Catalytic Iron-Mediated Triene Carbocyclizations: Stereoselective Five-Membered Ring Forming Carbocyclizations

James M. Takacs,* Young-Chan Myoung, and Lawrence G. Anderson

Department of Chemistry, University of Nebraska–Lincoln, Lincoln, Nebraska 68588-0304

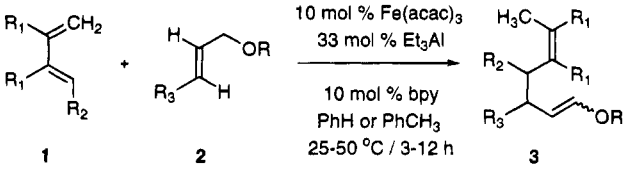
Received August 11, 1994®

The full details of investigations into the regiochemistry and stereochemistry of iron-catalyzed carbocyclizations of 2,7,9-decatriene derivatives to form five-membered carbocyclic ring systems are described. The roles of the allylic substituent, the alkene geometry, diene substitution, and the influence of resident stereogenic centers incorporated in the tether chain connecting the reacting 1,3-diene and alkene subunits are discussed.

Transition-metal-mediated carbon–carbon bond construction reactions are becoming increasingly important in organic synthesis.[1] Of particular note are the growing number of new metal-mediated carbocyclization reactions,[2–15] novel stoichiometric and catalytic cyclization reactions that provide the synthetic chemist with an increasingly versatile array of strategy-level reactions for the construction of ring systems relevant to natural products synthesis. Our interest is in defining new catalytic transition-metal-mediated carbocyclization strategies and in understanding the role of the catalytic metal center in controlling the reaction selectivity.

Two primary considerations have guided our studies into the development of new synthetic methodologies in this area. (1) The homogeneous metal catalyst is chosen so as to promote the facile carbon–carbon bond construction between readily accessible, stable, mutually nonreactive functionalities, functionalities such as the unactivated alkene and diene moieties described herein that might be readily introduced in the normal course of synthesis. This in contrast to methods that require the presence of C–H activating groups, C–X functional groups, or highly strained functionalities in the substrate, groups whose sole purpose is to facilitate the metal-mediated carbon–carbon construction, and whose introduction into the substrate and/or subsequent removal from the product typically requires extra synthetic steps. Trost has coined the term, "atom economy" to describe this idea in the context of his studies on catalytic palladium-mediated carbocyclizations of unsaturated substrates.[16] (2) To the fullest extent possible, we seek to exploit metal-centered-effects as the dominant directing effect on the reaction selectivity (*i.e.*, chemoselectivity, regioselectivity, diastereoselectivity, and stereoinduction). In light of these considerations, we have focused on reactions in which the unsaturated functionalities within the substrate molecule first template around the metal center and then undergo cycloisomerization to a well-ordered metallacyclic intermediate forming the crucial carbon–carbon bond via oxidative cyclization (coupling). In such reactions, the structures and reactivities of the relevant organometal intermediates play a dominant role in controlling the regiochemical and stereochemical course of the carbon–carbon bond construction.

We have recently reported the catalytic iron-mediated cross-coupling reaction of a 1,3-diene with an allylic ether, illustrated below in the coupling of the 1,3-diene **1** with the allylic ether **2**.[17] The active catalyst is conveniently prepared in situ via the reduction of iron(III) 2,4-pentanedioate ($Fe(acac)_3$) by 3.1 equiv of triethylaluminum (Et_3Al). The coupled product **3** can be described, at least formally, as a [4 + 4]-homologue of the classical Alder ene reaction.



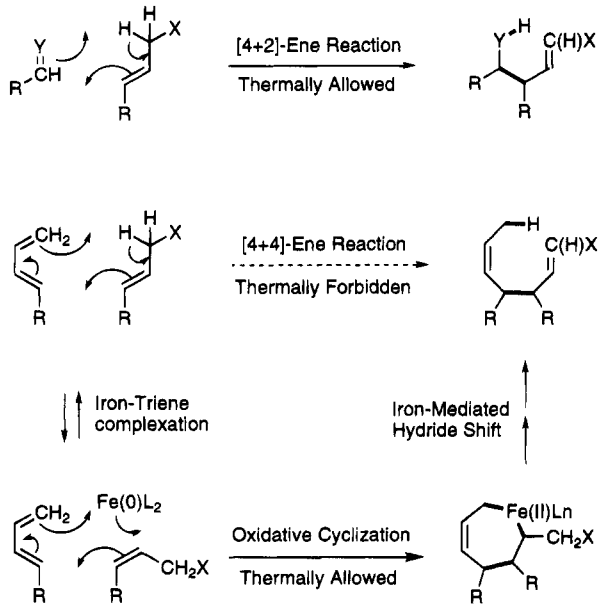
Our continuing efforts are directed toward developing this methodology for the efficient carbocyclization of trienes.[18–24] A number of variations of the ene reaction (*e.g.*, thermal,[25] Lewis acid-catalyzed,[25] and more recently, catalytic transition-metal-mediated[4,16,26] and met-

® Abstract published in *Advance ACS Abstracts,* October 15, 1994.

(1) Hegedus, L. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1993.
(2) Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545–6.
(3) Rigby, J. H.; Ogbu, C. O. *Tetrahedron Lett.* **1990**, *31*, 3385–8.
(4) Pearson, A. J.; Zettler, M. W. *J. Am. Chem. Soc.* **1989**, *111*, 3908–18.
(5) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813–1819.
(6) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323–34.
(7) Lautens, M.; Tam, W.; Edwards, L. G. *J. Org. Chem.* **1992**, *57*, 8–9.
(8) Oppolzer, W.; DeVita, R. J. *J. Org. Chem.* **1991**, *56*, 6256–7.
(9) Larock, R. C. *Pure Appl. Chem.* **1990**, *62*, 653–60.
(10) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965–6.
(11) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343–6.
(12) Brunner, H.; Muschiol, M.; Prester, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 652–653.
(13) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42.
(14) Takacs, J. M.; Zhu, J. *Tetrahedron Lett.* **1990**, *31*, 1117–20.
(15) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678–9.
(16) Trost, B. M. *Science (Washington, D. C.)* **1991**, *254*, 1471–7.
(17) Takacs, J. M.; Anderson, L. G.; BinduMadhavan, G. V.; Creswell, M. W.; Seely, F. L.; Devroy, W. F. *Organometallics* **1986**, *5*, 2395–8.
(18) Takacs, J. M.; Weidner, J. J.; Takacs, B. E. *Tetrahedron Lett.* **1993**, *34*, 6219–6222.
(19) Takacs, J. M.; Myoung, Y. C. *Tetrahedron Lett.* **1992**, *33*, 317–320.
(20) Takacs, J. M.; Newsome, P. W.; Kuehn, C.; Takusagawa, F. *Tetrahedron* **1990**, *46*, 5507–5522.
(21) Takacs, B. E.; Takacs, J. M. *Tetrahedron Lett.* **1990**, *31*, 2865–8.
(22) Takacs, J. M.; Anderson, L. G.; BinduMadhavan, G. V.; Seely, F. L. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1013–5.
(23) Takacs, J. M.; Anderson, L. G.; Creswell, M. W.; Takacs, B. E. *Tetrahedron Lett.* **1987**, *28*, 5627–30.
(24) Takacs, J. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1987**, *109*, 2200–2.

0022-3263/94/1959-6928$04.50/0

Scheme 1. An Iron-Mediated Stepwise Equivalent to the Thermally Forbidden [4 + 4]-Homologue of the Alder Ene Reaction



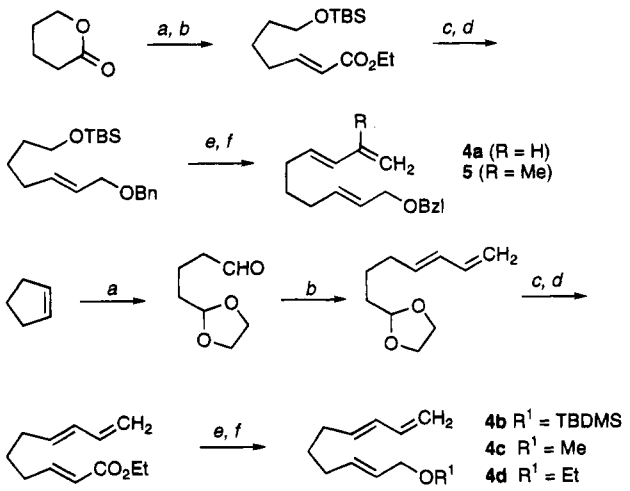
allo-ene reactions[27]) are under development and several are now widely used as strategy-level reactions in organic synthesis. In contrast, the thermally-forbidden [4 + 4]-ene homologue, and its operational equivalent illustrated in Scheme 1, were unknown prior to our work. Consequently, the catalytic iron-mediated ene reaction makes available a new bond construction strategy for synthesis. This paper describes the full details of our studies into the iron-catalyzed carbocyclizations of 2,7,9-decatriene ethers to form five-membered carbocyclic ring systems. In particular, we describe our current understanding of the fundamental substrate and reaction parameters that influence the chemical efficiency and stereoselectivity of the cyclization.

Results and Discussion

A range of decatriene substrates undergo intramolecular five-membered ring-forming iron-catalyzed ene-carbocyclization with good efficiency. These facile intramolecular cyclizations are somewhat surprising in light of the results obtained in our early attempts at intermolecular coupling of 4-substituted 1,3-dienes or 3-substituted allylic ethers.[17,22] Under reaction conditions where 2,3-dimethyl-1,3-butadiene (DMB) undergoes facile coupling to the parent allyl benzyl ether (**2a**) (R = CH_2Ph; R^3 = H), 1,3-octadiene (**1b**) (R^1 = H; R^2 = C_4H_9) fails to couple to **2a**. Similarly, DMB fails to couple to crotyl benzyl ether (**2b**) (R = CH_2Ph; R^3 = CH_3). The role of intramolecularity in accelerating the rate of classical five-membered ring-forming reactions is well documented;[28] however, it is prudent to recognize that such effects differ substantially given the conformational requirements of organometal intermediates.[29-33]

Factors Influencing the Chemical Efficiency of Iron-Catalyzed Carbocyclization. The parent (2*E*,7*E*)-1-(benzyloxy)-2,7,9-decatriene ether (**4a**) is prepared in a straightforward manner as illustrated in Scheme 2, method A. The route features the one-pot half-reduction–two-carbon homologation procedure we introduced several years ago for the elaboration of esters and lactones.[34] **4a** is efficiently cyclized under our standard conditions (dropwise addition of 3.1 equiv of Et_3Al to a cooled (0–5 °C) solution of **4a**, 10–20 mol% $Fe(acac)_3$, and an equivalent amount of 2,2′-bipyridine (bpy) in 10 mL of benzene, or preferably toluene) or by addition of

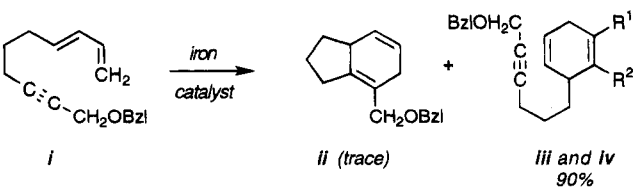
Scheme 2



[a] **Method A**: (a) (1) 1.1 Li[$(EtO)_2P(O)CHCO_2Et$], THF, −78 °C, (2) 1.1 DIBAL-H, −78–25 °C (83%); (b) TBDMSCl, Et_3N, cat. DMAP, DCM (100%); (c) 2.2 DIBAL-H, THF, 0 °C (92%); (d) NaH, $PhCH_2Br$, DMF, (78%); (e) cat. *p*-TsOH, MeOH (97%); (f) (1) $(COCl)_2$, DMSO, Et_3N, DCM, (2) Li[$Ph_2P(O)C(R)HCHCH_2$], HMPA, THF (R = H (58%), R = Me (52%)). **Method B**: (a) (1) O_3, CH_2Cl_2–$HOCH_2CH_2OH$, −78 °C, (2) *p*-TSA, 25 °C, (3) $NaHCO_3$, (4) Me_2S; (b) Li[$Ph_2P(O)CH_2CHCH_2$], HMPA, THF (78%); (c) cat. HCl, aqueous acetone (60%); (d) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN (74%); (e) 2.2 DIBAL-H, THF, 0 °C (74%); (f) NaH, R^1I, DMF, (R^1 = Me, 83%; R^1 = Et, 87%); (g) TBDMSCl, Et_3N, cat. DMAP, DCM (R^1 = TBDMS, 89%).

(29) For example, consider the facility with which certain macrocyclic ring systems are formed via the nickel-mediated cyclization of bis-allylic bromides. See: Corey, E. J.; Kirst, H. A. *J. Am. Chem. Soc.* **1972**, *94*, 667.

(30) In contrast, attempts to execute the iron-catalyzed intramolecular [4 + 2]-cycloaddition of a simple five-membered ring-forming dienyne substrate met with failure. The iron-catalyzed intermolecular cycloaddition of simple 1,3-dienes with disubstituted alkynes is well known.[31-33] Treatment of dienyne **i** with the standard iron catalyst effects the rapid consumption of starting material, yet, only a trace amount of the expected intramolecular cycloaddition product **ii** is formed. Surprisingly, intermolecular pathways are preferred to the intramolecular reaction. A mixture of regioisomeric intermolecular cycloaddition products, **iii** (R^1 = $(CH_2)_3CH$=CHCH=CH_2, R^2 = Ph), and **iv** (R^1 = Ph, R^2 = $(CH_2)_3CH$=CHCH=CH_2), are isolated in high yield. In contrast, similar nickel- and rhodium-catalyzed [4 + 2]-cycloadditions proceed in an intramolecular fashion.[10,15]



(25) Boyd, G. V. In *Chemistry of Double Bonded Functional Groups*; S. Patai, Ed.; Wiley: Chichester, UK, 1989; Vol. 2, Part 1, pp 477–525.

(26) Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992**, *114*, 773–774.

(27) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941–8.

(28) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(31) Carbonaro, A.; Greco, A.; Dall'Asta, G. *J. Org. Chem.* **1968**, *33*, 3948–3950.

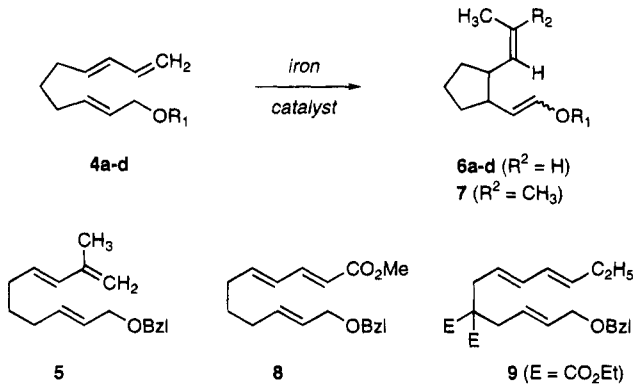
(32) Genet, J. P.; Ficini, J. *Tetrahedron Lett.* **1979**, *20*, 1499–1502.

(33) Dieck, H. t.; Diercks, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 778–779.

(34) Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257–1260.

4a to a solution of prereduced iron catalyst and followed by stirring the resulting mixture at ambient or slightly elevated temperature (50–55 °C) for 3–12 h.[35] It is noteworthy that triene **4a** undergoes regioselective ene-carbocyclization to yield only the disubstituted cyclopentane **6a** ($R^1 = CH_2Ph$, $R^2 = H$), the product resulting from carbon–carbon bond formation between the internal ends of the diene and alkene moieties. To date, no evidence for the products resulting from regioisomeric sites of C–C bond construction has been found in the reaction of any five-membered ring-forming substrate. The factors which influence the chemical efficiency and the stereochemistry of the cyclization to form five-membered rings are discussed below.

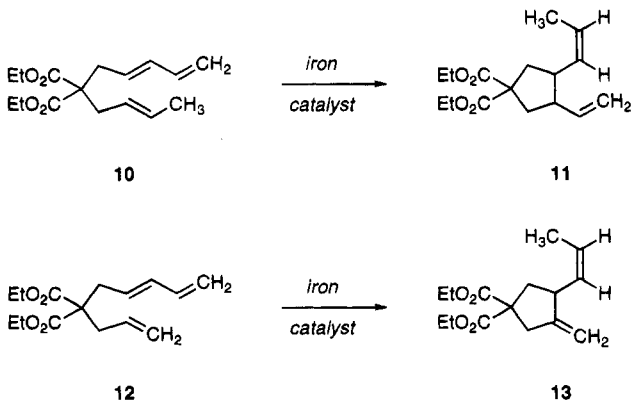
The choice of ligand plays an important role in the efficiency of the ene carbocyclization reaction.[22] Unless otherwise noted 2,2′-bipyridine (bpy), added in equimolar amounts to the $Fe(acac)_3$, is the ligand employed for the cyclizations described herein. Certain diazadienes,[36] pyridyl imines, pyridyl oxazolines, and bis-oxazolines[18] are also applicable for this chemistry. 1,10-Phenanthroline can be employed; however, in several cases the stereoselectivity of cyclization is somewhat diminished. In the case of triene ether **4a**, no reaction was observed when 1 equiv (relative to the amount of iron present) of bis(diphenylphosphino)ethane (diphos), (+)-DIOP, or triphenylphosphine is used in place of the bpy ligand or when 2 equiv of bpy are added. Similarly, strongly coordinating solvents shut down the catalytic reaction. In contrast to the reaction in benzene or toluene, no cyclization is observed in THF or ether solvent. Benzene was originally employed as the reaction solvent of choice; however, toluene affords comparable results and its use in place of benzene is recommended.



In general, additional substituents on the diene moiety slow down the rate of iron-catalyzed cyclization. Nonetheless, the 9-substituted triene **5** cyclizes in good yield (>65%) to afford cyclopentane **7** ($R^1 = CH_2Ph$, $R^2 = CH_3$). A direct competition experiment, in which the reaction is monitored at low conversion, shows that **4a** is consumed roughly 50% faster than the methyl-substituted triene **5**. Other disubstituted-dienes have not yet been extensively examined. In preliminary studies we find that the carboxymethyl-substituted substrate **8** yields a complex mixture of reaction products, and the ethyl-substituted substrate **9** fails to react under the standard conditions.

The double bond geometries of the 1,3-diene and alkene subunits play important roles in the efficiency of the cyclization. The iron-catalyzed cyclizations of other *E*/*Z*-triene stereoisomers have been examined, and while they give rise to interesting stereochemical consequences (*vide infra*), they generally cyclize with lower efficiency (<50% yield) and often complex mixtures of noncyclized products are obtained along with the desired cyclized products.[21,37] *Consequently, (2E,7E)-2,7,9-decatrienes are the preferred substrate for five-membered ring-forming cyclization.* A number of very good methods for the stereoselective preparation of the 1,3-diene moiety have been developed.[38]

Many of the triene substrates that we have investigated to date bear an allylic oxygen substituent on the alkene subunit; however, this functionality is not required for cyclization.[39] For example, triene **10** undergoes ene carbocyclization to divinylcyclopentane **11** in 79% yield. Furthermore, triene **12**, which lacks the required hydrogen-bearing substituents at the terminus for the ene carbocyclization mode, nonetheless undergoes efficient iron-catalyzed cyclization. The product mixture, isolated in 80% yield, consists of predominantly **13** (about 80% of the mixture) along with a mixture of at least three other isomers. Thus, triene **12** undergoes carbocyclization via a formal hydrovinylation pathway. No attempt has been made as yet to optimize this hydrovinylation reaction.



The cyclized products obtained from triene ether substrates bearing an allylic oxygen substituent contain latent aldehyde functionality that is useful for subsequent synthetic transformations. With such substrates, there is a potential role for the oxygen protecting group in the cyclization reaction.[22] Comparing the reactivity of the series of trienes **4a–d** (R^1 = CH_2Ph, CH_3, CH_2CH_3, TBDMS) in direct competition experiments, at low conversion we find only small differences (10–30%) in

(35) The preformed iron catalyst solution is kinetically unstable toward deposition of metallic iron. Consequently, in cases where the substrate is stable to the addition of Et_3Al, more reproducible results are obtained when the iron is reduced in the presence of the triene substrate. It should be noted that neither Et_3Al nor $Fe(acac)_3$ alone is sufficient to catalyze the ene carbocyclization of **4**. For a more detailed discussion of the catalyst preparation, see ref 20.

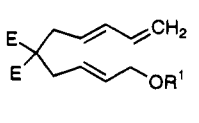
(36) Dieck, H. t.; Diercks, R.; Stamp, L.; Bruder, H.; Schuld, T. *Chem. Ber.* **1987**, *120*, 1943–50.

(37) Mode selectivity is typically a serious problem faced when developing new transition-metal-catalyzed cyclization reactions. Transition metal catalysts often have several reaction modes available for organic substrates. Optimizing the desired mode relative to competing modes is usually done empirically. In the present chemistry the mass balance for the cyclization reactions is generally high. Two undesired reaction modes compete in cases where the iron-catalyzed cyclization is not favorable: iron-catalyzed alkene (and/or diene) isomerization and iron-mediated reduction. These two side reactions usually account for the remainder of the reaction products.

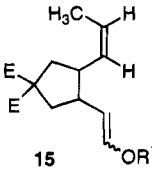
(38) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley-Interscience: New York, 1990.

(39) For example, see the successful cyclization of compound **22** in ref 21.

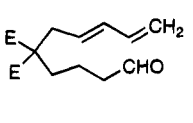
the relative rates of cyclization. Similarly, the benzyl ether **14a** ($R^1 = CH_2Ph$) and the silyl ether **14b** (R^1 = TBDMS) undergo iron-catalyzed carbocyclization to **15** in 90 and 70% yields, respectively.[40] However some oxygen protecting group is apparently required for successful iron-catalyzed carbocyclization. The allylic alcohol **14c** ($R^1 = H$) affords the acyclic aldehyde **16** in low yield upon treatment with the iron catalyst,[41] but no detectable cyclization. Similarly, not all types of protecting groups are suitable. For example, the allylic acetate **14d** ($R^1 = Ac$) fails to cyclize under the standard reaction conditions. *Overall, we find that benzyl or silyl protecting groups are generally the most successful.*



14a-d

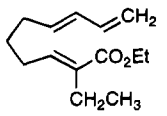


15

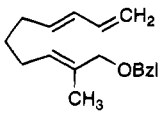


16

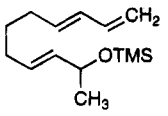
Additional substituents on the alkene moiety can be tolerated if they are electron-withdrawing in nature. For example, triene ester **17** undergoes iron-catalyzed ene-carbocyclization in high yield;[20] however, the analogous allylic ether-containing substrate **18** fails to cyclize under the standard conditions. Similarly, the methyl-substituted triene **19** did not cyclize under the standard conditions.



17



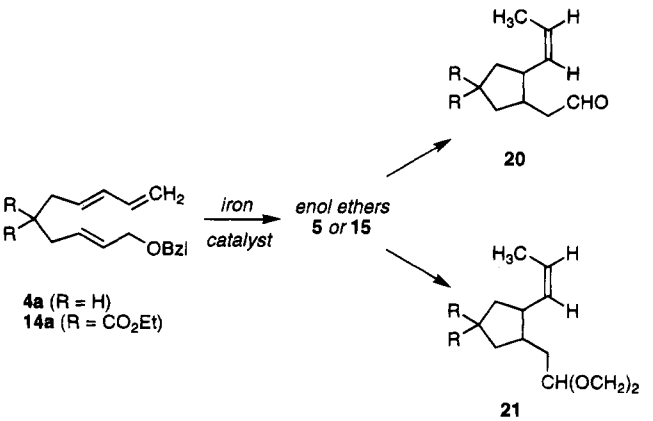
18



19

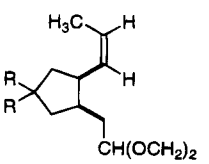
Stereochemical Aspects of the Iron-Catalyzed Carbocyclization. In the preceding paragraphs, we discussed aspects of the iron-catalyzed cyclization that relate to the efficiency of the process. There are several important stereochemical aspects to the cyclization as well. These include the stereochemistry of the newly formed double bonds in the product, the relative stereochemistry of the substituents on the newly formed cyclopentane ring (simple diastereoselectivity[42]), and in the case of chiral substrates stereoinduction from a resident stereogenic center. Our current understanding of these stereochemical aspects is discussed below.

Stereochemistry of the Newly Formed Double Bonds. The iron-catalyzed cycloisomerization of triene ether **4a** ($R^1 = CH_2Ph$) affords a 60:40 mixture of diastereomeric enol ethers **5** ($R^1 = CH_2Ph$). Similarly, **14a** ($R^1 = CH_2Ph$) affords a 60:40 mixture of enol ethers **15** ($R^1 = CH_2Ph$). The diastereomeric products are isomeric about the newly formed enol ether double bond. This lack of stereochemical control in formation of the enol ether is of little practical consequence, since it is subsequently removed upon hydrolysis to aldehyde **20** (aqueous HCl in acetone) or acetalization (excess $HOCH_2CH_2OH$/cat. *p*-TsOH or PPTS/THF/25 °C) to the corresponding ethylene acetal **21**. Besides liberating synthetically useful functionality, these latter conversions have an additional practical benefit. In most of the cyclizations studied to date, the isomeric starting materials and product enol ethers have similar elution characteristics on normal phase silica. Hydrolysis or acetalization of the crude reaction product removes this degeneracy,[37] greatly facilitating the isolation of the desired cyclized material. Typically, the enol ethers are not purified after iron-catalyzed cyclization; rather the crude reaction mixture is subjected to acetalization or hydrolysis conditions, the resulting crude product analyzed by capillary GC or HPLC, and the desired product isolated by chromatography on silica.

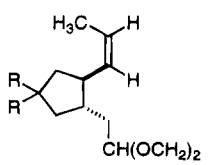


While the enol ether double bond is formed in (or possibly equilibrated to) essentially a stereorandom mixture, the second double bond generated in the course of the ene carbocyclization is formed with high stereochemical control. *The propenyl side chain is always formed predominantly (>95%) with the Z-geometry as indicated.* It should be noted that small amounts of two regioisomeric alkenes are detected in some cases. These will be discussed below, *vide infra*.

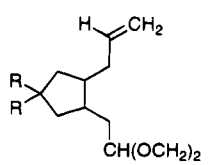
Relative Stereochemistry of the Substituents on the Newly Formed Cyclopentane Ring. Formation of a carbon–carbon single bond between two sp^2-hybridized centers can in principal give rise to two racemic diastereomers. Heathcock termed the preference for formation of one of these diastereomers over the other as simple diastereoselection.[42] In the present case iron-catalyzed cyclization of triene **4** or **14** could afford, after acetalization, either disubstituted cyclopentane *cis*-**21** or *trans*-**21**. In the event, cyclization of the (2*E*,7*E*)-triene **4a** gives predominantly the corresponding *cis*-disubstituted cyclopentane *cis*-**21a** (81% overall yield). The product is judged to be predominantly a single stereoisomer (>96%)[43] by capillary gas chromatographic analysis of the crude acetalization product and confirmed by high field ^1H and ^{13}C NMR spectroscopic analysis.



cis-**21a** (R = H)
b (R = CO_2Et)



trans-**21a** (R = H)
b (R = CO_2Et)



22

(40) We have not isolated *cis*-**22a** in pure form; however, the same saturated product is formed by hydrogenation of *cis*-**21a** and samples enriched in *cis*-**22a**. This experimental result and the available spectroscopic data from samples enriched in *cis*-**22a** lead to the tentative assignment of the structure as shown.

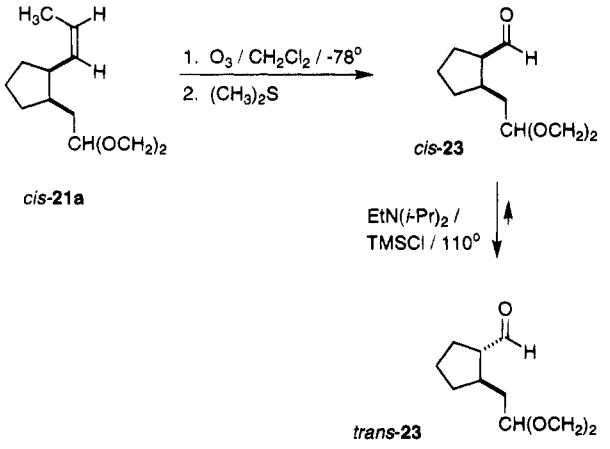
(41) Hubert, A. J.; Georis, A.; Warin, R.; Teyssie, P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 366–370; see also ref 36.

(42) Heathcock, C. H. In *Asymmetric Synthesis: Stereodifferentiating Addition Reactions, Part B*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, pp 110–212.

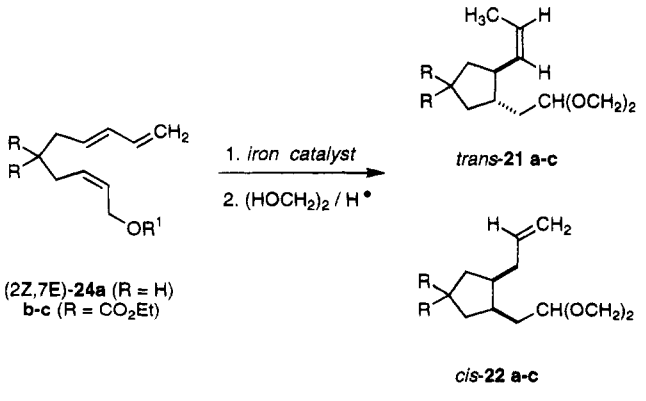
(43) We have been unable to isolate and rigorously characterized all of the other isomers formed in the cyclization; however, no other resolved peak accounts for more than 0.5% of the peak area in the capillary GC chromatograph (FID detection).

The cis relative stereochemistry in *cis*-**21a** was established as outlined in Scheme 3. Ozonolysis affords the half-protected dialdehyde *cis*-**23**. Attempts to effect the acid- or base-catalyzed epimerization of *cis*-**23** under a variety of conditions suffered from competing addition and aldol reactions. As a result, an attempt was made to prepare the silyl enol ether, with the expectation that subsequent hydrolysis could be used to establish the relative stereochemistry. Surprisingly, under the conditions of attempted silyl enol ether formation (Hunigs base/TMSCl/110 °C) *cis*-**23** undergoes base-catalyzed epimerization to the more stable diastereomer *trans*-**23**.

Scheme 3. Establishing the Cis Relative Stereochemistry of Product Obtained from 4a

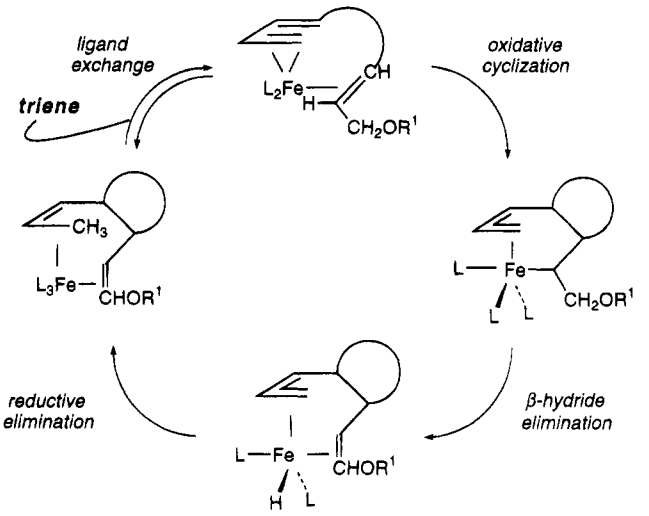


The sense and extent of simple diastereoselection observed in the five-membered ring forming cyclizations of trienes is markedly dependent upon the geometry of the double bond in the 2-position of the triene substrate. In contrast to the (2*E*,7*E*)-triene **4a**, cyclization of the isomeric (2*Z*,7*E*)-triene **24a** affords predominantly the trans-disubstituted cyclopentane, *trans*-**21a**. Only about 2% of *cis*-**21a** is formed, but the mixture also contains about 10% of a cis-disubstituted cyclopentane to which structure *cis*-**22a** is tentatively assigned.[40]



The observation that either *cis*-**21** or *trans*-**21** can be obtained stereoselectively depending on the choice of triene substrate stereochemistry is intriguing. Unfortunately, we find that the chemical yields for the cyclization of 2*Z*-triene substrates tend to be lower than for the 2*E*-diastereomer (44% in the case of **24a**) and the degree of stereoselectivity is highly dependent on the exact structure of the substrate. For example, the geminal disubstituted (2*Z*,7*E*)-triene **24b** ($R^1 = CH_2Ph$) cyclizes with poor selectivity affording a 2:1 *trans*-**21b**:*cis*-**22b** mixture in 63% yield. Surprisingly, the sense of stereoselectivity can be reversed by the nature of the oxygen protecting group. The (2*Z*,7*E*)-triene **24c** ($R^1 = CH_3$) cyclizes in 43% yield giving a 1:2 *trans*-**21c**:*cis*-**22c** mixture.

Scheme 4. A Working Model for the Catalytic Iron-Mediated Carbocyclizations of Trienes



To summarize the observations regarding simple diastereoselection, *we find that (2E,7E)-decatrienes (e.g., **4** or **14**) reliably give cis-disubstituted cyclopentanes (i.e., cis-**21a,b**) with high simple diastereoselectivity*. (2*Z*,7*E*)-Triene substrates are somewhat unpredictable. In some cases *trans*-disubstituted cyclopentanes are obtained with good selectivity, in others the selectivity and/or chemical yield is poor.

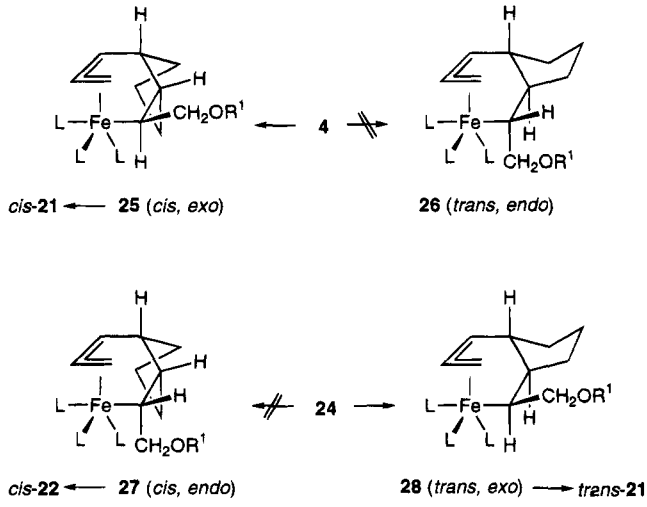
A detailed understanding of the origin of the simple diastereoselectivity is not yet at hand, however consider our working model for the catalytic cycle as outlined in Scheme 4. This hypothesis, which is consistent with mechanistic studies on the iron-mediated diene-to-alkene cross-coupling reaction carried out by Grevels and coworkers[44] and labeling studies carried out in our laboratory,[17] accounts for the different pathways followed by the two stereoisomeric triene substrates. Note that all of the new stereocenters in the product are generated relative to each other in the oxidative cyclization of triene complex. (This includes any stereoinduction from resident stereogenic centers in the tether connecting the diene and alkene functionalities, *vide infra*.)

The origin of the simple diastereoselection (and stereoinduction, *vide infra*) is apparently tied up in the diastereoselective complexation and/or selective oxidative cyclization of the intermediate triene complexes. For the (2*E*,7*E*)-triene substrate (*i.e.*, **4** or **14**) two diastereomeric iron–triene complexes are possible, the complexes differing with respect to facial discrimination in complexation of the alkene moiety.[45] Oxidative cyclization of the triene complex is a process that must be stereospecific and syn. Therefore, each complex must lead to a different diastereomeric metallacycle, one possessing a cis ring fusion and arising via a pseudo-exo mode of cyclization (*e.g.*, **25**) and the other possessing a trans ring fusion and arising via a pseudo-endo mode (*e.g.*, **26**) (Scheme 5). The observed product is *cis*-**21**, implicating metallacycle **25**

(44) Aliyama, T.; Grevels, F.-W.; Reuvers, J. G. A.; Ritterkamp, P. *Organometallics* **1983**, *2*, 157–160.

(45) Equivalently, complexation of the iron to the other face of the diene system would give rise to the enantiomeric series of products.

Scheme 5. A Hypothesis for the Origin of Simple Diastereoselection in Five-Membered Ring-Forming Cyclizations

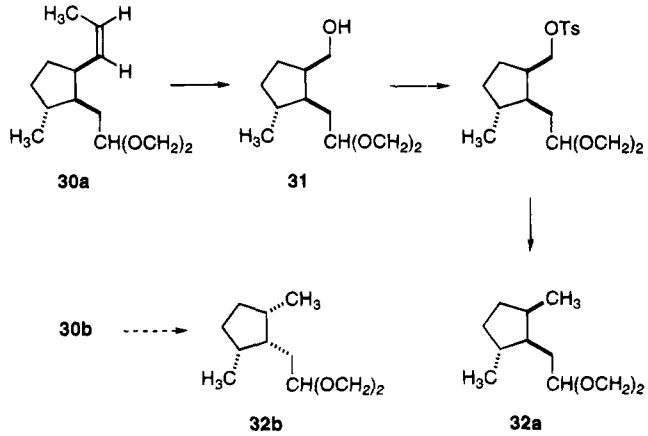


as the relevant intermediate. By similar reasoning, metallacycle **28** accounts for the formation of *trans*-**21** from the (2*Z*,7*E*)-triene **24**.

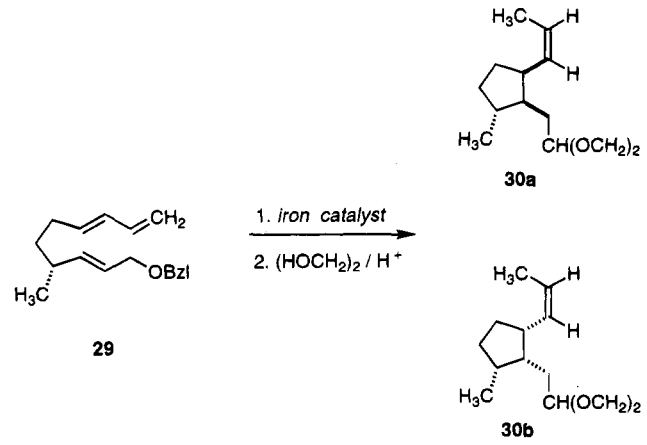
The results obtained to date point to an empirical model for five-membered ring formation in which the formation of a pseudo-exo intermediate is preferred over formation of a pseudo-endo intermediate. That is (2*E*,7*E*)-triene ether **4** apparently reacts via the pseudo-exo intermediate **25** to give predominantly the *cis*-cyclopentane. The (2*Z*,7*E*)-triene ether **24** also reacts via a pseudo-exo intermediate (*i.e.*, **28**); however, **28** bears a *trans*-fused bicyclic ring system and consequently leads to the observed cyclopentane *trans*-**21**. In this latter substrate the small amount of *cis*-**22** obtained possesses a terminal alkene side chain, a result which suggests that reaction via the pseudo-endo mode of cyclization controls the propenyl side chain double bond regiochemistry. This model accounts for the results observed to date and further suggests that not only the alkene geometry, but the diene geometry and the length and nature of the tether chain connecting the diene and alkene functionalities will influence the sense and extent of simple diastereoselection observed in iron-catalyzed cyclization. These latter expectations have been born out experimentally in related substrates.[21,23]

Diastereoselectivity in the Cyclization of Substrates Containing a Resident Stereogenic Center: 1,2- and 1,3-Stereoinduction. Substrates containing a resident stereogenic center in the carbon chain connecting the diene and alkene functionalities can give rise to additional stereoisomers upon ene carbocyclization. For example, consider the iron-catalyzed cyclization of triene **29**, a triene that possesses a resident methyl-bearing stereocenter adjacent to the alkene subunit. The cyclization could reasonably give any of four isomeric cyclopentanes, the ratio of which would depend upon the extent of the simple diastereoselectivity and the 1,2-stereoinduction. Since triene **29** possesses the (2*E*,7*E*)-stereochemistry, we expect high simple diastereoselection and a cis relative stereochemistry between the propenyl and acetal-bearing side chains (*i.e.*, structure **30**). This leaves the issue of 1,2-stereoinduction from the resident methyl substituent, and therefore, potentially two diastereomers, **30a** and **30b**, are expected. In the event, iron-catalyzed carbocyclization/acetalization proceeds in

Scheme 6. Conversion of Cyclization Product 30a to 32a



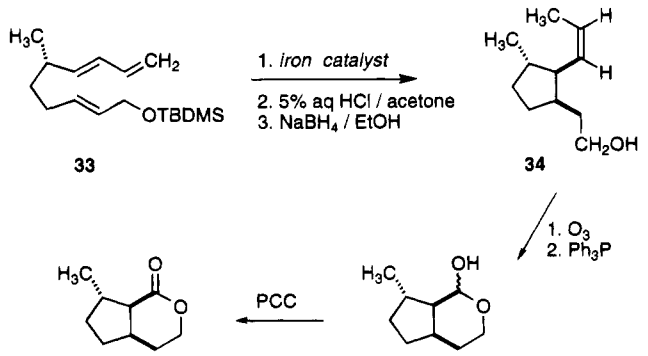
62% overall yield and a single cyclopentane is isolated. Capillary GC analysis of the crude reaction mixture after acetalization fails to resolve any other isomer in more than a few tenths of a percent abundance. Spectroscopic analysis supports the conclusion that the 1,2-stereoinduction, even by the relatively nonsterically demanding methyl-substituent, is greater than 99:1.



The trans-sense of 1,2-stereoinduction, that is stereoselective formation of **30a**, is established by conversion to the dimethyl derivative **32a**. Ozonolysis of **30a** followed by $NaBH_4$ workup gives the primary alcohol **31** (Scheme 6). Treatment with *p*-toluenesulfonyl chloride in pyridine gives the intermediate tosylate, which undergoes displacement with $LiEt_3BH$ to give the dimethyl derivative **32a**. Capillary GC analysis of this product shows a single dimethyl derivative. ^1H NMR analysis at 300 MHz shows two methyl resonances and the 75 MHz ^{13}C NMR spectrum shows a total of 10 carbon resonances, spectral characteristics that are consistent with structure **32a**. Had the cyclization of **29** given **30b**, conversion to the dimethyl derivative **32b** would have given a compound with higher symmetry, and a maximum of seven carbon resonances could have been observed in the ^{13}C NMR spectrum.

Similar cyclization results are obtained with the substrate containing a substituent adjacent to the diene subunit. Triene **33** cyclizes with a high level of 1,2-stereoinduction. In this particular case, the crude cyclization product is hydrolyzed to the aldehyde (5% aqueous HCl in acetone) and then reduced ($NaBH_4$ in ethanol) to afford a single isolated alcohol **34** in 53% overall yield. The structure of **34** is confirmed by

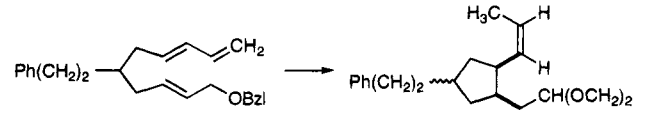
conversion to the monoterpene natural product mitsugashiwalactone (**35**)[46-49] via the sequence: (a) ozonolysis with reductive workup; and (b) oxidation of the intermediate lactol to the lactone. Triene **33** is prepared in enantiomerically enriched form starting from (−)-citronellene, and consequently, (−)-mitsugashiwalactone is produced. The product from the iron-catalyzed cyclization of triene **33** was also converted to (+)-isoiridomermecin.[19]



33 34

Mitsugashiwalactone (**35**)

While 1,2-stereoinduction is exceptionally high in these cyclizations, the extent of 1,3-stereoinduction is low.[18] For example, consider the (2-phenylethyl)-substituted triene **36**. The resident benzyl-bearing stereocenter resides in a 1,3-relationship to either the diene or alkene functionalities. Cyclization of **36** under the standard conditions affords a mixture of two acetals in a 2.1:1 ratio. Given the modest selectivity, the preferred sense of stereoinduction has not been determined.



36 37

Conclusions

The catalytic iron-mediated ene carbocyclization of triene ethers provides a useful new method for the stereoselective preparation of functionalized cyclopentanes. The sense and degree of simple diastereoselection is dependent upon the (2*E*/2*Z*)-alkene geometry. (2*E*,7*E*)-Decatriene ether substrates give rise to five-membered ring products in which the two newly formed stereocenters have the cis relative stereochemistry. In general, these latter substrates cyclize with high regioselectivity and stereoselectivity. Overall, (2*E*,7*E*)-trienes are the preferred substrate for five-membered ring formation using this iron catalyst system. (2*Z*,7*E*)-Decatriene ether substrates generally give rise to the stereoisomeric product possessing the trans relative stereochemistry, although the level of simple diastereoselection is variable and highly dependent upon the structure of the tether chain and the nature of the ether protecting group. Decatrienes possessing a nonchelating substituent adjacent to either the diene or the alkene functionalities cyclize with high 1,2-stereoinduction in such a manner that the resident center and the newly formed stereocenter have the trans relative stereochemistry. Synthetic application of this novel bond construction for the construction of functionalized five-membered ring and related ring systems are in progress.

Experimental Section

General Procedures. Unless otherwise noted, all reactions are carried out under an atmosphere of nitrogen, all reactions were run at ambient temperature, all temperatures are measured externally, and all temperatures are reported in degrees Celsius. The following abbreviations have been used in the experimental section: m = meters; min = minutes; h = hours; satd = saturated; anhyd = anhydrous; calcd = calculated. Preparative chromatographic purification is performed using Davison 60−200 mesh/150 Å pore size silica gel (Fisher Scientific) or Amicon 200−425 mesh/60 Å pore size flash gel (Amicon Corp, Danvers, MA). Preparative high performance liquid chromatography (HPLC) is performed using a Dynamax-60A (8 mm, 25 × 2.14 cm) silica gel column (Rainin, Woburn, CA).

Solvents and Reagents. THF, ether, benzene, and toluene are distilled under nitrogen from sodium benzophenone ketyl prior to use. Extra care is taken to ensure that the toluene or benzene used in the catalytic iron chemistry is dry and oxygen-free. A volume of 1−2 mL of diglyme per liter of benzene/toluene is added as a ketyl solublizing agent. Furan and 2-methylfuran are distilled under nitrogen from lithium aluminum hydride just prior to use. Hexanes (Hex) and ethyl acetate (EtOAc) are purified by distillation. Acetonitrile is distilled from CaH_2 and stored over 4Å sieves. Dichloromethane (DCM) is passed through a column of alumina or distilled from CaH_2. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) are dried over 4Å sieves, distilled under reduced pressure, and then stored over 4Å sieves. Pyridine (pyr) is distilled under nitrogen from KOH. Hexamethylphosphoramide (HMPA) is dried over CaH_2 (5−10 h, 60 °C), distilled under reduced pressure, and then stored over 4Å molecular sieves.

Iron(III) 2,4-pentanedioate (ferric acetylacetonate, Lancaster Synthesis or Aldrich Chemicals) is either recrystallized (benzene/hexane or ethanol) and then dried under vacuum (0.01 mm, 25 °C), or (preferably) sublimed (0.05 mm, 100 °C). 2,2′-Bipyridine (bpy) is sublimed (0.01 mm, 65 °C). Triethylaluminum (Aldrich Chemicals) is used as a 1.9 M solution in toluene. After several months of use, stock solutions of triethylaluminum are replaced. Diisobutylaluminum hydride (DIBAL-H) is used as a 1.5 M solution in toluene. 9-BBN is used as a 0.5 M solution in THF. *n*-Butyllithium (n-BuLi) is used as a 2.5 M solution in hexanes. All other reagents and solvents received from commercial sources are used without further purification.

Analytical Instrumentation and Data. Thin layer chromatographic (TLC) analyses are performed on EM Science silica gel 60F-254 or Analtech silica gel HLF (0.25 mm) precoated analytical plates and visualized by applying a solution of 5% phosphomolybdic acid in methanol or by using a hand-held short wavelength UV lamp (254 nm). Analytical gas chromatographic (GC) measurements are performed on a Varian Series 6000 or 3500 gas chromatograph equipped with a 30 m Durabond DB-5 or DB-17 0.25 mm film thickness fused silica capillary column (J & W Scientific, Folsom, CA) using H_2 as the carrier gas and flame ionization detection. Analytical HPLC measurements are performed on a Varian Vista Series 54 chromatograph equipped with a EM Merck Hibar×e2 Si 60 (5 mm, 23 × 0.8 cm) silica gel column using HPLC grade (EM Science Omnisolve) solvents and a Varian Vari-Chrom variable wavelength UV detector set at 250 nm. Retention

(46) Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron* **1990**, *46*, 3535−46.
(47) Mikami, K.; Takahashi, K.; Nakai, T. *Synlett* **1989**, 45−46.
(48) Nugent, W. A.; Hobbs, F. W. J. *J. Org. Chem.* **1986**, *51*, 3376−8.
(49) Ohta, H.; Kobori, T.; Fujisawa, T. *J. Org. Chem.* **1977**, *42*, 1231−1235.

times for GC- and HPLC-detected peaks are reported in minutes. The relative amounts of each component calculated are as percent area and are uncorrected for relative response. ^1H and ^{13}C NMR spectra are obtained on a Varian VXR-200, Varian XL-300, wide-bore GE/Nicolet NT 360, GE Omega 300, or GE Omega 500 spectrometer. Unless otherwise noted, all NMR spectra were obtained on solutions in $CDCl_3$. ^1H spectral data are reported in ppm from an internal standard tetramethylsilane or residual chloroform as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (reported in Hertz), interpretation. All ^{13}C spectra are decoupled with waltz-16 decoupling. For some compounds the number of attached hydrogens is determined using the DEPT pulse sequence. ^{13}C spectral data (s = no attached hydrogens, d = CH, t = CH_2, q = CH_3) are reported in ppm from an internal standard $CDCl_3$. Infrared (IR) spectra are obtained on a Perkin-Elmer 298 Infrared or Analect RFX-65 FT-IR spectrophotometer using NaCl plates (neat sample), NaCl solution cells (CCl_4 or $CHCl_3$), or the Attenuated Total Reflectance technique[50] (ATR, neat, ZnSe crystal). Selected absorbances are reported in wavenumber (cm^{-1}) and the relative intensities described as follows: br = broad; s = strong; m = moderate; w = weak; or numerically as% absorbance. Analytical samples are purified by several recrystallizations or by chromatography on silica followed by bulb-to-bulb distillation. Combustion analyses are performed by Desert Analytics (Tucson, AZ) or M-H-W Laboratories (Phoenix, AR). High resolution mass spectral (HRMS) determinations are performed by the Midwest Center for Mass Spectrometry (Lincoln, NE) on a Kratos MS-50 mass spectrometer.

Preparation of Ethyl (*E*)-7-Hydroxy-2-heptenoate. To a cooled (−78 °C) solution of triethyl phosphonoacetate (14.3 mL, 70.0 mmol) and n-BuLi (29.5 mL, 74 mmol) in THF (250 mL) is added δ-valerolactone (6.50 mL, 65.0 mmol) dropwise. After 10 min DIBAL-H (56.0 mL, 84.0 mmol) is added dropwise at the rate of 1 mL/min. The resulting solution is slowly warmed to ambient temperature (6 h) and then cooled (0 °C) and quenched by the careful addition of $Na_2SO_4 \cdot 10H_2O$ (15 g), added in several portions over 45 min. After an additional 12 h, ether (100 mL), Celite (5 g), and anhyd Na_2SO_4 (10 g) are added. The resulting slurry is filtered and the salts washed with ether (3 × 100 mL). The combined organics are dried, filtered, and concentrated. Chromatography on silica (60−200 mesh, 50:50 Hex:EtOAc) yields 8.23 g (83%) of ethyl 7-hydroxy-2-heptenoate as a 90:10 *E*:*Z*-mixture. Analytical data for ethyl (*E*)-7-hydroxy-2-heptenoate: ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (dt, 1 H, J = 7.0, 15.6 Hz), 5.77 (dt, 1 H, J = 1.6, 15.6 Hz), 4.12 (q, 2 H, J = 7.1 Hz), 3.59 (t, 2 H, J = 6.2 Hz), 2.18 (m, 2 H), 1.92 (br s, 1 H), 1.5−1.6 (m, 4 H), 1.23 ppm (t, 3 H, J = 7.1 Hz); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 166.7, 148.8, 121.5, 62.4, 60.2, 32.0, 31.8, 24.2, 14.2; IR (CCl_4) 3637 (m, OH), 3487 (br s, OH), 1722 (s, C=O), 1655 (s, C=C). Anal. Calcd for $C_9H_{16}O_3$: 62.77% C; 9.36% H. Found: 62.91% C, 9.55% H.

Preparation of Ethyl (*E*)-7-((*tert*-Butyldimethylsilyl)oxy)hept-2-enoate. To a cooled (0 °C) solution of ethyl (*E*)-7-hydroxy-2-heptenoate (6.33 g, 36.8 mmol), *tert*-butyldimethylchlorosilane (TBDMSCl, 6.65 g, 44.1 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.23 g, 1.8 mmol) in DCM (150 mL) is added triethylamine (7.8 mL, 56 mmol) dropwise. The resulting mixture is stirred (12 h) and then partitioned between ether (400 mL)−brine (100 mL). The organic extract is washed with brine (4 × 100 mL) and then dried, filtered, and concentrated. Chromatography on silica (60−200 mesh, 90:10 Hex:EtOAc) yields 10.5 g (100%) of ethyl (*E*)-7-((*tert*-butyldimethylsilyl)oxy)hept-2-enoate as a colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (ddd, 1 H, J = 6.8, 7.0, 15.6 Hz), 5.82 (ddd, 1 H, J = 1.5, 1.5, 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 3.61 (m, 2 H), 2.20 (m, 2 H), 1.51 (m, 4 H), 1.28 (t, 3 H, J = 7.2 Hz), 0.89 (s, 9 H), 0.43 (s, 6 H); ^{13}C (75.5 MHz, $CDCl_3$) δ 168.0, 149.1, 121.4, 62.7, 60.1, 32.2, 32.0, 26.0, 24.4, 18.4, 14.3, 5.31; IR (CCl_4) 1720 (s), 1650 (m). Anal. Calcd for $C_{15}H_{30}O_3Si$: 62.89% C; 10.56% H. Found: 62.97% C, 10.76% H.

Preparation (*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-hepten-1-ol. To a cooled (0 °C), stirred solution of ethyl (*E*)-7-((*tert*-butyldimethylsilyl)oxy)hept-2-enoate (8.22 g, 28.0 mmol) in THF (100 mL) is added dropwise a solution of DIBAL-H (41.0 mL, 61.5 mmol). The resulting solution is stirred (0 °C, 3 h) and then quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ (7.0 g), added in several portions over 1 h. After an additional 1 h, ether (100 mL), Celite (5 g), and anhyd Na_2SO_4 (10 g) are added. The resulting slurry is filtered, and the salts were washed with ether (3 × 150 mL). The combined organics are dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Chromatography on silica (60−200 mesh, 70:30 Hex:EtOAc) yields (*E*)-7-((*tert*-butyldimethylsilyl)oxy)-2-hepten-1-ol (6.27 g, 92%) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (m, 2 H), 4.08 (d, 2 H, J = 4.5 Hz), 5.62 (m, 2 H), 2.07 (m, 2 H), 1.8 (br, 1 H), 1.50 (m, 2 H), 1.40 (m, 2 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 133.0, 129.1, 63.6, 63.0, 32.2, 31.9, 25.9, 25.3, 18.3, −5.3; IR (CCl_4) 3400 (br, OH). Anal. Calcd for $C_{13}H_{28}O_2Si$: 63.87% C; 11.55% H. Found: 63.49% C, 11.62% H.

Preparation of (*E*)-1-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-heptene. To a stirred suspension of sodium hydride (0.74 g, 31 mmol) in DMF (100 mL) is added dropwise a solution of (*E*)-7-((*tert*-butyldimethylsilyl)oxy)-2-hepten-1-ol (6.20 g, 25.6 mmol) in DMF (10 mL). The resulting suspension is stirred (1 h) and then cooled (0 °C) and benzyl bromide (4.70 mL, 39.5 mmol) added dropwise. The resulting solution is slowly warmed to ambient temperature, stirred (12 h), carefully quenched by the addition of water (ca. 2 mL), and partitioned between ether (300 mL)−water (100 mL). The organic layer is washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Chromatography on silica (60−200 mesh, 70:30 Hex:EtOAc) yields 1-(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-heptene (6.66 g, 78%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.6−5.7 (m, 2 H), 4.49 (s, 2 H), 3.96 (d, 2 H, J = 5.3 Hz), 3.60 (t, 2 H, J = 6.2 Hz), 2.0−2.1 (m, 2 H), 1.4−1.5 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 138.5, 134.7, 128.3, 127.8, 127.5, 126.4, 71.9, 70.9, 63.0, 32.4, 32.1, 26.0, 25.4, 18.4, −5.3; IR (neat) 3030 (m), 2929 (s), 2885 (s), 2856 (s), 1496 (m), 1471 (s), 1462 (s), 1454 (s), 1405 (m). Anal. Calcd for $C_{20}H_{34}O_2$: 71.80% C; 10.24% H. Found: 71.88% C, 10.52% H.

Preparation of (*E*)-1-(Benzyloxy)-2-hepten-7-ol. A solution of (*E*)-1-(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-heptene (6.66 g, 19.9 mmol) in acidic methanol (100 mL, 10 mg p-TsOH) stands overnight (12 h) and then is quenched by the addition of satd aqueous sodium bicarbonate (ca. 2 mL). The mixture is partitioned between ether (300 mL)−water (100 mL). The organic layer is washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 70:30 Hex:EtOAc) yields (*E*)-1-(benzyloxy)-2-hepten-7-ol (4.26 g, 97%) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.65 (m, 2 H), 4.48 (s, 2 H), 3.95 (d, 2 H, J = 5.8 Hz), 3.63 (t, 2 H, J = 6.3 Hz), 2.08 (m, 2 H), 1.55 (m, 2 H), 1.44 (m, 2 H), 1.32 (br s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.7, 134.2, 127.6, 127.3, 126.2, 71.8, 70.8, 62.7, 32.2, 31.9, 25.1; IR (CCl_4) 3411 (br, OH), 1496 (m), 1454 (s), 1405 (m). Anal. Calcd for $C_{14}H_{20}O_2$: 76.32% C; 9.15% H. Found: 76.21% C, 9.26% H.

Preparation and Dienylations of (*E*)-1-(Benzyloxy)-2-heptenal. To a cooled (−78 °C) solution of oxalyl chloride (1.90 mL, 21.8 mmol) and DMSO (3.10 mL, 43.7 mmol) in DCM (100 mL) is added dropwise over 15 min a solution of (*E*)-1-(benzyloxy)-2-hepten-7-ol (4.10 g, 18.2 mmol) in DCM (30 mL). The resulting cloudy mixture is stirred (30 min) and then triethylamine (23.0 mL, 165.0 mmol) added dropwise. The cooling bath is removed and the solution warmed to room temperature over 45 min. The resulting mixture is diluted with ether (400 mL) and washed with water (100 mL) and brine (2 × 100 mL). The organic layer is dried ($MgSO_4$), filtered, and concentrated and the resulting yellow oil filtered through a plug of silica (60−200 mesh, 70:30 Hex:EtOAc) to

(50) P. A. Wilks, J. *Am. Lab.* **1972**, *4*, 42.

yield (*E*)-1-(benzyloxy)-2-heptenal (3.98 g, 99%), which is used without further purification.

a. Preparation of (2*E*,7*E*)-1-(Benzyloxy)-2,7,9-decatriene (4a, $R^1 = CH_2Ph$). To a cooled (−78 °C) solution of allyldiphenylphosphine oxide[51] (5.30 g, 21.9 mmol) and HMPA (7.0 mL, 40 mmol) in THF (90 mL) is added dropwise a solution of n-BuLi (9.00 mL, 22.5 mmol). The resulting red solution is stirred (5 min) and then a solution of (*E*)-1-(benzyloxy)-2-heptenal (3.98 g, 18.2 mmol) in THF (20 mL) added dropwise over 30 min. The resulting solution is slowly warmed to ambient temperature (8 h) and then quenched by the addition of water (ca. 5 mL). The reaction mixture is concentrated in vacuo and the residue partitioned between Hex:EtOAc (400 mL, 70:30)−water (100 mL). The organic layer is washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) yields **4a** (2.36 g, 58%) as a clear oil: GC analysis (DB-5, 100−250 °C @ 10 °C/min) 16.0 (2.3%), 16.8 (97.7%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 6.31 (ddd, 1 H, *J* = 10.1, 10.3, 16.9 Hz), 6.04 (dd, 1 H, *J* = 10.3, 15.2 Hz), 5.6 (m, 3 H), 5.08 (d, 1 H, *J* = 16.9 Hz), 4.96 (d, 1 H, *J* = 10.1 Hz), 4.50 (s, 2 H), 3.97 (d, 2 H, *J* = 5.8 Hz), 2.10 (m, 4 H), 1.50 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.0, 134.7, 134.2, 133.8, 131.1, 128.2, 127.6, 127.4, 126.4, 114.7, 71.8, 70.8, 32.0, 31.7, 28.5; IR (CCl_4) 3031 (m), 3009 (m), 2930 (s), 2855 (s), 1453 (m). Anal. Calcd for $C_{17}H_{22}O$: 84.24% C; 9.15% H. Found: 84.53% C, 9.20% H.

b. Preparation of (2*E*,7*E*)-1-(Benzyloxy)-9-methyl-2,7,9-decatriene (5). Using the procedure described in part a (2-methyl-2-propenyl)diphenylphosphine oxide[51] (0.886 g, 3.50 mmol) is reacted with n-BuLi (1.50 mL, 3.75 mmol) and (*E*)-1-(benzyloxy)-2-hepten-1-al (0.69 g, 3.14 mmol) in THF (55 mL)/HMPA (1.44 mL, 8.28 mmol) to afford after chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) predominantly (2*E*,7*E*)-**5** (0.412 g, 52%) as a clear oil: GC Analysis (DB-5, 100−250 °C @ 5 °C/min) 17.7 (8.6%), 18.5 min (91.4%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (m, 5 H), 6.04 (d, 1 H, *J* = 15.8 Hz), 5.5−5.6 (m, 3H), 4.76 (s, 2 H), 4.41 (s, 2 H), 3.88 (d, 2 H, *J* = 5.3 Hz), 1.9−2.1 (m, 4 H), 1.73 (s, 3 H) overlapping with 1.1−1.8 (m, 6 H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 141.9, 138.3, 134.3, 133.0, 130.2, 128.2, 127.6, 127.4, 126.4, 71.8, 70.8, 32.2, 31.8, 28.7, 18.7; IR (neat, ATR) 2923 (s), 2853 (s), 1723 (m), 1607 (m), 1495 (m), 1453 (s), 1438 (s).

Preparation of 5-(1,3-Dioxolan-2-yl)-1-pentanal.[52] A stream of ozonized oxygen gas is bubbled through a cooled (0 °C) solution of cyclopentene (6.40 mL, 75 mmol), Sudan III indicator, and ethylene glycol (50 mL) in dry DCM (250 mL) until the color due to Sudan III dissipates. The cold bath is removed, then *p*-toluenesulfonic acid (1.215 g) is added and the mixture stirred at ambient temperature (90 min). $NaHCO_3$ (2.147 g) is added followed after 15 min by the addition of dimethyl sulfide (12 mL). The resulting mixture is stirred (12 h) and then partitioned with water (75 mL) and the aqueous layer extracted with DCM (2 × 100 mL). The combined organics are washed with water (2 × 75 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica (230−400 mesh, 80:20 Hex:EtOAc) affords 2.45 g of 5-(1,3-dioxolan-2-yl)-1-pentanal (contains some of the bis-ethylene acetal): TLC analysis (80:20 Hex:EtOAc) R_f 0.17; ^{1}H NMR (major component, 300 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.4 Hz, 1 H), 4.84−4.79 (m, 1 H), 3.94−3.77 (m, 4 H), 2.46 (t, *J* = 6.7 Hz, 2 H), 1.78−1.62 (m, 4 H); ^{13}C NMR (75 MHz) δ 202.0 (s), 104.2 (d), 103.9 (d), 64.7 (t), 43.4 (t), 33.5 (t), 32.8 (t), 18.4 (t), 16.3 (t); IR (neat) 1719 (C=O, 67% absorbance); HRMS analysis (EI, $C_7H_{12}O_3$ $(M - H)^+$ = 143.0706), found *m/z* 143.07055.

Preparation of (5*E*)-1,1-(Ethylenedioxy)-5,7-octadiene. To a cooled (−78 °C) solution of allyldiphenylphospine oxide[51] (10.4 g, 43.0 mmol) and HMPA (16.5 mL, 94.6 mmol) in THF (500 mL) is added n-BuLi (18.9 mL, 47.3 mmol) dropwise. After 15 min, a solution of 5-(1,3-dioxolan-2-yl)-1-pentanal (6.2 g, 43.0 mmol) in THF (20 mL) is added dropwise to the red solution. The resulting mixture is slowly warmed to ambient temperature (10 h) and then quenched by the addition of water (100 mL). The organic solvents are removed in vacuo and the residue extracted with ether (50 mL). The organic layer is washed with brine (4 × 30 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica (95:5 = Hex:EtOAc) affords (5*E*)-1,1-(ethylenedioxy)-5,7-octadiene (5.63 g, 78%): TLC analysis (90:10 = Hex:EtOAc) R_f = 0.24; GC analysis (DB-17, 100−260 °C @ 5 °C/min) 6.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30−6.42 (m, 1H), 6.07−6.16 (m, 1H), 5.72−5.79 (m, 1H), 4.99−5.17 (m, 2H), 4.90 (t, 1H, *J* = 5 Hz), 3.88−4.04 (m, 4H), 2.19 (q, 1H, *J* = 5 Hz), 1.69−1.77 (m, 2H), 1.56−1.65 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9 (d), 135.3 (d), 132.1 (d), 115.5 (t), 105.1 (d), 65.5 (t), 34.0 (d), 33.0 (t), 24.2 (t); FT-IR (ATR) 2947 (s), 2875 (s), 1652 (m), 1603 (m), 1410 (s), 1131 (s), 1004 (s). Anal. Calcd for $C_{10}H_{16}O_2$: 71.39% C; 9.59% H. Found: 71.52% C, 9.37% H.

Preparation of Ethyl (2*E*,7*E*)-2,7,9-Decatrien-1-oate. A solution of (5*E*)-1,1-(ethylenedioxy)-5,7-octadiene (5.63 g, 20.1 mmol) and conc HCl (20 drops) in 50% aqueous acetone (150 mL) is refluxed (5 h) and then extracted with DCM (4 × 20 mL). The combined organic layers are washed with brine and concentrated. Concentrated HCl (20 drops) in 50% aqueous acetone (150 mL) is added, refluxed (5 h), and then extracted with DCM (4 × 15 mL). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (95:5 Hex:EtOAc) affords 2.5 g (60%) of aldehyde: TLC analysis (95:5 Hex:EtOAc) R_f = 0.26; GC analysis (DB-17, 100−260 °C @ 5 °C/min) 3.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.26−6.39 (m, 1H), 6.04−6.14 (m, 1H), 5.62−5.72 (m, 1H), 4.99−5.16 (m, 2H), 2.47 (t, 2H, *J* = 6.0 Hz), 2.16 (q, 2H, *J* = 7 Hz), 1.75−1.82 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.7 (C=O), 138.3 (d), 135.0 (d), 133.4 (d), 116.8 (t), 44.5 (t), 33.1 (d), 22.8 (t); FT-IR (ATR) 2925 (s), 1724 (s), 1004 (s), 899 (s).

To a cooled (0 °C), stirred solution of anhyd LiCl (1.11 g, 26.1 mmol), DBU (3.10 mL, 20.7 mmol), and triethyl phosphonoacetate (4.38 mL, 22.1 mmol) in dry acetonitrile (150 mL) is added a solution of the above aldehyde (2.50 g, 20.1 mmol) in acetonitrile (20 mL) dropwise over a period of 10 min.[53] The reaction mixture is then stirred for 20 min, the ice bath removed, and the resulting solution stirred (25 °C) for an additional 12 h. Water (20 mL) is added, the organic solvent removed in vacuo, and the residue partitioned with ether (50 mL). The organic layer is washed with brine (2 × 20 mL) and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (90:10 Hex:EtOAc) affords the unsaturated ester (2.89 g, 74%): TLC analysis (90:10 Hex:EtOAc) R_f = 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (ddd, 1 H, *J* = 6.0, 7.0, 15.6 Hz), 6.34 (ddd, 1 H, *J* = 10.1, 10.1, 17.0 Hz), 6.09 (dd, 1 H, *J* = 10.1, 15.0 Hz), 5.86 (dt, 1 H, *J* = 1.5, 1.5, 15.6 Hz), 5.70 (td, 1 H, *J* = 7.0, 15.0 Hz), 5.13 (d, 1 H, *J* = 17.0 Hz), 5.01 (d, 1 H, *J* = 10.1 Hz), 4.22 (q, 2 H, *J* = 7.2 Hz), 2.23 (m, 4 H), 1.61 (m, 2 H), 1.32 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.1 (s), 149.7 (d), 137.4 (d), 134.6 (d), 132.0 (d), 121.8 (d), 115.6 (t), 60.6 (t), 32.2 (t), 32.0 (t), 27.9 (q), 14.7 (q); IR (CCl_4) 1722 (s, C=O). Anal. Calcd for $C_{12}H_{18}O_2$: 74.19% C; 9.34% H. Found: 74.27% C, 9.50% H.

Preparation of (2*E*,7*E*)-2,7,9-Decatrien-1-ol. To a cooled (0 °C), stirred solution of ethyl (2*E*,7*E*)-2,7,9-decatrien-1-oate (2.89 g, 14.9 mmol) in THF (200 mL) is added DIBAL-H (21.9 mL, 32.8 mmol) dropwise. After 4 h, the ice bath is removed and the reaction quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ (5 g), Celite (5 g), and ether (100 mL). After 1 h, the mixture is filtered and concentrated. Chromatography on silica (90:10 Hex:EtOAc) affords the decatrienol (1.68 g, 74%) as a clear oil: TLC analysis (80:20 Hex:EtOAc) R_f = 0.14; GC analysis (DB-17, 100−260 °C @ 5 °C/min) 7.97 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (ddd, 1 H, *J* = 6.6, 10.2, 16.9 Hz), 6.04 (dd, 1 H, *J* = 10.2, 15.2 Hz), 5.50−5.67 (m, 3 H), 5.07 (d, 1 H, *J* = 16.9 Hz), 4.95 (d, 1 H, *J* = 10.2 Hz), 4.02 (d, 2 H, *J* = 3.8 Hz), 3.1 (br s, 1 H), 2.1 (m, 4 H), 1.47 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.2 (d), 134.8 (d), 132.3 (d), 131.2 (d),

(51) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029−4032.

(52) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150−156.

(53) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

129.4 (d), 114.8 (t), 63.2 (t), 32.0 (t), 31.7 (d), 28.6 (t); IR (CCl_4) 3620 (m, OH), 3300 (br s, OH), 1600 (m), 1430 (m). Anal. Calcd for $C_{10}H_{16}O$: 78.89% C; 10.69% H. Found: 78.53% C, 10.69% H.

General Procedure for the O-Alkylation of (2*E*,7*E*)-2,7,8-Decatrien-1-ol. To a cooled (0 °C), stirred suspension of sodium hydride (0.33 g, 13.7 mmol) in DMF (60 mL) is added dropwise a solution of (2*E*,7*E*)-2,7,8-decatrien-1-ol in DMF (10 mL). After 15 min the cooling bath is removed, the reaction mixture stirred an additional 45 min and then recooled (0 °C), and the alkyl halide added dropwise. The reaction mixture is warmed to ambient temperature (12 h) and then quenched by the careful addition of water (ca. 2 mL). The resulting mixture is partitioned between ether (100 mL)–water (50 mL) and the organic layer washed with brine (2 × 50 mL), dried, filtered, and concentrated. Chromatography on silica (60–200 mesh, Hex:EtOAc) affords the desired ether as a colorless oil.

a. Preparation of (2*E*,7*E*)-1-Methoxy-2,7,9-decatriene (4b, $R^1 = CH_3$). Using the general procedure given above (2*E*,7*E*)-2,7,9-decatrien-1-ol (1.50 g, 8.9 mmol) reacts with sodium hydride (0.33 g, 13.7 mmol) and iodomethane (0.83 mL, 13.3 mmol) in DMF (60 mL) to afford after chromatography on silica (60–200 mesh, 95:5 Hex:EtOAc) **4b** (1.56 g, 83%) as a colorless oil: GC analysis (DB-5, 100–250 °C @ 5 °C/min) 4.1 (97.4%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.31 (ddd, 1 H, J = 10.1, 10.1, 17.0 Hz), 6.05 (ddd, 1 H, J = 1.3, 11.5, 16.3 Hz), 5.63 (m, 3 H), 5.08 (d, 1 H, J = 17.0 Hz), 4.95 (dd, 1 H, J = 10.1 Hz), 3.86 (d, 2 H, J = 5.8 Hz), 3.31 (s, 3 H), 2.08 (m, 4 H), 1.49 (m, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 137.2, 134.8, 134.2, 131.2, 126.5, 114.8, 73.2, 57.6, 31.9, 31.7, 28.5; IR (CCl_4) 3033 (m), 3066 (m), 2981 (m), 2927 (s), 2854 (s), 2821 (s), 1653 (m), 1452 (m). Anal. Calcd for $C_{11}H_{18}O$: 79.46% C; 10.91% H. Found: 79.30% C, 10.87% H.

b. Preparation of (2*E*,7*E*)-1-Ethoxy-2,7,9-decatriene (4c, $R^1 = CH_2CH_3$). Using the general procedure given above (2*E*,7*E*)-2,7,9-decatrien-1-ol (1.00 g, 5.9 mmol) reacts with sodium hydride (0.22 g, 9.3 mmol) and iodoethane (0.66 mL, 8.2 mmol) in DMF to afford after chromatography on silica (60–200 mesh, 95:5 Hex:EtOAc) **4c** (0.93 g, 87%) as a colorless oil: GC analysis (DB-5, 100–250 °C @ 5 °C/min) 5.1 (91.8%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.31 (ddd, 1 H, J = 10.2, 10.2, 16.9 Hz), 6.05 (ddd, 1 H, J = 0.6, 10.2, 15.4 Hz), 5.64 (m, 3 H), 5.08 (ddd, 1 H, J = 0.6, 1.4, 16.9 Hz), 4.95 (ddd, 1 H, J = 0.7, 1.4, 10.2 Hz), 3.86 (d, 2 H, J = 5.7 Hz), 3.46 (q, 2 H, J = 7.0 Hz), 2.08 (m, 4 H), 1.49 (m, 2 H), 1.21 ppm (t, 3 H, J = 7.0 Hz); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 137.1, 134.9, 133.8, 131.1, 126.8, 114.6, 71.2, 65.2, 31.8, 31.6, 38.4, 15.1; IR (neat) 3006 (m), 2974 (m), 2929 (s), 2856 (s), 1452 (m), 1441 (m). Anal. Calcd for $C_{12}H_{20}O$: 79.95% C; 11.18% H. Found: 80.07% C, 11.24% H.

Preparation of (2*E*,7*E*)-2-((*tert*-Butyldimethylsilyl)-oxy)-2,7,9-decatriene (4d, R^1 = TBDMS). To a warmed (50 °C), stirred solution of (2*E*,7*E*)-2,7,9-decatrien-1-ol (1.54 g, 10.1 mmol) and imidazole (1.72 g, 25.3 mmol) in DMF (50 mL) is added slowly a solution of TBDMSCl (2.29 g, 15.2 mmol) in DMF (10 mL). The resulting mixture is kept at 50 °C for 5 h, cooled, and stirred for 10 h at room temperature. The mixture is partitioned between ether (75 mL)–water (75 mL). The ether layer is washed with saturated $NaHCO_3$ and brine and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (95:5 = Hex:EtOAc) affords **4d** (2.40 g, 89%) as a colorless oil: TLC analysis (90:10 = Hex:EtOAc) R_f = 0.78; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24–6.40 (m, 1H), 6.00–6.10 (m, 1H), 5.5–5.78 (m, 3H), 4.95–5.13 (m, 2H), 4.13 (d, 2H, J = 5.0 Hz), 2.10–2.13 (m, 4H), 1.45–1.60 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.2 (d), 137.2 (d), 134.7, 131.3 (d), 130.6 (d), 129.6 (d), 114.7 (t), 63.9 (t), 32.0 (t), 31.6 (d), 28.7 (t), 26.0 (q), –5.1 (q); FT-IR (ATR) 2927, 2855, 1471, 1254, 1057, 1003. Anal. Calcd for $C_{16}H_{30}OSi$: 72.11% C; 11.35% H. Found: 72.22% C, 11.22% H.

General Procedure for the Preparation of Trienes via the Alkylation of (*E*)-2,4-Pentadienylpropanedioic Acid Diethyl Ester. To a solution of sodium hydride (1.2 equiv) in a mixture of THF (200 mL) and DMSO (10 mL) is added (*E*)-2,4-pentadienylpropanedioic acid diethyl ester[54] (registry number 55693-36-2) dropwise. After 15 min, the alkyl halide is added dropwise. After 12 h, the reaction mixture is carefully quenched by the addition of water and then partitioned between ether (100 mL)–water (300 mL) and the aqueous layer extracted with ether (2 × 75 mL). The combined organic extracts are washed with brine (2 × 75 mL), dried, and concentrated. Chromatography on silica (260–400 mesh, Hex:EtOAc) affords the desired malonate derivative.

a. (3*E*)-6,6′-Dicarboethoxy-1,3,8-decatriene (10). Using the procedure described above (*E*)-2,4-pentadienylpropanedioic acid diethyl ester (1.452 g, 6.42 mmol) reacts with sodium hydride (0.17 g, 7.1 mmol) and 1-bromo-2-butene (Aldrich Chemicals, predominately trans, 0.66 mL, 6.42 mmol) in THF (250 mL)–DMSO (7 mL) to afford after chromatography on silica (260–400 mesh, 90:10 Hex:EtOAc) **10** (1.48 g, 82%) as a colorless oil: TLC analysis (90:10 Hex:EtOAc) R_f 0.36; GC analysis (DB-17, 100–260 °C @ 5 °C/min) 15.14 (78%), 15.38 min (6%), 15.55 (13%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.02–6.36 (m, 2H), 5.48–5.55 (m, 2H), 5.2–5.34 (m, 1H), 4.99–5.06 (overlapping d, 2H, J = 16.8, 10.1 Hz), 4.17 (q, 4H, J = 7.0 Hz), 2.64 (d, 2H, J = 7.3 Hz), 2.56 (overlapping d, 2H, J = 7.0 Hz), 1.64 (d, 3H, J= 6.0 Hz), 1.24 (overlapping t, 6H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8 (s), 136.5 (d), 134.8 (d), 129.8 (d), 128.0 (d), 124.5 (d), 116.2 (t), 60.9 (t), 57.4 (q), 35.7 (t), 35.5 (t), 17.8 (q), 13.9 (q); IR (neat) 2979 (s), 1736 (s, C=O). Anal. Calcd for $C_{16}H_{24}O_4$: 68.54% C; 8.63% H. Found: 68.67% C, 8.78% H.

b. (3*E*)-6,6′-Dicarboethoxy-1,3,8-nonatriene (12). Using the procedure described above (*E*)-2,4-pentadienylpropanedioic acid diethyl ester (1.253 g, 5.54 mmol) reacts with sodium hydride (0.146 g, 6.09 mmol) and 1-bromo-2-propene (0.48 g, 5.54 mmol) in THF (150 mL)–DMSO (5 mL) to afford after chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) **12** (1.28 g, 86%) as a colorless oil: TLC analysis (95:5 Hex:EtOAc) R_f 0.33; GC analysis (DB-17, 100–260 °C @ 5 °C/min) 13.3 min (7%), 13.5 (90%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.02–6.36 (m, 2H), 5.44–5.76 (m, 2H), 5.13–5.15 (dd, 2H), 4.99–5.06 (dd, 2H, J = 16.8, 10.1 Hz), 4.18 (overlapping q, 4H, J = 7.0 Hz), 2.64 (t, 2H, J = 7.0 Hz), 1.24 (overlapping t, 6H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.4 (s), 136.4 (d), 134.8 (d), 132.1 (d), 127.7 (d), 118.9 (t), 116.1 (t), 61.0 (t), 57.3 (s), 36.8 (t), 35.8 (t), 13.9 (q); IR (neat) 1736 (s, C=O). Anal. Calcd for $C_{15}H_{21}O_4$: 67.39% C; 8.29% H. Found: 67.04% C, 8.31% H.

c. (2*E*,7*E*)-1-(Benzyloxy)-5,5-dicarboethoxy-2,7,9-decatriene (14a, $R^1 = CH_2Ph$). A cooled (0 °C) solution of (*E*)-1-(benzyloxy)-2-buten-4-ol (1.20 g, 6.24 mmol), CBr_4 (3.10 g, 9.36 mmol), and triphenylphosphine (2.04 g, 7.8 mmol) in DCM (50 mL) is stirred for 30 min (0 °C) and then warmed to room temperature (2.5 h). The resulting mixture is poured into water (50 mL) and extracted with ether (3 × 50 mL). The combined ether extracts are washed with water (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated. The residue is triturated with hexanes and refiltered and the filtrate concentrated. Chromatography on silica (95:5 Hex:EtOAc) affords (*E*)-4-(benzyloxy)-1-bromobut-2-ene (1.31 g, 87%) as a yellow oil: TLC analysis (95:5 Hex:EtOAc) R_f 0.40; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26–7.36 (s, 5H), 5.91–5.98 (m, 2H), 4.52 (s, 2H), 4.04 (d, 2H, J = 4 Hz), 3.97 (d, 2H, J = 6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 131.5, 128.4, 128.2, 127.5, 72.1, 69.2, 31.8; FT-IR (neat) 1736 (s, C=O).

Using the alkylation procedure described above (*E*)-2,4-pentadienylpropanedioic acid diethyl ester (0.89 g, 3.9 mmol) reacts with sodium hydride (0.103 g, 4.3 mmol) and (*E*)-4-(benzyloxy)-1-bromobut-2-ene (0.94 g, 3.9 mmol) in THF (70 mL)–DMSO (5 mL) to afford after chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) **14a** (1.364 g, 90%) as a colorless oil: TLC analysis (95:5 Hex:EtOAc) R_f 0.1; HPLC analysis (90:10 Hex:EtOAc, 1.5 mL/min) 5.4 (100%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (s, 5H), 5.98–6.3 (m, 2H), 5.54–5.6 (m, 1H), 5.39–5.6 (m, 2H), 4.89–5.06 (dd, 2H, J = 16.8, 10.1 Hz), 4.38 (s, 2H), 4.08 (overlapping q, 4H, J = 7.2 Hz), 3.87

(54) Danishefsky, S.; Tsai, M. Y.; Dynak, J. *J. Chem. Soc., Chem. Commun.* **1975**, *1*, 7–8.

(d, 2H, J = 5.4 Hz), 2.56 (d, 4H, J = 6.6 Hz), 1.14 (overlapping t, 6H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5 (s), 136.5 (d), 135.0 (d), 130.1 (d), 128.2 (d), 127.6 (d), 127.0 (d), 116.3 (t), 71.7 (t), 70.2 (t), 61.1 (t), 57.5 (s), 35.7 (t), 35.5 (t), 14.0 (q); IR (neat) 1733 (s, C=O); HRMS analysis (EI, $C_{23}H_{30}O_5$ = 386.2094), found 386.2082 *m/z*.

d. (2*E*,7*E*)-1-(*tert*-Butyldimethylsiloxy)-5,5-dicarboethoxy-2,7,9-decatriene (14b, R^1 = TBDMS). To a stirred suspension of potassium carbonate (0.70 g, 4.95 mmol) and triphenylphosphine (1.62 g, 6.25 mmol) in CCl_4–DCM (4:1) is added *trans*-4-(*tert*-butyldimethylylsiloxy)-2-buten-1-ol (0.500 g, 2.5 mmol). The reaction mixture is refluxed (70 °C, 12 h) during which time a brown precipitate forms. The resulting mixture is filtered through Celite, concentrated, and then filtered through silica (TLC standard grade without binder, 95:5 Hex:EtOAc) to afford *trans*-4-(*tert*-butyldimethylsiloxy)-1-chloro-2-butene (0.42 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87–5.84 (br m, 2 H), 4.20–4.18 (br s, 2 H), 4.09–4.06 (br m, 2 H), 0.9 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1 (d), 125.4 (d), 62.6 (t), 44.6 (t), 25.9 (q, $C(CH_3)_3$), 18.4 (s, $C(CH_3)_3$), −5.2 (q, $SiCH_3$); IR (ATR–ZnSe, neat) 1253 (54% transmittance, CH_2Cl). Anal. Calcd for $C_{10}H_{21}OClSi$: 54.39% C; 9.59% H. Found: 54.46% C, 9.45% H.

Using the alkylation procedure described above (*E*)-2,4-pentadienylpropanedioic acid diethyl ester (1.48 g, 6.5 mmol) reacts with sodium hydride (172 mg, 7.15 mmol) and *trans*-4-(*tert*-butyldimethylsiloxy)-1-chloro-2-butene (1.44 g, 6.5 mmol) in THF (5 mL)–DMSO (20 mL) to afford after chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) **14b** (1.75 g, 66%) as a pale yellow oil: TLC analysis (90:10 Hex:EtOAc) R_f 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (ddd, 1 H, J = 10.3, 10.3, 16.9 Hz), 6.06 (dd, 1 H, J = 14.5, 10.5 Hz), 5.62 (td, 1 H, J = 5.1, 15.3 Hz), 5.48 (m, 2 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, 4 H, J = 7.0 Hz), 1.22 (t, 6 H, J = 7.2 Hz), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz) δ 170.6 (s), 136.5 (d), 134.9 (d), 133.9 (d), 127.9 (d), 123.7 (d), 116 (t), 63.3 (t), 61.1 (t), 59.5 (s), 35.5 (t), 35.2 (t), 25.8 (q), 18.2 (s), 14.0 (q), −5.3 (q); IR (salt plate) 1725 (45% absorbance, C=O). Anal. Calcd for $C_{22}H_{38}O_5Si$ = 64.35% C, 9.33% H. Found: 64.16% C, 9.43% H.

e. (2*Z*,7*E*)-1-(Benzyloxy)-5,5-dicarboethoxy-2,7,9-decatriene (24b, R^1 = CH_2Ph). A cooled (0 °C) solution of (*Z*)-1-(benzyloxy)-2-buten-4-ol (13.30 g, 74.6 mmol), CBr_4 (37.10 g, 112 mmol), and triphenylphosphine (24.47 g, 93.3 mmol) in DCM (400 mL) is stirred for 30 min (0 °C) and then warmed to room temperature (2.5 h). The resulting mixture is poured into water (100 mL) and extracted with ether (3 × 100 mL). The combined ether extracts are washed with water (3 × 30 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated. The residue is triturated with hexanes and refiltered and the filtrate concentrated. Chromatography on silica (95:5 Hex:EtOAc) affords (*Z*)-4-(benzyloxy)-1-bromobut-2-ene (12.10 g, 67%) as a yellow oil: TLC analysis (95:5 Hex:EtOAc) R_f 0.30; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.70–6.0 (m, 2H), 4.54 (s, 2H), 4.17 (d, 2H, J = 6 Hz), 3.99 (d, 2H, J = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 131.0, 128.3, 128.3, 127.7, 72.4, 64.8, 26.4; FT-IR (neat) 2862 (s), 1454 (m).

Using the alkylation procedure described above (*E*)-2,4-pentadienylpropanedioic acid diethyl ester (2.67 g, 11.8 mmol) reacts with sodium hydride (0.312 g, 13 mmol) and (*Z*)-4-(benzyloxy)-1-bromobut-2-ene (1.05 g, 5.4 mmol) in THF (300 mL)–DMSO (20 mL) to afford after chromatography on silica (260–400 mesh, 90:10 Hex:EtOAc) **24b** (0.87 g, 71%) as a colorless oil: TLC analysis (95:5 Hex:EtOAc) R_f 0.12; HPLC analysis (90:10 Hex:EtOAc, 1.5 mL/min) 5.1 (100%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (s, 5H), 6.0–6.36 (m, 2H), 5.66–5.82 (m, 1H), 5.36–5.56 (m, 2H), 4.98–5.14 (overlapping d, 2H, J = 10.1, 16.8 Hz), 4.49 (s, 2H), 4.15 (overlapping q, 4H, J = 7.2 Hz), 4.05 (d, 2H, J= 5.4 Hz), 2.65 (d, 4H, J = 7.6 Hz), 1.23 (overlapping t, 6H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5 (s), 136.4 (d), 135.0 (d), 128.2 (d), 127.6 (d), 126.0 (d), 116.3 (t), 72.2 (t), 65.7 (t), 61.2 (t), 57.2 (s), 35.6 (t), 30.6 (t), 14.0 (q); IR (neat) 2979 (s), 2934 (m), 1732 (s, C=O), 1453 (m), 1204 (s); HRMS analysis (EI, $C_{23}H_{30}O_5$ = 386.2084), found 386.2077 *m/z*.

f. (2*Z*,7*E*)-1-Methoxy-5,5-dicarboethoxy-2,7,9-decatriene (24c, R^1 = CH_3). Using the procedure described above (*E*)-2,4-pentadienylpropanedioic acid diethyl ester (1.451 g, 6.42 mmol) reacts with sodium hydride (0.243 g, 10.1 mmol) and (*Z*)-4-methoxy-1-bromo-2-butene (1.53 g, 9.27 mmol) in THF (65 mL)–DMSO (6 mL) to afford after chromatography on silica (260–400 mesh, 90:10 Hex:EtOAc) **24c** (1.80 g, 91%) as a colorless oil: TLC analysis (90:10 Hex:EtOAc) R_f 0.28; ^{1}H NMR (360 MHz; $CDCl_3$) δ 6.27 (ddd, 1H, J = 10.2, 10.4, 16.9 Hz), 6.08 (dd, 1H, J = 10.4, 15.1 Hz), 5.67 (dtt, 1H, J = 1.5, 6.4, 11.2 Hz), 5.36–5.55 (m, 2H), 5.11 (d, 1H, J = 15.9 Hz), 5.02 (br d, 1H, J = 10.6 Hz), 4.1–4.25 (overlapping q, 4H), 3.95 (d, 2H, J = 6.8 Hz), 3.31 (s, 3H), 2.4 (overlapping d, 4H), 1.24 (overlapping t, 6H, J = 7.1 Hz); ^{13}C (50 MHz, $CDCl_3$) δ 170.6 (s), 136.5 (d), 135.1 (d), 130.1 (d), 127.8 (d), 126 (d), 116.4 (t), 58.1 (t), 61.3 (t), 58.0 (q), 57.3 (s), 35.7 (t), 30.7 (t), 14.0 (q); IR (neat) 1733 (s, C=O), 1652 (w, C=C), 1602 (w); HRMS analysis (EI, $C_{17}H_{26}O_5$ = 310.1781), found 310.1786 *m/z*.

Preparation of (2*E*,7*E*)-1-(Benzyloxy)-4-methyl-2,7,9-decatriene (29). To a stirred orange slurry of pyridinium chlorochromate (1.38 g, 6.41 mmol), sodium bicarbonate (0.54 g, 6.43 mmol), and Celite (2.64 g) in DCM (200 mL) is added dropwise a solution of (*E*)-1-(benzyloxy)-4-methyl-2-hepten-7-ol[55] (1.01 g, 4.32 mmol) in DCM (20 mL). The resulting brown slurry is stirred (3 h), diluted with ether (200 mL), filtered through Celite, and concentrated. The resulting brown liquid is taken up in ether (250 mL), filtered through Celite, and concentrated. The resulting yellow oil is filtered on silica (60–200 mesh, 70:30 Hex:EtOAc) and concentrated to yield ca. 1 g of (*E*)-7-(benzyloxy)-4-methyl-5-heptenal as yellow oil which is used without further purification.

To a cooled (−78 °C) solution of allyldiphenylphosphine oxide[51] (1.14 g, 4.70 mmol) and HMPA (1.70 mL, 1.75 g, 9.77 mmol) in dry THF (60 mL) is added dropwise 2.2 mL of a solution of n-butyllithium (2.5 M in hexanes, 5.5 mmol). The resulting red solution is stirred (10 min), and a solution of the above aldehyde (ca. 1 g, 4 mmol) in THF (5 mL) added dropwise over 10 min. The resulting solution is warmed to room temperature over 6 h and quenched by the additions of water (ca. 5 mL). The resulting solution is concentrated and partitioned with Hex:EtOAc (70:30, 100 mL)–water (50 mL). The organic layer is washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260–400 mesh, 98:2 to 80:20 Hex:EtOAc) yields **29** (0.95 g, 86% overall from starting alcohol) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 6.30 (ddd, 1 H, J = 16.9, 10.3, 10.2 Hz), 6.07 (dd, 1 H, J = 15.2, 10.3 Hz), 5.68 (dt, 1 H, J = 15.2, 7.0 Hz), 5.57 (m, 2 H), 5.10 (d, 1 H, J = 16.9 Hz), 4.95 (d, 1 H, J = 10.2 Hz), 4.51 (s, 2 H), 3.99 (m, 2 H), 2.0–2.2 (m, 2 H), 1.4 (m, 3 H), 1.00 ppm (d, 3 H, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.9, 138.3, 137.1, 135.0, 130.9, 128.2, 127.6, 127.4, 124.8, 114.6, 71.8, 70.9, 36.1, 36.0, 30.3, 20.4; IR (CCl_4) 3030 (m), 2980 (s), 2910 (s), 2860 (s), 1500 (s). Anal. Calcd for $C_{18}H_{24}O$: 84.32% C; 9.43% H. Found: 84.63% C, 9.55% H.

(3*R*)-3-Methyl-6,6-(ethylenedioxy)-1-hexene. To a cooled (0 °C), stirred solution of 1,1-dimethyl-2-(3(*R*)-methyl-4-pentenyl)oxirane[56] (4.394 g, 28.5 mmol) in ether (300 mL) is added paraperiodic acid (7.80 g, 34.2 mmol) in three portions over the course of 1.5 h. The resulting mixture is warmed to room temperature and stirred for 5 h, and then anhyd $NaHCO_3$ (7 g) is added. After stirring an additional 2 h the organic layer is dried ($MgSO_4$) and filtered.

To the resulting ether solution is added ethylene glycol (10 mL) and *p*-TsOH (25 mg). After 10 h the ether solution is transferred to a separatory funnel and washed with satd aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica (90:10 Hex:EtOAc) affords (3*R*)-3-methyl-6,6-(ethylenedioxy)-1-hexene (2.50 g, 56%) as a colorless oil: TLC analysis (90:10 Hex:EtOAc) R_f = 0.45; GC

(55) (*E*)-1-(Benzyloxy)-4-methyl-2-heptenol is prepared via the route analogous to that outlined in ref 20, Scheme 4.

(56) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988–2006.

analysis (DB-5, 100–260 °C @ 5 °C/min) 3.9 min; $[\alpha]_D$ −4.93° (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.58–5.78 (m, 1H), 4.84–5.00 (overlapping d's, 2H), 4.80–4.83 (t, 1H, *J* = 5 Hz), 3.9–4.0 (m, 2H), 3.8–3.9 (m, 2H), 2.0–2.2 (m, 1H), 1.6–1.7 (m, 2H), 1.30–1.45 (m, 2H), 0.98 (d, 3H, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2 (d), 113.0 (t), 104.7 (d), 64.8 (t), 37.6 (d), 31.6 (t), 30.6 (t), 20.2 (q); FT-IR (ATR) 2953, 2874, 1411. Anal. Calcd for $C_9H_{16}O_2$: 69.19% C; 10.32% H. Found: 68.97% C, 10.51% H.

(5*E*)-1,1-(Ethylenedioxy)-4(*R*)-methyl-5,7-heptadiene. A stream of ozonized oxygen gas is bubbled through a cooled (−78 °C) mixture of (3*R*)-3-methyl-6,6-(ethylenedioxy)-1-hexene (4.85 g, 30.87 mmol), Sudan (III) indicator (3 drops), and anhyd $NaHCO_3$ (0.5 g) until the color due to the Sudan (III) dissipates. The cold reaction mixture is then flushed with N_2, and triphenylphosphine (8.5 g, 32.4 mmol) is added. The resulting mixture is stirred for 1 h (−78 °C), warmed to room temperature, and stirred for an additional 10 h. The solvent is removed in vacuo and the residue partitioned between ether (150 mL)–water (100 mL). The organics are dried ($MgSO_4$), and concentrated to yield 3.55 g (73%) of crude aldehyde which is used without further purification: TLC analysis (90:10 Hex:EtOAc) R_f = 0.2; GC analysis (DB-5, 100–260 °C @ 5 °C/min) 6.5 min; ^1H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.90 (t, 1H, *J* = 5 Hz), 3.9–4.0 (m, 2H), 3.8–3.9 (m, 2H), 2.35–2.50 (m, 1H), 1.8–2.0 (m, 1H), 1.7–1.8 (m, 2H), 1.45–1.60 (m, 1H), 1.15 (d, 3H, *J* = 7 Hz).

To a cooled (−78 °C) solution of allyldiphenylphospine oxide[51] (2.13 g, 8.79 mmol) and HMPA (3.4 mL, 19.3 mmol) in THF (200 mL) is added n-BuLi (3.87 mL, 9.7 mmol) dropwise. After 15 min a solution of the crude aldehyde (1.39 g, 8.79 mmol) in THF (60 mL) is added dropwise to the red reaction mixture. The resulting mixture is allowed to warm to room temperature (over 3 h) and then quenched by the addition of water (10 mL) and the volatile solvents removed in vacuo. The residue is partitioned between ether (50 mL)–water (30 mL). The organic layer is washed with brine (4 × 30 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica (95:5 Hex:EtOAc) affords (5*E*)-1,1-(ethylenedioxy)-4(*R*)-methyl-5,7-heptadiene (1.18 g, 73%): TLC analysis (90:10 Hex:EtOAc) R_f = 0.5; GC analysis (DB-5, 100–260 °C @ 5 °C/min) 7.7 (94%), 7.4 (6%); $[\alpha]_D$ −4.77° (*c* 1.03, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 6.2–6.4 (m, 1H), 5.90–6.10 (m, 1H), 5.48–5.60 (m, 1H), 4.90–5.10 (overlapping d's, 2H), 4.80 (t, 1H, *J* = 5 Hz), 3.8–4.0 (m, 4H), 2.1–2.3 (m, 1H), 1.6–1.7 (m, 2H), 1.3–1.5 (m, 2H), 1.00 (d, 3H, *J* = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.3 (d), 137.2 (d), 129.5 (d), 114.8 (t), 104.5 (d), 64.7 (t), 36.5 (d), 31.3 (t), 30.8 (t), 20.3 (q); FT-IR (ATR) 2952, 2870, 1604. Anal. Calcd for $C_{11}H_{18}O_2$: 72.49% C; 9.95% H. Found: 72.31% C, 10.03% H.

(2*E*,7*E*)-Methyl 6(*R*)-Methyl-2,7,9-decatrienoate. A solution of (5*E*)-1,1-(ethylenedioxy)-4(*R*)-methyl-5,7-heptadiene (253 mg, 1.40 mmol) and *p*-TsOH (60 mg) in 50% aqueous acetone (12 mL) is stirred (25 °C, 5 h) and then extracted with DCM (4 × 10 mL). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (95:5 Hex:EtOAc) affords 142.7 mg (70%) of aldehyde: TLC analysis (95:5 Hex:EtOAc) R_f = 0.2; GC analysis (DB-5, 100–260 °C @ 5 °C/min) 4.2 (93%), 3.9 (6%); ^1H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.2–6.4 (m, 1H), 5.90–6.10 (m, 1H), 5.40–5.55 (m, 1H), 4.90–5.15 (m, 2H), 2.40 (t, 2H, *J* = 6.0 Hz), 2.10–2.20 (m, 1H), 1.6–1.7 (m, 2H), 1.00 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2 (s), 139.3 (d), 136.9 (d), 130.2 (d), 115.4 (t), 41.7 (t), 36.2 (d), 28.7 (t), 20.3 (q); FT-IR (ATR) 1726 (C=O).

To a cooled (0 °C), stirred solution of anhyd LiCl (0.24 g, 5.6 mmol), triethyl phosphonoacetate (0.95 mL, 4.77 mmol), and DBU (0.67 mL, 4.47 mmol) in dry acetonitrile (25 mL) is added a solution of the above aldehyde (0.600 g, 4.34 mmol) in acetonitrile (10 mL) dropwise over a period of 10 min.[53] After 15 min, the ice bath is removed and the resulting solution stirred (25 °C) for an additional 2 h. Water (10 mL) is added, the volatile organics removed via rotovap, and the residue partitioned with ether (50 mL). The organic layer is washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (90:10 Hex:EtOAc) affords (2*E*,7*E*)-methyl 6(*R*)-methyl-2,7,9-decatrienoate (0.850 g, 94%): TLC analysis (90:10 Hex:EtOAc) R_f = 0.5; capillary GC analysis (DB-5, 100–260 °C @ 5 °C/min) 11.1 (7%), 11.6 (93%); $[\alpha]_D$ −19.67° (*c* 1.14, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 6.85–7.0 (m, 1H), 6.2–6.4 (m, 1H), 5.90–6.10 (m, 1H), 5.80 (d, 1H, *J* = 15 Hz), 5.45–5.60 (m, 1H), 4.95–5.15 (overlapping d's, 2H), 4.15 (q, 2H, *J* = 7.0 Hz), 2.10–2.25 (m, 3H), 1.40–1.50 (m, 2H), 1.25 (t, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.1 (s), 148.6 (d), 139.6 (d), 136.8 (d), 129.8 (d), 121.1 (d), 114.9 (t), 59.7 (t), 35.9 (d), 34.8 (t), 29.7 (t), 20.1 (q), 14.0 (q); FT-IR (ATR) 1718 (C=O), 1653 (C=C). Anal. Calcd for $C_{13}H_{20}O_2$: 74.96% C; 9.68% H. Found: 74.72% C, 9.65% H.

(2*E*,7*E*)-6(*R*)-Methyl-2,7,9-decatrien-1-ol. To a cooled (0 °C), stirred solution of decatrienoate (4.60 g, 22.1 mmol) in THF (200 mL) is added DIBAL-H (32.4 mL, 48.6 mmol) dropwise. After 5 h, the ice bath is removed and the reaction quenched by the addition of $Na_2SO_4{\cdot}10H_2O$ (5 g), Celite (5 g), and ether (200 mL). After 1 h, the mixture is filtered and the filtrate dried ($MgSO_4$), refiltered, and concentrated. Chromatography on silica (95:5 Hex:EtOAc) affords the decatrienol (2.95 g, 80%) as a clear oil: TLC analysis (95:5 Hex:EtOAc) R_f = 0.05; GC analysis (DB-5, 130–260 °C @ 5 °C/min) 4.6 (4%), 4.9 (96%); $[\alpha]_D$ −17.87° (*c* 0.89, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 6.2–6.4 (m, 1H), 5.90–6.10 (m, 1H), 5.62–5.67 (m, 2H), 5.50–5.65 (dd, 1H), 4.90–5.10 (m, 2H), 4.08 (d, 2H, *J* = 7.0 Hz), 2.10–2.25 (m, 1H), 2.04 (s, 1H), 1.95–2.05 (m, 2H), 1.39 (q, 2H, *J* = 8 Hz), 1.01 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6 (d), 137.2 (d), 132.7 (d), 129.4 (d), 129.0 (d), 114.8 (t), 63.4 (t), 36.1 (t), 36.1 (d), 29.8 (t), 20.2 (q); FT-IR (ATR) 3200–3400 (br s, OH), 1456 (m). Anal. Calcd for $C_{11}H_{18}O$: 79.46% C; 10.91% H. Found: 79.51% C, 11.04% H.

(2*E*,7*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-6(*R*)-methyl-2,7,9-decatriene (33). To a warmed (60 °C), stirred solution of decatrienol (0.414 g, 2.49 mmol) and imidazole (0.424 g, 6.23 mmol) in DMF (30 mL) is added slowly a solution of TBDMSCl (0.56 g, 3.74 mmol) in DMF (10 mL). The resulting mixture is kept at 60 °C for 1 h, cooled, and partitioned between ether (75 mL)–water (75 mL). The ether layer is washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (90:10 Hex:EtOAc) affords **33** (0.680 g, 97%) as a colorless oil: TLC analysis (90:10 Hex:EtOAc) R_f = 0.8; GC analysis (DB-5, 130–260 °C @ 5 °C/min) 8.1 (10%), 8.4 (90%); $[\alpha]_D$ −10.23° (*c* 1.03, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 6.2–6.4 (m, 1H), 5.90–6.10 (m, 1H), 5.4–5.7 (overlapping m, 3H), 4.92–5.13 (m, 2H), 4.12 (d, 2H, *J* = 4.0 Hz), 2.10–2.25 (m, 1H), 1.95–2.17 (m, 2H), 1.30–1.40 (q, 2H, *J* = 8.0 Hz), 1.00 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6, 137.4, 131.0, 129.5, 129.3, 114.8, 64.0, 36.3, 36.2, 29.9, 26.0, 25.0, 20.3, 18.4; FT-IR (ATR) 2926, 2854, 1471, 1462. Anal. Calcd for $C_{17}H_{32}OSi$: 72.79% C; 11.50% H. Found: 72.80% C, 11.35% H.

Preparation of Ethyl 3-(2-Phenylethyl)-4-pentenoate. A solution of (*E*)-5-phenyl-2-penten-1-ol (RN 75553-23-0, 5.00 g, 31 mmol) and proprionic acid (2 mL) in triethyl orthoacetate (40 mL) is heated to reflux for 2 h and then the excess orthoacetate removed by distillation (760 Torr). To the residue is added water (10 mL) and the resulting mixture is stirred overnight. The reaction mixture is diluted with EtOAc (200 mL), washed with brine (3 × 100 mL), dried, and concentrated. Bulb-to-bulb distillation affords ethyl 3-(2-phenylethyl)-4-pentenoate (6.10 g, 85%) as a clear oil: GC analysis (DB-5, 100–250 °C @ 5 °C/min) 13.9 (100%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.13–7.30 (m, 5H), 5.68 (m, 1H), 5.08 (td, 1H, *J* = 0.9, 15.7 Hz), 5.07 (td, 1H, *J* = 0.8, 11.5 Hz), 4.10 (q, 2H, *J* = 7.1 Hz), 2.52–2.67 (m, 3H), 2.34 (m, 2H), 1.69 (m, 2H), 1.22 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 142.0, 140.6, 128.3, 128.2, 125.7, 115.6, 60.1, 40.15, 40.1, 36.1, 33.2, 14.2; IR (neat, ATR) 1734 (s, C=O); HRMS analysis (EI, $C_{15}H_{20}O_2$ = 232.1458), found *m/z* 232.1462.

Preparation of 3-(2-Phenylethyl)-4-penten-1-ol. To a cooled (−78 °C) solution of ethyl-3-(2-phenylethyl)-4-pentenoate (10.0 g, 43 mmol) in THF (300 mL) is added dropwise DIBAL-H (63 mL, 95 mmol). The resulting solution is slowly warmed to ambient temperature and then quenched by the

careful added of ice (ca. 10 g). The resulting mixture is partitioned between ether (300 mL)−5% aqueous H_2SO_4 (200 mL) and the aqueous layer extracted with ether (100 mL). The combined organic layers are washed with brine (2 × 200 mL), dried, and concentrated. Bulb-to-bulb distillation affords 3-(2-phenylethyl)-4-penten-1-ol (6.10 g, 92%) as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16−7.39 (m, 5H), 5.69 (m, 1H), 5.16 (dd, 1H, J = 2.0, 9.5 Hz), 5.13 (ddd, 1H, J = 0.7, 2.0, 17.8 Hz), 3.67 (m, 2H), 2.53−2.83 (m, 2H), 2.37−2.50 (broad m, 1H), 2.19−2.35 (m, 1H), 1.57−1.89 (m, 4H); ^{13}C NMR (50.4 MHz, $CDCl_3$) δ 142.6, 142.4, 128.5, 128.4, 125.7, 115.6, 60.9, 40.8, 37.8, 37.1, 33.5; HRMS analysis (EI, $C_{13}H_{22}O$ = 190.1353), found m/z 190.1357.

Preparation (*E*)-5-(2-Phenylethyl)-2,6-heptadien-1-ol. To a cooled (−78 °C) solution of oxalyl chloride (2.50 mL, 28 mmol) and DMSO (4.1 mL, 5.8 mmol) in DCM (300 mL) is added a solution of 3-(2-phenylethyl)-4-penten-1-ol (5.00 g, 28.9 mmol) in DCM (30 mL) dropwise over 15 min. The resulting cloudy mixture is stirred (30 min) and then triethylamine (18.3 mL, 132 mmol) added dropwise. The cooling bath is removed and the mixture warmed to room temperature over 45 min. The resulting mixture is partitioned between ether (400 mL)−water (100 mL). The organic layer is washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil is filtered through a plug of silica (60−200 mesh, 70:30 Hex:EtOAc) to yield 4.91 g (99%) of (*E*)-3-(2-phenylethyl)-4-pentenal as a clear oil, which is used without further purification: GC analysis (DB-5, 100−250 °C @ 5 °C/min) 6.4 (2.6%), 7.9 (95.5%), 9.3 (1.9%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.69 (t, 1 H, J = 2.1 Hz), 7.26 (m, 2H), 7.17 (m, 3H), 5.68 (m, 1H), 5.10 (overlapping d, 2H), 2.65 (m, 2H), 2.58 (m, 1H), 2.45 (m, 2H), 1.69 (m, 2H).

To a stirred mixture of anhyd LiCl (1.86 g, 33.6 mmol), triethyl phosphonoacetate (6.70 mL, 33.7 mmol), and DBU (5.10 mL, 34.1 mmol) in acetonitrile (90 mL) is added dropwise a solution of crude (*E*)-3-(2-phenylethyl)-4-pentenal (6.33 g, 33.6 mmol) in acetonitrile (10 mL).[53] After 5 min, the reaction is quenched by the addition of water (ca. 2 mL) and then concentrated and the residue taken up in ether (200 mL). The organics are washed with brine (2 × 100 mL), dried, filtered, and concentrated. The resulting yellow oil is filtered through a plug of silica (60−200 mesh, 70:30 Hex:EtOAc) to yield ethyl (*E*)-5-(2-phenylethyl)-2,6-heptadienoate (7.46 g, 99%) as a clear yellow oil which is used without further purification.

To a cooled (−78 °C), stirred solution of crude ethyl (*E*)-5-(2-phenylethyl)-2,6-heptadienoate (7.01 g, 27.0 mmol) in THF (250 mL) is added dropwise a solution of DIBAL-H (40.0 mL, 60.0 mmol). The resulting solution is stirred (3 h) and then quenched by the careful addition of Na_2SO_4·$10H_2O$ (11 g). After an additional 4 h (25 °C), ether (200 mL), Celite (7 g), and anhyd Na_2SO_4 (10 g) are added. The resulting slurry is filtered, and the salts washed with ether (3 × 150 mL). The combined organics are dried, filtered, and concentrated. Chromatography on silica (60−200 mesh, 80:20 Hex:EtOAc) yields (*E*)-5-(2-phenylethyl)-2,6-heptadien-1-ol (5.00 g, 86%) as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1−7.3 (m, 5 H), 5.5−5.7 (m, 3 H), 5.08 (d, 1 H, J = 5.4 Hz), 5.01 (dd, 1 H, J = 2.1, 14.0 Hz), 4.06 (br d, 2 H, J = 3.2 Hz), 2.4−2.7 (m, 2 H), 2.11 (m, 3 H), 1.5−1.8 (m, 3 H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 142.5, 142.1, 130.8, 130.5, 128.3, 128.2, 125.6, 115.0, 63.6, 43.3, 37.7, 36.0, 33.3; IR (CCl_4) 3618 (m, OH), 3485 (br s, OH), 3084 (m), 1604 (m). Anal. Calcd for $C_{15}H_{20}O$: 83.28% C; 9.32% H. Found: 83.06% C, 9.40% H.

Preparation of (*E*)-1-(Benzyloxy)-5-(2-phenylethyl)-2-hepten-7-ol. To a cooled (0 °C), stirred suspension of sodium hydride (0.69 g, 28.8 mmol) in DMF (150 mL) is added dropwise a solution of (*E*)-5-(2-phenylethyl)-2,6-heptadien-1-ol (4.33 g, 20.0 mmol) in DMF (10 mL). The resulting mixture is stirred (20 min (0 °C), 30 min (25 °C)), and then recooled (0 °C) and benzyl bromide (3.30 mL, 27.7 mmol) added dropwise. The resulting solution is warmed to ambient temperature (3 h), carefully quenched by the addition of water (ca. 2 mL), and then partitioned between ether (300 mL)−water (100 mL). The organic extract is washed with brine (2 × 100 mL), dried, filtered, and concentrated to afford a yellow oil. Chromatography on silica (60−200 mesh, 95:5 Hex:EtOAc) yields 6.47 g of (*E*)-1-(benzyloxy)-5-(2-phenylethyl)-2,6-heptadiene (80% pure by GC analysis) which is used without further purification. Analytical data for the major component: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 10 H), 5.60 (m, 3 H), 5.04 (m, 2 H), 4.54 (s, 2 H), 4.46 (m, 2 H), 3.95 (d, 2 H, J = 4.9 Hz), 2.58 (m, 2 H), 2.1 (m, 3 H), 1.5−1.7 (m, 2 H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 143.2, 142.8, 139.1, 138.9, 133.1, 123.0, 128.9, 128.9, 128.45, 128.35, 128.2, 128.1, 126.2, 115.6, 72.7, 72.2, 71.3, 43.9, 38.5, 36.6, 34.0.

To a stirred solution of (*E*)-1-(benzyloxy)-5-(2-phenylethyl)-2,6-heptadiene (80% pure by GC analysis, 5.72 g) in THF (120 mL) is added a solution of 9-BBN (35.5 mL, 17.8 mmol) dropwise over 0.5 h. The resulting solution is stirred (2.5 h) and then cooled (0 °C) and 30% aqueous hydrogen peroxide (6.8 mL, 67 mmol) and 3.0 M aqueous NaOH (5.6 mL, 17 mmol) simultaneously added dropwise. The resulting solution is stirred (2 h) and then concentrated and the residue partitioned between ether (250 mL)−satd aqueous sodium bicarbonate (150 mL). The organic extract is washed with brine (2 × 150 mL), dried, filtered, and concentrated. Chromatography on silica (60−200 mesh, 70:30 Hex:EtOAc) yields (*E*)-1-(benzyloxy)-5-(2-phenylethyl)-2-hepten-7-ol (4.59 g, 71% overall from (*E*)-5-(2-phenylethyl)-2,6-heptadien-1-ol) as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19 (m, 10 H), 5.54 (m, 2 H), 4.37 (s, 2 H), 3.86 (d, 2 H, J = 4.7 Hz), 3.52 (t, 2 H, J = 6.6 Hz), 2.48 (m, 2 H), 2.01 (m, 2 H), 1.48 (m, 6 H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 142.5, 138.3, 132.3, 128.30, 128.27, 128.24, 127.7, 127.5, 125.6, 71.8, 70.7, 60.7, 36.38, 36.32, 35.5, 33.9, 33.0; IR (neat, ATR) 3405 (br, OH), 1603 (m); HMRS analysis (FAB, $C_{22}H_{28}O_2Li$: 331.2249), found m/z 331.2236.

Preparation of (2*E*,7*E*)-1-(Benzyloxy)-5-(2-phenylethyl)-2,7,9-decatriene (36). To a cooled (−78 °C) solution of oxalyl chloride (0.60 mL, 6.9 mmol) and DMSO (0.98 mL, 12.7 mmol) in DCM (100 mL) is added dropwise a solution of (*E*)-1-(benzyloxy)-5-(2-phenylethyl)-2-hepten-7-ol (2.04 g, 6.3 mmol) in DCM (15 mL). The resulting cloudy solution is stirred (30 min) and then triethylamine (4.4 mL, 31 mmol) added dropwise. The cold bath is removed and the resulting mixture warmed to room temperature over 90 min. The reaction mixture is washed sequentially with water (100 mL) and brine (2 × 100 mL), dried, filtered, and concentrated. The resulting yellow oil is filtered through a plug of silica (60−200 mesh, 70:30 Hex:EtOAc) to yield 2.04 g (99.9%) of (*E*)-7-(benzyloxy)-3-(2-phenylethyl)-5-heptenal as a clear liquid which is used without further purification.

To a cooled (−78 °C) solution of allyldiphenylphosphine oxide[51] (1.76 g, 7.30 mmol) and HMPA (2.50 mL, 14.4 mmol) in THF (100 mL) is added dropwise of a solution of n-BuLi (2.80 mL, 7.0 mmol). The resulting red solution is stirred (5 min, −78 °C) and then a solution of (*E*)-7-(benzyloxy)-3-(2-phenylethyl)-5-heptenal (2.04 g, 6.30 mmol) in THF (20 mL) added dropwise over 30 min. The resulting solution is slowly warmed to ambient temperature (8 h) and then quenched by the addition of water (ca. 5 mL). The reaction mixture is concentrated in vacuo and the residue partitioned between Hex:EtOAc (70:30, 400 mL)−water (100 mL). The organic layer is washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 95:5 Hex:EtOAc) yields **36** (1.71 g, 78%) as a clear oil: GC analysis (DB-5, 100−250 °C @ 5 °C/min) 17.17 (89.0%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1−7.3 (m, 10 H), 6.32 (ddd, 1 H, J = 10.1, 10.3, 17.0 Hz), 6.04 (dd, 1 H, J = 10.3, 15.1 Hz), 5.7−5.6 (m, 3 H), 5.09 (dd, 1 H, J = 1.8, 17.0 Hz), 4.97 (dd, 1 H, J = 1.8, 10.1 Hz), 4.50 (s, 2 H), 3.90 (d, 2 H, J = 4.0 Hz), 2.61 (t, 2 H, J = 8.1 Hz), 2.12 (m, 4 H), 1.60 (m, 3 H); ^{13}C NMR (50.5 MHz, $CDCl_3$) δ 142.5, 138.4, 137.1, 133.0, 132.6, 132.4, 128.2, 127.7, 127.4, 125.6, 114.9, 71.7, 70.7, 37.4, 36.4, 36.1, 35.0, 33.0; IR (CCl_4) 3087 (m), 3064 (m), 3028 (m), 3008 (m), 2973 (m), 2919 (s), 2856 (m), 1603 (m). Anal. Calcd for $C_{25}H_{30}O$: 86.66% C; 8.73% H. Found: 86.51% C, 8.79% H.

General Procedures for the Five-Membered Ring-Forming Iron-Catalyzed Ene Carbocyclization of Trienes and Subsequent Cleavage of the Mixture of Enol Ethers. Method A. Addition of the Triene Substrate to a Solution of Preformed Iron Catalyst. To a stirred solution (0−25 °C) of $Fe(acac)_3$ (10−25 mol % calculated on substrate), 2,2′-

bipyridine (1.1 equiv relative to iron), and 0.5 mL of furan[20] in dry oxygen-free benzene or toluene (30 mL) is added dropwise a solution of triethylaluminum (3.1 equiv relative to iron). The resulting black solution is stirred (5–15 min, 25 °C) and then a solution of triene substrate (1 equiv) in 5 mL of benzene or toluene is added dropwise. The resulting reaction mixture is stirred (25–50 °C) for 3–15 h, filtered through a plug of silica (60–200 mesh, 1:1 Hex:EtOAc), and concentrated to afford the crude mixture of enol ethers.

Method B. Generation of the Active Iron Catalyst in the Presence of the Triene Substrate (Method B). To a stirred solution (0–25 °C) of triene substrate (1 equiv), $Fe(acac)_3$ (10–25 mol % calculated on substrate), and 2,2′-bipyridine (1.1 equiv relative to iron) in dry oxygen-free benzene or toluene (30 mL) is added dropwise a solution of triethylaluminum (3.1 equiv relative to iron). The resulting deep purple solution is stirred (25–50 °C) following the disappearance of starting material by TLC analysis (typically 3–15 h), filtered through a plug of silica (60–200 mesh, 1:1 Hex:EtOAc), and concentrated to afford the crude mixture of enol ethers.

Acetalization of the Crude Enol Ether Mixture. A solution of the crude mixture of enol ethers in THF (ca. 5 mL) and excess ethylene glycol (ca. 1 mL) is acidified with *p*-TsOH (ca. 20 mg). Upon complete conversion of the enol ethers as judged by TLC analysis, the reaction mixture is partition between ether (ca. 50 mL)–satd aqueous $NaHCO_3$ (ca. 50 mL). The organic layer is washed with brine (ca. 50 mL), dried ($MgSO_4$), filtered, and concentrated to afford the crude mixture of acetals. The ratio of diastereomeric acetals is determined by capillary GC analysis of the crude acetal mixture. Chromatography on silica (Hex:EtOAc eluent) affords the purified product.

a. Cyclization of 4a (R^1 = CH_2Ph; method A). Treatment of **4a** (304.6 mg, 1.14 mmol) with the catalyst prepared from $Fe(acac)_3$ (126 mg, 0.36 mmol), bpy (63 mg, 0.40 mmol), Et_3Al (0.60 mL, 1.14 mmol), and furan (0.5 mL) in dry oxygen-free benzene (35 mL, 50 °C, 15 h) affords 303.7 mg of a crude mixture of enol ethers. Acetalization according the procedure described above affords a crude mixture of acetals: GC analysis (DB-5, 100–250 °C @ 5 °C/min) 6.45 (6.0%, *trans*-**21a**), 6.87 (4.0%, *trans*-**22a**), 7.10 min (90.0%, *cis*-**21a**). Chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) yields 200.0 mg (81%) of predominantly *cis*-**21a** as a clear oil: ^1H NMR (major isomer, 200 MHz, $CDCl_3$) δ 5.2–5.5 (m, 2 H), 4.79 (dd, 1 H, J = 5.2, 5.2 Hz), 3.7–4.0 (m, 4 H), 2.8–3.0 (m, 1 H), 1.8–2.1 (m, 1 H), 1.2–1.8 ppm (m, 8 H) overlapping with 1.57 (dd, 3 H, J = 6.6, 1.6 Hz); ^{13}C NMR (major isomer, 50.5 MHz, $CDCl_3$) δ 131.6, 123.5, 104.5, 64.7, 64.6, 39.8, 39.5, 35.4, 32.2, 30.6, 23.0, 13.0 ppm; IR (neat, ATR ZnSe crystal) 3007 (m), 2946 (s), 2868 (s), 1474 (m), 1451 (m), 1434 (m), 1407 (s). Anal. Calcd for $C_{12}H_{20}O_2$: 73.43% C; 10.27% H. Found: 73.57% C, 10.27% H.

b. Cyclization of 5 (method B). Treatment of **5** (350.0 mg, 1.36 mmol) with the catalyst derived from $Fe(acac)_3$ (127.0 mg, 0.36 mmol), bpy (68.0 mg, 0.43 mmol), furan (0.5 mL), and Et_3Al (0.60 mL, 1.14 mmol) in dry oxygen-free benzene (30 mL, 50 °C, 12 h) affords 401 mg of a crude mixture of starting triene and enol ethers. Acetalization as per the procedure described above affords a crude mixture of acetals: GC analysis of the acetal region (DB-5, 100–250 °C @ 5 °C/min) 8.30 (92.8%), 8.57 min (7.2%). Chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) yields 170.0 mg of recovered **7** and 79.0 mg of predominantly **7** as a clear oil: ^1H NMR (major isomer, 300 MHz, $CDCl_3$) δ 4.98 (d, 1 H, J = 9.6 Hz), 4.78 (dd, 1 H, J = 10.5, 5.5 Hz), 3.93 (m, 2 H), 3.80 (m, 2 H), 2.76 (m, 1 H), 2.0 (m, 1 H), 1.2–1.8 (m, 14 H, (includes some solvent)) overlapping with 1.66 (s, 3 H) and 1.59 ppm (s, 3 H); ^{13}C NMR (major isomer, 75.5 MHz, $CDCl_3$) δ 125.6, 104.4, 64.7, 64.5, 41.1, 39.6, 35.4, 32.3, 31.6, 30.4, 26.0, 23.0, 22.6, 18.0, 14.1 ppm; IR (neat, ATR ZnSe crystal) 2945 (s), 2869 (s), 1473 (m), 1450 (m), 1435 (m).

c. Cyclization of 10 (method B). Treatment of **10** (336.0 mg, 1.20 mmol) with the catalyst prepared from $Fe(acac)_3$ (63.6 mg, 0.18 mmol), bpy (28.0 mg, 0.18 mmol), and Et_3Al (0.29 mL, 0.55 mmol) in dry toluene (10 mL, 25 °C, 12 h) affords 265 mg of a crude mixture of dienes. Chromatography on silica (95:5 Hex:EtOAc) yields 250 mg (79%) of predominantly **11** as a clear oil: TLC analysis (90:10 Hex:EtOAc) R_f = 0.4; capillary GC analysis (DB-17, 100–260 °C @ 5 °C/min) 14.5 (4%), 15.0 (12%), 15.6 (9%), 15.7 min (75%); ^1H NMR (200 MHz, $CDCl_3$) δ 5.65–5.83 (m, 1H), 5.40–5.58 (m, 1H), 5.2–5.34 (m, 1H), 4.95–5.05 (m, 2H), 4.2–4.6 (q, 4H, J = 7.0 Hz), 1.62 (d, 3H, J = 6.0 Hz), 1.25 (t, 6H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 138.4, 130.1, 124.7, 114.9, 61.2, 59.1, 47.1, 40.4, 39.9, 38.7, 13.9, 13.0 ppm; FT-IR (neat) 1734 (s), 1446 (m). Anal. Calcd for $C_{16}H_{24}O_4$: 68.54% C; 8.63% H. Found: 68.58% C, 8.50% H.

d. Cyclization of 12 (method B). Treatment of **12** (254.3 mg, 0.95 mmol) with the catalyst prepared from $Fe(acac)_3$ (50 mg, 0.14 mmol), bpy (22 mg, 0.14 mmol), and Et_3Al (0.23 mL, 0.44 mmol) in dry toluene (10 mL) affords 254.4 mg of a crude mixture of dienes. Chromatography on silica (95:5 Hex:EtOAc) yields 201.0 mg (80%) of predominantly **13** as a clear oil: TLC analysis (95:5 Hex:EtOAc) showed a single component R_f = 0.36; GC analysis (DB-1701, 100–260 °C @ 5 °C/min) 12.6 (10%), 13.2 (6%), 13.5 (4%), 14.1 min (80%); ^1H NMR (200 MHz, $CDCl_3$) δ 5.5–5.7 (m, 1H), 5.18–5.28 (m, 1H), 4.72–4.92 (m, 2H), 4.40 (q, 4H, J = 7.0 Hz), 2.8–3.1 (m, 2H), 2.5–2.7 (m, 2H), 1.9–2.0 (m, 1H), 1.63 (d, 3H, J = 6.0 Hz), 1.25 (t, 6H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 151.0, 131.5, 125.6, 107.0, 61.4, 58.6, 41.1, 40.6, 40.0, 14.0, 13.0; FT-IR (neat) 1734 (s). Anal. Calcd for $C_{15}H_{22}O_4$: 67.65% C; 8.33% H. Found: 67.74% C, 8.37% H.

e. Cyclization of 14a (R^1 = CH_2Ph; method A). Treatment of **14a** (385.0 mg, 0.996 mmol) with the catalyst derived from $Fe(acac)_3$ (53.0 mg, 0.15 mmol), bpy (23.0 mg, 0.15 mmol), and Et_3Al (0.24 mL, 0.46 mmol) in dry toluene (15 mL, 25 °C, 12 h) affords 400 mg of a crude mixture of enol ethers. Acetalization as per the procedure described above affords 380 mg of a crude mixture of acetals. Chromatography on silica (95:5 Hex:EtOAc) yields 340.0 mg (100%) of *cis*-**21b** as a clear oil: TLC analysis (90:10 Hex:EtOAc) R_f = 0.13; GC analysis (DB-1701, 200–260 °C @ 2 °C/min) 9.7 min (100%, *cis*-**21b**); ^1H NMR (200 MHz, $CDCl_3$) δ 5.45–5.55 (m, 1H), 5.28 (t, 1H, J = 11.0 Hz), 4.84 (t, 1H, J = 5 Hz), 4.18 (q, 4H, J = 7 Hz), 3.80–3.96 (m, 4H), 3.05–3.13 (m, 1H), 2.4–2.6 (m, 2H), 2.2–2.35 (m, 1H), 2.00–2.15 (m, 2H), 1.5–1.75 (m, 2H), 1.55 (d, 3H, J = 7 Hz), 1.25 (t, 6H, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5, 128.2, 126.8, 103.8, 64.7, 64.5, 61.3, 59.1, 40.0, 39.3, 39.0, 38.5, 34.5, 13.9, 12.9; FT-IR (ATR) 1734 (s), 1729 (s). Anal. Calcd for $C_{18}H_{28}O_6$: 63.51% C; 8.29% H. Found: 63.47% C, 8.36% H.

f. Cyclization of 14b (R^1 = TBDMS; 60:40 (2*E*,7*E*): (2*Z*,7*E*) mixture; method A). Treatment of **14b** (223.0 mg, 0.54 mmol) with the catalyst derived from $Fe(acac)_3$ (29.0 mg, 0.08 mmol), bpy (13.0 mg, 0.08 mmol), and Et_3Al (0.13 mL, 0.25 mmol) in dry toluene (15 mL, 25 °C, 12 h) affords a crude mixture of enol ethers. Acetalization as per the procedure described above affords a crude mixture of acetals. Chromatography on silica (95:5 Hex:EtOAc) yields 156.0 mg (70%) of a mixture of acetals: TLC analysis (80:20 Hex:EtOAc) R_f = 0.15; GC analysis (DB-17, 200–260 °C @ 2 °C/min) 8.90 (15%, *trans*-**21b**), 9.66 (34%, *cis*-**22b**), 9.80 min (51%, *cis*-**21b**). IR and NMR spectra are consistent with this mixture.

g. Cyclization of 24a (R = H, R^1 = CH_2Ph; method B). Treatment of **24a** (336.1 mg, 1.37 mmol) with the catalyst derived from $Fe(acac)_3$ (126.7 mg, 0.36 mmol), bpy (57.3 mg, 0.37 mmol), Et_3Al (0.60 mL, 1.14 mmol), and furan (0.5 mL) in dry oxygen-free benzene (25 mL, 25 °C, 12 h) affords a crude mixture of enol ethers. Acetalization as described above affords crude mixture of acetals: GC analysis of the acetal region (DB-5, 100–250 °C @ 5 °C/min) 6.3 (0.8%), 6.7 (88.0%, *trans*-**21a**), 7.1 (9.2%, *cis*-**22a**), 7.2 min (2.1%, *cis*-**21a**). Chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) yields 44.9 mg of recovered **24a** and 120.0 mg (44%) of predominantly *trans*-**21a** as a clear liquid: ^1H NMR (major isomer, 300 MHz, $CDCl_3$) δ 5.44 (m, 1 H), 5.21 (ddd, 1 H, J = 9.6, 9.6, 1.7 Hz), 4.83 (dd, 1 H, J = 6.0, 5.8 Hz), 3.93 (m, 2 H), 3.80 (m, 2 H), 2.30 (m, 1 H), 1.2–2.0 (m, 9 H) overlapping with 1.58 (dd, 3 H, J = 6.8, 1.7 Hz); ^{13}C NMR (major isomer, 50.5 MHz, $CDCl_3$) δ 135.3, 124.3, 104.8, 65.3, 65.1, 45.2, 43.6, 38.8, 33.1, 32.7,

24.2, 13.7 ppm; IR (CCl_4) 3004 (m), 2938 (s), 2910 (m), 2869 (s), 1450 (m), 1434 (m), 1405 (m); HRMS analysis ($C_{12}H_{20}O_2$ = 196.1463), found 196.1463 *m/z*.

h. Cyclization of 24b (R = CO_2Et, R^1 = CH_2Ph). Treatment of **24b** (255.2 mg, 0.66 mmol) with the catalyst derived from $Fe(acac)_3$ (35.0 mg, 0.10 mmol), bpy (15.5 mg, 0.10 mmol), and Et_3Al (0.16 mL, 0.31 mmol) in dry toluene (15 mL) affords 222 mg of a crude mixture of enol ethers. Acetalization as per the procedure described above affords 207 mg of a crude mixture of acetals. Chromatography on silica (95:5 Hex:EtOAc) yields 140 mg (62%) of a mixture of acetals as a clear oil: TLC analysis (90:10 Hex:EtOAc) R_f = 0.2; GC analysis (DB-1701, 200–260 °C @ 2 °C/min) 8.8 min (64%, *trans*-**21b**), 9.6 min (36%, *cis*-**22b**); ^1H NMR (200 MHz, $CDCl_3$) δ 5.65–5.83 (m, 1 H), 5.45–5.55 (m, 1H), 5.28 (t, 1H, J = 11.0 Hz), 4.95–5.05 (m, 2H), 4.84 (t, 1H, J = 5 Hz), 4.18 (q, 4H, J = 7 Hz), 3.80–3.96 (m, 4H), 3.0–3.15 (m, 1H), 2.4–2.6 (m, 2H), 2.2–2.35 (m, 1H), 2.00–2.15 (m, 2H), 1.5–1.75 (m, 2H), 1.5–1.6 (d, 3H, J = 7 Hz), 1.20–1.30 (t, 6H, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 172.7, 172.5, 137.2, 132.1, 128.2, 126.8, 115.9, 104.0, 103.9, 103.8, 64.8, 64.8, 64.7, 64.5, 61.3, 59.1, 58.7, 43.8, 42.0, 40.0, 39.3, 39.0, 38.52, 37.9, 37.3, 34.5, 33.4, 14.1, 13.9, 12.9; FT-IR (ATR) 1726 (s). Anal. Calcd for $C_{18}H_{28}O_6$: 63.51% C; 8.29% H. Found: 63.57% C, 8.34% H.

i. Cyclization of 29 (method B). Treatment of **29** (264.4 mg, 1.03 mmol) with the catalyst derived from $Fe(acac)_3$ (126.4 mg, 0.36 mmol), bpy (62.1 mg, 0.40 mmol), Et_3Al (0.60 mL, 1.14 mmol), and furan (0.5 mL) in dry oxygen-free benzene (40 mL, 55 °C, 10 h) affords 233 mg of a crude mixture of enol ethers. Acetalization according to the procedure described above affords the crude acetal **30a**: GC analysis (DB-5, 100–250 °C @ 5 °C/min) 7.6 min (100%). Chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) yields 131.8 mg (62%) of **30a** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.2–5.4 (m, 2 H), 4.79 (dd, 1 H, J = 6.4, 3.9 Hz), 3.9–4.0 (m, 2 H), 3.8–3.9 (m, 2 H), 3.04 (m, 1 H), 0.9–1.9 (m, 8 H) overlapping with 1.59 (dd, J = 6.6, 1.5 Hz, 3 H) and 0.99 (d, 3 H, J = 6.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.2, 123.0, 104.0, 64.7, 64.6, 46.6, 39.2, 28.2, 34.1, 32.7, 31.6, 19.9, 13.0 ppm; IR (neat, ATR ZnSe crystal) 2947 (s), 2922 (s), 2868 (s), 1472 (m), 1449 (m), 1435 (m); HMRS analysis ($C_{13}H_{22}O_2$ = 210.1621), found 210.1621 *m/z*.

j. Cyclization of 33 and Subsequent Conversion to 34 (method A). Treatment of **33** (416 mg, 1.48 mmol) with the catalyst derived from $Fe(acac)_3$ (79 mg, 0.22 mmol), bpy (35 mg, 0.22 mmol), and Et_3Al (0.36 mL, 0.36 mmol in dry toluene (25 mL, 55 °C, 12 h) to afford 580 mg of a crude mixture of enol ethers. Treatment with 5% aqueous HCl (1 mL) in acetone (10 mL, 25 °C, 2 h) followed by aqueous workup (EtOAc–aqueous $NaHCO_3$) affords 320 mg of crude aldehyde. The crude aldehyde is treated with $NaBH_4$ (129 mg, 3.42 mmol) in ethanol (25 °C, 10 h), quenched by the addition of 10% aqueous HCl, and extracted with EtOAc/Hex (50:50, 2 × 10 mL). The combined organic extracts are dried and concentrated and the residue chromatographed on silica (90:10 Hex:EtOAc) to yield 131.3 mg (53%) of **34** as a clear oil: TLC analysis (80:20 Hex:EtOAc) R_f = 0.30; GC analysis (DB-5, 130–260 °C @ 5 °C/min) 4.90 (1%), 4.59 min (99%); $[\alpha]_D$ = −28.9° (*c* 1.2, CCl_4); ^1H NMR (500 MHz, $CDCl_3$) δ 5.45–5.60 (m, 1H), 5.30 (m, 1H), 3.60–3.70 (m, 2H), 2.4–2.5 (q, 1H, J = 7.2 Hz), 2.0–2.2 (m, 1H), 1.8–1.95 (m, 2H), 1.6–1.75 (m, 2H), 1.63–1.66 (br d, 3H, J = 4.4 Hz), 1.3–1.5 (m, 2H), 1.1–1.3 (m, 1H), 0.98 (d, 3H, J = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2 (d), 124.1 (d), 62.4 (t), 47.5 (d), 40.5 (d), 38.6 (d), 34.7 (t), 33.4 (t), 31.4 (t), 19.9 (q), 13.1 (q); FT-IR (ATR) 3311 (OH), 1456. Anal. Calcd for $C_{11}H_{20}O$: 78.51% C; 11.98% H. Found: 78.43% C, 11.76% H.

k. Cyclization of 36 (method A). Treatment of **36** (280.0 mg, 0.81 mmol) with the catalyst derived from $Fe(acac)_3$ (44.4 mg, 0.12 mmol), bpy (23.0 mg, 0.15 mmol), and Et_3Al (0.22 mL, 0.42 mmol) in dry oxygen-free benzene (20 mL, 25 °C, 12 h) affords a crude mixture of enol ethers. Acetalization as per the procedure described above affords a crude mixture of acetals: GC analysis of the acetal region (DB-5, 100–250 °C @ 10 °C/min) 14.3 (36.8%), 14.4 min (63.2%). Chromatography on silica (260–400 mesh, 95:5 Hex:EtOAc) yields 96.0 mg (40.0%) of a mixture of stereoisomeric cyclopentanes **37** as a clear liquid: ^1H NMR (200 MHz, $CDCl_3$) δ 7.26 (m, 5 H), 5.2–5.5 (m, 2 H), 4.82 (dd, 1 H, J = 5.2, 5.2 Hz), 3.8–4.0 (m, 4 H), 2.9–3.0 (m, 1 H), 2.55–2.65 (m, 2 H), 1.3–2.2 (m, 12 H), 1.0–1.3 ppm (m, 1 H); ^{13}C NMR (50.5, $CDCl_3$) δ 142.7, 132.9, 131.1, 128.2, 128.1, 125.5, 123.9, 122.9, 104.3, 64.7, 64.5, 40.3, 39.5, 39.40, 39.37, 38.87, 38.83, 38.78, 38.58, 38.51, 36.7, 35.8, 35.4, 35.0, 34.8, 12.9, 12.8 ppm; IR (CCl_4) 3027 (m), 1741 (s, C=O), 1453 (m), 1446 (m). Anal. Calcd for $C_{20}H_{28}O_2$: 79.96% C; 9.39% H. Found: 80.21% C, 9.59% H.

Preparation of (−)-Mitsugashiwalactone (35) from Cyclization Product 34. A solution of 90 mg (0.53 mmol) of **34** in 15 mL of CH_2Cl_2, a small amount of anhyd $NaHCO_3$, and 2–3 drops of Sudan III is cooled to −78 °C and treated with ozonized oxygen gas until the color due to Sudan III dissipates. The system is flushed with N_2 (−78 °C, 10 min), warmed to room temperature, and quenched by the addition of triphenylphosphine (147 mg, 0.56 mmol, 4 h). The solvent is removed in vacuo and the residue partitioned between DCM (50 mL)–water (25 mL). The organic layer is washed with water (25 mL), dried, filtered, and concentrated. Chromatography on silica gel (80:20 Hex:EtOAc) affords intermediate lactol as a clear oil: TLC analysis (80:20 Hex:EtOAc) R_f = 0.3; GC analysis (DB-5, 100–260 °C @ 5 °C/min) 4.33 (13%), 4.25 (87%) min; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (d, 1H, J = 2.4 Hz), 3.88–3.97 (m, 1H), 3.49–3.56 (m, 1H), 2.95 (br s, 1H) 2.35–2.40 (m, 1H), 2.25–2.38 (m, 1H), 1.90–2.10 (m, 2H), 1.70–1.80 (m, 1H), 1.3–1.5 (m, 4H), 1.15–1.25 (m, 1H), 0.99 (d, 3H, J = 6 Hz).

To a stirred orange slurry of pyridium chlorochromate (0.407 g, 1.89 mmol), Celite (200 mg), and $NaHCO_3$ (159 mg, 1.89 mmol) in DCM (5 mL) is added the intermediate lactol described above (59 mg, 0.38 mmol) in DCM (3 mL). After 15 min the ice bath is removed and the resulting brown mixture is stirred at ambient temperature (6 h). The resulting mixture is diluted with ether (10 mL), filtered through Florisil, and concentrated. Chromatography on silica (80:20 Hex:EtOAc) yields 24.8 mg (42%) of mitsugashiwalactone[46–49] as a yellow solid: $[\alpha]_D$ = −1.9° (*c* = 1.23, CCl_4); TLC analysis (70:30 Hex:EtOAc) R_f = 0.35; GC analysis (DB-5, 130–260 °C @ 5 °C/min) 7.0 min; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (ddd, 1H, J = 3, 6, 11 Hz), 4.15 (ddd, 1H, J = 3, 6, 11 Hz), 2.45–2.60 (m, 1H), 2.33 (t, 1H, J = 11 Hz), 2.1–2.23 (m, 1H), 1.92–2.04 (m, 2H), 1.81–1.90 (m, 1H), 1.42–1.54 (m, 1H), 1.2–1.35 (m, 1H), 1.15–1.21 (m, 1H), 1.16 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0 (s), 67.2 (t), 50.5 (d), 39.8 (d), 36.6 (d), 34.7 (t), 33.0 (t), 29.6 (t), 20.2 (q); FT-IR (ATR) 1726.

Acknowledgment. Financial support of this work by the National Institutes of Health (GM34927) is gratefully acknowledged. We thank R. Chidambaram, F. Clement, S. Mehrman, and B. Takacs for assistance in the preparation and cyclization of certain of the trienes. High resolution mass spectral analyses were performed by the Midwest Center for Mass Spectrometry.