Synthesis of Furans by Base-Catalyzed Cyclization–Isomerization of β- and γ-Alkynyl Allylic Alcohols

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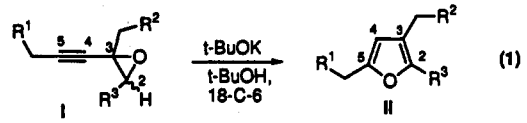
β- and γ-alkynyl allylic alcohols **3**, **13**, **26**, available through Pd-mediated coupling of appropriate vinylic halides and terminal alkynes, cyclize and subsequently isomerize to furans **4**, **17**, and **32** upon treatment with KO-*t*-Bu in *t*-BuOH–THF at 25–60 °C. The methodology has been used to prepare 2,3-, 2,4-, and 2,3,5-substituted furans. Reactions in *t*-BuOD as cosolvent lead to deuterium incorporation consistent with concurrent pathways in which direct 5-*exo-dig* or 5-*endo-dig* cyclization of the alkynyl allylic alcohol competes with prior isomerization to an allene intermediate which subsequently cyclizes by 5-*exo*- or 5-*endo-dig* pathways.

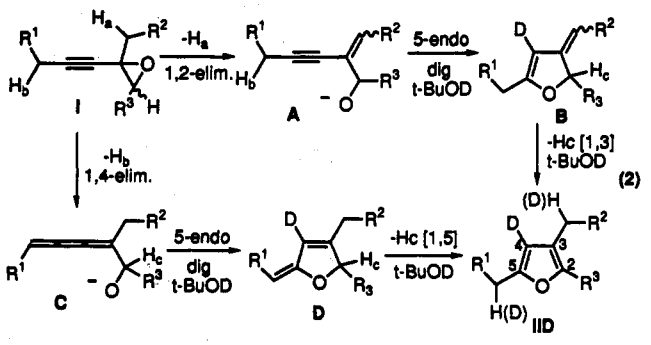
Introduction

We recently described a new synthesis of furans through base-catalyzed isomerization of alkynyloxiranes (eq 1).[1]



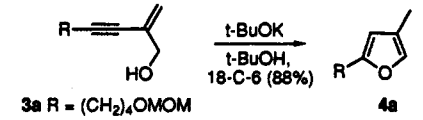
(1)

Deuterium-labeling studies showed that the reaction proceeds by initial 1,2- and 1,4-elimination and subsequent anionic cyclization of the resulting vinylacetylene and cumulene alkoxides **A** and **C** to intermediates **B** and **D** (nonisolable) which isomerize to the furan products **IID** (eq 2). Only partial deuteration took place at the C-5 CH_2



(2)

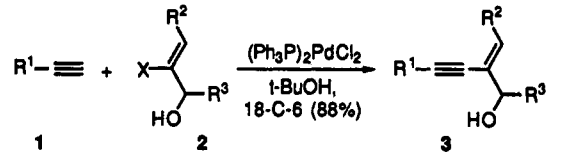
and C-3 CH_3 positions (R^2 = H) indicative of conducted tour mechanisms for these isomerizations.[2] Additional support for the 1,2-elimination pathway came from our finding that the 2-alkynyl-2-propenol **3a** affords furan **4a** in 88% yield upon treatment with KO-*t*-Bu (eq 3). As we



(3)

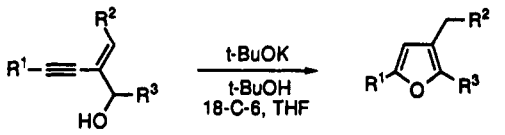
examined these reactions in greater detail we discovered additional alkoxide–catalyzed syntheses of furans which we now disclose.

Table I. Synthesis of β-Alkynyl Allylic Alcohols 3



entry	R^1	R^2	R^3	X	yield, %
1	$(CH_2)_4OMOM$ (**1a**)	H	H	Br (**2a**)	85 (**3a**)
2	$(CH_2)_4OMOM$ (**1a**)	H	Et	Br (**2b**)	91 (**3b**)
3	*i*-Pr (**1b**)	H	Et	Br (**2b**)	92 (**3c**)
4	CH_2OMOM (**1c**)	Bu	H	I (**2c**)	73 (**3d**)
5	CH_2OMOM (**1c**)	Bu	Me	I (**2d**)	58 (**3e**)

Table II. Base-Catalyzed Cyclization–Isomerization of β-Alkynyl Allylic Alcohols to Furans



entry	series	R^1	R^2	R^3	time,[a] h	yield, %
1	**a**	$(CH_2)_4OMOM$	H	H	2[b]	88
2	**b**	$(CH_2)_4OMOM$	H	Et	3	96
3	**c**	*i*-Pr	H	Et	6	84
4	**d**	CH_2OMOM	Bu	H	3	66
5	**e**	CH_2OMOM	Bu	Me	3	78[c]

[a] At 25 °C. [b] At 60 °C. [c] See eq 4.

β-Alkynyl Allylic Alcohols. Alcohols **3a–e** were prepared by Pd-promoted coupling of the terminal alkynes **1a–c** with vinylic halides **2a–d** (Table I).[3] Exposure of these alcohols to KO-*t*-Bu in THF–*t*-BuOH containing 18-crown-6 at 25–60 °C afforded the furans **4a–e** in moderate to high yield (Table II). In the case of alcohol **3e** (entry 5) a small amount of the elimination product, furan **5**, was also produced (eq 4). Presumably, this byproduct arises through 1,6-elimination of the initial cyclization product **E** and subsequent isomerization of the exo methylene enol ether **F**.

The cyclohexenylalkyne **3f** afforded a different type of elimination byproduct upon treatment with KO-*t*-Bu. In

(1) Marshall, J. A.; DuBay, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1450.
(2) Almy, J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 4459.
(3) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.

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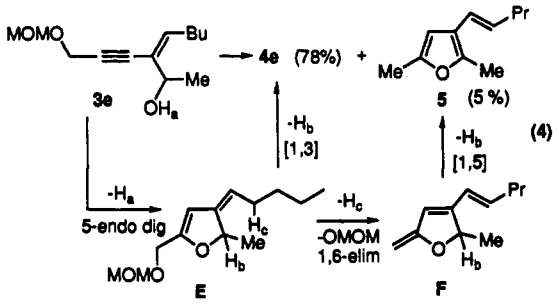
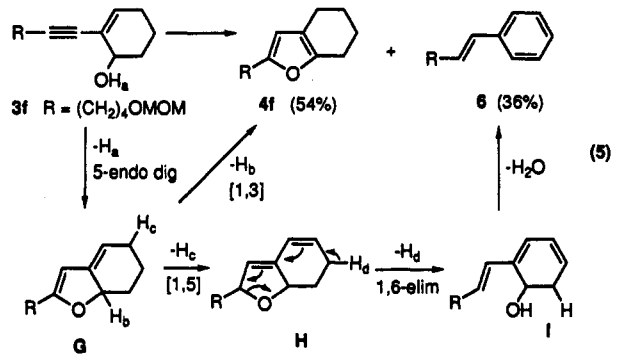
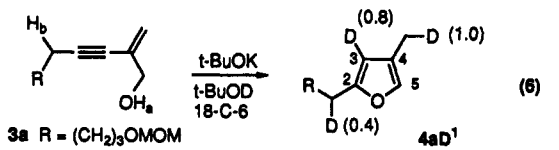


this case the styrene **6** was isolated in 36% yield along with furan **4f** (eq 5). This unexpected product is thought to arise through isomerization of the initial cyclic product



G to **H** followed by 1,6-elimination to cyclohexadienol **I** and dehydration. Intermediate **I** could also be formed from **3f** by sequential 1,5 hydrogen shifts.

To secure evidence for the major furan-forming pathways we examined the reaction of the alkynylpropenol **3a** in *t*-BuOD–THF. The product, furan **4aD^1**, incorporated deuterium at the C-4 CH_3 (1.0D), C-3 (0.8D), and the C-2 CH_2 (0.4D) positions according to analysis of the ^{1}H NMR spectrum (eq 6).[4] A control experiment with furan **4a**,



18-C-6, and *t*-BuOK in *t*-BuOD–THF under the cyclization conditions showed no deuterium uptake at any of these three positions. The presence of deuterium at the C-2 CH_2 implicates the allenylpropenol **K** as shown in Figure 1. This intermediate could cyclize by a 5-*exo-dig* or a 5-*endo-dig* pathway[5] leading to intermediates **L** and **M** whose subsequent isomerization would afford the trideuterio furan **4aD^3**. Direct 5-*endo-dig* cyclization of the alkynylpropenol would lead via **J** to the dideuterated product **4aD^2**. The isolated product **4aD^1** contains less than one deuterium at C-3, contrary to the expectation from Figure 1. Possibly the 1,3-isomerization of vinylacetylene **3a** to **K** takes place, in part, by a conducted tour mechanism without deuterium uptake.[2]

As a test of the allenylpropenol pathway we examined the cyclization of alcohol **10** (eq 7). Treatment of this

(4) (a) Compounds, both actual and hypothetical, containing deuterium are designated by the compound number and the suffix **D**. Isotopomers are distinguished through use of superscripts corresponding to the order of their appearance in the discussion. (b) Control experiments established incorporation of deuterium at C-5 of the furan products under the experimental conditions.

(5) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

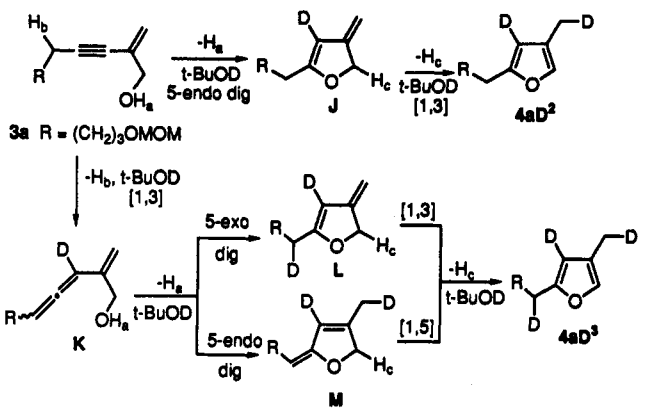
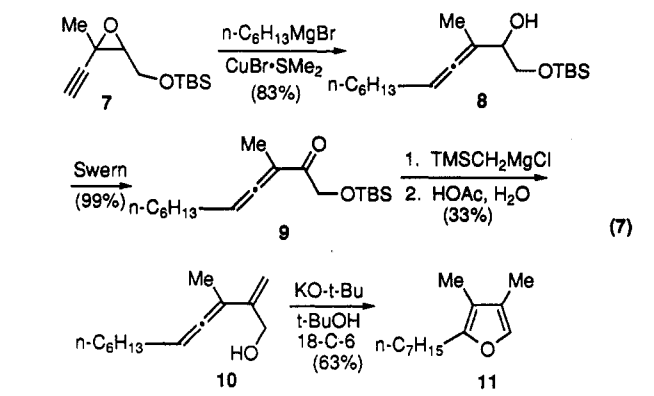
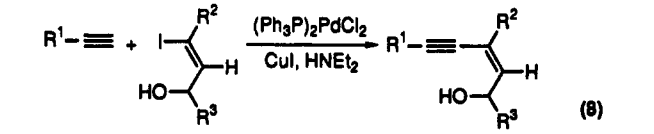


Figure 1. Proposed cyclization–isomerization pathway for β-alkynyl allylic alcohols.

alcohol with KO-*t*-Bu, as for **3a–f**, led to furan **11** in 63% yield.

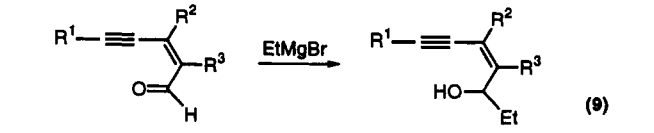


γ-Alkynyl Allylic Alcohols. In view of the foregoing results with **3a–f** it seemed reasonable to expect the isomeric (*Z*)-alkynylpropenols **13** to undergo an analogous base-catalyzed cyclization. The prototype system **13a** was prepared by Pd-promoted coupling of alkyne **1a** with the (*Z*)-3-iodo-2-propen-1-ol **12a** (eq 8).[3] Exposure of **13a** to

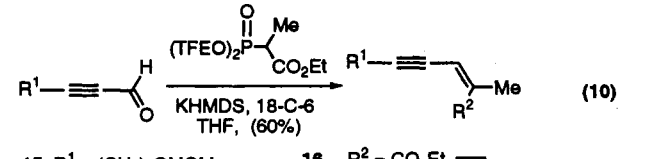


1a R^1 = $(CH_2)_4OMOM$, **12a** R^2 = CH_3, R^3 = H — **13a**
1d R^1 = Bu, **12b** R^2 = $(CH_2)_2OMOM$, R^3 = Et — **13e**

the cyclization conditions effected its smooth conversion to furan **17a** in 71% yield (Table III). The homologues **13b–d** were prepared as indicated in eqs 9 and 10. The



14a R^1 = $(CH_2)_4OMOM$, R^2 = Me, R^3 = H (80%) — **13b**
14b R^1 = $(CH_2)_3OMOM$, R^2 = H, R^3 = Me (76%) — **13d**



15 R^1 = $(CH_2)_3OMOM$ — **16** R^2 = CO_2Et → DIBAH → **13c** R^2 = CH_2OH

Table III. Base-Catalyzed Cyclization–Isomerization of *cis*-γ-Alkynyl Allylic Alcohols to Furans

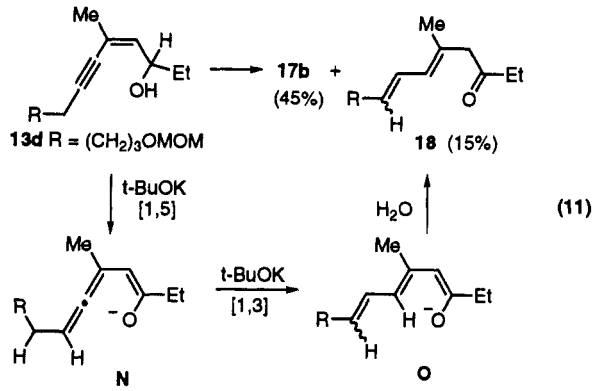
13 17

entry	series	R^1	R^2	R^3	R^4	time,[b]	yield, %
1	**a**	$(CH_2)_4OR^a$	Me	H	H	2[c]	71 (**17a**)
2	**b**	$(CH_2)_4OR^a$	Me	H	Et	3	45[d] (**17b**)
3	**c**	$(CH_2)_3OR^a$	H	Me	H	2	80 (**4a**)
4	**d**	$(CH_2)_3OR^a$	H	Me	Et	3	82 (**4b**)
5	**e**	Bu	$(CH_2)_2OR^a$	H	Et	3	9[e] (**17e**)

[a] R = MOM. [b] At 25 °C. [c] At 60 °C. [d] See eq 11. [e] See eq 12.

former two cyclized to the furans **17b** and **4a**, respectively (Table III, entries 2 and 3). Alcohols **13c** and **13d** afford the same furan products, **4a** and **4b**, as the exocyclic isomers **3a** and **3b** but in somewhat lower yield (Table III, entries 3 and 4 vs Table II, entries 1 and 2).

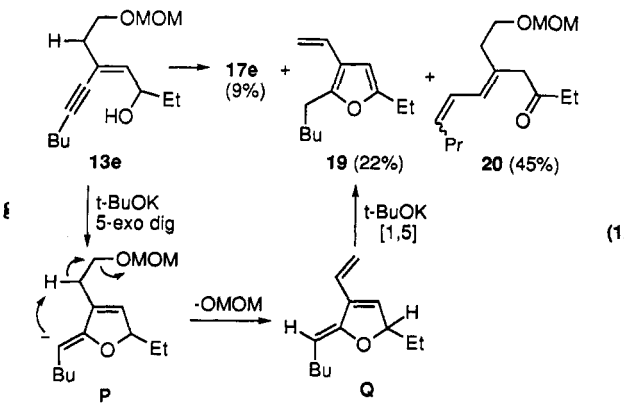
Alcohol **13b** gave furan **17b** in only 45% yield (entry 2). This product was accompanied by 15% of dienone **18** as an *E*/*Z* mixture (eq 11). Presumably, **18** results from



(11)

alkoxide-assisted 1,5-isomerization of the carbinyl H leading to enolate **N** followed by 1,3-allene–diene prototropy to give the extended enolate **O** which undergoes kinetic protonation upon workup.

Base treatment of carbinol **13e** afforded the furan **17e** in only 9% yield (Table III, entry 5). In this case the vinylfuran **19** was isolated in 22% yield along with dienone **20** (*E*:*Z* mixture) in 45% yield. Furan **19** is thought to arise through intramolecular vinyl anion-assisted elimination of the initial cyclization intermediate **P**, as illustrated in eq 12. The formation of dienone **20** parallels that of **18** as outlined in eq 11.



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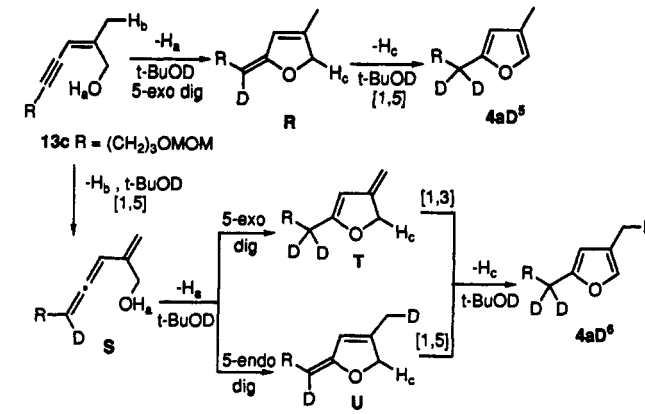
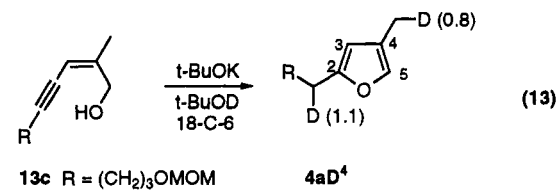


Figure 2. Proposed cyclization–isomerization pathways for γ-alkynyl allylic alcohols.

To probe the furan-forming pathways in more detail we carried out the cyclization of alcohol **13c** in *t*-BuOD–THF and analyzed the ^1H NMR spectrum of the product **4aD**[4] to ascertain the position and relative incorporation of deuterium (eq 13). As expected, the C-2 CH_2 substituent

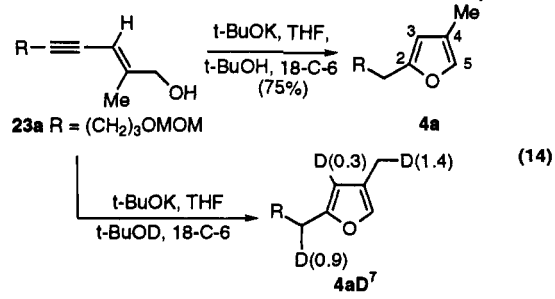


(13)

was significantly deuterated (1.1D).[4] However, incorporation of deuterium at the C-4 CH_3 (0.8D) indicated the intervention of pathways other than direct 5-*exo*-*dig* cyclization. These are depicted in Figure 2. Thus, 1,5-isomerization of **13c** would lead to the allenylpropenol **S** which can then cyclize to intermediates **T** or **U**, analogous to **L** or **M** in Figure 1. As before, incomplete deuteration at the C-2 CH_2 (or C-4 CH_3) can be attributed to competing conducted tour pathways for the prototropic shifts.[2]

On the basis of the deuterium studies it can be surmised that the *cis*-γ-alkynyl allylic alcohol **13c** undergoes appreciable isomerization to the vinyl allene **S** prior to cyclization. Accordingly, the cis geometry of **13c** should not be a prerequisite for cyclization. To test this hypothesis we synthesized a series of *trans*-γ-alkynyl allylic alcohols (**23a–d**) by Swern–Wittig homologation[6] of propargylic alcohols **21a–c** and then DIBAH reduction of the intermediate (*E*)-conjugated esters **22a–d** (Table IV).

As expected, base treatment of alcohol **23a** under the standard conditions afforded furan **4a** in high yield (eq 14). When the reaction was performed in *t*-BuOD–THF

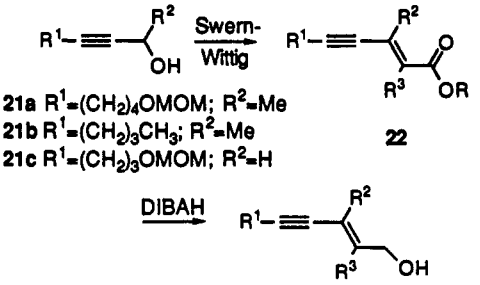


(14)

considerable deuterium incorporation took place at the C-4 CH_3 position (1.4D) as well as C-3 (0.3D), suggesting

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

Table IV. Synthesis of *trans*-γ-Alkynyl Allylic Alcohols 23

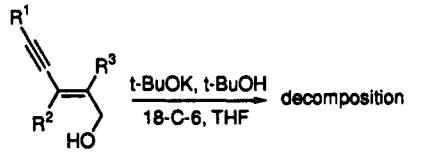


entry	series	R¹	R²	R³	yield, % 22	23
1	a	$(CH_2)_3OMOM$	H	Me	83[a]	95
2	b	$(CH_2)_4OMOM$	Me	H	63[b]	70
3	c	$(CH_2)_3CH_3$	Me	Me	89[c]	95
4	d	$(CH_2)_3OMOM$	H	H	82[d]	95

[a] $Ph_3PC(CH_3)CO_2Me$ (R = Me). [b] $(MeO)_2P(O)CH_2CO_2Me$, NaH, DMSO (R = Me, Z:E = 60:40). [c] KHMDS, THF, 18-C-6 $(TFEO)_2P(O)CH(Me)CO_2Et$, (R = Et). [d] Ph_3PCHCO_2Me (R = Me).

that reversible exchanges occur en route to the allene and the (*Z*)-alkynylpropenol intermediates which then cyclize as outlined in Figure 2.[4]

Base treatment of the other *trans*-γ-alkynyl allylic alcohols **23b–d** led to extensive decomposition (eq 15).

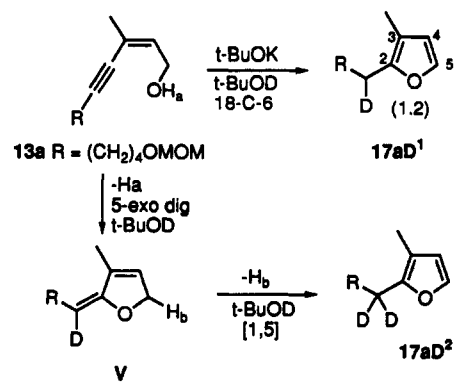


(15)

23b $R^1 = (CH_2)_4OMOM$, $R^2 = Me$, $R^3 = H$
23c $R^1 = (CH_2)_3CH_3$, $R^2 = R^3 = Me$
23d $R^1 = (CH_2)_3OMOM$, $R^2 = R^3 = H$

This is to be expected for **23b** and **23d** as they lack a substituent at R^3 thereby precluding conversion to allenyl isomers. However, **23c**, with a CH_3 at this position, should isomerize. Furthermore, we have already demonstrated that the analogous allenyl compound **10** cyclizes to furan **11** in 63% yield (eq 7). Evidently, the CH_3 substituent R^2 in **23c** impedes acetylene–allene prototropy relative to alternative nonproductive reactions.

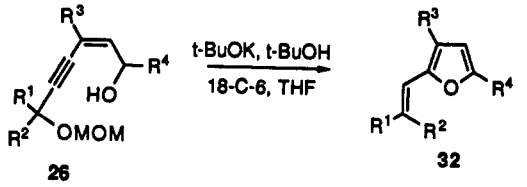
Interestingly, when the *cis*-γ-alkynyl allylic alcohol **13a** was treated with KO-*t*-Bu in *t*-BuOD the product **17aD**[1] was exclusively deuterated at the C-2 CH_2, after correction for furan exchange at the 5-position (eq 16). Accordingly, the major pathway is direct 5-*exo-dig* cyclization followed



(16)

by 1,5-prototropy.[5] Incomplete deuterium incorporation can be explained by a conducted tour proton transfer pathway.[2]

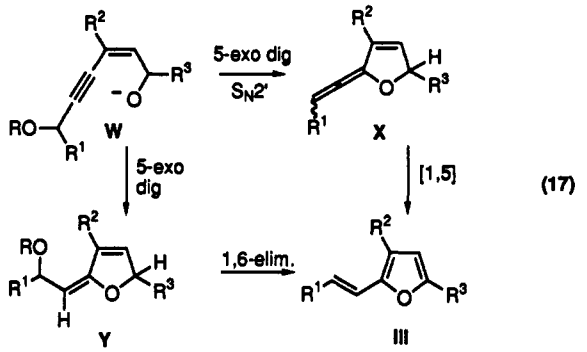
Table V. Base-Catalyzed Cyclization–Isomerization of γ-Alkynyl Allylic Alcohols to Vinyl Furans



entry	series	R¹	R²	R³	R⁴	yield,[a] %
1	a	H	H	Bu	H	77
2	b	H	H	Bu	Et	97
3	c	n-C_6H_{13}	H	Me	H	73[b,c]
4	d	n-C_6H_{13}	Me	Me	H	85[d]

[a] At 25 °C. [b] E:Z = 5:1. [c] Contains 11% of adduct **33** (eq 20). Prolonged reaction time (8 h) afforded 84% of (*E*)-**32c**. [d] E:Z = 2:1.

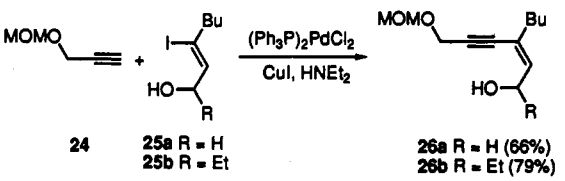
With this result in mind we examined *cis*-γ-alkynyl allylic alcohols with a potential leaving group (OR) at the propargylic center in the hopes of facilitating cyclization by a direct 5-*exo-dig* S_N2' pathway, as depicted in eq 17.



(17)

Subsequent isomerization would afford the vinylfuran **III**. Such structures are of interest as possible subunits of various natural products.[7]

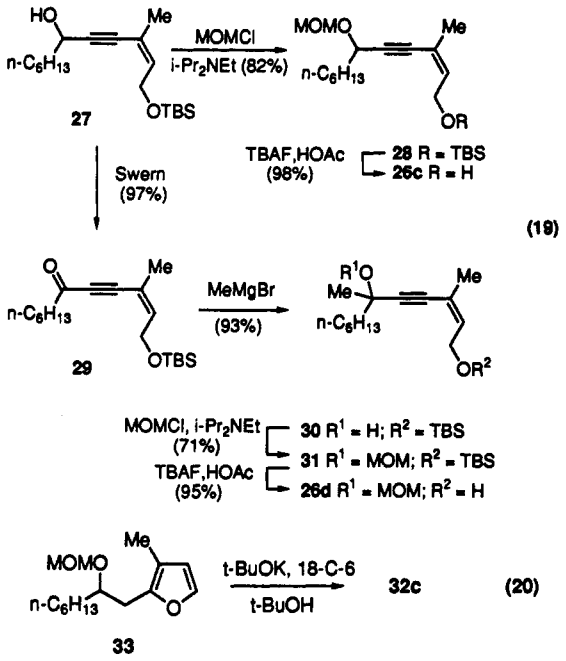
Appropriate allylic alcohols, **26a** and **26b**, were prepared by Pd-catalyzed coupling of vinylic iodides **25a** and **25b** with MOM-protected propargyl alcohol **24** (eq 18).[3] Upon



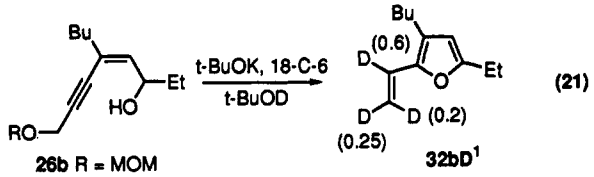
(18)

treatment with KO-*t*-Bu under the usual conditions each afforded the vinylfuran **32a** and **b**, respectively, in high yield (Table V, entries 1 and 2). The secondary and tertiary MOM ethers **26c** and **d** (eq 19) likewise afforded the corresponding vinylfurans, **32c** and **d** (Table V, entries 3 and 4). These exothermic reactions proceed extremely rapidly, even at 0 °C. In contrast, the previously examined (*Z*)-vinylacetylenes **13a–e** require several hours at 25–60 °C for complete reaction (Table III). Interestingly, the secondary MOM ether **26c** afforded 11% of protonolysis product **33**. Treatment of this furan ether with KO-*t*-Bu under the cyclization conditions led to the vinylfuran **32c** in high yield, but only after prolonged exposure (eq 20).

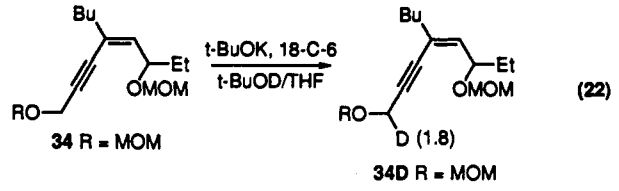
(7) Cf. D'Ambrosio, M.; Fabbri, D.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 63. Williams, D.; Anderson, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332.



Deuterium labeling studies with alcohol **26b** showed unexpected incorporation at all three positions in the vinylic side chain of the furan product (eq 21). A control



experiment with vinylfuran **32b** gave no incorporation of deuterium. However, the bis-MOM ether **34** showed appreciable exchange at the propargylic position (eq 22).



Accordingly, we can view the formation of **32bD1** as a 5-*exo-dig* process accompanied by exchange as depicted in Figure 3.[5] Elimination of the OMOM group in this system closely follows cyclization as evidenced by the absence of MOM-containing furan product with **26a, b,** and **d.** The isolation of the MOM-containing byproduct **33** from **26c** (Table V, entry 3) suggests that a pathway analogous to that shown in Figure 2 may also be operative in which the incipient vinyl anion precursors of, e.g., **R** and **U** undergo competitive E1cB elimination and protonolysis reactions.

The foregoing studies demonstrate that both 5-*exo-dig* and 5-*endo-dig* cyclizations are favorable processes with β-allenyl, β-alkynyl, and γ-alkynyl allylic alcohols. The initial cyclization products undergo rapid 1,3- and/or 1,5-proton shifts leading to furans. The allenyl systems cyclize more readily than the alkynyl isomers except when an anion-stabilizing leaving group is present at the propargylic position, as in **26.** These findings delineate the scope and limitations of base-initiated furan synthesis from α- and β-alkenyl allylic alcohols.[8]

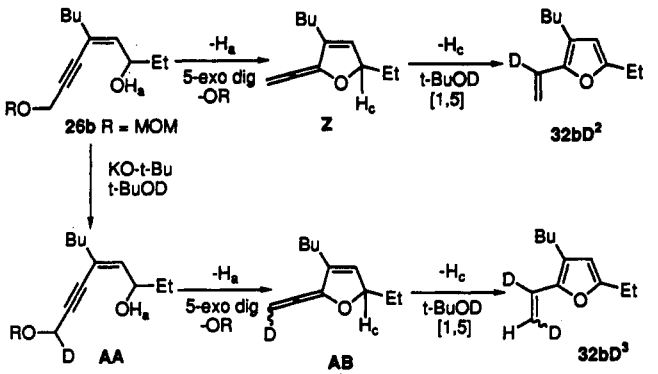


Figure 3. Proposed cyclization–elimination–isomerization pathway for γ-alkynyl allylic alcohols with propargylic leaving groups.

Experimental Section[9]

2-Bromo-1-penten-3-ol (2b). The method of Cosseau[10] was employed. HBr gas (14.4 g, 0.18 mol) was introduced with a gas dispersion tube to a stirred solution of 25.0 g (0.12 mol) of Et_4NBr in 120 mL of CH_2Cl_2 at 0 °C, and then 10.0 g (0.12 mmol) of 1-pentyn-3-ol was added. The reaction mixture was brought to rt, after 3 h, the mixture was cooled to 0 °C, diluted with 120 mL of Et_2O, and filtered, and solvent was distilled under reduced pressure. Bulb-to-bulb distillation of the residue afforded 16.3 g (83%) of vinyl bromide **2b** (bp 50 °C at 1.0 Torr) as a clear colorless oil: IR (cm^{-1}, film) 3382, 1626; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (d, J = 1.9 Hz, vinyl H), 5.55 (d, J = 1.9 Hz, vinyl H), 4.00 (t, J = 6.5 Hz, C*H*OH), 1.90 (s, OH), 1.59–1.75 (m, CH_2CH_3), 0.90 (t, J = 7.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 137.1, 117.2, 77.3, 28.1, 9.5; HRMS calcd for C_5H_9BrO (M^+) 163.9837, found 163.9844.

(*Z*)-2-Iodo-2-hepten-1-ol (2c). The method of Ensley[11] was employed. To a solution of 19.0 g (0.17 mol) of 2-heptyn-1-ol and 0.31 g (1.89 mmol) of AIBN was added 16.9 g (63 mmol) of tributyltin hydride. The reaction mixture was slowly heated to 85 °C, and after 3 h, it was cooled to rt and distilled under vacuum. The unreacted alkyne was removed first (bp 90–100 °C at 0.7 Torr) followed by 21.9 g (87%) of the vinylstannane (bp 130 °C at 0.7 Torr) as a clear, colorless oil.

To a solution of the above vinylstannane in 540 mL of CCl_4 was added 34.5 g (136 mmol) of I_2. The reaction mixture was allowed to stir at rt. After 20 min, most of the CCl_4 was distilled under reduced pressure. The residue was diluted with ether and washed with saturated aqueous sodium thiosulfate and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Tin byproducts were eluted with hexane then 10% EtOAc–hexane was used to elute 12.4 g (95%) of vinyl iodide **2c** as a clear, yellow oil: IR (cm^{-1}, film) 3318, 1645; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (tt, J = 6.9, 1.2 Hz, vinyl H), 4.23 (t, J = 1.2 Hz, CH_2OH), 2.15 (dt, J = 6.9, 7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.80 (bs, OH), 1.32–1.42 (m, $CH_2CH_2CH_3$), 0.90 (t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 136.2, 108.0, 71.4, 35.4, 30.4, 22.3, 13.9; HRMS calcd for $C_7H_{13}IO$ (M^+) 240.0011, found 240.0002.

8-(Methoxymethoxy)-2-methylene-3-octyn-1-ol (3a). The method of Sonogashira[3] was employed. To a solution of 3.47 g (25.3 mmol) of vinyl bromide **2a** in 80 mL of Et_2NH at room temperature was added 0.37 g (0.53 mmol) of $(Ph_3P)_2PdCl_2$, 0.40 g (2.11 mmol) of CuI, and 3.00 g (21.1 mmol) of 6-(meth-

(8) For related studies of cumulenols, γ-alkynyl allylic alcohols, and allenols see: Pompes, J. A.; Hoff, S.; Montijir, P. P.; Brandsma, L.; Arens, J. F. *Rec. Trav. Chim.* **1969**, *88*, 119. Hoff, S.; Brandsma, L.; Arens, J. F. *Rec. Trav. Chim.* **1969**, *88*, 609. Schreurs, P. H. M.; Meijer, J.; Vermeer, P.; Brandsma, L. *Tetrahedron Lett.* **1976**, 2387.

(9) For a summary of experimental protocols, see: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960.

(10) Cousseau, J. *Synthesis* **1980**, 805.

(11) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 403.

oxymethoxy)-1-hexyne (**1a**). The reaction mixture was stirred for 4 h, and then it was diluted with ether and saturated aqueous ammonium chloride. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc–hexane) afforded 3.54 g (85%) of enyne **3a** as a clear, light yellow oil: IR (cm^{-1}, film) 3433, 2224, 1622, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (dd, J = 1.5, 1.5 Hz, vinyl H), 5.36 (s, vinyl H), 4.60 (s, OCH_2O), 4.08 (d, J = 1.5 Hz, CH_2OH), 3.54 (t, J = 6.1 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.35 (t, J = 6.9 Hz, CH_2CC), 1.76–1.58 (m, $CH_2CH_2CH_2OMOM$ and OH); ^{13}C NMR (75 MHz, $CDCl_3$) 131.7, 118.8, 96.3, 91.5, 78.8, 67.2, 65.4, 55.1, 28.8, 25.3, 19.1; HRMS calcd for $C_{11}H_{17}O_3$ (M^+ – H) 197.1178, found 197.1171.

2-[4-(Methoxymethoxy)butyl]-4-methylfuran (4a). A. From Alcohol 3a. To a solution of 0.87 g (3.28 mmol) of 18-crown-6 and 0.37 g (3.28 mmol) of KO-*t*-Bu in 7.0 mL of *t*-BuOH was added 0.10 g (0.47 mmol) of alcohol **3a** in 1 mL of THF. The reaction mixture was allowed to stir at ~60 °C for 2 h, and then it was cooled to room temperature. The reaction mixture was diluted with ether and quenched with 10% aqueous K_2CO_3. The aqueous layer was extracted with ether, and the combined organic layers were washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc–hexane) afforded 115 mg (88%) of furan **4a** as a clear colorless oil: IR (cm^{-1}, film) 2932, 2878, 1616, 1115, 1044; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, H5), 5.84 (s, H3), 4.60 (s, OCH_2O), 3.58 (t, J = 7.0 Hz, CH_2OMOM), 3.37 (s, OCH_3), 2.59 (t, J = 7.0 Hz, $CH_2(CH_2)_3OMOM$), 1.96 (s, 3 H, CCH_3), 1.73–1.60 (m, $CH_2CH_2CH_2OMOM$); ^{13}C NMR (75 MHz, $CDCl_3$) 156.1, 137.3, 120.4, 107.7, 96.4, 67.4, 55.1, 29.2, 27.8, 24.8, 9.8; HRMS calcd for $C_{11}H_{18}O_3$ (M^+ – H) 198.1259, found 198.1256.

B. From Alcohol 13c. To a solution of 1.00 g (3.78 mmol) of 18-crown-6 and 0.42 g (3.78 mmol) of KO-*t*-Bu in 8.0 mL of *t*-BuOH was added 0.15 g (0.76 mmol) of alcohol **13c** in 1 mL of THF. The reaction mixture was allowed to stir at rt for 2 h, and then it was diluted with ether and quenched with 10% aqueous K_2CO_3. The aqueous layer was extracted with ether, and the combined organic layers were washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.12 g (80%) of furan **4a** as a clear colorless oil.

C. From Alcohol 23a. To a solution of 1.00 g (3.78 mmol) of 18-crown-6 and 0.42 g (3.78 mmol) of KO-*t*-Bu in 8.0 mL of *t*-BuOH was added 0.15 g (0.76 mmol) of alcohol **23a** in 1 mL of THF. The reaction mixture was allowed to stir at rt for 12 h, and then it was diluted with ether and quenched with 10% aqueous K_2CO_3. The aqueous layer was extracted with ether, and the combined organic layers were washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.11 g (75%) of furan **4a** as a clear colorless oil.

2-[4-(Methoxymethoxy)-1-deuteriobutyl]-4-(deuteriomethyl)-3,5-dideuteriofuran (4aD[1]). A 0.25 g (6.31 g-atom) piece of potassium in 2.5 mL of *t*-BuOD was heated to ~65 °C with stirring until all of the potassium had reacted. The reaction mixture was then cooled to rt, and 1.67 g (6.31 mmol) of 18-crown-6 was added, followed by a solution of 0.25 g (1.26 mmol) of alcohol **3a** in 1 mL of THF. The reaction mixture was allowed to stir for 9 h, it was diluted with ether and quenched with 10% K_2CO_3, and then the layers were separated. The aqueous layer was extracted with ether, and the layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.18 g (72%) of furan **4aD[1]** as a clear colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 0.95 H, H5), 5.84 (s, 0.20 H, H3), 4.60 (s, OCH_2O), 3.58 (t, J = 7.0 Hz, CH_2OMOM), 3.37 (s, 3.00 H, OCH_3), 2.56–2.59 (m, 1.60 H, $CHD(CH_2)_3OMOM$), 1.93–1.96 (m, 2.00 H, CCH_2D), 1.73–1.60 (m, $CH_2CH_2CH_2OMOM$); MS 198 $C_{11}H_{18}O_3$ (3), 199 $C_{11}H_{17}O_3D$ (22), 200 $C_{11}H_{16}O_3D_2$ (42), 201 $C_{11}H_{15}O_3D_3$ (25), 202 $C_{11}H_{14}O_3D_4$ (8).

2-[1-Deuterio-4-(methoxymethoxy)butyl]-4-(deuteriomethyl)furan (4aD[4]). The procedure described for **4aD[1]** was employed with 0.25 g (1.26 mmol) of alcohol **13c** affording 0.20 g (80%) of furan **4aD[4]** as a clear colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 0.85 H, C5 H), 5.84 (s, C3 H), 4.60 (s, CH_2OCH_3), 3.58 (t, J = 7.0 Hz, CH_2OMOM), 3.37 (s, 3.00 H, OCH_3), 2.56–2.59 (m, 0.90 H, $CHD(CH_2)_3OMOM$), 1.93–1.96 (m, 2.20 H, CCH_2D), 1.73–1.60 (m, $CH_2CH_2CH_2OMOM$);[12] MS 198 $C_{11}H_{18}O_3$ (3), 199 $C_{11}H_{17}O_3D$ (37), 200 $C_{11}H_{16}O_3D_2$ (37), 201 $C_{11}H_{15}O_3D_3$ (19), 202 $C_{11}H_{14}O_3D_4$ (4).

(*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3,4-epoxy-3-methyl-1-pentyne (7). To a solution of 5.0 g (52.0 mmol) of (*Z*)-3-methyl-2-penten-4-yn-1-ol and 18.0 g of Na_2HPO_4 in 200 mL of CH_2Cl_2 at 0 °C was added 18.0 g (104 mmol) of *m*-CPBA. The bath was removed, and after 2 h, the reaction mixture was poured into water and ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford 5.29 g (91%) of epoxy alcohol as a clear colorless oil.

To a solution of the above epoxy alcohol in 100 mL of CH_2Cl_2 was added 7.1 mL (51.0 mmol) of Et_3N, 12.8 g (46.4 mmol) of TBSCl, and 0.28 g of DMAP. After 4 h, the reaction mixture was quenched with water and ether, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by filtration through silica gel (10% EtOAc–hexane) afforded 10.3 g (98%) of silyl ether **7** as a clear light yellow oil: IR (cm^{-1}, film) 3310, 1092; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88, 3.78 (ABX, J_{AB} = 11.7 Hz, J_{AX} = 5.1 Hz, J_{BX} = 5.2 Hz, CH_2OTBS), 3.01 (X of ABX, J_{AX} = 4.9 Hz, J_{BX} = 5.2 Hz, epoxide H), 2.35 (s, CCH), 1.55 (s, CCH_3), 0.89 (s, $SiC(CH_3)_3$), 0.08 (s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 81.1, 72.8, 64.1, 62.9, 51.3, 25.9, 23.0, 18.3, –5.2; HRMS calcd for $C_8H_{13}O_2Si$ (M^+ – Bu) 169.0685, found 169.0689. Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.66; H, 9.80. Found: C, 63.55; H, 9.71.

1-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-3,4-undecadien-2-ol (8). The method of Oehlschlager[13] was employed. To a stirred solution of 5.52 mL of 2.0 M hexylmagnesium bromide in ether in 20 mL of a 3:2 mixture of ether and DMS at –60 °C was added 1.00 g (4.86 mmol) of $CuBr{\cdot}SMe_2$. After 10 min, a solution of 1.00 g (4.42 mmol) of alkynyloxirane **7** in 5 mL of ether was added slowly. After 1 h, the reaction mixture was warmed to rt and allowed to stir an additional 15 min. The reaction was quenched with saturated ammonium chloride and filtered through a pad of Celite. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc–hexane) afforded 1.15 g (83%) of allene **8** as a clear light yellow oil: IR (cm^{-1}, film) 3456, 1966, 1114, 837; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17 (m, allene H), 4.01 (m, CHOH), 3.67, 3.53 (ABX, J_{AB} = 10.1 Hz, J_{AX} = 3.7 Hz, J_{BX} = 7.3 Hz, CH_2OTBS), 2.47 (d, J = 4.2 Hz, OH), 1.96 (dt, J = 7.3, 6.8 Hz, $CH_2(CH_2)_4CH_3$), 1.70 (d, J = 2.9 Hz, CCH_3), 1.34–1.43 (m, $CH_2(CH_2)_4CH_3$), 0.89 (s, $SiC(CH_3)_3$), 0.87 (t, J = 6.9 Hz, CH_2CH_3), 0.06 (s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 200.6, 99.4, 93.0, 72.5, 66.1, 31.7, 29.2, 29.0, 28.7, 25.8, 22.6, 18.3, 15.8, 14.0, –5.4.

1-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-3,4-undecadien-2-one (9). The method of Swern[14] was employed. To a solution of 0.48 mL (5.52 mmol) of oxalyl chloride in 15 mL of CH_2Cl_2 at –78 °C was added 0.52 mL (7.36 mmol) of DMSO. After 15 min, a solution of 1.15 g (3.68 mmol) of alcohol **8** in 5 mL of CH_2Cl_2 was added at –78 °C with stirring. After an additional 15 min, 2.05 mL (14.7 mmol) of Et_3N was added, and the reaction mixture was warmed to rt. The mixture was then diluted with ether and quenched with water, and the layers were separated. The organic layer was washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced

(12) Deuterium content was estimated from the integrated ^1H NMR spectrum by comparison of the integral of an appropriate nondeuterated singlet (reference peak) with those integrals of signals arising from partially deuterated positions. Instrument parameters for accurate integration were established with the corresponding undeuterated samples, and small corrections for the nonlinearity of the integrator were applied as needed. The deuterated and nondeuterated samples were run sequentially at similar concentrations. Control experiments showed deuterium incorporation only at C5 in **4a** and **17a**. Therefore, deuteration of that position was accorded no mechanistic significance in reactions leading to **4aD** and **17aD** products.

(13) Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587.

(14) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

pressure. Purification by flash chromatography on silica gel (15% EtOAc–hexane) afforded 1.13 g (99%) of allenic ketone **9** as a clear light yellow oil: IR (cm^{-1}, film) 1947, 1698, 1159; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (tq, J = 2.8, 6.9 Hz, allene H), 4.58 (s, CH_2OTBS), 1.96 (dt, J = 7.4, 6.9 Hz, $CH_2(CH_2)_4CH_3$), 1.70 (d, J = 2.8 Hz, CCH_3), 1.24–1.44 (m, $CH_2(CH_2)_4CH_3$), 0.89 (s, $SiC(CH_3)_3$), 0.87 (t, J = 7.0 Hz, CH_2CH_3), 0.07 (s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 210.2, 198.4, 100.7, 95.1, 66.7, 31.6, 28.8, 28.7, 28.2, 25.8, 22.5, 18.5, 14.0, 13.5, -5.4; HRMS calcd for $C_{17}H_{31}O_2Si$ ($M^+ - CH_3$) 295.2093, found 295.2083.

3-Methyl-2-methylene-3,4-undecadien-1-ol (10). The method of Peterson[15] was employed. To a stirred solution of 1.10 g (3.54 mmol) of ketone **9** in 15 mL of ether at -40 °C was added 3.5 mL (3.54 mmol) of 1.0 M [(trimethylsilyl)methyl]magnesium chloride in Et_2O. After 1 h, the reaction was warmed to rt and allowed to stir an additional 5 min. The reaction was quenched with saturated ammonium chloride and filtered through a pad of Celite. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.76 g (54%) of the alcohol as a clear light yellow oil.

The method of Boeckman[16] was employed. The above alcohol was dissolved in 8 mL of a 3:1 mixture of HOAc–H_2O and allowed to stir at rt. After 2.5 h, the reaction mixture was diluted with ether, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification with flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.23 g (61%) of alcohol **10** as a clear light yellow oil: IR (cm^{-1}, film) 3329, 1944, 891; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (bs, allene H), 5.15 (s, methylene H), 5.03 (s, methylene H), 4.19 (t, J = 5.3 Hz, CH_2OH), 2.01 (dt, J = 6.5, 6.8 Hz, $CH_2(CH_2)_4CH_3$), 1.85 (d, J = 2.7 Hz, CCH_3), 1.62 (t, J = 6.5 Hz, OH), 1.24–1.44 (m, $CH_2(CH_2)_4CH_3$), 0.86 (t, J = 6.7 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 203.6, 144.8, 109.6, 99.2, 92.8, 64.7, 31.6, 29.1, 29.0, 28.8, 22.6, 18.0, 16.9; HRMS calcd for $C_{13}H_{22}O$ (M^+) 194.1671, found 194.1670.

3,4-Dimethyl-1-heptylfuran (11). To a solution of 1.56 g (5.92 mmol) of 18-crown-6, 5.9 mL (5.92 mmol) of 1.0 M potassium *tert*-butoxide in THF, and 0.56 mL (5.92 mmol) of *tert*-butyl alcohol was added 0.23 g (1.18 mmol) of alcohol **10** in 1 mL of THF. After being stirred for 3 h, the reaction mixture was diluted with ether and quenched with 10% aqueous K_2CO_3. The aqueous layer was extracted with ether, and the combined organic layers were washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (2.5% EtOAc–hexane) afforded 75 mg (63%) of furan **11** as a clear colorless oil: IR (cm^{-1}, film) 737; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (q, J = 1.2 Hz, furan H), 2.49 (t, J = 7.6 Hz, $CH_2(CH_2)_5CH_3$), 1.89 (d, J = 1.2 Hz, CCH_3), 1.84 (s, CCH_3), 1.50–1.60 (m, $CH_2(CH_2)_4CH_3$), 1.20–1.30 (m, $CH_2(CH_2)_4CH_3$), 0.85 (t, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 151.5, 136.2, 120.9, 114.3, 31.9, 29.2, 29.1, 28.6, 26.3, 22.7, 14.1, 8.4, 7.9; HRMS calcd for $C_{13}H_{22}O$ (M^+) 194.1671, found 194.1668. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.26; H, 11.39.

(*Z*)-5-Iodo-7-(methoxymethoxy)-4-hepten-3-ol (12b). To a solution of 25.0 g (0.15 mol) of 7-(methoxymethoxy)-4-heptyn-3-ol in 300 mL of THF was added 68 mL (0.23 mol) of 3.4 M Red-Al in toluene.[17] After 24 h, the reaction mixture was cooled to -78 °C, quenched with 70.0 g (0.28 mol) of iodine, and then warmed to rt. Saturated $Na_2S_2O_3$ was added, and the layers were separated. The organic layer was washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Fractional distillation afforded 13.1 g (52%) of protonolysis product (bp 90–100 °C at 0.5 Torr) and 12.2 g (28%) of vinyl iodide **12b** (bp 110–120 °C at 0.5 Torr) as a clear light yellow oil: IR (cm^{-1}, film) 3418, 1644, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (dt, J = 7.6, 1.2 Hz, vinyl H), 4.60 (s, OCH_2O), 4.22 (dt, J = 6.7, 6.8 Hz, $CHOH$), 3.66 (t, J = 6.3 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.75 (tt, J = 6.3, 1.2 Hz, CH_2CH_2OMOM), 1.81 (bs, OH), 1.52–1.68 (m, CH_2CH_3), 0.95 (t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 139.7, 104.3, 77.5, 66.1, 60.4, 55.3, 45.3, 29.1, 21.0, 14.2, 9.6; HRMS calcd for $C_9H_{16}O_2I$ ($M^+ - OH$) 283.0195, found 283.0189.

(*Z*)-10-(Methoxymethoxy)-4-methyl-4-decen-6-yn-3-ol (13b). The method of Swern[14] was employed as described for ketone **9**. From 0.46 g (2.32 mmol) of alcohol **13a** was obtained 0.41 g (89%) of aldehyde **14a** as a clear, faint yellow oil: IR (cm^{-1}, film) 2212, 1682, 1606, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, CHO), 6.51 (bs, vinyl H), 4.61 (s, OCH_2O), 3.61 (t, J = 6.1 Hz, CH_2OMOM), 3.35 (s, OCH_3), 2.52 (dt, J = 2.3, 7.0 Hz, CH_2CC), 1.79–1.86 (m, CH_2CH_2OMOM), 1.82 (s, CCH_3).

To the above aldehyde in 8 mL of ether was added 0.70 mL (2.09 mmol) of 3.0 M EtMgBr in Et_2O at rt. The reaction mixture was allowed to stir for 1 h, and then it was quenched with saturated aqueous NH_4Cl and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (25% EtOAc–hexane) afforded 0.40 g (85%) of alcohol **13b** as a clear, colorless oil: IR (cm^{-1}, film) 3418, 2216, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (bs, vinyl H), 4.67 (t, J = 7.0 Hz, $CHOH$), 4.61 (s, OCH_2O), 3.61 (t, J = 6.2 Hz, CH_2OMOM), 3.35 (s, OCH_3), 2.42 (dt, J = 2.1, 7.0 Hz, CH_2CC), 1.77–1.84 (m, CH_2CH_3), 1.74 (s, CCH_3), 1.63–1.70 (m, CH_2CH_2OMOM), 0.91 (t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 151.2, 106.7, 96.4, 93.0, 77.5, 73.5, 66.2, 55.1, 28.9, 27.8, 16.9, 16.3, 10.0; HRMS calcd for $C_{13}H_{22}O_3$ (M^+) 226.1569, found 226.1571. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.75.

(*Z*)-8-(Methoxymethoxy)-2-methyl-2-octen-4-yn-1-ol (13c). To a solution of 0.45 g (1.87 mmol) of ester **16** in 20 mL of ether at -78 °C was added 2.75 mL (4.12 mmol) of 1.5 M DIBAH in toluene. The reaction mixture was allowed to stir for 1 h, and then it was quenched with water and warmed to rt. The reaction mixture was diluted with ether and 10% HCl, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography afforded 0.33 g (89%) of alcohol **13c** as a clear, colorless oil: IR (cm^{-1}, film) 3422, 2213, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (t, J = 1.9 Hz, vinyl H), 4.61 (s, OCH_2O), 4.29 (s, CH_2OH), 3.62 (t, J = 6.2 Hz, CH_2OMOM), 3.35 (s, OCH_3), 2.43 (dt, J = 1.9, 7.0 Hz, CH_2CC), 1.84 (s, CCH_3), 1.75–1.82 (m, $CH_2CH_2CH_2OMOM$), 1.72 (bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$) 148.8, 106.8, 96.3, 92.9, 77.5, 66.1, 63.7, 55.1, 28.8, 20.1, 16.3.

(*Z*)-11-(Methoxymethoxy)-5-methyl-4-undecen-6-yn-3-ol (13d). The method of Swern[14] was employed as described for ketone **9**. From 0.50 g (2.36 mmol) of alcohol **13c** was obtained 0.49 g (98%) of aldehyde **14b** as a clear, faint yellow oil.

To the above aldehyde in 10 mL of ether was added 0.91 mL (2.74 mmol) of 3.0 M EtMgBr in Et_2O at rt. The reaction mixture was allowed to stir for 2 h, and then it was quenched with saturated aqueous NH_4Cl and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (25% EtOAc–hexane) afforded 0.45 g (82%) of alcohol **13d** as a clear, colorless oil: IR (cm^{-1}, film); ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (dd, J = 1.4, 7.1 Hz, vinyl H), 4.60 (s, OCH_2O), 4.45 (dt, J = 6.5, 6.6 Hz, $CHOH$), 3.54 (t, J = 6.1 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.36 (t, J = 6.8 Hz, CH_2CC), 1.82 (d, J = 1.4 Hz, CCH_3), 1.80–1.44 (m, $CH_2CH_2CH_2OMOM$ and CH_3CH_2CHOH), 0.90 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 138.3, 120.5, 96.4, 94.6, 79.4, 72.0, 67.2, 55.1, 29.7, 28.9, 25.5, 23.6, 19.2, 9.7; HRMS calcd for $C_{14}H_{24}O_3$ (M^+) 240.1725, found 240.1730.

(*Z*)-Ethyl 8-(Methoxymethoxy)-2-methyl-2-octen-4-ynoate (16). The method of Still[18] was employed. To a solution of 5.54 g (16.0 mmol) of the Still trifluoroethyl phosphonopropionate and 10.6 g (40.0 mmol) of 18-crown-6 in 275 mL of THF at 0 °C was added 32.0 mL (16.0 mmol) of 0.5 M KHMDS in THF. The reaction mixture was stirred for 15 min, it was cooled to -78 °C, and then a solution of 2.50 g (16.0 mmol) of aldehyde **15** in 25 mL of THF was added over 0.5 h. After 3 h, the reaction mixture

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was warmed to rt and diluted with ether and saturated aqueous NH_4Cl, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography afforded 3.23 g (84%) of a 4:1 separable mixture of *Z* and *E* esters **16** as clear, colorless oils: IR (cm^{-1}, film) 2213, 1703, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (t, J = 2.3 Hz, vinyl H), 4.61 (s, OCH_2O), 4.22 (q, J = 7.2 Hz, $CO_2CH_2CH_3$), 3.62 (t, J = 6.2 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.49 (dt, J = 2.3, 7.0 Hz, CH_2CC), 1.96 (s, CCH_3), 1.78–1.87 (m, $CH_2CH_2CH_2OMOM$), 1.30 (t, J = 7.2 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 166.3, 136.9, 118.0, 98.3, 96.3, 78.3, 66.0, 60.3, 54.9, 28.6, 19.7, 16.6, 14.1; HRMS calcd for $C_{13}H_{19}O_4$ (M^+ – H) 239.1283, found 239.1284. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.72; H, 8.31.

8-(Methoxymethoxy)-3-octyn-2-ol (21a). To a solution of 4.50 g (31.6 mmol) of 6-(methoxymethoxy)-1-hexyne (**1a**) in 65 mL of THF was added 12.7 mL (31.6 mmol) of a 2.5 M solution of *n*-BuLi in hexanes at –78 °C. The reaction mixture was allowed to stir for 30 min, and then 1.8 mL (31.6 mmol) of acetaldehyde was added. After 30 min, the reaction mixture was quenched with saturated ammonium chloride at –78 °C and allowed to warm to room temperature, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield 5.80 g (98%) of alcohol **21a** as a clear light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, OCH_2O), 4.47–4.51 (m, CHOH), 3.53 (t, J = 6.1 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.22 (dt, J = 7.0, 1.9 Hz, CH_2CC), 1.52–1.73 ($CH_2CH_2CH_2OMOM$ and OH), 1.40 (d, J = 6.5 Hz, $CHCH_3$).

Methyl (*E*)-8-(Methoxymethoxy)-2-methyl-2-octen-4-ynoate (22a). The method of Ireland[6] was employed. To a solution of 2.5 mL (28.4 mmol) of oxalyl chloride in 70 mL of CH_2Cl_2 at –78 °C was added 2.7 mL (37.9 mmol) of DMSO. After 15 min, a solution of 3.00 g (19.0 mmol) of alcohol **21c** in 5 mL of CH_2Cl_2 was added at –78 °C with stirring. After an additional 15 min, 10.6 mL of Et_3N was added, and the reaction mixture was warmed to 0 °C. After 30 min at 0 °C, a solution of 8.59 g (24.7 mmol) of methyl 2-(triphenylphosphoranylidene)propionate in 25 mL of CH_2Cl_2 was added all at once and the reaction was warmed to rt. After 2 h, the reaction mixture was partially concentrated under reduced pressure and filtered through a plug of silica gel. The filtrate was washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (25% EtOAc–hexane) afforded 3.54 g (83%) of ester **22a** as a clear, colorless oil: IR (cm^{-1}, film) 2213, 1714, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (t, J = 2.2 Hz, vinyl H), 4.61 (s, OCH_2O), 3.73 (s, CO_2CH_3), 3.62 (t, J = 6.2 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.53 (dt, J = 2.2, 7.0 Hz, CH_2CC), 2.01 (s, CCH_3), 1.81–1.93 (m, $CH_2CH_2CH_2OMOM$); ^{13}C NMR (75 MHz, $CDCl_3$) 167.7, 137.7, 120.4, 102.7, 96.4, 77.8, 65.9, 55.1, 51.9, 28.7, 16.7, 15.1; HRMS calcd for $C_{12}H_{17}O_4$ (M^+ – H) 225.1127, found 225.1127. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.79; H, 8.07.

Methyl (*E*)-9-(Methoxymethoxy)-3-methyl-2-nonen-4-ynoate (22b). The method of Swern[14] was employed as described for ketone **9**. From 2.50 g (13.4 mmol) of alcohol **21a** was obtained 2.47 g (100%) of ketone as a clear yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, OCH_2O), 3.53 (t, J = 6.0 Hz, CH_2OMOM), 3.34 (s, OCH_3), 2.39 (t, J = 6.7 Hz, CH_2CC), 2.30 (s, $C(O)CH_3$), 1.66–1.69 (m, $CH_2CH_2CH_2OMOM$).

To a solution of 2.6 mL (16.0 mmol) of trimethylphosphonoacetate in 130 mL of DMSO was added 0.40 g (16.0 mmol) of 95% NaH at rt. After gas evolution ceased, a solution of the above ketone in 5 mL of DMSO was added slowly, and the mixture was allowed to stir for 12 h. The reaction mixture was diluted with ether and quenched with water, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc–hexane) afforded 2.0 g (63%) of a separable 2:3 mixture of *E* and *Z* esters **22b** as clear, colorless oils: IR (cm^{-1}, film) 2224, 1714, 1616, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, vinyl H), 4.61 (s, OCH_2O), 3.68 (s, CO_2CH_3), 3.54 (t, J = 6.1 Hz, CH_2OMOM), 3.35 (s, OCH_3), 2.38 (t, J = 6.8 Hz, CH_2CC), 2.25 (s, CCH_3), 1.54–1.70 (m, $CH_2CH_2CH_2OMOM$); ^{13}C NMR (75 MHz, $CDCl_3$) 166.6, 139.0, 122.7, 96.4, 95.3, 83.2, 67.0, 55.1, 51.0, 28.8, 25.1, 20.1, 19.2; HRMS calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362, found 240.1355. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.79; H, 8.31.

Ethyl (*E*)-2,3-Dimethyl-2-nonen-4-ynoate (22c). The method of Swern[14] was employed as described for ketone **9**. From 1.24 g (9.82 mmol) of alcohol **21b** was obtained 1.00 g (82%) of ketone as a clear colorless oil: IR (cm^{-1}, film) 2213, 1681; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (t, J = 6.9 Hz, CH_2CC), 2.30 (s, $C(O)CH_3$), 1.37–1.57 (m, $CH_2CH_2CH_3$), 0.91 (t, J = 7.3 Hz, CH_2CH_3); HRMS calcd for C_7H_9O ($M^+ - CH_3$) 109.0657, found 109.0653.

The method of Still[18] was employed as described for ester **16** affording 1.39 g (89%) of ester **22c** as a clear, colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, J = 7.1 Hz, CO_2CH_2), 2.38 (t, J = 7.0 Hz, CH_2CC), 2.11 (s, CCH_3), 2.05 (s, CCH_3), 1.39–1.56 (m, $CH_2CH_2CH_3$), 1.28 (t, J = 7.1 Hz, $CO_2CH_2CH_3$), 0.91 (t, J = 7.4 Hz, $CH_2CH_2CH_3$).

(*E*)-8-(Methoxymethoxy)-2-methyl-2-octen-4-yn-1-ol (23a). To a solution of 1.60 g (7.07 mmol) of ester **22a** in 30 mL of ether at –78 °C was added 10.4 mL (15.6 mmol) of 1.5 M DIBAH in toluene. The reaction mixture was allowed to stir for 1 h, it was quenched with water, warmed to rt, and diluted with ether and 10% HCl, and then the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (50% EtOAc–hexane) afforded 1.34 g (94%) of alcohol **23a** as a clear, colorless oil: IR (cm^{-1}, film) 3412, 2213, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51 (t, J = 2.0 Hz, vinyl H), 4.61 (s, OCH_2O), 4.07 (s, CH_2OH), 3.63 (t, J = 6.2 Hz, CH_2OMOM), 3.35 (s, OCH_3), 2.46 (dt, J = 1.9, 6.9 Hz, CH_2CC), 1.85 (s, CCH_3), 1.79–1.85 (m, $CH_2CH_2CH_2OMOM$), 1.49 (bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$) 148.6, 105.0, 96.3, 93.1, 78.0, 66.6, 66.2, 55.1, 29.0, 16.3, 16.2.

(*E*)-8-(Methoxymethoxy)-2-octen-4-yn-1-ol (23d). The procedure described for ester **22a** afforded 3.75 g (82%) of ester **22d** as a clear, colorless oil.

To a solution of 1.75 g (7.73 mmol) of ester **22d** in 30 mL of ether at –78 °C was added 11.3 mL (17.0 mmol) of 1.5 M DIBAH in toluene. The reaction mixture was allowed to stir for 1 h, it was quenched with water, warmed to rt, and diluted with ether and 10% HCl, and then the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford 1.50 g (98%) of alcohol **23d** as a clear, faint yellow oil: IR (cm^{-1}, film) 3412, 2213, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (dt, J = 15.9, 5.4 Hz, vinyl H), 5.70 (dt, J = 15.9, 1.8 Hz, vinyl H), 4.61 (s, OCH_2O), 4.17 (dd, J = 5.4, 1.7 Hz, CH_2OH), 3.61 (t, J = 6.2 Hz, CH_2OMOM), 3.35 (s, OCH_3), 2.41 (dt, J = 1.8, 7.0 Hz, CH_2CC), 1.75–1.84 (m, CH_2CH_2OMOM), 1.43 (bs, OH).

(*Z*)-3-Iodo-2-hepten-1-ol (25a). The procedure described for iodide **12b** was employed. From 15.0 g (0.13 mmol) of 2-heptyn-1-ol was obtained 5.35 g (35%) of protonolysis product (bp 65–75 °C at 0.30 Torr) and 14.5 g (45%) of vinyl iodide **25a** (bp 85–90 °C at 0.30 Torr) as a clear light yellow oil: IR (cm^{-1}, film) 3322, 1644; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (tt, J = 5.9, 1.2 Hz, vinyl H), 4.18 (t, J = 5.9 Hz, CHOH), 2.47 (dt, J = 7.3, 1.2 Hz, $CH_2CH_2CH_2CH_3$), 1.45–1.55 (m, $CH_2CH_2CH_3$ and OH), 1.23–1.35 (m, CH_2CH_3), 0.90 (t, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 133.4, 110.5, 67.2, 44.9, 31.3, 21.4, 13.9; HRMS calcd for $C_7H_{13}IO$ (M^+) 240.0011, found 240.0010.

(*Z*)-6-(Methoxymethoxy)-3-methyl-2-dodecen-4-yn-1-ol (26c). To a solution of 0.68 g (1.84 mmol) of silyl ether **28** and 0.16 mL (2.77 mmol) of glacial acetic acid in 7 mL of THF was added 2.8 mL (2.77 mmol) of 1.0 M TBAF in THF. After 8 h, the reaction mixture was diluted with ether and water, and the layers were separated. The organic layer was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (25% EtOAc–hexane) afforded 0.46 g (98%) of alcohol **26c** as a clear colorless oil: IR (cm^{-1}, film) 3416, 2213, 1634; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (tq, J = 6.7, 1.4 Hz, vinyl H), 4.91, 4.59 (AB, J = 6.7 Hz, OCH_2O), 4.44 (t, J = 6.6 Hz, CHOMOM), 4.27 (bd, J = 6.2 Hz, CH_2OH), 3.37 (s, OCH_3), 1.86 (d, J = 1.4 Hz, vinyl CH_3), 1.71–1.78 (m, $CH_2CHOMOM$), 1.28–1.69 (m, $CH_2CH_2CH_2CH_2CH_3$ and OH), 0.87 (t, J = 6.8 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 136.4,

120.4, 94.5, 93.4, 83.9, 66.6, 61.5, 56.0, 36.2, 32.1, 29.3, 25.7, 23.5, 22.9, 14.4; HRMS calcd for $C_{15}H_{26}O_3$ (M^+) 254.1882, found 254.1872.

(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2-dodecen-4-yn-6-ol (27). To a solution of 32.5 g (0.15 mol) of freshly distilled (*Z*)-5-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-3-penten-1-yne in 500 mL of THF at −78 °C was added 68 mL (0.17 mol) of 2.5 M *n*-BuLi in hexanes. The reaction mixture was allowed to stir for 15 min, and then 25.9 mL (0.19 mol) of heptaldehyde was added. After 15 min, the reaction was slowly warmed to rt and allowed to stir an additional 30 min, and then it was diluted with ether and quenched with water. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Bulb-to-bulb distillation (130 °C; 0.75 Torr) afforded 44.9 g (90%) of alcohol **27** as a clear yellow oil: IR (cm^{-1}, film) 3358, 2213, 1635, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (tq, J = 5.2, 1.4 Hz, vinyl H), 4.50 (dt, J = 5.7, 6.5 Hz, C*H*OH), 4.32 (dq, J = 5.2, 1.2 Hz, CH_2OTBS), 1.83 (dd, J = 1.2, 1.4 Hz, CCH_3), 1.67–1.75 (m, $CH_2(CH_2)_4CH_3$ and OH), 1.38–1.44 (m, $CH_2(CH_2)_3CH_3$), 1.25–1.36 (m, $CH_2CH_2CH_2CH_3$), 0.89 (s, $SiC(CH_3)_3$), 0.87 (t, J = 7.2 Hz, CH_2CH_3), 0.06 (s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 136.8, 118.3, 95.2, 83.0, 62.8, 62.2, 37.9, 31.8, 29.0, 26.0, 25.2, 23.0, 22.6, 18.4, 14.0, −5.1; HRMS calcd for $C_{15}H_{27}O_2Si$ ($M^+ - t$-Bu) 267.1780, found 267.1771.

(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-(methoxymethoxy)-3-methyl-2-dodecen-4-yne (28). To a solution of 0.55 g (1.69 mmol) of alcohol **27** in 7 mL of CH_2Cl_2 was added 0.89 mL (5.08 mmol) of ethyldiisopropylamine and 0.19 mL (2.54 mmol) of MOMCl. After 12 h, the reaction mixture was diluted with ether and water, and the layers were separated. The organic layer was washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification with flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.51 g (82%) of methoxymethoxy ether **28** as a clear colorless oil: IR (cm^{-1}, film) 2187, 1675, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (tq, J = 5.0, 1.5 Hz, vinyl H), 4.92, 4.97 (AB, J = 6.8 Hz, OCH_2O), 4.45 (t, J = 6.6 Hz, C*H*OMOM), 4.32 (dq, J = 5.0, 1.3 Hz, CH_2OTBS), 3.37 (s, OCH_3), 1.83 (dd, J = 1.3, 1.5 Hz, CCH_3), 1.69–1.78 (m, $CH_2(CH_2)_4CH_3$), 1.41–1.54 (m, $CH_2(CH_2)_3CH_3$), 1.21–1.39 (m, $CH_2CH_2CH_2CH_3$), 0.88 (s, $SiC(CH_3)_3$), 0.87 (t, J = 6.9 Hz, CH_2CH_3), 0.05 (s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) 137.3, 118.6, 94.4, 93.2, 84.1, 66.5, 62.7, 55.9, 36.2, 32.1, 29.4, 26.3, 25.7, 23.4, 23.0, 18.7, 14.4, −4.8; HRMS calcd for $C_{21}H_{39}O_3Si$ (M^+ − H) 367.2668, found 367.2658.

3-Butyl-2-vinylfuran (32a). To a solution of 1.56 g (5.89 mmol) of 18-crown-6, 0.25 g (1.18 mmol) of alcohol **26a**, and 0.56 mL (5.89 mmol) of *t*-BuOH was added 5.9 mL (5.89 mmol) of 1.0 M KO-*t*-Bu in THF. After being stirred for 15 min, the reaction mixture was diluted with ether and quenched with 10% aqueous K_2CO_3. The aqueous layer was extracted with ether, and the combined organic layers were washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (2.5% EtOAc–hexane) afforded 0.14 g (77%) of furan **32a** as a clear colorless oil: IR (cm^{-1}, film) 1684, 1639, 720; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 1.8 Hz, C-5 H), 6.51 (dd, J = 11.3, 17.4, C*H*CH_2), 6.24 (d, J = 1.8 Hz, C-4 H), 5.56 (dd, J = 1.5, 17.4 Hz, CHC*H*H), 5.09 (dd, 1.5, 11.3 Hz, CHCH*H*), 2.41 (t, J = 7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.44–1.50 (m, $CH_2CH_2CH_2CH_3$), 1.25–1.35 (m, CH_2CH_3), 0.90 (t, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 148.8, 141.6, 123.7, 123.6, 112.9, 110.8, 32.9, 24.6, 22.7, 14.3; HRMS calcd for $C_{10}H_{14}O$ (M^+) 150.1045, found 150.1045.

3,8-Bis(methoxymethoxy)-5-butyl-4-octen-6-yne (34). To a solution of 0.30 g (1.25 mmol) of alcohol **26b** in 5 mL of CH_2Cl_2 was added 0.65 mL (3.74 mmol) of ethyldiisopropylamine and 0.14 mL (1.87 mmol) of MOMCl. After 12 h, the reaction mixture was diluted with ether and water, and the layers were separated. The organic layer was washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification with flash chromatography on silica gel (2.5% EtOAc–hexane) afforded 0.30 g (83%) of methoxymethoxy ether **34** as a clear faint yellow oil: IR (cm^{-1}, film) 1632, 1047; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (d, J = 9.0 Hz, vinyl H), 4.72 (s, $CH_2OCH_2OCH_3$), 4.65, 4.51 (AB, J = 6.5 Hz, $CHOCH_2O$), 4.41 (dt, J = 9.0, 6.6 Hz, C*H*OMOM), 4.36 (s, CH_2OMOM), 3.37 (s, OCH_3), 3.35 (s, OCH_3), 2.13 (dd, J = 6.4, 7.4 Hz, $CH_2(CH_2)_2CH_3$), 1.25–1.69 (m, $CH_2CH_2CH_3$ and $CHCH_2CH_3$), 0.91 (t, J = 7.4 Hz, CH_2CH_3), 0.87 (t, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 137.4, 125.8, 94.4, 94.1, 89.3, 83.8, 75.9, 55.4, 55.3, 54.5, 36.7, 30.3, 28.2, 21.9, 13.8, 9.7; HRMS calcd for $C_{14}H_{23}O_4$ (M^+ − Et) 3225.1596, found 225.1595.

3,8-Bis(methoxymethoxy)-8-deuterio-5-butyl-4-octen-6-yne (34D). A 0.24 g (0.83 g-atom) piece of potassium in 2.0 mL of *t*-BuOD was heated to ~65 °C with stirring until all of the potassium had reacted. The solution was then cooled to rt, and 1.10 g (4.15 mmol) of 18-crown-6 was added, followed by a solution of 0.24 g (0.83 mmol) of alcohol **34** in 1 mL of THF. The reaction mixture was allowed to stir for 10 min, it was diluted with ether and quenched with 10% K_2CO_3, and then the layers were separated. The aqueous layer was extracted with ether, and the layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc–hexane) afforded 0.18 g (75%) of furan **34D** as a clear colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (d, J = 9.0 Hz, vinyl H), 4.72 (s, $CH_2OCH_2OCH_3$), 4.65, 4.51 (AB, J = 6.5 Hz, $CHOCH_2O$), 4.41 (dt, J = 9.0, 6.6 Hz, C*H*OMOM), 4.36 (m, 0.20 H, C*H*DOMOM), 3.37 (s, OCH_3), 3.35 (s, OCH_3), 2.13 (dd, J = 6.4, 7.4 Hz, $CH_2(CH_2)_2CH_3$), 1.25–1.69 (m, $CH_2CH_2CH_3$ and $CHCH_2CH_3$), 0.91 (t, J = 7.4 Hz, CH_2CH_3), 0.88 (t, J = 7.3 Hz, CH_2CH_3).[12]

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Supplementary Material Available: Selected ^1H NMR spectra and experimental procedures not included in the published paper (58 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.