A Chelation-Controlled Ester Enolate Claisen Rearrangement

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The Ireland ester enolate Claisen rearrangement gives rise to *Z*-trisubstituted alkenes due to heteroatom-enforced control over the conformation of the transition state. An oxygen-bearing functional group at the tertiary carbinol center, which can coordinate to the enolate metal via a seven-membered chelated transition state, provides the control element to explain the selectivity. α,β-Disubstituted unsaturated carboxylic acids are also formed with high diastereoselectivity.

Introduction

In the course of the Claisen rearrangement, both a new carbon–carbon double bond and a new carbon–carbon single bond are formed, the stereochemical fates of which are direct consequences of the chairlike transition states through which the rearrangement normally proceeds. It has long been realized that the enolate geometry determines the relative stereochemistry α and β to the carbonyl moiety in the γ,δ-unsaturated carbonyl compounds produced, and methods for the selective formation of either *E*- or *Z*- enolates have been developed.[1–5] However, stereochemical control over the geometry of the newly formed double bond has been less comprehensively explored. Examination of the two transition states **1a** and **1b** (Scheme 1) validates the natural preference for *E* olefins from secondary alcohols. A pseudoequatorial disposition of R^2 puts transition state **1b** at lower energy than transition state **1a** which is disfavored because of the pseudo-1,3-diaxial interaction present. Moreover, it has been shown that *E* selectivity is greatly enhanced by increased steric bulk of the substituents R^2 and X (Scheme 1).[1] Esters or vinyl ethers derived from tertiary alcohols, on the other hand, do not generally give olefins with high selectivity by conventional methods.

The challenge of preferentially obtaining *Z*-olefins from the Claisen rearrangement lies in modifying the structure of the transition states in order to favor participation by transition state conformation **1a**. Yamamoto and coworkers[6] obtained *Z* selectivity in the rearrangement of allyl vinyl ethers (**1**, X = H) by complexation with bulky organoaluminum reagents. In so doing, they apparently introduced a new steric interaction which makes transition state **1a** more favorable. We envisaged that a metal ester enolate such as **3** (M = Li, MgX, B, Zn, Sn, etc.) derived from secondary or tertiary allylic alcohols bearing a coordinating ligand L would rearrange via transition state **3a** which would be rendered more stable than transition state **3b** by chelation, thus generating Z-olefinic acids (Scheme 2).

Results and Discussion

By utilizing coordination of an ether oxygen (at the carbinol center) to the enolate metal to provide preorganization of the substrate, via a seven-membered chelate (eq 1), our approach to alkene selectivity has been successful in reactions of tertiary carbinol esters.[7,8] Acting as a control element, oxygen efficiently positions the ethereal side chain in the pseudoaxial orientation prior to rearrangement.

When 1-methoxy-2-(propionyloxy)-2-methyl-3-butene (**4**) was added to a suspension of bromomagnesium diethylamide[9] (Et_2NMgBr) in ether at −10 °C and the mixture warmed and stirred at room temperature for 1–2 h, it was smoothly converted to carboxylic acid **5*Z*** along with 20% of the corresponding alkene isomer **5*E*** (as determined by ^1H NMR spectroscopy). Greater selectivity was achieved by modifying the solvent composition. Thus, the use of more strongly Lewis basic solvents such as THF, DME, and hexamethylphosphoramide (HMPA) enhanced the formation of the *Z*-isomer (Table 1). In addition, maintaining the reaction mixture at a temperature between 0 and 5 °C also had a beneficial effect. Optimum conditions for *Z* selectivity therefore involve a

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(5) Ziegler, F. E. *Chem. Rev.* 1988, *88*, 1423.

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(8) For a heteroatom-controlled [2,3]-Wittig rearrangement, see: Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 4631. β-Hydroxy allylic esters have been used in the Claisen rearrangement to provide a diastereocontrol element. See: Kurth, M. J.; Yu, C.-M. *Tetrahedron Lett.* **1984**, *25*, 5003. See also: Oh, T.; Wrobel, Z.; Rubenstein, S. M. *Tetrahedron Lett.* **1991**, *32*, 4647.

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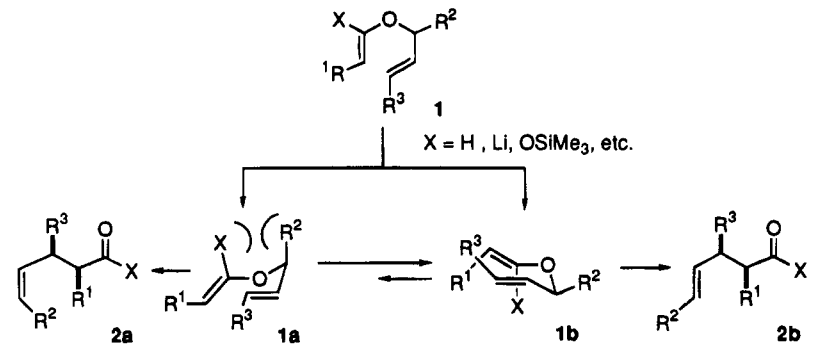
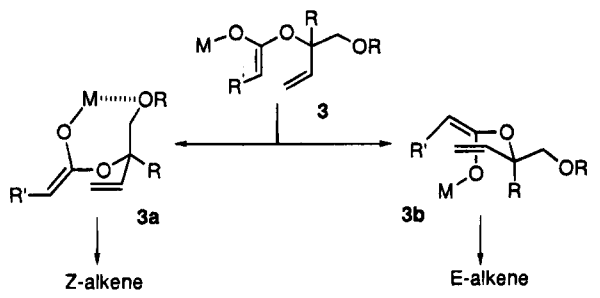
Scheme 1



Scheme 2



solvent mixture comprised of ether–THF in a ratio of 2:1 with an added 1.0 equiv (relative to the ester) of HMPA (Table 1, entry 6).

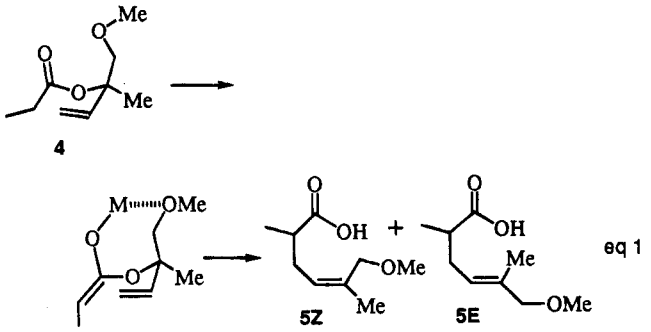


Table 1

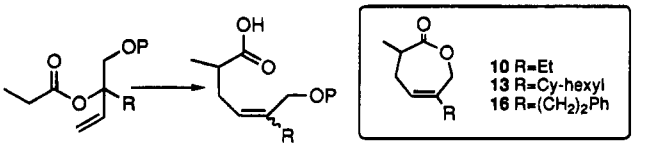
entry	solvent	additive (equiv)	T (C)	yield (%)	Z:E ratio
1	Ether		−10 °C to rt	73	79:21
2	THF		−10 °C to rt	63	86:14
3	DME		−10 °C to rt	53	86:14
4	Et_2O/THF (2:1)		−10 °C to rt	79	88:12
5	Et_2O/THF (2:1)	HMPA (1.0)	−10 °C to 0 °C	86	93:7
6	Et_2O/THF (2:1)	HMPA (1.0)	−10 °C to 0 °C	87	96:4
7	Et_2O/THF (2:1)	HMPA (1.6)	−10 °C to 0 °C	71	94:6
8	Et_2O/THF (2:1)	HMPA (1.6)	−10 °C to rt	90	91:9
9	Et_2O/THF (2:1)	HMPA (3.2)	−10 °C to rt	17	78:22

Reactions with numerous different metals using oxygen as the control element were investigated using ester **4**, for example, M = Li, Cp_2ZrCl, ZnBr, and $TiCl_3$, but reactions with these metals did not yield a *Z*:*E* ratio greater than 80:20. Different solvents, ether, THF, DME, toluene, and combinations thereof improved the ratio (for examples, see Table 1), although higher temperatures decreased the selectivity as did the use of more HMPA. The nature of the halogen in the halomagnesium enolate also does not play a significant role in determining the selectivity as rearrangement of the chloromagnesium or iodomagnesium enolate resulted in essentially the same *Z*:*E* selectivity as the bromomagnesium enolate.

A series of esters of tertiary alcohols was synthesized in order to test the generality of the process. The results (Table 2) were obtained using the conditions described in Table 1, entry 6.

Consistently high *Z*-selectivity was achieved for substrates which differed in the nature of the substituent at the carbinol center. With the bulky cyclohexyl group (i.e., **11**), rearrangement yields exclusively the *Z*-γ,δ-unsaturated carboxylic acid **12Z**. The superb efficiency of the chelation effect can be seen by a comparison of the results from the rearrangement of the enolate with the corresponding trimethylsilyl ketene acetal (Table 2). The alkene geometry in the unsaturated carboxylic acid was determined by ^1H NOE difference experiments. An alternative method for assignment of alkene geometry was formation of a lactone after hydrolysis of the methoxymethyl ether.[10]

Table 2



	P[a]	method	Z:E	yield (%)	lactone yield (%)
4, R = Me	Me	A	**5Z**:**5E** 96:4	87	
4, R = Me	Me	B	**5Z**:**5E** 46:54	60	
6, R = Et	Me	A	**7Z**:**7E** 93:7	92	
6, R = Et	Me	B	**7Z**:**7E** 50:50	62	
8, R = Et	MOM	A	**9Z**:**9E** 95:5	85	**10**, 60
8, R = Et	MOM	B	**9Z**:**9E** 50:50	60	
11, R = Cy-hexyl	MOM	A	**12Z**:**12E** >99:1	81	**13**, 77
11, R = Cy-hexyl	MOM	B	**12Z**:**12E** 64:36	65	
14, R = $(CH_2)_2Ph$	MOM	A	**15Z**:**15E** 90:10	85	**16**, 78

[a] A = rearranged as the BrMg enolate. B = rearranged as the TMS ketene acetal.

A determining factor in the observed alkene selectivity is likely to be the degree of association of the various magnesium species present during the reaction. It may be assumed that changing the solvent composition from ether to the more Lewis basic mixture of Et_2O–THF–HMPA had the effect of displacing the equilibria between possible polymeric magnesium species in such a way that small aggregates or possibly monomeric species became predominant. The probability for the intramolecular coordination, central to our stereoselective rearrangement, was therefore enhanced.

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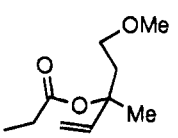
The magnesium enolates of secondary allylic esters were apparently too unstable at or above −10 °C and underwent cleavage, possibly via ketene formation,[2] to give the allylic alcohol. Also of interest was the effect of the length of the carbon tether between the coordinating heteroatom and the carbinol center. The results show that more than one carbon renders the reaction nonselective. Ester **17** rearranged to give the carboxylic acids in a *Z*/*E* ratio of 40:60. The magnesium−sulfur coordinating pair, while leading to *Z*-selectivity as illustrated by the rearrangement of ester **18** to give an 84:16 (*Z*/*E*) ratio of olefinic acids, was low yielding (35%).



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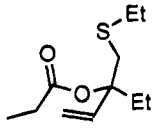

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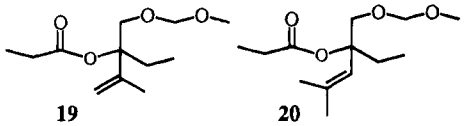
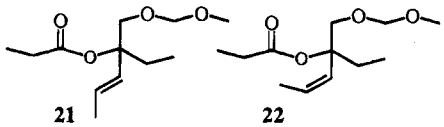
We were particularly interested in the study of substituted allyl esters because of the generation of vicinal chiral centers. Stereocontrol at the adjacent α,β stereocenters of the γ,δ-unsaturated carboxylic acid in addition to control over geometry of the newly forming alkene would be highly advantageous. Alkyl substituents were introduced on the alkene to evaluate their effect on the *E*:*Z* ratio under the rearrangement conditions as well as to study the relative stereochemistry at the α,β centers. The substituted alkenes chosen to evaluate the efficacy of the chelation control were **19**−**22**.



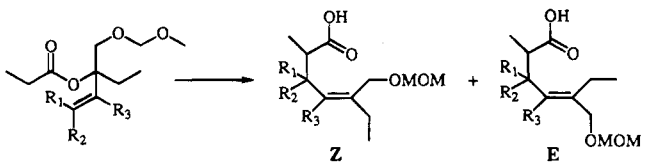
19 **20**



21 **22**

These esters were then rearranged via a bromomagnesium enolate as well as their corresponding (trimethylsilyl)ketene acetal in order to assess the effectiveness of the chelation-assisted rearrangement (Table 3). The results clearly show that an outstanding degree of selectivity was achieved in the rearrangement. As previously observed with large groups at the carbinol center, increased substitution on the double bond provided even enhanced selectivity. ^{1}H NOE difference experiments confirmed the *Z* geometry of the resulting γ,δ-unsaturated carboxylic acids. It is of interest to note that esters **20**−**22** did not rearrange at 0 °C but required ambient temperature and only ester **19** rearranged at 0 °C. Alkyl substitution on the alkene apparently generates steric interactions in the transition state, therefore requiring a higher temperature for the ester enolate to rearrange.

Table 3.



Z **E**

ester	method[a]	R_1	R_2	R_3	*Z*:*E*	yield(%)
19	A	H	H	Me	**23*Z*:23*E*** >97:3	91
19	B	H	H	Me	**23*Z*:23*E*** 60:40	66
20	A	Me	Me	H	**24*Z*:24*E*** 92:8	63
20	B	Me	Me	H	**24*Z*:24*E*** 61:39	64
21	A	H	Me	H	*syn*-**25*Z*:25*E*** >97:3	89
21	B	H	Me	H	*syn*-**25*Z*:25*E*** 60:40	60
22	A	Me	H	H	*anti*-**26*Z*:26*E*** >97:3	63
22	B	Me	H	H	*anti*-**26*Z*:26*E*** 36:64	65

[a] A = rearranged as the BrMg enolate. B = rearranged as the TMS ketene acetal.

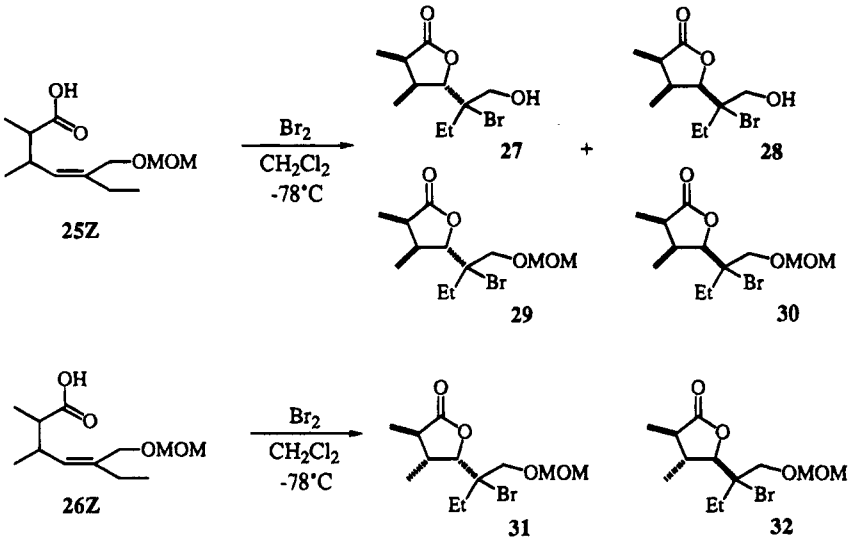
Claisen rearrangements are sometimes subject to loss of stereochemical integrity presumably due to rearrangement via either a boatlike or chairlike transition state conformation.[5] The high degree of selectivity illustrated here is remarkable and can be rationalized by both a stereoselective deprotonation (vide infra) and the chelation effect, which is expected to impart a strong bias over the reactive transition state conformation.

Rearrangement of esters **21** and **22** gave the acids **25*Z*** and **26*Z*** (Table 3) bearing two new vicinal chiral centers. To determine the relative stereochemistry at these two centers, bromolactonization of the (*Z*)-acids **25*Z*** and **26*Z*** was carried out (Scheme 3). In the bromolactonization of acid **25*Z***, a mixture of four compounds was obtained due to the cleavage of the MOM group. The overall yield of the bromolactonization was 85% (60% of alcohols **27** and **28**, 5:1 ratio, and 25% of bromides **29** and **30**). The stereochemistry at the asymmetric centers on the lactone ring was determined by ^{1}H NOE difference experiments. Correspondingly, the *Z*-acid **25*Z*** was found to have *anti* stereochemistry at the vicinal stereocenters. The *Z*-acid **26*Z*** was lactonized in 55% yield (**31**/**32**:1/2) and was found to have *syn* stereochemistry at the adjacent stereogenic centers.

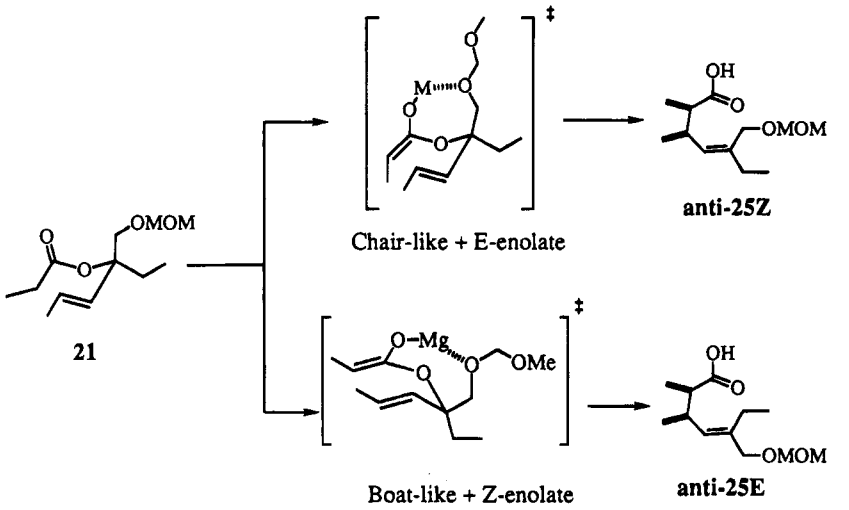
The relative stereochemistry at the α and β centers is governed by the geometry of both the enolate and the alkene. In the chelation-controlled rearrangement of ester **21**, the *anti*-*Z*-acid **25*Z*** was observed accompanied by minor amounts of the E-acid. Acid anti-**25*Z*** can be obtained only via a chairlike conformation of the transition state and an *E*-enolate. A boatlike conformation of the transition state and a Z-enolate would give the correct stereoisomer at the vicinal stereocenters, but the wrong alkene geometry under chelation control (Scheme 4). Syn acids would be obtained in the other two possible transition state possibilities, i.e., if the *E* enolate of **21** rearranged via a boatlike conformation, a syn *E*-acid would be obtained, or if the *Z* enolate rearranged via a chairlike conformation, the corresponding syn *Z*-acid would be formed. Because of the observed high degree of selectivity in the enolate rearrangements, relative to rearrangements of the ketene acetal, the nonchelated transition state conformations have been discounted.

Our results suggested that the (*E*)-bromomagnesium enolate was generated upon ester deprotonation with bromomagnesium diethylamide in the presence of HMPA. That led us to investigate the enolate geometry obtained after deprotonation of the allyl ester with Et_2NMgBr. Attempts to trap the bromomagnesium enolate of ester **8** as a silyl ketene acetal led to the recovery of starting material if the reaction was quenched after several hours at 0 °C or rearranged acid if the quench was carried out after the reaction had warmed to ambient temperature. Furthermore, deprotonation of *tert*-butyl propionate under the rearrangement conditions (12 h, 0 °C) led to the

Scheme 3



Scheme 4



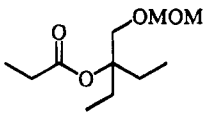
formation of the Claisen condensation product[9] in 60% yield. These results strongly suggested that ester deprotonation under the reaction conditions was very slow and that the bromomagnesium enolate rearranges or condenses as soon as it is formed. Thus, an alternate route was going to be necessary in order to determine the enolate geometry.

Since the bromomagnesium ester enolate could not be trapped effectively, a Li to Mg transmetalation route was investigated.[11] Ester **21** was deprotonated at −78 °C with LDA followed by addition of a solution of $MgBr_2{\cdot}Et_2O$ in ether at −78 °C. The reaction mixture was then slowly warmed to 0 °C, and 1 equiv of HMPA was added. Warming the reaction to ambient temperature and stirring for 2 h produced acid anti-**25Z** in 67% yield, which was identical to the acid obtained from the rearrangement of the bromomagnesium enolate of **21** by deprotonation using Et_2NMgBr under the previously described conditions. (In some cases, 3−5% of the corresponding *E*-isomer was obtained thus suggesting incomplete transmetalation.) The lithium ester enolate must have been almost completely transmetalated to the bromomagnesium enolate, otherwise, a mixture of *E*- and *Z*-acids would have been the expected products based on previous studies with lithium enolates. Indeed, in the rearrangement of ester **21** via the TMS ketene acetal, a mixture of *E*- and *Z*-acids was obtained (Table 3). The transmetalation is expected to have occurred with retention of the enolate geometry.[11] Thus, it follows that the geometry of the enolate formed when ester **21** is deprotonated with Et_2NMgBr is the same as the geometry of the enolate resulting from the deprotonation of **21** with LDA since the same acid, *anti*-**25Z**, is produced from both reactions. In order to verify the geometry of the enolate formed using LDA, ester **33** was chosen as a model substrate.

Ester **33** was then deprotonated with LDA in THF at −78 °C, and the resulting lithium enolate was trapped as the *tert*-butyldimethylsilyl ketene acetal. The resulting silyl ketene acetal was shown by a ^1H NMR NOE difference experiment to have *E* alkene geometry. Therefore, on the basis of our transmetalation experiments, it can be concluded that the enolate generated from the deprotonation of the tertiary allylic esters with Et_2NMgBr has the *E* geometry also.[2,3,12]

(11) For a transmetalation from Li to Zr, see: Evans, D. A.; Mc Gee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. For a transmetalation from Li to MgBr, see: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(12) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.



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In summary, the chelation-controlled Claisen rearrangement yields *Z*-trisubstituted alkenes with high selectivity. The introduction of alkyl substituents on the alkene increases the selectivity even more. The *Z*-selectivity in the chelation-controlled Claisen rearrangement was rationalized by postulation of formation of a 7-membered ring chelate in the transition state prior to rearrangement. The outstanding selectivity observed strongly supports the proposed chelated chairlike conformation of the transition state. As a result of the conformational control, the rearrangement proceeds to give γ,δ-(*Z*)-unsaturated carboxylic acids with outstanding stereocontrol at the α,β stereogenic centers as well as the alkene.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium benzophenone ketyl prior to each use. Methylene chloride (CH_2Cl_2) and pyridine were distilled from calcium hydride. Hexane, chloroform ($CHCl_3$), methanol (MeOH), and ethyl acetate (EtOAc) were distilled prior to use. Toluene was distilled from sodium metal prior to use. All reactions were performed under an atmosphere of nitrogen. *J* values are given in Hz.

Chromatography refers to flash chromatography as reported by Still.[13]

Preparation of Esters, Table 4: **Preparation of α-Hydroxyketones.** *n*-Butyllithium (27.2 mL of a 1.6 M solution, 44 mmol) was added under a nitrogen atmosphere to a cooled (−25 °C) solution of diisopropylamine (4.34 g, 44 mmol) in THF (50 mL). After 10 min, a solution of the methyl ketone was added dropwise and the mixture stirred for an additional 10 min at −25 °C. Chlorotrimethylsilane (9.0 g, 84 mmol) was added quickly and the mixture warmed to room temperature and stirred for 2.5 h, at which time it was diluted with pentane, washed with cold saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Evaporation under vacuum gave the corresponding silyl enol ether.

2-Cyclohexyl-2[(-trimethylsilyl)oxy]ethene: yield (99%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.19 (9H, s), 1.0−1.25 (6H, m,), 1.6−1.9 (5H, m), 3.95 (1H, s), 4.2 (1H, s).

2-[(Trimethylsilyl)oxy]-4-phenylbut-1-ene: yield (99%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.22 (9H, s), 2.37 (2H, t, J = 7.7 Hz), 2.78 (2H, t, J = 7.7 Hz), 4.06 (2H, s), 7.25 (3H, m), 7.35 (2H, m).

m-Chloroperbenzoic acid (4.7 g of an 85% mixture, 23 mmol) was added portionwise to a cooled (0 °C) solution of the enol silyl ether in dichloromethane (300 mL). After being stirred at 0 °C under nitrogen for 30 min and then at room temperature for 2 h, the reaction was treated with saturated sodium sulfite (50 mL) to destroy excess peroxide. The organic phase was washed with saturated sodium bicarbonate and dried over anhydrous sodium sulfate. It was then concentrated and treated with tetrabutylammonium fluoride (21 mL of a 1.0 M solution, 21 mmol). After being stirred for 45 min at room temperature, the mixture was evaporated under vacuum. Chromatography of the residue on silica using 40% ethyl acetate / hexane as eluent gave a pale yellow liquid.

Hydroxymethyl cyclohexyl ketone: yield 41%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.16−2.45 (6H, m), 1.60−1.85 (5H, m), 2.37 (1H, tt, J = 3.3, 11.5), 4.30 (2H, s); IR cm^{-1} (film) 3450, 1705.

3-Benzyl-1-hydroxyacetone: yield 47%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.10 (1H, s,), 2.73 (2H, t, J = 7.7Hz), 2.97 (2H, t, J = 7.7Hz), 4.19 (2H, s), 7.13−7.32 (5H, m); IR cm^{-1} (film) 3405, 1714, 1597, 1490, 1446, 1399. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.88; H, 7.42

Methoxyacetone (**34**), used in the preparation of ester **4**, is commercially available from Aldrich.

1-Methoxy-2-butanone (35). A mixture of 1-hydroxy-2-butanone (1.1 g, 0.012 mol), methyl iodide (13.7 g, 0.096 mol), and silver oxide (3.14 g, 0.013 mol) in acetonitrile was heated at reflux for 24 h under a nitrogen atmosphere with the exclusion of light. After being cooled to ambient temperature, it was diluted with ethyl acetate and filtered over Celite. The filtrate was fractionated to give **35** as a colorless liquid containing small amounts of solvent (0.5 g, 41%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, t, J = 7.7 Hz), 2.46 (2H, q, J = 7.7 Hz), 3.41 (3H, s) 4.01 (2H, s); IR cm^{-1} (film) 1700.

Preparation of α-Methoxymethoxy Ketones. Chloromethyl methyl ether (1.19 g, 0.017 mol) was added to a cooled solution (0 °C) of the hydroxymethyl ketone (0.014 mol) and *N,N*-diisopropylethylamine (2.5 g, 0.020 mol) in dichloromethane (10 mL). The mixture was stirred under nitrogen for 1 h at 0 °C then overnight at room temperature. It was then diluted with dichloromethane and washed successively with water, 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine. The solution was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a pale yellow liquid.

1-(Methoxymethoxy)-2-butanone (36): yield 80%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, t, J = 7.2 Hz), 2.47 (2H, q, J = 7.2 Hz), 3.38 (3H, s), 4.17 (2H, s), 4.68 (2H, s); IR cm^{-1} (film) 1699; 75 MHz ^{13}C NMR δ 6.87, 31.94, 55.43, 71.82, 96.49, 208.75 MS (EI) *m/z* 87 (M^+ − 45 (C_2H_5O)).

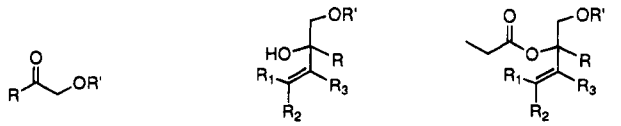
1-(Methoxymethoxy)methyl cyclohexyl ketone (37): yield 90%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.20−1.5 (6H, m), 1.6−1.8 (4H, m), 2.45 (1H, m), 3.38 (3H, s), 4.24 (2H, s), 4.67 (2H, s); IR cm^{-1} (film) 1708; MS (EI) *m/z* 140 (M^+ − 45 (C_2H_5O)).

1-(Methoxymethoxy)-4-phenyl-2-butanone (38): yield 80%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.77 (2H, t, J = 7.7 Hz), 2.93 (2H, t, J = 7.7 Hz), 3.36 (3H, s), 4.12 (2H, s), 4.65 (2H, s), 7.19 (3H, m), 7.28 (2H, m); IR cm^{-1} (film) 3050, 3017, 1700.

Preparation of Allylic Alcohols (39−43). Vinylmagnesium bromide (23.2 mL of a 1.0 M solution in ether, 0.023 mol) was added to a cooled solution (−78 °C) of the ketone in diethyl ether (50 mL). The mixture was stirred at −78 °C for 1 h and then was quenched with saturated ammonium chloride solution (50 mL). The two phases were separated and the aqueous phase extracted with ether. The combined ether solutions were dried over anhydrous sodium sulfate and then evaporated under vacuum. The residue was chromatographed on silica gel using 25% ethyl acetate/hexane as eluent. The resulting allylic alcohol was obtained as a colorless liquid.

1-Methoxy-2-methyl-3-buten-2-ol (39): yield 60%; bp 55 °C/30 mmHg; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, s), 3.25 (1H, AB, J = 9.3 Hz), 3.32 (1H, AB, J = 9.3 Hz), 3.39 (3H, s), 5.12 (1H, dd, J = 1.6, 11 Hz), 5.31 (1H, dd, J = 1.6, 17.6 Hz); 5.92 (1H, dd, J = 11, 17.6 Hz); IR cm^{-1} (film) 3417, 3070, 1627; MS (EI) *m/z* 101.15 (M^+ − 15).

Table 4. Preparation of Substituted Allylic Propionates



ketone	R	R′	alcohol	R_1	R_2	R_3	ester
34	Me	Me	**39**	H	H	H	**4**
35	Et	Me	**40**	H	H	H	**6**
36	Et	MOM	**41**	H	H	H	**8**
37	Cy-hexyl	MOM	**42**	H	H	H	**11**
38	$(CH_2)_2Ph$	MOM	**43**	H	H	H	**14**
36	Et	MOM	**44**	H	H	Me	**19**
36	Et	MOM	**45**	Me	Me	H	**20**
36	Et	MOM	**46**	Me	H	H	**21**
36	Et	MOM	**47**	H	Me	H	**22**

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3-(Methoxymethyl)-4-penten-3-ol (40): yield 62%. Due to the volatility of this compound it was used without purification in the subsequent acylation step: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.7 Hz), 1.48 (1H, qd, J = 7.7, 13.7 Hz), 1.60 (1H, qd, J = 7.7, 13.7 Hz), 3.3 (2H, AB, J = 9.3 Hz), 3.37 (3H, s), 5.18 (1H, dd, J = 1.6, 11 Hz), 5.29 (1H, dd, J = 1.6, 17.6 Hz), 5.8 (1H, dd, J = 11, 17.6 Hz); IR cm^{-1} (film) 3400, 3050, 1628.

3-[(Methoxymethoxy)methyl]-4-penten-3-ol (41): yield 60%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.7 Hz), 1.47 (1H, qd, J = 7.7, 13.7 Hz), 1.61 (1H, qd, J = 7.7, 13.7 Hz), 2.29 (1H, br s), 3.36 (3H, s), 3.50 (2H, AB J = 10.5 Hz), 4.64 (2H, s), 5.20 (1H, dd, J = 1.6, 11 Hz), 5.32 (1H, dd, J = 1.6, 17.5 Hz), 5.81 (1H, dd, J = 11, 17.5 Hz); MS (EI) m/z 142 (M^+ − 18); IR cm^{-1} (film) 3420, 3056, 1616.

1-(Methoxymethoxy)-2-cyclohexyl-3-buten-2-ol (42): yield 76%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.92−1.28 (6H, m), 1.52 (1H, tt, J = 3.3, 11.5 Hz), 1.6−1.88 (4H, m), 2.20 (1H, br s), 3.36 (3H, s), 3.57 (2H, s), 4.64 (2H, s), 5.21 (1H, dd, J = 1.6, 11 Hz), 5.31 (1H, dd, J = 1.6, 17 Hz), 5.84 (1H, dd, J = 1.6, 17 Hz); IR cm^{-1} (film) 3467, 3077,1633; MS (EI) m/z 197 (M^+ − 17).

1-Phenyl-3-[(methoxymethoxy)methyl]-4-penten-3-ol (43): yield 57%; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.76 (1H, ddd, J = 5.5, 11.5, 13.5 Hz), 1.93 (1H, ddd, J = 5.5, 11.5, 13.5 Hz), 2.63 (1H, ddd, J = 5.5, 13.5, 13.5 Hz), 2.71 (1H, ddd, J = 5.5, 13.5, 13.5 Hz), 3.37 (3H, s), 3.54 (2H, AB, J = 9.9 Hz), 4.66 (2H, s), 5.28 (1H, dd, J = 1.6, 11 Hz), 5.42 (1H,dd, J = 1.6, 17 Hz), 5.96 (1H, dd, J = 11, 17 Hz), 7.18 (3H, m), 7.25 (2H, m); IR cm^{-1} (film) 3467, 3076, 3053, 3018, 1597, 1489, 1446; MS (EI) m/z 219 (M^+ − 17).

Synthesis of 3-[(methoxymethoxy)methyl]-2-methyl-1-penten-3-ol (44). To a stirred solution of 2-bromopropene (2.42 g, 20 mmol) in ether (1 mL) cooled to −78 °C (dry ice/acetone bath) was added a 1.7 M solution of *tert*-butyllithium in pentane (25 mL, 40 mmol). The mixture was then warmed to room temperature and stirred overnight. The mixture was cooled again to −78 °C, and a solution of 1-(methoxymethoxy)-2-butanone (**36**) (1.32 g, 10 mmol) in THF (10 mL) was added dropwise to the reaction mixture. After addition, the reaction mixture was allowed to warm to room temperature and stir for several hours. It was then quenched with saturated sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The organic layer was then dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography on silica gel (6/1 hexane−ethyl acetate) gave the alcohol as a colorless oil (1.25 g, 72%): 300 MHz ^{1}H NMR δ 0.81 (t, 3H, J = 7.1), 1.52 (qd, 1H, J = 7.1, 14.4), 1.58 (qd, 1H, J = 7.1, 14.4), 1.71 (s, 3H), 2.59−2.66 (bs,1H), 3.34 (s, 3H), 3.41 (d, 1H, J = 10.4), 3.70 (d, 1H, J = 10.4), 4.63 (s, 3H), 4.96 (bs, 1H), 5.05 (bs, 1H); 75 MHz ^{13}C NMR δ 6.8, 19.2, 27.8, 55.4, 74.4, 77.0, 97.2, 112.1, 146.6; IR (cm^{-1}) 3456, 2928, 1635, 1445, 1147, 1107; MS m/e (CI: isobutane) 157, 129, 125 (M^+ − 49, 100), 97. Anal. Calcd for $C_9H_{18}O_3$: C, 62.02; H, 10.42. Found: C, 61.79; H, 10.44.

Synthesis of 3-[(methoxymethoxy)methyl]-5-methyl-4-hexen-3-ol (45). 3-[(methoxymethoxy)methyl]-5-methyl-4-hexen-3-ol (**45**) was prepared in 58% yield by following the same procedure used to prepare 3-[(methoxymethoxy)methyl]-2-methyl-1-penten-3-ol (**44**): 300 MHz ^{1}H NMR δ 0.90 (t, 3H, J = 7.7), 1.57 (dq, 1H, J = 13.7, 7.7), 1.71 (dq, 1H, J = 13.7, 7.7), 1.73 (d, 3H, J = 1.1), 1.87 (d, 3H, J = 1.1), 3.38 (s, 3H), 3.45 (d, 1H, J = 9.9), 3.54 (d, 1H, J = 9.9), 4.67 (s, 2H), 5.11 (qq, 1H, J = 1.1, 1.65); 75 MHz ^{13}C NMR δ 7.8, 18.7, 27.2, 31.2, 55.2, 75.1, 77.1, 97.1, 126.4, 136.6; IR (cm^{-1}) 3458, 2923, 1664, 1446, 1147, 1107; MS m/e (CI: isobutane) 189 (M^+ + 1), 171 (M^+ − 17, 100, 139, 127). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.86; H, 10.69.

Synthesis of *cis*-3-[(methoxymethoxy)methyl]-4-hexen-3-ol (46). *Cis*-3-[(Methoxymethoxy)methyl]-4-hexen-3-ol (**46**) was prepared in 77% yield by following the same procedure used to prepare 3-[(methoxymethoxy)methyl]-2-methyl-1-penten-3-ol (**44**): 300 MHz ^{1}H NMR δ 0.93 (t, 3H, J = 7.7), 1.58 (qd, 1H, J = 7.7, 13.7), 1.70 (qd, 1H, J = 7.7, 13.7), 1.86 (dd, 3H, J = 1.65, 7.7), 3.38 (s, 3H), 3.46 (d, 1H, J = 9.9), 3.58 (d, 1H, J = 9.9), 4.67 (s, 2H), 5.28 (dq, 1H, J = 1.65, 12), 5.62 (dq, 1H, J = 7.7, 12); 75 MHz ^{13}C NMR δ 7.6, 14.0, 30.8, 55.2, 75.3, 76.0, 97.2, 127.9, 132.2; MS m/e (CI: isobutane) 174 (M^+ + 1), 157 (M^+ − 17, 100), 153, 125, 113.

Cis-1-Bromopropene was prepared as described by Fuller and Walker.[14]

Preparation of Allylic Alcohol 47: Synthesis of 3-[(Methoxymethoxy)methyl]-4-hexyn-3-ol. An excess of propyne (more than 0.6 g, 15 mmol) was condensed in a flask cooled to −78 °C containing THF (6 mL). A 1.0 M solution of ethylmagnesium bromide (15 mL, 15 mmol) was added dropwise to the propyne solution. After addition, the acetone−dry ice bath was removed and the mixture allowed to warm to room temperature and stir for 1 h. It was then cooled to 0 °C, and a solution of 1-(methoxymethoxy)-2-butanone (**36**) (0.66 g, 5 mmol) in THF (2 mL) was added dropwise. After addition, the ice bath was removed and the mixture was stirred for an additional hour. It was then diluted with EtOAc and quenched with saturated ammonium chloride. The aqueous layer was extracted with EtOAc. The organic layer was then dried over sodium sulfate and concentrated to give a slightly yellow-colored oil (0.83 g, 100%) which was used without further purification: 300-MHz ^{1}H NMR δ 1.02 (t, 3H, J = 7.7), 1.64 (qd, 1H, J = 7.7, 14.2), 1.69 (qd, 1H, J = 7.7, 14.2), 1.83 (s, 3H), 2.70−2.90 (bs, 1H), 3.4 (s, 3H), 3.56 (AB, 2H, J = 9.3), 4.7 (AB, 2H, J = 7.1); 75 MHz ^{13}C NMR: δ 3.5, 8.5, 31.8, 55.7, 71.2, 75.6, 80.3, 81.1, 97.5; IR (cm^{-1}) 3431, 2932, 2235, 1456, 1213, 1147, 1100, 1047; MS m/e (CI: isobutane) 173 (M^+ + 1), 155 (M^+ − 31, 100), 123, 111. Anal. Calcd for $C_9H_{16}O_3 \cdot 0.1H_2O$: C, 62.21; H, 9.33. Found: C, 61.92; H, 9.24.

Synthesis of *trans*-3-[(methoxymethoxy)methyl]-4-hexen-3-ol (47). To a solution of lithium aluminum hydride (0.19 g, 5 mmol) and sodium methoxide (0.54 g, 10 mmol) in THF (50 mL) cooled to 0 °C was added a solution of 3-[(methoxymethoxy)methyl]-4-hexyn-3-ol (0.43 g, 2.5 mmol) in THF (25 mL).[15] The mixture was then brought to reflux during 5 h. It was quenched with water and filtered through Celite. The aqueous layer was extracted with ethyl acetate. The organic layer was then dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography on silica gel (8/1 hexane−ethyl acetate) gave the alcohol as a colorless oil (0.32 g, 73%): 300-MHz ^{1}H NMR δ 0.87 (t, 3H, J = 7.7), 1.50 (qd, 1H, J = 7.7, 14.4), 1.61 (qd, 1H, J = 7.7, 14.4), 1.73 (dd, 3H, J = 1.65, 6.6 Hz), 2.35−2.55 (bs, 1H) 3.37 (s, 3H), 3.48 (AB, 2H, J = 9.9 Hz), 4.65 (s, 2H), 5.43 (dq, 1H, J = 1.65, 15.4), 5.74 (dq, 1H, J = 6.6, 15.4); ^{1}H NOE difference: irradiation at 5.43 ppm, signal at 1.73 ppm, +2.7%; 75 MHz ^{13}C NMR δ 7.2, 17.4, 30.2, 55.2, 74.2, 74.9, 97.1, 125.2, 133.7; IR (cm^{-1}): 3454, 2927, 1663, 1445, 1146, 1107, 1048; MS m/e (CI: isobutane) 157 (M^+ − 17, 100), 125.

Preparation of Allyl Esters 4, 6, 8, 11 and 14. Propionic anhydride (1.06 g, 8.23 mmol) was added to a solution of the allylic alcohol (7.48 mmol), triethylamine (2.22 g, 22.4 mmol), and (dimethylamino)pyridine (0.13 g, 1.05 mmol, 0.14 equiv) in dichloromethane (2 mL). The solution was stirred at room temperature under an atmosphere of nitrogen until TLC indicated the completion of the reaction (4−96 h). The solution was then diluted with ethyl acetate and washed sequentially with water, 5% hydrochloric acid, saturated sodium bicarbonate solution, and brine. After being dried over anhydrous sodium sulfate, the solution was evaporated in vacuo and the residue chromatographed on silica gel (25% ethyl acetate/hexane) to furnish a colorless liquid.

1-Methoxy-2-(propionyloxy)-2-methyl-3-butene (4): 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.4 Hz, 3H), 1.55 (s, 3H), 2.30 (q, J = 7.4 Hz, 2H), 3.38 (s, 3H), 3.54 (AB, J = 10.75 Hz, 2H), 5.18 (d, J = 11.3 Hz, 1H), 5.23 (d, J = 16.9 Hz, 1H), 6.03 (dd, J = 11.3, 16.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.8, 20.9, 28.2, 59.4, 77.6, 81.6, 114.6, 139.7, 173.7; MS (EI) m/z 98 (M^+ − 74

(14) *cis*-1-Bromopropene, used in the synthesis of alcohol **46**, was prepared from the bromination of *trans*-crotonic acid followed by bromodecarboxylation of the resulting *erythro*-2,3-dibromobutanoic acid. Fuller, C. E.; Walker, D. G. *J. Org. Chem.* **1991**, *56*, 4066.

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($C_2H_5CO_2H$)); IR cm^{-1} (film) 3069, 1710, 1625. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.66; H, 9.33.

3-(Propionyloxy)-3-(methoxymethyl)-4-pentene (6): 300 MHz ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.4 Hz, 3H), 1.78 (dq, J = 15.2, 7.2 Hz, 1H), 2.10 (dq, J = 15.2, 7.2 Hz, 1H), 2.32 (q, J = 7.4 Hz, 2H), 3.34 (s, 3H), 3.69 (d, J = 10.75 Hz, 1H), 3.76 (d, J = 10.75 Hz, 1H), 5.22 (d, J = 16.9 Hz, 1H), 5.24 (d, J = 11.3 Hz, 1H), 5.87 (dd, J = 16.9, 11.3 Hz, 1H); MS (EI) m/z 112 (M^+ − 74 ($C_2H_5CO_2H$)); IR cm^{-1} (film) 3071, 1720, 1628.

3-(Propionyloxy)-3-[(methoxymethoxy)methyl]-4-pentene (8): 300 MHz ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.83 (dq, J = 14.4, 7.2 Hz, 1H), 2.11 (dq, J = 14.4, 7.2 Hz, 1H), 2.34 (q, J = 7.2 Hz, 2H), 3.34 (s, 3H), 3.84 (d, J = 10.75 Hz, 1H), 3.91 (d, J = 10.75 Hz, 1H), 4.60 (s, 2H), 5.23 (d, J = 18.1 Hz, 1H), 5.24 (d, J = 11.3 Hz, 1H), 5.89 (dd, J = 11.3, 18.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.9, 8.9, 26.9, 28.2, 55.1, 69.7, 83.9, 96.8, 114.9, 138.7, 173.5; MS (EI) m/z 142 (M^+ − 74 ($C_2H_5CO_2H$)); IR cm^{-1} (film) 3071, 1720, 1628. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.11; H, 9.26. Found: C, 60.91; H, 9.29.

1-(Methoxymethoxy)-2-(propionyloxy)-2-cyclohexyl-4-butene (11): 300 MHz ^1H NMR ($CDCl_3$) δ 1.0−1.33 (m, 6H), 1.11 (t, J = 7.4 Hz, 3H), 1.6−1.8 (m, 4H), 2.15 (dddd, J = 12.0, 12.0, 3.3, 3.3 Hz, 1H), 2.35 (q, J = 7.4 Hz, 2H), 3.31 (s, 3H), 4.08 (AB, J = 10.75 Hz, 2H), 4.6 (s, 2H), 5.12 (d, J = 16.8 Hz, 1H), 5.23 (d, J = 11.3 Hz, 1H), 5.82 (dd, J = 11.3, 16.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.9, 26.1, 26.2, 27.0, 28.3, 42.3, 55.2, 67.6, 86.2, 96.8, 114.9, 136.7, 173.5; MS (EI) m/z 196 (M^+ − 74 ($C_2H_5CO_2H$)); IR cm^{-1} (film) 3082, 1726, 1638. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.70; H, 9.72.

1-Phenyl-3-(propionyloxy)-3-[(methoxymethoxy)-methyl]-4-pentene (14): 300 MHz ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3H), 2.07 (ddd, J = 13.8, 10.5, 6.1 Hz, 1H), 2.35 (q, J = 7.2 Hz, 2H), 2.44 (ddd, J = 13.8, 10.5, 6.1 Hz, 1H), 2.62 (m, 2H), 3.35 (s, 3H), 3.93 (AB, J = 10.5 Hz, 2H), 4,63 (s, 2H), 5.29 (d, J = 11.7 Hz, 1H), 5.30 (d, J = 17.0 Hz, 1H), 5.98 (dd, J = 17.1, 11.7 Hz, 1H), 7.14−7.21 (m, 3H), 7.24−7.31 (m, 2H); MS (EI) M^+ 292; IR cm $^{-1}$ (film) 3077, 3053, 3018, 1729, 1634. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.68; H, 8.23.

3-Methyl-5-methoxy-1-pentenyl 3-Propionate (17): 300 MHz ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, J = 7.7), 2.06 (dt, 1H, J = 14.2, 7.1), 2.16 (dt, 1H, J = 14.2, 7.1), 2.27 (q, 2H, J = 7.7), 3.29 (s, 3H), 3.42, (t, 2H, J = 7.1), 4.3 (d, 1H, J = 11.5), 5.16, (d, 1H, J = 17.6), 5.97 (dd, 1H, J = 11.5, 17.6); ^{13}C NMR ($CDCl_3$) δ 8.8, 24.0, 28.4, 38.8, 58.3, 68.4, 81.5, 113.2, 141.3, 173.5.

3-Thioethoxymethyl)-1-pentenyl 3-Propionate (18): 300 MHz ^1H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 7.7), 1.13 (t, 3H, J = 7.7), 1.22 (t, 3H, J = 7.7), 1.83, (dq, 1H, J = 7.1, 14.2), 2.17 (dq, 1H, J = 7.1, 14.2), 2.33 (q, 2H, J = 7.7), 2.53 (q, 2H, J = 7.7), 3.11 (d, 1H, J = 13.2), 3.21 (d, 1H, J = 13.2), 5.22 (d, 1H, J = 11.5), 5.23 (d, 1H, J = 11.5), 5.86 (dd, 1H, J = 17.6, 11.5); ^{13}C NMR ($CDCl_3$) δ 7.6, 9.3, 15.0, 27.6, 28.6, 29.4, 38.8, 85.0, 115.2, 140.0, 173.8.

Synthesis of 3-[(Methoxymethoxy)methyl]-2-methyl-1-pentenyl 3-Propionate (19). To a solution of 3-[(methoxymethoxy)methyl]-2-methyl-1-penten-3-ol (0.79 g, 4.55 mmol) in THF (7 mL) was added a 1.0 M solution of ethylmagnesium bromide (5 mL, 5 mmol). The mixture was stirred for 20 min.[16] Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.68; H, 8.23. A solution of propionyl chloride (0.84 g, 9.1 mmol) in THF (9 mL) was then added to the reaction mixture. After being stirred for 2 h, the reaction mixture was then quenched with saturated sodium bicarbonate. The aqueous layer was extracted with EtOAc. The resulting organic layer was then dried over sodium sulfate and condensed. Purification of the residue by flash chromatography on silica gel (10/1 hexane−ethyl acetate) gave the ester as a colorless oil (0.79 g, 76%): 300 MHz ^1H NMR δ 0.78 (t, 3H, J = 7.7), 1.11 (t, 3H, J = 7.7), 1.71 (s, 3H), 1.88 (qd, 1H, J = 7.7, 14.8), 2.00 (qd, 1H, J = 7.7, 14.8), 2.33 (q, 2H, J = 7.7), 3.33 (s, 3H), 3.93 (d, 1H, J = 10.4), 3.98 (d, 1H, J = 10.4), 4.60 (s, 2H), 4.94,(s, 1H), 5.00 (s, 1H); 75 MHz ^{13}C NMR δ 7.0, 8.9, 18.9, 25.4, 28.1, 55.1, 68.0, 86.0, 96.7, 112.4, 143.9, 173.3; IR (cm^{-1}) 2934, 1729, 1635, 1456, 1191, 1149, 1109, 1051; mass spectrum m/e (CI: isobutane) 231 (M^+ + 1), 168, 157 (M^+ − 73, 100), 169, 129, 125. Anal. Calcd for $C_{12}H_{22}O_4 \cdot 0.2H_2O$: C, 61.64; H, 9.59. Found: C, 61.48; H, 9.51.

Synthesis of 3-[(Methoxymethoxy)methyl]-5-methyl-4-hexenyl 3-Propionate (20). The synthesis of 3-[(methoxymethoxy)methyl]-5-methyl-4-hexenyl 3-propionate (**20**) was carried out in 76% yield by following the same procedure used to prepare 3-[(methoxymethoxy)methyl]-2-methyl-1-pentenyl 3-propionate (**19**): 300 MHz ^1H NMR δ 0.86 (t, 3H, J = 7.7), 1.09 (t, 3H, J = 7.7), 1.71 (s, 3H), 1.72 (s, 3H), 1.95 (qd, 1H, J = 7.7, 12.5), 2.04 (qd, 1H, J = 7.7, 12.5), 2.29 (q, 2H, J = 7.7), 3.34 (s, 3H), 3.76 (d, 1H, J = 9.9), 3.88 (d, 1H, J = 9.9), 4.61 (s, 2H), 5.21 (bs, 1H); 75 MHz ^{13}C NMR δ 7.7, 8.9, 18.8, 26.9, 27.9, 28.2, 55.1, 69.3, 83.7, 96.7, 124.3, 135.1, 172.9; IR (cm^{-1}) 2931, 1729, 1664, 1455, 1192, 1148, 1050; MS m/e (CI: isobutane) 231 (M^+ + 1), 171 (M^+ − 59, 100), 139. Anal. Calcd for $C_{13}H_{24}O_4 \cdot 0.3H_2O$: C, 62.55; H, 9.86. Found: C, 62.64; H, 9.62.

Synthesis of 3-[(methoxymethoxy)methyl]-*cis*-4-hexenyl 3-Propionate (21). 3-[(Methoxymethoxy)methyl]-*cis*-4-hexenyl 3-propionate (**21**) was prepared in 87% yield by following the same procedure used to prepare 3-[(methoxymethoxy)methyl]-2-methyl-1-pentenyl 3-propionate (**19**); 300 MHz ^1H NMR δ 0.89 (t, 3H, J = 7.7), 1.16 (t, 3H, J = 7.7), 1.73 (dd, 3H, J = 1.65, 7.1), 1.96 (qd, 1H, J = 7.7, 13.7), 2.08 (qd, 1H, J = 7.7, 13.7), 2.33 (q, 2H, J = 7.7), 3.36 (s, 3H), 3.83 (d, 1H, J = 10.4), 3.91 (d, 1H, J = 10.4), 4.63 (s, 2H), 5.41 (dq, 1H, J = 1.65, 12), 5.59 (qd, 1H, J = 7.1, 12); ^1H NOE difference, irradiation at 5.41 ppm, signal at 5.59 ppm, +2.6%; 75 MHz ^{13}C NMR δ 7.4, 8.8, 14.0, 27.8, 27.9, 55.0, 69.2, 84.1, 96.7, 126.6, 129.9, 172.9; IR (cm^{-1}) 2934, 1726, 1650, 1455, 1191, 1148, 1050; MS m/e (CI: isobutane) 231 (M^+ + 1), 169, 157 (M^+ − 73, 100), 125, 97. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.86; H, 9.23. Found: C, 62.48; H, 9.57.

Synthesis of 3-[(Methoxymethoxy)methyl]-*trans*-4-hexenyl 3-Propionate (22). 3-Methoxymethoxy)methyl]-*trans*-4-hexenyl 3-propionate (**22**) was prepared in 90% yield by following the same procedure used to prepare 3-[(methoxymethoxy)methyl]-2-methyl-1-pentenyl 3-propionate (**19**): 300 MHz ^1H NMR δ 0.84 (t, 3H, J = 7.7), 1.11 (t, 3H, J = 7.7), 1.73 (dd, 3H, J = 1.65, 6.0), 1.82 (qd, 1H, J = 7.7, 15), 2.06 (qd, 1H, J = 7.7, 15), 2.31 (q, 2H, J = 7.7), 3.34 (s, 3H), 3.82 (d, 1H, J = 10.4), 3.88 (d, 1H, J = 10.4), 4.62 (s, 2H), 5.55 (dq, 1H, J = 1.65, 15.6), 5.68 (dq, 1H, J = 6.0, 12); 75 MHz ^{13}C NMR δ 7.14 8.9, 17.7, 27.3, 28.2, 55.1, 69.8, 83.8, 96.7, 126.0, 131.3, 173.4; IR (cm^{-1}) 2932, 1729, 1456, 1188, 1147, 1050; MS m/e (CI: isobutane) 231 (M^+ + 1), 169, 157 (M^+ − 73, 100, 125).

Claisen Rearrangements, Table 2: Procedure A. Claisen Rearrangements of the Bromomagnesium Enolate. A solution of diethylamine (0.077 g, 1.05 mmol) in ether (5 mL) was cooled to 0−5 °C. Methylmagnesium bromide (0.35 mL of a 3 M solution in ether, 1.05 mmol) was added, and the mixture was then heated at reflux for 15 min. After the mixture was cooled to room temperature, HMPA (63 mg, 0.35 mmol) was added and the mixture further cooled to −10 °C. A cooled solution of the appropriate ester (0.35 mmol) in THF (2.8 mL) was then added. After 15 −20 min at −10 °C, the mixture was warmed to 0 °C and was maintained at that temperature for 18 h. An acid quench (10% hydrochloric acid) followed by a sodium bicarbonate workup afforded the γ,δ-unsaturated acid. **Tables 2 and 3: Procedure B. Claisen Rearrangements of the Trimethylsilylketene Acetal.** A solution of diisopropylamine (106 mg, 1.05 mmol) in THF (5 mL) was cooled to −5 °C. *n*-Butyllithium (0.68 mL of a 1.6 M solution, 1.05 mmol) was added, and after 15 min at −5 °C, the solution was further cooled to −78 °C and a solution of the appropriate ester (0.35 mmol) in THF (2 mL) was added. The solution was stirred at −78 °C for 15 min, and then triethylamine (106 mg, 1.05 mmol) followed by chlorotrimethylsilane (0.114 g, 1.05 mmol) were added. The cooling bath was then removed, and the reaction mixture was allowed to

(16) Evans, D. D.; Evans, D. E.; Lewis, G. S.; Palmer, P. J.; Weyell, D. J. *J. Chem. Soc.* **1963**, 3578.

warm to room temperature over 30 min. The mixture was then heated at reflux for 4 h. An acid quench (10% hydrochloric acid) followed by an aqueous sodium bicarbonate workup furnished the acid. The geometry of the alkenes was determined by ^{1}H NOE difference experiments.

2,5-Dimethyl-6-methoxy-4(*Z*)-hexenoic Acid (5). From ester **4**; procedure A, 87%; *Z*/*E* 96:4; procedure B, 60%; *Z*/*E* 46:54: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 7.2 Hz, 3H), 1.75 (d, J = 1 Hz, 3H), 2.24 (ddd, J = 14.2, 7.3, 7.3 Hz, 1H), 2.43 (obscured ddd, J = 14.2, 7.3, 7.3, Hz, 1H), 2.50 (obscured ddq, J = 7.2, 7.2, 7.2 Hz, 1H), 3.27 (s, 3H), 3.90 (AB J = 11.5 Hz, 2H), 5.33 (ddm, J = 7.2, 7.2 Hz, 1H); MS (EI) M$^+$ 172; IR cm^{-1} (film) 3400, 1697. Treatment of acid **5** with excess ethereal diazomethane furnished the methyl ester (90%). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.66; H, 9.77.

2-Methyl-5-methoxy-4(*Z*)-heptenoic Acid (7). From ester **6**; procedure A, 92%; *Z*/*E* 93:7; procedure B, 62%; *Z*/*E* 50:50: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7.3 Hz, 3H), 1.8 (d, J = 6.6 Hz, 3H), 2.10 (q, J = 7.3 Hz, 2H), 2.26 (broad ddd, J = 14.2, 7.3, 7.3 Hz, 1H), 2.45 (broad, obscured ddd, J = 14.2, 7.3, 7.3, 1H) 2.5 (obscured ddq, J = 6.6, 6.6, 6.6 Hz, 1H), 3.28 (s, 3H), 3.93 (ABq, J = 11.0 Hz, 2H), 5.34 (dd, J = 7.2, 7.2 Hz, 1H); MS (EI) M$^+$ 186; IR cm^{-1} (film) 3426, 1700 cm^{-1}.

2-Methyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic Acid (9). From ester **8**; procedure A 85%; *Z*/*E* 95:5; procedure B, 60%; *Z*/*E* 50:50: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H), 2.13 (q, J = 7.4 Hz, 2H), 2.27 (ddd, J = 14.2, 7.3, 7.3 Hz, 1H), 2.40–2.58 (m, 2H), 3.37 (s, 3H), 4.07 (AB, J = 10.9 Hz, 2H), 4.60 (s, 2H), 5.35 (broad t, 1H, J = 7.3 Hz); MS (EI) m/z 171 (M$^+$ − 45 (CO_2H)); IR cm^{-1} (film) 3400–3200, 1698. Treatment of acid **9** with excess ethereal diazomethane furnished the methyl ester (85%). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.39; H, 9.60.

2-Methyl-5-cyclohexyl-6-(methoxymethoxy)-4(*Z*)-hexenoic Acid (12). From ester **11**; procedure A 81%; *Z*/*E* > 99:1; procedure B, 65%, *Z*/*E* 64:34: 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.05–1.35 (m, 6H), 1.2 (d, J = 6.8 Hz, 3H), 1.67 (dm, J = 12.8 Hz, 1H), 1.75 (m, 3H), 2.0 (ddt, J = 11, 11, 2 Hz, 1H), 2.29 (broad ddd, J = 14.2, 7.2, 7.2 Hz, 1H), 2.49 (partly obscured, broad ddd, J = 14.2, 7.2, 7.2 Hz, 1H), 2.52 (partly obscured, qdd, J = 6.8, 6.8, 6.8 Hz, 1H), 3.39 (s, 3H), 4.05 (AB J = 10.9 Hz, 2H), 4.60 (s, 2H), 5.35 (broad dd, J = 7.2, 7.2 Hz, 1H); MS (EI) m/z 225 (M$^+$ − 45 (CO_2H)); IR cm^{-1} (film) 3400–3200, 1685. Treatment of acid **12** with excess ethereal diazomethane furnished the methyl ester (90%). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.44; H, 9.83.

2-Methyl-5-[(methoxymethoxy)methyl]-7-phenyl-4(*Z*)-heptenoic Acid (15). From ester **14**; procedure A, 1 h at room temperature 85%, *Z*/*E* 90:10: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 3H), 2.19 (broad ddd, J = 14.2, 7.3, 7.3 Hz, 1H), 2.29–2.49 (m, 4H), 2.67 (t, J = 7.3 Hz, 2H), 3.31 (s, 3H), 4.02 (AB, J = 10.75 Hz, 2H), 4.53 (s, 2H), 5.28 (broad t, J = 7.3 Hz, 1H), 7.09–7.2 (m, 3H), 7.18–7.32 (m, 2H); MS (EI) M$^+$ 292; IR cm^{-1} (film) 3400–3200, 3050, 3017, 1696. Treatment of acid **15** with excess ethereal diazomethane furnished the methyl ester (88%). Anal. Calcd for $C_{17}H_{24}O_4$: C, 70.55; H, 8.55. Found: C, 70.51; H, 8.61.

Preparation of Lactones. A mixture of the appropriate 6-[(methoxymethoxy)methyl]hexenoic acid (0.14 mmol) and pyridinium *p*-toluenesulfonate (0.36 g, 1.42 mmol) in 2-butanone (5 mL) was heated at reflux for 18 h. Evaporation of the mixture under vacuum followed by chromatography of the residue on silica gel using 25% ethyl acetate/hexane as eluent furnished the lactone.[10]

2-Methyl-5-ethylhex-4-en-6-olide (10). From acid **9**, yield 60%: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 2.02 (dq, J = 1.6, 7.4 Hz, 2H), 2.23 (ddm, J = 18.3, 12.1 Hz, 1H), 2.35 (dm, J = 18.3 Hz, 1H), 3.29 (ddq, J = 12.1, 6.1, 6.1 Hz, 1H), 4.2 (d, J = 14.8 Hz, 1H), 5.05 (d, J = 14.8 Hz, 1H), 5.47 (very broad s, 1H); MS (EI) M$^+$ 154; IR cm^{-1} (film) 1729.

2-Methyl-5-cyclohexyl-hex-4-en-6-olide (13). From acid **12**, yield 77%: 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.0–1.4 (m, 6H), 1.21 (obscured d, J = 6.2 Hz, 3H), 1.56–1.90 (m, 5H), 2.25 (ddm, J = 18.3, 12.8 Hz, 1H), 2.38 (ddd, J = 18.3, 8.2, 4.1 Hz, 1H), 3.32 (ddq, J = 12.8, 6.5, 6.5 Hz, 1H), 4.28 (d, J = 15.1 Hz, 1H), 5.04 (d, J = 15.1 Hz, 1H), 5.41 (broad dt, J = 2.5, 2.5 Hz, 1H); MS (EI) M$^+$ 208; IR cm^{-1} (film) 1729; 75 MHz ^{13}C NMR δ 17.0, 25.8, 26.2, 26.2, 31.3, 31.4, 33.8, 33.8, 45.5, 66.4, 123.4, 141.0, 177.4.

2-Methyl-5-(2-phenylethyl)hex-4-en-6-olide (16). From acid **15**, yield 78%: 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.6 Hz, 3H), 2.24 (ddm, J = 17, 12 Hz, 1H), 2.3 (obscured, 1H), 2.3 (partly obscured t, J = 7.5 Hz, 2H), 2.67 (ddd, J = 13.3, 7.5, 7.5 Hz, 1H), 2.75 (ddd, J = 13.3, 7.5, 7.5 Hz, 1H), 3.28 (qdd, J = 6.0, 6.0, 12.0 Hz, 1H), 4.20 (d, J = 15.3 Hz, 1H), 5.0 (ddt, J = 15.3, 2.0, 2.0 Hz, 1H), 5.45 (v broad s, 1H), 7.1–7.35 (m, 5H); MS (EI) M$^+$ 230; IR cm^{-1} (film) 3051, 3017, 1729, 1596; 75 MHz ^{13}C NMR δ 17.0, 33.8, 33.9, 34.4, 39.2, 66.9, 126.2, 126.3, 128.5, 128.6, 135.2, 141.2, 177.1.

General Procedure for the Rearrangement of Esters 19–22 as Bromomagnesium Enolates. Table 3, Procedure A: Synthesis of *anti*-2,3-Dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic Acid (25). To a solution of diethylamine (0.1 mL, 0.99 mmol) in ether (6 mL) cooled to 0 °C (ice bath) was added a 3.0 M solution of MeMgBr in ether (0.33 mL, 0.99 mmol). The mixture was brought to reflux during 15 min and then allowed to cool to room temperature. HMPA (0.06 mL, 0.33 mmol) was added, and the reaction mixture was cooled to −10 °C and stirred for 3 min. A solution of 3-[(methoxymethoxy)methyl]-*trans*-4-hexenyl 3-propionate (**21**) (76 mg, 0.33 mmol) in THF (3 mL) was added and the resulting mixture stirred for 20 min. The ice–NaCl bath was then removed, and the mixture was stirred for 2 h. It was finally quenched with 10% HCl and washed with saturated sodium bicarbonate. Then, the aqueous layer was reacidified with 10% HCl and extracted with EtOAc. It was dried over sodium sulfate and concentrated to yield a yellowish oil (66 mg, 89% yield, ratio *Z*/*E*: >97/3): 300 MHz ^{1}H NMR of *Z*-acid δ 1.01 (d, 3H, J = 6.0), 1.02 (t, 3H, J = 7.7), 1.10 (d, 3H, J = 7.1), 2.12 (dq, 2H, J = 7.7, 1.65), 2.26 (qd, 1H, J = 7.1, 8.2), 2.76 (qdd, 1H, J = 6.0, 8.2, 10.4), 3.38 (s, 3H), 4.03 (d, 1H, J = 11.5), 4.13 (d, 1H, J = 11.5), 4.61 (s, 2H), 5.11 (d, 1H, J = 10.4); ^{1}H NOE difference, irradiation at 5.11 ppm, signal at 2.12 ppm, +6%, signal at 2.26 ppm, +7%: 75 MHz ^{13}C NMR δ 12.9, 15.1, 19.7, 28.2, 35.2, 45.8, 55.5, 64.9, 96.1, 131.3, 138.8, 182.1; IR (cm^{-1}) 2958, 1701, 1453, 1211, 1147, 1099, 1041; MS *m*/*e* (CI: isobutane) 231 (M$^+$ + 1), 171 (M$^+$ − 59, 100), 169, 157. Anal. Calcd for $C_{12}H_{22}O_4$·0.1H_2O: C, 62.12; H, 9.58. Found: C, 62.07; H, 9.64

Synthesis of 2,4-Dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic Acid (23). 2,4-Dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic acid (**23**) was prepared in 91% yield (*Z*/*E*: >97:3) by following the same procedure used to prepare *anti*-2,3-dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic acid (**25**): 300 MHz ^{1}H NMR *Z*-acid δ 0.96 (t, 3H, J = 7.7), 1.11 (d, 3H, J = 7.1), 1.71 (s, 3H), 2.15 (bq, 2H, J = 7.7), 2.29 (dd, 1H, J = 8.2, 13.7), 2.48 (dd, 1H, J = 6.6, 13.7), 2.62 (dqd, 1H, J = 6.6, 7.1, 8.2), 3.38 (s, 3H), 4.02 (d, 1H, J = 11), 4.08 (d, 1H, J = 11), 4.60 (s, 2H); ^{1}H NOE difference, irradiation at 1.71 ppm, signal at 2.15 ppm, +3.2%, signal at 2.62 ppm, +2.7%; 75 MHz ^{13}C NMR δ 12.5, 15.9, 17.6, 23.9, 37.4, 38.1, 55.1, 65.6, 95.7, 131.4, 134.4, 182.4 IR (cm^{-1}) 2958, 1698, 1457, 1145, 1097, 1038; MS *m*/*e* (CI: isobutane) 231 (M$^+$ + 1), 213, 169 (M$^+$ − 61, 100). Anal. Calcd for $C_{12}H_{22}O_4$·0.2H_2O: C, 61.78; H, 9.49. Found: C, 61.48; H, 9.51.

Synthesis of 5-[(Methoxymethoxy)methyl]-2,3,3-trimethyl-4(*Z*)-heptenoic Acid (24). 5-[(Methoxymethoxy)methyl]-2,3,3-trimethyl-4(*Z*)-heptenoic acid (**24**) was prepared in 63% yield (*Z*/*E*: 92:8) by following the same procedure used to prepare *anti*-2,3-dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic acid (**25**): 300-MHz ^{1}H NMR δ 1.00 (t, 3H, J = 7.7), 1.14 (d, 3H, J = 7.1), 1.21 (s, 3H), 1.22 (s, 3H), 2.11 (q, 2H, J = 7.7), 2.55 (q, 1H, J = 7.1), 3.39 (s, 3H), 4.14 (d, 1H, J = 11), 4.20 (d, 1H, J = 11), 4.64 (s, 2H), 5.41 (s, 1H); ^{1}H NOE difference, irradiation at 5.41 ppm, signal at 2.11 ppm, +7%, signal at 2.55 ppm, +4%; 75 MHz ^{13}C NMR δ 12.6, 13.0, 26.1, 26.7, 29.6, 37.5, 49.6, 55.2, 64.6, 96.0, 135.9, 138.0, 181.2; IR (cm^{-1}) 2958, 1626, 1456, 1210, 1147, 1042; MS *m*/*e* (CI:

isobutane) 245 ($M^+ + 1$), 227, 183 ($M^+ - 61$, 100). Anal. Calcd for $C_{13}H_{23}O_4$: C, 63.91; H, 9.90. Found: C, 63.66; H, 9.91.

Synthesis of *syn*-2,3-Dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic Acid (26). *syn*-2,3-Dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic acid (**26**) was prepared in 63% yield (*Z*/*E*: >97:3) by following the same procedure used to prepare *anti*-2, 3-dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic acid (**25**). In the rearrangement of ester **22**, it was necessary to stop the reaction after 30 min. At longer reaction times a mixture of the two diastereomers was obtained due to epimerization at the α-carbon: 300 MHz ^{1}H NMR δ 1.00 (t, 3H, *J* = 7.7), 1.00 (d, 3H, *J* = 7.1), 1.14 (d, 3H, *J* = 7.1), 2.10 (dq, 2H, *J* = 7.7, 1.1), 2.32 (dq, 1H, *J* = 7.1, 7.1), 2.78 (ddq, 1H, *J* = 7.1, 7.1, 9.9), 3.38 (s, 3H), 4.01 (d, 1H, *J* = 11.5), 4.15 (d, 1H, *J* = 11.5), 4.60 (s, 2H), 5.26 (d, 1H, *J* = 9.9); ^{1}H NOE difference, irradiation at 5.26 ppm, signal at 2.10 ppm, +4.8%, signal at 2.32 ppm, +3%; 75 MHz ^{13}C NMR δ 12.5, 13.3, 17.6, 27.89, 34.5, 45.2, 55.1, 64.3, 95.6, 131.3, 137.8, 181.3; IR (cm^{-1}) 2956, 1697, 1448, 1283, 1148, 1099, 1040; MS *m*/*e* (CI: isobutane) 231 ($M^+ + 1$), 169, 157 ($M^+ - 73$, 100), 125, 97. Anal. Calcd for $C_{12}H_{22}O_4 \cdot 0.2H_2O$: C, 61.64; H, 9.59. Found: C, 61.65; H, 9.53.

Bromolactonization of the Carboxylic Acids (Scheme 3): General Procedure. To a solution of *anti*-2,3-dimethyl-5-[(methoxymethoxy)methyl]-4(*Z*)-heptenoic acid (**25Z**) (0.187 g, 0.81 mmol) cooled to −78 °C in dichloromethane (4 mL) was added dropwise a 0.5 M solution of bromine (2.43 mL, 1.21 mmol). The reaction mixture was stirred at −78 °C for 30 min and then quenched with a saturated aqueous solution of sodium sulfite. The organic layer was then washed with a saturated solution of sodium bicarbonate and dried over magnesium sulfate. Dichloromethane was evaporated, and a mixture of bromo lactones was obtained (194 mg, 75%). Separation of the isomers by flash chromatography (2/1 hexane/ethyl acetate) and NMR analysis gave the deprotected alcohol bromo lactones **27** and **28** (132 mg, 60%, **27**/**28**: 5/1) and the protected alcohol bromo lactones **29** and **30** (62 mg, 25%). The stereochemistry was determined by ^{1}H NOE difference.

Bromo lactone 27: 300 MHz ^{1}H NMR δ 1.10 (t, 3H, *J* = 7.1), 1.11 (d, 3H, *J* = 6), 1.18 (d, 3H, *J* = 7.7), 1.97 (q, 2H, *J* = 7.1), 2.80 (ddq, 1H, *J* = 9.9, 3.3, 6), 3.10 (dq, 1H, *J* = 9.9, 7.7), 3.84 (d,1H, *J* = 12), 3.93 (d, 1H, *J* = 12), 4.19 (dd, 1H, *J* = 3.3); ^{1}H NOE difference irradiation at 3.10 ppm, signal at 1.18 ppm, +4.5%, signal at 2.80 ppm, +3%; irradiation at 4.19 ppm, signal at 1.11 ppm, +5 ppm; 75 MHz ^{13}C NMR δ 8.7, 10.2, 28.0, 34.2, 37.3, 64.2, 76.2, 86.9, 180.1; IR (cm^{-1}) 3958, 2972, 1758, 1456, 1383, 1346, 1188, 1044, 981; MS *m*/*e* (CI: isobutane) 266 ($M^+ + 1$), 131, 113 ($M^+ - 152$, 100).

Bromo lactone 28: 300 MHz ^{1}H NMR δ 0.98 (t, 3H, *J* = 7.7), 1.11 (d, 3H, *J* = 6.6), 1.23 (d, 3H, *J* = 7.7), 1.73 (dq, 1H, *J* = 14.2, 7.7), 1.81 (dq, 1H, *J* = 14.2, 7.7), 2.57 (t, 1H, *J* = 6.6), 2.82 (dq, 1H, *J* = 7.7, 7.7), 3.03 (qdd, 1H, *J* = 7.7, 6.6, 12.1), 3.73 (dd, 1H, *J* = 6.6, 12.1), 4.17 (d, 1H, *J* = 12.1), 4.25 (dd, 1H, *J* = 6.6, 12.1); 75 MHz ^{13}C NMR δ 6.4, 13.1, 17.5, 28.6, 34.5, 40.7, 53.9, 66.7, 86.4, 175.9.

Bromo lactone 31: 300 MHz ^{1}H NMR δ (in C_6D_6) 0.79 (t, 3H, *J* = 7.1), 0.84 (d, 3H, *J* = 6.5), 1.25 (d, 3H, *J* = 6.5), 1.39 (dq, 1H, *J* = 14.2, 7.1), 1.49 (dq, 1H, *J* = 14.2, 7.1), 1.63 (dq, 1H, *J* = 9.9, 6), 2.35 (ddq, 1H, *J* = 9.9, 10.4, 6.5), 3.11 (s, 3H), 3.31 (dd, 1H, *J* = 1.1, 11), 3.60 (dd, 1H, *J* = 1.1, 11), 3.97 (d, 1H, *J* = 10.4), 4.27 (AB, 2H, *J* = 6.6); ^{1}H NOE difference irradiation at 1.25 ppm, signal at 1.63 ppm, +2%, signal at 2.80 ppm, +2%.

Bromo lactone 32: 300 MHz ^{1}H NMR: δ (in C6D6) 0.61 (d, 3H, *J* = 6.5), 0.91 (t, 3H, *J* = 7.1), 1.07 (d, 3H, *J* = 7.1), 1.56 (dq, 1H, *J* = 14.2, 7.1), 1.64 (dq, 1H, *J* = 14.2, 7.1), 1.66 (dq, 1H, *J* = 14.2, 7.1), 1.99 (ddq, 1H, *J* = 7.1, 14.2, 6.5), 3.09 (s, 3H), 3.74 (d, 1H, *J* = 10), 3.83 (d, 1H, *J* = 7.1), 3.94 (d, 1H, *J* = 10), 4.31 (d, 1H, *J* = 6), 4.34 (d, 1H, *J* = 6); ^{1}H NOE difference irradiation at 0.61 ppm, signal at 1.56 ppm, +7%, signal at 1.99 ppm, +5%, signal at 3.83 ppm, +3.6%.

Synthesis of 3-[(Methoxymethoxy)methyl]pentyl 3-Propionate (33). To a solution of 1-[(methoxymethoxy)methyl]-2-butanone (0.66 g, 5 mmol) in THF (25 mL) cooled to −20 °C was added a 3.2 M solution of EtMgBr (1.7 mL, 5.5 mmol). The reaction mixture was stirred at −20 °C for 1 h and was quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and condensed under vacuum. Flash chromatography (20% ethyl acetate/hexane) gave the alcohol as a colorless oil (0.41 g, 52%): 300 MHz ^{1}H NMR δ 0.88 (t, 6H, *J* = 7.1), 1.52 (q, 2H, *J* = 7.1), 1.64−1.74 (bs, 1H), 3.38 (s, 3H), 3.43 (s, 2H); 4.65 (s, 2H); IR (cm^{-1}) 3465, 2959, 1454, 1145, 1109, 1048; MS *m*/*e* (CI: isobutane) 163 ($M^+ + 1$), 145 ($M^+ - 17$, 100), 131, 101. 3-[(methoxymethoxy)methyl]pentyl 3-propionate (**33**) was prepared in 54% yield by following the same procedure used to prepare 3-[(methoxymethoxy)methyl]-2-methyl-1-pentenyl 3-propionate: 300 MHz ^{1}H NMR δ 0.85 (t, 6H, *J* = 7.1), 1.10 (t, 3H, *J* = 7.7), 1.88 (q, 2H, *J* = 7.1), 1.89 (q, 2H, *J* = 7.1), 2.28 (q, 2H, *J* = 7.7), 3.36 (s, 3H), 3.75 (s, 2H), 4.61 (s, 2H).

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Supporting Information Available: Copies of proton spectra for compounds **10**, **13**, **16**−**18**, **22**, **27**, **31**−**33**, **36**, **37**, **39**, **41**−**43**, **46**, and **47** and complete NMR data with proton assignments (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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