SmI_2/Pd(0)-Mediated Intramolecular Coupling between Propargylic Esters and Tethered Aldehydes or Ketones

José M. Aurrecoechea,* Roberto Fañanás, Mónica Arrate, José M. Gorgojo, and Natalia Aurrekoetxea

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain

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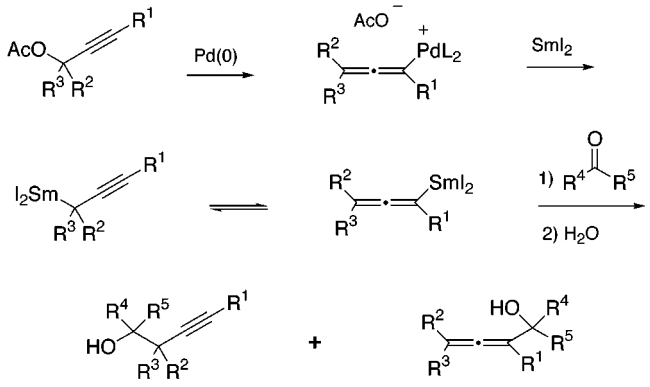
A SmI_2/Pd(0)-promoted intramolecular coupling between propargylic esters and carbonyl compounds is described. The reaction affords homopropargyl cycloalkanol products. Cyclopentanols are formed in high yields when ketones are employed as the carbonyl components, but aldehydes are found not to be suitable partners in these reactions. Particularly remarkable is the efficient formation of products with adjacent functionalized quaternary centers. These cyclizations take place with low diastereoselectivity about the newly created propargylic and carbinol stereogenic centers except when these two centers are quaternary or in the presence of groups capable of both chelating trivalent samarium and facilitating retroaldol−aldol-type equilibria in the product. In this latter case, the strategic combination of chemoselective carbonyl addition and SmI_2/Pd(0)-promoted cyclization provides ready and convenient stereocontrolled access to functionalized cyclopentanols from unprotected 1,5-dicarbonyl starting materials. The analogous formation of cyclohexanols is limited by low cyclization yields and lack of stereoselectivity.

Introduction

Samarium diiodide (SmI_2) has become a popular reagent in recent years due to its ability to promote chemo-, regio-, and stereoselective radical and/or organometallic C−C bond-forming processes from a wide variety of substrates.[1] The SmI_2-promoted couplings of carbonyl groups with other functionalities has been the most developed area of study, and numerous combinations are now available to the synthetic chemist. Particularly valuable are those processes leading to cyclic structures[2] that retain some of the functionality present in the substrates (especially unsaturated groups), as the products can be further elaborated into more complex targets. The allylation, propargylation, and allenylation of carbonyl compounds all fit the latter requirement. SmI_2 is known to promote couplings of carbonyl compounds with allylic derivatives[3] and vinyloxiranes[4] where these substrates behave, in a formal sense, as nucleophilic allylating agents. Analogously, propargylic esters and phosphates, as well as alkynyloxiranes, behave as synthetic equivalents of the propargyl-allenyl anion when treated with SmI_2 in the presence of aldehydes or ketones.[5,6] However, while alkynyloxiranes afford allenic alcohols with complete regioselectivity,[5] the intermolecular reactions of propargylic esters and phosphates generally afford mixtures of homopropargyl and allenic alcohols where the latter predominate.[6] This last reaction requires the use of catalytic amounts of Pd(0) and is thought[6a] to involve the initial formation of an allenylpalladium complex that is rapidly reduced to an equilibrium mixture of allenic and propargylic organosamarium intermediates[7] that finally add to the carbonyl group (Scheme 1). The use of a suitably located tether of appropriately short length between the carbonyl and propargylic ester functionalities (Scheme 2) was expected[8] to result in intramolecular cyclization[9] with formation of alkyne products exclusively because of the strain involved in the genera-

Scheme 1



* Corresponding author. Phone: 34-946 01 2578, fax: 34-944 64 8500, e-mail: qopaufem@lg.ehu.es.

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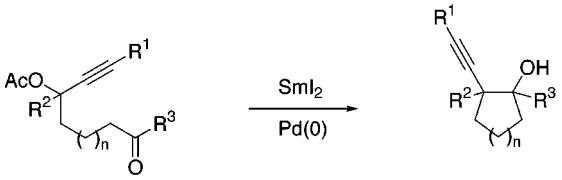
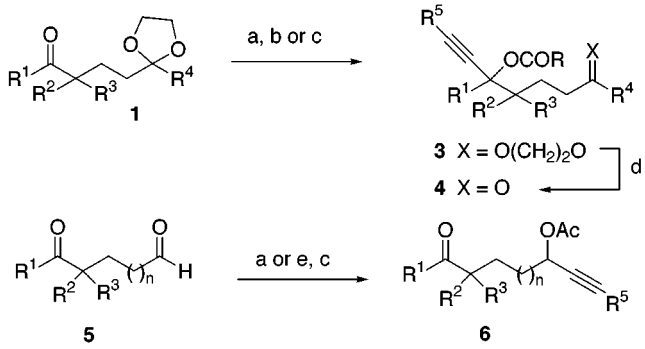
Scheme 2



tion of a cyclic allene. This paper reports the SmI_2/Pd(0)-promoted intramolecular cyclization of tethered propargyl esters and aldehydes or ketones to afford homopropargyl cycloalkanols. In a formal sense, this strategy represents a new entry into propargyl anion synthons suitable for intramolecular carbonyl additions. The homopropargyl alcohol subunit present in the products has importance as a component of a number of biologically interesting molecules[10] as well as a versatile functionality capable of useful synthetic transformations.[11]

Scheme 3



(a) R^5–≡–H (**2**), *n*-BuLi; (b) BzCl. (c) Ac_2O / Et_3N / DMAP. (d) Me_2CO / H_2O / *p*-TsOH or AcOH / H_2O. (e) (i) R^5–≡–H (**2**), *n*-BuLi; (ii) $(i\text{-PrO})_3TiCl$.

Table 1. Preparation of Propargylic Esters 6 from Ketoaldehydes 5

R^1	R^2	R^3	R^5	*n*	**6** (%)[a]
$(CH_2)_3$		CO_2Et	H	1	**6a** (32)[b]
$(CH_2)_3$		CO_2Et	*n*-Bu	1	**6b** (70)[c]
$(CH_2)_4$		CO_2Et	H	1	**6c** (81)[c]
$(CH_2)_4$		CO_2Et	*n*-Bu	1	**6d** (70)[c]
Me	Me	CO_2Et	H	1	**6e** (49)[c]
Me	Me	CO_2Et	*n*-Bu	1	**6f** (63)[c]
$(CH_2)_3$		H	H	1	**6g** (69)[c,d]
$(CH_2)_3$		CO_2Et	H	2	**6h** (63)[c]
$(CH_2)_4$		CO_2Et	H	2	**6i** (66)[c]

[a] Overall yield from **5** (two steps). [b] Addition of ethynyllithium to **5**. [c] Addition of ethynyltitanium triisopropoxide to **5**. [d] Overall alkynylation yield (see Experimental Section).

Results and Discussion

The substrates required for this study were prepared from either suitable monoprotected dicarbonyl derivatives **1** by a straightforward three-step sequence (Scheme 3) or more directly from unprotected keto aldehydes **5** by chemoselective alkynylation of the aldehyde carbonyl group, followed by acetylation of the resulting crude alcohol (Scheme 3; Table 1). As shown in Table 1, the use of Reetz's procedure[12] with alkynyl titanium triisopropoxide reagents was much more efficient than the alternative use of the more conventional lithium reagent.

Synthesis of Cyclopentanols. Initial studies were conducted on simple acyclic propargylic esters **4a**–**h** (eq 1, Table 2) by adding a mixture of **4** and $Pd(PPh_3)_4$ (5–6 mol % with respect to **4**) to SmI_2 (2.0–4.8 equiv) in THF at 25 °C. Substrates **4a**,**b** and **4e**–**h**, containing a ketone carbonyl group, produced good yields of the respective homopropargyl cyclopentanols **7**. Both terminal and internal alkynes participate effectively in the cyclization, and allenic products derived from an alternative intermolecular coupling[6a] were not detected. Small amounts of benzyl alcohol, probably the result of competing elimination[13] of alkoxide anion from a presumed organosamarium intermediate, were also obtained in the

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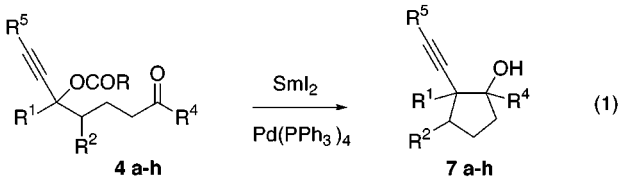
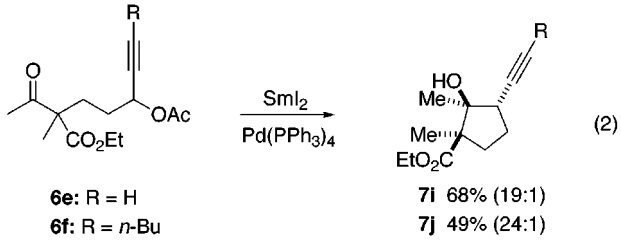
Table 2. Preparation of Cyclopentanols 7a−h from Esters[a] 4a−h (eq 1)



4	R^1	R^2	R^4	R^5	**7** (%)	*cis*/*trans* ratio[b]
4a	H	Bn	Me	H	**7a** (87)	*c*
4b	H	Bn	Me	*n*-Bu	**7b** (91)	*d*
4c	H	Bn	H	H	**7c** (9)[e]	*d*
4d	H	Bn	H	*n*-Bu	**7d** (8)	*f*
4e	H	H	Me	$(CH_2)_2OBn$	**7e** (72)	1:1.9
4f	H	H	Me	CH_2OBn	**7f** (64)	1.1:1
4g	Me	H	Me	$(CH_2)_2OBn$	**7g** (61)	6.7:1
4h	Me	H	Me	CH_2OBn	**7h** (72)	7.0:1

[a] All esters are benzoates except for acetate **4e**. [b] *Cis*, *trans* refer to isomers with alkynyl and OH groups in a relative *cis* or *trans* orientation, respectively. [c] Mixture of four diastereomers in a ratio of 1.5 (two isomers):1.5:1. [d] Mixture of four diastereomers in a ratio of 1.6 (two isomers):1 (two isomers). [e] 11.2 mol % of catalyst was used. [f] A 5.2:1 *cis*/*trans* or *trans*/*cis* ratio.

reactions of substrates **4f** and **4h**. The effective generation of two contiguous functionalized quaternary centers with good stereoselectivity from esters **4g** and **4h** (eq 1, Table 2) is particularly remarkable. In contrast to the behavior observed with ketones, the results obtained for **4c** and **4d** (eq 1, Table 2) indicate that aldehyde carbonyl groups are not suitable partners for this cyclization reaction as complex reaction mixtures and low yields of products were obtained with those substrates. The method was also extended to β-ketoesters **6e**,**f** (eq 2). Reaction conditions for these substrates were worked out after previous experimentation with substrate **6a** (vide infra) and involved dropwise addition of SmI_2 to **6e**,**f** and Pd-$(PPh_3)_4$ at 25 °C.

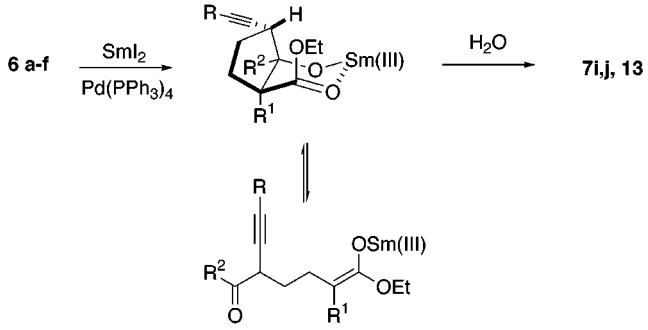


6e: R = H
6f: R = *n*-Bu

7i 68% (19:1)
7j 49% (24:1)

As shown in Table 2, cyclopentanols derived from tertiary propargyl esters **4g**,**h** were formed with moderate stereoselectivity, whereas simple secondary propargyl esters **4a**−**f** reacted in general with low or no selectivity. In contrast, secondary propargyl esters **6e**,**f**, featuring a ketone carbonyl group with an α-alkoxycarbonyl substituent, afforded the corresponding cyclopentanol products **7i**,**j** with very high stereoselectivity (eq 2); out of four possible isomers one was obtained in at least a 19:1 ratio. The very high stereoselectivity observed in the formation of **7i**,**j** probably stems out of both the chelating ability of the CO_2Et group toward Sm(III) and the intervention of retroaldol−aldol-type processes[14] in the cyclized samarium alkoxides (Scheme 4). This has been shown to

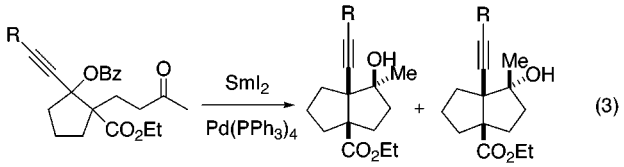
Scheme 4



be the case for SmI_2-induced cyclizations leading to closely related products under similar aprotic conditions.[14a] Thus, in the preferred conformation of the cyclized samarium alkoxide the alkynyl group would occupy the convex face of the bicyclic structure generated by chelation (Scheme 4).

The stereochemical assignments for alcohols **7e**,**f** were readily made after the observation of NOE's between H-2 and C_1-Me that were larger in the *cis*-isomers (10−12% vs 3−5%). Similar NOE studies performed on major **7i** indicated a *trans*-relationship between the alkynyl and OH groups (see Supporting Information), and this was supported by the large pyridine-induced downfield shift[15] observed for the propargylic methine protons of the major **7i**,**j** isomers ($\Delta\delta \approx 0.58-0.61$). A *cis*-relationship between the CO_2Et and OH groups in the major **7i**,**j** isomers was initially assigned based on literature precedent,[14] and confirmed by comparison of the IR carbonyl stretching frequencies in dilute solutions with relevant literature examples.[14b,c] For **7g**,**h** small NOE's were observed between the Me groups of the major **7g** isomer, but a meaningful comparison with the minor isomer could not be made due to the small magnitude of the effects and overlap between the resonances of the OH and one of the Me groups in the latter. NOE studies on **7h** were precluded by the impossibility to separate both isomers. A *cis* stereochemistry between the alkynyl and OH substituents was tentatively assigned to the major **7g**,**h** isomers based on the relative pyridine-induced downfield shifts of the C_2-Me protons that were much more pronounced in the minor (*trans*) isomers of **7g**,**h** ($\Delta\delta \approx 0.28-0.33$) as compared to the major (*cis*) ones ($\Delta\delta \approx 0.05-0.08$).

Synthesis of Bicyclic Alcohols. (a) Five-Membered Ring Formation. We also sought to extend this cyclization to the formation of bicyclic products. The successful cyclization of **4i**,**j** (eq 3) underlines the potential of this methodology for the preparation of bicyclic structures with three contiguous quaternary centers.



4i: R = H
4j: R = *n*-Bu

8a 51% (2.7:1 diasteromer ratio)
8b 60% (one isomer)

Thus, terminal propargylic ester **4i**, under the conditions

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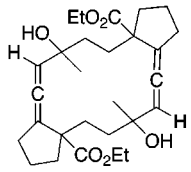
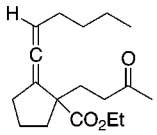
utilized for **4a**, afforded the desired alcohol **8a** (46%, 2.7:1 diastereomeric mixture), accompanied by a product tentatively assigned the dimeric structure **9** (14%). This assignment is supported by IR, ^{1}H- and ^{13}C NMR, as well as MS data. The formation of **9** is the result of two sequential intermolecular[6a] and intramolecular SmI_2/Pd(0)-mediated couplings between two molecules of **4i**. The yield of the bicyclic products was slightly improved (51%) by working at lower concentrations (a factor of 2.5) and increasing the amount of catalyst to 10 mol %. However, the amount of dimer isolated remained the same, and higher dilutions led only to longer reaction times without noticeable changes in the relative amounts of **8a** to **9**. Interestingly, the internal alkyne **4j** cyclized in good yield to afford bicyclic alcohol **8b** as a single diastereomer, along with a small amount of allene **10** (11%), presumably formed by early protonation of an organosamarium intermediate.[16] For best results this reaction had to be run at 60 °C. Lower temperatures resulted in increasing amounts of allene **10** at the expense of cyclized product.

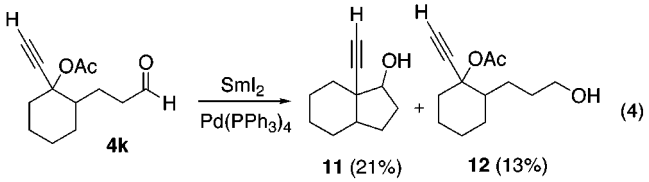


9



10

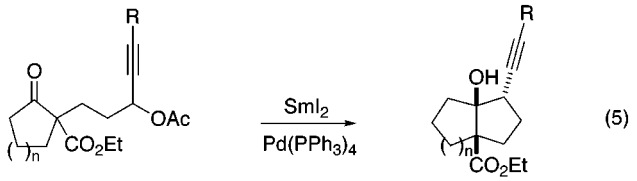
The reactivity of aldehyde **4k** (eq 4) was also explored in an attempt to gain advantage of the bias toward cyclization brought about by the existing ring in the substrate. Addition of **4k** and $Pd(PPh_3)_4$ to SmI_2 at different temperatures led only to very complex mixtures. The desired product **11** was obtained in low yield (21%, one diastereomer) when SmI_2 was added to the solution of **4k** and the catalyst at 40 °C. Therefore, it is concluded that the use of aldehydes is not compatible with this methodology.



4k **11** (21%) **12** (13%) (4)

The relative stereochemistry assigned to bicyclic alcohols **8a** was based on the observation that the *endo* Me carbinol substituent in the major isomer had ^{1}H and ^{13}C NMR resonances that were shielded with respect to the corresponding resonances in the minor isomer.[17a] This preference for a *cis*-relationship between alkynyl and OH groups is in line with that observed for similarly substituted cyclopentanols **7g**,**h**. The absence of the minor isomer of alcohols **8b** and **11** for comparison purposes precluded any stereochemical assignment for these substances.

Table 3. Preparation of Cyclopentanols 13 from Esters 6a−d (eq 5)

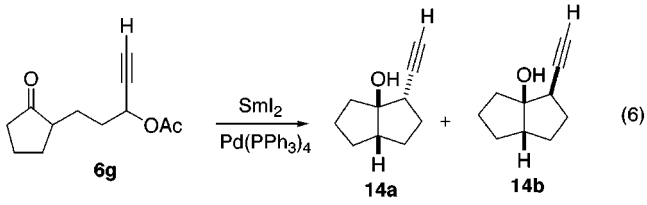


6a-d **13a-d** (5)

ester	R	*n*	**13** (%)	diast ratio
6a	H	1	**13a** (87)	*a*
6b[b]	*n*-Bu	1	**13b** (62)	*a*
6c[b]	H	2	**13c** (88)	24:1
6d[b]	*n*-Bu	2	**13d** (70)	*a*

[a] A single isomer was obtained. [b] 10−12.6 mol % Pd catalyst was used.

As expected (vide supra), secondary propargylic acetates **6a**−**d** with a tethered β-ketoester provided bicyclic alcohols **13** with excellent stereocontrol (eq 5, Table 3). A strong dependence on the order of addition of reagents was found in these reactions. Thus, when a mixture of **6a** and $Pd(PPh_3)_4$ was added to SmI_2 at room temperature, the starting material was consumed immediately and the expected product **13a** was obtained as a single diastereomer. However, the high reactivity toward SmI_2 of the β-ketoester[14c] relative to the propargylic ester functionality also led to side reactions that produced large amounts of untractable polar material, significantly lowering the cyclization yield (24%). By adding the SmI_2 solution dropwise to the solution of **6a** and $Pd(PPh_3)_4$, a comparatively high concentration of the allenylpalladium complex, relative to SmI_2, is maintained throughout the reaction, thus avoiding competing side reactions between the β-ketoester and SmI_2. Bicyclic alcohol **13a** was obtained in this way in 87% yield as a single diastereomer. Similar reaction conditions were applied to substrates **6b**−**d** (eq 5, Table 3) and **6e**,**f** (vide supra) with comparable outcomes. Not surprisingly, the cyclic ketone **6g**, lacking the ethoxycarbonyl substituent, produced a mixture of bicyclic alcohols **14** with low selectivity (eq 6).



6g **14a** **14b** (6)

57% (1.5:1)

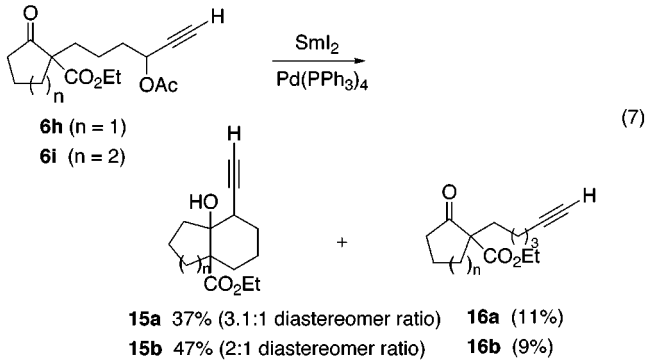
Analogously to the **7i**,**j** cases discussed above, the stereochemical assignments of bicyclic alcohols **13** relied on a combination of NOE studies, pyridine-induced shifts, and IR data. Thus, NOE's (9−10%) were observed between the OH and the propargylic methine proton of **13**, indicating a *trans*-relationship between the alkynyl and OH functionalities in the major cyclization products. This assignment was supported by the large pyridine-induced deshielding[15] experienced by the propargylic methine protons ($\Delta\delta \approx 0.51-0.84$) when comparing the

(16) (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237−5240. (b) It is also interesting that allene **10** was isolated as a single diastereomer. An example of very high diastereoselectivity in allene formation from a propargyl ester and SmI_2/Pd(0) has been previously reported: Vanalstyne, E. M.; Norman, A. W.; Okamura, W. H. *J. Am. Chem. Soc.* **1994**, *116*, 6207−6216.

(17) (a) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987; pp 137−146. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic compounds*; John Wiley & Sons: New York, 1994; p 776.

^{1}H NMR spectra taken in pyridine-d_5 and $CDCl_3$. The *cis*-relationship between the CO_2Et and OH groups was based again on the observed carbonyl stretching frequencies in dilute solutions.[14b,c] For bicyclic products **14** a *cis* ring fusion was assumed from ring strain considerations.[17b] Stereochemical assignments at C_2 followed from the larger pyridine-induced[15] deshielding experienced by the *exo*-propargylic proton in the major (*trans*) isomer ($\Delta\delta \approx 0.37$) as compared to the corresponding shift in the *endo*-proton of the minor (*cis*) isomer ($\Delta\delta \approx 0.09$).

Synthesis of Bicyclic Alcohols. (b) Six-Membered Ring Formation. The analogous formation of six-membered rings was much less efficient (eq 7). The desired products **15** were obtained in low yields as mixtures of diastereomers with low diastereoselectivity. The alkynes **16** were formed in significant amounts as byproducts in these reactions. A likely explanation is that a slower cyclization rate in these cases would cause the protonation of the presumed organosamarium intermediate to compete efficiently with cyclization.



(7)

Conclusions

When treated with SmI_2/Pd(0), propargylic esters undergo intramolecular reductive coupling to tethered aldehydes or ketones to afford homopropargyl cycloalkanol products. Efficient couplings, in terms of yield and diastereoselectivity, are realized for five-membered ring formation from substrates containing either a ketone carbonyl group and a tertiary propargylic ester or a β-ketoester. Resident ether and ester functionalities incorporated in the substrates have been shown to be compatible with this chemistry. The available data in SmI_2-promoted reactions indicate that this will also be the case for other useful functionality.[1]

Experimental Section

General. All reactions involving air- and moisture-sensitive materials were performed using standard benchtop techniques.[18] Diiodoethane was purified as reported.[19] Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. Other solvents were routinely purified using literature procedures.[20] Flash column chromatography[21] was performed on silica gel (230−400 mesh). HPLC purifications were carried out with either a LiChrosorb Si60 (7 μm, 25 × 2.5 cm, column 1) or a μPorasil (10 μm, 19 × 1.5 cm, column 2) column using a refraction index detector. Preparative thin-layer chromatography was performed on silica gel plates (Si60+F254, 17 μm, 20 × 20 cm, 0.25 mm). In Kugelrhor distillations the bp refers to the external oven air temperature. ^{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. GC-MS analysis were performed at 70−280 °C (20 °C/min) with a stationary phase of methylphenylsilicone (0.25 μm, 30 m × 0.25 mm).

Preparation of 1-(1-Benzyl-4-oxopentyl)prop-2-ynyl Benzoate (4a). A solution of *N*-(3-phenylpropylidene)cyclohexylamine (4.81 g, 22.39 mmol) in THF (30 mL) was slowly added to LDA [prepared from diisopropylamine (3.8 mL, 26.82 mmol and *n*-butyllithium (1.5 M, 15.6 mL, 23.5 mmol) in THF (75 mL)] at −78 °C under Ar. The resulting solution was warmed to −20 °C, stirred at this temperature for 90 min, and recooled to −78 °C. A solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[22] (5.18 g, 26.86 mmol) in THF (15 mL) was then added, and the mixture was allowed to reach rt and stirred further 18 h. After quenching with saturated NH_4Cl (20 mL), the aqueous layer was extracted with diethyl ether, and the combined organic layers were washed successively with 1 M HCl, 1 M NaOH, and brine, and dried (Na_2SO_4). Evaporation of the solvents left an oil that was purified by flash chromatography (20% EtOAc/hexanes) yielding 2.86 g (51%) of 2-benzyl-4-(2-methyl-1,3-dioxolan-2-yl)butanal (**1a**) as a yellowish oil: ^{1}H NMR δ 1.17 (s, 3H), 1.4−1.7 (m, 4H), 2.5−2.7 (m, 2H), 2.90 (dd, J = 13.4, 6.9 Hz, 1H), 3.7−3.8 (m, 4H), 7.0−7.2 (m, 5H), 9.56 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 22.6, 23.5, 34.8, 35.7, 52.8, 64.3, 109.3, 126.1, 128.2, 128.7, 138.5, 203.9.

A solution of **1a** (1.10 g, 4.43 mmol) in THF (13 mL) was added dropwise to a solution of ethynyllithium[23] (4.87 mmol) in THF (36 mL) at −78 °C. The mixture was stirred at the same temperature for 20 min, allowed to reach rt, and stirred further 1 h. To the well-stirred solution was added neat benzoyl chloride (1.03 mL, 8.87 mmol), and the mixture was stirred at room temperature for 1 h and quenched with water (13 mL). The whole was extracted with diethyl ether, and the organic extracts were dried (Na_2SO_4). The crude product was purified by flash chromatography (10% EtOAc/hexanes) to yield 1-[1-benzyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl]prop-2-ynyl benzoate (**3a**) (93%, 7:3 diastereomeric mixture) as a colorless oil: ^{1}H NMR δ 1.29 (s, 3H, major diast), 1.30 (s, 3H, minor diast), 1.6−1.9 (m, 4H), 2.2−2.3 (m, 1H), 2.53 (d, J = 2.0 Hz, 1H, minor diast), 2.56 (d, J = 2.0 Hz, 1H, major diast), 2.7−3.0 (m, 2H), 3.8−3.9 (m, 4H), 5.57 (dd, J = 4.1, 2.0 Hz, 1H, major diast), 5.62 (dd, J = 3.9, 2.1 Hz, 1H, minor diast), 7.2−7.6 (m, 8H), 7.9−8.0 (m, 2H); ^{13}C NMR δ 23.3, 23.6, 24.2, 35.8, 36.1, 36.5, 43.6, 43.9, 64.0, 66.0, 66.2, 74.9, 75.1, 77.2, 79.3, 79.4, 109.3, 109.4, 125.7, 128.0, 128.1, 128.6, 128.8, 129.3, 129.4, 132.7, 139.2, 139.6, 164.6; IR (neat) ν 3286, 2119, 1730 cm^{-1}. Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.15; H, 6.92. Found: C, 76.17; H, 6.76.

A solution of **3a** (1.20 g, 3.17 mmol) and *p*-TsOH (50 mg) in acetone (100 mL) was stirred at 35 °C for 48 h. After adding saturated aqueous $NaHCO_3$ (20 mL), the mixture was evaporated to dryness and partitioned between EtOAc (60 mL) and water (20 mL). The aqueous layer was extracted with EtOAc and the organic extracts were dried (Na_2SO_4). The crude product was purified by flash chromatography (10% EtOAc/hexanes) to yield the ketone **4a** (98%, 7:3 diastereomeric mixture) as a thick oil: ^{1}H NMR δ 1.8−1.9 (m, 1H), 1.9−2.0 (m, 1H), 2.07 (s, 3H, major diast), 2.10 (s, 3H, minor diast), 2.2−2.3 (m, 1H), 2.4−2.6 (m, 3H), 2.6−2.8 (m, 1H), 2.9−3.0 (m, 1H), 5.56 (dd, J = 3.8, 2.2 Hz, 1H, major diast), 5.60 (dd, J = 3.8, 2.3 Hz, 1H, minor diast), 7.1−7.3 (m, 5H), 7.4−7.5 (m, 2H), 7.5−7.6 (m, 1H), 7.95 (d, J = 7.9 Hz, 2H, minor diast),

(18) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis Via Boranes*; John Wiley & Sons: New York, 1975; pp 191−261.
(19) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778−1786.
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(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(22) Flannery, R. E.; Hampton, G. K. *J. Org. Chem.* **1972**, *37*, 2806−2810.
(23) Midland, M. M.; McLoughlin, J. I.; Werley, R. T. *Org. Synth.* **1989**, *68*, 14−24.

8.02 (d, J = 7.8 Hz, 2H, major diast); ^{13}C NMR δ 23.7, 24.1, 29.7, 29.8, 36.5, 37.1, 41.1, 41.2, 43.3, 43.6, 66.1, 66.5, 75.3, 75.4, 79.2, 79.4, 126.2, 126.4, 128.4, 128.5, 128.9, 129.1, 129.4, 129.5, 129.7, 133.3, 139.2, 139.5, 165.2, 207.9, 208.1; IR (neat) ν 3280, 2110, 1730 cm^{-1}. Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.00; H, 6.63. Found: C, 78.67; H, 6.64.

Preparation of 1-(1-Benzyl-4-oxopentyl)hept-2-ynyl Benzoate (4b). *n*-Butyllithium (1.5 M, 5.1 mL, 7.54 mmol) was added to a solution of 1-hexyne (1.10 mL, 9.59 mmol) in THF (15 mL) at −78 °C under Ar, and the resulting solution was stirred at the same temperature for 30 min. A solution of **1a** (1.70 g, 6.85 mmol) in THF (20 mL) was added, the reaction mixture was allowed to reach rt and stirred further 1 h before adding neat benzoyl chloride (1.60 mL, 13.71 mmol). After stirring the mixture 1 h at room temperature, it was quenched with water (15 mL) and extracted with diethyl ether. The organic extracts were dried (Na_2SO_4), and the crude product was purified by flash chromatography (15% EtOAc/hexanes) to yield 1-[1-benzyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl]hept-2-ynyl benzoate (**3b**) (2.91 g, 98%, ∼2:1 diastereomeric mixture) as a viscous oil: ^{1}H NMR δ 0.92 (t, J = 7.0 Hz, 3H, minor diast), 0.93 (t, J = 7.0 Hz, 3H, major diast), 1.29 (s, 3H, major diast), 1.30 (s, 3H, minor diast), 1.4−1.8 (m, 8H), 2.2−2.3 (m, 3H), 2.71 (dd, J = 13.8, 7.3 Hz, 1H, minor diast), 2.76 (dd, J = 13.8, 7.0 Hz, 1H, major diast), 2.91 (dd, J = 13.8, 7.3 Hz, 1H, major diast), 2.98 (dd, J = 13.8, 7.0 Hz, 1H, minor diast), 3.8−4.0 (m, 4H), 5.57 (td, J = 4.2, 2.1 Hz, 1H, major diast), 5.62 (td, J = 4.1, 2.0 Hz, 1H, minor diast), 7.2−7.6 (m, 8H), 7.9−8.0 (m, 2H); ^{13}C NMR δ 13.5, 18.4, 21.9, 23.6, 24.2, 24.7, 30.5, 30.6, 36.3, 36.6, 37.2, 44.5, 44.7, 64.5, 67.1, 67.3, 75.9, 75.9, 87.5, 87.6, 109.9, 109.9, 125.9, 126.1, 128.2, 128.3, 129.0, 129.2, 129.6, 130.0, 130.1, 132.8, 139.9, 140.4, 165.4; IR (neat) ν 2230, 1720 cm^{-1}.

A solution of **3b** (2.90 g, 6.70 mmol) and *p*-TsOH (100 mg) in acetone/water (40:1, 205 mL) was stirred at 35 °C for 7 h. After adding a saturated $NaHCO_3$ solution (20 mL), the mixture was evaporated to dryness and partitioned between diethyl ether (100 mL) and water (20 mL). The aqueous layer was extracted with diethyl ether, the combined organic layers were dried (Na_2SO_4), and the solvents were evaporated. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to yield the diastereomeric mixture (2.2:1) of ketone **4b** (2.60 g, 99%) as a thick oil: ^{1}H NMR δ 0.9 (m, 3H), 1.4−1.6 (m, 4H), 1.7−2.0 (m, 2H), 2.06 (s, 3H, major diast), 2.10 (s, 3H, minor diast), 2.1−2.3 (m, 3H), 2.4−2.7 (m, 3H), 2.95 (dd, J = 14.1, 6.9 Hz, 1H), 5.6 (m, 1H), 7.1−7.3 (m, 5H), 7.4−7.5 (m, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.95 (d, J = 7.3 Hz, 2H, minor diast), 8.02 (d, J = 7.2 Hz, 2H, major diast); ^{13}C NMR δ 13.3, 18.2, 21.7, 23.7, 24.2, 29.4, 29.5, 30.3, 30.4, 36.6, 37.2, 41.0, 41.2, 43.6, 43.9, 66.7, 67.0, 75.5, 75.6, 87.7, 87.8, 125.9, 126.1, 128.2, 128.3, 128.8, 128.9, 129.5, 129.7, 129.8, 132.9, 139.4, 139.8, 165.1, 207.7, 207.8; IR (neat) ν 2220, 1740 cm^{-1}. Anal. Calcd for $C_{26}H_{30}O_3$: C, 79.95; H, 7.74. Found: C, 79.63; H, 7.74.

Preparation of 1-(1-Benzyl-4-oxobutyl)prop-2-ynyl Benzoate (4c). The procedure used in the preparation of **1a** was followed starting from 2-(2-iodoethyl)-1,3-dioxolane[24] to yield 2-benzyl-4-(1,3-dioxolan-2-yl)butanal (**1b**) (63%): ^{1}H NMR δ 1.6−1.8 (m, 4H), 2.6−2.8 (m, 2H), 2.9−3.0 (m, 1H), 3.8−3.9 (m, 4H), 4.83 (t, J = 4.0 Hz, 1H), 7.1−7.3 (m, 5H), 9.68 (d, J = 1.9 Hz, 1H); ^{13}C NMR δ 22.4, 30.8, 34.9, 52.7, 64.6, 103.7, 126.2, 128.3, 128.7, 138.5, 203.9; IR (neat) ν 1730 cm^{-1}.

The procedure used in the preparation of **3a** was followed from **1b** to yield 1-[1-benzyl-3-(1,3-dioxolan-2-yl)propyl]prop-2-ynyl benzoate (**3c**) (84%, 7:3 diastereomeric mixture) as a viscous oil: ^{1}H NMR δ 1.6−1.9 (m, 4H), 2.2−2.3 (m, 1H), 2.54 (d, J = 1.5 Hz, 1H, minor diast), 2.56 (d, J = 1.5 Hz, 1H, major diast), 2.7−3.0 (m, 2H), 3.8−3.9 (m, 4H), 4.85 (m, 1H), 5.56 (br s, $W_{1/2}$ = 8.0 Hz, 1H, major diast), 5.62 (br s, $W_{1/2}$ = 7.7 Hz, 1H, minor diast), 7.2−7.6 (m, 8H), 7.94 (d, J = 7.7 Hz, 2H, minor diast), 8.02 (d, J = 7.6 Hz, 2H, major diast); ^{13}C NMR δ 24.0, 24.5, 31.3, 31.4, 36.4, 36.9, 43.9, 44.3, 64.8, 66.3, 66.6, 75.0, 75.2, 79.4, 79.7, 104.3, 104.4, 126.1, 126.3, 128.3, 128.5, 129.0, 129.1, 129.7, 133.1, 139.4, 139.9, 165.2; IR (neat) ν 3280, 2120, 1730 cm^{-1}. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.63. Found: C, 75.86; H, 6.76.

A solution of **3c** (0.95 g, 2.6 mmol) in acetic acid/water (1:1, 2 mL) was stirred and refluxed for 1 h. After cooling, the solution was made neutral with saturated K_2CO_3 and extracted with diethyl ether. The combined organic extracts were washed with brine and dried (Na_2SO_4). Purification by flash chromatography (15% EtOAc/hexanes) afforded the aldehyde **4c** (0.82 g, 7:3 diastereomeric mixture) as a colorless oil that contained ∼14% of the starting acetal. HPLC purification (Column 2, 15% EtOAc/hexanes, 6 mL/min) provided the pure sample: ^{1}H NMR δ 1.8−1.9 (m, 1H), 1.9−2.1 (m, 1H), 2.2−2.3 (m, 1H), 2.5−2.6 (m, 3H), 2.60 (d, J = 2.1 Hz, 1H, overlapped with mult at 2.5−2.6), 2.7−2.8 (m, 1H), 2.9−3.0 (m, 1H), 5.5−5.6 (m, 1H), 7.1−7.6 (m, 8H), 7.9−8.0 (m, 2H), 9.73 (br s, $W_{1/2}$ = 3.6 Hz, 1H); ^{13}C NMR δ 22.1, 22.4, 36.5, 37.1, 41.5, 41.6, 43.3, 43.7, 65.9, 66.5, 75.4, 75.6, 78.9, 79.4, 126.3, 126.5, 128.4, 128.6, 128.9, 129.1, 129.5, 129.7, 133.3, 138.9, 139.3, 165.2, 201.6; IR (neat) ν 3290, 2110, 1730 cm^{-1}.

Preparation of 5-(Benzyloxy)-1-(4-oxopentyl)pent-2-ynyl Ethanoate (4e). A solution of ethyl 4-acetylbutyrate (11.80 g, 75.0 mmol), ethylene glycol (5.5 mL, 98.6 mmol), and *p*-TsOH (1.70 g, 8.8 mmol) in benzene (150 mL) was refluxed in a Dean−Stark for 4 h. The residue after evaporation of the solvent was partitioned between H_2O (125 mL) and EtOAc (125 mL), and the aqueous layer was extracted with EtOAc. The combined organic layers were evaporated affording ethyl 4-(2-methyl-1,3-dioxolan-2-yl)butanoate (14.60 g, 96%) as a colorless liquid that was used in the next step without further manipulation: ^{1}H NMR δ 1.17 (t, J = 7.1 Hz, 3H), 1.24 (s, 3H), 1.61−1.67 (m, 4H), 2.24 (distorted t, 2H), 3.83−3.87 (m, 4H), 4.05 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.1, 19.4, 23.6, 34.1, 38.1, 60.6, 64.4, 109.5, 173.3. A portion of this material (2.00 g, 10 mmol) was dissolved in toluene (20 mL) at −78 °C under Ar and DIBALH (1.0 M in hexanes, 10.5 mL, 10.5 mmol) was added dropwise. The resulting suspension was stirred for 30 min at −78 °C before adding MeOH (0.4 mL). The mixture was allowed to warm to −10 °C, MeOH/H_2O (1:1, 1.10 mL) was added, and the reaction was allowed to reach rt. Anhydrous Na_2SO_4 (2 g) was added, and the mixture was stirred for 15 min. The resulting suspension was filtered through Celite and the solids were washed with EtOAc. The crude after evaporation was purified by flash chromatography (15% EtOAc/hexanes) to yield 4-(2-methyl-1,3-dioxolan-2-yl)butanal[25] (**1c**) (900 mg, 57%) as a colorless liquid: ^{1}H NMR δ 1.23 (s, 3H), 1.61−1.66 (m, 4H), 2.39 (distorted t, 2H), 3.84 (m, 4H), 9.67 (d, J = 1.6 Hz, 1H); ^{13}C NMR δ 16.6, 23.7, 38.3, 43.8, 64.6, 109.7, 202.3.

n-Butyllithium (1.37 M, 2.8 mL, 3.9 mmol) was added dropwise to a solution of 4-(benzyloxy)but-1-yne (0.64 g, 4.0 mmol) in THF (20 mL) at −78 °C under Ar, and the mixture was stirred for 30 min. A solution of **1c** (0.61 g, 3.9 mmol) in THF (6 mL) was added, and the mixture was allowed to reach rt and stirred 3 h at this temperature. Water (20 mL) was added, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4). The crude product was treated with Et_3N (0.87 mL, 6.2 mmol), Ac_2O (0.78 mL, 8.2 mmol), and 4-(dimethylamino)pyridine (DMAP) (0.14 g, 1.3 mmol) for 14 h at room temperature. The mixture was evaporated under reduced pressure, and the residue was dissolved in diethyl ether (40 mL). The solution was successively washed with 1 M HCl, 1 M NaOH, and brine and dried (Na_2SO_4). The crude product was purified by flash chromatography (20% EtOAc/hexanes) to afford 5-(benzyloxy)-1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]pent-2-ynyl ethanoate (**3e**) (0.92 g, 65%, over two steps) as a thick oil: ^{1}H NMR δ 1.53 (s, 3H), 1.5−1.7 (m, 6H), 2.04 (s, 3H), 2.51 (t, J = 7.0 Hz, 2H), 3.56 (t, J = 7.0 Hz, 2H), 3.88 (m, 4H), 4.52 (s, 2H), 5.34 (m, 1H), 7.2−7.3 (m, 5H); ^{13}C NMR δ 19.6, 20.1, 21.0, 23.7, 35.0,

(24) Larson, G. L.; Klesse, R. *J. Org. Chem.* **1985**, *50*, 3627.

(25) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585−4595.

38.4, 64.2, 64.5, 68.2, 72.9, 78.6, 82.7, 109.8, 127.5, 128.3, 138.5, 169.9; IR ($CHCl_3$) ν 2240, 1745 cm^{-1}.

The hydrolysis procedure used in the preparation of **4b** was applied to **3e** to afford the ketone **4e** (92%) as a thick oil: ^1H NMR δ 1.6−1.7 (m, 4H), 2.04 (s, 3H), 2.10 (s, 3H), 2.43 (br t, 2H), 2.51 (td, J = 7.0, 1.7 Hz, 2H), 3.56 (t, J = 7.0 Hz, 2H), 4.52 (s, 2H), 5.34 (br s, $W_{1/2}$ = 11.9 Hz, 1H), 7.32 (m, 5H); ^{13}C NMR δ 19.1, 20.1, 20.9, 29.8, 34.1, 42.8, 63.8, 68.1, 72.9, 78.2, 83.0, 127.5, 128.3, 138.0, 169.9, 208.0; IR ($CHCl_3$) ν 2280, 1740, 1720 cm^{-1}; HRMS calcd for $C_{17}H_{21}O_2$ (M − AcO) 257.1542, found 257.1545; HRMS (FAB) calcd for $C_{19}H_{25}O_4$ (M+1) 317.1753, found 317.1749.

Preparation of 5-(Benzyloxy)-1-methyl-1-(4-oxopentyl)pent-2-ynyl Benzoate (4g). To a solution of LDA (41.3 mmol) in THF (60 mL) at 0 °C under Ar was added dropwise acetone dimethylhydrazone[26] (3.72 g, 37.2 mmol). The resulting suspension was stirred for 2 h at 0 °C, and 2-(2-iodoethyl)-2-methyl-1,3-dioxolane[24] (10.0 g, 41.3 mmol) was added. The mixture was allowed to warm to room temperature and was stirred further 2 h. Water (50 mL) was added, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in a 1:1 mixture of THF and 2.5% HCl (120 mL) at 0 °C, and the mixture was stirred 2 h at the same temperature. Water (30 mL) and saturated Na_2CO_3 (30 mL) were added, and the whole was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated, and the crude was purified by flash chromatography (40% EtOAc/hexanes) to yield 5-(2-methyl-1,3-dioxolan-2-yl)pentan-2-one (**1d**)[27] (3.40 g, 53%) as a yellowish oil: ^1H NMR δ 1.25 (s, 3H), 1.5−1.6 (m, 4H), 2.07 (s, 3H), 2.40 (t, J = 6.8 Hz, 2H), 3.8−3.9 (m, 4H); ^{13}C NMR δ 18.2, 23.6, 29.7, 38.1, 43.4, 64.5, 109.7, 208.6; IR ($CHCl_3$) ν 1720 cm^{-1}.

The alkynylation procedure previously described for the preparation of **3b** was followed from 4-(benzyloxy)but-1-yne and ketone **1d** to afford 5-(benzyloxy)-1-methyl-1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]pent-2-ynyl benzoate (**3g**) (71%) as a thick oil: ^1H NMR δ 1.33 (s, 3H), 1.6−1.7 (m, 4H), 1.78 (s, 3H), 1.8−1.9 (m, 1H), 1.9−2.0 (m, 1H), 2.56 (t, J = 7.0 Hz, 2H), 3.60 (t, J = 7.0 Hz, 2H), 3.8−3.9 (m, 4H), 4.54 (s, 2H), 7.2−7.5 (m, 8H), 7.99 (d, J = 7.8 Hz, 2H); ^{13}C NMR δ 18.9, 20.2, 23.7, 26.8, 38.9, 41.9, 64.5, 68.4, 72.8, 76.0, 81.3, 82.5, 109.8, 127.5, 128.1, 128.2, 129.4, 131.2, 132.5, 138.1, 164.4; IR ($CHCl_3$) ν 2220, 1715 cm^{-1}.

The hydrolysis procedure used in the preparation of **4b** was applied to **3g** to afford the ketone **4g** (85%) as a thick oil: ^1H NMR δ 1.78 (s, 3H), 1.8−2.0 (m, 4H), 2.13 (s, 3H), 2.49 (t, J = 1.7 Hz, 2H), 2.56 (t, J = 7.0 Hz, 2H), 3.60 (t, J = 7.0 Hz, 2H), 4.54 (s, 2H), 7.2−7.4 (m, 8H), 7.99 (d, J = 7.8 Hz, 2H); ^{13}C NMR δ 18.6, 20.1, 26.8, 29.7, 41.1, 43.2, 68.4, 72.8, 75.7, 81.0, 82.8, 127.5, 128.2, 128.3, 128.7, 129.4, 131.1, 132.6, 138.1, 164.6, 208.3; IR ($CHCl_3$) ν 2230, 1720 cm^{-1}; HRMS calcd for $C_{25}H_{28}O_4$ 392.1988, found 392.1988.

Preparation of 2-(Ethoxycarbonyl)-1-ethynyl-2-(3-oxobutyl)cyclopentyl Benzoate (4i). Ethyl 2-oxocyclopentanecarboxylate (5.00 g, 32.05 mmol) was added dropwise at room temperature to a suspension of NaH (0.756 g, 31.52 mmol) in dry dimethoxyethane. The mixture was stirred until complete disappearance of solid NaH. 2-(2-Iodoethyl)-2-methyl-1,3-dioxolane[24] (7.15 g, 29.42 mmol) was then added and the mixture refluxed overnight. After cooling to room temperature, the solvent was evaporated and the residue was treated with water (20 mL), acidified with 3 M HCl, and extracted with diethyl ether. After drying and evaporation of the solvent, the crude product was purified by flash chromatography (20% EtOAc/hexanes) to yield ethyl 1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-oxocyclopentanecarboxylate (**1e**) (53%) as an oil: ^1H NMR δ 1.24 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H), 1.5−1.7 (m, 3H), 1.8−2.1 (m, 4H), 2.2−2.6 (m, 3H), 3.9−4.0 (m, 4H), 4.14 (q, J = 7.1 Hz, 1H), 4.16 (q, J = 7.1 Hz, 1H); ^{13}C NMR δ 13.7, 19.2, 23.3, 27.7, 32.6, 33.6, 37.4, 59.3, 60.8, 64.2, 109.0, 170.5, 214.2; IR (neat) ν 1760, 1730 cm^{-1}.

The alkynylation procedure previously described for the preparation of **3a** was followed from ketone **1e** to yield 2-(ethoxycarbonyl)-1-ethynyl-2-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]cyclopentyl benzoate (**3i**) (94%, 97:3 diastereomeric mixture) as a thick oil: ^1H NMR δ 1.21 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H), 1.5−1.8 (m, 6H), 2.2−2.4 (m, 3H), 2.60 (s, 1H), 2.8−2.9 (m, 1H), 3.8−3.9 (m, 4H), 4.1−4.2 (m, 2H), 7.3−7.4 (m, 2H), 7.4−7.5 (m, 1H), 8.00 (d, J = 7.1 Hz, 2H); ^{13}C NMR δ 13.9, 19.0, 19.7, 23.6, 25.4, 27.3, 29.2, 33.7, 34.0, 34.2, 36.7, 60.5, 62.0, 64.4, 75.1, 76.8, 81.2, 81.8, 85.3, 109.4, 128.1, 129.3, 129.7, 130.1, 130.4, 132.8, 132.9, 164.1, 172.8; IR (neat) ν 3260, 2100, 1730 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.21; H, 6.93.

The hydrolysis procedure used in the preparation of **4b** was applied to **3i** to yield the ketone **4i** (93%, 97:3 diastereomeric mixture) as an oil: ^1H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 1.7−1.9 (m, 2H), 1.9−2.0 (m, 2H), 2.16 (s, 3H), 2.3−2.6 (m, 5H), 2.62 (s, 1H), 2.8−2.9 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.5−7.6 (m, 1H), 8.03 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ 13.6, 18.8, 24.6, 29.3, 29.4, 36.4, 38.6, 38.9, 60.4, 61.4, 75.2, 79.2, 80.9, 81.5, 127.9, 129.1, 129.7, 129.9, 132.6, 163.7, 172.3, 206.6, 206.8; IR (KBr) ν 3260, 2120, 1730 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.76; H, 6.78. Found: C, 70.85; H, 6.84.

Preparation of Ethyl 1-(3-Acetoxynon-4-ynyl)-2-oxocyclopentanecarboxylate (6b). *n*-Butyllithium (1.6 M, 1.25 mL, 2 mmol) was added to a solution of 1-hexyne (0.164 g, 2 mmol) in THF (15 mL) at −78 °C. After stirring the resulting solution for 30 min, chlorotitanium triisopropoxide (0.521 g, 2 mmol) was added and the clear solution stirred at −78 °C for 1 h. This solution was then added via cannula to a stirred solution of **5a**[28] (0.424 g, 2 mmol) in THF (15 mL) which had been previously cooled to −78 °C. At the end of the addition (ca. 30 min) the color of the reaction mixture was a light brown. After stirring at −78 °C for 30 min, the mixture was allowed to reach rt over a period of 2 h 30 min, kept at the same temperature for 1 h, and poured over 1 M HCl (25 mL). The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was dissolved in Et_3N (4.9 mL, 35.2 mmol) and to this solution were successively added Ac_2O (285 μL, 3.02 mmol) and DMAP (47 mg, 0.385 mmol). The resulting solution was stirred at room temperature for 15 h, after which the solvent was evaporated and the residue was dissolved in diethyl ether (30 mL). The solution was successively washed with 1 M HCl, 1 M NaOH, and brine and dried (Na_2SO_4). The crude acetate was purified by flash chomatography (15% EtOAc/hexanes) to afford 0.472 g (70%, two steps) of pure **6b**: ^1H NMR δ 0.83 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.2−1.5 (m, 4H), 1.5−1.7 (m, 2H), 1.7−2.0 (m, 5H), 1.98 (s, 3H, overlapped with mult at 1.7−2.0), 2.0−2.5 (m, 5H), 4.09 (qd, J = 7.1, 1.2 Hz, 2H), 5.25 (tt, J = 6.0, 1.9 Hz, 1H); ^{13}C NMR δ 13.4, 13.9, 18.2, 19.4, 20.9, 21.7, 28.9, 30.3, 30.3, 32.9, 37.6, 59.5, 61.2, 64.0, 76.8, 86.5, 169.7, 170.6, 214.2; IR (neat) ν 2240, 1750−1730 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 67.63; H, 8.49.

Preparation of Ethyl 1-(4-Acetoxyhex-5-ynyl)-2-oxocyclopentanecarboxylate (6h). Ethyl 2-oxocyclopentanecarboxylate (10.0 g, 64.03 mmol) was slowly added under Ar to a suspension of NaH (1.56 g, 65.1 mmol) in dry dimethoxyethane (100 mL). After the evolution of hydrogen had ceased, 5-bromopent-1-ene (7.08 g, 59.76 mmol) was added, and the mixture was refluxed for 40 h. After cooling, the resulting suspension was filtered, the solid was washed with diethyl ether, and the washings were added to the filtrate. After removing the solvent under reduced pressure, water (75 mL) was added, the mixture

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(27) Joshi, N. N.; Mandapur, V. R.; Chadha, M. S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2963−2966.

(28) Prepared following the procedure described in ref 29 for ethyl 1-(2-formylethyl)-2-oxocyclohexanecarboxylate.

(29) Cope, A. C.; Synerholm, M. E. *J. Am. Chem. Soc.* **1950**, *72*, 5228−5232.

(30) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931−5943 (cited in Supporting Information).

was acidified with concentrated HCl, and the whole was extracted with diethyl ether. The organic extracts were dried (Na_2SO_4) and the crude after evaporation was purified by flash chromatography (10% AcOEt/hexanes) to afford 12.0 g (90%) of ethyl 1-(pent-4-enyl)-2-oxocyclopentanecarboxylate as an oil: ^{1}H NMR δ 1.24 (t, J = 7.1 Hz, 3H), 1.3−1.6 (m, 3H), 1.8−2.1 (m, 6H), 2.2−2.6 (m, 3H), 4.15 (q, J = 7.1 Hz, 2H), 4.9−5.0 (m, 2H), 5.7−5.8 (m, 1H); ^{13}C NMR δ 13.8, 19.4, 23.9, 32.6, 33.0, 33.7, 37.7, 60.1, 61.0, 114.7, 137.8, 170.7, 214.5; IR (neat) ν 1750, 1730, 1640 cm^{-1}.

A portion of this alkene (0.50 g, 2.23 mmol) was dissolved in CH_2Cl_2/CH_3OH (16 mL/3 mL) at −78 °C, and a mixture of ozone/oxygen (0.7 A, 100 L/h) was bubbled through the solution until this had turned into a light blue. Ar was then bubbled through the solution at −78 °C until colorless, and the solution was allowed to reach rt. Dimethyl sulfide (0.3 mL, 4.46 mmol) was added, and the mixture was stirred at room temperature for 12 h. The solution was evaporated to a volume of ca. 5 mL, and the residue was partitioned between CH_2Cl_2 (50 mL) and water (15 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography to yield 0.38 g (75%) of ethyl 1-(4-oxobutyl)-2-oxocyclopentanecarboxylate (**5e**) as an oil: ^{1}H NMR δ 1.22 (t, J = 7.1 Hz, 3H), 1.5−1.8 (m, 3H), 1.8−2.1 (m, 4H), 2.1−2.6 (m, 5H), 4.12 (q, J = 7.1 Hz, 2H), 9.72 (s, 1H); ^{13}C NMR δ 13.4, 16.8, 19.0, 32.1, 32.4, 37.1, 43.1, 59.5, 60.6, 170.2, 201.1, 213.8; IR (neat) ν 1755, 1730 cm^{-1}.

The alkynylation procedure used in the preparation of **6b** was followed from ethynyllithium[23] and **5e** to afford the acetate **6h** (63%) as an oil: ^{1}H NMR δ 1.24 (t, J = 7.1 Hz, 3H), 1.3−1.7 (m, 3H), 1.7−1.8 (m, 2H), 1.9−2.0 (m, 4H), 2.07 (s, 3H), 2.1−2.6 (m, 4H), 2.43 (d, J = 2.0 Hz, overlapped with mult at 2.1−2.6), 4.1−4.2 (m, 2H), 5.32 (ddd, J = 9.0, 6.4, 2.5 Hz, 1H); ^{13}C NMR δ 13.5, 19.1, 19.7, 20.3, 32.2, 32.3, 32.5, 34.1, 37.2, 59.7, 60.7, 62.6, 73.4, 80.4, 169.0, 170.2, 213.8; IR (neat) ν 3270, 2120, 1750, 1730 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.27; H, 7.54. Found: C, 65.15; H, 7.57.

3-Benzyl-2-ethynyl-1-methylcyclopentanol (7a). Representative Procedure for SmI_2/Pd(0) Reductive Cyclizations of Substrates 4 and 6g. A SmI_2 solution in THF was prepared as reported from Sm metal and either diiodoethane,[16a] diiodomethane,[1b] or iodine.[1b] A solution of **4a** (0.350 g, 1.05 mmol) and $Pd(PPh_3)_4$ (55.2 mg, 0.052 mmol) in THF (10 mL) was added to the SmI_2 solution (2.3 mmol) in THF (12 mL) at 25 °C under Ar. The mixture was stirred for 2.5 h and then poured over a saturated K_2CO_3 solution (4 mL). Water (2 mL) was then added and the mixture stirred for 3 min. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried (Na_2SO_4). The crude after evaporation of the solvent was purified by flash chromatography (20% EtOAc/hexanes) to yield the title alcohol as a mixture of four diastereomers (colorless oil, 194 mg, 87%). One of the isomers (33% of the mixture) could be separated by HPLC (column 2, 15% EtOAc/hexanes, 5 mL/min): t_R 21 min; ^{1}H NMR δ 1.39 (s, 3H), 1.4−1.6 (m, 1H), 1.6−1.8 (m, 4H), 2.0−2.2 (m, 1H), 2.24 (d, J = 2.4 Hz, 1H), 2.47 (dd, J = 10.7, 2.4 Hz, 1H), 2.55 (dd, J = 13.4, 9.5 Hz, 1H), 3.07 (dd, J = 13.4, 4.3 Hz, 1H), 7.2−7.3 (m, 5H); ^{13}C NMR δ 26.0, 27.6, 39.2, 40.7, 46.8, 49.6, 72.3, 80.1, 83.7, 126.0, 128.2, 129.1, 140.6; IR (neat) ν 3380, 3300, 2110 cm^{-1}; HRMS calcd for $C_{15}H_{18}O$ 214.1358, found 214.1361.

The other three isomers were characterized as a mixture: ^{1}H NMR δ 1.35, 1.36 and 1.51 (s, 3H), 1.6−3.1 (m, 10H), 7.2−7.3 (m, 5H); ^{13}C NMR δ 26.1, 27.0, 27.4, 28.1, 28.5, 28.8, 37.5, 38.1, 38.6, 39.4, 42.3, 43.4, 45.8, 47.2, 47.2, 47.6, 49.5, 72.7, 73.9, 75.6, 79.4, 81.4, 82.0, 82.6, 82.7, 125.6, 125.7, 128.1, 128.1, 128.7, 128.8, 128.9, 140.2, 141.3, 141.4; HRMS calcd for $C_{15}H_{18}O$ 214.1358, found 214.1359.

(1*R,4*S**,5*R**)- and (1*R**,4*R**,5*R**)-Ethyl 5-Ethynyl-4-hydroxy-4-methylbicyclo[3.3.0]octanecarboxylate (*cis*-8a, *trans*-8a).** Prepared as described for **7a** by adding a solution of $Pd(PPh_3)_4$ (78.7 mg, 0.073 mmol) and **4i** (0.260 g, 0.734 mmol) in THF (20 mL) to SmI_2 (1.62 mmol) in THF (30 mL). After 90 min the usual workup afforded a crude product that was purified by flash chromatography (15% EtOAc/hexanes) to yield in successive order of elution *cis*-**8a** (64 mg), *trans*-**8a** (24 mg) (51% overall yield) and the dimer **9** (22 mg, 14%) as colorless oils. Data for *cis*-**8a**: ^{1}H NMR δ 1.29 (t, J = 7.1 Hz, 3H), 1.31 (s, 3H, C_4−CH_3, overlapped with triplet at 1.29), 1.3−2.1 (m, 8H), 2.26 (s, 1H), 2.6−2.7 (m, 2H), 3.65 (br s, 1H), 4.1−4.2 (m, 2H); ^{13}C NMR δ 14.1, 21.7 (C_4-*C*H$_3$), 26.7, 35.7, 37.9, 38.6, 40.6, 61.4, 63.6, 64.9, 72.8, 82.2, 85.0, 176.6; IR (neat) ν 3550, 3430, 3280, 2100, 1730 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_2$ (M^+-18) 218.1307, found 218.1286. Data for *trans*-**8a**: ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 1.3−1.5 (m, 2H), 1.51 (s, 3H, C_4−CH_3), 1.7−2.0 (m, 6H), 2.0−2.1 (m, 1H), 2.25 (s, 1H), 2.42 (ddd, J = 13.1, 11.2, 7.6 Hz, 1H), 2.6−2.7 (m, 1H), 4.1−4.2 (m, 2H); ^{13}C NMR δ 14.1, 26.4 (C_4-*C*H$_3$), 27.3, 32.9, 37.8, 39.2, 40.0, 60.8, 61.2, 64.4, 72.8, 81.1, 86.7, 175.4; IR (neat) ν 3500, 3300, 2100, 1720 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.98; H, 8.55. Data for **9**: ^{1}H NMR δ 1.1−1.4 (m, 14H), 1.19 (t, J = 7.1 Hz, overlapped with mult at 1.1−1.4), 1.35 (s, overlapped with mult at 1.1−1.4), 1.4−1.9 (m, 10H), 2.0−2.6 (m, 8H), 3.46 (br s, $W_{1/2}$ = 7.4 Hz, 2H), 4.0−4.2 (m, 4H), 5.18 (t, J = 4.2 Hz, 2H); ^{13}C NMR δ 14.1, 23.9, 28.3, 29.0, 30.1, 32.2, 37.6, 58.8, 61.5, 72.3, 106.6, 111.5, 176.5, 195.0; IR (neat) ν 3540, 3480, 1980, 1720 cm^{-1}; HRMS calcd for $C_{28}H_{40}O_6$ 472.2825, found 472.2825.

Ethyl 5-(Hex-1-ynyl)-4-hydroxy-4-methylbicyclo[3.3.0]-octanecarboxylate (8b). Prepared as described for **7a** by adding a solution of **4j** (0.24 g, 0.58 mmol) and $Pd(PPh_3)_4$ (64 mg, 0.06 mmol) in THF (17 mL) to SmI_2 (1.3 mmol) in THF (38 mL) at 65 °C. After 20 min the usual workup and flash chromatography (15% EtOAc/hexanes) afforded in order of elution the allene **10** (27 mg, 16%) and the bicyclic alcohol **8b** (102 mg, 60%) as colorless oils and single isomers. Data for **8b**: ^{1}H NMR δ 0.85 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.3−1.4 (m, 6H), 1.44 (s, 3H), 1.7−1.9 (m, 6H), 1.9−2.0 (m, 1H), 2.10 (t, J = 6.7 Hz, 2H), 2.38 (ddd, J = 13.0, 11.3, 7.5 Hz, 1H), 2.5−2.6 (m, 1H), 4.0−4.2 (m, 2H); ^{13}C NMR δ 13.5, 14.1, 18.5, 21.9, 26.4, 27.2, 31.1, 32.9, 37.7, 39.4, 40.1, 60.5, 61.5, 64.2, 81.4, 82.3, 84.7, 175.6; IR (neat) ν 3490, 2220, 1730 cm^{-1}; HRMS calcd for $C_{18}H_{28}O_3$ 291.1960 (M − 1), found 291.1965. Data for ethyl 2-(hex-1-enylidene)-1-(3-oxobutyl)-cyclopentanecarboxylate **(10)**: ^{1}H NMR δ 0.88 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.3−1.4 (m, 4H), 1.5−1.6 (m, 1H), 1.7−1.9 (m, 4H), 1.9−2.1 (m, 3H), 2.11 (s, 3H), 2.2−2.3 (m, 1H), 2.4−2.5 (m, 3H), 4.10 (q, J = 7.1 Hz, 2H,), 5.19 (tt, J = 6.7, 3.6 Hz, 1H); ^{13}C NMR δ 13.9, 14.2, 22.1, 24.8, 29.0, 29.8, 31.3, 31.4, 31.6, 35.7, 40.3, 55.3, 60.6, 94.8, 108.1, 174.8, 198.2, 208.3; IR (neat) ν 1960, 1730 cm^{-1}; HRMS calcd for $C_{18}H_{28}O_3$ 292.2038, found 292.2036.

1-Ethynylbicyclo[4.3.0]nonan-9-ol (11). A solution of acetate **4k** (0.115 g, 0.518 mmol) and $Pd(PPh_3)_4$ (38 mg, 0.036 mmol) in THF (10 mL) was placed in a water bath at 40 °C. A SmI_2 solution [prepared from Sm (0.214 g, 1.42 mmol), diiodoethane (0.365 g, 1.30 mmol) and THF (10 mL)] was added dropwise at such a rate as to allow the disappearance of the SmI_2 characteristic blue color before the next drop was added. The addition was continued until the blue color persisted (at that point 7 mL had been added over 1 h). Workup as described above and flash chromatography (20% EtOAc/hexanes) afforded in order of elution the bicyclic alcohol **11** (18 mg, 21%, one isomer), as a volatile oil, and the hydroxyester **12** (16 mg, 13%). Data for **11**: ^{1}H NMR δ 1.2−1.8 (m, 12H), 2.0−2.2 (m, 3H), 2.14 (s, overlapped with mult at 2.0−2.2), 4.2−4.3 (m, 1H); ^{13}C NMR δ 20.4, 22.0, 22.9, 24.5, 25.4, 29.2, 41.7, 44.2, 69.0, 81.5, 90.0; IR (neat) ν 3700−3200, 2140 cm^{-1}; HRMS calcd for $C_{11}H_{16}O$ 164.1201, found 164.1164. Data for 1-ethynyl-2-(3-hydroxypropyl)cyclohexyl acetate **(12)**: ^{1}H NMR δ 1.2−1.4 (m, 4H), 1.4−1.9 (m, 9H), 2.03 (s, 3H), 2.60 (s, 1H), 2.73 (br d, J = 11.9 Hz, 1H), 3.67 (t, J = 6.5 Hz, 2H); ^{13}C NMR δ 22.0, 23.3, 24.9, 26.3, 28.3, 30.5, 36.1, 45.6, 63.2, 76.4, 80.0, 80.8, 169.3; IR (neat) ν 3430, 3310, 2220, 1750 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1419.

(1*R,4*S**,5*S**)-Ethyl 4-Ethynyl-5-hydroxybicyclo[3.3.0]-octanecarboxylate (13a). Representative Procedure for SmI_2/Pd(0) Reductive Cyclizations of Substrates 6a−f and 6h,i.** A solution of SmI_2 [prepared from Sm (0.291 g, 1.93

mmol) and diiodoethane (0.508 g, 1.81 mmol] in THF (11.5 mL) was added dropwise to a solution of **6a** (0.198 g, 0.707 mmol) and $Pd(PPh_3)_4$ (46.4 mg, 0.04 mmol) in THF (8 mL) at such a rate as to allow the disappearance of the SmI_2 characteristic blue color before the next drop was added. The addition was continued until the blue color persisted (at that point approximately 11 mL had been consumed). The usual workup, followed by flash chromatography (10% EtOAc/hexanes), afforded 0.136 g (87%) of the product as an oil: ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 1.5−1.7 (m, 4H), 1.7−1.9 (m, 2H), 2.0−2.1 (m, 2H), 2.14 (d, J = 2.4 Hz, 1H), 2.2−2.3 (m, 1H), 2.4−2.5 (m, 1H), 2.87 (ddd, J = 11.7, 6.8, 2.4 Hz, 1H, H-4), 2.99 (s, 1H, OH), 4.17 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.0, 24.2, 29.8, 34.9, 37.6, 38.4, 42.8, 60.8, 60.9, 70.4, 83.6, 92.9, 176.0; IR (neat) ν 3490, 3295, 2110, 1720 cm^{-1}; FT-IR (~0.01 M in $CHCl_3$) ν 1699 cm^{-1}; HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1252.

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Supporting Information Available: Copies of ^{1}H NMR spectra for **1a**, **1b**, **1e**, **3b**, **3d**, **3e**−**h**, **3k**, **4c**−**h**, **4j**, **4k**, **5e**, **5f**, **6e**, **6f**, **7**, *cis*-**8a**, **8b**, **9**−**12**, **13a**, **14** and experimental procedures for **4d**, **4f**, **4h**, **4j**, **4k**, **6a**, **6c**−**g**, **6i**, **7b**−**j**, **13b**−**d**, **14**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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