Iterative Enolate Claisen Rearrangements: Versatile Route to Optically Pure 2,7-Nonadiene-5-carboxylic Acids

John C. McKew and Mark J. Kurth*,[1]

Department of Chemistry, University of California, Davis, California 95616

Received March 18, 1993

A short, versatile, and diastereoselective method of preparing 2,7-nonadiene-5-carboxylic acids by an iterative enolate Claisen rearrangement procedure has been developed. Homochiral (*E*)- and (*Z*) secondary allylic alcohols **1–4**, prepared from (*S*)-(−)-ethyl lactate, were esterified with acetic acid and enolized, and the resulting silyl ketene acetals were warmed to room temperature to effect [3,3]-sigmatropic rearrangement to 4-hexenoic acids **5–8**. Esterification of these acids with alcohols **1–4** followed by a second enolate Claisen rearrangement delivered the targeted 2,7-nonadiene-5-carboxylic acids with high diastereoselectivity. This second [3,3]-sigmatropic rearrangement provides well-placed and potentially synthetically useful functionality and stereochemistry.

We continue to be interested in exploring transformations which proceed with double diastereoselectivity.[2] Two recent reports from our laboratories of reactions which exploit this concept are referred to in Figure 1 where the (2*R*,6*R*)-(+)-2,6-bis(benzyloxymethyl)piperidine chiral auxiliary of **I** directs iodolactonization with 92% crotyl and 90% *re*-face selectivity[3] while double diastereoselective 1,3-dipolar cycloaddition of **II** proceeds with 92% olefin and complete face selectivity.[4] As part of a broadly-based study of double diastereoselectivity as it pertains to the iodolactonization reaction, we required stereoselective access to dienoic acids of generalized structure **III**. Herein, we report the preparation of these acids by an iterative Claisen rearrangement strategy[5] which employs chiral allylic alcohols **1–4**.

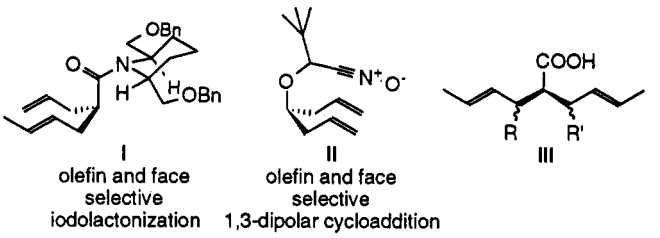
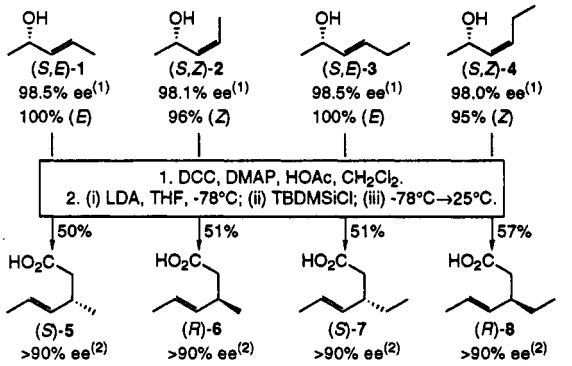


Figure 1.

(*E*)- and (*Z*)-Allylic Alcohols. We have reported a six-step, preparative-scale synthesis of homochiral (*E*)- or (*Z*) secondary allylic alcohols starting from (*S*)-(−)-ethyl lactate.[6] Using this methodology, the four allylic alcohols depicted in Scheme I were prepared for application in the present study. Since the optical purity and the olefin stereochemical homogeneity of these alcohols are critical control elements in the enolate-Claisen chemistry reported here, Mosher derivatives were prepared to assess these two stereochemical features. As illustrated in Scheme I, capillary GC analysis of each compound's enantiomeric excess was found to be ≥98% while the olefin geometry was found to vary from essentially complete (*E*)-geometry to ≃95% (*Z*)-geometry.

Scheme I



(1)These enantiomeric and olefin purities were determined by capillary GC analysis of the corresponding Mosher esters. (2)After $RCO_2H \rightarrow RCH_2OH$ reduction and subsequent Mosher ester formation (**5-8** → **5M-8M**), the minor enantiomer was not detected.

Enolate Claisen Rearrangements to (*E*)-3-Alkyl-4-hexenoic Acids. The rearrangement of allylic acetates to 4-hexenoic acids have previously been explored using Johnson ortho ester,[7] Eschenmoser *N*,*N*-dimethylacetamide,[8] and Ireland ketene acetal[9] Claisen rearrangements.[10] 1,3-Dicyclohexylcarbodiimide-mediated coupling of acetic acid with the alcohols in Scheme I gave acetates which, after enolization and *tert*-butyldimethylsilyl chloride quench, delivered the corresponding silyl ketene acetals. Warming these THF solutions to room temperature cleanly produced hexenoic acids **5-8**.[11] In order to establish the enantiomeric purity of these Claisen rear-

(1) Sloan Foundation Fellow (1987–1991) and NIH RCDA recipient (1989–1994; EC00182).

(2) (a) Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844–5. (b) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303–5. (c) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738–9. (d) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618–20.

(3) Najdi, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241–4.

(4) Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259–62.

(5) For extensive reviews of tandem and iterative rearrangements, see: (a) Ziegler, F. E. Consecutive Rearrangements. In *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Chapt. 7.3, Vol. 6. (b) Nakai, T.; Mikami, K. *Kagaku no Ryoiki* **1982**, *36*, 661–72 [*Chem. Abstr.* **1983**, *98*, 16001K].

(6) McKew, J. C.; Kurth, M. J. *Org. Prep. Proced. Int.* **1993**, *25*, 125–30.

(7) Johnson, W. S.; Werthermann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–3.

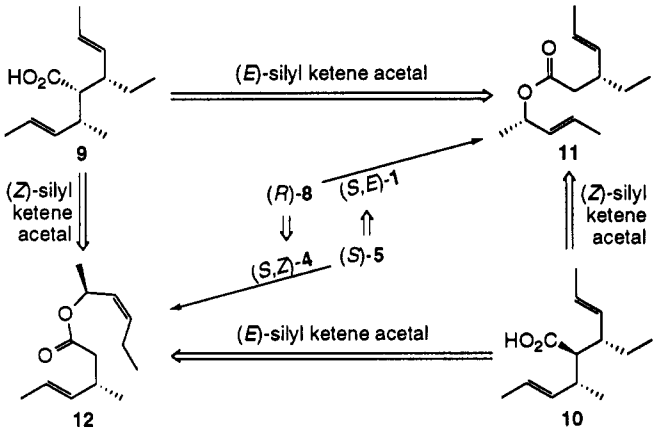
(8) (a) Felix, D.; Gshwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030–42. (b) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425–9.

(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–77.

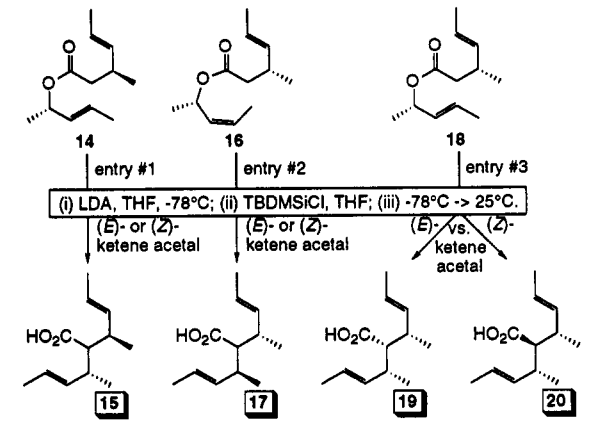
(10) For a recent example where all three methods were investigated, see: Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504–15.

0022-3263/93/1958-4589$04.00/0

Scheme II



Scheme III



entry #1					
cap. GC[1]	⇒	95.7%	⇐	4.3%	not detected
^{19}F-NMR[2]	93%		1%	6%	not detected
calculated[3]	96.0%		0%	3.8%	0.2%
entry #2					
cap. GC[1]	⇒	90.9%	⇐	4.1%	5.0%
calculated[3]	0.3%		90.2%	3.9%	5.6%
entry #3					
cap. GC[1]	⇒	5.2%	⇐	90.6%	4.1%
calculated[3]	4.9%		1.9%	89.6%	3.7%

[1]$LiAlH_4$ reduction to the corresponding dienols (**15** → **15a**; **17** → **17a**; **19** → **19a**; **20** → **20a**) followed by capillary GC analysis. [2]Dienols **15a**, **17a**, **19a**, and **20a** were converted to their corresponding Mosher esters and analyzed by ^{19}F-NMR. [3]These calculations assume 100% 1,3- and 1,4-charity transfer, take into account the enantiomeric purity as well as *E/Z* ratio of each starting alcohol, and incorporate the 96:4::*E*:*Z*:silyl ketene acetal ratio in the second enolate Claisen rearrangement.

rangement products, each acid was reduced with lithium aluminum hydride to the corresponding primary alcohol (83–90%) which was then converted to its Mosher ester derivative. Unfortunately, capillary gas chromatographic, high-performance liquid chromatographic, and ^{19}F-NMR analysis failed to differentiate the two diastereomers [i.e., Mosher derived from **5** vs **6** (**5M** vs **6M**) and **7** vs **8** (**7M** vs **8M**)]. However, irradiating the vinylic methyl doublet of a 93:7 mixture of **5M**/**6M** collapses the C-5 vinylic protons to a set of baseline resolved doublets; similar results were obtained with **7M**/**8M**. Using this process, the enolate Claisen rearrangements depicted in Scheme I were all judged to deliver hexenoic acids with >90% ee as, in each case, the doublet for the minor diastereomer could not be detected.

Enolate Claisen Rearrangements to (*E,E*)-4,6-Dialkyl-2,7-nonadiene-5-carboxylic Acids. The interplay between "Claisen rearrangement order" and "silyl ketene acetal geometry", the two control elements operative in construction of dienoic acids by an iterative enolate Claisen rearrangement protocol, are illustrated in Scheme II. For example, one could envision constructing dienoic acid **9** either by sequence no. 1 consisting of (*S,Z*)-**4** → (*R*)-**8**[+(*S,E*)-**1**] → **11** → [(*E*)-silyl ketene acetal] → **9** *or* by sequence no. 2 consisting of (*S,E*)-**1** → (*S*)-**5**[+(*S,Z*)-**4**] → **12** → [(*Z*)-silyl ketene acetal] → **9**; these sequences employ the same two allylic alcohols in opposite Claisen rearrangement order and require opposite silyl ketene acetal geometries in the two second sigmatropic rearrangements. Since we have enantioselective access to both enantiomers of the (*E*)-3-alkyl-4-hexenoic acids, the enantiomer of **9** would be available from either (*S*)-**7** + (*S,Z*)-**2** through a (*Z*)-silyl ketene acetal or (*R*)-**6** + (*S,E*)-**3** through an (*E*)-silyl ketene acetal. Esters **11** and **12** are also potential precursors to dienoic acid **10**, the C-5 epimer of **9**, by simply reversing the silyl ketene acetal geometry of the second enolate Claisen rearrangement.

Further analysis of Scheme II uncovers two issues which distinguish the competing routes to **9** (or **10**). Firstly, there is a potential difference in the stereochemical purity of the starting allylic alcohols as our (*S*)-(−)-ethyl lactate route delivers (*E*)-olefins with stereospecificity while (*Z*)-olefins are obtained with only ≃95% stereoselectivity. Secondly, the literature suggests that (*E*)-silyl ketene acetals are obtained with greater stereoselectivity than are the corresponding (*Z*)-silyl ketene acetals.[12] Calculations which assume 100% 1,3- and 1,4-chirality transfer[13] take into account the enantiomeric purity as well as *E/Z* ratio of each starting alcohol and incorporate the silyl ketene acetal *E/Z* ratio in the second enolate Claisen rearrangement, accurately predicting both the diatereomeric and enantiomeric excess of the dienoic acid arising from these two competing routes. This system of analysis makes it straightforward to select the more discriminating reaction sequence.

Dienoic acid **15** (Scheme III) was selected as the first target for this iterative enolate Claisen rearrangement protocol. DCC/DMAP coupling of hexenoic acid (*S*)-**5** with allylic alcohol (*S,E*)-**1** produced hexenoate **14** in 73% yield. Because of the symmetry in **15**, ketene acetal geometry of the intermediate formed upon deprotonation of **14** with lithium diisopropylamide is a nonissue; both the (*Z*)- and the (*E*)-ketene acetal of **14** lead to **15** which is obtained in 81% distilled yield. Dienoic acid **17**, the enantiomer of **15**, and dienoic acid **19**, a *meso*-isomer of **15**, are the impurities possible in this iterative enolate Claisen rearrangement route to **15**. To establish the stereoselectivity of (*S*)-**5** → **15**, these two dienoic acids were independently prepared; **17** from ester **16** and **19** from ester **18**.

(11) (a) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737–40. (b) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201–14.

(12) Silyl ketene acetal selectivity is typically 95% (*E*) with LDA/THF/−78 °C while only 85% (*Z*) with LDA/HMPA/THF/−78 °C. See: Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650–7.

(13) (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–52. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1–72. (c) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825–28.

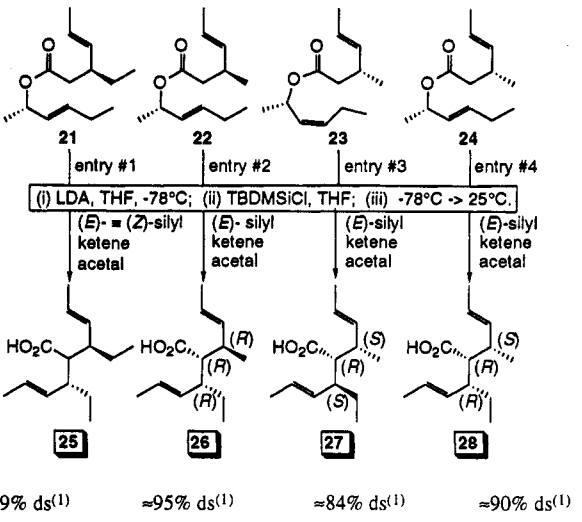
A quantitative method for determining the diastereomeric excess of these acids (**15**, **17**, and **19**) was developed which consisted of lithium aluminum hydride (84–94% yield) reduction to the corresponding dienols (**15a**, **17a**, and **19a**, respectively) followed by capillary GC (carbowax DB210) analysis. (*d,l*)-Alcohols **15a**/**17a** as well as *meso* alcohols **19a** and **20a** were baseline resolved. Unfortunately, attempts to resolve enantiomers **15a** and **17a** with chiral GC columns were unsuccessful, so we turned to ^{19}F-NMR analysis of their corresponding Mosher derivatives. Inspection of the data presented in Scheme III leads to three important observations. Firstly, entry no. 1 delivers dienoic acid **15** with significantly higher diastereoselectivity than entry no. 2 delivers its antipode (**17**). While not surprising in light of the variable purities of the starting allylic alcohols used in the respective iterative Claisen rearrangements (see Scheme I), this result does underscore the importance of high optical as well as olefin geometry purity in the starting materials. Secondly, detection of *meso* acid **20** in the product mixture from entry no. 3 means the silyl ketene acetal (*E*) to (*Z*) ratio for **18** → **19** + **20** is (*E*)/(*Z*) = 96:4. This "kinetic enolate selectivity" ratio can be extrapolated to the other iterative enolate Claisen rearrangements with inherent structural similarities. Thirdly, the ^{19}F-NMR data establishes that dienoic acid **15** is obtained in 97.4% ee which means that the second Claisen rearrangement proceeds with nearly 100% 1,4-asymmetric induction.

Attention was next turned to the iterative enolate Claisen rearrangement preparation of dienoic acid **25** which, like **15**, enjoys Claisen rearrangement substrate symmetry. As a consequence, silyl ketene acetal geometry is not a reaction control element in **21** → **25**. The 99% diastereoselectivity (ds) for **25** is corroborated by ^{1}H- and ^{13}C-NMR data for **25** and parallels both the results and insights gained with **14** → **15**.

Preparation of dienoic acid **26** employed two (*E*)-allylic alcohols; (*S,E*)-**1** was used to prepare hexenoic acid (*S*)-**5** which was then esterified with (*S,E*)-**3** to give ester **22**. Subsequent enolization of **22** followed by *O*-silylation of the intermediate enolate and [3,3]-sigmatropic rearrangement delivered **26** with ≃95% ds (^{1}H-NMR). Thus, in terms of olefin geometry for the two allylic alcohol components, this sequence is similar to **1** → **5** → **15** and **3** → **7** → **25**. However, there is a major difference in these three iterative Claisen rearrangement sequences in that **22** → **26** is (*E*)-ketene acetal dependent while rearrangements **14** → **15** and **21** → **25** are ketene acetal geometry independent. The calculated 98.5% ds of **15** versus the 95% ds of **26** reflects this added constraint. Indeed, these minor variances in overall selectivity illustrate that the most difficult stereocontrol element in iterative Claisen rearrangements is purity of starting allylic alcohols, not (*E*)-silyl ketene acetal geometry.

As a "worst case" series, **2** → **6** → **27** was examined next. Here, in addition to requiring the less pure (*Z*)-alcohols for the preparation of each Claisen rearrangement precursor, the second [3,3]-sigmatropic rearrangement is also ketene acetal dependent. On the basis of the stereochemical purities of two starting allylic alcohols [(*S,Z*)-**2** and (*S,Z*)-**4**] and assuming 96% (*E*)-silyl ketene acetal selectivity in the second Claisen rearrangement, dienoic acid **27** should be obtained in 84% ds [note the stereochemical descriptors of (*S*)\(*R*)\(*S*) at the three contiguous stereocenters in **27**]. Calculations suggest that detectable

Scheme IV



(1)These represent calculated diastereoselectivities of the depicted isomer.

quantities (i.e., ≃4%) of three other isomers would also be obtained [the (*S*)\(*S*)\(*S*) isomer (i.e., the enantiomer of **26**; 4.5%), the (*R*)\(*R*)\(*S*) isomer (**28**; 3.7%), and the (*S*)\(*R*)\(*R*) isomer (4.5%)].

Finally, the series **2** → **6** → **28** was studied. This sequence parallels **2** → **6** → **18** + **19** in that (*Z*)- and (*E*)-allylic alcohols are employed and both have ketene acetal-dependent second rearrangements; they differ in that the product from **18** is *meso* while the product from **24** is chiral. Anticipated contaminating isomers of (*R*)\(*R*)\(*S*)-**28** are (*R*)\(*R*)\(*R*)-**26** (4.7%; trace detected in the ^{1}H-NMR) and the (*R*)\(*S*)\(*S*) diastereomer (i.e., the carboxylic acid epimer of **28**). Thus, while 100% 1,3- and 1,4-chirality transfer will deliver **28** with only ≃90% ds from the two allylic alcohol components, this dienoic acid is obtained with essentially complete enantioselectivity! The same exceptional optical purity is manifest with each iterative Claisen rearrangement depicted in Scheme IV.

These results establish that an iterative enolate Claisen rearrangement protocol affords real potential in the stereoselective preparation of dienoic acids of general structure III. The important control elements are allylic alcohol olefin/optical purity and 1,3-/1,4-chirality transfer as manifest by chair and ketene acetal selectivity.[14] Double diastereoselective iodolactonization studies on these acids will be reported in due course.

Experimental Section

General. Tetrahydrofuran (THF) was refluxed over and distilled from sodium–potassium benzophenone ketyl immediately prior to use. Dichloromethane (CH_2Cl_2) was refluxed over and distilled from P_2O_5. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured at 300, 75, and 282 MHz, respectively, and chemical shifts are reported in ppm downfield from internal tetramethylsilane (^{1}H and ^{13}C NMR) or Cl_2CF_2 (^{19}F NMR). Elemental analyses were performed at the Gailbrath Laboratories, Knoxville, TN. Mass spectra were obtained with VG TRIO2 (high resolution; VG-11-250 data system) and VG ZAB-HS-2F (FAB) analytical instruments by Dr. Dan Jones (Facility for Advanced Instrumentation, University of California, Davis). Capillary gas chromatography was performed on a Hewlett-Packard 5890A

(14) For a pertinent discussion of ester enolate Claisen rearrangement transition states, see: Nagatsuma, M.; Shirai, F.; Sayo, N.; Nakai, T. *Chem. Lett.* **1984**, 1393–6.

gas chromatograph under the following conditions: column DB210, 30m × 0.25mm, carrier gas H_2, linear velocity 44.2 cm/s.

Method I. General Procedure for the Synthesis of Allylic Esters. To a solution of DCC (1.1 equiv) and DMAP (0.1 equiv) in CH_2Cl_2 (0.5 mL/mmol acid) under a nitrogen atmosphere was added the appropriate acid (1.0 equiv) dropwise. Within 3 min of the addition of the acid, a white precipitate was visible and the requisite alcohol[6] (1.0 equiv) was added dropwise. The reaction times ranged from 3–6 h for simple acetates to 16–24 h for more hindered esters. When the reaction was deemed complete by TLC analysis, the dicyclohexylurea precipitate was removed by suction filtration and the filter cake was washed with CH_2Cl_2 (2×). The combined filtrates were then washed with 1 N HCl (1×) and brine (1×), dried over potassium carbonate, and filtered. For higher boiling esters, the solvent was removed by rotary evaporation and the product was purified by flash chromatography on silica gel (1–2% EtOAc/hexane as eluent). The acetates are low boiling, volatile compounds which cannot be concentrated by rotary evaporation. Thus, after drying, the CH_2Cl_2 was removed by atmospheric distillation, and the crude esters were purified by gravity column on silica gel using 2% ether in pentane as eluent. Fractions containing the acetate were concentrated by distillation to yield the esters as clear, colorless (or pale yellow) oils.

(−)-(*S,E*)-3-Penten-2-yl Acetate. After 3 h, method I and acetic acid (4.88 g, 81.3 mmol), (*S,E*)-**1** (7.00 g, 81.3 mmol), DCC (18.5 g, 89.4 mmol), and DMAP (0.99 g, 8.13 mmol) gave the title compound as a pale yellow oil (7.31 g, 69%): $[\alpha]^{20}_D$ −65.5° (*c* 1.2, EtOH); FT-IR (neat) 2981, 1738, 1679, 1240, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.5 Hz, 3 H), 1.68 (dd, J = 6.3, 1.6 Hz, 3 H), 2.02 (s, 3 H), 5.29 (quintet, J = 6.6 Hz, 1 H), 5.46 (ddq, J = 15.2, 6.8, 1.6 Hz, 1 H), 5.71 (dq, J = 15.3, 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.6, 20.2, 21.4, 71.1, 128.1, 130.8, 170.3. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.70; H, 9.44.

(+)-(*S,Z*)-3-Penten-2-yl Acetate. After 6 h, method I and acetic acid (1.39 g, 23.2 mmol), (*S,Z*)-**2** (2.0 g, 23.2 mmol), DCC (5.27 g, 25.6 mmol), and DMAP (0.28 g, 2.32 mmol) gave the title compound as a pale yellow oil (2.48 g, 83%): $[\alpha]^{20}_D$ +20.3° (*c* 1.01, EtOH); FT-IR (neat) 3024, 2982, 1739, 1664, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 6.5 Hz, 3 H), 1.70 (dd, J = 6.9, 1.7 Hz, 3 H), 2.01 (s, 3 H), 5.34–5.41 (m, 1 H), 5.53–5.69 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.2, 20.6, 21.3, 66.8, 127.1, 130.3, 170.3. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.24; H, 9.63.

(−)-(*S,E*)-3-Hexen-2-yl Acetate. After 10 h, method I and acetic acid (3.00 g, 49.9 mmol), (*S,E*)-**3** (5.00 g, 49.9 mmol), DCC (11.3 g, 54.9 mmol), and DMAP (0.61 g, 4.93 mmol) gave the title compound as a pale yellow oil (6.12 g, 86%): $[\alpha]^{20}_D$ −64.1° (*c* 1.20, EtOH); FT-IR (neat) 2969, 1741, 1673, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3 H), 1.28 (d, J = 6.3 Hz, 3 H), 1.97–2.08 (m, 2 H), 2.02 (s, 3 H), 5.30 (quintet, J = 6.5 Hz, 1 H), 5.44 (ddt, J = 15.4, 6.7, 1.4 Hz, 1 H), 5.74 (dt, J = 15.3, 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.1, 20.3, 21.4, 25.1, 71.1, 128.4, 134.8, 170.3. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.40; H, 9.89.

(+)-(*S,Z*)-3-Hexen-2-yl Acetate. After 11 h, method I and acetic acid (1.29 g, 21.5 mmol), (*S,Z*)-**4** (2.15 g, 21.5 mmol), DCC (4.87 g, 23.6 mmol), and DMAP (0.26 g, 2.15 mmol) gave the title compound as a pale yellow oil (1.86 g, 61%): $[\alpha]^{20}_D$ +3.0° (*c*, 1.05, EtOH); FT-IR (neat) 3017, 2968, 1739, 1660, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3 H), 1.23 (d, J = 6.5 Hz, 3 H), 1.97 (s, 3 H), 2.01–2.20 (m, 2 H), 5.25–5.32 (m, 1 H), 5.44 (dt, J = 10.9, 7.4 Hz, 1 H), 5.58–5.63 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.0, 21.2, 22.3, 66.9, 128.7, 134.5, 170.1. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.42; H, 10.20.

(−)-(*S,E*)-3-Penten-2-yl (*S,E*)-3-Methyl-4-hexenoate (14). After 15 h, method I and (*S*)-**5** (1.00 g, 7.80 mmol), (*S,E*)-**1** (0.67 g, 7.80 mmol), DCC (1.77 g, 8.58 mmol), and DMAP (0.10 g, 0.78 mmol) gave **14** as a pale yellow oil (1.12 g, 73%): $[\alpha]^{20}_D$ −9.4° (*c* 1.04, EtOH); FT-IR (neat) 3032, 2965, 1735, 1678, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.7 Hz, 3 H), 1.24 (d, J = 6.4 Hz, 3 H), 1.60 (d, J = 5.8 Hz, 3 H), 1.66 (d, J = 6.2 Hz, 3 H), 2.14–2.30 (m, 2 H), 2.54–2.63 (m, 1 H), 5.25–5.50 (m, 4 H), 5.68 (dq, J = 15.2, 6.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.0, 18.2, 20.7, 34.2, 42.9, 71.2, 124.2, 128.2, 131.3, 135.7, 172.3. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.52; H, 10.17.

(+)-(*S,Z*)-3-Penten-2-yl (*R,E*)-3-Methyl-4-hexenoic Acid (16). After 18 h, method I and (*R*)-**6** (0.32 g, 2.50 mmol), (*S,Z*)-**2** (0.22 g, 2.50 mmol), DCC (0.57 g, 2.75 mmol), and DMAP (0.03 g, 0.25 mmol) gave **16** as a pale yellow oil (0.31 g, 63%): $[\alpha]^{20}_D$ +3.9° (*c* 1.46, $CHCl_3$); FT-IR (neat) 3023, 2932, 1778, 1206 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 3 H), 1.25 (d, J = 6.4 Hz, 3 H), 1.62 (d, J = 5.8 Hz, 3 H), 1.70 (dd, J = 6.9, 1.5 Hz, 3 H), 2.15–2.34 (m, 2 H), 2.53–2.69 (m, 1 H), 5.25–5.75 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.2, 17.8, 20.3, 20.6, 33.8, 42.6, 66.5, 123.8, 127.0, 130.4, 135.2, 171.9; HRMS (FAB$^+$) Calcd for $[C_{12}H_{20}O_2 + H]^+$ 197.1541, obsd 197.1510.

(−)-(*S,E*)-3-Penten-2-yl (*R,E*)-3-Methyl-4-hexenoate (18). After 17 h, method I and (*R*)-**6** (0.64 g, 4.99 mmol), (*S,E*)-**1** (0.43 g, 4.99 mmol), DCC (1.13 g, 5.49 mmol), and DMAP (0.06 g, 0.50 mmol) gave **18** as a colorless oil (0.61g, 62%): $[\alpha]^{20}_D$ −51.4° (*c* 1.70, $CHCl_3$); FT-IR (neat) 3031, 2965, 1734, 1678, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 3 H), 1.25 (d, 6.4 Hz, 3 H), 1.62 (d, J = 5.8 Hz, 3 H), 1.68 (dd, J = 6.6, 0.6 Hz, 3 H), 2.22 (t, J = 7.2 Hz, 2 H), 2.56–2.71 (m, 1 H), 5.24–5.53 (m, 4 H), 5.71 (dq, J = 15.3, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.6, 17.8, 20.3, 20.4, 33.8, 42.3, 70.8, 123.8, 127.9, 130.9, 135.2, 171.9. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.62; H, 10.43.

(−)-(*S,E*)-3-Hexen-2-yl (*S,E*)-3-Ethyl-4-hexenoate (21). After 24 h, method I and (*S*)-**7** (0.97 g, 6.79 mmol), (*S,E*)-**3** (0.68 g, 6.79 mmol), DCC (1.54 g, 7.47 mmol), and DMAP (0.08 g, 0.68 mmol) gave **21** as a colorless oil (1.05 g, 69%): $[\alpha]^{20}_D$ −27.3° (*c* 1.06, EtOH); FT-IR (neat) 2966, 1734, 1674, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 1.20–1.30 (m, 1 H), 1.24 (d, J = 6.4 Hz, 3 H), 1.30–1.45 (m, 1 H), 1.61 (dd, J = 6.3 Hz, 1.5 Hz, 3 H), 1.94–2.08 (m, 2 H), 2.10–2.44 (m, 2 H), 5.18 (ddq, J = 15.2, 8.2, 1.5 Hz, 1 H), 5.29 (quintet, J = 5.3 Hz, 1 H), 5.35–5.48 (m, 2 H), 5.71 (dt, J = 15.3, 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.4, 13.2, 17.8, 20.4, 25.1, 27.7, 40.6, 41.2, 70.7, 125.5, 128.7, 133.5, 134.5, 172.0; HRMS (FAB$^+$) calcd for $[C_{14}H_{24}O_2 + H]^+$ 225.1854, obsd 225.1841.

(−)-(*S,E*)-3-Hexen-2-yl (*S,E*)-3-Methyl-4-hexenoate (22). After 16 h, method I and (*S*)-**5** (1.00 g, 7.80 mmol), (*S,E*)-**3** (0.78 g, 7.80 mmol), DCC (1.77 g, 8.58 mmol), and DMAP (0.09 g, 0.78 mmol) gave **22** as a pale yellow oil (1.24 g, 76%): $[\alpha]^{20}_D$ −10.2° (*c* 1.01, EtOH); FT-IR (neat) 3029, 2965, 1735, 1672, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96–1.04 (m, 6H), 1.27 (d, J = 6.4 Hz, 3 H), 1.62 (d, J = 5.8 Hz, 3 H), 1.97–2.10 (m, 2 H), 2.17–2.31 (m, 2 H), 2.53–2.71 (m, 1 H), 5.27–5.57 (m, 4H), 5.73 (dt, J = 15.2, 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.2, 17.8, 20.3, 20.4, 25.1, 33.7, 42.3, 70.8, 123.8, 128.6, 134.6, 135.2, 171.9. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.34; H, 10.55.

(−)-(*S,Z*)-3-Hexen-2-yl (*R,E*)-3-Methyl-4-hexenoate (23). After 17 h, method I and (*R*)-**6** (0.64 g, 4.99 mmol), (*S,Z*)-**4** (0.50 g, 4.99 mmol), DCC (1.13 g, 5.49 mmol), and DMAP (0.06 g, 0.50 mmol) gave **23** as a colorless oil (0.60 g, 57%): $[\alpha]^{20}_D$ −10.2° (*c* 1.01, EtOH); FT-IR (neat) 3016, 2966, 1734, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96–1.01 (m, 6H), 1.25 (d, J = 6.3 Hz, 3 H), 1.62 (d, J = 5.4 Hz, 3 H), 2.05–2.18 (m, 2 H), 2.19–2.32 (m, 2 H), 2.54–2.69 (m, 1 H), 5.28–5.52 (m, 4 H), 5.60–5.71 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.8, 20.3, 20.9, 21.0, 33.8, 42.2, 66.6, 123.8, 128.8, 134.5, 135.2, 171.8. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.57; H, 10.42.

(−)-(*S,E*)-3-Hexen-2-yl (*R,E*)-3-Methyl-4-hexenoate (24). After 30 h, method I and (*R*)-**6** (0.53 g, 4.10 mmol), (*S,E*)-**3** (0.41 g, 4.10 mmol), DCC (0.93 g, 4.51 mmol), and DMAP (0.05 g, 0.41 mmol) gave **24** as a colorless oil (0.60 g, 69%): $[\alpha]^{20}_D$ −55.2° (*c* 1.38, $CHCl_3$); FT-IR (neat) 3031, 2966, 1734, 1674, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89–1.05 (m, 6 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.62 (d, J = 5.8 Hz, 3 H), 1.93–2.11 (m, 2 H), 2.14–2.35 (m, 2 H), 2.53–2.70 (m, 1 H), 5.27–5.52 (m, 4H), 5.74 (dt, J = 15.3, 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.0, 17.6, 20.2, 25.0, 33.7, 42.1, 70.7, 123.7, 128.5, 134.5, 135.1, 171.7. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.38; H, 10.57.

Method II. General Procedure for the Enolate Claisen Rearrangement of Allylic Esters. To a round-bottom flask equipped with a stir bar and maintained under a nitrogen atmosphere was added freshly distilled diisopropylamine (1.1 equiv; 0.2 M in dry THF). This solution was cooled to 0 °C and *n*-BuLi (1.1 equiv of a solution in hexanes) was added over 1–2 min. After stirring 10 min at 0 °C, the resulting LDA solution was cooled to −78 °C and the appropriate allylic ester (1.0 equiv)

in dry THF (2 mL/mmol) was added dropwise (generally 5–10 min addition time). Within 5 min of ester addition, *tert*-butyldimethylsilyl chloride (TBDMSCl; 1.15 equiv) in dry THF (minimum amount to dissolve; generally 1–3 mL) was added in one portion via cannula. The reaction was stirred 5 min at −78 °C and then the cooling bath was removed and stirring continued for 24–36 h. Workup [consisting of dilution with 2–3 volumes of pentane, washing the organic layer with ice-cold H_2O (1×), back extracting the aqueous layer with pentane (2×), and concentrating the combined organic layers by rotary evaporation] gave the desired *tert*-butyldimethylsilyl ester which was hydrolyzed by stirring a THF (0.2 M)/3 N aqueous HCl (10 equiv) mixture at room temperature for 3 h (some very hindered nonadienoic acids required 7 h for hydrolysis). At this time, THF was removed *in vacuo* and the remaining aqueous solution was made basic with cold 10% aqueous NaOH and washed with petroleum ether (1×). The aqueous layer was then acidified with 3 N aqueous HCl and extracted with ether (4×), and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Finally, vacuum distillation delivered the acid as a viscous, colorless oil.

(+)-(*S,E*)-3-Methyl-4-hexenoic Acid [(*S*)-5]. Method II and (*S,E*)-3-penten-2-yl acetate (0.55 g, 4.32 mmol), LDA (4.54 mmol), and TBDMSCl (0.716 g, 4.76 mmol) gave (*S*)-**5** (0.270 g, 49%) as a colorless oil: $[\alpha]^{20}_D$ +26.8° (*c* 1.10, EtOH); bp 110–112°C/2.5 mmHg; FT-IR (neat) 3031, 3450–2750, 2967, 1711, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.03 (d, *J* = 6.8 Hz, 3 H), 1.62 (d, *J* = 5.9 Hz, 3 H), 2.25 (dd, *J* = 15.0, 7.5 Hz, 1 H), 2.34 (dd, *J* = 15.0, 7.1 Hz, 1), 2.75–2.99 (m, 1 H), 5.35 (ddq, *J* = 15.3, 6.8, 1.3 Hz, 1 H), 5.47 (dq, *J* = 15.5, 5.8, 1 H), 10.8–11.5 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.2, 20.3, 33.7, 42.1, 124.5, 135.3, 179.6. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.60; H, 9.34.

(−)-(*R,E*)-3-Methyl-4-hexenoic Acid [(*R*)-6]. Method II and (*S,Z*)-3-penten-2-yl acetate (2.14 g, 16.7 mmol), LDA (18.4 mmol), and TBDMSCl (2.90 g, 19.2 mmol) gave (*R*)-**6** (1.08 g, 51%) as a colorless oil. The spectral data for this compound are identical to its enantiomer [(*S*)-**5**] except for the specific rotation; $[\alpha]^{20}_D$ −22.4° (*c* 1.27, EtOH).

(+)-(*S,E*)-3-Ethyl-4-hexenoic Acid [(*S*)-7]. Method II and (*S,E*)-3-hexen-2-yl acetate (5.43 g, 38.2 mmol), LDA (42.0 mmol), and TBDMSCl (6.61 g, 43.9 mmol) gave (*S*)-**7** (2.79 g, 51%) as a colorless oil: $[\alpha]^{20}_D$ +3.65° (*c* 1.16, EtOH); bp 93–96°C/1.4 mmHg; FT-IR (neat) 3500–2750, 2966, 1712, 967, 942 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 3 H), 1.24–1.34 (m, 1 H), 1.65 (dd, *J* = 6.4, 1.5 Hz, 3 H), 2.22–2.41 (m, 3 H), 5.22 (ddq, *J* = 15.2, 7.8, 1.5 Hz, 1 H), 5.49 (dq, *J* = 15.3, 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.4, 17.8, 27.7, 40.1, 40.7, 125.9, 133.2, 179.4. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.56; H, 9.99.

(−)-(*R,E*)-3-Ethyl-4-hexenoic Acid [(*R*)-8]. Method II and (*S,Z*)-3-hexen-2-yl acetate (1.66 g, 11.7 mmol), LDA (12.8 mmol), and TBDMSCl (2.02 g, 13.4 mmol) gave (*R*)-**8** (0.936 g, 57%) as a colorless oil. The spectral data for this compound are identical to its enantiomer [(*S*)-**7**] except for the specific rotation; $[\alpha]^{20}_D$ −2.21° (*c* 1.00, EtOH).

(+)-(*R,R,E,E*)-4,6-Dimethylnona-2,7-diene-5-carboxylic Acid (15). Method II and **14** (1.01 g, 5.14 mmol), LDA (5.65 mmol), and TBDMSCl (0.89 g, 5.91 mmol) gave **16** (0.82 g, 81%) as a colorless oil: $[\alpha]^{20}_D$ +14.4° (*c* 1.38, $CHCl_3$); bp 110–112°C/1.6 mmHg; FT-IR (neat) 3400–2700, 3030, 2969, 1705, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 7.4 Hz, 3 H), 1.60–1.71 (m, 2 overlapping dd, 6 H), 2.13 (dd, *J* = 9.3, 5.9 Hz, 1 H), 2.38–2.51 (m, 2 H), 5.22 (ddq, *J* = 15.3, 8.4,, 1.5 Hz, 1 H), 5.32–5.50 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 17.8, 18.3, 19.4, 36.7, 36.9, 56.1, 125.4, 125.5, 132.5, 134.2, 180.2. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.06; H, 10.08.

(−)-(*S,S,E,E*)-4,6-Dimethylnona-2,7-diene-5-carboxylic Acid (17). Method II and **16** (0.22 g, 1.12 mmol), LDA (1.23 mmol), and TBDMSCl (0.19 g, 1.28 mmol) gave **17** (0.08 g, 38%) as a colorless oil. The spectroscopic data for this compound are identical to its enantiomer (**15**) except for the specific rotation; $[\alpha]^{20}_D$ −14.5° (*c* 1.38, $CHCl_3$).

(±)-(4*R*,5R*,6S*,E,E*)-4,6-Dimethylnona-2,7-diene-5-carboxylic Acid (19). Method II and **18** (0.30 g, 1.53 mmol), LDA (1.68 mmol), and TBDMSCl (0.27 g, 1.76 mmol) gave **19** (0.19 g, 65%) as a viscous, colorless oil: bp 125–130°C/1.8 mmHg; FT-IR (neat) 3400–2700, 3031, 2974, 1704, 965 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, *J* = 6.8 Hz, 6 H), 1.65 (dd, *J* = 6.1, 0.81 Hz, 6 H), 2.20 (t, *J* = 7.6 Hz, 1 H), 2.46 (sextet, *J* = 7.2 Hz, 2 H), 5.29 (ddq, *J* = 15.2, 8.1, 1.4 Hz, 2 H), 5.47 (dq, *J* = 15.1, 6.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.1, 17.9, 36.6, 56.5, 124.9, 134.3, 180.4; HRMS (FAB$^+$) calcd for $[C_{12}H_{20}O_2 + H]^+$ 197.1541, obsd 197.1542.

(−)-(*R,R,E,E*)-4,6-Dimethylnona-2,7-diene-5-carboxylic Acid (25). Method II and **21** (0.95 g, 4.22 mmol), LDA (4.64 mmol), and TBDMSCl (0.73 g, 4.86 mmol) gave **25** (0.48 g, 50.3%) as a viscous, colorless oil: $[\alpha]^{20}_D$ −2.36° (*c* 1.18, $CHCl_3$); bp 125–130°C/1.8 mmHg; FT-IR (neat) 3500–2700, 2965, 1706, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, *J* = 7.4 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H), 1.11–1.35 (m, 2 H), 1.35–1.58 (m, 2 H), 1.64–1.77 (m, 6 H), 2.09–2.24 (m, 2 H), 2.29 (dd, *J* = 10.3, 4.6 Hz, 1 H), 4.96 (ddq, *J* = 15.2, 9.3, 1.6 Hz, 1 H), 5.29–5.50 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.6, 12.0, 18.0, 25.7, 26.5, 44.5, 44.7, 54.1, 127.3, 127.7, 130.3, 131.8, 181.0; HRMS (FAB$^+$) calcd for $[C_{14}H_{24}O_2 + H]^+$ 225.1854, obsd 225.1862.

(+)-(*R,R,E,E*)-4-Ethyl-6-methylnona-2,7-diene-5-carboxylic Acid (26). Method II and **22** (0.81 g, 4.43 mmol), LDA (4.24 mmol), and TBDMSCl (0.67 g, 4.43 mmol) gave **26** (0.51 g, 62%) as a viscous, colorless oil: $[\alpha]^{20}_D$ +14.75° (*c* 1.34, $CHCl_3$); bp 140–144°C/1.5 mmHg; FT-IR (neat) 3400–2900, 3031, 2966, 1702, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, *J* = 7.3 Hz, 3 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.10–1.31 (m, 1 H), 1.40–1.52 (m, 1 H), 1.67 (d, *J* = 5.21 Hz, 3 H), 1.71 (dd, *J* = 6.4, 1.5 Hz, 3 H), 2.10–2.33 (m, 2 H), 2.45–2.60 (m, 1 H), 4.98–5.10 (m, 1 H), 5.33–5.53 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 12.1, 18.4, 20.2, 26.0, 37.2, 45.0, 56.3, 126.0, 128.1, 132.3, 132.5, 181.2; HRMS (FAB$^+$) calcd for $[C_{13}H_{22}O_2 + H]^+$ 211.1698, obsd 211.1699.

(+)-(4*S*,5*R*,6*S*,*E,E*)-4-Ethyl-6-methylnona-2,7-diene-5-carboxylic Acid (27). Method II and **23** (0.54 g, 2.55 mmol), LDA (2.81 mmol), and TBDMSCl (0.44 g, 2.94 mmol) gave **27** (0.20 g, 37%) as a viscous, colorless oil: $[\alpha]^{20}_D$ +2.68° (*c* 1.85, $CHCl_3$); bp 121–125°C/1.8 mmHg; FT-IR (neat) 3500–2750, 3030, 2966, 1704, 1453, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.8 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.19–1.36 (m, 1 H), 1.41–1.55 (m, 1 H), 1.63–1.70 (m, 6 H), 2.11–2.38 (m, 2 H), 2.41–2.56 (m, 1 H), 5.18–5.29 (m, 1 H), 5.33–5.53 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 12.0, 18.0, 18.8, 26.3, 36.7, 44.7, 55.2, 125.6, 127.3, 130.5, 134.0, 181.0. HRMS (FAB$^+$) calcd for $[C_{13}H_{22}O_2 + H]^+$ 211.1698, obsd 211.1679.

(+)-(4*R*,5*R*,6*S*,*E,E*)-4-Ethyl-6-methylnona-2,7-diene-5-carboxylic Acid (28). Method II and **24** (0.51 g, 2.44 mmol), LDA (2.69 mmol), and TBDMSCl (0.42 g, 2.81 mmol) gave **28** (0.19 g, 37%) as a viscous, pale yellow oil: $[\alpha]^{20}_D$ +5.83° (*c* 1.29, $CHCl_3$); bp 116–119°C/1.4 mmHg; FT-IR (neat) 3500–2700, 3028, 2968, 1706, 1453, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, *J* = 7.3 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 1.09–1.25 (m, 1 H), 1.40–1.55 (m, 1 H), 1.65 (d, *J* = 5.7 Hz, 3 H), 1.68 (d, *J* = 6.4 Hz, 3 H), 2.10–2.32 (m, 2 H), 2.40–2.59 (m, 1 H), 5.08 (dd, *J* = 15.1, 9.1 Hz, 1 H), 5.26–5.57 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.9, 16.0, 17.9, 24.9, 36.4, 44.5, 55.7, 124.6, 127.1, 132.1, 134.6, 180.5. HRMS (FAB$^+$) calcd for $[C_{13}H_{22}O_2 + H]^+$ 211.1698, obsd 211.1690.

Method III. General Procedure for the Lithium Aluminum Hydride Reduction of Acids. A THF (1.5 mL/mmol $LiAlH_4$) slurry of lithium aluminum hydride (1.5–2.0 equiv) was introduced into a round-bottom flask fitted with a condenser (under a nitrogen atmosphere) followed by dropwise addition of the requisite carboxylic acid (1.0 equiv) in dry THF (2 mL/mmol of acid). When the addition was complete, the reaction was brought to reflux for 12 h. The mixture was then cooled to 0 °C and diluted with ether (4 mL/mmol of acid). Water (1.5 mL/mmol of acid) was cautiously added followed by addition of a 20% sulfuric acid solution (2 mL/mmol of acid). The resulting mixture was stirred at room temperature for 30 min, separated into two layers, and the aqueous layer was extracted with ether (4×). The combined organic extracts were washed with brine (1×), dried over potassium carbonate, filtered, and concentrated by rotary evaporation. The alcohols thus obtained were pale yellow to colorless oils which were pure as judged by ^{1}H NMR. These alcohols were used without further purification for subsequent steps.

(+)-(*S,E*)-3-Methyl-4-hexen-1-ol. Following method III, (*S*)-**5** (0.25 g, 1.95 mmol) was reduced with $LiAlH_4$ (0.11 g, 2.93 mmol) to give the title compound as a pale yellow oil (0.20 g, 90%); $[\alpha]^{20}_D$ +40.8° (*c* 1.18, $CHCl_3$); FT-IR (neat) 3351–3332, 3028, 2963, 1452, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, *J* = 6.7

Hz, 3 H), 1.42–1.49 (br s, 1 H), 1.50–1.61 (m, 2 H), 1.64 (dd, J = 5.7, 1.4 Hz, 3 H), 2.23 (septet, J = 6.9 Hz, 1 H), 3.64 (t, J = 6.6 Hz, 2 H), 5.30 (ddq, J = 15.2, 7.6, 1.3 Hz, 1 H), 5.44 (dq, J = 15.1, 6.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.9, 21.1, 33.8, 39.7, 61.3, 123.6, 136.9. HRMS (FAB$^+$) calcd for $[C_7H_{14}O + H]^+$ 115.1123, obsd 115.1130.

(−)-(*R,E*)-3-Methyl-4-hexen-1-ol. Following method III, (*R*)-**6** (0.11 g, 0.89 mmol) was reduced with $LiAlH_4$ (0.05 g, 1.33 mmol) to give the title compound as a pale yellow oil (0.09 g, 88%). The spectral data for this compound was identical to its enantiomer's (previous experimental) except for the specific rotation; $[\alpha]^{20}_D$ −33.5° (c 1.18, $CHCl_3$).

(+)-(*S,E*)-3-Ethyl-4-hexen-1-ol. Following method III, (*S*)-**7** (0.10 g, 0.70 mmol) was reduced with $LiAlH_4$ (0.04 g, 1.06 mmol) to give the title compound as a pale yellow oil (0.08 g, 83%); $[\alpha]^{20}_D$ +20.4° (c 1.09, $CHCl_3$); FT-IR (neat) 3348–3327, 2933, 1672, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3 H), 1.15–1.51 (m, 4H), 1.59–1.70 (m, 1 H), 1.66 (dd, J = 6.4, 1.5 Hz, 3 H), 1.90–2.05 (m, 1 H), 3.58–3.67 (m, 2 H), 5.16 (ddq, J = 15.2, 8.9, 1.5 Hz, 1 H), 5.42 (dq, J = 15.3, 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.6, 17.9, 28.4, 37.9, 41.6, 61.4, 125.3, 135.3. HRMS (FAB$^+$) calcd for $[C_8H_{16}O + H]^+$ 129.1279, obsd 129.1292.

(−)-(*R,E*)-3-Ethyl-4-hexen-1-ol. Following method III, (*R*)-**8** (0.10 g, 0.70 mmol) was reduced with $LiAlH_4$ (0.04 g, 1.06 mmol) to give the title compound as a pale yellow oil (0.08 g, 87%). The spectral data for this compound was identical to its enantiomer's (previous experimental) except for the specific rotation; $[\alpha]^{20}_D$ −17.9° (c 1.09, $CHCl_3$).

(+)-(*R,R,E,E*)-4,6-Dimethyl-5-(hydroxymethyl)nona-2,7-diene (15a). Following method III, **15** (0.10 g, 0.51 mmol) was reduced with $LiAlH_4$ (0.06 g, 1.53 mmol) to give **15a** as a pale yellow oil (0.08 g, 84%): capillary GC data (injection port 220 °C, oven 70 °C/2 min/2 °C/min, retention time 13.14 min); $[\alpha]^{20}_D$ +72.9° (c 1.14, $CHCl_3$); FT-IR (neat) 3387–3347, 3028, 2963, 1452, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 1.21–1.34 (m, 1 H), 1.44 (br s, 1 H), 1.61–1.76 (m, 6 H), 2.23–2.48 (m, 2 H), 3.53–3.72 (m, 2 H), 5.37–5.58 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.3, 18.0, 19.5, 36.0, 36.9, 51.1, 62.0, 123.9, 124.4, 135.7, 136.8. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.78; H, 12.33.

(−)-(*S,S,E,E*)-4,6-Dimethyl-5-(hydroxymethyl)nona-2,7-diene (17a). Following method III, **17** (0.08 g, 0.42 mmol) was reduced with $LiAlH_4$ (0.03 g, 0.85 mmol) to give **17a** as a pale yellow oil (0.07 g, 84%). The spectral data for this compound was identical to its enantiomer's (**15a**) except for the specific rotation; $[\alpha]^{20}_D$ −58.6° (c 1.11, $CHCl_3$).

(±)-(4*R,5*R**,6*S**,*E,E*)-4,6-Dimethyl-5-(hydroxymethyl)-nona-2,7-diene (19a).** Following Method III, **19** (0.10 g, 0.52 mmol) was reduced with $LiAlH_4$ (0.04 g, 1.04 mmol) to give **19a** as colorless oil (0.09 g, 94%): capillary GC data (injection port 220°C, oven 70 °C/2 min/2 °C/min, retention time 13.33 min); FT-IR (neat) 3372–3337, 2964, 1670, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.9 Hz, 6 H), 1.32 (t, J = 5.7 Hz, 1 H), 1.41 (quintet, J = 5.7 Hz, 1 H), 1.66 (d, J = 4.6 Hz, 6 H), 2.24–2.46 (m, 2 H), 3.65 (t, J = 5.5 Hz, 2 H), 5.36–5.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.6, 18.0, 36.4, 50.5, 62.3, 123.6, 137.1. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.95; H, 11.83.

Method IV. General Procedure for the Preparation of Mosher Derivatives. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)-phenylacetic acid[15] [(*R*)-MTPA (99%, $[\alpha]^{20}_D$ +72° (c = 1.6, CH_3OH), 1.5 equiv] in dry CH_2Cl_2 (5 mL/mmol) was added dropwise to a CH_2Cl_2 (2 mL/mmol) solution of DCC (1.5 equiv) under a nitrogen atmosphere. Within 5 min, a solution of the appropriate alcohol (1.0 equiv) in CH_2Cl_2 (4 mL/mmol) was added dropwise followed by addition of a CH_2Cl_2 (40 mL/mmol) solution of DMAP (0.1 equiv). Stirring was continued until TLC analysis indicated complete disappearance of the starting alcohol, primary alcohols taking from 3–5 h and more hindered alcohols requiring overnight. Workup was accomplished by filtering the reaction mixture through glass wool and Celite, washing the filtrate with 1 N HCl (1×) and brine (1×), and drying over potassium carbonate. Filtration followed by rotary evaporator concentration yielded the crude product contaminated with dicyclohexylurea. Purification was accomplished by chromatography on a short silica gel column using an EtOAc/hexane eluent; wide fraction cuts were taken to ensure no loss of minor diastereomers. Concentration yielded a pale yellow oil contaminated with a small amount of dicyclohexylurea. Due to small impurities in the region of 120–140 ppm in the ^{13}C NMR spectra, the quaternary aromatic carbons were not always assigned a resonance in the following experimentals.

(*S,E*)-3-Methyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (5M). Method IV and (*S,E*)-3-methyl-4-hexen-1-ol (0.03 g, 0.25 mmol), (*R*)-MTPA (0.09 g, 0.37 mmol), DCC (0.08 g, 0.37 mmol), and DMAP (3 mg, 0.03 mmol) produced **5M** as a pale yellow oil (0.05 g, 64%). Integration of the doublet at 5.34 ppm formed upon irradiation of the signal at 1.62 ppm revealed the ratio of **5M**/**6M** to be ≥95:5: FT-IR (neat) 3066, 2956, 1750, 1716, 1668, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.7 Hz, 3 H), 1.58–1.79 (m, 2 H), 1.62 (dd, J = 6.1, 1.2 Hz, 3 H), 2.04–2.22 (m, 1 H), 3.54 (s, 3 H), 4.18–4.39 (m, 2 H), 5.20 (ddq, J = 15.2, 7.9, 1.3 Hz, 1 H), 5.34 (dq, J = 15.2, 6.2 Hz, 1 H), 7.34–7.47 (m, 3 H), 7.48–7.60 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 17.8, 20.9, 33.6, 35.2, 55.4, 65.0, 127.3, 128.8, 129.5, 135.5, 166.5.

(*R,E*)-3-Methyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (6M). Method IV and (*R,E*)-3-methyl-4-hexen-1-ol (0.03 g, 0.26 mmol), (*R*)-MTPA (0.09 g, 0.39 mmol), DCC (0.08 g, 0.39 mmol), and DMAP (3 mg, 0.03 mmol) produced **6M** as a pale yellow oil (0.09 g, 99%). Integration of the doublet at 5.38 ppm formed upon irradiation of the doublet at 1.63 ppm revealed the ratio of **6M**/**5M** was found to be ≥95:5; FT-IR (neat) 3032, 2957, 1750, 1716, 1668, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.7 Hz, 3 H), 1.48–1.80 (m, 2 H), 1.63 (d, J = 6.1 Hz, 3 H), 2.10–2.23 (m, 1 H), 3.54 (s, 3 H), 4.21–4.39 (m, 2 H), 5.22 (ddq, J = 15.8, 8.4, 1.0 Hz, 1 H), 5.38 (dq, J = 15.2, 6.2 Hz, 1 H), 7.34–7.48 (m, 3 H), 7.49–7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.8, 20.9, 33.6, 35.2, 55.4, 65.0, 124.5, 127.3, 128.4, 128.7, 129.5, 135.6, 166.6.

(*S,E*)-3-Ethyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (7M). Method IV and (*S,E*)-3-ethyl-4-hexen-1-ol (0.03 g, 0.38 mmol), (*R*)-MTPA (0.09 g, 0.38 mmol), DCC (0.12 g, 0.57 mmol), and DMAP (3 mg, 0.03 mmol) produced **7M** as a pale yellow oil (0.09 g, 100%). Integration of the doublet at 5.33 ppm formed upon irradiation of the doublet at 1.64 ppm revealed the ratio of **7M**/**8M** to be ≥95:5; FT-IR (neat) 2933, 1749, 1716, 1669, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.4 Hz, 3 H), 1.19–1.62 (m, 3 H), 1.64 (dd, J = 6.4, 1.6 Hz, 3 H), 1.66–1.99 (m, 2 H), 3.54 (s, 3 H), 4.21–4.40 (m, 2 H), 5.06 (ddq, J = 15.2, 8.8, 1.5 Hz, 1 H), 5.33 (dq, J = 15.2, 6.4 Hz, 1 H), 7.35–7.46 (m, 3 H), 7.47–7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.5, 17.9, 28.2, 33.4, 41.2, 55.4, 65.1, 126.3, 127.3, 128.3, 129.5, 133.8, 166.5.

(*R,E*)-3-Ethyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (8M). Method IV and (*R,E*)-3-ethyl-4-hexen-2-ol (0.03 g, 0.23 mmol), (*R*)-MTPA (0.08 g, 0.35 mmol), DCC (0.07 g, 0.35 mmol), and DMAP (3 mg, 0.3 mmol) produced **8M** as a pale yellow oil (0.07 g, 78%). Integration of the doublet at 5.34 ppm formed upon irradiation of the doublet at 1.65 ppm revealed the ratio of **8M**/**7M** to be ≥95:5; FT-IR (neat) 3066, 2963, 1749, 1716, 1669, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.4 Hz, 1 H), 1.09–1.44 (m, 2 H), 1.45–1.60 (m, 1 H), 1.65 (dd, J = 6.3, 1.6 Hz, 3 H), 1.70–1.95 (m, 2 H), 3.55 (s, 3 H), 4.19–4.27 (m, 1 H), 4.31–4.39 (m, 1 H), 5.09 (ddq, J = 15.2, 8.9, 1.6 Hz, 1 H), 5.34 (dq, J = 15.4, 6.3, 1 H), 7.34–7.47 (m, 3 H), 7.49–7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.5, 17.9, 28.2, 33.3, 41.2, 55.4, 65.1, 126.3, 127.3, 128.3, 129.5, 133.8, 166.5.

(*R,E*)-2-[(*R,E*)-1-Methyl-2-butenyl]-3-methyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate. Method IV and **15a** (0.04 g, 0.20 mmol), (*R*)-MTPA (0.07 g, 0.30 mmol), DCC (0.06 g, 0.30 mmol), and DMAP (2 mg, 0.02 mmol) produced the title compound as a pale yellow oil (0.08 g, 100%). The ^{19}F NMR revealed three peaks which were integrated to yield the product ratios reported in Scheme III; FT-IR (neat) 3029, 2935, 1748, 1716, 1668, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.41–1.52 (m, 1 H), 1.59 (d, J = 5.9 Hz, 3 H), 1.62 (d, J = 5.0 Hz, 3 H), 2.23–2.44 (m, 2 H), 3.53 (s, 3 H), 4.24–4.26 (m, 2 H), 5.09–5.48 (m, 4H), 7.33–7.47 (m, 3 H), 7.48–7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.0, 17.9, 19.6, 36.3,

(15) For comments regarding variance in the optical purity of this reagent, see: Uskokovi'c, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742–4.

36.6, 47.6, 55.4, 66.0, 124.5, 125.0, 127.4, 128.3, 129.5, 133.9, 135.6, 166.7; ^{19}F NMR ($CDCl_3$, Cl_2CF_2 as a standard and set to zero) δ −65.07.

(*S*,*E*)-2-[(*S*,*E*)-1-Methyl-2-butenyl]-3-methyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate. Method IV and **17a** (0.04 g, 0.20 mmol), (*R*)-MTPA (0.07 g, 0.30 mmol), DCC (0.06 g, 0.30 mmol), and DMAP (3 mg, 0.02 mmol) produced the title compound as a pale yellow oil (0.07 g, 95%): FT-IR (neat) 3028, 2962, 1746, 1716, 1668, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 1.39–1.50 (m, 1 H), 1.57 (d, J = 6.0 Hz, 3 H), 1.63 (d, J = 5.0 Hz, 3 H), 2.28 (q, J = 6.6 Hz, 1 H), 2.37 (q, J = 6.7 Hz, 1 H), 3.53 (s, 3 H), 4.16 (dd, J = 11.4, 5.0 Hz, 1 H), 4.36 (dd, J = 11.4, 4.3 Hz, 1 H), 5.15–5.51 (m, 4H), 7.34–7.47 (m, 3 H), 7.48–7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.0, 17.9, 19.6, 36.5, 38.3, 47.7, 55.3, 65.9, 124.5, 124.9, 127.4, 128.3, 129.5, 133.9, 135.6, 166.7; ^{19}F NMR ($CDCl_3$, Cl_2CF_2 as a standard and set to zero) δ −65.11.

(2*R,3*S**,*E*)-2-[(*R**,*E*)-1-Methyl-2-butenyl]-3-methyl-4-hexen-1-yl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate.** Method IV and **19a** (0.04 g, 0.20 mmol), (*R*)-MTPA (0.07 g, 0.30 mmol), DCC (0.06 g, 0.30 mmol), and DMAP (2 mg, 0.02 mmol) produced the title compound as a pale yellow oil (0.08 g, 100%); FT-IR (neat) 2967, 1749, 1716, 1669, 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 6H), 1.43–1.55 (m, 1 H), 1.63 (d, J = 4.9 Hz, 6H), 2.22–2.38 (m, 2 H), 3.53 (s, 3 H), 4.23 (dd, J = 11.5, 4.3 Hz, 1 H), 4.31 (dd, J = 11.5, 4.6 Hz, 1 H), 5.17–5.51 (m, 4H), 7.34–7.47 (m, 3 H), 7.48–7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.5, 17.9, 36.2, 47.1, 55.4, 65.6, 124.3, 127.3, 128.3, 129.5, 135.9, 166.7; ^{19}F NMR ($CDCl_3$, Cl_2CF_2 as a standard and set to zero) δ −65.05.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-9108231) for financial support of this research.

Supplementary Material Available: ^{1}H-NMR data for **16**, **21**, **25**, **27**, and (−)-(*R*,*E*)-3-ethyl-4-hexen-1-ol and ^{13}C-NMR data for **19**, **26**, **28**, and (+)-(*S*,*E*)-3-methyl-4-hexen-1-ol (9 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.