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STRUCTURAL AND STEREOCHEMICAL HOMOLOGY BETWEEN THE MACROLIDE AND POLYETHER ANTIBIOTICS

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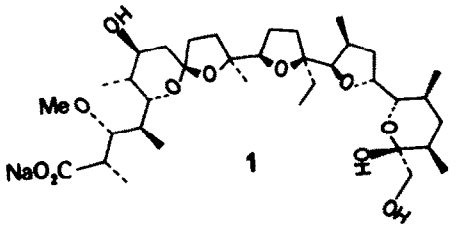
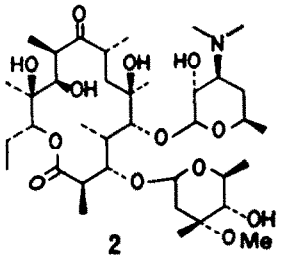
Summary - Structural and stereochemical similarities transcending the polyether and macrolide antibiotic classes are outlined. Significant correlations are highlighted between the macrolides mycinamicins I-V and the polyethers norboritomycins A and B and antibiotic X-14766A over a structural sequence derived from seven biosynthetic subunits.
The analogy is extended by comparison of a model which describes the stereochemistry of all the 16-membered macrolides with the Cane-Celmer-Westley PAPA prototype which summarises the stereochemistry of all the monovalent bisdispiroketal polyether antibiotics. Although the subunit constitution varies in individual cases the absolute configuration maintains its consistency at five of six asymmetric centres over the seven subunit sequence.

The polyethers[1] and macrolides[2] are two major antibiotic classes produced as secondary metabolites of actinomycetes. Monensin-A (1) a polyether and erythromycin-A (2) a macrolide are examples which find extensive use in veterinary and clinical medicine respectively. The commercial potential of new polyether and macrolide antibiotics has prompted vigorous screening programmes since their discovery in the 1950s, and to date more than 80 polyether and 100 macrolides have been isolated and their structures determined.





Striking structural and stereochemical similarities have been identified between individual members <u>within</u> each class.[3,4,5] This report highlights significant structural and stereochemical homology which exist <u>between</u> members of the two classes. In particular, attention is drawn to similarities which exist between the 16-membered macrolides and the monovalent dispiroketal class of polyether antibiotics.

Cane, Celmer and Westley described[3] two structural prototypes, designated APPA and PAPA which define the stereochemistry along the backbone of more than 30 polyether

structures (Figure 1).

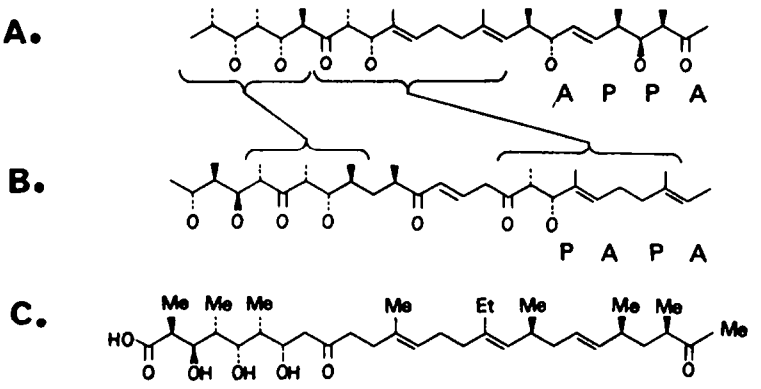


Figure 1. A. APPA polyene prototype. B. PAPA polyene prototype. C. Monensin-A polyene precursor.

Examination of polyene C shows that it can be accommodated within the APPA prototype. The bracketed segments highlight homologous sequences between the two prototypes. The designations APPA and PAPA arise from the sequence of the first four biosynthetic subunits of each prototype derived from acetate (A) and propionate (P). The PAPA prototype summarises many antibiotic structures which have alternative starting sequences, e.g. narasin ($P_4A_3B_2A_1$) and the norboritomycins-A and -B (PAAP) as detailed in Figure 4.

These prototypes derive from a consideration of the structure and stereochemistry of postulated preformed polyenes, which are believed to be the biosynthetic precursors to the parent antibiotics. This can be illustrated by comparing the polyene of the proposed biosynthetic pathway for monensin-A (Figure 2) with the APPA prototype (Figure 1).

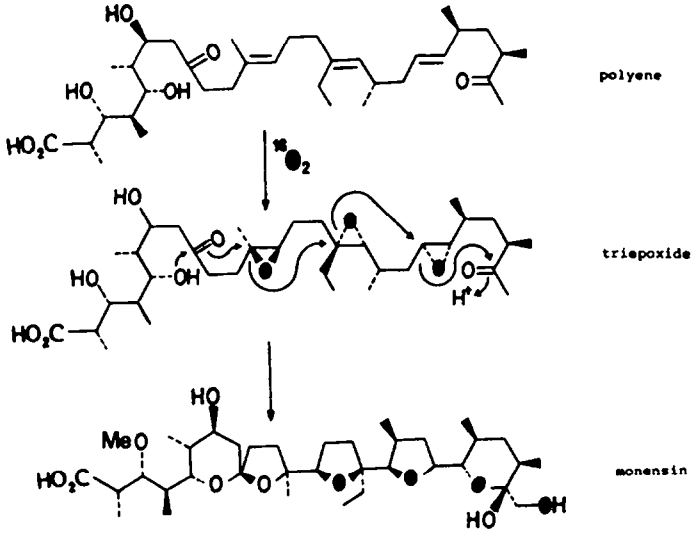


Figure 2. A cascade cyclisation mechanism of an intermediate triepoxide has been proposed[12,15] on the basis of oxygen-18 incorporation into monensin-A after fermentation of *S. cinnamonensis* under an atmosphere of $^{18}O_2$.

The homologous structural units and degree of stereochemical uniformity which exists between the putative polyene precursors for each polyether, throughout the series, led the authors to suggest the existence of a common genetic basis influencing the biosynthesis of these antibiotics.

Remarkably, a similar situation exists for the macrolide class of antibiotics. Celmer has described[5] a model which can predict the stereochemistry at a particular asymmetric centre along the backbone of individual members of the macrolide series.

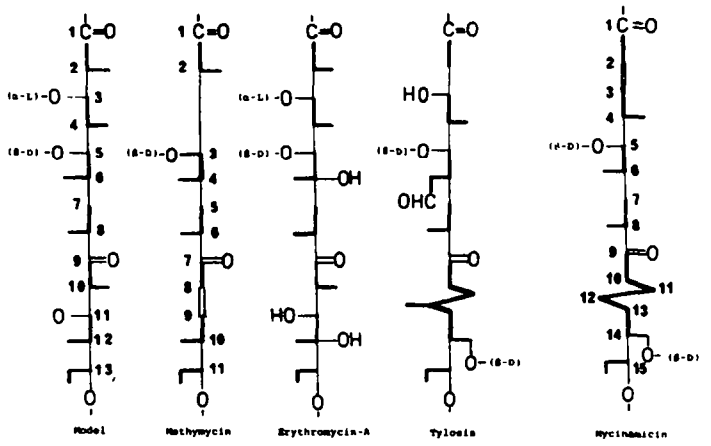


Figure 3. Configurational model[5] and absolute configuration of representative examples of the macrolide antibiotics. The model and structures of the macrocyclic lactones are represented linearly as Fischer projections. The model extends to predict the absolute configuration and conformation of attached glycosides at C-3 and C-5.

The model has proved entirely reliable for all 12- and 14-membered macrolides, and can be adapted to include the 16-membered macrolides by the insertion of a two carbon unit between C-10 and C-11 of the model. In the latter instance, where alkyl functionality is present at C-14 of a 16-membered macrolide, it is found to have the opposite configuration to that predicted by the model,[6,7] e.g. tylosin and mycinamicin-IV in Figure 3.

Although they have quite distinct modes of action[1,2] it is tempting to speculate that the polyether and macrolide antibiotics may themselves have evolved from a common genetic source. In this context, their similar origins from derivatives of C2-C4 carboxylic acids is significant and well documented.[8] Complementary studies[9,10,11] supplied from a number of laboratories have shown that the stereochemical course of the key condensation processes operating during the biosynthesis of the antibiotics is identical for representative examples from each of the two classes. Investigations[12,13,14,15,17] aimed at addressing the origin of the oxygen atoms in the macrolide and polyether antibiotics have revealed a high degree of oxygen retention at alternate carbon atoms along the backbone. These oxygens derive via a classical polyketide pathway from the carboxylic acids utilised in the biosynthesis of the antibiotics.

Highlighted below are structural and stereochemical observations which further support a common origin for these two antibiotic groups.

The polyethers have been classified[16] by virtue of their ability to complex metal ions, and further subclassified by structure. A recent biosynthetic investigation[17] on the monovalent dispiroketal polyether, narasin (3), supports the proposal[3] that these antibiotics derive from the cascade cyclisation of a diepoxide intermediate, generated by the microbial oxidation of a preformed polyene (Figure 4). If this analysis is extrapolated to the remaining 15 dispiroketal polyethers we can arrive at a series of polyene intermediates which are constructed from distinct sequences of acetate (A), propionate (P) and butyrate (B). The stereochemistry of the functionality present along the backbone of these proposed intermediates is summarised by the Cane-Celmer-Westley PAPA prototype.

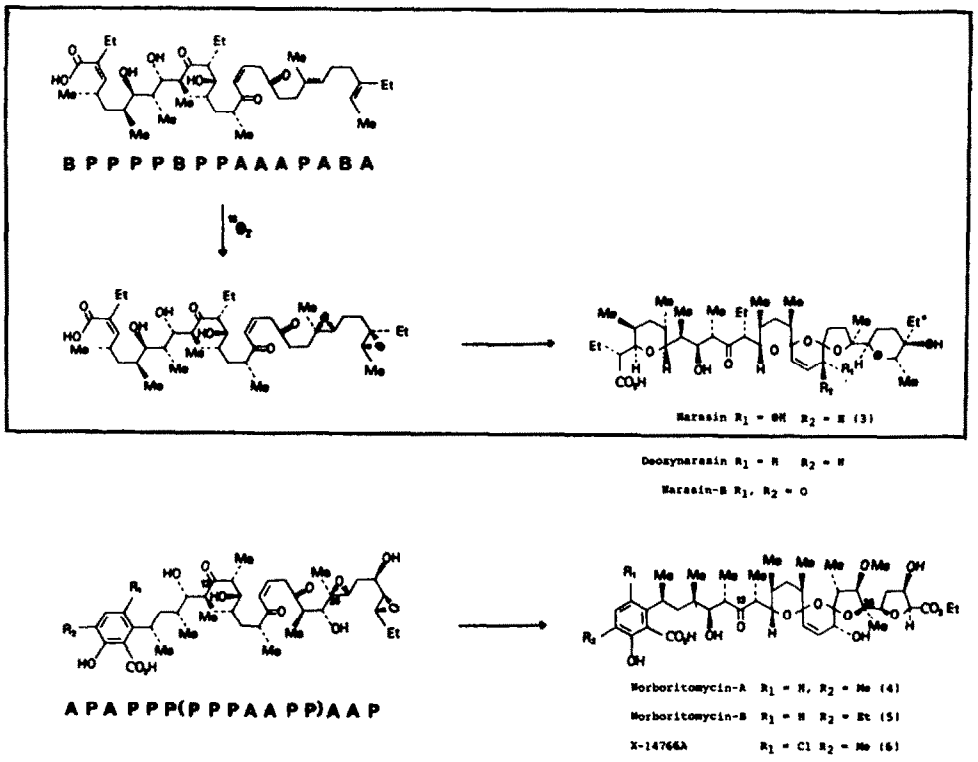
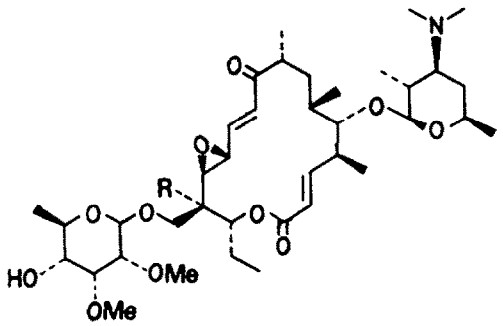
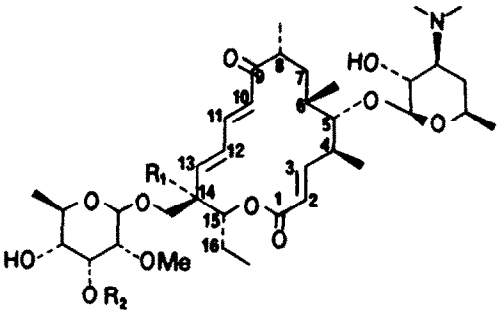


Figure 4. The incorporation of oxygen-18 into narasin[17] after fermentation of S. aureofaciens under an $^{18}O_2$ atmosphere lends support to the intermediacy of a diepoxide during biosynthesis. This analysis can be extended to intimate the existence of analogous diepoxide intermediates during the biosynthesis of each dispiroketal antibiotic.

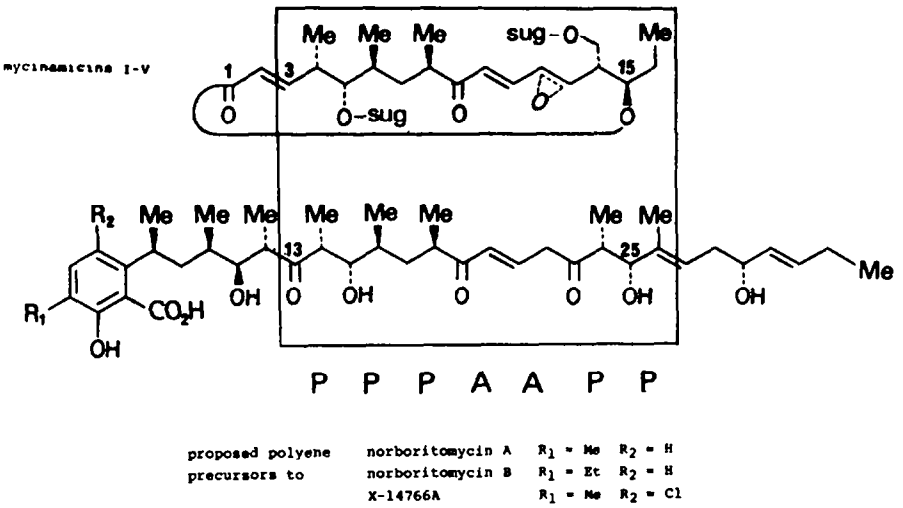


	R
Mycinamicin I	H (7)
Mycinamicin II	OH (8)



	R1	R2	
Mycinamicin III	H	H	(9)
Mycinamicin IV	H	CH_3	(10)
Mycinamicin V	OH	CH_3	(11)

An analysis of the macrolide antibiotic structures[18] reveals that the structure and stereochemistry of the 16-membered mycinamicins I-V,[19,20] (7-11) correlate closely with noboritomycins-A (4) and B[21] (5) and antibiotic X-14766A[22] (6), between carbons 3-16 of the macrolides and 13-26 of the polyether antibiotic precursors (Figure 5).



proposed polyene precursors to	norboritomycin A	R_1 = Me R_2 = H
	norboritomycin B	R_1 = Et R_2 = H
	X-14766A	R_1 = Me R_2 = Cl

Figure 5. Structural and stereochemical correlations over a seven subunit sequence between the mycinamicins and the biosynthetic polyene precursors to the norboritomycin antibiotics. The stereochemistry at C-15 of the macrolides is opposite to that at C-25 of the polyene precursors.

The subunit constitution of PPPAAPP over these carbons is the same, with five of the six asymmetric centres possessing an identical absolute configuration. The stereochemistry at C-15 of the mycinamicins (7-11) and C-25 of the noboritomycins (4 and 5) and X-14766A (6) is opposite with respect to each class which implies the action of reducing enzymes, of distinct origin, acting at these centres during biosynthesis. Interestingly, although the subunit constitution matches only in the above examples, the stereochemical homology persists for all the monovalent dispiroketal polyethers and throughout the entire 16-membered macrolide series. This is best illustrated by comparing a stereochemical model which summarises the 16-membered macrolides, with that of the polyether PAPA stereochemical prototype (Figure 6). There are many 16-membered macrolide structures[1] which do not possess alkyl functionality at C-12, bringing the structural

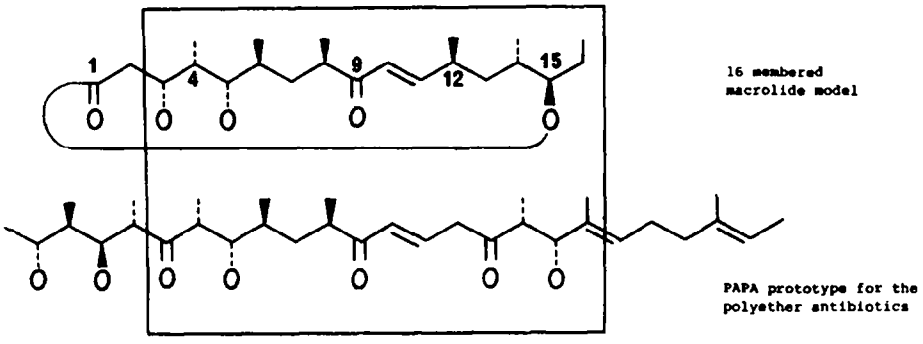


Figure 6. Correlation between a 16-membered macrolide model and the Cane-Celmer-Westley PAPA prototype which summarises the stereochemistry of the bisdispiroketal polyether antibiotics. For members of the leucomycin, spiramycin and maridomycin groups the alkyl functionality of the macrolide model at C-4 is replaced by a methoxyether with the same absolute configuration and the carbonyl functionality at C-9 is reduced to an alcohol with the 9$\underline{S}$ configuration.

[1]e.g. Leucomycin, spiramycin, maridomycin and aldgamycin groups.

analogy between the model and the PAPA prototype much closer in those instances.

The genes coding for the biosynthetic enzymes of those structurally homologous units within the mycinamicins, norboritomycins and antibiotic X-14766A have apparently remained closely associated with each other throughout the evolutionary course of each individual system, and most likely derive, themselves, from a unique primordial gene cluster. In the more general case, where the biosynthetic subunit constitution varies from one antibiotic to the next, but the stereochemistry remains constant, it seems likely that there exists a common gene cluster which gives rise to an enzyme system that dictates rigid stereochemical control, but is less discriminating with respect to the substrate it will act upon. Such properties may have profound implications in the future development of genetically engineered organisms aimed at producing new hybrid antibiotics[23,24] not only within each class[25] but between members of the two classes.

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