support of this research. Fellowships from the Chevron Corporation (J.H.M.) and the Regents of the University of California (J.H.M., W.A.K.) are also gratefully acknowledged. We thank J. Stille, K. Mislow, and the J. Michl research group for valuable discussions and suggestions.

Supplementary Material Available: Tables of crystallographic data, bond lengths, and angles, atomic coordinates, and structure factors for (+)-(*SS*)-**6**, and figures showing atom numbering and crystal packing (36 pages). Ordering information is given on any current masthead page.

Iodocyclization of Allylic Alcohol Derivatives Containing Internal Nucleophiles. Control of Stereoselectivity by Substituents in the Acyclic Precursors

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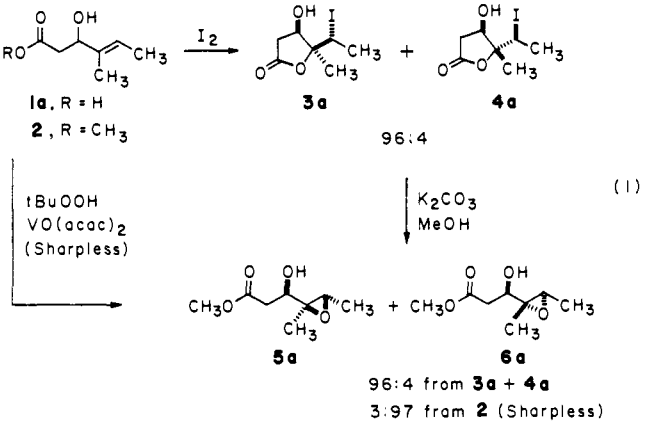
Abstract: The effect of various substituents on the diastereoselectivity of a number of kinetically controlled iodocyclizations has been studied. The reaction of 3-hydroxy-4-alkenoic acids (**1a–n**) with iodine in a neutral two-phase medium gives stereoselective ring closure, usually to the *cis*-3-hydroxy-4-iodoalkyl lactone. The stereoselectivity is unaffected by protection of alcohol moiety (**1b,c**), but replacement of the hydroxyl group with a methyl substituent (**1e**) lowers the stereoselectivity significantly. A 2-methyl substituent (**1j–m**) can have a dramatic effect on the diastereoselectivity of the reaction. Esters and ketones (**10a–c**) undergo a related iodocyclization with similar stereoselectivity. In the absence of an internal nucleophile (**13**, **16**) iodohydrin formation results in reversed diastereoselectivity of iodine attack.

Halolactonization of unsaturated carboxylic acids or their salts has been widely utilized since Bougault's initial systematic study early in this century.[1] The reaction has been invaluable both in synthesis and in structure elucidation, but for many years its potential to produce highly functionalized products with stereochemical control at two adjacent centers in the lactone ring itself remained unexplored.[2] Recent activity in the field of acyclic stereoselection has, however, included several studies[3] which demonstrate that synthetically useful levels of asymmetric induction, directed by substituents in acyclic precursors, can be achieved in the iodolactonization of substituted alkenoic acids. We describe in this paper our investigation of iodolactonization and related reactions directed by an oxygen substituent in the 3-position of 4-alkenoic acids,[4] esters, and other allylic alcohol derivatives. We have found that even though the product distributions often show high stereoselectivity in a predictable way, there are some striking anomalies which underscore the mechanistic subleties of the reaction.

Results and Discussion

Iodolactonization of 3-Hydroxy-4-alkenoic Acids. When the 3-hydroxy-4-alkenoic acid **1a** is treated at 0 °C with iodine in a two-phase reaction mixture of ether–tetrahydrofuran–aqueous bicarbonate, the major product is the iodo lactone **3a** with the iodoethyl and hydroxyl groups cis. The ratio of diastereomers (cis (**3a**):trans (**4a**)) is high (96:4), and it can be quantified easily in this case and those described later by high-pressure liquid chromatographic analysis of the crude reaction mixture. The stereochemical assignments are made by methanolysis of the iodo lactone mixture, producing the epoxides **5a** and **6a**, which can be compared by capillary gas chromatography to an authentic mixture prepared by Sharpless epoxidation[5] of the corresponding allylic alcohol ester **2**. Since the stereoselectivity of the Sharpless



(1)

reaction is quite predictable, this is a reliable method for assigning stereochemistries to the iodo lactone products, and it also serves as an indirect check of the lactone product ratios. It is noteworthy that the iodolactonization–methanolysis sequence complements the Sharpless procedure by producing mainly the *threo*-hydroxy epoxide where the major Sharpless diastereomer is erythro.

(1) Bougault, M. J. *C. R. Hebd. Seances Acad. Sci.* **1904**, *139*, 864.
(2) For reviews of halolactonization, see: (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171. (b) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 272.
(3) For recent examples of stereoselective halocyclization controlled by substituents in predominantly acyclic precursors, see: (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. (b) Terashima, S.; Hayashi, M.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2733 and previous papers in the series. (c) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (d) Takana, S.; Hirama, M.; Ogasawara, K. *J. Org. Chem.* **1980**, *45*, 3729. (e) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (f) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625. (g) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, *32*, 335.
(4) (a) Preliminary systematic study: Chamberlin, A. R.; Dezube, M.; Dussault, P. *Tetrahedron Lett.* **1981**, *22*, 4611. (b) First example (bromolactonization): Nakaminami, G.; Nakagawa, M.; Shioi, S.; Sugiyama, Y. *Ibid.* **1967**, 3983. (c) Recent synthetic application: Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114.
(5) Sharpless, K. B. *Aldrichim. Acta* **1979**, *12*, 63. In addition, the stereochemistry of the iodo lactones **3a** and **3h** have been determined by X-ray crystallographic analysis (see ref 4a and 9).

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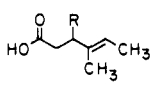
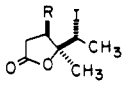
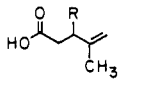
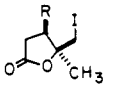
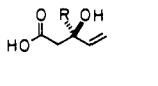
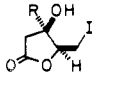
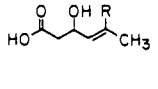
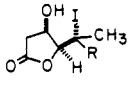
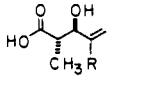
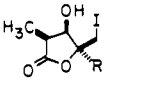
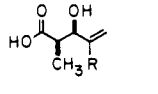
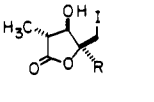
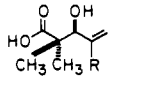
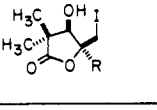
Table I. Iodolactonization of 4-Alkenoic Acids to Butyrolactones

Starting Acid (**1a-n**)	R =	cis-Lactone Product (**3a-n**)	Product Ratio[a] cis	trans	Yield of Butyrolactones[b]
	a, OH b, $OSiR_3$ c, OAc		96 96 94	4 4 6	82% 84%[c] 70%
	d, OH e, CH_3		95 60	5 40[d,e]	74% 72%
	f, H g, CH_3		93 95[f]	7 5	66% 85%[g,h]
	h, H i, CH_3		>95 <10	<5 >90	49%[i] 8%[i]
	j, H k, CH_3		87 90	13 10[d]	41% 94%
	l, H m, CH_3		77 42	23 58	74%[g] 81%
	n, CH_3		72	28	93%

[a] Determined by HPLC of the crude reaction mixture and methanolysis as described in the text. [b] Although crude lactone mixtures were generally otherwise homogeneous by TLC and HPLC, they were routinely subjected to flash chromatography on silica (10 g/g), which did not separate the diastereomers. [c] Yield based on ethyl ester of **1d**, which was hydrolyzed in situ before iodolactonization. [d] Because these diastereomers did not separate by HPLC, their ratio was determined by ^1H NMR integration. [e] Stereochemical assignments may be reversed. [f] Stereochemistry determined by X-ray crystallography. See ref 9. [g] Yield without chromatography. [h] Crude product gave satisfactory elemental analysis. [i] The low yield is due to competitive δ-lactone formation; in this case the other lactone isomers separate during chromatography. [j] The yield of δ-lactones is ~90%.

The cis iodo lactone product **3a** is assumed to be thermodynamically less stable than the minor trans isomer, although efforts to verify this assumption by conducting the reaction under Bartlett's "thermodynamic" conditions[3a] not surprisingly produced only complex mixtures. We have demonstrated, however, that the separated iodo lactones do not equilibrate when resubjected to the reaction conditions. Predominance of the kinetic product is fully expected under these conditions, since it is well established that such aqueous systems usually result in kinetic control of the halolactonization process.[2] On the other hand, it is not at all obvious why the cis isomer, rather than the trans, is indeed the kinetic product. The difficulty in rationalizing similar results for a methyl-directed kinetically controlled iodolactonization has been discussed,[3a] although in that case the "kinetic ratio" is on the order of 75:25 instead of 96:4.

This problem notwithstanding, the hydroxyl-directed reaction in a number of related cases produces the same high ratio of cis to trans isomers, as shown in Table I. The yields generally are good, and the crude product mixture usually is clean (even analytically pure—see **3g** in the Experimental Section). Several points are worth noting from among these examples. First, the diastereomer ratio is insensitive to the substitution pattern of the double bond for substrates which lead exclusively to γ-lactones (**1a,d,f**). The ratio is also unaffected by protection of the alcohol group, either as the *tert*-butyldimethylsilyl ether or the acetate (**1b,c**). This finding clearly rules out hydrogen bonding by the hydroxyl group (either to the approaching electrophile or internally to the carboxyl group) as a factor which might affect the stereoselectivity of the reaction. An example which involves a more symmetrically substituted double bond (**1h**) gives a mixture of γ- and δ-lactones, but the γ-lactone can still be isolated in fair yield. One might have naively predicted the γ-lactone to predominate heavily in this case, based on published (nonhydroxyl-directed) examples of γ-iodo lactone formation;[2,6] however, the hydroxyl group in allylic alcohols is known to direct attack of nucleophiles on the corresponding halonium ions to the position away from the alcohol in the absence of other overwhelming electronic factors.[7,8] This effect in the iodolactonization reaction partially outweighs the stereoelectronic preference for five-membered ring formation and thus increases the proportion of δ-lactone formed over that which might have been expected.

One reaction with a directing methyl group in place of the alcohol moiety was examined, a change which results in greatly diminished stereoselectivity (compare **1d** and **1e**, from 95:5 to 60:40). Precedent for this low selectivity is found in a similar published example of kinetically controlled iodolactonization directed by a methyl group.[3a] One of the most interesting findings was that a *tertiary* alcohol (**1g**) is every bit as effective in controlling the stereochemistry of the reaction[9] as is a secondary alcohol group, a surprising result considering that hydrogen bonding is not a factor and one normally views methyl as being more sterically demanding than hydroxyl. This example, along with several others to follow, implies that subtle conformational or electronic factors are responsible for the observed stereoselectivity in kinetically controlled iodolactonizations.

Several other cases, involving 2-substituted substrates, further illustrate the fascinating selectivity pattern of these reactions. A small but significant reduction in stereoselectivity is found when the *threo*- and *erythro*-2-methyl-3-hydroxy-4-pentenoic acids[10] **1j** and **1l** are subjected to the usual iodolactonization conditions. Likewise, for the corresponding *threo*-2,4-dimethyl acid **1k** the ratio is slightly attenuated, but the predominant product is still the cis diastereomer. In direct contrast, however, the erythro isomer **1m** leads to a mixture favoring the trans lactone! The *gem*-dimethyl analogue **1n**, on the other hand, cyclizes as usual to give mainly the cis isomer, although with reduced stereoselectivity.

A particularly interesting result was obtained in the reaction of **1i**, in which the double bond is more highly substituted in the 5-position. It was expected that this substitution pattern would

(6) One of the few counterexamples to the general preference for γ- over δ-lactone formation (except in cases of overriding electronic factors or ring strain) is that 4-hexenoic acid reportedly gives the δ-lactone upon treatment with iodine: Staninets, V. I.; Shilov, E. A.; Koryak, E. B. *Zh. Org. Khim.* **1968**, *4*, 268.

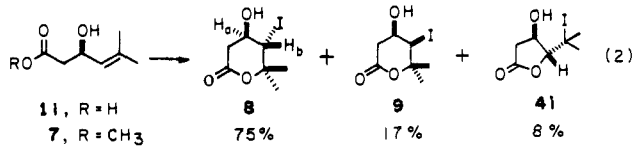
(7) (a) Midland, M. M.; Holtermann, R. L. *J. Org. Chem.* **1981**, *46*, 1227 and references cited therein. (b) Bellucci, G.; Berti, G.; Bianchini, R.; Ingrosso, G.; Mastrorilli, E. *Gazz. Chim. Ital.* **1976**, *106*, 955 and references cited therein.

(8) An analogous regioselectivity has also been noted in reactions of epoxy alcohols: Buchanan, J. G.; Sable, H. Z. "*Selective Organic Transformations*"; Thyagarajan, B. S., Ed.; Wiley: New York, 1972; Vol. 2, p. 1.

(9) The stereochemistry of **3g** was established by X-ray crystallography. The necessary distinction of C(08) from O(03) was made during the latter stages of refinement based upon thermal parameters, bond distances, and location of methyl hydrogen atom on a difference Fourier map. Each of these three criteria implied the same stereochemistry for each of the two crystallographically independent molecules in the asymmetric unit. The final unweighted *R* faction was 0.053. Further crystallographic details, including a view of the molecular structure, are provided as supplementary material: Tables I–VI, crystal data and experimental parameters, positional parameters, hydrogen atom parameters, bond distances, and bond angles.

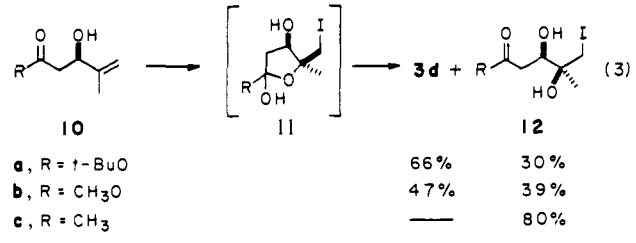
(10) We use Heathcock's convention of threo/erythro nomenclature: Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727. The starting threo acids **1j** and **1k** were prepared from their ethyl esters (no epimerization occurred during saponification), which in turn were available by the threo-selective methylation procedure reported by Frater and by Seebach: (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Seebach, D.; Wasmuth, D. *Ibid.* **1980**, *63*, 197. The corresponding erythro isomers were isolated from a mixture resulting from the condensation of lithio ethyl propionate with either acrolein or methacrolein.

result in predominantly δ-lactone formation, which was indeed the case. Treatment of **1i** with iodine under the standard con-



ditions gave three lactones: **8**, **9**, and **4i**. The major product is the δ-lactone **8** (75%; IR 1730 cm^{-1}), for which the structure assignment is based in part on a proton NMR axial–axial coupling of 10.5 Hz for H_a and H_b, indicating that the alcohol and iodine groups both are equatorial. This product is not separable from 8% of a γ-lactone (**4i**, IR 1780 cm^{-1}), but when the mixture of these two lactones is subjected to methanolysis, a *single* (>99%) epoxide is produced which is identical by capillary gas chromatography to the minor epoxide[11] produced by Sharpless epoxidation of the allylic alcohol **7**. This result establishes that the γ-lactone must be the trans isomer and shows that the inseparable γ- and δ-lactones **8** and **4i** both arise from attack by iodine on the same face (β) of the double bond. This is the *opposite* face, however, compared to most of the previously discussed reactions which produce γ-lactones. In fact, the diastereoface selectivity of iodine attack on **1i** in this case is reversed (5:1) compared with the examples in Table I, where it is usually ca. 1:10. The conclusion to be drawn from this example is that a (*Z*)-methyl substituent on the double bond causes a reversal of the usual diastereoface selectivity of attack by iodine.

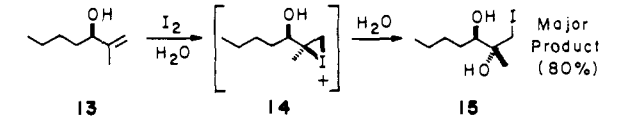
Reactions of 3-Hydroxy-4-alkenoic Esters with Iodine. The reaction of unsaturated esters with halogen electrophiles has been reported previously.[3a,12] We chose to investigate reaction of the *tert*-butyl and methyl esters **10a** and **10b** in order to test the effect on stereoselectivity of an internal nucleophile much weaker than a carboxylate salt. In the case of **10a**, treatment with iodine–THF–ether–aqueous bicarbonate gives the same two lactone diastereomers that were produced from the corresponding unsaturated acid. Futhermore, their ratio (90:10) is very nearly the same in the ester reaction as it was for the acid **1d**, in spite of the different internal nucleophiles and the obvious solubility differences of the two substrates in the two-phase reaction medium. The lactones, however, are not the only major products produced in this case. A second pair of diastereomeric products was isolated, also in a ratio of 90:10. These isomers proved to be the iodo diol **12** and its diastereomer, which were identified spectrally and by

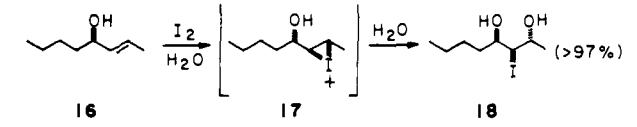


conversion to the corresponding epoxides (Na_2CO_3–methanol). These results suggest the initial stereoselective production of a pair of cyclic diastereomeric cationic intermediates which are trapped by water to give a 90:10 mixture of hemiortho ester diastereomers (**11a** predominating), which then collapse either to lactones by loss of the alcohol group or to iodo diols by opening of the tetrahydrofuran ring. Similar results were obtained for the methyl ester **10b**, except for minor differences in the relative amounts of lactone vs. iodo diol. Thus, although the product distribution is more complex, the diastereoface selectivity of attack by iodine on the allylic double bond is the same (α preferred) for these esters as it is for the corresponding carboxylic acids.

This result prompted us to test a ketone, which also would be expected to form a cyclic intermediate (**11c**) but which can only give rise to an iodo diol. Indeed, the ketone **10c** does react with iodine under the usual conditions to give a 90:10 mixture of two iodo diols. We believe that the major isomer is **12c** by analogy with the ester reaction, but we were unable to rigorously verify this assignment because of the instability of the ketone iodo diols to the basic conditions required to form the epoxide for direct comparison to Sharpless epoxide mixtures.

Stereoselectivity in the Absence of Carbonyl Neighboring-Group Participation. With the exception of **1i** and **1m**, all iodocyclization substrates discussed thus far give products which derive from attack predominantly on the α-face of the double bond. Because of the two anomalous examples, we wondered to what extent neighboring-group participation by the carbonyl group actually influences the face of the double bond attacked by the electrophile. We therefore subjected several simple allylic alcohols to the usual iodolactonization conditions with the intent of producing iodohydrins by intermolecular trapping (by water) of the resulting iodonium ions. These products should reflect the preference of iodine attack on the double bond in the *absence* of intramolecular nucleophilic participation, assuming kinetic control of both reactions (see "Conclusions"). The substitution patterns of the allylic alcohol substrates **13** and **16** were chosen to correspond to the acids **1d** and **1h** in order to make a direct comparison of intra- vs. intermolecular nucleophilic participation. The results of these two reactions are interesting both for their regio and stereochemical outcomes. The substrate **13** gives a 20:80 mixture of iodo diols favoring **15**, indicating preferential iodine attack on the β-face of the double bond.[13] This result is in contrast to nearly exclusive





α-attack on the acid **1d**, even though the allylic alcohol substitution patterns are identical. None (≤5%) of the regioisomer was detected in either case. On the other hand, reaction of the more symmetrically substituted allylic alcohol **16** results not only in a somewhat more stereoselective reaction than for **13**, but also in a complete reversal of regioselectivity, giving **18** as the predominant isomer (>97%).[14] This acyclic product also is produced by attack of iodine on the β-face (as opposed to mainly α-attack in **1h**), followed by regioselective reaction with water at the position more remote from the oxygen substituent.[7,8]

Product identification in both of these cases follows from 250-MHz proton NMR spectra and correlation of the epoxides produced from the iodo diols (K_2CO_3, MeOH) with authentic epoxy alcohols prepared by Sharpless epoxidation of the same starting allylic alcohols. In particular, the lack of a substantial downfield methyl shift (the chemical shift of methyl protons β to an iodine group occurs near 1.8 ppm[15]) clearly distinguishes **15** and its stereoisomer from the respective regioisomers, and the Sharpless correlation fixes the stereochemistry of each. The iodohydrin **18** also is distinguishable from its regioisomer based on the observed high-field methyl resonance (1.5 ppm) and on the fact that this methyl doublet does not collapse to a singlet when the methine proton α to iodine (4.21 ppm) is irradiated. The

(11) The usual erythro selectivity of the vanadium-catalyzed epoxidation is reversed when the substitution pattern of the double bond is as in **7**;[5] thus the *minor* Sharpless product in this case is the erythro isomer.

(12) (a) Arnold, R. T.; Campos, M. M.; Lindsay, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 1044 and references cited therein. (b) Jäger, V.; Günther, H. J. *Tetrahedron Lett.* **1977**, 2543.

(13) A similar stereo- and regiochemical outcome has been observed in the bromination of allylic alcohols.[7]

(14) This is the expected regiochemical result, although the selectivity is higher than related additions reported previously.[7]

(15) Gordon, A. J.; Ford, R. A. "The Chemists Companion"; Wiley-Interscience: New York, 1972; p 256 and references therein.

assignment of stereochemistry to the major product is complicated in this case because the iodo diol **18** gives two major epoxides when treated with base. That one of these corresponds to the major Sharpless epoxide derived from **16** and the other does *not* correspond to the minor Sharpless epoxy alcohol is the behavior expected for the nearly symmetrical iodo diol **18**.[16] The potential of this latter stereo- and regioselective iodohydrin synthesis as a means of producing *threo*-1,3-diols derived from **18** is obvious and is currently being explored in more depth.

Conclusions

The reactions described in this paper constitute a general synthetic route to 3-hydroxyl-4-alkyl-γ-butyrolactones. The stereoselectivity of the reaction often is high, even in the case where a tertiary alcohol is the directing group. The stereochemical outcome of the reaction usually is predictable, providing 3,4-cis-γ-lactones except in a few anomalous instances. The reasons for the observed stereoselectivity are not completely understood, but a number of mechanistic conclusions may be drawn:

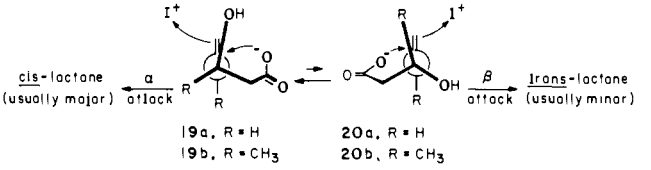
1. It is unlikely that hydrogen bonding by the directing alcohol group, either to the electrophile or internally to the carboxyl group, is a factor affecting the stereoselectivity. If it were, silylation or acetylation should change the product ratio, which is not the case.[17]

2. Intramolecular transfer of I^+ to the double bond via an acyl hypoiodite[3a] probably is not responsible for the stereoselectivity, since esters (which cannot form hypoiodites under these conditions) give nearly the same product ratios as do the corresponding acids. Complexation of the alcohol group with halogen followed by selective delivery to one face of the double bond is unlikely under the aqueous reaction conditions.[7b]

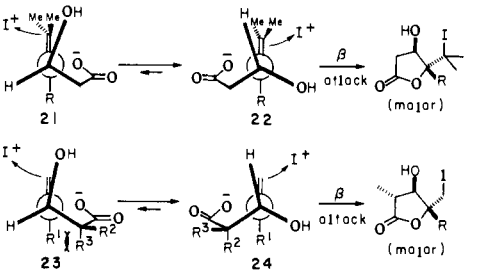
3. Although it is conceivable that the product ratios reflect an unexpected thermodynamic preference, it is quite unlikely that the reaction is under thermodynamic rather than kinetic control for several reasons: (a) literature precedent[2,3a] indicates that neutral, aqueous conditions provide kinetic control of halolactonization, (b) the product ratios do not change with time, (c) the separated lactone diastereomers do not interconvert when resubjected to the reaction conditions, and (d) since γ-lactones are generally more stable than δ-lactones,[18] six-membered ring products should not predominate under thermodynamic control when the alternative product is a γ-lactone.

4. Another mechanistic possibility involves the concept of acyclic orbital overlap control recently elaborated by Houk.[19] This explanation in the case at hand argues for attack of iodine on the allylic alcohol rotated slightly from its most stable ground-state conformation, followed by ring closure. If this were occurring in these kinetically controlled iodolactonization reactions, however, one would expect iodine to attack the same face of the double bond independent both of the substitution pattern at C-2 (**1k** vs. **1m**) and the source of the nucleophile (intramolecular **1d** vs. intermolecular **13**). The iodolactonization results clearly indicate the contrary. On the other hand, the stereochemistry of iodohydrin formation from allylic alcohols without internal nucleophiles *is* consistent with this explanation.

5. Taken as a whole, our results are consistent with a more or less concerted[20] iodocyclization process; i.e., one with significant participation by the internal nucleophile in the transition state.[21] This hypothesis requires that there be only two conformations, **19a** and **20a**, which resemble the transition state. Although



(5)



predicting a priori which of these is more favorable would be difficult,[22] it is **19a** which leads to the cis product (i.e., α-attack of iodine) and **20a** to the minor trans isomer. This picture serves to explain the stereochemical outcome of the unexpected and anomalous examples which have been discussed. Specifically, the tertiary alcohol **1g** reacts stereoselectively because **19** should be favored over **20** regardless of whether R = H or CH_3.[23] On the other hand, because a cis substituent on a double bond enhances the preference for the conformer with the α-hydrogen in the C=C plane,[23] **22** is more favorable than **21**, resulting in a reversal of the usual stereoselectivity in this case. Finally, perhaps the most revealing example is **1m**, which shows "reversed" stereoselectivity (i.e., β-attack by I_2) even though **1j**, **1k**, **1l**, and **1n** do not. We believe that the explanation for this result is simply that the usually favorable transition state **23** suffers from steric congestion when R^1 and R^3 *both* are methyl (i.e., **1m**, but not **1j,k,l,n**), so that **24** is the preferred transition state (i.e., β-attack) in that case. If $R^1 = R^2 = R^3 = CH_3$, on the other hand, **23** and **24** are both subject to this type of interaction, and **23** remains more favorable (although the selectivity is lowered).

6. The reason that the face of the allylic alcohol attacked by iodine during iodolactonization is opposite that attacked in a similarly substituted double bond with no internal nucleophile (**1d** vs. **13** and **1h** vs. **18**) is unclear at present, although this stereoselective acyclic iodohydrin formation promises to be an efficient means of preparing *threo*-1,3-diols.

Experimental Section[24]

Synthesis of 3-Hydroxy-4-alkenoic Acids 1a–n. General Procedures. Method A. To a dry flask containing ~1 M dilithioacetate[25] in THF at −78 °C was added a THF solution of the appropriately substituted propenal (1 equiv). The solution was stirred for 1 h, quenched with 2.0 equiv of glacial acetic acid, diluted with saturated aqueous sodium bicarbonate, and washed 2 times (Et_2O). The aqueous layer was then acidified with 1 N HCl, saturated with NaCl, extracted 3X (ethyl ace-

(16) The *tert*-butyldimethylsilyl ether of **16** also undergoes (somewhat less stereoselective) iodohydrin formation, and the major iodohydrin formed gives silyated **18** upon treatment with base.

(17) It has also been suggested that internal hydrogen bonding to the π-bond occurs (Nakaminami, G.; Shioi, S.; Sugiyama, Y.; Isemura, S.; Shibuya, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2624). This idea is also ruled out.

(18) Hall, H. K., Jr.; Brandt, M. K.; Mason, R. M. *J. Am. Chem. Soc.* **1958**, *80*, 6420.

(19) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

(20) For discussions of the concertedness of iodolactonization, see: (a) Williams, D. L. H.; Bienvenue-Goetz, E.; Dubois, J. E. *J. Chem. Soc. B* **1969**, 517. (b) doAmaral, L.; Melo, S. C. *J. Org. Chem.* **1973**, *38*, 800. (c) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1864. (d) Reference 2b summarizes similar evidence for both iodolactonization and other, related processes.

(21) An alternative mechanism involving a rapid iodonium ion preequilibrium followed by preferential closure of the diastereomeric iodonium ion leading to the 3,4-*cis*-lactone is very similar to a concerted reaction; i.e., the transition states both would resemble the partly cyclized species **19** and **20**. The stereochemical arguments presented for the concerted process would therefore also apply to this nonconcerted mechanism.

(22) Calculations show that the ground-state conformation of allyl alcohol in which the C—O and the C=C bonds are eclipsed is the more favorable by the small margin,[23] but this analysis does not take into account possibly significant *reactivity* differences between **19** and **20** which could certainly overshadow simple ground-state conformation arguments.

(23) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.

(24) The experimental section reports spectral assignments according to the numbering scheme which designates the ring oxygen as atom 1. Note that although this is correct according to the "2-furanone" nomenclature system preferred by Chemical Abstracts, it differs from the more informal but commonly used "butyrolactone" numbering system in which the carbonyl carbon is atom 1.

(25) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509.

tate), and dried ($MgSO_4$). Removal of solvents in vacuo followed by flash chromatography (ether–petroleum ether) gave the pure acid.

Method B. Hydrolysis of 3-Hydroxy-4-alkenoic Alkyl Esters. To a dry flask containing a THF solution of 1 equiv of lithioethyl acetate[26] at −78 °C (or *tert*-butyl ester or methyl ester at −95 °C) was added a THF solution of the appropriately substituted propenal (1 equiv), and the solution was allowed to stir at −78 °C for 1 h. The reaction mixture was quenched with 1.5 equiv of glacial acetic acid, diluted with saturated aqueous sodium bicarbonate, extracted into ether, washed with brine, and dried ($MgSO_4$). Removal of solvent in vacuo followed by distillation or flash chromatography (ether and petroleum ether) gave the pure ester, which was then dissolved in THF (1 M), and 2–3 equiv aqueous sodium hydroxide (1 M) was added. The reaction mixture was heated at reflux for 0.5–2 h, diluted with saturated aqueous sodium bicarbonate, and extracted into ether. The aqueous layer was acidified (1 N HCl) and the carboxylic acid isolated as in method A. The acids all exhibited the IR spectra characteristic of a hydroxycarboxylic acid: 3440 (OH), ~3000 (br CO*OH*), 2960 (CH), 1720 (*C*OOH) cm^{-1}.

Spectral and chromatographic details for the individual starting materials **1a–1n**, the corresponding esters, and **10a**, **10b**, **10c**, **13**, and **16** are provided as supplementary material.

Iodolactonization of 3-Hydroxy-4-alkenoic Acids. Synthesis of Lactones 3a–n. General Procedure. The 3-hydroxy-4-alkenoic acid **1a**–n (1 mmol) was dissolved in ether (1 mL) and saturated aqueous sodium bicarbonate (5 mL) at 0 °C. A 0 °C solution of 3 equiv of iodine in THF (3 mL) was added to the stirred mixture. The flask was protected from light and stirred for 3–5 h at 0 °C and then quenched with saturated aqueous sodium sulfite. The reaction mixture was diluted with saturated aqueous sodium bicarbonate, extracted into ether, washed with brine, and dried ($MgSO_4$). Removal of solvents in vacuo generally yielded a product homogeneous by TLC. Flash chromatography (ether–petroleum ether) gave a mixture of diastereomers, otherwise pure. Products were stored at −20 °C under argon protected from light. The ratio of diastereomers was determined by HPLC analysis (μ-porasil) of the crude reaction mixtures.

In order to assign stereochemistry to each diastereomer, the lactone mixtures were converted to the corresponding epoxides by methanolysis according to the following procedure. To a dried flask was added the lactone mixture dissolved in methanol (1 M) at 0 °C. Three equivalents of either sodium methoxide or sodium carbonate was then added, and the resulting solution was stirred 0.25–1 h at 0 °C. The reaction mixture was then diluted with saturated sodium bicarbonate, extracted with ether, and dried (Na_2SO_4). Removal of solvents in vacuo and filtration through Florisil gave a mixture of epoxides which were analyzed by capillary gas chromatography. Authentic methyl ester epoxy alcohols for comparison were prepared by Sharpless epoxidation[5] of the methyl esters of the corresponding acids. The methyl esters of the acids **1a**–n were prepared by treatment of each acid with diazomethane. These esters, and the allylic alcohols **13** and **16**, were epoxidized by using the erythro selective vanadium-catalyzed Sharpless procedure.[5]

***rel*-(4*R*,5*S*,6*R*)-Dihydro-4-hydroxy-5-(1-iodoethyl)-5-methyl-2-(3*H*)-furanone (3a).** The acid **1a** (150 mg, 1.04 mmol) yielded 220 mg (82%) of the lactones **3a** and **4a**: mp 96–97 °C; HPLC 5.28 min (96%) and 6.04 min (4%); R_f 0.30 (10:1 ether–petroleum ether); ^1H NMR δ 1.53 (s, $3H_8$), 2.00 (d, J = 7.0 Hz, $3H_7$), 2.51 (dd, J = 1.6, 4.0 Hz, OH), 2.60 (apparent d, J = 18.0 Hz, $1H_{3\alpha}$), 3.03 (apparent ddd, J = 1.6, 5.5, 18.0 Hz, $1H_{3\beta}$), 4.34 (dd, J = 4.0, 5.5 Hz, $1H_4$), 4.50 (q, J = 7.0 Hz, $1H_6$); IR ($CDCl_3$) 3580, 2984, 1780, 1450, 1415, 1385, 1248, 1170, 1078, cm^{-1}; mass spectrum, m/e (relative intensity) 270 (M^+, 1.26), 199 ($M^+ - C_3H_3O_2$, 21.41), 143 ($M^+ - I$, 50.8), 127 (I, 8.20), 125 ($M^+ - H_2O$, I, 100). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.11; H, 4.11; I, 47.01. Found: C, 31.16; H, 4.21; I, 47.12.

Methanolysis of the lactone mixture **3a** and **4a** (260 mg, 0.96 mmol) yielded 143 mg (85%) of epoxides **5a** and **6a**: GC 7.09 min (4%) and 7.37 min (96%) compared by coinjection with Sharpless mixture, 7.07 min (85%) and 7.32 min (15%); R_f 0.34 (ether); ^1H NMR δ 1.28 (s, 3 H, CH_3), 1.29 (d, J = 6.2 Hz, 3 H, CH_3), 2.55 (apparent d, J = 6.6 Hz, $2H_2$), 2.81 (d, J = 4.78 Hz, OH), 3.10 (q, J = 6.2 Hz, $1H_5$), 3.71 (s, 3 H, OCH_3), 3.83 (m, $1H_3$); IR ($CDCl_3$) 3460, 3000, 2960, 1735, 1440, 1380, 1173, 1045 cm^{-1}; high-resolution mass spectrum (EI) calculated for $C_8H_{14}O_4$, M^+ 174.0892, found, M^+ 174.0837.

***rel*-(4*R*,5*S*,6*R*)-Dihydro-5-(1-iodoethyl)-5-methyl-4-(*tert*-butyldimethylsiloxy)-2(3*H*)-furanone (3b).** The methyl ester of acid **1b** (500 mg, 1.84 mmol) was hydrolyzed according to method B, and without isolation the solution was treated directly with the reagents for lactonization yielding 600 mg (85%) of the crude lactones **3b** and **4b**: mp 70–72 °C; R_f 0.20 (1:1 ether–petroleum ether); ^1H NMR (80 MHz, $CDCl_3$) δ 0.18 (s, 3 H, $SiCH_3$), 0.26 (s, 3 H, $SiCH_3$), 0.96 (s, 9 H, *t*-Bu), 1.60 (s, $3H_8$), 2.04 (d, J = 6.0 Hz, $3H_7$), 2.45 (apparent dd, J = 1.0, 18.0 Hz, $1H_{3\beta}$), 3.00 (apparent dd, J = 5.0, 18.0 Hz, $1H_{3\alpha}$), 4.30 (dd, J = 1.0, 5.0 Hz, $1H_4$), 4.51 (q, J = 6.0 Hz, $1H_6$); IR ($CDCl_3$) 3500, 2950, 1780, 1460, 1380 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_{13}H_{25}O_3I$, $M^+ - t$-Bu, 326.9914, found, m/e (relative intensity) 326.9916 ($M^+ - t$-Bu, 47.98), 284.9 (19.3), 282.9 (36.6), 97 (25.2), 75.0 (100).

Methanolysis of the lactone mixture **3b** and **4b** (300 mg, 0.78 mmol) yielded 200 mg (89%) of epoxides **5b** and **6b**: GC 11.59 min (4%) and 11.40 min (96%) compared by coinjection with Sharpless mixture, 11.59 min (93%) and 11.40 min (7%); R_f 0.40 (4:1 ether–petroleum ether); ^1H NMR (80 MHz, $CDCl_3$) δ 0.12 (s, 3 H, $SiCH_3$), 0.19 (s, 3 H, $SiCH_3$), 0.96 (s, 9 H, *t*-Bu), 1.32 (s, 3 H, CH_3), 1.35 (d, J = 7.0 Hz, 3 H, CH_3), 2.5 (m, $3H_{2,3}$), 3.0 (m, $1H_5$), 3.72 (s, 3 H, OCH_3); IR (neat) 3490, 3020, 2960, 2860, 1740, 1460, 1440, 1255, 1215 cm^{-1}.

***rel*-(4*R*,5*S*,6*R*)-Dihyro-4-acetoxy-5-(1-iodoethyl)-5-methyl-2(3*H*)-furanone (3c).** The acid **1c** (63.3 mg, 34 mmol) yielded 74 mg (70%) of the crude lactones **3c** and **4c**: mp 98–102 °C; HPLC 4 min (94%) and 4.4 min (6%); R_f 0.70 (4:1 ether–petroleum ether); ^1H NMR (80 MHz, $CDCl_3$) δ 1.65 (s, $3H_8$), 2.05 (d, J = 7.0 Hz, $3H_7$), 2.17 (s, 3 H, C-(O)CH_3), 2.56 (apparent d, J = 18.0 Hz, $1H_{3\beta}$), 3.20 (apparent dd, J = 5.5, 18.0 Hz, $1H_{3\alpha}$), 4.52 (q, J = 7.0 Hz, $1H_6$), 5.25 (d, J = 5.5 Hz, $1H_4$); IR ($CDCl_3$) 2960, 2920, 2830, 1789, 1755, 1370, 1250, 1178 cm^{-1}. The relative stereochemistry was established by HPLC coinjection with the product from acetylation of lactone **3a**.

***rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-5-methyl-2(3*H*)-furanone (3d).** The acid **1d** (130 mg, 1.00 mmol) yielded 190 mg (79%) of the lactones **3d** and **4d**: mp 46–50 °C; HPLC 13.8 min (5%) and 15.9 min (95%); R_f 0.35 (ether); ^1H NMR δ 1.56 (s, $3H_8$), 2.65 (apparent dd, J = 1.5, 18.0 Hz, $1H_{3\beta}$), 3.04 (apparent dd, J = 5.5, 18.0 Hz, $1H_{3\alpha}$), 3.29 (d, J = 4.8 Hz, OH), 3.49 (ABq, $\Delta\nu_{AB}$ = 25.0, J_{AB} = 10.3 Hz, $2H_6$), 4.39 (ddd, J = 1.5, 4.8, 5.5 Hz, $1H_4$); minor isomer **4d** observed at δ 4.51 (m, 1 H); IR ($CDCl_3$) 3450, 2989, 2938, 1780, 1412, 1382, 1272, 1160, 1080 cm^{-1}; mass spectrum, m/e (relative intensity) 256 (M^+, 14.5), 228 (M^+ – CO, 42.6), 185 ($M^+ - C_3H_3O_2$, 100), 129 ($M^+ - I$, 8.8), 127 (I, 7.25). Anal. Calcd for $C_6H_9O_3I$: C, 28.13; H, 3.54; I, 49.58. Found: C, 28.23; H, 3.64; I, 49.36.

Methanolysis of the lactone mixture **3d** and **4d** (110 mg, 42.9 mmol) yielded 72.3 mg (105%) of crude epoxides **5d** and **6d**: GC 6.08 min (5%) and 6.29 min (95%) compared by coinjection with Sharpless mixture, 6.08 min (95%) and 6.29 min (5%); R_f 0.52 (ether); ^1H NMR δ 1.36 (s, 3 H, CH_3), 2.59 (apparent dd, J = 5.2, 8.1 Hz, $2H_2$), 2.61 (br s, OH), 2.85 (apparent d, J = 4.4 Hz, $1H_5$), 2.87 (apparent d, J = 4.4 Hz, $1H_5$), 3.72 (s, 3 H, OCH_3), 3.92 (dd, J = 5.2, 8.1 Hz, $1H_3$); IR ($CDCl_3$) 3480, 2960, 2925, 1730, 1440, 1280 cm^{-1}.

***rel*-(4*R*,5*S*)-Dihydro-5-(iodomethyl)-4,5-dimethyl-2(3*H*)-furanone (3e).** The acid **1e** (490 mg, 3.83 mmol) yielded 700 mg (72%) of the lactones **3e** and **4e**: R_f 0.60 (ether); ^1H NMR (80 MHz, $CDCl_3$) δ 1.20 (d, J = 7.5 Hz, 3 H, CH_3), 1.55 (s, $3H_8$), 2.7 (m, $3H_{3,4}$), 3.46 (apparent s, $2H_6$), minor isomer observed at δ 1.48 (s, $3H_8$), 3.38 (s, $2H_6$). Integration of the C_5 methyl gave a **3e** to **4e** ratio of 60:40 (stereochemical assignments uncertain); IR ($CDCl_3$) 3450, 1775, 1640, 1380, 1260, 1155 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_7H_{11}O_2I$, M^+ 253.9804, found, m/e (relative intensity) 253.9772 (M^+, 5.9), 238.9 (M^+ – OH, 2.7), 230.9 (34.9), 126.9 (I, 7.9), 113.0 (100).

***rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-2(3*H*)furanone (3f).** The acid **1f** (407 mg, 3.51 mmol) yielded 560 mg (66%) of the lactones **3f** and **4f**: HPLC 12.0 min (93%) and 13.7 min (7%); R_f 0.30 (ether); ^1H NMR δ 2.62 (apparent d, J = 18.2 Hz, $1H_{3\beta}$), 2.85 (apparent dd, J = 5.6, 18.2 Hz, $1H_{3\alpha}$), 3.41 (apparent d, J = 6.6 Hz, $2H_6$), 3.55 (br s, OH), 4.60 (dd, J = 3.6, 6.6 Hz, $1H_5$), 4.66 (dd, J = 3.6, 5.6 Hz, $1H_4$), minor isomer **4f** observed at δ 2.97 (apparent dd, J = 6.6, 18.2 Hz, $1H_{3\beta}$), 3.33 (apparent d, J = 6.6 Hz, $2H_6$), 4.42 (m, $2H_{4,5}$); IR ($CDCl_3$) 3450, 2930, 1780, 1328, 1170, 1015 cm^{-1}; mass spectrum, m/e (relative intensity) 242 (M^+, 87.7), 214 (M^+ – CO, 52.2), 171 ($M^+ - C_3H_3O_2$, 66.5), 127 (I, 28.9), 115 ($M^+ - I$, 89.7), 97 ($M_+ - H_2O - I$, 100); high-resolution mass spectrum (EI) calcd for $C_5H_7O_3I$, M^+ 241.94401, found, M^+ 241.9440.

Methanolysis of the lactone mixture **3f** and **4f** (605 mg, 2.50 mmol) yielded 120 mg (33%) of epoxides **5f** and **6f**: GC 8.52 min (7%) and 8.85 min (93%); R_f 0.36 (ether); ^1H NMR δ 2.64 (apparent dd, J = 5.9, 7.4 Hz, $2H_2$), 2.81 (m, $2H_5$), 2.97 (br s, OH), 3.07 (m, $1H_4$), 3.73 (s, 3 H, OCH_3), 4.00 (m, $1H_3$); IR ($CDCl_3$) 3400, 2960, 1740, 1440, 1375, 1175, 1110, 1060, 1010 cm^{-1}.

***rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-4-methyl-2(3*H*)-furanone (3g).** The acid **1g** (250 mg, 1.92 mmol) yielded 417 mg (85%) of the lactones **3g** and **4g**: mp 102–107 °C; HPLC 4.7 min (96%) and 6.5 min (4%); R_f 0.42 (ether). **3g**: ^1H NMR δ 1.49 (s, 3 H, CH_3), 2.35 (br s, OH), 2.72 (ABq, $\Delta\nu_{AB}$ = 28.7, J_{AB} = 19.1 Hz, $2H_3$), 3.43 (dABq,

(26) Sullivan, D. F.; Woodbury, M. W.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038.

$\Delta\nu_{AB}$ = 23.9, J_{AB} = 11.0, J_{AX} = 7.5, J_{BX} = 5.6 Hz, $2H_6$), 4.52 (dd, J = 5.6, 7.5 Hz, $1H_{5\alpha}$); ($CDCl_3$) 3150, 2975, 2898, 1792, 1460, 1380, 1210, 1165, 1090 cm^{-1}. Anal. Calcd for $C_6H_9O_3I$; C, 28.13; H, 3.54. Found: C, 28.40; H, 3.32. Found for crude sample: C, 28.08; H, 3.42. The stereochemistry was determined by X-ray crystallography.[9] On one run **3g** was separated from **4g** by HPLC. **4g**: ^1H NMR δ 1.49 (s, 3 H, CH_3), 2.61 (br s, OH), 2.74 (apparent s, $2H_3$), 3.29 (dABq, $\Delta\nu_{AB}$ = 26.5, J_{AB} = 10.8, J_{AX} = 6.5, J_{BX} = 6.5 Hz, $2H_6$), 4.53 (apparent t, J = 6.5 Hz, $1H_{5\beta}$); IR ($CDCl_3$) 3160, 2984, 2898, 1798, 1460, 1380, 1212, 1090 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_6H_9O_3I$, M^+ 255.9596, found, m/e (relative intensity) 255.9597 (M^+, 0.5), 129.0 (M^+ - I, 17.2) 126.9 (I, 7.7), 85.0 (51.4), 44 (CO_2, 100).

***rel*-(4*R*,5*S*,6*R*)-Dihydro-4-hydroxy-5-(1-iodoethyl)-2(3*H*)-furanone (3h).** The acid **1h** (260 mg, 2.00 mmol) yielded 250 mg (49%) of **3h**: mp 61–62 °C; R_f 0.33 (3:2 ether–petroleum ether); ^1H NMR δ 2.09 (d, J = 6.6 Hz, $3H_7$), 2.68 (apparent d, J = 17.7 Hz, $1H_{3\beta}$), 2.86 (apparent dd, J = 5.2, 17.7 Hz, $1H_{3\alpha}$), 2.28 (br s, OH), 4.30 (dq, J = 10.8, 6.6 Hz, $1H_6$), 4.42 (dd, J = 3.1, 10.8 Hz, $1H_5$), 4.76 (dd, J = 5.2, 3.1 Hz, $1H_4$); IR ($CDCl_3$) 3450, 2930, 1770, 1450, 1380, 1338, 1165, 1092 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_6H_9O_3I$, M^+ 255.9597, found, m/e (relative intensity) 255.9598 (M^+, 2.3), 184.9 ($M^+ - C_3H_3O_2$, 14.5), 129.0 (M^+ - I, 36.5), 111.0 (M^+ - I - H_2O, 100).

Methanolysis of the lactone **3h** (207 mg, 0.81 mmol) yielded 74 mg (58%) of crude epoxide **5h**: GC 6.43 min (100%) compared by coinjection with Sharpless mixture, 6.20 min (65%) and 6.41 min (35%); R_f 0.64 (ether); ^1H NMR δ 1.33 (d, J = 5.4 Hz, 3 H, CH_3), 2.61 (apparent dd, J = 5.9, 7.0 Hz, $2H_2$), 2.79 (dd, J = 2.2, 4.4 Hz, $1H_4$), 3.06 (dq, J = 2.2, 5.4 Hz, $1H_5$), 3.72 (s, 3 H, OCH_3), 4.02 (m, $1H_3$); IR ($CDCl_3$) 2450, 2950, 2930, 1735, 1640, 1440, 1170, 1060 cm^{-1}.

In another run, the crude reaction mixture was purified by HPLC to give three lactones: **3h**, 12.0 min (65.0%); 18.7 (13.6%, IR 1735 cm^{-1}); 23.5 (21.4%, IR 1740 cm^{-1}). The other γ-lactone was not detected.

Iodolactonization of Acid 1i. The acid **1i** (240 mg, 1.58 mmol) yielded three products, in order of increasing polarity:

***rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-iodo-6,6-dimethyl-2(3*H*)-dihydropyranone (8) and *rel*-(4*R*,5*R*)-dihydro-4-hydroxy-5-(1-iodo-1-methylethyl)-2(3*H*)-furanone (4i):** 302 mg (83%); R_f 0.50 (ether). ^1H NMR: **8**, δ 1.26 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 2.58 (br s, OH), 2.60 (apparent dd, J = 9.3, 18.5 Hz, $1H_{3\beta}$), 3.08 (apparent dd, J = 6.5, 18.5 Hz, $1H_{3\alpha}$), 4.15 (d, J = 10.5 Hz, $1H_{5\beta}$), 4.28 (m, $1H_{4\alpha}$); **4i**, δ 1.94 (s, $3H_7$), 2.06 (s, $3H_8$), 3.88 (m, $1H_{5\beta}$), 4.62 (m, $1H_{4\alpha}$). Ratio of **8**:**4i** is 90:10 by C_6 methyl integration: IR ($CDCl_3$) 3434, 2984, 1781, 1730, 1269, 1113 cm^{-1}.

Methanolysis of **8** and **4i** (80 mg, 0.3 mmol) yielded 48 mg (92%) of a single epoxide: GC 7.08 min (100%) compared by coinjection with Sharpless mixture, 7.05 min (14%) and 7.65 min (86%); R_f 0.40, (ether); ^1H NMR (80 MHz, $CDCl_3$) δ 1.22 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 2.53 (apparent dd, J = 6.0, 7.8 Hz, $2H_2$), 2.60 (d, J = 5.8 Hz, $1H_4$), 3.1 (br s, OH), 3.57 (s, 3 H, OCH_3), 3.75 (m, $1H_3$); IR (neat) 3450, 2960, 1735, 1400, 1386, 1170, 1030 cm^{-1}.

***rel*-(4*R*,5*R*)-Dihydro-4-hydroxy-5-iodo-6,6-dimethyl-2(3*H*)-dihydropyranone (9):** 63 mg (17%); R_f 0.25 (ether); ^1H NMR δ 1.62 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.30 (br s, OH), 2.73 (apparent dd, J = 8.8, 18.0 Hz, $1H_{3\beta}$), 2.95 (apparent ddd, J = 1.0, 5.8, 18.0 Hz, $1H_{3\alpha}$), 3.69 (m, $1H_{4\alpha}$), 4.62 (dd, J = 1.0, 3.5 Hz, $1H_{5\alpha}$); IR ($CDCl_3$) 3431, 2985, 2937, 1729, 1266, 1146 cm^{-1}.

Methanolysis of **9** (25 mg, 0.1 mmol) yielded 15 mg (95%) of an epoxide mixture: GC 7.09 min (6%) and 7.67 min (94%) compared by coinjection with Sharpless mixture, 7.09 min (11%) and 7.67 min (89%); R_f 0.40 (ether); ^1H NMR (80 MHz, $CDCl_3$) δ 1.32 (s, 6 H, CH_3), 2.55 (apparent dd, J = 5.0, 7.0 Hz, $2H_2$), 2.70 (br s, OH), 2.75 (d, J = 7.5 Hz, $1H_4$), 3.71 (s, 3 H, OCH_3), 3.85 (m, $1H_3$).

***rel*-(3*S*,4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-3-methyl-2-(3*H*)-furanone (3j).** The ethyl ester of the acid **1j** (72 mg, 0.5 mmol) was hydrolyzed in 3 mL of water and 1 mL of THF with excess sodium hydroxide (55 mg, 1.4 mmol). The reaction mixture was heated at reflux and neutralized (concentrated HCl), and then without further workup the general procedure for iodolactonization was followed, yielding 51 mg (42%) of crude lactones **3j** and **4j**: HPLC 3.8 min (87%) and 4.24 min (13%); R_f 0.55 (2:1 ether–petroleum ether); ^1H NMR δ 1.27 (d, J = 7.4 Hz, 3 H, CH_3), 2.48 (br s, OH), 2.75 (dq, J = 4.8, 7.4 Hz, $1H_{3\alpha}$), 3.43 (apparent d, J = 8.4 Hz, $2H_6$), 4.56 (m, $1H_5$), 4.50 (m, $1H_4$); IR ($CDCl_3$) 2440, 2980, 2940, 2880, 1770, 1450, 1415, 1345, 1170, 1040 cm^{-1}. Anal. Calcd for $C_6H_9O_3I$: C, 28.13; H, 3.54; I, 47.58. Found: C, 28.38; H, 4.11; I, 47.01.

***rel*-(3*S*,4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-3,5-dimethyl-2-(3*H*)-furanone (3k).** The acid **1k** (285 mg, 1.98 mmol) yielded 502 mg (94%) of the lactones **3k** and **4k**: mp 83–85 °C; HPLC 6.2 min (100%, diastereomers were inseparable); R_f 0.63 (2:1 ether–petroleum ether); ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 7.2 Hz, 3 H, CH_3), 1.53 (s, $3H_8$), 2.97 (dq, J = 5.3, 7.2 Hz, $1H_{3\alpha}$), 3.32 (d, J = 5.3 Hz, OH), 3.45 (ABq, $\Delta\nu_{AB}$ = 15.1, J_{AB} = 10.0 Hz, $2H_6$), 4.23 (apparent, t, J = 5.3 Hz, $1H_4$); IR ($CDCl_3$) 3440, 2970, 2935, 2890, 2870, 1765, 1025, 1440, 1410, 1375, 1329, 1265, 1160 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_7H_{11}O_3I$, M^+ 269.9753, found, m/e (relative intensity) 269.9751 (M^+, 8.2), 252.9 ($M^+ - H_2O$, 25.2), 241.9 (M^+ - CO, 36.6), 196.9 (25.8), 143.0 (M^+ - I, 20.4), 126.9 (I, 25.0), 117.0 (100).

Methanolysis of the lactone mixture **3k** and **4k** (14.3 mg, 0.05 mmol) yielded 16.4 mg (178%) of crude epoxides **5k** and **6k**: GC major epoxide **5k**, 7.4 min (73%), corresponded to minor Sharpless epoxide when coinjected, 7.2 min (81%) and 7.4 min (19%); R_f 0.29 (4:1 ether–petroleum ether); ^1H NMR (80 MHz, $CDCl_3$) δ 1.25 (d, J = 6.5 Hz, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 2.75 (m, $3H_{2\beta,5}$), 3.50 (m, $1H_4$), 3.75 (s, 3 H, OCH_3).

***rel*-(3*R*,4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-3-methyl-2-(3*H*)-furanone (3l).** The ethyl ester of the acid **1l** (150 mg, 0.95 mmol) was hydrolyzed as in the preceeding procedure and then iodolactonized according to the general procedure, yielding 180 mg (74%) of crude lactones **3l** and **4l**: HPLC 4.56 min (77%) and 4.88 min (23%); R_f 0.60 (2:1 ether–petroleum ether); ^1H NMR δ 1.29 (d, J = 7.7 Hz, 3 H, CH_3), 2.46 (br s, OH), 2.74 (dq, J = 5.2, 7.7 Hz, $1H_{3\beta}$), 3.43 (dABq, $\Delta\nu_{AB}$ = 19.2, J_{AB} = 10.3, J_{AX} = 6.6, J_{BX} = 8.2 Hz, $2H_6$), 4.31 (dd, J = 4.4, 5.2 Hz, $1H_4$), 4.71 (ddd, J = 4.4, 6.6, 8.2 Hz, $1H_5$); IR ($CDCl_3$) 3440, 3040, 2960, 2920, 2860, 1770, 1440, 1410, 1320, 1170, 1070 cm^{-1}. **4l**: ^1H NMR δ 1.35 (d, J = 7.0 Hz, 3 H, CH_3), 2.89 (m, $1H_{3\beta}$), 3.10 (m, $2H_6$), 3.92 (dd, J = 6.6, 7.0 Hz, $1H_4$), 4.10 (ddd, J = 5.2, 7.0, 10.3 Hz, $1H_5$).

***rel*-(3*R*,4*R*,5*R*)- and *rel*-(3*R*,4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-3,5-dimethyl-2(3*H*)-furanone (4m, 3m).** The acid **1m** (38.0 mg, 0.26 mmol) yielded 57 mg (81%) of the lactones **4m** and **3m**: HPLC 7.3 min (58%) and 8.3 min (42%); R_f 0.60 (2:1 ether–petroleum ether). **4m**: ^1H NMR δ 1.34 (d, J = 7.1 Hz, 3 H, CH_3), 1.55 (s, $3H_8$), 2.68 (dq, J = 7.1, 8.0 Hz, $1H_{3\beta}$), 3.02 (d, J = 5.2 Hz, OH), 3.45 (apparent d, J = 7.1 Hz, $2H_6$), 4.05 (apparent d, J = 5.2 Hz, $1H_4$), minor isomer **3m** observed at δ 1.34 (d, J = 7.3 Hz, 3 H, CH_3), 1.61 (s, $3H_8$), 2.85 (dq, J = 7.3, 8.7 Hz, $1H_{3\beta}$), 3.28 (d, J = 4.3 Hz, OH), 3.45 (apparent d, J = 7.1 Hz, $2H_6$), 4.09 (apparent d, J = 4.3 Hz, $1H_4$); IR ($CDCl_3$) 3420, 2980, 1768, 1450, 1335, 1270, 1240, 1160, 1095 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_7H_{11}O_3I$, M^+ 269.9753, found, m/e (relative intensity) 269.9751 (M^+, 5.04), 241.9 (M^+ - CO, 28.3), 184.9 (23), 143.0 M^+ - I, 4.2), 126.9 (I, 3.2), 117.0 (38.5), 100.1 ($M^+ - CO_2$ - I, 21.0), 85.0 (49.5), 58.0 (100).

Methanolysis of the lactones **4m** and **3m** (44.0 mg, 0.16 mmol) yielded 36.7 mg (129%) of crude epoxide mixture **6m** and **5m**: GC major epoxide **6m**, 7.6 min, corresponded to major Sharpless epoxide when coinjected, 7.61 min (100%), minor epoxide **5m**, 7.3 min; R_f 0.44, (4:1 ether–petroleum ether); ^1H NMR **5m** δ 1.20 (d, J = 6.9 Hz, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 2.50 (br s, OH), 2.58 (d, J = 4.8 Hz, $1H_5$), 2.72 (dq, J = 4.8, 6.9 Hz, $1H_{2\alpha}$), 2.80 (d, J = 4.8 Hz, $1H_5$), 3.72 (m, $1H_3$), 3.74 (s, 3 H, OCH_3), **6m** δ 1.27 (d, J = 6.9 Hz, 3 H, CH_3), 1.36 (s, 3 H), 2.30 (br s, OH), 2.58 (d, J = 4.8 Hz, $1H_5$), 2.72 (dq, J = 5.5, 6.9 Hz, $1H_{2\alpha}$), 2.85 (d, J = 4.8 Hz, $1H_5$), 3.72 (m, $1H_3$), 3.74 (s, 3 H, OCH_3).

***rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-3,3,5-trimethyl-2-(3*H*)-furanone (3n).** The acid **1n** (500 mg, 3.16 mmol) yielded 856 mg (93%) crude of the lactones **3n** and **4n**: mp 84–86 °C; HPLC 5.3 min (28%) and 6.6 min (72%); R_f 0.55 (ether); ^1H NMR (80 MHz, $CDCl_3$) δ 1.24 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 2.95 (br s, OH), 3.45 (ABq, $\Delta\nu_{AB}$ = 15.4, J = 12.0 Hz, $2H_6$), 4.15 (d, J = 6.0 Hz, $1H_4$); IR ($CDCl_3$) 3451, 2983, 1765, 1283, 1147, 1033 cm^{-1}. Anal. Calcd for $C_8H_{13}O_3I$: C, 33.80; H, 4.61; I, 44.69. Found: C, 33.96; H, 4.83; I, 44.90.

Methanolysis of the lactone mixture **3n** and **4n** (70.5 mg, 0.25 mmol) yielded 37 mg (86%) of epoxides **5n** and **6n**. Major isomer **5n**, R_f 0.42, was compared by cospotting (TLC) with the Sharpless mixture, R_f 0.49 (major) and R_f 0.42 (minor isomer) (4:1 ether–petroleum ether): ^1H NMR (80 MHz, $CDCl_3$) δ 1.24 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 2.65 (apparent dd, J = 14.0 Hz, $2H_6$), 2.67 (br s, OH), 3.38 (s, 3 H, OCH_3), 4.25 (apparent s, $1H_3$); IR 3450, 2980, 1750, 1460, 1385, 1060 cm^{-1}.

***rel*-(3*R*,4*S*)-*tert*-Butyl-3,4-Dihydroxy-5-iodo-4-methylpentanoate (12a) and *rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-5-methyl-2-(3*H*)-furanone (3d).** The *tert*-butyl ester of acid **10a** (186 mg, 1.0 mmol) yielded 170 mg (66%) of lactones which by spectral and chromatographic comparison with the iodolactonization product from the acid **1d** was a 9:1 mixture of **3d**–**4d**. A second chromatographic fraction (100 mg, 33%) consisting of a 9:1 mixture of **12a** and its diastereomer was also isolated: R_f 0.76 (ether); ^1H NMR δ 1.28 (s, 3 H, CH_3), 1.48 (s, 9 H, *t*-Bu), 2.48 (apparent dd, J = 5.3, 7.4 Hz, $2H_2$), 2.56 (s, OH), 3.40 (ABq, $\Delta\nu_{AB}$ = 33.5, J_{AB} = 10.1 Hz, $2H_5$), 3.82 (d, J = 3.3 Hz, OH), 4.17 (ddd, J = 3.3, 5.3, 7.4 Hz, $1H_3$), minor isomer observed at δ 2.65 (dd), 3.42 (d), 3.62 (d), 4.05 (m); IR 3440, 2980, 2930, 1715, 1370, 1155 cm^{-1}. Anal. Calcd for $C_{10}H_{19}O_4I$: C, 36.36; H, 5.80; I, 38.45. Found: C, 36.60; H,

5.92; I, 38.42. The epoxide mixture derived from **12a** gave a major product, R_f 0.34, which corresponded by TLC to the minor Sharpless epoxide,[5] R_f 0.34 and R_f 0.39 (1:1 acetone–dichloromethane).

***rel*-(3*R*,4*S*)-Methyl 3,4-Dihydroxy-5-iodo-4-methylpentanoate (12b) and *rel*-(4*R*,5*S*)-Dihydro-4-hydroxy-5-(iodomethyl)-5-methyl-2(3*H*)-furanone (3d).** The methyl ester of **10b** (144 mg, 1.00 mmol) yielded 135 mg (47%) of lactones which by spectral and chromatographic comparison with the iodolactonization product from the acid **1d** was **3d**. A second chromatographic fraction consisting of a 9:1 mixture of **12b** and its diastereomer was also isolated: R_f 0.13 (2:1 ether–petroleum ether); ^{1}H NMR δ 1.30 (s, 3 H, CH_3), 2.54 (br s, OH), 2.59 (apparent dd, J = 5.3, 7.6 Hz, $2H_2$), 3.34 (ABq, $\Delta\nu_{AB}$ = 32.4, J = 10.1 Hz, $2H_5$), 3.59 (br s, OH), 3.75 (s, 3 H OCH_3), 4.23 (m, $1H_3$), minor isomer observed at δ 2.72 (dd), 3.25 (m), 4.08 (m); IR ($CDCl_3$) 3460, 2980, 2960, 1730, 1440, 1200, 1170 cm^{-1}. Anal. Calcd for $C_7H_{13}O_4I$: C, 29.17; H, 4.85; I, 44.07. Found: C, 29.39; H, 4.73; I, 43.81. Methanolysis of the lactone and iodo diol mixture gave an epoxide mixture analyzed by GC: 7.32 min (9%) and 7.74 min (91%) compared by coinjection with Sharpless mixture, 7.35 min (96%) and 7.73 min (4%).

***rel*-(4*R*,5*S*)-4,5-Dihydroxy-6-iodo-5-methylhexan-2-one (12c).** The hexanone **10c** (240 mg, 1.87 mmol) yielded 440 mg (87%) of iodo diols: HPLC 1.6 min (90%) and 1.92 min (10%); R_f 0.20, (5:1 ether–petroleum ether); ^{1}H NMR δ 1.28 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 2.61 (br s, OH), 2.70 (apparent dd, J = 4.6, 7.63 Hz, $2H_2$), 3.39 (ABq, $\Delta\nu_{AB}$ = 13.0, J = 10.0 Hz, $2H_5$), 3.65 (dd, J = 2.7, 5.8 Hz, OH), 4.25 (m, $1H_3$), minor isomer observed at δ 1.27 (s, 3 H), 3.50 (ABq, J = 10.0, 2 H), 3.62 (br s, OH), 4.17 (m, 1 H); IR ($CDCl_3$) 3446, 2979, 1712, 1359, 1167, 1079 cm^{-1}; high-resolution mass spectrum calcd for $C_7H_{13}O_3I$, M^+ 271.9909, found, m/e (relative intensity) 271.9875 (M^+, 0.1), 253.8 ($M^+ - H_2O$, 15.8), 236.9 ($M^+ - H_2O$ – OH, 100), 134.0 (52.9), 126.9 (I, 30.4), 110.0 (43.5), 95 (38.6).

***rel*-(2*S*,3*R*)- and *rel*-(2*R*,3*R*)-2,3-Dihydroxy-1-iodo-2-methylheptane (15).** The heptenol **13** (200 mg, 1.56 mmol) yielded 360 mg (86%) of a mixture of **15** and its diastereomer in a ratio of 4:1 by ^{1}H NMR integration: R_f 0.24 and 0.33 (1:1 petroleum ether–ether); ^{1}H NMR δ 0.91 (t, J = 7.0, 3 H), 1.28 (s, 3 H), 1.34 (m, 4 H), 1.58 (m, 2 H), 2.20 (br s, OH), 3.32 (apparent d, J = 10.3 Hz, 2 H), 3.62 (m, 1 H), minor isomer observed at δ 2.50 (m), 2.90 (m), 3.10 (m); IR (neat) 3450, 2959, 2930, 1710, 1460, 1378, 1193, 1035 cm^{-1}; high-resolution mass spectrum (EI) calcd for $C_8H_{17}O_2I$, M^+ 272.0274, found, m/e (relative intensity) 255.0235 ($M^+ - OH_2$, 0.43), 126.9 (I, 1.3), 87.0 (17.7), 69.0 (58.3), 59.0 (100), 58.0 (20.1).

Methanolysis of the iodo diol mixture (76 mg, 0.3 mmol) yielded 15.6 mg (44%) of an epoxide mixture: GC 4.8 min (80%) and 5.2 min (20%) compared by coinjection with Sharpless mixture, 4.8 min (97%) and 5.2 min (3%); R_f 0.60 (ether); ^{1}H NMR δ 0.92 (t, J = 7.0 Hz, 3 H), 1.34 (s, 3 H), 1.37 (m, 6 H), 2.08 (br s, OH), 2.61 (d, J = 6.6 Hz, 1 H), 2.90 (d, J = 6.6 Hz, 1 H), 3.65 (m, 1 H), minor isomer observed at δ 2.66 (d, J = 6.6 Hz, 1 H), 2.78 (d, J = 6.6 Hz, 1 H), 3.30 (m, 1 H); IR 3460, 2960, 2935, 2879, 1460, 1389, 1369, 1060 cm^{-1}.

***rel*-(2*R*,3*R*,4*R*)-2,4-Dihydroxy-3-iodooctane (18).** Octenol **16** (249 mg, 1.95 mmol) yielded 385 mg (73%) of the iodo diol **18**: HPLC 3.15 min (98%) and 4.05 min (2%); R_f 0.30 (2:1 ether–petroleum ether); ^{1}H NMR δ 0.92 (m, 3 H), 1.35 (m, 4 H), 1.45 (d, J = 6.3 Hz, 3 H), 1.65 (m, 2 H), 2.44 (d, J = 4.0 Hz, OH), 2.60 (d, J = 4.0 Hz, OH), 3.19 (m, 1 H), 4.13 (m, $1H_4$), 4.21 (dd, J = 5.2, 5.3 Hz, $1H_3$); IR 3380, 2960, 2938, 2882, 1450, 1375, 1039, 932 cm^{-1}.

Methanolysis of the iodo diol **18** (133 mg, 1.04 mmol) gave 54 mg (67%) of crude epoxides: GC 18.32 min (75%), 18.87 min (25%) compared by coinjection with Sharpless mixture, 18.29 min (70%) and 19.09 min (30%); R_f 0.31 (1:1 ether–petroleum ether); ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.00 (m, 3 H), 1.45 (d, J = 6.0 Hz, 3 H), 1.55 (m, 6 H), 2.42 (br s, OH), 2.75 (m, 1 H), 3.07 (dq, J = 3.5, 6.0 Hz, 1 H), 3.75 (m, 1 H).

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Registry No. 1a, 86335-87-7; **1b**, 86335-88-8; **1c**, 86335-89-9; **1d**, 81357-29-1; **1e**, 86335-90-2; **1f**, 81357-28-0; **1g**, 38004-74-9; **1h**, 13893-40-8; **1i**, 86335-91-3; **1j**, 86335-92-4; **1k**, 86363-11-3; **1l**, 86335-93-5; **1m**, 86363-12-4; **1n**, 86335-94-6; **3a**, 81357-35-9; **3b**, 81357-36-0; **3c**, 86335-95-7; **3d**, 81357-34-8; **3e**, 86335-96-8; **3f**, 81357-33-7; **3g**, 86335-97-9; **3h**, 81357-37-1; **3i**, 86335-98-0; **3j**, 86390-88-7; **3k**, 86390-89-8; **3l**, 86390-90-1; **3m**, 86390-91-2; **3n**, 86335-99-1; **4a**, 86336-00-7; **4b**, 86336-01-8; **4c**, 86336-02-9; **4d**, 86390-92-3; **4e**, 86336-03-0; **4f**, 86390-93-4; **4g**, 86336-04-1; **4i**, 86336-05-2; **4j**, 86390-94-5; **4k**, 86390-95-6; **4l**, 86390-96-7; **4m**, 86390-97-8; **4n**, 86336-06-3; **5a**, 81357-40-6; **5b**, 86336-07-4; **5d**, 81357-39-3; **5f**, 81357-38-2; **5h**, 81357-41-7; **5k**, 86363-13-5; **5m**, 86363-14-6; **5n**, 86336-08-5; **6a**, 81357-42-8; **6b**, 86363-15-7; **6d**, 81422-56-2; **6f**, 81422-55-1; **6k**, 86363-16-8; **6m**, 86363-17-9; **6n**, 86336-09-6; **7** epoxide (isomer 1), 86336-10-9; **7** epoxide (isomer 2), 86336-11-0; **8**, 86336-12-1; **9**, 86336-13-2; **10a**, 86336-14-3; **10b**, 81357-44-0; **10c**, 44809-62-3; **12a** (isomer 1), 86336-15-4; **12a** (isomer 2), 86336-16-5; **12b** (isomer 1), 86336-17-6; **12b** (isomer 2), 86336-18-7; **12c** (isomer 1), 86336-19-8; **12c** (isomer 2), 86336-20-1; **13**, 13019-19-7; **13** epoxide (isomer 1), 53837-92-6; **13** epoxide (isomer 2), 53837-93-7; **15** (isomer 1), 86336-21-2; **15** (isomer 2), 86336-22-3; **16**, 4798-61-2; **16** epoxide (isomer 1), 84049-79-6; **16** epoxide (isomer 2), 84049-80-9; **18**, 86336-23-4; dilithioacetate, 31509-80-5.

Supplementary Material Available: Tables I–VI, crystal data and experimental parameters, positional parameters, hydrogen atom parameters, bond distances, and bond angles, a drawing of structure **3g**, and preparation of the starting materials (15 pages). Ordering information is given on any current masthead page.