Synthetic approaches to butenolides

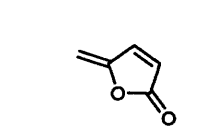
D. W. KNIGHT

Chemistry Department, University Park, Nottingham, NG7 2RD, UK

Reviewing the literature published between 1976 and 1992

1 Introduction

Butenolides occupy a literally central position between butyrolactone and furan structures, both in terms of synthetic chemistry and biosynthesis. These compounds also form an important and diverse group of natural products in their own right, encompassing both fatty acid and terpenoidal biosynthetic origins, and they display a wide range of biological activities. Very simple examples include the buttercup metabolite protoanemonin, the butter flavour component bovolide, and the related component of mushroom flavour, long-chain butenolides represented by acarenoic acid and methyl lichensterinate, and the highly unsaturated ylidenebutenolide lissoclinolide. However, the bulk of natural butenolides are terpenoid in origin. These range from the simple monoterpenoid mintlactones to numerous sesquiterpenes, representing most of the major biosynthetic classes and exemplified by confertifolin, aristolactone, and furodysinin lactone. Other examples include the paniculides and the highly oxidized metabolites freelingyne and the piscicidal vallapin.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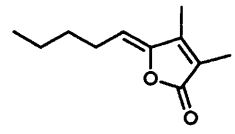
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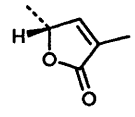
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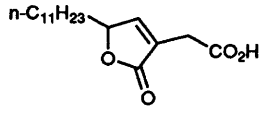
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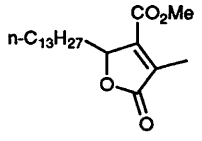
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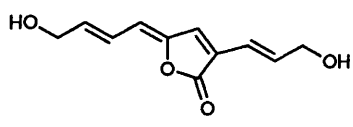
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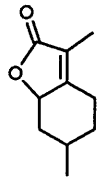
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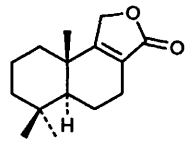
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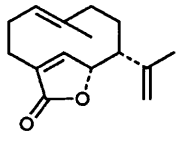
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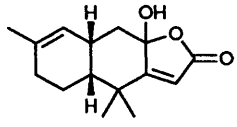
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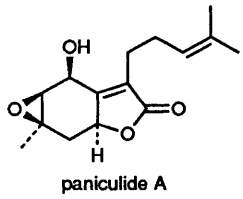
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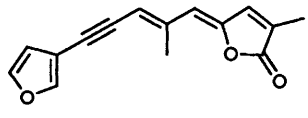
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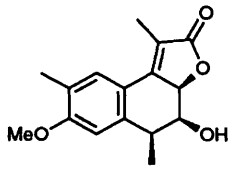
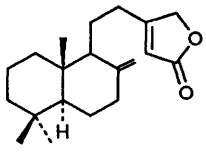

vallapin

Butenolide diterpenes are represented amongst the labdanes and the related jolkinolide E, while sesterterpene representatives include the PLA_2 inhibitor manoalide and the unusual and cytotoxic carotenoid metabolite luffariolide A. Digitoxin and related cardenolides are perhaps the most widely known members of the butenolide family. Two final and unique examples are the seed germination stimulant strigol and members of the securinine alkaloids, such as 4-epiphyllanthine.



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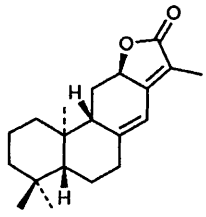

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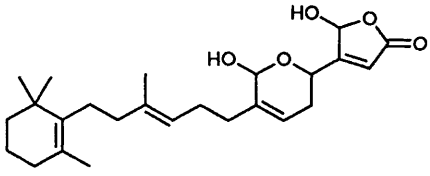

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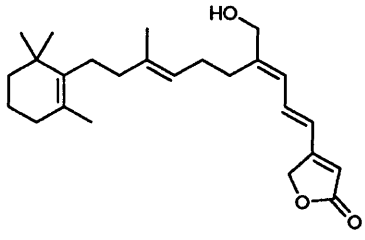
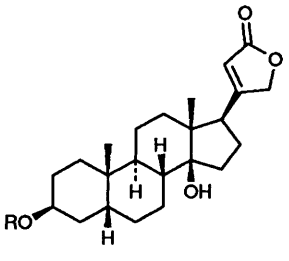
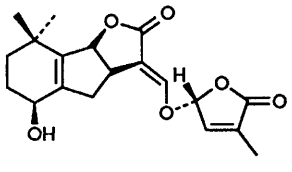


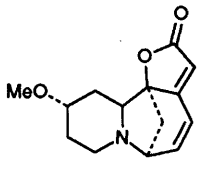
luffariolide A



digitoxin



strigol



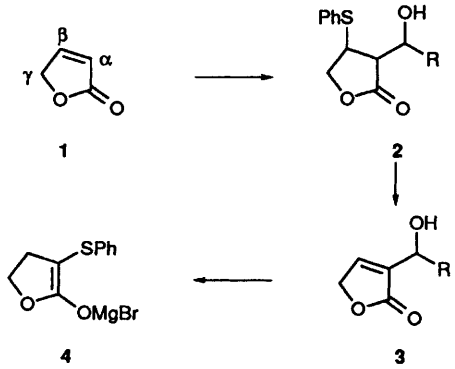
4-epiphyllanthine

For the purpose of this review, the term 'butenolide' specifically refers to the conjugated or Δ^2-butenolides; other, more systematic, names include but-2-en-4-olides and 2(5H)-furanones. The substituent positions in butenolide structures are referred to as indicated in formula **1**. The literature has been surveyed from 1976, the year of publication of the last extensive review of this topic,[1] up to 1992 inclusively. An attempt has been made to be reasonably comprehensive, but complete coverage is not claimed. The material has been arranged primarily on the basis of structural types, in order to facilitate access. Thus, monosubstituted and polysubstituted examples are grouped in separate sections. Clearly, in many cases, the same methodology can be applied to syntheses of members of the different groups. Where this has been reported, every effort has been made to provide cross references; the imagination of the reader will be required when this is not the case. Applications of many of the methods to natural product synthesis have been included in order to emphasize the utility of the strategy concerned.

The parent butenolide **1**, which is commercially available, can be prepared by Baeyer–Villiger oxidation of furan-2-carboxaldehyde,[2] using hydrogen peroxide/formic acid or from furan itself, in 62–71% yield by treatment with bromine in acetic acid/acetic anhydride.[3]

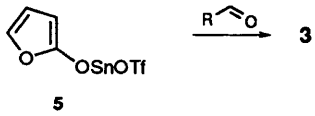
2 α-Substituted butenolides

A neat method for the conversion of the parent butenolide **1** into the α-substituted homologues **3** consists of sequential Michael addition of thiophenolate and aldol condensation of the resulting enolate to give intermediates **2**.[4] Conventional oxidative elimination of sulfur completes the sequence, which unfortunately fails when ketones are used as electrophiles. The isomeric enolate **4** can be generated from the corresponding α,α-bis-(phenylthio)-butyrolactone by treatment with ethylmagnesium bromide; similar condensation and elimination steps then lead to the same α-substituted butenolides **3**.[5]



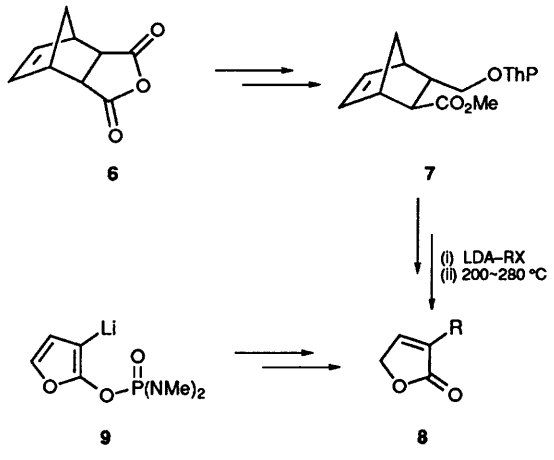
1 **2** **3** **4**

In general, α-alkoxy- and silyloxy-furans react with electrophiles, usually under the influence of a Lewis acid, to give γ-substituted butenolides by reaction at the other α-position of the furan nucleus.[83-92] An exception is the stannyl triflate **5**, which reacts largely at the β-position of the furan, thus providing a non-anionic route to the α-hydroxyalkyl-butenolides **3**.[6]



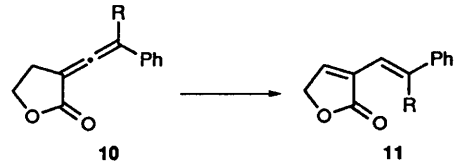
5

An alternative strategy, which allows the indirect generation of an anionic centre at the α position of a butenolide, begins with the easily prepared Diels–Alder adduct **6**, which can be readily converted into the monoester **7**. Enolization and alkylation under standard conditions, lactonization, and finally a *retro*-Diels–Alder reaction delivers the monosubstituted butenolides **8**.[7] Limiting factors are the restriction to allylic and benzylic halides as electrophiles, as is usual with ester enolates, and in some cases the high temperature [200–280°C] required in the last step. This idea has been employed elsewhere,[79–82,233,234] as the adduct **6** and relatives thereof also effectively prevent competition from Michael additions which could interfere in reactions between butenolides themselves and nucleophiles. Another way of generating a β-carbanion in a butenolide precursor involves the use of a diaminophosphate group to direct deprotonation to the β-position of a furan, rather than to the much more usual α'-site. The resulting anion **9** reacts with aldehydes, ketones, and benzylic bromides, but not with other alkylating agents, to provide the butenolides **8**, together with some of the deconjugated isomers, in *ca.* 50% yield, following brief exposure to formic acid.[8]

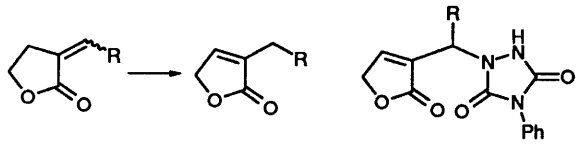


6 **7** **9** **8**

The fact that Δ^2-butenolides contain an endocyclic, conjugated double bond suggests that alkene positional isomerization should provide a number of approaches to them. The above examples[6,8] already attest to the ease of isomerization of Δ^3-butenolides; α-alkylidenebutyrolactones similarly are useful as precursors to Δ^2-butenolides. For example, the α-allenylbutyrolactones **10** are converted into butenolides **11** upon exposure to dicobalt octacarbonyl, by a formal [1.3]-hydride shift;[9] of more general use is the finding that many rhodium(I) hydride complexes, of the type which are well known to induce alkene migrations, readily catalyse the isomerization of aklylidene lactones **12** into the butenolides **13**,[33,35,171,172,202,227] in generally good yields.[10]



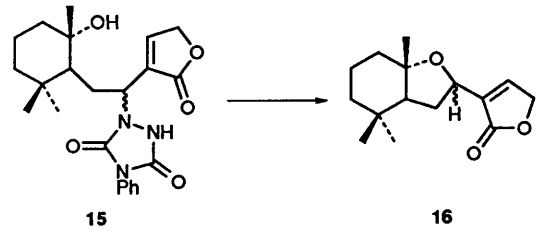
10 **11**



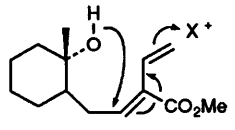
12 **13** **14**

An alternative way of achieving this type of isomerization, and at the same time incorporating an additional functional group, is to employ an ene reaction; for example, by using 2-phenyltriazoline-3,5-dione as the enophile, the alkylidene lactones **12** can be converted into the butenolides **14**, in generally excellent yields.[11]

Using this strategy, the ancistrofuran precursor **16** has been prepared by cyclization of the initial ene product **15**. A rather elegant alternative to this method features cation-driven cyclizations of the dienoate **17** [X = PhSe, Br, or O (from peracid)]; the natural compound itself is accessed by a related but stepwise process.[12]

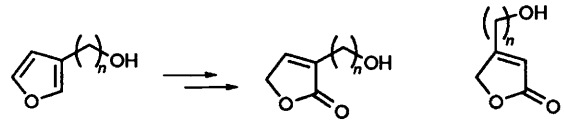


15 **16**



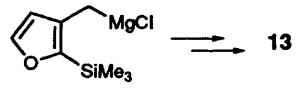
17

In general, α-silylfurans are converted into butenolides when oxidized by buffered peracids[94] and into γ-hydroxybutenolides by singlet oxygen.[116,117] By using the hydroxyalkyl functions in the furans (**18**; $n = 1$ or 2) to direct metallation to the adjacent α-position, regioselective introduction of a trimethylsilyl group can be achieved; subsequent peracid oxidation then leads to the synthetically useful butenolides **19**.[13]



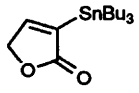
18 **19** **20**

The isomeric hydroxyalkyl lactones **20**[19] can be obtained *via* the same strategy, after first blocking the more reactive α-position by using a phenylthio group. One use of this type of silylated furan is as a precursor to the Grignard reagent **21**.[14] Coupling the latter with alkyl iodides, using dilithium tetrachlorocuprate as the catalyst, followed by oxidation constitutes an alternative route to the α-substituted butenolides **13**. The corresponding β-substituted butenolides can be similarly obtained.



21

An extra degree of synthetic flexibility is offered by the α-stannylbutenolide **22**, prepared from the corresponding phenylthiobutenolide by a desulfurylative-stannylation reaction, which undergoes smooth palladium(0)-catalysed couplings with aryl iodides and presumably many related Stille-type coupling reactions.[15]



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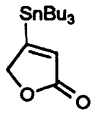
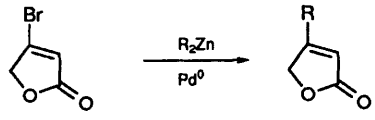
3 β-Substituted butenolides

The β-isomer **23** of the foregoing stannylbutenolide **22** similarly provides a wide range of opportunities for the preparation of β-substituted butenolides.[15]



23

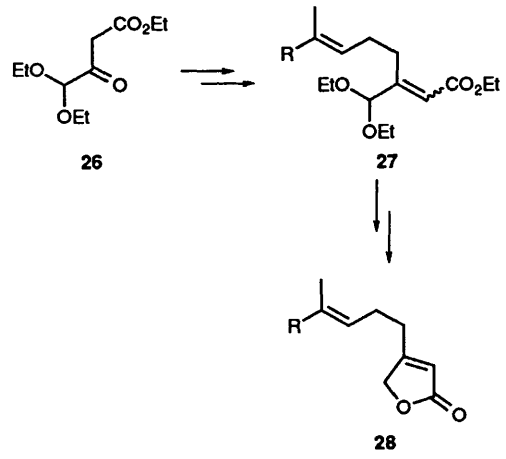
Formally, the 'inverse' approach to this method of producing β-substituted butenolides **25** features palladium(0)-catalysed coupling reactions between dialkylzincs and the β-bromobutenolide **24**.[16] Such butenolides can also be obtained from the bromide **24** by an alternative, if somewhat capricious combination of Michael addition and elimination reactions, usually using lithium dialkylcuprates as the nucleophiles.[17]



24 25

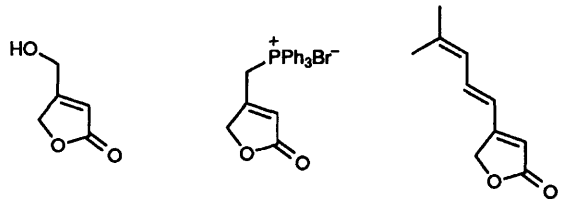
A more convoluted approach to this type of butenolide begins with the keto-ester **26**, which is first alkylated using an allylic chloride then saponified and finally decarboxylated and homologated to the unsaturated esters **27** by a Wadsworth–Emmons condensation. Acid-catalysed ring closure and borohydride reduction of the resulting γ-ethoxybutenolides (Section 5.2) completes this synthesis of butenolides **28**, which are useful precursors of the furanoterpenes perillene and dendrolasin.[18]

A similar olefination reaction, but of diacetoxyacetone, was the key step in a preparation of β-hydroxymethylbutenolide **29**.[19] (See also reference 14.) This compound occurs naturally as a metabolite of *Siphonodon australe* and is also useful as a precursor of the phosphonium salt **30** [*cf.* reference 195]. One application of the latter is in a non-stereoselective synthesis of Scobinolide **31**, which



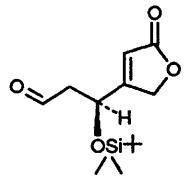
26 27 28

is found in the fungus *Psathyrella scobinacea*, and an *E*/*Z* mixture of which has been isolated from *Senecio clevelandii*.[20] However, these reports suggest that a better route to the salt **30** is from 3,3-dimethylacrylic acid, as outlined below.[205]



29 30 31 E-Scobinolide

A different approach to the unsaturated esters **27** in general features a Peterson olefination as the key step.[21] Another example of the way in which a Wadsworth–Emmons reaction can be employed in this area is illustrated in the synthesis of (*S*)-manoalide diol **33b**.[22] Starting from 2-deoxy-D-ribose, the butenolide **32** was prepared to form the alkene linkage, as in the foregoing examples. A second Wadsworth–Emmons condensation was then used to obtain the central trisubstituted olefinic bond; the synthesis[117,118] was completed by selectively reducing the carboxylate function of ester **33a** by mixed anhydride formation and treatment with sodium borohydride.



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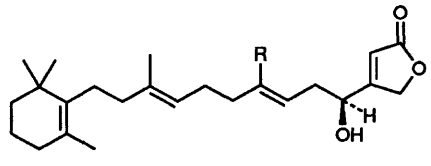
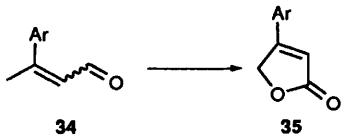
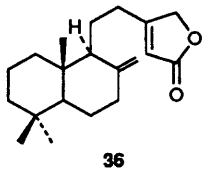


33 a; R = CO_2Bn
b; R = CH_2OH

β-Substituted butenolides, *e.g.* **35**, can also be prepared by PDC oxidations of TMS cyanohydrins derived from β,β-disubstituted-α,β-unsaturated aldehydes, *e.g.* **34**.[23] Yields are variable (40–75%) and the method is rather limited in that mixtures are obtained when both positions γ- to the aldehyde carry hydrogens and are thus open to oxidation. This method has been used to prepare the labdadienolide **36** starting from manool, but the isolated yield from the oxidation step was only 16%.[24]



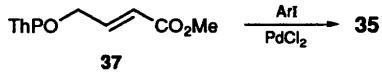
34 **35**



36

Esters corresponding to the aldehydes **34** can be oxidized to butenolides using the allylic oxidant selenium dioxide; yields are increased by adding a little perchloric acid which apparently increases the reactivity of the oxidant by protonation of the Se = O bond.[25] The method is limited to substituents lacking an α-photon (aryl; tert-alkyl).

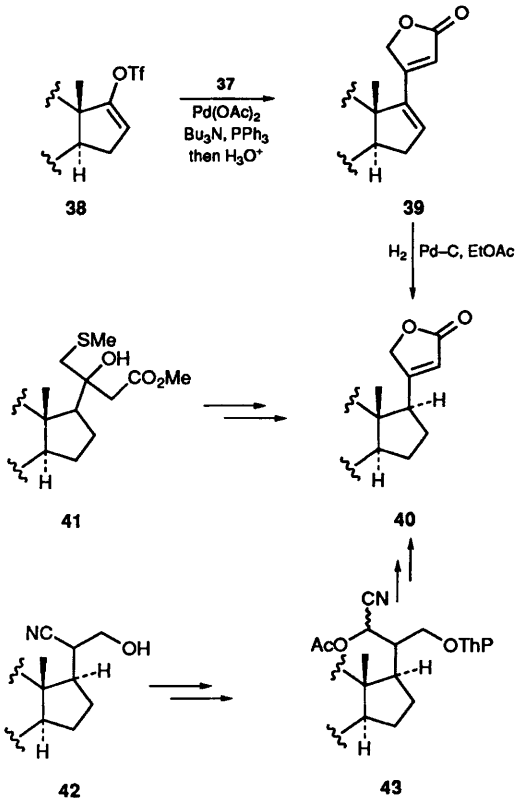
An alternative access to β-arylbutenolides **35** is provided by an application of the Heck reaction in which aryl iodides are coupled with the unsaturated ester **37** under solid–liquid phase transfer conditions using palladium(II) chloride as the catalyst.[26] Yields are in the range of 48–71%; extensions of the method to more highly substituted examples have not been reported.



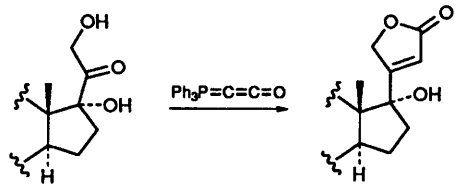
37

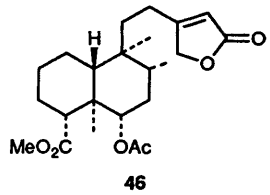
This approach has been applied to the elaboration of the β-substituted butenolide unit in the cardenolides **39** by coupling between an enol triflate **38**, derived from a steroidal 17-one, and the ester **37**, followed by lactonization induced by an acidic ion exchange resin.[27] Completion of the synthesis involves a regiospecific hydrogenation using conventional conditions to give the final product **40**. The β-substituted butenolide function present in the cardenolides has been prepared in a number of different ways involving construction of the lactone ring using anionic chemistry. For example, a Reformatsky reaction has been used to obtain the hydroxyester **41** from the corresponding α-methylthioketone; subsequent acid- and base-treatments lead to the desired products **40**.[28]

A more extended but nevertheless efficient approach also begins with a steroidal 17-one, Knoevenagel condensation of which with ethyl cyanoacetate followed by borohydride reduction leads to the cyano alcohol **42**. Alcohol protection, Dibal-H reduction, and treatment with cyanide then affords the protected cyanohydrin **43**. Brief exposure to acid gives the corresponding β-hydroxybutyrolactone and thence the butenolide **40**, following chlorination and thermal elimination.[29]



The Bestmann ketenylidene phosphorane method[155] has been used in a much shorter approach to the 17-hydroxy-cardenolides **45** from the hydroxy ketones **44**.[30] This procedure was also found to be the best of a number of alternatives for the elaboration of the butenolide function in the insect antifeedant ajugarin IV **46**.[31]

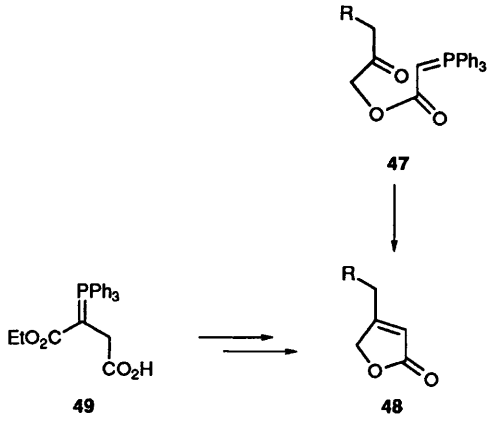




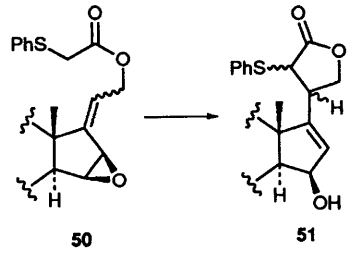
46

Other Wittig-based methods leading to β-substituted butenolides **48** include an intramolecular version in which the likely intermediate **47** in the Bestmann method is prepared in stepwise manner by ester formation between an α-bromo-acid and an α-bromoketone followed by quaternization

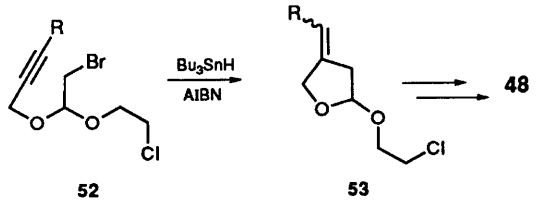
and elimination of hydrogen bromide.[32] Overall yields are generally high in both models and in cardenolide synthesis, but the methodology is not appropriate for the elaboration of ring-fused butenolides, starting with cyclic α-bromoketones.



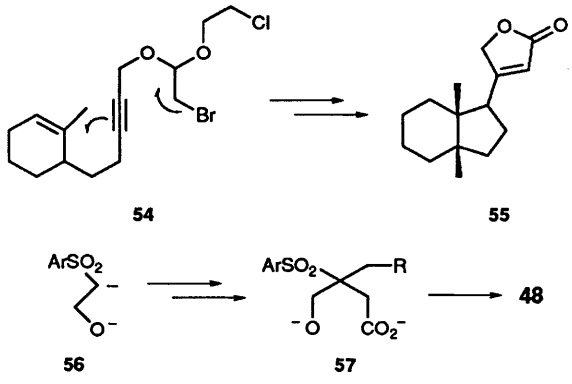
The phosphorane **49**, derived from maleic anhydride, undergoes smooth Wittig reactions with aldehydes; subsequent selective reduction of the ester function using sodium diethylaluminium hydride leads to the corresponding β-alkylidenebutyrolactones, isomerization[10] of which completes the sequence.[33] During a synthesis of digitoxigenin, the butenolide function was introduced by a palladium-induced rearrangement of the allylic epoxide **50**, with concomitant cyclization.[34] Oxidative elimination of the sulfenyl function from the resulting butyrolactone **51** then completed the sequence.



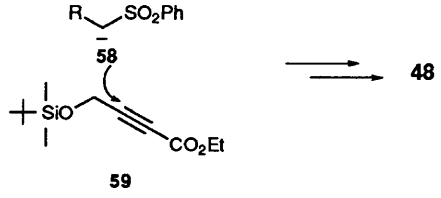
A contribution to butenolide synthesis from the burgeoning area of radical chemistry is the finding that the acetylenic mixed acetals **52** undergo smooth cyclization when treated with tributyltin radicals;[35] the resulting acetals **53** are readily converted into examples of the butenolides **48**, following oxidation and isomerization.[10,35]



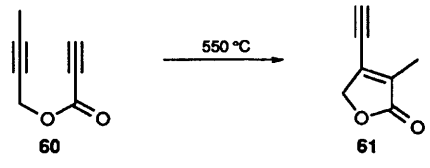
A tandem version starting with the acetal **54** can be used for the preparation of the cardenolide fragment **55**. Sequential alkylation of the sulfone dianion **56**[41,206,225] by an alkyl halide and iodoacetate leads to the hydroxy-acids **57** and thence to the butenolides **48**.[36] The method can also be used to prepare γ-substituted butenolides.



A more direct but unfortunately less efficient approach to the lactones **48**, developed during synthesis of the insect antifeedant ajugarin 1, (*cf.* reference 31) features Michael addition[236,245] of a sulfone **58** to the acetylenic ester **59**.[37] Overall yields are ~45% after completion of the route by lactonization and reductive removal of the sulfur function.



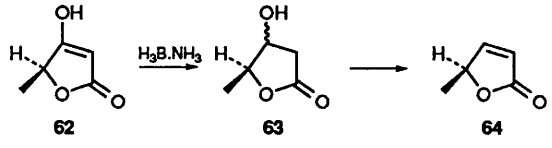
The potentially useful alkynyl butenolide **61** is available from an unusual reaction in which the ester **60** is subjected to gas-phase pyrolysis; the mechanism probably consists of a tandem ene/[1.5]-hydride shift sequence.[38]



4 γ-Substituted butenolides

4.1 Simple derivatives

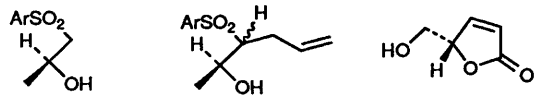
A number of approaches to enantiomers of the simplest γ-substituted butenolide, Angelicalactone **64** [(*S*)-enantiomer shown], have been developed which may be more generally useful. For example, the tetronic acid **62** is available in two steps from ethyl L-lactate; reduction of the alkene function[105,258] using the borane-ammonia complex and dehydration of the resulting, largely *trans*-hydroxy-butyrolactone **63** completes the sequence.[39]



Other precursors include γ-hydroxymethyl-butenolide derivatives (see below)[40] and the hydroxy-sulfone **65**, obtained by yeast reduction of the corresponding keto-sulfone.[41,206]

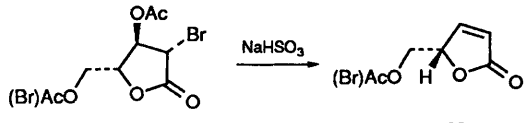
In contrast to the related β-hydroxy-esters, the derived Frater-type dianions[36,206,225] do not couple to allyl bromide with any significant degree of stereoselectivity. Conversion of the separable epimers **66** into lactone **64** then proceeds along conventional lines. The (+)-(*S*)-enantiomer **64** has also been prepared from (L)-tartaric acid by a relatively lengthy route.[42]

Similarly, a number of routes are available for the elaboration of the useful (*S*)-hydroxymethyl butenolide **67**. Starting with



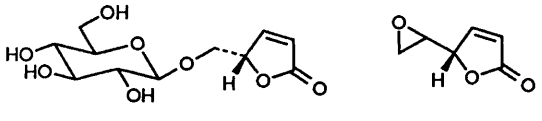
65 **66** **67**

(*R*)-isopropylideneglyceraldehyde derived from D-mannitol, the necessary homologation can be achieved either by condensation with lithioacetate[43] or through a *cis*-selective Wittig reaction.[44]
The latter route appears to be the more practical. Alternatives include overall oxidative removal of the two secondary functions from the D-ribono-1,4-lactone derivative **68** by an apparently unprecedented elimination to give a mixture of the acetoxy and bromo derivatives **69**[45] and the more conventional deoxygenations of D-ribono-1,4-lactone by pyrolysis of a derived cyclic orthoformate.[46,47]



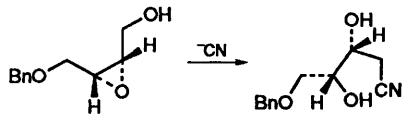
68 **69**

These reports also outline approaches to (−)-umbelactone[206-208] and to lactone **67**, starting from the corresponding butyrolactone,[46] and to the natural butenolide glycoside ranunculin **70**, by coupling lactone **67** to glucopyranosyl bromide.[47]
Further methods for effecting this type of bis-deoxygenation, but of ascorbic acid derivatives have been detailed;[48] using these methods, useful γ-substituted butenolides such as either enantiomer of the epoxides **71** can be prepared.[49]



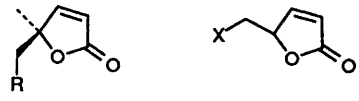
70 **71**

Almost inevitably, butenolide **67** has also been prepared by a route which utilizes an asymmetric Sharpless epoxidation as the source of chirality.[50] Thus, the epoxy-alcohol **72** so obtained reacts with cyanide *via* a prior Payne rearrangement to give the homologue **73** and thence the target, as its *O*-benzyl ether.



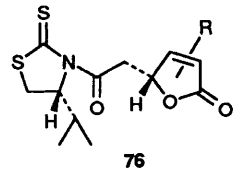
72 **73**

Closely similar chemistry has been used to obtain the γ,γ-disubstituted butenolides **74**.[51] Various methods for preparing the derivatives (**75**; X = OR, Br, SPh, NR_2) have also been described, starting either with the hydroxymethyl lactone **67**[52] or by condensation of an appropriate epoxide with the dianion of phenylselenoacetic acid.[53,57]



74 **75**

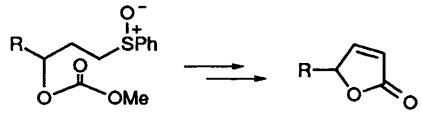
Almost complete stereocontrol is observed in condensations between γ-hydroxy-butenolides and chiral *N*-acetyl thiazolidine thiones, leading to the useful butenolides **76**.[54]



76

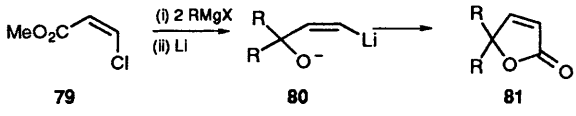
4.2 Methods using carbanions

Formation of the 2,3-bond using carbanion chemistry is the least common of the three possibilities described in this section. An intramolecular version features cyclization of the readily prepared sulfinyl carbonates **77** using LDA as the base, followed by pyrolytic elimination of the sulfur function, leading to generally excellent yields of the butenolides **78**.[55]



77 **78**

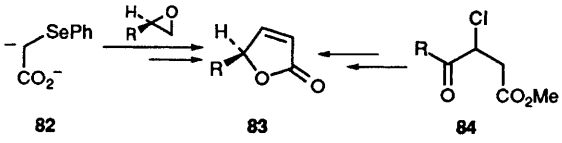
Alternatively, the chloroacrylate **79**, available in three steps from propargyl alcohol, reacts sequentially with two equivalents of a Grignard reagent and then lithium metal to give the intermediate vinyl carbanion **80**, carboxylation of which leads to the γ,γ-disubstituted butenolides **81**.[56]



79 **80** **81**

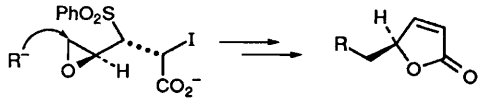
Methods involving formation of the 3,4 bond constitute some of the most generally applicable and useful approaches to butenolides. For example,

condensations between the dianion **82** and an epoxide, which can be homochiral as shown, followed by lactonization [DCC-DMAP] and a facile oxidative elimination of the selenide group lead to the lactones **83** in 70–75% overall yields.[57] The analogous sulfur version of this approach was reported some ten years previously and continues to find applications.[58] The same chiral butenolides can also be accessed by yeast reductions of the chloro-keto esters **84**; optical purities can be excellent.[59]



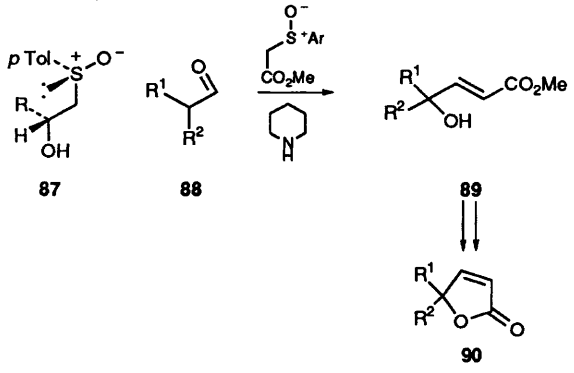
82 **83** **84**

A rather different way in which the homochiral butenolides **86** can be constructed from an epoxide starts with the epoxy-sulfone **85**, also prepared using yeast reduction (but of the corresponding keto-sulfone) to generate the chiral centre,[41,206] and consists of sequential copper-catalysed attack by a Grignard reagent and homologation using iodoacetate[36] as shown.[60] A weakness in this approach is the poor returns from the last two steps.



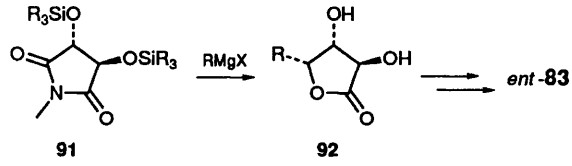
85 **86**

The sulfoxide analogues **87** of the first formed intermediates in the foregoing method can be generated by reduction of the corresponding keto-sulfoxides.[61] Either epimer at the secondary alcohol position can be obtained, depending on the reducing agent and the final products **86** have enantiomeric enrichments in excess of 90%; however, similarly poor yields are obtained in the later, closely related homologation and elimination steps.
A rather more efficient sulfur-based procedure is to subject the hydroxy-sulfoxides **87** to a Pummerer rearrangement and then homologate the resulting hydroxy-aldehydes using nucleophilic acetate.[62] A sulfoxide rearrangement is also featured in an approach to the disubstituted butenolides **90** by condensations of the aldehydes **88** with sulfinylacetate which lead to the unsaturated esters **89**.[63] The sequence is completed by Michael addition of thiophenolate, which allows formation of the corresponding butyrolactone, and elimination.



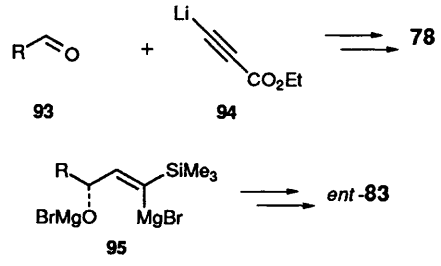
87 **88** **89** **90**

A very different approach to the chiral butenolides **83** features attack of a Grignard reagent onto the C_2-symmetric imide **91**, derived from tartrate, followed by stereoselective borohydride reduction and acidification to give the dihydroxy lactones **92** and finally reductive removal of the two hydroxyl groups (triiodoimidazole, Ph_3P, Zn); final enantiomeric enrichments can be ≥ 98%.[64]



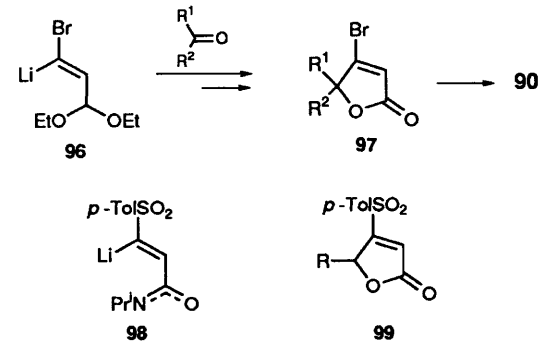
91 **92**

Of the many possibilities for constructing a butenolide **78**, by formation of the 4,5 bond, perhaps the simplest approach is by condensation of an aldehyde **93** with the acetylide **94**, followed by Lindlar hydrogenation. Although conceptually straightforward, the experimental details require close attention.[65] Reduction of 1-trimethylsilylpropargylic alcohols using Bu^iMgBr-Cp_2TiCl_2(cat.) leads smoothly to the dianionic intermediate **95**; subsequent carboxylation and desilylation (TBAF) provides an alternative.[66] The availability of chiral, non-racemic starting alcohols means this approach should be well suited to the asymmetric preparation of γ-substituted butenolides **83**.



93 **94** **95**

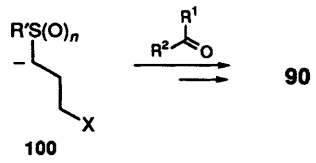
The β-lithio acrolein derivative **96** represents a more reactive example of the same principle; the resulting β-bromobutenolides **97**, obtained following mild acidic hydrolysis and manganese dioxide oxidation, can be debrominated using tin hydride to give the final products **90**.[67,106] The related dianionic species **98** condenses smoothly with aldehydes leading to β-sulfonyl butenolides **99**; removal of the sulfur function is not described.[68]



96 **97** **98** **99**

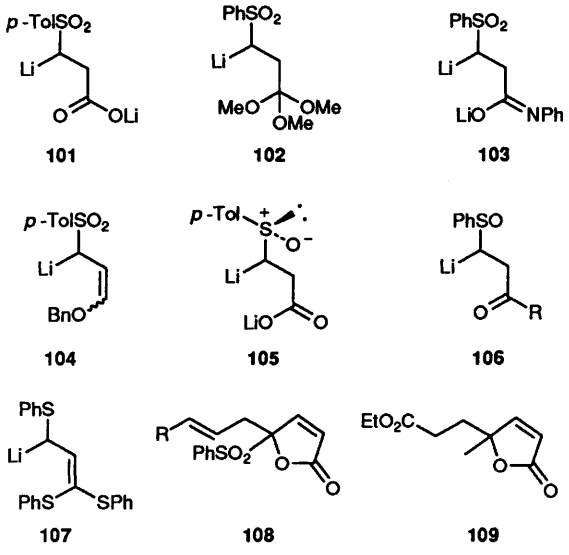
A widely used method for preparing butenolides **90** involves condensations between a three carbon unit

100, having a (masked) carboxylic acid function [X] at the distal position, and an aldehyde or ketone, followed by lactonization and oxidative elimination of the sulfur group.



100

Examples of this include the acid derivative itself **101**,[69] the orthoester **102**,[70] the related amide dianion **103**,[71] the allyl sulfone **104**,[72] the sulfoxide analogues **105**[73] and **106**,[74] and the tris-sulfenyl-propene **107**.[75,106] Overall yields using the sulfones **102** and **103** are generally high.



101 102 103 104 105 106 107 108 109

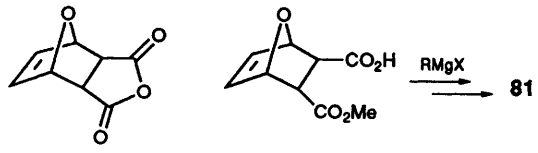
Attempts to achieve asymmetric induction using analogues of the sulfone **103** derived from (*R*)-α-methylbenzylamine were not successful but at least the chiral ligand could be used to allow separation of the resulting diastereomers. Much the same is true of the generally less useful chiral sulfoxides **105** and derivatives of sulfoxides **106** where asymmetry is incorporated either at sulfur or the carbonyl position.

In favourable circumstances, preformed butenolides can be homologated by enolization and reaction with an electrophile. For example, such intermediates derived from γ-sulfonyl-butenolides react with allylic or benzylic halides, but not saturated alkyl halides, to give the lactones **108**.[76] The sulfonyl group can be cleanly removed using tin hydride. Similarly, the lithium enolate of angelica lactone **64** reacts with ethyl acrylate to give the ester **109**.[77] Unfortunately, in examples both of other electrophiles and isomeric methyl-substituted butenolides, mixtures of products arising from attack at the α- and γ-positions are usually obtained. The 'reverse' disconnection is also possible. Thus, ethoxybutenolides (Section 5.2) react with two equivalents of an alkyl lithium in tetrahydrofuran to give the disubstituted butenolides **81**, after Jones oxidation of the resulting lactol.

γ-Substituted butenolides **78** can be similarly prepared from the corresponding γ-hydroxybutenolide.[78]

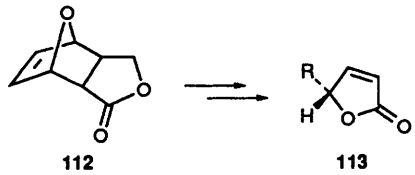
4.3 From maleic anhydride/furan Diels–Alder adducts

Generally excellent yields of the γ,γ-disubstituted butenolides **81** can be secured by reaction between the half-ester **111**, obtained by methanolysis of the Diels–Alder adduct **110**, and an excess of a Grignard reagent followed by cycloreversion at 150 ~ 180°C.[79]



110 111

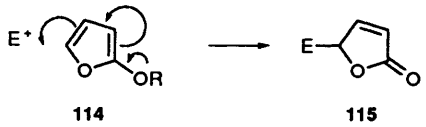
Prior methanolysis is not necessary as it was later found that the initial anhydride **110**[7,233,234] reacts equally well with Grignard reagents.[80] Secondary Grignard reagents tend to add only once, leading to γ-monosubstituted butenolides.[81] As the dimethyl ester derived from the anhydride **110** is a *meso*-isomer, it is amenable to resolution by selective hydrolysis using porcine liver esterase [PLE]; subsequent regioselective reduction of the resulting half-ester (*cf.* **111**) affords the chiral butyrolactone **112**. Sequential reduction to the corresponding lactol using Dibal-H, reaction with an organometallic nucleophile, Jones oxidation, and cycloreversion gives the chiral γ-substituted butenolides **113** in good overall yield and with generally excellent enantiomeric enrichments.[82]



112 113

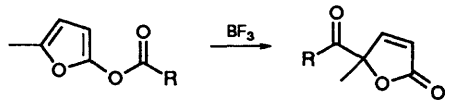
4.4 From furans

Homologations of simple butenolides by enolization are not in general particularly productive.[76,77] A much more effective tactic is to begin with a 2-oxyfuran derivative **114** as these often react smoothly and regiospecifically with electrophiles to give good yields of the γ-substituted butenolides **115**, although α-selective exceptions are known.[6] Lewis acids usually feature as catalysts in such reactions and an appropriate choice is important. Illustrative of the method is the rearrangement of the acyloxyfurans **116** to the butenolides **117** (40–65%) upon exposure to boron trifluoride etherate.[83]

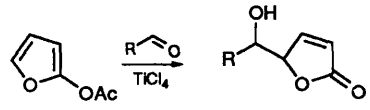


114 115

More generally useful is the finding that the acetyloxyfuran **118**, produced by anodic oxidation of furan itself, undergoes efficient condensations with aldehydes in the presence of titanium(IV) chloride to give the γ-substituted butenolides **119**.[84]

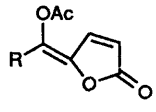


116 **117**



118 **119**

In contrast, a similar condensation with acetyl chloride leads to the ylidenebutenolide **120**. The corresponding 2-silyloxyfuran **121** reacts similarly with orthoesters to give good yields of the acetals **122** and with diethyl acetals to give the corresponding ethers **123**.[85]



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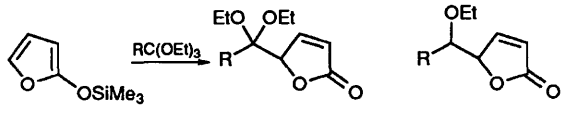
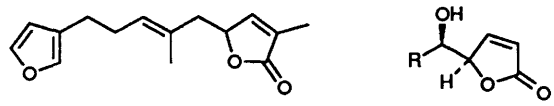
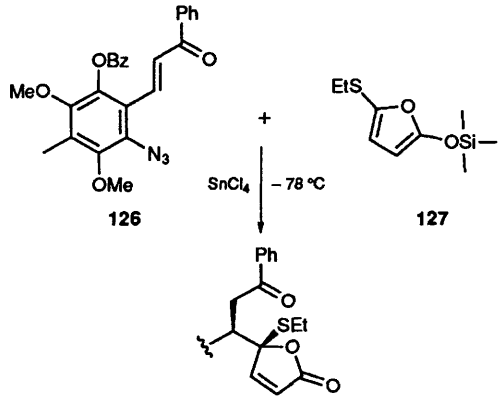


121 **122** **123**

More extensive studies of the synthetic potential of furan **121** have revealed that alkylations by allylic halides are best performed using silver trifluoroacetate as the trigger, neatly illustrated by a total synthesis of the natural butenolide freelignite **124**,[86] but that reactions with aldehydes are best catalysed by triethylsilyl triflate.[87] By a judicious choice of conditions,[141] the latter condensations can be highly stereoselective, leading to either the *erythro* or the *threo* (shown) isomers **125**, and can be used to obtain γ-*C*-glycosylated butenolides by highly stereoselective condensations with sugar-derived aldehydes or imines.[88] Subsequent results suggest that silver triflate is one of the best reagents for effecting alkylations by primary alkyl iodides.[89] Being relatively soft nucleophiles, these intermediates are good participants in Michael additions. An example is the preparation of the butenolide **128**, an early intermediate in an approach to the mitomycins, by the addition of furan **127** to the enone **126**; however, the transformation may not involve a simple Michael addition, but rather a Diels–Alder cycloaddition followed by an acid-catalysed rearrangement.[90] Nonetheless, an example of such a Michael addition has been reported in the reaction of 2-methoxyfuran with a cyclic enone, induced by trimethylsilyl iodide.[91]



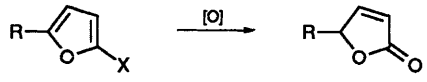
124 **125**



126 **127**

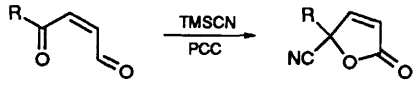
128

A variety of furans **129** carrying heteroatomic substituents in an α-position can be oxidized, using hydrogen peroxide or various peracids, to the corresponding butenolides **130**. These include borates [**129**; X = $B(OMe)_2$],[92] selenides (**129**; X = SePh),[93] and silanes (**129**; X = $SiMe_3$).[13,14,94] Often some, or all, of the initial product is the Δ^3-butenolide and so an additional isomerization step is required to reach the final product **130**.



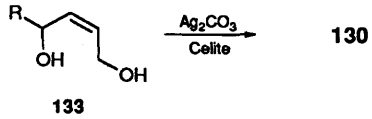
129 **130**

A different way in which a furan can be converted into a butenolide is by low temperature photo-oxygenation which leads to the *cis*-enediones **131**; further oxidation with PCC in the presence of trimethylsilyl cyanide leads to the γ-cyano butenolides **132**.[95]



131 **132**

Diols **133** which correspond to the foregoing diones, are regioselectively oxidized to γ-substituted butenolides **130** by treatment with Fetizon's reagent.[96]

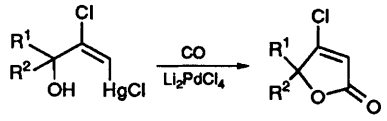


133 **130**

4.5 Other methods

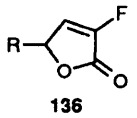
A somewhat inefficient addition of mercury(II) chloride to propargylic alcohols leads to the vinyl mercurals **134**; a subsequent palladium-catalysed carbonylation step[236-243] leading to the chlorobutenolides **135** is,

however, very efficient.[97] Closely related tellurium chemistry can be used to prepare the parent butenolides **90** directly, although only in moderate overall yields.[98]



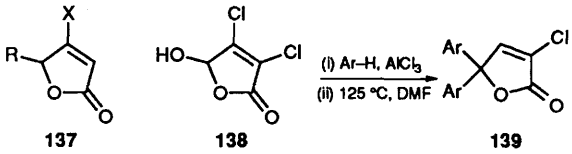
134 **135**

Chiral γ-substituted butenolides **83** can be obtained by acid-catalysed ring closure of chiral 2,3-allenylcarboxylic acids; a limitation with this method is the availability of the starting materials.[99] The α-fluoro-butenolides **136** can be obtained by a related process.[100]



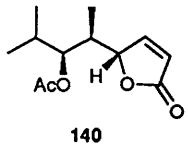
136

An overall 5-*endo-trig* cyclization of methyl 2,3-allenecarboxylates to give the bromobutenolides (**137**; X = Br) can be effected in essentially quantitative yield by using molecular bromine.[101] Such cyclizations can also be carried out using many of the other electrophiles usually associatedywith this type of reaction, to give the lactones (**137**; X = HgOAc, I, PhS, PhSe) in variable yields.[102] This type of cyclization,[164,204,232] in this case induced by acid, may well be the last step in the formation of the diaryl butenolides **139** from the hydroxy-butenolide **138**, using Friedel–Crafts conditions followed by thermolysis in DMF.[103] Simple γ-aryl butenolides can be obtained directly from γ-hydroxy-butenolide, but only in moderate yields.[104]



137 **138** **139**

During the development of iterative approaches to polypropionates, some potentially useful butenolide chemistry has been exploited, such as the preparation of the γ-substituted butenolide **140** from the corresponding tetronic acid by reduction and subsequent elimination.[39,258] The report also contains some useful preparations of alkoxy-substituted butenolides, the topic of the next section.[105]

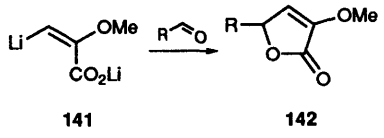


140

5 Hydroxy- and alkoxy-substituted butenolides

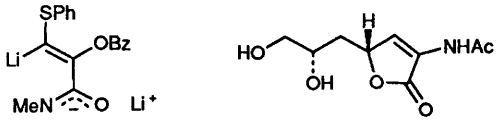
5.1 α-Hydroxy- and alkoxy-butenolides

Direct lithiation of α-methoxyacrylic acid (or derived secondary amides) using t-butyl lithium gives the dianion **141**, which condenses with aldehydes, leading to the α-methoxy-butenolides **142**.[106] As is often, but not always, the case with this type of chemistry, the rapidity and simplicity compensate for the rather poor yields.[67,75,133,139,161,170,208–210]



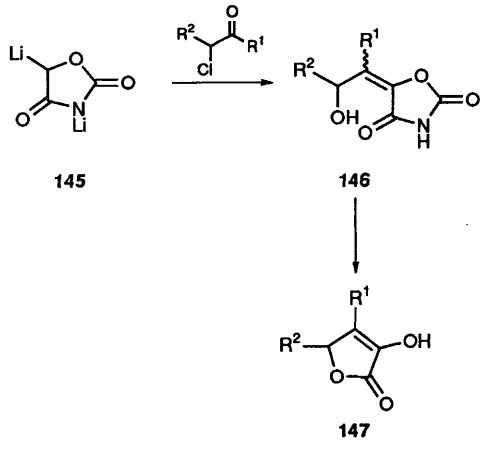
141 **142**

The related dianion **143** gives rather better returns of the corresponding α-benzyloxy-butenolides; this method was the most successful of a number tried for the synthesis and hence structural proof of the natural acetylamino-butenolide Leptosphaerin **144**, carried out by White and his colleagues.[107]



143 **144**

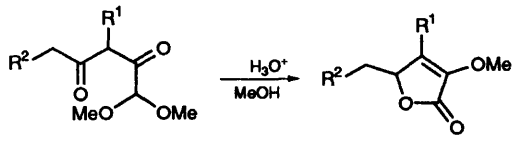
Another dianionic species, the oxazolidinedione **145**, is useful as a general precursor to the α-hydroxy-butenolides **147**, following condensation with an α-chloro-ketone and hydrolysis of the intermediate **146**.[108] The latter is presumably formed by base-triggered rearrangement of the initial Darzens product.



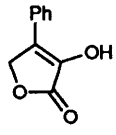
145 **146** **147**

An alternative approach to α-methoxy-butenolides **149** is by acid-catalysed cyclization of the acetylacetone derivatives **148**; the mechanism appears to involve a [1.3]-hydride shift.[109] A double carbonylation of styrene, using dicobalt octacarbonyl as the catalyst under phase transfer conditions, leads to the α-hydroxy-butenolide **150** in 65% yield; further studies are needed to fully define the utility of this reaction.[110]

A more general approach to this type of β-substituted hydroxy-butenolide **152** consists of condensation of the α-oxodiesters **151** with formaldehyde, palladium(0)-catalysed cleavage of the allyl esters, and decarboxylation.[111]



148 149



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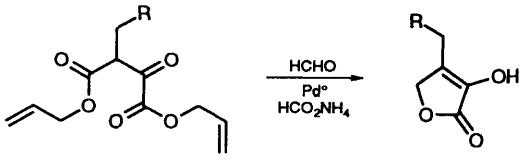


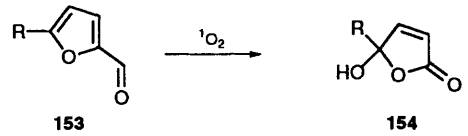
151 152

No discussion of β-hydroxy- or alkoxy-butenolides is given here as these are the tetronic acids and derivatives, a separate class of compound which is beyond the scope of this review.

5.2 γ-Hydroxy- and alkoxy-butenolides

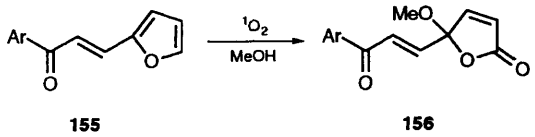
5.2.1 From furans

Photo-oxygenation of furan derivatives is one of the most popular ways of preparing γ-hydroxy-butenolides. For example, such a reaction of the furfurals **153**[112] or the corresponding furoic acids[113] leads to the lactones **154** in ~ 70% yields.[112] Rose bengal immobilized on Sephadex A25 is an especially useful sensitizer in these cases. Similarly, furfuryl alcohol can be converted into the parent γ-hydroxy-butenolide in 97% yield.[112]



153 154

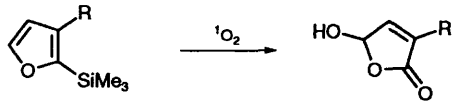
Other unsaturated functions can be tolerated and when the oxidations are carried out in methanol, γ-methoxybutenolides are produced, as illustrated by the conversion of furan **155** into the lactone **156**.[114]



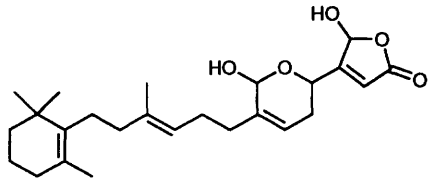
155 156

Problems of regioselectivity arise when 3-substituted or unsymmetrical 3,4-disubstituted furans are subjected to this type of oxidation; however, various carbonyl functions can act as effective control elements.[115]

Undoubtedly, the major recent advance in this area has been the discovery that an α-trimethylsilyl group, when incorporated into the furan (*e.g.* **157**),[13,14,94] facilitates each step of the sequence, especially the now regiospecific collapse of the intermediate endoperoxide, leading to the final producs **158**.[116] (See also reference 123). This means that such silylfurans can serve as masked γ-hydroxy-butenolides during a synthetic sequence; the final step of a total synthesis of manoalide **159** as well as of (*E*)-neomanoalide was just such a sequence.[117]

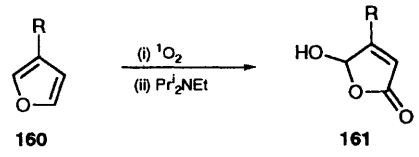


157 158

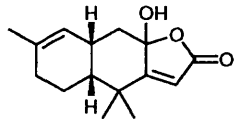


159

However, in some cases, it will no doubt be troublesome to incorporate the silicon function regioselectively. It is therefore interesting that a method has been developed for the regiospecific photo-oxygenation of 3-alkylfurans **160** to the lactones **161**.[118] The key is to induce decomposition of the intermediate endoperoxide using a highly hindered base which will only abstract the less sterically encumbered proton. This tactic has been successfully applied to syntheses of furodysinin lactone **162** and to relatives of manoalide **159**.[22]

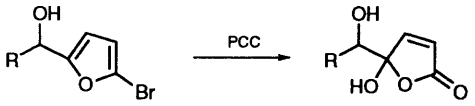


160 161

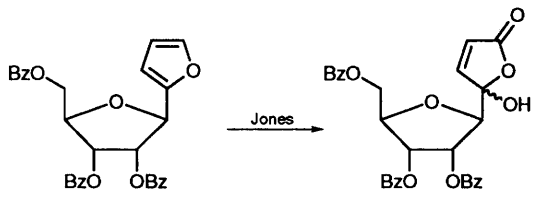


162

A number of other oxidative methods have also been used to convert furan derivatives into γ-hydroxy-butenolides. These include treatment of the bromofurfuryl alcohols **163** with pyridinium chlorochromate (PCC), resulting in the formation of the γ-hydroxy-butenolides **164** in 60–75% yields;[119] Jones oxidation of the β-D-ribofuranosyl derivate **165** to give the C-nucleoside precursor **166** in 93% yield;[120] and oxidation of trimethylsilyloxyfurans **121** to γ-acyloxy-[145] and -sulfonyloxy-butenolides by treatment with iodosobenzene and the appropriate acid.[121]

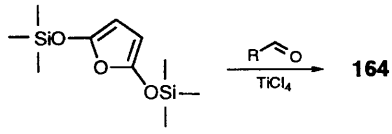


163 164



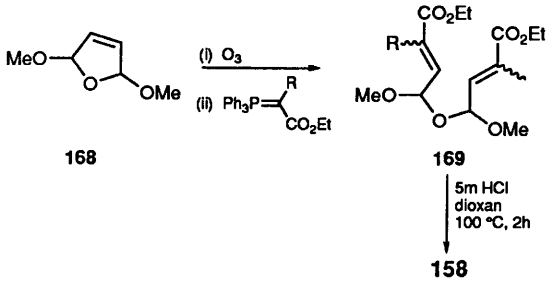
165 166

A rather different way in which such furans can be transformed into γ-hydroxy-butenolides **164** is to use a version of the Lewis acid catalysed condensation reaction **114** → **115**,[85-89] but starting with the bis-(silyloxy)furan **167**, derived from a succinic anhydride.[122]



167

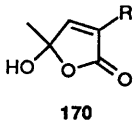
A rather different approach to the hydroxy-butenolides **158** starts from the furan oxidation product **168** and involves sequential ozonolysis and Wittig homologation, leading to the dienes **169**. Subsequent, rather brutal, acidolysis then gives the final products **158** in ~ 60% overall yields, along with the corresponding (*E*)-aldehydo-acid.[123]



168 169 158

5.2.2 Other methods

Carbonylations of terminal alkynes which use dicobalt octacarbonyl as the catalyst in the presence of iodomethane to yield the γ-hydroxy-butenolides **170** are best carried out using solid–liquid phase transfer conditions[124] rather than those originally reported.[125] Attempts to use other alkylating agents have only been partially successful. Symmetrical alkynes can similarly be converted into the alkoxy-butenolides **171**, but using a rhodium carbonyl catalyst[247,248] in the presence of an alcohol, R^2OH.[126]



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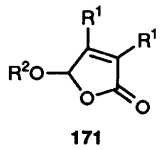
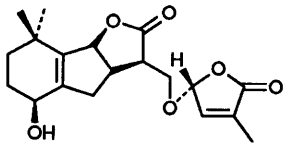


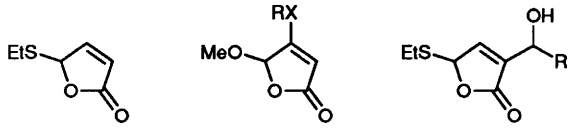
171

Methods for introducing the γ-hydroxy-butenolide function into the naturally occurring germination stimulant strigol **172** all rely on enolate alkylation by the sodium salt of γ-bromo-α-methyl-butenolide,[127] the potassium salt in the presence of HMPA,[128] or improvements of these.[129]

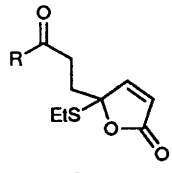


172

A variety of other heterosubstituted butenolides can be obtained from the parent γ-hydroxy- or alkoxy-butenolides. Lewis acid catalysed exchange of the latter with ethanethiol leads to the thiol derivative **173**[130] whereas a Michael addition–elimination sequence can be used to prepare the β-amino- or thio-derivatives (**174**; X = R^1N or S) from the corresponding halobutenolides.[131] A useful enolate can be generated from the thiol derivative **173**, which reacts with differing regioselectivities depending upon the electrophile used. Thus, reactions with aldehydes give the α-substituted homologues **175** whereas additions to Michael acceptors lead to the γ-substituted butenolides **176**.[132]

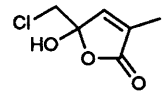


173 174 175



176

The natural γ-hydroxy-butenolide lepichlorin **177** has been prepared by a route which features β-lithioacrylate chemistry.[133] As outlined above,[106] such methodology while usually very brief is often rather ineffecient; this example is no exception.



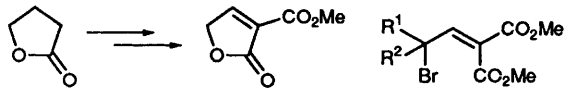
177

As both γ-hydroxy- and γ-alkyloxy-butenolides are readily reduced to the corresponding γ-unsubstituted analogues using, for example, sodium borohydride,[18] the foregoing methods could all in principle be of use in the preparation of butenolides in general.

6 Butenolides substituted with alkoxycarbonyl groups

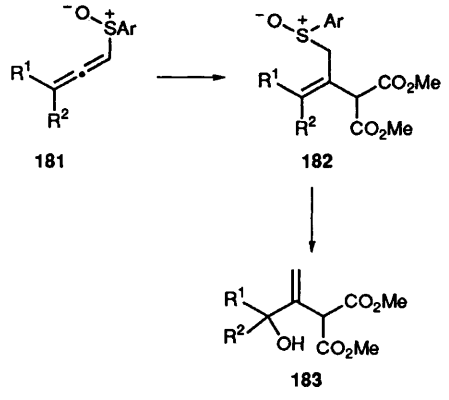
Starting from butyrolactone **178**, the α-methoxycarbonyl butenolide **179** is best prepared

by sequential condensations with dimethyl carbonate and the relatively more reactive thiophenylation reagent *S*-phenyl benzenesulfonothioate, $PhSSO_2Ph$, followed by oxidative elimination of the sulfur group.[134] Alternatively, the ylidenemalonates **180** undergo smooth elimination of bromomethane upon thermolysis in xylene to provide γ,γ-disubstituted homologues of lactone **179**.[135]



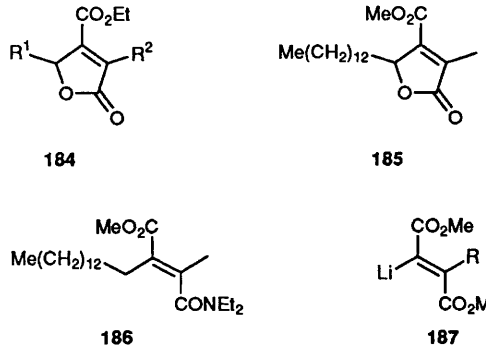
178 **179** **180**

A more convoluted approach begins with addition of malonte to the allenic sulfoxides **181**; subsequent [2.3]-sigmatropic rearrangement of the resulting adduct **182** leads to the hydroxy diesters **183** and thence, upon lactonization and isomerization, to α-methoxycarbonyl butenolides.[136]



181 **182** **183**

β-Alkoxycarbonyl butenolides **184** are readily obtained in general by starting with a β-keto-ester which is alkylated using an α-bromo-acid; subsequent dehydrative cyclization and isomerization completes this approach.[137] A natural product containing this structural feature is methyl lichensterinate **185**; a synthesis has as a key step the Lewis acid catalysed condensation of methyl α-ketopalmitate with (diethylamino)propyne[191-193] to give the amide **186**. The synthesis is completed by allylic bromination and bicarbonate induced cyclization.[138] The fumarate derived vinyl anions [**187**; $R = NR_2$, OR′ or SR′][106] condense with aldehydes to give β-methoxycarbonyl butenolides directly in 30–83% yields.[139]

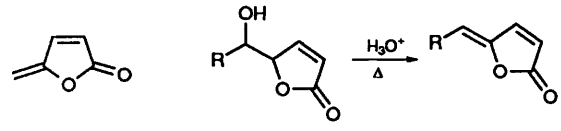


184 **185**

186 **187**

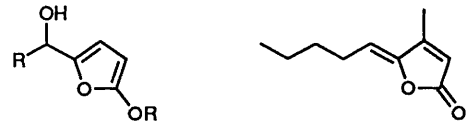
7 Ylidenebutenolides

The simplest member of this group, the naturally occurring protanemonin **188**, can be obtained from 5-hydroxymethylfurfural by sequential photo-oxygenation, borohydride reduction,[18] and dehydration.[140] The γ-substituted butenolides **189** are easily prepared by tin(IV) chloride-catalysed condensations of the α-silyloxyfuran **121** with aldehydes;[87] dehydration brought about by treatment with tosic acid in hot benzene leads to the ylidenebutenolides **190** in excellent overall yields.[141]



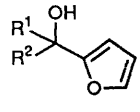
188 **189** **190**

Ylidenebutenolides **190** can also be obtained in *ca.* 70% yields from the alkoxyfurans (**191**; R = Me) by treatment with zinc bromide[142] or from the corresponding methyl ethers using trimethylsilyl iodide.[143] The latter method has been used to prepare bovolide **192**, a butter flavour component.



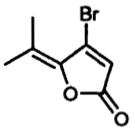
191 **192**

As an alternative to the foregoing Lewis acid induced preparation of lactones **189**, the related furans (**191**; R = Bu^t) can be obtained from the corresponding lithiofuran and an aldehyde or ketone; conversion to butenolides **190**, in 44–81% overall yields, simply requires treatment with tosic acid in aqueous tetrahydrofuran.[144] α-Stannylfurans can be oxidized, *via* an intermediate γ-acetoxybutenolide,[121] to butenolides **190** using lead(IV) acetate.[145] In extreme cases, no substituents are necessary on the furan ring to facilitate oxidation; the tertiary carbinols **193** are converted directly into the corresponding ylidenebutenolides using PDC in DMF.[146] Yields are only high, however, when both chain substituents are aryl groups. Related hydroxyalkylfurans can also be oxidized using phenylselenenyl chloride, apparently by a rather convoluted mechanism.[147]



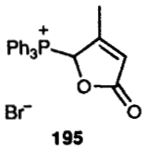
193

Dehydrobromination is another way of generating an ylidenebutenolide, as in the case of the potentially useful bromo derivative **194**; the intermediate butenolide was prepared by starting with an effectively 5-*endo-trig* bromolactonization[99-102, 164, 204, 232] of the corresponding 2,3-allenyl ester.[148]



194

Phosphonium salts derived from butenolides offer an alternative but often non-stereoselective entry into ylidenebutenolides. An example is the preparation of the retinoic acid analogue **196**, using the ylide derived from the salt **195**.[149]



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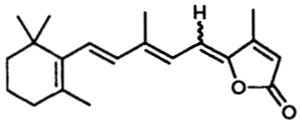
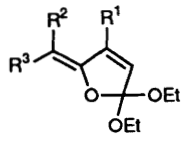


196

The lactone double bond can also be prepared *via* an intramolecular Wittig reaction. Thus, addition of an enolizable α-diketone to the salt **198**, followed by cyclization, leads to the useful 'semi-protected[250]' ylidenebutenolides **197** in respectable yields.[150]



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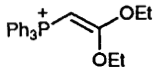
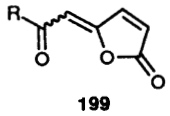


198

In the reverse sense, to the use of ylides from salt **195**, ylidenebutenolides **199** are available from condensations between stabilized phosphorylides and maleic anhydrides. In the case of (**199**; R = OBu^t), the corresponding, relatively unstable, carboxylic acid can be obtained by treatment with mineral acid,[151] while the thiolates (**199**; R = MeS), obtained in the same manner, can be desulfurized, using Raney nickel, to give the lactones **190** as isomeric mixtures.[152] In examples of unsymmetrical anhydrides, attack usually occurs regioselectively to give the isomers **200**.[153]



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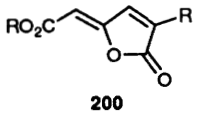
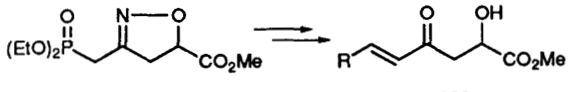
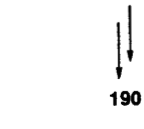


200

A rather lengthy route to ylidenebutenolides **190** has, as a key intermediate, the phosphonate **201**, obtained by a [1.3]-dipolar addition reaction. Subsequent N–O bond cleavage, hydrolysis, and olefination leads to the esters **202** and thence to the final products (after borohydride reduction, cyclization, and dehydration).[154]

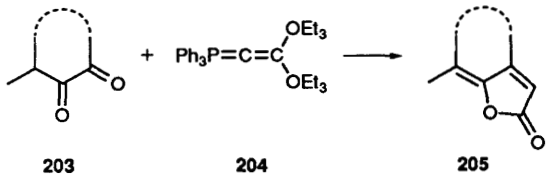


201 202



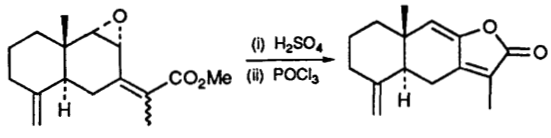
190

A further application of Bestmann's ketenylidene phosphorane chemistry[30–32] is in the direct formation of cyclic and acyclic butenolides **205** by condensations between enolizable 1,2-diones **203** and the phosphorane **204**.[155] Usually, good to excellent yields are obtained.

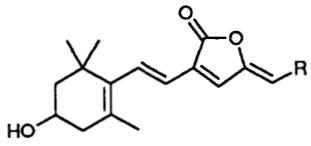


203 204 205

A Wadsworth–Emmons homologation is a key step in the preparation of the epoxy-ester **206**, the penultimate precursor of (±)-8,9-dehydroasterolide **207**.[156] Related lithio-sulfone chemistry has proven suitable for the elaboration of the carotenoid-based ylidenebutenolides **208** (R = polyene chain) in which the vital alkene functions are generated by facile elimination of benzenesulfinic acid.[157]



206 207

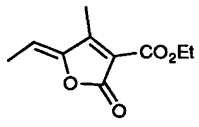


208

The rather labile ylidenebutenolide **209** and related, ring-fused, structures are available from condensations between morpholine enamines and ketomalonates followed by cyclization of the resulting alcohols.[158] Such products are often useful as Michael acceptors. Michael reactions are especially important for the preparation of examples of ring-fused butenolides in general, including ylidenebutenolides. Particularly useful in this respect is the β-vinylbutenolide **210**,[178] which condenses smoothly with β-dicarbonyls to give, for example, the tricyclic system **211**, following dehydration.[159] Another useful aspect of this type of product is that the corresponding sulfoxides readily rearrange to the transposed alcohols **212**.

A total synthesis of the phytoalexin lettucenin A featured as a central, but somewhat inefficient, step the radical-mediated rearrangement of the dibromomethyl dienone **213** to the hydroazulene **214**, a ring expansion method developed some time ago by Barton's group.[160]

β-Lithioacrylate chemistry[106] can also be applied to the synthesis of ylidenebutenolides by condensations of the weakly nucleophilic anion **215** with acid chlorides to give the lactones **216**.[161] Once again,[106] yields are only moderate but the method is rapid and relatively simple.



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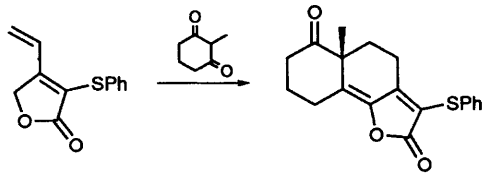

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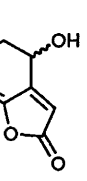

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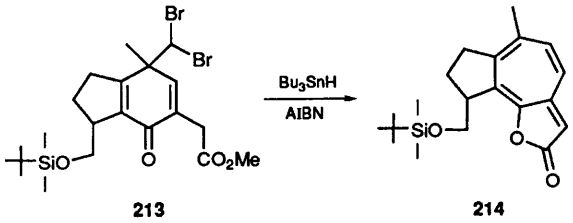

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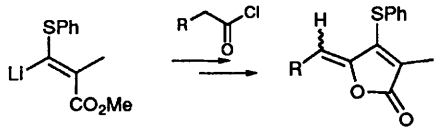
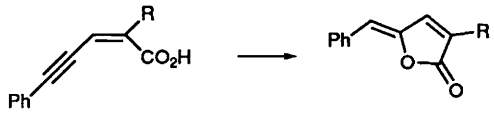


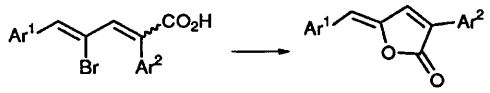
215 216

Cyclizations of acetylenic or allenic acids also constitute important approaches to ylidenebutenolides. For example, exposure of the enynoic acids **217** to mercuric oxide in hot DMF gives good yields of the corresponding lactones **218**.[162]



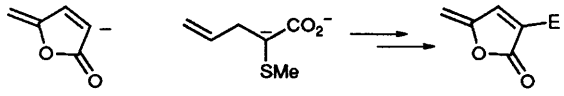
217 218

Direct thermolysis in *o*-dichlorobenzene can also be used to effect such cyclizations when the substrates are ylidenemalonic acids.[163] Ylidenebutenolides can be prepared from 3,4-allenecarboxylic acids by 5-*exo*-*trig*-iodolactonization,[99-102,204,232] presumably followed by *in situ* elimination.[164] The diaryl butenolides **220** can be obtained from the dienoic acids **219**, prepared from an α-bromocinnamaldehyde and an arylacetic acid, by treatment with base.[165]



219 220

A synthetic equivalent of the putative anion **221** is the dianion **222**; following reaction with an electrophile (E), the resulting acid is subjected to iodolactonization and separate elimination steps to give the final products **223**.[166] These products could be useful as Michael acceptors in further syntheses.

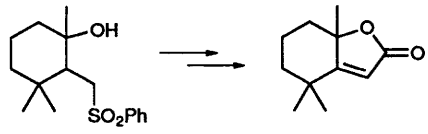


221 222 223

A final route to butenolides **190** is by reactions between trichloroacetic acid and 1-alkenes, mediated by $RuCl_2(PPh_3)_2$; the initial products are α,α-dichlorobutyrolactones.[167]

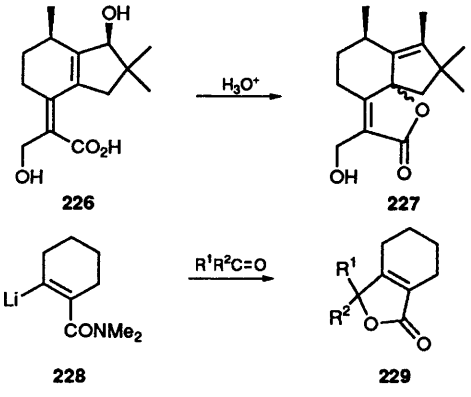
8 Ring-fused butenolides

Cation-mediated cyclization of geranylphenyl sulfone leads to the cyclohexanol **224**; subsequent carboxylation, lactonization, and elimination completes this straightforward approach to the actinidiolide derivative **225**.[168]



224 225

Acid catalysis also plays a key role in a synthesis of 8,9-deoxyalliacol B **227** from the hydroxy-acid **226**.[169] More general approaches to ring-fused butenolides include a further application of β-lithioacrylamide chemistry[106] in which the vinyl anion **228** is condensed with carbonyls to give the adducts **229** directly,[170] and a radical cyclization in which treatment of the acetylene **230** with the usual tributyltin hydride/AIBN combination leads to the butenolides **232** following oxidation and isomerization, for which rhodium trichloride[10] is a particularly suitable catalyst,[171] of the initially formed tetrahydrofuran **231**.[172] Both methods are generally efficient throughout, at least with these relatively simple examples.



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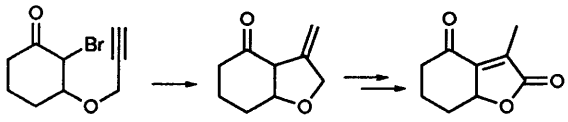
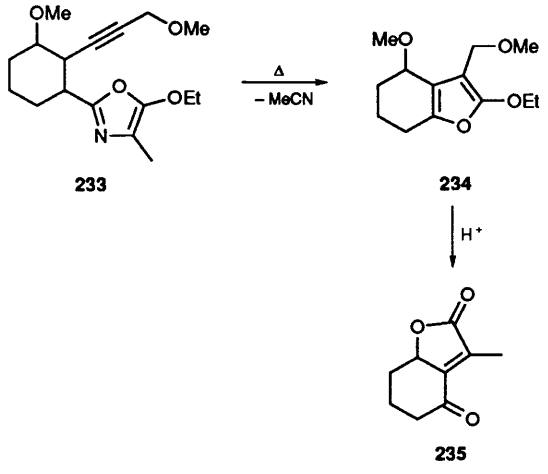


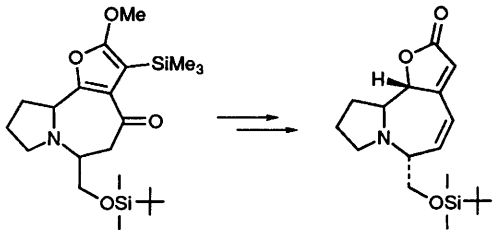
230 231 232

An initial model study[173] established the viability of a novel approach to annulated butenolides and furans by intramolecular Diels–Alder cyclization of an acetylenic oxazole (*e.g.* **233**) which leads to the furan **234**, following expulsion of acetonitrile from the initial cycloadduct. In this particular example, acid-catalysed hydrolysis also results in rearrangement to the butenolide **235**.[174]

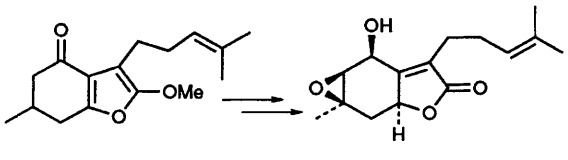


233 234 235

The potential of this methodology is demonstrated in syntheses of the norsecurinine precursor **237** from the initial cycloadduct **236**, this time without rearrangement, and of the precursor **238** to paniculide A **239**.[175] As is often the case, the synthesis was completed only after some of the more obvious options failed.

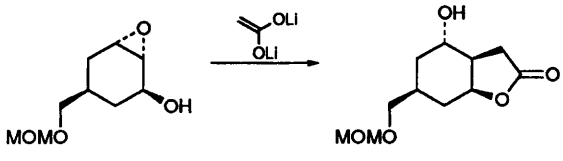


236 237



238 239

A key step in a different approach to the more highly oxygenated paniculides B and C relies on hydroxide-directed attack of dilithioacetate onto the epoxy alcohol **240**, to give the butyrolactone **241**.[176] Subsequent, established chemistry then leads to the known precursor **242**.[177]



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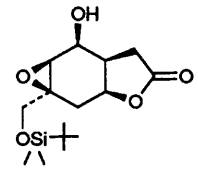
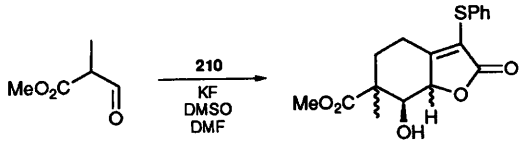
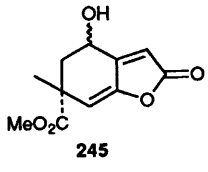


242

The highly electrophilic Michael butenolide **210**[159] has also been used as a precursor to the Paniculides **239** by condensation with the malonaldehyde **243** followed by rearrangement[159] of the initial adduct **244** to the later intermediate **245**.[178]

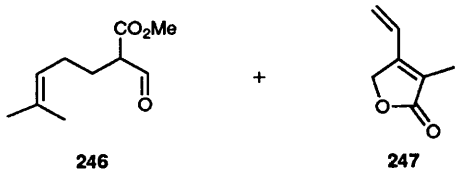


243 244

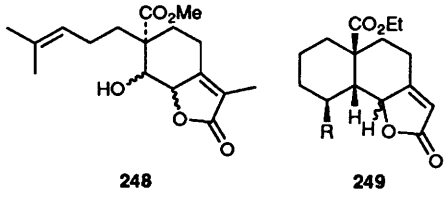


245

The same idea, but using the alternative Michael acceptor **247**, has been used to obtain the furoventalene precursor **248** from the malonaldehyde derivative **246**.[179] Similarly, the useful sesquiterpene precursors **249** have been prepared from β-vinylbutenolide itself and α-ethoxycarbonylcyclohexanones.[180]

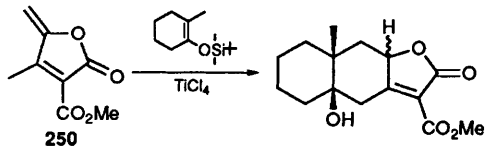


246 247



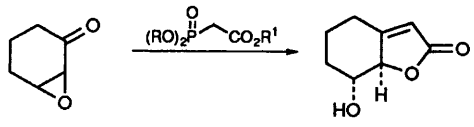
248 249

Generally, the foregoing Michael chemistry is not especially efficient, but relatively advanced precursors are produced from two much simpler reactants. A different type of Michael addition using the γ-methylenebutenolide **250** as the acceptor has been used to prepare the elemane and eudesmane precursor **251**.[181]



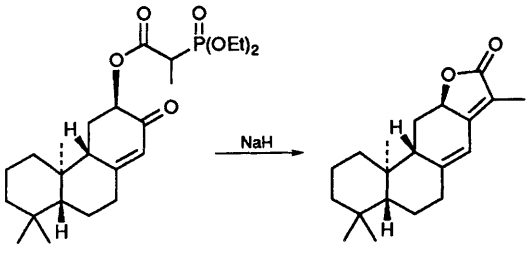
250 **251**

A simple approach to annulated butenolides **253** is by Wadsworth–Emmons homologation of the corresponding epoxy-ketone **252**;[156] however, only the (*Z*)-isomer of the intermediate mixture of alkenes cyclizes to the lactone.[182]



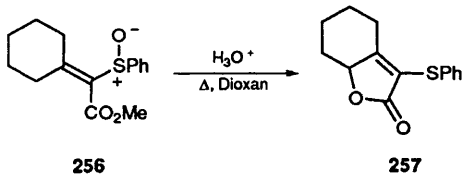
252 **253**

Less ambiguous is the intramolecular version exemplified in the conversion of the phosphonate **254** into jolkinolide E **255**.[183] The precursors **254** are best obtained from the corresponding α-hydroxyketones using a mixed anhydride formed from a phosphonoacetic acid and TFAA,[184] although an alternative approach starts with a methyl vinyl ketone function; sequential oxidation by manganese(III) acetate in the presence of chloroacetic acid leads to the key hydroxyketone derivatives.[185]



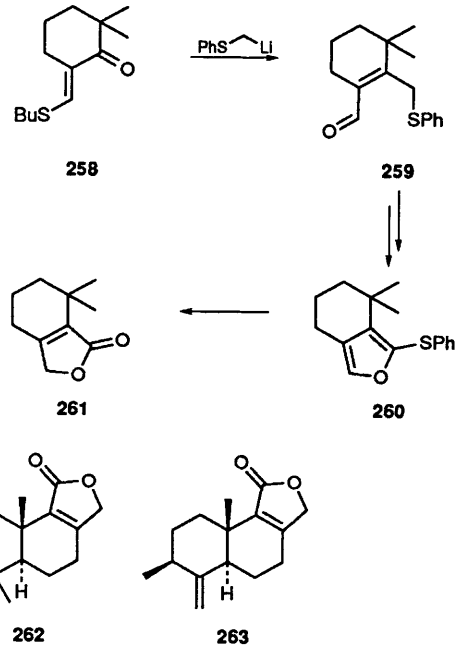
254 **255**

Sulfur chemistry plays a key role in a number of approaches to annulated butenolides. An unusual route to annulated butenolides (*e.g.* **257**) features a vinylogous Pummerer rearrangement of a sulfinyl ester (*e.g* **256**); extensions to more highly substituted systems could suffer from problems of regioselectivity.[186]



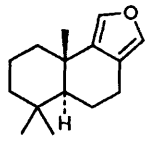
256 **257**

A more general approach begins with the preparation of an α-thiomethylene ketone **258** which is homologated using phenylthiomethyl lithium. Pummerer rearrangement of the sulfoxide derived from the resulting thiomethyl aldehyde **259** leads to the corresponding furan **260** and thence to the butenolide **261** following slow acid hydrolysis.[187] Applications of this methodology include preparations of isodrimenin **262** and the coloratadienolide **263**.



258 **259** **260** **261** **262** **263**

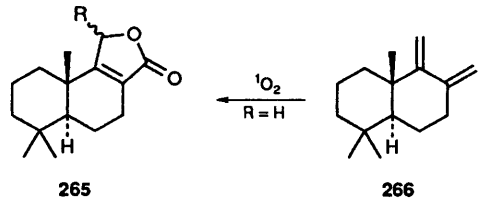
An alternative method for the homologation of thiomethylene ketones **258** is to use dimethylsulfonium methylide; the resulting thiolactols are then easily converted into the corresponding furans (*e.g.* euryfuran, **264**). Treatment of the latter with bromine in methanol leads largely to drimenin, while photo-oxygenation[115] occurs regioselectively to give valdiviolide **265** (R = OH).[188]



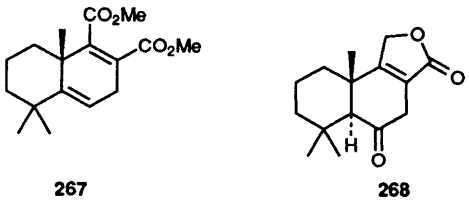
264

Photo-oxygenation is the key step in a related approach to confertifolin **265** (R = H) from the diene **266**; unfortunately, the yield is only 20%.[189] The Diels–Alder adduct **267** is also a useful precursor to both Isodrimenin **262** and fragrolide **268**.[190]

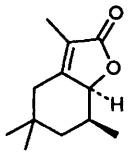
The condensation of ketones with (diethylamino)propyne, catalysed by magnesium bromide, is a useful method for the preparation of unsaturated amides, which can be used as precursors to butenolides.[138] When 2,3-epoxycycloalkanones are the starting materials, the resulting amides (*e.g.* **269**) can be readily converted into a variety of butenolides **270–272**.[191]



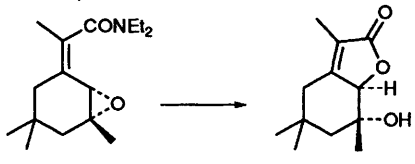
265 266



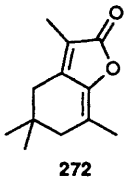
267 268



270

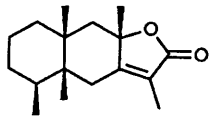


269 271



272

The methodology has been used to synthesize (+)-eremophilenolide **273**[192] and can be extended to include the conversion of α-silyloxyketones (*e.g.* **274**) into annulated butenolides **275**.[193]



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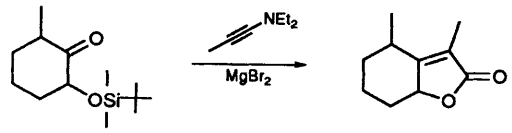
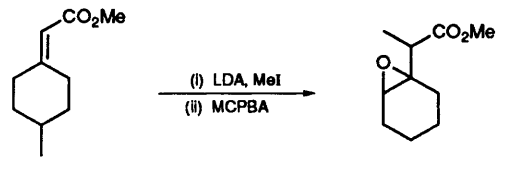
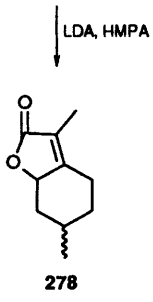


274 275

A somewhat related route has been used to obtain the mintlactone isomers **278** by sequential deconjugative methylation of the unsaturated ester **276**, epoxidation, and base-induced rearrangement of the resulting epoxy ester **277**.[194]

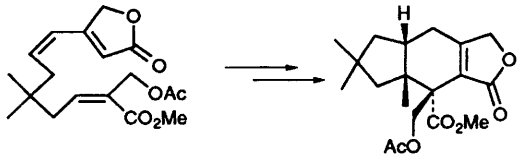


276 277

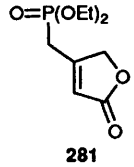


278

During the early stages of a total synthesis of marasmic acid, the ring system **280** was established by an intramolecular Diels–Alder reaction of the β-alkenylbutenolide **279**, followed by base-catalysed isomerization.[195] The precursor was prepared using the phosphonate **281**, which will be of value in other syntheses as well as complementing the corresponding Wittig method using salt **30**.[19,20]

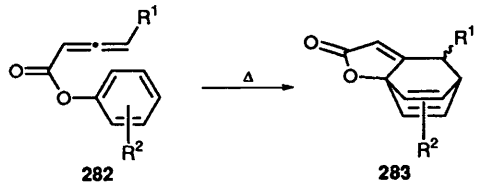


279 280



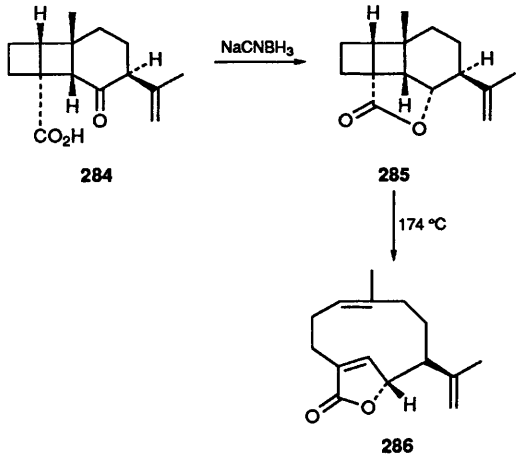
281

A much more unusual Diels–Alder cyclization in which a phenyl group acts as the diene has been used to obtain the annulated butenolides **283** by heating the allenic esters **282** in xylene.[196]



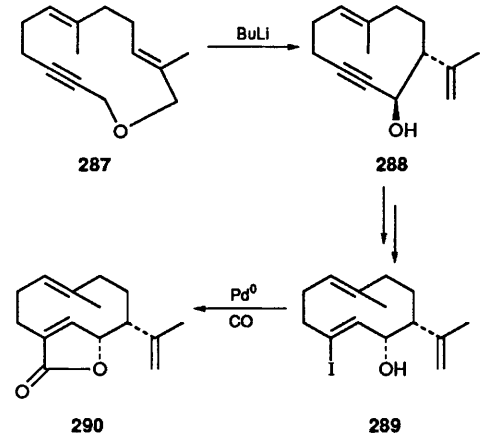
282 283

A photochemical [2 + 2] cycloaddition between cyclobutene-1-carboxylic acid and (+)-isopiperitenone is a key feature of a neat synthesis of the isoaristolactone isomer **286**. Reduction of the initial photoadduct **284** leads to the lactone **285** which undergoes a thermal electrocyclic ring-opening to give the final product in 26% overall yield.[197]



284 285 286

(±)-aristolactone itself (**290**) has been obtained by a clever application of a [2.3]-Wittig rearrangement in which the cyclic ether **287** is converted into the cyclic enyne **288**. Subsequent Mitsunobu inversion, alkyne reduction using Red-Al, and trapping of the resulting vinylalane using *N*-iodosuccinimide leads to the penultimate precursor **289**, carbonylation[237] of which completes the synthesis.[198]



287 288 290 289

Thus, authentic isoaristolactone differs from aristolactone **290** in the configuration of the alkene function; the latter can be transformed into the former by exposure to dilute acid.[197]

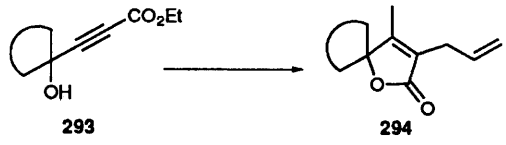
Routes to spiro-butenolides are detailed below; lower homologues can serve as precursors to ring-fused butenolides as in the Lewis acid catalysed rearrangement of the spiro-β-lactones **291** to the α-chlorobutenolides **292**.[199]

291 292

9 Spiro-butenolides

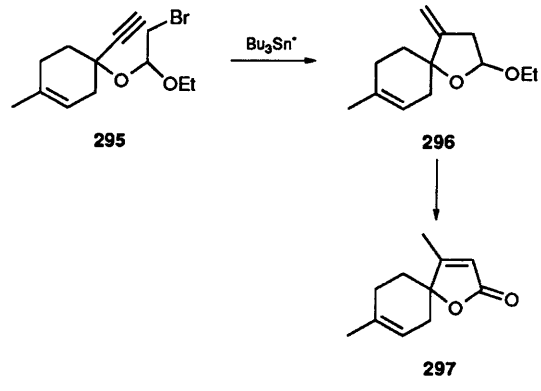
Clearly, many of the foregoing methods could be adapted to the elaboration of spiro-butenolides; the following are approaches specifically designed to produce this type of lactone.

The useful lithio-propynoate **94**[65] condenses smoothly with cycloalkanones to provide the adducts **293**; a subsequent Michael addition/trapping sequence leads to the spiro-lactones (*e.g.* **294**) in good yields.[200]



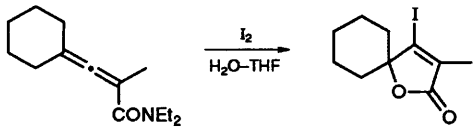
293 294

Unsubstituted spiro-butenolides can be similarly prepared from cycloalkenones by reaction with the dianion of 3-phenylsulfinyl-propionic acid followed by elimination, but not in especially good overall yields.[201] Radical cyclizations[35,172,227,228] can also be used to access such butenolides, as illustrated by a synthesis of (±)-andirolactone **297** from the mixed acetal **295**; Jones oxidation of the intermediate acetal **296**, obtained in *ca.* 70% yield, and isomerization[10] by silica gel completes the sequence.[202]



295 296 297

Essentially the same cyclization can be carried out using the corresponding bromo ester, mediated either photochemically[203] or by tin hydride/AIBN.[227] An isolated example (**298** → **299**) indicates that iodocyclizations of allenecarboxamides[99-102,148,164,232] could be a useful route to functionalized spiro-butenolides.[204]



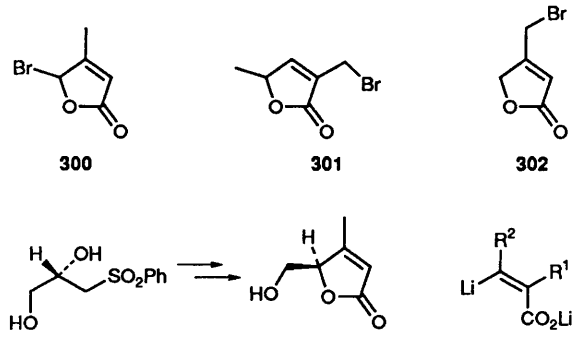
298 299

10 Multi-substituted butenolides

As is the case in the foregoing section, many of the methods outlined above could be extended to include examples of polysubstituted butenolides. The following are procedures which have largely only been or can only be applied to such targets.

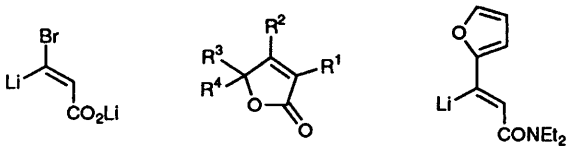
Some synthetically useful bromobutenolides can be prepared by allylic bromination of the corresponding methylbutenolides; these include the γ-bromo

derivative **300** and the α-methyl isomer, together with the bromomethyl derivatives **301** and **302**,[19,20] the latter being best prepared from methyl senecioate.[205] The yeast reduction product **303**,[41] obtained, essentially optically pure, successfully undergoes sequential, but non-stereoselective, alkylations[36,41] by iodomethane and sodium iodoacetate to give (*R*)-umbelactone **304**,[46] following lactonization and elimination, in 30% overall yield.[206] Other approaches to the latter, as the racemate, include acid-induced rearrangement of the corresponding epoxy-enoate,[207] and a relatively efficient condensation of the β-lithioacrylate **305** ($R^1 = H$; $R^2 = Me$)[106] with benzyloxyethanal.[208]



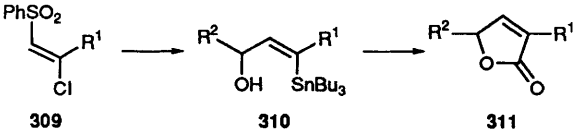
300 **301** **302** **303** **304** **305**

Approaches based on the intermediacy of the corresponding β-bromo dianion **306** followed by Michael addition/elimination to introduce the β-methyl substituent are less attractive due to the poor yields obtained in the last step. The foregoing is but a single example of a much more general approach in which dianions **305** are reacted with aldehydes or ketones to give polysubstituted butenolides **307** in 40–60% isolated yields.[209] The related β-lithioamide **308** is similarly useful in butenolide synthesis;[106] perhaps surprisingly, this intermediate is generated directly from the parent amide using lithium tetramethylpiperidide (LTMP) without competition from deprotonation at the α-site of the furan.[210]



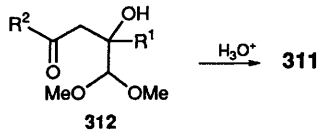
306 **307** **308**

A different way to construct an α,γ-disubstituted butenolide **311** has the chlorosulfone **309** as the starting material. Michael additions of lithiostannane and condensation with an aldehyde, R^2CHO, leads, after elimination, to the vinylstannane **310**, carboxylation of which, by tin–lithium exchange,[239] completes the sequence.[211]



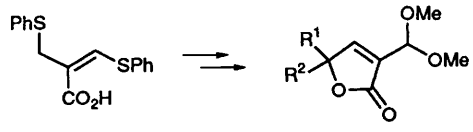
309 **310** **311**

Aldol reactions between a lithio- or *O*-silyl-enolate and an α-keto-acetal lead to the adducts **312**; subsequent acid-catalysed reorganization provides another approach to the butenolides **311**. Both steps proceed in ~ 70% yield.[212] A related but slightly less efficient route has the alkylation of an acid enolate using an α-chloro acetal as the key step.[213]



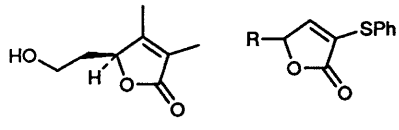
312

Related to this are condensations between the dianion derived from the bis-sulfenyl species **313** and ketones; methanolysis aided by silver nitrate completes this efficient preparation of the potentially useful butenolides **314**.[214]



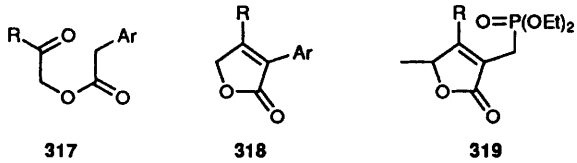
313 **314**

Formation of the butenolide alkene linkage by an aldol-type condensation has been further exploited in a synthesis of the hydroxyethyl butenolide **315** from 2-deoxy-D-ribose,[215] and in a preparation of the α-thiobutenolides **316** from an α-acetoxy aldehyde and the lithium enolate of ethyl phenylthioacetate.[216]



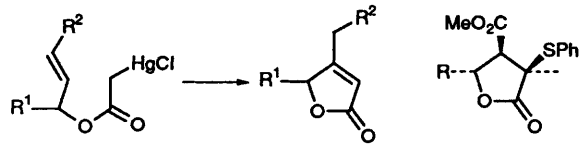
315 **316**

Intramolecular variants are also useful, as in the synthesis of the α-arylbutenolides **318** from the esters **317**, the latter being available from the corresponding arylacetic acid by esterification using an α-halo ketone.[217] A similar intramolecular aldol condensation provides the useful phosphonates **319** from the corresponding propionates.[218]



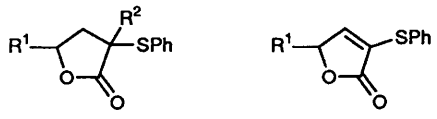
317 **318** **319**

Palladium (0)-induced cyclizations of the α-mercurio esters **320** lead to good yields of the butenolides **321**; unfortunately, a stoichiometric quantity of the palladium reagent Li_2PdCl_4 is required.[219] A similar disconnection, but featuring an intramolecular Michael addition, can be used to obtain the butenolide precursors **322**.[220]



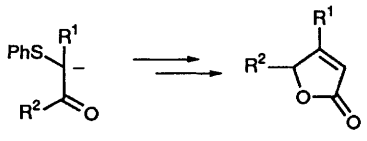
320 321 322

Another viable method for formation of the alkene bond in a butenolide is by reactions between an α-seleno- or α-sulfenyl-carboxylate enolate (*e.g.* **82**) and an epoxide.[57,58] This method can be extended to include most types of substituted butenolides, starting from the initial adducts **323**.[221] For example, simple oxidative elimination of sulfur provides α,γ-disubstituted butenolides whereas, when $R^2 = H$, Pummerer rearrangement of the derived sulfoxide leads to the useful Michael acceptor **324**, allowing the preparation of both β,γ-**326** and α,β, γ-substituted analogues.



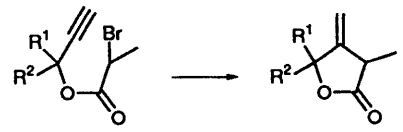
323 324

More highly substituted homologues of the α-sulfenyl butenolides **324** can be obtained by intramolecular Wadsworth–Emmons condensations.[222] Closely related to this is the extremely efficient Lewis acid catalysed thioalkylation of ketene bis-(trimethylsilyl)acetals.[223] The sulfinyl analogues of α-sulfenyl butenolides **324** have also been prepared but by a rather different sequence which proceeds by way of a vinyl sulfoxide.[224] A reverse way to construct the same bond is by homologation of the α-phenylthioketone anions **325** using iodoacetate;[36,41,206] subsequent borohydride reduction and, again, oxidative elimination of the thiol group completes this efficient approach to β,γ-substituted butenolides **326**.[225]



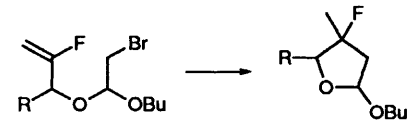
325 326

Manganese(III) acetate can be used to induce the addition of a variety of esters to unactivated alkenes; when α-chloro esters are used, α-halobutyrolactones are obtained and thence butenolides following elimination from the corresponding iodolactone.[226] Unfortunately, the yields are not spectacular, especially from the initial addition (33–53%). What are now regarded as more standard radical processes are generally more productive. For example, the usual combination of tributyltin hydride and AIBN is highly suited to the transformation of the α-bromo-esters **327** into the β-methylene-lactones **328**,[203,227] which can easily be isomerized[10] to the corresponding butenolides.

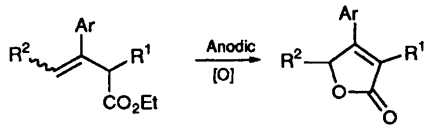


327 328

Under similar conditions, the acetals **329** cyclize to give the alternative butenolide precursors **330**.[228] Anodic oxidation of the β,γ-unsaturated esters **331** is effective as a route to the polysubstituted butenolides **332** only when the β-substituent is an aryl group.[229]

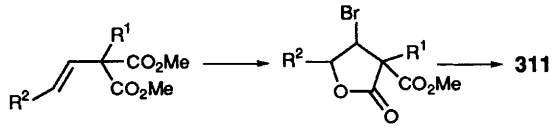


329 330

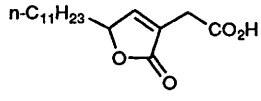


331 332

Bromolactonization of the readily available vinylmalonates **333** leads smoothly to the β-bromobutyrolactones **334**; degradation to the corresponding α,γ-disubstituted butenolides **311** occurs slowly upon exposure to sodium iodide in hot 3-pentanone.[230] The method has been exemplified by a preparation of the natural butenolide acarenoic acid **335**. A detailed study has been performed on related eliminations from α-bromobutyrolactones.[231]

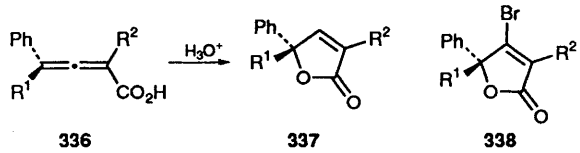


333 334 311



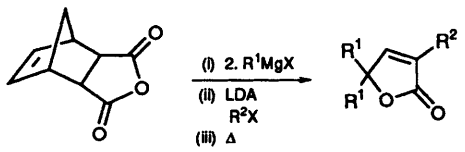
335

Cyclization[99–102,164,204] of the phenyl substituted allene carboxylic acids **336** requires only an acid catalyst to give good yields of the butenolides **337** although with hydrogen bromide the potentially useful β-bromo derivatives **338** are obtained.[232]

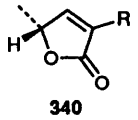


336 337 338

A combination of methods[7,79–81] for homologation of the Diels–Alder adduct **6** represents an efficient approach to the trisubstituted butenolides **339**[233] and also, to the chiral γ-methyl derivatives **340**.[234]



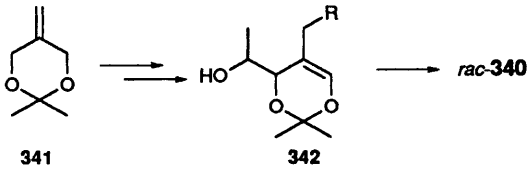
6 339



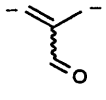
340

The dimethyl derivative **340** (R = Me) is a component of mushroom flavour while the butyl analogue is one of the volatile *Streptomyces* lactones.

A general approach to these, as racemates **rac-340**, features homologation of the methylene dioxane **341** by sequential deprotonation, using Bu^sLi, and reaction with acetaldehyde and an alkyl halide to give the alcohols **342**.[235] Overall, this sequence can be summarized by the hypothetical dianion **343**.

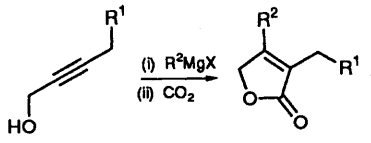


341 342



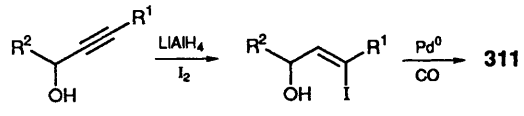
343

As already described, various acetylenes are the starting materials in many viable approaches to butenolides. A further example is a very simple route to disubstituted butenolides **345** by the addition of Grignard reagents to propargylic alcohols **344**, followed by carboxylation.[236]



344 345

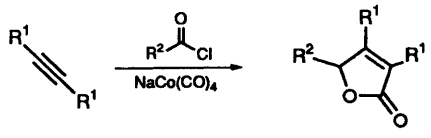
An attractive alternative consists of hydride reduction of a secondary propargylic alcohol **346** and iodination of the resulting vinylalane which leads to the (*Z*)-iodo-alcohols **347** and thence to the α,γ-disubstituted butenolides **311**[198] following palladium(0)-catalysed carbonylation.[237]



346 347

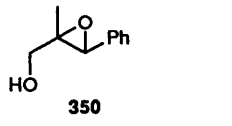
Propargylic alcohols can also be converted into butenolides **311** by regioselective hydrozirconation and carbonylation in 50–70% overall yields,[238] or by formation of an intermediate vinylstannane.[211,239]

Reaction between a disubstituted alkyne **348**, an acid chloride, and $NaCo(CO)_4$ followed by acidolysis of the resulting cobalt complex leads directly to the butenolides **349**.[240] Regioselection is clearly a problem with unsymmetrical alkynes although both phenyl and t-butyl groups are placed largely in the α-position of the final butenolide when in competition with methyl substituents in the acetylenic substrate.



348 349

A remarkable triple carbonylation occurs in the conversion of the epoxy alcohol **350** into the butenolide **351** under phase transfer conditions.[241] Unfortunately, a similar yield (~ 35%) of the product of single carbonylation **352** is obtained.



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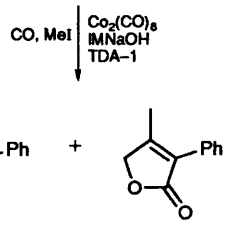
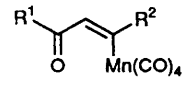


351 352

A neat way to exploit the power of palladium(0)-catalysed carbonylation reactions is in the conversion of the vinyl triflates **353** into α,β-disubstituted butenolides **354**.[242] An especially attractive feature is that the triflates **353** are derived from the corresponding β-keto esters in two steps.

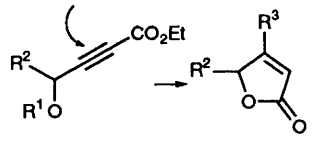
353 354

The vinyl manganese species **355**, formed by sequential insertion of carbon monoxide and a 1-alkyne into an alkylmanganese pentacarbonyl complex, are similarly useful.[243] The same overall transformation can be carried out using an acylpentacarbonyl chromate and a 1-alkyne.[244] A significant feature of many of these methods, especially the latter, is the non-acidic nature of the required conditions.



355

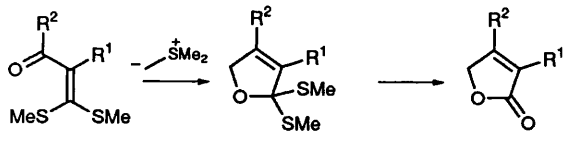
Michael additions of Grignard reagents or lithium divinylcuprates to the ynoates **356**, (*cf.* reference 37) obtained using lithiopropynoate **94**,[65] constitutes a general approach to the β,γ-disubstituted butenolides **357**,[245] while palladium-catalysed α-arylation of these intermediates gives variable yields (32–93%) of the α-arylbutenolides **311** ($R^1 = Ar$).[246]



356 **357**

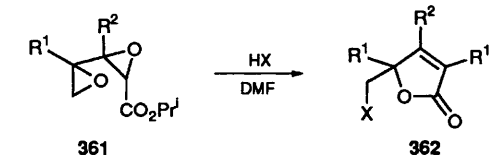
A direct conversion of internal alkynes into α,β-disubstituted butenolides using the water gas shift reaction will probably only be useful for the elaboration of symmetrically substituted species.[247] More highly substituted analogues can be prepared by a related method in which the carbonylation[126] is carried out in the presence of a 1-alkene and with similar limitations.[248]

The foregoing drawbacks also apply to a very simple method for the conversion of aldehydes (RCH_2CHO) into α,β-disubstituted butenolides **345** ($R^1 = R^2$) by exposure to carbon monoxide in sulfuric acid; the first step is presumably an aldol condensation.[249] The readily available ketene dithioacetals **358** can be epoxidized using dimethylsulfonium methylide[188] leading, after rearrangement, to the potentially useful and partly protected[150] forms, **359**, of the corresponding α,β-disubstituted butenolides **360**.[250] Mild acid treatment of the intermediates **359** generates the corresponding furan[187] which can be alkylated at the remaining free α-position, allowing the preparation of α,β,γ-trisubstituted homologues.

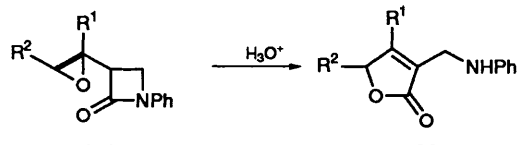


358 **359** **360**

Epoxides also feature in other routes to butenolides. For example, exposure of the diepoxy-ester **361** to HCl or HBr in DMF leads to the dihalo-butenolides **362**[251] while a related acid-catalysed rearrangement of the β-lactams **363** results in formation of the aminomethyl-lactones **364**.[252]

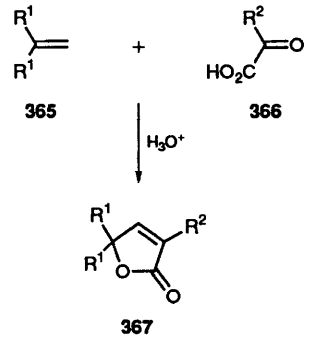


361 **362**



363 **364**

1,1-Disubstituted alkenes **365** participate in reactions with α-oxocarboxylic acids **366** under (Lewis) acidic conditions, leading eventually to α,γ,γ-trisubstituted butenolides **367** in moderate yields which are somewhat offset by the simplicity of the method.[253]

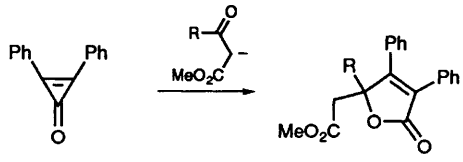


365 **366** **367**

Baeyer–Villiger oxidation is effective for the conversion of the cyclobutenones **368** into the corresponding butenolides **369**.[254] The enones **368** are obtained from cycloadditions of alkynes to keteniminium salts derived from tertiary amides.

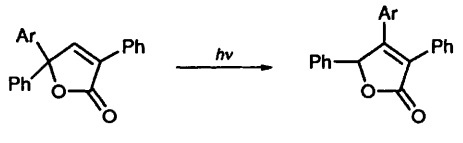
368 **369**

Although somewhat limited in its scope, a mechanistically interesting butenolide synthesis is the conversion of diphenylcyclopropenone **370** into the α,β-diphenyl butenolides **371** by condensation with the sodium salt of an acetoacetate.[255]



370 **371**

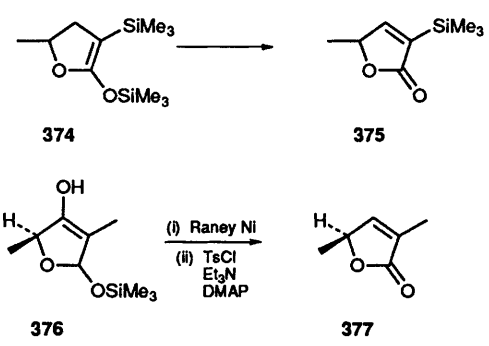
Similar reactions with sodiomalonate lead to ylidenebutenolides. A useful but again somewhat restricted photochemical rearrangement is illustrated by the transformation of the α,γ,γ-trisubstituted butenolide **372** into the corresponding α,β,γ-isomer **373**.[256]



372 **373**

Finally, two methods which approach butenolides from opposite ends of the oxidation scale: the silyl enol ether **374** can be converted into the butenolide **375** in an example of a more general reaction whereby unsaturation can be introduced into such

intermediates by treatment with an allyl carbonate and a palladium catalyst,[257] while sequential hydrogenation and dehydration[39,105] of the tetronic acid **376** is an efficient way to obtain the butenolide **377**.[258]



The tetronic acid was prepared using an intramolecular Grignard reaction; however, discussion of this class of hydroxy-butenolides is beyond the scope of this present review!

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