Synthesis of Pseudopterane Analogues by Intramolecular S_E2' Cyclization

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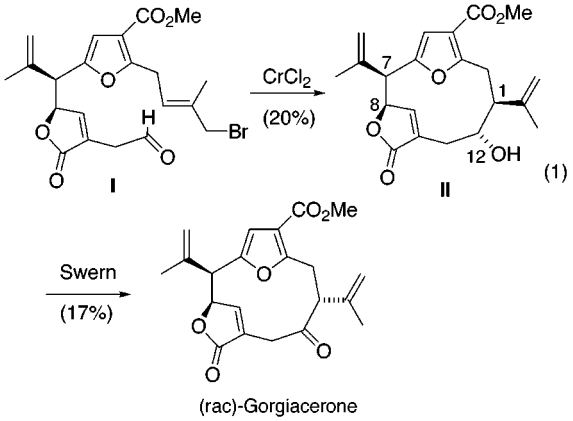
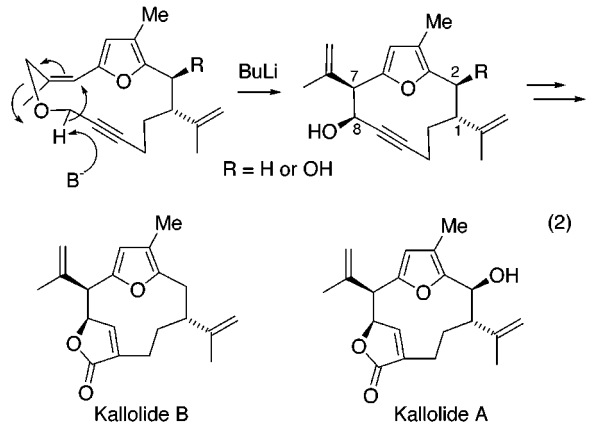
Intramolecular Barbier-type additions of allylmetal intermediates derived from the allylic halides **13** and **14** and the allylic acetate **18** to aldehydes were examined as possible routes to pseudopterolide natural products. The halides cyclized upon treatment with $SnCl_2$ or $CrCl_2$ to afford a mixture of diastereomeric products **16a**−**d**. In contrast, the acetate **18** afforded largely the 1,7-syn products **16a** and **16b** upon treatment with 5 mol % $Pd(PPh_3)_4$ and Et_2Zn. When InI was employed in place of the Et_2Zn, the syn,trans product **16a** was formed exclusively. This intermediate was converted to the *syn*,*cis*- and *syn*,*trans*-butenolides **24** and **26**. In the latter case, thermolysis of the *tert*-butyl ester at 210 °C followed by esterification with $TMSCHN_2$ gave the methyl ester **35**, an analogue of pseudopterolide.

Gorgonian corals of the *Pseudopterogoria* genus produce a number of diterpenoid secondary metabolites that incorporate a 12-membered carbocyclic ring with embedded furan and butenolide moieties.[1] First recognized as a unique structural class in 1982,[2] several members of this small subgroup of natural products have been found to possess promising medicinal properties as inflammatory and cytotoxic agents.[1−3]

To date, relatively little effort has been invested in synthetic approaches to this interesting class of cyclophane-type compounds.[4] In 1990, Paquette and coworkers reported the synthesis of a pseudopterolide analogue that they later converted to gorgiacerone.[5] The key elements of their approach were the cyclization of the allylic bromo aldehyde **I** by an allylchromium S_E2' addition (1/12 bond formation). This reaction proceeded in only 20% yield, but afforded a single diastereomer **II** that was later shown to possess the *syn*-1,7/*cis*-7,8/*anti*-8,12 relative stereochemistry (eq 1).[5] Fortuitously, Swern oxidation of this alcohol proceeded with inversion of the isopropenyl stereocenter to afford racemic gorgiacerone.[5b] The yield of this conversion was also low.



Our previous approaches to the pseudopteranes have employed [2,3]Wittig ring contractions of cyclic allylic propargylic ethers.[4c,6] The resulting *anti*-1,7/*cis*-7,8 carbocyclic intermediates were produced as single diastereomers in high yield (eq 2). The subsequent



butenolide construction also proceeded efficiently and with high stereoselectivity. This approach was first applied to kallolide B.[6] A similar sequence has recently been successfully utilized in the total synthesis of kallolide A.[7] Both syntheses were carried out with enantioenriched intermediates and thus serve to establish the previously unknown absolute configuration of these substances.

The work we now describe explores the possibility of employing an intramolecular S_E2' Barbier-type cyclization of a halo aldehyde intermediate to construct the pseudopterane ring system through 7/8 bond formation. This approach bears a relationship to our previous [2,3]-

(1) Fenical, W. *J. Nat. Prod.* **1987**, *50*, 1001.
(2) Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.
(3) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 574.
(4) (a) Marshall, J. A.; Nelson, D. *Tetrahedron Lett.* **1988**, *29*, 741. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703. (c) Marshall, J. A.; Yu, B.-C. *J. Org. Chem.* **1994**, *59*, 324.
(5) (a) Paquette, L. A.; Rayner, C. M.; Doherty, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 4078. (b) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926. (c) Paquette, L. A. *Chemtracts—Org. Chem.* **1992**, *5*, 141.
(6) (a) Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796. (b) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729.
(7) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962.

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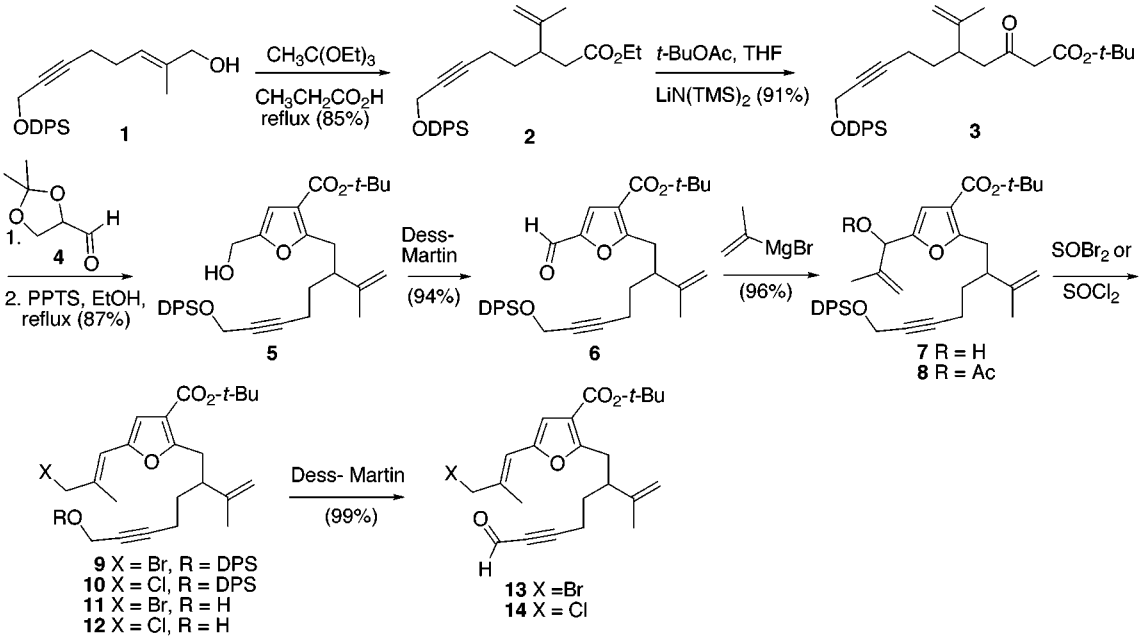
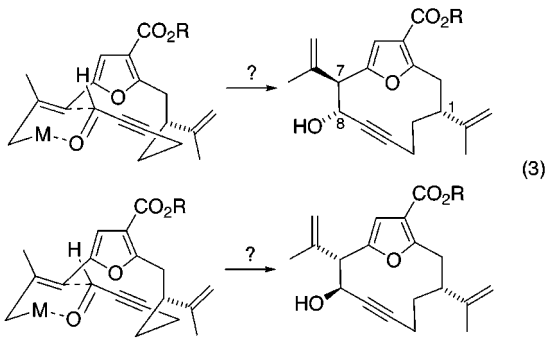
Scheme 1



Wittig strategy insofar as the site of bond formation and the reaction environments are comparable (eq 3). How-

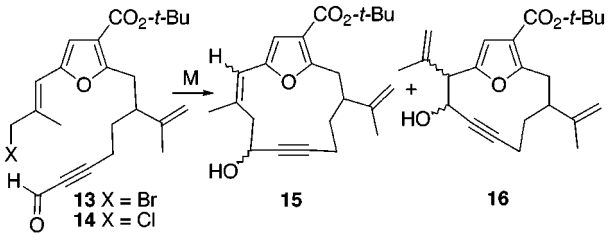


(3)

ever, the roles of electrophile and nucleophile are reversed. The present S_E2' approach is directed toward those pseudopterolide members of the family in which the furan ring bears a carboxyl rather than a methyl substituent. In such a case, the use of nucleophilic and/or strongly basic reagents required for the [2,3]Wittig rearrangement would be inadvisable owing to the carbonyl reactivity of the ester and the enhanced acidity of the furyl α-methylene protons. The fundamental issues to be examined in the Barbier cyclization are (1) the efficiency of the process with several different allylic metal intermediates and (2) the degree, if any, to which the C-1 isopropenyl substituent exerts control over (a) the relative configuration at C-7 (remote stereocontrol) and (b) the relative (cis/trans) stereochemistry at C-7/C-8, as depicted in eq 3.

The synthesis of an appropriate halo aldehyde substrate to test the synthetic plan commenced with the allylic alcohol **1**, prepared in six steps from 4-pentyn-1-ol.[7] Ortho ester Claisen rearrangement with triethyl orthoacetate afforded ester **2** in high yield (Scheme 1).[8] This ester was converted to the β-keto ester **3** by condensation with *tert*-butyl acetate. The use of methyl or ethyl acetate in this reaction proved unsatisfactory because of self-condensation. Furan formation was effected by treatment of ester **3** with glyceraldehyde acetonide (neat) and subsequent heating with PPTS in EtOH.[5] The derived alcohol **5** was oxidized to aldehyde **6** by the Dess−Martin periodinane protocol.[9] Addition of isopropenylmagnesium bromide afforded the alcohol **7**, which yielded the rearranged bromide **9** upon treatment with thionyl bromide. The chloride **10** could be likewise prepared with thionyl chloride. Cleavage of the DPS ether of **9** or **10** with TBAF and ensuing Dess−Martin periodinane oxidation[9] gave the cyclization substrates, bromo aldehyde **13**, and the chloro analogue **14**.

Table 1. Barbier Cyclizations of Bromo and Chloro Aldehydes 13 and 14



aldehyde	M	Solvent	yield, %	15:16
13	In	EtOH-H_2O	33	100:0
13	$SnCl_2$	DMPU-THF	38	0:100
14	$CrCl_2$	THF	70	0:100

Aldehydes **13** and **14** were subjected to a number of Barbier-type cyclization conditions (Table 1). The use of the labile bromo aldehyde **13** with indium powder[10] gave the 14-membered cyclic product as a mixture of diastereoisomers in 33% yield. On the basis of stability considerations derived from molecular mechanics calculations, it is assumed that the *Z* isomer predominates.[11]

(8) Henrick, C. A.; Schaub, R.; Siddall, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 5374.

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

(10) Marshall, J. A. *Chemtracts—Org. Chem.* **1997**, *10*, 481.

(11) Molecular mechanics calculations (Macromodel 5.0;[12] MM2 force field) showed relative energies of 283 and 311 kJ/mol for the *Z* and *E* syn isomers of the methyl ester analogue of **15**.

Scheme 2

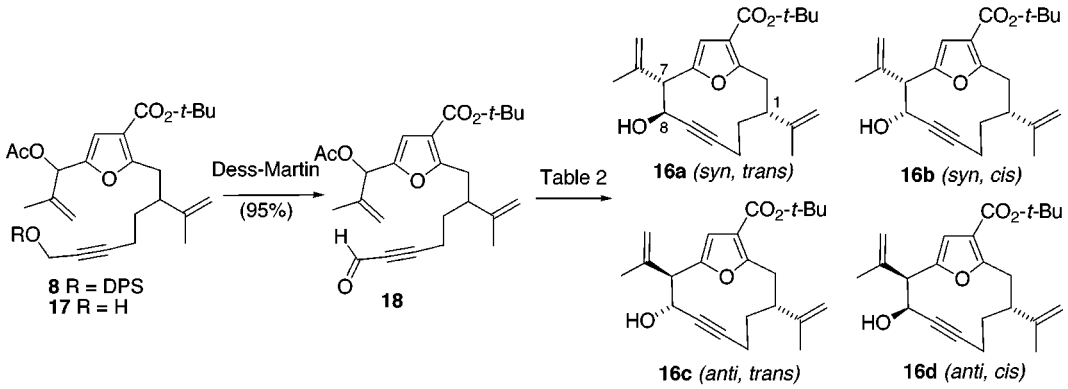


Table 2. Cyclizations of Allylzinc Intermediates Derived from Allylic Chloride 14 or Allylic Acetate 18

14 or **18** —5 mol% $Pd(PPh_3)_4$, THF, M→ **16a** + **16b** + **16c/d**
(*syn,trans* *syn,cis* *anti,trans/cis*)

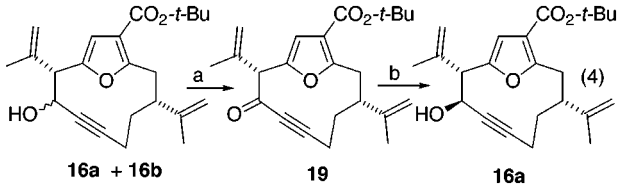
entry	aldehyde	M	yield, %	**16a**:**16b**:**16c/d**
1	**18**	Et_2Zn	46	30:65:5
2	**18**	Et_2Zn [a]	70	25:70:5[a]
3	**14**	Et_2Zn	52	80:20:0
4	**18**	InI	44	100:0:0

[a] reaction at 0 °C [c]

However, owing to the intractable nature of the mixture, this assignment could not be substantiated. When $SnCl_2$ was employed in the metalation reaction with bromide **13**, the branched products **16** were formed in 38% yield as an inseparable mixture.[13] Treatment of chloride **14** with $CrCl_2$ led to a 3:2:2 ratio (^{1}H NMR analysis) of an inseparable mixture of branched products **16** in 70% yield.

In view of the unpromising nature of these experiments and the solvolytic lability of the allylic halides **13** and **14**, we decided to pursue an alternative approach in which the aldehyde acetate **18** would serve as the precursor of the transient allylmetal species. This aldehyde was easily prepared from the allylic acetate intermediate **8** by cleavage of the DPS ether with TBAF and ensuing Dess−Martin periodinane oxidation (Scheme 2).[9]

Treatment of acetate **18** with 5 mol % $Pd(PPh_3)_4$ and excess Et_2Zn[14] afforded a transient allylic zinc species that cyclized in situ, affording a separable mixture of branched products **16a** and **16b**, in 46% yield (Table 2, entry 1). A small amount of byproduct, inseparable from **16a**, could be detected by ^{1}H NMR analysis. When the cyclization was conducted at 0 °C a crystalline product separated from the mixture (Table 2, entry 2). X-ray structure analysis showed it to be the syn,cis isomer **16b**. Both **16a** and **16b** yielded ketone **19** upon oxidation with the Dess−Martin periodinane reagent (eq 4).[9] The structure of **16a** can therefore be unambiguously assigned as syn,trans. Reduction of ketone **19** with L-Selectride led to the syn,trans isomer **16a**, exclusively.

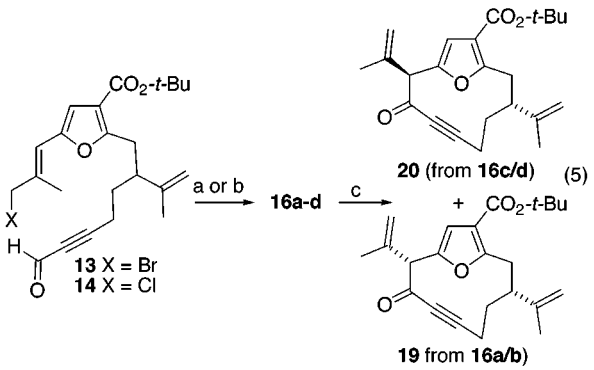


a)Dess-Martin periodinane; b) Li(*s*-Bu)$_3$H

The chloro aldehyde **14** was also examined in the Pd(0)-catalyzed allylzinc cyclization experiments (Table 2, entry 3). In this case, the intermediate allylzinc chloride cyclized to an 80:20 mixture of syn,trans and syn,cis isomers **16a** and **16b** in 52% yield. Evidently, the counterion (OAc vs Cl) exerts a significant effect on the diastereoselectivity of these cyclizations.

Acetate **18** could be converted to a transient allylic indium species via oxidative transmetalation of the putative π-allyl palladium acetate with InI (Table 2, entry 4).[15] This intermediate cyclized in situ to the *syn,trans*-alcohol **16a** as the sole product in 44% yield.

With the identity of alcohols **16a**/**16b** and the derived ketone **19** established, it was now possible to probe the stereochemistry of the products obtained in the earlier Barbier cyclizations. Accordingly, oxidation of the product mixture from bromide **13** and $SnCl_2$ afforded an inseparable 65:35 mixture of ketone **19** and a second isomer that is assumed to be the anti product **20** (eq 5). Likewise,



a) **13**, $SnCl_2$ (**16a/b**:**16c/d** = 65:35); b)**14**, $CrCl_2$ (**16a/b**:**16c/d** = 40:60)
c) Dess-Martin periodinane

(12) Global minimum multiple conformer searching was carried out with the Monte Carlo subroutine in BATCHMIN through multiple-step interations (typically 1000) until the minimum energy conformer was found multiple times. 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.

(13) Cf. Inai, T.; Nishida, S. *Synthesis* **1993**, 395.

(14) (a) Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 787. (b) Yasui, K.; Gato, Y.; Yamiji, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7619.

(15) Following these initial results, we turned our attention to analogous in situ formation of allenylindium reagents from propargylic mesylates and the intermolecular addition of these reagents to chiral and achiral aldehydes. Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696.

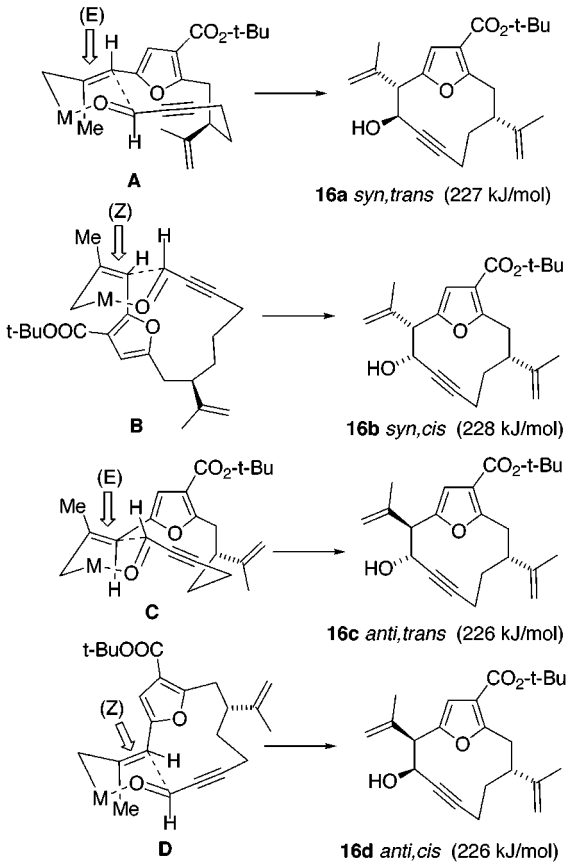


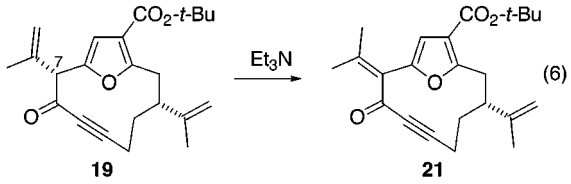
Figure 1. Chairlike transition-state arrangements leading to macrocycles and calculated relative energies of the products **16a**−**d**.

the products from allylic chloride **14** and $CrCl_2$ yielded a 40:60 mixture of **19** and **20**. Thus, the allylic $SnBrCl_2$ and $CrCl_2$ cyclizations produce significant amounts of the anti products **16c**/**16d**, whereas **16a** and **16b** are the major or exclusive adducts from the allylzinc and allylindium experiments. It was not possible to separate the two anti products **16c** and **16d** from each other or from **16a**. Hence, an unambiguous structure assignment could not be made.

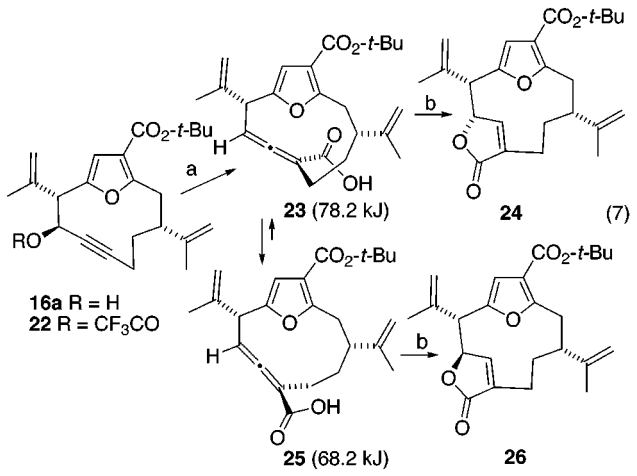
Evidently, subtle factors are responsible for the varying stereochemical outcomes of these experiments. Presumably, the cyclizations proceed through chairlike transition states (Figure 1).[16] However, the nature of the metal and the counterion significantly influence the stereochemical outcome. For M = In(OAc)I or ZnCl the syn,trans adduct **16a** is highly favored, whereas for M = ZnOAc the syn,-cis isomer **16b** predominates (Table 2, entries 4 and 3 vs 1 and 2). By comparison, the allylic zinc intermediate from *trans*-crotyl benzoate affords a 70:30 mixture of anti and syn products with benzaldehyde under comparable conditions.[14b] Intramolecular additions of such allylic zinc intermediates have not previously been examined, nor have branched acyclic allylic esters been utilized as organozinc precursors.

Interestingly, almost none of the anti products **16c** and **16d** are formed in the In- or Zn-mediated cyclizations. On the other hand, when M = $SnBrCl_2$ or $CrCl_2$, significant amounts of these products are produced. The relative energies of the four cyclic products **16a**−**16d** are nearly equal according to molecular mechanics calculations.[12] Therefore, relatively early and presumably chairlike transition states depicted as **A**−**D** in Figure 1 would be expected. By analogy to intermolecular additions of allylmetal reagents to aldehydes, we would expect the trans products to arise from the *(E)*-allylmetal intermediates and vice versa.[16,17] **A** and **C** are diastereomeric as a consequence of the remote isopropenyl substituent; **B** and **D** are similarly related. Our current understanding of the variables in the analogous intermolecular additions are inadequate to allow meaningful extrapolations to the present applications. From a synthetic point of view, the outcome of the Pd(0)/InI experiment leading to the syn,-trans product **16a** is the most interesting result. This isomer can also be secured through reduction of ketone **19**.

The C1 and C7 isopropenyl substituents of all known pseudopteranes are anti.[1−3] In an attempt to establish this stereochemistry through epimerization of the C-7 isopropenyl stereocenter,[5] we treated ketone **19** with Et_3N. However, as expected, the sole product of this reaction was the isopropylidene isomer **21** (eq 6).[18] In fact, ketone **19** isomerized to **21** upon passage through silica gel. In view of this ready isomerization no further efforts were expended on epimerization experiments.



With a view toward preparing analogues of pseudopterolides for biological evaluation, we subjected alcohol **16a** to Pd-(0)-catalyzed carbonylation−lactonization (eq 7).[6] This conversion was achieved via the trifluoroacetate **22**. The three-step process was executed without purification of the intermediate ester **22** and acid **23**.



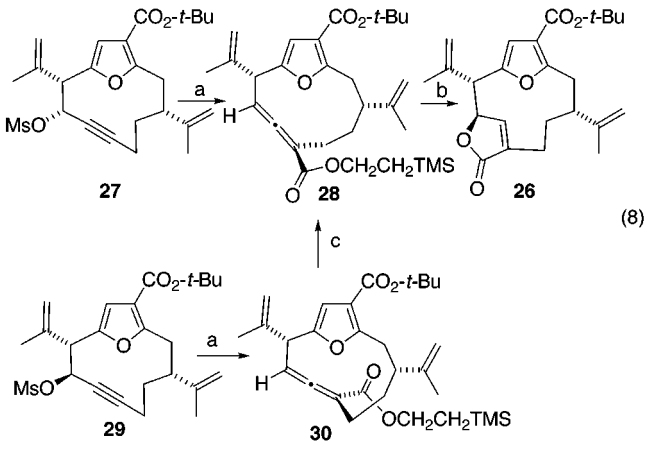
(16) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(17) Allylchromium reagents derived from allylic halides and $CrCl_2$ afford anti adducts regardless of the stereochemistry of the starting halide.[16] Thus, it can be surmised that equilibration of these reagents is relatively fast. On the other hand, crotyltin trichloride has been shown to undergo a rather slow *E*/*Z* isomerization affording a 2:1 mixture favoring the *E* isomer. Nartuta, Y.; Nishigaichi, Y.; Maruyama, K. *Tetrahedron* **1989**, *45*, 1067.

(18) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796.

Our initial run through of this sequence produced a single butenolide product in 38% yield. A second trial gave a 1:1 mixture of diastereomeric butenolides in 53% yield. A third attempt afforded a 1:2 mixture in 50% yield. Comparison of conditions for the three sequences revealed that the reaction times for the hydrocarbonylation step were 6, 3, and 1.5 h, respectively. We suspected that the intermediate allenic acid **23** was isomerizing to varying degrees under the hydrocarbonylation reaction conditions.[6b] Accordingly, the major product from reactions taking place in the shortest time would contain the largest amount of the kinetic allenic acid isomer **23**. At longer reaction times, we might expect a greater degree of isomerization and a larger predominance of the more stable isomer. Molecular mechanics calculations support this hypothesis. Allenic acid **23** was found to be 10 kJ higher in energy than its isomer **25**. Thus, it would appear that equilibration of the allenic acids had taken place in our initial hydrocarbonylation to afford the more stable isomer **25** as the sole intermediate. Subsequent cyclization of this acid gave rise to the *syn,trans*-butenolide **26**. In the third hydrocarbonylation, which ran for only 1.5 h, the syn,cis isomer **23**, representing the kinetic product, predominated.

In accord with this analysis, the *syn,cis*-mesylate **27** afforded the *syn,trans*-lactone **26** as the sole product in 78% yield by a slight variation of the foregoing experiment in which carbonylation was conducted in the presence of $TMSCH_2CH_2OH$, affording an intermediate allenic ester **28** (eq 8). This ester was treated with Ph_3P under conditions known to cause equilibration,[6b] but no isomeric ester was produced. Cleavage of the ester with TBAF and subsequent exposure of the derived acid to $AgNO_3$ afforded the aforementioned *syn,trans*-lactone **26** (eq 8).

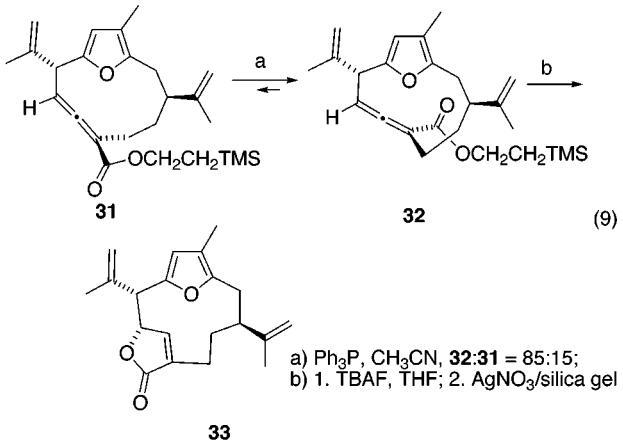


a) Pd (PPhj$_3$)$_4$, CO, THF, $TMSCH_2CH_2OH$; b) 1. TBAF, THF 2. $AgNO_3$, hexanes; c) Ph_3P, CH_3CN

(8)

When the *syn,trans*-mesylate **29** was subjected to the foregoing carbonylation sequence, a mixture of allenic esters **28** and **30**, favoring the former (70:30), was produced. Treatment of this mixture with Ph_3P, as before, afforded allenic ester **28** exclusively. Equilibration of the allenic acids **23** and **25** was not examined because of their instability.

These results stand in sharp contrast to our previous findings with the anti analogues **31** and **32** of allenic esters **28** and **30**. In that case, equilibration led to an 85:15 mixture favoring **32**, the precursor of the anti,cis butenolide diastereomer **33** (eq 9). Thus, the remote C1

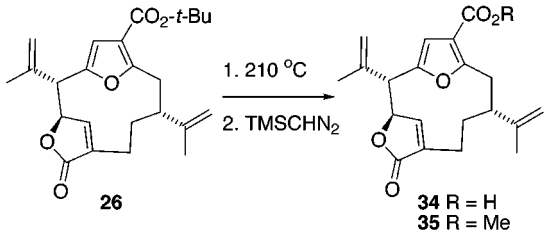


a) Ph_3P, CH_3CN, **32**:**31** = 85:15; b) 1. TBAF, THF; 2. $AgNO_3$/silica gel

(9)

isopropenyl substituent exerts a profound effect on the relative stabilities of the allenic acid and ester precursors of these bridged butenolides. The origin of this remote stereocontrol is not evident from inspection of computer-generated structures. Although our synthetic route bears no relationship to the biosynthetic process, it is an interesting coincidence that all known pseudopterane natural products possess the anti,cis stereochemistry, as in kallolide B (**33**).

A number of pseudopterane natural products incorporate a carbomethoxy substituent at C4. Accordingly, it was of interest to effect the transformation of *tert*-butyl ester **26** to the methyl analogue. Several potential problems must be addressed in consideration of this transformation. To begin with, base-catalyzed methanolysis would probably fail both for steric reasons and because of the likely instability of the butenolide toward methoxide. In addition, conventional acid-catalyzed cleavage of the *tert*-butyl ester would undoubtedly cause decomposition of the furan moiety and possibly effect double-bond isomerization of the isopropenyl groupings. For these reasons, we settled upon a thermal cleavage of the *tert*-butyl ester. While this avoided the potential problems associated with strongly basic or acidic reactions, self-destruction of the resultant acid at the elevated temperature required for the thermolysis remained a possibility. In the event, it was found that brief immersion of a thin layer of the viscous *tert*-butyl ester **26** in an oil bath preheated to 210 °C followed by treatment of the crude product of this reaction with $TMSCHN_2$ afforded the methyl ester **35** in near-quantitative yield (eq 10). Interestingly, the elimination did not proceed in refluxing decalin (bp 190 °C).



(10)

These investigations demonstrate the feasibility of employing oxidative transmetalation[15] of π-allylpalladium intermediates to effect Barbier-type cyclizations leading to products with the pseudopterane structural motif. Although such cyclizations can be highly stereoselective, in the present case 1/7 bond formation leads to the unnatural syn diastereomer.

Experimental Section

Ethyl 8-(*tert*-Butyldiphenylsilyloxy)-5-isopropenyl-6-octynoate (2). To a stirred solution of 6.60 g (16.8 mmol) of allylic alcohol **1**[7] in 21.6 mL (118 mmol) of triethyl orthoacetate was added 0.75 mL (1.01 mmol) of propionic acid. The solution was heated to reflux. After 16 h, the reaction mixture was allowed to cool to room temperature, diluted with Et_2O, and quenched with aqueous 10% HCl solution. The organic layer was washed with 10% HCl, brine, and saturated aqueous $NaHCO_3$ solution. The aqueous washes were extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to afford 6.60 g (85%) of the ethyl ester **2**: IR (neat) 1747; ^{1}H NMR ($CDCl_3$) δ 7.79−7.68 (4H, m), 7.47−7.34 (m, 6H), 4.83 (s, 1H), 4.78 (s, 1H), 4.32 (t, J = 2.2 Hz, 2H), 4.12 (qd, J = 1.5, 7.3 Hz, 2H), 2.75−2.62 (m, 1H), 2.37 (d, J = 7.4 Hz, 2H), 2.2−2.0 (m, 2H), 1.67 (s, 3H), 1.61−1.49 (m, 2H), 1.24 (td, J = 0.8, 7.1 Hz, 3H), 1.07 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 172.7, 145.6, 136.2, 133.9, 130.2, 128.1, 113.4, 85.6, 79.2, 60.7, 53.5, 43.4, 39.5, 32.3, 27.3, 19.7, 19.0, 17.2, 14.8 ppm. Anal. Calcd for $C_{29}H_{38}O_3Si$: C, 75.28; H, 8.28. Found: C, 75.01; H, 8.26.

***tert*-Butyl 10-(*tert*-Butyldiphenylsilyloxy)-5-isopropenyl-3-oxo-8-decynoate (3).** To a stirred solution of 24.6 mL (24.6 mmol) of 1.0 M $LiN(TMS)_2$ in THF in 22 mL of THF at −78 °C was added 3.18 mL (23.6 mmol) of *t*-BuOAc. The solution was allowed to stir for 1 h, and then 5.20 g (11.2 mmol) of ethyl ester **2** was added as a solution in 4.5 mL of THF. The reaction mixture was allowed to warm gradually to room temperature, quenched with 10% HCl solution, and diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl solution and brine. The aqueous portion was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to give 5.28 g (88%) of β-keto ester **3**: IR (neat) 2236, 1748, 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (4H, dd, J = 1.7, 7.5 Hz), 7.46−7.36 (6H, m), 4.8 (2H, J = 1.9 Hz), 4.3 (2H, t, J = 1.9 Hz), 3.32 (2H, s), 2.77−2.64 (1H, m), 2.58 (2H, t, J = 7.3 Hz), 2.9−2.0 (2H, m), 1.65 (3H, s), 1.65−1.49 (2H, m), 1.47 (9H, s), 1.07 (9H, s) ppm; ^{13}C NMR ($CDCl_3$) δ 202.4, 145.7, 136.2, 130.2, 128,1, 113.3, 79.3, 58.5, 53.5, 51.4, 47.6, 41.9, 32.4, 28.5, 27.3, 19.5, 17.2 ppm. Anal. Calcd for $C_{33}H_{41}O_4Si$: C, 74.39; H, 8.32. Found: C, 74.18; H, 8.30.

2-[2-Isopropenyl-7-(*tert*-butyldimethylsilyloxy)-5-heptynyl]-3-carbo-*tert*-butoxy-5-(hydroxymethyl)furan (5). To 3.00 g (5.63 mmol) of β-keto ester **3** was added 1.47 g (11.26 mmol) of glyceraldehyde acetonide (**4**). The reaction mixture was stirred at room temperature for 96 h. A solution of 2.82 g (2.82 mmol) of PPTS in 5.6 mL of EtOH was added. The reaction mixture was heated to 80 °C for 35 min, allowed to cool to room temperature, diluted with Et_2O, and quenched with $NaHCO_3$ solution. The organic extracts were washed with $NaHCO_3$ and brine. The aqueous portion was extracted with ether, and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes to afford 2.88 g (4.91 mmol, 87%) of furan **5**: IR (neat), 1707; ^{1}H NMR ($CDCl_3$) δ 7.8−7.7 (4H, m), 7.46−7.36 (m, 6H), 6.49 (s, 1H), 4.74 (s, 1H), 4.71 (s, 1H), 4.49 (d, J = 6.2 Hz, 2H), 4.32 (t, J = 1.9 Hz, 2H), 3.13−2.99 (m, 2H), 2.77−2.67 (m, 1H), 2.20−2.0 (m, 2H), 1.67 (s, 3H), 1.62−1.57 (m, 2H), 1.55 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 163.7, 160.8, 152.5, 145.9, 136.2, 133.9, 130.2, 128.2, 116.8, 113.5, 109.4, 85.9, 81.2, 79.0, 57.7, 53.5, 46.0, 32.5, 31.9, 28.8, 27.3, 19.7, 18.7, 17.2 ppm. Anal. Calcd for $C_{36}H_{44}O_5Si$: C, 73.68; H, 7.90. Found: C, 73.81; H, 8.02.

2-[2-Isopropenyl-7-(*tert*-butyldimethylsilyloxy]-5-heptynyl]-3-carbo-*tert*-butoxy-5-formylfuran (6). To a stirred solution of 2.80 g (4.77 mmol) of furanyl alcohol **5** in 78 mL of CH_2Cl_2 at room temperature was added 2.40 g (5.70 mmol) of Dess−Martin periodinane reagent.[9] The reaction was allowed to stir at room temperature for 30 min, and then 6.0 g (24 mmol) of $Na_2S_2O_3$ in $NaHCO_3$ solution was added. When the stirred solution turned clear and colorless, the organic portion was washed with $NaHCO_3$ and brine. The aqueous portion was extracted with ether, and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes to afford 2.63 g (4.50 mmol, 94%) of furanyl aldehyde **6**: IR (cm^{-1}) 1720, 1690; ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 7.70 (dd, J = 1.9, 6.7 Hz, 4H), 7.45−7.26 (m, 6H), 4.71 (s, 1H), 4.66 (s, 1H), 4.29 (t, J = 1.9 Hz, 2H), 3.2 (dd, J = 4.8, 8.9 Hz, 1H), 3.08 (dd, J = 7.9, 1.4 Hz, 1H), 2.80−2.72 (m, 1H), 1.65 (s, 3H), 1.62−1.53 (m, 2H), 1.55 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 177.7, 166.3, 162.2, 150.9, 145.1, 136.1, 130.2, 128.1, 118.9, 114.1, 85.5, 82.3, 79.2, 58.5, 46.0, 32.7, 32.0, 28.7, 27.3, 19.7, 18.5, 17.2 ppm.

2-[2-Isopropenyl-7-(*tert*-butyldimethylsilyloxy)-5-heptynyl]-3-carbo-*tert*-butoxy-5-(1-hydroxy-2-methyl-2-propenyl)furan (7). To a stirred suspension of 0.52 g (21.5 mol) of Mg in 5.4 mL of THF at room temperature was added 0.76 mL (8.62 mmol) of 2-bromopropene. The resulting Grignard reagent was added by cannula to a stirred solution of 2.52 g (4.31 mmol) of furanyl aldehyde **6**. The reaction was quenched with saturated aqueous NH_4Cl and brine. The aqueous washes were extracted with Et_2O, and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 20% EtOAc−hexanes as eluent to provide 2.60 g (96%) of allylic alcohol **7**: IR 3471, 2861, 2235, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73−7.69 (m, 4H), 7.45−7.26 (m, 6H), 6.45 (s, 1H), 5.14 (s, 1H), 5.03 (d, J = 5.0 Hz, 1H), 4.99 (s, 1H), 4.69 (s, 1H), 4.64 (s, 1H), 4.29 (s, 3H), 3.13−2.94 (m, 2H), 2.70−2.60 (m, 1H), 2.16−1.94 (m, 2H), 1.69 (s, 3H), 1.67 (s, 3H), 1.59−1.57 (m, 2H), 1.53 (s, 9H), 1.05 (s, 9H) ppm; ^{13}C NMR 163.7, 160.5, 153.2, 145.7, 144.4, 136.1, 133.9, 130.2, 128.1, 116.6, 113.5, 112.8, 108.58, 108.55, 85.9, 81.1, 79.0, 71.7, 53.5, 46.2, 46.2, 32.4, 32.3, 32.0, 31.9, 28.8, 27.3, 19.7, 19.1, 18.5, 17.2 ppm. Anal. Calcd for $C_{39}H_{60}O_5Si$: C, 74.72; H,8.04. Found: C, 74.48; H, 8.08.

2-[2-Isopropenyl-7-(*tert*-butyldimethylsilyloxy)-5-heptynyl]-3-carbo-*tert*-butoxy-5-(1-acetoxy-2-methyl-2-propenyl)furan (8). To a stirred solution of 1.5 g (2.4 mmol) of allylic alcohol **7** in 9.6 mL of pyridine at room temperature was added 29 mg (0.24 mmol) of DMAP followed by 0.45 mL (4.8 mmol) of acetic anhydride. After 1 h, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with ether. The organic phase was washed with brine. The aqueous portion was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes to afford 1.5 g (2.3 mmol, 94%) of allylic acetate **8**: ^{1}H NMR δ 7.72−7.66 (s, 4H), 7.45−7.33 (m, 6H), 6.51 (s, 1H), 6.10 (s, 1H), 5.08 (s, 1H), 5.00 (s, 1H), 4.68 (s, 1H), 4.61 (s, 1H), 4.29 (s, 2H), 3.16−2.90 (m, 2H), 2.68−2.57 (m, 1H), 2.20−1.94 (m, 2H), 2.09 (s, 3H), 1.71 (s, 3H), 1.62 (s, 3H), 1.60−1.55 (m, 2H), 1.52 (s, 9H), 1.05 (s, 9H) ppm.

***syn,trans*-Propargylic Alcohol 16a. A. $SnCl_2$ Cyclization of Allylic Bromide 13.** To a stirred solution of 25 mg (0.056 mmol) of bromo aldehyde **13** in 1.0 mL of THF and 0.3 mL of DMPU was added 13 mg (0.067 mmol) of $SnCl_2$. After 18 h, an additional 18 mg (0.01 mmol) of $SnCl_2$ was added, and then after 6 h, another 18 mg (0.01 mmol) portion of $SnCl_2$ was added. The reaction mixture was stirred for 12 h, quenched with 10% HCl, and diluted with ether. The organic extracts were washed with 10% HCl and brine. The aqueous portion was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography to provide 8.0 mg (38%) of alcohol **16a** as the major component of a mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 6.51 (s, 1H), 5.2 (s, 1H), 5.1 (s, 1H), 4.9 (s, 1H), 4.75 (s, 1H), 4.59−4.52 (m, 1H), 3.56 (d, J = 9.9 Hz, 2H), 3.45 (d, J = 12.7, 1H), 3.39 (d, J = 13.0 Hz, 1H), 2.19−1.98 (m, 2H), 1.91 (s, 3H), 1.77 (s, 3H), 1.54 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 158.9, 151.2, 148.0, 140.9, 117.5, 112.9, 110.8, 107.1, 88.5, 80.6, 78.5, 65.3, 54.3, 44.7, 32.2,

31.0, 28.3, 23.0, 19.3, 19.1. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.60. Found: C, 74.24; H, 8.58.

B. Cyclization of the Allylic Zinc Species from Allylic Acetate 18. To a stirred solution of 50 mg (0.12 mmol) of allylic acetate **18** in 1.2 mL of THF under Ar was added 13 mg (12 μmol) of $Pd(PPh_3)_4$ followed by 0.24 mL (0.24 mmol) of 1.0 M Et_2Zn in hexanes. After 2 h, the reaction mixture was quenched with water and diluted with ether. The organic extracts were washed with brine, and the aqueous portion was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to provide 6 mg (15%) of *syn,trans*-alcohol **16a** and 13 mg (31%) of the *syn,cis*-alcohol **16b**.

C. Cyclization of the Allylic Zinc Species from Allylic Chloride 14. To a stirred solution of 0.53 g (1.3 mmol) of chloro aldehyde **14** in 130 mL of THF at room temperature under Ar was added 76 mg (0.13 mmol) of $Pd(PPh_3)_4$ followed by 3.14 mL (3.14 mmol) of 1.0 M Et_2Zn in hexanes. After 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with ether. The organic extracts were washed with $NaHCO_3$ and brine. The aqueous portion was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to provide 200 mg (41%) of *syn,-trans*-alcohol **16a** and 54 mg (11%) of the *syn,cis*-alcohol **16b**.

D. InI Cyclization of Allylic Acetate 18. To a stirred solution of 80 mg (0.18 mmol) of allylic acetate **18** in 9.0 mL of THF and 3.0 mL of HMPA under Ar was added 19 mg (0.018 mmol) of $Pd(PPh_3)_4$ followed by 83 mg (0.28 mmol) of InI. After 40 min, the reaction mixture was quenched with water and diluted with ether. The organic extracts were washed with brine, and the aqueous portion was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to provide 30 mg (44%) of *syn,trans*-alcohol **16a** as the only product.

E. From L-Selectride Reduction of Ketone 19. To a stirred solution of 20 mg (54 μmol) of ketone **19** in 0.54 mL of THF at −78 °C was added 65 μL (65 μmol) of L-Selectride. After 1 h, the TLC showed consumption of ketone. The reaction was quenched with water and diluted with ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to provide 21 mg (100%) of alcohol **16a**.

***syn,cis*-Propargylic Alcohol 16b.** To a stirred solution of 47 mg (0.11 mmol) of allylic acetate **18** in 0.55 mL of THF at 0 °C was added 6.3 mg (5.5 μmol) of $Pd(PPh_3)_4$ followed by 0.11 mL (0.11 mmol) of 1.0 M Et_2Zn in hexanes. After 3 h, an additional 0.055 mL (0.055 mmol) of 1.0 M Et_2Zn in hexanes was added. The reaction mixture was quenched after an additional 3 h with saturated aqueous $NaHCO_3$ solution and diluted with ether. The organic phase was washed with $NaHCO_3$ and brine. The aqueous portion was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to provide 23 mg (56%) of alcohol **16b** and 8 mg (14%) of **16a** containing a small amount of impurity consistent with **16c/d** based on analysis of extraneous peaks in the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 6.51 (s, 1H), 5.28 (s, 1H), 5.12 (s, 1H), 4.85 (s, 1H), 4.75 (s, 1H), 4.65 (d, J = 10.0 Hz, 1H), 3.8−3.76 (m, 2H), 3.46 (d, J = 13.4, 1H), 2.81−2.64 (m, 2H), 2.23−2.10 (m, 1H), 2.06−1.95 (m, 1H), 1.91 (s, 3H), 1.78 (s, 3H), 1.54 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 173.7, 168.7, 160.5, 158.2, 149.8, 128.0, 125.1, 120.9, 118.9, 99.0, 90.8, 89.8, 73.7, 63.6, 55.2, 42.5, 40.9, 32.8, 29.5, 29.3 ppm. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 81.6. Found: C, 74.31; H, 8.17.

2-(2-Isopropenyl-7-hydroxy-5-heptynyl)-3-carbo-*tert*-butoxy-5-(1-acetoxy-2-methyl-2-propenyl)furan (17). To a stirred solution of 0.48 g (0.72 mmol) of allylic acetate **8** in 7.2 mL of THF at 0 °C was added a premixed solution of 1.4 mL (1.4 mmol) of 1.0 M TBAF in THF and 82 μL (1.4 mmol) of acetic acid. After being stirred for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The organic layer was washed with water and brine. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography with 20% EtOAc−hexanes as eluent to afford 290 mg (94%) of propargylic alcohol **17**: IR 3495, 1763, 1723 cm^{-1}; ^{1}H NMR δ 6.50 (s, 1H), 6.12 (s, 1H), 5.10 (s, 1H), 5.03 (s, 1H), 4.69 (s, 1H), 4.65 (s, 1H), 4.23 (s, 2H), 3.17−2.93 (m, 2H), 2.77−2.69 (m, 1H), 2.22−2.00 (m, 2H), 2.11 (s, 3H), 1.74 (s, 3H), 1.64 (s, 3H), 1.63−1.54 (m, 2H), 1.55 (s, 9H) ppm. Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.90; H, 8.10.

2-(2-Isopropenyl-7-formyl-5-heptynyl)-3-carbo-*tert*-butoxy-5-(1-acetoxy-2-methyl-2-propenyl)furan (18). To a stirred solution of 0.29 g (0.67 mmol) of propargylic alcohol **17** in 11 mL of CH_2Cl_2 was added 0.57 g (1.4 mmol) of Dess−Martin periodinane reagent.[9] After 30 min at room temperature, the reaction was quenched with 1.2 g (4.6 mmol) of $Na_2S_2O_3$ in 5 mL of saturated $NaHCO_3$ solution and diluted with Et_2O. The mixture was allowed to stir until clear, and then the organic phase was washed with $NaHCO_3$ and brine. The aqueous washes were extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to give 270 mg (94%) of acetylenic aldehyde **18**: ^{1}H NMR δ 9.16 (s, 1H), 6.51 (s, 1H), 6.11 (s, 1H), 5.10 (s, 1H), 5.03 (s, 1H), 4.74 (s, 1H), 4.68 (s, 1H), 3.18−2.95 (m, 2H), 2.73−2.65 (m, 1H), 2.44−2.24 (m, 2H), 2.10 (s, 3H), 1.73 (s, 3H), 1.65 (s, 3H), 1.64−1.55 (m, 2H), 1.54 (s, 9H) ppm. Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.26; H, 7.57.

Ketone 19. A. From the *syn,trans*-Alcohol 16a. To a stirred solution of 23 mg (62 μmol) of alcohol **16a** in 1.0 mL of CH_2Cl_2 was added 53 mg (120 μmol) of Dess−Martin periodinane reagent.[9] After 3 h, the reaction was quenched with 110 mg (0.43 mmol) of $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ and diluted with ether. The organic phase was washed with $NaHCO_3$ and brine. The aqueous portion was extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to provide 23 mg (100%) of *syn*-ketone **19**: ^{1}H NMR ($CDCl_3$) δ 6.0 (s, 1H), 5.20 (s, 1H), 5.00 (s, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 4.29 (s, 1H), 3.53 (d, J = 3.4 Hz, 1H), 3.48 (d, J = 3.5 Hz, 1H), 2.77−2.69 (m, 2H), 2.33−2.23 (m, 2H), 2.08 (s, 1H), 1.92 (s, 3H), 1.79 (s, 3H), 1.56 (s, 9H) ppm.

B. From the *syn,cis*-Alcohol 16b. The above procedure was followed with 23 mg (62 μmol) of alcohol **16b** in 1.0 mL of CH_2Cl_2 to which was added 53 mg (120 μmol) of Dess−Martin periodinane reagent.[9] The syn ketone **19** was obtained in 81% yield.

***syn,trans*-Butenolide 26. A. From the *syn,cis*-Alcohol 16a.** To a stirred solution of 60 mg (0.16 mmol) of *syn,trans*-propargylic alcohol **16a** in 1.6 mL of THF under CO were added 18 mg (0.016 mmol) of $Pd(PPh_3)_4$ and 39 μL (0.34 mmol) of 2,6-lutidine. The reaction mixture was cooled to 0 °C, and 27 μL (0.19 mmol) of trifluoroacetic anhydride was added. The reaction mixture was allowed to stirred for 1 h, and then 0.11 mL (6.4 mmol) of water was added. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The solvent was removed under reduced pressure. Hexane (3.2 mL) was added followed by 54 mg (0.32 mmol) of $AgNO_3$. The reaction vessel was covered with aluminum foil, and the reaction mixture was stirred overnight and then filtered and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to afford 23 mg (38%) of *syn,trans*-butenolide **26**: ^{1}H NMR ($CDCl_3$) δ 6.80 (s, 1H), 6.21 (s, 1H), 5.29 (s, 1H), 5.20 (s, 1H), 5.03 (s, 1H), 4.96 (s, 1H), 4.79 (s, 1H), 4.00 (s, 1H), 3.32−3.20 (m, 1H), 2.75−2.60 (m, 2H), 2.50−2.38 (m, 1H), 2.25−2.15 (m, 1H), 1.97 (s, 3H), 1.79 (s, 3H), 1.82−1.70 (m, 1H), 1.56 (s, 9H) 1.05−0.90 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 174.7, 163.2, 160.4, 150.9, 147.4, 146.9, 141.1, 137.4, 116.9, 115.2, 111.3, 109.1, 82.6, 80.8, 48.6, 41.9, 34.9, 31.7, 29.7, 28.3, 22.9, 19.2 ppm. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 71.63; H, 7.78.

B. From the Allenic Ester 28. To a stirred solution of 70 mg (0.14 mmol) of allenic ester **28** in 7 mL of anhydrous DMF at room temperature under nitrogen was added 0.28 mL (0.28

mmol) of 1.0 M TBAF in THF over a 1-min period. The reaction mixture was stirred for 2 h and then quenched with 5 mL of water and 15 mL of ether. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulted allenic acid was dissolved in 2.8 mL of acetone, and 47 mg (0.28 mmol) of $AgNO_3$ was added. The reaction vessel was covered with aluminum foil, and the mixture was stirred overnight and then filtered and concentrated. The crude product was purified by flash column chromatography with 10% EtOAc−hexanes as eluent to afford 44 mg of *syn,trans*-butenolide **26**.

***syn,cis*-Mesylate 27.** To a solution of 60 mg (0.16 mmol) of *syn,cis*-propargylic alcohol **16b** in 1.6 mL of CH_2Cl_2 under Ar at −78 °C was added 0.09 mL (0.64 mmol) of Et_3N followed by 0.025 mL (0.32 mmol) of MsCl. After 2 h, saturated aqueous $NaHCO_3$ and ether were added, the mixture was 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. The solvent was removed under reduced pressure to afford 71 mg (100%) of mesylate **27** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.52 (s, 1H), 5.40 (m, 1H), 5.28 (s, 1H), 5.12 (s, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 3.90 (m, 1H), 3.46 (m, 1H), 3.02 (s, 3H), 2.78−2.65 (m, 2H), 2.23−2.10 (m, 2H), 2.06−1.95 (m, 2H), 1.95 (s, 3H), 1.78 (s, 3H), 1.54 (s, 9H), 1.30−1.00 (m, 2H) ppm.

***syn,trans*-Allenic Ester 28.** To a solution of 71 mg (0.16 mmol) of *syn,cis*-mesylate **27** in 1.6 mL of THF under CO at room temperature was added 33 mg (0.016 mmol) of $Pd(PPh_3)_4$, 0.34 mL (2.4 mmol) of 2-(trimethylsilyl)ethanol, and 0.075 mL (0.64 mmol) of 2,6-lutidine. After 2 h, the reaction mixture was diluted with ether and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography with 2.5% EtOAc−hexanes as eluent to afford 75 mg (93%) of allenic ester **28** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.31 (s, 1H), 5.73 (m, 1H), 5.06 (s, 1H), 5.03 (s, 1H), 4.82 (s, 1H), 4.76 (s, 1H), 4.27 (m, 1H), 4.16 (t, 2H), 3.17−3.10 (m, 1H), 2.84−2.73 (m, 1H), 2.52−2.40 (m, 1H), 2.39−2.18 (m, 2H), 1.95−1.80 (m, 2H), 1.86 (s, 3H), 1.76 (s, 3H), 1.58 (s, 9H), 0.95 (t, 2H), 0.00 (s, 9H) ppm.

***syn,trans*-Mesylate 29.** To a solution of 50 mg (0.13 mmol) of *syn,trans*-propargylic alcohol **16a** in 1.3 mL of CH_2Cl_2 under Ar at −78 °C was added 0.073 mL (0.52 mmol) of Et_3N followed by 0.020 mL (0.26 mmol) of MsCl. After 3 h, saturated aqueous $NaHCO_3$ and ether were added, the mixture was 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. The solvent was removed under reduced pressure to afford 57 mg (92%) of mesylate **29** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.40 (s, 1H), 5.32 (m, 1H), 5.20 (s, 1H), 5.15 (s, 1H), 4.90 (s, 1H), 4.75 (s, 1H), 3.80−3.75 (m, 1H), 3.55−3.42 (m, 1H), 3.08 (s, 3H), 2.82−2.75 (m, 2H), 2.30−2.00 (m, 2H), 1.91 (s, 3H), 1.78 (s, 3H), 1.80−1.60 (m, 2H), 1.54 (s, 9H), 1.32−1.05 (m, 2H) ppm.

Butenolide Methyl Ester 35. A thin film of 19 mg (0.047 mmol) of *syn,trans*-butenolide *tert*-butyl ester **26** was immersed in a 210 °C oil bath for 15 min. The solid film was transformed into yellow droplets within 1 min. After 15 min, the flask was cooled to room temperature, and 0.8 mL of MeOH was added. To the solution was added 0.1 mL (0. 2 mmol) of 2.0 M $TMSCHCN_2$ in hexanes dropwise. The reaction mixture was allowed to stir for 30 min, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with 10% EtOAc−hexanes as eluent to afford 16 mg (94%) of butenolide methyl ester **35**: ^{1}H NMR ($CDCl_3$) δ 6.76 (s, 1H), 6.26 (d, J = 1.2 Hz, 1H), 5.26 (s, 1H), 5.17 (s, 1H), 4.99 (s, 1H), 4.94 (s, 1H), 4.76 (dd, J = 1.2, 1.5 Hz, 1H), 3.99 (s, 1H), 3.77 (s, 3H), 3.24 (m, 1H), 2.73−2.60 (m, 2H), 2.41 (m, 1H), 2.10 (m, 1H), 1.95 (s, 3H), 1.77 (s, 3H), 1.76 (m, 1H), 0.91 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 174.7, 164.2, 161.5, 151.4, 147.3, 146.7, 141.0, 137.5, 115.3, 115.2, 111.4, 108.8, 82.5, 51.4, 48.6, 41.9, 35.0, 31.7, 22.9, 22.8, 19.3 ppm.

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Supporting Information Available: Experimental procedures for **9**−**14** and **24**, an ORTEP diagram for **16b**, and ^{1}H NMR spectra for all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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