Nitrosamine Removal from Trifluralin with Hydrochloric Acid. Trifluralin (30 g), containing 68 ppm of NDPA, was stirred with 6 mL of concentrated hydrochloric acid at 70 °C for 30 min. Then, the layers were separated and the organic fraction was washed with 10 mL of 10% sodium carbonate solution. The organic fraction was assayed for NDPA by the gas chromatograph method and <1 ppm was detected.

Also, the aqueous acid layer was neutralized with cold 20% sodium hydroxide solution and extracted with 6 mL of methylene chloride. Assay of the methylene chloride layer for NDPA showed <1 ppm.

Nitrosamine Removal from Ethalfluralin with Hydrogen Chloride Gas. Ethalfluralin (100 g), containing 65 ppm of EMANA, was heated to 70 °C. Then hydrogen chloride gas was bubbled through the reaction mixture at a rate of 90 mL/min. Samples were removed periodically and washed with 10% sodium carbonate solution, dried, and analyzed for EMANA. After 30 min of hydrogen chloride gas treatment, less than 1 ppm of EMANA was detected.

Nitrosamine Removal from Trifluralin with Sulfuric Acid. Trifluralin (100 g), containing 68 ppm of NDPA, was heated to 70 °C and 20 mL of 85% sulfuric acid was added. The reaction mixture was stirred vigorously for 30 min and then the layers were separated. The organic layer was washed with 10% sodium carbonate solution and analysis for NDPA showed <1 ppm. The aqueous acid layer was neutralized with 20% sodium hydroxide solution and extracted with 20 mL of methylene chloride. Analysis of the methylene chloride layer for NDPA showed 73 ppm.

Destruction of NDPA in Carbon Tetrachloride. One-hundred microliters of NDPA were dissolved in 5 mL of carbon tetrachloride contained in a 10-mL reaction flask equipped with a gas inlet adapter, magnetic stirrer, and a condenser attached to a dry ice–alcohol cold trap containing 5 mL of carbon tetrachloride. Hydrogen chloride gas was added at a rate of 12 mL/min subsurface at 50 °C. Samples were removed at various intervals and after 75 min of reaction time, 5 mL of 10% sodium carbonate solution was added.

Then, assay of the separated reaction mixture showed <1 μg/mL of NDPA. The sodium carbonate layer showed also <1 μg/mL of NDPA. Assay of the carbon tetrachloride layer from the cold trap showed 11 μg/mL of NDPA.

Treatment of Trifluralin with Iodine. To 30 g of trifluralin containing 68 ppm of NDPA was added 0.1 g of iodine. The reaction was heated at 70 °C for 1 h. Then air was passed through the mixture to remove excess iodine. A sample was analyzed for NDPA and showed 78 ppm.

Removal of BENA from Benefin. To 30 g of benefin containing 20 ppm of BENA was added 0.1 g of molecular bromine at 70 °C. The reaction mixture was stirred for 1 h. Then, 10 mL of 5% sodium carbonate solution was added. The layers were separated and the organic layer showed 1 ppm of BENA upon analysis.

Nitrosamine Removal from Trifluralin with Molecular Bromine. Trifluralin (30 g), having an average nitrosamine assay of 68 ppm, was heated to 70 °C and 0.2 g of molecular bromine was added at the surface interface. The reaction mixture was allowed to stir at 70 °C for 20 min. Then the trifluralin sample was washed with 10 mL of 10% sodium carbonate solution and the organic layer was isolated. A sample was sent for gas chromatographic assay of NDPA and less than 1 ppm of NDPA was detected.

Removal of NDPA from Trifluralin with *N*-Bromosuccinimide. Trifluralin (30 g), with an average assay of 68 ppm NDPA, was heated to 70 °C and 0.5 g of *N*-bromosuccinimide was added. The reaction mixture was stirred at 70 °C for 30 min. A sample was analyzed by gas chromatography and showed 1.7 ppm of NDPA.

Removal of NDPA from Trifluralin with Chlorine Gas. A 30-g portion of trifluralin (68 ppm of NDPA) was heated to 110 °C and chlorine was bubbled through the reaction mixture at a rate of 15 mL/min. Samples were taken periodically and assayed for NDPA. After 2 h, approximately 1.2 ppm of NDPA was detected.

Registry No.—Trifluralin, 1582-09-8; ethalfluralin, 55283-68-6; benefin, 1861-40-1; EMANA, 68630-39-7; BENA, 4549-44-4.

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(9) W. Rohde, *Justus Liebigs Ann. Chem.*, **151**, 366 (1869).
(10) While this paper was being reviewed, a paper by Swern and co-workers described macro denitrozation results using methanol and hydrogen chloride gas. See: S. K. Vohra, G. W. Harrington, and D. Swern, *J. Org. Chem.*, **43**, 1671 (1978).
(11) Our thanks to Dr. Herschel D. Porter and Mr. Kenneth H. Fuhr of Eli Lilly and Co. for the synthesis of nitrosamine standards.
(12) 2,6-Dinitro-*N,N*-dipropyl-4-(trifluoromethyl)benzenamine.
(13) *N*-Butyl-*N*-ethyl-2,6-dinitro(trifluoromethyl)benzenamine.
(14) 4-(1-Methylethyl)-2,6-dinitro-*N,N*-dipropylbenzenamine.
(15) *N*-Ethyl-*N*-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)benzenamine.
(16) See Experimental Section.
(17) See Experimental Section.
(18) U. Klement and A. Schmidpeter, *Angew. Chem.*, **80**, 444 (1968).
(19) Our thanks to Dr. Ed Day for analysis of some samples by the Thermal Energy Analyzer technique.
(20) E. S. Sanson and Y. B. Tewari, N.C.I. Frederick Cancer Research Center, Frederick, Md. Paper presented at the 5th Annual Nitrosamine Workshop, August 21–24, 1977.

Synthesis of α-Methylene-γ-butyrolactones by Rearrangements of Cyclopropylcarbinyl Substrates

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α-Methylene-γ-butyrolactones can be viewed as derivatives of homoallylic alcohols, potentially obtainable from rearrangements of cyclopropylcarbinyl derivatives. In order to test this concept, the cyclopropylcarbinyl derivatives **3a–7a** were prepared. Acid-catalyzed rearrangements of **3a** and **4a**, solvolytic rearrangements of **5a**, and $AgClO_4$-induced rearrangements of **6a** and **7a** gave the α-methylene-γ-butyrolactone **10** in good yields. The unsaturated substrates **3b–6b** were similarly prepared and shown to rearrange to α-methylene lactone **16**, showing that a suitably placed double bond can direct the regiochemistry of these rearrangements. Lactone **16** has a double bond in a position characteristic of many naturally occurring lactones.

The α-methylene-γ-butyrolactone ring is present in a wide variety of sesquiterpenes and other naturally occurring compounds.[2] Many of these compounds have biological activity; some have been shown to have tumor-inhibiting activity.[3] The α-methylene-γ-butyrolactone ring has been suggested to be of central importance to the biological activities of these compounds. Thus, considerable research activity has been directed toward the synthesis of α-meth-

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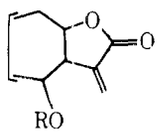
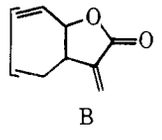
ylene-γ-butyrolactones,[4] and a number of total syntheses of naturally occurring lactones have recently appeared.[5]

In most naturally occurring α-methylene-γ-butyrolactones, the lactone ring is fused to a six-, seven-, or ten-membered ring which frequently bears additional nearby functionality. About one-half of the naturally occurring lactones have an additional oxygen substituent as shown in A (R = H or acyl), while about one-fourth have an additional double bond as shown in B.[6]



A



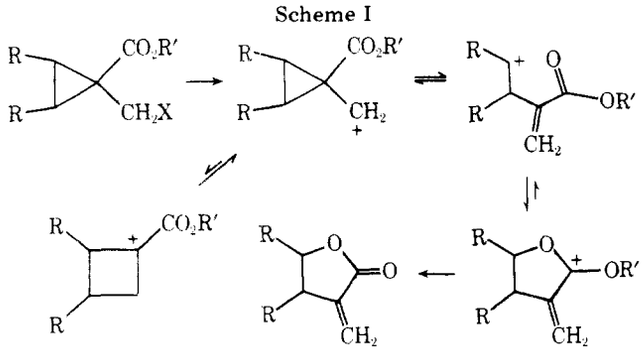
B

Much of the early work on the synthesis of α-methylene-γ-butyrolactones was directed toward the synthesis of the α-methylene-γ-butyrolactone ring itself with relatively little attention given to the additional functionality frequently found in the naturally occurring lactones. Most of the lactones with tumor-inhibiting activity possess the additional oxygen functionality of type A,[3a] and a number of reports of the synthesis of such lactones have appeared recently,[5d,e,7] culminating in the successful synthesis of the tumor inhibitor vernolepin by several groups.[5d] Although several unsaturated lactones of type B have been prepared,[5a-c,7e,g] there has been no methodology specifically directed toward the synthesis of lactones of this type.

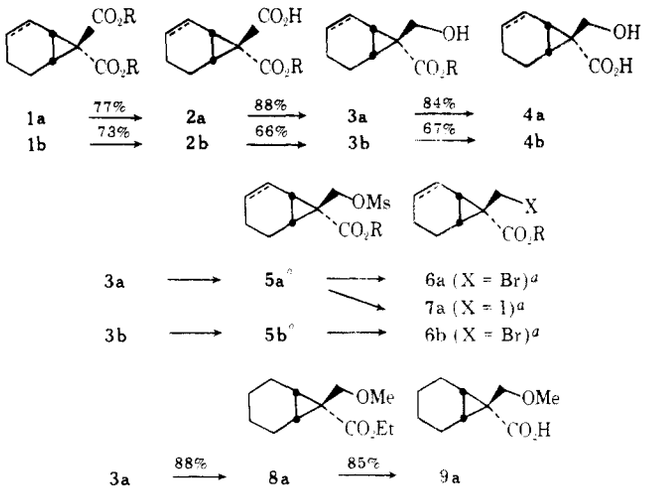
Several years ago, we reported preliminary results on a novel approach to the synthesis of α-methylene-γ-butyrolactones, involving rearrangements of carboxy- or carboalkoxy-substituted cyclopropylcarbinyl derivatives.[8] The mechanistic rationale for these rearrangements, shown in Scheme I, is based on the well-known rearrangements of cyclopropylcarbinyl cations,[9,10] with interception of the (solvated) homoallyl cation by the neighboring carboxyl group. (Such interception of cyclopropylcarbinyl or cyclobutyl cations would be less favorable because of ring strain.) According to this mechanistic rationale, either of two cyclopropane bonds could be broken, and mixtures of isomeric lactones might be expected to result from cyclopropanes not having a plane of symmetry. We anticipated that the ring openings could be directed by functionality in an adjacent ring. For example, a suitably placed double bond (as in compounds **3b–6b**) might direct (and assist) the cyclopropane ring opening by stabilizing a developing positive charge; such a directed ring opening would be expected to lead to lactones of structural type B.

We have studied rearrangements of cyclopropylcarbinyl derivatives having the cyclopropane ring fused to a six-membered ring in some detail. We have found a number of conditions under which the α-methylene-γ-butyrolactone **10** can be isolated from these rearrangements in good yields and high purity. We have additionally found that a suitably placed double bond in the cyclopropylcarbinyl substrate can control the regiochemistry of the rearrangement, resulting in the

Scheme I



Scheme II



a, R = Et, saturated six-membered ring;
b, R = Me, unsaturated six-membered ring

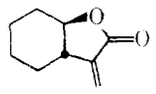
[a] Used in subsequent reactions without purification.

synthesis of an α-methylene-γ-butyrolactone (**16**) of type B.[11]

Results

Synthesis of the Cyclopropylcarbinyl Substrates. The cyclopropylcarbinyl substrates **3a–9a** and **3b–6b** were prepared by the routes shown in Scheme II. The stereochemistry of the substrates is a consequence of the selective saponification of the diesters **1a**[12] and **1b**[13] to the crystalline exo monoacids **2a**[12b] and **2b**, respectively. Conversion of **2a** to hydroxy ester **3a** was originally carried out by sodium borohydride reduction of the derived acid chloride;[8] this conversion has been carried out in higher yields (and greater reproducibility) by sodium borohydride reduction of the derived carbonate.[14]

Rearrangements of Saturated Substrates. We have studied the solvolytic, acid-catalyzed, and silver ion induced rearrangements of the cyclopropylcarbinyl substrates **3a–9a** under a variety of conditions, and have isolated the cis-fused α-methylene-γ-butyrolactone **10** from a variety of these reactions in good to high yields and purities. The cis ring fusion was assigned by comparison of the IR and NMR spectra of **10** with published values for this compound[15] and for the analogous trans lactone **14**,[15] and by comparison with an independently prepared sample of **14**. The best conditions for the



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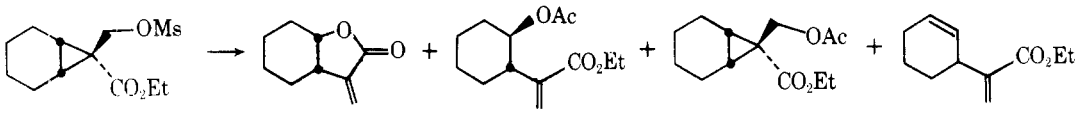
preparation of **10** are summarized in Table I.

Solvolysis of the mesylate ester **5a** in acetic acid or acetic acid/potassium acetate gave a mixture of the α-methylene lactone **10**, the homoallylic acetate **11**, the cyclopropylcarbinyl acetate **12**, and the diene **13**[16] (see Scheme III). For comparison, literature results on a related system lacking the CO_2Et group are included in Scheme III.[17,18] Solvolysis of **5a** in the less nucleophilic medium trifluoroacetic acid proceeded more rapidly to give a mixture containing lactone **10** in somewhat greater amounts. This mixture was not characterized in detail.

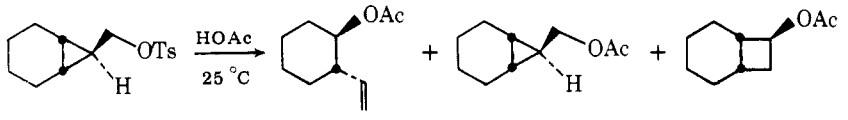
Heating solutions of mesylate ester **5a** in dry aprotic solvents (dioxane, ethylene dichloride, acetonitrile) resulted in product mixtures consisting predominantly of diene **13** and lactone **10**, with diene predominating over lactone (by VPC).

Scheme III



5a **10** **11** **12** **13**

conditions	percentage of product by VPC			
HOAc, KOAc, RT, 12 h	26	34	12	24
HOAc, RT, 12 h	30	28	6	30
HOAc, 80 °C, 3 h	36	30	4	27



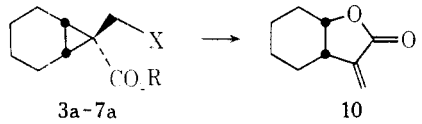
65%[a] 62%[b] 22%[a] 34%[b] 4%[b]

[a] Reference 17a (yield of corresponding alcohol after $LiAlH_4$ treatment). [b] Reference 17b.

The rearrangement in dioxane was examined in detail. The addition of small amounts of water to the reaction mixture caused the lactone to predominate over the diene (for mechanistic rationale, see Discussion section); the addition of $LiClO_4$ also favored the lactone (to a smaller extent).[19] The remaining diene could be easily removed by a simple column chromatography, and lactone **10** was isolated in 68% yield (see Table I).[16]

The possibility of using the hydroxy ester **3a** directly as a substrate was initially examined under very harsh conditions. Treatment of **3a** with 48% HBr and $ZnBr_2$ (EtOH, 100 °C, 6 h) gave a mixture of products containing lactone **10**.[8,20] Treatment of **3a** with concentrated H_2SO_4 (ice temperature, 2 h) gave a 50% yield of **10** after chromatography.[20,21] We were eventually able to effect rearrangement of hydroxy ester **3a** to lactone **10** under somewhat milder conditions ($HClO_4$ in dioxane), which bear some similarity to those used successfully with the mesylate ester **5a**. The only significant byproduct was the diene **13**, which again was easily removed by column chromatography, giving the lactone **10** in 67% yield (see Table I).

Table I. Rearrangements Forming Lactone 10

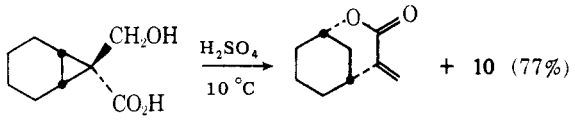


3a-7a **10**

substrate	conditions	isolated yield of 10, %	VPC purity of 10, %
3a	$HClO_4$, dioxane, reflux, 5 h	67	98.4[a]
4a[b]	$HClO_4$, dioxane, 75 °C, 1.5 h	77	97[a]
4a[b]	CF_3CO_2H, 40 °C, 91 h	84	90
5a	$LiClO_4$, dioxane,[c] 80 °C, 4 h	68[d]	>99
6a	$AgClO_4$, H_2O, dioxane, RT, 4 h; 65 °C, 2 h	74[d]	>99
6a	$AgClO_4$, H_2O, DME, RT, 6 h	63[d]	>99
7a	$AgClO_4$, H_2O, dioxane, RT, 6 h	81[d]	>99
7a	$AgClO_4$, H_2O, ether, −78 °C, 7 h	64[d]	97.4

[a] Traces of trans lactone **14** were observed in the NMR spectra. [b] Other conditions (e.g., TsOH, benzene, 70 °C, 2 h; and H_2SO_4, benzene, 10 °C, 2 h) caused the conversion of **4a** to **10** in slightly lower yields and purity. [c] Replacement of dioxane by other ether solvents (dimethoxyethane, diethyl ether) resulted in similar rearrangements in which **10** was a slightly smaller proportion of the crude product. [d] Overall yield from hydroxy ester **3a**.

It was anticipated that formation of byproducts in these rearrangements might be minimized by use of substrates having a more nucleophilic neighboring group. Therefore, rearrangements of hydroxy acid **4a** were examined. A variety of acidic reagents were found to effect the conversion of **4a** to the lactone **10**. Under many conditions, the bridged lactone **15**[22] was found to be a byproduct. When **4a** was treated with concentrated sulfuric acid at 10 °C, lactone **15** accounted for



4a **15** (22%)

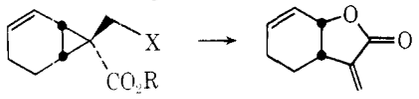
22% of the product mixture. Formation of **15** was minimized by the use of milder conditions, and under some conditions fairly pure lactone **10** could be isolated by simple evaporative distillation of the crude reaction product (see Table I). Formation of bridged lactone **15** was generally not a problem with the other substrates (having an ester neighboring group). However, in the reaction (above) of hydroxy ester **3a** with H_2SO_4, a small amount (about 5%) of **15** was detected in the NMR spectrum of the crude reaction product (as well as in a chromatography fraction).

To find yet milder conditions for effecting these rearrangements, we have investigated silver ion induced reactions. We first investigated the reactions of methyl ethers **8a** and **9a** with silver perchlorate, as silver ion has been reported to promote rearrangements of cyclopropylcarbinyl ethers.[23] Under some conditions, lactone **10** was obtained in fair to good yields,[8] but the reactions were not always reproducible.[24] We then turned our attention to silver ion induced rearrangements of the halo esters **6a** and **7a**.

We found that the reactions of both bromo ester **6a** and iodo ester **7a** with silver perchlorate proceeded smoothly under several sets of conditions to give the lactone **10** together with the diene **13**. As in the solvolytic rearrangements of the mesylate ester **5a**, the addition of small amounts of water to the reaction mixtures increased the proportion of lactone in the crude product. (The addition of $LiClO_4$ had little effect.) The diene was easily removed as before by a simple column chromatography. Lactone **10** could be isolated in 70–80% overall yields from hydroxy ester **3a** (see Table I).

Rearrangements of Unsaturated Substrates. We have examined the solvolytic, acid-catalyzed, and silver ion induced rearrangements of the unsaturated cyclopropylcarbinyl substrates **3b–6b** under a number of conditions similar to

Table II. Rearrangements Forming Lactone 16



3b-6b 16

substrate	conditions	isolated yield of 16, %	VPC purity of 16,[a] %
3b	$HClO_4$, dioxane, 70 °C, 3.5 h	69	>90
4b	$HClO_4$, dioxane, 85–90 °C, 1.5 h	75	96.5
4b	CF_3CO_2H, dioxane, 62–64 °C, 121 h	72	>99
4b	TsOH, benzene, 89–90 °C, 2 h	89	95.8
5b	$LiClO_4$, H_2O, dioxane, 100 °C, 2 h	63[b]	98
6b	$AgClO_4$, H_2O, dioxane, RT, 6.5 h	87[b]	91

[a] Traces of trans lactone **17**[25] were observed by VPC in some of the products: first entry (~2%), second entry (1.1%), fourth entry (4.2%), fifth entry (<1%), sixth entry (1.8%). [b] Overall yield from hydroxy ester **3b**.

those used successfully for the saturated substrates **3a–7a**. The α-methylene lactone **16** was isolated in very good yields under a variety of conditions (see Table II) with only a simple (evaporative) distillation necessary for purification in most cases.[11] In these reactions, no significant byproducts were identified. The ring fusion in **16** was assigned cis stereochemistry by comparison of the IR and NMR spectra of **16** with those of an authentic sample.[7g]

Isolation of lactone **16** from the rearrangement reactions demonstrates that the regiochemistry of the rearrangements is directed by a suitably placed double bond.[26] The double bond also enhances the rearrangement reactions. A comparison of the reactions of hydroxy esters **3a** and **3b** with $HClO_4$ in dioxane (70 °C, same oil bath) showed that the rearrangement of **3b** to **16** was about two to three times faster than the corresponding rearrangement of **3a** to **10**.

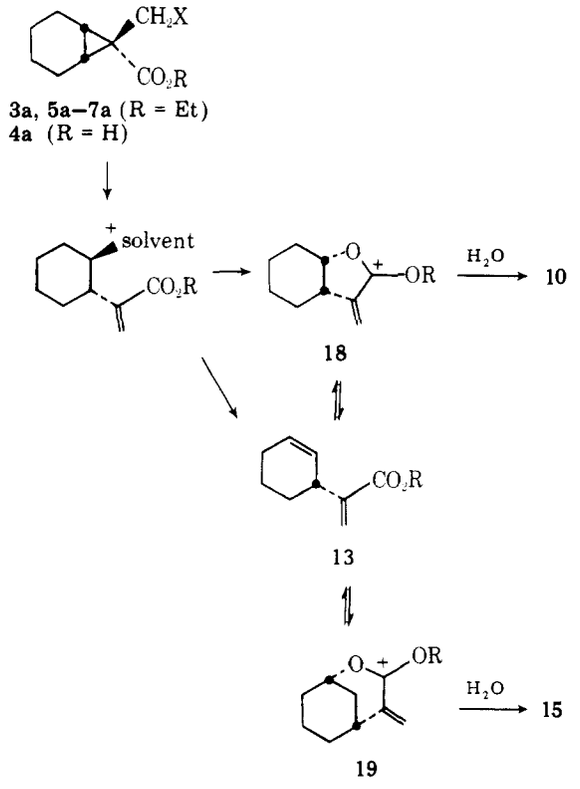
Discussion

Although neighboring group participation in solvolytic reactions is well known, few examples have been reported in rearrangements of cyclopropylcarbinyl derivatives.[28] The major effect of neighboring group participation in our system appears to be the predominance of cis lactone products.[29] This result can be accounted for by the mechanistic rationale shown (for the saturated cases) in Scheme IV. This scheme also accounts for (1) the increase in lactone product when small amounts of water are added to the reaction mixtures (when R ≠ H) and (2) the occasional formation of small amounts of the bridged lactone **15** as a byproduct (especially when R = H).[30]

In the interest of preparing trans-fused lactones, a number of rearrangement reactions in the presence of larger amounts of water and in the presence of KOAc were carried out. We hoped that trans homoallylic products (such as acetate **11**) could be made to predominate and that these would be convertible to trans lactones. Under some conditions, trans lactones and/or products believed to be trans homoallylic alcohols or acetates were formed, but the reactions were not clean. When a trans lactone was formed, the product mixture invariably contained a considerable amount of cis lactone as well. In many cases, unrearranged cyclopropylcarbinyl derivatives accounted for a considerable portion of the product mixture, indicating a limitation to the utility of increasing the nucleophilicity of the reaction medium.

Several attempts were made to prepare an epimeric cyclopropylcarbinyl substrate (i.e., exo CO_2R, endo CH_2X) in order

Scheme IV



to determine the effect of substrate stereochemistry on the rearrangements,[31] but we were unable to prepare a sufficient amount of such a substrate to study this question.[32] We have given little attention to alternate methods of preparing the cyclopropylcarbinyl substrates; a number of other routes can be envisioned. Moreover, since homoallyl derivatives can be obtained from cyclobutyl as well as cyclopropylcarbinyl derivatives,[9,17c,33] cyclobutyl substrates might similarly be useful precursors to α-methylene-γ-butyrolactones.

This work demonstrates that α-methylene-γ-butyrolactones can be prepared in high yields from rearrangements of cyclopropylcarbinyl substrates. The mild conditions under which the rearrangements occur and the fact that a choice of different reaction conditions is available suggest that these reactions would be compatible with a number of functional groups. It is of particular interest that the rearrangements of an unsymmetrical substrate can be directed by a suitably placed double bond to give an unsaturated lactone (**16**) of type B (see introduction) as a product. We are currently investigating the possibility of directing this rearrangement by other nearby functional groups, with a view toward preparing α-methylene lactones of type A.

Experimental Section

General. All reactions were carried out under a nitrogen atmosphere. All transfers of liquids were accomplished with nitrogen-flushed syringes. The verb "concentrated" refers to the evaporation of solvent under reduced pressure (water aspirator) using a rotary evaporator. The term "evaporative distillation" refers to a short-path (bulb-to-bulb) distillation in a Kugelrohr apparatus under oil pump vacuum. The temperature following in parentheses refers to the oven temperature.

Melting points were determined on a Fisher-Johns hot stage melting point apparatus or on a Thomas Hoover capillary melting point apparatus. Infrared (IR) spectra were obtained using a Perkin-Elmer Infracord Model 137 spectrometer. Proton nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60 spectrometer. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (0.00) as an internal reference. Mass spectra were obtained using a Hitachi Perkin-Elmer Model RMU-7E instrument. Vapor phase chromatographic (VPC) analyses were performed on a Varian Aerograph Model 90-P instrument using he-

lium as the carrier gas at the column temperature indicated;[34] the retention time of a hydrocarbon standard under the given conditions is included. For VPC peaks, the retention time is given in minutes relative to that of air, followed by percentage of the total peak area, and where possible the probable assignment. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Materials. Commercially available compounds were used without further purification unless otherwise noted. Ether (as reaction solvent) and tetrahydrofuran (THF) were distilled from sodium and benzophenone. Benzene was obtained as the last half of the distillation of benzene. Dimethoxyethane (DME) was distilled from $LiAlH_4$. Dioxane was distilled from CaH_2 unless otherwise noted. Acetone was distilled from $CaSO_4$. Pentane was obtained by stirring petroleum ether (30–60 °C) with concentrated H_2SO_4, drying over K_2CO_3, and distilling; the fraction having a boiling point less than 41.5 °C was used. Ether (for reaction workups), methylene chloride, methanesulfonyl chloride, ethyl chloroformate, and methyl chloroformate were distilled. Triethylamine was distilled from CaH_2. The diester **1a**[12] was prepared from cyclohexene and diethyl diazomalonate by the procedure of Peace and Wulfman.[13c] The acid ester **2a** was prepared by saponification of **1a** with 1.2 equiv of KOH in aqueous ethanol as reported.[12b] An authentic sample of the trans lactone **14** was prepared as described by Grieco.[4a] $LiClO_4$ and $AgClO_4$ were obtained from Alfa Inorganics; the latter was stored in a desiccator under nitrogen.

***exo*-7-(Hydroxymethyl)-*endo*-7-(carbethoxy)norcarane (3a).** Sodium hydride (0.2 g of a 57% dispersion in oil, 5 mmol) was washed with pentane (3 × 5 mL); the washing liquids were removed by pipet. To the residue was added 40 mL of THF and 0.484 g (2.28 mmol) of acid ester **2a**,[12b] and the resulting mixture was stirred at room temperature for 5 min. Ethyl chloroformate (0.24 mL, 2.5 mmol) was added, and the mixture was stirred at room temperature for 2 h.[14] Then 0.6 g (16 mmol) of sodium borohydride was added, and the mixture was stirred for an additional 6.5 h. The resulting mixture was slowly added to a cold buffer solution (6.8 g (39 mmol) of K_2HPO_4 and 5.8 g (43 mmol) of KH_2PO_4 in 150 mL of water) and stirred for 20 min. The solution was acidified to pH 1, diluted with 300 mL of water to dissolve the salts, and then extracted with four 30-mL portions of methylene chloride and with 15 mL of ether. The combined organic extracts were washed with 15 mL of saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and evaporatively distilled (170 °C), giving 0.396 g (88%) of hydroxy ester **3a** as a colorless liquid: IR (film) 2.9, 3.4, 5.80, 7.31, 8.50, 9.0, 9.75 μm; NMR (CCl_4) δ 1.28 (t, J = 7 Hz) overlapping with 1.0–1.55 (br) (total 9 H), 1.55–2.1 (br, 4 H), 3.08 (br s, 1 H, OH), 3.40 (s, 2 H), 4.20 (q, J = 7 Hz, 2 H); mass spectrum, m/e (rel intensity) 198 (M^+, 33), 180 (36), 153 (61), 152 (100), 134 (75), 107 (85), 106 (74), 79 (98). VPC analysis[34a] (155 °C, $C_{16}H_{34}$ = 3.0 min) showed the major peak at 2.4 min.

Hydroxy ester **3a** was also prepared in lower yield by conversion of acid ester **2a** to the acid chloride (oxalyl chloride, benzene, 25 °C, 4 h) followed by reduction ($NaBH_4$, THF, reflux 1 h, room temperature, 16 h). Preparative VPC followed by evaporative distillation yielded an analytical sample. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.65; H, 9.34.

***exo*-7-(Hydroxymethyl)-*endo*-7-carboxynorcarane (4a).** To a stirred solution of 0.934 g (4.72 mmol) of hydroxy ester **3a** in 80 mL of ethanol/water (1:1) was added 1.6 g (40 mmol) of NaOH. The resulting mixture was heated at reflux for 11 h, cooled, neutralized, and added to 50 mL of saturated $NaHCO_3$. The basic solution was extracted with methylene chloride and ether, and the organic layers were discarded. The aqueous layers were acidified to pH 1 and extracted with five portions of methylene chloride and one portion of ether. The combined organic extracts were dried ($MgSO_4$), concentrated, and recrystallized from hexane/CCl_4 (5:1) to give 0.670 g (83%) of white crystals: mp 86.5–87.5 °C; IR ($CHCl_3$) 2.8–4.2, 5.88, 6.96, 7.20, 9.60, 9.80 μm; NMR ($CDCl_3$) δ 1.0–2.2 (10 H), 3.57 (s, 2 H), 7.18 (s, 2 H, OH). A sample of **4a** from a similar experiment was recrystallized four times from hexane/CCl_4, giving white crystals: mp 87–87.5 °C; mass spectrum, m/e (rel intensity) 152 ($M^+ - H_2O$, 100), 124 (53), 110 (45), 107 (92), 91 (46), 79 (84), 67 (86). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.59; H, 8.26.

Mesylate of *exo*-7-(Hydroxymethyl)-*endo*-7-(carbethoxy)-norcarane (5a). To a stirred solution of 1.069 g (5.39 mmol) of hydroxy ester **3a** in 40 mL of methylene chloride was added 1.15 mL (0.84 g, 8.3 mmol) of triethylamine,[35] and the solution was cooled in an ice bath for 15 min. To the resulting solution was added 0.50 mL (0.74 g, 6.5 mmol) of methanesulfonyl chloride dropwise. The resulting mixture was stirred at 0 °C for 45 min and then diluted with 150 mL of cold methylene chloride and washed successively with 40-mL portions of cold water, 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried ($MgSO_4$, cooled in an ice bath), concentrated, and placed under oil pump vacuum for 1 h at 0 °C, giving 1.521 g (102%) of mesylate ester **5a** as a yellow liquid: IR (film) 3.4, 5.79, 7.41, 8.50, 10.7, 12.3 μm; NMR (CCl_4) δ 1.30 (t, J = 7 Hz) overlapping with 1.1–2.2 (total 13 H), 2.93 (s, 3 H), 3.37 (m, 0.5 H, impurity), 4.12 (s) overlapping with 4.20 (q, J = 7 Hz) (total 4 H). The mesylate ester **5a** was stable in the freezer for at least several weeks. However, at room temperature it decomposed completely in about 1 day, and it was unstable to VPC analysis.

***exo*-7-(Bromomethyl)-*endo*-7-(carbethoxy)norcarane (6a).** To a solution of 620 mg (2.24 mmol) of mesylate ester **5a**[36] in 15 mL of acetone was added 550 mg (6.3 mmol) of lithium bromide. The resulting solution was stirred at room temperature (precipitate forms) for 6.5 h and then added to 75 mL of saturated NaCl and worked up.[37] The crude product was placed under oil pump vacuum for 1.5 h, leaving 588 mg (100%) of bromo ester **6a** as a pale yellow liquid: IR (film) 3.4, 5.79, 8.20, 8.50 μm; NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz) overlapping with 1.0–2.2 (total 13 H), 3.43 (s, 2 H), 4.23 (q, J = 7 Hz, 2 H). VPC analysis[34b] (170 °C, $C_{16}H_{34}$ = 8.4 min) showed the major peak at 13.7 min. Bromo ester **6a** was normally stored in the freezer.

***exo*-7-(Iodomethyl)-*endo*-7-(carbethoxy)norcarane (7a).** To a solution of 634 mg (2.29 mmol) of mesylate ester **5a**[36] in 15 mL of acetone was added 701 mg (4.68 mmol) of sodium iodide. The resulting yellow solution was stirred at room temperature (precipitate forms) for 6 h and then added to 75 mL of saturated NaCl and worked up.[37] The crude product was placed under oil pump vacuum for 1 h at 0 °C, leaving 726 mg (103%) of iodo ester **7a** as an amber liquid: IR (film) 3.4, 5.78, 8.42, 8.50 μm; NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz) overlapping with 1.0–2.2 (total 13 H), 3.33 (s, 2 H), 3.50 (q, J = 7 Hz, 0.3 H, impurity), 4.26 (q, J = 7 Hz, 2 H). The iodo ester **7a** was stable in the freezer for at least several weeks. However, it turned black if left at room temperature for several hours, and it was unstable to VPC analysis.

***exo*-7-(Methoxymethyl)-*endo*-7-(carbethoxy)norcarane (8a).** Sodium hydride (0.6 g of a 57% dispersion in oil, 14 mmol) was washed with pentane three times. To the residue was added 40 mL of THF and 0.455 g (2.30 mmol) of hydroxy ester **3a**. The resulting mixture was stirred for 15 min, and 0.35 mL (0.80 g, 5.62 mmol) of iodomethane was added. After stirring for an additional 5 h, the mixture was added to methylene chloride overlaid with water. The layers were separated, and the aqueous layer was extracted twice with methylene chloride and with ether. The combined organic layers were dried ($MgSO_4$), concentrated, and evaporatively distilled (155 °C) to give 0.429 g (88%) of methyl ether ester **8a** as a colorless liquid: IR (film) 3.4, 5.80, 8.51, 9.1 μm; NMR (CCl_4) δ 1.28 (t, J = 7 Hz) overlapping with 1.0–2.0 (total 13 H), 3.24 (CO_2CH_3) overlapping with 3.30 (CH_2O) (total 5 H), 4.15 (q, J = 7 Hz, 2 H). VPC analysis[34a] (130 °C, $C_{15}H_{32}$ = 3.1 min) showed the major peak at 2.6 min (99% of peak area). A sample of **8a** from a separate experiment had mass spectrum m/e 212 (M^+), 181, 180, 167, 152, 135, 134, 107, and 79. Preparative VPC followed by evaporative distillation yielded an analytical sample. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.50. Found: C, 67.69; H, 9.73.

***exo*-7-(Methoxymethyl)-*endo*-7-carboxynorcarane (9a).** To a solution of 0.694 g (3.27 mmol) of methyl ether ester **8a** in 85 mL of 95% ethanol was added 4.2 g (64 mmol) of KOH (85%) in 75 mL of water. The mixture was heated at reflux for 54 h, cooled, added to 250 mL of water, and extracted with ether. The ether layer was discarded. The aqueous layer was acidified to pH 1 and extracted with ether (3 × 50 mL) and methylene chloride (5 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give a white solid. Recrystallization from hexane gave 0.515 g (86%) of methyl ether acid **9a** as white crystals: mp 67.5–68.5 °C; IR (CCl_4) 3.0–4.0, 5.86, 6.94, 7.06, 8.36, 8.97, 9.10 μm; NMR (CCl_4) δ 1.0–2.1 (10 H), 3.32 (CH_3O) overlapping with 3.40 (CH_2O) (total 5 H), 11.9 (s, 1 H); mass spectrum,[38] m/e 166 ($M^+ - H_2O$), 152, 107, 79. The product of a separate experiment was recrystallized from pentane to give an analytical sample, mp 64.5–65 °C. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.43; H, 8.76.

Rearrangement of 5a in HOAc. A solution of 279 mg (1.01 mmol) of mesylate ester **5a** in 5 mL of acetic acid was stirred at room temperature for 12 h and then added to cold saturated $NaHCO_3$ overlaid with ether and worked up.[37] The crude product was evaporatively distilled (155 °C) to give 186 mg of liquid.[39] VPC analysis[34b] (165 °C, $C_{16}H_{34}$ = 10.6 min) showed major peaks at 4.0 (29.9%), 8.1 (30.3%), 14.0 (27.8%), and 17.2 min (5.5%). A reaction carried out in the presence of KOAc (269 mg of **5a**, 5 mL of HOAc, 275 mg of KOAc, 12 h at room temperature) similarly yielded 189 mg of product[39] having major components at the above retention times in respective VPC area ratios of 24.3, 25.5, 33.5, and 12.0%. The products were combined, and the major components were isolated by preparative VPC.

The first component was identified as diene **13** by comparison of

its IR and NMR spectra with those of an authentic sample.[16] The mass spectrum[40] showed *m/e* 180 (M^+), 152, 134, 107, 106, 105, 91, and 79.

The second component was identified as α-methylene lactone **10** by comparison of its IR and NMR spectra with those reported by Marshall.[15]

The third component was identified as homoallylic acetate **11** from the following data: IR (film) 3.4, 5.74, 5.82, 6.16, 7.32, 7.87, 8.08, 8.68, 9.67 μm; NMR ($CDCl_3$) δ 1.1–2.3 (br) overlapping with 1.30 (t, J = 7 Hz) and 1.94 (CH_3CO) (total 14 H), 2.4–3.0 (br m, 1 H), 4.08 (q, J = 7 Hz, 2 H), 4.6–5.2 (br m, 1 H), 5.58 (s, 1 H), 6.20 (s, 1 H); mass spectrum,[40] *m/e* (rel intensity) 240 (M^+, 4), 198 (38), 180 (100), 153 (61), 152 (89), 151 (73), 134 (57), 124 (68), 107 (43). Evaporative distillation yielded an analytical sample.[40] Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.35; H, 8.93.

The fourth component was identified as acetate **12** from the following data: IR (film) 3.4, 5.74, 7.34, 8.15, 8.50, 9.75 μm; NMR ($CDCl_3$) δ 1.0–1.6 (br) overlapping with 1.28 (t, J = 7 Hz) (total 9 H), 1.6–2.2 (br) overlapping with 2.05 (CH_3CO) (total 7 H), 4.08 (s) overlapping with 4.22 (q, J = 7 Hz) (total 4 H); mass spectrum,[40] *m/e* (rel intensity) 240 (M^+, 3), 195 (33), 181 (79), 180 (100), 152 (83), 151 (62), 135 (69), 134 (67), 107 (88), 106 (55), 79 (62). The IR and NMR spectra corresponded to those of an independently prepared sample (0.121 g of hydroxy ester **3a**, 8 mL of pyridine, 4 mL of acetic anhydride, 1 h at 100 °C and then room temperature for 14 h). Preparative VPC followed by evaporative distillation yielded an analytical sample. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.00; H, 8.66.

Rearrangement of 4a in H_2SO_4. Isolation of Bridged Lactone 15. A solution of 142 mg (0.84 mmol) of hydroxy acid **4a** in 5 mL of concentrated sulfuric acid was stirred at 10 °C for 1 h. The resulting mixture was poured into cold water and extracted with five portions of ether. The combined ether extracts were washed with saturated $NaHCO_3$, and the aqueous phase was extracted with ether. The combined organic layers were dried ($MgSO_4$), concentrated, and evaporatively distilled (160 °C) to give 132 mg of a colorless liquid.[39] VPC analysis[34b] (160 °C, $C_{16}H_{34}$ = 6.7 min) showed two major peaks at 6.2 (76.5%) and 7.6 min (22%). The two major components were isolated by preparative VPC.

The first component was identified as α-methylene lactone **10** by its IR and NMR spectra. The mass spectrum showed *m/e* (rel intensity) 152 (M^+, 29), 124 (100), 123 (39), 95 (56), and 67 (48).

The second component was identified as the bridged lactone **15** by comparison of its IR and NMR spectra with those of an authentic sample.[22] The mass spectrum showed *m/e* (rel intensity) 152 (M^+, 100), 124 (48), 95 (36), 81 (42), and 67 (34).

Preparation of α-Methylene Lactone 10. (a) Rearrangement of 3a in $HClO_4$/Dioxane. To a solution of 225 mg (1.13 mmol) of hydroxy ester **3a** in 5 mL of dioxane was added 5 drops of perchloric acid (61%). The reaction mixture was heated at reflux for 5 h, cooled, added to 50 mL of saturated $NaHCO_3$, and worked up.[41] The crude product was chromatographed[42] and evaporatively distilled (155 °C) to give 116 mg (67%) of **10** as a colorless liquid.[43] VPC analysis[34b] (155 °C, $C_{15}H_{32}$ = 8.5 min) showed the major peak at 9.8 min (98.4% of peak area).

In a similar experiment (211 mg of **3a**, 5 mL of dioxane, 7 drops of $HClO_4$, 75 °C, 3.5 h), the crude product was evaporatively distilled to give 170 mg of a colorless liquid having IR and NMR spectra consistent with a mixture of **10** and the diene **13**. VPC analysis[34b] (150 °C, $C_{15}H_{32}$ = 6.8 min) showed two major peaks at 4.2 (25%, **13**) and 8.8 min (72%, **10**).

(b) Rearrangement of 4a in $HClO_4$/Dioxane. To a solution of 254 mg (1.49 mmol) of hydroxy acid **4a** in 7 mL of dioxane was added 5 drops of perchloric acid (61%). The reaction mixture was heated at 75 °C for 1.5 h, cooled, and added to 25 mL of saturated $NaHCO_3$. The resulting mixture was worked up,[37] and the crude product was evaporatively distilled (155 °C) to give 176 mg (77%) of **10** as a colorless liquid.[43] VPC analysis[34b] (150 °C, $C_{15}H_{32}$ = 6.2 min) showed peaks at 7.8 (97.1%, **10**) and 9.2 min (2.1%, **15**).

(c) Rearrangement of 4a in CF_3CO_2H. A solution of 164 mg (0.96 mmol) of hydroxy acid **4a** in 5 mL of trifluoroacetic acid was heated at 40 °C for 91 h. The resulting mixture was cooled and added to 75 mL of saturated $NaHCO_3$ overlaid with ether and then worked up.[37] The crude product was evaporatively distilled (155 °C) to give 123 mg (84%) of **10** as a pale yellow liquid. The IR and NMR spectra were similar to those of **10** isolated above by preparative VPC. A small doublet at δ 6.49 in the NMR spectrum suggested the presence of bridged lactone **15**. VPC analysis[34b] (140 °C, $C_{15}H_{32}$ = 7.0 min) showed two major peaks at 8.6 (89.8%, **10**) and 10.4 min (6.7%, **15**).

(d) Rearrangement of 5a in $LiClO_4/H_2O$/Dioxane. To a solution of 264 mg (0.96 mmol) of mesylate ester **5a**[44] in 5 mL of dioxane was added 24 mg (1.33 mmol) of water and 294 mg (2.76 mmol) of $LiClO_4$. The resulting mixture was heated at 80 °C for 4 h, cooled, and added to saturated $NaHCO_3$. The resulting mixture was worked up,[41] and the crude product was chromatographed[42] and evaporatively distilled (155 °C) to give 100 mg (68% from **3a**) of **10** as a colorless liquid.[43] VPC analysis[34b] (165 °C, $C_{15}H_{32}$ = 5.8 min) showed a single peak at 8.2 min.

In a separate (preliminary) experiment (94 mg of **5a**, 1.0 mL of dioxane, 25 mg of water, 71 mg of $LiClO_4$, 3 h at 80 °C), VPC analysis[34b] (150 °C) of the crude product showed two major peaks at 5.4 (27%, **13**) and 11.7 min (71%, **10**).

(e) Rearrangement of 6a in $AgClO_4$/Water/Dioxane. To a solution of 270 mg (1.03 mmol) of bromo ester **6a** (from preparation described above) in 10 mL of dioxane was added 23 mg (1.28 mmol) of water and 360 mg (1.74 mmol) of $AgClO_4$. The reaction mixture was stirred for 4 h at room temperature (precipitate forms) and for 2 h at 65 °C, and then was cooled, added to aqueous NaCl/$NaHCO_3$, and worked up.[37] The crude product was chromatographed[42] and evaporatively distilled (155 °C) to give 118 mg (74% from **3a**) of **10** as a pale yellow liquid.[43] VPC analysis[34b] (170 °C, $C_{15}H_{32}$ = 7.0 min) showed a single peak at 10.0 min.

In a separate (preliminary) experiment (46 mg of **6a**, 5 mL of dioxane, 12 mg of H_2O, 170 mg of $AgClO_4$, 4 h at room temperature and 3 h at 55 °C), VPC analysis[34b] (165 °C, $C_{15}H_{32}$ = 4.2 min) of the crude product showed two major peaks at 2.9 (22%, **13**) and 6.0 min (65%, **10**).

(f) Rearrangement of 6a in $AgClO_4$/Water/DME. To a solution of 261 mg (1.00 mmol) of bromo ester **6a** (from preparation described above) in 10 mL of DME was added 21 mg (1.17 mmol) of water and 461 mg (2.22 mmol) of $AgClO_4$. The reaction mixture was stirred at room temperature for 6 h (precipitate forms) and then added to aqueous NaCl/$NaHCO_3$. The resulting mixture was worked up,[37] and the crude product was chromatographed[42] and evaporatively distilled (155 °C) to give 97 mg (63% from **3a**) of **10** as a colorless liquid.[43] VPC analysis[34b] (170 °C, $C_{15}H_{32}$ = 7.0 min) showed a single peak at 9.7 min.

In a separate (preliminary) experiment (272 mg of $AgClO_4$, 5 mL of DME, 17 mg of H_2O, 6 mg of $C_{13}H_{28}$ (internal standard), 51 mg of **6a**, 5 h at room temperature), VPC analysis[34b] (165 °C) of the crude product showed the standard peak at 2.6 min and two major peaks at 4.1 (16%, **13**) and 8.5 min (73%, **10**).

(g) Rearrangement of 7a in $AgClO_4$/Water/Dioxane. To a solution of 313 mg (1.02 mmol) of iodo ester **7a** (from preparation described above) in 10 mL of dioxane was added 22 mg (1.22 mmol) of water and 421 mg (2.03 mmol) of $AgClO_4$. The reaction mixture was stirred for 6 h at room temperature (precipitate forms) and then added to 75 mL of aqueous NaCl/$NaHCO_3$. The resulting mixture was worked up,[37] and the crude product was chromatographed[42] and evaporatively distilled (155 °C) to give 125 mg (81% from **3a**) of **10** as a pale yellow liquid.[43] VPC analysis[34b] (170 °C, $C_{15}H_{32}$ = 3.8 min) showed a single peak at 5.7 min.

In a separate (preliminary) experiment (52 mg of **7a**, 3 mL of dioxane, 30 mg of water, 237 mg of $AgClO_4$, 4.75 h), VPC analysis[34b] (165 °C, $C_{14}H_{30}$ = 6.3 min) of the crude product showed major peaks at 6.3 (18%, **13**) and 13.0 min (76%, **10**). The NMR spectrum was consistent with a product mixture containing primarily **10** and **13**.

(h) Rearrangement of 7a in $AgClO_4$/Water/Ether. To a mixture of 311 mg (1.01 mmol) of iodo ester **7a**, 10 mL of ether, and 20 mg (1.1 mmol) of water cooled in a dry ice/acetone bath was added 440 mg (2.1 mmol) of $AgClO_4$, and the resulting mixture was stirred at −78 °C for 7 h (precipitate forms). The mixture was added to aqueous NaCl/$NaHCO_3$ and worked up,[37] and the crude product was chromatographed[42] and evaporatively distilled (155 °C) to give 98 mg (64% from **3a**) of **10** as a clear yellow liquid having IR and NMR spectra similar to those of **10** isolated above by preparative VPC. VPC analysis[34b] (170 °C, $C_{15}H_{32}$ = 4.0 min) showed one major peak at 5.8 min (97.4%, **10**).

***exo*-7-Carboxy-*endo*-7-(carbomethoxy)-2-norcarene (2b).** To a solution of 10.075 g (48.0 mmol) of diester **1b**[13] in 140 mL of methanol was added 4.40 g (67 mmol) of potassium hydroxide (85%) in 50 mL of water over a period of 20 min. The resulting solution was stirred at room temperature for 24 h and then diluted with 25 mL of water and washed with methylene chloride (4 × 25 mL). The combined organic layers were extracted with saturated $NaHCO_3$ (2 × 25 mL) and discarded. The aqueous layers were combined, acidified to pH 1, and extracted with methylene chloride (6 × 20 mL) and ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 8.410 g (89%) of white solid: mp 137.5–140 °C; IR ($CHCl_3$) 2.8–4.2, 5.75, 5.90, 6.95, 7.51, 7.85, 9.01 μm; NMR ($CDCl_3$) δ 1.6–2.4 (6 H), 3.74 (s, 3 H), 5.8–6.1 (m, 2 H), 9.4 (s, 1 H). A portion of the product was recrystallized from methylene chloride/pentane to give white crystals: mp 142.5–143.5 °C; mass spectrum, *m/e* (rel

intensity) 196 (M^+, 4), 178 (60), 164 (45), 146 (100), 118 (77), 91 (100), 79 (64). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.08; H, 6.15.

***exo*-7-(Hydroxymethyl)-*endo*-7-(carbomethoxy)-2-norcarene (3b).** Using a procedure similar to that used for the conversion of **2a** to **3a**, 3.80 g (19.3 mmol) of acid ester **2b** (mp 137–139 °C) was treated successively with sodium hydride (43.7 mmol) in 100 mL of THF, 1.62 mL (21 mmol) of methyl chloroformate in 60 mL of THF, and 4.5 g (118 mmol) of sodium borohydride. Workup and distillation as before yielded 2.332 g (66%) of the hydroxy ester **3b** as a cloudy oil: IR (film) 2.9, 3.4, 5.78, 6.97, 8.41, 8.85 μm; NMR (CCl_4) δ 1.0–2.3 (6 H), 2.67 (s, 1 H, OH), 3.50 (s, 2 H), 3.66 (s, 3 H), 5.6–5.9 (2 H). VPC analysis[34b] (168 °C, $C_{16}H_{34}$ = 7.9 min) showed the major peak at 7.7 min (98% peak area). A portion of the product was further purified by chromatography on Florisil: mass spectrum, *m/e* (rel intensity) 182.0964 (M^+, 4) (calcd for $C_{10}H_{14}O_3$: 182.0943), 164 (22), 132 (66), 105 (67), 104 (100), 91 (60), 86 (61), 79 (77), 77 (53).

***exo*-7-(Hydroxymethyl)-*endo*-7-carboxy-2-norcarene (4b).** Using a procedure similar to that used for the conversion of **3a** to **4a**, 0.308 g (1.69 mmol) of hydroxy ester **3b** was treated with 0.24 g (6.0 mmol) of NaOH in 20 mL of methanol/water (1:1). Workup and recrystallization (ether/pentane) gave white crystals [0.166 g, mp 100–101 °C, and 0.026 g, mp 99.5–101 °C (total yield 67%)]: IR ($CHCl_3$) 2.8–4.1, 5.86 μm; NMR ($CDCl_3$)[45] δ 1.6–1.8 (2 H), 1.9–2.2 (4 H), 3.64 (s, 2 H), 5.85 (br s, 2 H), 6.7 (br s, 2 H, OH). A sample of **4b** from a similar experiment had mass spectrum *m/e* 168 (M^+, 9), 150 (49), 132 (86), 105 (85), 104 (93), 90 (67), 79 (91), 77 (65), and 72 (100). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.25.

Mesylate of *exo*-7-(Hydroxymethyl)-*endo*-7-(carbomethoxy)-2-norcarene (5b). Using a procedure similar to that used for the conversion of **3a** to **5a**, 271 mg (1.49 mmol) of hydroxy ester **3b** in 20 mL of methylene chloride and 0.31 mL (2.2 mmol) of triethylamine was treated with 0.21 mL (2.7 mmol) of methanesulfonyl chloride. After workup, the crude product was used immediately in the following experiment. A sample of mesylate ester **5b** prepared in a similar experiment had IR (film) 3.4, 5.78, 7.40, 8.37, and 8.52 μm; the NMR (CCl_4) showed singlets at δ 2.99 (CH_3SO_3) and 3.68 (CO_2CH_3) and a pair of doublets (J = 11 Hz) at δ 4.00 and 4.42 (CH_2O).

***exo*-7-(Bromomethyl)-*endo*-7-(carbomethoxy)-2-norcarene (6b).** Using a procedure similar to that used for the conversion of **5a** to **6a**, mesylate ester **5b** (entire crude product from the above experiment) was treated with 0.55 g (6.3 mmol) of lithium bromide in 25 mL of acetone (0 °C for 0.5 h followed by room temperature for 6 h). The mixture was added to 30 mL of saturated NaCl and worked up[37] to give 662 mg of crude bromo ester **6b**, which was used without delay in a rearrangement reaction (below). A sample of bromo ester **6b** prepared in a similar experiment had IR (film) 3.4 and 5.8 μm; the NMR[45] ($CDCl_3$) showed a singlet at δ 3.67 (CO_2CH_3) overlapping with a pair of doublets (J = 10.5 Hz) at δ 3.27 and 3.73 (CH_2Br).

Preparation of α-Methylene Lactone 16. (a) Rearrangement of 3b in $HClO_4$/Dioxane. Using a procedure similar to that used for the conversion of **3a** to **10**, 298 mg (1.64 mmol) of hydroxy ester **3b** was treated with 6 drops of perchloric acid (60–62%) in 12 mL of dioxane at 70 °C for 3.5 h. The crude product was chromatographed on 20 g of Florisil. Elution with 3% ether in methylene chloride yielded two fractions containing **16**,[46] 45 (18%) and 125 mg (51%). VPC analysis[34b] (160 °C) of the first fraction showed peaks at 5.4 (2%), 8 (7.9%, **17**), and 9.7 min (90.1%, **16**). VPC analysis (same conditions) of the second fraction showed peaks at 9.8 (98%, **16**) and 10.7 min (2%).

(b) Rearrangement of 4b in $HClO_4$/Dioxane. Using a procedure similar to that used for the conversion of **4a** to **10**, 110 mg (0.65 mmol) of hydroxy acid **4b** in 5 mL of dioxane was treated with 0.2 mL of perchloric acid (61%) for 1.5 h at 85–90 °C. The crude product was evaporatively distilled (160 °C) to give 73 mg (75%) of **16** as a colorless liquid.[46] VPC analysis[34b] (162 °C, $C_{16}H_{34}$ = 13.8 min) showed peaks at 11.4 (1.08%, **17**) and 14.2 min (96.5%, **16**).

(c) Rearrangement of 4b in CF_3CO_2H/Dioxane. To a solution of 103 mg (0.613 mmol) of hydroxy acid **4b** in 0.6 mL of dioxane was added 0.6 mL of CF_3CO_2H. The mixture was heated at 62–64 °C for 121 h and then cooled and allowed to stand at room temperature for 24 h. The resulting mixture was poured into saturated $NaHCO_3$ and worked up.[37] The crude product was evaporatively distilled (131 °C) to give 66 mg (72%) of **16** as a colorless liquid.[46] VPC analysis[34b] (162 °C, $C_{16}H_{34}$ = 8.0 min) showed a peak at 8.5 min (>99% of peak area).

(d) Rearrangement of 4b in TsOH/Benzene. To a solution of 109 mg (0.64 mmol) of hydroxy acid **4b** in 5 mL of benzene was added 87 mg (0.45 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting mixture was heated at 85–90 °C for 2 h, and then was cooled, poured into saturated $NaHCO_3$, and worked up.[41] The crude product was evaporatively distilled (156 °C) to give 85 mg (89%) of **16** as a colorless liquid.[46] VPC analysis[34b] (162 °C, $C_{16}H_{34}$ = 13.8 min) showed peaks at 11.8 (4.2%, **17**) and 14.2 min (95.8%, **16**).

(e) Rearrangement of 5b in $LiClO_4/H_2O$/Dioxane. Mesylate ester **5b** was prepared from 145 mg (0.80 mmol) of hydroxy ester **3b** by a similar procedure to that described above for the preparation of **5b**. The entire crude product in 4 mL of dioxane was added to a solution of 0.63 g (5.9 mmol) of $LiClO_4$ in 0.15 mL (8.3 mmol) of water. The resulting mixture was heated at 100 °C for 2 h and then cooled and added to 20 mL of water. The mixture was extracted with four portions of ether and three portions of methylene chloride, and the combined organic extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and evaporatively distilled (145 °C) to give 86 mg of a colorless liquid containing dioxane (by VPC). The dioxane was removed by evaporative distillation (105 °C), leaving 74 mg (63% from **3b**) of lactone **16** as a colorless liquid.[46] VPC analysis[34b] (162 °C, $C_{16}H_{34}$ = 6.8 min) showed the major peak at 6.2 min (98% of peak area, **16**) with less than 1% at 5.3 min (**17**).

(f) Rearrangement of 6b in $AgClO_4$/Water/Dioxane. To a solution of 662 mg of bromo ester **6b** (entire crude product from the preparation described above) in 15 mL of dioxane was added 34 mg (1.9 mmol) of water and 500 mg (2.4 mmol) of $AgClO_4$. The reaction mixture was stirred at room temperature for 6.5 h (precipitate forms) and then added to aqueous NaCl/$NaHCO_3$ and worked up.[37] The crude product was evaporatively distilled (120 °C) to give 195 mg (87% from **3b**) of **16** as a light yellow liquid.[46] VPC analysis[34b] (155 °C, $C_{16}H_{34}$ = 8.9 min) showed peaks at 2.9 (1.8%), 3.7 (3.9%), 7.4 (1.8%, **17**), and 9.1 min (91%, **16**).

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Registry No.—**1b**, 15833-44-0; **2a**, 21505-39-5; **2b**, 68582-75-2; **3a**, 43210-05-5; **3b**, 68582-72-9; **4a**, 68630-29-5; **4b**, 68630-28-4; **5a**, 68582-69-4; **5b**, 68582-73-0; **6a**, 68582-70-7; **6b**, 68582-74-1; **7a**, 68582-71-8; **8a**, 43210-11-3; **9a**, 68582-76-3; **10**, 16822-06-3; **11**, 68582-77-4; **12**, 68582-78-5; **13**, 54109-53-4; **15**, 57428-15-6; **16**, 60916-75-8; **17**, 68645-72-7; ethyl chloroformate, 541-41-3.

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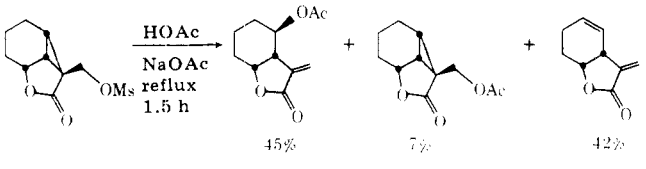

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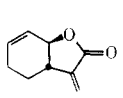
(25) A comparison sample of the trans lactone **17** was obtained as follows. Steam distillation of hydroxy acid **4b** with a small amount of H_2SO_4 yielded



17

product mixtures consisting of varying amounts of cis lactone **16** and another lactone assigned the trans ring fusion **17**. (Similar steam distillation of **4a** produced mixtures of cis and trans lactones **10** and **14**.) Lactone **17** was purified by preparative VPC and had the following spectral data: IR ($CHCl_3$) 3.4, 5.69, 6.01, 7.91, 8.78 μm; NMR ($CDCl_3$) δ 1.6–2.2 (br, 4 H), 3.6 (m, 1 H), 4.8 (m, 1 H), 5.4–6.2 (br, –CH=CH–) overlapping with 5.61 (d, J = 2 Hz) (total 3 H), 6.23 (d, J = 2 Hz, 1 H); mass spectrum, *m/e* (rel intensity) 150 (M^+, 45), 132 (100), 106 (43), 105 (44), 94 (52), 91 (63), 79 (69), 77 (84), 39 (72).
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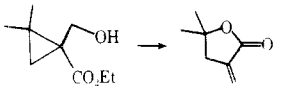

i ii

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(30) When R = H, deprotonation of either cation **18** or **19** (giving **10** or **15**, respectively) should be facile. When R ≠ H, addition of water to cation **19** may be sterically relatively unfavorable owing to conformational effects.
(31) In prostaglandin syntheses employing solvolyses of bicyclic cyclopropylcarbinyl derivatives, the yields of homoallylic products were much greater when the carbon bearing the leaving group was endo rather than exo.[10a]
(32) A major problem is the relative unreactivity of the endo CO_2R group; for example, several attempts to selectively reduce the endo CO_2Et group of ester acid **2a** gave either no reaction or, under more severe conditions, the diol.
(33) Compare K. G. Taylor, V. N. Nichols, R. Isaac, and G. S. Poindexter, *J. Org. Chem.*, **39**, 1761 (1974).
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(36) The mesylate ester **5a** was prepared in a separate but similar experiment to that reported above; 1.065 g of hydroxy ester **3a** was converted to 1.455 g of mesylate ester (98% crude yield).
(37) Extracted with 2–4 portions of methylene chloride and 2–4 portions of ether, and the combined organic extracts were dried ($MgSO_4$) and concentrated.
(38) Taken of the product from a similar experiment.
(39) The NMR spectrum was consistent with the product being a mixture of the components isolated by preparative VPC.
(40) Obtained on a sample from reaction of **5a** with HOAc/KOAc at 100 °C (purified by preparative VPC; IR and NMR spectra were comparable to those described here).
(41) Extracted with 2–5 portions of ether, and the combined organic extracts were dried ($MgSO_4$) and concentrated.
(42) Chromatography was carried out on 20 g of Florisil. Byproduct diene was removed by elution with 1:2 pentane/methylene chloride. The product was eluted with 3% ether in methylene chloride.
(43) IR and NMR spectra were essentially identical with those of **10** isolated above by preparative VPC.
(44) The mesylate ester **5a** was prepared in a separate but similar experiment to that reported above; 408 mg of hydroxy ester **3a** was converted to 561 mg of mesylate ester (99% crude yield).
(45) NMR with $CHCl_3$ as an internal reference.
(46) Identified as α-methylene lactone **16** by comparison of its IR and NMR spectra with those of an authentic sample supplied by Professor Marino; see ref 7g.