Catalytic Palladium-Mediated Bisdiene Carbocyclizations: Bisdiene to Enediene Cycloisomerizations

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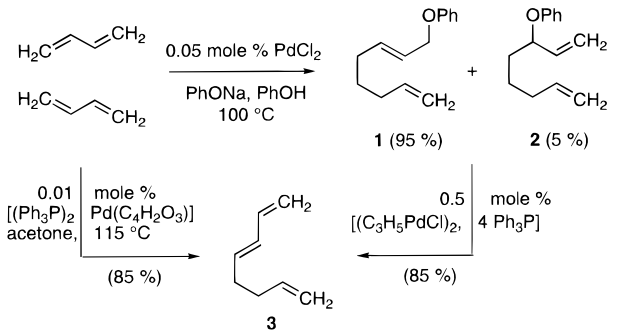
Abstract: The palladium-catalyzed cycloisomerization of acyclic bisdienes to cyclized enedienes defines a novel strategy for the stereoselective cyclization of certain unsymmetric bisdiene substrates to form functionalized five- and six-membered rings. The full details of our investigation into this novel cycloisomerization, including our observations on substrate requirements, stereoselectivity, the influence of the catalyst precursor, and some mechanistic insights drawn from deuterium labeling studies, are discussed.

Transition metal catalyzed cyclization reactions have defined a number of new synthetic strategies for assembling structurally complex ring systems. Those cyclizations that proceed catalytic in metal are particularly noteworthy and may contribute toward meeting the need for environmentally benign chemical synthesis strategies for pharmaceutical and agrochemical products. Palladium-catalysis is playing a significant role in this area, and a number of efficient, stereoselective palladium-mediated carbocyclization strategies are under development in laboratories around the world.[1]

We have been interested in the palladium-catalyzed intramolecular cyclizations of certain tetraenes: specifically, substrates that contain two 1,3-diene moieties within their structures. Our intramolecular cyclization chemistry builds upon the known intermolecular linear dimerization-trapping of certain 1,3-dienes, principally 1,3-butadiene. The butadiene linear dimerization-trapping reaction, originally termed diene telomerization, has a rather long history. It was first reported in 1967, independently by Smutny[2] and by Hagihara and co-workers,[3] and has at least occasionally found industrial application. Its development continues to be a topic of significant interest in both the academic and patent literature.[4]

The original reports describing the metal-catalyzed butadiene dimerization-trapping employed soluble palladium complexes as the metal catalyst precursor. Subsequently, a variety of metals (*e.g.*, nickel, platinum, rhodium, and iridium) were shown to catalyze diene telomerization; however, palladium is still generally the metal of choice. In his 1967 paper, Smutny[2] reported that 1,3-butadiene undergoes efficient palladium-catalyzed linear dimerization with incorporation of phenol upon treatment with palladium dichloride or the allylpalladium chloride dimer to afford functionalized octadienes, as a mixture of predominantly the 1-phenoxy-2,7-octadiene (**1**) with minor amounts of the 3-substituted-1,7-octadiene isomer (**2**). The mixture could be efficiently converted to 1,3,7-octatriene (**3**) by subsequent palladium-catalyzed elimination of phenol. Hagihara and co-workers[3] also reported that the reaction with alcohol trapping reagents afforded predominantly 1-alkoxy-2,7-octadienes but additionally found that in the absence of trapping reagent treatment of butadiene with the bis(triphenylphosphine)-(maleic anhydride)palladium(0) complex afforded 1,3,7-octatriene directly.



In 1989, we reported what to our knowledge are the first examples of an intramolecular variant of this diene dimerization-trapping reaction. This cyclization strategy provides a chemically efficient and stereoselective method for the construction of functionalized ring systems using both intermolecular[5−8] and intramolecular trapping reagents.[9−11] Furthermore, it complements the recently developed nickel-catalyzed [4 + 4]-cycloaddition reactions of such substrates.[12,13] For example, the simple bisdiene substrate **4**, which affords a bicyclo[3.6.0]undecadiene ring skeleton using nickel(0)-catalysis, undergoes palladium-catalyzed cyclization in the presence of phenol to afford the five-membered carbocycle **5** in high yield and isomeric purity.[13]

Naturally, we were curious as to whether a cycloisomerization mode akin to Hagihara's direct conversion of 1,3-butadiene to 1,3,7-octatriene would also be facile. We find that in the

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(1) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975−1015.
(2) Smutny, E. *J. Am. Chem. Soc.* **1967**, *89*, 6793−4.
(3) Takahashi, S.; Shibano, T.; Hagihara, N. *Tetrahedron Lett.* **1967**, 2451−3.
(4) Takacs, J. M. in *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Ed.; Pergamon Press: Oxford, 1995; Vol. 12; pp 785−96, and references cited therein.
(5) Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989**, *54*, 5193−5.
(6) Takacs, J. M.; Zhu, J. *Tetrahedron Lett.* **1990**, *31*, 1117−20.
(7) Takacs, J. M.; Chandramouli, S. V. *Organometallics* **1990**, *9*, 2877−80.
(8) Takacs, J. M.; Lawson, E. C. *Organometallics* **1994**, *13*, 4787−93.
(9) Takacs, J. M.; Chandramouli, S. V. *J. Org. Chem.* **1993**, *58*, 7315−7.
(10) Takacs, J. M.; Chandramouli, S. V. *Tetrahedron Lett.* **1994**, *35*, 9165−8.
(11) Takacs, J. M.; Chandramouli, S. V.; Shoemaker, R. *Tetrahedron Lett.* **1994**, *35*, 9161−4.
(12) Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089−94, and references cited therein.
(13) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678−9.

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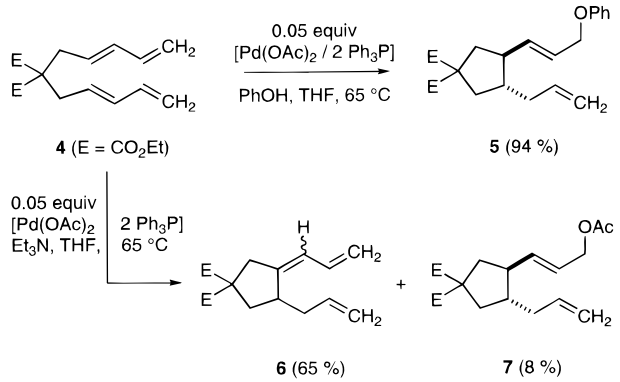
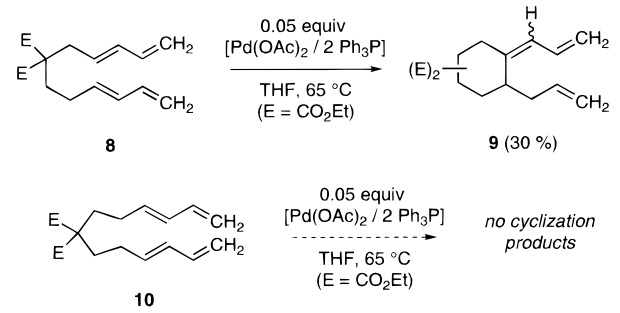


absence of added trapping reagent bisdiene **4** undergoes palladium-catalyzed cycloisomerization to give **6** in 65% yield (0.05 equiv $[Pd(OAc)_2/2Ph_3P]$, Et_3N, THF, 65 °C). Herein, we discuss the full details of our investigation into the palladium-catalyzed cycloisomerization of acyclic bisdienes to cyclized enedienes, including our observations on substrate requirements, stereoselectivity, the influence of the catalyst precursor, and some mechanistic insights drawn from deuterium labeling studies.

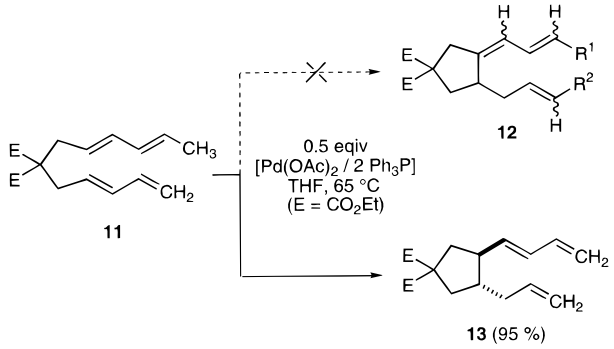
Results and Discussion

While the cycloisomerization of bisdiene **4** to cyclized enediene **6** establishes the equivalent of the Hagihara butadiene-to-octatriene conversion as we had hoped, the reaction is not particularly facile under the conditions examined. **6** is formed as a 1:1 mixture of double bond stereoisomers, and a small amount of the product formed by trapping with acetate (*i.e.*, **7**, 8% yield) is also isolated. The acetate trapping reagent is inadvertently introduced with the palladium catalyst precursor, and **7** may be an intermediate enroute to **6**. The results are even worse for the homologous bisdienes **8** and **10**. Palladium-catalyzed cyclization of **8** affords a mixture of four isomeric cycloisomerization products **9** in only 30% yield, and attempted cyclization of **10** failed to produce any of the anticipated seven-membered ring cycloisomerization product.

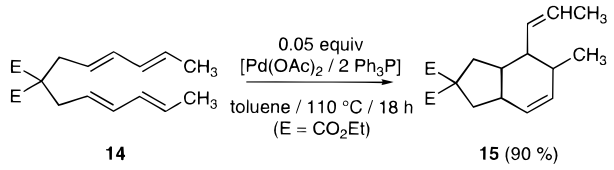


The cycloisomerization of bisdiene **11** proves to be much more interesting. At the onset, this substrate, being unsymmetrical, seemed an unlikely candidate for cyclization. Substrates in which the two 1,3-diene subunits are substituted differently can in principle react via a number of isomeric reaction pathways. The telomerization literature, although rather extensive, fails to identify strategies for controlling regio- and/or chemoselectivity in such cases. For example, the linear dimerization of simple unsymmetrical 1,3-dienes (e.g., isoprene or piperylene) and the attempted selective cross coupling of different 1,3-dienes usually afford a severe mixture of isomeric products. In the case of **11**, it was not clear whether there would be a significant preference for the more or less substituted diene in the starting material to give rise to 1,3-diene moiety in the cyclized product (*i.e.*, **12a** ($R^1 = CH_3$, $R^2 = H$) vs **12b** ($R^1 = H$, $R^2 = CH_3$), and furthermore, each of the two internal double bonds in **12** could give rise to two geometrical isomers.

Nonetheless, we recognized that it would be critical to find control elements to efficiently direct the cyclization of unsymmetrical substrates, so **11** was prepared and subjected to palladium-catalyzed cyclization. To our surprise, structure **12** is not formed. Instead, the cycloisomerization proceeds via a slightly different mode and affords **13** in near quantitative yield and high isomeric purity (>95%). Enediene **13** is formally the result of palladium-catalyzed carbocyclization followed by apparent intramolecular transfer of an allylic hydrogen (*vide infra*), and the conversion of an acyclic bisdiene to a cyclized enediene defines a new palladium-mediated reaction mode of bisdienes. The overall transformation, like several other metal-mediated cycloisomerizations,[14,15] can be thought of as a vinylogue of the Alder-ene reaction; in this case, formally a [6 + 2]ene cyclization. The reaction puts into place a new 1,3-diene and a terminal alkene in the cyclized product. These functionalities should prove useful for further synthetic manipulations and elaboration, for example, via subsequent inter- or intramolecular cycloaddition.



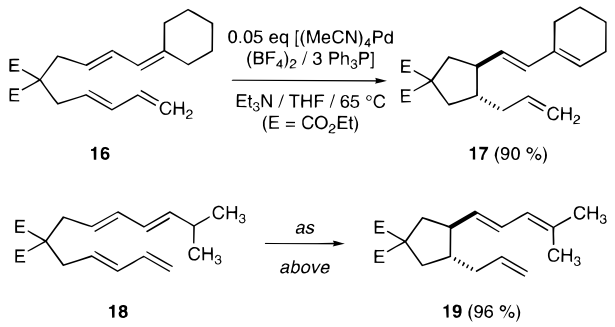
Substrate Scope and Limitations. We next investigated the reaction of bisdiene substrate **14**. This substrate differs from **11** in that both 1,3-diene moieties are 1,4-disubstituted, and we find that its palladium-catalyzed reaction proceeds via yet another cycloisomerization mode. Spectroscopic analysis establishes the gross structure as resulting from [4 + 2]-cycloaddition as depicted in structure **15**. Catalytic metal-mediated cycloaddition reactions are a popular subset of cycloisomerization reaction,[16] but while **14** affords cycloadducts in high yield (90%), a mixture of stereoisomers is obtained, and we have not pursued developing this particular reaction mode further.



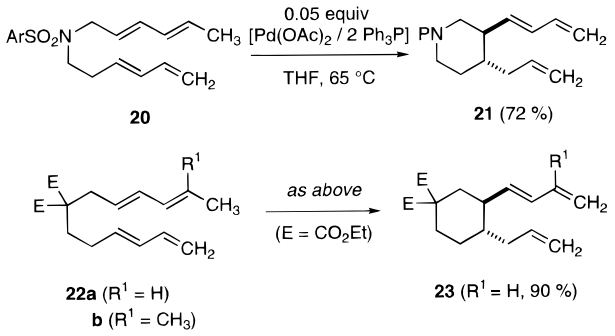
Since the bisdiene to enediene cycloisomerization pathway involves cleavage of an allylic C−H bond, we wondered whether the nature of the allylic group was important. We prepared unsymmetric bisdiene substrates bearing allylic methylene and allylic methine hydrogens and find that they react similar to bisdiene **11**. Palladium-catalyzed cycloisomerization of bisdiene **16** affords enediene **17** (90%), and **18** affords **19** (96%). Each cycloisomerization proceeds so as to afford

(14) For example, see: Takacs, J. M.; Myoung, Y.-C.; Anderson, L. G. *J. Org. Chem.* **1994**, *59*, 6928−42.
(15) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34−42.
(16) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.

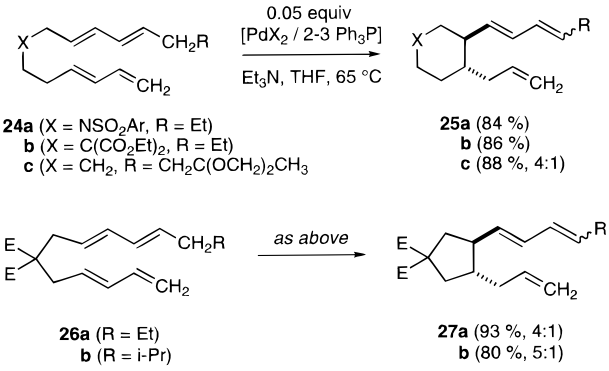
predominantly the trans relative stereochemistry between substituents on the newly formed cyclopentane ring (*vide infra*) and the E-geometry in the newly formed diene side chain. The reader may note the use of a different palladium catalyst precursor in these two cases (**16** and **18**) as compared to the cyclization of **11**. The choice of the catalyst precursor is discussed in detail below.



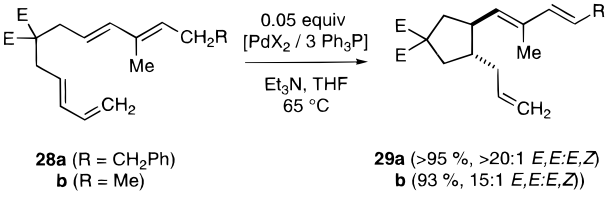
The palladium-catalyzed cycloisomerization is also applicable to the formation of certain six-membered ring systems. For example, bisdienes **20** and **22a** undergo palladium-catalyzed cyclization (0.05 equiv of $[Pd(OAc)_2/2-3Ph_3P]$, THF, 65 °C) to afford the functionalized *N*-sulfonyl piperidine **21** and cyclohexyl derivative **23**, respectively. The yields are good (72 and 90%, respectively), and the six-membered ring product is produced in high isomeric purity (>95% one isomer). The presence of additional methyl substituents on the diene, however, inhibits the cyclization. In contrast to the efficient five-membered ring forming cyclization of **16** and related substrates (*vide infra*), bisdiene **22b** fails to cyclize under the conditions examined (0.05 equiv of $[(MeCN)_4Pd(BF_4)_2/2Ph_3P]$, Et_3N, THF, 65 °C, 24 h).



Stereochemical Issues. In our preliminary communication,[17] we reported that bisdienes **24a** and **b** undergo palladium-catalyzed cycloisomerization in refluxing THF to afford enedienes **25a** and **b** in good yield (84 and 86%, respectively) and high isomeric purity. We now find that while the newly formed 1,4-disubstituted-1,3-diene subunit within the upper side chain is always formed with predominantly the *E,E*-geometry, in many cases, a 4−5:1 mixture of isomers is obtained. Specifically, it is the double bond within the 1,3-diene moiety that resides more remote to the newly formed ring that gives rise to the isomeric mixture. For example, bisdiene **24c** undergoes palladium-catalyzed cycloisomerization to afford **25c** as a 4:1 *E,E:E,Z* mixture in 88% yield. Similar results are obtained in five-membered ring forming cyclizations; **26a** affords **27a** as a 4:1 *E,E:E,Z* mixture (93%). Even in the case of **27b**, which bears a relatively sterically demanding isopropyl substituent, a 5:1 *E,E:E,Z* mixture is obtained. In retrospect, our early experiments were carried out with prolonged reflux times, conditions under which palladium-catalyzed alkene isomerization may have influenced the *E,E:E,Z* ratio.



The substitution pattern of the bisdiene also strongly influences the diastereoselectivity. In contrast to **26**, the substituted bisdienes **28a** and **b** undergo palladium-catalyzed cycloisomerization (0.05 equiv of $[(MeCN)_4Pd(BF_4)_2/2Ph_3P]$, Et_3N, THF, 65 °C, 24 h) with high diastereoselectivity. For example, **28a** affords the (*E,E*)-isomer **29a** with high selectivity (>20:1 *E,E:E,Z*) and in high yield (>95%). **28b** reacts similarly (15:1 *E,E:E,Z*, 93% yield). The influence of the methyl substituent in the reaction of **28** is reminiscent of the effect found by Hauser and co-workers[18] in palladium-catalyzed elimination of allylic acetates. We carried out the palladium-catalyzed elimination of the unsubstituted allylic acetate **30a** and **30b**. In accord with Hauser's observations, the unsubstituted allylic acetate **30a** affords a 1.6:1 *E:Z* mixture of dienes **32a**, while the methyl-substituted analogue **30b** affords **32b** with high stereoselectivity (>20:1 *E:Z*). The dramatically improved stereoselectivity in the latter case can be rationalized by considering the conformations available to the presumed intermediate η^3-allylpalladium complex (*i.e.*, **31a** and **31g**). In the case of R = methyl, the gauche conformer **31g** suffers from significant nonbonded interactions that should strongly disfavor it relative to the anti conformer **31a**, the latter presumably leading to the observed (*E*)-diene. These results suggest that elimination via an η^3-allylpalladium complex may play an important role in the mechanism of the cycloisomerization reaction (*vide infra*).



The five-membered ring forming substrate bearing a free hydroxyl group, bisdiene **33**, reacts slowly (>24 h) in refluxing THF. Its palladium-catalyzed cyclization proceeds more readily in acetonitrile (11 h) and affords a 1.6:1 mixture of diastereomers epimeric at the hydroxyl-bearing stereocenter (*i.e.*, 1.6:1 **34a**:**34b**, 66%). The *trans*-relative stereochemistry between the side chains in **34a** and **b** (as illustrated) is made on the following basis. Hydrogenation of a mixture of **34a** and **b** (1 atm H_2, EtOH, 5% Rh on Al_2O_3, 24 h) gives the corresponding mixture of **35a** and **b**. PCC oxidation affords predominantly cyclopentanone **36** (>95% trans). Base catalyzed equilibration of **36** with its less favorable cis isomer **37** confirms the trans relative stereochemistry of the side chains in **36** and, therefore, in **34a** and **b**. Stereoselective reduction of the carbonyl in **36** (Li(*s*-Bu)$_3$BH, THF, −78 °C) re-forms **35b**, enabling the assignment

(17) Takacs, J. M.; Zhu, J.; Chandramouli, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 773−4.

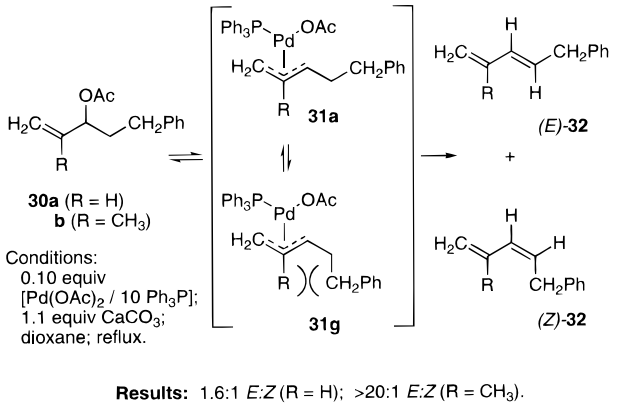
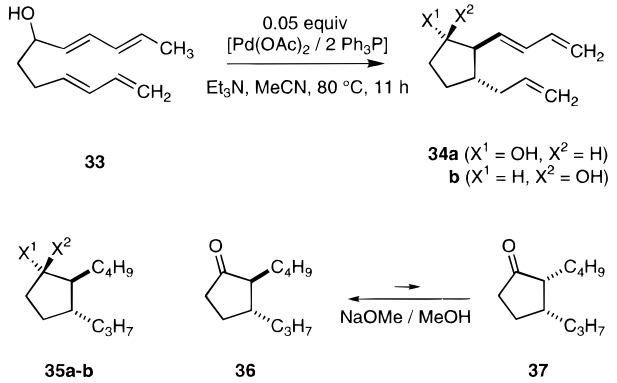
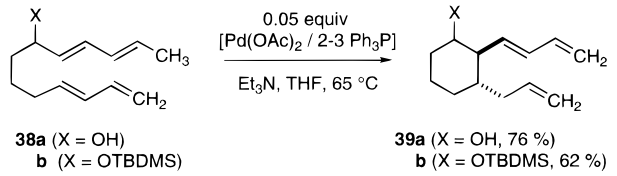


Figure 1. The influence of alkene substituents on the stereoselectivity of palladium-catalyzed elimination of allylic acetates.[18]

of the β hydroxyl stereochemistry as shown in **34b** to the minor isomer formed in the palladium-catalyzed cyclization of **33**.



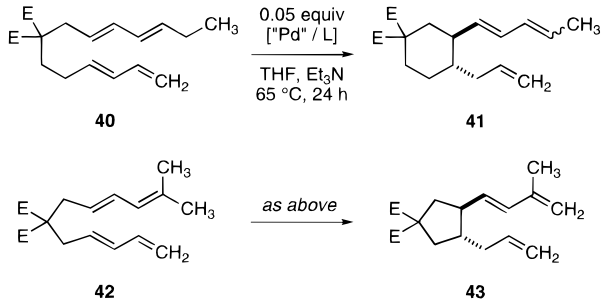
While the five-membered ring forming substrate **33** affords a 1.6:1 mixture of diastereomers, its homologue **38a** affords a more favorable 5:1 mixture (76% yield). The all equatorial isomer of **39a** predominates. Surprisingly, alcohol **38a** is both more reactive and more selective than the silyl ether **38b** derived from it. The latter substrate reacts relatively slowly in refluxing THF and affords a 1.7:1 mixture of the diastereomeric products **39b** (62% yield).



It should be noted that high levels of stereoinduction have been observed in mechanistically related palladium-catalyzed cascade cyclizations of six-membered ring forming bisdiene substrates.[9−11] While the issue of stereoinduction has not yet been examined in depth for this bisdiene to enediene cycloisomerization mode, the cyclization of **38a** and the results of the related cascade cyclizations make the prospects appear promising.

Catalyst Precursor, Ligand, and Solvent Considerations. We find that a variety of solvents are suitable for these palladium-catalyzed cyclizations (*e.g.*, THF, 2-propanol, methanol, acetonitrile, dichloromethane, and toluene). Among these, acetonitrile, alcohol, and alcohol−THF mixtures seem to afford the most active catalyst solutions. Adding 5−10 equiv of triethylamine as a co-catalyst is usually beneficial. Our working model for the catalytic cycle presumes a palladium(0) species as the active catalyst, and the role of the triethylamine is presumably that of reducing agent for the palladium(II) catalyst precursor, although it could as well function as an external base in the catalytic cycle (*vide infra*).

To assess the influence of the catalyst precursor and ligand in a systematic way, we carried out a series of reactions using substrates **40** and **42**. Based on the results discussed above, the former was expected to undergo relatively facile palladium-catalyzed cycloisomerization. The latter is expected to be a more demanding substrate. We noted above, for example, that bisdiene **22b** failed to cyclize using the standard $Pd(OAc)_2$ catalyst system and that the successful cycloisomerizations of bisdienes **16** and **18** required a different palladium catalyst precursor.



A large number of palladium(II) salts have been shown to be effective catalyst precursors for the telomerization of butadiene.[4] A small group of these was examined for the cycloisomerization of compound **40**, under an otherwise standard set of reaction conditions (0.05 equiv of [palladium complex/ $3Ph_3P$], THF, 5 equiv of Et_3N, 65 °C, 24 h). To summarize the findings: (1) $Pd(OAc)_2$, $Pd(OTFA)_2$, and $(MeCN)_4Pd(BF_4)_2$ each afford product **41** in yields approaching quantitative, albeit as an *E,E:E,Z* isomer mixture; (2) $(Ph_3P)_4Pd$ and $Pd_2(dba)_3$ in THF or in methanol proceed to approximately 50% conversion; and (3) $PdCl_2$, $(PhCN)_2PdCl_2$, and allylpalladium chloride dimer fail to give an active catalyst under these conditions. A similar study using bisdiene **42** verified that it is indeed a substantially less reactive substrate. Among the catalyst precursors screened, only $(MeCN)_4Pd(BF_4)_2$ gives complete reaction under the conditions given above. In contrast, $Pd(OAc)_2$ gives less than 50% cyclization even after prolonged reaction times (48 h).

The added phosphine ligand was also systematically varied using an otherwise standard set of reaction conditions (0.05 equiv of $Pd(OAc)_2$, 5 equiv of Et_3N, THF, 65 °C, 24 h). We find that **40** cyclizes to **41** in near quantitative yield using any of the following ligands: Ph_3P (2 or 3 equiv per palladium, the former conditions affording perhaps a slightly more reactive catalyst); tri(2-furyl)phosphine (3 equiv); dppb (1 equiv); or dppe (1 equiv). The successful use of the strongly chelating bisphosphine ligand, dppe, is particularly surprising. To effect efficient cyclization of **42**, however, $(MeCN)_4Pd(BF_4)_2$ is required. Using this catalyst precursor, the cycloisomerization of **42** proceeds: (1) in yields approaching quantitative using Ph_3P (2 or 3 equiv per Pd), tri(4-fluorophenyl)phosphine (3 equiv), tri(*o*-tolyl)phosphine (3 equiv), tri(*n*-butyl)phosphine (3 equiv), and dppb (1 equiv); (2) to approximately 40% conversion using tri(2-furyl)phosphine (3 equiv) or triphenylarsine (3 equiv); and (3) to approximately 10% conversion using dppe (1 equiv). The results obtained with tri(2-furyl)phosphine and triphenylarsine are particularly surprising in light of the report that these two ligands afford exceptionally reactive palladium catalyst for coupling reactions.[19]

(18) Hauser, F. M.; Tommasi, R.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1988**, *53*, 4886−7.

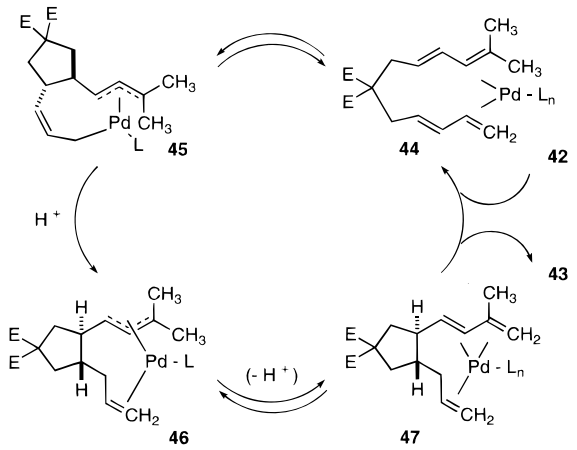


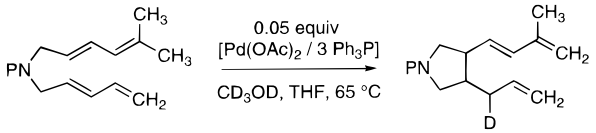
Figure 2. A working model for the palladium-catalyzed bisdiene to enediene cycloisomerization, illustrated for the conversion of **42** to **43**.

Labeling Studies and Mechanistic Insights. To guide the development of a new reaction, it is often useful to postulate a chemically reasonable model that accounts for the observed regio- and stereoselectivity. Our model for the palladium-catalyzed bisdiene to enediene cycloisomerization is illustrated in Figure 2 for the isomerization of **42** to **43**. The catalytic cycle is largely in analogy to that proposed by Jolly and co-workers for the telomerization of butadiene.[20,21] Three key features stand out. (1) The carbon−carbon bond forming event occurs via oxidative cyclization of the alkene complex **44** to form a palladacycle such as **45**. (2) The proton that is ultimately delivered to the propenyl (bottom) side chain is not delivered intramolecularly. (3) The 1,3-diene forming event is directly analogous to the palladium-catalyzed elimination of allylic alcohol derivatives (e.g., Figure 1).[22,23]

This model helps to rationalize several key aspects of the observed cyclization. It suggests that the preferred trans relative stereochemistry of the side chains in the product originates from the kinetically or thermodynamically preferred formation of the trans-fused bicyclic metallacycle **45**. Currently, we favor the view that the formation of **45** is reversible under the reaction conditions and the preference for the observed trans product derives from the thermodynamic preference for the trans-fused **45** relative to its cis-fused diastereomer.[24−27] Related trapping reactions provide some support for this view. The palladium-catalyzed reaction of a common bisdiene substrate affords different cis:trans product ratios as a function of the trapping reagent used;[5] a result that is consistent with equilibration of a metallacycle akin to **45** with its cis-fused diastereomer.

The structure of metallacycle **45** can also be used to rationalize the mode selectivity observed in the cyclization. **45** contains both η^1- and η^3-allyl moieties,[28] and, as illustrated in Figure 2, a hydrogen must be delivered to the side chain derived from the less substituted diene to account for the formation of **43**. Chemically, this logically follows from a structure like **45**. Alkyl substituents situated at the allyl terminus, as the methyl groups are in structure **45**, should stabilize the η^3-allyl moiety. However, such an arrangement would destabilize a corresponding η^1-allyl complex. It therefore makes sense that the less substituted diene should give rise to the η^1-allyl moiety, and, as such, it is activated to receive the hydrogen via S_E2' protonation (*i.e.*, conversion of **45** to **46**).[29] Furthermore, recall that bisdiene **28** affords a mixture of two double bond isomers and that it is only the double bond that resides more remote to the newly formed ring (C−C bond) that gives rise to the *E,E: E,Z* mixture. Again, this is easily rationalized in the context of Figure 2. The alkene that ends up nearer the newly formed C−C bond should be formed exclusively with the E-geometry, since it is part of the anti η^3-allyl moiety within intermediates **45** and **46**.

The model outlined in Figure 2 is supported by the results of several isotopic labeling experiments. For example, the intermolecular delivery of hydrogen to the bottom side chain (*i.e.*, **45** to **46**) is verified by carrying out the palladium-catalyzed cyclization of bisdiene **48** in the presence of a deuterium source. When the reaction of **48** is run in THF alone, palladium-catalyzed cycloisomerization proceeds in 85% yield. When the reaction is carried out in the presence of CD_3OD, **49** is formed with approximately 90% deuterium incorporation in the propenyl side chain. Furthermore, the deuterium is incorporated stereoselectively as is expected from our previously reported studies.[11]



48 (P = (p-$CH_3C_6H_4$)SO_2) **49**

Two deuterated analogues, each bearing a single suitably disposed CD_3 substituent (*i.e.*, **50a** and **50b**), were prepared in high stereoisomeric and isotopic purity, and each was individually cyclized in order to further probe mechanistic aspects of the cycloisomerization reaction. Specifically, we were interested in the details concerning loss of hydrogen (deuterium) in going from presumed intermediate **46** to **47** (Figure 2). First, recall that the influence of the methyl substituent on diastereoselectivity in the cyclization of **28** and its analogy to palladium-

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(21) Benn, R.; Jolly, P. W.; Joswig, T.; Mynott, R.; Schick, K. P. *Z. Naturforsch.* **1986**, *41b*, 680−91.

(22) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075−8.

(23) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301−4.

(24) A similar analysis has been used to rationalize the selectivity observed in nickel(0)-catalyzed bisdiene [4 + 4]cycloaddition reactions. See: Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451−4.

(25) Gugelchuk, M. M.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 330−9.

(26) A similar analysis has been used to rationalize the selectivity observed in zirconium-catalyzed diene cycloisomerization reactions. See: Knight, K. S.; Wang, D.; Waymouth, R. M.; Ziller, J. *J. Am. Chem. Soc.* **1994**, *116*, 1845−54.

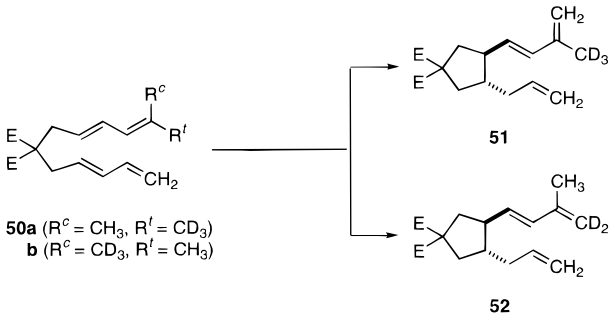
(27) Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *1994*, 9457−63.

(28) It should be recognized that the metallacycle **45** is only one of several interconvertible bis(allyl)palladium complexes that are potential intermediates in this chemistry. Its relevance to the reaction, while speculative, is supported by the ability to rationalize the observed selectivities and by the relevance of (η^1,η^3-octadienyl)palladium complexes in the 1,3-butadiene dimerization chemistry. For example, see: Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 283−95, and the related references cited above.

(29) This argument suggests that a suitably disposed electron withdrawing substituent, that is a substituent that would stabilize a Pd−C σ bond, should prefer to be part of the η^1-allyl moiety. This prediction exactly accounts for the products that we obtain in the reactions of bisdienes containing a dienoate subunit: Takacs, J. M.; Strakhov, A.; Athalye, R. V.; Zhu, J. Unpublished results.

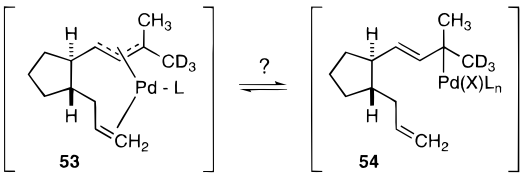
(30) A reviewer suggested that in the absence of an added proton source (e.g., CH_3OH in analogy to the cyclization of **48**) bisdienes **50a** and **50b** should afford a mixture of di-, tri-, and tetradeuterated products. However, two points should be noted. (1) If formed, only relatively small amounts of tetra deuterated **51** and trideuterated **52** could be expected given the large isotope effect favoring loss of hydrogen over deuterium. (2) While no methanol is added to these reactions, the presumed in situ reduction of Pd(II) to Pd(0) by triethylamine does provide a proton source in these reactions. See, for example, the discussion in the following: Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177−80, and references cited therein.

catalyzed allylic acetate elimination (Figure 1) is fully consistent with the proposed intermediacy of an η^3-allyl such as **46** in route to **47**. Bisdienes **50a** and **50b** each cyclize in near quantitative yield to a mixture of **51** and **52** (0.05 equiv of $[(MeCN)_4Pd(BF_4)_2/2Ph_3P]$, Et_3N, THF, 65 °C, 24 h).[30] Product **51** arises via loss of hydrogen; product **52** by loss of deuterium. The mixture is easily characterized by ^2H NMR, and comparing integration for the resonances due to $-CD_3$ and $-CD_2$, shows that each reaction proceeds with a large isotope effect favoring loss of hydrogen over deuterium. A 5:1 **51**:**52** mixture is obtained from the cyclization of **50a** and an 11:1 **51**:**52** mixture from compound **50b**.



We draw three conclusions from the results of the deuterium labeling experiments described above. (1) The cycloisomerization is not strictly intramolecular; specifically, the hydrogen is not transferred intramolecularly. (2) There is a relatively large isotope effect (>5) for the step involving loss of the hydrogen (*i.e.*, Figure 2, **46** to **47**). (3) Hydrogen can be lost from either methyl substituent (R^t or R^c), but there must be a small inherent preference for loss of hydrogen from the substituent labeled R^t which is superimposed on the isotope effect k_H/k_D to account for the higher selectivity for the formation of **51** from **50b** than **50a**.

The generally accepted mechanism for the formation of a diene from an η^3-allyl palladium complex (η^3-allyl metal complexes, in general) proceeds via isomerization to the corresponding η^1-allyl complex followed by β-hydride elimination. In the present case, one could invoke isomerization of **53** to **54** followed by β-hydride elimination. However, k_H/k_D is typically small for β-hydride elimination;[31−33] for example, 2.3 ± 0.2 in Schwartz' classic study of β-hydride elimination in an isotopically labeled iridium complex (*i.e.*, n-$C_6H_{13}C(H)$-$DCH_2Ir(PPh_3)_2CO$).[33] This is much smaller than we find for the reactions of **50a,b**. Furthermore, the apparent (albeit small) preference for loss of hydrogen from the position labeled R^t does not follow from reaction via an η^1-allyl complex such as **54**. In such a complex, the R^c and R^t substituents are essentially equivalent. These considerations have led us to propose that instead hydrogen is lost directly from **53** (equivalently, **46** in Figure 2) via base promoted deprotonation.[34] Recent studies on the palladium-catalyzed elimination of allylic carbonates and acetates support this possibility.[35,36]



Conclusions

At the onset of our studies into palladium-catalyzed cyclizations of bisdienes we recognized that it would be crucial to find control elements that efficiently direct the cyclization of unsymmetrical bisdiene substrates. We previously reported one general strategy, the use of intramolecularity to direct regiochemistry. An intramolecularly disposed nucleophile can efficiently control the site of nucleophile attack in certain cascade cyclizations.[9−11] The bisdiene to enediene cycloisomerization described herein defines a second strategy by virtue of the unexpectedly facile ene reaction mode available to this class of unsymmetrical bisdienes.

Using this chemistry, functionalized five- and six-membered rings are generally formed in high yield and with high diastereoselectivity. The cyclization establishes the trans relative stereochemistry between the unsaturated side chains on the newly formed ring. Control over the double bond geometries can be high, although, in some cases, mixtures arise from the failure to control the double bond geometry most remote to the newly formed C−C bond. In such cases, an additional diene substituent can help control the geometry. In general, electron donating substituents on the diene slow the rate of cycloisomerization. Labeling studies show that the hydrogen is not transferred intramolecularly, and the large isotope effect associated with its loss suggests that deprotonation rather than β-hydride elimination is mechanistically important. The bisdiene to enediene cycloisomerization puts into place a new 1,3-diene and a terminal alkene in the cyclized product, functionalities that should prove useful for further synthetic manipulations and elaboration. Such strategies form the basis for synthetic applications that are currently in progress.

Experimental Section[37]

NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) on General Electric Omega 300 or 500, GE-Nicolet 360 MHz, or Varian VXR 200 spectrometers. ^{13}C spectra were decoupled with Waltz 16 decoupling and reported in ppm from an internal standard deuterochloroform, and, in most cases, resonances are assigned by DEPT, HETCOR, and/or APT experiments. In such cases the number of attached protons is indicated in parentheses by s = quaternary carbon; d = methine; t = methylene; and q = methyl. Infrared spectra were obtained on an Analect RFX-65 FT-IR spectrometer from thin films using the Attenuated Total Reflectance (ATR) technique or Perkin Elmer 1600 FTIR using salt plate. IR wavelengths are reported in cm^{-1}, and, in some cases, peak assignments and intensities (as percent absorbance) are reported in parentheses. Combustion analyses were performed by M-H-W Analytical Labs, Phoenix, AZ. High Resolution Mass Spectral determinations were performed by the Midwest Center for Mass Spectrometry, Lincoln, NE on a Kratos MS-50 mass spectrometer.

Preparation of 6,6-(Diethylcarboxy)-1,3,8,10-dodecatetraene (11).[38] To a stirred suspension of NaH (157 mg, 5.9 mmol) in 20 mL of THF was added a solution of (*E*)-2,4-pentadienyl-propanedioic acid diethyl ester[39] (CAS registry number 55693-36-2, 1.49 g, 5.93 mmol) in 5 mL

(31) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457−63.
(32) Brainard, R. L.; Whitesides, G. M. *Organometallics* **1985**, *4*, 1550−7.
(33) Evans, J.; Schwartz, J.; Urquhart, P. W. *J. Organomet. Chem.* **1974**, *81*, C37−9.
(34) For similar arguments in a related palladium-catalyzed reaction, see: Chrisope, D. R.; Beak, P.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 230−8.
(35) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1−2.
(36) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* In press.
(37) For additional details concerning the general experimental procedures and analytical information, see Supporting Information.
(38) Prepared by adapting the method of Bäckvall: Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609−13.
(39) CAS registry number 55693-36-2: Danishefsky, S.; Tsai, M. Y.; Dynak, J. *J. Chem. Soc., Chem. Commun.* **1975**, 7−8.

of THF. To the resulting solution was added $Pd(OAc)_2$ (44.0 mg, 0.20 mmol) and Bu_3P (0.20 mL, 0.79 mmol). The mixture was heated to reflux, and then a solution of (2*E*,4*E*)-2,4-hexadien-1-yl acetate (459.0 mg, 3.27 mmol) in THF (10 mL) was added dropwise. After 18 h at reflux, the reaction mixture was cooled to room temperature, quenched by the addition of water (50 mL), and extracted with ether (3 × 25 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica (230−400 mesh, 97:3 Hex:EtOAc) afforded bisdiene **11** (759.0 mg, 76%): TLC analysis (95:5 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 6.14−6.30 (m, 1 H), 5.80−6.10 (m, 3 H), 5.4−5.62 (m, 2H), 5.20−5.40 (m, 1H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 10 Hz), 4.15 (q, 4 H, J = 6.9 Hz), 2.58 (overlapping d, 4 H, J = 6.4 Hz), 1.58 (d, 3 H, J = 6.7 Hz), 1.17 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz) δ 170.6 (s), 136.5 (d), 134.9 (d), 134.5 (d), 131.0 (d), 128.4 (d), 127.9 (d), 124.1 (d), 116.1 (t), 61.1 (t), 57.7 (s), 35.8 (t), 35.7 (t), 17.8 (q), 14.0 (q); IR (ATR) 1728 (s, C═O), 1652 (w), 1601 (m); HRMS ($C_{18}H_{26}O_4$ = 306.1830) found *m/z* 306.1829.

Cyclization of Bisdiene 11. A solution of **11** (306.0 mg, 1.0 mmol), $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), and Ph_3P (26−39 mg, 0.10−0.15 mmol) in THF (5 mL) was heated to reflux for 14 h, then cooled, and concentrated via rotovap. Chromatography on silica (95:5 Hex:EtOAc) afforded cyclopentane **13** (290.0 mg, 95%): ^{1}H NMR (360 MHz) δ 6.34 (ddd, 1 H, J = 10.3, 10.4, 17.0 Hz, H), 6.10 (dd, 1 H, J = 10.4, 15.1 Hz, H), 5.83−5.74 (m, 1 H), 5.70 (dd, 1 H, J = 8.5, 15.1 Hz, H), 5.18−4.96 (m, 4 H), 4.21 (q, 4 H, J = 7.1 Hz), 2.58−2.51 (m, 2 H), 2.37−2.22 (m, 2 H), 2.00 (dd, 1 H, J = 13.5, 12.9 Hz), 1.75 (m, 3 H), 1.28 (t, 6 H, J = 7.1 Hz); ^{13}C NMR (50 MHz) δ 172.6 (s), 172.5 (s), 136.9 (d), 136.7 (d), 136.1 (d), 131.9 (d), 115.8 (t), 115.7 (t), 61.4 (t), 58.4 (s), 48.6 (d), 45.1 (d), 46.6 (t), 39.5 (t), 37.1 (t), 14.0 (q); IR (neat) 1733 (s, C═O), 1649 (m, C═C), 1641 (C═C); HRMS analysis (EI, $C_{18}H_{26}O_4$ = 306.1831) found *m/z* 306.1828.

Preparation of (3*E*,8*E*)-1-Cyclohexyl-6,6-(dicarboethoxy)-1,3,8,10-undecatetraene (16).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (CAS registry number 55693-36-2, 1.28 g, 5.67 mmol) and NaH (136.0 mg, 5.7 mmol) in THF (25 mL) was added $Pd(OAc)_2$ (36.0 mg, 0.16 mmol) and Bu_3P (0.20 mL, 0.80 mmol). The resulting brown solution was brought to reflux, and then (2*E*)-5-cyclohexyl-2,4-butadien-1-yl acetate[40] (0.50 g, 2.6 mmol) in THF (5 mL) was added. The resulting mixture was refluxed overnight (8 h), then cooled to room temperature, and quenched by the addition of water (20 mL). The mixture was extracted with ether (3 × 75 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) afforded bisdiene **16** (860.0 mg, 92%): TLC analysis (95:5 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.39−6.15 (m, 2 H), 6.12−5.96 (m, 1 H), 5.69−5.67 (m, 1 H), 5.57−5.41 (m, 1 H), 5.40−5.24 (m, 1 H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 10 Hz), 4.15 (q, 4 H, J = 7.1 Hz), 2.63 (overlapping d, 4 H, J = 7.4 Hz), 2.25 (br s, 2 H), 1.98 (br s, 2 H), 1.51 (br s, 6 H), 1.21 (t, 6 H, J = 7.1 Hz); ^{13}C NMR (75 MHz) δ 170.6 (s), 142.5 (s), 136.5 (d), 134.9 (d), 130.2 (d), 127.9 (d), 124.1 (d), 121.4 (d), 116.0 (t), 60.9 (t), 57.7 (s), 37.0 (t), 36.0 (t), 35.7 (t), 29.0 (t), 28.3 (t), 27.6 (t), 26.6 (t), 13.9 (q); IR (salt plate) 1720 (C═O, 83), 1655 (C═C, 60); Combustion analysis ($C_{22}H_{32}O_4$ = 73.30% C, 8.95% H) found 73.06% C, 8.88% H.

Cyclization of Bisdiene 16. A solution of **16** (180.0 mg, 0.500 mmol), $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol) in THF (5 mL) was heated to reflux. After 24 h at reflux, chromatography on silica (95:5 Hex:EtOAc) afforded the cyclized enediene **17** (160.0 mg, 90%): TLC analysis (95:5 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.03 (d, 1 H, J = 15.6 Hz), 5.84−5.55 (m, 2 H), 5.39−5.24 (m, 1 H), 5.05−4.89 (m, 2 H), 4.16 (q, 4 H, J = 6.8 Hz), 2.54−2.37 (m, 2 H), 2.35−1.45 (m, 14 H), 1.21 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (75 MHz) δ 172.5 (s), 136.8 (d), 135.2 (s), 134.5 (d), 127.9 (d), 127.4 (d), 115.6 (t), 61.2 (t), 58.2 (s), 48.9 (d), 45.2 (d), 40.9 (t), 39.5 (t), 36.9 (t), 25.7 (t), 24.5 (t), 22.5 (t), 22.4 (t), 13.9 (q); IR (salt plate) 1724 (C═O, 72), 1645 (C═C, 45); Combustion analysis ($C_{22}H_{32}O_4$ = 73.30% C, 8.95% H) found 73.45% C, 8.81% H.

(40) The preparation of this compound is described in the Supporting Information.

Preparation of (3*E*,8*E*,10*E*)-12-Methyl-6,6-(dicarboethoxy)-1,3,8,10-tridecatetraene (18).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (CAS registry number 55693-36-2, 1.50 g, 6.6 mmol) and NaH (157.0 mg, 6.6 mmol) in THF (60 mL) was added $Pd(OAc)_2$ (40.0 mg, 0.18 mmol) and Bu_3P (0.20 mL, 0.80 mmol). The resulting brown solution was brought to reflux, and then (2*E*,4*E*)-6-methyl-2,4-heptadien-1-ol acetate[40,41] (CAS registry number 80595-43-3, 0.500 g, 2.98 mmol) in THF (5 mL) was added. The resulting mixture was refluxed overnight (12 h), then cooled to room temperature, and quenched by the addition of water (25 mL). The mixture extracted with ether (3 x 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) afforded bisdiene **18** (840.0 mg, 84%): TLC analysis (95:5 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 6.41−6.16 (m, 1 H), 6.14−5.82 (m, 3 H), 5.63−5.44 (m, 2 H), 5.41−5.28 (m, 1 H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 10 Hz), 4.15 (q, 4 H, J = 7.1 Hz), 2.61−2.55 (m, 4 H), 2.25 (septet, 1 H, J = 6.5 Hz), 1.22 (t, 6 H, J = 7.1 Hz), 0.96 (d, 6 H, J = 6.5 Hz); ^{13}C NMR (75 MHz) δ 170.7 (s), 141.0 (d), 136.6 (d), 134.9 (d), 134.8 (d), 127.9 (d), 126.7 (d), 124.5 (d), 116.2 (t), 61.1 (t), 57.8 (s), 35.9 (t), 35.8 (t), 30.9 (d), 22.2 (q), 14.1 (q); IR (salt plate) 1722 (**C**═O, 88), 1640 (C═C, 30); Combustion analysis ($C_{10}H_{30}O_4$ = 71.82% C, 9.04% H) found 72.09% C, 9.02% H.

Cyclization of Bisdiene 18. A solution of **18** (167.0 mg, 0.5 mmol), $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol) in THF (5 mL) was heated to reflux. After 20 h at reflux, chromatography on silica (95:5 Hex:EtOAc) afforded the cyclized enediene **19** (160.0 mg, 96%): TLC analysis (90:10 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 6.31−6.14 (m, 1 H), 5.84−5.65 (m, 2 H), 5.42−5.28 (m, 1 H), 5.07−4.9 (m, 2 H), 4.2 (overlapping q, 4 H, J = 7.1 Hz), 2.56−1.78 (m, 8 H), 1.74 (overlapping s, 6 H), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75 MHz) δ 172.6 (s), 172.5 (s), 136.9 (d), 133.9 (s), 132.5 (d), 127.8 (d), 124.7 (d), 115.6 (d), 61.3 (t), 58.3 (s), 49.0 (d), 45.2 (d), 40.9 (t), 39.5 (t), 37.1 (t), 25.8 (q), 18.2 (q), 13.9 (q); IR (salt plate) 1732 (C═O, 79), 1648 (C═C, 53); Combustion analysis ($C_{20}H_{30}O_4$ = 71.82% C, 9.04% H) found 72.00% C, 8.96% H.

Preparation of *N*-Hexadien-2,4-yl-*N*-hexadien-3,5-yl, *p*-Toluene Sulfonamide (20). To a cooled (−78 °C) solution of (*E*)-*N*-(3,5-hexadienyl) *p*-toluene sulfonamide (1.50 g, 6.0 mmol) and HMPA (0.25 mL, 13.2 mmol) in THF (200 mL) was added a solution of *n*-BuLi (2.50 mL (2.5 M), 6.3 mmol). The resulting mixture was stirred for 0.5 h, and then a solution of 2,4-hexadienyl chloride (0.82 g, 7.0 mmol) in THF (5 mL) was added. The resulting mixture was slowly warmed to room temperature, then quenched by the addition of water (50 mL), and concentrated in vacuo. The residue was extracted with EtOAc (100 mL), and the organic extract washed with brine (2 × 50 mL), then dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica afforded recovered starting material (0.43 g) and bisdiene **20** (0.92 g, 46%): ^{1}H NMR (360 MHz) δ 7.67 (d, J = 8.2 Hz, 2 H), 7.27 (d, J = 8.2 Hz, 2 H), 6.25 (ddd, J = 17.0, 10.2, 10.2 Hz, 1 H), 5.94−6.11 (m, 3 H), 5.67 (dq, J = 14.6, 6.8 Hz, 1 H), 5.55 (dt, J = 15.2, 7.1 Hz, 1 H), 5.32 (dt, J = 14.9, 6.8 Hz, 1 H), 5.1o (d, J = 17.0 Hz, 1 H), 5.00 (d, J = 10.2 Hz, 1 H), 3.80 (d, J = 6.8 Hz, 2 H), 3.15 (t, J = 7.4 Hz, 2 H), 2.41 (s, 3 H), 2.26−2.33 (m, 2 H), 1.73 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (50 MHz) δ 143.0 (s), 137.0 (s), 136.7 (d), 134.2 (d), 133.0 (d), 130.5 (d), 130.3 (d), 130.2 (d), 129.5 (d), 127.0 (d), 124.5 (d), 115.7 (t), 49.8 (t), 46.5 (t), 31.7 (t), 21.3 (q), 17.9 (q); IR (ATR) 1653 (m, C═C), 1337 (s, SO_2), 1153 (s, SO_2); Combustion analysis ($C_{19}H_{25}NO_2S$ = 68.84% C, 7.60% H) found 68.89% C, 7.79% H.

Cyclization of Bisdiene 20. To a stirred solution of **20** (250.0 mg, 0.76 mmol) in THF (5 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (26−39 mg, 0.10−0.15 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting mixture was heated to reflux (40 h) to afford, after chromatography on silica (95:5 Hex:EtOAc), unreacted bisdiene **20** (50.0 mg) and piperidine **21** (180.0 mg, 72%): ^{1}H NMR (360 MHz) δ 6.27 (ddd, 1 H, J = 16.8, 10.4, 10.1 Hz), 6.14 (dd, 1 H, J = 15.1, 10.4 Hz), 5.69−5.58 (m, 1 H), 5.32 (dd, 1 H, J = 15.1, 8.8 Hz), 5.17−4.93 (m, 4 H), 3.80−3.64 (m, 2 H), 2.42 (s, 3 H), 2.28−2.24 (m, 1 H), 2.22−2.17 (m, 1 H), 2.12 (dddd, 1 H, J = 11.0, 11.0, 8.8, 4.0 Hz),

(41) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825−9.

2.00 (dd, 1 H, J = 11.0, 11.0 Hz), 1.82−1.73 (m, 2 H), 1.34 (dddd, 1 H, J = 12.5, 12.5, 12.5, 4.4 Hz), 1.14−1.06 (m, 1 H); ^{13}C NMR (50 MHz) δ 143.3 (s), 136.4 (d), 135.6 (d), 133.8 (d), 133.6 (d), 133.0 (s), 129.5 (d), 127.6 (d), 116.7 (t), 50.9 (t), 46.3 (t), 44.6 (d), 39.5 (d), 37.4 (t), 29.6 (t), 21.4 (q); IR (ATR) 1651 (m, C═C), 1640 (m), 1341 (s, SO_2), 1162 (s, SO_2); Combustion analysis ($C_{19}H_{25}NO_2S$ = 68.84% C, 7.60% H) found 69.00% C, 7.42% H.

Preparation of 7,7-(Diethylcarboxyl)-1,3,9,11-tridecatetraene (22a). To a mixture of (*E*)-(3,5-hexadienyl)propanedioic acid diethyl ester[40] (1.780 g, 7.4 mmol) and NaH (300 mg, 12 mmol) in DMSO (60 mL) was added 2,4-hexadienyl chloride (1.030 g, 8.9 mmol). The resulting mixture was stirred overnight (12 h), then quenched by the careful addition of water (50 mL), and extracted with EtOAc (100 mL). The organic extract washed with saturated aqueous NH_4Cl (50 mL) and brine (2 × 50 mL), then dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica afforded bisdiene **22a** (2.200 g, 99%): ^{1}H NMR (360 MHz) δ 6.26−6.84 (m, 1 H), 5.99−6.12 (m, 3 H), 5.61−5.72 (m, 2 H), 5.33−5.42 (m, 1 H), 4.97−5.14 (m, 2 H), 4.13−4.22 (m, 4 H), 2.67 (d, J = 7.6 Hz, 2 H), 1.96−2.06 (m, 4 H), 1.74 (d, J = 6.9 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (50 MHz) δ 171.0 (s), 136.9 (d), 134.3 (d), 133.6 (d), 131.4 (d), 131.1 (d), 128.4 (d), 124.3 (d), 115.2 (t), 61.0 (t), 57.3 (s), 35.9 (t), 31.7 (t), 27.0 (t), 17.9 (q), 14.0 (q); IR (ATR) 1726 (s, br. **C**═O), 1653 (m, C═C), 1602 (m, C═C); Combustion analysis ($C_{19}H_{28}O_4$ = 71.22% C, 8.81% H) found 71.11% C, 8.88% H.

Cyclization of Bisdiene 22a. To a stirred solution of **22a** (270.0 mg, 0.84 mmol) in THF (5 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (26−39 mg, 0.10−0.15 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting mixture was heated to reflux (16 h) to afford, after chromatography on silica (95:5 Hex:EtOAc), **23** (240 mg, 90%): ^{1}H NMR (360 MHz) δ 6.34−6.24 (ddd, 1 H, J = 17.0, 10.3, 10.3 Hz), 6.06 (dd, 1 H, J = 15.1, 10.3 Hz), 5.72−5.66 (m, 1 H), 5.45 (dd, 1 H, J = 15, 9.0 Hz), 5.13−4.92 (m, 4 H), 4.22 (q, 1 H, J = 7.2 Hz), 4.20 (q, 1 H, J = 7.2 Hz), 4.13 (q, 2 H, J = 7.2 Hz), 2.37-2.23 (m, 3 H), 1.96 (dddd, 1 H, J = 12.4, 12.4, 9.0, 3.2 Hz), 1.81−1.48 (m, 5 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.21 (t, 3 H, J = 7.2 Hz), 1.16−1.25 (m, 1 H); ^{13}C NMR (50 MHz) δ 172.0 (s), 170.8 (s), 137.7 (d), 137.6 (d), 136.9 (d), 136.4 (d), 131.8 (d), 116.0 (t), 115.4 (t), 61.2 (t), 60.9 (t), 54.7 (s), 42.7 (d), 40.6 (d), 38.3 (t), 37.5 (t), 30.7 (t), 27.4 (t), 14.0 (q), 13.9 (q); IR (neat) 1730 (C═O), 1640 (C═C); HRMS analysis ($C_{19}H_{28}O_4$ = 320.1984) found *m/z* 320.1988.

Preparation of *N*-(2,4-Octadienyl),*N*-(3,5-hexadienyl), *p*-Toluene Sulfonamide (24a). To a cooled (0 °C) solution of (4*E*)-1,4-octadien-3-ol (7.80 g, 61.9 mmol) in CH_2Cl_2 (100 mL) was added $SOCl_2$ (5.0 mL, 69 mmol). The reaction mixture was warmed to room temperature, stirred for 3 h, and then partitioned with water (100 mL). The aqueous layer was extracted with EtOAc (50 mL), and the combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was distilled (aspirator pressure, 70−80 °C) to afford a mixture of octadienyl chlorides (7.10 g, 85%) which were used without further purification.

To a cooled (−78 °C) solution of (*E*)-*N*-(3,5-hexadienyl) *p*-toluene sulfonamide (1.310 g, 5.2 mmol) and HMPA (0.25 mL, 13.2 mmol) in THF (50 mL) was added a solution of *n*-BuLi (2.50 mL (2.5 M), 6.3 mmol). The resulting mixture was stirred for 0.5 h, and then a solution of 2,4-octadienyl chloride (0.839 g, 6.2 mmol) in THF (5 mL) was added. The resulting mixture was slowly warmed to room temperature, then quenched by the addition of water (50 mL), and concentrated in vacuo. The residue was extracted with EtOAc (100 mL), and the organic extract was washed with brine (2 × 50 mL), then dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica afforded bisdiene **24a** (0.750 g, 41%): ^{1}H NMR (360 MHz) δ 7.68 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 6.26 (ddd, J = 16.9, 10.1, 10.1 Hz, 1 H), 5.91−6.10 (m, 2 H), 5.66 (dt, J = 14.9, 6.9 Hz, 1 H), 5.55 (dt, J = 15.3, 7.0 Hz, 1 H), 5.33 (dt, J = 14.8, 6.8 Hz, 1 H), 5.10 (d, J = 16.9 Hz, 1 H), 5.00 (d, J = 10.1 Hz, 1 H), 3.81 (d, J = 6.9 Hz, 2 H), 3.16 (t, J = 7.3 Hz, 2 H), 2.41 (s, 3 H), 2.26−2.33 (m, 2 H), 2.00−2.06 (m, 2 H), 1.36−1.42 (m, 2 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (50 MHz) δ 142.8 (s), 137.0 (s), 136.6 (d), 135.5 (d), 134.2 (d), 132.9 (d), 130.4 (d), 129.4 (d), 128.9 (d), 126.9 (d), 124.7 (d), 115.6 (t), 49.7 (t), 46.4 (t), 34.4 (t), 31.6 (t), 22.1 (t), 21.2 (q), 13.4 (q); IR (ATR) 1653 (m, C═C), 1599 (m, Ar), 1338 (s, SO_2), 1154 (s, SO_2); Combustion analysis ($C_{21}H_{29}NO_2S$ = 70.15% C, 8.13% H) found 70.49% C, 8.27% H.

Cyclization of Bisdiene 24a. To a stirred solution of **24a** (250.0 mg, 0.70 mmol) in THF (5 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (26−39 mg, 0.10−0.15 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting mixture was heated to reflux (20 h) to afford, after chromatography on silica (95:5 Hex:EtOAc), piperidine **25a** (215.0 mg, 86%): ^{1}H NMR (500 MHz) δ 6.10 (dd, 1 H, J = 15.1, 10.4 Hz), 5.97 (dd, 1 H, J = 15.1, 10.3 Hz), 5.71 (dt, 1 H, J = 15.1, 6.4 Hz), 5.58−5.70 (m, 1 H), 5.17 (dd, 1 H, J = 15.1, 9.0 Hz), 4.98−4.93 (m, 2 H), 3.80−3.76 (m, 1 H), 3.68−3.63 (m, 1 H), 2.42 (s, 3 H), 2.31−2.06 (m, 5 H), 1.94 (dd, 1 H, J = 12.1, 12.1 Hz), 1.74−1.61 (m, 2 H), 1.23 (dddd, 1 H, J = 12.3, 12.3, 12.3, 4.2 Hz), 1.06−1.00 (m, 1 H), 1.00 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (50 MHz) δ 143.3 (s), 136.0 (d), 135.8 (d), 133.5 (d), 133.1 (s), 130.5 (d), 129.5 (d), 128.6 (d), 127.6 (d), 116.6 (t), 51.2 (t), 46.4 (t), 44.6 (d), 39.6 (d), 37.5 (t), 29.7 (t), 21.4 (q); IR (ATR) 1658 (m, C═C), 1640 (m, C═C), 1342 (s, SO_2), 1163 (s, SO_2); Combustion analysis ($C_{21}H_{29}NO_2S$ = 70.15% C, 8.13% H) found 70.49% C, 8.37% H.

Preparation of 7,7-(Diethylcarboxyl)pentadeca-1,3,9,11-tetraene (24b). To a mixture of (*E*)-(3,5-hexadienyl)propanedioic acid diethyl ester[40] (950 mg, 4.0 mmol) and NaH (200 mg, 8 mmol) in THF (75 mL) was added 2,4-octadienyl chloride (600 mg, 4.5 mmol). The resulting mixture was stirred overnight (12 h), then quenched by the careful addition of water (50 mL), and concentrated in vacuo. The residue was extracted with EtOAc (100 mL), and the organic extract was washed with brine (2 × 50 mL), then dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica (95:5 Hex:EtOAc) afforded bisdiene **24a** (1.160 g, 87%): ^{1}H NMR (360 MHz) δ 6.21−6.30 (m, 1 H), 5.91−6.06 (m, 3 H), 5.52−5.67 (m, 2 H), 5.30−5.38 (m, 1 H), 4.93−5.09 (m, 2 H), 4.15 (q, J = 7.1 Hz, 4 H), 2.63 (d, J = 7.6 Hz, 2 H), 1.93-2.03 (m, 6 H), 1.32−1.42 (m, 2 H), 1.21 (t, J = 7.1 Hz, 6 H), 0.86 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz) δ 171.0 (s), 136.9 (d), 134.5 (d), 133.9 (d), 133.6 (d), 131.4 (d), 129.9 (d), 124.5 (d), 115.2 (t), 61.0 (t), 57.4 (s), 35.9 (t), 34.6 (t), 31.8 (t), 27.0 (t), 22.3 (t), 14.0 (q), 13.6 (q); IR (ATR) 1729 (s, C═O), 1653 (m, C═C), 1602 (w, C═C); HRMS analysis ($C_{21}H_{32}O_4$ = 348.2321) found *m/z* 348.2310.

Cyclization of Bisdiene 24b. To a stirred solution of **24b** (250.0 mg, 0.74 mmol) in THF (5 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (26−39 mg, 0.10−0.15 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting mixture was heated to reflux (40 h) to afford, after chromatography on silica (95:5 Hex:EtOAc), **25b** (210 mg, 84%): ^{1}H NMR (500 MHz) δ 6.02 (dd, 1 H, J = 15.1, 10.3 Hz), 5.99 (ddt, 1 H, J = 15.1, 10.3, 1.4 Hz), 5.72−5.64 (m, 1 H), 5.63 (dt, 1 H, J = 15.1, 7.4 Hz), 5.32 (dd, 1 H, J = 15.1, 9.1 Hz), 4.96−4.92 (m, 2 H), 4.24−4.20 (m, 2 H), 4.20−4.10 (m, 2 H), 2.37−2.26 (m, 3 H), 2.06 (dq, 2 H, J = 7.4, 7.4 Hz), 1.93 (dddd, 1 H, J = 12.3, 12.3, 9.1, 3.6 Hz), 1.78 (dddd, 1 H, J = 13.8, 3.5, 3.5, 3.5 Hz), 1.72−1.61 (m, 2 H), 1.50 (dd, 1 H, J = 13.3, 12.3 Hz), 1.25 (t, 3 H, J = 7.1 Hz), 1.20 (t, 3 H, J = 7.1 Hz), 1.20−1.10 (m, 1 H), 1.02 (dddd, 1 H, J = 12.3, 12.3, 12.3, 3.5 Hz), 0.99 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (50 MHz) δ 172.2 (s), 171.0 (s), 136.7 (d), 134.8 (d), 131.4 (d), 116.0 (t), 61.2 (t), 61.0 (t), 54.8 (s), 42.8 (d), 38.4 (t), 37.8 (t), 30.8 (t), 27.5 (t), 25.5 (t), 14.1 (q), 14.0 (q), 13.5 (q); IR (ATR) 1729 (s, C═O), 1652 (m, C═C), 1640 (m, C═C); HRMS analysis ($C_{21}H_{32}O_4$ = 348.2301) found *m/z* 348.2289.

Preparation of (8*E*)-1,8,10-Undecatrien-3-ol. To a cooled (0 °C) solution of (6*E*)-6,8-nonadienal[40,42] (4.40 g, 31.9 mmol) in THF (75 mL) was added vinylmagnesium bromide (1.0 M, 35.0 mL, 35.0 mmol). After 2 h, the mixture was quenched by the addition of water (75 mL) and partitioned with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (230−400 mesh, 80:20 Hex:EtOAc) afforded the allylic alcohol (4.21 g, 80%): TLC analysis (80:20 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 6.40−6.16 (m, 1 H), 6.11−5.93 (m, 1 H), 5.91−5.67 (m, 2 H), 5.26−4.84 (m, 4 H), 4.17−3.94 (m, 1 H), 2.53−1.93 (m, 2 H), 1.62−1.12 (m, 6 H); ^{13}C NMR (75 MHz) δ 141.2 (d), 137.1 (d), 134.9 (d), 130.9 (d), 114.5 (t), 114.3 (t), 72.8 (d), 36.6 (t), 32.3 (t), 28.9 (t), 24.7 (t); IR (ATR) 3650−3200 (OH, 55); Combustion analysis ($C_{11}H_{18}O$ = 79.46% C, 10.91% H) found 79.69% C, 10.75% H.

(42) Craig, D.; Geach, N. J.; Pearson, C. J.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 6071−98.

Preparation of (3*E*,9*E*)-1,3,9-Undecatrienyldiphenylphosphine oxide. Adapting the procedure of Yamamoto,[43] chlorodiphenylphosphine (1.10 mL, 6.0 mmol) was added to a cooled (0 °C) solution of (8*E*)-1,8,10-undecatrien-3-ol (1.0 g, 6.0 mmol) and pyridine (1.00 mL, 13.2 mmol) in ether (50 mL). The resulting mixture was stirred for 2 h, and then $NaHSO_4 \cdot H_2O$ (7 g) was added. The resulting mixture stirred for an additional 0.5 h and then filtered through Celite, and the filtrate was concentrated in vacuo. The residue was taken up in xylenes (100 mL), and the resulting solution was refluxed for 8 h. The xylenes were removed by short path distillation, and the residue was purified by chromatography on silica (260−400 mesh, 100 EtOAc) to afford the allylic phosphine oxide (1.30 g, 62%): TLC analysis (100 EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 7.79−7.15 (m, 10 H), 6.28−6.04 (m, 1 H), 5.97−5.76 (m, 1 H), 5.59−5.40 (m, 1 H), 5.37−5.22 (m, 2 H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 7.5 Hz), 2.96 (dd, 2 H, J = 6.0, 13.6 (J_{H-P}) Hz), 1.95−1.70 (m, 4 H), 1.10 (s, 4 H); ^{13}C NMR (75 MHz) δ 136.8 (d), 134.7 (d), 131.2 (d), 130.6 (d), 128.1 (d), 114.2 (t), 34.3 (t, J_{C-P} = 70 Hz), 31.9 (t), 31.8 (t), 28.1 (t), 27.8 (t); HRMS ($C_{23}H_{27}OP$ = 350.1800) found *m/z* 350.1787.

Preparation of Bisdiene 24c. To a cooled (−78 °C) solution of (3*E*,9*E*)-1,3,9-undecatrienyldiphenylphosphine oxide (2.45 g, 6.99 mmol) and HMPA (1.85 mL, 2.20 mmol) in THF (50 mL) was added *n*-BuLi (2.5 M, 3.10 mL, 7.75 mmol). After 30 min, a solution of the ethylene ketal of levulinal[40,44] (1.01 g, 6.99 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to slowly warm to room temperature overnight (8 h). The reaction mixture was quenched by the addition of water (75 mL) and partitioned with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 80:20 Hex:EtOAc) afforded bisdiene **24c** (1.01 g, 53%): TLC analysis (80:20 Hex:EtOAc) R_f 0.5; ^{1}H NMR (300 MHz) δ 6.38−6.17 (m, 1 H), 6.07−5.81 (m, 3 H), 5.74−5.37 (m, 3 H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 7.5 Hz), 3.89 (br s, 4 H), 2.29−1.84 (m, 6 H), 1.77−1.55 (m, 2 H), 1.46−1.16 (m, 7 H); ^{13}C NMR (75 MHz) δ 137.1 (d), 134.9 (d), 132.0 (d), 131.5 (d), 130.9 (d), 130.3 (d), 130.2 (d), 114.5 (t), 64.4 (t), 38.6 (t), 32.2 (t), 28.8 (t), 28.5 (t), 26.9 (t), 23.7 (q); HRMS ($C_{18}H_{28}O_2$ = 276.2089) found *m/z* 276.2099.

Cyclization of Bisdiene 24c. To a solution of **24c** (251.0 mg, 0.91 mmol) in THF (5 mL) was added $Pd(OAc)_2$ (10.0 mg, 0.05 mmol), Ph_3P (36.0 mg, 0.014 mmol), and Et_3N (0.64 mL). The resulting solution was refluxed for 24 h. Filtration through silica (260−400 mesh, 95:5 Hex:EtOAc) afforded enediene **25c** (220 mg, 88%) as a 4:1 (*E:Z*) mixture of double bond isomers: TLC analysis (95:5 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.18−5.81 (m, 2 H), 5.78−5.32 (m, 3 H), 4.97−4.81 (m, 2 H), 3.96 (s, 4 H), 2.56−2.35 (m, 2 H), 2.31−1.98 (m, 4 H), 1.86−1.59 (m, 6 H); ^{13}C NMR (75 MHz) δ 138.7 (d), 138.0 (d), 134.5 (d), 130.5 (d), 126.7 (d), 116.2 (t), 65.3 (t), 47.4 (d), 43.2 (t), 42.4 (d), 39.7 (t), 34.4 (t), 31.9 (t), 26.6 (t), 24.5 (t); Combustion analysis ($C_{18}H_{28}O_2$ = 78.21% C, 10.21% H) found 78.40% C, 10.17% H.

Preparation of 6,6-(Diethylcarboxy)-1,3,8,10-tetradecatetraene (26a). To a mixture of (*E*)-(3,5-octadienyl)propanedioic acid diethyl ester (1.80 g, 6.7 mmol) and NaH (300 mg, 12 mmol) in DMSO (100 mL) was added pentadienyl chloride (0.82 g, 8.0 mmol). The resulting mixture was stirred for 2 h, then quenched by the careful addition of water (50 mL), and extracted with EtOAc (100 mL). The organic extract washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL), then dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica afforded bisdiene **26a** (2.05 g, 91%): ^{1}H NMR (360 MHz) δ 6.28 (ddd, J = 16.9, 10.1, 10.1 Hz, 1 H), 5.94−6.12 (m, 3 H), 5.49−5.64 (m, 2 H), 5.33−5.41 (m, 1 H), 5.11 (d, J = 16.9 Hz, 1 H), 5.01 (d, J = 10.1 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 4 H), 2.64 (d, J = 7.0 Hz, 2 H), 2.62 (d, J = 7.0 Hz, 2 H), 2.02 (q, J = 7.2 Hz, 2 H), 1.35−1.42 (m, 2 H), 1.22 (t, J = 7.1 Hz, 6 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz) δ 170.7 (s), 136.6 (d), 134.9 (d), 134.7 (d), 133.8 (d), 129.9 (d), 128.0 (d), 124.4 (d), 116.2 (t), 61.1 (t), 57.8 (s), 36.0 (t), 35.8 (t), 34.6 (t), 22.3 (t), 14.1 (q), 13.6 (q); IR (ATR) 1729 (s, C═O), 1652 (w, C═C), 1601 (w, C═C); Combustion analysis ($C_{20}H_{30}O_4$ = 71.86% C, 8.98% H) found 71.82% C, 9.04% H.

Cyclization of Bisdiene 26a. To a solution of **26a** (500.0 mg, 1.50 mmol) in THF (10 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (26.0 mg, 0.10 mmol), and Et_3N (0.64 mL). The resulting solution was refluxed for 40 h. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) afforded triene **27a** (470.0 mg, 93%): ^{1}H NMR (360 MHz) δ 6.03−5.95 (m, 2 H), 5.80−5.60 (m, 2 H), 5.37 (dd, 1 H, J = 8.5, 13.8 Hz), 5.03−4.94 (m, 2 H), 4.16 (overlapping q's, 4 H, J = 7.1 Hz), 2.52−2.45 (m, 2 H), 2.33−1.71 (m, 8 H), 1.23 (overlapping t's, 6 H, J = 7.1 Hz), 0.99 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (50 MHz) δ 172.6 (s), 172.5 (s), 136.8 (d), 134.9 (d), 132.9 (d), 131.5 (d), 128.9 (d), 115.7 (t), 61.3 (t), 58.3 (s), 48.7 (d, major isomer), 45.3 (d, minor isomer), 45.1 (d, major isomer), 43.1 (d, minor isomer), 40.7 (t), 39.5 (t), 37.1 (t), 25.5 (t), 14.0 (q), 13.4 (q); IR (neat) 1734 (br s, C═O), 1641 (m, C═C); HRMS analysis ($C_{20}H_{30}O_4$ = 334.2142) found *m/z* 334.2143.

Preparation of (3*E*,8*E*,10*E*)-13-Methyl-6,6-(dicarboethoxy)-1,3,8,10-tetradecatetraene (26b).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (CAS registry number 55693-36-2, 1.37 g, 6.04 mmol) and NaH (145.0 mg, 6.04 mmol) in THF (50 mL) was added $Pd(OAc)_2$ (37.0 mg, 0.17 mmol) and Bu_3P (0.17 mL, 0.68 mmol). The resulting solution (turns brown) was brought to reflux, and then (2*E*,4*E*)-7-methyl-2,4-octadien-1-yl acetate[40] (0.50 g, 2.75 mmol) was added. The resulting mixture was refluxed overnight (8 h), then cooled to room temperature, and quenched by the addition of water (50 mL). The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 90:10 Hex:EtOAc) afforded bisdiene **26b** (870.0 mg, 91%): TLC analysis (90:10 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 6.38−6.17 (m, 1 H), 6.16−5.85 (m, 3 H), 5.61−5.43 (m, 2 H), 5.41−5.27 (m, 1 H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 7.5 Hz), 4.18 (q, 4 H, J = 7.2 Hz), 2.63 (overlapping d, 4 H), 1.92 (t, 2 H, J = 6.95 Hz), 1.61 (septet, 1 H, J = 6.9 Hz), 1.22 (t, 6 H, J = 7.2 Hz), 0.86 (overlapping s, 6 H); ^{13}C NMR (75 MHz) δ 170.7 (s), 136.6 (d), 134.9 (d), 134.7 (d), 132.8 (d), 130.8 (d), 127.9 (d), 124.5 (d), 116.2 (t), 61.2 (t), 57.8 (s), 41.9 (t), 35.9 (t), 28.4 (d), 22.2 (q), 14.1 (q); IR (salt plate) 1721 (C═O, 82), 1635 (C═C, 55); Combustion analysis ($C_7H_{10}O_4$ = 72.38% C, 9.26% H) found 72.49% C, 9.13% H.

Cyclization of Bisdiene 26b. To a solution of **26b** (174.0 mg, 0.5 mmol) in THF (5 mL) was added Ph_3P (20.0 mg, 0.075 mmol), $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting solution was refluxed for 24 h. Chromatography on silica (260−400 mesh, 90:10 Hex:EtOAc) afforded enediene **27b** (140.0 mg, 80%) as a 4:1 mixture of *E*- and *Z*-isomers: TLC analysis (90:10 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 6.11−5.85 (m, 2 H), 5.82−5.64 (m, 1 H), 5.62−5.46 (m, 1 H), 5.43−5.26 (m, 1 H), 5.16−4.88 (m, 2 H), 4.15 (q, 4 H, J = 7.1 Hz), 2.78−1.54 (m, 8 H), 1.20 (t, 6 H, J = 7.1 Hz), 0.97 (d, 3 H, J = 6.7 Hz), 0.85 (d, 3 H, J = 6.7 Hz); ^{13}C NMR (75 MHz) δ 177.4 (s), 170.6 (s), 140.4 (d), 136.7 (d), 132.9 (d), 131.6 (d), 136.9 (d), 115.6 (t), 61.2 (t), 58.2 (s), 48.6 (d), 45.1 (d), 40.6 (t), 39.4 (t), 37.0 (t), 30.8 (d), 22.2 (q), 14.0 (q); IR (salt plate) 1730 (C═O, 95), 1638 (C═C, 58); Combustion analysis ($C_{21}H_{32}O_4$ = 72.38% C, 9.26% H) found 72.46% C, 9.12% H.

Preparation of Methyl-Substituted Heptadienol Derivatives. (a) (4*E*)-4-Methyl-7-phenyl-1,4-heptadien-3-ol. To a cooled (0 °C) solution of (2*E*)-2-methyl-5-phenyl-2-pentenal (CAS Registry number 56161-69-4, 2.00 g, 11.5 mmol) in THF (50 mL) was added vinylmagnesium bromide (1.0 M in ether, 14.0 mL, 14 mmol) dropwise. The resulting solution was slowly warmed to room temperature and stirred overnight (8 h). The reaction mixture was quenched by the addition of water (75 mL) and extracted with ether (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 80:20 Hex:EtOAc) afforded the heptadienol (2.30 g, 99%): TLC analysis (80:20 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 7.37−7.17 (m, 5 H), 5.94−5.72 (m, 1 H), 5.56 (t, 1 H, J = 6.2 Hz), 5.29 (d, 1 H, J = 16.8 Hz), 5.17 (d, 1 H, J = 9.8 Hz), 4.53 (d, 1 H, J = 7.2 Hz), 2.72 (t, 2 H, J = 7.4 Hz), 2.41 (dt, 2 H, J = 6.2, 7.7 Hz), 1.58 (s, 3 H); ^{13}C NMR (75 MHz) δ 141.8 (d), 139.1 (d), 128.5 (d), 128.4 (d), 128.2 (d), 126.8 (d), 114.8 (t), 78.1 (d), 35.9 (t), 29.5 (t), 11.8 (q); IR (salt plate) 3300 (OH, 80), 1645 (C═C, 48); Combustion analysis ($C_{14}H_{18}O$ = 83.12% C, 8.97% H) found 83.28% C, 8.79% H.

(43) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029−32.

(44) Zhou, W.-s.; Wei, G.-p. *Synthesis* **1990**, 822−4.

(b) (4*E*)-4-Methyl-1,4-heptadien-3-ol. To a cooled (0 °C) solution of 2-methyl-2-pentenal (9.00 mL, 82.8 mmol) in THF (50 mL) was added vinyl magnesium bromide (1 M in ether, 100 mL, 100 mmol) dropwise over 15 min. The resulting mixture was slowly warmed to room temperature over 3 h, then recooled to 0 °C, and quenched by the addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 80:20 Hex:EtOAc) afforded the heptadienol (9.20 g, 88%): TLC analysis (80:20 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 5.9−5.75 (m, 1 H), 5.43 (t, 1 H, J = 7.5 Hz), 5.25 (d, 1 H, J = 17.2 Hz), 5.11 (d, 1 H, J = 9.9 Hz), 4.48 (d, 1 H, J = 5.4 Hz), 2.02 (q, 2 H, J = 7.5 Hz), 1.57 (s, 3 H), 0.95 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (75 MHz) δ 139.3 (d), 135.2 (s), 128.5 (d), 114.6 (t), 76.5 (d), 20.8 (t), 13.8 (q), 11.6 (q); IR (salt plate) 3377 (OH, 75), 1640 (C═C, 32); Combustion analysis ($C_8H_{14}O$ = 76.13% C, 11.19% H) found 76.15% C, 10.96% H.

Preparation of Methyl-Substituted Heptadienyl Acetate Derivatives. (a) (4*E*)-4-Methyl-7-phenyl-1,4-heptadien-3-ol Acetate. To a cooled (0° C) solution of (4*E*)-4-methyl-7-phenyl-1,4-heptadien-3-ol (740.0 mg, 3.70 mmol), DMAP (41.0 mg, 0.4 mmol), and Et_3N (1.10 mL, 7.4 mmol) was added Ac_2O (0.80 mL, 7.4 mmol). The resulting solution was stirred overnight (8 h) and then quenched by the addition of water (50 mL). The mixture was extracted with ether (3 × 50 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (230−400 mesh, 90:10 Hex:EtOAc) afforded the heptadienyl acetate (800.0 mg, 89%): TLC analysis (90:10 Hex:EtOAc) R_f 0.7; ^{1}H NMR (300 MHz) δ 7.35−7.09 (m, 5 H), 5.87−5.69 (m, 1 H), 5.65−5.52 (m, 2 H), 5.29−5.09 (m, 2 H), 2.69 (t, 2 H, J = 7.7 Hz), 2.37 (dt, 2 H, J = 6.8, 7.6 Hz), 2.1 (s, 3 H), 1.55 (s, 3 H); ^{13}C NMR (75 MHz) δ 169.8 (s), 135.3 (d), 132.9 (d), 128.8 (d), 128.4 (d), 128.2 (d), 128.0 (d), 127.9 (d), 125.8 (d), 116.3 (t), 79.2 (d), 35.4 (t), 29.6 (t), 21.1 (q), 12.2 (q); IR (salt plate) 1721 (C═O, 70), 1660 (C═C, 55); Combustion analysis ($C_{16}H_{20}O_2$ = 78.70% C, 8.30% H) found 78.59% C, 8.55% H.

(b) (4*E*)-4-Methyl-1,4-heptadien-3-ol Acetate. To a cooled (0 °C) solution of (4*E*)-4-methyl-1,4-heptadien-3-ol (9.20 g, 73 mmol), DMAP (820.0 mg, 7.3 mmol), and Et_3N (21.0 mL, 146 mmol) was added Ac_2O (15.0 mL, 146 mmol) dropwise. The resulting dark brown mixture was stirred overnight (8 h) and then partitioned between ether:hexanes 1:1 (100 mL) and water (150 mL). The aqueous layer was extracted with ether (3 × 100 mL), and the combined organics dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60−200 mesh, 90:10 Hex:EtOAc) afforded the heptadienyl acetate (11.00 g, 90%): TLC analysis (90:10 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 5.85−5.65 (m, 1 H), 5.55 (d, 1 H, J = 5.7 Hz), 5.45 (t, 1 H, J = 7.1 Hz), 5.27−5.05 (m, 2 H), 2.12−1.90 (m, 5 H), 1.55 (s, 3 H), 2.27 (t, 3 H, J = 7.7 Hz); ^{13}C NMR (75 MHz) δ 169.6 (s), 135.3 (d), 131.4 (s), 130.7 (d), 116.1 (t), 76.5 (d), 20.9 (q), 20.7 (t), 13.6 (q), 11.9 (q); IR (salt plate) 1741 (C═O, 63), 1655 (C═C, 60); Combustion analysis ($C_{10}H_{16}O_2$ = 71.39% C, 9.59% H) found 71.50% C, 9.60% H.

Preparation of Methyl-Substituted Bisdienes. (a) (3*E*,8*E*,10*E*)-10-Methyl-13-phenyl-6,6-(dicarboethoxy)-3,8,10-tridecatetraene (28a).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (CAS registry number 55693-36-2, 600.0 mg, 2.65 mmol) and NaH (63.0 mg, 2.65 mmol) in THF (50 mL) was added Bu_3P (0.13 mL, 0.52 mmol) and $Pd(OAc)_2$ (28.0 mg, 0.13 mmol). To the resulting brown solution was added (4*E*)-4-methyl-7-phenyl-1,4-heptadien-3-ol acetate (323.0 mg, 1.33 mmol), and the resulting mixture was refluxed overnight (8 h). The mixture was concentrated, and the residue was chromatographed on silica (260−400 mesh, 95:5 Hex:EtOAc) to afford the bisdiene **28a** (410.0 mg, 75%): TLC analysis (95:5 Hex:EtOAc) R_f 0.1; ^{1}H NMR (300 MHz) δ 7.34−7.12 (m, 5 H), 6.38−6.22 (m, 1 H), 6.16 −6.01 (m, 2 H), 5.64−5.49 (m, 1 H), 5.48−5.29 (m, 2 H), 5.18−4.95 (m, 2 H), 4.19 (q, 4 H, J = 7.4 Hz), 2.67 (d, 6 H, J = 7.9 Hz), 2.44 (d, 2 H, J = 7.8 Hz), 1.67 (s, 3 H), 1.25 (t, 6 H, J = 7.4 Hz); ^{13}C NMR (75 MHz) δ 170.7 (s), 141.8 (d), 138.9 (d), 136.6 (d), 136.5 (d), 134.9 (d), 134.8 (d), 133.7 (d), 130.8 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.9 (d), 125.7 (d), 120.3 (d), 116.1 (t), 61.1 (t), 57.9 (s), 36.1 (t), 36.0 (t), 35.9 (t), 29.9 (t), 14.0 (q), 12.2 (q); IR (salt plate) 1720 (C═O, 75), 1630 (C═C, 20); Combustion analysis ($C_{26}H_{34}O_4$ = 76.06% C, 8.35% H) found 76.16% C, 8.16% H.

(b) (3*E*,8*E*,10*E*)-10-Methyl-6,6-(dicarboethoxy)-1,3,8,10-tridecatetraene (28b).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (CAS registry number 55693-36-2, 5.40 g, 23.8 mmol) and NaH (571.0 mg, 23.8 mmol) in THF (200 mL) was added Bu_3P (0.73 mL, 2.9 mmol) and $Pd(OAc)_2$ (160.0 mg, 0.71 mmol). To the resulting brown solution was added (4*E*)-4-methyl-1,4-heptadien-3-ol acetate (2.00 g, 11.9 mmol), and the resulting mixture was refluxed overnight (8 h). The mixture was cooled to room temperature and quenched by the addition of water (25 mL). The mixture was extracted with ether (3 × 75 mL), and the combined organic extracts was dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) afforded the bisdiene **28b** (3.10 g, 77%): TLC analysis (95:5 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.35−6.17 (m, 1 H), 6.13−5.97 (m, 2 H), 5.61−5.46 (m, 1 H), 5.41−5.23 (m, 2 H), 5.08 (d, 1 H, J = 16.7 Hz), 4.98 (d, 1 H, J = 7.5 Hz), 4.17 (q, 4 H, J = 7.0 Hz), 2.64 (d, 4 H, J = 8.2 Hz), 2.10 (t, 2 H, J = 7.9 Hz), 1.66 (s, 3 H), 1.21 (t, 6 H, J = 6.6 Hz), 0.96 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz) δ 170.7 (s), 139.1 (d), 136.6 (d), 134.9 (d), 133.7 (d), 132.5 (s), 128.1 (d), 119.8 (d), 116.1 (t), 61.1 (t), 57.9 (s), 36.1 (t), 35.8 (t), 21.2 (t), 14.1 and 13.9 (overlapping q's), 12.1 (q); IR (salt plate) 1731 (C═O, 84), 1640 (C═C, 55); Combustion analysis ($C_{20}H_{30}O_4$ = 71.82% C, 9.04% H) found 71.74% C, 8.97% H.

Cyclizations of Methyl-Substituted Bisdienes. (a) Cyclization of Bisdiene 28a. To a solution of **28a** (205.0 mg, 0.5 mmol) in THF (5 mL) was added $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting solution was refluxed for 24 h, then cooled, and filtered through silica (260−400 mesh, 95:5 Hex:EtOAc) to afford quantitative recovery of enediene **29a**: TLC analysis (95:5 Hex:EtOAc) R_f 0.1; ^{1}H NMR (300 MHz) δ 7.38−7.08 (m, 5 H), 6.14 (d, 1 H, J = 15.1 Hz), 5.88−5.64 (m, 2 H), 5.23 (d, 1 H, J = 9.1 Hz), 5.11−4.89 (m, 2 H), 4.28−4.11 (m, 4 H), 3.56−3.41 (m, 3 H), 2.75−2.16 (m, 5 H), 1.97−1.71 (m, 6 H), 1.33−1.18 (m, 6 H); ^{13}C NMR (75 MHz) δ 172.6 (s), 172.5 (s), 140.6 (s), 136.8 (d), 135.7 (d), 134.6 (d), 132.9 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 115.6 (t), 61.3 (t), 46.1 (d), 44.3 (d), 40.7 (t), 39.5 (t), 39.1 (t), 37.2 (t), 13.9 (q); IR (salt plate) 1724 (C═O, 62), 1631 (C═C, 19); Combustion analysis ($C_{26}H_{34}O_4$ = 76.06% C, 8.35% H) found C, 75.89% C, 8.15% H.

(b) Cyclization of Bisdiene 28b. To a solution of **28b** (167.0 mg, 0.5 mmol) in THF (5 mL) was added $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20 mg, 0.075 mmol), and Et_3N (0.4 mL, 2.5 mmol). The resulting mixture was refluxed for 24 h, then cooled, and filtered through silica (260−400 mesh, 95:5 Hex:EtOAc) to afford quantitative recovery of enediene **29b**: TLC analysis (95:5 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.11 (d, 1 H, J = 15.6 Hz), 5.84−5.64 (m, 1 H), 5.62−5.49 (m, 1 H), 5.13 (d, 1 H, J = 9.1 Hz), 5.05−4.82 (m, 2 H), 4.23−4.12 (m, 4 H), 2.56−2.41 (m, 3 H), 2.28−2.15 (m, 1 H), 1.81−1.69 (m, 8 H), 1.27−1.18 (m, 6 H); ^{13}C NMR (75 MHz) δ 172.9 (s), 172.7 (s), 136.8 (d), 135.8 (d), 134.8 (s), 131.7 (d), 122.8 (d), 115.5 (t), 61.2 (t), 58.4 (s), 46.2 (d), 44.2 (d), 40.8 (t), 39.5 (t), 37.3 (t), 18.1 (q), 13.9 (q), 12.9 (q); IR (salt plate) 1730 (C═O, 63), 1635 (C═C, 45); Combustion analysis ($C_{20}H_{30}O_4$ = 71.82% C, 9.04% H) found 71.66% C, 9.25% H.

Preparation of Hydroxy-Substituted Bisdienes. (a) (2*E*,4*E*,9*E*)-6-Hydroxy-(2,4,9,11)-dodecatetraene (33). A suspension of dry, finely divided magnesium powder (CERAC 400 mesh, 1.41 g, 57.9 mmol) in dry THF (75 mL) was activated by the addition of ethylene dibromide (0.41 mL, 0.89 g, 4.8 mmol) and sonication for ca. 20 min. To this activated suspension was added 1-iodo-3,5-hexadiene[40,45] (4.01 g, 19.3 mmol) as a solution in THF (15 mL, 0.2 mL/min). After complete addition of the iodide the solution is sonicated for 15 min, maintaining the temperature at ca. 20 °C with a water bath. Formation of the Grignard reagent was accompanied by formation of a thick whitish gray slurry. The sonicator was replaced with a magnetic stirrer, and 2,4-hexadienal (1.95 g, 19.3 mmol, 95%) was added as a solution in THF (10 mL, 0.2 mL/min). Upon complete addition, the reaction mixture was stirred an additional 1.5 h and then quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organics were dried ($MgSO_4$),

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filtered, and concentrated. Chromatography on silica afforded bisdiene **33** (1.72 g 50%) as a colorless oil: TLC analysis (90:10 Hex:EtOAc) R_f 0.31; GC analysis (J & W Scientific 30 m DB-17, 100−260 °C @ 5 °C/min) 11.3 (86%) and 11.5 min (14%); ^{1}H NMR (300 MHz) δ 6.28 (td, 1 H, J = 16.9, 10.3 Hz), 6.15 (dd, 1 H, J = 15.0, 10.5 Hz), 5.98−6.09 (m, 1 H), 5.63−5.75 (m, 2 H), 5.53 (dd, 1 H, J = 15.2, 7.1 Hz), 5.07 (d, 1 H, J = 16.8 Hz), 4.95 (d, 1 H, J = 10.0 Hz), 4.11 (q, 1 H, J = 6.6 Hz), 2.14 (q, 2 H, J = 7.5 Hz), 1.74 (d, 3 H, J = 6.9 Hz), 1.49−1.69 (m, 2 H); ^{13}C NMR (125 MHz) δ 137.2 (d), 134.5 (d), 133.1 (d), 131.5 (d), 131.1 (d), 130.9 (d), 130.1 (d), 115.1 (t), 72.2 (d), 36.7 (t), 28.5 (t), 18.1 (t); IR (ATR, ZnSe) 3348 (broad, OH stretch), 1652 (m, C═C); HRMS analysis (EI, $C_{12}H_{18}O$ = 178.1358) found *m/z* 178.1354.

(b) (2*E*,4*E*,10*E*)-6-Hydroxy-2,4,10,12-tridecatetraene (38a). Following the procedure described above, the reaction of (2*E*)-1-iodo-4,6-heptadiene[46] (CAS registry number 114251-12-6, 11.0 g, 49.3 mmol) with Mg (CERAC 400 mesh powder, 2.40 g, 98.8 mmol) and 2,4-hexadienal (5.48 g, 54.2 mmol) afforded bisdiene **38a** (5.43 g, 57%): TLC analysis (90:10 Hex:EtOAc) R_f 0.3; GC analysis (J & W Scientific 30 m DB-17, 100−260 °C @ 5 °C/min) 13.7 (85%), 13.8 min (15%); ^{1}H NMR (360 MHz) δ 6.28 (td, 1 H, J = 17.4, 10.1 Hz), 6.14 (dd, 1 H, J = 15.1, 10.4 Hz), 5.98−6.06 (m, 2 H), 5.62−5.73 (m, 2 H), 5.53 (dd, 1 H, J = 15, 7 Hz), 5.06 (d, 1 H, J = 16.5 Hz), 4.93 (d, 1 H, J = 10.4 Hz), 4.1 (q, 1 H, J = 7.1 Hz), 2.09 (q, 2 H, J = 6.5 Hz), 1.73 (dd, 3 H, J = 6.6, 1.3 Hz), 1.37−1.62 (m, 4 H); ^{13}C NMR (50 MHz) δ 137.2 (d), 134.9 (d), 133.2 (d), 131.2 (d), 130.9 (d), 130.8 (d), 129.9 (d), 114.8 (t), 72.6 (d), 36.7 (t), 32.3 (t), 25.0 (t), 18.1 (q); IR (ATR, ZnSe) 3346 (broad, OH), 1653 (m, C═C); HRMS analysis (EI, $C_{13}H_{20}O$ = 192.1515) found *m/z* 192.1509.

Cyclizations of Hydroxy-Substituted Bisdienes. (a) Cyclization of Bisdiene 33. To a solution of **33** (178.0 mg, 1.0 mmol) in acetonitrile (5 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (39 mg, 0.15 mmol), and Et_3N (0.4 mL, 2.5 mmol). The resulting mixture was refluxed for 11 h, then cooled, and filtered through silica (260−400 mesh, 93:7 Hex:EtOAc) to afford a 1.6:1 mixture of alcohols **34a**:**34b** (117.9 mg, 66%). Spectral data for the individual isomers are obtained on enriched chromatography fractions. **34a**: ^{1}H NMR (500 MHz) δ 6.31 (dt, 1 H, J = 16.9, 10.1 Hz), 6.11 (dd, 1 H, J = 14.9, 10.5 Hz), 5.77−5.69 (m, 1 H), 5.52 (dd, 1 H, J = 14.9, 9.0 Hz), 5.13−4.93 (m, 4 H), 3.85 (q, 1 H, J = 7.7 Hz), 2.26−2.21 (m, 1 H), 2.01−1.39 (m, 8 H); ^{13}C NMR (125 MHz) δ 137.7 (d), 137.5 (d), 136.5 (d), 133.7 (d), 116.4 (t), 116.3 (t), 78.9 (d), 58.8 (d), 43.6 (d), 39.2 (t), 33.2 (t), 28.3 (t); IR (ATR) 3342 (br s, OH), 1640 (m, C═C), 1602 (w, C═C); Combustion analysis ($C_{12}H_{18}O$ = 80.85% C, 10.18% H) found 80.70% C, 10.49% H. **34b**: ^{1}H NMR (500 MHz) δ 6.35 (dt, 1 H, J = 16.9, 10.1 Hz), 6.14 (dd, 1 H, J = 15.5, 10.1 Hz), 5.81−5.71 (m, 2 H), 5.14 (dd, 1 H, J = 17.0, 0.8 Hz), 5.03−4.94 (m, 3 H), 4.17 (m, 1 H), 2.29−2.24 (m, 1 H), 2.08−1.49 (m, 5 H), 1.29−1.24 (m, 1 H); ^{13}C NMR (125 MHz) δ 137.4 (d), 137.0 (d), 134.7 (d), 133.1 (d), 115.9 (t), 115.4 (t), 76.4 (d), 54.8 (d), 41.2 (d), 38.2 (t), 33.5 (t), 28.7 (t); IR (ATR) 3391 (br s, OH), 1640 (m, C═C); HRMS analysis (EI, $C_{12}H_{18}O$ = 178.1358) found *m/z* 178.1361.

(b) Cyclization of Bisdiene 38a. To a solution of **38a** (192.0 mg, 1.0 mmol) in THF (5 mL) was added $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), Ph_3P (39 mg, 0.15 mmol), and Et_3N (0.4 mL, 2.5 mmol). The resulting mixture was refluxed for 24 h, then cooled, and chromatographed on silica (260−400 mesh, 93:7 Hex:EtOAc) to afford **39a** (major diastereomer, 120.0 mg, 62.5%) and **39a** (minor diastereomer, 25.9 mg, 13.5%). **Major diastereomer**: ^{1}H NMR (300 MHz) δ 6.32 (dt, 1 H, J = 16.9, 10.3 Hz), 6.15 (dd, 1 H, J = 15.2, 10.3 Hz), 5.76−5.62 (m, 1 H), 5.38 (dd, 1 H, J = 15.1, 9.6 Hz), 5.13 (dd, 1 H, J = 16.9, 1.3 Hz), 5.01 (dd, 1 H, J = 10.0, 1.4 Hz), 4.96−4.89 (m, 2 H), 3.23 (dt, 1 H, J = 10.0, 4.0 Hz), 2.23−2.15 (m, 1 H), 2.04−1.92 (m, 3 H), 1.81−1.59 (m, 4 H), 1.31−1.16 (m, 3 H), 0.94−0.82 (m, 1 H); ^{13}C NMR (75 MHz) δ 136.5 (d), 136.3 (d), 135.2 (d), 135.1 (d), 116.4 (t), 116.1 (t), 72.6 (d), 55.5 (d), 40.0 (d), 38.5 (t), 33.2 (t), 30.3 (t), 23.3 (t); IR (ATR) 3565 (w, OH), 3417 (br, OH), 1640 (m, C═C), 1603 (w, C═C); Combustion analysis ($C_{13}H_{20}O$ = 81.20% C, 10.48% H) found 81.08% C, 10.53% H. **Minor diastereomer**: ^{1}H NMR (500 MHz) δ 6.33 (dt, 1 H, J = 16.9, 10.2 Hz), 6.09 (ddt, 1 H, J = 15.5, 10.2, 0.8 Hz), 5.77−5.68 (m, 2 H), 5.1 (d, 1 H, J = 17.1 Hz), 5.00 (dd, 1 H, J = 10.1, 1.6 Hz), 4.97−4.93 (m, 2 H), 3.87 (br s,1 H), 2.22−2.18 (m, 1 H), 1.92−1.88 (m, 1 H), 1.81-1.42 (m, 8 H), 0.96−0.93 (m, 1 H); ^{13}C NMR (125 MHz) δ 137.1 (d), 136.9 (d), 136.0 (d), 133.0 (d), 115.9 (t), 115.7 (t), 70.6 (d), 50.5 (d), 38.6, 34.8, 32.9, 30.4, 19.6 (t); IR (ATR) 3565 (w, OH), 3400 (br s, OH), 1651 (m, C═C), 1646 (m, C═C).

Preparation of (4*E*,6*E*)-Ethyl 2-(carboethoxy)-4,6-nonadienoate. To a cooled (0 °C) solution of (4*E*)-1,4-heptadien-3-ol[40,47] (14.0 g, 125 mmol) in CH_2Cl_2 (150 mL) was added $SOCl_2$ (18.6 g, 156 mmol). After ca. 4 h, the reaction mixture was partitioned between ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with additional ether (100 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was distilled (aspirator pressure) to afford a mixture of heptadienyl chlorides (8.07 g, 50%) which was used without further purification.

To a cooled (0 °C) mixture of NaH (1.64 g, 68.2 mmol) and DMSO (29.0 mL, 372 mmol) in THF (100 mL) was added diethyl malonate (19.8 mL, 124 mmol) in THF (5 mL). Upon complete addition, the cold bath was removed, and the resulting mixture was stirred (room temperature) for ca. 1 h. Afterwards, a solution of heptadienyl chlorides (8.10 g, 62 mmol) in THF (5 mL) was added. After 8 h, the reaction mixture was quenched by the addition of water (50 mL) and extracted with ether (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) afforded the malonate derivative (7.65 g, 50%): TLC analysis (95:5 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.03−5.78 (m, 2 H), 5.61−5.47 (m, 1 H), 5.45−5.36 (m, 1 H), 4.09 (q, 4 H, J = 7.2 Hz), 3.29 (dd, 1 H, J = 7.4, 7.6 Hz), 2.54 (t, 2 H, J = 7.4 Hz), 1.97 (q, 2 H, J = 7.4 Hz), 1.16 (t, 3 H, J = 7.2 Hz), 0.88 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (75 MHz) δ 168.5 (s), 135.2 (d), 133.1 (d), 128.5 (d), 126.1 (d), 60.9 (t), 51.7 (d), 31.5 (t), 25.2 (t), 13.8 (q), 13.1 (q); IR (ZnSe, ATR) 1731 (93, C═O), 1635 (C═C, 42); Combustion analysis ($C_{14}H_{22}O_4$ = 66.12% C, 8.72% H) found 66.16% C, 8.63% H.

Preparation of (3*E*,5*E*,11*E*)-7,7-(Dicarboethoxy)-1,3,9,11-tetradecatetraene (40). To a mixture of NaH (800.0 mg, 33.1 mmol) in DMSO (60 mL) was added (4*E*,6*E*)-ethyl 2-(carboethoxy)-4,6-nonadienoate (7.45 g, 29.3 mmol) in DMSO (10 mL) dropwise. The resulting mixture was stirred at room temperature for 0.5 h, after which a solution of 1-iodo-3,5-hexadiene[40,48] (6.10 g, 29.3 mmol) in DMSO (5 mL) was added. The resulting solution was stirred overnight (ca. 8 h), then quenched by the addition of water (50 mL), and extracted with ether (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (95:5 Hex:EtOAc) afforded bisdiene **40** (7.50 g, 76%): TLC analysis (95:5 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.34−6.21 (m, 1 H), 6.08−5.91 (m, 3 H), 5.67−5.59 (m, 2 H), 5.35−5.28 (m, 1 H), 5.09 (d, 1 H, J = 16.9 Hz), 4.96 (d, 1 H, J = 10.0 Hz), 4.17 (q, 2 H, J = 7.2 Hz), 2.65 (d, 2 H, J = 7.6 Hz), 2.06 (q, 2 H, J = 7.4 Hz), 1.95 (m, 4 H), 1.24 (t, 3 H, J = 7.2 Hz), 0.99 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (75 MHz) δ 171.1 (s), 136.9 (d), 135.6 (d), 134.4 (d), 133.7 (d), 131.4 (d), 128.7 (d), 124.5 (d), 115.2 (t), 61.1 (t), 57.9 (s), 35.8 (t), 31.7 (t), 27.0 (t), 25.4 (t), 14.0 (q), 13.3 (q); FT-IR (ATR, ZnSe) 1727 (C═O, 75), 1610 (C═C, 25); Combustion analysis ($C_{20}H_{30}O_4$ = 71.83% C, 9.04% H) found 71.90% C, 8.97% H.

Cyclization of Bisdiene 40. To a solution of **40** (167.0 mg, 0.5 mmol) in THF (5 mL) was added $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting solution was refluxed for 24 h, then cooled, and filtered through silica (60−230 mesh, 95:5 Hex:EtOAc) to afford enediene **41** (160.0 mg, 96%) as a mixture of *E*- and *Z*-double bond isomers (approximately 1:1): TLC analysis (95:5 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.38−6.21 (m, 0.5 H), 6.04−5.83 (m, 1.5 H), 5.73−5.45 (m, 1.5 H), 5.42−5.17 (m, 1.5 H), 4.97−4.81 (m, 2 H), 4.26−3.99 (m, 4 H), 2.37−1.79 (m, 4 H), 1.74−1.58 (m, 5 H), 1.29−1.07 (m, 8 H); ^{13}C NMR (75 MHz) δ 172.1 (s), 170.8 (s), 136.7 (d), 136.6 (d), 134.4

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(d), 131.1 (d), 131.2 (d), 129.1 (d), 127.5 (d), 126.2 (d), 124.6 (d), 115.9 (t) 61.1 (t,) 60.8 (t), 54.7 (s), 43.0 (d), 42.7 (d), 40.6 (d), 40.5 (d), 38.3 (t), 38.2 (t), 37.6 (t), 30.7 (t), 27.4 (t), 17.8 (q), 13.9 (q), 13.8 (q); IR (salt plate) 1729 (80, **C**=O), 1625 (C=C, 45); Combustion analysis ($C_{20}H_{30}O_4$ = 71.82% C, 9.04% H) found 71.91% C, 8.94% H.

Preparation of (4*E*,9*E*)-2-Methyl-7,7-(dicarboethoxy)-2,4,9,11-dodecatetraene (42). To a cooled (0 °C) solution of isopropyl triphenylphosphonium iodide (2.50 g, 5.8 mmol) in THF (40 mL) was added *n*-BuLi (2.5 M, 1.76 mL, 4.40 mmol), and the mixture stirred for 0.5 h. (2*E*,7*E*)-5,5-(Dicarboethoxy)-2,7,9-decatrien-1-al[40] (1.18 g, 4.01 mmol) was then added, and the resulting mixture was stirred overnight (8 h). The mixture was quenched by the addition of water (50 mL), and the mixture was extracted with ether (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) afforded bisdiene **42** (1.00 g, 78%) as a pale yellow oil: TLC analysis (95:5 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.38−6.21 (m, 2 H), 6.16−6.06 (m, 1 H), 5.67 (d, 1 H), 5.58−5.42 (m, 1 H), 5.38−5.22 (m, 1 H), 5.08 (d, 1 H, J = 16.9 Hz), 4.98 (d, 1 H, J = 9.3 Hz), 4.15 (q, 4 H, J = 7.2 Hz), 4.09 (dd, 2 H, J = 1.2, 5.0 Hz), 2.61 (d, 4 H, J = 7.0 Hz), 1.62 (s, 6 H), 1.22 (t, 6 H, J = 7.2 Hz); ^{13}C NMR (75 MHz) δ 170.8 (s), 136.6 (d), 134.9 (d), 130.9 (d), 128.1 (d), 124.6 (d), 123.9 (d), 116.2 (t), 61.2 (t), 57.8 (s), 36.1 (t), 35.7 (t), 25.8 (q), 18.1 (q), 14.1 (q); IR (ATR, ZnSe) 1727 (C=O, 98), 1694 (C=C, 26); Combustion analysis ($C_{19}H_{28}O_4$ = 71.22% C, 8.81% H) found 71.38% C, 8.80% H.

Cyclization of Bisdiene 42. To a solution of **42** (160.0 mg, 0.5 mmol) in THF (5 mL) was added $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting solution was refluxed for 24 h, then cooled, and filtered through silica (60−230 mesh, 95:5 Hex:EtOAc) to afford quantitative recovery of enediene **43** as a pale yellow oil: TLC Analysis (90:10 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.15 (d, 1 H, J = 15.7 Hz), 5.79−5.71 (m, 1 H), 5.45 (m, 1 H), 5.08 (d, 1 H, J = 16.4 Hz), 4.96 (d, 1 H, J = 10.7 Hz), 4.88 (s, 2 H), 4.15 (q, 4 H, J = 7.2 Hz), 2.52−2.48 (m, 2 H), 2.31−2.19 (m, 2 H), 2.05−1.97 (m, 1 H), 1.82 (s, 3 H), 1.23 (t, 6 H, J = 7.2 Hz); ^{13}C NMR (75 MHz) δ 172.6 (s), 141.7 (s), 136.7 (d), 133.8 (d), 131.6 (d), 115.7 (t), 115.1 (t), 61.3 (t), 58.2 (s), 48.8 (d), 45.1 (d), 40.7 (t), 39.5 (t), 37.03 (t), 18.6 (q), 13.9 (q); IR (ATR, ZnSe) 1728 (C=O, 92), 1623 (C=C, 25); Combustion analysis ($C_{19}H_{28}O_4$ = 71.22% C, 8.81% H) found 71.07% C, 8.69% H.

Cyclization of Bisdiene 48. (a) In the Absence of a Deuterium Source. To a solution of **48** (147.0 mg, 0.44 mmol) in THF (6 mL) was added $Pd(OAc)_2$ (5.1 mg, 0.023 mmol) and Ph_3P (11.9 mg, 0.045 mmol). The resulting solution was refluxed for 12 h, then cooled, and concentrated. Chromatography on silica (60−230 mesh, 85:15 Hex:EtOAc) afforded the nondeuterated enediene **49** (125.2 mg, 85%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.08 (d, J = 15.6 Hz, 1H), 5.70−5.58 (m, 1H), 5.26 (dd, J = 15.6, 8.5, Hz, 1H), 4.98−4.87 (m, 4H), 3.53−3.45 (m, 2H), 2.98 (dd, J = 9.5, 9.5 Hz, 1H), 2.91 (br dd, J = 10 Hz, 1H), 2.43 (s, 3H), 2.34 (apparent p, J = 8 Hz, 1H), 2.30−2.17 (m, 1H), 1.87−1.70 (overlapping m's, 2H), 1.75 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.4 (s), 141.2 (s), 135.4 (d), 135.3 (d), 134.0 (s), 129.6 (d), 128.0 (d), 127.5 (d), 116.7 (t), 116.3 (t), 53.0 (t), 52.5 (t), 47.5 (d), 44.2 (d), 35.6 (t), 21.5 (q), 18.4 (q); IR (neat) 1677 (m), 1641 (m, C=C); HRMS analysis ($C_{19}H_{25}NO_2{}^{32}S$ = 331.1606) found *m/z* 331.1576.

(b) In the Presence of Deuterated Methanol. To a solution of **48** (144.0 mg, 0.43 mmol) in THF (6 mL) and CD_3OD (1 mL) was added $Pd(OAc)_2$ (5.1 mg, 0.023 mmol) and Ph_3P (11.9 mg, 0.045 mmol). The resulting solution was refluxed for 12 h, then cooled, and concentrated. Chromatography on silica (60−230 mesh, 85:15 Hex:EtOAc) afforded 10.0 mg of recovered bisdiene and the monodeuterated enediene **49** (104.0 mg, 72%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.08 (d, J = 15.6 Hz, 1H), 5.70−5.58 (m, 1H), 5.26 (dd, J = 15.6, 8.5, Hz, 1H), 4.98−4.87 (m, 4H), 3.53−3.45 (m, 2H), 2.98 (dd, J = 9.5, 9.5 Hz, 1H), 2.91 (dd, J = 9.5, 10 Hz, 1H), 2.43 (s, 3H), 2.34 (apparent p, J = 8 Hz, 1H), 2.30−2.17 (m, 1H), 1.87−1.80 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.4 (s), 141.2 (s), 135.4 (d), 135.3 (d), 134.0 (s), 129.6 (d), 128.0 (d), 127.5 (d), 116.7 (t), 116.3 (t), 53.0 (t), 52.5 (t), 47.5 (d), 44.1 (d), 35.6 (CH_2CH=CH_2 and C(D)HCH=CH_2), 35.2 (C(D)HCH=CH_2), 34.8 (C(D)HCH=CH_2), 21.5 (q), 18.4 (q); HRMS analysis ($C_{19}H_{24}NO_2{}^{32}SD$ = 332.1669) found *m/z* 332.1669.

Preparation of Deuterium-Labeled Bisdienes-Part 1. (a) (2*E*,4*E*)-Ethyl 2-Methyl-6-(triisopropylsiloxy)-2,4-hexadienoate. To a solution of carboethoxyethylidene triphenylphosphorane (4.70 g, 12.8 mmol) in CH_2Cl_2 (15 mL) was added (2*E*)-4-(triisopropylsiloxy)-2-butenal[40,49] (2.82 g, 11.7 mmol). The mixture stirred overnight, after which the mixture was filtered through Celite, and the filtrate was concentrated. Chromatography on silica (60−230 mesh, 80:20 Hex:EtOAc) afforded the unsaturated ester (3.55 g, 93%) as a single stereoisomer: TLC analysis (90:10 Hex:EtOAc) R_f 0.5; ^{1}H NMR (300 MHz) δ 7.21 (d, 1 H, J = 11.7 Hz), 6.74−6.62 (m, 1 H), 6.12 (dt, 1 H, J = 15.3, 4.2 Hz), 4.39 (d, 2 H, J = 6.4 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 1.93 (s, 3 H), 1.21 (t, 3 H, J = 7.1 Hz), 1.06−1.02 (m, 21 H); ^{13}C NMR (75 MHz) δ 168.4 (s), 140.2 (d), 137.5 (d), 124.1 (d), 63.3 (t), 60.4 (t),17.8 (q), 14.2 (q), 12.4 (q), 12.3 (d); IR (salt plate) 1704 (C=O, 78), 1642 (C=C, 64), 1611 (48); Combustion analysis ($C_{18}H_{34}O_3Si$ = 66.21% C, 10.50% H) found 66.23% C, 10.66% H.

(b) (2*E*,4*E*)-Ethyl 2-(Trideuteromethyl)-6-(triisopropylsiloxy-)2,4-hexadienoate. To a cooled (0 °C) mixture of ethyl 2-(diethoxyphosphinyl)-3,3,3-(trideutero)propionate[40] (3.82 g, 15.8 mmol) and NaH (380.0 mg, 15.8 mmol) in THF (100 mL) was added (2*E*)-4-(triisopropylsiloxy)-2-butenal[40,49] (3.82 g, 15.8 mmol). After 2 h, the reaction was quenched by the addition of water (25 mL), and the resulting mixture was extracted with ether (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60−200 mesh, 90:10 Hex:EtOAc) afforded the unsaturated ester (3.76 g, 72%) as a single stereoisomer (>95% deuterium incorporation at the C_2-methyl group determined by NMR): TLC analysis (90:10 Hex:EtOAc) R_f 0.4; ^{1}H NMR (300 MHz) δ 7.20 (d, 1 H, J = 12.6 Hz), 6.73−6.58 (m, 1 H), 6.11 (dt, 1 H, J = 14.6, 4.2 Hz), 4.38 (d, 2 H, J = 4.2 Hz), 4.18 (q, 4 H, J = 6.9 Hz), 1.27 (t, 3 H, J = 6.9 Hz), 0.98 (br s, 21 H); ^{13}C NMR (75 MHz) δ 168.5 (s), 140.3 (d), 137.6 (d), 126.4 (s), 124.1 (d), 63.3 (t), 60.4 (t), 17.9 (q), 11.9 (d); IR (ATR, ZnSe) 1704 (C=O, 72), 1644 (C=C, 35); HRMS ($C_{18}H_{31}D_3O_3Si$ = 329.2466) found *m/z* 329.2472.

Preparation of Deuterium-Labeled Bisdienes-Part 2. (a) (2*E*,4*E*)-1,1-Dideutero-2-methyl-6-(triisopropylsiloxy)-2,4-hexadien-1-ol. To a cooled (0 °C) slurry of $LiAlD_4$ (2.80 g, 66 mmol) in THF (275 mL) was added (2*E*,4*E*)-ethyl 2-methyl-6-(triisopropylsiloxy)-2,4-hexadienoate (34.00 g, 104 mmol). The mixture was stirred overnight (8 h), slowly warming to room temperature. After recooling to 0 °C, the mixture was quenched by the careful addition of water (20 mL) and 10% aqueous HCl (75 mL). The mixture was extracted with ether (2 × 100 mL), and the combined ether layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica (60−200 mesh, 80:10 Hex:EtOAc) afforded the deuterated alcohol (27.60 g, 93%) as a single stereoisomer (>95% deuterium incorporation at C_1 as determined by NMR): TLC analysis (80:10 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.61−6.44 (m, 1 H), 6.03 (d, 1 H, J = 1.2 Hz), 5.72 (dt, 1 H, J = 15.3, 4.9 Hz), 4.29 (d, 2 H, J = 4.9 Hz), 3.05 (br s, 1 H), 1.72 (s, 3 H), 1.06−1.02 (m, 21 H); ^{13}C NMR (75 MHz) δ 136.4 (s), 132.2 (d), 125.0 (d), 124.2 (d), 67.4 (5 line pattern, J_{C-D}), 63.6 (t), 17.8 (q), 13.7 (q), 12.3 (d); IR (salt plate) 3330 (OH, 40), 1640 (C=C, 66); HRMS ($C_{16}H_{30}D_2O_2Si$ = 286.2297) found *m/z* 286.2286.

(b) (2*E*,4*E*)-2-(Trideuteromethyl)-6-(triisopropylsiloxy)-2,4-hexadien-1-ol. To a cooled (−78 °C) solution of (2*E*,4*E*)-ethyl 2-(trideuteromethyl)-6-(triisopropylsiloxy)-2,4-hexadienoate (1.63 g, 4.95 mmol) in THF (50 mL) was added LAH (1.5 M in THF, 9.90 mL, 14.9 mmol). The mixture was warmed to room temperature, and, after ca. 2 h, quenched by the addition of an aqueous solution of Rochelle salt (1 M, 50 mL). The mixture was extracted with ether (2 × 100 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60−200 mesh, 80:20 Hex:EtOAc) afforded the deuterated alcohol (960.0 mg, 65%) as a single stereoisomer: TLC analysis (80:20 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.61−6.45 (m, 1 H), 6.06 (d, 1 H, J = 11.0 Hz), 5.75 (dt, 1 H, J = 14.7, 5.0 Hz),

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4.32 (d, 2 H, J = 4.3 Hz), 4.02 (s, 2 H), 2.46−2.20 (br s, 1 H), 1.10−1.03 (br s, 21 H); ^{13}C NMR (75 MHz) δ 136.4 (s), 132.5 (d), 124.9 (d), 124.3 (d), 68.2 (t), 63.6 (t), 17.9 (q), 11.9 (d); IR (ATR) 3560−3205 (br, OH, 50); HRMS ($C_{17}H_{29}D_3O_2$ = 287.2361, M − C_3H_7 = 244.1813) found *m/z* 244.1807).

Preparation of Deuterium-Labeled Bisdienes-Part 3. (a) (2*E*,4*E*)-1-(Triisopropylsiloxy)-5-(trideuteriomethyl)-2,4-hexadiene. To a cooled (0 °C) solution of (2*E*,4*E*)-1,1-dideutero-2-methyl-6-(triisopropylsiloxy)-2,4-hexadien-1-ol (8.52 g, 30.0 mmol), DMAP (2.20 g, 18 mmol), and Et_3N (4.30 mL, 30 mmol) in CH_2Cl_2 (100 mL) was added *p*-TsCl (6.83 g, 36.0 mmol). After 2 h, ether (100 mL) was added, and the mixture was filtered through Celite. The filtrate was washed sequentially with 50 mL portions of 10% aqueous K_2CO_3, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford tosylate, which was immediately carried forward.

To a cooled (−78 °C) solution of the crude tosylate (7.21 g, 16.5 mmol) in THF (25 mL) was added $LiEt_3BD$ (1 M in THF, 25.0 mL, 25.0 mmol). The resulting mixture was slowly warmed to room temperature overnight (8 h) and then quenched by the addition of methanol (2 mL). Chromatography on silica (60−200 mesh, 95:5 Hex:EtOAc) afforded the deuterated hexadienol derivative (6.00 g, 75%) in high isomeric (>98%) and isotopic (>95% deuterium incorporation at the CD_3-group) purity by NMR analysis: TLC analysis (95:5 Hex:EtOAc) R_f 0.7; ^{1}H NMR (300 MHz) δ 6.59−6.43 (m, 1 H), 5.85 (d, 1 H, J = 1.2 Hz), 5.64 (dt, 1 H, J = 15.3, 4.9 Hz), 4.31 (d, 2 H, J = 4.9 Hz),1.75 (s, 3 H), 1.06−1.02 (m, 21 H); ^{13}C NMR (75 MHz) δ 138.6 (s), 126.1 (d), 124.6 (d), 124.2 (d), 63.6 (t), 17.8 (q), 25.2 (seven line pattern, J_{C-D}), 13.7 (q), 12.3 (d); IR (salt plate) 1640 (C═C, 76); HRMS ($C_{16}H_{29}D_3OSi$ = 271.2411) found *m/z* 271.2415.

(b) (2*E*,4*Z*)-1-(Triisopropylsiloxy)-5-(trideuteriomethyl)-2,4-hexadiene. To a cooled (0 °C) solution of (2*E*,4*E*)-2-(trideuteromethyl)-6-(triisopropylsiloxy)-2,4-hexadien-1-ol (4.00 g, 13.4 mmol) and Et_3N (3.0 mL, 21 mmol) in CH_2Cl_2 (75 mL) was added $MeSO_2Cl$ (1.40 mL, 18 mmol) dropwise. The resulting mixture was slowly warmed up to room temperature and, after 8 h, partitioned between ether (50 mL)−water (50 mL). The aqueous layer was re-extracted with ether (50 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated to afford the mesylate (4.0 g), which was immediately carried forward.

To a cooled (−78 °C) solution of the crude mesylate in THF (25 mL) was added $LiEt_3BH$ (1.0 M IN THF, 16.5 mL, 16.5 mmol). The resulting mixture was slowly warmed to room temperature overnight (8 h) and then quenched by the addition of water (50 mL). The mixture was extracted with ether (3 × 100 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 90:10 Hex:EtOAc) afforded the deuterated hexadienol derivative (3.20 g, 88%) in high isomeric (>98%) and isotopic (>95% deuterium incorporation at the CD_3-group) purity by NMR analysis: TLC analysis (90:10 Hex:EtOAc) R_f 0.7; ^{1}H NMR (300 MHz) δ 6.58−6.44 (m, 1 H), 5.85 (d, 1 H, J = 6.9 Hz), 5.65 (dt, 1 H, J = 15.2, 6.2 Hz), 4.32 (d, 2 H, J = 6.2 Hz), 1.78 (s, 3 H), 1.10 (br s, 21 H); ^{13}C NMR (75 MHz) δ 129.7 (d), 127.2 (s), 126.1 (d), 124.6 (d), 63.8 (t), 25.8 (q), 17.9 (q), 15.2 (d); HRMS ($C_{16}H_{29}D_3OSi$ = 271.2411) found *m/z* 271.2407.

Preparation of Deuterium-Labeled Bisdienes-Part 4. (a) (2*E*,4*E*)-5-(Trideuteriomethyl)-2,4-hexadien-1-ol. To a solution of (2*E*,4*E*)-1-(triisopropylsiloxy)-5-(trideuteriomethyl)-2,4-hexadiene (5.74 g, 21.4 mmol) in THF (25 mL) was added tetrabutylammonium fluoride (1.0 M, 32 mL, 32 mmol). After ca. 2 h, the mixture was concentrated in vacuo, and the residue was purified by flash chromatography on silica (60−200 mesh, 80:20 Hex:EtOAc) to afford the deuterated hexadienol (800 mg, 35%) in high isomeric (>95%) and isotopic (>95% deuterium incorporation at the CD_3-group) purity by NMR analysis: TLC analysis (80:20 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.59−6.43 (m, 1 H), 5.85 (d, 1 H, J = 1.2 Hz), 5.64 (dt, 1 H, J = 15.3, 4.9 Hz), 4.02 (d, 2 H, J = 4.9 Hz), 1.64 (s, 3 H); ^{13}C NMR (75 MHz) δ 135.1 (s), 129.1 (d), 127.6 (d), 124.2 (d), 62.9 (t), 24.8 (seven line pattern, J_{C-D}), 17.8 (q); IR (salt plate) 3318 (OH, 45), 1654 (C═C, 27); HRMS ($C_7H_9D_3O$ = 115.1076) found *m/z* 115.1079.

(b) (2*E*,4*Z*)-5-(Trideuteromethyl)-2,4-hexadien-1-ol.[50] To a solution of (2*E*,4*Z*)-1-(triisopropylsiloxy)-5-(trideuteriomethyl)-2,4-hexadiene (240.0 mg, 1.00 mmol) in THF (2 mL) was added triethylamine trihydrofluoride (0.25 mL, 1.0 mmol). After 8 h, the mixture was concentrated in vacuo, and the residue was purified by flash chromatography on silica (230−400 mesh, 95:5 Hex:EtOAc) to afford the deuterated hexadienol (50.0 mg, 45%) in high isomeric (>98%) and isotopic (>95% deuterium incorporation at the CD_3-group) purity by NMR analysis: TLC analysis (80:20 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.45−6.29 (m, 1 H), 5.76 (d, 1 H, J = 10.8 Hz), 5.67−5.54 (m, 1 H), 4.07 (d, 2 H, J = 6.1 Hz), 3.51−3.22 (br s, 1 H), 1.72 (s, 3 H); ^{13}C NMR (75 MHz) δ 135.3 (s), 128.9 (d), 127.7 (d), 124.2 (d), 62.9 (t), 25.6 (q), 17.3 (seven line pattern, J_{C-D}); IR (ATR) 3560−3240 (OH, 65), 1657 (66, C═C); HRMS ($C_7H_9D_3O$ = 115.1076) found *m/z* 115.1076.

Preparation of Deuterium-Labeled Bisdienes-Part 5. (a) (2*E*,4*E*)-1-Acetoxy-5-(trideuteriomethyl)-2,4-hexadiene. To a cooled (0 °C) mixture of (2*E*,4*E*)-5-(trideuteriomethyl)-2,4-hexadien-1-ol (700.0 mg, 6.1 mmol), Et_3N (1.80 mL, 12.2 mmol), and DMAP (67.0 mg, 0.6 mmol) was added Ac_2O (1.20 mL, 12.2 mmol). The resulting mixture was slowly warmed to room temperature and then partitioned between ether−hexanes (1:1, 20 mL) and water (50 mL). The aqueous layer was re-extracted with ether (2 × 75 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica (60−230 mesh, 95:5 Hex:EtOAc) afforded the deuterated hexadienyl acetate (760.0 mg, 80%): TLC analysis (95:5 Hex:EtOAc) R_f 0.3; Capillary GC analysis (J & W Scientific 30 m DB 1701, 100−275 °C @ 5 °C/min) showed a peak at 2.70 min (99.4% of the peak area); ^{1}H NMR (300 MHz) δ 6.59−6.43 (m, 1 H), 5.85 (d, 1 H, J = 5.2 Hz), 5.64 (dt, 1 H, J = 15.3, 4.9 Hz), 4.41 (d, 2 H, J = 4.9 Hz), 1.83 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR (75 MHz) δ 169.7 (s), 136.1 (s), 130.6 (d), 123.7 (d), 123.2 (d), 64.5 (t), 24.5 (seven line pattern, J_{C-D}), 20.1 (q), 13.7 (q); IR (salt plate) 1736 (C═O, 88), 1654 (C═C, 43); HRMS ($C_9H_{11}D_3O_2$ = 157.1182) found *m/z* 157.1186.

(b) (2*E*,4*Z*)-1-Acetoxy-5-(trideuteriomethyl)-2,4-hexadiene. To a cooled (0 °C) mixture of (2*E*,4*Z*)-5-(trideuteriomethyl)-2,4-hexadien-1-ol (250.0 mg, 2.20 mmol), Et_3N (0.60 mL, 4.4 mmol), and DMAP (25.0 mg, 0.22 mmol) was added Ac_2O (0.40 mL, 4.4 mmol). The resulting mixture was stirred for 8 h, slowly warming to room temperature. The reaction was quenched by the addition of water (50 mL), and the mixture was extracted with ether (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 80:20 Hex:EtOAc) afforded the deuterated hexadienyl acetate (290.0 mg, 84%): TLC analysis (95:5 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.48−6.31 (m, 1 H), 5.73 (dd, 1 H, J = 10.6, 4.8 Hz), 5.61−5.43 (m, 1 H), 4.48−4.42 (m, 2 H), 1.96 (s, 3 H), 1.95 (s, 3 H); ^{13}C NMR (75 MHz) δ 170.2 (s), 136.6 (s), 131.0 (d), 123.9 (d), 123.2 (d), 64.8 (t), 25.5 (q), 20.5 (q), 17.1 (seven line pattern, J_{C-D}); IR (ATR) 1736 (C═O, 99), 1660 (C═C, 62); HRMS ($C_9H_{11}D_3O_2$ = 157.1182) found *m/z* 157.1180.

Preparation of Deuterium-Labeled Bisdienes 50a and 50b. (a) (2*E*,4*E*,9*E*)-2-(Trideuteriomethyl)-7,7-(dicarboethoxy)-2,4,9,11-dodecatetraene (50a).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (870.0 mg, 3.85 mmol) and NaH (46.0 mg, 1.9 mmol) in THF (22 mL) was added Bu_3P (0.10 mL, 0.4 mmol) and $Pd(OAc)_2$ (24.0 mg, 0.1 mmol). To the resulting brown solution was added (2*E*,4*E*)-1-acetoxy-5-(trideuteriomethyl)-2,4-hexadiene (250.0 mg, 1.75 mmol). The resulting mixture was refluxed overnight (8 h), then cooled to room temperature, and quenched by the addition of water (25 mL). The mixture was extracted with ether (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica (260−400 mesh, 90:10 Hex:EtOAc) afforded the deuterated bisdiene **50a** (390.0 mg, 69%) as an inseparable 9:1 (4*E*:4*Z*) mixture of isomers (>95% deuterium at the CD_3-group as determined by NMR): TLC analysis (90:10 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.28−6.08 (m, 2 H), 6.06−5.92 (m, 1 H), 5.67 (d, 1 H, J = 6.4 Hz), 5.51−5.36 (m, 1 H), 5.31−5.18 (m, 1 H), 5.08 (d, 1 H, J = 16.9 Hz), 4.98 (d, 1 H, J = 9.3 Hz), 4.15 (q, 4 H, J = 7.2 Hz), 4.09 (dd, 2 H, J = 1.2, 5.0 Hz), 2.61 (overlapping d,

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4 H, $J = 7.0$ Hz), 1.62 (s, 3 H), 1.22 (t, 6 H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz) δ 170.4 (s), 136.4 (d), 134.7 (d), 133.8 (d), 130.7 (d), 127.9 (d), 124.5 (d), 115.8 (t), 60.8 (q), 57.6 (s), 35.9 (t), 35.6 (t), 25.7 (seven line pattern, J_{C-D}), 17.8 (q), 13.8 (q); IR (salt plate) 1731 (C═O, 93), 1654 (C═C, 37); HRMS ($C_{19}H_{25}D_3O_4$ = 323.2176) found *m/z* 323.2171.

(b) (2*Z*,4*E*,9*E*)-2-(trideuteriomethyl)-7,7-(dicarboethoxy)-2,4,9,11-dodecatetraene (50b).[38] To a solution of (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[39] (795.0 mg, 3.5 mmol) and NaH (85.0 mg, 3.52 mmol) in THF (15 mL) was added Bu_3P (0.10 mL, 0.4 mmol) and $Pd(OAc)_2$ (22.0 mg, 0.1 mmol). To the resulting brown solution was added (2*E*,4*Z*)-1-acetoxy-5-(trideuteriomethyl)-2,4-hexadiene (250.0 mg, 1.6 mmol) in THF (5 mL). The resulting mixture was refluxed overnight (8 h), then cooled to room temperature, and quenched by the addition of water (25 mL). The mixture was extracted with ether (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica (260−400 mesh, 90:10 Hex:EtOAc) afforded the deuterated bisdiene **50b** (340.0 mg, 66%) as an inseparable 12:1 (4*E*:4*Z*) mixture of isomers (>95% deuterium at the CD_3-group as determined by NMR): TLC analysis (90:10 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.29−6.09 (m, 1 H), 6.07−5.9 (m, 1 H), 5.68 (d, 1 H, $J = 11.2$ Hz), 5.52−5.37 (m, 1 H), 5.33−5.16 (m, 1 H), 5.08 (d, 1 H, $J = 16.7$ Hz), 4.98 (d, 1 H, $J = 10$ Hz), 4.09 (q, 4 H, $J = 7.0$ Hz), 2.57 (overlapping d, 4 H, $J = 7.4$ Hz), 1.65 (s, 3 H), 1.15 (t, 6 H, $J = 7.0$ Hz); ^{13}C NMR (75 MHz) δ 170.4 (s), 136.4 (d), 134.7 (d), 133.8 (s), 130.7 (d), 127.9 (d), 124.5 (d), 123.7 (d), 115.8 (t), 60.8 (t), 57.6 (s), 35.9 (t), 35.5 (t), 25.5 (q), 17.1 (seven line pattern, J_{C-D}), 13.8 (q); IR (ATR) 1720 (C═O, 83); HRMS ($C_{19}H_{25}D_3O_4$ = 323.2176) found *m/z* 323.2179.

Cyclization of Deuterium-Labeled Bisdienes. (a) Cyclization of Bisdiene 50a. To a solution of **50a** (162.0 mg, 0.5 mmol) in THF (5 mL) was added $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting solution was refluxed for 24 h, then cooled, and filtered through silica (260−400 mesh, 95:5 Hex:EtOAc) to afford a mixture of deuterated enedienes **51** and **52** (160.0 mg, 98.9%) as a pale yellow oil: TLC analysis (90:10 Hex:EtOAc) R_f 0.3; ^{1}H NMR (300 MHz) δ 6.15 (d, 1 H, $J = 15.7$ Hz), 5.79−5.71 (m, 1 H), 5.45−5.39 (m, 1 H), 5.08−4.81 (m), 4.88 (s, 2 H, 4.15 (q, 4 H, $J = 7.2$ Hz), 2.52−2.21 (m, 4 H), 1.82 (s, 3 H), 1.23 (t, 6 H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz) δ 172.6 (s), 141.7 (s), 136.7 (d), 133.8 (d), 131.6 (d), 115.7 (t), 115.1 (t), 61.3 (t), 58.2 (s), 48.8 (d), 45.1 (d), 40.7 (t), 39.5 (t), 37.0 (t), 18.6 (q), 13.9 (q); ^{2}H NMR (500 MHz) δ 4.82 (−C(═**C**D$_2$)CH$_3$), 1.78 (═C(**C**D$_3$)═CH$_2$); IR (salt plate) 1725 (C═O, 51); HRMS ($C_{19}H_{25}D_3O_4$ = 323.2176) found *m/z* 323.2170.

(b) Cyclization of Bisdiene 50b. To a solution of **50b** (160.0 mg, 0.5 mmol) in THF (5 mL) was added $(MeCN)_4Pd(BF_4)_2$ (11.0 mg, 0.025 mmol), Ph_3P (20.0 mg, 0.075 mmol), and Et_3N (0.35 mL, 2.5 mmol). The resulting solution was refluxed for 24 h, then cooled, and filtered through silica (260−400 mesh, 95:5 Hex:EtOAc) to afford a mixture of deuterated enedienes **51** and **52** (quantitative) as a pale yellow oil: TLC analysis (90:10 Hex:EtOAc) R_f 0.2; ^{1}H NMR (300 MHz) δ 6.11 (d, 1 H, $J = 15.9$ Hz), 5.82−5.62 (m, 1 H), 5.49−5.33 (m, 1 H), 5.05−5.76 (m), 4.12 (q, 4 H, $J = 7.2$ Hz), 2.55−2.38 (m, 2 H), 2.31−1.62 (m, 6 H), 1.21 (t, 6 H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz) δ 172.4 (s), 141.5 (s), 136.6 (d), 133.8 (d), 131.6 (d), 115.6 (t), 114.9 (t), 61.2 (t), 58.2 (s), 48.7 (d), 45.1 (d), 40.7 (t), 39.4 (t), 36.9 (t), 13.9 (q); ^{2}H NMR (500 MHz) δ 4.91 (C(═**C**D$_2$)CH$_3$), 1.77 (C(═CH$_2$)**C**D$_3$); IR (ATR) 1723 (C═O, 94), 1641 (C═C, 52); HRMS ($C_{19}H_{25}D_3O_4$ = 323.2176) found *m/z* 323.2167.

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Supporting Information Available: Experimental procedures and characterization data for syntheses of the bisdiene substrates (27 pages). See any current masthead page for ordering and Internet access instructions.

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