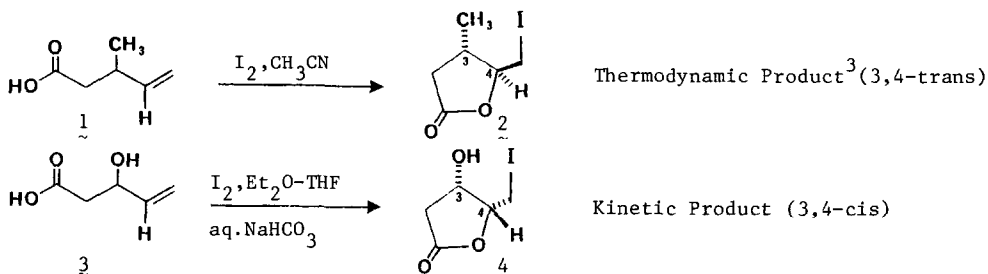


STEREOSELECTIVE IODOLACTONIZATION OF ACYCLIC UNSATURATED 3-HYDROXYACIDS

A. Richard Chamberlin,* Milana Dezube, and Patrick Dussault
 Department of Chemistry
 University of California
 Irvine, California 92717

Summary: A stereoselective method for preparing 3-hydroxy-4-alkyl- γ -lactones is reported. Iodolactonization of 3-hydroxy-4-alkenoic acids produces predominantly the thermodynamically less stable 3,4-*cis* products, which undergo methanolysis to threo-epoxyalcohols.

Halolactonization has been used successfully to cyclize a number of simple acyclic olefinic acids,¹ but for many years its potential to achieve stereoselection in substituted acyclic systems was unstudied. Recently, Terashima and Jew reported² a bromolactonization which stereoselectively provides optically active α -hydroxy acids from acyclic precursors. Bartlett and Myerson have since shown³ that the iodolactonization of certain acyclic olefinic acids (eg 1) under thermodynamic conditions (I_2 , CH_3CN) results in high asymmetric induction (via the equilibration of a protonated iodolactone intermediate) to the more stable trans-isomer, 2.⁴ In this

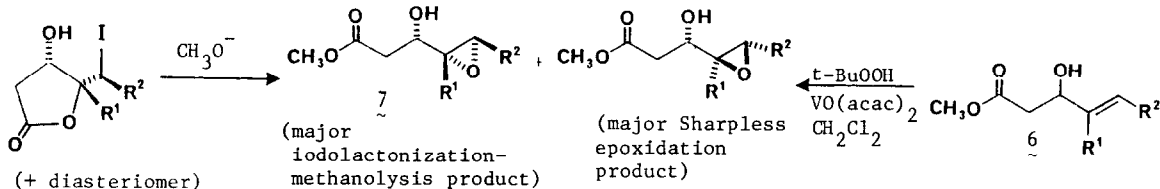


communication we report that the iodolactonization of acyclic hydroxy olefinic acids such as 3 under kinetic conditions⁵ also proceeds with reasonably high asymmetric induction, giving rise mainly to thermodynamically less stable 3,4-cis-iodolactones such as 4.^{6,7}

The unsaturated hydroxyacid precursors shown in the Table were prepared in good yield by condensing dilithioacetate⁸ with the appropriate commercially available aldehydes at $-78^\circ C$ in THF solution. Iodolactonization under modified conditions of kinetic control⁵ (3 I_2 , aqueous $NaHCO_3$ -THF-ether 2:1:1) proceeds to completion within approximately 3hr. at $0^\circ C$. As the Table shows, the reaction is regio- and stereoselective for acids 5a-5d, giving the γ -lactone with the 3,4-substituents in the less stable cis arrangement as the major product in each case. Although protection of the alcohol is not necessary in these reactions, one silylated precursor (5d) gave a ratio of iodolactones essentially identical to the corresponding free alcohol 5c. Not un-

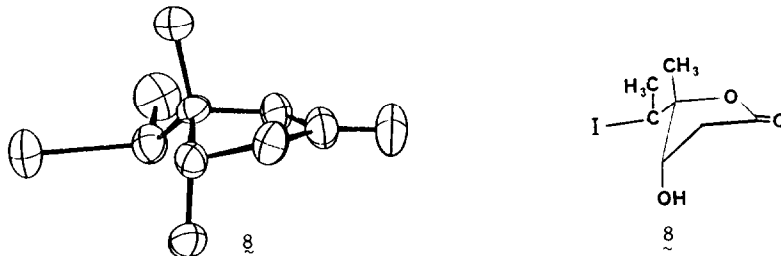
expectedly, in the case of the 1,2-disubstituted alkene 5e, a mixture of 5- and 6-membered ring iodolactones is formed; in this instance, however, the cis- γ -isomer is easily separated by flash chromatography from both the trans- γ -product and the 6-membered ring isomers, providing the diastereomer-free cis- γ -lactone in 49% yield from 5e.

The iodolactones⁹ were converted to epoxy alcohols in ~90% yield by methanolysis (2 equiv MeONa/MeOH, 0°C, or K₂CO₃/MeOH, 25°C). These epoxides were identified by comparison (12m capillary gas chromatography) to authentic mixtures prepared by Sharpless epoxidation¹⁰ of the corresponding methyl esters 6,¹¹ and by their infrared and 250MHz NMR spectra. The stereochemical



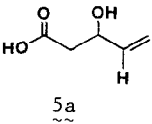
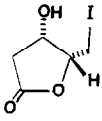
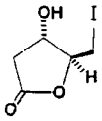
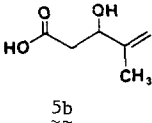
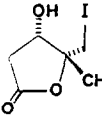
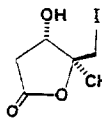
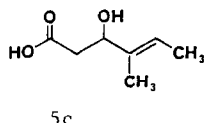
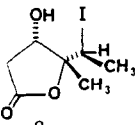
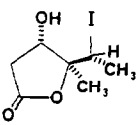
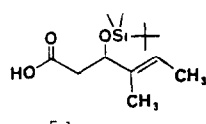
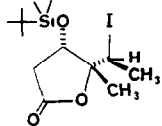
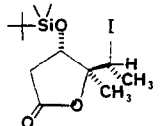
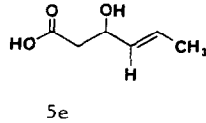
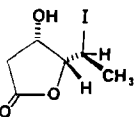
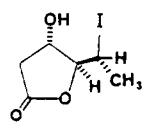
assignments for the iodolactones from which these epoxides were derived were thus firmly established; even so, a single-crystal x-ray structure¹² was obtained for the lactone 8, confirming beyond a doubt the proposed stereochemical course of the iodolactonization.

It is important to note that this iodolactonization-methanolysis sequence gives the same two epoxides as does Sharpless epoxidation (VO(acac)₂, t-BuOOH, CH₂Cl₂; 0°C),¹⁰ but the two methods give the opposite relative stereochemistries of alcohol and epoxide groups. This simple two-step procedure may thus be synthetically useful as a way to prepare three epoxy alcohols (7) unavailable by other stereoselective methods.¹³ Other synthetic uses of the iodolactones currently are being explored, as are additional examples to further define the scope of the reaction. Experiments bearing on the mechanistic reasons for the observed stereoselectivity will be discussed in a later paper.



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Iodolactonization of Unsaturated Hydroxyacids with Iodine in Ether-THF-Aqueous Bicarbonate^a

Unsaturated Hydroxy Acid	Iodolactone Products ^b		Yield ^c	Lactone Isomer Ratio ^d (cis:trans)
	<u>cis</u>	<u>trans</u>		
 5a			66%	93:7
 5b			74%	95:5
 5c			82%	96:4
 5d			84% ^e	96:4
 5e			49% ^f	100:0 ^f

a. 3 equiv. I₂, ether/THF/saturated aqueous bicarbonate 1/1/2, 0°C, 3hr; b. All products are racemic. The lactone diastereomers generally were not easily separable on TLC; c. Flash chromatography gave mixtures of diastereomers, otherwise pure. d. Determined by conversion to the epoxides and gc analysis, as described in the text; e. The starting material for this reaction was the methyl ester of 5d, which was hydrolyzed to 5d (ether/THF/KOH, 20°C) followed by *in situ* iodolactonization (added saturated bicarbonate, 3I₂, 0°C, 3hr.); f. Some of the δ-lactone is formed in this reaction, but it and the minor γ-lactone diastereomer separate cleanly from the major γ-lactone. The 100:0 ratio thus, in this case only, does not represent the ratio produced, but rather that isolated.

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6. All attempts to carry out these reactions under thermodynamic control³ gave numerous by-products
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11. The methyl esters were prepared by addition of α -lithio methyl acetate (methyl acetate, LDA, THF, -95°C , 3 min.) to the appropriate commercially available aldehydes at -95°C .
12. Crystals of 8 grew from CCl_4 /toluene as colorless triangularly shaped prisms in space group $P2_1/n$ with $a=6.579(1) \text{ \AA}$, $b=14.634(3) \text{ \AA}$, $c=9.954(2) \text{ \AA}$, and $\beta=105.55(1)^{\circ}$. Of the 2164 unique data collected with Mo K α radiation, 1602 were considered observed. A Patterson synthesis located the iodine atom, and the remaining nonhydrogen atoms as well as eight of the eleven hydrogens were located in subsequent Fourier difference syntheses. Full-matrix least-squares refinements using anisotropic temperature factors for the non-hydrogen atoms and fixed isotropic temperature parameters for the hydrogens yielded a final conventional R factor of .060.
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