Diastereoselective Cycloisomerizations of Enediynes via Palladium Catalysis

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Abstract: Considerations of atom economy drive a search for reactions that are simple additions which, performed intramolecularly, are cycloisomerizations. Exposure of acyclic enediynes to a catalyst generated by mixing a Pd(0) complex with acetic acid normally in the presence of a phosphine ligand creates [5.6.5] and [6.6.5] tricycles with extraordinary diastereoselectivity of remote stereogenic centers. Effects of substituents on the tethers as well as the olefinic and acetylenic bonds reveal a wide tolerance of functionality. While geminal substitution facilitates the cycloisomerization, it is not required. Allylic oxygen plays a role as a regioselectivity control element. Cycloisomerization dominates over allylic ionization in such cases by proper tuning of the ligand. The mechanism of this reaction appears to vary depending upon the structure of the substrate. In the normal cases, the process involves three stages, initiation, propagation, and termination. Chemoselective initiation at the acetylenic linkage closest to one of the chain's termini occurs by hydropalladation. Propagation entails intramolecular carbametalations. Termination by β-hydrogen elimination generates a hexatriene that undergoes high rotoselectivity in its disrotatory cyclization to generate the final product. Blocking formation of the hexatriene shuts down reaction. With substrates bearing a γ-siloxypropiolate as the acetylenic initiator, cycloisomerization forms a tricycle with different positions of the double bonds. In contrast to the case of the other substrates, blocking formation of a hexatriene does not shut down cycloisomerization. Invoking a novel intramolecular Diels–Alder reaction of a dienylpalladium intermediate derived from the diyne moiety with the olefin, likely assisted by coordination to palladium, accounts for our observations. The ease of availability of the acyclic substrates because of the versatility of the acetylenes combined with the high chemo-, regio-, and diastereoselectivity makes this atom-economical reaction a very practical approach for the construction of polycycles.

Considerations of effective use of raw materials and minimization of waste generation call for the evolution of reactions that are simple additions, i.e., the ideal atom-economical reaction.[1] Such processes, performed intramolecularly, are cycloisomerizations. Catalysis by transition metals provides kinetic pathways to achieve rather unusual cycloisomerizations. Particularly noteworthy in this regard are the cobalt-catalyzed processes whose use in the synthesis of complex molecules has been highly successful.[2] Our discovery of the ability to effect palladium catalyzed cycloisomerizations of enynes to monocycles[3,4] raises the question of the degree of complexity that can be created in a single step by such cycloisomerizations. In extending the number of unsaturations present in the substrate in order to increase the number of rings that will be formed, cognizance of the problem of β-hydrogen elimination of each transition metal intermediate in the polycyclization suggests the use of substrates that restrict this cyclization termination step until all rings are constructed. The lower reactivity of vinylmetal intermediates toward β-hydrogen elimination makes enepolyynes attractive substrates.[5]

Scheme I outlines at least four mechanistic possibilities by which an enediyne may cyclize under the influence of an HPdX species generated *in situ* by oxidative addition of Pd(0) to acetic acid. Formation of **B** vs **D** derives from the competition between the two acetylenic bonds a and b, respectively, of **A** in initiating the cyclization process. If acetylene bond a initiates reaction to form **B**, an intramolecular Diels–Alder reaction completes the cycloisomerization to the tricycle. Formation of **D** by initiation of cyclization with acetylene bond b opens the prospect for at least three modes of behavior. An intramolecular Diels–Alder reaction forms **G**, which also derives from a series of two intramolecular carbametalations (**D** → **E** → **G**). A number of different regioisomeric products (**H**–**K**) may form dependent upon the favorability of the possible β-hydrogen eliminations. Alternatively, if **E** suffers β-hydrogen elimination faster than further carbametalation to form **F**, disrotatory thermal cyclization of the triene will form a unique diene H.

Analogy for the behavior of the proposed intermediates **D** and **E** stems from the studies of the intramolecular Heck reaction.[6-9] The ambiguities of the initiation step are removed in this cyclization, since the oxidative addition to the vinyl halide starts the cascade. However, the complexity of the process can be appreciated by the dependence of product on reaction conditions (eq 1).[9b] Apparently, the presence of halide has a major influence

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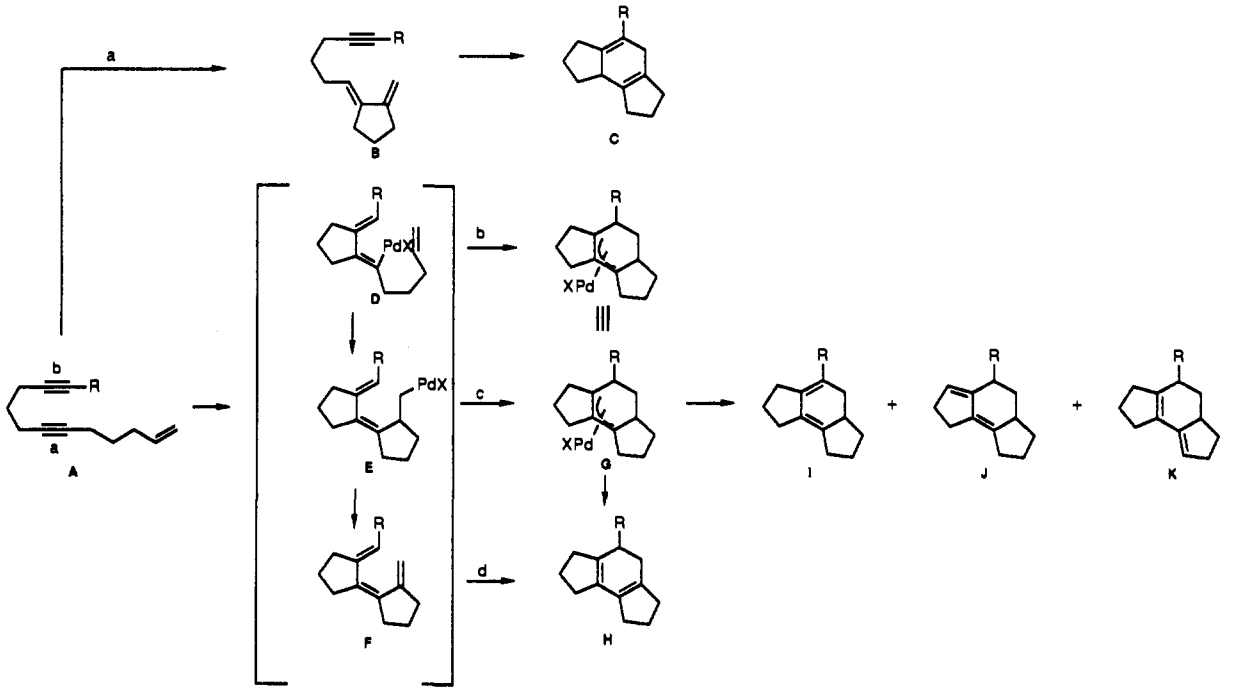
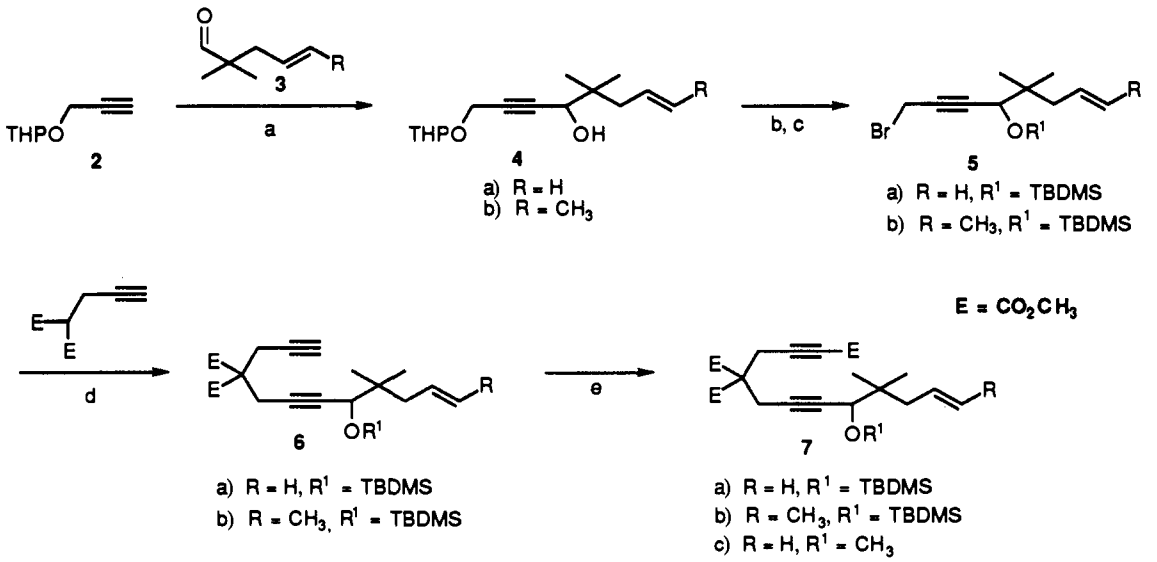
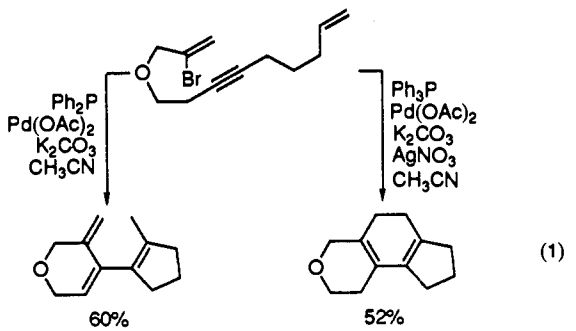
Scheme I. Reaction Pathways from an Enediyne to a Tricycle



Scheme II. Enediyne Synthesis According to Dissconnect 1a[a]



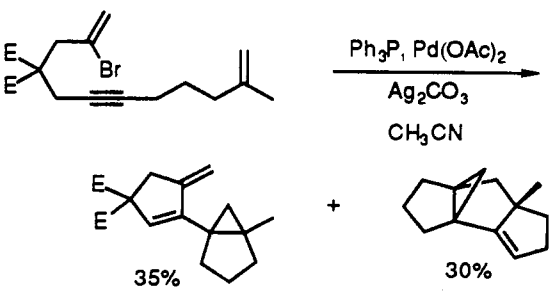
[a](a) C_4H_9Li, THF, −78 °C, 94%. (b) $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 44–94%. (c) Ph_3P, Br_2, CH_2Cl_2, 0 °C, 89–96%. (d) NaH, THF, room temperature, 73–74%. (e) $LiN(TMS)_2$, THF, −78 °C, $ClCO_2CH_3$, 67–83%.



(1)

on the reaction. Blocking the terminal β-hydrogen elimination pathway reveals yet another dimension to these cyclizations in which the organopalladium species bites back upon the intermediate diene to form cyclopropyl[7,8a,c] products (eq 2).[9b]

The potential practical advantages of cycloisomerizations and the fundamental questions regarding the reaction pathways



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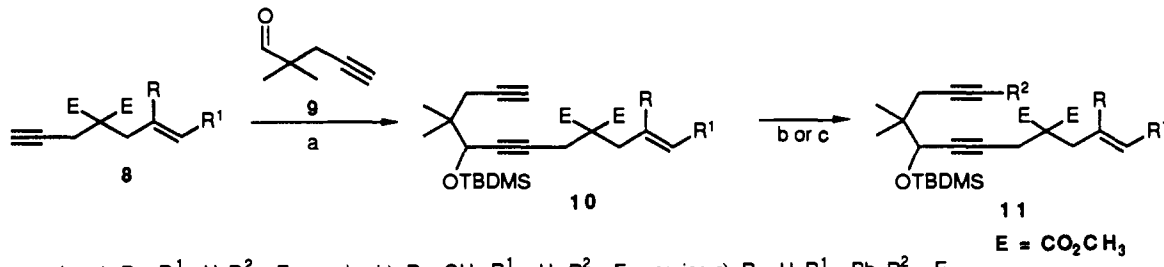
possible and the response of the reaction to catalyst conditions induced us to study the cycloisomerizations of enepolyynes. In this paper, we report the results of our initial studies.[10]

Synthesis of Substrates

The attractiveness of the acetylene cyclizations stems in part from the versatility of acetylenes as building blocks due to the

(10) For a preliminary report of a portion of this work, see: Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791.

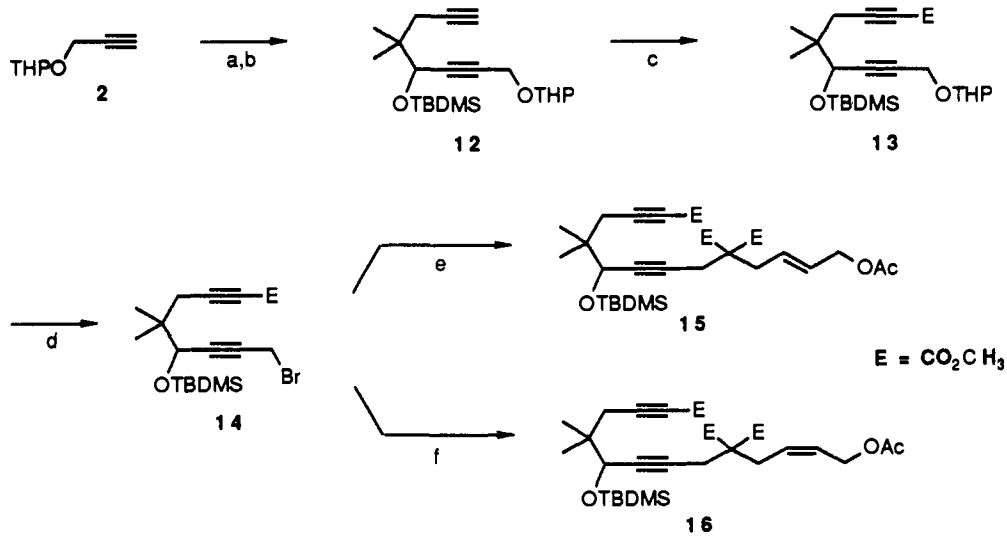
Scheme III. Enediyne Synthesis According to Disconnect 1b[a]



series a) R = R¹ = H, R² = E series b) R = CH₃, R¹ = H, R² = E series c) R = H, R¹ = Ph, R² = E, series d) R = H, R¹ = Ph, R² = CH₂OCH₃

[a](a) LiN(TMS)₂, THF, −78 °C;TBDMSCl, $C_3H_4N_2$, DMF, room temperature, 63–80%. (b) LiN(TMS)₂, THF, $ClCO_2CH_3$, −78 °C, 56–69%. (c) LiN(TMS)₂, THF, CH_3OCH_2Br, −78 °C, 65%.

Scheme IV. Enediyne Synthesis According to Disconnect 1c[a]



[a](a) C_4H_9Li, THF, −78 °C, **9**, 84%. (b) $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 87%. (c) nC_4H_9Li, CH_3OCOCl, THF, −78 °C, 69%. (d) Ph_3P, Br_2, CH_2Cl_2, 0 °C, 88%. (e) **17**, NaH, THF, room temperature, 80%. (f) **18**, NaH, THF, room temperature, 82%.

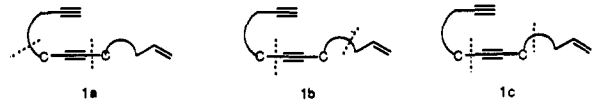
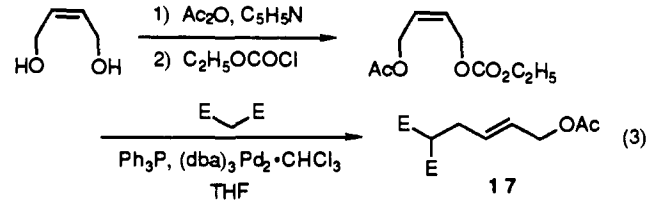


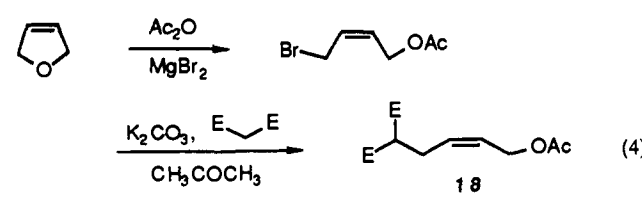
Figure 1. Bond Disconnects.

nucleophilicity of terminal acetylenes and electrophilicity of propargyl halides. Two basic convergent strategies are employed: (1) construction of the enyne fragment and attachment of the remaining acetylenic unit and (2) construction of a diyne fragment and attachment of the olefinic unit.

In our first approach, we linked the three main fragments together as in **1a** (Figure 1 and Scheme II), wherein the enyne is constructed first as an electrophilic partner. In our second approach, we employed the disconnects illustrated in **1b** (see Figure 1 and Scheme III), wherein the enyne is first constructed as a nucleophilic partner. In both cases, dimethyl propargylmalonate is the lynchpin. For disconnect **1a**, using the acetylene of propargylmalonate as the initiator, alkylation with propargyl bromide **5a,b** provides substrates **7a,b** (Scheme 1). Using a similar sequence, the methyl ether **7c** was also synthesized. For the first step of this sequence, the aldehyde **3b**, obtained by alkylation of the metallaenamine of isobutyraldehyde with E-crotyl chloride, was employed as an impure starting material directly from the hydrolysis of the alkylation reaction. Generation of the acetylide anion of **6** or **8** in the presence of the malonate unit creates no problems as long as the temperature remains low (−78 °C). Thus, for disconnect **1b**, the enyne **8**, prepared by standard allylation of dimethyl propargylmalonate, can be added readily to aldehyde **9** to provide enediynes **10a–c**. Further, the acetylide anion generated from the newly created terminal acetylene can be acylated (to **11a–c**) or alkylated (to **11d**).

In order to explore the effects of olefin geometry and allylic substituents, enediynes **15** and **16** were synthesized utilizing a strategy based upon disconnect **1c** wherein the diyne is first constructed as an electrophilic partner (Scheme IV). The nucleophilic partners 17 and 18 were synthesized according to eqs 3[11] and 4.[12]





In order to explore the role of gem alkyl substitution, substrates containing such substitution in only one tether (e.g. **23a,b**) and in neither tether (e.g. **23c**, **29a–d**) were synthesized utilizing

(11) Genet, J. P.; Ferroud, D. *Tetrahedron Lett.* **1984**, *25*, 3579.
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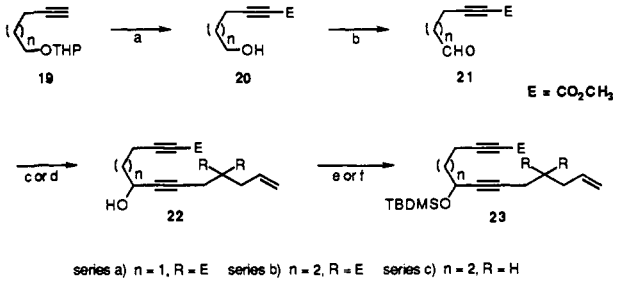
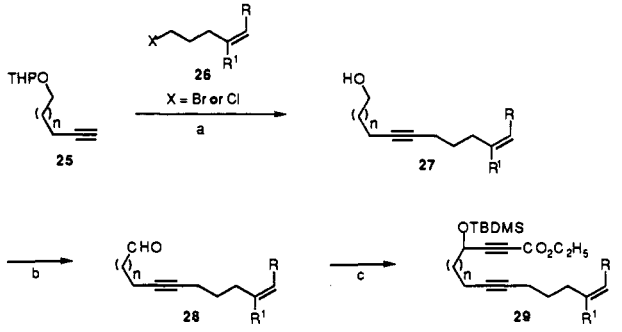
Scheme V. Synthesis of Enediynes Lacking Geminal Substitution According to Disconnect 1b[a]



series a) n = 1, R = E series b) n = 2, R = E series c) n = 2, R = H

[a](a) nC_4H_9Li, THF, −78 °C, $ClCO_2CH_3$ then TsOH, CH_3OH, H_2O, room temperature, 70–78%. (b) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, $(C_2H_5)_3N$, 80–89%. (c) **8a**, $LiN(TMS)_2$, THF, −78 °C. (d) **24**, nC_4H_9Li, THF, −78 °C. (e) $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 76–87%. (f) TBDMS-Cl, $C_3H_4N_2$, DMF, room temperature, 52% for two steps.

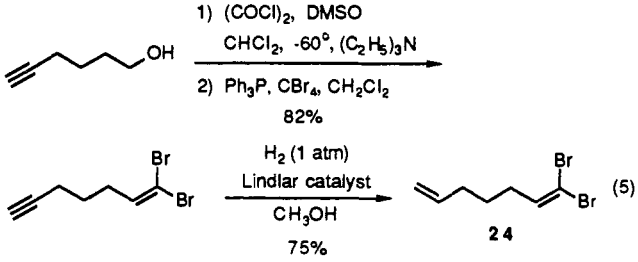
Scheme VI. Synthesis of Enediynes with No Geminal Substitution According to Variation of Disconnect 1a[a]



series a) R = R¹ = H, n = 1 series b) R = R¹ = H, n = 2
series c) R = CH3, R¹ = H, n = 1 series d) R = H, R¹ = CH3, n = 1

[a](a) C_4H_9Li, THF–HMPA, **26**, 0 °C → room temperature, then TsOH, CH_3OH, H_2O, room temperature, 58–66%. (b) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, $(C_2H_5)_3N$, 66–83%. (c) $LiC{\equiv}CCO_2C_2H_5$, THF, −78 °C, then $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0 °C, 33–56%.

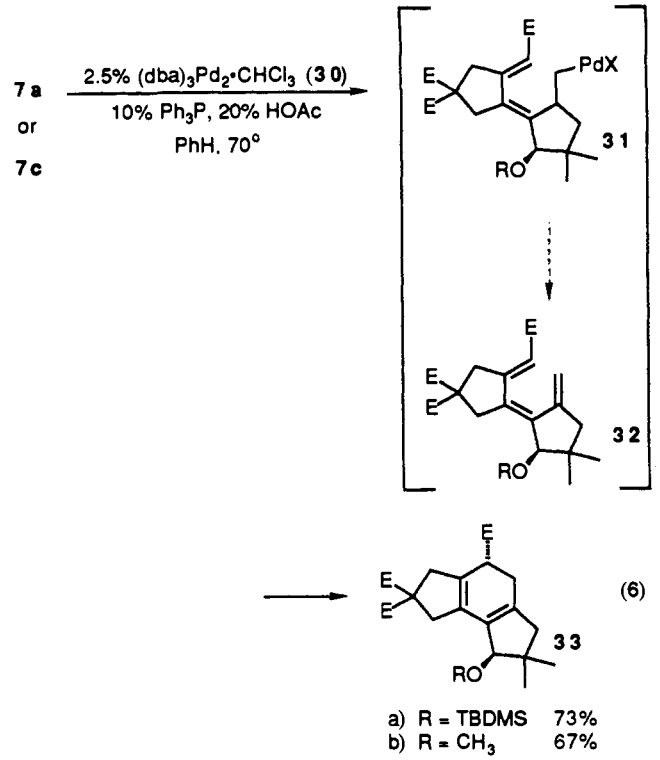
disconnect **1b** (Scheme V) and a variation of **1a** (Scheme VI). For the synthesis of enediyne **23c**, the requisite 1-lithiohept-1-yn-6-ene was generated *in situ* by treatment of the dibromide **24** available from 5-hexyn-1-ol according to eq 5 with 2 equiv of *n*-butyllithium.[13]



(5)

Cyclizations

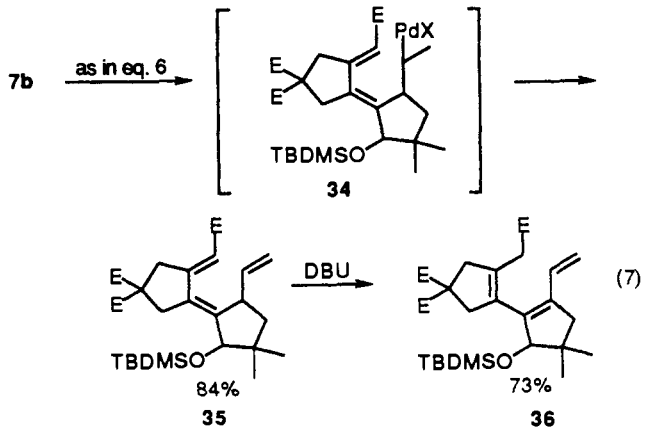
Our first attempt to effect polycyclization used enediyne **7a** (eq 6). Heating a 0.16 M solution of **7a** in benzene-d_6 in the presence of 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ (**30**), 10% triphenylphosphine (TPP), and 20% acetic acid in an NMR tube showed the clean disappearance of starting material and the appearance of a single product. Mass spectroscopy establishes it is isomeric to starting material. The presence of three saturated esters is indicated by IR (1730 cm^{-1}) and ^{13}C NMR (δ 174.21, 172.82, 172.77) spectroscopy. Two tetrasubstituted double bonds are indicated by the absence of olefinic protons in the ^1H NMR spectrum and the presence of four olefinic carbons in the ^{13}C NMR spectrum (δ 138.38, 133.07, 131.89, 126.88). The ^1H NMR spectrum shows three isolated geminal AB systems (δ 3.24 and 3.16, δ 3.13 and 3.03, δ 2.25 and 2.02), an uncoupled proton adjacent to oxygen (δ 4.33), and an ABX at δ_A 2.43 (dd, J = 17.7, 10.1 Hz), δ_B 2.58 (dd, J = 17.7, 10.9 Hz), and δ_X 3.38 (dd, J = 10.9, 10.1 Hz). This data indicate that the cycloisomer has structure **33a**. The large vicinal coupling constants for the ABX are characteristic of cyclohexadienes.[14] Chromatographically and spectroscopically, the compound is homogenous—indicating only a single diastereomer is formed which is tentatively assigned the stereochemistry depicted (*vide infra*). Changing the steric demands of the oxygen substituent by switching it from TBDMS to methyl had no effect on the steric course of the reaction—only one diastereomeric product **33b** was observed.



(6)

a) R = TBDMS 73%
b) R = CH_3 67%

The formation of the tricycle is consistent with either a direct cyclization of **31** or β-hydrogen elimination to **32** followed by disrotatory cyclization. To gain insight into this mechanism, we examined the substrate bearing a vinyl methyl group **7b**, which



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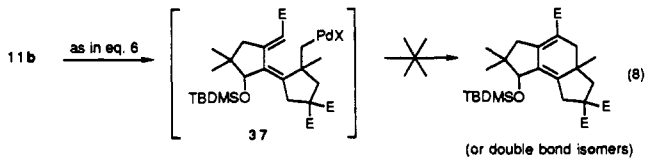
offers the prospect of a σ-palladium intermediate like **34** to β-hydrogen eliminate toward this substituent. It may be antic-

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

(14) Rabideau, P. W.; Sygula, A. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes and Related Hydroaromatic Compounds*; Rabideau, P. W., Ed.; VCH: New York, 1989; Chapter 3.
(15) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.
(16) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271.

ipated that a direct cyclization of an intermediate like **31** may not be influenced by this additional substituent, whereas β-hydrogen elimination toward this substituent would preclude the hexatriene–cyclohexadiene cyclization. In the event, cyclization does proceed but with production of the bicycle **35** as a 1:1.3 diastereomeric mixture. The presence of three double bonds was apparent from the two sets of six signals for the olefinic carbons in the ^{13}C NMR spectrum [δ 155.80 (155.01), 148.46 (149.45), 141.72 (142.28), 132.99 (133.53), 116.06 (115.90), and 114.33 (114.00)]. The presence of the β,β-disubstituted enoate is apparent from the signals for the vinylic proton (δ 6.33 and 5.91) adjacent to the ester appearing as fine triplets exhibiting only allylic coupling and from the IR band for a conjugated ester (1704 cm^{-1}). The presence of the monosubstituted olefin was apparent from the signals for the olefinic hydrogens at δ 5.66, 5.06, and 4.88 in the ^1H NMR spectrum. Heating this compound in the presence of DBU isomerizes the mixture to a single compound **36**. All the ester groups are attached to saturated carbons (IR 1730 cm^{-1}, ^{13}C NMR signals at δ 172.64, 172.61, and 171.32). Although the molecule still contains three double bonds (^{13}C NMR signals at δ 139.28, 138.19, 133.38, 132.45, 130.77, and 115.88), only one bears hydrogens and is monosubstituted (δ 6.32, dd, J = 17.6, 10.6 Hz; 5.12, d, J = 17.6 Hz; 5.08, d, J = 10.6 Hz). In addition to a broad singlet for a hydrogen adjacent to oxygen (δ 4.24), the remainder of the spectrum showed isolated methylene groups (δ 3.25 and 2.93, J = 16.4 Hz; δ 2.40 and 2.13, J = 15.3 Hz; and δ 3.13, s, 4H). The above spectral data confirm the assignment as depicted in **36**.

While this result verifies the formation of σ-palladium intermediates **31** and **34**, we wanted to test the feasibility of their direct cyclization by precluding β-hydrogen elimination. The fact that we observed no reaction of substrate **11b**, which should be capable of at least forming the σ-palladium species **37**, suggests that, in this crowded environment, further cyclization does not occur (eq 8) (*vide infra*). That the source of the failure to cyclize



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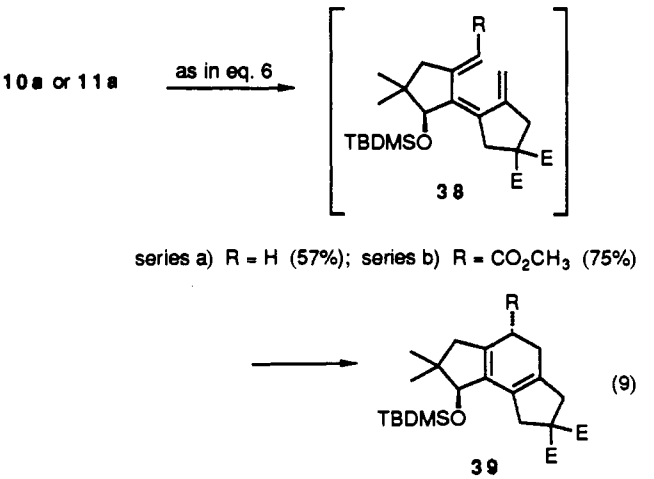
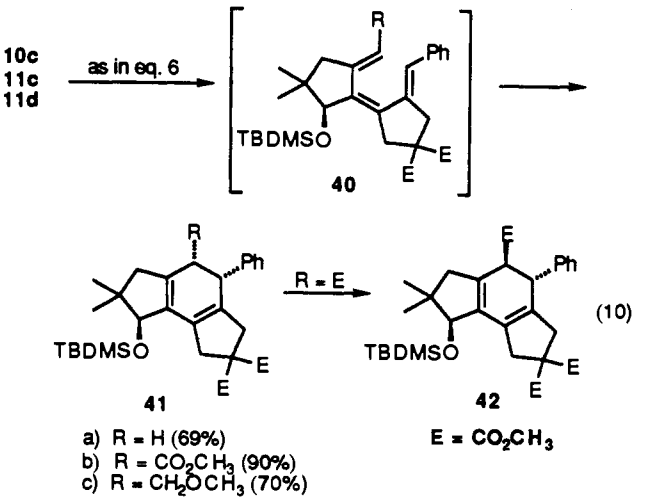
does not stem from the change in substitution pattern of **11b** compared to **7a** derives from the successful cycloisomerization of **11a** (eq 9), which also gives the cycloisomer **39b** as a single



(9)

diastereomer.

A substrate bearing a terminal olefinic substituent lacking hydrogens to preclude β-hydrogen elimination toward this group in the σ-palladium intermediate such as phenyl participates without complications (eq 10). In all cases, the cycloisomer is

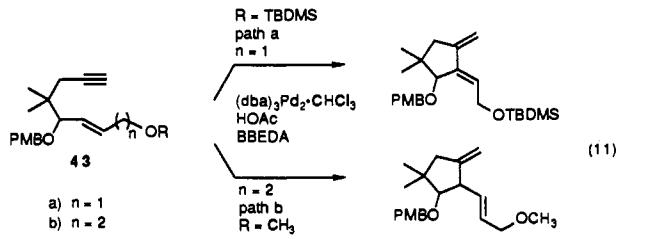


(10)

a single diastereomer which on the basis of a disrotation of the purported hexatriene **40** should be the isomer **41**. When R = CO_2CH_3, the 11.2-Hz coupling constant suggests a *trans* vicinal relationship between the ester and the phenyl substituents as in **42**. The stereochemistry may result from a facile epimerization of the kinetic *cis* isomer **41b** to the thermodynamically more stable *trans* isomer due to the high acidity of the proton adjacent to the ester. To test this proposal, the methoxymethyl derivative **11d**, which will generate a kinetically much less acidic product, was cycloisomerized. Again, the cycloisomer forms as a single diastereomer for which the vicinal coupling constant indicates the expected *cis* stereochemistry as depicted in **41c**—an observation in support of the above proposal. This example also illustrates the ability to utilize a dialkyl-substituted acetylenic initiator without complications.

There is no requirement for the acetylene initiator to be disubstituted. The terminal acetylenic substrates **10a** (eq 9) and **10c** (eq 10) cycloisomerize under identical conditions—again in the case of **10c** to a single diastereomeric product **41a**.

We had previously shown that the regioselectivity of the cycloisomerization of 1,6-enynes was influenced by substituents. In particular, oxygen at the allylic position as in **43a** serves as a regiochemical control element wherein it directs the β-hydrogen elimination away from the carbon-bearing oxygen (eq 11, path a). Moving this substituent to the homoallylic position as in **43b** leads to formation of the "normal" Alder ene type product (eq 11, path b).[17]

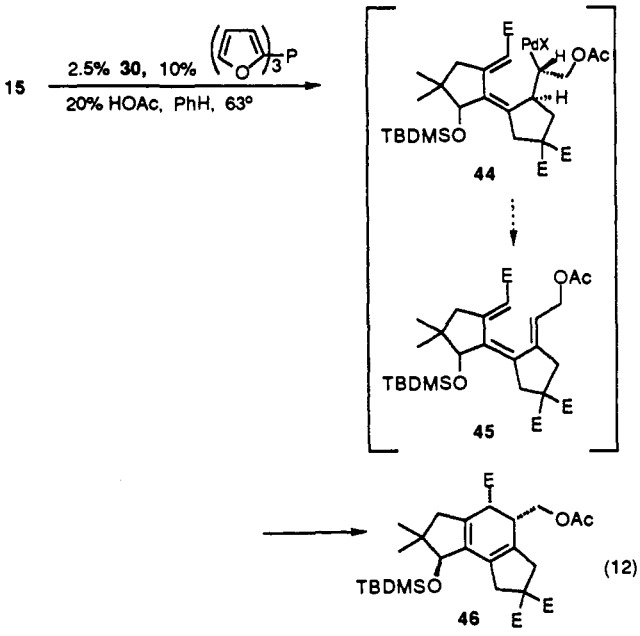


(11)

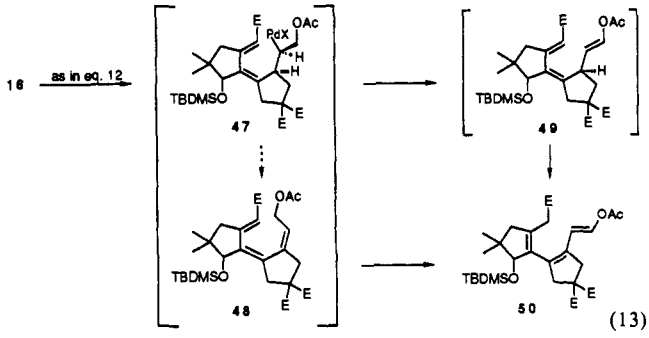
Cycloisomerization of allylic acetates **15** and **16** explores this issue as well as the chemoselectivity associated with allylic activation[18] competing with cyclization and the role of olefin geometry on the reaction. Under our normal reaction conditions with TPP as ligand, reaction of *E*-allylic acetate **15** gave a rather complex product mixture. Surmising the multiple pathways did

(17) Trost, B. M.; Chan, C. Unpublished observations.
(18) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. Trost, B. M. *Fundam. Res. Homogeneous Catal.* **1984**, *4*, 117. Trost, B. M. *J. Organomet. Chem.* **1986**, *300*, 263. Also see: Godleski, S. A. In *Comprehensive Organic Synthesis* Trost, B. M., Fleming I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, U.K., 1991; Chapter 3.3.

derive from Pd-catalyzed allylic activation, a less electron rich ligand should decrease this undesired pathway relative to our cycloisomerization. Indeed, switching the ligand to trifurylphosphine[19] gave a 61% yield of the cycloisomer **46** as a single diastereomer (eq 12). The vicinal coupling constant of the cyclohexadienyl protons indicates a *cis* relationship, as expected from the stereochemistry of the starting material. Contrary to the case of the cycloisomerization of **11c**, no epimerization of the product was observed.



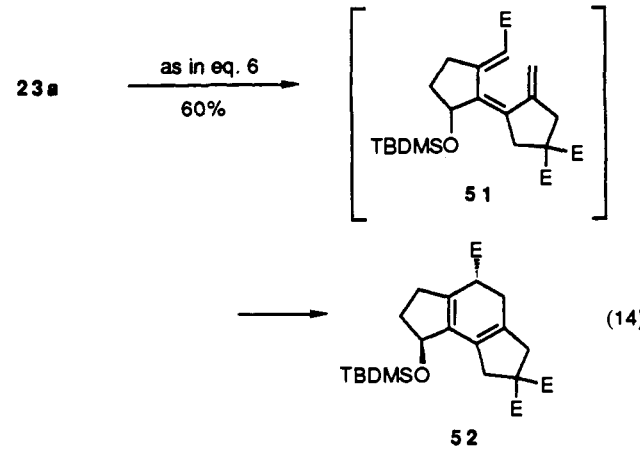
In stark contrast to the above, subjection of the Z isomer **16** to the same reaction conditions did not produce any tricycle (eq 13). The presence of three double bonds in this product was



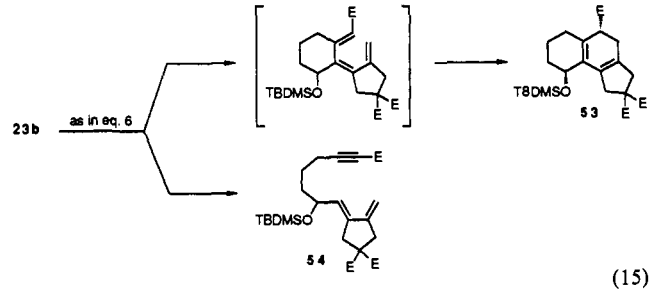
apparent from the ^{13}C NMR spectrum (δ 137.70, 137.17, 135.31, 134.62, 131.57, 110.82). That two of the double bonds were tetrasubstituted and one disubstituted (δ 7.29, d, J = 12.8 Hz; 6.06, d, J = 12.8 Hz) was indicated in the ^1H NMR spectrum. The presence of four isolated methylene groups (δ 3.22 and 3.03, J = 16.1 Hz; 3.19 and 3.12, J = 16.4 Hz; 3.00 and 2.93, J = 15.9 Hz; 2.31 and 2.10, J = 16.0 Hz) was also apparent in this spectrum. This data support the assignment of structure **50** to the cycloisomer which could be derived by one of two paths: (1) a 1,5-hydrogen shift from the triene **49**, the product of β-hydrogen elimination from the initial bicycle **47**, or (2) a 1,7-hydrogen shift[20] being faster than disrotatory cyclization of triene **48**. This dramatic effect of olefin geometry on the course of the reaction supports the notion that 1,3,5-hexatrienes are intermediates in the cycloisomerization to tricycles (*vide infra*).

(19) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(20) For a leading reference, see: Enas, J. D.; Palenzuda, J. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 1355.

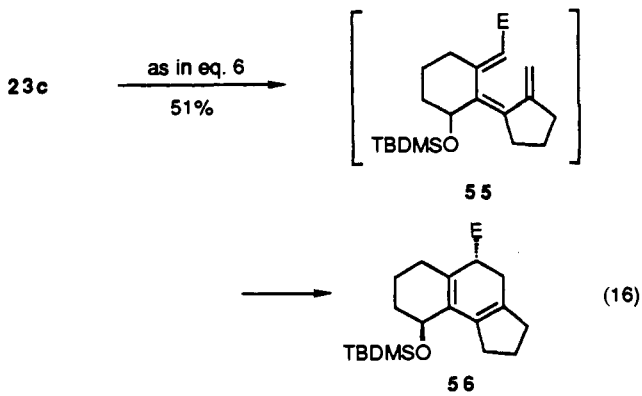
The role of geminal substitution was probed. Removing such substitution in the dialkyne tether as in **23a** still led to smooth cycloisomerization to the tricycle under standard conditions (eq 14). Increasing this tether length, however, led to a more



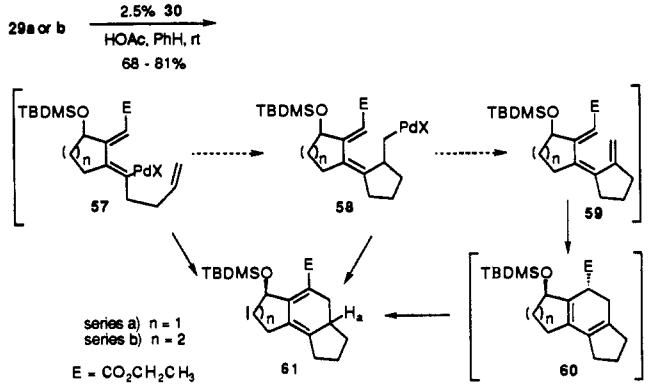
complicated product mixture whose analysis suggested the presence of the tricycle **53** (eq 15) as well as the monocycle **54**.



It can be conjectured that the combination of increasing the tether length and removing the gem alkyl substitution sufficiently slows the initial diyne cyclization that the enyne cyclization which possesses both a more favorable three carbon tether and geminal substitution dominates. Predicting that removal of the geminal substitution in the enyne tether of **23b** might allow the diyne cyclization to compete, we explored the cycloisomerization of **23c** (eq 16). Much to our delight, the diastereomerically pure cycloisomer **56** was isolated in 51% yield. Thus, while geminal substitution clearly aids the process, it is not required.

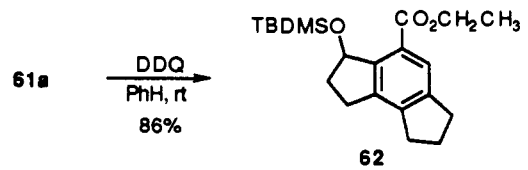


With substrates lacking geminal substituents, the reaction exhibits a sensitivity to the position of substitution. Thus, placing the oxygen substituent proximal to the propiolate unit as in **29a** (eq 17) gave a complicated mixture of products under our standard conditions. On the other hand, cycloisomerization of **29a** proceeded at room temperature in the absence of any phosphine



(17)

to give the tricycle **61** in 81% yield, again as a single diastereomer. The presence of two tetrasubstituted double bonds was apparent from the four olefin carbons in the ^{13}C NMR spectrum (δ 154.90, 144.53, 130.60, 117.55) and the absence of any vinylic protons in the ^{1}H NMR spectrum. The chemical shifts of the olefinic carbons as well as the ester carbonyl carbon (δ 167.75) combined with the IR carbonyl frequency at 1694 cm^{-1} indicate a conjugated ester. The carbon skeleton was confirmed by dehydrogenation with DDQ to the aromatic **62** (eq 18). Increasing the diyne tether by one carbon has little effect on the reaction. Thus, substrate **29b** cycloisomerized with the same catalyst but at 56 °C to produce only the conjugated dienoate **61b**.



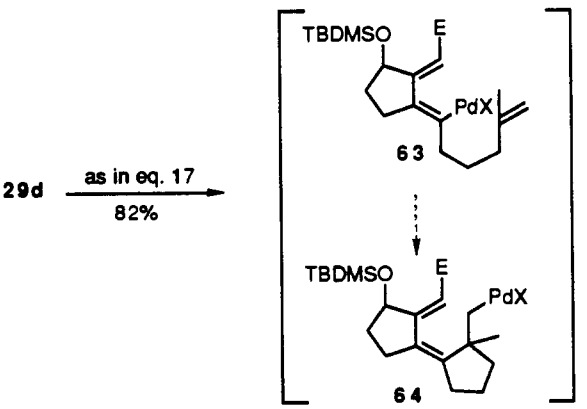
(18)

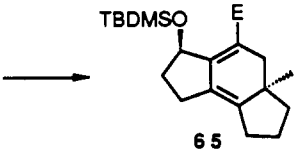
Our previous results would suggest that **60** should have been the product that would likely derive from a disrotatory closure of the 1,3,5-hexatriene **59**. The intermediacy of **60** would require that it be less stable than dienoate **61**, which is contrary to molecular mechanics calculations (which indicate **60** is *more* stable by 4.4 kcal/mol)[21] and to our previous experiences. For example, equilibration of tricycles like **33**, **39**, or **41** with DBU does not produce the corresponding conjugated dienoates. Precluding formation of triene **59** as in substrates **29d** should further test the likelihood of its involvement in the cycloisomerization. This reaction proved sensitive to the quantity of acetic acid present. Addition of acetic acid to the propiolate ester competed with cycloisomerization when equivalent amounts were employed. On the other hand, use of 5 mol % acetic acid provided the cycloisomer **65** in excellent yields—in contrast to our earlier experience in the cycloisomerization of **11b**.

Probing the stereochemical course of this reaction proved particularly enlightening. The *Z* olefinic substrate **29c** (eq 20) produced a 1:2 mixture of the cycloisomers **68** and **69**. Whereas, the tricycle **68** was a single diastereomer, the bicycle **69** was a mixture of stereoisomers which equilibrate in the presence of base to a single conjugated triene **70**. The *Z* (or *endo*) stereochemistry of the methyl group in **68** is suggested by the 7.0-Hz vicinal coupling constant for the vicinal cyclohexadienyl protons.

Discussion

Enediynes undergo smooth cycloisomerizations to provide [5.6.5] and [6.6.5] tricycles with excellent chemo- and diastereoselectivity even though the stereogenic centers may be quite





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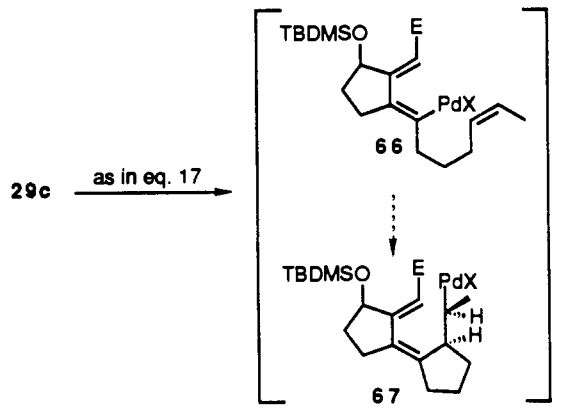
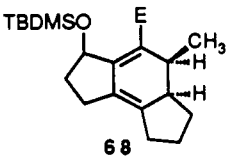
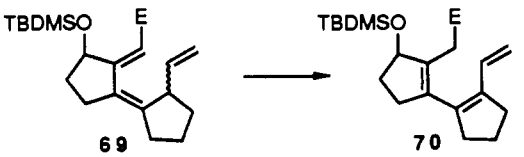




(20)

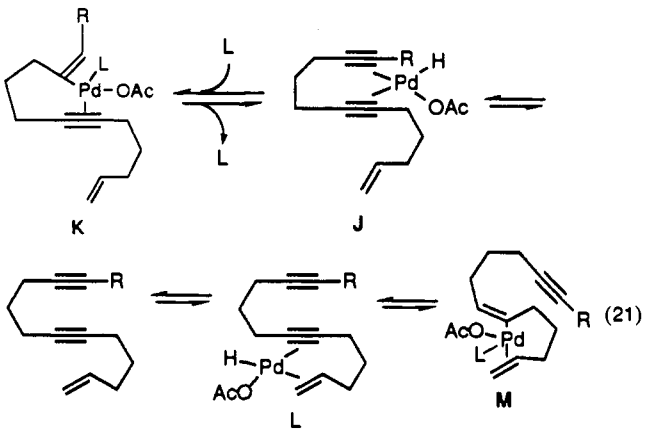


distal with respect to each other. Considering the ease with which the requisite acyclic substrates may be available, this synthetic approach to fused polycycles should be quite useful. While we have only examined two ring systems, prospects for constructing other ring systems appear good. Geminal substitution is clearly beneficial though not required. Several advantages exist for this method compared to a Heck type polycyclization. First, a cycloisomerization is intrinsically more atom economical. Second, the reaction conditions can be more precisely defined so that complications that may be caused by extraneous species like halide ions can be avoided. Third, the substrates may frequently be more readily accessible, since vinyl halides as employed in the Heck process are commonly made from the acetylenes.

The process can be thought to involve three stages—initiation, propagation, and termination. Initiation appears to involve bidentate coordination and reversible hydropalladation of a reactive $L_nPd(H)OAc$ formed *in situ* from Pd(0) and acetic acid

(21) Performed using the molecular mechanics program available in the CAChe Work System.

(eq 21).[22] In principle, such coordination and hydropalladation

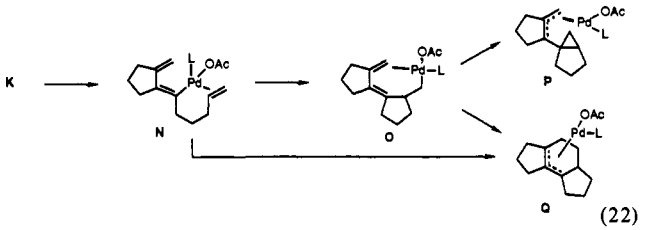


(21)

could occur with either the diyne as in **J** → **K** or the enyne as in **L** → **M** (eq 21). Experiments indicate that the former path, which is required for polycyclization, is preferred; however, the reasons for its success are unclear. *A priori*, formation of **L** and perhaps **M** as well as **J** and **K** may be occurring reversibly. These equilibria then may be displaced toward **K** by its more favorable propagation steps—i.e., carbametalation of an acetylene being more favorable than that of an olefin.[23] Such an explanation may also account for the chemoselectivity of the hydropalladation of **J**. In principle, hydropalladation of either acetylene is feasible, yet only hydropalladation of the acetylene distal to the olefin can lead to polycyclization. While steric or electronic arguments may explain the chemoselectivity when the initiator acetylene is terminal or bears an electron withdrawing group, such arguments disappear when it is dialkyl substituted. Reversible hydropalladation may account for the observation. The ability for a propiolate to function as an initiator stands in contrast to our earlier observations in the cycloisomerizations of 1,6-enynes.[22]

The ability of the substrate to be a bidentate ligand to the metal determines whether this cyclization succeeds. Such initial coordination is comfortably accommodated by either a three- or four-carbon tether. Geminal substitution facilitates this coordination geometry presumably for the same reasons this substitution favors cyclization.

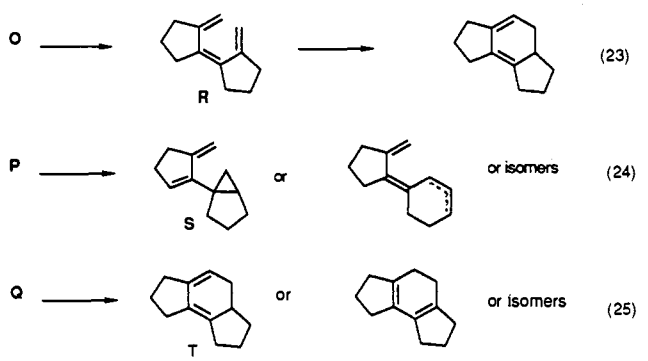
Propagation involves the cascade of carbametalation reactions (eq 22). Coordination of the vinyl group in **K** may trigger the



(22)

intramolecular carbametalation to **N** followed by carbametalation to **O**. Further carbametalation of **O** can continue the propagation to form either **P** or **Q**. Isolation of products derived from **P** in polycyclizations via Heck chemistry suggests that this process should dominate over cyclization to **Q**.[7b,8a,c,9] This precedent detracts from an interpretation invoking the transformation **O** → **Q** as the sequence for tricycle formation. An alternative envisions the cycloaddition of the remote double bond of **N** to the diene to form **Q** directly. While such a reaction has not been previously noted,[24] the reactivity of a dimethylenecycloalkane as a Diels–Alder diene may favor such a path in this case. Metal coordination to promote Diels–Alder reactions has been previously noted.[25] Thus, the palladium coordination as depicted in **N** could favor this process.[26] The intervention of this pathway becomes an attractive explanation for the formation of **61a,b**, **65**, and **68** (*vide infra*).

Termination normally involves β-hydrogen elimination which can occur from **O**, **P**, or **Q** (eqs 23–25). In the first case (eq 23),



(23)

(24)

(25)

the hexatriene would be anticipated to undergo disrotatory cyclization to form the observed tricycles. The products of such an elimination in the second case (eq 24) are not normally seen. The products in the third case (eq 25) may be a variety of diene isomers, since such an elimination can occur in four directions from **Q**.

Of the multitude of pathways possible, most evidence supports the path via double carbametalation to **O** followed by β-elimination to hexatriene **R** for the majority of these reactions. The formation of **35** in the cyclization of **7b** (eq 7) supports the intervention of the σ-palladium species **34** and, by analogy, its equivalent in the other cyclizations (e.g. **31** in eq 6)—verifying the double carbametalation. The unique formation of a single regioisomeric diene in eqs 6, 9, 10, 12, and 14–16 argues against pathways invoking **Q**. For **Q** to be involved, there would have to be either a strong kinetic bias for formation of the observed diene regioisomer in each case or a rapid equilibration of the kinetic diene(s) to the observed isomer, which would have to be the thermodynamically most stable one. Neither of these requirements appears likely.

Furthermore, the stereochemical observations support the involvement of the hexatriene **R**. Cyclization of **7b** produces almost an equimolar mixture of the diastereomeric bicycles **35** (eq 7)—a fact that indicates the intramolecular carbametalation proceeds with little stereodiscrimination. If σ-palladium species **31** directly cyclized, a diastereomeric mixture of products should have resulted, since the diastereomer bearing the σ-palladium substituent β should intramolecularly carbametalate from the β-face and vice versa for the α isomer. Our observation of a single diastereomer in all cases strongly implies that the product stereochemistry is *not* related to the stereochemistry of the carbametalation, which is random.

Cyclization of the *E* and *Z* allylic acetates **15** and **16** strongly reinforces these conclusions. Our previous work indicated that there was a strong substituent effect on the regioselectivity of the β-hydrogen elimination in the cycloisomerization of enynes (cf.

(22) For the first use of this catalyst system, see: Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1988**, *110*, 7255. Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. Also, see ref 7a.

(23) (a) Trost, B. M.; Burgess, K. *Chem. Commun.* **1985**, 1084. (b) Negishi, E. I.; Tour, J.M. *Tetrahedron Lett.* **1986**, *27*, 4869. (c) Trost, B. M.; Pfrengle, W.; Urable, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923. (d) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19. (e) Also see ref 7b.

(24) Compare ref 2a and the following. McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666. Wakatsuki, Y.; Kuramitou, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549.

(25) Compare: Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. Matsuda, I.; Shibata, M.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1987**, *28*, 3361. Mach, K.; Antropiusova, H.; Petrusova, L.; Turecek, F.; Hanus, V. *J. Organomet. Chem.* **1985**, *289*, 331; tom Dieck, H.; Dreicks, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *22*, 778.

(26) For examples of σ-aryl- or σ-vinylpalladium complex assisted nucleophilic attack on an olefin, see: Bouyssi, D.; Balme, G.; Fornet, G.; Monterio, N.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 1641 and references cited therein.

eq 11).[15-17] Thus, by adding an oxygen substituent to the allylic position, we disfavor the β-elimination observed in **34** to favor 1,3,5-hexatriene formation. That prediction was fully validated (eq 12). Since carbametalation and β-hydrogen elimination are *cis-syn* processes, the stereochemistry of the triene is determined by the stereochemistry of the olefin. Thus, the *Z* triene **48** results from the *Z* olefin **16** and preferentially undergoes a 1,7-hydrogen shift[20] to give the observed product. It is possible that steric strain overcomes electronic effects in determining the regioselectivity of the β-hydrogen elimination, in which case the 1,3,6-triene **49** results. To explain these observations on the basis of a differential rate of intramolecular carbapalladation of **44** and **47** is much less convincing.

More direct evidence for the 1,3,5-hexatriene route derives from our studies of the cycloisomerization of **23c** (eq 16). In almost all cases, following the course of the reaction by NMR spectroscopy shows a clean growth of signals for the final tricycle as the signals of the starting material disappeared. However, in the case of **23c**, a set of signals built up and decayed with time that corresponded neither to starting material nor product. The signals (δ 5.60, d, J = 1.6 Hz, vinyl; 5.24, d, J = 2.8 Hz, CHOTBDMS; 5.20, s, and 5.14, s, $=CH_2$) correspond to those expected for hexatriene **55** (eq 16). Obtaining an IR spectrum at the maximum concentration of this intermediate reveals strong absorptions at 1709 and 1632 cm^{-1} indicative of an unsaturated ester as present in **55**. The slower rate of disrotatory cyclization of **55** compared to its 5,5 ring analogue **51** derives from the poorer overlap of a dialkylidenecyclohexane compared to a dialkylidenecyclopentane.[27] It should be noted that previous authors [9a] observed a preference for reactions of the type **O** → **P** over **O** → **Q** (eq 22)—a fact that also argues against the latter pathway here.

A distinct change occurs with substrates **29a** or **b** which is not simply an effect of the absence of geminal substituents. Furthermore, whereas the isopropenyl terminator shut down the principal cyclization path in our earlier cycloisomerizations (eq 8), this substitution has no effect on this cyclization (eq 19). The $A_{1,3}$ strain introduced in monocycle **57** combined with the steric demands of our normal catalysts disfavors the requisite initial carbapalladation sufficiently so that cycloisomerization to tricycles no longer occurs. Reducing the steric demands of the catalyst by using a "ligandless" system restores smooth polycyclization but to a different diene regioisomer **61** (eq 17). In rationalizing this product via the same pathway as before (i.e., via **58** → **59** → **60**), isomerization of the kinetic diene **60** to the observed diene **61** would have to occur rapidly and the equilibrium would have to lie completely on the side of **61**. The fact that molecular mechanics calculations[21] suggest that **61a** is more than 4 kcal/mol *less* stable than **60a** makes this pathway unlikely. The success of the cyclization of **29d** under these conditions which is precluded from forming a 1,3,5-hexatriene also argues against the hexatriene pathway.

In this case, the π-allyl intermediate **Q**, which can form from either **57** or **58**, appears a more likely intermediate. The preference for dienes **61a** and **b** then derives from the preference for deprotonation of the most acidic hydrogen, i.e., that adjacent to the ester group. Stereochemical considerations lead us to suggest a direct cyclization of **57** rather than intramolecular carbametalation of **58** as the source of the **Q** analogue. As shown in the cyclization of **29c** (eq 20), there is very low stereodiscrimination in the intramolecular carbametalation step leading to **69**, which forms as a diastereomeric mixture; yet **61a,b**, **65**, and **68** are all single diastereomers! Thus, a pathway which decouples the stereochemistry of the product from that of an intramolecular carbametalation again appears required. Since the hexatriene pathway cannot be operative, what are the alternatives? A most reasonable prospect is the direct intramolecular cycloaddition of **57** or **63** to form the tricyclic π-allylpalladium intermediate. This process should be facilitated by palladium coordination to the olefin. The fact that these cyclizations proceed *in the absence of any phosphine ligands* suggests that coordination of palladium with the olefin, which phosphine coordination will interrupt, plays a very important role.[26]

Scheme VII. Transition Stations of the Diels–Alder Reaction of Palladadiene

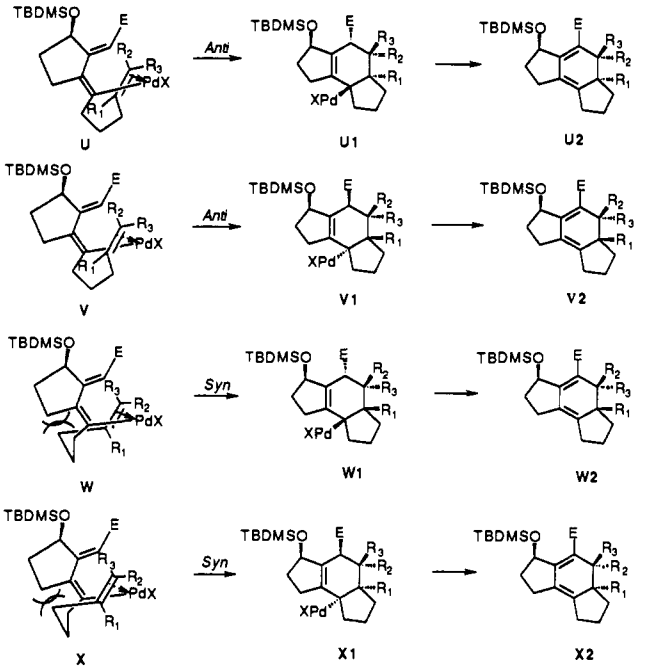


Table I. Calculated Geometrical Parameters of Lowest Energy Transition State Possessing C_S Symmetry

bond	calcd bond length, Å	angle	calcd bond angle, deg	dihedral angle	calcd angle, deg
C_1C_2	1.36	$C_1C_2C_3$	123	$C_1C_2C_3C_4$	42
C_2C_3	1.42	$C_2C_3C_4$	120	$C_2C_3C_4C_5$	0
C_3C_4	1.35	$C_1C_6C_5$	106		
C_1C_6	2.06	$H_1C_1H_1$	108		
CH	1.21	$C_1C_2H_2$	120		
		$C_2C_3H_3$	118		

Scheme VII illustrates the four possible transition states for such an intramolecular Diels–Alder reaction. The two *syn* transition states (**W** and **X**) are disfavored by the nonbonded interactions between the cyclopentane ring and the tether linking the diene and dienophile.[28] Transition state **U** is favored over **V** because the dienophile approaches the diene from the sterically less hindered face distal to the TBDMSO group. On the basis of this model, we suggest the stereochemistry depicted for **61a,b**, **65**, and **68**. The formation of **69** as the major product in the cycloisomerization of **29c** would have to result from a slower rate of intramolecular cycloaddition of a *Z*-1,2-disubstituted olefin compared to a monosubstituted or a 1,1-disubstituted olefin.

An important feature of the mechanism of the initial cycloisomerizations invoking electrocyclization of the 1,3,5-hexatriene is the prospect for decoupling the diastereoselectivity of the overall process from that of the intramolecular carbametalation. The geometry of the transition state for the disrotatory closure of 1,3,5-hexatriene to 1,3-cyclohexadiene has been calculated to be a C_s symmetric structure resembling a distorted hexatriene (eq 26 and Table I).[29] On the basis of this information, the two possible disrotatory transition states (ts) for the electrocyclizations

(27) We had previously noted a significant rate difference in TMM–PdL_2 cycloadditions to dialkylidenecyclopentanes compared to dialkylidenecyclohexanes. Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483 and unpublished results.

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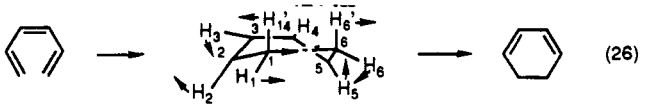
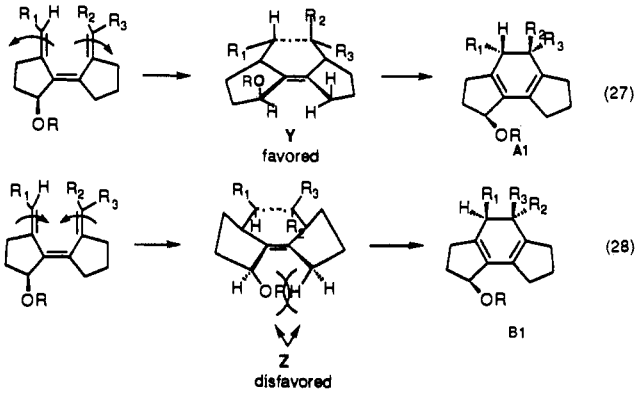

(26)

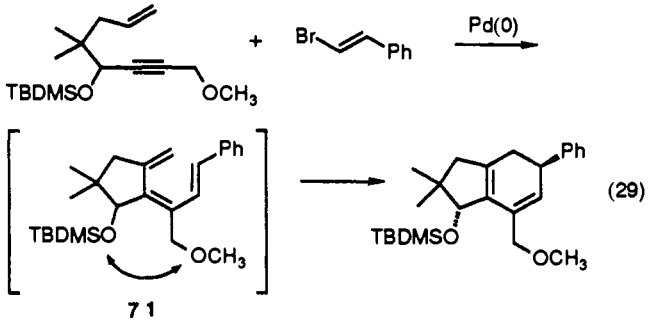
described in this paper are depicted in eqs 27 and 28. Structure **Z** of eq **28** is strongly destabilized due to the steric congestion


(27)

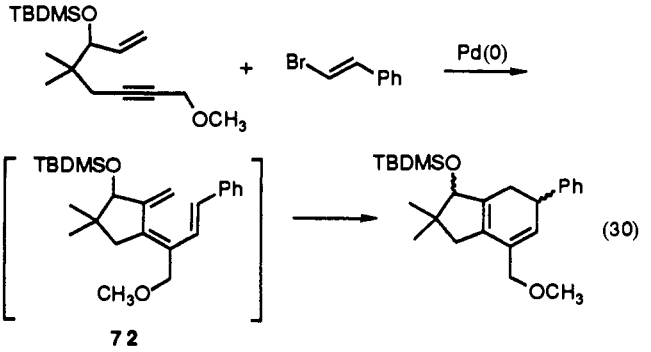
(28)

between the OR group and the methylene group of the adjacent ring as depicted. This interaction is relieved in transition state **Y** of eq 27. This steric preference for ts **Y** is reinforced by an electronic factor. There is a stabilizing interaction between the σ^*_{C-OR} and π bonds in ts **Y**, since the C–OR bond is parallel to the π orbital of the double bond.[30] This stabilizing interaction does not exist in ts **Z** due to the orthogonality of the C–OR bond to the π orbital of the double bond. Thus, both steric and stereoelectronic factors favor ts **Y**, which predicts the stereochemistry depicted in **U1** for the products. This analysis forms the basis of the stereochemical assignments. While the stereochemical course of such electrocyclic processes has been extensively studied with respect to its being con- or disrotatory,[31] discrimination between the two conrotatory or two disrotatory modes (roto- or torquoselectivity) has not been explored.[32-34] The results herein demonstrate that diastereoselectivity among quite remote centers can be controlled by rotoselectivity. Subsequent to our work, Meyer et al. recorded similar observations in their studies of polycyclizations initiated via a Heck vinylation.[9a]

Support for the above interpretation derives from the very high diastereoselectivity in the alkylative cyclization of enynes (eq 29) whose origin is the rotoselectivity of an intermediate


(29)

hexatriene **71**.[23c] In this case, the buttressing between the siloxy group and the methoxymethyl (cf. the oxygen substituent and one of the newly formed ring carbons in the current case, see eqs 27 and 28) is responsible for the rotoselectivity. Remove this buttressing as in triene **72** (eq 30) and the rotoselectivity disappears.


(30)

The successful employment of the allylic acetates **15** and **16** demonstrates the wide potential for applicability to a broad spectrum of substrates by proper choice of catalyst system. Since these reaction conditions are quite similar to those employed for Pd(0) catalyzed allylic alkylations,[18] reactions that could result from ionization of the allylic acetate may compete with the cycloisomerization. The complex product mixture obtained under our standard conditions using TPP as ligand may derive from the allylic ionization successfully competing with the cycloisomerization. Using a poorer donor ligand should decrease the ability of the resultant Pd(0) complex to effect ionization of an allylic acetate yet maintain its basicity to be protonated by acetic acid to generate the active catalyst for cycloisomerization. Trifurylphosphine, which is claimed to be a poorer σ-donor than TPP,[19] has the appropriate electronic balance, as indicated by the excellent yield of the cycloisomer **46** (eq 12).

The chemistry outlined herein demonstrates that the Pd-catalyzed enediyne cyclization can be an effective method for the construction of the fused tricycles from acyclic compounds. The high atom economy of cycloisomerization combined with the excellent diastereoselectivity makes this methodology useful for the synthesis of complex polycycles. Moreover, the starting materials can be easily obtained by the reaction of the acetylide with carbonyl compounds or halides. Since this polycyclization propagates the stereochemistry of a propargyl alcohol to other centers with high diastereoselectivity, the availability of such alcohols by asymmetric reduction of alkynones or asymmetric addition of acetylides to aldehydes converts the sequence into an enantiocontrolled production of polycycles. The utility of this method for the design of new synthetic strategies for the construction of complex natural products is under current investigation.

Experimental Section

Reactions were generally run under a positive pressure of dry nitrogen. Anhydrous solvents or reaction mixtures were transferred by oven-dried syringe or cannula. Solvents were generally distilled before use: acetonitrile, benzene, dichloromethane, dichloroethane, diisopropylamine, dimethylformamide, lutidine, pyridine, and triethylamine from calcium hydride; ether and tetrahydrofuran (THF) from sodium benzophenone ketyl. Dimethyl sulfoxide was dried using freshly activated 3A molecular sieves. All reactions were run under a blanket of nitrogen.

Flash chromatography following the method of Still[35] employed E. Merck silica gel (Kieselgel 60, 200–400 mesh). Analytical thin-layer chromatography was performed with 0.2-mm coated commercial silica gel plates (E. Merck, DC-Plaskitkfolien, Kieselgel 60 F_{254}).

Proton nuclear magnetic resonance spectra were measured at 200, 300, or 400 MHz on a Varian Gemini 200, Gemini 300, or XL-400 instrument, respectfully, as indicated. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and determined relative to the proton signal of the solvent ($CDCl_3$, 7.26 ppm). NMR

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(31) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; Chapter 7.
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(33) For roto- or torquoselectivity in four-electron cases, see: Trost, B. M.; McDougal, P.G. *J. Org. Chem.* **1984**, *49*, 458. Kallel, E. A.; Wang, Y.; Spellmeyer, D. C.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 6759.
(34) For a Pd-catalyzed oxyhexatriene cyclization, see: Hettrick, C. M.; Scott, W. J. *J. Am. Chem. Soc.* **1991**, *113*, 4903 and references cited therein.
(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

data are reported in the following form: chemical shift (multiplicity, coupling constant(s) in Hz, number of hydrogens). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; and b, broad. ^{13}C NMR spectra were fully decoupled, and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and determined relative to the carbon signals of the solvent ($CDCl_3$, 7 7.0 ppm).

Infrared spectra were recorded in 0.1 mm path length sodium chloride cavity cells on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer using polystyrene as a reference (1601 cm^{-1}) or on a Nicolet 205 FT-IR spectrometer and are reported in wavenumbers (cm^{-1}).

Melting points were determined using a Thomas-Hoover oil bath apparatus in open capillary tubes and are uncorrected. Boiling points are also uncorrected.

Analytical gas chromatography was performed on a Varian 3700 gas chromatograph using a 25 m by 0.25 mm polydimethylsiloxane column from Alltech.

Microanalyses were performed by Robertson Laboratory, Inc., Madison, NJ. High-resolution mass spectra were performed by the mass spectrometry facility of the University of California at San Francisco.

Preparation of 5-(*tert*-Butyldimethylsiloxy)-9,9-bis(methoxycarbonyl)-4,4-dimethyl-1-dodecene-6,11-diyne (6a). To a solution of the THP ether of propargyl alcohol (7.00 g, 50.00 mmol) in THF (60 mL) at −78 °C was added *n*-butyllithium (37.30 mL, 47.80 mmol) dropwise. After the reaction mixture was stirred at −78 °C for 40 min, a solution of 2,2-dimethyl-4-pentenal[36] (5.10 g, 45.54 mmol) in THF (10 mL) was added at -78 °C. After 30 min at −78 °C, the cooling bath was removed and stirring was continued for 2.5 h. The mixture was quenched with saturated aqueous ammonium chloride and extracted with ether. The organic layer was washed with water and brine, dried (K_2CO_3), filtered, concentrated, and flash chromatographed (hexane/ether = 5:1–2:1–1:1) to give **4a** as an oil (10.6 g, 94%). IR ($CDCl_3$): 3612, 2965, 2251, 1130, 1119, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.84 (m, 1H), 5.08 (d, J = 15.4 Hz, 1H), 5.07 (d, J = 11.6 Hz, 1H), 4.82 (t, J = 3.0 Hz, 1H), 4.31 (m, 2H), 4.12 (d, J = 6.1 Hz, 1H), 3.84 (m, 1H), 3.52 (m, 1H), 2.13 (m, 2H), 1.77 (d, J = 6.1 Hz, 1H), 1.76 (m, 2H), 1.56 (m, 4H), 0.97 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.11, 117.72, 96.91, 85.53, 82.25, 70.23, 62.02, 54.16, 42.66, 38.53, 30.14, 25.20, 22.48, 22.39, 22.30, 18.90.

To a solution of alcohol **4a** (4.00 g, 16.00 mmol) and 2,6-lutidine (3.73 mL, 32.00 mmol) in dichloromethane (25 mL) at 0 °C was added TBDMSOTf (4.30 mL, 18.70 mmol) dropwise. After being stirred at room temperature for 3.5 h, the reaction mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 20:1) to give the TBDMS ether of alcohol **4a** as an oil (5.53 g, 94%).

To a solution of triphenylphosphine (4.17 g, 15.93 mmol) in dichloromethane (50 ml) at 0 °C was added bromine (0.80 mL, 15.20 mmol) dropwise. After the reaction mixture was stirred at 0 °C for 10 min, a solution of the above compound (5.30 g, 14.48 mmol) in dichloromethane (10 mL) was added at 0 °C. After 1 h at 0 °C and 1 h at room temperature, the mixture was poured into water and extracted with hexane. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), filtered, and concentrated to give a residue along with some white precipitate. The residue was diluted with hexane, filtered, and concentrated to give a liquid residue, which was filtered through a silica gel plug with hexanes as eluent to give bromide **5a** as an oil (4.81 g, 96%)[37] after concentration *in vacuo*. IR ($CDCl_3$): 2959, 2931, 2858, 1471, 1252, 1209, 1143, 1084 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.03 (m, 2H), 4.06 (d, J = 1.9 Hz, 1H), 3.95 (d, J = 1.9 Hz, 2H), 2.09 (m, 2H), 0.91 (s, 6H), 0.90 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H).

To a suspension of sodium hydride (0.1224 g, 3.06 mmol) (60%, washed with pentane) in THF (2 mL) was added a solution of dimethyl propargylmalonate (0.520 g, 3.06 mmol) in THF (4 mL). After the reaction mixture was stirred for 10 min, a solution of bromide **5a** (0.88 g, 2.55 mmol) in THF (4 mL) was added. The reaction mixture was stirred at room temperature overnight, quenched with water, and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 15:1) to give the title compound as an oil (0.824 g, 74%). IR ($CDCl_3$): 3310, 2958, 1740, 1639, 1604, 1438, 1297, 1250, 1217, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.03 (m, 2H), 3.97 (t, J = 1.7 Hz, 1H), 3.75 (s, 3H), 3.748 (s, 3H), 3.04 (d, J = 1.7 Hz, 2H), 2.98 (d, J = 2.4 Hz, 2H), 2.06 (m, 2H), 2.02 (t, J = 2.4 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 3H), 0.86 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.51, 135.50, 117.21, 84.01, 79.57, 78.49, 71.53, 70.62, 56.56, 52.85, 42.49, 39.03, 25.62, 22.92, 22.73, 22.39, 17.97, −4.86, −5.68. HRMS Calcd for $C_{24}H_{38}O_5Si$ (M^+): 434.2489. Found: 434.2476.

Preparation of Methyl 9-(*tert*-Butyldimethylsiloxy)-5,5-bis(methoxycarbonyl)-10,10-dimethyl-12-tridecene-2,7-diynoate (7a). To a solution of acetylene **6a** (0.722 g, 1.66 mmol) in THF (15 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (1 M in THF, 1.83 mL, 1.83 mmol) dropwise and, after stirring at −78 °C for 30 min, methyl chloroformate (0.19 mL, 2.46 mmol). After the mixture was stirred at −78 °C for 30 min and then at room temperature for 1.5 h, it was quenched with water and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 4:1) to give the title compound **7a** as an oil (0.676 g, 83%). IR ($CDCl_3$): 2957, 1741, 1717, 1639, 1604, 1437, 1268, 1216, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.03 (m, 2H), 3.97 (t, J = 1.7 Hz, 1H), 3.77 (s, 6H), 3.75 (s, 3H), 3.14 (s, 2H), 3.04 (d, J = 1.7 Hz, 2H), 2.05 (m, 2H), 0.89 (s, 9H), 0.87 (s, 3H), 0.86 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.02, 153.83, 135.41, 117.27, 84.55, 83.24, 79.08, 75.54, 70.61, 56.30, 53.08, 52.43, 42.49, 39.03, 25.60, 23.30, 23.00, 22.44, 22.39, 17.96, −4.81, −5.60. Anal. Calcd for $C_{26}H_{40}O_7Si$: C, 63.38; H, 8.18; MW, 492.2543. Found: C, 63.55; H, 8.14; MW, 492.2524.

Preparation of Methyl 9-(*tert*-Butyldimethylsiloxy)-5,5-bis(methoxycarbonyl)-10,10-dimethyl-12-tetradecene-2,7-diynoate (7b). Compound **6b** was prepared in identical fashion to **6a** by using (*E*)-2,2-dimethyl-4-hexanal instead of 2,2-dimethyl-4-pentenal. IR ($CDCl_3$): 3310, 2958, 2930, 2857, 1740, 1438, 1296, 1251, 1217, 1207, 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.40 (m, 2H), 3.95 (s, 1H), 3.75 (s, 6H), 3.03 (d, J = 1.5 Hz, 2H), 2.98 (d, J = 2.5 Hz, 2H), 2.01 (t, J = 2.5 Hz, 1H), 1.98 (m, 2H), 1.65 (d, J = 4.5 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.83 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.52, 127.73, 127.61, 84.08, 79.22, 78.40, 71.59, 70.33, 56.45, 52.95, 41.06, 39.12, 25.58, 22.81, 22.61, 22.37, 22.29, 17.94, 17.86, −4.69, −5.57.

Following the above protocol for **7a**, acetylene **6b** (0.490 g, 1.09 mmol) was converted to its anion with lithium bis(trimethylsilyl)amide (1 M in THF, 1.2 mL, 1.2 mmol) and reacted with methyl chloroformate (0.13 mL, 1.64 mmol) to give 0.37 g (67% yield) of the title compound **7b** after the same workup. IR ($CDCl_3$): 2958, 2930, 2857, 1741, 1716, 1437, 1261, 1216, 1082 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.40 (m, 2H), 3.95 (t, J = 1.7 Hz, 1H), 3.76 (s, 6H), 3.74 (s, 3H), 3.13 (s, 2H), 3.03 (d, J = 1.7 Hz, 2H), 1.95 (m, 2H), 1.65 (d, J = 4.6 Hz, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.82 (s, 3H), 0.09 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.00, 153.84, 127.79, 127.50, 84.59, 83.15, 78.71, 75.41, 70.30, 56.15, 53.17, 52.55, 41.50, 39.11, 25.55, 23.17, 22.85, 22.36, 22.28, 17.91, 17.84, −4.74, −5.59. Anal. Calcd for $C_{27}H_{42}O_7Si$: C, 64.00; H, 8.35; MW, 506.2700. Found: C, 64.21; H, 8.34; MW, 506.2711.

Preparation of Methyl 9-Methoxy-5,5-bis(methoxycarbonyl)-10,10-dimethyl-12-tridecene-2,7-diynoate (7c). The *O*-methyl compound was prepared in exactly analogous fashion to the silylated analogue as in Scheme II except that **4a** was O-methylated in standard fashion using **4a** (2.91g, 11.5 mmol), sodium hydride (0.69 g, 17.3 mmol of a 60% oil dispersion, washed with pentane), and methy idodide (4.93 g, 34.7 mmol) in 40 mL of THF at room temperature for 2 h to give 2.95 g (96% yield) of the methyl ether. Conversion to the bromide (65%), alkylation with dimethyl propargylmalonate (91% yield), and methoxycarbonylation (62%) in identical fashion for the silyl ether gave the title compound.

Methyl-2-carbomethoxy-2-propargyl-7,7-dimethyl-6-methoxydec-9-en-4-yne. IR ($CDCl_3$): 3310, 1740, 1639, 1604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (m, 1H), 5.04 (d, J = 16.4 Hz, 1H), 5.03 (d, J = 11.4 Hz, 1H), 3.76 (s, 3H), 3.54 (t, J = 1.9 Hz, 1H), 3.35 (s, 3H), 3.07 (d, J = 2.0 Hz, 2H), 3.00 (d, J = 2.7 Hz, 2H), 2.08 (m, 2H), 2.04 (t, J = 2.7 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 135.4, 117.1, 83.9, 79.5, 78.4, 71.5, 70.5, 56.5, 52.8, 42.4, 39.0, 25.5, 22.8, 22.6, 22.3, 17.9, −4.8, −5.6. HRMS: Calcd for $C_{19}H_{26}O_5$: 334.1781. Found: 334.1771.

7c. IR ($CDCl_3$): 2957, 1741, 1716, 1637, 1606, 1437, 1269, 1215, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (m, 1H), 5.01 (m, 2H), 3.75 (s, 6H), 3.73 (s, 3H), 3.51 (t, J = 1.9 Hz, 1H), 3.32 (s, 3H), 3.12 (s, 2H), 3.04 (d, J = 1.9 Hz, 2H), 2.06 (m, 2H), 0.89 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.98, 153.83, 135.00, 117.66, 83.07, 81.58, 80.43, 79.02, 75.41, 57.13, 56.24, 53.20, 52.59, 42.78, 38.00, 23.23, 22.84, 22.48.

Preparation of 9,9-Bis(methoxycarbonyl)-4,4-dimethyl-11-dodecene-1,6-diyn-5-ol. A mixture of dimethyl propargylmalonate (6.20 g, 36.50

(36) Salomon, R. G.; Ghosh, S. *Org. Synth.* **1984**, *62*, 125.
(37) Sonnet, P. E. *Synth. Commun.* **1976**, *6*, 21.

mmol), potassium carbonate (15.13 g, 109.50 mmol), and allyl bromide (7.89 mL, 109.5 mmol) in acetone (100 mL) was heated at reflux for 24 h, cooled, filtered, concentrated, and flash chromatographed (hexane/ether = 2:1) to give compound **8a**[38] as a colorless liquid (7.60 g, 99%).

To a solution of compound **8a** (2.003 g, 9.54 mmol) in THF (50 mL) at −78 °C, was added lithium bis(trimethylsilyl)amide (1 M in THF, 9.54 mL, 9.54 mmol) dropwise. After this mixture was stirred at −78 °C for 30 min, a solution of 2,2-dimethyl-4-pentynal[39] (1.00 g, 9.09 mmol) in THF (5 mL) was added. After the mixture was stirred at −78 °C for 2 h and the reaction was quenched with water at −78 °C, the mixture was warmed to room temperature, extracted with ether (3 × 60 mL), washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 1.2:1) to give the title compound as a light-yellow liquid (2.30 g, 79%). IR ($CDCl_3$): 3611, 3308, 2957, 2258, 1736, 1650, 1438, 1295, 1222, 1206 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.61 (m, 1H), 5.17 (d, J = 15.1 Hz, 1H), 5.14 (d, J = 8.0 Hz, 1H), 4.23 (d, J = 5.5 Hz, 1H), 3.74 (s, 6H), 2.85 (d, J = 2.0 Hz, 2H), 2.70 (d, J = 7.4 Hz, 2H), 2.33 (dd, J = 16.6, 2.6 Hz, 1H), 2.18 (dd, J = 16.6, 2.6 Hz, 1H), 2.01 (t, J = 2.6 Hz, 1H), 1.86 (d, J = 5.5 Hz, 1H), 1.05 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.53, 131.97, 119.90, 82.60, 81.86, 81.25, 70.37, 69.41, 57.08, 52.55, 38.35, 36.71, 27.89, 22.96, 22.50, 21.99. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; MW, 320.1624. Found: C, 67.40; H, 7.53; MW, 320.1631.

Preparation of 8-(*tert*-Butyldimethylsiloxy)-4,4-bis(methoxycarbonyl)-9,9-dimethyl-1-dodecene-6,11-diyne (10a). To a solution of the above alcohol (2.10 g, 6.56 mmol) and 2,6-lutidine (1.53 mL, 13.12 mmol) in dichloromethane (8 mL) at 0 °C was added TBDMSOTf (2.26 mL, 9.84 mmol) dropwise. The reaction mixture was stirred at 0 °C for 2 h, quenched with water (20 mL), extracted with ether (3 × 40 mL), washed with saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 10:1) to give the title compound **10a** as a colorless liquid (2.30 g, 80%). IR ($CDCl_3$): 3308, 2957, 2258, 1736, 1438, 1295, 1252, 1221, 1206, 1135, 1079 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.61 (m, 1H), 5.16 (d, J = 15.5 Hz, 1H), 5.12 (d, J = 8.2 Hz, 1H), 4.16 (t, J = 1.8 Hz, 1H), 3.73 (s, 6H), 2.84 (d, J = 1.8 Hz, 2H), 2.79 (d, J = 7.6 Hz, 2H), 2.26 (dd, J = 16.5 Hz, 2.6 Hz, 1H), 2.15 (dd, J = 16.5, 2.6 Hz, 1H), 1.96 (t, J = 2.6 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.54, 132.11, 119.78, 83.21, 82.30, 80.23, 69.95, 69.54, 57.05, 52.48, 39.05, 36.64, 27.77, 25.57, 22.91, 22.53, 21.93, 17.91, −4.79, -5.59. Anal. Calcd for $C_{24}H_{38}O_5Si$: C, 66.32; H, 8.81. Found: C, 66.48; H, 8.54.

Preparation of Methyl 6-(*tert*-Butyldimethylsiloxy)-10,10-bis(methoxycarbonyl)-5,5-dimethyl-12-tridecene-2,7-diynoate (11a). Following the procedure for the preparation of **7**, acetylene **10a** (1.15 g, 2.65 mmol), lithium bis(trimethylsilyl)amide (1 M in THF, 2.92 mL, 2.92 mmol), and methyl chloroformate (0.25 mL, 3.18 mmol) in THF (25 mL) gave after workup and flash chromatography (hexane/ether = 5:1) the title compound **11a** as a colorless oil (0.90 g, 69%). IR ($CDCl_3$): 2956, 2236, 1736, 1710, 1437, 1294, 1260, 1220, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.15 (d, J = 17.0 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.11 (d, J = 1.8 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 6H), 2.83 (d, J = 1.8 Hz, 2H), 2.77 (d, J = 7.6 Hz, 1H), 2.43 (d, J = 17.0 Hz, 1H), 2.31 (d, J = 17.0 Hz, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.45, 154.36, 132.00, 119.82, 87.97, 82.70, 80.74, 74.75, 69.70, 56.96, 52.48, 52.23, 39.55, 36.65, 27.70, 25.52, 22.87, 22.81, 22.12, 17.86, −4.83, −5.67. HRMS. Calcd for $C_{22}H_{31}O_7Si$ (M − $^tC_4H_9$): 435.1839. Found: 435.1855. Anal. Calcd for $C_{26}H_{40}O_7Si$: C, 63.38; H, 8.18. Found: C, 63.24; H, 8.16.

Preparation of Methyl 6-(*tert*-Butyldimethylsiloxy)-10,10-bis(methoxycarbonyl)-5,5,12-trimethyl-12-tridecene-2,7-diynoate (11b). To a suspension of sodium hydride (pentane washed) (60%, 0.324 g, 8.10 mmol) in THF (5.0 mL) was added a solution of dimethyl malonate (1.31 g, 7.71 mmol) in THF (5.0 mL). After the reaction mixture was stirred for 15 min, 3-chloro-2-methylpropene (1.50 mL, 15.42 mmol) was added. After 24 h at room temperature and then at reflux overnight, the mixture was quenched with water and extracted with ether, washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 5:1) to give compound **8b** as a colorless oil (1.10 g, 63.7%).

Lithium bis(trimethylsilyl)amide (1 M in THF, 4.22 mL, 4.22 mmol) was added dropwise to a solution of compound **8b** (0.90 g, 4.02 mmol) in THF (20 mL) at −78 °C. After the reaction mixture was stirred at −78 °C for 40 min, a solution of 2,2-dimethyl-4-pentynal[39] (0.53 g, 4.82 mmol) in THF (5 mL) was added. After the mixture was stirred for 2 h at −78 °C and the reaction was quenched with water (50 mL) at −78 °C, the mixture was warmed to room temperature, extracted with ether (3 × 60 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a residue, which was dissolved in DMF (15 mL). Imidazole (0.82 g, 12.06 mmol) followed by TBDMSCl (0.908 g, 6.03 mmol) was added. After the mixture was stirred at room temperature overnight, it was quenched with water (50 mL), extracted with ether (3 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 10:1) to give compound **10b** as a colorless liquid (1.44 g, 80%). IR ($CDCl_3$): 3308, 2956, 2931, 2858, 1736, 1438, 1298, 1251, 1213, 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.90 (bs, 1H), 4.82 (bs, 1H), 4.16 (t, J = 1.7 Hz, 1H), 3.72 (s, 6H), 2.88 (d, J = 1.7 Hz, 2H), 2.82 (s, 2H), 2.26 (dd, J = 16.5 Hz, 2.7 Hz, 1H), 2.14 (dd, J = 16.5 Hz, 2.7 Hz, 1H), 1.96 (t, J = 2.7 Hz, 1H), 1.65 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.92, 140.08, 116.40, 83.28, 82.28, 80.34, 70.00, 69.29, 56.46, 52.58, 39.49, 39.03, 27.67, 25.51, 23.05, 22.76, 22.52, 21.87, 17.86, −4.81, −5.67.

Following the same procedure as for **7**, acetylene **10b** (1.17 g, 2.61 mmol) lithium bis(trimethylsilyl)amide (1 M in THF, 2.90 mL, 2.90 mmol), and methyl chloroformate (0.40 mL, 5.22 mmol) in THF (10 mL) gave after workup and flash chromatography (hexane/ether = 4:1) **11b** as a colorless oil (0.90 g, 68%). IR ($CDCl_3$): 2956, 2931, 2858, 2236, 1736, 1710, 1650, 1437, 1261, 1213, 1184, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.80 (s, 1H), 4.11 (t, J = 1.7 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.719 (s, 3H), 2.87 (d, J = 1.7 Hz, 1H), 2.81 (s, 2H), 2.43 (d, J = 17.2 Hz, 1H), 2.31 (d, J = 17.2 Hz, 1H), 1.64 (s, 3H), 1.02 (s, 3H), 1.015 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.86, 154.43, 140.01, 116.42, 88.02, 82.79, 80.86, 74.63, 69.50, 56.39, 52.59, 52.39, 39.54, 27.58, 25.48, 23.03, 22.82, 22.74, 22.08, 17.83, −4.83, −5.73. Anal. Calcd for $C_{27}H_{42}O_7Si$: C, 64.00; H, 8.35. Found: C, 64.22; H, 8.09.

Preparation of 4,4-Bis(methoxycarbonyl)-1-phenyl-(1*E*)-hepten-6-yne. A mixture of dimethyl propargylmalonate (2.78 g, 16.35 mmol), cinnamyl chloride (2.75 g, 17.99 mmol), and potassium carbonate (6.78 g, 49.05 mmol) in acetone (50 mL) was refluxed for 24 h, cooled, and concentrated. Water (30 mL) was added. The mixture was extracted with ether (3 × 60 mL), and the organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed to give the title compound as a liquid (4.10 g, 87%). IR ($CDCl_3$): 3309, 2956, 1735, 1438, 1215 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 6.52 (d, J = 15.7 Hz, 1H), 6.00 (dt, J = 15.7 Hz, 7.5 Hz, 1H), 3.76 (s, 6H), 2.97 (d, J = 7.5 Hz, 2H), 2.85 (d, J = 2.6 Hz, 2H), 2.06 (t, J = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.44, 137.32, 134.90, 128.66, 127.66, 126.48, 126.42, 123.41, 78.90, 71.51, 57.27, 52.57, 35.83, 22.85. HRMS. Calcd for $C_{17}H_{18}O_4$ (M^+): 286.1205. Found 286.1206. Anal. Calcd for $C_{17}H_{18}O_4$ (M^+): C, 71.31; H, 6.34. Found: C, 71.38; H, 6.38.

Preparation of 9,9-Bis(methoxycarbonyl)-4,4-dimethyl-12-phenyl-(1*E*)-dodecene-1,6-diyn-5-ol. To a solution of the above alkylated malonate (1.84 g, 6.43 mmol) in THF (40 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (6.43 mL, 6.43 mmol) dropwise. After the mixture was stirred at −78 °C for 40 min, a solution of 2,2-dimethyl-4-pentynal (0.778 g, 7.07 mmol) in THF (5 mL) was added. After the reaction mixture was stirred at −78 °C for 1.5 h and the reaction was quenched with water (30 mL) at −78 °C, the mixture was warmed to room temperature, extracted with ether (3 × 60 mL), washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatography (hexane/ether = 2:1) to give the title compound as a colorless oil (1.61 g, 63%). IR ($CDCl_3$): 3612, 3308, 2957, 2253, 1735, 1438, 1214, 1032 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 6.52 (d, J = 15.8 Hz, 1H), 6.01 (dt, J = 15.8, 7.7 Hz, 1H), 4.26 (bd, J = 6.1 Hz, 1H), 3.76 (s, 6H), 2.95 (d, J = 7.7 Hz, 2H), 2.89 (d, J = 1.9 Hz, 2H), 2.35 (dd, J = 16.7, 2.6 Hz, 1H), 2.20 (dd, J = 16.7, 2.6 Hz, 1H), 2.03 (t, J = 2.6 Hz, 1H), 1.85 (d, J = 6.1 Hz, 1H). 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.55, 137.26, 134.93, 128.69, 127.71, 126.48, 123.39, 82.74, 81.87, 81.33, 70.42, 69.45, 57.44, 52.61, 38.38, 36.11, 27.93, 23.25, 22.53, 22.05. HRMS. Calcd for $C_{23}H_{25}O_5$ (M − CH_3): 381.1702. Found: 381.1704. Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12, Found: C, 72.64; H, 7.07.

Preparation of 8-(*tert*-Butyldimethylsiloxy)-4,4-bis(methoxycarbonyl)-9,9-dimethyl-1-phenyl-(1*E*)-dodecene-6,11-diyne (10c). Following the usual silylation procedure, the above alcohol (1.44 g, 3.65 mmol), 2,6-lutidine (0.85 mL, 7.30 mmol), and TBDMSOTf (1.26 mL, 5.48 mmol) in dichloromethane (6 mL) gave after normal workup and flash chromatography (hexane/ether = 6:1) the title compound **10c** as a colorless

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(39) Magnus, P.; Pricipe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483.

oil (1.835 g, 99%). IR ($CDCl_3$): 3309, 2957, 2930, 1736, 1438, 1251, 1215, 1079 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 6.52 (d, J = 15.7 Hz, 1H), 6.00 (dt, J = 15.7, 7.7 Hz, 1H), 4.20 (bs, 1H), 3.75 (s, 6H), 2.95 (d, J = 7.7 Hz, 2H), 2.89 (d, J = 1.8 Hz, 2H), 2.30 (dd, J = 16.7, 2.6 Hz, 1H), 2.19 (dd, J = 16.7, 2.6 Hz, 1H), 1.98 (t, J = 2.6 Hz, 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.57, 137.36, 134.87, 128.70, 127.68, 126.50, 123.56, 83.37, 82.32, 80.29, 70.01, 69.60, 57.42, 52.57, 39.11, 36.00, 27.84, 25.61, 23.19, 22.60, 22.01, 17.94, -4.70, -5.54. HRMS. Calcd for $C_{30}H_{42}O_5Si$ (M^+): 510.2802. Found: 510.2821.

Preparation of Methyl 6-(*tert*-Butyldimethylsiloxy)-10,10-bis(methoxycarbonyl)-5,5-dimethyl-13-phenyl-(12*E*)-dodecene-2,7-diynoate (11c). Following the usual methoxycarbonylation procedure, **10c** (1.41 g, 2.76 mmol) lithium bis(trimethylsilyl)amide (1 M in THF, 2.90 mL, 2.90 mmol), and methyl chloroformate (0.235 mL, 3.04 mmol) gave after normal workup and flash chromatography (hexane/ether = 5:1) the title compound **11c** as a colorless oil (0.88 g, 56%). IR ($CDCl_3$): 2956, 2931, 2236, 1736, 1710, 1437, 1261, 1215, 1184, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 6.50 (d, J = 15.8 Hz, 1H), 6.00 (dt, J = 15.8, 7.8 Hz, 1H), 4.15 (bs, 1H), 3.77 (s, 3H), 3.75 (s, 6H), 2.94 (d, J = 7.8 Hz, 2H), 2.88 (bs, 2H), 2.46 (d, J = 17.1 Hz, 1H), 2.34 (d, J = 17.1 Hz, 1H), 1.06 (s, 3H), 1.05 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.48, 154.37, 137.26, 134.89, 128.68, 127.69, 126.46, 123.40, 87.96, 82.85, 80.78, 74.81, 69.73, 57.32, 52.56, 52.24, 39.59, 36.00, 27.75, 25.55, 23.14, 22.86, 22.18, 17.89, -4.75, -5.63. Anal. Calcd for $C_{32}H_{44}O_7Si$: C, 67.57; H, 7.80; MW, 568.2856. Found: C, 67.25; H, 7.82; MW, 568.2831.

Preparation of 8-(*tert*-Butyldimethylsiloxy)-13-methoxy-4,4-bis(methoxycarbonyl)-9,9-dimethyl-1-phenyl-(1*E*)-tridecene-6,11-diyne (11d). To a solution of acetylene **10c** (0.626 g, 1.23 mmol) in THF (10 mL) at -78 °C was added lithium bis(trimethylsiyl)amide (1 M in THF, 1.35 mL, 1.35 mmol) dropwise. After the mixture was stirred at -78 °C for 1.5 h, bromomethyl methyl ether (0.15 mL, 1.85 mmol) was added. After the mixture was stirred at -78 °C for 2 h and at room temperature for an additional 2.5 h, water (20 mL) was added. The mixture was extracted with ether (3 × 20 mL). The organic layer was washed with brine (30 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 5:1) to give the title compound **11d** as a colorless oil (0.44 g, 65%). IR ($CDCl_3$): 2957, 2931, 2857, 1736, 1438, 1292, 1250, 1214, 1186, 1090 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.20 (m, 1H), 6.50 (d, J = 15.6 Hz, 1H), 5.98 (dt, J = 15.6, 7.6 Hz, 1H), 4.18 (s, 1H), 4.10 (s, 2H), 3.74 (s, 6H), 3.38 (s, 3H), 2.94 (d, J = 7.6 Hz, 2H), 2.88 (s, 2H), 2.32 (d, J = 16.5 Hz, 1H), 2.22 (d, J = 16.5 Hz, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.56, 137.14, 134.80, 128.67, 127.68, 126.42, 123.32, 84.79, 83.30, 80.02, 77.69, 69.43, 60.11, 57.21, 52.67, 39.27, 25.83, 28.05, 25.53, 22.99, 22.71, 21.97, 17.89, -4.73, -5.65. Anal. Calcd for $C_{32}H_{46}O_6Si$: C, 69.28; H, 8.36. Found: C, 69.31; H, 8.49.

Preparation of 4-(*tert*-Butyldimethylsiloxy)-5,5-dimethyl-1-(2′-tetrahydropyranyloxy)-2,7-octadiyn-4-ol (12). To a solution of the THP ether of propargyl alcohol (5.60 g, 40.00 mmol) in THF (100 mL) at -78 °C was added *n*-butyllithium (34.73 mL, 38.2 mmol) dropwise. After the mixture was stirred at -78 °C for 50 min, a solution of 2,2-dimethyl-4-pentynal (4.00 g, 36.40 mmol) in THF (15 mL) was added at -78 °C. After the mixture was stirred at -78 °C for 1 h and at room temperature 1 h, the reaction was quenched with saturated aqueous ammonium chloride (50 mL), and the reaction mixture was extracted with ether (3 × 60 mL). The organic layers were washed with brine (50 mL), dried (K_2CO_3), filtered, concentrated, and flash chromatographed (hexane/ether = 2:1) to give the alcohol as a yellow oil (7.60 g, 84%). IR ($CDCl_3$): 3612, 3308, 2964, 2251, 1129, 1120, 1037, 1023 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (m, 1H), 4.30 (m, 3H), 3.82 (m, 1H), 3.52 (m, 1H), 2.35 (dd, J = 16.7, 2.6 Hz, 1H), 2.21 (dd, J = 16.7, 2.6 Hz, 1H), 2.01 (t, J = 2.6 Hz, 1H), 1.92 (d, J = 6.2 Hz, 1H), 1.78 (m, 2H), 1.56 (m, 4H), 1.08 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.97, 85.03, 82.99, 81.84, 70.39, 69.38, 62.02, 54.15, 38.42, 30.13, 27.91, 25.18, 22.61, 22.02, 18.87. HRMS. Calcd for $C_{14}H_{17}O_2$ ($M - H_2O - CH_3$): 217.1229. Found: 217.1219.

Using the normal silylation procedure, the above alcohol (4.257 g, 17.00 mmol), 2,6-lutidine (3.96 mL, 34.00 mmol), and TBDMSOTf (4.69 mL, 20.04 mmol) in dichloromethane (20 mL) gave after the usual workup and flash chromatography (hexane/ether = 15:1) the title compound **12** as a colorless oil (5.40 g, 87%). IR ($CDCl_3$): 3308, 2957, 2931, 2250, 1471, 1253, 1118, 1079, 1038, 1023 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.83 (t, J = 3.2 Hz, 1H), 4.30 (s, 2H), 4.25 (s, 1H), 3.84 (m, 1H), 3.53 (m, 1H), 2.30 (dd, J = 16.6 Hz, 2.6 Hz, 1H), 2.18 (dd, J = 16.6, 2.6 Hz, 1H), 1.96 (t, J = 2.6 Hz, 1H), 1.78 (m, 2H), 1.56 (m, 4H), 1.03 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.74, 85.69, 82.27, 81.83, 69.98, 69.64, 62.10, 62.05, 54.05, 39.08, 30.19, 27.79, 25.59, 25.26, 22.61, 21.99, 19.00, 17.94, -4.74, -5.56. HRMS. Calcd for $C_{21}H_{35}O_3Si$ ($M^+ - 1$): 363.2355. Found: 363.2342.

Preparation of Methyl 6-(*tert*-Butyldimethylsiloxy)-5,5-dimethyl-9-(2′-tetrahydropyranyl-oxy)-2,7-nonadiynoate (13). *n*-Butyllithium (12.74 mL, 14.00 mmol) was added dropwise to a solution of the above compound (5.10 g, 14.01 mmol) in THF (50 mL) at -78 °C. After 1 h at -78 °C, methyl chloroformate (1.30 mL, 16.81 mmol) was added. After the mixture was stirred at -78 °C for 1.5 h and the reaction was quenched with water (40 mL) at -78 °C, the mixture was allowed to warm to room temperature and was extracted with ether (3 × 60 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 8:1) to give compound **13** as a colorless oil (4.20 g, 69%). IR ($CDCl_3$): 2955, 2931, 2236, 1709, 1262, 1077, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.81 (t, J = 3.2 Hz, 1H), 4.29 (s, 2H), 4.20 (d, J = 1.5 Hz, 1H), 3.83 (m, 1H), 3.76 (s, 3H), 3.52 (m, 1H), 2.46 (d, J = 17.0 Hz, 1H), 2.34 (d, J = 17.0 Hz, 1H), 1.78 (m, 2H), 1.56 (m, 4H), 1.06 (s, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.38, 96.80, 87.96, 85.14, 82.30, 74.80, 69.78, 62.08, 62.04, 53.99, 52.26, 39.58, 30.16, 27.75, 25.56, 25.23, 22.91, 22.22, 18.95, 17.91, -4.76, -5.62. HRMS. Calcd for $C_{19}H_{29}O_5Si$ ($M - {}^tC_4H_9$): 365.1784. Found: 365.1789.

Preparation of Methyl 9-Bromo-6-(tert-butyldimethylsiloxy)-5,5-dimethyl-2,7-nonadiynoate (14). Bromine (0.254 mL, 4.92 mmol) was added dropwise to a solution of triphenylphosphine (1.35 g, 5.16 mmol) in dichloromethane (15 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 10 min, a solution of THP ether **13** (1.978 g, 4.69 mmol) in dichloromethane (10 mL) was added. The reaction mixture was stirred at 0 °C for 45 min and then at room temperature for 75 min. The reaction was quenched with water (30 mL), and the reaction mixture was extracted with hexane (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 10:1) to give the title compound **14** as a colorless oil (1.66 g, 88%). IR ($CDCl_3$): 2968, 2931, 2236, 1710, 1262, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.22 (t, J = 1.9 Hz, 1H), 3.94 (d, J = 1.9 Hz, 2H), 3.77 (s, 3H), 2.46 (d, J = 17.0 Hz, 1H), 2.34 (d, J = 17.0 Hz, 1H), 1.06 (s, 3H), 1.05 (s, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.34, 87.70, 86.62, 81.06, 74.88, 69.70, 52.28, 39.74, 27.74, 25.54, 22.92, 22.19, 17.90, 13.81, -4.74, -5.63.

Preparation of Methyl 14-Acetoxy-6-(*tert*-butyldimethylsiloxy)-10,10-bis(methoxycarbonyl)-5,5-dimethyl-(12*E*)-tetradecene-2,7-diynoate (15). A solution of malonate **17**[11] (0.2879 g, 1.18 mmol) in THF (2 mL) was added dropwise to a suspension of sodium hydride (0.0472 g, 1.18 mmol) (60%, washed with pentane) in THF (1 mL). After the mixture was stirred for 15 min, a solution of bromide **14** (0.431 g, 1.07 mmol) in THF (2 mL) was added. The reaction mixture was stirred at room temperature overnight, and the reaction was quenched with water. The reaction mixture was extracted with ether, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 1:1) to give the title compound **15** as an oil (0.484 g, 80%). IR ($CDCl_3$): 2956, 2931, 2858, 2236, 1736, 1714, 1604, 1437, 1259, 1212, 1077 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.71 (dt, J = 15.5, 6.1 Hz, 1H), 5.56 (dt, J = 15.5, 7.7 Hz, 1H), 4.99 (d, J = 6.1 Hz, 2H), 4.11 (s, 1H), 3.75 (s, 3H), 3.73 (s, 6H), 2.82 (d, J = 1.70 Hz, 2H), 2.77 (d, J = 7.2 Hz, 2H), 2.37 (d, J = 16.9 Hz, 1H), 2.30 (d, J = 16.9 Hz, 1H), 2.05 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.94, 170.32, 154.41, 129.43, 128.65, 87.94, 82.82, 80.37, 74.69, 69.50, 64.33, 56.84, 52.66, 52.38, 39.52, 35.11, 27.60, 25.49, 22.94, 22.83, 22.08, 20.67, 17.85, -4.81, -5.69. HRMS. Calcd for $C_{28}H_{41}O_8Si$ ($M - OCH_3$): 533.2571. Found: 533.2591. Anal. Calcd for $C_{29}H_{44}O_9Si$: C, 61.67; H, 7.85. Found: C, 61.42; H, 7.63.

Preparation of Methyl 5-Acetoxy-2-(methoxycarbonyl)-(3*Z*)-pentenoate (18). A mixture of 1-acetoxy-4-bromo-(2*Z*)-butene[12] (3.80 g, 21.70 mmol), dimethyl malonate (8.60 g, 65.14 mmol), and potassium carbonate (9.00 g, 65.14 mmol) in acetone (60 mL) was refluxed for 24 h, cooled, and concentrated. Water (50 mL) was added. The mixture was extracted with ether (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (hexane/ether = 3:1 to 2:1) to give the title compound **18** as a colorless oil (3.50 g, 66%). IR ($CDCl_3$): 2956, 1734, 1438, 1237, 1160, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.61 (m, 2H), 4.64 (d, J = 6.4

Hz, 2H), 3.74 (s, 6H), 3.44 (t, J = 7.6 Hz, 1H), 2.71 (t, J = 7.3 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.05, 169.30, 129.71, 126.90, 59.85, 52.43, 51.08, 26.65, 20.61. HRMS. Calcd for $C_9H_{12}O_4$ (M – HOAc): 184.0736. Found: 184.0750.

Preparation of Methyl 14-Acetoxy-6-(*tert*-butyldimethylsiloxy)-10,10-bis(methoxycarbonyl)-5,5-dimethyl-(12*Z*)-tetradecene-2,7-diynoate (16). A solution of malonate **18** (0.2443 g, 1.00 mmol) in THF (2 mL) was added to a suspension of sodium hydride (0.040 g, 1.00 mmol) (60%, washed with pentane) in THF (1 mL). After the reaction mixture was stirred for 15 min, a solution of bromide **14** (0.365 g, 0.90 mmol) in THF (2 mL) was added. The reaction mixture was stirred at room temperature overnight, the reaction was quenched with water, and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed to give the title compound **16** as an oil (0.423 g, 82%). IR ($CDCl_3$): 2956, 2931, 2858, 2236, 1737, 1714, 1437, 1259, 1215, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (dt, J = 11.1, 6.9 Hz, 1H), 5.48 (m, 1H), 4.62 (d, J = 6.9 Hz, 2H), 4.11 (d, J = 1.8 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 6H), 2.84 (m, 4H), 2.42 (d, J = 17.1 Hz, 1H), 2.31 (d, J = 17.1 Hz, 1H), 2.06 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.87 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.05, 170.32, 154.41, 128.51, 127.27, 87.97, 82.91, 80.32, 74.68, 69.53, 59.97, 56.73, 52.75, 52.39, 39.51, 30.27, 27.57, 25.49, 22.98, 22.82, 22.07, 20.66, 17.84, -4.84, –5.72. HRMS. Calcd for $C_{28}H_{41}O_8Si$ (M – OCH_3): 533.2571. Found: 533.2551. Anal. Calcd for $C_{29}H_{44}O_9Si$: C, 61.67; H, 7.85. Found: C, 61.73; H, 7.73.

Preparation of Methyl 6-Hydroxy-2-hexynoate (20a). *n*-Butyllithium (14.20 mL, 18.42 mmol) was added dropwise to a solution of the THP ether of 4-pentyn-1-ol (2.813 g, 16.74 mmol) in THF (30 mL) at –78 °C, followed after 2 h by addition of methyl chloroformate (1.94 mL, 25.11 mmol). After the mixture was stirred for 1 h at –78 °C and for 7 h at room temperature, water (50 mL) was added. The mixture was extracted with ether (3 × 60 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a residue, which was dissolved in methanol (50 mL). Water (5 mL) followed by *p*-toluenesulfonic acid (0.5 g) was added. After the mixture was stirred at room temperature overnight, solid sodium bicarbonate (2 g) was added. The mixture was stirred for 5 min and concentrated. Water (50 mL) was added. The mixture was extracted with ether (3 × 50 mL), and the organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 1:2) to give alcohol **20a** as a colorless liquid (1.85 g, 78%). IR ($CDCl_3$): 3627, 2956, 2238, 1711, 1436, 1266, 1082, 1060 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.74 (m, 2H), 2.47 (t, J = 7.0 Hz, 2H), 1.84 (m, 2H), 1.43 (t, J = 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.41, 89.07, 73.12, 60.96, 52.34, 30.08, 14.92. HRMS. Calcd for $C_7H_{10}O_3$ (M^+): 142.0630. Found: 142.0627.

Preparation of Methyl 6-Oxo-2-hexynoate (21a). DMSO (0.85 mL, 11.0 mmol) was added dropwise to a solution of oxalyl chloride (0.50 mL, 5.50 mmol) in dichloromethane (12 mL) at –50 to –60 °C. After 2 min, a solution of alcohol **20a** (0.71 g, 5.0 mmol) in dichloromethane (5 mL) was added within 5 min and stirring was continued for an additional 15 min, at which point triethylamine (3.5 mL, 25.0 mmol) was added. After an additional 5 min, the mixture was allowed to warm to room temperature. Water (25 mL) was added. The mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 1:1) to give the title compound **21a** as a light-yellow oil (0.56 g, 80%). IR ($CDCl_3$): 2956, 2835, 2730, 2245, 1716, 1436, 1270, 1083 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 3.75 (s, 3H), 2.79 (t, J = 7.2 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.88, 154.06, 87.09, 73.36, 52.37, 41.11, 11.42. MS *m/e*: 139 (0.2), 111 (85.9), 108 (73.6), 79 (41.8), 53 (100). HRMS. Calcd for $C_7H_8O_3$ (M^+): 140.0473. Found: 140.0473.

Preparation of Methyl 6-Hydroxy-10,10-bis(methoxycarbonyl)-12-tridecene-2,7-diynoate (22a). Lithium bis(trimethylsilyl)amide (4.96 mL, 4.96 mmol) was added dropwise to a solution of acetylene **8a** (1.04 g, 4.96 mmol) in THF (40 mL) at –78 °C. After 30 min, a solution of aldehyde **21a** (0.66 g, 4.72 mmol) in THF (5 mL) was added. After the reaction mixture was stirred at –78 °C for 30 min and the reaction was quenched with water also at –78 °C, the mixture was warmed to room temperature and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 1:1) to give the title compound **22a** as a colorless oil (0.71 g, 43%). IR ($CDCl_3$): 3606, 2956, 2242, 1735, 1713, 1602, 1437, 1292, 1266, 1222, 1207 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.16 (d, J = 17.0 Hz, 1H), 5.14 (d, J = 9.9 Hz, 1H), 4.47 (m, 1H), 3.76 (s, 3H), 3.74 (s, 6H), 2.82 (s, 2H), 2.77 (d, J = 7.3 Hz, 2H), 2.50 (m, 2H), 1.92 (m, 2H), 1.83 (d, J = 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.50, 154.32, 131.87, 119.98, 88.45, 83.43, 80.90, 73.30, 60.91, 57.02, 52.60, 52.38, 36.66, 35.31, 22.86, 14.34. HRMS. Calcd for $C_{17}H_{19}O_7$ (M – CH_3): 335.1131. Found: 335.1116. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.32; H, 6.05.

Preparation of Methyl 6-(*tert*-Butyldimethylsiloxy)-10,10-bis(methoxycarbonyl)-12-tridecene-2,7-diynoate (23a). Following a standard silylation procedure, alcohol **22a** (0.63 g, 1.80 mmol), 2,6-lutidine (0.42 mL, 3.60 mmol), and TBDMSOTf (0.62 mL, 2.70 mmol) in dichloromethane (5 mL) gave after the usual work-up, and flash chromatography (hexane/ether = 3:1) the title compound **23a** as a colorless oil (0.73 g, 87%). IR ($CDCl_3$): 2956, 2241, 1736, 1713, 1437, 1262, 1222, 1206, 1095, 1076 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.15 (m, 2H), 4.43 (m, 1H), 3.76 (s, 3H), 3.73 (s, 6H), 2.82 (d, J = 1.8 Hz, 2H), 2.77 (d, J = 7.6 Hz, 2H), 2.48 (m, 2H), 1.88 (m, 2H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.48, 154.38, 132.00, 119.87, 88.99, 83.94, 79.65, 73.14, 61.28, 56.98, 52.54, 52.35, 36.58, 36.40, 25.53, 22.82, 17.89, 14.23, –4.90, –5.50. HRMS. Calcd for $C_{23}H_{33}O_7Si$ (M – CH_3): 449.1996. Found: 449.1997. Anal. Calcd for $C_{24}H_{36}O_7Si$: C, 62.04; H, 7.81. Found: C, 62.40; H, 7.75.

Preparation of Methyl 6-Hydroxy-2-hexynoate (20b). Following the procedure for **20a**, the THP ether of 5-hexyn-1-ol (4.00 g, 21.98 mmol), *n*-butyllithium (18.60 mL, 24.18 mmol), and methyl chloroformate (2.55 mL, 32.97 mmol) in THF (50 mL) gave after the same workup and flash chromatography (hexane/ether = 1:1.5) alcohol **20b** as a colorless oil (2.40 g, 70%). IR ($CDCl_3$): 3627, 2954, 2239, 1711, 1436, 1265, 1080 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.67 (m, 2H), 2.40 (m, 2H), 1.69 (m, 4H), 1.41 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.45, 89.44, 73.10, 61.86, 52.29, 31.40, 23.70, 18.15. HRMS. Calcd for $C_8H_{12}O_3$ (M^+): 156.0786. Found: 156.0784.

Preparation of Methyl 6-Oxo-2-hexynoate (21b). Following the procedure for **21a** oxalyl chloride (0.50 mL, 5.50 mmol) in DMSO (0.85 mL, 11.0 mmol), alcohol **20b** (0.78 g, 5.0 mmol) and triethylamine (3.5 mL, 25.0 mmol) in dichloromethane (total 17 mL) gave after the usual workup and flash chromatography (hexane/ether = 1:1) the title compound **21b** as a light yellow oil (0.686 g, 89%). IR ($CDCl_3$): 2956, 2895, 2832, 2730, 2241, 1716, 1436, 1265, 1081 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 3.76 (s, 3H), 2.63 (t, J = 7.1 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.90 (p, J = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.05, 154.17, 88.01, 73.71, 52.32, 42.16, 19.78, 17.70. HRMS. Calcd for $C_8H_{10}O_3$ (M^+): 154.0630. Found: 154.0631.

Preparation of Methyl 7-(*tert*-Butyldimethylsiloxy)-11,11-bis(methoxycarbonyl)-13-tetradecene-2,8-diynoate (23b). Following the procedure for **22a**, acetylene **8a** (0.975 g, 4.64 mmol), lithium bis(trimethylsilyl)-amide (1 M in THF, 4.64 mL, 4.64 mmol), and aldehyde **21b** (0.68 g, 4.42 mmol) in THF (total 35 mL) gave after the same workup and flash chromatography (hexane/ether = 1:2) alcohol **22b** as a light-yellow oil (0.82 g, 51%).

This alcohol (0.75 g, 2.06 mmol), 2,6-lutidine (0.48 mL, 4.12 mmol), and TBDMSOTf (0.71 mL, 3.09 mmol) in dichloromethane (2.5 mL) following the usual silylation procedure and workup gave after flash chromatography (hexane/ether = 2:1) the title compound **23b** as a colorless oil (0.75 g, 76%). IR ($CDCl_3$): 2956, 2931, 2858, 2238, 1736, 1713, 1437, 1260, 1220, 1206, 1093, 1079 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.15 (m, 2H), 4.35 (m, 1H), 3.75 (s, 3H), 3.73 (s, 6H), 2.82 (d, J = 1.7 Hz, 2H), 2.77 (d, J = 7.6 Hz, 2H), 2.37 (m, 2H), 1.70 (m, 4H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.51, 154.43, 132.09, 119.76, 89.35, 84.63, 79.15, 73.16, 62.33, 57.04, 52.48, 52.28, 37.55, 36.57, 25.56, 23.04, 22.85, 18.25, 17.91, –4.88, –5.43. HRMS. Calcd for $C_{24}H_{35}O_7Si$ (M – CH_3): 463.2152. Found: 463.2136. Anal. Calcd for $C_{25}H_{38}O_7Si$: C, 62.74; H, 8.01. Found: C, 62.75; H, 7.98.

Preparation of Methyl 7-(*tert*-Butyldimethylsiloxy)-13-tetradecen-2,8-ynoate (23c). Following the procedure for the preparation of **21a**, oxalyl chloride (3.57 mL, 39.29 mmol), DMSO (6.07 mL, 78.56 mmol), 5-hexyn-1-ol (3.50 g, 35.71 mmol), and triethylamine (25.0 mL, 178.5 mmol) in dichloromethane (total 85 mL) gave, after the usual workup, a solution of 5-hexynal in dichloromethane (ca. 250 mL).

Triphenylphosphine (37.41 g, 141.8 mmol) was added to the above solution followed by carbon tetrabromide[13] after cooling to 0 °C. After the reaction mixture was stirred for 1 h and the reaction was quenched with saturated aqueous sodium bicarbonate, the mixture was extracted with hexane. The organic layer was washed with saturated aqueous sodium bicarbonate, water, and brine, dried ($MgSO_4$), filtered, and concentrated to give a residue with some solid. Hexane was added, and the resulting mixture was filtered, concentrated, and flash chromatographed (hexane)

to give 1,1-dibromo-1-hepten-6-yne (**24**) as a colorless liquid (7.40 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (t, J = 7.3 Hz, 1H), 2.22 (m, 4H), 1.98 (t, J = 2.6 Hz, 1H), 1.68 (m, 2H).

To a stirred solution of the above compound (7.30 g) in methanol (40 mL) and pyridine (5 mL) was added 5% Pd/$BaSO_4$ (0.50 g). The flask was evacuated and repeatedly flushed with hydrogen contained in a balloon. The reaction was monitored by GC. After completion, the mixture was filtered through Celite. The filtrate was diluted with ether. The organic layer was washed with water and saturated aqueous $CuSO_4$ solution and was filtered through a silica gel plug with hexane as eluent. The filtrate was concentrated to give 1,1-dibromo-1,6-heptadiene as a colorless liquid (5.50 g, 75%). IR ($CDCl_3$): 3081, 2932, 2861, 1641, 1621, 1456, 1440 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.39 (t, J = 7.2 Hz, 1H), 5.79 (m, 1H), 5.00 (m, 2H), 2.12 (m, 4H), 1.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.67, 138.10, 115.27, 88.88, 32.86, 32.23, 26.79.

n-Butyllithium (5.46 mL, 8.47 mmol) was added dropwise to a solution of 1,1-dibromo-1,6-heptadiene (1.05 g, 4.13 mmol) in THF (10 mL) at −78 °C. After 1 h, the bath was removed. After the reaction mixture was stirred for 1.5 h at room temperature and cooled to −78 °C, a solution of aldehyde **21b** in THF (5 mL) was added. After the reaction mixture was stirred at −78 °C for 2 h and the reaction was quenched with water (30 mL) at −78 °C, the mixture was extracted with ether (3 × 50 mL), and the organic layers were dried ($MgSO_4$), filtered, and concentrated to give the alcohol **22c** as a yellow residue (0.85 g). IR ($CDCl_3$): 3610, 2954, 2239, 1711, 1436, 1266 cm^{-1}.

After crude alcohol **22c** was dissolved in DMF (6 mL), imidazole (0.844 g, 12.39 mmol) followed by TBDMSCl (0.934 g, 6.20 mmol) was added. The mixture was stirred at room temperature overnight, the reaction was quenched with water (20 mL), and the reaction mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 10:1) to give the title compound **23c** as a colorless liquid (0.77 g, 52%). IR ($CDCl_3$): 2956, 2931, 2858, 2238, 1710, 1645, 1436, 1260, 1091, 1080 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.00 (m, 2H), 4.37 (bs, 1H), 3.75 (s, 3H), 2.36 (m, 2H), 2.15 (m, 4H), 1.72 (m, 4H), 1.59 (m, 2H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.50, 138.07, 115.26, 89.55, 84.59, 81.56, 72.96, 62.47, 52.43, 37.63, 32.62, 27.62, 25.60, 23.17, 18.25, 17.98, 17.83, −4.78, −5.35. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.18; H, 9.09.

Preparation of 9-Decen-4-yn-1-ol (27a). *n*-Butyllithium (12.55 mL, 13.81 mmol) was added dropwise to a solution of the THP ether of 4-pentyn-1-ol (2.21 g, 13.15 mmol) in THF (30 mL) at 0 °C followed by a solution of 5-bromo-1-pentene (2.06 g, 13.81 mmol) in HMPA (30 mL) after 30 min. After the reaction mixture was stirred at 0 °C for an additional 30 min and at room temperature for 6 h, the reaction was quenched with water (50 mL), the mixture was extracted with hexane (4 × 50 mL), and the organic layers were washed with water (3 × 40 mL) and brine (40 mL) and were concentrated to give a yellow residue which was dissolved in methanol (50 mL). Water (2 mL) followed by *p*-toluenesulfonic acid (0.3 g) was added. The mixture was stirred at room temperature overnight. Solid sodium bicarbonate (2 g) was added. The mixture was stirred for 5 min and concentrated. Water (40 mL) was added. The mixture was extracted with ether (3 × 50 mL), and the ether extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 2:1) to give the title compound **27a** as a colorless oil (1.15 g, 66%). IR ($CDCl_3$): 3627, 3080, 2942, 2249, 1435, 1052 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.00 (m, 2H), 3.76 (t, J = 6.1 Hz, 2H), 2.78 (tt, J = 6.9, 2.4 Hz, 2H), 2.14 (m, 4H), 1.74 (p, J = 6.5 Hz, 2H), 1.58 (m, 2H), 1.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.20, 115.08, 80.63, 79.63, 61.99, 32.62, 31.57, 28.12, 17.93, 15.20. HRMS. Calcd for $C_{10}H_{16}O$ (M^+): 152.1201. Found: 152.1187.

Preparation of 9-Decen-4-ynal (28a). Following the Moffatt–Swern procedure for the preparation of **21a**, oxalyl chloride (0.69 mL, 7.13 mmol), DMSO (1.16 mL, 15.05 mmol), alcohol **27a** (1.04 g, 6.84 mmol), and triethylamine (4.79 mL, 34.2 mmol) in dichloromethane (total 25 mL) gave after the same workup and flash chromatography (hexane/ether = 20:1) the title compound **28a** as an oil (0.72 g, 70%). IR ($CDCl_3$): 3080, 2935, 2861, 2841, 2732, 2249, 1727, 1641 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 5.78 (ddt, J = 17.1, 10.3, 6.7 Hz, 1H), 5.00 (m, 2H), 2.62 (t, J = 7.1 Hz, 2H), 2.49 (m, 2H), 2.10 (m, 4H), 1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.20, 138.11, 115.11, 81.17, 78.10, 42.83, 32.55, 27.93, 17.84, 11.96. HRMS. Calcd for $C_{10}H_{13}O$ (M^+ − H): 149.0966. Found: 149.0962.

Preparation of Ethyl 4-(*tert*-Butyldimethylsiloxy)-12-tridecene-2,7-diynoate (29a). Lithium bis(trimethylsilyl)amide (4.84 mL, 4.84 mmol) was added dropwise to a solution of ethyl propiolate (0.4743 g, 4.84 mmol) in THF (15 mL) at −78 °C. After 75 min, a solution of aldehyde **28a** (0.66 g, 4.40 mmol) in THF (5 mL) was added at −78 °C. After the mixture was stirred at −78 °C for 1.5 h and the reaction was quenched with water at −78 °C, the mixture was allowed to warm to room temperature and was extracted with ether (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 3:1) to give the product alcohol as a colorless liquid (0.68 g, 62%). IR ($CDCl_3$): 3605, 2939, 2244, 1709, 1255 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.02 (m, 2H), 4.68 (q, J = 6.3 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.38 (m, 2H), 2.24 (d, J = 6.3 Hz, 1H), 2.13 (m, 4H), 1.94 (m, 2H), 1.58 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.55, 138.12, 115.17, 87.08, 81.54, 78.53, 62.04, 61.21, 35.83, 32.62, 28.01, 17.90, 14.53, 13.73. HRMS. Calcd for $C_{15}H_{20}O_3$ (M^+): 248.1412. Found: 248.1414.

Silylation using the standard protocol of the above alcohol (0.65 g, 2.62 mmol) with 2,6-lutidine (0.61 mL, 5.24 mmol) and TBDMSOTf (0.90 mL, 3.93 mmol) in dichloromethane (4 mL) gave, after the usual workup and flash chromatography (hexane : ether = 25 : 1), the title compound **29a** as a colorless oil (0.745 g, 79%). IR ($CDCl_3$): 2958, 2932, 2236, 1708, 1255, 1100 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.02 (m, 2H), 4.64 (t, J = 6.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.31 (m, 2H), 2.15 (m, 4H), 1.89 (m, 2H), 1.55 (d, J = 7.3 Hz, 2H), 1.31 (t, J = 7.1 Hz, 2H), 0.91 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.68, 138.19, 115.11, 88.17, 80.98, 78.76, 76.39, 61.82, 61.22, 37.02, 32.66, 28.11, 25.53, 17.93, 14.49, 13.75, −4.85, −5.48. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45; MW, 362.2277. Found: 69.22; H, 9.12; MW, 362.2286.

Preparation of 10-Undecen-5-yn-1-ol (27b). Following the procedure for the preparation of **27a**, the reaction of the THP ether of 5-hexyn-1-ol (3.34 g, 18.35 mmol), *n*-butyllithium (17.5 mL, 19.3 mmol), and 5-bromo-1-pentene (2.87 mL, 19.27 mmol) in THF (40 mL) and HMPA (40 mL) gave, after the same workup and flash chromotography (hexane/ether = 2.5:1), the title compound **27b** as a colorless oil (1.76 g, 58%). IR ($CDCl_3$): 3626, 3080, 2941, 2249, 1641, 1455, 1436, 1054, 1024 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.00 (m, 2H), 3.67 (m, 2H), 2.18 (m, 6H), 1.68 (m, 2H), 1.58 (m, 4H), 1.32 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.29, 115.04, 80.28, 80.11, 62.46, 32.64, 31.79, 28.21, 25.24, 18.34, 17.97. HRMS. Calcd for $C_{11}H_{18}O$ (M^+): 166.1357. Found: 166.1335.

Preparation of 10-Undecen-5-ynal (28b). Following the normal Moffatt–Swern protocol as utilized in the preparation of **21a**, oxalyl chloride (1.03 mL, 11.27 mmol), DMSO (1.74 mL, 22.5 mmol), alcohol **28a** (1.70 g, 10.24 mmol), and triethylamine (7.17 mL, 51.2 mmol) in dichloromethane (total 30 mL) gave, after the usual workup and flash chromatography (hexane/ether = 10:1), the title compound **28b** as an oil (1.20 g, 71%). IR ($CDCl_3$): 3080, 2940, 2862, 2845, 2729, 2248, 1723, 1641 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 5.79 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.02 (dd, J = 17.1, 1.4 Hz, 1H), 4.98 (dd, J = 10.7, 1.4 Hz, 1H), 2.57 (t, J = 6.6 Hz, 2H), 2.24 (m, 2H), 2.12 (m, 4H), 1.81 (p, J = 7.0 Hz, 2H), 1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.21, 138.17, 115.10, 81.18, 79.03, 42.69, 32.62, 28.08, 21.46, 18.04, 17.90. HRMS. Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1202.

Preparation of Ethyl 4-(*tert*-Butyldimethylsiloxy)-13-tetradecene-2,8-diynoate (29b). Following the procedure for the preparation of **29a**, ethyl propiolate (0.388 g, 3.96 mmol), lithium bis(trimethylsilyl)amide (1 M in THF, 3.96 mL, 3.96 mmol), and aldehyde **28b** (0.59 g, 3.6 mmol) in THF (total 20 mL) gave, after the usual workup and flash chromatography (hexane/ether = 3:1), the product alcohol as a liquid (0.59 g, 63%). IR ($CDCl_3$): 3689, 3604, 2987, 2941, 2247, 1709, 1255 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (ddt, J = 17.1 Hz, 10.3, 6.8 Hz, 1H), 5.00 (m, 2H), 4.54 (q, J = 6.2 Hz, 1H), 4.24 (q, J = 7.9 Hz, 2H), 2.25 (m, 2H), 2.15 (m, 4H), 1.94 (d, J = 6.2 Hz, 1H), 1.90 (m, 2H), 1.68 (m, 2H), 1.58 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.61, 138.22, 115.08, 87.51, 80.79, 79.44, 62.03, 61.71, 35.82, 32.63, 28.09, 24.24, 18.13, 17.92, 13.72. HRMS. Calcd for $C_{16}H_{20}O_2$ (M-H_2O): 244.1463. Found: 244.1460.

Employing the usual silylation procedure, the above alcohol (0.65 g, 2.48 mmol), 2,6-lutidine (0.58 mL, 4.96 mmol), and TBDMSOTf (0.85 mL, 3.72 mmol) in dichloromethane (3 mL) gave, after the normal workup and flash chromatography (hexane/ether = 30:1), the title compound **29b** as a colorless oil (0.833 g, 89%). IR ($CDCl_3$): 2957, 2932, 2252, 1708, 1254, 1099 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (ddt, J

= 17.1, 10.3, 6.8 Hz, 1H), 5.00 (dd, J = 17.1, 1.9 Hz, 1H), 4.98 (dd, J = 10.3, 1.9 Hz, 1H), 4.50 (t, J = 6.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.18 (m, 6H), 1.82 (m, 2H), 1.60 (m, 4H), 1.31 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.74, 138.27, 115.05, 88.41, 80.51, 79.67, 76.32, 62.34, 61.79, 36.76, 32.65, 28.18, 25.54, 24.36, 18.20, 17.97, 17.93, 13.76, -4.89, -5.40. Anal. Calcd for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.63; MW, 376.2433. Found: C, 70.49; H, 9.61; MW, 376.2444.

Preparation of (9*Z*)-Undecen-4-yn-1-ol (27c). *n*-Butyllithium (6.25 mL, 100 mmol) was added dropwise to a solution of 5-chloro-1-pentyne (10.2 g, 100 mmol) in ether (250 mL) at -78 °C followed by sequential addition of methyl iodide (12.45 mL, 200 mmol) and HMPA (18 mL) after 2.5 h. After the mixture was stirred at -78 °C for 1 h and at room temperature for 2 h, the reaction was quenched with water and extracted with hexane. The organic layer was washed with water (3 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and filtered. The solvent was removed by distillation. The residue was distilled at 145–148 °C/760 mmHg to give 6-chloro-2-hexyne as a colorless liquid (7.50 g, 64%).[40] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.65 (t, J = 6.4 Hz, 2H), 2.32 (m, 2H), 1.95 (m, 2H), 1.77 (t, J = 2.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.17, 43.67, 31.51, 15.90, 3.14.

To a stirred solution of 6-chloro-2-hexyne (7.0 g, 60.0 mmol) in methanol (20 mL) and pyridine (5 mL) was added 5% Pd/$BaSO_4$ (0.35 g). The flask was evacuated and repeatedly flushed with hydrogen contained in a balloon. The reaction was monitored by GC. After completion, the reaction mixture was filtered through Celite. The filtrate was diluted with ether and washed with saturated aqueous $CuSO_4$, water, and brine, respectively, dried ($MgSO_4$), and filtered. The solvent was removed by distillation and the residue distilled at 135–138 °C/760 mmHg to give 6-chloro-(2*Z*)-hexene as a colorless liquid (6.20 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.51 (m, 1H), 5.37 (m, 1H), 3.54 (t, J = 6.6 Hz, 2H), 2.21 (m, 2H), 1.82 (m, 2H), 1.63 (dd, J = 6.7 Hz, 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.70, 125.62, 44.37, 32.11, 23.78, 12.51.

n-Butyllithium (12.6 mL, 13.8 mmol) was added dropwise to a solution of the THP ether of 4-pentyn-1-ol (2.21 g, 13.15 mmol) in THF (30 mL) at 0 °C followed after 30 min by HMPA (8 mL) and a solution of 6-chloro-(2*Z*)-hexene (1.90 g, 16.03 mmol) in THF (5 mL). After the mixture was stirred at 0 °C for 10 min and at room temperature for 4 h, the reaction mixture was quenched with water (50 mL), and the reaction mixture was extracted with hexane (3 × 60 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (50 mL) and were concentrated to give a yellow residue which was dissolved in methanol (50 mL). Water (5 mL) followed by *p*-toluenesulfonic acid (0.5 g) was added. The mixture was stirred at room temperature overnight. Solid sodium bicarbonate (2 g) was added. The mixture was stirred for 5 min and concentrated. Water (50 mL) was added. The mixture was extracted with ether (3 × 50 mL). The organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 2:1) to give alcohol **27c** as a colorless oil (1.43 g, 59%). IR ($CDCl_3$): 3622, 3015, 2938, 2864, 1435, 1052 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48 (m, 1H), 5.36 (m, 1H), 3.76 (q, J = 6.0 Hz, 2H), 2.28 (tt, J = 6.8, 2.4 Hz, 2H), 2.16 (m, 4H), 1.72 (m, 2H), 1.62 (dd, J = 6.0, 0.8 Hz, 3H), 1.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.80, 124.82, 80.88, 79.44, 62.05, 31.41, 28.68, 25.74, 17.98, 15.20, 12.52. HRMS. Calcd for $C_{11}H_{18}O$ (M^+): 166.1358. Found: 166.1384.

Preparation of (9*Z*)-undecen-4-ynal (28c). Following the Moffatt–Swern protocol for the preparation of **21a**, oxalyl chloride (0.84 mL, 9.28 mmol), DMSO (1.43 mL, 18.55 mmol), alcohol **27c** (1.40 g, 8.43 mmol) and triethylamine (5.9 mL, 42.2 mmol) in dichloromethane (total 30 mL) were reacted to give, after the usual workup and flash chromatography (hexane/ether = 10:1), the title compound **28c** as a liquid (1.15 g, 83%). IR ($CDCl_3$): 3015, 2937, 2862, 2841, 2732, 1727, 1650, 1604, 1437, 1408, 1057 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (t, J = 1.3 Hz, 1H), 5.50 (m, 1H), 5.35 (m, 1H), 2.62 (td, J = 7.0, 1.3 Hz, 2H), 2.50 (m, 2H), 2.12 (m, 4H), 1.62 (d, J = 6.7 Hz, 3H), 1.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.48, 129.73, 124.84, 81.32, 77.94, 42.84, 28.51, 25.67, 17.90, 12.51, 11.91. HRMS. Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1207.

Preparation of Ethyl 4-(*tert*-Butyldimethylsiloxy)-(12*Z*)-tetradecene-2,7-diynoate (29c). Following the procedure for the preparation of **29a**, reaction of ethyl propiolate (0.395 g, 4.03 mmol), lithium bis(trimethylsilyl)amide (1 M in THF, 4.03 mL, 4.03 mmol), and aldehyde **28c** (0.60 g, 3.68 mmol) in THF (total 20 mL) gave, after the same workup and and flash chromatography (hexane/ether = 3:1), an alcohol as a colorless liquid (0.380 g, 40%).

Silylation of the above alcohol (0.36 g, 1.37 mmol) with 2,6-lutidine (0.32 mL, 2.74 mmol) and TBDMSOTf (0.47 mL, 2.06 mmol) in dichloromethane (3 mL) in the same fashion as before gave, after the same workup and flash chromatography (hexane/ether = 20:1), the title compound **29c** as a colorless oil (0.422 g, 82%). IR ($CDCl_3$): 3014, 2932, 2859, 1709, 1255, 1099 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49 (m, 1H), 5.36 (m, 1H), 4.65 (dd, J = 7.0, 5.8 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.30 (m, 2H), 2.15 (m, 4H), 1.88 (m, 2H), 1.61 (d, J = 6.4 Hz, 3H), 1.52 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.37, 129.78, 124.83, 88.14, 81.17, 78.54, 76.19, 61.91, 61.03, 36.85, 28.67, 25.78, 25.49, 17.98, 17.91, 14.45, 13.76, 12.55, -4.97, -5.53. Anal. Calcd for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.63; MW, 376.2434. Found: C, 69.81; H, 9.32; MW, 376.2438.

Preparation of 9-Methyl-9-decen-4-yn-1-ol (27d). *n*-Butyllithium (6.67 mL, 10.67 mmol) was added dropwise to a solution of the THP ether of 4-pentyn-1-ol (1.63 g, 9.70 mmol) in THF (30 mL) at 0 °C followed after 45 min by HMPA (3.4 mL) and a solution of 5-bromo-2-methyl-1-pentene[41] (1.74 g, 10.67 mmol) in THF (2 mL). After the mixture was stirred at 0 °C for 1 h and at room temperature overnight and the reaction was quenched with water (50 mL), the mixture was extracted with hexane (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (50 mL) and were concentrated to give a yellow residue which was dissolved in methanol (50 mL). Water (2 mL) followed by *p*-toluenesulfonic acid (0.3 g) was added. The mixture was stirred at room temperature overnight. Solid sodium bicarbonate (2 g) was added. The mixture was stirred for 5 min and concentrated. Water (40 mL) was added. The mixture was extracted with ether (3 × 50 mL). The organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, concentrated, and flash chromatographed (hexane/ether = 2:1) to give compound **27d** as a colorless liquid (0.98 g, 61%). IR ($CDCl_3$): 3622, 3077, 2944, 2886, 2849, 1649, 1435, 1051 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72 (bs, 1H), 4.68 (bs, 1H), 3.76 (q, J = 5.7 Hz, 2H), 2.28 (tt, J = 6.8, 2.4 Hz, 2H), 2.14 (tt, J = 7.1, 2.4 Hz, 2H), 2.08 (t, J = 7.6 Hz, 1H), 1.74 (m, 2H), 1.72 (s, 3H), 1.61 (m, 2H), 1.52 (t, J = 5.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.36, 110.38, 80.74, 79.55, 61.99, 36.69, 31.41, 26.79, 22.13, 18.06, 15.18. HRMS. Calcd for $C_{11}H_{18}O$ (M^+): 166.1358. Found: 166.1363.

Preparation of 9-Methyl-9-decen-4-ynal (28d). Following the Moffatt–Swern protocol for the preparation of **21a**, oxalyl chloride (0.604 mL, 6.64 mmol), DMSO (1.03 mL, 13.29 mmol), alcohol **27d** (0.94 g, 6.04 mmol), and triethylamine (4.23 mL, 30.2 mmol) in dichloromethane (total 20 mL) reacted to give, after the same workup and flash chromatography (hexane/ether = 20:1), aldehyde **28d** as a colorless liquid (0.61 g, 66%). IR ($CDCl_3$): 3077, 2941, 2864, 2842, 2731, 1727, 1649, 1438 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 4.72 (bs, 1H), 4.68 (bs, 1H), 2.62 (t, J = 7.0 Hz, 2H), 2.49 (m, 2H), 2.12 (tt, J = 7.0, 2.4 Hz, 2H), 2.07 (t, J = 7.63 Hz, 2H), 1.71 (s, 3H), 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.47, 145.29, 110.40, 81.21, 78.05, 42.84, 36.62, 26.62, 22.11, 17.98, 11.91. HRMS. Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1196.

Preparation of Ethyl 4-(*tert*-Butyldimetylsiloxy)-12-methyl-12-tridecene-2,7-diynoate (29d). Following the protocol for the preparation of **29a**, ethyl propiolate (0.395 g, 4.03 mmol), lithium bis(trimethylsilyl)amide (1 M in THF, 4.03 mL, 4.03 mmol), and aldehyde **28d** (0.60 g, 3.66 mmol) in THF (total 20 mL) reacted to give, after the same workup and flash chromatography (hexane/ether = 3:1), an alcohol as a colorless liquid (0.38 g, 39.6%).

Silylation of the above alcohol (0.38 g, 1.45 mmol) with 2,6-lutidine (0.34 mL, 2.92 mmol) and TBDMSOTf (0.50 mL, 2.19 mmol) in dichloromethane (3 mL) under the same conditions and workup as before followed by flash chromatography (hexane/ether = 20:1) gave the title compound **29d** as a colorless liquid (0.48 g, 88%). IR ($CDCl_3$): 2932, 2859, 1709, 1650, 1255, 1099 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72 (bs, 1H), 4.68 (bs, 1H), 4.63 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.30 (m, 2H), 2.13 (m, 2H), 2.08 (t, J = 7.9 Hz, 1H), 1.87 (m, 2H), 1.71 (s, 3H), 1.60 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.71, 145.32, 110.38, 88.13, 81.07, 78.62, 76.18, 61.90, 61.01, 36.82, 36.71, 26.76, 25.48, 22.15, 18.05, 17.90, 14.44, 13.75, -4.98, -5.54. Anal. Calcd for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.63. Found: C, 70.47; H, 9.35.

Preparation of 1β-(*tert*-Butyldimethylsiloxy)-5α,7,7-tris(methoxycarbonyl)-2,2-dimethyl-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[*e*]in-

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dene (33a). A solution of substrate **7a** (0.080 g, 0.163 mmol) in benzene-d_6 (1.0 mL) followed by acetic acid (1.9 uL, 0.033 mmol) was added to a mixture of $Pd_2(dba)_3$·$CHCl_3$ (0.00422 g, 0.0041 mmol) and triphenylphosphine (0.00422 g, 0.0163 mmol) in an NMR tube. After being shaken vigorously, the reaction mixture was heated at 70 °C for 4 h, cooled, concentrated, and flash chromatographed (hexane/ether = 4:1) to give **33a** as an oil (0.058 g, 73%). IR ($CDCl_3$): 2958, 2860, 1730, 1460, 1436, 1256, 1200, 1165, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.33 (bs, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.38 (dd, J = 10.9, 10.1 Hz, 1H), 3.24 (dd, J = 17.3, 1.8 Hz, 1H), 3.16 (dd, J = 17.3, 1.8 Hz, 1H), 3.13 (d, J = 17.4 Hz, 1H), 3.03 (d, J = 17.4 Hz, 1H), 2.58 (dd, J = 17.7, 10.9 Hz, 1H), 2.43 (dd, J = 17.7, 10.1 Hz, 1H), 2.25 (d, J = 17.0 Hz, 1H), 2.02 (d, J = 17.0 Hz, 1H), 1.05 (s, 3H), 0.98 (s, 3H), 0.90 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.21, 172.82, 172.77, 138.38, 133.07, 131.89, 126.88, 84.28, 58.49, 52.63, 52.53, 51.69, 48.80, 43.04, 41.77, 41.23, 40.30, 28.24, 27.88, 26.01, 23.75, 18.13, –2.97, –4.30. HRMS. Calcd for $C_{26}H_{40}O_7Si$ (M^+): 492.2543. Found: 492.2545.

Preparation of 1β-Methoxy-5α,7,7-tris(methoxycarbonyl)-2,2-dimethyl-2,3,4,5,7,8-hexhydro-1*H*,6*H*-cyclopenta[*e*]indene (33b). A solution of substrate **7c** (0.064 g, 0.163 mmol) in benzene (1.5 mL) followed by acetic acid (1.9 μL, 0.033 mmol) was added to a mixture of $Pd_2(dba)_3$·$CHCl_3$ (0.00422 g, 0.00408 mmol) and triphenylphosphine (0.00427 g, 0.0163 mmol). The reaction mixture was stirred at 72–75 °C for 6 h, cooled, concentrated, and flash chromatographed (hexane/ether = 1.5:1) to give product **33b** as a colorless oil (0.043 g, 67%). IR ($CDCl_3$): 2956, 2929, 1733, 1602, 1584, 1436, 1272, 1201, 1170, 1086 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (bs, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.41 (s, 3H), 3.37 (dd, J = 10.1, 9.4 Hz, 1H), 3.17 (bs, 2H), 3.12 (bs, 2H), 2.62 (dd, J = 17.9, 9.4 Hz, 1H), 2.45 (dd, J = 17.9, 10.1 Hz, 1H), 2.31 (d, J = 17.4 Hz, 1H), 2.03 (d, J = 17.4 Hz, 1H), 1.10 (s, 3H), 1.097 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.07, 172.87, 172.68, 139.15, 131.80, 130.77, 127.14, 92.91, 58.67, 58.50, 52.77, 51.82, 49.20, 42.14, 41.93, 41.08, 39.43, 29.78, 27.44, 22.64. HRMS. Calcd for $C_{21}H_{28}O_7$ (M^+): 392.1835. Found: 392.1813.

Preparation of 3-(*tert*-Butyldimethylsiloxy)-2-{2′-[(methoxycarbonyl)-methyl]-1′-cyclopentyl}-4,4-dimethyl-1-vinylcyclopentane (36). A solution of substrate **7b** (0.041 g, 0.081 mmol) in benzene-d_6 (0.8 mL) followed by acetic acid (4.6 μL, 0.081 mmol) was added to a mixture of $Pd_2(dba)_3$·$CHCl_3$ (0.0021 g, 0.00203 mmol) and triphenylphosphine (0.0021 g, 0.0081 mmol) in an NMR tube. The reaction mixture was heated at 72–76 °C for 1.5 h, cooled, concentrated, and flash chromatographed (hexane/ether = 5:1) to give **35** (0.0365 g, 89%). IR ($CDCl_3$): 2956, 2860, 2259, 1730, 1704, 1462, 1438, 1202, 1075 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.03, 171.96, 171.81, 167.83, 167.66, 155.80, 155.01, 149.45, 148.46, 142.28, 141.72, 133.53, 132.99, 116.06, 115.90, 114.33, 114.00, 84.09, 57.54, 57.39, 52.67, 52.49, 50.91, 45.00, 44.75, 44.33, 41.59, 41.24, 40.46, 40.12, 40.03, 39.58, 38.75, 26.36, 25.96, 25.86, 25.73, 25.31, 22.55, 21.60, 18.07, 18.03, –4.17, –4.24, –4.41, –4.90. HRMS. Calcd for $C_{27}H_{42}O_7Si$ (M^+): 506.2700. Found: 506.2706.

A solution of **35** (0.070 g, 0.138 mmol) and DBU (0.005 mL) in benzene-d_6 (0.8 mL) in a NMR tube was heated at 80 °C for 28 h, cooled, concentrated, and flash chromatographed (hexane/ether = 4:1) to give triene **36** as an oil (0.051 g, 73%). IR ($CDCl_3$): 2956, 2930, 2860, 2258, 1730, 1460, 1438, 1260, 1200, 1070, 1010 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.32 (dd, J = 17.6 Hz, 10.6 Hz, 1H), 5.12 (d, J = 17.6 Hz, 1H), 5.08 (d, J = 10.6 Hz, 1H), 4.24 (s, 1H), 3.74 (s, 6H), 3.64 (s, 3H), 3.25 (d, J = 16.4 Hz, 1H), 3.13 (m, 4H), 2.93 (d, J = 16.4 Hz, 1H), 2.40 (d, J = 15.3 Hz, 1H), 2.13 (d, J = 15.3 Hz, 1H), 1.06 (s, 3H), 1.00 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), –0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.64, 172.61, 171.32, 139.28, 138.19, 133.38, 132.45, 130.77, 115.88, 86.32, 57.84, 52.60, 51.37, 44.41, 43.53, 41.93, 34.49, 27.63, 25.72, 23.20, 17.86, –4.44, –5.10. HRMS. Calcd for $C_{27}H_{42}O_7Si$ (M^+): 506.2700. Found: 506.2715.

Preparation of 1-(*tert*-Butyldimethylsiloxy)-7,7-bis(methoxycarbonyl)-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[e]indene (39a). Following the standard protocol, $Pd_2(dba)_3$·$CHCl_3$ (0.00864 g, 0.00835 mmol), triphenylphosphine (0.00875 g, 0.0334 mmol), substrate **10a** (0.145 g, 0.334 mmol), and acetic acid (0.0057 mL, 0.1002 mmol) in benzene (3 mL) gave, after 2.5 h at 65 °C and the usual workup (flash chromatography, hexane/ether = 10:1), cycloisomer **39a** as a colorless oil (0.083 g, 57%). IR ($CDCl_3$): 2956, 2930, 2858, 1731, 1436, 1258, 1200, 1170, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.32 (bs, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.24 (d, J = 17.1 Hz, 1H), 3.10 (d, J = 17.1 Hz, 1H), 3.06 (d, J = 17.4 Hz, 1H), 2.90 (d, J = 17.4 Hz, 1H), 2.20 (m, 5H), 1.96 (d, J = 16.9 Hz, 12H), 1.06 (s, 3H), 0.99 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.05, 172.70, 137.84, 133.05, 130.82, 128.87, 84.46, 58.44, 52.77, 52.63, 49.16, 43.19, 42.77, 40.56, 28.62, 26.17, 24.73, 24.10, 23.50, 18.33, –2.64, –4.07. HRMS. Calcd for $C_{24}H_{38}O_5Si$ (M^+): 434.2489. Found: 434.2488.

Preparation of 1β-(*tert*-Butyldimethylsiloxy)-4α,7,7-tris(methoxycarbonyl)-2,2-dimethyl-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[*e*]indene (39b). Following the standard protocol, $Pd_2(dba)_3$·$CHCl_3$ (0.00510 g, 0.00493 mmol), triphenylphosphine (0.01032 g, 0.0394 mmol), acetic acid (0.0023 mL, 0.0394 mmol), and substrate **11a** (0.097 g, 0.197 mmol) in benzene (1 mL) gave, after 2.5 h at 80 °C and the usual workup (flash chromatography, hexane/ether = 4:1), cycloisomer **39b** as a yellow oil (0.073 g, 75%). IR ($CDCl_3$): 2955, 2931, 1732, 1436, 1259, 1200, 1171, 1075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.35 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 3.31 (t, J = 9.2 Hz, 1H), 3.23 (d, J = 17.1 Hz, 1H), 3.15 (s, 1H), 3.11 (s, 1H), 2.90 (d, J = 17.1 Hz, 1H), 2.61 (dd, J = 17.3, 8.5 Hz, 1H), 2.47 (dd, J = 17.3, 10.1 Hz, 1H), 2.23 (d, J = 16.8 Hz, 1H), 2.15 (d, J = 16.8 Hz, 1H), 1.07 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.10, 172.86, 172.81, 135.89, 133.79, 131.18, 128.77, 84.22, 58.61, 52.55, 52.45, 51.55, 47.55, 43.12, 42.82, 41.72, 40.21, 27.86, 26.63, 25.98, 23.56, 18.11, –3.08, –4.34. Anal. Calcd for $C_{26}H_{40}O_7Si$: C, 63.38; H, 8.18; MW, 492.2543. Found: C, 63.12; H, 8.33; MW, 492.2518.

Preparation of 1β-(*tert*-Butyldimethylsiloxy)-7,7-bis(methoxycarbonyl)-2,2-dimethyl-5α-phenyl-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[*e*]-indene (41a). Following the standard protocol, $Pd_2(dba)_3$·$CHCl_3$ (0.00481 g, 0.00465 mmol), triphenylphosphine (0.00487 g, 0.0186 mmol), substrate **10c** (0.095 g, 0.186 mmol), and acetic acid (0.0021 mL, 0.037 mmol) in benzene (3.0 mL) gave, after 20 h at 55–60 °C and the usual workup (flash chromatography, hexane/ether = 8:1), cycloisomer **41a** as a colorless oil (0.066 g, 69%). IR ($CDCl_3$): 2956, 2930, 2894, 2859, 1732, 1436, 1258, 1199, 1169, 1074 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 2H), 7.19 (m, 3H), 4.40 (s, 1H), 3.693 (s, 3H), 3.69 (s, 3H), 3.65 (m, 1H), 3.33 (d, J = 17.4 Hz, 1H), 3.21 (d, J = 17.4 Hz, 1H), 2.87 (d, J = 16.20 Hz, 1H), 2.70 (d, J = 16.20 Hz, 1H), 2.65 (dd, J = 18.0, 10.3 Hz, 1H), 2.26 (m, 2H), 1.92 (d, J = 17.3 Hz, 1H), 1.07 (s, 3H), 1.02 (s, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.15, 172.84, 144.84, 138.19, 133.43, 133.30, 130.70, 128.68, 127.96, 126.55, 84.54, 58.55, 52.51, 52.43, 49.01, 42.97, 42.02, 41.76, 40.64, 34.76, 28.41, 26.07, 23.84, 18.19, –2.92, –4.21. Anal. Calcd for $C_{30}H_{42}O_5Si$: C, 70.55; H, 8.29; MW, 510.2802. Found: C, 70.53; H, 8.18; MW, 510.2785.

Preparation of 1β-(*tert*-Butyldimethylsiloxy)-4β,7,7-tris(methoxycarbonyl)-2,2-dimethyl-5α-phenyl-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta-[*e*]indene (41b). Following the standard protocol, $Pd_2(dba)_3$·$CHCl_3$ (0.00552 g, 0.00533 mmol), triphenylphosphine (0.00558 g, 0.0213 mmol), substrate **11c** (0.121 g, 0.213 mmol), and acetic acid (0.00244 mL, 0.0426 mmol) in benzene (2 mL) gave, after 6.5 h at 70–72 °C and the usual workup (flash chromatography, hexane/ether = 4:1), cycloisomer **41b** as a colorless oil (0.109 g, 90%). IR ($CDCl_3$): 2955, 2931, 2858, 1733, 1656, 1604, 1436, 1259, 1076 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 3H), 7.03 (m, 2H), 4.51 (bs, 1H), 2.94 (d, J = 11.2 Hz, 1H), 3.89 (d, J = 11.2 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.35 (s, 3H), 3.31 (bs, 2H), 3.05 (d, J = 17.5 Hz, 1H), 2.64 (d, J = 17.5 Hz, 1H), 2.38 (d, J = 17.4 Hz, 1H), 2.13 (d, J = 17.4 Hz, 1H), 1.11 (s, 3H), 0.98 (s, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.33, 171.46, 137.99, 134.65, 133.76, 130.11, 128.41, 128.16, 127.25, 84.12, 58.44, 52.67, 51.05, 49.09, 47.74, 44.59, 43.37, 41.38, 40.48, 28.16, 26.17, 23.76, 18.31, –2.47, –3.94. Anal. Calcd for $C_{32}H_{44}O_7Si$: C, 67.57; H, 7.80; MW, 568.2856. Found: C, 67.71; H, 8.07; MW, 568.2860.

Preparation of 1β-(*tert*-Butyldimethylsiloxy)-7,7-bis(methoxycarbonyl)-4α-(methoxymethylene)-5α-phenyl-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[*e*]indene (42c). Following the standard protocol, $Pd_2(dba)_3$·$CHCl_3$ (0.00443 g, 0.00428 mmol), triphenylphosphine (0.00448 g, 0.017 mmol), substrate **11d** (0.0950 g, 0.171 mmol), and acetic acid (0.003 mL, 0.0513 mmol) in benzene (1.2 mL) gave, after 6 h at 80 °C and the usual workup (flash chromatography, hexane/ether = 5:1), cycloisomer as a yellow oil (0.067 g, 70%). IR ($CDCl_3$): 2956, 2930, 2895, 2858, 1732, 1271, 1258, 1200, 1120, 1074 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 3H), 7.06 (m, 2H), 4.39 (s, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 3.60 (m, 1H), 3.28 (m, 4H), 3.18 (s, 3H), 3.13 (d, J = 17.5 Hz, 1H), 2.91 (m, 1H), 2.59 (d, J = 17.5 Hz, 1H), 2.28 (d, J = 17.1 Hz, 1H), 1.79 (d, J = 17.1 Hz, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.94, 172.82, 137.93, 137.84, 136.49, 134.13, 130.72, 129.29, 128.13, 126.85, 84.17, 71.57, 58.61, 58.26, 52.56, 46.66, 42.92, 42.67, 41.39, 41.19, 40.37, 28.79, 25.98, 23.76, 18.14, –2.84, –4.15. Anal. Calcd for $C_{32}H_{46}O_6Si$: C, 69.28; H, 8.36; MW, 554.3064. Found: C, 69.34; H, 8.25; MW, 554.3073.

Preparation of 5α-(Acetoxymethylene)-1β-(*tert*-butyldimethylsiloxy)-4α,7,7-tris(methoxycarbonyl)-2,2-dimethyl-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[e]indene (46). Following the standard protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00232 g, 0.00224 mmol), trifurylphosphine (0.00208 g, 0.00895 mmol), acetic acid (0.00257 mL, 0.0448 mmol) and substrate **15** (0.0505 g, 0.0898 mmol) in benzene (1.0 mL) gave, after 1.5 h at 63 °C and the usual workup (flash chromatography hexane/ether = 2:1), cycloisomer **46** as a colorless oil (0.031 g, 61%). IR ($CDCl_3$): 2956, 2931, 2858, 1734, 1436, 1257, 1199, 1165, 1077 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.36 (bs, 1H), 4.17 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 3.43 (d, J = 7.4 Hz, 1H), 3.18 (m, 3H), 3.05 (m, 2H), 2.31 (d, J = 17.1 Hz, 1H), 2.22 (d, J = 17.1 Hz, 1H), 2.03 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.70, 172.64, 171.57, 171.12, 136.32, 134.91, 131.43, 130.76, 83.83, 62.71, 58.64, 52.78, 52.69, 51.43, 47.47, 44.54, 43.44, 41.08, 40.03, 37.27, 27.74, 25.94, 23.45, 20.69, 18.08, –3.05, –4.38. Anal. Calcd for $C_{29}H_{44}O_9Si$: C, 61.68; H, 7.85. Found: C, 61.59; H, 7.85.

Preparation of 2-[2′-(2″-Acetoxyvinyl)-4′,4′-bis(methoxycarbonyl)-1′-cyclopentenyl]-3-(*tert*-butyldimethylsiloxy)-1-[(methoxycarbonyl)methyl]-4,4-dimethylcyclopentene (50). Following the standard protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00269 g, 0.0026 mmol), trifurylphosphine (0.0024 g, 0.0104 mmol), acetic acid (0.00298 mL, 0.052 mmol), and substrate **16** (0.0585 g, 0.104 mmol) in benzene (1.0 mL) gave, after 2.5 h at 62–64 °C and the usual workup (flash chromatography, hexane/ether = 2:1), product **50** as a yellow oil (0.051 g, 87%). IR ($CDCl_3$): 3090, 3030, 2956, 2931, 2858, 1735, 1654, 1612, 1436, 1259, 1238, 1121, 1076 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 12.8 Hz, 1H), 6.06 (d, J = 12.8 Hz, 1H), 4.19 (bs, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.22 (d, J = 16.1 Hz, 1H), 3.19 (d, J = 16.4 Hz, 1H), 3.12 (d, J = 16.4 Hz, 1H), 3.03 (d, J = 16.1 Hz, 1H), 3.00 (d, J = 15.9 Hz, 1H), 2.93 (d, J = 15.9 Hz, 1H), 2.31 (d, J = 16.0 Hz, 1H), 2.13 (s, 3H), 2.10 (d, J = 16.0 Hz, 1H), 1.06 (s, 3H), 1.01 (s, 3H), 0.82 (s, 9H), 0.00 (s, 3H), –0.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.58, 172.44, 171.59, 168.16, 137.70, 137.17, 135.31, 134.62, 131.57, 110.82, 85.87, 57.47, 52.77, 51.53, 48.28, 44.45, 42.32, 40.26, 34.75, 27.49, 25.65, 25.48, 22.97, 20.44, 17.78, –4.59, –5.16. Anal. Calcd for $C_{29}H_{44}O_9Si$: C, 61.68; H, 7.85; MW, 564.2755. Found: C, 62.10; H, 8.04; MW, 564.2756.

Preparation of 1β-(*tert*-Butyldimethylsiloxy)-4α,7,7-tris(methoxycarbonyl)-2,3,4,5,7,8-hexahydro-1*H*,6*H*-cyclopenta[e]indene (52). Following the general protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00546 g, 0.00528 mmol), triphenylphosphine (0.00553 g, 0.0211 mmol), substrate **23a** (0.098 g, 0.211 mmol), and acetic acid (0.00363 mL, 0.098 mmol) in benzene (1.5 mL) gave, after 3.5 h at 55.57 °C and the usual workup (flash chromatography, hexane/ether = 3:1), cycloisomer **52** as an oil (0.059 g, 60%). IR ($CDCl_3$): 2955, 2931, 2857, 1732, 1436, 1259, 1199, 1171, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.95 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.42 (t, J = 9.1 Hz, 1H), 3.28 (d, J = 16.2 Hz, 1H), 3.11 (m, 2H), 2.92 (d, J = 17.2 Hz, 1H), 2.64 (dd, J = 16.4, 9.1 Hz, 1H), 2.25–2.55 (m, 4H), 1.70 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.36, 127.97, 172.85, 136.31, 134.07, 131.63, 58.63, 52.70, 52.60, 51.79, 42.73, 41.88, 39.66, 34.18, 31.64, 26.81, 25.68, 17.70, –4.45, –5.02. Anal. Calcd for $C_{24}H_{36}O_7Si$: C, 62.04; H, 7.81. Found: C, 61.83; H, 7.96.

Preparation of 9β-(*tert*-Butyldimethylsiloxy)-5α-(methoxycarbonyl)-2,3,4,5,7,8,9-octahydro-1*H*-benz[e]indene (56). Following the general protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00807 g, 0.0078 mmol), triphenylphosphine (0.00817 g, 0.0312 mmol), substrate **23c** (0.1412 g, 0.390 mmol) and acetic acid (0.0047 mL, 0.078 mmol) in benzene (2 mL) reacted to give, after 11 h at 70 °C and the usual workup (flash chromatography hexane/ether = 20:1), cycloisomer **56** as a colorless oil (0.0720 g, 51%). IR ($CDCl_3$): 2953, 2933, 2858, 1728, 1600, 1436, 1255, 1081 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.32 (m, 1H), 3.66 (s, 3H), 3.10 (dd, J = 8.8, 6.7 Hz, 1H), 2.16–2.60 (m, 7H), 2.05 (m, 1H), 1.85 (m, 4H), 1.60 (m, 2H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.44, 134.05, 133.70, 131.35, 128.19, 65.78, 51.65, 46.09, 35.23, 31.79, 31.06, 29.32, 26.92, 25.98, 22.47, 18.07, 16.82, –4.18, –4.23. HRMS. Calcd for $C_{21}H_{34}O_2Si$ (M^+): 362.2277. Found: 362.2272.

Preparation of 3-(*tert*-Butyldimethylsiloxy)-4-(methoxycarbonyl)-2,3,5,5a,7,8-hexahydro-1H,6H-cyclopenta[e]indene (61a). Following the general protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00736 g, 0.0071 mmol), substrate **29a** (0.103 g, 0.2845 mmol), and acetic acid (4.9 μL, 0.085 mmol) in benzene (1.5 mL) reacted to give, after 28 h at room temperature and the usual workup (flash chromatography hexane/ether = 20:1), cycloisomer **61a** as a colorless oil (0.083 g, 81%). IR ($CDCl_3$): 2958, 2930, 2857, 1694, 1673, 1603, 1273, 1245, 1073 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.38 (d, J = 4.0 Hz, 1H), 4.28 (m, 1H), 4.16 (m, 1H), 2.86 (dd, J = 16.5, 8.5 Hz, 1H), 2.07–2.60 (m, 6H), 1.90 (m, 3H), 1.60 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.25 (m, 1H), 0.84 (s, 9H), 0.13 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.75, 154.90, 144.53, 130.60, 117.55, 72.56, 59.73, 41.87, 35.15, 33.88, 29.88, 28.75, 25.69, 24.87, 24.65, 17.88, 14.28, –4.63, -4.99. HRMS. Calcd for $C_{17}H_{25}O_3Si$ ($M^{-t}C_4H_9$): 305.1573. Found: 305.1553.

Preparation of 6-(*tert*-Butyldimethylsiloxy)-5-(methoxycarbonyl)-2,3,-3a,4,6,7,8,9-octahydro-1H-benz[e]indene (61b). Following the general protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00536 g, 0.00518 mmol), substrate (0.0779 g, 0.207 mmol), and acetic acid (0.0036 mL, 0.062 mmol) in benzene (1.2 mL) reacted to give, after 28 h at 54 °C and the usual workup (flash chromatography, hexane/ether = 30:1), the title compound as a colorless oil (0.053 g, 68%). ^1H NMR (400 MHz, $CDCl_3$): δ 5.58 (t, J = 3.0 Hz, 1H), 4.19 (m, 2H), 2.76 (dd, J = 16.1, 7.0 Hz, 1H), 2.18–2.55 (m, 4H), 2.07 (m, 2H), 1.72–2.00 (m, 4H), 1.55 (m, 2H), 1.41 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.18 (m, 1H), 0.83 (s, 9H), 0.06 (s, 3H), –0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.62, 148.54, 146.30, 126.33, 121.02, 64.35, 59.91, 39.18, 33.92, 31.86, 30.90, 28.94, 26.38, 25.64, 24.91, 17.86, 17.14, 14.13, –4.89, –5.19. HRMS. Calcd for $C_{18}H_{27}O_3Si$ ($M-{}^tC_4H_9$): 319.1729. Found: 319.1739.

Preparation of 3-(*tert*-Butyldimethylsiloxy)-4-(methoxycarbonyl)-2,3,7,8-tetrahydro-1*H*,6*H*-cyclopenta[e]indene (62). A solution of DDQ (0.05721 g, 0.252 mmol) in benzene (1.5 mL) was added to a solution of diene **61a** (0.083 g, 0.229 mmol) in benzene (0.5 mL). After 6.5 h at room temperature, the mixture was concentrated and flash chromatographed (hexane/ether = 20:1) to give the title compound **62** as a colorless oil (0.071 g, 86%). IR ($CDCl_3$): 2958, 2931, 2856, 1711, 1621, 1592, 1286, 1191, 1068. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 5.88 (d, J = 5.1 Hz, 1H), 4.32 (m, 2H), 3.00 (m, 1H), 2.92 (dt, J = 7.6, 3.4 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 2.66 (ddd, J = 15.9, 8.5, 2.1 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 3H), 1.38 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), 0.14 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.30, 145.07, 144.45, 141.44, 125.82, 124.21, 75.18, 60.32, 35.77, 32.35, 31.24, 28.35, 25.73, 25.64, 25.02, 17.98, 14.17, –4.82, –4.97. Calcd for $C_{20}H_{29}O_3Si$ ($M^+ - CH_3$): 345.1886. Found: 345.1896. Anal. HRMS. Calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 69.98; H, 9.20.

Preparation of 3-(*tert*-Butyldimethylsiloxy)-4-(methoxycarbonyl)-5a-methyl-2,3,5,5a,7,8-hexahydro-1*H*,6*H*-cyclopenta[e]indene (65). Following the standard protocol, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00172 g, 0.00166 mmol), substrate **29d** (0.025 g, 0.0665 mmol), and acetic acid (0.2 μL, 0.0033 mmol) in benzene (1 mL) reacted to give, after 20 h at 53 °C and the usual work-up (flash chromatography, hexane/ether = 20:1), cycloisomer **65** as a colorless oil (0.0205 g, 82%). IR ($CDCl_3$): 2957, 2930, 2857, 1694, 1673, 1605, 1472, 1254, 1178, 1086, 1078, 1064 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.43 (d, J = 3.8 Hz, 1H), 4.20 (m, 2H), 2.72 (d, J = 17.0 Hz, 1H), 2.42 (m, 2H), 2.30 (m, 1H), 2.15 (m, 1H), 2.14 (d, J = 17.0 Hz, 1H), 1.80 (m, 4H), 1.60 (m, 1H), 1.45 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 0.88 (s, 3H), 0.82 (s, 9H), 0.11 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.10, 153.74, 149.03, 129.49, 115.89, 72.26, 59.78, 43.10, 41.19, 37.77, 34.83, 27.79, 25.52, 24.90, 22.45, 21.71, 17.77, 14.29, –4.94, –5.03. HRMS. Calcd for $C_{22}H_{36}O_3Si$(M^+): 376.2434. Found: 376.2442.

Cyclization of Enediyne 29c. A solution of substrate **29c** (0.0449 g, 0.119 mmol) in benzene-d_6 (1.0 mL) was added to an NMR tube charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (0.00308 g, 0.00298 mmol) followed by acetic acid (2.05 μL, 0.0357 mmol). After 23 h at room temperature and 4 h at 53 °C, the crude proton NMR spectrum indicated that the mixture contained compounds **68** and **69** plus a small amount of **70** with the ratio of **68** to **69** of 3 to 5 and the diastereomeric ratio of **69** of 4 to 1. The mixture was cooled, concentrated, and flash chromatographed (hexane/ether = 20:1) to give a mixture of compounds **68**, **69**, and **70** as a colorless oil (0.032 g, 71%). From the ^1H NMR spectrum (300 MHz, $CDCl_3$) of this mixture, the following signals for vinyl hydrogens assigned to the 3.9:1 diastereomeric mixture of **69** were discerned: δ 6.34 (s, major), 6.26 (s, minor), 5.63 (ddd, J = 17.3, 10.9, 5.3 Hz, major), 5.57 (ddd, J = 18.7, 10.9, 5.6 Hz, minor).

The above mixture was heated with DBU (one drop) in benzene-d_6 (1.0 mL) at 80 °C for 16 h at which point the proton NMR spectrum indicated that the mixture contained a ratio of 1:2 **68**/**70**. The reaction mixture was cooled, concentrated, and flash chromatographed (hexane/ether = 25:1) to give **68** (R_f = 0.33) (0.009 g, 20%) and **70** (R_f = 0.29) (0.019 g, 42%).

Compound **68**. IR ($CDCl_3$): 2960, 2931, 1693, 1674, 1600, 1258, 1230, 1092, 1073, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.43 (d, J = 3.9 Hz, 1H), 4.20 (m, 2H), 2.90 (m, 1H), 2.70 (m, 1H), 2.42 (m, 2H), 2.18 (m, 2H), 1.85 (m, 3H), 1.44–1.70 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H), 0.83 (s, 9H), 0.71 (d, J = 6.9 Hz, 3H), 0.11 (s, 3H), 0.01 (s,

3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.67, 153.45, 142.96, 129.18, 123.45, 72.67, 59.74, 45.81, 35.15, 30.08, 29.73, 27.66, 25.67, 24.84, 24.65, 17.86, 14.28, 11.56, –4.65, –5.03.

Compound **70**. IR ($CDCl_3$): 2958, 2931, 2857, 1727, 1627, 1602, 1257, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.43 (dd, J = 17.4, 10.7 Hz, 1H), 5.02 (m, 3H), 4.09 (q, J = 7.1 Hz, 2H), 3.08 (m, 2H), 2.50 (m, 4H), 2.28 (m, 2H), 1.87 (m, 2H), 1.62 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.94, 138.66, 138.54, 137.37, 134.63, 132.47, 114.03, 79.01, 60.22, 36.39, 33.28, 33.05, 32.10, 31.62, 25.67, 21.74, 17.89, 13.98, –4.80, –5.31. HRMS. Calcd for $C_{22}H_{36}O_3Si$ (M^+): 376.2434. Found: 376.2408.

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