Total Synthesis of the Pseudopterane (−)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B

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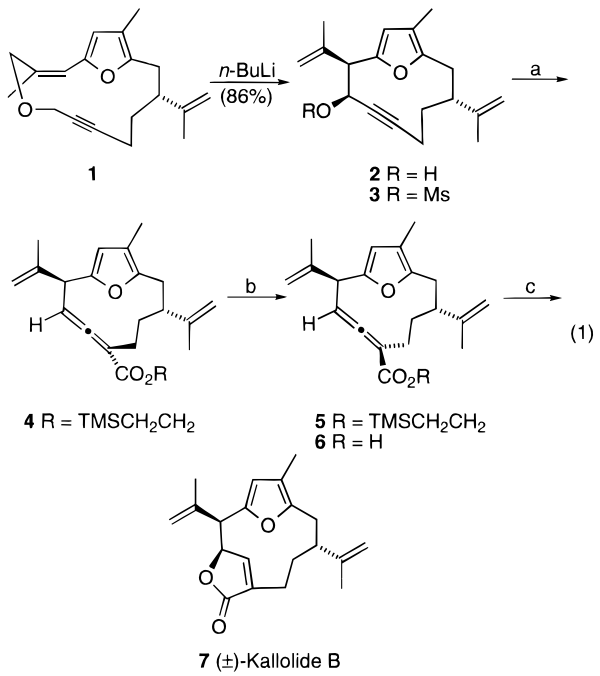
A total synthesis of the enantiomer **35** of kallolide B was achieved starting from *(S)*-(−)-perillyl alcohol (**8**). Oxidative cleavage to the ester aldehyde **11** was effected by treatment of the epoxide **9** with H_5IO_6 followed by CH_2N_2. The allenyl ketone **13**, obtained by $SnCl_2$-promoted addition of 1-bromo-2-butyne to aldehyde **11** and subsequent Swern oxidation, cyclized to the furan **14** in the presence of catalytic $AgNO_3$. Homologation of the derived aldehyde **15** with CBr_4−Ph_3P followed by *n*-BuLi and CH_2O led to the propargylic alcohol **17**. Formylation of the furan **17** (*s*-BuLi, DMF) and then Still−Horner−Emmons homologation yielded the *(Z)*-conjugated ester **22**. Conversion of the propargylic alcohol function to the chloride **23** and ester reduction (DIBAL-H) furnished the chloro alcohol **24,** which formed the cyclic ether **25** upon treatment with NaH. Ether **25** underwent a highly diastereoselective [2,3]Wittig ring contraction to the propargylic alcohol **26**. The derived mesylate **36** was converted to the allenic ester **37** with CO and $TMSCH_2CH_2OH$ in the presence of $Pd(PPh_3)_4$. Ester **37** was isomerized to the diastereomer **39** with Ph_3P in CH_3CN. Ester cleavage with TBAF followed by cyclization of the acid intermediate with catalytic $AgNO_3$ led to butenolide **35**, identical to kallolide B according to comparison of NMR spectra, but of opposite optical rotation.

We recently described a stereoselective synthesis of the furanocyclic pseudopterane diterpene, kallolide B, as a racemate.[1] The synthetic sequence incorporated a number of interesting chemical transformations and several applications of molecular mechanics as a predictive tool for stereochemically critical steps. The key elements of the approach featured a remarkably diastereoselective [2,3]Wittig ring contraction of the cyclic propargyl allylic ether **1**, affording alcohol **2** as the only product in 86% yield (eq 1).



a. $(Ph_3P)_4Pd$, CO,$TMSCH_2CH_2OH$; b. Ph_3P; c. $AgNO_3$

Failing to effect conversion of propargylic alcohol **2** to the requisite butenolide by the conventional procedure,[2,3] we developed a new route *via* the mesylate **3** employing Pd(0)-catalyzed alkoxycarbonylation with CO and *β*-TMS ethanol. Lactonization to (±)-kallolide B (**7**) was achieved by treatment of allenic acid **6** with $AgNO_3$.

The only other synthesis of a pseudopterane natural product reported to date is that of racemic gorgiacerone, by Paquette and co-workers.[4] While confirming the overall structure and relative stereochemistry of these pseudopteranes, the foregoing syntheses leave the question of absolute configuration unresolved. The original structure assignments to currently known members of the pseudopterane family did not address this issue. It was for that reason, along with a desire to more closely examine some of the key tranformations in our synthesis of the racemate, that we decided to carry out a parallel enantioselective synthesis of kallolide B.

For our starting material we selected *(S)*-(−)-perillyl alcohol (**8**). Both enantiomers of this monoterpene are commercially available, but cost considerations led to our choice of the less expensive *(S)* enantiomer.[5] Hydroxyl-directed epoxidation afforded a diastereomeric mixture of epoxides **9** that was subjected to periodate cleavage after distillation.[6] Esterification of the resultant acid **10** yielded the ester aldehyde **11** in high overall yield. Addition of the stannane reagent derived from 1-bromo-2-butyne and $SnCl_2$[7] gave the allenylcarbinol **12** as a diastereoisomeric mixture. Oxidation then afforded the allenone **13**, which cyclized to furan **14** in 96% yield upon exposure to catalytic $AgNO_3$ in acetone.[8] Side chain

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

(1) Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796.
(2) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
(3) *Cf.* Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.
(4) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.
(5) Aldrich Chemical Co., Milwaukee, WI. The 1995 catalogue lists the *(R)* enantiomer at $26.00/g and the *(S)* enantiomer at $2.12/g.
(6) This sequence was first performed by Clark Sehon in our laboratory.
(7) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621.
(8) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960. Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *54*, 7169. Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.

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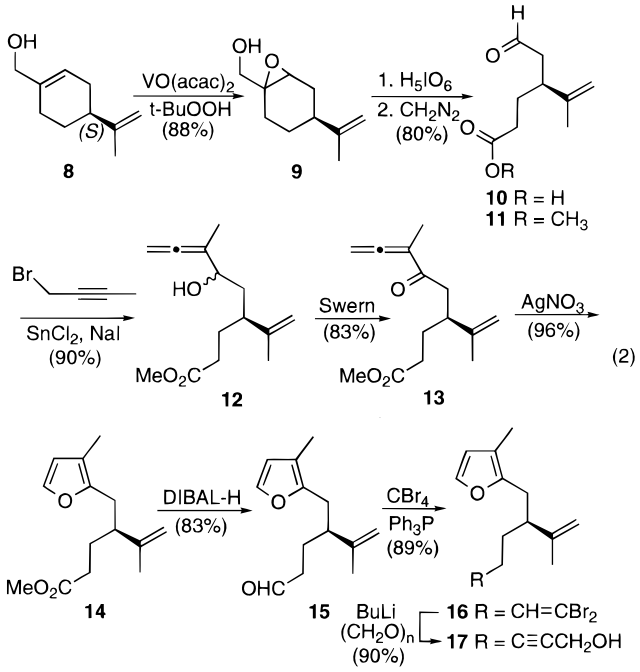
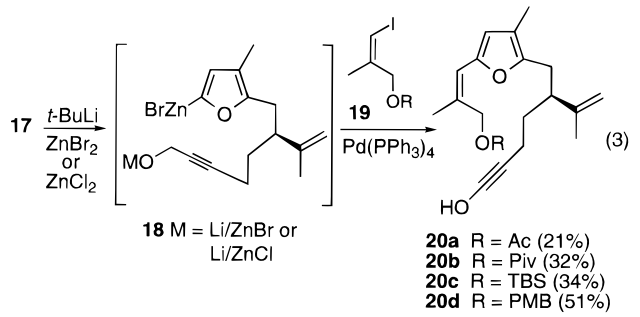
extension was effected *via* the aldehyde **15** through application of the Corey−Fuchs protocol[9] and subsequent homologation to propargylic alcohol **17** with paraformaldehyde (eq 2).

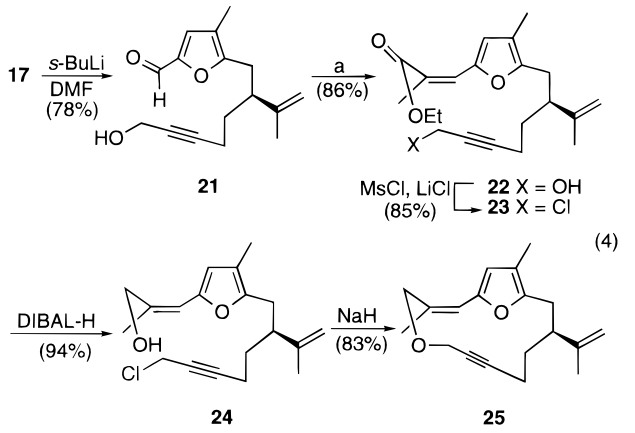


With the aim of improving convergency, we examined Patterson's approach for introduction of a *(Z)*-allylic alcohol side chain to furan **17**.[10] Accordingly, the furanylzinc intermediate **18**, prepared *in situ* by lithiation and treatment with $ZnBr_2$ or $ZnCl_2$, was coupled with vinylic iodides **19a**−**d** in the presence of $Pd(PPh_3)_4$. Best results were obtained with the *p*-methoxybenzyl ether **19d** (eq 3). Unfortunately, futher manipulations of these labile



intermediates proceeded in poor yield. Accordingly, we reexamined our previous sequence for introduction of the *(Z)*-allylic alcohol moiety.

Thus, formylation of furan **17** by sequential treatment with *s*-butyllithium and DMF afforded the aldehyde **21** in 78% yield. Still−Horner−Emmons homologation yielded the *(Z)*-conjugated ester **22**.[11] Conversion of the alcohol function to the chloride **23**[12] and subsequent reduction of the ester with DIBAL-H led to the chloro alcohol **24** in excellent yield. Cyclization was smoothly effected by slow addition of chloro alcohol **24** to a suspension of NaH in refluxing toluene containing 18-crown-6 (eq 4).



a) $(CF_3CH_2O)_2P(O)CH(Me)CO_2Et$, KHMDS, 18-C-6, THF

The next stage of the synthesis entailed diastereoselective [2,3]Wittig ring contraction of the cyclic allylic propargylic ether **25**. As this rearrangement was previously executed with the racemate **1**,[1] success could be confidently predicted in the present case. However, it is of some interest to briefly discuss the considerations underlying the rationale for this seemingly risky strategy.

Previous work had shown that the [2,3]Wittig rearrangement of *(Z)* allylic ethers affords mainly *syn* products in acyclic systems.[13] Barring unforeseen constraints resulting from the cyclic nature of ether **1** (**25**), a similar stereochemical outcome could be expected for the ring contraction. In the case at hand, the existing isopropenyl-substituted center allows for the possible formation of two *syn* diastereomers. At first sight, it might appear that this remote stereocenter would exert little influence on the reaction, in which case a nearly 1:1 mixture of these two products would be produced. However, we felt that the isopropenyl substituent would likely enforce a preferred conformation on the macrocyclic ether ring. On the basis of the premise that the [2,3]-Wittig rearrangement proceeds through a reactant-like transition state with nearly concerted H-abstraction and C−C bond formation,[14] this preferred ground state conformation could be used to predict the stereochemical outcome of the reaction.

To find the low energy conformers, we performed molecular mechanics calculations on ether **1** with MacroModel 4.5 using the MM2 force field and the Monte Carlo method for global minimization.[15] The calculated lowest energy conformer is depicted in Figure 1. It can be seen that in this conformer there is a nearly colinear arrangement between one of the propargylic C−H bonds and the reacting π-system of the allylic double bond (dashed line). Concerted bond formation with removal of this colinear hydrogen would result in the indicated *cis*,*anti*-isomer **2** with the relative stereochemistry of kallolide B. A conformer comparable to **1**, but with the orientation of

(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(10) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron Lett.* **1989**, *45*, 5283.
(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(12) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.
(13) *Cf.* Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105.
(14) For *ab initio* calculations on the [2,3]Wittig rearrangement, see: Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421. For relevant experimental findings, see: Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375. Tomooka, K.; Igarhashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795.
(15) The program Macromodel V4.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multiple step iterations (typically 1000) until the minimum energy conformer was found multiple times (10 or more). For a description of the program, see: (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

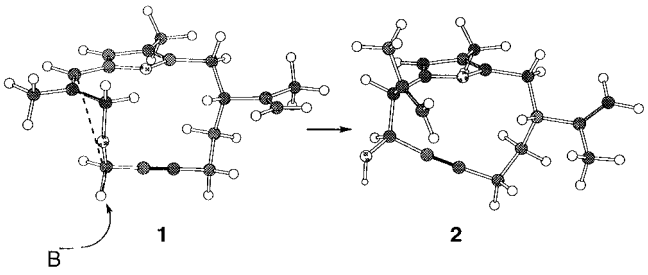
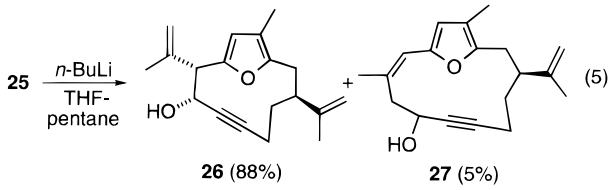


Figure 1. Calculated global minimum for propargylic ether **1** and the [2,3]Wittig product **2** showing the relationship between the abstracted propargylic hydrogen and the migration terminus.

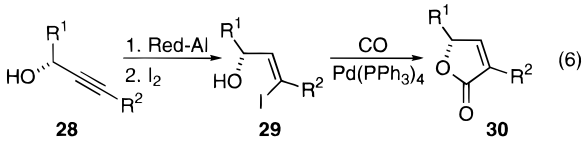
propargylic CH_2 and furyl double bond that would lead to the *cis*, *syn*-diastereomer of **2**, was over 2 kcal/mol higher in energy. Thus, it would be predicted that the rearrangement should favor **2** over the alternative *cis* isomer.

In fact, this prediction was confirmed experimentally. In the racemic series, ether **1** gave the crystalline alcohol **2** as the only detectable product in 86% yield.[1] The relative stereochemistry of **2** was confirmed by X-ray structure analysis. When this rearrangement was performed on a larger scale with the nonracemic ether **25**, the analogous *syn* product **26** was isolated in 88% yield along with alcohol **27** (5%), the product of [1,2]Wittig rearrangement (eq 5).[13] The ratio of alcohols **26:27** did



not increase when the rearrangement was conducted at −95 °C.[13] This latter product could not be completely separated from the major alcohol **26**, so the assignment of structure must be considered as provisional.

Alcohol **26** would appear to possess appropriate functionality and stereochemistry for straightforward conversion to kallolide B, or its enantiomer, by the routine sequence depicted in eq 6.[16] However, as was found in



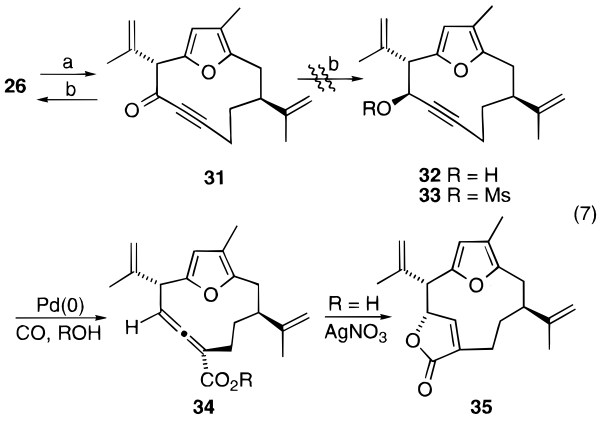
our previous work with the racemic counterpart **2**,[1] attempted addition of Red-Al to the triple bond could not be effected.[2] Even after prolonged reaction times, only starting propargylic alcohol was recovered. Reactions at elevated temperatures led to decomposition products. These findings were confirmed with alcohol **26**.

The methodology that eventually proved successful in the racemic series involved treatment of the mesylate **3** with $Pd(PPh_3)$ in the presence of CO and β-(trimethylsilyl)ethanol to afford the allenic ester **4**. Unfortunately, this reaction proceeded with inversion of stereochemistry and led, after ester cleavage and butenolide formation, to an epimer of kallolide B. We therefore attempted to prepare the epimeric alcohol **32**, which by the same sequence would afford allenic ester **34** and then, via the derived acid, kallolide B (**35**) directly. Our previous efforts to invert alcohol **2** under Mitsunobu conditions were not successful.[17] Only products of direct esterification were obtained.

A second general approach to alcohol inversion involves oxidation−reduction. In fact, alcohol **26** could be oxidized to ketone **31** with the Dess-Martin reagent[18] or with PDC in DMF.[19] Interestingly, none of the isomeric isopropylidene ketone was produced in either reaction.[20] We had previously found that the racemic alcohol **2** gave only the isopropylidene ketone upon Swern oxidation.[1] When ketone **31** was treated with Et_3N in CH_2Cl_2 the isopropylidene isomer was formed as the sole product within 3 h at rt.

Reduction of ketone **31** with various hydrides led to alcohol **26** as the exclusive or near-exclusive product. Retrospectively, this result is not surprising as molecular mechanics calculations show that the isopropenyl substituent adjacent to the carbonyl of ketone **31** adopts an axial-like orientation, effectively blocking α-face approach.[15]

As we were unable to produce alcohol **32**, we could not implement the alkoxycarbonylation strategy depicted in eq 7. Accordingly, we decided to proceed along previous lines *via* the allenic ester **37**. This was smoothly produced as a single isomer from mesylate **36**.



[a] Dess-Martin or PDC in DMF
[b] DIBAL-H or $LiAlH_4$ or $LiAl(O\text{-}t\text{-}Bu)_3H$ or K-Selectride

We previously found that the racemic allenoate **4** was converted to a 1:3 mixture of diastereomers **4** and **5**, favoring the latter, upon heating with Ph_3P in benzene.[1,21] With a larger amount of the nonracemic allenoate **37** in hand, we were able to examine this equilibration in greater detail. Treatment of ester **37** with DABCO or $(2\text{-furyl})_3P$ in benzene at 50−55 °C or with neat Me_2S for prolonged periods gave recovered starting material. Slow isomerization was observed with Ph_3P in benzene,

(16) *Cf.* Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org.Chem.* **1987**, *52*, 3883. For a recent application, see: Hoye, T. R.; Hunpal, P. E.; Jimínez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517.

(17) According to the procedure of: Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

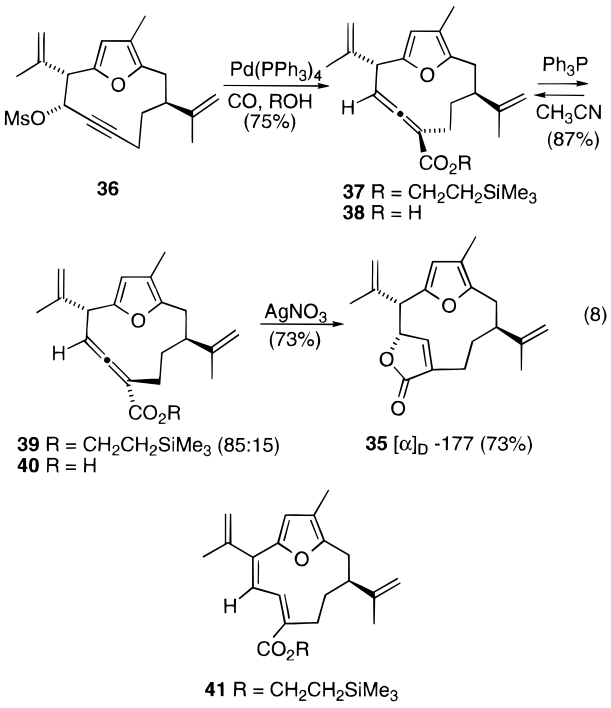
(18) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. Ireland, R. E.; Lin, L. *J. Org. Chem.* **1993**, *58*, 2899.

(19) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(20) Paquette and co-workers report that a related isopropenyl-substituted furanocyclic alcohol precursor of racemic gorgiacerone is epimerized without double bond isomerization upon oxidation with PDC.[4]

(21) The use of Ph_3P for the isomerization of acetylenic esters and ketones to conjugated dienoates and dienones has been reported. Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659. Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933.

toluene, or acetonitrile at 50−55 °C. Of the three solvents, acetonitrile gave the cleanest result, affording an 85:15 mixture of the isomerized allenoate **39** and starting material, free of byproducts. The same ratio of these two esters was obtained starting from the former attesting to the attainment of a true equilibrium. At elevated temperatures in benzene, a significant amount of the conjugated trienoate **41** was produced as a mixture of double bond isomers (eq 8).[21]



36 **37** R = $CH_2CH_2SiMe_3$ **38** R = H

39 R = $CH_2CH_2SiMe_3$ (85:15) **40** R = H

35 $[\alpha]_D$ -177 (73%)

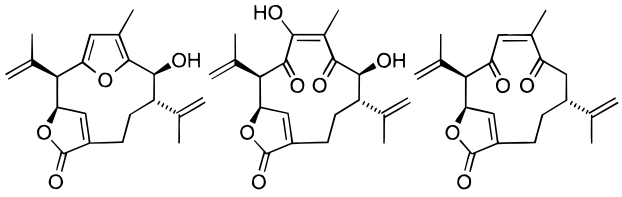
41 R = $CH_2CH_2SiMe_3$

Cleavage of the β-TMS ethyl ester **39** with TBAF afforded the corresponding acid, **40**. None of the isomeric acid **38** was formed in this reaction. Treatment of acid **40** with catalytic $AgNO_3$ in acetone or supported on silica gel[8] afforded nonracemic kallolide B (**35**), $[\alpha]_D$ −177, as a crystalline compound, mp 119 °C.

The ^1H and ^{13}C NMR spectra were identical to those of natural kallolide B and our racemic sample. However, the natural product has a reported rotation of $[\alpha]_D$ +123.[22] Thus, natural kallolide B (**7**) is enantiomeric to **35**. The discrepancy in the magnitude of the two rotations may result from impurities in the sample of the natural material, which was noncrystalline.

Fenical and co-workers converted kallolide A (**42**) to a hexahydro compound identical to that derived similarly from kallolide B through catalytic hydrogenation and concomitant hydrogenolysis.[22] They also determined that kallolide C (**43**) is formed upon oxidation of kallolide A with singlet oxygen. In view of these correlations, and the fact that they share the same organism, we can assign the absolute configurations to A and C as depicted in **42** and **43**.

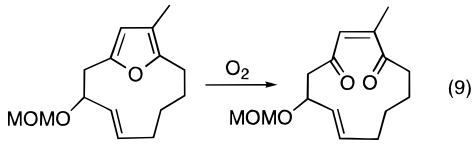
In 1987, Anderson and co-workers reported the isolation and structure elucidation of gersemolide (**44**) from a soft coral indigenous to the cold temperate intertidal waters off the coastline of British Columbia.[23] The discovery of this and related furanocembranolides in both cold water corals and tropical gorgonians is of some



42 Kallolide A **43** Kallolide C **44** Gersemolide

taxonomic interest. Futhermore, the occurrence of enedione compounds along with their furan counterparts raises the question as to the relationship between the two. Specifically, are the enediones present in the organism or are they artifacts arising from air oxidation of the furans during isolation? To answer this question we passed air through a solution of synthetic (−)-kallolide B in ethyl acetate. The material was recovered unchanged after a reaction time of 13 days. It was also similarly unaffected by oxygen after 3 days. It therefore appears likely that gersemolide (**44**) is not an artifact of kallolide B.

That such an oxidation is possible was shown by similar exposure of the furanocycle **45**[24] to air. Enedione **46** was thereby produced in 47% yield after 7 days (eq 9).



45 **46**

The foregoing synthesis allows unambiguous assignment of absolute stereochemistry to the kallolides. It features a remarkably diastereoselective [2,3]Wittig ring contraction whose success can be attributed to a remote isopropenyl substituent. The highly selective conversion of propargylic mesylate **36** to the butenolide moiety of kallolide B is also worth noting. We have found that this sequence is well suited to the synthesis of other variously substituted nonracemic butenolides.[25]

Experimental Section[26]

(*S*)-1,2-Epoxyperillyl Alcohol (9). To 3.306 g (21.74 mmol) of (*S*)-(−)-perillyl alcohol (**8**) in 100 mL of CH_2Cl_2 at 0 °C under nitrogen was added 55.0 mg (0.195 mmol) of $VO(acac)_2$ followed by 5.90 mL of 5−6 M *tert*-butyl hydroperoxide in decane.[6] After 3 h at 0 °C, 2.7 mL (36.9 mmol) of dimethyl sulfide was added. After 50 min, water was added, the mixture was stirred vigorously, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined colorless organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and solvent was distilled under reduced pressure. Short-path distillation afforded epoxide **9** (3.204 g, 88%) (bp 87−98 °C, 1.0 mm) as a slightly yellow liquid: IR (film) ν 3417, 1646, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.71 (2H, d, J = 15 Hz), 3.55−3.65 (2H, m), 3.29−3.36 (1H, m), 2.03−2.16 (4H, m), 1.80−1.86 (1H, m), 1.70 (3H, s), 1.59−1.68 (1H, m), 1.18−1.47 (2H, m); ^{13}C NMR ($CDCl_3$) δ major diastereomer 148.5, 109.0, 64.4, 60.0, 56.7, 55.7, 36.6, 30.1, 25.7, 23.6; minor diastereomer,

(22) Look, S. A.; Burch, M. T.; Fenical, W.; Zheng, Q.-t.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
(23) Williams, D.; Anderson, R. J.; VanDuyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332.
(24) Marshall, J. A.; Wang, X-j. *J. Org. Chem.* **1992**, *57*, 3387.
(25) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.
(26) Unless otherwise stated, ^1H and ^{13}C NMR spectra were determined at 300 and 100.6 MHz, respectively, on dilute solutions of sample in $CDCl_3$. Solvent removal was achieved on a rotary evaporator under aspirator vacuum. For typical experimental protocols, see: Marshall, J. A.; Wang, X-j. *J. Org. Chem.* **1991**, *56*, 960.
(27) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

partial 148.6, 109.1, 64.5, 60.4, 40.7, 24.5, 20.7, 20.1. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.58.

(*S*)-5-Formyl-4-isopropenylheptanoic Acid (10). To a mechanically stirred solution of 16.1 g (95.6 mmol) of epoxide **9** in 478 mL of THF−H_2O (10:1) at 0 °C was added 45.8 g (201 mmol) of H_5IO_6 in one portion. After 3 h, ether and water were added and the cloudy white aqueous layer was separated and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure to afford a yellow oil (18.0 g). This material was used in the next transformation without further purification: IR (film) ν 3450 (br), 1750, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.67 (1H, t, J = 3.0 Hz), 4.85 (1H, s), 4.80 (1H, s), 2.67−2.69 (1H, m), 2.46 (2H, dt, J = 7.3, 2.2 Hz), 2.18−2.38 (2H, m), 1.69−1.87 (2H, m).

Methyl (*S*)-5-Formyl-4-isopropenylheptanoate (11). Into a well-stirred solution of 18.0 g of the above acid **10** in 300 mL of ether at 0 °C was slowly poured (nitrogen gas evolution) an ethereal solution of diazomethane,[28] prepared by using a Diazald Kit (Aldrich Chemical Co.), until a yellow color persisted. After 2 min, 8 mL of acetic acid was added, causing the solution to become colorless. After 5 min, excess saturated aqueous $NaHCO_3$ was added, and the aqueous layer was separated and extracted with ether. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, and filtered, and solvent was removed under reduced pressure. Short path distillation afforded methyl ester **11** (14.0 g, 80% from epoxide **9**) (bp 65−90 °C, 0.50−0.85 mm) as a yellow liquid: $[\alpha]_D$ −14.8 (*c* 1.30, $CHCl_3$); IR (film) ν 1735, 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.67 (1H, t, J = 2.0 Hz), 4.84 (1H, q, J = 2.0 Hz), 4.78 (1H, d, J = 1.0 Hz), 3.66 (3H, s), 2.63 (1H, m), 2.43−2.48 (2H, m), 2.23−2.30 (2H, m), 1.69−1.78 (2H, m), 1.65 (3H, m); ^{13}C NMR ($CDCl_3$) δ 201.4, 201.3, 144.5, 113.3, 51.5, 47.2, 40.8, 31.5, 27.7, 18.5. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.31; H, 8.74.

Methyl (*S*)-6-Hydroxy-4-isopropenyl-7-methyl-7,8-nonadienoate (12). To 1.28 g (9.59 mmol) of 1-bromo-2-butyne in 40 mL of DMPU at rt under nitrogen were simultaneously added 2.19 g (11.34 mmol) of $SnCl_2$ and 1.71 g (11.34 mmol) of NaI, and the resulting mixture was stirred for 4 h protected from light in a flask wrapped with aluminum foil.[7] The foil was removed, the bright yellow solution was cooled to 0 °C, and 1.61 g (8.72 mmol) of aldehyde **11** in 40 mL of DMPU was added over a 10-min period. After 20 h at 0 °C, the reaction mixture was diluted with ether and 10% aqueous HCl with efficient stirring, and the resulting white mixture was filtered through a pad of Celite 521 with the aid of ether. The aqueous layer was separated and diluted with brine and water and then extracted with ether. The combined extracts were washed with 10% aqueous HCl and then saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 1:1) afforded allenol **12** (1.87 g, 90%) as an oil: $[\alpha]_D$ −10.5 (*c* 1.27, $CHCl_3$); IR (film) ν 3387, 1958, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ major diastereomer 4.85 (1H, d, J = 1.2 Hz), 4.77−4.80 (1H, m), 4.71−4.76 (2H, m), 3.95 (1H, dd, J = 9.2, 2.3 Hz), 3.65 (3H, s), 2.41−2.44 (1H, m), 2.16−2.39 (4H, m), 1.68−1.73 (3H, m), 1.62−1.67 (3H, m), 1.54−1.80 (2H, m); minor diastereomer, partial 4.07 (1H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ major diastereomer 204.7, 174.2, 146.4, 145.7, 113.5, 102.2, 76.6, 70.0, 51.4, 43.2, 38.8, 28.3, 17.5, 14.5; minor diastereomer, partial 174.1, 113.4, 75.8, 71.2, 43.5, 32.0, 27.7, 17.9, 13.9. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.44; H, 9.27.

Methyl (*S*)-4-Isopropenyl-7-methyl-6-oxo-7,8-nonadienoate (13). To a solution of 0.82 mL (9.42 mmol) of oxalyl chloride in 16 mL of CH_2Cl_2 under nitrogen at −78 °C was added 1.34 mL (18.8 mmol) of DMSO dropwise.[27] After 15 min, 1.80 g (7.53 mmol) of allenol **12** in 12 mL of CH_2Cl_2 was added dropwise, and then, after 15 min, 3.78 mL (27.1 mmol) of Et_3N was added and the resulting white mixture allowed to warm to rt. Ether and water were added, and the aqueous layer was separated and extracted with ether. The combined extracts were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and then dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 5:1) provided allenone **13** (1.47 g, 83%) as an oil: $[\alpha]_D$ −11.2 (*c* 1.61, $CHCl_3$); IR (film) ν 1962, 1933, 1736, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (2H, m), 4.76 (1H, m), 4.70 (1H, s), 3.64 (3H, s), 2.77 (1H, m), 2.65 (2H, m), 2.19−2.26 (2H, m), 1.76 (3H, m), 1.67−1.72 (2H, m), 1.64 (3H, s); ^{13}C NMR ($CDCl_3$) δ 215.8, 199.3, 173.5, 145.1, 112.2, 103.6, 78.3, 51.2, 42.8, 42.6, 31.6, 27.5, 18.5, 12.8. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.91; H, 8.49.

Methyl (*S*)-4-Isopropenyl-5-(3-methyl-2-furyl)pentanoate (14). To a solution of 1.42 g (6.02 mmol) of allenone **13** in 46 mL of acetone at rt was added 204 mg (1.20 mmol) of $AgNO_3$, and the resulting mixture was stirred under nitrogen in the dark.[8] After 4.5 h, 204 mg of Na_2CO_3 was added, and the solvent was removed under reduced pressure. The residue was immediately chromatographed on silica gel (hexanes: ether, 10:1) to provide furan **14** (1.31 g, 92%) as a colorless oil: $[\alpha]_D$ +5.8 (c 1.82, $CHCl_3$); IR (film) ν 1738, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (1H, d, J = 1.6 Hz), 6.14 (1H, d, J = 1.6 Hz), 4.75 (1H, m), 4.67 (1H, s), 3.64 (3H, s), 2.60−2.64 (2H, m), 2.35−2.50 (1H, m), 2.14−2.27 (2H, m), 1.94 (3H, s), 1.63−1.66 (3H, m), 1.68−1.75 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.9, 149.3, 145.9, 139.8 (two lines), 112.5, 112.3, 51.4, 46.0, 32.0, 30.8, 27.3, 18.6, 10.0. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.97; H, 8.58.

(*S*)-4-Isopropenyl-5-(3-methyl-2-furyl)pentanal (15). To 796 mg (3.37 mmol) of ester **14** in 9.6 mL of anhydrous toluene under nitrogen at −78 °C was added 2.70 mL (4.04 mmol) of 1.5 M DIBAL-H in toluene down the side of the flask over a period of 10 min. After 4 h, 1.3 mL of methanol was carefully added down the side of the flask, the cold bath was removed, and ether and 10% aqueous HCl were added. The aqueous layer was separated and extracted with ether. The combined extracts were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 7:1) afforded aldehyde **15** (580 mg, 83%) as a colorless oil: $[\alpha]_D$ +7.6 (*c* 1.13, $CHCl_3$); IR (film) ν 1730, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.72 (1H, t, J = 0.7 Hz), 7.20 (1H, s), 6.14 (1H, s), 4.77 (1H, s), 4.69 (1H, s), 2.56−2.67 (2H, m), 2.40−2.48 (1H, m), 2.30−2.38 (2H, m), 1.94 (3H, s), 1.64 (3H, s), 1.60−1.75 (2H, m); ^{13}C NMR ($CDCl_3$) δ 202.3, 149.3, 146.0, 139.9 (two lines), 114.8, 112.6, 112.5, 45.9, 41.8, 30.7, 24.4, 18.5. Anal. Calcd for $C_{15}H_{20}O_2$: C, 75.69; H, 8.80. Found: C, 75.82; H, 8.79.

2-[(*S*)-6,6-Dibromo-2-isopropenyl-5-hexenyl]-3-methylfuran (16). To 1.66 g (6.28 mmol) of Ph_3P in 6.0 mL of CH_2Cl_2 at rt under nitrogen was added 1.05 g (3.14 mmol) of CBr_4, causing a brown coloration and a mildly exothermic reaction.[9] After 40 min, 1.00 mL (7.22 mmol) of Et_3N was added, causing a deep purple coloration. The reaction mixture was cooled to 0 °C, 323 mg (1.57 mmol) of aldehyde **15** in 3.5 mL of CH_2Cl_2 was added, and then the mixture was allowed to warm to rt. After 8 h, the mixture was partially concentrated on a rotary evaporator such that a moderately thick purple slurry was formed. Filtration through a pad of Et_3N-deactivated silica gel with minimal CH_2Cl_2 for transfer, followed by elution with hexanes, gave a solid-containing filtrate that was filtered through a sintered glass funnel, and the solvent was removed under reduced pressure. The resulting oily solid was triturated with hexanes, and filtered through sintered glass with hexanes and the solvent was removed under reduced pressure to afford an orange oil. Flash chromatography on silica gel (hexanes) afforded dibromide **16** (497 mg, 87%) as an oil: $[\alpha]_D$ −5.3 (*c* 1.69, $CHCl_3$); IR (film) ν 3072,1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (1H, s), 6.34 (1H, t, J = 7.3 Hz), 6.14 (1H, s), 4.77 (1H, s), 4.70 (1H, s), 2.54−2.62 (2H, m), 2.44 (1H, m), 1.96−2.07 (2H, m), 1.94 (3H, s), 1.66 (3H, s), 1.47 (2H, m); ^{13}C NMR ($CDCl_3$) δ 149.4, 146.0, 139.8 (two lines), 138.4, 114.6, 112.5, 112.2, 88.6, 46.1, 31.0, 30.9, 30.3, 18.7. Anal. Calcd for $C_{14}H_{18}OBr_2$: C, 46.44; H, 5.01. Found: C, 46.37; H, 4.99.

(*S*)-6-Isopropenyl-7-(3-methyl-2-furyl)-2-heptyn-1-ol (17). To 865 mg (2.39 mmol) of dibromide **16** in 18.4 mL of THF under nitrogen at −78 °C was added 2.01 mL (5.02 mmol) of

(28) Boer, T. J.; Backer, H. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 250. AL-180 Aldrich Technical Bulletin.

n-BuLi in hexanes down the side of the flask over a period of 3 min. After 1 h, the cold bath was removed for 1 h, and then the reaction mixture was recooled to −78 °C and 718 mg (23.9 mmol) of dry solid paraformaldehyde was added in one portion. The reaction mixture was allowed to warm slowly to rt over a period of 3 h. After 1 h, ether and water were added, and the aqueous layer was separated and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 2:1) afforded furan alcohol **17** (500 mg, 90%) as an oil: $[\alpha]_D$ −17.8 (*c* 1.60, $CHCl_3$); IR (film) ν 3376, 2224, 1644, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (1H, d, J = 1.5 Hz), 6.14 (1H, d, J = 1.5 Hz), 4.76 (1H, s), 4.70 (1H, s), 4.23 (2H, s), 2.51−2.64 (3H, m), 2.05−2.30 (2H, m), 1.94 (3H, d, J = 2.4 Hz), 1.64 (3H, s), 1.54−1.62 (2H, m); ^{13}C NMR ($CDCl_3$) δ 149.4, 145.8, 139.7, 114.6, 112.5, 112.2, 86.1, 78.4, 51.3, 45.6, 31.3, 30.7, 18.7, 16.8, 10.0. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.63.

2-Formyl-4-methyl-5-[(*S*)-7-hydroxy-2-isopropenyl-5-heptynyl]furan (21). To 746 mg (3.21 mmol) of furan alcohol **17** in 44 mL of THF under nitrogen at −78 °C was added 1.27 M *s*-BuLi in cyclohexane (8.82 mL, 11.2 mmol) over a period of 5 min. The solution was warmed to 0 °C for 21 min and then recooled to −78 °C, and 2.5 mL (32.1 mmol) of DMF was added dropwise. After 1.5 h at −78 °C, the reaction was quenched with 7.5 mL of methanol. Water and ether were added, the mixture was allowed to come to rt, and the aqueous layer was separated and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 1:2) afforded aldehyde **21** (622 mg, 74%) as a yellow oil: $[\alpha]_D$ −14.0 (*c* 1.37, $CHCl_3$); IR (film) ν 3423, 1674, 1519 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.46 (1H, s), 7.03 (1H, s), 4.78 (1H, t, J = 1.3 Hz), 4.72 (1H, s), 4.24 (2H, s), 2.67−2.75 (4H, m), 2.05−2.25 (1H, m), 2.02 (3H, s), 1.66 (3H, s), 1.55−1.63 (2H, m), 1.57 (1H, s); ^{13}C NMR ($CDCl_3$) δ 176.7, 157.9, 150.5, 144.8, 125.3, 119.0, 113.0, 85.4, 78.9, 51.3, 45.0, 31.4, 31.1, 18.6, 16.7, 9.9.

Ethyl (*Z*)-2-Methyl-3-[(*S*)-4-methyl-5-(2-isopropenyl-7-hydroxy-5-heptynyl)-2-furyl]-2-propenoate (22). To a solution of 2.75 g (7.93 mmol) of ethyl bis(trifluoroethyl)-phosphonopropionate[11] and 4.20 g (15.9 mmol) of 18-crown-6 in 50 mL of THF under nitrogen at −78 °C was added 15.9 mL (7.93 mmol) of 0.5 M KHMDS in toluene over a period of 5 min. After 1.5 h, 824 mg (3.17 mmol) of aldehyde **21** in 6 mL of THF was added dropwise and 2 mL of THF was used to rinse the addition flask. After 1.5 h, the cold (−78 °C) solution was poured into a rapidly stirring saturated solution of aqueous NH_4Cl at room temperature with the aid of an ether rinse. The mixture was diluted with water, and the aqueous layer was separated and extracted with ether. The combined extracts were washed with 10% aqueous HCl, 10% aqueous K_2CO_3, and brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 7:4) gave ester alcohol **22** (942 mg, 86%) as a yellow oil: $[\alpha]_D$ -11.6 (c 1.29, $CHCl_3$); IR (film) ν 3429, 2225, 1714, 1643, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (1H, s), 6.37 (1H, d, J = 1.5 Hz), 4.77 (1H, s), 4.73 (1H, s), 4.27 (2H, q, J = 7.1 Hz), 4.23 (2H, m), 2.58−2.63 (4H, m), 2.05−2.20 (1H, m), 2.05 (3H, s), 1.92 (3H, s), 1.64 (3H, s), 1.53−1.60 (2H, m), 1.56 (1H, s), 1.34 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 169.2, 150.6, 148.1, 145.7, 123.4, 123.2, 117.5, 115.9, 112.5, 85.6, 78.9, 60.6, 51.2, 45.3, 31.0, 30.9, 21.4, 18.5, 16.6, 14.1, 9.8.

Ethyl (*Z*)-2-Methyl-3-[(*S*)-4-methyl-5-(2-isopropenyl-7-chloro-5-heptynyl)-2-furyl]-2-propenoate (23). To a solution of 935 mg (2.71 mmol) of ester alcohol **22**, 230 mg (5.43 mmol) of dry LiCl, and 0.69 mL (5.96 mmol) of 2,6-lutidine in 14 mL of DMF under nitrogen at 0 °C was added 0.42 mL (5.43 mmol) of MsCl dropwise.[12] After 17 h at 0 °C, the cold solution was poured into water at rt and the aqueous layer was separated and extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$ and brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 10:1) afforded chloro ester **23** (838 mg, 85%) as an orange oil: $[\alpha]_D$ −14.4 (*c* 1.30, $CHCl_3$); IR (film) ν 2235, 1719, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83 (1H, s), 6.44 (1H, s), 4.76 (1H, s), 4.71 (1H, s), 4.25 (2H, q, J = 7.2 Hz), 4.13 (2H, t, J = 2.3 Hz), 2.53−2.61 (3H, m), 2.09−2.21 (2H, m), 2.05 (3H, s), 1.93 (3H, s), 1.63 (3H, s), 1.54−1.58 (2H, m), 1.32 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.0, 151.1, 148.8, 146.1, 125.1, 123.5, 118.3, 117.0, 113.1, 87.8, 75.6, 60.9, 46.0, 31.7, 31.4, 22.0, 19.1, 17.3, 14.8, 10.4. Anal. Calcd for $C_{21}H_{27}O_3Cl$: C, 69.51; H, 7.50. Found: C, 69.44; H, 7.43.

(*Z*)-2-Methyl-3-[(*S*)-4-methyl-5-(2-isopropenyl-7-chloro-5-heptynyl)-2-furyl]-2-propen-1-ol (24). To 838 mg (2.31 mmol) of chloro ester **23** in 23 mL of CH_2Cl_2 under nitrogen at −78 °C was added 1.0 M DIBAL-H in hexanes (6.9 mL, 6.93 mmol) down the side of the flask over 5 min. After 2 h at −78 °C, a small amount of ester **23** was observed by TLC assay so additional 1.0 M DIBAL-H in hexanes (1.15 mL, 1.16 mmol) was added. After 1 h, the solution was quenched with saturated aqueous potassium sodium tartrate, and ether was added. After being stirred vigorously for 1 h at rt, the mixture was filtered through a sintered glass funnel with ether rinsings, and the aqueous layer of the filtrate was separated and extracted with ether. The combined extracts were washed with saturated aq. potassium sodium tartrate and brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on Et_3N-deactivated silica gel (20% EtOAc in hexanes) afforded furan **24** (699 mg, 94%) as an oil: $[\alpha]_D$ −19.9 (*c* 1.40, $CHCl_3$); IR (film) ν 3371, 2235, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.02 (1H, s), 5.97 (1H, s), 4.78 (1H, d, J = 1.5 Hz), 4.71 (1H, s), 4.42 (2H, d, J = 5.9 Hz), 4.14 (2H, t, J = 2.1Hz), 2.55−2.64 (4H, m), 2.02−2.17 (3H, m), 1.98 (3H, d, J = 1.2 Hz), 1.92 (3H, s), 1.66 (3H, s), 1.81 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 150.3, 149.6, 146.1, 135.8, 117.1, 116.5, 113.1, 112.9, 87.8, 75.8, 63.7, 46.3, 31.9, 31.7, 31.3, 23.3, 19.3, 17.5, 10.5. Anal. Calcd for $C_{19}H_{25}O_2Cl$: C, 71.12; H, 7.85. Found: C, 71.01; H, 7.88.

(*S*,*Z*)-3,14-Dimethyl-11-isopropenyl-5,14-dioxabicyclo-[11.2.1]hexadeca-2,1(15),13-trien-7-yne (25). To a well-stirred mixture of 384 mg (15.2 mmol) of NaH, 4.06 g (15.2 mmol) of 18-crown-6, and 250 mL of dry toluene under nitrogen at reflux was added a solution of 699 mg (2.18 mmol) of chloro alcohol **24** in 50 mL of dry toluene over a period of 4.25 h by means of a syringe pump. The mixture was cooled to 0 °C and carefully quenched with saturated aqueous NH_4Cl with efficient stirring. Water was added, and then the aqueous layer was separated and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography of the brown oil on Et_3N-deactivated silica gel (5% EtOAc in hexanes) provided ether **25** (515 mg, 83%) as a greenish-yellow viscous oil: $[\alpha]_D$ +87.4 (*c* 1.17, $CHCl_3$); IR (film) ν 2267, 2242, 2217, 1644, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (1H, s), 5.94 (1H, s), 5.56 (1H, d, J = 11.5 Hz), 4.89 (1H, s), 4.85 (1H, s), 4.08 (2H, t, J = 2.0 Hz), 3.92 (1H, d, J = 11.5 Hz), 3.21−3.16 (1H, m), 2.67−2.50 (2H, m), 2.18−2.09 (2H, m), 1.89 (3H, s), 1.87 (3H, s), 1.72 (3H, s), 1.45−1.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 150.6, 149.2, 147.0, 132.0, 118.0, 117.1, 113.4, 112.7, 87.5, 67.5, 56.8, 42.3, 31.0, 29.8, 22.2, 19.5, 17.1, 10.1.

(2*S*,3*R*,8*S*)-2,8-Diisopropenyl-11-methyl-13-oxabicyclo-[8.2.1]dodeca-3,5-dien-4-yn-3-ol (26). To 426 mg (1.50 mmol) of ether **25** in 42 mL of THF:pentane (1:1) at −78 °C under nitrogen was added dropwise 2.52 M *n*-BuLi (3.0 mL, 7.50 mmol). After 1.5 h, the solution was quenched with saturated aqueous NH_4Cl and allowed to reach rt, and ether and water were added. The aqueous layer was separated and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 4:1) afforded propargylic alcohol **26** (375 mg, 88%) as a white crystalline solid: mp 73−75 °C; $[\alpha]_D$ +60.6 (*c* 1.11, $CHCl_3$); IR (film) ν 3447, 2242, 2217, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 (1H, s), 5.24 (1H, s), 5.11 (1H, t, J = 1.5 Hz), 4.77 (1H, s), 4.70 (1H, t, J = 1.6 Hz), 4.53 (1H, bs), 3.77 (1H, d, J = 5.2 Hz), 2.60−2.44 (3H, m), 2.24−1.96 (3H, m), 1.94 (3H, s), 1.92 (3H, s), 1.73 (3H, s), 1.59−1.51 (1H, m), 1.34 (1H, dt, J = 13.5, 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 150.3, 149.5, 149.1, 142.0, 116.7, 115.5, 111.4, 110.9, 89.1, 81.4, 64.9,

52.7, 46.7, 31.8, 31.5, 23.8, 19.9, 19.7, 10.3. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.95; H, 8.44.

Continued elution gave a mixture of **26** and the isomeric [1,2]Wittig product **27** (22.5 mg, 5%): ^{1}H NMR ($CDCl_3$) δ partial 5.91 (1H, s), 4.90 (1H, s), 4.84 (1H, s), 4.3 (1H, bd, J = 10 Hz), 4.02 (1H, t, J = 11 Hz), 3.28−3.38 (1H, m), 2.19−2.26 (2H, m), 1.96 (3H, s), 1.89 (3H, s), 1.58 (3H, s), 1.17−1.40 (2H, m).

Mesylate 36. To 180 mg (0.633 mmol) of propargylic alcohol **26** in 7.0 mL of CH_2Cl_2 under nitrogen at −78 °C was added 0.36 mL (2.53 mmol) of Et_3N followed by 0.10 mL (1.27 mmol) of MsCl. After 4 h, saturated aqueous $NaHCO_3$ and ether were added, the mixture allowed to reach rt, and the aqueous layer was separated and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to afford 230 mg (100%) of mesylate **36** as a yellow oil. This material was used directly in the next transformation without further purification: IR (film) ν 2226, 1641, 1378, 1175, 924 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.28 (1H, overlapping dt, J = 6.4, 2.9 Hz), 5.15, (1H, s), 5.05 (1H, t, J = 1.5 Hz), 4.78 (1H, s), 4.72 (1H, t, J = 1.6 Hz), 4.03 (1H, d, J = 6.4 Hz), 3.08 (3H, s), 2.71−2.65 (1H, m), 2.57−2.44 (2H, m), 2.20−2.14 (1H, m), 2.05−1.85 (1H, m), 2.01 (3H, s), 1.91 (3H, d, J = 0.6 Hz), 1.73 (3H, d, J = 0.3 Hz), 1.59−1.52 (1H, m), 1.36 (1H, t, J = 7.3 Hz).

Allenic Ester 37. A yellow solution of 58 mg (0.0633 mmol) of $Pd_2(dba)_3$ and 133 mg (0.506 mmol) of Ph_3P in 3.8 mL of THF under nitrogen at rt was stirred for 25 min, at which time a solution of 230 mg (0.633 mmol) of mesylate **36**, 0.46 mL (3.17 mmol) of 2-(trimethylsilyl)ethanol, and 0.15 mL (1.27 mmol) of 2,6-lutidine was added in 3.8 mL of THF, causing an olive-drab coloration. Immediately after the addition, the atmosphere above the solution was purged for 10 min with CO, and then the reaction mixture was stirred under a static carbon monoxide atmosphere for 1.5 h, during which time the solution became yellow. Ether was added, the resulting mixture was filtered through a pad of Celite 521 with the aid of ether, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes:ether, 25:1) afforded allenic ester **37** (195 mg, 75%) as a yellow oil: $[\alpha]_D$ +336.0 (c 1.21, $CHCl_3$); IR (film) ν 1955, 1705, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.90 (1H, s), 5.61 (1H, d, J = 2.7 Hz), 5.06 (1H, s), 4.98 (1H, s), 4.75 (1H, s), 4.67 (1H, d, J = 1.2 Hz), 4.18 (1H, d, J = 3.2 Hz), 4.13 (2H, overlapping dt, J = 8.9, 7.3 Hz), 2.44−2.75 (4H, m), 1.76−1.86 (2H, m), 1.86 (6H, s), 1.76 (3H, s), 0.97−1.08 (1H, m), 0.95 (2H, dt, J = 1.5, 7.3 Hz), 0.04 (9H, d, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.5, 167.5, 150.2, 148.4, 144.0, 133.8, 128.7, 115.6, 112.5, 110.8, 108.5, 103.0, 96.2, 62.8, 48.7, 46.0, 32.0, 30.9, 21.8, 20.4, 17.3, 9.7, −1.5. Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79. Found: C, 72.84; H, 8.82.

Allenic Ester 39. A solution of 50 mg (0.121 mmol) of allenic ester **37** and 64 mg (0.242 mmol) of Ph_3P in 6.4 mL of CH_3CN was heated to 55 °C in a sealed flask for 92 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexanes:ether, 25:1), affording allenic esters **39** and **37** (32.6 mg) and a mixture of the allenic esters and Ph_3P (49.3 mg). Flash chromatography of this latter mixture on silica gel (hexanes:ether, 25:1) and combination with the purified samples afforded 43.3 mg (87% yield) of the esters **39** and **37** as an 85:15 mixture. Further purification by flash chromatography (hexanes:ether, 25:1) afforded pure allenic ester **39** (28.3 mg, 57%) and **37** (7.6 mg, 15%): $[\alpha]_D$ −120.2 (c 1.46, $CHCl_3$); IR (film) ν 1945, 1706, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.84 (1H, s), 5.76 (1H, m), 5.27 (1H, s), 5.00 (1H, s), 4.84 (1H, s), 4.79 (1H, s), 2.42−2.59 (4H, m), 2.30−2.38 (1H, m), 2.15 (1H, dq, J = 3.9, 14.6), 1.88 (6H, s), 1.76 (3H, s), 1.26−1.53 (2H, m), 0.99 (2H, dd, J = 7.3, 10.0 Hz), 0.03 (9H, s); ^{13}C NMR ($CDCl_3$) δ 213.2, 168.2, 150.9, 149.2, 147.6, 143.0, 115.3, 113.7, 111.0, 109.4, 101.4, 96.0, 63.1, 46.0, 44.4, 30.1, 29.1, 24.9, 21.2, 19.8, 17.5, 9.8, −1.4. Anal. Calcd for $C_{25}H_{36}O_3$: C, 72.77; H, 8.79. Found: C, 72.80, H, 8.84.

Allenic Acid 40. To a solution of 27.3 mg (0.0662 mmol) of allenic ester **39** in 3.3 mL of DMF at rt under nitrogen was added 0.13 mL (0.132 mmol) of 1.0 M TBAF in THF over a 1-min period, causing at first an opaque green coloration that then faded to a clear light brown/yellow color. After 2 h, ether and water were added, and the aqueous layer was separated and extracted with ether. The combined extracts were washed with brine. The combined washings were back-extracted with ether, and then the ether extract was washed with brine. The combined organic extracts were dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (30% EtOAc in hexanes) afforded allenic acid **40** (19.2 mg, 93%) as a yellow oil: $[\alpha]_D$ −99.7 (c 1.36, $CHCl_3$); IR (film) ν 2925 (br), 1938, 1676, 1571 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.85 (1H, s), 5.82−5.85 (1H, m), 5.23 (1H, s), 5.00 (1H, s), 4.83 (1H, s), 4.79 (1H, d, J = 1.2 Hz), 4.06 (1H, d, J = 7.3 Hz), 1.24−2.85 (7H, m), 1.88 (6H, s), 1.76 (3H, s), 0.90−0.95 (1H, m); ^{13}C NMR ($CDCl_3$) δ 214.1, 172.9, 150.8, 149.2, 147.5, 142.8, 115.4, 113.9, 111.1, 109.5, 101.0, 96.4, 46.0, 44.4, 30.2, 29.1, 24.7, 21.1, 19.8, 9.8.

(−)-Kallolide B (35). A. $AgNO_3$ in Acetone Procedure. To a solution of 13.5 mg (0.0432 mmol) of allenic acid **40** in 0.8 mL of acetone under nitrogen at rt was added 1.5 mg (8.64 μmol) of $AgNO_3$. After being stirred in the dark for 4.5 h, the reaction mixture was diluted with ether and filtered through a pad of Celite 521, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (15% EtOAc in hexanes) afforded (−)-kallolide B (**35**) (9.2 mg, 68%) as a white solid, mp 119 °C.

B. $AgNO_3$ on Silica Gel Procedure. To a solution of 16.5 mg (0.0528 mmol) of allenic acid **40** in 0.41 mL of hexanes and 0.08 mL of CH_2Cl_2 at rt was added 9.0 mg (5.3 μmol) of 10% $AgNO_3$ on silica gel. After being stirred in the dark for 5.5 h, the reaction mixture was diluted with ether and filtered through a pad of Celite 521, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (15% EtOAc in hexanes) afforded (−)-kallolide B (**35**) (12.0 mg, 73%) as a white solid: mp 119 °C; $[\alpha]_D$ −177 (c 0.68, $CHCl_3$); IR ($CDCl_3$) ν 1749, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.68 (1H, s), 5.86 (1H, s), 5.36 (1H, d, J = 3.1 Hz), 5.01 (1H, d, J = 1.2 Hz), 4.99 (1H, s), 4.88 (1H, s), 4.76 (1H, d, J = 1.2 Hz), 3.74 (1H, d, J = 3.9 Hz), 2.65−2.69 (1H, m), 2.34−2.50 (3H, m), 2.15 (1H, bd, J = 13.5 Hz), 1.97 (3H, s), 1.88 (3H, s), 1.78 (3H, s), 1.62−1.69 (1H, m), 0.85 (1H, dt, J = 13.8, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 175.3, 149.9, 149.3, 148.0, 146.7, 142.0, 136.7, 116.3, 114.5, 112.2, 110.7, 81.1, 48.9, 42.1, 34.6, 30.2, 23.1, 21.9, 19.6, 9.8. The analytical sample was secured by sublimation at 98−100 °C (0.005mm Hg). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.79. Found: C, 76.79; H, 7.80.

Cyclic Enedione 46. A stream of air was passed over a stirring solution of 153 mg (0.611 mmol) of furan **45**[24] in 6.1 mL of EtOAc at rt for 7 d. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexanes:ether, 6:1 to 1:1 to 1:2) to afford 31.2 mg of starting furan **45** and 76.6 mg of cyclic enedione **46** (47%) as an oil: IR (film) ν 1694, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.23 (1H, d, J = 1.5 Hz), 5.61−5.69 (1H, m), 5.24−5.59 (1H, m), 4.71, 4.52 (2H, ABq, J = 6.8 Hz), 4.41−4.49 (1H, m), 3.35 (3H, s), 2.73−2.86 (2H, m), 2.31−2.38 (3H, m), 1.96−2.01 (1H, m), 1.92 (3H, d, J = 12.1 Hz), 1.35−1.62 (2H, m).

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Supporting Information Available: Selected ^{1}H and ^{13}C NMR spectra for key intermediates (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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