture. It is of interest however that the second cleaved and reshaped structure overlaps the target molecule in the manner intended in the Still strategy (C_8-C_1-C_5 segment), including the position of the carbonyl group.

Figure 31 shows a table with the scoring system for the first cleaved and reshaped (S)-carvone as a precursor (72%, Figure 30). Each functional group and its equivalent in the target molecule is defined, and a % score is assigned based on the ease of chemical conversion. Each score is then converted into a ratio score which reflects the relative importance of the function with regard to others present in the molecule. A loss of 10% was imposed on this precursor because of the necessity to cleave, and 4% for chemical manipulations. Since there is good carbon framework convergence, a small bonus of 2% was given. The sum of the ratio scores and the losses and bonuses give the final score of 72%. Clearly this number is only a relative indication of the suitability of (S)-carvone as a precursor, and a final careful assessment must be done by the investigator.

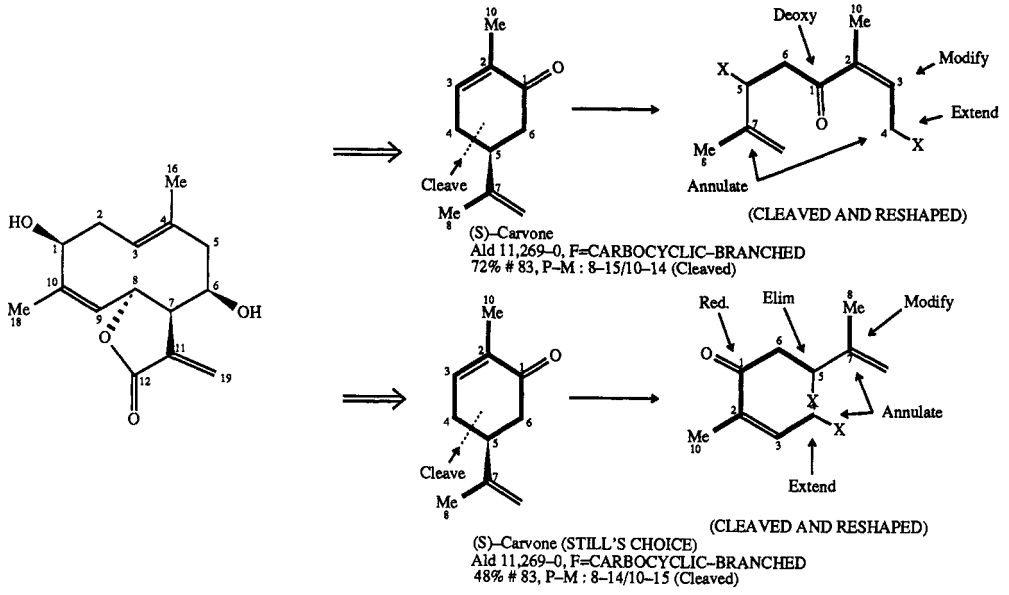

Figure 30. Cleavage and reshaping of (S)-carvone as a possible precursor to eucannabinolide

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-------------- PRECURSOR SCORING DETAILS ---------------

Name  = (S)-Carvone
Ref   = Ald 11,269-0
File  = CARBOCYCLIC-BRANCHED  (Main file)   #  83
Score = 72%   ,  cleaved between  5 and  4

 Prec  Mol  MatchKind  FunctP    FunctM       Ratio  Score
 ----  ---  ---------  ------    ------       -----  -----

   1     3   Chain      KET       ALKENE         8%    50%
   2     4   Branch     BRDoub    BRDoub        14%   100%
   3     5   Chain      ALKENE    NoF            7%    50%
   4     6   Extremity  OX        CXX           17%    50%
   5     1   Chain      OX      r OX      r     20%   100%
   6     2   Chain      NoF       NoF            7%   100%
   7    10   Chain      METLEN    METLEN        13%   100%
   8    18   Extremity  Me        Me             7%   100%
  10    16   Extremity  Me        Me             7%   100%

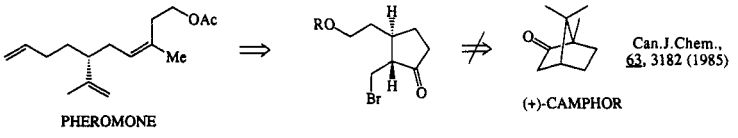
Losses and bonuses :
       -10 %   Cleave loss
        -4 %   Too many chemical manipulations to do
         2 %   Precursor size bonus
```

Figure 31. Scoring system for (S)-carvone matching C_9-C_1-C_6 of eucannabinolide after cleavage.

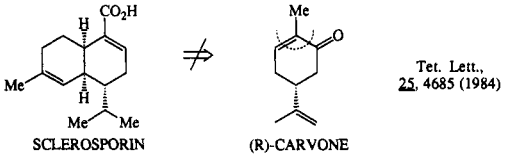
The program will not consider two important aspects in its heuristic search method. Firstly it cannot relate a substructure in a target molecule to a precursor if the latter must undergo skeletal rearrangements such as ring expansions and contractions involving C-C bonds. The CLEAVE and RESHAPE option in the present version allows one cleavage per operation only. The program will heavily penalize the cleavage of acyclic chains into smaller chains (ex. via a vicinal diol). Although this feature may present some limitations, it was introduced in order to discourage the use of "small fragments" that may result from such operations. As previously mentioned, emphasis is placed on the convergence of as much functional and stereochemical information as possible between target and precursor. Chiral-non racemic precursors will be favored over their racemic counterparts. Secondly, the program will *not* consider bond forming processes between two precursor molecules. For example, it will find a six-carbon acyclic precursor and two three-carbon precursors separately for the same six-carbon (or longer) substructure in the target. When cyclic structures are involved, preference will be given to a direct overlap with a monocyclic or bicyclic etc. precursor, or to an acyclic precursor. In the latter case, an "annulation" reaction will be

suggested by the program in the TRANSFORMATIONS option. The program does not think in terms of a Diels-Alder reaction for example, when it analyzes a carbocyclic target molecule such as forskolin. Rather, it will search for the best carbocyclic match, preferably with usable functionality. In this regard, the Chiron Program differs fundamentally in its search method from other synthesis planning programs such as LHASA,[65] CAMEO,[66] SECS,[67] EROS,[68] SYNGEN[69] and related ones.[70] Figure 32 illustrates some limitations of the Chiron Program.

- THE PROGRAM DOES NOT RECOGNIZE SKELETAL REARRANGEMENTS



- THE PROGRAM WILL NOT CLEAVE TWICE (EXCISION)



- THE PROGRAM WILL NOT COMBINE TWO PRECURSORS TO FORM A BOND

- THE PROGRAM DOES NOT TAKE PROTECTIVE GROUPS INTO ACCOUNT

Figure 32. Some limitations of the Chiron Program.

The key words describing the transformations needed to be done in the forward sense may appear to be too general in some instances (ex. "annulate" when a large macrocycle is involved!). Nevertheless their appearance has a stimulating effect on the eye-mind processing of visual information. A trivial key word such as "branch", alone or in conjunction with "annulate" for example, may trigger a cascade of possible chemical transformations in one's mind involving organometallic reagents as well as cycloannulation reactions (see punctatin A,[30] Figure 19 A) Is it possible that seeing L-glutamic acid drawn in the perspective that matches the "lower" substructure of α-kainic acid, in combination with the simple words "annulate" and "CX" (i.e. formation of a C-C bond), could lead the user to think of an intramolecular ene reaction as planned and executed by Oppolzer?[31] (Figure 19 C).

The ability to see matching precursor structures in combination with the key transformations to be done can have important implications in synthesis planning. Thus, the scenario for a total or partial synthesis from a precursor is presented in a condensed format that allows one to consider the correct sequence as well as the proper timing of the reactions. There is also a strong pedagogical element in this type of representation.

Since it is possible to interface the Chiron Program with other programs involved in the retrieval of chemical reactions,[70] the user can obtain many literature examples of the transformations indicated by key words.

THE PRECURSOR DATA BASE

There are at present *1088* chiral non-racemic, *301* racemic, and *619* achiral precursors in the data base, which have been compiled from the literature and from commercial sources. The optically active precursors are at least of 90% optical purity and they originate from asymmetric synthesis, from natural sources, directly or via synthesis, from resolution, and from enzymatic or microbiological processes. Precursors less than three carbon atoms are not included in the data base. Precursors have been saved in appropriate files depending on their carbon frameworks (acyclic-5, acyclic-6, carbocyclic, aromatic, etc.) and they consist of "essential" and "non-essential" atoms depending on their potential utility in the matching process. For example, protective groups (ex. acetate) are not essential and will not be taken into account in the search process. An exocyclic methylene group is not essential since it can be cleaved to a ketone for example. However, it will be considered as part of the precursor if it is needed for the match. The program automatically assigns essential atoms when a precursor is saved and there are provisions for batch transfers of many precursors. This feature allows for a rapid build-up of proprietary data bases in the Chiron Program.

SYNOPSIS – MAN, MACHINE AND HEURISTICS IN TYNTHESIS PLANNING

We have shown that man's experience, intuition,creativity and logic in finding new and exciting strategies in total synthesis can greatly benefit from an enhancement of the eye-to-mind processing of visual information. Our powers of perception and analysis of structural, functional and stereochemical features in molecules are limited by what we

can actually "see" and relate to precedents and to stored knowledge. In order to sharpen our visual and relational powers in synthesis planning, we must consciously put the enormous untapped resources of the brain's bilateral asymmetry to our advantage. The psychobiological implication of the sequential thought process in synthesis planning as proposed in this article must be brought to light in the classroom and exploited to advantage in the laboratory. In this regard, we hope that the heuristic search method for synthetic precursors using the computer program and the underlying philosophy of the *Chiron Approach* to total synthesis is a step in that direction.

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