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Reflections on the total synthesis of natural products: Art, craft, logic, and the chiron approach

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Abstract

An overview is given of various strategies aimed at the total synthesis of natural products, with particular emphasis on some clinically important molecules. Of necessity, total synthesis must also incorporate the elements of absolute stereochemistry, and the ultimate objective of obtaining enantiomerically pure or enriched products. In this regard, the Chiron Approach which capitalizes on the recognition and eventual use of readily available, chiral non-racemic starting materials, has been very successful over the years. A number of examples from the author's laboratory are illustrated and discussed.

INTRODUCTION

It is almost fifty years ago that Woodward and Doering completed the total synthesis of quinine (ref. 1). Even by today's standards such a molecule presents a substantial level of structural complexity and a veritable challenge. Considering the methods then available for stereocontrolled bond formation, and the lack of sophisticated spectroscopic techniques, the synthesis of quinine which is taken as a representative example, is in fact a remarkable accomplishment. Each decade that followed brought forth increasingly impressive accomplishments in the area of total synthesis (ref. 2). Today, practically every class of organic natural product can be reached by synthesis (ref. 3). In this regard it is of interest to briefly review the trends that have been followed during the past fifty years or so as shown in Fig. 1.

PERIOD	TREND	INCENTIVE / OBJECTIVE
1950's – 1960's	Classical syntheses of selected natural products	• target conquest • mechanistic insights
1970's – 1980's	Multi-step, strategy and transformation - based syntheses	• stereochemical control • enantiomeric purity
1990's	Design and synthesis of new types of man made molecules	• selectivity, recognition, function

Fig. 1. Trends in the total synthesis of natural products.

The milestone achievements in total synthesis during the fifties and sixties as exemplified by alkaloids, triterpenes, steroids, and various antibiotics to mention a few were textbook examples of target conquest. Control of absolute stereochemistry and the implementation of a basic strategy that would be applicable to other members of the same class but differing in functional or stereochemical features were not necessarily primordial issues. Nevertheless, a number of these syntheses are considered as "classics" in the annals of the total synthesis of natural products (ref. 4).

The seventies and eighties witnessed an amazing display of ingenuity and creativity in the development of novel, stereocontrolled bond-forming reactions. Asymmetric synthesis had come of age and many well-known reactions now have their "asymmetric" versions (ref. 5). This, coupled with great advances in instrumentation brought forth a new and exciting era of stereocontrolled total syntheses of an impressive cross-section of complex natural products (ref. 2). Innovative methods for chemo, stereo and site-selective chemical transformations became available with a steady influx of new protective groups (ref. 6). Parallel advances in organometallic chemistry, including transition metals, in separation methods, and in computational chemistry added to the arsenal of tools, means and techniques with which the synthetic

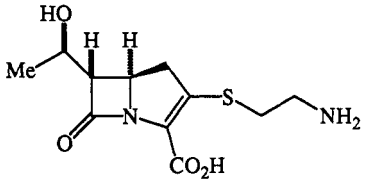
chemist could face new challenges in total synthesis. In spite of unavoidable difficulties in day-to-day laboratory operations (compatibility, yields, cost, by-products, etc.) it appears that the synthetic organic chemist has finally "arrived". While the means seem to be at our disposal to tackle almost any synthesis challenge, the requirements, the expectations, and the rigors of time constraints, etc. pose formidable problems of logistics sometimes. Having reached such heights in the construction of complex organic molecules, one must now view total synthesis with a different perspective. What then will some of the incentives and objectives be in the nineties and even beyond? (Fig. 1)

One of these areas could involve an even closer interface between biology and chemistry. Major advances have been made in molecular biology, pharmacology, and protein crystallography. Indeed, the crystal structures of an impressive number of complex enzymes have been analyzed to a reliable level of resolution (ref. 7). The active sites of many biologically relevant enzymes can now be "seen" through the help of computer graphics, with occluded organic molecules and covalently linked enzyme-substrate intermediates (ref. 8). The synthetic chemist can therefore visualize within reasonable limits, postulated interactions of various types with the biological targets (electrostatic, hydrophobic, hydrophilic H-bonding, etc.). Through the advent of molecular modeling and modern techniques of computational chemistry, it is possible to further probe the overall structural features of an organic molecule in conjunction with its biological host (ref. 9). Chemical refinements, adjustments through synthesis, coupled with the above mentioned notions may now lead to a novel structure to be synthesized. If this is done on a natural product molecule at the outset, what results is a new-generation, semi-natural product with the prospects of interesting activity. Such molecules can also result from studies of structure-activity relationships, molecular modeling and other computational techniques as applied to unnatural molecules in a medicinal chemistry context (ref. 10). Finally, it is not excluded that with the knowledge of a biological parameter regarding a specific molecule, or a class of molecules, there may emerge a totally novel target molecule to synthesize.

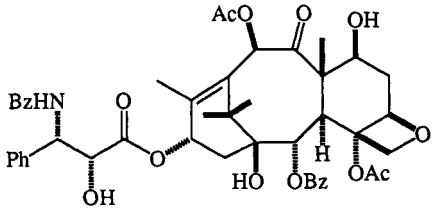
Thus, one aspect of total synthesis for the present and the near future may involve new breeds of man-made molecules, generated through logic, intuition, and basic knowledge in combination with computer generated 3-dimensional structures. There are of course several other reasons for being involved in the total synthesis of natural and unnatural products which will not be elaborated upon here.

TOTAL SYNTHESIS OF CLINICALLY RELEVANT MOLECULES

Nature has been a generous and constant supplier of intriguing organic molecules with diverse biological functions. Many of these are life-saving drugs that are used in their original form or as a pharmacologically acceptable variant. In other instances, active but toxic natural products have been ingeniously investigated by synthetic organic chemists in order to separate the two activities, obliterating side-effects while maintaining the benefits of the drug. While many of these important natural products are available in large quantities for world-wide supply through fermentation (ex. antibiotics such as



THIENAMYCIN
(IMIPENEM)



TAXOL

Fig. 2. Thienamycin, manufactured by total synthesis, and taxol, awaiting an industrially viable synthesis.

erythromycin), there are instances where nature is not so generous and the fermentation scientist must intervene. In spite of much progress in this area, particularly with the advent of sophisticated techniques in molecular biology, one must often turn to total synthesis as the only viable means to produce a given natural product as a drug. Economics obviously will play a decisive role in such cases.

A relevant example is thienamycin, an unusual carbapenem-type antibiotic, which is presently manufactured by total synthesis (ref. 11) (Fig. 2). This is a particularly good example because of its relative structural complexity compared to other antibiotics of similar size, also produced by total synthesis. Much ingenuity has gone in the design and implementation of an economically viable large

scale synthesis process for thienamycin. Also, the discovery of this class of unusual β-lactam antibiotic has instigated a great influx of novel synthetic methods in this area from the industrial as well as the academic community (ref. 12).

Another example involves the potent antitumor agent taxol (ref. 13) where total synthesis presents several problems from practical and logistic viewpoints (ref. 14). The lack of a rapidly replenishable natural source for producing large quantities of taxol, makes the prospects of its production by total synthesis an attractive and highly desirable objective. Inspection of the structure of taxol quickly reveals the numerous obvious difficulties in assembling such a formidable target. Issues involving functional group chemistry and absolute stereochemistry only magnify the heights and depths of the hills and valleys to traverse en route to the summit. As if these obstacle were not enough, there is an added imposition that an industrially and economically viable total synthesis comprise no more than 20 steps with acceptable overall yield.

THE PLIGHT OF THE SYNTHETIC ORGANIC CHEMISTRY – WHAT IF ANY TO SYNTHESIZE?

As outlined in the previous sections, total synthesis has evolved to a point that it must be practiced with a purpose that transcends intellectual curiosity, sheer challenge or other reasons for conquest. For an academic scientist, natural product synthesis provides an ideal forum for discovering synthetic methods and for testing their feasibility. Perhaps one of the most rewarding aspects of natural product synthesis remains in the rigorous training it provides for young collaborators in preparation for their independent careers in research.

For reasons that need not be elaborated in this article, there seems to be a prevailing sense of urgency to define new roles for the synthetic organic chemist presently. This self-imposed malaise may in part be the consequence of impressive advances in molecular biology and related fields, the obvious public attention this generates, and the lack of awareness as to how organic synthesis can provide chemical solutions to biological problems. There are however, many exciting prospects for advancing the frontiers of both disciplines through organic synthesis (ref. 15).

For the purpose of discussion, it is of interest to depict the process of organic synthesis in general, and of total synthesis of natural products in particular, in "human terms", i.e. in an ordered set of conscious and unconscious events that are mostly controlled by the individual investigator, from the inception of an idea to is realization (Fig. 3).

A.	Choice of target molecule	⇒	Relevance
B.	Perceptive powers and seeing through the mind's eye	⇒	Personal bias, reflex, heuristic analysis, open-eyed serendipity
C.	Emergence of a strategy	⇒	Individual prowess, creativity
D.	Generation of a synthesis plan	⇒	Attention to detail, possible fixation (caution!)
E.	Execution	⇒	Efficiency, practicality
F.	Endurance	⇒	What price synthesis (agony and ecstasy)?
G.	Contribution to science	⇒	New concepts, reactions, reagents, processes
H.	Recognition	⇒	Rewards, fame, fortune, legacy

Fig. 3. "Living" through a total synthesis

With the above perspective, it is clear that "living through" a total or partial synthesis can be an exciting, rewarding and very fulfilling endeavor. Again, with an acute sense of awareness of advances on the biological front, the synthetic organic chemist is in an ideal position to use his or her analytical, creative, and deductive skills in an effort to find relevant target molecules for synthesis, or to provide chemical insights into complex biological phenomena through the aegis of synthesis.

Nature generates the problems
Chemistry finds solutions
Biology has the last word...

SOME GUIDELINES FOR THE TOTAL SYNTHESIS OF PHARMACOLOGICALLY IMORTANT MOLECULES

As synthesis targets become more and more abundant every day, the launching of a new project involving total synthesis must meet a number of "conditions". While different investigators may have their own independent views on the subject depending on their interests, by and large, the following list of criteria can be considered once a target molecule has been selected.

a. efficient methodology and realistic planning, which is directly related to cost.
b. versatile and flexible strategies which will allow the synthesis of analogs for biological testing in addition to the main target.
c. regiocontrol, stereocontrol and predictive power which are related to the purity of the final product.
d. balancing the tightrope of protective groups, which translates into practicality (and overall efficiency).
e. optical and enantiomeric purity of the final product, which is directly related to biological activity.

It is rare that *all* of the above listed criteria are fully satisfied in a given synthesis. However, much can be learned from the experience of total synthesis even in the case of "failed" attempts.

Total or partial synthesis in an industrial context can be viewed much the same way with regard to the intellectual and scientific input. There are however a number of other key features to be considered which are outside the realm of this article (market potential, etc.). There are obviously many other more "practical" aspects of synthesis in industry such as disposal and restrictions of certain chemicals, solvents, clinical purity of products, etc. which are not prime factors for concern in an academic environment.

THE QUEST FOR ENANTIOMERICALLY PURE (ENRICHED) PRODUCTS AND THE IMPACT OF THE CHIRON APPROACH

For practical and aesthetic reasons, it is now common practice to plan syntheses in such a way so as to produce an enantiomerically pure (or enriched) target molecule. This has become a virtual necessity in pharmaceutical research laboratories since stereochemistry is the common denominator between chemistry and biology (ref. 16).

Excluding microbiological, enzymatic and related processes (ref. 17), there are basically three main strategies to adopt when the synthesis of an enantiomerically pure molecule is considered. The simplest approach would involve resolution of a racemic final compound or an intermediate (ref. 18). While there is reason to consider such a strategy, it offers neither a general solution to the problem, nor an intellectually rewarding sense of achievement. The other approach calls for the use an enantiomerically

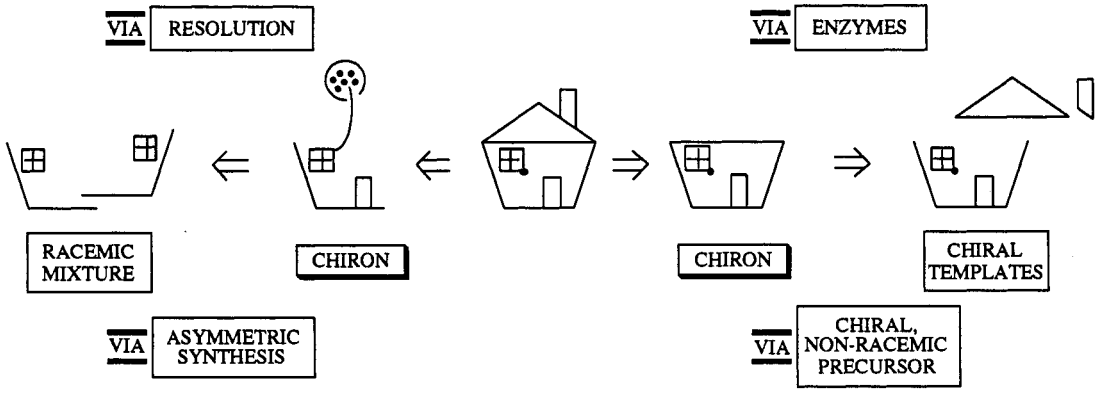


Fig. 4. Access to enantiomerically pure (enriched) targets – the Chiron Approach

pure starting material which can be obtained by resolution, by an asymmetric process or by relying on nature's "small" natural products such as amino acids, carbohydrates, hydroxy acids, terpenes and related compounds (Fig. 4). In all three cases, the enantiomerically or diastereomerically pure, or enriched molecules are used as chiral templates upon which specific transformations are performed en route to chirons (chiral synthons) (ref. 19, 20, 21).

The third approach would rely *totally* on asymmetric processes to generate an appropriate starting material, and to perform critical bond-forming operations on advanced intermediates as well (ref. 5).

As has been discussed elsewhere (ref. 19-21), the chiron approach relies on the recognition of chiral substructures in the target molecule. Disconnections in a retrosynthetic mode are made with minimum perturbation of existing stereogenic centers. This generates chirons with a maximum overlap of functional groups, of stereochemical features, and of carbon framework with the target molecule (or a given substructure). One of the main differences between the chiron approach and the synthon approach is that conservation of stereochemistry is at a premium in the former. In the synthon approach (ref. 22), it is mostly the type of functional groups present in the target molecule and chemical feasibility in the forward sense (or precedent), that dictate the strategy. Thus, a β-hydroxyketone subunit can be related to an aldehyde and an enolate equivalent of the ketone as synthons in the retrosynthesis. This approach pioneered by E.J. Corey (ref. 23) is widely used in synthesis, and in some way it is encoded in our way of thinking about bond disconnections when analyzing a target molecule.

In the chiron approach, it is the type of chiral substructure present in the molecule that will dictate the strategy inasmuch as it can be related to an appropriately functionalized intermediate (chiron). Such molecules normally contain one to five or six stereogenic centers and can originate from nature, (terpenes, carbohydrates, etc.), from asymmetric reactions on achiral substrates, from resolution of racemates, and from enzymatic and related sources. By relating a target structure to chiral starting materials at the outset, the scenario for a synthesis plan is established. The main issue now deals with proceeding in the forward direction using the inherent or newly-created chirality and building from there.

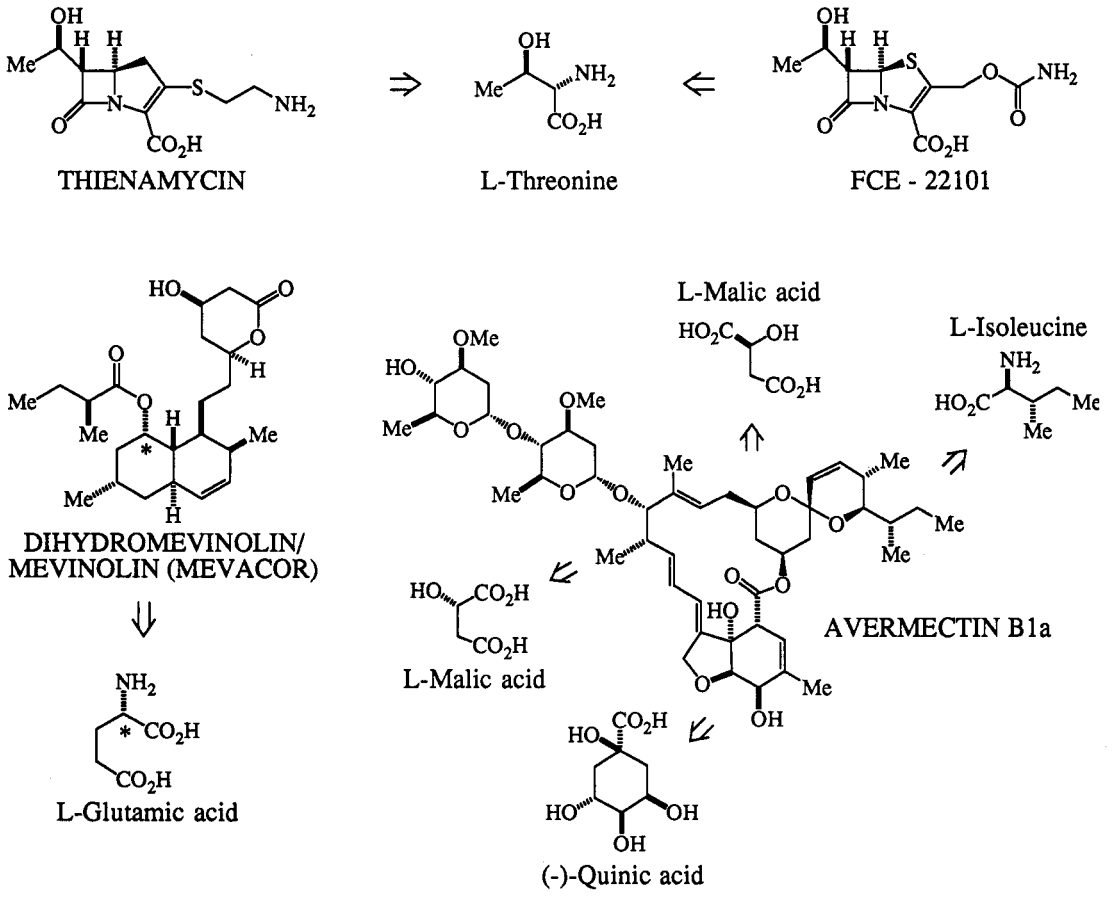


Fig. 5. Total synthesis of clinically important natural products and related compounds using the Chiron Approach.

The chiron approach has aesthetic appeal and predictive power combined with practicality in many instances. In fact, the number of natural products synthesized from chiral templates involving amino acids (ref. 24), carbohydrates (ref. 19, 25), hydroxy acids (ref. 26) and terpenes (ref. 27) alone is impressive.

Relating chiral substructures to appropriate enantiomerically pure starting materials can be difficult especially when such templates are "hidden" in the complex framework of a target molecule. One wonders how much we miss as a result of our limited powers of perception. This aspect that relates visual contact with reflex action and heuristic analysis has been discussed in psychobiological terms elsewhere (ref. 21). This type of limited perception has led to the development of a computer program that is capable of interrelating target structure with appropriate precursors from a data base in ways that defy human visual analysis (ref. 21, 28).

One of our strategies in the area of natural product synthesis over the years has been to capitalize on the use of chiral templates as starting materials. Utilizing amino acids, carbohydrates, hydroxy acids and carbocyclic natural products, we have completed the total synthesis of a number of pharmacologically relevant and clinically important natural products, as well as related compounds.

For example, the potent β-lactam antibiotic thienamycin (imipenem) (ref. 11) was synthesized from L-threonine as a template, recognizing its convergence with the "left" hand portion of the target (ref. 29) (Fig. 5). Of interest was the development of methods that effectively replace the amino group by a carbon substituent (ref. 30), and the discovery of modes of assembling the heterobicyclic structure. The half penem-half-thienamycin structure FCE-22101 (ref. 31) was also synthesized from L-threonine (ref. 32). Another example is the total synthesis of avermectin B_{1a} aglycone from L-malic acid, L-isoleucine and (−)-quinic acid.(ref. 33, 34) Each individual chiral template was chemically manipulated in a systematic way en route to specific substructures leading to highly functionalized subunits. The final assembly of such units presented another challenge which is evident from inspection of the structure of the target molecule.

A third example of a clinically relevant natural product is dihydromevinolin (ref. 35,36) which is closely related to mevinolin (mevacor) (ref. 37). Here, a disconnective analysis led us to L-glutamic acid as a chiral template which is literally concealed in ring A of the octahydronaphthalene subunit.

Interestingly, thienamycin, mevinolin and avermectin B_{1a} are commercially important products. Except for thienamycin which is produced by total synthesis starting with dihydroxyacetone and proceeding through an asymmetric functionalization (ref. 11), the other two (avermectin B_{1a} and mevinolin) are produced by fermentation. The synthetic efforts by our group and other groups have nevertheless laid a strong chemical foundation for the possibility of preparing semi-synthetic analogs and other transformation products.

THE COMMON PRECURSOR STRATEGY

Another strategy that we have adopted in our group is admirably suited to the synthesis of molecules containing identical or biosynthetically related subunits. The polyene antifungal antibiotic amphotericin B (ref. 38) has four sets of alternating 1,3-diol groups, in addition to two other subunits that are derived from propionate, acetate and related biosynthetic pathways (Fig. 6, subunits A, B, C). Our strategy consisted in the synthesis of these subunits from a common progenitor, namely L-glutamic acid (ref. 39). The readily available (4*R*)-4-hydroxymethyl butyrolactone, and the corresponding butenolide were used as building blocks for all three subunits thus rendering the synthesis plan extremely convergent, since a common precursor was used for seemingly different substructures.

In a related context, we had previously shown the versatility of such lactone templates in generating acyclic motifs bearing a predetermined combination of substitution patterns of C-methyl and hydroxy groups with a high degree of stereochemical control (ref. 21, 40). Figure 7 illustrates the general reiterative strategy that leads to diastereomeric acids and lactones containing alternating "propionate-derived" groups. It is noteworthy to point out that during each sequence, the stereochemistry of incoming groups (Me, OH) can be controlled by the disposition of vicinal groups. The nature of the ring junction in the butenolide in the second, third, etc. templates is a function of the stereochemistry of the terminal epoxide which is totally tunable.

The second example is the synthesis of ionomycin (ref. 41, 42), where, once again we unraveled L-glutamic acid as a hidden progenitor for virtually the entire C_1-C_{22} acyclic subunit of the molecule (Fig. 8). Using butyrolactone and butenolide templates derived from the amino acid, we were able to systematically introduce the alternating C-methyl substitution pattern with complete stereochemical control.

In the previous two examples a common precursor was used to construct different subunits of one and the same target molecule. Another efficient utilization of this strategy is to use a common precursor to synthesize *a series of stereochemically related members of a family of natural products*. Fig. 9 shows this notion in the case of heteroyohimbine alkaloids that can be synthesized from D-glucose (ref. 43, 44).

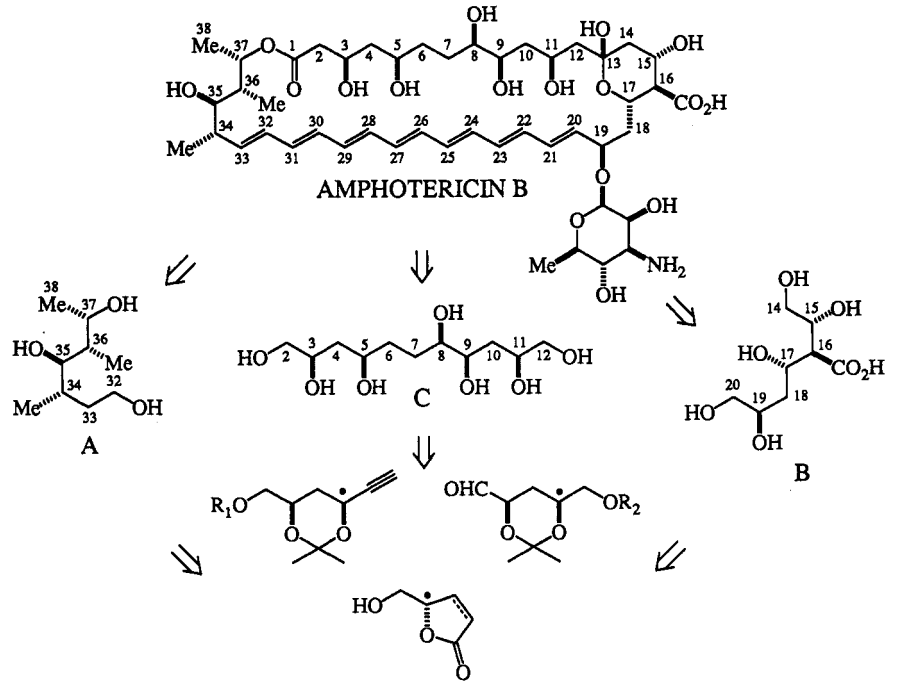


Fig. 6. Synthesis of subunits in amphotericin B from common butanolide / butenolide precursors using the Chiron Approach.

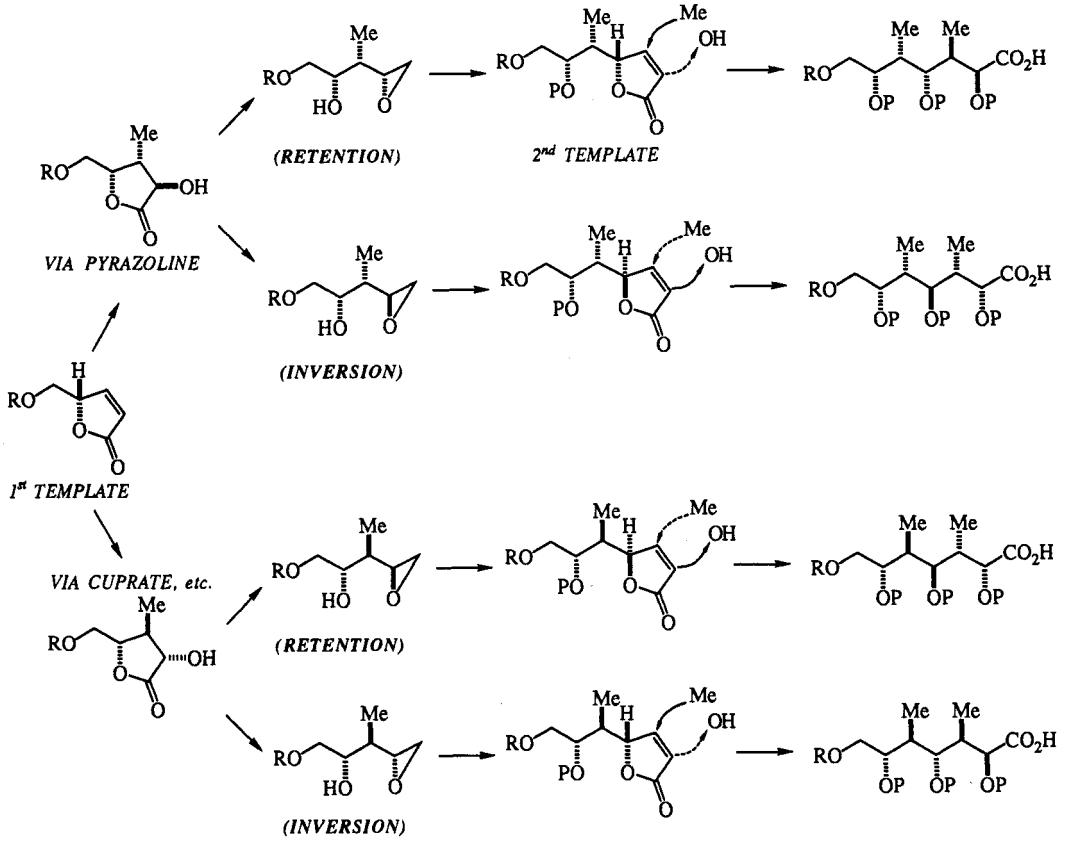


Fig. 7. The replicating lactone strategy for polypropionate motifs.

Although this necessitates "stripping" all the hydroxyl groups and replacing them with carbon substituents, the strategy is quite efficient since sequential C-functionalization of unsaturated intermediates is involved with essentially complete stereochemical control. As can be seen in Figure 9, the members of this group differ in their stereochemical orientation at C-19 and C-20. These can be readily controlled in the chirons derived from the carbohydrate template by Mitsunobu inversion (C-19 for ajmalicine) and tetrahydroalstonine, and by reductive methods to control the ring junctions (C19/C-20, tetrahydroalstonine, rauniticine).

Whereas D-glucose was a visually recognizable chiral template upon which to build the heteroyohimbines as shown in Figure 9, it is of interest to see how it was used in the synthesis of (+)-meroquinene (ref. 45, 46) which is a biogenetic precursor to other alkaloids such as quinine and cinchonamine (Fig. 9). It is evident that all the hydroxyl groups in D-glucose must be destroyed en route to the construction of the carbon skeleton of (+)-meroquinene, which can be regarded as a stereochemically wasteful procedure. However, the D-glucose framework is efficiently used to install the two vicinal C-substituents by a sequential stereocontrolled one-step conjugate addition and enolate trapping protocol on a readily available enone.

Inevitably, a ketone deoxygenation and an oxidative cleavage must be done in order to reach the dialdehyde intermediate which was subjected to a reductive amination reaction to insert the nitrogen atom. Considering the size of the target molecule, meroquinene, a more expeditions synthetic approach can be envisaged, perhaps proceeding through fewer steps from the carbocyclization readily available acyclic N-protected intermediates (ref. 47). Control of absolute stereochemistry would still remain as a limiting factor for the synthesis of enantiomerically pure meroquinene, hence the validity of the chiron approach.

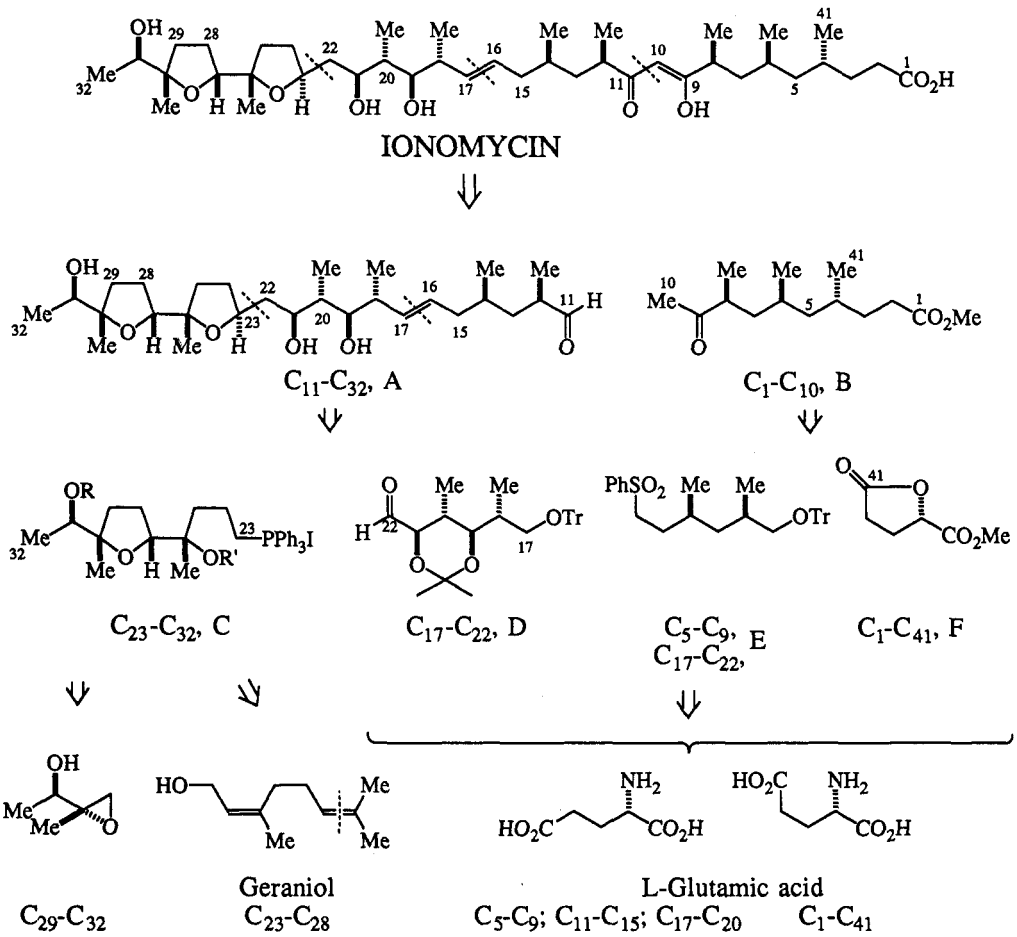


Fig. 8. Stereochemical decoding of ionomycin and the emergence of L-glutamic acid as a common progenitor via butanolide templates.

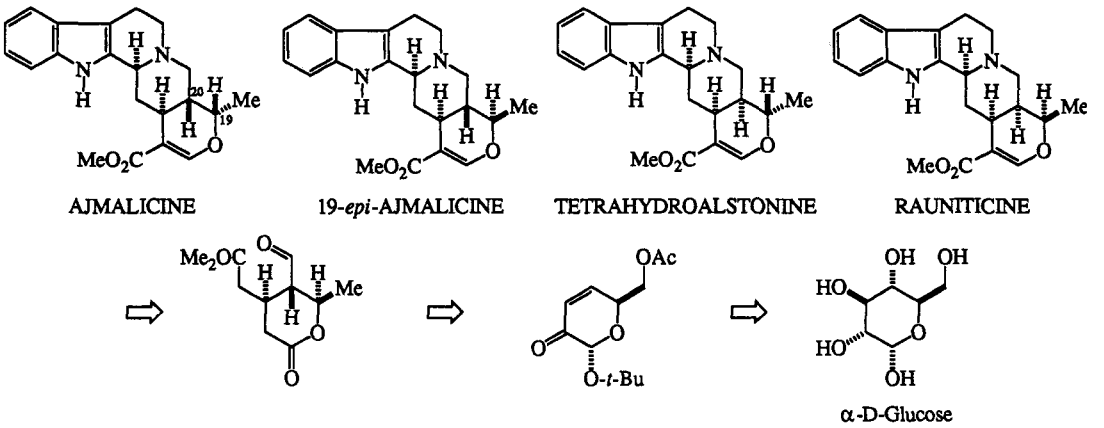


Fig. 9. Access to heteroyohimbine alkaloids from D-glucose as a common precursor.

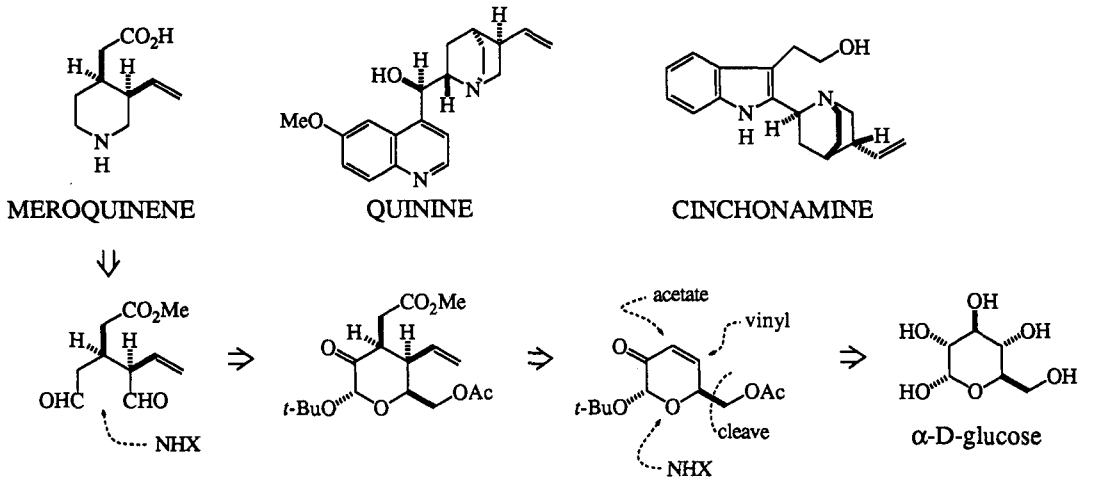


Fig. 10. Synthesis of (+)-meroquinene from D-glucose.

TOTAL SYNTHESIS USING QUINIC ACID AS A CHIRAL TEMPLATE

(−)-Quinic acid is a versatile and readily available polyfunctionalized cyclohexane. Because of the presence of a carboxyl group and four hydroxyl groups with specific dispositions, it can be considered as an ideal starting material for the total synthesis of a variety of carbocyclic natural products. Indeed the literature records a number of such uses (ref. 48).

We have capitalized on the unique arrangement of the functional groups in (−)-quinic acid in relation to the carbocyclic substructures of a number of natural products, as well as to heterocyclic structures. In the latter cases, the cyclohexane motif could be chemically modified and oxidatively cleaved to match non-carbocyclic counterparts. The hexahydrobenzofuran portion of avermectin B_{1a} was synthesized from (−)-quinic acid in our efforts directed toward the total synthesis of the parent anthelmintic agent (Fig. 5) (ref. 49). Current work in our laboratory has focussed on the elaboration of rings D and E of (−)-reserpine form (−)-quinic acid as summarized in Fig. 11 (ref. 50,51).

The vicinal diol unit in ring E of reserpine can be found in quinic acid in addition to a "usable" carbocyclic acid group. After differential protection of the hydroxyl groups, the challenge remains to find stereocontrolled methods for introducing an acetic acid side chain and a methoxycarbonyl group in quinic acid. This was done by transforming quinic acid into an enone precursor, and functionalizing the carbonyl group to introduce a carboxyl equivalent and an appropriate ester enolate equivalent for a stereocontrolled Michael-type addition. Thus, not only did quinic acid provide a suitable chiral template for the elaboration of ring E, but the inherent chirality permitted the introduction of the carbon substituents in a highly stereocontrolled manner (ref. 52).

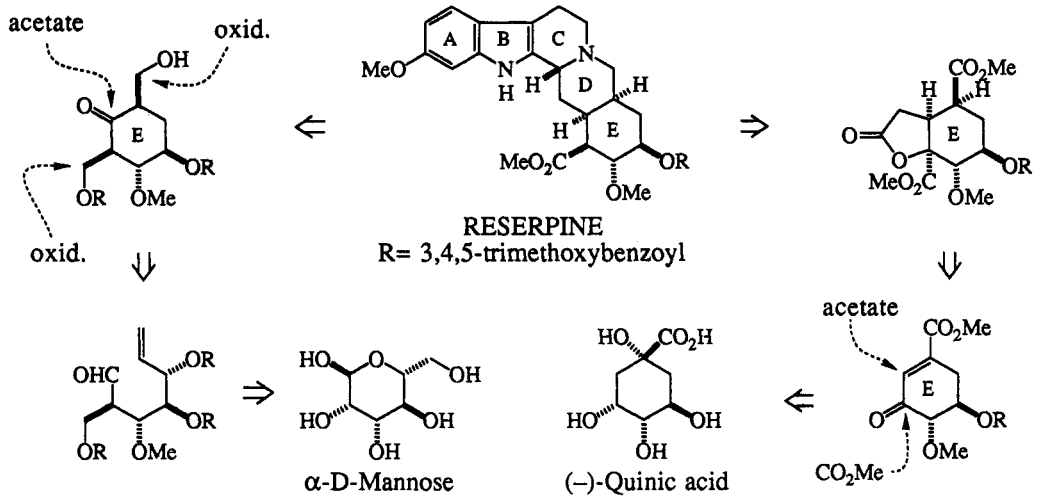


Fig. 11. Approaches to the synthesis of ring E of (–)-reserpine from D-mannose and (–)-quinic acid.

A carbohydrate precursor approach to ring E was also developed in our laboratories some time ago (Fig. 11). The key reaction was an intramolecular nitrile oxide cyclization from the appropriately functionalized aldehyde. The latter was prepared from α-D-mannose in a stereocontrolled hydroxymethylation at C-2 via the corresponding exocyclic olefin (ref. 53).

The visual connection between (+)-palytantin and its aldehyde analog frequentin, and quinic acid is an obvious one as seen in Fig. 12.

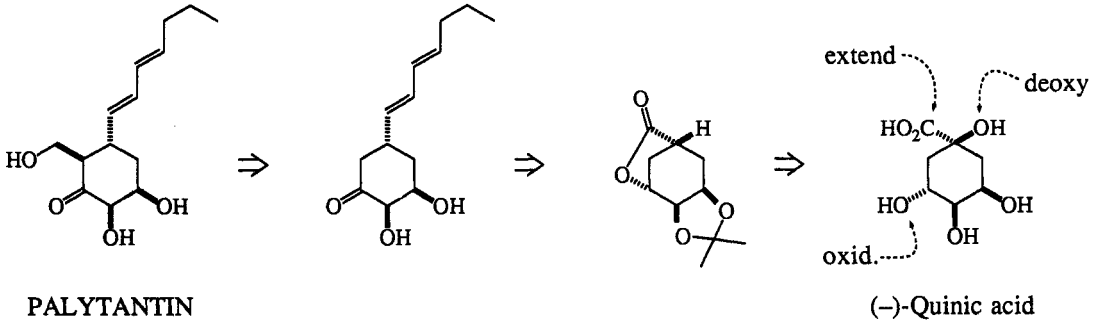


Fig. 12. Total synthesis of (+)-palytantin from (–)-quinic acid.

Once the desired orientation of the *cis*-diol unit in quinic acid is "matched" with the diol in palytantin, the task at hand would be to systematically manipulate the carbocyclic template in order to introduce the two carbon substituents. Trivial as this may seem, the hydroxymethylation reaction required the elaboration of specific conditions, and a change to O-silyl protective groups in order to control the site-selectivity of the enolate alkylation (secondary vs tertiary sites!) (ref. 54, 55).

(–)-TETRAHYDROLIPSTATIN

Lipstatin and its hydrogenated analog tetrahydrolipstatin are among a small group of naturally occurring β-lactones with pharmacologically important profiles. Lipstatin, isolated in 1987 and its tetrahydro derivative are potent inhibitors of pancreatic lipase (ref. 56). Tetrahydrolipstatin is presently undergoing clinical trials as an antiobesity agent. In view of the potential marketing prospects, it is of interest to consider a totally synthetic route to this class of β-lactones. There are at present six reported total syntheses of tetrahydrolipstatin, with varying degrees of efficiency and practical applicability (ref. 57-62) (Fig. 13).

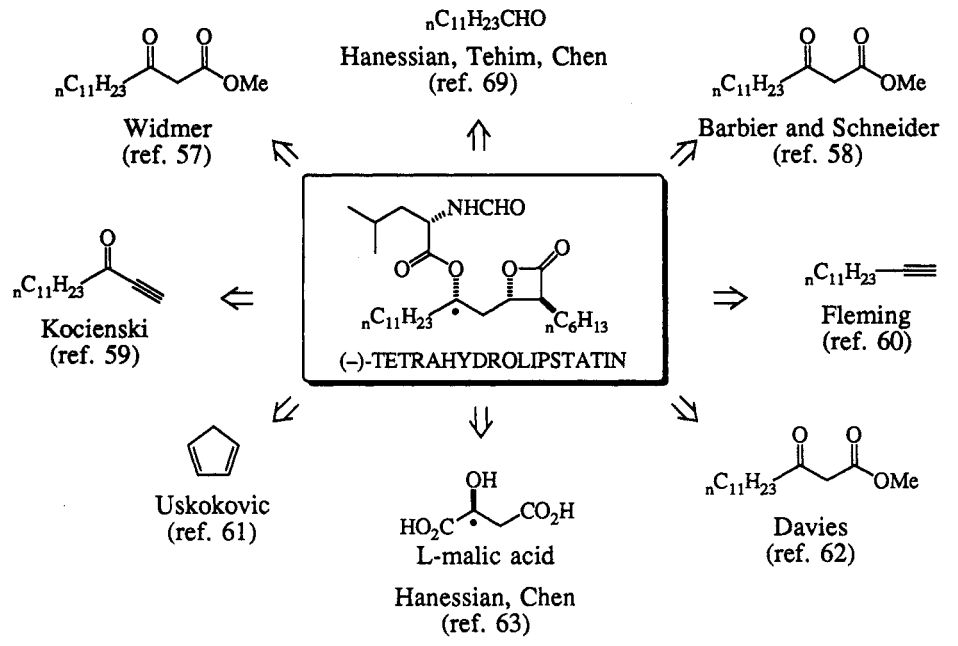


Fig. 13. Starting materials used in the total synthesis of (–)-tetrahydrolipstatin.

It is interesting that each synthesis has a conceptually different approach in their key steps even though four out of six syntheses utilize a chiral non-racemic 3-benzyloxy-tetradecanal. Our initial approach which was completed shortly after the original syntheses of Barbier and Schneider (ref. 58) relied on the utilization of L -malic acid as a chiral template (ref. 63), and its elaboration to the above mentioned aldehyde (Fig. 14).

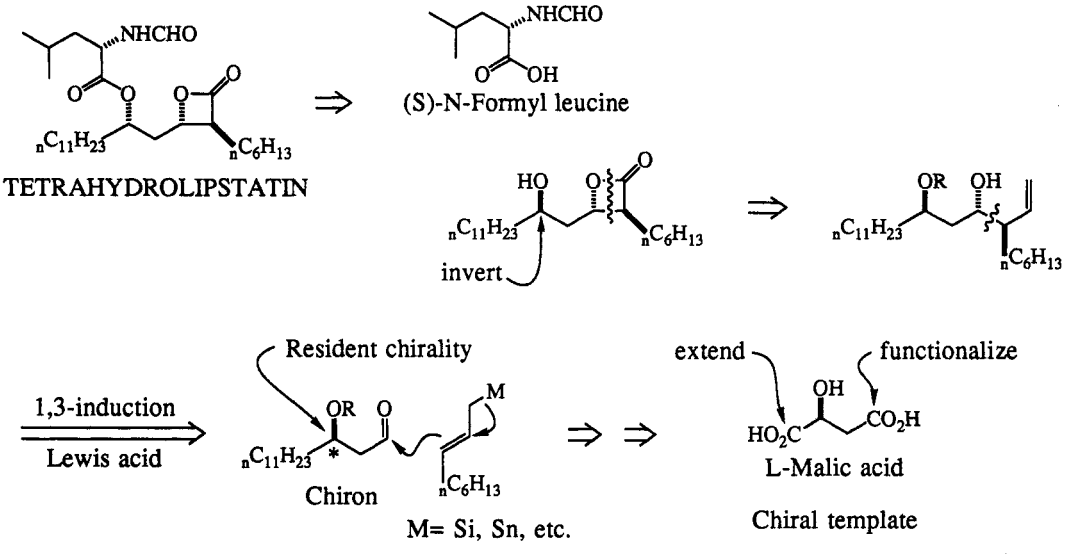


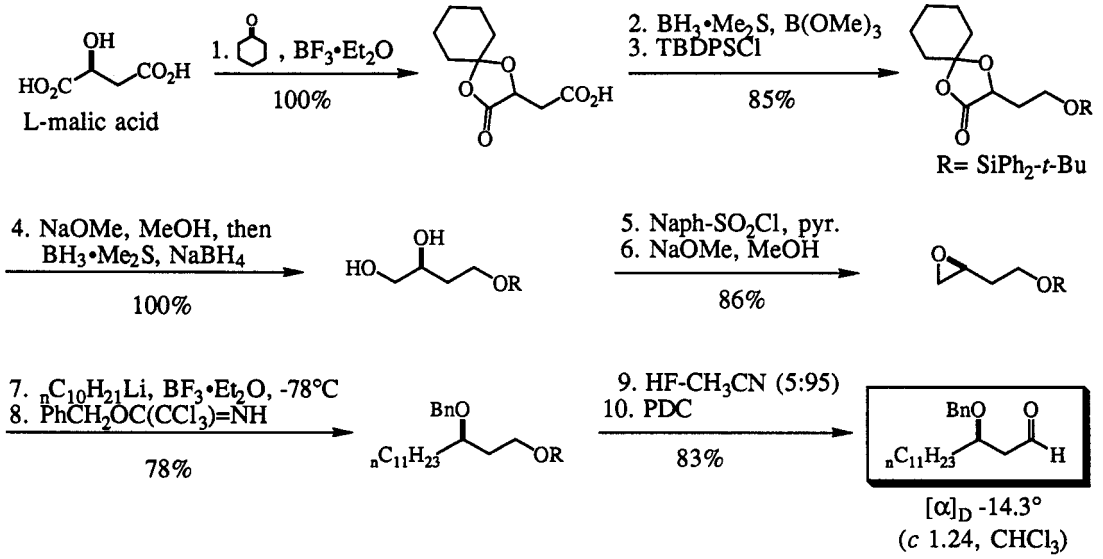
Fig. 14. Disconnective analysis of (–)-tetrahydrolipstatin and the emergence of L-malic acid as a chiral template-resident-chirality dependent 1,3-asymmetric alkenylation.

Relying on asymmetric induction of a resident β-alkoxy group, a key step was the γ-alkyl allylsilane-mediated functionalization of the aldehyde to provide a terminal olefin as a precursor to the carboxylic acid, and eventually the target molecule. Of the four possible diastereomers that could be formed in the Lewis acid catalyzed step for the introduction of the nonenyl side-chain, only the isomer with an epimerizable carbon center would be useful for the ultimate synthesis in addition to the desired isomer of course. Once

the β-lactone formed, the esterification was envisaged to take place via a Mitsunobu reaction (ref. 64) with inversion of configuration as already demonstrated previously (ref. 57,58).

Scheme 1 illustrates the route leading to enantiomerically pure (R)-3-benzyloxytetradecanal from L-malic acid (ref. 63). The same aldehyde has been expediently produced from the asymmetric hydrogenation of the corresponding β-keto ester in high enantiomeric purity (ref. 58,62). In spite of the relatively high overall yield, the L-malic acid template route is impractical on an industrial scale in view of the number of steps needed to elaborate the relatively simple target aldehyde. As in many other instances where several reactive functional groups are present (CO_2H, OH), temporary protection and deprotection are inevitable, hence the number of extra steps. However, the stereochemical integrity of the original L-malic acid remains intact and the target aldehyde is enantiomerically pure.

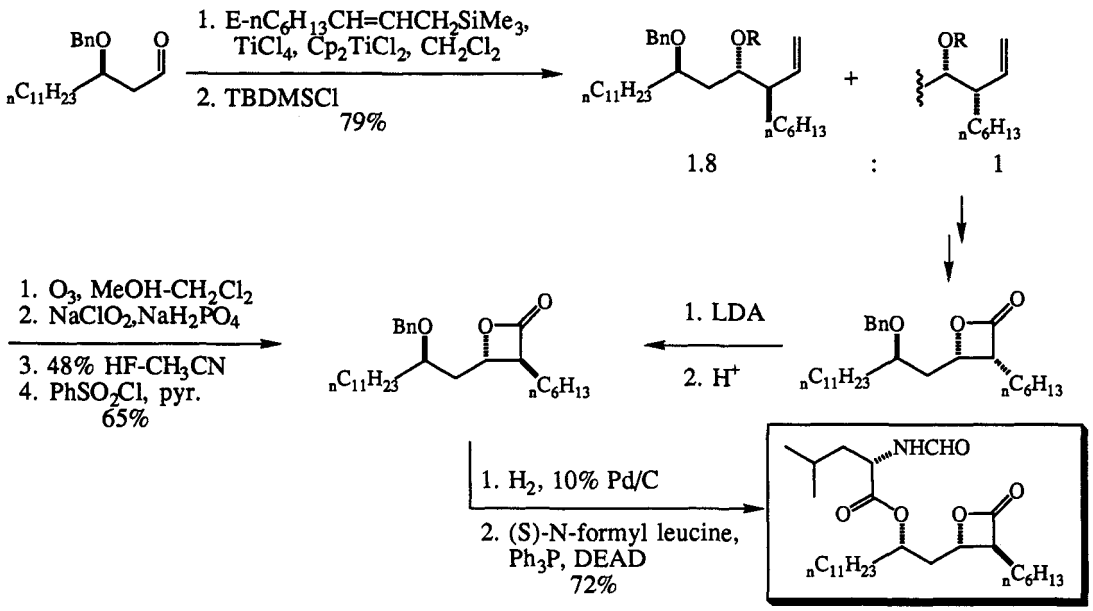
Scheme 1. Stereocontrolled synthesis of a key aldehyde from L-malic acid.



After extensive studies on the effect of various Lewis acids, it was found that the treatment of the aldehyde with E-7-nonenyl 1-trimethylsilane in the presence of $TiCl_4$ and Cp_2TiCl_2 in dichloromethane at -78°C, gave the most favorable isomer distribution. Under these conditions the desired *anti/anti* isomer and the undesired but epimerizable *anti/syn* isomer were formed in a ratio of 1.8:1. Only traces of a third isomer (*syn/syn)* could be detected with none of the fourth. Unfortunately inclusion of several additives and other Lewis acids only diminished the ratio of the isomers, favoring the *anti/syn* isomer. The corresponding reactions with E-7-nonenyl 1-tributylstannane also led to an unimpressive ratio of the wanted, epimerizable and a third isomer ($TiCl_4$, THF, -78°C, 7:10:1 respectively). The major two isomers could be easily separated by chromatography as their TBDMS ethers. The major isomer was converted into the desired β-lactone by sequential oxidative cleavage of the terminal olefin, oxidation to the corresponding acid, deprotection and lactonization in high overall yield. In view of the disposition of the hexyl side-chain, it was possible to effect partial epimerization by treatment with LDA followed by a proton quench. Unfortunately the steric bias is not large enough to ensure complete epimerization to the desired *trans*-lactone. In an alternative approach alkylation of a β-lactone with n-hexyl iodide via the corresponding enolate was not successful. Mulzer and Kerkmann (ref. 65) have shown that alkylation of β-lactones are favored when an α-substituent is already present which is not the case here. Finally, hydrogenolysis and introduction of the N-formyl L-leucine unit via a Mitsunobu reaction completed the synthesis affording enantiomerically pure (−)-tetrahydrolipstatin identical in all respects with the authentic natural product. The synthesis comprises 8 steps from the readily available aldehyde (ref. 58,66), and proceeds in 36% overall yield.

Although the Lewis acid mediated C-allylation of aldehydes with allyl trimethylsilanes (ref. 67) and allyl tri-alkylstannanes (ref. 68) are well known reactions, the extension of this methodology to γ-substituted allylic systems such as the E-nonenyl moiety used in the work has been seldom explored. In spite of the relatively high overall yield (36%) and the brevity of steps from the aldehyde, the stereochemical outcome of the key Lewis acid-catalyzed C-nonenylation reaction (Scheme 2) is not condusive to large scale production.

Scheme 2. Total synthesis of (–)-tetrahydrolipstatin.



An alternative approach presently in progress relies on a "totally asymmetric" route starting from lauraldehyde and proceeds in 9 steps in an overall yield of 21-26% making use of only one protective group. This highly stereocontrolled route utilizes reagent and substrate control in key steps, and it has the potential for optimization to large-scale production (ref. 69).

SYNOPSIS

Progress in the total synthesis of natural products since the synthesis of urea by Wöhler in 1828 has been phenomenal. With a constant flow of novel natural products that have intricate structures and interesting biological activities, every decade seems to have generated its own target molecules as challenges to the synthetic chemist (Fig. 15). Armed with an impressive armamentarium of modern synthetic methods, and aided by state-of-the-art instrumental techniques, these challenges have been met head-on with extremely gratifying results (ref. 70). Complex frameworks of natural products with an abundance of stereogenic centers and seemingly untouchable concatenations of functionality have succumbed to the ingenuity and creativity of the synthetic organic chemist.

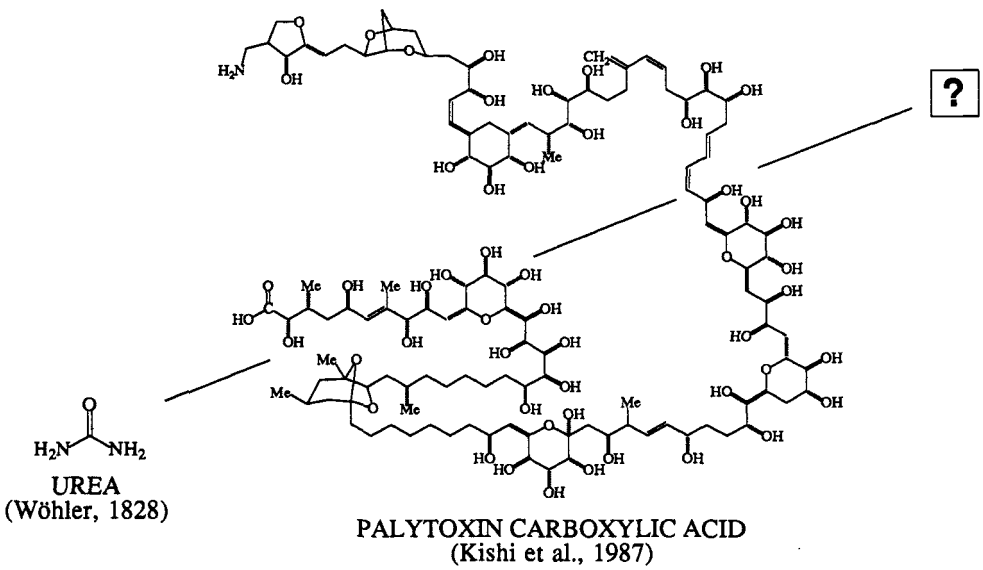


Fig. 15. Conquest of natural products by synthesis – From urea, the first and smallest organic natural product, to palytoxin, the largest but not the last...

Through the advent of modern preparative methods coupled with other tools (enzymes, biotechnology, etc.), we are capable of preparing an unlimited variety of chiral, non-racemic precursors even if the premium in efficiency or number of steps is sometimes high. A major stumbling block remains however in assembling such subunits particularly in extended structures bearing multiple functionality. The assembly of larger structural units through C-C bond formation relies, with few exceptions, on the union of nucleophilic (anionic) and electrophilic (aldehyde, ketone, ester, etc.) components. The Julia-type coupling of sulfone anions (ref. 71), phosphorous-based anion or ylid methodology (ref. 72), enolate anions (ref. 73), and occasionally organometallic species (ref. 74) are among the handful of methods presently available. The successful applications of these methods however depends on the nature and disposition of functionality in the substrates which are invariably masked by protective groups. Coordination with cations, steric factors, aggregation, solvent effects and related phenomena frequently result in unreactivity or inefficient conversions. Thus, a seemingly uneventful climb (save for frequent rests and detours) may come to a grinding halt in front of an impasse not far from the summit. Perhaps it is at such times that the synthetic organic chemist is at his or her best, for rare are the documented cases of "abandoned" syntheses. Although we invariably pay a price for our original synthesis plan sometime during the execution stage, there are many lessons learned and rewards earned as a result of one of the ultimate experiences in synthesis - that of producing a certain quantity of a biologically relevant natural product from laboratory chemicals using art, craft and logic.

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