Computer-Assisted Perception of Similarity Using the Chiron Program: A Powerful Tool for the Analysis and Prediction of Biogenetic Patterns

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The stereochemical and functional patterns in a family of complex natural products derived from a common biosynthetic pathway can be easily visualized through the generation of Fischer and extended projections using the Chiron computer program. Application of this protocol to a series of polyether antibiotics reveals interesting trends in their patterns of substitution as well as in stereochemical relationships.

INTRODUCTION

The notion of relatedness or similarity is a fundamental aspect of human perception. Be it on the street, at home, or in the work environment, the mind's eye is continuously interrelating images, objects, and shapes, processing thoughts into images and vice versa.[1] In the words of Aristotle, "Thought is impossible without an image", a notion that is admirably suited to our profession and to the subdiscipline of synthetic organic chemistry. Indeed much of our chemical thinking is done through the imagery of structures which we "see" or "generate" in written forms. What we do with such structures depends on the task at hand. Consider for instance, the important objective of devising strategies for the total or partial synthesis of pharmacologically important molecules which may or may not be biogenetically related. Invariably the first step is to draw the chemical structure of the molecule(s) no matter how simple or complex. Provided one starts with an unbiased attitude, what follows immediately after the structure is drawn is a fascinating series of events where mind meets the eye, resulting in an uncontrollable outburst of reflex thoughts that make you "see" the synthesis through reaction types (Diels–Alder, etc.) or through the emergence of substructures that resemble a familiar smaller molecule (chiron or synthon).[2] A synthesis plan is roughly formulated, and soon, one is faced with a heuristic feature of dimensionality and perspective, hence of chirality. The problem is all the more critical when one is dealing with relatively complex natural products harboring several stereogenic centers, and when a series of target structures are being considered.[3] Chemical ingenuity in generating functional groups through specific reactions and creative bond construction protocols are set aside momentarily in order to address such issues as stereochemistry, symmetry, topology, and possible relationships between substructures within one and the same molecule. The problem is compounded if more than one structure is the objective of a general and practical synthesis plan.

CHIRON PROGRAM

Being cognizant of the inherent limitations of visual analysis in relation to rapid stereochemical decoding and translating flat two-dimensional structures into perspective structures, we developed the Chiron computer program as an aid to synthesis planning.[2,4,5] We had previously shown[4] that among numerous options available in the program, those that generated Fischer and extended projections were most useful in rapidly relating entire structures or substructures with regard to functional groups and absolute stereochemistry. Another unique feature is the possibility to show identical (superimposable) or enantiomeric chiral substructures within the framework of one molecule or occurring in two different molecules (IDENT. and ENANT. options).

Four carbon or longer chains (acyclic, cyclic, etc.) harboring one to several stereogenic centers are instantly located, color-coded, and displayed on the screen showing the direction of juxtaposition at the extremity of the chain. The discovery of such common subunits greatly facilitates the design of synthesis strategies where one and the same chiral precursor (Chiron) can be utilized in order to construct the corresponding substructure in the respective target molecules.

Another feature in the Chiron program is a rapid processing of structures in order to find "similar" shapes among chemically or biogenetically unrelated structures (the MATCH option). Here a "smaller" C_{n-1} carbon skeleton will match a "larger" $C_{n+1,2}$, etc. structure regardless of functional of stereochemical overlap of existing groups. This type of matching of substructures allows for a rapid and rough search for possible synthetic precursors by adjustment of functionality that coincidentally matches a corresponding one in the target molecule. It could also be used for a 2-D type pharmacophore search after some adjustments.

In this paper, we show additional examples of the utility of the Chiron program in interrelating chiral substructures in molecules that are biogenetically related in part or totally and in the matching of structures with common or similar substructures.

BIOGENETIC RELATIONSHIPS AMONG POLYETHER ANTIBIOTICS

This class of antibiotics, produced by actinomycetes, has been the subject of extensive structural, synthetic, and medicinal studies.[6] Their primary biological activity is manifested in their ability to interfere with the transport of ions across membranes, since they are powerful ion-sequestering agents, hence the name ionophore antibiotic. Their intriguing structures have been elucidated mainly by elegant X-ray crystallographic studies[7] and a number of total syntheses have been reported based on ingenious strategies.[8] In a seminal paper published in 1983 by Cane et al.,[9] a proposal was made for a unified stereochemical model where the structural and functional regularity in the polyether antibiotics was interpreted on a biosynthetic basis. Using monensin A[10,11] as a prototype, a triene-to-triepoxide pathway was proposed and further elaborated to account for the structures and substitution patterns of a large number of polyether antibiotics.[12] Taking a group of compounds that are originally derived from acetate-

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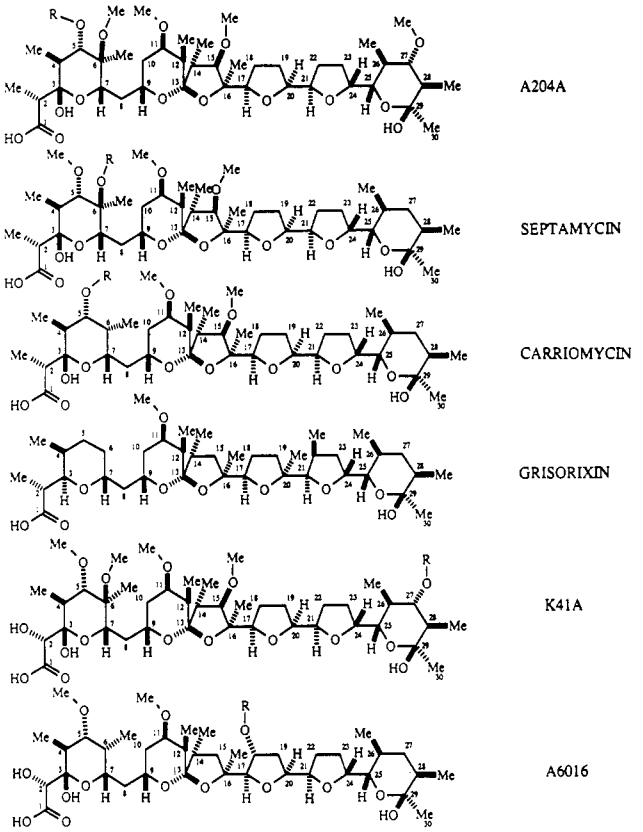


Figure 1. Structures of some C-30 backbone polyether antibiotics (group A; R = glycosides).

propionate-propionate-acetate starter units (APPA), it was concluded that, in spite of the numerous possibilities, the configuration of the hydroxy and methyl-bearing carbon atoms within the first 12 biogenetic units was constant throughout the series. These observations and other empirical summaries of known structural data led Cane and co-workers[9] to formulate a model which could be potentially useful in the search and identification of new types of polyether antibiotics. A related empirical configurational model was developed earlier by Celmer[13] for the macrolide antibiotics, where considerable stereoregularity can be found. In this study, the macrocyclic lactone structures were depicted as Fischer projections which greatly facilitated the direct visual comparisons of particular substitution patterns at individual carbon atoms along the chain. In the absence of automatic perception tools (computers, etc.) at the time of the Celmer study, it is presumed that the Fischer projections were generated either visually or by manually opening the lactone ring of an appropriate molecular model and then stretching the carbon skeleton to produce the acyclic equivalent from which the generalized configurational model was derived.

The possibility to instantly generate Fischer and extended projections in the Chiron program, coupled with the recognition of identical and enantiomeric subunits, provides a powerful tool to study biogenetic relationships among a group of closely related polyfunctional compounds such as the polyether antibiotics, macrolides, etc. Figure 1 depicts six structures selected among the C-30 monovalent monospiroketal polyether antibiotics and their glycosidic variants. Using a combination of the Grid and Template drawing options, these structures were "ligned up" in such a way so as to facilitate the perception of functional and stereochemical similarity or divergence visually.

Utilizing the Fischer and extended options in the CASA (Computer Assisted Stereochemical Analysis) module, the corresponding projections were generated, and they are shown in Figures 2 and 3, respectively. Their "left-to-right" and "top-to-bottom" alignments, respectively, on the screen or on hardcopy allows for a facile comparison of substitution patterns and stereochemistry at individual carbon atoms or among sets of carbon atoms along the chain. For example, with the aid of these projections, one notices greater homology of substituents between A204,[14] septamycin,[15] and carriomycin[16] (with minor exceptions) on the one hand, and between grisorixin[17] and nigericin,[18] the C-29 hydroxymethyl analog of grisorixin (not shown), on the other. There is also a very close relationship between A204 and K41A[19] where the C-2 methyl group in the former is replaced by a hydroxyl group in the latter, yet maintaining a C-2 D-glycero relationship in both. Antibiotic A6106[20] resembles K41A (C_1–C_5, C_7–C_{14}, C_{19}–C_{26}, etc.), but its oxidation pattern at other sites is sufficiently diverse; hence, its probable emergence from a different triepoxide progenitor. In fact, Cane and collaborators[9] have proposed a common triepoxide precursor for A204 and K41A (and B), since the difference lies in the nature of the group at C-2. Likewise, the pairs septamycin–carriomycin and grisorixin–nigericin have been proposed to arise from two triepoxides, respectively.[9] For the purpose of a visual comparison of groups of polyether antibiotics having the most common functional and stereochemical features, we have grouped them as shown in Figure 1 (group A), being cognizant that from a biogenetic point of view they may be grouped somewhat differently.[9] The corresponding Fischer and extended projections as generated automatically by the program are shown in Figures 2 and 3, respectively. Here too, the facility with which such projections are available to the user is noteworthy. In these projections, substituents other than OH, Me, and H are perceived as CX (alkyl or branch) or OX (for ethers, including cyclic ethers). This stereochemical decoding feature is important when the ring junctions of the tetrahydropyrans and tetrahydropyran rings are concerned. Thus, in order to present these structures in acyclic forms while maintaining the stereochemical integrity at each stereogenic center, the C–O–C bonds are "broken" at each end and an "OX" substituent is attached. In other words, the C-2 and C-4 carbons of a tetrahydrofuran ring will each carry an oxygen and a hydrogen (or other substituent) in the acyclic projection. The program will not reconvert a Fischer or extended projection back to the original structure.

A second group of starter APPA unit polyether antibiotics (group B) is shown in Figure 4, which consists of lonomycin A[21] and C, mutalomycin,[22] and etheromycin.[23] The first two (including lonomycin B which is the C-3 anomer of A) are proposed to arise from a single triepoxide, while each of the other two have their individual progenitors.[9] Their Fischer and extended projections are illustrated in Figures 5 and 6, where it can be seen that etheromycin, a C-6 glycosidic analog, differs from the lonomycin group in the presence or absence of OH and Me groups at specific sites (C-10, C-12, C-22, C-23). Mutalomycin is identical to lonomycin A except for the presence of methoxy groups at C-23 and C-27, as well as the methylation of the C-11 hydroxy group in the latter.

Monensin A[10] and laidlomycin[24] are polyether antibiotics of the same biogenetic origin as are the other members discussed above, except that they consist of a 26-carbon backbone. The biosynthesis of monensin A has been elegantly studied by Cane and Day and their co-workers.[11]

Aided by the simplification of these complex structures through their Fischer projections, a C-25 "basic model" structure was generated that includes the minimum number

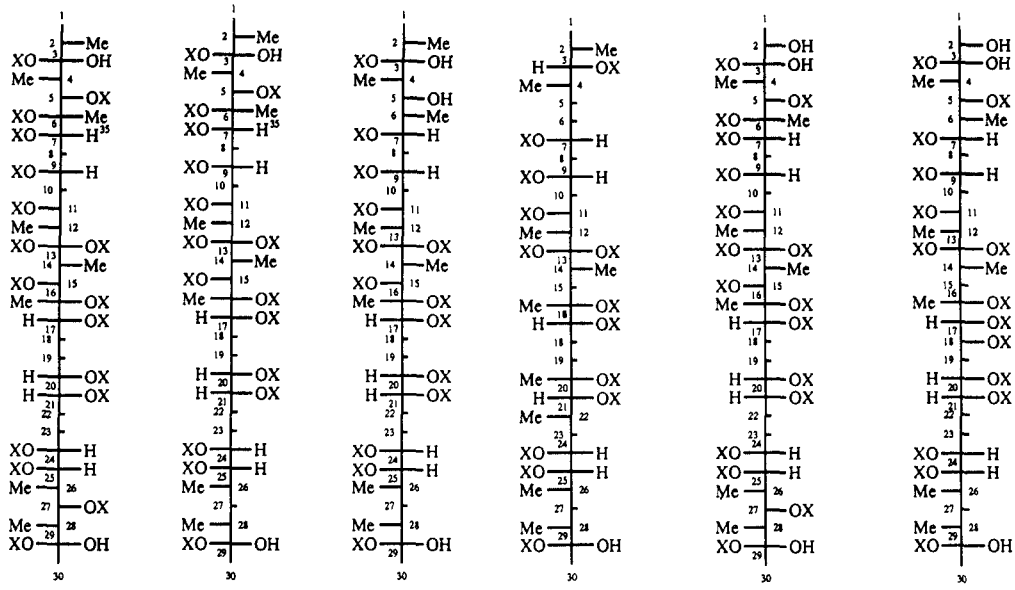


Figure 2. Fischer projections generated by the Chiron program (X = ether carbon or glycoside).

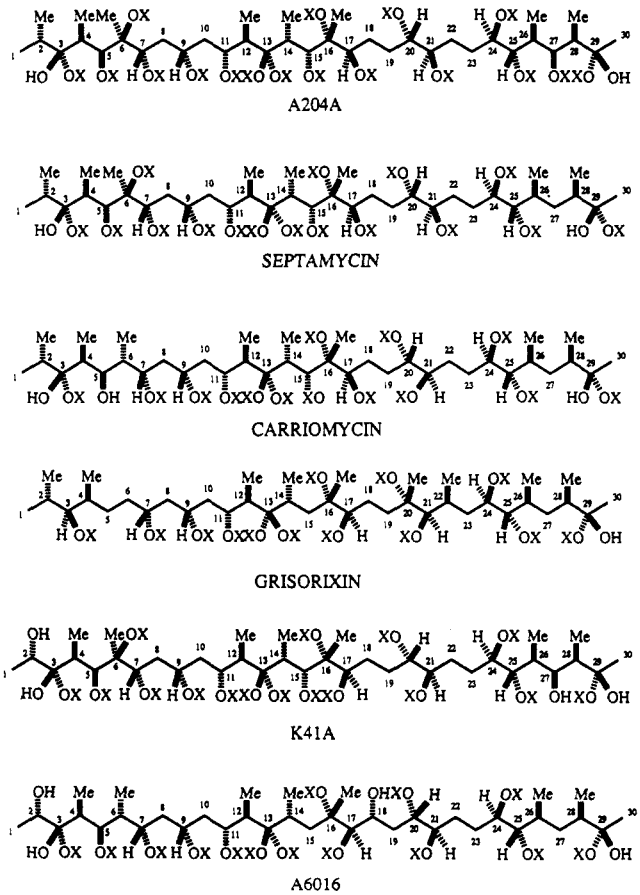


Figure 3. Extended projections generated by the Chiron program (X = ether carbon or glycoside).

of oxygen and C-methyl substituents that are present in virtually all the examples of APPA-derived ionophores (Figure 7). In other words, the polyether antibiotics shown in Figures 1 and 4 and their close analogs all share this basic structure including the stereochemistry and substituents as shown.[9] Further inspection of the structures shows that additional substituents (mainly methyl and alkoxy) can be present as a result of variations in biogenetic pathways and the type of precursors. Model II contains, in addition to the basic structure, OX and methyl substituents found in a subgroup

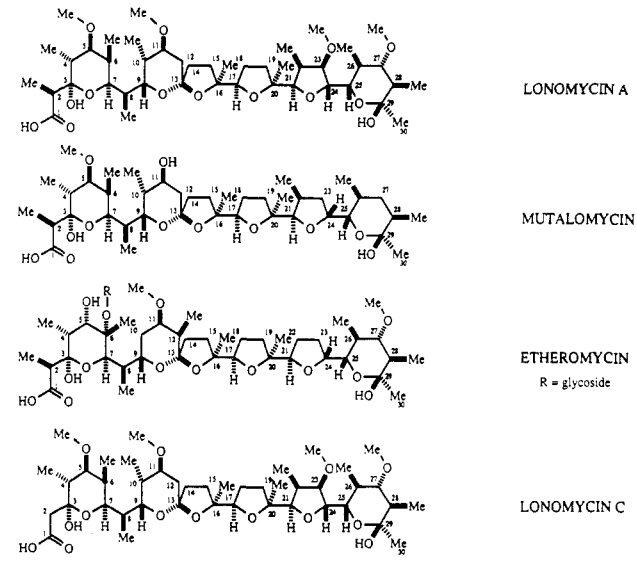


Figure 4. Structures of some C-30 backbone polyether antibiotics (group B).

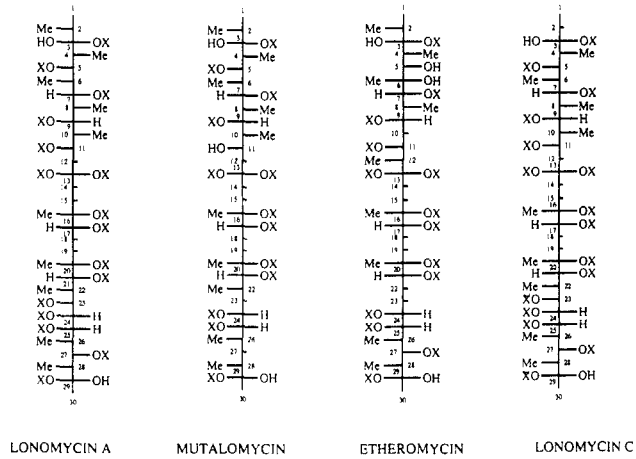


Figure 5. Fischer projections generated by the Chiron program (X = ether carbon or glycoside).

but not in all these compounds. When the entire C-1–C-30 structures are analyzed as their Fischer projections, an interesting stereochemical feature is unveiled (Figure 8). *The*

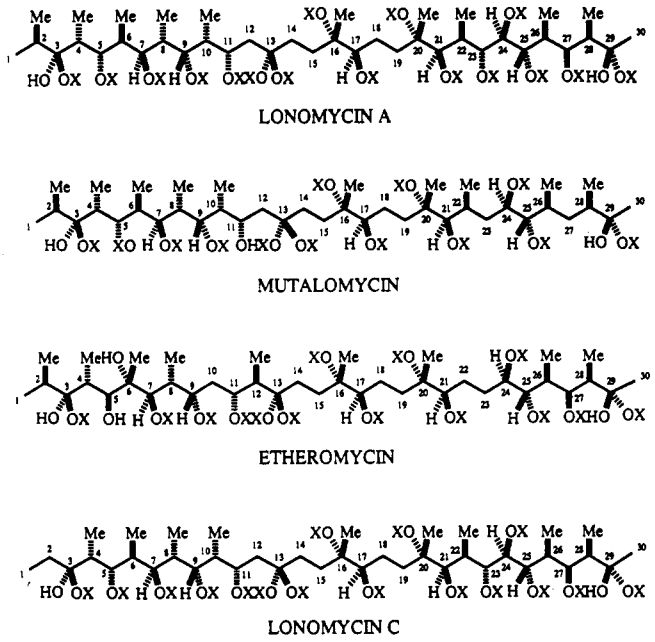


Figure 6. Extended projections generated by the Chiron program (X = ether carbon or glycoside).

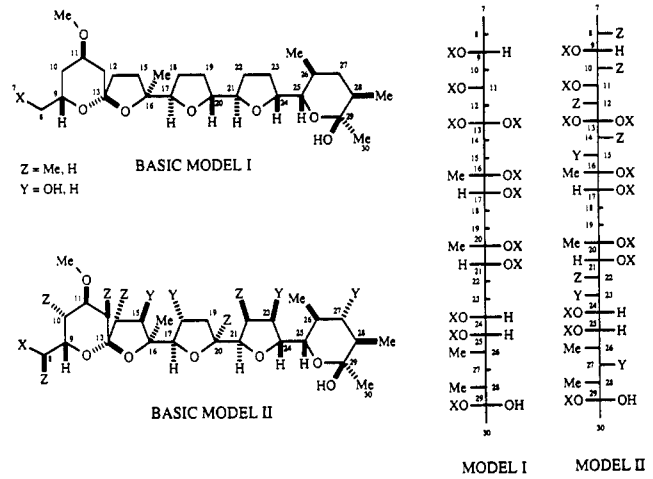


Figure 7. Basic biogenetic models for group A and B polyether antibiotics.

C-1–C-7 segments of one group of compounds (group A) has an enantiomeric relationship to the same segment in another group (group B). A composite projection, model III, is shown in Figure 8 where, with a few exceptions, C-methyl and OH substituents at C-1–C-7 have the opposite senses of chirality. Thus, the polyether antibiotics A-204A, septamycin, carriomycin, nigericin, and grisorixin (group A) belong to the "right-hand" branch in model III. Except for the presence of an OH group at C-2, K41A and A6106 are also in this class. On the other hand, lonomycin A and B, mutalomycin, and etheromycin (group B) belong to the "left-hand" branch in the model. A distinctive feature in group A structures (right-hand branch) is the absence of a C-methyl group at C-8 and at C-10 and the presence of a C-methyl group at C-12/C14. Thus, the biosynthesis of the group of polyether antibiotics that originates from a starter APPA unit proceeds with a basic stereochemical homogeneity and regularity throughout the series up to C-8 (C-4 in monensin) as pointed out in the Cane–Celmer–Westley prototype.[9] The reasons for the enantiomeric divergence for the C-1–C-7 segment in groups A and B are not clear. Evidently when the C-8 carbon originates from acetate rather than propionate, such as in A-204A, the subsequent elaboration of the chain involving two propionate units or their equivalents

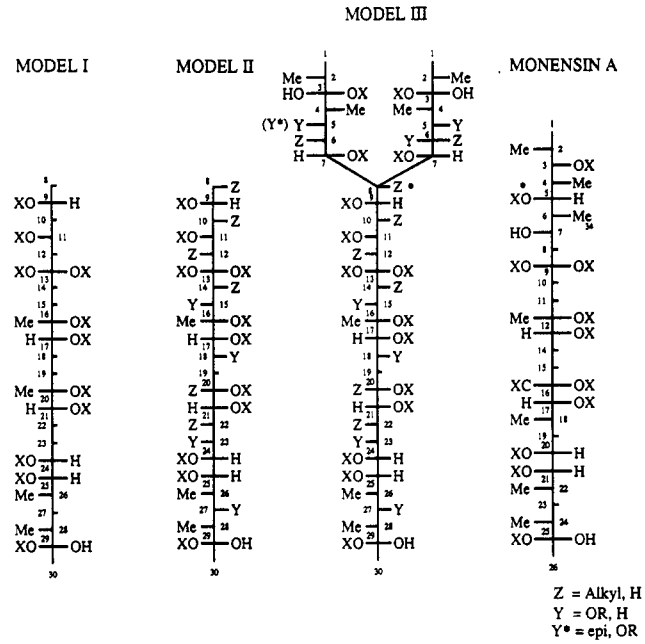


Figure 8. Composite biogenetic models for group A and B antibiotics.

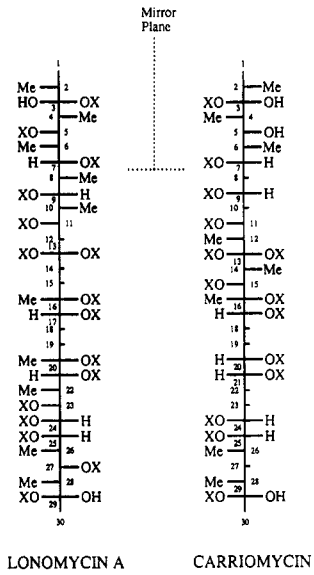


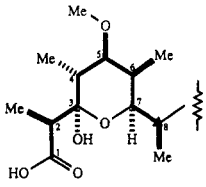
Figure 9. Stereochemical correlation between group A and group B polyether antibiotics.

terminating with a carboxyl group generates the enantiomeric C-1–C-7 segment. Whether this involves epimerization at enolizable sites or it is inherent in the biosynthetic pathway where molecular oxygen is also involved at some sites, is not known.

It is of interest that monensin A and laidlomycin belong to the lonomycin-type group (group B) and that the last propionate subunit follows the pattern seen in the left-hand branch (compare C-1–C-4 in monensin A with C-5–C-8 in model III). Monensin A is therefore an "incomplete" lonomycin A with a "missing" C-1–C-4 segment corresponding to two extra terminating propionate subunits.

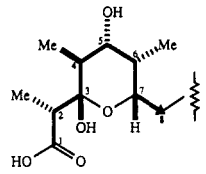
Figure 9 shows the Fischer projections of lonomycin A and carriomycin, illustrating the stereochemical and functional homology among the three from C-8 to C-30 (C_4–C_{26} in monensin). Figure 10 shows an example of the Enantiomer option in the Chiron program where the enantiomeric relationship at C-1–C-8 in lonomycin A and carriomycin is perceived and illustrated.

On the basis of the biogenetic principles proposed by Cane and co-workers[9] and the easily generated Fisher and extended



LONOMYCIN A

The C1–C8 and C1–C8 segments are enantiomeric (non-superimposable).



CARRIOMYCIN

Figure 10. ENANT. option showing the mirrow image (enantiomeric) relationship at C1–C8 in lonomycin A and carriomycin.

projections using the Chiron program, the stereochemical and functional features of new polyether antibiotics belonging to the APPA subclass can be predicted in a tentative manner. Thus, if the partial or total stereochemical pattern of the carboxy-terminal C-1–C-7 subunits and/or the presence or absence of key groups (e.g., C-8, C-10, C-12, methyl, or methylene) are known through degradative studies for example, a new antibiotic can be classified as belonging to group A or group B with the help of the composite model shown in Figure 8.

It is evident that other classes of biogenetically related natural products can be visualized in perspectives that facilitate the study of their stereochemical and functional interrelationships and progeny using the Chiron program.

APPENDIX

Chiron version 4.21 is a multiuser program written in Pascal (75 000 lines). It is available on UNIX (Silicon Graphics 4-D Series), VAX and Microvax, and Apple (MacII, MacChriron version 1.1). For a hardware diagram, see ref 4.

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