Table VII. Final Fractional Coordinates ($\times 10^4$) for **16** with Estimated Standard Deviations in Parentheses

atom	x	y	z
N(1)	1636 (1)	2891 (3)	2291 (1)
N(2)	1410 (1)	-1681 (3)	4975 (1)
O(1)	2488 (1)	1937 (2)	3472 (1)
O(2)	1135 (1)	3655 (2)	3584 (1)
O(3)	582 (1)	4983 (2)	2306 (1)
O(4)	228 (1)	3014 (2)	1185 (1)
O(5)	967 (1)	412 (2)	1494 (1)
O(6)	2142 (1)	-726 (2)	2552 (1)
O(7)	1108 (1)	-1123 (3)	5338 (1)
O(8)	1511 (1)	-3017 (3)	4970 (1)
C(1)	2183 (1)	1105 (3)	3780 (1)
C(2)	2198 (1)	-465 (3)	3720 (1)
C(3)	1946 (1)	-1344 (3)	4111 (1)
C(4)	1644 (1)	-735 (3)	4552 (1)
C(5)	1570 (1)	781 (3)	4578 (1)
C(6)	1816 (1)	1691 (3)	4193 (1)
C(7)	1701 (2)	3307 (3)	4184 (1)
C(8)	1056 (2)	5164 (3)	3476 (2)
C(9)	450 (2)	5461 (3)	2887 (2)
C(10)	15 (1)	5174 (3)	1717 (1)
C(11)	210 (1)	4576 (3)	1148 (1)
C(12)	515 (2)	2364 (4)	732 (1)
C(13)	551 (2)	741 (4)	832 (1)
C(14)	1149 (2)	-1091 (3)	1590 (1)
C(15)	1489 (1)	-1401 (3)	2317 (1)
C(16)	2507 (1)	-1113 (3)	3227 (1)

tion reduced R to 0.183, 0.113, and 0.157 for **7**, **10**, and **16**, respectively; these values dropped to 0.074, 0.084, and 0.095 on allowing anisotropic thermal motion in the refinement. All of the hydrogen atoms involved in hydrogen bonding and most of the remaining hydrogen atoms were visible in difference maps and were included in subsequent refinement cycles with fixed idealized geometry (C-H, N-H 0.95 Å); only overall isotropic temperature factors U_{iso} for H atoms were allowed to refine. All the atoms of **7**, but especially the aromatic ring, showed large thermal motion and/or small disorder. For computational convenience the aromatic ring was constrained to refine as a rigid group with C-C = 1.395 Å and C-C-C = 120°. At the conclusion of the refinements, the values of R and $R_w = [\sum w\Delta^2/\sum F_o^2]^{1/2}$ were respectively 0.053 and 0.061 for **7**, 0.032 and 0.034 for **10** and 0.053 and 0.061 for **16**. Atomic scattering factors for carbon, nitrogen, and oxygen were taken from ref 59, and those for hydrogen were taken from ref 60. For the refinements, weights were derived from the counting statistics, and difference electron-density maps computed at the conclusion of refinements were essentially featureless. The final fractional coordinates for non-hydrogen atoms with estimated standard deviations for **7**, **10**, and **16** are given in Tables V-VII, respectively. Tables of thermal parameters, molecular dimensions, hydrogen atom positions, mean-plane data, crystal-packing diagrams, and structure factor listings are available as supplementary material.

Acknowledgment. G.F. thanks N.S.E.R.C. Canada for continuing financial support via operating grants.

Registry No. 1, 30787-74-7; **2**, 65112-33-6; **3**, 65112-34-7; **4**, 81336-34-7; **6**, 65112-35-8; **7**, 65112-36-9; **8**, 94707-40-1; **9**, 65112-37-0; **10**, 65112-38-1; **10**·(±)-1-phenylethylamine, 94707-41-2; **10**·$^1/_2$(1,2-diaminoethane), 94731-57-4; **11**, 94707-43-4; **11**·NH_3, 94707-44-5; **11**·*t*-$BuNH_2$, 94707-45-6; **11**·K, 94707-48-9; **12**, 94707-46-7; **13**, 94707-47-8; **14**, 65198-21-2; **15**, 64975-19-5; **17**, 64975-20-8; **19**, 94707-42-3; **21**, 94731-58-5; 2,6-dimethylanisole, 1004-66-6; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; LiI, 10377-51-2.

Supplementary Material Available: Thermal parameters, calculated hydrogen coordinates, mean plane data, molecular dimensions, stereoviews of packing diagrams, and listings of observed and calculated structure amplitudes for **7**, **10**, and **16** (38 pages). Ordering information is given on any current masthead page.

Stereoselective Total Synthesis of the Complement Inhibitor K-76

John E. McMurry* and Mark D. Erion

Contribution from the Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853. *Received October 31, 1984*

Abstract: A 21-step stereoselective total synthesis of (±)-K-76 is reported starting from 6-acetoxy-4-methyl-4-hexenal (**23**) and 3-methoxy-2-cyclohexenone (**6**). The key steps in the synthesis are the demonstration that alkylidenecyclopropanes such as **27** can serve as initiators for electrophile-induced polyene cyclizations, the development of a new method for conversion of organomercurials such as **28** into olefins, and the demonstration that phenyl boronate protecting groups can serve to moderate the basicity of 1,2-diols such as **39**.

The human complement system consists of more than 20 serum proteins that function collectively to protect the host from invading microorganisms.[1] Several cellular events, termed the inflammatory response, are closely associated with the action of complement. This response aids in the defense of the host by localizing lymphocytes (cells that mediate immunological reactions) and phagocytes (cells that ingest immune complexes) at the site of infection.

The inflammatory response can also be detrimental to the host. Persistent stimulation of the complement system can lead to chronic inflammation and local tissue damage. This self-destructive pathway is characteristic of rheumatoid arthritis and many other immune-complex diseases.[2] Although the biological factors that account for the acute hypersensitivity associated with these diseases are not completely understood, available evidence clearly implicates complement activation as a key step. Thus, some control of the inflammatory response might be possible upon development of agents that inhibit activation of the complement system.

K-76 (**5**), a fungal metabolite recently isolated[3] from *Stachybotrys complementi* nov. sp. K-76 as the result of a massive screening effort involving over 3000 strains of fungi, has been

(1) For reviews of complement action and the inflammatory response, see: (a) Frank, M. M. *Rev. Infect. Dis.* **1979**, *1*, 483. (b) Reid, K. B. M.; Porter, R. R. *Annu. Rev. Biochem.* **1981**, *50*, 433. (c) Mayer, M. M. *Sci. Am.* **1973**, *229*, 54.

(2) Shen, T. Y. In "Burger's Medicinal Chemistry", 4th ed.; Wolff, M. E., Ed.; John Wiley and Sons: New York, 1981; Vol. 3, pp 1206-1209.

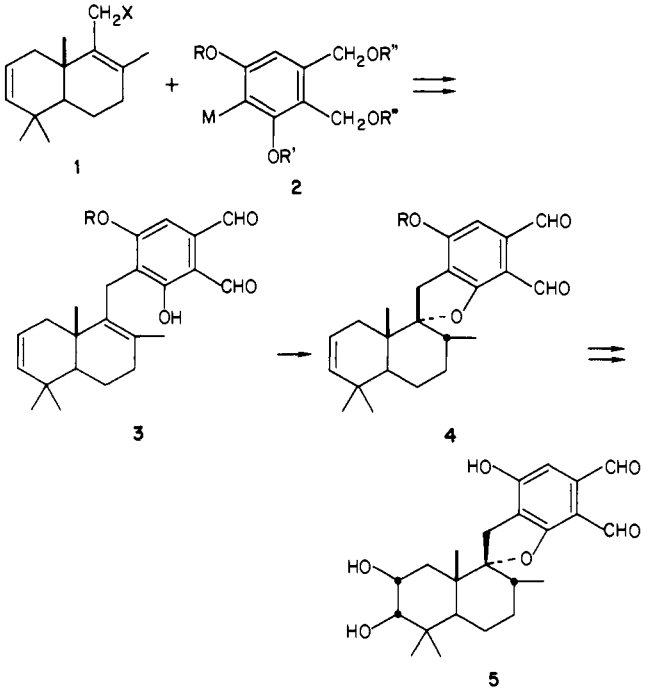
(3) Kaise, H.; Shinohara, M.; Miyazaki, W.; Izawa, T.; Nakano, Y.; Sugawara, M.; Sugawara, K. *J. Chem. Soc., Chem. Commun.* **1979**, 726.

0002-7863/85/1507-2712$01.50/0

reported to exhibit dramatic anticomplement activity, interrupting inflammatory processes by specific inhibition of the C5 step in complement activation.[4] This remarkable biological property, coupled with a highly functionalized structure, prompted us to undertake a total synthesis of the molecule.[5]

Our initial plan was simple. As outlined in Scheme I, we intended to couple a suitable aromatic fragment **2** with bicyclic allylic bromide **1**. Completion of the synthesis would then follow by acid-catalyzed cyclization of unsaturated phenol **3** (trans-diaxial addition) and hydroxylation of olefin **4**.

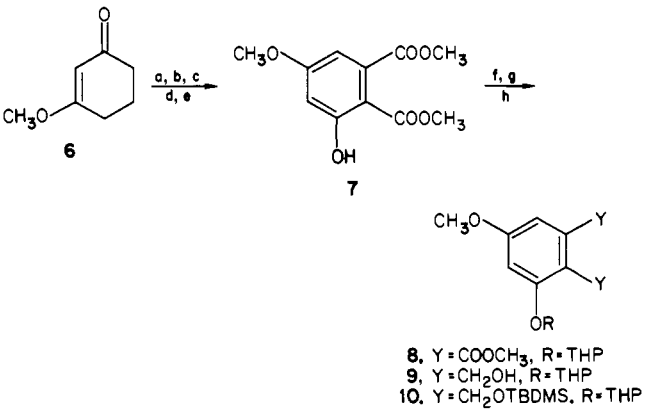
Scheme I



Synthesis of Aromatic Fragment 10. Aromatic fragment **10** was prepared in excellent overall yield from 3-methoxy-2-cyclohexenone (**6**) by a route involving only four manipulations. Thus, in a single flask, ketone **6** was treated with KH and chlorotrimethylsilane to yield an enol silyl ether[6] that underwent rapid Diels–Alder reaction on addition of dimethyl acetylenedicarboxylate.[7] Heating to 120 °C in the same flask effected a retro-Diels–Alder reaction with loss of ethylene, and chromatography of the crude reaction product on silica gel effected hydrolysis of the silyl ether link. Phenol **7** could thus be prepared in 71% overall yield. Protection of phenol **7** as its tetrahydropyranyl (THP) ether and reduction of the two ester groups with $LiAlH_4$ gave diol **9**, which was protected by reaction with 2 equiv of *tert*-butylchlorodimethylsilane to yield **10**. The steps are summarized in Scheme II.

Synthesis of Bicyclic Allylic Bromide 16. Allylic bromide **16** was prepared in 44% overall yield from ethyl farnesate (**11**) by the six-step route shown in Scheme III. Because literature methods for introduction of the A-ring double bond by conversion of the organomercurial into an alcohol[9] or alkyl halide[10] followed by

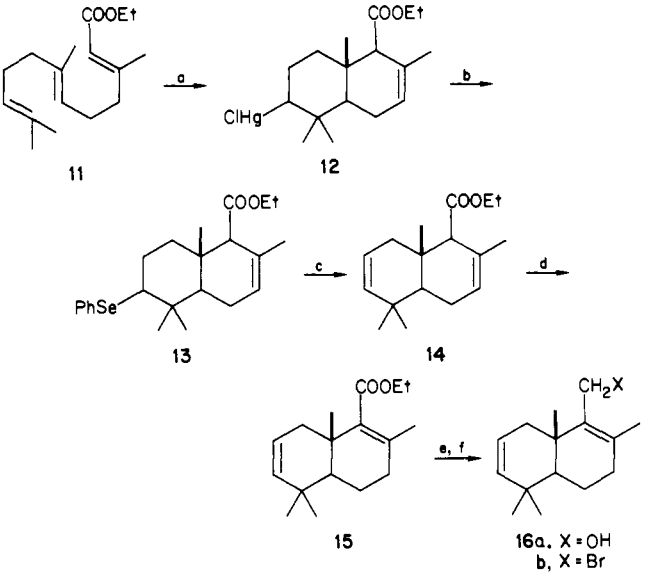
Scheme II



(a) KH, THF; (b) TMSCl; (c) DMAD; (d) 120 °C; (e) SiO_2 chromatography; (f) dihydropyran, H^+; (g) $LiAlH_4$, ether; (h) *tert*-butylchlorodimethylsilane

dehydration or dehydrohalogenation proved inefficient, we devised a new method. We found that brief photolysis of **12** with a sunlamp in the presence of 2 equiv diphenyl diselenide gave the corresponding phenyl organoselenide **13** in high yield.[11] Oxidation of **13** with sodium periodate then gave dienic ester **14** in 83% overall yield.

Scheme III



(a) $Hg(OTFA)_2$, then NaCl; (b) $(PhSe)_2$, light; (c) $NaIO_4$; (d) KH, then *t*-BuOH; (e) $LiAlH_4$, ether; (f) PBr_3

Compounds related to **14** but having a saturated A-ring are known[12] to be more stable as β,γ-unsaturated esters than as conjugated ester isomers. We found, however, that introduction of the A-ring double bond shifted the relative stabilities of B-ring double-bond isomers and allowed us to carry out the thermodynamically favorable conversion of **14** to **15** on treatment with base. Reduction of **15** with $LiAlH_4$, followed by reaction of the allylic alcohol **16a** with PBr_3 in ether, gave allylic bromide **16b**.

Attempted Synthesis of K-76. Coupling[13] of **10** and **16b** to yield **17** was readily accomplished by lithiation[14] of aryl ether **10** with *n*-butyllithium in the presence of tetramethylethylenediamine (TMEDA), followed by alkylation with allylic bromide **16b**. Removal of the silane protecting groups from **17** by treatment with tetrabutylammonium fluoride followed by Swern oxidation[15]

(4) (a) Miyazaki, W.; Tamaoka, H.; Shinohara, M.; Kaise, H.; Izawa, T.; Nakano, Y.; Kinoshita, T.; Hong, K.; Inoue, K. *Microbiol. Immunol.* **1980**, *24*, 1091. (b) Hong, K.; Kinoshita, T.; Miyazaki, W.; Izawa, T.; Inoue, K. *J. Immunol.* **1979**, *122*, 2418.

(5) For an alternative approach to K-76, see: Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551.

(6) Gammill, R. B.; Bryson, T. A. *Synthesis* **1976**, 401.

(7) Subba Rao, G. S. R.; Sashi Kumar, V. P. *Indian J. Chem.* **1979**, *18B*, 543.

(8) (a) Julia, M.; Colomer, E.; Julia, S. *Bull. Soc. Chim. Fr.* **1966**, 2397. (b) Kurbanov, M.; Semenovsky, A. V.; Smit, W. A.; Shmelev, L. V.; Kucherov, V. F. *Tetrahedron Lett.* **1972**, 2175.

(9) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.

(10) For a study of this reaction, see: Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461.

(11) This reaction has also been noted recently by Russell: Russell, G. A.; Tashtoush, H. *J. Am. Chem. Soc.* **1983**, *105*, 1398.

(12) Van Tamelen, E. E.; Schwartz, M. A.; Hessler, E. J.; Storni, A.; *J. Chem. Soc., Chem. Commun.* **1966**, 409.

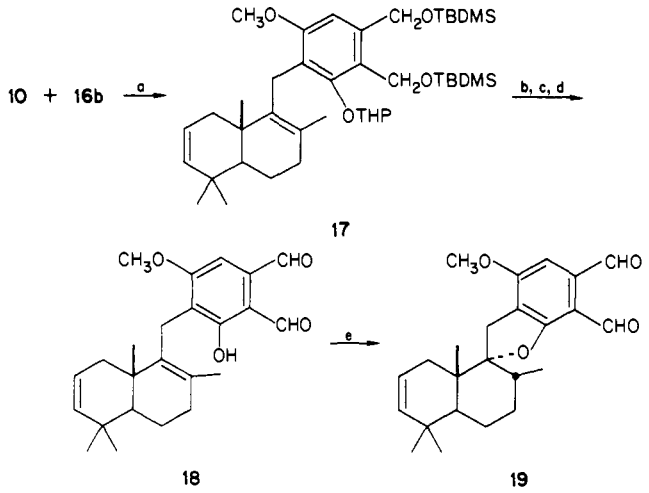
(13) Cf.: Trammell, G. L. *Tetrahedron Lett.* **1978**, 1525.

(14) Christensen, H. *Synth. Commun.* **1975**, *5*, 65.

and acidic hydrolysis then gave phenol **18**. Although **18** appeared sensitive to prolonged acid treatment, the desired trans-diaxial cyclization to yield benzofuran **19** could be accomplished in 56% yield by treatment of **18** with excess Amberlyst ion-exchange resin in CH_2Cl_2.

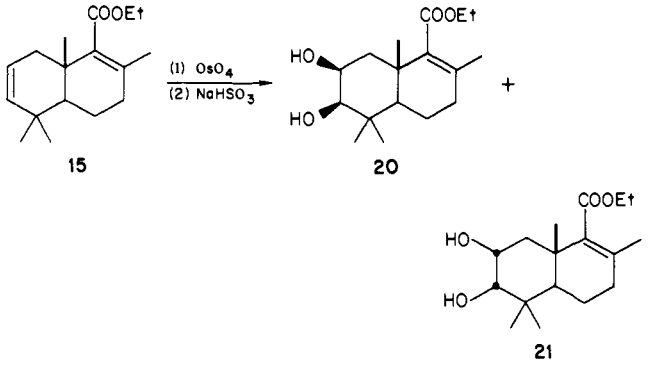
Success now appeared imminent since only 2 steps remained—hydroxylation of the A-ring double bond from the presumably less-hindered α face of the molecule and demethylation of the methyl aryl ether. Much to our surprise, however, hydroxylation of **19** proved impossible. Treatment of **19** with OsO_4 under a great variety of conditions in many solvents either destroyed the molecule totally or gave recovered starting material (Scheme IV).

Scheme IV

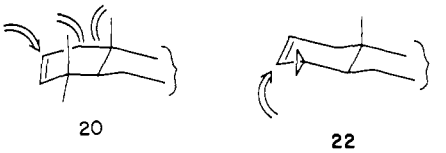


(a) n-BuLi, TMEDA; (b) $(Bu)_4NF$; (c) $(COCl)_2$, Me_2SO, Et_3N; (d) H_3O^+; (e) Amberlyst, CH_2Cl_2

Upon finding that olefin **19** could not be hydroxylated, our immediate response was to introduce the necessary hydroxyl groups prior to attachment of the aryl ring. We therefore explored the reaction of unsaturated ester **15** with OsO_4. Hydroxylation of **15** proceeded smoothly, but analysis of the product by NMR indicated that the reaction occurred with the wrong stereochemistry to yield **20** rather than **21** as the major product (2:1 ratio). This stereochemical result suggests that the predominant reaction course is not through the expected chair-like conformation of the A-ring but rather through a boat-like conformation. Although our result was unexpected, a possibly related result has been observed by Barton[16] in a study of the reaction of $2\beta,3\beta$-epoxylanostane with HBr.



A consideration of factors involved in controlling the hydroxylation stereochemistry of olefin **15** led us to conclude that the severe 1,3-diaxial interaction between methyl groups at C4 and C10 was responsible for holding the A-ring in a boat-like conformation during reaction with OsO_4, thus opening the top face to attack. If this interaction could be relieved, the A-ring should adopt a normal chair conformation and should undergo hydroxylation from the bottom, less hindered, face. Molecular models indicate that the desired relief of strain and consequent change of A-ring geometry can be effected if the *gem*-dimethyl substituents at C4 are replaced by a spiro-fused cyclopropane ring, as in **22**. After hydroxylation of **22**, hydrogenolysis of the cyclopropane ring should generate the necessary *gem*-dimethyls.



A Revised Plan for the Synthesis of K-76. Cyclopropyl olefin **29** was prepared by the route shown in Scheme V. Thus, selective ozonolysis[17] of geranyl acetate at −78 °C led to aldehyde **23**, which underwent Wittig reaction with cyclopropylidenetriphenylphosphorane to yield the alkylidenecyclopropane derivative **24a**. Basic hydrolysis of the acetoxy group gave the corresponding alcohol **24b** in 66% yield from **23**; reaction with PBr_3 gave allylic bromide **25**; and alkylation with the dianion of methyl acetoacetate[18] gave **26**. Keto ester **26** was then converted into cyclization substrates **27a** and **27b** by reaction with diethyl chlorophosphate and with *tert*-butylchlorodimethylsilane, respectively.

Considerable doubt existed in our minds as to whether polyene **27** would undergo mercuric ion induced cyclization in the desired manner. Although a successful synthesis of K-76 requires mercuric ion addition to the alkylidenecyclopropane bond to generate a tertiary cyclopropyl carbocation, the alternative mode of addition to generate a secondary cyclopropylcarbinyl carbocation might seem preferable. Nevertheless, some of our previous experience[19] with additions to unsymmetrical alkylidenecyclopropanes suggested that the desired mode of reaction might predominate.

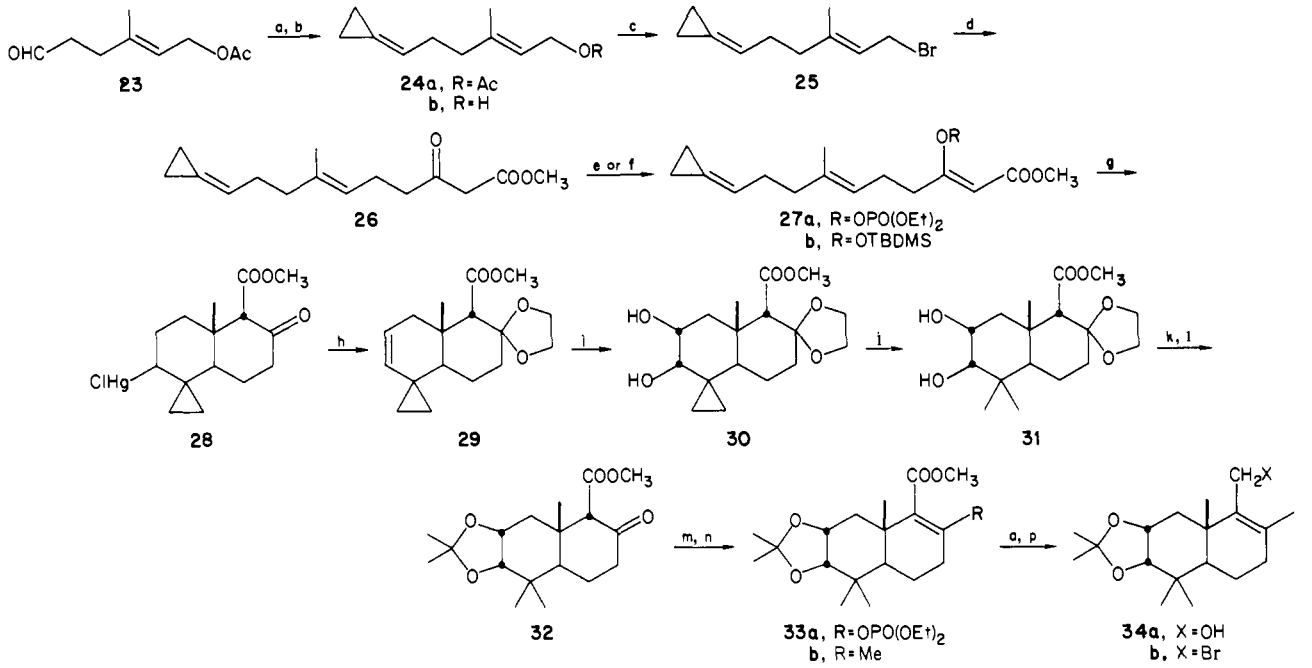
In practice, treatment of alkylidenecyclopropane **27a** with mercuric trifluoroacetate, followed by hydrolysis and anion exchange with sodium chloride, led only to a poor yield of tricyclic product. Reaction of the more nucleophilic enol silyl ether **27b** under the same conditions, however, gave cyclized organomercurial **28** in 57% isolated yield. Ketalization,[20] followed by introduction of the A-ring double bond, was accomplished in 91% yield by our newly developed method involving initial conversion to the organoselenium intermediate and subsequent oxidative elimination with hydrogen peroxide. Use of this method proved to be of critical importance, since attempted conversion of **28** into either the corresponding alcohol or iodide yielded largely ring-opened products.

With cyclopropyl olefin **29** now available, hydroxylation was undertaken. The remarkable effect of the cyclopropane ring was clearly evident from a comparison of the reactions of osmium tetroxide with **29** and the analogous *gem*-dimethyl compound **15**. Whereas hydroxylation of **15** had required the use of stoichiometric quantities of OsO_4 for 72 h, hydroxylation of **29** was accomplished in 20 h at room temperature with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide.[21] As expected, the desired α-diol **30** was obtained as the major product in 88% yield, along with a small amount of the β-diol (12:1 ratio).

With the problem of hydroxylation stereochemistry now solved, the cyclopropane ring was hydrogenolyzed in quantitative yield by reaction in acetic acid solution with hydrogen (50 psi) over a PtO_2 catalyst to yield **31**. Deketalization in aqueous acid, followed by protection of the A-ring diol as its acetonide, gave keto ester **32**, which was converted into unsaturated ester **33b** by

(15) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(16) Barton, D. H. R.; Lewis, D. A.; McGhie, J. F. *J. Chem. Soc.* **1957**, 2907.
(17) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.
(18) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(19) McMurry, J. E.; Coppolino, A. P. *J. Org. Chem.* **1973**, *38*, 2821.
(20) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 1357.
(21) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

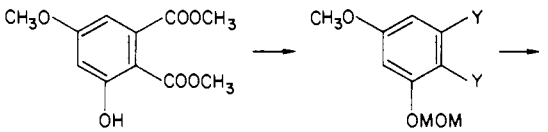
Scheme V

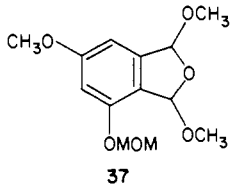


(a) cyclopropylidenetriphenylphosphorane; (b) K_2CO_3, CH_3OH; (c) PBr_3; (d) CH_3COCH_2COOMe, BuLi, NaH; (e) $ClPO(OEt)_2$; (f) *tert*-butylchlorodimethylsilane; (g) $Hg(OTFA)_2$, then NaCl; (h) $TMSOCH_2CH_2OTMS$; $(PhSe)_2$, light; then H_2O_2; (i) OsO_4, NMO; (j) H_2, PtO_2; (k) H_3O^+; (l) acetone, H^+; (m) $ClPO(OEt)_2$; (n) $(CH_3)_2CuLi$; (o) $LiAlH_4$; (p) MsCl, LiBr

reaction[22] of lithium dimethylcopper with the derived diethyl enol phosphate **33a**. Reduction of **33b** with $LiAlH_4$ and treatment of the resulting alcohol **34a** with methanesulfonyl chloride and lithium bromide then gave allylic bromide **34b**.

Completion of the K-76 Synthesis. With the hydroxylation problem solved, the remainder of the synthesis was expected to follow closely the route already outlined in Scheme IV. Instead of using silyl ether **10** as the aromatic piece for coupling with allylic bromide **34b**, however, increased efficiency in the overall synthesis was obtained by using acetal **37**. This acetal was prepared in 78% overall yield from phenol **7** by sequential formation of the methoxymethyl (MOM) ether, reduction of the ester groups with $LiAlH_4$, Swern oxidation to yield dialdehyde **36**, and treatment with toluenesulfonic acid in methanol.





Attempted coupling of bromide **34b** with the lithio derivative of **37** under conditions previously established for the coupling of **10** and **16b** was not successful. When the corresponding arylcopper[23] derivative of **37** was used, however, coupling occurred smoothly. Brief treatment with aqueous acid then effected one-step hydrolysis of the acetonide, acetal, and MOM ether protecting groups to give **39** in 59% overall yield from **16a**.

At this point, two steps remained in the synthesis—cyclization of the olefinic phenol portion and demethylation of the methyl aryl ether. Although we had previously established efficient conditions for the cyclization step in our earlier study of the **18** → **19** transformation, phenol **39** gave no cyclized product under these or any other acidic conditions. In spite of a lengthy study involving many different protic and Lewis acids in many different solvents, we were unable to effect the conversion of phenol **39** to benzofuran **41**. Either starting material was recovered, the molecule was destroyed, or (with $SnCl_4$) six-membered-ring ether formation was found.

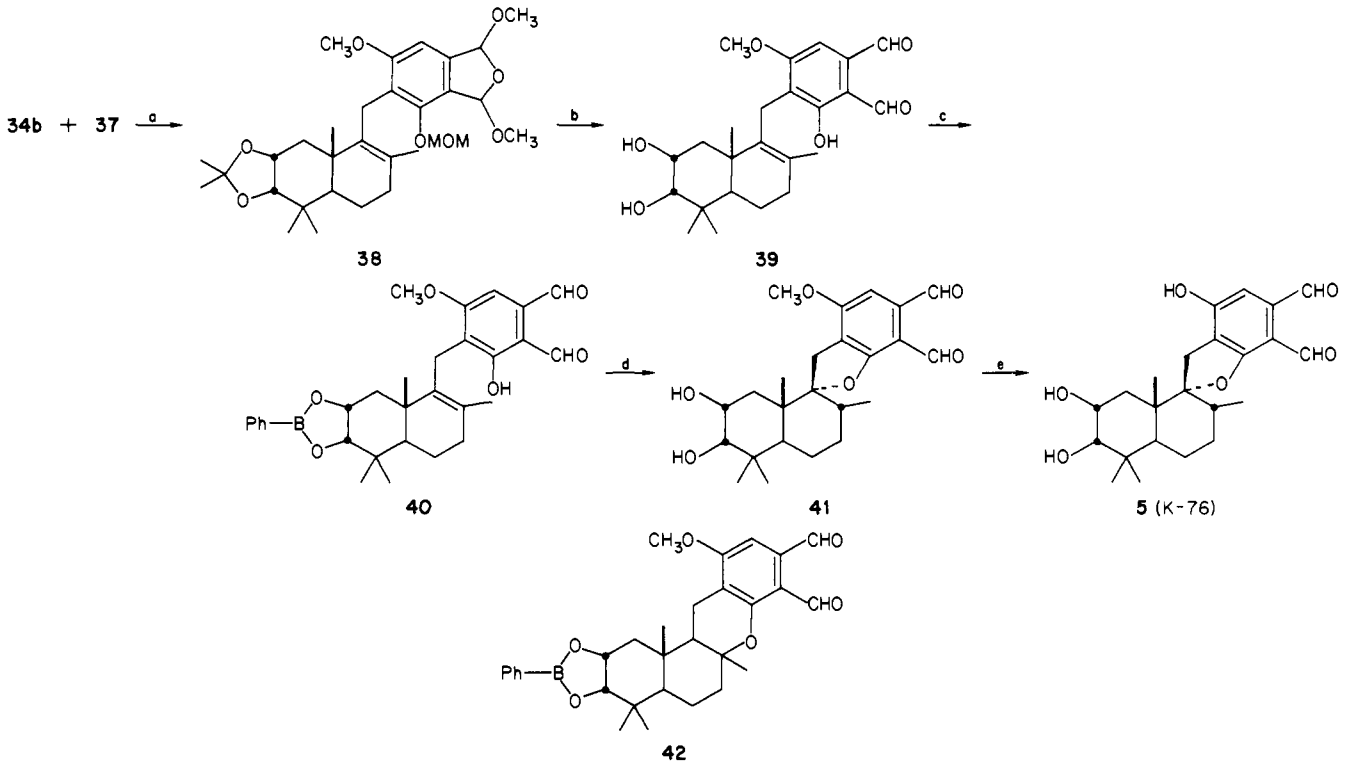
What is the reason for the dramatic difference in behavior toward acids of **18** and **39**? The only structural difference between the two molecules is the presence (in **39**) or absence (in **18**) of the two A-ring hydroxyl groups. Thus, we concluded that the diminished reactivity of **39** toward acid-catalyzed cyclization might be due to the basicity of these hydroxyl groups, which could hinder protonation of the B-ring double bond and make the molecule more susceptible to acid-catalyzed decomposition. If this analysis is correct, the hydroxyls need to be protected in a manner that renders them less basic.

We chose phenyl boronate[24] as the protecting group on the hypothesis that overlap of the oxygen lone-pair electrons with the vacant boron orbital should effectively deactivate the oxygens toward protonation. After preparation of cyclic boronate **40** by stirring a benzene solution of diol **29** with phenyl boric acid, NMR analysis showed a large downfield shift for the C2 and C3 protons of **40** relative to those of diol **39**, presumably due to the expected lower electron density on the C2 and C3 oxygens. Further evidence for the electron-withdrawing effect of the boron was provided by observation of greatly enhanced acid stability for **40** vs. **39**. Treatment of **40** with a large excess of Amberlyst ion-exchange resin in benzene solution for 4 days at room temperature, followed by brief exposure to dilute aqueous NaOH to remove the boronate protecting group, gave a mixture of *O*-methyl K-76 **41** and the isomeric benzopyran **42** in a ratio of 1.7:1. Chromatography on silica gel then provided the pure **41** in 45% yield from **40**.

Completion of the K-76 synthesis was accomplished by treating a solution of **41** in hexamethylphosphoramide with lithium *tert*-

(22) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.
(23) Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1981**, *103*, 7672.
(24) Cf.: Ferrier, R. J. In "Advances in Carbohydrate Chemistry and Biochemistry"; Tipson, R. S., Horton, D., Eds.; Academic Press, Inc.: New York, 1978; Vol. 35, pp 31–80.

Scheme VI



butylthiolate,[25] followed by chromatography on silica gel. Unlike the synthetic (±)-K-76 obtained in the previously reported synthesis,[5] our material solidified readily and could be crystallized from ether–pentane as pale yellow crystals. Comparison of the synthetic material with an authentic sample of natural material provided by Dr. Hirotsugu Kaise, Otsuka Pharmaceutical Co., indicated that the two were indistinguishable by IR, 300-MHz ^1H NMR in both pyridine-d_5 and acetone-d_6, ^{13}C NMR, mass spectrometry, and normal and reversed-phase HPLC. A summary of the concluding transformations is shown in Scheme VI.

Conclusions. A stereoselective total synthesis of (±)-K-76 was accomplished from 6-acetoxy-4-methyl-4-hexenal (**23**) and 3-methoxy-2-cyclohexenone (**6**) in 21 steps with an overall yield of 3.1%. Most important among the steps are the demonstration that alkylidenecyclopropanes such as **27** can serve as initiators for electrophile-induced polyene cyclizations, the development of a new method for conversion of organomercurials such as **28** into olefins, and the demonstration that phenyl boronates can serve as protecting groups to moderate the basicity of 1,2-diols such as **39**.

Experimental Section

Phenol 7. A solution of 3-methoxy-2-cyclohexenone[26] (**6**) (7.16 g, 56.8 mmol) in tetrahydrofuran (10 mL) was added to a chilled (0 °C) suspension of potassium hydride (2.15 g, 53.8 mmol) in tetrahydrofuran (45 mL) over 15 min. The reaction was then warmed to room temperature and stirred for 15 h. The resulting thick orange slurry was cooled to 0 °C and treated with freshly distilled chlorotrimethylsilane (7.1 mL, 56 mmol) in one portion. After being stirred vigorously for 15 min, the pale-yellow mixture was cooled further to −78 °C, and dimethyl acetylenedicarboxylate (7.0 mL, 57 mmol) was added dropwise. The reaction temperature was then raised to 50 °C over a period of 1 h. After an additional hour, the orange solution was diluted with xylenes (45 mL), and the remaining tetrahydrofuran was distilled as the temperature was slowly raised to 120 °C. After 12 h the resulting dark brown solution was cooled, diluted with ether, washed with water, dried ($MgSO_4$), and concentrated to an orange oil. Chromatography on a short column of silica gel (20% ethyl acetate–hexanes) gave a white solid, which was recrystallized (50% ether–hexanes) to afford 9.15 g (71%) of phenol **7** as colorless needles: mp 72.5–73.0 °C; IR ($CDCl_3$) 3400–3100, 2850, 1735, 1665, 1615, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.54 (s, 2 H), 3.92 (s, 6 H), 3.83 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 164.0, 163.4, 136.8, 107.3, 102.3, 101.7, 55.2, 52.1; mass spectrum, calcd for $C_{11}H_{12}O_6$ 240.0634, found 240.0636. Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 55.04; H, 5.03.

Tetrahydropyranyl Ether 10. *p*-Toluenesulfonic acid (55 mg) was added to a chilled (0 °C) solution of phenol **7** (3.48 g, 14.8 mmol) and dihydropyran (12.2 g, 145 mmol) in CH_2Cl_2 (5 mL). After the mixture was left to stand for 12 h at 0 °C, the pink solution was diluted with ether (100 mL), washed with 1 N NaOH, water, and brine, dried ($MgSO_4$), and concentrated to a yellow oil. Chromatography on silica gel (25% ethyl acetate–hexanes) gave 3.85 g (82%) of the tetrahydropyranyl ether **8** as a white solid: mp 81–83 °C; IR (film) 1730, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.12 (d, J = 2 Hz, 1 H), 6.93 (d, J = 2 Hz, 1 H), 5.49 (m, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 4.00–3.57 (m, 2 H), 2.00–1.45 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 165.3, 163.5, 154.7, 129.1, 113.9, 106.9, 106.0, 96.0, 61.2, 55.3, 52.2, 52.0, 29.5, 24.7, 17.7; mass spectrum, calcd for $C_{16}H_{20}O_7$ 324.1209, found 324.1225.

A solution of diester **8** (3.53 g, 10.9 mmol) in ether–benzene (2–1, 18 mL) was added dropwise to a stirred 0 °C suspension of lithium aluminum hydride (587 mg, 15.5 mmol) in ether (20 mL). The resulting gray mixture was then warmed to 25 °C. After 2 h, the reaction was recooled to 0 °C, quenched by adding a saturated solution of ammonium chloride (8 mL), and then dried ($MgSO_4$), filtered, and concentrated to a colorless oil. Chromatography on silica gel (70% ethyl acetate–hexanes) yielded 2.91 g (99%) of diol **9** as a colorless solid: mp 61.5–63.5 °C; IR ($CDCl_3$) 3380, 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.67 (d, J = 3 Hz, 1 H), 6.57 (d, J = 3 Hz, 1 H), 5.28 (m, 1 H), 4.71 (s, 2 H), 4.62 (s, 2 H), 3.81 (s, 3 H), 3.85–3.30 (m, 4 H), 2.00–1.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 156.0, 142.1, 121.0, 107.6, 101.6, 97.6, 63.4, 62.6, 55.3, 55.0, 30.3, 24.8, 19.0; mass spectrum, calcd for $C_{14}H_{20}O_5$ 268.1311, found 268.1313.

A mixture of this diol (2.71 g, 10.1 mmol), imidazole (4.20 g, 61.7 mmol), and *tert*-butylchlorodimethylsilane (4.57 g, 30.3 mmol) was stirred at room temperature for 24 h. The resulting cloudy yellow solution was diluted with ether and washed successively with water, 2 N HCl, and 0.1 M phosphate buffer. The organic layer was then dried ($MgSO_4$) and concentrated to a yellow oil, which was purified by chromatography on silica gel (5% ethyl acetate–hexanes) to obtain 4.68 g (93%) of disilyl ether **10** as a low-melting solid: mp 38–44 °C; IR (film) 1600, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.90 (d, J = 2 Hz, 1 H),

(25) Wolfe, S.; Ducep, J.-B.; Greenhorn, J. D. *Can. J. Chem.* **1975**, *53*, 3435.

(26) Ralls, J. W.; Wildmann, W. E.; McCaleb, K. E.; Wilds, A. L. U.S. Patent 2674627; *Chem. Abstr.* **1955**, *49*, 1813c.

6.67 (d, J = 2 Hz, 1 H), 5.40 (m, 1 H), 4.94 (s, 2 H), 4.78 (s, 2 H), 3.84 (s, 3 H), 3.85–3.62 (m, 2 H), 2.00–1.37 (m, 6 H), 1.02 (s, 9 H), 0.95 (s, 9 H), 0.15 (s, 6 H), 0.09 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 159.9, 155.2, 143.7, 118.2, 104.5, 100.0, 96.7, 62.2, 61.9, 55.6, 55.1, 30.4, 25.9, 25.2, 18.8, 18.4, 18.2, −5.4; mass spectrum, calcd for $C_{26}H_{48}O_5Si_2$ 496.3040, found 496.3043.

Cyclization of Ethyl Farnesate To Yield 12. To a chilled (−5 °C) solution of ethyl farnesate (2.81 g, 10.5 mmol, 4:1 *E*:*Z*) and nitromethane (7 mL) was added a solution of mercuric trifluoroacetate (4.73 g, 11.1 mmol) in nitromethane (15.5 mL) over 20 min. After an additional 5 min, the red-brown mixture was treated with saturated aqueous sodium chloride and then stirred vigorously for 20 min. The resulting red-brown mixture was diluted with hexanes–ether (9–1), washed with water and brine, dried ($MgSO_4$), and concentrated to a brown foam. Column chromatography on silica gel (8% ethyl acetate–hexanes) gave a partially solidified colorless oil. Trituration from hexanes afforded 3.71 g (71%) of predominantly bicyclic organomercurial **12** as a white solid (trace of the exomethylene and α,β-unsaturated olefinic isomers): IR ($CDCl_3$) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.50 (m, 1 H), 4.12 (q, J = 7 Hz, 2 H), 2.85 (m, 1 H), 2.80 (dd, J = 14, 3 Hz, 1 H), 1.59 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 0.97 (s, 3 H).

Diene Ester 14. A steady stream of argon was passed through a mixture of organomercurial **12** (3.85 g, 7.71 mmol), diphenyl diselenide (2.88 g, 9.31 mmol), and benzene (40 mL) for 15 min. This solution was then stirred directly above a sunlamp. After 5 min, the resulting yellow mixture was diluted with hexanes (100 mL) and passed through a pad of Celite to remove the mercuric salts. The filtrate was placed directly onto a column of silica gel. After the excess diphenyl diselenide was washed from the column with hexanes, a diastereotopic mixture of 3α-phenyl and 3β-phenyl selenides was eluted with 7% ethyl acetate–hexanes. Removal of the solvent afforded 2.25 g of a nearly colorless oil: IR (film, mixture of olefinic isomers) 1780, 1730, 1650, 1580 cm^{-1}.

This mixture was dissolved in THF–H_2O (170 mL, 3–1) and cooled to 0 °C. Sodium periodate (5.0 g, 23 mmol) was then added in one portion and the colorless solution warmed slowly to room temperature. After 12 h, the reaction was diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated to a yellow oil. Chromatography on silica gel (hexanes to 3% ethyl acetate–hexanes) gave 1.69 g (83%) of diene ester **14** as a colorless oil (<10% of β,γ-exocyclic and α,β-double-bond isomers): IR (film) 1780, 1730, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65–5.30 (m, 3 H), 4.15 (m, 2 H), 2.94 (br s, 1 H), 2.20–1.60 (m, 5 H), 1.62 (d, J = 1 Hz, 3 H), 1.27 (m, 3 H), 0.96 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H).

Allylic Alcohol 16a. To a suspension of potassium hydride (172 mg, 4.29 mmol) in DME (55 mL) was added a solution of diene ester **14** (1.03 g, 3.90 mmol) in DME (20 mL). This mixture was heated at 60 °C until hydrogen evolution has ceased (30 min). After the mixture was cooled to room temperature, the dark brown solution was treated with *t*-BuOH (5 mL) in one portion. The resulting orange solution was stirred 5 min and then poured over water and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to a yellow oil. This oil was dissolved in 5% ethyl acetate–hexanes and filtered through a plug of silica gel to afford 9.28 mg (90%) of a colorless oil. ^{1}H NMR and capillary GC indicated a 5.2–1 ratio of α,β- to β,γ-unsaturated esters: IR (film) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (m, 2 H), 4.21 (q, J = 7 Hz, 2 H), 2.2–1.4 (m, 7 H), 1.65 (s, 3 H), 1.31 (t, J = 7 Hz, 3 H), 1.18 (s, 3 H), 0.97 (s, 3 H), 0.91 (s, 3 H).

A solution of this mixture in ether (5 mL) was added to a chilled (0 °C) vigorously stirred suspension of lithium aluminum hydride (222 mg, 5.94 mmol) in ether (15 mL). The gray mixture was then warmed to 23 °C and stirred for 15 h. At the end of this period, the reaction was quenched by careful addition of saturated aqueous ammonium chloride (1 mL). After being dried ($MgSO_4$), the mixture was filtered, concentrated, and purified by chromatography on silica gel (15% ethyl acetate–hexanes) to give 481 mg (74%) of allylic alcohol **16a** (<5% of double-bond isomers) as a colorless solid: mp 85–88 °C; IR ($CDCl_3$) 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 5.46 (m, 2 H), 4.19 (d, J = 11.5 Hz, 1 H), 4.06 (d, J = 11.5 Hz, 1 H), 2.20–1.90 (m, 4 H), 1.78 (s, 3 H), 1.55–1.20 (m, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.0, 138.0, 133.0, 121.4, 58.3, 48.5, 37.1, 37.0, 34.8, 33.4, 31.7, 22.2, 20.3, 19.6, 19.3.

Allylic Bromide 16b. Freshly distilled phosphorus tribromide (91 μL, 0.96 mmol) was added dropwise to a chilled (0 °C) solution of the allylic alcohol **16a** (425 mg, 1.93 mmol) in ether (3.5 mL). After 10 min, the reaction mixture was carefully treated with methanol (0.25 mL) and then diluted with ether (40 mL) and poured over H_2O (10 mL). The ether layer was separated and successively washed with 5% aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated to afford 539 mg (99%, >95% pure) of bromide **16b** as a colorless oil. This sample was immediately used in the next step: IR (film) 1640, 1467, 1370, 1200, 725, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 5.44 (m, 2 H), 4.08 (d, J = 3 Hz, 2 H), 2.26–1.95 (m, 4 H), 1.78 (s, 3 H), 1.63–1.27 (m, 3 H), 1.03 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H).

Coupling of 10 and 16b To Yield 17. Dry tetramethylethylenediamine (536 μL, 3.53 mmol) was added dropwise to *n*-butyllithium (1.50 mL, 2.2 M solution in hexane, 3.28 mmol) at 23 °C. After the mixture was cooled to 0 °C, a solution of **10** (1.68 g, 3.38 mmol) in hexanes (0.4 mL) was added over 3 min. The resulting yellow solution was stirred 1.25 h and then treated with allylic bromide **16b** (540 mg, 1.93 mmol) in hexanes (0.7 mL). The reaction mixture was warmed to room temperature and stirred for 15 h. At the end of this period, the colorless mixture was diluted with ether, washed with water, 2 N HCl, water (until neutral pH), and brine, dried ($MgSO_4$), and concentrated to a pale-yellow oil. Chromatography on silica gel (4% ethyl acetate–hexanes) afforded 878 mg (65% from alcohol **16a**) of **17** as a colorless oil: IR (film) 1600, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 6.96 (s, 1 H), 5.38 (m, 2 H), 4.87 (s, 2 H), 4.90–4.70 (m, 3 H), 3.77 (s, 3 H), 3.55 (m, 2 H), 2.20–1.35 (m, 16 H), 0.98 (s, 9 H), 0.92 (s, 9 H), 0.10 (s, 6 H), 0.09 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.8, 153.7, 140.6, 134.4, 136.2, 126.7, 123.0, 122.6, 105.3, 104.4, 65.2, 62.3, 57.4, 55.2, 49.2, 38.5, 37.2, 35.0, 34.8, 32.0, 31.1, 26.0, 25.9, 25.2, 24.7, 22.6, 21.2, 20.8, 20.1, 19.6, 18.4, 18.2, −5.2, −5.4; mass spectrum, calcd for $C_{41}H_{70}O_5Si_2$ 698.4762, found 698.4771.

Dialdehyde 18. A solution of tetrabutylammonium fluoride (4.66 mL, 1 M solution in tetrahydrofuran, 4.66 mmol) was added dropwise to a solution of disilane **17** (815 mg, 1.17 mmol) in tetrahydrofuran (8.0 mL). After 30 min, the resulting yellow solution was diluted with ether and washed with water and brine. The organic layer was dried ($MgSO_4$), concentrated, and purified by chromatography (50% ethyl acetate–hexane) to yield 550 mg (100%) of the corresponding diol as a colorless foam: IR ($CDCl_3$) 3400, 1600, 1570 cm^{-1}; NMR ($CDCl_3$, 60 MHz, partial ^{1}H NMR of diastereotopic mixture) δ 6.70 (s, 1 H), 5.40 (m, 2 H), 3.79 (s, 3 H), 3.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) 52 peaks.

Dry dimethyl sulfoxide (248 μL, 3.49 mmol) in CH_2Cl_2 (0.75 mL) was added dropwise to a cold (−78 °C) solution of oxalyl chloride (150 μL, 1.71 mmol) in CH_2Cl_2 (2.5 mL). After an additional 5 min, the diol (273 mg, 0.61 mmol) in CH_2Cl_2 (1.1 mL) was added to this clear colorless solution. The resulting white slurry was vigorously stirred for 45 min, treated with triethylamine (938 μL, 6.73 mmol), and then slowly warmed to room temperature. After 1.3 h, the reaction was poured over water and extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$), and concentrated to afford 280 mg of crude dialdehyde as a pale yellow foam: IR ($CDCl_3$) 1680, 1580, 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz, partial ^{1}H NMR of diastereotopic mixture) δ 10.53 (s, 1 H), 10.47 (s, 1 H), 7.18 (s, 1 H), 5.40 (m, 2 H), 4.72 (m, 1 H), 3.88 (s, 1 H), 3.51 (m, 2 H).

The crude dialdehyde (236 mg, 0.51 mmol) was dissolved in acetic acid–THF–water (3–2–1, 15 mL) and stirred at room temperature for 13 h. The resulting pale-yellow solution was then diluted with ether and washed with saturated aqueous $NaHCO_3$, water, and brine. The organic phase was dried ($MgSO_4$), concentrated to a yellow foam, and chromatographed on silica gel (17% ethyl acetate–hexanes) to obtain 166 mg (86% from diol) of phenol **18** as a colorless foam: IR (film) 1685, 1630, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 12.84 (s, 1 H), 10.79 (s, 1 H), 10.11 (s, 1 H), 6.93 (s, 1 H), 5.39 (m, 2 H), 3.95 (s, 3 H), 3.47 (d, J = 7 Hz, 2 H), 2.10–1.02 (m, 7 H), 1.46 (s, 3 H), 0.96 (s, 6 H), 0.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 195.2, 191.8, 163.4, 163.0, 137.6, 135.6, 134.6, 128.0, 125.0, 121.7, 112.4, 110.5, 55.8, 49.0, 38.7, 37.1, 34.9, 34.5, 31.8, 22.7, 22.4, 20.5, 19.8, 19.4; mass spectrum, calcd for $C_{24}H_{30}O_4$ 382.2144, found 382.2142.

Benzofuran 19. A solution of phenol **18** (215 mg, 0.56 mmol) and CH_2Cl_2 (4 mL) was treated with dry Amberlyst ion-exchange resin (750 mg, dried at 110 °C under high vacuum) in one portion. After 8.5 h at room temperature, the resulting orange mixture was filtered and the Amberlyst beads thoroughly washed with CH_2Cl_2. The combined filtrates were then washed with water, dried ($MgSO_4$), and concentrated to a white solid contaminated with a pale-yellow oil. This material was triturated with hexanes to yield 121 mg (56%) of benzofuran **19** as a colorless solid: IR ($CDCl_3$) 1670, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.72 (s, 1 H), 10.41 (s, 1 H), 7.03 (s, 1 H), 5.39 (m, 2 H), 3.94 (s, 3 H), 3.17 (d, J = 18 Hz, 1 H), 2.86 (d, J = 18 Hz, 1 H), 2.05 (d, J = 16 Hz, 1 H), 1.90–1.56 (m, 7 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.94 (s, 3 H), 0.76 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.5, 188.4, 166.3, 159.4, 138.6, 137.7, 120.6, 120.3, 112.4, 103.3, 100.2, 56.0, 43.8, 41.3, 37.1, 34.9, 31.6, 31.3, 31.2, 30.5, 23.6, 22.3, 16.3, 15.6; mass spectrum, calcd for $C_{24}H_{30}O_4$ 382.2144, found 382.2142.

6-Acetoxy-(*E*)-4-methyl-4-hexenal (23). Acetic anhydride (22.3 mL, 0.24 mol) was added dropwise to a cooled (0 °C) solution of geraniol (33.0 g, 0.21 mmol), dry pyridine (43.1 mL, 0.54 mol), and CH_2Cl_2 (100

mL). After the mixture was warmed to room temperature, the reaction was stirred for 4 h. The resulting colorless solution was then diluted with CH_2Cl_2 (900 mL), cooled to −78 °C, and treated with a stream of ozone (prepared in oxygen with a Welsbach Laboratory Ozonator, Model T-480, 8 psi, 0.9 flow). The progress of the reaction was monitored by TLC (20% ethyl acetate–hexanes). After only a trace of geranyl acetate could be detected (4.5 h) by TLC (<5% detected by capillary GC), the ozone flow was discontinued, and the pale-yellow solution was treated with acetic acid (230 mL) followed by zinc dust (120 g). The resulting gray slurry was slowly warmed to room temperature, stirred for 2 h, and then filtered through a pad of Celite. The light orange filtrate was diluted with pentane (2 L) and washed with 0.5 N HCl. The combined aqueous washes were reextracted with pentane. The combined organic layers were washed with 5% aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated to 23.4 g (61%) of aldehyde **23** as a nearly colorless oil (greater than 95% pure by capillary GC): bp 93–95 °C (2 mm); IR (film) 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.77 (t, J = 1.4 Hz, 1 H), 5.35 (t, J = 8 Hz, 1 H), 4.57 (d, J = 7 Hz, 2 H), 2.60–2.30 (m, 4 H), 2.03 (s, 3 H), 1.72 (br s, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.3, 170.6, 139.7, 119.0, 60.7, 41.4, 31.1, 20.6, 16.2.

Alkylidenecyclopropane 24b. Sodium hydride (3.80 g of a 50% oil dispersion, 79.2 mmol) and cyclopropyltriphenylphosphonium bromide (31.3 g, 81.0 mmol) were suspended in dry DME (150 mL) and heated for 12 h at 60 °C.[27] While maintaining this temperature, the orange reaction mixture was treated over 4 h with a solution of aldehyde **23** (13.48 g, 79.2 mmol) in DME (70 mL) by a syringe pump. The resulting tan mixture was stirred an additional 2 h, cooled to room temperature, diluted with hexanes, and poured over water. The hexane layer was separated, washed with water, dried ($MgSO_4$), and filtered through a short pad of silica gel. After 500 mL of 5% ethyl acetate–hexanes was passed through the silica gel pad, the filtrate was concentrated to provide **24a** as a yellow oil, which was typically hydrolyzed without further purification. A sample of slightly higher purity could be obtained by column chromatography on silica gel (4% ethyl acetate–hexanes): IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 5.72 (m, 1 H), 5.40 (t, J = 7 Hz, 1 H), 4.49 (d, J = 7 Hz, 2 H), 2.30–2.10 (m, 4 H), 2.06 (s, 3 H), 1.73 (br s, 3 H), 1.04 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 170.6, 141.6, 121.3, 118.3, 117.2, 61.0, 38.9, 29.7, 20.6, 16.2, 1.9, 1.5.

Hydrolysis of the acetate was accomplished by dissolving crude **24a** in methanol (350 mL) containing pulverized K_2CO_3 (12g). After being vigorously stirred for 1 h, the reaction mixture was filtered, concentrated, and distilled (75 °C, kugelrohr, 0.4 mm) to afford 7.95 g (66% from aldehyde **23**) of alcohol **24b** as a colorless oil (<5% geraniol by capillary GC): IR (film) 3320, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.68 (m, 1 H), 5.37 (t, J = 7 Hz, 1 H), 4.10 (d, J = 7 Hz, 2 H), 2.35–2.00 (m, 4 H), 1.92 (s, 1 H), 1.63 (br s, 3 H), 0.96 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 139.0, 123.5, 121.2, 117.5, 59.1, 39.0, 30.0, 16.0, 2.0, 1.7.

Allylic Bromide 25. Phosphorus tribromide (1.35 mL, 14.2 mmol) was added over 20 min to a 0 °C solution of allylic alcohol **24b** (4.31 g, 28.3 mmol) in hexane (14 mL). After being stirred an additional 5 min, the reaction mixture was treated dropwise with methanol (0.6 mL), diluted with pentane, and washed with 5% aqueous $NaHCO_3$, water, and brine. The organic layer was then dried ($MgSO_4$) and concentrated to yield 6.11 g (100%) of bromide **25** as a colorless oil: IR (film) 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.80–5.30 (m, 2 H), 4.03 (d, J = 8 Hz, 2 H), 2.35–2.10 (m, 4 H), 1.73 (br s, 3 H), 1.02 (m, 4 H).

β-Keto Ester 26. Sodium hydride (50% oil dispersion, 1.63 g, 34.0 mmol) was washed with hexanes, suspended in THF (50 mL), and cooled to 0 °C. Methyl acetoacetate (3.61 g, 31.1 mmol) was added dropwise to this suspension over 15 min. After the reaction mixture was stirred an additional 1 h, *n*-butyllithium (13.6 mL, 2.29 M in hexanes, 31.1 mmol) was added over 5 min. The resulting orange solution was stirred for 15 min and then treated with a solution of allylic bromide **25** (6.11 g, 28.3 mmol) and THF (14 mL). After the reaction temperature was maintained for 1 h, the pale-yellow mixture was poured over 2 N HCl and extracted with ether. The ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to a yellow oil. Chromatography of silica gel gave 5.17 g (75%) of β-keto ester **26** as a colorless oil: IR (film) 1750, 1720, 1650, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 5.80 (m, 1 H), 5.15 (t, J = 7 Hz, 1 H), 3.80 (s, 3 H), 3.50 (s, 2 H), 2.70–2.05 (m, 8 H), 1.68 (s, 3 H), 1.03 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 201.6, 167.0, 135.9, 122.0, 120.6, 117.3, 51.6, 48.5, 42.4, 38.9, 29.9, 21.8, 15.4, 1.7, 1.3.

Enol Silyl Ether 27b. A solution of β-keto ester **26** (5.17 g, 20.7 mmol), imidazole (3.94 g, 57.8 mmol), *tert*-butylchlorodimethylsilane (4.36 g, 28.9 mmol), and DMF (11 mL) was stirred for 24 h at room temperature. The resulting pale-yellow solution was diluted with ether and washed with 2 N HCl, water, and brine. The organic layer was then dried ($MgSO_4$), concentrated and chromatographed rapidly through a short column of silica gel (4% ethyl acetate–hexanes) to afford 6.79 g (90%) of enol silane **27b** as a colorless oil: IR (film) 1720, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) 5.77 (m, 1 H), 5.22 (t, J = 7 Hz, 1 H), 5.10 (s, 1 H), 3.68 (s, 3 H), 3.03–2.68 (m, 2 H), 2.50–2.03 (m, 6 H), 1.63 (s, 3 H), 0.98 (s, 9 H), 0.88 (m, 4 H), 0.23 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.1, 167.8, 135.6, 123.2, 120.4, 117.9, 98.6, 50.5, 39.3, 33.4, 30.4, 25.6, 25.5, 18.0, 15.9, 2.1, 1.7, −4.8.

Cyclization of 27b To Yield 28. To a chilled (−5 °C) vigorously stirring biphasic solution of silane **27b** (11.13 g, 30.5 mmol) and nitromethane (55 mL) was added dropwise a solution of mercuric trifluoroacetate (13.67 g, 32.1 mmol) in nitromethane (27 mL) over 30 min. Mercury(0) precipitated during this addition to result in a gray suspension. After the mixture was stirred an additional 10 min, brine was introduced in one portion and the resulting heterogeneous gray mixture vigorously stirred for 30 min. After dilution with water, the mixture was extracted with CH_2Cl_2, and the combined extracts were partially concentrated. The remaining yellow solution was then diluted with ether and washed with water. The organic phase was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (20% ethyl acetate–hexanes) to obtain 8.46 g (57%) of organomercurial **28** (<5% of the C-9 epimer) as a colorless solid: mp 140–142 °C dec; IR ($CDCl_3$) 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3 H), 3.38 (br d, J = 13 Hz, 1 H), 3.01 (d, J = 1.5 Hz, 1 H), 2.96 (m, 1 H), 2.79 (m, 1 H), 2.40–1.93 (m, 3 H), 1.65–1.15 (m, 4 H), 0.99 (s, 3 H), 0.70 (m, 2 H), 0.38 (m, 1 H), 0.07 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 205.9, 168.9, 68.7, 68.6, 51.9, 41.9, 40.2, 39.9, 38.5, 28.5, 23.5, 23.1, 19.3, 11.2, 9.3.

Olefin 29. A solution of organomercurial **28** (235 mg, 0.484 mmol), the bis(trimethylsilyl) ether of ethylene glycol (160 μL, 0.78 mmol), and CH_2Cl_2 (1 mL) was added dropwise to a chilled (0 °C) solution of trimethylsilyl trifluoromethanesulfonate (4 μL) in CH_2Cl_2 (0.4 mL).[20] After standing for 7 h at 0 °C, the light-brown mixture was poured over water, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated, and triturated with ether–hexanes to yield 218 mg (85%) of organomercurial as a white solid: mp 150–153 °C dec; IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.00–3.83 (m, 4 H), 3.67 (s, 3 H), 3.37 (dm, J = 13 Hz, C-3 H_a), 2.48 (d, J = 1.7 Hz, C-9 H_e), 2.37 (dd, J = 12, 3.9 Hz, C-5), 2.24 (m, C-2 H_a, C-7 H_a), 1.88 (dq, J = 13.3, 3.9 Hz, C-2 H_a), 1.68–1.45 (m, 4 H), 1.28–1.15 (m, 1 H), 1.19 (s, 3 H), 1.70 (m, 2 H), 0.43 (m, 1 H), −0.06 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.2, 108.5, 69.4, 64.3, 63.8, 60.0, 51.1, 41.0, 40.7, 38.3, 32.0, 28.3, 22.9, 20.5, 19.0, 11.4, 9.2.

A mixture of the organomercurial prepared above (1.08 g, 2.00 mmol), diphenyl diselenide (7.25 g, 23.2 mmol), and benzene (40 mL) was degassed with several freeze–thaw cycles and then stirred directly above a sunlamp for 2 min. After the reaction was initiated, the yellow mixture was stirred in the dark for 1.5 h. The white mercuric salts that had precipitated during the course of the reaction were then removed by dilution of this mixture with hexanes, followed by filtration through a pad of Celite. The filtrate was placed directly onto a column of silica gel. After the excess diphenyl diselenide was washed from the column with hexanes, a mixture of 3α- and 3β-phenyl selenides was eluted with 7% ethyl acetate–hexanes. Removal of the solvent gave 853 mg (93%) of a colorless oil: IR (film) 1735, 1580 cm^{-1}.

A chilled (0 °C) solution of phenyl selenides (853 mg, 1.86 mmol) and THF (40 mL) was treated with 30% aqueous hydrogen peroxide (1.20 mL, 10.6 mol) in one portion. The colorless solution was warmed slowly to room temperature and stirred for 15 h. The reaction was then diluted with ether, washed with water, dried ($MgSO_4$), and concentrated to a yellow oil. Chromatography on silica gel (ethyl acetate–hexanes; 0% to 15% step gradient) gave 546 mg (91% from organomercurial **28**) of olefinic cyclopropane **29** as a colorless foam: IR ($CDCl_3$) 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.45 (ddd, J = 9.7, 5.5, 2.1 Hz, 1 H), 4.91 (dd, J = 9.7, 2.1 Hz, 1 H), 4.00–3.83 (m, 4 H), 3.67 (s, 3 H), 2.65 (d, J = 1.8 Hz, C-9 H_e), 2.44 (dd, J = 12.1, 3.9 Hz, 1 H), 2.28 (dt, J = 13.3, 5.0 Hz, 1 H), 1.93–1.61 (m, 3 H), 1.35–1.20 (m, 2 H), 1.13 (s, 3 H), 0.88 (m, 2 H), 0.66 (m, 1 H), 0.27 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 135.8, 121.5, 108.6, 64.4, 63.9, 59.5, 51.1, 38.2, 36.8, 36.1, 33.3, 31.5, 19.9, 19.7, 9.1, 8.7.

Diol 30. A chilled (0 °C) solution of vinyl cyclopropane **29** (2.323 g, 7.72 mmol), *N*-methylmorpholine *N*-oxide (1.25 g, 9.27 mmol), THF (10 mL), *t*-BuOH (4 mL), and water (2 mL) was treated with a benzene solution of osmium tetroxide (150 μL, 0.16 M in benzene, 24 μmol). After the mixture was warmed to room temperature, the reaction was stirred for 12 h and then treated with a second portion of osmium tetroxide solution (100 μL). As the reaction progressed, diol **30** crystallized from solution as a white solid. After being stirred an additional 8 h, the resulting tan mixture was treated with 5% aqueous $NaHSO_3$. The mixture was vigorously stirred for 15 min and then poured over water, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to a tan solid.

(27) Utimoto, K.; Tamura, M.; Sisido, K. *Tetrahedron* **1973**, *29*, 1169.

This solid was triturated with ether to give 1.70 g of pure diol **30** as a colorless solid. The ether-soluble fraction was chromatographed on silica gel (50% ethyl acetate–hexanes) to obtain an additional 125 mg of diol **30**, along with 153 mg of the isomeric 2β,3β-diol and 322 mg of the starting olefin **29**. The recovered **29** was recycled to afford an additional 263 mg of diol **30**. After one recycle, the two isomeric diols were isolated in a 12 to 1 ratio and an overall yield of 88%. An analytical sample of **30** was prepared by recrystallization from CH_2Cl_2: mp 244–246 °C; IR (KBr) 3450, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.02–3.84 (m, 5 H), 3.69 (s, 3 H), 2.90 (d, J = 3.2 Hz), 2.67 (dd, J = 11.4, 4.3 Hz, 1 H), 2.53 (d, J = 1.6 Hz), 2.26 (m, 1 H), 2.02 (m, 1 H), 1.88 (m, 1 H), 1.70–1.50 (m, 3 H), 1.18 (s, 3 H), 1.20–1.05 (m, 2 H), 0.58 (m, 2 H), 0.35 (m, 1 H), 0.20 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.9, 108.6, 79.1, 67.3, 64.5, 63.9, 60.0, 51.4, 40.7, 39.4, 32.3, 31.8, 23.1, 19.4, 18.5, 7.9, 5.0; mass spectrum, calcd for $C_{17}H_{26}O_6$ 326.1729, found 326.1727. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.32; H, 8.05.

Diol 31. A Parr catalytic hydrogenation vessel was charged with cyclopropane **30** (1.60 g, 4.78 mmol), acetic acid (65 mL), and platinum oxide (200 mg). After being shaken under hydrogen (520 psi) for 48 h, the reaction mixture was filtered and concentrated to a waxy-white solid. Trituration with ether–hexanes afforded 1.60 g (99%) of diol **31** as white crystals: mp 246–247 °C; IR ($CDCl_3$) 3470, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08–3.84 (m, 5 H), 3.67 (s, 3 H), 3.41 (d, J = 2.7 Hz, C-3 H_e), 2.47 (d, J = 1.8 Hz, C-9 H_e), 2.34–2.20 (m, 2 H), 1.80–1.41 (m, 5 H), 1.18 (s, 3 H), 1.05 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.2, 108.8, 79.1, 66.0, 64.5, 63.9, 62.1, 51.4, 39.8, 38.9, 38.2, 38.0, 33.4, 28.6, 22.3, 21.7, 18.9; mass spectrum, calcd for $C_{17}H_{28}O_6$ 328.1886, found 328.1881. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 61.98; H, 8.65.

β-Keto Ester 32. Diol **31** (1.60 g, 4.75 mmol) was dissolved in 2 N HCl–THF (1–1, 60 mL) and stirred at room temperature. After 36 h, the colorless solution was diluted with CH_2Cl_2 and the aqueous layer neutralized with 1 N NaOH. The aqueous layer was then separated and extracted several more times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated to afford 1.39 g of crude dihydroxy β-keto ester as a colorless solid. This material was sufficiently pure (>95%) for use in the next step: IR ($CDCl_3$) 3480, 1720, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.03 (m, 1 H), 3.69 (s, 3 H), 3.47 (s, 1 H), 2.99 (d, J = 1.7 Hz, C-9 H_e), 2.98–2.85 (m, 1 H), 2.56 (dd, J = 3.3, 13 Hz, 1 H), 2.50–2.40 (m, 1 H), 2.08 (m, 2 H), 2.00–1.40 (m, 4 H), 1.12 (s, 3 H), 1.00 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.6, 168.7, 78.3, 70.0, 65.5, 51.9, 41.8, 39.3, 38.2, 37.8, 37.2, 28.3, 21.6, 21.5.

A mixture of crude diol (1.39 g, 4.75 mmol), Amberlyst (130 mg), and acetone (85 mL) was stirred at room temperature for 2 h. The reaction was then filtered, concentrated, and chromatographed on silica gel (15% ethyl acetate–hexanes) to afford 1.34 g (85%) of acetonide **32** as a colorless solid. An analytical sample was prepared by recrystallization from ether: mp 155–157 °C; IR ($CDCl_3$) 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.20 (m, 1 H), 3.72 (d, J = 4.3 Hz, 1 H), 3.66 (s, 3 H), 3.02 (m, 1 H), 2.94 (d, J = 1.7 Hz, 1 H), 2.50 (m, 2 H), 2.02 (m, 1 H), 1.75–1.50 (m, 3 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.17 (s, 3 H), 0.95 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 205.8, 168.7, 107.2, 82.5, 71.2, 70.3, 51.7, 41.8, 39.5, 39.0, 38.7, 35.1, 28.5, 28.0, 26.2, 23.8, 22.8, 20.9; mass spectrum, calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1923. Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.80; H, 8.59.

Enol Phosphate 33a. A mixture of β-keto ester **32** (1.43 g, 4.40 mmol), sodium hydride (228 mg of 50% oil dispersion, 4.74 mmol), and DME (25 mL) was heated at 50 °C until hydrogen evolution had ceased (45 min). The resulting pale-yellow solution was then cooled to room temperature and treated with diethyl chlorophosphate (0.717 mL, 4.96 mmol). After 15 h, the colorless reaction mixture was poured over a saturated aqueous solution of NH_4Cl and extracted with ether. The combined extracts were washed successively with 5% aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated to give 2.01 g of crude enol phosphate **33a**. The resulting waxy-white solid was typically taken directly to the next step, although a sample of slightly higher purity could be obtained by either chromatography on silica gel (40% ethyl acetate–hexanes) or crystallization from ether: mp 155–157 °C; IR ($CDCl_3$) 1715, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.20 (m, 2 H), 4.10 (m, 4 H), 3.71 (s, 3 H), 3.70 (1 H), 2.53 (m, 2 H), 1.83–1.45 (m, 5 H), 1.44 (s, 3 H), 1.31 (m, 6 H), 1.30 (s, 3 H), 1.20 (s, 3 H), 1.08 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.9, 146.8, 146.4, 127.4, 127.0, 107.1, 82.2, 71.3, 64.2, 63.9, 51.3, 44.0, 38.3, 37.6, 34.9, 28.4, 28.2, 27.8, 26.2, 23.1, 20.0, 17.8, 15.9, 15.6. Anal. Calcd for $C_{22}H_{37}O_8P$: C, 57.38; H, 8.10. Found: C, 57.25; H, 7.90.

α,β-Unsaturated Ester 33b. Methyllithium (2.1 M in ether, 16.4 mL, 35.3 mmol) was added over 5 min to a chilled (0 °C) suspension of CuI (3.36 g, 17.6 mmol) in ether (5 mL). The resulting clear colorless solution was stirred for 40 min, cooled to −78 °C, and then treated with a solution of crude enol phosphate **33a** (2.01 g) in ether–benzene (10 mL). After 5 min, the pale-yellow solution was warmed to −23 °C and stirred for 2.5 h. At the end of this period, the red-brown reaction mixture was poured over saturated aqueous ammonium chloride (10 mL). The aqueous layer was then extracted several times with ether. The combined extracts were washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$), and concentrated to afford 1.43 g of crude ester **33b** as a colorless oil. This material was sufficiently pure for use in the next step. In a separate experiment, the crude product was chromatographed on silica gel (4% ethyl acetate–hexanes) to give pure **33b** as a colorless oil: IR ($CDCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.22 (m, 1 H), 3.72 (1 H), 3.71 (s, 3 H), 2.10 (m, 2 H), 1.72–1.42 (m, 5 H), 1.61 (s, 3 H), 1.46 (s, 3 H), 1.31 (s, 3 H), 1.15 (s, 3 H), 1.08 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.0, 137.0, 132.8, 106.9, 82.4, 72.6, 50.8, 44.5, 38.7, 37.3, 35.0, 32.1, 28.5, 27.8, 26.2, 23.3, 20.7, 19.8, 18.1.

Allylic Alcohol 34a. A vigorously stirred suspension of lithium aluminum hydride (370 mg, 9.75 mmol) in ether (15 mL) was cooled to 0 °C and treated dropwise with a solution of crude ester **33b** (1.43 g) in ether (10 mL). The resulting gray mixture was stirred for 2 h, before the reaction was quenched by a careful addition of saturated aqueous ammonium chloride (2 mL). After drying ($MgSO_4$), the mixture was filtered, concentrated, and purified by chromatography on silica gel (20% ethyl acetate–hexane) to obtain 905 mg (71% from β-keto ester **32**) of alcohol **34a** as a colorless solid. An analytical sample was prepared by recrystallization from ether–pentane: mp 96–97 °C; IR ($CDCl_3$) 3600, 3450, 1450, 1380, 1215, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.27 (m, 1 H), 4.18 (d, J = 11.7 Hz, 1 H), 4.05 (d, J = 11.7 Hz, 1 H), 3.72 (d, J = 4.3 Hz, 1 H), 2.05 (m, 2 H), 1.72 (s, 3 H), 1.70–1.35 (m, 5 H), 1.45 (s, 3 H), 1.32 (s, 3 H), 1.08 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.0, 132.5, 106.9, 82.3, 72.1, 57.6, 45.5, 38.5, 35.1, 33.4, 28.6, 27.8, 26.2, 23.4, 19.9, 19.2, 18.4; mass spectrum, calcd for $C_{18}H_{30}O_3$ 294.2195, found 294.2173. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.37; H, 10.19.

Allylic Bromide 34b. Methanesulfonyl chloride (50 μL, 0.65 mmol) was added dropwise to a chilled (−50 °C) solution of alcohol **34a** (112 mg, 0.38 mmol), triethylamine (106 μL, 0.76 mmol), and CH_2Cl_2 (1.75 mL). The resulting white suspension was stirred for 45 min and then treated with a solution of lithium bromide (112 mg, 1.30 mmol, dried at 110 °C for 12 h at 0.1 mm) in THF (0.25 mL). The colorless mixture was warmed slowly to −20 °C and stirred for 1 h. At the end of this period, the reaction was poured over water and extracted with pentane. The pentane extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to obtain 136 mg of crude allylic bromide **34b**. This colorless oil was used immediately in the next step without further purification (>95% pure): IR (film) 1650, 1465, 1385, 1370, 1220, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 4.30–3.85 (m, 2 H), 4.03 (d, J = 5 Hz, 1 H), 3.73 (d, J = 5 Hz, 1 H), 2.2–1.2 (m, 7 H), 1.72 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.09 (s, 3 H), 0.96 (s, 3 H), 0.91 (s, 3 H).

Methoxymethyl Ether 35. A cooled (0 °C) mixture of phenol **7** (5.00 g, 20.8 mmol), K_2CO_3 (17.3 g, 125 mmol), triethylamine (15.8 mL, 113 mmol), and acetone (25 mL) was treated dropwise with chloromethyl methyl ether (7.85 mL, 103 mmol) and then warmed to room temperature. After 15 h, the resulting yellow mixture was diluted with ether and washed successively with 1 N NaOH, 1 N HCl, and water. The organic phase was dried ($MgSO_4$), concentrated, and then rapidly chromatographed through a short column of silica gel (30% ethyl acetate–hexanes) to obtain 5.89 g (99%) of methoxymethyl (MOM) ether **35** as a colorless oil: IR ($CDCl_3$) 1725, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.13 (d, J = 2 Hz, 1 H), 6.90 (d, J = 2 Hz, 1 H), 5.17 (s, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 165.4, 160.7, 155.1, 129.6, 119.0, 107.4, 106.0, 94.7, 56.0, 55.5, 52.3.

Dialdehyde 36. A solution of diester **35** (5.30 g, 18.6 mmol) in ether (20 mL) was added to a chilled (0 °C) suspension of lithium aluminum hydride (1.06 g, 27.9 mmol) in ether (50 mL) over 20 min. The mixture was slowly warmed to room temperature and stirred for 2 h. After being recooled to 0 °C, the reaction was quenched by adding a saturated solution of ammonium chloride. The gray mixture was then dried ($MgSO_4$), filtered, concentrated, and chromatographed on silica gel (70% ethyl acetate–hexanes) to obtain 4.24 g (100%) of diol as a white solid: mp 48.5–50 °C; IR ($CDCl_3$) 3350, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.65 (br s, 2 H), 5.17 (s, 2 H), 4.67 (s, 2 H), 4.57 (s, 2 H), 3.80 (s, 3 H), 3.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 156.3, 142.2, 120.6, 107.5, 100.8, 100.5, 94.9, 63.2, 55.9, 55.0.

Dry dimethyl sulfoxide (4.04 mL, 57.0 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a cold (−78 °C) solution of oxalyl chloride (2.45 mL, 27.9 mmol) in CH_2Cl_2 (13 mL). After an additional 5 min, the diol (2.55 g, 11.2 mmol) in CH_2Cl_2 (20 mL) was added to this clear colorless solution. The resulting white slurry was vigorously stirred for 45 min, treated with triethylamine (16.2 mL, 116 mmol), and then slowly

warmed to room temperature. After 1.3 h, the reaction mixture was poured over water and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), concentrated, and rapidly passed through a short column of silica gel (25% ethyl acetate–hexanes). Removal of the solvent gave 2.22 g (89%) of dialdehyde **36** as a pale-yellow oil: IR (film) 1675, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.49 (s, 1 H), 10.47 (s, 1 H), 6.98 (d, J = 2.4 Hz, 1 H), 6.91 (d, J = 2.4 Hz, 1 H), 5.29 (s, 2 H), 3.88 ns, 3 H), 3.51 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.0, 189.0, 164.4, 161.5, 140.0, 118.7, 105.7, 104.4, 94.6, 56.1, 55.4.

Cyclic Dimethyl Acetal 37. A solution of dialdehyde **36** (2.22 g, 9.90 mmol), *p*-toluenesulfonic acid (5 mg), methanol (5 mL), and dichloromethane (50 mL) was stirred at 0 °C. After 1 h, the colorless solution was treated with potassium carbonate (5 g) and hexanes (200 mL), filtered, and concentrated to a pale-yellow oil. This material was rapidly passed through a short column of alumina (Woelm, activity 1, 20% ethyl acetate–hexanes) to yield 2.44 g (91%) of two diastereomeric cyclic dimethyl acetals **37** (1.5–1.0, trans–cis) as a colorless oil: IR (film) 2830, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.66 (m, 1 H), 6.53 (m, 1 H), 5.36 (d, J = 2 Hz, 0.4 H), 5.28 (d, J = 2 Hz, 0.4 H), 6.11 (s, 0.6 H), 5.93 (s, 0.6 H), 5.20 (2 H, two peaks), 3.80 (s, 3 H), 3.47 (s, 3 H), 3.46, 3.40, 3.39, 3.36 (6 H); ^{13}C NMR ($CDCl_3$) δ 162.8, 153.2, 141.5, 119.2, 106.2, 105.3, 104.3, 103.1, 99.8, 94.2, 56.0, 55.6, 54.2, 53.8, 53.5, 53.3; mass spectrum, calcd for $C_{13}H_{18}O_6$ 270.1103, found 270.1096.

Coupling of Allylic Bromide 34b with Acetal 37 To Yield 39. *tert*-Butyllithium (334 μL, 1.73 M in pentane, 0.578 mmol) was added dropwise to a cooled (−78 °C) solution of MOM ether **37** (474 mg, 1.75 mmol), in tetramethylethylenediamine (305 μL, 2.02 mmol) and dry THF (1.8 mL). After 1 h, the dark brown solution was treated with copper(I) cyanide (165 mg, 1.84 mmol) in one portion. The mixture was warmed slowly until all the copper(I) cyanide had dissolved and then recooled to −78 °C and stirred for 1.5 h. At the end of this period, the resulting orange solution was treated with a solution of crude allylic bromide **34b** (360 mg, 1.0 mmol) in THF (1.0 mL) and warmed slowly to −15 °C. After 8 h, the reaction was poured over water and ether. The ether phase was separated, washed with water and brine, dried ($MgSO_4$), and concentrated to a yellow oil. Column chromatography on silica gel (20% ethyl acetate–hexanes) gave 510 mg of a diastereomeric mixture of acetonides **38** contaminated with MOM ether **37** (about 10%).

This material was dissolved in a mixture of *i*-PrOH (5 mL), 2 N HCl (5 mL), and THF (0.5 mL) and stirred for 15 h at room temperature. The resulting pale-yellow solution was then diluted with water and the product extracted with CH_2Cl_2. The combined extracts were washed with 5% aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated to a yellow oil. Chromatography on silica gel (50% to 80% ethyl acetate–hexanes; step gradient) afforded 246 mg of phenol **39** as a colorless foam (59% from allylic alcohol **34a**). An analytical sample was prepared by crystallizing **39** from 50% ethyl acetate–hexanes: mp 90.5–93 °C; IR ($CDCl_3$) 3440, 1690, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.87 (s, 1 H), 10.79 (s, 1 H), 10.10 (s, 1 H), 6.93 (s, 1 H), 3.96 (s, 3 H), 3.94 (m, 1 H), 3.48 (s, 2 H), 3.42 (s, 1 H), 2.05–1.25 (m, 7 H), 1.47 (s, 3 H), 1.07 (s, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 195.3, 191.9, 163.6, 163.2, 135.8, 127.4, 124.7, 112.6, 110.6, 78.6, 67.0, 56.0, 44.1, 40.4, 38.3, 38.1, 34.2, 28.4, 22.9, 21.8, 21.3, 20.4, 18.4; mass spectrum, calcd for $C_{24}H_{32}O_6$ 416.2199, found 416.2204. Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.69.

Phenyl Boronate 40. A mixture of phenol **39** (80 mg, 0.19 mmol), $MgSO_4$ (300 mg), phenylboric acid (24 mg, 0.19 mmol), and benzene (5 mL) was stirred for 15 h at room temperature. After the mixture was filtered, the solvent was removed to afford 96 mg (100%) of phenylborate **40** as a pale-yellow solid. An analytical sample was prepared by crystallization from 50% ethyl acetate–hexanes: mp 189–190 °C; IR ($CDCl_3$) 1700, 1635, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.87 (s, 1 H), 10.77 (s, 1 H), 10.06 (s, 1 H), 7.80 (dd, J = 8, 1 Hz, 2 H), 7.45 (t, J = 7 Hz, 1 H), 7.35 (t, J = 7 Hz, 2 H), 6.87 (s, 1 H), 4.58 (m, 1 H), 4.04 (d, J = 4 Hz, 1 H), 3.87 (s, 3 H), 3.49 (d, J = 17 Hz, 1 H), 3.37 (d, J = 17 Hz, 1 H), 2.42 (m, 1 H), 2.05 (m, 2 H), 1.70–1.55 (m, 1 H), 1.38 (s, 3 H), 1.23 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 193.9, 190.4, 162.1, 161.4, 134.2, 133.3, 131.3, 129.9, 126.3, 123.2, 111.0, 109.1, 83.5, 74.1, 72.8, 54.4, 44.3, 39.3, 38.6, 34.9, 33.3, 26.9, 22.3, 21.5, 19.0, 18.5, 17.5; mass spectrum, calcd for $C_{30}H_{35}O_6B$ 502.2527, found 502.2522. Anal. Calcd for $C_{30}H_{35}O_6B$: C, 71.72; H, 7.02. Found: C, 71.47; H, 6.90.

***O*-Methyl K-76 (41).** A solution of cyclic phenylboronate **40** (96 mg, 0.19 mmol) and benzene (4.5 mL) was treated with Amberlyst (325 mg) and then vigorously stirred at room temperature. After 17 h, the reaction was determined to be about 45% complete by ^1H NMR. At this time, more Amberlyst (300 mg) was added to the reaction mixture. After a total of 37 h, the mixture was filtered and the Amberlyst beads rinsed with ether, benzene, and CH_2Cl_2. The filtrate was then washed with 1 N NaOH (4×), water, and brine, dried ($MgSO_4$), and concentrated to a yellow oil. The regioisomeric cyclized products were separated on a silica gel column (50% ethyl acetate–hexanes) affording 22 mg (28%) of the desired *O*-methyl K-76 **41** as a waxy colorless solid along with 13 mg (17%) of a mixture of tetrahydropyran as a colorless oil (R_f values on silica gel plates with 50% ethyl acetate–hexanes were 0.20 and 0.12 for the furan and isomeric pyrans, respectively). Reisolation of the starting cyclic phenylboronate was accomplished by acidifying the base washes with 2 N HCl followed by extraction with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated, and chromatographed (35% ethyl acetate–hexanes) to yield 36 mg of the starting phenylboronate **40**. Thus, based on recovered starting material, the yield of *O*-methyl K-76 **41** was 45%. An analytical sample was prepared by recrystallization from ethyl acetate–hexanes: mp 120–122 °C; IR ($CDCl_3$) 3450, 1750, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.70 (s, 1 H), 10.41 (s, 1 H), 7.01 (s, 1 H), 4.02 (m, 1 H), 3.92 (s, 3 H), 3.40 (d, J = 2 Hz, 1 H), 3.18 (d, J = 17.6 Hz, 1 H), 2.82 (d, J = 17.6 Hz, 1 H), 2.05–1.30 (8 H), 1.05 (s, 3 H), 1.03 (s, 3 H), 0.89 (s, 3 H), 0.76 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.5, 188.6, 166.2, 159.6, 138.6, 120.4, 112.6, 103.5, 100.1, 78.4, 66.2, 56.0, 43.4, 39.3, 38.3, 36.7, 33.2, 31.2, 30.9, 28.5, 21.8, 20.6, 16.9, 15.4; mass spectrum, calcd for $C_{24}H_{32}O_6$ 416.2199, found 416.2199. Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.45, H, 8.05.

(±)-K-76 (5). A deoxygenated solution of HMPA (0.83 mL) and 2-methyl-2-propanethiol (50 μL, 0.44 mmol) was treated dropwise with *n*-butyllithium (170 μL of a 2.4 M solution in hexanes, 0.41 mmol). After the addition was complete, a portion of the colorless solution was added (200 μL, 0.08 mmol) to a solution of methyl ether **41** (16.5 mg, 0.04 mmol) in HMPA (0.4 mL). The resulting yellow solution was stirred for 7 h at room temperature before the reaction was poured over 0.1 N NaOH and washed with CH_2Cl_2. The aqueous layer was acidified with 2 N HCl and extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to 12.5 mg of a yellow oil. Chromatography on silica gel (1–1 ethyl acetate–hexane) gave 12 mg (75%) of (±)-K-76 (**5**) as a waxy solid. This material was crystallized from ether–pentane to afford pale-yellow crystals—decomposition point data: Samples of (±)-K-76 and natural K-76 were sealed in capillary tubes under argon. The most consistent results were obtained by lowering these tubes into a preheated oil bath, recording any changes in the solid after 30 sec, and then removing the tube followed by raising the bath temperature 5 °C. Natural K-76 darkened slightly at 169 °C and eventually liquefied at 272 °C (brown). (±)-K-76 darkened at 184 °C and eventually liquefied at 278 °C: IR (KBr) 3400, 3100, 1670, 1590 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 10.58 (s, 1 H), 10.35 (s, 1 H), 6.88 (s, 1 H), 3.98 (m, 1 H), 3.32 (s, 1 H), 3.29 (d, J = 17.5 Hz, 1 H), 2.93 (d, J = 17.5 Hz, 1 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 0.90 (s, 3 H), 0.79 (d, J = 6.5 Hz, 3 H); ^1H NMR (pyridine-d_5, 300 MHz) δ 11.02 (s, 1 H), 10.71 (s, 1 H), 7.24 (s, 1 H), 4.35 (m, 1 H), 3.76 (s, 1 H), 3.49 (d, J = 17.5 Hz, 1 H), 3.03 (d, J = 17.5 Hz, 1 H), 2.53 (d, J = 12 Hz, 1 H), 2.40 (t, J = 12 Hz, 1 H), 1.85–1.30 (6 H), 1.29 (s, 3 H), 1.04 (s, 3 H), 0.95 (s, 3 H), 0.83 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (Me_2SO-d_6) δ 192.5, 187.4, 166.8, 158.6, 138.1, 118.6, 110.4, 108.6, 99.8, 77.6, 64.9, 43.1, 39.0, 38.2, 36.1, 33.0, 30.9, 30.6, 29.1, 22.0, 20.4, 16.7, 15.5; mass spectrum, calcd for $C_{23}H_{30}O_6$ 402.2042, found 402.2031.

Acknowledgment. This work was funded by research Grant AM-31723 from the National Institutes of Health and by NRSA Training Grant 5732-GM-07223. We thank Dr. Hirotsugu Kaise, Otsuka Pharmaceutical Co., Japan, for providing an authentic sample of K-76.