Stereoselective Hydrogen Transfer Reactions Involving Acyclic Radicals. Tandem Substituted Tetrahydrofuran Formation and Stereoselective Reduction: Synthesis of the C_{17}–C_{22} Subunit of Ionomycin[1]

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The tandem iodoetherification reaction and stereoselective reduction of acyclic radicals has been used in the stereocontrolled synthesis of substituted tetrahydrofurans. Such a tetrahydrofuran intermediate is regioselectively cleaved using Me_2BBr to reveal the acyclic array **2** which represents the C_{17}–C_{22} subunit of ionomycin. In experiments that provide for a better understanding of hydrogen transfer reactions involving acyclic radicals, a significant improvement in the stereoselectivity is observed when the two substituents at the stereogenic center α to the radical are imbedded in a cycle ("cycle effect"). A mechanistic rationale is discussed.

Introduction

The electrophile-induced cyclization involving double bonds has been used with considerable success in the synthesis of polysubstituted heterocycles.[4] Steric and electronic effects of substituents at the allylic or homoallylic position of the acceptor double bond offer some control over the relative stereochemistry of the newly created sp^3 centers in kinetically-controlled cyclofunctionalizations[4] such as halolactonization or haloetherification reactions.[5] In many cases the geometry of the olefin has been shown to influence the stereochemical outcome of the reaction. For example, *cis* (Z) olefins possessing an allylic substituent undergo cyclization with high stereoselectivity to give heterocycles in which the relative stereochemistry between the initial allylic substituent and the appendage at the site of ring closure is *trans*.[6] These results can be rationalized by considering 1,3-allylic interactions.[7] (Relative to the transition states leading to *trans* ring products, those giving rise to *cis* ring stereochemistry in the heterocyclic products are destabilized by 1,3-allylic congestion; hence, a preference for *trans* ring products is observed.) The same stereochemical bias should be exhibited in electrophilic cyclizations involving terminally disubstituted olefins, which embody the requisite (Z) olefin geometry to invoke 1,3-allylic interactions. The iodoetherification of such olefins could be of further synthetic utility if the resultant tertiary iodides could be manipulated in a chemo- and stereoselective manner. Recently, we[8] and others[9-12] have reported that radical-based reductions and allylations of tertiary and secondary halides can be performed with a high degree of stereocontrol. In this paper, we describe a strategy whereby iodoetherification and radical reduction are used in tandem to prepare in an efficient and stereoselective manner highly functionalized tetrahydrofuran derivatives. Although

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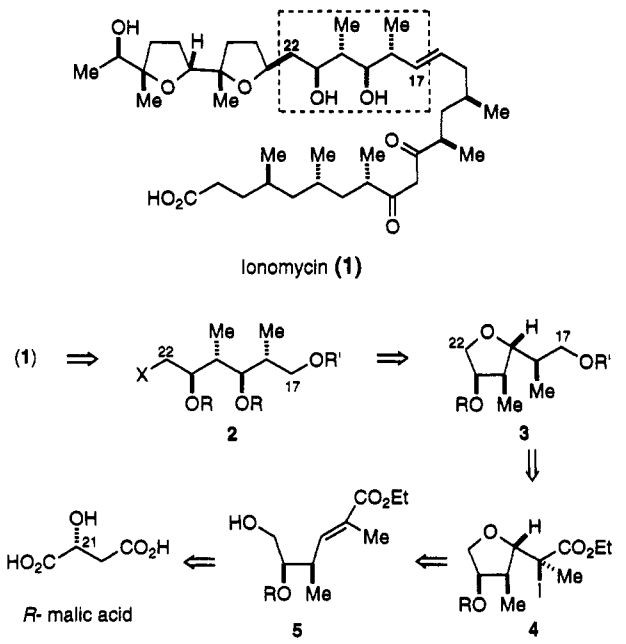
0022-3263/94/1959-1166$04.50/0

Scheme 1



tetrahydrofurans are often obvious building blocks in synthesis, they could serve also as precursors to acyclic molecules, an approach which is exemplified in the synthesis of the C_{17}–C_{22} subunit of ionomycin.[13] Experiments providing for a better understanding of hydrogen transfer reactions involving acyclic radicals and their mechanistic rationale are also discussed.

Results and Discussion

Synthesis of the C_{17}–C_{22} Subunit of Ionomycin. Our strategy for the synthesis of the subunit **2** is shown in Scheme 1. Previous experience[14] indicated that compounds such as **2** could be readily obtained from the regioselective fragmentation of appropriately substituted tetrahydrofurans such as **3**. The synthesis of this intermediate could be expedited by employing the tandem iodoetherification/radical reduction sequence to establish two of the four required stereocenters. Such an approach would proceed via a terminally disubstituted olefin **5** which should be readily accessible from *R*-malic acid by using standard transformations. The kinetically-controlled iodocyclization of olefin **5** should produce tetrahydrofuran **4** in which the relative stereochemistry at C_3 and C_4 (numbering as shown in Scheme 2) is *trans*. The rationale for this is evident from an analysis of possible transition states (Scheme 2). In comparison to the *trans*-predictive transition states **9** and **10**, the *cis*-predictive transition states **7** and **8** are substantially destabilized by 1,3-allylic strain and bisecting 1,3-allylic interactions,[7] respectively, and consequently the *trans* product **4** should predominate.[15] Indeed, the validity of this hypothesis was borne out by the iodocyclization of the disubstituted olefin **15**.

Depicted in Scheme 3 is the synthesis of **15** from diethyl (*R*)-malate. The dianion of diethyl (*R*)-malate (**11**) was reacted with methyl iodide to provide *erythro* adduct **12** in 69% yield (*ca.* 10:1 stereoselectivity).[16] Reduction of diester **12** with borane–dimethyl sulfide complex and treatment of the resultant crude triol with 3,3-dimethoxypentane gave acetal **13** in 55% yield from ester **12**. Swern oxidation of **13** and subsequent Wittig olefination afforded α,β-unsaturated ester **14** in 65% yield from alcohol **13**. Hydrolysis of the pentylidene proceeded uneventfully to yield diol **15**, the key intermediate with which our tandem iodocyclization/radical reduction protocol could be tested.

Cyclization of **15** under kinetic conditions (I_2, $NaHCO_3$, THF, 25 °C)[4] produced the expected iodoester **16** as a single diastereomer which was immediately converted to acetate **17**.

The next task at hand was the reduction of the tertiary iodide **17** in a stereoselective manner to define the remaining stereocenter located adjacent to the tetrahydrofuran ring. We were pleased to note that when **17** was treated with Bu_3SnH at −78 °C in the presence of a catalytic amount of triethylborane, **18** was obtained in 78% yield (>50:1). Although the stereochemical outcome of the radical reduction could not be determined at this juncture, it was later shown to favor the *anti* (C_2–C_3) adduct. However, the C_3–C_4 relative stereochemistry of **18** could be assigned by NOE analysis.[17a] Irradiation of the C_4 hydrogen resonance produced a 4.2% enhancement of the C_2 hydrogen signal, a 2.2% increase in the C_2 methyl signal, and only a 1.3% enhancement of the C_3 hydrogen signal. When the C_3 proton resonance was irradiated, the C_4 methyl resonance showed a 2.5% increase in signal while the C_4 hydrogen resonance was unchanged (complete NOE data for **18** are found in the supplementary material). These observations are consistent with a *trans* relationship between the substituents on C_3–C_4 of adduct **18**.[17b]

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(15) Transition state **10** could be particularly favorable in this reaction for electronic reasons since the methyl group at C_4 is in an optimal orientation to stabilize by hyperconjugation the positive charge developing on the double bond during formation of the iodonium or π complex. (a) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533–4540. (b) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672–677. (c) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. E., III. *J. Org. Chem.* **1987**, *52*, 4191–4202. (d) See ref 11.

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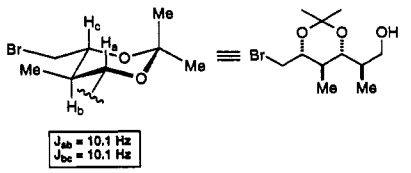
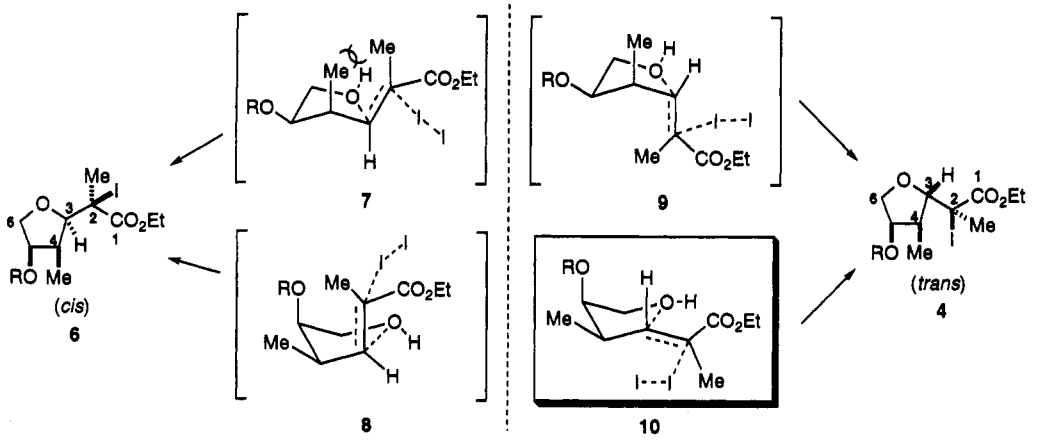


This relative stereochemistry is also consistent with the observed ^{13}C resonances of acetal carbons (98.4, 29.7 and 18.7 ppm); see Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

Scheme 2



At this stage we were faced with the regioselective cleavage of the tetrahydrofuran ring to furnish the C_{17}–C_{22} ionomycin fragment. Prior to ring cleavage, ester **18** was reduced with $LiAlH_4$ to give the diol **19**, which was subsequently acylated to afford the diacetate **20**. Exposure of **20** to Me_2BBr in CH_2Cl_2 at 0 °C gave exclusively the primary bromide **21** which was not isolated but was immediately converted into the C_{17}–C_{22} ionomycin fragment **22** (65%).

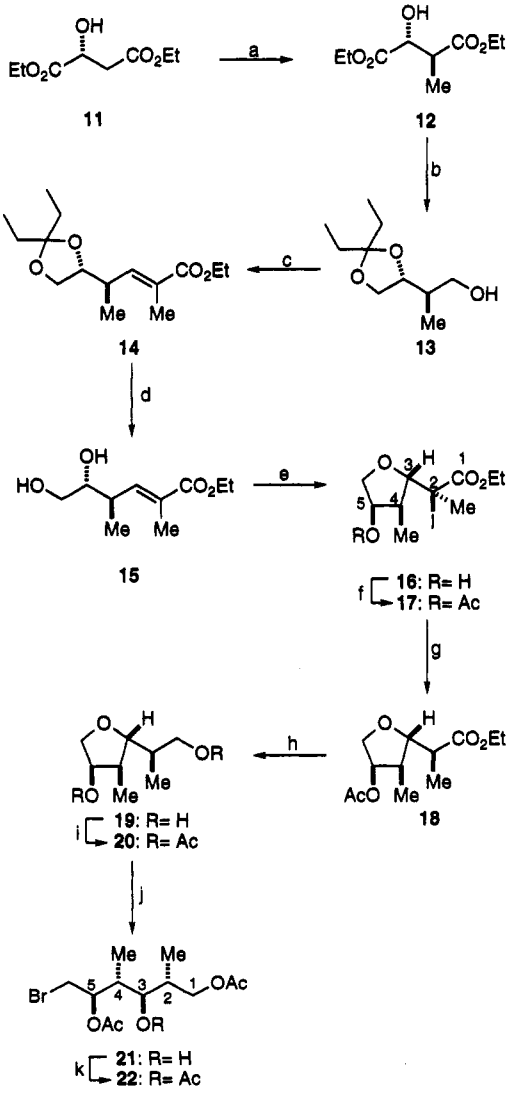
The relative stereochemistry at C_2–C_3 of triacetate **22** (and thus the stereochemistry arising from the radical reduction of **17**) was elucidated from NMR studies of benzylidene acetal **30**, which could be derived from intermediate **19** (Scheme 4). Alcohol **19** was converted by a series of standard protecting group manipulations to acetate **26**. Ring cleavage of **26** using Me_2BBr proceeded smoothly to provide bromide **27** which was subsequently dehalogenated with Bu_3SnH. Removal of the acetate function was then followed by benzylidene acetal formation under standard conditions to provide compound **30** in 90% yield.

Analysis of the ^1H NMR spectra of **30** revealed coupling constants between H_a and H_c (11.1 Hz), between H_d and H_c (10.1 Hz), and between H_b and H_c (4.6 Hz), which are consistent with a *trans* relative stereochemistry of the C_2 and C_3 substituents in **30**. In addition, NOE analysis revealed a network of resonances consistent with structure **30** (Scheme 4). Strong enhancements between each of the axial hydrogens at H_a and H_d with the benzylidene hydrogen were evident, as were weaker NOE effects between the C_2 methyl hydrogens and each of the axial hydrogens at H_a and H_d. Irradiation of H_c induced a 2.3% enhancement of the H_b signal, leaving the H_a resonance completely unaffected. These measurements confirm that the reduction of iodide **17** had generated the *anti* (C_2–C_3) isomer **18** as the major product.

Thus, compound **22** contains all of the required stereocenters in the C_{17}–C_{22} ionomycin subunit and is differentially functionalized in a way which is suitable for further elaboration. This synthesis features two key transformations, iodoetherification and radical reduction, both of which show a high level of stereocontrol. In particular, the reduction of tetrahydrofuranyl ester **17** exhibited unusually good stereocontrol and prompted us to explore the radical-mediated reductions of ring-containing α-halo esters in the following study.

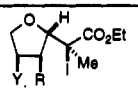
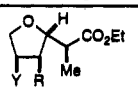
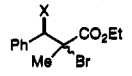
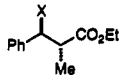
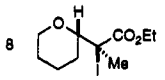
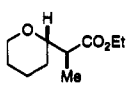
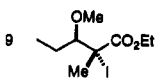
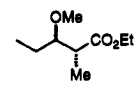
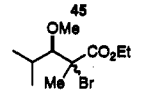
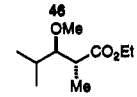
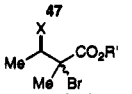
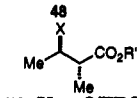
Study of the Radical-Mediated Reductions of Acyclic Tertiary Iodides. That the reduction of tertiary

Scheme 3[a]



[a] Key: (a) LDA (2 equiv), THF, HMPA (1 equiv), −78 °C; MeI (1.5 equiv), −78 to +25 °C, 69%; (b) (i) BH_3·Me_2S (2.5 equiv), THF, reflux, 2.5 h, (ii) $Et_2C(OMe)_2$ (2.0 equiv), *p*-TsOH (0.02 equiv), DMF, 25 °C, 24 h, 55%; (c) (i) DMSO, $(COCl)_2$, iPr_2NEt, (ii) $Ph_3PC(Me)CO_2Et$ (1.3 equiv), 25 °C, 2 h, 65%; (d) 1 N HCl, THF, 25 °C, 18 h, 86%; (e) I_2 (6 equiv), $NaHCO_3$ (6 equiv), THF, 25 °C, 18 h; (f) AcCl, Pyr, CH_2Cl_2, 25 °C, 2 h, 64% from **15**; (g) $HSnBu_3$ (2 equiv), Et_3B (0.5 equiv), toluene, −78 °C, 30 min, 78%; (h) $LiAlH_4$ (5 equiv), THF, 25 °C, 2.5 h; (i) AcCl, Pyr, THF, 25 °C, 2 h, 87%; (j) Me_2BBr (5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 to 25 °C, 7 h; (k) AcCl, Pyr, THF, 25 °C, 2 h, 65% from **20**.

Table 1. Radical Reduction[a]

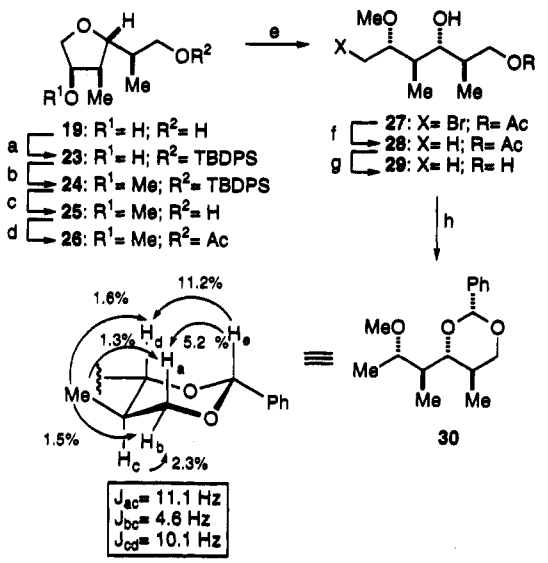
entry	halo ester	product	ratio[b] *anti:syn*	yield (%)
				
1	17: Y = OAc; R = Me	18: Y = OAc; R = Me	>50:1	78
2	31: Y = OAc; R = H	32: Y = OAc; R = H	9:1[c]	80
3	33: Y = H; R = Me	34: Y = H; R = Me	>50:1	90
4	35: Y = H; R = H	36: Y = H; R = H	12:1[d]	91
				
5	37: X = OMe	38: X = OMe	32:1	90
6	39: X = F	40: X = F	20:1	88
7	41: X = Me	42: X = Me	2:1	85
8	 43	 44	>50:1	86
9	 45	 46	1.1:1[e]	89
10	 47	 48	8:1	86
				
11	49: X = OTBS; R′ = Me	50: X = OTBS; R′ = Me	1.2:1[e]	89
12	51: X = OMe; R′ = Et	52: X = OMe; R′ = Et	3:1	70

[a] All reactions were carried out at a concentration of 0.1 M in toluene at −78 °C using 2.0 equiv of *n*-Bu_3SnH and a catalytic amount of AIBN. Initiation was accomplished by irradiation using a sunlamp (CGE 275-W bulb). [b] Ratios were determined for crude reaction isolates, before chromatography. Ratios >20:1 were established by GLC, while ratios <20:1 were determined by ^1H NMR spectroscopy and/or GLC. [c] 6:1 ratio at 50 °C. [d] Reaction performed at −30 °C since the reaction mixture is not homogeneous at −78 °C. [e] 8:1 ratio at 23 °C. [f] Reaction performed as described in a but in dichloromethane.

iodide 17 (Table 1, entry 1) could proceed stereoselectively to give the *anti* product 18 was not surprising. We[8] and others[9,10] have found that stereochemical information can be relayed by a stereogenic center which is adjacent to an acyclic radical. Several noteworthy features govern the stereochemical outcome of these reactions. Delocalized by the adjacent carbonyl (i.e., an ester functionality),[8-10] these radicals have a planar geometry, and the reaction proceeds through a transition state in which 1,3-allylic congestion is relieved. The *anti* selectivity can be significantly enhanced when an electronegative oxygen or a fluorine atom (rather than a carbon atom) is located at the stereogenic center α to the radical (Table 1, entries 5–7).[8,18] Although these elements are present in substrate 17, the *magnitude* of the stereoselection (>50:1) is striking, particularly in comparison to the 32:1 ratio (entry 5) that we had observed[8a] as the highest for the reduction of substrates in which there is no ring adjacent to the radical center. To probe the origin(s) of this enhancement, we prepared a number of cyclic and acyclic α-halo esters and studied their reductions under radical conditions (Table 1). The synthesis of these substrates was straightforward and is illustrated in Scheme 5.

It is obvious from Table 1 that the presence of a ring has a profound effect on the stereoselectivity. As shown by entry 4 (Table 1), the reduction of tetrahydrofuranyl iodoester 35 gave a ratio of 12:1 favoring the *anti*[19] product

Scheme 4[a]



[a] Key: (a) iPr_2NEt (2.0 equiv), TBDPSCl (2.5 equiv), CH_2Cl_2, 25 °C, 4 h, 74%; (b) NaH (1.5 equiv), MeI (3.0 equiv), DMF, 25 °C, 18 h; (c) *n*-Bu_4NF (3.0 equiv), THF, 25 °C, 4 h, 91% (from **23**); (d) AcCl (5.0 equiv), pyridine (8.0 equiv), CH_2Cl_2, 25 °C, 18 h, 97%; (e) Me_2BBr (6.0 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 3 h; (f) $HSnBu_3$ (2.0 equiv), AIBN (0.2 equiv), hexane, reflux, 1 h, 77% (from **26**); (g) 2 N aqueous NaOH, MeOH, 25 °C, 1.5 h, 74%; (h) benzaldehyde dimethyl acetal (3.0 equiv), *p*-TsOH (0.3 equiv), CH_2Cl_2, 25 °C, 18 h, 90%.

(18) The relative stereochemistry of reduced products **38**, **40**, **44**, **46**, **48**, **50**, and **52** was deduced by correlation of ^1H NMR results. In all cases the methyl group α to the ester resonates slightly upfield for the *anti* diastereomers which is in agreement with previously published results. Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024–2030.

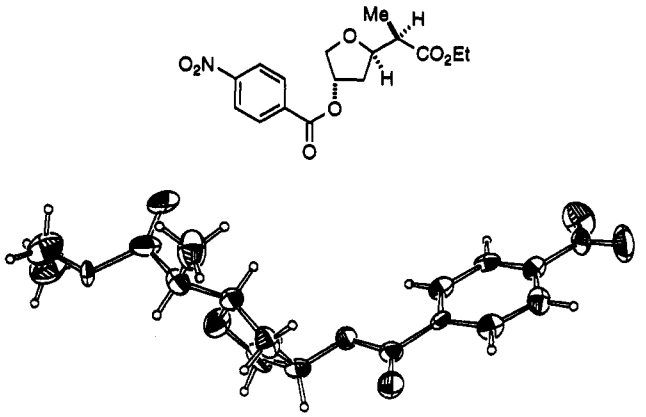
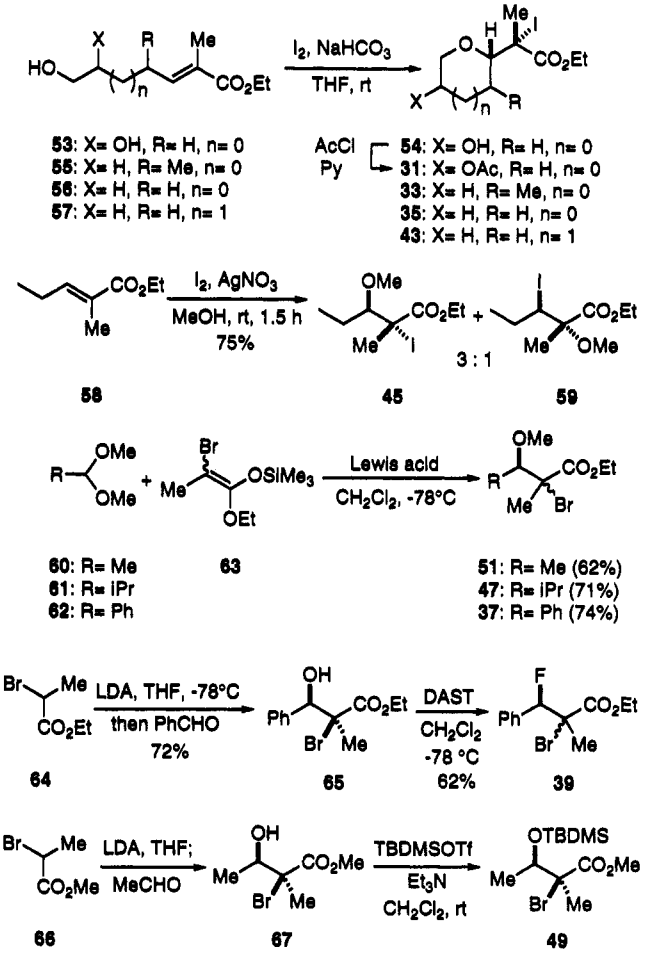


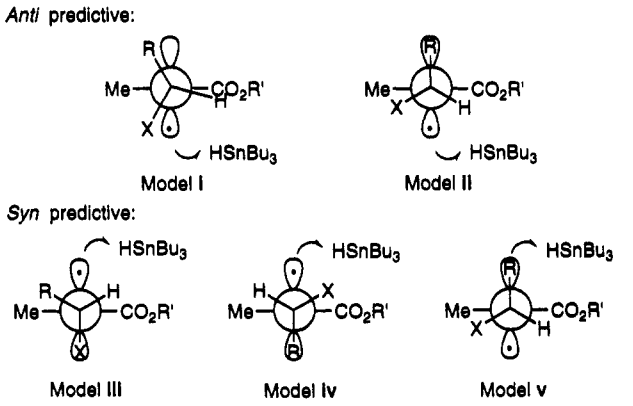
Figure 1. X-ray crystal structure of compound 68.

Scheme 5



36. Excellent selectivity was observed in the reduction of the homologous tetrahydropyran derivative **43** (entry 8). In contrast to these cyclic substrates, their acyclic counterpart **45** reduced under radical conditions with no selectivity even at −78 °C (entry 9). A similar comparison can be made between the substituted tetrahydrofuran **33** (>50:1) and its acyclic counterpart **47** (8:1). The enhancement in *anti* selectivity exhibited by the reduction of tertiary iodide **17** therefore appears to originate mainly

Scheme 6



from the presence of a ring adjacent to the radical ("cycle effect").

The influence exerted by ring substitution on the stereoselectivity of the reduction is shown also by Table 1. In comparison to the absence of ring substitution (entry 4, 12:1), acetate substitution at C_5 (entry 2) produced a ratio of only 9:1 after tributyltin hydride reduction at −78 °C. The reason for this decreased stereoselectivity is not clear but may involve problems of a physicochemical nature, since the reduction of **31** demonstrates little sensitivity to temperature.[20] Methyl substitution at C_4 in the cyclic substrates has a similar beneficial effect on the stereoselectivity of the radical reduction as substitution in the acyclic series (*cf.* entries 9 and 10). It is of particular interest to note that substitution in these cyclic derivatives could influence the reaction from the face of the ring *opposite* to that of the radical center; as a consequence, a study to evaluate the electronic as well as steric components of radical stereocontrol has been initiated in our laboratory.

Mechanistic Considerations. Various transition-state models have been proposed to explain the stereoselection exhibited by systems in which the acyclic radical is flanked by a carbonyl and a stereogenic center (Scheme 6). Model **i**[9d] suggests conformational control via minimization of allylic strain. This model could account for the proportion of *anti* and *syn* products solely by the facial differentiation imparted by the relative sizes of R and X. However, this early attempt to model the behavior of acyclic radicals has some shortcomings. Although steric factors and allylic strain are no doubt key controlling elements, this model cannot rationalize on steric grounds alone the impressive ratios obtained when there is little size differentiation between X and the geminal hydrogen, as in the case when X = fluorine (Table 1, entry 6). Moreover, experiments show that one cannot reverse the stereochemical preference from *anti* to *syn* simply by increasing the steric bulk of X (relative to R), as demonstrated by entries 11 and 12.[21]

Model **ii**, which has been suggested by various groups,[8,22,23] has found indirect support recently in ESR studies (Giese[24]) and semiempirical calculations of ground-state conformations (Liotta,[8c] Giese,[24] and Renaud[25]). These studies show that the geometry of the ground-state

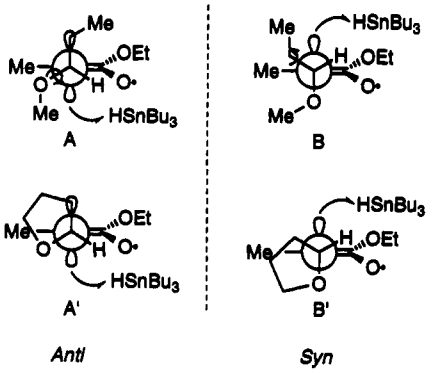
(19) The stereochemistry of cyclic products **34**, **36**, and **44** was established by correlation of NMR results with *anti* product **32** whose structure was established by X-ray analysis of derivative **68** (Figure 1). The ^{1}H NMR resonance of the methyl group α to the ester in compounds **32**, **34**, **36**, and **44** appears consistently upfield from the corresponding signal for the respective *syn* diastereomer; see ref 18.

(20) The reduction of **31** is an example which exhibits little sensitivity to temperature; the *anti*/*syn* ratio is 9:1 at −78 °C and 6:1 at 50 °C. A more typical behavior is demonstrated by the reduction of **37**, in which the selectivity decreases when the temperature of the reaction is increased (32:1 at −78 °C *versus* 7:1 at 50 °C). All reductions are usually performed at two temperatures.

radical is similar to that of the reacting radical depicted by model ii. Our reasons[8] to favor this model are based on both steric and electronic arguments. From a steric standpoint, this transition state should be preferred since destabilizing allylic 1,3-interactions[22] are alleviated. In addition, when R is the largest group, secondary steric interactions would be minimal if the C–R bond is orthogonal to the radical plane. From an electronic standpoint, this transition state could be additionally stabilized in two ways. Firstly, the opposition of the ester and X groups should reduce intramolecular electrostatic repulsions when X is a heteroatom, such as oxygen or fluorine. This may well be an important contributing factor governing stereoselectivity and could account for the impressive ratio (20:1) observed when X = F (Table 1, entry 6), for which a solely steric argument cannot rationalize.[26] A second electronic effect which may lower the transition-state energy involves an interaction between the radical and the C–R bond. A radical that has relatively low SOMO energy may be stabilized through hyperconjugation with the functionality (R vs X) that possesses the highest HOMO.[27,28] In other words, an electron-poor radical could be stabilized by overlapping with the best electron-donating substituent, which is R (rather than X) in this case; in model ii this effect is manifested in the alignment of the σ_{C-R} bond with the singly occupied p orbital.[29]

Even though model ii can account for the *anti* preference, a better understanding of this reaction would require rationalization of the differences in ratio observed for various related substrates, such as those between cyclic and acyclic analogues. One way in which this problem can be approached is to consider, in addition to the *anti* transition-state model, possible *syn*-predictive transition-state models since the product ratio is governed by the difference in *anti* and *syn* transition state energies. Since cyclic substrates react with greater selectivity than their acyclic counterparts ("cycle effect"), this transition state energy difference must be greater for the former series. Hence, we set out to determine which pair of transition-state models reflected best the differences in the stereoselectivity between cyclic substrates (e.g., **35**) and their acyclic analogues (e.g., **45**). Since model ii appears to be operative in the *anti* manifold for these reductions, this problem reduces to a search for the transition state model that leads to the minor *syn* product.[30] The *syn*-predictive transition states (models iii, iv, and v) considered are depicted in Scheme 6.

Scheme 7. Comparison of Models ii (*Anti*) and iii (*Syn*)



A Search for the *Syn*-Predictive Transition-State Model. In the first scenario, models ii and iii are used as the basis of *anti* and *syn* prediction, respectively, and Scheme 7 depicts comparatively the pairs of transition states for the acyclic and cyclic analogues. A cursory examination shows little differentiation, in terms of significant steric destabilization, between the *syn*-predictive transition states for the acyclic (**B**) and cyclic (**B'**) cases; indeed, both appear free of severe 1,3-allylic interactions since the smallest substituent (H) is situated closest to the ester.[24] One obvious difference between the acyclic and cyclic sets of transition states is that the ring conformationally restricts the rotational freedom of the residues corresponding to methoxy (X) and ethyl (R) groups. As a consequence, hydrogen transfer may be more facile for the cyclic derivatives than for their acyclic counterparts since the freely rotating residues at R and X in the latter could obstruct the incoming tributyltin hydride. However, this effect is present in both **A'** and **B'**, and so it is not obvious why the energy difference between **A'** and **B'** should be greater than that between **A** and **B**.

Depicted in Scheme 8 are a second set of transition states which are derived from models ii (*anti*) and iv (*syn*). Indirect support for iv as the *syn*-predictive model is found in the semiempirical calculations performed by both Liotta[8c] and Giese,[24] which show that the second most stable ground-state conformer of the radical has the same geometry as the reacting radical depicted by model iv. Furthermore, this pair of transition-state models could account for the "cycle effect". Although the *anti*-predictive models **A** and **A'** appear to differ little in steric interactions and therefore in energy, *syn*-predictive models **C** and **C'** differ in the severity of the steric congestion between the alkoxy and ester groups. Due to its involvement in the delocalization of the radical, the ester has severely

(21) (a) A few cases in the literature (see ref 10a) do in fact show that silyloxy groups at X can reverse the selectivity to favor the *syn* product. However, there was an additional change made to the substrates in these studies, aside from the change in silyloxy group (X); a neopentyl group replaced the methyl that is situated α to the ester. The reversal in selectivity may therefore be attributed to steric congestion imparted by the neopentyl group rather than silyloxy group in the transition state. (b) See also ref 10m for a discussion.

(22) This model, in which X corresponds to the medium-sized substituent, was first proposed by Hart in his pioneering work on acyclic radicals (see ref 9).

(23) This conformer is included in the "dynamic" model proposed by Giese, Curran, and Porter, which is based solely on steric considerations. Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–303.

(24) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H. G. *Tetrahedron Lett.* **1992**, 1863–1866.

(25) Renaud, P.; Björup, P.; Carrupt, P.-A.; Schenk, K.; Schubert, S. *Synlett* **1992**, 211–213.

(26) Recently, in separate studies, Giese *et al.* have shown by ESR and calculation that radicals generated from **37** and **39** have the same conformation as that shown in transition-state model ii. Interestingly, the conformation of the radical generated from the methyl analog **41** is the same as that depicted in transition-state model i. Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, 5885–5888.

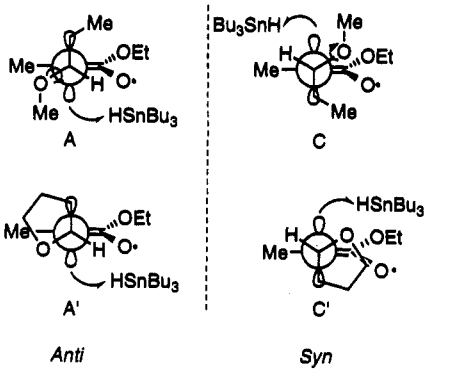
(27) This is supported by the *low* ratio (12:1) noted when a pentafluorophenyl group is substituted in place of a phenyl group at R; see refs 8c,d.

(28) Bernardi, F.; Bottoni, A.; Fossey, J.; Sorba, J. *THEOCHEM* **1989**, *183*, 301–309 and references cited therein.

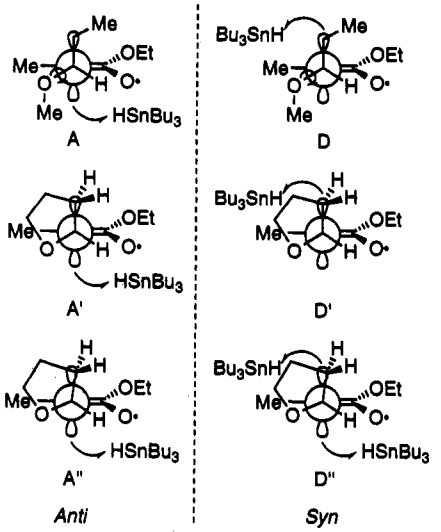
(29) Another interpretation of our results involves the notion of transition-state hyperconjugation. According to this hypothesis, the energy of the activated complex, in a reaction in which bonds are formed, is lowered by the delocalization of electrons comprising an antiperiplanar vicinal σ bond into the σ^* orbital of the bond being formed. Therefore, it is possible to imagine that when ii reacts with Bu_3SnH, the σ^{**} orbital will be stabilized by the adjacent σ_{C-R} bond. (a) Bodepudi, V. R.; Le Nobel, W. J. *J. Org. Chem.* **1991**, *56*, 2001–2006. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540–4552.

(30) An analysis of transition states for stereoselective reductions has been performed by Curran: see ref 10m.

Scheme 8. Comparison of Models ii (*Anti*) and iv (*Syn*)



Scheme 9. Comparison of Models ii (*Anti*) and v (*Syn*)



restricted rotational freedom and assumes an orientation in which it is sterically compressed against the alkoxy group in **C**. The magnitude of this interaction would be considerably greater in **C'** because of the conformational rigidity conferred by the ring. In other words, the energy difference between **C'** and **A'** appears to be larger than that between **C** and **A**. As a consequence, models **ii** and **iv** would predict better stereoselectivity for the reaction of cyclic substrates than their acyclic analogues.

A third possible scenario (Scheme 9) which is consistent with experimental results is based on a comparison of models **ii** and **v**. Model **v** predicts *syn* product formation from attack of tributyltin hydride from the same face of the radical on which R is situated (*syn* attack). This mode of attack should be more prevalent when the alkyl (R) group is small, since the relative transition-state (**v**) energy should vary proportionally with the size of R. An examination of **D** and **D'** suggests that the effective shielding provided by the ring (R) to the top face of the radical in **D'** is greater than that offered by a freely rotating alkyl group (R) in **D**. In other words, model **D'** is disfavored energetically relative to **D** whereas transition states **A** and **A'** are relatively similar in energy. Thus, these models would predict better stereoselectivity for the reaction of the cyclic derivatives than that of their acyclic counterparts.

Aside from the *size* of R, another feature that could influence the proportion of *syn* attack in this model is the *orientation* of R as defined by the dihedral angle between the radical p orbital and the adjacent C–R bond. Slight offsets in the alignment of the C–R bond with respect to the radical p orbital as shown in **D''** could affect the ability of the annular hydrogens to block the radical's top face. It may well be possible to establish a quantitative relationship between this angle and the degree of diastereofacial discrimination.

In summary, two *syn*-predictive transition-state models, **iv** and **v**, could be used in combination with *anti*-predictive model **ii** to explain the "cycle effect". However, only the combination of models **ii**/**v** has the advantage of providing a simple explanation for the increase in stereoselectivity concomitant with the size increase of R in the acyclic series. Namely, when R is ethyl, isopropyl, and phenyl (entries 9, 10, and 5), the *anti*/*syn* ratios are 1:1, 8:1, and >25:1, respectively. In contrast, this phenomenon is less easily rationalized by the combination of models **ii**/**iv**; the enhancement in stereoselectivity must somehow originate from an impediment of tin hydride attack by R in **iv**, which raises the transition-state energy. Theoretical calculations and ESR measurements have been initiated to explore these hypotheses.

Conclusion

The synthesis of the C_{17}–C_{22} fragment of ionomycin described herein highlights the utility of the tandem iodoetherification/radical reduction protocol, which provides rapid access to highly functionalized molecules with excellent stereocontrol.

The use of conformationally-rigidified substrates in this study has led to a more in-depth understanding of the factors influencing the stereoselectivity demonstrated in the reductions of acyclic radicals which are flanked by a carbonyl and a stereogenic center. From a mechanistic standpoint, the contribution of *syn* attack on the radical to *syn* (minor) product formation has been considered in this study. From a strategic point of view, the "cycle effect" may offer a way to improve the stereoselectivity of reactions involving acyclic radicals. Thus, the temporary linkage of substituents corresponding to X and R (either covalently, through metal chelation, or hydrogen bonding) would produce a substrate that resembles **17** and should improve the diastereoselectivity of the radical-mediated reaction. Such a strategy is currently being examined in our laboratories.

Experimental Section

General Methods. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX400 spectrometer and are referenced to TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. CI and EI mass spectra were recorded on an MF 50 TATC instrument operating at 70 eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter at the sodium D line with a 1-dm path length, 1-mL cell. Capillary GC analyses were performed on a Shimadzu GC-9AM instrument using a 0.25-mm × 25-m Chromatopac C-R3A column. Flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm) using nitrogen pressure. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25-mm) Merck silica gel F-254 plates. All reactions were conducted under a positive nitrogen atmosphere in oven-dried glassware using standard syringe techniques. Tetrahydrofuran (THF), ether and toluene were distilled from sodium/benzophenone immmediately prior to use. Dichloromethane (CH_2Cl_2), HMPA, $(iPr)_2EtN$, and diisopropylamine were distilled from calcium hydride. Methanol was distilled from magnesium.

Diethyl (2*R*,3*S*)-3-Methylmalate (12).[16] To a stirred, cold (0 °C) solution of diisopropylamine (40 mL, 285 mmol) in THF (125 mL) was added dropwise a 1.6 M solution of *n*-butyllithium in hexanes (164 mL, 262 mmol). The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. A solution of diethyl (*R*)-malate (21.7 g, 114 mmol) in THF (20 mL) and HMPA (18.8 mL, 114 mmol) was added dropwise, and the mixture was then stirred at −78 °C for 15 min. Subsequently, the mixture was allowed to slowly warm to −20 °C over a period of 2 h. The orange mixture was stirred at −20 °C for 15 min and cooled to −78 °C prior to the dropwise addition of methyl iodide (10.6 mL, 171 mmol). The orange mixture was maintained at −78 °C for 30 min and then warmed to room temperature over 1 h and stirred for 45 min at room temperature. To the cold (0 °C) reaction mixture was added a 10% aqueous citric acid solution (430 mL). The product was extracted with EtOAc (3×), and the combined extracts were washed with H_2O and brine (1×). The orange layer was dried over $MgSO_4$, filtered, and evaporated to dryness to give the crude product as a dark orange oil. Purification on a Waters LC-500 with two SiO_2 columns in 20% EtOAc/hexane at 250 mL/min provided compound **12**[16] (11.6 g, 50%) as an 8:1 mixture of isomers. A sample of the *RS* isomer was obtained by further chromatography: $[\alpha]^{22}_D$ +9.3° (*c* 1.65, Et_2O) (lit.[16b] $[\alpha]^{20}_D$ = +9.75° (*c* 1.896, Et_2O)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0, 172.5, 72.2, 61.5, 60.5, 42.9, 13.8, 12.6.

(*R*,*R*)-β-Methyl-2,2-diethyl-1,3-dioxolane-4-ethanol (13). To a cold (0 °C) solution of ester **12**[16] (1.0 g, 4.9 mmol) in THF (6 mL) was added dropwise 10 M borane–dimethyl sulfide complex (1.23 mL, 12.3 mmol). After the resultant mixture was stirred for 15 min, the reaction was gently refluxed for 2.5 h. During the first hour dimethyl sulfide was distilled off. The reaction mixture was cooled to 0 °C, and MeOH (10 mL) was added. Excess MeOH and THF were removed by rotary evaporation. Successive codistillation with MeOH (2×) using a rotary evaporator removed most of the boron byproducts giving a colorless oil. The crude product (650 mg) was dried *in vacuo* for 24 h and was then used in the next reaction without further purification. To a solution of this triol (650 mg, 4.9 mmol) and 3,3-dimethoxypentane (1.94 g, 14.7 mmol) in DMF (4.9 mL) was added *p*-toluenesulfonic acid (46 mg, 0.24 mmol), and the resultant solution was stirred at room temperature for 16 h. The mixture was then diluted with ether, washed successively with saturated aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), filtered, and evaporated to furnish a pale yellow liquid. *Note*: The product is volatile; use caution during evaporation! Purification by flash chromatography (30% EtOAc in hexanes) provided the desired compound **13** as a single isomer (510 mg, 55% from **12**): $[\alpha]^{25}_D$ −15.9° (*c* 1.01, $CHCl_3$); IR (neat) ν_{max} 3440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 1.63 (q, *J* = 7.2 Hz, 2H), 1.64 (q, *J* = 7.6 Hz, 2H), 1.83–1.89 (m, 1H), 2.86 (dd, *J* = 2.8, 8.6 Hz, 1H), 3.58–3.70 (m, 3H), 3.90–3.95 (dt, *J* = 8.6, 6.0 Hz, 1H), 4.10–4.14 (dd, *J* = 6.0, 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 113.4, 81.4, 69.6, 67.8, 39.2, 29.9, 29.5, 13.0, 8.1, 8.0; HRMS calcd for $C_{10}H_{21}O_3$ (M^+ + H) 189.1491, found 189.1496.

Ethyl (4*R*)-4-[(4*R*)-2,2-Diethyl-1,3-dioxolan-4-yl]-2-methyl-2-pentenoate (14). To a cold (−78 °C) solution of oxalyl chloride (1.34 mL, 15.3 mmol) in CH_2Cl_2 (25 mL) was added DMSO (1.98 mL, 27.8 mmol), and the resultant mixture was stirred for 20 min. Subsequently, a solution of alcohol **13** (2.23 g, 13.9 mmol) in CH_2Cl_2 (30 mL) was added dropwise. After the reaction mixture was stirred for 1 h at −78 °C, $(iPr)_2EtN$ (12.1 mL, 69.6 mmol) was introduced, the cooling bath was removed, and the reaction mixture was stirred for 1.5 h at room temperature. (Carbethoxyethylidene)triphenylphosphorane (6.56 g, 18.1 mmol) was then added, and the resultant suspension was stirred at room temperature for 2 h, after which time only a trace amount of aldehyde was evident by TLC analysis. The reaction mixture was diluted with EtOAc, washed successively with H_2O (3×) and brine (2×), dried ($MgSO_4$), filtered, and stripped of solvent. After the resultant slush was triturated with hexane and filtered, the filtrate was evaporated to dryness to afford a yellow oil. Purification by HPLC (8% EtOAc in hexanes) provided compound **14** as a light yellow oil (2.20 g, 65%): $[\alpha]^{25}_D$ −7.1° (*c* 1.17, $CHCl_3$); IR (neat) ν_{max} 1710, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 7.6 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.58–1.71 (m, 4H), 1.86 (d, *J* = 1.3 Hz, 3H), 2.63–2.72 (m, 1H), 3.52–3.60 (m, 1H), 3.98–4.05 (m, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 6.70 (dd, *J* = 1.3, 9.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.1, 142.9, 128.3, 112.9, 79.5, 68.2, 60.5, 36.6, 29.7, 29.5, 16.0, 14.2, 12.6, 8.2, 7.9; HRMS calcd for $C_{13}H_{21}O_4$ ($M^+ - C_2H_5$) 241.1440, found 241.1430. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.69; H, 9.88.

Ethyl (4*R*,5*R*)-5,6-Dihydroxy-2,4-dimethyl-2-hexenoate (15). To a solution of ester **14** (2.20 g, 9.08 mmol) in THF (45 mL) was added dropwise 1 N aqueous HCl (24 mL). After the reaction mixture was stirred at room temperature overnight, it was diluted with EtOAc, and solid NaCl was added to the resultant mixture. The aqueous layer was extracted with EtOAc (2×), and the combined organic extracts were washed with brine (2×), dried ($MgSO_4$), filtered and evaporated to dryness to afford a yellow oil. Purification by flash chromatography (50% EtOAc in hexanes) provided compound **15** as an oil (1.78 g, 97%): $[\alpha]^{25}_D$ +25.7° (*c* 1.26, $CHCl_3$); IR (neat) ν_{max} 3400, 1700, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.88 (d, *J* = 1.6 Hz, 3H), 2.08 (br, 1H), 2.09 (br, 1H), 2.66–2.76 (m, 1H), 3.52–3.58 (m, 1H), 3.62–3.65 (m, 1H), 3.68–3.77 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 6.69 (dd, *J* = 1.3, 10.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.2, 142.9, 129.0, 75.5, 64.6, 60.7, 36.1, 16.1, 14.2, 12.7; MS (CI) *m/e* 203 (M^+ + H); HRMS calcd for $C_{10}H_{18}O_4$ (M^+) 202.1205, found 202.1188. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.02; H, 9.17.

Ethyl (2*S*)-2-[(2*S*,3*R*,4*R*)-4-Acetoxy-3-methyltetrahydrofuran-2-yl]-2-iodopropionate (17). To a cold (0 °C) solution of diol **15** (2.04 g, 10.1 mmol) in THF (50 mL) were added successively $NaHCO_3$ (5.08 g, 60.5 mmol) and I_2 (15.4 g, 60.5 mmol). After the mixture was allowed to warm to room temperature, it was stirred overnight. The reaction mixture was then diluted with EtOAc and washed successively with saturated aqueous $Na_2S_2O_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to give alcohol **16** as a pale yellow oil. To a cold (0 °C) solution of the crude alcohol in CH_2Cl_2 (50 mL) were successively added dropwise pyridine (6.5 mL, 80.7 mmol) and acetyl chloride (3.6 mL, 50.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Subsequently, the solution was diluted with ether and washed successively with H_2O, 10% aqueous citric acid, H_2O, and brine. After the organic layer was dried ($MgSO_4$), filtered, and concentrated, a yellow oil was obtained. Purification by flash chromatography (10% EtOAc in hexanes) provided acetate **17** as an oil (2.37 g, 64%). *Note*: The product was stored in the freezer wrapped in aluminum foil: $[\alpha]^{25}_D$ +26.2° (*c* 1.12, $CHCl_3$); IR (neat) ν_{max} 1725 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.64 (s, 3H), 2.07 (s, 3H), 2.22–2.31 (m, 1H), 3.66 (dd, J_{AB} = 10.1 Hz, J_{AX} = 2.8 Hz, 1H), 3.69 (dd, J_{AB} = 10.1 Hz, J_{BX} = 4.2 Hz, 1H), 3.97–4.09 (m, 2H), 4.57 (d, *J* = 7.6 Hz, 1H), 5.11–5.15 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.4, 170.6, 88.7, 76.9, 72.8, 62.2, 42.1, 39.8, 25.4, 20.8, 14.5, 13.7; MS (CI) *m/e* 371 (M^+ + H); HRMS calcd for $C_{12}H_{20}O_5I$ (M^+ + H) 371.0357, found 371.0390.

Ethyl (2*S*)-2-[(2*S*,3*R*,4*R*)-4-Acetoxy-3-methyltetrahydrofuran-2-yl]propionate (18). To a cold (−78 °C) solution of **17** (997 mg, 2.69 mmol) in freshly distilled toluene (13 mL) was successively added dropwise Bu_3SnH (1.45 mL, 5.39 mmol) and a 1 M solution of Et_3B in hexane (539 mL, 5.39 mmol). The reaction mixture was stirred at −78 °C for 30 min, and a 1 M solution of tetrabutylammonium fluoride in THF (8.1 mL, 8.1 mmol) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 15 min. After the reaction mixture was evaporated to dryness and triturated with ether, the resultant suspension was filtered through a Celite pad. The filtrate was concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (15% EtOAc in hexanes) provided compound **18** as a colorless oil (509.7 mg, 78%): $[\alpha]^{25}_D$ +66.0° (*c* 1.17, $CHCl_3$); IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.90 (d, *J* = 6.7 Hz, 3H), 1.01 (t, *J* = 7.3 Hz, 3H), 1.16 (d, *J* = 7.3 Hz, 3H), 1.68 (s, 3H), 1.92–2.02 (m, 1H), 2.62–2.69 (m, 1H), 3.76 (dd, J_{AB} = 10.3 Hz, J_{AX} = 1.9 Hz, 1H), 3.84 (dd, J_{AB} = 10.3 Hz, J_{BX} = 4.4 Hz, 1H), 4.01–4.06 (m, 3H), 5.13–5.17 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.8, 170.7, 85.2, 72.4, 60.5, 43.3, 39.9, 20.9, 14.2, 13.2, 11.2; MS (CI) *m/e* 245 (M^+ + H);

HRMS calcd for $C_{11}H_{17}O_5$ ($M^+ - CH_3$) 229.1075, found 229.1063. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.81; H, 8.34.

(2*R*)-1-Acetoxy-2-[(2*S*,3*R*,4*R*)-4-acetoxy-3-methyltetrahydrofuran-2-yl]propane (20). To a cold (0 °C) solution of **18** (919 mg, 3.77 mmol) in THF (20 mL) was added portionwise $LiAlH_4$ (715 mg, 18.8 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 2.5 h. After the mixture was recooled to 0 °C, Celite (2.15 g), H_2O (2.15 mL), 2 N aqueous NaOH (2.15 mL), and H_2O (6.44 mL) were then added sequentially. The resultant suspension was stirred at 0 °C until the mixture became white and was then filtered through a Celite pad, which was rinsed well with EtOAc. The filtrate was concentrated to furnish the crude product which was purified by flash chromatography (70% EtOAc in hexanes) to give diol **19** as a colorless oil (601 mg, 99%): ^{1}H NMR (400 MHz, C_6D_6) δ 0.70 (d, J = 5.1 Hz, 1H), 0.83 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 1.54–1.65 (m, 2H), 2.74 (t, J = 6.3 Hz, 1H), 3.42 (dd, J_{AB} = 9.4 Hz, J_{AX} = 1.7 Hz, 1H), 3.46 (dd, J = 6.3, 8.9 Hz, 1H), 3.55 (dd, J_{AB} = 9.4 Hz, J_{BX} = 4.0 Hz, 1H), 3.56–3.62 (m, 1H), 3.66 (t, J = 5.4 Hz, 2H); HRMS calcd for $C_8H_{17}O_3$ (M^+ + H) 161.1177, found 161.1159. Compound **19** (298 mg, 1.86 mmol) was treated with acetyl chloride and pyridine in CH_2Cl_2 in the same manner as described above for compound **17** to afford the desired compound **20** (398 mg, 87%) as a colorless oil after flash chromatography (20% EtOAc in hexanes): $[\alpha]^{25}_D$ +61.2° (*c* 1.10, $CHCl_3$); IR (neat) ν_{max} 1740 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.86 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 1.70 (s, 3H), 1.73 (s, 3H), 1.77–1.89 (m, 2H), 3.55 (dd, J = 5.1, 9.6 Hz, 1H), 3.71 (dd, J_{AB} = 10.4 Hz, J_{AX} = 1.7 Hz, 1H), 3.78 (dd, J_{AB} = 10.4 Hz, J_{BX} = 4.3 Hz, 1H), 4.11 (dd, J = 7.0, 10.8 Hz, 1H), 4.32 (dd, J = 5.1, 10.8 Hz, 1H), 5.12–5.16 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0, 170.7, 85.6, 72.2, 65.9, 40.0, 35.9, 20.9, 14.5, 11.2; MS (CI) *m/e* 245 (M^+ + H); HRMS calcd for $C_{12}H_{21}O_5$ (M^+ + H) 245.1389, found 245.1411. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.62; H, 8.28.

(2*R*,3*R*,4*R*,5*R*)-1,3,5-Triacetoxy-6-bromo-2,4-dimethylhexane (22). To a cold (0 °C) solution of **20** (54.6 mg, 0.224 mmol) in CH_2Cl_2 (1.2 mL) was successively added dropwise Et_3N (46.8 mL, 0.336 mmol) and a 1.41 M solution of Me_2BBr in CH_2Cl_2 (794 mL, 1.12 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for a total of 7 h, after which time starting material was still evident by TLC analysis. Consequently, more Me_2BBr solution (159 mL, 0.22 mmol) was added to the reaction mixture, which was then stirred at room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of 10 mL of cold saturated aqueous $NaHCO_3$ in one portion. The resultant mixture was diluted immediately with ether, and the layers were separated. The ether layer was washed successively with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to give alcohol **21** as a colorless oil. Treatment of a solution of **21** in CH_2Cl_2 with acetyl chloride and pyridine in the same manner as described for compound **17** furnished, after flash chromatography (20% EtOAc in hexanes), compound **22** as a colorless oil (53 mg, 65%): $[\alpha]^{25}_D$ +24.3° (*c* 1.13, $CHCl_3$); IR (neat) ν_{max} 1745 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.72 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 1.67 (s, 3H), 1.75 (s, 3H), 1.76 (s, 3H), 1.92–2.00 (m, 1H), 2.24–2.29 (m, 1H), 3.15 (dd, J = 8.4, 11.1 Hz, 1H), 3.56 (dd, J = 2.5, 11.1 Hz, 1H), 3.95–4.00 (m, 2H), 4.90 (dd, J = 5.5, 7.5 Hz, 1H), 5.26–5.30 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0, 170.4, 170.1, 76.4, 73.1, 65.4, 37.4, 34.8, 32.3, 21.0, 20.8, 14.6, 12.5; MS (CI) *m/e* 367 (M^+ + H); HRMS calcd for $C_{14}H_{24}BrO_6$ (M^+ + H) 367.0757, found 367.0761. Anal. Calcd for $C_{14}H_{23}BrO_6$: C, 45.79; H, 6.31. Found: C, 46.12; H, 6.40.

(2*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-[(2*R*,3*R*,4*R*)-4-hydroxy-3-methyltetrahydrofuran-2-yl]propane (23). To a solution of diol **19** (289 mg, 1.80 mmol) in CH_2Cl_2 (9.0 mL) was added successively *N*,*N*-diisopropylethylamine (628 μL, 3.61 mmol), *tert*-butyldiphenylsilyl chloride (1.17 mL, 4.51 mmol), and (*N*,*N*-dimethylamino)pyridine (44.1 mg, 0.36 mmol), and the reaction mixture was stirred at room temperature for 4 h. The resultant solution was then diluted with ether and washed sequentially with saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to furnish a colorless oil, which was purified by flash chromatography (20% EtOAc in hexanes) to provide compound **23** as a colorless oil (535 mg, 74%): $[\alpha]^{25}_D$ +30.8° (*c* 1.06, $CHCl_3$); IR (neat) ν_{max} 3420 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.76 (d, J = 5.5 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.25 (s, 9H), 1.75–1.78 (m, 1H), 1.90–1.95 (m, 1H), 3.52 (dd, J = 1.8, 9.4 Hz, 1H), 3.61–3.69 (m, 3H), 3.82 (dd, J = 6.9, 9.8 Hz, 1H), 4.03 (dd, J = 5.1, 9.9 Hz, 1H), 7.29–7.31 (m, 6H), 7.85–7.88 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.6, 134.0, 133.9, 129.5, 127.6, 85.2, 75.4, 74.4, 65.6, 40.9, 39.3, 26.9, 19.3, 14.2, 11.4; HRMS calcd for $C_{24}H_{34}O_3Si$ ($M^+ - C_4H_9$) 341.1572, found 341.1573. Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.04; H, 8.67.

(2*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-[(2*R*,3*R*,4*R*)-4-methoxy-3-methyltetrahydrofuran-2-yl]propane (24). To a cold (0 °C) solution of **23** (211.4 mg, 0.53 mmol) in DMF (3 mL) was added NaH (19.1 mg, 0.79 mmol), and the resultant mixture was stirred for 20 min at 0 °C. After iodomethane (99 μL, 1.59 mmol) was added dropwise, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with ether and washed successively with saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated to yield crude **24** as a pale yellow oil. Purification by flash chromatography (5% EtOAc in hexanes) gave compound **24** as a colorless oil (156 mg, 69%): $[\alpha]^{25}_D$ +42.2° (*c* 1.08, $CHCl_3$); IR (neat) ν_{max} 2925, 2880, 2845, 1455, 1435, 1110 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 1.11 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.25 (s, 9H), 1.95–1.99 (m, 2H), 3.00 (s, 3H), 3.34–3.36 (m, 1H), 3.63 (dd, J = 4.4, 9.5 Hz, 1H), 3.75–3.80 (m, 2H), 3.84 (dd, J = 6.7, 9.8 Hz, 1H), 4.07 (dd, J = 5.1, 9.9 Hz, 1H), 7.21–7.25 (m, 6H), 7.85–7.89 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.6, 134.0, 133.9, 129.5, 127.6, 86.1, 83.7, 70.4, 65.5, 57.4, 39.8, 39.2, 26.9, 19.2, 14.3, 11.5; HRMS calcd for $C_{21}H_{27}O_3Si$ ($M^+ - C_4H_9$) 355.1730, found 355.1758. Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79. Found: C, 73.02; H, 8.97.

(2*S*,3*S*)-3-[(2*R*,4*R*,5*R*)-5-Methyl-2-phenyl-1,3-dioxan-4-yl]-2-methoxybutane (30). To a solution of the crude product **24** (1.34 mmol) in THF (7 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (4.0 mL, 4.0 mmol), and the resultant mixture was stirred at room temperature for 4 h. Concentration of the reaction mixture and purification by flash chromatography (50% EtOAc in hexanes) afforded compound **25** as a colorless oil (212 mg, 91%): ^{1}H NMR (400 MHz, C_6D_6) δ 0.90 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.61–1.65 (m, 1H), 1.72–1.78 (m, 1H), 2.87 (t, J = 6 Hz, 1H), 2.96 (s, 3H), 3.24–3.27 (m, 1H), 3.52 (dd, J = 4, 9 Hz, 1H), 3.59–3.71 (m, 4H). Acetyl chloride (433 μL, 6.08 mmol) was added dropwise to a cold (0 °C) solution of **25** (212 mg, 1.22 mmol) and pyridine (787 μL, 9.73 mmol) in CH_2Cl_2 (6 mL). After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred overnight. The resultant solution was then diluted with ether and water, and the two layers were separated. The organic layer was successively washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification by flash chromatography (20% EtOAc in hexanes) gave compound **26** as a colorless oil (236 mg, 97%): ^{1}H NMR (400 MHz, C_6D_6) δ 1.03 (d, J = 6 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.73 (s, 3H), 1.73–1.83 (m, 1H), 1.84–1.94 (m, 1H), 3.00 (s, 3H), 3.30–3.33 (m, 1H), 3.62 (dd, J = 4, 10 Hz, 1H), 3.67 (dd, J = 5, 10 Hz, 1H), 3.77 (dd, J = 1, 10 Hz, 1H), 4.17 (dd, J = 7, 10 Hz, 1H), 4.42 (dd, J = 4, 10 Hz, 1H). To a cold (0 °C) solution of compound **26** (58.7 mg, 0.271 mmol) in CH_2Cl_2 (1.5 mL) was added successively triethylamine (56.7 μL, 0.407 mmol) and a 1.66 M solution of Me_2BBr in CH_2Cl_2 (980 μL, 1.63 mmol). The reaction mixture was then stirred for 3 h (bath temperature *ca.* 5 °C; TLC: 30% EtOAc in hexanes). Subsequently, the reaction mixture was poured into a stirred saturated aqueous $NaHCO_3$ solution (*ca.* 10 mL) and diluted with ether. The organic layer was washed successively with water and brine, dried ($MgSO_4$), filtered, and concentrated to give compound **27** as a colorless oil. To a solution of crude **27** in hexane (1.5 mL) was added sequentially tributyltin hydride (146 μL, 0.543 mmol) and AIBN (8.9 mg, 0.054 mmol). The reaction mixture was gently refluxed for 1 h and was then cooled to room temperature prior to the addition of a 1 M solution of Bu_4NF in THF (813 mL). The resultant mixture was stirred for 10 min and then concentrated. Purification of the residue by flash chromatography (15% EtOAc in hexanes) afforded

compound **28** as a colorless oil (45.7 mg, 77%): ^{1}H NMR (400 MHz, C_6D_6) δ 0.77 (d, J = 7 Hz, 3H), 0.96 (d, J = 6 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 1.74 (s, 3H), 1.79–1.85 (m, 1H), 2.09–2.12 (m, 1H), 2.98 (s, 3H), 3.08 (quint, J = 6 Hz, 1H), 3.37 (dd, J = 3, 8 Hz, 1H), 3.77 (br, 1H), 4.27 (dd, J = 8, 11 Hz, 1H), 4.55 (dd, J = 5, 11 Hz, 1H); HRMS calcd for $C_{11}H_{21}O_4$ (M^+ – H) 217.1440, found 217.1447. To a solution of **28** (31.4 mg, 0.144 mmol) in MeOH (1 mL) and H_2O (500 μL) was added 2 N aqueous NaOH (216 μL), and the resultant mixture was stirred for 1.5 h at room temperature. Subsequently, the reaction mixture was diluted with EtOAc and washed successively with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil, which was purified by flash chromatography (40% EtOAc in hexanes) to furnish compound **29** as a colorless oil (18.9 mg, 74%): ^{1}H NMR (400 MHz, C_6D_6) δ 0.65 (d, J = 7 Hz, 3H), 0.99 (d, J = 6 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 1.38–1.47 (br, 1H), 1.69–1.73 (m, 1H), 1.84–1.89 (m, 1H), 2.99 (s, 3H), 3.18 (quint, J = 6 Hz, 1H), 3.43 (dd, J = 4, 8 Hz, 1H), 3.59 (dd, J = 4, 10 Hz, 1H), 3.90 (dd, J = 3, 10 Hz, 1H), 4.20–4.35 (br, 1H); HRMS calcd for $C_9H_{21}O_3$ (M^+ + H) 177.1491, found 177.1507. To a solution of **29** (18.9 mg, 0.107 mmol) and benzaldehyde dimethyl acetal (48 μL, 0.32 mmol) in CH_2Cl_2 (1.5 mL) was added *p*-toluenesulfonic acid (6.1 mg, 0.03 mmol), and the resultant solution was stirred at room temperature overnight. Diisopropylethylamine (6 μL, 0.03 mmol) was added, and the mixture was evaporated to dryness. Purification of the residue by flash chromatography (2.5% EtOAc in hexanes) provided compound **30** as a colorless oil (25.6 mg, 90%): IR (neat) ν_{max} 2970, 2930, 1460, 1395, 1100, 1030, 700 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.56 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 7.3 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H), 2.11–2.16 (m, 2H),[31] 3.16 (s, 3H), 3.22 (t, J = 11.1 Hz, 1H), 3.29 (dd, J = 2.7, 10.1 Hz, 1H), 3.49–3.52 (m, 1H), 3.99 (dd, J = 4.6, 11.0 Hz, 1H), 5.40 (s, 1H), 7.16–7.30 (m, 3H), 7.73–7.76 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.0, 128.6, 128.1, 126.0, 101.5, 86.4, 76.8, 73.5, 55.9, 38.6, 31.5, 16.4, 12.5; HRMS calcd for $C_{16}H_{24}O_3$ (M^+) 264.1726, found 264.1713. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.76; H, 9.47.

Ethyl (2*S*)-2-[(2*S*,4*R*)-4-Acetoxytetrahydrofuran-2-yl]-2-iodopropionate (31). To a stirred solution of ethyl (5*S*)-5,6-dihydroxy-2-methylhex-2-enoate (**53**)[32] (660 mg, 3.53 mmol) in dry THF (15 mL) was added successively $NaHCO_3$ (1.48 g, 17.7 mmol) and iodine (4.48 g, 17.7 mmol). After being stirred for 24 h, the mixture was diluted with ether (60 mL) and washed sequentially with 10% aqueous $Na_2S_2O_3$ (4 × 15 mL) and brine (2 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated to give an oil, which was subsequently dissolved in CH_2Cl_2 (15 mL). This solution was cooled to 0 °C prior to the successive addition of pyridine (1.14 mL, 14.1 mmol) and acetyl chloride (1.00 mL, 14.1 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and then diluted with ether (100 mL). The organic layer was washed sequentially with water (2 × 20 mL), saturated aqueous NH_4Cl (20 mL), and brine (20 mL), dried with $MgSO_4$, and concentrated. Flash chromatography (10% EtOAc in hexanes) of the residue gave compound **31** (579 mg, 64%) as a colorless oil: $[\alpha]^{25}_D$ –1.2° (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 1740, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7 Hz, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.17 (ddd, J = 15, 10, 6 Hz, 1H), 2.44 (ddt, J = 14, 6, 1 Hz, 1H), 3.99 (dt, J = 10, 1 Hz, 1H), 4.11 (dd, J = 10, 4 Hz, 1H), 4.25 (qd, J = 7, 4 Hz, 2H), 4.42 (dd, J = 10, 6 Hz, 1H), 5.32–5.34 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2, 170.3, 82.6, 74.9, 74.3, 61.9, 42.9, 37.4, 24.8, 20.9, 13.4; HRMS calcd for $C_{11}H_{17}IO_5$ (M^+) 356.0122, found 356.0064. Anal. Calcd for $C_{11}H_{17}IO_5$: C, 37.10; H, 4.81. Found: C, 37.42; H, 4.66.

Ethyl (2*S*)-2-[(2*S*,3*R*)-3-Methyltetrahydrofuran-2-yl]-2-iodopropanoate (33). To a stirred solution of ethyl (4*R*)-2,4-dimethyl-6-hydroxyhex-2-enoate (**55**)[33] (400 mg, 2.15 mmol) in dry THF (11 mL) was added successively solid $NaHCO_3$ (903 mg, 10.8 mmol) and iodine (2.73 g, 10.8 mmol). After the mixture was stirred for 24 h at room temperature, it was diluted with ether (30 mL), washed successively with 10% aqueous $Na_2S_2O_3$ (4 × 10 mL) and brine (2 × 7 mL), and dried over $MgSO_4$. Solvent removal afforded adduct **33** as an oil (550 mg, 82%): IR (neat) ν_{max} 1730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 1.54–1.65 (m, 1H), 2.00 (s, 3H), 2.09–2.15 (m, 1H), 2.42–2.55 (m, 1H), 3.86 (td, J = 8, 5 Hz, 1H), 3.98 (ddd, J = 5, 4, 3 Hz, 1H), 4.17 (d, J = 4 Hz, 1H), 4.20–4.30 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.9, 90.0, 69.8, 62.0, 43.2, 36.7, 34.9, 24.5, 21.5, 13.6; MS (CI, CH_4) *m/e* (relative intensity) 312 (M^+, 6), 185 (M^+ – I, 29), 85 (100); HRMS calcd for $C_{10}H_{17}IO_4$ (M^+) 312.0224, found 312.0200.

Ethyl 2-Tetrahydrofuran-2-yl-2-iodopropanoate (35). To a mixture of ethyl 2-methyl-6-hydroxyhex-2-enoate (**56**)[34] (200 mg, 1.07 mmol) and solid $NaHCO_3$ (270 mg, 3.21 mmol) in THF (2.9 mL) was added iodine (1.36 g, 5.35 mmol), and the resultant mixture was stirred at room temperature for 20 h. Subsequently, the mixture was diluted with EtOAc (40 mL), and the organic layer was washed sequentially with saturated aqueous $Na_2S_2O_3$ (2 × 30 mL) and brine (30 mL). After the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, the resultant residue was purified by flash chromatography (10% EtOAc in hexanes) to afford pure compound **35** (208 mg, 62%) as a colorless oil: IR (neat) ν_{max} 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7 Hz, 3H), 1.90–2.01 (m, 3H), 2.02 (s, 3H), 2.21–2.32 (m, 1H), 3.85–4.02 (m, 2H), 4.18–4.32 (m, 2H), 4.39–4.46 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.1, 82.7, 69.8, 61.2, 43.3, 29.7, 26.0, 23.7, 13.2; MS (CI, CH_4) *m/e* (relative intensity) 299 (M^+ + H, 100), 171 (M^+ – I, 57); HRMS calcd for $C_{10}H_{17}IO_3$ (M^+) 312.0200, found 312.0224.

Ethyl 2-Bromo-2-methyl-3-methoxy-3-phenylpropionate (37). A solution of LDA was prepared by the addition of a 1.6 M solution of *n*-BuLi in hexanes (8.8 mL, 14 mmol) to a cold (0 °C) solution of diisopropylamide (2.0 mL, 14 mmol) in dry THF (6 mL). After 20 min, the solution was cooled to –78 °C, and a solution of ethyl 2-bromopropionate (1.56 mL, 12.0 mmol) in THF (2 mL) was added. The reaction mixture was stirred at –78 °C for 5 min prior to the addition of freshly distilled trimethylsilyl chloride (2.5 mL, 20 mmol). After the mixture was allowed to warm to room temperature, the solvents were removed *in vacuo* and replaced with dry hexane. The salts were removed by filtration, and the filtrate was concentrated *in vacuo* to afford the desired silyl ketene acetal **63**, which was used directly in the subsequent reaction. To a cold (–78 °C), stirred solution of benzaldehyde dimethyl acetal (1.2 mL, 8.0 mmol) in dry CH_2Cl_2 (15 mL) was added $TiCl_4$ (0.88 mL, 8.0 mmol), and the resultant solution was stirred for 5 min prior to the addition of a solution of silyl ketene acetal **63** in CH_2Cl_2 (3 mL). After 30 min, water (10 mL) and ether (30 mL) were added to the reaction mixture, and the layers were separated. The organic layer was successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The crude material was purified by flash chromatography (4% EtOAc in hexane) to afford bromide **37** (1.78 g, 74%) as a colorless oil (*ca.* 1:1 mixture of diastereomers): IR ($CHCl_3$) ν_{max} 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 and 1.36 (t, J = 7 Hz, 3H), 1.74 and 1.78 (s, 3H), 3.25 and 3.34 (s, 3H), 4.10–4.40 (m, 2H), 4.76 and 4.92 (s, 1H), 7.30–7.55 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.6, 169.9, 135.5, 134.9, 129.5, 128.7, 128.6, 128.4, 128.0, 127.6, 86.4, 86.0, 65.4, 62.2, 62.0, 60.4, 57.8, 57.7, 23.1, 21.3, 14.0, 13.9; MS (CI, CH_4) *m/e* 301 (M^+ + H), 303 (M^+ + H). Anal. Calcd for $C_{13}H_{17}BrO_7$: C, 51.84; H, 5.69. Found: C, 51.79; H, 5.67.

Ethyl 2-Bromo-2-methyl-3-fluoro-3-phenylpropionate (39). To a cold (–78 °C), stirred solution of the lithium enolate of ethyl 2-bromopropionate (**64**) (generated from LDA) in dry THF (8 mL) was added a solution of benzaldehyde (0.50 mL, 4.9 mmol) in THF (1 mL). After 10 min, saturated aqueous NH_4Cl (14 mL) was added to the reaction mixture, and the layers were separated.

(31) The J_{CD} coupling constant (Scheme 4) was identified by successively decoupling the resonances at 0.56 ppm and 1.12 ppm and subtracting the resulting spectra from the normal spectrum. These experiments were performed at 600 MHz.

(32) Compound **53** was prepared from (*R*)-malic acid by using procedures reported previously for ethyl 5,6-dihydroxyhex-2-enoate; see ref 15a.

(33) Compound **55** was prepared in two steps from α-methylbutyrolactone: (i) DIBAL, CH_2Cl_2, –78 °C; (ii) (carbethoxyethylidene)triphenylphosphorane.

(34) Compound **56** was prepared from the Swern oxidation of 4-(*tert*-butyldimethylsiloxy)butanol and subsequent treatment of the resultant aldehyde with (carbethoxyethylidene)triphenylphosphorane. McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390.

The aqueous layer was extracted with ether (2×), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexane) to afford the pure adduct **65** (518 mg, 37%) and the corresponding epoxide. To a cold (−78 °C), stirred solution of the alcohol **65** (135 mg, 0.469 mmol) in dry CH_2Cl_2 (5 mL) was added DAST (55 mL, 0.56 mmol), and the resultant mixture was allowed to warm to room temperature. After 30 min, water (5 mL) was added, and the mixture was poured into ether (30 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (5% EtOAc in hexane) to afford a *ca.* 1:1 mixture of fluorides **39** (83.4 mg, 62%). Colorless oil: IR (neat) ν_{max} 1740 cm^{-1}; MS (CI, CH_4) *m/e* 289 (M^+ + H), 269; HRMS calcd for $C_{12}H_{14}FBrO_2$ (M^+) 288.0161, found 288.0171. Less polar isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7 Hz, 3H), 1.82 (s, 3H), 4.34 (q, *J* = 7 Hz, 2H), 6.12 (d, *J* = 43 Hz, 1H), 7.45 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.47, 133.82 (d, *J* = 21 Hz), 129.14, 127.70, 127.14, 94.93 (d, *J* = 180 Hz), 62.61, 58.50 (d, *J* = 31 Hz), 21.14, 13.86. More polar isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7 Hz, 3H), 1.82 (s, 3H), 4.26 (dq, *J* = 2, 7 Hz, 2H), 6.05 (d, *J* = 44 Hz, 1H), 7.37 (s, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.9 (d, *J* = 7 Hz), 134.4 (d, *J* = 22 Hz), 129.2, 128.2, 127.2 (d, *J* = 8 Hz), 95.1 (d, *J* = 185 Hz), 62.5, 62.17 (d, *J* = 25 Hz), 22.1, 13.8. Anal. Calcd for $C_{12}H_{14}BrFO_2$: C, 49.85; H, 4.88. Found: C, 49.74; H, 4.94.

Ethyl 2-Bromo-2-methyl-3-phenylbutanoate (41). To a stirred solution of 1-chloro-1-phenylethane (740 mg, 5.26 mmol) and silyl ketene acetal **63** (prepared as described above for compound **37**; *ca.* 10 mmol) in dry CH_2Cl_2 (10 mL) was added a catalytic amount of Ph_3CSbCl_6. After 1 h, water (5 mL) and ether (50 mL) were added. The organic layer was successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), and dried over $MgSO_4$. Concentration of the organic layer gave a residue, which was purified by flash chromatography (5% EtOAc in hexane) to afford a 1:1 mixture of bromides **41** (766 mg, 51%). Colorless oil (*ca* 1:1 mixture of diastereomers): IR (neat) ν_{max} 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 and 1.31 (t, t, *J* = 7 Hz, 3H), 1.39 and 1.56 (d, d, *J* = 7 Hz, 3H), 1.82 and 1.85 (s, s, 3H), 3.65 (q, *J* = 7 Hz, 1H), 4.16 and 4.25 (respectively: m and q, *J* = 7 Hz, 2H), 7.25–7.35 (m, 5H); MS (CI, CH_4) *m/e* 287 (M^+ + H), 285 (M^+ + H).

Ethyl 2-Tetrahydropyran-2-yl-2-iodopropanoate (43). To a stirred solution of ethyl 6-hydroxy-2-methylhept-2-enoate (**57**)[35] (200 mg, 1.07 mmol) in dry THF (11 mL) was added successively $NaHCO_3$ (270 mg, 3.21 mmol) and iodine (1.36 g, 5.35 mmol). After the reaction mixture was stirred for 24 h, it was diluted with ether (30 mL), washed successively with 10% aqueous $Na_2S_2O_3$ (4 × 10 mL) and brine (2 × 7 mL), and dried over $MgSO_4$. Removal of solvent afforded adduct **43** as an oil (208 mg, 62%): IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7 Hz, 3H), 1.37–1.60 (m, 4H), 1.93–2.01 (m, 1H), 2.01 (s, 3H), 2.18–2.26 (m, 1H), 3.43 (td, *J* = 11, 3 Hz, 1H), 3.85–3.95 (m, 2H), 4.15–4.35 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.2, 82.3, 69.1, 61.6, 42.4, 26.5, 25.5, 24.6, 23.8, 13.7; MS 313 (M^+ + H, 95), 267 (M^+ − OEt, 10), 239 (M^+ − CO_2Et, 2), 185 (M^+ − I, 50); HRMS calcd for $C_{10}H_{17}IO_3$ (M^+) 312.0223, found 312.0224. Anal. Calcd for $C_{10}H_{17}IO_3$: C, 38.48; H, 5.49. Found: C, 38.20; H, 5.46.

Ethyl (2*R,3*R**)-2-Iodo-2-methyl-3-methoxypentanoate (45).** To a solution of ethyl 2-methylpent-2-enoate (**58**)[36] (509 mg, 3.58 mmol) in absolute methanol (27 mL) was successively added $AgNO_3$ (731 mg, 4.30 mmol) and iodine (1.09 g, 4.30 mmol). The reaction mixture was stirred at room temperature in the dark for 1.5 h and filtered. After the filtrate was concentrated, the resultant residue was dissolved in ether and successively washed with 10% $Na_2S_2O_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a residue, which was purified by flash chromatography (2% EtOAc in hexanes) to afford iodide **45** and its regioisomer (3-iodo-2-methoxy) in a 3:1 ratio (808 mg, 75%). Iodide **45** can be obtained in pure form by additional flash chromatography under the same conditions. Colorless oil: IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7 Hz, 3H), 1.33 (t, *J* = 7 Hz, 3H), 1.49–1.74 (m, 1H), 1.97 (s, 3H), 2.15–2.35 (m, 1H), 3.47 (s, 3H), 3.83 (dd, *J* = 2, 10 Hz, 1H), 4.21–4.32 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.2, 87.5, 61.6, 60.9, 43.8, 24.9, 23.9, 13.6, 12.0; MS (CI, NH_3) *m/e* (relative intensity) 318 (M^+ + NH_4, 100), 301 (M^+ + H, 6); HRMS calcd for $C_9H_{17}IO_3$ (M^+) 300.0256, found 300.0240. Anal. Calcd for $C_9H_{17}IO_3$: C, 36.01; H, 5.71. Found: C, 35.99; H, 5.77.

Ethyl 2-Bromo-2,4-dimethyl-3-methoxypentanoate (47). To a cold (−78 °C), stirred solution of Ph_3CSbCl_6 (260 mg, 0.450 mmol) in dry CH_2Cl_2 (25 mL) was added sequentially isobutyraldehyde dimethyl acetal (1.1 mL, 9.0 mmol) and a solution of silyl ketene acetal **63** (prepared as described above for compound **37**; 9 mmol) in CH_2Cl_2. The mixture was stirred at −78 °C for 30 min before being quenched with saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. Flash chromatography (7% EtOAc in hexanes) afforded compound **47** (1.71 g, 70%). Colorless oil (*ca.* 1:1 mixture of diastereomers): IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7 Hz), 1.01 (d, *J* = 7 Hz, 3H), 1.02 (d, *J* = 7 Hz, 3H), 1.14 (d, *J* = 7 Hz, 3H), 1.33 (t, *J* = 7 Hz, 6H), 1.70 (dh, *J* = 5, 7 Hz, 1H), 1.84 (s, 6H), 2.27 (dh, *J* = 3, 7 Hz, 1H), 3.45 (s, 3H), 3.60 (d, *J* = 5 Hz, 1H), 3.66 (s, 3H), 3.77 (d, *J* = 3 Hz, 1H), 4.23 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.9, 170.7, 89.3, 88.6, 66.1, 63.0, 62.9, 61.9, 61.4, 32.3, 29.4, 24.5, 22.6, 22.1, 21.8, 19.0, 17.8, 14.0, 13.8; MS (CI, CH_4) *m/e* (relative intensity) 267 (M^+ + H, 62).

Methyl 2-Bromo-2-methyl-3-[(*tert*-butyldimethylsilyl)oxy]butanoate (49). To a cold (0 °C), stirred solution of diisopropylamine (1.66 mL, 11.8 mmol) in THF (12 mL) was added dropwise a 2.5 M solution of butyllithium in hexanes (4.51 mL, 11.3 mmol), and the resultant mixture was stirred for 20 min. The mixture was then cooled to −78 °C, and methyl 2-bromopropionate (1.20 mL, 10.8 mmol) was added. After 10 min, acetaldehyde (0.60 mL, 11 mmol) was added. The reaction mixture was stirred for another 15 min and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). After the resultant mixture was allowed to reach room temperature, it was diluted with ether (50 mL) and washed successively with water (2 × 5 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the aldol adduct **67** (576 mg, 25%) and the corresponding epoxide (316 mg, 23%). Adduct **67**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6 Hz, 3H), 1.85 (s, 3H), 2.79 (d, *J* = 4 Hz, 1H), 3.82 (s, 3H), 4.15 (dq, *J* = 6, 4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.4, 71.8, 67.9, 53.3, 23.0, 17.6. To a solution of the bromo alcohol **67** (490 mg, 2.32 mmol) in dry CH_2Cl_2 (8 mL) was added sequentially $EtN(iPr)_2$ (315 mg, 2.44 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (737 mg, 2.78 mmol). The mixture was stirred at −20 °C for 10.5 h and then at 25 °C for another 20 min. Ether (60 mL) was added, and the organic phase was washed successively with water (5 mL) and brine (5 mL). After the organic layer was dried over $MgSO_4$, filtered, and concentrated, the resultant residue was purified by flash chromatography (5% EtOAc in hexanes) to give the silylated product **49** (635 mg, 84%) as a colorless oil: IR (neat) ν_{max} 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.83 (s, 9H), 1.31 (d, *J* = 6 Hz, 3H), 1.81 (s, 3H), 3.78 (s, 3H), 4.33 (q, *J* = 6 Hz, 1H); ^{13}C NMR (less polar bromide) (50.3 MHz, $CDCl_3$) δ 171.3, 72.1, 62.3, 52.7, 25.5, 20.3, 17.9, 17.7, −4.1, −5.4; ^{13}C NMR (more polar bromide) (50.3 MHz, $CDCl_3$) δ 171.2, 72.8, 66.4, 52.9, 25.7, 21.9, 19.5, 18.0, −4.2, −4.9; MS (CI, CH_4) *m/e* (relative intensity) 327, 325 (M^+ + H, 42); HRMS calcd for $C_{11}H_{22}O_3BrSi$ (M^+ − Me) 309.0521, found 309.0513. Anal. Calcd for $C_{12}H_{25}BrSiO_3$: C, 44.30; H, 7.75. Found: C, 44.43; H, 7.88.

Ethyl 2-Bromo-2-methyl-3-methoxybutanoate (51). To a cold solution (−78 °C) of Ph_3CSbCl_6 (231 mg, 0.400 mmol) in dry CH_2Cl_2 (9 mL) was added acetaldehyde dimethyl acetal (423 μL, 4.00 mmol) and silyl ketene acetal **63** (prepared as described above for compound **37**; 4.00 mmol). The mixture was stirred at −78 °C for 30 min before being quenched with saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and dried over $MgSO_4$. After the solution was

(35) Compound **57** was prepared from 5-[(*tert*-butyldimethylsilyl)oxy]pentanol; see ref 33.

(36) Compound **58** was prepared from propanal and (carbethoxyethylidene)triphenylphosphorane.

filtered and concentrated under reduced pressure, flash chromatography of the resultant residue afforded compound **51** (590 mg, 62%). Colorless oil (*ca.* 1:1 mixture of diastereomers): IR (neat) ν_{max} 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 6 Hz, 3H), 1.32 (t, J = 7 Hz, 6H), 1.36 (d, J = 6 Hz, 3H), 1.81 (s, 6H), 3.34 (s, 3H), 3.45 (s, 3H), 3.80 (q, J = 6 Hz, 1H), 4.01 (q, J = 6 Hz, 1H), 4.20–4.32 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (more polar bromide) δ 170.6, 80.2, 61.7, 61.0, 57.5, 20.8, 13.8, 12.9; MS (CI, CH_4) m/e (relative intensity) 239 (M^+ + H, 60), 241 (M^+ + H, 55).

General Procedure for the Reduction of α-Halo Esters with Tri-*n*-butyltin Hydride. To a cold (−78 °C), stirred solution of halide and AIBN (0.15 equiv) in dry toluene (or CH_2Cl_2; 0.1 M) was added $HSnBu_3$ (2 equiv), and the reaction mixture was irradiated for 30 min (sun lamp, 275 W) at −78 °C and then concentrated. The residue was taken up in hexane and treated with a 1.0 M solution of n-Bu_4NF in THF (2.5 equiv) for 5 min at room temperature. After filtration of the solution through a short pad of silica and solvent removal, a residue was obtained and subsequently purified by flash chromatography to afford the pure *anti* diastereomers.

Ethyl (2*S*)-2-[(2*S*,4*R*)-4-Acetoxytetrahydrofuran-2-yl]-propionate (32). Iodo adduct **31** (40 mg, 0.11 mmol) was treated with $HSnBu_3$ to afford reduced product **32** (21 mg, 80%) as a 9:1 mixture of isomers. Major (*anti*) product: colorless oil; $[\alpha]^{25}_D$ +13.1° (*c* 0.95, $CHCl_3$); IR (neat) ν_{max} 1745 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 1.81 (ddd, J = 14, 10, 6 Hz, 1H), 2.07 (s, 3H), 2.13 (ddd, J = 14, 5, 1 Hz, 1H), 2.55 (dq, J = 8, 7 Hz, 1H), 3.79 (ddd, J = 10, 2, 1 Hz, 1H), 4.12 (dd, J = 10, 5 Hz, 1H), 4.18 (q, J = 7 Hz, 2H), 4.26 (ddd, J = 10, 8, 6 Hz, 1H), 5.27–5.30 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.3, 170.6, 79.5, 74.7, 73.1, 60.4, 44.7, 36.1, 21.0, 14.1, 13.3; MS (CI, CH_4) m/e 231 (M^+ + 1), 185 (M^+ − OEt), 171 (M^+ − OAc). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.58; H, 8.08. Minor (*syn*) product: colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.95 (ddd, J = 13, 10, 6 Hz, 1H), 2.06 (s, 3H), 2.12 (tdd, J = 14, 5, 1 Hz, 1H), 2.56 (q, J = 7 Hz, 1H), 3.79 (ddd, J = 10, 2, 1 Hz, 1H), 4.06 (dd, J = 10, 5 Hz, 1H), 4.15 (q, J = 7 Hz, 2H), 4.18 (ddd, J = 10, 7, 6 Hz, 1H), 5.26–5.28 (m, 1H).

Ethyl (2*S*)-2-[(2*S*,3*R*)-3-Methyltetrahydrofuran-2-yl]propanoate (34). Iodo adduct **33** (40 mg, 0.13 mmol) was treated with $HSnBu_3$ to afford reduced product **34** (19 mg, 80%) as a >50:1 mixture of isomers. Colorless oil: IR ($CHCl_3$) ν_{max} 1730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, J = 7 Hz, 3H), 1.16 (d, J = 7 Hz, 3H), 1.26 (t, J = 7 Hz, 3H), 1.48–1.59 (m, 1H), 2.02–2.09 (m, 1H), 2.57 (quint, J = 7 Hz, 1H), 3.62 (dd, J = 6, 2 Hz, 1H), 3.80 (td, J = 4, 1 Hz, 2H), 4.15 (q, J = 7 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.4, 86.8, 67.0, 60.1, 44.3, 36.0, 34.8, 18.9, 14.0, 13.1; HRMS calcd for $C_{10}H_{19}O_3$ (M^+ + H) 187.1334, found 187.1310.

Ethyl 2-Tetrahydrofuran-2-ylpropanoate (36).[37] Iodo adduct **35** (44 mg, 0.15 mmol) was treated with $HSnBu_3$ in CH_2Cl_2 to afford reduced product **36**[37] (23 mg, 91%) as a 12:1 mixture of isomers. Major (*anti*) product: IR (neat) ν_{max} 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 7 Hz, 3H), 1.26 (t, J = 7 Hz, 3H), 1.50–1.60 (m, 1H), 1.82–1.94 (m, 2H), 1.95–2.06 (m, 1H), 2.47–2.57 (m, 1H), 3.72–3.79 (m, 1H), 3.83–3.90 (m, 1H), 3.98–4.05 (m, 1H), 4.13–4.22 (q, J = 7 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.7, 80.3, 67.9, 60.1, 45.0, 28.8, 25.5, 14.0, 13.3; MS (CI, CH_4) m/e (relative intensity) 172 (M^+, 6); HRMS calcd for $C_9H_{16}O_3$ (M^+) 172.1099, found 172.1147. Minor (*syn*) product: colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.61–1.70 (m, 1H), 1.82–2.03 (m, 3H), 2.50 (q, J = 7 Hz, 1H), 3.70–3.85 (m, 2H), 3.96 (q, J = 7 Hz, 1H), 4.13 (q, J = 7 Hz, 2H).

Ethyl 2-Methyl-3-methoxy-3-phenylpropionate (38).[38] Bromo adduct **37** (45 mg, 0.15 mmol) was treated with $HSnBu_3$ to afford reduced product **38**[38] (30 mg, 90%) as a 32:1 mixture of isomers. Major (*anti*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 2.67–2.82 (m, 1H), 3.16 (s, 2H), 4.11–4.36 (m, 3H), 7.28–7.45 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.1, 138.8, 128.2, 128.0, 127.5, 85.8, 60.2, 56.6, 47.0, 14.1, 13.9; MS (CI, CH_4) m/e (relative intensity) 223 (MH^+, 7), 191 (100), 135 (57); HRMS calcd for $C_{13}H_{19}O_3$ (M^+) 222.1256, found 222.1253. Minor (*syn*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, J = 7 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 2.68–2.81 (m, 1H), 3.23 (s, 3H), 3.91–4.09 (m, 2H), 4.41 (d, J = 7 Hz, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.6, 139.5, 128.0, 127.5, 126.9, 84.2, 59.9, 56.8, 47.2, 13.7, 12.3; MS (CI, CH_4) m/e (relative intensity) 223 (M^+ + H, 10), 191 (100), 135 (66); HRMS calcd for $C_{13}H_{19}O_3$ (M^+) 222.1256, found 222.1263.

Ethyl 2-Methyl-3-fluoro-3-phenylpropionate (40). Bromo adduct **39** (39 mg, 0.14 mmol) was treated with $HSnBu_3$ to afford reduced product **40** (25 mg, 88%) as a 20:1 mixture of isomers. Major (*anti*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 2.89–3.11 (m, 1H), 4.23 (q, J = 7 Hz, 2H), 5.55 (dd, J = 9, 6 Hz, 1H), 7.30–7.47 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.5, 137.0 (d, J = 20 Hz), 129.0, 128.4, 126.6 (d, J = 6 Hz), 95.5 (d, J = 174 Hz), 60.7, 46.2 (d, J = 25 Hz), 14.0, 13.1 (d, J = 12 Hz); MS (CI, NH_3) m/e (relative intensity) 228 (M^+ + NH_4, 92), 208 (100); HRMS calcd for $C_{12}H_{15}FO_2$ (M^+) 210.1056, found 210.1012. Minor (*syn*) diastereomer: colorless oil; IR ($CHCl_3$) ν_{max} 1730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (t, J = 7 Hz, 3H), 1.28 (d, J = 7 Hz, 3H), 2.81–3.07 (m, 1H), 4.07 (q, J = 7 Hz, 2H), 5.73 (dd, J = 6, 47 Hz, 1H), 7.20–7.47 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.8 (d, J = 9 Hz), 138.2 (d, J = 20 Hz), 128.5, 128.5, 125.8 (d, J = 7 Hz), 94.3 (d, J = 177 Hz), 60.7, 46.6 (d, J = 25 Hz), 14.0, 11.8 (d, J = 4 Hz); MS (CI, NH_3) m/e (relative intensity) 228 (M^+ + NH_4, 100), 208 (98); HRMS calcd for $C_{12}H_{15}FO_2$ (M^+) 210.1056, found 210.1042.

Ethyl 2-Methyl-3-phenylbutanoate (42). Bromo adduct **41** (82 mg, 0.29 mmol) was treated with $HSnBu_3$ to afford reduced product **42** (50 mg, 85%) as a 2:1 mixture of isomers. Major (*anti*) diastereomer: colorless oil; IR (neat) ν_{max} 1730 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, J = 7 Hz, 3H), 1.25 (d, J = 7 Hz, 3H), 1.29 (t, J = 7 Hz, 3H), 2.50–2.65 (m, 1H), 2.82–2.98 (m, 1H), 4.18 (q, J = 7 Hz, 2H), 7.15–7.38 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 176.0, 144.2, 128.2, 127.3, 126.2, 60.0, 46.6, 43.3, 20.4, 16.1, 14.1; MS (CI, CH_4) m/e (relative intensity) 207 (M^+ + H, 100); HRMS calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1289. Minor (*syn*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, J = 7 Hz, 3H), 1.18 (d, J = 7 Hz, 3H), 1.27 (d, J = 7 Hz, 3H), 2.58–2.72 (m, 1H), 2.97–3.11 (m, 1H), 3.92 (q, J = 7 Hz, 2H), 7.14–7.38 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.1, 144.7, 127.8, 127.1, 126.0, 59.5, 46.4, 42.3, 17.4, 14.0, 13.6; MS (CI, CH_4) m/e (relative intensity) 207 (M^+ + H, 100); HRMS calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1311. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.90.

Ethyl 2-Tetrahydropyran-2-ylpropanoate (44). Iodo adduct **43** (35 mg, 0.11 mmol) was treated with $HSnBu_3$ to afford reduced product **44** (18 mg, 86%) as a >50:1 mixture of isomers. Colorless oil: IR (neat) ν_{max} 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, J = 7 Hz, 3H), 1.20 (m, 1H), 1.25 (t, J = 7 Hz, 3H), 1.41–1.69 (m, 4H), 1.83–1.88 (m, 1H), 2.49 (dq, J = 7, 8 Hz, 1H), 3.36–3.49 (m, 2H), 3.95 (m, 1H), 4.14 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.1, 79.3, 68.5, 60.1, 45.7, 28.3, 25.8, 23.2, 14.1, 12.8; HRMS calcd for $C_{10}H_{18}O_3$ (M^+) 186.1256, found 186.1255.

Ethyl (2*R,3*R**)-2-Methyl-3-methoxypentanoate (46).** Iodo adduct **45** (179 mg, 0.590 mmol) was treated with $HSnBu_3$ in CH_2Cl_2 to afford reduced product **46** (92.0 mg, 89%) as a 1.1:1 mixture of isomers. *Anti* isomer: colorless oil; IR (neat) ν_{max} 1740 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 1.39–1.70 (m, 2H), 2.61–2.79 (m, 1H), 3.34 (s, 3H), 4.16 (q, J = 7 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.1, 83.2, 60.2, 57.4, 42.5, 22.6, 14.2, 12.3, 8.7; MS (CI, NH_3) m/e (relative intensity) 192 (M^+ + NH_4, 100), 175 (M^+ + H, 31); HRMS calcd for $C_8H_{15}O_2$ (M^+ − OMe) 143.1072, found 143.1055. *Syn* isomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (t, J = 7 Hz, 3H), 1.17 (d, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 1.47–1.69 (m, 2H), 2.51–2.68 (m, 1H), 3.35–3.49 (m, 1H), 3.36 (s, 3H), 4.10–4.25 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.8, 83.1, 60.1, 57.7, 42.8,

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24.3, 14.0, 11.5, 9.5; MS (CI, CH_4) *m/e* (relative intensity) 175 (M^+ + H, 100), 143 (72), 129 (72).

Ethyl (2*R,3*R**)-2,4-Dimethyl-3-methoxypentanoate (48).** Bromo adduct **47** (40.0 mg, 0.15 mmol) was treated with $HSnBu_3$ to afford reduced product **48** (24 mg, 86%) as an 8:1 mixture of isomers. Major (*anti*) isomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 1.09 (d, J = 7 Hz, 3H), 1.28 (t, J = 7 Hz, 3H), 1.75–1.92 (m, 1H), 2.58–2.72 (m, 1H), 3.22 (dd, J = 4, 8 Hz, 1H), 3.41 (s, 3H), 4.16 (q, J = 7 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.6, 87.8, 60.7, 60.3, 42.9, 29.8, 20.1, 16.1, 14.2, 13.7; MS (CI, CH_4) *m/e* (relative intensity) 189 (M^+ + H, 48), 157 (100), 143 (68). Minor (*syn*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 1.18 (d, J = 7 Hz, 3H), 1.28 (t, J = 7 Hz, 3H), 1.64–1.80 (m, 1H), 2.55–2.69 (m, 1H), 3.24 (t, J = 6 Hz, 1H), 3.42 (s, 3H), 4.15 (q, J = 7 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.6, 87.7, 60.9, 60.3, 42.4, 31.5, 19.7, 17.9, 14.2, 11.5; MS (CI, CH_4) *m/e* (relative intensity) 189 (M^+ + H, 31), 157 (100), 143 (36).

Methyl 2-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]butanoate (50).[39] Bromo adduct **49** (259 mg, 0.790 mmol) was treated with $HSnBu_3$ in CH_2Cl_2 to afford reduced product **50**[39] (175 mg, 89%) as a 1.2:1 mixture of isomers. Colorless oil: IR (neat) ν_{max} 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 6H), 0.86 (s, 9H), 0.87 (s, 9H), 1.08 (d, J = 7 Hz, 3H), 1.13 (d, J = 6 Hz, 3H), 1.14 (d, J = 6 Hz, 3H), 1.15 (d, J = 7 Hz, 3H), 2.42 (dq, J = 6, 7 Hz, 1H), 2.49 (q, J = 7 Hz, 1H), 3.66 (s, 3H), 4.00 (dq, J = 6, 7 Hz, 1H), 4.09 (q, J = 6 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.6, 175.5, 70.2, 69.5, 51.4, 48.1, 47.5, 25.7, 21.9, 20.6, 17.9, 12.7, 11.9, −4.3, −5.0, −5.2; MS (CI, CH_4) *m/e* (relative intensity) 247 (M^+ + H, 26).

Ethyl 2-Methyl-3-methoxybutanoate (52).[40] Bromo adduct **51** (40 mg, 0.17 mmol) was treated with $HSnBu_3$ to afford reduced product **52**[40] (19 mg, 70%) as a 3:1 mixture of isomers. Major (*anti*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, J = 7 Hz, 3H), 1.12 (d, J = 6 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 2.51–2.68 (m, 1H), 3.32 (s, 3H), 3.49–3.62 (m, 1H), 4.16 (q, J = 7 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.9, 78.2, 60.2, 56.4, 45.2, 15.5, 14.1, 12.2. Minor (*syn*) diastereomer: colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (d, J = 6 Hz, 3H), 1.18 (d, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 2.44–2.59 (m, 1H), 3.34 (s, 3H), 3.50–3.61 (m, 1H), 4.10–4.22 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.7, 77.8, 60.2, 56.6, 45.4, 16.7, 14.2, 12.3.

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Supplementary Material Available: ^1H or ^{13}C NMR spectra of those compounds for which combustion analysis is not available (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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