allyl 2-acetamido-2,6-dideoxy-6-fluoro-α-D-mannopyranoside in 99% yield. The product (50 mg), 1.2 equiv of palladium(II) acetate, and 2.5 equiv of sodium acetate in 95% acetic acid (5 mL) were mixed and stirred at 50 °C for 18 h, and the solvent was removed under vacuum. The residue was applied to silica gel chromatography, eluted with ethyl acetate/methanol (2/1) to obtain **24** in 73% yield. ^{1}H NMR (D_2O) δ 1.9 (3 H, s, NAc), 3.5 (1 H, dd, J = 10.3, 10.3 Hz, H-4), 3.72 (1 H, m, H-5), 3.93 (1 H, dd, J = 4.5, 10.3 Hz, H-3), 4.16 (1 H, d, J = 4.5 Hz, H-2), 4.46 (2 H, m, H-6), 4.9, 5.0 (1 H, s, H-1).

9-Deoxy-9-fluoro-*N*-acetylneuraminic Acid (4). A solution of **24** (20 mg) and pyruvic acid sodium salt (255 mg, 30 equiv) in 0.1 M potassium phosphate buffer (pH 7.5, 10 mL) in the presence of *N*-acetylneuraminic acid aldolase (100 units) was incubated at 37 °C for 8 days. The reaction mixture was lyophilized and chromatographed with Bio-Gel P-2 column to give **4** in 22% yield. The physical data were in accordance with reported.[34]

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Total Synthesis of Furanocembranolides. 1. Stereocontrolled Preparation of Key Heterocyclic Building Blocks and Assembly of a Complete *seco*-Pseudopterane Framework

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Abstract: A retrosynthetic strategy for the total synthesis of pseudopterolide and allied pseudopteranes is presented. This scheme is dependent upon early elaboration of suitable 2,5-difunctionalized 3-furoate esters. To this end, the pair of useful substrates **21** and **24** was readily synthesized from 2,3-*O*-isopropylidene-D-glyceraldehyde and methyl 4-(phenylthio)acetoacetate. The conversion of both of these intermediates into furanolactone **27** was next studied. The best method for gaining suitable control of stereochemistry involved condensation of **24** with methyl 3-formylpropionate under conditions of boron trifluoride catalysis. Transformation of the (phenylthio)methyl substituent of **27** into the requisite isopentenyl side chain was next accomplished in five steps. Because alkylation α to the lactone carbonyl in **46** could be realized only in modest yield, this final segment of the intended macrocyclic ring was introduced earlier by more convergent means. Indeed, the coupling of **24** to **52** proved to be efficient and highly diastereoselective. Following an unsuccessful attempt to introduce the isopentenyl side chain after elaboration of the butenolide subunit, the chemical sequence was reversed. The dual selenenylation strategy for oxidation of both relevant pendant groups was notably effective for this purpose. The subsequent chemospecific attachment of the isobutenyl fragment onto bromide **62** was achieved by palladium(0)-catalyzed coupling to a vinylstannane in a process that promises considerable versatility. Further chemical manipulation gave rise to the seco-pseudopterane **71**, thereby completing the intermediate stages of the total synthesis of the pseudopterane ring system.

Extensive investigation of marine invertebrates belonging to the genera *Alcyonacea*, *Lophogorgia*, and *Gorgonacea* by several research groups has led to the identification and characterization of a host of cembranoids, many of which possess potent biological activity. The biogenetic considerations underlying formation of these macrocycles have been reviewed,[2] as has synthetic activity in the area.[3] Among the many metabolites produced by these organisms is a small subgroup that possesses furano and butenolide structural segments in combination. Pseudopterolide (**1**), a representative furanocembranolide, is a potent cytotoxic agent that inhibits cell cleavage but not nuclear division,[4] giving an effect similar to that triggered by cytochalasin D. Pukalide (**2a**)[5] and epoxypukalide (**2b**)[6] are also characterized by the presence of one or two fused oxirane rings, an appreciable number of stereogenic centers, as well as carbomethoxy and isopropenyl appendages. However, the central ring is now 14-membered. The structurally related aldehyde known as lophotoxin (**3**) is recognized to be a particularly powerful neuromuscular toxin.[7] More highly oxygenated and nitrogen-containing analogues of these systems continue to be identified at a rapid pace.[8]

A 3-methyl group in the furan ring characterizes other less oxygenated analogues. Of these, kallolide A (**4a**), a potent antiinflammatory agent with efficacy equivalent to indomethacin,[9] shares with kallolide B (**4b**) an irregular pseudopterane carbon skeleton. Their formation presumably stems from the coupling of two geranyl units. Rubifolide (**5**)[10] and coralloidolide A (**6**),[11]

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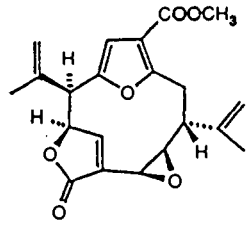
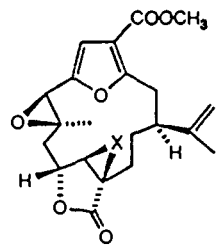
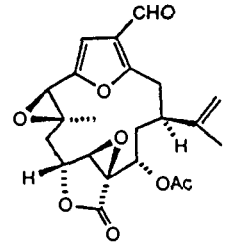


1



2a, X = unsaturation
b, X = O



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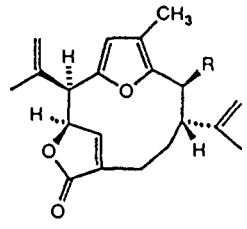
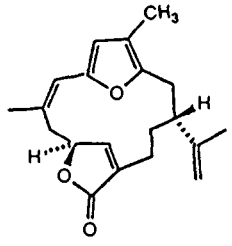


4a, R = OH
b, R = H



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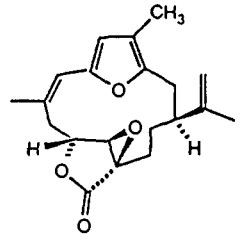


6

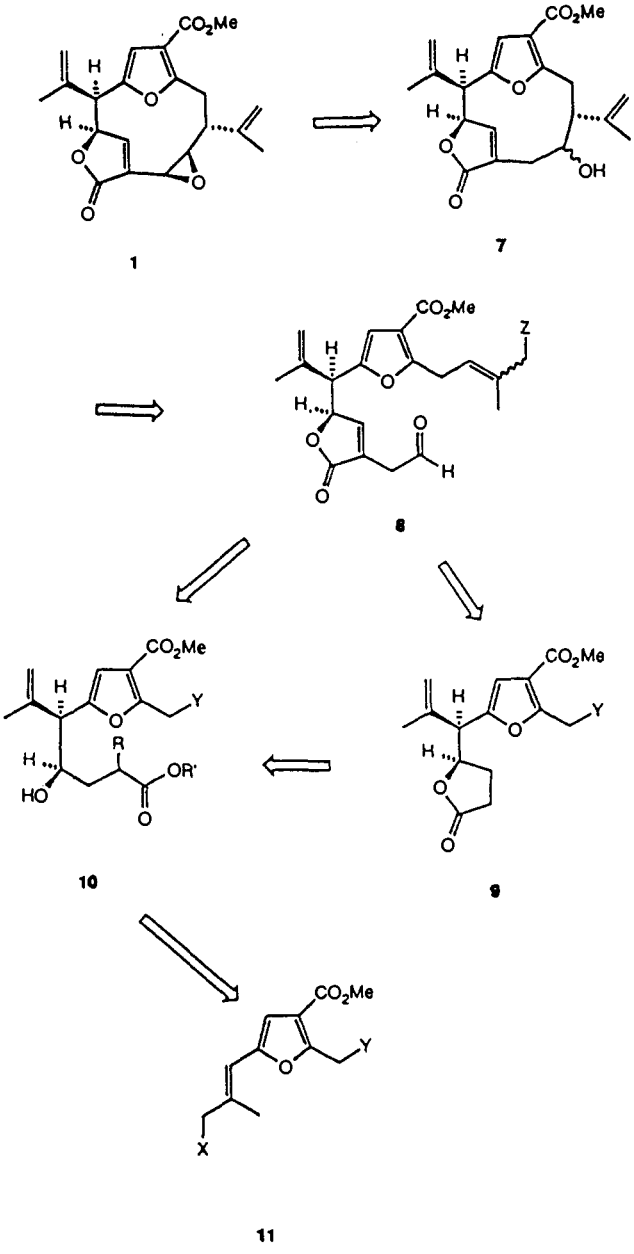
on the other hand, arise more plausibly by rearrangement of a cembrane precursor. That a structural similarity to **2** and **3** exists is of more than passing interest,[12] since **5** and **6** are metabolites of a temperate zone soft coral and gorgonian, respectively, while **2** and **3** are collected from coelenterates that grow in tropical reef environments.

Despite the biomedical potential of many of these targets, synthetic accomplishments in the area have been few and rather preliminary in nature.[13] Although these early developments foreshadow promising applications to the problem of eventual furanocembranolide total synthesis, major hurdles remain to be dealt with successfully. In this and the accompanying paper,[14a] we describe a fundamentally different approach to the preparation of the pseudopterane ring system.[14b] Specific attention is given herein to a strategy for the stereocontrolled conjoining of the furan and butenolide building blocks, both suitably functionalized for the eventual elaboration of pseudopteranes.

Results and Discussion

Strategy and Retrosynthetic Analysis. The general strategy we have opted to follow is presented in Scheme I. Butenolide **7** was

Scheme I



viewed as a key intermediate from which **1** could be derived by suitable dehydration and regiocontrolled epoxidation with steric approach control. Closure of the macrocyclic ring was to derive from deployment of one of several possible cyclization strategies involving **8** as substrate. This stage necessarily had to offer sufficient flexibility to allow for introduction of an activating group Z as needed. The size and complexity of **7** did not allow for confident a priori prediction of which ring-forming reaction might prove most adaptable to our needs.

Another obvious disconnection involves the side chain α to the lactone carbonyl in **8**. Past experience by others[15] suggested that condensation between the enolate anion of **9** and a suitable electrophilic species would be an effective avenue for the construction of **8**. On the other hand, a more convergent route, wherein the side chain is present when the butyrolactone ring is assembled, would bypass the need for generating a reactive intermediate at this stage.

Proceeding with the retrosynthetic analysis, we projected a key carbonyl condensation step involving **11** to set the appropriate

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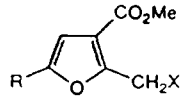
relative stereochemistry at the two vicinal centers in **10**. A desirable objective was attainment of maximum homogeneity at these sites. For reasons to be developed, equal attention was given to direct and indirect introduction of the β-hydroxyl group in **10**.

In the selection of starting materials, recognition of an expeditious means for elaborating trisubstituted furans of type **11** was to play a crucial role. A particularly significant structural feature in **11** was the presence of the 3-carbomethoxy group, which was expected to stabilize the furan ring to a substantial level against adventitious oxidation. Beyond that, rapid incorporation of the pair of side chains was paramount.

Furan Ring Assembly and Functionalization. Literature precedent suggested that arrival at a suitably functionalized furan was not apt to be realized efficiently by direct acylation methods. Kutney and co-workers had determined, for example, that acetylation of **12a** could only be achieved in low yield with acetic anhydride and phosphoric acid at 65 °C.[16] When the labile acetoxy group was lacking as in **12b**, Vilsmeier formylation could be realized in 40% yield only when reaction temperatures of 130 °C were employed.[17]

12a, X = OAc
b, X = H

13a, R = CH_3CO, X = OAc
b, R = HCO, X = H



14a, R = HCO
b, R = $HOCH_2$

In contrast, the condensation of glucose with methyl acetoacetate[18] followed by periodate oxidation[19] has been reported to give **14a** (69%). Substitution of glucose by 2,3-*O*-isopropylidene-D-glyceraldehyde (**15**)[20] and acidic hydrolysis of the resulting aldol product similarly has been recognized to produce **14b** in good yield.[21] The decision was therefore made to adapt this methodology to our needs. These expectations met with considerable success (Scheme II).

The reactivity of **16**[22] toward **15** is sufficiently high that **18** is produced in 60% yield following direct treatment of crude **17** with aqueous acetic acid. The best method for arrival at aldehyde **19** was that of Swern (90%).[23] Reaction of **19** with 2-propenylmagnesium bromide produced allylic alcohol **20**, whose exposure to thionyl chloride and pyridine in ether[24] at 0 °C gave the rearranged chloride **21** as a single isomer in 93% yield. The instability of this chloride dictated that it not be purified, but used directly. Rather unexpectedly, **21** isomerizes in part to **22** when stored in a freezer for several days. Distinction between the two

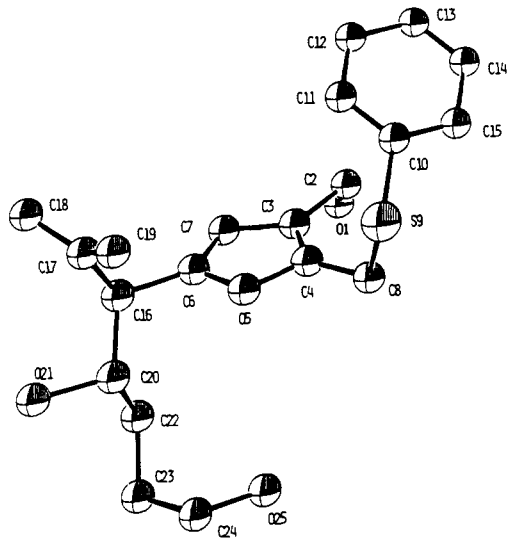


Figure 1. Computer-generated drawing of **30** derived from the X-ray coordinates, with hydrogens omitted for clarity.

Table I. Hydride Reductions of **29**

conditions	28:27	yield (%)
$NaBH_4$, MeOH, −20 °C	84:16	70
$Li(O^tBu)_3AlH$, THF, 0 °C	78:22	82
$NaAlH_2(OCH_2O(CH_2)_2OMe)_2$	78:22	75
$ZnBH_4$, Et_2O, 0 °C	55:45	90

stereoisomers could be easily accomplished by NOE studies. For example, irradiation of the vinyl methyl singlet in **21** induces a large integral enhancement of its furan proton signal. This effect is not seen in **22**. Unfortunately, **22** could not be obtained sufficiently free of **21** for indpendent evaluation of its reaction stereoselectivity.

With **20** readily available, acetate **23** was also prepared and transformed by the method of Trost[25a] into allylstannane **24** (64%). The 82:18 isomeric distribution was not expected to be of stereochemical consequence in subsequent condensation reactions.[26]

Condensation Reactions of 2-[(Phenylthio)methyl]-3-furancarboxylates. The $CrCl_2$-promoted coupling of **21** with methyl 3-formylpropionate[25b] in tetrahydrofuran was examined first. Standard conditions for this process afforded a mixture of the hydroxy esters **26**, the direct cyclization of which gave the chromatographically separable lactones **27** and **28** (15:85 ratio, 92% combined yield) (Scheme III). Temperature variations had no apparent effect on the product distribution. Application of the cyclic transition-state hypothesis[27] (see **25**) to the specific example at hand suggested that **28** should dominate. This conclusion was substantiated by lithium aluminum hydride reduction of **28** to the highly crystalline triol **30** and X-ray analysis of the latter (Figure 1).

It was reasoned that **29**, the oxidized form of **26**, may well be subject to stereocontrolled hydride reduction according to guidelines given by the Felkin–Anh model (see **A**).[28] Cram model considerations (see **B**)[29] predict the same result, although adoption

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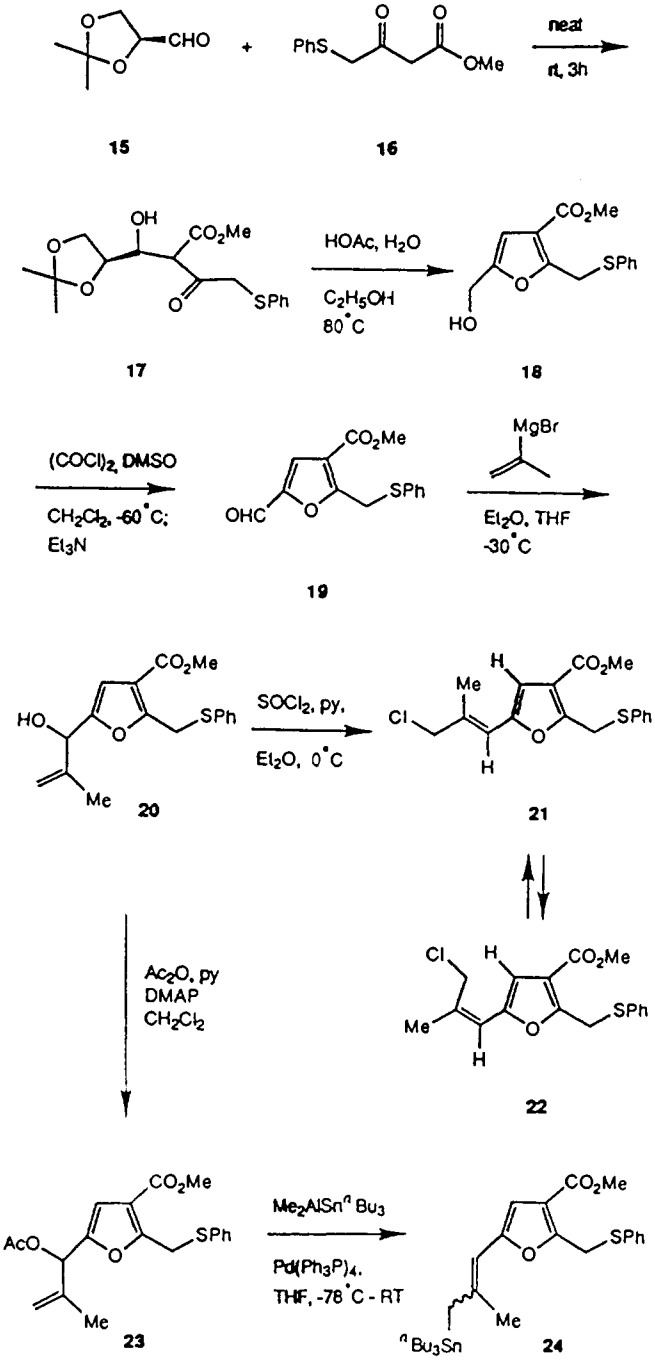
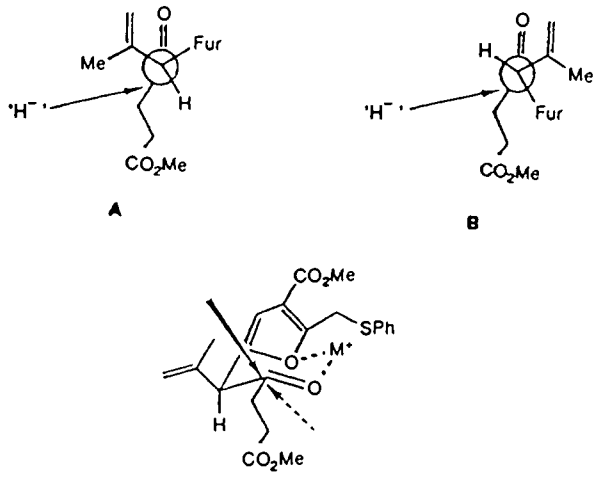
Scheme II



by the system of the indicated conformation would be sterically impeded. The chelation control model **C**[30] offers no clear-cut distinction regarding the preferred π-facial direction of hydride attack at the ketone carbonyl.

In actual fact, several reductions involving reagents of low coordinating ability performed on **29** furnished as the major hydroxy ester the same stereoisomer that was obtained in the Cr(II)-catalyzed process (Table I). Obviously, this ketone is too heavily functionalized to be assessed in terms of simple transition-state models.

Since the condensation leading to **26** was so efficient and easily scaled up, several attempts were made at inversion of its hydroxyl stereochemistry. However, the response of **26** to Mitsunobu conditions[31] ($C_6H_5CO_2H$, CF_3CO_2H, or HCO_2H) was to undergo



elimination with formation of **31**.[32] The mesylate derivative of **26** was likewise transformed into **31** when heated with such reagents as KO_2/18-crown-6, CsOAc/DMF, and KOH/CH_3OH. Regioselective hydrolysis of **26** to **32** proved entirely feasible, but Mitsunobu inversion on this intermediate gave **27**:**28** ratios that did not exceed 70:30.[32]

In view of our requirements for better control over the production of **27**, Lewis acid-catalyzed condensation of the (*Z*)- and (*E*)-allylstannanes **24** with methyl 3-formylpropionate was examined. The use of boron trifluoride etherate, when coupled with the usual acid-catalyzed lactonization, reproducibly delivered a 6:1 mixture of **27** and **28** in 67% yield (Scheme IV). Other catalysts were determined to be less effective, as observed in other contexts.[26] Since the preponderance of the desired erythro isomer was highest stemming from **24**, this approach was utilized to arrive at quantities of **27**.

Construction of an Appropriate C-2 Substituent. The success of the scenario just described prompted chemical modification of the C-2 substituent in a manner akin to that projected in our retrosynthetic scheme, viz., **9** → **8**. Furan **18** contains two differentially masked aldehyde functions. Since its CH_2OH group has already been shown to be adaptable to our needs (Schemes II–IV), proper homologation of the CH_2SPh substituent became the next item for consideration. Advantage was taken of the acidity of the α-thio protons in **33** during exposure to potassium hexamethyldisilazide in combination with *S*-phenyl benzenethiosulfonate[33] (Scheme V). These conditions made available the bissulfide **34** (89%). Subsequent conversion to aldehyde **35** was readily achieved by silver perchlorate-promoted hydrolysis in benzene/water mixtures.[34] In a move that was designed to provide the furanacetaldehyde **38**, **35** was condensed with ylide **36**. However, subsequent unmasking of the carbonyl group by hydrolysis of enol ether **37** was unsuccessful under an extensive array of conditions.

In order to realize an alternate satisfactory conversion to **41**, alcohol **39** was prepared and transformed into bromide **40a**[35] and chloride **40b**.[36] All of these steps were notably efficient (89–98%). The same trend was not followed during initial attempts to attach the remaining portion of the side chain to these halogenated intermediates. Condensation with the lower-order[37] and high-

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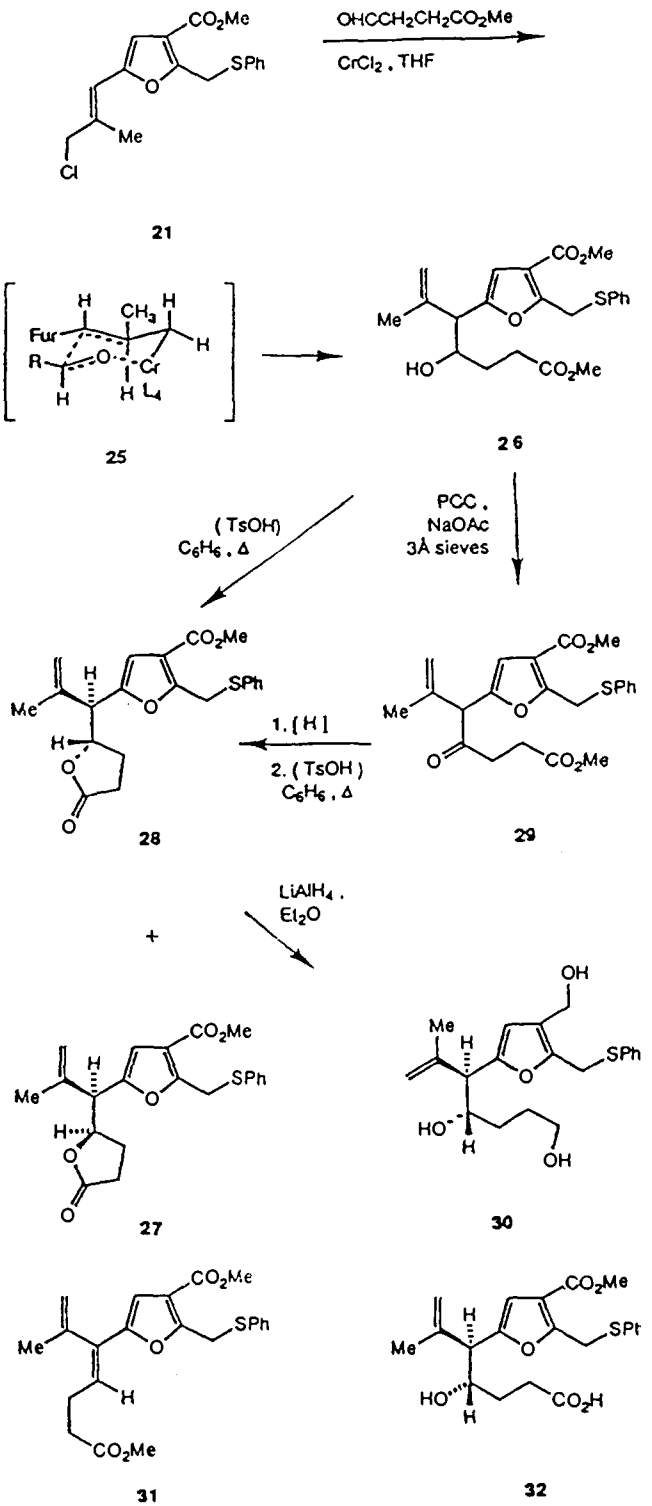
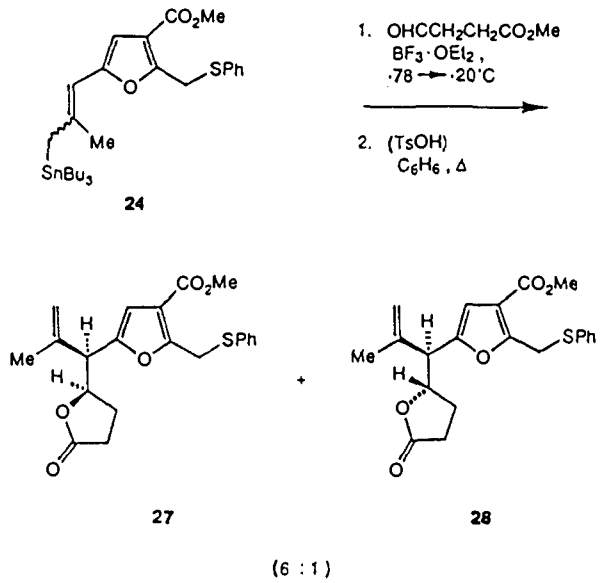
(33) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(34) Mukaiyama, T.; Kobayashi, S.; Kamio, K.; Takei, H. *Chem. Lett.* **1972**, 237.
(35) The alternate use of CBr_4 and Ph_3P [Joullie, M. M.; Chen, K.-M.; Semple, J. E. *J. Org. Chem.* **1985**, *50*, 3997; Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *Ibid.* **1977**, *42*, 353; Smith, A. B., III; Thompson, A. S. *Ibid.* **1984**, *49*, 1471] was less effective in providing **40a** (67%).
(36) (a) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339. (b) Yoshii, E.; Takeda, K.; Sato, M.-A. *Ibid.* **1986**, 3903.
(37) (a) Fried, J. H.; Untch, K. G.; Kluge, A. F. *J. Am. Chem. Soc.* **1972**, *94*, 7287. (b) Vig, O. P.; Chander, F.; Ram, B. *Ind. J. Chem.* **1974**, 1156.

Scheme III



er-order lithium cuprates[38] derived from 1-bromo-2-methyl-1-propene gave **41** (19–30%) admixed with dimer **42** (42–55%) as a consequence of induced radical formation. More favorable to our purposes, however, was the utilization of the vinylmagnesium bromide in the presence of Kochi's catalyst.[39] The yield of **41** was maximized at 64% when 10% of Li_2CuCl_4 was employed.[40]

Scheme IV



Although these model studies were reassuring, it remained to demonstrate the potential of this pathway on furanolactone **27**. As before, potassium hexamethyldisilazide proved to be the most efficient base for regioselective sulfenylation as in **43** (70%, Scheme VI). Unlike the parent example, however, this reaction could not be performed on gram quantities of material without incurring drastic reductions in yield. On the positive side, unmasking of the aldehyde and reduction to alcohol **44** were particularly efficient steps (92% overall) as long as the sodium borohydride reaction mixture was kept at −20 °C or below to deter opening of the lactone ring. The mesylate derived from **44** was very unstable and consequently was not isolated. Simple solvent removal and introduction of a cold (0 °C) solution of lithium bromide in tetrahydrofuran via cannula resulted in very rapid conversion to bromide **45**. The coupling reaction leading to **46** proceeded with variable efficiency until filtration of the Grignard solution before use was found to obviate this problem. Exercise of this precaution routinely delivered **46** in 55% yield.

Scheme VI demonstrates that an isopentenyl side chain can be evolved from a CH_2SPh substituent in the presence of a butyrolactone subunit. With successful attainment of this minimum objective, alkylation α to the lactone carbonyl as in **8** became the next focus of attention.

Lactone Alkylation Step. In preparation for attachment of the appropriately oxygenated side chain, **46** was transformed into its enolate with lithium diisopropylamide and allowed to react with methyl iodide. The yield of **47** based on modest recovery (8%) of unreacted **46** was 70% (Scheme VII). At this stage, the plan called for the utilization of electrophiles that carry two β-oxygen atoms, such that controlled hydrolysis would make available the acetaldehyde derivative and set the stage for possible Prins-type macrocyclization. However, $ICH_2CH(OC_2H_5)_2$ and related compounds proved totally unreactive despite generation of the anion resulting from deprotonation of **46** with a wide range of bases having different counterions and use of several solvent systems. The situation was improved somewhat when 2-(2-iodoethoxy)tetrahydropyran and 1-bromo-2-[(*tert*-butyldiphenylsilyl)oxy]ethane were employed. In both instances, the presence of HMPA as an additive was shown to be essential. The level of unreacted **46** recovered from these reactions was too high to permit their consideration as viable steps in the projected synthetic scheme. Thus, despite allowance for the retrieval of

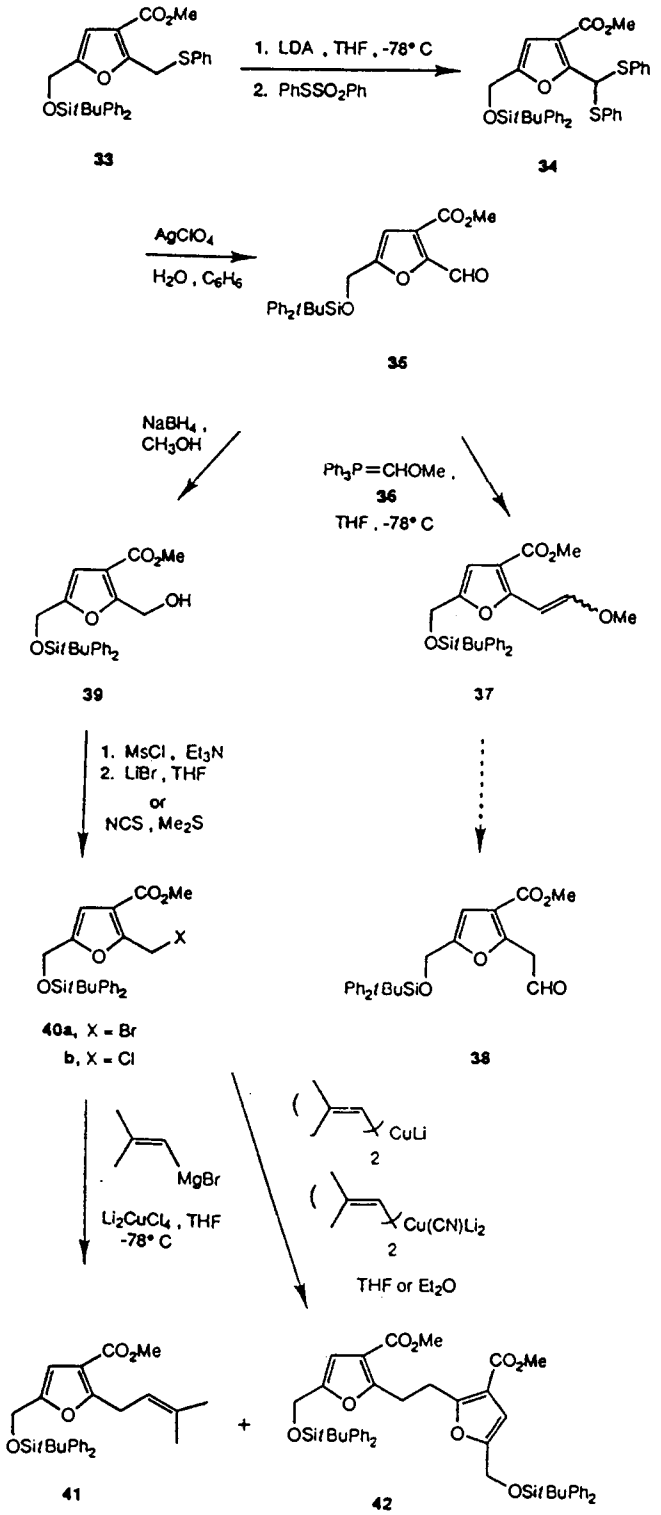
(38) Lipshutz, B. H.; Parker, D.; Kozlowski, J. A.; Miller, R. D. *J. Org. Chem.* **1983**, *48*, 3334. The yields of this reaction are drastically reduced in ether solvent [Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938].

(39) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

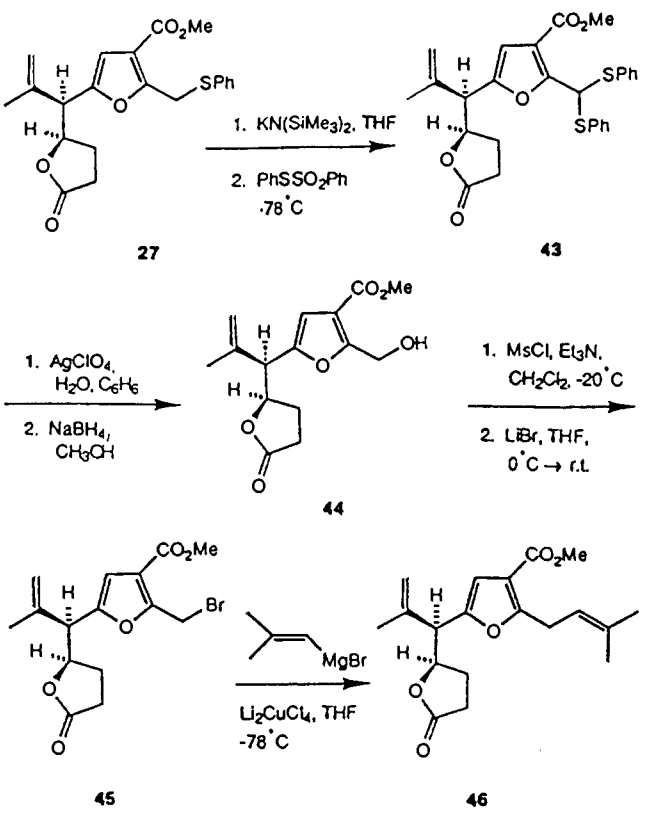
(40) (a) Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912. (b) Tanis, S. P. *Tetrahedron Lett.* **1982**, 3115.

(41) (a) Takeda, A.; Shinhama, K.; Tsuboi, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1903. (b) Kumazawa, S.; Nishihara, K.; Kato, T.; Kitahara, Y.; Komae, H.; Hayashi, N. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1530. (c) Gopichand, Y.; Prasad, R. S.; Chakravarti, K. K. *Tetrahedron Lett.* **1973**, 5177. (d) Fukamiya, N.; Yasuda, S. *Chem. Ind. (London)* **1979**, 126.

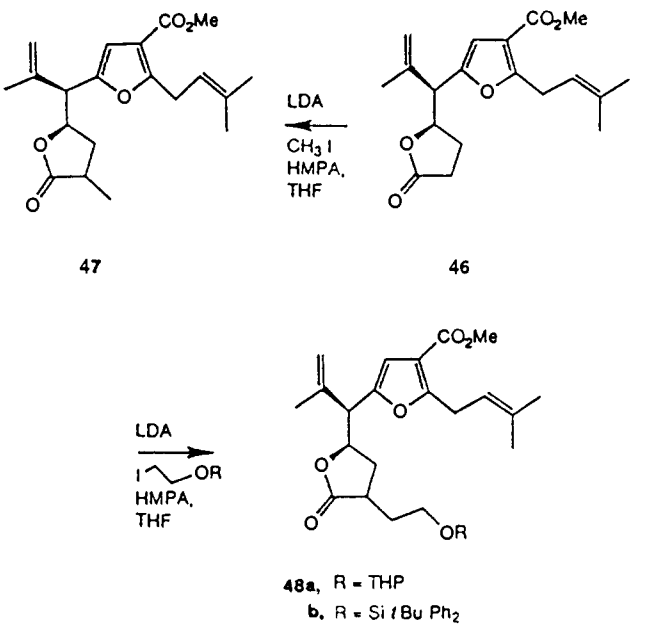
Scheme V



Scheme VI



Scheme VII



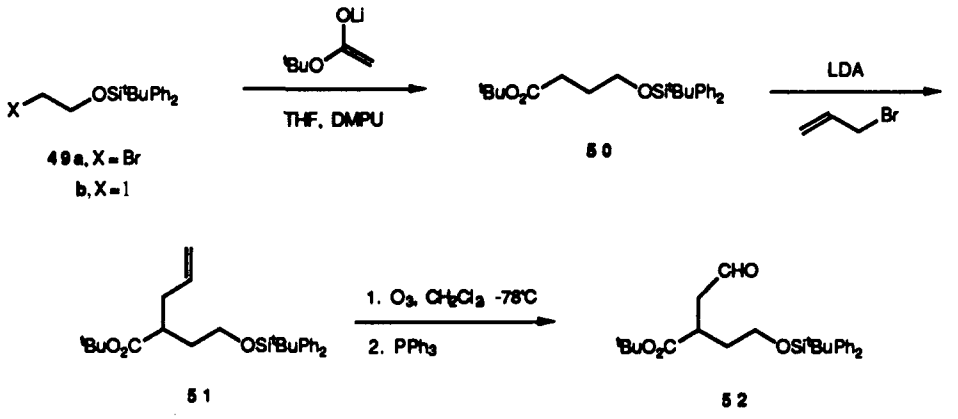
unchanged **46**, the yields of **48a** and **48b** were maximized at only 41 and 26%, respectively.

These findings signaled that incorporation of the requisite side chain might be more profitably accomplished concurrent with installation of the butyrolactone ring. The resultant increase in convergency would also prove desirable.

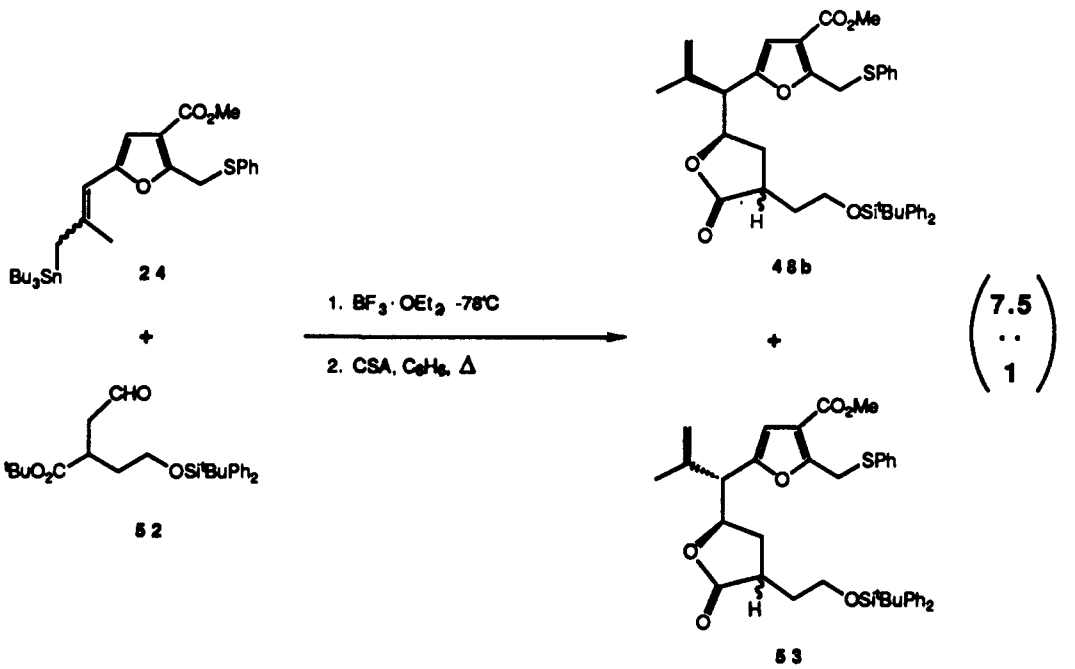
Convergent Construction of an Advanced Intermediate. The desired breakthrough materialized once aldehyde **52** became available (Scheme VIII). Following conversion of 2-bromoethanol to its silyl ether **49a**, the electrophilicity of the reagent was enhanced by conversion to iodide **49b**. The tetrahydropyranyl ether analogue of **49b** was also investigated and found to be less convenient in terms of its stability during ensuing reactions and, most importantly, less amenable to deblocking in the presence of sensitive functional groups.[32] Sequential alkylation of lithio *tert*-butyl acetate with **49b** and allyl bromide proceeded via **50** to deliver **51** efficiently. Ozonolysis of **51** under conditions where the ozonide was degraded by triphenylphosphine gave **52** in 90% yield.

Advantage was then taken of the fact that allylstannane **24** provided predominantly the erythro adduct upon boron trifluoride-catalyzed reaction with methyl 3-formylpropionate. Thus, **52** was condensed with **24** in the presence of this Lewis acid and subsequently heated with a catalytic quantity of 10-camphorsulfonic acid to effect lactonization. These conditions provided a 7.5:1 mixture of **48b** and **53** in 78% yield (Scheme IX). The major constituent (**48b**) was assigned the indicated stereochemistry chiefly on the basis of precedent and direct comparison of key

Scheme VIII



Scheme IX



portions of its ^1H NMR spectrum with those of the somewhat less substituted congeners produced earlier. The distribution of diastereomers **48b** and **53** was noted to be very similar to the trans/cis ratio present in the allyltin precursor. Although the stereochemistry of allylstannane/aldehyde condensations was reported to have little effect on the reaction diastereoselectivity,[26] the possibility that this might not be the case here led to attempts to prepare pure trans **24**. Unfortunately, this was not accomplished, and the issue remains unresolved. In our view, the stereochemical details surrounding this process require more exhaustive scrutiny.

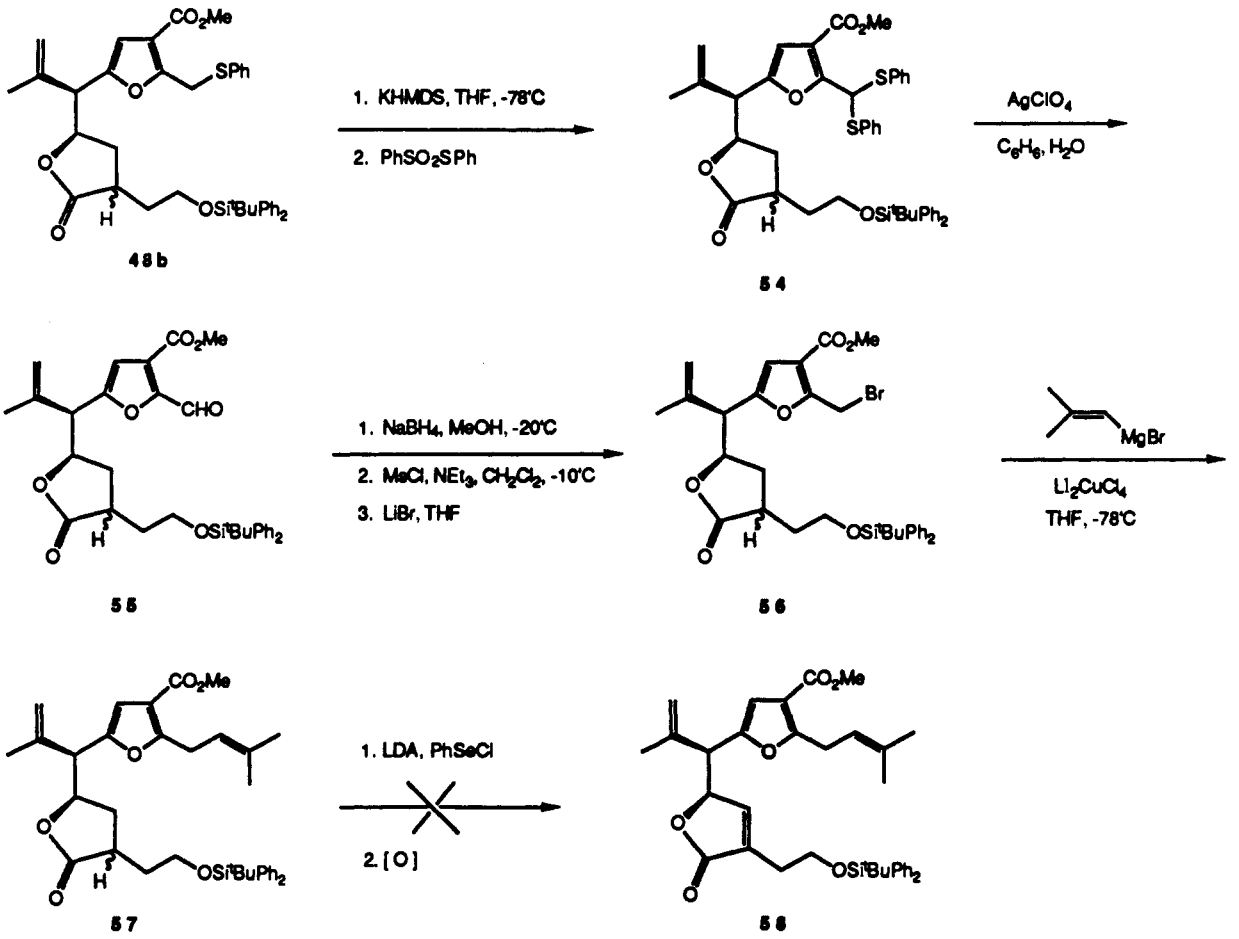
The additional stereogenic center in **48b** did not present a complication of any note, since the epimers invariably co-eluted at every stage. To simplify matters further, **48b** was also not separated from **53** in the expectation that the relative proportion of the minor constituent would diminish as the synthetic scheme was more deeply penetrated.

The isopentenyl side chain was next introduced as outlined in Scheme X. The regioselective deprotonation of **48b** and phenylthiolation of this anion to give **54** could be reproducibly accomplished in 70% yield. Furthermore, the presence of the (*tert*-butyldiphenylsiloxy)ethyl substituent now permitted the scale of the reaction to be substantially increased without affecting efficiency. Dissolution of **54** in a two-phase benzene/water mixture, followed by controlled portionwise addition of silver perchlorate, proceeded to give aldehyde **55**. This conversion was notably efficient (95%) as long as the silver salt was not used in large excess. The three-step conversion of **55** to bromide **56** also met with considerable success. Displacement of bromide ion in **56** by the isobutenyl Grignard reagent required the presence of Kochi's catalyst[39] to be effective. However, an excess of the copper reagent had to be avoided because of kinetically competitive dimerization to the 1,2-difuranylethane under these circumstances. By suppression of this process, **57** could be obtained in 40–50% yield.

The approach just outlined was obviously designed to introduce the butenolide double bond last so as to avoid potential complications stemming from conjugate addition of the isobutenylcuprate to the unsaturated lactone. Quite unexpectedly, however, the enolate anion of **57** could not be selenenylated since its isopentenyl double bond proved labile to these conditions. This turn of events necessitated that the sensitive butenolide subunit be introduced earlier in the synthesis. The following section describes such an approach, which ultimately provides a successful solution to the problem.

Concurrent Oxidation of Two Side Chains. Faced with the inability to transform **57** into **58**, an equally direct but alternative strategy for introduction of the butenolide double bond was designed (Scheme XI). Immediate recourse was made to generation of the dianion of **48b** in tetrahydrofuran with 2 equiv of potassium hexamethyldisilazide. To our delight, this reactive intermediate smoothly underwent 2-fold phenylselenenylation with formation of **59** (74%). Subsequent application of silver perchlorate technology[42] made possible the controlled hydrolysis of **59** to **60**. This

Scheme X



aldehyde was acquired efficiently (97%), thus allowing conversion to butenolide **61** through the agency of sodium metaperiodate.

Several features of the transformation of **48b** into **61** are worthy of comment. Although selenoacetals are well established synthetic intermediates,[43] little use is made of selenothioacetals in synthesis. A new stereogenic center is thereby generated in **59**, but this is of little consequence in view of the imminent hydrolysis. No information is available to advise us as to whether silver(I) ion exhibits a greater kinetic preference for attack at sulfur or selenium. Where abstraction of one or the other of these groups in an aqueous medium is concerned, the question is moot since arrival at either hemiacetal eventuates in generation of the carbonyl group. Ideal for our purposes was the fact that oxidative elimination of the phenylselenenyl substituent remaining in **60** could be expeditiously carried out (90%) to introduce a most crucial double bond.

Once **61** had been transformed into bromide **62** as before, we had arrived at that point where the isopentenyl side chain had to be introduced. As expected, the cuprate methodology that had been successful in Scheme X now resulted in rapid conjugate addition of the organometallic reagent to the butenolide subunit.[32] In order to circumvent this problem, we sought to prepare vinylstannane **63** for the purpose of effecting palladium(0)-catalyzed coupling[44] to **62**. When the Grignard reagent derived from 1-bromo-2-methylpropene[44a] gave only small amounts of impure **63** on reaction with trimethyltin chloride, recourse was made instead to the lithium reagent.[45] This modification provided the pure vinylstannane in acceptable yield.

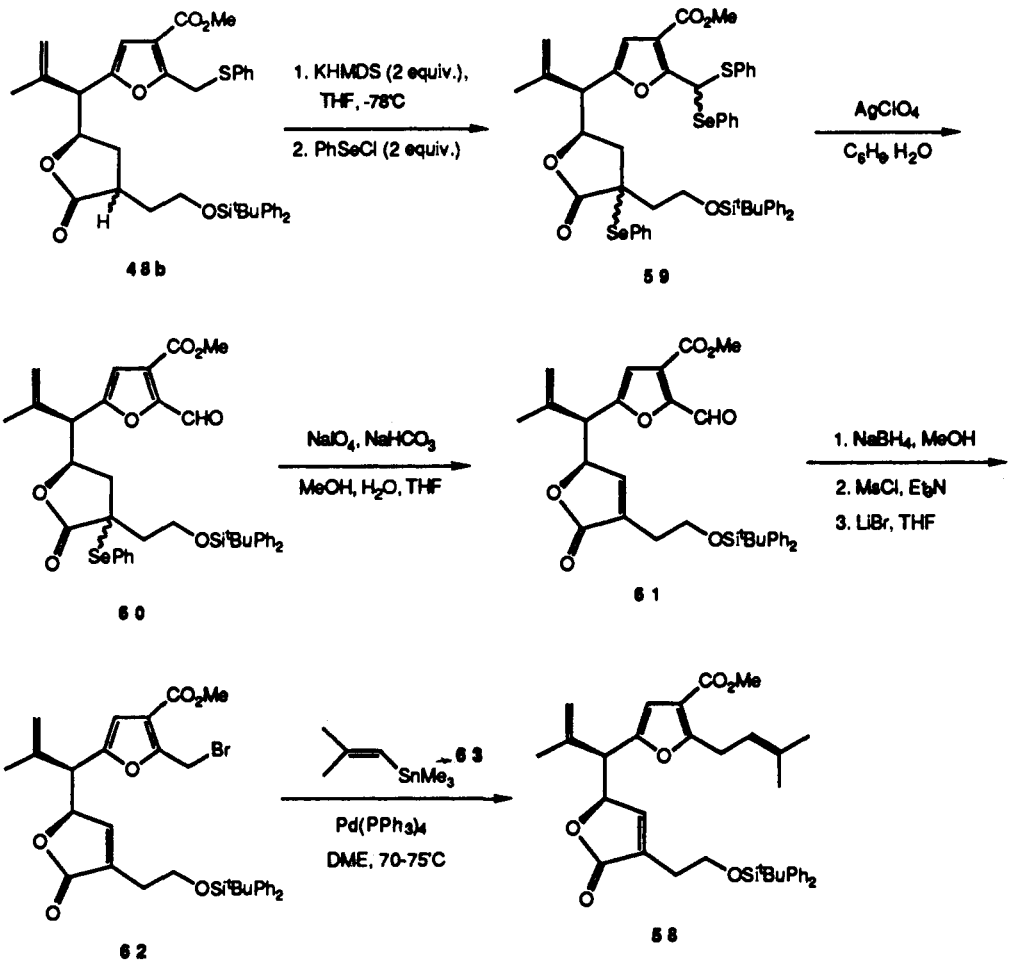
Dissolution of **62** and **63** in 1,2-dimethoxyethane,[46] treatment with a catalytic quantity of tetrakis(triphenylphosphine)palladium, and heating to 70–75 °C conveniently achieved the desired conversion to **58** in a very clean condensation reaction. The efficiency of this coupling scheme (75%) nicely set the stage for ultimate crafting of the targeted *seco*-pseudopterane.

Elaboration of the Acetaldehyde Unit. For purposes already discussed, it was desirable to remove the silyl residue in **58** while cleanly leaving behind the intact β-hydroxyethyl substituent. Initial experiments in this direction showed the deprotection step to be more problematical than anticipated. Use of benzyltrimethylammonium[48] or tetra-*n*-butylammonium fluorides[49] did indeed promote formation of *tert*-butyldiphenylsilyl fluoride. However, spectral analysis of the isolated product proved totally incongruent with those features expected for **64**. For instance, no hydroxyl group and no butenolide double bond were in evidence. Also, a third (ketonic) carbonyl group had obviously been generated. The composite data pointed convincingly to **67** as the end product of this unusually simple deprotection maneuver.

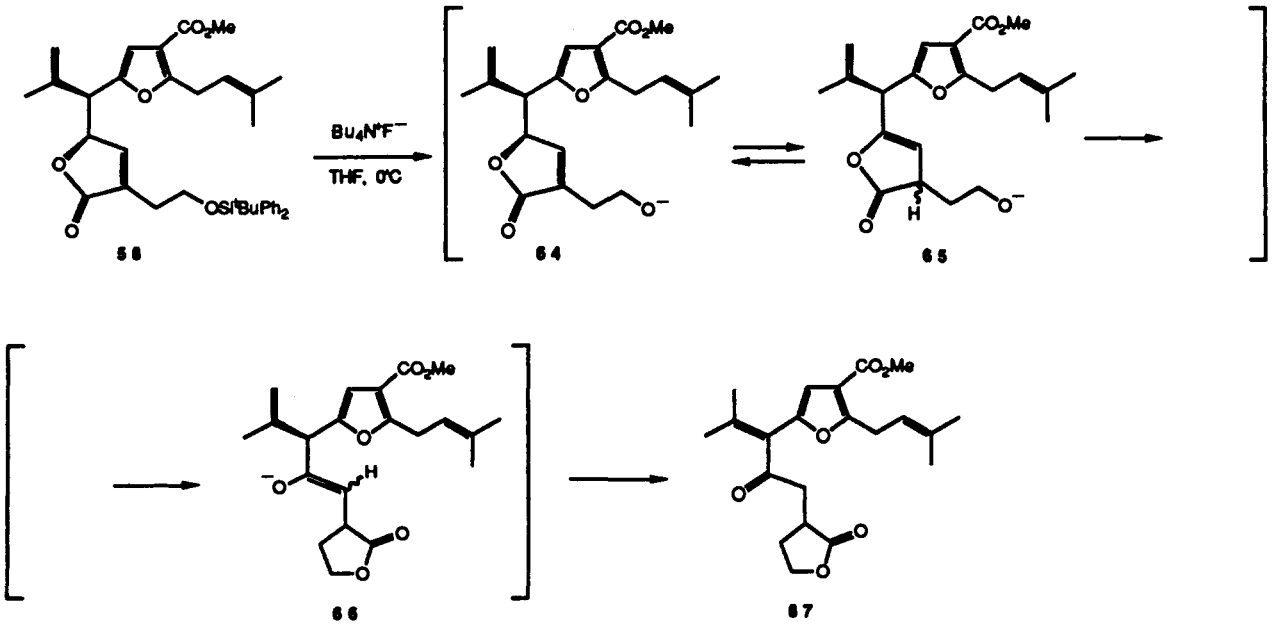
The formation of **67** may be rationalized in the manner summarized in Scheme XII. Butenolides are known to experience double bond migration under acidic conditions;[50] with an alcohol present, ring cleavage to an aldehyde ester usually operates. In

(42) Mukaiyama, T.; Kobayashi, S.; Kamio, K.; Takei, H. *Chem. Lett.* **1972**, 237.
(43) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986.
(44) (a) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (b) Milstein, D.; Stille, J. K. *Ibid.* **1979**, *101*, 4992. (c) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
(45) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1974**, 3365.
(46) In tetrahydrofuran as solvent, the conversion to **58** was notably inefficient (10–20%). The use of chloroform improved matters significantly (71%). Substitution of $PdCl_2(CH_3CN)_2$ as the catalyst.[44a,47] was found to give the desired product in low yield (12%).
(47) (a) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. (b) Crisp, G. T.; Scott, W. J.; Stille, J. K. *Ibid.* **1984**, *106*, 7500.
(48) (a) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025. (b) Paquette, L. A.; Blankenship, C.; Wells, G. J. *Ibid.* **1984**, *106*, 6442.
(49) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(50) Ducher, S.; Michet, A. *Bull. Soc. Chim. Fr.* **1969**, 1640. See also: Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625.

Scheme XI



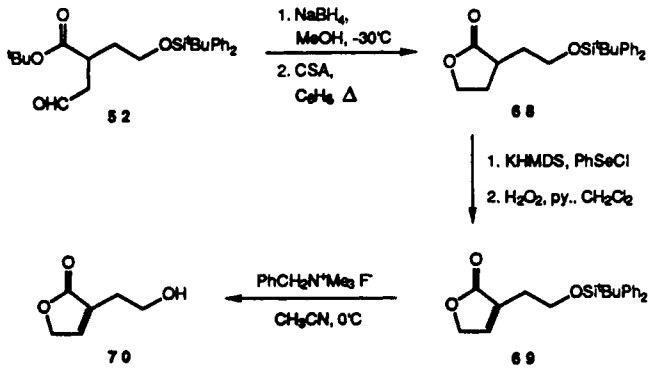
Scheme XII



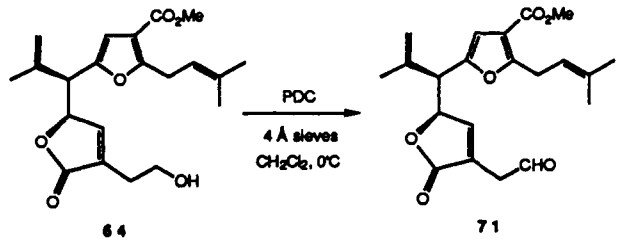
the present case, it appears that either basic quaternary ammonium fluoride reagent finds it possible to induce analogous isomerization to **65**. Once this event has occurred, translactonization must operate effectively to deliver the enolate of keto lactone **66**. Following proton transfer within this intermediate, the terminal double bond migrates into conjugation.

This complication prompted a more detailed scrutiny of the desilylation step in model system **69**, as prepared from **52** (Scheme XIII). We determined that cleavage of the O–Si bond using various fluoride ion sources was, in general, an ill-advised protocol. Curiously, the one exception was benzyltrimethylammonium fluoride in cold acetonitrile; this reagent gave rise to **70** in 92% yield. Adaptation of these conditions to **58** did furnish the desired **64**, but in low yield (ca. 10%) and admixed with a much greater amount of **67**. Variations in reaction temperature did not improve matters. Evidently, the reactivity of butenolides such as **58** and

Scheme XIII



Scheme XIV



69 is dictated to some considerable degree by the nature of their substitution. The serviceability of benzyltrimethylammonium fluoride may stem from its high crystallinity and resulting greater ease of purification from basic impurities and capacity for being dried.

Following definition of the deleterious consequences of alkaline deprotection methods on **58**, it was soon determined that acidic conditions could be employed with considerably greater success. Both Dowex resin in methanol[51] and hydrofluoric acid in aqueous acetonitrile[52] transformed **58** into **64**. The latter reaction proved to be an especially clean one. Chromatographic purification to remove the silicon-containing byproduct(s) was best achieved on silica gel, provided that the eluant consisted of petroleum ether admixed with 5–20% ethanol.

The oxidation of **64** to **71** (Scheme XIV) proved not to be trivial. To exmplify matters, complete resinification occurred under Swern conditions.[53] Many other reagent combinations were equally unsatisfactory. However, recourse to pyridinium dichromate[54] in dichloromethane containing 4-Å molecular sieves at 0 °C lent itself to providing the colorless oily aldehyde in satisfactory yield.

Overview. Efficient coupling of the functionalized building blocks **24** and **52** has been achieved. This crucial C–C bond formation was demonstrated to proceed with an 85% diastereoselectivity preference for the formation of furanobutyrolactone **48b**. Once this subtarget had yielded to synthesis, its conversion to **58** was achieved by means of a small number of chemoselective reactions that illustrated functional group manipulation in the context of densely substituted intermediates. It now appears that dual selenenylation of molecules typified by **48b** can serve as a powerful method for the controlled introduction of aldehyde groups and butenolide subunits. It should be placed high on the list of choices for such operations when applicable. The eventual acquisition of **71**, although quite successful, reemphasizes the subtle difficulties that can be encountered in this area of synthesis.

The *seco*-pseudopterane **71** has been produced in 14 steps from 2,3-*O*-isopropylidene-D-glyceraldehyde. This rather direct entry to a molecule of this level of complexity has implications far beyond the projected Prins-type ring closure.[14b] Since one cannot feel comfortable with any present state-of-the-art macrocyclization methodologies that involve the linkage of two carbon atoms in the presence of more highly oxidized centers, versatility is mandatory for the subtle control of chemical events. The palladium(0)-catalyzed condensation of bromide **62** with a vinylstannane such as **63** was projected to offer such advantages. The anticipated ready availability of structurally varied tin reagents related to **63** should make possible a venue adequate for achieving controlled ring closure with arrival at the pseudopterane nucleus. Studies directed toward the application of this strategy are described in the following article in this issue.[14a]

Experimental Section

Methyl 2-[(Phenylthio)methyl]-5-(hydroxymethyl)-3-furoate (18). A mixture of **16**[22] (43 g, 192 mmol) and **15**[20] (23 g, 174 mmol) was allowed to stand at room temperature for 18 h. The viscous oil thus obtained was dissolved in ethanol (150 mL), treated with a mixture of glacial acetic acid (100 mL) and water (80 mL), and heated at reflux for 6 h. After cooling and dilution with ether (1 L), the solution was washed with 10% sodium hydroxide solution (3 × 200 mL), water (2 × 200 mL), and brine (250 mL) prior to drying. Concentration under reduced pressure followed by chromatography on silica gel (elution with 20 → 50% ethyl acetate in petroleum ether) afforded **18** as a pale yellow oil (29 g, 60%): IR (neat, cm^{-1}) 3420, 2950, 1708, 1560, 1220, 1070, 770, 740, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.25 (m, 3 H), 6.50 (s, 1 H), 4.51 (s, 2 H), 4.40 (s, 2 H), 3.72 (s, 3 H), 1.98 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.4, 156.8, 153.4, 134.2, 131.5, 128.5, 127.0, 115.0, 108.0, 56.4, 51.2, 30.6; MS *m/z* (M^+) calcd 278.0613, obsd 278.0580. Anal. Calcd for $C_{14}H_{14}O_4S$: C, 60.42; H, 5.07; S, 11.52. Found: C, 60.06; H, 5.11; S, 11.25.

Methyl 2-[(Phenylthio)methyl]-5-formyl-3-furoate (19). A solution of oxalyl chloride (7.6 mL, 86.4 mmol) in dichloromethane (500 mL) was cooled to −60 °C, treated dropwise with dimethyl sulfoxide (12.8 mL, 180 mmol) in the same solvent (40 mL), and stirred at −60 °C for 10 min. A solution of **18** (20 g, 72 mmol) in dichloromethane (50 mL) was introduced dropwise, and stirring was maintained at −60 °C for an additional 15 min. Triethylamine (50 mL, 360 mmol) was introduced, and the reaction mixture was allowed to warm to room temperature over 45 min. Water (200 mL) and ether (1 L) were added, and the organic layer was separated and washed sequentially with saturated $NaHCO_3$ solution (2 × 200 mL), 5% $KHSO_4$ solution (250 mL), water (250 mL), and brine (250 mL) prior to drying. Concentration gave 18 g (90%) of **19** as a pale yellow oil after filtration through a pad of Florisil: IR (neat, cm^{-1}) 2960, 2850, 1725, 1685, 1595, 1265, 1235, 1080, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 7.41 (s, 1 H), 7.38 (m, 2 H), 7.28 (m, 3 H), 4.44 (s, 2 H), 3.75 (s, 3 H); MS *m/z* (M^+) calcd 276.0456, obsd 276.0448. This material was used without further purification.

Methyl 2-[(Phenylthio)methyl]-5-(1-hydroxy-2-methyl-2-propenyl)-3-furoate (20). A solution of 2-propenylmagnesium bromide in dry tetrahydrofuran (80 mL) was prepared from 5.6 mL (64 mmol) of 2-bromopropene and 1.56 g (64 mmol) of magnesium turnings (iodine initiation). To a solution of **19** (18 g, 65 mmol) in ether (200 mL) and tetrahydrofuran (200 mL) cooled to −30 °C was added the Grignard solution via cannula. After 30 min, the reaction mixture was quenched by dropwise addition of saturated NH_4Cl solution (20 mL) followed by warming to room temperature, at which point further dilution was made with ether (500 mL). The organic layer was decanted and the solids washed with ether (3 × 100 mL). The combined organic phases were washed with water (2 × 200 mL), dried, and concentrated. The residue was purified by silica gel chromatography (elution with 20% ethyl acetate in petroleum ether) to give **20** (15 g, 74%) as a colorless oil: IR (neat, cm^{-1}) 3460, 2960, 1720, 1610, 1575, 1075; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 2 H), 7.20 (m, 3 H), 6.42 (s, 1 H), 5.10 (s, 1 H), 4.97 (s, 1 H), 4.94 (s, 1 H), 4.33 (s, 2 H), 3.71 (s, 3 H), 2.04 (br s, 1 H), 1.62 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.5, 157.1, 154.2, 143.5, 134.4, 132.0, 128.7, 127.3, 115.1, 112.8, 107.7, 71.1, 51.4, 30.9, 18.4; MS *m/z* (M^+) calcd 318.0926, obsd 318.0936. Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70; S, 10.07. Found: C, 64.00, H, 5.95; S, 10.19.

Methyl 2-[(Phenylthio)methyl]-5-(3-chloro-2-methyl-1(*E*)-propenyl)-3-furoate (21). To a solution of **20** (208 mg, 0.65 mmol) in cold (0 °C) dry ether (3 mL) under argon was added redistilled pyridine (57 mg, 0.72 mmol) followed by thionyl chloride (77 mg, 0.65 mmol). After 5 min, the reaction mixture was diluted with ether (15 mL) and water (5 mL), and the aqueous layer was further extracted with ether (2 × 10 mL). The combined ethereal phases were washed with water (2 × 5 mL), dried, and concentrated. The yellow oil thus obtained was essentially pure (^1H NMR and TLC). Since it was found to be unstable to purification methods, simple repetitive azeotropic distillation with benzene (5 × 20 mL) was applied, and **21** was isolated as a pale yellow

(51) Corey, E. J.; Ponder, J. W.; Ulrich, T. *Tetrahedron Lett.* **1980**, *21*, 137.
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(53) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
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oil (205 mg, 93%): IR (neat, cm^{-1}) 2980, 1720, 1600, 1080; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.25 (m, 3 H), 6.53 (s, 1 H), 6.24 (s, 1 H), 4.42 (s, 2 H), 4.12 (s, 2 H), 3.73 (s, 3 H), 1.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.3, 156.6, 151.1, 134.7, 134.4, 131.7, 128.7, 127.2, 117.0, 116.0, 110.4, 52.0, 51.3, 30.9, 16.6; MS m/z (M^+) calcd 336.0587, obsd 336.0566.

On standing in the refrigerator for several days, **21** was found to equilibrate with its *Z* isomer. Although this stereoisomeric chloride (**22**) could not be obtained entirely free of **21**, its spectral properties were determined to be as follows: IR (neat, cm^{-1}) 2960, 2930, 1715, 1605, 1225, 1075; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2 H), 7.25 (m, 3 H), 6.40 (s, 1 H), 5.95 (s, 1 H), 4.42 (s, 2 H), 3.73 (s, 3 H), 3.61 (s, 2 H), 2.02 (s, 3 H); MS m/z (M^+) calcd 336.0587, obsd 336.0595.

Methyl 2-[(Phenylthio)methyl]-5-(1-acetoxy-2-methyl-2-propenyl)-3-furoate (23). A solution of **20** (15 g, 47.2 mmol) in dichloromethane (400 mL) was treated at room temperature with pyridine (5.8 mL, 70.8 mmol), acetic anhydride (5.3 mL, 56.6 mmol), and 4-(dimethylamino)-pyridine (490 mg, 4.0 mmol). After being stirred for 5 h, the reaction mixture was evaporated in vacuo, and the residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 14 g (82%) of **23**. The acetate was obtained as a colorless oil: IR (neat, cm^{-1}) 2960, 1745, 1720, 1655, 1620, 1220, 1075, 1025; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2 H), 7.25 (m, 3 H), 6.54 (s, 1 H), 6.09 (s, 1 H), 5.08 (s, 1 H), 5.02 (s, 1 H), 4.39 (m, 2 H), 3.72 (s, 3 H), 2.09 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.4, 163.3, 157.8, 150.6, 140.0, 134.5, 132.0, 128.7, 127.3, 115.2, 113.9, 109.8, 71.1, 51.4, 30.9, 20.9, 19.0; MS m/z (M^+) calcd 360.1032, obsd 360.1025. Anal. Calcd for $C_{19}H_{20}O_5S$: C, 63.32; H, 5.59. Found: C, 63.23; H, 5.63.

Methyl 2-[(Phenylthio)methyl]-5-[3-(tri-*n*-butylstannyl)-2-methyl-1-propenyl]-3-furoate (24). To a solution of hexabutylditin (14.4 g, 25 mmol) in cold (−20 °C) tetrahydrofuran (100 mL) was added *n*-butyllithium (16.6 mL of 1.5 M in hexanes, 25 mmol), and the mixture was stirred for 30 min before being cooled to −78 °C. Dimethylaluminum chloride (25 mL of 1.0 M in hexanes, 25 mmol) was introduced, and stirring was maintained for 1 h. At this point, a solution of tetrakis(triphenylphosphine)palladium(0) (1.0 g, 0.86 mmol) in tetrahydrofuran (40 mL) was added, followed by **23** (6 g, 16.6 mmol) dissolved in the same solvent (40 mL). The reaction mixture was allowed to warm to room temperature over 1 h, stirred at this temperature for 4 h, and cooled to 0 °C while 25 mL of 10% ammonium hydroxide solution was slowly added and dilution made with ether (300 mL). The reaction mixture was poured into hexane (500 mL), filtered through a pad of Celite, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 1 → 10% ethyl acetate in petroleum ether) to give stannane **24** (6.3 g, 64%) as a pale yellow oil (84:16 mixture of geometric isomers): IR (neat, cm^{-1}) 2960, 2925, 1720, 1625, 1600, 1220, 1075; ^1H NMR (300 MHz, C_6D_6) δ 7.40 (m, 2 H), 6.97 (m, 3 H), 6.48 (s, 1 H), 5.96 (s, 0.84 H), 5.76 (s, 0.16 H), 4.45 (s, 0.84 H), 4.38 (s, 1.16 H), 3.35 (s, 2 H), 3.33 (s, 1 H), 1.87 (s, 1 H), (s, 2 H), 1.65–0.70 (series of m, 29 H); MS m/z ($M^+ - Bu_3SnC_4H_6$) calcd 247.0423, obsd 247.0480.

Chromium(II) Chloride-Promoted Coupling of 21 to Methyl 3-Formylpropionate. To a cold (0 °C) suspension of chromium(II) chloride (Aldrich, 497 mg, 3.56 mmol) in dry tetrahydrofuran (9 mL) under argon was added methyl 3-formylpropionate[25b] (207 mg, 1.78 mmol) followed by **21** (600 mg, 1.78 mmol) dissolved in tetrahydrofuran (6 mL). The reaction mixture was stirred at room temperature for 15 h and then diluted with water (15 mL) and ethyl acetate (60 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the combined organic phases were washed with water (20 mL), dried, and evaporated. The residue was chromatographed on silica gel (elution with 5 → 30% ethyl acetate in petroleum ether) to afford recovered **21** (128 mg, 21%) and an inseparable mixture of hydroxy ester **26** and lactones **27**/**28** (ca. 4:1), each as an 85:15 mixture of diastereomers (350 mg, 60% based on recovered starting material).

The spectral properties of the hydroxy ester **26** are as follows: IR (neat, cm^{-1}) 3500, 2950, 1775, 1715, 1610, 1565, 1075, 785, 750, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.24 (m, 3 H), 6.40 (s, 0.15 H), 6.35 (s, 0.85 H), 5.00 (s, 1 H), 4.96 (s, 1 H), 4.40 (s, 2 H), 3.94 (m, 1 H), 3.72 (s, 3 H), 3.68 (s, 0.45 H), 3.66 (s, 2.55 H), 3.28 (d, J = 9 Hz, 1 H), 2.56–2.34 (m, 2 H), 2.20 (d, J = 3 Hz, 1 H), 1.70 (s, 3 H), 1.69 (m, 2 H).

A sample of this mixture (149 mg, 0.47 mmol) in benzene (50 mL) containing a catalytic quantity of 10-camphorsulfonic acid was heated at reflux under a Dean–Stark trap for 2 h. The cooled solution was concentrated to ca. 5 mL, diluted with ether acetate (15 mL), and filtered through a small pad of silica gel. Concentration of the eluate followed by column chromatography (silica gel, elution with 50 → 100% ether in petroleum ether) afforded **28**/**27** as an 85:15 colorless, oily mixture of diastereomers (140 mg, 98%).

For **28**: IR (neat, cm^{-1}) 2960, 1780, 1715, 1650, 1610, 1070, 750, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.24 (m, 3 H), 6.44 (s, 1 H), 4.96 (br s, 1 H), 4.95 (s, 1 H), 4.79 (dd, J = 14.8, 8 Hz, 1 H), 4.40 (d, J = 14.8 Hz, 2 H), 3.72 (s, 3 H), 3.45 (d, J = 8 Hz, 1 H), 2.48 (m, 2 H), 2.30 (m, 1 H), 1.97 (m, 1 H), 1.63 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 176.3, 163.4, 156.6, 151.9, 140.6, 134.4, 131.7, 128.6, 127.0, 115.4, 115.2, 108.3, 79.1, 51.6, 30.5, 28.2, 26.2, 20.7; MS m/z (M^+) calcd 386.1188, obsd 386.1159. Anal. Calcd for $C_{21}H_{22}O_5S$: C, 65.27; H, 5.74. Found: C, 65.02; H, 5.87.

Oxidation of 26. To a cold (0 °C), magnetically stirred mixture of pyridinium chlorochromate (232 mg, 1.08 mmol), fused sodium acetate (13 mg), powdered 3-Å molecular sieves (270 mg), and dry dichloromethane (10 mL) was added the diastereomeric mixture of hydroxy esters **26** (208 mg, 0.54 mmol) in the same solvent (5 mL). After 5 min, the reaction mixture was allowed to warm to room temperature and was stirred there for 1.5 h. Dilution with ether (50 mL), filtration through a small pad of Florisil, and solvent evaporation were followed by silica gel chromatography of the residue. Elution with 40% ether in petroleum ether furnished 97 mg (47%) of **29** as a pale yellow oil: IR (neat, cm^{-1}) 2850, 1720, 1610, 1565, 1075; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2 H), 7.22 (m, 3 H), 6.52 (s, 1 H), 5.08 (s, 1 H), 4.92 (s, 1 H), 4.50 (s, 1 H), 4.40 (s, 1 H), 4.39 (s, 1 H), 3.72 (s, 3 H), 3.68 (s, 3 H), 2.86 (dt, J = 18, 6 Hz, 1 H), 2.72 (dt, J = 18, 6 Hz, 1 H), 2.56 (t, J = 6 Hz, 2 H), 1.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 203.5, 172.8, 163.5, 157.1, 149.9, 139.8, 134.5, 131.8, 128.7, 127.2, 116.4, 115.5, 109.4, 59.2, 51.8, 51.4, 36.1, 30.8, 27.9, 21.3; MS m/z (M^+) calcd 416.1294, obsd 416.1342. Anal. Calcd for $C_{22}H_{24}O_6S$: C, 63.45; H, 5.81. Found: C, 63.38; H, 5.84.

Prototypical Reduction–Lactonization of 29. A cold (−20 °C), magnetically stirred solution of **29** (30 mg, 0.07 mmol) in dry methanol (5 mL) was treated with sodium borohydride (10 mg). After 5 min, the reaction mixture was allowed to warm to 0 °C, stirred for an additional 10 min, and quenched by dropwise addition of water (2 mL). Dilution with ether (15 mL) was followed by further extraction of the aqueous layer with more ether (3 × 10 mL). The combined organic phases were washed with water (10 mL), filtered through a small pad of Celite, and evaporated. The residue was taken up in dry benzene (5 mL), refluxed under a Dean–Stark trap in the presence of catalytic 10-camphorsulfonic acid for 2 h, and worked up in the predescribed manner. There was isolated 18 mg (64%) of an 84:16 mixture of **28** and **27** as a colorless oil. The results of additional experiments conducted in a similar manner are compiled in Table I.

Hydride Reduction of 28. A stirred slurry of lithium aluminum hydride (32 mg, 0.84 mmol) in dry ether (3 mL) was cooled to −20 °C and treated dropwise with lactone **28** (80 mg, 0.21 mmol) dissolved in ether (3 mL). The reaction mixture was allowed to warm to room temperature, stirred for an additional 30 min, and quenched at 0 °C with ethyl acetate. The usual workup followed by silica gel chromatography (elution with 8% isopropyl alcohol in dichloromethane) afforded **30** (60 mg, 80%) as a white solid, the crystals of which were grown from isopropyl alcohol at room temperature and suited to X-ray crystallographic analysis: IR ($CHCl_3$, cm^{-1}) 3360, 2920, 1015; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 2 H), 7.26 (m, 3 H), 6.02 (s, 1 H), 5.00 (m, 2 H), 4.19 (s, 2 H), 4.05 (s, 2 H), 4.01 (ddd, J = 7.5, 7.5, 0.8 Hz, 1 H), 3.65 (m, 2 H), 3.32 (d, J = 9.1 Hz, 1 H), 1.78 (s, 4 H), 1.75 (s, 3 H), 1.74–1.30 (m, 3 H); MS m/z ($M^+ - C_4H_7O_2$) calcd 275.1106, obsd 275.1141.

X-ray Crystallographic Analysis of 30. Small crystals of **30** ($C_{20}H_{26}O_4S$) marginally suitable for X-ray diffraction studies formed with space group symmetry $P2_1/c$ and cell constants of a = 16.646 (2) Å, b = 9.575 (2) Å, c = 12.593 (3) Å, and β = 92.61 (8)° for Z = 4 and a calculated density of 1.201 g/cm^3. Of the 2688 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 1124 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined using full-matrix least-squares techniques.[55] Hydrogen atoms were placed in calculated positions, assigned isotropic temperature factors corresponding to their attached atoms, but not refined. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.092. No abnormally short intermolecular contacts were noted. Tables II, III, and IV containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **30** from the final X-ray coordinates.

Lewis Acid-Catalyzed Condensation of 24 with Methyl 3-Formyl-

(55) The following library of crystallographic programs was used: MULTAN 80, P. Main, University of York, York, England, 1980; ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN, 1970; SDP Plus V1.1, I. Okaya and B. A. Frenz B. A. Frenz and Associates, College Station, TX, 1984.

propionate. To a solution of methyl 3-formylpropionate (90 mg, 0.78 mmol) in dry dichloromethane (10 mL) at −78 °C was added freshly distilled boron trifluoride etherate (0.16 mL, 1.26 mmol). Subsequently, **24** (371 mg, 0.63 mmol) dissolved in dichloromethane (5 mL) was introduced, and the mixture was allowed to warm to −20 °C before being quenched with water (5 mL) and dichloromethane (30 mL). The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with water, dried, and evaporated. The residual yellow oil was taken up in benzene (25 mL) and heated with a catalytic quantity of *p*-toluenesulfonic acid under a Dean–Stark trap for 2 h. After concentration and silica gel chromatography (elution with 10 → 60% ether in petroleum ether) to give a 7:1 mixture of **27** and **28** (163 mg, 67%). Rechromatography afforded pure **27** as a white solid, mp 76 °C: IR ($CHCl_3$, cm^{-1}) 2960, 1780, 1715, 1650, 1610, 1070, 750, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.26 (m, 3 H), 6.41 (s, 1 H), 4.99 (br s, 1 H), 4.93 (s, 1 H), 4.74 (dd, J = 15.0, 8.4 Hz, 1 H), 4.40 (d, J = 15.0 Hz, 2 H), 3.74 (s, 3 H), 3.45 (d, J = 8.4 Hz, 1 H), 2.45 (m, 2 H), 2.07 (m, 1 H), 1.88 (m, 1 H), 1.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 176.1, 163.0, 156.8, 151.3, 140.6, 134.1, 131.1, 128.4, 126.8, 114.8, 114.5, 108.2, 78.5, 51.1, 51.0, 30.0, 27.9, 26.0, 20.6; MS m/z (M^+) calcd 386.1188, obsd 386.1159. Anal. Calcd for $C_{21}H_{22}O_5S$: C, 65.27; H, 5.74. Found: C, 65.37; H, 6.00.

Methyl 2-[(Phenylthio)methyl]-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-furoate (33). To a solution of **18** (289 mg, 1.04 mmol) in dichloromethane (5 mL) was added triethylamine (0.17 mL, 1.25 mmol), *tert*-butyldiphenylchlorosilane (0.30 mL, 1.14 mmol), and a few crystals of 4-(dimethylamino)pyridine. The resulting mixture was stirred at room temperature for 2 h and then diluted with ether (50 mL) and water (10 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic phases were washed with water (10 mL), dried, and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with 10% ether in petroleum ether) provided **33** (498 mg, 93%) as a colorless oil: IR (neat, cm^{-1}) 2955, 2930, 2860, 1720, 1115, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.40 (m, 8 H), 7.25 (m, 3 H), 6.37 (s, 1 H), 4.56 (s, 2 H), 4.38 (s, 2 H), 3.71 (s, 3 H), 1.05 (s, 9 H); MS m/z ($M^+ - OCH_3$) calcd 485.1607, obsd 485.1623. Anal. Calcd for $C_{30}H_{32}O_4SSi$: C, 69.78; H, 6.25. Found: C, 69.40; H, 6.29.

Methyl 2-[Bis(phenylthio)methyl]-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-furoate (34). Cold (−5 °C) diisopropylamine (169 μL, 1.21 mmol) was treated dropwise with *n*-butyllithium (0.80 mL of 1.5 M in hexane, 1.21 mmol). After 5 min, dry tetrahydrofuran (4 mL) was added, and the resulting solution was stirred for 30 min at −5 → 0 °C before being cooled to −78 °C and treated dropwise with a solution of **33** (482 mg, 0.93 mmol) in the same solvent (8 mL). After 40 min, *S*-phenyl benzenethiosulfonate (233 mg, 0.93 mmol) in tetrahydrofuran (10 mL) was introduced rapidly in one portion. The reaction mixture was stirred at −78 °C for 30 min, quenched with water (10 mL), and diluted with ether (30 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic phases were washed with water (10 mL), dried, and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with 55 → 90% toluene in petroleum ether) afforded **34** (518 mg, 89%) as a colorless oil: IR (neat, cm^{-1}) 2940, 2860, 1715, 1210, 1115, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 4 H), 7.43 (m, 10 H), 7.24 (m, 6 H), 6.36 (s, 1 H), 6.32 (s, 1 H), 4.57 (s, 2 H), 3.65 (s, 3 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.2, 156.1, 154.1, 135.6, 133.5, 133.3, 133.1, 129.8, 128.8, 128.2, 127.8, 114.8, 107.5, 58.6, 51.3, 50.9, 26.8, 19.3; MS m/z ($M^+ - SC_6H_5$) calcd 515.1713, obsd 515.1700. Anal. Calcd for $C_{36}H_{36}O_4S_2Si$: C, 69.20; H, 5.81. Found: C, 69.52; H, 5.98.

Methyl 2-Formyl-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-furoate (35). A solution of **34** (101 mg, 0.16 mmol) in benzene (2 mL) and water (29 μL) was treated with silver perchlorate (67 mg, 0.32 mmol) in the absence of light. After 10 min, an additional 67 mg of silver perchlorate was added, followed 10 min later by 1 g of magnesium sulfate. The slurry was filtered through a small pad of neutral alumina (elution with 50% ethyl acetate in petroleum ether), and the eluate was concentrated under reduced pressure to leave a colorless oil. Flash chromatography of this material (silica gel, elution with 70% toluene in petroleum ether) afforded **35** (63 mg, 93%) as a colorless oil: IR (neat, cm^{-1}) 2950, 2930, 2860, 1725, 1685, 1235, 1115, 1070; ^1H NMR (300 MHz, C_6D_6) δ 10.18 (s, 1 H), 7.70 (m, 4 H), 7.23 (m, 6 H), 6.51 (s, 1 H), 4.35 (s, 2 H), 3.27 (s, 3 H), 1.10 (s, 9 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 365.0845, obsd 365.0827. Anal. Calcd for $C_{24}H_{26}O_5Si$: C, 68.22; H, 6.20. Found: C, 68.27; H, 6.41.

Wittig Reaction of 35. To a slurry of (methoxymethyl)triphenylphosphonium chloride (59 mg, 0.17 mmol) in tetrahydrofuran (1 mL) at −5 °C was added potassium hexamethyldisilazide (0.17 mL of 0.9 M in tetrahydrofuran) dropwise. The resulting orange-red solution was stirred at −5 to 0 °C for 20 min, cooled to −78 °C, and treated dropwise with **35** (61 mg, 0.14 mmol). The mixture was stirred at −78 °C for 30 min and then allowed to warm to −20 °C before being quenched with sodium sulfate decahydrate (250 mg). The slurry was filtered through a small column of neutral alumina, the eluate was evaporated, and the residue was purified by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether). The two isomeric enol ethers were thereby separated.

Less polar isomer: 40 mg (62%); IR (neat, cm^{-1}) 2930, 2860, 1710, 1638, 1235, 1215, 1115, 1065; ^1H NMR (300 MHz, C_6D_6) δ 7.75 (m, 4 H), 7.55 (m, 1 H), 7.20 (m, 5 H), 6.80 (m, 2 H), 6.60 (s, 1 H), 4.50 (s, 2 H), 3.45 (s, 3 H), 3.15 (s, 3 H), 1.15 (s, 9 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 393.1158, obsd 393.1165. More polar isomer: 12 mg (18%).

Methyl 2-(Hydroxymethyl)-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-furoate (39). To sodium borohydride (26 mg, 0.76 mmol) in anhydrous methanol (5 mL) at −20 °C was added **35** (240 mg, 0.58 mmol) dissolved in the same solvent (1 mL). The reaction mixture was warmed to 0 °C, stirred for 15 min, and quenched with water (0.5 mL). Following dilution with ethyl acetate (20 mL) and water (5 mL), the aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the combined organic phases were dried, concentrated, and filtered through a small pad of silica gel. Chromatography of the residue on silica gel (elution with 10 → 30% ethyl acetate in petroleum ether) afforded **39** (236 mg, 98%) as a colorless oil: IR (neat, cm^{-1}) 3380, 2960, 2940, 2860, 1720, 1265, 1115, 708; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.44 (m, 6 H), 6.42 (s, 1 H), 4.75 (s, 2 H), 4.60 (s, 2 H), 3.85 (s, 3 H), 1.06 (s, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 164.8, 160.5, 152.9, 135.5, 129.7, 127.6, 115.2, 108.0, 58.4, 57.7, 26.6, 19.1; MS m/z ($M^+ - OCH_3$) calcd 393.1522, obsd 393.1525. Anal. Calcd for $C_{24}H_{28}O_4Si$: C, 67.90; H, 6.65. Found: C, 67.73; H, 6.74.

Methyl 2-(Bromomethyl)-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-furoate (40a). To **39** (1.0 g, 2.36 mmol) in dry dichloromethane (20 mL) at −5 °C was added redistilled triethylamine (0.39 mL, 2.80 mmol) followed by methanesulfonyl chloride (0.20 mL, 2.58 mmol). The resulting solution was stirred at −5 °C for 30 min and then poured into a separatory funnel containing ice water (10 mL) and dichloromethane (50 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic solutions were dried and concentrated under reduced pressure to give the mesylate as a white solid: IR ($CHCl_3$, cm^{-1}) 2940, 1725, 1175, 1075; ^1H NMR (60 MHz, $CDCl_3$) δ 7.80–7.38 (m, 10 H), 6.55 (s, 1 H), 5.42 (s, 2 H), 4.68 (s, 2 H), 3.85 (s, 3 H), 2.98 (s, 3 H), 1.05 (s, 9 H). This material was dissolved in tetrahydrofuran (4 mL) and added dropwise to a solution of anhydrous lithium bromide (1.32 g, 15.3 mmol) in dry tetrahydrofuran at 5 °C. After an additional 3 min, the ice–water bath was removed, and the reaction mixture was stirred at room temperature for 25 min, at which point ether (60 mL) and water (15 mL) were introduced. The organic phase was washed with water (15 mL), the water layer was extracted with ether (2 × 30 mL), and the combined organic layers were dried and concentrated. Chromatography of the residue on silica gel (elution with 5% ether in petroleum ether) afforded **40a** (1.02 g, 89%) as a colorless oil: IR (neat, cm^{-1}) 2960, 2940, 2865, 1720, 1115, 1070, 705; ^1H NMR (300 MHz, C_6D_6) δ 7.74 (m, 4 H), 7.23 (m, 6 H), 6.40 (s, 1 H), 4.50 (s, 2 H), 4.40 (s, 2 H), 3.36 (s, 3 H), 1.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.0, 154.6, 154.5, 135.5, 132.9, 129.8, 127.7, 116.3, 108.5, 58.6, 51.6, 26.7, 21.2, 19.2; MS m/z ($M^+ - C_4H_9$) calcd 429.0158, obsd 429.0189. Anal. Calcd for $C_{24}H_{27}BrO_4Si$: C, 59.14; H, 5.58. Found: C, 58.83; H, 5.75.

Methyl 2-(Chloromethyl)-5-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-furoate (40b). To recrystallized *N*-chlorosuccinimide (25 mg, 0.19 mmol) in dry dichloromethane (1 mL) at 0 °C was added redistilled dimethyl sulfide (15.5 mL, 0.21 mmol). After this milky white suspension was cooled to −20 °C, a solution of **39** (73 mg, 0.17 mmol) in dichloromethane (1 mL) was slowly introduced via cannula. The reaction mixture was stirred at 0 °C for 3 h and then diluted with brine (3 mL) and ether (10 mL). The aqueous phase was extracted with ether (2 × 4 mL), and the combined organic solutions were washed with brine, dried, and concentrated under reduced pressure. Chromatography of the residue on silica gel (elution with 10 → 40% ether in petroleum ether) afforded **40b** (41 mg, 90% based on recovered alcohol) and unreacted **39** (29 mg, 40%).

For **40b**: colorless oil; IR (neat, cm^{-1}) 2960, 2935, 2860, 1725, 1115, 1080, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 4 H), 7.48 (m, 6 H), 6.45 (s, 1 H), 4.86 (s, 2 H), 4.63 (s, 2 H), 3.86 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 163.2, 154.6, 154.4, 135.6, 133.0, 129.8, 127.8, 116.6, 108.3, 58.6, 51.8, 35.6, 26.8, 19.3; MS m/z ($M^+ - OCH_3$) calcd 411.1183, obsd 411.1168. Anal. Calcd for $C_{24}H_{27}ClO_4Si$: C, 65.07; H, 6.14. Found: C, 65.38; H, 6.28.

Cuprate Coupling to 40a. The isobutenylmagnesium bromide was prepared by adding 1-bromo-2-methylpropene (0.92 mL, 10.0 mmol) to

magnesium turnings (0.24 g, 10.0 mmol) in tetrahydrofuran (5 mL) over 1 h with heating and iodine initiation.

To **40a** (218 mg, 0.45 mmol) in cold (−78 °C), dry tetrahydrofuran (8 mL) was added dilithium tetrachlorocuprate (23 μL of 1.0 M solution in tetrahydrofuran, 0.023 mmol) followed 5 min later by 0.27 mL of the Grignard solution (0.54 mmol) in one portion. The reaction mixture was stirred at −78 °C for 30 min and then diluted with ether (20 mL) and water (5 mL). The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic solutions were washed with 5% sodium bicarbonate solution (5 mL) and water (5 mL) prior to drying and concentration. Chromatography of the residue on silica gel (elution with 5 → 30% ethyl acetate in petroleum ether) afforded 116 mg (56%) of **41**, 12 mg (6%) of recovered **40a**, and 56 mg (15%) of dimer **42**.

For **41**: colorless oil; IR (neat cm^{-1}) 2940, 2865, 1720, 1625, 1115, 1070, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.75 (m, 4 H), 7.20 (m, 6 H), 6.53 (s, 1 H), 5.43 (m, 1 H), 4.46 (s, 2 H), 3.80 (d, J = 7.2 Hz, 2 H), 3.43 (s, 3 H), 1.63 (s, 3 H), 1.58 (s, 3 H), 1.13 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 164.2, 162.0, 135.5, 133.2, 129.6, 127.6, 118.5, 112.9, 108.0, 58.6, 51.1, 26.9, 26.7, 25.6, 19.2, 17.8; MS m/z ($M^+ - 1$) calcd 461.2148, obsd 461.2129. Anal. Calcd for $C_{28}H_{34}O_4Si$: C, 72.69; H, 7.41. Found: C, 72.56, H, 7.46.

For **42**: white solid, mp 135 °C; IR (KBr, cm^{-1}) 2940, 2865, 1720, 1115, 1070, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 8 H), 7.40 (m, 12 H), 6.39 (s, 2 H), 4.57 (s, 4 H), 3.78 (s, 6 H), 3.28 (s, 4 H), 1.05 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 164.1, 160.2, 152.4, 135.6, 133.2, 129.7, 127.7, 114.1, 108.2, 58.6, 51.2, 26.8, 26.2, 19.2; MS m/z (M^+) calcd 814.3390, obsd 814.3373.

Sulfenylation of 27. Lactone **27** (238 mg, 0.62 mmol) was dissolved in dry tetrahydrofuran (10 mL), cooled to −78 °C, and treated with potassium hexamethyldisilazide (1.30 mL of 0.5 M in toluene, 0.65 mmol). After 30 min of stirring, *S*-phenyl benzenethiosulfonate (162 mg, 0.65 mmol) in tetrahydrofuran (5 mL) was introduced in one portion. After an additional 15 min, water (1 mL) was added and the mixture was allowed to warm to room temperature. After dilution with ether and water, the aqueous layer was extracted with ether, and the combined organic phases were dried and concentrated. The residue was chromatographed on silica gel (elution with 10% ethyl acetate in toluene) to afford **43** (214 mg, 70%) as a colorless oil; IR (neat, cm^{-1}) 2960, 1780, 1715, 1610, 1565, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 4 H), 7.25 (m, 6 H), 6.38 (s, 1 H), 6.36 (s, 1 H), 5.01 (br s, 2 H), 4.83 (q, J = 9.5 Hz, 1 H), 3.65 (s, 3 H), 3.49 (d, J = 7.5 Hz, 1 H), 2.50 (m, 2 H), 2.34 (m, 1 H), 2.00 (m, 1 H), 1.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 176.3, 163.0, 155.7, 152.7, 140.6, 133.7, 133.4, 133.1, 132.9, 128.8, 128.8, 128.3, 128.1, 115.6, 108.1, 79.2, 51.6, 51.4, 50.5, 28.3, 26.2, 21.0; MS m/z ($M^+ - SC_6H_6$) calcd 385.1110, obsd 385.1118. Anal. Calcd for $C_{27}H_{26}O_5S_2$: C, 65.56; H, 5.30. Found: C, 65.87; H, 5.66.

Hydrolysis of 43. To a solution of **43** (106 mg, 0.21 mmol) in benzene (5 mL) and water (40 μL) was added silver perchlorate (89 mg, 0.42 mmol). After 10 min, anhydrous magnesium sulfate (0.5 g) was also added, and the slurry was filtered through neutral alumina (elution with 50% ethyl acetate in petroleum ether). The eluate was concentrated, and the resulting colorless oil was subjected to flash chromatography (silica gel, elution with 40% ethyl acetate in petroleum ether). The aldehyde was obtained as a white solid: mp 77 °C (61 mg, 97%); IR (neat, cm^{-1}) 2960, 1775, 1725, 1675, 1525, 1240, 1180, 1072; ^1H NMR (300 MHz, C_6D_6) δ 10.18 (s, 1 H), 6.54 (s, 1 H), 4.66 (t, J = 1.3 Hz, 1 H), 4.64 (s, 1 H), 4.09 (br q, 1 H), 3.27 (s, 3 H), 2.96 (d, J = 9 Hz, 1 H), 1.60 (m, 2 H), 1.50–1.10 (series of m, 2 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 178.3, 175.9, 161.9, 158.3, 151.6, 139.5, 127.2, 116.8, 110.7, 78.8, 52.4, 52.3, 28.2, 26.5, 20.9; MS m/z (M^+) calcd 292.0947, obsd 292.0969. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.82; H, 5.80.

Chemoselective Reduction of the Lactone Aldehyde. A cold (−20 °C), magnetically stirred solution of the preceding aldehyde (158 mg, 0.54 mmol) in methanol (5 mL) was treated with sodium borohydride (18 mg). After 5 min, water and dichloromethane were added. The aqueous layer was extracted with dichloromethane, and the combined organic phases were washed once with water, dried, and concentrated. Chromatography of the residue on silica gel (elution with 60% ethyl acetate in petroleum ether) afforded **44** (133 mg, 84%) as a colorless oil: IR (neat, cm^{-1}) 3460, 2960, 1775, 1715, 1610, 1565, 1230, 1180, 1085; ^1H NMR (300 MHz, C_6D_6) δ 6.51 (s, 1 H), 4.75 (s, 1 H), 4.74 (s, 2 H), 4.72 (s, 1 H), 4.22 (ddd, J = 8.2, 8.0, 6.8 Hz, 1 H), 3.65 (br s, 1 H), 3.40 (s, 3 H), 3.07 (d, J = 8.2 Hz, 1 H), 1.86 (m, 2 H), 1.41 (s, 3 H), 1.55–1.15 (series of m, 2 H); ^{13}C NMR (20 MHz, C_6D_6, ppm) 175.4, 164.6, 161.1, 152.6, 141.4, 115.8, 115.3, 108.7, 78.7, 57.1, 52.0, 51.3, 28.1, 26.2, 20.7; MS m/z (M^+) calcd 294.1103, obsd 294.1099.

Bromide 45. A solution of **44** (59 mg, 0.20 mmol) in dichloromethane (3 mL) was cooled to −10 °C and treated sequentially with triethylamine (33 μL, 0.24 mmol) and methanesulfonyl chloride (17 μL, 0.22 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 20 min. The dichloromethane was evaporated under a stream of argon, at which point an excess of anhydrous lithium bromide in tetrahydrofuran (2 mL) was added at 0 °C. After being warmed to room temperature, the reaction mixture was stirred for 30 min and then treated with ether (10 mL) and water (4 mL). The separated organic phase was washed with water (4 mL), and the aqueous layers were extracted with ether (2 × 10 mL). The dried organic solutions were concentrated to leave a residue that was purified by MPLC on silica gel (elution with 35% ethyl acetate in petroleum ether). There was isolated 62 mg (87%) of **45** as a colorless oil: (R (neat, cm^{-1} 2960, 1776, 1720, 1612, 1562, 1250, 1215, 1180, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1 H), 5.03 (s, 1 H, 5.02 (s, 1 H), 4.89 (q, J = 8.0 Hz, 1 H), 4.82 (d, J = 11.1 Hz, 1 H), 4.74 (d, J = 11.1 Hz, 1 H), 3.85 (s, 3 H), 3.53 (d, J = 8.1 Hz, 1 H), 2.45 (m, 2 H), 2.30 (m, 1 H), 1.98 (m, 1 H), 1.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 176.2, 163.1, 154.6, 153.4, 140.5, 116.6, 115.9, 109.1, 79.1, 52.0, 51.7, 28.2, 26.3, 21.3, 20.8; MS m/z (M^+) calcd 358.0239 and 356.0259, obsd 358.0276 and 356.0305. Anal. Calcd for $C_{15}H_{17}BrO_5$: C, 50.44; H, 4.80. Found: C, 50.98; H, 5.19.

Cuprate Coupling to 45. To a solution of bromide **45** (59 mg, 0.17 mmol) in cold (−78 °C), dry tetrahydrofuran (8 mL) was added Kochi's catalyst[39] (0.17 mL of 0.10 M in tetrahydrofuran, 0.017 mmol), and this mixture was stirred for 5 min before isobutenylmagnesium bromide (0.83 mL of 0.40 M in tetrahydrofuran, 0.33 mmol) was introduced in one portion. After 15 min, ether and ammonia buffer were added before warming to room temperature. The organic phase was washed with water prior to drying and concentration. The residue was chromatographed on silica gel (elution with 25–35% ethyl acetate in petroleum ether) to return 15.8 mg (27%) of unreacted **45** and 15.6 mg (43% based on recovered material) of **46** as a colorless oil: IR (neat, cm^{-1}) 2920, 1780, 1717, 1610, 1570, 1072; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1 H), 5.25 (m, 1 H), 4.99 (s, 2 H), 4.87 (m, 1 H), 3.80 (s, 3 H), 3.70 (m, 2 H), 3.49 (d, J = 7.7 Hz, 1 H), 2.65–1.78 (series of m, 4 H), 1.71 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 176.4, 164.2, 161.0, 150.6, 141.2, 134.3, 118.5, 115.3, 113.2, 108.3, 79.5, 51.7, 51.2, 28.2, 26.8, 26.2, 25.6, 20.9, 17.9; MS m/z (M^+) calcd 332.1624, obsd 332.1654.

Alkylation Reactions of 46. A. Methyl Iodide. To diisopropylamine (0.15 mL, 1.05 mmol) at −20 °C was added *n*-butyllithium (0.63 mL of 1.59 M in hexanes, 1.0 mmol), and the solution was stirred up to 0 °C for 25 min. The flask was cooled to 30 °C and 5 mL of dry tetrahydrofuran introduced.

A cold (−78 °C) solution of lactone **46** (13.7 mg, 0.041 mmol) in dry tetrahydrofuran (1 mL) was treated dropwise with 0.47 mL (0.094 mmol) of the lithium diisopropylamide solution. After 40 min, methyl iodide (15 μL, 0.24 mmol) and hexamethylphosphoramide (7 μL, 0.041 mmol) were added at the same time. The reaction mixture was stirred at −78 °C for 30 min before it was warmed to −20 °C and quenched with water (0.5 mL). After further dilution with ether (15 mL) and water (4 mL), the aqueous phase was extracted with ether (3 × 10 mL), and the combined organic solutions were washed with water (10 mL) prior to drying and concentration. Chromatography of the residue on silica gel (elution with 15–40% ethyl acetate in petroleum ether) gave **47** (9.1 mg, 70% based on recovered starting material) and 1.1 mg (8%) of unreacted **46**.

For **47**: colorless oil; IR (neat, cm^{-1}) 2970, 1780, 1717, 1610, 1570, 1075; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1 H), 5.25 (m, 1 H), 5.00 (br s, 2 H), 4.87 (m, 1 H), 3.80 (s, 3 H), 3.70 (m, 2 H), 3.46 (d, J = 7.7 Hz, 1 H), 2.49 (m, 1 H), 2.32 (m, 1 H), 2.02 (m, 1 H), 1.71 (s, 9 H), 1.26 (d, J = 7.1 Hz, 3 H); MS m/z (M^+) calcd 346.1806, obsd 346.1793.

B. 2-(2-Iodoethoxy)tetrahydropyran. The tetrahydropyranyl ether of 2-bromoethanol was prepared according to precedent.[56] Stirring this material with excess sodium iodide in acetone at room temperature as described below for 6 h provided the iodo compounds in 91% yield. A cold (−78 °C) solution of **46** (18 mg, 0.055 mmol) in dry tetrahydrofuran (2 mL) and hexamethylphosphoramide (0.2 mL) was treated with lithium diisopropylamide (0.29 mL of 0.55 M, 0.16 mmol) and stirred for 45 min. The iodide (37 mg, 0.16 mmol) was introduced and the reaction mixture was allowed to warm to room temperature over 30 min. After an additional 3 h, saturated sodium bicarbonate solution and ether were added, and the mixture was stirred rapidly for 15 min before the layers were separated. The organic phase was washed several times with water, dried, and concentrated. The residue was chromatographed on silica gel (elution with 20 → 35% ethyl acetate in petroleum ether) to give **48a** (9.6 mg, 41%) as a colorless oil: IR (neat, cm^{-1}) 2960, 2870, 1775, 1715, 1015; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (s, 1 H), 5.21 (br t, 1 H), 4.98 (m, 1 H), 4.88 (m, 1 H), 4.80–4.44 (m, 2 H), 3.79 (s, 3 H), 3.95–3.58 (m, 2 H), 3.48 (m, 2 H), 3.26 (m, 1 H), 2.83 (m, 0.5 H), 2.60–1.40

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(series of m, 12.5 H), 1.70 (s, 9 H); MS m/z ($M^+ - C_5H_8O$) calcd 376.1886, obsd 376.1927.

C. 1-Bromo-2-[(*tert*-butyldiphenylsilyl)oxy]ethane (49a). A solution of 2-bromoethanol (5.67 mL, 0.080 mol) in dichloromethane (250 mL) was treated with *tert*-butyldiphenylchlorosilane (21.8 mL, 0.084 mol), followed by 4-(dimethylamino)pyridine (1.96 g, 0.016 mol) in dichloromethane (11 mL), and finally triethylamine (14.2 mL, 0.088 mol). The resulting solution was stirred at room temperature for 24 h and treated with water (30 mL). The aqueous phase was extracted with dichloromethane, and the combined organic layers were washed once with water, dried, and concentrated. Silica gel chromatography of the residue (elution with 2.5% ethyl acetate in petroleum ether) afforded **49a** as a colorless oil which solidified when placed in a refrigerator (26.1 g, 90%): IR (film, cm^{-1}) 3080, 3020, 2970, 2940, 2895, 2870, 1475, 1465, 1430, 1190, 1120, 1030, 830, 705; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.70 (m, 4 H), 7.50–7.35 (m, 6 H), 3.97 (t, J = 6.5 Hz, 2 H), 3.46 (t, J = 6.5 Hz, 2 H), 1.13 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 135.6, 133.3, 129.8, 127.7, 64.0, 33.1, 26.8, 19.3; MS m/z ($M^+ - t$-Bu) calcd 304.9997, obsd 305.0033.

D. 1-Iodo-2-[(*tert*-butyldiphenylsilyl)oxy]ethane (49b). To anhydrous sodium iodide (20 g, 0.13 mol) in dry acetone (300 mL) under argon at room temperature was added a solution of **49a** (26.1 g, 0.072 mol) in acetone (50 mL). The resulting mixture was stirred at room temperature for 36 h, diluted with ether (1000 mL), and filtered through a pad of basic alumina. After solvent evaporation, the residue was chromatographed on the same absorbent (elution with 2.5% ethyl acetate in petroleum ether) to give **49b** as a viscous, colorless oil (28.3 g, 95%). This material solidified when placed in a refrigerator: IR (neat, cm^{-1}) 3080, 2965, 2945, 2865, 1125, 1085, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.41 (m, 6 H), 3.86 (t, J = 6.7 Hz, 2 H), 3.21 (t, J = 6.7 Hz, 2 H), 1.07 (s, 9 H); MS m/z ($M^+ - IC(CH_3)_3$) calcd 226.0814, obsd 226.0775. Anal. Calcd for $C_{18}H_{23}IOSi$: C, 52.68; H, 5.65. Found: C, 52.89; H, 5.82.

***tert*-Butyl 4-[(*tert*-Butyldiphenylsilyl)oxy]butyrate (50).** To a solution of *tert*-butyl acetate (4.87 g, 42.0 mmol) in tetrahydrofuran (50 mL) at −78 °C was added dropwise via cannula a freshly prepared solution of lithium diisopropylamide (46.2 mmol) in tetrahydrofuran (50 mL) precooled to −78 °C. After 45 min at −78 °C, a solution of **49b** (17.2 g, 42.0 mmol) in tetrahydrofuran (10 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone was added dropwise via cannula. Additional DMPU (40 mL) was introduced, and the reaction mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, stirred overnight (ca. 18 h), and poured into ether (200 mL) and water (200 mL). The aqueous phase was extracted with ether (2 × 200 mL), and the combined organic extracts were washed with brine (50 mL), dried, and concentrated in vacuo. The residue was purified by silica gel chromatography (elution with 3% ethyl acetate in petroleum ether) to give **50** (12.35 g, 74%) as a colorless oil: IR (neat, cm^{-1}) 3065, 2930, 2860, 1725, 1155, 1110, 705; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.36 (m, 6 H), 3.68 (t, J = 6.1 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 H), 1.84 (m, 2 H), 1.43 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 172.8, 135.5, 133.8, 129.5, 127.6, 79.9, 62.9, 32.0, 28.1, 28.0, 26.9, 19.2; MS m/z ($M^+ - OC(CH_3)_3$) calcd 325.1624, obsd 325.1592. Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.36; H, 8.62.

***tert*-Butyl 2-Allyl-4-[(*tert*-butyldiphenylsilyl)oxy]butyrate (51).** A cold (−78 °C), magnetically stirred solution of **50** (10.65 g, 0.027 mol) in anhydrous tetrahydrofuran (250 mL) was treated dropwise with a solution of lithium diisopropylamide in hexane/tetrahydrofuran (35.9 mL of 0.82 M, 29.4 mmol). After 45 min, freshly distilled allyl bromide (2.54 mL, 29.4 mmol) was added, and stirring was maintained for an additional hour before the reaction mixture was allowed to warm to 0 °C. Treatment with water (30 mL) and ether (150 mL) was followed by ether extraction (2 × 50 mL) of the aqueous layer. The combined organic phases were washed with water (50 mL), dried, and evaporated to leave a residue that was chromatographically purified (silica gel, elution with 2.5% ethyl acetate in petroleum ether). There was obtained 11.27 g (96%) of **51** as a colorless oil: IR (neat, cm^{-1}) 3070, 2962, 2925, 2860, 1725, 1642, 1155, 1115; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.40 (m, 6 H), 5.75 (m, 1 H), 5.05 (m, 2 H), 3.68 (t, J = 6.9 Hz, 2 H), 2.60 (m, 1 H), 2.30 (m, 2 H), 1.87 (m, 1 H), 1.74 (m, 1 H), 1.40 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 174.6, 135.6, 135.6, 135.5, 133.9, 133.9, 129.5, 129.5, 127.6, 127.6, 116.5, 80.1, 61.7, 42.3, 36.5, 34.5, 28.1, 26.9, 19.2; MS m/z ($M^+ - OC(CH_3)_3$) calcd 365.1955, obsd 365.1946. Anal. Calcd for $C_{27}H_{38}O_3S$: C, 73.93; H, 8.73. Found: C, 73.44; H, 8.65.

Ozonolysis of 51. A cold (−78 °C) solution of **51** (4.82 g, 13.2 mmol) in dichloromethane (250 mL) was ozonolyzed until the solution just became blue (ca. 10 min). After the solution was purged with oxygen for 10 min, triphenylphosphine (3.81 g, 14.5 mol) was introduced, and the reaction mixture was allowed to warm to room temperature where stirring was maintained for 5 h. Following solvent removal, the residue was filtered through a small pad of silica gel to remove triphenylphosphine oxide and finally purified by flash chromatography (silica gel, elution with 15% ethyl acetate in petroleum ether). There was isolated 4.36 g (90%) of **52** as a colorless, viscous oil: IR (neat, cm^{-1}) 3065, 2930, 2860, 2720, 1725, 1155, 1115, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1 H), 7.66 (m, 4 H), 7.36 (m, 6 H), 3.72 (m, 2 H), 3.03 (m, 1 H), 2.77 (dd, J = 9.0, 17.5 Hz, 1 H), 2.51 (dd, J = 17.5, 4.8 Hz, 1 H), 1.97 (m, 1 H), 1.69 (m, 1 H), 1.41 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 200.1, 173.6, 135.4, 133.5, 129.6, 127.6, 80.7, 61.4, 45.2, 37.0, 34.3, 27.9, 26.8, 19.1; MS m/z ($M^+ - OC(CH_3)_3$) calcd 367.1739, obsd 367.1734. Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23. Found: C, 70.65; H, 8.25.

Boron Trifluoride-Catalyzed Condensation of 52 with 24. To a solution of **52** (1.73 g, 3.93 mmol) in dry dichloromethane (40 mL) at −78 °C was added freshly distilled boron trifluoride etherate (0.95 mL, 7.86 mmol). Subsequently, **24** (2.32 g, 3.93 mmol) dissolved in the same solvent (10 mL) was introduced, and the mixture was stirred at −78 °C for 10 min before it was warmed to −40 °C and quenched with saturated sodium bicarbonate solution (5 mL). The two-phase system was stirred rapidly as room temperature was approached. The organic layer was washed with saturated sodium bicarbonate solution (2×) and water, dried, and evaporated. The residue was subjected to silica gel chromatography (elution with 10–20% ethyl acetate in petroleum ether). There was isolated 2.49 g (86%) of colorless, oily diastereomeric hydroxy esters: IR (neat, cm^{-1}) 3510, 3070, 2960, 2930, 2860, 1720, 1610, 1155, 1115, 1075, 743, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.82 (m, 4 H), 7.38 (m, 2 H), 7.20 (m, 6 H), 6.96 (m, 3 H), 6.54 (s, 0.5 H), 6.53 (s, 0.4 H), 6.51 (s, 0.1 H), 4.83 (m, 2 H), 4.29 (s, 2 H), 4.12 (m, 0.6 H), 3.97 (m, 0.4 H), 3.78 (m, 2 H), 3.35 (s, 1.8 H), 3.345 (s, 1.2 H), 3.25 (d, J = 9 Hz, 0.6 H), 3.20 (d, J = 9 Hz, 0.4 H), 3.10 (m, 0.6 H), 2.86 (m, 0.4 H), 2.14–1.20 (series of m, 5 H), 1.61 (s, 1.8 H), 1.52 (s, 1.2 H), 1.35 (s, 3 H), 1.34 (s, 6 H), 1.18 (s, 7 H), 1.17 (s, 2 H); MS m/z ($M^+ - HOC(CH_3)_3$-*t*-Bu) calcd 611.1893, obsd 611.1908. Anal. Calcd for $C_{43}H_{54}O_7SSi$: C, 69.51; H, 7.32. Found: C, 69.64; H, 7.52.

The hydroxy esters (2.40 g, 3.24 mmol) in benzene (100 mL) was azeotroped under Dean–Stark conditions for 1 h. Dry, recrystallized 10-camphorsulfonic acid (10 mg) was added after the mixture was cooled to room temperature, and heating was resumed for an additional 2 h. The benzene was removed under reduced pressure to leave a residue, which was chromatographed on silica gel (elution with 15% ethyl acetate in petroleum ether) to afford a white foam consisting of **48b** and **53** in a 7.5:1 ratio (1.95 g, 90%): IR (neat, cm^{-1}) 3070, 2950, 2860, 1775, 1715, 1610, 1565, 1225, 1120, 1110, 1070, 830, 785, 745, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.38 (m, 8 H), 7.23 (m, 3 H), 6.44 (s, 0.87 H), 6.38 (s, 0.13 H), 4.94 (m, 2 H), 4.80 (m, 0.65 H), 4.60 (m, 0.35 H), 4.39 (s, 1 H), 4.38 (s, 1 H), 3.90–3.63 (m, 2 H), 3.71 (s, 3 H), 3.42 (m, 1 H), 2.75 (m, 1 H), 2.40–1.87 (series of m, 3 H), 1.75–1.55 (m, 1 H), 1.61 (s, 1.6 H), 1.60 (s, 1.4 H), 1.05 (s, 9 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 611.1801, obsd 611.1805. Anal. Calcd for $C_{39}H_{44}O_6SSi$: C, 70.03; H, 6.63. Found: C, 69.69; H, 7.08.

Phenylsulfenylation of 48b. A cold (−78 °C), magnetically stirred solution of **48b** (140 mg, 0.21 mmol) in dry tetrahydrofuran (10 mL) was treated dropwise with potassium hexamethyldisilazide (0.64 mL of 0.5 M in toluene, 0.32 mmol). After 30 min, a solution of *S*-phenyl benzenethiosulfonate (53 mg, 0.21 mmol) in tetrahydrofuran (2 mL) was rapidly introduced, and the resulting mixture was stirred at −78 °C for 1 h. Water (5 mL) and ether (10 mL) were added. Following warming to room temperature, the aqueous phase was extracted with ether (2×), and the combined organic layers were washed once with water, dried, and evaporated. The residue was purified by silica gel chromatography (elution with 15% ethyl acetate in petroleum ether) to give **54** (110 mg, 68%) as an off-white foam; IR (neat, cm^{-1}) 2965, 2860, 1775, 1715, 1115, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.40 (m, 10 H), 7.24 (m, 6 H), 6.36 (s, 0.92 H), 6.35 (s, 0.9 H), 6.32 (s, 0.18 H), 4.98 (m, 2 H), 4.82 (m, 0.5 H), 4.62 (m, 0.5 H), 3.95 (m, 1 H), 3.90–3.15 (series of m, 2 H), 3.64 (s, 3 H), 2.80 (m, 1 H), 2.44 (m, 3 H), 1.80 (m, 1 H), 1.66 (s, 3 H), 1.06 (s, 4 H), 1.05 (s, 5 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 719.1919, obsd 719.1938. Anal. Calcd for $C_{45}H_{48}O_6S_2Si$: C, 69.55; H, 6.23. Found: C, 69.48; H, 6.60.

Silver Ion-Promoted Hydrolysis of 54. To a rapidly stirred mixture of **54** (201 mg, 0.26 mmol), benzene (10 mL), and water (0.1 mL) was added 270 mg (1.30 mmol) of silver perchlorate. After 5 min, hydrolysis was not complete (TLC analysis) so additional portions of the silver salt were introduced portionwise until no **54** remained. Following the addition of magnesium sulfate and ether, the mixture was filtered through a small pad of silica gel (ether as eluant) and evaporated. The residue was purified by chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) to give 141 mg (95%) of **55** as a white foam: IR (neat, cm^{-1}) 3070, 2950, 2930, 2860, 1775, 1725, 1675, 1600, 1245, 1175,

1115, 1075, 745, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.65 (m, 4 H), 7.43 (m, 6 H), 6.74 (s, 0.4 H), 6.73 (s, 0.4 H), 6.70 (s, 0.1 H), 6.69 (s, 0.1 H), 5.06 (m, 2 H), 4.94 (m, 0.5 H), 4.80 (m, 0.5 H), 4.15–3.50 (series of m, 3 H), 3.93 (s, 0.3 H), 3.92 (s, 2.7 H), 2.82 (m, 1 H), 2.48–2.05 (series of m, 2 H), 1.71 (s, 3 H), 1.75–1.50 (m, 2 H), 1.05 (s, 9 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 517.1665, obsd 517.1674. Anal. Calcd for $C_{33}H_{38}O_7Si$: C, 68.96; H, 6.66. Found: C, 69.21; H, 7.07.

Reduction of 55. To a solution of **55** (250 mg, 0.44 mmol) in dry methanol (20 mL) at −30 °C was added a slight excess of sodium borohydride. After 5 min, reduction was complete (TLC analysis). Ethyl acetate (1 mL) was introduced, and the mixture was allowed to warm to room temperature. Additional ethyl acetate and 0.1 M hydrochloric acid were added, and the mixture was stirred rapidly for 10 min. The product was extracted into ethyl acetate, and the combined organic phases were washed twice with water, dried, and evaporated. Purification by means of silica gel chromatography (elution with 50% ethyl acetate in petroleum ether) afforded the alcohol (230 mg, 92%) as a white foam: IR (neat, cm^{-1}) 3460, 2960, 2930, 2860, 1775, 1723, 1612, 1115, 1090, 710; ^{1}H NMR (300 MHz, C_6D_6) δ 7.73 (m, 4 H), 7.25 (m, 6 H), 6.94 (m, 1 H), 6.58 (s, 0.5 H), 6.57 (s, 0.5 H), 4.90–4.65 (m, 4 H), 4.44 (m, 0.5 H), 4.36 (br s, 0.5 H), 4.28 (m, 0.5 H), 4.10 (m, 0.5 H), 3.60 (m, 2 H), 3.38 (s, 1.6 H), 3.36 (s, 1.4 H), 3.13 (d, J = 8.7 Hz, 0.5 H), 3.12 (d, J = 8.3 Hz, 0.5 H), 2.45 (m, 1 H), 2.20 (m, 0.6 H), 2.00 (m, 0.6 H), 1.78 (m, 1 H), 1.44 (s, 1.5 H), 1.41 (s, 1.5 H), 1.50–1.20 (series of m, 0.8 H), 1.14 (s, 4 H), 1.13 (s, 4 H), 1.12 (s, 1 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 519.1841, obsd 519.1840. Anal. Calcd for $C_{33}H_{40}O_7Si$: C, 68.72; H, 6.99. Found: C, 68.39; H, 7.41.

Bromide 56. A cold (−10 °C), magnetically stirred solution of the above alcohol (198 mg, 0.34 mmol) in dichloromethane (15 mL) was treated with triethylamine (56 μL, 0.41 mmol), followed gy methanesulfonyl chloride (29.4 μL, 0.37 mmol). After 20 min, the dichloromethane was removed under a stream of argon, and a precooled (0 °C) solution of lithium bromide (excess) in tetrahydrofuran (5 mL) was added to the mesylate. Reaction was complete following warming to room temperature (TLC analysis). The reaction mixture was diluted with ether, filtered through a plug of silica gel, and evaporated. Column chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) afforded **56** as a colorless oil: IR (neat, cm^{-1}) 2960, 2930, 2860, 1775, 1722, 1115, 1075, 745, 708; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 4 H), 7.34 (m, 6 H), 6.54 (s, 0.87 H), 6.48 (s, 0.13 H), 4.95 (m, 2 H), 4.87–4.58 (m, 3 H), 3.86 (s, 0.4 H), 3.85 (s, 2.6 H), 3.72–3.58 (m, 2 H), 3.45 (m, 1 H), 2.68 (m, 1.6 H), 2.37–1.95 (series of m, 3.4 H), 1.70 (s, 1.6 H), 1.69 (s, 1.4 H), 1.06 (s, 4.2 H), 1.05 (s, 4.8 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 583.0980, obsd 583.0972. Anal. Calcd for $C_{33}H_{39}BrO_6Si$: C, 61.96; H, 6.15. Found: C, 62.01; H, 6.54.

Cuprate Coupling to 56. A cold (−78 °C), magnetically stirred solution of **56** (20 mg, 0.031 mmol) in dry tetrahydrofuran (3 mL) was treated with lithium tetrachlorocuprate (63 μL of 0.10 M in tetrahydrofuran, 0.0063 mmol) followed by (2-methylpropenyl)magnesium bromide (158 μL of 0.40 M in tetrahydrofuran, 0.063 mmol). After 5 min, an additional 63-μL portion of Li_2CuCl_4 and an additional 158 μL of the Grignard solution were added. Ten minutes later, ammonia buffer (1 mL) and ether (3 mL) were introduced, and the mixture was stirred rapidly while being warmed to room temperature. The aqueous phase was extracted with ether, and the combined organic layers were washed once with water, dried, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) provided **57** (7.6 mg, 40%) as a colorless oil: IR (neat, cm^{-1}) 2930, 2860, 1775, 1715, 1115, 1075, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.40 (m, 6 H), 6.45 (s, 0.92 H), 6.38 (s, 0.05 H), 6.36 (s, 0.03 H), 5.25 (br t, 0.8 H), 4.96 (m, 1.8 H), 4.86 (m, 0.8 H), 4.70 (m, 0.6 H), 3.79 (s, 3 H), 3.80–3.60 (m, 4 H), 3.45 (m, 1 H), 2.88–2.65 (m, 1.3 H), 2.45 (m, 3.7 H), 1.71 (s, 3.5 H), 1.70 (s, 3.5 H), 1.68 (s, 2 H), 1.05 (s, 4.5 H), 1.04 (s, 4.5 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 557.2343, obsd 557.2351.

2-Fold Selenenylation of 48b. To **48b** (4.2 g, 6.3 mmol) in tetrahydrofuran (150 mL) at −78 °C was added potassium hexamethyldisilazide (27.6 mL of 0.5 M in toluene, 13.8 mmol), and the resulting solution was stirred for 40 min before introduction of a solution of phenylselenyl chloride (2.6 mg, 13.8 mmol) in THF (50 mL). The reaction mixture was stirred at −78 °C for 1 h, quenched with water (25 mL), diluted with ether (500 mL), and warmed to room temperature. The separated aqueous phase was extracted with ether (2 × 50 mL), and the combined organic layers were washed once with water (250 mL), dried, and evaporated. Following column chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether), there was isolated 4.55 g (74%) of **59** as a pale yellow oil: IR (neat, cm^{-1}) 3070, 2960, 2930, 2860, 1765, 1715, 1180, 1115, 1070, 745, 710, 695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.15 (m, 25 H), 6.36 (s, 0.5 H), 6.35 (s, 0.5 H), 6.28 (s, 1 H), 4.90 (m, 2 H), 4.68 (m, 1 H), 4.05 (m, 1 H), 3.85 (m, 1 H), 3.64 (s, 0.6 H), 3.63 (s, 2.4 H), 3.39 (d, J = 9.1 Hz, 0.55 H), 3.38 (d, J = 9.1 Hz, 0.45 H), 2.41 (m, 2 H), 2.06 (m, 2 H), 1.58 (s, 1.2 H), 1.56 (s, 0.9 H), 1.54 (s, 0.9 H), 1.04 (s, 6.5 H), 1.03 (s, 1.5 H), 1.00 (s, 0.5 H), 0.99 (s, 0.5 H); MS, the molecular ion peak was observed, but was too transient for high-resolution measurement. Anal. Calcd for $C_{51}H_{52}O_6SSiSe_2$: C, 62.57; H, 5.35. Found: C, 62.97; H, 5.74.

Silver Ion-Promoted Hydrolysis of 59. To a solution of **59** (5.9 g, 6.0 mmol) in benzene (200 mL) and water (20 mL) was added silver perchlorate (5.0 g, 24 mmol) in small portions until the starting material was consumed (TLC analysis). Ether (200 mL) was added, and the mixture was filtered through a pad of Celite. The filtrate was washed with 10% ammonium hydroxide solution (2 × 100 mL), water (150 mL), and brine (150 mL) prior to drying. Solvent evaporation followed by flash chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) furnished **60** (4.2 g, 97%) as a colorless oil; IR (neat, cm^{-1}) 3070, 2930, 2860, 1765, 1725, 1680, 1245, 1180, 1115, 1075, 745, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 0.85 H), 10.14 (s, 0.15 H), 7.67 (m, 4 H), 7.58 (d, J = 5.5 Hz, 2 H), 7.41 (m, 6 H), 7.32 (m, 3 H), 6.67 (s, 0.85 H), 6.63 (s, 0.15 H), 4.95 (m, 2 H), 4.76 (m, 1 H), 4.05 (m, 1 H), 3.94 (s, 2.55 H), 3.93 (s, 0.45 H), 3.85 (m, 1 H), 3.50 (d, J = 9.8 Hz, 0.85 H), 3.45 (d, J = 9.8 Hz, 0.15 H), 2.45 (m, 2 H), 2.05 (m, 2 H), 1.62 (s, 3 H), 1.03 (s, 9 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 673.1227, obsd 673.1194. Anal. Calcd for $C_{39}H_{42}O_7SeSi$: C, 64.19; H, 5.80. Found: C, 64.22; H, 5.99.

Oxidative Elimination within 60. To a solution of **60** (1.85 g, 2.54 mmol) in methanol (120 mL) and tetrahydrofuran (10 mL) was added water (12 mL) followed by sodium bicarbonate (260 mg, 3.05 mmol) and sodium periodate (1.25 g, 5.84 mmol). The reaction mixture was stirred vigorously for 5 h, concentrated, and diluted with ether (200 mL) and water (50 mL). The aqueous phase was further extracted with ether (2 × 50 mL), and the combined organic solutions were washed with brine (2 × 50 mL), dried, and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, elution with 15 → 30% ethyl acetate in petroleum ether) to give 1.30 g (90%) of butenolide **61** as a colorless oil: IR (neat, cm^{-1}) 2960, 2930, 2860, 1765, 1725, 1680, 1590, 1115, 1075, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 0.14 H), 10.07 (s, 0.86 H), 7.57 (m, 4 H), 7.33 (m, 6 H), 7.16 (d, J = 2 Hz, 0.87 H), 7.06 (s, 0.13 H), 6.66 (s, 0.87 H), 6.64 (s, 0.13 H), 5.23 (dd, J = 8.5, 2.0 Hz, 1 H), 5.00 (s, 1 H), 4.98 (s, 1 H), 3.85 (s, 3 H), 3.78 (t, J = 6 Hz, 2 H), 3.60 (d, J = 8.5 Hz, 0.13 H), 3.46 (d, J = 8.5 Hz, 0.87 H), 2.44 (t, J = 6 Hz, 2 H), 1.70 (s, 0.4 H), 1.69 (s, 2.6 H), 0.96 (s, 7.8 H), 0.94 (s, 1.2 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 515.1556, obsd 515.1541.

Reduction of 61. Aldehyde **61** (3.4 g, 6.0 mmol) was reduced with sodium borohydride (380 mg, 10 mmol) in methanol (100 mL) at −20 °C in the manner described above. The resulting alcohol, purified by silica gel chromatography (elution with 30% ethyl acetate in petroleum ether), was obtained as a colorless oil (3.4 g, 99%): IR (neat, cm^{-1}) 3460, 2960, 2930, 2860, 1763, 1720, 1115, 1095, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.22 (d, J = 1.5 Hz, 0.87 H), 7.12 (s, 0.13 H), 6.95 (m, 6 H), 6.51 (s, 0.87 H), 6.48 (s, 0.13 H), 5.23 (dd, J = 8.4, 1.5 Hz, 1 H), 5.04 (s, 1 H), 5.00 (s, 1 H), 4.76 (s, 2 H), 3.81 (t, J = 6.0 Hz, 2 H), 3.80 (s, 3 H), 3.78 (br s, 1 H), 3.52 (d, J = 8.4 Hz, 0.13 H), 3.47 (d, J = 8.4 Hz, 0.87 H), 2.53 (t, J = 6.0 Hz, 2 H), 1.74 (s, 3 H), 1.04 (s, 7.8 H), 1.02 (s, 1.2 H); MS m/z ($M^+ - C(CH_3)_3$ calcd 517.1664, obsd 517.1673. Anal. Calcd for $C_{33}H_{38}O_7Si$: C, 68.96; H, 6.67. Found: C, 68.86; H, 6.82.

Bromide 62. To a solution of the above alcohol (157 mg, 0.274 mmol) in dichloromethane (5 mL) at −10 °C under nitrogen was added methanesulfonyl chloride (23 μL, 0.301 mmol) followed by triethylamine (46 μL, 0.328 mmol). After 25 min, the solvent was removed under a stream of nitrogen, and a solution of anhydrous lithium bromide (120 mg, 1.37 mmol) in tetrahydrofuran (5 mL) was introduced. The reaction mixture was allowed to warm to room temperature over 15 min, diluted with ether (20 mL), and filtered through a thin pad of silica gel. Evaporation of the filtrate followed by flash chromatography of the residue (silica gel, elution with 15% ethyl acetate in petroleum ether) gave **62** (174 mg, 100%) as a colorless oil: IR (neat, cm^{-1}) 2960, 2930, 2860, 1765, 1720, 1115, 1070, 710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 7.22 (s, 0.87 H), 7.12 (s, 0.13 H), 6.53 (s, 0.87 H), 6.49 (s, 0.13 H), 5.25 (dd, J = 1.5, 8.2 Hz, 1 H), 5.04 (s, 1 H), 5.01 (s, 1 H), 4.78 (d, J = 11 Hz, 1 H), 4.73 (d, J = 11 Hz, 1 H), 3.85 (s, 3 H), 3.85 (t, J = 6 Hz, 2 H), 3.50 (d, J = 8.1 Hz, 1 H), 2.52 (t, J = 6 Hz, 2 H), 1.78 (s, 0.39 H), 1.74 (s, 2.61 H), 1.04 (s, 7.8 H), 1.02 (s, 1.2 H); MS m/z ($M^+ - C(CH_3)_3$) calcd 581.0778, obsd 581.0798. Anal. Calcd for $C_{33}H_{37}O_6SiBr$: C, 62.14; H, 5.85. Found: C, 62.14; H, 6.12.

Palladium(0)-Catalyzed Coupling of 62 to 63. A solution of **62** (50 mg, 78 mmol) in 1,2-dimethoxyethane (4 mL) was added stannane **63**[44a] (34 mg, 156 μmol) followed by tetrakis(triphenylphosphine)palladium

(5 mg, 5 mol %). The reaction mixture was flushed with nitrogen and heated under reflux at 70–75 °C for 11 h. After cooling, the solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) to give **58** as a colorless oil (36 mg, 75%): IR (neat, cm^{-1}) 2970, 2940, 2870, 1760, 1715, 1575, 1450, 1440, 1430, 1210, 1120, 1080, 920, 830, 710; ^1H NMR (300 MHz, C_6D_6) δ 7.75–7.66 (m, 4 H), 7.32–7.16 (m, 6 H), 6.65 (d, J = 1.3 Hz, 1 H), 6.59 (s, 1 H), 5.41 (br t, J = 7.2 Hz, 1 H), 4.88–4.69 (m, 3 H), 3.79 (d, J = 7.4 Hz, 2 H), 3.74 (t, J = 6.3 Hz, 2 H), 3.46 (s, 3 H), 3.16 (d, J = 7.9 Hz, 1 H), 2.40 (t, J = 6.3 Hz, 2 H), 1.63 (s, 3 H), 1.58 (s, 3 H), 1.47 (s, 3 H), 1.12 (s, 9 H); MS m/z (M^+) calcd 612.2906, obsd 612.2912.

Treatment of 58 with Tetra-*n*-butylammonium Fluoride. To a cold (0 °C), magnetically stirred solution of **58** (24 mg, 0.039 mmol) in tetrahydrofuran (3 mL) at 0 °C was added a solution of tetra-*n*-butylammonium fluoride in the same solvent (43 μL of 1.0 M, 0.043 mmol). After 2.5 h, ether (20 mL) and water (5 mL) were introduced, and the separated aqueous layer was extracted with ether (2 × 20 mL). The combined organic phases were washed with brine (10 mL), dried, and concentrated in vacuo. The residue was purified by silica gel chromatography (elution with 10 → 40% ethyl acetate in petroleum ether) to give **67** as a colorless oil (7 mg, 48%): IR ($CHCl_3$, cm^{-1}) 2960, 2930, 1770, 1715, 1695, 1445, 1380, 1220, 1160, 1080, 1030; ^1H NMR (300 MHz, C_6D_6) δ 6.56 (s, 1 H), 5.41–5.37 (m, 1 H), 3.88–3.71 (m, 2 H), 3.60 (dt, J = 2.0, 9.0 Hz, 1 H), 3.48 (s, 3 H), 3.38–3.28 (m, 1 H), 2.90 (dd, J = 3.5, 18 Hz, 1 H), 2.68–2.53 (m, 1 H), 2.43–2.32 (m, 1 H), 1.82–1.65 (m, 2 H), 1.81 (s, 3 H), 1.61 (s, 3 H), 1.59 (s, 3 H), 1.51 (s, 3 H); MS m/z (M^+) calcd 374.1729, obsd 374.1708.

α-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]butyrolactone (68). A cold (−10 °C), magnetically stirred solution of **52** (1.00 g, 2.27 mmol) in anhydrous methanol (10 mL) was treated portionwise with sodium borohydride (90 mg, 2.38 mmol). After 10 min, ethyl acetate (50 mL) and 0.1 M hydrochloric acid (10 mL) were added, and the reaction mixture was stirred vigorously while it was warmed to room temperature over 10 min. Dilution with more ethyl acetate (50 mL) was followed by washing of the organic phase with water (30 mL) and reextraction of the combined aqueous layers with ethyl acetate (3 × 50 mL). The composite organic solution was washed with brine (20 mL), concentrated in vacuo, dissolved in benzene (100 mL), and reevaporated to remove residual water. More benzene (100 mL) and 10-camphorsulfonic acid (100 mg) were next added, and this solution was heated under a Dean–Stark trap for 1 h. After cooling and concentration in vacuo, the pure product was isolated by flash chromatography (silica gel, elution with 10 → 20% ethyl acetate in petroleum ether). There was obtained 700 mg (84%) of **68** as white needles: mp 119.5–120 °C (from ethyl acetate/petroleum ether); IR (Nujol, cm^{-1}) 3080, 3060, 2960, 2940, 2870, 1775, 1475, 1465, 1435, 1395, 1380, 1365, 1215, 1165, 1030, 1020, 945, 830, 745, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.64 (m, 4 H), 7.50–7.35 (m, 6 H), 4.32 (dt, J = 2.6, 8.8 Hz, 1 H), 4.23–4.12 (m, 1 H), 3.90–3.80 (m, 1 H), 3.76–3.65 (m, 1 H), 2.80–2.66 (m, 1 H), 2.37–2.14 (m, 2 H), 1.99–1.85 (m, 1 H), 1.70–1.55 (m, 1 H), 1.06 (s, 9 H); MS m/z (M^+) calcd 311.1103, obsd 311.1129. Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.70; H, 7.66. Found: C, 71.69; H, 7.78.

Phenylselenenylation–Oxidation of 68. To a solution of **68** (575 mg, 1.56 mmol) in tetrahydrofuran at −78 °C was added potassium hexamethyldisilazide (4.68 mL of 0.5 M in toluene, 2.34 mmol). After 20 min, a solution of phenylselenenyl chloride (360 mg, 1.87 mmol) in tetrahydrofuran (5 mL) was introduced, and the reaction mixture was stirred for 1 h at −78 °C, treated with water (5 mL) and ether (30 mL), and allowed to warm to room temperature. More ether (50 mL) was added, and the separated aqueous phase was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 5–10% ethyl acetate in petroleum ether) to give the selenide as a colorless oil (707 mg, 87%); IR (neat, cm^{-1}) 3040, 3030, 2970, 2940, 2870, 1740, 1475, 1430, 1375, 1210, 1175, 1115, 1095, 1035, 955, 830, 745, 710, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.64 (m, 4 H), 7.56 (d, J = 7.3 Hz, 2 H), 7.50–7.36 (m, 7 H), 7.32–7.26 (m, 2 H), 4.33–4.18 (m, 2 H), 4.07–3.94 (m, 1 H), 3.87 (quint, J = 5.4 Hz, 1 H), 2.68 (dt, J = 14.8, 9.8 Hz, 1 H), 2.32 (ddd, J = 14.3, 5.5, 1.7 Hz, 1 H), 2.20–2.00 (m, 2 H), 1.05 (s, 9 H); MS m/z (M^+ − $C(CH_3)_3$) calcd 467.0581, obsd 467.0605. Anal. Calcd for $C_{28}H_{32}O_3SeSi$: C, 64.22; H, 6.16. Found: C, 64.28; H, 6.26.

The above selenide (262 mg, 0.501 mmol) in dihloromethane (20 mL) at 0 °C was treated with pyridine (158 mg, 2.00 mmol) followed by hydrogen peroxide (0.255 mL of 30% in water, 2.50 mmol) and water (0.20 mL). The reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature. After 2 h, the mixture was poured into ether (80 mL) and washed with water (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL) prior to drying and evaporation. The residue was subjected to chromatography on silica gel (elution with 10 → 40% ethyl acetate in petroleum ether) to give **69** as a colorless oil (161 mg, 88%), which slowly crystallized (mp 45–46 °C): IR ($CHCl_3$, cm^{-1}) 3010, 2980, 2960, 2930, 2870, 2860, 1755, 1475, 1450, 1430, 1385, 1350, 1115, 1065, 915, 830, 705; ^1H NMR (300 MHz, C_6D_6) δ 7.73–7.65 (m, 4 H), 7.25–7.17 (m, 6 H), 6.11 (t, J = 1.6 Hz, 1 H), 3.76 (q, J = 1.8 Hz, 2 H), 3.70 (t, J = 6.3 Hz, 2 H), 2.36 (dt, J = 1.6, 6.4 Hz, 2 H), 1.12 (s, 9 H); MS m/z (M^+ − $C(CH_3)_3$) calcd 309.0947, obsd 309.0969. Anal. Calcd for $C_{22}H_{26}O_3Si$: C, 72.10; H, 7.16. Found: C, 72.03; H, 7.17.

3-(2-Hydroxyethyl)-2(5*H*)-furanone (70). To a solution of **69** (43 mg, 0.12 mmol) in acetonitrile (0.5 mL) at 0 °C was added anhydrous benzyltrimethylammonium fluoride (24 mg, 0.14 mmol). After 9 h at this temperature, ethyl acetate (5 mL) was added, and the reaction mixture was filtered through a thin pad of Florisil using additional ethyl acetate (75 mL). After concentration in vacuo, the residue was washed with petroleum ether (3 × 2 mL) to remove the silyl fluoride and leave **70** as a colorless oil (14.3 mg, 92%); IR ($CHCl_3$, cm^{-1}) 3460 (br), 3010, 2960, 2940, 1750, 1350, 1215, 1085, 1060, 835; ^1H NMR (300 MHz, C_6D_6) δ 6.02 (quint, J = 1.5 Hz, 1 H), 3.72 (q, J = 1.8 Hz, 2 H), 3.37 (t, J = 6 Hz, 2 H), 2.13 (tq, J = 6.1, 1.7 Hz, 2 H), 1.2 (br s, 1 H); MS m/z (M^+ − H_2O) calcd 110.0368, obsd 110.0372.

Desilylation of 58. A solution of **58** (28 mg, 46 mmol) in acetonitrile (2 mL) was treated with a 5% solution of 40% hydrofluoric acid in acetonitrile (2 mL), stirred at room temperature for 2.5 h, and diluted with dichloromethane (20 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (20 mL), dried, and concentrated. Purification of the residue on silica gel (elution with 5 → 20% ethanol in petroleum ether) gave **64** as a colorless oil (13 mg, 76%): IR (neat, cm^{-1}) 3460, 2910, 1755, 1715, 1445, 1225, 1075; ^1H NMR (300 MHz, C_6D_6) δ 6.56 (s, 1 H), 6.49 (d, J = 0.8 Hz, 1 H), 5.42 (t, J = 7.2 Hz, 1 H), 4.70 (AB, $\Delta\nu$ = 10.9 Hz, J = 9.7 Hz, 2 H), 4.69 (dd, J = 7.0, 1.3 Hz, 1 H), 3.90–3.70 (m, 2 H), 3.55–3.35 (m, 5 H), 3.16 (d, J = 7.2 Hz, 1 H), 2.21 (t, J = 6.1 Hz, 2 H), 1.63 (s, 3 H), 1.60 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 172.0, 163.0, 149.7, 146.6, 140.3, 133.3, 131.9, 118.2, 114.2, 112.8, 107.8, 79.4, 59.3, 49.9, 49.2, 28.2, 26.2, 24.7, 20.4, 16.9; MS (CI) m/z (M^+ + 1) calcd 375.18, obsd 375.10.

Oxidation of 64. To a suspension of crushed, activated 4-Å molecular sieves (50 mg) and pyridinium dichromate (10 mg, 27 μmol) in dichloromethane (0.5 mL) at 0 °C was added a solution of **64** (5 mg, 13 μmol) in the same solvent (1.5 mL) via cannula. The reaction mixture was stirred at 0 °C for 2.5 h under nitrogen, after which time ether (20 mL) was added and the resulting solid was removed by filtration through a thin pad of Florisil and washed with ether (40 mL). The filtrate was concentrated in vacuo and dried by azeotropic distillation with benzene to give 4 mg (80%) of **71** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 2960, 2930, 2860, 1760, 1715, 1215, 1075; ^1H NMR (300 MHz, C_6D_6) δ 9.01 (s, 1 H), 6.66 (br s, 1 H), 6.54 (s, 1 H), 5.40 (m, 1 H), 4.90–4.65 (m, 3 H), 3.78 (m, 2 H), 3.45 (s, 3 H), 3.16 (d, J = 7.1 Hz, 1 H), 2.69 (s, 2 H), 1.63 (s, 3 H), 1.59 (s, 3 H), 1.37 (s, 3 H), 1.37 (s, 3 H); MS (CI) m/z (M^+ + 1) calcd 373.17, obsd 373.00.

Acknowledgment. The generous financial support of the National Cancer Institute (CA-12115) is acknowledged. The X-ray crystallographic analysis was performed by Dr. James Springer (Merck Institute), whose cooperation is greatly appreciated.

Registry No. 15, 22323-80-4; **16**, 71483-05-1; **18**, 126822-57-9; **19**, 126822-67-1; (±)-**20**, 126822-58-0; **21**, 139896-94-9; **22**, 139896-95-0; (±)-**23**, 126822-69-3; (*E*)-**24**, 126822-59-1; (*Z*)-**24**, 126822-68-2; (±)-**26** (isomer 1), 139896-96-1; (±)-**26** (isomer 2), 139896-97-2; (±)-**27**, 139896-98-3; (±)-**28**, 139896-99-4; (±)-**29**, 139913-67-0; (±)-**30**, 139913-90-9; (±)-**31**, 139897-00-0; (±)-**32**, 139897-01-1; **33**, 139897-02-2; **34**, 139897-03-3; **35**, 139897-04-4; **36**, 20763-19-3; (*E*)-**37**, 139897-05-5; (*Z*)-**37**, 139897-06-6; **39**, 139897-07-7; **39** mesylate, 139897-39-5; **40a**, 139897-08-8; **40b**, 139897-09-9; **41**, 139897-10-2; **42**, 139897-11-3; (±)-**43**, 139897-12-4; (±)-**44**, 139897-13-5; (±)-**44** aldehyde, 139897-40-8; (±)-**45**, 139897-14-6; (±)-**46**, 139897-15-7; **47**, 139897-16-8; **48a**, 139897-18-0; (±)-**48b** (isomer 1), 126822-61-5; (±)-**48b** (isomer 2), 126822-70-6; (±)-**48b** (hydroxy ester, isomer 1), 139897-41-9; (±)-**48b** (hydroxy ester, isomer 2), 139974-72-4; **49a**, 139897-19-1; **49b**, 126822-71-7; **50**, 139897-20-4; (±)-**51**, 126822-72-8; (±)-**52**, 126822-60-4; (±)-**53** (isomer 1), 139897-21-5; (±)-**53** (isomer 2), 139897-22-6; (±)-**53** (hydroxy ester, isomer 1), 139974-73-5; (±)-**53** (hydroxy ester, isomer 2), 139974-74-6; (±)-**54** (isomer 1), 139897-23-7; (±)-**54** (isomer 2), 139897-24-8; (±)-**55** (isomer 1), 139897-25-9; (±)-**55** (isomer 2), 139897-26-0; (±)-**55** (alcohol, isomer 1), 139897-42-0; (±)-**55** (alcohol, isomer 2), 139897-43-1; (±)-**56** (isomer 1), 139897-27-1; (±)-**56** (isomer 2), 139897-28-2; (±)-**57** (isomer 1), 139897-29-3; (±)-**57** (isomer

2), 139897-30-6; (±)-**58**, 139897-33-9; **59**, 139897-31-7; (±)-**60** (isomer 1), 139913-91-0; (±)-**60** (isomer 2), 139897-32-8; (±)-**61**, 126822-62-6; (±)-**61** alcohol, 139896-15-4; (±)-**62**, 126822-63-7; (±)-**64**, 139897-38-4; (±)-**67**, 139897-34-0; (±)-**68**, 139897-35-1; (±)-**68** phenylselenide, 139897-44-2; **69**, 139897-36-2; **70**, 139897-37-3; (±)-**71**, 139896-05-2; CH_2=$C(CH_3)MgBr$, 13291-18-4; $OHC(CH_2)_2CO_2Me$, 13865-19-5; $(CH_3)_2C$=$CHMgBr$, 38614-36-7; (±)-$Br(CH_2)_2OTHP$, 59146-56-4; (±)-$I(CH_2)_2OTHP$, 139897-17-9; $Br(CH_2)_2OH$, 540-51-2; t-BuO_2CCH_3, 540-88-5; $(CH_3)_2C$=$CHSnMe_3$, 20484-24-6.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **30** (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of Furanocembranolides. 2. Macrocyclization Studies Culminating in the Synthesis of a Dihydropseudopterolide and Gorgiacerone. Related Furanocembranolide Interconversions[1]

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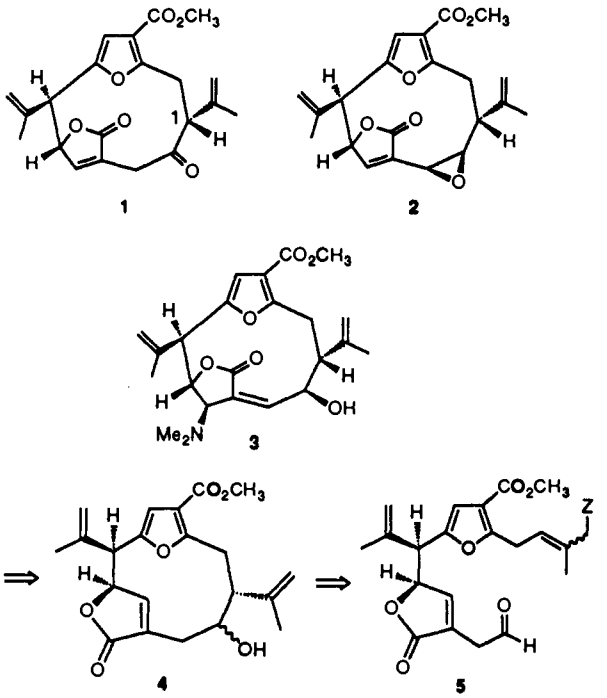
Abstract: The acetaldehydes **7**, **14**, **22**, and **29** were screened for their ability to undergo macrocyclization. These substrates were made available as a consequence of the generality of Pd(0)-catalyzed vinylstannane couplings to bromides **12**. Although molecular mechanics calculations indicated there to be no conformational deterrent to ring closure, **7** failed to undergo intramolecular Prins reaction and **14** did not enter into allylsilane–carboxaldehyde condensation. Fortunately, while **22** gave no evidence for ring closure under conditions of reductive coupling, its *E* isomer **29** was stereoselectively transformed into the dihydropseudopterolide **17**, the stereochemical features of which were unequivocally established by X-ray crystallography. The overall course of this reaction was determined to be in good accord with the results of MODEL calculations of product stabilities. The availability of **17** made possible a total synthesis of gorgiacerone (**1**). A related approach to tobagolide (**3**) was also investigated. When initial experiments established the feasibility of transforming pseudopterolide (**2**) into tobagolide, the dimethylamino group was directly incorporated into several butenolides. Of these, **34b** was sufficiently stable to be converted to **35**. Still more impressive was the successful conversion of **37** into bromo aldehyde **40**. However, these intermediates proved to be too sensitive for eventual crafting into furanocembranolide derivatives.

Gorgiacerone (**1**),[3] pseudopterolide (**2**),[4] tobagolide (**3**),[5] and structurally related cembranoids[6] represent important synthetic targets.[7] A unique opportunity for developing new technologies for molecular construction is thereby offered.[8] Furthermore, accomplishments in this area may also hold application for assault on other biomedically important furanocembranolides represented by pukalide[6a,c] and lophotoxin.[6b,d] In the preceding paper in this series,[1] the details of a possible synthetic entry into this class of compounds via **4** and **5** were given. In particular, a suitably stereocontrolled assembly of the key heterocyclic building blocks was described, and the feasibility of gaining access to **5** (Z = H) was demonstrated.



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