Stereoselective Total Synthesis of the Pseudopterolide Kallolide A

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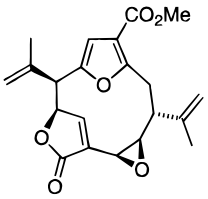
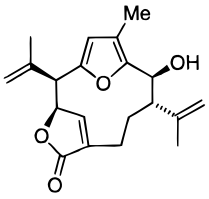
A total synthesis of the pseudopterolides, kallolide A (**36**) and kallolide A acetate (**35**), has been achieved. The racemic forms were prepared from the syn adduct **20** of furan **13** and stannane **17** (BF_3·OEt_2-promoted addition) via the 15-membered propargylic allylic ether **25**. [2,3]Wittig ring contraction led to the cis, anti, cis product **26**. Alcohol **26** was transformed to butenolide **34** with net retention of configuration by $Pd(PPh_3)_4$-catalyzed carbonylation of the mesylate **27** and ensuing $AgNO_3$-catalyzed cyclization of the derived allenic acid **29**. Solvolysis of the SEM ether (at C2) **34** in acetic acid or aqueous *t*-BuOH afforded racemic kallolide A acetate (**35**) and kallolide A (**36**), respectively, with inversion of stereochemistry by an S_N1 process. Key elements of stereocontrol, including the steric outcome of the [2,3]Wittig ring contraction, the allenic ester isomerization, and the solvolysis reactions, were predicted from molecular mechanics calculations. The C8 and C2 epimers **45** and **46** of the cis, anti, cis kallolide A SEM ether precursor **34** were also prepared. The synthetic route originated from the anti adduct **19** of aldehyde **13** and the allylic chloride **16** and CuCl (cat), $HSiCl_3$, and *i*-Pr_2NEt. Adduct **19** was subjected to the same sequence as the syn counterpart **20** to produce the trans, anti, cis [2,3]Wittig ring contraction product **42**. The derived allenoate **44** afforded a 1:1 mixture of butenolides **45** and **46** upon sequential treatment with TBAF and $AgNO_3$. Finally, the natural enantiomer (+)-**36** of kallolide A was synthesized from the enantioenriched syn adduct (+)-**20**, prepared by addition of allylic stannane **17** to aldehyde **13** promoted by a modified chiral acyloxyborane Lewis acid.

Octocorals of the genus *Pseudopterogorgia* produce, among other metabolites, diterpenoids of the rare pseudopterane family. Several of these possess significant biological activity. Thus pseudopterolide, the first member of the family to be structurally elucidated, exhibits potent cytotoxicity,[1] and kallolide A, the subject of this report, is an antiinflammatory agent with activity comparable to that of indomethacin.[2]



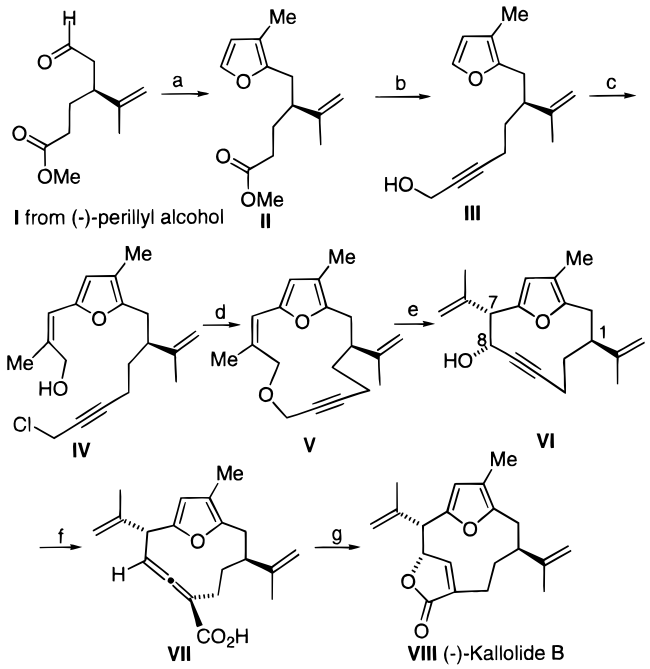
Pseudopterolide



Kallolide A

We recently described a synthesis of (−)-kallolide B, a close relative of kallolide A, starting from the terpene (−)-perillyl alcohol (Scheme 1).[3,4] That synthesis featured a remarkably diastereoselective [2,3] Wittig ring contraction (**V** → **VI**) in which the absolute stereochemistry of the created C7/C8 stereocenters was directed by the remote C1 isopropenyl center. Also notable was the highly diastereoselective hydrocarbonylation (**VI** → **VII**) and subsequent allenic ester isomerization leading to the bridged butenolide moiety (**VII** → **VIII**) with the correct relative configuration.

Scheme 1. Synthetic Route to *ent*-Kallolide B[a]



[a] (a) Furan homologation; (b) side-chain extension; (c) furan formylation−chain extension; (d) macrocyclization; (e) [2,3]Wittig ring contraction; (f) hydrocarbonylation; (g) equilibration, then Ag^+-catalyzed allenoic acid cyclization.

The successful outcome of the foregoing total synthesis prompted our investigation of a parallel route to kallolide A (Scheme 2). Accordingly, construction of the macrocyclic ether **XII**, followed by [2,3]Wittig rearrangement, would presumably lead to the trans, anti, cis carbocycle **XIII**. Ensuing hydrocarbonylation and allenic ester

(1) Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.
(2) Look, S. A.; Burch, M. T.; Fenical, W.; Zhen, Q.-t.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
(3) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729.
(4) For a review of synthetic efforts in this area see Marshall, J. A. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 1.

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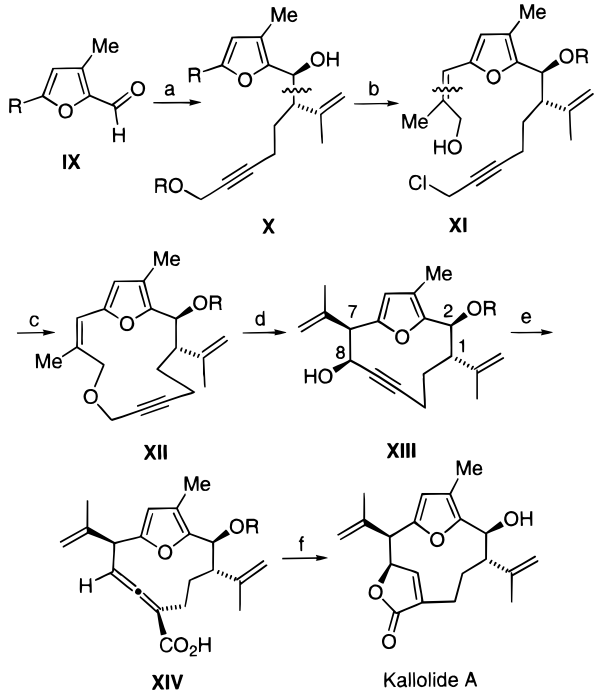
Scheme 2. Proposed Route to Kallolide A[a]



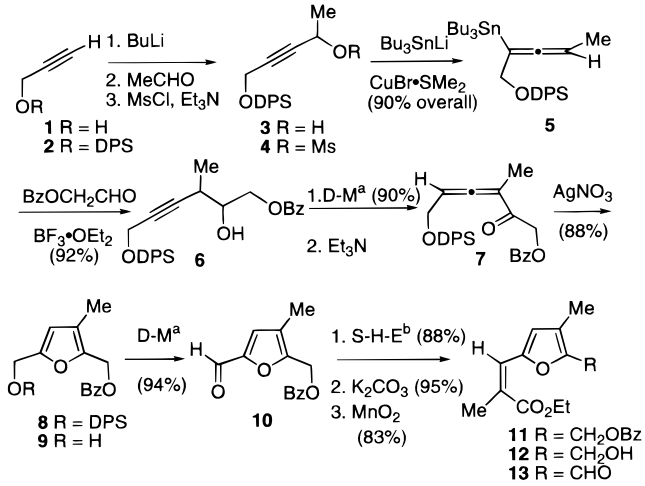
[a] (a) Anti-selective allylmetal addition; (b) side-chain homologation; (c) macrocyclization; (d) [2,3]Wittig ring contraction; (e) hydrocarbonylation−equilibration; (f) Ag^+-catalyzed allenoic acid cyclization.

isomerization would produce the allenic acid **XIV** which would be cyclized to the butenolide. Subsequent removal of the alcohol protecting group would complete the synthesis. These suppositions assume that the C1 isopropenyl grouping would maintain its dominant role in controlling relative stereochemistry with minimal perterbation by the neighboring oxygen substituent. However, the extent of that control was by no means certain.

We formulated a highly convergent construction of the macrocyclic ether intermediate **XII**. Two significant achiral fragments, aldehyde **13** and allylic stannane **17**, comprise the key elements of the synthetic approach. Allyl and allenylmetal addition reactions were expected to play a key role in controlling relative and ultimately absolute stereochemistry at C1/C2 and C8. From the precedent in Scheme 1, it could be predicted that the C7/C8 relative stereochemistry in **XIII** would be influenced by transition state considerations and by the C1 isopropenyl substituent.

The synthesis of the aldehyde fragment **13**, outlined in Scheme 3, starts with the DPS ether **2** of propargyl alcohol (**1**) which was subjected to our allenylstannane homologation sequence to afford racemic **5**.[5] The BF_3-promoted addition of this stannane to α-(benzoyloxy)-acetaldehyde followed by oxidation and treatment with mild base to effect isomerization of the propargylic ketone proceeded in high yield. The derived allenone **7** was smoothly cyclized with catalytic $AgNO_3$ in acetone affording furan **8**.[6] Desilylation with TBAF and subsequent oxidation with the Dess−Martin periodinane reagent[7] yielded aldehyde **10** which was subjected to Still−

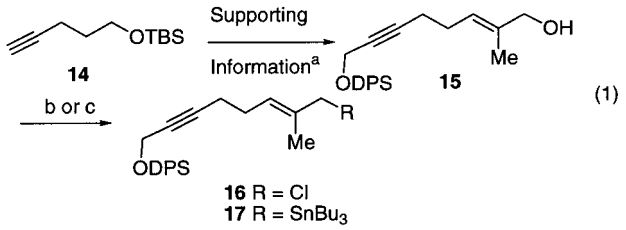
Scheme 3[a]



[a] (a) Dess−Martin periodinane reagent; (b) Still−Horner−Emmons reagent; $(CF_3CH_2O)_2POCH(Me)CO_2Et$, KHMDS, THF, 18-crown-6.

Horner−Emmons homologation.[8] The resulting (*Z*)-unsaturated ester benzoate **11** was selectively saponified with ethanolic K_2CO_3. Oxidation of alcohol **12** was best achieved with MnO_2. Alternative methods (Swern,[9] Dess−Martin, TPAP[10]) gave complex mixtures of products.

The next phase of our plan called for introduction of the anti homoallylic alcohol array (**IX** → **X**) with a propargylic ether terminus appropriate for the eventual [2,3]-Wittig ring contraction (**XII** → **XIII**). For the former transformation we planned to employ an allylic indium reagent generated in situ through metathesis of the allylic stannane **17** with $InBr_3$.[11] Stannane **17** was prepared from alcohol **15** via the transient mesylate and Bu_3SnLi (eq 1).[12]



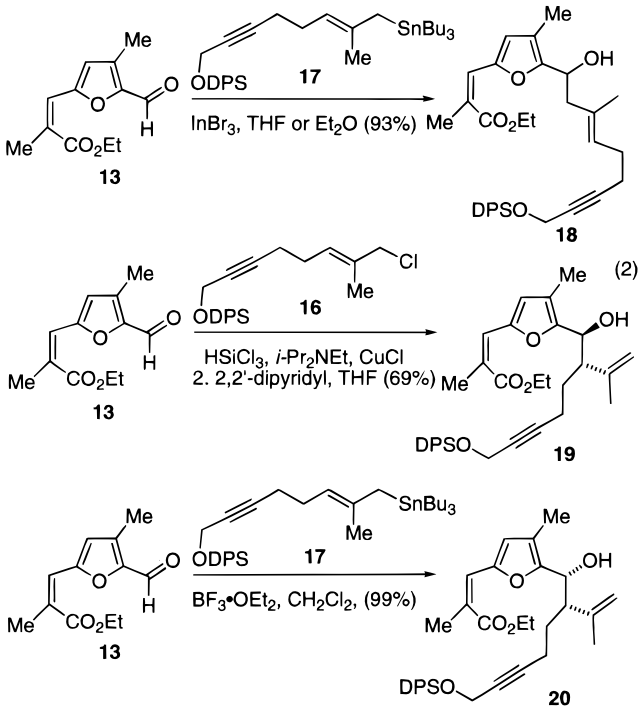
(1)

(a) (1) BuLi, (2) $(CH_2O)_n$, (3) DPSCl, Im, (4) MeOH, CCl_4, ultrasound, (5) Swern oxidation, (6) $Ph_3P{=}C(Me)CO_2Me$, (7) $(i\text{-}Bu)_2AlH$ (50% overall); (b) PPh_3, CCl_4, $(i\text{-}Pr)_2NEt$ (90%); (c) BuLi, MsCl, THF, −78 °C, then Bu_3SnLi.

Unexpectedly, addition of the allylic indium species from stannane **17** and $InBr_3$ afforded mainly the linear adduct **18** in a variety of solvents and at temperatures between 0° and −78 °C. In THF, adduct **18** was the sole product. Reactions in other solvents (EtOAc, CH_2Cl_2, Et_2O) afforded linear and syn/anti mixtures of branched adducts in modest yield (eq 2).

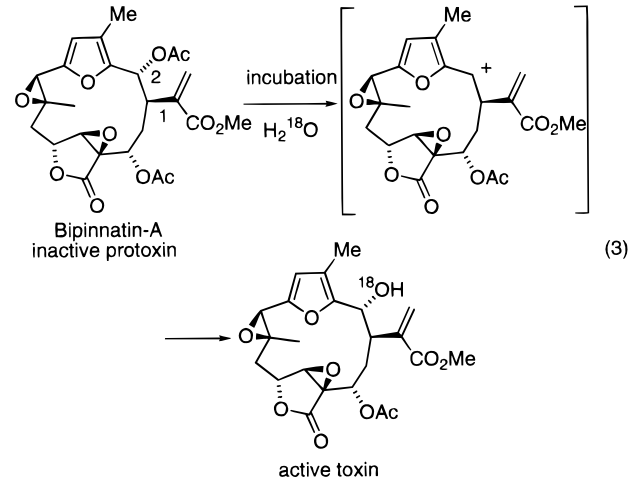
The branched anti adduct **19** could be synthesized by addition of the allylic trichlorosilane, generated in situ

(5) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
(6) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.
(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Ireland, R. E.; Lin, L. *J. Org. Chem.* **1993**, *58*, 2899.
(8) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(10) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(11) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. Marshall, J. A. *Chemtracts-Org. Chem.* **1997**, *10*, 481.
(12) Weigand, S.; Brückner, R. *Synthesis* **1996**, 475.



from allylic chloride **16**.[13] This addition requires nucleophilic assistance. With DMF as the nucleophile a 75:25 mixture of anti and syn adducts **19** and **20** was isolated in 55% yield. 2,2′-Bipyridyl was more effective giving a 95:5 mixture of anti and syn adducts in 69% yield.[14] Formation of the syn adduct **20**, on the other hand, was efficiently achieved through BF_3-promoted addition of allylic stannane **17** to aldehyde **13**.

The efficiency of this latter addition reaction and the desire to eventually prepare enantioenriched kallolide A prompted our consideration of the syn adduct **20** as the macrocyclic precursor. Our thinking along these lines was influenced by the work of Abrahamson who showed that certain furanocembranes undergo S_N1 solvolysis upon incubation (eq 3).[15] This reaction has biological



implications as illustrated for bipinnatin-A (eq 3). It was found that bipinnatin-A exhibits cytotoxicity only after

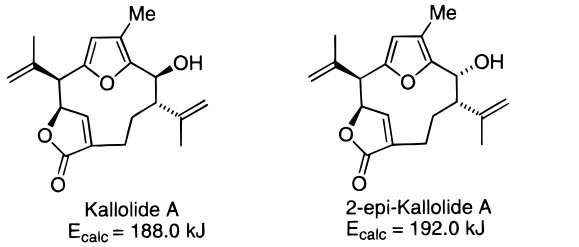
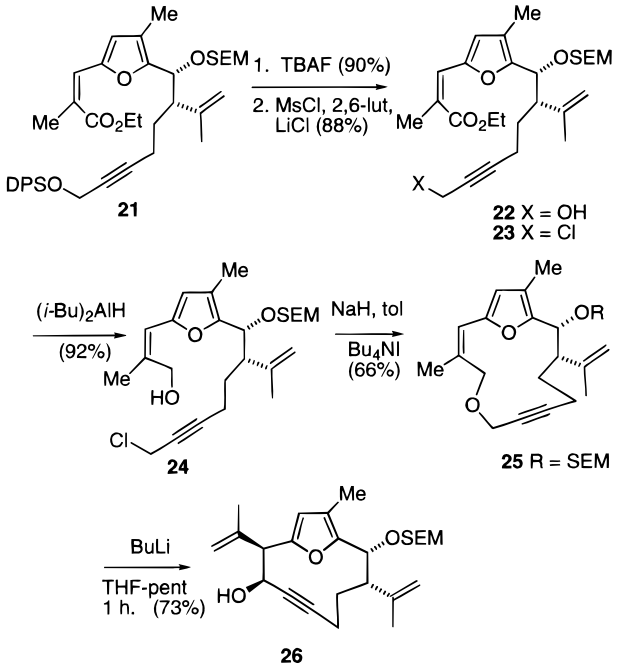


Figure 1. Calculated minimum energies for kallolide A and its C2 epimer.

Scheme 4



preincubation in an aqueous buffer medium. The active toxin is generated by hydrolysis of the C2 acetate. When the incubation was performed in $H_2{}^{18}O$ the alcohol product was highly ^{18}O-enriched, suggestive of an S_N1 process.

We reasoned that a similar sequence might provide a means for epimerizing the C2 position of a kallolide A precursor. In anticipation of such a maneuver, we performed molecular mechanics calculations on kallolide A and its C2 epimer (Figure 1).[16] These calculations indicated that the C2 epimer is substantially higher in energy than kallolide A. Accordingly we elected to implement this strategy.

The syn alcohol **20** was protected as the SEM ether **21** (Scheme 4). Selective deprotection of the DPS ether gave the propargylic alcohol **22** which was converted to chloride **23**. Reduction of the ester function and treatment of the derived chloro alcohol **24** with NaH and Bu_4NI in refluxing toluene (slow addition) gave the

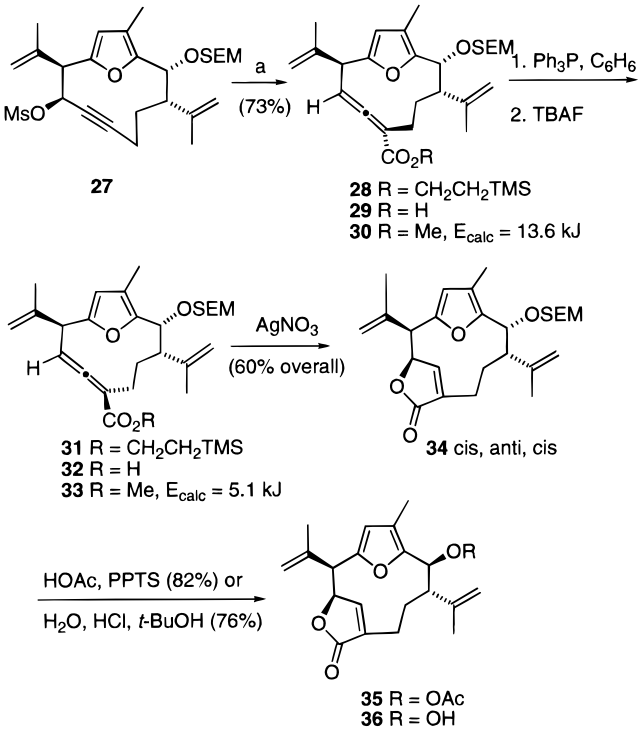
(13) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. Kobayashi, S.; Yasuda, M.; Nishio, K. *Synlett* **1996**, 153.

(14) Angell, R. M.; Barrett, A. G. M.; Braddock, D. C.; Swallow, S.; Vickery, B. D. *Chem. Commun.* **1997**, 919.

(15) Hyde, E. G.; Thornhill, S. M.; Boyer, A. J.; Abrahamson, S. N. *J. Med. Chem.* **1995**, *38*, 4704.

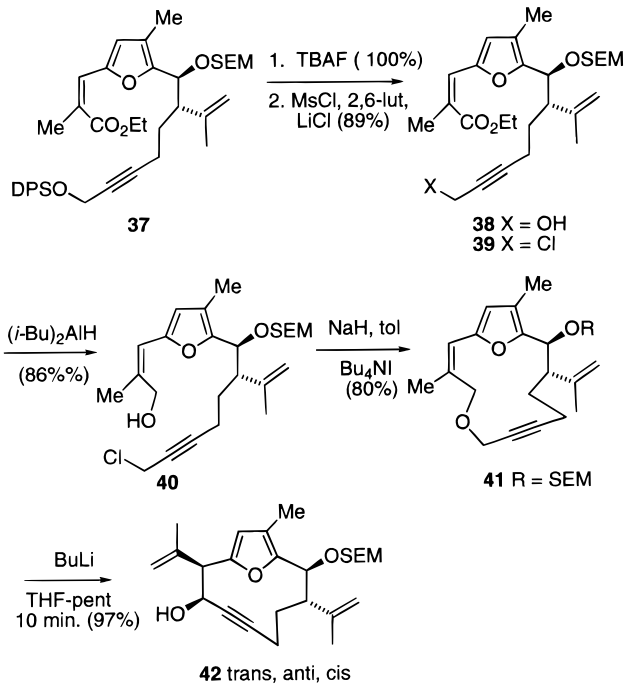
(16) The program Macromodel V5.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multiple step interations (typically 1000) until the minimum energy conformer was found multiple times (10 or more). For a 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.

Scheme 5[a]



[a] (a) Pd_2dba_3, Ph_3P, CO, $TMSCH_2CH_2OH$, THF.

Scheme 6



macrocyclic allylic propargylic ether **25** in 66% yield. This ether underwent [2,3] Wittig ring contraction to the cis, anti, cis product **26** in 73% yield. An unidentified byproduct (not a stereoisomer) was formed in 10% yield. The stereochemistry of alcohol **26** was confirmed by X-ray structure analysis of the 2,4-dinitrobenzoate derivative.[17]

The conversion of alcohol **26** to butenolide **34** followed along the lines of our kallolide B synthesis.[3] Thus the mesylate **27** afforded the allenic ester **28** with catalytic $Pd(PPh_3)_4$ and CO in THF containing TMS ethanol. This reaction proceeds with inversion of stereochemistry. Treatment of ester **28** with Ph_3P in benzene afforded a 95:5 mixture favoring the isomerized allenoate **31**. This outcome was predicted from molecular mechanics calculations which showed a significant energy difference (5.1 vs 13.6 kJ) for the two isomers.[16]

Selective cleavage of the TMS ethyl ester was effected with TBAF, and the derived acid **32** cyclized to butenolide **34** in the presence of catalytic $AgNO_3$. As predicted, solvolytic deprotection of the SEM ether **34** with HOAc and PPTS afforded racemic kallolide A acetate **35**. The use of 3 N HCl and *tert*-butyl alcohol led to racemic kallolide A (**36**). The ^1H and ^{13}C NMR spectra of both compounds were identical to those of the respective natural products. In agreement with our calculations, kallolide A acetate contained none of the C2 epimer. However, ca. 10% of the C2 epimer was formed in the hydrolysis reaction of SEM ether **34**.

As a matter of interest, the anti adduct **19** was likewise subjected to the foregoing sequence. In contrast to its cis counterpart **25**, the trans macrocyclic propargylic allylic ether **41** underwent rapid and near-quantitative [2,3]Wittig ring contraction to the trans, anti, syn product **42** (Scheme 6).

Molecular mechanics calculations provide a possible explanation for the contrasting behavior of macrocyclic ethers **25** and **41**. Figure 2 shows the calculated global minimum structures for **25** and **41**.[16] The reacting centers in the latter structure are separated by only 3.7 Å compared to 4.4 Å in the former. In addition, the abstracted propargylic H is more favorably oriented for a concerted collinear removal with concomitant C−C bond formation in **41**.[3,18]

The mesylate derivative **43** of alcohol **42** was subjected to the hydrocarbonylation−isomerization sequence (Scheme 7). Unlike **28**, allenoate **44** underwent significant decomposition upon attempted equilibration with Ph_3P in benzene. However, ester cleavage with TBAF and subsequent exposure of the acidic products to $AgNO_3$ afforded a nearly 1:1 mixture of isomeric butenolides **45** and **46** in 95% yield. Evidently, isomerization of allenoate **44** must take place under the TBAF conditions. Molecular mechanics calculations show an energy difference of only 0.8 kJ between allenoate **44** (R = Me) and its allene diastereomer.[16] Thus the isolation of nearly equal amounts of butenolides **45** and **46** suggests that equilibration most likely occurs prior to ester cleavage. Butenolide **46** was obtained by treatment of racemic kallolide A with SEMCl, thereby confirming its structure, and by inference, that of butenolide **45**.

The original structure assignment for kallolide A was based on spectroscopic characteristics and an X-ray crystal structure analysis of the acetate, isolated as a minor constituent of the octocoral along with kallolide A and B. However, the absolute configuration was not determined. Our synthesis of (−)-kallolide B enabled assignment of absolute configuration to that metabolite and, since kallolide A was isolated from the same source, it seems reasonable to assume that the two would be of the same configuration. This assumption could be easily tested by a minor modification of our synthetic sequence.

(17) The structure determination was performed by Dr. Michal Sabat of this department.

(18) Wu, Y. D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421.

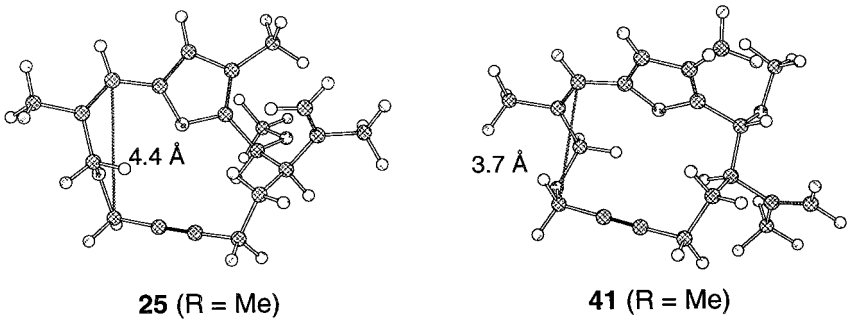
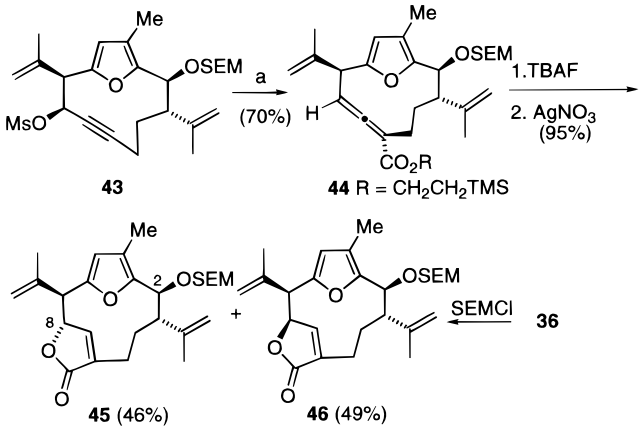


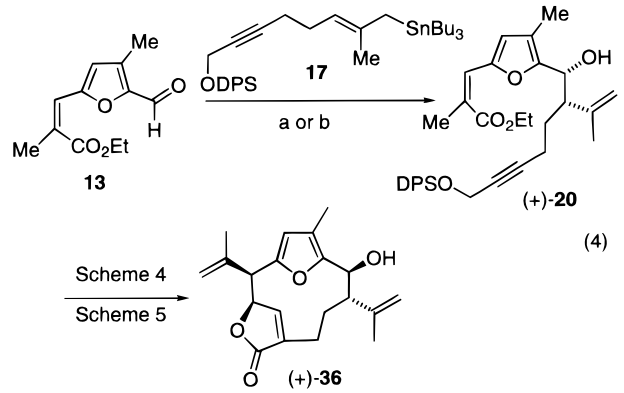
Figure 2. Chem 3D representations of calculated minimum energy structures for ethers **25** (R = Me) and **41** (R = Me) showing interatomic distances between atoms involved in the [2,3]Wittig ring contraction.

Scheme 7[a]



[a] (a) Pd_2dba_3, Ph_3P, CO, $TMSCH_2CH_2OH$, THF.

To that end, the addition of allylstannane **17** to aldehyde **13** was conducted in the presence of Keck's Ti−BINOL catalyst (eq 4).[19] With stoichiometric amounts of the



a) 1 eq $Ti(O\text{-}i\text{-}Pr)_4$, 1 eq *(M)*-BINOL 4 Å MS, THF; 31% yield, 52% ee

b) 1 eq $2,6\text{-}(MeO)_2C_6H_3COO$ CO_2H CO_2H OH 1 eq BH_3•THF, EtCN, 2 eq Tf_2O; 24% yield, 90% ee

chiral Lewis acid, adduct (+)-**20** of 52% ee was obtained in 31% yield. The Yamamoto chiral acyloxyborane catalyst gave adduct (+)-**20** of 90% ee in 24% yield.[20] Again a full equivalent of the chiral Lewis acid was required. Following the sequence outlined in Schemes 4 and 5, we converted alcohol (+)-**20** of 90% ee to (+)-kallolide A. The observed rotation of +133 was in excellent agreement with the reported value of +145 for the natural product.[2]

These studies establish the absolute configuration of kallolide A.[21] They also reveal subtle conformational effects engendered by the C2 oxygen substituent of cyclic esters **25** vs **41** and allenoates **28** and **44**. In addition, they underscore the value of molecular mechanics calculations as a predictive tool in these macrocyclic systems.

Experimental Section

1-[(*tert*-Butyldiphenylsilyl)oxy]-2-propyne (2). To a solution of 2.24 g (40 mmol) of propargyl alcohol and 6.8 g (100 mmol) of imidazole in 8 mL of DMF was added 13.19 g (48 mmol) of *tert*-butyldiphenylsilyl chloride dropwise at 0 °C. The reaction was brought to room temperature and stirred overnight until the starting material was totally consumed (TLC analysis, 25% ethyl acetate in hexanes). The reaction mixture was diluted with water and extracted with hexanes. The combined hexane extracts were washed with water and brine and dried over anhydrous $MgSO_4$. The solution was concentrated, and the residue was directly used for next step without further purification. A small portion was chromatographed on silica gel (10% ether in hexanes) to give a white solid product. ^{1}H NMR ($CDCl_3$): 7.74−7.70 (m, 4 H), 7.47−7.36 (m, 6 H), 4.32 (d, 2 H, J = 2.5 Hz), 2.39 (t, 1 H, J = 2.5 Hz), 1.07 (s, 9 H). ^{13}C NMR ($CDCl_3$): 135.6, 133.0, 129.8, 127.7, 73.0, 52.5, 26.7, 19.1. IR (cm $^{-1}$, neat): 3316.

5-[(*tert*-Butyldiphenylsilyl)oxy]-3-pentyn-2-ol (3). To a solution of the above alkyne **2** in THF (400 mL) was added 20.8 mL of *n*-BuLi in hexanes (2.5 M, 52 mmol) at −78 °C. The solution was stirred for 1 h at that temperature, and then 8.96 mL (160 mmol) of acetaldehyde was added dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and extracted with ether. The organic extracts were combined and washed with water and brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure, and the residue was used for the next step without further purification. A small portion was chromatographed on silica gel (15% ethyl acetate in hexanes) to give a clear liquid. ^{1}H NMR ($CDCl_3$): 7.75−7.71 (m, 4 H), 7.47−7.33 (m, 6 H), 4.44 (qt, 1 H, J_q = 6.8 Hz, J_t = 2.0 Hz), 4.37 (d, 2 H, J = 2.0 Hz), 1.35 (d, 3 H, J = 6.8 Hz), 1.07 (s, 9 H). ^{13}C NMR ($CDCl_3$): 135.7, 133.2, 129.8, 127.6, 87.1, 82.4, 58.3, 52.6, 26.7, 24.0, 19.1. IR (cm^{-1}, neat): 3356, 1590; Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.43; H, 7.78.

(19) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827.

(20) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561. Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653.

(21) The furanocembrane bipinnatin J has recently been converted to kallolide A through photochemical ring contraction. Rodriguez, A.; Shi, J.-G.; *J. Org. Chem.* **1998**, *63*, 420.

1-[(*tert*-Butyldiphenylsilyl)oxy]-2-(tributylstannyl)-2,3-pentadiene (5). To a solution of the above alcohol **3** in CH_2Cl_2 (400 mL) was added 13.95 mL (100 mmol) of Et_3N, and the mixture was cooled to −78 °C. Methanesulfonyl chloride (3.7 mL, 48 mmol) was added dropwise by a syringe, and the mixture was stirred for over 1 h until TLC analysis showed no starting material. The mixture was treated with $NaHCO_3$, warmed to room temperature, and extracted with ether. The extracts were combined, washed with water and brine and dried over $MgSO_4$. The residue was azeotropically dried with benzene and used for the next step without further purification.

To a solution of 11.3 mL (80 mmol) of diisopropylamine and 32 mL (80 mmol) of 2.5 M *n*-butyllithium in hexane in 160 mL of THF was added at 0 °C 21.5 mL (80 mmol) of tributyltin hydride dropwise, and the mixture was stirred for 15 min at 0 °C. The solution was cooled to −78 °C, and 16.4 g (80 mmol) of $CuBr{\cdot}SMe_2$ was added from a powder delivery funnel. After 30 min, the above mesylate **4** in 20 mL of THF was added dropwise. After 1 h the reaction was quenched by pouring into saturated NH_4Cl/concentrated NH_4OH (9:1) (500 mL) with stirring until the precipitate dissolved. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were washed with water and brine and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel (hexanes followed by 5% ether in hexanes) to give 22.02 g of colorless product (90% overall yield from propargyl alcohol). ^{1}H NMR ($CDCl_3$): 7.71 (d, 4 H, J = 6.8 Hz), 7.45−7.34 (m, 6 H), 4.68 (qt, 1 H, J_q = 7.0 Hz, J_t = 2.9 Hz), 4.35−4.22 (m, 2 H), 1.62 (d, 3 H, J = 7.0 Hz), 1.58−1.46 (m, 6 H), 1.37−1.24 (m, 6 H), 1.06 (s, 9 H), 0.98 (dd, 6 H, J_1 = 7.3 Hz, J_2 = 9.8 Hz), 0.89 (t, 9 H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 202.5, 135.6, 133.9, 129.4, 127.5, 94.7, 78.0, 65.7, 29.0, 27.3, 26.8, 19.2, 14.2, 13.7, 10.4. IR (cm^{-1}, neat): 1936, 1466. Anal. Calcd for $C_{33}H_{52}OSiSn$: C, 64.81; H, 8.57, Found: C, 64.80; H, 8.54.

2-(Benzoyloxy)acetaldehyde. To a solution of *cis*-2-butene-1,4-diol (8.2 mL, 100 mmol) in CH_2Cl_2 (400 mL) was added 40.2 mL (300 mmol) of triethylamine. The mixture was cooled to 0 °C and 27.8 mL (240 mmol) of benzoyl chloride was added dropwise. The reaction mixture was brought to room temperature and stirred overnight. Water was added, and the mixture was extracted with ether. The combined extracts were washed with water and brine and dried over $MgSO_4$. After removal of solvent the residue was chromatographed on silica gel (10% ether in hexanes) to give 26.3 g (89%) of dibenzoate. ^{1}HNMR ($CDCl_3$): 8.05 (d, 4 H, J = 8.0 Hz), 7.57 (t, 2 H, J = 8.0 Hz), 7.44 (t, 4 H, J = 8.0 Hz), 5.96 (t, 2 H, J = 5.0 Hz), 5.02 (d, 4 H, J = 5.0 Hz). ^{13}C NMR ($CDCl_3$): 166.3, 133.0, 130.0, 129.7, 128.4, 60.6.

To a solution of 23.7 g (80 mmol) of the above dibenzoate in 400 mL of wet CH_2Cl_2 (saturated with water before use) was bubbled O_3 at −78 °C until the solution turned blue. Excess ozone was purged with nitrogen then 31.5 g (120 mmol) of Ph_3P was added. The solution was allowed to warm to room temperature. After 30 min, the solvent was removed and the residue was chromatographed on silica gel (25% EtOAc in hexanes followed by 70% EtOAc in hexanes) to give 17.3 g (66%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$): 9.72 (s, 1 H), 8.12−8.08 (m, 2 H), 7.60 (m, 1 H), 7.50−7.44 (m, 2 H), 4.89 (s, 2 H). IR (cm^{-1}, neat): 1730, 1719.

6-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-1-(benzoyloxy)-4-hexyn-2-ol (6). To a mixture of 5.2 g (32 mmol) of 2-(benzoyloxy)acetaldehyde and 9.68 g (15.8 mmol) of allenylstannane **5** in 150 mL of CH_2Cl_2 was added 6.01 mL (47.4 mmol) of $BF_3{\cdot}OEt_2$ dropwise at −78 °C. The reaction was closely monitored by TLC. After total consumption of allenylstannane (2 h), methanol was added followed by saturated $NaHCO_3$ to quench the reaction. The mixture was allowed to warm to room temperature and extracted with ether. The extracts were combined and washed with saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed on silica gel (20% ether in hexanes) to give 7.05 g (92%) of a colorless oil. ^{1}H NMR ($CDCl_3$): 8.05 (d, 2 H, J = 8 Hz), 7.76−7.69 (m, 4 H), 7.58 (t, 1 H, J = 6.8 Hz), 7.49−7.35 (m, 8 H), 4.50 (dd, 1 H, J_1 = 3.4 Hz, J_2 = 11.7 Hz), 4.36 (d, 2 H, J = 1.5 Hz), 4.35 (m, 1 H), 3.78 (ddd, 1 H, J_1 = 3.4 Hz, J_2 = 3.4 Hz, J_3 = 7.3 Hz), 2.73−2.64 (m, 1H), 2.27 (br, 1 H), 1.21 (d, 3 H, J = 6.8 Hz), 1.05 (s, 9 H). ^{13}C NMR ($CDCl_3$): 135.6, 133.3, 133.1, 129.9, 129.7, 129.6, 128.4, 127.6, 85.8, 81.2, 72.9, 67.2, 52.8, 30.1, 26.7, 19.1, 16.4. IR (cm^{-1}, neat): 3471, 2242, 1722, 1276. Anal. Calcd for $C_{30}H_{34}O_4Si$: C, 74.04; H, 7.04. Found: C, 73.92; H, 7.06.

2-(Benzoyloxy)methyl-3-methyl-5-[[(diphenyl-*tert*-butylsilyl)oxy]methyl]furan (8). To a solution of 1.02 g (2.49 mmol) of Dess−Martin periodinane reagent in CH_2Cl_2 was added 1.10 g (2.26 mmol) of alcohol **6**. After 1 h the reaction was quenched with a solution of 2.5 g (1.6 mmol) of $Na_2S_2O_3{\cdot}5H_2O$ in 10 mL of saturated $NaHCO_3$. The resulting solution was stirred for 10 min and extracted with ether. The extracts were combined and washed with water and brine and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed on silica gel (20% ether in hexanes) to give 0.99 g (90%) of a mixture of allenyl and alkynyl ketones judging from NMR and IR. This mixture in 10 mL of CH_2Cl_2 and 3.45 mL (24.9 mmol) of Et_3N at −78 °C was allowed to slowly warm to room temperature with stirring overnight. The solvent was removed under vacuum, and the residue was passed through a pad of silica gel with 10% ether in hexanes. After removal of solvent, the residue, allenone **7**, was used for the next step without further purification.

To the solution of the above allenone **7** in acetone was added 31 mg (0.18 mmol) of $AgNO_3$, and the solution was heated at reflux for 1 h. After total consumption of starting material the mixture was passed through a pad of Celite and washed with ether. The solvent was removed, and the residue was chromatographed on silica gel (10% ether in hexanes) to give furan **8**, a colorless oil. ^{1}H NMR ($CDCl_3$): 8.12 (d, 2 H, J = 6.8 Hz), 7.79−7.74 (m, 4 H), 7.57 (tt, 1 H, J_1=1.5 Hz, J_2=7.8 Hz), 7.48−7.39 (m, 8 H), 6.07 (s, 1 H), 5.31 (s, 2 H), 4.69 (s, 2 H), 2.14 (s, 3 H), 1.13 (s, 9 H). ^{13}C NMR ($CDCl_3$): 166.3, 153.8, 144.4, 135.6, 133.3, 132.9, 130.1, 129.7, 129.65, 128.3, 127.6, 121.0, 110.7, 59.0, 56.9, 26.7, 19.2, 9.9. IR (neat): 1710, 1588. Anal. Calcd. for $C_{30}H_{32}O_4Si$: C, 74.35; H, 6.65. Found: C, 74.31; H, 6.65.

2-[(Benzoyloxy)methyl]-3-methyl-5-(hydroxymethyl)-furan (9). To a solution of 3.0 g (6.2 mmol) of furan **8** in 60 mL of THF was added 24.8 mL (24.8 mmol) of tetrabutylamonium fluoride in THF (1.0 M) at − 78 °C. The solution was slowly allowed to warm to room temperature with stirring overnight. After total consumption of the starting material, the reaction was quenched with water and extracted with ether. The extracts were combined and washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (25% ethyl acetate in hexanes) to give 1.5 g (99%) of alcohol **9** as a colorless oil. ^{1}H NMR ($CDCl_3$): 8.05−8.01 (m, 2 H), 7.53 (tt, 1H, J_1=1.5 Hz, J_2=7.3 Hz), 7.44−7.38 (m, 2 H), 6.14 (s, 1 H), 5.25 (s, 2 H), 4.55 (s, 2 H), 2.34 (br, 1 H), 2.09 (s, 3 H). ^{13}C NMR ($CDCl_3$): 166.4, 153.9, 144.9, 133.0, 129.9, 129.7, 128.3, 121.3, 111.1, 57.4, 56.8, 9.8. IR (cm^{-1}, neat): 3397, 1722. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.19; H, 5.76.

Furan Ester 11. To a solution of 3.15 g (7.68 mmol) of Dess−Martin periodinane reagent in CH_2Cl_2 was added 1.40 g (5.69 mmol) of alcohol **9** at 0 °C. After total consumption of starting material, 6.3 g (40 mmol) of $Na_2S_2O_3{\cdot}5H_2O$ in saturated $NaHCO_3$ was added, and the solution was stirred for 10 min. The solution was extracted with ether, and the organic extracts were combined, washed with water and brine, and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue, aldehyde **10**, was directly used for the Still−Horner−Emmons reaction without further purification.

To a mixture of 4.92 g (14.2 mmol) of ethyl bis(1,1,1-trifluoroethyl) 2-phosphonopropionate and 7.52 g (28.4 mmol) of 18-crown-6 was added 28.4 mL (14.2 mmol) of potassium bis(trimethylsilyl)amide (0.5 M in hexane) dropwise at −78 °C. The solution was stirred for 40 min, and aldehyde **10** was added dropwise. After 30 min, the reaction was quenched with

saturated NH_4Cl and warmed to room temperature. The mixture was extracted with ether, and the extracts were combined, washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (10% ether in hexanes) to give 1.65 g (88%) of ester **11** as a colorless oil. ^{1}H NMR ($CDCl_3$): 8.04 (d, 2 H, J = 7.3 Hz), 7.54 (t, 1 H, J = 7.3 Hz), 7.41 (t, 2 H, J = 7.3 Hz), 6.78 (s, 1 H), 6.44 (s, 1 H), 5.25 (s, 2 H), 4.26 (q, 2 H, J = 6.8 Hz), 2.11 (s, 3 H), 2.07 (s, 3 H), 1.29 (t, 3 H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): 168.4, 166.2, 150.1, 145.2, 133.0, 129.9, 129.7, 128.3, 126.3, 123.3, 122.5, 115.7, 60.6, 56.7, 21.5, 14.1, 9.8. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.62; H, 6.13.

Furan Ester Aldehyde 13. To a solution of 2.78 g (8.47 mmol) of diester **11** in 80 mL of ethanol was added 2.80 g of K_2CO_3 at room temperature. The mixture was stirred at room temperature until all the starting material was consumed (3 h, TLC analysis), and then it was filtered through a pad of Celite and washed with ether to remove solid K_2CO_3. The solvent was removed, the residue was dissolved in 850 mL of CH_2Cl_2, and 7.45 g (84.7 mmol) of MnO_2 was added. After the completion of the reaction (6 h), the mixture was filtered through a pad of Celite and the solvent was removed. The residue was chromatographed on Et_3N-deactivated silica gel (10% ether in hexanes) to give 1.56 g (83%) of aldehyde **13** as a colorless solid: mp 51.5−52.5 °C. ^{1}H NMR ($CDCl_3$): 9.69 (s, 1 H), 6.80 (s, 1 H), 6.44 (q, 1 H, J = 1.5 Hz), 4.29 (q, 2 H, J = 7.3 Hz), 2.35 (s, 3 H), 2.11 (d, 3 H, J = 1.5 Hz), 1.32 (t, 3 H, J = 7.3). ^{13}C NMR ($CDCl_3$): 168.0, 154.1, 147.6, 132.6, 121.6, 116.7, 61.2, 21.8, 14.1, 10.4. IR (cm^{-1}, neat): 1710, 1674.

(*E*)-8-[(*tert*-Butyldiphenylsilyl)oxy]-1-chloro-2-methyl-2-octen-7-yne (16). To a solution of 5.40 g (13.8 mmol) of alcohol **15** in 20 mL of THF was added 30 mL of CCl_4, 4.80 mL (27.56 mmol) of Hunig's base, and 7.22 g (27.6 mmol) of Ph_3P. The mixture was brought to reflux for 4 h until no starting material was detected by TLC. Most of the solvent was removed, and the oily residue was poured into 100 mL of hexanes. Filtration, concentration, and chromatography on silica gel with 5% ether in hexanes provided 5.10 g (90%) of chloride **16** as a colorless liquid. ^{1}H NMR ($CDCl_3$): 7.75−7.71 (m, 4 H), 7.45−7.36 (m, 6 H), 5.55 (t, 1 H, J = 5.9 Hz), 4.32 (br, 2 H), 4.01 (s, 2 H), 2.22 (br, 4 H), 1.75 (s, 3 H), 1.07 (s, 9 H). ^{13}C NMR ($CDCl_3$): 135.6, 133.3, 132.9, 129.7, 128.9, 127.6, 84.8, 78.9, 52.9, 52.1, 27.2, 26.7, 19.2, 18.6, 14.3. IR (cm^{-1}, neat): 2331, 1474, 1431. Anal. Calcd for $C_{25}H_{31}ClO_2Si$: C, 73.05; H, 7.60. Found: C, 73.15; H, 7.69.

Anti Adduct: Alcohol 19. To a solution of 41.0 mg (0.10 mmol) of chloride **16** in 0.20 mL of THF were added 3.0 mg (0.03 mmol) of CuCl, 15.1 μL (0.15 mmol) of trichlorosilane, and 26.1 μL (0.15 mmol) of Hunig's base successively at room temperature. After 1 h, 15.6 mg (0.1 mmol) of dipyridyl and 11.1 mg (0.05 mmol) of aldehyde **13** in 0.20 mL of CH_2Cl_2 was added at −40 °C. The reaction was closely monitored by TLC, and when the aldehyde was consumed (usually within 1 h), the reaction was quenched with water and extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (20% ether in hexanes) to give 46 mg of alcohol **19** as a colorless liquid with a trace of the syn isomer **20** and the linear adduct **18** (**19:18** = 18:1). ^{1}H NMR ($CDCl_3$): 7.71−7.68 (m, 4 H), 7.45−7.33 (m, 6 H), 6.92 (s, 1 H), 6.48 (s, 1 H), 5.07 (b, 1 H), 5.00 (s, 1 H), 4,49 (dd, 1 H, J_1 = 3.4 Hz, J_2 = 10.2 Hz), 4.27 (s, 2 H), 4.26 (q, 2 H, J = 7.3 Hz), 2,72 (dt, 1 H, J_d = 3.4 Hz, J_t = 10.2 Hz), 2.18−1.87 (m, 2 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.74 (s, 3 H), 1.60 (br, 1 H), 1.44−1.12 (m, 2 H), 1.32 (t, 3 H, J = 7.3 Hz), 1.04 (s, 9 H). ^{13}C NMR ($CDCl_3$): 168.1, 149.33, 149.26, 143.4, 135.6, 133.3, 129.7, 127.6, 124.8, 124.7, 120.4, 116.7, 116.3, 84.9, 78.6, 66.5, 60.5, 52.9, 52.4, 27,6, 26.7, 21.5, 19.1, 17.7, 16.7, 14.2, 9.8. IR (cm^{-1}, neat), 3493, 1710.

Syn Adduct: Alcohol 20. To a solution of 0.43 g (1.9 mmol) of aldehyde **13** and 2.55 g (3.8 mmol) of stannane **17** in CH_2Cl_2 was added 0.27 mL (2.3 mmol) of BF_3·OEt_2 complex dropwise at −78 °C. The reaction was monitored by TLC until the starting material was consumed (normally less than 15 min). Methanol was added followed by saturated NH_4Cl. The mixture was allowed to warm to room temperature. The organic layer was separated, and the water layer was extracted with ether. The organic extracts were combined, washed with saturated NH_4Cl, water, and brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (20% ether in hexanes) to yield 1.27 g (99%) of adduct **20** as a colorless liquid. ^{1}H NMR ($CDCl_3$): 7.76−7.71 (m, 4 H), 7.45−7.37 (m, 6 H), 6.85 (s, 1 H), 6.44 (s, 1 H), 4.75 (s, 1 H), 4.69 (s, 1 H), 4.52 (dd, 1 H, J_1 = 6.4 Hz, J_2 = 2.0 Hz), 4.33 (s, 2 H), 4.25 (q, 2 H, J = 6.8 Hz), 2.67 (t, 1 H, J_1 = 10.3 Hz, J_2 = 2.0 Hz), 2.29−1.95 (m, 3 H), 2.04 (s, 3 H), 1.98 (s, 3 H), 1.88 (d, 1 H, J = 6.4 Hz), 1.66−1.56 (m, 1 H), 1.50 (s, 3 H), 1.32 (t, 3 H, J = 6.8 Hz), 1.07 (s, 9 H). IR (cm^{-1}, neat), 3471, 3075, 1714.

***Syn* Alcohol (+)-20. A. CAB Procedure.** To a suspension of 84.6 mg (0.27 mmol) of mono[(2,6-dimethoxybenzoyl)-oxy]tartaric acid in 0.15 mL of MeCN was added 0.30 mL (0.30 mmol) of BH_3·THF (1.0 M in THF) at 0 °C dropwise. Gas was evolved, and the solid dissolved. After 1 h the solution was cooled to −78 °C, and trifloroacetic anhydride was added followed by furan **13** in 0.10 mL of MeCN. Allylic stannane **17** in 0.10 mL of MeCN was added by syringe pump over 3 h at −78 °C. The reaction was kept at −78 °C for another 12 h and quenched with MeOH followed by saturated $NaHCO_3$. The mixture was allowed to warm to room temperature and extracted with ether. The extracts were combined, washed with aqueous $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure. The residue was chromatographed on Et_3N-deactivated silica gel (20% ether in hexanes) to afford 16 mg (24%) of alcohol (+)-**20** as a colorless liquid and 11 mg of recovered aldehyde **13**. Also isolated was enyne **17** (R = H) from protonolysis of stannane **17**. The aqueous layer and washings were combined and acidified with 4 N HCl and extracted with ethyl acetate to recover the ligand; $[\alpha]_D$ = +18.7. HPLC analysis (Chiral-OB column) of alcohol (+)-**20** indicated an ee of 90%.

B. Modified Keck Procedure. To a solution of 57.2 mg (0.20 mmol) of (*R*)-BINOL and 100 mg of flame-dried 4 Å powered molecular sieves in 0.50 mL of CH_2Cl_2 was added 59 μL (0.20 mmol) of titanium tetraisopropoxide at room temperature. The mixture was refluxed for 1.5 h and then cooled to −78 °C. To this mixture were added 44.4 mg (0.20 mmol) of aldehyde **13** and 146 mg (0.22 mmol) of stannane **17**. The mixture was brought to −20 °C and stirred for 10 h. TLC showed only a trace of product had formed. The mixture was brought to 0 °C for 4 h, and 1 mL of saturated $NaHCO_3$ was added to quench the reaction. The mixture was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel to give 37 mg (31%) of product. HPLC analysis (Chiral-OB column) indicated a 54:46 mixture of syn and anti adducts of 52% and 68% ee.

SEM Ether 21. To a solution of 1.00 g (1.67 mmol) *syn*-alcohol **20** in 20 mL of CH_2Cl_2 was added 0.87 mL (5.0 mmol) of Hunig's base followed by 0.59 mL (3.3 mmol) of 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) dropwise at −78 °C. The solution was slowly warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (10% ether in hexanes) to give 1.21 g (99%) of ether **21** as a colorless liquid. ^{1}H NMR ($CDCl_3$): 7.77−7.70 (m, 4 H), 7.44−7.36 (m, 6 H), 6.88 (s, 1 H), 6.47 (s, 1 H), 4.69 (s, 2 H), 4.56 (d, 1 H, J = 6.8 Hz), 4.50 (d, 1 H, J = 6.8 Hz), 4.49 (d, 1 H, J = 10.2 Hz), 4.32 (s, 2 H), 4.26 (q, 2 H, J = 7.3 Hz), 3.72 (ddd, 1 H, J_1 = J_2 = 8.8 Hz, J_3=1.0 Hz), 3.44 (ddd, 1 H, J_1 = J_2 = 8.8 Hz, J_3=1.0 Hz), 2.80 (dt, 1 H, J_d = 2.9 Hz, J_t = 10.2 Hz), 2.27−2.08 (m, 3 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.62−1.52 (m, 1 H), 1.50 (s, 3 H), 1.32 (t, 3 H, J = 7.3 Hz), 1.07 (s, 9 H),

0.89 (t, 2 H, J = 8.8 Hz), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$): 168.2, 149.3, 148.5, 142.8, 135.6, 133.3, 129.6, 127.6, 124.8, 124.2, 121.2, 115.9, 114.0, 92.2, 85.4, 78.4, 71.2, 65.2, 60.5, 53.0, 49.8, 29.1, 26.7, 21.5, 19.7, 19.1, 18.0, 16.8, 14.2, 9.8, −1.4. Anal. Calcd for $C_{43}H_{60}O_6Si_2$: C, 70.84; H, 8.29. Found: C, 70.88; H, 8.36. IR (cm^{-1}, neat) 3075, 1714.

Alcohol 22. To a solution of 1.60 g (2.19 mmol) of DPS ether **21** in 25 mL of THF was added 8.8 mL (8.8 mmol) of TBAF (1.0 M in THF) at −78 °C. After 20 min, the solution was warmed to 0 °C. The reaction was quenched with water after total consumption of the DPS ether (2 h). The organic layer was separated, and the water layer was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (15% ethyl acetate in hexanes) to give 0.97 g (90%) of alcohol **22** as a colorless liquid. ^{1}H NMR ($CDCl_3$): 6.60 (s, 1 H), 6.35 (br, 1 H), 4.69 (s, 2 H), 4.54 (d, 1 H, J = 6.8 Hz), 4.49 (d, 1 H, J = 10.2 Hz), 4.48 (d, 1 H, J = 6.8 Hz), 4.29 (q, 2 H, J = 7.3 Hz), 4.25 (m, 2 H), 3.71 (ddd, 1 H, J_1 = 2.0 Hz, $J_2 = J_3$ = 8.8 Hz), 3.43 (ddd, 1 H, J_1 = 2.0 Hz, $J_2 = J_3$ = 8.8 Hz), 2.89 (dt, 1 H, J_d = 2.9 Hz, J_t = 10.2 Hz), 2.34−2.08 (m, 4 H), 2.04 (s, 3 H), 1.97 (s, 3 H), 1.60−1.50 (m, 1 H), 1.48 (s, 3 H), 1.31 (t, 3 H, J = 7.3 Hz), 0.9 (t, 2 H, J = 8.8 Hz), 0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$): 169.3, 149.2, 148.4, 142.7, 125.2, 122.5, 121.0, 114.9, 114.2, 92.1, 85.8, 79.0, 70.8, 65.2, 60.9, 51.3, 49.3, 28.7, 21.4, 19.6, 18.1, 16.6, 14.1, 9.7, −1.4. IR (cm^{-1}, neat), 3455 (br), 2951, 1714. Anal. Calcd for $C_{27}H_{42}O_6Si$: C, 69.72; H, 8.89. Found: C, 66.02; H, 8.69.

Chloride 23. A flask charged with 0.33 g (7.8 mmol) of LiCl was flame dried for 5 min under vacuum (1 mmHg). Then 3.0 mL of dry DMF and 0.91 mL (7.8 mmol) of 2,6-lutidine were added, and the mixture was stirred to dissolve the LiCl. The mixture was cooled to 0 °C, and 0.96 g (2.0 mmol) of propargylic alcohol **22** (which was azeotropically dried with benzene three times before use) in 3 mL of dry DMF was added followed by 0.45 mL (5.9 mmol) of methanesulfonyl chloride. After 12 h at 0 °C, the yellow mixture was quenched with water and extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (10% ether in hexanes) to give 0.85 g (88%) of chloride **23** as a colorless liquid and 70 mg (7%) of starting alcohol. ^{1}H NMR ($CDCl_3$): 6.80 (s, 1 H), 6.45 (br, 1 H), 4.68 (s, 2 H), 4.54 (d, 1 H, J = 6.8 Hz), 4.48 (d, 1 H, J = 10.7 Hz), 4.47 (d, 1 H, J = 6.8 Hz), 4.26 (q, 2 H, J = 7.3 Hz), 4.15 (br, 2 H), 3.71 (ddd, 1 H, J_1 = 2.0 Hz, $J_2 = J_3$ = 8.8 Hz), 3.43 (ddd, 1 H, J_1 = 2.0 Hz, $J_2 = J_3$ = 8.8 Hz), 2.78 (dt, 1 H, J_d = 2.7 Hz, J_t = 10.7 Hz), 2.31−2.09 (m, 4 H), 2.04 (s, 3 H), 1.97 (s, 3 H), 1.73−1.53 (m, 1 H), 1.48 (s, 3 H), 1.31 (t, 3 H, J = 7.3 Hz), 0.90 (t, 2 H, J = 8.8 Hz), 0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$): 168.4, 149.3, 148,3, 142.6, 124.6, 124.2, 121.2, 115.6, 114.2, 92.1, 87.4, 75.1, 71.0, 65.3, 60.5, 49.8, 31.3, 28.9, 21.5, 19.6, 18.1, 16.8, 14.2, 9.8, −1.5. IR (cm^{-1}, neat) 3075, 2951, 2233, 1722. Anal. Calcd for $C_{27}H_{41}ClO_5Si$: C, 63.69; H, 8.12. Found: C, 63.72; H, 8.16.

Alcohol 24. To a solution of 0.75 g (1.5 mmol) of chloride **23** in 15 mL of CH_2Cl_2 was added 3.68 mL (3.7 mmol) of DIBAl-H (1.0 M in hexanes) at −78 °C. After complete consumption of the ester, the reaction was quenched with 50 mL of saturated sodium potassium tartrate. The mixture was allowed to warm to room temperature, another 50 mL of saturated sodium potassium tartrate was added, and the mixture was stirred until the solution turned clear. The organic layer was separated, and the water layer was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel (25% ethyl acetate in hexanes) to give 0.63 g (92%) of chloro alcohol **24** as a colorless liquid. ^{1}H NMR ($CDCl_3$): 6.02 (br, 1 H), 5.94 (s, 1 H), 4.69 (s, 2 H), 4.53 (d, 1 H, J = 6.8 Hz), 4.48 (d, 1 H, J = 10.3 Hz), 4.47 (d, 1 H, J = 6.8 Hz), 4.45 (dd, 1 H, J_1 = 5.9 Hz, J_2 = 13.2 Hz), 4.36 (dd, 1 H, J_1 = 5.9 Hz, J_2 = 13.2 Hz), 4.14 (br, 2 H), 3.72 (ddd, 1 H, J_1 = 2.0 Hz, $J_2 = J_3$ = 8.8 Hz), 3.44 (ddd, 1 H, J_1 = 2.0 Hz, $J_2 = J_3$ = 8.8 Hz), 2.82 (dt, 1 H, J_d = 2.7 Hz, J_t = 10.3 Hz), 2.30−2.02 (m, 3 H), 1.96 (s, 3 H), 1.95 (s, 3 H), 1.61−1.53 (m, 1 H), 1.49 (s, 4 H), 0.9 (t, 2 H, J = 8.8 Hz), 0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$):151.0, 146.8, 142.7, 136.9, 120.5, 115.7, 114.0, 111.7, 91.8, 87.3, 75.2, 70.9, 65.3, 63.0, 49.8, 31.2, 28.7, 22.5, 19.3, 18.0, 16.8, 9.6, −1.5. IR (cm^{-1}, neat): 3430, 3075, 2233.

Cyclic Ether 25. A mixture of 0.12 g (4.9 mmol) of sodium hydride, 1.31 g (4.9 mmol) of 18-crown-6, 20 mg of tetrabutylammonium iodide, and 120 mL of toluene (freshly distilled from calcium hydride) was heated to reflux. To the mixture was added 0.33 g (0.71 mmol) of chloro alcohol **24** in 30 mL of toluene by syringe pump over 4 h. After the addition, the mixture was heated for 6 h until all the chloro alcohol was consumed. The mixture was cooled to room temperature and filtered through a pad of silica gel. The solvent was removed, and the residue was chromatographed on Et_3N-deactivated silica gel (10% ether in hexanes) to give 0.18 g (66%) of macrocyclic ether **25** as a colorless liquid. ^{1}H NMR ($CDCl_3$): 6.08 (br, 1 H), 5.92 (s, 1 H), 4.86 (s, 1 H), 4.85 (d, 1 H, J = 4.9 Hz), 4.78 (s, 1 H), 4.74 (d, 1 H, J = 6.8 Hz), 4.61 (br, 2 H), 4.56 (d, 1 H, J = 6.8 Hz), 4.15 (d, 1 H, J = 15.1 Hz), 4.03 (d, 1 H, J = 15.1 Hz), 3.73 (ddd, 1 H, J_1 = 6.8 Hz, $J_2 = J_3$ =10.3 Hz), 3.45 (ddd, 1 H, J_1 = 6.8 Hz, $J_2 = J_3$ =10.3 Hz), 3.33 (ddd, 1 H, $J_1 = J_2$ = 4.9 Hz, J_3 = 9.8 Hz), 2.39−2.04 (m, 3 H), 2.00 (s, 3 H), 1.90 (s, 3 H), 1.78 (s, 3 H), 1.80−1.72 (m, 1 H), 0.93 (ddd, 1 H, J_1 = 1.0 Hz, J_2 = 3.4 Hz, J_3 = 6.8 Hz), 0.89 (ddd, 1 H, J_1 = 1.0 Hz, J_2 = 3.4 Hz, J_3 = 6.8 Hz) 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$): 150.5, 147.5, 144.3, 132.9, 119.1, 117.4, 113.1, 112.9, 93.0, 87.2, 77.5, 72.7, 67.5, 65.4, 56.8, 47.8, 25.6, 22.2, 21.1, 18.1, 17.2, 9.6, −1.5. IR (cm^{-1}, neat): 3073, 2960.

Alcohol 26. To a solution of 100 mg (0.23 mmol) of macrocyclic allylic propargylic ether **25** in 23 mL of THF−pentane (1:1) was added 0.28 mL (0.69 mmol) of *n*-butyllithium (2.5 M in hexanes) at −78 °C. The solution quickly turned red. The reaction was quenched with 10 mL of saturated ammonium chloride after 1 h and allowed to warm to room temperature. The mixture was extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on Et_3N-deactivated silica gel to give 65 mg (73%) of propargylic alcohol **26** as a colorless liquid with 9 mg (10%) of an unidentified isomer, and 11 mg (11%) of starting material. Upon cooling, alcohol **26** solidified. ^{1}H NMR ($CDCl_3$): 6.04 (s, 1 H), 5.32 (s, 1 H), 5.05 (s, 1 H), 4.77 (br, 1 H), 4.75 (br, 1 H), 4.72 (s, 1 H), 4.68 (d, 1 H, J = 6.8 Hz), 4.64 (d, 1 H, J = 6.8 Hz), 4.57 (dt, 1 H, J_d = 10.0 Hz, J_t = 2.3 Hz), 3.73 (ddd, 1 H, J_1 = 6.8 Hz, $J_2 = J_3$ = 10.0 Hz), 3.77−3.68 (m, 1 H), 3.49 (ddd, 1 H, J_1 = 6.8 Hz, $J_2 = J_3$ = 10.0 Hz), 2.65 (t, 1 H, J = 13.5 Hz), 2.40−2.30 (m, 1 H), 2.18 (d, 1 H, J = 6.8 Hz), 2.01 (s, 3 H), 1.97−1.90 (m, 1 H), 1.86 (s, 3 H), 1.84 (s, 3 H), 1.72−1.68 (m, 2 H), 0.92 (ddd, 1 H, J_1 = 0.5 Hz, J_2 = 1.5 Hz, J_3 = 6.8 Hz), 0.88 (ddd, 1 H, J_1= 0.5 Hz, J_2 = 1.5 Hz, J_3=6.8 Hz), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$): 150.6, 149.4, 147.8, 141.0, 118.5, 114.0, 111.4, 111.2, 92.6, 89.1, 81.3, 70.7, 65.5, 63.1, 53.3, 52.0, 26.6, 23.5, 20.6, 19.0, 18.1, 9.7, −1.5. IR (cm^{-1}, neat): 3458, 3073, 2951. Anal. Calcd for $C_{25}H_{38}O_4Si$: C, 69.72; H, 8.89. Found: C, 69.57; H, 8.90.

Allenic Ester 28. To a solution of 170 mg (0.39 mmol) of propargylic alcohol **26** in 5 mL of CH_2Cl_2 was added 0.32 mL (1.80 mmol) of Hunig's base followed by 0.10 mL (1.4 mmol) of MsCl at −78 °C. After total consumption of the alcohol (1 h), the solution was quenched with 5 mL of saturated NH_4Cl, warmed to room temperature, and extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was azeotropically dried with benzene. The residue was used for next step without further purification.

To a solution of 41 mg (0.045 mmol) of Pd_2dba_3 in 5 mL of THF was added 94 mg (0.36 mmol) of Ph_3P under nitrogen. The purple solution quickly turned to yellow. After 10 min, a

solution of the above mesylate in 1 mL of THF, 0.97 mL (6.75 mmol) of 2-(trimethylsilyl)ethanol, and 0.21 mL (1.8 mmol) of 2,6-lutidine in 3 mL of THF was added to the yellowish solution, and the flask was rinsed with 2 mL of THF. The solution turned green. The flask was fitted with a balloon of carbon monoxide, and the reaction was monitored by TLC. After total consumption of the mesylate (about 1 h), the solvent was removed and the residue was chromatographed on Et_3N-deactivated silica gel to give 160 mg (73%) of allenic ester **28** as a colorless liquid. Extended reaction time caused isomerization of this allenic ester. ^{1}H NMR ($CDCl_3$): 5.81 (s, 1 H), 5.66 (dd, 1 H, $J_1 = 2.4$ Hz, $J_2 = 4.9$ Hz), 5.07 (br, 1 H), 5.05 (s, 1 H), 4.90 (s, 1 H), 4.86−4.84 (m, 1 H), 4.84−4.82 (m, 1 H), 4.58 (d, 1 H, $J = 6.8$ Hz), 4.51 (d, 1 H, $J = 6.8$ Hz), 4.33 (d, 1 H, $J = 4.9$ Hz), 4.22 (m, 2 H), 3.68 (ddd, 1 H, $J_1 = 6.8$ Hz, $J_2 = 10.3$ Hz, $J_3 = 13.0$ Hz), 3.41 (ddd, 1 H, $J_1 = 6.8$ Hz, $J_2 = 10.3$ Hz, $J_3 = 13.0$ Hz), 2.88−2.76 (m, 1 H), 2.33 (br, 1 H), 2.13−2.02 (m, 2 H), 1.98 (s, 3 H), 1.89 (br, 6 H), 1.47 (ddd, 1 H, $J_1 = 2.4$ Hz, $J_2 = 5.9$ Hz, $J_3 = 13.2$ Hz), 1.04−0.98 (m, 2 H), 0.92−0.85 (m, 2 H), 0.05 (s, 9 H), − 0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$): 212.6, 168.6, 151.9, 148.3, 147.3, 142.6, 118.1, 115.1, 111.8, 108.9, 101.3, 96.6, 92.5, 70.3, 65.4, 62.9, 50.4, 47.1, 25.9, 24.9, 21.4, 20.5, 18.1, 17.3, 9.6, −1.5, −1.6. IR (cm^{-1}, neat): 3075, 2951, 1953, 1714. Anal. Calcd for $C_{31}H_{50}O_5Si_2$: C, 66.62; H, 9.02. Found: C, 66.74; H, 9.12.

Butenolide 34. To a solution of 120 mg (0.22 mmol) of allenic ester **28** in 50 mL of benzene was added 14 mg (0.054 mmol) of Ph_3P, and the mixture was refluxed over 2 days. TLC showed little isomerization. The solution was concentrated to 1 mL, and another 56 mg (0.22 mmol) of Ph_3P was added. The resulting mixture was refluxed for another 24 h whereupon TLC analysis showed complete isomerization. The solvent was removed, and the residue (allenic ester **31**) was directly used for the next step. A small portion was purified for characterization. ^{1}H NMR ($CDCl_3$): 5.75 (s, 1 H), 5.60 (dd, 1 H, $J_1 = 3.9$ Hz, $J_2 = 4.9$ Hz), 5.13 (s, 1 H), 5.07 (s, 1 H), 4.88 (s, 1 H), 4.83 (s, 1 H), 4.64−4.62 (m, 3 H), 4.26 (d, 1 H, $J = 4.9$ Hz), 4.10 (ddd, 2 H, $J_1 = 2.0$ Hz, $J_2 = 7.3$ Hz, $J_3 = 9.3$ Hz), 3.71 (ddd, 1 H, $J_1 = 7.8$ Hz, $J_2 = 9.8$ Hz, $J_3 = 9.3$ Hz), 3.46 (ddd, 1 H, $J_1 = 7.8$ Hz, $J_2 = 9.8$ Hz, $J_3 = 9.3$ Hz), 2.80 (ddd, 1 H, $J_1 = 3.9$ Hz, $J_2 = J_3 = 14.2$ Hz), 2.46 (ddd, 1 H, $J_1 = 2.0$ Hz, $J_2 = J_3 = 14.2$ Hz), 2.42−2.32 (m, 1 H), 1.94 (s, 3 H), 1.89 (s, 3 H), 1.87 (s, 3 H), 1.74−1.64 (m, 2 H), 0.94−0.86 (m, 4 H), 0.00 (s, 18 H). ^{13}C NMR ($CDCl_3$): 211.8, 167.0, 147.8, 147.7, 142.3, 118.5, 113.3, 111.4. 109.3, 108.8, 103.3, 94.1, 92.7, 71.4, 65.4, 62.9, 56.4, 43.9, 33.5, 27.1, 22.5, 22.0, 18.1, 17.4, 9.8, −1.5. Anal. Calcd for $C_{31}H_{50}O_5Si_2$: C, 66.62; H, 9.02. Found: C, 66.74; H, 9.12.

To a solution of the above allenic ester **31** in 2 mL of DMF was added 0.43 mL (0.43 mmol) of tetrabutylammonium fluoride (1.0 M in THF) dropwise at −78 °C, and the mixture was brought to 0 °C after the addition. After total consumption of the ester (2 h), the solution was quenched with 5 mL of water and extracted with ether. The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was azeotropically dried with benzene. The residue was used for next step without further purification.

To a solution of allenic acid **32** in 5 mL of acetone was added 108 mg (0.65 mmol) of silver nitrate. The mixture was stirred at room temperature until the acid was totally consumed (usually more than 1 day). The mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (10% ether in hexanes) to give 62 mg (60% from allenic ester **31**) of butenolide **34** as a colorless solid and 2.0 mg (2%) of another isomer (presumably the C8 epimer). ^{1}H NMR ($CDCl_3$): 5.87 (s, 1 H), 5.28 (s, 2 H), 5.15 (s, 1 H), 4.91 (s, 1 H), 4.76 (s, 1 H), 4.59 (s, 3 H), 3.71 (ddd, 1 H, $J_1 = 7.3$ Hz, $J_2 = 9.8$ Hz, $J_3 = 8.8$ Hz), 3.69 (s, 1 H), 3.44 (ddd, 1 H, $J_1 = 7.3$ Hz, $J_2 = 8.8$ Hz, $J_3 = 9.8$ Hz), 2.47−2.33 (m, 3 H), 2.01−1.82 (m, 2 H), 1.97 (S, 3 H), 1.92 (S, 3 H), 1.84 (S, 3H), 0.88 (app.t. 2 H, $J = 8.8$ Hz), −0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$): 175.1, 151.1, 149.5, 148.5, 147.6, 141.8, 135.6, 119.1, 115.6, 112.2, 111.5, 92.5, 81.8, 70.2, 65.5, 49.6, 48.9, 30.6, 23.1, 22.7, 20.5, 18.1, 9.6, − 1.5. IR (cm^{-1}, neat): 3075, 1755.

Kallolide A Acetate (35). To a solution of 3.0 mg (0.007 mmol) of SEM ether **34** in 0.5 mL of acetic acid was added 1.7 mg (0.007 mmol) of PPTS at room temperature. The mixture was stirred for 2 days until most of the starting material was consumed. The solvent was removed, and the residue was chromatographed on silica gel (25% ether in hexanes) to give 2.0 mg (82%) of kallolide A acetate (**35**). ^{1}H NMR ($CDCl_3$): 6.64 (br, 1 H), 5.89 (s, 1 H), 5.57 (d, 1 H, $J = 11.6$ Hz), 5.40 (d, 1 H, $J = 4.9$ Hz), 5.16 (br, 1 H), 5.01 (s, 1 H), 4.87 (s, 1 H), 4.77 (s, 1 H), 3.78 (d, 1 H, $J = 4.9$ Hz), 3.09 (dd, 1 H, $J_1 = 7.3$ Hz, $J_2 = 11.6$ Hz), 2.44 (ddd, 1 H, $J_1 = 2.9$ Hz, $J_2 = 13.2$ Hz, $J_3 = 13.2$ Hz), 2.14 (d, 1 H, $J = 13.2$ Hz), 2.05 (s, 3 H), 1.97 (s, 6 H), 1.69 (s, 3 H), 1.67 (m, 1 H), 0.44 (dt, 1 H, $J = 2.9$ Hz, $J = 13.2$ Hz). ^{13}C NMR ($CDCl_3$): 175.4, 170.5, 151.7, 147.2, 146.1, 143.8, 141.7, 137.4, 121.5, 114.9, 114.7, 112.3, 80.8, 66.6, 48.7, 46.0, 33.2, 22.0, 21.6, 20.9, 18.0, 9.5. IR (thin film, cm^{-1}) 1753, 1720.

Kallolide A (36). To a solution of 2.0 mg (0.004 mmol) of butenolide **34** in 1 mL of *tert*-butyl alcohol was added 0.3 mL of 3 M HCl. The mixture was stirred at room temperature for 3 days. Saturated $NaHCO_3$ was added, and the mixture was extracted with ether. The combined ether extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (25% ethyl acetate in hexanes) to remove a small amount of the C2 epimer (ca. 10%). Removal of solvent from the main fraction afforded 1.1 mg (76%) of kallolide A (**36**) as a colorless solid. ^{1}H NMR ($CDCl_3$): 6.65 (br, 1 H), 5.90 (s, 1 H), 5.40 (d, 1 H, $J = 4.9$ Hz), 5.29 (s, 1 H), 5.01 (dt, 1 H, $J_d = 5.9$ Hz, $J_t = 1.5$ Hz), 4.81 (s, 1 H), 4.36 (d, 1 H, $J = 11.2$ Hz), 3.79 (d, 1 H, $J = 4.9$ Hz), 2.87 (dd, 1 H, $J_1 = 7.3$ Hz, $J_2 = 11.2$ Hz), 2.41 (m, 1 H), 2.11 (m, 1 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.80 (s, 3 H), 1.63 (m, 1 H), 0.43 (m, 1 H). ^{13}C NMR ($CDCl_3$): 175.5, 151.2, 149.6, 146.1, 144.0, 141.7, 137.2, 119.9, 116.6, 114.9, 112.3, 80.9, 65.2, 49.8, 48.8, 33.1, 22.0, 21.6, 17.3, 9.6. IR (thin film, cm^{-1}): 3498, 1750.

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Supporting Information Available: ^{1}H NMR spectra for **2**, **3**, **13**, **14**, **15**, **18**, **19**, **20**, **24**, **25**, **28**, **31**, **34**, **35**, **36**, **40**, **42**, **44**, **45**, **46**, eq 1. Experimental procedures and spectral data for **14**, **15**, **17**, **18**, (+)-**21**, (+)-**22**, (+)-**23**, (+)-**24**, (+)-**25**, (+)-**26**, 2,4-dinitrobenzoate of **26**, (−)-**28**, (+)-**34**, (+)-**35**, (+)-**36**, **37**, **38**, **39**, **40**, **41**, **42**, **44**, **45**, **46** Macromodel Log Files for **25**, **34/28**, **41**, **44/**epi-**44**, **35**, **2**-epi **35**, **36**, **2-**epi **36** (44 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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