Asymmetric Synthesis of the Diterpenoid Marine Toxin (+)-Acetoxycrenulide

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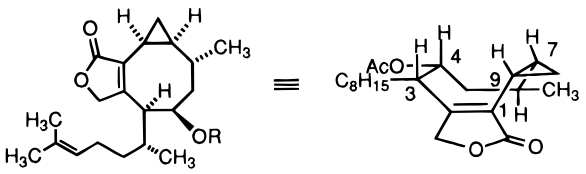
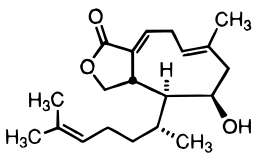
Abstract: An enantioselective route to the marine toxin (+)-acetoxycrenulide is described. The early stages of the synthesis feature the conversion of (*R*)-citronellol into a butenolide whose sole stereogenic center is provided by the terpenic alcohol. Three contiguous chiral carbon atoms are subsequently set in the requisite absolute configuration by conjugate addition of an enantiopure allylphosphonamide reagent. The resulting product is transformed during several steps into a primary selenoxide whose thermal activation in dimethylacetamide at 220 °C promotes sequential 1,2-elimination and Claisen rearrangement. The cyclooctenone core of the target is formed in this step. The final stages of the synthesis involve a series of fully stereoselective reactions including Simmons−Smith cyclopropanation and controlled Dibal-H reduction. The naturally occurring dextrorotatory enantiomer of acetoxycrenulide was ultimately acquired.

Acetoxycrenulide (**1a**),[1] the most prominent member of a limited group of structurally unusual diterpenes that includes pachylactone,[2] several crenuacetals,[3] crenuladial,[4] and a 17-acetoxy derivative,[5] was first isolated independently by Fenical[6] and Sims[7] in 1983 from small brown seaweeds of the family Dictyotaceae and from the sea hare *Aplysia vaccaria* known to feed on this algae. Acetoxycrenulide is recognized to be highly toxic to herbivorous reef-dwelling fish at very low concentrations (10 μg/mL). *A. vaccaria* presumably concentrates **1a** as a chemical defense mechanism to ward off potential predation in its natural habitat.[6,7] The structure of **1a** was originally assigned on the basis of detailed spectroscopic analysis and ultimately confirmed by X-ray crystallographic analysis of a closely related derivative. The substance is a regular diterpenoid possessing an unprecedented bicyclo[6.1.0]nonane framework to which is appended α,β-unsaturated γ-lactone and acetoxyl functionalities. The stereogenic center in the alkenyl side chain is of the *R* configuration.



1a, R = Ac
b, R = H

hν



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Evidence has recently been provided by Guella and Pietra that the crenulatan skeleton present in **1a** may originate from the photoisomerization of xenicane diterpenes by the sun at low tide.[8] These workers showed that irradiation of **2** in either $CHCl_3$ or CH_3OH results in conversion to **1b**. Although the mechanistic details of this interesting intramolecular rearrangement are lacking, the possibility has been established that the final step in crenulide biosynthesis may not be enzymatic but solar-induced.

Synthetic Plan

As a consequence of the unusual structural features and biological properties of **1a**, its enantioselective total synthesis was undertaken. The end game was designed to showcase the capacity of the Claisen rearrangement for direct elaboration of the cyclooctanoid core in properly stereocontrolled fashion.[9] Thus, **3** was set as an advanced objective (Scheme 1). It was anticipated that the rigidly locked, twisted tublike ground-state conformation of **3** would constitute a reliable template for stereocontrolled cyclopropanation from the open β-face, for 1,2-reduction of the ketone carbonyl to set the hydroxyl cis to the three-membered ring, and for introduction of the butenolide double bond by organoselenium-based methodology. Our earlier studies in this area revealed the key fact that the side chain had to be incorporated prior to arrival at **3**. Most relevant

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(1) Preliminary communication: Paquette, L. A.; Wang, T.-Z.; Pinard, E. *J. Am. Chem. Soc.* **1995**, *117*, 1455.

(2) Ishitsuka, M.; Kusumi, T.; Kakisawa, H.; Kawakami, Y.; Nagai, Y.; Sato, T. *Tetrahedron Lett.* **1983**, *24*, 5117.

(3) Kusumi, T.; Muanza-Nkongolo, D.; Goya, M.; Ishitsuka, M.; Iwashita, T.; Kakisawa, H. *J. Org. Chem.* **1986**, *51*, 384.

(4) Tringali, C.; Oriente, G.; Piattelli, M.; Geraci, C.; Nicolosi, G.; Breitmaier, E. *Can. J. Chem.* **1988**, *66*, 2799.

(5) König, G. M.; Wright, A. D.; Sticker, O. *Tetrahedron* **1991**, *47*, 1399.

(6) Sun, H. H.; McEnroe, F. J.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 1903.

(7) Midland, S. L.; Wing, R. M.; Sims, J. J. *J. Org. Chem.* **1983**, *48*, 1906.

(8) Guella, G.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1539.

(9) Paquette, L. A. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, England, 1994; pp 313−336.

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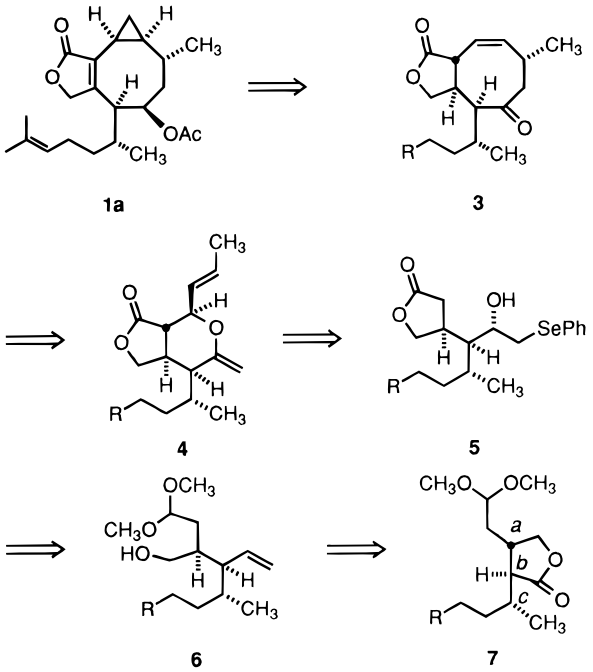
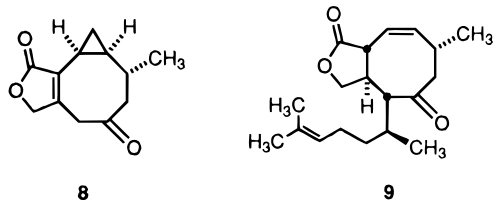
Scheme 1



in this connection were the observations that **8** could not be made to enter into alkylation chemistry[10] and that **9** was not



amenable to epimerization α to the ketone carbonyl (the side chain in **9** is projected axially).[11] Models suggest that the requisite enolization is not facile because an α-proton is not properly stereoaligned with either flanking π-system. The carbocyclic framework in both examples is evidently quite rigid.

Since a cyclopropanation step constitutes an integral part of the synthetic plan, it is not realistic to expect the 6-methyl-5-hepten-2-yl side chain to survive intact because of the inherently greater reactivity of its double bond.[12] Consequently, a β-*tert*-butyldiphenylsiloxy group at R has been utilized as a satisfactory surrogate.

The cyclooctenone ring in **3** was expected to be made available by thermal activation of **4**. Should a chairlike [3.3] sigmatropic transition state be adopted as expected, it is required that the propenyl substituent possess an *E* configuration in order to properly set the configuration of the secondary methyl group in **3**. Arrival at **4** was anticipated by an aldol reaction with crotonaldehyde followed by acid-catalyzed cyclization and selenoxide elimination.

The three contiguous stereogenic centers in hydroxy acetal **6** were to be set in its cyclic precursor **7**. In an earlier phase of this investigation, the stereogenicity present at position c in the side chain was used as the point of reference for correlating the absolute stereochemistry of the other chiral centers. However, this protocol ultimately would lead to a diastereomer of **1a**.[11] Consequently, a different stratagem is required to set the absolute configurations at sites a and b very reliably and without concern for the configurational characteristics at position c. The present paper details the successful realization of this plan and presents additional peripheral observations recorded along the way.[1]

Results and Discussion

Setting the Contiguous Stereocenters in a Lactone of Type 7. From the outset, (*R*)-citronellol (**10a**) was regarded to be the appropriate natural source of the alkenyl side chain in **1a**. Material of 96.3% ee[13] was sequentially acetylated, ozonolyzed, and subjected to reduction with the borane−dimethyl sulfide complex to afford the monoesterified diol **11a** in quantitative yield (Scheme 2). Equally efficient was the silylation of **11a** with *tert*-butyldiphenylsilyl chloride and ensuing hydrolytic removal of the acetate functionality. Oxidation of the primary hydroxyl site in **11c** followed by esterification with diazomethane furnished **12b**.

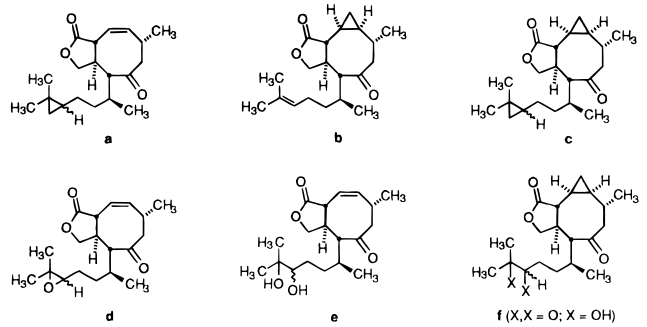
From the retrosynthetic perspective, **12b** was considered to be an ideal intermediate for the elaboration of **15**. Two routes to this butenolide were evaluated. In the first, **12b** was C-allylated, and **13** so formed was ozonolyzed and directly reduced with sodium borohydride. Spontaneous cyclization occurred to deliver the γ-lactone **14**, which in turn was transformed into **15** by means of α-selenenylation and oxidation. We came to favor this route in view of its efficiency (80% for **12b** → **14**, 87% for **14** → **15**) and the ease with which it could be scaled up. These features were not found in the second approach, which was modeled on an earlier report by Yao and Wu.[14] The aldol condensation leading to **16a** could not be accomplished with >62% efficiency. A similar complication surfaced in the acid-catalyzed cyclization of **16b** to **17**. After rather tedious chromatographic purification, this lactone could be secured in only 60% yield. Most unsatisfactory of all was β-elimination of the protected hydroxyl group in **17** to give **15** (44%). While this alternative was certainly interesting and served to deliver an end product identical in all respects with that produced earlier, it was not as practical and was abandoned.

Attention was now directed to the homologation of **15** with total absolute control over the two new stereogenic centers being

(10) (a) Ezquerra, J.; He, W.; Paquette, L. A. *Tetrahedron Lett.* **1990**, *31*, 6979. (b) Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.* **1995**, *60*, 1435.

(11) He, W.; Pinard, E.; Paquette, L. A. *Helv. Chim. Acta* **1995**, *78*, 391.

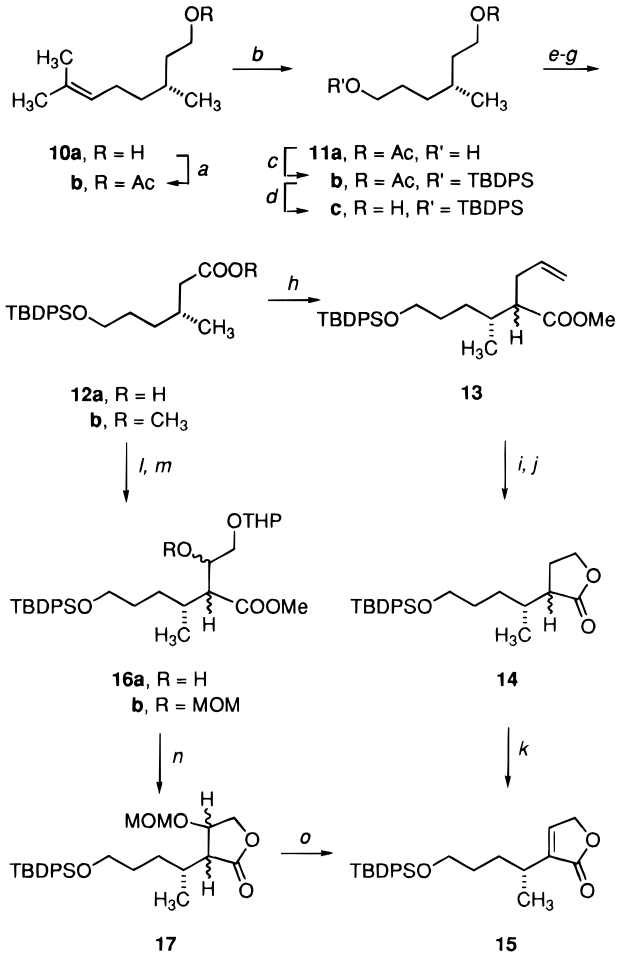
(12) This conclusion is supported by trial experiments performed on **9** (Pinard, E., 1993). Thus, Simmons−Smith cyclopropanation of **9** with diethylzinc (1.2 equiv) and diiodomethane (8 equiv) in benzene at 20 °C gave mixtures of **9**, **a**, **b**, and **c**. The product distribution was dependent, of course, on the timing of the quench but most often approximated 15:15:35:35. Treatment of **9** with 2 equiv of diethylzinc provided **c** as the only detectable product (70% isolated). No cyclopropanation was observed with $CH_2N_2/Pd(OAc)_2$ or Me_3Al/CH_2I_2. Although **9** could be regioselectively transformed into epoxide **d** and diol **e** (as 1:1 diastereomeric mixtures) with controlled amounts of MCPBA and OsO_4/pyridine, and these intermediates could be stereoselectively cyclopropanated as in **f**, no means was found for ultimate removal of the oxygen atoms from the side chain.



(13) (*R*)-Citronellol of this optical purity was generously provided to us by Dr. Susumu Akutagawa of the Takasago Research Institute (Tokyo), whom we thank.

(14) Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157.

Scheme 2[a]



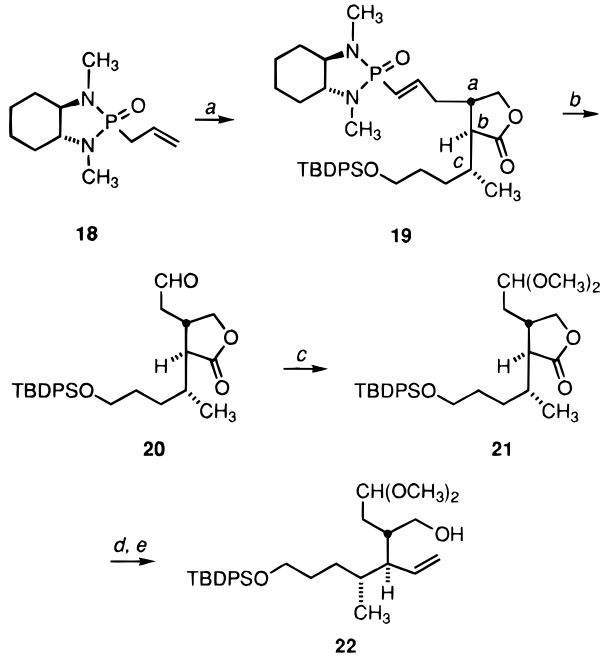
[a] (a) Ac_2O, py, CH_2Cl_2, 0 °C; (b) O_3, CH_2Cl_2, −78 °C, $BH_3{\cdot}SMe_2$, 0 °C; (c) TBDPSCl, Et_3N, CH_2Cl_2; (d) K_2CO_3, CH_3OH; (e) PDC, 4 Å molecular sieves, CH_2Cl_2; (f) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O; (g) CH_2N_2, Et_2O; (h) LDA, THF, −78 °C, $CH_2{=}CHCH_2Br$, THF, HMPA; (i) O_3, CH_2Cl_2, −78 °C, Ph_3P, room temperature; (j) $NaBH_4$, CH_3OH, H_3O^+; (k) $KN(SiMe_3)_2$, THF, PhSeCl, H_2O_2, py, CH_2Cl_2, 0 °C → room temperature; (l) LDA, $OHCCH_2OTHP$, THF, −78 °C; (m) MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C; (n) 10% H_2SO_4, THF; (o) DBU, THF, C_6H_6, 70 °C.

introduced. It soon became clear that the reagent selected for participation in the conjugate addition must have the intrinsic ability to ensure a high degree of organization in the associated transition state and thereby guarantee the stereochemical outcome. Few reagents do this well. Among these, we came to favor the α-allylphosphonamide **18** recently described by Hanessian et al.[15] The high-level capacity exerted by **18** on the facial selectivity of C-allylation essentially guarantees that the configuration at site a in **19** be *R*. The usual thermodynamic advantage of positioning large vicinal groups trans to each other on a five-membered ring serves to fix the configuration at site b. The consequences of this asymmetric Michael addition is that **19** is formed as the only detectable product (Scheme 3). This important intermediate harbors stereogenic centers properly defined for advancing to **1a**.

Ozonolysis of **19** reflected removal of the chiral auxiliary with formation of aldehyde **20**. The latter was subjected to the action of trimethyl orthoformate in the presence of a catalytic quantity of acid, thereby delivering acetal **21** without loss of stereochemical integrity. In preparation for deployment of the

(15) (a) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudouin, S. *J. Org. Chem.* **1993**, *58*, 5032. (b) Hanessian, S.; Gomtsyan, A. *Tetrahedron Lett.* **1994**, *35*, 7509.

Scheme 3[a]



[a] (a) *n*-BuLi, THF, −78 °C, **15**; (b) O_3, $CH_2Cl_2{-}CH_3OH$, −78 °C, Me_2S; (c) $HC(OCH_3)_3$, (TsOH), CH_3OH; (d) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −78 °C; (e) $(C_6H_5)_3PCH_3^+Br^-$, $KN(SiMe_3)_2$, THF, 0 °C → room temperature.

key Claisen rearrangement, **21** was reduced to the lactol and treated with methylenetriphenylphosphorane. As will become apparent below, this maneuver also sets the stage for ready elaboration of that γ-lactone unit that constitutes ring A of acetoxycrenulide.

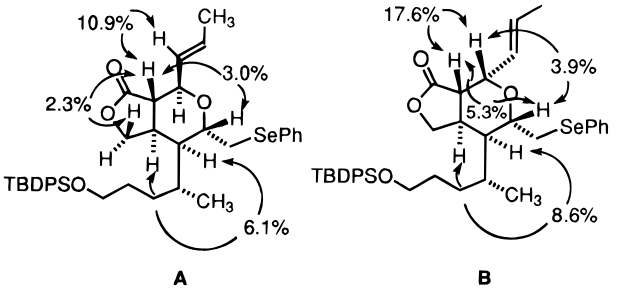
Implementation of the Claisen Rearrangement. Mild acidic hydrolysis of **22** resulted in intramolecular nucleophilic attack on the liberated aldehyde by the neighboring hydroxyl substituent. The resultant colorless oily lactol was uneventfully oxidized to **23**. In the setting of Scheme 4, **23** is recognized to possess an enolizable center exploitable for the introduction of an additional carbon chain at C_α complementary to that existing at C_β. The issue of the oxidation level at C_β could not be deferred,[16] and consequently **23** was ozonolyzed to produce the nor-aldehyde, which was condensed with (phenylseleno)-methyllithium[17] to afford **24**. It was interesting to find that **24** was a single diastereomer, presumably as a consequence of adherence by the nucleophile to a Cram-like transition-state trajectory. This finding was more a matter of convenience than of substance since the stereogenic carbinol center developed in this process was soon to be eliminated.[18] Due to the impending aldol condensation, the hydroxyl group in **24** had to be temporarily protected in a base-insensitive manner. Exposure of this intermediate to 2-methoxypropene in the presence of phosphorus oxychloride[19] proved serviceable, giving rise to the acetal in 96% yield. Predictably,[10,11] the anion of the protected lactone underwent condensation with (*E*)-crotonaldehyde predominantly from its less sterically encumbered surface. Another potential problem, that of generating a 1:1 mixture epimeric at the carbinol center, turned out not to pose any serious difficulties, nor was the finding that some deprotection of the

(16) Aldol condensations of **21** with (*E*)-crotonaldehyde gave a mixture of two epimeric alcohols, neither of which could be induced to undergo cyclization during attempted generation of a phenylselenonium ion. For example, *N*-(phenylseleno)phthalimide and *p*-toluenesulfonic acid left the alcohols unchanged, while benzeneselenenyl chloride induced quite rapid decomposition.

(17) Seebach, D.; Peleties, N. *Chem. Ber.* **1972**, *105*, 511.

preexisting hydrolylic center a concern, since it was to be removed in the very next maneuver. Nonetheless, we were moved to suppress this side reaction, a feat that was easily accomplished by adding a small amount of triethylamine to the drying solution ($MgSO_4$) and the chromatography solvent system. When these guidelines were adopted, good yields of **25** were realized.

By heating the inseparable 1:1 aldol mixture with a catalytic amount of *p*-toluenesulfonic acid in benzene, closure to the tetrahydropyran **26** could be effected. Although the primary product was invariably the β-crotyl epimer **26a**, the ratio of **26a:26b** was seen to vary as a function of reaction time. This result did not occasion surprise, since independent resubmission of **26b** to the reaction conditions returned a 4:1 mixture of **26a:26b**. This ratio appears to be a good approximation of the thermodynamic equilibrium. The interconversion is believed to proceed by acid-catalyzed retro-Michael opening of the tetrahydropyran ring followed by proton-induced readdition from one face of the conjugated diene π-surface or the other. The stereochemistry unique to **26a**,**b** was established by NOE experiments, the more important details of which are summarized in formulas **A** and **B**.

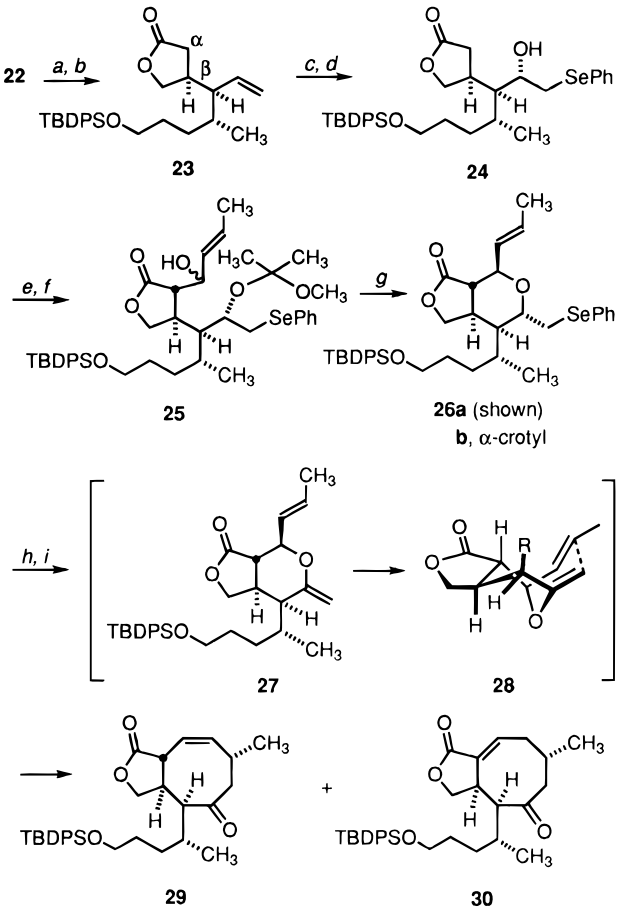


A **B**

The cyclooctenone segment of acetoxycrenulide was about to be fashioned from **26a**. The trans nature of the ring fusion and the *E* stereochemistry of the crotyl double bond are of central importance for controlling proper introduction of the ring unsaturation and secondary methyl group. Following the oxidation of this advanced intermediate with sodium periodate, the stage was set for concurrent selenoxide elimination and Claisen rearrangement. Application of those conditions found to be conveniently workable during model studies, viz. diethylamine-buffered mesitylene at 162 °C, only brought on extensive decomposition. The reluctance of **27** to engage as readily in [3.3] sigmatropy was not unanticipated. For reasons alluded to before, the examples studied earlier were either free of the side chain or carried it into the chairlike transition state in an equatorial disposition. The scenario for **27** is one in which the large pendant chain must be projected axially as depicted in **28**. Although the energetic costs associated with the desired conversion to **29** were certain to be higher, the manner in which this factor had to be dealt with experimentally was approached empirically.

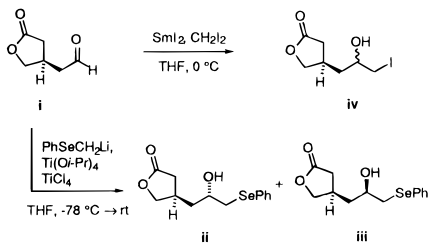
Since it seemed that the polar characteristics of Claisen transition states might be better accommodated by performing the rearrangement in a polar aprotic solvent, the response of the selenoxide to being heated in dimethylformamide at 220 °C was next examined. As before, diethylamine was also added to neutralize the electrophilic PhSeOH liberated during the generation of **27** and to guard against unwanted processes induced from that direction. These conditions led predominantly to **30**. A small amount of **29** was detected, and the combined yield was disappointingly low. When recourse was made

Scheme 4[a]



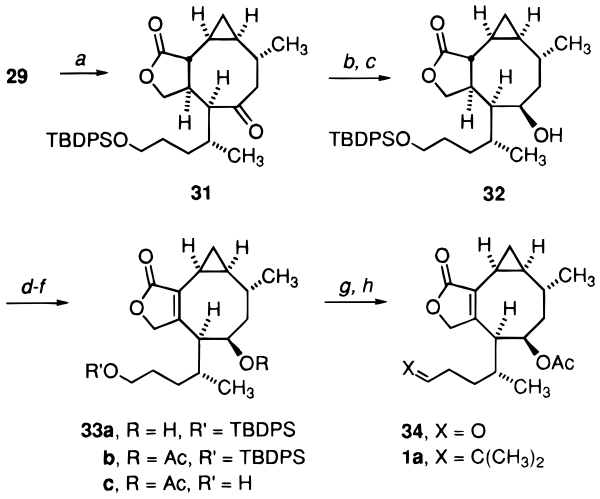
[a] (a) 5% HCl, THF; (b) PDC, 4 Å molecular sieves, CH_2Cl_2; (c) O_3, CH_2Cl_2, −78 °C, $(C_6H_5)_3P$; (d) $(C_6H_5Se)_2CH_2$, *n*-BuLi, THF, −78 °C; (e) $CH_2{=}C(OCH_3)CH_3$, $POCl_3$; (f) LDA, THF, (*E*)-$CH_3CH{=}CHCHO$, −78 °C; (g) (TsOH), C_6H_6, Δ; (h) $NaIO_4$, $NaHCO_3$, CH_3OH, H_2O; (i) $(C_2H_5)_3N$, $CH_3CH_2OCH{=}CH_2$, $CH_3CON(CH_3)_2$, 220 °C, sealed tube.

(18) In model studies performed on the less substituted aldehyde **i** (He, W. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1991), other approaches to the substitution plan present in **24** were found to be more problematic. Since nucleophilic organotitanium reagents are recognized to exhibit excellent selectivity for aldehydes and ketones, it was expected that exposure of **i** to $(PhSeCH_2)Ti(O\textit{i}\text{-}Pr)_3$ would result in smooth 1,2-addition to the side chain. However, admixture of **i** with this reagent, prepared from $PhSeCH_2Li$ and $ClTi(O\textit{i}\text{-}Pr)_3$ as detailed by Reetz (Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1), led only to the recovery of unchanged aldehyde. When recourse was made instead to $(PhSeCH_2)ClTi(O\textit{i}\text{-}Pr)_2$, generated in situ from $PhSeCH_2Li$, $Ti(O\textit{i}\text{-}Pr)_4$, and $TiCl_4$, high selectivity was observed with resultant production of **ii** and **iii** in isolated yields of 33% and 43%, respectively, following chromatographic separation. Chemoselective addition was also realized with SmI_2/CH_2I_2 (Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3891. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693), but an inseparable mixture of stereoisomeric hydroxy iodides **iv** was produced in low (44%) yield. Although **iv** should in principle be amenable to conversion into **ii** and **iii** by exposure to PhSeNa (Grieco, P. A.; Noguez, J. A.; Masaki, Y. *Tetrahedron Lett.* **1975**, 4213. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. Miyoshi, N.; Kondo, K.; Murai, S.; Sonada, N. *Chem. Lett.* **1979**, 909), this transformation has not been attempted. Evidently, the stereoselectivity encountered in the production of **24** is a direct consequence of the neighboring stereogenic center.



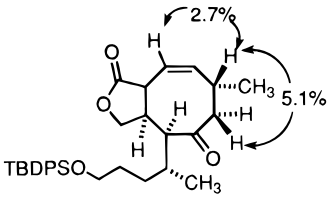
(19) Kluge, A. F.; Untch, K. G.; Field, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

Scheme 5[a]



[a] (a) CH_2T_2, $(C_2H_5)_2Zn$, C_6H_6, room temperature; (b) $(i\text{-}Bu)_2AlH$ (2 equiv), CH_2Cl_2, −78 °C; (c) Ag_2CO_3−Celite, C_6H_6, Δ; (d) $KN(SiMe_3)_2$, THF, −78 °C, PhSeCl, $NaIO_4$, $NaHCO_3$, CH_3OH, H_2O; (e) Ac_2O, DMAP, CH_2Cl_2; (f) py·HF, CH_3CN, H_2O; (g) PDC, 4 Å molecular sieves, CH_2Cl_2; (h) $(CH_3)_2C{=}P(C_6H_5)_3$, THF, −78 °C → room temperature.

instead to a tertiary amine (specifically triethylamine) as buffer, less conjugation materialized (**29:30** = 1:1), but considerable decomposition, was again noted. It seemed possible that the vinyl ether functionality in **27** was the most sensitive component of this intermediate. Consequently, to ward off any possible attack at this site by a reactive selenium species, the system was next provided with an excess of ethyl vinyl ether that should prove more available and more reactive. When this innovation was implemented, the combined yield of **29** and **30** rose to 53%. Finally, the replacement of DMF by *N*,*N*-dimethylacetamide as solvent was met with a significant reduction in the proportion of conjugated isomer formed. These highly favorable conditions afforded **29** in 55% yield and **30** in only 7% yield and were adapted to the production of reasonable quantities of the desired cyclooctenone. The stereochemical assignment to **30** was confirmed by means of the NOE method as shown in **C**.



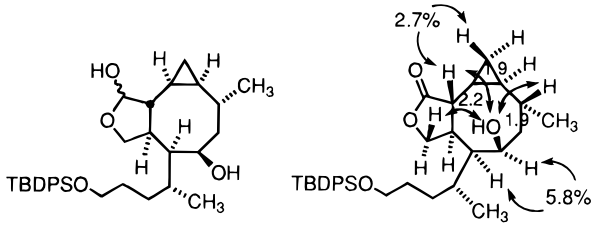
C

Completion of the Synthesis. For maximum conciseness, **29** was first subjected to the Simmons−Smith cyclopropanation reaction.[20] Since this substrate is believed to adopt a conformation that uniquely exposes the β-face of its double bond, efficient conversion to **31** was expected and realized (Scheme 5). The information gained from the model studies[10,11] proved relevant in this instance (92% yield). Although **31** could be readily desilylated with pyridinium fluoride in aqueous acetonitrile, experiments involving the pyridinium dichromate oxidation of this alcohol revealed the derived aldehyde to be quite labile.[21] As a result, attempts to perform a Wittig reaction on this intermediate were to no avail. For these reasons, the sequence of steps was inverted.

(20) Sawada, S.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2669.

(21) The possibility is real that intramolecular aldolization is the root cause of this instability. This aspect of the problem was not investigated.

Although it was hoped that the ketone carbonyl could be reduced chemoselectively, this was found not to be possible because of its significant steric screening. The first indication of sluggish reactivity surfaced when **31** was treated with sodium borohydride in methanol. Above room temperature, only conversion to the triol was observed.[22] The conclusion that the lactone ring was being reduced first was supported by a number of observations, including the fact that keto lactol was produced cleanly following exposure to 1 equiv of Dibal-H at −78 °C.[22] In the end, advantage was taken of this reactivity ordering by treating **31** with 2 equiv of Dibal-H to give the hydroxy lactol **35** as an inseparable mixture of epimers. Without purification,



35 **D**

the overreduced product was oxidized chemoselectively with Fetizon reagent to deliver **32** in 87% overall yield. The configuration of the carbinol carbon in **32**, anticipated to be *S* on the basis of steric approach control, was corroborated by NOE experiments (see **D**).

Without protection of the hydroxyl group, **32** was treated sequentially with 2 equiv of potassium hexamethyldisilazide and benzeneselenyl chloride. Upon direct oxidation of the resulting selenides with sodium periodate, the unsaturated lactone **33a** was obtained as a colorless, crystalline, dextrorotatory ($[\alpha]^{25}_D$ +28.8) solid in 87% yield. Acetylation of this substance gave rise to **33b** and completed elaboration of the fully functionalized cyclooctanoid core.

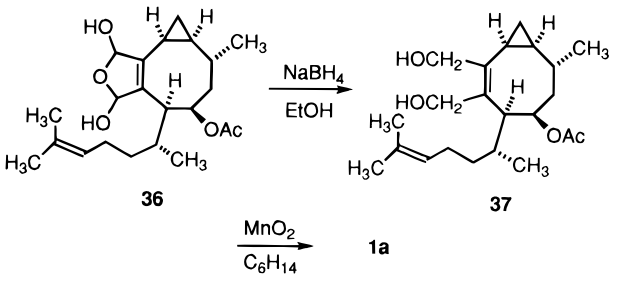
Modification of the side chain was accomplished conventionally and without difficulty (Scheme 5). It is noteworthy, however, that the advanced intermediates **33a**−**c** and **34**, as well as acetoxycrenulide (**1a**), itself, exhibit line-broadened ^1H and ^{13}C NMR spectra at ambient temperature. In each case, warming of the solution to 60 °C caused nicely resolved signals to appear. Evidently, the introduction of a double bond into the medium ring is accompanied by a modest heightening of the barriers to conformational interconversion.

The synthetic acetoxycrenulide obtained in this manner proved to be spectroscopically identical with the natural material by direct comparison with spectra provided to us by Professor James Sims. The optical rotation of our sample, construed to be 96.3% ee in view of its direct link to **10a**, was $[\alpha]^{23}_D$ +20.1 (*c* 1.8, $CHCl_3$). This value is in excellent agreement with the $[\alpha]_D$ value of +21.5 reported by Tringali and co-workers who obtained their material by manganese dioxide oxidation of diol **37** derived in turn from optically pure crenuladial (**36**). The optical rotations given by Fenical (+13) and Sims (+13.6) are of considerably smaller magnitude although comparable in sign.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 instrument. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC-300 instrument as denoted. Mass spectra were recorded at The Ohio State University Chemical Instrument Center. Elemental analyses

(22) Wang, T.-Z. Unpublished observations from this laboratory.



36 **37**

were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were predried by standard methods. All reactions involving nonaqueous solutions were performed under an inert atmosphere. Unless otherwise indicated, all separations were carried out under flash chromatography conditions on silica gel 60 (230−400 mesh, 60 Å) using the indicated solvents. The organic extracts were dried over anhydrous magnesium sulfate. The purity of all compounds was shown to be ≥95% by high-field ^{1}H NMR analysis. Optical rotations are based on concentrations of g/100 mL.

(3*R*)-3,7-Dimethyl-6-octen-1-ol Acetate (10b). A solution of (*R*)-citronellol (5.0 g, 0.03 mol, 96.3% ee) in CH_2Cl_2 (150 mL) was cooled to 0 °C and successively treated with pyridine (10.3 mL, 0.13 mol), DMAP (390 mg, 3.2 mmol), and acetic anhydride (9 mL, 0.1 mol). After 45 min of stirring at this temperature, the reaction mixture was diluted with CH_2Cl_2 and washed in turn with 1 N HCl, water, saturated $NaHCO_3$ solution, and brine prior to drying and solvent evaporation. The residue was distilled in vacuo in a Kugelrohr apparatus to provide **10b** (6.34 g, 100%) as a faintly yellow oil which was used without further purification: IR ($CHCl_3$, cm^{-1}) 1745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (m, 1H), 4.16−4.03 (m, 2 H), 2.25−1.82 (m, 2 H), 2.04 (s, 3 H), 1.73−1.12 (series of m, 5 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.9, 131.1, 124.5, 62.9, 36.9, 35.4, 29.4, 25.6, 25.3, 20.9, 19.2, 17.5; MS *m/z* (M^+ − HOAc) calcd 138.1409, obsd 138.1424; $[\alpha]^{20}_D$ +3.7 (*c* 3.29, $CHCl_3$).

(3*R*)-3-Methyl-1,6-hexanediol 1-Acetate (11a). Ozone was bubbled into a solution of **10b** (25.0 g, 0.13 mol) in CH_2Cl_2 (150 mL) at −78 °C for 2 h, and the resulting blue reaction mixture was deoxygenated with N_2 for 10 min until decoloration. At −78 °C, borane−dimethyl sulfide complex (50 mL, 0.5 mol) was introduced dropwise, the colorless mixture was carefully warmed to 0 °C, and stirring was maintained at this temperature for 3 h prior to the slow addition of 1 N HCl (250 mL). After 45 min of vigorous stirring, the aqueous layer was separated and extracted with CH_2Cl_2 (3×). The combined organic layers were washed successively with saturated $NaHCO_3$ solution, saturated NH_4Cl solution, and brine and concentrated in vacuo to provide **11a** (22.0 g, 100%) as a colorless oil which was used without purification. A small sample was flash distilled for analysis: IR ($CHCl_3$, cm^{-1}) 3400, 1730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16−4.02 (m, 2 H), 3.61 (t, J = 6.5 Hz, 2 H), 2.02 (s, 3 H), 1.70−1.32 (series of m, 6 H), 1.25−1.13 (m, 1 H), 0.91 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.2, 62.9, 62.8, 35.4, 32.7, 30.0, 29.6. 20.9, 19.3; MS *m/z* (M^+ + H) calcd 175.1334, obsd 175.1353; $[\alpha]^{20}_D$ +4.5 (*c* 1.30, $CHCl_3$). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.02; H, 10.59.

(3*R*)-6-(*tert*-Butyldiphenylsiloxy)-3-methyl-1-hexanol Acetate (11b). A solution of *tert*-butyldiphenylsilyl chloride (85.4 g, 0.31 mol), DMAP (3.5 g, 29 mmol), and triethylamine (50 mL, 0.36 mol) in CH_2Cl_2 (200 mL) cooled to 0 °C was treated dropwise with alcohol **11a** (50.0 g, 0.29 mol). The reaction mixture was stirred overnight at room temperature, diluted with CH_2Cl_2, washed successively with 1 N HCl, saturated $NaHCO_3$ solution, saturated NH_4Cl solution, and brine, and then dried. Solvent removal provided **11b** (118.0 g, 100%) as a colorless oil which was used without further purification. A small sample was flash distilled for analysis: IR ($CHCl_3$, cm^{-1}) 1750; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.44 (m, 4 H), 7.42−7.34 (m, 6 H), 4.11−4.06 (m, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 2.03 (s, 3 H), 1.68−1.34 (series of m, 6 H), 1.26−1.19 (m, 1 H), 1.05 (s, 9 H), 0.89 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.1, 135.5, 134.1, 129.5, 127.6, 64.1, 63.0, 35.4, 32.9, 29.8, 29.6, 26.9, 20.9, 19.4, 19.2; MS *m/z* (M^+ − H) calcd 411.2356, obsd 411.2315; $[\alpha]^{20}_D$ +2.6 (*c* 3.46, $CHCl_3$). Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79. Found: C, 73.15; H, 8.93.

(3*R*)-6-(*tert*-Butyldiphenylsiloxy)-3-methyl-1-hexanol (11c). A mixture of **11b** (4.48 g, 0.01 mol) and K_2CO_3 (4.5 g, 0.033 mol) in methanol (50 mL) and water (50 mL) was heated at reflux for 4 h, cooled to 0 °C, and neutralized with concentrated HCl. The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried and concentrated to provide **11c** (4.0 g, 100%) as a colorless oil which was used without further purification. A small sample was flash distilled for analysis: IR ($CHCl_3$, cm^{-1}) 3600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4 H), 7.42−7.35 (m, 6 H), 3.71−3.60 (m, 4 H), 1.64−1.50 (m, 4 H), 1.47−1.30 (m, 2 H), 1.26−1.10 (m, 2 H), 1.05 (s, 9 H), 0.88 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 135.5, 134.1, 129.5, 127.6, 64.2, 61.1, 39.8, 33.0, 29.9, 29.2, 26.9, 19.6, 19.2; $[\alpha]^{20}_D$ +2.4 (*c* 3.1, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}O_2Si$: C, 74.54; H, 9.25. Found: C, 74.78; H, 9.51.

(3*R*)-6-(*tert*-Butyldiphenylsiloxy)-3-methylhexanoic Acid (12a). To a solution of **11c** (20.0 g, 54.1 mmol) in CH_2Cl_2 (400 mL) was added 4 Å molecular sieves (27 g) and pyridinium dichromate (27.0 g, 71.8 mmol). The mixture was stirred at room temperature for 1 h, diluted with ether (1 L), and filtered through a Celite pad. The filtrate was concentrated to leave a deeply colored material which was eluted through a short column of silica gel to remove residual chromium salts (elution with 25% ethyl acetate in hexanes). The yellowish aldehyde so obtained (17.5 g) was dissolved in *tert*-butyl alcohol (500 mL) containing 2-methyl-2-butene (80 mL). With cooling in ice water, this mixture was treated during 10 min with a solution of $NaClO_2$ (35.0 g, 0.38 mol) and $NaH_2PO_4{\cdot}H_2O$ (37.0 g, 0.27 mol) in water (260 mL) and stirred at room temperature for 6 h. Most of the *tert*-butyl alcohol was removed on a rotary evaporator. The residual material was diluted with water (300 mL), acidified to pH 2 with 5% HCl, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 25% ethyl acetate in hexanes) gave 14.5 g (70%) of **12a** as a colorless oil which was directly esterified: IR ($CHCl_3$, cm^{-1}) 3550, 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.66 (m, 4 H), 7.42−7.35 (m, 6 H), 3.66 (t, J = 6.3 Hz, 2 H), 2.34 (dd, J = 5.8, 15.0 Hz, 1 H), 2.15 (dd, J = 8.1, 15.0 Hz, 1 H), 2.00−1.93 (m, 1 H), 1.63−1.54 (m, 2 H), 1.52−1.33 (m, 1 H), 1.31−1.19 (m, 2 H), 1.06 (s, 9 H), 0.97 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.6, 135.6, 134.0, 129.5, 127.6, 63.9, 41.5, 32.8, 29.9 (2 C), 26.9, 19.6, 19.2; $[\alpha]^{20}_D$ +3.4 (*c* 3.85, $CHCl_3$).

Methyl (3*R*)-6-(*tert*-Butyldiphenylsiloxy)-3-methylhexanoate (12b). A solution of **12a** (18.0 g, 46.8 mmol) in ether (300 mL) was cooled to 0 °C and treated with an ethereal solution containing excess diazomethane (prepared from *N*-methylnitrosourea). The yellow solution was left to stand at room temperature for 1 h, and the excess reagent was destroyed with acetic acid. The ether solution was washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 4% ethyl acetate in hexanes) furnished 15.3 g (82%) of the ester as a viscous, colorless oil: IR ($CHCl_3$, cm^{-1}) 1731; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.63 (m, 4 H), 7.48−7.34 (m, 6 H), 3.67 (t, J = 5.9 Hz, 2 H), 3.66 (s, 3 H), 2.32 (dd, J = 14.5, 6.0 Hz, 1 H), 2.12 (dd, J = 14.5, 8.0 Hz, 1 H), 1.97 (m, 1 H), 1.65−1.07 (series of m, 4 H), 1.05 (s, 9 H), 0.94 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.6, 135.6, 134.1, 129.5, 127.6, 64.0, 51.3, 41.6, 32.8, 30.2, 30.0, 26.9, 19.7, 19.2; MS *m/z* (M^+) calcd 398.2277, obsd 398.2253; $[\alpha]^{23}_D$ +2.9 (*c* 2.32, $CHCl_3$). Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.29; H, 8.59.

Methyl (3*R*)-2-Allyl-6-(*tert*-butyldiphenylsiloxy)-3-methylhexanoate (13). To a solution of lithium diisopropylamide [prepared from 4.54 mL (32.4 mmol) of diisopropylamine and *n*-butyllithium (18.6 mL of 1.6 M, 29.8 mmol) in 100 mL of dry THF at −78 °C] was added a solution of **12b** (9.10 g, 22.9 mmol) in 30 mL of dry THF over 10 min. After 70 min of stirring, HMPA (9 mL) was added followed by allyl bromide (10 mL, excess). The reaction mixture was stirred for 2 h at −78 °C and warmed to 0 °C, the reaction was quenched with saturated NH_4Cl solution, and the mixture was extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to leave a colorless liquid which was used directly in the next step. A small aliquot was chromatographed on silica gel (elution

with 4% ethyl acetate in hexanes) for spectroscopic and analytical purposes: IR ($CHCl_3$, cm^{-1}) 1728; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73−7.60 (m, 4 H), 7.45−7.33 (m, 6 H), 5.74 (m, 1 H), 5.08−4.98 (m, 2 H), 3.68−3.64 (m, 2 H), 2.40−2.17 (series of m, 3 H), 1.80−1.31 (series of m, 6 H), 1.27−1.12 (m, 2 H), 1.06 (s, 4.5 H), 1.05 (s, 4.5 H), 0.91 (d, J = 6.2 Hz, 1.5 H), 0.89 (d, J = 6.2 Hz, 1.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.4, 175.2, 136.1, 136.0, 135.6, 134.1, 129.5, 127.6, 127.5, 116.4, 116.3, 64.0, 51.1, 51.0, 50.5, 34.9, 34.1, 32.9, 30.7, 30.4, 30.2, 29.9, 26.9, 19.2, 16.7, 16.6; MS *m/z* (M^+) calcd 438.2590, obsd 438.2573. Anal. Calcd for $C_{27}H_{38}O_3Si$: C, 73.93; H, 8.73. Found: C, 73.95; H, 8.71.

3-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]dihydro-2(3*H*)-furanone (14). Ester **13** produced above was dissolved in CH_2Cl_2 (200 mL), cooled to −78 °C, and ozonolyzed until a blue color was sustained (ca. 45 min). The excess ozone was removed by bubbling N_2 through the system for 10 min, at which point triphenylphosphine (12.0 g, 45.8 mmol) was introduced and the mixture was kept at room temperature overnight. Solvent evaporation afforded an orange oil which was dissolved in methanol (100 mL), cooled to −10 °C, and treated with $NaBH_4$ (2.6 g, 76 mmol) in small portions. After 30 min of stirring, the mixture was warmed to room temperature for 6 h, acidified to pH 3 with 5% HCl, and extracted with ethyl acetate. The combined organic phases were washed with dilute $NaHCO_3$ solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) gave 6.53 g of lactone. Continued elution with 50% ethyl acetate in hexanes furnished 1.2 g of uncyclized methyl ester which was treated with K_2CO_3 in methanol to give an additional 1.0 g of **14** (total overall yield from **12b** of 80%): IR ($CHCl_3$, cm^{-1}) 1766; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.46−7.35 (m, 6 H), 4.34−4.12 (m, 2 H), 3.70−3.63 (m, 2 H), 2.62−2.46 (m, 1 H), 2.24−1.93 (m, 3 H), 1.66−1.21 (m, 4 H), 1.06 (s, 9 H), 1.02 (d, J = 6.8 Hz, 1.5 H), 0.87 (d, J = 6.8 Hz, 1.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 178.9, 178.5, 135.5, 134.0, 129.6, 129.5, 127.6, 66.4, 66.3, 63.9, 63.8, 44.6, 43.6, 33.0, 32.1, 31.1, 30.2, 29.3, 26.9, 24.9, 22.9, 19.2, 17.4, 15.3; MS *m/z* (M^+) calcd 410.2277, obsd 410.2247. Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.10; H, 8.39.

3-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]-2(5*H*)-furanone (15). To a solution of potassium hexamethyldisilazide (38.2 mL of 0.5 M in toluene, 19.1 mmol) in anhydrous THF (120 mL) cooled to −78 °C was added **14** (6.50 g, 15.9 mmol) dissolved in 36 mL of THF. After 1 h, a solution of benzeneselenenyl chloride (3.70 g, 19.2 mmol) in THF (16 mL) was introduced, and the reaction mixture was stirred for 30 min before the reaction was quenched with saturated NH_4Cl solution and the mixture extracted with ether. The combined organic phases were washed with brine, dried, and concentrated to leave 11.0 g of an orange liquid which was dissolved in CH_2Cl_2 (200 mL) at 0 °C. Pyridine (7.5 mL) and 30% hydrogen peroxide (11.5 mL) were added in sequence, and the mixture was warmed to room temperature for 20 min prior to dilution with ether. The separated organic layer was washed with saturated $NaHSO_3$ solution, 5% HCl, saturated $NaHCO_3$ solution, and brine prior to drying and concentration. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 5.7 g (87%) of the oily lactone **15**: IR ($CHCl_3$, cm^{-1}) 1753; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4 H), 7.44−7.34 (m, 6 H), 7.01 (dd, J = 2.9, 1.6 Hz, 1 H), 4.74 (t, J = 1.6 Hz, 2 H), 3.67 (m, 2 H), 2.60 (m, 1 H), 1.72−1.50 (series of m, 4 H), 1.15 (d, J = 6.9 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.7, 143.0, 139.3, 135.6, 134.0, 129.6, 127.6, 69.9, 63.8, 31.2, 30.4, 30.1, 26.9, 19.2, 19.0; MS *m/z* (M^+) calcd 408.2121, obsd 408.2140; $[\alpha]^{22}_D$ −6.7 (*c* 1.56, $CHCl_3$). Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.55; H, 7.99.

3-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]dihydro-4-(methoxymethoxy)-2(3*H*)-furanone (17). To a cold (−78 °C) solution of lithium diisopropylamide (1.4 mL of 0.3 M in THF) was added **12b** (130 mg, 0.33 mmol) dissolved in 0.8 mL of THF. After 1 h, a solution of $OHCCH_2OTHP$ (71 mg, 0.49 mmol) in 0.5 mL of THF was introduced, and the reaction mixture was stirred for 30 min before the reaction was quenched with saturated NH_4Cl solution and the mixture extracted with ether. The combined ethereal layers were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 25% ethyl acetate in hexanes) to give 110 mg (62%) of **16a** as a mixture of diastereomeric aldols (^1H NMR analysis), which were directly protected.

The above isomeric mixture (100 mg, 0.18 mmol) dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C was treated in turn with diisopropylethylamine (0.16 mL, 0.90 mmol) and chloromethyl methyl ether (60 μL, 0.78 mmol). After 40 min, the reaction mixture was allowed to warm to room temperature, stirred for 12 h, diluted with ether, and washed with saturated $NaHCO_3$ solution and brine. After drying and solvent evaporation, the residue was chromatographed on silica gel (elution with 20% ethyl acetate in hexanes) to give 96 mg (89%) of **16b**.

A 90 mg (0.15 mmol) sample of **16b** in THF (2.5 mL) was treated with 1 mL of 10% H_2SO_4 solution, stirred for 24 h, diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Chromatographic purification of the residue on silica gel (elution with 20% ethyl acetate in hexanes) furnished **17** as a colorless oil (41 mg, 60%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.41 (m, 6 H), 4.62 (s, 2 H), 4.38 (m, 1 H), 4.26 (m, 1 H), 4.17 (m, 1 H), 3.68 (m, 2 H), 3.35 (s, 3 H), 2.66 (t, J = 4.5 Hz, 1 H), 2.11 (m, 1 H), 1.69−1.35 (m, 4 H), 1.06 (s, 9 H), 0.93 (d, J = 6.9 H, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (major isomer) 177.0, 135.5, 133.9, 129.6, 127.6, 95.9, 74.4, 72.3, 63.8, 55.9, 50.9, 32.4, 30.7, 30.2, 26.9, 19.2, 16.4; MS *m/z* (M^+) calcd 470.2488, obsd 470.2514.

Conversion of 17 to 15. A solution of **17** (40 mg, 0.085 mmol) in benzene (1.5 mL) was treated with DBU (70 μL, 0.42 mmol), heated at 70 °C for 9 h, and concentrated. The yellow residue was subjected to silica gel chromatography (elution with 20% ethyl acetate in hexanes) to afford 15 mg (44%) of **15**, which proved spectroscopically identical with the material obtained above.

(3*S*,4*S*)-3-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]dihydro-4-[(*E*)-3-(octahydro-1,3-dimethyl-2*H*-1,3,2-benzodiazaphosphol-2-yl)allyl]-2(3*H*)-furanone *P*-Oxide (19). A cold (−78 °C), magnetically stirred solution of **18** (2.04 g, 8.9 mmol) in dry THF (65 mL) was treated with *n*-butyllithium (6.0 mL of 1.6 M in hexanes, 9.6 mmol). After 3 min, a solution of **15** (3.65 g, 8.9 mmol) in the same solvent (45 mL) at −78 °C was introduced via a cannula. The mixture was stirred for 30 min before the reaction was quenched with saturated NH_4Cl solution and the mixture extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and evaporated. Chromatography on silica gel (elution with 6% methanol in ethyl acetate) returned 400 mg of unreacted **15** and afforded 4.1 g (81% based on recovered starting material) of **19**, a viscous colorless oil: IR (neat, cm^{-1}) 1780, 1630; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.38 (m, 6 H), 6.54 (m, 1 H), 5.54 (dd, J = 20.8, 16.6 Hz, 1 H), 4.28 (dd, J = 9.2, 7.4 Hz, 1 H), 3.85 (dd, J = 9.2, 5.8 Hz, 1 H), 3.64 (t, J = 6.1 Hz, 2 H), 2.74 (m, 1 H), 2.48 (d, J = 10.8 Hz, 3 H), 2.44 (d, J = 10.2 Hz, 3 H), 2.38−2.19 (m, 3 H), 2.02−1.80 (m, 4 H), 1.63−1.05 (series of m, 11 H), 1.03 (s, 9 H), 0.98 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 177.5, 148.0 (d, J = 3.1 Hz), 135.4, 133.9, 129.5, 127.5, 123.3 (d, J = 150.4 Hz), 70.8, 64.5 (d, J = 7.3 Hz), 63.74, 63.69, 50.1, 38.3 (d, J = 19.5 Hz), 36.9, 33.3, 30.4, 29.9, 28.7, 28.5, 28.1, 28.0, 26.8, 24.2, 24.1, 19.1, 16.7; MS *m/z* (M^+) calcd 636.3511, obsd 636.3474; $[\alpha]^{23}_D$ −20.7 (*c* 1.7, $CHCl_3$).

(3*S*,4*S*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]tetrahydro-5-oxo-3-furanacetaldehyde (20). Ozone was bubbled through a solution of **19** (6.0 g, 9.4 mmol) in CH_2Cl_2 (200 mL) and methanol (50 mL) at −78 °C until a blue color was sustained. Excess ozone was removed by a flow of N_2. Dimethyl sulfide (18 mL) was added, and the mixture was warmed to room temperature for 1.5 h prior to being extracted with ether. The combined ethereal phases were washed with brine (2×), dried, and evaporated. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in hexanes) provided 3.36 g (79%) of **20** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1772, 1724; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1 H), 7.68−7.65 (m, 4 H), 7.43−7.36 (m, 6 H), 4.52 (dd, J = 9.4, 7.7 Hz, 1 H), 3.77 (dd, J = 9.4, 6.7 Hz, 1 H), 3.67 (t, J = 5.9 Hz, 2 H), 2.83−2.76 (m, 2 H), 2.59 (dd, J = 19.4, 10.2 Hz, 1 H), 2.20 (dd, J = 7.5, 3.8 Hz, 1 H), 1.65−1.44 (m, 5 H), 1.05 (s, 9 H), 1.00 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.2, 177.0, 135.6, 134.0, 129.6, 127.6, 71.2, 63.8, 49.7, 48.0, 33.1, 32.4, 30.4, 30.0, 26.9, 19.2, 16.9; MS *m/z* ($M^+ + 1$) calcd 453.2461, obsd 453.2466; $[\alpha]^{20}_D$ −26.0 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{27}H_{36}O_4Si$: C, 71.71; H, 8.02. Found: C, 71.51; H, 8.03.

(3*S*,4*S*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]tetrahydro-5-oxo-3-furanacetaldehyde 3-(Dimethyl acetal) (21). A solution of **19** (3.36 g, 7.4 mmol) in trimethyl orthoformate (30 mL) and methanol (12 mL) was stirred with *p*-toluenesulfonic acid monohydrate (105 mg, 0.55 mmol) for 10 min. Solid $NaHCO_3$ was introduced, the mixture was extracted with ether, and the combined extracts were washed with brine and dried prior to concentration. The residue was purified by silica gel chromatography (elution with 25% ethyl acetate in hexanes) to give 3.31 g (90%) of **21** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1780, 1595, 1435; ^1H NMR (300 MHz, C_6D_6) δ 7.78 (m, 4 H), 7.24 (m, 6 H), 3.98 (m, 2 H), 3.65 (t, $J = 6.0$ Hz, 2 H), 3.39 (t, $J = 8.7$ Hz, 1 H), 2.99 (s, 3 H), 2.98 (s, 3 H), 2.14 (m, 1 H), 1.82 (dd, $J = 9.5$, 3.0 Hz, 1 H), 1.66−1.49 (m, 7 H), 1.18 (s, 9 H), 0.84 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 176.5, 136.0, 134.4, 129.9, 128.0, 103.2, 71.2, 64.2, 53.2, 52.4, 49.7, 36.2, 34.7, 32.7, 31.0, 30.4, 27.1, 19.5, 16.3; MS *m/z* ($M^+ - H$) calcd 497.2723, obsd 497.2704; $[\alpha]^{25}_D$ −6.4 (*c* 1.36, $CHCl_3$). Anal. Calcd for $C_{29}H_{42}O_5Si$: C, 69.84; H, 8.49. Found: C, 69.85; H, 8.51.

(3*S*,4*S*,5*R*)-8-(*tert*-Butyldiphenylsiloxy)-3-(hydroxymethyl)-5-methyl-4-vinyloctanal Dimethyl Acetal (22). A cold (−78 °C), magnetically stirred solution of **21** (3.31 g, 6.65 mmol) in CH_2Cl_2 (50 mL) was treated with Dibal-H (8.0 mL of 1.0 M in hexanes, 8.0 mmol) and stirred for 25 min, and the reaction was quenched with saturated NH_4Cl solution. Saturated Rochelle's salt solution was introduced, and the resultant mixture was stirred for 15 min and extracted with ether. The combined organic phases were washed with brine (2×), dried, and evaporated. Chromatography of the residue on silica gel (elution with 40% ethyl acetate in hexanes) afforded 3.21 g (97%) of the lactol as a colorless, oily mixture of epimers: IR (neat, cm^{-1}) 3435; ^1H NMR (300 MHz, C_6D_6) δ (major isomer) 7.96 (m, 4 H), 7.39 (m, 6 H), 5.31 (t, $J = 2.7$ Hz, 1 H), 4.33 (t, $J = 5.5$ Hz, 1 H), 4.26 (t, $J = 8.0$ Hz, 1 H), 3.94 (t, $J = 8.8$ Hz, 1 H), 3.81 (t, $J = 6.3$ Hz, 2 H), 3.21 (s, 6 H), 2.57 (d, $J = 6.7$ Hz, 1 H), 2.01−1.66 (series of m, 9 H), 1.34 (s, 9 H), 0.97 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm (major isomer) 136.0, 134.5, 129.9, 127.9, 103.9, 101.0, 72.5, 64.4, 58.1, 52.7, 52.1, 38.7, 36.6, 33.8, 31.6, 30.8, 27.1, 19.5, 16.5; MS *m/z* ($M^+ - H_2O$) calcd 482.2852, obsd 482.2854.

A suspension of methyltriphenylphosphonium bromide (10.6 g, 29.7 mmol) in dry THF (200 mL) at 0 °C was treated with potassium hexamethyldisilazide (56 mL of 0.5 M in toluene, 28.0 mmol). After 30 min, the resulting yellow solution was treated with the above lactol (4.73 g, 9.5 mmol) in 50 mL of the same solvent. The reaction mixture was warmed to room temperature for 4.5 h, the reaction was quenched with saturated NH_4Cl solution, and the mixture was diluted with ether, washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 25% ethyl acetate in hexanes) provided 4.1 g (80%) of **22** as a colorless oil: IR (neat, cm^{-1}) 3490, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 4 H), 7.24 (m, 6 H), 5.44 (dt, $J = 17.0$, 10.2 Hz, 1 H), 4.99 (dd, $J = 10.2$, 2.4 Hz, 1 H), 4.91 (dd, $J = 17.0$, 2.4 Hz, 1 H), 4.50 (br t, 1 H), 3.66 (t, $J = 6.5$ Hz, 2 H), 3.63 (m, 1 H), 3.47 (br d, $J = 11.0$ Hz, 1 H), 3.13 (s, 3 H), 3.12 (s, 3 H), 1.92 (m, 1 H), 1.79 (m, 4 H), 1.58 (m, 3 H), 1.43 (m, 1 H), 1.19 (s, 9 H), 0.76 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.5, 136.0, 134.5, 129.9, 128.1, 117.0, 103.9, 64.6, 63.4, 52.8, 52.1, 50.7, 37.8, 33.2, 32.7, 31.8, 30.4, 27.1, 19.5, 15.7; $[\alpha]^{23}_D$ +6.1 (*c* 1.3, benzene). Anal. Calcd for $C_{30}H_{46}O_4Si$: C, 72.24; H, 9.30. Found: C, 72.21; H, 9.32.

(4*S*)-4-[(1*S*)-1-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]-allyl]dihydro-2(3*H*)-furanone (23). A solution of **22** (1.55 g, 3.1 mmol) in THF (60 mL) ws stirred with 5% HCl (7 mL) for 7 h, diluted with ether, and washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried, concentrated, and chromatographed on silica gel (elution with 25% ethyl acetate in hexanes) to give 1.1 g (78%) of the lactol as a colorless oil: IR (neat, cm^{-1}) 3420, 1640; ^1H NMR (300 MHz, C_6D_6) δ (major isomer) 7.79 (m, 4 H), 7.23 (m, 6 H), 5.35 (m, 2 H), 4.82 (m, 2 H), 4.09 (t, $J = 8.2$ Hz, 1 H), 3.64 (t, $J = 6.5$ Hz, 2 H), 3.45 (t, $J = 8.3$ Hz, 1 H), 2.49 (m, 1 H), 1.93 (m, 1 H), 1.84 (dd, $J = 12.3$, 7.1 Hz, 1 H), 1.62−1.20 (series of m, 7 H), 1.19 (s, 9 H), 0.66 (d, $J = 6.8$ Hz, 3 H).

A solution of the above lactol (0.89 g, 1.77 mmol) in CH_2Cl_2 (30 mL) was treated with 1.0 g of 4 Å molecular sieves and 1.00 g (2.66 mmol) of pyridinium dichromate. The mixture was stirred at room temperature for 6 h, diluted with ether (60 mL), filtered through a short path of silica gel, and concentrated. The residue was chromatographed on silica gel (elution with 15% ethyl acetate in hexanes) to give 777 mg (97%) of **23** as a colorless oil: IR (neat, cm^{-1}) 1785; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.41 (m, 6 H), 5.53 (dt, $J = 17.0$, 10.0 Hz, 1 H), 5.13 (dd, $J = 10.3$, 1.8 Hz, 1 H), 5.03 (dd, $J = 17.0$, 1.8 Hz, 1 H), 4.27 (dd, $J = 9.0$, 7.8 Hz, 1 H), 3.86 (t, $J = 9.0$ Hz, 1 H), 3.65 (t, $J = 6.5$ Hz, 2 H), 2.65 (m, 2 H), 2.12 (dd, $J = 17.0$, 10.0 Hz, 1 H), 1.94 (m, 1 H), 1.60−1.15 (series of m, 5 H), 1.06 (s, 9 H), 0.82 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 176.8, 135.6, 134.9, 134.0, 129.6, 127.6, 118.5, 72.4, 63.9, 51.8, 37.0, 34.1, 33.1, 31.3, 30.0, 26.9, 19.2, 14.5; MS *m/z* ($M^+ - H$) calcd 449.2512, obsd 449.2480; $[\alpha]^{20}_D$ −2.8 (*c* 1.7, benzene). Anal. Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found: C, 74.58; H, 8.42.

(4*S*)-4-[(1*S*,2*R*)-5-(*tert*-Butyldiphenylsiloxyl)-1-[(1*S*)-1-hydroxy-2-(phenylselenyl)ethyl]-2-methylpentyl]dihydro-2(3*H*)-furanone (24). Into a solution of **23** (655 mg, 1.47 mmol) in CH_2Cl_2 (25 mL) at −78 °C was bubbled ozone until a blue color persisted. Following the introduction of an N_2 stream for 15 min, triphenylphosphine (1.0 g, 3.8 mmol) was introduced, and the mixture was warmed to room temperature for 5 h prior to dilution with ether. The organic phase was washed with brine, dried, and evaporated to leave a residue, chromatography of which on silica gel (elution with 25% ethyl acetate in hexanes) gave 570 mg (87%) of the aldehyde as a colorless oil: IR (neat, cm^{-1}) 1790, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, $J = 1.0$ Hz, 1 H), 7.65 (m, 4 H), 7.41 (m, 6 H), 4.62 (dd, $J = 9.3$, 7.9 Hz, 1 H), 3.79 (t, $J = 9.0$ Hz, 1 H), 3.71 (t, $J = 5.6$ Hz, 2 H), 2.93 (m, 1 H), 2.51 (dd, $J = 17.3$, 8.6 Hz, 1 H), 2.13 (dd, $J = 17.3$, 10.4 Hz, 1 H), 1.83−1.44 (series of m, 6 H), 1.07 (s, 9 H), 0.92 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR 75 MHz, $CDCl_3$) ppm 203.1, 175.7, 135.5, 133.8, 129.7, 127.7, 72.4, 63.4, 59.3, 33.7, 33.4, 32.3, 31.7, 30.5, 26.9, 19.2, 15.9; MS *m/z* ($M^+ - H$) calcd 451.2304, obsd 451.2333; $[\alpha]^{23}_D$ −44.3 (*c* 1.45, $CHCl_3$). Anal. Calcd for $C_{27}H_{36}O_4Si$: C, 71.64; H, 8.02. Found: C, 71.38; H, 7.88.

To a solution of bis(phenylseleno)methane (192 mg, 0.59 mmol) in THF (15 mL) at −78 °C was added *n*-butyllithium (0.41 mL of 1.6 M in hexanes, 0.65 mmol). After 40 min of stirring, the anion solution was transferred via cannula to a solution of the above aldehyde (221 mg, 0.49 mmol) in THF (20 mL) at −78 °C. The reaction mixture was stirred for 40 min, the reaction quenched with saturated NH_4Cl solution, and the mixture extracted with ether. The combined ethereal layers were washed with brine, dried, and evaporated. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to give 245 mg (80%) of **24** as a colorless oil: IR (neat, cm^{-1}) 3500, 1785; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.47 (m, 2 H), 7.42 (m, 6 H), 7.22 (m, 3 H), 4.47 (t, $J = 8.2$ Hz, 1 H), 3.96 (t, $J = 9.2$ Hz, 1 H), 3.61 (m, 1 H), 3.57 (t, $J = 6.5$ Hz, 2 H), 3.02 (dd, $J = 12.8$, 3.1 Hz, 1 H), 2.88 (m, 1 H), 2.74 (dd, $J = 12.8$, 10.3 Hz, 1 H), 2.47 (m, 2 H), 2.17 (dd, $J = 7.0$, 1.6 Hz, 1 H), 1.47 (m, 6 H), 1.05 (s, 9 H), 0.82 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 176.7, 135.5, 133.9, 133.4, 129.7, 129.3, 128.3, 127.8, 127.6, 73.1, 67.8, 63.7, 50.3, 38.3, 35.6, 34.4, 34.3, 31.0, 30.7, 26.9, 19.2, 15.7; MS *m/z* (M^+) calcd 624.2174, obsd 624.2186; $[\alpha]^{23}_D$ +13.5 (*c* 1.0, $CHCl_3$).

(3a*S*,4*R*,6*S*,7a*R*)-7-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]hexahydro-6-[(phenylselenyl)methyl]-4-[(*E*)-1-propenyl]-3*H*-furo[3,4-*c*]pyran-3-ene (26). A solution of **24** (80 mg, 0.13 mmol) in 2-methoxypropene (2 mL) was treated with 1 drop of phosphorus oxychloride and stirred at room temperature for 2.5 h, the reaction was quenched with a few drops of triethylamine, and the mixture was passed down a short column of silica gel packed with 20% ethyl acetate in hexanes containing 2% triethylamine. The eluate was concentrated and the residue purified by chromatography on silica gel (elution with 15% ethyl acetate in hexanes, 3% in $(C_2H_5)_3N$) to provide 85 mg (96%) of the acetal as a colorless oil: IR (neat, cm^{-1}) 1780; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4 H), 7.50 (m, 2 H), 7.42 (m, 6 H), 7.22 (m, 3 H), 4.44 (t, $J = 8.1$ Hz, 1 H), 4.00 (dd, $J = 10.2$, 8.7 Hz, 1 H), 3.98 (m, 1 H), 3.65 (t, $J = 6.4$ Hz, 2 H), 3.43 (dd, $J = 12.6$, 3.4 Hz, 1 H), 3.24 (s, 3 H), 2.87 (m, 2 H), 2.47 (dd, $J = 17.0$, 8.0 Hz, 1 H), 2.18 (dd, $J = 17.0$, 12.2 Hz, 1 H), 1.86 (m, 1 H), 1.70−1.33 (series of m, 3 H), 1.31 (s, 3 H), 1.29 (s, 3 H), 1.22 (m, 2 H), 1.07 (s, 9 H), 0.83 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 176.8, 135.6, 133.9,

133.0, 129.9, 129.6, 129.2, 127.6, 127.2, 101.5, 73.3, 70.4, 63.8, 49.0, 47.7, 36.0, 34.3, 34.0, 33.1, 31.8, 30.7, 26.9, 25.5, 24.6, 19.2, 15.8; MS *m/z* (M^+) calcd 696.2749, obsd 696.2754; $[\alpha]^{23}_D$ −7.5 (*c* 1.0, $CHCl_3$).

To a solution of lithium diisopropylamide [prepared from 0.47 mL (3.4 mmol) of diisopropylamine and *n*-butyllithium (2.2 mL of 1.55 M in hexanes, 3.4 mmol) in 25 mL of THF] at −78 °C was added a solution of the above acetal (1.8 g, 2.6 mmol) in 13 mL of THF. The reaction mixture was stirred at this temperature for 1 h, treated with a solution of crotonaldehyde (640 mg, 9.1 mmol) in THF (4 mL), and stirred for an additional 20 min. The reaction was quenched with saturated NH_4Cl solution and the mixture extracted with ether. The combined organic phases were washed with brine, dried over magnesium sulfate (triethylamine and $NaHCO_3$ were added to inhibit deprotection), and concentrated. The residue was chromatographed on silica gel (elution with 30% ethyl acetate in hexanes containing 3% triethylamine) to furnish 1.8 g (91%) of **25** as an inseparable aldol mixture.

The aldols were dissolved in benzene (400 mL), treated with *p*-toluenesulfonic acid (55 mg, 0.29 mmol), and heated under a Dean−Stark trap with removal of water for 7 h. The benzene was evaporated, and the residue was subjected to silica gel chromatography (elution with 10% ethyl acetate in hexanes) to afford 785 mg (49%) of **26a** and 230 mg (14%) of **26b**.

26a: colorless oil; IR (neat, cm^{-1}) 1765; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.51 (m, 2 H), 7.41 (m, 6 H), 7.25 (m, 3 H), 5.86 (m, 1 H), 5.62 (m, 1 H), 4.23 (dd, J = 8.3, 6.5 Hz, 1 H), 4.13 (m, 2 H), 4.00 (dd, J = 11.4, 8.4 Hz, 1 H), 3.63 (m, 2 H), 3.25 (dd, J = 12.3, 6.7 Hz, 1 H), 3.08 (dd, J = 12.3, 8.0 Hz, 1 H), 2.61 (m, 1 H), 2.28 (dd, J = 14.5, 10.0 Hz, 1 H), 1.89 (m, 1 H), 1.75 (d, J = 6.5 Hz, 3 H), 1.65−1.09 (series of m, 5 H), 1.06 (s, 9 H), 0.92 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.9, 135.5, 133.8, 133.1, 129.6, 129.4, 129.1, 128.2, 127.7, 127.6, 127.3, 73.0, 70.9, 69.3, 63.7, 42.7, 41.0, 39.6, 33.9, 30.8, 30.4, 26.9, 19.1, 17.9, 17.2; MS *m/z* (M^+) calcd 676.2487, obsd 676.2496; $[\alpha]^{23}_D$ +4.8 (*c* 1.87, $CHCl_3$).

26b: colorless oil; IR (neat, cm^{-1}) 1765; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.53 (m, 2 H), 7.39 (m, 6 H), 7.22 (m, 3 H), 5.87 (ddq, J = 15.2, 6.3, 1.2 Hz, 1 H), 5.58 (ddq, J = 15.2, 6.1, 1.6 Hz, 1 H), 4.60 (t, J = 6.0 Hz, 1 H), 4.31 (dd, J = 8.5, 6.7 Hz, 1 H), 4.03 (dd, J = 12.0, 8.5 Hz, 1 H), 3.62 (m, 3 H), 3.18 (dd, J = 12.5, 3.4 Hz, 1 H), 3.02 (dd, J = 12.5, 7.0 Hz, 1 H), 2.84 (m, 2 H), 1.98 (m, 1 H), 1.72 (d, J = 6.5 Hz, 3 H), 1.67−1.08 (series of m, 5 H), 1.06 (s, 9 H), 0.87 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.7, 135.5, 133.80, 133.77, 133.3, 130.0, 129.7, 129.0, 127.7, 127.0, 126.0, 74.6, 72.9, 68.8, 63.6, 44.3, 41.4, 35.8, 34.5, 32.6, 31.9, 30.8, 26.9, 19.2, 17.9, 17.7; MS *m/z* (M^+) calcd 676.2487, obsd 676.2481.

Equilibration of 26b with 26a. A solution of **26b** (340 mg, 0.5 mmol) in benzene (80 mL) was refluxed for 4 h in the presence of *p*-toluenesulfonic acid (15 mg, 0.08 mmol). The same chromatographic separation as described above led to the isolation of 205 mg (60%) of **26a** and the return of 50 mg (15%) of **26b**.

(3a*R*,4*S*,7*R*,9a*R*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]-3a,4,7,9a-tetrahydro-7-methylcycloocta[*c*]furan-1,5(3*H*,6*H*)-dione (29) and (3a*R*,4*S*,7*S*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]-3a,4,7,8-tetrahydro-7-methylcycloocta[*c*]furan-1,5(3*H*,6*H*)-dione (30). Into a solution of **26a** (213 mg, 0.32 mmol) in methanol (15 mL) and water (1.5 mL) was introduced sodium periodate (86 mg, 0.4 mmol) and sodium bicarbonate (40 mg, 0.5 mmol). The mixture was stirred for 30 min, and the resulting white suspension was diluted with water to a total volume of 200 mL prior to extraction with CH_2Cl_2 (3 × 80 mL). The combined organic phases were washed with water, dried, and evaporated to leave the selenoxide which was divided into two equal portions. Each lot was dissolved in 9 mL of dimethylacetamide, transferred into a pressure tube, and treated with ethyl vinyl ether (0.75 mL) and triethylamine (0.25 mL). The sealed tubes were heated at 220 °C in a Wood's metal bath for 20 min, cooled, diluted with water, and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) gave 92 mg (55%) of **29** and 12 mg (7%) of **30**.

29: colorless oil; IR (neat, cm^{-1}) 1785, 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.40 (m, 6 H), 5.83 (m, 1 H), 5.65 (m, 1 H), 4.28 (s, 1 H), 4.25 (d, J = 3.0 Hz, 1 H), 3.67 (t, J = 5.7 Hz, 2 H), 2.83 (dd, J = 14.0, 9.4 Hz, 1 H), 2.65 (dd, J = 11.4, 6.9 Hz, 1 H), 2.56−2.24 (series of m, 4 H), 1.81 (m, 1 H), 1.57 (m, 2 H), 1.43 (m, 1 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.11 (m, 1 H), 1.05 (s, 9 H), 0.79 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.1, 175.3, 140.5, 135.5, 133.8, 129.7, 127.7, 123.6, 67.9, 63.6, 56.8, 54.8, 44.2, 39.4, 32.6, 30.7, 29.8, 28.9, 26.9, 22.9, 19.2, 17.9; MS *m/z* (M^+ − H) calcd 517.2774, obsd 517.2745; $[\alpha]^{23}_D$ −17.5 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{32}H_{42}O_4Si$: C, 74.09; H, 8.16. Found: C, 74.25; H, 8.46.

30: colorless oil; IR (neat, cm^{-1}) 1770, 1710, 1685; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.40 (m, 6 H), 6.78 (ddd, J = 10.2, 8.6, 3.2 Hz, 1 H), 4.59 (t, J = 8.9 Hz, 1 H), 4.33 (t, J = 8.4 Hz, 1 H), 3.69 (t, J = 5.9 Hz, 2 H), 3.29 (m, 2 H), 2.61 (dt, J = 13.1, 10.5 Hz, 1 H), 2.41 (dd, J = 10.6, 5.5 Hz, 1 H), 2.30 (m, 1 H), 2.24 (t, J = 8.8 Hz, 1 H), 1.78 (m, 2 H), 1.61 (m, 2 H), 1.46 (m, 1 H), 1.26 (m, 1 H), 1.14 (d, J = 6.7 Hz, 3 H), 1.06 (s, 9 H), 0.87 (d, J = 9.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 215.0, 171.0, 137.1, 135.5, 133.8, 130.0, 129.7, 127.7, 66.6, 63.7, 57.1, 54.1, 38.5, 34.1, 33.9, 30.3, 28.8, 28.6, 26.9, 24.1, 19.2, 17.7; MS *m/z* (M^+ − H) calcd 517.2774, obsd 517.2780; $[\alpha]^{23}_D$ −51.4 (*c* 2.0, $CHCl_3$).

(3a*R*,4*S*,7*R*,7a*S*,8a*S*,8b*R*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]octahydro-7-methyl-1*H*-cyclopropa[3,4]cycloocta[1,2-*c*]furan-1,5(2*H*)-dione (31). A solution of **29** (252 mg, 0.48 mmol) in benzene (20 mL) was treated with diethylzinc (0.95 mL of 1.1 M in toluene, 1.0 mmol) and diiodomethane (0.5 mL, 5.8 mmol). The reaction mixture was stirred at room temperature for 1.5 h, the reaction quenched with saturated NH_4Cl solution (25 mL), and the mixture diluted with ether. The separated organic phase was washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexanes) provided 240 mg (92%) of **31** as a colorless oil; IR (neat, cm^{-1}) 1790, 1705; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.40 (m, 6 H), 4.25 (m, 1 H), 4.13 (dd, J = 11.1, 8.6 Hz, 1 H), 3.69 (t, J = 5.8 Hz, 2 H), 3.05 (dd, J = 11.3, 6.6 Hz, 1 H), 2.59−2.38 (m, 2 H), 2.25 (d, J = 10.2 Hz, 1 H), 1.82−1.39 (series of m, 5 H), 1.21 (d, J = 2.3 Hz, 3 H), 1.16 (m, 2 H), 1.06 (s, 9 H), 1.01 (m, 1 H), 0.85 (d, J = 6.3 Hz, 3 H), 0.80 (m, 2 H), 0.28 (dd, J = 10.7, 5.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.6, 176.6, 135.5, 133.8, 129.7, 127.6, 67.6, 63.6, 55.5, 55.1, 44.3, 43.7, 35.1, 33.1, 29.9, 28.9, 26.8, 23.1, 20.4, 19.1, 18.2, 13.8, 9.5; MS *m/z* (M^+) calcd 532.3009, obsd 532.3003; $[\alpha]^{23}_D$ +8.6 (*c* 1.86, $CHCl_3$). Anal. Calcd for $C_{33}H_{44}O_4Si$: C, 74.39; H, 8.32. Found: C, 74.67; H, 8.66.

(3a*R*,4*S*,5*R*,7*R*,7a*S*,8a*S*,8b*R*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]decahydro-5-hydroxy-7-methyl-1*H*-cyclopropa[3,4]-cycloocta[1,2-*c*]furan-1-one (32). A solution of **31** (285 mg, 0.54 mmol) in CH_2Cl_2 (12 mL) cooled to −78 °C was treated with Dibal-H (1.6 mL of 1.0 M in hexanes, 1.6 mmol) and stirred for 15 min. The reaction was quenched with saturated NH_4Cl solution, and the mixture was acidified with 5% HCl to pH 3 and extracted with ethyl acetate. The combined organic extracts were dried and evaporated, and the residual oil was filtered through a short column of silica gel (elution with 50% ethyl acetate in hexanes) to give 260 mg (91%) of a 2:1 stereoisomeric mixture of hydroxy lactols (^1H NMR analysis). This material was dissolved in benzene (90 mL), treated with silver carbonate on Celite (3.0 g, ca. 10 equiv), stirred at the reflux temperature for 10 min, cooled, and filtered through a small pad of silica gel (elution with 30% ethyl acetate in hexanes). Lactone **32** was obtained in quantitative yield as a colorless oil: IR (neat, cm^{-1}) 3520, 1770; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 4.47 (dd, J = 11.5, 7.7 Hz, 1 H), 4.23 (t, J = 7.2 Hz, 1 H), 4.17 (m, 1 H), 3.68 (m, 2 H), 2.65 (dd, J = 13.5, 9.9 Hz, 1 H), 2.35 (m, 1 H), 2.07 (dd, J = 6.0, 3.3 Hz, 1 H), 1.77 (dd, J = 13.8, 6.1 Hz, 1 H), 1.63−1.12 (series of m, 8 H), 1.09 (d, J = 6.6 Hz, 3 H), 1.06 (s, 9 H), 1.00 (m, 1 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.63 (m, 2 H), 0.24 (q, J = 5.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.1, 135.5, 133.9, 129.6, 127.6, 71.4, 70.6, 63.8, 47.5, 47.3, 44.7, 43.6, 36.8, 31.6, 30.7, 29.8, 26.8, 23.5, 20.8, 19.2, 16.9, 14.2, 9.2; MS *m/z* ($M^+ - C_4H_8$) calcd 478.2508, obsd 478.2494; $[\alpha]^{23}_D$ +29.3 (*c* 2.17, $CHCl_3$).

(4*S*,5*R*,7*R*,7a*S*,8a*S*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]-3,4,5,6,7,7a,8,8a-octahydro-5-hydroxy-7-methyl-1*H*-cyclopropa[3,4]cycloocta[1,2-*c*]furan-1-one (33a). A solution of **32** (107 mg, 0.20 mmol) in THF (5 mL) at −78 °C was treated with

potassium hexamethyldisilazide (0.96 mL of 0.5 M in toluene, 0.48 mmol), stirred for 1 h, and treated with benzeneselenenyl chloride (92 mg, 0.48 mmol) dissolved in 0.8 mL of THF. The mixture was stirred for 15 min before the reaction was quenched with saturated NH_4Cl solution and the mixture extracted with ether. The combined organic phases were washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated to leave a residue which was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes). There was obtained 104 mg (83% based on recovered **32**) of a 2:1 mixture (^{1}H NMR analysis) of selenides and 10 mg of unreacted **32**.

The above selenides (104 mg, 0.15 mmol) were dissolved in methanol (10 mL) and water (0.65 mL), treated with sodium periodate (104 mg, 0.48 mmol) and sodium bicarbonate (52 mg, 0.62 mmol), stirred for 1 h, diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and evaporated. Chromatographic purification of the residue (silica gel, elution with 30% ethyl acetate in hexanes) afforded **33a** (70 mg, 87%) as a white solid: mp 141−142 °C; IR ($CHCl_3$, cm^{-1}) 3640, 1755, 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.40 (m, 6 H), 4.97 (dd, J = 17.3, 2.5 Hz, 1 H), 4.67 (dd, J = 17.3, 2.8 Hz, 1 H), 4.32 (br s, 1 H), 3.64 (m, 2 H), 3.08 (d, J = 8.2 Hz, 1 H), 1.87 (m, 1 H), 1.72 (m, 3 H), 1.50 (m, 4 H), 1.25 (m, 2 H), 1.04 (s, 9 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.96 (m, 2 H), 0.35 (q, J = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.8, 168.8, 135.5, 133.8, 129.6, 127.9, 127.6, 72.3, 69.8, 63.7, 48.8, 48.4, 33.1, 31.8, 30.2, 28.3, 26.8, 26.0, 23.7, 19.1, 17.4, 10.0, 8.1; MS *m/z* (M^+) calcd 432.3009, obsd 532.3010; $[\alpha]^{23}_D$ +28.8 (*c* 1.67, $CHCl_3$). Anal. Calcd for $C_{33}H_{44}O_4Si$: C, 74.39; H, 8.32. Found: C, 74.00; H, 8.32.

(4*S*,5*R*,7*R*,7a*S*,8a*S*)-4-[(1*R*)-4-(*tert*-Butyldiphenylsiloxy)-1-methylbutyl]-3,4,5,6,7,7a,8,8a-octahydro-5-hydroxy-7-methyl-1*H*-cyclopropa[3,4]cycloocta[1,2-*c*]furan-1-one Acetate (33b). A solution of **33a** (171 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was treated with acetic anhydride (0.28 mL, excess) and DMAP (70 mg, 0.57 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with ether (20 mL), washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in hexanes) gave 183 mg (99%) of **33b** as a colorless oil: IR (neat, cm^{-1}) 1765, 1740, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.40 (m, 6 H), 5.44 (br s, 1 H), 4.76 (dd, J = 17.0, 2.4 Hz, 1 H), 4.67 (dd, J = 17.0, 2.7 Hz, 1 H), 3.62 (m, 2 H), 3.15 (d, J = 8.3 Hz, 1 H), 2.01 (s, 3H), 1.91 (dd, J = 15.4, 4.4 Hz, 1 H), 1.81−1.06 (series of m, 9 H), 1.03 (s, 9 H), 0.97 (d, J = 6.6 Hz, 6 H), 0.93 (m, 1 H), 0.37 (q, J = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.2, 169.8, 166.8, 135.5, 133.7, 129.6, 128.7, 127.6, 72.0, 71.4, 63.6, 47.3, 43.9, 32.9, 31.9, 30.0, 29.0, 26.8, 25.9, 23.4, 21.3, 19.1, 17.0, 10.1, 8.2; MS *m/z* (M^+ − H) calcd 573.3036, obsd 573.3027; $[\alpha]^{23}_D$ +21.0 (*c* 1.9, $CHCl_3$). Anal. Calcd for $C_{35}H_{46}O_5Si$: C, 73.13; H, 8.07. Found: C, 73.51; H, 8.33.

(4*S*,5*R*,7*R*,7a*S*,8a*S*)-3,4,5,6,7,7a,8,8a-Octahydro-5-hydroxy-4-[(1*R*)-4-hydroxy-1-methylbutyl]-7-methyl-1*H*-cyclopropa[3,4]cycloocta-[1,2-*c*]furan-1-one 5-Acetate (33c). A solution of **33b** (153 mg, 0.27 mmol) in CH_3CN (8 mL) was treated with pyridinium fluoride solution [prepared by adding 1 mL of 48% HF to a mixture of CH_3CN (1 mL) and pyridine (2.4 mL) at 0 °C] in three equal aliquots of 0.33 mL over 6 h. The mixture was then diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with 5% HCl, saturated $NaHCO_3$ solution, and brine prior to drying and solvent evaporation. Chromatography of the residue gel (elution with 90% ethyl acetate in hexanes) afforded 77 mg (87%) of **33c** as a colorless oil: IR (neat, cm^{-1}) 3495, 1770, 1740, 1665; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (br s, 1 H), 4.83 (dd, J = 17.2, 2.3 Hz, 1 H), 4.76 (dd, J = 17.2, 2.8 Hz, 1 H), 3.61 (m, 2 H), 3.20 (d, J = 8.1 Hz, 1 H), 2.01 (s, 3 H), 1.90 (dd, J = 14.8, 4.3 Hz, 1 H), 1.82−1.22 (series of m, 7 H), 1.12 (m, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 3 H), 0.92 (m, 1 H), 0.34 (q, J = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.0, 169.6, 166.1, 128.9, 72.3, 71.4, 62.4, 47.6, 43.9, 33.2, 31.8, 30.2, 29.3, 25.9, 23.2, 21.1, 17.1, 10.3, 8.4; MS *m/z* (M^+) calcd 336.1939, obsd 336.1938; $[\alpha]^{23}_D$ +41.9 (*c* 1.0, $CHCl_3$).

(α*R*,4*S*,5*R*,7*R*,7a*S*,8a*S*)-3,4,5,6,7,7a,8,8a-Octahydro-5-hydroxy-γ,7-dimethyl-oxo-1*H*-cyclopropa[3,4]cycloocta[1,2-*c*]furan-4-butyraldehyde Acetate (34). A solution of **33c** (55 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was treated with pyridinium dichromate (80 mg, 0.21 mmol) and 4 Å molecular sieves (80 mg), stirred at room temperature for 80 min, diluted with ether (10 mL), and filtered through a short column of silica gel. There was obtained 44 mg (80%) of **34** as a colorless oil: IR (neat, cm^{-1}) 1775, 1750, 1735, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (br s, 1 H), 4.85 (m, 2 H), 3.18 (d, J = 8.1 Hz, 1 H), 2.52 (m, 2 H), 2.02 (s, 3 H), 1.91−1.60 (series of m, 5 H), 1.47 (m, 1 H), 1.31 (m, 1 H), 1.04 (m, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 3 H), 0.35 (dd, J = 10.7, 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.7, 173.7, 169.6, 165.3, 129.2, 72.1, 71.2, 47.7, 43.9, 41.3, 32.8, 29.3, 27.6, 25.9, 23.2, 21.1, 16.7, 10.4, 8.4; MS *m/z* (M^+) calcd 334.1758, obsd 334.1769; $[\alpha]^{23}_D$ +43.3° (*c* 1.5, $CHCl_3$).

Acetoxycrenulide (1a). A suspension of vacuum-dried isopropyltriphenyl phosphonium bromide (50 mg, 0.13 mmol) in cold (0 °C) THF (2 mL) was treated with *n*-butyllithium (0.10 mL of 1.5 M in hexanes, 0.15 mmol), and an oranged-colored solution resulted. This solution was cooled to −78 °C, treated with **34** (28 mg, 0.084 mmol) dissolved in THF (1 mL), stirred for 5 min at −78 °C, and warmed to room temperature for 10 min. The reaction was quenched with saturated NH_4Cl solution and the mixture extracted with ether. The combined organic layers were dried and concentrated to leave a residue which was chromatographed on silica gel (elution with 25% ethyl acetate in hexanes). There was isolated 23 mg (79%) of **1a**, which exhibits a ^{1}H NMR spectrum identical with those of natural acetoxycrenulide:[6,7] ^{13}C NMR (75 MHz, $CDCl_3$, 60 °C) ppm 173.9, 169.6, 166.2, 132.4, 128.8, 123.6, 72.4, 71.4, 47.5, 43.9, 35.7, 32.9, 29.3, 25.9, 25.5 (2 C), 23.3, 21.1, 17.6, 17.1, 10.4, 8.4; $[\alpha]^{23}_D$ +20.1 (*c* 1.8, $CHCl_3$). The highest reported optical rotation for **1a** is +21.5.[4]

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