^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, OH), 1.60 (s, C6 vinyl CH_3), 1.77 (s, C2 vinyl CH_3), 1.93 (t, J = 2.5 Hz acetylenic H), 1.97–2.24 (m, allylic, propargylic CH_2s), 4.09 (d, J = 4 Hz, CH_2OH), 5.15 (m, H7), 5.27 (t, J = 7 Hz, H3); MS, m/e 191 (M – 1), 177 (M – CH_3), 159 (M – H_2O – CH_3). Anal. Calcd for $C_{13}H_{20}O$: C, 81.25; H, 10.42. Found: C, 81.20; H, 10.51.

(2*Z*,6*E*)-1-Chloro-2,6-dimethyl-2,6-undecadien-10-yne (31). Following the procedure described for the preparation of allylic chloride **5**, 400 mg (9.0 mmol) of LiCl, 1.10 g (4.70 mmol) of the allylic alcohol **30**, 1.07 mL (9.12 mmol) of 2,6-lutidine in 6 mL of DMF, and 0.71 mL (9.12 mmol) of methanesulfonyl chloride afforded, after purification by column chromatography on silica gel (2% EtOAc–hexanes), 1.01 g (91%) of chloride **31** as a colorless oil: IR (film) ν 2970, 2940, 2920, 2860, 2120, 1670, 1445, 1435, 1380, 1255, 700, 630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, C6 vinyl CH_3), 1.79 (s, C2 vinyl CH_3), 1.93 (t, J = 2.5 Hz, acetylenic H), 2.0–2.2 (m, allylic, propargylic, CH_2s), 4.04 (s, CH_2Cl), 5.17 (m, H7), 5.35 (t, J = 7 Hz, H3); MS, m/e 175 (M – 1 – HCl), 161 (M – CH_2Cl), 159 (M – HCl – CH_3).

(6*E*,10*Z*)-7,11-Dimethyl-12-chloro-6,10-dodecadien-2-yn-1-ol (32). The procedure described for alcohol **9** was employed with 2.1 mL (5.14 mmol) of 2.5 M *n*-BuLi, 1.082 g (5.14 mmol) of acetylene **31**, and 0.38 g (8.22 mmol) of paraformaldehyde in 8 mL of THF. Column chromatography on silica gel (15% EtOAc–hexanes) afforded 1.166 g (94%) of a light yellow oil: IR (film) ν 3450, 2980, 2920, 2870, 2290, 2230, 1650, 1450, 1380, 1255, 1135, 1030, 850, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (t, J = 6 Hz, OH), 1.59 (s, C7 vinyl CH_3), 1.08 (s, C11 vinyl CH_3), 1.95–2.25 (m, allylic, propargylic CH_2s), 4.04 (s, CH_2Cl), 4.23 (d, J = 6 Hz, CH_2OH), 5.15 (m, H6), 5.34 (t, J = 6 Hz, H10); MS, m/e 204 (M – HCl), 189 (M – HCl – Me), 171 (M – HCl – Me – H_2O).

(3*Z*,7*E*)-3,7-Dimethyl-1-oxa-3,7-cyclotridecadien-11-yne (33). The cyclization procedure described for ether **10** was followed by using 1.639 g (0.068 mol) of alcohol **32** and 0.02 g of 1,10-phenanthroline in 350 mL of THF and 4.5 mL of hexamethylphosphoramide to which 3.4 mL of 2.0 M ethylmagnesium bromide in THF was added at 0 °C. The resulting mixture was heated for 5 h at reflux. Following workup and chromatography on silica gel (1% EtOAc–hexanes), 0.582 g (42%) of cyclic ether **33** was isolated as a colorless oil: IR (film) ν 2950, 2920, 2850, 2280, 2220, 1670, 1445, 1380, 1360, 1140, 1090, 1070, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, vinyl CH_3), 1.72 (s, vinyl CH_3), 2.0–2.2 (m, allylic, CH_2s), 4.04 (s, allylic carbinyl CH_2), 4.16 (s, propargylic carbinyl CH_2), 5.11 (t, J = 7 Hz, vinyl H), 5.26 (t, J = 7 Hz, vinyl H); MS, m/e 204 (M), 189 (M – CH_3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.35; H, 9.80. Found: C, 82.26; H, 9.89.

Continued elution afforded 0.358 g (25%) of the dimer **34**: mp 80–81 °C (pentane); IR (KBr) ν 2980, 2940, 2850, 2290, 2220, 1460, 1440, 1250, 1180, 1060, 900, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, vinyl CH_3), 1.71 (s, vinyl CH_3), 1.9–2.3 (m, allylic CH_2s), 4.04 (s, allylic carbinyl CH_2), 4.10 (s, propargylic carbinyl CH_2), 5.10 (t, J = 7 Hz, vinyl H), 5.42 (t, J = 7 Hz, vinyl H); MS, m/e 408 (M), 393 (M – CH_3). Anal. Calcd for $C_{28}H_{40}O_2$: C, 82.35; H, 9.80. Found: C, 82.23; H, 9.90.

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Stereocontrolled Synthesis of Highly Oxygenated Acyclic Systems via the Enolate Claisen Rearrangement of O-Protected Allylic Glycolates

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Enolate Claisen rearrangement of *E*- and *Z*-allylic glycolates yields the *syn*- and *anti*-2-alkoxy-3-alkyl 4-enoates, respectively, in good yields (60–90%) and with high internal diastereoselectivity. Incorporation of the glycolate Claisen procedure into an iterative sequence consisting of Claisen rearrangement and homologation by addition of vinyl nucleophiles results in the efficient, stereocontrolled generation of remotely functionalized, highly oxygenated acyclic systems. This strategy is demonstrated in stereoselective syntheses of pine sawfly pheromone **42** and tocopherol side-chain intermediate **30**.

Introduction

Advances in the technology associated with the isolation and characterization of complex organic molecules have resulted in the identification of an impressive number of new acyclic and macrocyclic natural products in recent years. Coincident with the discovery of novel, biologically significant acyclic compounds has been an intense focus on synthetic strategies which address the unique challenge of these systems.[1] In particular, attention has been directed to the development of new methods for the stereorational homologation of an existing acyclic intermediate. This type of linear elaboration is particularly well-suited to the synthesis of compounds of polyketide or polyisoprene origin, since the repeating structural units of these systems could, in principle, arise from the iterative application of a single, short homologation sequence.[2,3] The potential advantages of a linear route to functionalized

(1) For recent reviews, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron Lett.* **1985**, *41*, 3569. (b) Bartlett, P. A. *Tetrahedron Lett.* **1980**, *36*, 2.

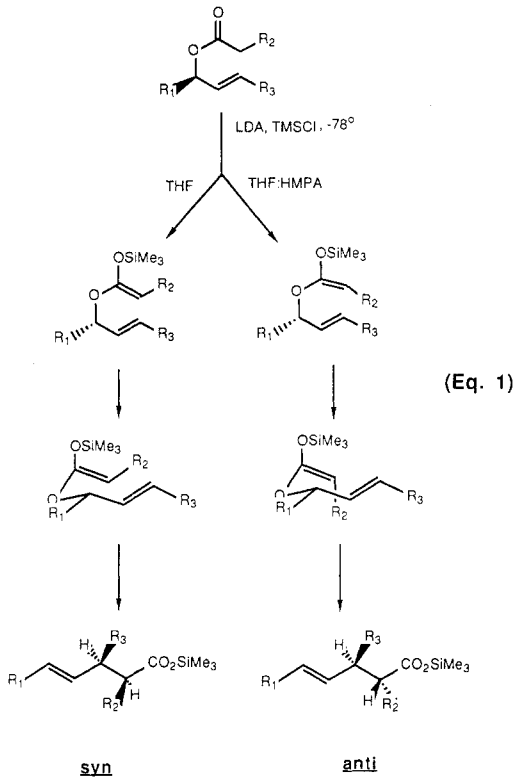
(2) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.-T.; Faulkner, D. J. *Ibid.* **1970**, *92*, 4463. (c) Faulkner, D. J.; Peterson, M. R. *Ibid.* **1973**, *95*, 553. (d) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505, 3512. (e) Chan, K.-K.; Cohen, N.; DeNoble, J. P.; Specian, A. C.; Saucy, G. *Ibid.* **1976**, *41*, 3497. (f) Chan, K.-K.; Specian, A. C.; Saucy, G. *Ibid.* **1978**, *43*, 3435. (g) Midland, M. M.; Tsai, D. J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3915.

(3) (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (b) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *Ibid.* **1985**, *50*, 420. (c) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (d) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (e) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147.

0022-3263/87/1952-3889$01.50/0

acyclic systems are offset to some degree by the rigid demands such a scheme places on the reactions used to extend the developing acyclic framework. Since stereochemical heterogenity at intermediate stages of an iterative sequence will be propagated in subsequent transformations, the successful implementation of a linear acyclic construction requires a complement of efficient, highly stereoselective C–C bond-forming reactions.

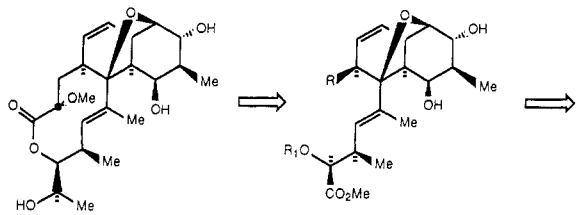
The Claisen and related [3,3] and [2,3] sigmatropic rearrangements occupy a prominent position among the available techniques for acyclic C–C bond formation by homologation of a functionalized allylic system.[4] The widespread application of the Claisen rearrangement and its many variants to the synthesis of both cyclic and acyclic targets can be attributed to the reliability of existing experimental procedures, the versatile disposition of the products with regard to further transformation and the predictable stereochemical outcome of the electrocyclic event.[5,6] Thus, rearrangement of a geometrically defined allyl vinyl ether results in the development of new, vicinal chirality as a result of the highly organized, six-center transition state of the reaction (see eq 1). A further



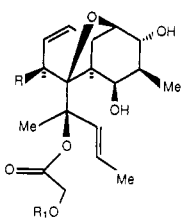
(Eq. 1)

consequence of the chairlike transition state proposed for the Claisen and related processes is the translation of stereochemical information from the original carbinol center of the allylic system to the newly formed chiral centers in the product, an observation that has been exploited to great advantage in the synthesis of acyclic systems which contain remote stereocenters.[7] Of critical importance to the stereochemical outcome of the Claisen rearrangement is the configuration of substituents appended to the allyl and vinyl groups, since these olefin geometries are reflected in the stereochemistry of the newly formed chiral centers of the product. Claisen modifications that fail to control enol stereochemistry yield diastereomeric mixtures of products, and considerable effort has been directed at the development of Claisen variants that rigorously define enol geometry.[8] Notable among the successes to date is the landmark work of Ireland,[9] who demonstrated that the stereochemistry of ester enolate formation is dramatically solvent dependent (eq 1). Under appropriate conditions, either *E*- or *Z*-allylic enolates can be selectively generated and trapped as the silyl ketene acetals, which undergo a facile Claisen rearrangement. The internal diastereoselectivity of these enolate Claisen rearrangements reflects the composition of the original enolate population, usually in the range 4–8:1.[10]

In conjunction with our synthetic program[11] directed at the nargenicin antibiotics (i.e., nodusmicin, **1**) we became interested in the potential of O-protected allylic glycolates as substrates for the enolate Claisen rearrangement. As shown in eq 2, rearrangement of glycolate **3** would intro-



1 ; nodusmicin 2



(Eq. 2)

3

duce the requisite functional and remote stereochemical elements of the nargenicin macrolide system in a single operation. While the enolate chemistry of α-alkoxycarbonyl systems has been extensively investigated in the context of stereocontrolled aldol additions,[12] the enolate

(4) Rhodes, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1.

(5) (a) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 8. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Bennett, G. B. *Synthesis* **1977**, 589.

(6) (a) Hill, R. K.; Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1967**, 619. (b) Hill, R. K.; Gilman, N. W. *Tetrahedron Lett.* **1967**, 1421. (c) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737. (d) Vittorelli, P.; Winkler, T.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457. (e) Vittorelli, P.; Hansen, H.-J.; Schmid, H. *Ibid.* **1975**, *58*, 1293. (f) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. (g) Perrin, C. L.; Faulkner, D. J. *Tetrahedron Lett.* **1969**, 2783. (h) Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 654.

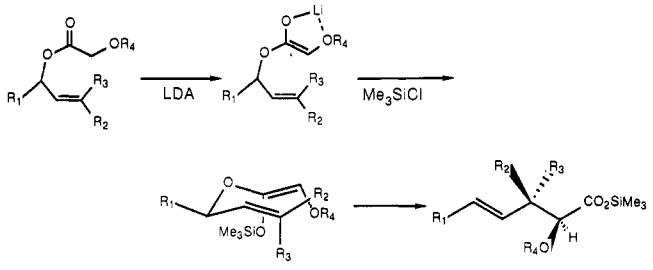
(7) For recent examples, see: (a) Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivasan, C. V. B. *J. Am. Chem. Soc.* **1982**, *104*, 1436. (b) Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617. (c) Heathcock, C. H.; Jarvi, E. T. *Ibid.* **1982**, *23*, 2825. (d) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5013, 5017. (e) Midland, M. M.; Tsai, D. J.-S. *J. Org. Chem.* **1984**, *49*, 1842. (f) Sayo, N.; Azuma, K.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 565. (g) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669.

(8) (a) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679. (b) Sucrow, W. *Ang. Chem., Int. Ed. Engl.* **1968**, *7*, 629. (c) Chapleo, C. B.; Hallet, P; Lythgoe, B.; Wright, P. W. *Tetrahedron Lett.* **1974**, 847. (d) Lythgoe, B.; Metcalfe, D. A. *Ibid.* **1975**, 2447. (e) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882. (f) Wilson, S. R.; Myers, R. S. *Ibid.* **1975**, *40*, 3309.

(9) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *Ibid.* **1976**, *98*, 2868.

(10) Several groups have reported exclusive diastereoselectivity for the enolate Claisen rearrangement using *t*-BuMe$_2$SiCl as the enolate trap; see ref 2a,b. See also: Nagatsuma, M.; Shirai, F.; Sayo, N.; Nakai, T. *Chem. Lett.* **1984**, 1393.

(11) Kallmerten, J. *Tetrahedron Lett.* **1984**, *25*, 2843. Kallmerten, J.; Plata, D. P. *Heterocycles* **1987**, *25*, 145–149.



(Eq 3)

Claisen rearrangement of these systems had received surprisingly little attention.[13] The ability of such systems to support a cyclic chelate of the enolate counterion (eq 3), thereby enhancing the enolate population, and the utility of the resulting Claisen products as intermediates in the synthesis of oxygenated, acyclic natural products motivated an investigation of the enolate Claisen rearrangement of O-protected allylic glycolates. Since the initiation of this work, several reports of related studies have appeared. Bartlett[14] has described the rearrangement of allylic lactate and mandelate esters; included in this report was the rearrangement of the enediolate obtained from a glycolic ester. Other workers have presented similar studies of enediolate rearrangements.[15] Coincident with our original communication[16] describing the rearrangement of O-protected allylic glycolates was a report by Burke and co-workers[17] describing the results of parallel studies. Herein we detail the results of our investigation of the highly diastereoselective enolate Claisen rearrangement of allylic glycolates and the iterative application of this reaction to the stereocontrolled synthesis of remotely functionalized acyclic systems.

Results and Discussion

Enolate Claisen Rearrangement of *E*- and *Z*-Allylic Glycolates. We have examined the rearrangement of 20 O-protected allylic glycolates (Table I) and have observed in each case the diastereoselective formation of a major isomeric product. Enolate Claisen rearrangement of *E*-allylic glycolates affords syn[39] products (entries 1, 3, 5, 7, 9, and 10), while *Z* glycolates give rise to the corresponding anti diastereomers (entries 2, 4, 6, 8, and 11–13). These results are consistent with the expectation that the enolate geometry capable of supporting a cyclic chelate predominates. In a typical rearrangement experiment, enolate generation (1 equiv of base added to ester in THF at −78 °C) is followed by immediate (within 2 min) addition of trimethylsilyl chloride. Rearrangement occurs upon warming to 0 °C, whereupon the products are isolated as the methyl esters by hydrolysis of the intermediate silyl esters and treatment with diazomethane. Diastereomer ratios were determined by HPLC or GC and ^{1}H NMR analysis. For a number of examples, the marked increase in yield over our earlier report[16] is attributable to the rapid addition of Me_3SiCl following enolate generation; at longer intervals, yields are diminished and significant amounts of allylic alcohol are recovered in the product mixture, implying decomposition of the ester enolate by a ketene mechanism.[18]

Our results for the rearrangement of crotyl glycolates **3** and **4** are in accord with those of other workers;[17] interestingly, these and the corresponding cinnamyl glycolates are among the least selective substrates examined. A notable increase in diastereoselectivity results from introduction of an α-substituent into the allylic system (entries 7–13); in the majority of α-substituted substrates studied a *single* diastereomer is obtained (to our analytical limits; see Table I). These results are significant with regard to the synthesis of enantiomerically pure acyclic intermediates, since new methods for asymmetric reduction of acetylenic ketones provide a convenient access to optically pure, secondary allylic alcohols.[19]

Stereochemical assignments of the products in Table I are based on comparison with materials prepared by an alternate synthetic route, conversion to stereochemically defined natural product targets, and/or correlation of ^{1}H NMR chemical shifts. Authentic samples of esters *syn*-**16a** and *syn*-**16b** were prepared by alkylation of the known[14a] 2-hydroxypentenoate **27**. A similar sequence was used to prepare samples of cinnamate derived esters *syn*-**17a** and *syn*-**17b** (Scheme I). Authentic mixtures of syn and anti diastereomers of these compounds were prepared by base-catalyzed epimerization of the corresponding syn isomer. Ester *syn*-**22b** was converted to the methyl analogue *syn*-**22a** by debenzylation and methylation; the relative stereochemistry of the *syn*-**22b** was established by conversion to alcohol **28**, a pheromone of the European elm bark beetle.[20] The stereochemical assignment for Claisen product *anti*-**26** is based on conversion to the antifungal metabolite avenaciolide **29**.[21] For the remaining examples, our assignment of major product stereochemistry is based on ^{1}H NMR chemical shifts which distinguish the syn and anti diastereomers[22] (Table II). Most consistently useful is the C_2 methine resonance; for every syn–anti pair examined to date, the C_2 methine of the syn diastereomer experiences a downfield shift relative to that of the anti. A downfield shift is also observed for the methyl ester resonance of syn diastereomers, although in a number of cases the chemical shift of this signal was sufficiently close for the two diastereomers so as to limit the general usefulness as a diagnostic tool.

To determine the role of the postulated cyclic chelate in the enolate Claisen rearrangement of allylic glycolates, we have examined the rearrangement of crotyl glycolate (**3**) under a variety of reaction conditions. As shown in Table III, optimum yields and diastereomer ratios are obtained by using "thermodynamic" conditions for enolate

(12) For example: (a) Adam, W.; Fick, H. *J. Org. Chem.* **1978**, *43*, 772. (b) Ciochetto, L.; Bergbreiter, D.; Newcomb, M. *Ibid.* **1977**, *42*, 2948. (c) Duggan, A.; Adams, M.; Brynes, P.; Meinwald, J. *Tetrahedron Lett.* **1978**, 4323. (d) Touzin, A. *Ibid.* **1975**, 1477. (e) Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 4972.

(13) Examples of the Claisen rearrangement of α-alkoxy esters in cyclic systems have been described: (a) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (c) Whitesell, J. K.; Helbina, A. M.; Matthews, R. S. *Ibid.* **1978**, *43*, 784.

(14) (a) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941. (b) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

(15) (a) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (b) Fujisawa, T.; Kohmama, H.; Tajima, K.; Sato, T. *Ibid.* **1984**, *25*, 5155.

(16) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177.

(17) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221.

(18) See, for example: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(19) See: Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J.-S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371 and references therein.

(20) Pearce, G. T.; Gore, W. E.; Silverstein, R. M.; Peacock, J. W.; Cuthbert, R. A.; Canier, G. N.; Simeone, J. B. *J. Chem. Ecol.* **1975**, *1*, 115. For a chiral synthesis, see: Mori, K. *Tetrahedron* **1977**, *33*, 289.

(21) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128.

(22) Heathcock has observed a similar correlation in the ^{13}C spectra of syn and anti aldol products: Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

Table I. Enolate Claisen Rearrangement of Allylic Glycolates

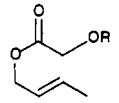
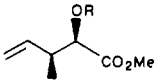
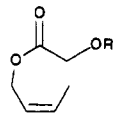
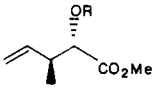
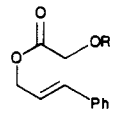
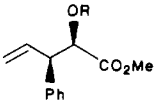
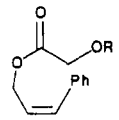
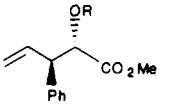
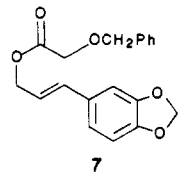
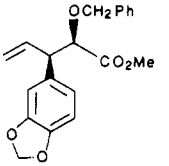
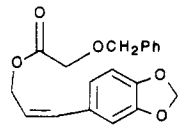
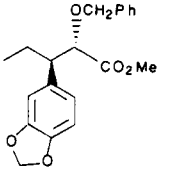
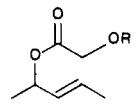
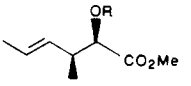
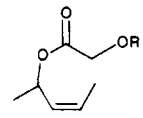
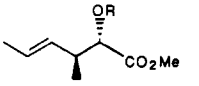
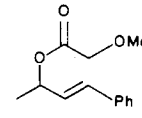
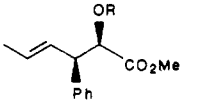
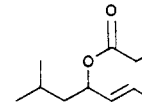
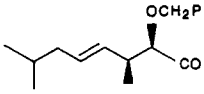
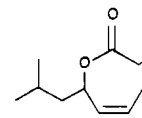
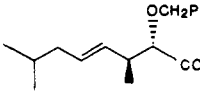
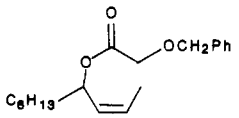
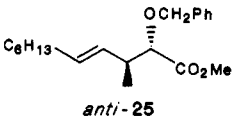
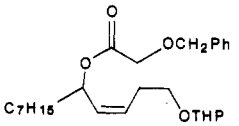
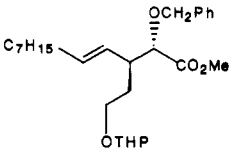
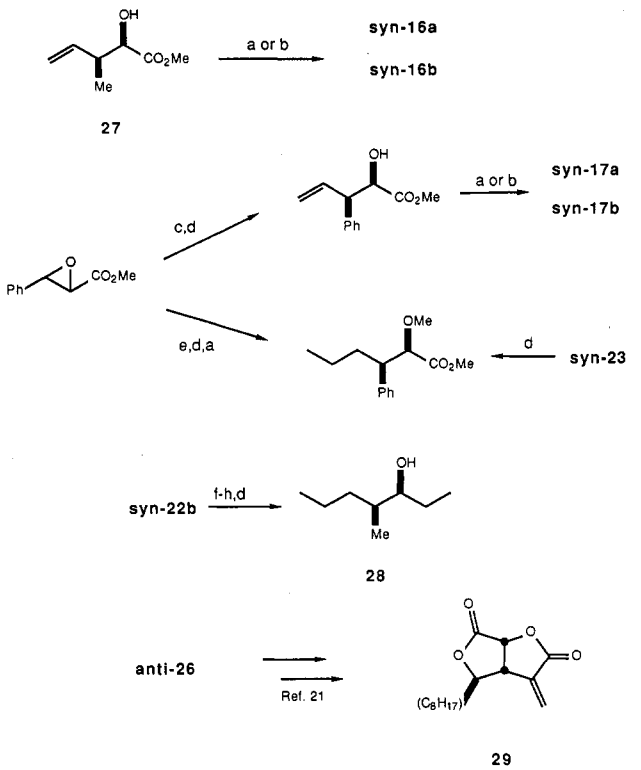
entry	ester	R	conditions (method)[a]	major product	yield,[b] %	syn/anti[c]
1	 **3**	**a**, Me	LDA (A)	 *syn*-**16**	95	8:1 (G)
		b, CH_2Ph	LDA (A)		90	>40:1 (G)[d]
2	 **4**	**a**, CH_3	LDA (A)	 *anti*-**16**	60	1:30 (G)
		b, CH_2Ph	LDA (A)		91	1:13 (H)
3	 **5**	**a**, CH_3	LDA (A)	 *syn*-**17**	36	>40:1 (G)[d]
			KHMDS (B)		64	>40:1 (G)[d]
		b, CH_2Ph	LDA (A)		67	>100:1 (H)[d]
			KHMDS (B)		83	11:1 (H)
4	 **6**		KHMDS (B)	 *anti*-**17b**	83	1:13 (H)
5	 **7**		KHMDS (B)	 *syn*-**18**	82	22:1 (H)
6	 **8**		KHMDS (B)	 *anti*-**18**	92	1:8 (H)
7	 **9**	**a**, CH_3	LDA (A)	 *syn*-**22**	91	13:1 (G)
			KHMDS (B)		72	>40:1 (G)[d]
		b, CH_2Ph	LDA (A)		90	>40:1 (G)[d]
		c, *p*-anisyl	LHMDS (A)		88	10:1 (H)
			KHMDS (A)		51	12:1 (H)
8	 **10**	**a**, CH_3	LDA (A)	 *anti*-**22**	93	1:15 (G)
		b, CH_2Ph	LDA (A)		44	>1:100 (H)[d]
9	 **11**		KHMDS (B)	 *syn*-**23**	75	>100:1 (H)[d]
10	 **12**	**a**, CH_3	LDA (A)	 *syn*-**24**	70	>40:1 (G)[d]
		b, CH_2Ph	LDA (A)		71	>100:1 (H)[d]
		c, *p*-anisyl	KHMDS (B)		71	>100:1 (H)[d]
11	 **13**		LDA (A)	 *anti*-**24b**	81	>1:100 (H)[d]

Table I (Continued)

entry	ester	R	conditions (method)[a]	major product	yield,[b] %	syn/anti[c]
12	 **14**		LDA (A)	 *anti*-**25**	74	>1:100 (H)[d]
13	 **15**		LDA (A)[e]	 *anti*-**26**	75	>1:100 (H)[d]

[a] Method A, enolate generation under thermodynamic conditions; see Experimental Section for details. Method B, enolate generated in the presence of Me_3SiCl. [b] All yields are for chromatographed material. [c] Diastereomer ratios determined by GC (G) or HPLC (H); limits of detection are 40:1 and 100:1, respectively, for representative systems. [d] Only one diastereomer was observed. [e] See ref 21.

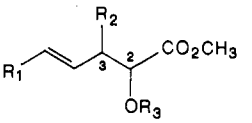
Scheme I. Correlation of Enolate Claisen Product Stereochemistry[a]



[a] Reagents: (a) MeI, Ag_2O; (b) $PhCH_2Cl$, Ag_2O; (c) $Me_3SiCCLi$, Et_2AlCl, then $AgNO_2$, KCN; (d) Pd–C, H_2; (e) H_3CCCLi, Et_2AlCl; (f) $LiAlH_4$, Et_2O; (g) MsCl, *n*-BuLi, Et_2O; (h) Me_2CuLi, Et_2O, –78 to 0 °C.

generation (i.e., inverse addition of LDA followed by a brief interval before addition of Me_3SiCl). Although the yield using potassium hexamethyldisilazide (KHMDS) was significantly reduced in the case of **3**, no appreciable counterion effect on diastereoselectivity was observed. For some substrates, (i.e., cinnamyl glycolates **5–8**), KHMDS is actually the preferred reagent (see Table I, entries 3–6, 9). Attempts to form the magnesium enolate (using magnesium hexamethyldisilazide or by addition of $MgBr_2{\cdot}Et_2O$ to the lithium enolate) resulted in severely attenuated yields. Of considerable interest is the fact that enolate generation under kinetic conditions results in only a slight diminution of diastereoselectivity. Similarly, enolate formation in the presence of Me_3SiCl results in no detectable change in diastereomer ratio. These results suggest that diastereoselectivity observed for O-protected

Table II. Diagnostic ^1H and ^{13}C Chemical Shifts[a,b] of Glycolate Claisen Products



	^1H			^{13}C		
	H(2)	H(3)	CO_2CH_3	C(2)	C(3)	CO_2CH_3
syn-**16a**	3.65	2.60	3.75	84.57	41.06	51.41
anti-**16a**	3.67	2.64	3.75	84.97	41.00	51.48
syn-**16b**	3.82	2.64	3.69	82.04	41.14	51.32
anti-**16b**	3.85	2.66	3.73	82.17	41.14	51.55
syn-**17b**	4.18	3.75	3.65	81.90	53.30	51.51
anti-**17b**	4.18	3.80	3.61	82.12	52.84	51.71
syn-**18**	4.06	3.62	3.61	81.88	52.87	51.61
anti-**18**	4.12	3.69	3.64	82.19	52.37	51.71
syn-**22a**	3.58	2.53	3.73	85.14	40.27	51.43
anti-**22a**	3.62	2.59	3.74	85.39	40.22	51.55
syn-**24b**	3.75	2.60	3.69	82.77	41.85	51.48
anti-**24b**	3.82	2.63	3.69	82.51	41.95	51.41

[a] ^1H and ^{13}C spectra were recorded in $CDCl_3$ at 500 MHz and 62 MHz, respectively. [b] Chemical shifts are reported in ppm downfield from internal Me_4Si.

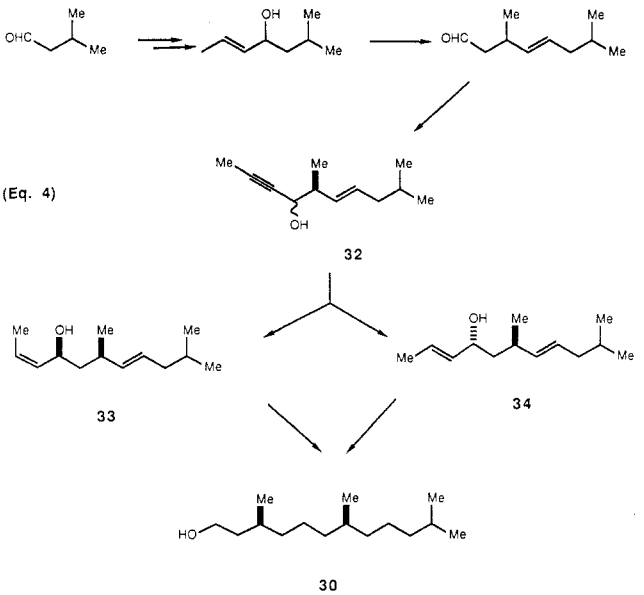
Table III. Effect of Reaction Conditions on Enolate Claisen Rearrangement of Glycolate 3

conditions[a]	base	trapping interval,[b] min	yield, %	16:17[c,d]
thermodynamic, THF, –78 °C	LDA	5	61	8.3:1
thermodynamic, THF, –78 °C	LDA	2	84	7.4:1
thermodynamic, THF, –78 °C	LDA	0	80	7.4:1
kinetic, THF, –78 °C	LDA	2	85	6.5:1
thermodynamic, THF, –78 °C	LiHMDS	2	81	7.7:1
thermodynamic, THF, –78 °C	KHMDS	2	31	7.5:1
thermodynamic, THF–HMPA,[e] –78 °C	LDA	2	67	5.2:1
thermodynamic, THF, $MgBr_2{\cdot}Et_2O$[f]	LDA	5	36	10.8:1

[a] Thermodynamic conditions for enolate generation = inverse addition of base to ester at –78 °C; kinetic conditions = ester added to base at –78 °C. [b] Time elapsed from completion of base addition to initial addition of Me_3SiCl. [c] Starting glycolate **3** contained 2% of the *Z* isomer; ratios are uncorrected. [d] Diastereomer ratios determined by GC using a 6-m 13% Carbowax 20M column. [e] Ca. 2 equiv of HMPA. [f] Ca. 2 equiv of $MgBr_2{\cdot}Et_2O$ added prior to base addition.

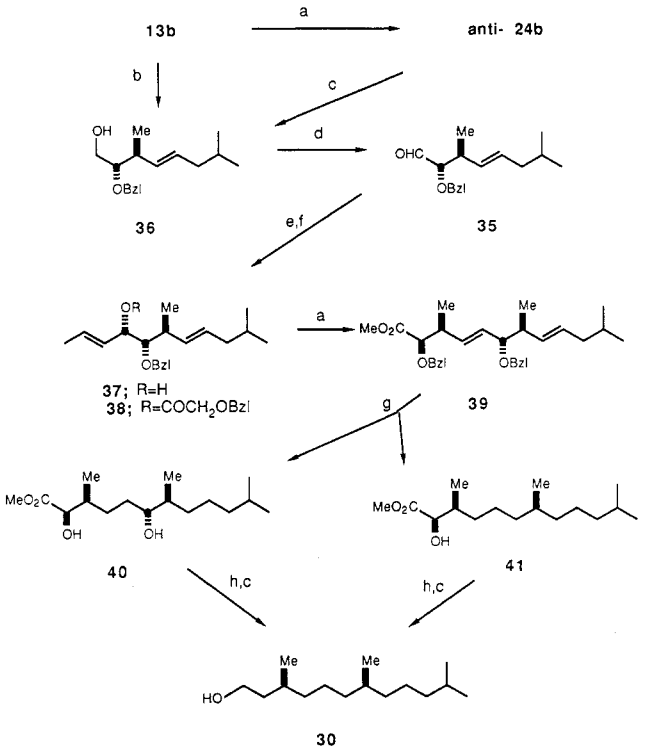
allylic glycolates is predominantly a kinetic effect, which may be a consequence of counterion coordination to the α-alkoxy ester prior to proton abstraction.[23]

Highly Oxygenated Acyclic Systems from Iterative Rearrangement of Allylic Glycolates. The rapid development of an extended acyclic framework by an iterative series of Claisen rearrangements has been demonstrated by Johnson and others in elegant syntheses of squalene and other natural products of polyisoprene origin.[2a-c] More recently, workers at Hoffman-LaRoche demonstrated that this strategy can be applied to the synthesis of acyclic systems containing elements of remote chirality.[2d-f] In their classic synthesis of the tocopherol side chain, **30**, a sequence of Claisen rearrangement and subsequent homologation by addition of an acetylenic nucleophile resulted in the formation of the epimeric alcohols **32** (eq 4). These alcohols were then separated and independently reduced to the *E*- and *Z*-allylic alcohols **33** and **34**, each of which could then serve as the substrate for a second Claisen rearrangement to establish the remote chiral relationship of the tocopherol system.[24]



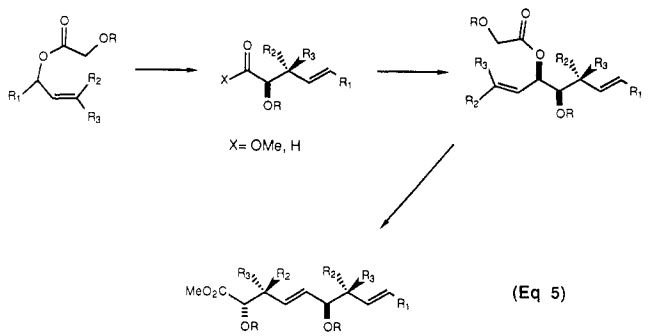
While elegant in concept, the Roche synthesis illustrates the potential liabilities of an iterative sigmatropic sequence. Failure to rigorously define the stereochemistry of either the sigmatropic or homologation process leads to remote diastereomeric mixtures, the separation of which can be a tedious, if not impossible, task. The high diastereoselectivity observed in the rearrangement of allylic glycolates and the potential of the α-alkoxy ester products for further stereocontrolled homologation by chelation-mediated[25] addition of a propenyl nucleophile to the carbonyl group, suggested to us that the glycolate Claisen protocol would be an excellent vehicle for an iterative sigmatropic series (eq 5). The result of such a sequence would be a five-carbon homologation of an acyclic substrate to give a new system bearing a 1,5 pattern of alkyl and alkoxy substituents, a relationship reminiscent of naturally occurring

Scheme II. Synthesis of Tocopherol Intermediate 30[a]



[a] Reagents: (a) LDA, THF, Me_3SiCl, −78 to 0 °C; then aqueous NH_4Cl, CH_2N_2; (b) LDA, THF, Me_3SiCl, −78 to 0 °C; then $LiAlH_4$; (c) $LiAlH_4$, Et_2O, 0 °C; (d) $(COCl)_2$, Me_3SO, NEt_3, CH_2Cl_2, −78 °C; (e) $((E)$-1-propenyl$)_2CuLi$, $MgBr_2 \cdot Et_2O$, Et_2O, −78 °C; (f) $BzlOCH_2COCl$, pyridine; (g) H_2, Pd/C, EtOH; (h) *p*-TsCl, pyridine.

acyclic and macrocyclic systems of polyketide origin. This scheme incorporates significant flexibility with regard to the stereochemistry of the remote centes, since a simple variation of allylic olefin geometry would result in an effective inversion of the remote chiral center bearing the alkyl substituent.



We have investigated the feasibility of this strategy in a synthesis of the Roche Vitamin E intermediate **30**.[2d-f,7c,25-27] On the basis of the analysis shown in eq 5, the required syn relationship of the tocopherol methyl groups would be established by rearrangement of a *Z*-al-

(23) Workers at Hoffman-LaRoche have observed a reversal of diastereoselectivity for the rearrangement of *O-tert*-butyldimethylsilyl-protected glycolates, indicating that the kinetic enolate for these substrates is the *E* isomer instead of the chelation-directed *Z* enolate. We thank Dr. Joel Barrish for informing us of these results.

(24) In a subsequent route to the tocopherol sidechain, the Roche group circumvented this difficulty by asymmetric reduction of an acetylenic ketone to establish the desired remote stereochemistry: (a) Chan, K.-K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. (b) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1980**, *45*, 582.

(25) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031.

(26) A preliminary account of this work has been reported: Kallmerten, J.; Balestra, M. *J. Org. Chem.* **1986**, *51*, 2855.

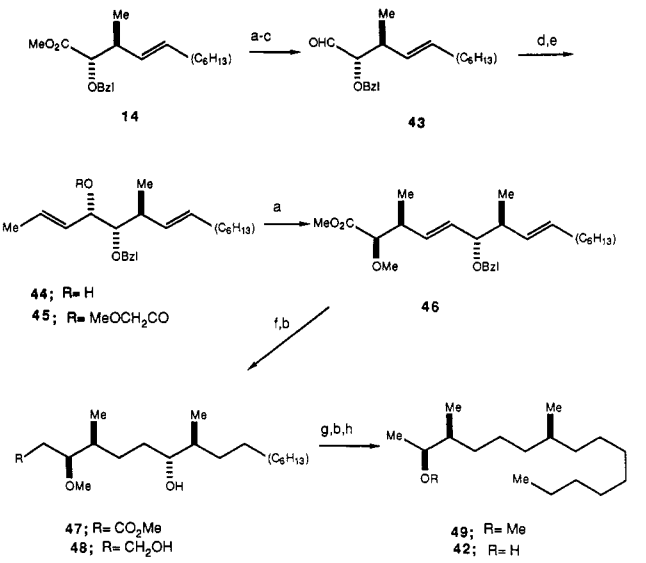
(27) (a) Takabe, K.; Uchiyama, Y.; Okisaka, K.; Yamata, T.; Katagiri, T.; Okazaki, T.; Oketa, Y.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1985**, *26*, 5153. (b) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (c) Berube, G.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 1558. (d) Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. (e) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Ibid.* **1981**, *22*, 4823. (f) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122 and references therein.

lylic glycolate followed by rearrangement of an *E*-glycolate; alternatively, the order could be reversed (i.e., rearrangement of an *E*-glycolate followed by rearrangement of a *Z*-glycolate). The choice of Claisen product *anti*-**24b** as the substrate for an examination of the homologation/Claisen sequence was motivated in part by the practical difficulties of obtaining the geometrically homogeneous (*Z*)-propenyllithium.[28] An alternative homologation strategy, in which the requisite allylic alcohol would be obtained from addition of a propynyl nucleophile to *syn*-**24b** or *anti*-**24b** followed by reduction to the desired *E*- or *Z*-allylic alcohol, was eliminated on the basis of preliminary studies that established the inadequacy of metalated propynes as effective nucleophiles in the chelation-controlled addition to α-alkoxy aldehydes.[29]

Conversion of Claisen product *anti*-**24b** to the corresponding aldehyde **35** was accomplished by reduction to the alcohol **36** and Swern oxidation (Scheme II). More conveniently, alcohol **36** could be obtained directly from glycolate **13** by Claisen rearrangement followed by reduction of the resulting silyl ester with $LiAlH_4$ prior to workup. Addition of (*E*)-propenylcuprate reagent to **35** proceeded in the predicted chelation-controlled mode to give allylic alcohol **37**. After flash chromatography to remove traces (<2%) of the undesired epimeric alcohol, **37** was acylated under standard conditions to give glycolate **38**, which underwent smooth Claisen rearrangement to afford, after workup, methyl ester **39** as the *only* observed product. That we had successfully established the desired syn relationship of the methyl substituents was confirmed by conversion of **39** to the tocopherol side chain **30**. Hydrogenation of **34** afforded a 1.4:1 mixture of diol **40** and **41**, resulting from hydrogenolysis of the allylic benzyl ether. Interestingly, we detected no evidence of epimerization of the allylic methyl group during hydrogenation of **39**; in contrast, the Roche workers observed significant epimerization upon catalytic hydrogenation of a related substrate.[2e] Alcohols **40** and **41** could be separated and independently converted to **30**; alternatively, exhaustive mesylation of the crude hydrogenation mixture followed by treatment with $LiAlH_4$ gave racemic **30** directly. No evidence of the diastereomer of **30** was observed in the 62-MHz ^{13}C NMR of the product mixture;[27f] analysis of an authentic mixture of **30** and its stereoisomer, prepared by hydrogenation of farnesol,[30] clearly reveals individual resonances.

In addition to introducing remote, oxygen-bearing acyclic centers in a highly stereoselective manner, the iterative glycolate Claisen protocol provides the ability to differentiate the individual hydroxyl groups, a feature that we anticipate will play an important role in the synthesis of extended polyketide-derived acyclic systems. A short synthesis of (±)-**42**, a pheromone of the pine sawfly,[31,32] serves to demonstrate this point. Reduction of Claisen product **14** and Swern oxidation of the resulting alcohol afforded aldehyde **43**, which was treated with (*E*)-propenyl-Grignard reagent to give a 14:1 mixture of the desired chelation-directed adduct **44** and its epimer (Scheme III). Separation by flash chromatography and acylation with *O*-methylglycolyl chloride yielded allylic glycolate **45**, which was subjected to enolate Claisen rearrangement to give, as the only detectable stereoisomer, **46**. Hydrogenation of **46** in methanol with palladium on carbon as catalyst resulted in significant hydrogenolysis, as well as epimerization of the allylic methyl groups, to give a complex mixture of products. When this hydrogenation was conducted in ethanol, both side reactions were suppressed, and the saturated alcohol **47** (accompanied by ≈5% of the hydrogenolysis product) was obtained. Conversion of **47** to our synthetic target was accomplished by reduction of the ester to diol **48**, formation of the ditosylate, reduction, and demethylation to give (±)-**42**, which exhibited physical and spectroscopic properties in excellent agreement with literature values.[33]

Scheme III. Synthesis of Pine Sawfly Pheromone 42[a]



[a] Reagents: (a) LDA, THF, Me_3SiCl, −78 to 0 °C; then aqueous NH_4Cl, CH_2N_2; (b) $LiAlH_4$, Et_2O, 0 °C; (c) $(COCl)_2$, NEt_3, Me_2SO, CH_2Cl_2, −78 °C; (d) ((*E*)-1-propenyl)Li, $MgBr_2 \cdot Et_2O$, THF, −78 °C; (e) $MeOCH_2COCl$, pyridine; (f) Pd–C, H_2, EtOH; (g) TsCl, pyridine; (h) Me_3SiI.

Conclusion

The enolate Claisen rearrangement of O-protected allylic glycolates provides a rapid, efficient, and highly stereocontrolled entry to functionalized acyclic intermediates. The iterative sequence consisting of Claisen rearrangement and chelation-directed addition of vinyl nucleophiles constitutes a stereoselective five-carbon homologation of an existing acyclic intermediate, that will rapidly generate the highly oxygenated skeleton of polyketide-derived natural products. We note that four of the eight possible diastereomers corresponding to intermediates **39** and **46** are accessible by variation of allylic olefin geometry. Inversion of the allylic carbinol center prior to Claisen rearrangement (by oxidation and chelation-controlled reduction)[15b,33] provides access to the remaining diastereomers, making this iterative sequence a versatile entry to extended acyclic systems.

While the above studies were carried out with racemic allylic alcohols, the corresponding chiral substrates are

(28) To our knowledge, a commercial source of pure (*E*)- or (*Z*)-halopropenes no longer exists.

(29) For example, addition of propynylmagnesium bromide to aldehyde **35** resulted in a 1:1 mixture of the epimeric acetylenic alcohols. Recently, we have observed a highly stereoselective addition of propynyl-Grignard reagent to α-hydroxy aldehydes protected as the methoxymethyl ethers (J. Kallmerten, M. Balestra and M. D. Wittman, unpublished results). Details will be reported separately.

(30) Koreeda has reported a similar reduction of methyl farnesoate; see ref 27f.

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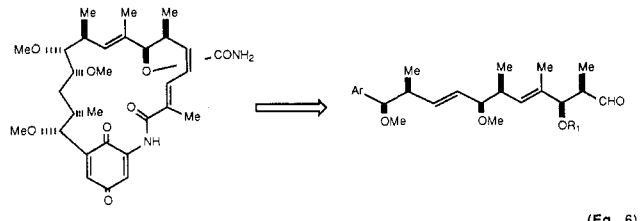
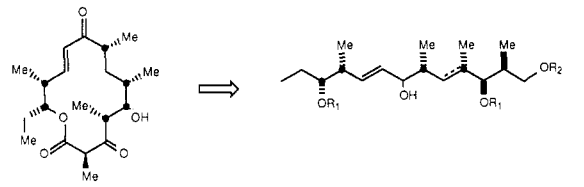
(32) For a review of recent syntheses of **42**, see: Mori, K. In *The Total Synthesis of Natural Products*; Ap Simon, J., Ed.; Wiley-Interscience: New York, 1984; Vol. 4, p 123.

(33) (a) Takahashi, T.; Miyazawa, M.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139. (b) Samuels, W. D.; Nelson, D. A.; Hallen, R. T. *Ibid.* **1986**, *27*, 3091.

available in high enantiomeric purity from reduction of the acetylenic ketones, and the iterative sequence thus represents an entry to highly functionalized, chiral acyclic intermediates. We further note the close similarity of intermediates **39** and **46** to key structural elements of the antitumor ansa macrolide macbecin I, **50**,[34] and the antibiotic narbomycin, **51**.[35] Application of the iterative glycolate protocol to the synthesis of these and other polyketide-derived natural products is in progress.



50; macbecin I (Eq. 6)



51; narbonolide

Experimental Section

Melting points were determined on a Thomas Hoover Unimelt capillary melting apparatus. Proton and carbon NMR spectra were determined on General Electric GN-500, Bruker WM-360, and Mohawk 250 spectrometers. All NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. IR spectra were recorded on a Beckman IR 4220 spectrometer.

Gas chromatographic analyses were performed on a Varian 3700 chromatograph equipped with thermal conductivity detectors and 10-m OV-225 (10%) or Carbowax 20 M (10%) columns. High-pressure liquid chromatographic analyses were performed on an IBM 934 ternary system equipped with an IBM 250 × 10 mm silica gel column. Elemental analysis was performed by E + R Microanalytical Laboratory, Inc., Corona, NY.

(*E*)-Pent-3-en-2-ol Methoxyacetate (9a). General Procedure for Preparation of Allylic Glycolates. The glycolate esters used in this study were prepared by addition of 1 equiv of the glycolyl chloride to a THF solution of the appropriate allylic alcohol and 3 equiv of pyridine. The following is a typical procedure. To a solution of (*E*)-pent-3-en-2-ol (5.14 g, 59.8 mmol) and pyridine (11.7 mL, 145 mmol) in THF (25 mL) at 0 °C was added a solution of methoxyacetyl chloride (5.38 g, 49.6 mmol) in THF (25 mL) over 30 min. After 2 h the reaction mixture was diluted with ether (100 mL) and washed with 5% HCl (100 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic fraction was dried over $MgSO_4$, evaporated in vacuo, and chromatographed on silica gel (10:1 hexane/ether) to yield **9a**, 5.56 g (71%), as a colorless oil: IR (neat oil) 1765, 1450, 1195, cm^{-1}; ^1H NMR (250 MHz) δ 5.76 (dq, J = 14.5, 6.5 Hz, 1 H), 5.45 (m, 2 H), 4.00 (s, 2 H), 3.45 (s, 3 H), 1.69 (dd, J = 6.5, 1.2 Hz, 3 H), 1.32 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 168.9, 130.0, 128.5, 77.2, 69.5, 58.6, 19.7, 17.0. An analytical sample was prepared by bulb-to-bulb distillation (50 °C, 0.1 mmHg). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.82; H, 9.10.

(*E*)-Pent-3-en-2-ol (phenylmethoxy)acetate (9b) was obtained from (*E*)-pent-3-en-2-ol with (phenylmethoxy)acetyl chloride in 71% yield as a clear oil: IR (neat oil) 1745, 1440, 1130 cm^{-1}; ^1H NMR (250 MHz) δ 7.33 (m, 5 H), 5.72 (m, 1 H), 5.45 (m, 2 H), 4.58 (s, 2 H), 4.03 (s, 2 H), 1.65 (d, J = 5.9 Hz, 3 H), 1.28 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 169.0, 136.8, 129.9, 128.1, 127.9, 127.5, 127.4, 72.6, 71.2, 66.8, 19.7, 17.1. An analytical sample was prepared by bulb-to-bulb distillation (100 °C, 0.1 mmHg). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.70; H, 7.86.

(*E*)-Pent-3-en-2-ol (4-methoxyphenoxy)acetate (9c) was obtained from (*E*)-pent-3-en-2-ol and [(4-methoxy)phenoxy]acetyl chloride[36] in 86% yield as a clear oil: IR (neat oil) 1760, 1505, 1180 cm^{-1}; ^1H NMR (250 MHz) δ 6.83 (m, 4 H), 5.75 (m, 1 H), 5.45 (m, 1 H), 4.53 (s, 2 H), 3.76 (s, 3 H), 1.68 (dd, J = 6.4, 0.8 Hz, 3 H), 1.31 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (62.9 MHz) δ 168.8, 154.8, 152.4, 130.5, 129.4, 116.2, 114.9, 72.6, 66.7, 55.9, 20.5, 17.9. An analytical sample was prepared by bulb-to-bulb distillation (110 °C, 0.1 mmHg). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.32; H, 7.39.

(*Z*)-Pent-3-en-2-ol methoxyacetate (10a) was obtained from (*Z*)-pent-3-en-2-ol and methoxyacetyl chloride in 67% yield as a clear oil: IR (neat oil) 1750, 1190, 1125 cm^{-1}; ^1H NMR (250 MHz) δ 5.77 (m, 1 H), 5.59 (m, 1 H), 5.39 (m, 1 H), 3.99 (s, 2 H), 3.44 (s, 3 H), 1.72 (d, J = 6.7 Hz, 3 H), 1.32 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 169.4, 129.8, 127.7, 70.0, 67.4, 59.2, 20.5, 13.1. An analytical sample was prepared by bulb-to-bulb distillation (50 °C, 0.1 mmHg). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.92; H, 9.05.

(*E*)-3-Phenylprop-2-en-1-ol methoxyacetate (5a) was obtained from (*E*)-cinnamyl alcohol and methoxyacetyl chloride in 84% yield as a clear oil: IR (neat oil) 1750, 1500, 1450 cm^{-1}; ^1H NMR (250 MHz) δ 7.31 (m, 5 H), 6.66 (br d, J = 15.9 Hz, 1 H), 6.28 (dt, J = 15.9, 6.4 Hz, 1 H), 4.81 (dd, J = 6.4, 1.1 Hz, 2 H), 4.06 (s, 2 H), 3.44 (s, 3 H); ^{13}C NMR δ 169.2, 135.4, 133.8, 127.9, 127.4, 125.9, 122.1, 68.9, 64.4, 58.4. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.5 mmHg). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.72; H, 7.08.

(*E*)-3-Phenylprop-2-en-1-ol (phenylmethoxy)acetate (5b) was obtained from (*E*)-cinnamyl alcohol and (phenylmethoxy)-acetyl chloride in 81% yield as a clear oil: IR (neat oil) 1750, 1435, 1110 cm^{-1}; ^1H NMR (250 MHz) δ 7.44–7.16 (m, 10 H), 6.66 (br d, J = 15.7 Hz, 1 H), 6.28 (dt, J = 15.7, 6.3 Hz, 1 H), 4.52 (dd, J = 6.3, 1.2 Hz, 2 H), 4.65 (s, 2 H), 4.14 (s, 2 H); ^{13}C NMR (125.8 MHz) δ 169.6, 136.8, 135.6, 134.1, 128.2, 128.0, 127.7, 127.6, 127.5, 126.2, 122.3, 72.8, 66.8, 64.8. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.1 mmHg). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.66; H, 6.57.

(*Z*)-3-Phenylprop-2-enol (phenylmethoxy)acetate (6) was obtained from (*Z*)-cinnamyl alcohol[37] and (phenylmethoxy)acetyl chloride in 94% yield as a clear oil: IR (neat oil) 1700, 1500, 1450 cm^{-1}; ^1H NMR (250 MHz) δ 7.18 (m, 10 H), 6.62 (br d, J = 12.0 Hz, 1 H), 5.73 (dt, J = 12.0, 6.9 Hz, 1 H), 4.86 (dd, J = 6.9, 1.7 Hz, 2 H), 4.56 (s, 2 H), 4.05 (s, 2 H); ^{13}C NMR δ 169.9, 136.9, 135.7, 133.2, 128.5, 128.3, 128.3, 128.2, 127.8, 127.4, 125.0, 73.1, 66.9, 61.5. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.5 mmHg). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.72; H, 7.08.

(*E*)-3-(1,3-Benzodioxol-5-yl)prop-2-enol (phenylmethoxy)acetate (7) was obtained from (*E*)-3-(1,3-benzodioxol-5-yl)prop-2-en-1-ol and (phenylmethoxy)acetyl chloride in 96% yield as a clear oil: IR (neat oil) 1740, 1490, 1480, 1440 cm^{-1}; ^1H NMR (360 MHz) δ 7.28 (m, 8 H), 6.66 (m, 1 H), 6.04 (m, 1 H), 5.81 (s, 2 H), 4.70 (br d, J = 6.8 Hz, 2 H), 4.57 (s, 2 H), 4.08 (s, 2 H); ^{13}C NMR δ 169.5, 147.6, 147.3, 136.9, 133.9, 130.1, 127.9, 127.4, 121.1, 120.5, 107.7, 105.4, 100.7, 72.7, 66.8, 64.8. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.5 mmHg). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.10; H, 5.80.

(*Z*)-3-(1,3-Benzodioxol-5-yl)prop-2-enol (phenylmethoxy)acetate (8) was obtained from (*Z*)-3-(1,3-benzodioxol-5-yl)prop-2-enol[38] and (phenylmethoxy)acetyl chloride in 97% yield

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as a clear oil: IR (neat oil) 1735, 1600, 1500, 1450 cm^{-1}; ^1H NMR (250 MHz) δ 7.24 (m, 8 H), 6.58 (m, 1 H), 5.90 (s, 2 H), 5.65 (dt, J = 12.0, 7.0 Hz, 1 H), 4.84 (dd, J = 6.6, 1.7 Hz, 2 H), 4.57 (s, 2 H), 4.06 (s, 2 H); ^{13}C NMR δ 170.0, 147.6, 147.0, 136.9, 133.0, 129.8, 128.4, 127.9, 123.9, 122.6, 108.7, 108.1, 101.0, 73.2, 67.0, 61.6. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.5 mmHg). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.13; H, 5.80.

(*E*)-1-Methyl-3-phenylprop-2-en-1-ol methoxyacetate (11) was obtained from (*E*)-1-methyl-3-phenylprop-2-en-1-ol and methoxyacetyl chloride in 85% yield as a clear oil: IR (neat oil) 1745, 1500, 1450 cm^{-1}; ^1H NMR (250 MHz) δ 7.30 (m, 5 H), 6.62 (br d, J = 16.2 Hz, 1 H), 6.19 (m, 1 H), 5.65 (m, 1 H), 4.03 (s, 2 H), 3.45 (s, 3 H), 1.45 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 168.7, 135.5, 131.2, 127.8, 127.6, 127.3, 125.9, 70.7, 69.1, 58.3, 19.6. An analytical sample was prepared by bulb-to-bulb distillation (210 °C, 0.5 mmHg). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.89; H, 7.40.

(*E*)-2-Methylhept-5-en-4-ol methoxyacetate (12a) was obtained from (*E*)-2-methylhept-5-en-4-ol and methoxyacetyl chloride in 95% yield as a clear oil: IR (neat oil) 1755, 965 cm^{-1}; ^1H NMR (500 MHz) δ 5.77 (m, 1 H), 5.38 (m, 2 H), 3.98 (s, 2 H), 3.44 (s, 3 H), 1.68 (d, J = 6.4 Hz, 3 H), 1.60 (m, 2 H), 1.39 (m, 1 H), 0.91 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 169.5, 129.6, 129.5, 74.1, 69.9, 59.2, 43.4, 24.4, 22.5, 22.3, 17.6. An analytical sample was prepared by bulb-to-bulb distillation (75 °C, 0.1 mmHg). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.91; H, 10.06. Found: C, 66.06; H, 9.97.

(*E*)-2-Methylhept-5-en-4-ol (phenylmethoxy)acetate (12b) was obtained from (*E*)-2-methylhept-5-en-4-ol and (phenylmethoxy)acetyl chloride in 98% yield as a clear oil: IR (neat oil) 1760, 970, cm^{-1}; ^1H NMR (250 MHz) δ 7.34 (m, 5 H), 5.75 (m, 2 H), 5.40 (m, 2 H), 4.60 (s, 2 H), 4.04 (s, 2 H), 1.68 (d, J = 6.0 Hz, 3 H), 1.60 (m, 2 H), 1.40 (m, 1 H), 0.91 (m, 6 H); ^{13}C NMR (62.9 MHz) δ 169.7, 137.3, 129.6, 128.6, 128.4, 128.0, 127.9, 74.1, 73.2, 67.4, 43.5, 24.5, 22.6, 22.5, 17.7. An analytical sample was prepared by bulb-to-bulb distillation (160 °C, 0.1 mmHg). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.87; H, 8.75. Found: C, 73.71; H, 8.60.

(*E*)-2-Methylhept-5-en-4-ol (4-methoxyphenoxy)acetate (12c) was obtained from (*E*)-2-methylhept-5-en-4-ol with (4-methoxyphenyl)acetyl chloride in 97% yield as a clear oil: IR (neat oil) 2955, 1757, 1508 cm^{-1}; ^1H NMR (500 MHz) δ 6.83 (m, 4 H), 5.75 (m, 1 H), 5.38 (m, 2 H), 4.53 (s, 2 H), 3.75 (s, 3 H), 1.68 (d, J = 7.8 Hz, 3 H), 1.55 (m, 2 H), 1.38 (m, 1 H), 0.88 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 168.5, 154.5, 152.1, 129.9, 129.4, 115.9, 114.6, 74.7, 66.5, 55.7, 43.4, 24.4, 22.6, 22.4, 17.6. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 0.1 mmHg). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.78; H, 8.45.

(*Z*)-2-Methylhept-5-en-4-ol (phenylmethoxy)acetate (13) was obtained from (*Z*)-2-methylhept-5-en-4-ol with (phenylmethoxy)acetyl chloride in quantitative yield as a clear oil: IR (neat oil) 1765, 1130 cm^{-1}; ^1H NMR (250 MHz) δ 7.30 (m, 5 H), 5.55 (m, 3 H), 4.61 (s, 2 H), 4.08 (s, 2 H), 1.77 (d, J = 6.0 Hz, 3 H), 1.63 (m, 2 H), 1.37 (m, 1 H), 0.95 (d, J = 5.1 Hz, 6 H); ^{13}C NMR (62.9 MHz) δ 169.5, 137.3, 129.1, 128.5, 128.4, 128.0, 127.9, 73.1, 69.1, 67.3, 43.6, 24.5, 22.7, 22.5, 13.4. An analytical sample was prepared by bulb-to-bulb distillation (160 °C, 0.1 mmHg). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.87; H, 8.75. Found: C, 72.96; H, 8.72.

(*Z*)-Dec-2-en-4-ol (phenylmethoxy)acetate (14) was obtained from (*Z*)-dec-2-en-4-ol and (phenylmethoxy)acetyl chloride in 95% yield as a clear oil: IR (neat oil) 1750, 1120 cm^{-1}; ^1H NMR (250 MHz) δ 7.42 (m, 5 H), 5.75 (m, 2 H), 5.42 (m, 1 H), 4.72 (s, 2 H), 4.15 (s, 2 H), 1.75 (dd, J = 7.2, 1.8 Hz, 3 H), 1.62 (m, 2 H), 1.30 (m, 8 H), 0.89 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (62.9 MHz) δ 169.6, 137.4, 128.9, 128.6, 128.4, 128.0, 127.9, 72.2, 70.7, 67.3, 34.6, 31.8, 29.1, 25.0, 22.6, 14.1, 13.5. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 0.1 mmHg). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.87; H, 9.46.

Rearrangement of Allylic Glycolates. General Procedure. Two general procedures were employed for enolate Claisen rearrangement of allylic glycolates. In the first (method A), enolate generation is achieved by addition of a standard (0.5 M) solution of lithium diisopropylamide (LDA) to a −78 °C solution (0.1–0.3 M) of the glycolate in THF. After 1–2 min, trimethylsilyl chloride (3 equiv) was added and the reaction mixture was allowed to warm slowly (≈1 h) to room temperature. In the second procedure (method B) a standard (0.5 M) solution of potassium hexamethyldisilazide (KHMDS) was added at −78 °C to a solution of glycolate (0.01–0.1 M) and trimethylsilyl chloride (3–4 equiv) in THF followed by slow (≈1 h) warming to 25 °C and workup. These procedures have been successfully executed on up to 100 mmol of glycolate. The following experimental procedures are representative:

Method A. Methyl (2*R,3*R**)-3-Methyl-2-(phenylmethoxy)hex-4-enoate (*syn*-22a).** To a solution of ester **9a** (1.10 g, 6.96 mmol) in THF (40 mL) at −78 °C was added LDA (17.6 mL, 0.5 M in THF, 8.80 mmol) over 30 s. The reaction was stirred 1.5 min and trimethylsilyl chloride (2.60 mL, 20.5 mmol) was added. The reaction was held at −78 °C for 10 min and then was allowed to warm to 25 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (8 mL). The mixture was acidified with 5% HCl (8 mL) and extracted with ether (3 × 25 mL). The organic fractions were treated with diazomethane, dried over $MgSO_4$, and chromatographed on silica gel (30:1 hexane/ether) to yield a 12.5:1 mixture of *syn*-**22a** and *anti*-**22a**, separable by GC, as a colorless oil (1.17 g, 98%). An analytical sample was prepared by HPLC and bulb-to-bulb distillation (50 °C, 0.1 mmHg): ^1H NMR (360 MHz) δ 5.50 (m, 1 H), 5.36 (m, 1 H), 3.73 (s, 3 H), 3.58 (d, J = 5.9 Hz, 1 H), 3.37 (s, 3 H), 2.53 (m, 1 H), 1.65 (d, J = 5.4 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 172.46, 131.67, 126.03, 85.14, 58.43, 51.43, 40.27, 17.82, 15.85. An analytical sample was prepared by HPLC followed by bulb-to-bulb distillation (50 °C, 0.1 mmHg). Anal. Calcd for $C_8H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.76; H, 9.50.

Method B. Methyl (2*R,3*S**)-3-Phenyl-2-(phenylmethoxy)pent-4-enoate (*anti*-17b).** To a solution of ester **6** (99 mg, 0.35 mmol) in THF (15 mL) at −78 °C was added trimethylsilyl chloride (0.19 mL, 1.47 mmol). The solution was stirred for 5 min and a solution of KHMDS (2.80 mL, 0.5 M in THF) was added rapidly by syringe. The reaction was stirred for 10 min at −78 °C and allowed to warm to 25 °C over 1 h. The reaction was quenched with saturated aqueous NH_4Cl (6 mL) and stirred overnight. The resulting mixture was partitioned between ether (12 mL) and 5% HCl (12 mL). The aqueous fraction was extracted with ether (3 × 10 mL) and the combined ether extracts were treated with excess diazomethane, dried over $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed on silica gel (10:1 hexane/ether) to yield a 20:1 mixture of *anti*-**17b** and *syn*-**17b** (86.4 mg, 83%) as a clear oil. An analytical sample of *anti*-**17b** was prepared by HPLC and bulb-to-bulb distillation (180 °C, 0.5 mmHg): IR ($CDCl_3$) 1745, 1205 cm^{-1}; ^1H NMR (250 MHz) δ 7.21 (m, 10 H), 6.25 (m, 1 H), 5.13 (m, 2 H), 4.67 (d, J = 12.2 Hz, 1 H), 4.36 (d, J = 12.2 Hz, 1 H), 4.18 (d, J = 5.5 Hz, 1 H), 3.80 (m, 1 H), 3.61 (s, 3 H); ^{13}C NMR δ 171.8, 140.0, 137.2, 136.3, 128.5, 128.2, 127.9, 127.8, 126.9, 117.6, 82.1, 72.8, 52.8, 51.7. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.12; H, 6.73.

Methyl (2*R,3*S**)-3-Methyl-2-(phenylmethoxy)hex-4-enoate (*syn*-22b).** Rearrangement of ester **9b** (method A) afforded a (40:1) mixture of *syn*-**22b** and *anti*-**22b** in 89% yield as a clear oil. An analytical sample of *syn*-**22b** was prepared by HPLC and bulb-to-bulb distillation (100 °C, 0.1 mmHg): IR (neat oil) 1750, 1200, cm^{-1}; ^1H NMR (250 MHz) δ 7.34 (m, 5 H), 5.47 (m, 1 H), 5.35 (m, 1 H), 4.68 (d, J = 11.9 Hz, 1 H), 4.38 (d, J = 11.9 Hz, 1 H), 3.75 (d, J = 6.1 Hz, 1 H), 3.71 (s, 3 H), 2.58 (m, 1 H), 1.63 (dd, J = 6.7, 1.2 Hz, 3 H), 1.06 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (90 MHz) δ 172.5, 137.5, 131.9, 128.3, 128.1, 127.9, 127.7, 126.1, 82.7, 72.5, 51.5, 40.4, 17.9, 16.1. Anal. Calcd for $C_{14}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 8.36.

Methyl (2*R,3*S**)-2-(4-Methoxyphenoxy)-3-methylhex-4-enoate (*syn*-22c).** Rearrangement of ester **9c** (method A) af-

(38) Prepared by Lindlar reduction of 3-(1,3-benzodioxol-5-yl)prop-2-yn-1-ol. Klemm, L. H.; Gopinath, K. W.; Hsu Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T. M. *Tetrahedron* **1966**, *22*, 1797.

(39) The stereochemical descriptors syn and anti refer to the relative orientation of substituents when the acyclic framework resulting from the electrocyclic event is depicted in an extended conformation. See: Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

forded a (12:1) mixture of *syn*-**22c** and *anti*-**22c** in 88% yield as a clear oil. An analytical sample of *syn*-**22c** was prepared by HPLC and bulb-to-bulb distillation (105 °C, 0.1 mmHg): IR (neat oil) 1760, 1500, 1220 cm^{-1}; ^1H NMR (250 MHz) δ 6.81 (m, 4 H), 5.49 (m, 2 H), 4.32 (d, J = 6.3 Hz, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 2.73 (m, 1 H), 1.66 (d, J = 5.4 Hz, 3 H), 1.16 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (62.9 MHz) δ 171.5, 154.4, 152.2, 131.2, 126.6, 116.4, 114.5, 82.0, 55.4, 51.6, 40.4, 17.8, 16.1. Anal. Calcd for $C_{14}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.33; H, 7.63.

Methyl (2*R,3*R**)-2-Methoxy-3-methylhex-4-enoate (*anti*-22a).** Rearrangement of ester **10a** (method A) afforded a (15:1) mixture of *anti*-**22a** and *syn*-**22a** in 94% yield as a clear oil. An analytical sample of *anti*-**22a** was prepared by HPLC and bulb-to-bulb distillation (50 °C, 0.1 mmHg): IR (neat oil) 1750, 1100, cm^{-1}; ^1H NMR (360 MHz) δ 5.44 (m, 2 H), 3.74 (s, 3 H), 3.62 (d, J = 4.9 Hz, 1 H), 3.39 (s, 3 H), 2.59 (m, 1 H), 1.65 (d, J = 4.9 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 172.4, 131.2, 126.2, 85.4, 58.8, 51.6, 40.2, 18.0, 16.9. Anal. Calcd for $C_8H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.87; H, 9.55.

Methyl (2*R,3*R**)-2-Methoxy-3-phenylpent-4-enoate (*syn*-17a).** Rearrangement of ester **5a** (method B) afforded *syn*-**17a** in 84% yield as a clear oil, which was homogeneous by HPLC: IR ($CDCl_3$) 1744, 1206 cm^{-1}; ^1H NMR (250 MHz) δ 7.26 (m, 5 H), 6.05 (m, 1 H), 5.12 (m, 2 H), 4.05 (d, J = 7.3 Hz, 1 H), 3.69 (m, 1 H), 3.67 (s, 3 H), 3.31 (s, 3 H); ^{13}C NMR δ 171.6, 139.5, 136.9, 128.3, 128.2, 126.8, 116.8, 84.5, 58.6, 53.1, 51.5. An analytical sample was prepared by bulb-to-bulb distillation (180 °C, 0.5 mmHg). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.94; H, 7.41.

Methyl (2*R,3*R**)-3-Phenyl-2-(phenylmethoxy)-pent-4-enoate (*syn*-17b).** Rearrangement of ester **5b** (method A) afforded *syn*-**17b** in 66% yield as a clear oil, homogeneous by HPLC: IR (neat oil) 1750, 1460, 1020 cm^{-1}; ^1H NMR (250 MHz) δ 7.22 (m, 10 H), 6.02 (m, 1 H), 5.07 (m, 2 H), 4.62 (d, J = 11.7 Hz, 1 H), 4.29 (d, J = 11.7 Hz, 1 H), 4.18 (d, J = 7.8 Hz, 1 H), 3.75 (t, J = 8.4 Hz, 1 H), 3.65 (s, 3 H); ^{13}C NMR (125.8 MHz) δ 171.7, 139.7, 137.1, 136.9, 128.5, 128.3, 128.1, 127.8, 127.6, 126.8, 117.0, 81.9, 72.6, 53.3, 51.5. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.2 mmHg). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.89; H, 6.77.

Methyl (2*R,3*R**)-2-Methoxy-3-phenylhex-4-enoate (*syn*-23).** Rearrangement of ester **11** (method B) afforded *syn*-**23** in 75% yield as a clear oil, which was homogeneous by HPLC: IR ($CDCl_3$) 1744, 1204 cm^{-1}; ^1H NMR (250 MHz) δ 7.17 (m, 5 H), 5.54 (m, 2 H), 3.92 (d, J = 7.5 Hz, 1 H), 3.60 (s, 3 H), 3.59 (m, 1 H), 3.21 (s, 3 H), 1.57 (d, J = 5.6 Hz, 3 H); ^{13}C NMR (90 MHz) δ 171.8, 140.4, 129.4, 128.2, 128.0, 127.8, 126.6, 84.8, 58.5, 52.3, 51.4, 17.8. An analytical sample was prepared by bulb-to-bulb distillation (200 °C, 0.5 mmHg). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.98; H, 7.93.

Methyl (2*R,3*R**)-3-(1,3-Benzodioxol-5-yl)-2-(phenylmethoxy)pent-4-enoate (*syn*-18).** Rearrangement of ester **7** (method B) afforded a (22:1) mixture of *syn*-**18** and *anti*-**18** in 82% yield as a clear oil. An analytical sample was prepared by HPLC and bulb-to-bulb distillation (180 °C, 0.5 mmHg): IR ($CDCl_3$) 1745, 1505, 1250 cm^{-1}; ^1H NMR (360 MHz) 7.17 (m, 5 H), 6.64 (m, 3 H), 5.90 (m, 1 H), 5.86 (s, 2 H), 5.02 (m, 2 H), 4.60 (d, J = 12.1 Hz, 1 H), 4.26 (d, J = 12.1 Hz, 1 H), 4.06 (d, J = 8.3 Hz, 1 H), 3.62 (m, 1 H), 3.61 (s, 3 H); ^{13}C NMR δ 171.7, 147.5, 146.4, 137.1, 133.5, 128.2, 127.9, 127.7, 121.7, 116.8, 108.9, 108.1, 100.7, 81.9, 72.7, 52.9, 51.6. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.58; H, 6.22. Found: C, 70.59; H, 6.22.

Methyl (2*R,3*S**)-3-[(1,3-Benzodioxol-5-yl)-phenyl]-2-(phenylmethoxy)pent-4-enoate (*anti*-18).** Rearrangement of ester 8 (method B) afforded a (8:1) mixture of *anti*-18 and *syn*-18 in 92% yield as a clear oil. An analytical sample was prepared by HPLC and bulb-to-bulb distillation (180 °C, 0.1 mmHg): IR ($CDCl_3$) 1745, 1505, 1490 cm^{-1}; ^1H NMR (360 MHz) δ 7.27 (m, 5 H), 6.73 (m, 3 H), 6.17 (m, 1 H), 5.93 (s, 2 H), 5.12 (m, 2 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.37 (d, J = 11.9 Hz, 1 H), 4.12 (d, J = 5.7 Hz, 1 H), 3.69 (m, 1 H), 3.64 (s, 3 H); ^{13}C NMR δ 171.7, 147.5, 146.4, 137.1, 136.3, 133.8, 128.2, 128.0, 127.8, 121.5, 117.4, 108.9, 108.1, 100.9, 82.2, 72.8, 52.4, 51.7. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.58; H, 5.92. Found: C, 70.41; H, 6.11.

Methyl (*E*)-(2*R,3*R**)-3,7-Dimethyl-2-methoxyoct-4-enoate (*syn*-24a).** Rearrangement of ester **12a** (method A) afforded *syn*-**24a** in 72% yield as a clear oil (62:1 with anti diastereomer by glass capillary GC): IR (neat oil) 1755, 1195, 970 cm^{-1}; ^1H NMR (250 MHz) δ 5.40 (m, 2 H), 3.73 (s, 3 H), 3.57 (d, J = 6.2 Hz, 1 H), 3.37 (s, 3 H), 2.55 (m, 1 H), 1.85 (t, J = 6.5 Hz, 2 H), 1.56 (m, 1 H), 1.04 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 173.0, 131.9, 130.4, 85.5, 58.5, 51.5, 41.9, 40.4, 28.4, 22.3, 22.2, 16.2. An analytical sample was prepared by bulb-to-bulb distillation (70 °C, 0.1 mmHg). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.72; H, 10.34. Found: C, 67.67; H, 10.25.

Methyl (*E*)-(2*R,3*S**)-3,7-dimethyl-2-(phenylmethoxy)-oct-4-enoate (*syn*-24b)** was prepared by rearrangement of ester **12b** (method A) and afforded *syn*-**24b** in 72% yield as a clear oil homogeneous by HPLC: IR (neat oil) 1755, 1205, 910, cm^{-1}; ^1H NMR (250 MHz) δ 7.32 (m, 5 H), 5.40 (m, 2 H), 4.67 (d, J = 11.7 Hz, 1 H), 4.38 (d, J = 11.7 Hz, 1 H), 3.75 (d, J = 6.6 Hz, 1 H), 3.69 (s, 3 H), 2.60 (m, 1 H), 1.85 (t, J = 6.6 Hz, 2 H) 1.56 (m, 1 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (62.9 MHz) δ 172.5, 137.5, 131.9, 130.4, 128.3, 127.9, 127.7, 82.8, 72.5, 51.5, 41.9, 40.5, 28.3, 22.2, 16.3. An analytical sample was prepared by bulb-to-bulb distillation (160 °C, 0.1 mmHg). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.46; H, 9.27.

Methyl (*E*)-(2*R,3*S**)-2-(4-Methoxyphenoxy)-3,7-dimethyloct-4-enoate (*syn*-24c).** Rearrangement of ester **12c** (method A) afforded *syn*-**24c** in 71% yield as a clear oil, homogeneous by HPLC: IR (neat oil) 1755, 1035 cm^{-1}; ^1H NMR (500 MHz) δ 6.82 (m, 4 H), 5.45 (m, 2 H), 4.32 (d, J = 6.4 Hz, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 2.75 (m, 1 H), 1.88 (t, J = 6.8 Hz, 2 H), 1.58 (m, 1 H), 1.18 (d, J = 7.0 Hz, 3 H), 0.86 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 171.7, 154.6, 152.5, 131.2, 131.1, 116.8, 114.8, 82.5, 55.7, 51.8, 41.9, 40.6, 28.4, 22.3, 22.2, 16.4. An analytical sample was prepared by bulb-to-bulb distillation (160 °C, 0.1 mmHg). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.46; H, 8.42.

Methyl (*E*)-(2*R,3*R**)-3-Methyl-2-(phenylmethoxy)undec-4-enoate (*anti*-24b).** Rearrangement of ester **14** (method A) afforded *anti*-**24b** in a 74% yield as a clear oil homogeneous by HPLC: IR (neat oil) 1755, 1205 cm^{-1}; ^1H NMR (250 MHz) δ 7.30 (m, 5 H), 5.42 (m, 2 H), 4.72 (d, J = 11.7 Hz, 1 H), 4.36 (d, J = 11.7 Hz, 1 H), 3.80 (d, J = 4.4 Hz, 1 H), 3.68 (s, 3 H), 2.62 (m, 1 H), 1.97 (m, 2 H), 1.26 (m, 10 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.88 (dis t, J = 5.1, 7.3 Hz, 3 H); ^{13}C NMR (62.9 MHz) δ 172.0, 137.5, 131.5, 130.1, 128.0, 127.7, 127.5, 82.3, 72.3, 51.2, 40.3, 32.3, 31.6, 29.3, 28.6, 22.4, 17.0, 13.9. An analytical sample was prepared by bulb-to-bulb distillation (160 °C, 0.1 mmHg). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.35; H, 9.30.

(*E*)-(2*R,3*R**)-3,7-Dimethyl-2-(phenylmethoxy)oct-4-enol (36).** To a solution of ester **13** (5.87 g, 24.7 mmol) in THF (660 mL) at −78 °C was added LDA (37.0 mmol in THF). After 2.5 min trimethylsilyl chloride (5.30 g, 49.0 mmol) was added over 2 min, stirred for 15 min, and allowed to stir at ambient temperature for 2 h. The reaction was then cooled to 0 °C and a solution of $LiAlH_4$ (2.80 g, 74.0 mmol) in THF (100 mL) was added. After 2 h the reaction was quenched by sequential addition of water (2.8 mL), 15% NaOH (2.8 mL), and water (8.4 mL). The mixture was filtered, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled (138–142 °C, 1.0 mmHg) to yield **36** (3.84 g, 60%) as a clear oil: IR (neat oil) 3400 (br), 1445, cm^{-1}; ^1H NMR (250 MHz) δ 7.30 (m, 5 H), 5.43 (m, 2 H), 4.60 (AB q, J = 27.0, 11.0 Hz, 2 H), 3.60 (m, 2 H), 3.38 (m, 1 H), 2.52 (m, 1 H), 2.10 (br s, 1 H), 1.89 (t, J = 7.0 Hz, 2 H), 1.62 (m, 1 H), 1.02 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 138.4, 132.7, 129.7, 128.3, 127.7, 127.6, 83.7, 72.4, 62.3, 42.0, 38.06, 28.4, 22.3, 22.2, 15.8. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.98. Found: C, 77.73; H, 10.08.

(*E*)-(2*R,3*R**)-3,7-Dimethyl-2-(phenylmethoxy)oct-4-enal (35).** To a solution of oxalyl chloride (4.36 mL, 50.3 mmol) in CH_2Cl_2 (150 mL) at −78 °C was added Me_2SO (7.10 mL, 100 mmol) over 1 min. A solution of **36** (4.00 g, 15.3 mmol) in CH_2Cl_2 (10 mL) was added to the reaction over 1.5 min. After 15 min triethylamine (10.14 mL, 76.2 mmol) was added and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 1.5 h, quenched with saturated aqueous NH_4Cl (50 mL), and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic fractions were washed with 20-mL portions of H_2O, 5% HCl, saturated $NaHCO_3$, and H_2O. The solution was dried ($MgSO_4$), the solvent evaporated in vacuo, and the residue was chromato-

graphed on silica gel (15:1 hexane/ethyl acetate) to yield **35** (3.97 g, 98%) as a clear oil: IR (neat oil) 1735, 1380, 970 cm^{-1}; ^1H NMR (250 MHz) δ 9.61 (d, J = 3.0 Hz, 1 H), 7.30 (m, 5 H), 5.43 (m, 2 H), 4.68 (d, J = 10.6 Hz, 1 H), 4.51 (d, J = 10.6 Hz, 1 H), 3.60 (dd, J = 4.7, 2.6 Hz, 1 H), 2.62 (m, 1 H), 1.88 (m, 2 H), 1.58 (m, 1 H), 1.08, (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 204.2, 137.4, 130.9, 130.7, 128.4, 127.9, 87.0, 72.8, 41.8, 39.1, 28.3, 22.2, 22.2, 16.9. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 0.1 mmHg). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.34; H, 9.29. Found: C, 78.21; H, 9.39.

(2*E*,7*E*)-(4*R,5*R**,6*R**)-6,10-Dimethyl-5-(phenylmethoxy)undeca-2,7-dien-4-ol (37).** To a suspension of Li shot (0.280 g, 40 mmol, 5% Na) in ether (100 mL) under argon atmosphere at 0 °C was added (*E*)-1-bromopropene (2.44 g, 20 mmol). The reaction was stirred at 0 °C for 2 h and added to a suspension of CuI (1.96 g, 10.3 mmol) in ether (100 mL) at −78 °C. The resulting mixture was added to a solution of **35** (0.657 g, 2.53 mmol) and $MgBr_2 \cdot Et_2O$ (0.327 g, 1.27 mmol). The reaction was stirred at −78 °C for 1 h, allowed to warm to ambient temperature, quenched with saturated NH_4Cl (50 mL), filtered, and extracted with ether (3 × 50 mL). The organic fractions were dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (30:1 hexane/ethyl acetate) to yield **37** (0.645 g, 84%) as a clear oil: IR (neat oil) 3450 (br), 1185, 960, cm^{-1}; ^1H NMR (250 MHz) δ 7.35 (m, 5 H), 5.73 (m, 1 H), 5.44 (m, 3 H), 4.67 (AB q, J = 25.8, 11.0 Hz, 2 H), 4.05 (m, 1 H), 3.18 (dd, J = 6.5, 3.9 Hz, 1 H), 2.48 (m, 2 H), 1.88 (t, J = 6.3 Hz, 2 H), 1.72 (dd, J = 6.0, 0.9 Hz, 3 H), 1.58 (m, 1 H), 1.11 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 138.6, 132.7, 131.1, 129.8, 128.4, 128.2, 127.8, 127.6, 87.2, 75.1, 73.6, 42.2, 39.1, 28.6, 22.4, 22.3, 18.4, 17.9. An analytical sample was prepared by bulb-to-bulb distillation (210 °C, 0.1 mmHg). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.29; H, 9.98.

(2*E*,7*E*)-(4*R,5*R**,6*R**)-6,10-Dimethyl-5-(phenylmethoxy)undeca-2,7-dien-4-ol (Phenylmethoxy)acetate (38).** To a solution of **37** (0.645 g, 2.14 mmol) and pyridine (0.186 g, 2.35 mmol) in THF (50 mL) at 0 °C was added a solution of (phenylmethoxy)acetyl chloride (0.423 g, 2.29 mmol) in THF (10 mL), and the resulting mixture allowed to warm to ambient temperature overnight. The reaction was filtered, washed with 10 mL of H_2O, and extracted with ether (3 × 15 mL). The organic fractions were combined, dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield **38** (0.937 g, 97%) as a clear oil: IR (neat oil) 1755, 1195, 965 cm^{-1}; ^1H NMR (250 MHz) δ 7.27 (m, 10 H), 5.82 (m, 1 H), 5.42 (m, 4 H), 4.64 (AB q, J = 19.8, 11.4 Hz, 2 H), 4.52 (AB q, J = 21.8, 13.0 Hz, 2 H), 3.97 (AB q, J =28.9, 16.2 Hz, 2 H), 3.30 (dd, J = 7.8, 4.6 Hz, 1 H), 2.40 (m, 1 H), 1.89 (m, 2 H), 1.69 (dd, J = 6.8, 1.6 Hz, 3 H) 1.60 (m, 1 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.88 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 169.6, 139.0, 137.5, 132.0, 131.8, 130.4, 128.8 128.6, 128.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 126.5, 84.9, 77.7, 75.6, 73.4, 67.6, 42.2, 39.2, 28.7, 22.6, 22.4, 18.9, 18.1.

Methyl (4*E*,8*E*)-(2*S,3*R**,6*R**,7*R**)-2,6-Bis(phenylmethoxy)-3,7,11-trimethyldodeca-4,8-dienoate (39).** To a solution of **38** (0.648 g, 1.44 mmol) in THF (50 mL) at −78 °C was added LDA (2.20 mmol) over 2.5 min. After 2 min, trimethylsilyl chloride (0.48 g, 3.78 mmol) was added. The reaction was stirred at −78 °C for 30 min and allowed to warm at room temperature. After 1 h the reaction was quenched with 10 mL of saturated aqueous NH_4Cl and extracted with ether (3 × 25 mL). The combined organic fractions were treated with excess diazomethane, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (30:1 hexane/ethyl acetate) to yield **39** (0.486 g, 73%) as a clear oil: IR (neat oil) 1750 cm^{-1}; ^1H NMR (500 MHz) δ 7.28 (m, 10 H), 5.56 (m, 1 H), 5.40 (m, 3 H), 4.69 (d, J = 12.0 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.39 (d, J = 12.0 Hz, 1 H), 4.26 (d, J = 12.0 Hz, 1 H), 3.83 (d, J = 6.0 Hz, 1 H), 3.69 (s, 3 H), 3.47 (t, J = 6.0 Hz, 1 H), 2.73 (m, 1 H), 2.32 (m, 1 H), 1.88 (m, 2 H), 1.58 (m, 1 H), 1.10 (d, J = 6.0 Hz, 3 H), 0.95 (d, J = 6.0 Hz, 3 H), 0.88 (d, J = 6.0 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 172.2, 139.0, 137.4, 135.1, 133.6, 130.2, 129.1, 128.3, 128.1, 128.0, 127.8, 127.6, 127.2, 83.8, 82.5, 72.6, 69.7, 51.7, 42.1, 41.7, 40.3, 28.5, 22.3, 22.3, 16.7, 16.1. An analytical sample was prepared by bulb-to-bulb distillation (250 °C, 0.1 mmHg). Anal. Calcd for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.63; H, 8.73.

Methyl (2*R,3*S**,6*R**,7*S**)-2,6-Dihydroxy-3,7,11-trimethyldodecanoate (40).** A solution of **39** (22 mg, 0.05 mmol) containing 10% Pd/C (2 mg) in methanol (5 mL) was stirred under an atmosphere of hydrogen for 2 days. The reaction was filtered and concentrated, and the residue was chromatographed on silica gel (5:1 hexane/ethyl acetate) to yield **40** (11.5 mg 81%) as a clear oil: IR (neat oil) 3440 (br), 1740, 1220, cm^{-1}; ^1H NMR (250 MHz) δ 4.20 (br s, 1 H), 3.78 (s, 3 H), 3.42 (m, 1 H), 2.89 (br s, 1 H), 2.01–1.05 (br m, 13 H), 0.87 (m, 12 H); ^{13}C NMR (125.8 MHz) δ 175.5, 76.2, 72.9, 52.5, 39.3, 38.9, 36.8, 32.1, 30.8, 29.6, 27.9, 25.0, 22.7, 22.5, 15.3, 13.8.

(3*R,7*R**)-3,7,11-Trimethyldodecan-1-ol (30).** To a solution of **40** (58.2 mg, 0.202 mmol) and pyridine (1 mL) in THF (25 mL) was added methanesulfonyl chloride (250 mg, 1.70 mmol). After 12 h the reaction was filtered, washed with $NaHCO_3$ (5 mL), and dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield the dimesylate (70.8 mg, 79%) as a clear oil: ^1H NMR (500 MHz) δ 5.04 (m, 1 H), 4.64 (m, 1 H), 3.81 (s, 3 H), 3.15 (s, 3 H), 3.02 (s, 3 H), 2.19 (m, 1 H), 1.9 (m, 1 H), 1.70 (m, 2 H), 1.53 (m, 1 H), 1.40, (m, 4 Hz), 1.20 (m, 6 H), 0.97 (dd, J = 8.9, 8.5 Hz, 6 H), 0.88 (d, J = 6.7 Hz, 6 H); ^{13}C NMR (125.8 MHz) δ 169.3, 87.0, 80.1, 52.6, 39.2, 38.7, 36.9, 35.5, 32.7, 28.7, 28.0, 27.4, 25.0, 22.7, 22.7, 22.6, 14.5, 14.5.

To a solution of $LiAlH_4$ (1.7 mg, 0.04 mmol) in ether (10 mL) at 0 °C was added a solution of dimesylate in ether (1 mL). The reaction was stirred at 25 °C for 2 h, then quenched with water (0.5 mL), filtered, and dried over ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and treated with MCPBA (4.3 mg, 0.03 mmol) overnight. The reaction was quenched with 10% aqueous Na_2SO_3 (1 mL) and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (15:1 hexane/ethyl acetate) to yield alcohol **30** (3.3 mg, 59%), as a pale oil: IR (neat oil) 3350 (br), 1380, 1155 cm^{-1}; ^1H NMR (250 MHz) δ 3.68 (m, 2 H), 1.70–1.02 (m, 18 H), 0.92–0.80 (m, 12 H); ^{13}C NMR (125.8 MHz) δ 61.3, 40.1, 39.4, 37.6, 37.4, 37.3, 32.9, 29.7, 28.0, 24.8, 24.4, 22.7, 22.6, 19.7. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 0.1 mmHg). Anal. Calcd for $C_{15}H_{32}O$: C, 78.87; H, 14.12. Found: C, 78.90; H, 14.17.

(4*E*)-(2*S,3*S**)-3-Methyl-2-(phenylmethoxy)undec-4-enal (43).** To a solution of ester **14** (10.20 g, 33.5 mmol) in THF (400 mL) at −78 °C was added LDA (50.0 mmol, 0.5 M in THF) over 2 min. After 4 min, trimethylsilyl chloride (7.20 g, 100 mmol) was added over a 1-min period. The reaction was held at −78 °C for 15 min and then was allowed to warm to ambient temperature. After 1.5 h, the reaction was cooled to 0 °C and a solution of $LiAlH_4$ (3.80 g, 100 mmol) in THF (50 mL) was added over 20 min. The reaction was quenched by sequential addition of water (4 mL), 15% NaOH (4 mL), and water (12 mL), filtered, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (30:1 hexane/ethyl acetate) to yield the alcohol (6.80 g, 70%) as a clear oil: IR (neat oil) 3400 (br), 975 cm^{-1}; ^1H NMR (500 MHz) δ 7.32 (m, 5 H), 5.47 (m, 1 H), 5.40 (m, 1 H), 4.65 (d, J = 11.5 Hz, 1 H), 4.53 (d, J = 11.5 Hz, 1 H), 3.60 (m, 2 H), 3.38 (m, 1 H), 2.49 (m, 1 H), 2.05 (br s, 1 H), 1.98 (q, J = 6.7 Hz, 2 H), 1.28 (m, 8 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.87 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 138.6, 131.7, 131.1, 128.4, 127.8, 127.7, 83.8, 72.5, 62.4, 38.1, 32.7, 31.8, 29.5, 28.9, 22.7, 15.9, 14.1. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 0.1 mmHg). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.72; H, 10.46.

To a solution of oxalyl chloride (1.43 g, 22.7 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added Me_2SO (1.77 g, 22.7 mmol). After 2.5 min a solution of the alcohol prepared above (1.0 mg, 3.5 mmol) in CH_2Cl_2 (2 mL) was added. After 15 min triethylamine (2.74 mL) was added and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 1 h and quenched by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield **43** (0.978 mg, 99%) as a pale oil: IR (neat oil) 1730, 970 cm^{-1}; ^1H NMR (500 MHz) δ 9.60 (d, J = 2.4 Hz, 1 H), 7.34 (m, 5 H), 5.44 (m, 2 H), 4.69 (d, J = 11.9 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 3.59 (dd, J = 4.9, 2.4 Hz, 1 H), 2.62 (m, 1 H), 1.98 (q, J = 6.7 Hz,

2 H), 1.30 (m, 8 H), 1.07 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 204.1 137.5, 132.3, 129.6, 128.4, 127.9, 87.1, 72.9, 39.1, 32.5, 31.7, 29.3, 28.8, 22.6, 16.8, 14.1.

(2*E*,7*E*)-(4*R,5*R**,6*R**)-6-Methyl-5-(phenylmethoxy)tetradeca-2,7-dien-4-ol (44).** To a suspension of Li shot (49 mg, 6.9 mmol) in ether (25 mL) under an argon atmosphere was added (*E*)-1-bromo-1-propene (420 mg, 3.4 mmol) over 2 min. After 2 h at 0 °C, the reaction was cooled to −78 °C, and a solution of $MgBr_2{\cdot}Et_2O$ (895 mg, 3.4 mmol) in 3:1 (v:v) ether/benzene (8 mL) was added. After 10 min the reaction was added to a solution of aldehyde **43** (100 mg, 0.34 mmol) in ether (50 mL). The reaction was warmed to ambient temperature after 30 min and quenched with 20 mL of saturated aqueous NH_4Cl. The aqueous fraction was extracted with ether (3 × 25 mL) and the combined organic fractions were dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel (30:1 hexane/ethyl acetate) to yield **44** (82.4 mg, 72%) as a clear oil: IR (neat oil) 3450 (br), 1450, 1375 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.35 (m, 5 H), 5.70 (m, 1 H), 5.43 (m, 3 H), 4.67 (AB q, J = 26.0, 11.0 Hz, 2 H), 4.05 (m, 1 H), 3.18 (dd, J = 6.5, 3.7 Hz, 1 H), 2.42 (m, 2 H), 1.9 (m, 2 H), 1.72 (dd, J = 6.5, 0.9 Hz, 3 H), 1.29 (m, 8 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.89 (t, J = 6.2 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 138.4, 131.3, 130.8, 130.8, 128.6, 128.4, 127.8, 127.7, 87.0, 75.1, 73.5, 38.9, 32.7, 31.8, 29.6, 28.9, 22.7, 18.3, 17.9, 14.1. An analytical sample was prepared by bulb-to-bulb distillation (180 °C, 0.1 mmHg). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.36. Found: C, 80.13; H, 10.26.

(2*E*,7*E*)-(4*S,5*S**,6*S**)-6-Methyl-5-(phenylmethoxy)tetradeca-2,7-dien-4-ol Methoxyacetate (45).** To a solution of **44** (0.850 mg, 2.58 mmol) and pyridine (0.305 mg, 3.86 mmol) in THF (50 mL) at 0 °C was added a solution of methoxyacetyl chloride (0.418 mg, 3.86 mmol) in THF (50 mL). After 1 h the reaction was filtered, washed with 1% $NaHCO_3$ (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield **45** (0.940 mg, 91%) as a pale, viscous oil: IR (neat oil) 1755, 1195, 1130 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.38 (m, 5 H), 5.79 (m, 1 H), 5.41 (m, 4 H), 4.66 (AB q, J = 23.6, 11.4 Hz, 2 H), 3.94 (AB q, J = 42.0, 15.8 Hz, 2 H), 3.35 (s, 3 H), 3.31 (m, 1 H), 2.36 (m, 1 H), 1.98 (m, 2 H), 1.68 (d, J = 6.3 Hz, 3 H), 1.28 (m, 8 H), 1.05 (d, J = 6.7 Hz, 3 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 169.3, 138.8, 131.6, 130.6, 128.2, 127.4, 127.4, 126.2, 84.7, 77.4, 75.1, 69.9, 59.2, 38.9, 32.7, 31.8, 29.5, 28.9, 22.7, 18.6, 17.9, 14.1. An analytical sample was prepared bulb-to-bulb distillation (160 °C, 0.1 mmHg). Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.58; H, 9.51. Found: C, 74.70; H, 9.54.

Methyl (4*E*,8*E*)-(2*R,3*S**,6*S**,7*S**)-3,7-Dimethyl-2-methoxy-6-(phenylmethoxy)pentadeca-4,8-dienoate (46).** To a solution of **45** (1.04 g, 2.59 mmol) in THF (200 mL) at −78 °C was added LDA (3.88 mmol in THF) over 2.5 min. After 5 min, trimethylsilyl chloride (0.558 g, 5.2 mmol) was added, and the reaction was held at −78 °C for 15 min and then allowed to warm to ambient temperature. After 1.5 h the reaction was quenched with saturated aqueous NH_4Cl (45 mL). The aqueous fraction was extracted with ether (3 × 40 mL) and the combined organic fractions were treated with diazomethane, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on silica gel (30:1 hexane/ethyl acetate) to yield **46** (0.843 g, 78%) as a clear oil: IR (neat oil) 1755, 1195 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.30 (m, 5 H), 5.48 (m, 4 H), 4.56 (d, J = 12.5 Hz, 1 H), 4.32 (d, J = 12.5 Hz, 1 H), 3.72 (s, 3 H), 3.63 (d, J = 6.9 Hz, 1 H), 3.47 (dd, J = 7.7, 6.9 Hz, 1 H), 3.38 (s, 3 H), 2.68 (m, 1 H), 2.30 (m, 1 H), 2.00 (m, 2 H), 1.27 (m, 8 H), 1.07 (d, J = 6.9 Hz 3 H), 0.93 (d, J = 7.2 Hz, 3 H), 0.88 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (90 MHz) δ 172.13, 139.30, 135.12, 132.6, 130.6, 130.3, 128.2, 127.7, 127.2, 85.2, 84.0, 69.9, 58.6, 51.6, 41.7, 40.1, 32.8, 31.9, 29.7, 28.9, 22.7, 16.5, 15.8, 14.1. An analytical sample was prepared by bulb-to-bulb distillation (175 °C, 0.1 mmHg). Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.67. Found: C, 75.08; H, 9.71.

Methyl (2*R,3*S**,6*R**,7*S**)-3-7-Dimethyl-6-hydroxy-2-methoxypentadecanoate (47).** To a solution of **46** (159 mg, 0.38 mmol) in ethanol (50 mL) was added 10% Pd/C (10 mg) and the reaction was stirred under an atmosphere of hydrogen gas for 2 h. The reaction mixture was filtered and concentrated in vacuo. The residue was chromatographed on silica gel (10:1 hexane/ethyl acetate) to yield **47** (105 mg, 83%) as a viscous oil: IR (neat oil) 1755, 1195 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.76 (s, 3 H), 3.68 (d, J = 4.2 Hz, 1 H), 3.42 (m, 1 H), 3.38 (s, 3 H), 1.92 (m, 1 H), 1.67 (m, 1 H), 1.52 (m, 2 H), 1.28 (m, 16 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.88 (m, 6 H); ^{13}C NMR (125.8 MHz) δ 173.0, 84.0, 76.3, 58.7, 51.7, 38.8, 36.7, 31.9, 31.8, 31.0, 30.0, 29.6, 29.6, 29.3, 27.3, 22.7, 15.4, 14.8, 14.1.

(2*R,3*S**,6*R**,7*S**)-3,7-Dimethyl-2-methoxypentadecane-1,6-diol (48).** To a solution of **47** (105 mg, 0.32 mmol) in ether (2 mL) was added $LiAlH_4$ (15 mg, 0.38 mmol) in ether (10 mL). After 30 min the reaction was quenched with water (0.5 mL), filtered, and concentrated in vacuo. The residual oil was chromatographed on silica gel (1:1 hexane/ethyl acetate) to yield diol **48** (85.4 mg, 94%) as a clear oil: IR (neat oil) 3400 (br), 1095 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.63 (m, 3 H), 3.43 (s, 3 H), 3.40 (m, 2 H), 3.13 (m, 1 H), 1.75 (m, 1 H), 1.52 (m, 1 H), 1.41 (m, 1 H), 1.27 (m, 17 H), 1.07 (m, 1 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.88 (m, 6 H); ^{13}C NMR (125.8 MHz) δ 85.9, 76.6, 62.0, 58.3, 38.8, 34.3, 31.9, 31.8, 31.5, 30.0, 29.6, 29.3, 29.0, 27.4, 22.7, 15.5, 15.4, 14.1. Anal. Calcd for $C_{19}H_{40}O_3$: C, 71.47; H, 12.66. Found: C, 71.37; H, 12.64.

(2*R,3*R**,7*R**)-3,7-Dimethyl-2-methoxypentadecane (49).** To a solution of **48** (37 mg, 0.12 mmol) in pyridine (3 mL) was added DMAP (15 mg, 0.12 mmol) and *p*-toluenesulfonyl chloride (47 mg, 0.25 mmol). After 3 h the reaction was diluted with ether (2 mL), filtered, concentrated in vacuo, and chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield the ditosylate as a clear oil. This oil was dissolved in THF (1 mL) and added to a solution of $LiAlH_4$ (8.0 mg, 0.213 mmol) in THF (3 mL) and the resulting mixture was stirred at reflux for 2.5 h. The reaction was quenched with water (20 μL), filtered, concentrated in vacuo, and chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield **49** (21 mg, 66%) as a colorless oil: IR (neat oil) 2960 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.31 (s, 3 H), 3.16 (m, 1 H), 1.56 (m, 2 H), 1.30 (m, 20 H), 1.06 (d, J = 6.2 Hz, 3 H), 0.86 (m, 9 H); ^{13}C NMR (125.8 MHz) δ 80.8, 56.4, 37.8, 37.5, 37.1, 32.8, 32.3, 32.0, 30.1, 29.7, 29.4, 27.1, 24.9, 22.7, 19.8, 15.4, 15.2, 14.1. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 0.1 mmHg). Anal. Calcd for $C_{18}H_{38}O$: C, 79.93; H, 14.16. Found: C, 80.13; H, 14.19.

(±)-(2*R,3*R**,7*R**)-3,7-Dimethylpentadecan-2-ol (42).** To a solution of **49** (11 mg, 0.04 mmol) and NaI (7 mg, 0.04 mmol) in CH_3CN (5 mL) was added a solution of trimethylsilyl chloride (5 mg, 0.04 mmol) in CH_3CN (1 mL). After 6 h the reaction was quenched by addition of methanol (1 mL) and water (1 mL). The mixture was extracted with ether (4 × 3 mL) and the combined organic fractions were washed with Na_2SO_3 solution (5 mL), dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield **42** (10.0 mg, 99%) as a clear oil: IR (neat oil) 3350, 1460 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.71 (m, 1 H), 1.00–1.52 (m, 26 H), 0.87 (m, 9 H); ^{13}C NMR (125.8 MHz) δ 71.4, 39.9, 37.4, 37.0, 33.1, 32.8, 31.9, 30.0, 29.7, 29.4, 27.1, 24.8, 22.7, 20.4, 19.8, 14.2, 14.1.

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Registry No. **3a**, 87763-61-9; **3b**, 87763-62-0; **4a**, 87763-67-5; **4b**, 87763-68-6; **5a**, 87763-61-9; **5b**, 89091-59-8; **6**, 109087-69-6; **7**, 109087-70-9; **8**, 109087-71-0; (±)-**9a**, 109087-72-1; (±)-**9b**, 109087-73-2; (±)-**9c**, 109087-74-3; (±)-**10a**, 109087-75-4; (±)-**10b**, 109087-76-5; (±)-**11**, 109087-77-6; (±)-**12a**, 109087-78-7; (±)-**12b**, 109087-79-8; (±)-**12c**, 109087-80-1; (±)-**13**, 102616-10-4; (±)-**14**, 102616-19-3; (±)-**14**-ol, 109087-99-2; **15**, 109087-81-2; (±)-*syn*-**16a**, 87763-64-2; (±)-*anti*-**16a**, 87763-70-0; (±)-*syn*-**16b**, 87763-65-3; (±)-*anti*-**16b**, 87763-71-1; (±)-*syn*-**17a**, 109087-82-3; (±)-*syn*-**17b**, 109087-83-4; (±)-*anti*-**17b**, 109087-84-5; (±)-*syn*-**18**, 109087-85-6; (±)-*anti*-**18**, 109087-86-7; (±)-*syn*-**22a**, 109087-87-8; (±)-*anti*-**22a**, 109087-88-9; (±)-*syn*-**22b**, 109087-89-0; (±)-*syn*-**22c**, 109087-90-3; (±)-*anti*-**22c**, 109087-91-4; (±)-*syn*-**23**, 109087-92-5; (±)-*syn*-**24a**, 109087-93-6; (±)-*syn*-**24b**, 109087-94-7; (±)-*syn*-**24c**, 109087-95-8; (±)-*anti*-**24b**, 109087-96-9; (±)-*anti*-**25**, 102616-20-6; (±)-*anti*-**26**, 109214-85-9; (±)-**30**, 87247-04-9; (±)-**35**, 102616-12-6; (±)-**36**, 102616-11-5; (±)-**37**, 102616-13-7; (±)-**38**, 102616-14-8; (±)-**39**, 102616-15-9; (±)-**40**, 102616-17-1; (±)-**40** (dimesylate), 109087-98-1; (±)-**41**, 102616-16-0; (±)-**42**, 102680-34-2; (±)-**43**, 102616-21-7;

(±)-44, 102616-22-8; (±)-45, 102616-23-9; (±)-46, 102616-24-0; (±)-47, 109088-00-8; (±)-48, 109088-01-9; (±)-48 (ditosylate), 109088-02-0; (±)-49, 109088-03-1; (±)-pent-3-en-2-ol, 42569-16-4; [4-methoxyphenoxy]acetyl chloride, 42082-29-1; methoxyacetyl chloride, 38870-89-2; benzyloxyacetyl chloride, 19810-31-2; (±)-(Z)-pent-3-en-2-ol, 60102-80-9; (E)-cinnamyl alcohol, 4407-36-7; (Z)-cinnamyl alcohol, 4510-34-3; (E)-3-(1,3-benzodioxol-5-yl)-prop-2-en-1-ol, 58095-76-4; (Z)-3-(1,3-benzodioxol-5-yl)prop-2-en-1-ol, 90359-53-8; (±)-(E)-1-methyl-3-phenylprop-2-en-1-ol, 84519-62-0; (±)-(E)-2-methylhept-5-en-4-ol, 109214-86-0; (±)-(Z)-2-methylhept-5-en-4-ol, 64727-70-4; (±)-(Z)-dec-2-en-4-ol, 109087-97-0; (E)-1-bromopropene, 590-15-8.

Copper(I)-Activated Addition of Grignard Reagents to Nitriles. Synthesis of Ketimines, Ketones, and Amines[1]

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The nucleophilic addition of Grignard reagents to nitriles, especially when using sterically demanding components, is effectively catalyzed by copper(I) salts. Alkyl and aromatic nitriles and a selection of Grignard reagents were employed to prepare sterically hindered ketimines after addition, ketones after a tandem addition–hydrolysis procedure, and branched primary amines after a tandem addition–reduction sequence.

Recently we described a convenient synthesis of branched primary amines using a tandem addition–reduction procedure.[3] Lithium–ammonia reduction was used in situ to reduce ketimines, prepared by addition of Grignard reagents to nitriles. In that study we noted—to our chagrin—that the addition of Grignard reagents to nitriles can be slow and even useless, particularly when the components are sterically hindered. Although the addition of Grignard reagents to nitriles has been known for a long time,[4] synthetically useful preparations using bulky reactants usually required harsh conditions such as refluxing in high boiling solvents (toluene,[5] isoamyl ether,[6] etc.) for extended periods or required large excesses of the Grignard reagent.[5a,b,d]

Early in the tandem addition–reduction study,[3] we realized that the addition of certain Grignard reagents to certain nitriles was slow and varied drastically with the reacting species. Consequently, it was essential to monitor (GLC) the addition step for completeness before proceeding with the reduction sequence.[7] One of the first problems arose with the attempted addition of bulky *tert*-butylmagnesium chloride to benzonitrile. After 1 h in refluxing THF, no ketimine product **1a** could be detected, and after 14 h only 8% was present (see Table I).

Table I. Ketimine 1a from *tert*-Butylmagnesium Chloride and Benzonitrile

	yield,[b] %	
reactn time,[a] h	no CuBr	cat. CuBr[c]
1	0	83
2	1	92
3	2	96
14	8	99

[a] Reaction time in refluxing THF using a 1:1.1 mol ratio of nitrile to Grignard reagent. [b] Percent formation of **1a** relative to unreacted benzonitrile was determined by GLC. [c] Two mole percent of cuprous bromide was immediately added after mixing the reactants, and then the mixture was quickly heated to reflux.

Obviously an activator was required if this nucleophilic addition was to be a synthetically useful reaction.[8] Since copper(I) in catalytic amounts is a known activator of certain Grignard reactions[9]—first noted by Kharasch and Tawney in the cuprous ion catalyzed conjugate addition of organomagnesium compounds to enones[10]—the above reaction was repeated with 2 mol % of CuBr. After only 1 h an 83% yield (GLC) of ketimine **1a** was realized, and the addition was essentially complete after 3–4 h in refluxing THF (see Table I). Clearly copper(I) had a dramatic activating effect.

This reaction between *tert*-butylmagnesium chloride and benzonitrile is now synthetically viable. For example, if the copper-activated addition reaction was worked up after

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