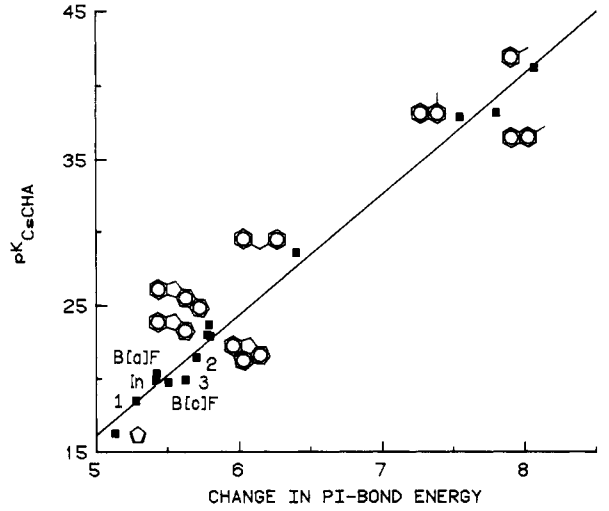

Figure 1. Correlation of pK_{CsCHA} with SCF-π ΔE_π values. The regression line is $pK = -23.153 + 7.887\Delta E_\pi$, $r = 0.993$.

saturated NH_4Cl. Under a red bulb the mixture was extracted with 50 mL of hexane and washed with 20 mL of NH_4Cl solution. The organic layer was dried over $MgSO_4$ and evaporated with 1 g of Florisil to dryness. This product was placed on a column (5 × 20 cm) packed with dry, deoxygenated Florisil under N_2 and eluted with degassed hexane. The solvent was evaporated to give a white solid. The solid was recrystallized from pentane at dry ice temperatures: yield 1.12 g (62%); mp 82.5–83.5 °C (lit.[4] mp 83–84 °C); ^1H NMR (CCl_4) δ 3.96 (m, 2 H), 5.88 (dt, J = 10, 4.5 Hz, 1 H), 6.42 (dt, J = 10, 2.5 Hz, 1 H), 6.75 (d, J = 7.5 Hz, 1 H), 7.15 (m, 5 H); mass spectrum, m/e 82 (7), 165 (100), 166 (44); low-voltage mass spectrum, m/e 165 (8), 166 (100), 167 (14). Note that even at low voltage some formation of M − 1 cannot be avoided.

6*H*-Benzo[*cd*]pyrene (3). This compound as donated by Professor I. Murata (Osaka University) and also prepared by his method[1] was purified by chromatography twice on alumina (Woelm, activity grade 1) under argon with degassed 1:3 benzene–hexane and was stored under argon in the dark.

Acidity Measurements. The spectra and extinction coefficients of the cesium salts and their equilibria with indicator hydrocarbons were determined as described previously.[5] Statistical corrections were applied to give results on a per-hydrogen basis.[6]

Acknowledgment. This work was supported in part by USPH Grant GM-12855 and NSF Grant CHE 79-10814.

Registry No. 1, 203-80-5; 2, 199-94-0; 3, 191-33-3; toluene, 108-88-3; 2-methylnaphthalene, 91-57-6; 1-methylnaphthalene, 90-12-0; diphenylmethane, 101-81-5; 9*H*-benzo[*def*]fluorene, 203-64-5; 10*H*-benzo[*b*]fluorene, 243-16-3; fluorene, 86-73-7; 7*H*-benzo[*c*]fluorene, 205-12-9; 11*H*-benzo[*a*]fluorene, 238-84-6; indene, 95-13-6; cyclopentadiene, 542-92-7; perinaphthenone, 548-39-0.

An Unexpected Product from the Peracid Oxidation of Furan Derivatives and a New ϵ-Lactone Synthesis

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Previous work in our laboratory has shown that certain furanosesquiterpenes are hepatotoxins.[1] The toxicity of these compounds is enhanced by the cytochrome oxidase enzyme system.[2] Efforts to elucidate the structures of in vitro metabolites are running concurrently with model studies involving the chemical oxidations of furans. This paper describes the results of the latter, using *m*-chloroperbenzoic acid (*m*CPBA), which is occasionally used as a mimic for cytochrome oxidase.[3]

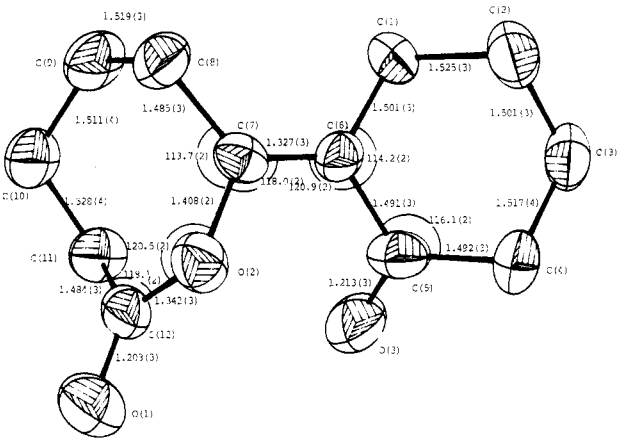
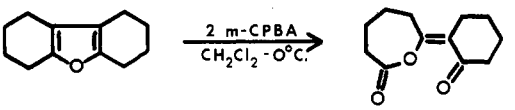


Figure 1. Perspective view of the molecular structure of lactone **2**.

In the only other example of peracid oxidation of a furanosesquiterpene, lindestrene, was shown to consume 1 mol of perbenzoic acid to form the γ-lactone via the NIH shift reaction.[4] In contrast, the reaction reported herein (eq 1) produces a stereospecific ϵ-lactone in nearly quantitative yield from the consumption of 2 mol of perbenzoic acid. The transformation is complete in 5 min at 0 °C. In an experiment where only 1 mol of peracid is used, only one-half of the furan substrate reacted to form the ϵ-lactone. Since no intermediate is observed during this procedure, the addition of both peracid molecules must be facile.



(1)

1 2

The basic structure for the new ϵ-lactone, **2**, followed directly from ^1H and ^{13}C NMR and IR spectroscopy. However, the stereochemistry about the double bond was not evident from these data and necessitated a single-crystal X-ray analysis. The results presented in Figure 1 clearly establish the detailed structure including the *Z* character of the olefinic moiety.

A second furan substrate, which is a better model for naturally occurring furan compounds, was also studied (eq 2). The major difference in the ^{13}C NMR data between structures **2** and **4** was the presence of a doublet at 190 ppm in the gated decoupled spectrum of **4**. Also, when **4** was derivatized with 2,4-DNP reagent, this resonance

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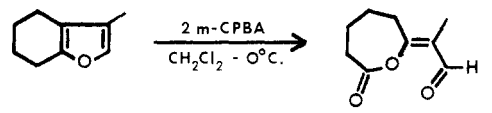


(2)

3 4

shifted. Thus, the presence of an aldehyde group was confirmed. Data for the rest of the structure is analogous to that from compound **2**. The stereochemistry of the double bond in **4** was not established by X-ray crystallography, but the NMR spectral similarities between compounds **2** and **4** appear to warrant the conclusion that **4** is also the *Z* isomer.

The general application of this reaction to other substrates has not been exercised, but its ease of manipulation, outstanding yield, and stereospecificity warrant further investigation. It should be particularly useful for lactone syntheses since the synthetic methodology for furan compounds is well-established.

The suggested reaction mechanism shown as Scheme I is proposed to proceed via a diepoxide intermediate which is consistent with the observations. Initial oxidation would be expected to occur at the more substituted double bond, forming intermediate **3a**.[5] The second addition could occur by either adding to the active enol ether **3a** to form **3b** or adding to the epoxide of **3a** to form a *trans*-hydroxy perester. Reactions reported in which addition to the epoxide were noted are considerably different than those observed.[5,6] First, the observed reaction occurs in <5 min at 0 °C, while the epoxide addition reaction required several hours at room temperature. Second, the epoxide addition reaction required a 2.8:1 excess of *m*CPBA to achieve a 52% yield with a 2:1 molar ratio of peracid to furan. Thus, we prefer to propose that the enol ether **3a** is more reactive to epoxidation than the epoxide addition reaction. The resultant diepoxide intermediate **3b** could rearrange to form **4** as shown in Scheme I. Repulsion between the existing epoxide of **3a** and the second peracid should likely promote *trans*-diepoxide formation.[5,7]

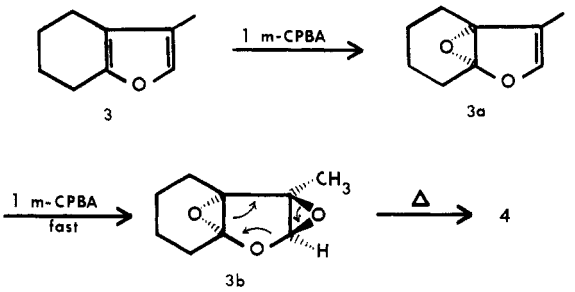
We ran the reaction with and without $NaHCO_3$ present to see if acid catalysis from the liberated benzoic acid was occurring. Both reactions gave the same product in identical yields and thereby eliminated this aspect from mechanistic consideration.

Summary. Two highly substituted furan derivatives have been epoxidized with *m*-chloroperbenzoic acid to give a functionalized and stereospecific ϵ-lactone in nearly quantitative yield. The reaction, which is completed in 5 min at 0 °C, is conducted under very mild conditions. It therefore may prove to be a facile synthetic route to lactones. An X-ray analysis of one of the products was used to confirm its stereochemistry. Finally, the reaction pathway is proposed to involve a *trans*-diepoxide intermediate.

Experimental Section

Proton and ^{13}C NMR spectra (fully decoupled and gated decoupled) were recorded with a Bruker WM 250 spectrometer. X-ray analysis was performed on a Nicolet R3m automated diffractometer at Nicolet XRD in Cupertino, CA. IR spectra were obtained from a Beckmann IR 5A spectrometer. Mass spectra were determined on a Varian CH-5 spectrometer. Solvents for

Scheme I



NMR spectra were purchased from Stohler Isotope Chemicals. Methylene chloride was obtained from Baker (reagent grade) and the *m*CPBA was purified by the procedure of Schwartz.[8]

Preparation of Perhydrobiphenylene Oxide (1). Perhydrobiphenylene oxide was prepared by a modification of a procedure reported in the literature.[9] It was isolated as a colorless oil with spectral properties identical with those reported.

Oxidation of Perhydrobiphenylene Oxide (1). To a cooled solution at 0 °C containing 0.95 g (5.47 mmol) of *m*CPBA and 0.70 g of $NaHCO_3$ was added 0.48 g (2.73 mmol) of **1** in 10 mL of CH_2Cl_2 dropwise. The reaction was stirred in an ice bath for 15 min. Sodium *m*-chlorobenzoate formed as a flocculent precipitate in the solution. The reaction mixture was washed with 10 mL of 10% $Na_2S_2O_3$, twice with 15 mL of 5% NaOH, and saturated NaCl and dried over $MgSO_4$. The solvent was removed by rotary evaporation, yielding 0.53 g (92%) of a white solid. Recrystallization from CH_2Cl_2–hexane (9:1) gave **2**: mp 111.5–112.5 °C; ^1H NMR ($CDCl_3$) 2.62 (2 H, t), 2.55 (2 H, t), 2.43 (4 H, m), 1.5–2.0 (8 H, m) ppm; ^{13}C NMR ($CDCl_3$) 201.5 (s, C-5), 172.3 (s, C-12), 150.6 (s, C-7), 125.7 (s, C-16), 42.6 (t), 33.2 (t), 29.6 (t), 28.8 (t), 27.1 (t), 25.2 (t), 24.7 (t), 23.1 (t) ppm; IR (KBr pellet) 1750, 1690, 1660, 1130, 1020 cm^{-1}; mass spectrum, *m/e* 208 (M^+), 125 (base peak). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.11, H, 7.67.

Preparation of 3-Methyl-4,5,6,7-tetrahydrobenzofuran (3). The ketal of ethyl 2-cyclohexanonecarboxylate (Aldrich) was prepared by a standard procedure, giving a yellow liquid (90% yield), bp 80–85 °C (1 mm) [lit.[10] bp 120–124 °C (8 mm)]. The ketal ester was added to 2 equiv of MeMgI to form the ketal alcohol (98%), bp 135–137 °C (16 mm) [lit.[10] bp 160–162 °C (20 mm)]. The ketal alcohol was dehydrated in benzene with a trace amount of *p*-toluenesulfonic acid, using a Dean–Stark water trap to form 2-isopropenylcyclohexanone ethylene ketal (92%): bp 94–95 °C (11 mm); IR (neat) 3020, 1650, 1445, 1155, 1070, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) 1.8 (3 H, s), 1.2–2.5 (9 H, m), 3.8 (4 H, s), 4.8 (2 H, s) ppm; ^{13}C NMR ($CDCl_3$) 146.1, 113.4, 111.1, 65.1, 65.0, 52.5, 37.0, 30.2, 25.9, 27.3, 23.7 ppm; mass spectrum, *m/e* 186 (M^+). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.56; H, 10.04.

The alkene was then epoxidized and cyclized to **3** by following a procedure from the literature.[11] The overall yield of **3** was 65% from ethyl 2-cyclohexanonecarboxylate and was isolated as a colorless liquid: bp 69–71 °C (10 mm) [lit.[12] bp 110 °C (13 mm)]; IR and ^1H NMR spectra were identical with those reported in the literature;[12] ^{13}C NMR ($CDCl_3$) 151.0, 136.8, 119.9, 117.9, 37.8, 23.4, 23.1, 20.6, 8.1 ppm; mass spectrum, *m/e* 136 (M^+).

Oxidation of 3. To a solution containing 1.18 g (6.84 mmol) of *m*CPBA in 20 mL of CH_2Cl_2 was added 0.5 g of $NaHCO_3$ and the mixture was cooled to 0 °C. To this mixture was added a solution containing 0.93 g (6.84 mmol) of **3** in 5 mL of CH_2Cl_2. After the mixture stood at 0 °C for 15 min an aliquot was removed, filtered, and transferred to a 5-mm NMR tube. The spectrum showed two peaks of equal intensity at 1.90 (d, J = 1 Hz) and

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1.80 (s) ppm. The former belonged to 3 and the latter to 4. A second addition was performed on the cooled mixture, using 1.18 g (6.84 mmol) of *m*CPBA in 5 mL of CH_2Cl_2. The reaction mixture was stirred for 15 min. An aliquot of this final solution showed only the single resonance at 1.80 ppm in the NMR spectrum. The CH_2Cl_2 solution was washed with 10 mL of $Na_2S_2O_3$ (10%), 20 mL of 5% NaOH, and twice with 15-mL portions of brine and dried over $MgSO_4$. Rotoevaporation of the CH_2Cl_2 gave 0.93 g (81%) of 4 as a clear oil: ^1H NMR ($CDCl_3$) 10.2 (1 H, s), 2.7 (4 H, m), 1.9 (4 H, m), 1.8 (3 H, s) ppm; ^{13}C NMR (gated decoupled) 189.8 (d), 170.7 (s), 164.8 (s), 123.9 (s), 33.7 (t), 31.2 (t), 25.4 (t), 23.4 (t), 9.0 (q) ppm; IR (neat) 2750, 1755, 1680, 1640, 1170, 1120, 1095, 995 cm^{-1}; mass spectrum, *m/e* 168 (M^+), 85 (base).

Preparation of 2,4-Dinitrophenylhydrazone Derivative of 4. A solution of 4 (170 mg, 1.01 mmol) in methanol was added to an acidic solution of 2,4-dinitrophenylhydrazine in methanol. The product was collected and repeated recrystallizations (ethyl acetate, ethanol, H_2O) gave an orange solid melting at 220–221.5 °C; ^{13}C NMR 171.7, 154.6, 154.3, 145.0, 138.5, 130.1, 129.7, 123.6, 119.5, 116.8, 33.9, 30.6, 26.6, 23.4, 11.5 ppm. Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.73; H, 4.63; N, 16.09. Found: C, 51.33; H, 4.62; N, 15.55.

X-ray Structural Determination of Lactone 2. Crystals of 2 were obtained by slow evaporation of a 9:1 CH_2Cl_2–hexane solution and a specimen suitable for X-ray analysis was mounted in a capillary. X-ray data collection was carried out on a Nicolet R3m automated diffractometer equipped with a Cu target X-ray tube (λ = 1.548 Å) and a graphite crystal monochromator.[13] Unit cell constants were determined to be a = 6.717 (1), b = 14.963 (2), and c = 10.923 (2) Å and β = 95.46 (1)° for a cell of monoclinic symmetry. Systematic absences of $0k0$ ($k = 2n+1$) and $h0l$ ($h + l = 2n + 1$) indicated the space group to be $P2_1/n$ (nonstandard setting of $P2_1/c$) which was confirmed by the successful solution and refinement of the structure. X-ray intensity data were measured for a total of 1117 independent reflections for $2\theta \leq 100°$, of which 1077 were considered observed with $I \geq 3\sigma(I)$. The structure was solved by direct methods which revealed the locations of all nonhydrogen atoms on the initial E map. The structure was refined to a final R value of 4.14% by full-matrix least-squares techniques with anisotropic thermal parameters for all nonhydrogen atoms. Hydrogen atoms were placed in idealized positions with isotropic thermal parameters. All structural determinations and refinement calculations were carried out with the SHELXTL package on the Nicolet R3m crystallographic system.[14] An experimental density measurement of 1.26 g/cm^3 agrees well with a calculated density of 1.27 g/cm^3 based upon four molecules of $C_{12}H_{16}O_3$ in a unit cell with a volume of 1092.9 Å^3. The final difference map revealed no abnormal features. The crystal structure of 2 consists of discrete molecules with the geometry shown in Figure 1.

Acknowledgment. We express our gratitude for financial support of this research by Montana State University and the National Science Foundation Grant CHE 7826160. We gratefully acknowledge the use of an R3m Crystallographic System provided by the Nicolet XRD Corporation. Our appreciation is further extended to J. A. S. Pribanic for technical assistance on the project and manuscript.

Registry No. 1, 1010-77-1; 2, 77136-84-6; 3, 1919-00-2; 4, 77136-85-7; ethyl 2-cyclohexanonecarboxylate, 1655-07-8; ethyl 2-cyclohexanonecarboxylate ketal, 13747-72-3; ethyl 2-cyclohexanonecarboxylate ketal alcohol, 66806-72-2; 2-isopropenylcyclohexanone ethylene ketal, 42798-04-9; 2-isopropenylcyclohexanone ethylene ketal epoxide, 77136-86-8; 4 2,4-dinitrophenylhydrazone derivative, 77136-87-9.

(13) Programs used for centering of reflections, autoindexing, refinement of cell parameters, axial photographs, and data collection were those described in: "Nicolet P3/R3 Data Collection Manual"; Calabrese, J. C., Ed.; Nicolet XRD Corporation: Cupertino, CA, 1980.

(14) Programs used for data reduction, Fourier syntheses, direct method structure solution, least-squares refinement, error analysis, least-squares planes calculation, and calculation of hydrogen position are those described in: "Nicolet SHELXTL Structure Determination Manual"; Sheldreck, G. M., Ed.; Nicolet XRD Corporation: Cupertino, CA, 1980.

Supplementary Material Available: Bond angles, bond distances, positional parameters, and thermal parameters for compound 2 (4 pages). Ordering information is given on any current masthead page.

Stereochemical Consequence of the Coupling of Lithium Dimethylcuprate with a Cyclopentenyl Allylic Lactone. Total Synthesis of *dl*-Iridomyrmecin

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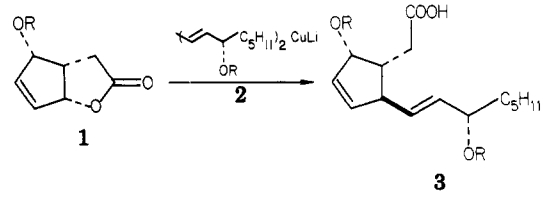
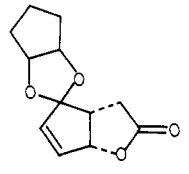
The coupling of allylic esters with lithium dialkylcuprates has received considerable attention since it was first reported by Crabbé and co-workers[2a] in 1969.[2] The studies by Goering and Singleton[2f] in 1976 clearly established that coupling of cyclic allylic acetates with lithium dimethylcuprate proceeds with anti attack and competitive α/γ substitution. More recently Trost[2h] has demonstrated in an elegant series of experiments that vinyl lactones react with alkylcyanocuprates, permitting chirality transfer via a net S_N2' process with inversion of configuration.

In contrast to the work with allylic acetates and vinyl lactones, the coupling of cyclopentenyl allylic lactones, first described by Corey,[2d] appears to be not so straightforward. For example, coupling of unsaturated lactone 1 with lithium dialkenylcuprate reagent 2 proceeds *without rearrangement and with complete inversion of configuration*, giving rise to carboxylic acid 3. The absence of any



R = *t*-Bu(Me)$_2$Si

product derived from S_N2' attack is surprising. In a closely related system,[2d] it was observed that reaction of cuprate 2 with cyclopentenyl allylic lactone 4 gave rise to comparable amounts of S_N2 and S_N2' products. The mode of attack (syn vs. anti) at the γ carbon was not specified.



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(1) Author to whom correspondence should be addressed at the Department of Chemistry, Indiana University, Bloomington, Indiana 47405.

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