Synthesis of the Pseudopterane 2,5-Furanocyclic Ring System by [2,3] Wittig Ring Contraction of Bridged Furan and Dihydrofuran Propargylic Ethers

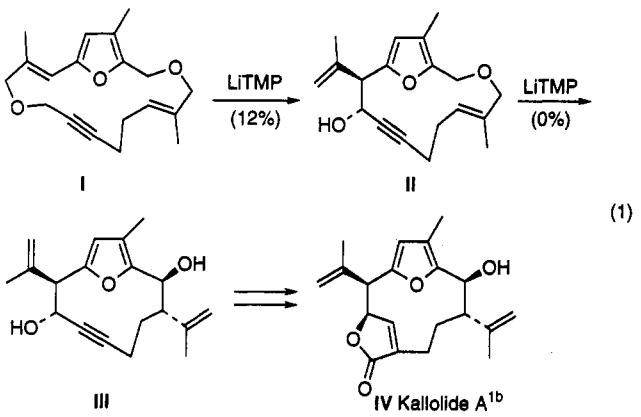
James A. Marshall* and Byung-chan Yu

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received September 20, 1993®

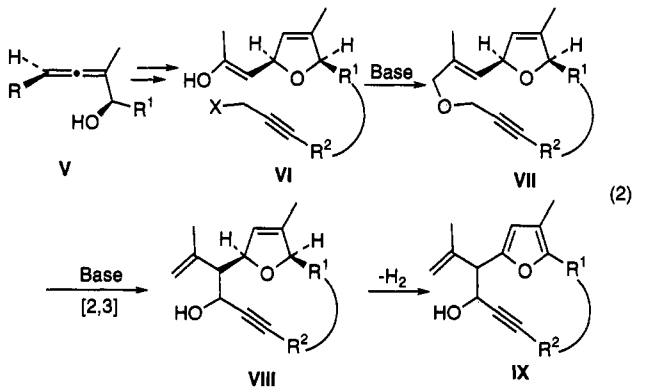
Two routes to the 2,5-furanocyclic ring system of the pseudopterane family of natural products are described. Both employ [2,3] Wittig ring contraction of a 15-membered allylic propargylic ether as the key step. The first route utilizes the bridged 2,5-dihydro furanocyclic ether **24** as the immediate precursor. Treatment with BuLi in THF–pentanes at −78 °C affords a 70:30 mixture of trans,anti and trans,syn diastereomers **29** and **31** in 68% yield. The acetate derivatives **30** and **32** are dehydrogenated to furan **33** by MnO_2 in ether. In the second route, the furano bridged (Z)-allylic propargylic ether **40Z** rearranges to furanocycle **41** in 73% yield upon treatment with LiTMP in THF–pentane at −78 °C.

Some years ago, we outlined a novel approach to the pseudopterane ring system **III** through consecutive [2,3] Wittig ring contractions of the 2,5-furanocyclic diether **I** (eq 1).[1] However, the plan was never fully implemented



because of low yields both in the cyclization leading to ether **I** and the ensuing ring contraction (**I** → **II**). Attempts to effect the second ring contraction (**II** → **III**) led to no useful product.

At the time, we attributed the failure of this route to ring strain in the intermediates **I**—**III** and the respective transition states of reactions producing them. According to molecular mechanics calculation, a significant component of the strain in **II** and **III** results from bending of the furan ring out of planarity by the bridging chain.[2] Accordingly, we formulated alternative strategies to the ring system of **III** in which construction of the furan ring follows carbocyclization.[3] One of these envisioned the [2,3] Wittig ring contraction of a *cis*-2,5-dihydro-2,5-furanocycle such as **VII** (eq 2). In this scenario, the cyclic ether **VII**



and the derived ring-contracted product are relatively unstrained. Furthermore, the formation of the strained furanocycle **IX** is assisted by the gain in aromatic resonance energy of the developing furan ring.

The requisite dihydrofuran precursor **VI** could presumably be prepared by $AgNO_3$-catalyzed cyclization of an allenol intermediate such as **V**.[4] Macro ring closure would be effected as with related 13- and 17-membered propargylic ethers.[1]

As a test of the basic strategy, a prototype system was synthesized starting from the monoprotected 1,5-pentanediol **1**.[5] Sequential Swern–Wittig homologations,[6] first with the phosphorylidene propionate reagent and then the dibromomethylene ylide,[7] afforded the dibromo diene **6**, which was transformed to enyne **7** by successive

* Abstract published in *Advance ACS Abstracts*, January 1, 1994.

(1) (a) Marshall, J. A.; Nelson, D. J. *Tetrahedron Lett.* **1988**, *29*, 741. Though originally assigned as cis, alcohol **II** is now thought to be the trans-isomer, as shown, on the basis of the ^1H NMR coupling constant of the carbinyl H which compares favorably to subsequently prepared trans-isomers of comparable structure. (b) Kallolide A: Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 574. c) This strategy has also been applied to other natural products. Cembranes: Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, *55*, 227. Germacranes: Takahashi, T.; Nemto, H.; Kanada, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499. Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883. *p*-Menthanes: Marshall, J. A.; Lebreton, J. *J. Org. Chem.* **1988**, *53*, 4108. Enediynes: Wender, P. A.; McKinny, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369. Doi, T.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 3465. Audrain, H.; Skrydstrup, T.; Ulibani, G.; Grierson, D. S. *Synlett* **1993**, 20.

(2) The program Macromodel V3.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multiple step iterations (300–1000) until the minimum energy conformer was found multiple times (10 or more). For a description of the program, see 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. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

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

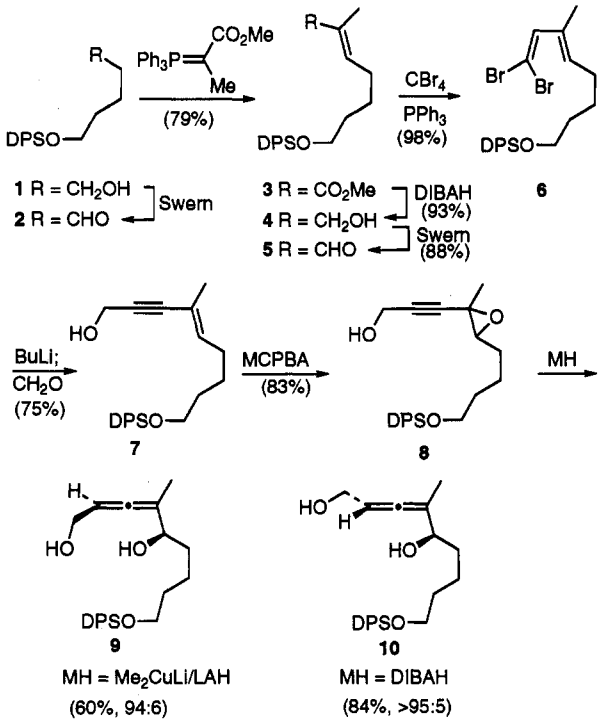
(4) *Cf.* Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1990**, *55*, 2995.

(5) *Cf.* McDougal, P. M.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

(6) *Cf.* Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

(7) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

0022-3263/94/1959-0324$04.50/0

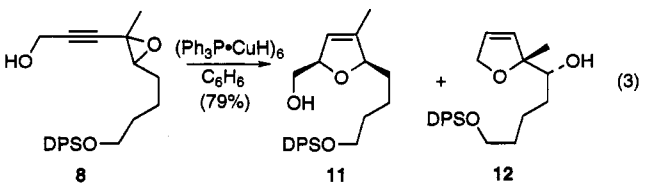


treatment with BuLi and CH_2O. Selective epoxidation of the double bond with MCPBA led to the alkynyloxirane **8**.

The conversion of alkynyloxirane **8** to the *syn*-allenol **9**, the immediate precursor of the requisite *cis*-2,5-dihydrofuran (e.g. **VI** in eq 2), requires an anti S_N2' addition of hydride. In general, S_N2' reductions of propargylic X systems with LAH and derived hydrides proceed by a syn (presumably stepwise) pathway when the X substituent is a relatively poor leaving group such as OH, OMe, or OAc.[8] An anti pathway prevails when sulfonates are employed with LAH.[9] Syn stereochemistry is also seen with certain alkynyl epoxycyclohexanes and LAH.[10]

We found that alkynyloxirane **8** underwent smooth S_N2' reduction with DIBAH affording essentially a single diol isomer according to ^1H NMR analysis of the dibenzoate. Initially we had no way of assigning stereochemistry to this product but subsequent studies showed it to be the undesired anti isomer **10** (syn S_N2' adduct). The syn diol **9** (anti S_N2' adduct) was obtained from **8** by brief treatment with a mixture of Me_2CuLi and LAH in THF at −78 °C.[11] This led to a 94:6 mixture of adducts **9** and **10** analyzed as the dibenzoates.

Interestingly, when the Ph_3P·CuH hexamer[12] was employed for the reduction, alkynyloxirane **8** afforded a nearly 1:1 mixture of the dihydrofurans **11** and **12** in 79% yield (eq 3). These products evidently arise from anti S_N2'

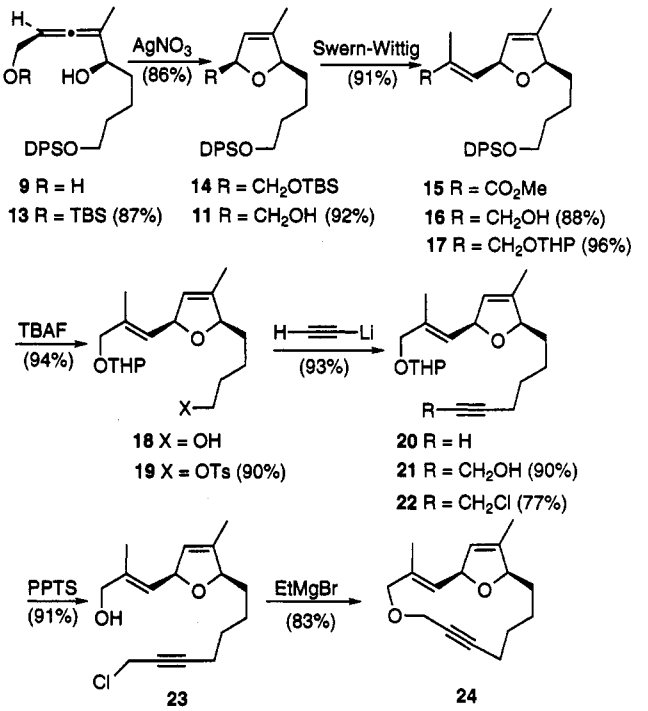


(3)

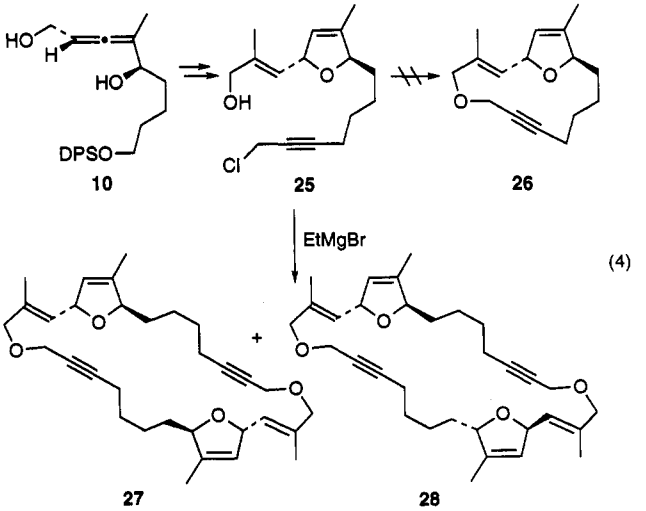
addition of hydride followed by Cu(I)-promoted cyclization of the resulting allenyl product.

(8) Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, *101*, 7302.

An authentic sample of the dihydrofuran **11** was prepared by treatment of the TBS-protected allenylcarbinol **13** with $AgNO_3$ in acetone then selective hydrolysis of the TBS ether with PPTS in ethanol.[4] Swern–Wittig homologation[6] led to the (*E*)-conjugated ester **15**, which was reduced with DIBAH to the allylic alcohol **16**. The THP ether **17** was desilylated with TBAF to afford alcohol **18**. Homologation of the tosylate **19** with the ethylenediamine complex of lithium acetylide[13] in DMSO and then lithiation with BuLi and addition of formaldehyde gave the propargylic alcohol **21**. The derived chloride **23** (MsCl, 2,6-lutidine, LiCl,[14] and then PPTS–EtOH) cyclized to the propargylic ether **24** upon exposure to EtMgBr in THF–HMPA. The ease of this cyclization supported our assignment of stereochemistry to dihydrofurans **11** and **14** and the allenylcarbinol precursor **9**.

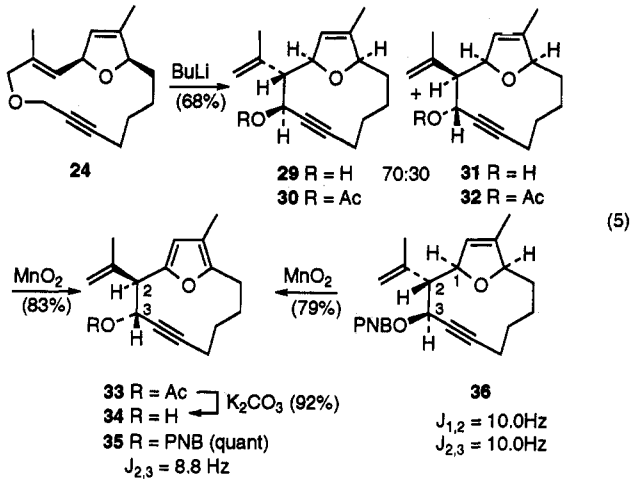


By the identical sequence, the trans-2,5-dihydrofuran chloro alcohol **25** was prepared from the *anti*-allenylcarbinol **10**. When subjected to the cyclization conditions, this substance slowly gave rise to a mixture of dimeric products **27** and **28** in 17% yield (eq 4). The highly strained monomeric ether **26** was not formed in detectable amounts.



(4)

Upon treatment with *n*-BuLi in THF–pentane at −78 °C, the cyclic propargylic ether **24** underwent facile [2,3] Wittig ring contraction affording a 70:30 mixture of diastereomeric products **29** and **31** in 68% yield (eq 5).

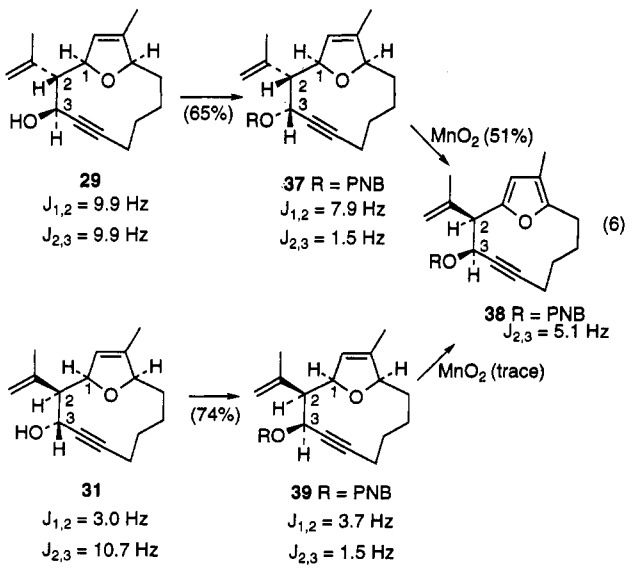


(5)

The derived mixture of acetates **30** and **32** gave rise to a single furan, **33**, in 83% yield on prolonged exposure to MnO_2 in ether at room temperature.[15] The *p*-nitrobenzoate derivative **35** provided crystals suitable for X-ray analysis which confirmed the trans stereochemistry.[15b] This derivative was also obtained by dehydrogenation of the *p*-nitrobenzoate **36** derived from the major [2,3] Wittig product **29**.

Attempted inversion of the carbinyl center of alcohol **34** with *p*-$NO_2C_6H_4CO_2H$ under Mitsunobu conditions failed to give the *cis*-*p*-nitrobenzoate **38**.[16] The trans isomer **35** was the sole product of this reaction. Presumably steric factors render backside approach at C-3 unfavorable.

On the other hand, alcohol **29**, the major [2,3] Wittig ring contraction product, afforded the inverted *p*-nitrobenzoate **37** in 65% yield under the foregoing conditions (eq 6). Assignment of relative stereochemistry is based



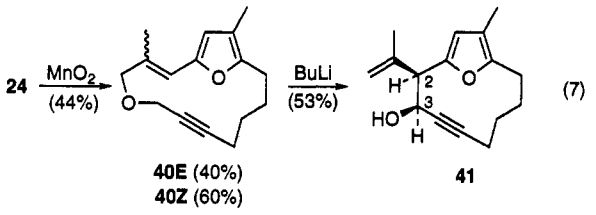
(6)

on ^1H NMR coupling constants, as indicated. Likewise, the minor ring-contracted alcohol **31** yielded the inverted *p*-nitrobenzoate **39**. Both **37** and **39** could be dehydrogenated to the furan **38**, an isomer of **35**. As expected, the ^1H NMR coupling constant of the carbinyl proton of the *cis* alcohol **38** (J = 5.1 Hz) was smaller than that of the trans isomer **35** (J = 8.8 Hz). Unfortunately, the foregoing dehydrogenations proceeded in low yield in contrast to the corresponding conversions of the trans acetates **30** and **32**.

Thus, both potential pathways from the [2,3] Wittig products **29/31** to the desired *cis* alcohol **38** (R = H) suffer from a low-yielding step. On the one hand, dehydrogenation of the trans acetate mixture **30/32** is efficient but inversion of the *trans* alcohol **34** fails. Contrastingly, inversion of **29/31** to the *cis*-dihydro ester **37/39** can be accomplished reasonably well but the ensuing dehydrogenation proceeds in low yield.

Several possible solutions to this problem were envisioned. However, before these could be examined, we chanced to observe that a sample of the furan ether **40E**, prepared in some model studies on the MnO_2 dehydrogenation reaction, had partially isomerized to the (*Z*)-isomer **40Z** on storage. Although the mechanism for this isomerization has not been ascertained, MM2 calculations indicate that **40Z** is some 21 kJ lower in energy than the (*E*)-isomer **40E**.[2]

We were pleased to find that when treated with *n*-BuLi in THF–pentane, the foregoing mixture readily underwent [2,3] Wittig ring contraction to afford a single product identified as the *cis*-isomer **41** by comparison with the previously prepared *trans* alcohol **34** (eq 7). It seems



(7)

reasonable that this alcohol arises mainly, if not exclusively, from **40Z**.[17] Encouraged by these results, we decided to examine a variant of our original strategy (eq 1) employing **40Z** as the carbocyclic precursor. It was hoped that the lower strain energy of this ether would allow for a more direct synthesis from a furan precursor. In fact, this approach proved highly feasible through use of our recently disclosed methodology for furan synthesis.[18]

(9) Bordon, W. T.; Corey, E. J. *Tetrahedron Lett.* **1969**, 313.

(10) DeVille, T. E.; Hurthouse, M. B.; Russell, S. W.; Weedon, B. C. L. *J. Chem. Soc. Chem. Commun.* **1969**, 754. Hlubusek, J. R.; Hora, J.; Russell, S. W.; Toube, T. P.; Weedon, B. C. L. *J. Chem. Soc. Perkin Trans. 1* **1974**, 848.

(11) Crabbé, P.; Barreiro, E.; Dollat, J. M.; Luche, J.-L. *J. Chem. Soc. Chem. Commun.* **1976**, 183. Ashby, E. C.; Korenowski, T. F.; Schwartz, R. D. *J. Chem. Soc. Chem. Commun.* **1974**, 157.

(12) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(13) Available from Aldrich Chemical Co., Milwaukee, WI.

(14) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

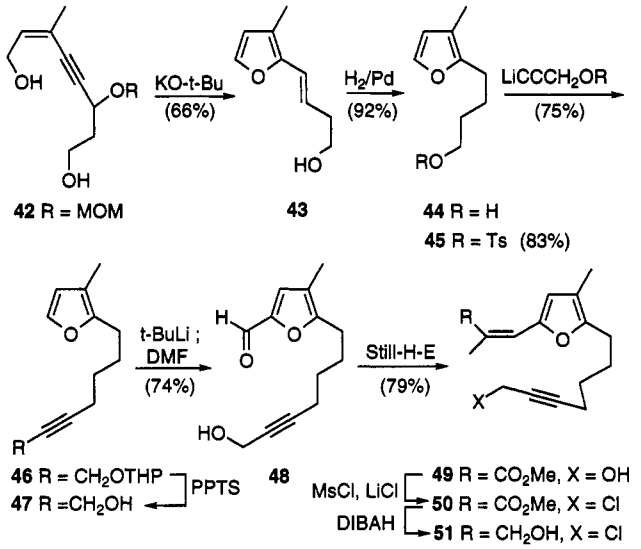
(15) (a) Fatiadi, A. J. *Synthesis* **1976**, 65. *Ibid.* **1976**, 133. (b) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(16) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3107.

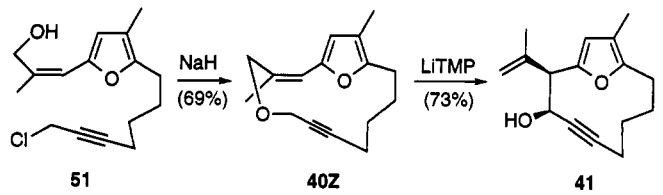
(17) Typically (*E*)-allylic ethers give rise to anti products whereas (*Z*)-allylic ethers yield syn products in such rearrangements, although exceptions are known. See Marshall, J. A. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.-in-Chief, Pattenden, G., Ed.; Pergamon Press, Oxford, 1991; Vol. 3, Chapter 3.11.

(18) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435.

Accordingly, the enynediol 42[19] was converted to furan 43 upon exposure to KO-*t*-Bu in THF–18-C-6 at room temperature. Hydrogenation led to alcohol 44 which was converted to the propargylic alcohol 47 *via* the tosylate 45 and the lithio derivative of the tetrahydropyranyl ether of propargyl alcohol. Furan formylation with *t*-BuLi and DMF led to aldehyde 48. Still–Horner–Emmons homologation[21] afforded the (*Z*)-conjugated ester 49 which was converted to chloride 50 with MsCl and LiCl in the presence of 2,6-lutidine. Reduction of the ester with DIBAH gave the chloro alcohol 51.

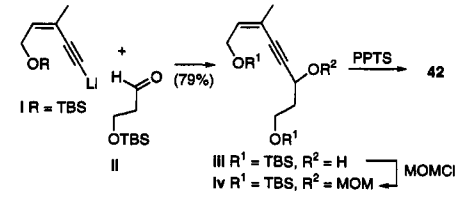


Attempted cyclization of chloro alcohol 51 with EtMgBr in THF–HMPA under our previously optimized conditions[1c] proceeded in only 10–20% yield. We eventually found that slow addition of 51 to refluxing toluene containing NaH and 18-crown-6 afforded ether 40Z in 60–70% yield. Ring contraction was smoothly effected with lithio 2,2,6,6-tetramethylpiperidide (LiTMP) in THF



pentane affording the *cis*-alcohol 41 in 73% yield as the sole product. Both this reaction and the preceeding cyclization showed no byproducts according to TLC analysis of the reaction mixture. We suspect that the lability of these furans to air oxidation may account for the lower than expected yields.

(19) Diol 42 was prepared by addition of the alkynyllithium *i* to aldehyde *ii* followed by MOM ether formation and TBS cleavage. The alcohol precursor of *i* is available from Aldrich Chemical Co., Milwaukee, WI.



(20) Still, W. C.; Gennari, C. *Tetrahderon Lett.* **1983**, *24*, 4405.

(21) For typical experimental protocols see Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960.

The present findings establish the viability of a [2,3] Wittig ring contraction strategy for the synthesis of 2,5-bridged furanocycles. Our previous lack of success with the application in eq 1 may stem from strain in the transition state for **I** → **II** engendered by the (*E*)-allylic ether geometry, or the inherent sensitivity of **I** and **II** to air oxidation, or a combination of these and other unknown factors. In any event, we can now turn our attention to modifications of this strategy and further elaboration of intermediates that will lead to representative pseudopterane natural products.

Experimental Section[21]

***rel*-(2*R*,5*R*)-4-Methyl-9-[(*tert*-butyldiphenylsilyl)oxy]-2,3-nonadiene-1,5-diol (9).** To a suspension of 22.6 g (119 mmol) of CuI in 100 mL of THF was added 169 mL (237 mmol) of 1.4 M MeLi in ether dropwise at 0 °C. As the resulting yellow color disappeared the solution was cooled to −78 °C and then 237 mL of 1 M LAH in THF was added. The resulting orange solution was stirred for 30 min and then 10.0 g (23.7 mmol) of the alkynyloxirane 8 in 20 mL of THF was added dropwise over 30 min. The resulting brown solution was stirred for 2.5 h. The reaction mixture was carefully quenched with Rochelle's salt at −78 °C and then 10% HCl was added. The aqueous layer was separated and extracted with ether. The extracts were washed with saturated $NaHCO_3$ and then with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 75% ether in hexanes gave 5.95 g (60%) of the diol 9 (94:6 anti:syn addition according to ^1H NMR anaylsis of the dibenzoate derivative): IR (film) ν 3346, 1965, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.33 (m), 5.39 (m), 4.08 (d, J = 5.7 Hz), 4.02 (brt), 3.65 (t, J = 6.2 Hz), 1.70 (d, J = 2.9 Hz), 1.70–1.40 (m), 1.03 (s) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) 136.0 (4C), 134.4 (2C), 130.0 (2C), 128.0 (4C), 106.2, 93.6, 73.2, 64.3, 60.9, 35.0, 32.8, 27.3 (3C), 22.2, 19.6, 14.6. A peak for the central carbon of the allene was not seen; MS (NH_3, CI) calcd for $C_{26}H_{36}O_3Si$, M^+ = 425. Found $M^+ - H_2O$ = 407, $M^+ - 2H_2O$ = 389. Anal. Calcd for $C_{26}H_{36}O_3$: C, 73.54; H, 8.54. Found: C, 73.35; H, 8.59.

The dibenzoate derivative was prepared by stirring a solution of 30 mg (0.047 mmol) of the diol 9, 43 mg (0.355 mmol) of benzoic acid, 51 mg (0.249 mmol) of DCC, and 17 mg of DMAP in 1 mL of THF for 5 h. The mixture was directly chromatographed on silica gel. Elution with 20% ether in hexanes gave 36.1 mg (92%) of the dibenzoate: IR (film) ν 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17–7.32 (m), 5.40 (m), 4.78 (d, J = 6.3 Hz), 3.61 (t, J = 6.2 Hz), 1.75 (d, J = 2.7 Hz), 1.70–1.40 (m), 0.99 (s) ppm; HRMS calcd for $C_{36}H_{35}O_5Si$ (M − Bu) 575.2254, found 575.2264.

The ^1H NMR spectrum indicated a 94:6 ratio of stereoisomers.

***rel*-(2*S*,5*R*)-4-Methyl-9-[(*tert*-butyldiphenylsilyl)oxy]-2,3-nonadiene-1,5-diol (10).** To a solution of 300 mg (0.710 mmol) of the alkynyloxirane 8 in 6 mL of CH_2Cl_2 was added 3.55 mL of 1.0 M DIBAH in hexanes dropwise at −15 °C. The solution was stirred for 1.5 h and then quenched with saturated Rochelle's salt. After 1 h water was added and the aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 75% ether in hexanes gave 254 mg (84%) of the diol 10 (a single isomer according to ^1H NMR anaysis of the dibenzoate derivative): IR (film) ν 3346, 1965, 1467, 1425, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.33 (m), 5.40 (m), 4.07 (d, J = 5.6 Hz), 4.00 (brt), 3.65 (t, J = 6.3 Hz), 1.95 (brs), 1.70 (d, J = 2.8 Hz), 1.60–1.40 (m) 1.03 (s) ppm.

Addition of $(Ph_3P \cdot CuH)_6$ to the Alkynyloxirane 8. To a solution of 30 mg (0.071 mmol) of the alkynyloxirane 8 in 0.5 mL of dry benzene was added 70 mg (0.36 mmol) of $(Ph_3P \cdot CuH)_6$.[18] The solution was stirred for 15 min and then the solvent was removed under reduced pressure. The residue was directly chromatographed on silica gel. Elution with 50% ether in hexanes gave 11.3 mg (38%) of the dihydro furan 12: IR (film) ν 3432, 3062, 1424, 1106 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.34 (m), 5.87 (brd, J = 6.2 Hz), 4.63 and 4.61 (ABX, J_{AB} = 13.1, J_{BX}

= 1.7 and J_{BX} = 1.9 Hz), 3.65 (brt), 3.43 (m), 2.10 (brs), 1.70–1.20 (m), 1.23 (s), 1.03 (s) ppm. Further elution gave 12.2 mg (41%) of the dihydrofuran **11**: IR (film) ν 3433, 2365, 1632, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.34 (m), 5.33 (d, J = 1.5 Hz), 4.79 and 4.58 (m), 3.66 (t, J = 6.0 Hz), 3.65 and 3.48 (ABX, J_{AB} = 11.5, J_{BX} = 5.0 Hz, J_{AX} could not be measured because of overlap with the triplet at 3.66 ppm), 1.86 (brs), 1.67 (s), 1.80–1.30 (m), 1.03 (s) ppm; HRMS calcd for $C_{25}H_{33}O_2Si$(M – CH_2OH) 393.2250, found 393.2251.

***rel*-(2*R*,5*R*)-2-(Hydroxymethyl)-4-methyl-5-[4-(*tert*-butyldiphenylsilyloxy)butyl]-2,5-dihydrofuran (11).** To a solution of 3.75 g (6.40 mmol) of the TBS ether **14** in 50 mL of absolute ethanol was added 450 mg (1.79 mmol) of PPTS. The solution was stirred for 24 h. Water was added and the aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 50% ether in hexanes gave 2.50 g (92%) of the alcohol **11**. The infrared and NMR spectra of this material were superimposable with those of the sample obtained above from oxirane **8**.

***rel*-(2*R*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-9-[(*tert*-butyldiphenylsilyl)oxy]-2,3-nonadien-5-ol (13).** To a solution of 10.4 g (24.5 mmol) of the diol **9** in 100 mL of CH_2Cl_2 were added 12.4 mL (122 mmol) of triethylamine, 4.43 g (29.4 mmol) of TBSCl, and 749 mg (6.1 mmol) of DMAP. The solution was stirred for 5 h and water was added. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 11.5 g (87%) of the alcohol **13**: IR (film) ν 3441, 1965, 1464, 1456, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.33 (m), 5.29 (m), 4.14 (dd, J = 6.1, 1.5 Hz), 4.01 (brdt), 3.65 (t, J = 6.4 Hz), 1.68 (d, J = 2.8 Hz), 1.70–1.40 (m), 1.03 (s), 0.88 (s), 0.06 (s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 135.6 (4C), 134.1 (2C), 129.5 (2C), 127.6 (4C), 104.4, 93.9, 72.7, 63.9, 61.8, 34.9, 32.4, 26.9 (3C), 25.9 (3C), 21.8, 19.2, 14.4 (2C), –5.1 (2C); HRMS calcd for $C_{28}H_{41}O_3Si_2$(M – Bu) 481.2594, found 481.2596.

***rel*-(2*R*,5*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-4-methyl-5-[4-[(*tert*-butyldiphenylsilyl)oxy]butyl]-2,5-dihydrofuran (14).** To a solution of 4.50 g (8.35 mmol) of the allenol **13** in 60 mL of a 5:1 mixture of acetone and water were added 2.84 g (16.7 mmol) of $AgNO_3$ and 1.67 g (16.7 mmol) of $CaCO_3$. The mixture was stirred for 3 h in the dark. Water was added and the aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 5% ether in hexanes gave 3.87 g (86%) of the dihydrofuran **14**: IR (film) ν 2355, 1464, 1251, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.33 (m), 5.43 (brs), 4.68 and 4.56 (m), 3.65 (t, J = 6.3 Hz), 3.62 and 3.47 (ABX, J_{AB} = 10.2, J_{AX} = 5.4 and J_{BX} = 5.9 Hz), 1.66 (s), 1.66–1.40 (m), 1.03 (s), 0.87 (s), 0.03 (s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 135.6 (4C), 134.1 (2C), 129.5 (2C), 127.6 (4C), 122.0, 87.7, 85.8, 67.3, 63.9, 34.6, 32.7, 26.9 (3C), 26.0 (3C), 21.4, 19.2, 18.4, 12.6, –5.2 (2C); HRMS calcd for $C_{32}H_{50}O_3Si_2$ 538.3299, found 538.3298. Anal. Calcd for $C_{32}H_{50}O_3Si_2$: C, 71.32; H, 9.35. Found: C, 71.17; H, 9.42.

***rel*-(4*S*,7*R*)-2,6-Dimethyl-1,4-dioxabicyclo[11.2.1]tetradec-2,5-dien-12-yne (24).** To a solution of 26.0 mg (0.092 mmol) of the chloro alcohol **23** in 12 mL of a 9:1 mixture of THF and HMPA was added 0.147 mL (1.47 mmol) of 1 M EtMgBr in THF dropwise at 0 °C. The solution was warmed to reflux temperature and stirred for 3 h. The solution was quenched with saturated NH_4Cl at room temperature. Water was added and the aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 18.7 mg (83%) of the cyclic ether **24**: IR (film) ν 2910, 1660, 1442, 1365, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dd, J = 8.6, 1.4 Hz), 5.45 (d, J = 8.5 Hz), 5.35 (brs), 4.71 (brs), 4.23 and 4.04 (ABX, J_{AB} = 15.7, J_{AX} = 2.0, J_{BX} = 1.9 Hz), 4.08 and 3.87 (AB, J = 14.9 Hz), 2.32–2.18 (m), 1.90–1.30 (m), 1.67 (d, J = 1.0 Hz), 1.66 (s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 134.1, 127.3, 123.8, 87.0, 86.7, 80.9, 78.4, 75.9, 59.4, 32.1, 27.6, 21.1, 18.3, 13.7, 12.4; mass spectrum (CI), m/e 246 (M + H).

Macrocyclization of Chloro Alcohol 25. The procedure described for ether **24** was followed with 50 mg (0.177 mmol) of the chloro alcohol **25** but stirring at reflux was prolonged to 18 h. The crude product was chromatographed on silica gel. Elution with 20% ether in hexanes gave 4.3 mg (10%) of a dimeric ether (**27** or **28**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (m), 5.28 (s), 4.64 (brt), 4.07 (t, J = 1.9 Hz), 3.93 (AB, J_{AB} = 11.7 Hz), 2.24 (m), 1.71 (s), 1.66 (s), 1.80–1.40 (m) ppm; mass spectrum (EI), m/e 492, calcd for $C_{32}H_{44}O_4$ 492.

Further elution gave 6.4 mg (7%) of a second diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (m), 5.28 (s), 4.68 (brs), 4.06 (brs), 3.92 (brs), 2.25 (m), 1.71 (s), 1.67 (s), 1.80–1.40 (m) ppm; mass spectrum (EI), m/e 492 calcd for $C_{32}H_{44}O_4$ 492.

***rel*-(1*S*,2*R*,3*R*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodec-11-en-4-yn-3-ol (31) and *rel*-(1*S*,2*S*,3*S*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodec-11-en-4-yn-3-ol (29).** To a solution of 100 mg (0.406 mmol) of the cyclic ether **24** in 40 mL of 1:1 THF–pentane was added 0.649 mL (1.63 mmol) of 2.5 M n-BuLi in hexane dropwise at –78 °C. The solution was stirred for 1 h and quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ether in hexanes gave 26.9 mg (27%) of the minor product (trans,anti,cis) **31** containing inseparable byproducts: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (s), 5.06 (s), 4.85 (brs), 4.52 (brd, J = 7.7), 4.32 (brd), 2.83 (dd, J = 10.7, 3.0 Hz), 2.40–2.00 (m), 1.79 (t, J = 0.6 Hz), 1.66 (s), 2.00–1.40 (m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 142.3, 119.7, 114.2, 88.0, 87.9, 86.0, 83.6, 60.5, 58.3, 32.8, 26.0, 24.0, 23.1, 18.9, 12.9.

Further elution gave 41.0 mg (41%) of the major product (trans,syn,cis) **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (s), 4.99 and 4.85 (s and s), 4.77 (brd, J= 9.9 Hz), 4.49 (brd, J = 7.7 Hz), 4.40 (m), 2.49 (dd, J = 9.9, 9.9 Hz), 2.45–2.20 (m), 1.67 (s), 1.80–1.40 (m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 139.2, 123.6, 115.7, 89.5, 85.9, 85.3, 84.6, 62.8, 62.3, 33.7, 24.6, 18.4, 12.5; HRMS calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1608.

***rel*-(1*S*,2*R*,3*R*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodec-11-en-4-yn-3-yl Acetate (30) and *rel*-(1*S*,2*S*,3*S*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodec-11-en-4-yn-3-yl Acetate (32).** The ring contraction was carried out as described for alcohols **29**/**31** on 116 mg (0.471 mmol) of the cyclic ether **24**. The crude product was chromatographed on silica gel. Elution with 30% ether in hexanes gave 98 mg (84%) of the [2,3] Wittig products **29**/**31** (70:30) and 7 mg (7%) of the unreacted ether. The alcohol mixture in 2 mL of pyridine was stirred with 1.86 mL of acetic anhydride and 10 mg of DMAP for 2 h. Pyridine and acetic anhydride were removed under reduced pressure and the residue was chromatographed on silica gel. Elution with 10% ether in hexanes gave 24 mg (21%) of the minor isomer **32**: IR (film) ν 1741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (brs), 5.38 (dt, J = 11.4, 2.1Hz), 4.88 and 4.68 (s and s), 4.88 (brs), 4.53 (brd), 3.02 (dd, J = 11.4, 3.0 Hz), 2.40–1.60 (m), 1.98 (d, J = 0.7 Hz), 1.71 (s), 1.67 (d, J = 0.7 Hz) ppm.

Further elution with 10% ether in hexanes gave 61 mg (54%) of the major isomer **30**: IR (film) ν 1741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (dt, J = 10.5, 2.1 Hz), 5.40 (d, J = 1.5 Hz), 4.85 and 4.75 (s and s), 4.78 (brd), 4.48 (brd), 2.60 (dd, J = 10.2, 10.2), 2.41–2.14 (m), 1.97 (s), 1.66 (s), 1.80–1.40 (m) ppm.

***rel*-(2*R*,3*R*)-2-(2-Propenyl)-11-methyl-1-oxabicyclo[8.2.1]-dodeca-10,12-dien-4-yn-3-yl Acetate (33).** To a solution of 9.0 mg (0.031 mmol) of the acetates **30** and **32** (70:30 mixture) in 1 mL of dry ether was added 125 mg (1.56 mmol) of γ-MnO_2. The suspension was stirred for 10 h and then filtered. The γ-MnO_2 was throughly washed with ether (~150 mL). The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with 10% ether in hexanes gave 7.5 mg (83%) of the furan **33**: IR (film) μ 2921, 1741, 1371 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (s), 5.52 (dt, J = 8.6, 2.5 Hz), 4.97 and 4.91 (s and s), 3.63 (d, J = 8.6 Hz), 2.57 (dt, J = 14.9, 4.2 Hz), 2.41 (ddd, J = 14.9, 9.5, 5.5 Hz), 2.04 (s), 1.90 (s), 1.84 (s), 2.20–1.80 (m), 1.60–1.54 (m), 1.23–1.14 (m) ppm; HRMS calcd for $C_{18}H_{22}O_3$ 286.1569, found 286.1563.

The assigned stucture was confirmed by a COSY experiment. Interestingly a NOE was observed between H2 and H3 in a NOESY experiment.

***rel*-(2*R*,3*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodeca-10,12-dien-4-yn-3-ol (34).** To a solution of 23 mg (0.080 mmol) of the acetate **33** in 1 mL of MeOH was added 5 mg of potassium carbonate. The solution was stirred for 1 h and then water was added. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 30% ether in hexanes gave 18 mg (92%) of the alcohol **34**: IR (film) ν 3404, 1374 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (s), 4.97 and 4.91 (s and s), 4.50 (m), 3.48 (d, J = 7.4 H), 2.55 (dt, J = 15.1, 4.7 Hz), 2.41 (ddd, J = 15.1, 6.1, 7.7 Hz), 1.90 (s), 1.87 (s), 2.10–1.10 (m) ppm; HRMS calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1457.

***rel*-(2*R*,3*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodeca-10,12-dien-4-yn-3-yl *p*-Nitrobenzoate (35). A. By Dehydrogenation of *p*-Nitrobenzoate 36.** To a solution of 25 mg (38 mmol) of the *p*-nitrobenzoate **36** in 2 mL of dry ether was added 275 mg (3.16 mmol) of γ-MnO_2. The suspension was stirred for 48 h and filtered. The γ-MnO_2 was throughly washed with ether (~200 mL), the filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with 5% ether in hexanes gave 4.0 mg (16%) of the unreacted dihydrofuran and 16.5 mg (66%) of the furan **35** as yellow needles: mp 92–93 °C; IR (CCl_4) ν 1723, 1520, 1344, 1267, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 and 8.19 (AB, J_{AB} = 9.0 Hz), 6.0 (s), 5.75 (dt, J = 8.7, 2.8 Hz), 4.97 (s), 3.84 (d, J = 8.8 Hz), 2.70–2.00 (m), 1.92 (s), 1.88 (s), 2.00–1.60 (m) ppm; HRMS calcd for $C_{23}H_{23}NO_5$ 393.1576, found 393.1570.

B. By Esterification of Alcohol 34. To a solution of 4.1 mg (0.017 mmol) of the alcohol **34** in 1 mL of THF was added 10 mg (0.50 mmol) of *p*-nitrobenzoic acid, 8.0 mg (0.16 mmol) of DCC, and 1 mg of DMAP. The solution was stirred 4 h and directly chromatographed on silica gel. Elution with 10% ether in hexanes gave 7.1 mg (quantitative) of the *p*-nitrobenzoate **35**.

***rel*-(1*R*,2*S*,3*S*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo-[8.2.1]dodec-11-en-4-yn-3-yl *p*-Nitrobenzoate (36).** To a solution of 20 mg (0.081 mmol) of the alcohol **29** in 1 mL of THF was added 41 mg (0.243 mmol) of *p*-nitrobenzoic acid, 34 mg (0.162 mmol) of DCC, and 5 mg of DMAP. The solution was stirred overnight and directly chromatographed on silica gel. Elution with 10% ether in hexanes gave 28.5 mg (89%) of the *p*-nitrobenzoate **36**: IR (film) ν 1728, 1523, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 and 8.14 (AB, J_{AB} = 8.0 Hz), 5.81 (d, J = 10.4 Hz), 5.45 (s), 4.89 (s), 4.85 (brs), 4.54 (brd), 2.83 (dd, J = ~10.0 and ~10.0 Hz), 2.50–2.10 (m), 1.80–1.40 (m), 1.71(s), 1.67 (s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 163.5, 150.5, 141.8, 139.6, 135.7, 130.8 (2C), 123.5 (2C), 123.4, 115.3, 89.7, 87.9, 85.1, 81.1, 65.9, 60.1, 33.5, 24.8, 24.4, 18.4, 12.5 ppm. The carbonyl carbon was not detected; HRMS calcd for $C_{22}H_{22}O_5N$ ($M - CH_3$) 380.1498, found 380.1493.

***rel*-(1*S*,2*S*,3*R*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo-[8.2.1]dodec-11-en-4-yn-3-yl *p*-Nitrobenzoate (37).** To a solution of 18 mg (0.073 mmol) of the alcohol **29** in 1 mL of benzene was added 48 mg (0.18 mmol) of PPh_3, 22 mg (0.18 mmmol) of *p*-nitrobenzoic acid, and 29 mL (0.183 mmol) of DEAD dropwise. The solution was stirred for 30 min, the solvent was removed at reduced pressure, and the residue was chromatographed on silica gel. Elution with 10% ether in hexanes afforded 18.9 mg (65%) of the *p*-nitrobenzoate **37**: IR (film) ν 2246, 1728, 1523, 1344, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 and 8.21 (AB, J_{AB} = 9.1 Hz), 5.64 (d, J = 1.5 Hz), 5.18 (brd, J = 7.9 Hz), 4.91 (s), 4.56 (brd), 2.59 (dd, J = 7.9, 1.5 Hz), 2.50–2.20 (m), 1.84 (s), 1.72 (s), 1.90–1.10 (m) ppm; HRMS calcd for $C_{22}H_{22}O_5N$ ($M - CH_3$) 380.1498, found 380.1496.

***rel*-(2*R*,3*S*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]dodeca-10,12-dien-4-yn-3-yl *p*-Nitrobenzoate (38). A. By Dehydrogenation of Dihydrofuran 37.** To a solution of 15 mg (38 mmol) of the *p*-nitrobenzoate **37** in 1 mL of dry ether was added 165 mg (1.90 mmol) of γ-MnO_2. The suspension was stirred for 100 h and filtered. The γ-MnO_2 was throughly washed with ether (~200 mL). The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with 10% ether in hexanes gave 4.1 mg (27%) of the cis product **38** and 7 mg (47%) of unreacted dihydrofuran: IR (film) ν 1728, 1533, 1343, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (AB, J = 8.6 Hz), 6.10 (s), 5.81 (dt, J = 5.1 Hz), 5.12 and 4.97 (s and s), 4.07 (d, J = 5.1 Hz), 2.52 (brt), 1.96 (s), 2.10–1.20 (m) ppm.

When the above procedure was carried out on *p*-nitrobenzoate **39**, a small amount of furan product was formed after 24 h according to TLC analysis.

B. By Esterification of Alcohol 41. To a solution of 10 mg (0.041 mmol) of the alcohol **41** in 1 mL of THF was added 16.8 mg (0.081 mmol) of DCC, 20.4 mg (0.12 mmol) of *p*-nitrobenzoic acid, and 1 mg of DMAP. The solution was stirred for 2 h and directly chromatographed on silica gel. Elution with 10% ether in hexanes gave 15.2 mg (95%) of the benzoate **38**.

***rel*-(1*S*,2*R*,3*S*,10*R*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo-[8.2.1]dodec-11-en-4-yn-3-yl *p*-Nitrobenzoate (39).** The inversion procedure described for *p*-nitrobenzoate **37** was followed with 6.2 mg (0.025 mmol) of the alcohol **31**. The solution was stirred for 1 h and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ether in hexanes afforded 7.4 mg (74%) of the *p*-nitrobenzoate **39**: IR (film) ν 1723, 1528, 1338, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 and 8.20 (AB, J_{AB} = 9.0 Hz), 5.80 (s), 5.76 (d, J = 1.5 Hz), 5.20 (brs), 4.86 and 4.76 (s and s), 4.65 (brd), 3.09 (dd, J = 1.5, 3.7 Hz), 2.45–2.20 (m), 1.83 (s), 1.81 (s), 1.80–1.40 (m) ppm.

(*E*)-2,6-Dimethyl-1,4-dioxabicyclo[11.2.1]tetradeca-2,4,6-trien-12-yne (40E and 40Z). The dehydrogenation procedure described for **38** was employed with 13 mg (0.53 mmol) of the dihydrofuran ether **24** (18 h reaction time). The crude product was chromatographed on silica gel. Elution with 5% ether in hexanes gave 4.8 mg (37%) of the furan ether **40E** along with 2.2 mg (16%) of the unreacted dihydrofuran ether. The *E*-isomer partially isomerized to the *Z*-isomer on standing: ^1H NMR (300 MHz, $CDCl_3$. The italicized peaks are attributable to **40E**) δ *6.17* and 6.04 (s), *6.01* and 5.94 (s), 4.73 and *4.03* (s), 4.09 (t, J = 2.1 Hz), *4.07* (s), 2.62 (m), 2.16 (d), *1.92* and 1.88 (s), 1.87 (s), 2.1–1.3 (m) ppm.

(*Z*)-2,6-Dimethyl-1,4-dioxabicyclo[11.2.1]tetradec-2,4,6-trien-12-yne (40Z). To a suspension of 60 mg (2.49 mmol) of NaH and 658 mg (2.49 mmol) of 18-crown-6 in 20 mL of toluene at reflux was added 100 mg (0.356 mmol) of the chloro alcohol **51** in 13 mL of toluene dropwise over 1.5 h. The solution was refluxed for 1.5 h and cooled to room temperature. Saturated NH_4Cl was added and the aqueous layer was extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on deactivated silica gel (5% Et_3N). Elution with 20% ether in hexanes gave 59.7 mg (69%) of the cyclic ether **40Z**: IR (film) ν 1421, 1528, 1431 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (1H, brs), 5.94 (1H, s), 4.73 (2H, s), 4.09 (3H, t, J = 2.1 Hz), 2.59 (2H, t, J = 6.0 Hz), 1.88 (3H, s), 1.87 (3H, s), 2.20–1.20 (6H, m) ppm; ^{13}C NMR (75MHz, $CDCl_3$) δ 150.0, 149.5, 131.2, 117.5, 116.1, 113.0, 87.3, 67.1, 56.4, 26.7, 24.8, 24.7, 21.7, 18.7, 9.5. One of the alkyne carbons is not detected; HRMS calcd for $C_{13}H_{20}O_2$ 244.1463, found 244.1473.

***rel*-(2*R*,3*S*)-2-(2-Propenyl)-11-methyl-10-oxabicyclo[8.2.1]deca-10,12-dien-4-yn-3-ol (41). A. [2,3] Wittig Ring Contraction of 40E/Z Mixture.** To a solution of 7.0 mg (0.0286 mmol) of the cyclic ether **40** (*E*:*Z*; 40:60) in 3 mL of 1:1 THF–pentane was added 0.12 mL of 2.5 M *n*-BuLi in hexane dropwise at −78 °C. The solution was stirred for 30 min and quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure (The ^1H NMR spectrum of crude **41** indicated only the cis-isomer). The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 3.7 mg (53%) of the *cis*-alochol **41**: IR (film) ν 3448, 1672, 1453, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (s), 5.24 and 5.06 (s and s), 4.58 (brs), 3.73 (d, J = 3.1 Hz), 2.65–2.40 (m), 1.93 (s), 1.89 (s), 2.20–1.50 (m) ppm; ^{13}C NMR (75MHz, $CDCl_3$) δ 149.4, 148.4, 140.7, 116.6, 114.6, 110.7, 88.5, 79.8, 63.8, 53.3, 25.9, 25.5, 25.4, 22.8, 20.3, 9.8; HRMS calcd for 244.1463, found 244.1460.

B. [2,3] Wittig Ring Contraction of 40Z. To a solution of 0.083 mL (0.491 mmol) of 2,2,6,6-tetramethylpiperidine in 1 mL of THF was added 0.196 mL (0.491 mmol) of 2.5 M *n*-BuLi in

hexanes dropwise at 0 °C. The solution was stirred for 10 min and then cannulated to a solution of 20 mg (0.0819 mmol) of the bicyclic ether **40Z** in 0.9 mL of 8:1 THF–pentanes dropwise at −78 °C. The resulting yellow solution was stirred for 30 min and quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The ^1H NMR of the crude product showed only the *cis*-isomer. The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 14.6 mg (73%) of the *cis*-alcohol **41**.

C. Hydrolysis of p-Nitrobenzoate 38. To a solution of 25.8 mg (0.0656 mmol) of the *p*-nitrobenzoates **38** and **35** (85:15, see below) in 1 mL of methanol was added 3 mg of K_2CO_3. The solvent was removed at reduced pressure. The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 13.3 mg (82%) of the *cis*-alcohol **41** and 1.6 mg (11%) of the *trans*-alcohol **34**.

Attempted Mitsunobu Inversion of 35. To a solution of 20.7 mg (0.084 mmol) of the alcohol **35** in 1 mL of benzene was added 15.4 mg (0.126 mmol) of *p*-nitrobenzoic acid and 33 mg (0.126 mmol) of PPh_3. The solution was cooled to 0 °C and then 19.8 mL (0.126 mmol) of DEAD was added dropwise. The solution was stirred for 20 min and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ether in hexanes gave 25.8 mg (78%) of an inseparable 85:15 mixture of the *trans*-**35** and *cis*-*p*-nitrobenzoate **38**.

3-Methyl-2-[(E)-4-hydroxy-1-butenyl]furan (43). To a solution of 3.30 g (15.4 mmol) of the diol **42** in 35 mL of THF was added 10.2 g (38.5 mmol) of *t*-BuOK portionwise. An exothermic reaction ensued and the mixture was cooled to 0 °C. The ice bath was removed and the mixture was stirred for 10 min at room temperature. It was then diluted with ether and quenched with 10% aqueous K_2CO_3. The aqueous layer was extracted with ether three times. The extracts were washed with 10% aqueous K_2CO_3 and then with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 50% ether in hexanes gave 1.55 g (66%) of the vinyl furan **43** (*E*:*Z*; 95:5), 401 mg (12%) of the uneliminated furan MOM ether,[18] and 191 mg (~9%) of 3-methyl-2-(1,3-butadienyl)furan, the product of *bis*-elimination: IR (film) ν 3356, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, d, J = 1.6 Hz, H5), 6.31 (1H, d, J = 15.8 Hz, vinyl H), 6.19 (1H, d, J = 1.6 Hz, H4), 6.01 (1H, dt, J = 15.8, 7.4 Hz, vinyl H), 3.72 (2H, t, J = 6.3 Hz, CH_2OH), 2.45 (2H, dt, J = 7.4, 6.2 Hz, allylic CH_2), 2.01 (3H, s, CH_3), 1.57 (1H, brs, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 140.8, 123.5, 119.6, 116.7, 113.8, 62.1, 36.5, 9.9; HRMS calcd for $C_9H_{12}O_2$ 152.0835, found 152.0837.

3-Methyl-2-(4-hydroxybutyl)furan (44). To a solution of 1.85 g (12.2 mmol) of the vinyl furan **43** in 20 mL of ethyl acetate was added 370 mg of 5% palladium on carbon. The suspension was stirred for 4.5 h under an atmosphere of hydrogen. The catalyst was removed by filteration and the filtrate was concentrated under reduced pressure to give 1.70 g (92%) of the alcohol **44**: IR (film) ν 3343, 1508, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (1H, d, J = 1.8 Hz), 6.13 (1H, d, J = 1.8 Hz), 3.62 (2H, t, J = 6.4 Hz), 2.57 (2H, t, J = 6.9 Hz), 1.93 (3H, s), 1.71–1.50 (4H, m) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 140.1, 114.2, 113.1, 63.0, 32.5, 25.9, 25.0, 10.2; HRMS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0994.

3-Methyl-2-[4-[(p-toluenesulfonyl)oxy]butyl]furan (45). To a solution of 1.70 g (11.0 mmol) of the alcohol **44** in 15 mL of CH_2Cl_2 was added 2.67 mL (33.0 mmol) of pyridine and 4.20 g (22 mmol) of TsCl. The solution was stirred overnight and then 2% HCl was added. The aqueous layer was separated and extracted with ether. The extracts were washed with saturated $NaHCO_3$ and then with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 2.83 g (83%) of the tosylate **45**: IR (film) ν 1600, 1513, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 and 7.34 (4H, AB, J = 8.3 Hz), 7.15 (1H, d, J = 1.8 Hz), 6.10 (1H, d, J = 1.8 Hz), 3.99 (2H, t, J = 6.1 Hz), 2.49 (2H, brt), 2.42 (3H, s), 1.66–1.56 (4H, m) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 150.6, 145.0, 140.3, 133.6, 130.2 (2C), 128.3 (2C), 114.5, 113.1, 70.7, 28.6, 25.4, 24.7, 22.0, 10.1; HRMS calcd for $C_{16}H_{20}O_4S$ 308.1082, found 308.1075.

3-Methyl-2-(7-hydroxy-5-heptynyl)furan (47). To a solution of 4.65 g (16.1 mmol) of 3-[tetrahydropyranyl)oxy]-1-propyne in 15 mL of DMPU was added 6.44 mL (16.1 mmol) of 2.5 M *n*-BuLi in hexanes dropwise at 0 °C. The solution was stirred for 30 min and 3.30 g (10.7 mmol) of the tosylate **45** in 15 mL of THF was added dropwise. The solution was stirred for 5 h and saturated NH_4Cl was added. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 1% ether in hexanes gave 4.0 g of the desired acetylene **46** as a mixture with unreacted propargyl THP ether. The mixture was carried to the next step without further purification. An analytical sample was prepared by removal of unreacted propargylic ether from the mixture under reduced pressure: IR (film) ν 3344, 1513, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, d, J = 1.8 Hz), 6.18 (1H, d, J = 1.8 Hz), 4.79 (1H, t, J = 3.2 Hz), 4.27 and 4.17 (2H, ABX, J_{AB} = 15.2, J_{BX} = 2.2, J_{BX} = 2.2 Hz), 3.88–3.46 (2H, m), 2.54 (2H, t, J = 7.3 Hz), 2.21 (2H, tt, J = 7.0, 2.2 Hz), 1.93 (3H, s), 1.86–1.23 (8H, m) ppm; HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1736.

To a solution of 4.0 g of the above THP ether **46** in 15 mL of ethanol was added 1.2 g (4.77 mmol) of PPTS. The solution was stirred for 36 h at room temperature and water was added. The aqueous layer was separated and extracted with ether five times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 20% ether in hexanes gave 1.55 g (75% for two steps) of the alcohol **47**: IR (film) ν 3354 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (1H, d, J = 1.8 Hz), 6.13 (1H, d, J = 1.8 Hz), 4.22 (2H, t, J = 2.1 Hz), 2.55 (2H, t, J = 7.2 Hz) , 2.21 (2H, tt, J = 7.0, 2.2 Hz), 1.93 (3H, s), 1.87–1.41 (5H, m) ppm; ^{13}C NMR δ 151.2, 140.1, 114.2, 113.1, 86.5, 79.0, 51.7, 28.3, 28.0, 25.7, 18.9, 10.2; HRMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1157.

3-Methyl-2-(7-hydroxy-5-heptynyl)-5-formylfuran (48). To a solution of 130 mg (0.676 mmol) of the hydroxy furan **47** in 1.5 mL of THF was added 1.39 mL (2.37 mmol) of 1.7 M *t*-BuLi in pentane dropwise at −78 °C. The solution was stirred for 1 h and then warmed to room temperature over 20 min. The solution was recooled to −78 °C and 0.523 mL (6.76 mmol) of dry DMF was added in one portion. The ice bath was removed and the solution was stirred for 1.5 h at room temperature. Water was added and the aqueous layer was separated and extracted with CH_2Cl_2 three times. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 75% ether in hexanes gave 75.8 mg (74%) of the aldehyde **48** containing an inseparable conjugated aldehyde impurity: IR (film) ν 3405, 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.44 (1H, s), 7.24 (1H, s), 4.23 (2H, d, J = 2.2 Hz), 2.67 (2H, t, J = 7.5 Hz) , 2.23 (2H, tt, J = 7.0, 2.2 Hz), 2.01 (3H, s), 1.83–1.49 (4H, m) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 159.7, 151.0, 126.0, 118.7, 85.8, 79.4, 51.7, 28.3, 27.2, 26.3, 18.8, 10.1; HRMS calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1093.

3-Methyl-2-(7-hydroxy-5-heptynyl)-5-[(Z)-2-methyl-2-carbomethoxy-1-propenyl] furan (49). To a solution of 1.97 g (5.95 mmol) of bis(2,2,2-trifluoroethyl) methoxycarbonyl ethylphosphonate and 3.19 g (11.9 mmol) of 18-crown-6 in 5 mL of THF was added 11.9 mL (5.95 mmol) of 0.5 M KHMDS in toluene dropwise at −78 °C. The solution was stirred for 30 min and then 524 mg (2.38 mmol) of the aldehyde **48** in 3 mL of THF was added dropwise. The solution was stirred for 40 min and quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with CH_2Cl_2. The extracts were washed with 10% aqueous K_2CO_3 and then with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in 5 mL of THF and treated with 7.14 mL of 1.0 M TBAF in THF. The solution was stirred for 30 min and water was added. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 50% ether in hexanes gave 547 mg (79%) of the *Z* conjugated ester **49**: IR (film) ν 3426, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (1H, s), 6.40 (1H, brs), 4.23 (2H, t, J = 2.2 Hz), 3.78 (3H, s), 2.53 (2H, t, J = 7.2

Hz), 2.21 (2H, tt, J = 7.0, 2.2 Hz), 2.03 (3H, d, J = 1.4 Hz), 1.92 (3H, s), 1.80–1.45 (4H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 152.1, 148.0, 124.2, 122.8, 116.8, 116.4, 79.0, 51.7, 51.2, 27.9, 27.3, 25.5, 21.4, 18.5, 9.8. One of acetylenic carbons is not detected; HRMS calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1510.

3-Methyl-2-(7-chloro-5-heptynyl)-5-[(*Z*)-2-methyl-3-carbomethoxy-1-propenyl] furan (50). To a solution of 250 mg (0.86 mmol) of the alcohol **49** in 1.5 mL of DMF was added 146 mg (3.44 mmol) of LiCl and 0.249 mL (3.44 mmol) of 2,6-lutidine. The solution was cooled to 0 °C and 0.199 mL (2.58 mmol) of MsCl was added dropwise. The solution was stirred for 5 h and quenched with water. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ether in hexanes gave 220 mg (83%) of the chloride **50**: IR (film) ν 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (1H, s), 6.44 (1H, d, J = 2.0 Hz), 4.12 (2H, t, J = 2.4 Hz), 3.77 (3H, s), 2.54 (2H, t, J = 7.3 Hz), 2.22 (2H, tt, J = 7.2, 2.2 Hz), 2.03 (3H, d, J = 1.0 Hz), 1.93 (3H, s), 1.80–1.45 (4H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 152.0, 148.0, 124.9, 122.5, 116.9, 116.7, 87.2, 75.3, 51.6, 31.2, 27.7, 27.4, 25.5, 21.5, 18.6, 9.8; HRMS calcd for $C_{17}H_{21}ClO_3$ 308.1179, found 308.1179.

3-Methyl-2-(7-chloro-5-heptynyl)-5-[(*Z*)-2-methyl-3-hydroxy-1-propenyl]furan (51). To a solution of 49 mg (0.159 mmol) of the ester **50** in 1 mL of CH_2Cl_2 was added 0.317 mL of 1.0 M DIBAH in hexanes at −78 °C. The solution was stirred for 1 h and quenched with saturated Rochelle salt. The aqueous layer was separated and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on deactivated silica gel (5% Et_3N). Elution with 50% ether in hexanes gave 39 mg (87%) of the chloro alcohol **51**: IR (film) ν 3364, 2236, 1431 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 6.37 (1H, brs), 5.91 (1H, s), 4.43 (2H, brs), 3.68 (3H, t, J = 2.3 Hz), 2.32 (2H, t, J = 7.3 Hz), 1.88 (2H, brt), 1.86 (3H, s), 1.76 (3H, s), 1.70–1.20 (4H, m) ppm; ^{13}C NMR (75 MHz, C_6D_6) δ 150.2, 136.4, 115.9, 115.8, 112.5, 87.3, 75.9, 62.8, 31.2, 27.9, 27.8, 25.5, 22.0, 18.6, 9.8. One of furan carbons is not detected; HRMS calcd for $C_{16}H_{21}ClO_2$ 280.1230, found 280.1233.

Acknowledgment. Support for these studies was provided by reseach Grant R01-GM29475 from the National Institute of General Medical Sciences. X-ray structure analysis was performed by Dr. Krzysztof Lewinski.

Supplementary Material Available: Experimental procedures for compounds **3–9, 15–23, iii, iv,** and **42**; ^{1}H NMR spectra of compounds **5, 6, 8–13, 15, 16, 18, 19, 21–25, 27–41, 43–50**; ORTEP plot for compound **35** (57 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.