

A SYNTHESIS OF γ -BUTYROLACTONE AND RELATED COMPOUNDS

Shinzo Kano*, Shiroschi Shibuya, and Tsutomu Ebata
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

Abstract Synthetic methods for γ -butyrolactone derivatives were reviewed. Contents were selected from the recent literatures.

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1. Introduction

Recently, there has been an increasingly large research devoted to developing synthetic routes to saturated and unsaturated γ -butyrolactones. This has been caused by large interests in several attractive biologically active derivatives including natural products and many of sesquiterpene tumor inhibitors possessing

α -methylene- γ -lactone structural feature, have been synthesized. Total synthesis of those natural products was always in hand before the stage of lactonization or introduction of methylene group at the α -position and much more efforts were made for a construction of complicated moieties including a stereoselective approach to the key intermediates in many cases. Although brief excellent reviews on the synthesis of unsaturated γ -lactones were published already^{1,2}, we wish to describe a general synthesis of γ -butyrolactones with references published after 1975. We wish to illustrate even a simple lactonization if it is a widely applicable reaction and/or it is the key step for a synthesis of some specific target molecules, since many facile and convenient methods for introduction of substituents or conversion to unsaturated derivatives have been well studied.

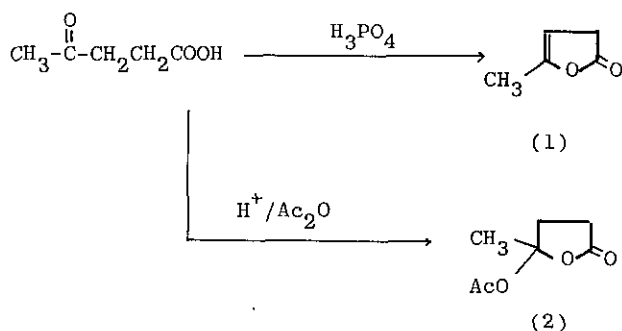
2. Lactonization of γ -hydroxy and γ -keto acids

Cyclization of γ -hydroxy and γ -keto acids is one of most typical manner for a synthesis of γ -butyrolactones and related compounds, with many of works dating back to the late 1800's². A numerous methods for the approach to γ -hydroxy and γ -keto acids have been investigated to synthesize γ -butyrolactones. For instances, following three major routes exist for this purpose.

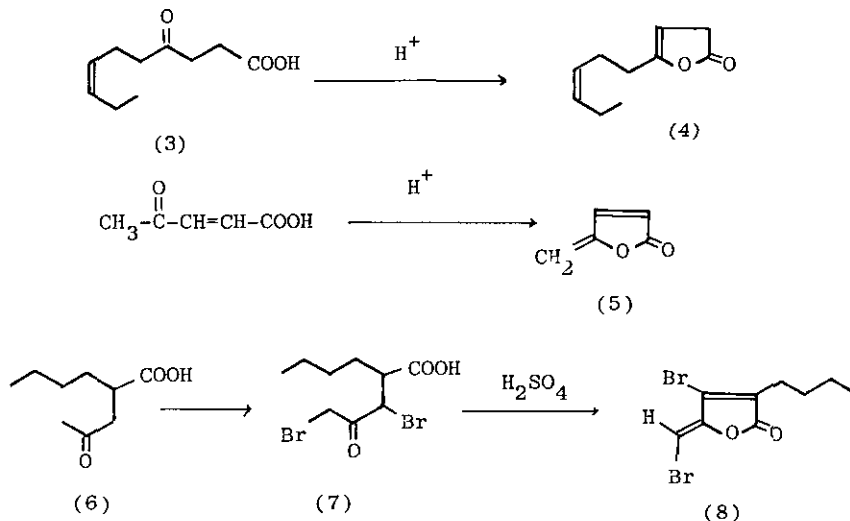
- i) Selective reduction of keto acids and hemi esters
- ii) Ring opening of epoxides with carbanionic acetate and its equivalents
- iii) The reaction of β -carbanionic propionate with ketones and aldehydes

We also wish to refer to a synthesis of some natural products possessing a γ -lactone unit accomplished through the above methods.

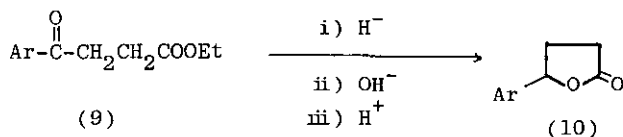
Actually, it is well known that cyclization of levullinic acid gave α -angelicalactone (1)³. Acid-catalyzed cyclization of levullinic acid in the presence of acetic anhydride afforded the acetoxy- γ -lactone (2)⁴.



Similarly, the *cis*-olefinically unsaturated γ -lactone (4), useful in perfumes, was synthesized by cyclization of the keto acid (3)⁵. Cyclization of acetyl-acrylic acid yielded the 4-methylene- $\Delta^{\alpha,\beta}$ -butenolide (5)⁶. In the course of a synthetic study of marine products possessing a γ -butyrolactone skeleton⁷, the lactone (8)⁸ was synthesized through bromination of the keto acid (6), followed by cyclization of the dibromo keto acid (7) with sulfuric acid in 28 % yield. In this reaction, sulfuric acid acted as an oxidizing agent as well as a dehydrating agent.



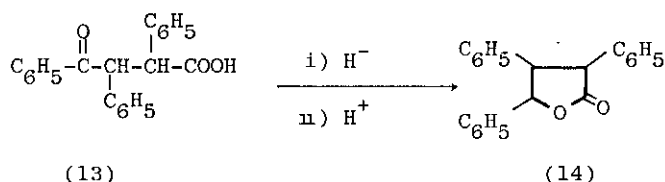
Meerwein-Pondorf reduction of ethyl β -benzoylpropionates (9), followed by hydrolysis of the γ -hydroxy esters gave 4-aryl- γ -butyrolactones (10)⁹. Similarly, reduction of the 4-oxo-(2-furanyl)butyric acid (11) with sodium borohydride, followed by lactonization afforded the butyrolactone (12), which had antiinflammatory activity^{10,11}.



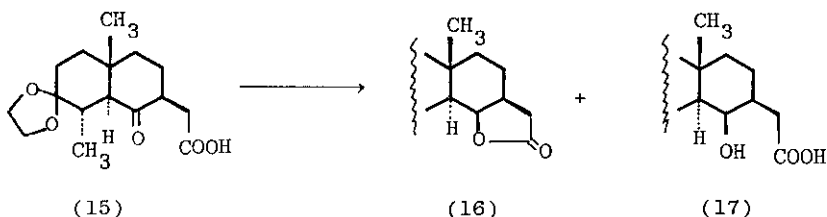
a: $Ar=4-CH_3O-C_6H_4-$; b: $Ar=3,4-(CH_3O)_2-C_6H_3-$; c: $Ar=4-n-C_4H_9-C_6H_4-$



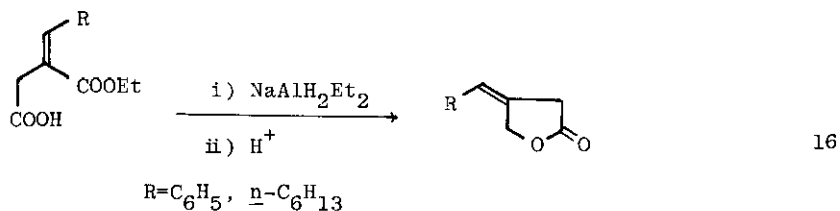
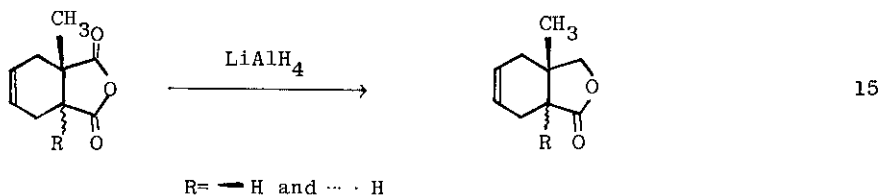
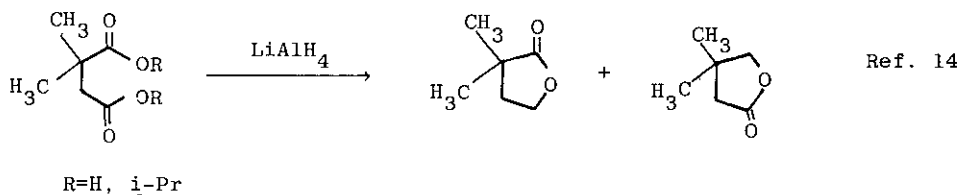
Hydride reduction of the diastereomeric keto acid (13) gave the four possible diastereomers of triphenyl- γ -butyrolactone (14)¹².

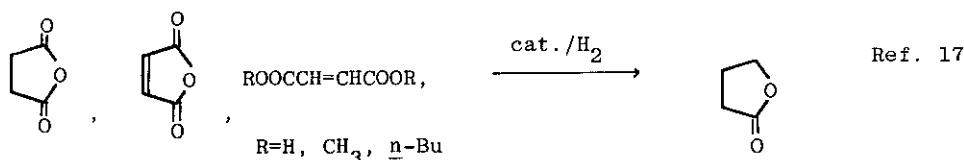


Reduction of the keto acid (15) with lithium in liquid ammonia in the presence of ammonium chloride gave the β -oriented γ -lactone (16) and the axial alcohol (17) in 69 % yield in a ratio of 43:26¹³.



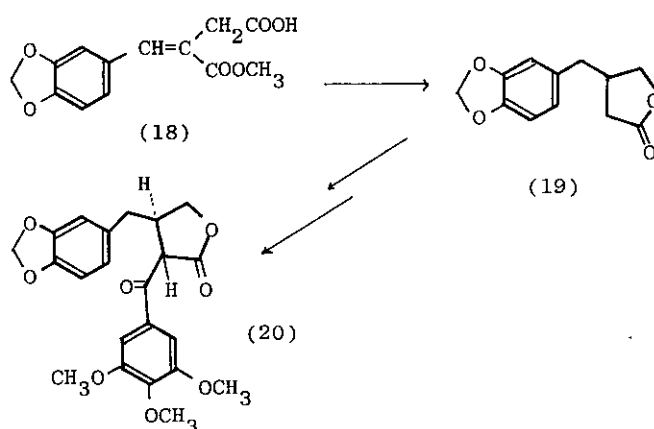
Reduction of succinic acid, maleic acid and fumaric acid derivatives is also effective for a synthesis of γ -butyrolactones. Some of works are illustrated below.



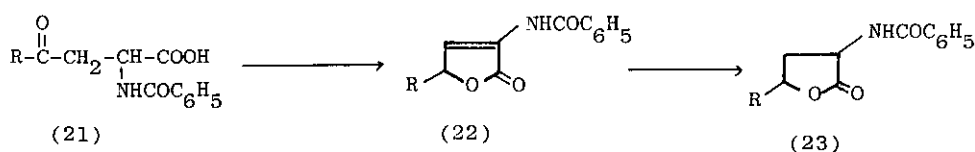


cat. = SiO_2/Au , SiO_2/Pd , CuAl , $\text{SiO}_2/\text{Cu-Al}$, $\text{SiO}_2/\text{Ag-Pd}$

Reduction of the hemi ester (18) with calcium borohydride (prepared by mixing sodium borohydride with calcium chloride), followed by the standard work-up yielded the lactone (19), which was the key intermediate for the synthesis of ($\pm$)-podorhizone (20)¹⁸.



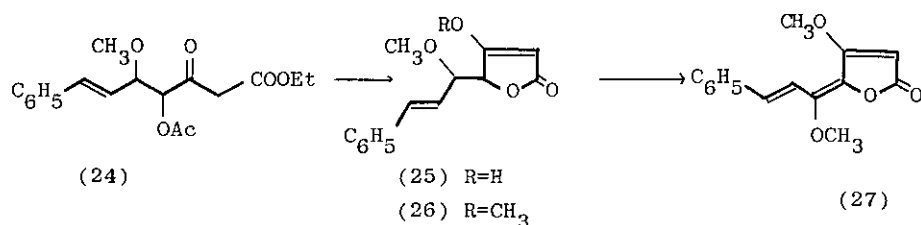
Cyclization of the benzamide of γ -keto- α -amino acids (21a) and (21b) with 10 % sulfuric acid-acetic acid afforded the $\Delta^{\alpha,\beta}$ -butenolides (22a) and (22b), respectively. Catalytic hydrogenation of (22) over Pd-C gave the saturated γ -butyrolactones (23a) and (23b)¹⁹.



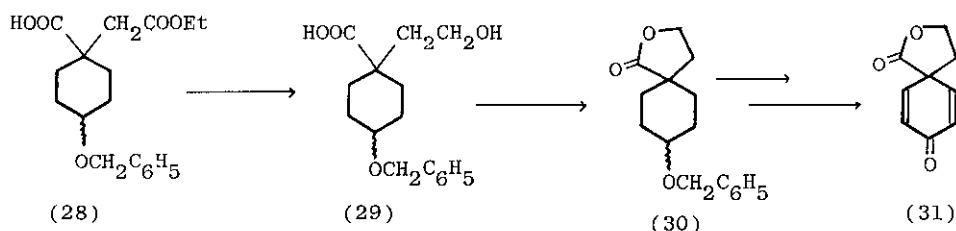
a: R=CH_3 ; b: $\text{R=C}_6\text{H}_5$

Treatment of the ester (24) with sodium methoxide in methanol at room temperature afforded the lactone (25), methylation of which with methanolic hydrochloric acid gave the methyl ether (26). Dehydrogenation of (26) with dichloro-

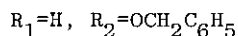
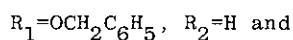
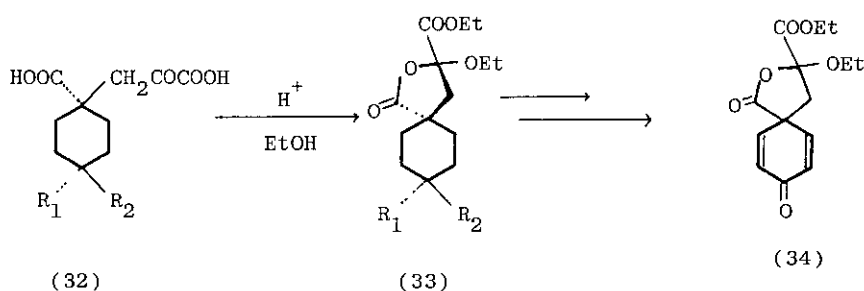
dicyanoquinone yielded piperolid (27)²⁰.



In order to prepare the cyclohexadienone derivative (31), the ester (28) was subjected to a partial reduction with lithium borohydride to give the alcohol (29). Cyclization of (29) with *p*-toluenesulfonic acid gave the spiro lactone (30), which was converted to the dienone (31)²¹.



The similar cyclohexadienone spiro lactone (34) was also obtained through the lactone (33), prepared by acid-catalyzed cyclization of the keto diacid (32) in the presence of ethanol²².

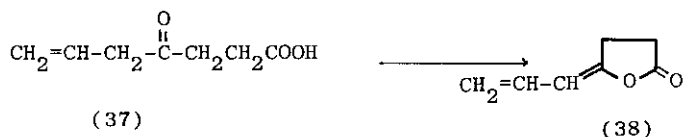


Tetronic acid (36a) was easily obtained by treatment of γ -hydroxy ester (35a) with perchloric acid. In a similar manner, the tetronic acids (36b)-(36d) were also obtained from the corresponding esters²³.

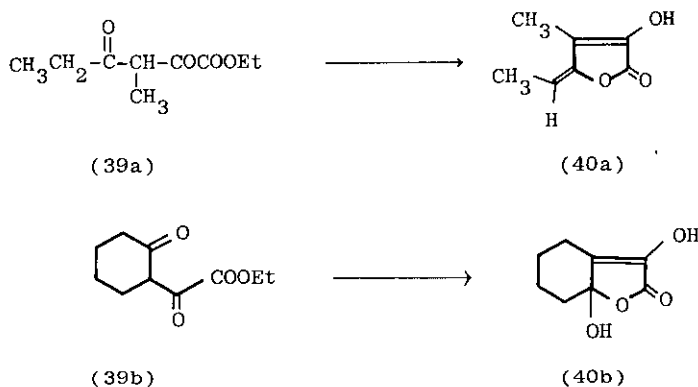


a: R=CH₃; b: R=C₆H₅; c: R=CH(CH₃)₂; d: R=n-Bu

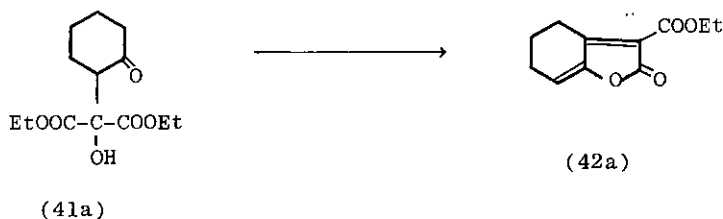
Cyclization of the γ -keto acid (37) gave the conjugated γ -methylene lactone (38)²⁴.

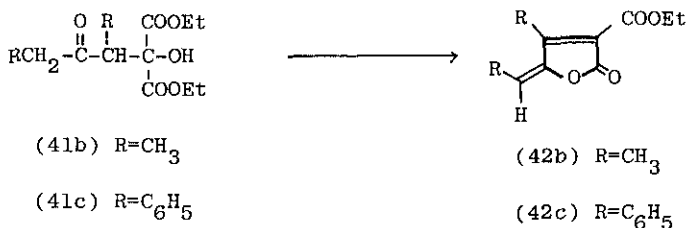


Cyclization of the α,γ -diketo ester (39a) gave the γ -methylene- $\Delta^{\alpha,\beta}$ -butenolide (40a), whereas ethyl (2-oxocyclohexyl)glyoxalate (39b) gave the benzofuranone derivative (40b)²⁵.

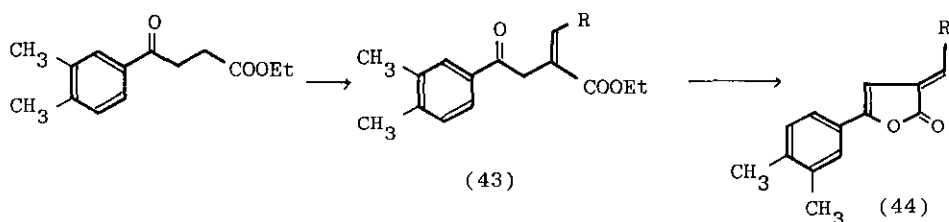


The diester (41a), prepared by condensation of pyrrolidine enamine of cyclohexanone with diethyl ketomalonate, was treated with phosphorus pentoxide in methanesulfonic acid to give the benzofuranone derivative (42a). In a similar fashion, the γ -methylene- $\Delta^{\alpha,\beta}$ -butenolides (42b) and (42c) were obtained from the diesters (41b) and (41c), respectively²⁶.



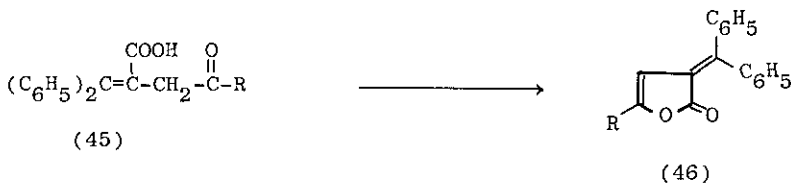


Following illustration is a synthesis of α -alkylidene- $\Delta^{\beta,\gamma}$ -butenolides. Condensation of ethyl β -(3,4-dimethylbenzoyl)propionate with benzaldehydes gave the α -benzylidene derivatives (43a)-(43c), treatment of which with sodium ethoxide in ethanol yielded (44a)-(44c), respectively²⁷.



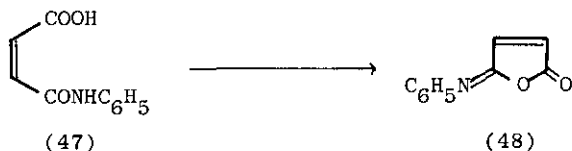
a: $\text{R} = \text{C}_6\text{H}_5$; b: $\text{R} = 4\text{-CH}_3\text{O-C}_6\text{H}_4$; c: $\text{R} = 3,4\text{-(OCH}_2\text{O)-C}_6\text{H}_3$

Cyclization of β -carbamoyl acids was also investigated. Treatment of the carboxylic acids (45a)-(45d) with acetic anhydride-perchloric acid gave the corresponding isoimidium perchlorates, deprotonation of which yielded the α -alkylidene- γ -amino- $\Delta^{\beta,\gamma}$ -butenolides (46a)-(46d), respectively²⁸.

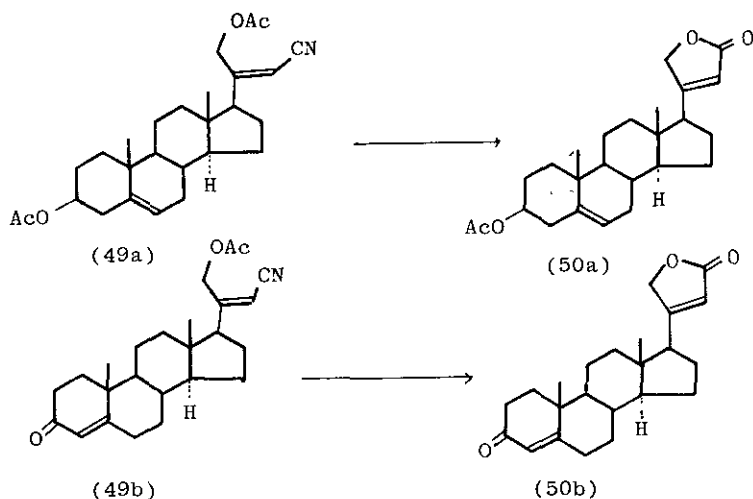


a: $\text{R} = \text{NEt}_2$; b: $\text{R} = \text{NHC}_6\text{H}_5$; c: $\text{R} = \text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array}$; d: $\text{R} = \text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \end{array}$

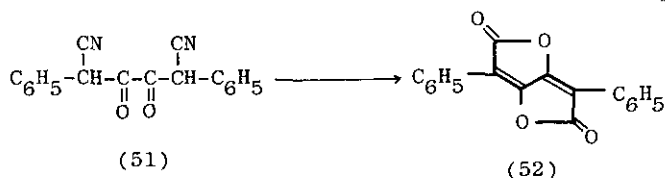
Maleinic monoamide (47) was treated with ketene in the presence of acetic anhydride to give the iminofuranone (48)²⁹.



Hydroxyacrylonitriles and amides were also used for a synthesis of $\Delta^{\alpha,\beta}$ -butenolides. The acidic cyclization of (49a) and (49b) with *p*-toluenesulfonic acid gave the corresponding 14 α -cardenolides (50a) and (50b), respectively³⁰.



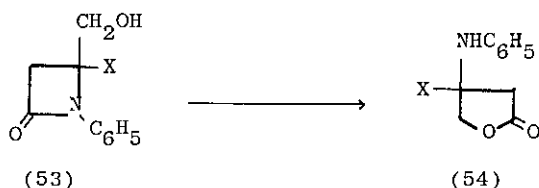
Cyclization of the nitrile (51), obtained by condensation of diethyl oxalate with benzyl cyanide, yielded the lactone (52)³¹.



Hydrolysis of (S)-(-) and (R)-(+)-4-hydroxydodecanitrile gave, after work-up under acidic conditions, (S)-(+)- γ -*n*-octyl- γ -lactone and (R)-(-)- γ -*n*-octyl- γ -lactone, respectively³².

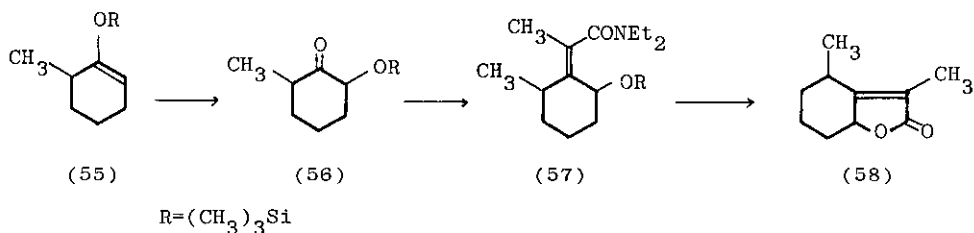


Treatment of 4-(hydroxymethyl)- β -lactams (53a) and (53b) with methanesulfonic acid in benzene afforded β -anilino- γ -butyrolactones (54a) and (54b), respectively^{33,34}.

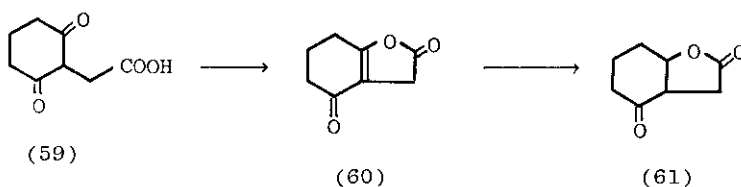


a: X=H; b: X=COOEt

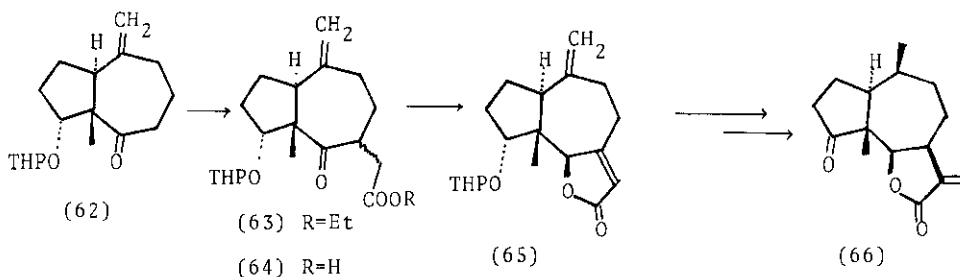
The ketone (56), obtained by oxidation of (55) with *m*-CPBA, was reacted with 1-diethylaminopropyne to give the amide (57), which upon treatment in acetone underwent ring closure yielding the lactone (58)³⁵.



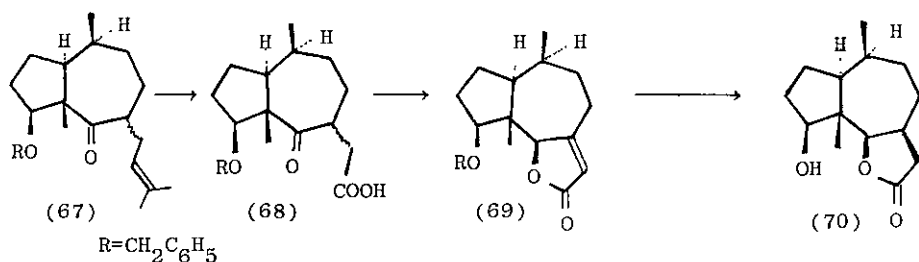
Carboxymethylation of ketones or hydroxymethylation of acids are often used for a synthetic approach to γ -butyrolactone derivatives. Carboxymethyl-1,3-cyclohexadione (59) was heated in acetic anhydride to give the enol lactone (60), which was hydrogenated to afford the saturated lactone (61)³⁶.



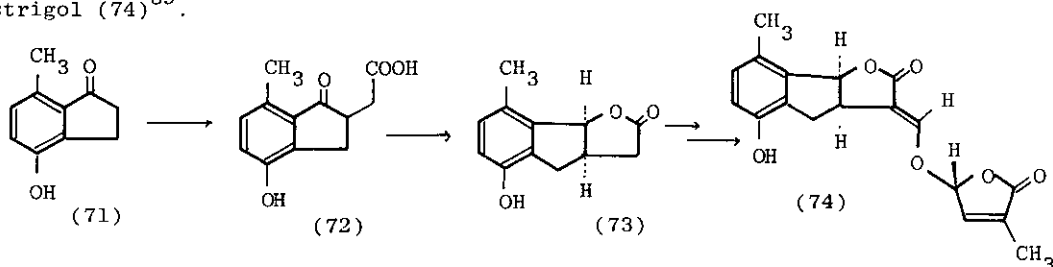
Ring closure of the keto acid (64), obtained by the reaction of lithiated ketone (62) with ethyl bromoacetate, followed by hydrolysis of the keto ester (63), afforded the butenolide (65), which was the key intermediate for a synthesis of ($\pm$)-damsin (66)³⁷.



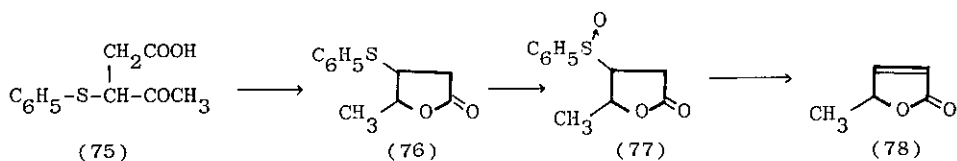
The keto acid (68), obtained by the cleavage of the prenyl double bond of (67) in a straightforward manner with ozone, followed by Jones oxidation, was cyclized with sodium acetate-acetic anhydride to give the butenolide (69). Catalytic hydrogenation of (69) over 5 % Pd-C afforded the *cis*-fused tricyclic lactone (70)³⁸.



Carboxymethylation of the ketone (71) with bromoacetic acid, followed by reduction of the resulting keto acid (72) with sodium borohydride gave the lactone (73), which was the key intermediate for the synthesis of the aromatic analogue of strigol (74)³⁹.

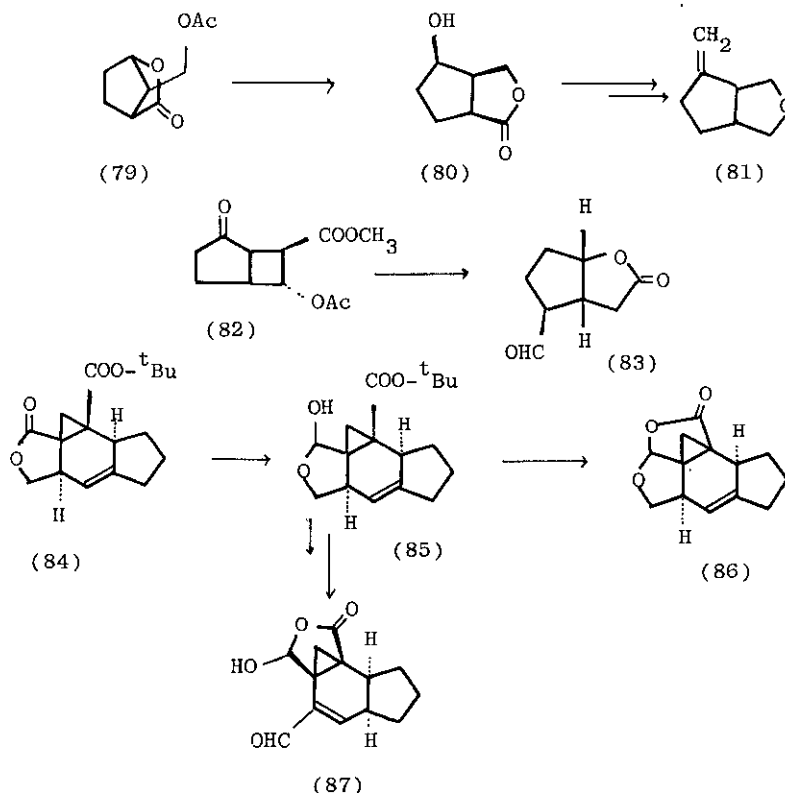


Carboxymethylation of phenylthioacetone with iodoacetic acid, followed by reduction of the acid (75) gave the lactone (76). Thermal decomposition of the sulfoxide (77) yielded the butenolide (78)⁴⁰.

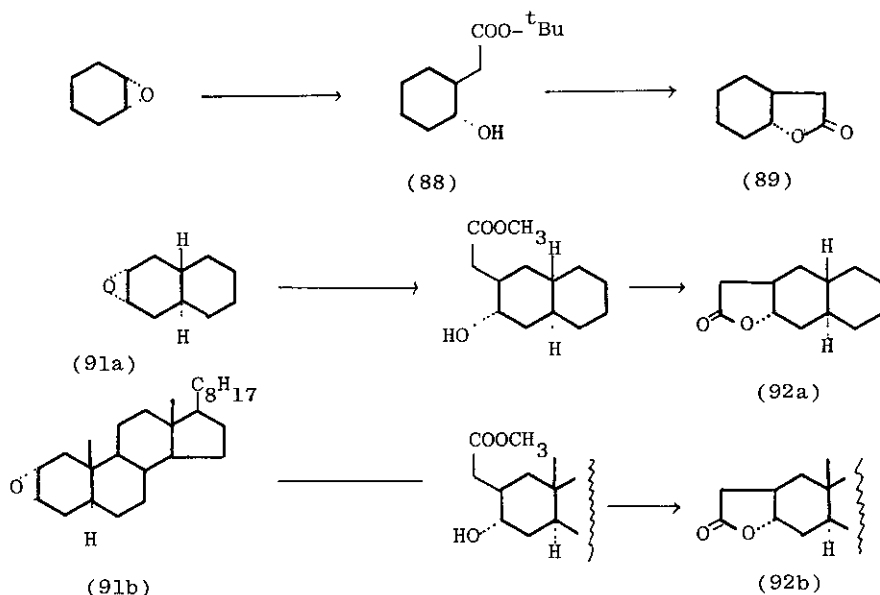


The lactone (80), the key intermediate for a synthesis of hop ether (81), was easily obtained through hydrolytic recyclization of (79)⁴¹. Reduction of the bicyclo keto ester (82) with sodium borohydride and sequential treatment with methanolic potassium hydroxide afforded the lactone (83)⁴², which was the 1-deoxy-prostaglandin intermediate. Similar lactonization was seen in the course of the total synthesis of (+)-marasnic acid. Reduction of (84) with diisobutylaluminum

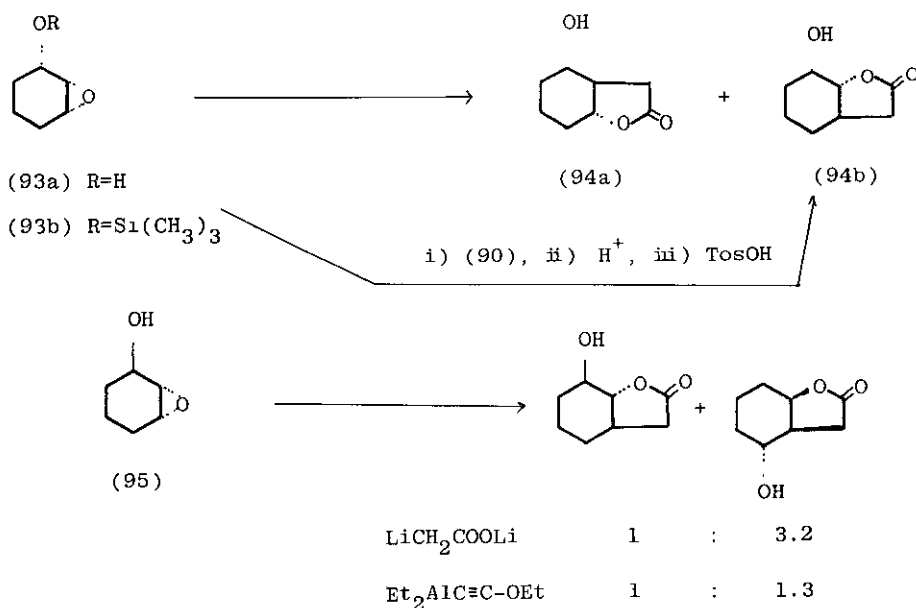
hydride gave the hemiacetal (85), which was easily converted to the hemiacetal (86) by exposure to trifluoroacetic acid⁴³. The hemiacetal (85) was converted to (+)-marasnic acid (87).



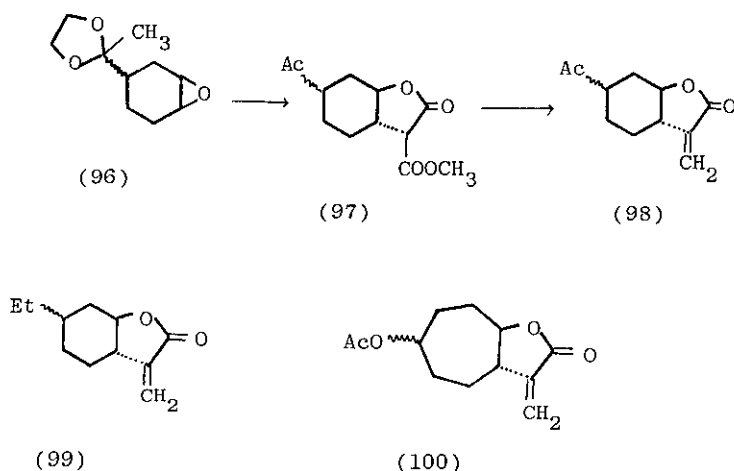
As seen in these illustrations, lactonization of hydroxy acids should be treated as an excellent procedure in all cases, if they were easily available. Cleavage of epoxides with carbanionic acetate or its equivalents has been examined for this purpose. The reaction of cyclohexene oxide with *t*-butyl lithioacetate afforded the hydroxy ester (88), which was cyclized to the lactone (89)⁴⁴. The yield of (88) raised by the use of diethyl-*t*-butoxycarbomethylalane ($\text{Et}_2\text{AlCH}_2\text{COO-}t\text{-Bu}$). For the purpose of ring opening of hindered epoxides, diethylethoxyethynylalane (90), $\text{Et}_2\text{AlC}\equiv\text{C-OEt}$, was employed as the effective carbanionic acetate equivalent. Thus, the reaction of the epoxides (91a) and (91b) with (90), followed by alcoholysis and ring-closure afforded the corresponding γ -butyrolactones (92a) and (92b), respectively.



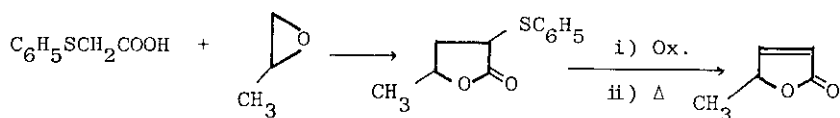
These reactions were extended to the ring opening of α -oxygenated epoxides. The reaction of the cis-hydroxy epoxide (93a) and its silyl ether (93b) with dilithioacetate gave a mixture of (94a) and (94b), after cyclization of the reaction intermediates with p-toluenesulfonic acid, in a 3:1 ratio. However, the same reaction by the use of (90) instead of dilithioacetate gave exclusively (94b)⁴⁵. Ring opening of the epoxide (95) was also investigated⁴⁵.



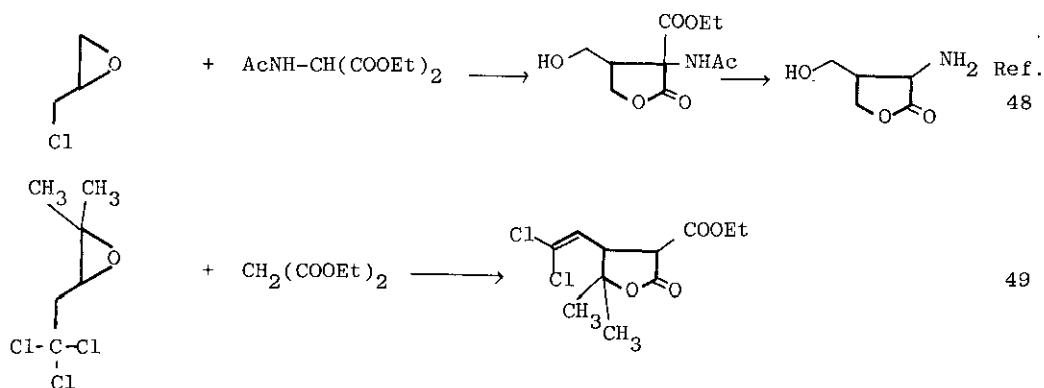
Treatment of the epoxide (96) with dimethyl sodium malonate in methanol and successive work-up under hydrolysis conditions gave the lactone (97), which was converted to the α -methylene- γ -lactone (98). In a similar way, the lactones (99) and (100) were also prepared⁴⁶.

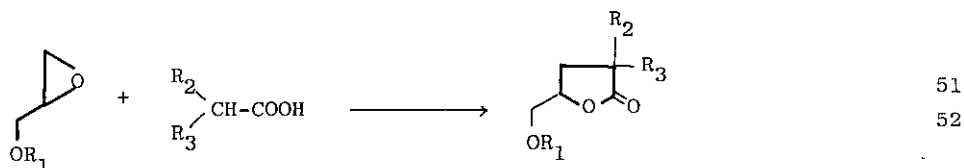
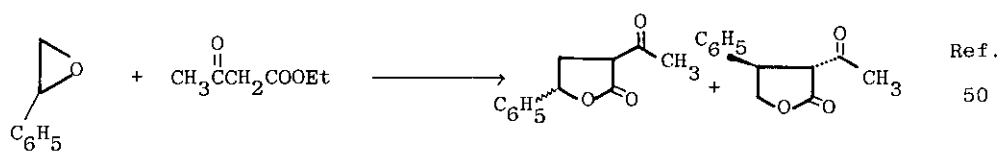


The reaction sequences of the reaction between dianion of phenylthioacetic acid and propene oxide yielding α -phenylthio- γ -butyrolactones provide a general method for a synthesis of a variety of $\Delta^{\alpha,\beta}$ -butenolides⁴⁷.

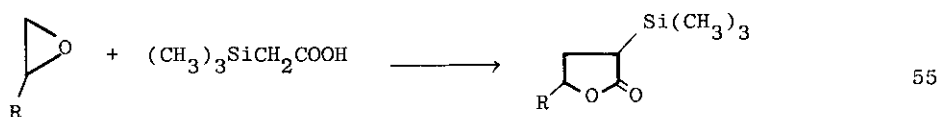
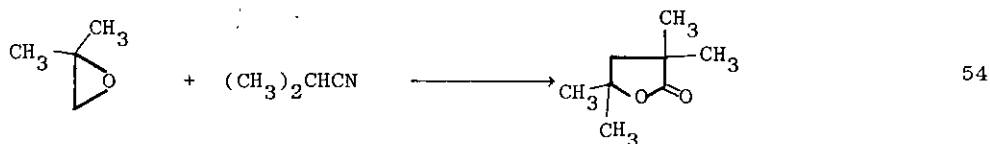
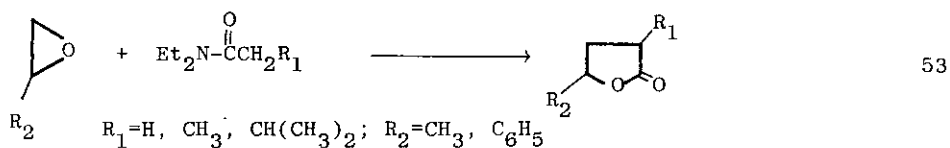


Similar typical illustrations are shown below.

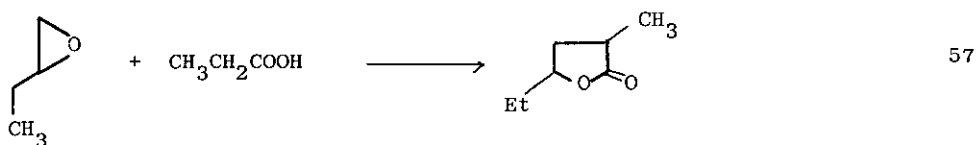
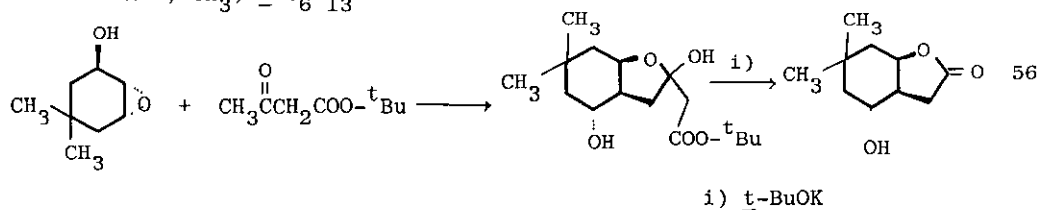


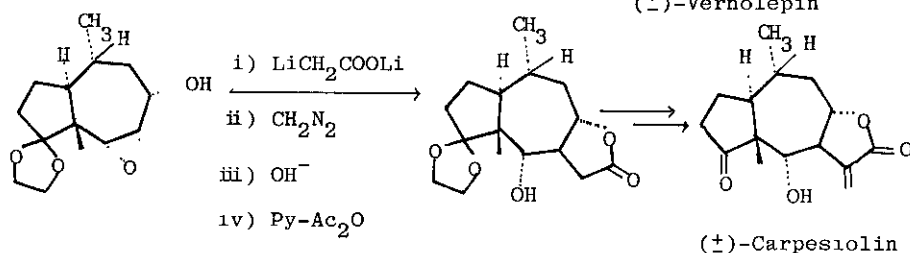
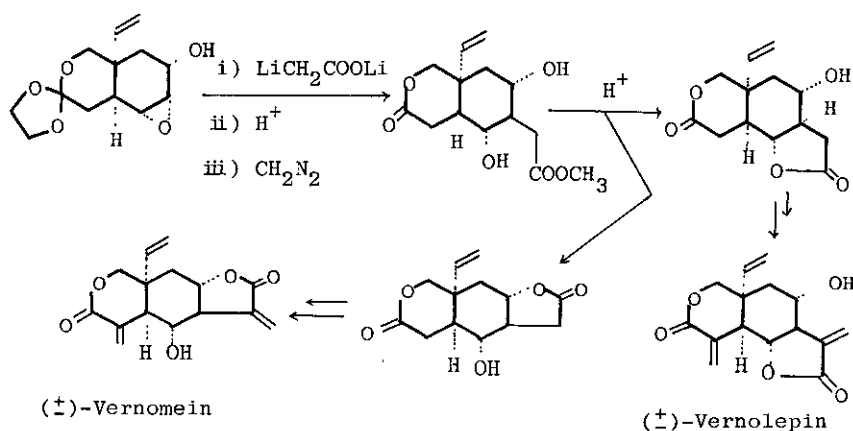
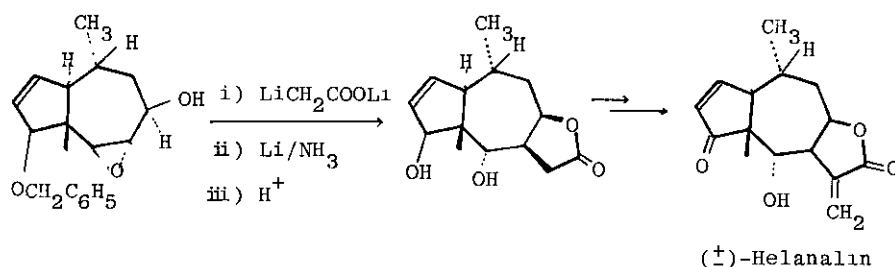


$\text{R}_1 = \text{C}_6\text{H}_5, \text{ allyl, Bu}; \text{R}_2 = \text{H, CH}_3; \text{R}_3 = \text{H, CH}_3, \text{ Et, Pr}; \text{R}_2\text{---R}_3 = \text{---}(\text{CH}_2)_5\text{---}$

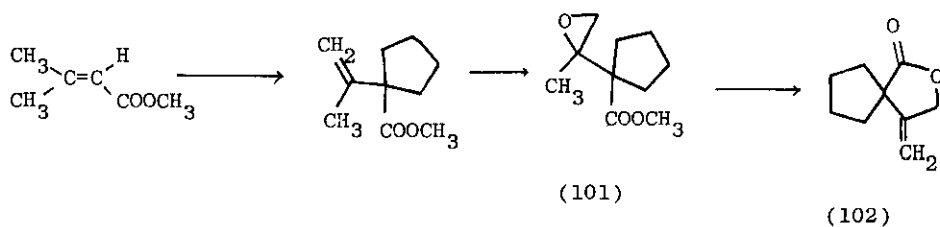


$\text{R} = \text{H, CH}_3, \text{ n-C}_6\text{H}_{13}$



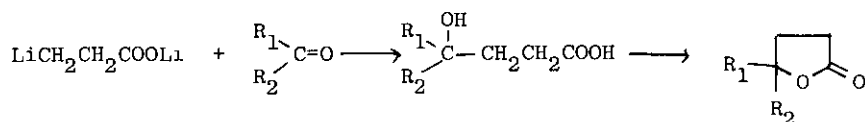


In the above cases, epoxides behave as an electrophile whereas in the following illustration, epoxide acts as a nucleophile. Lactonization of the epoxy ester (101), obtained through condensation of methyl methacrylate with tetramethylene bromide and following epoxidation of β,γ -unsaturated ester, afforded the spiro- β -methylene- γ -butyrolactone (102)⁶¹.



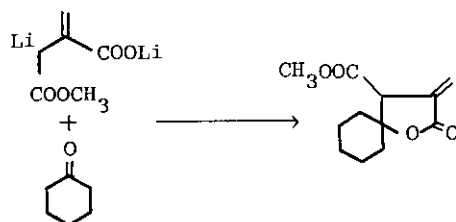
γ -Hydroxy acids can be easily obtained by the reaction of lithium β -lithio-propionate, obtained from β -bromopropionic acid, with aldehydes or ketones. These

acids underwent cyclization with p-toluenesulfonic acid to the corresponding γ -butyrolactones⁶².

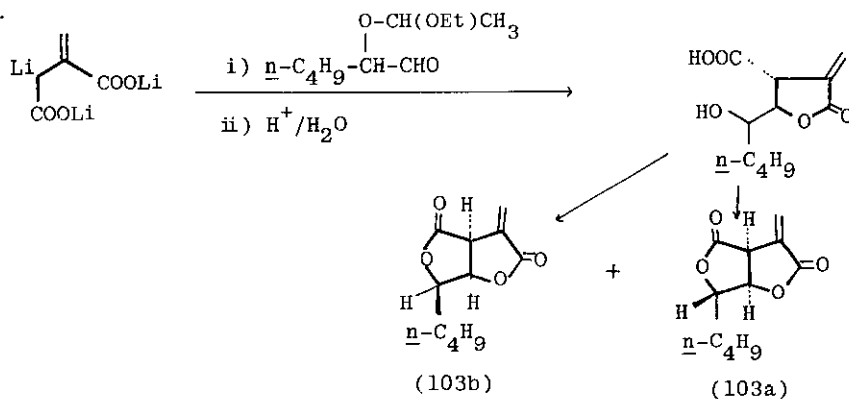


R_1	R_2
1 ---Pr	H
2 C_6H_5	CH_3
3 $\text{n-C}_6\text{H}_{13}$	CH_3
4 $\text{---}(\text{CH}_2)_4\text{---}$	
5 $\text{---}(\text{CH}_2)_5\text{---}$	

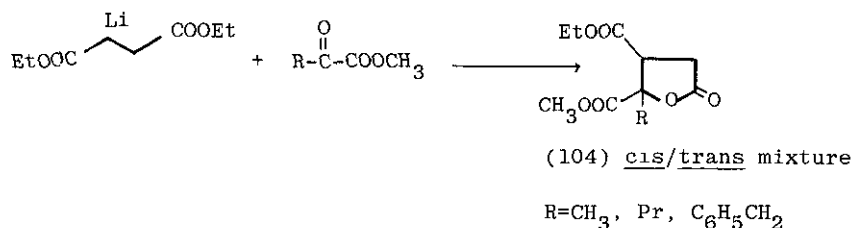
The reaction of dianion of itaconic acid monoester or trianion of itaconic acid with aldehydes or ketones provides a direct method for a preparation of α -methylene- γ -lactones^{63,64}. One example is illustrated below.



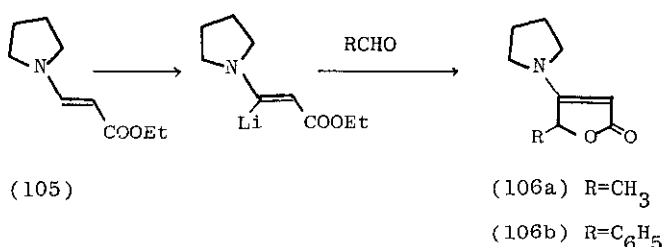
Canadenosolid (103a) and epi-canadenosolid (103b) were prepared by this method⁶³.



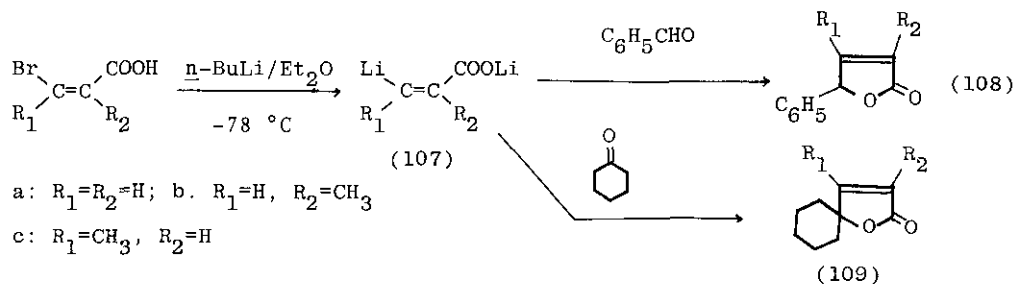
Condensation of diethyl lithiosuccinate with α -keto esters afforded γ -butyrolactone 3,4-dicarboxylate (104)⁶⁵.



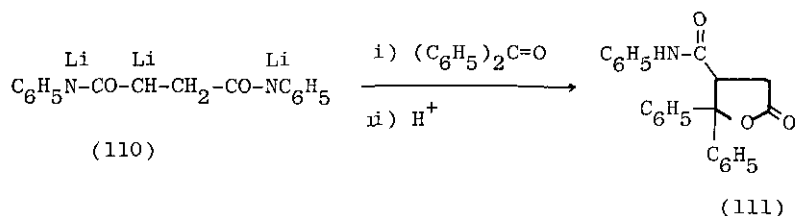
The lithio salt of ethyl 3-pyrrolidinylpropenoate (105), obtained by treatment of (105) with *t*-butyllithium in tetrahydrofuran at -113 °C, was used for a direct synthesis of the pyrrolidino- $\Delta^{\alpha,\beta}$ -butenolides. Thus, γ -methyl (106a) and γ -phenyl derivative (106b) were obtained⁶⁶.



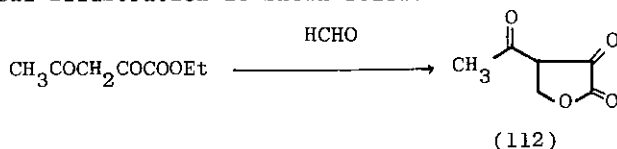
Following reaction is useful for a synthesis of γ,γ -disubstituted $\Delta^{\alpha,\beta}$ -butenolides. The reaction of lithiated carboxylate (107) with benzaldehyde and cyclohexanone afforded (108) and (109), respectively⁶⁷.



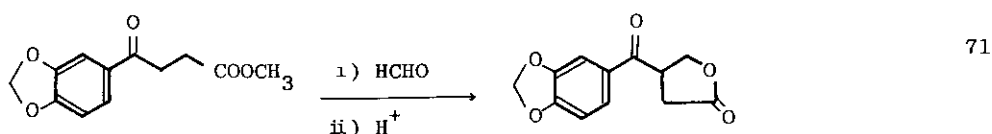
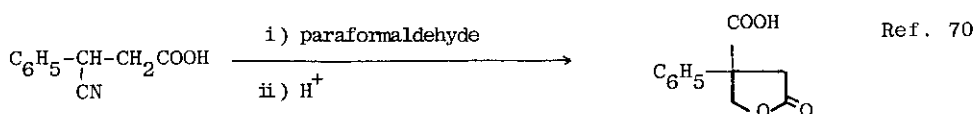
Condensation of 1,3,6-trilithiosuccinanilide (110) with benzophenone gave the lactone (111), after work-up under acidic conditions⁶⁸.



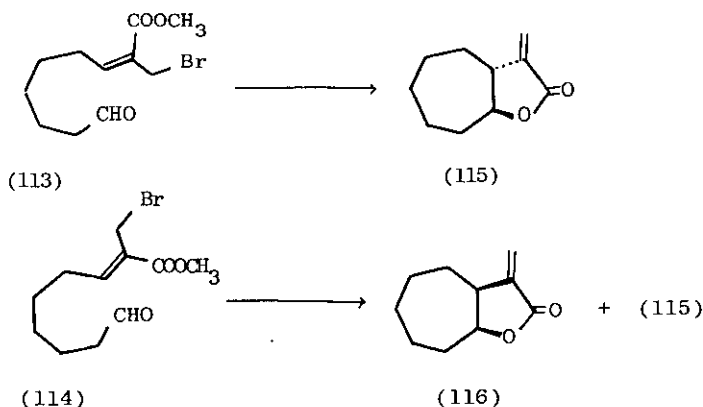
In the course of the study of a method for a synthesis of α,β -unsaturated carbonyl compounds, β -acyl- α -keto- γ -lactones such as (112), precursors of α -methylene ketones, were synthesized by hydroxymethylation of α,γ -diketo esters⁶⁹. A typical illustration is shown below.



Some γ -butyrolactones possessing negative group at the β -position were synthesized through hydroxymethylation-cyclization procedure.



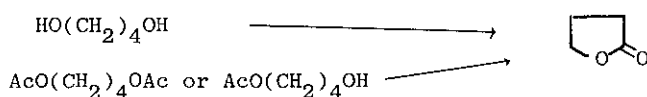
The Reformatsky type reaction of the methyl bromomethacrylate derivative (113) by the use of zinc dust or zinc/copper couple gave *cis*-fused α -methylene- γ -lactone (115). In the case of the same reaction of *E*-isomer (114) yielded a mixture of (115; 46 %) and (116; 12 %)⁷².



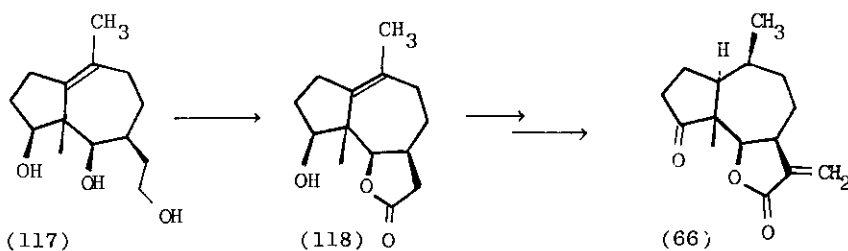
3. Oxidative lactonization of diols

Oxidative cyclization of tetramethylene glycols is sometimes used for a synthesis of γ -butyrolactone derivatives. The reaction would proceed, most possibly, via oxidation of lactol intermediates.

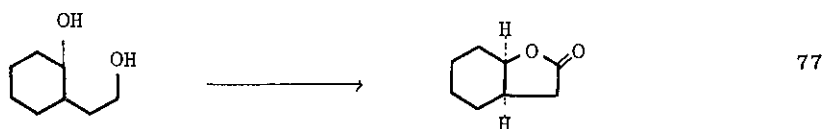
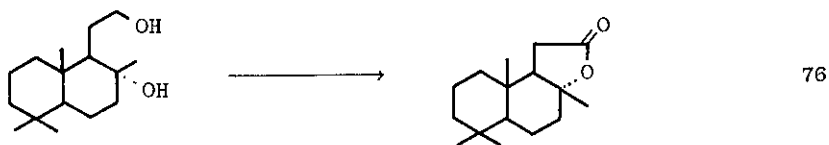
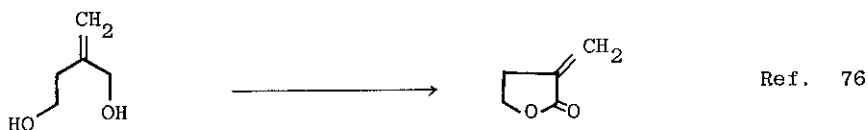
Catalytic oxidation of tetramethylene glycol in the presence of In, Tl, Ga, Al or Zn at 545 °C gave γ -butyrolactone⁷³. γ -Butyrolactone was also obtained by passing a stream of hydrogen, tetramethylene glycol diacetate or monoacetate and methanol at 190–200 °C in the presence of copper chromite-magnesia catalyst containing magnesium oxide, magnesium hydroxide and manganese mono-oxide⁷⁴.

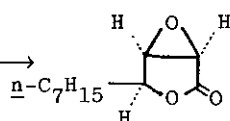
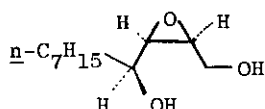


Catalytic oxidation of the diol (117) under atmosphere of oxygen in the presence of platinum catalyst afforded the lactone (118), which was the key intermediate for the total synthesis of (+)-damsin (66)⁷⁵.



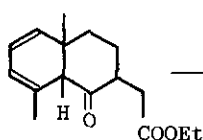
Silver carbonate/celite is quite useful for a construction of γ -lactone moiety through a partial oxidation of diols. Some typical illustrations are shown below.



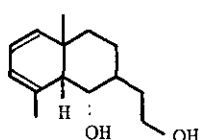


Ref. 78

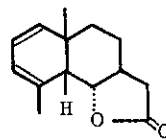
This oxidative lactonization was well applied to a synthesis of the key intermediate (121) leading to α - and β -santonin. The diol (120), obtained by the reduction of the keto ester (119), was oxidized with silver carbonate/celite to give (121)⁷⁹.



(119)

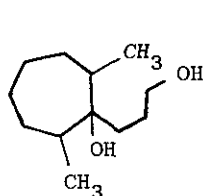


(120)

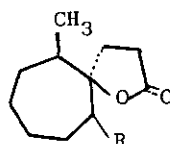


(121)

Oxidation of the diol (122) with alkaline potassium permanganate gave a stereoisomeric mixture of the spiro lactone (123)⁸⁰.



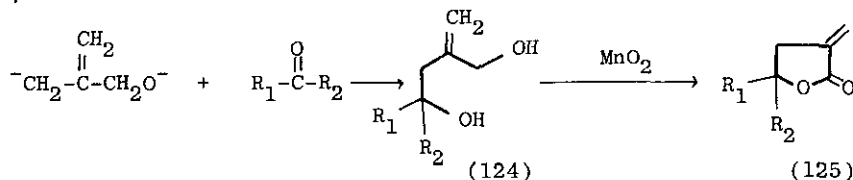
(122)



(123)

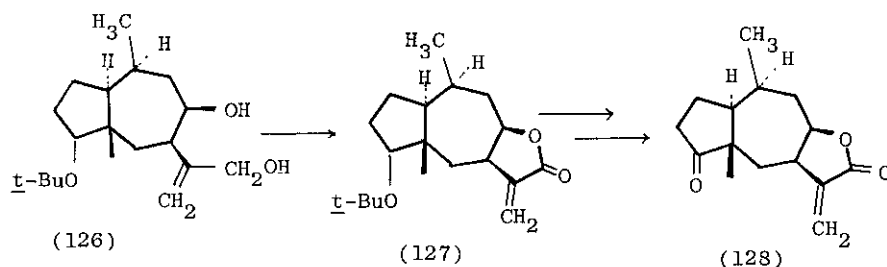
R = $\cdots$ CH₃ and
R = --- CH₃

Manganese dioxide is very effective for a synthesis of α -methylene- γ -lactone moiety through a partial oxidation of α -methylene-1,4-glycols. Dianion of methallyl alcohol, prepared by treatment of methallyl alcohol with potassium *t*-butoxide-*n*-butyllithium, was reacted with ketones to give the diols (124). Oxidation of (124) with manganese dioxide afforded γ -substituted α -methylene- γ -lactones (125)⁸¹.

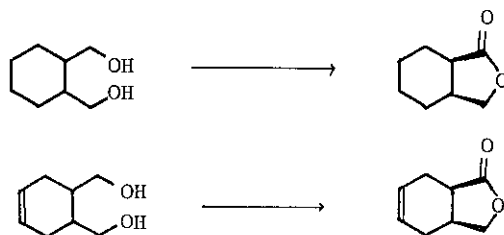


R₁=R₂=*n*-Bu; R₁=R₂=Et; R₁-R₂=-(CH₂)₅-

Similarly, oxidation of the diol (126) with manganese dioxide afforded the desired α -methylene- γ -lactone (127), which was further converted to confertin (128)⁸².



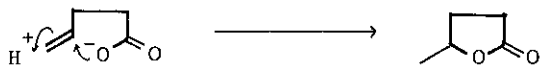
Horse liver alcohol dehydrogenase-catalyzed oxidation of cis-1,2-bis-(hydroxymethyl)cyclohexane and cis-1,2-bis(hydroxymethyl)cyclohexa-4-ene, involving FMN-mediated recycling of catalytic amounts of NAD^+ coenzyme, gave optically pure lactone, respectively⁸³.



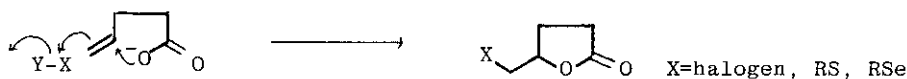
4. Cyclization of β,γ - and γ,δ -unsaturated acids

In this section, we describe a synthesis of γ -butyrolactones by the use of β,γ - and γ,δ -unsaturated acids and esters as starting materials. Two major procedures exist for this purpose.

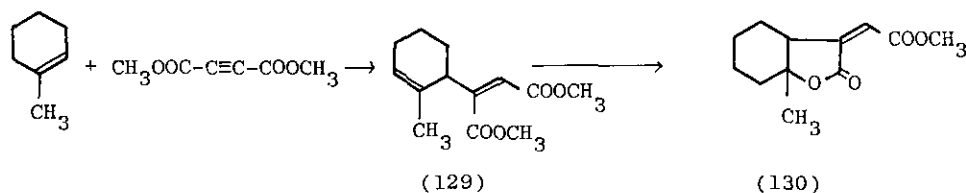
i) Acid-catalyzed cyclization



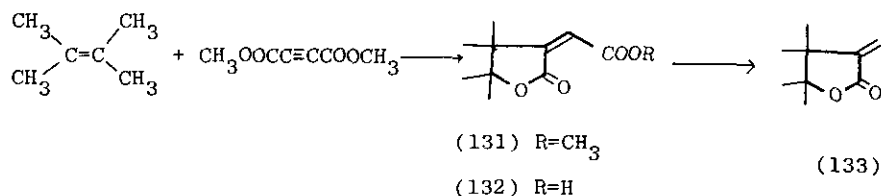
ii) Cyclization involving halogenation, hydrosulfenylation and hydroselenenylation



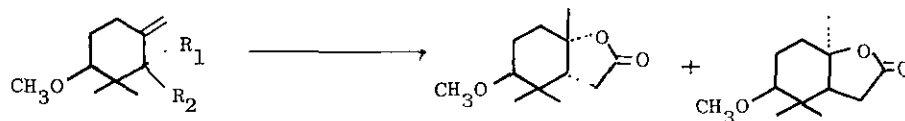
First, we describe an acid-catalyzed lactonization and then wish to refer to recent advances in halolactonization and sulfonyl- and selenyl-induced lactonization. At the first of this section as a typical illustration, ring closure of the diester (129) should be shown. The diester (129), derived from 1-methylcyclohexene and dimethyl acetylenedicarboxylate, was cyclized with 80 % sulfuric acid to give the lactone (130)⁸⁴.



Decarboxylation of (132), obtained by hydrolysis of the ester (131) with copper-quinoline at 120 °C afforded the α -methylene- γ -lactone (133)⁸⁴.



Treatment of a mixture of (134a) and (134b) with an acid afforded a mixture of the lactone (135a) and (135b) in a ratio shown below⁸⁵.



(134a) $\text{R}_1=\text{CH}_2\text{COOH}$, $\text{R}_2=\text{H}$

(135a)

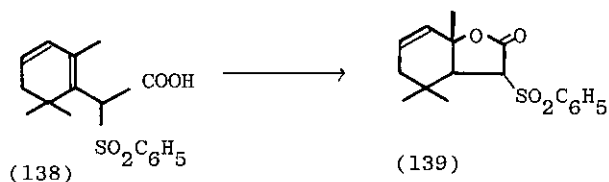
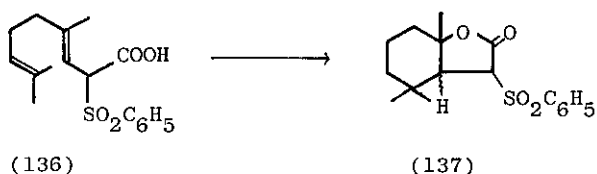
(135b)

(134b) $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}_2\text{COOH}$

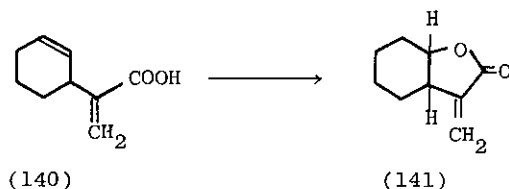
acid	135a/134b
SnCl_4	60/40
90 % H_2SO_4	80/20
98 % H_2SO_4	96/4

Cyclization of (136) with sulfuric acid-acetic acid /or BF_3 afforded

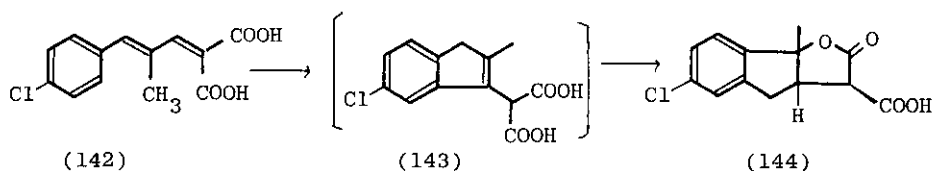
the lactone (137) in 70-75 % yield. Similarly, the cyclohexadieneacetic acid derivative (138) gave the lactone (139)⁸⁶.



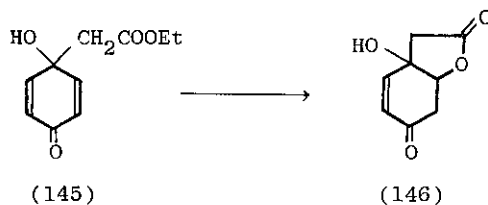
This acid-catalyzed cyclization was applied to a synthesis of α -methylene- γ -lactone (141). Cyclization of (140) gave (141) with stereoselectivity⁸⁷.



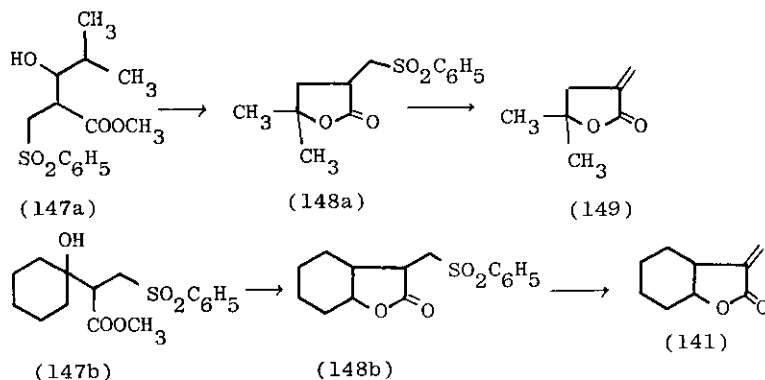
Treatment of the dicarboxylic acid (142) with conc. sulfuric acid yielded the indenofuranocarboxylic acid (144) through intramolecular alkylation and concomitant lactonization of the intermediate (143)⁸⁸.



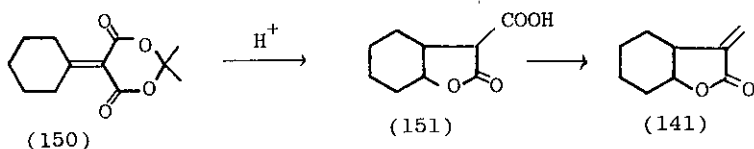
Hydrolysis of the ester (145) under acidic conditions gave 64 % yield of the lactone (146), which exhibited a strong inhibition of Shay ulceration⁸⁹.



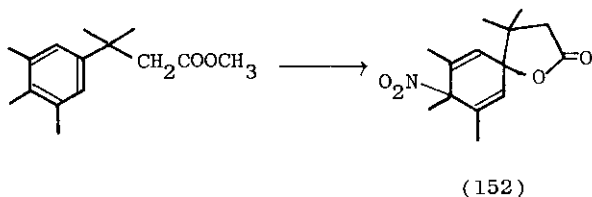
Ring closure of the hydroxy esters (147a) and (147b) with conc. sulfuric acid gave the lactone (148a) and (148b), respectively. These were converted to the corresponding α -methylene- γ -lactones (149) and (141), respectively, by treatment with sodium carbonate⁹⁰.



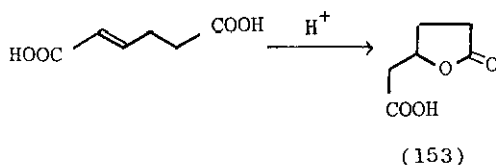
Cycloalkylidene-Meldrum's acid (150) was treated with sulfuric acid to give the lactone (151)⁹¹, possibly via the corresponding β,γ -isomerization. (151) was further converted to (141).



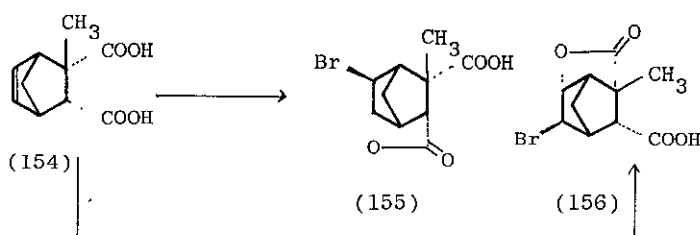
It might be rather exotic to show the following example. Nitration of methyl β -3,4,5-trimethylphenyl- β,β -dimethylpropionate with potassium nitrate in sulfuric acid gave the nitrated spiro γ -lactone (152)⁹².



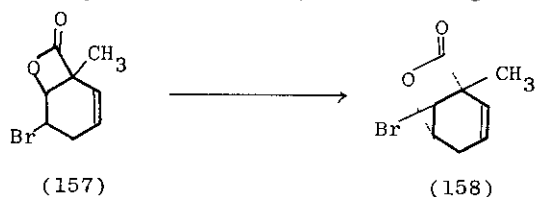
Dihydromuconic acid was converted to γ -carboxymethyl- γ -lactone (153)⁹³.



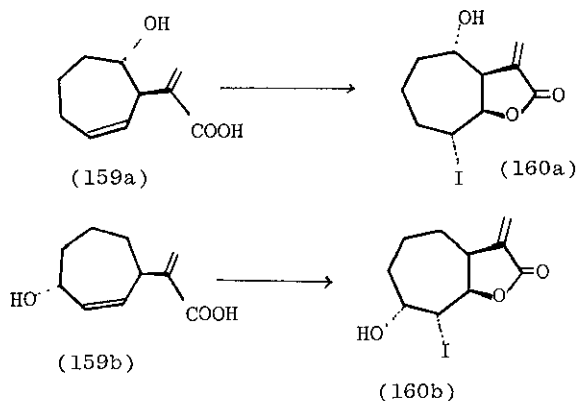
Halolactonization⁹⁴ of γ,δ -unsaturated acids is widely applied to a synthesis of γ -butyrolactone derivatives. Although this cyclization originates from the work of Fittig's and has long history, many typical illustrations can be found in the recent literatures. In the study of the bromolactonization of the norbornene dicarboxylic acid, Ranganathan⁹⁵ found that the structure of the particular lactone formed was dependent on the pH of the reaction medium. On the reaction of (154) with bromine in aqueous solution at pH 3, the preferred course of reaction involved more highly substituted carboxylic function to give (156) as the product; in contrast, the same reaction in sodium bicarbonate at pH 8 proceeded with the least substituted carboxylic function to give (155) as the product.



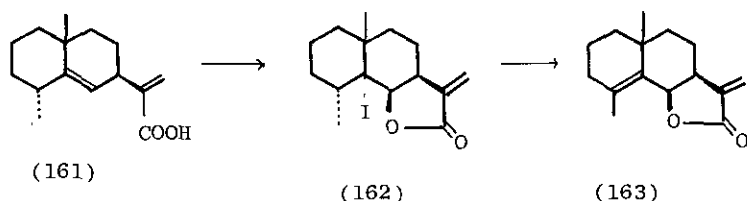
In the lactonization by this method, β -lactone (157), kinetically favoured product, easily isomerized to thermodynamically more favoured γ -isomer (158) by heating at 130 °C through concomitant 1,2-bromine migration⁹⁶.



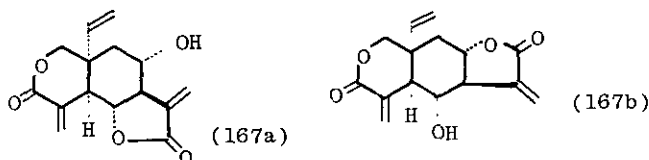
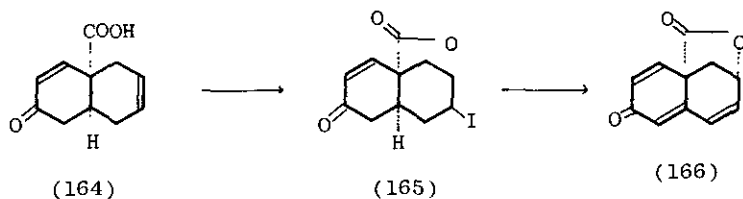
In the application of this lactonization, the hydroxy acids (159a) and (159b) were cyclized to the corresponding iodolactones (160a) and (160b), respectively⁹⁷.



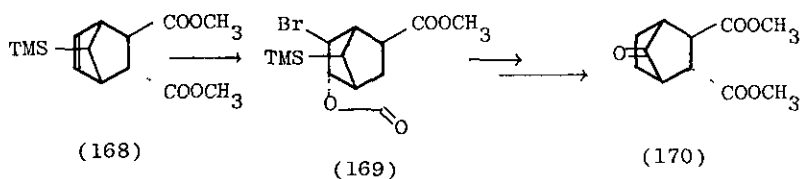
In the synthetic studies directed to frulanolide (163), the unsaturated acid (161) was converted to the iodolactone (162) by treatment with potassium triiodide in sodium bicarbonate aqueous solution. Dehydroiodonation to yield (163) was effected by treatment with DBN⁹⁸.



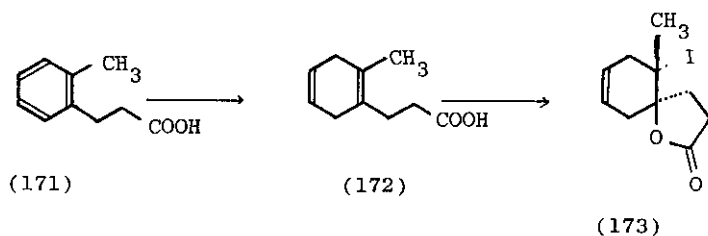
Iodolactonization of the acid (164), followed by dehydroiodonation of the iodolactone (165) with DBU, gave the trienone (166), which was used in the total synthesis of (+)-vernolepin (167a) and (+)-vernomenin (167b)⁹⁹.



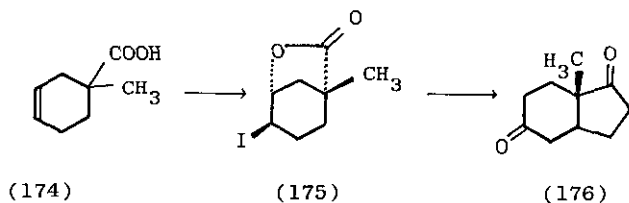
Bromolactonization of the Diels-Alder adduct (168) of dimethyl fumarate and trimethylsilylcyclopentadiene gave the bromolactone (169), which was further converted to (170)¹⁰⁰.



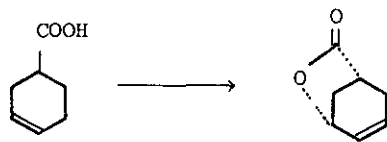
Iodolactonization was used for the separation of the Birch reduction product (172) from the mixture of the starting material (171) and the tetrahydro product. The desired dihydro product (172) was separated by conversion into the neutral iodospiro lactone (173)¹⁰¹. Unsaturated acids can be customarily regenerated from halolactones^{102, 103}.



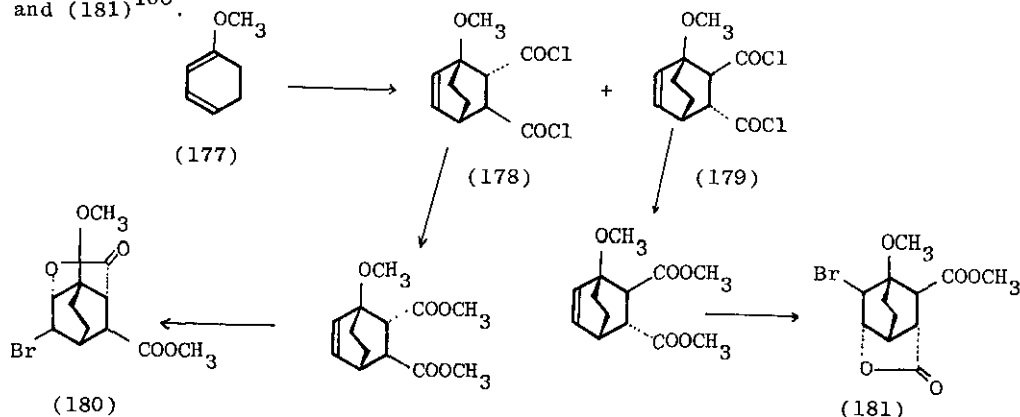
Iodolactonization of 1-methyl-3-cyclohexenoic acid (174) with iodine and potassium iodide in aqueous sodium bicarbonate afforded the iodolactone (175)¹⁰⁴, which was the key intermediate in a synthetic study directed toward the formation of trans-8-methyl-1,5-hydroindandione (176).



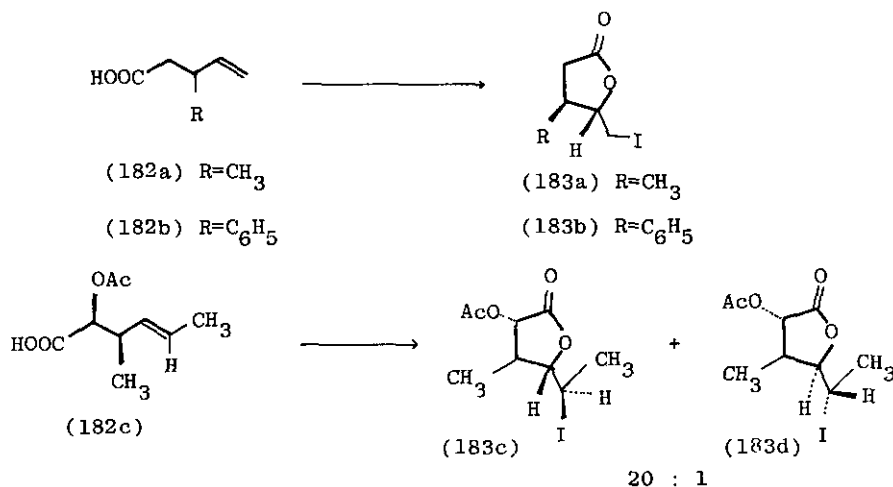
The following conversion, through iodolactonization and dehydroiodonation, was reported by Trost aimed at the prostanoïd synthesis¹⁰⁵.



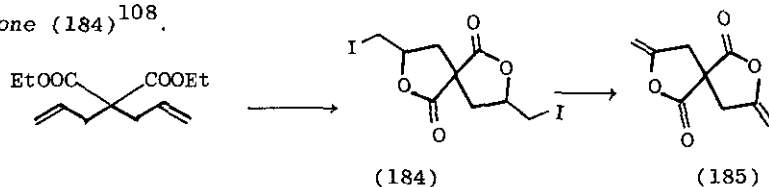
The Diels-Alder adducts (178) and (179), obtained by the reaction between 1-methoxycyclohexa-1,3-diene (177) and fumaryl chloride, were determined by separating their methyl esters and then converting each to the bromolactones (180) and (181)¹⁰⁶.



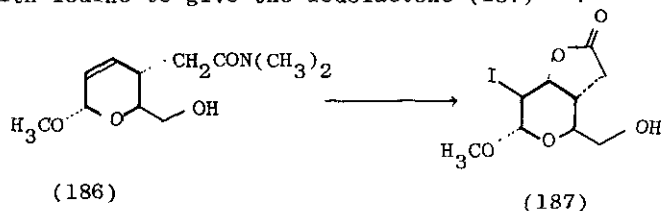
Iodolactonization of alkenoic acids (182a)-(18c) proceeded with high stereo-selectivity to give (183a)-(183c), respectively¹⁰⁷.



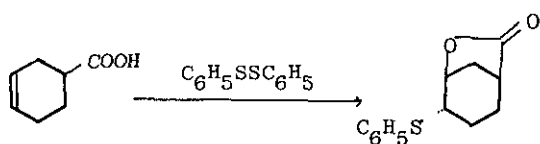
The novel spirobis- γ -methylenebutylolactone (185) was prepared through iodolactonization of diethyl diallylmalonate, followed by dehydroiodination of the lactone (184)¹⁰⁸.



One of important application of this lactonization is illustrated in a stereocontrolled synthesis of thromoxane E_2 from D-glucose¹⁰⁹. The amide (186) was treated with iodine to give the iodolactone (187)¹⁰⁹.



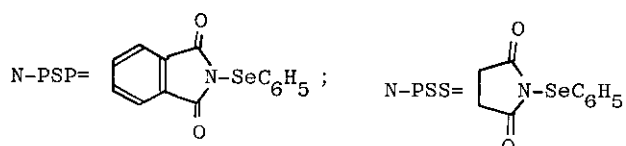
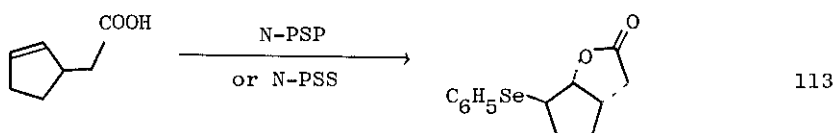
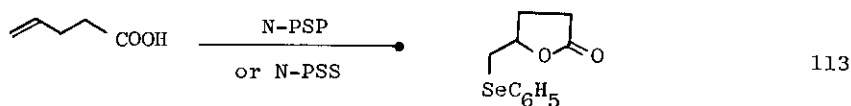
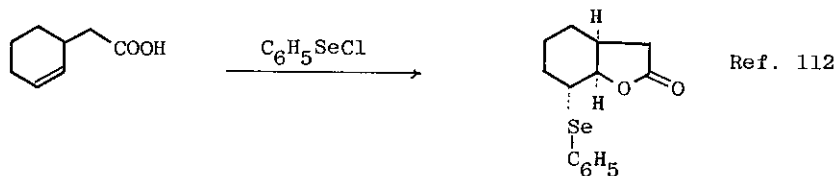
Hydrosulphenylation and hydroselenylation are applied to a synthesis of sulfenylated and selenylated γ -lactones from alkenoic acid. Some illustrations are shown below.



Ref.

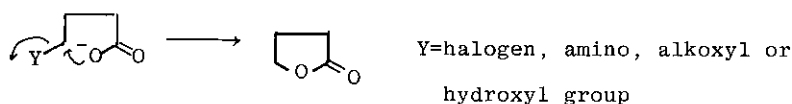
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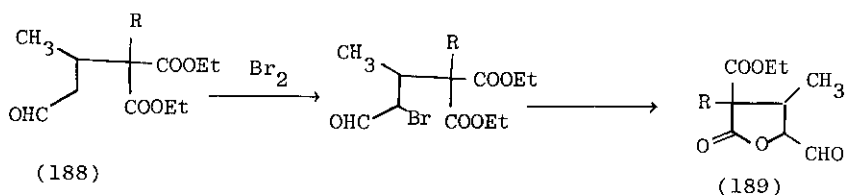


5. Lactonization of acids and esters possessing a leaving group at γ -position

In this section, we describe a cyclization of γ -substituted butyric acid and esters as shown below.

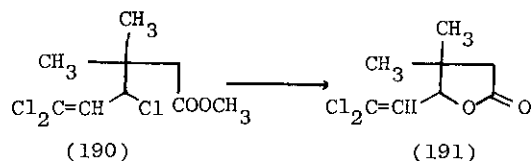


The most typical example is illustrated in a synthesis of γ -formyl- γ -butyrolactone (189) by bromination of (188) ¹¹⁴.

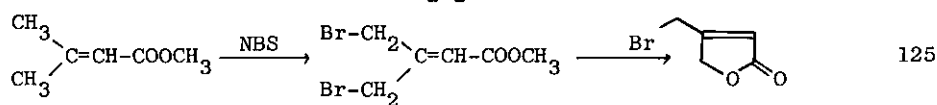
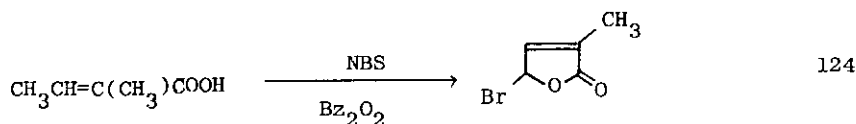
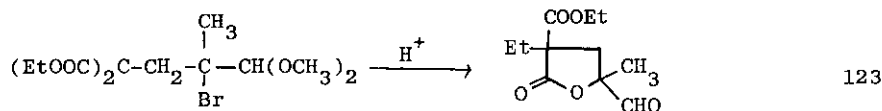
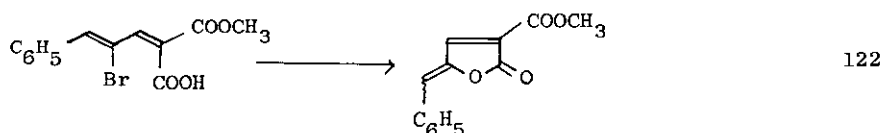
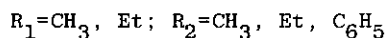
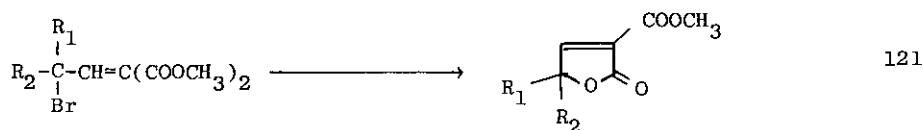
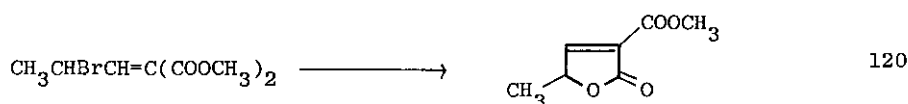
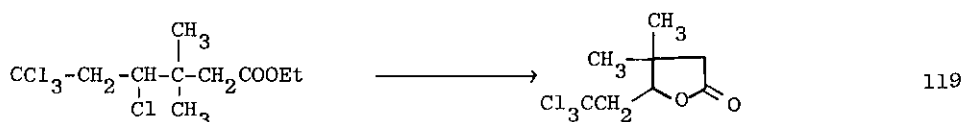
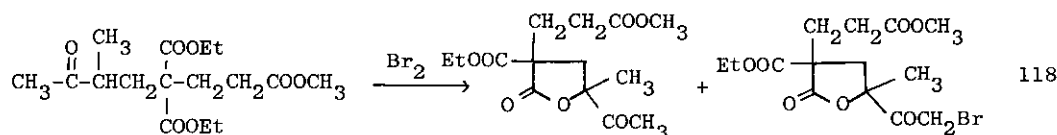
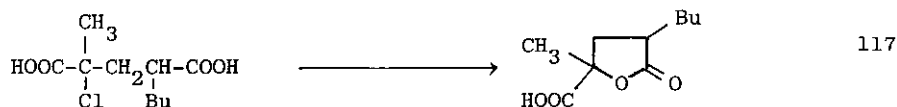
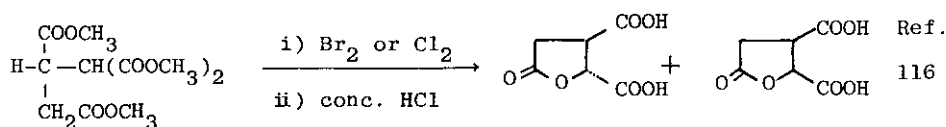


R=Et, Pr, Bu, benzyl, C_6H_5

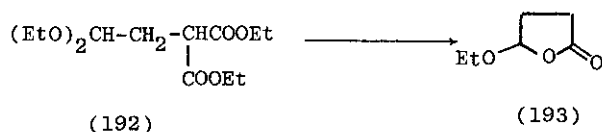
The ester (190) was heated in methanol in the presence or absence of sulfuric acid to give the lactone (191) ¹¹⁵.



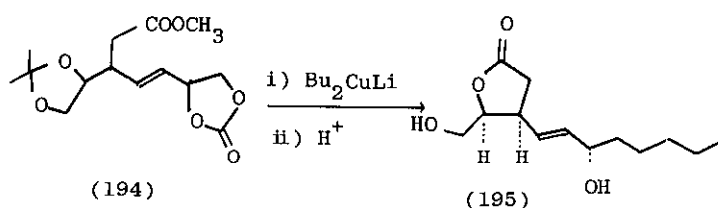
Preparation of lactones through the similar procedure is illustrated below.



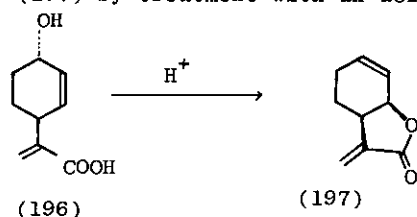
Ethoxyl and alkoxy groups are also used as a leaving group in a cyclization providing γ -lactones. Saponification of the diester (192) gave the diacid, which underwent thermal decarboxylation with elimination of ethanol to give the γ -ethoxy- γ -butyrolactone (193)¹²⁶.



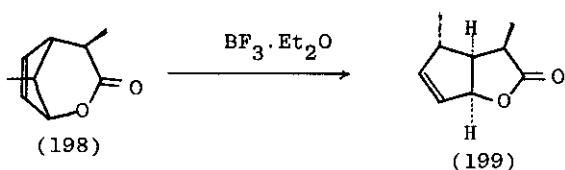
n-Butylation of (194) with dibutyl copperlithium, followed by treatment with acid afforded the γ -butyrolactone (195)¹²⁷.



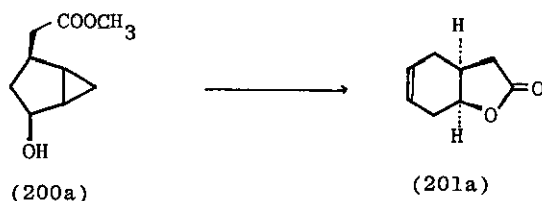
Hydroxy alkenoic acids are also used for a synthesis of γ -butyrolactones under acidic conditions. The hydroxy acid (196) is easily converted to the α -methylene- γ -lactone (197) by treatment with an acid¹²⁸.

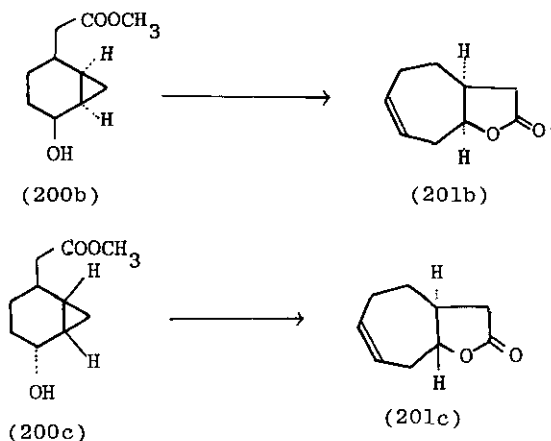


In a similar fashion, the lactone (198) was converted to (199)¹²⁹.

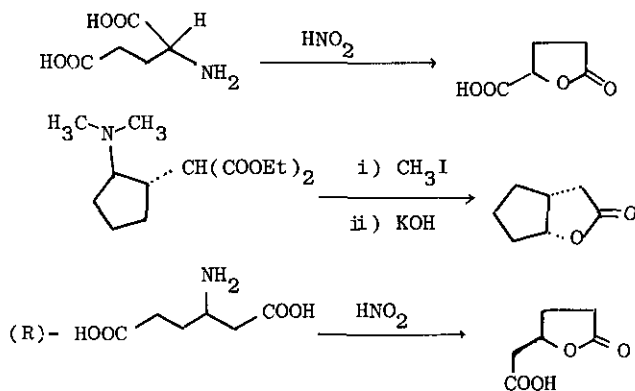


Treatment of (200a)—(200c) with perchloric acid yielded the lactones (201a)–(201c), respectively¹³⁰.



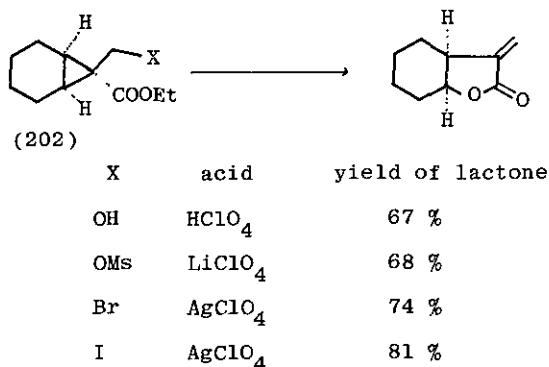


Quaternary ammonium and diazonium salts were also used as a leaving group in the synthesis of γ -lactones as illustrated below.

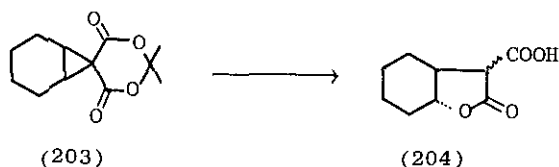


6. Formation of γ -butyrolactones from cyclopropanecarboxylic acids

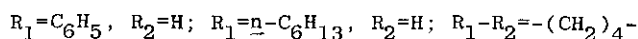
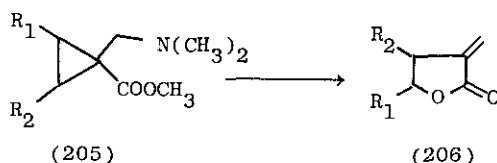
A route for a synthesis of γ -butyrolactone derivatives by acid and metal-ion rearrangement of functionally substituted cyclopropanes originates from the initial work of Hudrlik's¹³⁴. A rearrangement of the ester (202) forming the α -methylene- γ -lactone was examined in detail¹³⁵.



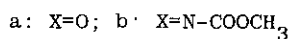
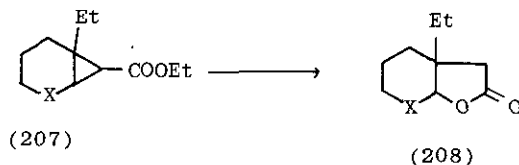
The cyclopropane acylal (203) was heated in aqueous acetone afforded α -carboxy- γ -lactone derivative (204)^{136, 137}.



Transformation of (205) to the corresponding α -methylene- γ -lactones was carried out by treatment with trimethylsilyl iodide, followed by distillative thermolysis¹³⁸.



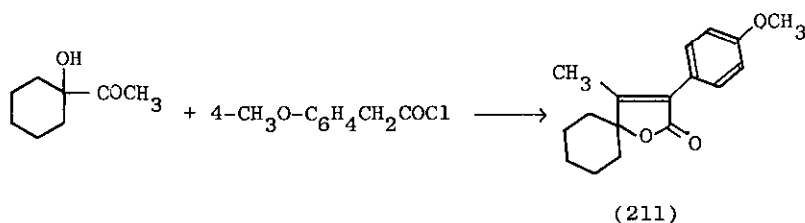
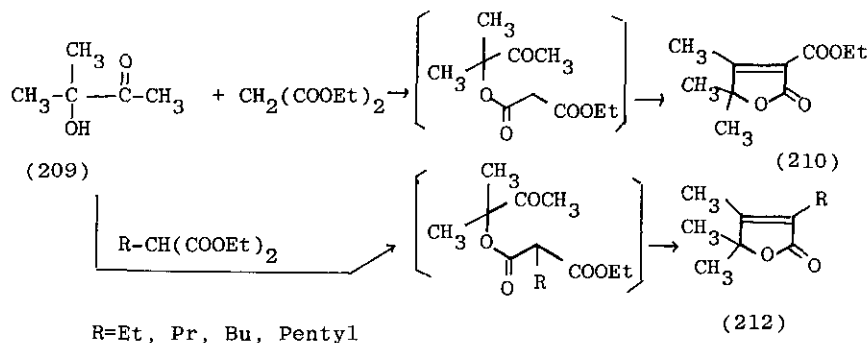
In the course of synthetic studies of eburanomine, an indole alkaloid, (207a) and (207b) were converted to (208a) and (208b), respectively¹³⁹.



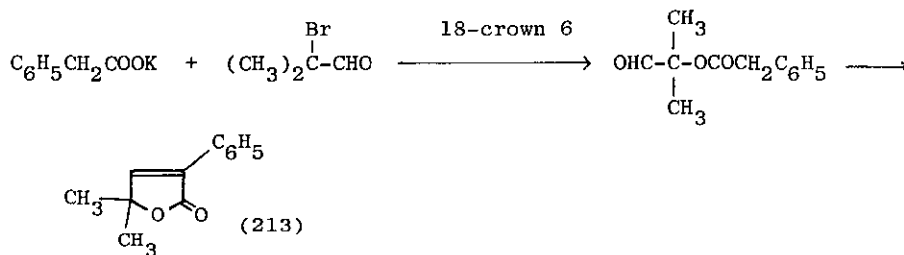
7. Formation of γ -butyrolactones by intramolecular Knoevenagel type reaction

It might be noted that the intramolecular Knoevenagel type reaction or intramolecular Wittig reaction might be rather classical methods for providing $\Delta^{\alpha,\beta}$ -butenolides. As the most typical illustration, a formation of the butenolide (210) should be given. Base-catalyzed condensation of α -hydroxy ketone (209) with diethyl malonate in the presence of sodium ethoxide in ethanol gave (210)¹⁴⁰. In a similar manner, condensation of 1-acetylcyclohexanol with 4-methoxyphenylacetyl chloride in benzene containing pyridine afforded the γ -spiro- $\Delta^{\alpha,\beta}$ -butenolide (211)¹⁴⁰. This reaction was applied to a synthesis of α -alkyl- $\Delta^{\alpha,\beta}$ -butenolides (212). Reaction of (209) with diethyl alkylmalonate in the presence of potassium carbonate, followed by cyclization of ester intermediates yielded the α -alkyl-butenolides (212)¹⁴¹. This reaction was also carried out in the presence of

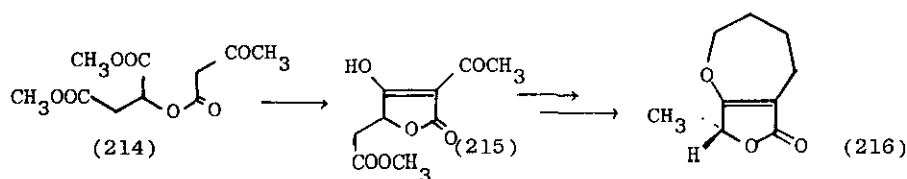
potassium carbonate at 210-220 °C¹⁴².



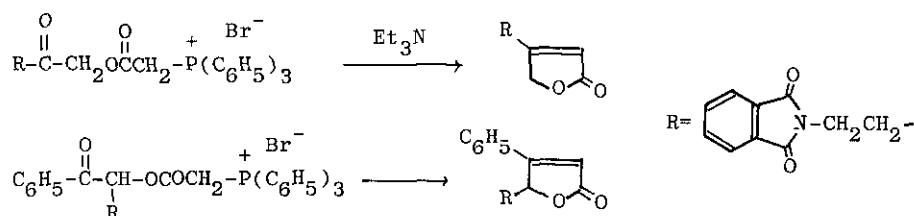
Esterification of (209) with butyryl chloride, followed by cyclization in the presence of potassium carbonate or sodium ethoxide gave (212; R=Et)¹⁴³. α -Phenyl- γ,γ -dimethylbutenolide (213) was prepared by this method¹⁴⁴ as shown below.



The acetoacetate (214), prepared by the reaction of ketene dimer with dimethyl malate, was cyclized with potassium t-butoxide afforded the oxofuranone (215), which was the key intermediate for the synthesis of (RS)-carlosic acid (216), isolated from *Penicillium charlesii*.¹⁴⁴

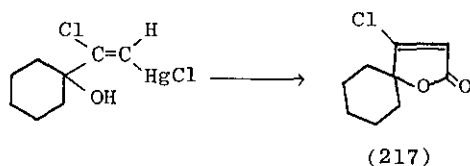


Intramolecular Wittig reaction is also applied to a synthesis of some $\Delta^{\alpha,\beta}$ -butenolides. One typical example is shown below¹⁴⁵.

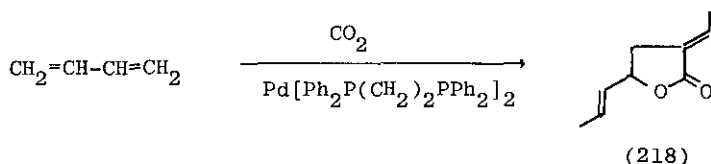


8. Lactonization involving metal-induced carboxylation

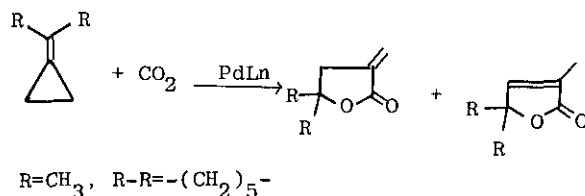
In this section, we describe a formation of γ -butyrolactone derivatives through insertion of CO and CO₂ or carboxylation of metalated intermediates. Vinylmercurials are known to give α,β -unsaturated esters by the reaction with CO in the presence of Pd-complex¹⁴⁶. This reaction was effectively applied to a synthesis of β -chloro- $\Delta^{\alpha,\beta}$ -butenolide (217) by the reaction of CO in the presence of Li₂PdCl₄ in THF in good yield¹⁴⁷.



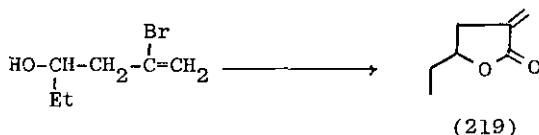
By this reaction, a variety of β -chloro- $\Delta^{\alpha,\beta}$ -butenolides were prepared¹⁴⁷. The α -ethyldiene- γ -lactone (218) was formed by the reaction of butadiene with CO₂ in the presence of Pd[Ph₂P(CH₂)₂PPh₂]₂ through CO₂ insertion mechanism¹⁴⁸.



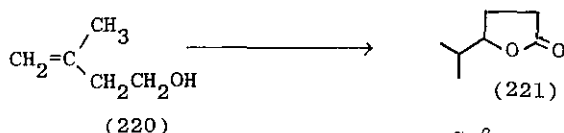
Cyclodimerization of methylenecyclopropane occurred in the presence of CO₂ and Pd(0)-phosphine complex catalyst to give the $\Delta^{\alpha,\beta}$ -butenolides as outlined below¹⁴⁹.



γ -Ethyl- α -methylene- γ -lactone (219) was directly obtained by the reaction of Ni(CO)₄ in moderate yield¹⁵⁰.



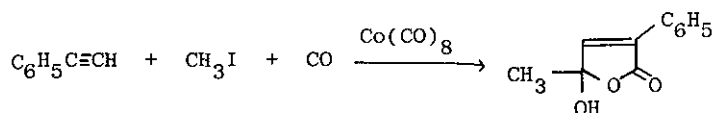
The reaction of the alcohol (220) with methyl iodide in benzene in the presence of rhodium trichloride gave γ -isopropyl- γ -lactone (221)¹⁵¹.



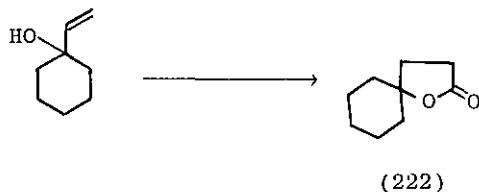
Palladium catalyzed synthesis of β -methyl- $\Delta^{\alpha,\beta}$ -butenolide was achieved by the reaction of iodoalkenol with CO in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$, potassium carbonate and hydrazine¹⁵². By this method, a variety of β,γ -disubstituted $\Delta^{\alpha,\beta}$ -butenolides were synthesized.



Stirring methyl iodide and phenylacetylene with $\text{Co}_2(\text{CO})_8$ in benzene in the presence of sodium hydroxide containing phase transfer catalyst, cetyltrimethylammonium bromide, under atmosphere of CO afforded γ -hydroxy- $\Delta^{\alpha,\beta}$ -butenolide¹⁵³.

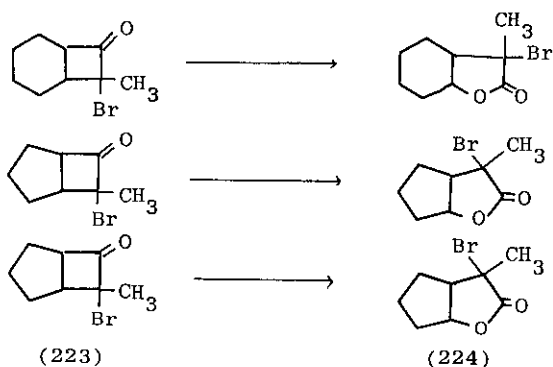


Titanium catalyzed hydromagnesiation reaction of olefinic alcohol providing γ -lactones was presented by Eisch¹⁵⁴. Treatment of 1-vinylcyclohexanol with ethylmagnesium bromide in the presence of cyclopentadienyltitanium chloride followed by treatment with CO_2 gave (222).

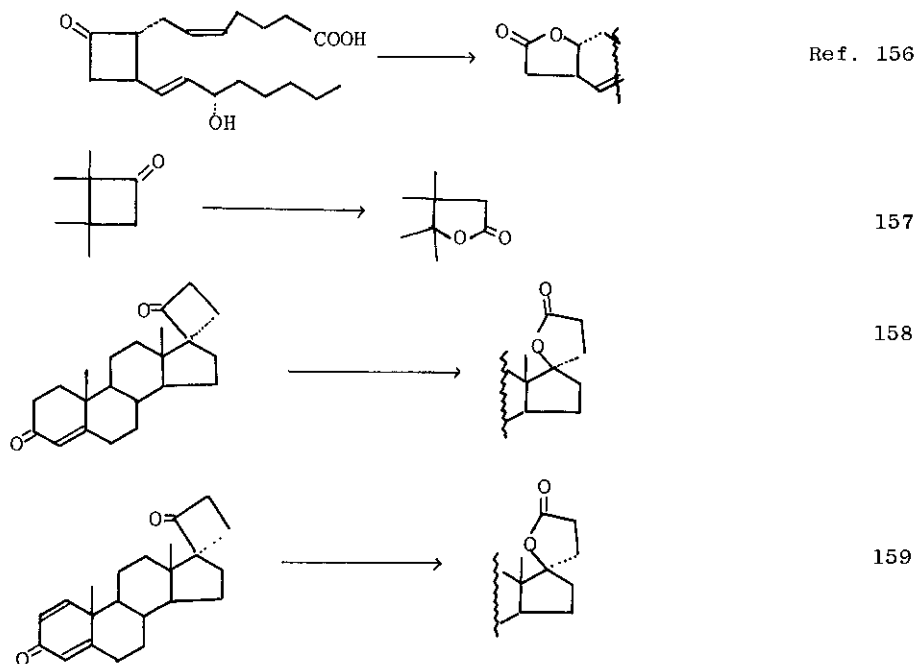


9. Ring expansion of cyclobutanone derivatives

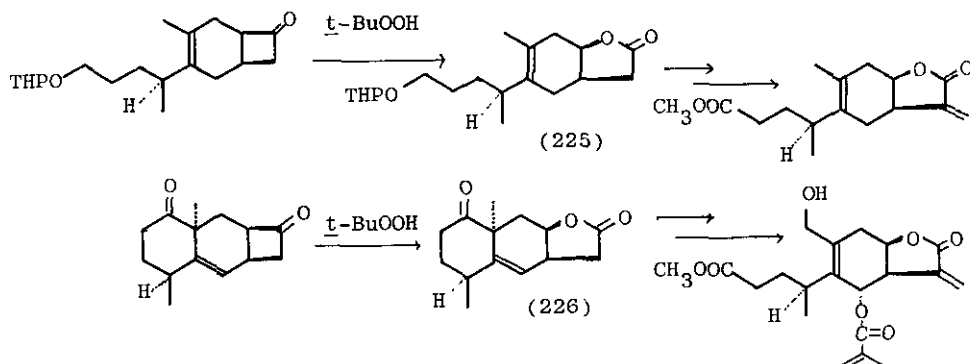
Ring expansion of cyclobutanone derivatives, sometimes, provides a useful method for a preparation of γ -butyrolactones and has been applied to a synthesis of key intermediates leading to natural products. The Baeyer-Villiger reaction of bromocyclobutanone (223) by the use of *m*-CPBA gave α -bromo- γ -lactones (224), which were easily converted to the corresponding α -methylene- γ -lactones¹⁵⁵.



Typical illustrations are shown below.

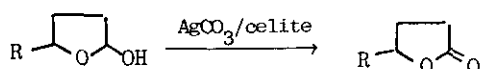


This ring expansion providing γ -butyrolactones was effectively applied to a synthesis of the key intermediate (225) leading to (+)-ivangulin¹⁶⁰ and (226) leading to (+)-eriolanin¹⁶¹.

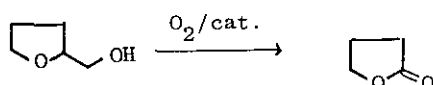
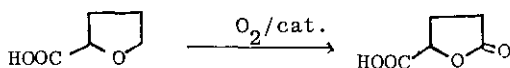
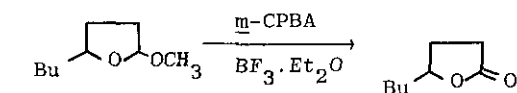


10. Methods starting from furan derivatives

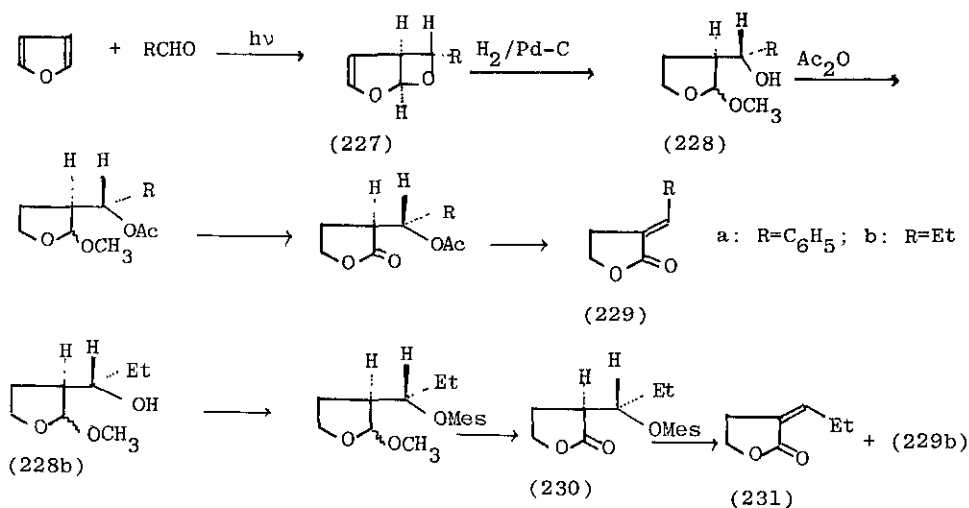
Many convenient methods for a conversion of furan derivatives including tetrahydrofurans to γ -butyrolactones have been reported. Electrochemical oxidation of tetrahydrofuran in the presence of alkali metal bromides on a Pt anode gave γ -butyrolactone¹⁶². Oxidation of tetrahydrofurfuryl alcohol by molecular oxygen also gave γ -butyrolactone¹⁶³. Liquid-phase oxidation of tetrahydrofurfuryl alcohol in the presence of B_2O_3 gave γ -butyrolactone¹⁶⁴. 2-Hydroxytetrahydrofurans can be easily oxidized with silver carbonate-celite in xylene under reflux¹⁶⁵. 2-Alkoxytetrahydrofuran derivatives are also oxidized by the use of *m*-CPBA in the presence of $BF_3 \cdot Et_2O$ to γ -butyrolactones¹⁶⁶. Liquid-phase catalytic oxidation of tetrahydrofuran-2-carboxylic acid with oxygen by using B_2O_3 as a catalyst in chlorobenzene gave γ -carboxy- γ -butyrolactone¹⁶⁴. Furan was easily converted to $\Delta^{\alpha,\beta}$ -butenolide by bromination in acetic acid containing acetic anhydride and sodium acetate, followed by thermolysis of the resulting black tar¹⁶⁷.



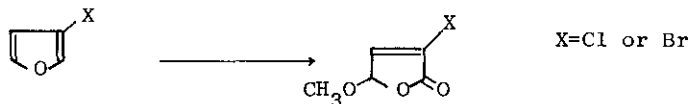
R=3-pyridyl, 4-pyridyl, 1-methylimidazol-2-yl



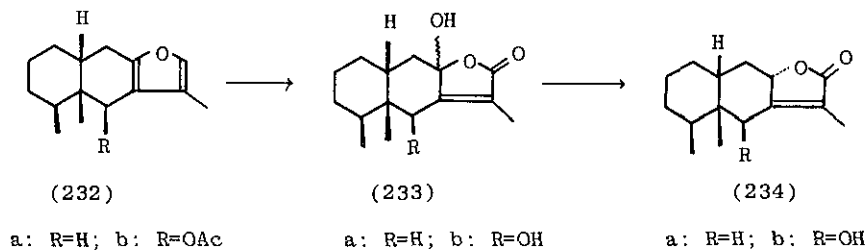
Photocycloaddition of furan and benzaldehyde or propionaldehyde gave the oxetane (227a) and (227b), which were elegantly converted to trans- α -alkylidene- γ -lactones (229a) and (229b), respectively¹⁶⁸ as outlined below. Mesylation of the intermediate (228b), followed by oxidation of the mesylated products with m-CPBA in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the 2-substituted γ -butyrolactone (230). Treatment of (230) with DBU gave a mixture of (229b) and the cis-isomer (231) in ratio of 23:16¹⁶⁸.



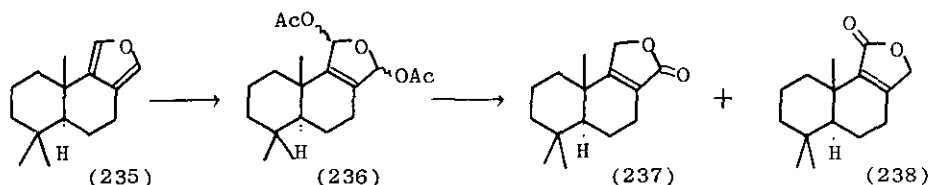
Photooxidation of 3-chloro or 3-bromofuran in methanol gave β -chloro or β -bromo- γ -methoxy- $\Delta^{\alpha,\beta}$ -butenolide¹⁶⁹.



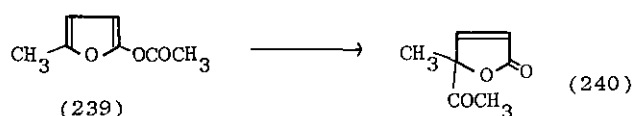
Photooxidation of the furanoeremophilane (232a) and ligularol (232b), followed by hydrolysis afforded (233a) and (233b), respectively. These were reduced with sodium borohydride to afford eremophilolide (234a) and its 6 β -OH derivatives (234b), respectively¹⁷⁰.



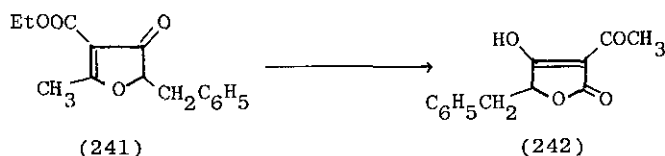
Oxidation of the furan (235) with lead tetraacetate afforded the diacetate (236), thermolysis of which gave the butenolide (237; 74 %) and (238; 17 %)¹⁷¹.



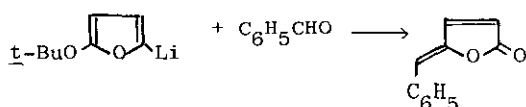
The acyloxyfuran (239) rearranged in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give the γ -acyl- $\Delta^{\alpha, \beta}$ -butenolide (240)¹⁷².



Treatment of the ethoxycarbonylfuranone (241) with aqueous potassium hydroxide gave the β -hydroxy- $\Delta^{\alpha, \beta}$ -butenolide (242)¹⁷³.

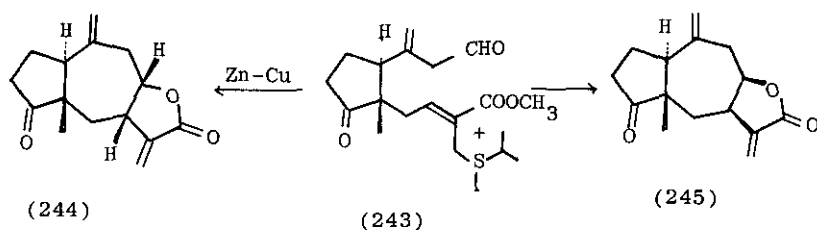


Lithiated 2-*t*-butoxyfuran was reacted with ketones, e.g., benzaldehyde gave γ -alkylidene- $\Delta^{\alpha, \beta}$ -butenolide, after treatment with *p*-toluenesulfonic acid¹⁷⁴.

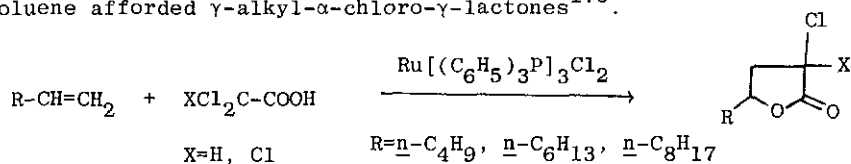


11. Miscellaneous routes to γ -butyrolactones including introduction of substituents

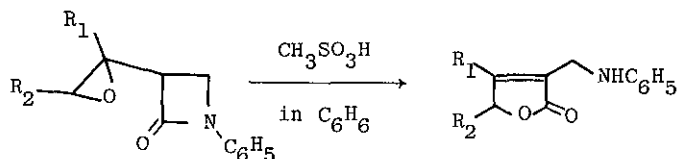
Although most of representative methods providing γ -butyrolactones were described already, some other unique methods for a construction of γ -butyrolactone and methods for introduction of substituents at the α -position should be described in this section. In the course of a total synthesis of confertin, Semmelhack reported a lactonization procedure. Cyclization of the sulfonium salt (243) with zinc-copper couple afforded the cis-fused α -methylene- γ -lactone (244); whereas treatment of (243) with excess bis(1,5-cyclooctadine)nickel(0) gave (245).



1-Alkenes were reacted with trichloroacetic acid or dichloroacetic acid in the presence of catalytic amount of dichloro tris[triphenylphosphin]rhuthenium(II) in toluene afforded γ -alkyl- α -chloro- γ -lactones¹⁷⁶.

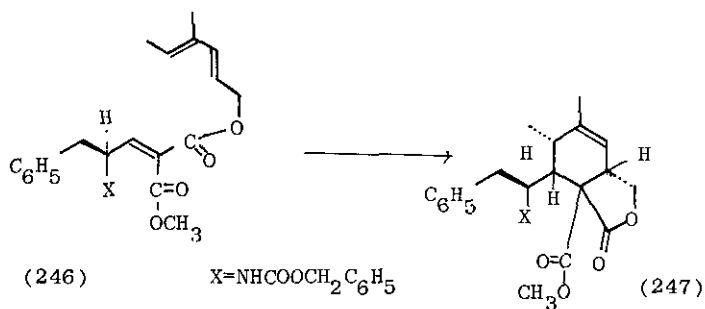


3-(α,β -Epoxy)- β -lactams were found to be easily convertible to α -aminomethyl- $\Delta^{\alpha,\beta}$ -butenolides as outlined below¹⁷⁷.

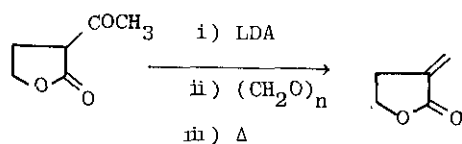


$\text{R}_1=\text{C}_6\text{H}_5, \text{R}_2=\text{H}; \text{R}_1=\text{C}_6\text{H}_5, \text{R}_2=\text{CH}_3; \text{R}_1-\text{R}_2=-(\text{CH}_2)_3-; \text{R}_1-\text{R}_2=-(\text{CH}_2)_4-$

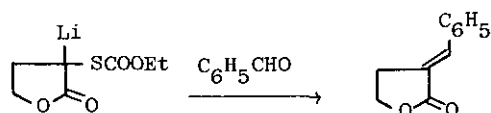
Intramolecular Diels-Alder reaction of (246) gave the lactone (247)¹⁷⁸.



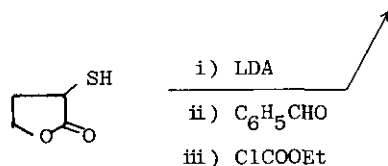
Introduction of methylene group at the α -position is also one of important subjects in this field. Finally, only recent representative methods were shown below.



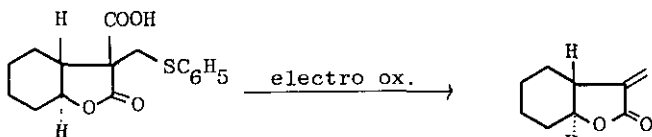
Ref. 179



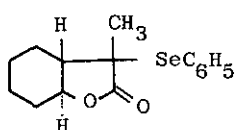
Ref. 180



181



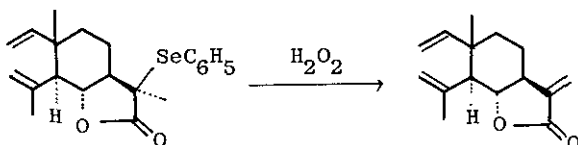
182



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12. Conclusion

As mentioned above, there have been reported a number of direct methods providing γ -butyrolactones. Many of them were prepared for the purpose of preparation of biologically active compounds, since many of them showed attractive biological activities. Furthermore, approaches to naturally occurring sesquiterpene γ -lactones have been increasingly developed. Now, synthetic study toward naturally occurring sesquiterpenoid γ -lactones should be treated as another subject, since a construction of γ -butyrolactone unit as a partial structure, have been well studied already. Recent advances in the synthetic chemistry of sesquiterpenoid γ -lactones will be discussed in another paper.

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