Recent Advances in the Chemistry of Unsaturated Lactones

Y. S. RAO

Department of Chemistry, Kennedy-King College, Chicago, Illinois 60621

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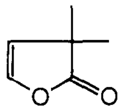
Contents

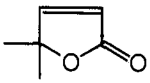
I. Introduction

The chemistry of butenolides was reviewed in 1964.[791] However, this review was not exhaustive in that several references were not included. A brief review of these compounds with special reference to naturally occurring lactones has also been published.[266] Other reviews about these lactones and hydroxy lactones or tetronic acids were published earlier.[445,447] The chemistry of *cis*-β-acylacrylic acids has also been reviewed.[21] The cyclization reaction of acetylenic acids to yield lactones has been reviewed as well.[23,376] Several theses on the chemistry of butenolides have been published (ref 477, 542, 661, 885, 900, 906, 1030, 1147).

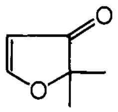
It has been observed that $\Delta^{\beta,\gamma}$-butenolides are isoelectronic with 5(4*H*)-oxazolones.[347] A similar comparison with oxazolone isomers would give the isomers shown below. It may be seen that unlike the oxazolone isomers, which can exist in five forms, there can only be three types of furanones: 2(3*H*), 2(5*H*), and 3(2*H*). Compound **6**, a $\Delta^{\beta,\gamma}$-butenolide with a β substituent, isoelectronic with 3-substituted isoxazolone is not known. Attempts to prepare **6** (R = C_6H_5) gave only β-phenyl-$\Delta^{\alpha,\beta}$-butenolide.[721] It is conceivable that if **6** (R = C_6H_5) is synthesized, it could be the starting material for a series of α-arylidene-β-aryl-$\Delta^{\beta,\gamma}$-butenolides (**7**) which are isoelectronic with 3-aryl-4-arylidene-5(4*H*)-isoxazolones (**8**).



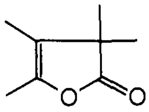
1
2(3*H*)-furanone (similar to 5(4*H*)-oxazolone)



2
2(5*H*)-furanone (similar to 5(2*H*)-oxazolone)



3
3(2*H*)-furanone (similar to 4(5*H*)-oxazolone)



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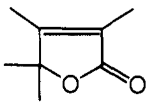
2(3*H*)-furanone (similar to 2(3*H*)-oxazolone)



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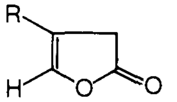
2(5*H*)-furanone (similar to 2(5*H*)-oxazolone)



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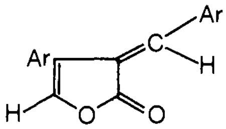

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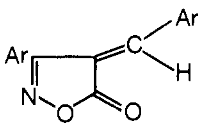

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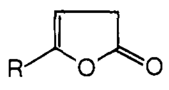
II. Scope of the Review

This review consists of recent advances in the chemistry of $\Delta^{\beta,\gamma}$-butenolides (**9**), $\Delta^{\alpha,\beta}$-butenolides (**10**), α-arylidene (alkylidene)-$\Delta^{\beta,\gamma}$-butenolides (**11**), and γ-arylidene (alkylidene)-$\Delta^{\alpha,\beta}$-butenolides (**12**). Also included for discussion are pulvinic acid (**13**) and its derivatives.

Cardenolides, isocardenolides, and pseudocardenolides with reference to their methods of preparation are also included. Recent advances in the chemistry of tetronic acids (**14**) are discussed. The chemistry of several naturally occurring lactones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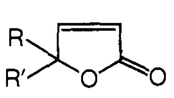
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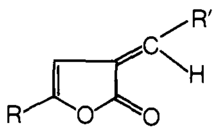
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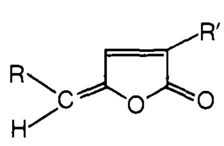
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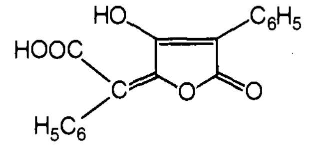
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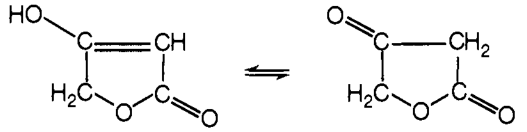
and synthetic approaches to α-methylenelactones **15** will be surveyed briefly. Bislactones and dilactones are also discussed. Not included are benzofuranones[712] and ascorbic and penicillic acids. Literature up to the end of February 1975 is reviewed.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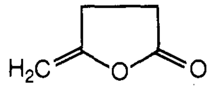
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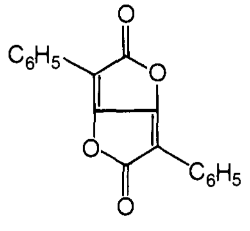
III. Nomenclature

The term "butenolide" for describing buteno- or crotonolactones was first employed by Klobb in 1898.[550,551] Though the butenolide nomenclature has been in vogue for quite sometime, along with the crotonolactone system, *Chemical Abstracts* currently has adopted the furanone system of naming these compounds. Thus $\Delta^{\beta,\gamma}$-butenolides are the 2(3*H*)-furanones and $\Delta^{\alpha,\beta}$-butenolides are 2(5*H*)-furanones. Compound **11** (R = R′ = C_6H_5) is called 3-phenylmethylene-5-phenyl-2(3*H*)-furanone, and **12** (R = R′ = C_6H_5) is 3-phenyl-5-phenylmethylene-2(5*H*)-furanone. Pulvinic acid (**13**) is 3-hydroxy-5-oxo-α,4-diphenyl-$\Delta^{2(5H),\alpha}$-furanacetic acid. Accordingly, pulvinic acid dilactone (**16**) is termed 3,6-diphenylfuro[3,2-*b*]furan-2,5-dione, and pulvinone (**17**) is 3-phenyl-4-hydroxy-5-phenylmethylene-2(5*H*)-furanone. In spite of this standardization of naming lactones, the crotonolactone and butenolide nomenclature still continues to be employed in the literature. In this review, the furanone-butenolide nomenclature will be used interchangeably, and for the pulvinic acid derivatives, trivial nomenclature will be used.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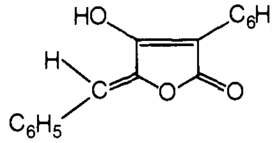
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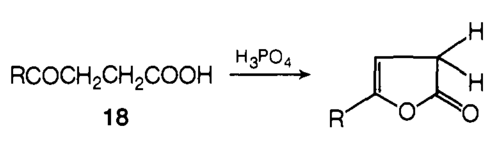
IV. Methods of Preparation

A. Synthesis of $\Delta^{\beta,\gamma}$-Butenolides (2(3*H*)-Furanones)

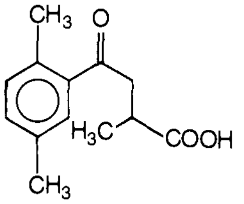
1. γ-Keto Acids

γ-Keto acids continue to be main sources for 2(3*H*)-furanones. Aliphatic acids may be cyclized by heating with orthophosphoric acid.[211] Compound **18** (R = C_2H_5) is prepared by the reaction of succinic anhydride with dichloroaluminoethyl, C_2H_5-$AlCl_2$.[421,422,806]


18

R = CH_3, C_2H_5, *n*-C_3H_7

Aromatic keto acids (R = Ar) may be lactonized by heating with acetic anhydride (ref 209–212, 344, 661, 785, 906). Acetyl chloride containing hydrogen chloride has been found to be equally effective in lactonization (ref 344, 507, 508, 829). Yet another method consists of heating the γ-keto acid to 300 °C and distilling the lactone under reduced pressure.[477,906] The pyrolysis of 3-(2,5-dimethylbenzoyl)-2-methylpropionic acid (**19**) and 3-(2,5-dimethylbenzoyl)butric acid (**20**) was at first supposed to yield the corresponding $\Delta^{\beta,\gamma}$-lactones.[477] These lactones have been shown since to contain the double bond in the α,β position.[906]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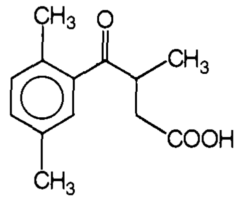
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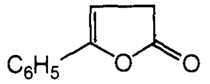
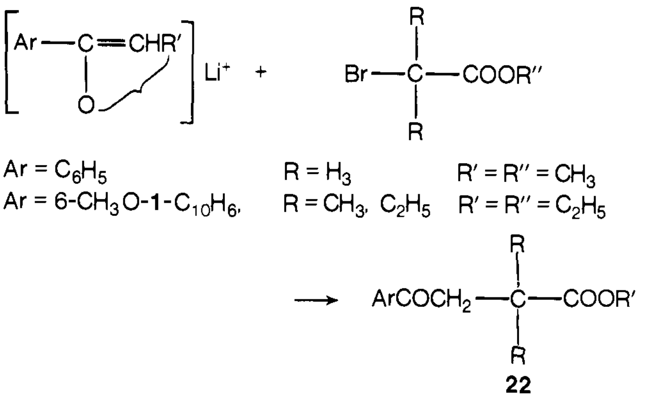
The cylization of β-benzoylpropionic acid to give 5-phenyl-2(3*H*)-furanone (**21**) has been studied extensively.[661] It was shown that acetic anhydride containing a trace of concentrated sulfuric acid, to help solubilize the γ-keto acid, at moderate temperatures gave 87% yield of **21**. The use of other catalysts, such as phosphoric and polyphosphoric acids and benzenesulfonic acid, in place of sulfuric acid did not raise the yields. Similarly, the usage of thionyl chloride or trifluoroacetic anhydride in place of acetic anhydride gave low yields. The use of nitrogen atmosphere and long reaction times was reported to yield 45% of **21**. A more recent method involves the use of dicyclohexylcarbodiimide in dioxane containing traces of concentrated sulfuric acid giving a 95% yield of the cyclized product.[793]


21

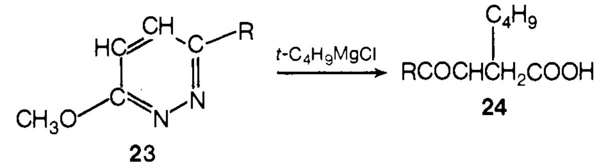
The required γ-keto acids are prepared by succinoylation of aromatic hydrocarbons or by the reaction of succinic and substituted succinic anhydrides with aryl Grignard reagents.[344] For highly substituted γ-keto acids (**22**), the reaction of α-bromo esters with lithio derivatives of acetophenone, acetonaphthone, and derivatives of these compounds is available.[507,508]


Ar = C_6H_5 R = H_3 R′ = R″ = CH_3

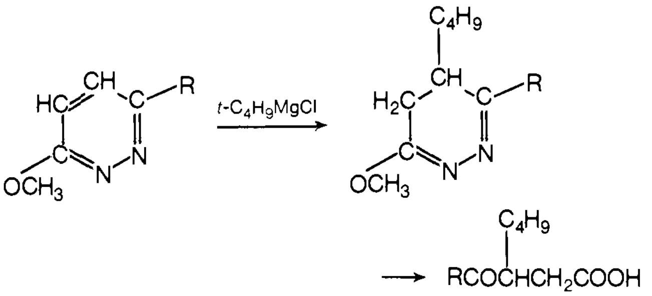
Ar = 6-CH_3O-1-$C_{10}H_6$, R = CH_3, C_2H_5 R′ = R″ = C_2H_5

22

A second method consists of treating 3-methoxy-6-alkyl(aryl)pyridazine (**23**) with *tert*-butylmagnesium chloride and hydrolyzing the intermediate product.

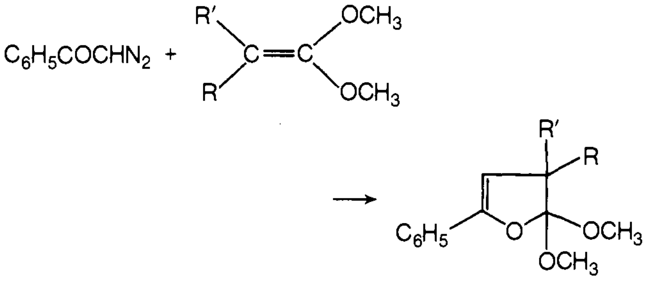


23 **24**



25

When benzoyldiazomethane is condensed with the dimethylacetal of a ketene derivative, compound **26** is obtained. Compound **26** may be considered to be the dimethyl acetal of γ-phenyl-α,α-disubstituted butenolide. Compound **26**, on reduction, gives γ-keto acids.[847,848]

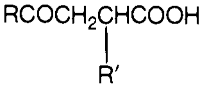


26

Other reagents used for cyclization are acetic anhydride, hydrogen chloride, and phosphorus pentachloride or stannic chloride in benzene.[956] Sulfuric acid (65%) causes cyclization of α,β-diphenyl-β-benzoylpropionic acid.[245,246]

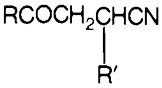
2. From α- (or β-)Aryl-β-aroylpropionic Acids

α-Aryl-β-aroylpropionic acids (**27**) may be prepared by the action of potassium cyanide on chalcones[17,377,771] and subsequent hydrolysis of the intermediate nitrile **28**. These compounds



$$\underset{R'}{RCOCH_2CHCOOH}$$

27

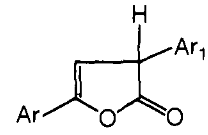


$$\underset{R'}{RCOCH_2CHCN}$$

28

may also be prepared by the Friedel-Crafts alkylation of β-aroylacrylic acids.[842] Compounds **27**, on heating with acetyl chloride[377] or acetic anhydride[842] or above their melting points, are reported to yield α,γ-diaryl-$\Delta^{\beta,\gamma}$-butenolides (**29**). It has been pointed out that some of these high-melting compounds are dimeric rather than monomeric.[17,661]

When β-benzoyl-α-methylpropionic acid (**30**) is heated with acetic anhydride, it is reported to yield α-methyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (**31**), melting at 84–86 °C. On the other hand, when **30** is heatd with acetic anhydride containing concentrated sulfuric acid, a compound **32** formulated as the $\Delta^{\alpha,\beta}$ isomer and melting at 226–227 °C is obtained. Recent work has shown that compound **31** is a yellow oil boiling at 134 °C (1 mm) and that the high-melting solid is dimer **33**.[604,661,906]



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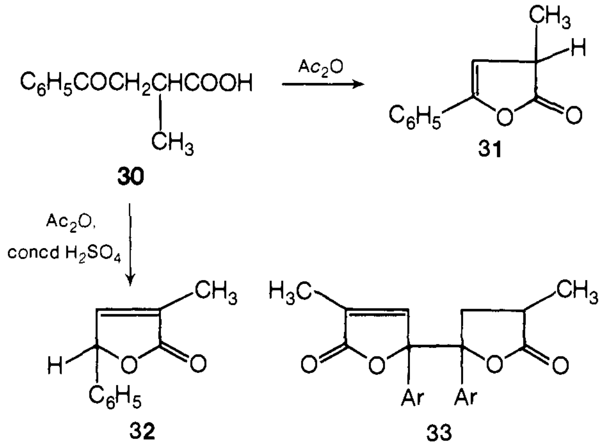
Ar = C_6H_5; Ar_1 = 4-ClC_6H_4
Ar = C_6H_5; Ar_1 = 2,4-$(CH_3)_2C_6H_3$
Ar = 4-$CH_3C_6H_4$; Ar_1 = 2,4-$(CH_3)_2C_6H_3$
Ar = 4-$C_6H_5C_6H_4$; Ar_1 = 2,4-$(CH_3)_2C_6H_3$
Ar = 2-tetralyl; Ar_1 = 2,4-$(CH_3)_2C_6H_3$
Ar = C_6H_5; Ar_1 = 2,4,6-$(CH_3)_3C_6H_2$
Ar = 1,2,4,5-$(CH_3)_4C_6H$; Ar_1 = C_6H_5
Ar = C_6H_5; Ar_1 = C_6H_5
Ar = C_6H_5; Ar_1 = 4-ClC_6H_4
Ar = C_6H_5; Ar_1 = 4-FC_6H_4
Ar = C_6H_5; Ar_1 = 4-$CH_3C_6H_4$
Ar = C_6H_5; Ar_1 = 2-$CH_3C_6H_4$
Ar = C_6H_5; Ar_1 = $C_6H_5CH_2$

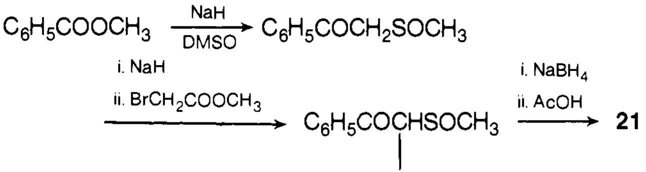


30 **31** **32** **33**

3. From Esters

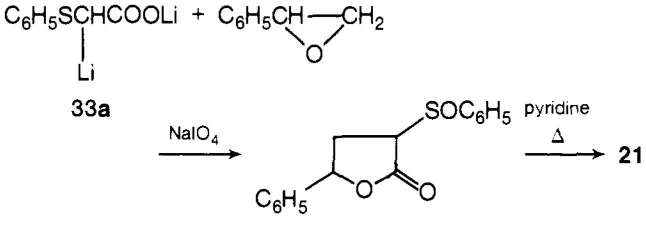
A multistep synthesis, starting from methyl benzoate, has been reported recently[591,592] (Scheme I).

SCHEME I



4. From Epoxides and Dianions

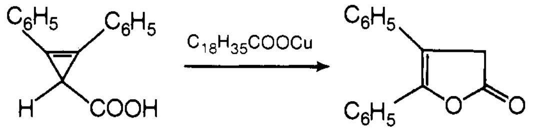
When phenylthioacetic acid in dry THF is treated with lithium diisopropylamide, the dianion **33a** is formed. Compound **33** at −60° gives with styrene oxide, a butyrolactone derivative, which on oxidation and pyrolysis in pyridine gives **21**.[503]



33a

5. From Cyclopropane Derivatives

When 2,3-diphenyl-2-cyclopropene-1-carboxylic acid (**34**) is heated in benzene in the presence of a catalytic amount of copper stearate, it rearranges to give β,γ-diphenyl-$\Delta^{\beta,\gamma}$-butenolide (**35**).[565]

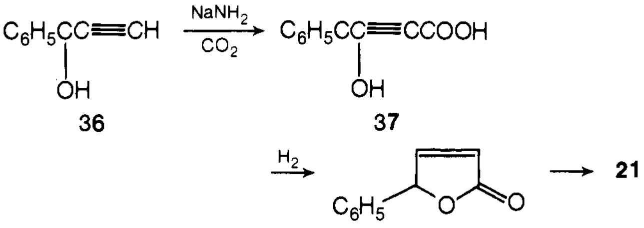


34 **35**

6. From Acetylenic Compounds

a. Acetylenic Acids

Carboxylation of phenylethynylcarbinol (**36**) in the presence of sodium amide gives 2-hydroxy-2-phenylprop-1-yne-1-carboxylic acid (**37**). Hydrogenation of **37** gives γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide (**38**) which isomerizes to **21**.[721]



$$C_6H_5\underset{OH}{\underset{|}{C}}C\equiv CH \xrightarrow[CO_2]{NaNH_2} C_6H_5\underset{OH}{\underset{|}{C}}C\equiv CCOOH$$

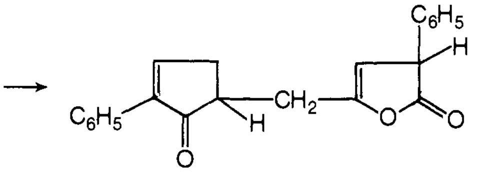
36 **37**

38

b. Metal Carbonyl Catalyzed Reactions

Allyl halides are treated with phenylacetylene in the presence of nickel tetracarbonyl dissolved in acetone to give **39**.[213] Similar reactions were carried out with 1-hexyne and 1-octyne.[215] In an alternate method allyl halides are treated with acetylene and carbon monoxide in the presence of nickel chloride and Mn-Fe alloy. The yield of lactones is about 25%.[685] In a more recent method, β-chlorovinylphenyl ketone has been reacted with acetone, with $Ni(CO)_4$ added as a catalyst.

$C_6H_5C\equiv CH + CH_2{=}CHCH_2Cl + Ni(CO)_4$



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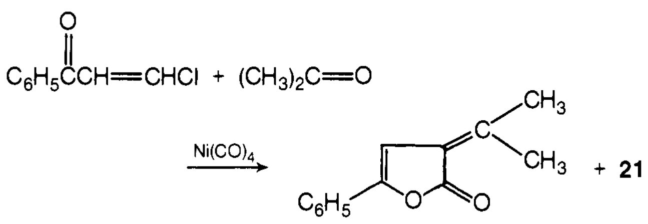


$$C_6H_5\overset{O}{\overset{\|}{C}}CH{=}CHCl + (CH_3)_2C{=}O$$

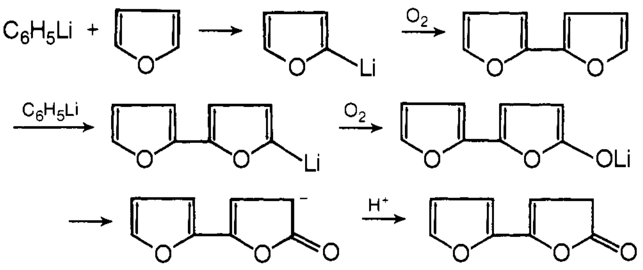
40

Ethyl acetate saturated with acetylene on treatment with benzoyl chloride and $Ni(CO)_4$ gives **21**.[687,1124,1125] Ethylene and carbon monoxide also react under 200 atm pressure at 160° in the presence of a catalyst of palladium iodide to give lactone derivatives.[593] Side reactions have been eliminated by adding aliphatic esters of C_{3-20} alcohols instead of ketonic solvents. Thus acetylene–acetyl bromide in ethyl acetate containing $Ni(CO)_4$ reacted to give α-angelica lactone. In a similar manner, compounds **21** and **39** are prepared.[1099]

7. From Furan Compounds

The reaction of furan with phenyllithium gives a 13% yield of γ-(2-furyl)-$\Delta^{\beta,\gamma}$-butenolide (**41**)[724] (Scheme II).

SCHEME II



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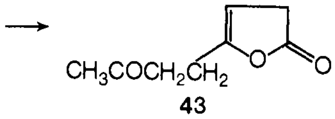
8. From Acetoacetic Ester Derivatives

Heating 4,7-dioxocaprylic acid (**42**) with acetic anhydride gives γ-(3-oxobutyl)-$\Delta^{\beta,\gamma}$-butenolide (**43**).[890] The reaction of sodioacetoacetate with ω-bromoacetophenone gives α-acetyl-γ-phenyl-$\alpha^{\beta,\gamma}$-butenolide (**44**) along with the $\Delta^{grka,\beta}$ isomer.

$CH_3COCH_2CH_2COCH_2CH_2COOH$

42



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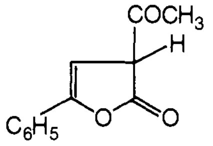

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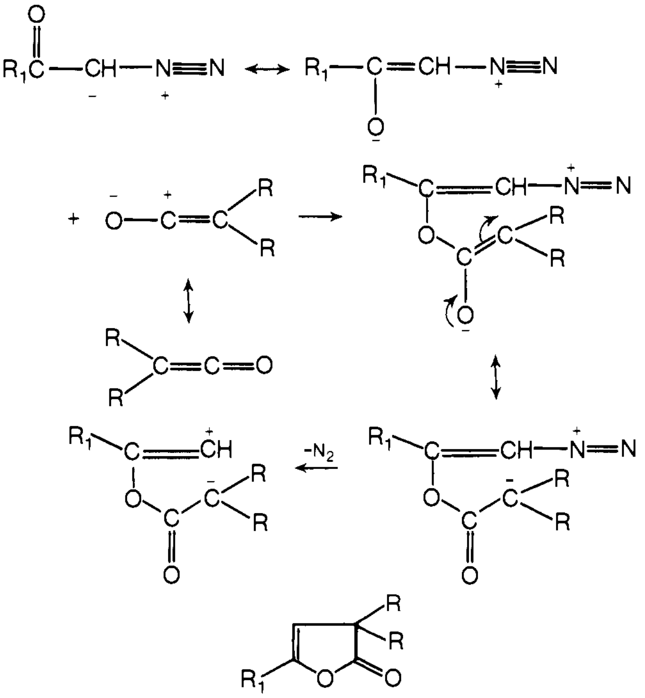
SCHEME III



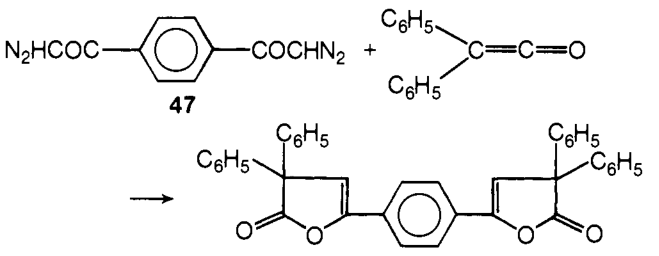
45

$R_1 = C_6H_5$, $R = C_6H_5$
R_1 = 4-$CH_3OC_6H_4$, $R = C_6H_5$
R_1 = 4-$NO_2C_6H_4$, $R = C_6H_5$
R_1 = 2-C_4H_4O, $R = C_6H_5$
$R_1 = C_{17}H_{35}$, $R = C_6H_5$
R_1 = 2-$C_{10}H_7$, R = H
R_1 = 4-IC_6H_4, $R = C_6H_5$
R_1 = 4-$C_6H_5C_6H_4$, $R = C_6H_5$

9. From Diazo Ketones and Ketene Derivatives

The reaction of diazo ketones with ketenes in ether in N_2 atmosphere at room temperature has been reported to give $\Delta^{\beta,\gamma}$-butenolides, products of 1,3-cycloaddition.[811-815] The following mechanism of Scheme III is suggested[812] for the $\Delta^{\beta,\gamma}$-butenolide formation.

Bisbutenolides **46** are obtained when the starting material consists of bis(diazo ketone). Bromination of **46** (R_1 = 4-$NO_2C_6H_4$, R = C_6H_5) gives the β-bromo derivatives. Compound **48** is obtained from tris(diazoacetylbenzene). A similar bis(butenolide) **49** is obtained from 1,5-diazoacetylthiophene. With dimethylketene and substituted diazo ketones, the corresponding α,α-dimethyl-$\Delta^{\beta,\gamma}$-butenolides **50** are obtained.[815]



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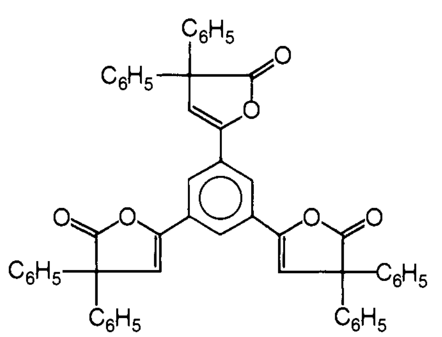

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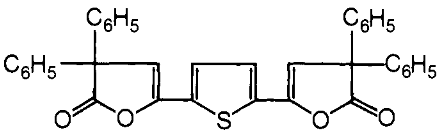

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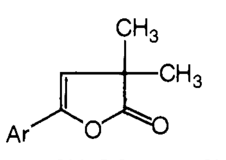
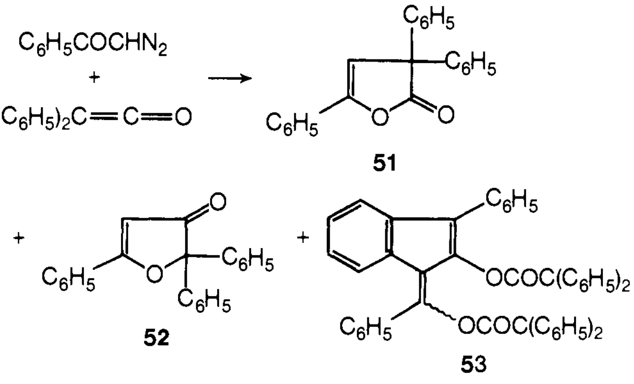


50, Ar = 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$

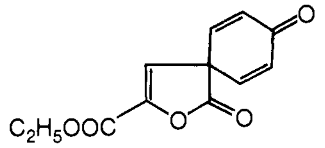
Thermolysis of α-diazo ketones also yields $\Delta^{\beta,\gamma}$-butenolides.[1029] A more detailed discussion of the thermal decomposition reaction is presented later.

The reaction of diazo ketones with ketenes has been recently employed in the synthesis of $\Delta^{\beta,\gamma}$-butenolides.[1057-1059,1122] It has been pointed out that in the reaction of α-diazoacetophenone and diphenylketene, the products obtained are α,α,γ-triphenyl-$\Delta^{\beta,\gamma}$-butenolide (**51**), 2,2,5-triphenyl-3(*H*)-furanone (**52**), and **53**.



10. From Pyruvic Acid Derivatives

Ethyl 4-hydroxyphenylpyruvate with phosgene and potassium *tert*-butoxide in *tert*-butyl alcohol gave the lactone **54** in 4% yield.[772]



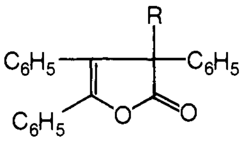
54

11. From γ-Aryl (Alkyl) Butyric Acids

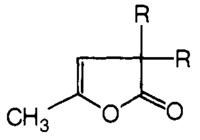
Recently, the oxidative cyclization of γ-arylbutyric acids by persulfate in the presence of silver or copper salts at 20–80 °C to γ-substituted $\Delta^{\beta,\gamma}$-butenolides has been reported.[1117]

12. From Other $\Delta^{\beta,\gamma}$-Butenolides

Alkylation of $\Delta^{\alpha,\beta}$-butenolides and $\Delta^{\beta,\gamma}$-butenolides in the presence of sodium hydride has been reported to give $\Delta^{\beta,\gamma}$-butenolides. Thus, α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide reacts with benzyl benzenesulfonate and NaH to give α,β,γ-triphenyl-α-benzyl-$\Delta^{\beta,\gamma}$-triphenylbutenolide. Similarly, alkylation of **55a** with methyl iodide in dimethyl sulfoxide and NaH gives α,β,γ-triphenyl-α-methyl-$\Delta^{\beta,\gamma}$-butenolide.[661] Similar alkylation of **21** with benzyl chloride gives α,α-dibenzyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide. α,α-Dibenzyl-γ-4-methoxyphenyl-$\Delta^{\beta,\gamma}$-butenolide is similarly obtained from γ-4-methoxyphenyl-$\Delta^{\beta,\gamma}$-butenolide. When compound **32** is treated with *n*-butyl chloride and NaH in Me_2SO, α-methyl-α-butyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide is obtained. With CH_3I and benzyl chloride, compound **32** gives α,α-dimethyl-v3g-phenyl-$\Delta^{\beta,\gamma}$-butenolide and **56**, a compound also obtained from α-benzyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide and methyl iodide. Both α and β-angelica lactones on methylation and benzylation in the presence of sodium hydride in Me_2SO give the same α,α,γ-trimethyl-$\Delta^{\beta,\gamma}$-butenolide (**56a**) and α,α-dibenzyl-γ-methyl-$\Delta^{\beta,\gamma}$-butenolides (**56b**).



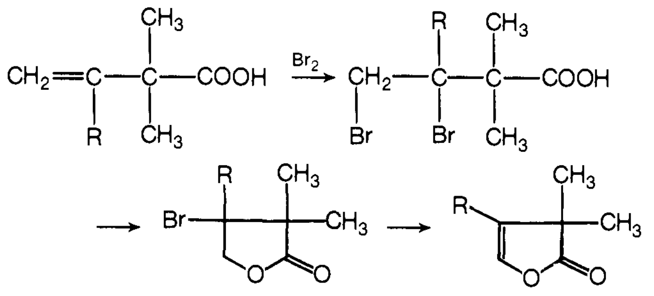
55a, R = CH_3
b, R = $C_6H_5CH_2$



56a, R = CH_3
b, R = $C_6H_5CH_3$

13. From Butenoic Acids

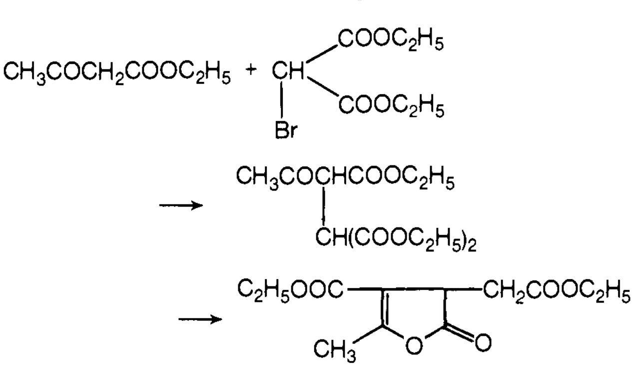
When 2,2,3-trimethyl-3-butenoic acid or 2,2-dimethyl-3-phenyl-3-butenoic acid is treated with bromine, the corresponding dibromo acid is obtained. On heating, the dibromo acid gives a β-bromobutyrolactone derivative, which on dehydrobromination with an amine gives a $\Delta^{\beta,\gamma}$-butenolide derivatives.[111,112]



R = CH_3, C_6H_5

14. *Condensation of Acetoacetic Ester with α-Bromo Dicarboxylates*

Condensation of acetoacetic ester with bromomalonic ester, diethyl α-bromosuccinate, and diethyl α-bromoglutarate yielded γ-oxo esters. On heating with H_3PO_4, these γ-oxo esters cyclize to give $\Delta^{\beta,\gamma}$-butenolides containing an ester function.[390,391]

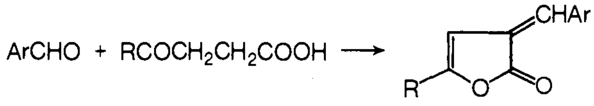


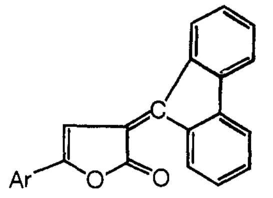
Compounds prepared by the above methods are listed in Table I in the Microfilm Edition (see paragraph at the end of this paper for ordering information).

B. Synthesis of α-Arylidene (Alkylidene)-γ-aryl (alkyl)-$\Delta^{\beta,\gamma}$-butenolides

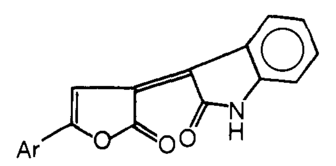
1. *From γ-Keto Acids by Perkin-Erlenmeyer Conditions*

Condensation of γ-keto acids with an aldehyde in the presence of acetic anhydride and sodium acetate still continues to be the largely used general method.[1126] This method has been used in synthesis of several arylidene butenolides (ref 308, 309, 439–442, 501, 502, 707, 823, 966, 970). It has been reported recently (ref 58, 59, 77, 434, 435, 1098) that cyclohexanone, fluorenone, and tetrachlorophthalic anhydride react with β-aroylpropionic acids under Perkin-Erlenmeyer conditions to give the corresponding butenolides **57**. Isatin condenses with β-aroylpropionic acids to give α-*N*-acetyloxindolydene butenolides **58**.[307] In a study of the degradation products obtained from Violacein, compound **58** (Ar = C_6H_5) has been synthesized.[80]



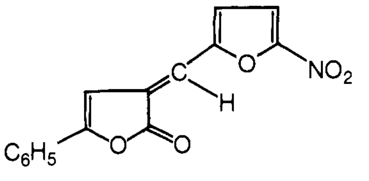


57, Ar = 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, C_6H_5



58, Ar = 4-ClC_6H_4, 4-$CH_3C_6H_4$, C_6H_5

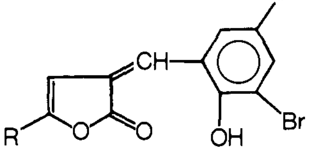
Ketones do not normally take part in Perkin-Erlenmeyer reactions, so the above methods constitute the first reported condensation of γ-keto acids with keto compounds. Recently it has been observed that acetone, methyl ethyl ketone, and 4-nitroacetophenone condense with β-aroylpropionic acids in the presence of potassium carbonate or sodium bicarbonate.[793] The condensation of 5-nitrofurfural with β-benzoylpropionic acid has been reported to give two geometric isomers of α-(5-nitrofurylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, (**59**).[501,502] It may be pointed out that benzaldehyde is reported to condense with β-benzoylpropionic acid to give a mixture of geometric isomers,[987] although the to geometric isomers have not been separated and characterized.



59

2. *From $\Delta^{\beta,\gamma}$-Butenolides*

α-Angelica lactone condenses with aromatic aldehydes in the presence of pyridine or triethylamine to give the corresponding α-arylidene derivatives.[259,1008,1127] A series of $\Delta^{\beta,\gamma}$-butenolides has been prepared and condensed with aromatic aldehydes[744,884] to give the corresponding arylidene butenolides. Under these conditions, 3,5-dibromosalicylaldehyde condenses with α-angelica lactone,[1008] γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, and γ-4-methyoxyphenyl-$\Delta^{\beta,\gamma}$-butenolide to give arylidene butenolides, **60**. Also isolated are the coumarin derivatives **61**.



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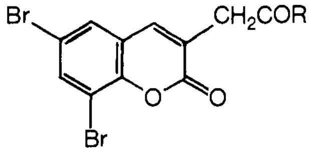
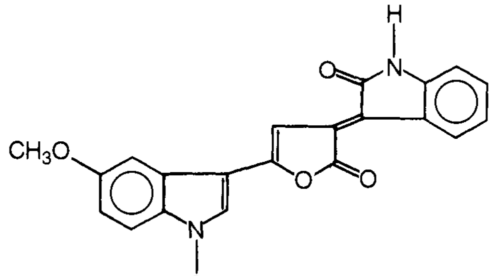


61

The lactone of β-veratroylpropionic acid is condensed with a series of aromatic aldehydes containing a nitro group in the ortho position.[431] Isatin also condenses with the lactone of γ-(5-methoxy-3-indolyl)-γ-oxobutyric acid to give **62**.[80]



62

Condensation of α-angelica lactone with silyl ynamines or diethylaminoacetylene gives the corresponding diethylaminoethylidene derivatives **63**.[339-341]

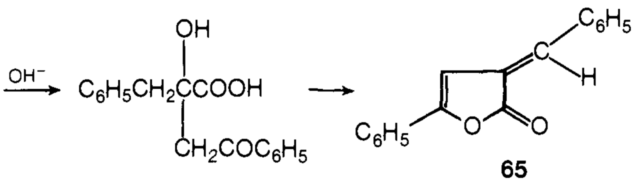
63

$R = CH_3,\ R_1 = H$
$R = CH_3,\ R_1 = CH_3$
$R = C_6H_5,\ R_1 = CH_3$
$R = R_1 = C_6H_5$
$R = CH_3,\ R_1 = C_6H_5$

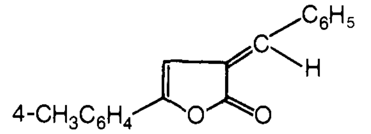
3. From Pyruvic Acid Derivatives

When phenylpyruvic acid condenses with acetophenone in the presence of a base an acid **64** is obtained. Compound **64** on heating with hydrochloric acid–acetic acid mixture give α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (**65**).[231,234] Under similar conditions, 4-methylacetophenone gave an acid, which on treatment with HCl–acetic acid gave a mixture of geometric isomers **66**.[231,237] The higher melting isomer was the same as that prepared from benzaldehyde and β-4-methylbenzoylpropionic acid.[149] The product from acetone and phenylpyruvic acid, **67**, condenses with benzaldehyde to give α,δ-dibenzylidenelevulinic acid, which on HCl–HOAc treatment gave the lactone **68**.[236] The lactone obtained from phenylpyruvic acid and benzyl methyl ketone was originally formulated as **69**.[235] This compound has since been shown to be **70**.[238] The compound, γ-(β-phenethyl)-α-benzylidene-$\Delta^{\beta,\gamma}$-butenolide (**71a**),[791] obtained from phenylpyruvic acid and benzalactone, is actually the $\Delta^{\alpha,\beta}$ isomer **71b**.[576]

$C_6H_5CH_2COCOOH + C_6H_5COCH_3$

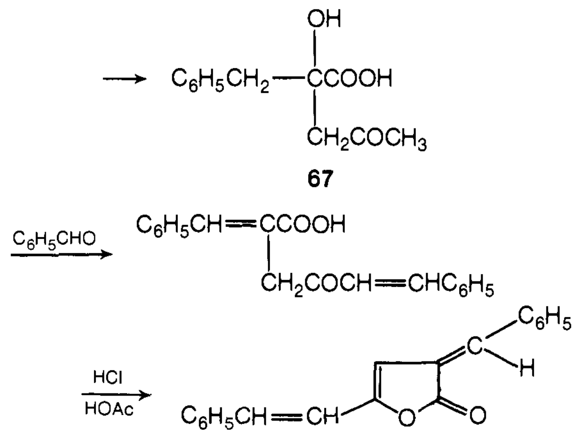


64 **65**



66

$C_6H_5CH_2COCOOH + CH_3COCH_3$



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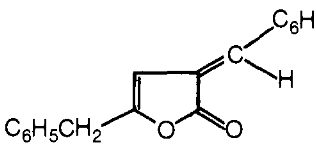
68

A recent method uses aroylpyruvic acids with phenyl iodoacetate to give butenolides **72**.[156]



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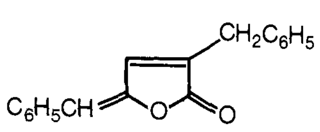

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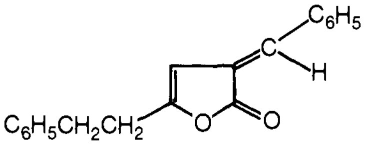
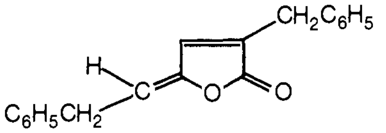
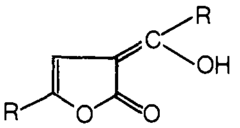


71a



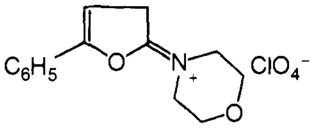
71b



72, R = C_6H_5, 4-ClC_6H_4, 4-Br C_6H_4, 2-thienyl

4. From Morpholinium Perchlorates of 5-Phenylfuran

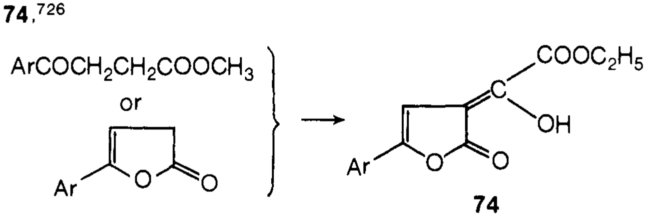
β-Benzoylpropionic acid is converted into the morpholide, which on treatment with acetic anhydride and perchloric acid gave **73**. Compound **73** reacted with aldehydes to give α-arylidenebutenolides. With 4-hydroxybenzaldehyde, α-4-hydroxybenzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide was obtained.[153,154] Since the morpholinium perchlorates are obtained from the γ-keto acids, this method is not of synthetic value. This method has also been employed to α-arylhydrazonobutenolide.[155]



73

5. By Condensation with Diethyl Oxalate

Condensation of γ-keto acid esters or $\Delta^{\beta,\gamma}$-butenolides with diethyl oxalate in the presence of sodium ethoxide gives **74**.[726]

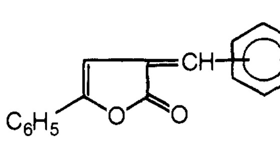


74

$Ar = C_6H_5,\ 4\text{-}CH_3OC_6H_4,\ 4\text{-}CH_3C_6H_4,\ 4\text{-}ClC_6H_4$

6. From Dialdehydes and γ-Keto Acids

Condensation of phthalaldehydes with β-benzoylpropionic acid gives the three isomeric butenolides **75**.[795] Under similar conditions, benzaldehyde condensed with the diketo acid **76** to give compound **77**.[793] Compound **76** gave a polymer with terephthaldehyde **78**.[793] It may be pointed out that γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (**21**) condenses with terephthaldehyde to give the bis butenolide **75** as well as monobutenolide **79**.[812,814] Also it has been observed that *o*-phthaldehyde condenses with β-benzoylpropionic acid in the presence of sodium methoxide to give 3-benzoyl-2-naphthoic acid (**80**).[650]



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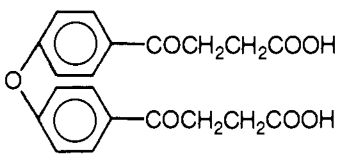

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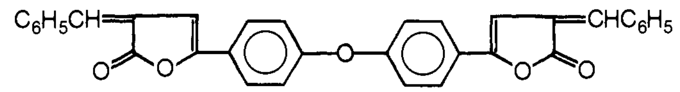

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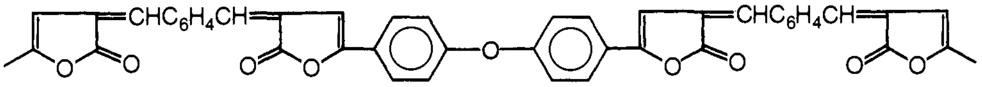

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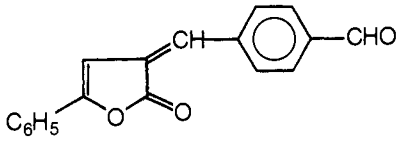

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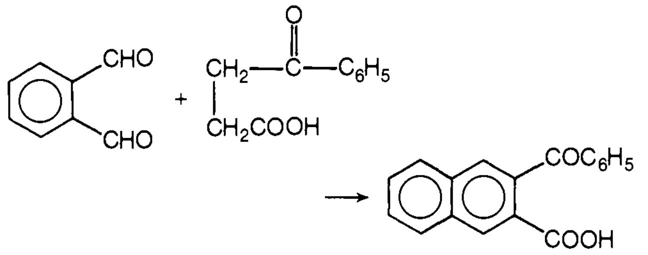
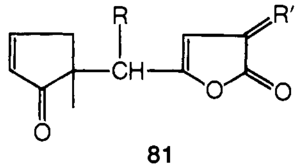


80

7. *From Acetylenic Derivatives*

Reaction of β-chlorovinyl phenyl ketone has been shown to react with acetone in the presence of $Ni(CO)_4$ added as a catalyst[184] to give γ-phenyl-α-isopropylidene-$\Delta^{\beta,\gamma}$-butenolide (**40**). Similarly prepared are compounds **81**.[689]

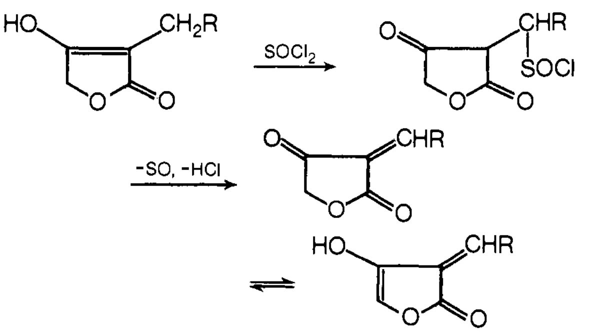


81

R = CH_3, R′ = cyclohexylidene
R = n-C_5H_{11}, R′ = cyclohexylidene
R = CH_3, R′ = $(CH_3)_2C{=}$
R = n-C_5H_{11}, R′ = $(CH_3)_2C{=}$

7. *From Tetronic Acid Derivatives*

When α-benzyltetronic acids react with thionyl chloride, α-benzylidene-β-hydroxy-$\Delta^{\beta,\gamma}$-butenolides (**82**) are obtained via the intermediate oxobutyrolactones.[738]



82, R = C_6H_5, 4-$CH_3C_6H_4$, 2,3-$(CH_3)_2C_6H_3$, 2,5-$(CH_3)_2C_6H_3$

Compounds prepared by the above methods are given in Table II (see Microfilm Edition).

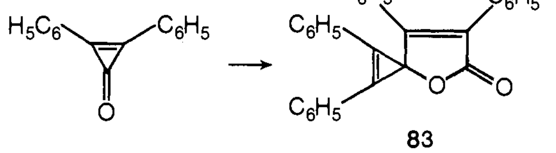
C. Synthesis of $\Delta^{\alpha,\beta}$-Butenolides (2(5*H*)-Furanones)

In the following sections, several methods for the synthesis of $\Delta^{\alpha,\beta}$-butenolides will be presented. The fact that the $\Delta^{\alpha,\beta}$-butenolide ring is present in natural products such as cardenolides explains why so many methods are available for the synthesis of this class of compounds. Not all the methods discussed below qualify as general methods and may be useful only in specific cases.

1. *From Cycloalkane Derivatives*

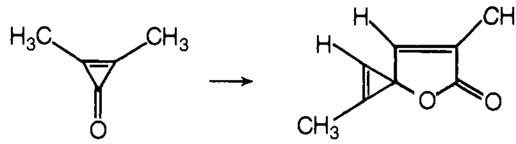
a. *Substituted Cyclopropanes*

When diphenylcyclopropenone is heated at 145–150 °C, diphenylacetylene and a dimer **83** are obtained. The yield of the dimer increased in the presence of bases.[157] When methylcyclopropenone is heated to 100 °C, compound **84** is obtained.[159] Under similar pyrolytic conditions, dipropylcyclopropenone yields only 4-octyne.[158] Breslow and coworkers[160] have earlier shown that Darling's lactone[264] is β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide. Recently it has been reported that cyclopropanedicarboxylic esters

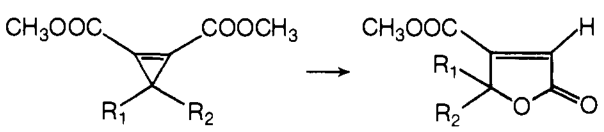


83

+ $C_6H_5C\equiv CC_6H_5$



84

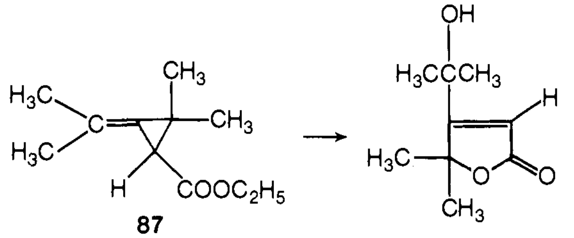


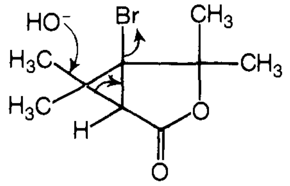
85 **86**

$R_1 = CH_3$, $R_2 = C_6H_5$
$R_1 = CH_3$, $R_2 = 2\text{-}C_{10}H_7$
$R_1 = R_2 = C_6H_5$
$R_1 = R_2 = 4\text{-}CH_3C_6H_4$

85 rearrange in benzene solution in the presence of Kieselguhr quantitatively to give $\Delta^{\alpha,\beta}$-butenolides **86**.[864]

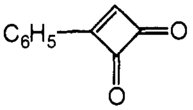
The compound ethyl 2,2-dimethyl-3-isopropylidenecyclopropane-1-carboxylate (**87**) is treated with bromine and lithium hydroxide successively to give the lactone **88**.[670] The free acid of **87** could be converted to a bromolactone **89**, which would react with hydroxide ion or water to give **88**.


87 **88**


89

b. Cyclobutane Derivatives

Phenylcyclobutadienequinone (**90**) reacts in a bomb at 150° with methanol to give β-phenyl-γ-methoxy-$\Delta^{\alpha,\beta}$-butenolide (**91**).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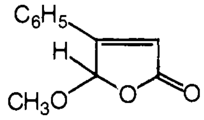
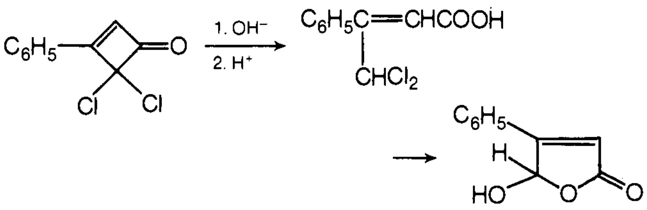
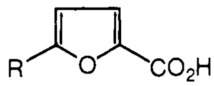

91

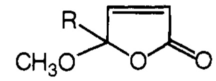
Treatment of 3-phenyl-4,4-dichlorobutenone with alkali gives α-dichloromethylcinnamic acid, which on further treatment with Ag salts lactonizes to the γ-hydroxy analog of **91**.[641]



2. *By Electrolytic Methods*

The anodic oxidation of 5-alkyl-2-furoic acids in protic solvents gives γ-alkyl-γ-methoxy-$\Delta^{\alpha,\beta}$-butenolides **92** and the γ-acetoxy analogs **93** as the principal products.[964,1133] The electrolytic decarboxylation of paraconic acids **94** in triethylamine-pyridine-water mixture with carbon electrodes gives 70–90% yields of unsaturated lactones.[963]

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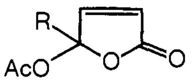
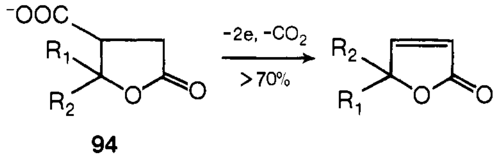

93

R = C_6H_{13}, $CH_3CH_2CH_2C(CH_3)_2$



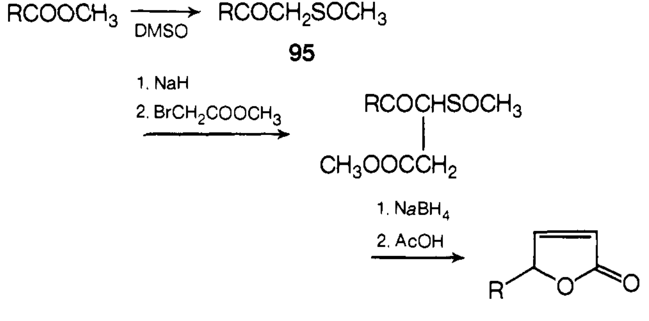
94

$R_1 = R_2 = CH_3$
$R_1 = CH_3$, $R_2 = n\text{-}C_3H_7$
$R_1 = CH_3$, $R_2 = n\text{-}C_6H_{13}$
$R_1 = H$, $R_2 = n\text{-}C_6H_{13}$
R_1, $R_2 = (\text{-}CH_2)_4$
R_1, $R_2 = (\text{-}CH_2)_5$
R_1, $R_2 = (\text{-}CH_2)_{11}$

3. *From β-Keto Sulfoxides*

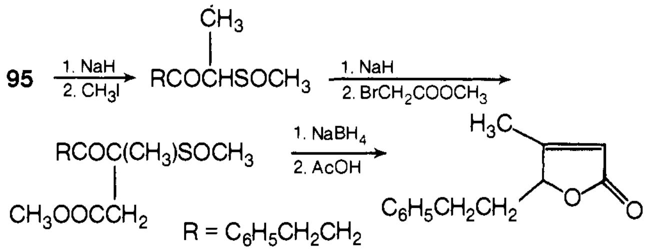
The methyl esters of a series of alkyl and aralkyl carboxylic acids are converted to the corresponding γ-alkyl (aralkyl) butenolides according to the reaction sequence in Scheme IV. Compound **95** could be the starting material for the synthesis of β-methyl-γ-alkylbutenolides via the β-methyl ketosulfoxide formed by methylation of **95** in the presence of sodium hydride (Scheme V). This method has also been successfully employed in the synthesis of γ-9-hydroxy-1-nonyl-$\Delta^{\alpha,\beta}$-butenolide.[592]

SCHEME IV



R = C_5H_{11}, $C_6H_5CH_2CH_2$, $n\text{-}C_{15}H_{31}$,
$CH_2{=}CH(CH_2)_8$

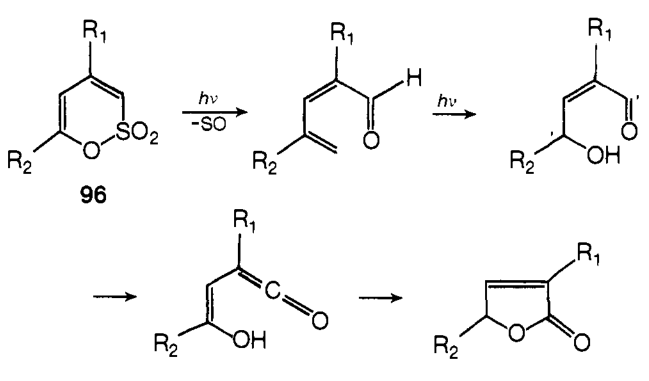
SCHEME V



R = $C_6H_5CH_2CH_2$

4. *Photolysis of Sultones*

The unsensitized photolysis of sultones **96** in ether solution results in 53–65% yield of the corresponding butenolides.

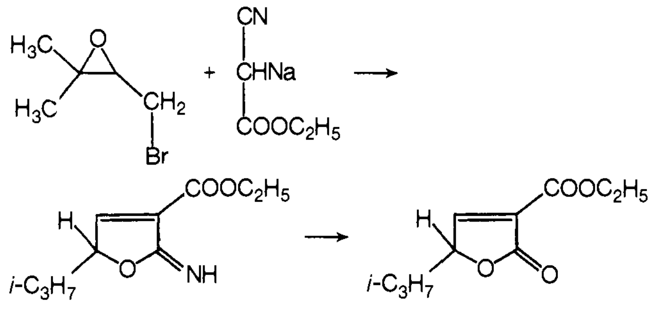


96

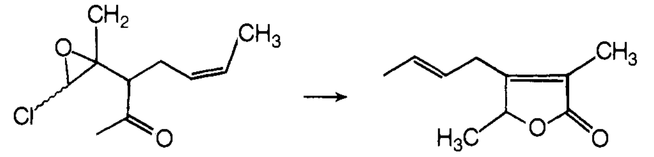
$R_1 = R_2 = CH_3$
$R_1 = CH_3$, $R_2 = C_6H_5$

5. *From Epoxides*

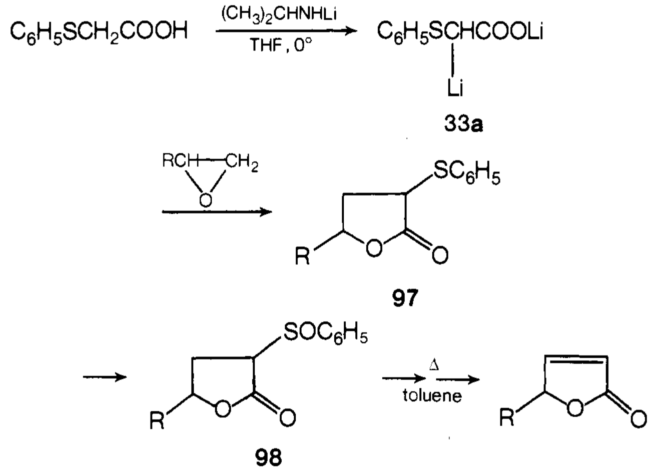
α-Bromo epoxides such as 2-bromo-2,3-epoxy-3-methylbutane, react with sodiocyanoacetic ester to give ethyl 2,5-dihydro-2-imino-5-isopropyl-2-furoate, which on acid hydrolysis



gives α-carboxyethyl-γ-isopropyl-$\Delta^{\alpha,\beta}$-butenolide.[981] With diethyl sodiomalonate, the bromo epoxide gives the above butenolide. With both 3-bromo-1,2-epoxybutane and 1-bromo-2,3-epoxybutane, the same butenolide, γ-ethyl-α-carboxyethyl-$\Delta^{\alpha,\beta}$-butenolide,[982] is obtained. 1-Chloro-1,2-epoxy-2-methyl-3-acetyl-5-hexene, on refluxing in xylene, gives α,γ-dimethyl-β-2-butenyl-$\Delta^{\alpha,\beta}$-butenolide.[171] In a recent method,



Uda and coworkers reported the reaction[503,985] of epoxides with dianion of phenylthioacetic acid. The intermediate α-phenylthiobutyrolactone is oxidized with sodium metaperiodate (or hydrogen peroxide or *m*-chloroperbenzoic acid) to the sulfoxide, which on pyrolysis at 110° gives the desired butenolides. This



$$C_6H_5SCH_2COOH \xrightarrow[\text{THF, } 0^\circ]{(CH_3)_2CHNHLi} C_6H_5S\underset{\displaystyle Li}{\underset{|}{C}}HCOOLi$$

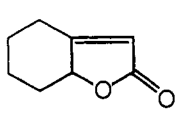
33a

97

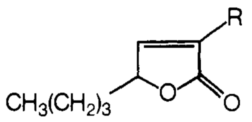
98

R = CH_3, $CH_3(CH_2)_3$, C_6H_5

method may be used for the synthesis of fused lactones such as **99**. The advantage of this method is that the dianion may be alkylated and the product in turn converted to a dianion similar to **33a** and used for the synthesis of α,γ-disubstituted butenolides **100**.



99

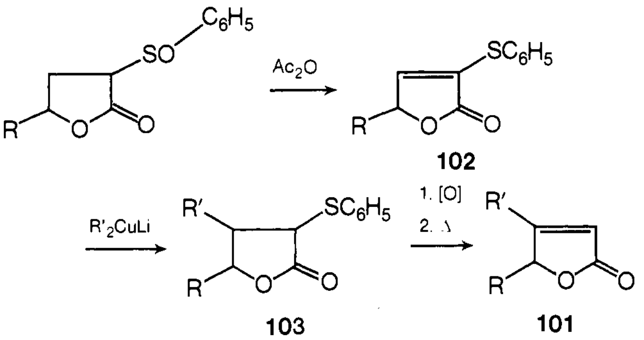


100, R = CH_3, C_2H_5

For the synthesis of β,γ-disubstituted butenolides **101**, Uda and coworkers[504] have used the α-phenylsulfinylbutyrolactone **98** as shown in Scheme VI.

Compound **102** adds to diethyl lithiomalonate to give the analog of **103** (R′ = $CH(COOC_2H_5)_2$). This compound on oxidation and pyrolysis gives **104**. However, with 1-morpholino-1-cyclopentene, **102** gives γ-cyclopentylidenebutenolide.

SCHEME VI

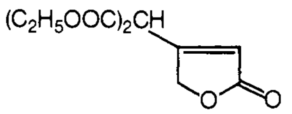


102

103

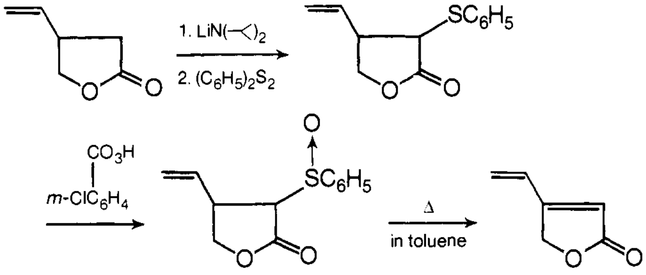
101

R = CH_3, R′ = CH_3; R = H, R′ = CH_3
R = CH_3, R′ = *n*-C_4H_9; R = H, R′ = *n*-C_4H_9
R = CH_3, R′ = CH_2═CH; R = H, R′ = CH_2═CH



104

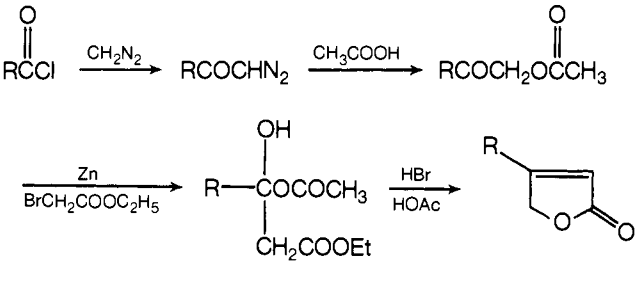
In a synthetic approach to sesquiterpene lactones, β-vinylbutenolide **105** (required for the annelation reaction) has been synthesized via the α-phenylthiolactone as shown below. The advantage of this method is that although **105** is an unstable compound, it may be stored as α-phenylsulfinyl-β-vinylbutyrolactone.[1062]



105

6. Reformatsky-Elderfield Reaction

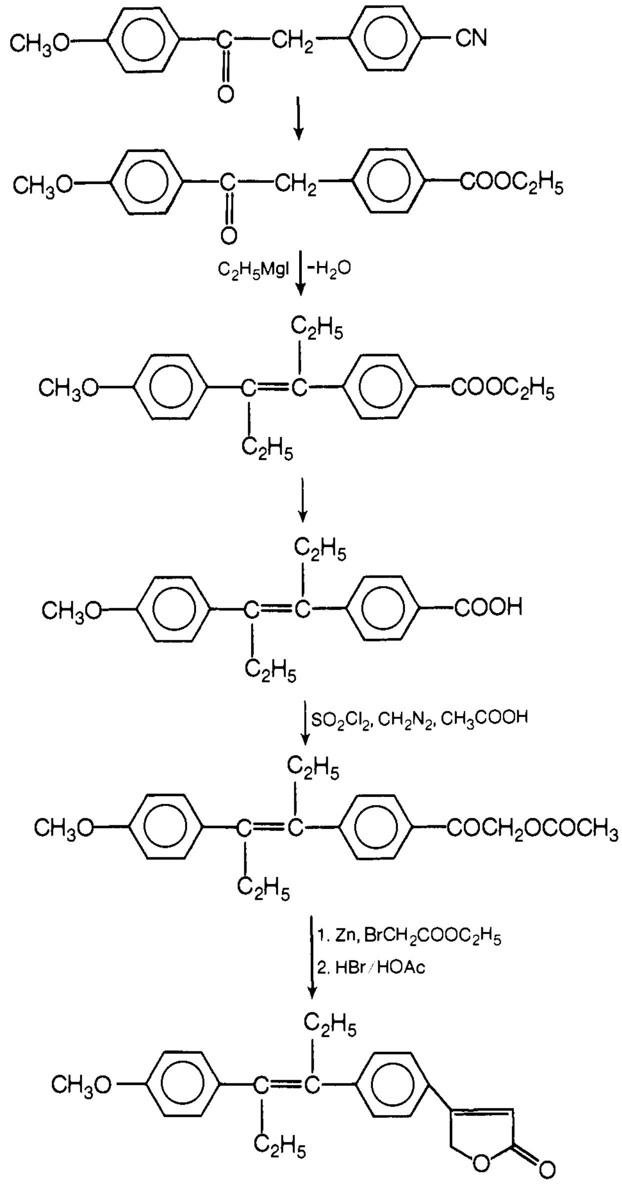
The reaction of acetoxy ketones with bromoacetic ester under Reformatsky conditions still continues to be the method of choice for the synthesis of $\Delta^{\alpha,\beta}$-butenolides. This method has been



employed for the synthesis of β-4-allyl-3-hydroxylphenyl-$\Delta^{\alpha,\beta}$-butenolide starting from 4-allyl-3-acetoxybenzoic acid.[313] Conine and Jones employed this method[225] and found that the yields varied from 3 to 69% in the final step.

In their efforts to synthesize β-vinyl-$\Delta^{\alpha,\beta}$-butenolide (**105**), Yoshikoshi and coworkers started with 3-hydroxypropionic acid and by the series of transformations given above got an overall yield of 12% of **105**. The intermediate, β-(2-acetoxyethyl)butenolide, was converted to **105** via the β-(2-bromoethyl) analog.[1062] Most recently the Reformatsky reaction was employed for the synthesis of β-(4-chlorophenyl)-$\Delta^{\alpha,\beta}$-butenolide.[984] The

SCHEME VII



106

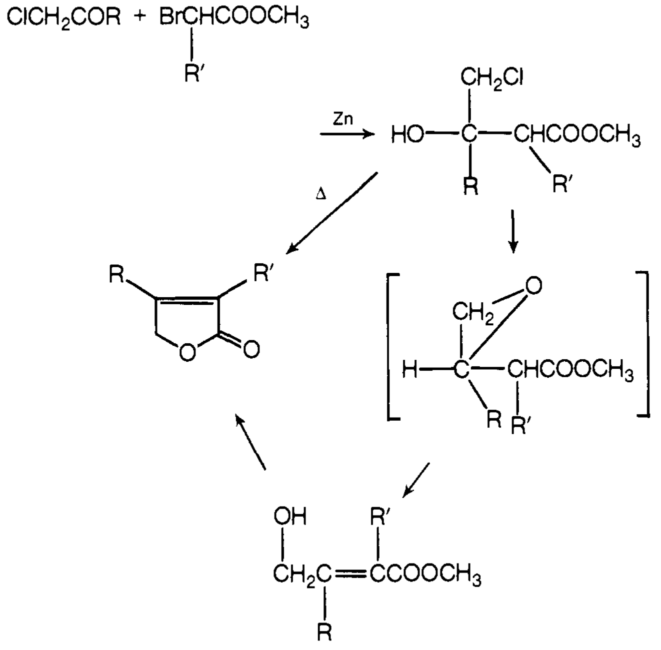
method has also found utility in the synthesis of 4-methoxy-4'-(β-$\Delta^{\alpha,\beta}$-butenolido)-α,α'-diethylstilbene (**106**)[620,621] (Scheme VII).

A series of butenolides with deoxybenzoin substituent in the β position has been reported.[740] In their studies of phenolic butenolides related to hexoestrol and stilboestrol, Campbell and Hunt prepared the saturated analog **107** of **106** with a hydroxy group instead of the methoxy group. It is noteworthy that when 3,4-di(*p*-acetoxyphenyl)-*n*-hexane is subjected to a Reformatsky reaction, only compound **107** is obtained and not the "dibutenolidohexane".[180] The hydroxy analog **106** has been prepared starting from 3,4-di(*p*-acetoxyphenyl)-*n*-hexene.

A variation of the Reformatsky reaction has been employed by Epstein and Sonntag.[320,321,900] Instead of α-acetoxy ketones, α-halo ketones were reacted with bromoacetic ester in the presence of zinc to give unstable Reformatsky adducts which were converted to $\Delta^{\alpha,\beta}$-butenolides either by pyrolysis or by conversion to unsaturated hydroxymethyl esters and photolysis of the latter (Scheme VIII). Under these conditions, 2-chlorocyclohexanone gave **99**. In a similar manner, β-cyclopentyl-$\Delta^{\alpha,\beta}$-butenolide was prepared.[789]

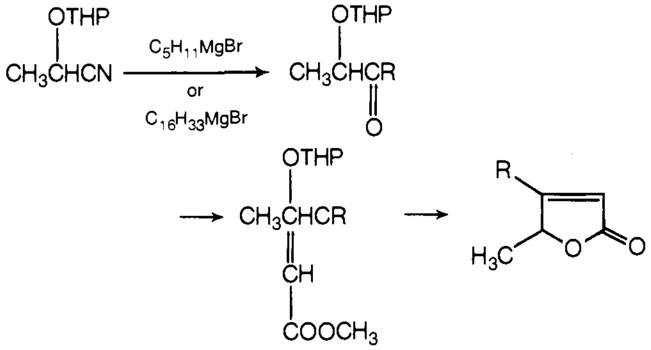
7. *From Cyanohydrins*

SCHEME VIII



R = CH_3 or C_6H_5
R' = H or CH_3

Cyanohydrins such as lactonitrile react in this tetrahydropyranyl ether form with alkyl Grignard reagents to give ketonic compounds. These compounds react with triethyl phosphonoacetate in the presence of sodium hydride to give **108**. Compound **108** cyclizes in the presence of $BF_3{\cdot}O(C_2H_5)_2$ in benzene to give **108a** in an overall yield of 25–30%.[901,902]

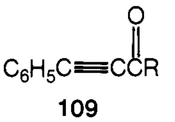


108

8. *From Acetylenic Compounds*

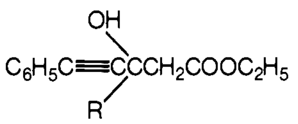
a. Acetylenic Carbonyl Compounds

When acetylenic carbonyl compounds such as phenylpropargylaldehyde, acetylphenylacetylene, and benzoylphenylacetylene are subjected to Reformatsky reaction with bromoacetic ester and subsequent dehydration of the hydroxy compounds, unsaturated esters are obtained, which readily cyclize to give lactones of the type **109**,[1035,1036]



$C_6H_5C\equiv C\overset{O}{\overset{\|}{C}}R$

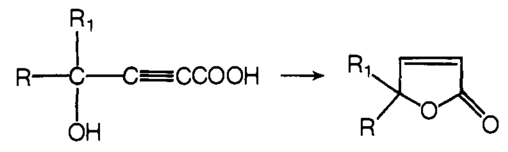
109



$C_6H_5C\equiv C\overset{OH}{\underset{R}{C}}CH_2COOC_2H_5$

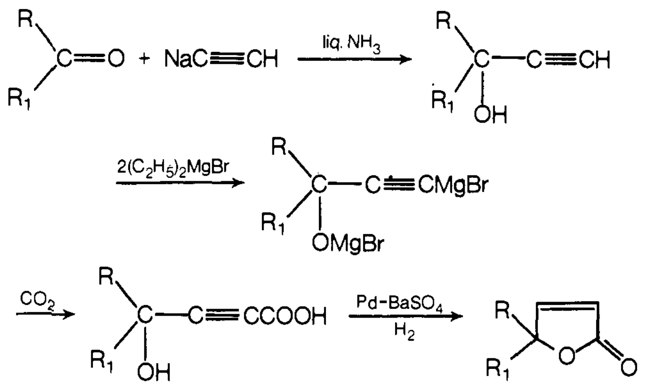
R = H, CH_3, or C_6H_5

The conversion of 4-hydroxy-2-pentynoic acid, 4-hydroxy-4-methyl-2-heptynoic acid, and 4-hydroxy-2-heptynoic acid to give corresponding γ-alkyl-$\Delta^{\alpha,\beta}$-butenolide by hydrogenation on $Pd/BaSO_4$ was reported earlier (ref 514 142 in 791). Essen-



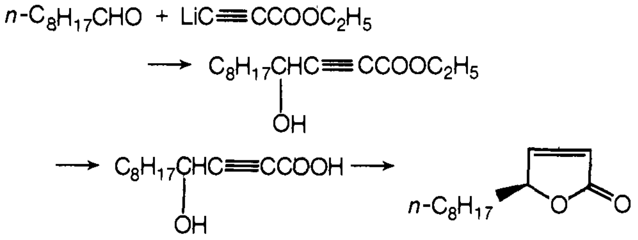
$R = CH_3, R_1 = H; R = R_1 = CH_3; R = n\text{-}C_3H_7, R_1 = H$

tially, the same method has been employed in the synthesis of a series of $\Delta^{\alpha,\beta}$-butenolides.[725]

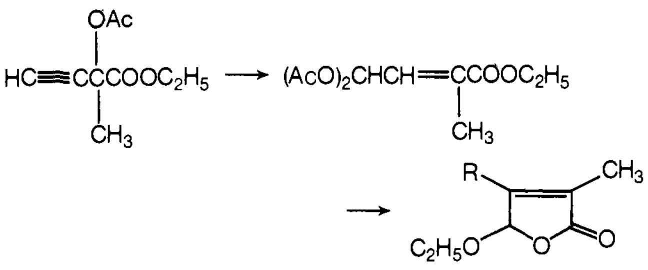


$R = C_2H_5, R_1 = H; R = R_1 = CH_3$
$R = n\text{-}C_3H_7, R_1 = H; R = CH_3, R_1 = C_2H_5$
$R = n\text{-}C_4H_9, R_1 = H; R = CH_3, R_1 = C_5H_{11}$
$R = n\text{-}C_5H_{11}, R_1 = H; R = R_1 = C_2H_5$
$R = n\text{-}C_6H_{13}, R_1 = H; R = C_2H_5, R_1 = C_3H_7$
$R = n\text{-}C_8H_{17}, R_1 = H$

A modification for the hydroxyacetylenic acid synthesis consists of treating an aldehyde with lithium carboxyethylacetylide and conversion of the intermediate hydroxyacetylenic ester to the acid and hydrogenation of the latter to the lactone.[465]

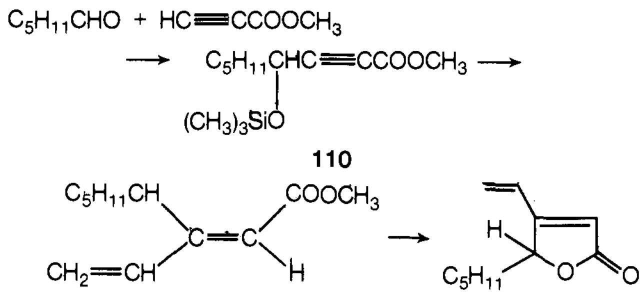


Treatment of ethyl 2-methyl-2-acetoxy-3-butynoate with silver acetate and acetic acid gives ethyl 2-methyl-4,4-diacetoxy-2-butenoate, which on treatment with alcoholic HCl gives two lactones.[995]



R = H, OH

In a recent method, methyl propynoate in THF was treated in sequence at −78 °C with *n*-butyllithium, hexanal, and trimethylchlorosilane to give methyl 4-trimethylsilyloxy-2-nonynoate (**110**). Further treatment of **110** with divinylcopperlithium and workup gave **111**, which was cyclized to β-vinyl-γ-*n*-pentyl-$\Delta^{\alpha,\beta}$-butenolide (**112**).[239]

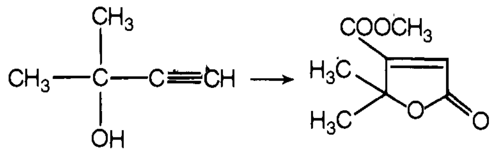


110

111 **112**

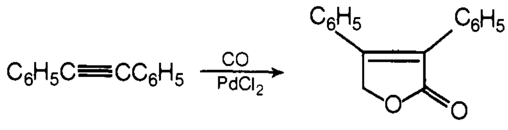
b. Carbonylation of Acetylenic Compounds

The Pd-catalyzed carbonylation of 2-methyl-3-butyn-2-ol in methanol containing hydrogen chloride is reported to give γ,γ-dimethyl-β-carboxymethyl-$\Delta^{\alpha,\beta}$-butenolide as one of the products.[974,976,1090]



113

Diphenylacetylene, on carbonylation in ethanol in the presence of $PdCl_2$, gives a 66% yield of α,β-diphenyl-$\Delta^{\alpha,\beta}$-butenolide (**114**).[977] Acetylene gets carbonylated with carbon monoxide in the presence of cobalt carbonyls to give **115**.[15]



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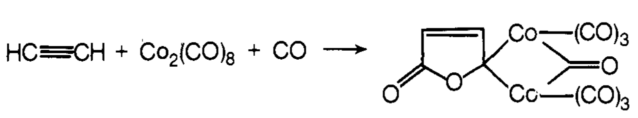
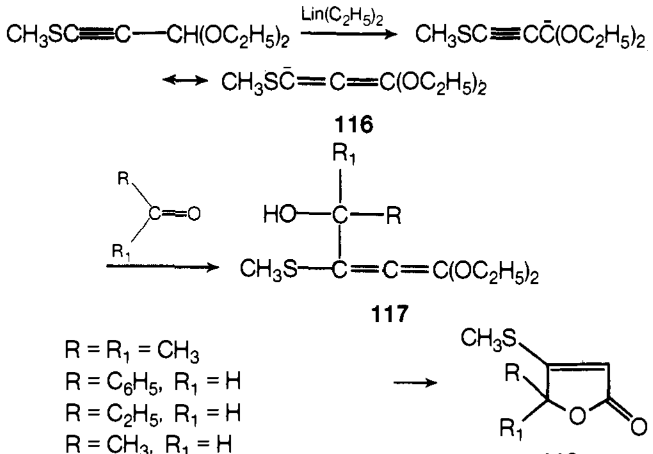


115

Allenic carbanions, **116**, generated by the action of lithium diethylamide on 3,3-diethoxy-1-methylthiopropyne, react with aldehydes and ketones to give **117**. Compound **117**, on treatment with alcoholic HCl, gives β-thiomethyl-$\Delta^{\alpha,\beta}$-butenolides (**118**).[183] The conversion of propiolic acid[882] and 4-benzoyl-2-methyl-3-butyn-1-al[994] to $\Delta^{\alpha,\beta}$-butenolides has also been reported. Similar reaction of propiolic acid and ethanol and 1-propanol is reported to yield $\Delta^{\alpha,\beta}$-butenolides.[172]



116

117

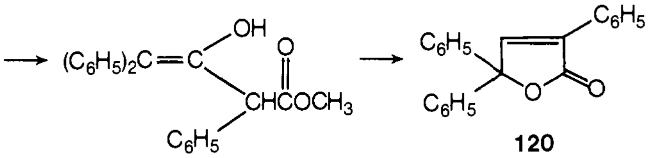
$R = R_1 = CH_3$
$R = C_6H_5, R_1 = H$
$R = C_2H_5, R_1 = H$
$R = CH_3, R_1 = H$
$R = n\text{-}C_7H_{15}, R_1 = H$

118

9. From Allenic Acids

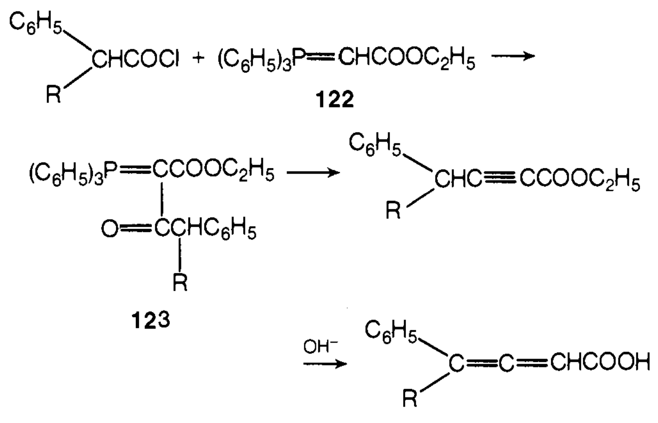
In the method given above,[183] a pseudoallenic compound has been used. The first use of an allenic compound for lactone synthesis was by Ziegler and Sauermilch,[1068] consisting of the following steps. Compound **119**, which on dehydration could conceivably give a highly arylated allene derivative, gave with $AlPO_4$ or boiling acetic anhydride or concentrated H_2SO_4 or PCl_3 or $SOCl_2$ α,γ,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide.

$(C_6H_5)_2C{=}CHMgBr + C_6H_5COCOOCH_3$



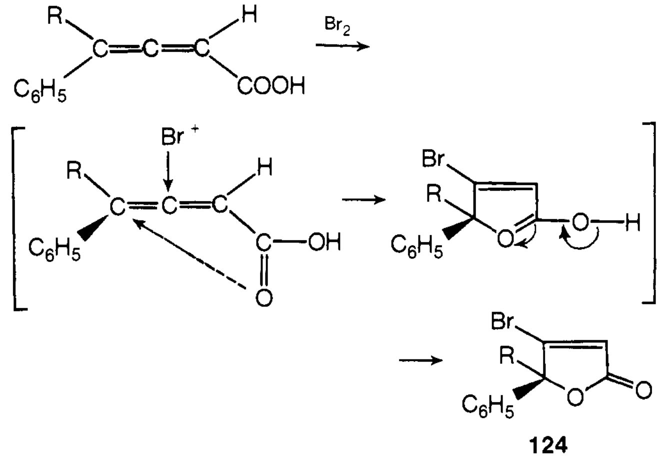
119 **120**

Phenylallenecarboxylic acids **121** have been prepared by reacting phenyl and α-substituted phenylacetyl chlorides with Wadsworth and Emmons reagent **122** to give **123**, followed by pyrolysis and treatment with alkali. Compounds **121**, on treatment with Br_2 in CCl_4, cyclize to give optically active $\Delta^{\alpha,\beta}$-butenolides **124**.[889]



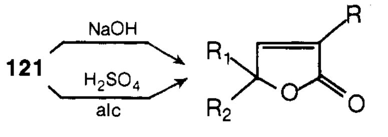
122 **123** **121**

R = CH_3, C_2H_5, *i*-C_3H_7, and *t*-C_4H_9



124

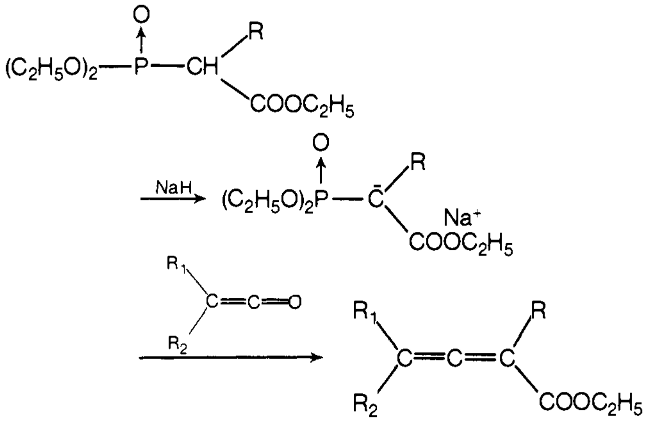
The desired allenecarboxylic acids have been synthesized by a different rute from Wadsworth–Emmons reagent and ketene derivatives (Scheme IX). Compound **121** cyclizes to racemic $\Delta^{\alpha,\beta}$-butenolides either with sodium hydroxide or aqueous alcohol containing sulfuric acid.[574]



R = C_6H_5, $R_1 = CH_3$, $R_2 = C_2H_5$
R = C_2H_5, $R_1 = CH_3$, $R_2 = C_6H_5$
R = CH_3, $R_1 = C_6H_5$, $R_2 = C_2H_5$
R = CH_3, $R_1 = C_6H_5$, $R_2 = CH_3$
R = C_2H_5, $R_1 = C_6H_5$, $R_2 = C_2H_5$
R = $R_1 = R_2 = C_6H_5$

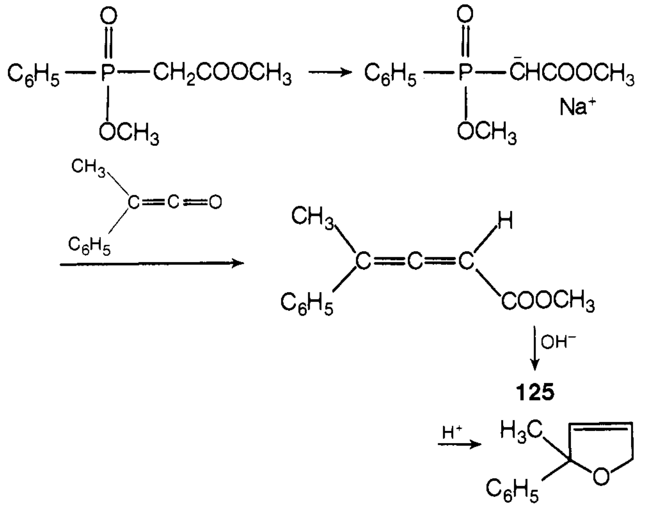
An optically active lactone γ-methyl-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide (**125**) has been synthesized recently by employing a similar method[711] (Scheme X).

SCHEME IX



121

SCHEME X



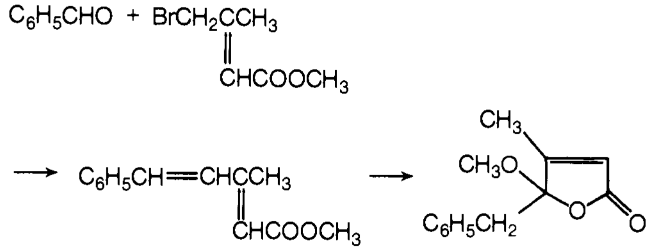
125

optically active

125

10. From Dienoic Acids

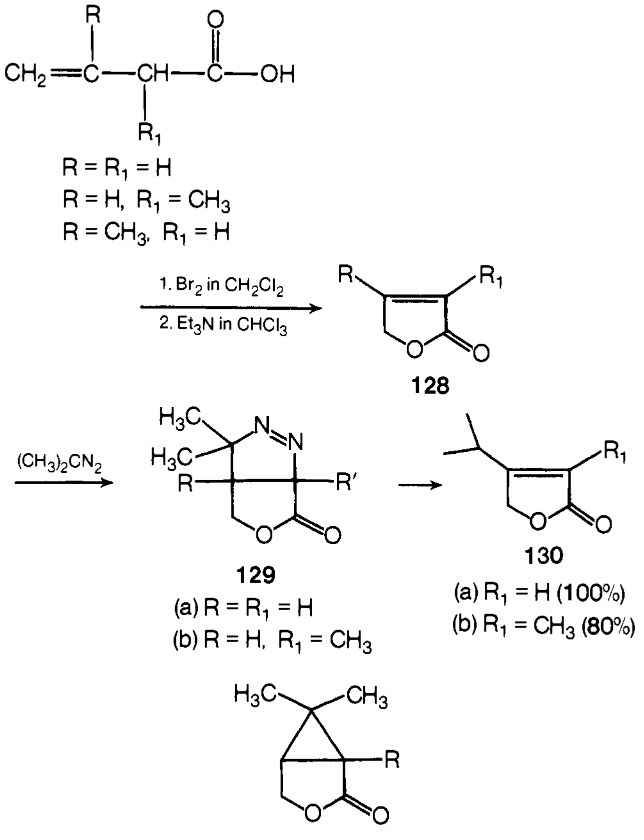
When methyl 3-methyl-5-phenylpentadienoate (**126**) is prepared from benzaldehyde and 4-bromo-3-methyl-2-butenoic acid methyl ester (methyl γ-bromosenecioate), a lactone, possibly **127**, is obtained as a by-product.[1034] Sodium 2,4-pentadienoate reacts with I_2 in KI at 50° to give a $\Delta^{\alpha,\beta}$-butenolide derivatives.[914]



126 **127**

11. From Vinylacetic Acids

α- or β-substituted butenolides are obtained in a one-step reaction from 3-butenoic acid, 2-methyl-3-butenoic acid, and 3-methyl-3-butenoic acid, by bromination and dehydrobromination with triethylamine in 27–75% yields.[360] Compound **128** adds to diazopropane to give **129.** On photolysis in benzene, compound **129b** gives a cyclopropane derivative, **131** along with **130b** and α-methyl-$\Delta^{\alpha,\beta}$-butenolide. With $\Delta^{\alpha,\beta}$-butenolide adduct, **130a** and **131** (R = H) are obtained in 50:50 yields.[359] A similar vinylacetic acid, 2-chloro-3-phenyl-4-piperidino-3-butenoic acid, loses HCl on heating to 80° under reduced pressure to give **132.**[513]



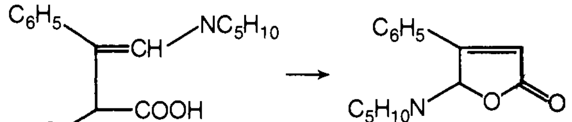
R = R_1 = H
R = H, R_1 = CH_3
R = CH_3, R_1 = H

128

129
(a) R = R_1 = H
(b) R = H, R_1 = CH_3

130
(a) R_1 = H (100%)
(b) R_1 = CH_3 (80%)

131

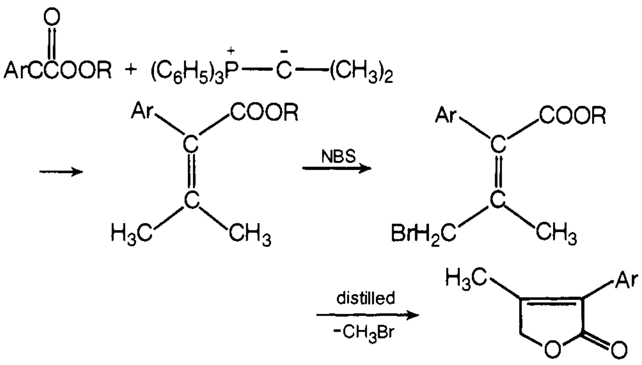


132

12. *From Miscellaneous Acids*

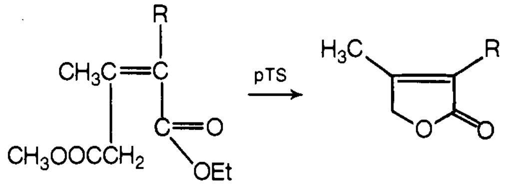
a. 3,3-Disubstituted-2-arylacrylic Acids

The Wittig reaction between arylglyoxylic esters and isopropylidenetriphenylphosphorane yields 2-aryl-3-methylcrotonic esters. These compounds are converted into monobromo derivatives, which on distillation lose methyl bromide to give $\Delta^{\alpha,\beta}$-butenolides in 16–27% yields.[613,784]



b. From 4-Acetoxybutenoic Acid Esters

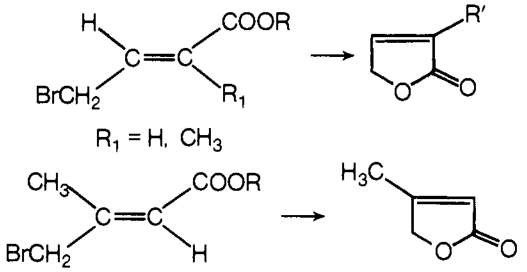
It has been reported that 3-acetoxymethyl-2-methyl-2-butenoic acid ethyl ester (**133**) and similar compounds are heated with polyphosphoric acid or *p*-toluenesulfonic acid to give $\Delta^{\alpha,\beta}$-butenolides in 44–77.5% yields.[294]



133 R = CH_3, H, C_2H_5

c. From γ-Bromo α,β-Unsaturated Carboxylic Acids and Their Methyl Esters

γ-Bromocrotonic acid, γ-bromotiglic acid and γ-bromosenecioic acid and their methyl esters are converted to $\Delta^{\alpha,\beta}$-butenolides when heated with iron powder at 125°.[622] When ethyl γ-bromocrotonate is heated, thermal lactonization is reported to occur.[1147] The bromination of tiglic acid with *N*-bromosuccinimide is reported to give α-methyl-$\Delta^{\alpha,\beta}$-butenolide as a by-product.[623]



R_1 = H, CH_3

d. From β-Arylamino Acrylates

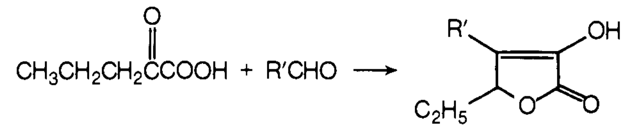
Oxaloacetic ester condenses with aromatic amines to give β-arylamino acrylates, which on reduction with lithium aluminum hydride in THF at 0° give β-arylamino-$\Delta^{\alpha,\beta}$-butenolides.[669] That he compounds are β-substituted and not α-substituted has been shown by independent synthesis from tetronic acid and aromatic amines. β-Anilino-$\Delta^{\alpha,\beta}$-butenolide is prepared from aniline and chloroacetoacetic ester.[144]

e. From Phenylsuccinic Acid Derivatives

Cyclization of 4-methoxyphenylsuccinic acid followed by reduction and dehydration yields α-*p*-anisyl-$\Delta^{\alpha,\beta}$-butenolide, also obtained from the naturally occurring sugiresinol.[525]

f. From 2-Oxobutyric Acid

Condensation of 2-oxobutyric acid with aldehydes in the presence of concentrated sulfuric acid is reported to give α-hydroxy-$\Delta^{\alpha,\beta}$-butenolides.[825]

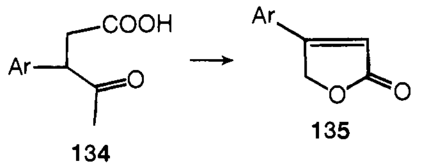


g. From β-Aryl-α-oxoglutaric Acids

In their studies on leucodrin, Perold and coworkers[756,757] observed that heating β-aryl-α-oxoglutaric acids **134** converts them to β-aryl-$\Delta^{\alpha,\beta}$-butenolides **135.**

h. From 5,5,5-Trifluorolevulinic Acid (136)

The lactone obtained by the dehydration of **136** was originally

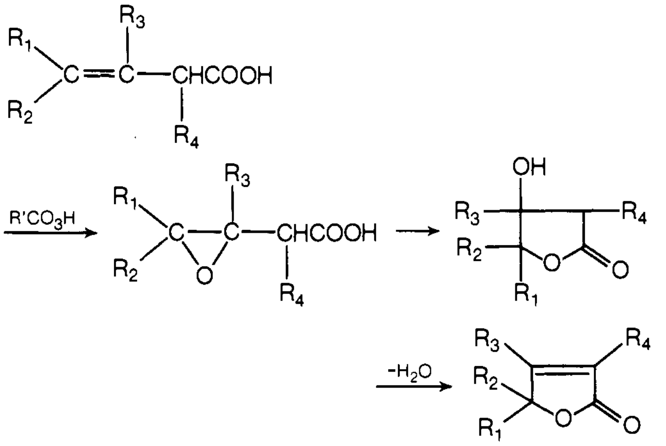

134 **135**

Ar = 4-$CH_3OC_6H_4$, 4-HOC_6H_4, C_6H_5

represented by Groth as a $\Delta^{\alpha,\beta}$-butenolide.[1100] The same compound was also designated as $\Delta^{\beta,\gamma}$-butenolide.[1101] From a study of infrared spectra, Filler and coworkers have established the $\Delta^{\alpha,\beta}$ nature of the double bond.[346]

i. From α,β Unsaturated Acids

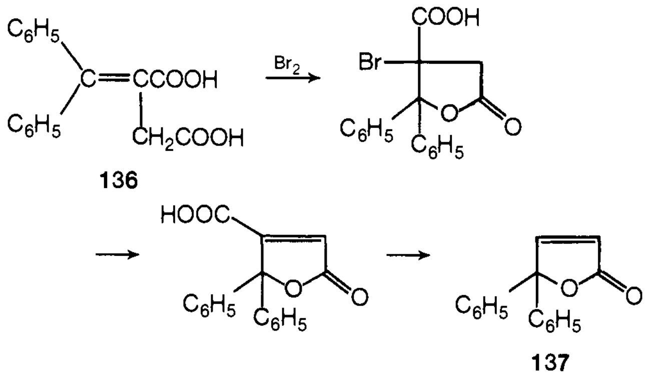
Epoxidation of α,β-unsaturated acids followed by heating with a catalytic amount of acid gives β-hydroxy-γ-lactones. These hydroxylactones may be subsequently dehydrated to give $\Delta^{\alpha,\beta}$-butenolides.[753]

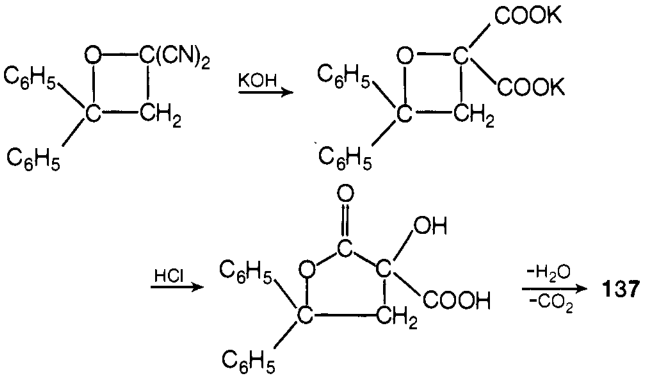


$R_1 = R_2 = R_3 = H$, $R_4 = CH_3$
$R_1 = C_2H_5$, $R_2 = R_3 = R_4 = H$
$R_1 = R_2 = H$, $R_3 = R_4 = CH_3$
$R_1 = R_4 = n\text{-}C_3H_7$, $R_2 = R_3 = H$
$R_1 = C_6H_5$, $R_2 = R_3 = R_4 = H$
$R_1 = H$, $R_2 = R_3 = R_4 = C_2H_5$
$R_1 = C_2H_5$, $R_2 = R_3 = H$, $R_4 = n\text{-}C_4H_9$
$R_1 = C_4H_9$, $R_2 = R_4 = H$, $R_3 = C_6H_5CH_2$

13. Stobbe Condensation

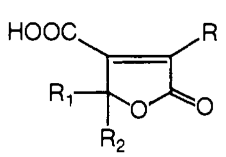
Diethyl succinate condenses with benzophenone in the presence of sodium ethoxide to give **136**.[512,924-926,1150] γ,γ-Diphenyl-$\Delta^{\alpha,\beta}$-butenolide (**137**) may also be prepared from the adduct between 1,1-diphenylethylene and carbonyl cyanide.[2,3]

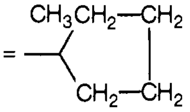

136 **137**



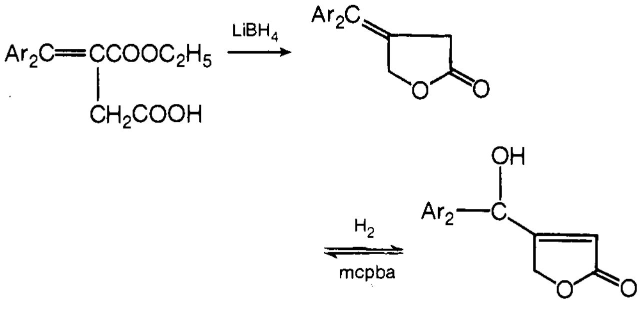
Under Stobbe reaction conditions, benzyl α-ketobutyrate in the presence of di-*tert*-butylsuccinate and potassium *tert*-butoxide underwent self-condensation to give α-hydroxy-β-methyl-γ-ethyl-γ-carboxy-$\Delta^{\alpha,\beta}$-butenolide (**138**) along with *tert*-butyl and benzyl esters of **138**.[37]

Stobbe's original work has shown that the itaconic acid derivatives similar to **136** add bromine to give bromolactones which on dehydrobromination yield carboxy butenolides **139**.[1150]


139

R = H, $R_1 = CH_3$, $R_2 = C_2H_5$
R = H, $R_1 = CH_3$, $R_2 = C_6H_5$
$R = CH_3$, $R_1 = R_2 = C_6H_5$
R = H, $R_1 = R_2 = -(CH_2)_4-$
R = H, $R_1 = R_2 =$ 

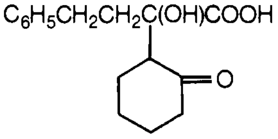
The condensation of piperonal with diethyl succinate followed by treatment with lithium borohydride and aqueous HCl led to the formation of β-3,4-methylenedioxybenzyl-$\Delta^{\alpha,\beta}$-butenolide. With 4,4′-dimethoxybenzophenone and diethyl succinate, the product obtained after reduction with lithium borohydride and *m*-chloroperbenzoic acid (mcpba) turns out to be β-$\Delta^{\alpha,\beta}$-butenolidyl-bis(4-methoxyphenyl)carbinol (**140**).[618]



140

14. Condensation of Pyruvic Acid Derivatives with Carbonyl Compounds

Most of the work in this field has been done by Cordier and coworkers.[229-238] Thus benzylpyruvic acid reacts with cyclohexanone in the presence of potassium hydroxide to give **141**, which undergoes acid-catalyzed cyclization to **142**.[229,230] With acetone, benzylpyruvic acid gives **143**, which on dehydration gives an ethylenic acid which exists as a $\Delta^{\alpha,\beta}$-butenolide, **144**.[544] With phenylpyruvic acid, methyl ethyl ketone gives **145** in the



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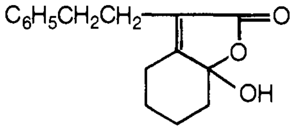
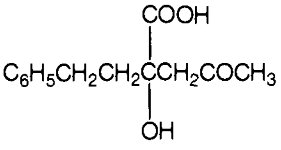
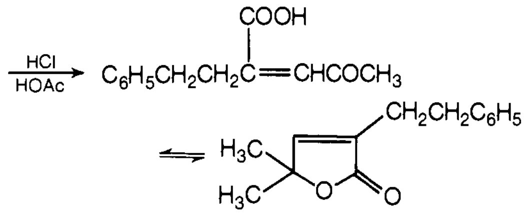


142



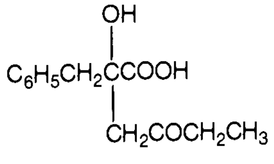
$\mathrm{C_6H_5CH_2CH_2\underset{OH}{\overset{COOH}{C}}CH_2COCH_3}$

143



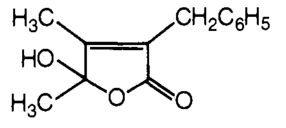
144

presence of KOH. However, in the presence of HCl-acetic acid, the product obtained is **146**.[522] The acid product obtained by the condensation of acetylacetone with phenylpyruvic acid gives a spiro dilactone, **147**, when heated with HCl-HOAc.[521]



$\mathrm{C_6H_5CH_2\underset{CH_2COCH_2CH_3}{\overset{OH}{C}}COOH}$

145



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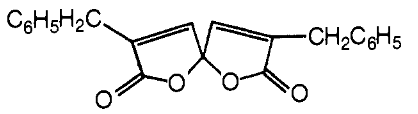
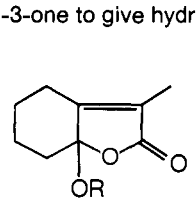


147

Similar condensation of acetone and pyruvic acid gives 2-methyl-2-hydroxylevulinic acid, which on dehydration gives 2-methyl-4-oxo-2-pentenoic acid existing in the form of, α,γ-dimethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide.[25] Condensation of pyruvic acid with cyclohexanone gives α-hydroxy-α-(2-ketocyclohexyl)propionic acid, which on treatment with acid gives **148**.[775] The above condensation reaction was reported to give 40% **148**[575] while Rosenmund and coworkers[1154] assumed it to have the structure **149**. Recent work has shown[776] that the original formulation of **148** is correct and that **148** may be dehydrated to give **150**. Pyruvic acid also condenses with 5α-androstan-17β-ol-3-one to give hydroxy acid **151** which may be cyclized to hydroxylactones similar to **148** and unsaturated lactones **151a**.[773] Similarly, *N*-methylpiperidin-4-one condenses with pyruvic acid to give hydroxy acid, easily cyclized to **152** in methanolic HCl.



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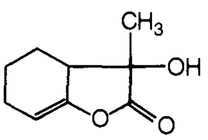

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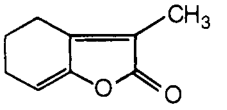
R = OH,OC$_2$H$_5$



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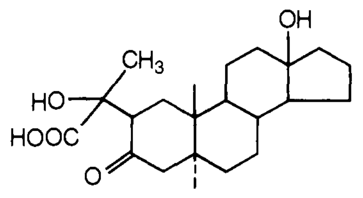
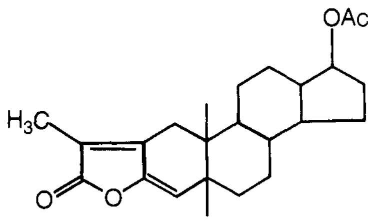
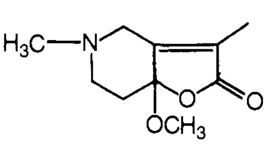


151

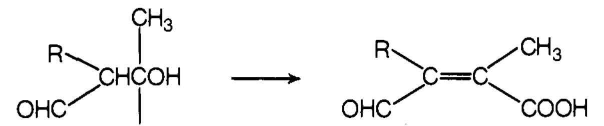


151a

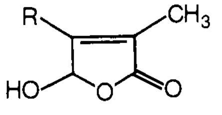


152

Condensation of ethyl pyruvate with a series of aldehydes such as *n*-butyraldehyde, 1-pentanal, hexanal, and heptanal in the presence of diethylamine gives **153**, which is dehydrated to the aldehydo carboxylic acid **154**. Compound **154** in its cis form exists as a hydroxylactone. Compound **155** gives an ether **156** by dehydration.[866] When glyoxylic acid is used instead of pyruvic acid in condensation with cyclohexanone in the presence of morpholine, γ-morpholinobutenolide similar to **148** is obtained, and it gives **148** on heating with ethanolic hydrochloric acid. Compound **148** is also obtained by the hydrolysis of 2-oxocyclohexylglycollic acid ethyl ester with hydrochloric acid-acetic acid. Steroidal compounds such as **151** are also prepared by the morpholine-catalyzed reaction of glyoxylic acid.[865] Acetophenone condenses with potassium pyruvate in the presence of KOH to give α-methyl-α-methoxy-β-benzoylpropionic acid (**157**). Compound **157** is converted to α-methyl-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide (**32**) according to the reaction sequence in Scheme XI.[604] The hydroxybutyrolactone derivative may be converted to a mixture of lactones similar to **158** and **32** by heating with triphenylphosphine in CCl$_4$.[278] The later method has been employed in the synthesis of α-methyl-γ-isobutyl-$\Delta^{\alpha,\beta}$-butenolide and α-methyl-γ-ethyl-$\Delta^{\alpha,\beta}$-butenolide. The latter compound was



153 **154**



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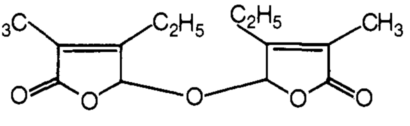
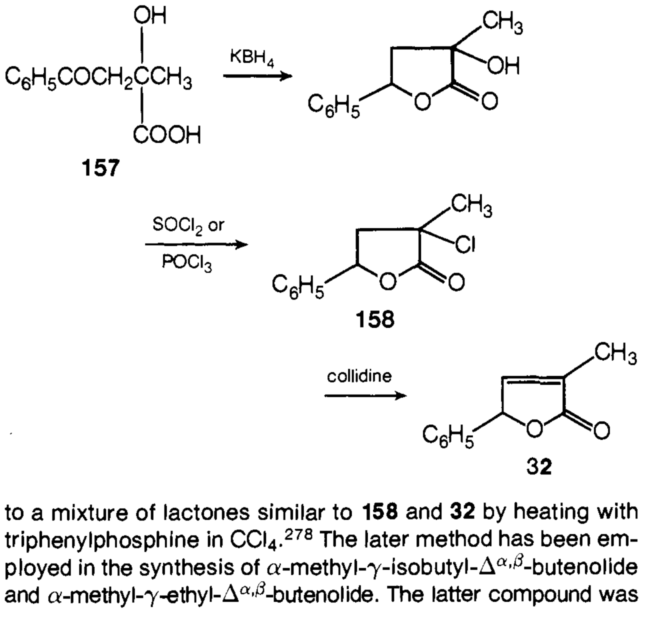
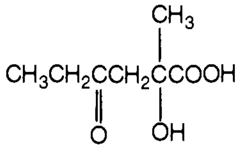


156

SCHEME XI

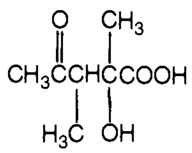


synthesized from 2-hydroxy-2-methyl-4-oxohexanoic acid (**159**), itself obtained from the condensation of methyl ethyl ketone with pyruvic acid. It may be pointed out that this compound was originally thought to be 2-hydroxy-2,3-dimethyl-4-oxopentanoic acid (**160**).[1154] The condensation of methyl propyl ketone with



$CH_3CH_2\underset{O}{\underset{\|}{C}}CH_2\overset{CH_3}{\underset{OH}{C}}COOH$

159

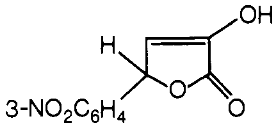


$CH_3\overset{O}{\overset{\|}{C}}\underset{H_3C}{CH}\overset{CH_3}{\underset{OH}{C}}COOH$

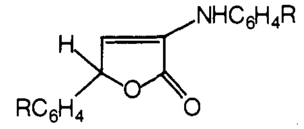
160

pyruvic acid in the presence of phosphoric acid yields α,γ-dimethyl-β-ethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide.[60]

Benzylidenepyruvic acids also act as good starting materials for $\Delta^{\alpha,\beta}$-butenolides. Thus, base-catalyzed condensation of 3-nitrobenzaldehyde with pyruvic acid gives the 3-nitrobenzylidenepyruvic acid, while in the presence of acid condensation occurs to give **161**.[915] Benzylidenepyruvic acids condense in aqueous medium with aromatic amines to give α-aminophenyl derivatives **162**.



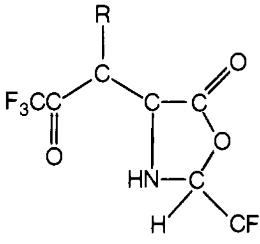
161



162

15. From Other Heterocyclic Compounds

Trifluoroacetic anhydride converts α-amino acids such as alanine, phenylalanine, and 2-aminobutyric acid to trifluoroacetyloxazolidine **163** and enol trifluoroacetates, **164**.[916,917] On heating with bases, compound **163** rearranges to give a $\Delta^{\alpha,\beta}$-butenolide derivative **165**. It has been observed that treatment of an α-amino acids with trifluoroacetic anhydride directly yields 2(5*H*)-furanones.



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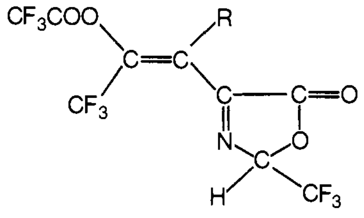

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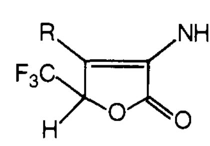

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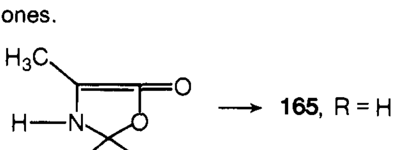
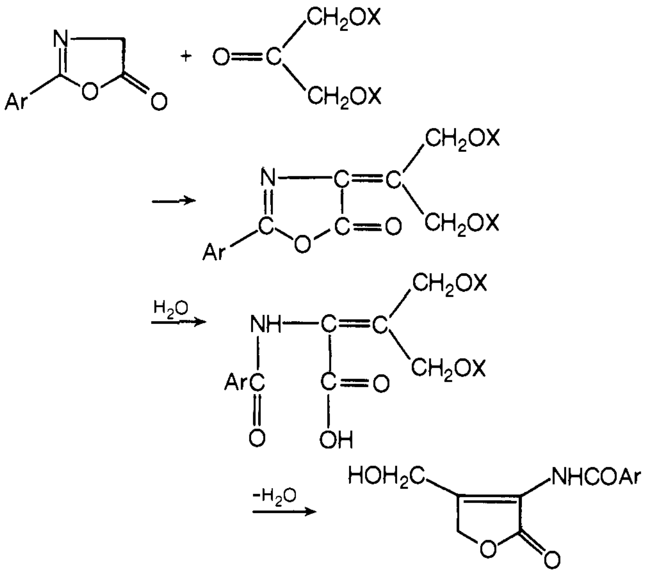
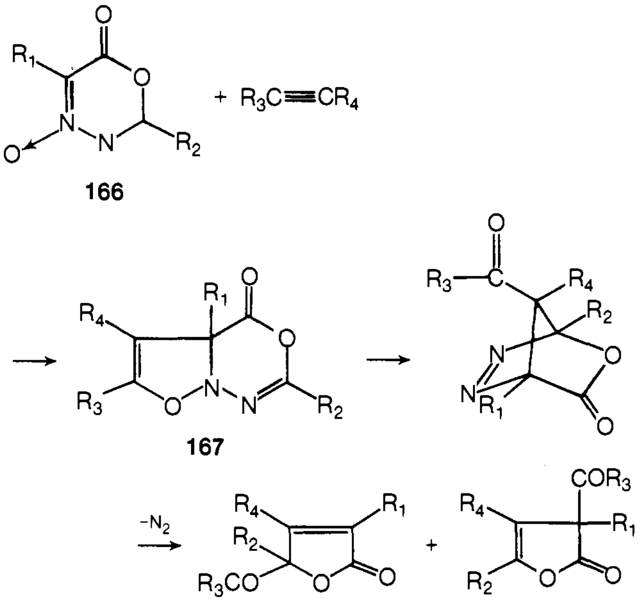


Another furanone derivative is obtained with a trifluoroacetyl group in the β position when alanine is heated with an excess trifluoroacetic anhydride to 160° in a bomb. Compound **165** (R = $COOCH_3$ or $COOC_2H_5$) may be prepared by acetylation with TFAA of aspartic acid monoester. The rearrangement of oxazolidone **163** to **165** (R = CH_3 or C_6H_5) in the presence of a base is also observed.

1,3-Dihydroxyacetone reacts with 2-aryl-5-oxazolone in the presence of lead tetraacetate in THF to give unsaturated oxazolones which are hydrolyzed and recyclized to give $\Delta^{\alpha,\beta}$-butenolides. The addition of ethyl vinyl ether protects the 1,3-dihydroxyacetone in situ.[954,1155]



Freeman and coworkers reported recently[1149,1196] that cycloaddition of acetylenes and acetylenic esters to 1,3,4-oxadiazin-6-one 4-oxides (**166**) produces α- or γ-acylbutenolides in good yields. The nature of R_2 and R_3 determines the nature of the end products. With highly electrophilic acyl groups $\Delta^{\beta,\gamma}$ isomers are obtained whereas the α,β isomers are obtained with less electrophilic groups.



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167

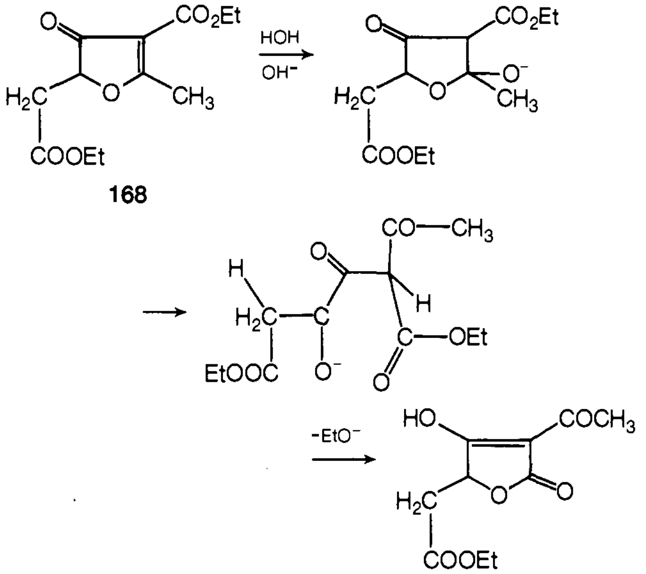
16. From 3(2H)-Furanones

Ring opening of 2-ethyl-4-ethoxycarbonyl-5-methyl-3(2*H*)-furanone with potassium hydroxide and subsequent ring closure leads to the formation of α-acetyl-γ-ethyltetronic acid.[277] A similar transformation of 5-amino-4-phenyl-3(2*H*)-furanone to α-phenyltetronic acid has also been reported.[988] Under similar conditions, compound **168** gives a tetronic acid derivative.[392,1104]

17. Oxidation of Phenolic and Furan Compounds

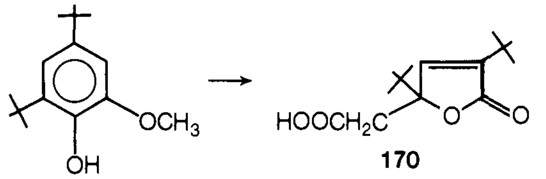
a. Chemical Oxidation

The autoxidation of 4,6-di-*tert*-butylguaiacol (**169**) in organic solvents in the presence of potassium *tert*-butoxide has been

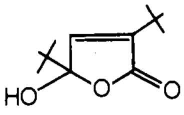


168

reported to give a 6% yield of the lactone **170**.[1159] Similar oxidations of 3,5-di-*tert*-butyl-2,6-dimethoxyphenol and 4-*tert*-butyl-2,6-dimethylphenol gave the corresponding lactones **171** and **172**.[301] The oxidation of 4-methylcatechol, 4-methyl-*o*-benzoquinone, 4-methylveratrole, and *p*-cresol with peracetic acid in acetic acid yields a mixture of lactones **173, 174,** and **175** in varying amounts.[338]



169 **170**



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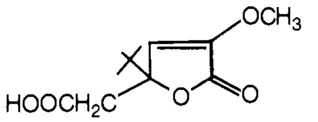

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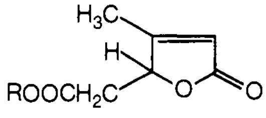

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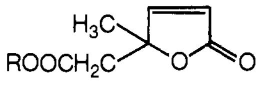

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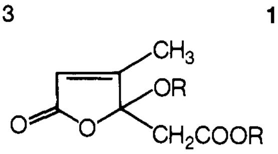

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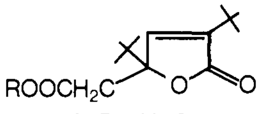
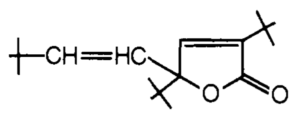
b. Photochemical Formation of Lactones from Phenols and Dienones

When 4,6-di-*tert*-butylresorcinol is irradiated in methanol in the presence of rose bengal with oxygen bubbling through, α,γ-di-*tert*-butyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide is obtained.[655] Under similar conditions, 4,6-di-*tert*-butylcatechol gives **176**.[655,657,837]



176, R = H, CH_3

Photolysis of 2,4,6-tri-*tert*-butyl-4-methoxy-2,5-cyclohexadienone gives bicyclopentanone, which on pyrolysis leads to the formation of isomeric pair of butenolides, **177** and **178**.[656] These photooxidation reactions involve singlet oxygen and excited triplet sensitizer and provide a model for enzymatic cleavage of phenolic rings.



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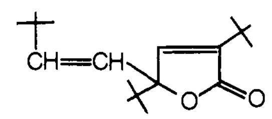

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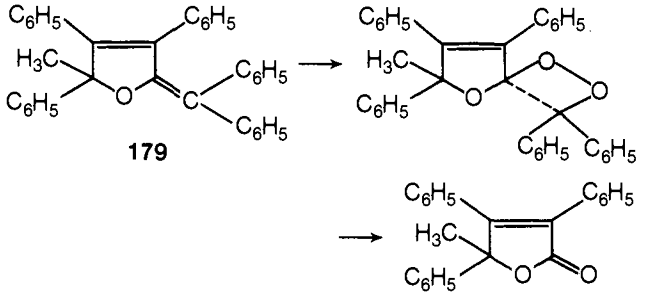
c. From Furan Derivatives

When the furan derivative **179**, is subjected to photosensitized oxidation, it gives oxygenated derivative, which on heating gives the lactone **180**. Compound **180** is also obtained from **179** by ozonolysis of the latter.[81-83]

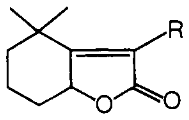


179 **180**

The conversion of 2-acetoxyfuran to β-angelica lactone by photolysis of the former in ether solution has been reported recently.[478,907] Under similar conditions, 2-methoxyfuran gives α-angelica lactone. The conversion of 2-acetoxyfuran to γ-acetoxy-$\Delta^{\alpha,\beta}$-butenolide has also been reported.[979] It is well known that furfural may be photooxygenated to γ-ethoxy-$\Delta^{\alpha,\beta}$-butenolide in ethanol.[584,1049] It should be pointed out that 2-acetoxyfuran may be obtained by the pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran[193,222,258] and may be halogenated to the corresponding γ-halo-$\Delta^{\alpha,\beta}$-butenolide.[312]

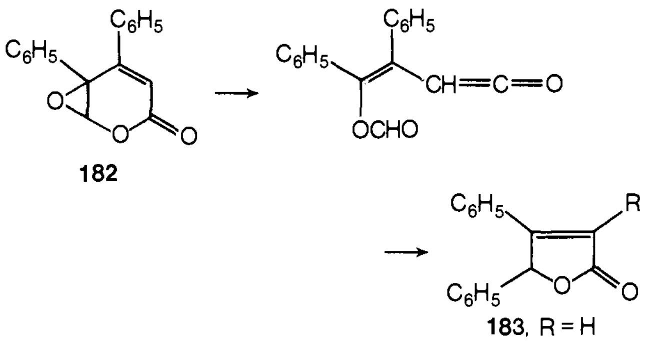
d. From β-Ionone

Oxidation of β-ionone with potassium permanganate is reported to yield **181** (R = OH).[163] Sensitized photooxidation of β-ionone similarly gives **181** (R = H) in a 12% overall yield.[703]



181

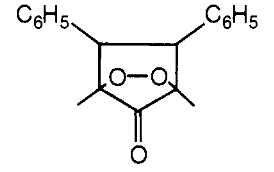
The α-pyrone epoxide **182** on uv irradiation is converted to β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide (**183**). Compound **182** is converted to **183** (R = H) in 86% yield on treatment with concentrated H_2SO_4 at 0 °C.[741] The compound obtained from tetracyclone



182

183, R = H

and chromium pentoxide, an endoperoxide **184**, is slowly converted to α,β,γ-triphenyl-α-benzoyl-$\Delta^{\beta,\gamma}$-butenolide **185**, which on heating to 210° yields α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide (**183**, R = C_6H_5).[71] Compound **185** is also obtained from 2,4,6-triphenylpyrylium 3-oxide (**185a**) by oxygenation in 36% yield. The yield increases to 41% by benzophenone-sensitized irradiation in benzene solution.[1019] Compound **185** is converted to a dilactone, the structure of which will be discussed later.



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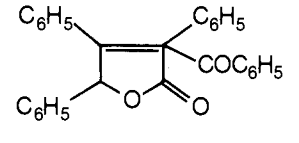

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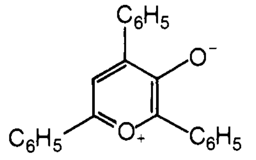
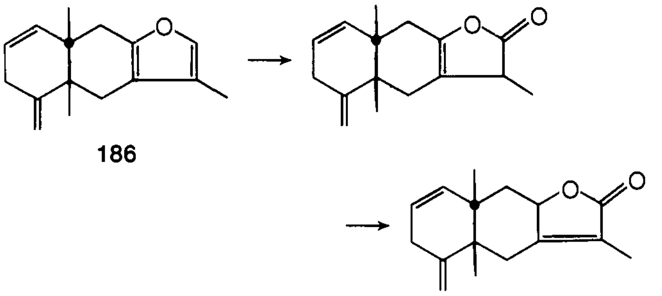


185a

e. Oxidation of Furans

The conversion of furan ring in naturally occurring compounds to $\Delta^{\alpha,\beta}$-butenolides has been reported by autoxidation,[1161] by catalytic oxidation,[727] and in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[678] Perbenzoic acid oxidation of lindestrene (**186**) is supposed to give an unstable $\Delta^{\beta,\gamma}$ lactone **186a** which isomerizes to the $\Delta^{\alpha,\beta}$ isomer **186b** on Al_2O_3.[952] 3-Isopropylfuran **187** is converted to γ-hydroxy-β-isopropyl-$\Delta^{\alpha,\beta}$-butenolide on oxidation with peracetic acid in $CHCl_3$. However, with *N*-bromosuccinimide, **187** gives β-isopropyl-$\Delta^{\alpha,\beta}$-butenolide. This reaction has been extended to the synthesis of digitoxigenin from the corresponding furyl derivative **188** by oxidation with peracetic acid.[269,337] With NBS, an isomer of digitoxigenin acetate (**189**) is obtained. The naturally occurring furocaespitane is converted by *m*-chloroperbenzoic acid to β-(3-bromo-4-chloro-4-methylcyclohexyl)-γ-methyl-$\Delta^{\alpha,\beta}$-butenolide.[400]



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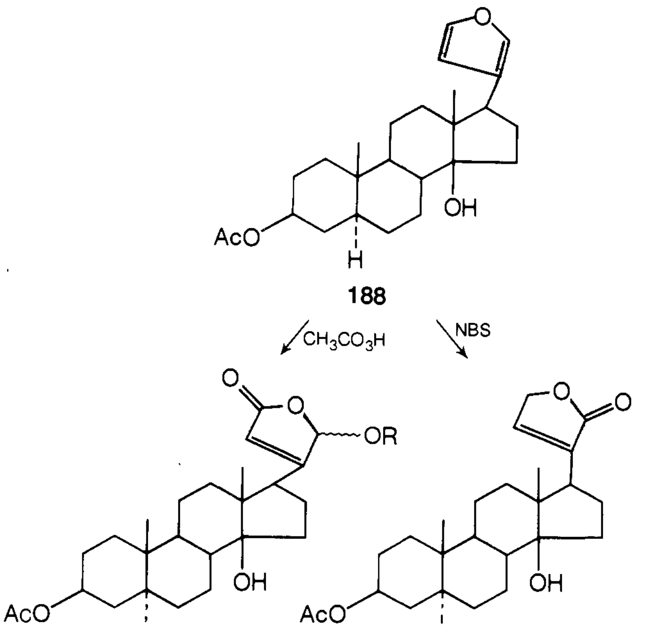
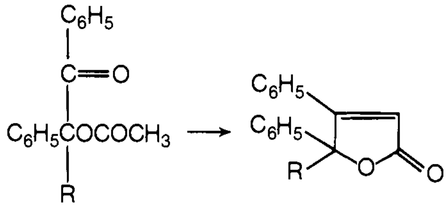


189 isomer of digitoxigenin acetate

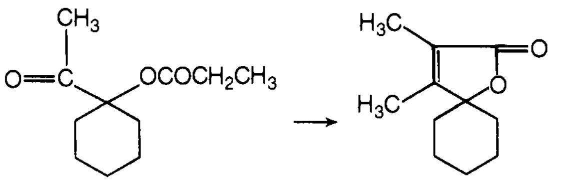
18. From Esters of α-Hydroxy Ketones

Bases such as alkali metal hydrides, alkali metal hydroxides, alkoxides, and amides react with esters of α-hydroxy ketones in solvents such as DMSO and DMF to give butenolides.[608,609]



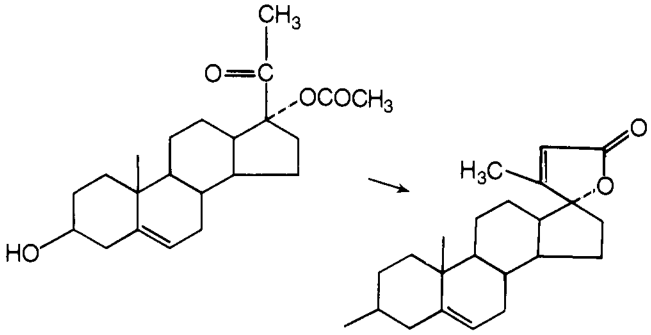
R = CH_3, C_6H_5

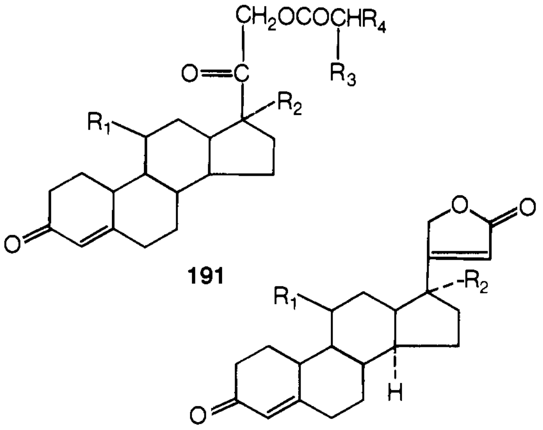
The compound 1-acetyl-1-propionyloxycyclohexane gives **190**.



190

This reaction may be utilized in the synthesis of steroidal lactones as follows. An extension of this reaction was in the synthesis of 22-methyl-3-oxo-14α-carda-4,20(22)-dienolide (**192**) from the corresponding Wittig reagent and sodium hydride in DMSO. Where R_1 and R_2 are hydroxyl groups in **191**, anhydrous potas-





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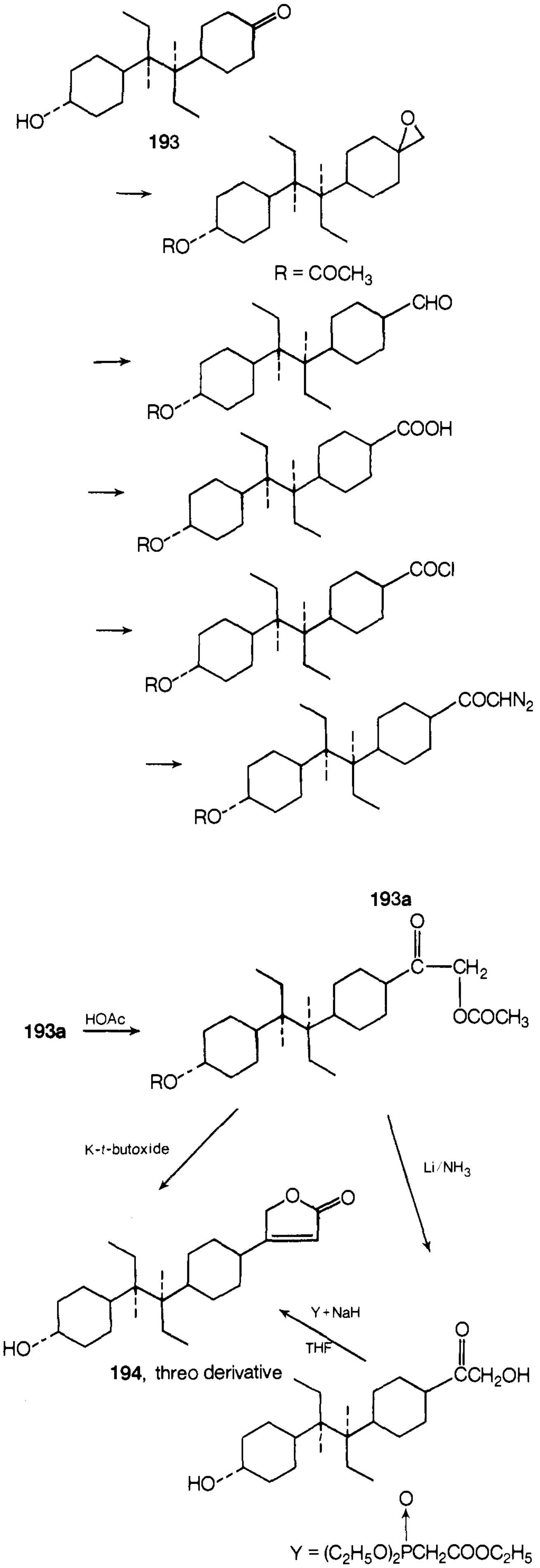
192

$R_1 = R_2 = H$, $R_3 = CH_3$, $R_4 = (C_6H_5)_3\overset{+}{P}Br^-$

SCHEME XII



sium carbonate in *tert*-butyl alcohol is used. With diethyl phosphonate instead of the usual Wittig reagent, K_2CO_3–*tert*-butyl alcohol reagent works as well.[607] This method has been employed in the synthesis of several inotropic cardenolides.[610-612]

19. *β-Cyclohexylbutenolides*

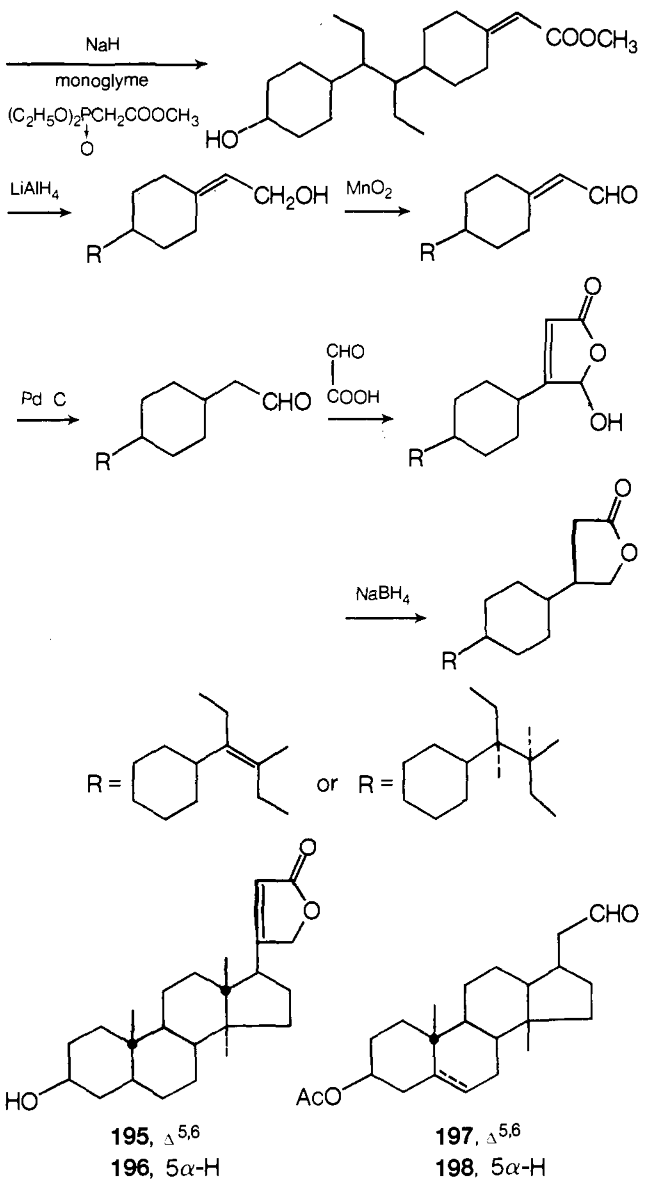
In a series of papers, Professor Inhoffen's group gives a detailed account of synthetic approaches to β-substituted cyclohexylbutenolides. Their first method employs 3-(4-oxocyclohexyl)-4-(4-hydroxycyclohexyl)hexane (**193**), which by a series of transformations given in Scheme II is converted to **194**.[497]

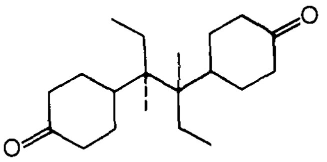
Compound **193** and its 3,4-unsaturated analog are the starting materials for a synthesis involving condensation with glyoxalic acid and subsequent reduction of the hydroxylactone with sodium borohydride.[495] A similar series of reactions have been employed in the synthesis of 3-β-hydroxy-$\Delta^{5(6)}$-14α-card-20(22)-enolide and 3-β-hydroxy-14α-card-20(22)-enolide, **195** and **196**, respectively, starting from **197** and **198**,[573] (Scheme XIII).

The pseudocardenolide **200** has been prepared starting from **199** by employing the acid chloride method shown in Scheme XIII.[495]

SCHEME XIII

193a





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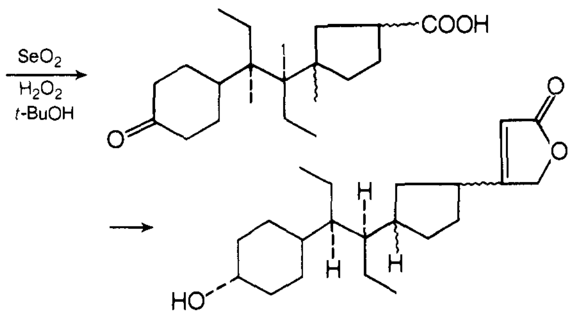
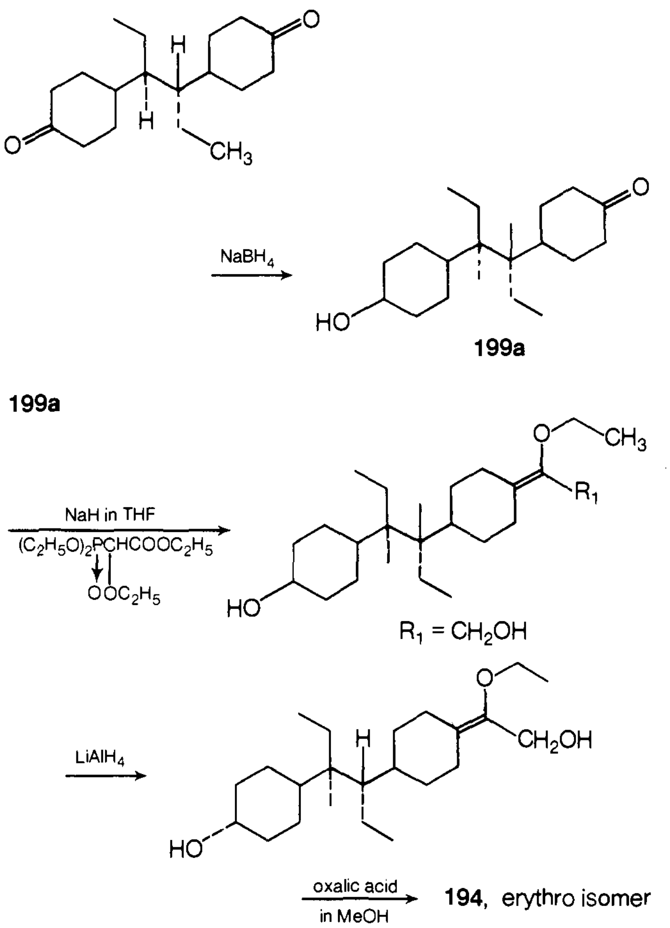
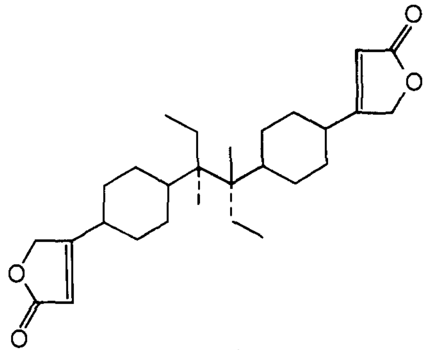


200

SCHEME XIV



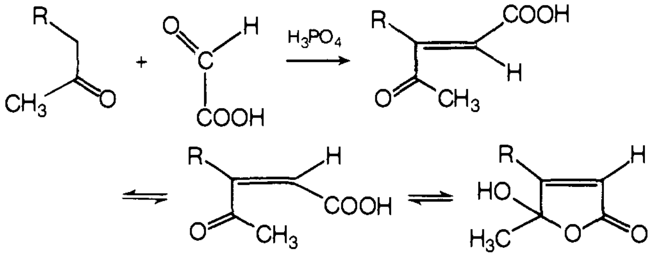
In a recent paper, compound **199** (erythro form) has been converted to erythro **194** in four steps according to Scheme XIV.[572] The dibutenolide **201** is prepared similarly.

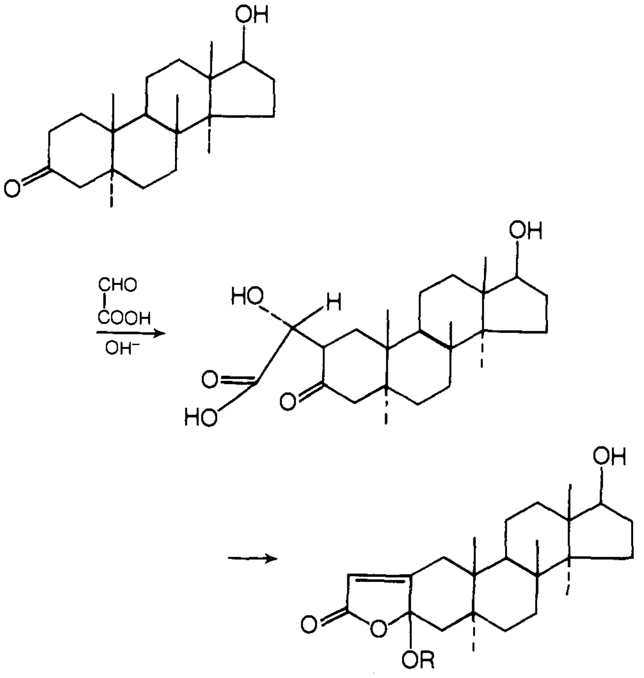


201

20. Condensation with Glyoxylic Acid

The condensation of glyoxylic acid with carbonyl compounds has been employed in the synthesis of butenolides as mentioned above.[495] This method has been employed for the synthesis of γ-hydroxybutenolides.[849] The corresponding γ-chlorobutenolides have also been prepared thus. A similar condensation of glyoxylic acid with 5-α-androstanolone in the presence of a base gives hydroxy acids which on heating with alcoholic HCl gives the lactone **202**.[268]





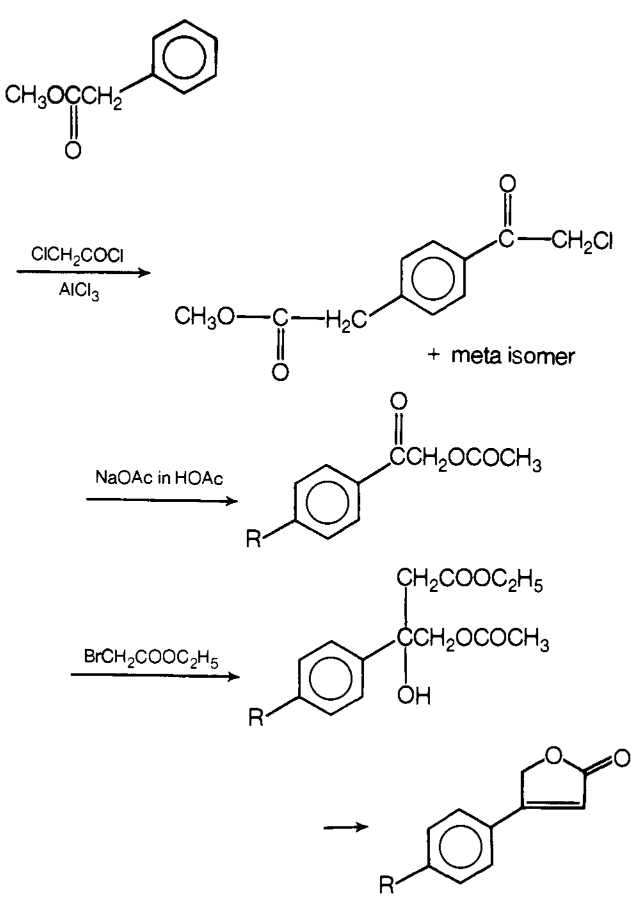
202

$R = C_2H_5$, $R = H$

21. By Friedel-Crafts Reaction

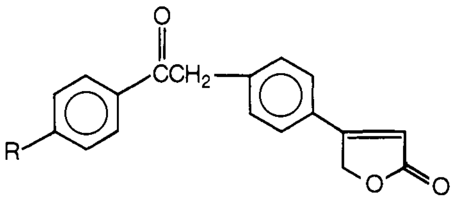
A combination of Friedel-Crafts reaction and Reformatsky reaction has been employed by Schmitt and coworkers for the synthesis of β-arylbutenolides containing a $-CH_2COOR$ substituent on the benzene ring.[854-857] The free acid **203** ($R = CH_2COOH$) is converted to the acid chloride and subjected to another Friedel-Crafts reaction with anisole and toluene to give **204**. The compound β-(4-methoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (**205**) is prepared in 51% yield by a slight modification of Reformatsky reaction as given in Scheme XV.

Compound **205** may be nitrated, chlorinated, and chlorosulfonated to give substituted lactones. Similar studies have been carried out with β-veratryl (**206**) and β-(2,4-dimethoxyphenyl)-$\Delta^{\alpha,\beta}$-butenolide (**207**). Compounds **205, 206,** and **207** have been acylated in the presence of anhydrous aluminum chloride with a series of acid chlorides.[855] The acylated compounds have been reduced to the corresponding hydroxy compounds. β-Carboxyphenyl-$\Delta^{\alpha,\beta}$-butenolides are prepared by heating chloroacetyl derivatives in anhydrous pyridine.



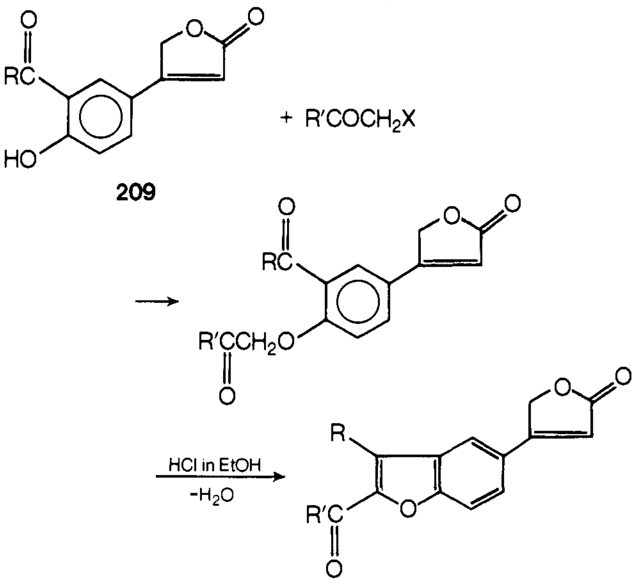
203

R = CH_2COOCH_3



204, R = CH_3O, CH_3

A series of benzofuranobutenolides (**208**) have been synthesized starting from butenolides containing hydroxy and acyl groups in the ortho position on the benzene ring, **209**. Compounds **208** are reduced to the corresponding alcohols.[853,856]



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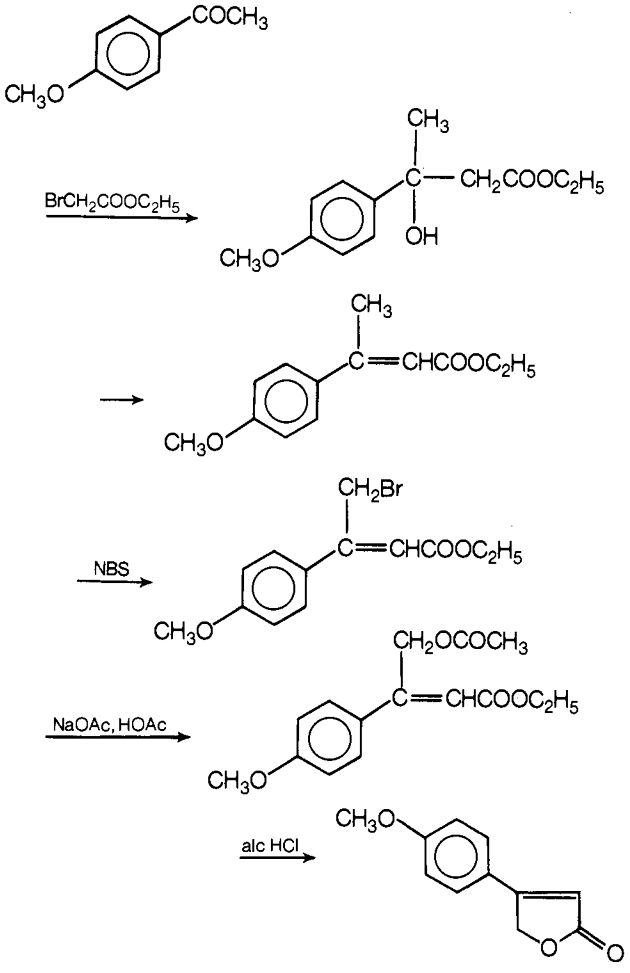
208

R = R' = allyl, R' = aryl

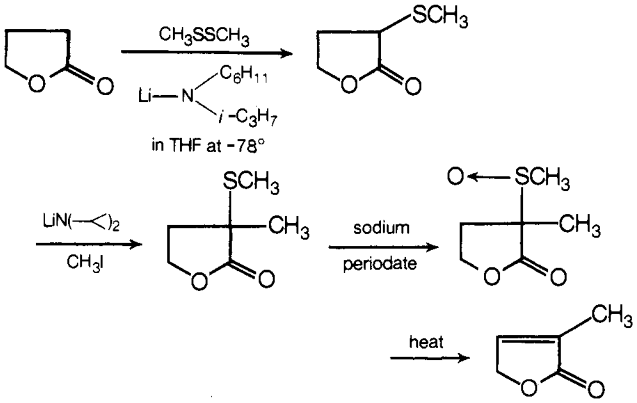
SCHEME XV



205

22. *From Butyrolactones*

Butyrolactones continue to be the starting material for butenolides. In a recent method, γ-butyrolactone has been shown to be converted to α-methyl-$\Delta^{\alpha,\beta}$-butenolide (**210**) in 75% yield via the thioether.[969] Bromination of γ-butyrolactone followed by dehydrobromination with triethylamine is the method due to Price and Judge for the synthesis of $\Delta^{\alpha,\beta}$-butenolide or γ-crotonolactone.[777] γ-Crotonolactone (**211**) itself was synthesized



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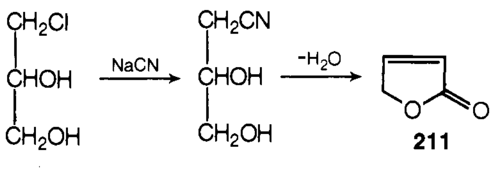
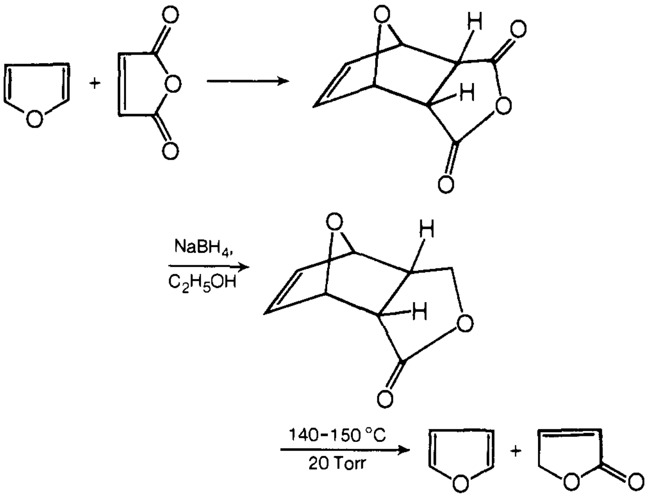


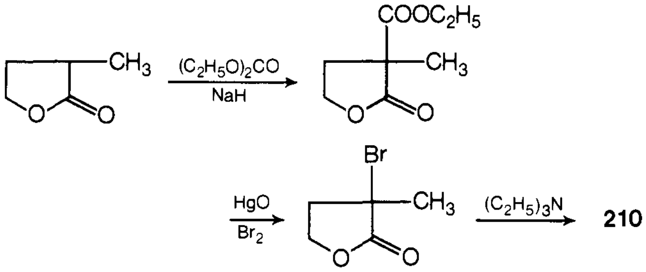
211

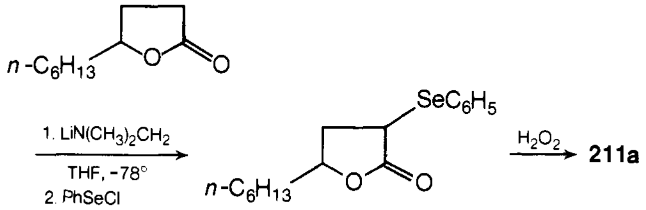
from glycerol-α-chlorohydrin as follows in 23% yield.[397] It is also obtained by the pyrolysis of β-hydroxy-γ-chlorobutyric acid.[1163,1164,1167] The method[777] has been adopted for the synthesis of labeled γ-crotonolactone.[850] A three-step synthesis giving an overall yield of 65.2% of **211** has been reported recently and consists of the following steps.[943]



211

Yet another method for the synthesis of **210** consists of the steps shown below.[494] Organoselenium compounds have been recently employed for the synthesis of γ-(n-hexyl)-$\Delta^{\alpha,\beta}$-butenolide (**211a**).[883] A similar method has been employed by Grieco and coworkers for the synthesis of γ-(n-hexyl-α-benzyl)-$\Delta^{\alpha,\beta}$-butenolide.[1129]

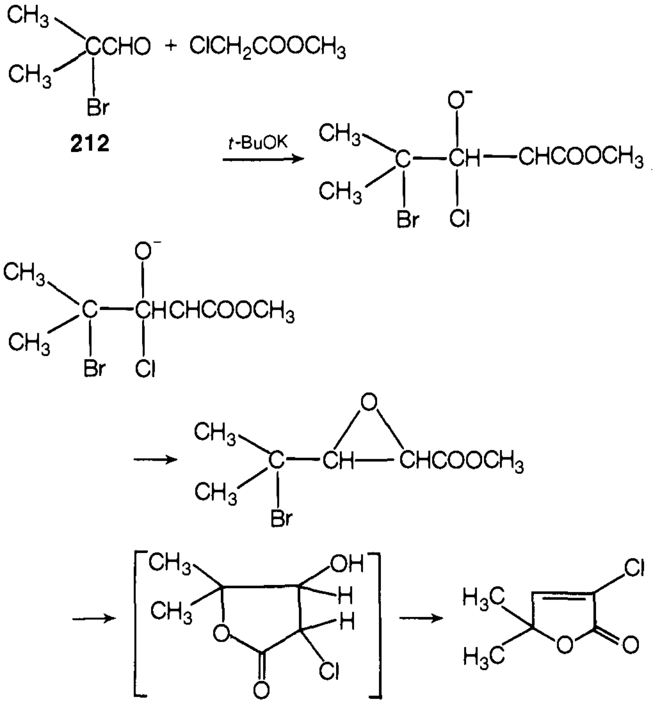


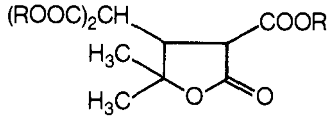


The reduction of α,β-diketo-γ-phenyl-γ-butyrolactone gives α,β-dihydroxy-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide.[252] Similar dihydroxy butenolides are prepared from tetronimides.[253] The conversion of 2,β-diketo-5-hydroxy-5,6-diphenyl-4-pyrone to α-hydroxy-β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide has been reported.[255] These transformations have been employed for the synthesis of hydroxy butenolides.[251,254,256,257] The reaction of tetronic acid with arylamines has been reported to give β-anilino derivatives.[334] Similar conversion of γ-butyrolactone to cyclohexylureido-$\Delta^{\alpha,\beta}$-butenolide has been reported.[627]

23. Darzen's Type of Synthesis

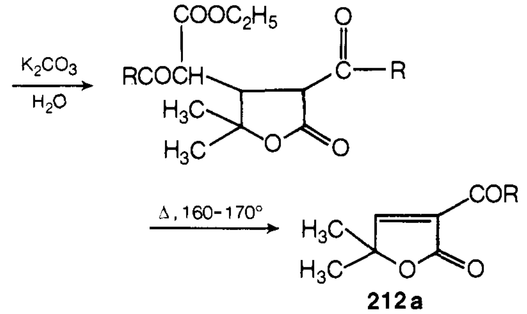
The reaction of α-halo aldehydes such as α-bromoisobutyraldehyde (**212**) with methyl chloroacetate is reported to give 14% yield of α-chloro-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide and 9% of methyl 4-bromo-4-methyl-2,3-epoxypentanoate.[951] The reaction of **212** with diethyl sodiomalonate has been reported[363] to give α-carboxyethyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide. A reinvestigation of this reaction showed that the product obtained is **213**.[949] The reaction of **212** with ethyl acetoacetate in the presence of a base such as NaOEt and K_2CO_3 is reported to proceed as in Scheme XVI, giving $\Delta^{\beta,\gamma}$-butenolides. However, in the presence of K_2CO_3, the products obtained are $\Delta^{\alpha,\beta}$-butenolides. A reinvestigation of this reaction showed **212a** is obtained.





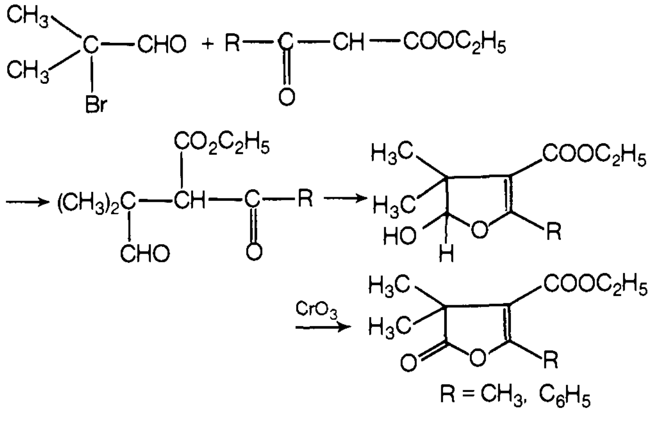
213

212 + $RCOCH_2COOC_2H_5$



R = CH_3, C_6H_5

SCHEME XVI

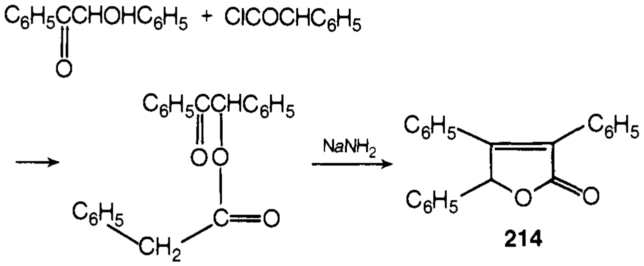


R = CH_3, C_6H_5

24. Condensation of Acyloins with Active Methylene Group Containing Compounds

McRae and Kuehner[663] reported the condensation of benzoin with ethyl cyanoacetate in the presence of sodium ethoxide to give α-cyano-β,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide. Benzoin was converted to the phenylacetate by treatment with phenylacetyl chloride, and the ester was cyclized to α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide (**214**).[782] In a latter modification, sodium amide in liquid ammonia was used.[661]

It has been observed that benzoin condenses with phenylacetic acid in the presence of triethylamine–acetic anhydride to give α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide.[793] Compound **214** was assumed to exist as a hydroxyfuran and its benzoyl derivative **215** was isolated by the lead tetraacetate oxidation of the compound obtained by the nitric acid oxidation of tetracyclone.[781] Compound **215** has been since shown to be α,β,γ-triphenyl-α-benzoyl-$\Delta^{\beta,\gamma}$-butenolid (**185**)[1059] and is debenzoylated to **214** on treatment with alkali. In a reexamination of the cyclization of benzoin phenylacetate (**216**), Rio and coworkers[816,820] have shown that **214** is obtained not only by Dilthey's method but also by the lactonization of α,β-diphenyl-β-benzoylpropionic acid in 65% H_2SO_4 (originally formulated as the $\Delta^{\beta,\gamma}$ isomer by Crawford[245,246]) and that **216** gives the intermediate β-hydroxy-α,β,γ-triphenylbutyrolactone **217** at low temperature. Compound **217** is also obtained by the Ivanov reaction between benzoin and the Ivanov reagent obtained from phenylacetic acid. Compound **214** may be O-methylated to give 2-methoxy-3,4,5-triphenylfuran and also C-alkylated to give $\Delta^{\beta,\gamma}$ derivative. Essentially, the same observations were made by McCoy and Weinheimer.[661] Compound **214** dimerizes in the presence of $K_3Fe(CN)_6$. It has been observed that **214** and the corresponding γ-hydroxy, γ-methoxy, and γ-acetoxy derivatives undergo photochemical isomerization to phenanthrene derivatives **218**, in the presence of a Woods filter and oxygen.[821,822]



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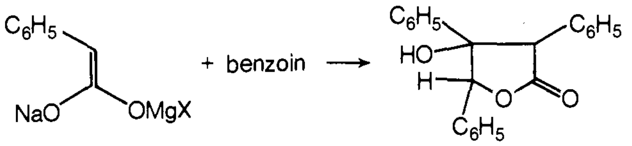
214



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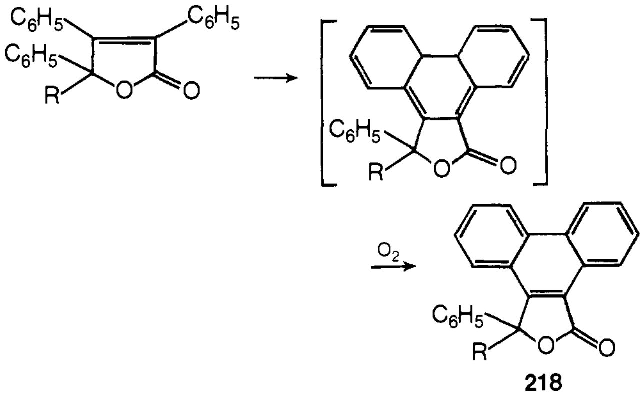
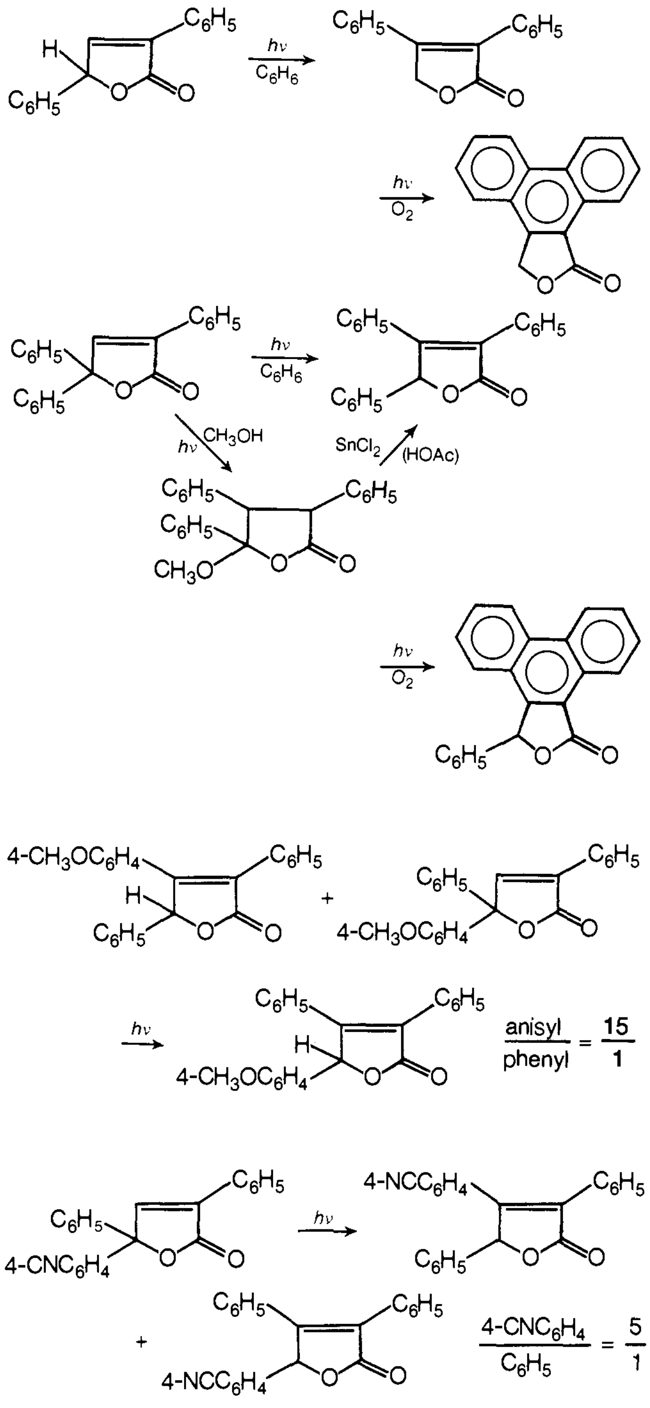


218

SCHEME XVII

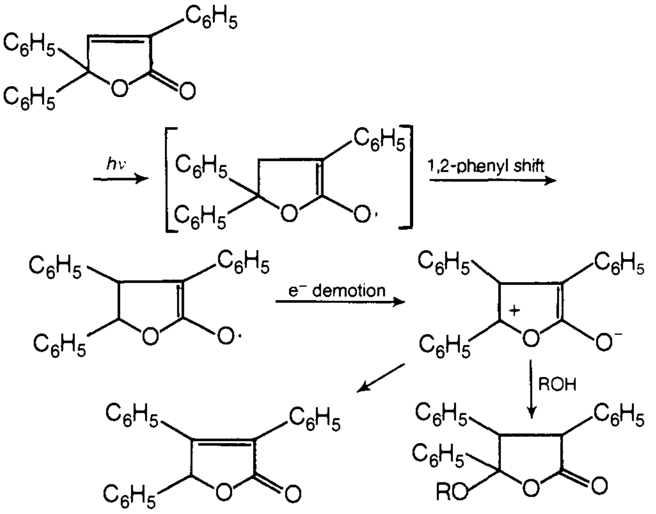


In a recent paper, Padwa and Dehm[1105] reported their studies on the isomerization of the following $\Delta^{\alpha,\beta}$-butenolides. They isolated products formed by migration of aryl group as also phenanthrene derivatives (see Scheme XVII).

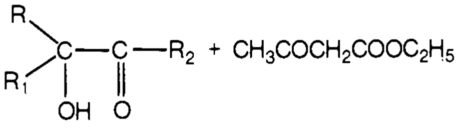
The mechanism in Scheme XVIII has been suggested to involve a triplet state. It may be pointed out that in their studies about pyrrolinones, Rio and Masure studied the dehydration of α-phenyl-β-benzoylpropionic acid[817-819] to give α,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide.

The condensation of acyloins **219** with acetoacetic ester in the presence of aluminum isopropoxide has been reported to give $\Delta^{\alpha,\beta}$ lactones **220.** Cyanoacetic ester and malonic ester have been used instead of acetoacetic ester. Compounds prepared thus are given as **221**.[1148] A similar condensation of malonic ester with acyloins has been carried out in the presence of pyridine–triethylamine. Compound **221** ($R_2 = R_3 = R_4 = CH_3$, $R_1 = COOC_2H_5$) is isolated with long reaction times, while the

SCHEME XVIII

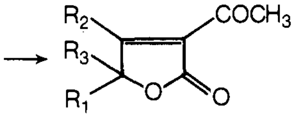


α-cyano analog is obtained in the presence of sodium ethoxide. Compound **219** reacts with diketene to give β,γ,γ-trimethyl-α-acetyl-$\Delta^{\alpha,\beta}$-butenolide. Compound **222** (**a** or **b**) is converted to the carboxy derivative, which on decarboxylation yields β,γ,γ-trimethyl-$\Delta^{\alpha,\beta}$-butenolide.[752]



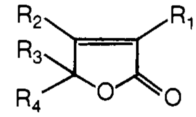
$RR_1C(OH)\text{—}C(=O)\text{—}R_2 + CH_3COCH_2COOC_2H_5$

219

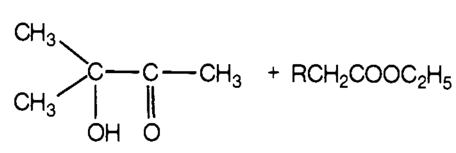


220, 57% yield

$R = R_1 = R_2 = CH_3$
$R = R_1 = H, R_2 = CH_3$
$R = C_2H_5, R_1 = H, R_2 = CH_3$

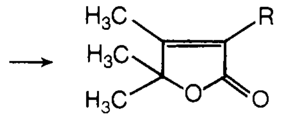


221a, $R_1 = COOC_2H_5$, $R_2 = R_3 = CH_3$, $R_4 = H$
b, $R_1 = CN$, $R_2 = R_3 = CH_3$, $R_4 = H$



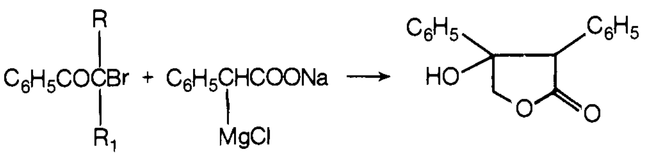
$(CH_3)_2C(OH)\text{—}C(=O)\text{—}CH_3 + RCH_2COOC_2H_5$

219, $R_1 = R_2 = R_3 = CH_3$

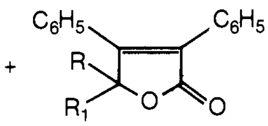


222a, R = CN
b, $R = COOC_2H_5$

Phenacyl bromide and 2-benzoyl-2-bromopropane react with Ivanov reagent **223** to give a hydroxybutyrolactone along with the $\Delta^{\alpha,\beta}$-butenolide in the mother liquor. The hydroxybutyrolactone may be dehydrated with p-toluenesulfonic acid in toluene.[1054]

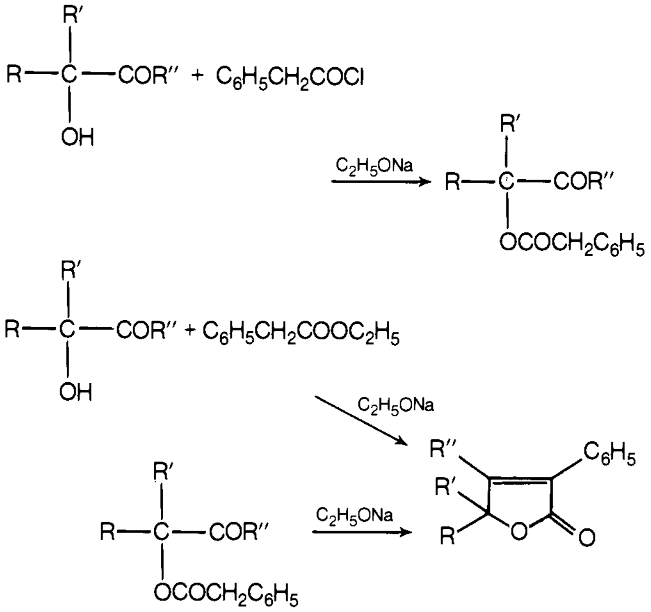


223

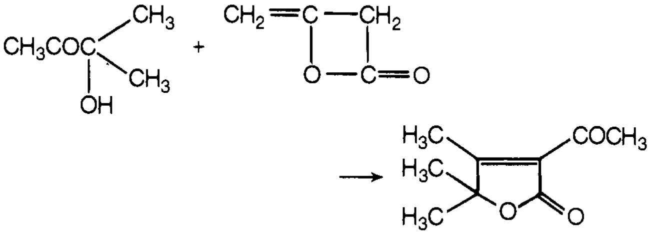


$R = R_1 = H$, $R = R_1 = CH_3$

In a series of papers, Avetisyan and coworkers have reported the condensation of acyloins with acids (or their derivatives) containing active methylene group. The methylene compounds include diethyl malonate, cyanoacetic ester, ethyl benzoylacetate, diketene, acetoacetic ester, ethyl phenylacetate, malonic acid ester chloride, and phenylacetyl chloride. The condensation catalysts are pyridine, triethylamine, and sodium ethoxide in aromatic hydrocarbon solvents usually at temperatures below the boiling point of the solvents.[39-57,1128] The acyloin compounds used in the reaction may be converted first to esters, and the esters are then cyclized to $\Delta^{\alpha,\beta}$-butenolides with sodium ethoxide. The butenolides obtained in these reactions with α-acetyl substituent have been treated with lithium aluminum hydride to give alcohol derivatives of butenolides. With diketene α-acetylbutenolides are obtained. A similar reaction has been reported by Lacey.[595,596]



$R = R' = R'' = CH_3$
$R = C_2H_5, R' = R'' = CH_3$
$R = R' = (CH_2)_5, R'' = CH_3$
$R = H, R' = R'' = C_2H_5$
$R = H, R' = R'' = C_3H_7$

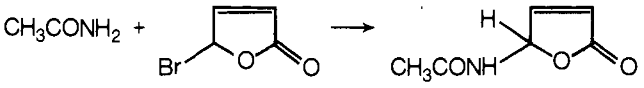


The α-carboxyethyl derivatives are converted into α-carbamoyl derivatives by treatment with amines.[56]

The condensation of benzil with malonodinitrile gives a product, which, by a series of transformations, is converted to α-cyano-β,γ-diphenyl-γ-ethoxy-$\Delta^{\alpha,\beta}$-butenolide.[1134]

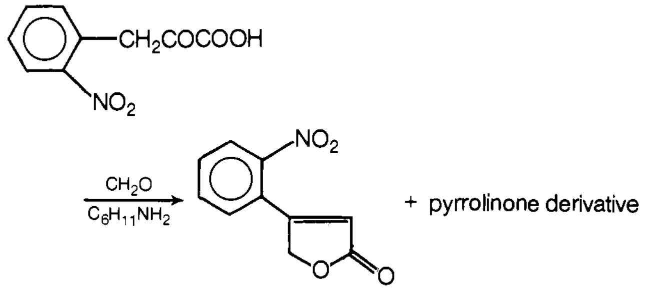
25. Aminobutenolides

The compound γ-acetamido-$\Delta^{\alpha,\beta}$-butenolide (**224**) has been isolated from a series of Fusarium species.[414,1028,1055] The



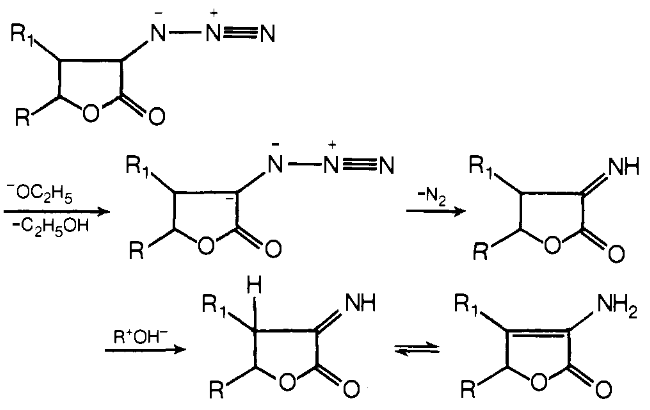
224

compound **224** is synthesized in 26% yield from acetamide and γ-bromo-$\Delta^{\alpha,\beta}$-butenolide.[169] In a study of the mechanism on Fischer indole synthesis, α-hydroxy-β-(2-nitrophenyl)-$\Delta^{\alpha,\beta}$-butenolide has been synthesized as follows. This compound could not be converted into the Plieninger intermediate α-amino-β-(2-anilino)-$\Delta^{\alpha,\beta}$-butenolide by reaction with ammonium formate.[739]



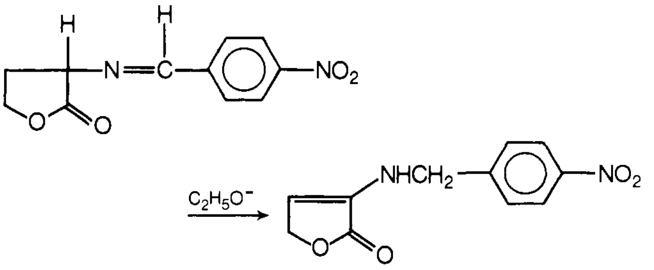
In a recent paper, Korte and coworkers reported that treatment of α-azido-γ-butyrolactones with catalytic amounts of sodium ethoxide leads to the elimination of 1 mol of N_2 with rearrangement to give α-aminobutenolides (Scheme XIX). Under similar conditions, α-4-nitrobenzylideneamino-γ-butyrolactone is converted to a butenolide derivative. α-Diazo-γ-butyrolactone, on photolysis or heating, gives a $\Delta^{\alpha,\beta}$-butenolide derivative.[858] Other aminobutenolides have been synthesized from aspartic acid[603] and acetylenic compounds.[659] The reactions of α,β-dihalo crotonolactones to give amino derivatives will be discussed later.

SCHEME XIX



R = R1 = H

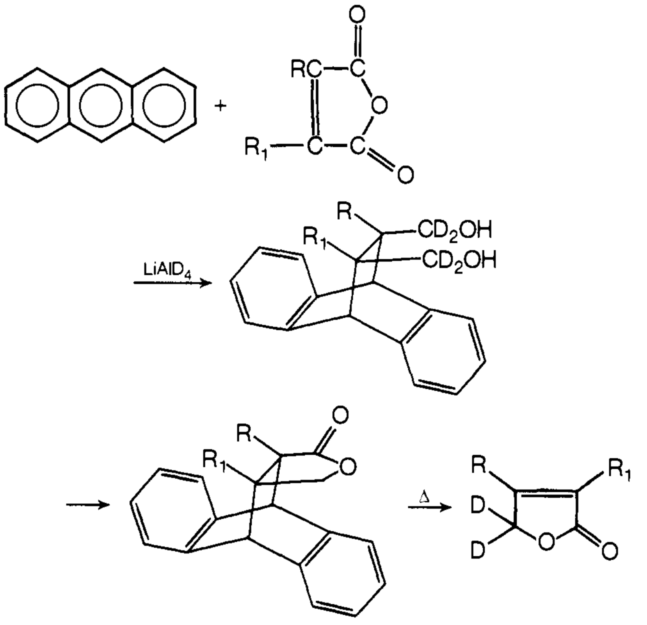
R = CH3, R1 = H; R = H, R1 = CH3



26. Pyrolysis of Diels-Alder Adducts

γ-Dideuteriobutenolides have been synthesized according to the sequence of reactions in Scheme XX.[399]

SCHEME XX

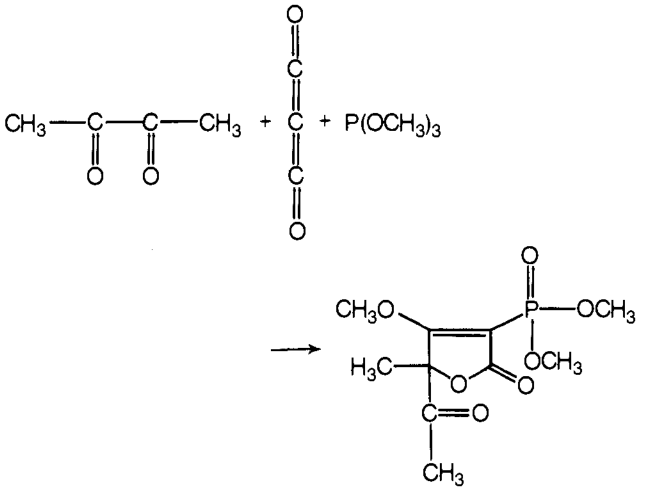


R = R1 = H, R = CH3, R1 = H,

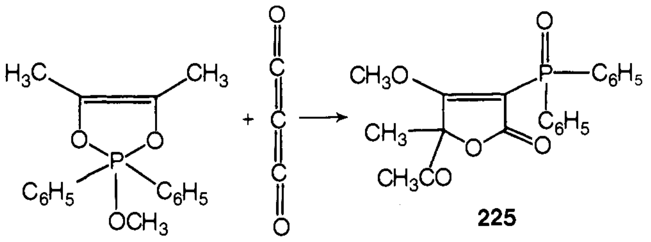
R = H, R1 = CH3

27. Phosphorus-Containing Butenolides

α-Diketones such as biacetyl react with carbon suboxide in the presence of trialkyl phosphites to give γ-acetyl-γ-methyl-β-methoxy-α-phosphoryl butenolides.[787]



When carbon suboxide is added to an adduct of biacetyl and methyl diphenylphosphinite, the buenolide **225** is obtained.



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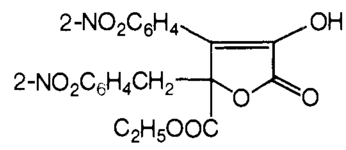
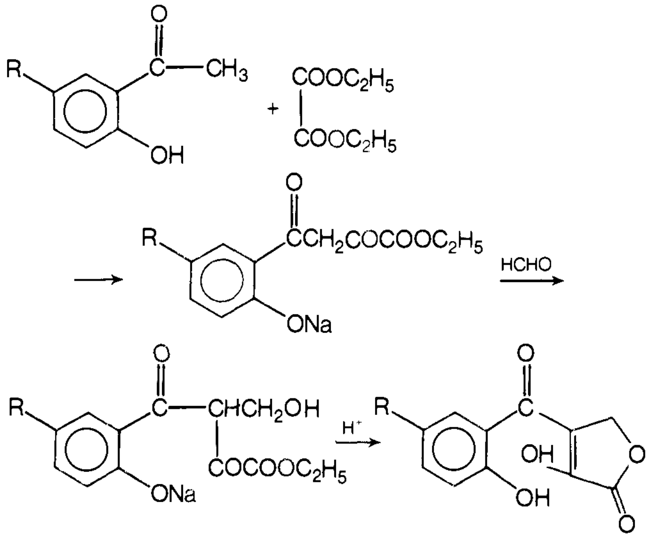
28. Condensation with Diethyl Oxalate

o-Nitrotoluene reacts with diethyl oxalate in the presence of sodium ethoxide to give **226**.[839,840] The reaction of a series of

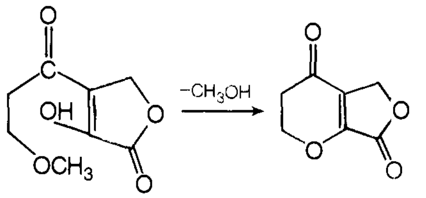


226

o-hydroxyacetophenones substituted in a position para to the hydroxy group, with diethyl oxalate in the presence of sodium ethoxide, has been reported. The end products are β-benzoyl-α-hydroxy-$\Delta^{\alpha,\beta}$-butenolides.[723,743] With α-hydroxy-β-3-

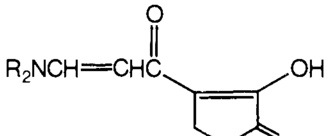


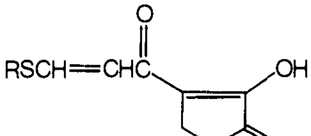
methoxypropionoyl-$\Delta^{\alpha,\beta}$-butenolide, it is possible to cause ring closure to give the corresponding reduced γ-pyrone butenolides **227**.[188,241] With the corresponding α-hydroxy-β-3-methoxy-



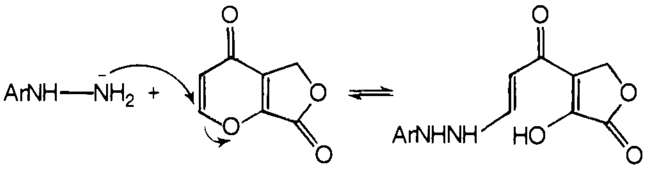
227

2-propenoyl-$\Delta^{\alpha,\beta}$-butenolide, a γ-pyrone butenolide **228** is obtained and its reactions with thiols and primary and secondary amines have been studied.[189] The products obtained are assigned the following structures. Compound **228** reacts with hy-



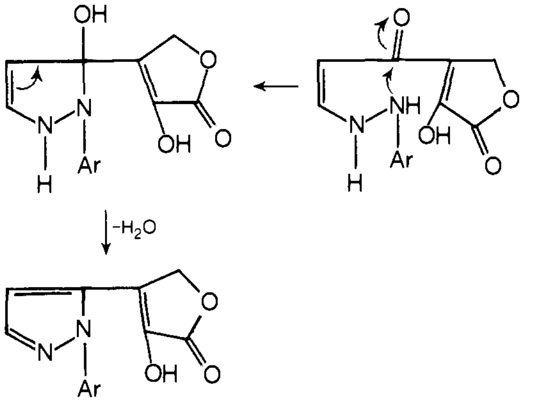


drazines with the ring opening of the γ-pyrone ring rather than the butenolide ring.[187] A series of acetophenones, 2-acetylthi-



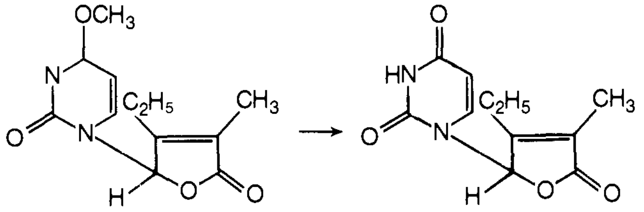
228

ophene, and 2-acetylbenzofuran are converted to 2-aroyl-α-hydroxybutenolides by this method[78]—condensation with diethyl oxalate, hydroxymethylation of the resulting pyruvic acid derivative and acid-catalyzed ring closure[296,746] in 50% yields. The condensation of diethyl ketone with diethyl oxalate in the presence of potassium ethoxide is reported to give the γ-lactone of 3-methyl-2,4-dihydroxy-2,4-hexadienoic acid, and this on reduction with Raney nickel gives α-hydroxy-β-methyl-γ-ethyl-$\Delta^{\alpha,\beta}$-butenolide.[323]



29. Synthesis Involving $\Delta^{\alpha,\beta}$-Butenolides

The reaction of α-methyl-β-ethyl-γ-bromo-$\Delta^{\alpha,\beta}$-butenolide (**229**) with 2,4-dimethoxypyrimidine gives 4-methoxypyrimidinyl derivative, which is hydrolyzed to γ-(uracil-1-yl)-β-ethyl-α-methyl-$\Delta^{\alpha,\beta}$-butenolide (**230**). When γ-bromo-$\Delta^{\alpha,\beta}$-butenolide is used instead of **229**, γ-(uracil-1-yl)-$\Delta^{\alpha,\beta}$-butenolide is obtained. The reaction consists of heating the furanone with the pyrimidine derivative in DMF in the presence of K_2CO_3. Alkylation of adenine with **229** gave γ-(6-amino-9*H*-purin-9-yl)-β-ethyl-α-methyl-$\Delta^{\alpha,\beta}$-butenoline (**230a**).[285,286]



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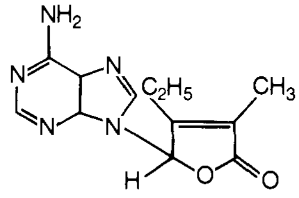
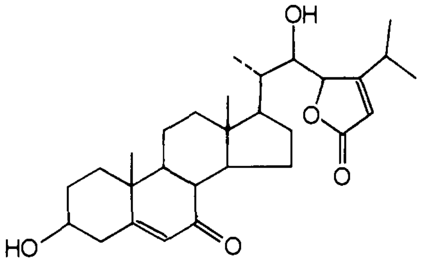


230a

Antheridiol (**231**) is a sex hormone isolated from the water mold *Achlya bisexualis*.[665] The reaction of γ-bromo-α-isopropyl-$\Delta^{\alpha,\beta}$-butenolide with 3β-hydroxy-7-keto-22,23-bis-nor-Δ^5-cholenaldehyde (**232**) under Reformatsky conditions gives **231a**, an isomer of **231**.[664] In a modified process, the 7-deoxy derivative of **232** is treated with the carbanion of β-isopropyl-$\Delta^{\alpha,\beta}$-butenolide in THF at −70° to give about 70% yield of 7-deoxyantheridiol, and this was converted into **231a** by photooxygenation and oxidative rearrangement.[666,667] The desired β-isopropylbutenolide has bee prepared from 1-acetoxy-3-methyl-2-butanone and ethyl bromoacetate. γ-Bromo-β-isopropyl-$\Delta^{\alpha,\beta}$-butenolide itself is obtained by the pyrolysis of



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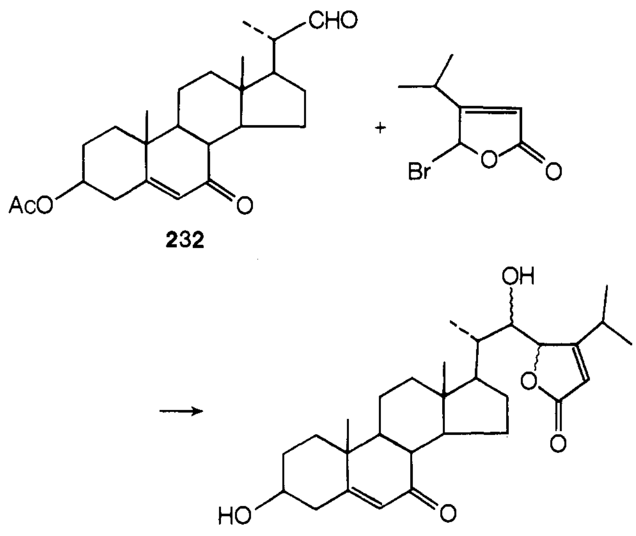


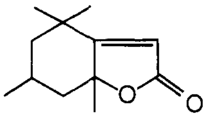
232

231a

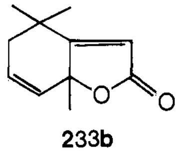
2,5-diacetoxy-3-isopropyl-2,5-dihydrofuran and addition of bromine to the end product. Alternately it is prepared by the addition of diazopropane to γ-bromo-$\Delta^{\alpha,\beta}$-butenolide.[668] The condensation reactions of the carbanions of $\Delta^{\alpha,\beta}$-butenolide, α-methyl-$\Delta^{\alpha,\beta}$-butenolide, and the aldehyde, 3β-acetoxy-22,23-bisnor-Δ^5-cholenaldehyde (7-deoxy-**232**) have been studied. The carbanions have been generated by treatment with trityllithium in THF.

30. Synthesis of Fused Butenolides

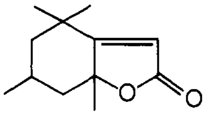
Several butenolides fused to cyclohexane ring or decalin ring have been reported: loliolide (**233c**), actinidiolide (**233b**), dihydroactinidiolide (**234**) and eremophilenolide (**235**). The structure of loliolide obtained from *Lolium perenne* has been established.[479] Digiprolactone has been isolated from *Digitalis purpurea* leaves, and it has been shown to be identical with loliolide.[1005-1007] Compound **234** is also isolated from the neutral fraction of the steam volatiles from tobacco,[66] from the essential oil of the leaves of *Actinidia polygama*,[838] and from photooxidation products of β-ionone.[703] Levantenolides **236** and **237** have been isolated from Turkish tobacco.[533] Loliolide and its analogs have been synthesized.[1170,1171,1186]



233a



233b



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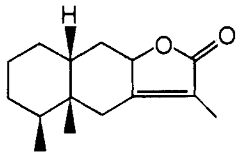

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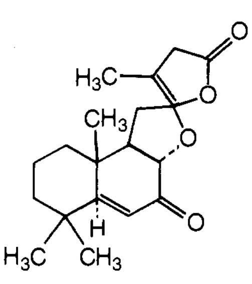

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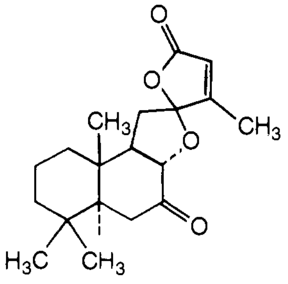

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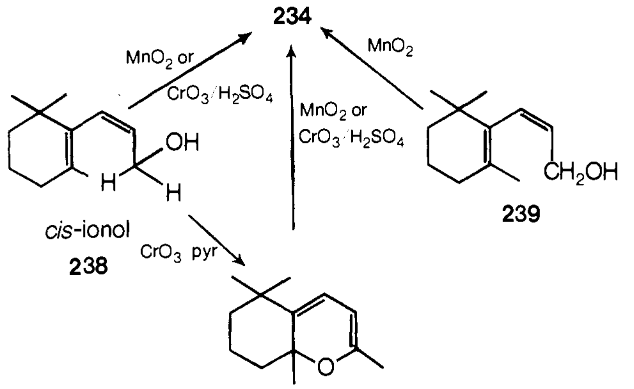
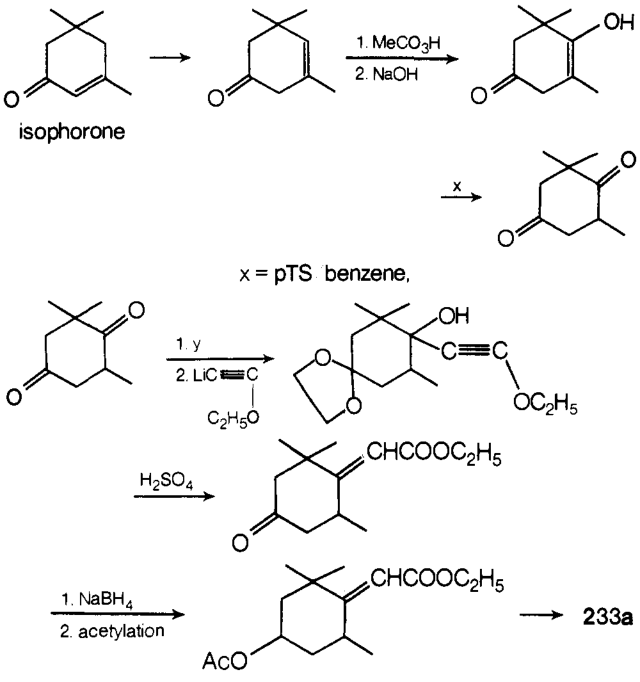
a. Oxidation Methods

A recent method for the synthesis of **234** consists of oxidation of alcohols **238** and **239**.[1088]



In the synthesis of loliolide, Sondheimer and coworkers employed selenium dioxide oxidation in the final step (Scheme XXI).[651]

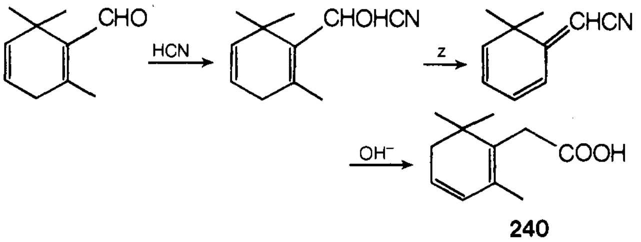
SCHEME XXI



x = pTS/benzene, y = ethylene glycol/pTS

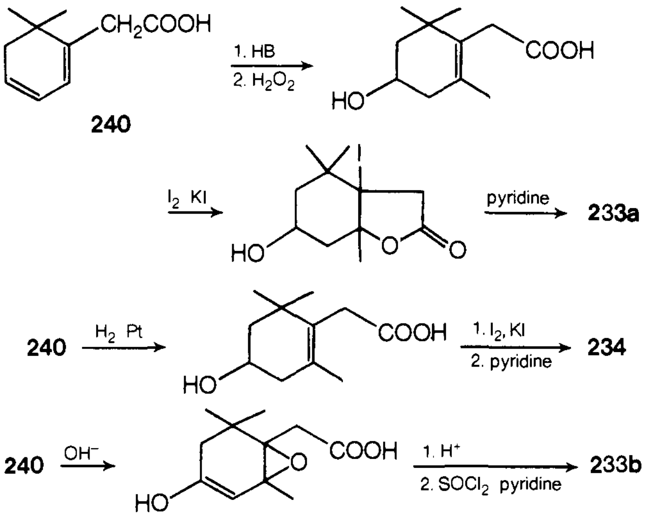
b. Starting from Homosafranic Acid

Loliolide, actinidiolide, and dihydroactinidiolide have all been synthesized in an elegant manner by Demole and Enggist.[276] The starting material is homosafranic acid (**240**), itself obtained from β-cyclocitral. Hydroboration of **240** followed by treatment with I_2 in KI gives the iodo lactone, which on heating with pyridine gives **233a**. Homosafranic acid is epoxidized and acidified to give a hydroxy lactone which on dehydration gives **233b**. Compound



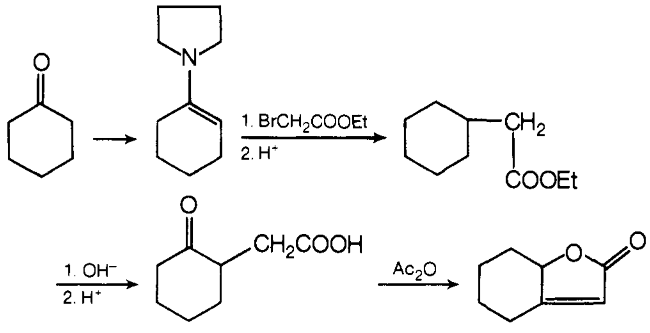
z = $POCl_3$/pyridine

234 is obtained from the reduced acid either via the epoxide, hydroxylactone, and dehydration or via the iodolactone and dehydrohalogenation.

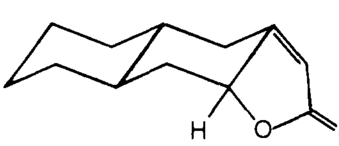


c. By Alkylation with Bromoacetic Ester

Cyclohexanone has been converted to **99** via the pyrrolidine enamine, alkylation with bromoacetic ester, hydrolysis of 2-ketocyclohexylacetic ester, and cyclization of the free acid with acetic anhydride.[1102] Compound **99** was also prepared by Wang and coworkers.[1015,1016] The enamine method is similar to the one employed by Minato and coworkers.[678] Chappell converted *trans*-1-decalone and *trans*-2-decalone by the enamine alkylation method to **241** and **242**.[196]



99



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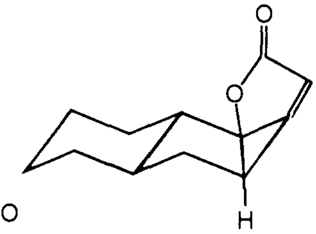
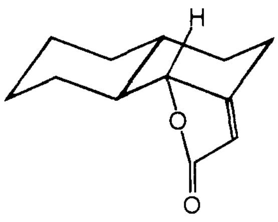


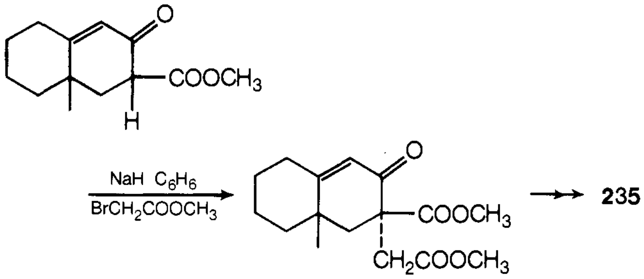
242

Compound **241** is also obtained by Reformatsky reaction of 3(e)-acetoxy-*trans*-2-decalone with bromoacetic ester followed by a series of transformations of the intermediate hydroxy esters. The Reformatsky reaction of 3(a)-acetoxy-2-decalone also leads to **241**. Also obtained is the butenolide **243**.

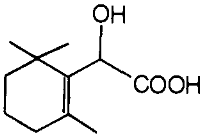


243

Finally the intermediate keto acetic ester may be obtained by the enolate anion alkylation of a suitable keto compound.[767]

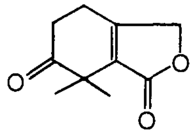


Bailey and coworkers synthesized **234** from 2,2,6-trimethylcyclohexene-1-glycolic acid (**244**), easily obtained from 2,2,6-trimethylcyclohexanone. Treatment of **244** with H_2SO_4 is reported to give **234** in 35% yield.[66]



244

A cyclohexenobutenolide **245** has been prepared for comparison with the pyrolysis product of bis(dehydrodihydroenemein) (**246**).[728] A compound similar to **99** with a 2-oxocyclohexyl substituent has been reported.[871] Pelletier and coworkers synthesized the fused lactone **247**, employing the steps in Scheme XXII.[754]



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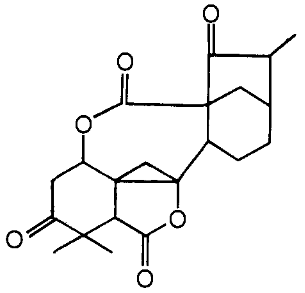

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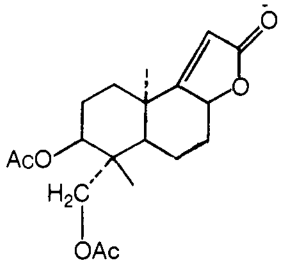
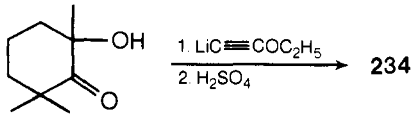


247

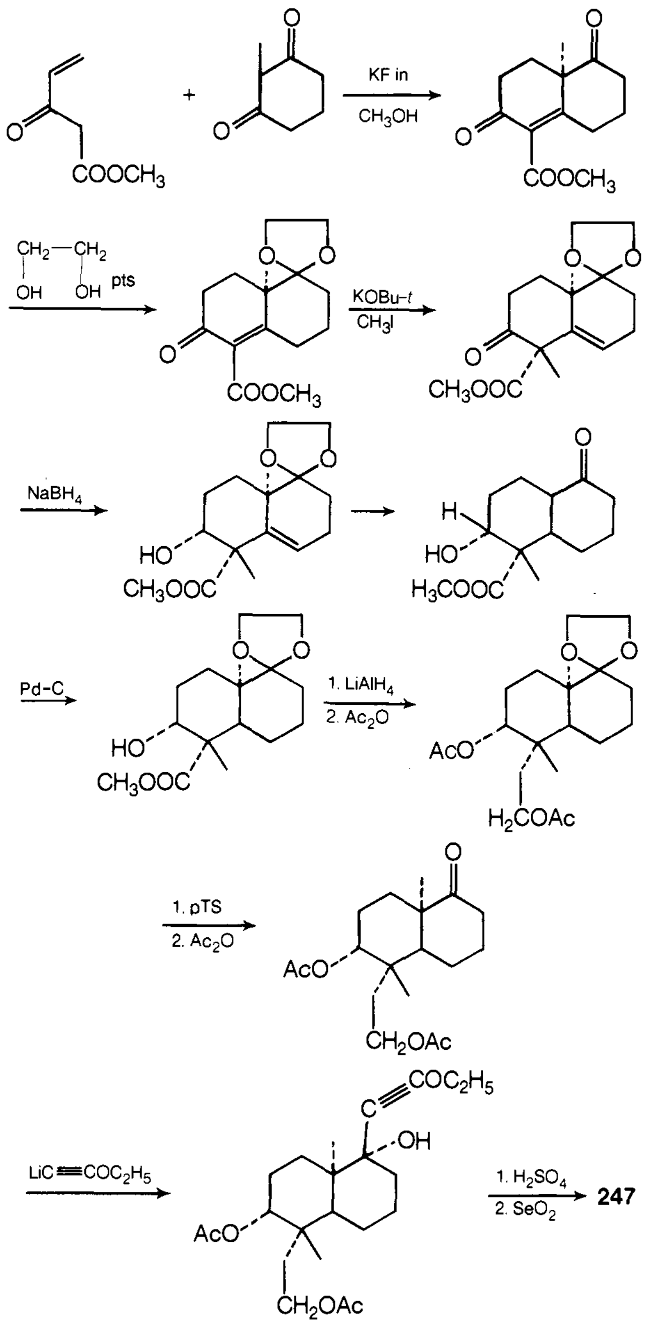
Finally Horii and coworkers have reported the synthesis of dihydroactinidiolide (**234**) and actinidiolide (**233b**) by employing the lithium ethoxyacetylide method.[1170,1171] This key step has been used for the synthesis of securinine and racemic loliolide.[1168-1171]



31. Butenolides Connected with Cephalosporin Synthesis

Several butenolides substituted in the α and β position with amino hydroxy or thio substituents have been synthesized in

SCHEME XXII



connection with studies on cephalosporin lactones. β-Aminoethyl-α-tetronic acid (**248**), is prepared from γ-butyrolactone according to the sequence in Scheme XXIII.[382,383]

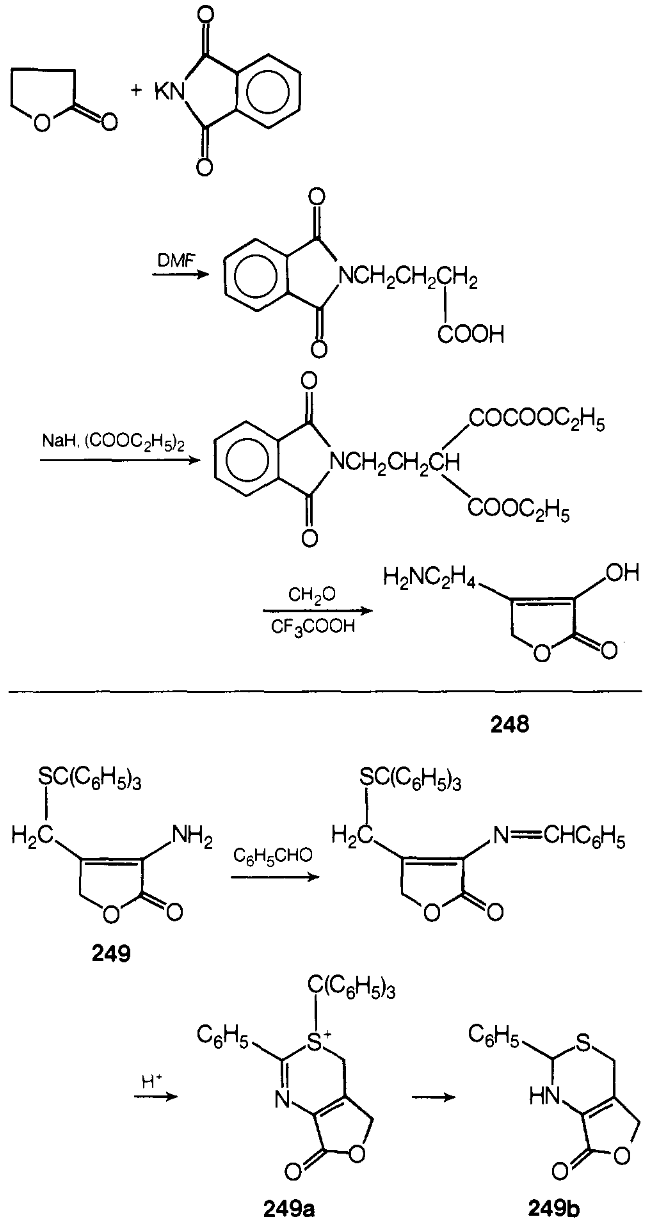
The reaction of β-triphenylmethylthiomethyl-α-hydroxy-$\Delta^{\alpha,\beta}$-butenolide (**249**) leads to the corresponding to α-amino derivative.[287,716,1156] Compound **249** condenses with benzaldehyde to give **249a**.

The *N*-acetyldihydrothiazine derivative has been synthesized by a different route.[1172] α-Hydroxy-β-thiomethyl-$\Delta^{\alpha,\beta}$-butenolide has been used for the synthesis of the dihydrothiazine derivative.[365-367]

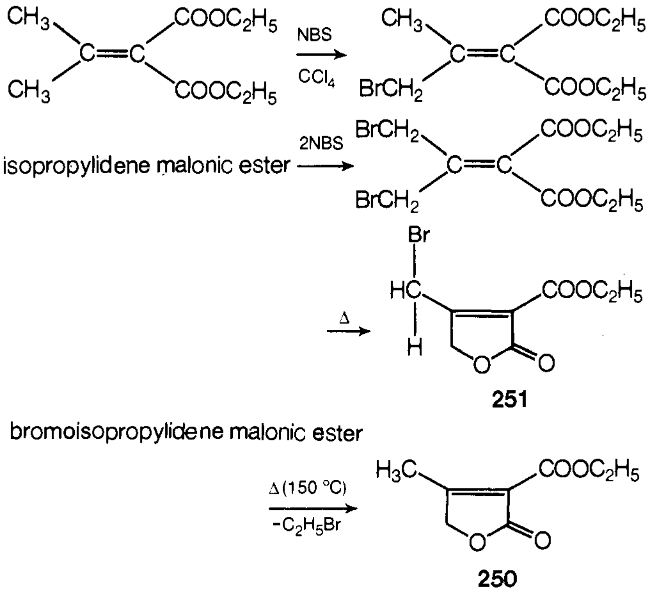
Similar studies on synthetic approach to cephalosporin involved the steps in Scheme XXIV. Compound **251** reacts with β-sodiothioacrylic ester to give **252**. Compound **250** is converted to α-isocyanato-β-methyl-$\Delta^{\alpha,\beta}$-butenolide via the acid chloride and azide.[426]

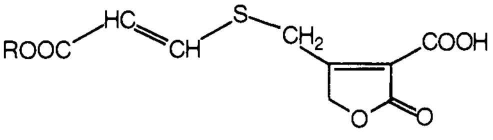
Similar studies on furo oxathiins were made by Beyerman and coworkers. They used RCHO-BF$_3$ complex in reaction with α-hydroxy-β-acetylthiomethyl-$\Delta^{\alpha,\beta}$-butenolide (**253**), prepared from pyruvic acid and diethylamine hydrochloride and treatment with thioacetic acid.[105,1157]

SCHEME XXIII



SCHEME XXIV



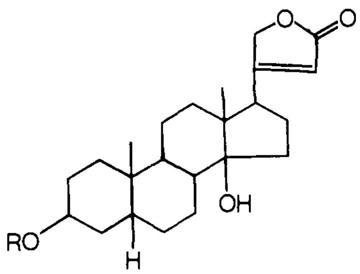


252

32. Synthesis Involving the Steroid Nucleus

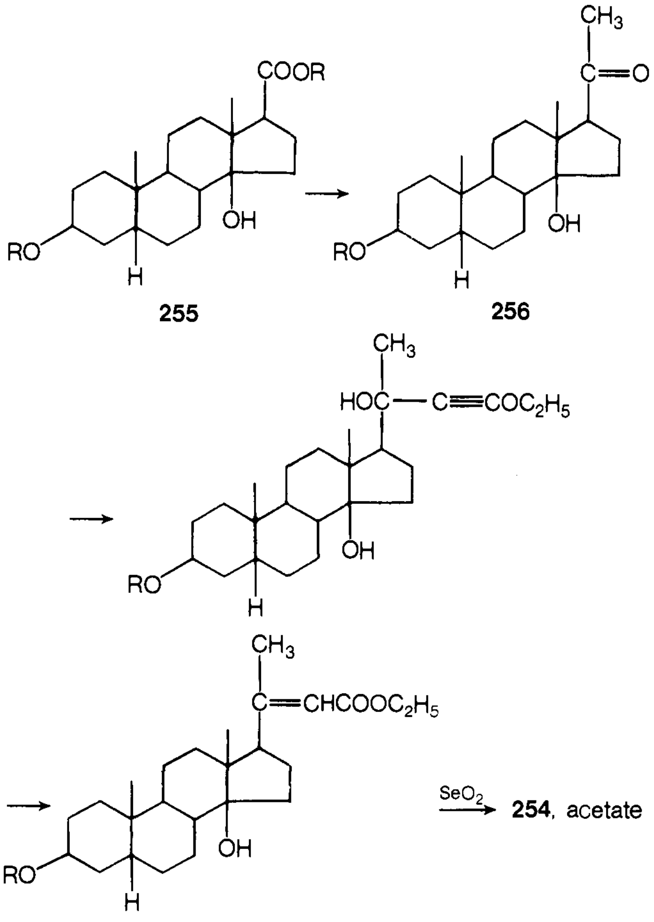
As pointed out earlier, the $\Delta^{\alpha,\beta}$-butenolide ring occurs in the aglycon moiety of the cardiac glycosides. The point of attachment of the steroidal ring in the cardenolides is to the β position of the butenolide ring. Isocardenolides, on the other hand, contain the steroidal ring attached to the butenolide in the γ position.[763] A third classification of cardenolides is the pseudocardenolide which does not contain a steroidal unit but has a β substituent in the lactone ring.[497] In recent years, synthesis of digitoxigenin, periplogenin, uzarigenin, and canarigenin have been reported.

a. Digitoxigenin (**254**)



254

Methyl 3β-acetoxy-14β-hydroxy-5β-etianate (**255**) is converted to 5β-pregnane-3β,14β-diol-20-one-3-acetate (**256**) with methyllithium. Reaction of **256** with lithium ethoxyacetylide followed by rearrangement of the acetylenic compound gives an α,β-unsaturated ester, which on SeO_2 oxidation gives digitoxigenin acetate.[262,263] The compound 14-deoxydigitoxigenin has been prepared from 3β-acetylnorlithiochloyl chloride. The α,β-unsaturated acid needed for SeO_2 oxidation is prepared by dehydrobromination in the presence of sodium *tert*-butoxide–sodium iodide.[844]



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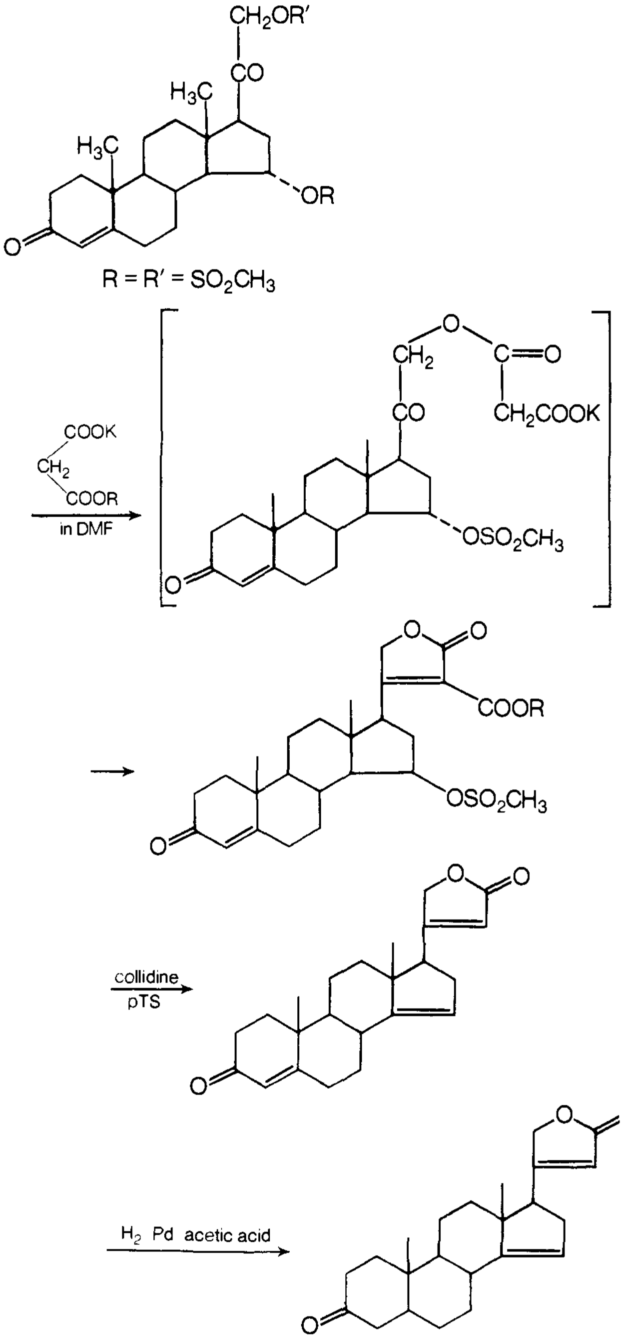
SCHEME XXV



257

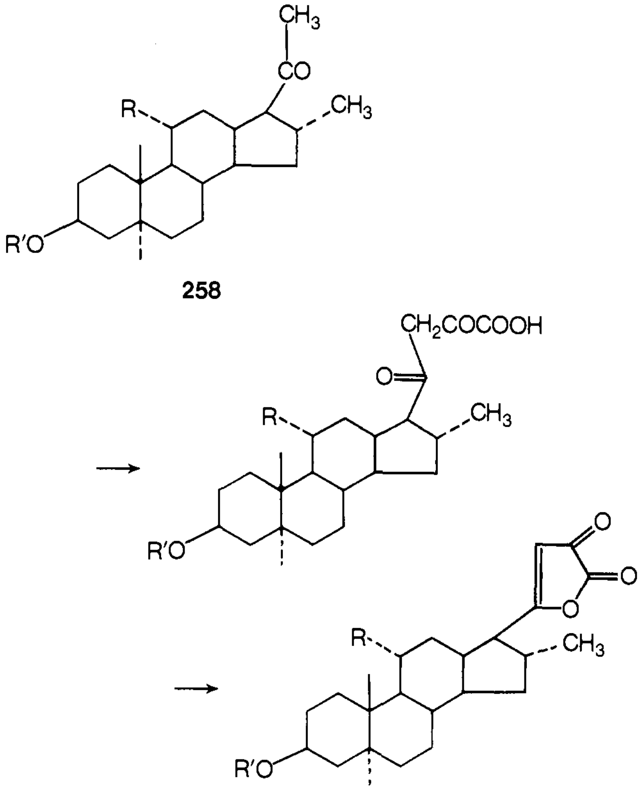
In a recent method, the acetate of **254** has been prepared according to Scheme XXV. Compound **257** is converted to **254** via the 14,15-epoxide of **257**.[370]

Diethyl oxalate condenses with a keto steroid such as **258** to give a diketo ester.[472] Also synthesized were 14-epidigitoxigenin and 3-deoxydigitoxigenin.[1077]

In other syntheses, the 14-hydroxy group was introduced into β-anhydrodigitoxigenin acetate.[61,315]

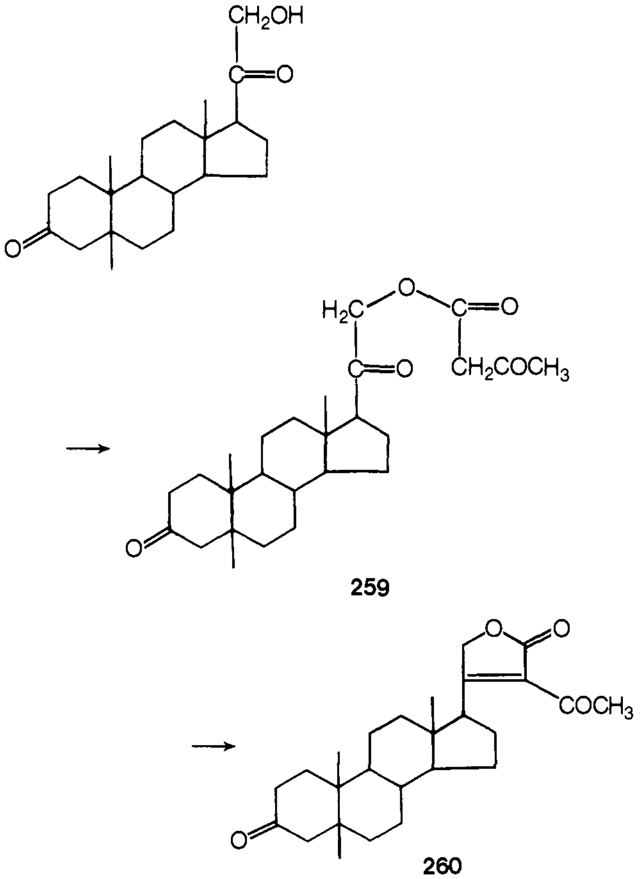
b. α-Acetyl-β-(androsten-17-yl)-$\Delta^{\alpha,\beta}$-butenolides

The method consists of reacting compounds such as preg-



258

nan-21-ol-3,20-dione with acetoacetic ester to give **259.** Sodium methoxide converts **259** to **260,** formed by intramolecular cyclization.[368]



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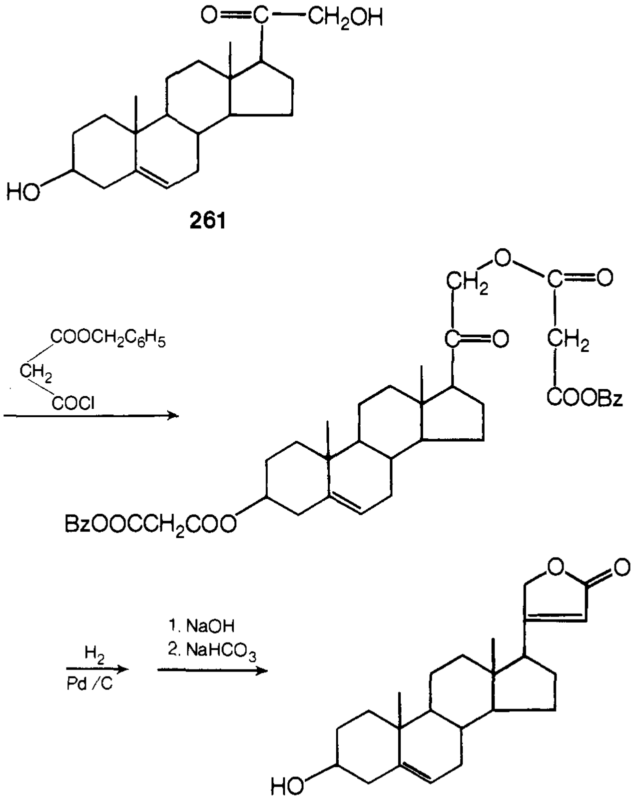
260

c. Syntheses Involving Malonic Esters

The reaction of oxo steroids such as **261** with malonic acid benzyl half-ester chloride gives the dibenzyl malonate ester. β-[Δ^5-Androstenol-3-yl-17]-$\Delta^{\alpha,\beta}$-butenolide (**262**) has been prepared thus.[369] Potassium half-ester malonate has been used for the syntheses of 3-oxo-5α-carda-14,20(22)-dienolide which is synthesized and converted to uzarigenin (**263**).[910] Canarigenin (**264**) has been synthesized from 3-oxocarda-4,14,20(22)-trienolide (**265**) by a series of transformations.[371]



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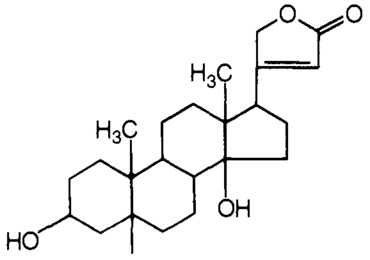
262



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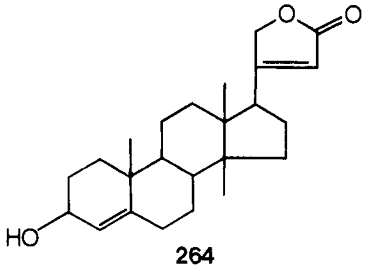

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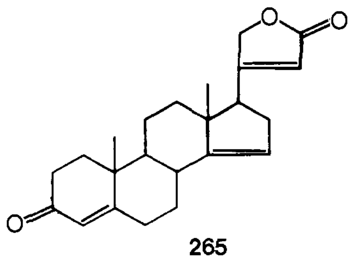
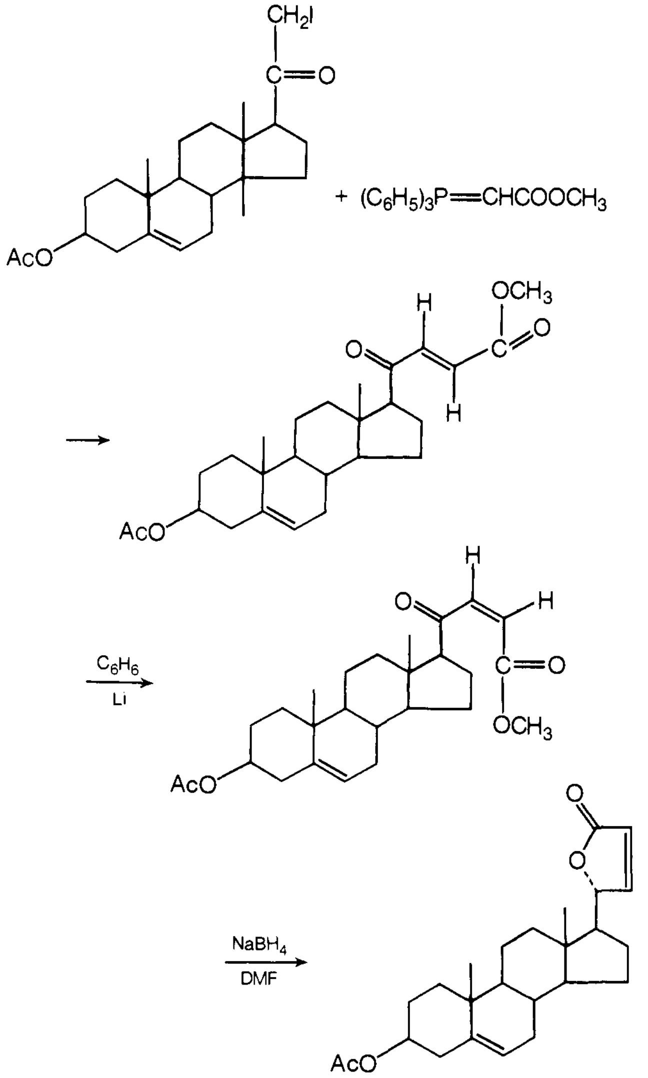


265

d. Wittigs Method

Pettit and coworkers started with the acetoxy iodoacetyl steroid for the synthesis of isocardenolide **266**.[759,763] Fritsch and coworkers also employed Wittig's reaction for the synthesis of β-[Δ^5-androstenol-(3β)-yl-17]-$\Delta^{\alpha,\beta}$-butenolide (**262**).[369]



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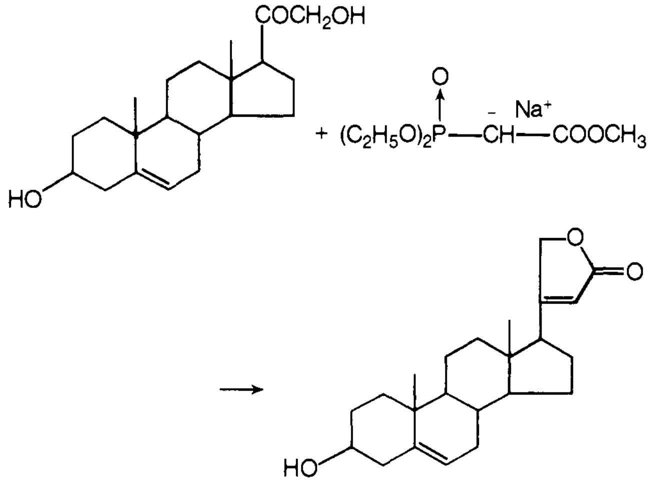
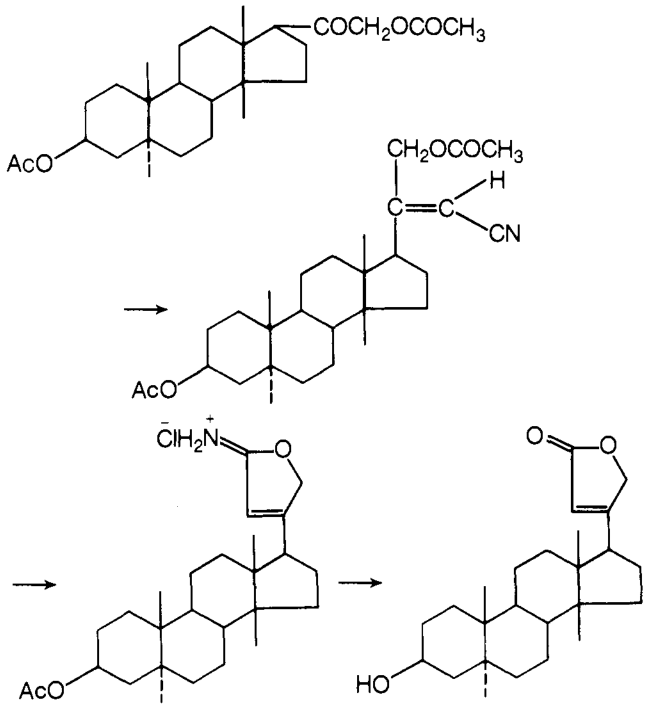


Diethyl cyanomethylphosphonate has been used for reaction with 3β-diacetoxy-20-oxo-5α-pregnane, and the intermediate cyano derivative cyclizes to give an iminolactone (Scheme XXVI). Hydrolysis of the latter compound gives cardenolides.[760,764]

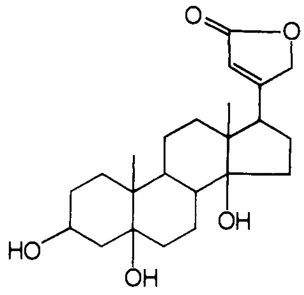
SCHEME XXVI



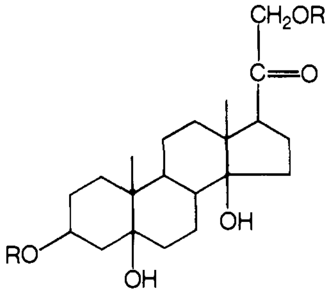
Finally activation with phosphorus derivatives has been employd to synthesize cardenolides[607] and substituted cardenolides with chlorine, fluorine and methyl substituents on the lactone ring.[299]

e. Miscellaneous Methods

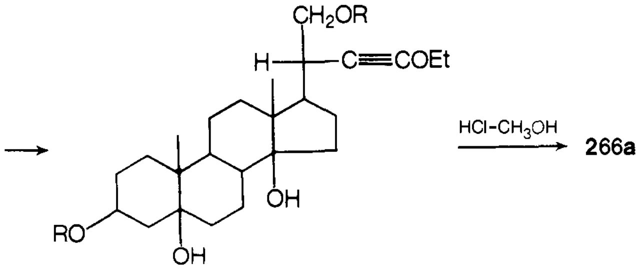
Periplogenin (**266a**) has been synthesized by the reaction of a dihydroxy steroidal derivative with lithium ethoxyacetylide.



266a

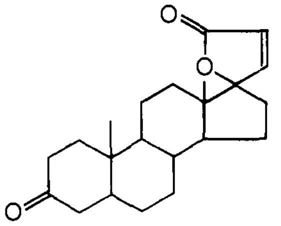


266b



The malonic acid condensation with a formyl steroid has been used for the synthesis of a spirolactone steroid **266c**.[93]

Compounds prepared by the above methods are listed in Table III (see Microfilm Edition).



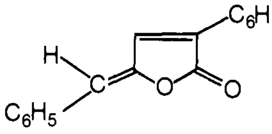
266c

It may be seen from the above discussion that the methods most commonly used for $\Delta^{\alpha,\beta}$-butenolide synthesis are Reformatsky reaction with its variations; lithium ethoxyacetylide method and the condensation of acyloins with active methylene group containing compounds.

D. Synthesis of γ-Arylidene (Alkylidene)-α-aryl (alkyl)-$\Delta^{\alpha,\beta}$-butenolides

1. *From Pulvinic Acid Derivatives*

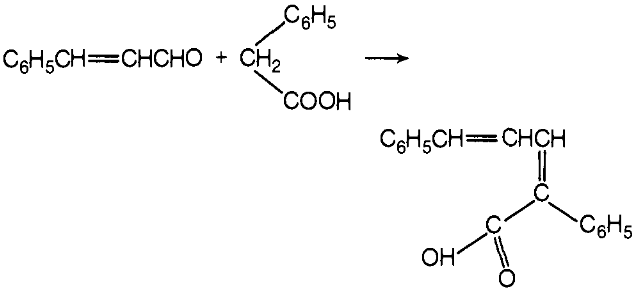
α-Phenyl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (**12**), called "Cornicularlactone" is obtained as one of the reduction products of pulvinic acid **13**.[24,905] The acid product, obtained by the reduction of **16** with Pd/C, is dihydropulvinic acid. This compound, on heating with acetic anhydride, gives carboxy cornicularlactone, which on distillation under vacuum undergoes decarboxylation to give **12**.



12, $R = R_1 = C_6H_5$

2. *From Bromo Acids*

Cinnamaldehyde condenses with phenylacetic acid to give 2,4-diphenylpenta-2,4-dienoic acid (**267**). The dibromide of **267**, formulated 2,5-dibromo-2,5-diphenyl-3-pentenoic acid and obtained by bromination of **267** in carbon tetrachloride, may be debrominated with diethylaniline to give **12**.[961] In a recent method, Saikachi and Taniguchi[835,836] observed that a bromo aldehyde **268** condenses with α-furylacetic acid and α-thenylacetic acid in the presence of acetic anhydride and triethylamine to give **269** in 16–17% yields.



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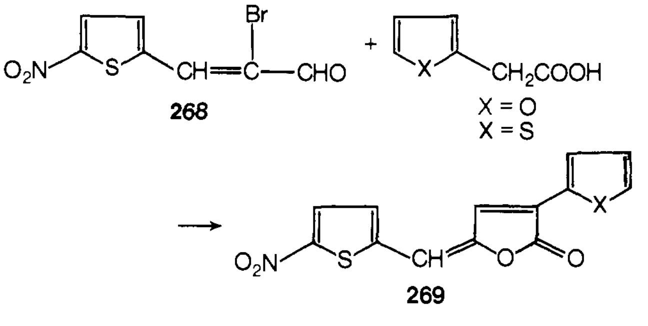

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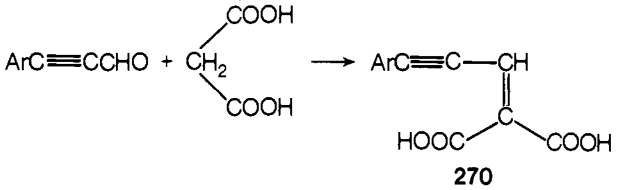
269

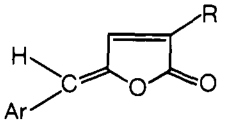
3. *From Phenylpropargylaldehyde and Malonic or Phenylacetic Acids*

In a series of papers, Pascual and coworkers reported the condensation of phenylpropargylaldehyde with malonic acid (ref 89, 90, 150 and those quoted in 791) to give propargylidenemalonic acids **270**. Isomerization of **270** to α-carboxy-γ-arylidene-$\Delta^{\alpha,\beta}$-butenolides may be effected by heating **270** in glacial acetic acid, by silver ion catalysis, or by directly heating a mixture of propargylaldehyde, malonic acid, and glacial acetic acid for 9 h. In place of malonic acid, one may use cyanoacetic acid and malonitrile to give the corresponding α-cyano-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (**271**).[150] Heating **271** (R = COOH) under vacuum gives γ-benzylidene butenolide.



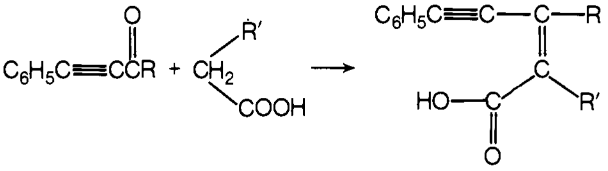
270

$Ar = C_6H_5, 4\text{-}ClC_6H_4, 4\text{-}CH_3C_6H_4, 4\text{-}CH_3OC_6H_4, 4\text{-}NO_2C_6H_4$, 5-nitrofuryl



271, R = COOH, CN

In a more recent method,[792] it has been observed that the condensation of phenylpropargylaldehyde (or a similar acetylenic ketone) with phenylacetic acid and substituted phenylacetic acids in the presence of acetic acid and triethylmine leads to the formation of **12** in 40–85% yields. The intermediate 2,5-diphenyl-2-yn-4-oic acid (**272**, R = H; R′ = C_6H_5) has cis configuration and undergoes acid-catalyzed isomerization readily. It may be pointed out that Wiley and coworkers[1033] observed that **272** gave 3,6-diphenyl-2-pyrone (**272a**) in the presence of mercuric sulfate



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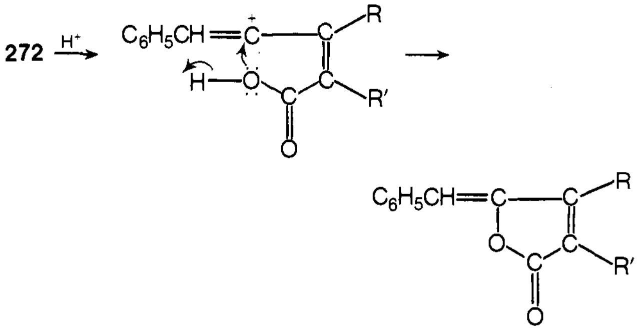
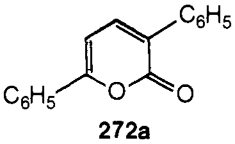




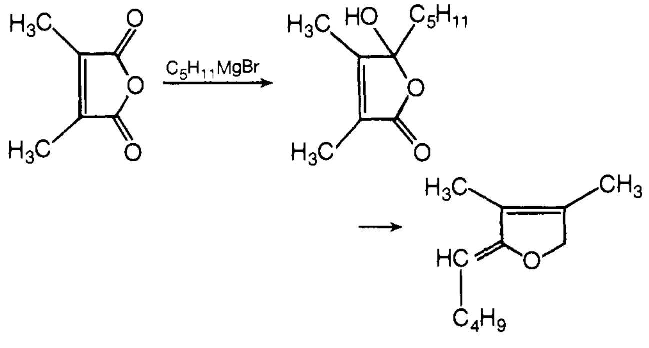
272a

and dilute sulfuric acid. Acetylenic acids similar to **272** have been reported to give $\Delta^{\alpha,\beta}$-butenolides.[1034-1036]

4. From Substituted Maleic Anhydrides

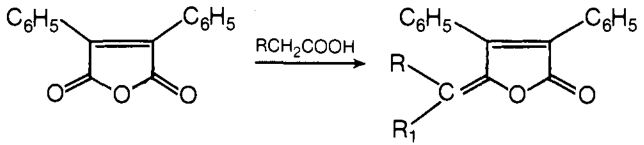
a. Grignard Method

Reaction of dimethylmaleic anhydride with *n*-pentylmagnesium bromide yields α,β-dimethyl-γ-pentyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide, which on dehydration with *p*-toluenesulfonic acid gives bovolide-γ-pentylidene-α,β-dimethyl-$\Delta^{\alpha,\beta}$-butenolide.[872] In a similar fashion, a whole series of γ-hydroxy-γ-alkyl-$\Delta^{\alpha,\beta}$-butenolides have been prepared from dimethylmaleic anhydride, and the intermediate hydroxy compounds have been dehydrated by heating with potassium bisulfate. A whole series of γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides have been prepared by this method but no yields are given.[601]



b. Condensation of Phenylacetic Acids

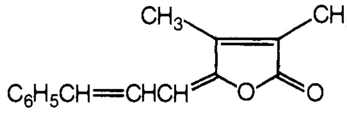
Diphenylmaleic anhydride is condensed with phenylacetic acid[224,378] and *m*-tolylacetic acid[1146] in the presence of sodium acetate to give **273**. Compound **273** on nitration and bromination yielded the corresponding butenolides (R_1 = Br, NO_2).



273

R = 3-$CH_3C_6H_4$, R_1 = H; R = C_6H_5, R_1 = H

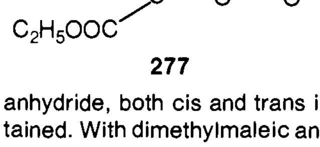
Dimethylmaleic anhydride under similar conditions condenses with phenylisocrotonic acid to give γ-cinnamylidene-α,β-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**274**).[601,960]



274

c. Wittig's Reaction

The reaction of citraconic, maleic, and dimethylmaleic anhydrides with the stable phosphorus ylides—carboethoxymethylenetriphenylphosphorane (**275**) and acetylmethylenetriphenylphosphorane (**276**)—occurred in most cases stereospecifically to give γ-lactones **277** and **278**. With methylmaleic anhydride, both cis and trans isomers of **277** and **278** are obtained. With dimethylmaleic anhydride, only the trans isomer is obtained. In the case of maleic anhydride, reaction does not occur and as such a Diels–Alder adduct of furan and maleic anhydride is employed and the final product undergoes a facile retro Diels–Alder reaction to give **279**.[387,1197,1198]



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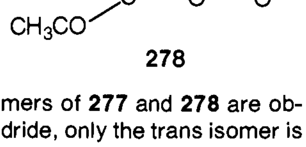

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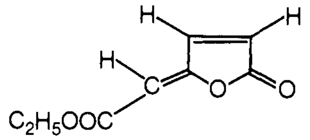

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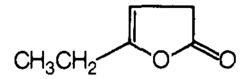
*5. From γ-Ethyl-$\Delta^{\beta,\gamma}$-butenolide (**280**)*

This method applies specifically to γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide **281**. Compound **280**, obtained from 4-oxohexanoic acid, which is obtained by the base-catalyzed condensation of 1-nitropropane and methyl acrylate, is treated with bromine in carbon disulfide. The dibromolactone was dehydrobrominated with triethylamine to give **281**.[520] A similar method was employed for the synthesis of protoanemonin.[1083]



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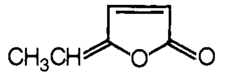

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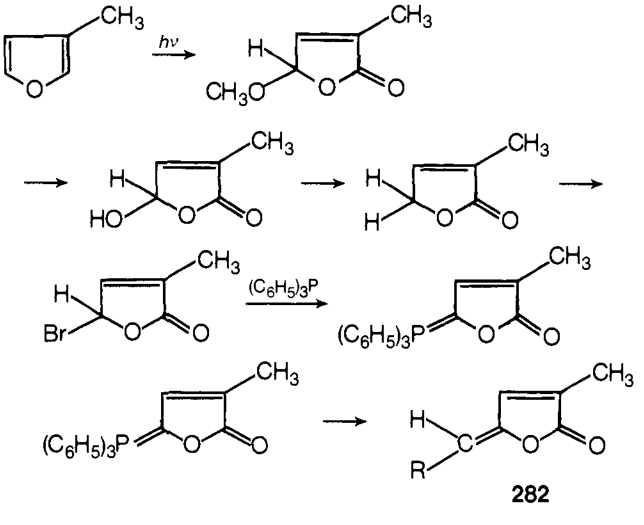
6. From Methyl Furoate

a. Grignard Reaction

When ethyl 5-bromo-2-furoate is treated with phenylmagnesium bromide, γ-diphenylmethylene-$\Delta^{\alpha,\beta}$-butenolide is obtained.[908]

b. Wittig Reaction

When 3-methylfuroic acid in methanol is photolyzed, it gives α-methyl-γ-methoxy-$\Delta^{\alpha,\beta}$-butenolide, which is converted to the bromo derivative[923] via the hydroxy and methylene compounds. The phosphonium ylide reacted with 4-nitrobenzaldehyde, anisaldehyde, and the aldehyde obtained from terpineol to give **282**. The exact sterochemistry of the end product is not known.[1096]



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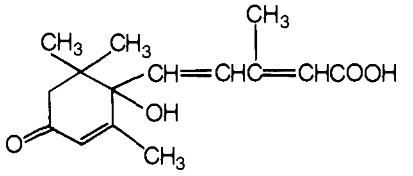
7. From Natural Products

Abscissic acid (**283**), on acid-catalyzed dehydration, gives the lactone **284**.[640] Another naturally occurring butenolide is called piperolide (**285**), β-methoxy-γ-(α-methoxycinnamylidene)-$\Delta^{\alpha,\beta}$-butenolide (ref 427, 430, 449, 755).

When D-galactonolactone is benzoylated extensively in pyridine, α-benzoyloxy-γ-phenacylmethylene-$\Delta^{\alpha,\beta}$-butenolide (**286**)[273] is obtained as the end product.

8. From γ-Aroylbutyric Acids

When a γ-aroylbutyric acid is treated with bromine in ether–



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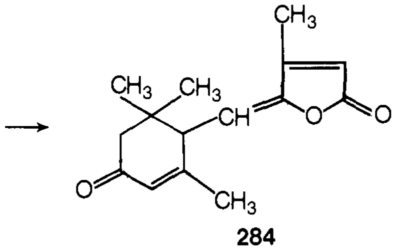

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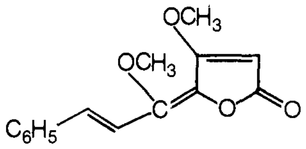

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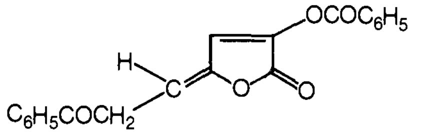

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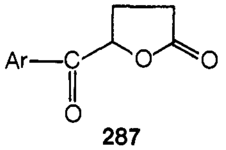
dioxane or ethyl acetate, cyclization occurs with the formation of γ-aroylbutyrolactone (**287**). Compound **287**, on heating with a mixture of acetic anhydride and *p*-toluenesulfonic acid, gives a mixture of geometric isomers of **288**.[1050,1051]

$ArCOCH_2CH_2CH_2COOH$ ⟶

Ar = 4-$CH_3OC_6H_4$, C_6H_5, 5-methyl-2-thienyl



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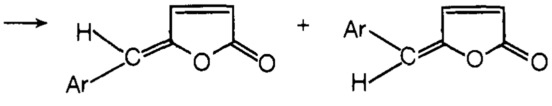

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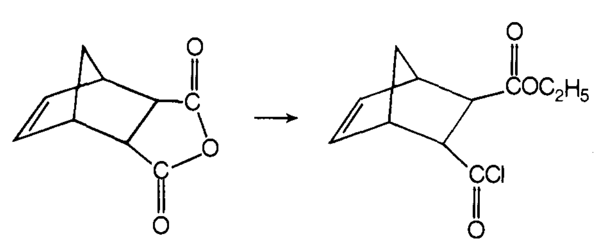
9. *From Phenylacetic Acid*

One of the products obtained from the reaction of 4-picoline *N*-oxide and phenylacetic anhydride is **273** (R = C_6H_5, R_1 = H), evidently formed from diphenylmaleic anhydride and phenylacetic acid.[223] Oxidative decarboxylation of phenylacetic acid, in the presence of cuprous ion catalyst, also leads to **273** (R = C_6H_5, R_1 = H).[1020] These methods are not of preparative value, since the yields are low.

10. *From Maleic Anhydride Adducts*

Diels–Alder adducts of maleic anhydride with cyclopentadiene and anthracene give the half-ester acid chloride **289** on successive treatments with an alcohol and thionyl chloride.[1012] Compound **289** on treatment with RCH_2ZnCl gave the keto acid, which on cylization and pyrolysis yields **291**.[1013] Instead of cyclopentadiene adducts, 9,10-anthraceno adducts may be employed. This method is applicable to γ-alkylidene butenolides of the type **291**. Roberts[824] has found that *endo*-norbornene-*cis*-5,6-dicarboxylic anhydride reacts with isopropylmagnesium bromide to give 3-isobutyryl-5-nobornene-2-carboxylic acid (**292a**). Compound **292a** reacts with thionyl chloride and ammonium hydroxide to give the lactone adduct, which on pyrolysis gives **293**.



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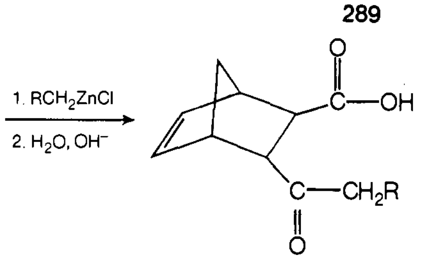

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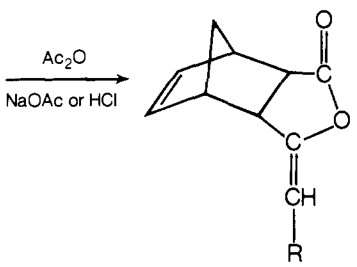

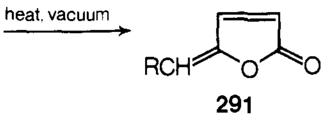

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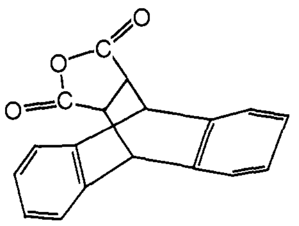

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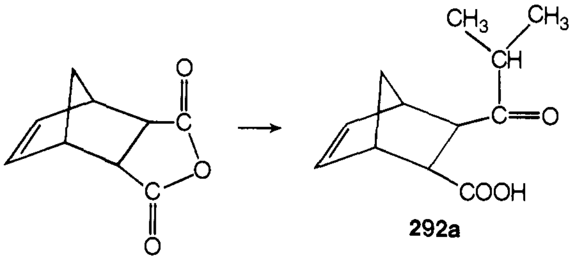
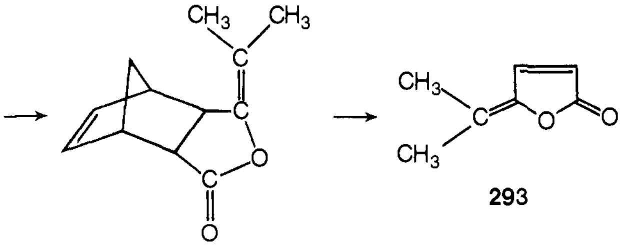


292a



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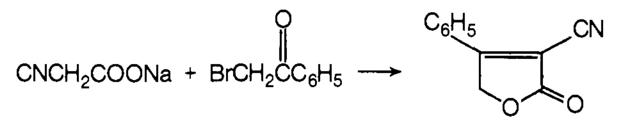
11. *From α-Halo Ketones*

When ω-bromoacetophenone is condensed with sodium cyanoacetate, α-cyano-β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (**294**) is obtained. Compound **294** condenses with benzaldehyde, acetophenone diethyl ketal, and other aldehydes in toluene in the presence of



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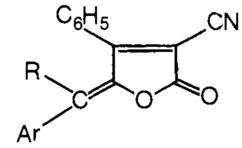
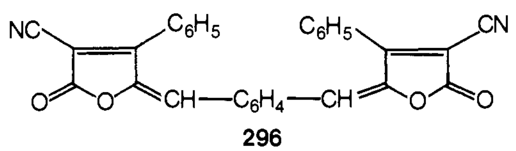
piperidine acetal to give the γ-benzylidene derivatives. With



295

Ar = C_6H_5, R = H
Ar = C_6H_5, R = CH_3
Ar = 4-$(CH_3)_2NC_6H_4$, R = H
Ar = 2,5-$(HO)_2C_6H_3$, R = H
Ar = 4-$(CH_3)_2NC_6H_4CH{=}CH$, R = H

terephthaldehyde, the corresponding bis(butenolide) is obtained, **296.** Potassium 4-nitrophenylacetate reacts with chloroacetone to give α-4-nitrophenyl-β-methyl-$\Delta^{\alpha,\beta}$-butenolide (**297**). This compound also condenses with aldehydes to give the corresponding γ-arylidene derivatives **298** useful as dyes.[354-357]



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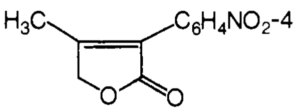

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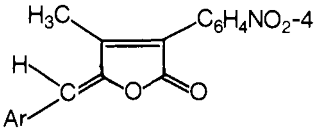

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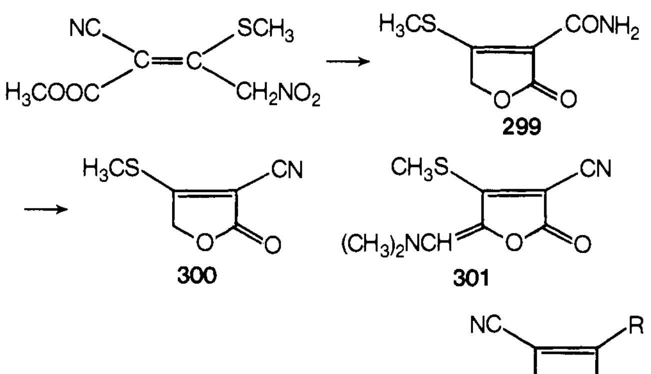
Methyl 2-cyano-3-methylthio-4-nitrocrotonate, on treatment with concentrated sulfuric acid, gives α-carbamoyl-β-thiomethyl-$\Delta^{\alpha,\beta}$-butenolide (**299**). The latter compound is converted to α-cyano-β-thiomethyl-$\Delta^{\alpha,\beta}$-butenolide (**300**). Compound **300** reacts with aromatic aldehydes, DMF, and *N*-methylpyrrolidone in the presence of $POCl_3$ to give the corresponding γ-ylidenebutenolides **301.** Compound **301** reacts with amines such as benzylamine and morpholine to give **302.**[899]



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300

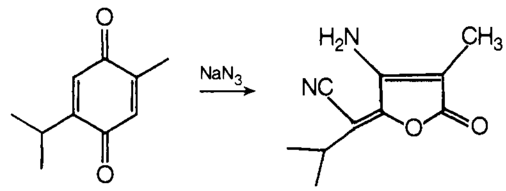
301

302

12. From Quinone Derivatives

a. From Azidoquinones

An excellent review article on azidoquinones and their reactions has been published recently.[690] The reaction of thymoquinone with sodium azide in trichloroacetic acid at 65° gives α-methyl-β-amino-γ-(1-cyano-2-methylpropylidene)-$\Delta^{\alpha,\beta}$-butenolide (**303**).[694,804,805] In a detailed study of these transformations, 3-amino-6-azido-2-methyl-5-isopropyl-1,4-benzoquinone (**304**) and the isomeric 2-amino-5-azido-3-isopropyl-6-methyl-1,4-benzoquinones were synthesized and converted to γ-lactones.[694] A similar stereoselective transformation of 2-azido-3-methyl-6-isopropyl-1,4-benzoquinone led to α-isopropyl-γ(1-cyanoethylidene)-$\Delta^{\alpha,\beta}$-butenolide. A series of γ-(cyanoalkylidene)-$\Delta^{\alpha,\beta}$-butenolides was prepared by this method. Products obtained included precursors of pulvinic acid (**13**).[695] The mechanism in Scheme XXVII has been suggested.[695,696,885]



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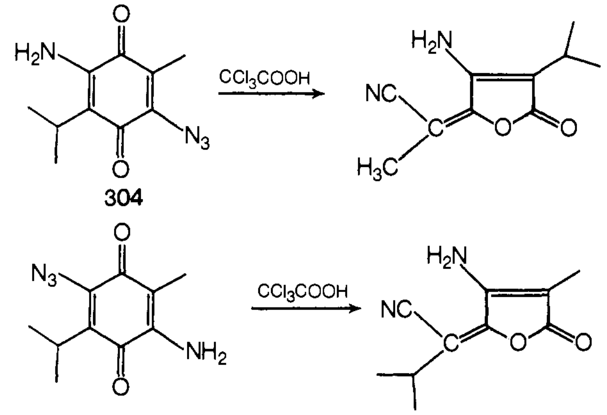

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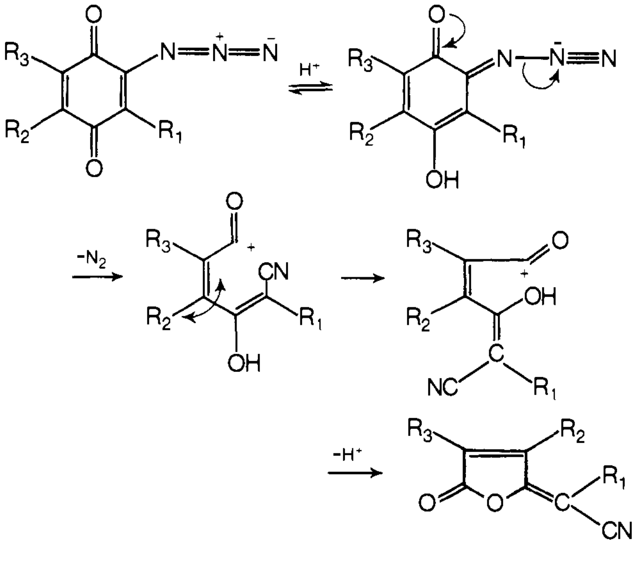
SCHEME XXVII

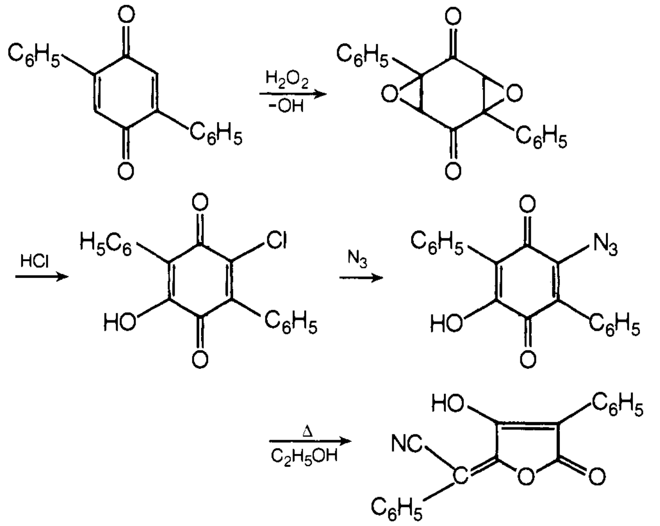


This rearrangement has been employed in the synthesis of vulpinic acid (methyl ester of **13**) (Scheme XXVIII).[691,696] The pyrolysis of 2-azido-3,6-diphenyl-1,4-benzoquinone led to the formation of α-phenyl-γ-(cyanobenzylidene)-$\Delta^{\alpha,\beta}$-butenolide.[692]

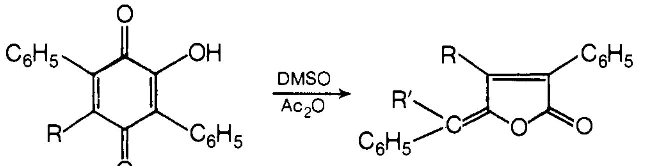
b. From Hydroxyquinones

When 2,4-dihydroxy-3,6-diphenyl-1,4-benzoquinone (polyporic acid) is heated with dimethyl sulfoxide–acetic anhydride mixture, pulvinic dilactone **16,** is obtained in high yield.[697,1030,1031] By starting with the appropriate benzoquinone derivatives, γ-arylidene butenolides have been obtained. The

SCHEME XXVIII



required hydroxy benzoquinones are prepared by known methods.[175,176] A mechanism to explain the formation of **305** is suggested.[697,1030,1031]



305

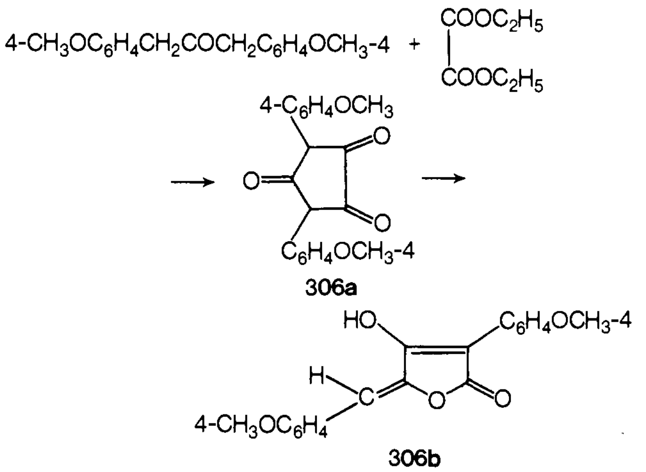
R = R' = H
R = Cl, R' = H
R = OCH_3, R' = H
R = H, R' = D

13. From Phenylpyruvic Acid

It has already been pointed out that benzyl methyl ketone and phenylpyruvic acid condense to give an acid which on cyclization gives α-benzyl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (**70**).[235,238] Similarly, the product obtained from phenylpyruvic acid and benzalacetone condensation is α-benzyl-γ-(2-phenylethylidene)-$\Delta^{\alpha,\beta}$-butenolide (**71b**).[576,791]

14. By Claisen Condensation

When bis(4-methoxybenzyl) ketone is condensed with diethyl oxalate in the presence of sodium ethoxide, 2,5-dianisylcyclopentane-1,3,5-trione (**306a**) is obtained. Compound **306a** on pyrolysis gives α-(4-methoxyphenyl)-β-hydroxy-γ-(4-methoxybenzylidene)-$\Delta^{\alpha,\beta}$-butenolide (**306b**).[733] **306b** could be methylated with CH_2N_2 to give the β-methoxy derivative or could be demethylated to give α-4-hydroxybenzylidene-β-hydroxy-γ-4-hydroxybenzylidene-$\Delta^{\alpha,\beta}$-butenolide, which is identical with the naturally occurring product, from the culture filtrate of *Aspergillus terreus*.



306a

306b

Compounds prepared by the above methods are listed in Table IV (see Microfilm Edition).

E. α-Methylene-γ-butyrolactones

An excellent review published in February 1975 lists all the methods of preparations of compounds **15.**[1131] Essentially the methods may be classified as (1) those involving formation and cyclization of an α-methylene-γ-hydroxy acid, (2) those involving eliminations and, (3) rearrangements. These methods have been explored extensively (ref 88, 115, 119, 260, 261, 406, 407, 411-413, 432, 643, 645-649, 675, 676, 731, 750, 973, 991, 1051-1053, 1116, 1127, 1129, 1130, 1135-1145, 1165).

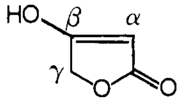
F. Naturally Occurring Lactones

The $\Delta^{\alpha,\beta}$ ring occurs widely in nature. No $\Delta^{\beta,\gamma}$-butenolide containing natural product has been isolated. It may be that the $\Delta^{\alpha,\beta}$ forms are more stable and hence more in abundance than the corresponding β,γ isomers. Several naturally occurring lactones along with their sources are tabulated (see in Table V in the Microfilm Edition). This is by no means a comprehensive list and some lactones might have been omitted. Pulvinic acid and other lactones, obtained from lichen substances, are discussed separately.

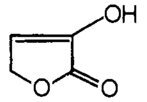
Most of the sesquiterpene lactones known have been mentioned in a review published earlier.[266]

G. Tetronic Acids

The chemistry of tetronic acids has been reviewed earlier by Haynes and Plimmer.[445] Several tetronic acids have been synthesized. Many of these tetronic acids have the α-hydroxy substituent, prepared as intermediates for the synthesis of cophalosphorin. The following are some of the methods employed for these syntheses (see also Tables VI in the Microfilm Edition).

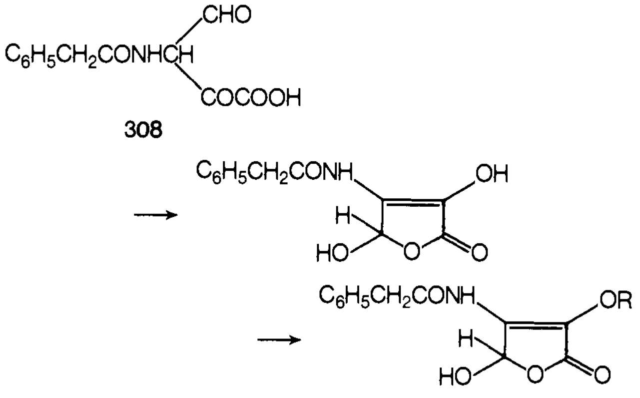


14, tetronic acid



307, α-tetronic acid

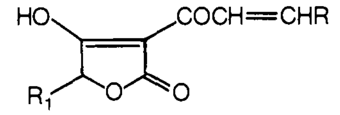
a. From Heterocycles. The compound 2,4-dioxo-3-phenylacetamidobutanoic acid (**308**) exists in the form of an α-hydroxytetronic acid. Compound **308** is prepared from 2-benzyl-4-oxazolylglyoxylamide and sodium hydroxide.[240]



308

R = CH_3, C_2H_5, $i\text{-}C_3H_7$, $t\text{-}C_4H_9$

b. From α-Acetyltetronic Acid. When a mixture of α-acetyltetronic acid and 4-chlorobenzaldehyde in methanol is treated



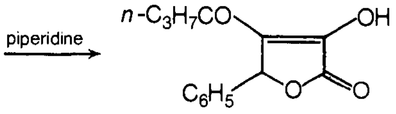
$R_1 = H$, $R = 4\text{-}ClC_6H_4$
$R_1 = CH_3$, $R = 4\text{-}ClC_6H_4$

309

with hydrogen chloride gas, **309** is obtained.[980]

c. From Pyruvic Acids. The condensation of butyrylpyruvic acid with aromatic aldehydes in the presence of piperidine leads to the formation of α-tetronic acids.[959] A whole series of β-acyl-γ-phenyl-α-tetronic acids are prepared by reaction of **310** and its analogs with acid anhydride, acyl halide, or ketene. The following mechanism explains the formation of **310.**

$n\text{-}C_3H_7COCH_2COCOOH + C_6H_5CHO$



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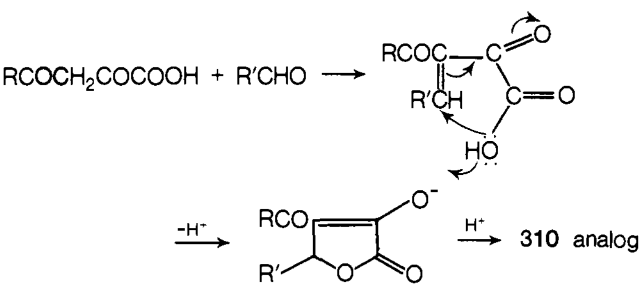
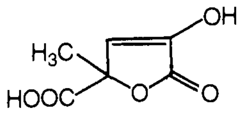


The structure of zymonic acid **311** has been shown to be α-hydroxy-γ-methyl-γ-carboxy-$\Delta^{\alpha,\beta}$-butenolide[1174] and not α-methyl-γ-carboxytetronic acid (**312**) as originally assumed.[927,1173]



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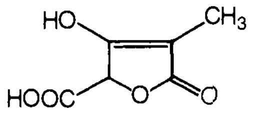
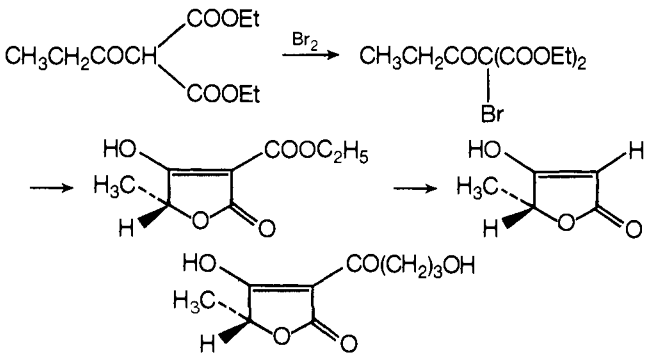


312

d. From Halogenoacyl Malonates. By a variation of the Benary–Haynes method, Mulholland and co-workers synthesized tetronic acids according to Scheme XXIX in 43–70% overall yields.[705] The compound γ-ethyltetronic acid may be prepared from γ-ethylidenetetronic acid (Scheme XXX).

The Mulholland method has been employed in the synthesis of optically active tetronic acids. Also prepared is γ,γ-diphenyltetronic acid. The *O*-acyl compounds are prepared in the presence of TlOEt and the products undergo Fries migration in the presence of $TiCl_4$ in nitrobenzene to give α-acyltetronic acids.[116] This method has been employed for the synthesis of (*S*)-carolic acid (**313**).[5,116]



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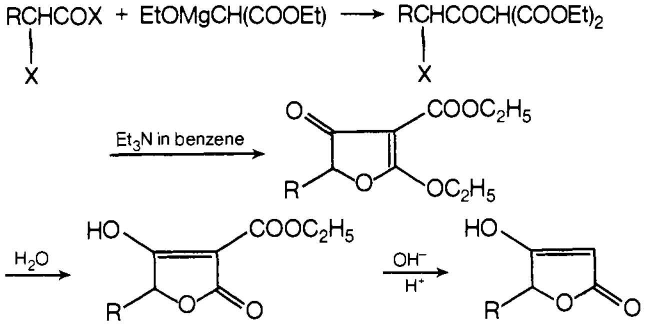
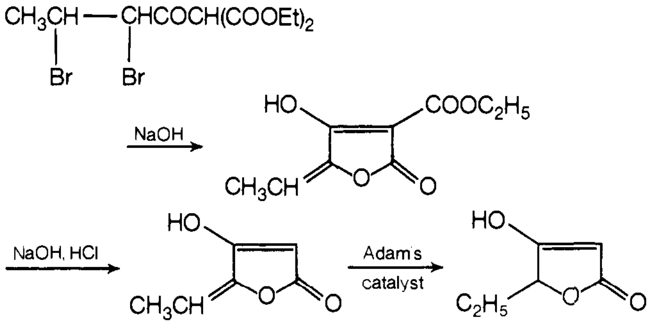
SCHEME XXIX

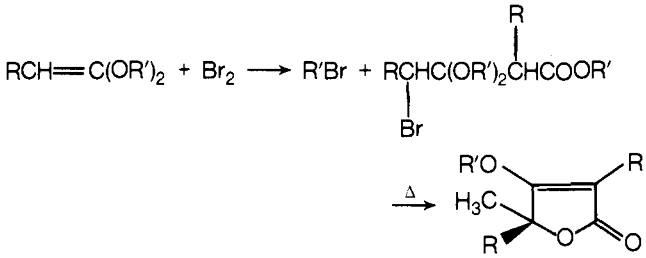


$R = H, CH_3, C_2H_5, C_6H_5$

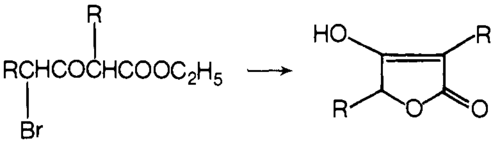
SCHEME XXX



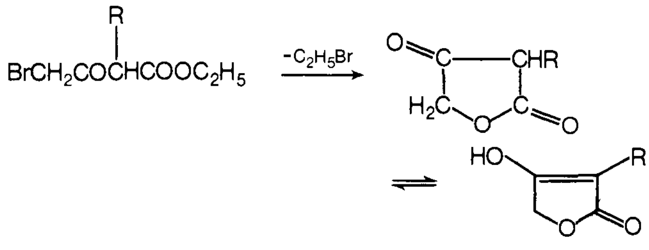
Bromination of ketene acetals gives dialkoxybromo esters. These compounds, on pyrolysis, give α-methyl (or phenyl) β-ethyltetronates.[662] The tetronic acids are prepared from the bromo keto esters. This method has been used in the synthesis of α-alkyltetronic acids. The starting material is bromoacetic ester with an alkyl substituent on the active methylene group.[803] α-Benzyltetronic acid is converted to a series of β-substituted derivatives by treatment with amines.



$R' = C_2H_5$, $R = CH_3$
$R' = C_2H_5$, $R = C_6H_5$

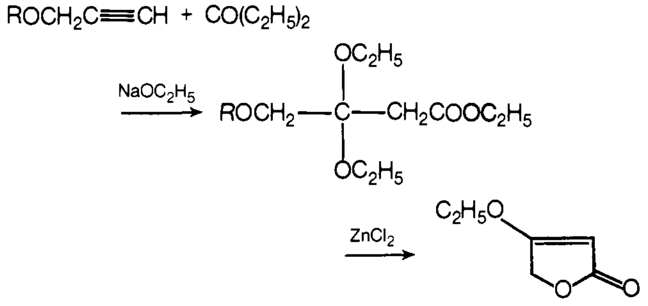


$R = CH_3, C_6H_5$



314

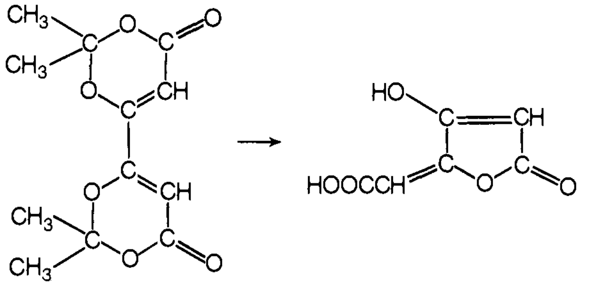
R = *n*-hexyl, *n*-octyl, *n*-cetyl, isobutyl, cyclohexyl, α-phenylethyl, γ-phenylpropyl, benzhydryl, *p*-nitrobenzyl, carbethoxymethyl, benzyl *e. From Acetylenic Compounds.* Ethyl tetronate (**315**) may be obtained from 2-propargyloxytetrahydropyran and ethyl carbonate in the presence of sodium ethoxide. The intermediate butyrate ester on heating with $ZnCl_2$ at 150° gives ethyl tetronate.[409]



$ROCH_2C\equiv CH + CO(C_2H_5)_2 \xrightarrow{NaOC_2H_5} ROCH_2-C(OC_2H_5)_2-CH_2COOC_2H_5 \xrightarrow{ZnCl_2}$

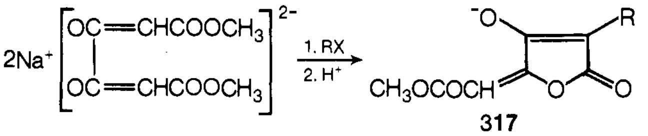
315

f. From Diketoadipic Acid Derivatives. The dioxane derivative **316** dissolves in concentrated sulfuric acid to give γ-carboxymethylenebutenolide.[913]



316

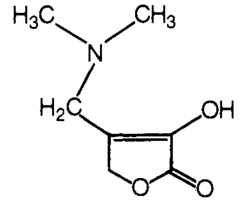
The disodium salt of ketipic acid is alkylated with alkyl halide to give **317**.[801]



317

R = CH_3, $C_6H_5CH_2$, $CH_2C\equiv CH$

g. Cephalosporin Intermediates. The condensation of pyruvic acid with dimethylamine hydrochloride and formaldehyde gives β-dimethylaminomethyl-α-tetronic acid hydrochloride (**318**).[384] Compound **318** exists as a zwitterion and reacts with potassium thioacetate to give the dilactone **319**. In their studies about cephalosporin derivatives, Beyerman and co-workers synthesized a whole series of α-benzamido-$\Delta^{\alpha,\beta}$-butenolides[1156] and α-tetronic acids.[1157] Similar butenolides synthesized are α-amino-β-triphenylmethylthiomethyl-$\Delta^{\alpha,\beta}$-butenolide.[287] Compounds similar to **318** have also been synthesized.[624,625]



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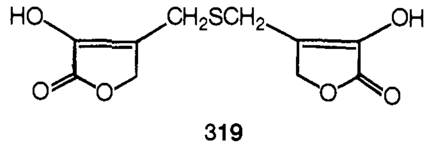
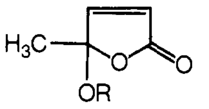


319

H. β-Acylacrylic Acids

A review article has been published recently on β-formylacrylic acids.[21] Much work on β-acylacrylic acids has been done by Hellstrom and co-workers. In theory three types of esters of β-acylacrylic acid can exist: the trans form, the cis form, and the cyclic form or the cyclic pseudo ester.[459,460,1186] Several methods are now available for the synthesis of *cis*-β-acylacrylic acid esters and the pseudo ester forms. These methods are discussed below. Compounds prepared by these methods are given in Table VII in the Microfilm Edition.

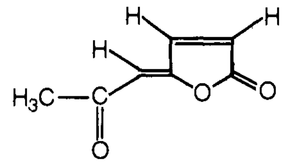
a. From γ-Bromo-α-angelica Lactone. When α-angelica lactone is brominated in CCl_4 with bromine, **320** is obtained.[1083]



320

The bromo compound on heating with the appropriate alcohol in the presence of triethylamine gives the pseudo ester.[454,1184] The pseudo ester of β-pivaloylacrylic acid is prepared from β-bromo-β-pivaloylpropionic acid and sodium acetate–acetic acid.[451,460] These compounds[452,459] have been tested for biological activity.

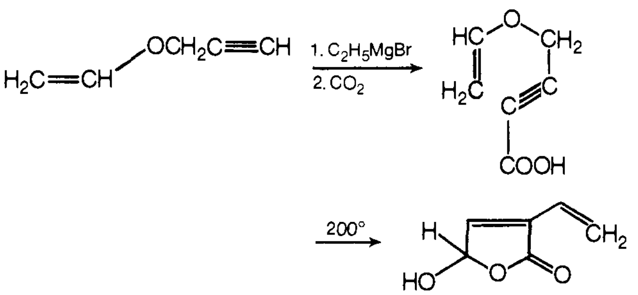
b. From Maleic Anhydride. The condensation of isopropenyl acetate with maleic anhydride in dichloromethane in the presence of anhydrous aluminum chloride is reported to yield the *Z* form of γ-acetonylidene-$\Delta^{\alpha,\beta}$-butenolide (**321**).[358] The *E* form of **321**[1118] is obtained by varying the workup conditions slightly. **321** has been used in the synthesis of maleyl- and fumarylacetones.



321

c. Claisen Rearrangement of Propynyl Vinyl Ether. γ-Hydroxy-α-vinyl-$\Delta^{\alpha,\beta}$-butenolide may be obtained by the Claisen rearrangement of an appropriate butenoic acid derivative (Scheme XXXI).[110] Prop-2-ynyl vinyl ether is converted into 4-vinyloxy-2-butynoic acid.

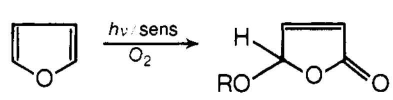
SCHEME XXXI



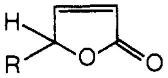
d. From Pyruvic Acid. The condensation of acetone with pyruvic acid gives *cis*-α-methyl-β-acetylacrylic acid. This compound exists as a hydroxy lactone, α,γ-dimethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide (**322**) and may be acetylated and methylated to give the corresponding γ-acetoxy and γ-methoxy derivatives[1024] (see also ref 46 in ref 791).

The condensation of pyruvic acid and ketone in the presence of orthophosphoric acid has been reported to give γ-hydroxybutenolides.[849] This method has been employed in the synthesis of α,β,γ-trimethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide and **322**.[310,311]

e. Photochemical Syntheses. Alcoholic solutions of furan, furfural, and furfuryl alcohol in irradiation in the presence of rose bengal or methylene blue give γ-ethoxy-$\Delta^{\alpha,\beta}$-butenolide (ref 556, 851, 852, 1114, 1115). In order to synthesize malealdehydic acid



esters, Schenck and coworkers prepared a series of γ-substituted butenolides of type **323**.[868] This method has been extended

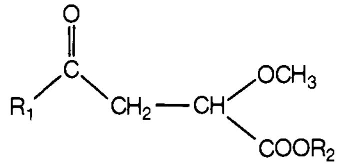


323

R = OH, Cl, $OCOCH_3$, $OCOC_6H_5$, $OCONHC_6H_5$

to the synthesis of the pseudoethyl ester of *cis*-β-acetylacrylic acid, starting from 2-methylfuran. The modifications include the use of eosin Y and vanadium pentoxide.[874,921] It may be pointed out that the amount of **323** (R = OC_2H_5) with thionyl chloride converts it to **323** (R = Cl).[324]

A study of the isomers of acetyl and benzoylacrylic acids and esters has been made by Sugiyama and co-workers.[931-935] They observed that on photochemical irradiation three types of reactions occurred: (i) trans to cis isomerization; (ii) formation of $\Delta^{\alpha,\beta}$-butenolides; and (iii) addition of elements of alcohol to the olefinic double bond to give **324.**



324

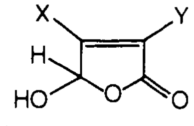
When the free acid *trans*-β-acetylacrylic acid is irradiated in methanol or without any solvent, the corresponding γ-methyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide[932] is produced.

It must be pointed that the ring-chain tautomerism of *cis*-β-aroylacrylic acids has been studied by Lutz and co-workers[629-631] (see also ref 219–223 in ref 791).

A summary of β-acylacrylic acids is given in Table VII in the Microfilm Edition.

I. Halogen-Substituted Furanones

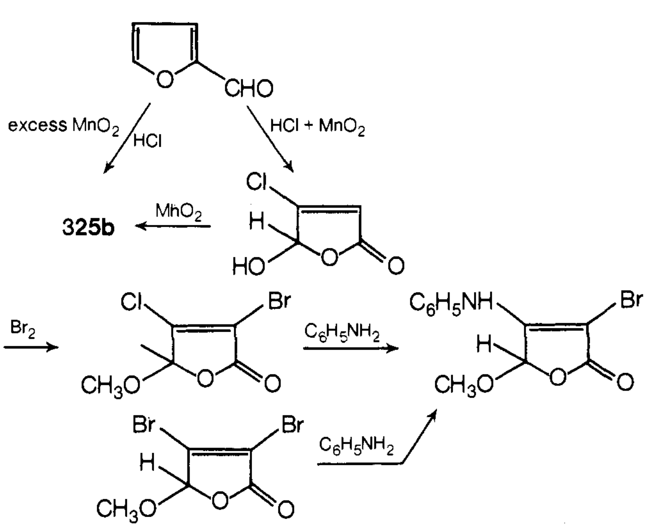
Mucochloric and mucobromic acids exist as hydroxy lactones.[997] It has been reported that α-bromo-β-chloro-β-formylacrylic acid exists as a cyclic structure.[1017] The halogen atoms on the lactone ring may be replaced by nucleophilic reagents. These nucleophilic substitution reactions will be discussed later.



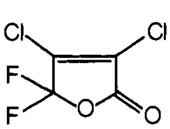
325a, X = Y = Br
b, X = Y = Cl
c, X = Cl, Y = Br

a. Preparation of Mucohalic Acids. When furfural is chlorinated in the presence of MnO_2 and dilute HCl, the product obtained is β-chloro-β-formylacrylic acid, isolated as β-chloro-γ-hydroxyl-$\Delta^{\alpha,\beta}$-butenolide.[424] Direct chlorination of furfural with Cl_2 at 90° is reported to give **325b.**[636] Treatment of methyl 3,4-dibromo-2,5-dimethoxytetrahydro-2-furoate with acid yields mainly α-bromo-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide.

The dihalo derivative similarly gives the α-chloro analog.[437] The β-chloro isomer is obtained from γ-hydroxytetronic acid and dilute hydrochloric acid.[170,709]



b. From Dichloromaleic Anhydride. The reaction of dichloromaleic anhydride with sulfur tetrafluoride gives α,β-dichloro-γ,γ-difluoro-$\Delta^{\alpha,\beta}$-butenolide (**326**).[113,335] Similarly, maleic anhydride reacts with SF_4 to give γ,γ-difluoro-$\Delta^{\alpha,\beta}$-butenolide.



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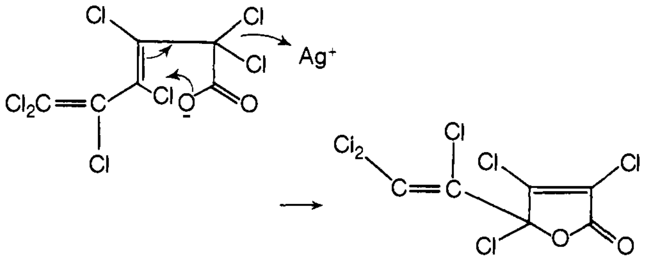
c. From Perchloro Compounds. Treatment of *cis*-perchloro-1,3-hexadiene-6-carboxylic acid with silver ion gives **327.**[826] Tetrachloro-2,2-dialkyl-2*H*-dihydropyrans (**328**) on treatment with fuming nitric acid gives **329**.[1089]

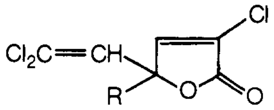


327

329

R = CH_3, C_2H_5

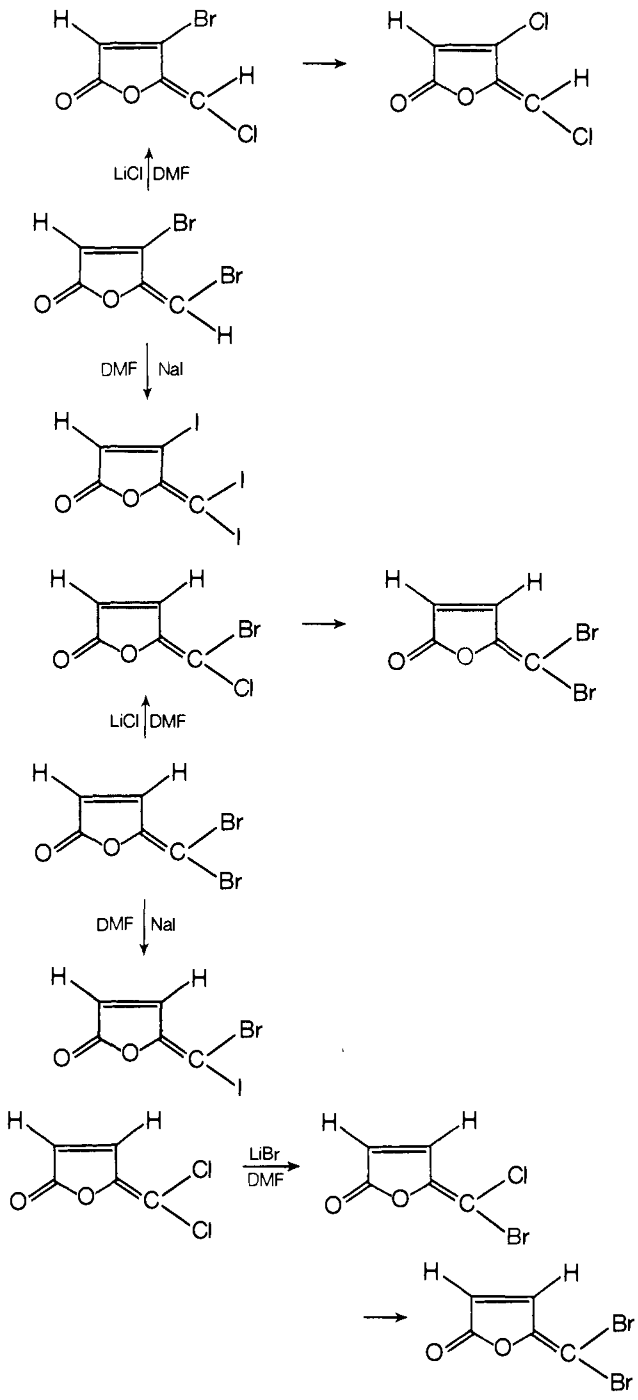
Finally the reaction of chlorofumaroyl chloride with dichloroethylene in the presence of anhydrous aluminum chloride gives **330.**[617]



330, R = OCH_3, Cl

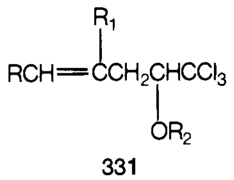
d. Halogen Exchange Reactions. Kemper and Winston[543] prepared a series of γ-dihalomethylene-$\Delta^{\alpha,\beta}$-butenolides by the halogen exchange reaction (Scheme XXXII). The γ-dichloromethylene analog[535,1041] has been polymerized with other monomers such as styrene and methyl methacrylate, and the properties of these polymers have been studied (ref 1037, 1039, 1040, 1042, 1045). It has been observed that polymers with

SCHEME XXXII



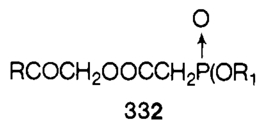
conjugate unsaturation are formed by a 1,4-addition mechanism followed by elimination of elements of hydrogen halide.

e. *From β-Aroylacrylic Acids.* The condensation of glyoxylic acid with ketones in dioxane in the presence of sulfuric acid gives β-aroylacrylic acids.[317] The acrylic acid type compounds are also obtained from compounds of the type **331** by heating with potassium methoxide in methanol.[1023] These compounds may be converted to halosubstituted lactones. It has been observed that diazo ketones ($RCOCHN_2$) or halo ketones react with Wadsworth–Emmons' reagent to give compounds of type **332**.



$RCH{=}C(R_1)CH_2CH(OR_2)CCl_3$

331

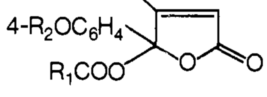


$RCOCH_2OOCCH_2P(\rightarrow O)(OR_1)_2$

332

These compounds may be cyclized with dicyclohexylcarbodiimide to give lactones.[718]

f. *By Reactions of Halogen-Substituted Lactones.* In their search for substances with neoplastic activity, Semonsky and coworkers synthesized a series of halogen-substituted lactones (ref 526, 875–881, 1069–1072). Mucobromic or mucochloric acids and substituted acetophenones in alcoholic solution at temperatures below 5 °C react to give α,β-dihalo-γ-phenacyl-$\Delta^{\alpha,\beta}$-butenolides.[881,997] Mucohalic acids react with alkyl Grignard reagents to give γ-alkyl-α,β-dihalo-$\Delta^{\alpha,\beta}$-butenolides.[880] α,β-Dihalo substituted lactones react with sodium salts of carboxylic acid to give **333**.[875]

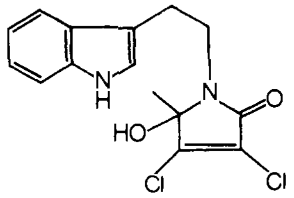


333

X = Br, R_1 = Et, R_2 = Me
X = Br, R_1 = Pr, R_2 = Me
X = Br, R_1 = *i*-Pr, R_2 = Me
X = Br, R_1 = amyl, R_2 = Me
X = Br, R_1 = Ph, R_2 = Me
X = Br, R_1 = 3,4-$CH_2O_2C_6H_3$, R_2 = Me
X = Cl, R_1 = Me, R_2 = Me
X = Br, R_1 = Me, R_2 = Bu
X = Cl, R_1 = Me, R_2 = Bu

Mucochloric or mucobromic acids also react with alkyl naphthyl ethers in the presence of H_3PO_4 and P_2O_5 to give γ-naphthyl derivatives.[876] An interesting reaction of β-bromo-γ-4-methoxyphenyl-γ-acetoxy-$\Delta^{\alpha,\beta}$-butenolide with amino acids to give *N*-(β-4-methoxybenzoyl-β-bromoacryloyl) amino acids.[583] Alkoxybenzenes also react with mucohalic acids in the presence of P_2O_5 for zinc chloride to give γ-4-alkoxyphenyl butenolides.[989,1071] The conversion of β-chloro-β-anisoylacrylic acid to γ-anisyl-β-chloro-$\Delta^{\alpha,\beta}$-butenolide has been effected by treatment with sodium borohydride.[1069] Diethylamine reacts with γ-methoxy-$\Delta^{\alpha,\beta}$-dihalocrotonolactones to give the corresponding β-diethylamino derivatives.[1072]

In a few cases it has been observed that when mucochloric acid reacts with amino compounds such as 2-amino-5-chlorothiazole, the corresponding γ-amino derivative is obtained.[63,68,715] Reaction with aziridine gives the corresponding γ-*N*-azirinyl derivative. With tryptamine, however, the product obtained is a pyrrolinone derivative **334**.[1045] It may be pointed out that aziridine reacts with the methyl ester of mucochloric acid to give β,γ-diaziridinyl-α-chloro-$\Delta^{\alpha,\beta}$-butenolide.

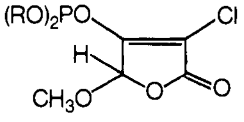


334

Bachman prepared a series of γ-4-nitroanilino derivatives for use as microbiocides by reacting mucochloric acid with anilines.[62]

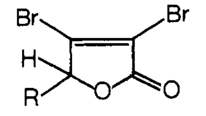
In a series of papers and patents, Beska and coworkers reported the reactions of mucohalic acids with thiols,[96] phenoxyalkylcarboxylic acids, hydrocarbons, phenylhydrazine, *trans*-2,2-dichloro-3-phenylcyclopropanecarboxylic acid, acetylenic alcohols, alkoxyalkyl alcohols, benzyl alcohols, and chloro-substituted alcohols (94–102, 796–799, 1044). Reactions of mucohalic acids with phenols, thiophenols, and amines have also been reported (ref 120, 274, 1063–1065).

The reaction of γ-alkoxy-α,β-dihalo-$\Delta^{\alpha,\beta}$-butenolides with trialkyl phosphites gives the corresponding phosphorus-containing $\Delta^{\alpha,\beta}$-butenolides **335**.[637-639,1186] In the presence of

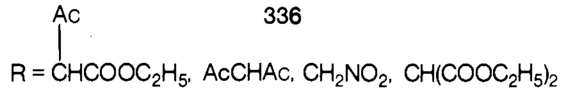


335

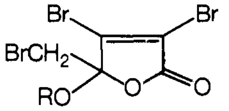
sodium bicarbonate mucobromic acid condenses with malonic acetoacetic esters, nitromethane, and pentane-2,4-dione to give **336**.[419,420] γ-Bromomethylene-α,β-dibromo-$\Delta^{\alpha,\beta}$-butenolide reacts with alcohols to give **337**.[527,528]



336



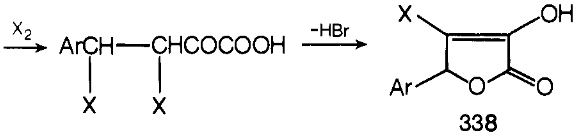
$R = \overset{Ac}{\overset{|}{C}}HCOOC_2H_5,\ AcCHAc,\ CH_2NO_2,\ CH(COOC_2H_5)_2$



337

g. From Pyruvic Acids. The condensation of pyruvic acid with aromatic aldehydes gives arylidenepyruvic acids. These compounds may be converted to β-halo-α-hydroxy-$\Delta^{\alpha,\beta}$-butenolides **338** via the dihalo compounds.[830]

$CH_3COCOOH + ArCHO \longrightarrow ArCH{=}CHCOCCOH$



$\xrightarrow{X_2} \underset{X}{\underset{|}{ArCH}}{-}\underset{X}{\underset{|}{C}}HCOCOOH \xrightarrow{-HBr}$

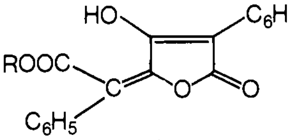
338

A summary of the dihalo butenolides is given in Table VIII in the Microfilm Edition.

V. Pulvinic Acid Derivatives

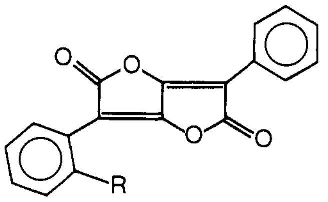
A. Introduction

Lichen substances contain yellow pigments, which are tetronic acids containing carboxyl function as in **13** below. Reviews have been published about systematization of these lichen substances and their biosynthesis.[702] Some of the compounds belonging to this class of compounds are given below (also see Table IX in the Microfilm Edition).

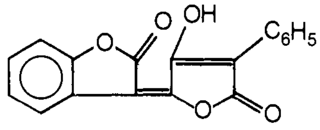


R = H, pulvinic acid
R = CH_3, vulpinic acid

13

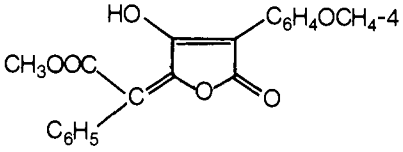


16

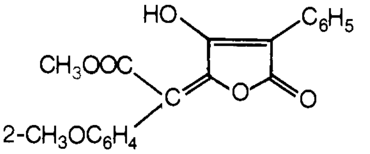


339
calycin

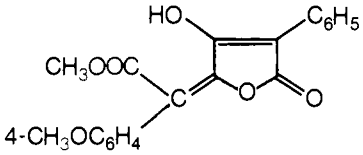
R = H, pulvinic dilactone
R = OH, calycin (incorrect formulation)



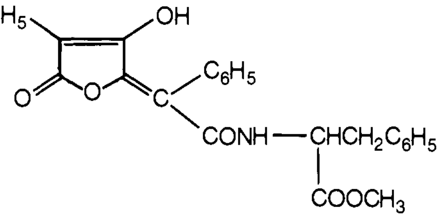
340
pinastric acid



341
leprapinic acid



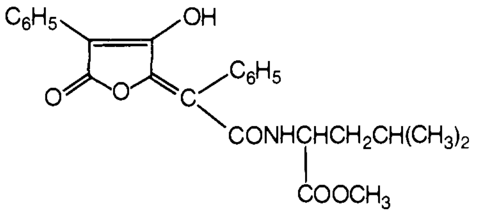
342
isopinastric acid



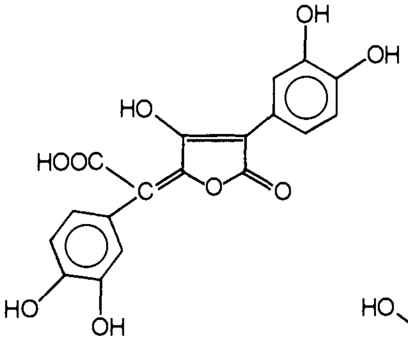
343
rhizocarpic acid

Degradative studies on vulpinic acid by Spiegel led to its formulation as **339**.[905] The products obtained by reduction of pulvinic dilactone (**16**) were also extensively studied.[24,1191] The structure of pinastric acid was originally assumed to be either **340** or **341**.[562,563] Asano and Kameda suggested **340** as the structure of pinastric acid.[34] This structure was later confirmed by Seshadri and coworkers.[6,9] Pinastric acid, however, was assigned structure **341** on the basis of its reaction with o-phenylenediamine, dimethylaniline, and sodium periodate,[417,418,683] and a compound called isopinastric acid was originally assigned the trans–trans structure **342**. It appears now that pinastric acid is α-4-methoxyphenyl-β-hydroxy-γ-phenylcarbomethoxymethylene-$\Delta^{\alpha,\beta}$-butenolide (**340**), and isopinastric acid is α-phenyl-β-hydroxy-γ-(4-methoxyphenyl)carbomethoxymethylene-$\Delta^{\alpha,\beta}$-butenolide (**341**). Work on **340, 341**, and **342** has been done by Seshadri and coworkers (ref 6–10, 415–418, 681–683). Recently, variegatic acid (**345**),[86,304,920] gomphidic acid (**346**),[919] and xerocomic acid (**347a** or **347b**)[918] have been reported. Possible biosynthetic pathways for vulpinic acid have been proposed either involving polyporic acid (ref 700, 701, 1030, 1031) and 2-phenylglyceraldehyde.[682] Biosynthesis of calycin has been shown to occur via vulpinic or pulvinic acids but not pulvinic dilactone.[634] It has also been observed that phenylalanine, phenyllactic acid, and polyporic acid with C-14 labels on them are readily incorporated into calycin and pulvinic dilactone.[632,635] Pulvinamide (**348**) has also been proposed as a key biosynthetic intermediate.[633]

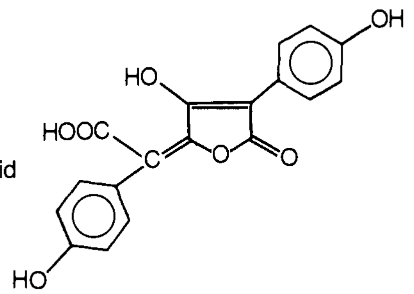
Pulvinic and vulpinic acids have been isolated from a series of lichen substances (ref 10, 13, 140, 141, 329, 466–471, 552, 710, 843, 1074–1076). Paper chromatography (786, 1003) and thin layer chromatography (91, 680) have been employed in identifying the lichen tetronic acids. Vulpinic acid, pulvinic acid, and other tetronic acids have been tested for biological activity (35, 162, 374, 394–396, 428, 577, 644, 713, 717, 896, 897, 992, 1014). It has been observed that vulpinic acid causes hyperthermia leading to death in foxes and wolves (896, 897).



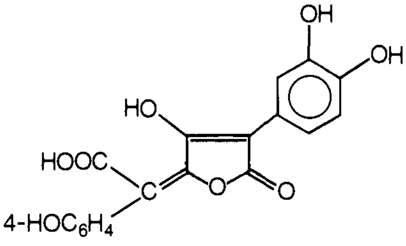
344
epanorin



345
variegatic acid

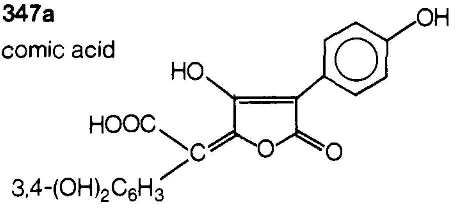


346
gomphidic acid

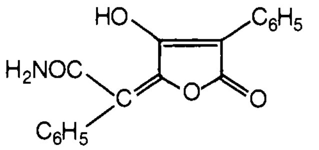


or

347a
xerocomic acid



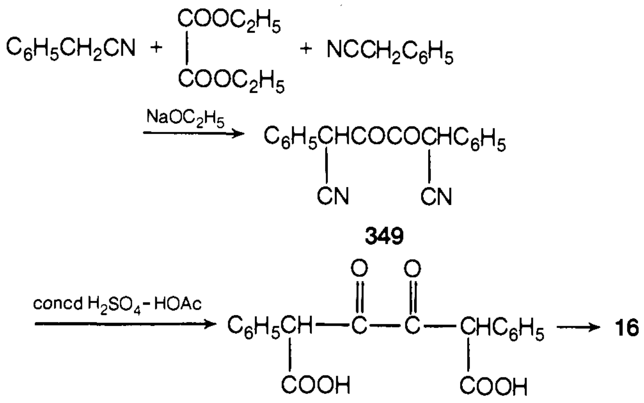
347b



348

B. Methods of Synthesis

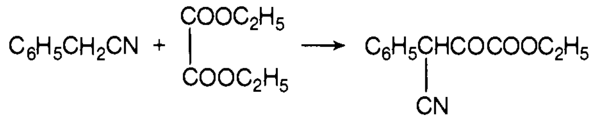
a. Volhard's Method. This method was first employed by Volhard[1189] and may be considered to be a general method for the synthesis of ketipic acid[911,912] derivatives (**349**) which on acid hydrolysis give pulvinic dilactone derivatives. The method consists of the condensation of diethyl oxalate with phenylacetonitrile in the presence of sodium ethoxide. This method has been modified subsequently by Asano and Kameda.[32] In the modified method, phenylacetonitrile is condensed with diethyl oxalate to give ethyl cyanophenylpyruvate (**350**). Compound **350** may be condensed with any aryl acetonitrile under Claisen conditions to give unsymmetrical ketipic acid derivative. The Volhard method and the Asano modification have been employed in the synthesis of substituted pulvinic acid derivatives (ref 9, 28, 32–34, 86, 660, 769, 131, 417, 530, 558, 562, 683, 940, 1189). In a more recent method, the condensation of **350** and its analogs with aryl acetonitriles is carried out in dimethoxymethane in the presence of sodium hydride at −10 °C.[86] The yields are about 50–60%.



$$C_6H_5CH_2CN + \begin{matrix}COOC_2H_5\\ |\\ COOC_2H_5\end{matrix} + NCCH_2C_6H_5 \xrightarrow{NaOC_2H_5} \begin{matrix}C_6H_5CHCOCOCHC_6H_5\\ |\qquad\quad\;\; |\\ CN\qquad\; CN\end{matrix}$$

349

$$\xrightarrow{\text{concd } H_2SO_4\text{-}HOAc} \begin{matrix}C_6H_5CH-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-CHC_6H_5\\ |\qquad\qquad\qquad |\\ COOH\qquad\qquad COOH\end{matrix} \longrightarrow 16$$



$$C_6H_5CH_2CN + \begin{matrix}COOC_2H_5\\ |\\ COOC_2H_5\end{matrix} \longrightarrow \begin{matrix}C_6H_5CHCOCOOC_2H_5\\ |\\ CN\end{matrix}$$

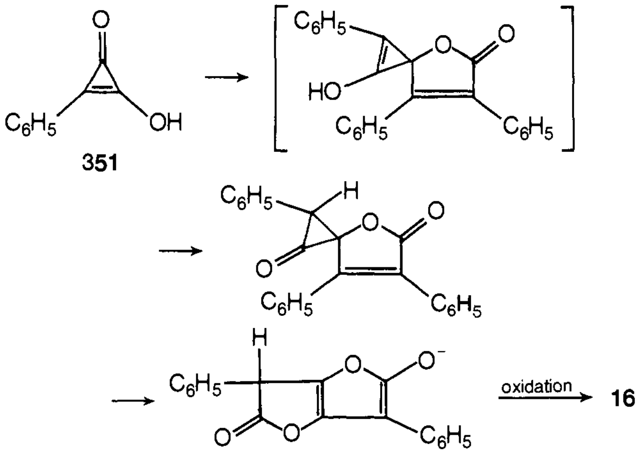
350

b. From Phenylacetyl Chloride. Phenylacetyl chloride condenses with oxalyl chloride in the presence of triethylamine and pyridine to give pulvinic dilactone[833] in 20% yield. This method is not a general method.

$$2C_6H_5CH_2COCl + ClCOCOCl \longrightarrow 16$$

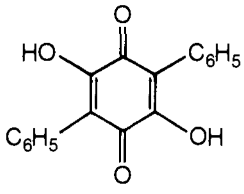
c. From Cyclopropenone Derivative. Farnum and coworkers[333] have reported that phenylhydroxycyclopropenone (**351**) is converted to pulvinic dilactone (**16**) on treatment with thionyl chloride in benzene at 40 °C. The conversion may proceed as shown in Scheme XXXIII.

SCHEME XXXIII



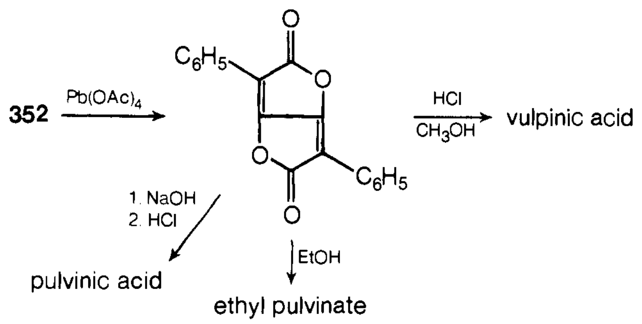
351

d. From Polyporic Acid Derivatives. Polyporic acid (**352**) and its analogs have been the sources for the synthesis of lichen tetronic acids. Biogenetic pathways for these substances involve polyporic acid.[701] Compound **352** occurs as a fungus pigment[557] and is readily prepared by Cain's method.[175,176] Polyporic acid is converted to pulvinic dilactone on oxidation with lead tetraacetate in glacial acetic acid.[361] The compound termed iso-



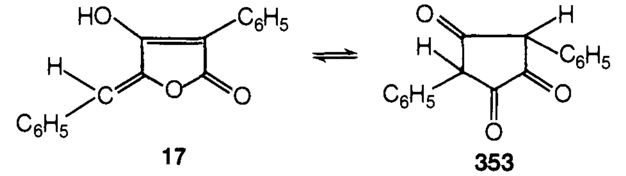
352

vulpinic acid by Spiegel[905] has been shown to be ethyl pulvinate. Moore and coworkers[697,1030,1031] employed dimethyl sulfoxide-acetic anhydride for the oxidation of polyporic acid. Pulvinic dilactone is obtained in 90% yield. Analogs of **16**, 4,4′-dimethoxypulvinic dilactone and 4,4′-dimethoxypulvinic dilactone, have also been prepared in 90% yield. The oxidation of atromentin (2,5-di-*p*-hydroxyphenyl-3,6-dihydroxy-1,4-benzoquinone) may be carried out in glacial acetic in the presence of hydrogen peroxide-hydrochloric acid.[558,1030]

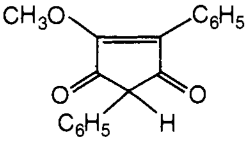


C. Reactions of Pulvinic Acid

Pulvinic acid may be decarboxylated by heating in quinoline with copper chromite. The product obtained is α-phenyl-β-hydroxy-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (**17**).[863] This compound on heating to 270 °C is converted to a cyclopentanetrione derivative **353**. Compound **353** has been converted to **17** on heating to 228°.[1111] It may be pointed out that vulpinic acid methyl ether[1001] (**354**) on heating with potassium hydroxide followed by acidification gives 2,5-diphenyl-3-methoxy-2-cyclopentene-1,4-dione (**355**), which is also obtained from *O*-methylpulvinone (**356**).[558] It may also be pointed out that cyclopentanetrione γ-lactone rearrangement was employed in the synthesis of α-(4-hydroxyphenyl)-β-hydroxy-γ-(4-hydroxybenzylidene)-$\Delta^{\alpha,\beta}$-butenolide, a natural product obtained from *Aspergillus terreus.*[733]



17 **353**



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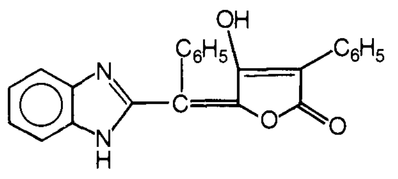


356

The reaction of pulvinic acid or vulpinic acid with *O*-phenylenediamine to give a benziminazole derivative **356** has been used as proof of the presence of a substituent in one benzene ring or the other (ref 8, 415, 418, 530, 681, 683, 863). It has been found, however, that ozonolysis gives a better insight into this information.[6,9,106] The products obtained are oxalic acid, benzoic acid, and benzoylformic acid ester or substituted benzoylformic acid ester.

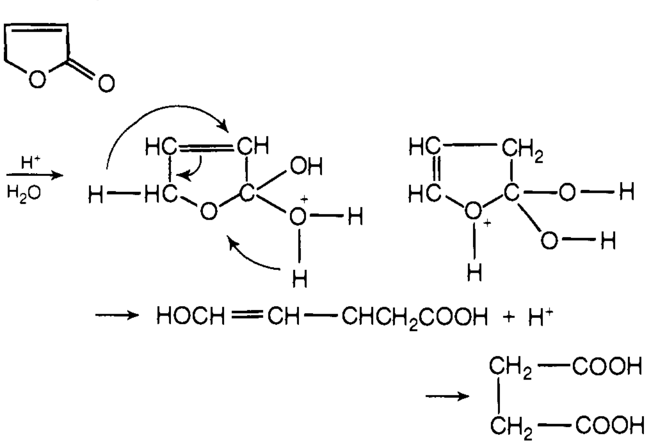
The reaction of pulvinic dilactone with phenylalanine methyl ester hydrochloride gave rhizocarpic acid (**343**), and reaction of **16** with L-leucine methyl ester hydrochloride gave epanorin (**344**).[362]

Mass spectra of pulvinic dilactone, calycin, vulpinic, pinastric and rhizocarpic acids have been reported with reference to their fragmentation patterns.[616,195,1195] Mass spectral data have been used to show that calycin has structure **339** and not **16** (R = OH) as originally assumed.[616]

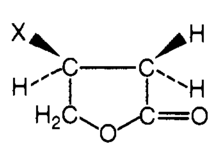
VI. Chemical Properties of Butenolides

A. Reaction with Acids and Bases

Distillation of $\Delta^{\alpha,\beta}$-butenolide in the presence of a trace of acid is reported to cause its conversion to succinic acid.[291] The product left in the flask after distillation of $\Delta^{\alpha,\beta}$-butenolide is mainly maleic acid with some traces of fumaric acid.

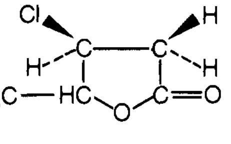


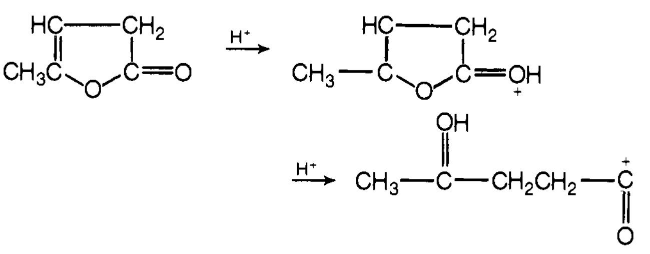
Treatment of $\Delta^{\alpha,\beta}$-butenolide with hydrogen chloride gas results in the formation of a butyrolactone derivative and not γ-chlorocrotonic acid which is obtained by hydrolysis with aqueous HCl. Reaction with hydrogen bromide gives the corresponding bromobutyrolactone.[288] Under similar conditions, β-angelica lactone gives the corresponding butyrolactone derivative.[289]



X = Cl, Br

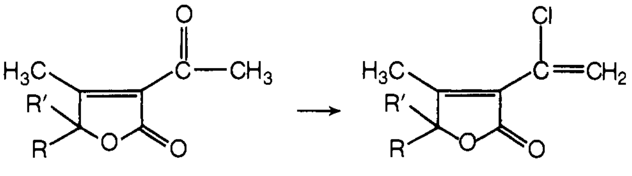
It may be pointed out that acid or base hydrolysis of $\Delta^{\beta,\gamma}$-butenolides gives γ-keto acids. Thus γ-pentacarboxylmangano-$\Delta^{\beta,\gamma}$-butenolide gives β-pentacarbonylmanganocarbonylpropionic acid on acid hydrolysis.[570] α-Angelica lactone gets protonated in excess FSO_3H-SbF_5 solution at −60° to give a ketocarboxonium ion, the structure of which is confirmed by NMR.[736]





B. Reaction with Acid Chlorides

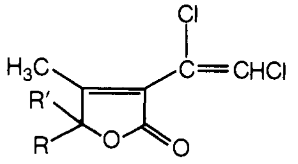
Acetyl-substituted butenolides such as **357** react with 1 equiv



357

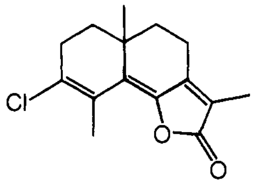
R = R′ = CH_3
R = CH_3, R′ = C_2H_5

of PCl_5 to give chlorovinyl butenolides. With 2 equiv of PCl_5, the products obtained are the dichlorovinyl derivatives **358**. It may

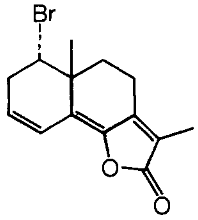


358

be pointed out that PCl_3 in acetic acid (or PBr_3 in acetic acid) has been reported to convert β-santonin to **359**,[1192] and the lactone ring remains intact. Under similar conditions, PBr_3 gives **360** and not the bromo analog of **359**.



359



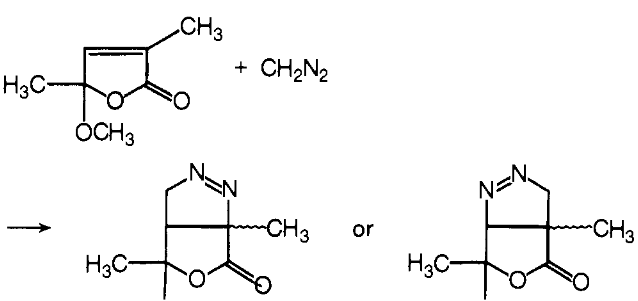
360

C. Reaction with Alcohols

Alcoholic hydrogen chloride converts $\Delta^{\alpha,\beta}$-butenolide to give ethyl oxobutanoate obtained by the isomerization of $\Delta^{\alpha,\beta}$-butenolide to the $\Delta^{\beta,\gamma}$-form followed by alcoholysis of the latter. Also obtained are γ-ethoxybutyrolactone, β-chloro-γ-butyrolactones, and products of hydrolysis or alcoholysis of these compounds.[290] Reaction of β-angelica lactone with ethanol in the presence of HCl gives ethyl levulinate as also γ-methyl-β-chlorobutyrolactone.[292] The compound α-chloro-$\Delta^{\alpha,\beta}$-butenolide reacts with alcoholic HCl to give β-formyl-α-chloropropionates, β-formylacrylates, and γ-alkoxy-$\Delta^{\alpha,\beta}$-butenolides.

D. Reaction with Diazomethane

Diazomethane reacts with α,γ-dimethyl-γ-methoxy-$\Delta^{\alpha,\beta}$-butenolide to give a pyrazoline derivative **361**.[311] Reaction of α-cyclohexylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides with diazomethane has been reported to give cyclopropane derivatives **362**.[58] With diazopropane, $\Delta^{\alpha,\beta}$-butenolides react to give two types of products **363** and **364**.[359] It may be pointed out that the reaction of diazomethane with γ-arylidene-α-aryl-$\Delta^{\alpha,\beta}$-butenolides (**365**) leads to the formation of C-alkylation products, β-methyl derivatives of **365**.[791]



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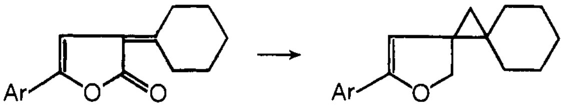
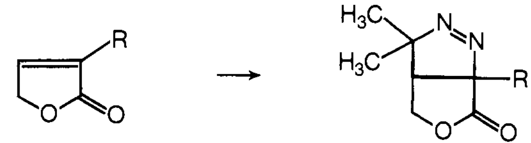


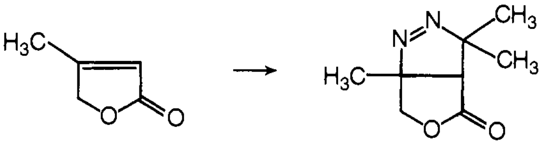
362

Ar = C_6H_5, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-ClC_6H_4



R = H or CH_3

363



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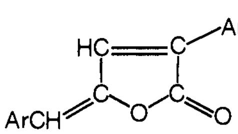
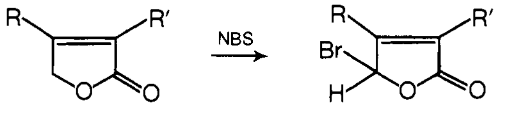


365

E. Reaction with *N*-Bromosuccinimide

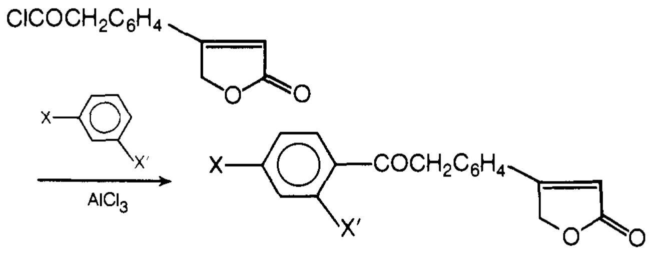
β-Methyl-$\Delta^{\alpha,\beta}$-butenolide (**366**) is brominated by NBS to give the γ-bromo derivative. The latter compound on hydrolysis gives *cis*-β-formylcrotonic acid, the product which may be considered to be an oxidation product of **366**.[228] On the other hand, treatment of a series of $\Delta^{\alpha,\beta}$-butenolides with NBS gives γ-bromo derivatives. The corresponding reactions with $\Delta^{\alpha,\beta}$-butenolide, β-ethyl-$\Delta^{\alpha,\beta}$-butenolide, and α,β-dimethyl-$\Delta^{\alpha,\beta}$-butenolide give γ-hydroxy derivatives of these compounds.[923]



R = C_6H_5, R′ = H; R = R′ = CH_3, R = C_6H_5, R′ = CH_3

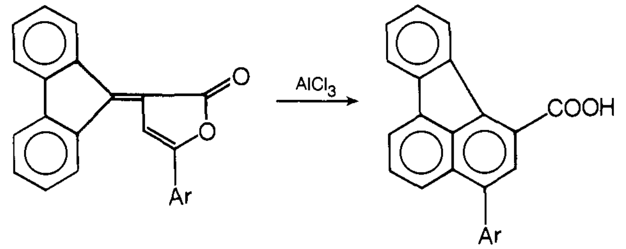
F. Reaction under Friedel–Crafts Conditions

The work of Schmitt and coworkers in employing the Friedel–Crafts reaction for the synthesis of $\Delta^{\alpha,\beta}$-butenolides has been discussed already. A similar reaction has been employed by Prigent and coworkers[778,779] who prepared a series of substituted $\Delta^{\alpha,\beta}$-butenolides **367** by this method. Filler and Leipold[348] prepared a series of substituted naphthoic acids by the reaction of α-arylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides. This type of a ring closure has been effected on 9-fluorenylidene butenolides[435] to give fluoranthenecarboxylic acids (**368**). α-



367

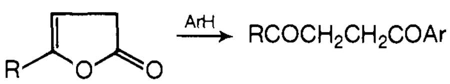
$X' = H, X = OCH_3$
$X' = H, X = OH$
$X' = H, X = \beta$-glucopyranosyloxy



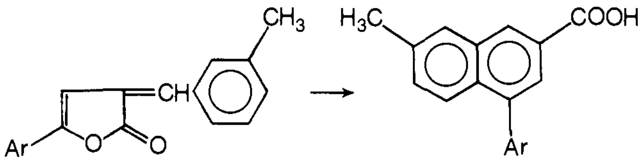
368

$Ar = C_6H_5, 4\text{-}ClC_6H_4, 4\text{-}CH_3C_6H_4, 4\text{-}CH_3OC_6H_3$

Angelica lactone and γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide have been reacted with benzene and toluene in the presence of $AlCl_3$ to give the corresponding 1,2-diacylethane derivatives.[209] A similar reaction with α-angelica lactone and benzene was reported by Eijkmann to give γ,γ-diphenylvaleric acid.[306,1107-1110]



It may be pointed out that the ring-closure reaction of α-arylidene-γ-aryl-$\Delta^{\beta,\beta}$-butenolides to naphthoic acids has been effected by a mixture of HCl and acetic acid. Thus El-Assal and Shehab[308,309] prepared a series of naphthoic acids **369** from α,β-tolylidene butenolides. They also reported that α-(2,3-dimethoxybenzylidene)-γ-(3,4-dichlorophenyl)- and α-(2,3-dimethoxybenzylidene)-γ-(2,5-dimethoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolides cyclize to the corresponding naphthoic acid derivatives. The butenolide from 5,6,7,8-tetrahydro-2-naphthaldehyde and β-(2,3-dichlorobenzoyl)propionic acid also cyclizes to an anthroic acid derivative.

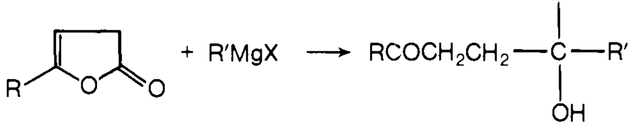


369

$Ar = 4\text{-}CH_3OC_6H_4, 4\text{-}CH_3C_6H_4, 4\text{-}ClC_6H_4, 3,4\text{-}(CH_3O)_2C_6H_3$

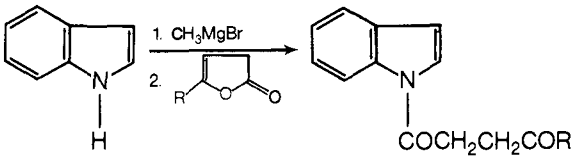
G. Reaction with Organometallic Compounds

Chiron and Graff reported that α-angelica lactone, γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, and its γ-benzyl analog react with aryl and aralkyl Grignard reagents to give keto alcohols of type **370**.[209]

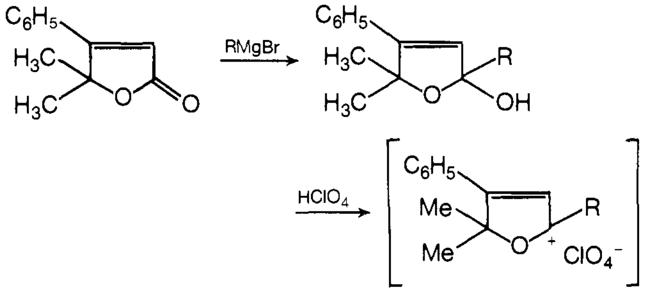


370

With indolylmagnesium bromide, both α-angelica lactone and γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide give the corresponding 1-acylindoles **371**.[534] The reaction of furanones with Grignard reagents has been used in the synthesis of a series of highly colored furylium perchlorate salts by Fabrycy and coworkers.[325-328]

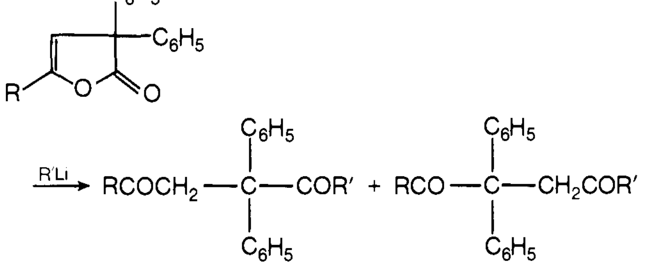


371

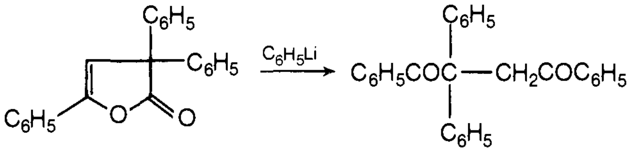


$R = C_6H_5, 4\text{-}CH_3C_6H_4$

Yates and coworkers reported that reaction of a series of $\Delta^{\beta,\gamma}$-butenolides with phenyllithium gave mixtures of diacylethanes (ref 103, 1057, 1058, 1122). A similar reaction has been employed by Lutz and co-workers recently.[1162] The compound α,α,γ-triphenyl-$\Delta^{\beta,\gamma}$-butenolide reacted with phenyllithium to give a 1,4-diketone, diphenylbenzoylphenacylmethane.



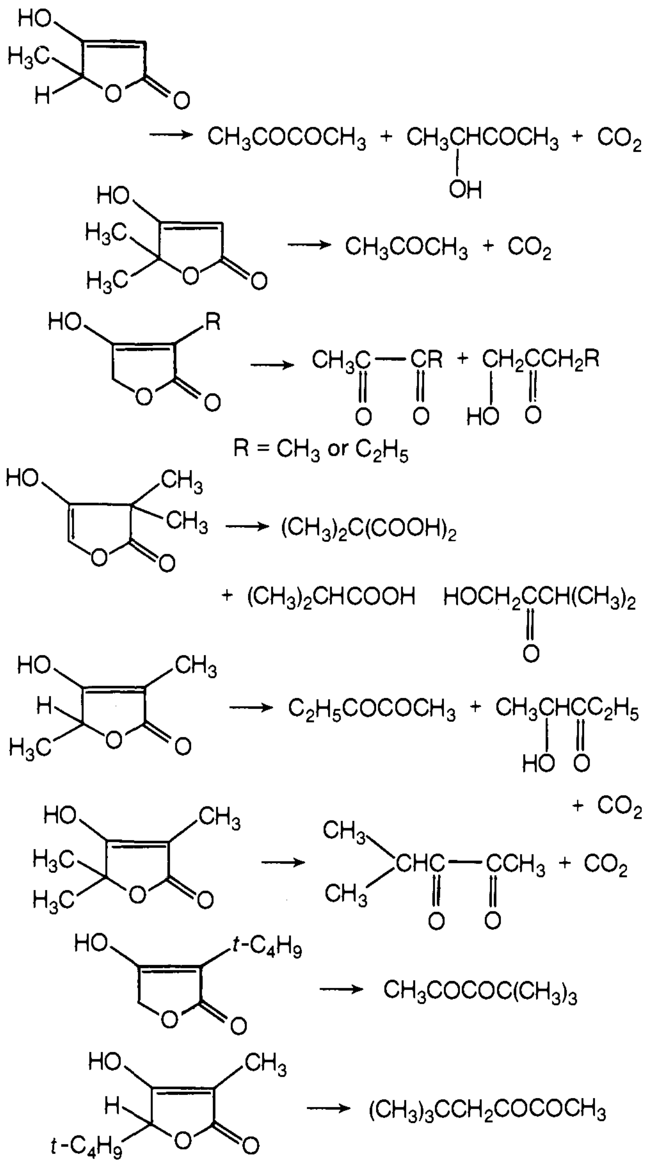
$R = CH_3, C_6H_5, t\text{-}C_4H_9, 4\text{-}CH_3C_6H_4;$
$R' = C_6H_5, \alpha\text{-}C_{10}H_7, t\text{-}C_4H_9$



H. Reaction with Enzymes

Tronche and coworkers studied the effects of α-phenyl-, α-p-tolyl, α-p-anisyl-, and α-p-chlorophenyl-$\Delta^{\beta,\gamma}$-butenolides on the activities of hepatic or renal sorbital dehydrogenase by injecting the former into mice. Correlation between the substituents on the benzene ring and enzymatic activity shows H > CH_3 > OCH_3. Hammett σ factors were determined (0.00 for H, -0.170 for CH_3, -0.268 for OCH_3, and $+0.227$ for Cl), and a correlation between electronic parameters and biological activity of butenolides was shown.[968] In studying the mechanism of chymotrypsin action, Bruice and co-workers studied the uv spectrum of β-phenyl-$\Delta^{\alpha,\beta}$-butenolide and found that the spectra of acylchymotrypsin intermediates formed during the ester hydrolysis catalyzed by chymotrypsin resemble α-benzylidene-γ-butyrolactone.[166]

SCHEME XXXIV



I. Reaction with Oxidizing Agents

The anodic oxidation in methanol of α-methoxy-γ,γ-dimethylaconic acid is reported to yield a mixture of α,α,β-trimethoxy-γ,γ-dimethylparaconic acid and terebic acid.[964] Oxidation of furan compounds such as 2-methylfuran and furfuryl alcohol with peracetic acid is reported to give α-hydroxy-γ-methyl-$\Delta^{\alpha,\beta}$-butenolide and $\Delta^{\alpha,\beta}$-butenolide, respectively.[122] Oxidation of furfural in ethanol in the presence of a sensitizer is reported to yield γ-ethoxy-$\Delta^{\alpha,\beta}$-butenolide (ref 271, 584, 851, 852, 1049, 1114, 1115). The oxidation of 2-acetylfuran with H_2O_2–V_2O_5 is reported to give $\Delta^{\alpha,\beta}$-butenolide along with 2-acetoxyfuran.[585] Photoxidation of 3-methylfuran and 3-methyl-2-furoic acid is reported to yield α-methyl-γ-ethoxy-$\Delta^{\alpha,\beta}$-butenolide.[331]

Reid and coworkers studied the oxidation of tetronic acids with CrO_3–H_2SO_4. Their results are summarized in Schemes XXXIV.[1080,1081]

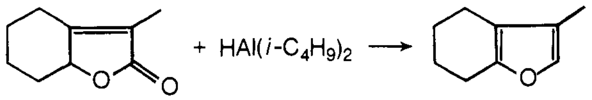
J. Reducing Agents

Hydrogenation of butenolides in the presence of palladium on charcoal result in hydrogenation with hydrogenolysis of the benzyl position with absorption of 2 mol of hydrogen. The compound α,α-dibenzyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide gives 2,2-dibenzyl-4-phenylbutyric acid in 96% yield. α-Phenyl-$\Delta^{\beta,\gamma}$-butenolide is converted to 4-phenylbutyric acid under similar conditions (45 psi for 16 h). With Adams catalyst (platinum on charcoal) $\Delta^{\beta,\gamma}$-butenolides are converted to a mixture of butanolides and the corresponding substituted butyric acids in the ratio of 4:1. The $\Delta^{\alpha,\beta}$ isomers are converted to butanolides under the same conditions. If isomerization to $\Delta^{\beta,\gamma}$-lactones occurs, then the butanolide is accompanied by a 12% conversion to butyric acid derivatives. McCoy reported the formation of α,α-dibenzyl-γ-methylbutanolide from the corresponding butenolide along with α,α-dibenzylvaleric acid.[661] Pulvinic dilactone is reduced to dihydropulvinic acid in the presence of Pd/C.[24,1191]

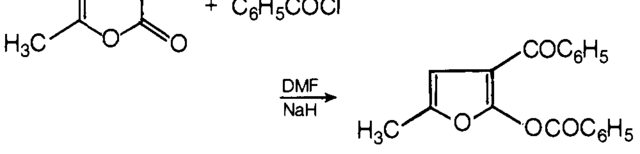
Sodium borohydride reduces 15-oxocardenolides to 15-α-hydroxycardenolides.[734] Lithium aluminum hydride reduction of butenolides has been reported earlier.[345,788,791]

K. Conversion to Furan Derivatives

Minato and Nagasaki have reported an elegant method for the conversion of fused $\Delta^{\alpha,\beta}$-butenolides to furan compounds.[677,678] Their method consists of adding diisobutylaluminum hydride in tetrahydrofuran to a solution of the lactone. The yields are 45–75%. The following is an example of the method.[1129]



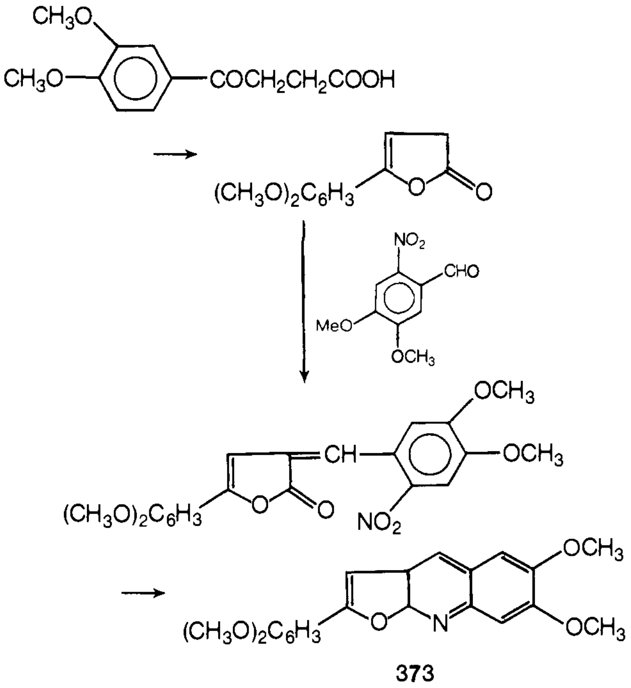
Benzoylation of α-angelica lactone in dimethylformamide in the presence of sodium hydride is reported to give a furan derivative **372**.[661]



372

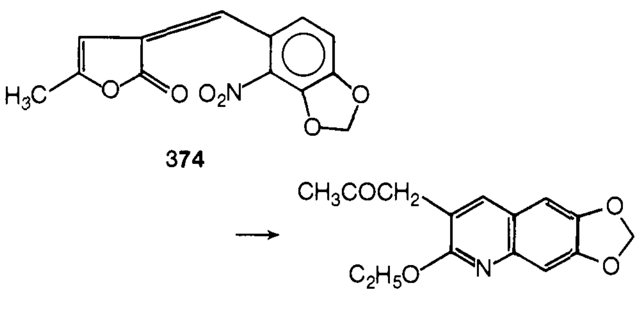
L. Conversion to Other Heterocycles

Furanoquinolines have been reported by the reduction of o-nitrobenzylidene butenolides.[431] The corresponding methylenedioxy derivative of **373** is also prepared thus.



373

o-Nitropiperonal reacts with α-angelica lactone in pyridine to give **374**. Compound **374** is converted to the quinoline derivative **375** when heated with triethyl phosphite.[492]

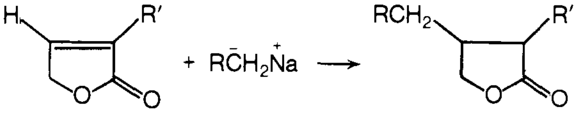


374

375

M. Alkylation of Butenolides

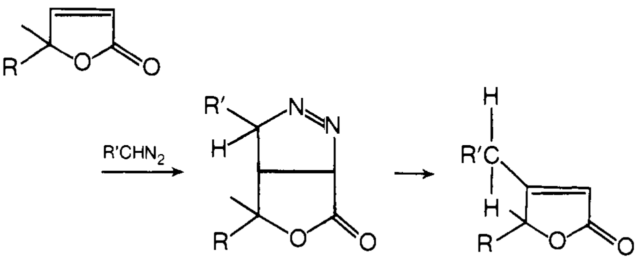
A study of the alkylations of butenolides **21**, **36**, and **55a** and γ-4-methoxyphenyl-$\Delta^{\beta,\gamma}$-butenolide under various conditions has been completed by McCoy[661] and has been discussed earlier. A similar study of the alkylation reaction has been reported by Rio and Hardy.[816,820] According to these authors, the alkylation of α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide in the presence of pulverized potassium hydroxide and dimethyl sulfate gives 2-methoxy-3,4,5-triphenylfuran exclusively, while alkylation in the presence of solid KOH and methyl iodide gives α,β,γ-triphenyl-α-methyl-$\Delta^{\beta,\gamma}$-butenolide, a product of C-methylation. More recently, Hornfeldt and coworkers reported that α-angelica lactone gets alkylated with methyl iodide in the presence of the base tetrabutylammonium hydrogen sulfate and sodium hydride to give a 26% yield of a mixture of three compounds: α,α-dimethyl- and α-methyl-α-angelica lactones and α-methyl-β-angelica lactone (**376**). Compound **376** is the only product obtained when the methylation is carried out with dimethyl sulfate.[198] When alkylations are carried out with picolyl anions, addition to the double bond is reported to occur.[146] Similar additions also occur with α-methyl- and α-ethyl-$\Delta^{\alpha,\beta}$-butenolides.[147] Pelletier and co-workers[1103] prepared a series of butenolides by an alkylation procedure consisting of treating butenolides with diazoalkanes and decomposing intermediate pyrazolines. When the β position is blocked as in the case of β-caromethoxy-$\Delta^{\alpha,\beta}$-butenolide, the product obtained is the α-alkylation product. It may be pointed out that the intermediate pyrazolines **363** obtained from α-methyl-$\Delta^{\alpha,\beta}$-butenolide and $\Delta^{\alpha,\beta}$-butenolide are converted to a mixture of products on photolysis. Alkylation and cyclopropane formation are competing reactions. However in the presence of a sensitizer, **378** and **379** are obtained in 88 and 99% yields, respectively.[359]



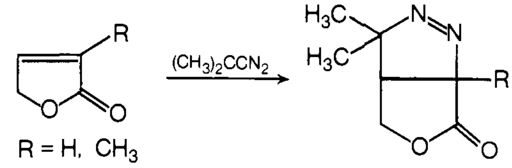
376

377

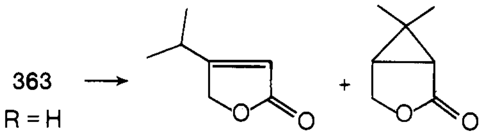
R = 2- or 4-pyridyl; R' = H, C_2H_5, CH_3



R = H, CH_3; R' = H, CH_3, C_2H_5, C_3H_7



363



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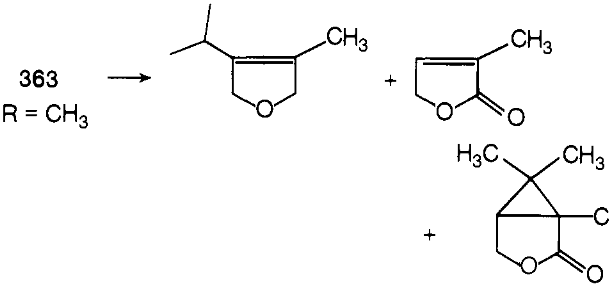
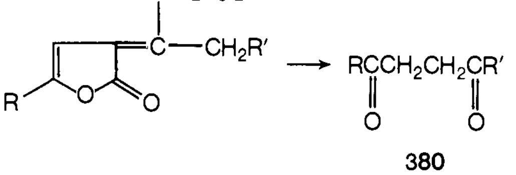


379

N. Conversion to Diketones

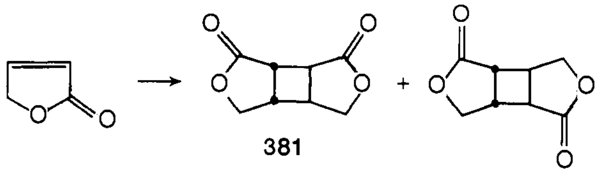
Ficini and coworkers prepared a series of α-diethylaminoethylidene compounds **63** from $\Delta^{\beta,\gamma}$-butenolides.[339-341] These compounds are converted to diketones **380** on acid hydrolysis.



380

O. Photochemical Reactions

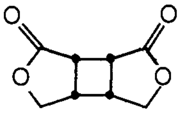
α-Angelica lactone is converted to methyl vinyl ketone when irradiated for 6 h in pentane solution. Only methyl vinyl ketone is obtained in 30% yield. Under similar conditions, α-methyl-α-angelica lactone gives a 40% yield of methyl propenyl ketone. A change of solvent to methanol or butanol did not significantly improve the yields.[1061] A similar photodecarbonylation of α-angelica lactone has been reported by Chapman and McIntosh.[200] On the other hand, Hg-vapor sensitized vapor-phase photolysis of $\Delta^{\alpha,\beta}$-butenolide gave 1-propyne, allene, and cyclopropene. The products obtained from β-methyl-$\Delta^{\alpha,\beta}$-butenolide were acetylene, ethylene, 1-propyne, 1,4-butadiene, 1-methylcyclopropene, 1-butyne, 1,2-butadiene, and a major quantity of 2-butyne.[578] Irradiation of $\Delta^{\alpha,\beta}$-butenolide in polar solvents with a low-pressure mercury lamp is reported to yield the anti photodimers **381** and **382**. These cyclobutane derivatives are characterized by ir, NMR, and ORD measurements. Compound **381** is formed by head-to-head dimerization, while **382** is formed by head to tail dimerization. Solid-phase irradiation



381

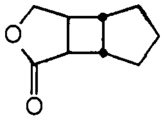
382

leads to the formation of **383**, a head-to-head syn dimer.[730] It is noteworthy that sensitized photolysis of 3-ethylidene-4,5-dihydro-2(3*H*)-furanone not only gave the cis isomer but also 3-vinyl-4,5-dihydro-2(3*H*)-furanone, formed from the cis isomer.[732]



383

Tada and coworkers observed that cyclopentene and cyclohexene add to $\Delta^{\alpha,\beta}$-butenolide photochemically to give **384** and **385**. The cycloaddition reaction is sensitized by acetone but not by acetophenone and quenched by dimethoxyethylene.[942]



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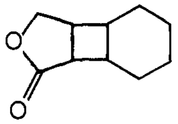
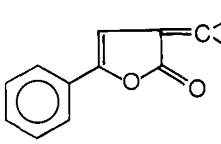


mixture of 3 isomers
385

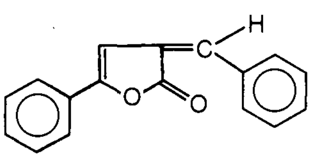
The compound α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (**65**) is reported to undergo two primary photochemical reactions: hydrogen abstraction from solvent and geometric isomerization when irradiated in 2-propanol solution with 3130-Å light. Compound **65** is assumed to be a mixture of geometric isomers and on irradiation gave only the syn isomer. On irradiation with 3650-Å light, **65** underwent isomerization. Aromatic hydrocarbons sensitized the reaction, and some sensitizers selectively caused cis–trans isomerization while others led to isomerization. An orbital symmetry correlation between the sensitizers and **65** was reported.[987,1200] According to Tokumaru and coworkers,[962] compound **65** efficiently reabsorbs fluorescence emitted by the hydrocarbon sensitizers, and the wavelength of the fluorescence seems to govern the reaction.

P. Geometric Isomerism among Butenolides

The possibility of the existence of geometric isomers of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (**65**) has been considered for a long time. Ullman and coworkers[987] claimed that the product obtained by the condensation of 3-benzoylpropionic acid and benzaldehyde under Perkin–Erlenmeyer conditions is a mixture of isomers although these were not separated and characterized. Thiele reported a melting point of 167 °C for what was purported to be a geometric isomer of **65**. The compound melting at 156 °C[1125] is designated the *E* isomer on the basis of NMR spectrum[642] by Maquestiau and co-workers. They reported that they did not isolate a mixture of **65a** and **65b** during the preparation.[1125] Compound **65a** with its *E* configuration is not isomerized by trifluoroacetic acid and is reported to have syn geometry. It now appears certain that the 156 °C melting isomer of **65** or the commonly known compound has the *E* configuration, while the *Z* configuration may be attributed to Thiele's 167 °C melting material[960] or Kohler and Conant's[560] 180 °C melting isomer. Until such time as this compound is isolated and characterized, any structure assignment is purely conjectural. Cordier, as mentioned earlier, isolated two isomers of α-benzylidene-γ-(p-tolyl)-$\Delta^{\beta,\gamma}$-butenolide (**66**).[231,237] Two geometric isomers of α-(5-nitrofurylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (**59**) have also been reported.[501,502]



65a



65b

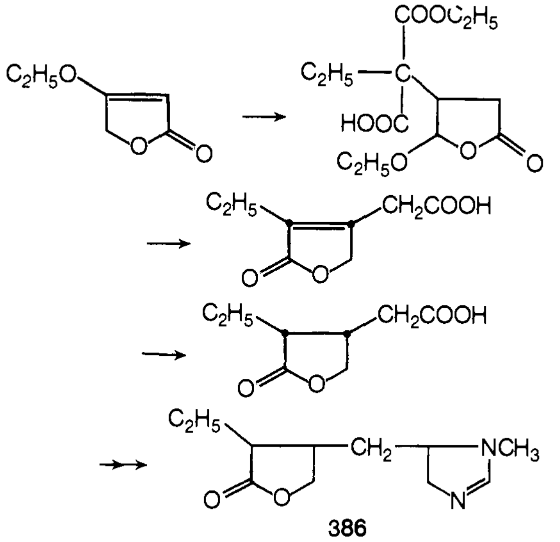
Although geometric isomerism is possible in the case of γ-benzylidene-α-phenyl-$\Delta^{\alpha,\beta}$-butenolide, attempted photoisomerization of **12** (R = R′ = H) resulted in extensive degradation of the lactone.[1030] Compound **12** (R = R_1 = H) has the trans-trans structure. This compound has been reported by others as well (ref 24, 792, 905, 961, **1191**). The cis–trans isomer is still not known. Geometric isomers of γ-4-methoxybenzylidene-$\Delta^{\alpha,\beta}$-butenolide (**288**) and its analogs have been reported and structural assignments have been made.[1050,1051]

Q. Polymerization of Lactones

$\Delta^{\alpha,\beta}$-Butenolide is homopolymerized in the presence of an anionic catalyst consisting sodium naphthenide, a tertiary amine, phosphine, or arsine in the absence of oxygen and water.[207,743] Avetisyan and co-workers prepared copolymers of α-carbethoxy-β,γ-dipropyl-$\Delta^{\alpha,\beta}$-butenolide and its α-cyano analog and styrene in the presence of boron trifluoride etherate.[40,43] The α-cyano and α-carbethoxy butenolides failed to copolymerize. Copolymerization of α-chlorovinyl-β,γ,γ-trimethyl-$\Delta^{\alpha,\beta}$-butenolide with acrylonitrile and methyl acrylate have been reported.[49] Copolymers of γ-dichloromethylene-$\Delta^{\alpha,\beta}$-butenolide and similar compounds with styrene have been reported (ref 1037, 1039, 1040, 1042, 1043).

R. Syntheses with Butenolide Compounds

In the synthesis of pilocarpine (**386**), γ-ethoxy-$\Delta^{\beta,\gamma}$-butenolide is converted to α-ethyl-β-carboxymethyl-$\Delta^{\beta,\gamma}$-butenolide by condensation with diethyl malonate.[271] Claisen condensation of α-ethyl-β-carbomethoxymethyl-$\Delta^{\alpha,\beta}$-butenolide with phthaloylglycyl chloride gives **387**, a key intermediate in the synthesis of **386**.[219,220]



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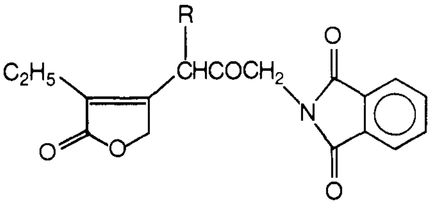
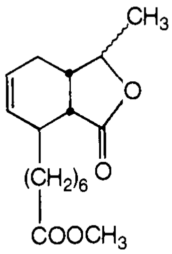


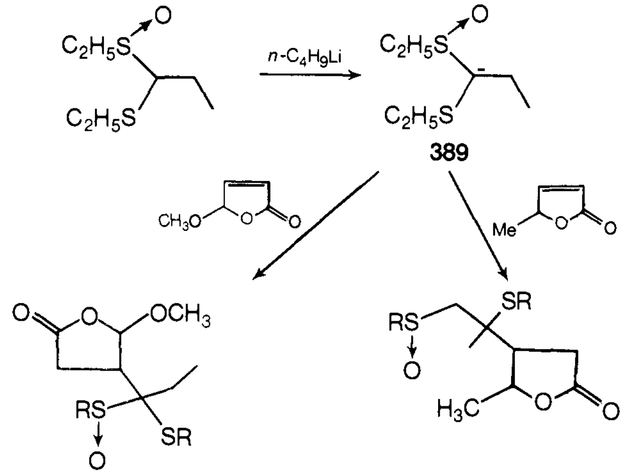
387
R = $COOC_2H_5$

In the synthesis of the prostaglandins, Wendler and coworkers reacted β-angelica lactone with methyl 8,10-undecadienoate to give **388**.[587] Schlessinger and co-workers reported



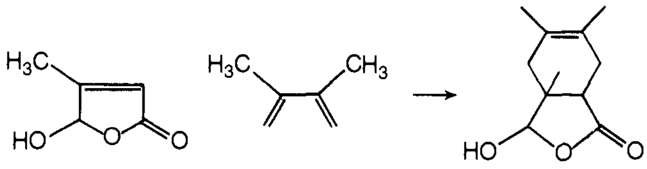
388

that the anion of diethyl acetal monosulfoxide **389** adds γ-methyl- and γ-methoxy-$\Delta^{\alpha,\beta}$-butenolide,[464] via a Diels–Alder



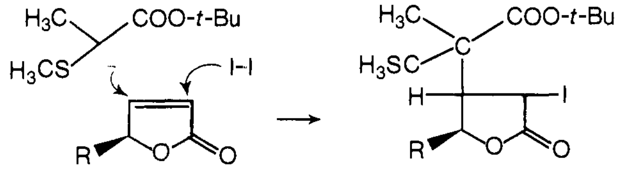
389

reaction in which β-methyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide acts as a dienophile toward 2,3-dimethylbutadiene to give **390**.[168] Similarly, γ-ethoxy-$\Delta^{\alpha,\beta}$-butenolide reacts with butadiene, 2,3-dimethylbutadiene, and cyclopentadiene to give adducts similar to **390**.[4]



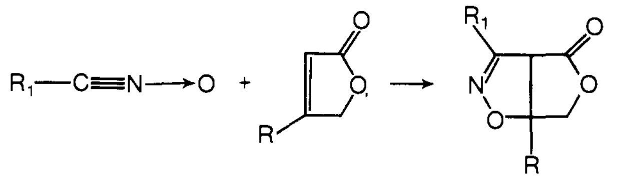
390

In their synthesis of avenciolide, Schlessinger and coworkers prepared and iodolactone, **391**, by this unusual reaction.[465]



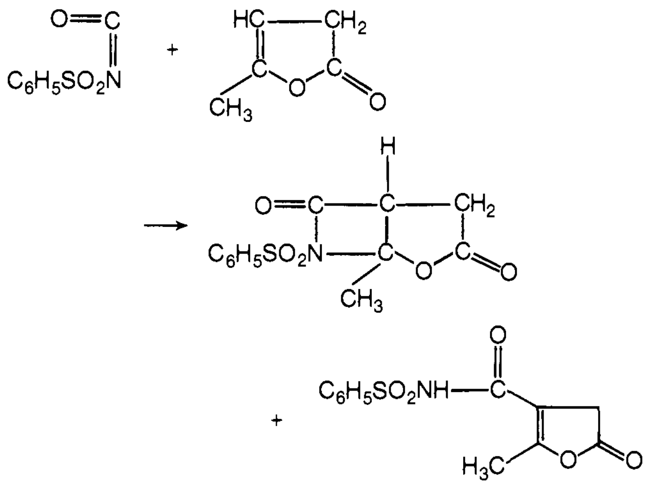
391

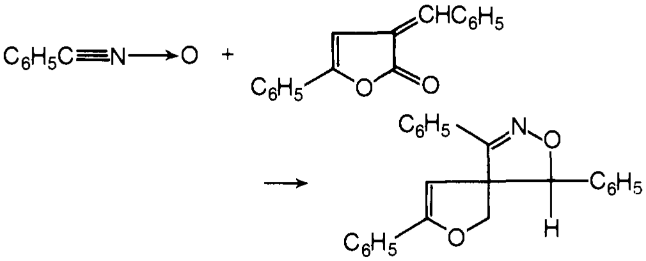
A series of cycloaddition products involving α-angelica lactone have been reported (Scheme XXXV). The coumarin derivative obtained from α-angelica lactone and salicylaldehyde has been converted to a series of heterocycles.[1026] Benzonitrile oxide reacts with β-substituted $\Delta^{\alpha,\beta}$-butenolides to give 1,3-dipolar addition products **392**.[671] Benzonitrile oxide reacts with α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide to give **393**.[795]



$R_1 = C_6H_5$, mesityl; R = H, *p*-tolyl **392**

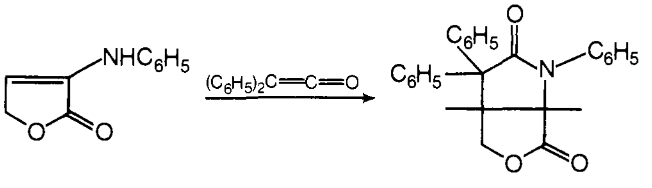
SCHEME XXXV





393

The reaction of α-phenylamino-$\Delta^{\alpha,\beta}$-butenolide with diphenylketene is reported to give 2,3,3a,4,6,6a-hexahydro-2,6-dioxo-1,3,3-triphenyl-1*H*-furo[3,4-*b*]pyrrole.[674]

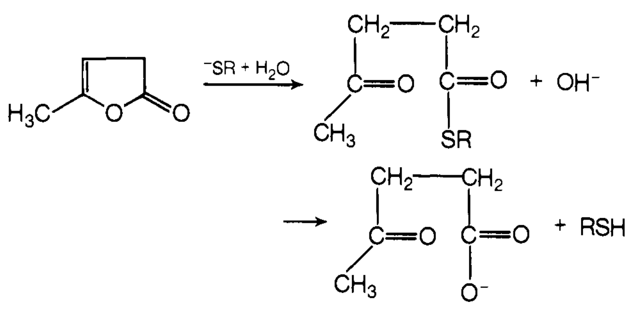


S. Reaction with Thiols

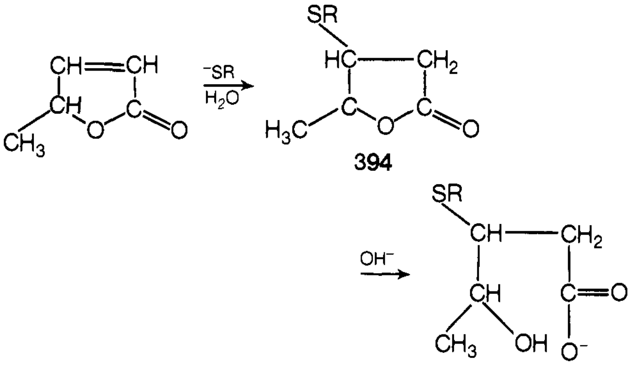
It is well known that thiols protect against the cardiotoxic activity of cardiac glycosides. Whether this protective action is due to the thiol's reaction with the lactone ring of cardenolide or not has been extensively investigated. The reactions of butenolides with sulfur-containing compounds have been studied at biological pH's.

Hellstrom and coworkers have reported that α-angelica lactone reacts with thioglycolic acid in water by ring opening with the formation of a thiol ester of levulinic acid in the first instance, followed by the formation of levulinate ion and thioglycolic acid (Scheme XXXVI).[456] These authors found that β-angelica lactone

SCHEME XXXVI

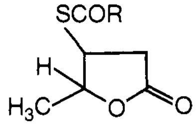


reacts with thioglycolic acid at 22 °C giving an adduct, 3-carboxymethylthio-4-hydroxyvaleric acid γ-lactone (**394**).[457] The



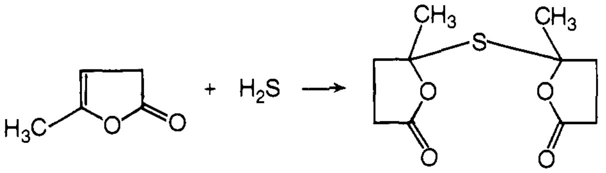
394

reaction of β-angelica lactone with thioacetic acid and thiobenzoic acid is reported to give β-thioacetyl and β-thiobenzoyl adducts **395**.[372] Reactions of α- and β-angelica lactones with thioacetic acid were studied, and it was found that α-angelica lactone gave *cis*-3-(acetylthio)-4-hydroxyvaleric acid lactone

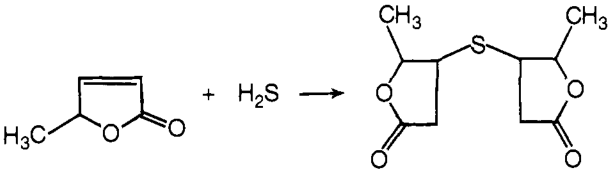


395

395 (R = CH_3), while β-angelica lactone gave the trans isomer of **395** (R = CH_3). The acetyl compounds gave the thio compound on ammonolysis. It was observed that $\Delta^{\alpha,\beta}$-butenolide adds HCl and thioacetic acid to give the corresponding β-substituted butyrolactone derivatives.[373] The reactions of α- and β-angelica lactones with hydrogen sulfide led to the formation of thiodilactones **396** and **397**.[1193]



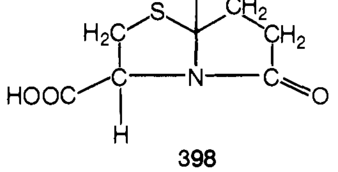
396



397

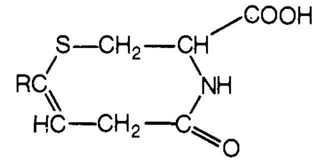
The compounds $\Delta^{\alpha,\beta}$-butenolide and α-methyl-, β-methyl-, and γ-methyl-$\Delta^{\alpha,\beta}$-butenolides were reacted with 1-propanethiol and α-toluenethiol, and the products were found to be the β-thiosubstituted lactones.[590] Michael addition of α-toluenethiol to $\Delta^{\alpha,\beta}$-butenolide has been reported, and the product undergoes retro-Michael reaction to give the pure starting materials.[516]

The reaction of cysteine with levulinic acid gives a pyrrolidinothiazolidine compound **398**.[737] The reaction of cysteine with



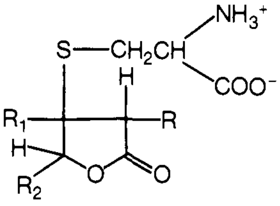
398

β-angelica lactone was reported to give an eight-membered lactone **399** (ref 50 in 791). Black recently repeated the reaction



399

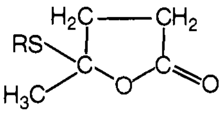
of cysteine with β- and α-angelica lactones, γ-ethyl-$\Delta^{\alpha,\beta}$-butenolide, γ-ethyl-$\Delta^{\beta,\gamma}$-butenolide, and penicillic acid and reported the isolation of lactones with α-angelica lactone and levulinic acid.[109] Hellstrom and co-workers ran the reaction of cysteine with α-angelica lactone and concluded that the product obtained is **398**, not **399** (R = CH_3),[458] based on NMR evidence. Kupchan and coworkers reported that cysteine reacts with $\Delta^{\alpha,\beta}$-butenolides to give β-thioadducts **400**,[590]



R = CH_3, $R_1 = R_2$ = H
$R_1 = CH_3$, $R = R_2$ = H
$R_2 = CH_3$, $R = R_1$ = H

400

Reaction of $\Delta^{\alpha,\beta}$-butenolide with *n*-octadecyl- and *n*-hexadecylthiols is reported to give β-substituted thiolactones.[489] Similar reactions with α-chloro, γ-methyl, and unsubstituted $\Delta^{\alpha,\beta}$-butenolides and α-angelica lactone with methyl-, ethyl-, isopropyl-, and *tert*-butylthiols have been conducted. With $\Delta^{\alpha,\beta}$-butenolides, only the β-substituted thio derivatives are obtained, while with α-angelica lactone the product is reported to be **401**.[293] The reactions are conducted in acid medium while

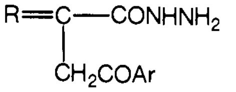


401, R = CH_3, C_2H_5

with α-chloro-$\Delta^{\alpha,\beta}$-butenolide, a basic medium is employed. Finally the reaction of α-amides of butenolides with phosphorus pentasulfide is reported to give α-thioamides.[52]

T. Reaction with Hydrazine and Hydroxylamine

Reaction of hydrazine with $\Delta^{\beta,\gamma}$-butenolides gives 6-arylpyridazin-3-one, also obtained from β-aroylpropionic acids.[726,842] In alcoholic solution in the cold, α-(9-fluorenylidene)-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides react to give open-chain compounds **402**, whereas in boiling alcohol, the products obtained are pyridazinones.[59] The compound α-benzoyl-β,γ,γ-trimethyl-$\Delta^{\alpha,\beta}$-butenolide reacts with phenylhydrazine to give a phenylhydrazine **403** which on cyclization with PCl_5 gives the diazophospholine derivative **404**.[39] Ducher and coworkers observed that α-angelica lactone reacts with hydrazine to give levulinoylhydrazine (**405**). β-Angelica lactone is first converted to the α isomer by hydrazine, and the final product obtained is **405**. Phenylhydrazine reacts with $\Delta^{\alpha,\beta}$-butenolide and α- and β-angelica lactones to give **406**.[178]

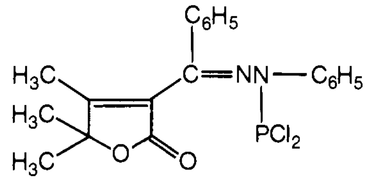


$$R{=}\underset{\displaystyle CH_2COAr}{\underset{|}{C}}{-}CONHNH_2$$

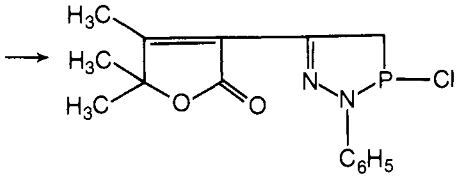
402

R = 9-fluorenylidene, Ar = C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$

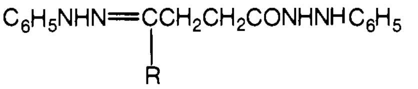
Fused butenolides react with hydrazine to give fused pyridazinones.[865] The reaction has been extended to the androstanolone–glyoxylic acid condensation product **202**. Condensation



403



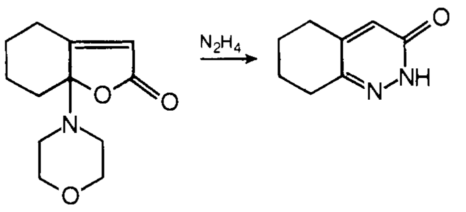
404

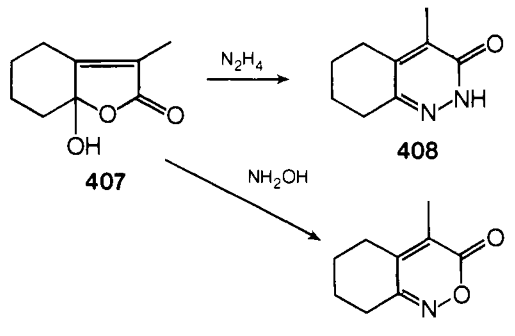


$$C_6H_5NHN{=}\underset{\overset{|}{R}}{C}CH_2CH_2CONHNHC_6H_5$$

406, R = H, CH$_3$

of **407** with hydrazine and hydroxylamine gives pyridazinone **408** and oxazinone **409**.[776] This reaction was extended to steroidal lactones as well.[773]





407 **408** **409**

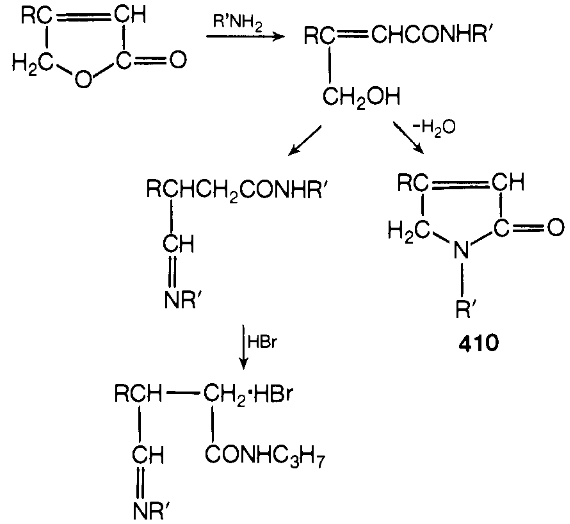
U. Reaction with Ammonia and Amines

Considerable confusion exists regarding the products obtained by the reactions of butenolides with ammonia and primary amines. In general, α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides react with ammonia or primary amines in benzene to give the propionamide derivatives. These compounds are converted to a cyclic pyrrolinone structure on heating with acetic anhydride or upon recrystallization[307] or on treatment with 6 N HCl.[501,502] Direct conversion to the pyrrolinone derivative is achieved by heating an alcoholic ammonia solution of the butenolide. No reactions of γ-arylidene-α-aryl-$\Delta^{\alpha,\beta}$-butenolides with amines or ammonia have been reported.

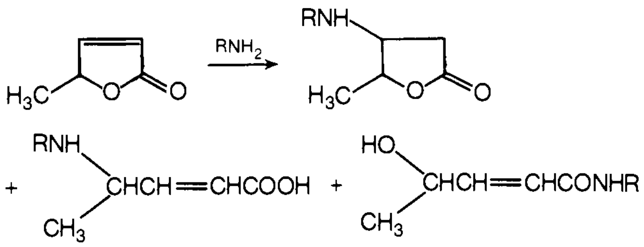
Dihalobutenolides (from mucochloric or mucobromic acids) are converted to the β-amino derivatives on treatment with amines. This reaction has been discussed in an earlier section.

1. With $\Delta^{\alpha,\beta}$-Butenolides

A study of the reaction of primary amines such as *n*-propylamine, *n*-butylamine, and tryptamine with strophanthidin has been reported by Elderfield and coworkers.[1079] They observed that Δ^3-pyrrolinones are obtained as the end products. Thus β-phenyl-$\Delta^{\alpha,\beta}$-butenolide reacted with *n*-propylamine in refluxing benzene for 12 h to give the pyrrolinone derivative **410** (R = C_6H_5; R′ = *n*-C_3H_7), which was too unstable for purification. An amido imine was the main product isolated and characterized as the hydrobromide. With primary amines in ethanol at −10 °C, mucobromic acid gave 4-bromo-5-hydroxy-5-alkyl-Δ^3-pyrrolin-2-ones.[880] Straight-chain amides were reported to be formed earlier when γ-*p*-anisyl-γ-hydroxy-α,β-dihalo-$\Delta^{\alpha,\beta}$-butenolides reacted with amines in alcoholic solution at temperatures below 20 °C. Jones and coworkers[518] summarized recently the reactions of amines on $\Delta^{\alpha,\beta}$-butenolides. According to them, three types of reactions are possible: (i) Michael addition of the base to the double bond in the lactone ring, (ii) attack by the base on the carbonyl carbon to give an amide derivative, (iii) attack on the γ position of the lactone to give a butenoic acid derivative with the base attached to the γ position of the acid.



410



β-Angelica lactone, when reacted with aqueous methylamine at room temperature, gave an 80% yield of β-methylamino derivative. With aqueous methylamine at 0 °C, the product obtained was a pyrrolinone derivative. With benzylamine in the presence or absence of water, the product was the Michael adduct.[519] When the reaction was carried out at 80 °C, the product was β-benzylamino-4-hydroxy-*N*-benzylpentanoamide. A similar reaction was carried out with guanosine and β-angelica lactone, and it was found that Michael addition was not favored.[517] A similar pyrrolinone formation has been reported.[658] It should be pointed out that an excellent review of these pyrrolinones and their preparations has been published recently.[817]

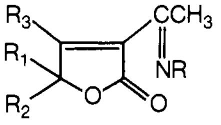
2. With $\Delta^{\beta,\gamma}$-Butenolides

Cromwell and co-workers reported that γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide reacts with morpholine to give β-benzoylpropionomorpholide, a product also obtained from β-benzoylpropionic acid and morpholine.[247] Reaction of **21** with ammonia, methylamine, and aniline in ether solution at room temperature for 1 day was reported to yield *N*-alkyl (or aryl)-β-benzoylpropionamides, all straight-chain compounds. Other amines such as cyclohexylamine, dimethylamine, and *sec*-benzylmethylamine were also employed.[248] In all these cases, the straight-chain compounds were obtained. Recently, the reaction of α,α-dimethyl-γ-(1-phenyl-3-methylpyrazol-4-yl)-$\Delta^{\beta,\gamma}$-butenolide (**411**) with benzylamine has been reported.[1078] Compound **411** gives an amide with benzylamine in benzene and a pyrrolidine derivative in ethanol. The amide may be cyclized to a pyrrolinone derivative. These are exclusively obtained when alcoholic solutions of ammonia and methylamine are employed.

Jones and Young[518] reported that α-angelica lactone reacted with aqueous methylamine at 0 °C to give 1,5-dimethyl-5-hydroxypyrrolidin-2-one. With aniline and benzylamine, only the amide was obtained. Aqueous benzylamine was reported to give a hydroxypyrrolidone derivative. It is noteworthy that the cyclic isomer of levulinanilide, 5-hydroxy-5-methyl-1-phenyl-2-pyrrolidone, has been obtained by filtration of a chloroform solution of the anilide through an acid ion-exchange column,[536] and its structure has been established by ir and NMR spectroscopy.

In a series of papers, Chiron and Graff reported the reaction of amines with $\Delta^{\beta,\gamma}$-butenolides.[209-212,602,785] The amides have been prepared in 90% yields by heating the amine and lactone to 180°. The hydroxypyrrolidones are prepared by Grignard reaction on succinimides. In a few cases when a dialkylamine was employed, it was observed that isomerization of $\Delta^{\beta,\gamma}$ to $\Delta^{\alpha,\beta}$ occurred. With aromatic amines, hydroxypyrrolidones were obtained. With α,γ-dimethyl-γ-(*p*-anisyl)-$\Delta^{\alpha,\beta}$-butenolide, α,α-dimethyl-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, and α,α-dimethyl-γ-(*p*-tolyl)-$\Delta^{\beta,\gamma}$-butenolide, aqueous solutions of amines gave only hydroxypyrrolidones. Infrared and ultraviolet spectral data have been employed to distinguish between these two types of compounds.

When other reactive functions are present in the lactone ring such as carboxylic acids, the corresponding amides are obtained.[42] α-Acetylbutenolides react with amines to give iminobutenolides **412**.[51] Tetronic acids react with arylamines to give β-arylaminobutenolides.[334] It has also been reported that heating α-carboxyethylbutenolides with dimethylamine in water at 150–200 °C yields the carboxamides.[47] Quinoline oxide alkylates α-carbamoyl-β-methylthio-$\Delta^{\alpha,\beta}$-butenolide in the γ position to give a γ,γ-bis(2-quinolyl) derivative.[899]



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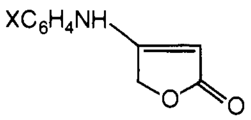
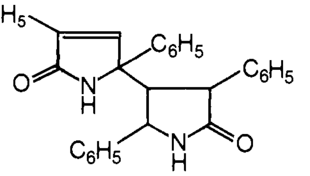


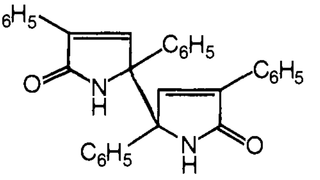
X = H, 4-Cl, 4-CH$_3$O, 4-NO$_2$, 4-CH$_3$

Reaction of γ-chloro-β,γ-dimethyl-α-ethyl-$\Delta^{\alpha,\beta}$-butenolide proceeds with ammonia to give a pyrrolinone derivative.[60] Ammonium acetate in acetic acid has also been employed for this conversion.[890]

The pyrrolinone 2-oxo-3,5-diphenyl-3-pyrroline, formulated earlier as 2-oxo-3,5-diphenyl-2-pyrroline, has been shown to be a mixture of two dimers **413** and **414** by Rio and Masure.[817-819] These authors report that α-phenyl-β-benzoylpropionitrile, which yielded **413** and **414** mixture on acid hydrolysis with 70 and 95% sulfuric acid,[794] reacts with ammonium acetate to give the known **415**.[1084,1085]



413



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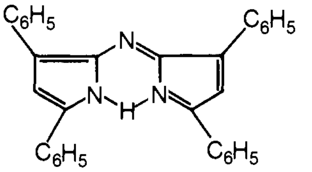
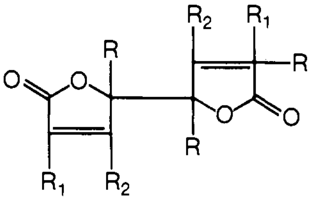


415

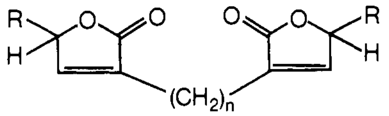
V. Dilactones

Several dilactones or lactone dimers have been described. In general these dilactones may have the structures of types **416–422**.



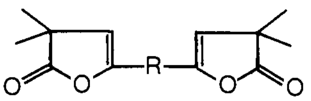
416

γ,γ(α,β-butenolide)



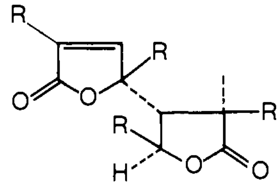
417

α,α



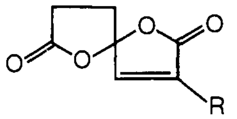
418

γ,γ



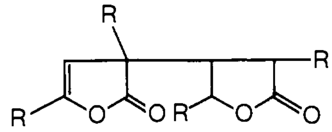
419

β,γ



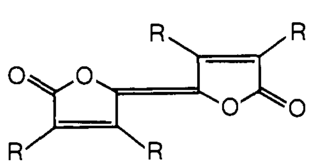
420

γ,γ(spiro lactone)



421

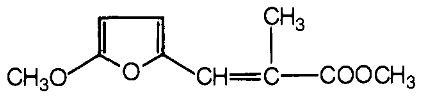
α,β



422

Dilactones of type **422** are also known as "Pechmann" dyes.[967] Dimethyl- and diphenylmaleic anhydrides are converted to bifurandiones **422** (R = CH$_3$, C$_6$H$_5$), when heated with triethyl phosphite.[1092] These bifurandiones are also obtained when phenyl-, diphenyl-, dimethyl-, and dichlorosuccinyl chlorides are treated with triethylamine in benzene.[1093] These deoxygenative dimerizations have been used for the preparation of dimers in 52% yield.[1091] α,α-Dilactones of type **417** are naturally occurring, and one such is ancepsenolide (**417**, *n* = 12, R = CH_3) and its β-hydroxy analog.[859-861,1194]

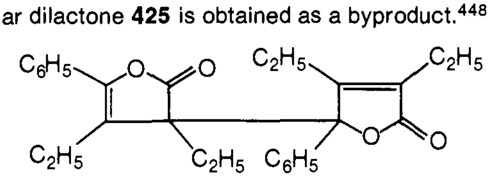
Spirolactones of type **420** have been reported.[892,894] Hydrolysis of the substituted methyl acrylate **423** in methyl alcohol with hydrochloric acid gives **420** (R = CH_3). A similar spirolactone, **147**, has been described earlier.[521]



423

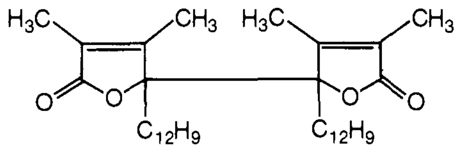
The compound anhydrotetronic acid (**424**) is an example of a β,β-dilactone.[177] An α,β-dilactone from an α-tetronic acid has been reported by Scarpati and coworkers.[846]

Compounds of type **418** have been reported by Ried and coworkers.[811-815] Their method consists of treating the appropriate ketene with a diazo ketone in a hydrocarbon solvent at −60 °C. A similar dilactone **425** is obtained as a byproduct.[448]



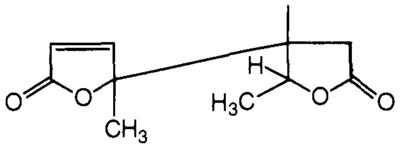
425

Several γ,γ-dilactones have been reported. One such compound is obtained from the 2,3-dimethyl-3-*p*-xenoylpropionic acid. Treatment of its lactone with Tollen's reagent gives **426**.[630]



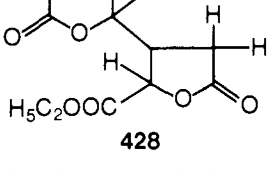
426

In the conversion of α-angelica lactone to β-angelica lactone with triethylamine, Lukes and coworkers isolated a dilactone **427**.[628] Acid hydrolysis of ethyl 5-amino-2-furoate is reported to produce **428** and its diastereoisomers.[549] Hornfeldt repeated the earlier work of Lukes and co-workers (conversion of α- to β-angelica lactone) and reported the isolation of three compounds to which she also assigned structures **429** and two forms of **427**, based on ir and NMR data.[481] Diastereoisomeric compounds **427** were reported earlier by Lukes and co-workers. According to Hornfeldt, Michael addition leads to the dimer formation.



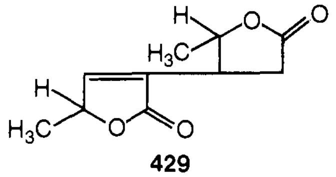
427

(γ-methyl-γ(γ-methyl-β-butanolide)-$\Delta^{\alpha,\beta}$-butenolide)



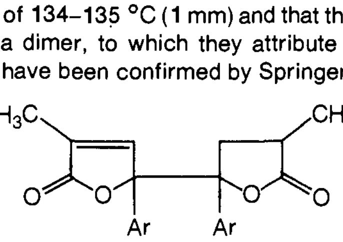
428

The compound α-methyl-γ-phenyl-$\Delta^{\alpha,\beta}$-butenolide has been reported by Ramirez and Rubin[788] to melt at 223 °C. Schreiber and co-workers[604] reported that the $\Delta^{\alpha,\beta}$ isomer is a liquid with a boiling point of 134–135 °C (1 mm) and that the 223° melting compound is a dimer, to which they attribute structure **430**. These results have been confirmed by Springer.[906]



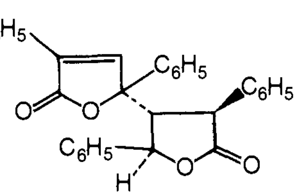
429

(γ-methyl-α(γ-methyl-β-butanolide)-$\Delta^{\alpha,\beta}$-butenolide)

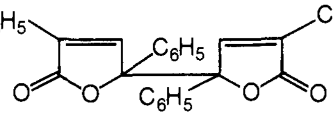


430

The compounds α,β-diphenyl-$\Delta^{\alpha,\beta}$-butenolide and α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide have been converted to dimers. The diphenylbutenolide gives two types of dimers **431** and **432**,



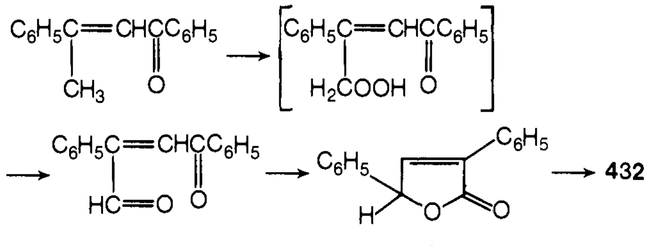
431

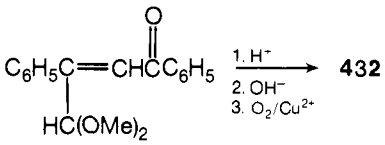


432

Compound **431** is obtained from the diphenyl butenolide by treatment with potassium hydroxide in methanol.[818] The hexaphenylphenyl analog of **431** could not be prepared, possibly because of steric hindrance of the phenyl groups. Oxidation of **431** gives **432**. Compound **432** is obtained by treatment of the triphenyl butenolide with potassium hydroxide in methanol followed by oxidation with potassium ferricyanide.[819] Oxidation of the enolate of α,β,γ-triphenyl-$\Delta^{\alpha,\beta}$-butenolide with $K_3Fe(CN)_6$ gives the hexaphenyl analog of **432**.[820]

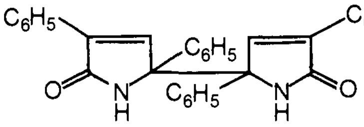
Compound **432** has been prepared by Volger and co-workers[998] from dypnone by treatment with cupric acetate in methanol containing pyridine and triethylamine while oxygen gas is bubbled through the reaction mixture. Under similar conditions, isomesityl oxide gives tetramethyl analog of **432**.[998,999] These authors also reported the conversion of β-benzoyl-α-phenylacrolein dimethyl acetal to **432** by acid hydrolysis followed by the cupric acetate catalyst oxidation. Compound **432** is also obtained by oxidation of α,γ-diphenyl-$\Delta^{\alpha,\beta}$-butenolide.[998] It may be





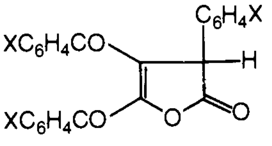
$$C_6H_5\underset{\displaystyle HC(OMe)_2}{C}{=}CH\overset{\displaystyle O}{\overset{\|}{C}}C_6H_5 \xrightarrow[2.\ OH^-\ \ 3.\ O_2/Cu^{2+}]{1.\ H^+} 432$$

pointed out that when the oxidation of dypnone is carried out in the presence of sodium methoxide, ammonia, and cupric amine–methoxide complexes, the product obtained is **433**.[1000]



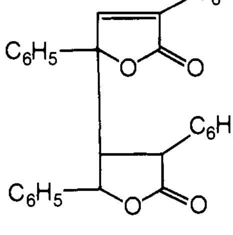
433

Compound **432** was prepared by Yates and Clark[1056] by the thermal decomposition of α-diazoacetophenone in dodecane at 140° in the dark for 12 h in 24% yield. Compound **432** was formulated as a dilactone containing $\Delta^{\alpha,\beta}$-lactone moieties. Wasserman and coworkers reported that the high-melting isomer obtained by the dehydration of α-phenyl-β-benzoylpropionic acid is dimeric and gave it the structure **432.** The photolysis of α-diazoacetophenone (**434**) also gave an 8% yield of **432**.[1029] This compound was also isolated by Strzelecka and coworkers in 9 to 17.3% yield by heating **434** and formulated as β,γ-diphenyl-$\Delta^{\beta,\gamma}$-butenolide, which it was supposed to be for a long time. Hammond and coworkers isolated **432** by the photolysis of **434** in solution.[244] Huisgen and coworkers isolated **432** by heating **434** in benzonitrile.[487,488] The silver salt catalyzed decomposition of α-diazoacetophenone has been studied by Takebayashi, Ibata, and co-workers. These authors reported the isolation of the dilactone, but they formulated it as a $\Delta^{\beta,\gamma}$-butenolide dilactone.[944-947] Since the melting point is reported to be 288–290 °C, it is quite likely that Takebayashi and Ibata's formulation of **432** as a $\Delta^{\beta,\gamma}$-lactone may be in error. As pointed out earlier, Ried and coworkers reacted diazo ketones with ketenes and isolated $\Delta^{\beta,\gamma}$-butenolides only.[811-815] This reaction was employed by Yates and co-workers[1058] and also by Kende.[540] When copper phthalocyanine was used as a catalyst in the decomposition of diazoacetophenone, the product obtained is **435**.[948]

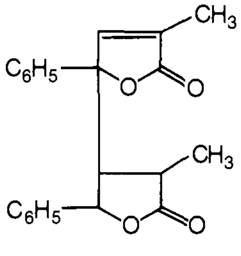


435

It should be pointed out that Yates and Clark[1056] isolated α,α,γ-triphenyl-$\Delta^{\beta,\gamma}$-butenolide when diphenylketene is added to α-diazoacetophenone. Finally, McCoy[661] studied a series of Michael dimers and isolated two dilactones **436** and **437**. A similar dimer has been reported by Filler and Piasek.[345]



436



437

VII. Physical Properties

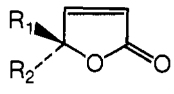
The spectral properties of butenolides have been extensively studied.

I. Infrared Spectra. The infrared spectra of β-angelica lactone in *n*-hexane, carbon tetrachloride, and chloroform have been reported. In chloroform solution the carbonyl band is split (1784 and 1759 cm^{-1}).[143] The integrated intensities of carbonyl stretching bands of β-angelica lactones have been measured in acetonitrile.[1048] Raubenheimer and DeKock correlated their HMO calculations with characteristic infrared data for the lactones.[801] Self-association of α,β-disubstituted-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolides has been studied as a function of the hydroxyl and carbonyl absorptions in the infrared.[568] The dihaloprotoanemonin derivatives show a split carbonyl group.[1038] Hydrogen bonding between lactones and solvents as *N*-methylacetamide has been studied.[800]

II. Ultraviolet Spectra. The uv spectral data of a series of hydroxybutenolides have been reported.[808] Both α- and β-hydroxybutenolides have essentially the same high intensity absorption in neutral solution (λ_{max}^{EtOH} $\sim$235 mμ). However, tetronic acids exhibit a bathochromic shift of 20–25 mμ when base is added, while the α-tetronic acids show a corresponding shift of 35–40 mμ. UV spectral data for a series of γ-arylidene-$\Delta^{\alpha,\beta}$-butenolides have been published.[1030] The uv data were employed to distinguish between pinastric and isopinastric acids.[417]

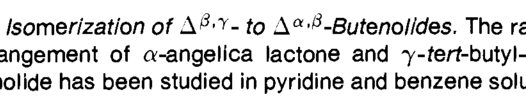
III. NMR Spectra. The τ values for the methyl groups in α- and β-angelica lactones have been measured in deuteriochloroform and benzene.[227] NMR data have been widely used in distinguishing between the $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ isomers.[661,906]

IV. Circular Dichroism Curves. Circular dichroism has been used as a means of determining the absolute configuration of butenolides.[87,983] In general, the sign of π-π^* Cotton effect is negative when the substituents $R_1 > R_2$ in polarizability and negative when $R_1 < R_2$.



V. Mass Spectra. Of all the physical methods for study of butenolides, this is by far the most widely used method. Mass spectra of $\Delta^{\alpha,\beta}$-butenolide, α- and β-angelica lactones have been studied. A double bond in the γ-lactone ring seems to give parent ions of much greater intensity than in saturated lactones.[1095] Alkyl or phenyl groups migrate from the γ position of a number of γ,γ-disubstituted $\Delta^{\alpha,\beta}$-butenolides under electron impact.[546] Mass spectra of several β- and α,β-substituted butenolides have been studied by Reinhoudt and Van de Graaf.[807] Mass spectral data for γ-methyl-γ-(2-furylmethyl)-$\Delta^{\alpha,\beta}$-butenolide have been studied.[626,1027] In all these fragmentations, cyclopropenone molecular ions have been detected. Mass spectra of tetronic acids[446] and fungal metabolites Aspertetronin A and B[73] have been determined. Carbon monoxide is eliminated in these instances. Kolsaker determined the spectra of α,β-unsaturated $\Delta^{\alpha,\beta}$-dilactones. The main feature in these spectra is consecutive carbon monoxide expulsion.[564] Ballantine and co-workers also studied the spectra α-arylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides.[75] Studies of the mass spectral fragmentations of pulvinic dilactone and pulvinic acid have also been reported.[195,616]

Microwave spectra have been employed to show that ring atoms and carbonyl oxygen are coplanar.[606] The ionization potentials of carbonyl ions pair orbitals in $\Delta^{\alpha,\beta}$-butenolides were examined, and a correlation of ionization potential shifts with changes in molecular bonding was obtained.[67] Dewar and coworkers employed heats of atomization of tautomeric forms of 2-hydroxyfuran to predict the stability of the isomeric forms of butenolides.[121] Where there is a choice between the two types of tautomerism, the $\Delta^{\alpha,\beta}$ form is favored over $\Delta^{\beta,\gamma}$.



46.514 46.631 47.180

VI. Isomerization of $\Delta^{\beta,\gamma}$- to $\Delta^{\alpha,\beta}$-Butenolides. The rate of rearrangement of α-angelica lactone and γ-*tert*-butyl-$\Delta^{\beta,\gamma}$-butenolide has been studied in pyridine and benzene solutions at different temperatures.[482]

VII. Tests for Butenolides. In addition to the Legal test[605] for identifying $\Delta^{\alpha,\beta}$-butenolides, the Baljet test is also employed.[72] Tollens reagent is also a good test for $\Delta^{\alpha,\beta}$-butenolides.

Several of these butenolides have been tested for biological activity (ref **19**, 179, **181**, 182, 203–205, 221, 274, 280–282, 318, 560, 579, 672, 715, 751, 798, 810, **841**, 972, 1023). Some butenolides have been identified in tobacco smoke, vegetable protein hydrolyzate, lignans (ref 275, 343, 523, 727, 938) in essential oils,[531] in saffron,[1066] heated glucose,[284,1011] moldy grains,[698,986] roasted filbert volatiles,[547] and volatile compounds in hops.[433] Protonanemonin has been used to prevent polymerization of acrylic acid,[436] and has been photolyzed;[931] its antibiotic activity has been discussed.[179] Ranunculin has been similarly studied.[352,353]

VIII. Addendum

This review has been updated to June **1976**.

A review on the preparation and reactions of unsaturated lactones was published in **1963**.[1200] A survey of the metal-catalyzed syntheses of lactones has also been made.[1201] Hornfeldt reviewed the tautomeric properties and reactions of thiolenones and butenolides.[1202] A recent review lists all the butenolides of marine origin.[1203] Several theses on butenolides have also been published.[1204-1206] Some recent papers on butenolides are given in ref **1311–1336**.

The remaining additional references discussed here are indexed according to the section designations in the main text.

IV.A.1. A series of 7-aryl-4,7-dioxoheptanoic acids were recently prepared. When the aryl group was 6-methoxy-2-naphthyl or 2-acetoxy-4-methoxyphenyl, treatment with cold acetic acid–concentrated sulfuric acid mixture gave $\Delta^{\alpha,\beta}$-butenolides. With boiling acetic anhydride, only $\Delta^{\beta,\gamma}$ isomers were obtained.[1207] Lactones were prepared from β-(2-phenylbenzoyl)propionic acids and reduced with $LiAlH_4$.[1208,1209] The dehydration reaction of levulinic acid to give angelica lactones was studied.[1210]

IV.A.2. A series of γ-aryl-$\Delta^{\beta,\gamma}$-butenolides with substituents in the α position have been prepared.[1211]

IV.A.6. Carbonylation of a vinyl mercurial such as (*E*)-2-chloro-3-hydroxy-**1**-propenylmercuric chloride in the presence of Pd gives 96% yield of β-chloro-$\Delta^{\alpha,\beta}$-butenolide.[1212]

In a recent paper the effect of various halide ions on the butenolide synthesis in the presence of metal carbonyls was discussed. It was observed that iodide was more effective than Br^- and Cl^- ions, and the activation effects were attributed to an equilibrium of the halide ion with $Ni(CO)_4$ to give $Ni(CO)_3X$.[1213] Reaction of iodobenzene with $Ni(CO)_4$ in the presence of styrene in THF gave a 19% yield of α,γ-diphenyl-$\Delta^{\beta,\gamma}$-butenolide. The yield improved to 25% in benzene medium.[1214] Phosphorus-substituted palladium halides were also used in lactone synthesis.[1215]

IV.A.9. Photolysis of α,β-epoxydiazomethyl ketones in benzene gave γ,γ-disubstituted or β,γ-disubstituted $\Delta^{\alpha,\beta}$-butenolides. However photolysis in benzene–methanol gave γ-hydroxy-α,β-unsaturated esters.[1216]

IV.A.10. Stecher and co-workers[1217] reported that arylidenepyruvic acids add bromine to give dibromo compounds, which tautomerize to $\Delta^{\alpha,\beta}$-butenolides. The latter serve as starting materials for the synthesis of trans α-bromocinnamic acids.

IV.A.11. The compound γ-ethyl-$\Delta^{\beta,\gamma}$-butenolide, prepared by Ogibin's method, isomerized to $\Delta^{\alpha,\beta}$-butenolide when treated with an acid.[1218]

IV.B.1. Mukaiyama and co-workers reported that α-angelica lactone reacts with benzaldehyde, hydrocinnamaldehye, and cinnamaldehyde in dichloromethane at 0 °C in the presence of BF_3–Et_2O to give γ-substituted-β-acetyl-γ-butyrolactones.[1219] With formaldehyde, α-angelica lactone gives *cis*-α-methyl-γ-butyrolactone.[1220]

IV.B.7. Reaction of **2**-chloro-5-phenyl-furan-3-aldehyde with sodium bisulfide is reported to give 5-phenyl-3-hydroxymethylene-2(3*H*)furan-2-thione.[1221]

IV.C.1.a. Dehmlow and co-workers[1222] reported that 2-methyl-3-phenylcyclopropenone reacts with cupric bromide to give the dimer, α-phenyl-β-methyl-γ-(1-(2-methyl-3-phenyl)-cyclopropenyl)-$\Delta^{\alpha,\beta}$-butenolide. Eicher et al. isolated a dilactone by reacting 2-phenylcyclopropenone with Cu^{2+} ion. This compound is obviously formed through the intermediate γ-(**1**-(2-phenyl)cyclopropenyl)-α-phenyl-$\Delta^{\alpha,\beta}$-butenolide.[1223] Eicher et al. also reacted 2-phenylcyclopropenone with enamines to give γ-spirocyclopentyl-$\Delta^{\alpha,\beta}$-butenolides.[1224] Büchi and co-workers observed that methyl 2-chloro-2,4-diphenyl-3-oxobutanoate, on decarbonylation in the presence of anhydrous sodium carbonate in xylene, gave a 5% yield of γ-methoxy-α,β-diphenyl-$\Delta^{\alpha,\beta}$-butenolide, formed via a cyclopropanone intermediate.[1225]

IV.C.8. Treatment of 3-phenylpropargyl alcohol with *n*-BuLi followed by carbonation gave α-phenyl-β-butyl-$\Delta^{\alpha,\beta}$-butenolide.[1226] Condensation 2-alkyne-**1**,4-diols with triethyl orthoacetate in the presence of catalytic amounts of pivalic acid gave various β-alkenyl-γ,γ-diaryl (or dialkyl)-butenolides.[1227]

IV.C.9. Details of preparation of **125** have been recently reported.[1228] The γ-ethyl analog of **125** has also been prepared.

IV.C.12. Tiglic acids substituted in the γ position with halides were recently prepared, and a small amount of them gave $\Delta^{\alpha,\beta}$-butenolides as impurities. These are probably formed via the isomeric angelates.[1229]

IV.C.13. An interesting synthesis of α,γ-dialkyl butenolides has been reported and consists of heating either α,β-diethylsuccinic acid or 3,4-diethylisoxazolone with nitrosylsulfuric acid.[1230] A new and improved synthesis of $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-butenolides, starting from γ-acetoxy-γ-butyrolactones, has also been reported.[1206,1231]

IV.C.17. Irradiation of pyrazole derivatives (3,3-dimethyl-5-alkyl-**1**,2-pyrazoline) in ether solution gave $\Delta^{\alpha,\beta}$-butenolides as one of several products.[1232] Oxygenation of 3,5-di-*tert*-butylpyrocatechol gave α,γ-di-*tert*-butyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide.[1233]

IV.C.19. The α-ethoxy analog of **194** has been prepared in a similar manner.[1234]

IV.C.20. Condensation of **1**,3-diketones with glyoxylic acid–amide adducts in acid medium gives α-benzamido-γ-alkyl (or aryl)-$\Delta^{\alpha,\beta}$-butenolides.[1235]

IV.C.22. Reaction of γ-butyrolactone with *N*-phenylthiophthalimide in the presence of lithium diisopropylamide gave α,α-bis(phenylthio)-γ-butyrolactone, which is converted to β-substituted butenolides.[1236] One of the products thus prepared, α-phenylsulfinyl-$\Delta^{\alpha,\beta}$-butenolide,[1237] can undergo Michael addition with the enolates of cyclopentanone, 2-ethoxycarbonylcyclohexanone, and ethyl *n*-valerate to give β-substituted butenolides.[1238] Sulfur-containing compounds were also employed in lactone synthesis.[1239,1240] Yoshikoshi and co-workers used β-vinylbutenolide for Michael additions.[1241] Triethyl phosphite is reported to isomerize α-arylidenebutyrolactone to α-arylmethyl-$\Delta^{\alpha,\beta}$-butenolide.[1242]

Dehydrohalogenation of β,γ-dichloropropionic acid or β-chlorobutyrolactone reportedly yields γ-crotonolactone.[1243]

IV.C.24. The required 3,5,5-trisubstituted furanones were prepared by the reaction of potassium phenylacetate with α-bromo-substituted aldehydes in the presence of **18**-crown-6 and ring closure of the intermediate ester.[1244,1245] α,β,γ-Triaryl-substituted lactones were prepared starting from the corresponding γ-keto acids and converted to triarylfurans with diisobutylaluminum hydride.[1246,1247]

IV.C.30. It has been observed that derivatives of blocked 2-oxocycloheptaneacetic acids rearrange in the presence of BF_3–Et_2O or acetic acid or acetic anhydride to give spiro $\Delta^{\alpha,\beta}$-butenolides.[1248] It was also reported that 2-phenylcyclohexanone-2-acetic acid also undergoes dehydrative rearrangement in the presence of polyphosphate or sulfuric acids to give a spiro butenolide.[1249] Michael addition of nitroolefins to cyclohexane-1,3-dione and analogs gave 3-substituted-6,7-dihydro-2-hydroxyiminobenzofuran-4(5*H*)-ones.[1250]

IV.D.2. A general method for the synthesis of γ-arylidene-α-aryl-$\Delta^{\alpha,\beta}$-butenolides in 70–85% yields starting from arylacetic acids and α-bromocinnamaldehydes has recently been reported.[1251] Schultz and Yee reported that 3-pentanone and dibenzyl ketone condense with diethyl ketomalonate in a mixture of P_2O_5 and methanesulfonic acid to give α-carbalkoxy-γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides.[1252]

IV.F. A new $\Delta^{\alpha,\beta}$-butenolide has been isolated from *Solidago serotina*.[1253] Several $\Delta^{\alpha,\beta}$-butenolides related to *cis*-clerodane were useful in characterizing several new diterpenoids.[1254,1255] The sponge *Spongia officinalis* also yielded several $\Delta^{\alpha,\beta}$-butenolides.[1256] The bicyclic diterpene lactone, Wightionolide, was isolated and characterized.[1257] Chemical reactions of Peridinin, an algal carotenoid, have been reported.[1258] A series of sesquiterpene lactones were isolated from *Athanasia* by Bohlmann and Grenz.[1259] The acetylenic sesquiterpene "Freelingyne", which has been synthesized earlier by Massy-Westropp and co-workers,[1197,1198] has been synthesized recently by Pattenden and Knight.[1260-1262] Strigol, a seed germination stimulant, has been isolated and characterized by Cook et al.[1263,1264] and has recently been synthesized.[1265,1266] Strigol analogs were also prepared by coupling γ-bromo-$\Delta^{\alpha,\beta}$-butenolide with sodium enolate of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone.[1267] Naturally occurring Osmunda lactone is shown to rearrange to 5-hydroxy-2-hexen-4-olide.[1268]

Finally, Variabilin was isolated from *Ircina variabilis* and has been shown to be a naturally occurring tetronic acid.[1269]

IV.G. Several new methods for the synthesis of tetronic acids have been reported. The starting materials are halogenated β-keto esters[1270] and enaminones.[1271,1272] Tetronic acids have been directly acylated in the presence of stannic chloride to give fused heterocyclic compounds such as 2*H*-furo[3,4-*b*]pyran-4,5-diones.[1273] Condensation of 2-acetyl-5-methyltetronic acid with aromatic aldehydes in the presence of piperidine followed by reduction gave 2-(3′-arylpropionyl)-5-methyltetronic acids useful as hypotensive reagents.[1274] Tetronic acids with the hydroxyl function in the α position have been prepared by reacting mercaptans with 4-dimethylsulfuranylidene–2,3-dioxotetrahydrofuran derivatives, and their reactions with ammonia and primary amines were studied.[1275-1278] Tetronic acid derivatives have been employed in the synthesis of cephalosporin analogs.[1279] Biosynthetic pathways for tetronic acids from *Penicillium charlesii* have been proposed.[1205] Treatment of acetoxytetronic acids in toluene with polyphosphoric acid gave α-acetyltetronic acids[1280] along with the parent tetronic acids.

IV.H. The pseudo ethyl esters of β-formylacrylic acids were studied.[1281,1282]

IV.I. The products of reaction of mucohalic acids with mercaptans have been characterized. Depending on the conditions of reaction, either α-thioaryl- or α,β-dithioaryl- or γ-thioarylfuranones are obtained.[1283,1284] Several fungicides based on mucohalic acids are also reported.[1285-1288] The compound α,β-dichloro-γ,γ-difluoro-2(5*H*)-furanone has been prepared from dichloromaleic anhydride and sulfur tetrafluoride.[1289]

V.C. The products of reduction of pulvinic acid with diborane in THF has been found to be effective in treatment of arthritis.[1290] Reactions of pulvinone with sodio derivative of methyl mercaptan and thiolacetic acid were reported to give the corresponding thio analogs.[1291] Pulvinone derivatives have also been isolated recently.[1292]

VI.D. Diazoalkanes, diazo esters, and diazo ketones add to 2(5*H*)-furanones, and the adducts undergo thermal decomposition to give alkylated furanones which are reduced to furans.[1103,1293] Similar cycloaddition of diazomethane to aconic acid to give alkylated furanones has been reported earlier.[1294]

VI.J. Ollis and co-workers[1295,1296] studied the stereoselective hydrogenation of disubstituted butenolides in the presence of Pd–$BaSO_4$. In all these cases the products are γ-butyrolactones; it was observed that the cis isomers are more stable thermodynamically than the trans isomers. Reaction of γ,γ-diethyl-$\Delta^{\alpha,\beta}$-butenolide with diethylaluminum chloride followed by hydrolysis gave 4-ethyl-2,4-hexadienoic acid.[1297,1298]

VI.O. The compounds γ-crotonolactone and β-angelica lactone give adducts with isopropyl alcohol when irradiated.[1299]

VI.P. A new method for the conversion of the *E* isomers of 5-phenyl-3-phenylmethylene-2(3*H*)-furanone and its analogs to *Z* isomers has been found. This method consists of heating the *E* isomers in polyphosphoric acid[1251] at 90° for 90 min.

VI.Q. Polylactones were prepared by polymerizing γ-crotonolactone and α-angelica lactone with *n*-BuLi and β-angelica lactone with BF_3–Et_2O. Styrene and acrylonitrile were used to form copolymers of γ-crotonolactone.[1300]

VI.T. Reaction of butenolides with hydrazine were recently studied.[1301-1303] Reaction of 5-phenyl-2(3*H*)-furanone with piperidine reportedly gave a piperidide.[1304] Similar reactions of furanones with amines has also been reported.

VI.V. Bifurandiones were obtained from substituted succinyl chlorides.[1307] Pauson et al. prepared bifurandiones from butenolide–cobalt complexes derived from monosubstituted acetylenes and carbon monoxide.[1308] Spectral data (uv) for phthalylidene-$\Delta^{\beta,\gamma}$-butenolides[1309] have been published. Finally reactions of $\Delta^{\beta,\gamma}$-butenolides with hydrazines have been reported.[1310]

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Supplementary Material Available. Tables I–IX, summarizing the compounds prepared (84 pp) [$\Delta^{\beta,\gamma}$-butenolides (I), α-arylidene (alkylidene)-γ-aryl (alkyl)-$\Delta^{\beta,\gamma}$-butenolide (II), $\Delta^{\alpha,\beta}$-butenolides (III), α-aryl (alkyl)-γ-arylidene-$\Delta^{\alpha,\beta}$-butenolides (IV), naturally occurring lactones (V), tetronic acids (VI), β-acylacrylic acids (VII), dihalo butenolides (VIII), pulvinic acid derivatives (IX)] will appear following these pages in the microfilm edition of this volume of the journal. Microfiche (4 × 6 in., 24X, negative, silver halide) of the supplementary material may be ordered directly from Business Operations, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Full bibliographic citation (journal, title of article, author) and prepayment ($2.50, U.S.; $3.00, PUAS, Canada; $3.50, other foreign countries) are required.

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