group and the second by the (*p*-aminobenzoyl)-L-glutamate. These planes meet at an angle of 84°. The α-carboxylate lies nearly in the latter plane while the γ-carboxylate is folded back and lies roughly parallel to the same plane. The conformation of the glutamate portion of methotrexate is different than that seen for the bound forms.[3] Considerable variability is observed in the confomation of the bound forms so there is evidently a large degree of conformational freedom in this part of the molecule.

The conformational parameters of most direct relevance to the binding of methotrexate are the three torsion angles (τ_1, τ_2, and τ_3) through the pteridine to *p*-aminobenzoyl linkage. Two of these angles, τ_2 and τ_3, are similar to those observed in methotrexate bound to DHFR while τ_1 is approximately 180° different.[3] Thus, the conformation observed here, for methotrexate, is similar to that suggested for bound dihydrofolate[3] that is, with the pteridine ring flipped over. It is possible that the conformation in the crystal is stabilized by the ring stacking or hydrogen bonding interactions described above. However, the constancy of the τ_2 and τ_3 torsion angles over three independent determinations of methotrexate bound to DHFR[3] and in the present structure suggests that this conformation is a potential energy minimum. Likewise, the two alternative dispositions of the pteridine ring appear to represent preferred geometries. These results are in disagreement with theoretical studies,[4,5] and are therefore of importance to those attempting to design new inhibitors of DHFR.

Acknowledgment. We thank Dr C. Schwalbe for encouragement and Professor H. C. Freeman for helpful discussions. This work was supported by a University of Sydney Special Projects Grant to I.G.

Supplementary Material Available: Tables of least-squares coordinates and thermal parameters for the non-hydrogen atoms of methotrexate (2 pages). Ordering information is given on any current masthead page.

Model for the Polyepoxide Cyclization Route to Polyether Antibiotics

W. Clark Still* and Arthur G. Romero

Department of Chemistry, Columbia University
New York, New York 10027

Received November 20, 1985

The polyepoxide cyclization mechanism of Westley and Cane for the biosynthesis of polyether antibiotics is appealing because of the simplicity with which the stereochemically complex polytetrahydrofuranoid segments are assembled from a basically achiral polyolefinic precursor.[1] While several previous synthesis of these materials have used such cyclizations in a stepwise manner,[2] the most effective route of this type would require only two steps from polyolefin, namely, polyepoxidation and polycyclization. In this paper we describe the direct preparation of a triepoxide closely related to the C9–C23 segment of monensin B from a triene precursor and its acid-catalyzed polycyclization to tristetrahydrofuranoid material (Scheme I).[3]

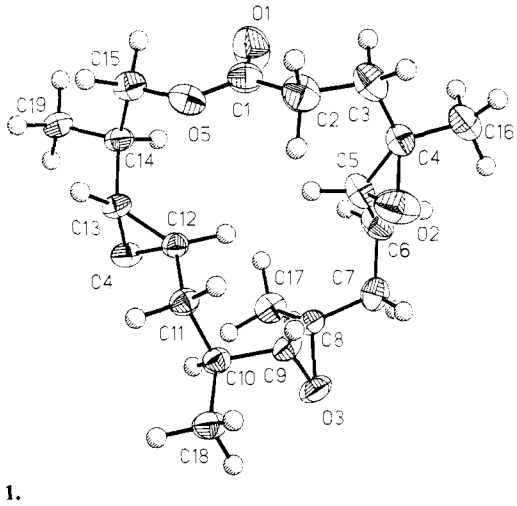
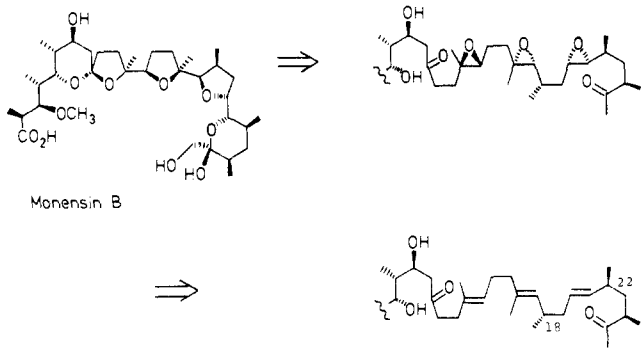
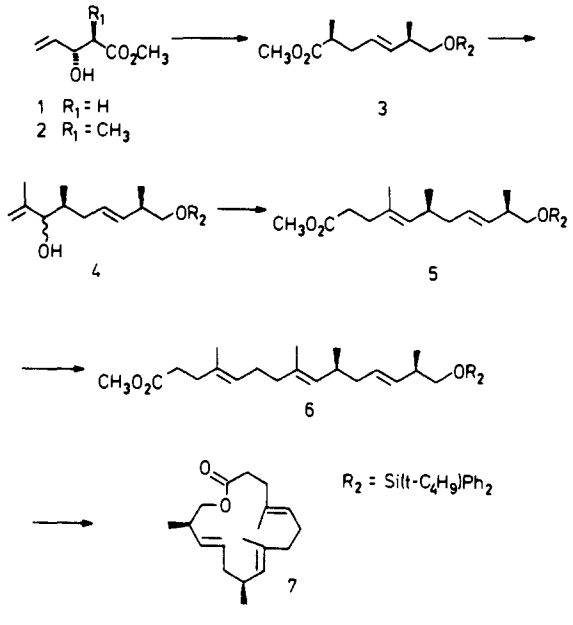


Figure 1.

Scheme I



Scheme II



The key synthetic problem of the polyene–polyepoxide–polyether approach is stereochemical control of the polyepoxidation. While enantioselective epoxidation offers a potential solution, current chiral epoxidation methodology necessitates adjacent hydroxyl groups and the fact that the disubstituted C20–C21 epoxide differs from the two trisubstituted epoxides enantiomerically in monensin makes such a scheme impractical. A more effective approach would use resident chirality at C18 and C22 of the monensin B triene for epoxidation stereocontrol.

Preparation of the appropriate triene follows established methodology and begins with hydroxypentenoic ester **1**. The second chiral center is established by β-hydroxy ester dianion

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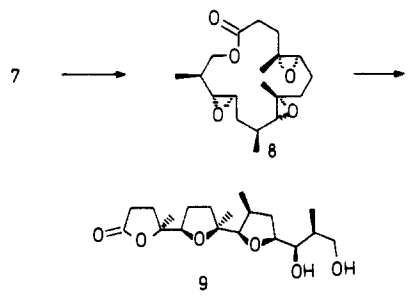
Scheme III



alkylation (stereoselection ca. 20:1),[4] and ester enolate Claisen rearrangement[5] via the *Z*-enol silyl ether separates the two asymmetric centers to give **3**. Stereocontrol in the rearrangement sequence was modest yielding a 4:1 mixture of diastereomers as a result of production of both *Z* and *E* ketene acetals (4:1) immediately prior to the rearrangement step. The identity of the major product as **3** was established by its conversion to *meso*-2,6-dimethylheptane-1,7-diol.[6] Standard Claisen methodology via **4** and **5** gave the triene **6**.

To allow the two chiral centers of triene **6** to control the required epoxidations efficiently, conversion to the corresponding 16-membered macrolide was carried out via the Mukaiyama procedure[7] (1 mM in CH_3CN, reflux, 1 h) yielding **7** in 68% yield (Scheme II). The macrolide was still a 4:1 diastereomeric mixture, but when it was epoxidized (MCPBA, $NaHCO_3$, CH_2Cl_2), a single triepoxide **8** was isolated by crystallization in 59% yield (74% based on diastereomerically pure **7**). Its X-ray structure is shown in Figure 1 and indicates that the two trisubstituted epoxides have the correct stereochemistry for monensin B and that the disubstituted epoxide is epimeric. The origin of the stereoselection observed is difficult to ascribe with confidence due to the kinetically controlled nature of the epoxidations. Furthermore, the flexibility of our 16-membered macrolide with its nine independent low-barrier torsional angles makes even a 60° resolution conformational analysis of the triene ground state impractical on a .34 MFLOP computer like a VAX 11/780.

To distinguish more clearly the product distribution from **7** itself, triepoxide **8** was deoxygenated ($N_2C(CO_2Me)_2$, $Rh_2(OAc)_4$, $PhCH_3$)[8] back to diastereomerically pure **7** and reepoxidized. High-field NMR showed a 20:1:1 mixture of triepoxides and demonstrates that the triepoxidation is highly stereoselective for **8**.

Although our triepoxide differs stereochemically from monensin B at one of the three epoxides, its polycyclization behavior provides strong support for the feasibility of the polyepoxide cyclization approach to the polyether antibiotics. Thus when **8** was saponified and worked up with excess HOAc, spontaneous cyclization to crystalline **9** (mp 89–90 °C) occurred in 94% yield.[9] The tricyclic structure shown was confirmed by X-ray crystallography (Scheme III).

To use such a scheme for natural ionophore synthesis, it will be necessary to alter the conformation of the macrocyclic triene and this will be the subject of further papers.[10]

Supplementary Material Available: Positional data and thermal parameters for crystal structures **8** and **9** (9 pages). Ordering information is given on any current masthead page.

(4) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825.
(5) Ireland, R. E.; Mueller, R. H.; Willard, A. F. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(6) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385.
(7) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, *49*.
(8) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, 251.
(9) Triepoxide **8** (39 mg) in 5.0 mL of 1:1 MeOH/H_2O (0 °C) was treated with 2.0 mL of 0.1 N aqueous NaOH and stirred for 3 h. Acetic acid (2.0 mL) was added with the mixture was stirred (25 °C) until the starting material was consumed (ascertained by TLC). Partitioning between CH_2Cl_2 and saturated $NaHCO_3$ followed by flash chromatography on silica gel gave crystalline **9** (40 mg, 94%, mp 176 °C).
(10) This work was supported by NIH Grant HL25634.

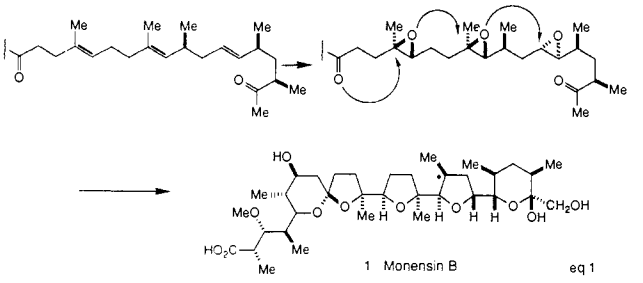
Epoxidation of Unsaturated Macrolides: Stereocontrolled Routes to Ionophore Subunits

Stuart L. Schreiber,* Tarek Sammakia, Bernard Hulin, and Gayle Schulte[1]

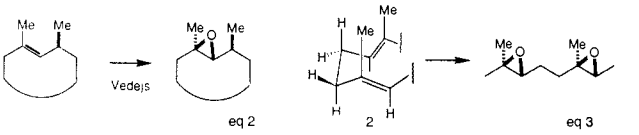
Sterling Chemistry Laboratory, Yale University
New Haven, Connecticut 06511

Received December 11, 1985

There has been considerable interest in the chemistry and biology of the polyether class of ionophores.[2] Recent studies on the biosynthesis of these materials by Cane, Celmer, and Westley led to the proposal that ether ring formation proceeds via polyene epoxidation and subsequent epoxide ring opening (eq 1).[3]



1 Monensin B eq 1



eq 2 2 eq 3

Nonbiological methods to mimic this process in a direct manner must address the absence of polar "directing" functionality[4] (e.g., hydroxyl substituent) in the vicinity of the olefin. One such method has emerged from a combination of studies on the conformational preferences and stereoselective reactions of macrocycles[5] and the directing property of a methyl substituent at allylic positions of unsaturated macrocycles.[6] In the latter study Vedejs and Gapinski reported that the epoxidation of an olefin containing the substitution pattern shown in eq 2 provided a single epoxide with the indicated stereochemistry. To address the problem of ionophore synthesis, we reasoned that a macrocycle containing a 1,5-diene could adopt the local conformation **2** (eq 3) that is free of torsional strain. Peripheral epoxidation[5] would result in the preferential formation of the *syn*-bisepoxide, a structural unit contained within the putative biogenetic intermediate. Herein we report on several applications of these principles that employ macrolides as templates

(1) Author to whom correspondence concerning X-ray crystallographic analysis should be addressed.
(2) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1983; Vol. 1–2.
(3) (a) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594. For experimental support in the specific case of monensin A, see: (b) Cane, D. E.; Liang, T.-C.; Hasler, H. *J. Am. Chem. Soc.* **1982**, *104*, 7274.
(4) Reviews of hydroxyl-directed epoxidation of olefins: (a) Berti, G. *Top. Stereochem.* **1973**, *7*, 93. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. (c) Kishi, Y. *Aldrichimica Acta* **1980**, *13*, 23. (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (e) Sheldon, R. A. In *Aspects of Homogeneous Catalysis*; Ugo, R. Ed.; D. Reidel Publishing Co.: Dordrecht, Holland, 1981; Vol. 4, p 3. (f) Sharpless, K. B.; Finn, M. G. In *Asymmetric Synthesis*; Morrison, J. D., Academic Press: New York, 1985; Vol. 5, p 247. (g) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 193. For recent contributions, see: (h) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Sato, F. *J. Am. Chem. Soc.* **1985**, *107*, 5541 and references cited therein.
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(6) (a) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058, and references cited therein. For a related observation, see: (b) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.

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