Synthesis of Trisubstituted Furans from Epoxypropargyl Esters by Sequential SmI_2-Promoted Reduction−Elimination and Pd(II)-Catalyzed Cycloisomerization

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A two-step one-pot synthesis of 2,3,5-trisubstituted furans **8** from 4,5-epoxyalk-2-ynyl esters **6** is described. The sequence is initiated by a SmI_2-promoted reduction that takes advantage of the ability of the alkynyloxirane moiety present in **6** to accept electrons from SmI_2. The resulting organosamarium species then eliminates an adjacent acetate or benzoate leaving group, leading to the formation of unstable 2,3,4-trien-1-ols **7**. Without isolation, these are cycloisomerized to furans **8** by treatment with a catalytic amount of a Pd(II) complex and a proton source. The whole sequence takes place under mild reaction conditions. Some useful functional groups such as cyano and α,β-unsaturated esters are tolerated, but benzyl- and silyl-protected hydroxyl groups are deprotected to some extent. Starting materials can be easily assembled using reliable reactions from acetylene, an aldehyde or ketone, and a vinyl halide fragment. This offers the possibility of introducing branched substituents at C-5 of the furan ring.

Introduction

Furans are an important class of heteroaromatic compounds that can be found as components in numerous natural products and substances with useful industrial applications.[1] They are also extensively utilized as useful synthetic intermediates in the preparation of acyclic, carbocyclic, and heterocyclic compounds.[2] Not surprisingly, considerable effort has been devoted in recent years to the development of synthetic methodology directed at the efficient preparation of polysubstituted furans.[3] In this regard, two general strategies have been commonly utilized that rely on either the structural modification of a preformed furan nucleus[3−5] or the cyclization of acyclic precursors. Regiochemical control and flexibility in the introduction of carbon substituents at a given position of the furan ring have been important considerations that have dictated in many cases a preference for the latter strategy.[3]

Among the methods employing acyclic precursors, those that generate the furan nucleus by intramolecular cyclization of oxygen nucleophiles onto a tethered carbon−carbon multiple bond have received particular attention. Thus, the synthesis of furans has been effected from alkynediols,[6] β- or γ-ketoalkynes,[7] β- or γ-alkynyl allylic alcohols,[8] allenyl ketones,[9] propargylic ketones,[10] and 1-alkynyl-2, 3-epoxy alcohols,[11] mainly under either metal- or base-promoted conditions. We have reported the synthesis of furan derivatives **III** from epoxypropargyl esters **I** by SmI_2/Pd(0)-promoted reduction−elimination followed by in situ cycloisomerization of the

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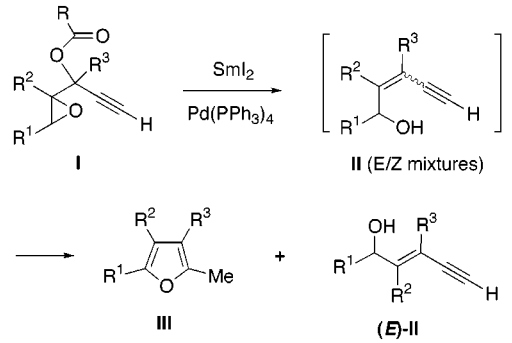
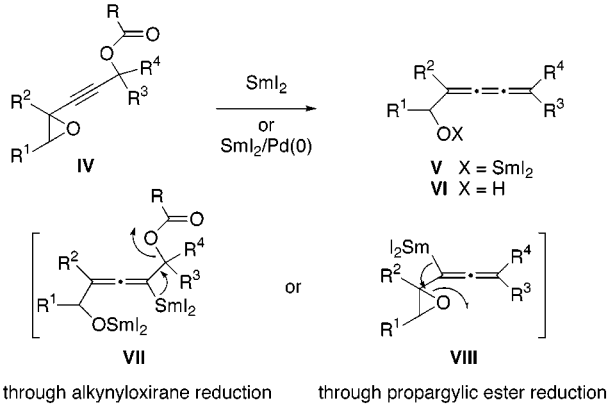
Scheme 1

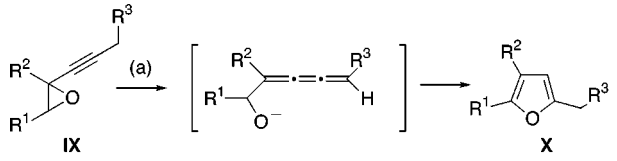


Scheme 2



so-formed γ-alkynyl allylic alcohols **II** (Scheme 1).[12] One serious limitation of this strategy for furan synthesis is that intermediates **II** are obtained as *E*/*Z* mixtures where only the minor (*Z*)-isomers cyclize to the corresponding furans while the major (*E*)-isomers remain unchanged.[13] It was reasoned that regioisomeric epoxypropargyl esters **IV** could also lead to furans via a different mechanism (Scheme 2). In substrates **IV** advantage could be taken of the reactivity of their alkynyloxirane[14] and propargylic ester[12,15] moieties toward SmI_2 and SmI_2/Pd(0), respectively. It was then conceivable that

Scheme 3[a]



[a] (a) *t*-BuOK, *t*-BuOH, 18-C-6, 60 °C.

organosamariums **VII** or **VIII** would be formed and subsequently expel an adjacent leaving group[15c−f,h] to eventually afford a hydroxymethyl-1,2,3-triene **VI**. Trienes related to **VI** have been suggested as key intermediates in the base-promoted cycloisomerization of alkynyloxiranes **IX** to furans **X** (Scheme 3).[16a] This paper reports the reactions of epoxyalkynol esters of type **IV** with SmI_2 to generate 1,2,3-trienes of type **VI**, and the subsequent in situ Pd-catalyzed cycloisomerization of **VI** to yield 2,3,5-trisubstituted furans of type **X** in a one-pot reduction−elimination−cycloisomerization sequence.[17]

Results and Discussion

Representative substrates **6** (see Table 1 for description) were prepared by epoxidation of enyne esters **5**, that were prepared following either one of the two synthetic routes depicted in Scheme 4. For esters **5a**−**i**, the lithium anions of readily available enynes **1** were reacted with appropriate aldehydes or ketones, and the resulting alkoxide was trapped in situ with benzoyl chloride (**5a**,**b**,**d**−**f**,**h**,**i**) or, alternatively, the corresponding alcohols (**4c**, **4g**) were isolated and acetylated under standard conditions. For the preparation of esters **5j**−**m**, the required alcohols **4j**−**m** were prepared by Sonogashira coupling[18] between vinyl bromide **3** and propargyl alcohols **2**.

In preliminary experiments, treatment of **6a** (Scheme 5) with 2.1 equiv of SmI_2 and a catalytic amount (5 mol %) of $Pd(PPh_3)_4$ at room temperature led to the rapid consumption of the starting material with formation of two products of higher polarity. Aqueous workup afforded a material with a ^{1}H NMR spectrum compatible with a diastereomeric mixture of alcohols **7a**. Characteristic features of this material were the absence of the benzoyl group aromatic protons and the presence of multiplets at δ ~4.1 and δ ~5.5 assigned to the carbinolic and allenic protons of **7a**, respectively. This material proved to be unstable, in agreement with previous reports on 1,2,3-trienes,[19,20] and further characterization was not feasible. It was also found that the initial reduction−elimination step could be performed with the same efficiency in the

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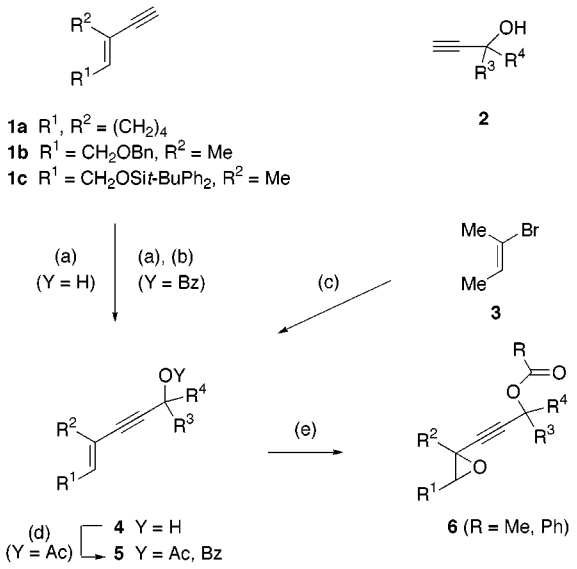
Table 1. Synthesis of Furans 8 from Epoxypropargyl Esters[a] 6

	6	R^1	R^2	R^3	R^4	R	Pd(II)	8	yield (%)
1	**6a**	$(CH_2)_4$		$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2(PPh_3)_2$	**8a**	80
2	**6a**	$(CH_2)_4$		$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2$	**8a**	51
3	**6a**	$(CH_2)_4$		$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2/PPh_3$[b]	**8a**	32
4	**6b**	$(CH_2)_4$		$(CH_2)_2Ph$	Me	Bz	$Pd(OAc)_2(PPh_3)_2$	**8b**	74
5	**6c**	$(CH_2)_4$		Me	Me	Ac	$Pd(OAc)_2(PPh_3)_2$	**8c**	73
6	**6d**	$(CH_2)_4$		$CHMe_2$	H	Bz	$Pd(OAc)_2(PPh_3)_2$	**8d**	76
7	**6e**	$(CH_2)_4$		Et	Et	Bz	$Pd(OAc)_2(PPh_3)_2$	**8e**	*c*
8[d]	**6e**	$(CH_2)_4$		Et	Et	Bz	$Pd(OAc)_2(PPh_3)_2$	**8e**	79
9[d]	**6e**	$(CH_2)_4$		Et	Et	Bz	$PdCl_2(MeCN)_2$	**8e**	70
10	**6f**	$(CH_2)_4$		$(CH_2)_3CN$	Me	Bz	$Pd(OAc)_2(PPh_3)_2$	**8f**	54
11	**6g**	$(CH_2)_4$		(E)-$(CH_2)_3CH{=}CHCO_2Et$	H	Ac	$Pd(OAc)_2(PPh_3)_2$	**8g**	52
12	**6h**	$CH_2{-}OBn$	Me	$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2(PPh_3)_2$	**8h**	31
13[d]	**6h**	$CH_2{-}OBn$	Me	$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2(PPh_3)_2$	**8h**	69[e]
14	**6i**	$CH_2{-}OP$[f]	Me	$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2(PPh_3)_2$	**8i**	*g*
15[d]	**6i**	$CH_2{-}OP$[f]	Me	$(CH_2)_2Ph$	H	Bz	$Pd(OAc)_2(PPh_3)_2$	**8i**	35[h]
16	**6j**	Me	Me	$(CH_2)_2Ph$	Me	Ac	$Pd(OAc)_2(PPh_3)_2$	**8j**	63
17	**6k**	Me	Me	CH_2OBn	H	Ac	$Pd(OAc)_2(PPh_3)_2$	**8k**	*g*
18[d]	**6k**	Me	Me	CH_2OBn	H	Ac	$Pd(OAc)_2(PPh_3)_2$	**8k**	31
19	**6l**	Me	Me	$(CH_2)_3CN$	Me	Ac	$Pd(OAc)_2(PPh_3)_2$	**8l**	78
20	**6l**	Me	Me	$(CH_2)_3CN$	Me	Ac	$PdCl_2(MeCN)_2$	**8l**	77
21	**6l**	Me	Me	$(CH_2)_3CN$	Me	Ac	$Pd(OAc)_2$	**8l**	69
22	**6m**	Me	Me	(E)-$(CH_2)_3CH{=}CHCO_2Et$	H	Ac	$Pd(OAc)_2(PPh_3)_2$	**8m**	70
23	**6m**	Me	Me	(E)-$(CH_2)_3CH{=}CHCO_2Et$	H	Ac	$PdCl_2(MeCN)_2$	**8m**	65
24	**6m**	Me	Me	(E)-$(CH_2)_3CH{=}CHCO_2Et$	H	Ac	$PdCl_2(PPh_3)_2$	**8m**	60

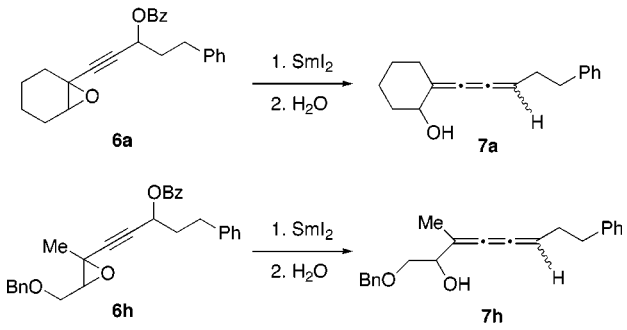
[a] Unless otherwise indicated, substrate **6** was treated with SmI_2 (2.1 equiv) at −5 °C, followed by H_2O (2 equiv), AcOH (2 equiv), and a Pd(II) complex (5 mol %) at room temperature. [b] 10 mol % of PPh_3, relative to **6**, was used. [c] Furan **8e** was obtained in trace amounts. [d] AcOH was omitted, and 20 equiv of H_2O were used. [e] Benzyl alcohol was isolated in 30% yield. [f] P = $SiPh_2t$-Bu. [g] Triene intermediate underwent degradation. No furan was obtained. [h] t-$BuPh_2SiOH$ isolated in 39% yield.

Scheme 4[a]

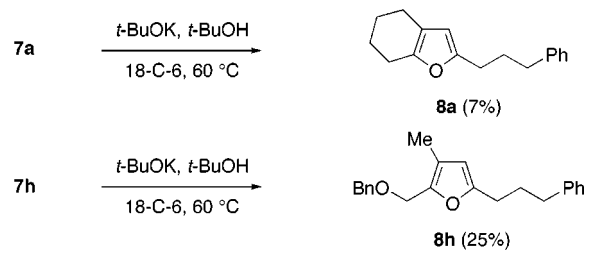


[a] (a) (i) n-BuLi, −78 °C; (ii) R^3COR^4, −78 °C → rt; (b) BzCl, 0 °C → rt. (c) **2**, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt. (d) Ac_2O, Et_3N, DMAP, rt. (e) MCPBA, CH_2Cl_2, 0 °C → rt.

Scheme 5



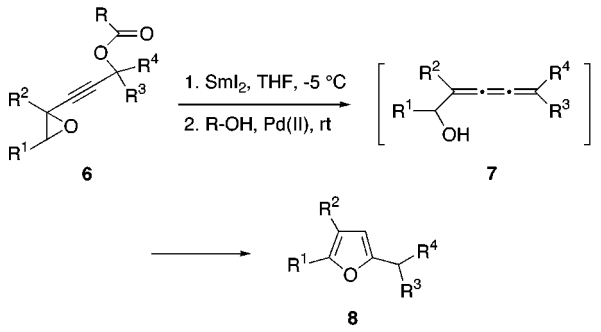
Scheme 6



absence of Pd(0), indicating that reduction of the alkynyloxirane[14] moiety takes place first to give **VII** (Scheme 2), followed by expulsion of the benzoate leaving group and formation of the alkoxide **V**. Similarly, starting from epoxypropargyl ester **6h**, treatment with SmI_2 at −5 °C afforded two products, assigned as the diastereomeric pair of alcohols **7h** (Scheme 5). In contrast to **7a**, the alcohols **7h** were sufficiently stable to allow quick purification by chromatography in silica gel, eventually leading to the isolation of **7h** in 71% yield. The ^1H and ^{13}C NMR spectra of these products were consistent with the proposed structures. Thus, ^1H NMR showed the expected carbinolic and allenic proton resonances, whereas the ^{13}C NMR spectrum displayed two characteristic resonances at δ ~200, assigned to the allenic-type sp-hybridized carbons of **7h**.

When **7a** was exposed to the basic conditions previously reported for isomerization of alkynyloxiranes to furans,[16] a process which is thought to proceed in part through trienes **VI**, a very low yield (7%) of furan **8a** was realized (Scheme 6). The similar treatment of **7h** also resulted in a low yield (25%) of furan **8h** (Scheme 6). Alternatively, the samarium alkoxide (i.e., **V**) obtained by treatment of **6a** with SmI_2 *and catalytic* $Pd(PPh_3)_4$ was protonated in situ with water (2 equiv) and then treated with an acidic resin. This resulted in a substantial improvement, with **8a** being isolated in 50% overall yield in a one-pot procedure starting from **6a**. However, these acidic conditions failed to promote the corresponding

Scheme 7

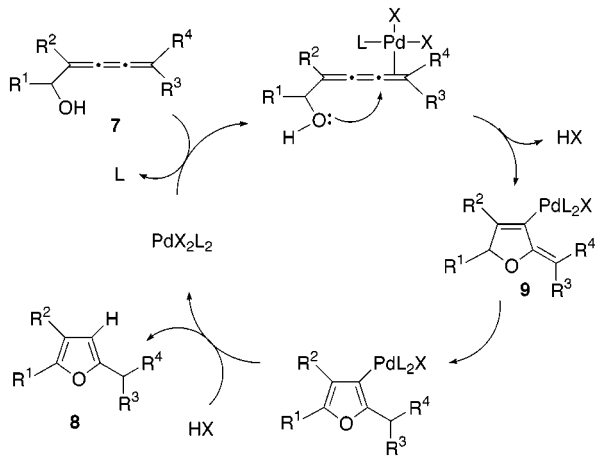


cyclization of **7h** to **8h**, as only degradation of **7h** was observed. For formation of **8a**, the acidic resin could be replaced by acetic acid (30 equiv) with similar efficiency (47% yield from **6a**). Significantly, no furan **8a** was obtained in the absence of resin or acetic acid, even under refluxing conditions; neither was cyclization effective if the initial reduction step was performed in the *absence* of Pd(0). These experiments appear to indicate that conversion of **7** to **8** requires both the presence of palladium and a proton source. On mechanistic grounds (vide infra) it is therefore likely that the actual promoter of cyclization is probably a Pd(II) species formed adventitiously from the Pd(0) catalyst when this is used in the initial reduction−elimination step. In fact, a number of examples have been described in recent years of Pd(II)-mediated cycloisomerization of a variety of unsaturated alcohols leading to substituted furans.[21] As shown below, this was also found to be case for 2,3,4-triene-1-ols **7**, generated from epoxypropargyl esters **6**, that cycloisomerize to 2,3,5-trisubstituted furans **8** (Scheme 7) under Pd(II)-catalyzed conditions.

After some experimentation, we found that appropriate conditions for formation of furans **8** involved initial treatment of **6** with SmI_2 (ca. 2.1 equiv) at −5 °C, followed, after consumption of the starting material (formation of **7** could be monitored by TLC), by addition at room temperature of a proton source and a Pd(II) complex (5 mol %). In this way, furans **8** were generally obtained in good yields under mild reaction conditions in a one-pot procedure starting from **6** (Scheme 7). The formation of **8** is readily interpreted in terms of intramolecular oxypalladation of an activated double bond of **7** to give a palladium *σ*-complex **9**, followed by tautomerization and protonolysis of the C−Pd bond (Scheme 8). The reverse order in the last two steps is also possible.

Results of the application of this procedure to the synthesis of trisubstituted furans **8** are collected in Table 1. The combined use of water and acetic acid (2 equiv each) as proton source gave conveniently short reaction times (usually 1−6 h) for the cyclization step. However, for acid-sensitive substrates and/or products (see formation of **8e**, **8h**, **8i**, **8k** in Table 1 and discussion below) this led to low yields or even no formation of furans **8**. In these cases, it was found that replacing the acetic acid by water (total 20 equiv)[7b] led to better results in still reasonable reaction times (∼20 h). It is likely that, under the former conditions, the role of acetic acid is to enhance the C−Pd bond protonolysis rate in the final step leading

Scheme 8



to **8** (Scheme 8). As Pd(II) source, $Pd(OAc)_2(PPh_3)_2$ was used in most cases with good results, but other palladium catalysts were also useful. For example, similar results were obtained with $PdCl_2(MeCN)_2$ as cyclization promoter (entries 9, 20, 23), while $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ gave inferior results (entries 2, 3, 21, 24).

From inspection of Table 1, it appears that the sequence **6**-to-**8** can be useful for formation of both monocyclic and bicyclic systems. The possibility of introducing α-branched alkyl chains at C-5 also appears feasible (as exemplified by R^4 = Me in entries 4, 5, 10, 16, 19) if ketones rather than aldehydes are employed in the preparation of intermediate precursors **4** or **5** (Scheme 4). Also practical from the strategic point of view is the flexibility possible in the assembly of the starting materials by using appropriate combinations of building blocks **1**−**3** and carbonyl derivatives R^3COR.[4] A number of functional groups are tolerated by the mild reaction conditions used throughout the synthesis of **8**, including substrate preparation, reduction, and cyclization steps. However, the method appears to be limited to aliphatic R^3, R^4 groups, as a substrate **6** derived from **1a** and benzaldehyde led to no furan formation. Some other limitations are also apparent from the results presented in Table 1. For example, hydroxyl groups protected as benzyl or TBDPS ethers undergo deprotection to some extent, as evidenced by the isolation of benzyl alcohol (30%) and *t*-$BuPh_2SiOH$ (39%) in entries 13 and 15, respectively. Since these protecting groups are stable under the typical SmI_2 reduction conditions,[14] it would appear that deprotection takes place during the cyclization step. It is remarkable that this was the case even in the absence of acetic acid (entries 13, 15). Therefore, it is likely that the combination of water and Lewis-acidic Sm(III) species (originated in the reduction step), with or without the intervention of Pd(II),[22] is capable of promoting alcohol deprotection in these cases.[23]

In conclusion, we have shown that 4,5-epoxyalk-2-ynyl esters are practical and convenient precursors of 2,3,5-trisubstituted furans. This transformation is readily

(21) See refs 6a, 8c, 8e, 8f, 8g. See also: Igarashi, S.; Haruta, Y.; Ozawa, M.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737−740. Larock, R. C.; Doty, M. J.; Han, X. J. *Tetrahedron Lett.* **1998**, *39*, 5143−5146.

(22) TBDMS ethers undergo hydrolysis with Pd(II)/H_2O, but the corresponding deprotection of TBDPS ethers under similar conditions has not been described. See: Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918−2919.

(23) The corresponding furans with unprotected hydroxymethyl (entries 12−15) or 2-hydroxyethyl (entries 17, 18) groups were not isolated. Besides the products indicated in Table 1, only complex uncharacterized mixtures were obtained in these reactions.

achieved, under mild reaction conditions, in a one-pot sequence comprising SmI_2-promoted reduction and Pd(II)-mediated cycloisomerization of intermediate 2,3,4-trien-1-ols. In retrosynthetic terms, this strategy allows the generation of the carbocyclic framework of the heterocyclic ring from one acetylene molecule (C-4 and C-5) and a disubstituted vinylic fragment (C-2 and C-3). The third substituent at C-5 is derived from aldehyde or ketone building blocks, and this also effectively introduces the possibility of α-branching at that position of the furan ring.

Experimental Section

General. All reactions involving air- and moisture-sensitive materials were performed using standard benchtop techniques.[24] Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. Acetic anhydride, acetone, benzylacetone, 5-oxohexanenitrile, 3-pentanone, CH_2Cl_2, and triethylamine were distilled from CaH_2. Solutions of SmI_2 in THF were prepared from Sm and either diiodoethane, diiodomethane, or iodine using literature procedures.[25] Flash column chromatography[26] was performed on silica gel (230−400 mesh). HPLC purifications were carried out with either LiChrosorb Si60 (7 μm, 25 × 2.5 cm, column 1) or μPorasil (10 μm, 19 × 1.5 cm, column 2) columns using a refraction index detector. Routine ^{1}H and ^{13}C NMR spectra were obtained at 250 and 62.9 MHz, respectively, using $CDCl_3$ as solvent and internal reference (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV.

General Procedure for Direct Preparation of Benzoates 5a,b,d−f,h,i from Enynes 1. In a typical experiment, *n*-BuLi (1.4 M, 10.5 mL, 15.0 mmol) was added dropwise to a solution of enyne **1** (19.0 mmol) in THF (62 mL) at −78 °C under Ar, and the resulting solution was stirred at the same temperature for 45 min. A solution of an appropriate aldehyde or ketone (13.8 mmol) in THF (25 mL) was added, and the reaction mixture was allowed to reach rt and stirred further 1 h. It was then cooled to 0 °C, and neat benzoyl chloride (2.90 g, 20.7 mmol) was added in one portion. After stirring the mixture 1 h at room temperature, it was quenched with water (20 mL) and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), and the crude product was purified by flash chromatography as indicated in the Supporting Information for the individual cases.

General Procedure for Preparation of Enynols 4 from Vinyl Bromide 3 and Propargylic Alcohols 2 (Sonogashira Coupling). In a typical experiment, a solution of **2** (21.0 mmol) in Et_2NH (16 mL) was added to a solution of *trans*-2-bromobut-2-ene (**3**) (2.13 mL, 21.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.35 g, 0.5 mmol), and CuI (0.38 g, 2.0 mmol) in Et_2NH (105 mL) under Ar. The resulting solution was stirred for 16 h at room temperature. Then a solution of NH_4Cl (100 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine. The residue after evaporation was purified by flash chromatography as indicated in the Supporting Information for the individual cases.

General Procedure for Acetylation of Enynols 4. In a typical experiment, a mixture of **4** (22.0 mmol), DMAP (0.81 g, 6.5 mmol), Et_3N (9.2 mL, 66.0 mmol), and Ac_2O (4.7 mL, 50.0 mmol) was stirred for 16 h at room temperature. The residue was poured over a mixture of H_2O/ice (20 mL). After separation of the layers, the organic layer was washed successively with 1 M HCl, 1 M NaOH, and brine. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The crude was purified by flash chromatography as indicated in the Supporting Information for the individual cases.

General Epoxidation Procedure. Preparation of 4,5-Epoxyalk-2-ynyl Esters 6. In a typical experiment, to a solution of the appropriate acetate or benzoate **5** (8.2 mmol) in CH_2Cl_2 (14 mL) at 0 °C was added MCPBA (57%, 6.54 g, 21.6 mmol). The solution was stirred for 30 min and allowed to warm to room temperature. After stirring the solution for 2 h at room temperature, 1 M NaOH (100 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with 1 M NaOH. The residue after evaporation was purified by flash chromatography as indicated in the Supporting Information for the individual cases.

Preparation of Furans 8 from Esters 6 with SmI_2/Pd(II). General Procedure. In a typical experiment, to a solution of SmI_2 (ca. 0.1 M, 0.58 mmol) in THF (5.8 mL) was added *via cannula* a solution of the ester **6** (0.27 mmol) in THF (3 mL) at −5 °C under Ar. The solution was stirred until consumption of the starting material as judged by TLC (2−5 h). The cooling bath was removed, and the reaction mixture was allowed to reach rt. If at that point excess SmI_2 remained (blue-tinted solution), dry air and Ar were successively bubbled for 5 min each upon which the color changed from blue to brown-green. To the resulting mixture were successively added H_2O (10.0 μL, 0.54 mmol), AcOH (31.0 mL, 0.54 mmol), and a Pd(II) complex (0.014 mmol) (see Table 1). In entries 8, 9, 13, 15, 18 (Table 1), this procedure was modified as follows. AcOH was not used, and the amount of H_2O was increased to 10 mL (5.4 mmol). The reaction mixture was stirred until complete dissappearance of the presumed trienol intermediate (3−20 h). Saturated K_2CO_3 (5 mL) was then added, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography as specified below for the individual cases.

2-(3-Phenylpropyl)-4,5,6,7-tetrahydrobenzofuran (8a). Prepared in 80% yield from benzoate **6a** after elution with hexanes. Colorless oil: ^{1}H NMR δ 1.73−1.93 (m, 4H), 2.04 (q, J = 7.5 Hz, 2H), 2.45 (apparent t, 2H), 2.62 (t, J = 6.0 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.75 (t, J = 7.6 Hz, 2H), 5.87 (s, 1H), 7.2−7.3 (m, 5H); ^{13}C NMR δ 22.1, 23.1, 23.2, 27.6, 29.8, 35.3, 105.8, 117.1, 125.7, 128.2, 128.4, 142.1, 148.7, 153.5; IR (neat) υ 3060, 2930, 2850, 1600, 1250, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O$: C, 84.94; H, 8.39. Found: C, 84.59; H, 8.34.

2-(3-Phenyl-1-methylpropyl)-4,5,6,7-tetrahydrobenzofuran (8b). Prepared in 74% yield from benzoate **6b** after elution with hexanes. Colorless oil: ^{1}H NMR δ 1.30 (d, J = 6.9 Hz, 3H), 1.78−1.99 (m, 5H), 2.04−2.21 (m, 1H), 2.49−2.50 (m, 2H), 2.51−2.65 (m, 3H), 2.68 (t, J = 8.0 Hz, 1H), 2.84−2.98 (hexaplet, J = 6.9 Hz, 1H), 5.93 (s, 1H), 7.11−7.35 (m, 5H); ^{13}C NMR δ 19.4, 22.1, 23.1, 32.8, 33.5, 37.5, 104.5, 116.8, 125.6, 128.2, 128.4, 142.5, 148.6, 157.9; IR ($CHCl_3$) υ 2940, 2880, 1610, 1460, 705 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O$: C, 84.98; H, 8.72. Found: C, 84.98; H, 8.75.

2-(1-Methylethyl)-4,5,6,7-tetrahydrobenzofuran (8c). Prepared in 73% yield from acetate **6c** after elution with hexanes: ^{1}H NMR δ 1.23 (d, J = 6.8 Hz, 6H), 1.67−1.87 (m, 4H), 2.37−2.42 (m, 2H), 2.54−2.59 (m, 2H), 2.84−2.92 (heptuplet, J = 6.8 Hz, 1H), 5.79 (s, 1H); ^{13}C NMR δ 21.3, 22.2, 23.1, 23.2, 27.8, 103.4, 116.9, 148.6, 159.7; IR ($CHCl_3$) υ 2980, 2960, 2860, 1650, 1450, 1230, 960, 920, 800, 740 cm^{-1}; HRMS calcd for $C_{11}H_{16}O$ 164.1201, found 164.1197.

2-(2-Methylpropyl)-4,5,6,7-tetrahydrobenzofuran (8d). Prepared in 76% yield from benzoate **6d** after elution with hexanes: ^{1}H NMR δ 0.94 (d, J = 6.6 Hz, 6H), 1.68−1.87 (m, 4H), 1.94 (heptuplet, J = 6.7 Hz, 1H), 2.38 (tt, J = 6.0, 1.9 Hz, 2H), 2.43 (d, J = 7.1 Hz, 2H), 2.55 (tt, J = 6.1, 1.9 Hz, 2H), 5.79 (s, 1H); ^{13}C NMR δ 22.1, 22.4, 23.1, 23.2, 27.9, 37.4, 106.5, 117.0, 148.7, 153.2; IR (neat) υ 2920, 2840, 1470, 1120 cm^{-1}; HRMS calcd for $C_{12}H_{18}O$ 178.1358, found 178.1355.

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2-(1-Ethylpropyl)-4,5,6,7-tetrahydrobenzofuran (8e). Prepared in 79% yield from benzoate **6e** after elution with hexanes. Colorless oil: ^{1}H NMR δ 0.86 (t, J = 7.3 Hz, 6H), 1.54−1.86 (m, 8H), 2.36−2.45 (m, 3H), 2.53−2.55 (m, 2H), 5.77 (s, 1H); ^{13}C NMR δ 11.8, 22.2, 23.2, 26.4, 42.3, 105.6, 116.7, 148.4, 156.6; IR ($CHCl_3$) υ 2960, 2940, 1760, 1220, 790 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O$: C, 81.18; H, 10.49. Found: C, 80.82; H, 10.59.

2-(4-Cyano-1-methylbutyl)-4,5,6,7-tetrahydrobenzofuran (8f). Prepared in 54% yield from benzoate **6f**. Elution with 3% EtOAc/hexanes, yielded **8f** as a colorless oil: ^{1}H NMR δ 1.21 (d, J = 6.7 Hz, 3H), 1.60−1.80 (m, 8H), 2.20−2.50 (m, 4H), 2.50−2.54 (m, 2H), 2.70−2.80 (m, 1H), 5.80 (s, 1H); ^{13}C NMR δ 17.0, 19.2, 22.0, 23.0, 32.5, 34.8, 104.8, 116.8, 119.7, 148.8, 156.7; IR (neat) υ 2930, 2220, 1235 cm^{-1}; HRMS calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1476.

2-[(*E*)-6-Ethoxycarbonylhex-5-enyl]-4,5,6,7-tetrahydrobenzofuran (8g). Prepared in 52% yield from acetate **6g** after elution with 2% EtOAc/hexanes. Colorless oil: ^{1}H NMR δ 1.28 (t, J = 7.1 Hz, 3H), 1.51−1.81 (m, 8H), 2.18−2.26 (m, 2H), 2.36−2.38 (m, 2H), 2.53−2.60 (m, 4H), 4.18 (q, J = 7.1 Hz, 2H), 5.78 (s, 1H), 5.81 (dt, J = 15.5, 1.6 Hz, 1H), 6.96 (dt, J = 15.5, 7.1 Hz, 1H); ^{13}C NMR δ 14.2, 22.0, 23.1, 27.4, 27.8, 31.8, 60.1, 105.7, 117.0, 121.3, 148.7, 149.0, 153.3, 166.6; IR (neat) υ 2930, 1730, 1655, 1260 cm^{-1}; HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1719.

1-Benzyloxy-3-methyl-8-phenylocta-3,4,5-trien-2-ol (7h). To a solution of SmI_2 (ca. 0.1 M, 1.22 mmol) was added a solution of benzoate **6h** (0.20 g, 0.44 mmol) at −5 °C under Ar. The reaction mixture was stirred for 1h and quenched with sat K_2CO_3 (10 mL). The layers were separated, the organic layer was extracted with EtOAc, and the combined organic extracts were washed with brine and dried (Na_2SO_4). The crude product was purified by flash chromatography (15% EtOAc/hexanes) to afford **7h** (71%, diastereomeric mixture) as a yellowish oil that decomposed slowly upon standing: ^{1}H NMR δ 1.71−1.83 (m) and 1.93−2.09 (m) (total 3H), 2.47−2.88 (m, 4H), 3.46−3.71 (m, 2H), 4.26 (br s, minor isomer) and 4.37 (br s, major isomer) (total 1H), 4.59−4.61 (m, 2H), 5.25−5.31 (m, minor isomer) and 5.52−5.61 (m,major isomer) (total 1H), 7.18−7.36 (m, 10H); ^{13}C NMR δ 15.6, 15.8, 19.1, 19.5, 28.3, 30.7, 34.0, 34.2, 34.9, 35.2 71.2, 71.3, 72.8, 72.9, 73.0, 73.1 73.3, 73.4, 92.9, 93.0, 99.9, 105.9, 106.0, 115.6, 125.6, 125.9, 127.7, 128.3, 128.4, 137.8, 137.9, 141.3, 141.4, 142.3, 156.5, 160.6, 200.5, 200.6; IR (neat) υ 3400, 1100, cm^{-1}.

2-Benzyloxymethyl-3-methyl-5-(3-phenylpropyl)-furan (8h). Prepared from benzoate **6h.** Elution with 2.5% EtOAc/hexanes afforded furan **8h** (69%) as a yellowish oil: ^{1}H NMR δ 1.89−2.07 (m, 5H), 1.97 (s, included in m at 1.89−2.07), 2.58−2.70 (quint, J = 7.5 Hz, 4H), 4.41 (s, 2H), 4.53 (s, 2H), 5.85(s, 1H), 7.18−7.38 (m, 10H); ^{13}C NMR δ 9.9, 27.5, 29.6, 35.3, 61.8, 71.5, 108.5, 119.8, 125.8, 127.6, 127.8, 128.3, 128.5, 138.3, 142.0, 145.4, 155.3; IR ($CHCl_3$) υ 3025, 2930, 2860, 1600, 1450, 1060, 740, 700 cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.45; H, 7.55. Found: C, 82.46; H, 7.63.

2-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyl-5-(3-phenylpropyl)furan (8i). Prepared from benzoate **6i**. Elution with 2.5% EtOAc/hexanes afforded furan **8i** (35%) as a yellowish oil. Further elution with 10% EtOAc/hexanes afforded *tert*-butyldiphenylsilanol[27] (39%). Data for **8i**: ^{1}H NMR δ 1.05 (s, 9H), 1.77 (s, 3H), 1.90 (quint, J = 7.5 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 4.58 (s, 2H), 5.77 (s, 1H), 7.23−7.46 (m, 11H), 7.72 (m, 4H); ^{13}C NMR δ 9.7, 19.3, 26.8, 27.5, 29.6, 35.2, 56.7, 108.3, 117.8, 125.7, 127.5, 128.3, 128.5, 129.5, 133.7, 135.7, 142.1, 147.2, 154.5; IR (neat) υ 2860, 1450, 1430, 1110, 1050, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{36}O_2Si$: C, 79.44; H, 7.75. Found: C, 79.01; H, 7.77.

5-(3-Phenyl-1-methylpropyl)-2,3-dimethylfuran (8j). Prepared in 63% yield from acetate **6j** after elution with hexanes. Colorless oil: ^{1}H NMR δ 1.31 (d, J = 7.0 Hz, 3H), 1.80−1.92 (m, 1H), 1.99 (s, 3H), 2.02−2.13 (m, 1H), 2.25 (s, 3H), 2.68 (t, J = 8.0 Hz, 2H), 2.78−2.86 (m, 1H), 5.85 (s, 1H), 7.21−7.37 (m, 5H); ^{13}C NMR δ 9.9, 11.2, 19.3, 32.6, 33.4, 37.5, 106.8, 113.9, 125.6, 128.2, 128.4, 142.5, 145.1, 157.2; IR (neat) υ 3080−3020, 2950, 1230, 950 cm^{-1}; HRMS calcd for $C_{16}H_{20}O$ 228.1514, found 228.1515.

5-(2-Benzyloxyethyl)-2,3-dimethylfuran (8k). Prepared in 31% yield from acetate **6k**. After flash chromatography (2% EtOAc/hexanes), the product was further purified by HPLC (Column 1, 5% EtOAc/hexanes, 8 mL/min), yielding **8k** as an oil: t_R = 33 min; ^{1}H NMR δ 1.89 (s, 3H), 2.16 (s, 3H), 2.87 (t, J = 7.0 Hz, 2H), 3.69 (t, J = 7.0 Hz, 2H), 4.54 (s, 2H), 5.84 (s, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR δ 9.9, 11.2, 28.8, 68.5, 72.9, 109.1, 114.3, 127.5, 127.6, 128.3, 138.3, 145.6, 149.7; IR (neat) υ 3080, 3020, 2920, 2850, 1100 cm^{-1}; HRMS calcd for $C_{14}H_{15}O_2$ (M-CH_3) 215.1072, found 215.1075.

5-(4-Cyano-1-methylbutyl)-2,3-dimethylfuran (8l). Prepared in 77% yield from acetate **6l**. After flash chromatography (5% EtOAc/hexanes), the product was further purified by HPLC (Column 1, 5% EtOAc/hexanes, 9 mL/min) yielding **8l** as an oil: t_R = 30 min; ^{1}H NMR δ 1.21 (d, J = 6.9 Hz, 3H), 1.25−1.84 (m, 4H), 1.89 (d, J = 0.5 Hz, 3H), 2.15 (s, 3H), 2.22−2.32 (m, 1H), 2.70−2.75 (m, 1H), 5.75 (s, 1H); ^{13}C NMR δ 9.8, 11.2, 17.1, 19.2, 23.1, 32.4, 34.7, 107.1, 113.9, 119.7, 145.4, 156.1; IR (neat) υ 3000−2850, 2240, 1460, 1230 cm^{-1}; HRMS calc for $C_{12}H_{17}O$ 191.1310, found: 191.1306.

5-[(*E*)-6-Ethoxycarbonylhex-5-enyl]-2,3-dimethylfuran (8m). Prepared in 70% yield from acetate **6m**. After flash chromatography (hexanes), the product was further purified by HPLC (Column 1, 1% EtOAc/hexanes, 9 mL/min) yielding **8m** as an oil: t_R = 19 min; ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 1.43−1.68 (m, 4H), 1.88 (s, 3H), 2.14 (s, 3H), 2.16−2.25 (m, 2H), 2.52 (t, J = 7.2 Hz, 2H), 4.17 (7.1, 2H), 5.73 (s, 1H), 5.80 (dt, J = 15.6, 1.4 Hz, 1H), 6.95 (dt, J = 15.6, 1.4 Hz, 1H); ^{13}C NMR δ 9.7, 11.1, 14.1, 27.3, 27.6, 31.7, 60.0, 107.9, 114.0, 121.3, 145.1, 148.9, 152.5, 166.5; IR (neat) υ 2990−2860, 1750, 1660, 1450, 1040 cm^{-1}; HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1561.

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Supporting Information Available: Preparation of **2**. Characterization data for **2**, **5**, **6**, **7h**. Copies of ^{1}H NMR spectra for **6**, **7h**, **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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