71-3; **23**, 118893-72-4; **24**, 87461-94-7; **25**, 119007-07-7; **26**, 118893-74-6; **29**, 119008-29-6; **30**, 118893-73-5; **31**, 99166-36-6; **31a**, 118893-75-7; **32a**, 99166-37-7; **32b**, 99166-38-8; **33a**, 118920-26-6; **33b**, 118893-76-8; **33c**, 118893-77-9; **34a**, 99166-39-9; **35**, 99166-41-3; **37a**, 99166-42-4; **37b**, 99166-43-5; **38**, 99166-44-6; (*E*)-**39**, 119007-08-8; (*Z*)-**39**, 119007-09-9; **40**, 91861-00-6; **41**, 99166-46-8; **42**, 99166-47-9; α-**43a**, 119008-30-9; β-**43a**, 118893-78-0; α-**43b**, 119007-10-2; β-**43b**, 119007-11-3; **44a**, 118893-79-1; **44b**, 99212-55-2; **45**, 99212-56-3; **46**, 119007-12-4; α-**47**, 118893-80-4; β-**47**, 119007-13-5; **48**, 99212-57-4; **49**, 119007-14-6; **50**, 99212-85-8; **51**, 99212-58-5; **52**, 118920-27-7; **53**, 118893-81-5; (*E*)-$BnOCH_2CH{=}CHCHO$, 69152-87-0; 2-furaldehyde, 98-01-1.

Supplementary Material Available: NMR spectra of synthetic and authentic samples of compound **2a** (1 page). Ordering information is given on any current masthead page.

Diastereoselective Synthesis of 2,3-Disubstituted Tetrahydrofuran Synthons via the Iodoetherification Reaction. A Transition State Model Based Rationalization of the Allylic Asymmetric Induction

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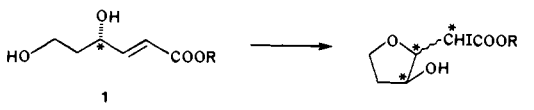
Contribution from Merck Frosst Canada, Inc., P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8. *Received June 29, 1988*

Abstract: The kinetically controlled iodoetherification reaction of ethyl (*S*,*E*)-4,6-dihydroxy-2-hexenoate (**1**) gives the synthetically useful synthon **2**, in which two new stereogenic centers have been generated, with selectivities up to 11:1. The mechanism of this allylic asymmetry transfer was probed by changing the allylic stereogenic substituent, and the order of efficacy for asymmetric induction was found to be F > OH ≥ OMe > Me. This result ruled out several proposed mechanisms of asymmetry transfer and led to the proposal of a transition-structure model, based on AM1 calculations. Our model rationalizes all of our results as well as those from the literature concerning selectivity and even relative rates of diastereomeric substrates.

The use of acyclic asymmetric induction has proven to be a valuable synthetic strategy, as judged by the large number of recently developed diastereoselective synthetic methods based on this mode of asymmetry transfer.[2] A reaction that is especially well-suited for this kind of asymmetry transfer is the formation of 5-membered rings by electrophilic activation of an allylic alcohol moiety.[3-12] The iodoetherification reaction (Scheme I) on which we will report here is part of this class of reactions.

Scheme I



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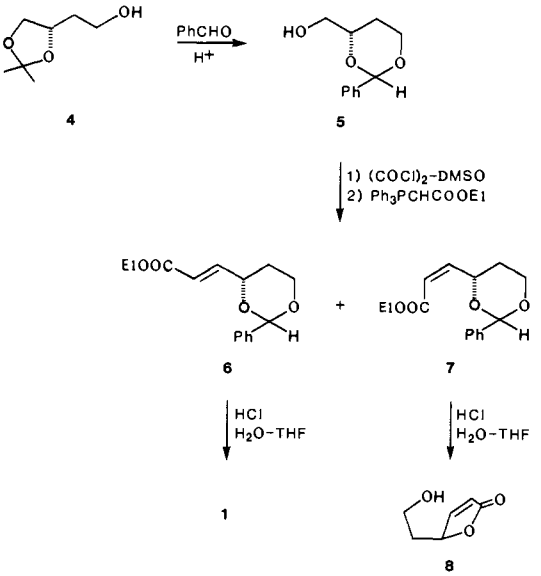
Scheme II



4 5 6 7 1 8

We became interested in allylic asymmetric induction in the formation of tetrahydrofuran derivatives after we had developed

(1) Present address: Bio-Mega, 2100 Cunard Street, Laval, Quebec H7S 2G5, Canada.

(2) Acyclic Allylic Induction. Epoxidations: Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589. Hydroboration: Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. Dihydroxylation: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. Cyclopropanation: Mohamadi, F.; Still, W. C. *Tetrahedron Lett.* **1986**, *27*, 893. Hydration: Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407.

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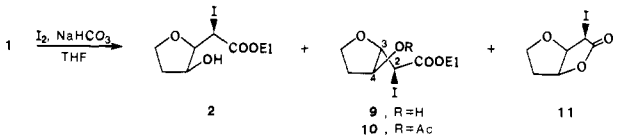
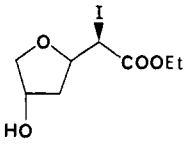
Scheme III



a method[13] which allows, via homoallylic asymmetric induction, the selective preparation of all eight diastereomers of **3**. This



3

method has already demonstrated its usefulness in the total synthesis of a natural product.[14] We now report our results on the allylic asymmetric induction in the kinetically controlled iodoetherification reaction. The synthetic potential of the reaction will be demonstrated by the stereoselective synthesis of synthon **2** (Scheme III). The mechanism of the allylic asymmetric induction will also be investigated by using various allylic inducer groups, and the results will be rationalized by using the mechanistic hypothesis previously described for the homoallylic series. This mechanistic scheme will also be used to rationalize some interesting results from the literature concerning rate differences between diastereomers.

Results and Discussion

Our investigation of the synthetic potential of allylic control in the iodoetherification reaction started with the simple allylic alcohol **1**. It differs from the literature examples of allylic control[4b-9] in that an α,β-unsaturated ester was used as the olefinic moiety.[15] This has two main advantages. First, no 6-membered-ring products were ever observed (NMR) in this system, because the intermediate olefin–I_2 π-complex is very unsymmetrical, favoring the nucleophilic attack of the β-carbon. Second, the products always have two new stereogenic centers and are abundantly functionalized for further synthetic manipulations.

The preparation of the desired optically active substrate **1** for the iodoetherification reaction is depicted in Scheme II. The starting acetonide **4**, for which an efficient preparation has been described,[13] was transketalized in the presence of a slight excess of benzaldehyde, with vacuum applied to the reaction mixture to displace the equilibrium to the acetal **5**. A one-pot Swern oxidation–Wittig reaction then afforded an easily separable mixture of *E* and *Z* isomers, **6** and **7**. The *E* isomer was hydrolyzed in aqueous acid–THF mixture to the desired diol **1**.

The iodoetherification reaction was run under kinetic[16] conditions, namely 5 equiv of I_2 and 3 equiv of $NaHCO_3$ in THF solvent at room temperature, with efficient stirring. After workup, a mixture of three products was obtained in nearly quantitative yield, and the spectrum suggested a 7.3:1:trace ratio of **2**, **9**, and **11**. The three components were separated by flash chromatography for a total 77% recovery of pure products.

The compound present in a trace amount had no ethoxy signal by NMR and had a 1775-cm^{-1} IR band characteristic of γ-lactones. On this basis, it was assigned structure **11**. The major compound was a hydroxy iodo ester, which, upon treatment with acid, was converted to the lactone **11**. A cis relative stereochemistry between hydroxyl and the iodoacetate chain must therefore have been present. The minor component of the reaction mixture was also a hydroxy iodo ester which remained unchanged after treatment with acid for 2 days at room temperature. The compound was converted to an acetate (**10**), and NOE experiments were performed[17] (Table III, in the supplementary material). The relative stereochemistry between the acetoxy and the iodoacetate chain was found to be trans, on the basis of the relatively strong enhancement observed at H_2 when H_4 is irradiated, and vice versa. The weakness of the H_3–H_4 mutual enhancements, as well as the presence of an Ac–H_3 enhancement, strengthened these conclusions.

The stereochemical outcome of the iodoetherification reaction of **1** under the conditions described therefore favors the formation of the cis-substituted tetrahydrofuran with a ratio of 7.3:1. This is consistent with analogous allylic hydroxyl directed 5-membered-ring cyclizations in the literature.[4b,8,9]

The next issue addressed was that of the stereochemistry of the carbon bearing the iodine atom, for which we have no direct evidence. We can however determine the absolute stereochemistry of this center in our various products on the basis of the following reasoning. In the homoallylic series,[13] we have determined the iodine bearing carbon stereochemistry on the basis of an X-ray diffraction analysis, and we have found that the reaction proceeds with overall trans addition across the olefin, in a stereospecific manner with respect to the olefin geometry. There are no obvious reasons why a similar mechanism should not be operative in the allylic series, and therefore, we shall consider a proof of stereospecificity with respect to the olefin geometry as a strong support for a similar trans-addition mechanism, from which we can deduce the absolute stereochemistry of our iodine-bearing stereocenters.

The stereochemistry of the iodoetherification reaction can be demonstrated as shown in Scheme IV. The *E*-olefin diol **1** is known to iodocyclize mostly to a cis product (**2**) which, upon acid treatment, gives a lactone (**11**). On the other hand, lactone **8**, isolated from an attempted preparation of the *Z*-olefin diol, should also iodocyclize to a cis-fused lactone, but with the opposite stereochemistry at the iodide-bearing stereocenter. When the reactions of Scheme IV were performed, two iodo lactones with identical elemental compositions but with different spectral properties, melting points, and optical rotations were obtained. The present reaction is therefore stereospecific, and assuming the same trans-addition mechanism as previously observed,[13] we assign the *R* absolute stereochemistry to the iodide-bearing stereocenter of products **2** and **11** and the *S* stereochemistry for that of the minor product **9**, as drawn. This assignment is consistent with

Scheme IV

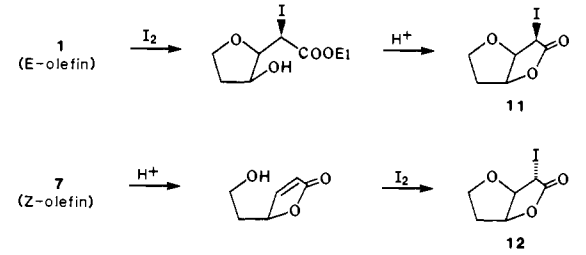
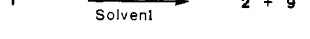


Table I. Solvent Effect on the Diastereoselectivity of the Iodoetherification Reaction of **1**



reaction solvent	cis:trans ratio[a]	reaction solvent	cis:trans ratio[a]
tetrahydrofuran	7.3:1	dichloromethane	*b*
ethyl acetate	11:1	chloroform	*b*
acetonitrile	5:1	toluene	*b*
ether	6:1		

[a] Determined by corrected HPLC peak surface ratio. All reactions were run to >90% conversion. [b] Very slow reaction, accompanied by the formation of many uncharacterized products.

(13) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533.
(14) Guindon, Y.; St-Denis, Y.; Daigneault, S.; Morton, H. E. *Tetrahedron Lett.* **1986**, *27*, 1237.
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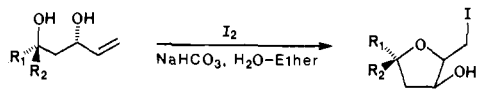
(16) Bartlett, P. A.; Richardson, D.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.
(17) Bernstein, M. A.; Morton, H. E.; Guindon, Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1155.

Scheme V



13 : R_1, R_2=O
14 : R_1=Alkyl or Aryl, R_2=H
15 : R_1=H, R_2=Alkyl or Aryl
16 : R_1=R_2=H

the literature data of other kinetically controlled analogous reactions with different electrophilic or nucleophilic groups.[4b,8]

Once the stereochemistry and ratio of products was established, it became desirable to improve the synthetic usefulness by increasing the diastereoselectivity of the reaction. Table I shows the diastereoselectivity of the reaction in various solvents. Clearly, ethyl acetate is the solvent of choice for the iodoetherification of **1**, giving an excellent chemical yield and a 11:1 ratio, favoring the cis diastereomer **2**.

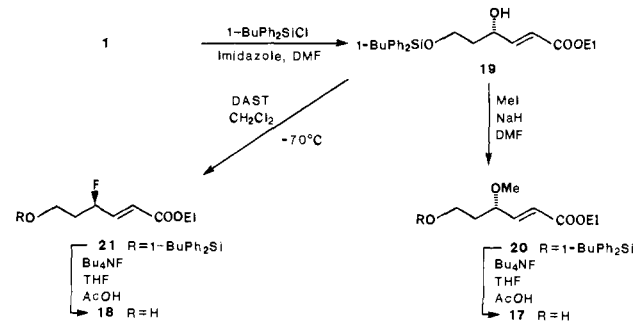
With a highly stereoselective preparation in hand, the synthetic use of chiron[18] **2** becomes interesting. The hydroxyl, iodide, and ester groups can be readily converted in chemo- and stereoselective manners into a variety of functional groups. Moreover, regioselective cleavage of the tetrahydrofuran ring with Me_2BBr[19] would open the way to 1,2,3 acyclic arrays of stereogenic centers. The use of **2** in the synthesis of natural products will be reported elsewhere.

Aside from the synthetic potential of the product, the induction of two new stereogenic centers with such selectivity, from the allylic position, is of great interest. We therefore turned our attention to unraveling the mechanistic origin of this allylic asymmetric induction, with the hope of finding a model that would rationalize our results and those of related systems in the literature.

Mechanism of Asymmetry Transfer. Allylic asymmetric induction in electrophile-driven cyclizations has been known for some time. Interesting levels of diastereoselectivity have been obtained in many of these reactions, and workers describing isolated cases have rationalized their results in terms of ground-state conformational preference, steric control, electrophile–allylic group chelation control, and combinations thereof.[4-6,11,20] Three groups have studied in detail various aspects of the allylic asymmetry transfer in these reactions, and their findings are summarized below.

Allylic asymmetric induction in the iodolactonization reaction (parent example, see **13** in Scheme V) was studied by the group of Chamberlin.[8] The bulk of their study was performed with hydroxyl as the allylic group, although they found acetoxy and (trialkylsilyl)oxy groups to be equally effective. A variety of substrates were used for iodolactonization that differed by the presence or absence of methyl substitution on all of the substrates positions. Most of these substrates gave a good selectivity for the product in which the stereogenic hydroxyl and the iodoalkyl side chain were cis. One notable exception was the case where the substrate olefin had a *Z* substitution pattern, these compounds giving mostly the δ-lactone, along with some γ-lactone, which was predominantly trans substituted on the ring. A complete rationale of their results was later published, in a joint study with Hehre's group.[21,22] This rationale was based on the difference in reactivity between the two faces of the olefin toward electrophiles. It was also suggested that the cyclic and acyclic versions of the halohydrin reaction show opposite sense of allylic asymmetric induction

Scheme VI



because the acyclic case requires a more fully developed halonium ion, whereas the cyclization reaction occurs on the π-complex before it undergoes charge separation.

In the study of allylic induction in the formation of tetrahydrofuran derivatives by iodoetherification, the group of Yoshida[4b,c] obtained similar results (**14–16** in Scheme V). Indeed, the product with a cis-substitution pattern on the tetrahydrofuran ring is always the major one, again with the exception of the substrates with *Z*-olefins for which the reaction was sluggish, producing mostly tetrahydropyran products along with some tetrahydrofuran products in which the trans arrangement on the ring is now predominant. Another important observation of this work is the reactivity difference between pairs of diastereomers, such as **14** and **15**, and for which a rationale based on an internal hydrogen bond in the transition state has been proposed.[23]

Finally, a third detailed study, by the groups of Reitz and Liotta,[6,9] dealt with the effect of substitution on electrophile-driven cyclic etherifications, with special emphasis on the effect of the reagent. The orientation effect of substituents was found to be consistent with the previously described studies, namely cis allylic induction from OR substituents, with the exception of substrates with *Z*-olefins. A different allylic stereogenic group, a methyl, was tested in this system and gave a 2.1:1 selectivity for the cis product.[24] Another important observation of this work was that the nature of the electrophile can affect the observed selectivity. The reversibility of the electrophile addition to the olefin appeared to be a key factor, a complete reversibility being essential for good selectivity.

As mentioned before, our current interest lies with the mechanistic basis of the allylic asymmetry transfer. Specifically, we are interested in understanding the molecular effects responsible for the selective formation of cis-substituted 5-membered-ring products, to better assess the scope and limitations of this mode of asymmetry transfer. The method we chose for elucidating these molecular effects is the variation of the stereogenic allylic group.

Most of the published allylic asymmetric induction studies, including the first part of this work, use a hydroxyl substituent as the allylic stereogenic group. In a mechanistic study, this group is quite complex since it can behave as a hydrogen-bond donor, a hydrogen-bond acceptor, a Lewis base for complexation of I_2, as well as an electron-withdrawing group in the $\pi-\sigma^*_{C-O}$ allylic interaction. As a first alternative, we used a methoxy substituent, which removes the H bond donor ability while retaining the other

(18) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon: Oxford, 1983.
(19) Guindon, Y.; Therien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680.
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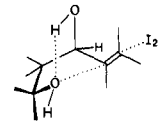
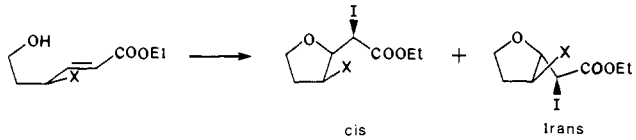
(22) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

(23) The transition-state model proposed to rationalize these observations has a crucial, geometry-determining hydrogen bond from the allylic alcohol (H-bond donor) to the nucleophilic oxygen (H-bond acceptor). We believe this is not a likely transition structure since (1) hydrogen free allylic inducer groups OAc, $OSiR_3$,[8] and OBn[9] are as efficient as OH in inducing a cis arrangement; (2) the proposed H bond would deactivate the nucleophilic oxygen in the transition state.



(24) This result is related to the 3:1 cis selectivity observed by Bartlett[12] in the iodolactonization reaction directed by an allylic methyl group.

Table II. Stereoselectivity of the Iodoetherification Reaction in THF Solvent with Various Allylic Stereogenic Groups



cis trans

X	substrate	cis:trans product ratio	products (cis, trans)
OH	**1**	7.2:1	**2**, **9**
F	**18**	9.3:1	**24**, **25**
OMe	**17**	6.6:1	**26**, **23**
Me	**22**	2.3:1	**27**, **28**

features. Next, we used a fluoride substituent, in which the H bond acceptor and I_2-complexing capabilities[25] are much lower than those of methoxy, but the $\pi-\sigma^*_{C-O}$ effect is stronger. Finally, we studied a methyl group, which lacks all the above effects and will serve as the reference for steric- and torsional-based effects.

The requisite substrates bearing methoxy (**17**) and fluoro (**18**) stereogenic groups were prepared as shown in Scheme VI. The first step to both compounds was the selective protection of the primary alcohol on diol **1** with *t*-$BuPh_2SiCl$.[26] The methoxyl group was obtained by reaction of the alcohol **19** with methyl iodide and sodium hydride in DMF. The fluoro substituent was introduced by reacting the alcohol **19** with DAST. Both these compounds were deprotected with tetrabutylammonium fluoride to give the desired substrates **17** and **18**.

The methyl substrate **22** was prepared by a DIBAH reduction of the commercially available α-methyl-γ-butyrolactone, followed by a Wittig reaction of the lactol with (carbethoxymethylene)-triphenylphosphorane.

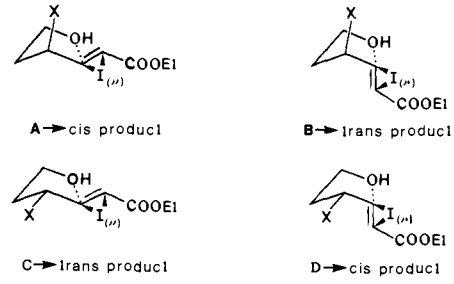
These three substrates were iodocyclized under the standard conditions already described for the hydroxyl substrate **1** in THF solvent. Although these conditions are not optimal for selectivity, they give reasonable rates of reaction in all cases.

The product stereochemistries were determined mostly by NOE.[17] The general trend observed for cis-substituted compounds was a strong NOE between the ring protons H_3 and H_4 (see **10** for the numbering system) whereas the trans compounds had a strong NOE between H_2 and H_4. Tables of NOE data are available as supplementary material. In the case of the minor isomer of the methoxy iodocyclized product **23**, the stereochemistry was unambiguously assigned by correlation with an authentic sample prepared from the corresponding hydroxyl compound **9** obtained in the iodocyclization of the hydroxyl substrate **1**.

The cis:trans ratios observed for the various inducer groups are presented in Table II. All the groups gave the cis-substituted product as the major one, with selectivity decreasing in the order F > OH ≥ OMe > Me. These results parallel the iodolactonization selectivities of Chamberlin,[8] the iodoetherification selectivities of Yoshida,[4b,c] and Reitz and Liotta,[6,9] as well as the closely related example described by Freeman and Robarge.[11]

Many conclusions on the mechanism of asymmetry transfer can be drawn from the observed order of potency of allylic substituents. First, despite the nice inverse relationship between the steric requirement of the allylic inducer group and the selectivity, the induction cannot be exclusively under steric control. The reason for this is best pictured in terms of the difference in size between the two substituents (the X group and the H atom) on the allylic carbon; under steric control, one would expect a large size difference (H vs Me) to give rise to a high selectivity, whereas two groups of similar sizes (H and F) should lead to a nonselective reaction. The opposite trend is observed.

Chart I. The Four Transition-State Conformations



A second conclusion from our results is that an internal delivery of iodonium ion by the allylic group or a stabilization of the transition structure by internal complexation of iodine or iodonium ion by this allylic group are not operative in our system. The fluoro group is inferior to an alkoxy group for complexing iodine,[25] and yet the former gives better levels of induction. Since our system has a very electron poor olefin, in which complexation control would be optimal, we can generalize the absence of complexation to the other cases reported in the literature.

A third conclusion regards the presence of an internal H bond in the transition state.[4b] Clearly, from our results, as good (X = OMe) and superior (X = F) inductions were observed in cases where the allylic substituent cannot be a hydrogen-bond donor. Moreover, our results also exclude a rationale based on the hydrogen bond acceptor capabilities of the allylic substituent, since the fluoro substituent would then be expected to be a weaker inducer.

The elimination of these possible mechanisms of direct stereochemical control in the reaction led us to a more detailed analysis of the global reaction mechanism, in order to find the molecular effects responsible for the observed allylic asymmetric induction.

Our earlier work in this field led to a rationalization of the homoallylic asymmetric induction observed in the kinetically controlled iodoetherification reaction.[13] The mechanistic hypotheses which were used and which should still be valid in the present allylic case were a rapid pre-equilibrium of iodine–olefin π-complexes, followed by a rate-limiting cyclization step. The deprotonation of this latter intermediate renders the reaction irreversible, trapping the kinetic product. This mechanism is close to the one proposed by Reitz, Liotta, and their co-workers,[6,9] for which they have demonstrated the necessity of a reversible first step for good selectivity.

Assuming this mechanistic scheme, the rapid equilibrium of π-complexes implies that the cyclization step of the reaction will dictate the stereochemical outcome. More precisely, only the relative energy of the cyclization step transition structures leading to the cis and trans products will determine the product ratio.[27,28] On the basis of AM1 calculations, we had determined that the transition structures for this type of cyclization reaction can be thought of as a chair (see Chart I), with only the five atoms forming the tetrahydrofuran in chair-atom positions.

Although direct comparison of the various transition structure energies would be ideal, this will be impossible due to the inherent difficulty of calculating transition structures. We will therefore revert to a model of the transition structure which will mimic as closely as possible the conformational energy profile of the actual transition structure, while being itself a ground state. One such model is the iodonium ion of the olefin, which features a planar, positively charged electrophilic carbon and an iodine atom above the plane of the olefin just as in the transition structure. This model was used successfully in the homoallylic series[13] and should be equally effective in the present case.

In the modeling of the present reaction, four possible transition structures need to be considered (Chart I). They can be pictured

(25) A low affinity of fluorine lone pairs for I_2 complexation is expected from theory and was demonstrated by recording the visible spectrum of I_2 in various solvents. Thus, the noncomplexing hexane solvent and 1-fluoropentane solvent gave purple solutions with identical spectra. On the other hand, solvents containing heteroatoms that can complex I_2, like butyl methyl ether and 1-pentanol, gave brown solutions and their spectra showed strong hypsochromic shifts.

(26) Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1975**, *53*, 2975.

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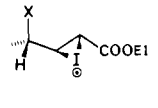
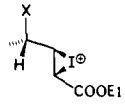
(28) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

Chart II. Standard Heats of Formation of the Four Transition-Structure Models



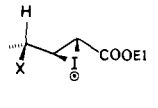
A1

X=F : 94.15 Kcal/mol
X=Me: 124.56 Kcal/mol



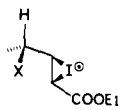
B1

X=F : 96.20 Kcal/mol
X=Me: 125.27 Kcal/mol



C1

X=F : 97.73 Kcal/mol
X=Me: 125.07 Kcal/mol



D1

X=F 98.25 Kcal/mol
X=Me: 127.91 Kcal/mol

as having the X inducer group axial (A and B) or equatorial (C and D) and the olefinic moiety pointing up (A and C) or down (B and D). Note that C and D are drawn as enantiomers of A and B, to make the stereochemical argument clear. The relative energy of these various conformers was probed by AM1 calculations, with transition state models A1–D1 (Chart II) in which the bond from the olefin to the allylic carbon was locked at a proper dihedral angle to preserve the chairlike conformation.

As the energies indicate (Chart II), the case where X = F strongly favors conformer A1, the model of conformer A transition structure which leads to the cis product. In the case where X = Me, the calculation again predicts conformer A1 to be favored, but by a much narrower margin. The experimental results were that both X = F and X = Me showed a preference for the cis product with selectivities of 9.3:1 and 2.3:1, respectively. The sense and magnitude of the calculation results with these stereogenic groups therefore agrees with the experimentally observed ratios of the diastereomers.

In the case where X = Me, the preference for conformer A, with the axial methyl, is not easily rationalized in terms of molecular effects.[29] Indeed, this preference is quite different from that of the ground-state olefin which, when locked in a chair form, prefers the equatorial-methyl and olefin-up conformation, C. The possibility that a steric interaction between the methyl group and the iodine atom in the transition state destabilizes conformer C was discarded on the basis of the absence of van der Waals contact in model C1. More intriguingly, the equatorial methyl group would also appear more reasonable in terms of hyperconjugative stabilization of the positive charge on the olefin β-carbon in the transition state.

The molecular effects involved in the preference for conformer A when X = F are, on the other hand, better defined. After removing the possibility of hydrogen bonds, iodine delivery, and steric effects, we will consider orbital effects. The transition structure of this reaction has a fair degree of positive character on the olefin β-carbon. It therefore is destabilizing to have the fluoride group equatorial with its strongly electron withdrawing C–F LUMO in conjugation with the π-system.[31] The system thus prefers a conformation where the C–F LUMO and the π-system are orthogonal (the "endo alkoxy effect"[32]), which is possible when the fluoride is axial. Finally, the preference for the olefin-up over olefin-down conformation (A and B) is due to torsional reasons, since the former is actually a staggered conformation whereas the latter is an eclipsed conformation.

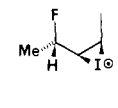
(29) It is interesting to note that a similar slight preference for an allylic methyl group to eclipse the olefin in an electrophilic reaction transition structure has been observed by K. N. Houk and co-workers.[30] Their study, however, dealt with nitrile oxide cycloadditions to an olefin, a reaction too different from ours for their steric-based rationale to be applied to our case. The similarity of our results may be fortuitous.

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

(31) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.

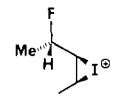
(32) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

Chart III. Standard Heats of Formation of the *Z*-Olefin-Derived Transition-Structure Models



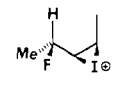
A2

99.09 Kcal/mol



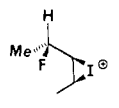
B2

97.15 Kcal/mol



C2

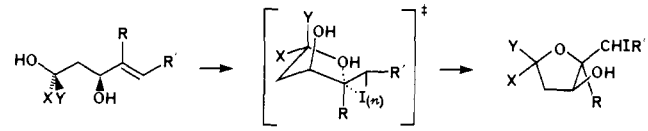
98.24 Kcal/mol



D2

101.81 Kcal/mol

Scheme VII



syn: X = alkyl or aryl, Y = H
anti: X = H, Y = alkyl or aryl
R, R' = H or Me

Transition-Structure Model and *cis*-Olefins. In several cases of 5-membered-ring electrophile-driven cyclization, namely three different iodoetherification[4b,9,11] systems and one iodolactonization[8] system, it has been reported that the sense of allylic asymmetric induction was completely reversed from cis- to trans-substituted product, by simply changing the starting olefin geometry from *E* to *Z*. This interesting phenomenon was modeled by using our transition-state approach, and the energies obtained for transition-structure models A2–D2 are reported in Chart III.

The results clearly indicate that A is no longer the favored conformer but that there now is a large preference for conformers B and C, which are both transition structures leading to the trans product. The models A2–D2 are suitable for the *cis*-olefin cases described in the literature,[4b,8,9,11] where the trans product was experimentally found to be the major product. Thus, in this case again, our transition-state model is in agreement with the experiment.

Transition-Structure Model and Relative Rate of Reaction of Diastereomers. A striking aspect of work of Yoshida and coworkers[4b,c] is the very large rate differences observed in the iodoetherification reaction of pairs of diastereomeric compounds with a 1,3 relationship of stereogenic centers (Scheme VII). It appears that the syn substrates react considerably faster than the corresponding anti substrates, enough to allow a clean kinetic resolution of mixtures of diastereomers. Comparison of the reaction conditions and times for these reactions with other examples reported in Yoshida's papers indicates that the rate difference does not originate from an acceleration of syn-diastereomer reaction, but rather from a retardation of that of the anti. In one of the reported cases, the anti diastereomer was so slow to react that the less kinetically favored tetrahydrofuran formation became predominant. In parallel with slower reaction rates, the general trend is that anti substrates are less diastereoselective for the formation of cis products than syn substrates are. These rate and selectivity results are readily rationalized with our transition-state model.

By simply considering the chairlike transition structures for the syn and anti substrates, it becomes obvious that the transition structure from the syn substrates bears the bulky substituent in the equatorial position (X), whereas the transition structure from the anti substrate has it axial (Y). Not only is the latter itself unfavorable but it also sets a strong 1,3 diaxial interaction between the bulky group and the stereogenic allylic hydroxyl in the usually preferred transition structure A. This therefore raises the energy of the anti substrate derived transition structures relative to that of the corresponding syn substrate, making the reaction slower.

The same 1,3 diaxial interaction is also responsible for the decreased cis-product selectivity observed with Yoshida's anti substrates. Indeed, such an interaction increases the energy of the transition structures with axial hydroxyl, such as A. Since the selectivity is proportional to the energy difference between the possible transition structures, raising the energy of the most stable one diminishes the gap to the next most stable, therefore decreasing the selectivity. Interestingly, this rationale also covers the unexpectedly low selectivity observed by Chamberlin,[8] in the iodolactonization reaction of their example **1m**. His proposed rationalization fits nicely into our model.

Concluding Remarks

In this study, we have developed a diastereoselective access to synthon **2**, using a kinetically controlled iodoetherification reaction that generates two new stereogenic centers with high selectivity. The mechanism of asymmetry transfer was studied by varying the allylic stereogenic center, which allows the elimination of several proposals from the literature. We then proposed a model based on AM1 calculations which rationalizes our results in terms of a chairlike transition structure. The good agreement between our model and our experimental results supports our initial mechanistic hypothesis of a rapidly reversible initial attack of iodine on the olefin, followed by a rate-determining cyclization step. Our chairlike transition structure model also rationalizes the selectivity and kinetics of several other examples of kinetically controlled electrophile-driven 5-membered-ring formation with asymmetry transfer from either the allylic or homoallylic position. This broad range of applicability makes our proposed rationalization even more attractive.

Finally, a word of caution about extending these results to other systems. As clearly demonstrated by Reitz, Liotta, and coworkers,[6] the selectivity of these reactions is linked to the rapid reversibility of the first electrophile–olefin interaction. However, all electrophiles may not suit the Curtin–Hammett condition (rapid preequilibrium relative to the rate-determining cyclization step) on which our model is crucially dependent. For some electrophiles, a significant portion of the reaction may be going through a pathway in which the initial electrophilic attack is apparently irreversible and therefore geometry determinant.

Experimental Section

General Procedures. Melting points were obtained on a Büchi apparatus and are corrected. NMR spectra (recorded in $CDCl_3$ unless otherwise noted) and NOE measurements were obtained on a Bruker AM-250 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Computational Methodology. All molecular geometries were created and initially optimized by using the Merck molecular modeling system.[33] Molecular orbital calculations were carried out by using the AM1[34] semiempirical method as implemented in the AMPAC package of programs.[35] All calculations were performed by using the RHF closed-shell method. All geometries were fully optimized unless otherwise indicated.

General Procedure for Iodocyclization. The acrylate alcohol is dissolved in the appropriate solvent under N_2 to make the substrate 0.2 M. Solid $NaHCO_3$ (3 equiv) is suspended in the solution. Iodine (5 equiv) is then dissolved, and rapid stirring is continued throughout the reaction. TLC monitoring of the reaction is representative only if the TLC aliquot contains the suspended solid and if any iodine is removed in vacuo prior to elution.

When all starting material has disappeared, the residual iodine is quenched by dropwise addition of a saturated solution of $Na_2S_2O_3$. The reaction mixture is then diluted with 1 volume of AcOEt, the phases are separated, and the aqueous phase is twice reextracted with AcOEt. The combined organic phases are dried on a little Na_2SO_4, the solvent is removed, and the residue is purified by flash chromatography.

(*S*)-4-(Hydroxymethyl)-2-phenyl-1,3-dioxane (5). The acetonide of (*S*)-1,2,4-butanetriol[13] (20 g, 137 mmol) was diluted with benzaldehyde (15.9 g, 150 mmol). A catalytic amount (130 mg, 0.68 mmol) of *p*-toluenesulfonic acid was then added to the mixture, which was stirred under 200 mmHg vacuum for a week. Solid K_2CO_3 was then added, and stirring was continued for 2 h. The solid was filtered, and the mixture was purified by flash chromatography to yield 17.5 g (66%) of a colorless oil. **5**: ^{1}H NMR δ 7.5 (m, 2 H), 7.4 (m, 3 H), 5.52 (s, 1 H), 4.27 (dd, J = 5, 11 Hz, 1 H), 3.95 (br t, 2 H), 3.63 (br s, 2 H), 2.45 (br s, 1 H), 1.89 (dq, J = 5 Hz, 12 Hz, 1 H), 1.40 (m, 1 H); $[\alpha]^{23}_D$ +6.8° (*c* 2.7, $CHCl_3$).

Ethyl (*E*)-3-[(*S*)-2-Phenyl-1,3-dioxan-4-yl]propenoate (6) and Ethyl (*Z*)-3-((*S*)-2-Phenyl-1,3-dioxan-4-yl)propenoate (7). These were prepared by Swern oxidation and Wittig reaction on **5**, by using the method previously described.[13] After workup, the residue was purified by chromatography with 15% AcOEt in hexane. After several mixed fractions, pure fractions of the slower compound **6** were obtained that contained 1.46 g (60%) of a white solid. An analytical sample was prepared by repeated crystallization from ether–hexane to give colorless plates, mp 67.5–68.5 °C. **6**: ^{1}H NMR δ 7.55 (m, 2 H), 7.38 (m, 3 H), 6.93 (dd, J = 4, 16 Hz, 1 H), 6.14 (dd, J = 2, 16 Hz, 1 H), 5.60 (s, 1 H), 4.58 (br d, 1 H), 4.33 (dd, J = 5, 11 Hz, 1 H), 4.21 (q, J = 7 Hz, 2 H), 4.03 (dt, J = 3, 12 Hz, 1 H), 1.92 (dq, J = 5, 13 Hz, 1 H), 1.70 (br d, 1 H), 1.29 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ −23.8° (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.67; H, 7.02.

The mixed fractions were resubmitted to chromatography to give the faster compound **7** as an oil: ^{1}H NMR δ 7.5 (m, 2 H), 7.35 (m, 3 H), 6.35 (dd, J = 6, 10 Hz, 1 H), 5.83 (dd, J = 1, 10 Hz, 1 H), 5.63 (s, 1 H), 5.54 (br t, 1 H), 4.31 (ddd, J = 1, 4, 10 Hz, 1 H), 4.20 (q, J = 7 Hz, 2 H), 4.11 (dt, J = 3, 10 Hz, 1 H), 1.9 (m, 2 H), 1.31 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ +13.6° (*c* 0.8, EtOH).

Ethyl (*S*,*E*)-4,6-Dihydroxy-2-hexenoate (1). The acetal **6** (3.40 g, 12.8 mmol) was dissolved in 70 mL of THF, and 40 mL of 1 M HCl was added. After 20 h at room temperature, the reaction was quenched with 3.5 g of solid $NaHCO_3$. Solid NaCl was added to separate the two liquid phases, and 70 mL of AcOEt was added. The phases were separated, the aqueous phase was extracted with another 70 mL of AcOEt, and the combined organic phases were dried on a little Na_2SO_4. Solvent evaporation and flash chromatography with 9:1 AcOEt–hexane yielded 1.75 g (79%) of a colorless oil, which freezes around 0 °C: ^{1}H NMR δ 6.97 (dd, J = 4, 15 Hz, 1 H), 6.11 (dd, J = 2, 15 Hz, 1 H), 4.6 (br s, 1 H), 4.21 (q, J = 7 Hz, 2 H), 3.9 (m, 2 H), 3.37 (br s, 1 H), 2.52 (br s, 1 H), 1.87 (m, 3 H), 1.31 (t, J = 7 Hz, 3 H); $[\alpha]^{23}_D$ −12.3° (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.03; H, 8.08.

Ethyl (2*R*,3*S*)-2-(3-Hydroxytetrahydrofuranyl)-(*R*)-iodoacetate (2), Ethyl (2*S*,3*S*)-2-(3-Hydroxytetrahydrofuranyl)-(*S*)-iodoacetate (9), and (1*S*,4*R*,5*R*)-4-Iodo-2,6-dioxabicyclo[3.3.0]-3-octanone (11). With use of the previously described iodocyclization procedure, 400 mg (2.3 mmol) of diol **1** was reacted. After 1 h, the reaction was worked up and flash chromatography gave three compounds. The faster fraction consisted of 492 mg (71%) of **2** as a colorless oil: ^{1}H NMR (C_6D_6) δ 4.66 (d, J = 8 Hz, 1 H), 4.37 (dd, J = 2, 8 Hz, 1 H), 4.1 (m, 1 H), 3.95 (q, J = 7 Hz, 2 H), 3.87 (m, 1 H), 3.68 (m, 1 H), 1.45 (m, 2 H), 0.89 (t, J = 7 Hz, 3 H); IR (neat) 3550, 1735 cm^{-1}; $[\alpha]^{23}_D$ +112° (*c* 3.3, $CHCl_3$); MS (CI, NH_3), *m/e* 300.993 96, calcd for $C_8H_{14}O_4I$ (MH^+) 300.993 69.

The middle fraction of the chromatography consisted of 32 mg (5%) of **9**, as a white solid: mp 69–70 °C; ^{1}H NMR (C_6D_6) δ 4.38 (m, 2 H), 4.12 (s, 1 H), 4.05 (d, J = 8 Hz, 1 H), 3.9 (m, 3 H), 3.73 (m, 1 H), 1.67 (m, 2 H), 0.94 (t, J = 7 Hz, 3 H); MS (CI, NH_3), *m/e* 300.993 57, calcd for $C_8H_{14}O_4I$ (MH^+) 300.993 69.

The last fraction of the chromatography consisted of 7.3 mg (1.2%) of **11**, as a white solid: mp 86.5–87 °C; ^{1}H NMR (C_6D_6) δ 3.94 (t, J = 3 Hz, 1 H), 3.81 (d, J = 5 Hz, 1 H), 3.47 (dd, J = 4, 5 Hz, 1 H), 3.25 (m, 2 H), 1.56 (m, 1 H), 1.1 (m, 1 H); IR (neat) 1775 cm^{-1}; $[\alpha]^{24}_D$ −132° (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_6H_7O_3I$: C, 28.37; H, 2.76. Found: C, 28.39; H, 2.86.

Conversion of 2 to Lactone 11. The alcohol ester **2** (75 mg) was dissolved in 3 mL of toluene, and 0.3 mg of *p*-toluenesulfonic acid monohydrate was added. After 15 min on a steam bath, the solution was cooled and filtered on a plug of silica gel. The silica gel was rinsed with 3 volumes of 1:1 AcOEt–hexane, and evaporation of the combined eluates gave a yellow solid. Recrystallization from hexane–CH_2Cl_2 afforded 57 mg (88%) of white needles in all respects identical with **11**.

(*R*)-5-(2-Hydroxyethyl)-2,5-dihydrofuran-2-one (8). The acetal **7** (127 mg, 0.48 mmol) was dissolved in 2 mL of 80% AcOH, and the mixture was heated to 45 °C for 2.5 h. The solvent was then evaporated, and the residue was purified by flash chromatography with AcOEt to give 30 mg (49%) of the desired product as an oil: ^{1}H NMR δ 7.56 (dd, J = 1, 6 Hz, 1 H), 6.13 (dd, J = 2, 6 Hz, 1 H), 5.26 (m, 1 H), 3.87 (m,

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2 H), 2.05 (m, 1 H), 1.87 (m, 1 H); IR (neat) 3400 (br), 1750, 1640 cm^{-1}; $[\alpha]^{23}_D$ +48.1° (*c* 3, $CHCl_3$); MS (CI, NH_3), *m/e* 146.081 74, calcd for $C_6H_8O_3 \cdot NH_4$ 146.081 72.

(1*S*,4*S*,5*R*)-4-Iodo-2,6-dioxabicyclo[3.3.0]-3-octanone (12). According to the general iodocyclization procedure, the lactone **8** (28 mg, 218 μmol) was reacted. After chromatography with 1:2 AcOEt–hexane eluent, 16.3 mg (30%) of a white solid were obtained, mp 99.5–100 °C. **12**: ^1H NMR δ 5.31 (t, *J* = 4 Hz, 1 H), 4.76 (d, *J* = 4 Hz, 1 H), 4.43 (s, 1 H), 4.15 (dt, *J* = 2, 9 Hz, 1 H), 4.02 (dt, *J* = 6, 9 Hz, 1 H), 2.43 (br dd, 1 H), 2.18 (m, 1 H); $[\alpha]^{23}_D$ +38.7° (*c* 1.4, $CHCl_3$); MS (CI, NH_3), *m/e* 254.951 72, calcd for $C_6H_7IO_3 \cdot H$ 254.951 82.

Ethyl (*S*,*E*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-4-hydroxy-2-hexenoate (19). A solution of 1.74 g (10 mmol) of **1** and 1.3 g of imidazole in 50 mL of DMF was cooled to 0 °C, and 2.70 g (11 mmol) of *tert*-butylchlorodiphenylsilane was added. After 30 min, the reaction was quenched with methanol at 0 °C for 10 min, and the solvents were evaporated. The residue was taken up in CH_2Cl_2, washed with water, dried over Na_2SO_4, and evaporated. This product was used directly in the preparation of **20** and **21**.

Ethyl (*S*,*E*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-4-methoxy-2-hexenoate (20). To a solution of 500 mg (1.21 mmol) of **19** and 820 mg (2.42 mmol) of methyl iodide in 2.4 mL of DMF was added 58 mg (2.4 mmol) of sodium hydride. After 3 h at room temperature, the base was quenched with solid ammonium acetate, followed by water. The solvents were removed in vacuo, and the residue was partitioned between water and ether. The organic phase was dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography with 1:7 AcOEt–hexane to give 310 mg (60%) of a clear oil: NMR δ 7.65 (m, 4 H), 7.38 (m, 6 H), 6.82 (dd, *J* = 6, 14 Hz, 1 H), 5.98 (dd, *J* = 1, 14 Hz, 1 H), 4.23 (q, *J* = 7 Hz, 2 H), 4.03 (q, *J* = 6 Hz, 1 H), 3.7 (m, 3 H), 3.30 (s, 3 H), 1.78 (q, *J* = 6 Hz, 2 H), 1.30 (t, *J* = 7 Hz, 3 H), 1.05 (s, 9 H); $[\alpha]^{23}_D$ -9.5° (*c* 3.2, $CHCl_3$); MS, *m/e* 381.187 90, calcd for $C_{23}H_{29}O_4Si$ (M - EtO) 381.188 59.

Ethyl (*S*,*E*)-6-Hydroxy-4-methoxy-2-hexenoate (17). With stirring, 2.21 mL of a 1 M solution of tetrabutylammonium fluoride in THF was added to a mixture of 235 mg (0.55 mmol) of **20** and 330 μL of acetic acid. After 40 h, the mixture was diluted with 0.1 M pH 7.21 phosphate buffer and extracted with ether. The organic phase was dried and evaporated, and the residue was purified by flash chromatography with 1:1 AcOEt–hexane eluent to give 65 mg (63%) of a clear oil: NMR δ 6.83 (dd, *J* = 5, 15 Hz, 1 H), 6.03 (dd, *J* = 1, 14 Hz, 1 H), 4.24 (q, *J* = 7 Hz, 2 H), 4.05 (q, *J* = 6 Hz, 1 H), 3.8 (m, 2 H), 3.36 (s, 3 H), 2.8–2.6 (m, 3 H), 1.3 (t, *J* = 7 Hz, 3 H); $[\alpha]^{23}_D$ -52.1° (*c* 0.8, $CHCl_3$); MS, *m/e* 206.140 03, calcd for $C_9H_{16}O_4$ 206.139 23.

Ethyl (*R*,*E*)-4-Fluoro-6-hydroxy-2-hexenoate (18). A solution of 1.15 g (2.78 mmol) of **19** in 0.9 mL of CH_2Cl_2 was cooled to -70 °C, and a solution of 540 mg (3.34 mmol) of (diethylamido)sulfur trifluoride (DAST) in 0.9 mL of CH_2Cl_2 was added over 5 min. After 1 h at -70 °C, the solution was allowed to warm up to room temperature and was diluted with 10 mL of $CHCl_3$. This organic phase was washed with 2 mL of 1 M pH 7.21 phosphate buffer, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography with 6:94 AcOEt–hexane eluent to give 536 mg of a yellowish oil that contained **21** and some of its dehydrofluorination product.

This mixture was diluted in 300 μL of AcOH, followed by 12.5 mL of 1 M tetrabutylammonium fluoride in THF. After 1.5 h at room temperature, the reaction was stopped by addition of 50 mL of 0.5 M pH 7.21 phosphate buffer and 50 mL of ether. The organic phase was separated, dried, and evaporated. The residue was chromatographed with 1:1 ether–toluene to give 93 mg of a colorless oil, along with 101 mg of fractions contaminated with the dehydrofluorination product: NMR δ 6.93 (ddd, *J* = 4, 14, 17 Hz, 1 H), 6.11 (dt, *J* = 14, 1 Hz, 1 H), 5.36 (dm, *J* = 42 Hz, 1 H), 4.23 (q, *J* = 7 Hz, 2 H), 3.84 (m, 2 H), 2.0 (m, 2 H), 1.30 (t, *J* = 7 Hz, 3 H); $[\alpha]^{24}_D$ +6.4° (*c* 0.8, $CHCl_3$); MS, *m/e* 176.0835, calcd for $C_8H_{13}FO_3$ 176.0849.

Ethyl (*E*)-6-Hydroxy-4-methyl-2-hexenoate (22). This compound was prepared by DIBAH reduction and Wittig reaction of the commercially available 3-methyl-2(3*H*)-furanone, by using the procedure described for the 4-methyl analogue.[13] From 2 g of lactone, 1.5 g (67%) of a clear oil were obtained: NMR δ 6.90 (dd, *J* = 8, 14 Hz, 1 H), 5.82 (d, *J* = 14 Hz, 1 H), 4.18 (q, *J* = 7 Hz, 2 H), 3.67 (br t, 2 H), 2.53 (quintet, *J* = 6 Hz, 1 H), 1.66 (q, *J* = 7 Hz, 2 H), 1.35 (br s, 1 H), 1.27 (t, *J* = 7 Hz, 3 H), 1.09 (d, *J* = 7 Hz, 3 H); IR (film) 3410 (br), 1720, 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*R*,3*S*)-2-(3-Methoxytetrahydrofuranyl)-(*R*)-iodoacetate (26) and Isomer (23). By the standard iodocyclization procedure, 30 mg (155 μmol) of **17** yielded, after flash chromatography with 1:4 AcOEt–hexane, 36 mg (72%) of a clear oil which was a mixture of two compounds, in a 6.6:1 ratio: NMR (C_6D_6) δ 4.77 (d, *J* = 9 Hz, 1 H major), 4.62 (d, *J* = 9 Hz, 1 H minor), 4.50 (dd, *J* = 3, 9 Hz, 1 H), 3.97 (m, 3 H), 3.78 (m, 4 H), 3.54 (t, *J* = 3 Hz, 1 H major), 3.07 (s, 3 H minor), 2.96 (s, 3 H major), 1.6–1.1 (m, 3 H), 0.9 (m, 4 H); MS, *m/e* 315.0890, calcd for $C_9H_{16}IO_4$ (MH^+) 315.0934.

Ethyl (2*S*,3*R*)-2-(3-Fluorotetrahydrofuranyl)-(*S*)-iodoacetate (24) and Ethyl (2*R*,3*R*)-2-(3-Fluorotetrahydrofuranyl)-(*R*)-iodoacetate (25). With use of the standard iodocyclization procedure, 20 mg (0.11 mmol) of **18** yielded a 9.4:1 mixture of two compounds, which were separated by flash chromatography to give 3.5 mg of **25** and 26 mg of **24**. Major compound **24**: NMR δ 5.44 (dm, *J* = 44 Hz, 1 H), 4.5 (m, 2 H), 4.27 (q, *J* = 7 Hz, 2 H), 4.18 (m, 2 H), 2.2 (m, 2 H), 1.31 (t, *J* = 7 Hz, 3 H); $[\alpha]^{22}_D$ -74.2° (*c* 0.8, $CHCl_3$); MS, *m/e* 302.989 35, calcd for $C_8H_{13}FIO_3$ (MH^+) 302.989 37. Minor compound **25**: NMR δ 5.31 (dm, *J* = 45 Hz, 1 H), 4.42 (dd, *J* = 8, 25 Hz, 1 H), 4.26 (q, *J* = 7 Hz), 4.1 (m, 3 H), 2.2 (m, 2 H), 1.27 (t, *J* = 7 Hz, 3 H); MS, *m/e* 302, 257, 214, 175, 89 (100).

Ethyl (2*RS*,3*RS*)-2-(3-Methyltetrahydrofuranyl)-(*RS*)-iodoacetate (28) and Ethyl (2*SR*,3*RS*)-2-(3-Methyltetrahydrofuranyl)-(*SR*)-iodoacetate (27). The general iodocyclization procedure was performed on 300 mg of **22** and gave 502 mg (97%) of yellow oil, a 2.3:1 mixture of **27** and **28**. Flash chromatography with 2:15 AcOEt–hexane eluent yielded the pure major product **27**, along with fractions that were mixtures of major and minor products. The NMR data were obtained from subtraction of spectra and confirmed by solvent studies and decoupling. Major product **27**: NMR (C_6D_6–acetone-d_6, 4:1) δ 4.37 (d, *J* = 9 Hz, 1 H), 4.21 (dd, *J* = 4, 9 Hz, 1 H), 3.93 (q, *J* = 7 Hz, 2 H), 3.60 (q, *J* = 7 Hz, 1 H), 3.45 (dt, *J* = 4, 8 Hz, 1 H), 2.2 (m, 1 H), 1.7 (m, 1 H), 1.2 (m, 1 H), 0.93 (t, *J* = 7 Hz, 3 H), 0.62 (d, *J* = 7 Hz, 3 H); MS, *m/e* 299.0115, calcd for $C_9H_{16}IO_3$ (MH^+) 299.0144. Minor product **28**: NMR (CD_3CN–C_6D_6, 2:1 v/v) δ 4.41 (d, *J* = 9 Hz, 1 H), 4.31 (q, *J* = 7 Hz, 2 H), 4.18 (dd, *J* = 9, 4 Hz, 1 H), 2.43 (m, 1 H), 1.65 (m, 1 H), 1.37 (t, *J* = 7 Hz, 3 H), 1.32 (d, *J* = 7 Hz, 3 H).

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Supplementary Material Available: Tables of NOE data for **10**, **24**, and **26–28** (3 pages). Ordering information is given on any current masthead page.