

Asymmetric Hydroxylation with Lipoxygenase: The Role of Group Hydrophobicity on Regioselectivity

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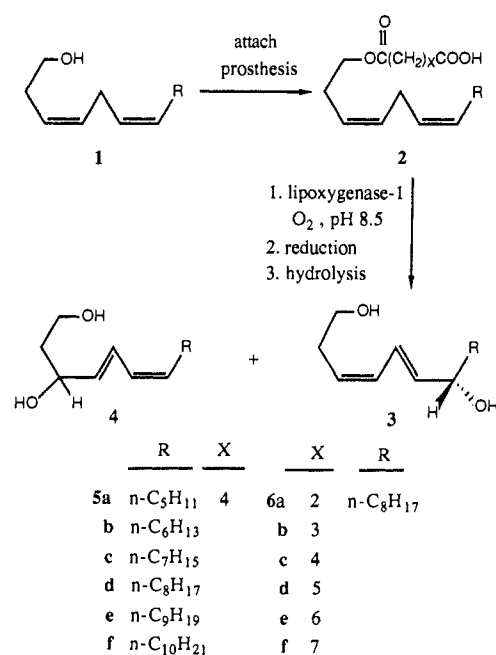
Abstract: Changes in the regioselectivity for the lipoxygenase 1 catalyzed oxidation of the unnatural substrates **5a-f** [(*Z,Z*)-HOOC(CH₂)₄C(=O)O(CH₂)₂CH=CHCH₂CH=CHR; R, **a-f** = *n*-C₅H₁₁-*n*-C₁₀H₂₁] to afford regioisomeric diols **3** [(*Z,E*)-HOCH₂CH₂CH=CHCH=CHCH(OH)R] and **4** [(*E,Z*)-HOCH₂CH₂CH(OH)CH=CH-CH=CHR] as a function of the hydrophobicity of the distal R group were investigated. The results demonstrate that the ratio of products **3/4** decreases steadily as the hydrophobicity of the distal group is increased incrementally from *n*-C₅H₁₁ to *n*-C₁₀H₂₁. Conversely, changes in the proximal group hydrophobicity by varying the prosthetic modifier for substrates **6a-e** [(*Z,Z*)-HOOC(CH₂)_XC(=O)O(CH₂)₂CH=CHCH₂CH=CHC₈H₁₇; X, **a-e** = 2-6] gave opposite changes in the regioselectivity of oxidation. For example, increasing the hydrophobicity of the proximal group from X = 4 to X = 6 led to an increase in the regioselective formation of diol **3**. Decreasing the value of X led to preferential formation of diol **4**. Hence, the regiochemical outcome of the enzyme-catalyzed reaction appears to be influenced by the hydrophobic differential between the proximal and distal groups. The data suggest that optimization of the regioselectivity for new substrates can be achieved by careful selection of modifier groups used in the design of substrate structure.

Our recent report on the overall enzymatic hydroxylation of pentadienols **1** via the adipoyl prosthetic modified substrates **2** (Scheme I, X = 4) using soybean lipoxygenase 1 (SBLO) noted that, in contrast to the broad substrate flexibility and high stereospecificity, the enzymatic reaction was not completely regioselective.¹ This observation was not unusual since even the natural substrate, linoleic acid, lacks complete regioselective oxidation, affording largely, but not exclusively, the 13-hydroperoxide. This peculiar proclivity of lipoxygenase to form regioisomeric mixtures with a variety of fatty acid congeners has been the focus of several reports, and the formation of these abnormal regioisomeric products has generally been attributed to the enzyme's ability to bind the substrate in both a head-to-tail and a reversed orientation.²⁻⁴ However, the means by which the enzyme regulates this directional mode of binding has not been clearly defined. A better understanding of this control mechanism would be extremely beneficial to the further synthetic development of our biocatalytic method. Consequently, to improve the scope of this reaction, we sought to determine whether the regiochemistry could be modulated by the choice of the specific prosthetic modifiers used in the construction of surrogate substrates. Central to this theme is the fundamental question of what structural features in the substrate structure **2** primarily influence the positional specificity of oxidation. It was of particular interest to differentiate the role in regioselection of the proximal⁵ and distal groups flanking the pentadienic system.⁶ Hence, we now report our results for the specificity of oxidation for the structurally related substrates **5** and **6** in which the hydrophobicity of the distal and proximal groups is varied incrementally. The results strongly suggest that the difference in the hydrophobic content between the proximal and distal groups significantly influences the positional specificity of oxygenation.

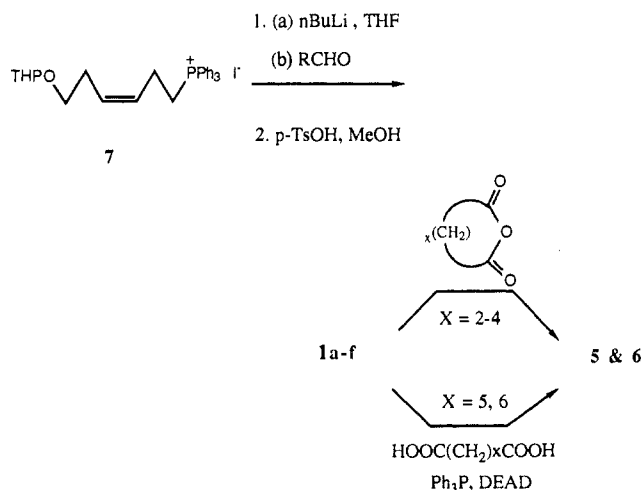
Results and Discussion

Preparation of Prosthetic Modified Substrates. As shown in Scheme II, the *Z,Z*-dienols **1a-f** were prepared by deprotonation of the known (*Z*)-phosphonium iodide (**7**)⁷ with 1.1 equiv of *n*-BuLi in tetrahydrofuran (THF) at -78 °C followed by condensation of the resulting ylide with the appropriate aldehydic partner in the presence of 10% hexamethylphosphoramide to afford **1** protected as the tetrahydropyranyl (THP) ether. Exposure of the crude THP ether to a catalytic amount of *p*-toluenesulfonic acid in methanol at 23 °C led to rapid removal of the protecting group to afford, after purification by flash silica gel chromatography, the *Z,Z*-dienol **1**. ¹³C NMR and thin-layer chromatographic (AgNO₃-impregnated silica gel) analyses revealed that each alcohol contained approximately 5% of the corresponding

Scheme I



Scheme II



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graphic (AgNO₃-impregnated silica gel) analyses revealed that each alcohol contained approximately 5% of the corresponding

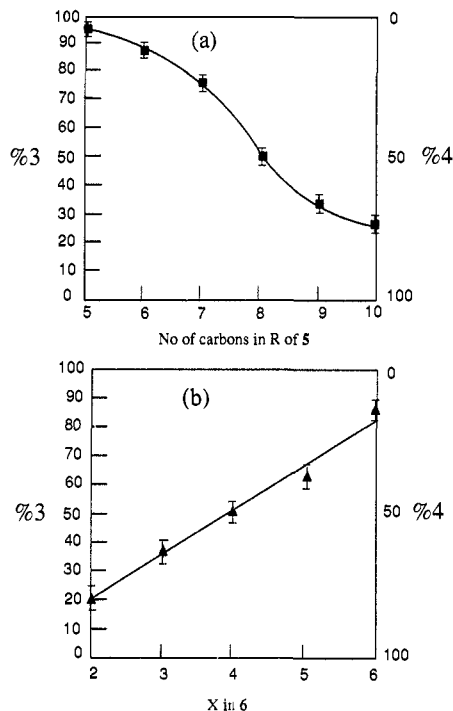


Figure 1. Regioselectivity of lipoxygenase 1 catalyzed oxidation of (a) substrates **5a-f** and (b) substrates **6a-e**. All data points are an average of three separate trials. The stereochemical assignments for **3** were previously shown¹ to be *Z,E* and *S* (i.e., as drawn, *vide supra*). Only the *E,Z*-diene geometry for **4** has been established. In cases where minor quantities of *E,E*-diene products were detected, these were included in determining the isomer ratios.

Z,E isomer. The undesired isomer could not be readily separated by chromatographic methods; consequently, the mixture of isomers was used for conversion to the modified substrate analogues.

The adipoyl-modified series **5a-f** was prepared in a straightforward manner that involved treatment of the dienols **1a-f** in dichloromethane solution with 1.5 equiv of adipic anhydride monomer,⁸ 2 equiv of pyridine, and a catalytic amount of 4-(dimethylamino)pyridine for approximately 1 h at 23 °C. The glutaryl and succinyl esters **6a** and **6b** could be synthesized in a similar fashion by condensation with glutaric and succinic anhydrides, respectively. By contrast, preparation of the pimeloyl (C7) and suberoyl (C8) esters **6d** and **6e** required an alternate procedure that was a modification of the Mitsunobu reaction.⁹ Thus, the alcohol **1d** in tetrahydrofuran solution at 0 °C was treated with a 3 molar excess of the corresponding C7 or C8 diacid and 1.1 equiv each of triphenylphosphine and diethyl azodicarboxylate to give the monoester products, which could be separated from excess diacid by column chromatography. Under these conditions, the formation of diester was generally restricted to 20% or less.

Regiospecificity of Lipoxygenase-Catalyzed Oxygenation. All enzymatic oxidations were conducted with 0.50 mmol of substrate

Table I. Regiospecificity for SBLO-Catalyzed Oxygenation of Modified Substrates

	X	R	3/4
5e	4		27:73
8	4		1:99
5b	4		87:13
9	4		77:23
10	3		45:55

and 0.5 equiv (w/w) of lipoxygenase 1¹⁰ (activity 150 000 units/mg of protein) in 30 mL of 0.2 M borate buffer (pH 8.5) at 0 °C for 1 h with an O₂ flow rate of 0.2 L min⁻¹. Substrate conversions were typically 70–80% complete under these conditions. Incubations were terminated by the addition of an excess of the mild hydroperoxide reducing agent 2-(methylthio)ethanol (7 h, 23 °C) followed by removal of water *in vacuo*. The reaction residue was then treated with KOH in MeOH solution (12 h, 23 °C) and extracted with ethyl acetate, and the crude products were partially purified on a short column of silica gel to remove traces of sulfide and sulfoxide. The ¹H NMR spectra of each product was consistent with the assigned *E,Z*-olefin stereochemistry, and the regiochemistry for each isomer was easily established by homonuclear decoupling experiments. The regioisomer ratios were determined by normal-phase HPLC analysis at 234 nm.¹¹ All values reported for the substrate regiospecificity are an average of three separate oxygenation trials and control experiments using purified¹² enzyme (DEAE-Sephadex) did not afford product ratios significantly different from those obtained with commercial SBLO. Also, terminating the enzyme reaction at 50% completion did not alter the product ratio. Additional controls in the absence of enzyme showed no measurable oxidation.

As shown in Figure 1a, regioselective formation of diol **3**, which corresponds to oxygenation at the "appropriate" olefin site, decreased with an increasing hydrophobic difference between the distal and proximal groups. For example, increasing the distal group from *n*-C₅H₁₁ to *n*-C₈H₁₇ resulted in a substantial decrease in selectivity from a 95:5 to a 1:1 ratio of **3/4**, respectively. Further increases in the hydrophobicity of the distal unit (C8 → C10) led to a reversal of selectivity with oxidation occurring mostly at the "inappropriate" olefin bond. This trend was also noted between substrates possessing terminal groups of similar length but having significantly different hydrophobic surface¹³ content. As shown in Table I, substrate **8**, which possesses two methyl appendages along the nine-carbon backbone, gave a 1:99 ratio of **3/4** compared to a 27:73 ratio of isomers for the unbranched nine-carbon group of **5e**. Also, while the length of the *n*-C₆H₁₃ and the CH₂CH₂-CH₂C₆H₅ groups of substrates **5b** and **9** are similar, the latter shows an increase in the amount of regioisomer **4**. However, it should be noted that hydrophobicity constants for *n*-alkyl groups increase uniformly as alkyl chains lengthen steadily from pentyl to decyl and a plot of hydrophobicity values vs the number of chain carbons is linear.¹⁴ The curve in Figure 1a displays a clear deviation from linearity, which may suggest that either an op-

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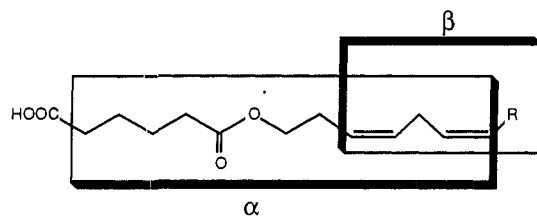
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 (5) For definitions of proximal and distal, see: Gunstone, F. D. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Haslam, E., Eds.; Pergamon Press: New York, 1979; pp 587–632.
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 (8) Hill, J. W. *J. Am. Chem. Soc.* **1930**, *52*, 4110–4114.
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timum "pocket fit"¹⁵ operates in concert with hydrophobic interactions or, possibly, that the hydrophobicity of the binding topography is not uniform.¹⁶

Similar trends in oxygenation specificity were observed for the lipoxygenase oxidation of substrates **6a–e** in which the hydrophobic differential of the proximal and distal groups derives from changes in only the prosthetic modifier, as seen in Figure 1b. Comparison of the specificity for the adipoyl-modified substrate (**6c**, $X = 4$), which afforded a 1:1 ratio of products with the less hydrophobic glutaryl ($X = 3$) and succinyl ($X = 2$) groups of substrates **6b** and **6a**, revealed a decrease in oxygenation at the "appropriate" olefin site; the regioisomers **3/4** were obtained in 36:64 and 26:74 ratios, respectively. Conversely, increasing the proximal group to the C7 pimeloyl (**6d**, $X = 5$) or the C8 suberoyl (**6e**, $X = 6$) enhanced the regioselectivity, again in favor of **3**. Hence, changes in hydrophobicity caused by the introduction of additional methylene groups into the substrate's prosthesis, which increases the hydrophobic difference of the proximal region relative to the distal group, are accompanied by a parallel increase in regioselective oxygenation at the normal olefin site. A related behavior was also observed when the proximal group was varied within substrates containing distal groups other than the n -alkyl termini of **5** or **6**. For example, a 77:23 ratio of isomers was obtained for the oxidation of **9** (Table I) when a C6 adipoyl modifier was used to assemble the substrate backbone, whereas this ratio decreases to 55:45 when the modifier unit was replaced by a C5 glutaryl unit as seen for **10**.

Conclusion. The present study illustrates the relevance of hydrophobic interactions to the positional specificity of oxygenation for lipoxygenase 1. The data presented herein do not exclude the carboxyl(ate) group¹⁷ or steric factors as regiocontrol elements; however, the regiochemical outcome appears to be strongly influenced by the hydrophobic differential between the proximal and distal units ascribed by the regions α and β shown in **11**.



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These results bear directly on the design of new unnatural substrates and suggest that maintaining a high degree of hydrophobicity in the structural subunit α will favor oxygenation at the "normal" olefin site leading to diol **3**. By contrast, in cases where the hydrophobic content of the β subunit predominates, then oxygenation in the abnormal regiochemical sense is the major outcome. These observations presently led us to presume that the enzyme is sensitive to these hydrophobic differences and primarily uses this structural parameter for controlling the directional mode of substrate binding. These guidelines should provide a means for optimizing the regioselectivity of the reaction by amplifying the hydrophobicity of the prosthetic group as needed. Application of these techniques to the enzymatic hydroxylation of other substrates is under investigation.

Experimental Section

¹H and ¹³C NMR spectra were obtained on either a Varian VXR 400 (400 MHz) or a Perkin-Elmer R-600 (60 MHz) spectrometer. Infrared spectra were determined on a Perkin-Elmer 1420 spectrometer. The

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abbreviation TF denotes thin film and hrms denotes high-resolution mass spectrum. All elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. HPLC analyses were performed on a Waters Model 501 system using a 25-cm SiO₂ (5- μ m) column monitoring at 234 nm and eluting with 2:98 2-propanol–hexane at a flow rate of 2.0 mL min⁻¹.

Soybean lipoxygenase was obtained from Sigma Co. type 1 and purified according to the procedure of Axelrod et al.¹² Control experiments conducted with substrates **5a**, **5d**, and **8** showed no appreciable difference (<3%) in regioselectivity from oxidations using either commercial or purified enzyme. Consequently, the commercial enzyme was typically used without additional purification; activity 150000 units/mg of protein as determined by the standard assay procedure. All aldehydes were obtained from Aldrich Chemical Co. and purified by distillation prior to use. All anhydrides and diacids, except as noted, were obtained from Aldrich and purified by recrystallization.

General Procedure for the Preparation of Dienols 1. (*Z,Z*)-3,6-Dodecadien-1-ol (**1a**). To a solution of 5.72 g (10 mmol) of phosphonium iodide **7** in 28 mL of tetrahydrofuran at -78 °C under a nitrogen atmosphere was added dropwise over a 10-min period 7 mL of 1.52 M *n*-BuLi followed by the addition of 3 mL of anhydrous hexamethylphosphoramide. The resulting orange-yellow solution was stirred for 1.5 h at -78 °C. Then was added a solution of 0.80 g (8 mmol) of hexanal in 5 mL of tetrahydrofuran; the mixture was stirred for 1 h at -78 °C and then an additional 30 min at 0 °C. The mixture was quenched by the addition of 100 mL of water and diluted with 50 mL of ether. The aqueous phase was extracted with 3 × 50 mL of ether, and the combined organic phases were washed with 50 mL of brine and dried over anhydrous MgSO₄. Evaporation of solvent gave a crude, viscous oil, which was dissolved in 30 mL of methanol at 23 °C followed by the addition of 50 mg of *p*-toluenesulfonic acid, and the mixture was stirred for 1 h at 23 °C. The mixture was diluted with 250 mL of ether, washed with 50 mL of saturated aqueous sodium bicarbonate solution, and dried over anhydrous MgSO₄. Evaporation followed by flash chromatography on a silica column in 1:40 ethyl acetate–hexane afforded 680 mg (47%) of dienol **1a**:^{18,19} IR (TF) 3380, 1090 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, $J = 7$ Hz, 3 H), 1.25 (m, 4 H), 2.05 (t, $J = 7$ Hz, 2 H), 2.20 (br s, 1 H, OH), 2.33 (q, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 3.62 (t, $J = 7$ Hz, 2 H), 5.25–5.56 (m, 4 H).

Yield (%) and Spectral Data for Dienols 1. **1b** (53%): IR (TF) 3410, 1055 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, $J = 7$ Hz, 3 H), 1.27 (br s, 8 H), 2.04 (q, $J = 7$ Hz, 2 H), 2.33 (q, $J = 7$ Hz, 2 H), 2.81 (t, $J = 7$ Hz, 2 H), 3.62 (t, $J = 7$ Hz, 2 H), 5.25–5.56 (m, 4 H); ¹³C (CDCl₃) δ 13.98, 25.55, 25.56, 27.35, 29.34, 29.68, 30.80, 31.74, 62.06, 125.31, 127.35, 130.48, 131.06; hrms calcd for C₁₃H₂₄O 196.1827, obsd m/e 196.1825 (M⁺), 178, 165, 164.

1c (53%): IR (TF) 3400, 1080 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, $J = 7$ Hz, 3 H), 1.25 (br s, 10 H), 2.05 (q, $J = 7$ Hz, 2 H), 2.21 (br s, 1 H, OH), 2.33 (q, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 3.62 (t, $J = 7$ Hz, 2 H), 5.25–5.56 (m, 4 H); ¹³C NMR (CDCl₃) δ 13.98, 22.52, 25.67, 27.20, 29.15, 29.33, 29.62, 30.75, 31.76, 62.06, 125.34, 127.37, 130.52, 131.11; hrms calcd for C₁₄H₂₆O 210.1983, obsd m/e 210.1978 (M⁺), 192, 179, 178.

1d (68%): IR (TF) 3375, 1100 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, $J = 7$ Hz, 3 H), 1.23 (br s, 12 H), 2.05 (q, $J = 7$ Hz, 2 H), 2.35 (br s, 1 H, OH), 2.36 (q, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 3.61 (t, $J = 7$ Hz, 2 H), 5.27–5.55 (m, 4 H); ¹³C NMR (CDCl₃) δ 13.80, 22.46, 25.64, 27.20, 29.14, 29.38, 29.62, 30.78, 30.88, 31.89, 62.06, 125.34, 127.37, 130.52, 131.11. Anal. Calcd for C₁₅H₂₈O: C, 80.29; H, 12.58. Found: C, 80.16; H, 12.54.

1e (42%): IR (TF) 3400, 1085 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, $J = 7$ Hz, 3 H), 1.23 (br s, 14 H), 2.05 (q, $J = 7$ Hz, 2 H), 2.35 (q, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 3.61 (t, $J = 7$ Hz, 2 H), 5.27–5.55 (m, 4 H); ¹³C NMR (CDCl₃) δ 13.92, 22.61, 25.66, 27.19, 29.11, 29.25, 29.55, 30.70, 30.72, 30.92, 31.83, 62.10, 125.48, 127.53, 130.68, 131.01. Anal. Calcd for C₁₆H₃₀O: C, 80.60; H, 12.68. Found: C, 80.44; H, 12.68.

1f (66%): IR (TF) 3390, 1100 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, $J = 7$ Hz, 3 H), 1.23 (br s, 16 H), 2.05 (q, $J = 7$ Hz, 2 H), 2.36 (q, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 3.61 (t, $J = 7$ Hz, 2 H), 5.27–5.55 (m, 4 H); ¹³C NMR (CDCl₃) δ 13.92, 22.61, 25.66, 27.19, 29.11, 29.25, 29.55, 30.62, 30.68, 30.72, 30.92, 31.83, 62.10, 125.48, 127.53, 130.68, 131.01. Anal. Calcd for C₁₇H₃₂O: C, 80.88; H, 12.78. Found: C, 81.02; H, 12.55.

1 (R = CH₂CH₂CH=C(CH₃)CH₂CH₂CH=C(CH₃)₂) (58%): IR (TF) 3400, 1085 cm⁻¹; ¹H NMR (CDCl₃) δ 1.65 (s, 6 H), 1.75 (s, 3 H), 2.01.9–2.15 (m, 10 H), 2.82 (t, $J = 7$ Hz, 2 H), 3.64 (t, $J = 7$ Hz, 2 H),

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5.10 (t, $J = 7$ Hz, 1 H), 5.21 (t, $J = 7$ Hz, 1 H), 5.30–5.61 (m, 4 H); hrms calcd for $C_{18}H_{30}O$ 262–2296, obsd m/e 262.2303 (M^+), 244, 229.

1 (R = $CH_2CH_2CH_2C_6H_5$) (52%); IR (TF) 3370, 1651, 1505 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.71 (m, 1 H), 2.12 (q, $J = 7$ Hz, 2 H), 2.33 (q, $J = 7$ Hz, 2 H), 2.65 (t, $J = 7$ Hz, 2 H), 2.82 (t, $J = 7$ Hz, 2 H), 3.65 (t, $J = 7$ Hz, 2 H), 5.30–5.55 (m, 4 H), 7.10–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.50, 26.48, 30.85, 31.13, 35.44, 61.96, 125.28, 125.60, 128.08, 128.50, 128.62, 129.97, 131.22, 142.48; hrms calcd for $C_{16}H_{22}O$ 230.1670, obsd m/e 230.1682 (M^+), 212, 200, 91.

General Procedure for the Preparation of Esters 5 or 6 from Anhydrides. Preparation of Adipate Ester **5d**. To a solution of 896 mg (4.0 mmol) of dienol **1d** in 8 mL of dichloromethane at 0 °C under a nitrogen atmosphere was added 768 mg (6 mmol) of adipic anhydride monomer^{8,20} followed by the addition of 0.65 mL of pyridine and 50 mg of 4-(dimethylamino)pyridine, and the mixture was stirred at 0 °C for 3 h. The mixture was diluted with 250 mL of ether and washed successively with 50 mL of 1.0 M HCl, 50 mL of water, and 25 mL of brine, and dried over anhydrous $MgSO_4$. Evaporation afforded a colorless semisolid, which was purified by flash silica chromatography eluting with 1:5 and then 1:1 ethyl acetate–hexane to afford 559 mg (40%) of **5d** as a colorless oil: IR (TF) 3100, 1755, 1740 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 12 H), 1.66 (m, 4 H), 2.07 (q, $J = 7$ Hz, 2 H), 2.24–2.45 (m, 6 H), 2.77 (t, $J = 7$ Hz, 2 H), 4.05 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.63, 24.16, 24.33, 25.78, 26.80, 27.06, 27.39, 29.35, 29.69, 29.86, 31.96, 33.74, 33.91, 63.60, 124.48, 127.44, 130.40, 130.98, 173.55, 179.20; hrms calcd for $C_{21}H_{36}O_4$ 352.2613, obsd m/e 352.2612 (M^+), 335, 307, 129, 60.

General Procedure for the Preparation of Esters 6 from Diacids. Preparation of Pimeloyl Ester **6d**. Compound **6d** was prepared according a modification of the Mitsunobu⁹ method as follows: to a solution of 960 mg (6.0 mmol) of pimelic acid and 576 mg (2.2 mmol) of triphenylphosphine in 16 mL of tetrahydrofuran at 23 °C under a nitrogen atmosphere was added a solution of 448 mg (2.0 mmol) of dienol **1d** in 1 mL of tetrahydrofuran. Then was added dropwise over a 1-h period a solution of 383 mg (2.2 mmol) of diethyl azodicarboxylate in 1 mL of tetrahydrofuran, and the mixture was stirred for 45 min at 23 °C. The solvent was then evaporated and the semisolid residue was purified by flash silica gel chromatography, eluting with 1:3 ethyl acetate–hexane to afford 325 mg (44%) of **6d**: IR (TF) 3490, 1755, 1730 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 14 H), 1.67 (m, 4 H), 2.06 (q, $J = 7$ Hz, 2 H), 2.24–2.45 (m, 6 H), 2.82 (t, $J = 7$ Hz, 2 H), 4.10 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.06, 22.81, 24.37, 24.68, 25.93, 26.86, 27.56, 28.75, 29.37, 29.98, 29.98, 32.18, 33.75, 34.01, 34.01, 63.74, 125.02, 126.84, 130.94, 131.18, 173.75, 179.06; hrms calcd for $C_{22}H_{38}O_4$ 366.2769, obsd m/e 366.2764 (M^+), 349, 321, 143, 60.

Yield (%) and Spectral Data for Esters 5 and 6. **5a** (62%): IR (TF) 3300, 1760, 1740 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 6 H), 1.66 (m, 4 H), 2.02 (q, $J = 7$ Hz, 2 H), 2.26–2.40 (m, 6 H), 2.76 (t, $J = 7$ Hz, 2 H), 4.09 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.99, 22.62, 23.94, 25.77, 27.10, 27.50, 28.93, 29.49, 31.64, 33.23, 33.69, 63.61, 124.60, 127.11, 130.86, 131.02, 173.64, 179.22; hrms calcd for $C_{18}H_{30}O_4$ 310.2143, obsd m/e 310.2166 (M^+), 293, 265, 129, 60.

5b (48%): IR (TF) 3350, 1765, 1740 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.87 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 8 H), 1.66 (m, 4 H), 2.03 (q, $J = 7$ Hz, 2 H), 2.30–2.41 (m, 6 H), 2.78 (t, $J = 7$ Hz, 2 H), 4.07 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.63, 23.86, 24.04, 25.72, 27.08, 27.53, 28.99, 29.50, 31.60, 33.33, 33.75, 63.58, 124.52, 127.07, 130.91, 131.14, 173.62, 179.18; hrms calcd for $C_{19}H_{32}O_4$ 324.2300, obsd m/e 324.2300 (M^+), 307, 279, 129, 60.

5c (43%): IR (TF) 3350, 1750, 1740 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.88 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 10 H), 1.67 (m, 4 H), 2.04 (q, $J = 7$ Hz, 2 H), 2.31–2.43 (m, 6 H), 2.79 (t, $J = 7$ Hz, 2 H), 4.08 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.43, 24.02, 24.08, 25.54, 26.80, 27.20, 28.90, 29.01, 29.59, 31.60, 33.64, 33.85, 63.57, 124.52, 127.07, 130.91, 131.14, 172.86, 178.78; hrms calcd for $C_{20}H_{34}O_4$ 338.2456, obsd m/e 338.2454 (M^+), 321, 293, 129, 60.

5e (51%): IR (TF) 3350, 1755, 1730 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.87 (t, $J = 7$ Hz, 3 H), 1.25 (br s, 10 H), 1.66 (m, 4 H), 2.03 (q, $J = 7$ Hz, 2 H), 2.30–2.41 (m, 6 H), 2.78 (t, $J = 7$ Hz, 2 H), 4.07 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.88, 22.49, 23.61, 23.89, 23.99, 25.40, 26.55, 26.66, 27.10, 28.92, 29.21, 29.44, 31.84, 33.61, 34.39, 63.57, 124.52, 127.07, 130.91, 131.14, 172.86, 178.78; hrms calcd for $C_{22}H_{38}O_4$ 366.2769, obsd m/e 366.2764 (M^+), 349, 321, 129, 60.

5f (70%): IR (TF) 3350, 1760, 1740 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.87 (t, $J = 7$ Hz, 3 H), 1.25 (br s, 12 H), 1.66 (m, 4 H), 2.03 (q, $J = 7$ Hz, 2 H), 2.30–2.41 (m, 6 H), 2.78 (t, $J = 7$ Hz, 2 H), 4.07 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.01, 22.47, 23.98, 24.01, 25.74, 26.35, 26.68, 26.96, 28.99, 29.36, 29.75, 29.77, 29.77, 31.57, 33.41, 33.59, 63.88, 124.52, 127.07, 130.91, 131.14, 173.36, 178.82; hrms calcd for $C_{23}H_{40}O_4$ 380.2926, obsd m/e 380.2923 (M^+), 363, 335, 129, 60.

6a (55%): IR (TF) 3400, 1755, 1735 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.90 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 12 H), 2.01 (q, $J = 7$ Hz, 2 H), 2.42 (q, $J = 7$ Hz, 2 H), 2.62 (q, $J = 7$ Hz, 2 H), 2.70 (q, $J = 7$ Hz, 2 H), 2.84 (t, $J = 7$ Hz, 2 H), 4.17 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.00, 22.62, 25.68, 26.77, 27.23, 28.91, 28.93, 29.50, 29.60, 31.84, 32.53, 61.90, 124.52, 127.48, 131.60, 131.73, 171.88, 178.42. Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.48; H, 9.88.

6b (60%): IR (TF) 3500, 1745, 1735 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 12 H), 1.94 (m, 2 H), 2.01 (q, $J = 7$ Hz, 2 H), 2.48 (m, 2 H), 2.51 (q, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 4.12 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 19.76, 22.63, 25.66, 26.81, 27.25, 29.26, 29.50, 29.58, 29.98, 31.87, 32.94, 33.16, 61.90, 124.44, 127.44, 130.76, 131.30, 172.51, 178.42. Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.90; H, 10.18.

6c (40%): same as **5d**.

6d (36%): IR (TF) 3100, 1760, 1730 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 14 H), 1.33 (m, 4 H), 1.63 (m, 4 H), 2.03 (q, $J = 7$ Hz, 2 H), 2.25–2.45 (m, 6 H), 2.82 (t, $J = 7$ Hz, 2 H), 4.10 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.96, 22.60, 24.46, 24.73, 25.73, 26.96, 27.25, 28.60, 28.77, 29.18, 29.54, 29.60, 31.87, 34.09, 34.18, 63.62, 124.44, 127.32, 130.69, 131.32, 173.85, 179.30. Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.08; H, 10.44. Found: C, 71.95; H, 10.42.

6e (36%): IR (TF) 3300, 1750, 1735 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.85 (t, $J = 7$ Hz, 3 H), 1.26 (br s, 12 H), 1.33 (m, 4 H), 1.62 (m, 4 H), 2.01 (q, $J = 7$ Hz, 2 H), 2.25–2.45 (m, 6 H), 2.80 (t, $J = 7$ Hz, 2 H), 4.14 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.86, 22.65, 24.42, 24.73, 25.73, 26.94, 27.25, 28.66, 28.74, 29.18, 29.55, 29.55, 31.87, 33.96, 34.10, 34.17, 63.66, 124.48, 127.33, 130.71, 131.28, 173.83, 179.22. Anal. Calcd for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59. Found: C, 72.62; H, 10.55.

8 (75%): IR (TF) 3300, 1755, 1745 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.60 (s, 6 H), 1.66 (m, 4 H), 1.68 (s, 3 H), 1.96–2.11 (m, 10 H), 2.41 (m, 4 H), 2.81 (t, $J = 7$ Hz, 2 H), 4.09 (t, $J = 7$ Hz, 2 H), 5.10 (t, $J = 7$ Hz, 1 H), 5.14 (t, $J = 7$ Hz, 1 H), 5.25–5.50 (m, 4 H). Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.96; H, 9.79.

9 (59%): IR (TF) 3250, 1750, 1730, 1620, 1510 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.68 (m, 4 H), 1.70 (m, 2 H), 2.10 (q, $J = 7$ Hz, 2 H), 2.30 (m, 6 H), 2.65 (t, $J = 7$ Hz, 2 H), 2.80 (t, $J = 7$ Hz, 2 H), 4.11 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H), 7.10–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.68, 23.76, 25.34, 26.52, 26.52, 31.02, 33.26, 33.78, 35.35, 63.71, 124.40, 125.56, 127.39, 128.29, 128.29, 129.60, 130.97, 142.22, 173.05, 178.72; hrms calcd for $C_{22}H_{22}O_4$ 350.1517, obsd m/e 350.1522 (M^+), 333, 305, 129, 60.

10 (66%): IR (TF) 3250, 1750, 1730, 1620 and 1510 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.71 (m, 2 H), 1.96 (m, 2 H), 2.12 (q, $J = 7$ Hz, 2 H), 2.40 (m, 6 H), 2.64 (t, $J = 7$ Hz, 2 H), 2.78 (t, $J = 7$ Hz, 2 H), 4.10 (t, $J = 7$ Hz, 2 H), 5.25–5.50 (m, 4 H), and 7.10–7.35 (m, 5 H); hrms calcd for $C_{21}H_{20}O_4$ 336.1361, obsd m/e 336.1340 (M^+), 319, 291, 115, 60.

General Procedure for the SBLO Oxidation of the Dienic Esters 5–10.

Oxygenation of Adipate Ester 5d. To a homogeneous solution of 176 mg (0.50 mmol) of adipate ester **5d** in 30 mL of 0.2 M borate buffer pH 8.5 at 0 °C was added 88 mg of lipoxygenase type 1 while O_2 was bubbled through the solution at a flow rate of 0.2 L min^{-1} . Foaming was controlled by the addition of a trace (<1 mg) amount of Antifoam B. The mixture was vigorously stirred while the flow of O_2 was maintained for 1 h at 0 °C. The reaction was quenched by the addition of 1.8 g (20 mmol) of 2-(methylthio)ethanol and the mixture was stirred for 7 h at 23 °C. The reaction mixture was reduced in volume to near dryness by careful removal of water in vacuo. The residue was suspended in 20 mL of MeOH followed by the addition of 5 g of KOH, and the mixture was stirred for 12 h at 23 °C. The mixture was diluted with water and extracted with 5 \times 50 mL portions of ethyl acetate. Evaporation of solvent afforded a yellow oil, which was filtered through a 2 \times 5 cm plug of silica gel in 1:5 ethyl acetate–hexane to afford 94 mg (78%) of a mixture of diols **3d** and **4d**. The ratio of **3d** to **4d** was determined to be 50:50 by normal-phase HPLC analysis using a 25-cm SiO_2 (5- μm) column eluting with 98:2 hexane–2-propanol at a flow rate of 2.0 mL min^{-1} . The retention times for **3d** and **4d** were 4.58 and 5.13 min, respectively. All chromatograms were recorded at 234 nm. All regioselectivity ratios are an average of three separate oxygenation trials.

(20) Adipic anhydride monomer was prepared according to ref 8 and stored as a solution in dichloromethane at –20 °C under a nitrogen atmosphere. The anhydride could be kept for several months under these conditions.

The isomeric mixture of diols **3d** and **4d** could be separated on a 20 × 20 cm Merck silica gel F₂₅₄ preparative layer (2-mm) plate in 1:5 ether-hexane. **3d**: IR (TF) 3330, 1030 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 10 H), 1.55 (m, 2 H), 2.45 (q, *J* = 7 Hz, 2 H), 3.67 (t, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 1 H), 5.45 (dd, *J* = 7, 10.4 Hz, 1 H), 5.68 (dd, *J* = 7, 15 Hz, 1 H), 6.14 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₅H₂₈O₂ 240.2089, obsd *m/e* 240.2086 (M⁺), 222, 207, 127, 31.

4d: IR (TF) 3330, 1030 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 10 H), 1.83 (m, 2 H), 2.19 (q, *J* = 7 Hz, 2 H), 3.88 (m, 2 H), 4.47 (q, *J* = 7 Hz, 1 H), 5.48 (dd, *J* = 7, 10.4 Hz, 1 H), 5.72 (dd, *J* = 7, 15 Hz, 1 H), 5.96 (dd, *J* = 10, 10.4 Hz, 1 H), 6.55 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₅H₂₈O₂ 240.2089, obsd *m/e* 240.2077 (M⁺), 222, 195, 75, 31.

Spectral Data for Oxidation Products 3 and 4. **3a**: IR (TF) 3340, 1035 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 6 H), 1.44 (m, 2 H), 2.40 (q, *J* = 7 Hz, 2 H), 3.69 (t, *J* = 7 Hz, 2 H), 4.09 (q, *J* = 7 Hz, 1 H), 5.46 (dd, *J* = 7, 10.4 Hz, 1 H), 5.73 (dd, *J* = 7, 15 Hz, 1 H), 6.15 (dd, *J* = 10, 10.4 Hz, 1 H), 6.52 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₂H₂₂O₂ 198.1619, obsd *m/e* 198, 1595 (M⁺), 180, 175, 127, 31.

4a: IR (TF) 3340, 1038 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 6 H), 1.82 (m, 2 H), 2.18 (q, *J* = 7 Hz, 2 H), 3.85 (m, 2 H), 4.45 (q, *J* = 7 Hz, 1 H), 5.47 (dd, *J* = 7, 10.4 Hz, 1 H), 5.65 (dd, *J* = 7, 15 Hz, 1 H), 5.98 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₂H₂₂O₂ 198.1619, obsd *m/e* 198.1624 (M⁺), 180, 162, 153, 75, 31.

3b: IR (TF) 3380, 1050 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 8 H), 1.44 (m, 2 H), 2.50 (q, *J* = 7 Hz, 2 H), 3.69 (t, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 1 H), 5.45 (dd, *J* = 7, 10.4 Hz, 1 H), 5.72 (dd, *J* = 7, 15 Hz, 1 H), 6.14 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₃H₂₄O₂ 212.1776, obsd *m/e* 212.1776 (M⁺), 194, 179, 127, 31.

4b: IR (TF) 3390, 1030 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 8 H), 1.70 (m, 2 H), 2.22 (q, *J* = 7 Hz, 2 H), 3.86 (m, 2 H), 4.47 (q, *J* = 7 Hz, 1 H), 5.48 (dd, *J* = 7, 10.4 Hz, 1 H), 5.65 (dd, *J* = 7, 15 Hz, 1 H), 5.97 (dd, *J* = 10, 10.4 Hz, 1 H), 6.55 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₃H₂₄O₂ 212.1776, obsd *m/e* 212.1764 (M⁺), 194, 167, 75, 31.

3c: IR (TF) 3330, 1055 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 10 H), 1.55 (m, 2 H), 2.45 (q, *J* = 7 Hz, 2 H), 3.67 (t, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 1 H), 5.45 (dd, *J* = 7, 10.4 Hz, 1 H), 5.72 (dd, *J* = 7, 15 Hz, 1 H), 6.14 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₄H₂₆O₂ 226.1932, obsd *m/e* 226.1958 (M⁺), 208, 193, 190, 127, 31.

4c: IR (TF) 3400, 1040 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 10 H), 1.68 (m, 2 H), 2.18 (q, *J* = 7 Hz, 2 H), 3.86 (m, 2 H), 4.46 (q, *J* = 7 Hz, 1 H), 5.48 (dd, *J* = 7, 10.4 Hz, 1 H), 5.68 (dd, *J* = 7, 15 Hz, 1 H), 5.97 (dd, *J* = 10, 10.4 Hz, 1 H), 6.55 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₄H₂₆O₂ 226.1932, obsd *m/e* 226.1952 (M⁺), 208, 190, 181, 75, 31.

3e: IR (TF) 3420, 1055 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 14 H), 1.55 (m, 2 H), 2.45 (q, *J* = 7 Hz, 2 H), 3.70 (t, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 1 H), 5.45 (dd, *J* = 7, 10.4 Hz, 1 H), 5.68 (dd, *J* = 7, 15 Hz, 1 H), 6.15 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₆H₃₀O₂ 254.2245, obsd *m/e* 254.2236 (M⁺), 236, 221, 127, 31.

4e: IR (TF) 3360, 1035 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 14 H), 1.82 (m, 2 H), 2.18 (q, *J* = 7 Hz, 2 H), 3.86 (m, 2 H), 4.46 (q, *J* = 7 Hz, 1 H), 5.49 (dd, *J* = 7, 10.4 Hz, 1 H), 5.71 (dd, *J* = 7, 15 Hz, 1 H), 5.97 (dd, *J* = 10, 10.4 Hz, 1 H), 6.55 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₆H₃₀O₂ 254.2245, obsd *m/e* 254.2248 (M⁺), 236, 209, 75, 31.

3f: IR (TF) 3360, 1045 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 16 H), 1.55 (m, 2 H), 2.45 (q, *J* = 7 Hz, 2 H), 3.68 (t, *J* = 7 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 1 H), 5.45 (dd, *J* = 7, 10.4 Hz, 1 H), 5.68 (dd, *J* = 7, 15 Hz, 1 H), 6.14 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₇H₃₂O₂ 268.2402, obsd *m/e* 268.2399 (M⁺), 250, 235, 127, 31.

4f: IR (TF) 3500, 1050 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.26 (br s, 16 H), 1.83 (m, 2 H), 2.18 (q, *J* = 7 Hz, 2 H), 3.87 (m, 2 H), 4.47 (q, *J* = 7 Hz, 1 H), 5.48 (dd, *J* = 7, 10.4 Hz, 1 H), 5.71 (dd, *J* = 7, 15 Hz, 1 H), 5.98 (dd, *J* = 10, 10.4 Hz, 1 H), 6.55 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₇H₃₂O₂ 268.2402, obsd *m/e* 268.2390 (M⁺), 250, 223, 75, 31.

4 (R = CH₂CH₂CH=C(CH₃)CH₂CH₂CH=C(CH₃)₂): IR (TF) 3380, 1050 cm⁻¹; ¹H NMR (CDCl₃) δ 1.60 (s, 6 H), 1.67 (s, 3 H), 1.78 (q, *J* = 7 Hz, 2 H), 1.98 (q, *J* = 7 Hz, 2 H), 2.06 (m, 4 H), 2.22 (q, *J* = 7 Hz, 2 H), 3.06 (m, 2 H), 3.80 (m, 2 H), 4.42 (q, *J* = 7 Hz, 1 H), 5.09 (t, *J* = 7 Hz, 1 H), 5.13 (t, *J* = 7 Hz, 1 H), 5.45 (dd, *J* = 7, 10.4 Hz, 1 H), 5.69 (dd, *J* = 7, 15 Hz, 1 H), 5.97 (dd, *J* = 10, 10.4 Hz, 1 H), 6.53 (dd, *J* = 10, 15 Hz, 1 H); hrms calcd for C₁₇H₃₂O₂ 268.2402, obsd *m/e* 268.2408 (M⁺), 250, 235, 223, 75, 31.

3 (R = CH₂CH₂CH₂C₆H₅): IR (TF) 3450, 1655, 1505 cm⁻¹; ¹H NMR (CDCl₃) δ 1.65 (m, 2 H), 1.80 (m, 2 H), 2.52 (q, *J* = 7 Hz, 2 H), 2.70 (t, *J* = 7 Hz, 2 H), 3.68 (t, *J* = 7 Hz, 2 H), 4.23 (q, *J* = 7 Hz, 1 H), 5.50 (dd, *J* = 7, 10.4 Hz, 1 H), 5.77 (dd, *J* = 7, 15 Hz, 1 H), 6.18 (dd, *J* = 10, 10.4 Hz, 1 H), 6.54 (dd, *J* = 10, 15 Hz, 1 H), 7.10-7.35 (m, 5 H); ¹³C NMR (CDCl₃) δ 26.98, 31.04, 35.45, 36.75, 61.84, 72.20, 125.19, 125.66, 127.20, 128.08, 128.12, 130.31, 136.75, 142.26; hrms calcd for C₁₆H₂₂O₂ 246.1620, obsd *m/e* 246.1627 (M⁺), 228, 91, 31.

4 (R = CH₂CH₂CH₂C₆H₅): IR (TF) 3420, 1655, 1505 cm⁻¹; ¹H NMR (CDCl₃) δ 1.65 (m, 2 H), 1.80 (m, 2 H), 2.28 (q, *J* = 7 Hz, 2 H), 2.70 (t, *J* = 7 Hz, 2 H), 3.87 (t, *J* = 7 Hz, 2 H), 4.47 (q, *J* = 7 Hz, 1 H), 5.54 (dd, *J* = 7, 10.4 Hz, 1 H), 5.67 (dd, *J* = 7, 15 Hz, 1 H), 6.06 (dd, *J* = 10, 10.4 Hz, 1 H), 6.54 (dd, *J* = 10, 15 Hz, 1 H), 7.10-7.35 (m, 5 H); hrms calcd for C₁₆H₂₂O₂ 246.1620, obsd *m/e* 246.1611 (M⁺), 228, 201, 91, 31.

Acknowledgment. We thank the National Science Foundation (Grant CHE 8906497) and Lilly Research Laboratories for their generous support of this work.