from ethyl acetate gave 0.190 g (28.5%) of 1-methyl-2,3-bis[1-(4-*n*-butylurazolyl)]indole: mp 190–193 °C dec; ^{1}H NMR ($CDCl_3$, δ) 0.91 (3 H, t), 0.94 (3 H, t) 1.1–1.8 (m, 8 H) (m, 3.45 (2 H, t), 3.48 (3 H, s), 3.57 (2 H, t), 7.0–7.7 (4 H, m), 7.7–8.5 (2 H, vbs).

Anal. Calcd for $C_{21}H_{27}O_4N_7$: C, 57.13; H, 6.16; N, 22.21. Found: C, 57.02; H, 5.27; N, 22.05.

Reaction of 1-Methylpyrrole with 4-Phenyl-1,2,4-triazoline-3,5-dione. A. In 20 mL of methylene chloride was dissolved 0.875 g (5.00 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione. A solution of 0.405 g (5.00 mmol) of 1-methylpyrrole in 10 mL of methylene chloride was added all at once. The solution on mixing turned bright green, then yellow-brown, and finally red-brown all within 1 min. After standing 30 min, the precipitate was filtered and washed to give 0.651 g (60.4%) of 1-methyl-2,5-bis[1-(4-phenylurazolyl)]pyrrole, mp 200–205 °C dec. Recrystallization from dilute ethanol gave an analytical sample: ^{1}H NMR (Me_2SO-d_6, δ) 3.564 (3 H, s), 6.41 (2 H, s), 7.53 (10 H, m), 7.5 (2 H, vb); ^{13}C NMR (Me_2SO-d_6, δ) 29.6 (CH_3), 106.2 (C-3,4 of pyrrole), 122.4 (C-2,5 of pyrrole), 126.4 (*o*-C's), 128.1 (*p*-C), 128.8 (*m*-C's), 131.4 (C-1), 151.1 and 151.9 (C=O's); IR (Nujol, cm^{-1}) 3130 (b, NH), 1692, 1717, 1752 (C=O's); 838, 813, 766, 720, 688 (aromatic).

Anal. Calcd for $C_{21}H_{17}N_7O_4$: C, 58.46; H, 3.97; N, 22.73. Found: C, 58.54; H, 4.14; N, 22.70.

Examination of the residue obtained by evaporation of the red filtrate in the reaction showed it to consist of a mixture of red polymer and recovered 1-methylpyrrole in an ca. 1:1 ratio.

B. In 20 mL of methylene chloride was dissolved 0.599 g (3.42 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione. This solution was added dropwise to a solution of 0.139 g (1.781 mmol) in 20 mL of methylene chloride at −60 °C. The red color of the azo compound disappeared as fast as it was added to give a yellow-green solution. At the end of the addition, the solution was allowed to warm to room temperature. As the solution reached room temperature, it turned dark red as the polymer formed. The precipitate was filtered and washed with methylene chloride to give 0.61 g (62.7%) of 1-methyl-2,5-bis[1-(4-phenylurazolyl)]prrole.

Evaporation of the filtrate gave a red polymer, whose ^{1}H NMR ($CDCl_3$) showed broad bands at δ 3.0 (3 H, vb), 6.2 (1 H, b), 6.5 (1H, b) and 7.4 (5 H, b), indicating that the polymer is 1:1.

Reaction of 1-Methylpyrrole with 4-*n*-Butyl-1,2,4-triazoline-3,5-dione. A. The reaction was run as in A above. The reaction mixture was chilled to −10 °C and filtered and the solid washed with cold methylene chloride to give 0.601 g (61.5%) of 1-methyl-2,5-bis[1-(4-*n*-butylurazolyl)]pyrrole, mp 187–189 °C dec. Recrystallization from ethyl acetate gave an analytical sample with 1 mol of ethyl acetate of crystallization. Heating at 110 °C removed the ethyl acetate: mp 190–192 °C dec; Anal. Calcd for $C_{17}H_{25}N_7O_4$: C, 52.16 H, 6.44 N, 25.05. Found: C, 52.39; H, 6.64; N, 25.04.

^{1}H NMR (Me_2SO-d_6, δ) 0.91 (6 H, t), 1.4 (8 H, m), 3.36 (3 H, s), 3.51 (4 H, t), 6.27 (2 H, s).

B. In 20 mL of methylene chloride was dissolved 0.243 g (3.00 mmol) of *N*-methylpyrrole, and the solution was cooled to −50 °C. To this solution was added dropwise a solution of 0.465 g (3.00 mmol) of 4-*n*-butyl-1,2,4-triazoline-3,5-dione in 20 mL of methylene chloride over a period of 1 h. The solution remained yellow during the addition but turned red as the solution warmed above 0 °C. The white precipitate was filtered to give 0.135 g of 1-methyl-2,5-bis[1-(4-*n*-butylurazolyl)]pyrrole, mp 186–188 °C dec. Extraction of the filtrate with aqueous potassium hydroxide, followed by acidification with hydrochloric acid, gave an oil that eventually solidified. Filtration gave 0.387 g of a red-purple solid. It was placed in 5 mL of benzene and an additional 0.053 g of the disubstited pyrrole filtered to give a total yield of 0.188 g (32%). The benzene was evaporated and the purple residue was dissolved in hot carbon tetrachloride and treated with charcoal. Cooling to −10 °C gave 0.197 g (27%) 1-methyl-2-[1-(4-*n*-butylurazolyl)]pyrrole, mp 101–103 °C. A second recrystallization gave an analytical sample: ^{1}H NMR ($CDCl_3$, δ) 0.93 (3 H, t), 1.1–1.9 (4 H, m), 350 (3 H, s), 3.58 (2 H, t), 6.09, 6.19 (2 H, AB), 6.59 (1 H, X, J_{AB} = 4.2, J_{AX} = 3.0, J_{BX} = 2.1), 7.1–8.0 (1 H, vb). Anal. Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.91; H, 6.79; N, 23.66.

Reaction of 1-Ethylcarbazole with 4-Phenyl-1,2,4-triazoline-3,5-dione. In 20 mL of methylene chloride was dissolved 0.875 g (5.00 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione, and 0.487 g (2.50 mmol) of 9-ethylcarbazole was added. The solution turned dark red instantly. After 3 h, the red color was essentially gone. After an additional 3 h, the precipitate was filtered to give 0.130 g (16.2%) of 1,3,5,7-tetraoxo-2,6-diphenylperhydro-*s*-triazolo[1,2-*a*]-*s*-triazole: ^{1}H NMR(Me_2SO-d_6, δ) 7.68 (s); ^{13}C NMR (Me_2SO-d_6, δ) 126.7 (*o*-C's), 129.4 (*m*- and *p*-C's), 129.8 (C-1), 145.4 (C=O); IR (Nujol, cm^{-1}) 1751, 1783, 1795 (sh, C=O's), 1165, 1013, 745, 729, 687, 643 (aromatic).

This compound was identical with that reported by Wamhoff and Wald.[3] Its IR, ^{1}H NMR, and ^{13}C NMR spectra were identical with those of sample prepared by heating a 1:1 molar mixture of 4-phenylurazole and 4-phenyl-1,2,4-triazoline-3,5-dione in anisole as reported by Wamhoff and Wald.[3]

Evaporation of the filtrate from the above reaction gave a residue whose ^{1}H NMR ($CDCl_3$) showed broad peaks at 1.25, 4.15 and 7.13 ppm together with a trace of unreacted 9-ethylcarbazole. Consideration of the integration and the material balance suggests that the polymer contains 9-ethylcarbazole and urazole residues in a 1:2 ratio. Changing the mole ratio of the reactants from 2:1 to 1:1 to 1:2 did not change the yield of or the composition of the polymer.

Registry No. **6a**, 90432-40-9; **6b**, 90432-41-0; **7**, 32494-23-8; **8a**, 90432-42-1; **8b**, 90432-43-2; **9** (R = Ph), 4233-33-4; **9** (R = Bu), 13482-57-0; **10**, 96-54-8; **15b**, 90432-44-3; 1-methylindole, 603-76-9; 1-ethylcarbazole, 19275-57-1; indole, 120-72-9.

Studies Directed toward the Synthesis of Ionomycin(I): Synthesis of the Furanoid Fragment

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A synthesis of the tetrahydrofuranoid fragment of the calcium ion selective ionophore ionomycin is described. The synthesis utilizes geraniol acetate to establish the carbon skeleton and the Sharpless asymmetric epoxidation to introduce chirality.

The ionophores as a class of natural products have recently attracted considerable attention,[1] perhaps due to their unique property in that they serve to transport metal ions across hydrophobic biological membranes[2] and the

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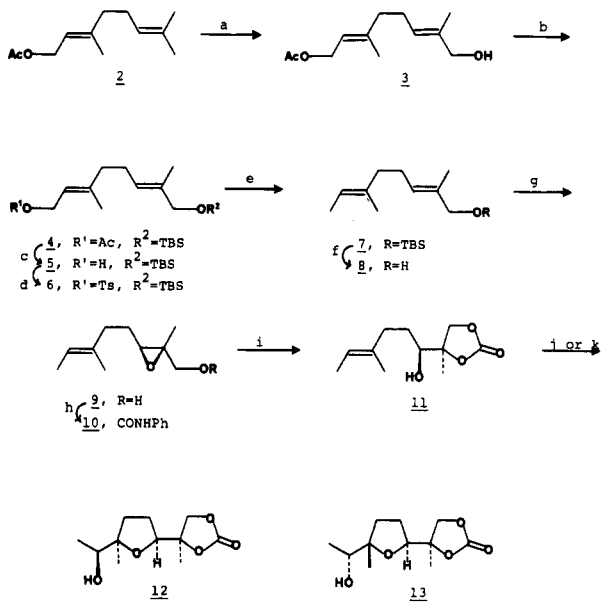
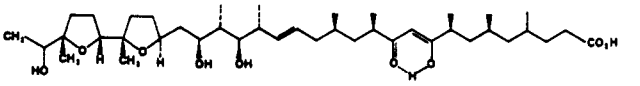
Scheme I[a]



[a] (a) SeO_2, *t*-BuOOH, salicylic acid; (b) TBSCl, DMF, imidazole; (c) MeOH, K_2CO_3; (d) *n*-BuLi, TsCl, THF; (e) $LiEt_3BH$; (f) *n*-Bu_4NF; (g) Ti(O-*i*-Pr)$_4$, (+)-diethyl-(L)-tartrate, *t*-BuOOH; (h) PhNCO, Et_3N, CH_2Cl_2; (i) $HClO_4$; H_2O, CH_3CN; (j) MCPBA; (k) VO(acac)$_2$, *t*-BuOOH, AcOH.

unique structural features embodied in their skeletal framework. This unique transport ability results in a variety of biological properties which include antimicrobial activity, growth promotion in ruminants, and cardiovascular effects. To the synthetic chemist they present a challenge in the development of stereorational routes which control the numerous chiral centers which adorn the ionophoric framework.

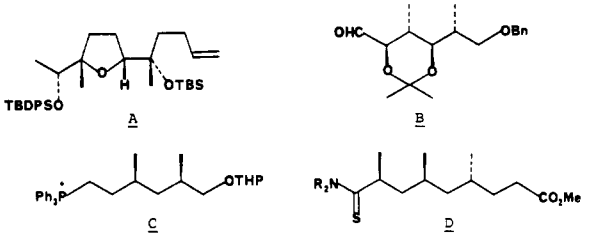
Among the ionophores, ionomycin 1,[3] isolated from *Streptomyces conglobatus* (ATCC 31005), is unique in that



Ionomycin 1

it chelates metal ions as dibasic acid and has much greater Ca^{2+} selectivity than does A23187 (calcimycin), the other major calcium-selective ionophore.[4] Furthermore, ionomycin has a much narrower range of cation selectivity (greater selectivity for Ca^{2+} than for Mg^{2+}). A second unique feature of ionomycin is that among the other known ionophores of its size it consists of two furanoid rings and a long acyclic carbon framework in contrast to the usual polycyclic structures found in other ionophores of its size.

In considering the synthesis of ionomycin, we envisioned as logical synthetic disconnections four substructures: section A, the bistetrahydrofuranoid fragment with the



second ring in an open form; section B, the diol containing unit; and the C and D units bearing the 1,3-dimethyl groups.

This report will describe our approach to the synthesis of the A fragment. We chose to prepare the second ring in an open form because this would facilitate the coupling of the A and B units. Alternate approaches in which both rings were formed were deemed less satisfactory due to potential problems in connecting the A and B units as well as securing the proper stereochemistry at C-23. Ionomycin numbering will be used throughout this paper.

Our approach to the A fragment (Scheme I) has its skeletal genesis in geraniol acetate **2** since it contains 10 of the necessary 13 carbon atoms with the correct placement of the 2 required tertiary methyl groups. The problem then is reduced to the introduction of the necessary oxygens with the appropriate chirality and correct relative stereochemistry. We envisioned that chirality could readily be introduced by the Sharpless asymmetric epoxidation[5] and the relative stereochemistry could easily be secured by a series of controlled epoxide opening reactions. Thus the transformation of geraniol acetate **2** to the tetrahydrofuran A proceeded with initial SeO_2-promoted allylic oxidation[6] to introduce a functional handle which is necessary for the asymmetric epoxidation and later for introduction of the remaining three carbon atoms. The resulting alcohol **3** which upon protecting-group juxtaposition gives the *tert*-butyldimethylsilyl derivative **5**. Since the C32 carbon of ionomycin is in the methyl oxidation state, the hydroxyl was removed by in situ preparation of the tosylate **6** and direct reduction with $LiEt_3BH$.[7] Other approaches that relied on initial isolation of either

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(2) For a review, see: Westly, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. Pressman, B. C. *Ann. Rev. Biochem.* **1976**, *45*, 501.

(3) (a) For isolation, see: Liu, W.-C.; Slusarchytc, D. S.; Astle, G.; Trejo, W. H.; Brown, W. E.; Meyers, E. *J. Antibiot.* **1978**, *31*, 815. (b) Structure determination: Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Pantier, W. L.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1979**, *101*, 3344.

(4) Study of calcium ion selectivity: Liu, C.-M.; Hermann, T. E. *J. Biol. Chem.* **1978**, *235*, 5892.

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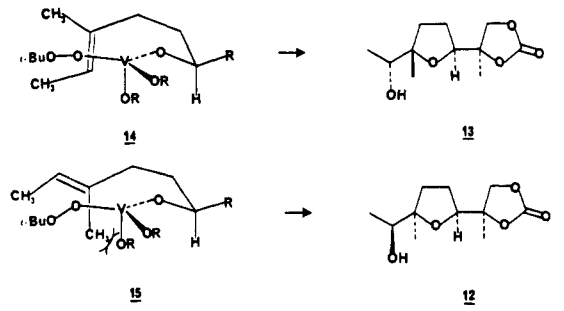
the tosylate, mesylate, or halide proved unsatisfactory due to the unstable nature of these derivatives. In fact, the one-pot procedure is quite simple and affords diene **7** in 90% yield. Deprotection of the silyl ether with n-Bu_4NF in THF[8] resulted in allylic alcohol **8** in 90% yield after flash chromatography[9] and Kugelrohr distillation. Treatment of alcohol **8** under the Sharpless conditions[5] gave a 70% chromatographed yield of the chiral epoxide **9**. Subsequent perchloric acid catalyzed rearrangement of the derived phenyl urethane **10** resulted in hydroxy carbonate **11**,[10] thus securing the C25–C27 chiral centers. The remaining centers at C30 and C31 were established by epoxidation of the alkene with MCPBA which gave the desired epoxide along with material resulting from acid-catalyzed cyclization to the tetrahydrofurans **12** and **13**. Since the tetrahydrofuran was the desired product, no attempt was made to find conditions that would allow isolation of the epoxide. In general, the mixture was treated with acetic acid to drive the reaction to completion, giving **12** and **13** in a combined yield of 90%. As expected from Kishi's earlier work in his lacilosid synthesis,[1y] the isomeric tetrahydrofurans were formed in a 1:1 ratio. In order to determine the spectral characteristics of the desired isomer, we carried out a $VO(acac)_2$-catalyzed epoxidation[11] which as expected gave a 20:1 mixture of the wrong isomer **13** and the desired diastereomer **12**. This



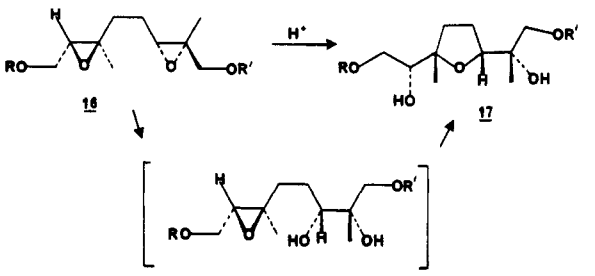
assertion was based on examination of the two likely transition states **14** and **15** where the primary interaction responsible for raising of the energy in transition state **15** is due to the interaction of the axial OR substituent on the vanadium with the internal vinyl methyl group which is absent in transition state **14**.

In fact, a computational comparison[12] of the two rotational conformations **14** and **15** in which the vanadium was not considered leads to a prediction favoring **15** by a factor of 9 to 1, thus reiterating the importance of the vanadium and its ligands in determining the final stereochemical outcome.

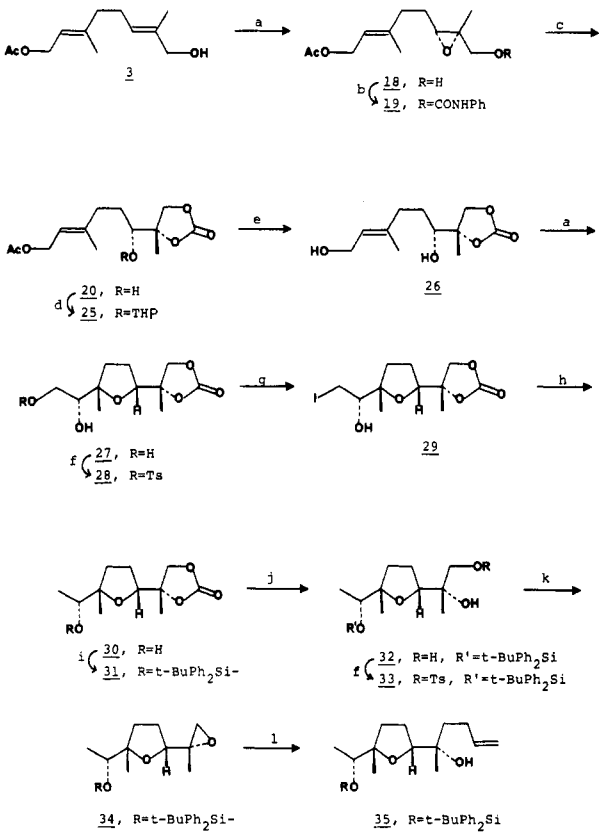
A comparison of the 360-MHz NMR spectra of the $VO(acac)_2$-derived product and the MCPBA-derived product allowed us to assign the more polar isomer as **13** and the less polar isomer as the desired isomer **12**. Unfortunately, the two isomers were not readily separable by chromatography.

At this point we had in hand the tetrahydrofuran fragment with its attendant stereochemistry, but the problems

Scheme II



Scheme III[a]



[a] (a) $Ti(O\text{-}i\text{-}Pr)_4$, (−)-diethyl D-tartrate, t-BuOOH; (b) PhNCO, Et_3N, CH_2Cl_2, room temperature; (c) $HClO_4$, CH_3CN, H_2O; (d) DHP, CH_2Cl_2, PCl_5; (e) K_2CO_3, MeOH, MeOH, Dowex H^+; (f) TsCl, pyridine, 0 °C; (g) NaI, 2-butanone, Δ; (h) Bu_3SnH, EtOH; (i) t-$BuPh_2SiCl$, DMF, imidazole; (j) $LiAlH_4$; (k) K_2CO_3, MeOH; (l) $CH_2{=}CHCH_2$-MgCl, THF, room temperature.

of inseparability of the two diastereomers **12** and **13**, coupled with the poor selectivity in the MCPBA epoxidation, makes this an impractical route for the synthesis of ionomycin. Also, it should be noted that in securing the initial absolute stereochemistry, we used the wrong tartrate enantiomer for simple economic reasons.

As a result of the above-mentioned problems, we explored an alternative approach which completely solves the problem of securing the C31–C32 stereochemistry. In examining the problem, we realized that in the first approach we removed the C32 hydroxyl early in the synthesis but that this hydroxyl could be employed to direct the stereochemistry of epoxidation at the C30–C31 olefinic bond by a second asymmetric epoxidation[5] which would then avoid the problems of diastereoselectivity.

In principle an acid-catalyzed opening of the chiral bisepoxide **16** (Scheme II) would provide the desired furan **17** with its attendant stereochemistry if the reaction proceeded by initial opening of the right epoxide followed by

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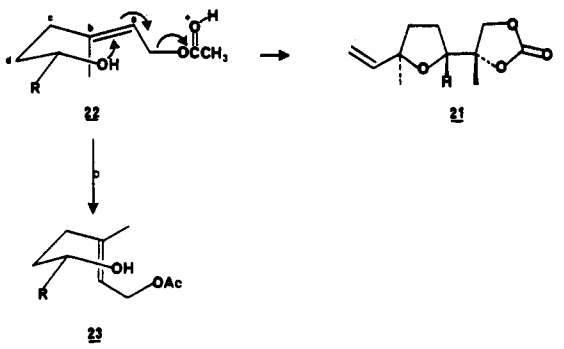
(11) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745. Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Ibid.* **1978**, *2741*.
(12) MM2 calculations were performed by using Allinger's program which is available from QCPE.

Scheme IV



22 21

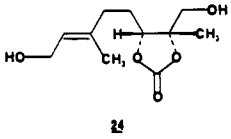
23

acid-catalyzed opening of the left epoxide with intramolecular hydroxyl participation. Of course, such an approach would rely on the ability to open the right epoxide prior to the left but this represents selectivity only dreamed of in light of the similarity of both epoxides.

A strategy that obviates this selectivity problem would be to form and open the epoxides sequentially as outlined in Scheme III. In this approach, hydroxygeraniol acetate **3** is epoxidized under the Sharpless condition[5] to afford the chiral epoxide **18**. Derivation as the urethane **19** followed by perchloric acid protonated rearrangement gives carbonate **20**.[10] If the acid-catalyzed rearrangement of the urethane is not done in the presence of sufficient H_2O, the major product of the reaction proved to be the tetrahydrofuran **21** which is presumably formed by acetate protonation and ring closure as illustrated in Scheme IV.

The stereochemistry illustrated is based on the preferred transition-state conformation **22** and on the lack of an Overhauser enhancement with irradiation of either the carbinyl proton or the methyl protons which albeit is negative evidence is not unexpected for trans-substituted tetrahydrofurans. Further evidence is also provided by an empirical force field calculations which gives a clear preference for the conformation **22** shown over the other likely possibility **23** in which the dihedral angle abcd is rotated 180°.[12]

The next step in the sequence required hydrolysis of the acetate and subsequent asymmetric epoxidation, but every attempt to remove the acetate under a variety of conditions (K_2CO_3, MeOH; THF LiOH; Ⓟ-NMe_3^+ ^-OH, MeOH) led to rearranged carbonate **24**. Attempted acid-catalyzed



24

hydrolysis (HCl, MeOH or Dowex H^+, MeOH) led to alkene **21**. Therefore the secondary hydroxyl was first protected as a THP derivative **25** (DHP, $POCl_3$, CH_2Cl_2) followed by acetate removal (MeOH, K_2CO_3, 0 °C, 2 h) and subsequent removal of the THP (MeOH, Dowex H^+, room temperature, 4 h) to afford the desired diol **26**. The second asymmetric epoxidation followed by in situ acid-catalyzed ring closure gave the desired tetrahydrofuran **27**.

The remaining steps of the sequence required adjustment of the C32 oxidation state and chain extension at C25. Attempts to remove the hydroxyl by $LiEt_3BH$[13] reduction of the epoxide prepared from tosylate **28** by treatment with K_2CO_3 in MeOH or by derivation of the primary hydroxyl with $(C_4H_8N)_2P(S)Cl$[14] or $C_6H_5OC(S)Cl$[15]

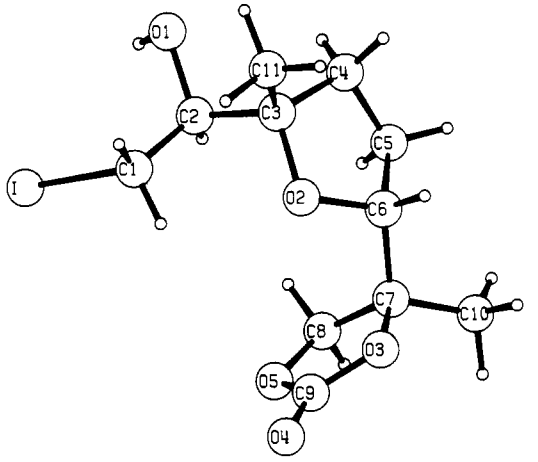


Figure 1.

followed by tributyltin hydride reduction proved entirely unsatisfactory. Attempts to reduce the epoxide or the tosylate **28** directly with $LiEt_3BH$ led to partial reduction of the carbonate. Problems with the thiono derivatives were primarily due to the inability to form these derivatives cleanly. We found that the best method to affect deoxygenation was through tri-*n*-butyltin hydride reduction of iodide **29**[16] prepared from tosylate **28** by a Finkelstein reaction. Reduction of the iodide to alcohol **30** proceeded cleanly at room temperature in 2 h when ethanol was used as solvent whereas the use of refluxing toluene, the usual conditions for these reactions, did not give a clean product. The use of ethanol has an additional advantage in that the byproduct Bu_3SnI may readily be precipitated from the reaction by conversion to the insoluble Bu_3SnF upon NaF treatment. It should also be noted that commercial *n*-Bu_3SnH did not work well in the reduction. Tri-*n*-butyltin hydride prepared from polymethylhydrosiloxane and bis(tri-*n*-butyltin) oxide[17] proved far superior and did not require AIBN catalysis.

Since the iodide **29** proved to be highly crystalline, we elected to perform an X-ray diffraction study to confirm our stereochemical assignments.[18] Examination of the stereoscopic ORTEP illustration confirms the assigned stereochemistry of the four chiral centers and sets the stage for completion of the synthesis of the tetrahydrofuranoid fragment (Figure 1).

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(18) Crystals of iodine **29** were obtained by recrystallization from diethyl ether at 0 °C. A crystal was mounted on a Syntex $P2_1$ automatic diffractometer and the space group determined to be $P2_1$ with $Z = 2$, $a = 7.557$ (3)°, $b = 10.898$ (3)°, $c = 9.169$ (3)°, $V = 697.6$ (5), $d_{calcd} = 1.69$ g/mL. Data were collected by using graphite monochromated Mo Kα radiation. Data were collected to $2\theta = 55°$. Of the 1923 data collected, 967 had intensity greater than $3\sigma(I)$. Computations were carried out an on Amdahl 470-V8 computer. Computer programs used during the structural analysis were SYNCOR (data reduction by W. Schmonsees), FORDAP (Fourier refinement by A. Zalkin), ORFLS (full-matrix least-squares refinement, Martin and Levy), ORTEP (thermal ellipsoid drawings by S. K. Johnson), HATOMS (hydrogen atom positions by A. Zalkin), and PLANES (least-squares planes by D. M. Blow). The structure contains one molecule of the iodide per asymmetric unit. The patterson function was used to find the position of the iodine atom and all non-hydrogen atoms were found in subsequent difference fouriers. Least-squares refinement with isotropic temperature factors gave $R_1 = 0.078$ and $R_2 = 0.088$. Hydrogen positions were located by difference fourier and added as fixed contributions to the structure factors assuming an isotropic temperature parameter of 1.1 times the thermal parameter of the atom to which the hydrogen was attached. Refinement to convergence gave $R_1 = 0.048$ and $R_2 = 0.060$. There were no significant peaks in the final difference Fourier.

The synthesis of the left quarter of ionomycin was completed by protection of the secondary alcohol **20** with *tert*-butyldiphenylchlorosilane[19] to give the silyl derivative **31**. Reduction of the carbonate with lithium aluminum hydride gave a diol **32** which was monotosylated and subjected to K_2CO_3 in methanol solution to form epoxide **34**. Treatment of the resulting epoxide **34** with allyl magnesium chloride in THF at room temperature for 24 h[20] led to clean conversion to the desired tetrahydrofuranoid fragment **35**.

At this point, four of the five chiral centers of the furanoid fragment are secured in both an absolute and relative sense. The fifth center will be fixed after the second piece is attached to the bisfuranoid fragment. Coupling of this fragment to the remaining pieces of ionomycin will be the subject of future reports.

Experimental Section

(*E*,*E*)-2,6-Dimethyl-1-(dimethyl-*tert*-butylsiloxy)-8-acetoxy-2,6-octadiene (4). To 25.0 g (0.117 mol) of alcohol **3** in 50 mL of dimethylformamide was added with stirring 39.7 g (0.58 mol) of imidazole followed by a solution of 19.5 g (0.13 mol) of dimethyl-*tert*-butylsilyl chloride in 30 mL of dimethylformamide. The reaction mixture was allowed to stir at room temperature for 24 h. Water (200 mL) was poured into the reaction flask and the mixture was extracted with dichloromethane (2 × 100 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to afford 38.0 g (~100%) of silyl acetate: IR (film) 2900, 2850, 1750, 1500, 1400, 1250, 1140, 1100, 1050 cm^{-1}; NMR ($CDCl_3$) δ 5.35 (m, 2 H), 4.6 (d, J = 7 Hz, 2 H), 4.0 (s, 2 H), 2.05–2.2 (m, 4 H), 2.05 (s, 3 H), 1.7 (s, 3 H), 1.6 (s, 3 H), 0.9 (s, 9 H). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.25; H, 10.42. Found: C, 66.14; H, 10.25.

(*E*,*E*)-3,7-Dimethyl-8-(dimethyl-*tert*-butylsiloxy)-2,6-octadienol (5). Anhydrous potassium carbonate (19.1 g, 0.13 mol) was added to the magnetically stirred solution of 45.0 g (0.13 mol) of silyl ether **4** in 125 mL of methanol at 0 °C. After 1 h, cold water (150 mL) was introduced and the reaction mixture was extracted with dichloromethane (3 × 75 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent afforded 35.0 g (90% of silyl derivative **5**: IR (film) 3400, 2960, 1470, 1400, 1270, 1080, 850, 800 cm^{-1}; NMR ($CDCl_3$) δ 5.35 (m, 2 H), 4.1 (d, J = 7 Hz, 2 H), 3.95 (s, 2 H), 2.1 (q, J = 5 Hz, 2 H), 2.0 (t, J = 5 Hz, 2 H), 1.65 (s, 3 H), 1.55 (s, 3 H), 0.85 (s, 9 H). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.6; H, 11.25. Found: C, 67.49; H, 11.22.

(*E*,*E*)-2,6-Dimethyl-1-(dimethyl-*tert*-butylsiloxy)-2,6-octadiene (7). To a magnetically stirred solution of allyl alcohol **5** (5.0 g, 0.017 mol) in 50 mL of dry tetrahydrofuran cooled to −78 °C was added via a syringe 12.5 mL of 1.6 M *n*-butyllithium. After 15 min, a solution of *p*-toluenesulfonyl chloride (3.5 g, 0.18 mol) in 25 mL of tetrahydrofuran was introduced. The temperature was allowed to rise to 0 °C and maintained for 2 h (progress of the reaction can be followed by TLC on silica). The flask was recooled to −78 °C and 26 mL (0.026 mol) of lithium triethylborohydride (1 M in tetrahydrofuran) was added. The temperature was allowed to rise to room temperature and stirring was continued overnight. Water (100 mL) was added and the reaction mixture was extracted with dichloromethane (2 × 50 mL). The organic layer was washed with cold water and brine and dried over anhydrous sodium sulfate. Filtration, evaporation of the solvent, and distillation afforded 4.2 g (90% yield) of diene **7**: IR (film) 2960, 2880, 1480, 1270, 1080, 850, 790 cm^{-1}; NMR ($CDCl_3$) δ 5.3 (t, J = 9 Hz, 1 H), 5.15 (q, J = 11 Hz, 1 H), 3.95 (br s, 2 H), 2.05 (q, J = 5 Hz, 2 H), 1.95 (t, J = 5 Hz, 2 H), 1.55 (s, 6 H), 1.5 (d, J = 7 Hz, 3 H), 0.85 (s, 9 H). Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.64; H, 11.94. Found: C, 71.58; H, 11.74.

(*E*,*E*)-2,6-Dimethyl-2,6-octadienol (8). A solution of tetrabutylammonium fluoride (30 mL, 1.0 M) in tetrahydrofuran was introduced dropwise into a solution of 4.1 g (0.015 mol) of silyl ether **7** in 40 mL of dry tetrahydrofuran. Stirring was continued overnight at room temperature. The solvent was evaporated and water (50 mL) was added to the residue. It was extracted with dichloromethane (3 × 25 mL). The dichloromethane layer was washed with brine and dried over anhydrous sodium sulfate. The solution was filtered, evaporated, and flash chromatographed on silica and distillation furnished 2.1 g (90%) of a colorless alcohol (**8**): IR (film) 3400, 2980, 1480, 1400, 1030, 850 cm^{-1}; NMR ($CDCl_3$) δ 5.4 (t, J = 7 Hz, 1 H), 5.2 (q, J = 10 Hz, 1 H), 4.0 (d, J = 6 Hz, 2 H), 2.1 (q, J = 7 Hz, 2 H), 2.0 (t, J = 7 Hz, 2 H), 1.7 (s, 3 H), 1.65 (s, 3 H), 1.6 (d, J = 7 Hz, 3 H), 1.35 (br s, OH). Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.68. Found: C, 77.61; H, 11.76.

(2*S*,3*S*)-2,6-Dimethyl-2,3-epoxyoct-6-enol (9). Into a three-necked flask fitted with a septum and argon inlet and charged with 25 mL of dichloromethane was introduced 3.68 g (0.013 mol) of titanium isopropoxide. The flask was cooled to −20 °C (dry ice/CCl_4) and 2.3 g (0.013 mol) of L-(+)-dimethyl tartrate was added. After 5 min, 2.0 g (0.013 mol) of dieneol **8** was introduced followed by 6.3 mL of 4.1 M anhydrous *tert*-butyl hydroperoxide[21] in dichloromethane. The resulting homogeneous mixture was stired overnight in the freezer. The next day the flask was placed in a dry ice/CCl_4 bath and 20 mL of 10% tartaric acid solution was added while stirring. After 30 min, the cooling bath was removed and stirring was continued until the solution became clear. After separating the aqueous layer, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration, evaporation of the solvent and chromatography on silica (ethyl acetate/hexane, 1:1, as eluent) furnished 1.5 g (70%) of pure epoxy alcohol **9**: IR (film) 3460, 3000, 1480, 1400, 1280, 1170, 820 cm^{-1}; NMR ($CDCl_3$) δ 5.25 (m, 1 H), 3.7 (d, J = 12 Hz, 1 H), 3.5 (d, J = 12 Hz, 1 H), 3.05 (t, J = 7.2 Hz, 1 H), 2.15 (m, 2 H), 1.7 (m, 2 H), 1.65 (s, 3 H), 1.6 (d, J = 6 Hz, 3 H), 1.3 (s, 3 H). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.58; H, 10.58. Found: C, 70.44; H, 10.46.

(6*E*)-(2*S*,3*S*)-2,6-Dimethyl-2,3-epoxy-6-octenyl Phenylcarbamate (10). To the magnetically stirred solution of epoxy alcohol **9** (1.8 g, 0.010 mol) in 25 mL of dichloromethane and containing 10 drops of triethylamine was added through a syringe (dropwise) 1.4 g (0.012 mol) of phenylisocyanate. Stirring was continued overnight at room temperature. The brown solution was washed with water and brine and finally dried over anhydrous sodium sulfate. Filtration, evaporation of the solvent, and chromatography on a short silica pad furnished 2.9 g (95%) of the urethane derivative **10**: $[\alpha]^{20}_D$ −13.8° (*c* 0.6, $CHCl_3$); IR (film) 3340, 3000, 1740, 1620, 1550, 1460, 1330, 1230, 1080 cm^{-1}; NMR ($CDCl_3$) δ 7.1–7.5 (Ar, 5 H), 6.7 (br s, NH), 5.25 (m, 1 H), 4.3 (d, J = 11 Hz, 1 H), 4.05 (d, J = 11 Hz, 1 H), 2.9 (t, J = 7.2 Hz, 1 H), 2.15 (m, 2 H), 1.7 (m, 2 H), 1.65 (s, 3 H), 1.6 (d, J = 8 Hz, 3 H), 1.35 (s, 3 H). Anal. Calcd for $C_{17}H_{23}O_3N$: C, 70.58; H, 7.95; N, 4.48. Found: C, 70.45; H, 7.87; N, 4.94.

Carbonate 11. A solution of 10 mL of 5% perchloric acid was added to a solution of 5.0 g (0.017 mol) of urethane **10** in 25 mL of acetonitrile. The reaction mixture was stirred at room temperature for 4 h (progress of the reaction was followed by TLC). Sodium bicarbonate solution was added and the mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration, evaporation of the solvent, and chromatography on silica gel (ethyl acetate/hexane, 1:1, as eluent) afforded 2.2 g (60%) of hydroxycarbonate **11**: $[\alpha]^{20}_D$ −15° (*c* 0.5, $CHCl_3$); IR (film) 3500, 3000, 1800, 1460, 1400, 1260, 1090 cm^{-1}; NMR ($CDCl_3$) δ 5.3 (q, J = 9.6 Hz, 1 H), 4.55 (d, J = 8 Hz, 1 H), 4.05 (d, J = 8 Hz, 1 H), 3.7 (d, J = 10 Hz, 1 H), 2.1–2.3 (m, 2 H), 1.65 (s, 3 H), 1.6 (d, J = 5 Hz, 3 H), 1.5 (s, 3 H), 1.4 (m, 2 H). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.73; H, 8.39.

Tetrahydrofuran 12. To a magnetically stirred solution of hydroxy carbonate **11** (0.6 g, 0.0028 mol) in 10 mL of dry benzene containing 20 mg of vanadium acetylacetonate was added 0.5 g (0.0056 mol) of *tert*-butyl hydroperoxide. After 6 h, a few drops of glacial acetic acid were added and stirring was continued for 2 h. Evaporation of the solvent and chromatography on silica gel (ethyl acetate as eluent) afforded 0.42 g (65%) of pure tet-

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rahydrofuran derivative **13** along with a small amount of isomer **12**: $[\alpha]^{20}_D$ −7.8° (*c* 0.6, $CHCl_3$); IR (film) 3500, 3000, 1800, 1460, 1400, 1310, 1270, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.45 (d, *J* = 8 Hz, 1 H), 4.1 (m, 1 H), 4.05 (d, *J* = 8 Hz, 1 H), 3.8 (q, *J* = 9.6 Hz, 1 H), 2.25 (m, 1 H), 2.0 (m, 1 H), 1.65 (m, 2 H), 1.4 (s, 3 H), 1.1 (s, 3 H), 1.05 (d, *J* = 6 Hz, 3 H). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.82. Found: C, 57.31; H, 7.99.

Preparation of Tetrahydrofurans 12 and 13 by MCPBA Oxidation. A solution of *m*-chloroperoxybenzoic acid (0.258 g, 0.0015 mol) in dichloromethane was added dropwise to a magnetically stirred solution of hydroxy carbonate **11** (0.26 g, 0.0012 mol) in 10 mL of dichloromethane at room temperature. After 3 h (TLC on silica indicated the disappearance of starting material), a few drops of glacial acetic acid were added and stirring was continued for 2 h more. Evaporation of the solvent and chromatography on silica gel furnished (250 mg, 91% yield) a mixture of isomers **12** and **13** in a 1:1 ratio as determined by NMR. HPLC separation indicated that the more polar isomers (*t* = 7.4 min, μ-Porosil, 34% EtOAc/Hex, 3.0 mL/min) was the undesired isomer **13** and the less polar material (*t* = 6.8 min) was the desired isomer **12**. This was established by coinjection with material derived from the $VO(acac)_2$-catalyzed epoxidation.

Asymmetric Epoxidation of (*E*,*E*)-Hydroxygeranyl Acetate (18). Into a three-necked flask (500 mL), fitted with a septum and an argon inlet, is introduced 100 mL of dichloromethane. The flask was cooled to −23 °C (dry ice/CCl_4) and 25 g (0.092 mol) of titanium isopropoxide was introduced via a syringe. To the magnetically stirred solution was added 16.75 g (0.092 mol) of unnatural (−)-diethyl tartarate in 30 mL of dichloromethane. After 5 min, 20.0 g (0.092 mol) of hydroxy acetate **3** in 50 mL of dichloromethane was added followed by 41 mL of 4.5 M anhydrous *tert*-butyl hydroperoxide.[21] The homogeneous mixture was stored overnight in the freezer (−15 °C). The flask was cooled to −23 °C (dry ice/CCl_4) and 100 mL of 10% tartaric acid was added. After 30 min, the cooling bath was removed and stirring was continued until the solution became clear. The organic layer was separated, washed with brine, and dried over anhydrous sodium sulfate. Filtration, evaporation of the solvent, and chromatography on silica gel (50% ethyl acetate/hexane as eluent) furnished 12.5 g (50%) of the pure epoxy alcohol **18**: $[\alpha]^{25}_D$ +5.86° (*c* 0.6, $CHCl_3$); IR (film) 3450, 2950, 1740, 1370, 1240, 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.7 (m, 2 H), 1.73 (s, 3 H), 2.05 (s, 3 H), 2.2 (m, 2 H), 3.02 (t, *J* = 6.5 Hz, 1 H), 3.6 (dd, *J* = 10 Hz, 1 H), 3.68 (dd, *J* = 9.6 Hz, 1 H), 4.6 (d, *J* = 7 Hz, 2 H), 5.4 (t, *J* = 7.75 Hz, 1 H). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.15; H, 8.77. Found: C, 62.97; H, 8.84.

Formation of Urethane 19. To a magnetically stirred solution of 12.5 g (0.054 mol) epoxy alcohol **18** in 75 mL of dichloromethane containing 2% triethylamine at 10 °C was added slowly 7.14 g (0.06 mol) of phenyl isocyanate. Stirring was continued at room temperature for 24 h. The dark brown solution was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and filtration on a short pad of silica gel afforded urethane derivative **19**: yield 17.9 g (94.7%); $[\alpha]^{25}_D$ +7.0° (*c* 0.5, $CHCl_3$); IR (film) 3310, 2940, 1730, 1710, 1600, 1530, 1440, 1220, 1060, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.7 (m, 2 H), 1.73 (s, 3 H), 2.05 (s, 3 H), 2.2 (m, 2 H), 2.9 (t, *J* = 6.2 Hz, 1 H), 4.07 (d, *J* = 11.7 Hz, 1 H), 4.2 (d, *J* = 11.8 Hz), 4.6 (d, *J* = 6.9 Hz, 2 H), 5.36 (t, *J* = 7 Hz, 1 H), 6.95 (br s, NH), 7.1–7.5 (Ar, 5 H). Anal. Calcd for $C_{19}H_{25}O_5N$: C, 65.7; H, 7.2; N, 4.03. Found: C, 65.55; H, 7.16; N, 4.04.

Rearrangement of Urethane 19 to Hydroxy Carbonate 20. The urethane derivative **19** (15.0 g, 0.043 mol) was dissolved in 100 mL of acetonitrile and 35 mL of 5% perchloric acid was added slowly at room temperature. After 4 h, water (150 mL) was added and the reaction mixture extracted with dichloromethane (3 × 50 mL). The organic layer was then washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and chromatography on silica gel (50% ethyl acetate/hexane as eluent) afforded 11.0 g (94%) of hydroxy carbonate **20**. Note that the carbonate cannot be distilled or treated with base, since this results in isomerization of the carbonate to the isomeric carbonate **24**: $[\alpha]^{25}_D$ +7.3° (*c* 0.4, $CHCl_3$); IR (film) 3460, 2940, 1800, 1730, 1390, 1240, 1070, 770, cm^{-1}; NMR ($CDCl_3$) δ 1.45 (m, 1 H), 1.5 (s, 3 H), 1.65 (m, 1 H), 1.8 (s, 3 H), 2.1 (s, 3 H), 2.2–2.4 (m, 2 H), 3.75 (m, 1 H), 4.1 (d, *J* = 8.3 Hz, 1 H), 4.55 (d, *J* = 8.3 Hz, 1 H), 4.65 (d, *J* = 8 Hz, 2 H), 5.45 (t, *J* = 7 Hz, 1 H). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.35; H, 7.35. Found: C, 57.43; H, 7.43.

Formation of the Tetrahydropyranyl Derivative 25. To the magnetically stirred solution of 10.0 g (0.036 mol) of hydroxy carbonate **20** in 50 mL of dichloromethane containing 0.1 g of phosphorus oxychloride was added 3 equiv of dihydropyran. Stirring was continued at room temperature for 24 h and 100 mL of water was added. The reaction mixture was neutralized with sodium bicarbonate solution and the aqueous layer extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and chromatography on silica gel (25% ethyl acetate in hexane as eluent) furnished 11.8 g (90%) of **25** as a mixture of diastereoisomers: IR (film) 2940, 1800, 1730, 1530, 1450, 1380, 1230, 1070, 900 cm^{-1}; NMR ($CDCl_3$) 1.45 (d, *J* = 2.4 Hz, 3 H), 1.5 (m, 6 H), 1.7 (s, 3 H), 1.75 (m, 2 H), 2.05 (d, *J* = 2.4 Hz, 3 H), 2.15 (m, 2 H), 3.45 (m, 1 H), 3.73 (dd, *J* = 7.2 Hz, 1 H), 3.8 (m, 1 H), 4.0 (dd, *J* = 12 Hz, 1 H), 4.5 (d, *J* = 9 Hz, 1 H), 4.6 (d, *J* = 9.6 Hz, 2 H), 4.75 (d, *J* = 9 Hz, 1 H), 5.35 (m, 1 H). Anal. Calcd for $C_{18}H_{28}O_7$b C, 60.67; H, 7.86. Found: C, 59.35; H, 7.97.

Hydrolysis of the Acetate 25. To a solution of 12.0 g (0.034 mol) of acetate **25** in 75 mL of methanol, cooled to 0 °C with an ice salt bath, was added 4.6 g (0.034 mol) of anhydrous potassium carbonate and the reaction mixture was vigorously stirred for 1 h. Water (150 mL) was added and the whole extracted with dichloromethane (3 × 50 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration, evaporation of the solvent, and chromatography on a pad of silica (25% EtOAc/hexane) afforded 9.5 g (90%) of allyl alcohol as a mixture of diastereoisomers: IR (film) 3420, 2930, 1800, 1450, 1390, 1190, 1120, 1070, 1030, 900, 770, 730 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (s, 3 H), 1.5 (m, 6 H), 1.65 (s, 3 H), 1.7 (m, 2 H), 2.05 (m, 2 H), 3.4 (m, 1 H), 3.7 (dd, *J* = 6.0 Hz, 1 H), 3.8 (m, 1 H), 3.98 (d, *J* = 8.6 Hz, 1 H), 4.1 (d, *J* = 7.0 Hz, 2 H), 4.5 (m, 1 H), 4.75 (d, *J* = 8.5 Hz, 1 H), 5.35 (t, *J* = 7.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.14; H, 8.28. Found: C, 60.85; H, 8.06.

Preparation of Diol 26. The tetrahydropyran derivative 10.0 g (0.031 mol) was dissolved in 50 mL of methanol, and the solution was stirred with 3 g of Dowex H^+ resin at room temperature. The solution was stirred for 24 h. Filtration and evaporation of solvent yielded 6.25 g (83%) of dihydroxy carbonate **26**: $[\alpha]^{25}_D$ +5.7° (*c* 0.6, $CHCl_3$); NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.6 (m, 2 H), 1.7 (s, 3 H), 2.1–2.3 (m, 2 H), 2.55 (br s, OH), 3.7 (d, *J* = 9.6 Hz, 1 H), 4.0 (*J* = 9.6 Hz, 1 H), 4.15 (d, *J* = 7.2 Hz, 2 H), 4.55 (d, *J* = 9.6 Hz, 1 H), 5.45 (t, *J* = 9.6 Hz, 1 H). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.82. Found: C, 56.07; H, 8.1.

Preparation of Furan (27). The procedure used for the preparation of epoxide **18** was used with the following amounts: 3.5 g (0.015 mol) of diol **26**, 4.0 g (0.015 mol) of titanium isoporpoxide, 3.09 g (0.015 mol) of (−)-diethyl tartarate, and 10 mL of 4.4 M *tert*-butyl hydroperoxide.[21] The tetrahydrofuran derivative **27** is obtained as a colorless solid, crystallized from ethyl acetate/hexane, mp 137–138 °C; yield 2.2 g (60%). Note that the product is quite soluble in water: $[\alpha]^{25}_D$ +9.4° (*c* 0.8, $CHCl_3$); IR (film) 3320, 3000, 1790, 1100, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (s, 3 H), 1.5 (s, 3 H), 1.7 (m, 2 H), 2.1 (m, 2 H), 2.6 (br s, OH), 3.55 (m, 1 H), 3.75 (m, 2 H), 4.06 (d, *J* = 8.5 Hz, 11 H), 4.1 (t, *J* = 7.2 Hz, 1 H), 4.45 (d, *J* = 8.5 Hz, 1 H). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.31. Found: C, 53.74; H, 7.29.

Preparation of Tosylate 28. A solution of 2.67 g (19.8 mmol) of the diol **27** in 11.0 mL of anhydrous pyridine at 0 °C was treated with 2.28 g (12.0 mmol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 0 °C overnight, poured into saturated $CuSO_4$ solution, and isolated with ether to give 3.66 g (82.5%) of tosylate **28** after crystallization: $[\alpha]^{25}_D$ 16.09° (*c* 21.0 $CHCl_3$); IR (film) 3530, 3030, 2980, 1805, 1610, 1370, 1190, 1180, 980, 730, 670 cm^{-1}; NMR ($CDCl_3$) δ 7.59 (AB_q $\Delta\nu$ = 138.7 Hz, J_{AB} = 8.5 Hz), 4.10 (AB_q split into doublets, J_{AB} = 9.71 Hz, *J* = 2.46, *J* = 5.9 Hz, 4 H), 4.08 (d of d, *J* = 6.7 Hz, *J* = 8.20 Hz, 1 H), 3.78 (m, 1 H), 2.46 (s, 3 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 11.58 (s, 3 H), 1.43 (s, 3 H), 1.15 (s, 3 H). Anal. Calcd for $C_{18}H_{24}O_8S$: C, 53.49; H, 6.04. Found: C, 53.75; H, 6.07.

Preparation of Iodide 29. A solution of 3.66 g (8.95 mmol) of tosylate **28** and 2.68 g (17.9 mmol) of NaI in 100 mL of 2-butanone was heated to reflux for 3 h. The mixture was cooled,

poured into saturated NaCl solution, and isolated with ether. Crystallization from ether gave 2.41 g (79.5%) as a first crop and 470 mg (14.7%) as a second crop: mp 109–110 °C; $[\alpha]^{25}_D$ +3.80° (c 1.06, $CHCl_3$); IR (film) 3500, 2990, 1805, 1250, 1190, 1080, 980, 780 cm^{-1}; NMR ($CDCl_3$) δ 4.24 (AB_q, $\Delta\nu$ = 140.0 Hz, J_{AB} = 8.47, 2 H), 4.12 (d of d, J = 6.81 Hz, J = 8.20 Hz, 1 H), 3.73 (m, 1 H), 3.50 (AB_q split into doublet, $\Delta\nu$ 129.35 Hz, J_{AB} = 10.38, J = 2.00 Hz, 2 H), 2.19 (m, 1 H), 2.07 (m, 1 H), 1.72 (m, 2 H), 1.47 (s, 3 H), 1.21 (s, 3 H). Anal. Calcd for $C_{11}H_{17}O_4I$: C, 37.10; H, 4.81; I, 35.63. Found: C, 37.16; H, 4.87; I, 35.57.

Preparation of Alcohol 30. A solution of 2.41 g (7.07 mmol) of iodide **29** in 20.0 mL of 95% EtOH at room temperature was treated with 1.87 mL (7.09 mmol) of tri-*n*-butyltin hydride. The mixture was stirred at room temperature for 2 h, and the EtOH was removed under reduced pressure and purified by flash chromatography with 50% EtOAc/hexane to afford 1.60 g (98.4%) of the alcohol **30** after Kugelrohr distillation (130 °C (0.1 torr)): IR (film) 3350, 2990, 1800, 1305, 1300, 1115, 1100, 1075, 980, 880 cm^{-1}; NMR ($CDCl_3$) δ 4.25 (AB_q, $\Delta\nu$ = 133.8 Hz, J_{AB} = 8.45 Hz, 2 H), 4.13 (t, 7.08 Hz, 1 H), 3.78 (q, J = 6.59 Hz, 1 H), 1.48 (s, 3 H), 1.15 (s, 3 H), 1.14 (d, J = 6.59 Hz, 3 H). anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.46; H, 7.70.

Preparation of Silyl Ether 31. A solution of 1.60 g (6.95 mmol) of alcohol **30**, 2.08 mL (8.00 mmol) of *tert*-butyldiphenylchlorosilane, 1.09 g (16.00 mmol) of imidazole, and 6.0 mL of DMF was heated to 60 °C for 3 h. The mixture was poured into saturated NaCl and extracted with ether (3 times). The combined ether layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography with 25% EtOAc/hexane gave the product silyl ether **31** which was crystallized from EtOAc/hexane to give 1.97 g (60.6%) as a first crop and 880 mg (27.1%) as a second crop: mp 154–155 °C; $[\alpha]^{25}_D$ +5.2° (c 2.8, $CHCl_3$); IR (film) 3007, 1810, 1120, 1100, 1075, 710 cm^{-1}; NMR ($CDCl_3$) δ 7.63 (m, 4 H), 7.42 (m, 6 H), 4.00 (AB_q, $\Delta\nu$ = 94.90, J_{AB} =v 8.33 Hz, 2 H), 4.03 (d of d, J = 6.70 Hz, J = 8.20 Hz, 1 H), 3.55 (q, J = 6.20 Hz, 1 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 1.05 (s, 9 H), 1.04 (d, J = 6.20 Hz).

Preparation of Epoxide 34. A solution of 1.80 g (3.84 mmol) of carbonate **31** in 50 mL of ether at 0 °C was treated with 146 mg (3.84 mmol) of $LiAlH_4$. The mixture was stirred at 0 °C for 3 h and then treated successively with 0.19 mL of H_2O, 0.38 mL of 10% NaOH, and 0.38 mL of H_2O. The resulting white suspension was filtered and concentrated to afford 1.79 g of crude diol which was flash chromatographed with 100% EtOAc to give 1.61 g (95.3%) of pure diol. An analytical sample was secured by Kugelrohr distillation (150 °C (0.1 torr): IR (film) 3400, 3008, 2990, 2930, 1595, 1435, 1380, 1100, 1050, 1025, 830, 785, 745, 710 cm^{-1}; NMR ($CDCl_3$) δ 7.70 (m, Ar), 7.40 (m, Ar), 3.76 (d of d, J = 6.48 Hz, J = 8.35 Hz, 1 H), 3.60 (q, J = 6.2 Hz, 1 H), 2.54 (AB_q, $\Delta\nu$ = 37.5 Hz, J_{AB} = 4.90 Hz, 2 H), 2.00 (m, 1 H), 1.79 1.25 (s, 3 H), 1.12 (s, 3 H), 1.06 (d, J = 6.28 Hz, 3 H), 1.01 (s, 9 H). Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 70.55; H, 8.65. Found: C, 70.50; H, 8.65.

A solution of 1.59 g (3.61 mmol) of the above diol in 5.0 mL of anhydrous pyridine at 0 °C was treated with 705 mg (3.70 mmol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 0 °C overnight, poured into saturated $CuSO_4$ solution, extracted with ether, and concentrated under reduced pressure to afford the crude tosylate **33** which was dissolved in 100 mL of anhydrous MeOH and treated with 600 mg (4.35 mmol) of K_2CO_3. After the mixture was stirred for 1 h at room temperature, the solution was poured into saturated NaCl solution, and extracted with ether (3 times). The combined ether layers were concentrated under reduced pressure and purified by flash chromatography with 25% EtOAc/hexane to afford 1.51 g (99%) of pure epoxide **34**: IR (film) 3045, 2990, 1585, 1435, 1380, 1120, 830, 790, 745, 710 cm^{-1}; NMR ($CHCl_3$) δ 7.69 (m, 4 H), 7.38 (m, 6 H), 3.76 (d of d, J 6.48 Hz, J = 8.35 Hz, 1 H), 3.62 (q, J = 6.27 Hz, 1 H), 2.532 (AB_q, $\Delta\nu$ = 37.47 Hz, J = 4.9 Hz, 2 H), 1.25 (s, 3 H), 1.12 (s, 3 H), 1.05 (d, J = 6.27, 3 H), 1.05 (s, 9 H). Anal. Calcd for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54. Found: C, 73.62; H, 8.52.

Preparation of Alkene 35. A solution of 1.50 g (3.58 mmol) of epoxide **34**, 15.0 mL of THF, and 3.0 mL of a 2.0 M solution of allylmagnesium chloride was stirred at room temperature of 36 h. The mixture was poured into saturated NH_4Cl solution and extracted with ether (3 times). The combined ether layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to afford the crude alkene. Chromatography on silica gel with 15% EtOAc/hexane gave 1.49 g (91%) of the pure alkene **35** as a viscous oil, after Kugelrohr distillation (bp 150 °C (0.1 torr)): IR (film) 3045, 3008, 2990, 1650, 1600, 1380, 1120, 940, 830, 750, 710 cm^{-1}; NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.40 (m, 6 H), 5.78 (m, 1 H), 4.94 (m, 2 H), 3.77 (t, J = 7.20 Hz, 1 H), 3.65 (q, J = 6.20 Hz, 1 H), 1.23 (s, 3 H), 1.10 (s, 3 H), 1.04 (s, 9 H), 1.00 (d, J = 6.20 Hz, 3 H). Anal. Calcd for $C_{29}H_{42}O_3Si$: C, 73.25; H, 9.56; Si, 6.34. Found: C, 73.89; H, 8.97; Si, 6.41.

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Supplementary Material Available: Tables of bond distances, bond angles, atomic coordinates, and thermal parameters, (4 pages). Ordering information is given on any current masthead page.

Biosynthesis of Antibiotics of the Virginiamycin Family. 4.[1] Biosynthesis of A2315A

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The biosynthesis of A2315A, **1**, has been studied by using stable isotope techniques. The basic skeleton of the antibiotic is constructed from seven acetate units together with the amino acids valine, glycine, alanine, and serine and a methyl group from methionine. The uncommon D-alanine unit is shown to arise from both D- and L-alanine with equal facility.

The antibiotic A2315A,[2] identical with madumycin II,[3] A15104V,[4] A17002F,[4] and CP-35,763,[5] is a complex macrocyclic compound isolated from *Actinomadura flava*[3] and various *Actinoplanes* species.[2,4-5] It is a member of the

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