NMR (300 MHz, $CDCl_3$) and TLC behavior in several solvent systems.[31]

Acknowledgment. We wish to thank the National Cancer Institute of the National Institutes of Health for a grant (CA-29108) in support of these studies. We also wish to thank Prof. Richard H. Schlessinger, Frederick E. Ziegler, and Philip DeShong for sharing their results with us prior to publication and the Upjohn Co. for providing authentic samples of tirandamycin A and streptolydigin.

Registry No. 1, 85880-71-3; **1**·Na, 97859-37-5; **3**, 103367-77-7; **3** (enol silyl derivative), 103367-78-8; **4**, 34958-43-5; **5**, 103367-73-3; **6**, 103367-74-4; **7**, 103383-24-0; **8**, 103367-75-5; **9**, 103421-92-7; **10**, 103367-76-6; **11**, 103367-82-4; **13**, 103421-25-6; **15**, 103367-83-5; **18**, 103367-84-6; **19**, 103367-85-7; **20** (isomer 1), 103367-86-8; **20** (isomer 2), 103421-26-7; **21**, 103383-25-1; **22**, 103367-79-9; **23**, 103367-88-0; **24**, 103367-87-9; **25**, 103367-89-1; **26**, 103383-26-2; **27**, 103367-90-4; **27** (allylic benzoate) (isomer 1), 103367-91-5; **27** (allylic benzoate) (isomer 2), 103421-27-8; **28**, 103367-92-6; **28** (alcohol), 103367-93-7; **29**, 103383-27-3; **29** (diol), 103367-94-8; **30**, 103367-95-9; **30** (epoxide), 103383-28-4; **30** (epoxide, alcohol), 103383-29-5; **32**, 97859-35-3; **33**, 103367-98-2; **34**, 95218-34-1; **35**, 81956-28-7; **36**, 103367-97-1; **37**, 97859-87-5; acetyl bromide, 506-96-7; 1,1-dibromopropene, 13195-80-7; 4,4,4-tribromo-3-methylbutan-2-one, 103367-80-2; 1,1-dibromo-2-methyl-1-buten-3-one, 103367-81-3; (*Z*)-2-bromo-1-ethoxy-1-propene, 34600-12-9; *p*-nitrobenzoyl chloride, 122-04-3; ethyl glycinate hydrochloride, 623-33-6; 2,4-dimethoxybenzaldehyde, 613-45-6; ethyl *N*-(2,4-dimethoxybenzoyl)glycinate, 103367-96-0.

Stereocontrolled Total Synthesis of (±)-Tirandamycin A

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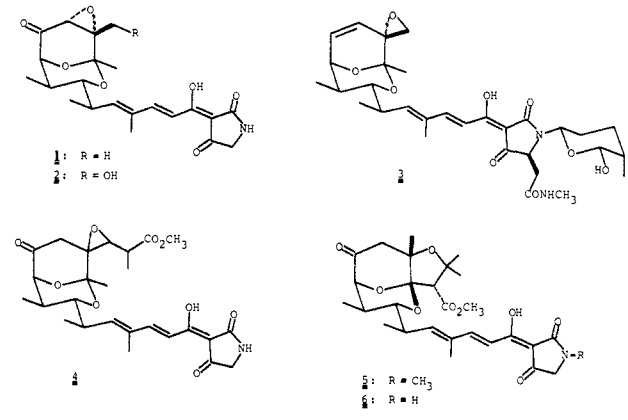
Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received November 18, 1985*

Abstract: A total synthesis of the title compound which is fundamentally different from previously reported routes or approaches is presented. The key stereochemical intermediate, acetylenic lactone **16**, is prepared in a sequence involving diethylpropynylalane-induced epoxide displacement and iodolactonization/epoxidation. An important step in this sequence is the protection of an α-hydroxy acid as its hexafluoroacetonide (**15**). Methodology for introduction of the dienoyl tetramic acid side chain was developed with the ketal acetonide **18** as a model substrate. The dienoic ester **22** was prepared via addition of vinyl cuprate **21** to methyl propiolate, and the tetramic acid unit was introduced via acylation of silyl malonamidate **25** followed by cyclization. Elaboration of the bicyclic ketal was accomplished via addition of lithio ketal **31** to lactone **32**. Direct cyclization of this material was not feasible, and a sequence involving stepwise ring closure was investigated. Intramolecular cycloaddition of an oxidopyrylium ylide (**41** → **43**) foiled one approach to generate enone ketal **9** after introduction of the double bond; the structure of the cycloadduct **43** was elucidated by crystallography. Enone **9** was eventually produced by cyclization of a reduced intermediate, via alcohol **45**, followed by oxidation and dehydrogenation of the alcohol, and the structure was verified by crystallography. From intermediate **45**, the methodology developed in the model systems was applied to the introduction of the dienoic ester side chain (→ **48**), the enone functionality (→ **49**), and the tetramic acid moiety (→ **53**). (±)-Tirandamycin A was produced from trifluoroacetic acid catalyzed cleavage of the *N*-(2,4-dimethoxybenzyl) group, as reported previously.

Tirandamycin A (**1**)[1] and its congeners **2**–**6**[2] comprise a class of RNA polymerase inhibitors which contain stereochemically intriguing bicyclic ketal units wedded to planar and highly enolic dienoyl tetramic acids (Chart I). Tirandamycin A itself has been the focus of a number of synthetic efforts in recent years,[6-15] culminating in total syntheses reported by Schlessinger,[16] DeShong,[17] Boeckman,[48] and their co-workers. Since the pioneering work of the Rinehart[6] and Ireland[8] groups, a number of common themes have appeared in the published work in this area, namely, use of the Kishi aldehyde[18] (or an equivalent) as the

Chart I



(1) (a) Isolation: Meyer, C. E. *J. Antibiot.* **1971**, *24*, 558. (b) Structure elucidation: MacKellar, F. A.; Grostic, M. P.; Olson, E. C.; Wnuk, R. J.; Branfman, A. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4943. Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077. Steyn, P. S.; Wessels, P. L. *S. Afr. J. Chem.* **1980**, *33*, 120–123. (c) Activity: Reusser, F. *Infec. Immunity* **1970**, *2*, 77–81.

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(11) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823.

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(17) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5219.

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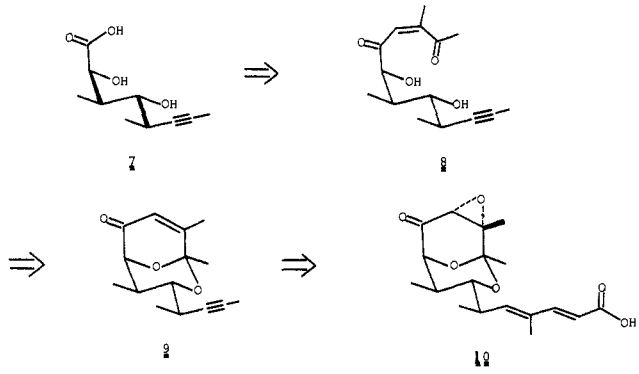
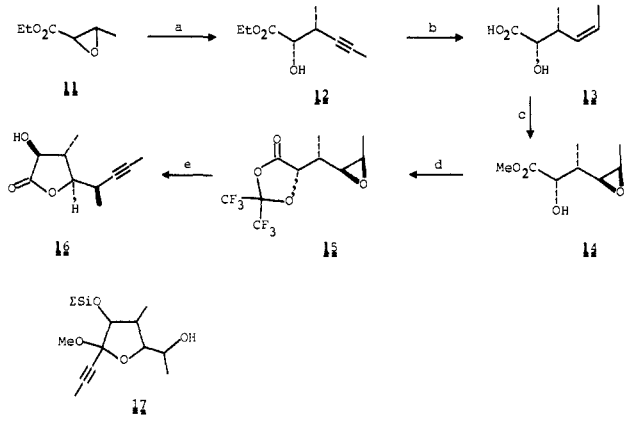
Scheme I



Scheme II[a]



[a] (a) $Et_2AlCCMe$, toluene, 0 °C, 11 h, 68%; (b) H_2/P-2 Ni, EtOH, room temperature, 99%; NaOH, EtOH, room temperature, 24 h, 89%; (c) I_2, $NaHCO_3$, MeCN, 0 °C, 3.5 h, 88%; Na_2CO_3, MeOH, room temperature, 3 days, 92%; (d) CF_3COCF_3, Na_2CO_3, CCl_4, room temperature, 2 days, 83%; (e) $Et_2AlCCMe$, toluene, 0 °C, 4 h, 78%.

stereochemical progenitor,[13,14,16] oxidation of a substituted furan for the generation of an enedione precursor to the ketal,[13-15] and introduction and control of the stereochemistry of the double bonds via Wittig reactions.[8,13,15,16] In both total syntheses, the acyl tetramic acid function was incorporated with a complex Horner–Wittig reagent.[11,12] We now describe a fundamentally different approach to the synthesis of tirandamycin A.

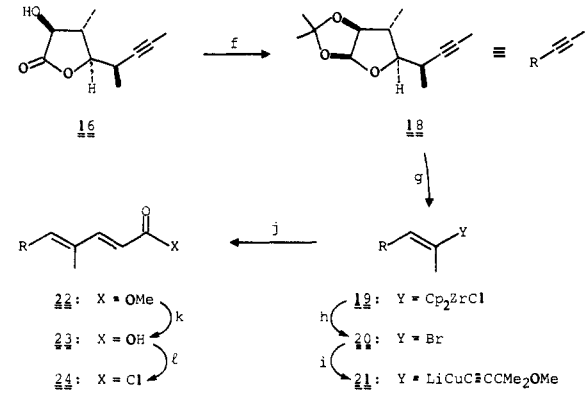
Synthetic Plan

Our synthetic plan as broadly outlined in Scheme I was influenced by two specific factors. First, we were attracted to an approach in which the tetramic acid moiety is incorporated at a late stage, starting with tirandamycic acid (**10**). This material is available from degradation of the natural product;[1b] hence such a strategy has potential utility for synthesis of the natural congeners or for structure–activity studies.[7] Second, we wanted to introduce the crucial stereocenters in a specific fashion early in the synthesis. Of the seven tetrahedral stereocenters in tirandamycin A, those due to the epoxide and the ketal carbon can be controlled straightforwardly.[8] The remaining four were to be assembled in acetylenic acid **7** (or its equivalent) by a sequence of epoxide formation and displacement reactions. The conversion of **7** to tirandamycic acid required operation at both ends of the molecule: elaboration of the carboxyl group to the enedione precursor to the bicyclic ketal and of the acetylene to the (*E*,*E*)-dienoic ester. The successful pursuit of the basic elements of this synthetic plan forms the topic of this report.

Incorporation of the Key Stereocenters

Lactone **16**, which is the form in which we generated and used the key intermediate **7**, was assembled essentially stereospecifically, as depicted in Scheme II. Reaction of ethyl α,β-epoxybutyrate (**11**) with diethylpropynylalane is selective for attack at the β-position, presumably as a result of the electrophilic character of

Scheme III[a]



[a] (f) *i*-Bu_2AlH, toluene, −78 °C, 1 h; $Me_2C(OMe)_2$, acetone, *p*-TsOH, room temperature, 24 h, 66%; (g,h) $HZrCp_2Cl$, benzene, room temperature, 4 h; NBS, room temperature, 1 h, 74%; (i,j) *sec*-BuLi, →[MeO(Me)$_2$CCCLi + CuBr(Me_2S)], ether/Me_2S, −78 °C, 1 h; ← $HCCCO_2Me$, −78 °C, 1 h, 52%; (k) aqueous NaOH, MeOH, room temperature, 24 h, 99%; (l) aqueous NaOH, *t*-BuOH, lyophilize; Cl-$(CO)_2Cl$, benzene, room temperature, 30 min.

the alane reagent. Reduction to the *cis*-alkene and hydrolysis of the ester afford hydroxy acid **13** in 65% overall yield. As we reported previously, this material can be epoxidized essentially stereospecifically by iodolactonization and methanolysis (70% yield for **13** → **14**, >20:1 ratio of isomers).[19]

The important stereocenters are already represented in epoxy ester **14**, to be revealed on a second propynyl displacement reaction. However, implementation of this strategy was complicated by interference from the other functional groups. For example, treatment of the *tert*-butyldimethylsilyl ether of **14** with diethylpropynylalane affords as the major product the propargylic ketal **17**, in which cyclization of the carboxyl group has interceded in the opening of the epoxide and the attack of the propynyl nucleophile. This problem can be neatly circumvented by a specific protection strategy. The hydroxy ester **14** affords ketal lactone **15** in the presence of hexafluoroacetone and K_2CO_3 (87% yield). In this compound, the carbonyl oxygen is constrained from attacking the epoxide for reasons both of geometry, because of restricted rotation within the lactone ring, and of electronics, because of the electron-withdrawing nature of the trifluoromethyl groups. Reaction of **15** with diethylpropynylalane thus proceeds without interference and at the less congested end of the epoxide as desired; in the ensuing workup, cyclization occurs with loss of the hexafluoroacetone moiety, giving the lactone **16** in 69% yield. This material is the cyclic form of acetylenic ester **7**, which we had envisaged as the key stereochemical intermediate in the synthesis.

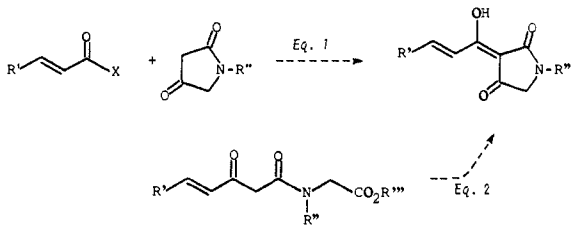
With the lactone **16** in hand, we explored methods for extension of the molecule in both directions: conversion of the acetylenic group into the dienoyl tetramic acid side chain and incorporation of the necessary functionality for convolution into the bicyclic ketal.

Methodology for Elaboration of the Dienoyl Tetramic Acid Moiety

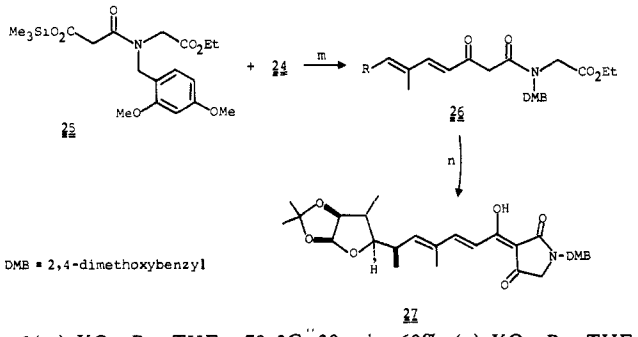
To provide a model system for the bicyclic ketal, we reduced lactone **16** to the lactol and protected the hydroxyl groups via acetonide **18** (Scheme III). As expected, hydrozirconation of the triple bond of **18** proceeds with high regio- and stereoselectivity,[20] as revealed on conversion to the vinyl bromide **20** with *N*-bromosuccinimide (75% yield). For direct formation of the dienoate ester, we investigated the zinc- and palladium-catalyzed coupling of vinyl zirconium intermediate **19** with methyl β-bromoacrylate. Although we confirmed Negishi's reported results

(19) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.
(20) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *27*, 373.

Chart II



Scheme IV[a]



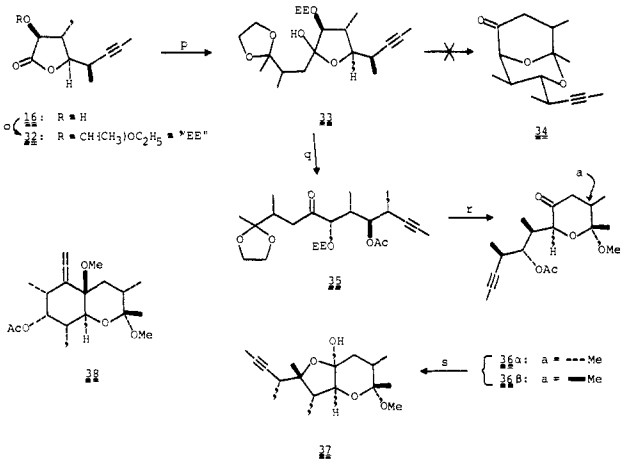
[a] (m) KO-*t*-Bu, THF, −78 °C, 30 min, 60%; (n) KO-*t*-Bu, THF, room temperature, 3 days, 94%.

with 3-hexyne as starting material,[21] we were unable to obtain the desired product from the more complex hydrozirconate **19**. On the other hand, lithiation of vinyl bromide **20**, conversion to the mixed cuprate **21**, and conjugate addition to methyl propiolate[23] provide the desired dienoate **22** in up to 80% yield. As discussed in more detail below, the selectivity for formation of the trans α,β double bond in this coupling process is variable, although ratios as high as 10:1 were observed on a small scale.

Direct coupling of the dienoyl moiety with a tetramic acid derivative would appear to be an expeditious way to incorporate that highly enolic functionality (eq 1 below, Chart II). Previous experience with this transformation has not been encouraging, however. For example, the Banyu group were able to reconstitute the closely related Bu-2313 congeners from the dienoic acid in only 11% yield,[7] and Rinehart et al. found with model substrates that O-acylation is the major course of reaction, even under conditions known to favor C-acylation of enolates.[6,24] We chose, therefore, to generate the acyl tetramic acid by cyclization of an *N*-(carboxyalkyl)-β-ketoamide (eq 2 below), as initially reported by Lacey[25] and later explored by Rinehart for the same purpose.[6]

The requisite cyclization substrate, β-ketoamide **26**, was synthesized from acid chloride **24** and silyl malonamidate **25** (Scheme IV). The coupling of malonic acid with ethyl *N*-(2,4-dimethoxybenzyl)glycinate[26] followed by silylation with bis(trimethylsilyl)acetamide provides silyl ester **25** in 95% overall yield. Alkaline hydrolysis of dienoate ester **22** and treatment of the sodium salt with oxalyl chloride in benzene afford the acid chloride **24**, also in 95% yield.[6] Both the acylation reaction and the subsequent cyclization of the β-ketoamide are best accomplished with potassium *tert*-butoxide as base. Thus, generation of the potassium

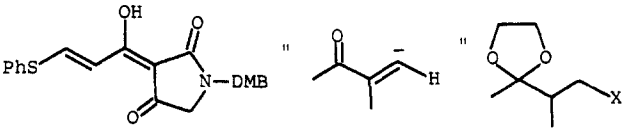
Scheme V[a]



[a] (o) $EtOCH{=}CH_2$, PPTS, CH_2Cl_2, 0 °C, 3 h, 99%; (p) **30** + *t*-BuLi, THF, −78 °C, 5 min, ←**32**, −78 °C, 45 min, 90%; (q) DMAP, Ac_2O, CH_2Cl_2, room temperature, 6 h, 82%; (r) PPTS, MeOH, reflux, 9 h, 82%; (s) K_2CO_3, MeOH, reflux.

enolate of **25** in THF (3 equiv) and addition of acid chloride **24** (−78 °C → room temperature), with hydrolysis and decarboxylation on workup, afford the desired β-ketoamide **26** in 60% yield. Treatment of this material with a slight excess of potassium *tert*-butoxide, also in THF, leads to N-protected tetramic acid **27** in 94% yield after 3 days at room temperature. By incorporating the glycinate moiety in the malonate reagent **25**, we were able to overcome the difficulty that confronted Rinehart et al. in their previous approach to this problem.[6]

By the same sequence, (*E*)-β-(phenylthio)acrylic acid was converted to the acyl tetramic acid **28**. Our intention was to protect this material and explore its reaction with cuprate **21** as



28 **29** **30**: X = Br; **31**: X = Li

a potentially more direct conversion of acetylene **18** to the acyl tetramic acid **27**. However, no effective method for protection of **28** was found[27] nor did the anion itself react with an excess of a model vinyl cuprate reagent.

Although the bis ketal moiety served as an effective model for the chemistry of Schemes III and IV, it proved to be too sensitive to acid to allow us to effect the trifluoroacetic acid catalyzed N-deprotection of the acyl tetramic acid **27**. However, as Rinehart's initial studies suggested[6] and as was later born out by the reported syntheses,[16,17] the bicyclic ketal moiety of tirandamycic acid itself is more robust and is able to survive the deprotection conditions.

Construction of the Bicyclic Ketal Unit

A number of synthetic equivalents of the enone anion **29** were explored for direct conversion of lactone **16** to dienone **8** or its equivalent. We encountered problems in their formation,[28] their

i (R = Me or SiΣ) *ii* *iii*

(21) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, 1027.

(22) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(23) Naf, F.; Degen, P. *Helv. Chim. Acta* **1971**, *54*, 1939. Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4395.

(24) Nor do other, more recent, approaches provide encouragement for the acylation of dienoic acids with unsubstituted tetramic acids; see: van der Baan, J. L.; Barnick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223. Jones, R. C. F.; Sumaria, S. *Tetrahedron Lett.* **1978**, 3173. Jones, R. C. F.; Peterson, G. E. *Tetrahedron Lett.* **1983**, *24*, 4751.

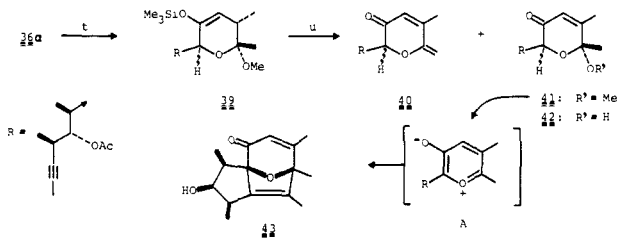
(25) Lacey, R. N. *J. Chem. Soc.* **1954**, 850.

(26) Weygand, F.; Steglich, W.; Bjarnason, J.; Akhtar, R.; Khan, N. M. *Tetrahedron Lett.* **1966**, 3483. Weygand, F.; Steglich, W.; Bjarnason, J.; Akhtar, R.; Chytil, N. *Chem. Ber.* **1968**, 3623.

(27) Reagents explored: silylation (BTMSA or trimethylsilyl triflate), alkylation (MeOH/H^+, ethyl vinyl ether/H^+, Me_2SO_4/KO-*t*-Bu, or CH_2N2), acylation (Ac_2O/pyridine), or BF_3 complexation.

(28) Attempts to generate vinylic anions from i–iii were unsuccessful or led to rearrangements.

Scheme VI[a]



[a] (t) Me_3SiCl, DBU, CH_2Cl_2, reflux, 4 h, 75%; (u) DDQ, HMDS, MeCN, room temperature, 3 h; (v) K_2CO_3, MeOH, reflux, 6.5 h, 36%.

reactivity toward the lactone carbonyl,[29] or their subsequent manipulation to provide the desired functionality.[30] Eventually we found that transmetalation of the ketal bromide **30** proceeds readily, to give lithio ketal **31** as a saturated equivalent of **29**, and that this reagent adds to the protected lactone **32** to provide the diketal diastereomers **33** in 90% yield. Conversion of this material to the bicyclo[3.3.1] ketal proved to be significantly more challenging than anticipated, however.

Formation of the tirandamycin ketal–enone subunit has been a thermodynamically and kinetically favorable process in most reported synthetic approaches[8-10,13,15] (but see ref 14). However, such does not appear to be the case for formation of the ketal **34**, in which the endocyclic double bond is absent. While treatment of **33** with mild acid catalysis (for example, pyridinium *p*-toluenesulfonate (PPTS) in acetone at 21 °C) results in loss of the ethoxyethyl and ketal protecting groups, a plethora of products is formed, none of which is the desired ketal **34** (Scheme V). On the assumption that release of the terminal hydroxyl from the hemiketal **33** is slow, i.e., that the difficulty is a kinetic one, this material was converted to the acyclic ketone **35** by acetylation (98% yield). In this way, we hoped to stage the ring closure by sequential release of the functional groups.

Indeed, treatment of ketone **35** with PPTS in methanol accomplishes the first step in this process, affording the tetrahydropyranones **36α** and **36β** in 58% and 24% yields, respectively. The relative configuration of these isomers was assigned by ^1H NMR spectroscopy: a 12.8-Hz coupling constant can be discerned for the methyne proton β to the ketone in isomer **36α**, indicative of its axial position. The methoxyl groups were assumed to have adopted the favored axial configuration in each compound. That these stereoisomers are not formed in equal amounts indicates that equilibration, perhaps via the enol ether, occurs under the reaction conditions. The use of more strongly acidic conditions for cyclization of **35** (*p*-toluenesulfonic acid) leads to the bicyclic allene **38**.[33]

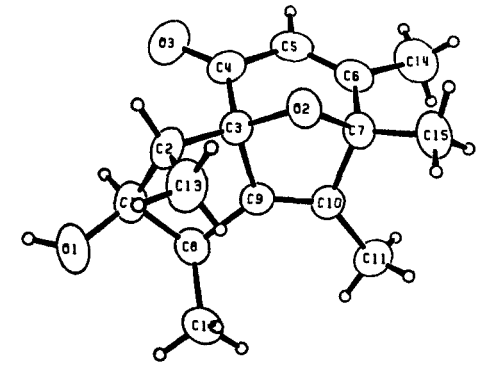


Figure 1. ORTEP structure of cycloadduct **43**.

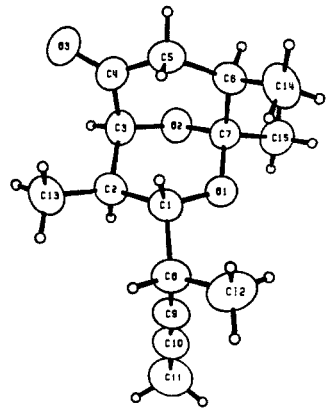
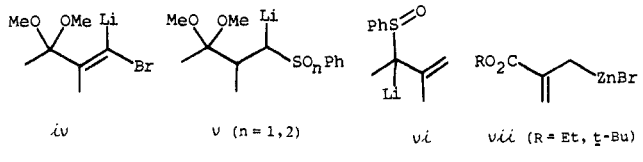


Figure 2. ORTEP structure of bicyclic ketone **34β**.

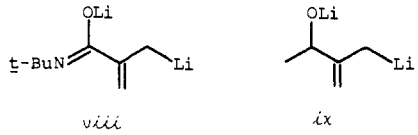
With the tetrahydropyran ring in place, the acetate ester was removed with KCN in 95% ethanol[34] to give the bicyclic hemiketals **37** (94% yield). Interference from the five-membered hemiketal proved to be a stumbling block in this approach as well, since **37** could not be closed to the [3.3.1] ring system either. Convinced at this point of the value of the enone double bond as a component of the cyclization substrate, we investigated methods for its introduction into the pyranone skeleton. After formation of the enol silane **39** with DBU and chlorotrimethylsilane (97% yield),[35] DDQ oxidation[36] was employed for generation of the enone (Scheme VI). A mixture of products ensues from this reaction (**40–42**); however, on treatment with PPTS in refluxing methanol they can be converted to the desired product **41** in 50% overall yield. Optimization of this transformation was not pursued, however, in light of the behavior of **41** under the alkaline conditions

(29) The following anions did not react with lactone **32** or the corresponding lactol:



iv v (n = 1,2) *vi* *vii* (R = Et, t-Bu)

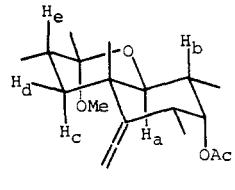
(30) The adducts between **32** and viii[31] and ix[32] could be formed; however, we were unable to elaborate the amide or carbinol moieties, respectively, to the methyl ketone. The adduct with ix led inexorably to a spirocyclic ketal.



viii *ix*

(31) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1980**, *45*, 4257.
(32) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680.

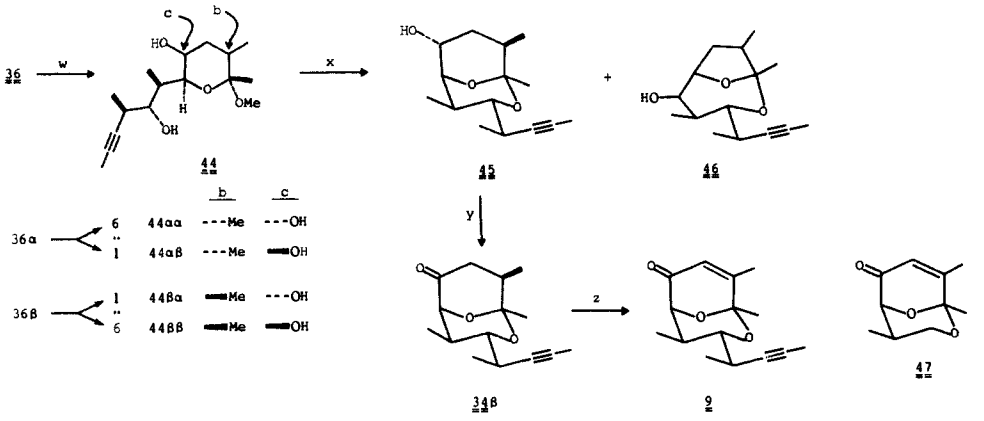
(33) Of the various stereoisomers which could arise from acid-catalyzed formation of **38**, the structure shown was deduced from the coupling constants depicted below and by the observation of a nuclear Overhauser enhancement of the signal for H_a on irradiation of that for H_c.



J_{ab} = 11.4 Hz
J_{cd} = 14.3 Hz
J_{ce} = 12.9 Hz
J_{de} = 3.5 Hz

(34) Mori, K.; Tominaga, M.; Tahigawa, T.; Matsui, M. *Synthesis* **1973**, 790.
(35) Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Nippon Kagaku Kaishi* **1981**, *54*, 3229.
(36) Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, 3455–3458.

Scheme VII[a]



[a] (w) *i*-Bu_2AlH, ether/hexane, 0 °C, 2 h, 85%; (x) PPTS, $CHCl_3$, reflux, 4 h, 86%; (y) PCC, CH_2Cl_2, room temperature, 24 h, 86%; (z) Me_3SiCl, DBU, CH_2Cl_2, reflux, 2 h, 99%; DDQ, HMDS, MeCN, room temperature, 10 h, 82%.

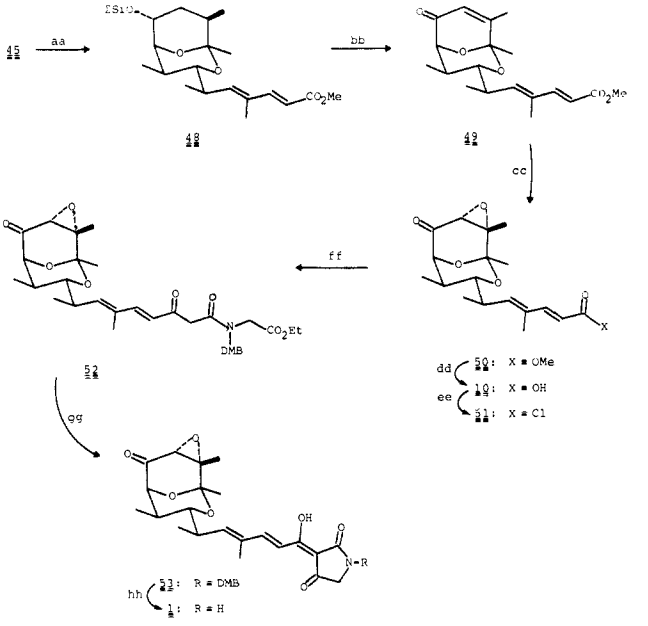
required for cleavage of the hindered acetate ester (Na_2CO_3 in refluxing methanol, 3 h): the tricyclic ether **43** is formed in 36% yield. This material, whose structure was determined by X-ray crystallography (Figure 1), arises from intramolecular cycloaddition of the acetylene to oxidopyrylium ylide A, in turn generated on enolization of **41** and loss of methoxide.[37]

We elected at this point to "protect" the ketone function by reduction. This step would avoid many of the problems we were encountering at the ketalization stage as well as simplify the protection strategy during elaboration of the dienoic acid side chain. Reduction of the major tetrahydropyranone **36**α with diisobutylaluminum hydride at −78 °C leads to a 6:1 mixture of diols **44**$\alpha\alpha$ and **44**$\alpha\beta$, respectively (Scheme VII). In the presence of a catalytic amount of PPTS in chloroform, this mixture undergoes cyclization to provide the bicyclic [3.3.1] ketal **45** in 76% overall yield, along with 11% of the [4.2.1] ketal **46** as a 1:1 mixture of stereoisomers. That the methyl adjacent to the ketal carbon had indeed been inverted during the conversion of **44**$\alpha\alpha$ to **45** was first suggested on the basis of NMR evidence and later confirmed by single-crystal X-ray analysis of the derived ketone **34**β (see below).

Reduction of the isomeric ketone **36**β likewise affords a 6:1 mixture of diols (**44**$\beta\beta$ and **44**$\beta\alpha$, respectively), and these diols lead to the same bicyclic ketals **45** and **46** described above, although in this case the [4.2.1] system is the predominant product (as the same 1:1 mixture of stereoisomers). It is clear that the configuration of the methyl group (b in structure **44**) is lost during the cyclization and that the hydroxyl stereochemistry (c in **44**) determines the mode of ring closure.

With the bicyclic ketal finally in hand, we explored methods for introduction of the enone functionality. Oxidation of the alcohol with pyridinium chlorochromate[38] proceeds uneventfully to give ketone **34**β, whose structure is depicted in Figure 2. Of a variety of methods explored for introduction of the conjugated double bond,[39] oxidation of the trimethylsilyl enol ether of **34**β with DDQ proved to be the most efficient, producing the enone **9** in 80% overall yield.[35,36] With the exception of resonances attributable to the side chains, the NMR spectral characteristics of **9** were similar to those reported for the bicyclic alcohol **47**.[9]

Scheme VIII[a]



[a] (aa) *t*-$BuMe_2SiCl$, DMAP, Et_3N, DMF, 90%; $HZrCp_2Cl$, benzene, room temperature, 9 h, and then NBS, room temperature, 1.5 h, 76%; *sec*-BuLi, THF, →$MeO(Me)_2CCCCu$, ←$HCCCO_2Me$, all at −78 °C, 76%; (bb) 48% HF, MeCN, 0 °C, 3 h, 100%; PCC, CH_2Cl_2, room temperature, 13 h, 97%; Me_3SiCl, DBU, CH_2Cl_2, reflux, 3 h, 98%; DDQ, HMDS, MeCN, room temperature, 6 h, 76%; (cc) DBU, *t*-BuOOH, THF, room temperature, 5 days, 64%; (dd) aqueous NaOH, *t*-BuOH, room temperature, 30 min; (ee) ClCOCOCl, benzene, room temperature, 30 min; (ff) **25** + KO-*t*-Bu, THF, −78 °C, 30 min, 73%; (gg) KO-*t*-Bu, THF, room temperature, 3 days, 95%; (hh) TFA, $CDCl_3$, room temperature, 11 h, 46%.

Although **9** was not a part of our eventual synthetic pathway,[42] the exploration of dehydrogenation methods at this stage facilitated

(37) Sammes and Street have recently explored a variety of applications of this reaction in natural-products synthesis: Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1983**, 666–668. Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1261–1265. Sammes, P. G.; Street, L. J. *J. Chem. Res.* **1984**, S196–197. See also: Feldman, K. S. *Tetrahedron Lett.* **1983**, *24*, 5585.

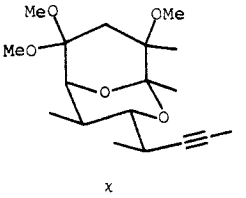
(38) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(39) (a) LiHMDS, PhSeBr, 58%; H_2O_2, 75% (ref 40). (b) $(PhSeO)_2O$, 55% (ref 41). (c) Me_3SiCl, DBU, NBS, 77%; DBU, Δ (low yield).

(40) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695.

(41) Barton, H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130.

(42) The enone **9** is resistant to ketalization or dithioketalization under normal conditions; however, it can be converted in 67% yield to the trimethoxy adduct x under high pressure (methanol, *p*-toluenesulfonic acid, 15 kbar, 40 °C, 48 h).



x

subsequent work when the more sensitive unsaturated side chain was in place.

(±)-Tirandamycic Acid Methyl Ester

After protection of the alcohol **45** as its *tert*-butyldimethylsilyl ether,[43] the dienoic ester side chain was introduced by using the sequence developed for the model substrate **18** (see Scheme III above). During our work in this system, we discovered that the *E*/*Z* stereoselectivity of the cuprate reaction (**21** → **22**) is critically dependent on solvent and reaction conditions. With THF as the solvent, the stereoselectivity is consistently higher than 14:1, whereas in ether, ratios as low as 2:1 were frequently obtained. The overall yield for conversion of **45** to the (*E*,*E*)-dienoate **48** is over 50% (Scheme VIII). Desilylation, oxidation to the ketone, and dehydrogenation of the silyl enol ether with DDQ also proceed efficiently, providing the enone **49** in 74% yield for the four-step process. As described by the Ireland group in their synthesis of tirandamycic acid,[8] epoxidation of the enone moiety is effected with *tert*-butyl hydroperoxide and Triton B catalysis. This reaction proceeds most cleanly if not carried to completion; otherwise, products of overoxidation become significant. In our hands, the methyl ester of (±)-tirandamycic acid, **50**, is produced in 64% yield based on 36% recovered starting material.

(±)-Tirandamycin A

The final stages in the synthesis were in turn an application of the method for introduction of the tetramic acid moiety which had been worked out using the model dienoate **22** (see Scheme IV above). Hydrolysis of the ester **50**, conversion to the acid chloride **51**,[6] and acylation of the malonamidate **25** afforded the β-ketoamide **52** (Scheme VIII, 53% yield (70% based on 75% conversion)). Potassium *tert*-butoxide catalyzed cyclization then provided *N*-(2,4-dimethoxybenzyl)tirandamycin A (**53**, 95% yield), the penultimate intermediate in the previously reported total syntheses as well.[16,17] Deprotection of **53** with trifluoroacetic acid and purification of (±)-tirandamycin A (**1**) by preparative TLC were carried out as previously described,[16,17] with the exception that a methylene chloride solution of the final product was washed with saturated aqueous Na-EDTA prior to final evaporation. This step removes the divalent metal ions that become chelated to tirandamycin during the chromatographic step and results in a dramatic improvement in the ^{1}H NMR spectrum of the product. We obtained racemic tirandamycin A in 46% purified yield; this material proved to be identical spectroscopically with an authentic sample of tirandamycin A.[44]

Experimental Section[45]

[1*R-[1β,2α,4α,6β,7α,8β(1*E*,2*E*,4*E*,6*R**)]]-3-[1-Hydroxy-4-methyl-6-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0^{2,4}]dec-8-yl)-2,4-heptadienylidene]-2,4-pyrrolidinedione (Tirandamycin A) (1).** A solution of **53** (see below; 7.8 mg, 14 μmol) in $CDCl_3$ (0.5 mL) was treated with trifluoroacetic acid (0.2 mL), and the resulting mixture was shaken for 11.5 h at which time NMR analysis indicated complete deprotection. The reaction mixture was poured on a stirred mixture of 5 g of ice and 10 mL of CH_2Cl_2. The aqueous phase was separated and extracted with four 10-mL portions of CH_2Cl_2. The CH_2Cl_2 solutions were washed with saturated aqueous $NaHCO_3$ and then worked up to afford 9.8 mg of a yellow residue which was applied to a 10- × 20-cm EM TLC plate (250 μm). The plate was developed with 9:1 CH_2Cl_2/MeOH under an atmosphere of argon. The band with an R_f of 0.3 was isolated with 4:1 EtOAc/MeOH, and after concentration the extract was dissolved in 10 mL of CH_2Cl_2 and washed with a concentrated aqueous solution of ethylenediaminetetraacetic acid (3 mL). Evaporation of the CH_2Cl_2 solution afforded a pale-yellow residue (2.6 mg, 46%) which was identical with natural tirandamycin (TLC, IR, MS, ^{1}H NMR): IR 1570, 1601, 1620, 1665, 1748, 3470 cm^{-1}; ^{1}H NMR δ 0.73 (d, 3, *J* = 7.1), 1.14 (d, 3, *J* = 6.9), 1.48 (s, 3), 1.58 (s, 3), 1.92 (d, 3, *J* = 1.0), 2.01 (m, 1), 2.87 (m, 1), 3.29 (s, 1), 3.58 (dd, 1, *J* = 2.0, 11.4), 3.83 (s, 2), 4.03 (d, 1, *J* = 6.1), 5.78 (s, 1), 6.22 (d, 1, *J* = 10.1), 7.16 (d, 1, *J* = 15.6), 7.58 (d, 1, *J* = 15.7); exact mass calcd for $C_{22}H_{27}NO_7$ 417.1778, found 417.1799.

[1*R-[1β,3β(1*S**),4α,5β]]-1,4,8-Trimethyl-3-(1-methyl-2-butynyl)-6-oxo-2,9-dioxabicyclo[3.3.1]non-7-ene (9). (A) [1*R**-[1β,3β-(1*S**),4α,5β,8α]]-1,4,8-Trimethyl-3-(1-methyl-2-butynyl)-6-((trimethylsilyl)oxy)-2,9-dioxabicyclo[3.3.1]non-6-ene.** A solution of ketone **34**β (62.5 mg, 0.25 mmol) in 5 mL of CH_2Cl_2 was treated with 1,8-diazabicyclo[5.4.1]undec-7-ene (DBU) (49 μL, 0.33 mmol) and chlorotrimethylsilane (40 μL, 0.31 mmol) and refluxed for 2 h. The reaction mixture was diluted with CH_2Cl_2, washed with cold 0.5 M HCl and saturated $NaHCO_3$ solution, and then worked up to afford 80.0 mg (99%) of the silyl enol ether as a white solid: mp 48–49 °C; IR 1051, 1122, 1243, 1676 cm^{-1}; ^{1}H NMR δ 0.21 (s, 9), 0.79 (d, 3, *J* = 7.1), 1.01 (d, 3, *J* = 7.3), 1.21 (d, 3, *J* = 7.1), 1.36 (s, 3), 1.80 (d, 3, *J* = 2.4), 2.28 (m, 1), 2.61 (m, 2), 3.67 (dd, 1, *J* = 3.4, 10.1), 3.99 (d, 1, *J* = 4.4), 4.80 (d, 1, *J* = 3.0). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.01; H, 9.38. Found: C, 67.09; H, 9.45.

(B) Compound 9. A solution of the above silyl enol ether (1.41 g, 43.8 mmol) in 60 mL of acetonitrile was treated with hexamethyldisilazane (0.37 mL, 17.5 mmol) followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.49 g, 65.7 mmol). The resulting mixture was stirred at room temperature for 10 h, and then the reaction mixture was concentrated. The residue was chromatographed with a 4:1 hexane/ether solvent system to afford **9** as a white solid: 895 mg, 82%; mp 93 °C; IR 1113, 1385, 1632, 1682 cm^{-1}; ^{1}H NMR δ 0.78 (d, 3, *J* = 7.1), 1.18 (d, 3, *J* = 7.1), 1.56 (s, 3), 1.83 (d, 3, *J* = 2.5), 1.92 (d, 3, *J* = 1.5), 2.49 (m, 1), 2.71 (m, 1), 3.28 (dd, 1, *J* = 2.6, 11.0), 4.10 (d, 1, *J* = 6.1), 6.11 (s, 1). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12. Found: C, 72.49; H, 7.99.

[1*R-[1β,2α,4α,6β,7α,8β(2*E*,4*E*,6*S**)]]-4-Methyl-6-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0^{2,4}]dec-8-yl)-2,4-heptadienoic Acid (Tirandamycic Acid) (10).** A slurry of **50** (274 mg, 783 μmol) in methanol (15 mL) was treated with 2 N KOH (1.96 mL, 3.91 mmol), and the resulting mixture was stirred at 60 °C for 1.5 h. The reaction mixture was concentrated, the residue was diluted with 10 mL of water, and the aqueous phase was washed with ether and then acidified to pH 1 with 2 M HCl. The precipitated oil was extracted with ethyl acetate and worked up to afford 306 mg of an oil which was chromatographed on silica gel. Elution with 1:1 hexane/EtOAc afforded tirandamycic acid (**10**) (238 mg, 90%) as a white solid: mp 179–180 °C; IR (film) 1621, 1688, 1729, 2400–3600 cm^{-1}; ^{1}H NMR δ 0.72 (d, 3, *J* = 7.1), 1.13 (d, 3, *J* = 6.9), 1.47 (s, 3), 1.57 (s, 3), 1.81 (d, 3, *J* = 1.0), 1.98 (m, 1), 2.81 (m, 1), 3.28 (s, 1), 3.56 (dd, 1, *J* = 2.0, 11.5), 4.03 (d, 1, *J* = 6.1), 5.83 (d, 1, *J* = 15.6), 6.11 (d, 1, *J* = 10.2), 7.45 (d, 1, *J* = 15.5). Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.24.

[2*R,3*S**]-Ethyl 2-Hydroxy-3-methyl-4-hexynoate (12).** A solution of *n*-butyllithium (41.8 mL, 96 mmol) in toluene (65 mL) was treated at 0 °C with excess propyne until the yellow solution turned into a white suspension. The mixture was stirred for 0.5 h and treated with a solution of diethylaluminum chloride in toluene (55.2 mL, 90 mmol). The mixture was stirred rapidly at 0 °C for 5.5 h and then treated with a solution of *trans*-ethyl 2,3-epoxybutyrate (5.85 g, 45 mmol) in toluene (20 mL). The resulting mixture was stirred at 0 °C for 11 h, and then $Na_2SO_4 \cdot 10H_2O$ (22 g) was added in portions. After the mixture stirred at room temperature for 2 h, 10 g of $MgSO_4$ was added, and stirring was continued for 0.5 h. The mixture was filtered, and the filtrate was concentrated to give 7.0 g of a yellow oil. Bulb-to-bulb distillation afforded **12** (5.24 g, 68% yield) as a pale-yellow oil which solidified upon standing. A sample was purified for analysis by sublimation (25 °C/0.7 torr) to give white crystals: mp 30.5–31.5 °C; IR 1725, 3550 cm^{-1}; ^{1}H NMR δ 1.15 (d, 3, *J* = 7), 1.31 (t, 3, *J* = 7), 1.80 (d, 3, *J* = 2.5), 2.9 (m, 2), 4.13 (d, 1, *J* = 6), 4.26 (q, 3, *J* = 7). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.45; H, 8.19.

(2*R,3*S**,4*Z*)-2-Hydroxy-3-methyl-4-hexenoic Acid (13).** The hydrogenation was performed with P-2 Nickel according to the procedure of Brown.[47] Nickel acetate tetrahydrate (5.35 g, 21.5 mmol) in 95%

(43) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(44) Authentic samples of tirandamycin A were kindly provided by Dr. R. L. Keene of The Upjohn Company and by Prof. Philip DeShong.

(45) **General.** Unless otherwise indicated, NMR spectra were obtained in $CDCl_3$ solution at 250 MHz; spectral data are presented as follows: chemical shift (relative to internal tetramethylsilane as 0 ppm) (multiplicity, number of protons, coupling constants in hertz). IR spectra were also obtained in $CDCl_3$ solution. Unless otherwise indicated, all reaction workups culminated in extraction with the indicated solvent, washing the organic layer with brine, drying over $MgSO_4$, and evaporation under reduced pressure on a rotary evaporator and finally under high vacuum. Diethyl ether, tetrahydrofuran, benzene, and toluene were dried by distillation from sodium/benzophenone. Dichloromethane (CH_2Cl_2) and acetonitrile were distilled from CaH. Chromatography was performed with Silica Gel 60 (E. Merck, Darmstadt) according to the method of Still,[46] using the indicated eluting solvent. Analytical thin-layer chromatography was performed on precoated plates (250 μm, Silica Gel 60, E. Merck, Darmstadt). Microanalyses were performed by the Microanalytic Laboratory, College of Chemistry, University of California, Berkeley.

(46) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(47) Brown, C. A.; Ahuja, V. J. *J. Org. Chem.* **1973**, *38*, 2226.

ethanol (450 mL) was treated with 1 M $NaBH_4$ solution in ethanol (21.5 mL, 21.5 mmol) to give a black suspension. After the mixture was flushed with hydrogen, ethylenediamine (3.60 mL, 53.7 mmol) and alkyne **12** (73.0 g, 429 mmol) in 50 mL of ethanol were added. The resulting mixture was stirred under an atmosphere of hydrogen until H_2 uptake ceased (24 h), the reaction mixture was filtered through Celite, and the filtrate was concentrated. Workup with ether afforded the *cis*-olefin (73.2 g, 99% yield) as a pale-yellow oil: IR 1725, 3550 cm^{-1}; ^1H NMR δ 0.98 (d, 3, J = 7), 1.28 (t, 3, J = 7), 1.64 (d, 3, J = 5.5), 3.0 (m, 2), 4.01 (d, 1, J = 5), 4.22 (q, 2), 5.1–5.8 (m, 2).

The above ester (73.2 g, 429 mmol) in 500 mL of ethanol was treated with 2 M aqueous NaOH (320 mL, 640 mmol). After stirring at 23 °C for 24 h, the reaction mixture was concentrated to a volume of 300 mL. The neutral material was removed by two ether extractions. The aqueous phase was acidified with 6 N HCl and then worked up with ether to afford **13** (54.9 g, 89%) as a pale-yellow solid: mp 57 °C; IR 1710, 2400–3500, 3550 cm^{-1}; ^1H NMR δ 1.05 (d, 3, J = 7), 2.68 (d, 3, J = 6), 3.0 (m, 1), 4.17 (d, 1, J = 4), 5.2–5.8 (m, 2), 7.4 (br s, 2). Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.16; H, 8.31.

(2*R,3*R**,4*R**,5*S**)-Methyl 4,5-Epoxy-2-hydroxy-3-methylhexanoate (14). (A) [3*R**,4*R**,5*S**(1*S**)]-3-Hydroxy-5-(1-iodoethyl)dihydro-2(3*H*)-furanone.** A solution of **13** (54.8 g, 381 mmol) in 1.1 L of acetonitrile was treated at 0 °C with $NaHCO_3$ (320 g, 3.81 mol) and iodine (290 g, 1.14 mol). The resulting mixture was stirred at 0 °C for 3.5 h and then partitioned between water and ether. The ether extracts were washed with saturated aqueous $Na_2S_2O_3$ and water and then worked up in the usual manner to give the iodolactone (90.1 g, 88%) as a yellow solid. An analytical sample was prepared by recrystallization from $CHCl_3$/hexane: mp 90–92 °C; IR 1780, 3450 cm^{-1}; ^1H NMR δ 1.29 (d, 3, J = 6.5), 2.04 (d, 3, J = 7.2), 2.36 (m, 1), 3.37 (dd, 1, J = 2.8, 9.3), 3.65 (br s, 1), 4.26 (d, 1, J = 10.7), 4.31 (dq, 1, J = 2.8, 7.2). Anal. Calcd for $C_7H_{11}IO_3$: C, 31.31; H, 4.11; I, 46.99. Found: C, 30.89; H, 4.09; I, 47.26.

(B) Compound 14. A solution of the iodolactone (43.2 g, 160 mmol) in 1.0 L of methanol was treated with anhydrous Na_2CO_3 (21.2 g, 200 mmol), and the resulting mixture was stirred at room temperature for 70 h in the absence of light. The reaction mixture was concentrated under reduced pressure, and the residue was worked up with ether to afford **14** (25.8 g, 92%) as a yellow liquid. A sample was purified for analysis by preparative GLC (6-ft × $^1/_4$-in. SE-30 column, 180 °C) to afford a colorless liquid: IR 1730, 3530 cm^{-1}; ^1H NMR δ 0.90 (d, 3, J = 7), 1.30 (d, 3, J = 5), 1.8 (m, 1), 3.10 (m, 3), 3.77 (s, 3), 4.37 (d, 1, J = 3); ^{13}C NMR δ 10.0, 13.0, 36.1, 52.5, 53.0, 57.8, 71.8, 174.8. Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.94; H, 8.10.

[5*R-[1*S**,2*R**,3*S**]]-2,2-Bis(trifluoromethyl)-5-(2,3-epoxy-1-methylbutyl)-1,3-dioxolan-4-one (15).** A 3-L flask equipped with a dry ice condenser was charged with a solution of epoxy ester **14** (77.8 g, 0.447 mol) in CCl_4 (1.5 L). A fine stream of hexafluoroacetone was introduced to the solution until a steady reflux of the ketone occurred. The resulting mixture was stirred at 23 °C for 2 h. The NMR spectrum of the reaction mixture indicated the formation of the hemiketal. The mixture was treated with anhydrous Na_2CO_3 (52.1 g, 0.492 mol), and stirring was continued for 46 h. The reaction mixture was filtered, and the filtrate was washed with two portions of water and with saturated aqueous $NaHCO_3$ and then worked up to give a yellow liquid (127.7 g). This material was distilled through a Vigreux column to give **15** (114.3 g, 83% yield) as a colorless liquid: bp 48 °C/20 torr; IR (film) 1200, 1850 cm^{-1}; ^1H NMR δ 1.03 (d, 3, J = 7), 1.33 (d, 3, J = 6.5), 1.98 (m, 1), 2.95 (dd, 1, J = 5, 9.5), 3.22 (dq, 1, J = 5, 6.5), 4.92 (d, 1, J = 1); ^{19}F NMR δ 30.85 (q, 3, J = 9), 31.75 (q, 3, J = 9). Anal. Calcd for $C_{10}H_{10}O_4F$: C, 38.97; H, 3.27. Found: C, 39.29; H, 3.23.

[3*R-[3α,4β,5α(1*S**)]]-3-Hydroxy-4-methyl-5-(1-methyl-2-butynyl)-dihydrofuran-2(3*H*)-one (16).** A solution of *n*-BuLi (83 mL, 0.20 mol) in toluene (180 mL) was treated at 0 °C with a stream of propyne, until an excess was indicated by reflux (dry ice condenser). To the white slurry was added a 1.8 M toluene solution of diethylaluminum chloride (94 mL, 0.167 mol). The reaction mixture was stirred at 0 °C for 3 h, and the lithium chloride was allowed to settle overnight in a freezer. A solution of epoxide **15** (7.02 g, 22.8 mmol) in toluene (50 mL) was treated dropwise at 0 °C with the alane solution (146 mL, 91.2 mmol) over a 15-min period. The reaction mixture was stirred at 0 °C for 4 h and then poured onto a mixture of ice and 1 N HCl. The organic material was extracted with ethyl acetate, and the extracts were washed with water and saturated $NaHCO_3$ and worked up to give a yellow oil (6.46 g). Crystallization from hexane/CH_2Cl_2 afforded **16** as a white solid (1.19 g; mp 88 °C). The mother liquor was chromatographed on silica gel to afford additional pure material: 2.04 g, 78% total yield; IR 1780, 3600 cm^{-1}; ^1H NMR δ 1.22 (d, 3, J = 7), 1.26 (d, 3, J = 7), 1.74 (d, 3, J = 2), 2.3–2.9 (m, 2), 3.80 (dd, 1, J = 3, 10), 4.05 (d, 1, J = 11), 4.2 (br s, 1); exact mass calcd for $C_{10}H_{14}O_3$ 182.0944, found 182.0934.

2-Methyl-2-(3-bromo-2-propyl)-1,3-dioxolane (30). Condensed HBr (3.0 mL, 0.10 mol) was added to ethylene glycol (27.1 g, 0.437 mol) at 0 °C. The resulting solution was treated dropwise at 0 °C with methyl isopropenyl ketone (5.65 g, 67.2 mmol). The reaction mixture was warmed to room temperature, stirred for 2 h, and then extracted with petroleum ether (3 × 50 mL). The combined extracts were washed with water and saturated aqueous $NaHCO_3$ solution and worked up to give 7.93 g of a brown liquid. Chromatography on 400 g of silica gel using a 9:1 hexane/ether solvent system afforded pure **30** (3.89 g, 27%) as a colorless liquid: ^1H NMR δ 1.12 (d, 3, J = 7), 1.24 (s, 3), 2.12 (m, 1), 3.10 (t, 1, J = 10), 3.68 (dd, 1, J = 3, 7), 3.91 (s, 4). Anal. Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27; Br, 38.22. Found: C, 40.25; H, 6.40; Br, 37.98.

[3*R-[3α(1*RS*),4β,5α(1*S**)]]-3-(1-Ethoxyethoxy)-4-methyl-5-(1-methylbut-2-ynyl)dihydrofuran-2(3*H*)-one (32).** A solution of hydroxy lactone **16** (3.64 g, 20 mmol) in CH_2Cl_2 (100 mL) was treated at 0 °C with ethyl vinyl ether (7 mL) and pyridinium *p*-toluenesulfonate (0.50 g). The resulting mixture was stirred at 0 °C for 3 h, then washed with water and saturated $NaHCO_3$, and worked up to give **32** (5.04 g, 99%) as a pale-yellow oil. A sample that was purified by flash chromatography exhibited the following spectral data: IR (film) 1140, 1170, 1690 cm^{-1}; ^1H NMR δ 1.20 (t, 3, J = 7.0), 1.21 (d, 3, J = 7.1), 1.28 (d, 3, J = 7.1), 1.40 (d, 3, J = 5.4), 1.78 (m, 3), 2.55 (m, 1), 2.79 (m, 1), 3.5–3.8 (m, 2), 3.86 (m, 1), 4.06, 4.13 (d's, 1, J = 10.8), 4.98, 5.19 (q's, 1, J = 5.4). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.12; H, 8.64.

[3*RS*,6*R-(1*RS*)-7*R**,8*S**,9*S**]-6-(1-Ethoxyethoxy)-2,2-(ethylenedioxy)-8-hydroxy-3,7,9-trimethyldodec-10-yn-5-one (33).** A solution of bromide **30** (2.00 g, 9.59 mmol) in THF (35 mL) was cooled to −78 °C and treated over a 5-min period with a 1.7 M *tert*-butyllithium solution (5.64 mL, 9.59 mmol) in pentane. The mixture was stirred at −78 °C for 5 min, and then a solution of lactone **32** (487 mg, 1.92 mmol) in THF (10 mL) was added over a 15-min period. After complete addition, the reaction mixture was stirred for 0.5 h at −78 °C and then warmed to −20 °C over 5 min, at which point water was added. The organic material was extracted twice with ether. The ether extracts were washed with water and worked up to give 1.26 g of a pale-yellow oil. This material was chromatographed on 200 g of silica gel with a 2:1 hexane/ethyl acetate solvent system. Concentration of the desired fractions gave **33** (665 mg, 90% yield) as a pale-yellow oil: IR (film) 1080, 1640 (weak), 3400 cm^{-1}; ^1H NMR δ 0.75–1.4 (m, 18), 1.78 (m, 3), 3.98 (m, 4); mass spectrum (70 eV), *m/e* 73, 366, 385. Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44. Found: C, 65.74; H, 9.59.

[1*R-[1β,3β(1*S**),4α,5β,8α]]-1,4,8-Trimethyl-3-(1-methyl-2-butynyl)-6-oxo-2,9-dioxabicyclo[3.3.1]nonane (34β).** A solution of **45** (see below; 1.98 g, 7.85 mmol) in 100 mL of CH_2Cl_2 was treated with pyridinium chlorochromate (2.53 g, 11.8 mmol) and stirred at room temperature for 24 h. The reaction mixture was diluted with ether and filtered through 4 cm of silica gel. The filtrate was concentrated to afford 1.68 g (86%) of **34β** as a white solid. An analytically pure sample was obtained by recrystallization from hexane/ether: mp 69 °C; IR 1076, 1123, 1156, 1723 cm^{-1}; ^1H NMR δ 0.77 (d, 3, J = 7.1), 1.08 (d, 3, J = 6.9), 1.26 (d, 3, J = 6.9), 1.43 (s, 3), 1.81 (d, 3, J = 2.4), 2.11 (dd, 1, J = 10.4, 18.6), 2.41 (m, 2), 2.68 (m, 1), 2.78 (ddd, 1, J = 1.8, 8.7, 18.6), 3.52 (dd, 1, J = 2.4, 11.0), 4.06 (dd, 1, J = 1.7, 6.1). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.13; H, 8.69.

[3*RS*,6*R-(1*RS*)-7*S**,8*S**,9*S**]-8-Acetoxy-6-(1-ethoxyethoxy)-2,2-(ethylenedioxy)-3,7,9-trimethyldodec-10-yn-5-one (35).** A solution of **33** (2.68 g, 7.13 mmol) in CH_2Cl_2 (45 mL) was treated with 4-(dimethylamino)pyridine (2.61 g, 21.4 mmol) and acetic anhydride (1.68 mL, 17.8 mmol). The resulting mixture was stirred at room temperature for 6 h, then partitioned between water and CH_2Cl_2, and worked up to give 2.91 g of a yellow oil which was chromatographed on silica gel (Waters Prep 500 HPLC). Elution with 4:1 hexane/EtOAc afforded 2.49 g (82%) of **35** as a colorless liquid: IR (film) 1235, 1750 cm^{-1}; ^1H NMR δ 0.87–1.2 (m's, 12), 1.28 (m, 6), 1.80 (m, 3), 2.13 (m, 3), 2.26 (m, 1), 2.50 (m, 2), 2.69 (m, 1), 2.76 (m, 1), 3.49 (m, 2), 3.95 (m, 4), 3.84, 4.23 (d's, 1, J = 2.9), 4.44, 4.58 (q's, 1, J = 5.2), 4.84, 4.88 (dd's, 1, J = 2.8, 9.6). Anal. Calcd for $C_{23}H_{38}O_7$: C, 64.76; H, 8.98. Found: C, 64.58; H, 8.99.

[2*R-[2α(1*S**,2*S**,3*S**),5β,6β]]-5,6-Dimethyl-6-methoxy-3-oxo-2-(2-acetoxy-1,3-dimethylhex-4-ynyl)tetrahydro-2*H*-pyran (36α) and the [2*R**-[2α(1*S**,2*S**,3*S**),5α,6β]]-Isomer 36β.** A solution of **35** (2.59 g, 6.07 mmol) in 50 mL of dry MeOH was treated with pyridinium *p*-toluenesulfonate (100 mg) and refluxed for 9 h. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. Workup gave 2.06 g of a pale-yellow oil which was chromatographed on silica gel (Waters

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Prep 500 HPLC) with a 9:1 hexane/EtOAc solvent system. Aside from the pure products **36α** (1.14 g, 58%) and **36β** (479 mg, 24%), a mixed fraction (86 mg) was isolated (87% total yield). A sample of **36α** was crystallized in hexane/ether to afford a white solid: mp 105 °C; IR 1245, 1725, 1740 cm^{-1}; ^1H NMR δ 0.87 (d, 3, J = 6.9), 0.95 (d, 3, J = 6.7), 1.12 (d, 3, J = 7.0), 1.37 (s, 3), 1.81 (d, 3, J = 2.4), 2.08 (m, 1), 2.09 (s, 3), 2.28 (dd, 1, J = 5.5, 17.0), 2.41 (dd, 1, J = 12.7, 17.0), 3.18 (s, 3), 3.89 (s, 1), 4.98 (dd, 1, J = 2.7, 10.3). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.56; H, 8.64.

[2*R-[2α(1*S**,2*S**,3*S**),5α,6β]]-5,6-Dimethyl-6-methoxy-3-oxo-2-(2-acetoxy-1,3-dimethylhex-4-ynyl)tetrahydro-2*H*-pyran (36β).** A sample of **36β** was crystallized in hexane/ether to afford a white solid: mp 94 °C; IR 1245, 1725, 1745 cm^{-1}; ^1H NMR δ 0.89 (d, 3, J = 6.9), 1.03 (d, 3, J = 6.6), 1.12 (d, 3, J = 7.1), 1.31 (s, 3), 1.81 (d, 3, J = 2.4), 2.10 (s, 3), 2.14 (m, 2), 2.65 (m, 1), 2.74 (m, 2), 3.24 (s, 3), 4.01 (d, 1, J = 1.4), 4.95 (dd, 1, J = 2.8). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.49; H, 8.84.

[2*R-[2α(1*S**,2*S**,3*S**),5β,6β]]-5,6-Dimethyl-6-methoxy-3-((trimethylsilyl)oxy)-2-(2-acetoxy-1,3-dimethylhex-4-ynyl)-5,6-dihydro-2*H*-pyran (39).** A solution of **36α** (1.62 g, 5.0 mmol) in 75 mL of CH_2Cl_2 was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (1.12 mL, 7.5 mmol) and chlorotrimethylsilane (0.83 mL, 6.5 mmol). The reaction mixture was refluxed for 4 h, then washed with cold 1% aqueous HCl and bicarbonate solution, and dried. Filtration and concentration afforded 2.03 g of a colorless oil. Chromatography (Waters Prep 500 HPLC) afforded pure **39** (1.48 g, 75%) as a colorless oil: IR 1235, 1683, 1747 cm^{-1}; ^1H NMR δ 0.22 (s, 9), 0.88 (d, 3, J = 6.9), 0.99 (d, 3, J = 7.0), 1.12 (d, 3, J = 7.1), 1.23 (s, 3), 1.80 (d, 3, J = 2.3), 2.10 (s, 3), 2.13 (m, 1), 2.49 (m, 1), 2.77 (m, 1), 3.18 (s, 3), 3.84 (m, 1), 4.92 (dd, 1, J = 1.2, 6.1), 5.04 (dd, 1, J = 2.8, 10.4). Anal. Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15. Found: C, 63.84; H, 9.25.

[2*R-[2α,6β(1*R**,2*R**,3*R**)]]-2,3-Dimethyl-6-(2-acetoxy-1,3-dimethyl-4-hexynyl)-2-methoxy-5,6-dihydro-2*H*-pyran-5-one (41).** A solution of **39** (1.14 g, 3.56 mmol) in 60 mL of acetonitrile was treated with 1,1,1,3,3,3-hexamethyldisilazane (0.30 mL, 1.42 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.97 g, 4.27 mmol). The resulting mixture was stirred at room temperature for 3 h and then concentrated. The residue was triturated with 1:1 hexane/ether and chromatographed twice on silica gel. Elution with 1:1 hexane/ether afforded **40** (312 mg) and **41** (267 mg, 23%) as a yellow solid: mp 123 °C; IR 1024, 1116, 1245, 1380, 1680, 1735 cm^{-1}; ^1H NMR δ 0.86 (d, 3, J = 6.9), 1.13 (d, 3, J = 7.1), 1.50 (s, 3), 1.82 (d, 3, J = 2.4), 1.97 (d, 3, J = 1.4), 2.10 (s, 3), 2.77 (m, 1), 2.87 (m, 1), 3.26 (s, 3), 4.23 (d, 1, J = 1.7), 5.01 (dd, 1, J = 2.8, 10.4), 5.89 (d, 1, J = 1.4). Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.04; H, 8.13. Found: C, 67.22; H, 8.09.

[6*R(1*S**,2*S**,3*S**)]-6-(2-Acetoxy-1,3-dimethyl-4-hexynyl)-3-methyl-2-methylene-5,6-dihydro-2*H*-pyran-5-one (40).** An analytically pure sample of **40** was obtained by crystallization of the above mixture from ether to afford **40** as a white solid: 245 mg, 22%; mp 137–139 °C; IR 1141, 1240, 1376, 1591, 1672, 1740 cm^{-1}; ^1H NMR δ 0.92 (d, 3, J = 6.9), 1.15 (d, 3, J = 7.0), 1.82 (d, 3, J = 2.3), 2.09 (d, 3, J = 1.2), 2.11 (s, 3), 2.79 (m, 1), 4.38 (d, 1, J = 2.13), 4.78 (s, 1), 5.01 (s, 1), 5.06 (dd, 1, J = 2.8, 10.3), 6.02 (s, 1). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.30; H, 7.64. Found: C, 70.23; H, 7.72.

[1*R,2*R**(2β,3β,4β,7β)]-11-Oxa-3-hydroxy-2,4,6,7,8-pentamethyltricyclo[5.3.1.0^{1,5}]undeca-5,8-dien-10-one (43).** A solution of **41** (223 mg, 692 μmol) in 90% aqueous MeOH (30 mL) was treated with K_2CO_3 (286 mg, 2.07 mmol) and refluxed for 6.5 h. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate and water. Workup as usual afforded 134 mg of a brown oil, which was chromatographed on silica gel. Elution with 2:1 hexane/EtOAc provided **43** (63 mg, 36%) as a white solid. Crystallization from pentane/ether afforded large single crystals (mp 147.5–148 °C) which were subjected to X-ray analysis (see below): IR 969, 1001, 1110, 1140, 1683, 3580 cm^{-1}; ^1H NMR δ 0.99 (d, 3, J = 7.4), 1.10 (d, 1, J = 9.4), 1.26 (s, 3, J = 7.0), 1.52 (s, 3), 1.82 (d, 3, J = 2.5), 1.97 (d, 3, J = 1.6), 2.64 (m, 1), 3.02 (dq, 1, J = 4.7, 7.4), 4.00 (m, 1), 5.47 (d, 1, J = 1.6); ^{13}C NMR δ 7.2, 10.3, 10.9, 19.2, 20.2, 35.2, 39.2, 80.2, 93.8, 100.0, 119.5, 142.2, 145.5, 166.8, 194.2; mass spectrum (70 eV), m/e 248 (M^+). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12. Found: C, 72.75; H, 8.04.

[2*R-[2α(1*S**,2*S**,3*S**),3β,5β,6β]]-5,6-Dimethyl-3-hydroxy-6-methoxy-2-(1,3-dimethyl-2-hydroxyhex-4-ynyl)tetrahydro-2*H*-pyran (44αα).** A solution of **36α** (4.60 g, 14.2 mmol) in 500 mL of ether was cooled to −78 °C and treated dropwise with a 1 M Dibal solution in hexane (64 mL, 64.0 mmol) over a 25-min period. The reaction mixture was stirred at −78 °C for 0.5 h and at 0 °C for 2 h, and then water (5.8 mL, 0.32 mmol) and NaF (13.5 g, 0.32 mol) were added. After the mixture stirred at room temperature for 16 h, $MgSO_4$ (20 g) was added and stirring was continued for 0.5 h. The reaction mixture was filtered, and the filtrate was washed with warm EtOAc. Concentration of the filtrate afforded 4.03 g of a white solid which was recrystallized from hexane/ether to afford **44αα** (2.83 g, 70%) as a white crystalline solid (mp 122 °C) and **44αβ** (0.59 g, 15%). Compound **44αα**: IR 1015, 1080, 3500, 3640 cm^{-1}; ^1H NMR δ 0.92 (d, 3, J = 6.1), 0.94 (d, 3, J = 7.0), 1.24 (s, 3), 1.25 (d, 3, J = 7.0), 1.65 (m, 2), 1.75 (m, 2), 1.81 (d, 3, J = 2.4), 2.08 (m, 2), 2.74 (m, 1), 3.23 (s, 3), 3.39 (dd, 1, J = 3.5, 8.5), 3.59 (m, 1), 3.72 (dd, 1, J = 2.1, 9.8). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.56; H, 9.87.

[1*R-[1α,3α(1*S**),4β,5α,6α,8β]]-6-Hydroxy-3-(1-methylbut-2-ynyl)-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonane (45).** A solution of diol **44αα** (2.78 g, 9.77 mmol) in 100 mL of chloroform was treated with pyridinium p-toluenesulfonate (150 mg) and refluxed for 4 h. The reaction mixture was washed with water and saturated $NaHCO_3$ and worked up to afford a colorless liquid (2.61 g). This material was purified by chromatography (2:1 hexane/EtOAc) to give 2.12 g (86%) of analytically pure **45**: IR 1130, 1160, 1212, 1234, 3430 cm^{-1}; ^1H NMR δ 0.85 (d, 3, J = 7.18), 0.99 (d, 3, J = 6.74), 1.23 (d, 3, J = 7.11), 1.34 (s, 3), 1.74 (m, 1), 1.82 (d, 3, J = 2.4), 1.94 (m, 1), 2.07 (m, 1), 2.5 (m, 1), 2.61 (d, 1, J = 9.68), 2.62 (m, 1), 3.74 (dd, 1, J = 2.37, 11.04), 3.80 (m, 1), 3.92 (m, 1). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 6.59. Found: C, 71.39; H, 6.50.

Methyl [2*E*,4*E*,6*R(1*S**-[1α,3α,4β,5α,6α,8β])]-6-(6-((*tert*-Butyldimethylsilyl)oxy)-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-yl)-4-methylhepta-2,4-dienoate (48). (A) [1*R**-[1β,3β(1*S**),4α,5β,6β,8α]]-6-((*tert*-Butyldimethylsilyl)oxy)-3-(1-methylbut-2-ynyl)-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonane.** A solution of alcohol **45** (800 mg, 3.17 mmol) in 50 mL of DMF was treated with triethylamine (0.88 mL, 6.35 mmol), 4-(dimethylamino)pyridine (1.55 g, 12.7 mmol), and *tert*-butyldimethylsilyl chloride (1.91 g, 12.7 mmol). The resulting mixture was stirred at 75 °C for 10 h and then poured into ice–water. The organic material was extracted with 4:1 hexane/ether. The extracts were washed with 1 N HCl and saturated $NaHCO_3$ and worked up to afford 1.18 g of an off-white solid. This material was chromatographed (19:1 hexane/ether) to give 1.043 g (90%) of the silyl ether of **45** as a white solid: mp 102–103 °C; IR 840, 1090, 1130, 1256 cm^{-1}; ^1H NMR δ 0.06 (d, 6, J = 0.5), 0.84 (d, 3, J = 7.2), 0.90 (s, 3), 0.94 (d, 3, J = 6.9), 1.21 (d, 3, J = 7.1), 1.74 (m, 2), 1.80 (d, 3, J = 2.4), 2.13 (m, 1), 2.43 (m, 1), 2.58 (m, 1), 3.72 (dd, 1, J = 2.3, 11.0), 3.79 (d, 1, J = 6.2), 3.92 (m, 1). Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45. Found: C, 69.04; H, 10.61.

(B) [1*R-[1β,3β(1*S**,2*E*),4α,5β,6β,8α]]-3-(3-Bromo-1-methylbut-2-enyl)-6-((*tert*-butyldimethylsilyl)oxy)-1,4,8-trimethyl-2,9-dioxabicyclo-[3.3.1]nonane.** A solution of the above silyl ether (949 mg, 2.59 mmol) in 60 mL of benzene was transferred via cannula into a flask containing $HZrCp_2Cl$ (3.12 g, 7.78 mmol of active hydride) and stirred at room temperature protected from light. After 9 h, solid N-bromosuccinimide (692 mg, 3.89 mmol) was added through a rubber tube. The mixture was stirred at room temperature for 1.5 h, diluted with 4:1 hexane/ether, filtered through 3 in. of silica gel, and concentrated under reduced pressure. Purification by chromatography (24:1 hexane/ether) gave 909 mg (76% yield) of the vinyl bromide as a white solid which was shown by ^1H NMR analysis to contain <4% of the *cis*-olefin: mp 52–53 °C; IR 1011, 1090, 1142, 1257, 1650 cm^{-1}; ^1H NMR δ 0.05 (s, 6), 0.77 (d, 3, J = 7.1), 0.90 (s, 9), 0.94 (d, 3, J = 1.2), 2.46 (m, 1), 3.76 (m, 1), 3.78 (m, 1), 5.99 (dd, 1, J = 1.2, 10.2); exact mass calcd for $C_{21}H_{39}BrO_3Si$ 448.1833, found 448.1840.

(C) Compound 48. To a solution of 3-methoxy-3-methylbutyne (136 μL, 1.39 mmol) in 2.0 mL of THF at 0 °C was added a 1.65 M solution of *n*-butyllithium in hexane (0.84 mL, 1.39 mmol). After 0.5 h, this solution was transferred via cannula to a slurry of CuBr–Me_2S (2.86 g, 1.39 mmol) in THF (2.0 mL) and dimethyl sulfide (1.5 mL). The resulting homogeneous, deep-orange solution was stirred at 0 °C for 0.5 h and then cooled to −78 °C. To a solution of the above vinyl bromide (595 mg, 1.27 mmol) (contaminated with 4% of the alkene) in 2 mL of THF at −78 °C was added a 1.25 M solution of *sec*-butyllithium in cyclohexane (2.02 mL, 2.53 mmol). After stirring for 1.5 h, this solution was transferred via cannula to the above cuprate solution, and the resulting mixture was stirred at −78 °C for 1 h. To this solution was added a −78 °C solution of methyl propiolate (124 μL, 1.39 mmol) in 3 mL of THF. After 1 h, the reaction was quenched at −78 °C by the addition of methanol (0.5 mL). Stirring at −78 °C was continued for 2 h, then saturated aqueous NH_4Cl was added, and the reaction mixture was warmed to room temperature. Workup with ether gave a yellow oil. Analysis of this material by ^1H NMR showed a 22:1 mixture of **48** and the corresponding α,β cis dienoate isomer, along with 15% alkene. Purification by chromatography (9:1 hexane/ether) gave 459 mg (76%) of pure **48**: mp 84–85 °C; IR 1010, 1090, 1174, 1284, 1626, 1709 cm^{-1}; ^1H NMR δ 0.05 (s, 6), 0.77 (d, 3, J = 7.1), 0.89 (s, 9), 0.96 (d, 3, J = 6.9), 1.09 (d, 3, J = 6.9), 1.31 (s, 3), 1.74 (m, 2), 1.93 (m, 1), 2.14 (m, 1), 2.67 (m, 1), 3.71 (d, 1, J = 6.2), 3.76 (s, 3), 3.84 (dd, 1, J = 1.7,

11.4), 3.89 (m, 1), 5.78 (d, 1, J = 15.6), 6.09 (d, 1, J = 9.8), 7.36 (dd, 1, J = 0.5, 15.8). Anal. Calcd for $C_{25}H_{44}O_5Si$: C, 66.33; H, 9.80. Found: C, 66.46; H, 9.97.

Methyl [2*E*,4*E*,6*R[1*S**-[1α,3α,4β,5α]]]-4-Methyl-6-(1,4,8-trimethyl-6-oxo-2,9-dioxabicyclo[3.3.1]non-7-en-3-yl)hepta-2,4-dienoate (49). (A) Methyl [2*E*,4*E*,6*R**[1*S**-[1α,3α,4β,5α,6α,8β]]]-6-(6-Hydroxy-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-3-yl)-4-methylhepta-2,4-dienoate.** A solution of **48** (469.6 mg, 1.04 mmol) in 10 mL of acetonitrile was treated at 0 °C with 48% HF (0.4 mL). The reaction mixture was stirred at 0 °C for 3 h and then neutralized with saturated $NaHCO_3$ solution. The organic material was worked up with ether to afford the alcohol (351 mg, 100% yield) as a white solid. A sample purified by chromatography exhibited the following physical and spectral data: mp 151 °C; IR 1220, 1626, 1710, 3480, 3580 cm^{-1}; ^1H NMR δ 0.79 (d, 3, J = 7.1), 1.01 (d, 3, J = 6.7), 1.10 (d, 3, J = 7.0), 1.33 (s, 3), 1.74 (m, 1), 1.78 (s, 3), 2.02 (m, 3), 2.60 (d, 1, J = 9.6), 2.71 (m, 1), 3.76 (s, 3), 3.86 (m, 3), 5.80 (d, 1, J = 15.7), 6.08 (d, 1, J = 9.9), 7.38 (d, 1, J = 15.6). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.22; H, 8.95.

(B) Methyl [2*E*,4*E*,6*R[1*S**-[1α,3α,4β,5α,8β]]]-4-Methyl-6-(6-oxo-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-6-en-3-yl)hepta-2,4-dienoate.** A solution of the above alcohol (351 mg, 1.04 mmol) in 15 mL of CH_2Cl_2 was treated with pyridinium chlorochromate (335 mg, 1.56 mmol) and stirred at room temperature for 13 h. The reaction mixture was diluted with ether and passed through a short column of silica gel, and the filtrate was concentrated to afford the ketone as a white solid (339 mg, 97%). A sample was recrystallized from hexane/ether to afford white crystals: mp 126 °C; IR 1017, 1176, 1628, 1722 cm^{-1}; ^1H NMR δ 0.70 (d, 3, J = 7.0), 1.10 (d, 3, J = 6.9), 1.14 (d, 3, J = 7.0), 1.42 (s, 3), 1.79 (d, 3, J = 1.2), 2.13 (dd, 1, J = 10.5), 2.36 (m, 1), 2.78 (m, 1), 2.96 (m, 1), 3.76 (dd, 1, J = 1.7, 11.2), 3.99 (dd, 1, J = 1.7, 6.1), 5.82 (d, 1, J = 15.7), 6.02 (d, 1, J = 6.1), 7.37 (dd, 1, J = 0.4, 15.8). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.59; H, 8.35.

(C) Methyl [2*E*,4*E*,6*R[1*S**-[1α,3α,4β,5α,8β]]]-4-Methyl-6-(1,4,8-trimethyl-6-((trimethylsilyl)oxy)-2,9-dioxabicyclo[3.3.1]non-6-en-3-yl)-hepta-2,4-dienoate.** A solution of the above ketone (849 mg, 2.53 mmol) in 40 mL of dichloromethane was treated with trimethylsilyl chloride (481 μL, 3.78 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (680 μL, 4.55 mmol). The resulting mixture was heated at reflux for 3 h, then washed with ice-cold 0.5 M HCl, saturated aqueous $NaHCO_3$, and water, and worked up to afford the silyl enol ether (1.02 g, 98%) as a pale-yellow oil: IR (film) 849, 872, 1168, 1623, 1675, 1740 cm^{-1}; ^1H NMR δ 0.21 (s, 3), 0.70 (d, 3, J = 7.1), 1.03 (d, 3, J = 7.3), 1.08 (d, 3, J = 7.0), 1.35 (s, 3), 1.78 (d, 3, J = 1.2), 1.81 (m, 1), 2.61 (m, 1), 2.72 (m, 1), 3.75 (s, 3), 3.78 (dd, 1, J = 1.9), 3.92 (d, 1, J = 4.3), 4.82 (d, 1, J = 3.0), 5.79 (d, 1, J = 15.7), 6.12 (d, 1, J = 10.0), 7.36 (d, 1, J = 15.8); exact mass calcd for $C_{22}H_{36}O_5Si$ 408.2333, found 408.2327.

(D) Compound 49. A solution of the silyl enol ether (412 mg, 1.01 mmol) in 12 mL of acetonitrile was treated at room temperature with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (344 mg, 1.52 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (85 μL, 0.404 mmol). The resulting mixture was stirred at room temperature for 6 h and concentrated, and the residue was triturated with 4:1 hexane/EtOAc and applied to a silica gel column. Elution with 4:1 hexane/EtOAc afforded 257.6 mg (76%) of **49** as a white crystalline solid: mp 121 °C; IR 1007, 1180, 1321, 1630, 1686, 1701 cm^{-1}; ^1H NMR δ 0.70 (d, 3, J = 7.1), 1.04 (d, 3, J = 7.0), 1.55 (s, 3), 1.79 (d, 3, J = 1.2), 1.93 (d, 3, J = 1.4), 1.97 (m, 1), 2.82 (m, 1), 3.40 (dd, 1, J = 1.1, 11.3), 3.77 (s, 3), 4.01 (d, 1, J = 6.1), 5.82 (d, 1, J = 15.6), 6.11 (m, 2), 7.39 (dd, 1, J = 0.4, 15.8). Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.08; H, 7.82.

Methyl [2*E*,4*E*,6*S[1*R**-[1β,2α,4α,6β,7α,8β]]]-4-Methyl-6-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0^{2,4}]dec-8-yl)hepta-2,4-dienoate (50). Method A.** A solution of **49** (228.2 mg, 0.683 mmol) in 6 mL of benzene was heated with ethylenediaminetetraacetic acid, disodium salt dihydrate (three crystals), *N*-benzyltrimethylammonium hydroxide (40% in MeOH; 62 μL, 0.137 mmol), and *tert*-butyl hydroperoxide (228 μL, 2.05 mmol). The resulting mixture was heated at reflux for 2 h, the same amounts of reagents were added once more, and reflux was continued for 4 h. The reaction mixture was cooled to room temperature and treated with dimethyl sulfide (1 mL) to decompose excess peroxide. After stirring for 0.5 h (negative peroxide test), the reaction mixture was diluted with ether, washed with Na_2SO_3 and $NaHCO_3$ solutions, and worked up to afford 241.6 mg of a pale yellow oil. ^1H NMR analysis indicated a 4:1 epoxide/enone mixture. This material was chromatographed on silica gel to afford recovered **49** (37.5 mg, 16%) and **50** (107.1 mg, 45%) as a white solid: mp 152 °C; IR 1013, 1180, 1632, 1721, 1730 cm^{-1}; ^1H NMR δ 0.71 (d, 3, J = 7.1), 1.11 (d, 3, J = 7.0), 1.47 (s, 3), 1.56 (s, 3), 1.78 (d, 3, J = 1.1), 1.98 (m, 1), 2.79 (m, 1), 3.28 (s, 1), 3.55 (dd, 1, J = 2.0, 11.4), 3.76 (s, 3), 4.02 (d, 1, J = 6.1), 5.83 (d, 1, J = 15.7), 6.05 (d, 1, J = 10.0), 7.36 (d, 1, J = 15.8). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.31; H, 7.56.

Method B. A solution of **49** (54.0 mg, 0.16 mmol) in 1 mL of THF was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (74 μL, 0.48 mmol) and *tert*-butyl hydroperoxide (49 μL, 0.48 mmol). The resulting mixture was stirred at room temperature for 5 days, then diluted with CH_2Cl_2, and poured on 1 M aqueous HCl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and worked up to give 51.9 mg of a yellow oil. Flash chromatography afforded 29.8 mg (53%) of **50** as a white solid: mp 152 °C.

[1*R-[1β,2α,4α,6β,7α,8β(2*E*,4*E*,8*S**)]]-*N*-(2,4-Dimethoxybenzyl)-*N*-(2-ethoxy-2-oxoethyl)-3-oxo-6-methyl-8-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0^{2,4}]dec-8-yl)-4,6-nonadienamide (52).** A solution of tirandamycic acid (**10**) (91.0 mg, 271 μmol) in 3.6 mL of *tert*-butyl alcohol was treated at room temperature with 0.1 M aqueous NaOH (2.71 mL, 271 μmol) for 0.5 h. After lyophilization, the residue was dissolved in benzene (13 mL) and treated at 10 °C with oxalyl chloride (0.50 mL, 5.7 mmol). The reaction mixture was warmed to room temperature for 0.5 h and then concentrated, and the residue was taken up in 6 mL of THF and cooled to −78 °C.

To a solution of **25** (276 mg, 813 μmol) in 3.4 mL of THF was added at room temperature bis(trimethylsilyl)acetamide (201 μL, 813 mmol). After stirring for 4 h, the solution was cooled to −78 °C and treated with a 0.6 M solution of potassium *tert*-butoxide in THF (1.35 mL, 813 μmol). After 0.5 h, the above acid chloride solution was added dropwise via cannula at −78 °C. After stirring for 0.5 h, the reaction mixture was warmed to room temperature, and the reaction was quenched with saturated NH_4Cl solution. Workup with ether afforded 351 mg of a light-orange oil which was chromatographed on silica gel. Elution with 2:1 hexane/EtOAc afforded recovered **10** (25.2 mg) and **52** (91.3 mg, 73% yield, 72% conversion) as a light-yellow oil: IR 1585, 1614, 1632, 1728, 1745 cm^{-1}; ^1H NMR (~3:1 of keto and enol tautomers, each as a mixture of amide rotamers) major keto form δ 0.69 (d, 3, J = 7.1), 1.09 (d, 3, J = 6.9), 1.27 (t, 3, J = 7.2), 1.46 (s, 3), 1.56 (s, 3), 1.77 (d, 3, J = 0.8), 1.99 (m, 1), 2.76 (m, 1), 3.27 (s, 1), 3.54 (dd, 1, J = 2.0, 11.4), 3.90 (s, 6), 4.02 (s, 2), 4.10 (d, 2, J = 4.4), 4.15 (d, 1, J = 7.1), 4.53 (s, 1), 5.82 (d, 1, J = 15.6), 5.93 (d, 1, J = 10.0), 6.45 (m, 2), 7.04 (m, 1), 7.12 (d, 1, J = 15.6); exact mass calcd for $C_{33}H_{43}NO_{10}$ 613.2888, found 613.2874.

[1*R-[1β,2α,4α,6β,7α,8β(1*E*,2*E*,4*E*,6*R**)]]-1-(2,4-Dimethoxybenzyl)-3-[1-hydroxy-4-methyl-6-(1,2,7-trimethyl-5-oxo-3,9,10-trioxatricyclo[4.3.1.0^{2,4}]dec-8-yl)-2,4-heptadienylidene]-2,4-pyrrolidinedione (53).** A solution of **52** (38.1 mg, 62.1 μmol) in 1.25 mL of THF was cooled to 0 °C and treated with a 0.6 M solution of potassium *tert*-butoxide in THF (124 μL, 74.6 μmol). The reaction mixture was warmed to room temperature and stirred for 72 h, then more potassium *tert*-butoxide (124 μL, 74.6 μmol) was added, and stirring was continued for 9 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 2 M HCl, and then worked up to afford **53** (33.5 mg, 95%) as a light-yellow oil, which was judged to be >90% pure by ^1H NMR analysis: IR 1575, 1615, 1706, 1728 cm^{-1}; ^1H NMR δ 0.71 (d, 3, J = 7.1), 1.13 (d, 3, J = 7.0), 1.47 (s, 3), 1.57 (s, 3), 1.89 (d, 3, J = 0.9), 2.1 (m, 1), 2.84 (m, 1), 3.28 (s, 1), 3.57 (dd, 1, J = 2.0, 11.5), 3.66 (s, 2), 3.81 (s, 3), 3.82 (s, 3), 4.02 (d, 1, J = 6.0), 4.58 (s, 2), 6.18 (d, 1, J = 10.1), 6.46 (m, 2), 7.12 (d, 1, J = 15.6), 7.18 (d, 1, J = 8.9), 7.53 (d, 1, J = 15.6); exact mass calcd for $C_{31}H_{37}NO_9$ 567.2469, found 567.2474.

Crystallographic Data. Both structures were solved by Patterson methods and refined by standard least-squares and Fourier techniques. Peaks corresponding to the expected positions of the hydrogen atoms were found by using difference Fourier techniques; hydrogens were included in the structure factor calculations in their expected positions but were not refined in least squares. Full details of the structure determinations are being deposited with the Cambridge X-ray structure determination archives.

Bicyclic Ketone 34. Space group $P2_1/C$, a = 15.1831 (22) Å, b = 8.0266 (14) Å, c = 11.9860 (15) Å, β = 98.661 (11)°, V = 1444.1 (4) Å^3, D_c = 1.15 g cm^{-3}, μ_{calcd} = 0.74 cm^{-1}. A total of 1896 unique reflections were collected; the final residuals for 164 variables refined against the 1356 data for which $F^2 > 3F^2$ were R = 4.01%, R_w = 5.30%, and GOF = 2.106. The R value for all 1896 data was 6.84%.

Tricyclic Cycloadduct 43. Space group $P2_1/n$, a = 9.7289 (15) Å, b = 13.4480 (19) Å, c = 10.3604 (15) Å, β = 102.812 (12)°, V = 1321.7 (6) Å^3, D_c = 1.25 g cm^{-3}, μ_{calcd} = 0.80 cm^{-1}. A total of 1727 unique reflections were collected; the final residuals for 164 variables refined against the 1447 data for which $F^2 > 3F^2$ were R = 3.52%, R_w = 5.30%, and GOF = 2.69. The R value for all 1727 data was 4.58%.

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Registry No. (±)-**1**, 85880-71-3; (±)-**9**, 103383-32-0; (±)-**10**, 103421-37-0; (±)-**12**, 103383-33-1; (±)-**13**, 103421-38-1; (±)-**13** (ethyl ester), 103368-33-8; (±)-**14**, 103368-35-0; (±)-**15**, 103368-36-1; (±)-**16**, 103368-37-2; (±)-**16**-ol (isomer 1), 103368-58-7; (±)-**16**-ol (isomer 2), 103421-42-7; (±)-**18**, 103368-59-8; (±)-**20**, 103368-60-1; (±)-**22** (isomer 1), 103368-61-2; (±)-**22** (isomer 2), 103421-43-8; (±)-**23**, 103368-62-3; (±)-**23**·Na, 103421-44-9; (±)-**23** (acid chloride), 103368-63-4; **25**, 103368-56-5; **25** (acid), 103368-64-5; (±)-**26**, 103368-65-6; (±)-**27**, 103368-66-7; (±)-**30**, 103368-38-3; **32**, 103368-39-4; **33**, 103368-40-7; (±)-**34**β, 103368-31-6; (±)-**34**β (TMS enol), 103368-32-7; **35**, 103368-42-9; (±)-**36**α, 103368-43-0; (±)-**36**β, 103421-39-2; (±)-**37**α, 103368-67-8; (±)-**38**, 103383-08-0; (±)-**39**, 103368-44-1; (±)-**40**, 103368-46-3; (±)-**41**, 103368-45-2; (±)-**43**, 103368-47-4; (±)-**44**$\alpha\alpha$, 103368-48-5; (±)-**44**$\alpha\beta$, 103421-40-5; (±)-**45**, 103368-41-8; (±)-**45** (TBDMS ether), 103368-49-6; (±)-**45** (bromosilyl derivative), 103368-50-9; (±)-**48**, 103368-51-0; (±)-**48** (disilated), 103368-52-1; (±)-**48** (desilated ketone), 103368-53-2; (±)-**49**, 103421-41-6; (±)-**49** (silyl enol), 103368-54-3; (±)-**50**, 103421-36-9; (±)-**51**, 103368-55-4; (±)-**52**, 103368-57-6; (±)-**53**, 97859-87-5; (±)-(*trans*)-ethyl 2,3-epoxybutyrate, 82769-14-0; [3*R**,4*R**,5*S**(1*S**)]-3-hydroxy-4-methyl-5-(1-iodoethyl)dihydro-2-(3*H*)-furanone, 103368-34-9; propyne, 74-99-7; hexafluroacetone, 684-16-2; methyl isopropenyl ketone, 814-78-8; ethyl vinyl ether, 109-92-2; 3-methoxy-3-methylbutyne, 13994-57-5; methyl propiolate, 922-67-8.

Supplementary Material Available: Experimental details for the synthesis and characterization of the compounds depicted in Schemes III and IV, as well as compounds **37** and **38** (5 pages). Ordering information is given on any current masthead page.

Influence of Propionate Side Chains on the Equilibrium Heme Orientation in Sperm Whale Myoglobin. Heme Resonance Assignments and Structure Determination by Nuclear Overhauser Effect Measurements

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Abstract: Sperm whale myoglobin was reconstituted with hemins methylated at the 2-, 4-, and 6- or 7-positions, and the corresponding metcyano complexes were studied by ^{1}H NMR spectroscopy. Nuclear Overhauser effects (NOEs) were observed between heme methyls attached to the same pyrrole ring and between heme methyls adjacent to a common meso position. The relative magnitudes of these effects could be relied on to identify heme methyl resonances and are proposed to be used as a simple method to reach spectral assignments. Along with selected and characteristic dipolar contacts with clearly identified peripheral protein side chains, the inter-methyl NOE allows direct determination of the heme orientation in the holoprotein. Thus, it was found that the replacement of either propionate side chain with a methyl does not affect the nature of the thermodynamically preferred isomer and does not perturb the equilibrium proportion of the two species.

The two alternate orientations of the heme in *b*-type hemoproteins involve a 180° rotation about the α,γ meso axis (A in Figure 1)[1,2] and have been shown to play key roles in the initial steps of the in vitro assembly from apoprotein and heme for myoglobin,[3] hemoglobin,[4] and cytochrome b_5.[5] In the former two proteins, preliminary evidence suggests that the in vivo assembly may proceed via similar pathways.[4,6] Moreover, not only does the initial step of the reaction between heme and apoprotein fail to distinguish between the two sides of the heme but both heme orientations remain populated to some degree at equilibrium, leading to equilibrium heme rotational disorder.[3,4] This equilibrium disorder in both mammalian myoglobin and hemoglobin A involves only 10–15% of the "reversed" heme orientation as in the lower part of A in Figure 1. However, considerably larger degrees of disorder have been found in insect hemoglobin,[7] fish myoglobin,[6] and mammalian myoglobin reconstituted with chemically modified 2,4-substituents.[8]

We have shown previously that the nature of the 2,4-substituents influences both the rate of heme reorientation and the position of the equilibrium between the two heme orientations.[8] In the present study, we extend our investigation to explore the influence of the modification of the heme 6- or 7-propionate chains on equilibrium heme orientation in sperm whale Mb. Holoproteins of sperm whale Mb at apparent equilibrium were prepared for the two modified hemes, 7-(2-carboxyethyl)-1,3,5,6,8-pentamethyl-2,4-divinylhemin and 6-(2-carboxyethyl)-1,3,5,7,8-pentamethyl-2,4-divinylhemin,[9] hereafter referred to as 6-

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