Synthesis of Δ^1-Butenolides[1]

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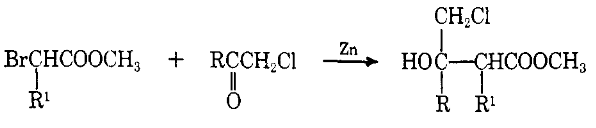
A new method for the synthesis of Δ^1-butenolides has been developed. The first step in all cases is the preparation of **3** *via* a Reformatsky reaction using α-chlorocarbonyl compounds as substrates. Compound **3** can be converted into the desired butenolide by one of two procedures. The first approach involves reaction of **3** ($R = CH_3$; $R_1 = H$) with base to give an epoxide intermediate which isomerizes to **4**. Compound **4** and related compounds were converted into the butenolides by photoirradiation in the presence of an acid catalyst indicating that this reaction may have general utility. The second method of converting **3** into a butenolide is by a thermal process which will give the desired product directly in many cases.

Molecules that contain a substituted 4-hydroxy-2-butenoic acid γ-lactone or Δ^1-butenolide function have been studied since before the turn of the century.[2] Numerous modes of preparation of Δ^1-butenolides have been reported;[2a] in fact a recent review article[2a] enumerates seventeen different approaches, some of which could be further divided. Unfortunately these methods suffer from one or more of the following faults: low yields, lack of versatility, difficulty in preparation of starting material, or unsuitable conditions or reagents for use with a polyfunctional starting material. While it is improbable that a method which does not suffer from any of the above difficulties will be found, our investigations indicate that a better general method than those now known is available.

Naturally occurring Δ^1-butenolides may be divided, roughly, into two groups, those which exist as separate rings and those which are part of a fused-ring system. Our initial studies have dealt with the synthesis of simple or model Δ^1-butenolides in order to develop a rather general approach before attacking the more involved naturally occurring analogs.

An α,β-unsaturated γ-lactone may be regarded as a trifunctional molecule containing double bond, acid, and alcohol functional groups. A serious limitation of current methods is the preparation of possible precursors to give the necessary trifunctional intermediates. Intermediates of the general type **3** were considered to be desirable since in theory they could be prepared by a Reformatsky reaction between easily obtainable α-bromo esters **1** and α-halo ketones **2**.



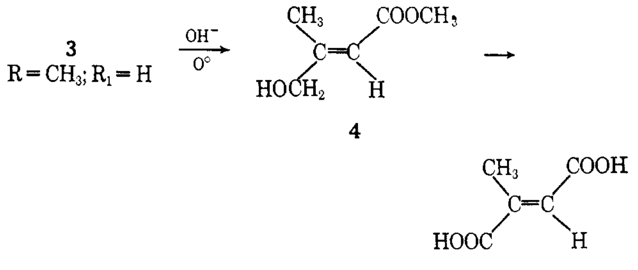
$$\underset{\textstyle \mathrm{R^1}}{\mathrm{BrCHCOOCH_3}} + \underset{\textstyle \mathrm{O}}{\mathrm{RCCH_2Cl}} \xrightarrow{\mathrm{Zn}} \mathrm{HO}\overset{\mathrm{CH_2Cl}}{\underset{\mathrm{R}}{\mathrm{C}}}\text{—}\underset{\mathrm{R^1}}{\mathrm{C}}\mathrm{HCOOCH_3}$$

1 **2** **3**

Although the use of two α-halo carbonyl compounds in the Reformatsky reaction might lead to two different Reformatsky reagents and a mixture of products, this difficulty was eliminated by use of relatively reactive bromo esters with chloro ketones. α-Chloro ketones have been reported to undergo the Reformatsky reaction only once[3,4] previously giving low yields.

The high yields (Table I, Experimental Section) using a variety of substrates and the stereospecificity of the chlorocyclohexanone case indicates the generality and usefulness of this variation of the Reformatsky reaction. A discussion of the stereochemistry of the Reformatsky products will be presented later in the paper. Unfortunately the materials prepared in the above reaction were not stable long enough to get acceptable elemental analysis, but the spectral data (infrared and nuclear magnetic resonance (nmr)) and the subsequent conversion of these materials in high yield to known compounds appeared to support their structures. The Reformatsky products could be converted into the corresponding Δ^1-butenolide by at least one of two pathways to be described.

Our initial efforts in converting **3** into Δ^1-butenolides were directed at dehydration and the preparation of γ-chloro α,β-unsaturated esters since Adams and Gianturco[5] were able to cyclize similar halogenated compounds in high yield. Unfortunately all attempts using acidic or other common dehydrating agents led to polymerization and low yields of olefins or gave starting material. Mild treatment of **3** ($R = CH_3$; $R_1 = H$) with base gave only a single product (**4**) in 96% yield. The *trans* nature of the hydroxymethyl and the carbomethoxy groups was suggested by spectral data and confirmed by oxidation and saponification of **4** to mesaconic acid (**5**). The reaction may be rationalized to proceed through an intermediate epoxide (**6**) where the formation of **6** from **3** ($R = CH_3$; $R_1 = H$) would require 1 molar equiv of base. The proton abstraction from the carbon ad-



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[1] Abstracted from a portion of the thesis submitted by A. C. Sonntag in partial fulfillment of the requirements for the Ph.D. Degree. Supported by the National Science Foundation Grant No. GP-5787.

[2] (a) For most of the literature before 1964, see Y. S. Rao, *Chem. Rev.*, **64**, 353 (1964). (b) A few leading references more current are G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964); C. R. Engel and G. Bach, *Steroids*, **3**, 593 (1964); L. Novotny, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **29**, 2182 (1964); S. Matsunaga, J. Okada, and S. Uyeo, *Chem. Commun.*, 525 (1965); E. Flury, E. Weiss, and T. Reichstein, *Helv. Chim. Acta*, **48**, 1113 (1965); P. S. Steyn, W. J. Conradie, C. F. Garbers, and M. J. de Vries, *J. Chem. Soc.*, 3075 (1965); H. Minator and T. Nagasacki, *ibid.*, 377 (1966); H. G. Lehmann, *Angew. Chem.*, **77**, 808 (1965); J. M. Ferland, Y. Lefebvre, R. Deghenghi, and K. Wiesner, *Tetrahedron Letters*, 3617 (1966).

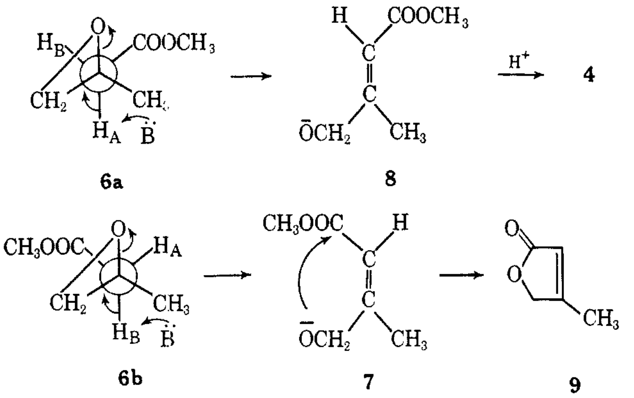
[3] A preliminary communication on some of this work has appeared: *ibid.*, 791 (1966).

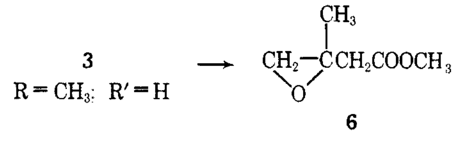
[4] S. Akioshi, K. Okuno, and S. Nagaham, *J. Am. Chem. Soc.*, **76**, 902 (1954).

[5] R. Adams and M. Gianturco, *ibid.*, **79**, 166 (1957).

jacent to the ester function to give a back-side opening of the newly formed epoxide with concurrent formation of the double bond and alkoxide ion requires only a catalytic amount of base. These two predictions are consistent with the fact that the best yields were obtained when slightly more than 1 equiv of base was used. If the base-catalyzed epoxide isomerization is assumed to proceed by a *trans* elimination, the stereospecificity of the reaction becomes apparent. A comparison of Newman projections which **6** may assume during elimination shows that there are fewer steric and electronic interactions when the carboxymethyl group is furthest away from the epoxide oxygen. Thus the preferred conformation would be **6a** rather **6b** (Scheme I). Abstraction of proton H_B from the less stable conformer **6b** would lead to the *cis*-alkoxide ion **7** which would then lactonize to **9**. Base abstraction of proton H_A in the preferred conformer **6a** would give ion **8** which on protonation would yield the observed **4**. Since the abstraction of proton H_B should occur to a limited extent, a small amount of **9** should be formed. Gas-liquid partition chromatography (glpc) of the crude reaction product indicated the presence of a small amount (2-3%) of **9**. The isomerization of β,γ-epoxy carbonyl compounds to γ-hydroxy α,β-unsaturated carbonyl compounds has been observed previously.[6,7]

Scheme I

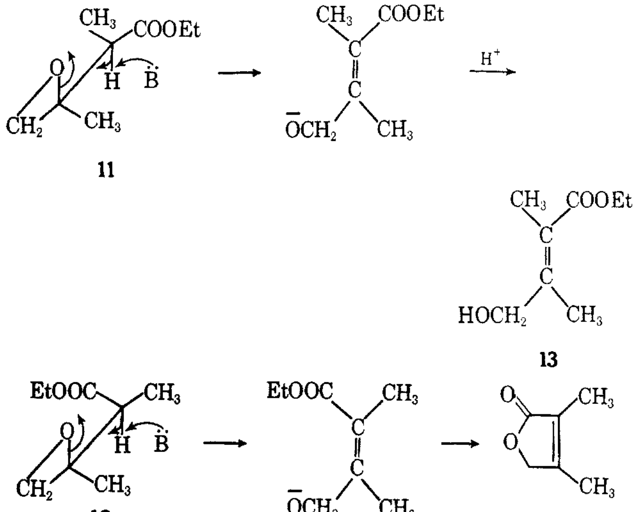




Although **4** was obtained in high yield, the problem of double-bond isomerization and lactonization remained. Many attempts at isomerization of **4** including strong acids, iodine, and palladium on charcoal, were unsuccessful giving only starting material or polymer. Photoirradiation studies proved to be a more fruitful approach to the desired butenolide. Irradiation of a solution of **4** containing a trace of HCl in a quartz cell with a high-pressure mercury arc gave rise to isomerization and transesterification to **9** in the same step and in good yields (74%).

In order to determine the generality of the above route a number of Reformatsky reaction products were studied. The Reformatsky reaction product from ethyl α-bromopropionate and chloroacetone (**3**, R = CH_3; R_1 = CH_3) as a pair of diastereomeric racemates was found to be unaffected by the mild base conditions used previously, but the known butenolide **10** could be prepared in 62% yield by treatment of **3** (R = CH_3; R_1 = CH_3) with an excess of sodium ethoxide followed by acidification and irradiation as before. Although the sodium ethoxide step above gave the best yields, the use of sodium amide under rather carefully controlled conditions proved more illuminating in terms of establishing the detailed route of the base reaction. When **3** (R = CH_3; R_1 = CH_3) was allowed to react with exactly one equivalent of sodium amide in liquid ammonia, two racemic products were obtained in a 61:39 ratio (glpc). The analytical, spectral, and chemical data indicated that these products were the racemic, diastereomeric epoxides **11** and **12**, providing evidence for the earlier proposal. Further consistency for the stereospecificity of the epoxide isomerization lies in the fact that treatment of **3** (R = CH_3; R_1 = CH_3) with an excess of sodium amide or the mixture of diastereomeric epoxides **11** and **12** with one third of an equivalent of sodium amide gave the expected two products (**10** and **13**) in about the same ratio as epoxide formation. Since **13** whose structure was assigned on the basis of analytical and spectral data was found in the largest amounts, it must have been formed from **11** while butenolide **10** must have come from **12** as shown in Scheme II.

Scheme II

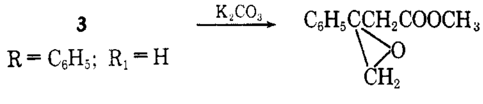


Although the Reformatsky reaction between methyl bromoacetate and phenacyl chloride proceeded smoothly to give **3** (R = C_6H_5; R_1 = H), the subsequent conversion by the base isomerization, irradiation sequence into the butenolide gave low yields which could not be improved upon. A second approach to the conversion of **3** (R = C_6H_5; R_1 = H) into the corresponding butenolide in high yield will be presented later. Two interesting facts were observed in this aspect of the work. First, it was possible to isolate 1,2-dibenzoylethane from the pot residue of the Reformatsky reaction work-up. This observation was the only instance in the study of side-product formation in the Reformatsky reaction of mixed α-halo sub-

[6] F. Sondheimer and S. Burstein, *Proc. Chem. Soc.*, 228 (1959); F. Sondheimer, S. Burstein, and R. Mechoulam, *J. Am. Chem. Soc.*, **82**, 3209 (1960).

[7] O. Isler, H. Lindlar, R. Ruegg, G. Saucy, and P. Zeller, *Helv. Chim. Acta*, **39**, 2041 (1956).

strates. Second, the epoxide intermediate, methyl 3,4-epoxy-3-phenylbutyrate (**14**), could be prepared in 83% yield by reaction of **3** (R = C_6H_5; R_1 = H) with potassium carbonate in acetone. The low yields of desired epoxide opened product presumably are due to the sensitivity of **14** to further reaction.



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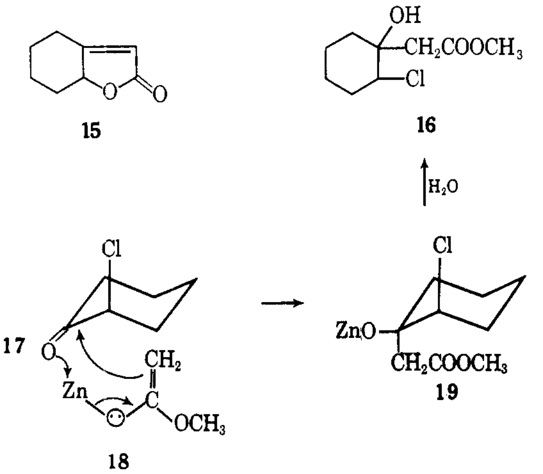
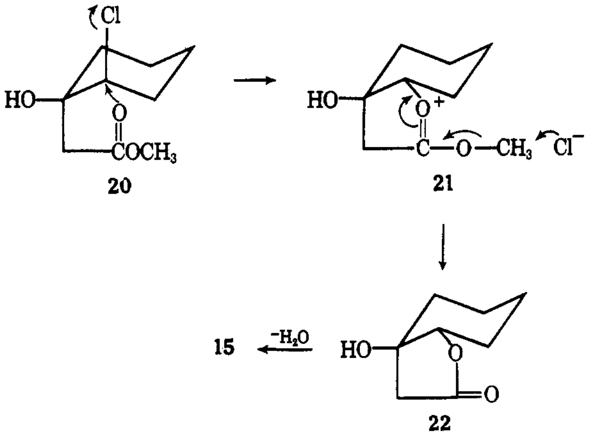
The model fused-ring system chosen to be studied was **15** (Scheme III). Our preliminary aim was to use the reaction sequence of base isomerization followed by irradiation from the chlorohydrin Reformatsky product **16**. Although the desired chlorohydrin could be prepared in excellent yield giving only one of the two possible isomers, base treatment of **16** gave only starting material plus a small amount of material which presumably is dehydrohalogenation product. The fact that the base reaction failed suggested that the chlorine and hydroxyl groups of **16** were *cis* to one another. The formation of the *cis* product exclusively can be rationalized by a consideration of the nature of the Reformatsky reagent and the conformation of the chloro ketone, chlorocyclohexanone (**17**). It has been shown[8] that, of the two conformers of **17**, the one in which the chlorine is axial is the preferred form particularly in nonpolar solvents. Further, the form where the chlorine is axial has been suggested[9] as being the most reactive toward nucleophilic reagents so that it seems likely that the axial chlorine conformation is the one reacting with the Reformatsky reagent. Accepting the structure of the Reformatsky reagent to be **18**,[10,11] a cyclic mechanism can be pictured for the reaction where steric factors would be important. Initial coordination of zinc with the carbonyl oxygen from the bottom, unhindered side with concurrent axial attack on the carbonyl carbon by the Reformatsky reagent would give **19** which on work-up would yield the observed product.

SCHEME III



Since **19** could not be converted into the epoxide as such, a number of attempts were made to invert the center containing the chlorine by reaction with iodide ion in order to use the sequence which had been developed but these attempts were unsuccessful. A successful, high-yield approach for converting **19** into the butenolide **15** was found involving a high-temperature cyclization and dehydration. The reaction is analogous to the work of Weinstock[12] who found that ethyl (*trans*-2-bromocyclopentyl) acetate was converted into a γ-lactone and ethyl bromide at 185° while the *cis* isomer gave only hydrogen bromide and olefin. In the present case reaction did not begin until a temperature of 210° was reached at which time methyl chloride could be collected. After gas evolution ceased, the temperature was raised to 235° and water collected. Distillation of the residue gave the desired butenolide (**15**) in high yield. Similar treatment of **3** (R = C_6H_5; R_1 = H) gave high yields of the 3-phenylbutenolide. Application of this technique to **3** (R = CH_3; R_1 = H; and R = CH_3; R_1 = CH_3) gave only small amounts of the corresponding butenolides. The low yields can probably be attributed to the instability of the Reformatsky products as well as the fact that their boiling points were close to the pyrolysis temperatures. Weinstock proposed a two-step ionic mechanism for the cyclization which was later substantiated by Denny and Ciacin[13] using ^{18}O-labeled esters. In the present study the reaction can be pictured as an initial displacement of chlorine by the ester carbonyl oxygen as in **20** to give the intermediate **21**. Chloride ion attack on the methyl group would lead to the hydroxy lactone **22** which then thermally dehydrates to **15**.



Steric hindrance of the ketone in the Reformatsky reaction plays an important role[14] and thus it seemed desirable to investigate variations in the preparation of **3** which would not be subject to this problem. We have indications that lithium ethoxyacetylide which is not subject to steric hindrance in attack on ketones[15] can be used to replace the Reformatsky reagent in the first step of the method. The reaction of 2-chlorocyclohexanone with lithium ethoxyacetylide proceeded smoothly to give the ethinyl carbinol (**23**) which was

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(8) E. J. Corey and E. Burke, *J. Am. Chem. Soc.*, **77**, 5418 (1955).

(9) J. W. Cornforth, R. H. Cornforth, and K. K. Matthew, *J. Chem. Soc.*, 11 (1959).

(10) H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).

(11) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1791 (1965).

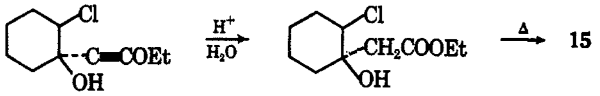
(12) J. Weinstock, *J. Am. Chem. Soc.*, **78**, 4967 (1956).

(13) D. B. Denny and J. Ciacin, *Tetrahedron*, 1377 (1964).

(14) G. Schappi and C. F. Seidel, *Helv. Chim. Acta*, **30**, 2199 (1947).

(15) Z. Norii, T. Yagami, and M. Hanaoka, *Chem. Commun.*. 7259 (1966).

not isolated but treated with dilute acid to give the chlorohydrin **24** in 54% yield. Normally in lithium ethoxyacetylide reactions the ethinyl carbinol is hydrated and water eliminated in the same step to give an α,β-unsaturated ester, but the presence of the chlorine apparently deactivates the hydroxyl group so that the reaction can be stopped at this point, an observation noted earlier in dehydration studies on **3**. The structure of **24** including the *cis* nature of the chlorine and hydroxyl groups was established by spectral data as well as the fact that it can be converted into **15** by the thermal reaction discussed earlier.



23 **24**

Experimental Section

All reactions were carried out under nitrogen and the distillations performed using a nitrogen capillary bleed. Infrared spectra were determined on a Beckman IR-5A spectrophotometer. Nmr spectra were obtained on a Varian A-60 or A56-60 instrument with values reported in parts per million shift from tetramethylsilane. Elemental analyses were carried out by Galbraith Laboratories Inc., Knoxville, Tenn. The adsorbant in all thin layer chromatographies was silica gel G. All of the glpc was run on an F & M Model 500 instrument with thermal conductivity detector using a 4 ft × 1/4 in. column packed with 20% Carbowax 20 M on Chromosorb W. The glpc data on relative amounts of various compounds was obtained from the areas under the curves and then calculating percentage contribution. Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

Reformatsky Reactions.—The reactions were run under approximately the same conditions with only slight variations; therefore, the details for one typical reaction are given. The yield and boiling point data are listed in Table I and the spectral data for the products are given in Table II. In all cases the zinc used was 20–30 mesh, reagent grade material which was acid washed and dried under high vacuum and the liquid reagents were distilled prior to use.

TABLE I

REFORMATSKY REACTION YIELDS

Compound	Yield, %	Bp, °C (mm)
3 (R = CH_3; R_1 = H)	79	38 (0.1)
3 (R = CH_3; R_1 = CH_3)[a]	63	68–74 (0.1)
3 (R = C_6H_5; R_1 = H)	67	130 (1)
16	84	84 (0.2)

[a] Ethyl ester in place of methyl ester.

TABLE II

SPECTRAL DATA FOR REFORMATSKY PRODUCTS

Compound	Infrared spectra, cm^{-1}	Nmr spectra, ppm
3 (R = CH_3; R_1 = H)	(Film) 3540, 1730	3.91 (1 H singlet), 3.76 (3 H singlet), 3.68 (2 H singlet), 2.70 (2 H singlet), 1.35 (3 H singlet)
3 (R = CH_3; R_1 = CH_3)[a]	(CCl_4) 3650, 1720	4.15 (2 H broadened quartet), 3.5 region (3 H complex multiplet), 2.8 (1 H multiplet), 1.25 (3 H singlet and 3 H triplet), 1.20 (3 H doublet)
3 (R = C_6H_5; R_1 = H)	(Film) 3620, 1730	7.30 (5 H multiplet), 4.50 (1 H singlet), 3.69 (2 H singlet), 3.35 (3 H singlet), 3.01 (2 H singlet)
16	(Film) 3670, 1730	4.15 (1 H complex triplet), 3.68 (3 H singlet), 3.30 (1 H singlet), 2.65 (2 H singlet), 1.75 region (8 H multiplet)

[a] Ethyl ester in place of methyl ester.

Methyl-4-chloro-3-hydroxy-3-phenylbutyrate (3, R = C_6H_5; R_1 = H).—To a three-necked flask containing a suspension of 34 g (0.52 mole) of zinc, 2.4 l. of absolute ether, 1.0 l. of absolute benzene, and a trace of iodine heated to the reflux point was added 10% of a reagent solution consisting of 80.4 g (0.527 mole) of methyl bromoacetate and 81.1 g (0.53 mole) of phenacyl chloride in 250 ml of absolute ether. The heating and stirring were discontinued until the reaction started. Stirring was begun and the remainder of the reagent solution was added at a rate to maintain a gentle reflux without additional heating. The reaction mixture was heated at reflux with stirring for an additional 14 hr, poured over ice, and the zinc complex was decomposed with dilute hydrochloric acid. The aqueous layer was separated and extracted with ether. The organic portions were combined, washed in succession with saturated sodium chloride and a saturated sodium bicarbonate, and dried over magnesium sulfate, and solvents were removed *in vacuo*. Distillation of the residue afforded 80.2 g (67%) of **3** (R = C_6H_5; R_1 = H), bp 130° (1 mm). The solid residue from distillation was recrystallized from carbon tetrachloride to give 1,2-dibenzoylethane: mp 147–148° (lit.[16] mp 142–143°), infrared spectra (film) 1685 cm^{-1}, nmr spectra 7.70 (10 H multiplet) and 3.42 ppm (4 H singlet).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.33; H, 6.01.

Methyl *trans*-4-Hydroxy-3-methyl-2-butenoate (4).—To 68 ml of a cold solution of 20% methanolic potassium hydroxide was added 40.4 g (0.24 mole) of **3** (R = CH_3; R_1 = H) with stirring. The reaction mixture was stirred 45 min at ice-bath temperature and acidified with 20% methanolic hydrogen chloride. The reaction mixture was adjusted to pH 6–7 (pH paper) by stirring the solution over solid sodium bicarbonate and filtered. The addition of ether to the filtrate caused a precipitate to form which was filtered and washed with ether. The combined organic material was dried over magnesium sulfate and distilled *in vacuo* to remove ether and methanol. Distillation of the residue gave a forerun of 11.5 g of starting **3** (R = CH_3; R_1 = H) and 21.5 g of **4** (96% yield based on unrecovered **3**) (R = CH_3; R_1 = H): bp 70–90° (0.5 mm) [lit.[17] bp 90–100° (6 mm)]; infrared spectra (film) 3500, 1715, 1650, and 848 cm^{-1}; nmr spectra 6.02 (1 H singlet), 4.94 (1 H singlet), 4.15 (2 H singlet), 3.69 (3 H singlet), and 2.09 ppm (3 H singlet).

Conversion of 4 into Mesaconic Acid.—To a stirred, cold solution of 7.0 g (54 mmoles) of **4** in 60 ml of acetone was added a solution of 10 g of chromium trioxide and 5 ml of sulfuric acid in 25 ml of water so that the temperature did not exceed 40°. The reaction was stirred at ice-bath temperature 1 hr and 4 ml of sulfuric acid was added. To the reaction mixture was added 30 ml of methanol and stirring was continued 20 min. The chromium complex was dissolved in 20 ml of concentrated hydrochloric acid, 50 ml of water was added, and the aqueous solution was continuously extracted with ether. The residue from evaporation of the ether was taken up in 35 ml of 20% methanolic potassium hydroxide and the solution was refluxed 2 hr. The acidified reaction mixture was continuously extracted with ether overnight and the ether was removed *in vacuo* to give a crystalline residue. Recrystallization from ethanol–water followed by vacuum sublimation yielded 2.18 g (31%) of **5**, mp 205–206° (lit.[18] mp 202°).

Anal. Calcd: neut equiv, 65.05. Found: neut equiv, 68.0.

4-Hydroxy-3-methyl-2-butenoic Acid γ-Lactone (9).—A solution of 7.57 g (58 mmoles) of **4** and 3 ml of a 20% methanolic hydrogen chloride solution in 550 ml of absolute methanol was purged with nitrogen and irradiated 1 hr in a quartz cell using a 550-w high-pressure mercury arc as a source. The solution was neutralized by the addition of solid sodium bicarbonate and the methanol was removed *in vacuo*. The residue in 100 ml of water was continuously extracted with ether for 10 hr. The ether was removed *in vacuo* and the water was removed by azeotropic distillation with benzene. Distillation through a Claisen column gave 4.20 g (74%) of **9**, bp 68–78° (0.25 mm). The analytical sample was obtained by distillation through a 15-in. spinning-

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[16] J. P. Schaeffer, *J. Org. Chem.*, **25**, 2027 (1960).

[17] M. Halmos and T. Mohacsi, *J. Prakt. Chem.*, **12**, 50 (1960).

[18] R. C. Weast, "Handbook Chemistry and Physics," 45 ed, Chemical Rubber Co., Cleveland, Ohio, p 329c.

band column: bp 58–62° (0.6 mm) [lit.[19] bp 106–107° (12 mm); infrared spectra (film) 1750 and 1640 cm^{-1} (but no 1889 cm^{-1} for the Δ^2-butenolide was observed); nmr spectra 5.78 (1 H singlet), 4.73 (2 H singlet), and 2.12 ppm (3 H singlet).

Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16. Found: C, 61.47; H, 6.31.

2,3-Dimethyl-4-hydroxy-2-butenoic Acid γ-Lactone (10).—A solution of 10.1 g (55 mmole) of **3** ($R = CH_3$; $R_1 = CH_3$) in 10 ml of absolute ethanol was slowly added to 1.45 g (63 mmole) of sodium metal dissolved in 50 ml of absolute ethanol. The reaction mixture was stirred at room temperature for 70 min, and a solution of 5 ml of 20% methanolic hydrogen chloride in 490 ml of methanol was added. The solution was purged with nitrogen and irradiated 115 min as described earlier. The reaction mixture was worked up as before and distilled through a Claisen column to give 3.97 g (62%) of butenolide **10**: bp 75–85° (0.1 mm), mp 32–35° (sealed capillary) [lit.[5,20] bp 64° (0.2 mm), mp 36–38°]; infrared spectra (film) 1745 and 1686 cm^{-1}; nmr spectra 4.62 (2 H singlet), 2.01 (3 H singlet), and 1.68 ppm (3 H singlet). The analytical sample was collected by glpc.

Anal. Calcd for $C_6H_8O_2$: C, 64.26; H, 6.18. Found: C, 64.29; H, 6.37.

The Reaction of 3 ($R = CH_3$; $R_1 = CH_3$) with 1 Molar Equiv of Sodium Amide.—To a solution of 2.14 g (0.55 mmole) of sodium amide in 2 l. of liquid ammonia was added 10 g (0.55 mmole) of **3** ($R = CH_3$; $R_1 = CH_3$) over a 10-min period. The mixture was stirred with refluxing 2 hr and the ammonia was evaporated over 1.5 hr. The residue was washed with ether, the ether was removed *in vacuo*, and the yellow liquid remaining was distilled through a Claisen column to give 2.0 g (25%) of a mixture (61:39) of **11** and **12** [bp 65–75° (15 mm)] which gave a positive periodic acid test;[21] infrared spectra (CCl_4) 3080 and 1730 cm^{-1}; nmr spectra 4.12 (2 H quartet), 2.5 (3 H multiplet), and 1.21 ppm (9 H multiplet). The analytical sample was obtained by glpc.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 60.74; H, 8.92.

The Reaction of 3 ($R = CH_3$; $R_1 = CH_3$) with Excess Sodium Amide.—To a stirred mixture of 7.92 g (0.20 mole) of sodium amide in 4.8 l. of liquid ammonia was added 33.5 g (0.18 mole) of **3** ($R = CH_3$; $R_1 = CH_3$) over 10 min. The mixture was refluxed with stirring 5.5 hr, the excess sodium amide was neutralized by the addition of 10 g of ammonium chloride, and the ammonia was evaporated over 4 hr. The residue was washed with ether, the ether was removed *in vacuo*, and the residue was vacuum distilled to give a mixture of 35% **10** and 65% **13**, bp 80–90° (1 mm). The same ratio of products could be obtained by the reaction of the epoxide mixture **11** and **12** with a small amount of sodium amide under the same conditions described above. Pure hydroxy ester **13** was obtained by preparative glpc: infrared spectra (CCl_4) 3620, 1710, and 1650 cm^{-1}; nmr spectra 4.18 (2 H quartet), 4.10 (2 H singlet), 3.69 (1 H singlet), 1.92 (3 H broadened singlet), 1.82 (3 H broadened singlet), and 1.28 ppm (3 H triplet).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.91. Found: C, 60.62; H, 8.94.

Methyl 3,4-Epoxy-3-phenylbutyrate (14).—A suspension of 20 g of potassium carbonate and 25 g (0.108 mole) of **3** ($R = C_6H_5$; $R_1 = H$) in 500 ml of acetone was refluxed 36 hr. Acetone was removed by distillation, 300 ml of water was added, and the solution was extracted with three 400-ml portions of ether. The combined ether solutions were dried and ether was removed in the usual manner. Distillation of the residue afforded 18.1 g (83%) of **14** [bp 84–87° (0.1 mm)] which gave a positive periodic acid test;[21] infrared spectra (film) 1730 cm^{-1}; nmr spectra 7.26 (5 H multiplet), 3.46 (3 H singlet), 3.00 (1 H doublet, $J = 5$ cps), 2.94 (2 H singlet), 2.68 ppm (1 H doublet, $J = 5$ cps).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.93; H, 6.50.

2-(2-Hydroxycyclohexylidine)acetic Acid γ-Lactone (15).—A small Claisen distilling apparatus was charged with 4.0 g (19.2 mmoles) of **16** and purged with nitrogen. The chlorohydrin **16** was heated to 210° for 20 min until gas evolution ceased and the temperature was raised to 235° for 50 min and a small amount of water was collected. The reaction mixture was cooled, taken up in ether, and dried over magnesium sulfate and ether was removed *in vacuo*. The residue was distilled to give 0.40 g of starting chlorohydrin **16** and 2.02 g (84% based on unrecovered **16**) of butenolide **15**: bp 100–120° (0.1 mm); mp (sealed capillary of material obtained from glpc) 27–28.5° (lit.[22] mp 24°); infrared spectra (film) 1748 and 1645 cm^{-1}; nmr spectra 5.68 (1 H singlet), 4.72 (1 H complex quartet), and 3.0–1.0-ppm region (8 H complex multiplet).

4-Hydroxy-3-phenyl-2-butenoic Acid Lactone.—Pyrolysis of **3** ($R = C_6H_5$; $R_1 = H$) in the manner described above gave 85% of the butenolide which after recrystallization from methanol was identical with authentic material prepared by the method of Elderfield[23] as evidenced by melting point (93–94°) and superimposable infrared spectra.

The Reaction of Chlorocyclohexanone with Lithium Ethoxyacetylide.—To a solution of 35.2 ml of 1.62 *M* *n*-butyllithium in hexane and 200 ml of absolute ether maintained at 0° was added 4.33 ml (57 mmoles) of freshly distilled ethoxyacetylene. The solution was stirred at room temperature for 0.5 hr, cooled to −20°, and to it was added over a 30-min period a solution containing 6.5 ml of 2-chlorocyclohexanone in 20 ml of absolute ether. The reaction mixture stirred 60 min at −10°, 60 ml of 1 *N* hydrochloric acid was added, the mixture was stirred 10 min, 30 ml of 6 *N* hydrochloric acid was added, and the solution was allowed to stand overnight at 4°. The aqueous phase was separated and extracted with ether; the ether portions were combined, washed with saturated sodium bicarbonate, and dried over magnesium sulfate. Removal of the ether and distillation gave a forerun of 1.1 g of 2-chlorocyclohexanone and 5.83 g (54% based on unrecovered 2-chlorocyclohexanone) of **24**, bp 78–92° (2 mm). A small amount of **24** was heated to 215° for 40 min, then 15 min at 240°. The reaction was cooled and the residue was distilled to give **15** identical in all respects with that prepared earlier.

Registry No.—**3** ($R = Ph$; $R_1 = H$), 6124-74-9; **3** ($R = CH_3$; $R_1 = CH_3$), 13970-37-1; **3** ($R = CH_3$; $R_1 = H$), 6124-72-7; **4**, 13866-57-4; **9**, 6124-79-4; **10**, 1575-46-8; **13**, 13866-60-9; **14**, 6124-78-3; **15**, 6051-17-8; **16**, 6124-75-0.

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