Ministry of Education, Science, and Culture and also by Foundation "Hattori Hokokai" and "Asahi Glass Foundation". Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining ^{13}C-NMR spectra on a Brucker AM-600 spectrometer and mass spectra on a JEOL JMS-DX303 spectrometer.

Supplementary Material Available: ^{1}H NMR spectra of $3H_2$, $4H_2$, and 8 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Investigation of a Model for 1,2-Asymmetric Induction in Reactions of α-Carbalkoxy Radicals: A Stereochemical Comparison of Reactions of α-Carbalkoxy Radicals and Ester Enolates

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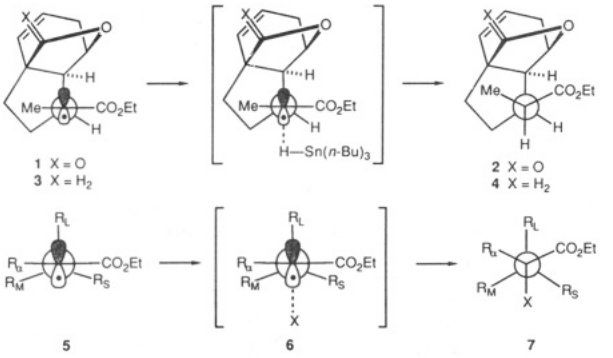
Received March 26, 1992

The stereochemical course of reductions and allylations of α-carbalkoxy radicals with chiral centers at the β-position are reported. Radicals without polar substituents, with alkoxyl or acetoxyl groups, and with hydroxyl groups at the β-position were examined. Reactions showed selectivities ranging from low (50:50) to high (99:1). The results are discussed in terms of transition-state models that emphasize the importance of (1) allylic conformational analysis (minimization of $A^{1,3}$ and $A^{1,2}$ strain), (2) torisonal strain (minimization of eclipsed interactions), and (3) stereoelectronic effects.

Introduction

Asymmetric stereoselection in free-radical reactions is a topic of current interest. For example, notable advances toward controlling absolute stereochemistry in radical additions to α,β-unsaturated amides and esters have been reported by the groups of Porter, Giese, and Curran.[1] High levels of asymmetric induction have also been observed by Hamon and Crich in reactions between α-carbalkoxy radicals and trialkyltin hydrides, allylic stannanes, and thiopyridones.[2] Another area of activity has been the development of reactions in which asymmetry at the β-position of an α-carbalkoxy radical influences the stereochemical course of an intermolecular reaction (1,2-asymmetric induction). For example, the Guindon group has reported reductions and allylations of β-alkoxy-α-carbalkoxy radicals that proceed with high diastereoselectivity.[3,4] Our own efforts, which have focused on the 1,2-symmetric induction problem, were stimulated by an observation recorded while undertaking a total synthesis of pleurotin. We discovered that radical **1** was reduced by tri-*n*-butyltin hydride to afford **2** with 16:1 diastereoselectivity.[5] We later noted that radical **3** was also reduced to **4** with 10:1 diastereoselectivity.[6] We rationalized these observations using the model set forth in Scheme I.[6] This model has the following features: (1) We assumed that the α-carbalkoxy radical was delocalized and thus subject to the conformational analysis usually applied to allylic systems. This assumption is supported by C_α—C(=O) rotational barriers reported for α-carbalkoxy and α-keto radicals.[7] (2) We suggested that the conformation leading to the lowest energy transition state was that in which $A^{(1,3)}$ interactions were minimized (H_β vs OEt or O•) and the largest allylic substituent was orthogonal to the π-bond. Placing the largest substituent orthogonal to the π-bond also minimized $A^{(1,2)}$ interactions. This suggestion seemed reasonable based on the role played by allylic strain in a variety of diastereoselective processes.[8,9] (3) We suggested

Scheme I



(1) (a) For a recent overview of progress in the area of acyclic stereocontrol in free-radical reactions, including a discussion of 1,2-asymmetric induction, see: Curran, D. P.; Giese, B.; Porter, N. A. *Acc. Chem. Res.* **1991**, 296. (b) Also see: Porter, N. A.; Lacher, B.; Chang, V. H.; Magnin, D. R.; *J. Am. Chem. Soc.* **1989**, *111*, 8309. Giese, B.; Zehnder, M.; Roth, M.; Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-B. *J. Am. Chem. Soc.* **1990**, *112*, 6741. Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, 1679. Porter, N. A.; Wu, W.-X.; McPhail, A. T. *Tetrahedron Lett.* **1991**, 707. Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002.

(2) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, 4205. Hamon, D. P. G.; Massey-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 332. Hamon, D. P. G.; Razzino, P.; Massey-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 722.

(3) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallee, J.-F. *Tetrahedron Lett.* **1990**, 2845.

(4) Guindon, Y.; Lavallee, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, 27.

(5) Hart, D. J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, 3749.

(6) Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(7) Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379.

(8) Johnson, R. *Chem. Rev.* **1968**, *68*, 375.

(9) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

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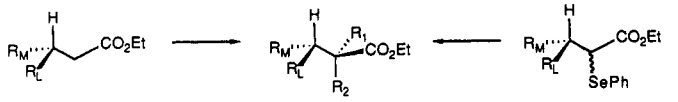
Table I. Protonation of Enolates and Reduction of Radicals Derived from Esters 8 and 9



8 10 R_1 = D R_2 = H; 11 R_1 = H R_2 = D 9

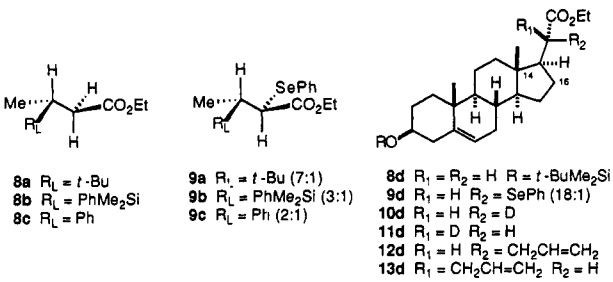
entry	R_L	R_M	reaction	condns[a]	% yield[b]	10:11[c]
1	*t*-Bu	Me	**8a** → **10a** + **11a**	A (enolate)	83	75:25 (75)
2	*t*-Bu	Me	**9a** → **10a** + **11a**	B	79	88:12[d] [83:17, 77%]
3	$SiMe_2Ph$	Me	**8b** → **10b** + **11b**	A (enolate)	80	83:17 (80)
4	$SiMe_2Ph$	Me	**9b** → **10b** + **11b**	B*	87	90:10 [87:13, 83%]
5	Ph	Me	**8c** → **10c** + **11c**	A (enolate)	93	61:39 (77)
6	Ph	Me	**9c** → **10c** + **11c**	B	84	42:58 [43:57, 77%]
7	C-14	C-16	**8d** → **10d** + **11d**	A (enolate)	86	75:25 (80)[e]
8	C-14	C-16	**9d** → **10d** + **11d**	B	79	88:12[e] [75:25, 79%]

[a] A = (1) LDA (1.0 equiv), THF, −78 °C; (2) *n*-BuLi (1.0 equiv); (3) CH_3CO_2D; B = Ph_3SnD, AIBN, THF, *hν*, −78 °C (*n*-Bu_3SnD was used in the entry marked with an asterisk). All free-radical reactions were also conducted in benzene at reflux, and slightly lower stereoselectivities were observed. [b] Isolated yield of mixture of products. [c] Product ratios were determined by ^{2}H-NMR for entries 1–4, by ^{1}H-NMR for entries 5–6, and by both techniques for entries 7–8. Deuterium incorporation was near 100% (MS and ^{1}H-NMR) for all radical reductions. Percent deuterium incorporation for protonations (entries 1, 3, 5, 7) was determined by mass spectrometry and is shown in parentheses. Product ratios and yields for experiments conducted in benzene at reflux (see footnote a) are shown in brackets. [d] Independent reduction of the major and minor diastereomers of **9a** gave 86:14 (89%) and 87:13 (91%) ratios of **10a** and **11a**, respectively. This suggests that the reductions pass through a common intermediate and that product stereochemistry is not a function of selenide stereochemistry. [e] Products for entries 7–8 are shown in Figure 1.

that reduction occurred anti to the large substituent to minimize torsional strain in the transition state. This suggestion was based on calculations by Houk that examine the addition of a hydrogen atom to propene.[10]

On the basis of the factors discussed above, a general model for 1,2-asymmetric induction in reactions of α-carbalkoxy radicals can be proposed as delineated in Scheme I (**5** → **6** → **7** where R_L, R_M, and R_S represent large, medium, and small groups, respectively). A twist on this model has also been proposed by Giese.[11] This paper describes our own efforts to explore the generality of the model proposed in Scheme I. From the onset of our study, we were aware that this model was identical to that used to rationalize the stereochemical course of certain ester enolate protonations and alkylations.[12] Thus, a comparison of the stereochemical behavior of protonation and alkylation reactions of ester enolates with the corresponding α-carbethoxy radicals will also be presented where possible.[13]

α-Carbalkoxy Radical Reductions Proceed by Hydrogen Atom Transfer to Carbon. Before studying the stereochemical course of α-carbalkoxy radical reductions with tin hydrides, we needed to establish that stereochemistry was controlled by transfer of a hydrogen atom directly to the α-carbon and rather than transfer to oxygen followed by tautomerization of the resulting enol. Thus, a benzene-d_6 solution of methyl α-bromopropanoate was treated with triphenyltin hydride in the presence of 500 mol % methanol-d_4. This experiment gave methyl propanoate as the sole product with no evidence of deuterium incorporation. Identical treatment of a benzene solution of methyl α-bromopropanoate with triphenyltin deuteride in the presence of 500 mol % of methanol gave only methyl



8a R_L = *t*-Bu; **8b** R_L = $PhMe_2Si$; **8c** R_L = Ph

9a R_L = *t*-Bu (7:1); **9b** R_L = $PhMe_2Si$ (3:1); **9c** R_L = Ph (2:1)

8d R_1 = R_2 = H R = *t*-$BuMe_2Si$; **9d** R_1 = H R_2 = SePh (18:1); **10d** R_1 = H R_2 = D; **11d** R_1 = D R_2 = H; **12d** R_1 = H R_2 = $CH_2CH{=}CH_2$; **13d** R_1 = $CH_2CH{=}CH_2$ R_2 = H

Figure 1. Substrates for enolate and α-carbalkoxy radical reactions.

2-deuteriopropanoate. Given that the rate of proton exchange between enols and alcohols is faster than tautomerization, we are confident that α-carbalkoxy radical reduction takes place by direct hydrogen atom transfer to the α-carbon.[14]

α-Carbalkoxy Radical Reductions (Allylations) and Enolate Protonations (Alkylations) Using Substrates without Electron-Withdrawing β-Substituents. Our studies focused on three classes of α-carbalkoxy radicals and ester enolates: (1) those without electron-withdrawing β-substituents, (2) those with electron-withdrawing β-substituents incapable of hydrogen bonding to the ester carbonyl group, and (3) those with hydroxyl groups at the β-position. This section describes our results with the first type of substrate. The esters used in this portion of our study are shown in Figure 1. Esters **8a–8d** were either purchased or prepared using literature procedures.[15–18] Selenides **9a–9d** were prepared by treating **8a–8d** with lithium diisopropylamide in tetrahydrofuran followed by addition of diphenyl diselenide.[19,20] This procedure gave

(10) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.

(11) Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett* **1991**, 424. This article suggests that formation of the major product occurs from a conformation in which the R_M–C_β–R_L bond angle is bisected by the C_α–R_α bond and the C_β–R_S bond lies in the same plane as the carbonyl group. It is also acknowledged that more twisted conformations which minimize R_L–R_α interactions (such as **5**) may also be important.

(12) Fleming, I.; Lewis, J. J.; *J. Chem. Soc., Chem. Commun.* **1985**, 149. McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. Yamamoto, Y.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 904.

(13) For a preliminary account of a portion of this study see: Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412.

(14) Capon, B.; Zucco, C. *J. Am. Chem. Soc.* **1982**, *104*, 7567. Kresge, J. *Chemtech* **1986**, 250. Identical deuteration studies were performed using **9c** as the substrate with identical results.

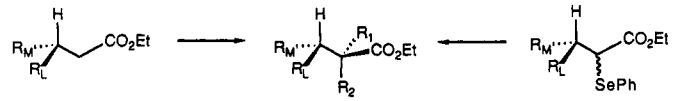
(15) Ester **8a** was prepared by catalytic hydrogenation of ethyl (*E*)-3,4,4-trimethyl-2-pentenoate: Weedon, A. C. *Can. J. Chem.* **1984**, *62*, 1933.

(16) Ester **8b** was prepared from ethyl crotonate and dimethyl(phenyl)silyllithium: Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520.

(17) Ester **8c** was prepared from acetophenone: Gallagher, G. Jr.; Webb, R. L. *Synthesis* **1974**, 122. Theine, A.; Traynham, J. G. *J. Org. Chem.* **1974**, *39*, 153.

(18) The preparation of ester **8d** is described in ref 13.

Table II. Allylation of Enolates and Radicals Derived from Esters 8 and 9



8 12 R_1 = $CH_2CH{=}CH_2$ R_2 = H; 13 R_1 = H R_2 = $CH_2CH{=}CH_2$ 9

entry	R_L	R_M	reaction	condns[a]	% yield[b]	12:13[c]
1	*t*-Bu	Me	**8a** → **12a** + **13a**	A (enolate)	57	92:8
2	*t*-Bu	Me	**9a** → **12a** + **13a**	B	69	62:38 [60:40, 65%]
3	$SiMe_2Ph$	Me	**8b** → **12b** + **13b**	A (enolate)	82	99:1
4	$SiMe_2Ph$	Me	**9b** → **12b** + **13b**	B	56	82:18 [78:22, 62%]
5	Ph	Me	**8c** → **12c** + **13c**	A (enolate)	88	67:33
6	Ph	Me	**9c** → **12c** + **13c**	B	86	26:74 [33:67, 70%]
7	C-14	C-16	**9d** → **12d** + **13d**	A (enolate)	91	97:3[d]
8	C-14	C-16	**9d** → **12d** + **13d**	B	90	90:10[d] [86:14, 88%]

[a] A = (1) LDA (1.0 equiv), THF, −78 °C; (2) $CH_2{=}CHCH_2Br$; B = $CH_2{=}CHCH_2Sn(n\text{-}Bu)_3$, AIBN, THF, *hν*, −78 °C. All free-radical reactions were also conducted in benzene at reflux, and slightly lower stereoselectivities were observed. [b] Isolated yield of mixture of products. [c] Product ratios determined by GC and/or ^{1}H-NMR. Product ratios and yields for experiments conducted in benzene at reflux (see footnote *a*) are shown in brackets. [d] Products for entries 7–8 are shown in Figure 1.

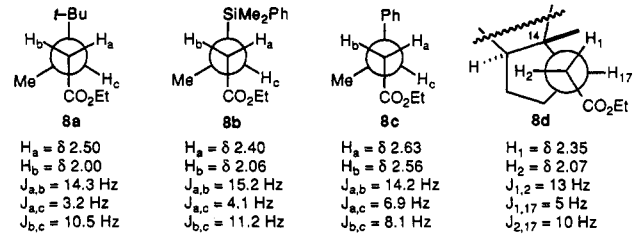
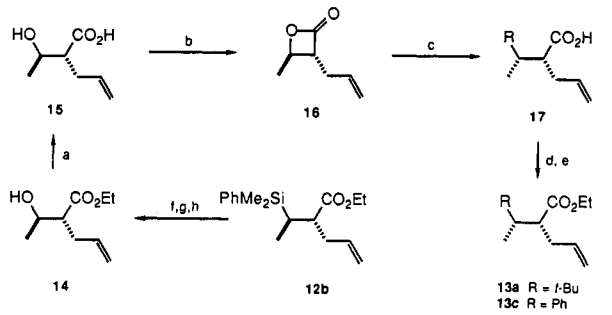


Figure 2. Selected chemical shifts and coupling constants for esters 8a–8d.

Scheme II[a]



[a] Key: (a) KOH, EtOH; (b) TsCl, pyridine; (c) RMgX, CuI, Me_2S; (d) $(COCl)_2$; (e) EtOH; (f) CF_3CO_2H, 50 °C; (g) MeOH, KF; (h) H_2O_2, 85 °C.

9a–9d in 54%, 61%, 72%, and 86% yields, respectively. In each case a mixture of diastereomeric selenides was obtained as indicated by the numbers in parentheses (Figure 1). In the case of **9a**, the diastereomeric selenides were separated by column chromatography. No attempt was made to establish the stereochemistry of the diastereomeric selenides, but if the selenenylations proceed with the same stereochemistry as the corresponding enolate alkylations, the indicated isomer is expected to predominate in each case (vide infra).

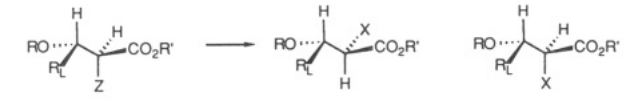
The results of a series of enolate deuterations and free-radical reductions using substrates **8a–8d** and **9a–9d** are presented in Table I. In the deuteration studies, the lithium enolates of esters **8a–8d** were generated using lithium diisopropylamide in tetrahydrofuran. One equivalent of *n*-butyllithium was then added to deprotonate the diisopropylamine, and the resulting solutions were quenched with acetic acid-d_1 at −78 °C to afford mixtures of **10** and **11**.[21] In the reduction studies, selenides **9a–9d** were treated with 3–6 equiv of triphenyltin deuteride or tri-*n*-butyltin deuteride and AIBN in tetrahydrofuran at −78 °C accompanied by irradiation using a 450-W medium-pressure mercury arc lamp.[22] When only 1–3 equiv of tin hydride were used, hydrogen atom transfer from solvent (THF) became competitive with the desired reduction. Product ratios (**10**:**11**) were determined by ^{2}H-NMR in all instances except entries 5–6 and by ^{1}H-NMR when possible. Stereochemcial assignments for **10a–10b** and **11a–11b** as well as **10d** and **11d** (entries 1–4 and 7–8) were based on the ^{1}H-NMR assignments for **8a**, **8b**, and **8d** presented in Figure 2.[23] Stereochemical assignments for compounds **10c** and **11c** (entries 5–6) were based on ^{1}H-NMR assignments reported elsewhere and rely upon the stereochemical assignments for **8c** presented in Figure 2.[24]

The results of a series of enolate alkylations and free-radical allylations are presented in Table II. In the alkylation studies, the lithium enolates of esters **8a–8d** were generated using lithium diisopropylamide in tetrahydrofuran and treated with allyl bromide at −78 °C to afford mixtures of **12** and **13**.[25] In the allylation studies, selenides **9a–9d** were treated with allyltri-*n*-butylstannane and AIBN tetrahydrofuran at −78 °C accompanied by irradiation using a 450-W medium-pressure arc lamp.[26] Product ratios (**12**:**13**) were determined by ^{1}H-NMR and/or gas chromatography and pure samples of each diastereomer were isolated when possible.

β-Hydroxy ester **14**, previously reported by Frater, played a critical role in the stereochemical assignments for compounds **12a–12c** and **13a–13c**.[27,28] Thus, **14** was used

(19) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.
(20) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(21) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.
(22) Reduction of halides: Kuivila, H. G.; Menapace, L. W.; Warner, C. R. *J. Am. Chem. Soc.* **1962**, *84*, 3584. Reduction of selenides: Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438.
(23) The assignments for **8a** and **8b** are based on the assumption that the large β-substituents (*t*-Bu and Me_2PhSi) will be anti to the carbethoxy group in the lowest energy conformation of each molecule. The assignments for **8d** are based on the assumption that C(14) will be predominantly anti to the carbethoxy group.
(24) Spassov, W. L.; Stefanova, R.; Ladd, J. A. *J. Mol. Struct.* **1977**, *36*, 93.
(25) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318.
(26) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
(27) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825.

Table III. Reduction and Allylation of β-Methoxy-α-carbalkoxy Radicals



24 R = Me R_L = Ph Z = Br
25 R = Me R_L = Me Z = Br
26 R = Ac R_L = *t*-Bu Z = PhSe

28a X = D
28b X = $CH_2CH{=}CH_2$
30a X = D
30b X = $CH_2CH{=}CH_2$
32a X = D
32b X = $CH_2CH{=}CH_2$

29a X = D
29b X = $CH_2CH{=}CH_2$
31a X = D
31b X = $CH_2CH{=}CH_2$
33a X = D
33b X = $CH_2CH{=}CH_2$

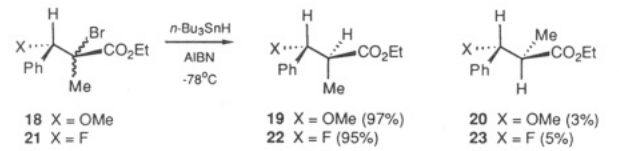
entry	R_L	R′	reaction	condns[a]	% yield[b]	**28:29** or **30:31**[c]
1	Ph	Me	**24** → **28a** + **29a**	A	69	77:23 [71:29, 61%]
2	Ph	Me	**24** → **28b** + **29b**	B	88	90:10[d] [80:20, 87%]
3	Me	Et	**25** → **30a** + **31a**	A	61	45:55 [43:57, 85%]
4	Me	Et	**25** → **30b** + **31b**	B	75	83:17 [70:30, 71%]
5	*t*-Bu	Et	**26** → **32a** + **33a**	A	76	86:14[d]
6	*t*-Bu	Et	**26** → **32b** + **33b**	B	82	89:11[d]

[a] A = *n*-Bu_3SnD, AIBN, THF, *hν*, −78 °C; B = $CH_2{=}CHCH_2Sn(n\text{-}Bu)_3$, AIBN, THF, *hν*, −78 °C. All free-radical reactions were also conducted in benzene at reflux, and slightly lower stereoselectivities were observed. [b] Isolated yield of mixture of products. [c] Product ratios were determined by ^{2}H-NMR for entries 1, 3, and 5 and by ^{1}H-NMR and/or GC for entries 2, 4, and 6. Deuterium incorporation was near 100% (MS and ^{1}H-NMR) for all radical reductions. Product ratios and yields for experiments conducted in benzene at reflux (see footnote *a*) are shown in brackets. [d] Identical product ratios were obtained when toluene was used in place of tetrahydrofuran at −78 °C.

to prepare authentic samples of **13a** and **13c** as shown in Scheme II. Hydrolysis of **14** with ethanolic potassium hydroxide gave β-hydroxy acid **15** in 85% yield. Treatment of **15** with *p*-toluenesulfonyl chloride and pyridine gave β-lactone **16** (77%).[28] Treatment of **16** with appropriate nucleophiles followed by conversion of the resulting acids (**17**) to esters (see Scheme II) gave samples of **11a** (55% from **16**) and **11c** (13% from **16**) and facilitated assignment of stereochemistry to the products derived from entries 1–2 andf 5–6.[29] The stereochemistry of the products formed in entries 3–4 was proven by correlating **12b** and **14**. Thus, Tamao–Fleming oxidation of **12b** gave **14** (28%) along with acid **15** (13%) as outlined in Scheme II.[30,31] The stereochemistry of **12d** and **13d** (entries 7–8) was based on the stereochemical course of related steroidal ester alkylations.[32]

The data presented in Tables I and II reveal that (1) the model for 1,2-asymmetric induction set forth in Scheme I predicts the stereochemical course of the free-radical reactions (with the exception of entry 6), (2) the stereochemical courses of the free-radical reactions qualitatively parallel those of the enolate reactions (with the exception of entries 5 and 6), and (3) the stereoselectivities of free-radical reductions and allylations are qualitatively the same, but quantitatively different. At this point we can only speculate about why the radicals derived from **9c** (entry 6) do not behave as expected and offer the suggestion that there may be little difference in size between methyl and phenyl groups within the context of the radical derived from **9c**.[33,34]

Scheme III

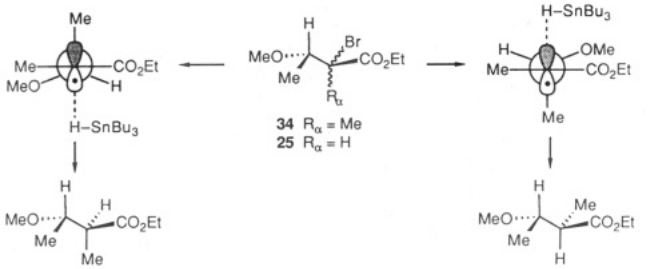


18 X = OMe
21 X = F

19 X = OMe (97%)
22 X = F (95%)

20 X = OMe (3%)
23 X = F (5%)

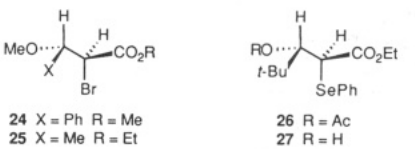
Scheme IV



34 R_α = Me
25 R_α = H

35

36



24 X = Ph R = Me
25 X = Me R = Et

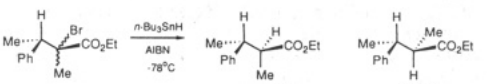
26 R = Ac
27 R = H

Figure 3. Substrates with electron-withdrawing β-substituents.

α-Carbalkoxy Radical Reductions (Allylations) Using Substrates with Electron-Withdrawing β-Substituents. The model set forth in Scheme I is dominated by steric effects. Guindon has suggested that electronic effects also influence the stereochemical course of reactions of α-carbalkoxy radicals. For example, α-carbalkoxy radicals of type **5** with electron-withdrawing substituents at the β-carbon undergo reduction (tri-*n*-butyltin hydride) and allylation (allyl tri-*n*-butylstannane) with remarkable levels of diastereoselectivity.[3,4] For ex-

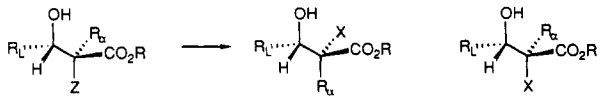
(28) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1977**, *40*, 1269.
(29) Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron* **1989**, *45*, 403.
(30) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37.
(31) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.
(32) Wicha, J.; Bal, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1282.
(33) It is known that phenyl groups show schizophrenic behavior when it comes to their effective size. For example, Allinger has reported that 1-methylphenylcyclohexane prefers a chair conformation with an axial phenyl group and, thus, there is precedent for unusual steric effects at carbon with geminal methyl and phenyl substituents (Allinger, N. L.; Tribble, M. T. *Tetrahedron Lett.* **1971**, 3259. Also see Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982; pp 145–156). This behavior even appears in the ^{1}H-NMR spectrum of **8c** (notice that J_{ab} is very nearly equal to J_{bc} and compare with the corresponding coupling constants in **8a**, **8b**, and **8d**).

(34) Guindon has been reported that reduction of **i** → **ii** (67%) + **iii** (33%) is also not very selective.[3] Although this result is in accord with the model proposed in Figure 1 (R_L = Ph, R_M = Me, and R_α = Me), the selectivity is lower than one might have anticipated.



i **ii** (67%) **iii** (33%)

Table IV. Reduction and Allylation of β-Hydroxy-α-carbalkoxy Radicals



37 R_L = Ph Z = Br R_α = H
38 R_L = Ph Z = Br R_α = Me
39 R_L = Me Z = PhSe R_α = H
27 R_L = t-Bu Z = PhSe R_α = H
40 R_L = t-Bu Z = PhSe R_α = Me

41a-e X = D or H
43a-c-d X = $CH_2CH{=}CH_2$

42a-e X = D or H
44a-c-d X = $CH_2CH{=}CH_2$

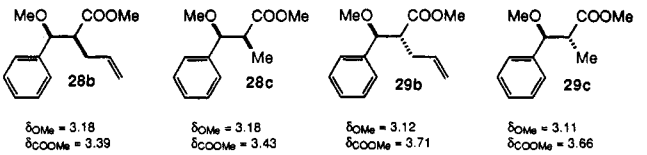
entry	R_L	R_α	reaction	condns[a]	% yield[b]	41:42 or 43:44[c]
1	Ph	H	**37 → 41a + 42a**	A	88	67:33
2	Ph	H	**37 → 43a + 44a**	B	91	87:13 [55:45, 79%]
3	Ph	Me	**38 → 41b + 42b**	A	80	89:11 [62:38, 78%]
4	Me	H	**39 → 41c + 42c**	A*	74	67:33 [58:42, 70%]
5	Me	H	**39 → 43c + 44c**	B	75	77:23 [40:60, 75%][d]
6	t-Bu	H	**27 → 41d + 42d**	A	71	50:50 [24:76, 92%]
7	t-Bu	H	**27 → 43d + 44d**	B	75	17:83 [3:97, 90%]
8	t-Bu	Me	**40 → 41e + 42e**	A	68	65:35 [33:67, 63%][e]

[a] A = n-Bu_3SnD, AIBN, THF, *hν*, −78 °C; B = $CH_2{=}CHCH_2Sn(n\text{-}Bu)_3$, AIBN, THF, *hν*, −78 °C; Ph_3SnD was used in the experiment marked with the asterisk. Reactions shown in entries 2–8 were also conducted in toluene at −78 °C. [b] Isolated yield of mixture of products. [c] Product ratios were determined by ^{2}H-NMR for entries 1, 4, and 6 and by ^{1}H-NMR and/or GC for all other entries. Deuterium incorporation was near 100% (MS and ^{1}H-NMR) for all radical reductions. Product ratios and yields for experiments conducted in toluene at −78 °C (see footnote *a*) are shown in brackets. [d] For comparison, treatment of ethyl 3-hydroxybutanoate with 2 equiv of LDA followed by alkylation using allyl bromide gives a 5:95 ratio of **43c** and **44c**, respectively.[27] [e] Independent reduction of pure **40** and its diastereomer using conditions A gave 65:35 and 70:30 ratios of **41e** and **42e**, respectively.

ample, reduction of **18** at −78 °C affords **19** and **20** in a 97:3 ratio and reduction of **21** gives a 95:5 ratio of **22** and **23**, respectively (Scheme III). Guindon has suggested that the intermediate radicals may react from conformations that minimize both $A^{1,3}$ strain and the electron-withdrawing effects of the β-substituent (alkoxy or fluoro) on the adjacent electron-deficient radical (low-energy SOMO). Liotta has recently performed semiempirical calculations that support these notions.[35] Thus, the model proposed in Scheme I has predictive value for such reactions if the electron-withdrawing β-substituent plays the role of R_M.[36]

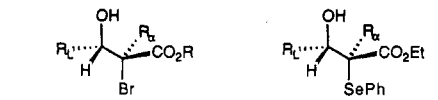
Most reactions of α-carbalkoxy radicals with electron-withdrawing groups at the β-position have been performed with alkyl groups playing the role of R_α (see **5** in Scheme I). We have examined the behavior of several systems where R_α is a hydrogen atom, and our results are recorded in Figure 3 and Table III.

The substrates selected for this study are shown in Figure 3 (**24–26**). Esters **24** and **25** were prepared in 85% and 61% yields, respectively, from the corresponding trans-α,β-unsaturated esters using *N*-bromosuccinimide in methanol.[37] Ester **26** was prepared using an aldol–acylation sequence. Thus, treatment of the lithium enolate of ethyl α-phenylselenenylacetate[38] with pivalaldehyde gave β-hydroxy ester **27** and its diastereomer in 69% yield as a 3:1 mixture.[39] Steglich acylation of this mixture gave



28b δ_{OMe} = 3.18, δ_{COOMe} = 3.39
28c δ_{OMe} = 3.18, δ_{COOMe} = 3.43
29b δ_{OMe} = 3.12, δ_{COOMe} = 3.71
29c δ_{OMe} = 3.11, δ_{COOMe} = 3.66

Figure 4. Selected chemical shifts for esters **28b**, **28c**, **29b**, and **29c**.



37 R_L = Ph R_α = H R = Me
38 R_L = Ph R_α = Me R = Et

39 R_L = Me R_α = H (3:1)
40 R_L = t-Bu R_α = Me (2:1)
27 R_L = t-Bu R_α = H (3:1)

Figure 5. β-Hydroxy ester substrates.

26 (51%) and its diastereomer (19%).[40] Stereochemical assignments for **26** and its diastereomer were based on a comparison of their ^{13}C chemical shifts.[41]

A series of reduction and allylation studies using esters **24–26** are documented in Table III. The structures of reduction products (**28a → 33a**) were proven by correlation with corresponding β-hydroxy esters (vide infra). The structures of allylation products **28b** and **29b** (entry 2) were based on a comparison of ^{1}H-NMR data with those reported for the threo and erythro isomers of methyl 2-methyl-3-methoxy-3-phenylpropanoate (**28c** and **29c**) as shown in Figure 4.[42] The structures of **30b–33b** (entries 4 and 6) were proven by correlation with the corresponding

(35) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallee, M.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912. We thank Dr. Liotta for informing us of these results prior to publication.

(36) The stereochemical course of most of β-alkoxy and β-(trialkylsiloxy)-α-carboalkoxy radical reactions are accommodated by structure **5** in Scheme I if the oxygen substituent is allowed to play the role of R_M.[3,4,11] The exceptions are three cases where R_α is a neopentyl group and trialkylsiloxy and methyl groups reside at the β-position.[11] These cases have been rationalized by a model related to that shown in Scheme I wherein the oxygen substituent plays the role of R_L. This explanation is not consistent with the stereoelectronic arguements advanced by Guindon and Liotta.[35]

(37) Ester **24** was prepared from methyl *trans*-cinnamate: Vishwakarma, L. C.; Walla, J. S. *J. Ind. Chem. Soc.* **1976**, *53*, 156. For ester **24** see: Pfister, K.; Howe, E. E.; Robinson, C. A.; Shabica, A. C.; Pietrusza, E. W.; Tishler, M. *J. Am. Chem. Soc.* **1949**, *71*, 1096. The preparation of **25** was based on the procedure of: Heasley, V. L.; Wade, K. E.; Aucoin, T. G.; Gipe, D. E.; Shellhamer, D. F.; Heasley, G. E. *J. Org. Chem.* **1983**, *48*, 1377.

(38) Brocksom, T. J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem.* **1974**, *39*, 2114.

(39) For related aldol condensations see: Lucchetti, J.; Krief, A. *Tetrahedron Lett.* **1978**, 2693. Our initial objective was to examine a bromo ether of type **24** where X = t-Bu. This plan was abandoned, however, when we found that treatment of methyl 4,4-dimethyl-2-pentenoate with NBS in methanol provided methyl *threo*-3-bromo-2-methoxy-4,4-dimethyl-2-pentenoate in 72% yield, rather than the desired regioisomer. The pronounced steric effect on the regiochemical course of this electrophilic addition is notable.

(40) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(41) For a relevant study see: Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(42) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. Our results in allylations of **24** (entry 2) agree with results reported by Guindon and Giese.[4,11]

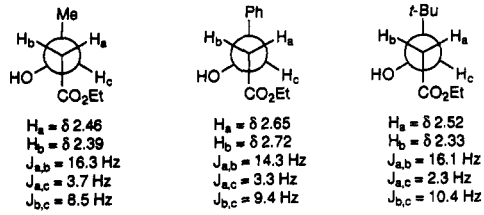


Figure 6. Selected chemical shifts and coupling constants for β-hydroxy esters.

β-hydroxy esters (vide infra).

The results shown in Table III are consistent with the model proposed in Scheme I and the aforementioned stereoelectronic arguements with the exception of the reduction of **25** (entry 3). It is notable that allylation of **25** (entry 4) does proceed as expected. This serves as a reminder that diastereoselectivity is clearly a function of reaction type (reduction vs allylation). The lack of selectivity in the reduction of **25**, however, is puzzling and suggests that *our* understanding of the relative importance of variables that control stereoselectivity is still limited. It has been reported that tri-*n*-butyltin hydride reduction of **34** gives a 3:1 mixture of **35** and **36**, respectively, and on the basis of semiempirical calculations it has been suggested that **35** and **36** may be derived from the radical conformations indicated in Scheme III.[35,43] The difference between **25** and **34** is merely the size of R_α. Diastereostereoselectivity in α-carbalkoxy radical reductions *does* generally parallel reduction of the size of R_α (vide infra), and all we can say at this point is that entry 3 is consistent with this trend.

α-Carbalkoxy Radical Reductions (Allylations) Using β-Hydroxy Esters. In an elegant series of experiments, Guindon recently demonstrated that diastereoselectivity in the reduction of β-alkoxy-α-carbalkoxy radicals can be reversed when the reactions are conducted in the presence of appropriate Lewis acid catalysts.[44] Chelation of the alkoxy and carbonyl groups to the metal is clearly responsible for the observed results. We examined reactions of a series of β-hydroxy-α-carbethoxy radicals with the hope that intramolecular hydrogen bonding might restrict conformational degrees of freedom and lead to high levels of stereoselectivity. The results of our study are outlined in Figure 5 and Table IV.

The β-hydroxy esters selected for this study (**37–40** and **27**) are shown in Figure 5. Esters **37** and **38** were prepared in 95% and 76% yields, respectively, from the corresponding cinnamates using *N*-bromosuccinimide in aqueous acetone.[45,46] Ethyl 2-hydroxybutanoate was purchased and converted to selenide **39** in 62% yield using standard procedures.[19,20] Selenide **40** was prepared in 69% yield by treating the lithium enolate of ethyl 2-phenylselenenylpropanoate[47] with pivalaldehyde, and **27** was prepared in a similar manner (vide supra). All of the selenides were obtained as diastereomeric mixtures as indicated in parentheses.[48]

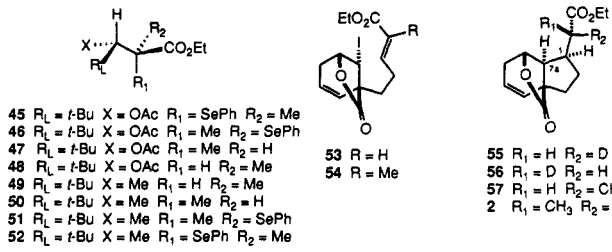


Figure 7. Selected substrates and products for Table V.

The results of a series of reductions and allylations of these β-hydroxy esters are shown in Table IV. The structures of reduction products for entries 1 (**41a** and **42a**), 4 (**41c** and **42c**), and 6 (**41d** and **42d**) were based on ^{1}H-NMR assignments for the corresponding unlabelled esters presented in Figure 6.[49] The structures of products for entries 3 (**41b** and **42b**) and 8 (**41e** and **42e**) were assigned by a comparison of ^{13}C spectral data with those reported for the corresponding methyl esters.[41] The structures of allylation products **43c** and **44c** (entry 5) were based on a comparison with authentic **43c**.[27] The structures of **43d** and **44d** (entry 7) were based on ^{13}C chemical shift data,[41] and the structures of **43a** and **44a** (entry 2) were based on conversion of these compounds to **28b** and **29b**, respectively. Thus, treatment of **43a** or **44a** with trimethyloxonium tetrafluoroborate and 1,8-bis(dimethylamino)naphthalene (proton sponge) gave β-methoxy esters **28b** (77%) and **29b** (77%).[50]

As mentioned above, the β-hydroxy esters obtained in entries 4 and 7 of Table IV were correlated with the esters obtained in entries 3 and 5 of Table III. Thus, subjecting a mixture of **41c** (58%) and **42c** (42%) to trimethyloxonium tetrafluoroborate and proton sponge gave **30a** (58%) and **31a** (42%) in 85% yield, and Steglich acylation of **44d** gave **33b** (82%).[51] Additional evidence for the structure the products obtained in entries 1 and 4 of Table III was obtained in a similar manner. For example, etherification of a mixture of **41a** (64%) and **42a** (36%) gave **28a** (62%) and **29a** (38%) in 88% yield, and methylation of **44c** (trimethyloxonium tetrafluoroborate and proton sponge) gave **31b** in 91% yield.

Several aspects of the data presented in Table IV are notable: (1) Products of type **42** and **44** would have been expected to predominate if reductions and allylations occured via intramolecularly hydrogen bonded intermediates. On the other hand, products of type **41** and **43** would have been predicted based on the steric model presented in Scheme I and the stereoelectronic arguements introduced by Guindon. It is clear that our hope for stereocontrol induced by intramolecular hydrogen bonding was not realized. (2) Although the stereoselectivites in entries 1–5 of Table IV are consistent with the model presented in Scheme I, the results of entries 6–8 indicate that the aforementioned steric–stereoelectronic model also fails to explain the data. (3) To see if diastereoselectivity was a

(43) Identical stereochemical results have been reported for reduction of the corresponding α-mercurial ester (see ref 11).

(44) Guindon, Y.; Lavallee, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701. We thank the BioMega group for providing us with a preprint of this work.

(45) For **37** see: Read, J.; Andrews, A. C. P. *J. Chem. Soc.* **1921**, *119*, 1774.

(46) The cinnamate precursor of **38** was a 10:1 mixture of *E* and *Z* isomers, respectively (Tay, M. K.; About-Joudet, Collignon, N. *Synth. Commun.* **1988**, *18*, 1349), and, thus, **38** was contaminated with approximately 10% of its diastereomer.

(47) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417.

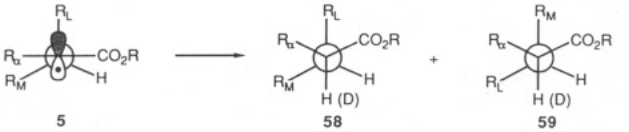
(48) The major diastereomers are shown in parentheses. The assignment for **39** is based on the expected behavior of the dianion of ethyl 2-hydroxybutanoate.[27] The assignment for **40** is based on ^{13}C chemical shifts of the corresponding acetate (vide infra).[41]

(49) For a useful discussion see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3(B), p 111.

(50) Diem, M. J.; Burow, D. F.; Fry, J. L. *J. Org. Chem.* **1977**, *42*, 1801.

(51) Our assignments for **30a** and **31a** agree with spectral assignments reported elsewhere: Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024. This article documents additional examples of β-alkoxy-α-carboalkoxy radical reductions. It is difficult, however, to clearly distinguish between the radical and ionic contributions to the reductions reported therein.

Table V. Effect of R_α on Reduction of Radicals of Type 5



5 58 59

entry	R_α	R_M	R_L	reaction[a-c]	% yield[d]	58:59[e]
1	H	OMe	Me	**25** → **30a** + **31a**	61	45:55
2	Me	OMe	Me	**34** → **35** + **36**	53	75:25[f,g]
3	H	OMe	Ph	**24** → **28a** + **29a**	69	77:23
4	Me	OMe	Ph	**18** → **19** + **20**	90	97:3[h]
5	H	OAc	*t*-Bu	**26** → **32a** + **33a**	82	86:14
6	Me	OAc	*t*-Bu	**45** or **46** → **47** + **48**	81	99:1
7	H	Me	*t*-Bu	**9a** → **10a** + **11a**	79	88:12
8	Me	Me	*t*-Bu	**51** + **52** → **50** + **49**	79	98:2
9	H	$-CH_2-$	C-7a	**53** → **55** + **56**	75	82:18[i]
10	Me	$-CH_2-$	C-7a	**54** → **2** + **57**	80	94:6

[a] General structures **58** and **59** refer to the major and minor products, respectively, expected based on the moel presented in Scheme I. The actual products are listed in the table with the structure corresponding to **58** appearing first. [b] For entries where R_α = H, reductions were conducted using tri-*n*-butyltin deuteride (entries 1, 3, 5) or triphenyltin deuteride (entries 7 and 9). For entries where R_α = Me, tri-*n*-butyltin hydride was used. [c] All reactions were conducted in THF at −78 °C with the exceptions of entries 2 and 4 (toluene, −78 °C) and entries 9 and 10 (benzene, 60 °C). [d] Isolated yield of mixture of products. [e] Product ratios were determined using appropriate ^{1}H-NMR, ^{2}H-NMR, and GC techniques. [f] Data taken from ref 35. [g] Similar results are reported in refs 11 and 51. [h] Data taken from ref 2. [i] This reaction also gave a small amount of the respective C-1 diastereomers of **55** and **56** (see Experimental Section).

function of radical precursor stereochemistry, we independently treated pure samples of **40** and its diastereomer with tri-*n*-butyltin hydride in tetrahydrofuran. Nearly identical mixtures of **41e** and **42e** were obtained in each case. (4) When reactions were conducted in toluene at −78 °C, more **42** and **44** were formed at the expense of **41** and **43**. In other words, stereoselectivity moved toward the products predicted by the hydrogen bonding model. (5) The stereoselectivity in entry 7 is consistent with results reported by Curran with a related α-carboxamido radical.[52] (6) There is no stereochemical correlation between free-radical allylation of **39** (entry 5) and the highly stereoselective alkylation of the dianion of ethyl 3-hydroxybutanoate.[27]

Stereoselectivity as a Function of the Size of R_α. When we were first examining the 1,2-asymmetric induction model presented in Scheme I (**5** → **6** → **7**) we felt that minor products might result from a diastereomeric transition state in which the site occupied by R_M and R_L in **6** are reversed. This analysis predicts that stereoselectivity should increase with the size of R_α. Results that support this prediction are set forth in Figure 7 and Table V.

The results of entries 1, 3, 5, and 7 are taken from Tables I–III and entries 2, 4, and 10 are taken from the literature.[2,6,11,35] The experiments presented in entries 6, 7, and 9 were performed as follows. The substrates for entry 6 (**45** and **46**) were prepared in 62% and 33% yields, respectively, by Steglich acylation of a 2:1 mixture of **40** and its diastereomer. Independent reduction of either **45** or **46** with tri-*n*-butyltin hydride gave **47** as the only detectable product. The stereochemistry of **47** was based on a comparison of ^{13}C NMR data with **32b** and **33b**.[41] The substrates for entry 8 (**51** and **52**) were prepared from **8a**. Thus, alkylation of the lithium enolate of **8a** gave a 93:7 ratio of **49** and **50**, respectively, in 84% yield. Treatment of this mixture with lithium diisopropylamide followed by PhSeSePh gave selenides **51** and **52**, albeit in 10% yield, as a 11:1 mixture of diastereomers. The stereochemical assignments for esters **49–52** were based on expectations using enolate alkylation models (vide supra). Reduction of **51** + **52** gave **50** as the major product. The substrate for entry 9 (**53**) has been previously reported.[58] The stereochemistry of **55** and **56** (entry 9) was assigned by analogy with the stereochemical course of cyclization of **54** (entry 10).[5,6]

The data in Table V indicate that stereoselectivity increases with the size of R_α, a conclusion also reached in other laboratories.[1a,35,59] This is consistent with the model set forth in Scheme I as one would expect the energy difference between transition state **6** and the diastereomeric transition state in wherein the positions of R_M and R_L are switched to increase as the size of R_α increases.[53] We note that reactions not predicted by the model proposed in Scheme I do not show a dramatic response to changing R_α from a hydrogen atom to a methyl group (compare entry 6 in Table I with the results shown in ref 34 as well as entries 6 and 8 in Table IV).

Summary and Conclusions

The issue of 1,2-asymmetric induction in reductions and allylations of several α-carbalkoxy radicals lacking electron-withdrawing groups at the β-position has been examined (Tables I and II). Stereoselectivities range from zero to extremely high (98:2). The stereochemical course of most of the reactions can be accommodated by the model presented in Scheme I. The results suggest that minimization of allylic strain ($A^{1,3}$ and $A^{1,2}$) and torsional strain is of importance in intermolecular reactions of such α-carbalkoxy radicals. Exceptions to the aforementioned trends arise when one of the β-substituents is a phenyl group and further studies are needed to understand steric and electronic effects in such systems.[54] It is also notable that protonations and alkylations of enolates related to the aformentioned α-carbalkoxy radicals usually proceed with the same stereochemical sense as the radical reductions and allylations, although there are quantitative differences.

(52) Curran, D. P.; Abraham, A. C.; Liu, H. *J. Org. Chem.* **1991**, *56*, 4335. This presents examples of β-acetoxy-α-carboxamido radical reductions and allylations related to those shown in Table III (entries 5 and 6) and Table IV (entries 6 and 7).

(53) It has been shown that when R_α = *t*-Bu for the system described by entries 3–4 in Table V, the stereoselectivity decreases (**58**:**59** = 6:1).[35] This would not be predicted by the two competing transition states described in the above discussion. An alternate source of minor products, which emphasizes the importance of stereoelectronic effects, has been suggested in this case (Scheme III).

(54) For a recent study discussing the effect of hyperconjugation on radical reactivity see: Le Noble, W. J.; Bodepudi, V. R. *J. Org. Chem.* **1991**, *56*, 2001.

This is of interest given the structural complexity of enolates relative to the corresponding radicals.[21]

Reductions and allylations of α-carbalkoxy radicals with electron-withdrawing groups at the β-position have also been examined (Table III). These systems complement studies from other groups.[3,4,11,35,52] The results are largely consistent with the model proposed in Scheme I, but differences between these substrates and those lacking polar substituents at the β-position (for example compare entry 6 of Table I with entry 1 of Table III), as well as other results (Scheme III) indicate that electronic effects may dominate the stereochemical course of these reactions.[55]

Reductions and allylations of β-hydroxy-α-hydroxy-α-carbalkoxy radicals have also been examined (Table IV). These reactions are not accommodated by the model proposed in Scheme I. In other words, they do not parallel the results of Table III in all cases. The stereochemical course of these reactions does show a solvent dependency. There is a shift in product distribution from the model proposed in Scheme I toward an intramolecular hydrogen-bonded model as one moves from tetrahydrofuran to toluene as solvent. The true nature of this solvent effect, however, remains uncertain.

Finally, we note that other free-radical reactions involving pseudoallylic systems may follow the stereochemical guidelines discussed herein.[56,57] We hope that these results will provide a handle for predicting the stereochemical course of certain intermolecular free-radical reactions with a high degree of confidence.

Experimental Section

^{1}H-NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. ^{13}C-NMR data are reported as follows: chemical shift (multiplicity determined from DEPT or INEPT spectra). Mass spectra were obtained at an ionization energy of 70 eV. All Grignard reagents and organolithiums were titrated prior to use with menthol using 1,10-phenanthroline as the indicator.[60] GC data was obtained on an HP Ultra II column (5% phenylmethylsilicon gum, 25 m), and conditions are reported as follows: [t_R (retention time); initial temperature (initial time) → (heating rate) → final temperature]. Spectral data for all new compounds are described herein. Detailed procedures are provided for representative compounds. Detailed procedures for all experiments, including reaction times and purification methods, can be found in the supplementary material.

***rel*-(2*R*,3*S*)-Ethyl 3,4,4-Trimethyl-2-(phenylselenenyl)-pentanoate (9a).** To a solution of 1.2 mL (8.6 mmol) of diisopropylamine in 5 mL of THF at −78 °C under Ar was added 5.4 mL (8.6 mmol) of 1.6 M *n*-BuLi in hexanes. The solution was stirred for 15 min, and 1.0 g (5.7 mmol) of ester **8a** in 2 mL of THF was added dropwise over a 15-min period. The mixture was stirred at −78 °C for 15 min, followed by dropwise addition of 3.56 g (11.4 mmol) of diphenyl diselenide in 3 mL of THF. The solution was stirred at −78 °C for 1 h, and 5 mL of saturated aqueous NH_4Cl was added. The mixture was diluted with 50 mL of ether, washed with two 50-mL portions of saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with hexanes followed by EtOAc–hexanes (1:10)) to afford 1.1 g (61%) of **9a**. This material was shown to be an 88:12 mixture of diastereomers by ^{1}H-NMR and GC [t_R (major) = 11.03 min; t_R (minor) = 10.88 min; 50 °C (2 min) → (20 °C min^{-1}) → 300 °C]: IR (neat) 1725 cm^{-1}; ^{1}H-NMR (major isomer, $CDCl_3$) δ 0.9 (s, 9 H, $C(CH_3)_3$), 1.1 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.2 (d, *J* = 7.1 Hz, 3 H, CH_3), 2.05 (m, 1 H, CH), 3.8 (d, *J* = 6.1 Hz, 1 H, CHSe), 3.9 (m, 2 H, OCH_2), 7.2–7.6 (m, 5 H, ArH); ^{13}C-NMR (major isomer, $CDCl_3$) δ 13.74 (q), 14.54 (q), 27.78 (q), 34.41 (s), 43.23 (d), 49.01 (d), 60.58 (t), 128.04 (d), 128.88 (d), 129.39 (s), 135.17 (d), 174.02 (s); MS *m/e* (relative intensity) 328 (M^+, 20), 57 (100); exact mass calcd for $C_{16}H_{24}O_2Se$ *m/e* 328.0941 and 326.0949, found *m/e* 328.0962 and 326.0956. Diagnostic signals for the minor isomer appeared in the ^{1}H-NMR spectrum at δ 0.85 (s, t-Bu) and 1.85 (m, CH).

***rel*-(2*S*,3*R*)-Ethyl 3-(Dimethylphenylsilyl)-2-(phenylselenenyl)butanoate (9b).** This material was prepared from **8b** (4.0 mmol). Purification was accomplished by chromatography over 40 g of silica gel (eluted with hexanes followed by EtOAc–hexanes (1:15)) to afford 1.58 g (72%) of **9b** as a 85:15 mixture of diastereomers by GC [t_R (major) = 10.80 min; t_R (minor) = 10.69 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C]: IR (neat) 1726 cm^{-1}; ^{1}H-NMR (major isomer, $CDCl_3$) δ 0.32 (s, 6 H, $Si(CH_3)_2$), 1.1 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.2 (d, *J* = 7.4 Hz, 3 H, CH_3), 1.65 (m, 1 H, CH), 3.65 (d, *J* = 11.0 Hz, 1 H, CHSe), 3.7–4.05 (m, 2 H, OCH_2), 7.3–7.7 (m, 10 H, ArH); ^{13}C-NMR (major isomer, $CDCl_3$) δ −4.11 (q), −3.82 (q), 13.68 (q), 14.89 (q), 21.41 (d), 50.73 (d), 60.50 (t), 127.61 (d), 128.04 (d), 128.75 (d), 128.79 (d), 134.02 (d), 134.55 (s), 135.44 (d), 137.127 (s), 172.57 (s); MS *m/e* (relative intensity) 391 and 389 ($M^+ - CH_3$, 1), 249 (41), 135 (96), 69 (100). Diagnostic signals for the minor isomer appeared in the ^{1}H-NMR spectrum at δ 1.15 (t, *J* = 7 Hz, CH_3).

***rel*-(2*R*,3*S*)-Ethyl 3-Phenyl-2-(phenylselenenyl)butanoate (9c).** This material was prepared from **8c** (10.4 mmol). Purification was accomplished by chromatography over a Lobar size-B column (eluted with 3% EtOAc in hexanes) to afford 1.95 g (54%) of **9c** as a 67:33 mixture of stereoisomers by ^{1}H-NMR: IR (neat) 1730 cm^{-1}; ^{1}H-NMR (major isomer, $CDCl_3$) δ 0.9 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.5 (d, *J* = 7 Hz, 3 H, $ArCH_3$), 3.25 (dq, *J* = 11.1, 7 Hz, 1 H, ArCH), 3.85 (dq, *J* = 7.1, 1 Hz, 2 H, OCH_2), 3.85 (d, *J* = 11.1 Hz, 1 H, SeCH), 7.2–7.6 (m, ArH); ^{1}H-NMR (minor isomer, $CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.35 (d, *J* = 7 Hz, 3 H, CH_3), 3.3 (dq, *J* = 11.1, 7 Hz, 1 H, ArCH), 3.9 (d, *J* = 11.1 Hz, 1 H, SeCH), 4.05 (m, 2 H, OCH_2), 7.2–7.6 (m, ArH); ^{13}C-NMR (major isomer, $CDCl_3$) δ 13.62 (q), 20.88 (q), 41.63 (d), 52.24 (d), 60.39 (t), 171.79 (s); ^{13}C-NMR (minor isomer, $CDCl_3$) δ 13.89 (q), 21.05 (q), 42.14 (d), 51.53 (d), 60.78 (t), 172.18 (s), aromatic signals from both isomers were observed from δ 126–143; MS *m/e* (relative intensity) 348 (M^+, 29), 346 (M^+, 14), 240 (2), 191 (17), 105 (100); exact mass calcd for $C_{18}H_{20}O_2Se$ *m/e* 348.0627 and 346.0636, found *m/e* 348.0628 and 346.0641, respectively.

***rel*-(20*S*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-(phenylselenenyl)pregn-5-en-21-oate (9d).** This material was prepared from **8d** (1.0 mmol). Purification was accomplished by chromatography over 10 g of silica column (hexanes followed by ether–hexanes (1:5)) followed by recrystallization from EtOH to give 234 mg (35%) of pure **9d** and 342 mg (51%) of a mixture of selenides. Selenide **9d**: mp 123–124 °C; IR (CCl_4) 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.05 (s, 6 H, $Si(CH_3)_2$), 0.7 (s, 3 H, CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.97 (s, 3 H, CH_3), 1.12 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.0–2.4 (m, 20 H, CH and CH_2 manifold), 3.45 (m, 1 H, HCO),

(55) In most of these cases, steric and electronic effects reinforce one another.

(56) For example, asymmetric induction in β-sulfinyl-α-keto radical cyclizations (Snider, B. B.; Wan, B. Y.-F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328) and intermolecular additions of β-sulfinyl-α-carbethoxy radicals (Beckwith, A. L. J.; Hersperger, R.; White, J. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1151) have recently been reported. Diastereoselectivity in these reactions can be explained by allowing the sulfoxide lone pair, the sulfoxide oxygen, and the *p*-tolyl group to play the roles of R_S, R_M, and R_L, respectively, in Scheme I. It is notable that the radical studied by Beckwith resembles the radical derived from **18** (Scheme IV) and shows the same high level of diastereoselectivity in intermolecular reactions. Beckwith has suggested that electronic effects (dipole–dipole repulsion between the S–O and CO_2Et groups) may be responsible conformational preferences of β-sulfinyl-α-carbethoxy radicals. Steric and electronic effects could also be contributing factors.

(57) For diastereoselective reactions of an acyclic benzylic radical in accord with Scheme I see: Curran, D. P.; Thoma, G. *Tetrahedron Lett.* **1991**, 6307. For a recent study that compares reactions of α-(silyloxy) and α-acetoxy radicals with their polar counterparts (carbonyl additions) see: Giese, B.; Damm, W.; Dickhaut, J.; Wetterich, R.; Sun, S.; Curran, D. P. *Tetrahedron Lett.* **1991**, 6097. For relevant articles that appeared while this manuscript was in proof see: Curran, D. P.; Thoma, G. *J. Am. Chem. Soc.* **1992**, *114*, 4436. Renaud, P.; Bjoruo, P.; Carrupt, P. A.; Schenk, K.; Schubert, S. *Synlett* **1992**, 211.

(58) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210.

(59) The results shown in entry 8 were also reported by others after submission of this manuscript: Giese, B.; Damm, W.; Wetterich, F.; Zeitz, J.-G. *Tetrahedron Lett.* **1992**, 1863.

(60) Watson, S. C.; Eastham, J. F. *Organomet. Chem.* **1967**, *9*, 165.

3.61 (d, J = 11.5 Hz, CHSe), 4.0 (m, 2 H, OCH_2), 5.3 (m, 1 H, =CH), 7.29 (m, 3 H, ArH), 7.6 (m, 2 H, ArH); ^{13}C-NMR ($CDCl_3$) δ -4.59 (q), 12.32 (q), 13.89 (q), 18.22 (s), 19.39 (q), 20.91 (t), 23.92 (t), 25.92 (q), 28.43 (t), 31.723 (t), 32.05 (t), 32.09 (d), 36.54 (s), 37.33 (t), 37.78 (t), 42.79 (t), 43.26 (s), 47.81 (d), 49.98 (d), 50.94 (d), 56.22 (d), 60.54 (t), 72.54 (d), 120.88 (d), 128.20 (d), 128.53 (d), 128.91 (d), 135.5 (d), 141.56 (s), 172.71 (s); MS m/e (relative intensity) 630 (M^+, 1), 628 (M^+, 1), 573 (3), 417 (100), 371 (14); exact mass calcd for $C_{35}H_{54}O_3SeSi$ m/e 630.2983, 628.3015, found m/e 630.2983 and 628.3018, respectively. Anal. Calcd for $C_{35}H_{54}O_3SeSi$: C, 66.67; H, 8.58. Found: C, 67.02; H, 9.05. ^{1}H-NMR (diagnostic signals for minor isomer, $CDCl_3$) δ 0.6 (s, CH_3), 1.25 (t, J = 7.1 Hz, CH_3), 3.7 (d, J = 11 Hz, CHSe), 4.1 (q, J = 7.1 Hz, OCH_2). The ratio of diastereomeric selenides in the crude was 95:5 by GC [t_R (major) = 17.92 min; t_R (minor) = 17.71 min; 200 °C (2 min) → (5 °C min^{-1}) → 300 °C].

***rel*-(2*R*,3*R*)-Ethyl 2-Deuterio-3,4,4-trimethylpentanoate (10a) and *rel*-(2*S*,3*R*)-Ethyl 2-Deuterio-3,4,4-trimethylpentanoate (11a). Deuteration of 8a.** To a solution of 0.092 mL (0.61 mmol) of diisopropylamine in 1 mL of THF at -78 °C under Ar was added 0.45 mL (0.61 mmol) of 1.5 M n-BuLi in hexanes. The solution was stirred for 15 min, and 100 mg (0.56 mmol) of ester **8a** in 1 mL of THF was added dropwise over a 15-min period. The mixture was stirred at -78 °C for 30 min, 0.45 mL (0.61 mmol) of 1.5 M n-BuLi in hexanes was added dropwise, and the solution was stirred an additional 15 min. A solution of 171 mg (2.8 mmol) of acetic acid-d in 1.0 mL of THF was added via syringe, and the solution was stirred at -78 °C for 20 min. The reaction mixture was quenched with 5 mL of saturated aqueous $NaHCO_3$ and extracted with two 10-mL portions of ether. The combined organic extracts were washed with three 25-mL portions of saturated aqueous $NaHCO_3$, two 25-mL portions of saturated aqueous NH_4Cl, dried ($MgSO_4$) and concentrated in vacuo to give 83.1 mg (83%) of a 75:25 mixture (^{2}H-NMR) of **10a** and **11a**. Deuterium incorporation was 77% based on integration of appropriate signals in the ^{1}H-NMR spectrum. **Reduction of 9a.** A solution of 50 mg (0.15 mmol) of selenide **9a**, 352 mg (1.0 mmol) of Ph_3SnD, and 3 mg of AIBN in 1 mL of THF was irradiated using a 450-W medium-pressure Hg arc lamp at -78 °C for 36 h. The reaction mixture was transferred to a 25-mL Erlenmeyer flask with 5 mL of ether and stirred with 5 mL of saturated aqueous KF. The mixture was passed through a column containing 1 g of $MgSO_4$, 1 g of alumina, and 1 g of silica gel (eluted with hexanes), and the eluant was concentrated in vacuo. The residue was chromatographed over 10 g silica gel (eluted with hexanes followed by EtOAc–hexanes (1:10)) to give 21.3 mg (79%) of an 88:12 mixture (^{2}H-NMR) of **10a** and **11a**: IR (neat) 1735 cm^{-1}; ^{1}H-NMR (**10a** and **11a**, $CDCl_3$) δ 0.89 (s, 9 H, $C(CH_3)_3$), 0.9 (d, J = 7.1 Hz, 3 H, CH_3), 1.23 (t, J = 6.9 Hz, 3 H, CH_3), 1.78 (m, 1 H, CH), 1.9–1.95 (dm, J = 10.7 Hz, 0.12 H, CHD of **11a**), 2.45 (bs, 0.88 H, CHD of **10a**), 4.2 (q, J = 6.9 Hz, OCH_2); ^{2}H-NMR (C_6H_6) δ 1.84 (bs, CHD of **10a**), 2.34 (bs, CHD of **11a**); ^{13}C-NMR (**10a** and **11a**, $CDCl_3$) δ 14.23 (q), 14.83 (q), 27.09 (q), 32.67 (s), 37.92 (d, CHD), 39.87 (d), 60.09 (t), 174.22 (s); exact mass calcd for $C_{10}H_{19}DO_2$ m/e 173.1526, found m/e 173.1529.

***rel*-(2*R*,3*R*)-Ethyl 2-Deuterio-3-(dimethylphenylsilyl)-butanoate (10b) and *rel*-(2*S*,3*R*)-Ethyl 2-Deuterio-3-(dimethylphenylsilyl)butanoate (11b). Deuteration of 8b.** Deuteration of **8b** (2.0 mmol) as described for **8a** gave 401 mg (80%) of an 83:17 mixture (^{1}H-NMR) of **10b** and **11b** after chromatography over silica gel. Deuterium incorporation was 80% based on mass spectral data. **Reduction of 9b**: Reduction of **9b** (0.12 mmol) using 292 mg (1.0 mmol) of n-Bu_3SnD and 5 mg of AIBN as described for **9a** gave 27 mg (87%) of a 90:10 mixture (^{1}H-NMR and ^{2}H-NMR) of **10b** and **11b**: IR (neat) 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.3 (s, 6 H, $Si(CH_3)_2$), 1.0 (d, J = 7.5 Hz, 3 H, CH_3), 1.2 (t, J = 7.1 Hz, 3 H, CH_3), 1.45 (m, 1 H, CH), 2.05 (dm, J = 11.1 Hz, 0.1 H, HCD of **11b**), 2.37 (m, 0.9 H, CHD of **10b**), 4.1 (q, J = 7.1 Hz, 2 H, OCH_2), 7.3–7.6 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ -5.35 (q), -5.06 (q), 14.19 (q), 14.34 (q), 16.37 (d), 36.50 (t, CHD), 60.07 (t), 127.72 (d), 129.01 (d), 133.86 (d), 137.27 (s), 173.84 (s); ^{2}H-NMR (C_6H_6) δ 2.58 (bs, CHD of **10b**), 2.61 (bs, CHD of **11b**); exact mass calcd for $C_{14}H_{21}DO_2Si$ m/e 251.1452, found m/e 251.1449.

***rel*-(2*R*,3*R*)-Ethyl 2-Deuterio-3-phenylbutanoate (10c) and *rel*-(2*S*,3*R*)-Ethyl 2-Deuterio-3-phenylbutanoate (11c). Deuteration of 8c.** Deuteration of **8c** (0.26 mmol) as described for **8a** gave 46 mg (93%) of a 61:39 mixture (^{1}H-NMR) of **10c** and **11c**. Deuterium incorporation was 77% based on mass spectral data. **Reduction of 9c.** Reduction of **9c** (0.26 mmol) using 176 mg (0.5 mmol) of Ph_3SnD and 2 mg of AIBN in 1 mL of THF as described for **9a** gave 23 mg (84%) of a 42:58 mixture (^{1}H-NMR) of **10c** and **11c**: IR (neat) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3 H, CH_3), 1.3 (d, J = 7.1 Hz, 3 H, CH_3), 2.52 (dt, J = 7.9, 2.0 Hz, 0.58 H, CHD of **11c**), 2.6 (dt, J = 6.9, 2.0 Hz, 0.42 H, CHD of **10c**), 3.3 (m, 1 H, ArCH), 4.1 (q, J = 7.1 Hz, 2 H, OCH_2), 7.1–7.4 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 14.11 (q), 21.71, 36.42 (d), 42.64 (t, CHD), 60.16 (t), 126.31 (d), 126.71 (d), 128.41 (d), 145.70 (s), 172.32 (s); exact mass calcd for $C_{12}H_{15}DO_2$ m/e 193.1213, found m/e 193.1213.

(20*R*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-deuteriopregn-5-en-21-oate (10d) and (20*S*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-deuteriopregn-5-en-21-oate (11d). Deuteration of 8d. Deuteration of **8d** (0.11 mmol) as described for **8a** gave 43 mg (86%) of a 75:25 mixture (^{1}H-NMR and ^{2}H-NMR) of **10d** and **11d**. Deuterium incorporation was 75% based on mass spectral data. **Reduction of 9d.** Reduction of **9d** (0.4 mmol) using 352 mg (1.0 mmol) of Ph_3SnD and 2 mg of AIBN in 1 mL of THF as described for **9a** gave 15 mg (79%) of an 88:12 mixture (^{1}H-NMR and ^{2}H-NMR) of **10d** and **11d**: ^{1}H-NMR (signals due to **10d**, C_6D_6) δ 0.1 (s, 3 H, CH_3), 0.5 (s, 6 H, $Si(CH_3)_2$), 0.89–1.1 (s, 20 H, $SiC(CH_3)_3$, CH_3, CH_2 manifold); 1.2–2.4 (m, 14 H, CH and CH_2 manifold), 2.3 (d, J = 4.7 Hz, 1 H, CHD), 2.37 (ddd, J = 13.3, 4.9, 2.2 Hz, 1 H, CHC=), 2.46 (m, 1 H, CHC=), 3.6 (m, 1 H, OCH); 4.0 (q, J = 7 Hz, 2 H, OCH_2); 5.4 (m, 1 H, =CH); ^{1}H-NMR (signals due to **11d**, C_6D_6) δ 2.04 (d, J = 9.7 Hz, 1 H, CHD); ^{2}H-NMR (C_6H_6) δ 1.95 (bs, CHD for **10d**), 2.21 (bs, CHD for **11d**); ^{13}C-NMR ($CDCl_3$) δ -4.35 (q), 12.40 (q), 14.53 (q), 18.33 (s), 19.49 (q), 21.11 (t), 24.81 (t), 26.13 (q), 28.52 (t), 28.56 (t), 32.23 (t), 32.30 (d), 32.66 (t), 34.95, 35.11, 35.26 (t, CHD), 36.89 (s), 37.52 (t), 37.69 (t), 42.05 (s), 43.51 (t), 47.1 (d), 55.78 (d), 59.90 (t), 72.88 (d), 121.46 (d), 141.53 (s), 172.95 (s); MS m/e (relative intensity) 457 (M^+, 1), 460 (2), 418 (100); exact mass calcd for $C_{29}H_{49}DO_3Si$ m/e 475.359, found m/e 475.3656. Anal. Calcd for $C_{29}H_{49}DO_3Si$: C, 73.26; H, 10.31. Found: C, 72.70; H, 10.59.

***rel*-(2*R*,3*R*)-Ethyl 2-Allyl-3,4,4-trimethylpentanoate (12a) and *rel*-(2*S*,3*R*)-Ethyl 2-Allyl-3,4,4-trimethylpentanoate (13a). Alkylation of 8a.** To a stirred solution of 0.12 mL (0.85 mmol) of diisopropylamine in 2 mL of THF at -78 °C under Ar was added 0.57 mL (0.85 mmol) of 1.5 M n-BuLi in hexanes. The solution was stirred for 15 min, and 100 mg (0.57 mmol) of ester **8a** in 2 mL of THF was added dropwise over a 15-min period. The mixture was stirred at -78 °C for 30 min, followed by dropwise addition of a solution of 0.63 g (1.14 mmol) of allyl bromide in 1 mL of THF. The solution was stirred at -78 °C for 1 h, and 5 mL of saturated aqueous NH_4Cl was added. The mixture was extracted with two 25-mL portions of ether, and the combined organic extracts were washed with two 10-mL portions of saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with EtOAc–hexanes (1:20)) to afford 69 mg (57%) of a 92:8 mixture of **12a** and **13a** by GC [t_R (major) = 5.9 min; t_R (minor) = 5.95 min; 50 °C (2 min) → (30 °C min^{-1}) → 300 °C]: IR (neat) 1732 cm^{-1}; ^{1}H-NMR (**12a**, $CDCl_3$) δ 0.9 (s, 9 H, $C(CH_3)_3$), 0.91 (d, J = 7.1 Hz, 3 H, CH_3), 1.23 (t, J = 7.1 Hz, 3 H, CH_3), 1.7 (dq, J = 7.1, 3.5 Hz, 1 H, CH), 2.18 (m, 1 H, CHC=), 2.35 (m, 1 H, CHC=), 2.55 (dt, J = 11.2, 3.6 Hz, 1 H, CHC(O)), 4.1 (q, J = 7.1 Hz, 2 H, CH_2O), 4.9–5 (m, 2 H, CH_2=), 5.7 (m, 1 H, CH=); ^{13}C-NMR (**12a**, $CDCl_3$) δ 11.02 (q), 14.15 (q), 27.84 (q), 32.53 (t), 33.87 (s), 45.25 (d), 45.81 (d), 59.74 (t), 116.51 (d), 136.03 (t), 176.42 (s); MS (GC-MS of **12a**) m/e (relative intensity) 213 (M + 1, 2), 197 (2), 167 (9), 155 (16), 128 (31), 115 (100), 57 (68); MS (GC–MS of **13a**) m/e (relative intensity) 213 (M + 1, 3), 197 (1), 167 (7), 155 (16), 128 (9), 115 (100), 57 (85). Identity of **13a** was established by GC–MS (vide supra) and by an independent synthesis (vide infra). Minor peaks due to **13a** were present in the ^{1}H- and ^{13}C-NMR spectra of **12a**. **Allylation of 9a.** A solution of 50 mg (0.15 mmol) of selenide **9a**, 331 mg (1.0 mmol) of allyltri-n-butyltin, and 5 mg of AIBN in 1 mL of THF was irradiated using a 450-W medium-pressure Hg arc lamp at -78 °C for 39 h. The reaction mixture was transferred to a 25-mL Erlenmeyer flask with 10 mL of hexanes and stirred with 3 mL of saturated aqueous KF for 8 h.

The mixture was washed with two 3-mL portions of hexanes and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with hexanes followed by EtOAc–hexanes (1:15)) to give 23 mg (71%) of a 62:38 mixture (^{1}H-NMR and GC) of **12a** and **13a**. This material was contaminated by 5% of ethyl 3,4,4-trimethyl-2-pentenoate (a mixture of *E* and *Z* isomers) as indicated by signals at δ 1.85 (=CCH_3) and 2.15 (=CCH_3) in the ^{1}H-NMR of the mixture.

***rel*-(2*R*,3*R*)-Ethyl 2-Allyl-3-(dimethylphenylsilyl)butanoate (12b) and *rel*-(2*S*,3*R*)-Ethyl 2-Allyl-3-(dimethylphenylsilyl)butanoate (13b). Alkylation of 8b.** Alkylation of **8b** (2.0 mmol), as described for **8a** gave 476 mg (82%) of **12b**: IR (neat) 1731 cm^{-1}; ^{1}H-NMR (**12b**, $CDCl_3$) δ 0.32 (s, 6 H, Si-$(CH_3)_2$), 0.99 (d, J = 7.5 Hz, 3 H, CH_3), 1.2 (d, J = 7.1 Hz, 3 H, CH_3), 1.4 (dq, J = 7.5, 5.5 Hz, 1 H, CH), 2.1 (m, 1 H, CHC=), 2.4 (m, 1 H, CHC=), 2.5 (ddd, J = 10.8, 5.5, 3.3 Hz, 1 H, CH), 4.0 (q, J = 7.1 Hz, 2 H, CH_2O), 4.95 (m, 2 H, CH_2=), 5.7 (ddt, J = 17, 10.2, 6.8 Hz, 1 H, CH=), 7.3–7.6 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ –3.9 (q), –3.74 (q), 11.42 (q), 14.22 (q), 22.39 (d), 33.65 (t), 46.65 (d), 59.95 (t), 116.10 (t), 127.70 (d), 128.99 (d), 133.97 (d), 136.29 (d), 138.02 (s), 175.25 (s); MS m/e (relative intensity) 275 ($M^+ - CH_3$, 6), 249 (34), 236 (5), 205 (2), 165 (4), 43 (100). No **13b** could be detected by ^{1}H-NMR. **Allylation of 9b.** Allylation of **9b** (0.25 mmol) of selenide using 827 mg (2.5 mmol) of allyltri-*n*-butyltin and 5 mg of AIBN in 1 mL of THF, as described for **9a**, gave 40 mg (56%) of an 82:18 mixture (^{1}H-NMR) of **12b** and **13b**: ^{1}H-NMR (signals due to **13b**, $CDCl_3$) δ 1.46 (m, 1 H, CH), 2.18 (m, 1 H, CHC=), 4.1 (m, 2 H, OCH_2). This material was contaminated with elimination products. This material was contaminated by 20% of ethyl 3-(phenyldimethylsilyl)-2-butenoate (a mixture of *E* and *Z* isomers) as indicated by signals at δ 6.1 (=CH) and 6.42 (=CH) in the ^{1}H-NMR of the mixture. **Epimerization of 12b.** To a solution of 50 mg (0.17 mmol) of ester **12b** in 2 mL of EtOH was added a solution of 5.9 mg (0.08 mmol) of sodium ethoxide in 3 mL of EtOH followed by warming under reflux at 70 °C for 9 h. The reaction mixture was quenched with 25 mL of saturated aqueous NH_4Cl and extracted with 25 mL of ether. The organic layer was washed with two 25-mL portions of saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo to afford 49 mg (98%) of a 60:40 mixture (^{1}H-NMR) of **12b** and **13b**.

***rel*-(2*R*,3*R*)-Ethyl 2-Allyl-3-phenylbutanoate (12c) and *rel*-(2*S*,3*R*)-Ethyl 2-Allyl-3-phenylbutanoate (13c). Alkylation of 8c.** Alkylation of **8c** (2.8 mmol), as described for **8a**, gave 580 mg (88%) of a 67:33 mixture by ^{1}H-NMR and GC [t_R (major) = 9.52 min; t_R (minor) = 9.9 min; 100 °C (2 min) → (5 °C min^{-1}) → 300 °C] of **12c** and **13c**: IR (neat) 1730 cm^{-1}; ^{1}H-NMR (signals due to **12c**, $CDCl_3$) δ 0.9 (t, J = 7.2 Hz, 3 H, CH_3), 1.3 (d, J = 7.1 Hz, 3 H, CH_3), 2.4 (m, 2 H, CH_2C=), 2.65 (m, 1 H, $CHCO_2$), 3.0 (m, 1 H, ArCH), 3.85 (q, J = 7.2 Hz, 2 H, OCH_2), 5.0 (m, 2 H, =CH_2), 5.7 (ddt, J = 17, 10.1, 7 Hz, 1 H, =CH), 7.2 (m, 5 H, ArH); ^{1}H-NMR (signals due to **13c**, $CDCl_3$) δ 1.25 (d, J = 7.1 Hz, 3 H, CH_3), 1.3 (t, J = 7.2 Hz, 3 H, CH_3), 1.9 (m, 1 H, CHC=), 2.2 (m, 1 H, CHC=), 4.2 (q, J = 7.2 Hz, 2 H, OCH_2), 4.8 (m, 2 H, CH_2=), 5.6 (m, 1 H, CH=); ^{13}C-NMR (signals due to **12c**, $CDCl_3$) δ 14.36 (q), 20.61 (q), 35.58 (t), 42.49 (d), 52.88 (d), 60.18 (t), 116.42 (t), 126.55 (d), 127.49 (d), 128.56 (d), 135.37 (d), 144.48 (s), 175.0 (s); ^{13}C-NMR (signals due to **13c**, $CDCl_3$) δ 13.97 (q), 18.84 (q), 34.12 (t), 41.91 (d), 52.88 (d), 59.81 (t), 116.63 (t), 126.41 (d), 127.49 (d), 128.19 (d), 135.51 (d), 144.68 (s), 174.18 (s); MS m/e (relative intensity) 232 (M^+, 2), 191 (20), 173 (1), 146 (2), 127 (18), 105 (100); exact mass calcd for $C_{15}H_{20}O_2$ m/e 232.1463, found m/e 232.1471. Analysis of the spectra of **12c** + **13c** was aided by preparation of an authentic sample of **13c** by an alternate route (vide infra). **Allylation of 9c.** Allylation of **9c** (0.14 mmol) using 331 mg (1.0 mmol) of allyltri-*n*-butyltin and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 28 mg (86%) of a 26:74 mixture (^{1}H-NMR and GC) of **12c** and **13c**.

(20*R*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-allylpregn-5-en-21-oate (12d) and (20*S*)-Ethyl 3β-(*tert*-Butyldimethylsiloxy)-20-allylpregn-5-en-21-oate (13d). Alkylation of 8d. Alkylation of **8d** (0.11 mmol), as described for **8a**, gave 49 mg (91%) of a 97:3 mixture by GC [t_R (major) = 14.49 min; t_R (minor) = 14.64 min; 200 °C (2 min) → (10 °C min^{-1}) → 300 °C] of **12d** and **13d**: mp 104–105 °C; IR (CCl_4) 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.05 (s, 6 H, $Si(CH_3)_2$), 0.7 (s, 3 H, CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.98 (s, 3 H, CH_3), 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 0.9–2.1 (m, 18 H, CH and CH_2 manifold), 2.1–2.4 (m, 5 H, CH and CH_2 manifold of $CHCO_2$ and CH_2C=), 3.5 (m, 1 H, CHO), 4.1 (q, J = 7.1 Hz, 2 H, OCH_2), 5.1 (m, 2 H, =CH_2), 5.3 (m, 1 H, =CH), 5.75 (m, 1 H, =CH); ^{13}C-NMR ($CDCl_3$) δ –4.58 (q), 12.01 (q), 14.25 (q), 18.24 (s), 19.41 (q), 20.90 (t), 23.84 (t), 25.93 (q), 26.97 (t), 31.84 (t), 31.90 (d), 32.08 (t), 36.48 (t), 36.58 (s), 37.37 (t), 37.51 (t), 42.02 (s), 42.83 (t), 47.47 (d), 50.20 (d), 52.25 (d), 56.10 (d), 59.77 (t), 72.59 (d), 116.48 (t), 120.95 (d), 135.49 (d), 141.64 (s), 175.32 (s); MS m/e (relative intensity) 499 ($M^+ - CH_3$, 1), 457 (65), 383 (7). Anal. Calcd for $C_{32}H_{54}O_3Si$: C, 74.71; H, 10.50. Found: C, 75.74; H, 10.05. **Allylation of 9d.** Allylation of **9d** (0.4 mmol) using 331 mg (1.0 mmol) of allyltri-*n*-butyltin and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 20 mg (90%) of a 90:10 mixture (GC) of **12d** and **13d**.

***rel*-(2*S*,3*R*)-Ethyl 2-Allyl-3,4,4-trimethylpentanoate (13a) from β-Lactone 16.** To a suspension of 167 mg (0.87 mmol) of CuI in 10 mL of THF under Ar atmosphere was added 1 mL of dimethyl sulfide. The solution was cooled to –30 °C followed by dropwise addition of a solution of 1.75 mL (1.75 mmol) of 1 M *t*-BuMgCl in THF. The mixture was stirred at –30 °C for 30 min, and a solution of 100 mg (0.79 mmol) of lactone **16** in 1 mL of THF was added and stirred at –30 °C for 1 h and at 0 °C for 1 h. The reaction mixture was quenched with 2 mL of 3 N aqueous HCl, diluted with 50 mL of ether, and washed with three 50-mL portions of saturated aqueous NH_4Cl. The organic layer was extracted with three 50-mL portions of 3 N aqueous NaOH, and the combined aqueous layers were acidified to pH 5 using 3 N aqueous HCl and extracted with three 50-mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in 3 mL of CH_2Cl_2, and a solution of 77.5 mg (0.61 mmol) of oxalyl chloride in 2 mL of CH_2Cl_2 was added followed by stirring at rt for 1 h. The mixture was concentrated in vacuo, the residue was dissolved in 2 mL of CH_2Cl_2, 1 mL of EtOH was added, and the solution was stirred at rt for 1 h. The mixture was quenched with 10 mL of water and extracted with two 5-mL portions of pentanes. The combined organic layers were washed with two 5-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to afford 97 mg (58%) of **13a**. This material was identical (^{1}H-NMR and GC coinjection) to **13a** prepared from **8a** and **9a**.

***rel*-(2*S*,3*R*)-Ethyl 2-Allyl-3-phenylbutanoate (13c) from β-Lactone 16.** Treatment of lactone **16** (3.96 mmol) with phenylmagnesium bromide [from Mg (8.7 mmol) and bromobenzene (8.7 mmol)], as described for the preparation of **13a**, gave 124 mg (13%) of **13c** and 418 mg of an uncharacterized mixture of elimination products. This material was identical (^{1}H-NMR and GC coinjection) to **13c** prepared from **8c** and **9c**.

***rel*-(2*R*,3*R*)-Ethyl 2-Allyl-3-hydroxybutanoate (14) and *rel*-(2*R*,3*R*)-2-Allyl-3-hydroxybutanoic Acid (15) from 12b.** To 200 mg (0.69 mmol) of ester **12b** cooled to 0 °C was added 393 mg (3.5 mmol) of trifluoroacetic acid followed by warming under reflux for 2.5 h. The mixture was concentrated in vacuo and the residue stirred with 132 mg (4.1 mmol) of MeOH and 162 mg (2.8 mmol) of KF at rt for 8 h. To the mixture was added 1.3 g (12.4 mmol) of 30% aqueous hydrogen peroxide at rt followed by warming under reflux at 85 °C for 12 h. The solution was diluted with 25 mL of water and extracted with three 20-mL portions of ether. The combined organic extracts were washed with 50 mL of saturated aqueous sodium bisulfite, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with hexanes followed by EtOAc–hexanes (1:10)) to give 33 mg (28%) of ester **14** and 13 mg (13%) of acid **15**. The materials were identical (^{1}H-NMR and TLC) to authentic material prepared by a literature procedure.[27]

Ethyl 3-Acetoxy-4,4-dimethyl-2-(phenylselenenyl)pentanoate (26). To a solution of 1.0 g (3.1 mmol) of **27** in 5 mL of CH_2Cl_2 was added 0.46 g (4.6 mmol) of acetic anhydride, 0.46 g (4.6 mmol) of triethylamine, and 37 mg (0.3 mmol) of 4-DMAP at rt followed by stirring for 24 h. The mixture was partitioned between 100 mL of ether and 50 mL of 2 N aqueous HCl and the organic phase washed with 50 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to MPLC over a lobar size B column (eluted with petroleum ether followed by EtOAc–petroleum ether (1:50)) to

afford 18.1 mg (1.6%) of a 1:1 mixture by GC [t_R (major) = 8.00 min; t_R (minor) = 8.12 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C] of **26** and its diastereomer, 0.22 g (19%) of the diastereomer and 0.57 g (51%) of **26**. Selenide **26**: IR (neat) 1745, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.93 (s, 9 H, $(CH_3)_3C$), 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 2.1 (s, 3 H, CH_3), 3.91 (d, J = 4.5 Hz, 1 H, CHSe), 4.06 (q, J = 7.1, 2 H, CH_2), 5.12 (d, J = 4.5 Hz, 1 H, CHO), 7.2–7.6 (m, 5 H, ArH); ^{13}C-NMR δ 13.50 (q), 20.56 (q), 25.93 (q), 35.82 (s), 46.89 (d), 60.89 (t), 77.20 (d), 128.16 (d), , 128.73 (s), 128.79 (d), 134.28 (d), 169.77 (s), 170.72 (s); exact mass calcd. for $C_{17}H_{24}O_4Se$ m/e 372.0846 and 370.0842, found m/e 372.0842 and 370.0855. Diastereomer of **26**: IR (neat) 1743, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (s, 9 H, $(CH_3)_3C$), 1.11 (t, J = 7.1 Hz, 3 H, CH_3), 2.1 (s, 3 H, CH_3), 3.69 (d, J = 9.1 Hz, 1 H, CHSe), 3.95 (m, 2 H, CH_2), 5.32 (d, J = 9.1 Hz, 1 H, CHO), 7.2–7.7 (m, 5 H, ArH); ^{13}C-NMR δ 13.88 (q), 20.81 (q), 26.33 (q), 36.02 (s), 45.66 (d), 61.05 (t), 79.36 (d), 128.60 (d), 128.77 (s), 129.16 (d), 135.40 (d), 170.35 (s), 170.45 (s); exact mass calcd for $C_{17}H_{24}O_4Se$ m/e 372.0846 and 370.0842, found m/e 372.0843 and 370.0844.

Ethyl 3-Hydroxy-4,4-dimethyl-2-(phenylselenenyl)pentanoate (27). To a solution of 0.51 mL (3.6 mmol) of diisopropylamine in 3 mL of THF at −78 °C under Ar was added 2.6 mL (3.6 mmol) of 1.4 M *n*-BuLi in hexanes. The solution was stirred for 15 min, and 0.8 g (3.3 mmol) of ethyl α-(phenylselenenyl)acetate in 1 mL of THF was added dropwise. The mixture was stirred at −78 °C for 20 min, followed by dropwise addition of 0.34 g (3.9 mmol) of trimethylacetaldehyde in 1 mL of THF. The solution was stirred at −78 °C for 1 h and quenched with 50 mL of saturated aqueous NH_4Cl. The mixture was extracted with 50 mL of ether. The organic layer was washed with 25 mL of saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to MPLC over a lobar size B column (eluted with EtOAc–petroleum ether (1:50)) to afford 0.75 g (69%) of **27** as a 3:1 mixture of diastereomers by ^{1}H-NMR: IR (neat) 3506, 1719 cm^{-1}; ^{1}H-NMR (major isomer, $CDCl_3$) δ 0.9 (s, 9 H, $(CH_3)_3C$), 1.13 (t, J = 7.1 Hz, 3 H, CH_3), 3.72 (bs, 1 H, OH), 3.88 (d, J = 2.0 Hz, 1 H, CHSe), 4.07 (m, 3 H, CH_2, CHO), 7.2–7.7 (m, 5 H, ArH); ^{1}H-NMR (diagnostic signals due to minor isomer, $CDCl_3$) δ 0.99 (s, $(CH_3)_3C$); ^{13}C-NMR (major isomer) δ 13.74 (q), 26.22 (q), 36.95 (s), 44.20 (d), 61.29 (t), 81.92 (d), 128.53 (d), 128.74 (s), 129.11 (d), 135.22 (d), 174.24 (s); exact mass calcd for $C_{15}H_{22}O_3Se$ m/e 330.0740 and 328.0742, found m/e 330.0737 and 328.0740.

***rel*-(2*R*,3*R*)-Methyl 2-Deuterio-3-methoxy-3-phenylpropanoate (28a) and *rel*-(2*S*,3*R*)-Methyl 2-Deuterio-3-methoxy-3-phenylpropanoate (29a). From 24.** Reduction of **24**[37] (0.4 mmol) using 818 mg (2.8 mmol) of Ph_3SnD and 10 mg of AIBN in 1 mL of THF, as described for **9a**, gave 51 mg (69%) of a 77:23 mixture (^{1}H-NMR and ^{2}H-NMR) of **28a** and **29a**: IR (neat) 1737 cm^{-1}; ^{1}H-NMR (**28a** + **29a**, $CDCl_3$) δ 2.55 (m, 0.77 H, CHD of **28a**), 2.8 (dm, J = 9.2 Hz, 0.23 H, CHD of **29a**), 3.2 (s, 3 H, OCH_3), 3.7 (s, 3 H, OCH_3), 4.6 (m, 1 H, OCH), 7.3 (m, 5 H, ArH); ^{13}C-NMR (**28a** and **29a**, $CDCl_3$) δ 43.03 (d, CHD), 51.59 (q), 56.83 (q), 80.01 (d), 126.5 (d), 128.03 (d), 128.58 (d), 140.56 (s), 171.43 (s); ^{2}H-NMR (**28a** and **29a**, C_6H_6) δ 2.4 (bs, CHD of **29a**), 2.8 (bs, CHD of **28a**); exact mass calcd for $C_{11}H_{13}DO_3$ m/e 195.0961, found m/e 195.0991. **From 41a and 42a.** To a solution of 50 mg (0.25 mmol) of a mixture of esters **41a** and **42a** (64:36, respectively) in 2 mL of CH_2Cl_2 was added 59.7 mg (0.28 mmol) of 1,8-bis(dimethylamino)naphthalene followed by 41.3 mg (0.28 mmol) of trimethyloxonium tetrafluoroborate. This mixture was stirred at rt for 24 h, diluted with 20 mL of CH_2Cl_2, and washed with two 10-mL portions of saturated aqueous NH_4Cl. The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed over 10 g of silica gel (eluted with EtOAc–hexanes (1:25)) to give 47 mg (88%) of a 62:38 mixture of **28a** and **29a** (^{1}H-NMR).

***rel*-(2*R*,3*R*)-Methyl 2-Allyl-3-methoxy-3-phenylpropanoate (28b) and *rel*-(2*S*,3*R*)-Methyl 2-Allyl-3-methoxy-3-phenylpropanoate (29b).** Allylation of **24**[37] (0.36 mmol) using 900 mg (2.56 mmol) of allyltri-*n*-butyltin and 10 mg of AIBN in 1 mL of THF, as described for **9a**, gave 75 mg (88%) of a 90:10 mixture by ^{1}H-NMR and GC [t_R (major) = 5.11 min; t_R (minor) = 5.35 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C) of **28b** and **29b**: IR (neat) 1733 cm^{-1}; ^{1}H-NMR (**28b**, $CDCl_3$) δ 2.4–2.7 (m, 2 H, $=CCH_2$), 2.8 (m, 1 H, CH), 3.2 (s, 3 H, OCH_3), 3.4 (s, 3 H, OCH_3), 4.3 (d, J = 8.6 Hz, 1 H, OCH), 4.9–5.2 (m, 2 H, $=CH_2$), 5.7–5.8 (m, 1 H, =CH), 7.3 (m, 5 H, ArH); ^{1}H-NMR (signals due to **29b**, $CDCl_3$) δ 1.6–1.7 (m, 1 H, =CCH), 2.05–2.15 (m, 1 H, =CCH), 3.11 (s, 3 H, OCH_3), 3.7 (s, 3 H, OCH_3), 5.58 (m, 1 H, =CH); ^{13}C-NMR (signals due to **28b**, $CDCl_3$) δ 33.27 (t), 51.18 (q), 53.60 (d), 56.84 (q), 83.84 (d), 116.62 (t), 127.21 (d), 128.24 (d), 128.51 (d), 135.35 (d), 139.37 (s), 173.02 (s); ^{13}C-NMR (signals due to **29b**, $CDCl_3$) δ 33.33 (t), 51.14 (q), 52.97 (d), 57.63 (q), 84.97 (d), 116.85 (t), 127.64 (d), 128.01 (d), 128.36 (d), 134.43 (d), 138.80 (s), 174.4 (s); exact mass calcd for $C_{14}H_{18}O_3$ m/e 234.1256, found m/e 234.1254.

***rel*-(2*R*,3*S*)-Ethyl 2-Deuterio-3-methoxybutanoate (30a) and *rel*-(2*S*,3*S*)-Ethyl 2-Deuterio-3-methoxybutanoate (31a). From 25.** Reduction of **25**[37] (0.4 mmol) using 818 mg (2.8 mmol) of n-Bu_3SnD and 10 mg of AIBN in 1 mL of THF, as described for **9a**, gave 40 mg (61%) of a 45:55 mixture (^{1}H-NMR) of **30a** and **31a**: IR (neat) 1737 cm^{-1}; ^{1}H-NMR (**30a** + **31a**, $CDCl_3$) δ 1.16 (d, J = 6.2 Hz, 3 H, CH_3), 1.22 (t, J = 7.1 Hz, 3 H, CH_3), 2.3 (m, 0.55 H, CHD of **31a**), 2.55 (dm, J = 7.1 Hz, 0.45 H, CHD of **30a**), 3.3 (s, 3 H, OCH_3), 3.7 (m, 1 H, CH), 4.1 (q, J = 7.1 Hz, 2 H, OCH_2); ^{13}C-NMR (**30a** and **31a**, $CDCl_3$) δ 14.18 (q), 19.17 (q), 41.46 (d, CHD), 56.31 (q), 60.34 (t), 73.59 (d), 171.49 (s); exact mass calcd for $C_7H_{13}DO_3$ m/e 147.0947, found m/e 147.0984. **From 41c and 42c.** Methylation a mixture of esters **41c** and **42c** (0.37 mmol) (55:45, respectively) in 2 mL of CH_2Cl_2 using 88.5 mg (0.41 mmol) of 1,8-bis(dimethylamino)naphthalene and 61 mg (0.41 mmol) of trimethyloxonium tetrafluoroborate, as described for **41a** and **42a**, gave 47 mg (85%) of a 55:45 mixture of **30a** and **31a** (^{1}H-NMR).

***rel*-(2*R*,3*S*)-Ethyl 2-Allyl-3-methoxybutanoate (30b) and *rel*-(2*S*,3*S*)-Ethyl 2-Allyl-3-methoxybutanoate (31b). From 25.** Allylation of **25**[37] (0.4 mmol) using 1.1 g (3.1 mmol) of allyltri-*n*-butyltin and 10 mg of AIBN in 1 mL of THF, as described for 9a, gave 62 mg (75%) of an 83:17 mixture by ^{1}H-NMR and GC [t_R (major) = 2.35 min; t_R (minor) = 2.43 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C] of **30b** and **31b**: IR (neat) 1733 cm^{-1}; ^{1}H-NMR (**30b**, $CDCl_3$) δ 1.1 (d, J = 6.2 Hz, 3 H, CH_3), 1.2 (t, J = 7.0 Hz, 3 H, CH_3), 2.2–2.5 (m, 2 H, $CH_2C=$), 2.5–2.6 (m, 1 H, CH), 3.31 (s, 3 H, OCH_3), 3.41 (m, 1 H, OCH), 4.1 (q, J = 7.0 Hz, 2 H, OCH_2), 5.0 (m, 2 H, $=CH_2$), 5.7 (m, 1 H, =CH); diagnostic ^{1}H-NMR (diagnostic signals for **31b**, $CDCl_3$) δ 3.28 (s, 3 H, OCH_3), 3.5 (m, 1 H, OCH); ^{13}C-NMR (signals due to **30b**, $CDCl_3$) δ 13.92 (q), 16.38 (q), 32.70 (t), 51.09 (d), 56.15 (q), 59.86 (t), 76.83 (d), 116.09 (t), 135.24 (d), 173.0 (s); ^{13}C-NMR (signals due to **30b**, $CDCl_3$) δ 15.83 (q), 23.05 (q), 31.73 (t), 51.16 (d), 56.22 (q), 77.18 (d), 116.24 (t), 134.96 (d), 173.5 (s); exact mass calcd for $C_{10}H_{18}O_3$ m/e 187.1334, found m/e 187.1345. **From 44c.** Methylation of **44c** (0.58 mmol) in 2 mL of CH_2Cl_2 using 137 mg (0.64 mmol) of 1,8-bis(dimethylamino)naphthalene and 94 mg (0.64 mmol) of trimethyloxonium tetrafluoroborate, as described for **41a** and **42a**, gave 98 mg (85%) of **31b** (^{1}H-NMR and GC coinjection).

***rel*-(2*R*,3*R*)-Ethyl 3-Acetoxy-2-deuterio-4,4-dimethylpentanoate (32a) and *rel*-(2*S*,3*R*)-Ethyl 3-Acetoxy-2-deuterio-4,4-dimethylpentanoate (33a). From 26.** Reduction of **26** (0.13 mmol) using 197 mg (0.67 mmol) of n-Bu_3SnD and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 22 mg (76%) of a 86:14 mixture (^{1}H-NMR) of **32a** and **33a**: IR (neat) 1744, 1717 cm^{-1}; ^{1}H-NMR (**32a** + **33a**, $CDCl_3$) δ 0.9 (s, 9 H $(CH_3)_3$), 1.2 (t, J = 7.1 Hz, 3 H, CH_3), 2.0 (s, 3 H, CH_3), 2.42 (dt, J = 10.1, 2.1 Hz, 0.14 H, CHD of **33a**), 2.53 (dm, J = 2.1 Hz, 0.86 H, CHD of **32a**), 4.1 (q, J = 7.1 Hz, 2 H, OCH_2), 5.11 (m, 1 H, CHO); ^{13}C-NMR (**32a** and **33a**, $CDCl_3$) δ 14.08 (q), 20.86 (q), 25.67 (q), 34.48 (s), 35.56 (d, CHD), 60.65 (t), 76.70 (d), 170.24 (s), 171.23 (s); MS m/e (relative intensity) 160 (1), 129 (2), 127 (3). Similar treatment of **26** with n-Bu_3SnD in toluene gave a 83:17 mixture (^{1}H-NMR) of **32a** and **33a** in 62% yield. **From 41d and 42d.** Acetylation of mixture of esters **41d** and **42d** (0.11 mmol) (24:76, respectively), as described for **27** → **26**, gave 21 mg (84%) of a 28:72 mixture of **32a** and **33a** (^{1}H-NMR).

***rel*-(2*R*,3*R*)-Ethyl 3-Acetoxy-2-allyl-4,4-dimethylpentanoate (32b) and *rel*-(2*S*,3*R*)-Ethyl 3-Acetoxy-2-allyl-4,4-dimethylpentanoate (33b). From 26.** Allylation of **26** (0.13 mmol) using 223 mg (0.67 mmol) of allyltri-*n*-butyltin and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 28 mg (82%) of an 89:11 mixture by ^{1}H-NMR and GC [t_R (major) = 4.43 min; t_R (minor) = 4.32 min; 100 °C (2 min) → (20 °C min^{-1}) → 300

°C] of **32b** and **33b**: IR (neat) 1738, 1717 cm^{-1}; ^{1}H-NMR (**32b**, $CDCl_3$) δ 0.91 (s, 9 H, $(CH_3)_3$), 1.2 (t, J = 7.1 Hz, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.28 (tm, J = 7.0 Hz, 2 H, =CCH_2), 2.70 (q, J = 7.3 Hz, 1 H, CH), 4.1 (q, J = 7.1 Hz, 2 H, CH_2), 5.0 (m, 2 H, =CH_2), 5.1 (d, J = 7.3 Hz, 1 H, CHO), 5.7 (m, 1 H, =CH); diagnostic ^{1}H-NMR (diagnostic signals for **33b**, $CDCl_3$) δ 4.79 (d, J = 3.5 Hz, CHO); ^{13}C-NMR (signals due to **32b**, $CDCl_3$) δ 14.08 (q), 20.68 (q), 26.06 (q), 33.44 (t), 35.54 (s), 46.33 (d), 60.52 (t), 79.04 (d), 116.78 (t), 135.08 (d), 170.27 (s), 173.43 (s); exact mass calcd. for $C_{14}H_{24}O_4$ m/e 256.1672, found m/e 256.1673. **From 44d.** Acylation of **44d** (0.1 mmol), as described for **27** → **26**, gave 20 mg (82%) of **33b** (^{1}H-NMR and GC coinjection): IR (neat) 1738, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (s, 9 H, $(CH_3)_3$), 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.1–2.6 (m, 2 H, =CCH_2), 2.85 (m, 1 H, CH), 4.1 (q, J = 7.1 Hz, 2 H, CH2), 4.79 (d, J = 3.5 Hz, 1 H, CHO), 5.05 (m, 2 H, =CH_2), 5.7 (m, 1 H, =CH); ^{13}C-NMR ($CDCl_3$) δ 14.14 (q), 20.84 (q), 26.07 (q), 35.41 (s), 36.19 (t), 46.47 (d), 60.27 (t), 79.89 (d), 117.24 (t), 134.88 (d), 170.54 (s), 172.29 (s); MS m/e (relative intensity) 215 ($M^+ - C_3H_5$, 1), 213 (1), 197 (1).

Ethyl 2-Bromo-3-hydroxy-2-methyl-3-phenylpropanoate (38). To a solution of 1.0 g (5.7 mmol) of ethyl α-methylcinnamate[46] in 40 mL of water and 20 mL of acetone was added 2.0 g (11.4 mmol) of NBS followed by 0.1 mL of H_2SO_4. The mixture was stirred at rt for 12 h, diluted with 100 mL of ether, and washed with 100 mL of saturated aqueous $NaHSO_3$. The aqueous layer was extracted with 50-mL portions of ether, and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with EtOAc–petroleum ether (1:40 followed by 1:20)) to afford 1.21 g (76%) of a 10:1 mixture (^{1}H-NMR) of **38** and its diastereomer: IR (neat) 3854, 1720 cm^{-1}; ^{1}H-NMR (**38**, $CDCl_3$) δ 1.3 (t, J = 7.1 Hz, 3 H, CH_3), 1.8 (s, 3 H, CH_3), 3.4 (bs, 1 H, OH), 4.3 (q, J = 7.1 Hz, 2 H, OCH_2), 5.4 (s, 1 H, CHO), 7.2–7.6 (m, 5 H, ArH); diagnostic ^{1}H-NMR (signals for diastereomer **38**, $CDCl_3$) δ 5.1 (s, OCH); ^{13}C-NMR (**38**, $CDCl_3$) δ 74.00 (q), 21.99 (q), 62.08 (s), 62.04 (t), 77.75 (d), 127.58 (d), 128.28 (d), 128.48 (d), 137.48 (s), 171.20 (s); exact mass calcd for $C_{12}H_{15}BrO_3$ m/e 288.0148 and 286.0234, found m/e 288.0166 and 286.0219.

Ethyl 3-Hydroxy-2-(phenylselenenyl)butanoate (39). Selenenylation of ethyl 3-hydroxybutanoate (7.6 mmol), as described for **8a**, gave 1.34 g (62%) of **39** as a 3:1 mixture of diastereomer by ^{1}H-NMR: IR (neat) 3445, 1725 cm^{-1}; ^{1}H-NMR (diagnostic signals due to major isomer, $CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 1.45 (d, J = 6.3, 3 H, CH_3), 2.75 (d, 1 H, OH), 3.55 (m, 1 H, CHSe), 4.10 (q, J = 7.1, 2 H, CH_2), 4.12 (m, 1 H, CHO), 7.3–7.6 (m, 5 H, ArH); ^{1}H-NMR (signals due to minor isomer, $CDCl_3$) δ 1.35 (d, J = 6.3 Hz, CH_3) 3.25 (bs, OH); ^{13}C-NMR (signals due to major isomer, $CDCl_3$) δ 13.94 (q), 20.94 (q), 50.53 (d), 61.18 (t), 68.20 (d), 127.74 (s), 128.46 (s), 129.09 (d), 135.40 (d), 172.55 (s); ^{13}C-NMR (diagnostic signals due to minor isomer) δ 20.26 (q), 53.29 (d) 66.37 (d), 127.84 (s), 128.55 (d), 135.32 (d), 172.9 (s) (other peaks obscured by signals from major isomer); MS m/e (relative intensity) 288 (M^+, 3), 286 (M^+, 18), 242 (49); exact mass calcd for $C_{12}H_{16}O_3Se$ m/e 288.0264 and 286.0362, found m/e 288.0314 and 286.0317.

***rel*-(2*R*,3*R*)-Ethyl 3-Hydroxy-2,4,4-trimethyl-2-(phenylselenenyl)pentanoate (40).** Treatment of the enolate of ethyl 2-(phenylselenenyl)propanate[47] (3.1 mmol) with trimethylacetaldehyde (3.7 mmol), as described for the preparation of **27**, gave 0.63 g of a 3.6:1 mixture (^{1}H-NMR) of **40** and its diastereomer, 57 mg of the diastereomer of **40**, and 28 mg of pure **40**: IR (neat) 3506, 1719 cm^{-1}; ^{1}H-NMR (diastereomer of **40**, $CDCl_3$) δ 0.95 (s, 9 H, $(CH_3)_3C$), 1.09 (t, J = 7.1 Hz, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 2.84 (d, J = 3.6 Hz, 1 H, OH), 3.9 (m, 1 H, CHO), 3.94 (q, J = 7.1, 2 H, CH_2), 7.2–7.6 (m, 5 H, ArH); ^{13}C-NMR (diastereomer of **40**, $CDCl_3$) δ 13.61 (q), 18.2 (q), 27.74 (q), 36.60 (s), 60.72 (t), 60.73 (t), 77.79 (d), 127.55 (s), 128.80 (d), 129.47 (d), 137.88 (d), 172.46 (s). Selenide **40**: ^{1}H-NMR ($CDCl_3$) δ 1.0 (s, 9 H, $(CH_3)_3C$), 1.22 (t, J = 7.1 Hz, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.68 (bs, 1 H, OH), 4.15 (m, 2 H, CH_2), 4.82 (bs, 1 H, CHO), 7.2–7.6 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.83 (q), 23.09 (q), 28.22 (q), 37.91 (s), 55.69 (s), 61.38 (t), 85.01 (d), 127.74 (s), 128.73 (d), 129.36 (d), 138.44 (d), 175.25 (s); exact mass calcd for $C_{16}H_{24}O_3Se$ m/e 344.0890 and 342.0898, found m/e 344.0880 and 342.0896.

***rel*-(2*R*,3*R*)-Methyl 2-Deuterio-3-hydroxy-3-phenylpropanoate (41a) and *rel*-(2*S*,3*R*)-Methyl 2-Deuterio-3-hydroxy-3-phenylpropanoate (42a).** Reduction of **37**[37] (1.9 mmol) using 2.8 g (9.6 mmol) of n-Bu_3SnD and 20 mg of AIBN in 2 mL of THF, as described for **9a**, gave 307 mg (88%) of a 67:33 mixture (^{1}H-NMR) of **41a** and **42a**: IR (neat) 3458, 1732 cm^{-1}; ^{1}H-NMR (**41a** + **42a**, $CDCl_3$) δ 2.65 (dt, J = 3.3, 2.2 Hz, 0.67 Hz, CHD for **41a**), 2.72 (dt, J = 9.4, 2.2 Hz, 0.33 H, CHD for **42a**), 3.4 (bs, 1 H, OH), 3.7 (s, 3 H, OCH_3), 5.1 (bs, 1 H, OCH), 7.3 (m, 5 H, ArH); ^{13}C-NMR (**41a** + **42a**, $CDCl_3$) δ 42.68 (d, CHD), 51.80 (q), 70.24 (d), 125.61 (d), 127.7 (d), 128.51 (d), 142.51 (s), 172.67 (s); ^{2}H-NMR (**41a** + **42a**, C_6H_6) δ 2.31 (bs, CHD, of **42a**), 2.46 (bs, CHD of **41a**); exact mass calcd for $C_{10}H_{11}DO_3$ m/e 181.0849, found m/e 181.0842.

***rel*-(2*R*,3*R*)-Methyl 2-Allyl-3-hydroxy-3-phenylpropanoate (43a) and *rel*-(2*S*,3*R*)-Methyl 2-Allyl-3-hydroxy-3-phenylpropanoate (44a).** Allylation of **37**[37] (0.38 mmol) using 0.8 g (2.27 mmol) of allyltri-n-butyltin and 5 mg of AIBN in 1 mL of THF, as described for **9a**, gave 81 mg (91%) of an 87:13 mixture by ^{1}H-NMR and GC [t_R (major) = 7.58 min; t_R (minor) = 7.44 min; 100 °C (2 min) → (10 °C min^{-1}) → 300 °C] of **43a** and **44a**. Further chromatography provided pure samples of each diastereomer: IR (**43a** + **44a**, neat) 3463, 1732 cm^{-1}; ^{1}H-NMR (**43a**, $CDCl_3$) δ 2.5 (m, 2 H, CH_2), 2.85 (m, 1 H, CH), 2.9 (bs 1 H, OH), 3.56 (s, 3 H, OCH_3), 5.0 (m, 3 H, =CH_2 and OCH), 5.75 (m, 1 H, =CH), 7.3 (m, 5 H, ArH); ^{1}H-NMR (**44a**, $CDCl_3$) δ 2.1–2.4 (m, 2 H, CH_2), 2.9 (m, 1 H, CH), 3.0 (bs, 1 H, OH), 3.67 (s, 3 H, OCH_3), 4.8 (m, 1 H, OCH), 5.0 (m, 2 H, =CH_2), 5.7 (m, 1 H, =CH), 7.3 (m, 5 H, ArH); ^{13}C-NMR (**43a**, $CDCl_3$) δ 31.48 (t), 51.51 (q), 52.78 (d), 73.84 (d), 116.75 (t), 126.09 (d), 127.76 (d), 128.30 (d), 135.32 (d), 141.35 (s), 174.52 (s); exact mass calcd for $C_{13}H_{16}O_3$ m/e 220.1099, found m/e 220.1092. Similar treatment of **37** with allyltri-n-butyltin in toluene gave a 55:45 mixture of **43a** and **44a** in 79% yield.

***rel*-(2*R*,3*S*)-Ethyl 3-Hydroxy-2-methyl-3-phenylpropanoate (41b) and *rel*-(2*S*,3*S*)-Ethyl 3-Hydroxy-2-methyl-3-phenylpropanoate (42b).** Reduction of **38** (1.7 mmol) using 507 mg (1.7 mmol) of n-Bu_3SnH and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 59 mg (80%) of a 89:11 mixture (^{1}H-NMR) of **41b** and **42b**: IR (neat) 3849, 1731 cm^{-1}; ^{1}H-NMR (**41b**, $CDCl_3$) δ 1.02 (d, J = 7.2 Hz, 3 H, CH_3), 1.25 (t, J = 7.0 Hz, 3 H, CH_3), 2.76 (m, 1 H, CH), 3.03 (d, J = 4.5 Hz, 1 H, OH), 4.17 (q, J = 7.0 Hz, 2 H, OCH_2), 4.73 (dd, J = 8.3, 4.5 Hz, 1 H, CHO), 7.2–7.5 (m, 5 H, ArH); diagnostic ^{1}H-NMR (**42b**, $CDCl_3$) δ 1.13 (d, J = 7.2 Hz, CH_3), 1.25 (t, J = 7.0 Hz, CH_3), 2.96 (d, J = 3.2 Hz, 1 H, OH), 4.73 (m, CHO); ^{13}C-NMR (signals due to **41b**, $CDCl_3$) δ 14.10 (q), 14.45 (q), 47.13 (d), 60.70 (t), 76.33 (d), 126.63 (d), 127.96 (d), 128.41 (d), 141.64 (s), 175.78 (s); ^{13}C-NMR (diagnostic signals due to **42b**, $CDCl_3$) δ 10.83 (q), 14.03 (q), 46.44 (d), 60.65 (t), 73.69 (d), 126.00 (d), 127.42 (d), 128.18 (d); exact mass calcd for $C_{12}H_{16}O_3$ m/e 208.1091, found m/e 208.1095. The assignment of stereochemistry was based on comparison with ^{13}C data of related compounds in literature.[41] Similar treatment of **38** with n-Bu_3SnH in toluene gave a 62:38 mixture (^{1}H-NMR) of **41b** and **42b** in 78% yield.

***rel*-(2*R*,3*S*)-Ethyl 2-Deuterio-3-hydroxybutanoate (41c) and *rel*-(2*S*,3*S*)-Ethyl 2-Deuterio-3-hydroxybutanoate (42c).** Reduction of **39** (0.17 mmol) using 352 mg (1.0 mmol) of Ph_3SnD and 5 mg of AIBN in 1 mL of THF, as described for **9a**, gave 17 mg (74%) of a 67:33 mixture (^{1}H-NMR) of **41c** and **42c**: IR (neat) 3445, 1733 cm^{-1}; ^{1}H-NMR (**41c** + **42c**, $CDCl_3$) δ 1.98 (d, J = 6.3 Hz, 3 H, CH_3), 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 2.36 (dt, J = 8.5, 2.5 Hz, 0.33 H, CHD for **42c**), 2.41 (dt, J = 3.3, 2.5 Hz, 0.67 H, CHD for **41c**), 3.0 (bs, 1 H, OH), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2), 4.15 (m, 1 H, OCH); ^{13}C-NMR (**41c** and **42c**, $CDCl_3$) 14.04 (q), 22.36 (q), 42.52 (d, CHD), 60.48 (t), 64.12 (d), 172.69 (s); ^{2}H-NMR (**41c** and **42c**, C_6H_6) δ 2.04 (bs, CHD for **42c**), 2.11 (bs, CHD for **41c**); exact mass calcd for $C_6H_{11}DO_3$ m/e 133.0849, found m/e 133.0870.

***rel*-(2*R*,3*R*)-Ethyl 2-Deuterio-3-hydroxy-4,4-dimethylpentanoate (41d) and *rel*-(2*S*,3*R*)-Ethyl 2-Deuterio-3-hydroxybutanoate (42d).** Reduction of **27** (0.3 mmol) using 444 mg (1.5 mmol) of n-Bu_3SnD and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 38 mg (71%) of a 50:50 mixture (^{1}H-NMR) of **41d** and **42d**: IR (neat) 3520, 1731 cm^{-1}; ^{1}H-NMR (**41d** + **42d**, $CDCl_3$) δ 0.90 (s, 9 H, $(CH_3)_3$), 1.25 (t, J = 7.1 Hz, 3 H, CH_3), 2.30 (dt, J = 10.6, 2.3 Hz, 0.5 H, CHD for **42d**), 2.48 (dt,

J = 2.3, 2.2 Hz, 0.5 H, CHD for **41d**), 2.8 (bs, 1 H, OH), 3.68 (m, 1 H, CHO), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2); ^{13}C-NMR (**41d** and **42d**, $CDCl_3$) δ 14.12 (q), 25.53 (q), 35.31 (s), 36.33 (d, CHD), 60.64 (t), 75.36 (d), 173.80 (s); MS m/e (relative intensity) 176 (M + 1, 1), 174 (M − 1), 117 (2). Similar treatment of **27** with n-Bu_3SnD in toluene gave a 24:76 mixture (^{1}H-NMR) of **41d** and **42d** in 92% yield.

***rel*-(2*S*,3*R*)-Ethyl 3-Hydroxy-2,3,4,4-tetramethylpentanoate (41e) and *rel*-(2*S*,3*R*)-Ethyl 3-Hydroxy-2,3,4,4-tetramethylpentanoate (42e).** Reduction of **40** (0.3 mmol) using 437 mg (1.5 mmol) of n-Bu_3SnH and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 23 mg (40%) of **41e** and 13 mg (23%) of **42e**. **41e**: IR (neat) 3497, 1711 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.89 (s, 9 H, $C(CH_3)_3$), 1.27 (d, J = 7.1 Hz, 3 H, CH_3), 1.34 (d, J = 7.2 Hz, 3 H, CH_3), 2.72 (dq, J = 7.2, 2.0 Hz, 1 H, CH), 3.16 (dd, J = 9.5, 2.0 Hz, 1 H, CHO), 3.68 (d, J = 9.5 Hz, 1 H, OH), 4.15 (q, J = 7.1 Hz, 2 H, CH_2); ^{13}C-NMR ($CDCl_3$) δ 13.96 (q), 18.14 (q), 26.17 (q), 36.02 (s), 38.36 (d), 60.66 (t), 82.69 (d), 177.60 (s); exact mass calcd for $C_{10}H_{20}O_3$ m/e 188.1444, found m/e 188.1428. **42e**: IR (neat) 3517, 1717 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (s, 9 H, $C(CH_3)_3$), 1.22 (d, J = 7.1 Hz, 3 H, CH_3), 1.26 (d, J = 7.1 Hz, 3 H, CH_3), 2.19 (bs, 1 H, OH), 2.69 (dq, J = 7.2, 4.1 Hz, 1 H, CH), 3.63 (d, J = 4.1 Hz, 1 H, CHO), 4.14 (q, J = 7.1 Hz, 2 H, CH_2); ^{13}C-NMR ($CDCl_3$) δ 12.88 (q), 14.09 (q), 26.51 (q), 35.53 (s), 41.13 (d), 60.53 (t), 78.12 (d), 177.15 (s). The assignment of stereochemistry was based on comparison of ^{13}C data with related compounds in literature.[41] Similar treatment of **40** with n-Bu_3SnH in toluene gave a 33:67 mixture by ^{1}H-NMR and GC [t_R (major) = 1.99 min; t_R (minor) = 2.36 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C] of **41e** and **42e** in 68% yield.

***rel*-(2*R*,3*S*)-Ethyl 2-Allyl-3-hydroxybutanoate (43c) and *rel*-(2*S*,3*S*)-Ethyl 2-Allyl-3-hydroxybutanoate (44c).** Allylation of **39** (0.17 mmol) using 394 mg (1.2 mmol) of allyltri-n-butyltin and 5 mg of AIBN in 1 mL of THF, as described for **9a**, gave 19 mg (69%) of a 77:23 mixture by ^{1}H-NMR and GC [t_R (major) = 5.17 min; t_R (minor) = 5.08 min; 50 °C (2 min) → (30 °C min^{-1}) → 300 °C] of **43c** and **44c**: IR (neat) 3451, 1730 cm^{-1}; ^{1}H-NMR (**43c**, $CDCl_3$) δ 1.21 (d, J = 6.3 Hz, 3 H, CH_3), 1.25 (t, J = 7 Hz, 3 H, CH_3), 2.2–2.6 (m, 4 H, CH, OH, CH_2 manifold), 3.95 (m, 1 H, HCO), 4.1 (q, J = 7 Hz, 2 H, CH_2O), 5–5.15 (m, 2 H, H_2C=), 5.75 (m, 1 H, HC=); diagnostic ^{1}H-NMR (**44c**, $CDCl_3$) δ 4.05 (m, 1 H, CH(O)); ^{13}C-NMR (**43c** and **44c**, $CDCl_3$) δ 13.53 (q), 14.29 (q), 20.3 (q), 21.37 (q), 31.79 (t), 33.6 (t), 51.93 (d), 52.14 (d), 60.53 (t), 67.83 (d), 67.88 (d), 116.69 (t), 117.1 (t), 134.77 (d), 135.54 (d), 174.52 (s), 174.67 (s). **43c**: (GC–MS) m/e (relative intensity) 173 (M + 1, 1), 157 (5), 128 (52), 109 (19), 100 (59), 82 (59), 55 (100). **44c**: (GC–MS) m/e (relative intensity) 173 (M + 1, 1), 157 (2), 128 (42), 109 (21), 100 (51), 82 (52), 55 (85). The signals assigned to the minor isomer (**44c**) were identical to those appearing in septra of **14** (vide supra). An authentic sample of **44c**[27] was prepared for the purpose of comparison. Similar treatment of **39** with allyltri-n-butyltin in toluene gave a 40:60 mixture of **43c** and **44c** in 75% yield.

***rel*-(2*R*,3*R*)-Ethyl 2-Allyl-3-hydroxy-4,4-dimethylpentanoate (43d) and *rel*-(2*S*,3*R*)-Ethyl 2-Allyl-3-hydroxy-4,4-dimethylpentanoate (44d).** Allylation of **27** (0.3 mmol) using 503 mg (1.5 mmol) of allyltri-n-butyltin and 5 mg of AIBN in 1 mL of THF, as described for **9a**, gave 8 mg (13%) of **43d** and 40 mg (62%) of **44d**. Ester **44d**: IR (neat) 3491, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (s, 9 H, $(CH_3)_3$), 1.26 (t, J = 7 Hz, 3 H, CH_3), 2.4 (m, 1 H, =CCH), 2.55 (m, 1 H, =CCH), 2.65 (ddd, J = 8.5, 6.7, 1.6 Hz, 1 H, CH), 3.26 (dd, J = 9.6, 1.6 Hz, 1 H, CH), 3.68 (d, J = 9.6 Hz, 1 H, OH), 4.13 (q, J = 7.1 Hz, 2 H, CH_2), 5.05 (m, 2 H, H_2C=), 5.72 (m, 1 H, HC=); ^{13}C-NMR ($CDCl_3$) δ 14.01 (q), 26.14 (q), 35.92 (s), 36.69 (t), 44.01 (d), 60.65 (t), 80.32 (d), 117.44 (t), 134.8 (d), 176.40 (s); MS m/e (relative intensity) 215 (M + 1, 1), 158 (8). Ester **43d**: IR (neat) 3500, 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.93 (s, 9 H, $(CH_3)_3$), 1.24 (t, J = 7 Hz, 3 H, CH_3), 2.05 (bs, 1 H, OH), 2.42 (m, 1 H, =CCH), 2.55 (m, 1 H, =CCH), 2.65 (ddd, J = 10.1, 6.0, 4.0 Hz, 1 H, CH), 3.6 (d, J = 6.0 Hz, 1 H, CH), 4.12 (qd, J = 7.1, 1.4 Hz, 2 H, CH_2), 5.05 (m, 2 H, H_2C=), 5.8 (m, 1 H, HC=); ^{13}C-NMR ($CDCl_3$) δ 14.16 (q), 26.22 (q), 33.30 (t), 35.82 (s), 47.22 (d), 60.36 (t), 78.41 (d), 116.60 (t), 135.77 (d), 175.45 (s); MS m/e (relative intensity) 215 (M + 1, 1), 173 (6). The assignment of stereochemistry was based on comparison of ^{13}C data with related compounds in literature.[41] Similar treatment of **27** with allyltri-n-butyltin in toluene gave a 3:97 mixture by ^{1}H-NMR and GC [t_R (major) = 3.26 min; t_R (minor) = 3.57 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C] of **43d** and **44d** in 75% yield.

***rel*-(2*R*,3*R*)-Ethyl 3-Acetoxy-2,4,4-trimethyl-2-(phenylselenenyl)pentanoate (45) and *rel*-(2*S*,3*R*)-Ethyl 3-Acetoxy-2,4,4-trimethyl-2-(phenylselenenyl)pentanoate (46).** Acylation of **40** (3.2 mmol), as described for **27** → **26**, gave 0.41 g (33%) of **46** and 0.76 g (62%) of **45**. Selenide **45**: IR (neat) 3506, 1719 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (s, 9 H, $(CH_3)_3C$), 1.06 (t, J = 7.1 Hz, 3 H, CH_3), 1.68 (s, 3 H, CH_3) 2.22 (s, 3 H, CH_3), 3.83 (m, 2 H, CH_2), 5.66 (s, 1 H, CHO), 7.2–7.6 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.61 (q), 20.38 (q), 21.08 (q), 27.97 (q), 37.75 (s), 57.22 (s), 60.87 (t), 79.60 (d), 127.40 (s), 128.66 (d), 129.44 (d), 138.23 (d), 170.39 (s), 171.46 (s); exact mass calcd for $C_{18}H_{26}O_4Se$ m/e 386.0998 and 384.1008, found m/e 386.0997 and 384.1006. Selenide **46**; IR (neat) 1743, 1717 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.06 (s, 9 H, $(CH_3)_3C$), 1.20 (t, J = 7.1 Hz, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 3.96 (q, J = 7.1 Hz, 2 H, CH_2), 5.35 (s, 1 H, CHO), 7.2–7.7 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.77 (q), 20.94 (q), 23.58 (q), 28.35 (q), 37.42 (s), 55.03 (s), 61.33 (t), 82.07 (d), 127.50 (s), 128.73 (d), 129.31 (d), 138.14 (d), 169.88 (s), 172.11 (s); exact mass calcd for $C_{18}H_{26}O_4Se$ m/e 386.0998 and 384.1008, found m/e 386.0994 and 384.1009.

***rel*-(2*S*,3*R*)-Ethyl 3-Acetoxy-2,3,4,4-tetramethylpentanoate (47) and *rel*-(2*R*,3*R*)-Ethyl 3-Acetoxy-2,3,4,4-tetramethylpentanoate (48). From 45.** Reduction of **45** (0.13 mmol) using 113 mg (0.39 mmol) of n-Bu_3SnH and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 17 mg (79%) of a 99:1 mixture by GC [t_R (major) = 3.31 min; t_R (minor) = 3.39 min; 100 °C (2 min) → (20 °C min^{-1}) → 300 °C] of **47** and **48**: IR (neat) 1745, 1725 cm^{-1}; ^{1}H-NMR (**47**, $CDCl_3$) δ 0.90 (s, 9 H, $C(CH_3)_3$), 1.19 (d, J = 8.0 Hz, 3 H, CH_3), 1.23 (d, J = 7.1 Hz, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.83 (dq, J = 8.0, 4.7 Hz, 1 H, CH), 4.07 (q, J = 7.1 Hz, 2 H, OCH_2), 4.75 (d, J = 4.7 Hz, 1 H, CHO); ^{13}C-NMR ($CDCl_3$) δ 14.04 (q), 16.93 (q), 20.79 (q), 26.12 (q), 35.30 (s), 40.29 (d), 60.24 (t), 81.33 (d), 170.41 (s), 173.67 (s); MS m/e (relative intensity) 231 (M^+ + 1, 1), 215 (M^+ − CH_3, 2). Similar treatment of **45** with n-Bu_3SnH in toluene gave a 99:1 mixture (^{1}H-NMR and GC) of **47** and **48** in 86% yield. **From 41e and 42e.** Acylation of a 54:46 mixture of esters **41e** and **42e** (0.1 mmol), as described for **27** → **26**, gave 16 mg (65%) of a 54:46 mixture (^{1}H-NMR and GC coinjection) of **47** and **48**.

***rel*-(2*S*,3*R*)-Ethyl 2,3,4,4-Tetramethylpentanoate (50) and *rel*-(2*R*,3*R*)-Ethyl 2,3,4,4-Tetramethylpentanoate (49). Alkylation of 8a.** Alkylation of **8a** (5.7 mmol) with iodomethane (13.0 mmol), as described for **8a** → **12a** + **13a**, gave 1.37 g (84%) of a 7:93 mixture by ^{1}H-NMR and GC [t_R (major) = 4.35 min; t_R (minor) = 4.22 min; 50 °C (2 min) → (20 °C min^{-1}) → 300 °C] of **50** and **49**: IR (neat) 1734 cm^{-1}; ^{1}H-NMR (signals due to **49**, $CDCl_3$) δ 0.83 (d, J = 7.2 HZ, 3 H, CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 1.05 (d, J = 7.1 Hz, 3 H, CH_3), 1.22 (t, J = 7.1 Hz, 3 H, CH_3), 1.8 (dq, J = 7.2, 4.1 Hz, 1 H, CH), 2.61 (dq, J = 7.1, 4.1 Hz, 1 H, CH), 4.09 (q, J = 7.1 Hz, 2 H, OCH_2); ^{13}C-NMR ($CDCl_3$) δ 10.60 (q), 13.19 (q), 14.15 (q), 28.01 (q), 33.81 (s), 39.82 (d), 43.33 (d), 60.04 (t), 177.68 (s): MS m/e (relative intensity) 185 (M^+ − 1, 1). Diagnostic signals for **50** appeared in ^{1}H-NMR at δ 2.74 (dq, J = 7.1, 3.1 Hz, CH). **Reduction of 51 and 52.** Reduction of an 11:1 mixture of esters **51** and **52** (0.12 mmol) using 213 mg (0.73 mmol) of n-Bu_3SnH and 2 mg of AIBN in 1 mL of THF, as described for **9a**, gave 17 mg (79%) of a 2:98 mixture by GC [t_R (major) = 4.27 min; t_R (minor) = 4.37 min; 50 °C (2 min) → (30 °C min^{-1}) → 300 °C] of **49** and **50**: ^{1}H-NMR (signals due to **50**, $CDCl_3$) δ 0.88 (s, 9 H, $C(CH_3)_3$), 0.93 (d, J = 7.2 Hz, 3 H, CH_3), 1.18 (d, J = 7.1 Hz, 3 H, CH_3), 1.22 (t, J = 7.1 Hz, 3 H, CH_3), 1.31 (dq, J = 7.2, 3.1 Hz, 1 H, CH), 2.75 (dq, J = 7.1, 3.1 Hz, 1 H, CH), 4.09 (q, J = 7.1 Hz, 2 H, OCH_2).

***rel*-(2*R*,3*S*)-Ethyl 2,3,4,4-Tetramethyl-2-(phenylselenenyl)pentanoate (51) and *rel*-(2*S*,3*S*)-Ethyl 2,3,4,4-Tetramethyl-2-(phenylselenenyl)pentanoate (52).** Selenenylation of a 93:7 mixture of esters **49** and **50** (2.68 mmol), as described for **8a**, gave 92 mg (10%) of **51** and **52**: IR (neat) 1725 cm^{-1}; ^{1}H-NMR (**51** + **52**, $CDCl_3$) δ 0.9 (s, 9 H, $C(CH_3)_3$) 1.2 (d, J = 7.1 Hz, 3 H, CH_3), 1.3 (d, J = 7.1 Hz, 3 H, CH_3), 1.6 (s, 3 H, CH_3), 2.55 (q, J = 7.1 Hz, 1 H, CH_3), 3.8 (m, 2 H, OCH_2), 7.2–7.6 (m, 5 H, ArH); ^{13}C-NMR (**51** + **52**, $CDCl_3$) δ 13.50 (q), 13.60 (q),

19.47 (q), 29.05 (q), 35.81 (s), 45.39 (d), 59.47 (s), 60.47 (t), 128.13 (s), 128.57 (d), 129.17 (d), 137.99 (d), 174.28 (s); MS *m/e* (relative intensity) 342 (M^+, 4), 340 (2) and 338 (1); exact mass calcd for $C_{17}H_{26}O_2Se$ *m/e* 342.1097, 340.1108, found *m/e* 342.1112 and 340.1148, respectively.

***rel*-(1*R*(*E*),5*R*,8*R*)-Ethyl 5-(8-Iodo-7-oxo-6-oxabicyclo-[3.2.1]oct-2-en-1-yl)-2-pentenoate (53).** To a solution of 432 mg (1.4 mmol) of the appropriate aldehyde[58] in 70 mL of dry benzene under Ar was added 541 mg (1.55 mmol) of 1-(carbethoxy)methylidenetriphenylphosphorane in one portion. The resulting solution was stirred at 75 °C for 2 h and solvent was removed in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with EtOAc–petroleum ether (1:10)) to give 412 mg (77%) of a mixture of **53** and its geometrical isomer as a colorless oil. This material was chromatographed (MPLC, lobar size A column, eluted with EtOAc–petroleum ether (1:5)) to give 25 mg of the *Z* isomer of **53** and 372 mg of ester **53**. *Z* isomer of **53**: IR (neat) 1781, 1713 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.8 (m, 1 H, CH), 2.05 (m, 1 H, CH), 2.5–3.0 (m, 4 H, CH_2 and CH), 4.15 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.55 (dd, *J* = 5.4, 1.6 Hz, 1 H, CHI), 4.75 (m, 1 H, HCO), 5.4 (dq, *J* = 9.5, 2.0 Hz, 1 H, =CH), 5.7–5.8 (m, 2 H, =CH), 6.2 (dt, *J* = 11.5, 7.4 Hz, 1 H, =CH); ^{13}C-NMR ($CDCl_3$) δ 14.28 (q), 23.35 (d), 23.35 (t), 28.96 (t), 30.10 (t), 48.43 (s), 60.01 (t), 76.27 (d), 120.76 (d), 126.82 (d), 129.83 (d), 147.78 (d), 166.21 (s), 171.51 (s); exact mass calcd. for $C_{14}H_{17}O_4I$ *m/e* 376.0172, found *m/e* 376.0113, respectively. Ester **53**: IR (neat) 1779, 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.7 (m, 1 H, CH), 2.0 (m, 1 H, CH), 2.2 (m, 2 H, =CCH_2), 2.5 (dm, *J* = 19.6 Hz, 1 H, =CCH), 2.75 (dm, *J* = 19.6 Hz, 1 H, =CCH), 4.1 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.4 (dd, *J* = 5.4, 1.5 Hz, 1 H, CHI), 4.7 (m, 1 H, CHO), 5.35 (dm, *J* = 9.5 Hz, 1 H, =CH), 5.8 (m, 2 H, =CH), 6.9 (dt, *J* = 15.6, 6.7 Hz, 1 H, =CH); ^{13}C-NMR ($CDCl_3$) δ 14.09 (q), 23.19 (d), 25.89 (t), 28.15 (t), 29.84 (t), 48.05 (s), 60.06 (t), 76.01 (d), 122.09 (d), 126.91 (d), 129.18 (d), 146.78 (d), 166.02 (s), 171.06 (s).

***rel*-(1*S*,3a*S*,7*S*,7a*S*)-Ethyl 1,2,3,6,7,7a-Hexahydro-α(*S*)-deuterio-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (55) and *rel*-(1*S*,3a*S*,7*S*,7a*S*)-Ethyl 1,2,3,6,7,7a-Hexahydro-α(*R*)-deuterio-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (56).** To a solution of 0.15 g (0.34 mmol) of iodo ester **53** and 1 mg of AIBN in 5 mL of dry benzene was added 175 mg (0.59 mmol) of *n*-Bu_3SnD in one portion. The reaction mixture was stirred under Ar at 60 °C for 5 h. The reaction mixture was then partitioned between 25 mL of acetonitrile and 25 mL of hexanes. The hexanes layer was extracted with 25 mL of acetonitrile, and the combined acetonitrile layers were washed once with 25 mL of hexanes and concentrated in vacuo. The residue was dissolved in 20 mL of petroleum ether and stirred with 5 mL of saturated aqueous KF for 30 min. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with EtOAc–petroleum ether (1:6)) to give 86 mg (86%) of a 92:8 mixture (^{1}H-NMR) of esters **55** + **56** and the respective C(1) diastereomers: IR (neat) 1772, 1730.7 cm^{-1}; ^{1}H-NMR (signals due to **55**, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.29 (m, 1 H, CH), 1.59 (m, 1 H, CH), 2.06 (m, 1 H, CH), 2.25 (m, 1 H, CH), 2.34 (m, 1 H, CHD), 2.38 (d, *J* = 10.2 Hz, 1 H, CH), 2.45 (m, 2 H, CH_2), 2.6 (m, 1 H, CH), 4.05 (q, *J* = 7.2 Hz, 2 H, OCH_2), 5.6 (dm, *J* = 9.2 Hz, =CH), 6.0 (dt, *J* = 9.2, 1.8 Hz, =CH); diagnostic ^{1}H-NMR (**56**, $CDCl_3$) δ 2.21 (dm, *J* = 7.6 Hz, CHD); ^{13}C-NMR ($CDCl_3$) δ 14.08 (q), 28.18 (t), 33.63 (d), 34.26 (t), 35.44 (t), 36.17 (d, CHD), 52.74 (d), 54.07 (s), 60.39 (t), 75.89 (d), 126.94 (d), 130.02 (d), 172.83 (s), 178.96 (s); ^{2}H-NMR (C_6H_6) δ 1.92 (bs, CHD of C(1) diastereomers), 2.04 (bs, CHD of **55**), 2.21 (bs, CHD of **56**); MS *m/e* (relative intensity) 252 (M^+ + 1, 2), 22 (3), 207 (10). Diagnostic ^{1}H-NMR peaks for the C(1) diastereomers of **55** and **56** appeared at δ 5.89 (dt, *J* = 9.2, 1.8 Hz, =CH). The ratio of the diastereomers **55** to **56** was 82:18 by integration of peaks at δ 2.04 and δ 2.21 in the 76.8-MHz ^{2}H-NMR spectrum of the mixture.

Acknowledgment. We thank the National Science Foundation for generous support of this research and one of the reviewers for helpful comments.

Supplementary Material Available: Full experimental details and selected ^{1}H, ^{2}H, and ^{13}C NMR spectra (163 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of Tetrahydropteridine C6-Stereoisomers, Including N^5-Formyl-(6*S*)-tetrahydrofolic Acid

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Received March 18, 1992

Chiral N1-protected vicinal diamines derived from amino acids were condensed with 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone, the nitro group reduced, and the amine deprotected. Oxidative cyclization of the resulting triaminopyrimidinone via quinoid pyrimidine intermediates gave a quinoid dihydropteridine, which was then reduced to a tetrahydropteridine C6-stereoisomer. Thus, 6(*R*)- and 6(*S*)-propyltetrahydropterin were stereospecifically synthesized (99% enantiomeric purity) in good yield from D- and L-norvaline, respectively. Reductive alkylation of (*p*-aminobenzoyl)-L-glutamate with a nitropyrimidine aldehyde derived from D- or L-serine similarly afforded, after cyclization and reduction, (6*R*)- or (6*S*)-tetrahydrofolic acid. The latter was then converted to the natural isomer of leucovorin by regioselective N5-formylation with carbonyl diimidazole/formic acid without loss of enantiomeric purity.

Introduction

There currently is no method for the stereospecific synthesis of the reduced pteridine cofactors tetrahydrofolic acid (**1a**) or tetrahydrobiopterin (**1b**). These are important not only for the investigation of enzymatic one-carbon transfer and aromatic amino acid hydroxylation[1] but also clinically. The former (**1a**), as the N5-formyl derivative (leucovorin), is used to potentiate the effects of 5-fluorouracil and in rescue therapy after high-dose methotrexate in the treatment of several forms of cancer. Leucovorin is also coadministered with trimetrexate for treatment of pneumonia caused by *Pneumocystis carinii*. The latter (**1b**) is used in replacement therapy for patients with genetic defects in the tetrahydrobiopterin biosynthetic pathway and is in clinical trials for the treatment of other neurological disorders.[2]

(1) *Folates and Pterins*; Blakley, R. L., Benkovic, S. J., Eds.; Wiley-Interscience: New York, 1985; Vols. 1-2.

0022-3263/92/1957-4470$03.00/0 © 1992 American Chemical Society