Total Synthesis of the Enantiomer of the Furanocembrane Rubifolide

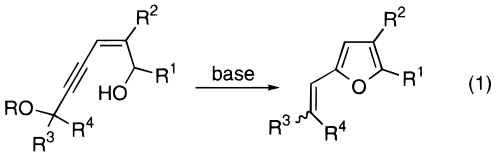
James A. Marshall* and Clark A. Sehon

Department of Chemistry , University of Virginia, Charlottesville, Virginia 22901

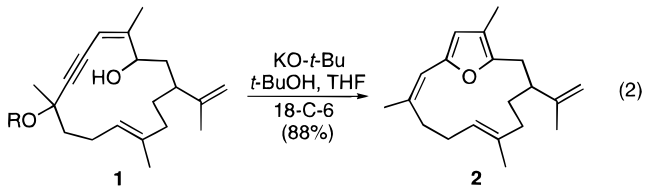
Received February 25, 1997[⊗]

The total synthesis of **57**, the enantiomer of the marine furanocembrane rubifolide (**3**), is described starting from (*S*)-(−)-perillyl alcohol (**5**). The successful route proceeded by oxidative cleavage of **5** to ester aldehyde **30** which was protected, reduced, and homologated to the acetylene **34**, the left-hand segment of the synthetic target. Addition to the right-hand aldehyde **39** afforded alcohol **40**. The carbonate derivative **41** was converted to the allenylstannane aldehyde **44**, which cyclized upon treatment with BF_3·OEt_2. Oxidation with the Dess−Martin periodinane reagent followed by treatment with Et_3N yielded allenone **45**. Allenone **45** cyclized to furan **46** in the presence of catalytic $AgNO_3$ on silica gel. Brief exposure to *p*-TsOH effected elimination of the OMOM ether, affording the diastereomeric (*Z*)-vinylfuran carbonates **47** and **49**. Saponification of the former led to alcohol **48**, which was converted to the final product by sequential treatment with $(CF_3CO)_2O$, then $Pd(PPh_3)_4$ and CO in THF−H_2O, and then $AgNO_3$ on silica gel. The resulting product, **57**, was identical to natural rubifolide on the basis of spectral comparison. The optical rotation was equal and opposite in sign to that of the natural material. A second, but unsuccessful approach is also described.

We recently described a method for the synthesis of 2-vinylfurans through base treatment of 2-hexen-4-yn-1-ols possessing a leaving group (OR) at the 6-position (eq 1).[1] This reaction was of interest as a possible key

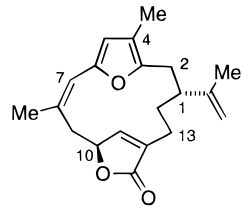


step in the synthesis of certain furanocembrane natural products.[2] Specifically, we thought that if R^1 and R^4 were connected by an appropriate carbon chain, then the resulting intraannular furan cyclization would afford a bridged vinylfuran with a (*Z*)-double bond, as is found in several furanocembrane natural products or potential synthetic precursors. In fact, model studies along those lines were highly promising. Enynol **1**, as a mixture of four racemic diastereomers, afforded the bridged (*Z*)-vinylfuran **2** in high yield upon exposure to KO-*t*-Bu (eq 2).[3]

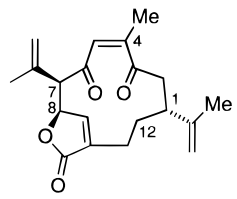


1 **2**

The bridged furan **2** is a skeletal analogue of the furanocembrane rubifolide (**3**), a secondary metabolite of the soft coral, *Gersemia rubiformis*, a subtidal species that inhabits the cold temperate waters off the coast of British Columbia. The structure of this natural product was deduced by Andersen and co-workers, largely through ^1H and ^{13}C NMR analysis.[4] The relative stereochemistry was assigned by virtue of the fact that gersemolide (**4**), a pseudopterane-related metabolite of known relative stereochemistry, was isolated from the same species of soft coral. The relative configuration of gersemolide, in turn, was established by VanDuyne and Clardy through X-ray diffraction.[4] The absolute configuration was assigned arbitrarily.



Rubifolide (**3**)



Gersemolide (**4**)

In addition to demonstrating the applicability of the methodology to furanocembranolide construction, we expected our synthesis to unambiguously establish the relative and absolute configuration of rubifolide and taxonomically related natural products. Remarkably, the absolute configuration of no member of this family is known.

Our starting material, and the basis for our eventual assignment of absolute configuration, was (*S*)-(−)-perillyl alcohol (**5**). As the story unfolds, it will be noted that this choice leads to a structure enantiomeric to that arbitrarily assigned to rubifolide. However, because the choice of (*R*) or (*S*) was arbitrary, we selected the latter for economic reasons.[5] Hydroxyl-directed epoxidation of **5** followed by periodate cleavage and treatment with *p*-TsOH in methanol afforded the ester acetal **6** in 52% overall yield, without purification of intermediates. Ester

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

(1) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 574.

(2) For a review, see: Paquette, L. A. *Chemtracts: Org. Chem.* **1992**, *5*, 141. The only other synthesis of a furanocembrane completed to date is that of racemic acerosolide. Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165.

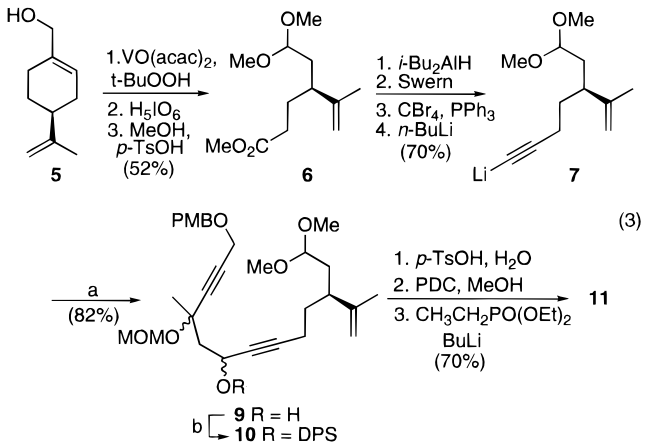
(3) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703.

(4) Williams, D.; Andersen, R. J.; VanDuyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332.

(5) Current prices for (*R*)- and (*S*)-perillyl alcohol from the 1995−96 Aldrich Chemical Catalog are $27.60/g and $1.36/g.

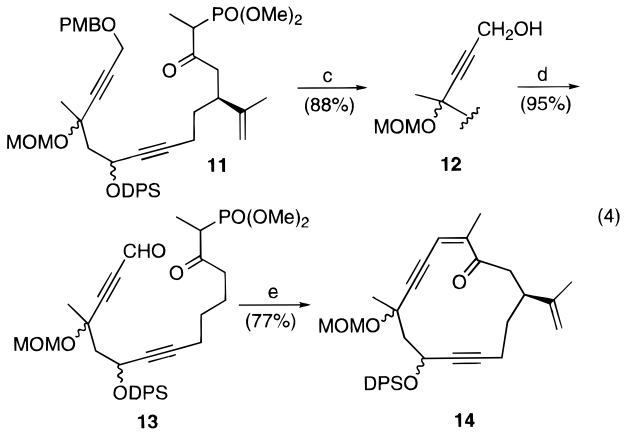
S0022-3263(97)00360-5 CCC: $14.00

6 was reduced to the aldehyde and subjected to Corey–Fuchs homologation[6] to give the acetylene in 70% yield, again without purification of intermediates. The lithio acetylide **7** gave the alcohol adduct **9**, as an equal mixture of four diastereomers, upon treatment with aldehyde **8**.[7] The DPS-protected alcohol **10** was converted to the aldehyde by acidic hydrolysis of the acetal and then oxidized to the methyl ester with PDC in methanol. This ester, without purification, was homologated to keto phosphonate **11** (eq 3).



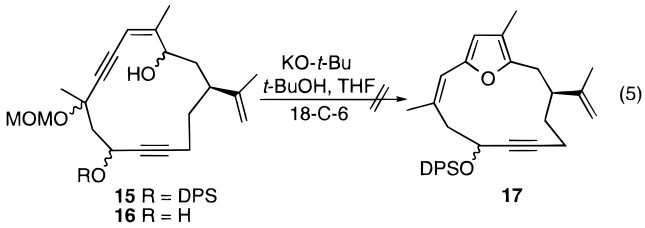
a) $PMBOCH_2C{\equiv}CC(Me)(OMOM)CH_2CHO$ (**8**) b) DPSCl, Im, DMF

Formation of the macrocyclic ring was achieved through removal of the PMB protecting group, oxidation of the derived alcohol **12**, and intramolecular Horner–Emmons cyclization[8] of the acetylenic aldehyde **13** (eq 4).

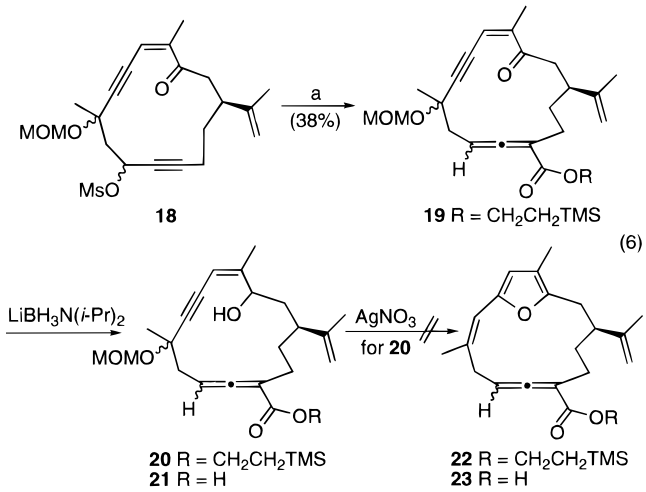


c) DDQ, H_2O d) Swern e) DBU, LiCl

Reduction of enone **14** with *i*-Bu_2AlH led to the alcohol **15** (as a mixture of eight diastereomers), a close homologue of alcohol **1**.[3] However it soon became apparent that the similarity between **1** and **15** was superficial, as treatment of the latter with KO-*t*-Bu led not to the expected furanocycle **17** but to the DPS-cleaved product **16**. We also attempted conversion of **15** to **17** with $AgNO_3$ on silica gel[9] without success. The alcohol **16** was likewise resistant to furan formation with base or $AgNO_3$, conditions that successfully converted **1** and various acyclic analogues to the corresponding furans (eq 5).[9]



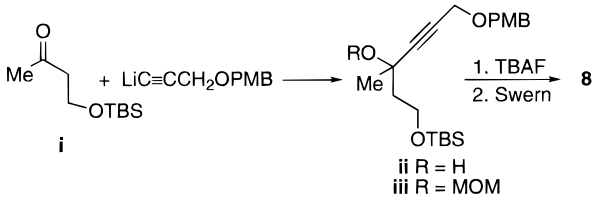
One obvious difference between alcohols **1** and **15** is the presence of an (*E*)-double bond in the former which is replaced by a triple bond in the latter. We surmized that this difference must, for steric reasons, be the cause of our failure to close the furan ring in **15**. Therefore we decided to convert alcohol **15** to the less constrained allenoate **20**, a precursor of the butenolide moiety of our targeted furanocembrane. This was achieved through Pd-catalyzed carbonylation of the mesylate **18** in the presence of β-TMS ethanol,[10] followed by selective reduction[11] of the enone ester **19**. Attempts to effect closure of the hydroxy ester **20** with $AgNO_3$ were, however, not successful. Prolonged exposure led only to recovered starting material. At elevated temperatures, decomposition of starting material occurred (eq 6).



a) $Pd(PPh_3)_4$, CO, $TMSCH_2CH_2OH$, THF

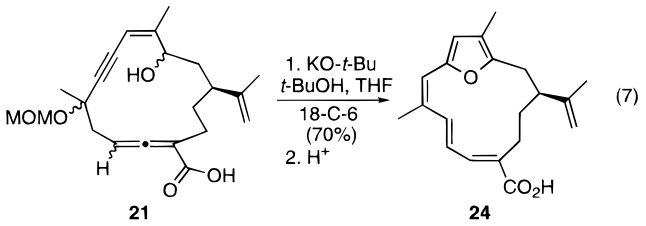
We did not examine the KO-*t*-Bu conditions with ester **20** because we felt that the strong base would cause isomerization of the allenoate to a conjugated dienoate. However, we thought that the acid **21**, as its potassium salt, might be less prone to isomerize. In fact, base treatment of acid **21** afforded a single bridged furan acid but, unfortunately, it was the conjugated trienoate **24** (probable structure). As no intermediates could be

(6) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(7) This aldehyde was prepared as follows:

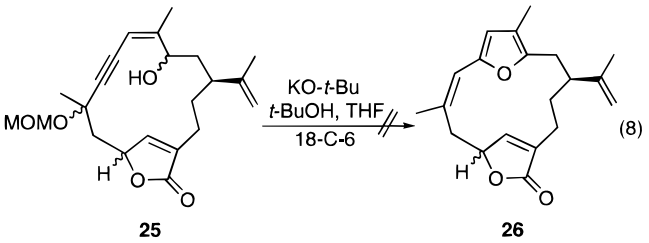


For details see the Supporting Information.
(8) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P. Masamune, S.; Roush, W. R. *Tetrahedron Lett.* **1984**, 2183.
(9) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.
(10) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.
(11) Singaram, B.; Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T. *J. Org. Chem.* **1994**, *59*, 6378.

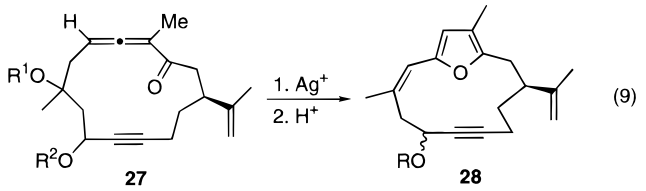
isolated, we could not ascertain if isomerization occured before or after furan closure (eq 7).



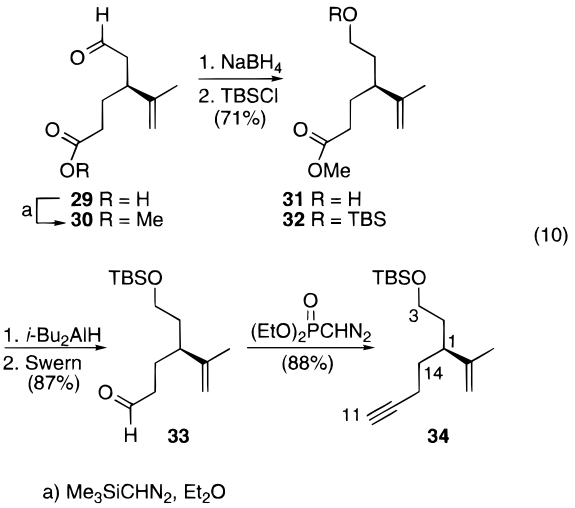
In a final attempt to effect the elusive furan ring closure, we converted acid **21** to the butenolide **25** with $AgNO_3$.[9] Butenolide **25** would appear to be a close analogue to the model enynol **1**. However, treatment of **25** with KO-*t*-Bu led to no identifiable products. Here base-promoted decomposition of the butenolide moiety is likely responsible for the lack of success (eq 8).



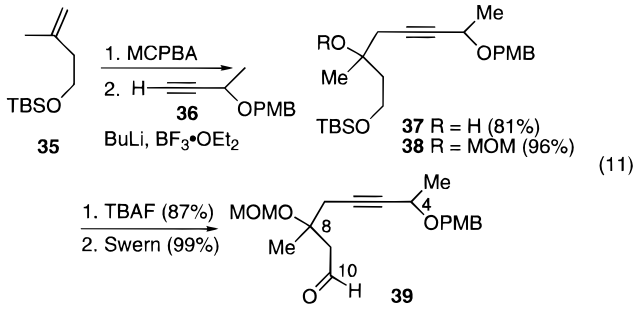
It was now clear that our enynol−furan cyclization methodology was not sufficiently energetic to overcome the steric factors associated with the formation of strained furanocycles such as **17**, **22**, and **26**.[12] In considering other options we turned to a furan synthesis based on Ag^+-catalyzed cyclization of allenones.[14] Our previous experience with this reaction had demonstrated its applicability to the efficient synthesis of 12- and 14-membered furanocycles under exceedingly mild conditions. For the case at hand, an intermediate such as **27** would be required (eq 9).



The approach was especially appealing because we could employ essentially the same starting materials and many of the same bond constructions that were used in the unsuccessful endeavor just described. Thus the intermediate aldehyde acid **29**, prepared as before from (*S*)-(−)-perillyl alcohol (**5**), was esterified with Me_3SiCHN_2 affording the methyl ester **30**. Without purification, this intermediate was reduced to alcohol **31** and protected as the TBS ether **32**. Reduction with *i*-Bu_2AlH and ensuing Swern oxidation afforded aldehyde **33**, which was converted to alkyne **34** with diazo(diethylphosphono)methane.[15] Alkyne **34** incorporates C11−14/1−3 of rubifolide, and the C1 isopropenyl substituent (eq 10).



Assemblage of the second substructure, **39**, started from the TBS-protected isopentenyl alcohol **35** (eq 11). Epoxidation and then addition of the lithio acetylide **36** and protection of the alcohol product **37** with MOMCl yielded the MOM ether **38**. Removal of the TBS group and oxidation afforded aldehyde **39**, incorporating the remaining ring carbons, C4−10, of rubifolide with the attached CH_3s at C4 and C8 (eq 11).



Addition of the lithio acetylide derived from **34** (BuLi) to aldehyde **39** led to alcohol **40** as an equal mixture of eight diastereomers in 86% yield. The methyl carbonate **41** was prepared (BuLi, $ClCO_2Me$) in 98% yield. Removal of the PMB protecting group (91% yield) followed by mesylate formation and addition of the cuprate from Bu_3SnLi and $CuBr\cdot SMe_2$ afforded the allenylstannane **42** in 84% overall yield.[14] Deprotection (TBAF) gave alcohol **43** (eq 12).

Alcohol **43** was oxidized, as the magnesium alkoxide, with ADD affording aldehyde **44** in 85% yield.[16] Treatment of allenylstannane aldehyde **44** with $BF_3\cdot OEt_2$ and subsequent Dess−Martin oxidation of the homopropar-

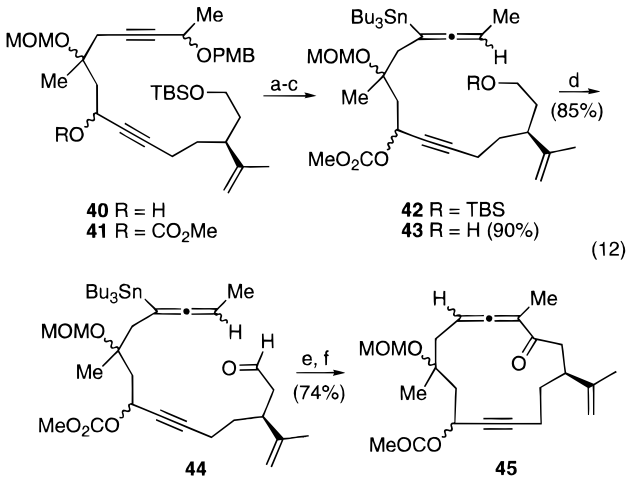
(12) Molecular mechanics calculations on the γ-alkynyl allylic alcohols **1** and **16** revealed no significant differences in geometry with regard to the allylic alcohol and its appended enyne substituent.[13] Thus the failure of the latter to cyclize is most likely the result of energy differences in the transition states. Calculations of these differences are, at present, beyond our capabilities. The calculated ground state conformation of the allenic acid **21** differed markedly from that of **1** and **16**. Significantly, the allylic OH of the latter two was favorably disposed to interact with the alkynyl moiety, whereas in **21** that OH was oriented away from the alkyne.

(13) The program Macromodel 4.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multiple step interactions (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.; 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.

(14) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 3387.

(15) Gilbert, S. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

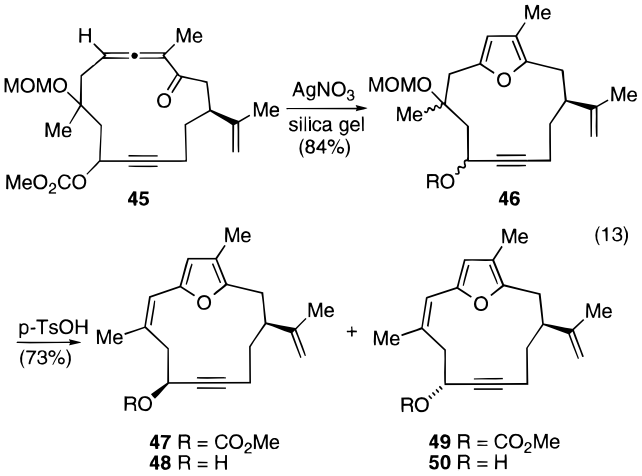
(16) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Soc. Chem. Jpn.* **1977**, *50*, 2773.



a. DDQ, MeCN, H_2O (91%); b. MsCl, Et_3N; c. "Bu_3SnCu" (84%); d. EtMgBr, ADD (85%); e. BF_3•OEt_2; f. Dess-Martin; Et_3N (74%)

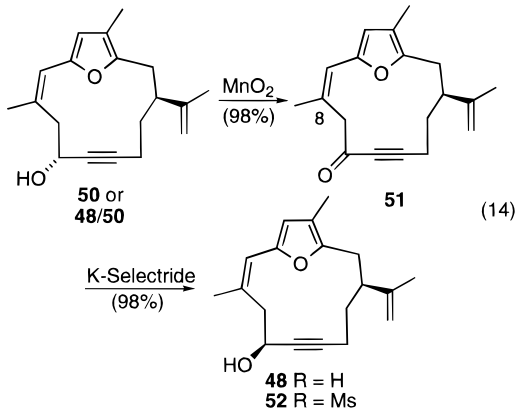
gylic alcohol and *in situ* isomerization of the resulting ketone[14] led to allenone **45** as a mixture of eight diastereomers in 74% yield.

Intraanular furan formation was effected in 84% yield by exposure of allenone **45** to 10% $AgNO_3$ on silica gel in hexane.[9] This conversion could not be realized with $AgNO_3$ in acetone under our previously reported conditions.[14] Mainly starting material was recovered from such attempts. The 2,5-furanocycle, **46**, underwent highly selective elimination to a 1:1 mixture of diastereomeric (*Z*)-vinylfurans **47** and **49** upon exposure to *p*-TsOH in CH_2Cl_2 at moderately high dilution to minimize polymerization. The high stereoselectivity of this reaction reflects the ~3 kcal/mol energy difference between the (*Z*)- and (*E*)-isomers, predicted by molecular mechanics calculation.[13] Attempts to effect this elimination on the propargylic alcohol (**46**, R = H) with KO-*t*-Bu led to recovered starting material or, under more forcing conditions, to decomposition.[17]

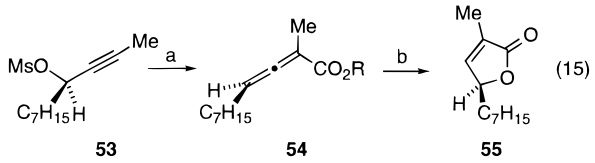


We had originally planned to convert the propargylic carbonates **47**/**49** to the related allenoic esters by the Tsuji Pd-catalyzed carbonylation methodology[18] and, after equilibration and ester cleavage, to close the butenolide ring.[19,20] However, treatment of the carbonates under Tsuji's conditions or with $Pd(PPh_3)_4$ and CO in THF−MeOH did not afford any of the desired ester, even at elevated temperatures. We therefore decided to pursue an alternative strategy. For this, we required the *syn*-alcohol **48**. Accordingly, carbonates **47**/**49** were saponified (K_2CO_3 in MeOH, 96% yield) to a separable 1:1 mixture of epimeric alcohols **48**/**50**. Oxidation of the mixture, or **50** alone, with MnO_2 gave the ketone **51**. The calculated lowest energy conformers of this ketone all show significant shielding of the "top face" of the carbonyl by the vinylic CH_3 substituent at C8 (Figure 1).[13]

We therefore surmized that hydride reduction would proceed with high diastereoselectivity. In accord with this prediction, reduction of **51** with K-Selectride gave rise to a single diastereomer, **48**, in high yield (eq 14). The configuration of the carbinyl stereocenter was verified through ^1H NMR analysis of the (*R*) and (*S*)-*O*-methylmandelate derivatives.[21] Additional support was secured through single-crystal X-ray structure analysis.[22]



We have previously shown that propargylic alcohols, such as **48**, can be converted to butenolides with inversion of configuration through Pd(0)-catalyzed hydrocarbonylation of the mesylate derivative (**53** → **54**) and $AgNO_3$-catalyzed cyclization of the intermediate allenic acid (**54** → **55**), as illustrated in eq 15.[10] When this sequence was



a. $Pd(PPh_3)_4$, CO, ROH; b. $AgNO_3$ (R = H)

applied to the mesylate derivative **52** of alcohol **48**, the expected product **57** (rubifolide) was formed in low yield. The problem seemed to reside with the lability of the mesylate under the conditions of its formation and during isolation. The corresponding trifluoroacetate **56**, though easily hydrolyzed, did not undergo destructive side reactions. Furthermore the carbonylation reaction proceeded smoothly to the allenic acid. The entire sequence from

(17) *Cf.* Marshall, J. A.; Bennett, C. E. *J. Org. Chem.* **1994**, *59*, 6110.
(18) Mandai, T.; Tsuji, J.; Tsujiguchi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 5865.
(19) Marshall, J. A.; Bartley, G. S.; Wallace E. M. *J. Org. Chem.* **1996**, *61*, 5729.
(20) Molecular mechanics calculations (Macromodel) indicated that the requisite allenoate diastereomer would be favored by several kcal/mol.[13]
(21) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.
(22) This analysis was performed by Dr. Michael Sabat of this department.

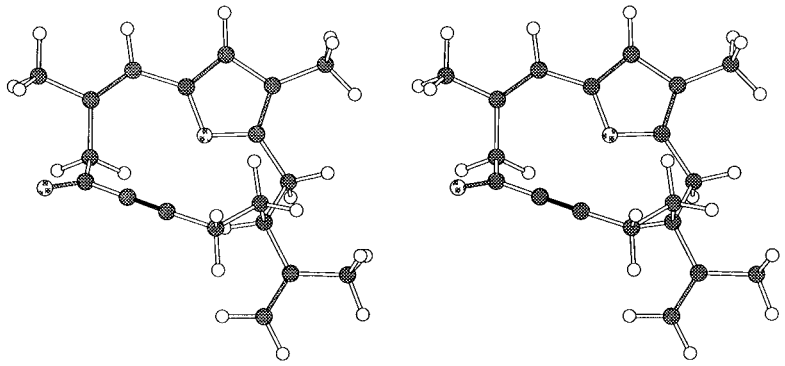
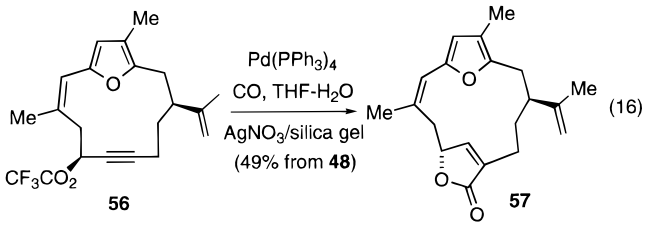


Figure 1. Stereoview Chem 3D structure of the lowest energy conformation of ynone **51**, as calculated by Macromodel v4.5 (MM2 force field), illustrating the facial bias at the carbonyl group.

alcohol to butenolide was best performed without isolation of any intermediate (eq 16).



(16)

The ^{1}H and ^{13}C NMR spectra of butenolide **57** were superimposable with those of rubifolide.[4,23] The optical rotation, however, was equal in magnitude but opposite in sign to that reported for the natural product. Thus, we have confirmed the relative and absolute configuration of natural rubifolide as initially, but arbitrarily, assigned.[4] The foregoing synthesis also highlights the utility of the $AgNO_3$/silica gel method for furan synthesis from allenones. Finally, the carbonylation of propargylic trifluoroacetates in aqueous THF and subsequent $AgNO_3$/silica gel cyclization to prepare chiral butenolides shows promise as a general method.

Experimental Section

(*S*)-1,2-Epoxyperillyl Alcohol. To a stirred solution of 20.0 g (0.12 mol) of (*S*)-(−)-perillyl alcohol and 0.60 g (2 mol %) of $VO(acac)_2$ in 320 mL of CH_2Cl_2 at 0 °C was slowly added 33.0 mL (0.18 mol) of ~5.5 M anhydrous *t*-BuOOH in decane. The mixture was allowed to reach rt and stir for 30 min; then 4.40 mL (60.0 mmol) of dimethyl sulfide was added and stirring was continued for 45 min. The solution was diluted with saturated $NaHCO_3$ and stirred for 1 h. The layers were separated, and the solution was extracted with CH_2Cl_2 . The organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (20−30% EtOAc−hexane) gave 20.1 g (99%) of the epoxy alcohol as a clear light yellow oil: IR (film) ν 3417, 3077, 2930, 1646 cm^{-1}; ^{1}H NMR δ 4.71 (d, 2H, J = 15.0 Hz), 3.55−3.65 (m, 2H), 3.29−3.36 (m, 1H), 2.03−2.16 (m, 4H), 1.80−1.86 (m, 1H), 1.70 (s, 3H), 1.59−1.68 (m, 1H), 1.18−1.47 (m, 2H); ^{13}C NMR δ major diastereomer 148.5, 109.0, 64.4, 60.0, 56.7, 55.7, 36.6, 30.1, 25.7, 23.6; minor diastereomer, partial 148.6, 109.1, 64.5, 60.4, 40.7, 24.5, 20.7, 20.1. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.58.

Methyl (*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-isopropenylhexanoate (32). To a stirred solution of 10.0 g (59.4 mmol) of (*S*)-1,2-epoxyperillyl alcohol in 300 mL of 19:1 THF−H_2O at 0 °C was slowly added 31.0 g (137.0 mmol) of periodic acid. The mixture was allowed to reach rt and stirred for 30 min. The solution was then diluted with water and Et_2O, and the aqueous phase was extracted with Et_2O. The organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a clear yellow oil. The oil was diluted with 150 mL of 4:1 benzene−MeOH, and 29.7 mL (59.4 mmol) of 2.0 M $TMSCHN_2$ in hexane was slowly added at 0 °C. The solution was stirred at rt for 30 min, and the solvent was removed under reduced pressure to give a clear bright yellow oil. The oil was diluted with 60 mL of MeOH and cooled to 0 °C, and 1.12 g (29.7 mmol) of $NaBH_4$ was added to the stirred solution. The solution was allowed to reach rt and stir for 30 min. The solution was then diluted with 10% HCl and Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure.

The residue was diluted with 20.0 mL of DMF, and 6.00 g (89.0 mmol) of imidazole was added followed by 8.95 g (59.5 mmol) of TBSCl. The solution was stirred for 30 min and then diluted with water and Et_2O. The layers were separated, and the aqueous phase was extracted with Et_2O. The organic extracts were washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (0−5% EtOAc−hexane) gave 13.2 g (74%) of the ester **32** as a clear light yellow oil: IR (film) ν 3077, 1742, 1438 cm^{-1}; ^{1}H NMR δ 4.78 (m, 1H), 4.69 (m, 1H), 3.65 (s, 3H), 3.54 (m, 2H), 2.23 (m, 3H), 1.84−1.45 (m, 8H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR δ 174.2, 145.9, 112.6, 61.2, 51.4, 43.2, 36.2, 32.1, 28.2, 25.9, 18.3, 17.8, −5.3. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.22; H, 10.81.

(*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-isopropenylhexan-1-ol (32.1). To a stirred solution of 12.1 g (40.3 mmol) of ester **32** in 115 mL of THF at −78 °C was added 93.0 mL (93.0 mmol) of 1.0 M DIBAH in hexane. The solution was stirred for 45 min. To this solution was slowly added 300 mL of Et_2O followed by 500 mL of saturated sodium potassium tartrate at −78 °C. The reaction solution was slowly warmed to rt and vigorously stirred overnight. The layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 10.8 g (98%) of alcohol **32.1** as a clear oil that was carried on without further purification: IR (film) ν 3348, 3076, 2857, 1642 cm^{-1}; ^{1}H NMR δ 4.75 (m, 1H), 4.69 (m, 1H), 3.62 (t, 2H, J = 6.4 Hz), 3.53 (m, 2H), 2.19 (m, 1H), 1.6 (m, 3H), 1.59−1.33 (m, 6H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 147.3, 112.4, 63.6, 61.9, 43.9, 36.9, 31.2, 29.9, 26.5, 18.8, 18.4, −4.8. Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.00; H, 11.88.

(*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-isopropenylhexanal (33). To a stirred solution of 1.09 mL (12.5 mmol) of oxalyl chloride in 75 mL of CH_2Cl_2 was slowly added 1.19 mL (16.7 mmol) of DMSO. The solution was stirred for 25 min, 2.28 g (8.36 mmol) of the foregoing alcohol was added in 5 mL of CH_2Cl_2, and stirring was continued for 25 min, after which 4.66 mL (33.4 mmol) of triethylamine was added and stirring was continued for 5 min. The mixture was allowed to reach rt and stirred for 1 h. The mixture was diluted with Et_2O and

(23) Copies of the spectra were kindly provided by Professor R. J. Andersen (University of British Columbia).

10% HCl. The organic phase was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (20% EtOAc−hexane) afforded 2.07 g (91%) of aldehyde **33** as a clear yellow oil: IR (film) υ 3075, 2857, 1728 cm^{-1}; ^1H NMR δ 9.76 (m, 1H), 4.80 (m, 1H), 4.70 (m, 1H), 3.68−3.46 (m, 2H), 2.37 (t, 2H, J = 7.3 Hz), 2.21 (m, 1H), 1.60 (s, 3H), 1.94−1.38 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 202.4, 145.8, 112.9, 61.1, 43.1, 41.9, 36.3, 25.9, 25.3, 18.2, 17.8, −5.4. Anal. Calcd for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18. Found: C, 66.44; H, 11.10.

(*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-isopropenylhex-1-yne (34). To a stirred solution of 32.1 mL (32.1 mmol) of 1.0 M KO-*t*-Bu in 670 mL of THF at −78 °C was added 5.77 g (29.6 mmol) of $N_2CHPO(OEt)_2$ in 15 mL of THF, and stirring was continued for 15 min. To this solution was slowly added 5.31 g (14.6 mmol) of aldehyde **33** in 10 mL of THF. After 30 min the solution was allowed to reach rt and stir for 1 h. The solution was diluted with Et_2O and brine, the organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by flash chromatography (1−2.5% EtOAc−hexane) afforded 4.72 g (90%) of alkyne **34** as a clear colorless oil: IR (film) υ 3314, 3077, 2860, 2119, 1645 cm^{-1}; ^1H NMR δ 4.78 (m, 1H), 4.73 (m, 1H) 3.55 (m, 1H), 3.50 (dt (apparent q), 1H J = 2.6 Hz), 2.32 (m, 1H), 2.20−1.98 (m, 2H), 1.92 (t, 1H, J = 2.6 Hz), 1.60 (m, 3H), 1.60−1.53 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 145.8, 112.6, 84.6, 68.1, 61.2, 42.7, 36.1, 32.1, 25.9, 18.3, 17.8, 16.4, −5.3. Anal. Calcd for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 72.22; H, 11.42.

3-[(4-Methoxybenzyl)oxy]-1-butyne (36). To a stirred suspension of 4.67 g (0.19 mol) of 95% NaH in 350 mL of THF at 0 °C was added 11.2 mL (0.14 mol) of (±)-3-butyn-2-ol. After 30 min, 26.0 mL (0.21 mol) of 4-methoxybenzyl chloride was added followed by a catalytic amount of Bu_4NI. The mixture was allowed to reach rt and stir for 2 d. The mixture was then diluted with H_2O and Et_2O, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Bulb-to-bulb distillation (aspirator pressure) gave 27.0 g (99%) of the alkyne **36** as a clear colorless oil: IR (film) υ 3286, 2106 cm^{-1}; ^1H NMR δ 7.30 (d, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.6 Hz), 4.58 (AB_q, 2H, J_{AB} = 11.4 Hz, $\Delta\upsilon$ = 8.5 Hz), 4.18 (d_q, 1H, J = 2.0 Hz, J = 6.6 Hz), 3.80 (s, 3H), 2.46 (d, 1H, J = 2.0 Hz), 1.96 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ 159.2, 129.8, 129.6, 113.7, 83.7, 72.0, 70.0, 63.7, 55.1, 21.9. Anal. Calcd for $C_{12}H_{12}O_2$: C, 75.76; H 7.42. Found: C, 75.76; H, 7.48.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1,2-epoxybutane (35.1). To a stirred solution of 11.7 mL (0.12 mol) of 3-methyl-3-buten-1-ol in 25 mL of DMF at rt was added 11.9 g (0.17 mol) of imidazole followed by 17.5 g (0.12 mol) of TBSCl. The solution was stirred for 30 min and then diluted with H_2O and Et_2O. The organic extracts were washed with H_2O and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The crude silyl ether **35** was diluted with 580 mL of CH_2Cl_2. To this solution was added 31.0 g (0.21 mol) of $NaHPO_4$ followed by 35.9 g (0.21 mol) of *m*-CPBA, and the mixture was stirred for 1 h. The crude reaction mixture was filtered and diluted with 10% NaOH and CH_2Cl_2. The organic layer was washed with 10% NaOH and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Bulb-to-bulb distillation (~1.0 mm at 50−60 °C) gave 19.9 g (79%) of the epoxide as a clear colorless oil: IR (film) υ 2928, 2855, 1472 cm^{-1}; ^1H NMR δ 3.72 (m, 12H), 2.63 (AB_q, 2H, J_{AB} = 4.8 Hz, $\Delta\upsilon$ = 32 Hz), 1.86 (ddd, 1H, J = 12.9 Hz, J = 5.9 Hz, J = 5.9 Hz), 1.69 (ddd, 1H, J = 13.9 Hz, J = 7.0 Hz, J = 7.0 Hz), 1.34 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 59.6, 55.4, 54.0, 39.7, 25.8, 21.4, 18.1, −5.4. Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.06; H, 11.18. Found: C, 61.35; H, 11.04.

1-[(*tert*-Butyldimethylsilyl)oxy]-7-[(4-methoxybenzyl)oxy]-3-methyl-5-octyn-3-ol (37). To a stirred solution of 15.8 g (83.0 mmol) of alkyne **36** in 185 mL of THF at −78 °C was added 34.0 mL (85.0 mmol) of 2.5 M BuLi in hexane, and the solution was stirred for 1 h. To this solution was added 10.2 mL (83.0 mmol) of $BF_3{\cdot}OEt_2$, and stirring was continued for 20 min, after which 10.0 g (42.0 mmol) of epoxide **35.1** was added. After 2 h, the solution was diluted with saturated $NaHCO_3$ and Et_2O and allowed to reach rt. The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (10% EtOAc−hexane) afforded 15.2 g (81%) of alcohol **37** as a clear colorless oil: IR (film) υ 3478, 2233, 1614 cm^{-1}; ^1H NMR δ 7.08 (AB_q, 4H, J = 8.8 Hz, $\Delta\upsilon$ = 120 Hz), 4.54 (AB_q, 2H, J = 11.0 Hz, $\Delta\upsilon$ = 81.0 Hz), 4.18 (q, 1H, J = 6.6 Hz), 1.34 (d, 3H, J = 1.5 Hz), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 159.6, 130.5, 129.9, 114.1, 82.8, 82.7, 73.0, 70.3, 64.6, 61.1, 55.5, 40.8, 32.9, 77.1, 26.2, 22.8, 18.4, −5.2. Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 67.74; H, 9.48.

1-[(*tert*-Butyldimethylsilyl)oxy]-7-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-3-methyl-5-octyn-1-ol (38). To a stirred solution of 14.9 g (37.0 mmol) of alcohol **37** in 75 mL of $CHCl_2$ at 0 °C was added 31.9 mL (0.18 mol) of diisopropylethylamine followed by 11.1 mL (0.15 mol) of MOMCl. The solution was allowed to reach rt and stir overnight. The solution was diluted with 10% HCl and CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 15.7 g (95%) of the MOM ether **38** as a clear yellow oil. The crude material was carried on without further purification: IR (film) υ 2237, 1613 cm^{-1}; ^1H NMR δ 7.18 (AB_q, 4H, J = 8.8 Hz, $\Delta\upsilon$ = 120 Hz), 4.76 (AB_q, 2H, J = 7.7 Hz, $\Delta\upsilon$ = 10.6 Hz), 4.5 (AB_q, 2H, J = 11 Hz, $\Delta\upsilon$ = 81 Hz), 4.19 (qt, 1H, J = 6.6 Hz, J = 1.8 Hz), 3.80 (s, 3H), 3.77 (t, 2H, J = 7.0 Hz), 3.39 (s, 3H), 2.54 (d, 2H, J = 1.8 Hz), 1.94 (m, 2H), 1.42 (d, 3H, J = 6.6 Hz), 1.37 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 159.1, 130.2, 129.6, 113.7, 91.1, 82.2, 76.8, 69.9, 64.2, 59.0, 55.4, 55.2, 41.6, 30.7, 25.9, 23.9, 22.3, 18.2, −5.3.

7-[(4-Methoxybenzyl)oxy]-3-(methoxymethoxy)-3-methyl-5-octyn-1-ol (38.1). To 17.7 g (35.0 mmol) of the neat silyl ether **38** was added 52.2 mL (52.0 mmol) of 1.0 M TBAF in THF at rt. The solution was stirred for 1 h and then diluted with H_2O and Et_2O, and the aqueous layer was extracted with Et_2O. The organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (20−40% EtOAc−hexane) provided 10.2 g (87%) of the alcohol as a clear yellow oil: IR (film) υ 3446, 2233, 1613 cm^{-1}; ^1H NMR δ 7.08 (ABq, 4H, J = 8.8 Hz, $\Delta\upsilon$ = 120 Hz), 4.77 (AB_q, 2H, J = 7.7 Hz, $\Delta\upsilon$ = 10.6 Hz), 4.54 (AB_q, 2H, J = 11 Hz, $\Delta\upsilon$ = 81 Hz), 4.18 (qt, 1H, J = 6.6 Hz, J = 1.8 Hz), 3.84 (t, 2H, J = 5.9 Hz), 3.80 (s, 3H), 3.39 (s, 3H), 2.60 (d, 2H, 1.5 Hz), 1.96 (m, 2H), 1.41 (s, 3H), 1.41 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ 159.6, 130.5, 130.0, 114.2, 91.5, 83.0, 78.7, 70.4, 64.6, 59.4, 56.0, 55.6, 41.6, 30.8, 23.9, 22.8. Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.59; H, 8.27.

7-[(4-Methoxybenzyl)oxy]-3-(methoxymethoxy)-3-methyl-5-octynal (39). To a stirred solution of 1.71 mL (20.0 mmol) of oxalyl chloride in 130 mL of CH_2Cl_2 at −78 °C was added 1.89 mL (26.0 mmol) of DMSO, and the solution was stirred for 20 min. To this solution was added 4.45 g (13.0 mmol) of the foregoing alcohol in 5 mL of CH_2Cl_2, and stirring was continued for 25 min. To this solution was added 7.41 mL (53.0 mmol) of Et_3N, and the solution was stirred for an additional 5 min at −78 °C and then allowed to reach rt and stir for 2 h. The mixture was diluted with 10% HCl and Et_2O. The aqueous layer was extracted with Et_2O. The organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford 4.40 g (99%) of the aldehyde **39** as a clear yellow oil. The crude material was carried on without further purification.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-isopropenyl-14-[(4-methoxybenzyl)oxy]-10-(methoxymethoxy)-10-methyl-6,12-pentadecadiyn-8-ol (40). To a stirred solution of 3.15 g (12.0 mmol) of alkyne **11** in 100 mL of THF at −78 °C was added 5.00 mL (13.0 mmol) of 2.5 M BuLi in hexane, and the solution was stirred for 1 h. To this solution was slowly added 4.40 g (13.0 mmol) of aldehyde **39** in 15 mL of THF. The solution was stirred for 10 min at −78 °C and allowed to reach rt. The solution was diluted with saturated NH_4Cl and Et_2O. The aqueous layer was extracted with Et_2O, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel

(15−25% EtOAc−hexane) afforded 6.17 g (87%) of the propargyl alcohol **40** as a clear orange oil: IR (film) υ 3441, 3071, 2234, 1614 cm^{-1}; ^{1}H NMR δ 7.07 (AB_q, 4H, J = 8.8 Hz, $\Delta\upsilon$ = 120 Hz), 4.85−4.64 (m, 5H), 4.42 (B of AB_q, 0.5H, J = 11 Hz) 4.40 (B of AB_q, 0.5H, J = 11.4 Hz), 4.18 (m, 1H), 3.80 (s, 3H), 3.51 (m, 2H), 3.39 (apparent d, 3H, J = 2.2 Hz), 3.25 (m, 1H), 2.74−2.53 (m, 2H), 2.34−1.93 (m, 5H), 1.66−1.32 (m, 14H), 0.88 (s, 9H), 0.02 (s, 6H). Anal. Calcd for $C_{35}H_{56}O_6Si$: C, 69.96; H, 9.39. Found: C, 69.84; H, 9.32.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-isopropenyl-14-[(4-methoxybenzyl)oxy]-8-(methoxycarbonyl)-10-(methoxymethoxy)-10-methyl-6,12-pentadecadiyne (41). To a stirred solution of 6.0 g (10.0 mmol) of alcohol **40** in 10 mL of THF at −78 °C was added 4.8 mL (12.0 mmol) of 2.5 M BuLi in hexane. After 1 h, 1.16 mL (15.0 mmol) of methyl chloroformate was added dropwise and the solution was allowed to reach rt and stir overnight. The solution was diluted with saturated $NaHCO_3$ and Et_2O. The aqueous phase was extracted with Et_2O, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (10−40% EtOAc−hexane) afforded 6.46 g (98%) of the carbonate **41** as a clear yellow oil: IR (film) υ 3072, 2234, 1753, 1612 cm^{-1}; ^{1}H NMR δ 7.29 (d, 2H, J = 8.4 Hz), 6.87, (d, 2H, J = 8.4 Hz), 5.48, (m, 1H), 4.82−4.65 (m, 5H), 4.42 (B of ABq, 1H, J = 11.0 Hz), 4.18 (q, 1H, J = 6.6 Hz), 3.83−3.77 (m, 3H), 3.80 (s, 3H), 3.52 (m, 2H), 3.38 (s, 3H), 2.62−2.43 (m, 2H), 2.35−1.98 (m, 5H), 1.80−1.20 (m, 13H), 0.89 (s, 9H), 0.02 (s, 6H). Anal. Calcd for $C_{37}H_{58}O_8Si$: C, 67.44; H, 8.87. Found: C, 67.33; H, 8.93.

(13*S*)-15-[(*tert*-Butyldimethylsilyl)oxy]-13-isopropenyl-8-(methoxycarbonyl)-6-(methoxymethoxy)-6-methyl-3,9-pentadecadiyn-2-ol (41.1). To a stirred solution of 2.61 g (3.90 mmol) of carbonate **41** in 40 mL of 18:1 CH_2Cl_2−H_2O at rt was added 1.16 g (5.10 mmol) of DDQ, and the mixture was stirred for 1 h. The mixture was filtered and diluted with H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (20−30% EtOAc−hexane) gave 1.93 g (91%) of the propargylic alcohol as a clear light orange oil: IR (film) υ 3453, 3071, 2243, 1755 cm^{-1}; ^{1}H NMR δ 5.49 (m, 1H), 4.79−4.65 (m, 4H), 4.50 (m, 1H), 3.78 (s, 3H), 3.52 (m, 2H), 3.37 (s, 3H), 2.62−2.43 (m, 2H), 2.35−1.98 (m, 5H), 1.80−1.20 (m, 13H), 0.88 (s, 9H), 0.02 (s, 6H). Anal. Calcd for $C_{29}H_{50}O_7Si$: C, 64.65; H, 9.35. Found: C, 64.58; H, 9.39.

(3*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-isopropenyl-8-(methoxycarbonyl)-10-(methoxymethoxy)-10-methyl-12-(tri-*n*-butylstannyl)-12,13-pentadecadien-6-yne (42). To a stirred solution of 1.89 g (3.50 mmol) of the foregoing propargylic alcohol in 35 mL of CH_2Cl_2 at −78 °C was added 10.0 mL (7.10 mmol) of Et_3N followed by 0.41 mL (5.30 mmol) of methanesulfonyl chloride. After 1 h, the mixture was diluted with saturated $NaHCO_3$ and Et_2O. The aqueous phase was extracted with Et_2O, the organic phase was washed with saturated $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude material was carried on without further purification.

A two-necked flask was equipped with a stirbar and a sidearm addition flask containing 1.45 g (7.10 mmol) of CuBr·SMe_2. The apparatus was evacuated and purged with argon several times. To this flask, under argon, were added 30 mL of THF and 1.10 mL (7.80 mmol) of diisopropylamine. To this solution at 0 °C was added 2.80 mL (7.10 mmol) of 2.5 M BuLi in hexane, and the solution was stirred for 20 min. To this solution was added 1.90 mL (7.10 mmol) of Bu_3SnH, and stirring was continued for 30 min. The solution was then cooled to −78 °C, and the CuBr·SMe_2 was added from the sidearm flask. After 45 min, the crude mesylate in 5 mL of THF was added and the mixture was stirred for 30 min. The mixture was poured into a solution of 9:1 NH_4Cl−NH_4OH and stirred until both phases were clear. The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (0−5% EtOAc−hexane) afforded 2.39 g (84%) of the allenylstannane **42** as a clear yellow oil: IR (film) υ 3071, 1932, 1754 cm^{-1}; ^{1}H NMR δ 5.42 (m, 1H), 4.83−4.61 (m, 4H), 4.54 (m, 1H), 3.78 (s, 3H), 3.52 (m, 2H), 3.36 (s, 1.5H), 3.35 (s, 1.5H), 2.41−1.97 (m, 7H), 1.71−1.19 (m, 32H), 1.00−0.73 (m, 26H), 0.03 (s, 6H).

(3*S*)-3-Isopropenyl-8-(methoxycarbonyl)-10-(methoxymethoxy)-10-methyl-12-(tri-*n*-butylstannyl)-12,13-pentadecadien-6-yn-1-ol (43). To a stirred solution of 1.21 g (1.50 mmol) of allenylstannane **42** in 6 mL of THF was added 0.27 mL (15.0 mmol) of H_2O followed by 5.90 mL (5.9 mmol) of 1.0 M TBAF in THF. The solution was stirred for 8 h at rt. The solution was diluted with H_2O and Et_2O, the aqueous layer was extracted with Et_2O, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (25% EtOAc−hexane) afforded 0.94 g (91%) of the alcohol **43** as a clear light yellow oil: IR (film) υ 3435, 3075, 2246, 1940, 1753 cm^{-1}; ^{1}H NMR δ 5.40 (m, 1H), 4.85−4.60 (m, 4H), 4.53 (m, 1H), 3.77 (s, 3H), 3.59 (m, 2H), 3.36 (s, 1.5H), 3.34 (s, 1.5H), 2.43−1.95 (m, 7H), 1.69−1.14 (m, 32H), 1.00−0.64 (m, 17H).

(3*S*)-3-Isopropenyl-8-(methoxycarbonyl)-10-(methoxymethoxy)-10-methyl-12-(tri-*n*-butylstannyl)-12,13-pentadecadien-6-ynal (44). To a stirred solution of 0.20 mL (2.14 mmol) of *t*-BuOH in 10 mL of THF at 0 °C was added 2.10 mL (2.10 mmol) of 1.0 M EtMgBr in THF, and the solution was stirred for 5 min. To this solution was added 0.88 g (1.30 mmol) of the alcohol **43** in 3 mL of THF. After 10 min, 0.54 g (2.14 mmol) of 1,1′-(azodicarbonyl)dipiperdine was added and the mixture was stirred for an additional 30 min. The mixture was diluted with brine, H_2O, and Et_2O. The aqueous layer was extracted with Et_2O. The organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (15% EtOAc−hexane) afforded 0.81 g (91%) of the aldehyde **44** as a clear light yellow oil: IR (film) υ 3074, 2714, 2248, 1935, 1753, 1727 cm^{-1}; ^{1}H NMR δ 9.64 (t, 1H, J = 2.4 Hz), 5.40 (m, 1H), 4.85−4.60 (m, 2H), 4.52 (m, 1H), 3.76 (s, 3H), 3.34 (S, 1.5H), 3.33 (s, 1.5H), 2.77 (m, 1H), 2.46−2.01 (m, 8H), 1.73−1.15 (m, 32H), 1.01−0.75 (m, 15H).

(14*S*)-2,6-Dimethyl-14-isopropenyl-8-(methoxycarbonyl)-6-(methoxymethoxy)-2,3-cyclotetradecadien-9-ynone (45). To a stirred solution of 0.77 mL (6.25 mmol) of BF_3·OEt_2 in 210 mL of CH_2Cl_2 at −78 °C was added 1.45 g (2.10 mmol) of the allenylstannane aldehyde **44** in 50 mL of CH_2Cl_2 over a period of 30 min. The solution was stirred overnight at −78 °C and then quenched with 5 mL of MeOH followed by saturated $NaHCO_3$. The solution was allowed to reach rt, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the addition product as a clear dark yellow oil. The oil was diluted with 21 mL of CH_2Cl_2, and 1.76 (4.20 mmol) of Dess−Martin[24] reagent was added to the solution. The mixture was stirred for 30 min at rt, poured into a solution of saturated $NaHCO_3$ containing 7.20 g (29.0 mmol) of $Na_2S_2O_3$·$5H_2O$, and stirred until clear. The aqueous layer was extracted with CH_2Cl_2, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a mixture of propargyl and allenyl ketones as a clear yellow oil. This oil was diluted with 9 mL of CH_2Cl_2, and 2.90 mL (21.0 mmol) of Et_3N was added. This mixture was stirred for 6 h, and the solvent was then removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (15−20% EtOAc−hexane) gave 0.63 g (74%) of the allenone **45** as a clear yellow oil: IR (film) υ 3077, 2238, 1944, 1750, 1674 cm^{-1}; ^{1}H NMR δ 5.73−5.20 (m, 2H), 4.89−4.64 (m, 4H), 3.80 (m, 3H), 3.39 (m, 3H), 3.28−2.42 (m, 3H), 2.40−1.92 (m, 4H), 1.87−1.07 (m, 13H).

MOM Furan 46. To a stirred solution of 0.31 g (0.77 mmol) of allenone **45** protected from light in 8.0 mL of hexane was added 0.65 g (0.39 mmol) of 10% $AgNO_3$ on silica gel. After 7 h, the mixture was filtered and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (10% EtOAc−hexane) afforded 0.26

(24) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

g (84%) of furan **46** as a clear light yellow oil: IR (film) υ 3073, 2234, 1751, 1646 cm^{-1}; ^1H NMR δ 5.98−5.82 (m, 1H), 5.62 (m, 0.25H), 5.49 (m, 0.25H), 5.25 (m, 0.25H), 5.10 (d, 0.25H, J = 9.5 Hz), 4.92−4.60 (m, 4H), 3.79 (m, 3H), 3.37 (m, 3H), 3.27−2.36 (m, 4H), 2.33−1.85 (m, 5H), 1.77−0.81 (m, 11H). Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.27; H, 8.03.

***syn*- and *anti*-(*Z*)-Vinyl Furans 47/49.** To a stirred solution of 80 mg (0.20 mmol) of the MOM ether furan **46** in 4 mL of CH_2Cl_2 was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred for 13 min and then quenched with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (5% EtOAc−hexane) gave 50 mg (73%) of the (*Z*)-vinyl furans **47**/**49** as a clear yellow oil: IR (film) υ 3071, 2234, 1748, 1646 cm^{-1}; ^1H NMR δ 6.09 (s, 0.5H), 5.99 (s, 0.5H), 5.92 (s, 1H), 5.65 (m, 0.5H), 5.13 (d, 0.5H, J = 11.0 Hz), 4.92 (m, 0.5H), 4.84 (m, 2.5H), 4.16 (t, 1H, J = 11.7 Hz), 3.82 (s, 1.5H), 3.80 (s, 1.5H), 3.59−3.39 (m, 0.5H), 3.32 (m, 0.5H), 3.02 (m, 0.5H), 2.82 (dd, 0.5H, J = 13.6, 7.0 Hz), 2.72−2.46 (m, 2H), 2.38−1.88 (m, 7H), 1.76 (m, 3H), 1.61−1.00 (m, 3H). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.52, H, 7.71.

***syn*- and *anti*-Furyl Alcohols 48 and 50.** To a stirred solution of 35 mg (0.10 mmol) of the carbonates **47**/**49** in 0.5 mL of MeOH was added a catalytic amount of potassium carbonate. The mixture was stirred for 2.75 h and then diluted with water and Et_2O. The aqueous layer was extracted with Et_2O, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (15% EtOAc−hexane) gave 27 mg (96%) of a 1:1 mixture of *syn* and *anti* alcohols **48** and **50** as a solid white powder. *Syn* isomer: ^1H NMR δ 6.10 (s, 1H), 5.91 (s, 1H), 4.83 (m, 2H), 3.36 (dd, 1H, J = 12.8, 1.8 Hz), 3.04 (m, 1H), 2.73 (dd, 1H, J = 13.2, 7.33 Hz), 2.69−2.52 (m, 2H), 2.12−2.03 (m, 2H), 1.99 (m, 3H), 1.91 (s, 3H), 1.91 (s, 3H), 1.75 (s, 3H), 1.71−1.39 (m, 1H), 1.31−1.15 (m, 2H); ^{13}C NMR δ 150.6, 149.0, 147.6, 131.2, 117.2, 116.4, 112.3, 111.1, 85.0, 83.4, 62.1, 43.5, 40.3, 30.0, 29.6, 27.9, 19.9, 16.5, 19.6; mp 114−115 °C; $[\alpha]_D$ +274.3 (c 0.37, CH_2Cl_2). Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.22; H, 8.56. *Anti* isomer: ^1H NMR δ 5.95 (s, 1H), 5.90 (s, 1H), 4.90 (bs, 1H), 4.84 (m, 1H), 4.31 (d, 1H, J = 10.3 Hz), 4.02 (dd, 1H, J = 12.1, 10.6 Hz), 3.34 (m, 1H), 2.77−2.50 (m, 2H), 2.31−1.96 (m, 2H), 1.91 (s, 3H), 1.89 (s, 3H), 1.76 (s, 3H), 1.55 (m, 1H), 1.40 (m, 1H), 1.26 (s, 1H).

***Syn* Furyl Alcohol 48.** To a stirred solution of 9.0 mg (32.0 μmol) of the *anti* isomer **50** in 0.3 mL of CH_2Cl was added 84.0 mg (0.96 mmol) of activated MnO_2, and the mixture was stirred overnight at rt. The mixture was filtered, and the solvent was removed to afford the ynone **51** as a bright yellow oil: ^1H NMR δ 6.03 (s, 1H), 5.98 (s, 1H), 4.90 (m, 3H), 3.24 (m, 1H), 2.88 (d, 1H, J = 10.6 Hz), 2.75−2.57 (m, 2H), 2.40−2.22 (m, 2H), 1.93 (s, 3H), 1.88 (s, 3H), 1.77 (s, 3H), 1.61−1.18 (m, 3H).

This oil was diluted with 0.3 mL of THF and cooled to −78 °C. To this stirred solution was added 39.0 mL of 1.0 M K-Selectride. After 15 min, the solution was diluted with saturated $NaHCO_3$ and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to afford 9.0 mg (∼99%) of the *syn* alcohol **48** as a solid white powder.

(−)-Rubifolide (57). To a stirred solution of 43 mg (0.15 mmol) of the *syn* furyl alcohol **48** and 1.7 mg (1.5 μmol) of Pd(PPh_3)$_4$ in 3.0 mL of THF under a CO atmosphere was added 37 μL (0.32 mmol) of 2,6-lutidine. The solution was cooled to 0 °C, and 24 μL (0.17 mmol) of trifluoroacetic anhydride was added. After complete ester formation (10 min), 0.11 mL (6.0 mmol) of H_2O was added and the mixture was allowed to reach rt and stir for 15 min. The solvent was then removed, and the oil was diluted with 1 mL of hexane and a drop of CH_2Cl_2 to ensure a homogeneous solution. To this stirred solution, protected from light, was added 51 mg (30 μmol) of 10% $AgNO_3$ on silica. The mixture was stirred for an additional 3 h and filtered, and the solvent was removed under reduced pressure. Flash chromatography on deactivated (5% Et_3N−hexane) silica gel (10% EtOAc−hexane) afforded 23 mg (49%) of (−)-rubifolide as a fine white powder: ^1H NMR δ 6.90 (bs, 1H), 6.06 (bs, 1H), 5.99 (s, 1H), 4.96 (dm, 1H, J = 11.7 Hz), 4.90 (m, 1H), 4.88 (bs, 1H), 3.23 (t, 1H, J = 11.7 Hz), 2.69 (dd, 1H, J = 11.7, 4.4 Hz), 2.60−2.30 (m, 4H), 2.09 (dm, 1H, J = 14.7 Hz), 1.98 (bs, 3H), 1.92 (bs, 3H), 1.74 (bs, 3H), 1.64 (m, 1H), 1.17 (apparent dt, 1H, J = 13.6, 3.7 Hz); ^{13}C NMR δ 174.5, 152.1, 149.9, 149.3, 145.4, 132.8, 127.0, 117.4, 117.1, 113.8, 112.9, 78.7, 43.3, 39.5, 31.2, 30.5, 25.7, 20.0, 19.2, 9.5; mp 160 °C; $[\alpha]_D$ −38.3 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.94; H, 7.82.

Acknowledgment. Support for this work was provided by Grant R01-GM29475 from the National Institutes for General Medical Sciences. We thank Professor Raymond Andersen for spectra of authentic rubifolide. We are grateful to Dr. Michael Sabat of this department for performing the X-ray analysis.

Supporting Information Available: Experimental procedures for **6**−**25**, ^1H NMR spectra for key intermediates, condensed Macromodel log file for ynone **28** with 3D structures of the four lowest energy conformers, and an ORTEP diagram for alcohol **48** (45 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.

JO970360D