bromo silyl ether **18b**): 11-*cis*-**10a** (23.4 mg, 5.4%), 11-*cis*,13-*cis*-**12a** (43.4 mg, 10%), 9-*cis*,11-*cis*,13-*cis*-**13a** (65.2 mg, 15%), and 9-*cis*,11-*cis*-**11a** (29.6 mg, 6.8%).

12,20-Tetramethyleneretinals 10b, 11b, 12b, and 13b. General Procedure. The seven-membered ring 12,20-tetramethyleneretinals were prepared by MnO_2 oxidation of the corresponding retinols according to the procedure described for the six-membered-ring 12,20-trimethyleneretinals **7b**, **8b**, and **9b**. The four seven-membered-ring isomers 11-*cis*-**10b**, 9-*cis*,11-*cis*-**11b**, 11-*cis*,13-*cis*-**12b**, and 9-*cis*,11-*cis*,13-*cis*-**13b** were prepared in yields ranging from 50 to 80%.

Preparation of Cyclized Product 29: Thermolyses of 12,20-Tetramethylene-9-*cis*,11-*cis*-retinol (11a) and -9-*cis*,11-*cis*,13-*cis*-retinol (13a). The 9-cis,11-cis-isomer **11a** (~2 mg) in freshly distilled hexanes (10 mL) was added under argon to a refluxing solution of hexanes (100 mL). Aliquots were removed at various time intervals and analyzed by high-pressure LC (Waters μ-porasil column, 15% ethyl acetate/skellysolve B). Essentially quantitative conversion of the retinol **11a** to the cyclized product **29** was complete in ~3 h. By contrast, the 9-cis,11-cis,13-cis-isomer **13a** was recovered unchanged (^{1}H NMR, high-pressure LC) after 4 h in refluxing hexanes.

Acknowledgment. The National Institutes of Health (USPHS Grant EY-02452 and NCI Contract CP-05715) provided financial support for this project. We also acknowledge the National Science Foundation Midwest Center for Mass Spectrometry for mass spectra, the Southern California Regional NMR Facility (supported by NSF Grant No. CHE79-16324) for 500-MHz spectra, and BASF (Ludwigshafen) for chemicals. Finally, we remain most grateful to Professor Robert R. Birge of this department for informative discussions.

Registry No. 5a, 83043-81-6; **5b**, 83043-82-7; **6a**, 85236-03-9; **6b**, 85236-04-0; **7a**, 83043-76-9; **7b**, 83043-75-8; **8a**, 83043-78-1; **8b**, 83043-77-0; **9a**, 83043-80-5; **9b**, 83043-79-2; **10a**, 85236-05-1; **10b**, 85236-06-2; **11a**, 85236-07-3; **11b**, 85236-08-4; **12a**, 85236-09-5; **12b**, 85236-10-8; **13a**, 85236-11-9; **13b**, 85236-12-0; **15a**, 38127-47-8; **15b**, 85236-13-1; **16a**, 83043-84-9; **16b**, 85236-14-2; **17a**, 85236-15-3; **17b**, 85236-16-4; **18a**, 83043-83-8; **18b**, 85236-17-5; **19**, 74723-00-5; **24**, 83060-55-3; **29**, 85236-18-6; 2-methoxy-2-methylbut-3-yne, 13994-57-5.

Supplementary Material Available: Spectral and analytical data (12 pages). Ordering information is given on any current masthead page.

Unified Stereochemical Model of Polyether Antibiotic Structure and Biogenesis[1a]

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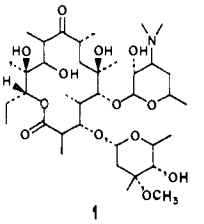
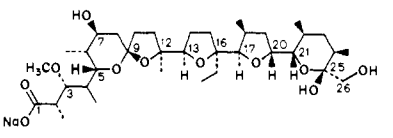
Abstract: A unified stereochemical model is proposed which correlates the structure and stereochemistry of a large number of polyether antibiotics and which suggests the biosynthetic basis for this perceived structural regularity. Two stereochemical prototypes, illustrated in Figure 3, parts A and B, summarize the stereochemical patterns of more than 30 different polyether antibiotics of the APPA and PAPA structural families.

Macrolide lactones[2] such as erythromycin (**1**) and the polyether antibiotics[3] typified by monensin (**2**) and lasalocid (**3**) are two important classes of antibiotics produced by actinomycetes. The two classes have been compared because the polyethers are branched-chain, polyoxygenated carboxylic acids and the macrolides are branched-chain, polyoxygenated carboxylic lactones. Apart from this formal resemblance, however, the structures, biochemical modes of action, and antimicrobial spectra of these two groups of metabolites are quite distinct. Specifically, whereas most macrolides act as inhibitors of protein biosynthesis at the ribosomal level,[4] the polyethers exert their effects by interfering with permeability barriers to ion transport across biological membranes.[3a,5] Erythromycin is one of the most widely used antibiotics in human medicine, whereas monensin and lasalocid are major agents in the control of coccidiosis in poultry and in the improvement of feed utilization in ruminant livestock. Nonetheless, intriguing structural parallels exist between these two important groups of natural products. The biogenetic basis of this structural similarity is the common origin of these complex natural products from the simple precursors acetate, propionate, and butyrate by a sequence of transformations analogous to, but certainly not identical, with classical saturated fatty acid biosynthesis.



1



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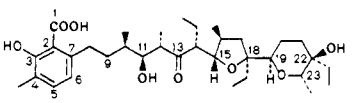

3

Some 150 macrolides have been characterized since the discovery of pikromycin in 1951.[6] In spite of the diversity of

(1) (a) This work was supported in part by a grant from the National Institutes of Health, No. GM22172. (b) Brown University. Fellow of the Alfred P. Sloan Foundation, 1978-1982. National Institutes of Health Research Career Development Award, 1978-1983. (c) Pfizer. (d) Hoffmann-La Roche.

(2) Reviews: Woodward, R. B. *Angew.Chem.* **1957**, *69*, 50. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

(3) (a) "Polyether Antibiotics: Carboxylic Ionophores" (Vol. I: Biology; Vol. II: Chemistry); Westley, J. W., Ed.; Marcel Dekker: New York, 1982. (b) Westley, J. W. *Annu. Rep. Med. Chem.* **1975**, *10*, 246. (c) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. (d) Westley, J. W. In "Antibiotics IV. Biosynthesis"; Corcoran, J. W., Ed.; Springer-Verlag: New York, 1981; pp 41-73.

(4) Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. "The Molecular Basis of Antibiotic Action", 1st ed.; Wiley: New York 1972; pp 332-341.

(5) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501.

(6) Mallams, A. K. "Kirk-Othmer: Encyclopedia of Chemical Technology"; 3rd Ed.; Wiley: New York, 1978; Vol. 2, p 937.

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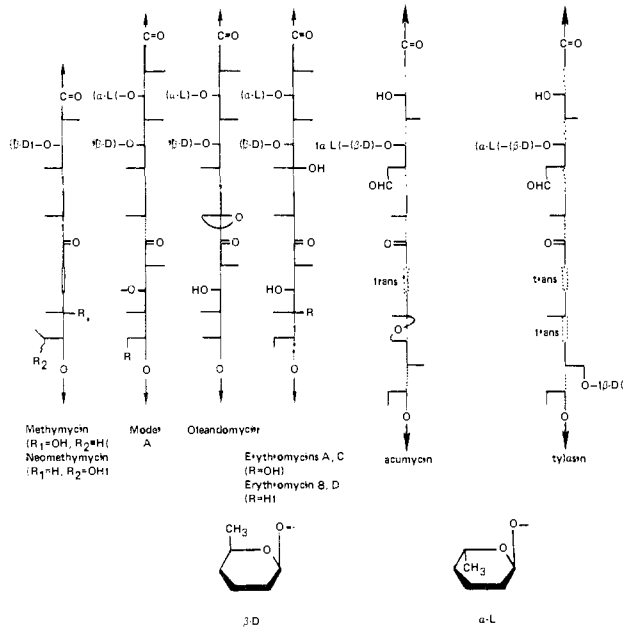
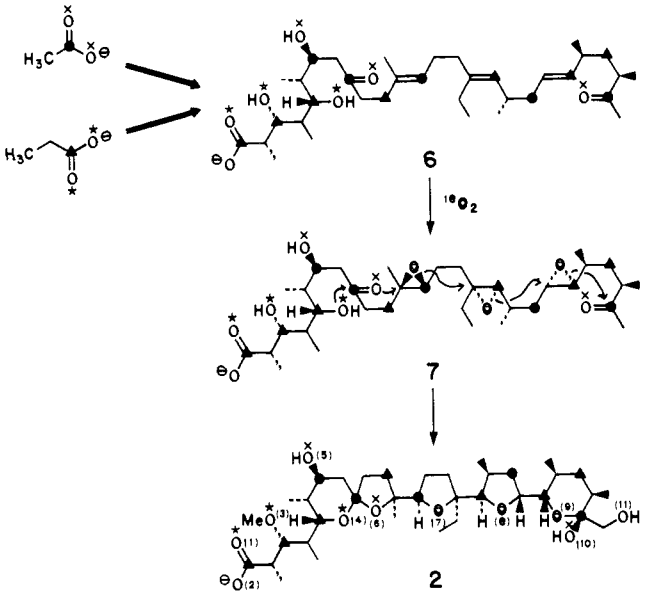
Scheme I. Generalized Macrolide Configurational Model



structures exhibited by the known macrolides, in 1965 Celmer was able to point out the considerable stereochemical regularity within this group of compounds and proposed a single stereochemical model to represent the entire class[7a] (model A, Scheme I). This purely empirical model, for which only few exceptions have since been found,[8] has served as a useful guide to structural and stereochemical characterization of new macrolides.[9] To date, however, no analogous stereochemical generalizations have been put forward for the more than 70 known polyether antibiotics, in spite of the enticing structural and biogenetic similarities to macrolides. In this paper we describe a useful stereochemical model for several of the polyether antibiotics and suggest a plausible biochemical and genetic basis for the perceived structural regularities among this important class of metabolites.

The 76 polyether antibiotics reported to date have been divided into four classes,[3a] of which the first class contains what have been termed monovalent and monovalent glycoside polyethers. The monovalent polyethers consist of three types: the nonspiroketal, spiroketal, and dispiroketal containing antibiotics, whereas the monovalent glycosides contain either one or two spiroketals. The other three classes are the divalent polyethers, the pyrrole ethers and the acyl tetronic acids.

Scheme II. Origin of the Oxygen Atoms of Monensin and Proposed Triene–Triepoxide Pathway



Monensin (**2**), dianemycin (**4**), and lenoremycin (**5**) belong to the first class of polyethers. Together with 10 other polyethers they have identical tetrahydropyranyl rings at the termini opposite to the carboxylic acid function (Figure 1). The first four biogenetic units giving rise to this ring in all cases are acetate, propionate, propionate, and acetate: $A_4P_3P_2A_1$ or, simply, APPA. If the structures of each of these branched-chain fatty acids are compared, beginning with the initial acetate subunit, a striking stereochemical homology becomes apparent. In spite of the variety of substitution patterns and the individual mix of acetate, propionate, and butyrate progenitors, the configuration of alkyl or oxygen substituents at any given position within the first 12 biogenetic subunits is constant throughout the entire series. These relationships can be summarized by the stereochemical model of the prototype APPA polyether illustrated in Figure 2A, shown along with its dianemycin variant, Figure 2B. For those APPA polyethers with 15 subunits, three alternative stereochemical patterns are known for subunits 13–15, as illustrated in Figures 2C, 2D, and 2E.

The APPA stereochemical prototype, illustrated in Figure 2A, summarizes the *structures* of a large number of related metabolites. As a purely empirical summary of known structural data, the model is of potential utility in the search for new types of polyether structures. On a more fundamental level, the recognition of recurrent structural and stereochemical patterns in a host of complex metabolites of diverse biological origin raises important questions concerning the biochemical and, ultimately, genetic basis of these apparent regularities. As a result of biosynthetic investigations carried out in several laboratories over the last decade, it is now well recognized that the universal building blocks of the polyether carbon skeleta are acetate, propionate, and butyrate.[3d] Little is known, however, about the details of the fundamental chain-building steps. Nonetheless, recent investigations of the biosynthesis of one member of the APPA class of polyethers, monensin A (**2**), have provided considerable details on the manner in which these metabolites are assembled and have led to a general *biochemical* model which suggests the basis for the observed

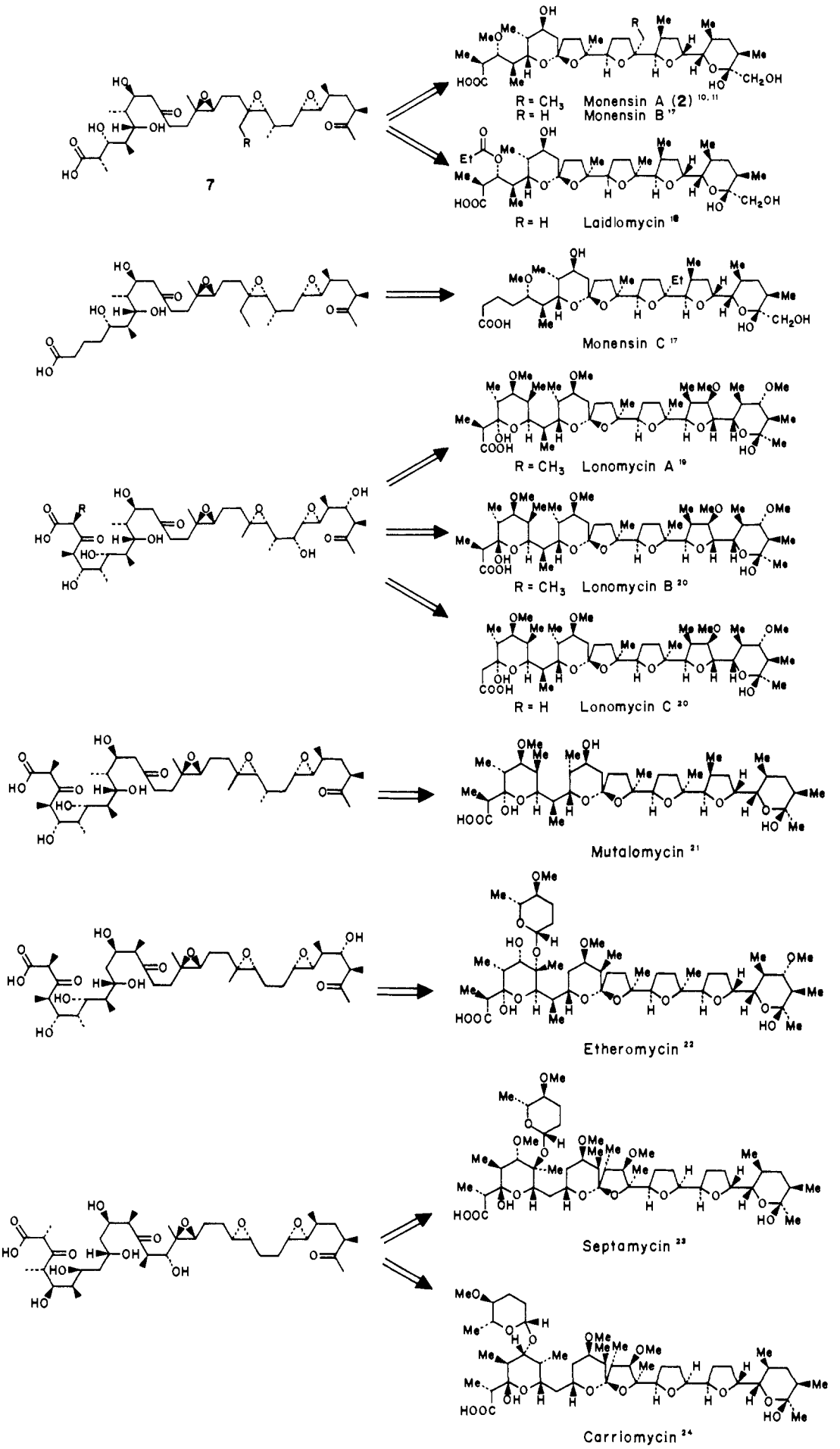
(7) (a) Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1801. (b) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413.

(8) Cf. Clardy, J.; Finer-Moore, J.; Weiler, L.; Wiley, D. C. *Tetrahedron*, **1981**, *37*, 91. Omura, S.; Matsubara, H.; Nakagawa, A.; Furusaki, A.; Matsumoto, T. *J. Antibiot.* **1980**, *33*, 915. Jones, N. O.; Chaney, M. O.; Kirst, H. A.; Wild, J. M.; Baltz, R. H.; Hamill, R. L.; Paschal, J. W. *Ibid.* **1982**, *35*, 420. Ganguly, A. K.; Liu, Y.-T.; Sarre, O.; Jaret, R. S.; McPhail, A. T.; Onan, K. K. *Tetrahedron Lett.* **1980**, 4699. Hayashi, H.; Kinoshita, K; Satoi, S. *J. Antibiot.* **1982**, *35*, 1243.

(9) Model A (Scheme I) represents a generalized macrocyclic lactone skeleton in which the absolute configuration at each of 10 endocyclic centers is specified by means of a Fischer projection.[7] It serves all the known 12- and 14-membered ring macrolides and includes chiral centers at C-3, C-5, C-6, and C-8 in 16-membered ring macrolides. In the latter group, the chirality at C-14 has now been established[8] for acumycin, tylosin, rosarimicin, and mycinolide IV and is the reverse of an earlier empirical prediction,[7b] while the chirality at C-15 is the same as at all comparable macrolide lactone termini. In all cases, any "extra" oxygen atoms are introduced at a given chiral center with retention of configuration, presumably at a late stage in the biosynthetic pathway. A corollary model[7] is applicable to all of the some 15 known D and L macrolide sugars (seven D and eight L) with specification of anomeric centers as β-D and α-L, i.e., identical absolute configurations. To date, one L and three D deoxy sugars have been identified as substituents of the monovalent monoglycoside class of polyethers. While most of the anomeric centers in polyether glycosides have the same chirality as those in macrolide glycosides, two exceptions having intriguing biosynthetic implications have been reported in the cases of 4-*O*-methyl-α-D-amicetoside in A204 (noted earlier by Westley, ref 3d, p 43) and 3,4-di-*O*-methyl-β-L-olivoside in X14868A.[46]

(10) Structure: Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 5737. Haney, M. E.; Hoehn, M. M. *Antimicrob. Agents Chemother.* **1968**, 349. Agtarap, A.; Chamberlin, J. W. *Ibid.* **1968**, 359. Lutz, W. K.; Winkler, F. K.; Dunitz, J. D. *Helv. Chim. Acta* **1971**, *54*, 1103. Pinkerton, M; Steinrauf, L. K. *J. Mol. Biol.* **1970**, *49*, 533.

(11) Biosynthesis: (a) Day, L. E.; Chamberlin, J. W.; Gordee, E. Z.; Chen, S.; Gorman, M.; Hamill, R. L.; Ness, T.; Weeks, R. E.; Stroshane, R. *Antimicrob. Agents Chemother.* **1973**, 410. (b) Cane, D. E.; Liang, T.-C.; Hasler, H. *J. Am. Chem. Soc.* **1981**, *103*, 5962. (c) Cane, D. E.; Liang, T.-C.; Hasler, H. *Ibid.* **1982**, *104*, 7274.


7
R = CH3 Monensin A (2) [10, 11]
R = H Monensin B [17]
R = H Laidlomycin [18]
Monensin C [17]
R = CH3 Lonomycin A [19]
R = CH3 Lonomycin B [20]
R = H Lonomycin C [20]
Mutalomycin [21]
Etheromycin [22]
Septamycin [23]
Carriomycin [24]

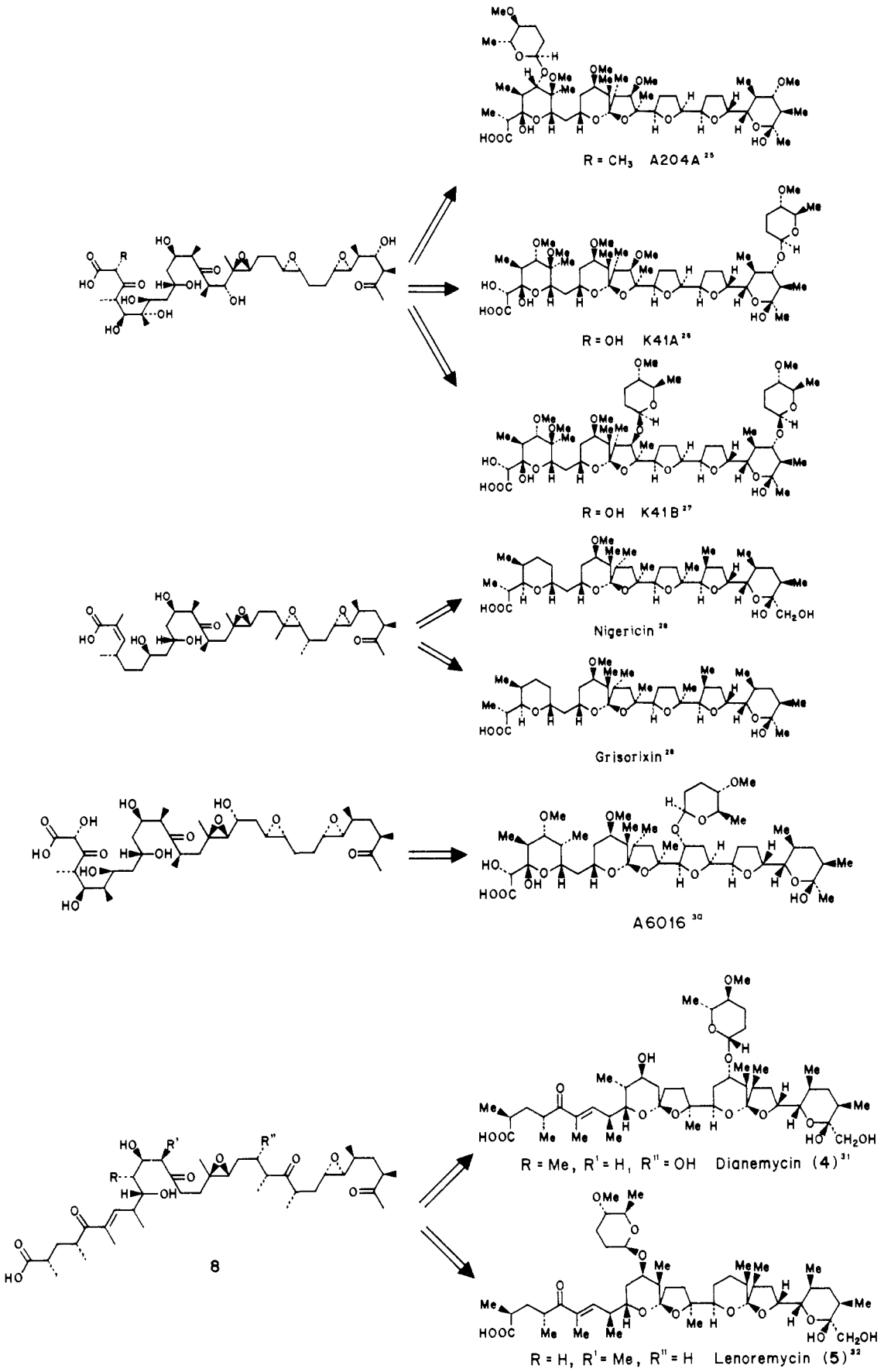


Figure 1. APPA polyethers and hypothetical triepoxide precursors.

stereochemical homogeneity among the entire class. Incorporations of [1-^{13}C,^{18}O] substrates have established that O(1), O(3), and O(4) of monensin are derived from the carboxylate oxygens of propionate, whereas O(5), O(6), and O(10) originate from the corresponding acetate oxygens (Scheme II).[11b,c] On the other hand, growth in the presence of $^{18}O_2$ has demonstrated that the

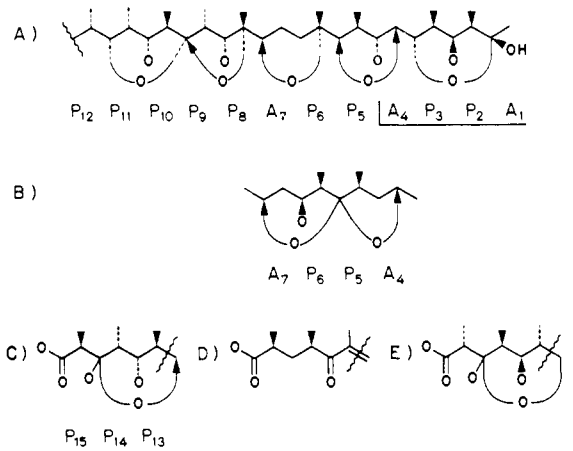


Figure 2. (A) Stereochemical prototype, subunits 1–12 of APPA polyethers; (B) dianemycin variant of APPA prototype; (C) lonomycin type, subunits 13–15; (D) dianemycin type, subunits 13–15; (E) carriomycin type, subunits 13–15.

three remaining ether oxygens O(7), O(8), and O(9) are derived from molecular oxygen.[11c] These results have been explained by positing that in the biosynthesis of monensin the first formed polyfunctional fatty acid would be the all-(*E*) triene **6**, which would undergo epoxidation at each double bond to give the (12*R*,13*R*,16*R*,17*R*,20*S*,21*S*)-triepoxide **7** (Scheme II). Attack of the C-5 hydroxyl of **7** at the C-9 carbonyl carbon would initiate a cascade of ring closures to generate all five ether rings of monensin with the observed stereochemistry. Most importantly, this monensin triepoxide model can, in fact, be extended to account for the stereochemistry of the remaining members of the APPA class of polyethers. These relationships are illustrated in Figure 1, in which the hypothetical triepoxide precursor is shown for each polyether product. It will be noted that each triepoxide would itself be formed from the corresponding all-(*E*) triene and that all triepoxides in this series have the same absolute configuration. The biogenetic model can be modified to include the dianemycin subgroup by postulating formation of the appropriate diepoxy triketone (**8**). The structural and stereochemical regularity of the eventually formed APPA polyethers, summarized by Figure 2A, is therefore the reflection of a more fundamental regularity already evident in the putative triene precursors. These trienes represent the presumed product of a purely reductive biosynthetic pathway utilizing acetate, propionate, and butyrate substrates linked by a series of condensation, reduction, dehydration, and reduction sequences. A stereochemical model which is the prototype of all the APPA polyene intermediates is illustrated in Figure 3A.

Unlike the APPA metabolites, the second major group of polyethers does not have a single starter unit for all members of the class. Among the most common sequences, illustrated in Figure 4, are $P_4A_3B_2A_1$, BABA, and PAPA. These four subunits appear in one of two closely related ring systems, either a tetrahydrofuran linked to a tetrahydropyran, or two adjacent five-membered ether rings, typified by the structures of lasalocid (**3**)[12,13] and isolasalocid (**9**),[14] respectively. Inspection of Figure 4 reveals the occurrence, in various combinations, of several additional key structural features, among which is a bis-spiroketal with a central dihydropyran ring (cf. **10**). Polyethers with a total of 16 subunits are characterized by the presence of a substituted benzoic acid (cf. **10**) derived from the last 4 units of the chain, while those with 15 subunits retain an open-chain carboxylic acid (cf. **11**). Figure 4 also illustrates the possible polyene–polyepoxide origins of each

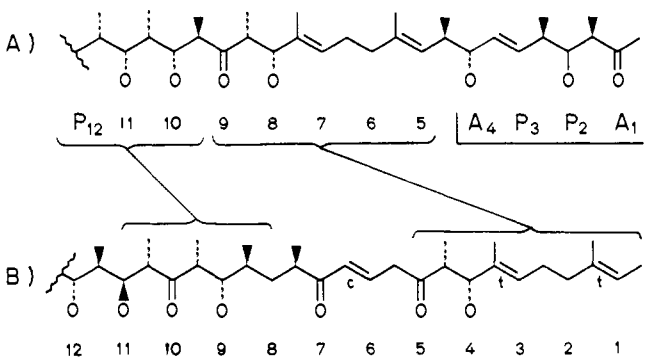


Figure 3. (A) APPA polyene prototype; (B) PAPA polyene prototype. The segments enclosed by brackets indicate the regions of structural homology between each of the polyene prototypes.

of these polyethers. In fact, a diepoxide intermediate such as **12** was suggested in 1974 by Westley to account for the cooccurrence of both lasalocid and isolasalocid.[14] This suggestion has received experimental support from the recent finding that oxygen atoms at C-1, C-3, C-11, C-13, and C-15 of lasalocid, but not those at C-19 and C-22, are derived from their respective acetate, propionate, and butyrate precursors.[15] In Figure 4 it is seen that an analogous set of diepoxide intermediates, each derived from the corresponding *E,E* diene, can account for all the remaining members of this second class of polyether antibiotics. A prototype configurational model, based on the polyene precursors and which summarizes the stereochemical regularities of the first 12 subunits of each hypothetical polyether precursor, is illustrated in Figure 3B. Lasalocid can be fitted to this model by assuming a deletion of the central $P_8A_7A_6P_5$ subunits of 16-unit polyether, while lysocellin (**13**),[16] with 11 subunits, can formally be derived from

(12) Structure: Westley, J. W.; Evans, R. H.; Jr.; Williams, T.; Stempel, A. *Chem. Commun.* **1970**, 71. Johnson, S. M.; Herrin, J.; Liu, S. J.; Paul, I. C. *J. Am. Chem. Soc.* **1970**, *92*, 4428.

(13) Biosynthesis: Westley, J. W.; Evans, R. H., Jr.; Harvey, G.; Pitcher, R. G; Pruess, D. L.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 288.

(14) Westley, J. W.; Blount, J. F.; Evans, R. H.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 597. See also ref 3d.

(15) Hutchinson, C. R.; Sherman, M. M.; Vederas, J. C.; Nakashima, T. T. *J. Am. Chem. Soc.* **1981**, *103*, 5953. See also Hutchinson, C. R.; Sherman, M. M.; McInnes, A. G.; Walter, J. A.; Vederas, J. C. *Ibid.* **1981**, *103*, 5956.

(16) (a) Structure: Ebata, E.; Kasahara, H.; Sekine, K.; Inoue, Y. *J. Antibiot.* **1975**, *28*, 118. Otake, N.; Koenuma, M.; Kinashi, H.; Sato, S.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1975**, 92. (b) Biosynthesis: Otake, N.; Seto, H.; Koenuma, M. *Agric. Biol. Chem.* **1978**, *42*, 1879.

(17) Gorman, M.; Chamberlin, J. W.; Hamill, R. L. *Antimicrob. Agents Chemother.* **1968**, 363. Naturally occurring 26-(2-phenethylurethanes) of monensin A and B have recently been isolated: Westley, J. W.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Liu, C.-M.; Miller, P. *J. Antibiot.* **1981**, *34*, 1248.

(18) Kitame, F.; Utsuhikawa, K.; Kohama, T.; Saito, T.; Kikuchi, M.; Ishida, N. *J. Antibiot.* **1974**, *27*, 884. Kitame, F.; Ishida, N. *Ibid.* **1976**, *29*, 759.

(19) (a) Structure: Omura, S.; Shibata, M.; Machida, S.; Sawada, J.; Otake, N. *J. Antibiot.* **1976**, *29*, 15. Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S; Saito, Y. *Tetrahedron Lett.* **1975**, 4147. (b) Biosynthesis: Seto, H.; Mizoue, K.; Otake, N. *J. Antibiot.* **1980**, *33*, 979.

(20) Seto, H.; Mizoue, K.; Otake, N,; Yamagishi, M.; Mizutani, T.; Hara, H.; Omura, S. *J. Antibiot.* **1978**, *31*, 929.

(21) Fehr, T.; King, H. D.; Kuhn, M. *J. Antibiot.* **1977**, *30*, 1977. Fehr, T.; Keller-Julsen, C.; King, H. D.; Loosli, H. R.; Kuhn, M.; von Wartburg, A. *Ibid.* **1979**, *32*, 535.

(22) Celmer, W. D.; Cullen, W. P.; Jefferson, M. T.; Moppett, C. E.; Routien, J. B.; Sciavolino, F. C. U.S. Patent 4 129 578, 1978.

(23) Keller-Julsen, C.; King, H. D.; Kis, Z. L.; von Wartburg, A. *J. Antibiot.* **1975**, *28*, 854.

(24) Imada, A.; Nozaki, Y.; Hasegawa, T.; Igarashi, S.; Yoneda, M. *J. Antibiot.* **1978**, *31*, 7. Otake, N.; Nakayama, H.; Miyanae, H.; Sato, S.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1977**, 590.

(25) Jones, N. D.; Chaney, M. O.; Chamberlin, J. W.; Hamill, R. L.; Chen, S. *J. Am. Chem. Soc.* **1973**, *95*, 3399.

(26) Shiro, M.; Nakai, H.; Nagashima, K.; Tsuji, N. *J. Chem. Soc., Chem. Commun.* **1978**, 682. Occolowitz, J. L.; Dorman, D. E.; Hamill, R. L. *Ibid.* **1978**, 683.

(27) Tsuji, N.; Nagashima, K.; Terui, Y.; Tori, K. *J. Antibiot.* **1979**, *32*, 169.

(28) Harned, R. L.; Hioy, P. H.; Corum, C. J.; Jones, K. L. *Antibiot. Chemother.* **1951**, *1*, 594. Steinrauf, L. K.; Pinkerton, M. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 29. See also Kubota, T.; Matsutani, S.; Shiro, M.; Koyana, H. *Chem. Commun.* **1968**, 1541.

(29) Gachon. P.; Kergomard, A.; Veschambre, H.; Estere, C.; Staron, T. *Chem. Commun.* **1970**, 1421. Alleaume, M.; Hickel, D. *Ibid.* **1970**, 1422.

(30) Otake, N.; Ogita, T.; Nakayama, H.; Miyamae, H.; Sato, S.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 875. Seto, H.; Nakayama, H.; Ogita, T.; Furihata, K.; Mizoue, K.; Otake, N. *J. Antibiot.* **1979**, *32*, 244.

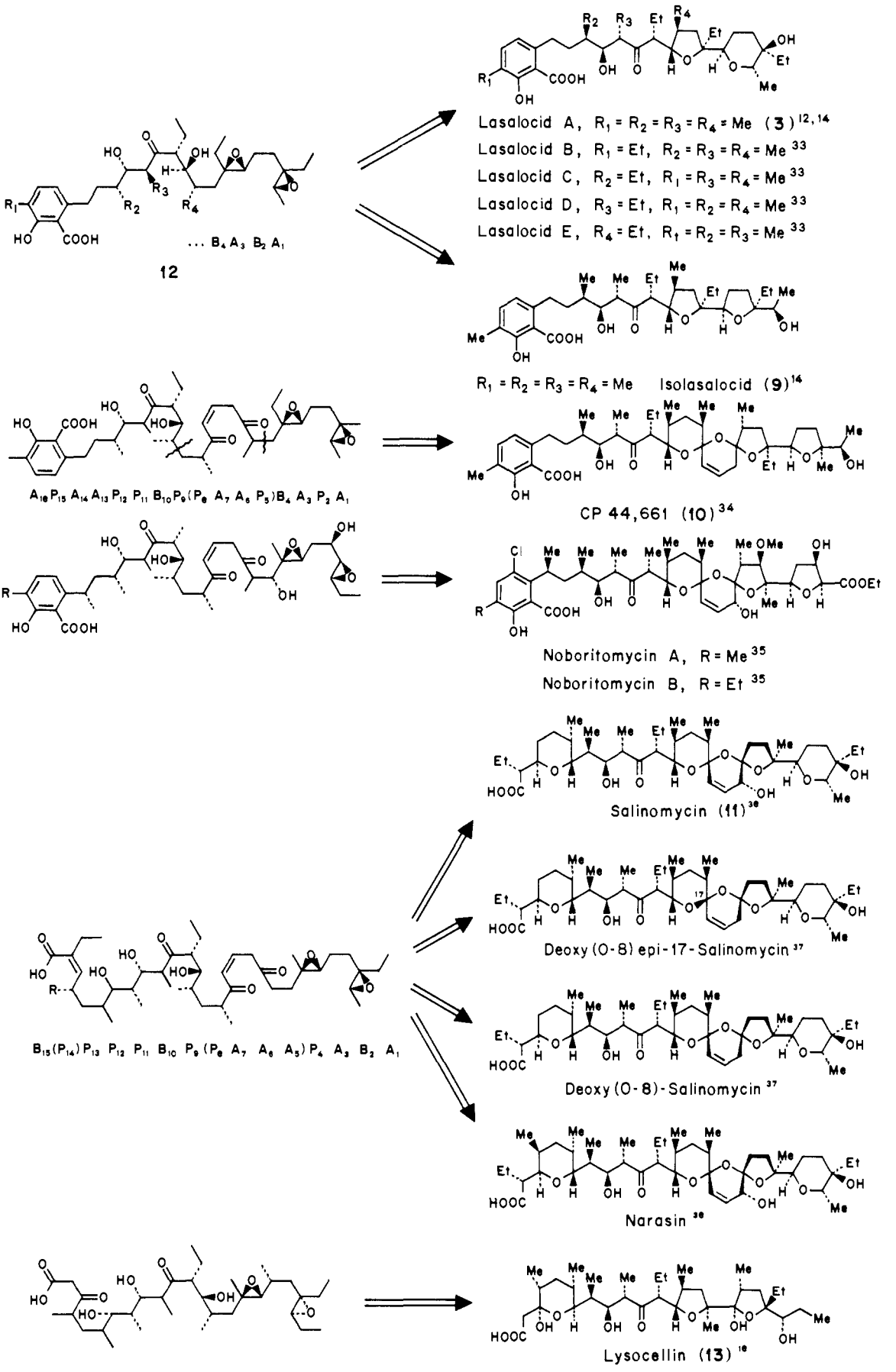


Figure 4. PAPA polyethers and hypothetical diepoxide precursors.

the 15-subunit prototype by deletion of an analogous $P_8A_7A_6A_5$ segment (Figure 4). Interestingly, in the formation of lysocellin, epoxidation of the *E* double bond connecting the P_1 and B_2 subunits takes place on the 3si, 4si face, instead of the 3re, 4re face characteristic of the other members of this polyether series.

It is intriguing to note that the stereochemical prototypes for the APPA- and PAPA-type polyenes illustrated in Figures 3A and 3B, respectively, are themselves closely related. A comparison of the two models indicates that subunits 5–12 of Figure 3A are essentially equivalent to a linear combination of subunits 1–5 and 9–11 of Figure 3B, save for the oxidation state of subunit 11 in Figure 3A. The perceived stereochemical homogeneities among such a diverse group of complex metabolites does raise tantalizing genetic and biochemical questions about the evolution, molecular organization, and mode of action of the multienzyme synthetases responsible for the biosynthesis of this family of compounds. It is intriguing to consider the possibility that the structural features of each polyene prototype are the expression of a polycistronic gene cluster containing structural genes corresponding to each of the enzymatic steps of the polyene chain-building sequence.[39] The genes coding for the polyene precursor of lasalocid A (**3**) may formally be derived from the corresponding gene cluster for CP-44661 (**10**) by excision of the six structural genes coding for the appropriate sequence of four condensations, a reduction, and a dehydration required for introduction of subunits 5–8, followed by fusion of the genomic sequences responsible for construction of subunits 1–4 and 9–16. Similarly, excision of the five genes responsible for subunits 6–8 and fusion of the resulting strands of DNA will in principle generate the proper sequence of structural genes for subunits 5–12 of the APPA polyenes.[40] Implicit in this genetic model is the suggestion that the enzymes catalyzing the sequential addition of subunits 9–11 of polyene prototype 3B perform their task on whatever substrate is presented to them, be it a chain derived from subunits 1–4, 1–5, or 1–8. One of the attractions of this hypothetical *genetic* model is that it avoids the necessity of evolutionary development of entirely new enzyme systems for each polyether antibiotic. Most importantly, of course, it is expected that continuing progress in the understanding of the genetics of antibiotic biosynthesis[41] and in the development of *Streptomyces* cloning vectors[42] will soon make it possible to test some of these as yet purely speculative notions.[43]

The stereochemical prototypes of Figures 2 and 3 are, of course, merely summaries of empirical observations. As with all empirical rules there will no doubt be exceptions, both real and apparent.[44] In principle these exceptions could result from fundamental variations in the primary chain-building reactions or reflect modifications which occur subsequent to biosynthesis of the parent branched-chain, polyene fatty acid. The empirical rules may therefore serve as a useful guide to experimental distinctions among the biosynthetic pathways leading to a wide variety of polyethers. For the moment the fact that two simple prototypes can summarize the stereochemical patterns of more than 30 different polyether antibiotics[45] emphasizes the potential generality of recent experimental observations of monensin[11b,c] and lasaloicid biosynthesis.[15] As a biosynthetic hypothesis, the polyene–polyepoxide model of polyether formation is of course amendable to direct verification.

Acknowledgment. We thank Professor C. Richard Hutchinson for his thoughtful comments on the ideas presented in this manuscript.

(31) (a) Structure: Hamill, R. L.; Hoehn, M. M.; Pittenger, G. E.; Chamberlin, J.; Gorman, M. *J. Antibiot.* **1969**, *22*, 161. Czerwinski, E. W.; Steinrauf, L. K. *Biochem. Biophys. Res. Commun.* **1971**, *45*, 1284. (b) Biosynthesis: Mizoue, K.; Seto, H.; Mizutani, T.; Yamagishi, M.; Kawashima, A.; Omura, S.; Ozeki, M.; Otake, N. *J. Antibiot.* **1980**, *33*, 144.

(32) Blount, J. F.; Evans, R. H.; Liu, C.-M.; Hermann, T.; Westley, J. W. *J. Chem. Soc., Chem. Commun.* **1975**, 853.

(33) Westley, J. W.; Benz, W.; Donahue, J.; Evans, R. H., Jr.; Scott, C. G.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 744.

(34) Tone, J.; Shibakawa, R.; Maeda, M.; Inoue, K.; Nishiyama, S.; Ishiguro, M.; Cullen, W. P.; Routien, J. B.; Chappell, L. R.; Moppett, C. E.; Jefferson, M. T.; Celmer, W. D. 18th Intersociety Conference on Antimicrobial Agents Chemother. Atlanta, Ga., Oct. 2–4, 1978.

(35) Keller-Julsen, C.; King, H. D.; Kuhn, M.; Loosli, H. R.; von Wartburg, A. *J. Antibiot.* **1978**, *31*. 820.

(36) (a) Structure: Kinishi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, 4955. (b) Biosynthesis: Seto, H.; Miyazaki, Y.; Fujita, K. I.; Otake, N. *Ibid.* **1977**, 2417.

(37) Westley, J. W.; Blount, J. F.; Evans, R. H., Jr.; Liu, C.-M. *J. Antibiot.* **1977**, *30*, 610.

(38) (a) Structure: Occolowitz, J. L.; Berg, D. H.; Dobono, M.; Hamill, R. L. *Biomed. Mass. Spectrosc.* **1976**, *3*, 272. (b) Biosynthesis: Dorman, D. E.; Paschal, J. W.; Nakatsukasa, W. M.; Huckstep, L. L.; Neuss, N. *Helv. Chim. Acta* **1976**, *59*, 2625.

(39) Genetic investigations have established that each of the two multifunctional polypeptides corresponding to the α and β subunits of yeast fatty acid synthetase maps to one of two genetically unlinked complex gene loci, *fas 1* (β) or *fas 2* (α): Schweizer, E.; Kuehn, L.; Castorph, H. *Hoppe-Seyler's Z. Physiol. Chem.* **1971**, *352*, 377. Kuehn, L.; Castorph, H.; Schweizer, E. *Eur. J. Biochem.* **1972**, *24*, 492. Schweizer, E.; Kniep, B.; Castorph, H.; Holzner, U. *Ibid.* **1973**, *39*, 353. Knobling, A.; Schiffman, D.; Sickinger, H.-D.; Schweizer, E. *Ibid.* **1975**, *56*, 359. Dietlein, G.; Schweizer, E. *Ibid.* **1975**, *58*, 177. An intact mRNA for the complete multifunctional peptide subunit of the homodimeric fatty acid synthetase of goose uropygial gland has been isolated, and the corresponding cDNA has been cloned and shown to hybridize to authentic messenger: Morris, S. M.; Nilson, J. H.; Jenik, R. A.; Winberry, L. K.; McDevitt, M. A.; Goodridge, A. G. *J. Biol. Chem.* **1982**, *257*, 3225.

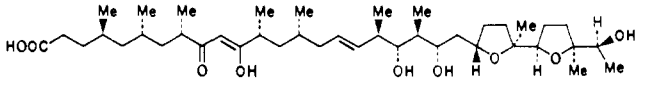
(40) For a discussion of the role of gene fusion in the evolution of eukaryotic fatty acid synthetases, see: Lynen, F. *Eur. J. Biochem.* **1980**, *112*, 431.

(41) Baltz, R. H. *J. Gen. Microbiol.* **1978**, *107*, 93. Baltz, R. H.; Seno, E. T. *Antimicrob. Agents Chemother.* **1981**, *20*, 214. Baltz, R. H.; Seno, E. T.; Stonesifer, J.; Matsushima, P.; Wild, G. M. *Microbiology (Engl. Trans.)*, **1981**, 371. Wang, Y.-G.; Davies, J. E.; Hutchinson, C. R. *J. Antibiot.* **1982**, *35*, 335. Ikeda, H.; Tanaka, H.; Omura, S. *Ibid.* **1982**, *35*, 507. Omura, S.; Ikeda, H.; Tanaka, H. *Ibid.* **1981**, *34*, 478. Hopwood, D. A.; Merrick, M. J. *Bacteriol. Rev.* **1977**, *41*, 595.

(42) Chater, K. F.; Hopwood, D. A.; Kieser, T.; Thompson, C. J. In "Current Topics in Microbiology and Immunology. Gene Cloning in Organisms Other than *E. coli*.", Hofschneider, P. H., Goebel, W., Eds.; Springer-Verlag: Berlin, 1982; pp 69–95.

(43) In a recent review, Hutchinson has also noted some of the structural and stereochemical regularities among the polyether antibiotics and discussed the genetic implications of the recurrence of these features: Hutchinson, C. R. *Acc. Chem. Res.* **1983**, *16*, 7.

(44) The antibiotic ionomycin (**14**), for example, while it has a number of features in common with the PAPA class of polyethers and can clearly be derived from a diepoxide precursor, cannot easily be reconciled with either stereochemical prototype in Figure 3A or 3B. Structure: Meyers, E.; Slusarchyk, D.; Kund, W.-C.; Liu, C.-M. U.S. Patent 3 873 693, 1975.



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(45) In addition to the substances illustrated in Figures 1 and 4, several additional polyethers are known which conform to the stereochemical prototypes of Figure 3. APPA: (a) A-130B and A-130C (cometabolites of lenoremycin; A-130C is epimeric at C-28): Tsuji, N.; Terui, Y.; Nagashima, K.; Tori, K.; Johnson, L. F. *J. Antibiot.* **1980**, *33*. 94. (b) Leuseramycin (30-dehydroxydianemycin): Mizutani, T.; Yamagishi, M.; Hara, H.; Kawashima, A.; Omura, S.; Ozeki, M.; Mizoue, K.; Seto, H.; Otake, N. *Ibid.* **1980**, *33*, 137. (c) CP-47433 and CP-47434: Tone, J.; Shibakawa, R.; Maeda, H.; Inoue, K.; Yamauchi, Y.; Tsukuda, K.; Yamada, M.; Cullen, W. P.; Chappel, L. R.; Moppett, C. E.; Oscarson, J. R.; Laplante, C. J.; Huang, L. H.; Celmer, W. D. 11th Int. *Cong. Chemother. and 19th Intersci. Conf. Antimicrob. Agents Chemother.* Boston, **1979**, Oct. 1–5, No. 103. PAPA: (d) X-14766A (6-chloronoboritomycin A) Liu, C.-M.; Hermann, T. E.; Prosser, B. La T.; Palleroni, N. J.; Westley, J. W.; Miller, P. A. *J. Antibiot.* **1981**, *34*, 133. Westley, J. W.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Liu, C.-M.; Blount, J. F.; Pitcher, R. G.; Williams, T. H.; Miller, P. A. *Ibid.* **1981**, *34*, 139. (e) 20-deoxynarasin and 20-deoxyepi-17-narasin: Nakatsukasa, W. M., et al. (Eli Lilly), U.S. Patent 4 141 907, 1979.

(46) Westley, J. W.; Liu, C.-M.; Blount, J. F.; Evans, R. H.; Sello, L. H.; Troupe, N.; Miller, P. A. *Proc. Int. Conf. Trends Antibiot. Res. Tokyo*, June 14–15, 1982, Japan Antibiot. Res. Assoc.; pp 125–134.