Deuterium Isotope Effects in the Reaction of 4,4-Dimethyldihydropyran with Dimethyldioxirane[1]

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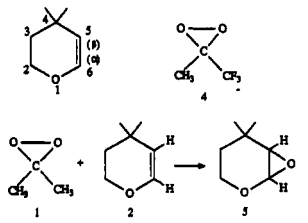
Received May 7, 1990 (Revised Manuscript Received October 23, 1990)

The reaction of dimethyldioxirane (1) with 4,4-dimethyl-2,3-dihydro-γ-pyran (2) gives the derived epoxide. Measured secondary deuterium isotope effects indicate that there is a greater degree of rehybridization at the β position (5-carbon) than at the α position (6-carbon) in the transition state leading to epoxide. The results are compared to those reported earlier in which 2 was oxidized by singlet oxygen to give the dioxetane.

Introduction

The reaction of dimethyldioxirane (1) with unsaturated materials provides a very efficient and mild method for introducing an epoxide group.[2] A number of recent reports demonstrate the power of 1 to solve problematic epoxidations.[3] There are now a number of examples[2] in which the reaction of 1 or its trifluoromethyl derivative 4[4] has been shown to proceed stereospecifically with retention. Thus, the epoxidation reaction is apparently concerted.



Use of the Hammett linear free-energy relationship in substituted styrenes[5] or ethyl cinnammates[6] has demonstrated that the reaction is electrophilic. With the goal of learning more about the details of the epoxidation reaction, we have studied the reaction of 4,4-dimethyl-2,3-dihydro-γ-pyran (2) and its deuterium substituted analogues 3α and 3β with 1. The choice of 2 as a substrate is dictated in part by its earlier use by Bartlett et al.[7] in a similar study involving reaction with singlet oxygen. In that work, the observed kinetic isotope effects ruled out a simple symmetric concerted mechanism for dioxetane formation.

Epoxidation of 2 by dimethyldioxirane to give 5 via a symmetrical transition state should proceed with identical degrees of hybridization change at the α (6) and β (5) positions. If, on the other hand, the epoxidation proceeds with a sensitivity to an expected greater electron density at the β position than an unsymmetrical transition state would result and could be reflected in the observed isotope effects.[8]

Scheme I

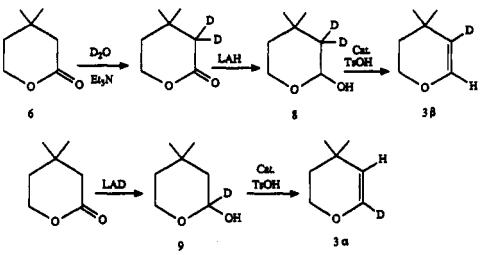


Table I. Secondary Deuterium Isotope Effects in the Dimethyldioxirane Epoxidations of Deuteriodihydropyrans

substrate	reaction conditions	k_H/k_D
	20% completion, 25 °C	0.810
		0.786
		0.786
		0.780
		0.780
		0.733
		0.733
average		0.773 ± 0.029 (±3.7% RSD)
	15% completion, −78 °C	0.624
		0.702
		0.691
		0.684
		0.703
average		0.681 ± 0.032 (± 4.8% RSD)
	20% completion, 25 °C	0.888
		0.849
		0.900
		0.876
		0.823
		0.795
		0.795
average		0.847 ± 0.043 (± 5.1% RSD)
	15% completion, −78 °C	0.871
		0.872
		0.871
		0.939
		0.937
average		0.898 ± 0.036 (±4.1% RSD)

Results

Synthesis of 2, 3α, and 3β. The synthesis of 2 followed in general that of Bartlett et al.[7] It proved to be advantageous to prepare the lactone 6 by LAH reduction of

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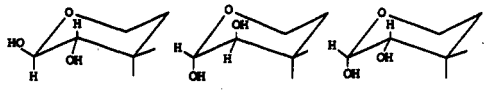
3,3-dimethylglutaric anhydride (7) rather than by sodium reduction as used in the earlier preparation. Lactone 6 was then reduced to the lactol, which was dehydrated to give 2. The deuterated analogues 3α and 3β were prepared as shown in Scheme I. In each case, the appropriate deuterated lactol 8 or 9 was dehydrated with a catalytic amount of tosyl acid.

Determination of Isotope Effects. Equimolar amounts of dihydropyran 2 and either 3α or 3β were treated with a solution of 1 in acetone. The minimum ratio of total substrate to 1 was 5:1. The reaction solutions were analyzed by GC–MS using selected ion monitoring. Data were collected at 25 °C (20% completion) and at −78 °C (15% completion). Under the conditions of excess substrate, the rate constants (Table I) can be calculated as follows where $[DHP]_0$ and $[DHP\text{-}d]_0$ are the initial concentrations of dihydropyran and dihydropyran-*d*, respectively, and $[DHP]_t$ and $[DHP\text{-}d]_t$ are the final concentrations of dihydropyran and dihydropyran-*d*, respectively:

$$k_H/k_D = \frac{\log ([DHP]_0/[DHP]_t)}{\log ([DHP\text{-}d]_0/[DHP\text{-}d]_t)}$$

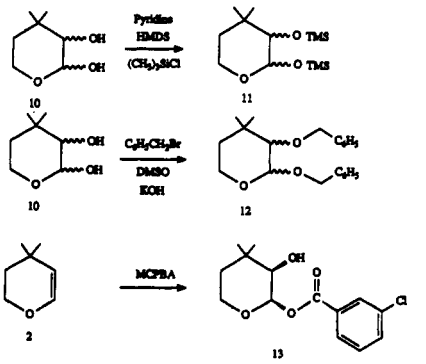
Product Studies. The reaction solutions used in the kinetic isotope studies were also analyzed over a mass range of 40–400 amu. The major product of the reaction had a molecular ion peak at 128.2 amu corresponding to addition of one oxygen atom to the dihydropyran substrate. This material presumably is the epoxide 5, although is proved to be too unstable to isolate. Epoxide 5 is derived from an enol ether and might be expected to be unstable. On the other hand, Adam et al. have recently shown[3d] that 1 can be used to produce epoxides of enol ethers derived from lactones. Apparently, the carbonyl group in the latter compounds has a moderating influence on the destabilizing effect of the ether oxygen. The methyl substituents at C-4 may also contribute to instability in 5. The ^{1}NMR spectrum of the reaction mixture shows an absorption at δ 4.8 (d, J = 2 Hz), which is reasonably assigned to one of the methine hydrogens (H-2) of 5. For comparison, H-2 of the epoxide formed from the parent 2,3-dihydrofuran is reported to absorb at δ 4.67 (J = 2.7 Hz)[3a] and 4.74 (J = 2.55 Hz).[3f] Attempts to isolate 5 by removal of solvent from the reaction solutions afforded the isomeric diols 10. The



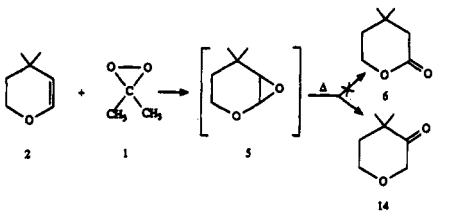
10a 10b 10c

structures of the diols have been investigated with the aid of ^{1}H NMR spectroscopy. The NMR spectrum of the diol mixture indicates the presence of two distinct sets of methine hydrogens (J = 7.8 and 1.5 Hz). The ratio of the isomeric diols varied from 2:1 to 1:1, respectively, from one preparation to another. Variable-temperature NMR measurements over the range of −90 to 100 °C gave no indication of conformational isomerization. A likely structural assignment for one of the diols is that of the trans isomer **10a**. The observed coupling constant (J = 7.8 Hz) is close to that expected[9] (J = 8–10 Hz) for diaxial methine hydrogens. Two possibilities need to be considered for the other diol isomer. One is the conformer **10b** of isomer **10a**. The second possibility is the diol with the cis configuration **10c**. Reliance on the methine H coupling constant (J = 1.5 Hz) alone does not permit an unequivocal choice between **10b** and **10c**, although reported coupling

Scheme II



Scheme III



constants tend to support somewhat the axial–equatorial arrangement (**10c**) for the hydrogens. In addition, the variable-temperature NMR results would seem to argue against conformer **10b** as a possibility.

We conclude that one of the diols should be assigned structure **10a**. This choice rests on the observed methine H coupling constant as well as on the predominant trend for diequatorial substitution[10] and the possibility for intramolecular hydrogen bonding. The second diol is tentatively assigned structure **10c** primarily on the basis of the lack of evidence for any conformational isomerization and the observed methine hydrogen coupling constant.

In an attempt to separate the diol isomers, the bis-[(trimethylsilyl)oxy] derivatives 11 were prepared. Chromatography of the product mixture on the Chromatotron led to isolation of the trans derivative **11a**, but all other chromatography fractions contained both isomers. Preparation of the 2,3-bis(benzyloxy)-4,4-dimethyltetrahydropyran derivatives (12) gave a mixture of the isomers that was inseparable using a variety of chromatographic methods. Attempts to prepare an authentic sample of 5 were without success. Treatment of 2 with *m*-chloroperbenzoic acid (MCPBA) gave only the adduct *trans*-2-(3′-chlorobenzoxy)-4,4-dimethyl-3-hydroxytetrahydropyran (13; Scheme II). Basic hydrolysis of 13 did lead to a 1:1 mixture of the isomeric diols 10.

Additional evidence for the involvement of 5 in the epoxidation reactions was obtained by thermolyzing the product mixtures from the reaction of 1 or MCPBA with 2. Preparative gas chromatography (column temperature 85 or 90 °C) of either of these reaction mixtures gave 4,4-dimethyltetrahydropyran-3-one (14) as the major product (Scheme III). It is likely that 14 is a thermal rearrangement product of epoxide 5. Such rearrangements are well-known.[11] Furthermore, it has been established that ring opening of alkoxy-substituted epoxides always occurs via cleavage at an alkoxy-bearing carbon.[11] Likewise, hydrogen has a much greater migratory aptitude than alkyl groups in such rearrangements. Operation of these factors in the case of 5 should lead to 14, as observed, rather than the lactone isomer 6.

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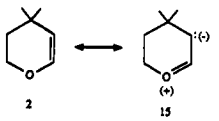
Discussion

The reaction of dimethyldioxirane (1) with 4,4-dimethyl-2,3-dihydro-γ-pyran (2) leads to unstable epoxide 5. Secondary deuterium isotope effects in the epoxidation reaction were obtained by running intermolecular competition reactions between 2 and its deuterated analogues 3α and 3β. The observed inverse kinetic isotope effects (Table I) are expected[8] when deuterium is substituted at a carbon undergoing rehybridization from sp^2 to sp^3. The measured isotope effects at 25 °C indicate a greater degree of rehybridization at the β position than at the α position in the transition state leading to epoxide. These results are not consistent with a mechanism involving a symmetrical transition state for the formation of 5. Rather, they demonstrate that the reaction is a nonsynchronous concerted process. This nonsynchronicity is consistent with a contribution of canonical structure 15 to the resonance hybrid of 2. The kinetic isotope effect study was repeated



2 15

at −78 °C. The measured inverse isotope effects are greater at the lower temperature (Table I) as expected.[12,13] The results again indicate that there is a greater degree of rehybridization at the β carbon than at the α carbon.

A comparison of the current results with those obtained earlier[7] in the reaction of singlet oxygen with 2 reveals some differences. As in the dioxirane reaction, the singlet oxygen reaction isotope effect results indicate a greater change in rehybridization at the β position of 2 than at the α position. Unlike the dioxirane reaction, however, the singlet oxygen reaction to give dioxetane showed no appreciable rehybridization at the α position when the reaction was run in acetonitrile and only a very small effect when benzene was the solvent.

It is also appropriate to compare the current results with those obtained in two related systems. In the first of these, Hanzlick and Shearer used deuterium isotope effects to investigate the mechanism of epoxidation by MCPBA.[14] In this work, deuterium isotope effects were measured at the α (carbon bearing the aromatic group) and the β (carbon distal to the site of aromatic substitution) positions in a series of 4-substituted styrenes. Their results show a significant degree of rehybridization (sp^2 to sp^3) at the β carbon while the α carbon remains essentially sp^2 hybridized. The authors interpreted their results as indicating an unsymmetrical transition state for the epoxidation reaction. In the second related study, Collman and co-workers measured[15] a secondary deuterium isotope effect in the competitive epoxidation of styrene and styrene-d_8 with the cytochrome P-450 model (tetraphenylporphyrinato)manganese(III) chloride (MnTPPCl), with hypochlorite used to activate the MnTPPCl. The authors first showed that the rates of epoxidation of styrene and styrene-d_8 were identical. The observed isotope effect (0.89) in the competitive epoxidation indicated that both olefinic carbons of the oxo–olefin complex have considerable sp^3 character. Since the observed isotope effect is the result of a competitive reaction between substrates with identical k_2 values, the effect must arise in the equilibrium for substrate binding. The authors conclude that their results support the existence of a true oxo–olefin intermediate.

Experimental Section

Instrumentation. ^1H NMR spectra were recorded with either a 300- or 60-mHz NMR spectrometer. ^{13}C NMR spectra were recorded on a 300-mHz spectrometer. Deuterated chloroform, acetone, toluene, and Freon-12 (Aldrich) were used as solvents. All chemical shifts are reported relative to internal TMS at δ 0.00. GC–MS work was accomplished using an HP-5992 Model gas chromatograph–mass spectrometer. The peakfinder program was used for product analysis, and the SIM (selected ion monitoring) program was used for obtaining ion ratios. Gas chromatography was performed on a Perkin-Elmer Sigma 2000 gas chromatograph interfaced with either a Model 3390A Hewlett-Packard or Model CR3A Shimadzu chromatopac integrator. Preparative GC work was performed on a Varian-Aerograph Model 700 gas chromatograph. Melting points were obtained on a commercial melting point apparatus and are uncorrected.

Materials. A. Solvents. Acetone (Aldrich reagent grade) was distilled from anhydrous potassium carbonate prior to use. Hexane, ethyl acetate, methylene chloride, dimethyl sulfoxide (Aldrich), and absolute ethanol (U.S. Industrial Chemicals Co.) were used as received. Anhydrous ethyl ether (Fisher Scientific) and tetrahydrofuran (Aldrich) were distilled from calcium hydride, then from sodium–benzophenone, and finally from lithium aluminum hydride prior to each use.

B. Reagents. Oxone ($2\,KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, DuPont) was obtained from Aldrich Chemical Co. and used as received. Thioanisole, methyl phenyl sulfoxide, *m*-chloroperbenzoic acid, lithium aluminum hydride, lithium aluminum deuteride, deuterium oxide, 3,3-dimethylglutaric acid, 3,3-dimethylglutaric anhydride, hexamethyldisilazane, benzyl bromide, and chlorotrimethylsilane (all obtained from Aldrich) were used as received.

C. Chromatography. Gas chromatography on the PE-Sigma 2000 was carried out with a J & W Scientific, Inc. DB-210 capillary column (15 m × 0.25 mm, liquid phase 0.0005 mm) or with a 3% OV-17 on Chromosorb W-HP (80–100 mesh, 4 ft × $^1/_8$ in.) column. GC on the Varian-Aerograph was accomplished using a Supelco 15% OV-25 on Chromosorb Q (80–100 mesh, 18 ft × $^1/_4$ in.) or a Supelco SF-96 methyl silicone (80–100 mesh, 18 ft × $^1/_8$ in.) column. GC–MS work was performed using a J & W Scientific, Inc. DB-5 (15 m × 0.528 mm, 0.0015-mm film thickness) megabore column. Dry flash chromatography was performed according to a modified procedure of Harwood[16] using Kieselgel 60 (230–400 mesh ASTM, P. J. Cobert and Associates). Thin-layer chromatography was accomplished on Eastman chromagran silica sheets or Analtech silica uniplates (20 × 20 cm, 250 μm). Chromatographic separations on the Chromatotron Model 7942T (Harrison Research) were accomplished using 1-mm Kieselgel 60 PF_{254} gypsum plates.

General Method for the Preparation of Dimethyldioxirane (1). The general method has been described.[17] Solutions obtained in this manner were assayed for dioxirane content using thioanisole (2 mL (0.20 mmol in acetone) to 1 mL of dioxirane solution). GLC analysis was conducted on a DB-210 capillary column with the following program: temperature 1 100 °C; time 1, 3 min; rate 20 °C/min; temperature 2, 180 °C; time 2, 4 min; detector 200 °C; injector, 200 °C; inlet *P*, 20 psi. Dioxirane concentrations were calculated based on the amount of phenyl methyl sulfoxide produced. Excess sulfide was used in order to suppress sulfone formation. GLC examination verified the absence of sulfone. Areas were corrected for detector response factors using solutions of the authentic compounds. The concentrations of dimethyldioxirane obtained were in the range of 0.05–0.12 M.

Preparation of 4,4-Dimethyl-2,3-dihydro-γ-pyran (2). Method A.[7] a. Synthesis of 4,4-Dimethyltetrahydropyran-2-one. Sodium metal (25 g, 1.09 mol) was placed in a 500-mL round-bottom flask equipped with a mechanical stirrer, a 500-mL dropping funnel containing 3,3-dimethylglutaric anhydride (20

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g, 0.141 mol) in 180 mL of warm absolute ethanol, and a reflux condenser protected with a drying tube. The alcoholic solution was added as quickly as possible, typically in 30 min. Heat was applied with a heating mantle and the solution refluxed overnight, during which time water (180 mL) was added slowly in order to replace the ethanol that was lost during the reflux. The solution was then acidified with concentrated HCl (90 mL) and extracted with ether (4 × 125 mL). The extracts were washed with H_2O (1 × 100 mL) and dried over a 3:1 mixture of $MgSO_4$–$KHCO_3$. The solvent was removed under reduced pressure (10–100 mmHg) and the residue was distilled (85–90 °C (7 mmHg)), affording 1.7 g of the lactone (isolated yield 8.5%). Purity was verified by TLC R_f value and NMR: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 6 H); 1.75 (t, 2 H, J = 6 Hz); 2.35 (s, 2 H); 4.40 (t, 2 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 28.50, 29.45, 35.56, 43.86, 63.32, 171.30. The proton NMR data are consistent with those previously reported.[7]

b. Synthesis of 4,4-Dimethyl-2,3-dihydro-γ-pyran. The lactone 4,4-dimethyltetrahydropyran-2-one (6.4 g, 0.049 mol) was dissolved in anhydrous diethyl ether (120 mL) in a three-necked 500-mL round-bottom flask equipped with a 250-mL addition funnel. Argon was passed through the cooled (−10 °C, ice–salt bath) solution. Lithium aluminum hydride (LAH; 0.60 g, 0.015 mol) in 130 mL of anhydrous ether was added dropwise over 10 min as the solution was stirred magnetically. The solution was stirred for 3 h as it was allowed to warm to room temperature. The reaction was quenched by the sequential addition of 0.7 mL of H_2O, 0.7 mL of 3 M NaOH, and 2.1 mL of H_2O. The solution was stirred for an additional 15 min, during which time a precipitate formed. The precipitate was filtered off and the solvent removed under reduced pressure (10–100 mmHg) to give 5.1 g of crude product. A catalytic amount of *p*-toluenesulfonic acid was added, and the mixture was distilled from 100–200 °C (25 mmHg). A colorless biphasic liquid was obtained. The organic layer was pipetted from the aqueous layer to give 2.9 g of the dihydropyran (isolated yield 52%). The product was characterized by NMR: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 6 H); 1.63 (t, 2 H, J = 5 Hz); 4.05 (t, 2 H, J = 5 Hz); 4.40 (d, 1 H, J = 7 Hz); 6.20 (d, 1 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 27.65, 30.42, 37.45, 62.92, 112.15, 141,64. The proton NMR data are consistent with those previously reported.[7]

Preparation of 4,4-Dimethyl-2,3-dihydro-γ-pyran (2). Method B. a. Preparation of 4,4-Dimethyltetrahydropyran-2-one.[18] All of the glassware used was flamed under argon just prior to use. Lithium aluminum hydride (2.2 g, 0.058 mol) in 150 mL of anhydrous THF was placed in a 500-mL round-bottom flask equipped with an addition funnel containing the anhydride (14.2 g, 0.10 mol) in 110 mL of THF, a low-temperature thermometer, and a mechanical stirrer. The LAH solution was cooled to −55 °C (dry ice–acetone). The solution of anhydride was added at a rate to maintain the reaction temperature at −55 ± 5 °C (usually 30 min). The reaction flask was gradually warmed to 0 °C and stirred for 20 min. The mixture was cooled to −15 °C, and 40 mL of 6 N HCl were added dropwise to quench the reaction. The cold bath was removed and the mixture stirred for an additional 20 min. The solution was extracted with ether (3 × 50 mL), and the combined extracts were dried over Na_2SO_4. The solvent was removed in vacuo (10–100 mmHg), and fractional distillation (126–128 °C (22 mmHg)) provided 9.1 g of the lactone (71.1% isolated yield). Spectroscopic data were identical with those given previously. This material was used to prepare **2** as described in the previous text.

Preparation of Deuterated Dihydropyrans. a. Synthesis of 4,4-Dimethyl-5-deuterio-2,3-dihydro-γ-pyran (3β).[7] The lactone 4,4-dimethyltetrahydropyran-6-one (13.61 g, 0.106 mol), 13.7 mL of D_2O, and triethylamine (1.13 g, 1.56 mL, TEA) were combined in a 500-mL round-bottom flask equipped with a magnetic stirring bar and an H_2O-cooled condenser. The solution was heated to 105 °C for 24 h. The TEA/D_2O was distilled off, and fresh TEA and D_2O were added. After seven exchanges, fractional distillation afforded 8.4 g of the lactone-d_2. (Note: Use of T-60 ^{1}H NMR indicated 100% incorporation of deuterium. Subsequent GC–MS measurements indicated 88.1% D-incorporation after reduction and elimination.) The lactone was dissolved in 150 mL of anhydrous ether in a 500-mL round-bottom flask equipped with a magnetic stirring bar and a 250-mL addition funnel containing LAH (0.79 g) in 200 mL of anhydrous ether. The reaction vessel was cooled to −10 °C, and the LAH solution was added dropwise. The reaction mixture was gradually warmed to room temperature (~3 h). The reaction was quenched by the sequential addition of 0.9 mL of H_2O, 0.9 mL of 3 M NaOH, and 2.7 mL of H_2O. The solution was stirred for 20 min, and the white precipitate that formed was filtered off. Solvent was removed, and a catalytic amount of *p*-TsOH was added. The mixture was distilled at 20 mmHg as the temperature was gradually raised to 150 °C (major fraction, 60–110 °C). Separation of the organic layer provided 2.52 g of the 5-deuterated dihydropyran (35% isolated yield): ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 6 H); 1.62 (t, 2 H, J = 6 Hz); 3.95 (t, 2 H, J = 6 Hz); 6.25 (s, 1 H); GC–MS 88.1% deuterium incorporation based on a comparison of the 97.1 and 98.1 base peaks for undeuterated and deuterated compounds, respectively.

b. Synthesis of 4,4-Dimethyl-6-deuterio-2,3-dihydro-γ-pyran (3α).[7] A 500-mL round-bottom flask containing 4,4-dimethyltetrahydropyran-2-one (8.4 g, 0.066 mol) in 150 mL of anhydrous ether was equipped with a magnetic stirring bar and a 500-mL addition funnel containing lithium aluminum deuteride (LAD; 0.79 g, 0.020 mol) in 200 mL of ether. The lactone solution was cooled to −10 °C and the LAD solution added dropwise. The solution was gradually warmed to room temperature (4 h). The reaction was quenched by the sequential addition of 0.9 mL of H_2O, 0.9 mL of 3 M NaOH, and 2.7 mL of H_2O. The solution was stirred for 20 min, and the white precipitate that formed was filtered off. The solvent was removed in vacuo (10–100 mmHg). A catalytic amount of *p*-TsOH was added and the mixture distilled at 10 mmHg (major fraction, 60–100 °C). The 6-deuterated dihydropyran was separated from the H_2O layer, affording 0.9 g of product (12% isolated yield). (Note: The yield described does not represent the true yield given by the procedure. A considerable amount of product was lost as a result of an equipment failure during distillation.): ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 6 H); 1.60 (t, 2 H, J = 5 Hz); 3.95 (t, 2 H, J = 5 Hz); 4.55 (s, 1 H); GC–MS 94.5% deuterium incorporation.

Competition Reactions with 1. Equimolar amounts of dihydropyran **2** and either dihydropyran-*5-d* (3β) or dihydropyran-*6-d* (3α) were combined to prepare a standard solution. A blank solution was then prepared using 2 mL of the standard solution and acetone. The volume of acetone used was the same as that used in the reactions in order to maintain approximately the same concentrations. Reaction solutions were prepared using 2 mL of the standard solution (7.5×10^{-5} mol each dihydropyran) and the amount of **1** required for the desired degree of reaction completion for the experiment performed: 2.8×10^{-5} mol of **1** for the ca. 20% completion reaction and 2.1×10^{-5} mol of **1** for the ca. 15% completion reaction. In each case, the minimum ratio of total substrate to **1** was 5:1. Two different sets of experiments were performed. The first set involved reaction to 20% completion at 25 °C. In the second set, reaction completion was 15% and the temperature was −78 °C. The solutions were allowed to react for 1 h under the chosen reaction conditions and were then analyzed by GC–MS. An independent GC experiment verified that total product formation remained unchanged after the 1 h reaction time. The concentration of the solution of **1** was determined separately, with use of the thioanisole method, at the time the solutions of **1** were added to the reaction solutions.

The kinetic data were obtained using a Hewlett-Packard Model 5992 GC–MS. The SIM proogram was used. GC–MS conditions were as follows: temperature 1, 20 °C; time 1, 7 min; rate 15 °C/min; temperature 2, 180 °C; time 2, 0 min; injector 130 °C; EM = 15; dwell times 100 ms; underresolved peak mode. At the end of the GC run the area for each ion peak was integrated by the program. In these experiments, the following peaks were monitored: the base peak (B) for dihydropyran (97.1), the base peak plus one (B + 1) for deuterated dihydropyran (98.1), the product molecular ion peak (128.2), and product molecular ion peak + 1 (129.2). The molecular ion peak areas were not used in the calculations. At the time of the experiment, we were not able to calibrate these areas independently with authentic material. Only changes in the B to B + 1 ratio of the competing dihydropyrans were used. These base peaks correspond to loss

(18) Bloomfield, J. J.; Lee, S. L. *J. Org. Chem.* **1967**, *32*, 3919.

of CH_3. For each day of data collection, a solution of nondeuterated dihydropyran was injected into the GC–MS and analyzed a minimum of three times. This procedure permits one to determine the ^{13}C contribution to the 98.1 (B + 1) component of the B to B + 1 ratio. The blank solution (dihydropyran–dihydropyran-*d*–acetone) was then analyzed. For each injection, the ^{13}C contribution to the B + 1 area was subtracted out to generate the corrected area, (B + 1)′. The B to (B + 1)′ ratio provides a true measure of the ratio of dihydropyran to dihydropyran-*d*. Since the total weight of dihydropyrans in the standard solution and reaction aliquots were known, the initial number of moles of each substrate could be calculated. The reaction solutions were then analyzed and the B to (B + 1)′ ratios determined. Since the concentration of 1 had been measured as previously described, the total number of moles of substrate reacted could be determined. This calculation assumes that 100% of 1 reacts with the dihydropyrans. In a separate control experiment, it was shown that >95% of 1 had reacted. In fact, if only 95% of 1 had reacted, the change in the reported isotope effects would be well within the reported relative standard deviations (Table I). At the end of the kinetic runs, the reaction solutions were analyzed using the Peakfinder program (40–400 amu). In each case, the reaction products were the epoxide (128.2 amu) accompanied by some diol.

Product Studies. a. GC–MS Product. For product studies, a 15% solution of 4,4-dimethyl-2,3-dihydro-γ-pyran in acetone was treated with an equimolar amount of freshly prepared 1. Analysis of this reaction solution by GC–MS showed a molecular ion peak at 128.2 amu corresponding to the epoxide **5**. Analysis of the reaction solution using ^1H NMR showed a new methine resonance at δ 4.8 (d, J = 2 Hz). Additional absorptions included a complex multiplet at 3.5–3.7. The NMR spectrum was complicated by strong resonances from the acetone solvent.

b. Isomeric Diols (10). Removal of the solvent in vacuo (20–100 mmHg) from the reaction solution gave a mixture of isomeric 2,3-dihydroxy-4,4-dimethyltetrahydropyrans. These diols are presumably the trans diol with diequatorial substituents **10a** and either the conformer **10b** of **10a** or the cis diol with the 2-hydroxyl group in the axial position **10c**. The ratio of isomers, as determined by NMR integration of the methine hydrogens, varied from 1:1 to 2:1 from one preparation to another: IR (neat) 3383 (OH), 2953, 1708, 1467, 1364, 1262, 1175, 1128, 1011, 956, 880, 850, 764 cm^{-1}; GC–MS molecular ion 146.2, base peak 72.3; NMR analysis could only be accomplished on the mixture of isomers; ^{13}C NMR ($CDCl_3$) δ 95.2 (CH), 92.5 (CH), 78.0 (CH), 74.9 (CH), 61.8 (CH_2), 60.8 (CH_2), 38.9 (CH_2), 34.5 (C), 33.8 (CH_2), 33.7 (C), 28.8 (CH_3), 25.6 (CH_3), 24.8 (CH_3), 18.5 (CH_3); ^1H NMR (assignments are based on the relative intensities of all protons in a sample containing a 2:1 mixture of the isomers) **trans diol 10a** (acetone-d_6) δ 1.05 (s, 3 H); 1.12 (s, 3 H); 1.4–1.7 (m, 2 H); 3.08 (d, 1 H, J = 7.8 Hz); 3.6–3.7 (m, 2 H); 4.65 (d, 1 H, J = 7.8 Hz); **diol 10b or 10c** (acetone-d_6) δ 1.07 (s, 3 H); 1.15 (s, 3 H); 1.3–1.8 (m, 2 H); 3.2 (d, 1 H, J = 1.5 Hz); 3.55–3.95 (m, 2 H); 5.0 (d, 1 H, J = 1.5 Hz). Anal. ($C_7H_{14}O_3$) C, H. Several additional (2–3) broad singlets in the 2.5–4.5 region were also evident. Variable-temperature NMR was carried out in acetone-d_6 and toluene-d_8 over the temperature range −90 to 100 °C. No evidence for conformational isomerization could be detected in this range.

c. *trans*-2-(3′-Chlorobenzoxy)-4,4-dimethyl-3-hydroxytetrahydropyran (13). A solution of **2** (1.0 g, 8.92 mmol) in distilled CH_2Cl_2 was prepared. The solution was stirred magnetically at 0 °C, and a 10% solution of $NaHCO_3$ was added (30 mL). MCPBA (1.70 g, 9.88 mmol) in 20 mL of CH_2Cl_2 was added dropwise over a 30-min period. The reaction mixture was stirred for an additional 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 10% $Na_2S_2O_3$ (3 × 25 mL or until the wash water gave a negative starch/iodide test). Finally, the organic layer was washed with 10% $NaHCO_3$ (1 × 25 mL) followed by a wash with 25 mL of a saturated brine solution. The organic layer was dried over anhydrous $MgSO_4$, and removal of solvent in vacuo (20–100 mmHg) afforded 1.90 g of the mono-*trans*-*m*-chlorobenzoate derivative of the diol as colorless prisms, mp 75–77 °C (75% isolated yield): IR (KBr) 3665 (OH), 3079, 2968, 2871, 1721 (C=O), 1575, 1466, 1423, 1366, 1297, 1246, 1175, 1134, 1066, 1011, 960, 897, 814, 766, 753, 737, 674, 626, 494 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 3 H); 1.30 (s, 3 H); 1.65–1.80 (m, 2 H); 2.4 (br s, 1 H); 3.57 (d, 1 H, J = 6.7 Hz); 3.9–4.1 (m, 2 H); 6.05 (d, 1 H, J = 6.7 Hz); 7.5–8.3 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 164.3, 134.5, 131.2, 129.8, 129.7, 128.0, 95.0, 74.9, 61.8, 37.0, 34.1, 27.6, 20.6. Anal. ($C_{14}H_{16}O_4Cl$) C, H, Cl.

d. Base Hydrolysis of *trans*-2-(3′-Chlorobenzoxy)-4,4-dimethyl-3-hydroxytetrahydropyran. The benzoate (0.65 g, 2.3 mmol) **13** was placed in a 5-mL round-bottom flask, and 2.6 mL of a 5% solution of NaOH (0.118 g, 2.88 mmol) was added. The flask was capped and the solution stirred magnetically for 3 days. The reaction solution was neutralized with 150 μL of 50% H_2SO_4. The white precipitate that formed was removed by filtration. Water was removed from the solution, leaving a white solid residue. This solid was subjected to reduced pressure (vacuum pump, 0.1 mmHg) for 1 h. Anhydrous diethyl ether was added to the flask, and some of the white solid dissolved. The ether solution was transferred to a round-bottom flask and the solvent was removed in vacuo (20–100 mmHg) to give 0.050 g of a clear, pale yellow oil. NMR analysis revealed that the product was a 1:1 mixture of the diols described previously.

e. 4,4-Dimethyl-2,3-bis[(trimethylsilyl)oxy]tetrahydropyran (11).[19] The isomeric mixture of diols (0.83 g, 5.7 mmol) was dissolved in 75 mL of pyridine. Hexamethyldisilazane (13 g, 81 mmol) and chlorotrimethylsilane (7.4 g, 69 mmol) were added, and the mixture was shaken for 30 s. After the mixture stood at room temperature for 30 min, a white ammonium chloride precipitate was observed. Equal volumes (75 mL) of cold H_2O and cold diethyl ether were added. The layers were separated and the aqueous layer extracted with ether (2 × 100 mL). The combined organic extracts were washed with cold 5% HCl (100 mL) and cold saturated $NaHCO_3$ (100 mL) and were then dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation (20–100 mmHg), affording 0.53 g of crude material. Spectroscopic analysis indicated that the derivatives of both diols had been prepared: ^1H NMR ($CDCl_3$) δ 0.90 (s); 0.93 (s); 0.98 (s); 1.2–1.65 (m); 3.04 (d, J = 7.7 Hz); 3.18 (d, J = 2.7 Hz); 3.40–3.92 (m); 4.52 (d, J = 7.7 Hz); 4.84 (d, J = 2.7 Hz); ratio of isomers = 3:1. Chromatography was accomplished on a Chromatotron with 210 mg of the mixture of TMS derivatives. Initial solvent composition (A_0) was 0.5% diethyl ether in hexane and final composition (A_f) was 2% ether in hexane. The gradient is given as follows where A_t represents the percent ether at time t:

$$A_t = A_0 + (A_f - A_0)(t/30)^3$$

Fractions were collected (40 × 8 mL) and analyzed by GPC with a DB-210 capillary column (temperature 1, 100 °C; time 1, 0 min; rate, 15 °C/min; temperature 2, 150 °C; time 2, 6–10 min; injector and detector temperature, 180 °C). Fractions 5–7 contained the trans isomer of **11** with >98% purity. The remaining fractions contained only a mixture of the isomers. The trans isomer was analyzed spectroscopically: ^1H NMR (toluene-d_8) δ 0.18 (s, 9 H); 0.25 (s, 9 H); 0.90 (s, 6 H); 1.05 (d of t, 1 H, J = 14 and 2.9 Hz); 1.34 (t of d, 1 H, J = 9.7 and 5.3 Hz); 3.13 (d, J = 7.7 Hz); 3.38 (t of d, 1 H, J = 14 and 2.9 Hz); 3.53 (m, 1 H); 4.68 (d, 1 H, J = 7.7 Hz); ^{13}C NMR (toluene-d_8) δ 97.04, 80.14, 61.01, 38.68, 35.22, 29.41, 19.96, 0.86, 0.66. Variable-temperature ^1H NMR was accomplished in toluene-d_8–Freon-12 (2:1; −70 to −110 °C), in toluene-d_8 (−70 to 25 °C), and in acetone-d_6 (20 to 50 °C). No significant changes in the spectra were observed. Anal. ($C_{13}H_{30}O_3Si_2$) C, H.

f. 2,3-Bis(benzyloxy)-4,4-dimethyltetrahydropyran (12). Freshly powdered KOH (1.5 g, 26.73 mmol) was added to 20 mL of dimethyl sulfoxide under a stream of argon. The mixture was stirred for 5 min at room temperature. A solution of 2,3-dihydroxy-4,4-dimethyltetrahydropyran (0.6343 g, 4.34 mmol) in 5 mL of dimethyl sulfoxide was added followed by benzyl bromide (1.45 g, 8.48 mmol). The reaction mixture was heated to 50 °C with an oil bath and stirred for 2 h. The reaction mixture was poured into 25 mL of H_2O and extracted with diethyl ether (5 × 20 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and saturated brine solution (2 × 25 mL) and were dried over anhydrous $MgSO_4$. Removal of solvent on a rotovap

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afforded the crude material (1.3 g) as a yellow viscous liquid. TLC analysis (silica gel, 2:8 ethyl acetate–hexane) indicated the presence of two major products (R_f 0.42 and 0.24). The crude material (0.85 g) was subjected to preparative TLC (silica gel, 20% ethyl acetate–hexanes). The band with R_f 0.42 was removed with acetone. Acetone was removed on a rotovap to afford a very pale viscous liquid (0.4351 g). Flash chromatography of the residue (R_f 0.42) on Kieselgel with 5% ethyl acetate–hexanes followed by 10% ethyl acetate–hexanes afforded 0.3925 g of the bis(benzyloxy) derivative as a colorless viscous liquid: IR (neat) 3064, 3030, 2950, 2870, 1606, 1496, 1454, 1362, 1249, 1215, 1148, 1098, 1028, 955, 734, 697 cm^{-1}; ^1H NMR and ^{13}C spectra indicated a mixture of the isomers of the bis(benzyloxy) derivative; ^1H NMR ($CDCl_3$) δ 0.99 (s), 1.01 (s), 1.03 (s), 1.18 (s), 1.35–1.65 (m), 2.94–3.20 (m), 3.37–3.96 (m), 4.41–4.68 (m), 4.73–4.95 (m), 7.10–7.45 (m, aromatic H). Variable-temperature ^1H NMR was accomplished in $CDCl_3$ over a temperature range of 22–55 °C. No significant changes in the spectrum were observed: ^{13}C NMR ($CDCl_3$) δ 20.98 and 21.57 (CH_3), 28.46 and 29.74 (CH_3), 33.65 and 34.87 (>C<, C-4), 38.33 and 38.77 (C-5, $-CH_2-$), 57.20 and 60.76 (C-6, $-CH_2-$), 69.24 and 70.58 ($-OCH_2Ph$), 72.31 and 74.71 ($-OCH_2Ph$), 81.98 and 83.72 (C-3, –CH–), 96.10 and 101.12 (C-2, –CH–), 127.31, 127.35, 127.41 and 127.45, 127.64, 127.69, 127.71 and 127.77, 128.12, 128.15, 128.21 and 128.27 (phenyl ring C), 138.05 and 138.20 (ipso C of phenyl), 138.73 and 138.97 (ipso C of phenyl); mass spectrum (EI, 70 eV) 235 (1, M^+, $-C_6H_5CH_2-$), 162 (5), 112 (8), 99 (12), 91 (100), 92 (8), 69 (1), 65 (4), 43 (1); mass calcd 326.41. Anal. ($C_{21}H_{26}O_3$): C, H.

g. 2-(Benzyloxy)-3-hydroxy-4,4-dimethyltetrahydropyran. The band at R_f 0.24 in the preparation of the bis(benzyloxy) compound was also separated and extracted with acetone. The solvent was removed on a rotovap to yield a pale yellow viscous liquid (0.1760 g). Flash chromatography of the residue (R_f 0.24) on Kieselgel with 5–15% ethyl acetate–hexanes afforded a very light yellow viscous liquid that solidified to a pale solid at 20 °C (0.1670 g): IR (neat) 3473 (OH), 3963, 3030, 2951, 2870, 1606, 1497, 1454, 1379, 1364, 1257, 1208, 1173, 1141, 1084, 1025, 979, 735 and 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s), 1.00 (s), 1.07 (s), 1.08 (s), 1.30–1.68 (m), 1.71 (br s), 2.07 (d, J = 9.4 Hz), 2.19 (d, J = 2.9 Hz), 3.10–3.95 (m), 4.40–4.60 (m), 4.75–4.95 (m), 7.20–7.45 (m, Ar H); ^{13}C NMR ($CDCl_3$) δ 19.50 and 21.43 (CH_3), 28.51 and 28.60 (CH_3), 33.57 and 34.02 (C-4, >C<), 37.26 and 38.40 (C-5, $-CH_2-$), 58.02 and 61.29 (C-6, $-CH_2-$), 69.85 and 70.68 ($-OCH_2Ph$), 74.61 and 76.56 (C-3, –CH–), 98.11 and 100.84 (C-2, –CH–), 127.62, 127.77, 127.91, 128.40 (phenyl ring C), 137.57 and 137.73 (ipso C of phenyl); Mass spectrum (EI, 70 eV) 145 (2.5, M^+, $-C_6H_5CH_2-$), 128 (1), 112 (4), 108 (2), 100 (4), 99 (58), 93 (8), 92 (100), 91 (92), 89 (2), 72 (10), 69 (5), 65 (11), 55 (5), 43 (57); mass calcd 236.20. Anal. ($C_{14}H_{20}O_3$): C, H.

h. 4,4-Dimethyltetrahydropyran-3-one (14). Method A. A solution of 1 (0.187 g, 2.6 mmol, 0.075 M, 35 mL) was added to 2 (0.30 g, 2.72 mmol) and the reaction solution fractionally distilled in order to remove most of the acetone solvent. The residual liquid was subjected to preparative GPC (SF-96 methyl silicone column, column temperature, 90 °C; injector and detector temperature, 190 °C; collector temperature, 200 °C; flow rate, 150 mL/min). The major product had a retention time of 5.5 min and was collected from multiple injections (10 × 100 μL) of the residual liquid. The ^1H NMR spectrum indicated that the collected material was a mixture with the major component being 14.

4,4-Dimethyltetrahydropyran-3-one (14). Method B. MCPBA (0.6310 g, 3.65 mmol) was added to 4,4-dimethyl-2,3-dihydro-γ-pyran (0.2870 g, 2.56 mmol) in 15 mL of benzene. The solution, which became warm immediately, was stirred magnetically for 1 h at room temperature. The solution was extracted with 5% $NaHCO_3$ (3 × 25 mL) followed by a saturated brine wash (2 × 25 mL). The organic layer was dried with $MgSO_4$. Preparative GC of the solution on a 18 ft × $^1/_4$ in. 15% OV-25 column (column temperature 100 °C; injector temperature 135 °C; detector temperature 180 °C; collector temperature 100 °C; flow rate 55–60 mL/min) allowed collection of the product at a retention time of 14 min as a colorless liquid (0.065 g): IR (neat) 2969, 2870, 1717 (C=O), 1467, 1432, 1386 and 1365 (*gem*-dimethyl), 1334, 1300, 1132, 1110 (COC), 1040, 1010, 979, 923, 856, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 6 H, *gem*-dimethyl), 1.90 (t, J = 5.67 Hz, 2 H), 3.91 (t, J = 5.67 Hz, 2 H), 4.04 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.23 $(CH_3)_2$, 39.18 (C-5, $-CH_2-$), 42.90 (C-4, >C<), 63.60 (C-6, $-CH_2-$), 72.02 (C-2, $-OCH_2-$), 212.42 (C-3, C=O); MS (EI, 70 eV) m/z (relative intensity) 128 (M^+, 51), 70 (94), 56 (8), 55 (100), 42 (24); mass calcd 128.16. Attempts to obtain an elemental analysis on the ketone indicated that it is very hygroscopic. It was converted to its 2,4-dinitrophenylhydrazone, which did give a correct analysis.

i. 4,4-Dimethyltetrahydropyran-3-one 2,4-bis(nitrophenyl)hydrazone: lemon yellow needles, mp 129–131 °C; IR (KBr) 3309, 2958, 1617, 1590, 1540, 1515, 1429, 1337, 1310, 1210, 1136, 1094, 1074, 1050, 922, 842, 832, 742, 706 cm^{-1}. Anal. ($C_{13}H_{16}H_4O_5$): C, H, N.

Acknowledgment. We gratefully acknowledge support of this work by The National Institutes of Health (Grant No. ES01984). Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the ACS, for partial support of this research. The Varian XL-300 NMR Spectrometer was purchased with partial support from The National Science Foundation. We also thank Professor R. E. K. Winter for valuable assistance with the GC–MS work. This manuscript was prepared while R. W.M. was a visiting professor at University College Cork, Ireland. I thank Professor M. A. McKervey and his colleagues at University College Cork for the Hospitality shown me during my visit.