Homoallylic Chiral Induction in the Synthesis of 2,4-Disubstituted Tetrahydrofurans by Iodoetherification. Synthetic Scope and Chiral Induction Mechanism[1]

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Abstract: Chiral induction generating two new stereogenic centers has been observed in the iodoetherification of optically active ethyl 5,6-dihydroxyhexenoate. Of the four possible isomeric tetrahydrofuran products, only two were obtained in ratios up to 12:1 favoring the trans orientation of the tetrahydrofuran substituents. The olefin geometry was found to control the chirality at the exocyclic iodide-bearing carbon. Inversion of the original stereogenic center with a Mitsunobu reaction gives a selective synthesis of the cis products and thus allows the selective preparation of all eight possible isomers of this useful tetrahydrofuran synthon. The origin of the diastereoselectivity of the reaction was investigated. On the basis of AM1 calculations, a chairlike transition structure was proposed. The conformational preferences of the two ends of the molecule were studied by using transition-structure models. The results were transported to the chairlike cyclization model, and the calculated energy differences were found to be in good agreement with the experimentally observed cis to trans ratios.

The directed activation of hydroxy olefins by electrophiles presents considerable potential in stereoselective synthesis. In the case of allylic alcohols, the proximity of the hydroxyl group to the prochiral olefin permits a high degree of asymmetric induction and numerous studies have been reported allowing for a predictable stereochemical outcome.[2] With homoallylic alcohols, such relay processes are expected to be of limited value owing to the remoteness of the hydroxyl group.

We have been developing approaches for the stereoselective formation of trans-2,4-disubstituted tetrahydrofurans from simple homoallylic precursors (Scheme I), foreseeing a subsequent dimethylboron bromide promoted ring opening that would afford a highly functionalized 1,3-*syn*-diol.[3,4] Pivotal to the success of such strategies is the initial cyclization reaction. From the onset we felt this cyclization would be best carried out under kinetically controlled conditions since the thermodynamic preference for the desired trans isomer is small.[5] Thus, electrophile-mediated cyclizations, which are known to be kinetically controlled under certain conditions, were investigated. Iodine was chosen as an electrophile to allow for further substitution reactions. This approach would result in the formation of two new stereogenic (chiral) centers via concomitant 1,3 and 1,4 asymmetric induction.

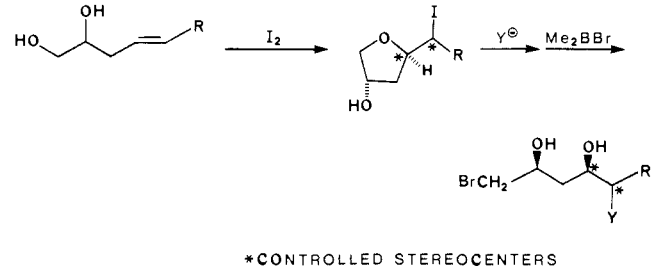
We are reporting here that the iodoetherification reaction of simple homoallylic alcohols results in the formation of trans-2,4-disubstituted tetrahydrofurans bearing an exocyclic stereogenic center with high stereoselectivity. Mechanistic aspects based on calculations of a reaction transition-structure model are presented.

Results and Discussion

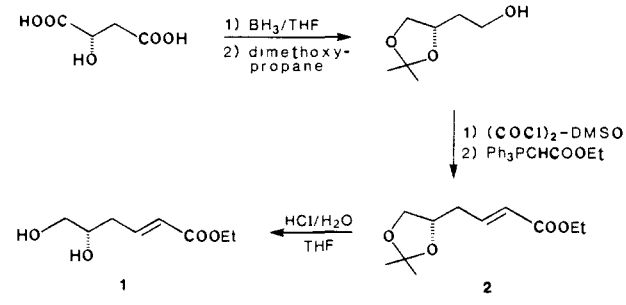
Cyclization Directed by a Hydroxyl Group. The substrate **1** for testing the homoallylic induction in the iodoetherification reaction was obtained as shown in Scheme II. Thus, (*S*)-malic acid was reduced to the triol and the resulting vicinal diol moiety protected as an isopropylidene by a modification of a published procedure.[6] The α,β-unsaturated ester was obtained by a one-pot Swern oxidation-Wittig reaction to give **2**, which was in turn deprotected under acidic conditions to afford the unsaturated ester **1**.

In order to maximize our chances of obtaining a good chirality transfer in the iodoetherification, we avoided "thermodynamic" reaction conditions, since the equilibrium mixture was not expected to be very rich in either isomer. Conditions inspired from Bartlett's "kinetic" conditions,[7] that is, in the presence of a base to make the last step of the reaction irreversible, were used. We were pleased to find that when the α,β-unsaturated ester **1** was treated

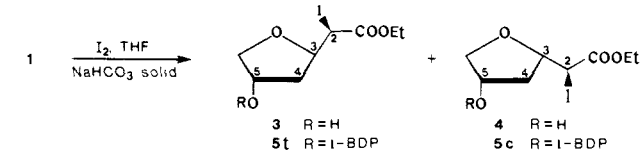
Scheme I



Scheme II



Scheme III



(1) We dedicate this paper to Professor E. C. Taylor, on the occasion of his 65th anniversary.

(2) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walkerand, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589. Mohamadi, F.; Still, W. C. *Tetrahedron Lett.* **1986**, *27*, 893. Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102. Fleming, I.; Lewis, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 149. Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601.

(3) Guindon, Y.; St. Denis, Y.; Daigneault, S.; Morton, H. E. *Tetrahedron Lett.* **1986**, *27*, 1237.

(4) Guindon, Y.; Thérien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680.

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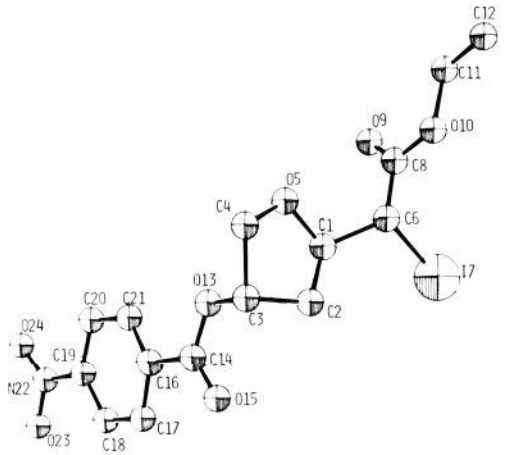
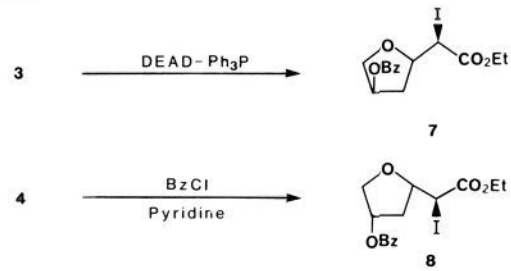


Figure 1. Computer-generated picture of **6**.

Scheme IV



with iodine (5 equiv) in the presence of solid $NaHCO_3$ (3 equiv) at room temperature, the reaction yielded a mixture of only two of the four possible diastereomers, **3** and **4** (Scheme III), in an interesting 4:1 ratio. Moreover, these compounds could be separated by flash chromatography. An especially important diagnostic signal in NMR was that of the proton geminal to iodine, a sharp doublet at δ 4.10 in the major isomer **3**, but at δ 4.76 in the minor isomer **4**.

Characterization of the two products requires the absolute stereochemistry of both newly formed stereogenic centers to be determined. The cis or trans relationship between the stereogenic C_5 hydroxyl and the iodoacetate chain has been assigned by NOE[8] using the silyl ether derivatives **5t** and **5c**. The major isomer was

shown to be trans, as judged by the proximity of one of the H_4 protons to H_3, while the other H_4 proton was close to H_5. For the minor isomer, one of the H_4 protons was found to give strong NOE into both H_3 and H_5, showing the cis relationship between H_3 and H_5, and thus between the hydroxyl and the iodoacetate chain.

The problem of the stereochemical assignment at the exocyclic carbon was addressed by X-ray structure analysis of **6**, the *p*-nitrobenzoyl ester derivative of **3**.

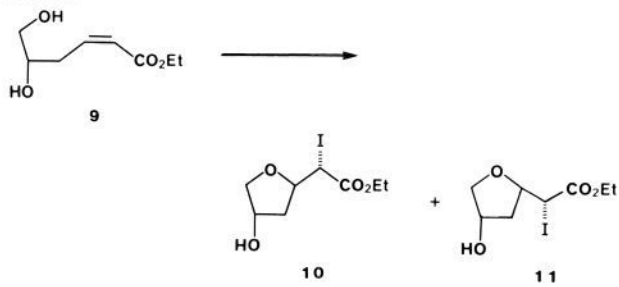
It is clear from the computer-generated picture of **6** (Figure 1) that the iodine-bearing carbon has the *R* absolute configuration. The relationship between the two new stereogenic centers implies

Table I. Solvent Effect on the Iodocyclization[a] Reaction of **1**

solvent	trans:cis[b] ratio	polarity,[c] dielectric constant	I_2 solubility (M)[d]
THF	4.5:1	7.58	4.87
DME	5.2:1	7.20	2.05
tert-butyl methyl ether	7:1		1.15
diethyl ether	8.6:1	4.34	0.88
isopropyl ether	12:1	3.88	0.27

[a] The reaction mixtures were made of 3 equiv of solid $NaHCO_3$, 5 equiv of iodine, and solvent to make the substrate 0.1 M. The reaction mixture of the two last entries of the table contained undissolved I_2. [b] The ratio was determined by NMR integration and was found to be independent of the conversion of the reaction. [c] Reference 49. [d] Determined by titration of a saturated solution with aqueous $Na_2S_2O_3$.

Scheme V



an addition of the iodine and the nucleophilic oxygen atom on opposite faces of the olefin, as would be expected from the generally accepted "iodonium type" mechanism.

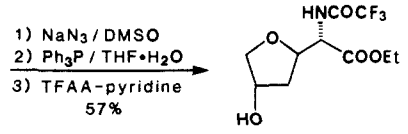
In the case of the minor isomer, the absolute stereochemistry of the iodine-bearing carbon was determined by chemical correlation, as shown in Scheme IV. Thus, examination of the structure proposed for the minor isomer **4** reveals that inversion of the stereochemistry of the hydroxyl center of **3** would lead to a molecule that is enantiomeric to **4**. To verify this hypothesis, the major isomer **3** was treated under Mitsunobu[9] conditions to give the benzoate **7**. The minor isomer **4** was in turn benzoylated with benzoyl chloride in pyridine to give the benzoate **8**. These two benzoates were found to have identical NMR and TLC behavior and had equal but opposite optical rotations. This not only proves that the minor isomer has the hydroxyl and the iodoacetate chain cis, but it also establishes its absolute configuration at the iodine-bearing carbon as being *S*, the opposite of the major compound. It follows that both iodocyclized materials have the same stereochemical relationship between the two former olefinic centers, which suggests a discrete mechanistic control in the reaction. We shall return to the mechanism of chiral transfer in a latter section.

In order to improve the synthetic potential of this iodoetherification reaction, it was desirable to increase the selectivity of the process. The effect of changing the reaction solvent is reported in Table I.

From this limited number of solvents, it appears that the polarity of the solvent is important and must be kept low for better selectivity. Indeed, excellent selectivities are attainable in diisopropyl ether. Unfortunately, the solvents of low polarity also exhibit slower rates, not only by intrinsic rate constant differences between solvents, but also because the high iodine concentrations required for good rates[10] are not available in apolar solvents. From a practical point of view, diethyl ether is a good solvent for the reaction of acrylate diol **1**, giving a complete conversion in 3 days and a synthetically useful ratio of 8.6:1, favoring the trans product **3**.

(5) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185.
(6) Hanessian, S.; Ugolini, A.; Thérien, M. *J. Org. Chem.* **1983**, *48*, 4427.
(7) For an application of thermodynamic and kinetic conditions to the same substrate, see: Gonzâlez, F. B.; Bartlett, P. A. *Org. Synth.* **1986**, *64*, 175.
(8) Bernstein, M. A.; Morton, H. E.; Guindon, Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1155. Tables of NOE data are available as supplementary material.
(9) Mitsunobu, O. *Synthesis* **1981**, 1.
(10) The concentration of iodine is very critical to the rate, since the rate expression was found to be second order in iodine for the reaction in THF in a series of rough kinetic experiments. This result is in agreement with those of other studies of similar reactions in organic solvents: see ref 11.
(11) Do Amaral, L.; and Melo, S. C. *J. Org. Chem.* **1973**, *38*, 800.

Scheme VI



The effect of olefin geometry was also investigated (Scheme V). The (*Z*)-acrylate **9** was iodocyclized to an 11:1 mixture of only two compounds, **10** and **11**. The major compound was again a trans-substituted tetrahydrofuran by NOE,[8] but it was different from the one previously obtained from the *E*-olefin **1**; in the NMR spectrum of the *tert*-butyldiphenylsilyl ether derivatives, the proton on the iodine-bearing carbon was a doublet (J = 7 Hz) at δ 4.29 for the major iodocyclization product of the *Z*-olefin **9** whereas it was a doublet (J = 9 Hz) at δ 4.23 for that of the *E*-olefin **1**. Because of the strong relationship observed between the two new stereogenic centers in the case of the *E* isomer, we assigned the stereochemistry of **10** and **11** at the iodine-bearing carbon as being the opposite configuration of that of the *E*-olefin.

From the synthetic viewpoint, this last finding of the olefin geometry significance, along with the previously described Mitsunobu inversion of the alcohol on the product, allows for complete control of the stereochemical outcome of the process and selective access to all eight possible isomers. Indeed, the three elements of stereocontrol required for this are available.

(a) The absolute configuration of the original stereogenic center can be selected a priori, by starting the synthesis of the acrylate diol with the appropriate malic acid. Both *R* and *S* are commercially available.

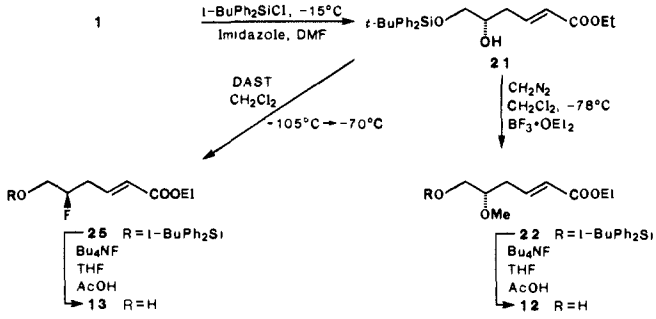
(b) The olefin geometry dictates the relative configuration of the two new stereocenters. An *l* relationship[12] is obtained from a *E*-olefin, and a *u* relationship is obtained from a *Z*-olefin.

(c) The relative stereochemistry of the original stereogenic center and the closest new stereocenter defines the cis or trans substitution pattern of the tetrahydrofuran ring. The iodocyclization reaction selectively yields the trans product. The cis product may be obtained by inverting the alcohol center with the Mitsunobu procedure.

As mentioned in the introduction, the synthetic potential of tetrahydrofuran derivatives such as **3** and its isomers is considerable. Indeed, the iodide is a potential leaving group, allowing for SN_2 displacement at that position. As an example of this, the reaction of **3** with NaN_3 followed by reduction and protection gave the *N*-trifluoroacetyl amino acid (Scheme VI). After proper manipulation of the iodo center, the tetrahydrofuran ring may be opened with Me_2BBr,[4] which would give highly and versatilely functionalized acyclic chains, with a 1,3,4 array of stereogenic centers. The iodide can also be removed with Bu_3SnH reduction, giving the corresponding tetrahydrofuran acetic acid derivatives, which have proven to be useful synthetic intermediates.[3]

Iodocyclization Directed by Other Substituents. Once the synthetic potential of this iodocyclization was assessed with the hydroxyl substituent, we became interested in the origin of the stereoselectivity in this homoallylic system. Unfortunately, unlike the allylic chiral induction in the iodoetherification[13,14] and related electrophile cyclization reactions,[15] which have proposed mechanistic rationalization,[16] homoallylic induction is quite rare[17-19] and seldom convincingly explained. In order to get further insight into the mechanism of chiral transfer, we chose to change the C_5 stereogenic substituent from OH to OMe, F, and Me. These substituents have different hydrogen-bond behavior and steric and electronic requirements and will allow characterization of the mode of chirality transfer.

Scheme VII



Scheme VIII

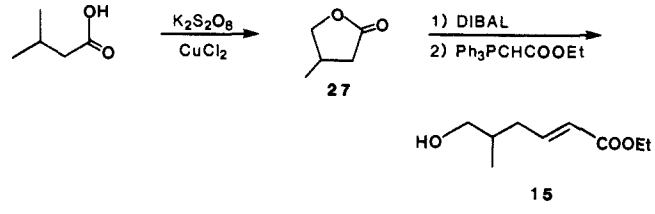


Table II. Effect of the X Substituent on the Composition of the Iodocyclized Product[a]

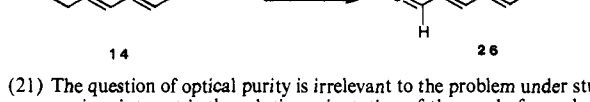
X	substr	cis:trans product ratio	products (cis, trans)
OH	**1**	1:4	**4**, **3**
OCH_3	**12**	1:4.6	**24**, **23**
F	**13**	1:6.3	**17**, **16**
CH_3	**15**	3.6:1	**28**, **29**

[a] Reaction conditions: 0.1 M substrate, 1 M I_2 in THF, with 3 equiv $NaHCO_3$ at room temperature. The cis to trans ratio was obtained by HPLC or NMR; see text. All reactions run to >85% conversion.

The synthesis of the methoxy acrylate substrate **12** is described in Scheme VII and is relatively straightforward. On the other hand, that of the fluoro acrylate substrate **13** (Scheme VII) was more problematic due to the intrinsic instability of an acrylate with a good leaving group in the δ position. In spite of this, we were able to obtain a 5:1 mixture of the desired **13** with the elimination product **14**. The iodocyclization was performed on this mixture, and we isolated, characterized, and quantified the products of the reaction.[20] The synthesis of the racemic[21] methyl substrate **15** is outlined in Scheme VIII.

The methoxy, fluoro, and methyl substrates were iodocyclized in THF at room temperature in the presence of 3 equiv of solid sodium bicarbonate and 5 equiv of I_2 with a substrate concentration of 0.2 M.[22] The ratio described for the hydroxy substrate

(12) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
(13) Tamaru, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 2885.
(14) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.
(15) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: London, 1984; Vol. 3, p 411.
(16) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672, and preceding papers in the series.
(17) Iodolactonization: Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. Epoxidation: Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690. Hydroboration: Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577. Hydrogenation: Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005. Hydration: Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407.
(18) Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079.
(19) Hatekeyama, S.; Sukurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333.
(20) The iodocyclization reaction was further complicated by the partial oxidation of **14** to the aldehyde **26**.



(21) The question of optical purity is irrelevant to the problem under study, since our prime interest is the relative orientation of the newly formed stereogenic centers with the original C_5 stereogenic center.

1 (Table I) in THF solvent was obtained under the same conditions.

An important aspect of a study dealing with chiral induction is proper product stereochemical characterization.[23] Since X-ray analysis cannot be performed on every compound, other means were envisaged to analyze the stereochemical outcome of the reactions. After the reactions were worked up, a crude NMR was recorded for later integration purposes. In the case of the fluoro products **16** and **17**, two diastereomeric products could be separated by flash chromatography. The major product **16** had its relative stereochemistry determined by our previously published NOE method.[8,24] The diastereomeric products from the methyl and methoxy substrates **15** and **13** could not be separated preparatively, and a careful solvent selection allowed the NOE experiments to be performed on the mixture.

Once the structures of these iodocyclized products were definitely established, their ratio could be examined. As reported in Table II, the fluoro substituent is found to be the best trans inducer, followed by equivalent methoxy and hydroxy substituents. The methyl group shows a definite reversal of the stereochemical preference, the cis product being major. This sharp contrast in substituent effect spurred our efforts to rationalize these unexpectedly effective homoallylic chirality transfers.

Proposed Mode of Chirality Transfer. The literature contains few examples of homoallylic chiral induction.[17-19] Among them, no rationalization of the observed selectivity seemed directly applicable to the present case. In a related reaction, namely a halolactonization governed by a homoallylic nitrogen substituent, Ohfune and co-workers[18] found that the major isomer formed was a cis product. However, it appears from the available experimental data that the reaction was performed under thermodynamic conditions, when iodine was the electrophile. Their results are in sharp contrast with our observed trans selectivity, and their chelation rationalization cannot be applied here.

On the other hand, iodocyclization reactions of substrates with allylic stereogenic centers have been well studied, and general trends have been found. In a broader sense, chiral allylic induction in various addition reactions to olefins has shown common behavior of stereoselectivity, and this has been attributed to many effects. Energy differences between conformers of the starting materials, or between suggested transition states (TS), have been invoked to rationalize the stereochemical results.[14,25] The conformational energy pattern of TS has been discussed in terms of electronic[26] and steric[27] interactions between the prochiral olefin and the stereogenic center. A series of papers by Hehre, Chamberlin, and co-workers discussed the influence of the ground-state (GS) reactivity as a function of conformation and rationalized iodolactonization results with this theory.[16]

Unfortunately, the remoteness of the chiral and prochiral centers in homoallylic induction renders their interaction much weaker and ill-defined. For this reason, a new model of homoallylic chiral induction was constructed. As it will be detailed below, this started with mechanistic considerations, which in turn pointed to which transition structure was geometry determining and therefore to be modeled. A crude transition-structure model was used to restrict the number of transition structures to be considered. Finally, two transition-structure models were used to analyze the conformational preferences of the two ends of the molecule in the transition state.

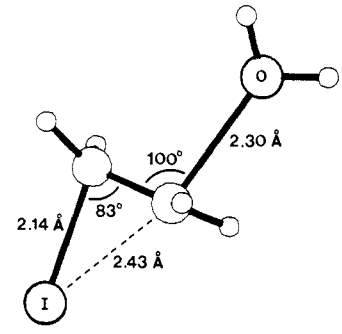
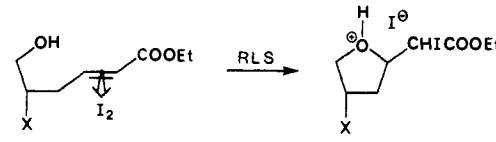


Figure 2. AM1-calculated transition structure.

Scheme IX



Mechanistic Considerations. In the situation under study, a set of diastereomeric reaction pathways under kinetic control, the ratio of products is determined exclusively by the relative energy of the various transition structures of the rate-determining step, provided all the previous steps are in rapid equilibrium.[28] With this in mind, we need some way of evaluating the relative energy of the various transition structures leading to the cis and trans products. A method of choice for this purpose is the AM1 semiempirical molecular orbital method.[29] A semiempirical method has the advantage of allowing calculations on molecules containing iodine atoms, instead of a surrogate, with a precision comparable to good ab initio methods.[29b]

The choice of transition structures to be calculated can first be guided by the literature data on the reaction mechanism. The current view is that the reaction starts with the fully reversible[30] attack of iodine on one of the faces of the olefin to form a charge-transfer complex, often referred to as a π complex. This complex can then cyclize in the rate-determining step through the nucleophilic attack of the terminal hydroxyl on one of the olefinic carbon atoms, with concomitant rupture of the I–I bond.[34] Involvement of an iodonium ion has been suggested[16] to be restricted to bimolecular reactions, which exhibit diastereoselectivities opposite to those of the cyclization reactions.

In view of this mechanism, the observed product distribution should be independent of the relative reactivity of the ground-state

(22) These conditions, although not optimal for synthetic purposes, gave a rapid reaction for the hydroxyl case and were chosen as standard. The ratios described for the fluoro, methoxy, and methyl substrates should therefore be considered as unoptimized.

(23) It should be stressed that the assignment of the stereochemistry of both major and the minor compounds is critical, especially since we found that all the iodocyclized products tend to decompose on standing neat or in solution. Liberation of HI causes the slow racemization of the iodide-bearing carbon, as judged by the appearance of new sets of peaks in old NMR samples. This epimerization was found to be quite easy in the methoxy case, significant peaks appearing in the NMR within 1 day standing in solution.

(24) The stereochemistry of the minor product **17** had to be assigned by comparison of its NMR spectrum with that of the minor methoxy compound **18**. These spectra are very similar except for the fluorine spin-coupling pattern.

(25) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E. *Tetrahedron Lett.* **1985**, *26*, 3915.

(26) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Franczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(27) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.

(28) DeTar, D. F. *J. Org. Chem.* **1986**, *51*, 3749. Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

(29) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Storch, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 3898.

(30) The reversibility of the electrophilic attack of Br_2 on an olefin has been demonstrated.[31] In the case of I_2, reversibility of the π complex formation has been implied[32,33] but, to our knowledge, not demonstrated. We also believe in the complete reversibility of the initial attack on the basis of the following argument. If the iodocyclization reactions are performed in the absence of a base (a minor change since we have shown our reaction to be zero order in base), a thermodynamic mixture of compound is obtained, demonstrating the reversible character of all the reaction steps at least as far back as the geometry determinant step. In the present reaction, the geometry determinant step is the initial formation of the π complex.

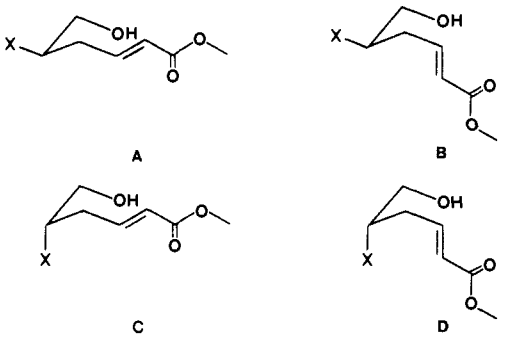
(31) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Am. Chem. Soc.* **1987**, *109*, 515. Belluci, G.; Bianchini, R.; Ambrosetti, R. *Ibid.* **1985**, *107*, 2464. Slebocka-Tilk, H.; Ball, R.; Brown, R. S. *Ibid.* **1985**, *107*, 4504. Brown, R. S.; Gedye, R.; Slebocka-Tilk, H.; Buschek, J. M.; Kopecky, K. R. *Ibid.* **1984**, *106*, 4515.

(32) Zhao, Y.-F.; Yan, S.-J. *J. Org. Chem.* **1985**, *50*, 2136.

(33) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III *J. Org. Chem.* **1987**, *52*, 4191.

(34) Bernett, R. G.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1985**, *50*, 2048. Williams, D. L. H.; Bienvenue-Goetz, E.; Dubois, J. E. *J. Chem. Soc. B* **1969**, 517.

Chart I. Four Possible Chairlike Arrangements of the Carbon Skeleton in the TS



olefin diastereotopic faces. A π-complex preequilibrium will obey Curtin's principle just as a preequilibrium of conformers. We will therefore focus on estimating the energy of the various possible transition structures of the rate-determining step, which is the attack of the terminal hydroxyl on one of the π-complex carbon atoms, to give the O-protonated iodotetrahydrofuran (Scheme IX).

Crude Transition-Structure Model. A first step to the energy minimization of a transition structure is the optimization of the product and reactant structures. Unfortunately, it was impossible to find an energy minimum for any kind of iodine–olefin interaction that could be called a π complex. Various geometry optimizations starting with I_2 or I^+I^- ion pairs, at several I–I and I–olefin distances and angles, either led to collapse of the ion pair and diffusion of I_2 at least 5 Å away from the olefin or led to the formation of an iodonium ion. In the absence of a stable reactant, the idea of localizing the reaction saddle point was abandoned in favor of the use of stable models of the transition structures.

A first such model was used to get a crude approximation of what the transition structure might look like for the cyclization step. This model is the saddle point of the addition reaction of water to the iodonium ion of ethylene. The AM1-calculated transition structure is shown in Figure 2.

The key features of this structure include a nearly planar electrophilic carbon atom (the out-of-plane angle of a substituent relative to the two others on that carbon is 5.7°), an attack of water at 100° from the C–C σ bond, and a distance between the nucleophilic oxygen and the electrophilic carbon of 2.30 Å. This calculated transition structure is similar to the HF/6-31G* transition structure calculated for the nucleophilic attack of water on protonated ethylene oxide,[35] where the angle of attack was 104.6° and the forming bond length was 2.19 Å.

Iodoetherification Transition-State Models. The application of these distances and angles to our actual substrate should limit the number of transition-structure conformers to be considered. Thus, in a cyclic arrangement with an O–C distance of 2.30 Å and an angle of 100°, the substrate is in a chair arrangement with almost no strain! Indeed, in an ideal cyclohexane chair, the 1,5 distance is 2.36 Å and the "angle of attack" is 90°. This type of cyclic arrangement, in which only the five atoms forming the tetrahydrofuran occupy chair atom positions, has already been suggested by Harding et al.[36] as a rationale for their 2,5 asymmetric induction in the intramolecular amidomercuration reaction.

The chair arrangement clearly defines four possible transition structure geometries (Chart I), of which A and D would give the cis product, whereas B and C would give the trans product. Note that C and D are drawn as enantiomers of A and B to make the stereochemical argument clear.

Considering these four structures, one realizes that two distinct factors will determine their relative energies: the "β" (A and C) or "α" (B and D) orientation of the electrophilic portion of the molecule and the "equatorial" (A and B) or "axial" (C and D) orientation of the substituent X on the chair. Because of the remoteness of the two protagonists, they may be considered

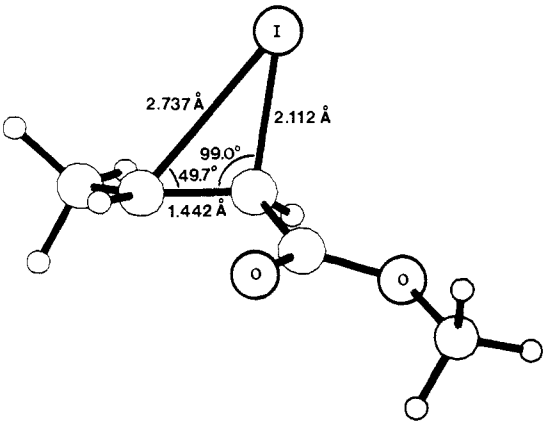
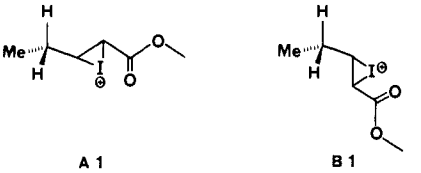


Figure 3. AM1-calculated iodonium ion of methyl crotonate.

Chart II. Standard Heats of Formation (kcal/mol) of Models for the *E*-Olefinic Moiety



A1 130.02 B1 131.66

separately.[37] Such an approach greatly helps the visualization of the stereoelectronic and steric effects involved for each group and facilitates the rationalizations and predictions without recourse to calculations.

Preferred Orientation of the Olefinic Moiety. For reasons previously mentioned, the conformational profile of the transition structure must be modeled. In the olefinic portion of the molecule, an important geometry-determining feature is the hybridization of the electrophilic carbon atom. Comparison of the transition structure of Figure 2 with the iodonium ion of methyl crotonate (Figure 3), also calculated by AM1, shows that these two species have a similar geometry around the key electrophilic carbon, as well as a similar position for the iodine atom. We therefore elected to use the iodonium ions of the various conformers, which are optimizable species by AM1, as models of the corresponding transition structures.

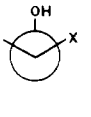
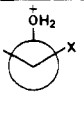
Models A1 and B1 (Chart II) were optimized with the only restriction that the bond between the ethyl group and the iodonium ion remains at a constant dihedral angle to preserve the chair form. The result is an energy difference of 1.6 kcal/mol favoring the rotamer having a β orientation of olefinic carbons in the transition-state model, thus indicating that A and C should be favored over B and D (Chart I).

Preferred Orientation of the X Substituent. The conformational preference of the hydroxyl end of the substrate will determine which of A or C should be the preferred transition-structure geometry. Since we are dealing with chair conformations, it is obvious that the least energetic orientation for a substituent is the equatorial one for steric and torsional reasons. Conformer A should therefore be, in the absence of any other strong effect, the major transition structure, leading to the cis product. Focusing on the nucleophilic end of the substrate, however, revealed its 1,2-disubstituted ethane nature. Several compounds such as 1,2-difluoroethane[38] and 2-fluoroethanol[39,40] have been shown to prefer a gauche arrangement of the heteroatomic substituents. This gauche arrangement translates into an axial preference in our transition-structure models and could possibly override the

(35) Ford, G. P.; Smith, C. T. *J. Am. Chem. Soc.* **1987**, *109*, 1325.
(36) Harding, K. E.; Burks, S. R. *J. Org. Chem.* **1981**, *46*, 3920.

(37) Through-bond effects for homoallylic situations are expected to be small. On the other hand, we found by MM2 calculations that even for the worst possible case (D, Chart I), there was no steric interaction between X and the olefinic moiety.
(38) Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* **1980**, *102*, 3987.
(39) Hagen, K.; Hedberg, K. *J. Am. Chem. Soc.* **1973**, *95*, 8263.
(40) Hoppilliard, Y.; Solgadi, D. *Tetrahedron* **1980**, *36*, 377.

Table III. AM1 Calculated Standard Heats of Formation of E, F, E2, and F2 (kcal/mol)[a]

	 E	 F	 E2	 F2
X = Me	−81.92	−81.49	104.78	104.12
X = F	−121.85	−122.58	75.98	69.61

[a] The energies reported are that of the most stable rotamer about the C–O bond. The O–C–C–C dihedral angle was locked at 60, 180, or 300° to preserve a chairlike form; calculations with this bond free show the same trends but introduced the OCCC deformation as a new variable.

normal equatorial preference. In order to clarify the situation, we decided to calculate the conformational energy profile of transition-structure models for this end of the molecule.

The choice of a transition-structure model will again be guided by the reaction mechanism. As the reaction progresses forward along the reaction coordinate, the nucleophilic oxygen atom acquires positive charge. Although the degree of charge of the transition structure is unknown, it must be somewhere between that of the ground-state alcohol and that of the protonated tetrahydrofuran. These two species will be modeled by 2-substituted propanols (E and F) and O-protonated 2-substituted propanols (E2 and F2), respectively. The energies of the various conformers, reported in Table III, are those for the most stable rotamer about the C–O bond.

The results indicate that, when X = F, the gauche form has a lower energy by 0.57 kcal/mol for the ground-state alcohol and by 6.37 kcal/mol for the protonated alcohol. This high gauche preference in the protonated form is rationalized in terms of a stronger $^{+}OH_2$–F hydrogen bond (AM1 has been shown to reproduce this type of internal H bond quite well),[41] as well as by a strengthening of the gauche effect[42] due to the increased oxygen electronegativity after protonation. It therefore follows that, for X = F, a strong preference (some kilocalories per mole) for the gauche form should be observed. The gauche form translates into the axial chair substituent, and such a large difference should easily override the weak torsional equatorial chair preference. The same applies, to a lesser degree because of the lesser electronegativity of X, in the cases of X = OH and X = OMe. Transition-structure model C should therefore be the major reaction pathway for these substituents, giving the trans product. This is in agreement with our experimental results where the more electronegative X groups gave better selectivities.

When X = Me, our models of the nucleophilic end of the transition structure indicate a 0.43 kcal/mol preference for the anti form in the ground-state alcohol and a 0.66 kcal/mol preference for the gauche form in the protonated form. The transition structure having a conformational preference somewhere between these two extremes, these two weak preferences basically cancel out, and our model suggests that no strong effect will override the expected preference of a methyl substituent on a chairlike arrangement.

This result points to A as the favored transition structure for X = Me, in agreement with the observed predominance of the cis product in the iodoetherification reaction.

Effect of the Olefin Geometry. The rationale described above was only concerned with *E*-olefins. However, our experimental results also include an example of cyclization of a substrate with the *Z*-olefin geometry (Scheme V), where the major product **10** had the same trans relationship between the tetrahydrofuran substituents as the product **3** from the *E*-olefin, but was obtained more selectively. In order to verify that our model also applies to *Z*-olefins, we calculated models G and H (Chart III).

The results indicate that the transition structure should prefer the β orientation, as for the case of the *E*-olefin. The energy difference between β and α is larger in the case of the *Z*-olefin (2.38 kcal/mol) than it was for *E*-olefins (1.63 kcal/mol). Since the other end of the molecule has a strong conformational bias in the transition state, an increased selectivity in the *Z*-olefin substrate can be expected, in agreement with the experimental results. This additional example further validates our model and its various hypotheses.

Conclusion

In this work, we have demonstrated the use of the iodoetherification reaction to generate 4-substituted 2-tetrahydrofuryliodoacetate esters with good diastereoselectivity. This reaction, in combination with the Mitsunobu reaction, allows the selective synthesis of all eight possible diastereomers of the (4-hydroxy-2-tetrahydrofuryl)iodoacetate esters, a useful chiron.[43]

The mechanism of the homoallylic chiral induction was also studied by changing the C_5 stereogenic group. The results were rationalized by using a reaction pathway model, which considers the two ends of the molecule separately. AM1 calculations were used to estimate transition-state energies for the various conformers, which then allowed the determination of the relative importance of various reaction pathways. The calculation results are in good agreement with the experiment,

We believe the model we have developed could be useful with other homoallylic induction cyclization reactions giving five-membered rings. It should however be borne in mind that the two ends of the molecule are not really independent and that very large electron-withdrawing groups, for example, could have a different behavior than a fluoride or hydroxyl. The effects of substitution at the olefin and at the allylic positions are also not accounted for in the present model and might not be a straightforward extension of our work.

Experimental Section

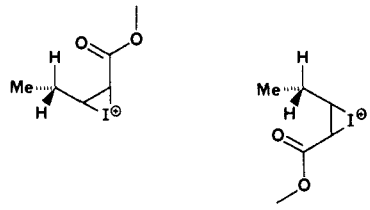
General Procedures. The NMR spectra and NOE experiments were recorded on a Bruker AM-250 spectrometer. Deuteriochloroform was used as the solvent and tetramethylsilane as the reference, unless otherwise noted. The melting points were obtained on a Büchi apparatus and are corrected. All minor compounds are described in the supplementary material.

Computational Methodology. All molecular geometries were created and initially optimized with the Merck molecular modeling system.[44] Molecular orbital calculations were carried out by the AM1[29] semiempirical method as implemented in the AMPAC package of programs.[45] All calculations were performed according to the RHF closed shell method. All geometries were fully optimized unless otherwise indicated. The transition state was characterized by force constant calculations, which showed a single negative eigenvector.

X-ray Crystal Analysis of the *p*-Nitrobenzoyl Ester of 6. Suitable crystals of **6** ($C_{15}H_{16}INO_7$) for X-ray diffraction studies formed as flat plates from diethyl ether–hexane with space group symmetry of $P2_12_12_1$ and cell constants of a = 10.088 (9) Å, b = 34.68 (2) Å, and c = 5.082 (5) Å for Z = 4 and a calculated density of 1.678 g/cm^3. Of the 1461 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 1128 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by full-matrix least-squares techniques.[46] The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.129. Even though the experimental data were corrected for a rather substantial absorption correction, refinement did not proceed well because of the iodine atom. No abnormally short intermolecular contacts were noted. Tables IX–XI, containing the final

(41) Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 8075.
(42) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.
(43) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*: Pergamon: Oxford, 1983.
(44) Gund, P.; Andose, J. D.; Rhodes, J. B.; Smith, G. M. *Science (Washington, D.C.)* **1980**, *208*, 1425. Smith, G. M.; Hangauer, D. G.; Andose, J. D.; Bush, B. L.; Fluder, E. M.; Gund, P.; McIntyre, E. F. *Drug Inf. J.* **1984**, *18*, 167. Halgren, T. A., unpublished work on the development of the force field program OPTIMOL.
(45) Lynn, L. L.; Pierce, T. H.; Reynolds, C. H. *QCPE Bull.* **1987**, *7* (*No. 523*), 37, IBM version. Dewar Research Group; Stewart, J. J. P. *QCPE Bull.* **1986**, *6* (*No. 506*), 24a, VAX/VMS version.
(46) The following library of crystallographic programs was used: Main, P. MULTAN 80; University of York: York, England, 1980. Johnson, C. K. *ORTEP-II*, Oak Ridge National Laboratory: Oak Ridge, TN, 1970. Okaya, Y.; Frenz, B. A. *SDP Plus V1.1*; B. A. Frenz and Associates: College Station, TX, 1984.

Chart III. Standard Heats of Formation (kcal/mol) of Models for the *Z*-Olefinic Moiety



G 130.65 H 133.03

fractional coordinates, temperature parameters, bond distances, and bond angles, are available as supplementary material.

General Procedure for Iodocyclization. The acrylate alcohol and 3 equiv of $NaHCO_3$ were placed in a flask with a magnetic stir bar. After the resultant mixture was purged with nitrogen, the appropriate solvent was added to make the solution 0.1 M in substrate. Under a blanket of N_2, 5 equiv of iodine was added to the well-stirred suspension and progress of the reaction was monitored by TLC. Care must be taken to obtain the TLC aliquots of the stirring solution, and I_2 must be removed in vacuo prior to elution.

After completion of the reaction, a saturated $Na_2S_2O_3$ solution was added dropwise until discoloration. The THF phase was diluted with 1 volume of AcOEt, and the aqueous phase was extracted again twice with AcOEt. The organics were dried on a little Na_2SO_4 and evaporated, and a crude NMR of the residue was obtained. The residue was then purified by flash chromatography.

Ethyl 5,6-*O*-Isopropylidene-(*S*,*E*)-5,6-dihydroxy-2-hexenoate (2). A cold (−78 °C) stirred solution of oxalyl chloride (1.92 mL, 22 mmol) in 50 mL of dry methylene chloride, under argon, was treated with a solution of DMSO (3.55 mL, 41 mmol) in the same solvent (10 mL). After the resultant mixture was stirred at −78 °C for 10 min, a solution of 1,2-*O*-isopropylidene-(*S*)-butane-1,2,4-triol[6,47] (2.92 g, 20 mmol) in 15 mL of methylene chloride was added. The resultant slurry was stirred at −78 °C for 40 min and then treated with diisopropylethylamine (17.5 mL, 100 mmol). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h to afford a yellow solution of *O*-isopropylidene-4-oxo-(*S*)-butane-1,2-diol.

This solution was cooled to 0 °C and treated with (carbethoxymethylene)triphenylphosphorane (17.4 g, 50 mmol) at 0 °C for 1 h and at room temperature for 4 h. The resultant solution was diluted with diethyl ether (300 mL), washed with water (3 × 50 mL), 10% aqueous $NaHSO_4$ (50 mL) and brine (2 × 400 mL), and dried over $MgSO_4$. Removal of solvent gave a viscous oil. Diethyl ether (150 mL) and hexane (150 mL) were added, and the mixture was kept at −10 °C for 15 h. Filtration of the white precipitate ($Ph_3P{=}O$) and removal of solvent gave a yellow oil, which was purified by flash chromatography. Elution of the column with a hexane–ethyl acetate mixture (85:15) gave 0.183 g (4%) of the *Z* isomer **20** as a colorless oil: ^1H NMR δ 6.31 (dt, J_d = 2 Hz, J_t = 7 Hz, 1 H), 5.88 (dt, J_d = 11.5 Hz, J_t = 2 Hz, 1 H), 4.20 (m, 1 H), 4.15 (q, J = 7 Hz, 2 H), 4.04 (dd, J = 6, 8 Hz, 1 H), 3.59 (dd, J = 6, 7 Hz, 1 H), 2.97 (m, 2 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 1.27 (t, J = 7 Hz, 3 H); IR (film) 2992, 1720, 1645, 1180 cm^{-1}; Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.52; H, 8.39.

Further elution of the column afforded 3.60 g (84%) of the *E* isomer **2**: ^1H NMR δ 6.92 (dt, J_d = 16 Hz, J_t = 7 Hz), 5.92 (dt, J_d = 16 Hz, J_t = 2 Hz, 1 H), 4.23 (m, 1 H), 4.20 (q, J = 7 Hz, 2 H), 4.07 (m, 1 H), 3.59 (m, 1 H), 2.5 (m, 2 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.30 (t, J = 7 Hz, 3 H); IR (film) 2994, 1727, 1661, 1372, 1269, 1172, 1064 cm^{-1}; $[\alpha]_D$ −18.0° (*c* 2.4, MeOH); MS *m/e* (relative intensity) 199 (43), 101 (100). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.42; H, 8.44.

Ethyl (*S*,*E*)-5,6-Dihydroxy-2-hexenoate (1). To a solution of ethyl 5,6-*O*-isopropylidene-(*S*,*E*)-5,6-dihydroxy-2-hexenoate **2**; 5.35 g, 25 mmol) in 100 mL of tetrahydrofuran was added 1 N HCl (66 mL). The reaction mixture was stirred at room temperature for 18 h. NaCl (100 g) and ethyl acetate (400 mL) were added. The organic layer was separated and washed with brine (2 × 50 mL). The aqueous washings were extracted with ethyl acetate (2 × 100 mL), the extracts washed with brine (25 mL), and the organic layers combined. Drying ($MgSO_4$) and removal of solvent gave 4.04 g (93%) of a viscous oil: ^1H NMR δ 6.96 (dt, J_d = 16 Hz, J_t = 7 Hz, 1 H), 5.91 (d, J = 16 Hz, 1 H), 4.18 (q, J = 7 Hz), 3.86 (m, 1 H), 3.68 (m, 1 H), 3.48 (m, 1 H), 2.58 (br s, 1 H), 2.39 (m, 2 H), 2.25 (br s, 1 H), 1.28 (t, J = 7 Hz, 3 H); IR (film) 3400, 1720, 1657, 1040 cm^{-1}. Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.52; H, 8.08.

Ethyl 2-[(2*R*,4*S*)(4-Hydroxytetrahydrofuran-2-yl)]-2(*R*)-iodoacetate (3) and Ethyl 2-[(2*S*,4*S*)(4-Hydroxytetrahydrofuran-2-yl)]-2(*S*)-iodoacetate (4). Using the previously described iodoetherification conditions, 1 g (5.75 mmol) of diol **1** yielded 1.48 g (86%) of a yellowish oil that was a 8.6:1 (by NMR) mixture of two compounds **3** and **4**. They were separated by flash chromatography in 1:1 AcOEt–hexane eluent to give 60 mg (4%) of the faster spot, 1.05 g (61%) of the slower one, and 390 mg (21%) of mixed fractions. Major compound **3**: ^1H NMR (C_6D_6) δ 4.62 (dt, J_d = 6 Hz, J_t = 9 Hz, 1 H), 4.10 (d, J = 9 Hz, 1 H), 3.92 (q, J = 7 Hz, 2 H), 3.81 (br s, 1 H), 3.63 (dt, J_d = 10 Hz, J_t = 1 Hz, 1 H), 3.53 (dd, J = 4, 10 Hz, 1 H), 2.09 (br dd, J = 6, 14 Hz, 1 H), 1.66 (br s, 1 H), 1.37 (ddd, J = 5, 9, 14 Hz, 1 H), 0.89 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ +57.7° (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{13}O_4I$: C, 32.02; H, 4.37; I, 42.29. Found: C, 31.83; H, 4.36; I, 42.47.

Ethyl 2-[(2*R*,4*R*)[4-(Benzoyloxy)tetrahydrofuran-2-yl]]-2(*R*)-iodoacetate (7). At −15 °C under N_2 atmosphere, a solution of 81 mg (0.46 mmol) of diethyl azodicarboxylate, 60 mg (0.49 mmol) of benzoic acid, and 100 mg (0.33 mmol) of alcohol **3** in 3 mL of dry THF was treated with a solution of 112 mg (0.43 mmol) of triphenylphosphine in 3.5 mL of dry THF. The reaction mixture was allowed to warm up to room temperature slowly and was stirred for 2 h. The solvent was then evaporated and the residue chromatographed in 1:3 AcOEt–hexane eluent to give 78 mg (58%) of a colorless oil: NMR (C_6D_6) δ 8.08 (dd, J = 8, 1 Hz, 2 H), 7.02 (m, 3 H), 5.04 (m, 1 H), 4.56 (d, J = 10 Hz, 1 H), 4.41 (m, 1 H), 3.92 (m, 3 H), 3.49 (dd, J = 11, 5 Hz, 1 H), 2.05 (m, 2 H), 0.86 (t, J = 7 Hz, 3 H); $[\alpha]^{24}_D$ +86.5° (*c* 3.2, $CHCl_3$); MS (CI, NH_3) calculated for $C_{14}H_{17}IO_5$ 405.01990, found 405.0200.

Ethyl 2-[(2*S*,4*S*)[4-(Benzoyloxy)tetrahydrofuran-2-yl]]-2(*S*)-iodoacetate (8). A mixture of 100 mg (0.33 mmol) of alcohol 4 and 40 μL (0.5 mmol) of pyridine was treated with 60 mg (0.43 mmol) of benzoyl chloride at 0 °C. After 5 h, the reaction mixture was diluted with $CHCl_3$, washed with 10% $CuSO_4$, and dried with Na_2SO_4. After evaporation, the residue was chromatographed in 1:3 AcOEt–hexane eluent to give 95 mg (71%) of a colorless oil, which was identical with **7** by TLC and NMR: $[\alpha]^{24}_D$ −86.0° (*c* 3.7, $CHCl_3$).

Ethyl (*S*,*Z*)-5,6-Dihydroxy-2-hexenoate (9). Following the procedure for the hydrolysis of **2** a solution of isopropylidene **20** (350 mg, 1.63 mmol) in tetrahydrofuran (16 mL) was treated with 1 N HCl (4.3 mL) for 18 h to afford 222 mg (78%) of a viscous oil: ^1H NMR δ 6.85 (dt, J_d = 2 Hz, J_t = 8 Hz, 1 H), 5.94 (dt, J_d = 2 Hz, J_t = 1 Hz, 1 H), 4.18 (q, J = 7 Hz, 2 H), 3.84 (m, 1 H), 3.67 (dd, J = 11, 3 Hz, 1 H), 3.54 (dd, J = 11, 6 Hz, 1 H), 2.68–2.95 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H); IR (film) 3385, 1715, 1643 cm^{-1}.

Ethyl 2-[(2*R*,4*S*)(4-Hydroxytetrahydrofuran-2-yl)]-2(*S*)-iodoacetate (10) and Ethyl 2-[(2*S*,4*S*)(4-Hydroxytetrahydrofuran-2-yl)]-2(*R*)-iodoacetate (11). Using the previously described iodoetherification conditions, 100 mg (0.57 mmol) of diol **9** was allowed to react with iodine in diethyl ether at room temperature for 48 h. The resultant product mixture was further treated with 203 mg (0.74 mmol) of *tert*-butyldiphenylsilyl chloride in 3.8 mL of dichloromethane containing triethylamine (87 mg, 0.86 mmol) and 4-(dimethylamino)pyridine (14 mg, 0.11 mmol) at room temperature for 14 h. The reaction mixture was diluted with ether, washed with water and brine, and dried over $MgSO_4$. Removal of solvent gave an oil, which was purified by flash chromatography (hexane–ethyl acetate, 9:1) to give 223 mg (72% overall) of a 11:1 mixture (NMR) of tetrahydrofurans **10** and **11**. Resubjection of this mixture to flash chromatography gave a pure sample of each isomer. Major compound **10**: ^1H NMR δ 7.60–7.66 (m, 4 H), 7.34–7.47 (m, 6 H), 4.43–4.52 (m, 2 H), 4.29 (d, J = 7 Hz, 1 H), 4.19 (m, 2 H), 3.83 (m, 2 H), 2.11 (br dd, J = 13, 7 Hz, 1 H), 1.75 (m, 1 H), 1.26 (t, J = 7 Hz, 3 H), 1.06 (s, 9 H); IR (film) 1730, 1108, 700 cm^{-1}.

Ethyl 2-[(2*S*,4*S*)(4-Hydroxytetrahydrofuran-2-yl)]-2(*S*)-azidoacetate. A solution of 3 g (10 mmol) of iodide **3** and 1.30 g (20 mmol) of sodium azide in 13 mL of DMSO was heated to 45 °C for 4 h. The solution was then diluted with 75 mL of cool water and extracted with diethyl ether (4 × 100 mL). The organic phase was washed with brine and dried over $MgSO_4$ before evaporation. The residue was flash chromatographed in 3:2 AcOEt–hexane to give 1.73 g (81%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 4.74 (ddd, J = 4, 6, 9 Hz, 1 H), 4.61 (br d, 1 H), 4.31 (q, J = 7 Hz, 2 H), 4.05 (dd, J = 3, 9 Hz, 1 H), 3.84 (d, J = 10 Hz, 1 H), 3.70 (d, J = 3 Hz, 1 H), 2.1 (m, 2 H), 2.00 (d, J = 3 Hz, 1 H), 1.35 (t, J = 7 Hz, 3 H); IR (film) 3400 (br), 2110, 1735 cm^{-1}; $[\alpha]^{23}_D$ −62.0° (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.87; H, 6.08; N, 19.15.

Ethyl 2-[(2*S*,4*S*)(4-Hydroxytetrahydrofuran-2-yl)]-2(*S*)-(trifluoroacetamido)acetate. The precursor azide (470 mg, 2.18 mmol) was treated with 1.14 g (4.36 mmol) of triphenylphosphine in 15 mL of THF. After 24 h of stirring, 63 μL (3.05 mmol) of water was added, and

(47) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.

stirring was continued for an additional 30 h. The mixture was then treated with 400 μL (2.83 mmol) of trifluoroacetic anhydride and 440 μL (5.45 mmol) of pyridine, and additional portions of these reagents were added after 24 h. At 48 h, 10 mL of 10% K_2CO_3 was added; the reaction was stirred for 1 h and brought to pH 4 with 1 M HCl. Extraction of this mixture with CH_2Cl_2, drying of the organic phase with Na_2SO_4, and evaporation gave a brown semisolid. Flash chromatography in 2:1 AcOEt–hexane gave 436 mg (70%) of a white foam: NMR δ 6.97 (br d, 1 H), 4.74 (m, 2 H), 4.58 (br s, 1 H), 4.29 (q, J = 7 Hz, 2 H), 4.01 (dd, J = 4, 9 Hz, 1 H), 3.79 (d, J = 9 Hz, 1 H), 2.09 (m, 1 H), 1.7 (m, 1 H), 1.32 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ +27.3° (c 0.9, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}F_3NO_5$: C, 42.11; H, 4.95; N, 4.91; F, 19.98. Found: C, 42.46; H, 5.22; N, 4.91; F, 21.79.

Ethyl 6-[(*tert*-Butyldiphenylsilyl)oxy]-5(*S*,*E*)-hydroxy-2-hexenoate (21). A solution of 3 g (17.2 mmol) of diol **1** and 2.34 g (34.5 mmol) of imidazole in 86 mL of dry DMF was treated with 5.21 g (19.0 mmol) of chloro-*tert*-butyldiphenylsilane. After 10 min, the reaction was diluted with 50 mL of diethyl ether, washed with 50 mL of water, and evaporated at 40 °C. The residue was chromatographed in 1:4 AcOEt–hexane to give 4.65 g (66%) of a colorless oil: ^{1}H NMR δ 7.67 (m, 4 H), 7.4 (m, 6 H), 6.95 (dt, J_d = 13 Hz, J_t = 7 Hz, 1 H), 5.87 (dt, J_d = 13 Hz, J_t = 1 Hz, 1 H), 4.19 (q, J = 7 Hz, 2 H), 3.88 (m, 1 H), 3.67 (dd, J = 3, 9 Hz, 1 H), 3.55 (dd, J = 6, 8 Hz, 1 H), 2.50 (d, J = 5 Hz, 1 H), 2.47 (br t, J = 6 Hz, 2 H), 1.28 (t, J = 7 Hz, 3 H), 1.09 (s, 9 H); $[\alpha]^{23}_D$ −4.8° (c 4, $CHCl_3$). Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.86; H, 7.82. Found: C, 70.26; H, 8.14.

Ethyl 6-[(*tert*-Butyldiphenylsilyl)oxy]-5(*S*,*E*)-methoxy-2-hexenoate (22). A solution of 200 mg (0.48 mmol) of alcohol **21** in 500 μL of CH_2Cl_2 was cooled to −78 °C, and 200 μL of BF_3·OEt_2 was added. A concentrated solution of CH_2N_2 in CH_2Cl_2 was then added dropwise, until TLC indicated the disappearance of the starting material. Excess of CH_2N_2 was then quenched with acetic acid, and the mixture was stirred on solid $NaHCO_3$ as it warmed up from −78 °C to room temperature. The filtered solution was evaporated and pumped to dryness. Flash chromatography in 1:9 AcOEt–hexane eluent yielded 113 mg (55%) of a colorless oil, along with polymethylene-contaminated fractions: ^{1}H NMR δ 7.66 (m, 4 H), 7.39 (m, 6 H), 6.97 (dt, J_d = 16 Hz, J_t = 7 Hz, 1 H), 5.87 (br d, J = 16 Hz, 1 H), 4.18 (q, J = 7 Hz, 2 H), 3.64 (m, 2 H), 3.36 (m, 1 H), 3.32 (s, 3 H), 2.47 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H), 1.06 (s, 9 H); $[\alpha]^{25}_D$ −12.3° (c 0.8, $CHCl_3$). Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.38; H, 8.03; Si, 6.58. Found: C, 70.17; H, 8.11; Si 6.25.

Ethyl (*S*,*E*)-6-Hydroxy-5-methoxy-2-hexenoate (12). The silyl ether **22** (100 mg, 235 μmol) was diluted with 56 μL (940 mmol) of acetic acid, and 2.3 mL of 1 M Bu_4NF in THF was added with stirring. After the resultant mixture stood overnight at room temperature, 10 mL of 0.1 M phosphate buffer (pH 7.21) was added, and the mixture was extracted with diethyl ether. Drying and evaporation left a residue, which was flash chromatographed in 2:1 AcOEt–hexane to give 39 mg (88%) of a clear oil: ^{1}H NMR δ 6.94 (dt, J_d = 16 Hz, J_t = 7 Hz, 1 H), 5.94 (dt, J_d = 16 Hz, J_t = 1 Hz, 1 H), 4.20 (q, J = 7 Hz, 2 H), 3.7 (m, 1 H), 3.5 (m, 2 H), 3.43 (s, 3 H), 2.46 (m, 2 H), 1.92 (t, J = 6 Hz, 1 H), 1.29 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ +14.0° (c 0.3, $CHCl_3$). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.33; H, 8.77.

Ethyl 2-[(2*R*,4*S*)(4-Methoxytetrahydrofuran-2-yl)]-2(*R*)-iodoacetate (23) and Ethyl 2-[(2*S*,4*S*)-(4-Methoxytetrahydrofuran-2-yl)]-2(*S*)-iodoacetate (24). On the previously described iodoetherification conditions, 29 mg (154 μmol) of acrylate **12** yielded, after flash chromatography in 1:3 AcOEt–hexane eluent, 31 mg (65%) of a colorless oil. This was an unseparable mixture of two compounds **23** and **24**, in a 4.6:1 ratio. The mixture had $[\alpha]^{23}_D$ +27.9° (c 0.5, $CHCl_3$) and a MH^+ peak (CI, NH_3) at 315.0095 (calcd 315.0093).

Major compound **23**: ^{1}H NMR (C_6D_6) δ 4.53 (dt, J_d = 6 Hz, J_t = 9 Hz, 1 H), 4.17 (d, J = 9 Hz, 1 H), 2.81 (s, 3 H), 2.28 (ddt, J_d = 6, 14 Hz, J_t = 1 Hz, 1 H), 1.34 (ddd, J = 5.9, 14 Hz, 1 H), 0.87 (t, J = 7 Hz, 3 H).

Ethyl (*R*,*E*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-fluoro-2-hexenoate (25). A solution of 548 mg (1.33 mmol) of alcohol **21** in 3 mL of $CFCl_3$ was cooled to −105 °C and treated with a solution of 186 μL of DAST in 1 mL of $CFCl_3$. After 20 min at that temperature, it was warmed to −80 °C and quenched with 0.5 M phosphate buffer (pH 7.21) and chloroform. The aqueous phase was separated and extracted with an additional portion of $CHCl_3$, and the organic phases were dried. After evaporation, the residue was purified by flash chromatography in 4:96 AcOEt–hexane to give 200 mg (36%) of a colorless oil: ^{1}H NMR δ 7.7 (m, 4 H), 7.4 (m, 6 H), 6.94 (dt, J_d = 16 Hz, J_t = 8 Hz, 1 H), 5.93 (br d, J = 16 Hz, 1 H), 4.64 (dm, J_d = 49 Hz, 1 H), 4.19 (q, J = 7 Hz, 2 H), 3.80 (d, J = 4 Hz, 1 H), 3.72 (t, J = 4 Hz, 1 H), 2.65 (m, 2 H), 1.29 (t, J = 7 Hz, 3 H), 0.6 (s, 9 H); $[\alpha]^{23}_D$ +4.7 (c 2.4, $CHCl_3$); MS (CI, NH_3) calcd for $C_{24}H_{31}FO_3Si + NH_4$ 432.2370, found 432.2365 (17); also present 395 (15, M − F), 337 (100, M − Ph).

Ethyl 2-[(2*S*,4*R*)(4-Fluorotetrahydrofuran-2-yl)]-2(*S*)-iodoacetate (16) and Ethyl 2-[(2*R*,4*R*)(4-Fluorotetrahydrofuran-2-yl)]-2(*R*)-iodoacetate (17). Under nitrogen atmosphere, a mixture of 300 mg (0.72 mmol) of the silyl ether **25** and 170 mg (2.9 mmol) of acetic acid was diluted with 7 mL of a 1 M solution of Bu_4NF in THF. This was stirred for 2 h at room temperature and quenched by addition of 20 mL of water. Ether extraction, Na_2SO_4 drying, and careful chromatography yielded 85 mg of a 5:1 (NMR) mixture of the desired product **13** along with ethyl (*E*,*E*)-6-hydroxy-2,4-hexadienoate (**14**). Attempts to resubmit this mixture to chromatography lead to the formation of more elimination product.

The iodoetherification reaction was performed on 30 mg of the 5:1 mixture (140 μmol of fluoro alcohol) under the previously described conditions. After 3 days at room temperature, the reaction was stopped. After workup, a crude NMR spectrum showed the absence of starting material, but the resulting mixture is quite complex.

Preparative TLC allowed separation of three pure compounds, the two iodocyclized diastereomers **16** and **17** and unreacted dienol ester **14**. Flash chromatography with careful solvent evaporation yielded pure major diastereomer **16** and a mixture of the minor diastereomer **17** and the dienal ester **26**. The dienal ester was identified by comparison of the NMR spectrum with that of authentic material. Major isomer **16**: ^{1}H NMR (C_6D_6) δ 4.52 (m, 1 H, 4.4 dt, J_d = 60 Hz, J_t = 3 Hz, 1 H), 4.07 (d, J = 10 Hz, 1 H), 3.9 (q, J = 7 Hz, 2 H), 3.85 (ddd, J = 25, 10, 1 Hz, 1 H), 3.36 (ddd, J = 33, 10, 3 Hz, 1 H), 2.32 (ddd, J = 17, 13, 5 Hz, 1 H), 1.23 (dddd, J = 33, 14, 9, 4 Hz, 1 H), 0.88 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ −41.5° (c 2, $CHCl_3$); MS (CI, NH_3) calcd for $C_8H_{13}FIO_3$ 302.9894, found 302.9894 (100).

(±)-Ethyl (*E*)-6-Hydroxy-5-methyl-2-hexenoate (15). The lactone **27**[48] (2 g, 20 mmol) was dissolved in 40 mL of dry diethyl ether and cooled to −78 °C. A solution of 5.7 g (40 mmol) of DIBAL in 40 mL of ether was added over 5 min, stirred until homogeneous, and left overnight at −78 °C. Quenching was effected at −78 °C by adding 6 mL of methanol, followed by 80 mL of silica gel containing 6 mL of water. The slurry was allowed to reach room temperature and was stirred for 2 h. The silica gel was filtered off and rinsed with ether, and the filtrate was evaporated.

The residue (1.75 g) was dissolved in 11 mL of THF and 20 mg of benzoic acid, and 11.83 g (34 mmol) of (carbethoxymethylene)triphenylphosphorane was added. This mixture was refluxed for 2 h, cooled, and evaporated. The residue was flash chromatographed in 1:1 ethyl acetate–hexane to yield 0.85 g (25%) of colorless oil: ^{1}H NMR δ 6.88 (dd, J = 8, 14 Hz, 1 H), 5.82 (d, J = 14 Hz, 1 H), 4.19 (q, J = 7 Hz, 2 H), 3.67 (br t, 2 H), 2.53 (m, 1 H), 1.66 (q, J = 7 Hz, 2 H), 1.36 (br s, 1 H), 1.30 (t, J = 7 Hz, 3 H), 1.09 (d, J = 7 Hz, 3 H); IR (film) 3420 (br), 1710, 1650 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.86; H, 9.61.

Ethyl 2-[(2*SR*,4*SR*)(4-Methyltetrahydrofuran-2-yl)](*SR*)-iodoacetate (28) and Ethyl 2-[(2*RS*,4*SR*)(4-Methyltetrahydrofuran-2-yl)](*RS*)-iodoacetate (29). Using 100 mg (0.58 mmol) of acrylate **15** in the usual procedure, a 97% yield of crude mixture was obtained, which contained two isomers **28** and **29** in a 3.6:1 ratio by NMR and HPLC (normal phase, 1.8% AcOEt in hexane, retention times 21 and 23 min): ^{1}H NMR (C_6D_6–CD_3OD, 2:1, v/v) δ 4.4 (m, 1 H minor), 4.29 (ddd, J = 6, 8, 15 Hz, 1 H major), 4.05 (d, J = 8 Hz, 1 H major), 4.03 (d, J = 8 Hz, 1 H minor), 3.93 (q, J = 7 Hz, 2 H), 3.73 (t, J = 6 Hz, 1 H major), 3.68 (m, 1 H minor), 3.11 (m, 1 H minor), 3.07 (t, J = 6 Hz, 1 H major), 2.11 (dt, J = 11, 5 Hz, 1 H major), 1.87 (m, 1 H). 1.69 (m, 1 H minor), 1.49 (dt, J = 12, 5 Hz), 0.96 (t, J = 7 Hz, 3 H), 0.94 (m, 1 H major), 0.67 (d, J = 7 Hz, 3 H major), 0.64 (d, J = 7 Hz, 3 H minor); MS (CI, NH_3) calcd for $C_9H_{15}IO_3$ 299.0144, found 299.0115 (51).

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Supplementary Material Available: Tables of NOE data for **5t**, **5c**, **10**, **23**, **24**, **16**, **28**, and **29**, preparation of 1,2-*O*-isopropylidene-(*S*)-butane-1,2,4-triol, descriptions of **4**, **11**, **24**, and **17**, and tables of the atomic positional and thermal parameters, bond distances, and bond angles for **6** (11 pages). Ordering information is given on any current masthead page.

(48) Nikishin, G. I.; Svitanko, I. V.; Troyansky, E. I. *J. Chem. Soc., Perkin Trans. 2* **1983**, 595.

(49) Gordon, A. J.; Ford, R. A. *The Chemist Companion*; Wiley-Interscience: New York, 1972; pp 4–13.